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Brief review

Economic burden of venous thromboembolism: a systematic review

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Abstract

Objective:
Deep vein thrombosis and pulmonary embolism – together referred to as venous thromboembolism (VTE) – result in a major burden on healthcare systems. However, to the authors' knowledge no comprehensive review of the economic burden of VTE has so far been published.

Methods:
A literature search was carried out to identify references published in English since 1997 using Medline, the Cochrane Library and the Health Economic Evaluations Database. The primary outcomes of interest were 'all-cause' VTE and VTE after major orthopedic surgery.

Results:
A total of 1,037 full research articles and abstracts were screened for inclusion in the review. Of these, ten cost-of-illness studies were identified that met the inclusion criteria and are included in the current review. The results of large US database analyses vary, indicating costs of the initial VTE of approximately US$3,000–9,500. The total costs related to VTE over 3 months (US$5,000), 6 months (US$10,000) and 1 year (US$33,000) were considerable. Studies conducted in the European Union indicate lower additional inpatient costs after VTE of €1,800 after 3 months and €3,200 after 1 year, which still represent a considerable impact on healthcare systems. Complications after VTE can be very expensive, with estimates of the additional cost of treating the post-thrombotic syndrome ranging from $426 to $11,700 and heparin-induced thrombocytopenia from $3,118 to $41,133. A limitation of studies using older data is that recent changes in the treatment of VTE may affect the generalizability of these findings.

Conclusions:
Complications associated with VTE are frequent and costly. In particular, the cost of complications resulting from prophylaxis and treatment of VTE, such as post-thrombotic syndrome and heparin-induced thrombocytopenia, had a considerable economic impact.

Introduction

Deep vein thrombosis (DVT) and pulmonary embolism (PE) – together referred to as venous thromboembolism (VTE) – result in a major burden on healthcare systems. With an estimated annual incidence of approximately 5–12 persons per 10,000[1–3], VTE is a common disorder. Approximately 10% of all hospital deaths can be attributed, at least in part, to PE[4].

DVT and PE are important causes of morbidity and mortality. Without prophylaxis, the risk is especially high in patients undergoing major orthopedic surgery[5], with an incidence of DVT without prophylaxis estimated at 40–60%[5]. Even with standard prophylaxis with enoxaparin or warfarin up to 4 weeks after surgery, 1.4–2.8% of patients develop symptomatic DVT after total

knee replacement (TKR) or total hip replacement (THR), and PE occurs in 0.4–1.2% of patients[6].

The prognosis for patients with VTE is characterized by the risk of recurrent events or post-thrombotic syndrome (PTS) and pulmonary hypertension after PE[7], resulting in an additional burden on healthcare systems. A Swedish prospective cohort study showed a cumulative recurrent VTE incidence of 7.0% after 1 year, 12.1% after 2 years, 15.0% after 3 years, 17.9% after 4 years and 21.5% after 5 years[8]. Long-term morbidity due to PTS is common and may be substantial. The most common symptoms of PTS are persistent or intermittent pain, heaviness, swelling, itching, tingling or cramping in the limb. About one-third to half of DVT patients will develop PTS, in most cases within 1–2 years of acute DVT[9].

Although the data show that VTE and its consequences constitute a considerable medical problem, to the authors' knowledge no comprehensive review of the substantial economic burden of VTE has so far been published. In this systematic literature review, the data on the economic impact of VTE in clinical practice are compiled, summarized and interpreted, with the focus particularly on VTE after THR and TKR.

Methods

A systematic literature review was carried out on the economic burden of VTE. The focus was on the costs of 'all-cause' VTE and of VTE after THR and TKR. A literature search was carried out for references published since 1997 using Medline (Dialog Data star), the Cochrane Library (including NHS Economic Evaluation Database), Health Economic Evaluations Database and Inside Conferences (for the identification of convention contributions and poster publications). This timeframe was chosen because the treatment patterns prior to 1997 were regarded as less relevant for the focus of the study. The literature search included the following search terms and keywords: 'Deep vein thrombosis OR pulmonary embolism OR venous thromboembolism OR thromboembolism' AND 'cost of illness OR cost of disease OR economic burden OR economics OR healthcare cost OR cost'. In addition, references were manually identified from the reference lists of key papers found during the searches and one study was manually identified as published online but not yet listed in literature databases. The search was restricted to studies published in English, French, German or Spanish – although only those with translations to English were included. In order to be included, studies had to identify and measure healthcare utilization and economic consequences of VTE, DVT and/or PE as well as associated complications (especially PTS and bleeding) in clinical practice. The included analyses primarily use healthcare claims databases, prospective/retrospective patient chart reviews and decision-analytic modeling. Cost of disease studies of VTE with a sole focus on specific subpopulations other than orthopedic surgical patients (focusing on medically ill patients and non-orthopedic surgical patients) were excluded. Full papers were obtained and formally assessed for all studies that appeared to be potentially relevant. In addition, available abstracts published by the International Society for Pharmacoeconomics and Outcomes Research/Value in Health and on Inside Conferences have been assessed and included if the presented data was relevant and sufficient for presentations in this review, acknowledging the limitation of this inclusion.

