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Healthcare Cost Impact of Continued Anticoagulation with Rivaroxaban versus Aspirin for Prevention of Recurrent Symptomatic Venous Thromboembolism in the EINSTEIN-CHOICE Trial Population

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Dr. Wells has received research funding from BMS/Pfizer; has participated on advisory board for Bayer Healthcare; has acted as a consultant to Janssen Scientific Affairs, LLC.; and has served on a writing committee for Itreas.

Dr. Prins has acted as a consultant to Pfizer, Janssen Scientific Affairs, LLC., and Daiichi Sankyo.

Dr. Beyer-Westendorf has received research funding and honoraria from Boehringer-Ingelheim, Daiichi Sankyo, Johnson & Johnson, Pfizer, Portola, and Bayer.

Dr. Lensing is an employee of Bayer Pharma AG.

Mrs. Ashton and Drs. Crivera and Zhao are employees of Janssen Scientific Affairs, LLC.

Dr. Schein was an employee of Janssen Scientific Affairs, LLC at the time of the study.

Drs. Haskell, Levitan, and Yuan are employees of Janssen Research & Development, LLC.

Mr. Laliberté, Mr. Lefebvre, and Mr. Lejeune are employees of Groupe d’analyse, Ltée a consulting company that has received research grants from Janssen Scientific Affairs, LLC.

Dr. Xiao was an employee of Groupe d’analyse, Ltée at the time of the study.

Dr. Prandoni has acted as a consultant to Bayer Pharma, Sanofi, and Pfizer; and has received honoraria from Bayer Pharma.

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ABBREVIATIONS:

DOT: duration of treatment

DVT: deep-vein thrombosis

EINSTEIN-CHOICE trial: Reduced-dosed Rivaroxaban in the Long-term Prevention of Recurrent Symptomatic Venous Thromboembolism

GI: gastrointestinal

PE: pulmonary embolism

PPPM: per patient per month

PTS: post-thrombotic syndrome

PVLE: present value of lifetime earnings

SLR: systematic literature review

US: United States

VTE: venous thromboembolism

WAC: wholesale acquisition cost
ABSTRACT

Background: Using data from the Reduced-dosed Rivaroxaban in the Long-term Prevention of Recurrent Symptomatic Venous Thromboembolism (EINSTEIN-CHOICE) trial, this study assessed cost impact of continued anticoagulation therapy with rivaroxaban vs. aspirin.

Methods: Total healthcare costs (2016USD) associated with rivaroxaban and aspirin were calculated as the sum of clinical event costs and drug costs from a US managed care perspective. Clinical event costs were calculated by multiplying event rate by cost of care. One-year Kaplan-Meier clinical event rates for recurrent pulmonary embolism, recurrent deep-vein thrombosis, all-cause mortality, and bleeding were obtained from EINSTEIN-CHOICE. Cost of care was determined by literature review. Drug costs were the product of drug price (wholesale acquisition cost) and treatment duration. A one-way sensitivity analysis was conducted.

Results: Rivaroxaban users had lower per patient per month (PPPM) clinical event costs compared with aspirin users ($123, $243, and $381 for rivaroxaban 10mg, rivaroxaban 20mg, and aspirin, respectively). However, vs. aspirin, PPPM total healthcare costs were $24 higher for rivaroxaban 10mg treated patients ($143 higher for rivaroxaban 20mg) due to higher cost of rivaroxaban. With a 15% discount for rivaroxaban 10mg, the lower cost of clinical events for the rivaroxaban-treated patients more than fully offset the higher drug costs, and yielded a $19 lower total healthcare cost.

Conclusions: Continued therapy with rivaroxaban 10mg and 20mg vs. aspirin was associated with lower clinical event costs but higher total healthcare costs; with a 15% drug discount rivaroxaban 10mg had lower total healthcare costs than aspirin.

