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Systematic literature review of treatment patterns for venous thromboembolism patients during transitions from inpatient to post-discharge settings

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Introduction: Direct oral anticoagulants (DOACs) have emerged as viable alternatives to traditional treatments such as vitamin K antagonists (VKAs) for venous thromboembolism (VTE). The objective of this review was to summarize evidence on the use of DOACs and VKAs to treat VTE in the US for patients transitioning from inpatient to post-discharge settings.

Materials and methods: A systematic review of the VTE literature identified studies published in English (January 1, 2011–December 31, 2016) that reported inpatient and post-discharge treatments and discharge location. Two reviewers screened abstracts, abstracted information from included studies, and assessed the quality of the study methodology and reporting.

Results: Forty-nine studies were included (24 clinical and 25 economic). A limited number of studies (eight clinical and three economic) examined VTE treatment patterns during transitions of care from inpatient to post-discharge settings, irrespective of anticoagulant (eg, DOAC, warfarin, heparin), and < 25% of all studies reported a post-discharge location. Three clinical studies that reported inpatient and outpatient treatment found better patient outcomes with DOAC vs warfarin. Fourteen economic studies reported that DOACs were associated with shorter hospital length of stay (LOS) and lower direct costs vs warfarin. No studies reported indirect costs.

Discussion: Although DOACs are associated with shorter LOS, lower costs, and better patient outcomes vs VKAs, it appears in one study that only a small percentage of patients with stable VTE who are discharged to home may be receiving DOACs.

Conclusion: These findings identified the potential areas of opportunity to improve the management of VTE through coordination of care from the inpatient to the outpatient settings.

Keywords: deep vein thrombosis, pulmonary embolism, anticoagulant, transition of care

Introduction

The number of adults with venous thromboembolism (VTE) in the US between 2002 and 2006 was estimated to be 1 million individuals, and this estimate is expected to double by 2050.[1] Furthermore, the Centers for Disease Control and Prevention reported that approximately 500,000 individuals in the US were hospitalized for VTE during the period 2007–2009.[2] The VTE-related cost estimate for 2014 ranged from $7 billion to $10 billion based on 375,000–425,000 incident cases in the US.[3] On a per-patient basis, 2014 annual incident costs were estimated at $12,000–$15,000.[3]

VTE treatment guidelines recommend anticoagulant therapy for 3 months following an acute event, with subsequent long-term or extended therapy depending on patient's risk of recurrence.[4] Other treatments include thrombolytics, the insertion of

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an inferior vena cava filter (IVCF), or a procedure to remove the clot (thrombectomy/embolectomy). Anticoagulant treatment options include the use of traditional oral and injectable therapies as well as the more recently developed direct oral anticoagulants (DOACs). Until 2009, vitamin K antagonists (VKAs) – primarily warfarin – were the only type of oral anticoagulant available. VKAs are effective in treating VTE, but they require frequent monitoring and have significant drug and food interactions. Indirect or injectable anticoagulants (IACs) include unfractionated heparin, low-molecular-weight heparin (LMWH; eg, enoxaparin), and fondaparinux. Currently, there are four DOAC therapies (dabigatran, rivaroxaban, apixaban, and edoxaban) available in the US, and each has been shown to be noninferior to VKAs in the treatment of VTE.[4–7] Because patients who are receiving DOAC therapies do not need heparin bridging and frequent monitoring DOACs may allow stable patients with VTE to be treated at home earlier than with VKAs.

Irrespective of type of anticoagulant used, once the acute event is addressed in the inpatient (IP)/emergency department (ED) setting, the condition is then managed in various health care (outpatient [OP], home care, and long-term care) settings and by a number of specialty types.[8] As such, successfully managing treatment of a VTE patient as care transitions between IP and OP settings can positively impact patient outcomes, as evidenced by a decrease in length of stay (LOS)[9] and the likelihood of readmission.[10] For VTE patients, successful transition of care relies on effective communication and coordination between clinicians and their patients/care takers, as well as patient adherence to the treatment regimen.[11]

The objectives of this review were to summarize the literature regarding the treatment of VTE with DOACs and VKAs in the IP and OP setting and to determine discharge location after patients leave the IP setting. Specifically, this review examines IP and OP treatment patterns, post-discharge location (eg, home, skilled nursing facility [SNF]), patient outcomes (eg, treatment adherence), and health care resource utilization (eg, hospital LOS) and costs (eg, direct, indirect) associated with VTE for patients who are transitioning from IP to OP settings.

Materials and methods

The literature review followed the PRISMA guidelines.[12,13] The databases that were searched were PubMed/MEDLINE, EMBASE, and the Cochrane Library. The appendix contains the clinical and economic search strategies (Tables S1 and S2, respectively) that display the Medical Subject Heading (MeSH) terms and keywords used in the search of the PubMed/MEDLINE database. The clinical search was directed at identifying the studies that reported IP and OP treatment patterns and clinical outcomes associated with VTE, irrespective of the study design. Similarly, the economic search was directed at identifying the studies that reported VTE-associated IP and OP health care resource utilization and costs, irrespective of the study design. For simplicity and consistency, we will refer to the studies retrieved from the clinical search as "clinical studies" and will likewise refer to the studies retrieved from the economic search as "economic studies". The systematic searches were supplemented by a manual review of bibliographies. Articles published in English that reported IP and post-discharge treatments for VTE published between January 1, 2011, and December 31, 2016, were included in the review. Studies were excluded during the abstract screening process if they were case studies, letters to the editor, editorials, commentaries, reviews, and studies that did not report patient outcomes (eg, study protocols) or studies that were conducted outside of the US.

Two reviewers independently screened the abstracts that were retrieved from the searches and also abstracted information for the final set of studies that were included in the review, using the same data abstraction form. During the abstraction process, the two reviewers also assessed the study methodology and reporting using the nonrandomized control trial (non-RCT) checklist from the National Institute for Health and Clinical Excellence (NICE)[14] for the clinical studies and the 2013 version of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS)[15] checklist for the economic studies. Any discrepancies between the two reviewers during the screening or abstraction process were resolved by consensus, and a third reviewer adjudicated unresolved disputes; the judgment of the third reviewer was considered final.

The four quality assessment categories from the NICE methodology that were used to assess the clinical studies included 1) selection bias, defined as systematic differences between the comparison groups; 2) performance bias, defined as systematic differences between the groups in the care provided, apart from the intervention under investigation; 3) attrition bias, defined as systematic differences between the comparison groups with respect to loss of participants; and 4) detection bias, defined as bias in how outcomes are ascertained, diagnosed, or verified. The economic studies were assessed using the CHEERS checklist that has 24 items with two-thirds of the items directed at the reporting of study methodology and with many items pertaining to economic models

rather than observational studies such as those included in this literature review. Consequently, model-related items that could not be assessed received a not applicable (NA) rating.

Results

Study selection and characteristics

The systematic searches of the PubMed/MEDLINE, EMBASE, and Cochrane Library databases retrieved 1,415 abstracts from the clinical search and 139 abstracts from the economic search, of which 1,391 clinical and 114 economic studies were excluded with reasons. Figures 1 and 2 show the PRISMA flow diagrams that display the clinical and economic search and review process, respectively, and the reasons for study exclusion. After completing the screening process and a full-text review, 24 clinical and 25 economic studies were included in the literature review.

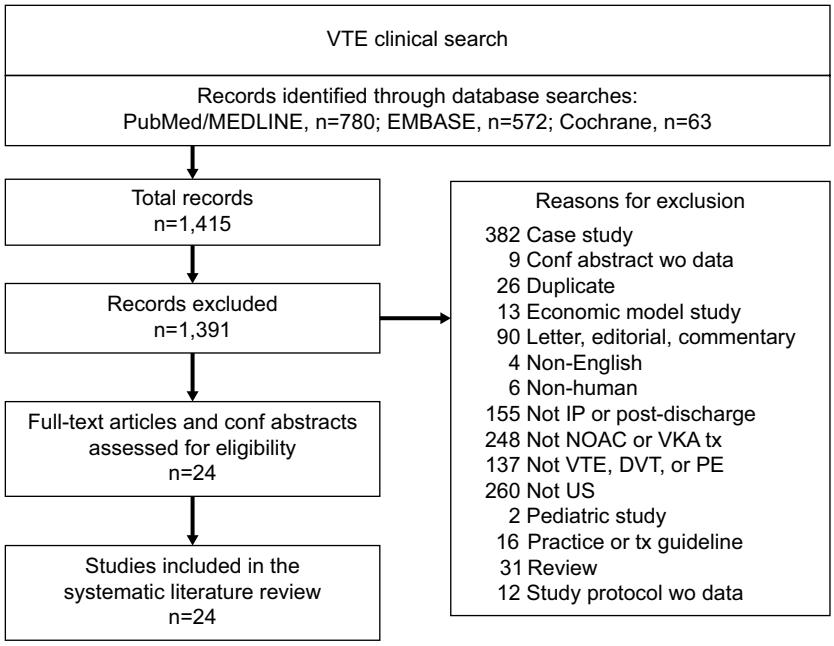

Figure 1 Clinical search results.
Abbreviations: Conf, conference; DVT, deep vein thrombosis; IP, inpatient; NOAC, new/novel oral anticoagulant; PE, pulmonary embolism; tx, treatment; VKA, vitamin K antagonist; VTE, venous thromboembolism; wo, without.

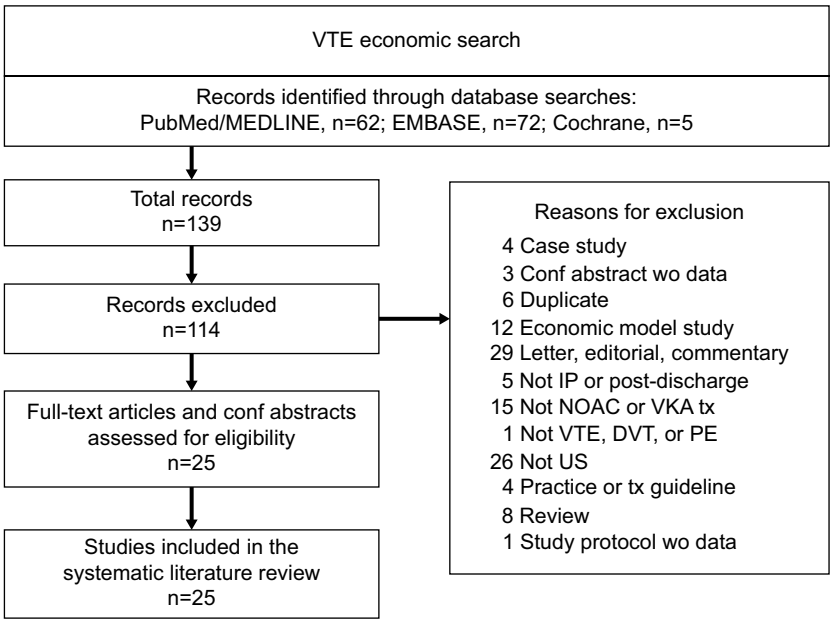

Figure 2 Economic search results.
Abbreviations: Conf, conference; DVT, deep vein thrombosis; IP, inpatient; NOAC, new/novel oral anticoagulant; PE, pulmonary embolism; tx, treatment; VKA, vitamin K antagonist; VTE, venous thromboembolism; wo, without.