Results

A total of 1,037 full research articles and abstracts were screened for inclusion in the review. Of the titles and abstracts screened, 951 publications were excluded (855 that were not cost-of-disease studies [i.e., studies that did not identify and measure either direct, indirect or intangible costs of VTE and its complications]; 90 cost-minimization, cost-effectiveness or cost-utility analyses of diagnostic procedures, screening or interventions in indications other than VTE prevention/treatment in patients undergoing major orthopedic surgery; one cost-of-disease study in other indications; four published comments/letters; one duplicate). In all, 86 studies were ordered as full papers and assessed in detail. Of these, 17 cost-of-illness studies were identified that met the inclusion criteria and were included in the review.

Economic burden of 'all-cause' venous thromboembolism: costs in the US

A total of ten studies assessed in depth the economic burden of DVT, PE and related complications (Table 1). Of these, seven were in the US and five studies reported the results of direct medical costs from large administrative claim, hospital and ambulatory care databases[10-14]. Bullano *et al.*[10] examined the costs per venous thromboembolic event in patients with a hospital claim of primary or secondary diagnosis of DVT and/or PE. Costs included were for inpatient care for the first venous thromboembolic event and costs of anticoagulation therapy and associated monitoring (inpatient and outpatient) (Table 1).

Rehospitalization due to recurrent VTE and costs of bleeding events (with or without hospitalization) from the index diagnosis to the end of eligibility or the study (21 months) were also included. Events were separated into DVT only, PE only and DVT plus PE, for which there were different lengths of hospital stay (Table 2). Recurrent and bleeding events had a clear

Table 1. Economic burden of 'all-cause' venous thromboembolism.

Reference and country	Year of data used/ costing year	Study design	Costing period	Results (costs, resource utilization)
Bullano *et al.* 2005 USA	1997–2001/ 1997–2001	Retrospective, observational cohort study of patients with a hospital claim with primary or secondary diagnosis of VTE ($n = 2,147$)	21 months	Costs per incident venous thromboembolic event: DVT: US$7,712 ± 18,339 PE: US$9,566 ± 13,512 DVT plus PE: US$12,200 ± 24,038 Mean costs of recurrent event: Per event: US$14,975 VTE: US$12,326 Bleeding: US$15,339 VTE plus bleeding: US$24,085 Average cost of bleed without hospitalization: US$239 ± 386 Average costs of warfarin: US$130 Average costs of monitoring: US$84 Average costs of in-office monitoring: US$127 Average costs of LMWH: US$703
Knight *et al.* 2005 USA	1999–2000/ 1999–2000	Retrospective, observational cohort study of patients with primary admission for DVT ($n = 953$) and PE ($n = 3,933$)	30 days	Total inpatient costs of VTE and related complications: DVT: US$3,018–5,040 PE: US$5,198–6,928
O'Brien and Caro 2002 USA	1997/1999	Retrospective, observational cohort study with patients discharged for DVT ($n = 29,295$)	6 months	6 months' inpatient costs: All DVT patients: US$10,072 US$9,784 without selected complications US$14,649 with PE US$17,169 with major bleeding US$12,142 with minor bleeding US$13,469 with drug-induced thrombocytopenia Cost of outpatient care ranged from US$2,394–3,369
MacDougall *et al.* 2006 USA	1997–2004/ 2004	Retrospective, observational cohort study of patients with a DVT or PE diagnosis ($n = 26,958$)	1 year	Mean annualized total costs: DVT: US$33,200 PE: US$31,300 DVT plus PE: US$38,300 Controls: US$2,800 PTS patients: US$47,600 vs. US$35,900 in matched controls with DVT and/or PE but no PTS
Spyropoulos and Lin 2007 USA	1998–2004/ 1998–2004	Retrospective, observational cohort study of patients with a primary or secondary discharge diagnosis of DVT or PE ($n = 14,044$)	1 year	Total inpatient and outpatient costs during 12 months: DVT as primary diagnosis: US$10,804 DVT as secondary diagnosis: US$7,594 PE as primary diagnosis: US$16,644 PE as secondary diagnosis: US$13,018 Hospital facility costs for DVT: US$8,228; PE: US$13,223 Hospital professional costs for DVT: US$898; PE: US$1,355 Outpatient procedure costs for DVT: US$821; PE: US$989 Mean hospital cost for re-admission for DVT: US$11,862 vs. US$9,805 for initial hospitalization Mean hospital cost for re-admission for PE: US$14,722 vs. US$14,146 for initial hospitalization
Groce 1998 USA	1996–1998/ 1998	Cohort study of 125 patients with acute DVT enrolled in an outpatient management strategy of DVT with LMWH	3 months	Total direct costs of outpatient treatment strategy: US$965 vs. inpatient treatment costs of US$3,436