Keywords: anticoagulants, cost comparison, economic analysis, extended treatment, aspirin, rivaroxaban, recurrent venous thromboembolism
INTRODUCTION

Venous thromboembolism (VTE), comprised of pulmonary embolism (PE) and deep-vein thrombosis (DVT), is the third leading cause of cardiovascular-associated death and presents a significant healthcare and economic burden in the United States (US).\(^1\) VTE recurrence has been estimated to occur in around 5-7% of patients per year after an initial episode.\(^2,3\)

Current treatment guidelines for VTE include long-term anticoagulation with dabigatran, rivaroxaban, apixaban or edoxaban for patients without cancer\(^4\). While extended anticoagulation therapy prevents recurrent VTE, treatment beyond 6-12 months of the initial VTE is often not undertaken due to perception that bleeding may outweigh benefits of continued therapy.\(^5\) The Reduced-dosed Rivaroxaban in the Long-term Prevention of Recurrent Symptomatic Venous Thromboembolism (EINSTEIN-CHOICE) trial compared efficacy and safety of treatment with rivaroxaban (10mg and 20mg daily) vs. aspirin (100mg daily) following 6-12 months of initial anticoagulation therapy. Rate of recurrent fatal or nonfatal VTE was significantly lower in the rivaroxaban- vs. aspirin-treated patients, without significant difference in major bleeding.\(^5\)

In the short term, recurrent VTE is associated with hospitalization or emergency room visits and testing for potential underlying conditions, such as screening for occult cancer.\(^6\) Recurrence is also associated with potential longer term consequences, such as post-thrombotic syndrome (PTS) and pulmonary hypertension.\(^7\) Evaluation of reduced costs associated with prevention of recurrent VTE is valuable for payers to better assess the value of extended anticoagulant therapy.

The objective of this study was to compare costs associated with extended treatment of rivaroxaban vs. aspirin using event rates from the EINSTEIN-CHOICE trial and cost data from published literature.

MATERIALS AND METHODS

Study Population

The study population was based on the EINSTEIN-CHOICE study population, which consisted of 3,365 adult patients (rivaroxaban 10mg once daily [QD]: 1,127; rivaroxaban 20mg QD: 1,107;...
and aspirin: 1,131) with confirmed symptomatic DVT and/or PE who had been treated for 6-12 months using anticoagulants. Patients were followed for up to 12 months during which symptomatic recurrent VTE and major bleeding were measured.\

**Cost Analysis Framework**

A cost comparison analysis was conducted to compare total healthcare direct costs in VTE patients who received extended treatment with daily rivaroxaban at 10mg and 20mg vs. daily aspirin 100mg. Total healthcare costs comprised drug cost and clinical event cost and were assessed over a one-year time horizon and converted to per patient per month (PPPM) costs.

\[
\text{Total healthcare cost} = \text{Drug costs} + \text{Clinical event costs} \\
= \sum_i \text{Duration}_{\text{drug},i} \times \text{Price}_{\text{drug},i} + \sum_j \text{Rate}_{\text{event},j} \times \text{Price}_{\text{event},j}
\]

Drug cost was defined as cost associated with rivaroxaban or aspirin use and calculated as duration of treatment (DOT) multiplied by drug price. Clinical event cost for five event types reported in EINSTEIN-Choice (recurrent DVT, recurrent PE, major bleeding, clinically relevant non-major bleeding, and all-cause mortality) were calculated for each treatment by multiplying the clinical event rate by cost of care for the event. The cost of care for an event (except for death) included costs associated with managing the event occurrence and the incremental medical cost during the one-year period following the event. Costs were estimated from a US managed care payer’s perspective as unit costs for clinical events were obtained from studies using national managed care, commercial, or Medicare healthcare insurance claims databases. No amounts representing charges were used as cost estimates in this analysis.