Table 1 displays the study characteristics for the 24 clinical and 25 economic studies that were included in the review. Across all studies, the mean age reported ranged between 47.0 and 69.2 years, and the percentage of patients who were male ranged between 33.8% and 61.5%. Less than 25% of all studies reported a discharge location. The lack of reporting on discharge location may be in part due to the finding that 38 of the 49 studies (78.0%) were conducted retrospectively and 28 of these 38 studies (73.7%) used administrative claims data which is a data source that does not typically contain information about discharge location.

Table 2 displays the number of studies reporting IP and OP treatments and outcomes. A little more than two-thirds of the studies reported an IP treatment (n=34), and about half

Table 1 Study characteristics

Characteristics	All studies (n=49)	Clinical studies (n=24)	Economic studies (n=25)
Patient demographics			
Mean age (years), range	47.0–69.2	47.0–68.7	47.2–69.2
% Male, range	33.8–61.5	40.0–61.5	33.8–58.8
Populations reported, n (%)			
VTE	13 (26.5)	4 (8.2)	9 (18.4)
DVT only	9 (18.4)	7 (14.3)	2 (4.1)
PE only	11 (22.4)	4 (8.2)	7 (14.3)
DVT+PE combination	14 (28.6)	9 (18.4)	5 (10.2)
VTE+atrial fibrillation	2 (4.1)	–	2 (4.1)
Discharge location reported, n (%)			
Studies reporting discharge	11 (22.4)	7 (29.2)	4 (16.0)
Home	6 (12.2)	5 (10.2)	1 (2.0)
Home or skilled nursing	3 (6.1)	–	3 (6.1)
OP (nonspecified)	3 (6.1)	2 (4.1)	1 (2.0)
IP-only study	17 (34.7)	7 (14.3)	10 (20.4)
Not reported	21 (40.8)	10 (20.4)	11 (20.4)

Note: Studies may report more than one type of discharge location.
Abbreviations: DVT, deep vein thrombosis; IP, inpatient; OP, outpatient; PE, pulmonary embolism; VTE, venous thromboembolism.

Table 2 Number of studies reporting treatments and outcomes

Characteristics	All studies (n=49)	Clinical studies (n=24)	Economic studies (n=25)
Treatments reported (n)			
IP DOAC	27	14	13
IP VKA	25	13	12
IP IAC	22	12	10
IP treatment not reported	15	5	10
OP DOAC	13	8	5
OP VKA	16	11	5
OP IAC	9	5	4
OP treatment not reported	26	12	14
Reported both IP and OP treatment	11	8	3
Outcomes reported (n)			
Hospital length of stay	25	11	14
Time to discharge	7	5	2
Readmission	12	5	7
Treatment response	8	8	–
Complications	17	8	9
Treatment discontinuation	4	4	–
Mortality	19	8	11
Treatment adherence	6	6	–
Health care resource utilization	22	12	10
Health care costs	28	3	25

Note: Studies may report more than one type of treatment and/or outcome.
Abbreviations: DOAC, direct oral anticoagulant; IAC, indirect or injectable anticoagulant; IP, inpatient; OP, outpatient; VKA, vitamin K antagonist.

reported an OP treatment (n=23). Eleven of the 49 studies (22.4%) reported both an IP and an OP treatment. Of note, the study counts are not mutually exclusive, and the 11 studies that reported both IP and OP treatments are included in the counts of studies reporting either an IP or an OP treatment separately. The most frequent IP treatments reported were DOACs (n=27), followed by VKAs (n=25), and then IACs (n=22). The most frequent OP treatments reported were VKAs (n=16; warfarin), followed by DOACs (n=13), and then IACs (n=9). The most frequent outcomes reported across the 49 studies included hospital LOS (n=25), health care resource utilization (n=22), mortality (n=19), complications (n=17), and costs (n=28). Of note, only 11 of the 49 studies (22.4%) reported a discharge location, and none of the studies reported indirect costs.

Quality assessment of study methodology and reporting

Table 3 contains a "NICE Quality Assessment" column with the ratings of bias for each clinical study using the NICE methodology, and Table 4 contains a "CHEERS Quality Assessment Deficient Items" column with a listing of the deficient or missing checklist items for each economic study using the CHEERS checklist methodology.

NICE assessment

Because 21 of the 24 clinical studies had retrospective designs, performance and attrition bias for these studies could not be assessed. With respect to selection bias, five studies were rated as having a low risk, eight studies were rated as having an unclear risk, and 11 studies were rated as NA for selection bias. For the four studies that were rated for attrition bias, three studies had a low risk and one study had an unclear risk because of the lack of detail reported (ie, conference abstract). Finally, 23 studies were rated as having a low risk of detection bias, and one study was rated as NA for detection bias.

CHEERS assessment

Overall, most of the studies received a "Yes" for identifying the study as an economic evaluation in the title and abstract (items 1–3); for providing a clear study objective and description of the population and setting (items 4 and 5); for explaining the choice of outcomes (items 7, 8, and 10); for a complete reporting of the results (items 18 and 19), discussion, and limitations (item 22); and for reporting conflict of interest and sources of support (items 23 and 24). Only a handful of studies received a rating of "No" for the lack of reporting on various items, except for the discount rate item (item nine) where none of the 25 studies reported a discount rate.

Outcomes (clinical search)

Table 3 displays the study details and findings for the 24 clinical studies that were included in the review following the search on clinical outcomes. Twenty-one studies had a retrospective design, one study was a prospective cohort study, and two studies identified patients retrospectively and then followed them prospectively.

Of the eight studies reporting both IP and OP treatments, seven reported both IP and OP DOAC use[16–22] (rivaroxaban, dabigatran, and apixaban), five reported IP VKA use[17–19,21,22] (warfarin) and seven reported OP VKA use[17–23] (warfarin), six reported IP IAC use,[17,18,20–23] (enoxaparin and LMWH), and four reported OP IAC use[17,18,21,22] (enoxaparin and LMWH).

Seventeen of the 24 studies (71.0%) did not report discharge location, seven of which were IP-only studies. When examining IP and OP treatments, and post-discharge location, eight of the 24 studies reported both IP and OP treatments and three of these eight studies reported discharge to home.[20–22] Among the 16 studies that did not report both IP and OP treatments, four studies reported discharge location including one study[24] that reported that patients were discharged to either home or a SNF, one study[25] that reported that patients were discharged to home, and two studies[26,27] that reported that patients were discharged to an OP setting but did not provide further detail about the OP setting.

With respect to hospital LOS, 11 of the 24 studies reported LOS, and among this group of studies, five[18,28–31] reported shorter hospital LOS for patients who received rivaroxaban vs warfarin with mean LOS ranging from 1.8 to 3.7 days for rivaroxaban and from 3.8 to 7 days for warfarin.

With respect to patient outcomes associated with IP and OP treatment, four studies reported both IP and OP treatment and treatment-related outcomes with two of the studies examining outcomes for patients discharged from the ED. Beam et al[20] examined whether DVT and/or PE could be successfully treated at home with a DOAC (rivaroxaban) for patients discharged from the ED. After 1 year of follow-up, none of the 106 patients in the study had VTE recurrence or a major or clinically relevant bleeding event while on therapy; however, three patients had recurrent DVT after stopping therapy. The second study was conducted by Falconieri et al[21] who examined the use of a transition of care program (facilitating anticoagulation for safer transitions [FAST]) for treating patients with DVT who presented with an acute uncomplicated DVT in the ED.

Table 3 Clinical studies

Study design/data source/study period	Patient population and setting	Outcomes reported in study	Treatments	Treatment patterns and transition of care results	NICE quality assessment	Comments
Bashir and coworkers (2015)[58] Retrospective claims analysis/NIS files of the AHRQ Healthcare Cost and Utilization Project/January 2005–December 2010	DVT, n=90,618; anticoagulant+CDT, n=3,649; anticoagulant alone, n=86,969; IP	Hospital LOS, complications, mortality, resource utilization, cost findings	IP: unspecified anticoagulants; OP: not reported (IP-only study)	4.1% underwent CDT in addition to anticoagulant therapy. Compared with anticoagulant therapy only, CDT was associated with higher rates of blood transfusion, PE, hemorrhage, vena cava filter placement, but not mortality. CDT patients had longer LOS and higher hospital costs	Low risk for selection, attrition, and detection bias	Discharge location not reported; sensitivity analyses indicated that differences were not likely to be due to an unmeasured confounder
Beam et al (2015)[20]						
Prospective observational study/ ED medical data/ March 25, 2013–April 30, 2014	DVT or PE, n=106; DVT, n=71; PE, n=30; DVT+PE, n=5; IP and OP	Readmission, Tx response, complications, discontinuation, mortality, Tx adherence, resource utilization	IP: enoxaparin, rivaroxaban; OP: rivaroxaban	Patients followed up for a mean of 389 days. No VTE recurrence or major bleeding event while on therapy; 3 patients had recurrent DVT after therapy cessation	Risk NA for selection bias; unclear risk for attrition bias, low risk for detection bias	Discharged home
Cai et al (2014)[26]						
Retrospective claims analysis/Truven Health MarketScan Database/ January 1, 2010–December 31, 2011	VTE, n=5,820; parenteral anticoagulant users, n=4,403; parenteral anticoagulant nonusers, n=1,417; OP	Tx response	IP: not reported; OP: warfarin	76.0% of those receiving warfarin also received an IAC. Median time from VTE diagnosis to warfarin initiation was shorter for IAC users than nonusers (5 vs 11 days)	Risk NA for selection and attrition bias; low risk for detection bias	OP-only study; discharge location not reported
Cefalo et al (2015)[23]						
Retrospective and prospective/tertiary referral hospital/ October 2008–December 2011 and May 2005–April 2008	PE, n=547; prospective cohort, n=298; retrospective cohort, n=249; IP and OP	Complications, mortality, resource utilization	IP: IV UH or LMWH; OP: warfarin	Compared with those younger than 65 years, patients aged 65+ years had more severe PE and higher 30-day mortality (11.0% vs 3.0%, $P<0.001$). Tx patterns were similar between the two age groups	Risk NA for selection and attrition bias; low risk for detection bias	Discharged to unspecified OP location. Patients aged 65+ years were most likely to present with submassive PE, whereas patients younger than 65 years were most likely to present with low-risk PE