(continued)

Table 1. Continued.

Reference and country	Year of data used/ costing year	Study design	Costing period	Results (costs, resource utilization)
Tillman *et al.* 2000 USA	1996–1998/ 1998	Prospective cohort study of 391 patients in an outpatient management strategy of DVT	3 months	Direct costs: Outpatient treatment: US$1,868 Inpatient treatment: US$4,696
Backman *et al.* 2004 Sweden	NS/1997	Randomized trial evaluating an inpatient treatment strategy ($n = 61$) vs. an outpatient strategy ($n = 63$) in treating acute DVT with LMWH	3 months	Total costs: Inpatient strategy: SEK15,600 (€1,804) Outpatient strategy: SEK11,500 (€1,330)
van den Belt *et al.* 1998 The Netherlands	NS/1993	Economic evaluation alongside a randomized trial comparing an inpatient treatment strategy of acute DVT using UFH ($n = 22$) versus outpatient strategy using LMWH ($n = 29$)	6 months	Total costs: Inpatient strategy: NLG8,609 (€3,906) Outpatient strategy: NLG3,081 (€1,398)
Annemans *et al.* 2002 Belgium	1998/NS	Retrospective patient chart review of 54 patients with PE from five centers	Inpatient stay (mean: 14.6 days)	Total average inpatient cost of PE: €3,394

DVT, deep vein thrombosis; LMWH, low molecular weight heparin; NLG, Netherlands Guilder; NS, not stated; PE, pulmonary embolism; PTS, post-thrombotic syndrome; SEK, Swedish Krona; UFH, unfractionated heparin; VTE, venous thromboembolism.

Table 2. Mean, or incremental, length of hospital stay and re-admissions due to venous thromboembolism.

Cause	Reference		
	Bullano *et al.* 2005	Spyropoulos and Lin 2007	MacDougall *et al.* 2006
Average length of hospital stay (days): all-cause			
DVT	5.3	5.6	7.0
PE	8.0	7.0	6.0
DVT and PE	8.3	—	9.0
	Oster *et al.* 2004	Ollendorf *et al.* 2002	Tilleul *et al.* 2006
Average length of hospital stay (days): after THR or TKR			
VTE	11.1 (THR 13.1, TKR 10.1)	—	—
DVT	—	11.5	THR 18.9, TKR 17.4
PE	—	12.4	THR 19.5, TKR 20.1
Incremental length of hospital stay (days): after THR or TKR vs. patients with no VTE			
VTE	4.5 (THR 5.9, TKR 3.4)	5.4	—
DVT	—	—	THR 3.9, TKR 3.3
PE	—	—	THR 4.6, TKR 6.0
	Knight *et al.* 2005*	O'Brien and Caro 2002†	Spyropoulos and Lin 2007‡
Frequency of hospital re-admission: all-cause (%)			
DVT	2.6	8.0	—
PE	3.1	1.5	—
DVT or PE	—	—	5.3
Bleeding	—	1.2	—

*Within 30 days of discharge; †within 6 months of discharge; ‡within 1 year of discharge.
DVT, deep vein thrombosis; PE, pulmonary embolism; THR, total hip replacement; TKR, total knee replacement; VTE, venous thromboembolism.

economic impact. During an average period of 21.3 months, 13.4% of patients experienced recurrent VTE, 7.9% experienced bleeding and 3.6% had recurrent VTE plus bleeding that required hospitalization. There were also costs of VTE prophylaxis with warfarin (plus at least one office visit attributable to warfarin monitoring), and outpatient low molecular weight heparin (LMWH) therapy (mean duration 14.2 days). In summary, the main cost drivers were initial inpatient treatment of VTE and subsequent recurrent events requiring hospitalization.