**Cost Analysis Inputs**

**Duration of Treatment**

The proportion of patients in the EINSTEIN-CHOICE trial with 6, 9-12, and 12 months intended DOT were similar across all treatment arms (about 19%, 21%, and 60%, respectively). The weighted average of intended DOT assuming 90% adherence, used to calculate base-case drug costs, was 9.4 months in all three cohorts.
Clinical Event Rates

In the EINSTEIN-CHOICE trial, the primary efficacy outcome was defined as fatal or nonfatal symptomatic recurrent VTE. Definitions of bleeding appear in the original study.\(^5\) One-year Kaplan-Meier rate differences of clinical events between two rivaroxaban cohorts (10mg, 20mg) and aspirin cohort, obtained from EINSTEIN-CHOICE, are presented in Table 1.

Unit Costs

Unit cost of rivaroxaban was estimated based on the 2016 wholesale acquisition cost (WAC) package price from Redbook.\(^8\) The monthly unit cost was estimated at $359.61 for a 30-pill package of 10mg or 20mg daily dose rivaroxaban. Since the 100mg aspirin package price is not available in Redbook, the drug price of $3.67 for a 90-pill package of 81mg aspirin tablet was used.

The one-year cost of care for patients with a clinical event compared to patients without the event was determined by conducting a systematic literature review (SLR) in the Medline (via PubMed) database. The search strategy and flowchart of study selection process are available in the online supplement. The SLR identified 309 studies reporting VTE and bleeding costs and 36 were considered eligible. After full-text review of the titles, 7 articles with cost findings were extracted.

Unit costs for both recurrent DVT and PE events were estimated at $60,000 per event based on incremental annual total all-cause healthcare costs associated with recurrent VTE (vs. non-recurrent VTE) estimated in two studies: $62,181 by Lefebvre et al.\(^7\) and $59,784 by Lin et al.\(^1\) (both in 2016 US dollars). As a result of the SLR, we identified two additional papers by Amin et al. that reported incremental cost of recurrent VTE and both studies cited findings from Lefebvre et al.\(^9,10\) The unit cost for major bleeding event was based on a study assessing the incremental annual total all-cause healthcare cost associated with major gastrointestinal (GI) bleeding (vs. no bleeding) among warfarin-treated patients with atrial fibrillation,\(^11\) taking into account differences in severity (i.e., proportion of fatal or intracranial bleeding) of major bleeding between cohorts observed in the EINSTEIN-CHOICE trial. The unit cost for major bleeding was set at $17,378, $19,411, and $18,594 per event for the rivaroxaban 10mg, rivaroxaban 20mg, and...
aspirin cohorts, respectively. The unit cost for clinically relevant non-major bleeding was set at $364 based on the estimated annual incremental cost associated with minor GI bleeding (vs. no bleeding) from the same study.\textsuperscript{11} Finally, to account for difference in mortality between treatments, we calculated the potential cost associated with death. The SLR identified two articles where the present value of lifetime earnings (PVLE) was reported as the average cost due to life loss in a VTE population.\textsuperscript{12,13} This human capital method estimates the value of labor taking into account life expectancy, workforce composition, earnings by age, and the discount rate. Based on Mahan et al. methodology, PVLE was weighted, by sex and age, to reflect a VTE population (i.e., older than US average) and the unit cost for all-cause mortality was set at $207,862. All costs were inflated to 2016 dollars based on the medical care component of the US Consumer Price Index (Table 1).

**Sensitivity Analysis**

To account for uncertainties surrounding inputs, a one-way sensitivity analysis was conducted, in which the total healthcare cost difference between cohorts was estimated by changing one input while keeping other inputs at their base-case values. Unit costs were varied by decreasing or increasing the base unit cost by 20%. Differences in clinical event rates between treatments were varied by ± 1 standard deviations of rate difference derived from the corresponding 95% confidence intervals obtained from the EINSTEIN-CHOICE trial (Table 1).\textsuperscript{14}

Moreover, WAC drug prices are frequently negotiated in the US healthcare market with rebates and discounts.\textsuperscript{15} Thus, a sensitivity analysis with a hypothetical conservative discount rate (15%) for rivaroxaban was also conducted. Analyses were conducted with Microsoft Excel 2016.