(*Continued*)

Table 3 (*Continued*)

Study design/data source/study period	Patient population and setting	Outcomes reported in study	Treatments	Treatment patterns and transition of care results	NICE quality assessment	Comments
Chen et al (2013)[59]						
Retrospective claims analysis/Thomson Reuters MarketScan database/January 1, 2006–March 31, 2008	VTE, n=8,040; IP and OP	Tx response, discontinuation, Tx adherence	IP: not reported; OP: warfarin	Among those with 2+ warfarin prescriptions, 34.0% were not compliant with warfarin therapy; noncompliance and discontinuation associated with higher likelihood of recurrent VTE	Unclear risk for selection bias, risk NA for attrition bias; low risk for detection bias	Discharge location not reported; association between Tx adherence and recurrent VTE remained in sensitivity analysis
Deitelzweig et al (2016)[28]						
Retrospective matched cohort/ MarketScan Hospital Drug Database/ November 2012–December 2013 (conf abstract)	DVT or PE, n=2,446; DVT, n=472; PE, n=751 in each rivaroxaban and warfarin group; IP	Hospital LOS, time to discharge	IP: warfarin, rivaroxaban; OP: not reported	Hospital LOS shorter for rivaroxaban (3.7 days) vs warfarin (5.2 days, $P<0.001$). Time to discharge also shorter for rivaroxaban vs warfarin (2.4 vs 3.9 days, $P<0.001$)	Low risk for selection and detection bias; risk NA for attrition bias	Discharge location not reported
Deitelzweig et al (2016)[27]						
Retrospective matched cohort/ Truven Health Analytics MarketScan databases/January 2011–December 2013	DVT, n=2,161 in nonmatched cohort (n=512 in rivaroxaban and 1,649 in LMWH/ warfarin groups); n=1,024 in matched cohort (n=512 in each tx group); OP	Resource utilization, cost findings	IP: not reported; OP: warfarin, rivaroxaban (OP only study)	Compared with those on warfarin, those on rivaroxaban had fewer all-cause and VTE-related hospitalizations and OP during the first 4 weeks after the initial encounter (no difference in ED visits). Mean costs were also lower for rivaroxaban users during this time period	Low risk for selection and detection bias; risk NA for attrition bias	OP-only study; results were similar in sensitivity analyses that extended the observation period until the end of data availability or insurance coverage
Deitelzweig et al (2015)[29]						
Retrospective matched cohort/ MarketScan Hospital Drug Database/ November 1, 2012–December 31, 2013 (conf abstract)	DVT or PE, n=2,446; DVT, n=472; PE, n=751 in each rivaroxaban and warfarin group; IP	Hospital LOS, time to discharge	IP: warfarin, rivaroxaban; OP: not reported	Hospital LOS was significantly shorter on rivaroxaban vs warfarin for both DVT (3.7 vs 5.0 days, $P<0.001$) and PE (3.8 vs 5.0 days, $P<0.001$); days to discharge was also significantly shorter for rivaroxaban, regardless of whether patients initiated with IACs	Low risk for selection and detection bias; risk NA for attrition bias	Discharge location not reported

(*Continued*)

Table 3 (*Continued*)

Study design/data source/study period	Patient population and setting	Outcomes reported in study	Treatments	Treatment patterns and transition of care results	NICE quality assessment	Comments
Desai et al (2016)[18]						
Retrospective observational cohort/ hospital medical records/January 2011–July 2014	VTE, n=414; discharged on rivaroxaban, n=72; discharged on warfarin, n=203; discharged on warfarin and enoxaparin, n=89; discharged on enoxaparin, n=50; IP and OP	Hospital LOS, readmission, complications	IP: warfarin, enoxaparin, rivaroxaban; OP: same	Patients discharged on rivaroxaban had significantly shorter LOS (3.5 days) than those discharged on warfarin (7.0 days, $P<0.001$), but not compared with those discharged on enoxaparin alone (3.0 days) or enoxaparin+warfarin (4.0 days). Bleeding and readmission rates were not significantly different	Unclear risk for selection bias, low risk for attrition and detection bias	Discharge location not reported
Falconieri et al (2014)[21]						
Retrospective/ Wellsoft system using hospital data/October 2013–March 2014	DVT, n=32; discharged from ED pre-FAST, n=8; discharged from ED post-FAST, n=7; admitted pre-FAST, n=9; admitted post-FAST, n=8; ED and OP	Readmission, complications, Tx adherence, resource utilization	ED: warfarin, enoxaparin, rivaroxaban; OP: same (discharged from ED)	A transition of care program resulted in 100.0% of patients attending a follow-up appointment (mean time until appointment =4.4 days). Patient satisfaction with the program was high	Unclear risk for selection bias, risk NA for attrition bias; low risk for detection bias	None of the patients at the 3- to 5-day follow-up phone call and 30-day phone call had any issues taking their anticoagulant, and none reported side effects of significant bleeding. One patient was re-admitted after discharge with a pulmonary embolism
Fang et al (2013)[60]						
Retrospective/ electronic databases from 4 healthcare delivery systems/ January 1, 2004–December 31, 2010 (conf abstract)	PE, n=5,600; IP and OP	Mortality	IP: not reported; OP: warfarin	After adjustment, lower times within therapeutic range (INR) were associated with higher mortality. Compared with time in therapeutic range >70.0%, adjusted death HRs were: 3.8 for those 40.0%–49.0% and 8.0 for those <40.0%	Risk NA for selection and attrition bias; low risk for detection bias	Discharged to unspecified OP location; the mean time in therapeutic range was 49.1%

(*Continued*)

Table 3 (*Continued*)

Study design/data source/study period	Patient population and setting	Outcomes reported in study	Treatments	Treatment patterns and transition of care results	NICE quality assessment	Comments
Jean et al (2017)[61]						
Retrospective chart review/hospital chart review/January 1, 2009–December 31, 2014	DVT or PE, n=457; DVT, n=220; PE, n=181; DVT+PE, n=56; IP	Tx response, mortality, Tx adherence	IP: enoxaparin, dalteparin, fondaparinux, warfarin, rivaroxaban; OP: not reported	Recurrent VTE in 5.0% of patients (no difference between oral and IACs), medication compliance issue in 5 patients of IAC group and 0 of oral group (P=0.008); 4 thrombotic events and 1 bleeding event listed as contributory diagnoses on the IP death summary	Risk NA for selection and attrition bias; low risk for detection bias	Discharge location not reported
Levy et al (2011)[62]						
Retrospective observational cohort/ Medical center database/April 2005–Jul 2007	DVT, n=200; anticoagulation, n=73; no anticoagulation, n=127; IP	Tx response, complications, mortality, resource utilization	IP: fractionated or UH, warfarin; OP: not reported	36.0% of patients with upper extremity DVT were put on anticoagulation therapy. Younger age, duplex evidence of an acute DVT, and involvement of multiple upper extremity segments were predictive of therapy initiation	Risk NA for selection and attrition bias; low risk for detection bias	Discharge location not reported; Two patients (1.0%) suffered PE, 2 other patients treated with warfarin died months after discharge from intracranial bleedings after minor falls
Liu et al (2013)[63]						
Retrospective/Truven Health MarketScan database/Jul 1, 2006–December 31, 2011 (conf abstract)	DVT and PE, n=153,908; IP	Discontinuation	IP: warfarin; OP: not reported	Mean therapy duration was 5 months; 74.8% discontinued within 1 year. Less likely to discontinue: if age >40 years, PE (vs DVT), atrial fibrillation. More likely to discontinue: if history of pregnancy, fracture, alcohol/ drug use, hormone therapy, and major bleeding in prior 6 months	Unclear risk for selection bias, risk NA for attrition bias; low risk for detection bias	Discharge location not reported

(*Continued*)

Table 3 (*Continued*)

Study design/data source/study period	Patient population and setting	Outcomes reported in study	Treatments	Treatment patterns and transition of care results	NICE quality assessment	Comments
Menzin et al (2014)[24]						
Retrospective/ Humedica database/ January 1, 2008–August 30, 2012	DVT and PE, n=2,060; DVT, n=864; PE, n=687; DVT+PE, n=509; IP and OP	Hospital LOS, readmission, Tx response, complications, mortality, resource utilization	IP: heparin, warfarin; OP: not reported	Heparin+warfarin had shorter mean LOS, fewer used ICU/ CCU, fewer with major bleeding, lower in-hospital mortality vs heparin alone; LOS longer for patients with DVT+PE (vs DVT alone) and patients aged >65 years; hospitalization for VTE recurrence: 7.5% at 1 year	Unclear risk for selection bias, risk NA for attrition bias; low risk for detection bias	Discharged to home or skilled nursing facility
Merli et al (2015)[30]						
Retrospective matched cohort/ Truven MarketScan Hospital Drug Database/January 2011–December 2013	DVT; unmatched: current rivaroxaban, n=134; current LMWH/warfarin, n=1,781; historical LMWH/warfarin, n=6,347 matched; current rivaroxaban, n=134; historical LMWH/warfarin, n=536; IP	Hospital LOS, readmission, resource utilization	IP: LMWH, warfarin, rivaroxaban; OP: not reported (IP-only study)	60.0% of rivaroxaban patients were admitted to the hospital vs 82.0% of historical matched LMWH/warfarin patients. Mean LOS was 2.6 days (rivaroxaban) vs 3.8 days	Low risk for selection bias and detection bias; risk NA for attrition bias	Discharge location not reported; admission rates adjusted for time-trend produced similar results
Roberts et al (2015)[31]						
Retrospective observational cohort/ hospital EMR/January 1, 2012–March 1, 2015	PE, n=158; warfarin+enoxaparin, n=82; rivaroxaban, n=76; IP	Hospital LOS, time to discharge	IP: warfarin, enoxaparin, rivaroxaban; OP: not reported	Median LOS was shorter for rivaroxaban patients (1.8 days) than for warfarin patients (2.7 days, $P<0.001$), as was the time to discharge ($P<0.001$)	Risk NA for selection and attrition bias; low risk for detection bias	Discharge location not reported; there were differences in baseline characteristics between Tx arms
Sharifi et al (2015)[16]						
Retrospective and prospective/not reported/September 2011–June 2013	DVT, n = 127; IP and OP	Hospital LOS, Tx response, complications, mortality, Tx adherence	IP: dabigatran, rivaroxaban, apixaban; OP: warfarin, dabigatran, rivaroxaban, apixaban	Mean LOS was 46 hours; no occurrences of PE, 2 patients with recurrent DVT (both switched to warfarin); 4 deaths not related to DVT; postthrombotic syndrome developed in 5 patients (3.0%), 2 of whom had been switched to warfarin	Risk NA for selection and attrition bias; low risk for detection bias	Discharge location not reported; mean follow-up was 22 months; compliance with compression stockings was low