An analysis by Knight *et al.*[11] using an administrative hospital database from 132 US hospitals yielded considerably lower inpatient costs (Table 1). The frequency of VTE-related re-admission within 30 days after discharge is given in Table 2. The inpatient and outpatient costs of patients with an in-hospital diagnosis of DVT were estimated by O'Brien and Caro[13]. Costs were assessed by VTE-related complication status (no complications, DVT with PE, major bleeding and minor bleeding) during the initial hospitalization (Table 2). Eight percent of patients were re-admitted to hospital within 6 months after discharge for DVT (Table 2). There were also considerable costs associated with outpatient care (Table 2).

Spyropoulos[14] reported an analysis of data from 30 managed-care organizations for a total of 14,000 patients with a primary or secondary discharge diagnosis of DVT or PE. Inpatient and outpatient costs of DVT, PE and subsequent rehospitalizations were assessed during a follow-up period of 12 months (Table 1). The primary cost drivers were hospital facility costs, followed by professional costs and lastly outpatient procedure costs (Table 1). They also reported a different length of stay for the initial hospitalization for DVT and PE (Table 2). A clear trend of early recurrence was observed for DVT and PE occurring in the first 30 days after the initial event (Table 2). Mean hospital costs for re-admission were considerably higher for recurrent DVT compared with costs for the initial hospitalization, but were comparable in the PE group (Table 1). The trend of early recurrence was identified as a main cost driver – over half of hospital re-admissions occur within 90 days – which may explain the similarity between the treatment costs over a 6-month period revealed by O'Brien and Caro[13] and the costs during 12 months reported by Spyropoulos[14].

In another US-based retrospective observational cohort study by MacDougall *et al.*[12], inpatient and outpatient direct costs related to the treatment of DVT, PE or DVT plus PE were examined. The frequency and costs of PTS after DVT and/or PE were evaluated (Table 1). All costs were compared with the costs of matched controls (i.e., patients with no DVT and/or PE or – for the PTS subcohort – patients with VTE, but no PTS during follow-up). The average length of hospital stay differed with the

Table 3. Frequency and costs of complications of 'all-cause' venous thromboembolism.

Reference and country	Follow-up period	Complications during initial hospitalization (vs. no complications)	
		Frequency	Costs
O'Brien and Caro 2002 USA	6 months	PE after DVT: 2.5% Major bleeding: 1.0% Minor bleeding: 1.4% HIT: 0.5%	US$3,915 US$5,628 US$2,419 US$3,118
		PTS	
		Frequency	Costs
Ramacciotti *et al.* 2006 Brazil	12 months	Mild-to-moderate PTS Severe PTS	US$426 US$1,188
		HIT	
		Frequency	Additional costs (vs. no HIT)
Creekmore *et al.* 2006 USA	Hospital stay	HIT: 0.43%	US$41,133

DVT, deep vein thrombosis; HIT, heparin-induced thrombocytopenia; PE, pulmonary embolism; PTS, post-thrombotic syndrome.

type of VTE (Table 2). The mean annualized total costs were considerably higher than those observed in the studies described above, which may in part be explained by the inclusion of recurrent VTE costs in the main cost calculations of this study. Two small studies have reported lower costs associated with VTE in the US (Table 1)[15,16]. However, it should be noted that both studies were conducted between 1996 and 1998 and may, therefore, not reflect current treatment standards.

Economic burden of 'all-cause' venous thromboembolism: costs by treatment strategy in the EU

Further studies have assessed the costs associated with VTE in Sweden[17], the Netherlands[18] and Belgium[19]. For Sweden, the costs of outpatient treatment compared with in-hospital treatment during a 3-month period were assessed by randomly assigning patients with acute DVT to one of two treatment strategies: patients assigned to the inpatient strategy were admitted to the ward and were expected to remain there as long as they needed inpatient care. Patients assigned to outpatient care were encouraged to leave hospital after sufficient recovery. Both groups were treated with a LMWH for at least 5 days. Treatment with warfarin began within 24 hours of the start of LMWH therapy and was continued for a minimum of 3 months. Outpatient treatment included a daily visit to the outpatient department at a primary care center. Direct medical costs were 26% greater for the inpatient strategy (Table 1). A similar design was used in a study in the Netherlands, resulting in marginally higher medical costs (Table 1)[18]. However, these results were based on a trial conducted in the early 1990s; hence current treatment practices may not be reflected in this study. In a retrospective patient chart review conducted in Belgium, the inpatient costs of treating 54 patients with PE were assessed (Table 1)[19].