**RESULTS**

In the base-case analysis, the PPPM drug cost was approximately $282 for rivaroxaban cohorts and $0.96 for the aspirin cohort (Table 2). Clinical event costs per patient were lower for all efficacy outcomes for rivaroxaban vs. aspirin, except for all-cause mortality for the rivaroxaban 20mg cohort (Table 2). Compared with the aspirin cohort, PPPM costs for bleeding events were lower for the rivaroxaban 10mg cohort, but not for the rivaroxaban 20mg cohort.
Rivaroxaban users had lower PPPM clinical event costs compared with aspirin users ($123, $243, and $381 for rivaroxaban 10mg, rivaroxaban 20mg, and aspirin, respectively). The expected loss of lifetime earnings for 12 months on rivaroxaban 10mg and 20mg were $1,060 lower and $208 higher per patient, respectively, compared with the aspirin cohort. The higher drug cost of rivaroxaban vs. aspirin made total healthcare costs for patients treated with rivaroxaban exceed those treated with aspirin (Figure 1).

With a 15% discount for rivaroxaban 10mg, lower clinical events cost for rivaroxaban-treated patients more than fully offset higher drug costs, and yielded a $19 lower PPPM total healthcare cost (Figure 2). With a 15% discount for rivaroxaban 20mg, PPPM total healthcare costs remained higher than aspirin but with a smaller difference ($101 PPPM).

The one-way sensitivity analysis for rivaroxaban 10mg vs. aspirin is illustrated in Figure 3. Inputs at the top have the highest impact on the total healthcare cost difference between cohorts. Drug cost was the leading cost driver; the total healthcare cost difference became in favor of rivaroxaban 10mg when lower drug costs or greater rate differences were assessed. Varying other inputs had a smaller impact on total healthcare cost difference and cost difference remained in favor of aspirin in the sensitivity analysis of these inputs. The same leading cost drivers were identified when assuming a 15% discount for rivaroxaban (Figure 4). For the comparison of rivaroxaban 20mg vs. aspirin, the cost difference remained in favor of aspirin in the sensitivity analysis across all inputs (data not shown).

**DISCUSSION**

In our cost comparison analysis, continued anticoagulation therapy with rivaroxaban 10mg and 20mg in VTE patients who had completed 6-12 months of initial anticoagulation therapy was associated with lower clinical event costs, but higher total healthcare costs, compared to aspirin. One-way sensitivity analysis showed that drug cost, rate difference of all-cause mortality, recurrent DVT, and recurrent PE had the highest impact on the total healthcare cost difference, which became in favor of rivaroxaban 10mg when greater rate differences in efficacy outcomes were assumed.
In the base-case analysis, the WAC-based drug cost produced a conservative estimate for total costs of rivaroxaban relative to aspirin since the WAC is a starting point with insurers generally paying significantly less through negotiation. Thus, this study evaluated the scenario of a 15% drug discount on rivaroxaban and showed that rivaroxaban 10mg had a lower total healthcare cost than aspirin after discount.

Appropriate management of VTE and reducing the risk of recurrent VTE is an increasing public health priority.\textsuperscript{16,17} The substantial burden of these events led the Surgeon General in 2008 to focus on countering the projected VTE trend;\textsuperscript{18} this continues to be one of eleven core areas of the US Department of Health and Human Services for improving patient safety.\textsuperscript{19} As VTE disproportionately affects the older population, it is anticipated that incidence of VTE, and thus risk of recurrence, will increase with an aging population.\textsuperscript{20} Multiple VTE events are associated with increased risk of chronic complications including pulmonary hypertension and PTS\textsuperscript{21} with burden and costs extending beyond the one-year time horizon of this study. Thus, it is plausible that recurrent VTE is associated with additional costs not captured in this study, resulting in an underestimation of total cost of VTE.\textsuperscript{22} Nonetheless, our analyses offer an indication of costs due to all-cause premature death in the VTE population in the one-year time horizon. Specifically, the study's estimated loss of income for these patients over one year of treatment (i.e. the sum of discounted earnings expected in each year of an average VTE population multiplied by the all-cause mortality rate) represents the expected loss of lifetime earnings due to premature death ($374, $1,642, and $1,434 for rivaroxaban 10mg, rivaroxaban 20mg, and aspirin, respectively). Future studies assessing costs over a longer period using alternative economic approaches, such as cost-effectiveness analyses, are warranted.