(*Continued*)

Table 3 (*Continued*)

Study design/data source/study period	Patient population and setting	Outcomes reported in study	Treatments	Treatment patterns and transition of care results	NICE quality assessment	Comments
Spyropoulos et al (2017)[19]						
Retrospective claims analysis/IMS PharMetrics Plus database/January 1, 2008–March 31, 2014	DVT, PE, or both, n=81,827; ACCP-recommended Tx duration adherent, n=60,550; nonadherent, n=21,277; IP and OP	Hospital LOS, Tx adherence, resource utilization, cost findings	IP: warfarin, rivaroxaban, dabigatran, apixaban; OP: same	74.0% were adherent to the ACCP-recommended Tx duration. Hospitalizations, VTE recurrence, bleeding events, and costs were lower among adherent patients	Risk NA for selection and attrition bias; low risk for detection bias	Discharge location not reported
Stein et al (2015)[25]						
Retrospective/manual review of medical records/January 2013–December 2014	DVT, n=96; admitted from ED, n=85; discharged from ED to home, n=11; IP and OP	Hospital LOS, time to discharge, resource utilization	IP: warfarin, enoxaparin, rivaroxaban; OP: not reported	88.5% hospitalized and 11.5% discharged from ED to home. 9 of 11 discharged home received LMWH, none received DOACs. 33.0% of hospitalized patients discharged in ≤2 days, 64.0% of these received enoxaparin and/or warfarin at discharge, 25.0% rivaroxaban	Risk NA for selection and attrition bias; low risk for detection bias	Discharged home (no other information reported)
Stein et al (2016)[22]						
Retrospective cohort study/medical records/January 2013–December 2014	PE, n=746; hospitalized, n=733; discharged to home, n=13; IP and OP	Hospital LOS, time to discharge, resource utilization	IP: LMWH, warfarin, DOAC; OP: same	16.2% were discharged within 2 days, and 1.7% (n=13) were discharged home. For the 13 home-treated patients, 9 received LMWH or warfarin, 4 received DOACs	Unclear risk for selection bias; risk NA for attrition and detection bias	1.7% discharged home, discharge location of remaining patients not reported
Streiff et al (2016)[17]						
Retrospective claims analysis/Humana database/January 1, 2013–May 31, 2015 (conf abstract)	VTE, n=2,428; rivaroxaban, n=707; LMWH, n=660; warfarin, n=1,061; setting not specified	Tx response	IP: LMWH, warfarin, rivaroxaban; OP: same as IP	VTE recurrence for rivaroxaban users was 28.0% less likely than for those using LMWH and 26.0% less likely than for warfarin users	Unclear risk for selection and attrition bias, low risk for detection bias	Discharge location not reported; median duration on initial LMWH, warfarin, and rivaroxaban was 1.0, 3.5, and 3.0 months, respectively

(*Continued*)

Table 3 (*Continued*)

Study design/data source/study period	Patient population and setting	Outcomes reported in study	Treatments	Treatment patterns and transition of care results	NICE quality assessment	Comments
Sussman et al (2015)[64]						
Retrospective claims analysis/hospital claims data/November 1, 2011–December 31, 2013 (conf abstract)	DVT and/or PE, n=46,214; IP	Resource utilization	IP: LMWH, fondaparinux, UH, rivaroxaban; OP: not reported (IP-only study)	Use of IACs (with or without warfarin) were more common than the use of DOACs (rivaroxaban); of the roughly 11.0% who received rivaroxaban, >90.0% also received an IAC	Risk NA for selection and attrition bias; low risk for detection bias	Discharge location not reported
Xie et al (2016)[65]						
Retrospective claims analysis/MarketScan database/January 2006–December 2011	DVT and PE, n=21,163; IP	Discontinuation	IP: warfarin; OP: not reported	21.4% discontinued with 3 months, 42.8% within 6 months, and 70.1% within 12 months. Reduced risk of discontinuation: PE (vs DVT), comorbid atrial fibrillation, thrombophilia, older age; increased risk of discontinuation: alcohol abuse, cancer history, bleeding, and catheter ablation	Unclear risk for selection bias, risk NA for attrition bias; low risk for detection bias	Discharge location not reported

Abbreviations: ACCP, American College of Chest Physicians; AHRQ, Agency for Healthcare Research and Quality; CCU, critical care unit; CDT, catheter-directed thrombectomy; conf, conference; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; ED, emergency department; EMR, electronic medical record; FAST, facilitating anticoagulation for safer transitions; IAC, indirect/injectable anticoagulant; ICU, intensive care unit; IMS, information management system; INR, international normalized ratio; IP, inpatient; IV, intravenous; LMWH, low-molecular-weight heparin; LOS, length of stay; NA, not applicable; NICE, National Institute for Health and Clinical Excellence; NIS, National Inpatient Sample; OP, outpatient; PE, pulmonary embolism; Tx, treatment; UH, unfractionated heparin; VTE, venous thromboembolism.

Table 4 Economic studies

Study design/ data source/study period	Patient population and setting	Outcomes reported in study	Treatments	Transition of care results	CHEERS quality assessment deficient items	Comments
Amin et al (2015)[54]						
Simulation/published data/2014–2018 (conf abstract)	VTE, n=1 million (hypothetical); IP and OP	Cost findings	IP: not reported; OP (see comments): dabigatran, rivaroxaban, apixaban, edoxaban, warfarin	Reduction in simulated direct costs for treated patients vs warfarin: apixaban ($11.5 M), edoxaban ($6.6 M), rivaroxaban ($4.2 M), dabigatran ($3.7 M)	3, 4, 5, 6, 8, 9, 13b, 14, 15, 16, 17, 20b	Discharge location not reported. The analysis was based on the published clinical trial data and did not report an OP setting, but is assumed to focus on costs of OP tx because of the timeframe used (1+ years)
Amin et al (2015)[42]						
Retrospective claims analysis/Truven Health Analytics Commercial and Medicare MarketScan databases/January 1, 2008–December 31, 2011	VTE, n=112,885; n=15,897, major bleeding; n=15,842, nonmajor clinically relevant bleeding; n=81,146, no bleeding; IP and OP	Hospital LOS, resource utilization, complications, cost findings	IP and OP: not reported	Compared with patients without bleeding, patients with major bleeding (14.0%) had an average of $45,367 additional direct medical costs, and patient with clinically relevant nonmajor bleeding (14.0%) had an average of $2,140 additional direct costs	1, 9	Discharge location not reported
Amin et al (2016)[50]						
Simulation/published data/January 1, 2008–December 31, 2011	VTE; n=not reported; IP and OP	Complications, mortality, cost findings	IP: not reported; OP (see comments): dabigatran, rivaroxaban, apixaban, edoxaban warfarin	Annual total medical cost avoidances per patient year (vs warfarin) were: –$4,440 for apixaban, –$2,971 for rivaroxaban, –$1957 for edoxaban, and –$572 for dabigatran	9, 13b, 15, 16, 20b	Discharge location not reported; results remained consistent under sensitivity analyses The analysis was based on the published clinical trial data and did not report an OP setting, but is assumed to focus on costs of OP tx because of the timeframe used (1+ years)

(*Continued*)

Table 4 (*Continued*)

Study design/ data source/study period	Patient population and setting	Outcomes reported in study	Treatments	Transition of care results	CHEERS quality assessment deficient items	Comments
Amin et al (2015)[51]						
Economic analysis/ published data/2014–2018	VTE, n=1 million (hypothetical); IP and OP	Cost findings	IP: not reported; OP (see comments): dabigatran, rivaroxaban, apixaban, edoxaban warfarin	Annual medical cost differences associated with DOACs vs warfarin were estimated to be: –$204 for dabigatran, –$140 for rivaroxaban, –$495 for apixaban, –$340 for edoxaban	4, 9, 15, 16	Discharge location not reported The analysis was based on published clinical trial data and did not report an OP setting, but is assumed to focus on costs of OP tx because of the timeframe used (1+ years)
Amin et al (2015)[56]						
Cost-avoidance analysis/published data/ "extended treatment"	VTE, n=2,936; dabigatran (n=681)/ rivaroxaban (n=602)/apixaban 2.5 mg (n=840)/ apixaban 5 mg (n=813); IP and OP	Complications, mortality, cost findings	IP: not reported; OP (see comments): dabigatran, rivaroxaban, apixaban vs placebo	Because of reduction in VTE recurrence vs placebo, overall medical costs avoided were: –$2,794 for dabigatran, –$2,948 for rivaroxaban, –$4,249 for apixaban 2.5 mg and –$4,244 for apixaban 5 mg	9, 13b, 14, 15, 16, 20b	Discharge location not reported; sensitivity analyses indicated that estimated cost avoidances are robust to random variations The analysis was based on the published clinical trial data and did not report an OP setting, but is assumed to focus on costs of OP tx because of the timeframe used (1+ years)
Amin et al (2014)[55]						
Cost analysis/ published data/1-year timeframe	VTE; n=not reported; IP and OP	Complications, mortality, cost findings	IP: not reported; OP (see comments): dabigatran, rivaroxaban, apixaban, edoxaban, warfarin	All DOACs associated with lower rate of bleeding and recurrent VTE/death (except for dabigatran) vs standard therapy; as a result, annual total medical cost differences were: –$146 for dabigatran, –$482 for rivaroxaban, –$918 for apixaban, and –$344 for edoxaban	9, 15	Discharge location not reported; in an alternative scenario analysis when Tx durations were normalized, all DOACs still produced cost reductions The analysis was based on the published clinical trial data and did not report an OP setting, but is assumed to focus on costs of OP tx because of the timeframe used (1 year)

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Table 4 (*Continued*)