Despite the considerably different analyses used, these findings are relatively consistent and indicate that in the US overall initial costs of DVT are in the region of US$10,000 and of PE are around US$15,000. When recurrent VTE costs are included these costs approximately double. Initial costs in the EU appear to be far less, at approximately €2,000–4,000; recurrent costs have not been reported.

Frequency and economic burden of complications related to 'all-cause' venous thromboembolism

Complications of VTE include the development of PE after DVT, bleeding, recurrent venous thromboembolic events (DVT, PE, DVT plus PE, VTE-related bleeding) and PTS. In the studies described above, these complications had a considerable economic impact (see Tables 1 and 3)[13,20,21].

The costs of mild-to-moderate PTS and severe PTS over 1 year were assessed in a prospective cohort study of 90 patients in Brazil (Table 3)[20].

Heparin-induced thrombocytopenia (HIT) is a serious complication of heparin therapy, mediated by the immune system, often resulting in devastating thromboembolic

Table 4. Economic burden of venous thromboembolism after major orthopedic surgery.

Reference and country	Year of data used/ costing year	Study design	Costing period cumulative incidence	Results (costs, resource utilization)
Caprini *et al.* 2003 USA	Various/2000	Literature-based Markov model to project the economic burden of long-term complications (PTS and recurrent DVT or PE) of primary DVT after THR	1 year (21.5%) (8.4%) (24.4%) (6.5%)	Annual projected costs (first year) of complications: Mild-to-moderate PTS: US$839 Severe PTS: US$3,817 Recurrent DVT: US$3,798 Recurrent PE: US$6,404
Ollendorf *et al.* 2002 USA	1998–1999/ NS	Retrospective cohort study of patients with MOS ($n = 105,562$) with or without VTE THR 37%, TKR 38%, hip fracture 26%	Inpatient stay (mean: 11.5–12.4 days)	Mean costs of inpatient care: DVT: US$17,114 PE: US$18,521 No VTE: US$9,345
Oster *et al.* 2004 USA	1993–1998/ 1999	Retrospective cohort study of patients with MOS ($n = 11,960$) using administrative claims data THR 26.5%, TKR 33%, hip fracture 40.5%	At index admission and after 90 days	Mean cost difference (costs of patients with VTE minus costs of controls without VTE): On index admission All procedures: US$17,552 THR: US$25,853 Major knee surgery: US$9,297 After 90 days All procedures: US$18,834 THR: US$27,034 Major knee surgery: US$7,351 Hip fracture repair: US$24,599 Post discharge VTE: US$5,765
McBride *et al.* 2007 Germany	2002/2003	Prospective observational cohort study in patients undergoing THR or TKR ($n = 309$)	3 months	Total inpatient and outpatient costs of THR: €11,686: Direct costs related to surgery: €10,731 Direct costs related to thrombosis prophylaxis: €313 Indirect costs: €954 Total costs of TKR: €12,270 Direct costs related to surgery: €12,018 Direct costs related to thrombosis prophylaxis: €398 Indirect costs: €252
Tilleul *et al.* 2006 France	Various/1999	Estimation of annual costs of VTE associated with MOS using a decision tree and various data sources (hospital database, physician survey, literature)	1 year	Total annual inpatient and outpatient costs per patient with VTE: €8,265 Main cost drivers: In-hospital DVT (€1,527) and PE treatment (€2,177) New hospital admission (for re-admission due to DVT: €2,682 and due to PE: €4,111) Costs for treating PTS: €3,778

DVT, deep vein thrombosis; MOS, major orthopedic surgery; NS, not stated; PE, pulmonary embolism; PTS, post-thrombotic syndrome; THR, total hip replacement; TKR, total knee replacement; VTE, venous thromboembolism.

outcomes[22]. In a retrospective patient chart analysis of patients receiving prophylaxis for VTE by Creekmore *et al.*[21], the incidence of HIT was comparable with the incidence determined by O'Brien and Caro[13] (Table 3). The cost of hospital admissions that included development of HIT was higher than admissions without HIT (Table 3), although this cost was considerably higher than the costs estimated for HIT over 6 months by O'Brien and Caro[13].