This study is subject to some limitations. First, since patient-level healthcare utilization data were not collected in the EINSTEIN-CHOICE trial, clinical event costs were estimated based on clinical event rates from the trial and unit costs for events from literature while real-world costs for managing clinical events may vary across hospitals/centers. However, the one-way sensitivity analysis varying unit cost yielded results consistent with the base-case suggesting that the study findings of rivaroxaban’s association with lower total healthcare cost compared to aspirin when a 15% drug discount is applied are robust across a range of relevant costs. Second, actual costs associated with a major bleed on rivaroxaban are not available and it is possible the costs differ
from a major bleeding on warfarin. In addition, costs of bleeding vary in the literature and hence the choice of reference used could influence our results. Nonetheless, we used a cost estimate that is derived from the cost of major bleeds (International Society of Thrombosis and Haemostasis definition), intracranial hemorrhage, and death. We chose this in order to be conservative and have a bias in favor of aspirin. Furthermore, a lower cost for major bleeding would not substantially change the final result as illustrated in the one-way sensitivity analysis. Third, the ±20% range of costs examined was arbitrary and results may differ over a wider set of costs. Fourth, this study did not include costs for secondary outcomes (e.g. stroke) reported in the EINSTEIN-CHOICE trial as these outcomes were rare and not reported differentially between treatments. Fifth, the assumption of equal healthcare cost prior to clinical events may not be true for patients who developed clinical events earlier versus later during follow-up. Additionally, this study evaluated the impact of extended treatment with rivaroxaban only on direct medical costs, not indirect costs, except for death where the cost associated with life loss in a VTE population was included. Many physicians are reluctant to continue anticoagulant therapy in patients in whom it is indicated presumably due to cost, inconvenience in the case of warfarin, or fear of bleeding. A wealth of data has now demonstrated that direct oral anticoagulants are safe, effective, and convenient. The EINSTEIN-CHOICE study demonstrates rivaroxaban is more effective than aspirin and our analysis suggests this choice comes with a very low cost increase. Adverse effects on health associated with recurrent VTE are difficult to quantify in costs but clearly result in negative effects on quality of life, in some case profoundly. Thus, it is probable that recurrent VTE reduces productivity and quality of life, which in turn would increase societal cost savings associated with rivaroxaban. Moreover, since analyses used data from the EINSTEIN-CHOICE trial, where patients received continuous care and close monitoring, the “real-world” applicability of this study may be questioned, but real-world settings patients have more comorbidities and are more susceptible to recurrence which would increase savings associated with rivaroxaban. Finally, although unit cost assumptions in this study were based on the US healthcare system, the EINSTEIN-CHOICE trial was conducted in an international setting; differences in healthcare systems may have affected results of this study.
CONCLUSIONS

Continued therapy with rivaroxaban 10mg and 20mg anticoagulation in VTE patients who had completed 6-12 months of initial anticoagulation therapy was associated with lower clinical event costs, but higher total costs, compared to aspirin. Nevertheless, rivaroxaban 10mg was associated with lower total healthcare costs when a 15% drug cost discount was applied.
ACKNOWLEDGMENTS

Guarantor

FL had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Author Contributions

PSW, MHP, JBW, AWAL, LH, BL, FL, VA, YX, DL, CC, PL, QZ, ZY, JS, and PP contributed substantially to the study design, data analysis and interpretation, and the writing and final approval of the manuscript. The authors would like to acknowledge Guillaume Poulin-Bellisle, of Groupe d’analyse, Ltée., who contributed to the systematic literature review.