Study design/ data source/study period	Patient population and setting	Outcomes reported in study	Treatments	Transition of care results	CHEERS quality assessment deficient items	Comments
Atay et al (2012)[49]						
Retrospective/ published data/1-year timeframe	VTE, n=1,774; AF, n=1,256; VTE, n=518; IP	Cost findings	IP: dabigatran, warfarin; OP: not reported (IP-only study)	Annual cost of coagulation management: $4,371,136 for dabigatran vs $1,385,494 for warfarin. Note: while dabigatran's cost was all due to the medication, the majority of the cost for warfarin was for lab and labor costs to monitor lab values	4, 9, 11b, 14, 17, 18	Discharge location not reported
Bookhart et al (2014)[44]						
Post hoc analysis clinical trial data/not reported	DVT or PE, n=812; DVT, n=326; PE, n=486; IP	Hospital LOS, resource utilization, cost findings	IP: rivaroxaban, enoxaparin, unspecified VKA; OP: not reported (IP-only study)	47.0% rivaroxaban and 48.0% enoxaparin/VKA hospitalized; rivaroxaban had shorter LOS (1.6 days), $3,419 lower total costs	6, 8, 9, 17, 20a	Discharge location not reported; the authors note that Canadian centers tend to hospitalize few patients for DVT, so results are largely based on PE patients
Coleman et al (2017)[52]						
Retrospective (longitudinal) claims analysis/Truven Health MarketScan Commercial Claims and Encounters Database/November 2011–July 2015	DVT or PE, n=32,787; rivaroxaban, n=10,929; warfarin, n=21,858; IP and OP	Cost findings	IP: not reported; OP: rivaroxaban, warfarin	During 12 month follow-up, rivaroxaban patients (vs warfarin) had lower IP (–$622) and OP (–$1,156) per patient costs, higher pharmacy costs ($661), and lower total costs (–$1,116)	6, 9	Discharge location not reported; Subgroup analyses: similar results when limited to DVT, no significant difference in total costs for PE
Coleman et al (2017)[38]						
Retrospective claims analysis/ Premier Perspective Comparative Hospital Database/ November 2012–March 2015	PE, n=6,932 (1:1 matched cohort rivaroxaban vs warfarin); IP	Hospital LOS, readmission, cost findings	IP: rivaroxaban, warfarin; OP: not reported (IP-only study)	Rivaroxaban use was associated with a 1.36-day shorter LOS and $2,304 reduction in total costs compared to parenterally bridged warfarin. No difference in VTE recurrence or major bleeding	6, 8, 9, 14, 18	Discharge location not reported; In a subanalysis limited to low-risk patients, rivaroxaban was associated with a $1,855 reduction

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Table 4 (*Continued*)

Study design/ data source/study period	Patient population and setting	Outcomes reported in study	Treatments	Transition of care results	CHEERS quality assessment deficient items	Comments
Dasta et al (2015)[45]						
Retrospective claims analysis/ Premier Perspective Comparative Hospital Database/ January 1, 2009– March 1, 2013	DVT or PE, n=64,503; PE, n=35,550; DVT, n=28,953; IP	Hospital LOS, resource utilization, cost findings	IP: warfarin, UH, LMWH, unspecified anticoagulant; OP: not reported (IP-only study)	Mean LOS was 4.7 (DVT) and 5.4 (PE) days, 9.9% (DVT) and 24.2% (PE) had ICU stay. For both cohorts, the first 3 days of hospitalization were costliest; costs stabilized on third day	6, 9, 10	Discharge location not reported
Deitelzweig et al (2016)[53]						
Retrospective propensity-score matched cohort/ Truven Health Analytic MarketScan Claims database/ January 2011– December 2013 (conf abstract)	DVT; n=512 in each group: rivaroxaban vs LMWH/warfarin; OP	Cost findings	IP: not reported; OP: rivaroxaban, LMWH, warfarin (OP only study)	Mean all-cause total costs lower for rivaroxaban vs LMWH/ warfarin over first 4 weeks (significant in weeks 1 and 2). Pharmacy costs significantly lower for rivaroxaban for each of the first 4 weeks	3, 4, 5, 6, 9, 14, 17, 22, 23, 24	OP study Discharge location not reported
Dubois et al (2015)[48]						
Retrospective chart review/Florida Hospital Orlando/ January 1, 2012– November 1, 2013 (conf abstract)	PE, n=59; rivaroxaban, n=10; SOC unmatched, n=47; SOC matched, n=10; IP	Hospital LOS, complications, cost findings	IP: rivaroxaban, IV UH, LMWH, fondaparinux; OP: not reported (IP-only study)	Rivaroxaban and SOC produced similar LOS, cost, and minor bleeds (there were no major bleeds)	1, 4, 5, 6, 8, 9, 14, 17, 18, 19, 23, 24	Discharge location not reported; in matched analysis, there were only 10 in each group

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Table 4 (*Continued*)

Study design/ data source/study period	Patient population and setting	Outcomes reported in study	Treatments	Transition of care results	CHEERS quality assessment deficient items	Comments
Fanikos et al (2013)[43]						
Retrospective, hospital chart and database/Brigham and Women's Hospital, Boston/September 2003–May 2010	PE, n=991; IP	Hospital LOS, readmission, resource utilization, complications, mortality, cost findings	IP: LMWH, UH, fondaparinux, bivalirudin, argatroban, lepirudin, warfarin; OP: not reported (IP-only study)	Mean total hospital cost per patient $8,764. Pharmacy costs ($966) were dominated by the use of LMWH ($232)	9, 14, 17	Discharge location not reported
Kahler et al (2015)[35]						
Case–control/ hospital administrative database and medical charts/January–December 2013	VTE, n=97; rivaroxaban, n=50; LMWH/warfarin, n=47; IP and OP	Mortality, cost findings	IP: rivaroxaban, LMWH, warfarin; OP: same	Over 6 months, cases treated with rivaroxaban had median total charges of $4,787 compared to $11,128 for controls treated with LMWH-warfarin; Of 47 control patients, 38.0% (all DVT) were treated at home	6, 14	Subgroup analysis of DVT and PE subgroups demonstrated lower charges and costs for rivaroxaban Discharge location not reported
Kahler and Kline (2014)[36]						
Case–control/ hospital data/6 months starting April 2013 (conf abstract)	VTE, n=32 (16 cases, 16 controls); IP and OP	Complications, mortality, cost findings	IP: rivaroxaban, other (not specified); OP: rivaroxaban	Median cost of care for cases (rivaroxaban) was $6,628 vs $12,021 for controls	3, 4, 5, 6, 7, 9, 11b, 14, 17, 21, 23, 24	Discharge location not reported

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Table 4 (*Continued*)

Study design/ data source/study period	Patient population and setting	Outcomes reported in study	Treatments	Transition of care results	CHEERS quality assessment deficient items	Comments
LaMori et al (2015)[33]						
Retrospective claims analysis/NIS database/2011	DVT and PE, n=330,044; DVT, n=143,417; PE, n=186,627; IP	Hospital LOS, readmission, mortality, cost findings	IP and OP: not reported	In 2011, fewer DVT hospitalization and lower initial hospitalization cost than for PE. Readmissions occurred in 4.2% of DVT and 4.0% of PE, with 75.0%–80.0% within same or following month as initial event. Among DVT, 54.0% discharged home, 17.0% home health, 12.0% skilled nursing	6, 8, 9, 14, 17	DVT patients: 53.8% had a routine discharge (to the patients home), 16.7% received home health care, 12.3% were discharged to a skilled nursing facility; PE patients, 54.9% had a routine discharge to home, 14.5% received home health care, and 9.2% were discharged to a skilled nursing facility
Lin et al (2014)[41]						
Retrospective claims analysis/ Truven Health Analytics MarketScan Commercial and Medicare databases/ January 1, 2007–December 31, 2011	VTE, n=43,784; recurrent, n=6,153; no recurrence, n=37,631; IP and OP	Hospital LOS, readmission, resource utilization, cost findings	IP: not reported; OP: UH, LMWH, warfarin, fondaparinux	Recurrent VTE occurred in 15.4% of commercially insured and 11.4% of Medicare insured patients within 12 months, despite anticoagulation therapy. Recurrent VTE associated with substantial resource utilization and costs	9, 14	Discharge location not reported
Margolis et al (2016)[32]						
Retrospective matched cohort/ Truven Health MarketScan Hospital Drug Database/ November 1, 2012–December 31, 2013	DVT or PE, n=2,446; PE, n=751; DVT, n=472; IP	Hospital LOS, time to discharge, resource utilization, mortality, cost findings	IP: rivaroxaban, warfarin; OP: not reported	Rivaroxaban had shorter LOS than warfarin (3.7 vs 5.2 days), shorter time to discharge (2.4 vs 3.9 days), and lower unadjusted mean total hospital costs ($8,688 vs $9,823); overall mean pharmacy costs not significantly different, but IP pharmacy costs were higher for rivaroxaban patients; in both cohorts, 86.0% discharged home and 13.0% transferred	6, 9	86.0% discharged home, 13.0% transferred to another facility, 1.0% other

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Table 4 (*Continued*)

Study design/ data source/study period	Patient population and setting	Outcomes reported in study	Treatments	Transition of care results	CHEERS quality assessment deficient items	Comments
Margolis et al (2016)[34]						
Retrospective matched cohort/ Truven Health MarketScan Hospital Drug Database/ November 1, 2012–December 31, 2013	PE, n=751 in each group: rivaroxaban vs warfarin; IP and OP	Hospital LOS, time to discharge, resource utilization, cost findings	IP: rivaroxaban, warfarin; OP: not reported	Rivaroxaban associated with shorter LOS (3.8 days) vs warfarin (5.4, $P<0.001$), as was time to discharge and total mean hospital costs ($8,473 vs $10,291 $P<0.001$)	6, 9	Most patients discharged to home or home health; 11.0%–13.0% transferred
Merli et al (2016)[47]						
Retrospective matched cohort/ Truven Health MarketScan Hospital Drug Database/ January 2011–December 2013	DVT, n=6,481 (unmatched cohort); n=670 (matched cohort); IP	Cost findings	IP: rivaroxaban, LMWH, warfarin; OP: not reported (IP-only study)	Index hospitalization costs were $1,508 less for rivaroxaban vs LMWH/warfarin users; main driver of difference is lower proportion of rivaroxaban patients hospitalized (60.0% vs 82.0%)	8, 9	Discharge location not reported; total hospital costs were also lower for rivaroxaban patients within 1, 2, 3, and 6 months (significantly within 1 and 3 months)
Raphael et al (2014)[40]						
Retrospective/ hospital data/January 2000–December 2010	PE, n=294; IVCF with heparin, n=91; IVCF without heparin, n=118; heparin without IVCF, n=55; no heparin, no IVCF, n=30; IP	Hospital LOS, resource utilization, complications, mortality, cost findings	IP: warfarin, heparin; OP: not reported (IP-only study)	Among warfarin patients, IVCF use was associated with fewer complications and lower overall costs	2, 6, 9, 14, 23	Discharge location not reported
Shorr et al (2014)[37]						
Retrospective claims analysis/claims data/ January 1, 2007–March 31, 2013 (conf abstract)	VTE, n=123,665 IP and OP	Hospital LOS, readmission, cost findings	IP: warfarin, enoxaparin, rivaroxaban, IVCF; OP: warfarin, enoxaparin, rivaroxaban	27.0% of patients were hospitalized at least once (any cause) within 1 year of VTE; 37.0% of those patients had at least one hospitalization for VTE. Subsequent hospitalization carried significant costs	3, 4, 6, 7, 9, 14, 17, 18, 22, 23, 24	Discharge location not reported