Economic consequences of venous thromboembolism after major orthopedic surgery

Total costs of venous thromboembolism after major orthopedic surgery in the US

Table 4 summarizes the economic burden of VTE after major orthopedic surgery. Using a large healthcare claims database, the economic burden of VTE after

major orthopedic surgery was estimated in the US[23]. In all, 2.2% of patients developed clinical VTE over a 90-day period after admission (DVT 1.7%, PE 0.4%, DVT plus PE 0.01%). Over 60% of cases occurred after hospital discharge. Cases were paired with age- and procedure-matched controls (two per case) without VTE after major orthopedic surgery. Patients who developed in-hospital VTE had a longer length of hospital stay related to orthopedic surgery compared with patients without VTE (Table 2). The mean billed charges for index admission, and at day 90, were higher for patients with VTE compared with controls (Table 4). For patients with post-discharge VTE, mean total costs were higher than for matched controls. Most of the differences in charges resulted from higher costs of inpatient care (either during the index admission for in-hospital VTE or re-admissions for post-discharge VTE).

Using data from discharge summaries and itemized bills from 220 acute care hospitals, Ollendorf *et al.*[24] examined the inpatient costs of VTE after major orthopedic surgery. During the initial hospital stay, DVT occurred in 0.7% of patients, and 0.4% of patients experienced PE (with or without DVT). The mean length of hospital stay in patients with DVT and PE was substantially higher than in patients with no VTE (Table 2). The mean total costs for patients who developed DVT or PE were almost twice as high compared with the costs of patients without VTE (Table 4).

Total costs of venous thromboembolism after major orthopedic surgery in the EU

In a study in France, the annual costs of prophylaxis and treatment of venous thromboembolic events associated with major orthopedic surgery were estimated from a national database and the literature[25]. The estimated incidence rate of in-hospital VTE after TKR and THR was 1.4% and 2.4%, respectively, and VTE increased the length of hospital stay (Table 2). The estimated main cost drivers were in-hospital DVT and PE treatment, costs related to hospital re-admission and costs for treating PTS (Table 4). If DVT or PE occurred after hospital discharge, the costs associated with these events were considerably higher compared with events that occurred in-hospital. Overall, the costs associated with VTE represented approximately half of the costs of major orthopedic surgery. Total annual costs of VTE associated with major orthopedic surgery in France were estimated to be €58 million: €28 million for inpatient care and €30 million for outpatient care[25].

The costs of thrombosis prophylaxis in patients undergoing THR or TKR and followed up over 3 months were estimated in a prospective observational cohort study in Germany[26]. The inpatient and outpatient costs of drugs, administration, monitoring (platelet counts) and rehospitalization for complications related to thrombosis prophylaxis were included. All patients received LMWH during hospitalization, and after discharge for a mean of 38 days, and 9% of patients received subsequent oral anticoagulation for a mean of 38 additional days. The mean direct cost of thrombosis prophylaxis accounted for less than 3% of overall costs (Table 4)[26].

Again, despite the considerably different analyses used, these findings are relatively consistent and indicate that after THR and TKR overall costs of VTE in the US are in the region of US$8,000–26,000 and in the EU appear to be less, at approximately €8,000–12,000.

Long-term complications of deep vein thrombosis after total hip replacement

In a US study, the economic burden over a year of complications of DVT after THR surgery was estimated using a literature-based Markov model[27]. The model reflected the natural history of DVT and projected long-term complication costs of DVT after THR using estimates from the literature. Costs for mild-to-moderate PTS, annual direct costs of severe PTS, and costs of diagnosis and treatment of recurrent DVT and PE are given in Table 4. These estimates are considerably less than the estimates of MacDougall *et al.*[12] of 'all-cause' PTS.

Discussion

The results of this systematic literature review have shown that VTE, and its consequences, have considerable economic impacts on healthcare systems. The results of large US database analyses vary, indicating costs of initial VTE of approximately US$3,000–9,500. The total costs related to VTE over 3 months (US$5,000), 6 months (US$10,000) and 1 year (US$33,000) were considerable. Studies conducted in the EU indicated lower additional inpatient costs after VTE of €1,800 after 3 months, and €3,200 after 1 year, which still represent a considerable impact on healthcare systems. Complications associated with VTE are frequent and costly. In particular, the cost of complications resulting from prophylaxis and treatment of VTE, such as HIT, had a considerable economic impact.

The main cost drivers in VTE appear to be the initial inpatient treatment cost and recurrent events requiring hospitalization. In US studies, 57–75% of the total costs were due to inpatient costs for the first venous thromboembolic event and recurrent events, with between 9% and 43% of the costs due to outpatient post-acute care. Outpatient costs over 1 year revealed in studies in the EU were approximately 30% of inpatient costs.