Financial/nonfinancial Disclosures

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REFERENCES


Table 1. Base-Case Inputs and Ranges Used in One-Way Sensitivity Analysis

<table>
<thead>
<tr>
<th>Unit cost (2016 US$)</th>
<th>Base-case input</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban (10mg and 20mg) cost, monthly</td>
<td>$359.61</td>
<td>$287.69</td>
<td>$431.53</td>
<td>Redbook 2016</td>
</tr>
<tr>
<td>Aspirin cost, monthly</td>
<td>$1.22</td>
<td>$0.98</td>
<td>$1.46</td>
<td>Redbook 2016</td>
</tr>
<tr>
<td>Recurrent DVT</td>
<td>$60,000</td>
<td>$48,000</td>
<td>$72,000</td>
<td>Lin et al, 2014; Lefebvre et al. 2013</td>
</tr>
<tr>
<td>Recurrent PE</td>
<td>$60,000</td>
<td>$48,000</td>
<td>$72,000</td>
<td>Lin et al, 2014; Lefebvre et al. 2013</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>$207,862</td>
<td>$166,290</td>
<td>$249,435</td>
<td>Mahan et al. 2011; Mahan et al. 2012</td>
</tr>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban 10mg</td>
<td>$17,378</td>
<td>$13,902</td>
<td>$20,853</td>
<td>Ghate et al. 2011</td>
</tr>
<tr>
<td>Rivaroxaban 20mg</td>
<td>$19,411</td>
<td>$15,529</td>
<td>$23,293</td>
<td>Ghate et al. 2011</td>
</tr>
<tr>
<td>Aspirin</td>
<td>$18,594</td>
<td>$14,876</td>
<td>$22,313</td>
<td>Ghate et al. 2011</td>
</tr>
<tr>
<td>Clinically relevant non-major bleeding</td>
<td>$364</td>
<td>$291</td>
<td>$437</td>
<td>Ghate et al. 2011</td>
</tr>
</tbody>
</table>

Rate difference/10,000 person-years (rivaroxaban 10mg vs. aspirin) taken from EINSTEIN-CHOICE trial

<table>
<thead>
<tr>
<th></th>
<th>Recurrent DVT</th>
<th>Recurrent PE</th>
<th>All-cause mortality</th>
<th>Major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-217</td>
<td>-121</td>
<td>-51</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>-280</td>
<td>-180</td>
<td>-80</td>
<td>-30</td>
</tr>
<tr>
<td></td>
<td>-155</td>
<td>-63</td>
<td>-23</td>
<td>30</td>
</tr>
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</table>

Clinically relevant non-major bleeding  

<table>
<thead>
<tr>
<th>Rate difference/10,000 person-years (rivaroxaban 20mg vs. aspirin) taken from EINSTEIN-CHOICE trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent DVT</td>
</tr>
<tr>
<td>Recurrent PE</td>
</tr>
<tr>
<td>All-cause mortality</td>
</tr>
<tr>
<td>Major bleeding</td>
</tr>
<tr>
<td>Clinically relevant non-major bleeding</td>
</tr>
</tbody>
</table>

US=United States; DVT=deep vein thrombosis; PE=pulmonary embolism.
Table 2. Drug and Clinical Event Costs in Rivaroxaban and Aspirin Cohorts