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Table 4 (*Continued*)

Study design/ data source/study period	Patient population and setting	Outcomes reported in study	Treatments	Transition of care results	CHEERS quality assessment deficient items	Comments
Weeda et al (2016)[46]						
Retrospective/ Hartford Hospital, CT/November 1, 2012–May 12, 2015	PE, n=190; IP	Hospital LOS, resource utilization, mortality, cost findings	IP: rivaroxaban, UH, LMWH, warfarin; OP: not reported (IP-only study)	Rivaroxaban was associated with lower adjusted hospital costs (range: –$3,835 to –$7,094) than heparin bridging to warfarin. Rivaroxaban patients also had a shorter adjusted LOS	6, 9, 14	Discharge location not reported
Weeda et al (2017)[39]						
Retrospective claims analysis/ Premier Perspective Comparative Hospital Database/ November 2012–September 2015	PE, n=8,824 (4,412 in each 1:1 matched cohort); IP	Hospital LOS, readmission, resource utilization, complications, mortality, cost findings	IP: rivaroxaban, UH, LMWH, fondaparinux, warfarin; OP: not reported (IP-only study)	Rivaroxaban was associated with shorter LOS (1.4 days) and lower costs (–$2,322) vs parenterally bridged warfarin. No difference in readmission for VTE or major bleeding	6, 9, 14	Discharge location not reported; Subanalysis on low-risk patients produced similar results

Abbreviations: AF, atrial fibrillation; CHEERS, Consolidated Health Economic Evaluation Reporting Standards; conf, conference; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; ICU, intensive care unit; IP, inpatient; IV, intravenous; IVCF, inferior vena cava filter; LMWH, low-molecular-weight heparin; LOS, length of stay; NIS, National Inpatient Sample; OP, outpatient; PE, pulmonary embolism; SOC, standard of care; UH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Stein et al[25] assessed the prevalence of home treatment with DOACs for patients who had been hospitalized for an acute PE. They found that 13 of 746 (1.7%) patients with PE, who were not hypoxic, were stable enough for home treatment and that four of the 13 patients (30.8%) received post-discharge DOACs with the remaining nine patients (69.2%) receiving LMWH or warfarin. Finally, Desai et al[18] compared outcomes associated with rivaroxaban, warfarin, enoxaparin, or warfarin+enoxaparin for patients hospitalized for VTE and discharged (discharge location was not reported). Patients who were discharged on rivaroxaban had a significantly shorter hospital LOS when compared with warfarin ($P<0.001$), but not when compared with enoxaparin or warfarin+enoxaparin; also, in-hospital bleeding rates and 6-month readmission rates were not significantly different across groups.

Outcomes (economic search)

Table 4 displays the study details and findings for the 25 economic studies that were included in the review following the search on economic outcomes. Seventeen studies had a retrospective design, two studies had a case–control design, three studies were cost models, two studies were simulation models, and one study was a post hoc analysis of hospital LOS and cost data from the EINSTEIN clinical trial.

Only four economic studies reported a discharge location; three reported discharge to home or a SNF,[32–34] and the fourth study[35] reported that 38.0% of patients were discharged to home, but did not report the discharge location for the remaining patients. Of the 21 economic studies that did not report a discharge location, 10 were IP-only studies. Only three of the 25 economic studies reported both IP and OP treatments.[35–37] All three studies reported both IP and OP DOAC, and two of the studies[35,37] reported IP and OP VKA (warfarin) with either enoxaparin or LMWH.

With respect to the health care resource utilization associated with the treatment for VTE, 14 studies reported hospital LOS, six studies reported readmission rates, and 10 studies reported on other types of health care resource utilization. Eight of the 14 studies that reported hospital LOS were IP-only studies and did not report a post-discharge treatment or location. The hospital LOS for the eight IP-only studies ranged from a mean of 3.2 days for PE patients receiving rivaroxaban[38,39] to a mean of 9.4 days for PE patients who received heparin plus an IVCF.[40] For the six studies that were not IP-only,[32–34,37,41,42] the hospital LOS ranged from a mean of 0.2 days for VTE patients with clinically relevant nonmajor bleeding during the 1-year follow-up period (no treatment reported)[42] to 8.4 days for patients with VTE recurrence at 1 year who were receiving VKAs or IACs.[41]

The readmission rates for the six studies that reported readmission ranged from 1.5% within 2 months of an initial PE event,[39] for patients receiving rivaroxaban, to 15.4% within a mean of 74 days from an initial VTE event,[41] for patients receiving VKAs or IACs. Three of the remaining four studies had readmission rates ≤4%[33,38,43] within a period of 2–3 months following an initial event, and the final study[37] had a readmission rate of 10.1% within 284 days of an initial VTE event for patients receiving DOACs, VKAs, or IACs. The other types of health care resource utilization that were reported included hospital and/or intensive care unit (ICU) stay,[34,44,45] OP and/or ED visits,[41,42] treatment of additional thrombotic events,[39,46] diagnostic procedures,[43] time from admission to first treatment dose,[32] and placement of an IVCF.[40]

With respect to direct and indirect costs associated with treatment for VTE, all 25 studies reported direct costs and none of the studies reported indirect costs. Ten studies were IP-only studies that focused on the cost of hospitalization. Five of the 10 studies[38,39,44,46,47] found a shorter LOS and lower hospital costs for rivaroxaban vs parenterally bridged warfarin for treating PE or DVT, and a sixth study[48] compared rivaroxaban to a standard of care and found no significant differences in hospital costs (study reported as a conference abstract). A seventh study[49] found higher costs with dabigatran vs warfarin when treating hospitalized VTE patients, and an eighth study[40] found lower hospital costs for IVCF plus heparin vs heparin alone to treat a PE within 90 days of joint replacement surgery. The remaining two studies evaluated hospital costs based on disease rather than treatment type and found the highest hospital costs in the first 3 days following an acute DVT ($1,594) or PE event ($1,735)[45] or found that nursing cost ($5,102) was the largest component of mean total hospitalization costs of $8,764 for treating PE between 2003 and 2010.[43]

For the 15 economic studies that were not IP only, 10 studies[32,34-36,50-55] found significantly lower costs for various DOACs vs warfarin, and one study[56] compared four DOACs (rivaroxaban, apixaban, dabigatran, and edoxaban) to placebo for extended treatment of VTE and found the lowest overall medical costs avoided was for dabigatran. The remaining four studies[33,37,41,42] did not compare costs based on the treatment.

Discussion

The objectives of this review were to summarize evidence on VTE treatment patterns in IP and OP settings and to deter-

mine discharge location after patients leave the IP setting. This review further sought to examine patient outcomes, resource utilization, and costs associated with VTE patients transitioning from one setting to the next. We were able to determine that patients used DOACs, LMWH, and warfarin in IP and OP settings. However, given the data available, it was unclear whether patients continued using the therapies prescribed as they moved from one setting to the next or if they were switched to a different therapy after leaving the IP setting. In short, our ability to report on treatment patterns during the transition from IP to OP status was constrained by the fact that only eight clinical studies and three economic studies reported both IP and OP treatments.

It is encouraging to see that within IP and OP settings, physicians are prescribing according to the CHEST guidelines for antithrombotic therapy in VTE.[4] Note that this simply means we are not seeing prescription of medication outside the class of "anticoagulant" or "antiplatelet," but our observation does not speak to the manner in which antithrombotics are being prescribed. For example, for VTE without a cancer diagnosis, it is suggested that DOACs be prescribed over VKAs and LMWH; on the other hand, for VTE with a cancer diagnosis, LMWH is recommended over the other therapies. With respect to the CHEST guidelines, there are other recommendations that go into specific detail about which antithrombotic therapy to use for different VTE cases. However, it should be noted that our study was not directed at delving into those specific details. Our main concern was finding out which treatments patients received within IP and OP care settings, the locations to where patients were discharged, and what treatment regimen, if any, they received post-discharge.

As part of the objective, we wanted to look at patient discharge location following release from the IP setting, but only a limited number of studies reported on discharge location. This could be explained by our finding that 78% of the identified studies were retrospective in nature and the majority of these studies (73.7%) were based on administrative claims data, which do not typically include information about discharge location. For the 11 studies that reported discharge, nine reported discharge for the most part to the home and to a lesser extent, SNFs, and two studies reported discharge to a nonspecified location. What would be interesting to examine is whether discharge to home was further broken down by strategy for care – for example, use of caregiver or self-care. We say this because specific discharge location – home or SNF – and strategy for care generally inform how acute or severe the VTE episode may have been.[57]

With respect to patient outcomes, several studies in this literature review found that DOACs were associated with shorter hospital LOS and lower costs when compared with warfarin. When examining health care resource utilization, six economic studies reported readmission rates that ranged from 1.5% for patients receiving rivaroxaban to 15.4% for patients receiving a VKA or IAC. The more notable gaps in the literature include the finding that none of the studies reported indirect costs such as work productivity. More studies are needed that examine VTE treatments when patients are transitioning from IP to OP settings and their associated outcomes including work productivity. Of note, is a study conducted by Stein et al[22] who examined the prevalence of using DOACs to treat patients with PE who were discharged from an emergency room to home and found that only four of the 13 patients with stable PE who were eligible to receive post-discharge DOACs actually received them. The authors did not report whether the decision to use a post-discharge DOAC was made by the clinician or may have been partly determined by the patient. The only study that surveyed patients about satisfaction with treatment and the process of transitioning care to an OP setting[21] did not examine patient satisfaction based on specific treatments such as DOACs vs VKAs – most likely because of the small sample size (n=6). More studies are needed that examine a patient's satisfaction with the treatment received during transition from IP to OP settings.

All literature reviews are limited by publication bias with respect to the articles that are available at the time that a search is conducted. Also, the articles in this review are published in English and publication constraints were placed on articles identified by the search with studies limited to those published 2011–2016. Also, 78.0% of all study designs were retrospective and 35.0% of all studies were IP only, which limits our ability to make statements about VTE treatment patterns as patients transition from IP to OP settings or what the post-discharge locations were.