Longer-term complications of VTE include recurrent VTE and the development of PTS. Recurrence rates were reported as being high and the incidence increased

with duration of follow-up and accord with estimates of recurrent VTE after DVT[8,28]. The costs of treatment of recurrent DVT were high (approximately US$12,000–15,000). PTS occurred in 3.8% of patients and caused substantial additional costs. In addition, chronic thromboembolic pulmonary hypertension is observed in approximately 3% of people who survive a PE[29], and is associated with considerable morbidity. However, the costs associated with chronic thromboembolic pulmonary hypertension remain unknown, but will add to the overall costs of long-term complications of VTE.

Patients undergoing major orthopedic surgery are classified as being at high risk of developing VTE. Even with VTE prophylaxis, the majority of studies included in this review indicated rates of VTE in patients who underwent major orthopedic surgery of between 1.1% and 3.3%. The incremental inpatient costs of patients with major orthopedic surgery who developed VTE were substantially higher compared with those patients with no VTE (approximately US$12,000–17,000 higher). With annual costs of treating VTE after major orthopedic surgery of approximately €8,000 indicated in a study from France[25], the economic burden of VTE in other countries seems to be less, but reasonably similar to that in the US. This may be due to the fact that costs beyond hospitalization are possibly more intensive and less cost-controlled in the US.

Limitations of the study: given the wide range of methodologies used to evaluate costs associated with VTE and its clinical sequelae, no meta-analysis of the data was possible. Moreover, it is important to consider the limitations of the various methods employed when drawing conclusions. Retrospective analyses using large administrative or hospital databases are always subject to limitations. The most relevant is the difficulty in isolating the medical costs associated with VTE, as these patients typically have multiple comorbid conditions. In the study reported by Bullano *et al.*[10], 59% of the patients had a history of active malignancy and rates of comorbid malignancy (32–35%) were also high in the study reported by MacDougall *et al.*[12]. The reason for the lower costs of VTE revealed by the study reported by Knight *et al.*[11] compared with the other US-based studies using claims databases could be a difference in the criteria used to identify VTE patients, resulting in differences in the cohorts between studies.

In pharmacoeconomic analyses using decision-analytic models, the burden of VTE was estimated using a variety of data sources and assumptions regarding the projected clinical and economic burden of VTE. The results were tested in sensitivity analyses by changing key parameters of the model within plausible ranges and have been shown to be robust. A limitation of studies using older data is that recent changes in the treatment of VTE may affect the generalizability of those findings. Finally, cost estimates vary from one analysis to another and reflect the range of healthcare services included, the proportion of patients who use them and the unit costs applied. Thus, results may not be applicable to different geographical regions because of differences in healthcare systems, medical practice and unit costs.

Despite the limitations described above, the systematic review of the literature reported here demonstrated the substantial economic burden of treating VTE and related complications, compared with the relatively low costs of thromboprophylaxis. VTE is a common disease in the general population and in patients undergoing major orthopedic surgery, and related complications are relatively frequent. If the economic consequences of the total number of venous thromboembolic events are included in the estimate, the potential economic burden of VTE on both public health and healthcare systems becomes clear. In a multinational cross-sectional study (VITAE) the estimated burden of VTE in six European countries (France, Germany, Italy, Spain, Sweden and the UK) per annum was 465,715 cases of DVT and 295,982 of PE, with 370,012 VTE-related deaths[30]. This reinforces the fact that there is an urgent need for effective VTE prophylaxis strategies, at least in those patients at high risk (e.g., after major orthopedic surgery). Although some form of prophylaxis is given to most major orthopedic surgery patients, studies have shown that the type, duration and intensity of prophylaxis are often insufficient[31,32]. There is a clear need for more effective strategies for prophylaxis to reduce the burden of this disease.

Transparency

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Declaration of financial/other relationships:
A.R. is employed by IMS Consulting as a consultant for Bayer HealthCare and, at the time of the study, T.S. worked for Steinle-Health Economics & Outcomes Research as a consultant for Bayer HealthCare and M.L. was an employee of Bayer HealthCare plc.

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References

1. Fowkes FJ, Price JF, Fowkes FG. Incidence of diagnosed deep vein thrombosis in the general population: systematic review. Eur J Vasc Endovasc Surg 2003;25:1-5