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rivaroxaban</td>
<td>Aspirin</td>
</tr>
<tr>
<td></td>
<td>10mg [A]</td>
<td>[C]</td>
</tr>
<tr>
<td></td>
<td>20mg [B]</td>
<td></td>
</tr>
<tr>
<td>Drug cost assessed over a one-year time horizon</td>
<td>$3,389</td>
<td>$3,387</td>
</tr>
<tr>
<td>Total drug cost (per patient)</td>
<td>$282.38</td>
<td>$282.22</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Clinical event cost assessed over a one-year time horizon</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary efficacy (PE or DVT)</td>
<td>$1,014</td>
<td>$1,116</td>
<td>$3,042</td>
<td>-$2,028</td>
<td>-$1,926</td>
</tr>
<tr>
<td>Recurrent PE</td>
<td>$492</td>
<td>$480</td>
<td>$1,218</td>
<td>-$1,216</td>
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<tr>
<td>Recurrent DVT</td>
<td>$522</td>
<td>$636</td>
<td>$1,824</td>
<td></td>
<td></td>
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<tr>
<td>All-cause mortality</td>
<td>$374</td>
<td>$1,642</td>
<td>$1,434</td>
<td>-$1,060</td>
<td>$208</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>$78</td>
<td>$142</td>
<td>$84</td>
<td>-$5</td>
<td>$58</td>
</tr>
<tr>
<td>Clinically relevant non-major bleeding</td>
<td>$8</td>
<td>$10</td>
<td>$9</td>
<td>-$1</td>
<td>$1</td>
</tr>
<tr>
<td>Total clinical event cost (per patient)</td>
<td>$1,475</td>
<td>$2,910</td>
<td>$4,569</td>
<td>-$3,095</td>
<td>-$1,659</td>
</tr>
<tr>
<td>Per patient per month</td>
<td>$122.88</td>
<td>$242.52</td>
<td>$380.78</td>
<td>-$257.90</td>
<td>-$138.25</td>
</tr>
</tbody>
</table>

US=United States; PE=pulmonary embolism; DVT=deep vein thrombosis.
FIGURES LEGENDS

**Figure 1.** Per person per month (PPPM) costs for 12 months extended anticoagulation therapy following initial 6-12 months of anticoagulation therapy for patients with VTE

**Figure 2.** Per person per month (PPPM) costs for 12 months extended anticoagulation therapy following initial 6-12 months of anticoagulation therapy for patients with VTE, with 15% rivaroxaban discount

**Figure 3.** Total healthcare cost difference between rivaroxaban 10mg- and aspirin-treated patients estimated in one-way sensitivity analysis of input parameters

**Figure 4.** Total healthcare cost difference between rivaroxaban 10mg- and aspirin-treated patients estimated in one-way sensitivity analysis of input parameters, with 15% rivaroxaban discount
Cost Difference Rivaroxaban 10 mg vs. Aspirin = $24
Cost Difference Rivaroxaban 20 mg vs. Aspirin = $143

Drug cost
Clinical event cost

*numbers have been rounded
Cost Difference Rivaroxaban 10 mg vs. Aspirin = -$19
Cost Difference Rivaroxaban 20 mg vs. Aspirin = $101

- Drug cost
- Clinical event cost

*Numbers have been rounded
Drug cost
All-cause mortality rate difference
Recurrent DVT rate difference
Recurrent PE rate difference
Recurrent DVT cost
All-cause mortality cost
Recurrent PE cost
Major bleeding rate difference
Clinically relevant non-major bleeding rate difference
Major bleeding cost
Clinically relevant non-major bleeding cost

Cost difference in favor of Rivaroxaban 10 mg
Cost difference in favor of Aspirin

Per Patient Per Month Total Cost Difference (2016 US$)
Cost difference in favor of Rivaroxaban 10 mg

Cost difference in favor of Aspirin

Per Patient Per Month Total Cost Difference (2016 US$)
Articles included in the review were published between 2008/01/01 and 2017/03/22. One investigator (DL) reviewed each article to determine if the study was potentially eligible based on the following criteria: (1) publication is available in English, and (2) publication has a US perspective. Titles and abstracts were then reviewed by two investigators (GPB and DL) and 36 studies were selected for full-text review. Disagreements were resolved through consensus.

**Literature search strategy:** Medline accessed via https://www.ncbi.nlm.nih.gov/pubmed/


**e-Figure 1. Flowchart of Study Selection Process**

[Flowchart diagram]

Potentially relevant articles identified through PubMed search (N = 309)

Articles excluded due to:
- Publication is not available in English (N = 19)
- Publication does not have a US perspective (N = 77)

Eligible publications after abstract screening (N = 30)

Articles excluded after title and abstract evaluation (N = 113)

Full-text articles retrieved from cross-references and hand searching (N = 6)

Articles excluded after full-text review (N = 29)

Included articles (N = 7)