Conclusion

Only a small number of studies were found that reported and/or characterized IP and OP treatments for VTE, discharge location, and outcomes. For the studies that did report this information, DOACs were associated with shorter LOS, lower costs, and better patient outcomes (eg, VTE recurrence) vs VKAs; however, one study reported that DOACs are not being utilized for eligible patients with stable VTE who are discharged to home. Although a small number of transition of care studies were found in this review that reported both IP and OP treatments and discharge location, the information contained in these studies may identify opportunities to improve the management of VTE through coordination

of treatment and care or may help inform decisions about VTE patients as they transition from inpatient or ED to post-discharge care.

Abbreviations

CHEERS, Consolidated Health Economic Evaluation Reporting Standards; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; ED, emergency department; IAC, injectable anticoagulant; ICU, intensive care unit; IP, inpatient; IVCF, inferior vena cava filter; LMWH, low-molecular-weight heparin; LOS, length of stay; MeSH, Medical Subject Heading; NICE, National Institute for Health and Clinical Excellence; OP, outpatient; PE, pulmonary embolism; RCT, randomized control trial; SNF, skilled nursing facility; VKA, vitamin K antagonist; VTE, venous thromboembolism

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Author contributions

All authors were involved in the conception and design, interpreting data, and writing and editing the manuscript. In addition, Virginia M Rosen was involved in data collection and analysis. All authors gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

Virginia M Rosen is an employee of Optum, Inc. who was a paid consultant to Pfizer and BMS in connection with the collection and analysis of the data and development of this manuscript. The authors report no other conflicts of interest in this work.

References

1. Deitelzweig SB, Johnson BH, Lin J, Schulman KL. Prevalence of clinical venous thromboembolism in the USA: current trends and future projections. *Am J Hematol*. 2011;86(2):217–220.
2. Centers for Disease Control and Prevention (CDC). Venous thromboembolism in adult hospitalizations - United States, 2007-2009. *MMWR Morb Mortal Wkly Rep*. 2012;61(22):401–404.
3. Grosse SD, Nelson RE, Nyarko KA, Richardson LC, Raskob GE. The economic burden of incident venous thromboembolism in the United States: a review of estimated attributable healthcare costs. *Thromb Res*. 2016;137:3–10.
4. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest*. 2016;149(2):315–352.
5. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med*. 2009;361(24):2342–2352.
6. EINSTEIN Investigators, Bauersachs R, Berkowitz SD, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363(26):2499–2510.
7. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369(9):799–808.
8. Lenchus JD. Transitions in the prophylaxis, treatment and care of patients with venous thromboembolism. *Adv Ther*. 2016;33(1):29–45.
9. Padron M, Miyares MA. Development of an anticoagulation stewardship program at a large tertiary care academic institution. *J Pharm Pract*. 2015;28(1):93–98.
10. Brock J, Mitchell J, Irby K, et al. Association between quality improvement for care transitions in communities and rehospitalizations among Medicare beneficiaries. *JAMA*. 2013;309(4):381–391.
11. Owens GM, Fine C, Harrington DW, et al. Improving transitions of care for patients with thromboembolic disease. *Am J Manag Care*. 2014;20(4 Suppl):S81–91.
12. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.
13. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*. 2009;6(7):e1000100.
14. National Institute for Health and Clinical Excellence [homepage on the Internet]. *The Guidelines Manual*. London: National Institute for Health and Clinical Excellence; 2009. www.nice.org.uk. Accessed November 23, 2018.
15. Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)-explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. *Value Health*. 2013;16(2):231–250.
16. Sharifi M, Freeman W, Bay C, Sharifi M, Schwartz F. Low incidence of post-thrombotic syndrome in patients treated with new oral anticoagulants and percutaneous endovenous intervention for lower extremity deep venous thrombosis. *Vasc Med*. 2015;20(2):112–116.
17. Streiff MB, Milentijevic D, Mccrae K, et al. Recurrent VTE in cancer patients treated with anticoagulation. *Journal of Clinical Oncology*. 2016;34(15_suppl):10024–10024.
18. Desai A, Desai A, Calixte R, et al. Comparing Length of Stay Between Patients Taking Rivaroxaban and Conventional Anticoagulants for Treatment of Venous Thromboembolism. *Lung*. 2016;194(4):605–611.
19. Spyropoulos AC, Preblick R, Kwong WJ, Lingohr-Smith M, Lin J. Is adherence to the American College of Chest Physicians recommended anticoagulation treatment duration associated with different outcomes among patients with venous thromboembolism? *Clin Appl Thromb Hemost*. 2017;23(6):532–541.
20. Beam DM, Kahler ZP, Kline JA. Immediate discharge and home treatment with rivaroxaban of low-risk venous thromboembolism diagnosed in two U.S. emergency departments: a one-year preplanned analysis. *Acad Emerg Med*. 2015;22(7):788–795.
21. Falconieri L, Thomson L, Oettinger G, et al. Facilitating anticoagulation for safer transitions: preliminary outcomes from an emergency department deep vein thrombosis discharge program. *Hosp Pract*. 2014;42(4):16–45.
22. Stein PD, Matta F, Hughes PG, et al. Home Treatment of pulmonary embolism in the era of novel oral anticoagulants. *Am J Med*. 2016;129(9):974–977.
23. Cefalo P, Weinberg I, Hawkins BM, et al. A comparison of patients diagnosed with pulmonary embolism who are ≥65 years with patients <65 years. *Am J Cardiol*. 2015;115(5):681–686.
24. Menzin J, Preblick R, Friedman M, Menzin J, Frean M, Jacqueline Kwong W. Treatment patterns and outcomes among hospitalized patients with venous thromboembolism in the United States: an analysis of electronic health records data. *Hosp Pract*. 2014;42(4):59–74.

25. Stein PD, Matta F, Hughes PG, et al. Home treatment of deep venous thrombosis in the era of new oral anticoagulants. *Clin Appl Thromb Hemost*. 2015;21(8):729–732.
26. Cai J, Preblick R, Zhang Q, Kwong WJ. Utilization of parenteral anticoagulants and warfarin: impact on the risk of venous thromboembolism recurrence in the outpatient setting. *Am Health Drug Benefits*. 2014;7(8):444–451.
27. Deitelzweig S, Laliberté F, Crivera C, et al. Hospitalizations and other health care resource utilization among patients with deep vein thrombosis treated with rivaroxaban versus low-molecular-weight heparin and warfarin in the outpatient setting. *Clin Ther*. 2016;38(8):e1803:1803–1816.
28. Deitelzweig S, Kline J, Margolis JM, et al. Comparison of rivaroxaban or warfarin use for venous thromboembolism on inpatient length of stay. *J Am Coll Cardiol*. 2065;2016;67(13 Supplement).
29. Deitelzweig S, Raut MK, Margolis J, et al. Hospital length of stay for deep vein thrombosis or pulmonary embolism among patients receiving rivaroxaban or warfarin. 20–25 June 2015, Toronto, ON, Canada. *Journal of Thrombosis and Haemostasis*. Conference: 25th Congress of the International Society on Thrombosis and Haemostasis, ISTH 2015.
30. Merli GJ, Hollander JE, Lefebvre P, et al. Rates of hospitalization among patients with deep vein thrombosis before and after the introduction of rivaroxaban. *Hosp Pract*. 2015;43(2):85–93.
31. Roberts KM, Knight TB, Padilla-Tolentino E, Murthy M, Peterson EJ. Length of stay comparison between rivaroxaban and warfarin in the treatment of pulmonary embolism: results from a real-world observational cohort study. *Thrombosis*. 2015;2015:1–6.
32. Margolis JM, Deitelzweig S, Kline J, et al. Shorter hospital stays and lower costs for rivaroxaban compared with warfarin for venous thrombosis admissions. *J Am Heart Assoc*. 2016;5(10):e003788.
33. LaMori JC, Shoheiber O, Mody SH, Bookhart BK. Inpatient resource use and cost burden of deep vein thrombosis and pulmonary embolism in the United States. *Clin Ther*. 2015;37(1):62–70.
34. Margolis JM, Deitelzweig S, Kline J, et al. Pulmonary embolism inpatients treated with rivaroxaban had shorter hospital stays and lower costs compared with warfarin. *Clin Ther*. 2016;38(11):2496–2503.
35. Kahler ZP, Beam DM, Kline JA. Cost of treating venous thromboembolism with heparin and warfarin versus home treatment with rivaroxaban. *Acad Emerg Med*. 2015;22(7):796–802.
36. Kahler ZP, Beam DM, Kline JA. Immediate discharge of low-risk venous thromboembolism: A cost and safety analysis. SAEM 2014. 2014;21(5 Suppl. 1):S16–S17.
37. Shorr AF, Johnston S, Jing Y, et al. Real-world cost of all-cause hospitalizations over a 12-month period after acute venous thromboembolism. *Circulation*. 2014;130.
38. Coleman CI, Fermann GJ, Weeda ER, et al. Is Rivaroxaban associated with shorter hospital stays and reduced costs versus parenteral bridging to warfarin among patients with pulmonary embolism? *Clin Appl Thromb Hemost*. 2017;23(7):830–837.
39. Weeda ER, Wells PS, Peacock WF, et al. Hospital length-of-stay and costs among pulmonary embolism patients treated with rivaroxaban versus parenteral bridging to warfarin. *Intern Emerg Med*. 2017;12(3):311–318.
40. Raphael IJ, Mckenzie JC, Zmistowski B, Brown DB, Parvizi J, Austin MS. Pulmonary embolism after total joint arthroplasty: cost and effectiveness of four treatment modalities. *J Arthroplasty*. 2014;29(5):933–937.
41. Lin J, Lingohr-Smith M, Kwong WJ. Incremental health care resource utilization and economic burden of venous thromboembolism recurrence from a U.S. payer perspective. *J Manag Care Pharm*. 2014;20(2):174–186.
42. Amin A, Bruno A, Trocio J, Lin J, Lingohr-Smith M. Incremental health care burden of bleeding among patients with venous thromboembolism in the United States. *J Manag Care Spec Pharm*. 2015;21(10):965–972.
43. Fanikos J, Rao A, Seger AC, Carter D, Piazza G, Goldhaber SZ. Hospital costs of acute pulmonary embolism. *Am J Med*. 2013;126(2):127–132.
44. Bookhart BK, Haskell L, Bamber L, Wang M, Schein J, Mody SH. Length of stay and economic consequences with rivaroxaban vs enoxaparin/vitamin K antagonist in patients with DVT and PE: findings from the North American EINSTEIN clinical trial program. *J Med Econ*. 2014;17(10):691–695.
45. Dasta JF, Pilon D, Mody SH, et al. Daily hospitalization costs in patients with deep vein thrombosis or pulmonary embolism treated with anticoagulant therapy. *Thromb Res*. 2015;135(2):303–310.
46. Weeda ER, Kohn CG, Peacock WF, et al. Rivaroxaban versus heparin bridging to warfarin therapy: impact on hospital length of stay and treatment costs for low-risk patients with pulmonary embolism. *Pharmacotherapy*. 2016;36(10):1109–1115.
47. Merli GJ, Hollander JE, Lefebvre P, et al. Costs of hospital visits among patients with deep vein thrombosis treated with rivaroxaban and LMWH/warfarin. *J Med Econ*. 2016;19(1):84–90.
48. Dubois C, Louzon P, Bhatheja R. Rivaroxaban vs. standard of care post ultrasound accelerated thrombolysis for pulmonary embolism. *Critical Care Medicine*. 2015;43(12):153.
49. Atay JK, Fiumara K, Piazza G, Fanikos J, Goldhaber SZ. Hospital budget implications of substituting dabigatran for warfarin in an anticoagulation service. *Clin Appl Thromb Hemost*. 2012;18(2):181–184.
50. Amin A, Bruno A, Trocio J, Lin J, Lingohr-Smith M. Real-world medical cost avoidance when new oral anticoagulants are used versus warfarin for venous thromboembolism in the United States. *Clin Appl Thromb Hemost*. 2016;22(1):5–11.
51. 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 vs warfarin or placebo in the US. *J Med Econ*. 2015;18(6):399–409.
52. Coleman CI, Baugh C, Crivera C, et al. Healthcare costs associated with rivaroxaban or warfarin use for the treatment of venous thromboembolism. *J Med Econ*. 2017;20(2):200–203.
53. Deitelzweig S, Laliberté F, Raut R, et al. Health care costs among patients diagnosed with deep vein thrombosis in the outpatient setting and treated with rivaroxaban versus low-molecular-weight heparin and warfarin. *Value in Health*. 2016;19(3):A45–A46.
54. Amin A, Bruno A, Trocio J, Lin J, Lingohr-Smith M. Estimated savings in medical costs when new oral anticoagulants are used for the treatment of patients with nonvalvular atrial fibrillation and venous thromboembolism vs. Warfarin in the U.S. *Value in Health*. 2015;18(3):A138.
55. Amin A, Jing Y, Trocio J, Lin J, Lingohr-Smith M, Graham J. Evaluation of medical costs associated with use of new oral anticoagulants compared with standard therapy among venous thromboembolism patients. *J Med Econ*. 2014;17(11):763–770.
56. Amin A, Jing Y, Trocio J, Lin J, Lingohr-Smith M, Graham J. Evaluation of medical costs avoided when new oral anticoagulants are used for extended treatment of venous thromboembolism based on clinical trial results. *J Thromb Thrombolysis*. 2015;40(2):131–138.
57. Choi M, Hector M. Management of venous thromboembolism for older adults in long-term care facilities. *J Am Acad Nurse Pract*. 2012;24(6):335–344.
58. Bashir R, Zack CJ, Zhao H, Comerota AJ, Bove AA. Comparative outcomes of catheter-directed thrombolysis plus anticoagulation vs anticoagulation alone to treat lower-extremity proximal deep vein thrombosis. *JAMA Intern Med*. 2014;174(9):1494–1501.
59. Chen SY, Wu N, Gulseth M, et al. One-year adherence to warfarin treatment for venous thromboembolism in high-risk patients and its association with long-term risk of recurrent events. *J Manag Care Pharm*. 2013;19(4):291–301.
60. Fang MC, Fan D, Witt DM, et al. The association of warfarin control with pulmonary embolism mortality: the CVRN VTE study. *Circulation*. 2013;128(suppl_22).
61. Jean GW, Kelly K, Mathew J, Larumbe E, Hughes R. Venous thromboembolism treatment outcomes in cancer patients and effect of third-party payers on anticoagulant choice. *Support Care Cancer*. 2017;25(1):59–66.