2. Heit JA, Silverstein MD, Mohr DN, et al. The epidemiology of venous thromboembolism in the community. Thromb Haemost 2001;86:452-63
3. Silverstein MD, Heit JA, Mohr DN, et al. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Intern Med 1998;158:585-93
4. Geerts WH, Pineo GF, Heit JA, et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:338S-400S
5. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians evidence-based clinical practice guidelines (8th Edition). Chest 2008;133:381S-453S
6. Edelsberg J, Ollendorf D, Oster G. Venous thromboembolism following major orthopedic surgery: review of epidemiology and economics. Am J Health Syst Pharm 2001;58(Suppl 2):S4-13
7. Kearon C. Natural history of venous thromboembolism. Circulation 2003;107:I22-30
8. Hansson PO, Sorbo J, Eriksson H. Recurrent venous thromboembolism after deep vein thrombosis: incidence and risk factors. Arch Intern Med 2000;160:769-74
9. Kahn SR. Frequency and determinants of the postthrombotic syndrome after venous thromboembolism. Curr Opin Pulm Med 2006;12:299-303
10. Bullano MF, Willey V, Hauch O, et al. 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;11:663-73
11. Knight KK, Wong J, Hauch O, et al. Economic and utilization outcomes associated with choice of treatment for venous thromboembolism in hospitalized patients. Value Health 2005;8:191-200
12. MacDougall DA, Feliu AL, Boccuzzi SJ, et al. Economic burden of deep-vein thrombosis, pulmonary embolism, and post-thrombotic syndrome. Am J Health Syst Pharm 2006;63:S5-15
13. O'Brien JA, Caro JJ. Direct medical cost of managing deep vein thrombosis according to the occurrence of complications. Pharmacoeconomics 2002;20:603-15
14. 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;13:475-86
15. Groce III JB,. Patient outcomes and cost analysis associated with an outpatient deep venous thrombosis treatment program. Pharmacotherapy 1998;18:175S-80S
16. Tillman DJ, Charland SL, Witt DM. Effectiveness and economic impact associated with a program for outpatient management of acute deep vein thrombosis in a group model health maintenance organization. Arch Intern Med 2000;160:2926-32
17. Backman K, Carlsson P, Kentson M, et al. Deep venous thrombosis: a new task for primary health care. A randomised economic study of outpatient and inpatient treatment. Scand J Prim Health Care 2004;22:44-9
18. van den Belt AG, Bossuyt PM, Prins MH, et al. Replacing inpatient care by outpatient care in the treatment of deep venous thrombosis – an economic evaluation. TASMAN Study Group. Thromb Haemost 1998;79:259-63
19. Annemans L, Robays H, Bruart J, et al. Variation in medical resource utilisation in the management of pulmonary embolism in Belgium. Acta Clin Belg 2002;57:11-18
20. Ramacciotti E, Gomes M, de Aguiar ET, et al. A cost analysis of the treatment of patients with post-thrombotic syndrome in Brazil. Thromb Res 2006;118:699-704
21. Creekmore FM, Oderda GM, Pendleton RC, et al. Incidence and economic implications of heparin-induced thrombocytopenia in medical patients receiving prophylaxis for venous thromboembolism. Pharmacotherapy 2006;26:1438-45
22. Jang IK, Hursting MJ. When heparins promote thrombosis: review of heparin-induced thrombocytopenia. Circulation 2005;111:2671-83
23. Oster G, Ollendorf DA, Vera-Llonch M, et al. Economic consequences of venous thromboembolism following major orthopedic surgery. Ann Pharmacother 2004;38:377-82
24. Ollendorf DA, Vera-Llonch M, Oster G. Cost of venous thromboembolism following major orthopedic surgery in hospitalized patients. Am J Health Syst Pharm 2002;59:1750-4
25. Tilleul P, LaFuma A, Colin X, et al. Estimated annual costs of prophylaxis and treatment of venous thromboembolic events associated with major orthopedic surgery in France. Clin Appl Thromb Hemost 2006;12:473-84
26. McBride D, Bruggenjurgen B, Roll S, et al. Management patterns of thrombosis prophylaxis and related costs in hip and knee replacement in Germany. Cent Eur J Med 2007;2:47-65
27. Caprini JA, Botteman MF, Stephens JM, 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
28. Leizorovicz A. Long-term consequences of deep vein thrombosis. Haemostasis 1998;28(Suppl 3):1-7
29. Pengo V, Lensing AW, Prins MH, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med 2004;350:2257-64
30. Cohen AT, Agnelli G, Anderson FA, et al. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. Thromb Haemost 2007;98:756-64
31. Arnold DM, Kahn SR, Shrier I. Missed opportunities for prevention of venous thromboembolism: an evaluation of the use of thromboprophylaxis guidelines. Chest 2001;120:1964-71
32. Warwick D, Friedman RJ, Agnelli G, et al. Insufficient duration of venous thromboembolism prophylaxis after total hip or knee replacement when compared with the time course of thromboembolic events: findings from the Global Orthopaedic Registry. J Bone Joint Surg Br 2007;89:799-807