62. Levy MM, Bach C, Fisher-Snowden R, Pfeifer JD. Upper extremity deep venous thrombosis: reassessing the risk for subsequent pulmonary embolism. *Ann Vasc Surg*. 2011;25(4):442–447.
63. Liu X, Xie L, Phatak H, et al. Persistence on warfarin therapy in patients with venous thromboembolism: a large US insurance database analysis. *Circulation*. 2013;128(suppl_22).
64. Sussman M, Lim J, Wang C, Friedman M, Sander S, Griffiths R. Characteristics and treatment patterns of patients with deep vein thrombosis and/or pulmonary embolism in the US hospital setting. *Blood*. 2015;126(23):2061.
65. Xie L, Liu X, Phatak H, et al. Warfarin discontinuation in patients with unprovoked venous thromboembolism: a large US insurance database analysis. *Am J Ther*. 2016;23(6):e1744–e1753.

Supplementary materials

Search strategies

Each search focused on articles that addressed inpatient (IP) and outpatient (OP) direct oral anticoagulant (DOAC) and vitamin K antagonist (VKA) treatment patterns for patients with venous thromboembolism (VTE) and was restricted to papers published in English since January 1, 2011. The PubMed/MEDLINE strategies appear in Tables S1 and S2, along with the number of abstracts retrieved.

Table S1 MEDLINE clinical search strategy – conducted December 1, 2016

Step	Search terms	Abstracts
1	Search (("Venous Thromboembolism"[Majr]) OR "Pulmonary Embolism"[Majr]) OR "Venous Thrombosis"[Majr]	63,522
2	Search (venous thromboemboli*[Title] OR vte[Title] OR venous thrombosis[Title] OR venous thromboses[Title] OR pulmonary thromboembolism*[Title] OR pulmonary embolism*[Title] OR deep venous thrombosis[Title] OR deep vein thrombosis[Title] OR deep vein thromboses[Title] OR deep venous thromboses[Title] OR dvt[Title]) Note: Steps 1 and 2 are keyword terms and Mesh indexing terms that are specific to the indications of interest.	36,211
3	Search #1 OR #2	69,728
4	Search clinical outcome*[Title/Abstract] OR Tx outcome*[Title/Abstract] OR discharge*[Title/Abstract] OR practice pattern*[Title/Abstract] OR Tx pattern*[Title/Abstract] OR patient management[Title/Abstract] OR long-term management[Title/Abstract] OR long-term Tx*[Title/Abstract] OR extended Tx[Title/Abstract] OR long-term care[Title/Abstract] OR extended care[Title/Abstract] OR outpatient*[Title/Abstract] OR IP*[Title/Abstract] OR home health care[Title/Abstract] OR home self-care[Title/Abstract] OR switch*[Title/Abstract] OR transition*[Title/Abstract] OR nursing home*[Title/Abstract] OR rehabilitation[Title/Abstract]	1,121,187
5	Search (((((("Tx Outcome"[Mesh]) OR "Practice Patterns, Physicians'"[Mesh]) OR "Patient Discharge"[Mesh]) OR "Long-Term Care"[Mesh]) OR "IPs"[Mesh]) OR "Ambulatory Care"[Mesh] Note: Steps 4 and 5 outline key terminology and Mesh terms that are specific to the concept of Tx patterns for IP and discharged patients.	914,978
6	Search #4 OR #5	1,871,693
7	Search #3 AND #6	10,207
8	Search dabigatran[Title/Abstract] OR rivaroxaban[Title/Abstract] OR apixaban[Title/Abstract] OR edoxaban[Title/Abstract] OR NOAC[Title/Abstract] OR anticoagulant*[Title/Abstract] OR VKA[Title/Abstract] OR vitamin K antagonist*[Title/Abstract] OR warfarin[Title/Abstract]	66,882
9	Search "Anticoagulants/therapeutic use"[Mesh] Note: Steps 8 and 9 are used to focus results to the drugs of interest.	50,512
10	Search #8 OR #9	94,383
11	Search #7 AND #10	4,010
12	Search prophylactic[Title] OR prophylaxis[Title] OR prevent*[Title] OR thromboprophyla*[Title] Note: Step 12 is included to eliminate articles that are primarily focused on prophylactic Tx.	289,300
13	Search #11 NOT #12	3,050
14	Search #13 NOT: Comment; Editorial; Letter; Meta-Analysis; Review	2,179
15	Search #14 Filters: Publication date from 2011/01/01 to 2016/12/31; English	790

Table S2 MEDLINE economic search strategy – conducted December 1, 2016

Step	Search terms	Abstracts
1	Search (("Venous Thromboembolism"[Majr]) OR "Pulmonary Embolism"[Majr]) OR "Venous Thrombosis"[Majr]	63,522
2	Search (venous thromboemboli*[Title] OR vte[Title] OR venous thrombosis[Title] OR venous thromboses[Title] OR pulmonary thromboembolism*[Title] OR pulmonary embolism*[Title] OR deep venous thrombosis[Title] OR deep vein thrombosis[Title] OR deep vein thromboses[Title] OR deep venous thromboses[Title] OR dvt[Title]) Note: Steps 1 and 2 are keyword terms and Mesh indexing terms that are specific to the indications of interest.	36,211
3	Search #1 OR #2	69,728
4	Search dabigatran[Title/Abstract] OR rivaroxaban[Title/Abstract] OR apixaban[Title/Abstract] OR edoxaban[Title/Abstract] OR NOAC[Title/Abstract] OR anticoagulant*[Title/Abstract] OR VKA[Title/Abstract] OR vitamin K antagonist*[Title/Abstract] OR warfarin[Title/Abstract]	66,882
5	Search "Anticoagulants/therapeutic use"[Mesh]	50,512
6	Search #4 OR #5	94,383
7	Search #3 AND #6	13,720
8	Search economic*[Title/Abstract] OR cost[Title/Abstract] OR costly[Title/Abstract] OR costs[Title/Abstract] OR price*[Title/Abstract] OR reimburs*[Title/Abstract] OR health resource utili*[Title/Abstract] OR resource utili*[Title/Abstract] OR resource use*[Title/Abstract] OR claim*[Title/Abstract]	680,024
9	Search "Economics"[Mesh]) OR "Health Care Costs"[Mesh] OR "Drug Utilization"[Mesh] OR "Health Resources/utilization"[Mesh] Note: Specific keywords and Mesh terminology in Steps 8 and 9 are incorporated to focus the results to economic areas of interest.	550,224
10	Search #8 OR #9	1,045,295
11	Search #7 AND #10	925
12	Search prophylactic[Title] OR prophylaxis[Title] OR prevent*[Title] OR thromboprophyla*[Title]	289,300
13	Search #11 NOT #12	558
14	Search #13 NOT: Comment; Editorial; Letter; Meta-Analysis; Review	339
15	Search #14 Filters: Publication date from 2011/01/01 to 2016/12/31; English	116