

Health-care Cost Impact of Continued Anticoagulation With Rivaroxaban vs Aspirin for Prevention of Recurrent Symptomatic VTE in the EINSTEIN-CHOICE Trial Population



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BACKGROUND: Using data from the Reduced-Dose 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 health-care costs (2016 USD) 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 DVT, 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 10 mg, rivaroxaban 20 mg, and aspirin, respectively). However, vs aspirin, PPPM total health-care costs were \$24 higher for patients treated with rivaroxaban 10 mg (\$143 higher for rivaroxaban 20 mg) due to higher cost of rivaroxaban. With a 15% discount for rivaroxaban 10 mg, 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 health-care cost.

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

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KEY WORDS: anticoagulants; aspirin; cost comparison; economic analysis; extended treatment; rivaroxaban; recurrent VTE

ABBREVIATIONS: DOT = duration of treatment; EINSTEIN-CHOICE trial = Reduced-Dose Rivaroxaban in the Long-Term Prevention of Recurrent Symptomatic Venous Thromboembolism; PE = pulmonary embolism; PPPM = per patient per month; SLR = systematic literature review; WAC = wholesale acquisition cost

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VTE, comprising pulmonary embolism (PE) and DVT, is the third leading cause of cardiovascular-associated death and presents a significant health-care and economic burden in the United States.¹ VTE recurrence has been estimated to occur in approximately 5% to 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 to 12 months of the initial VTE is often not undertaken because of the perception that bleeding may outweigh the benefits of continued therapy.⁵ The Reduced-Dose Rivaroxaban in the Long-Term Prevention of Recurrent Symptomatic Venous Thromboembolism (EINSTEIN-CHOICE) trial compared efficacy and safety of treatment with rivaroxaban (10 and 20 mg daily) vs aspirin (100 mg daily)

following 6 to 12 months of initial anticoagulation therapy. The 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 ED 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 postthrombotic syndrome 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 with rivaroxaban vs aspirin, using event rates from the EINSTEIN-CHOICE trial and cost data from the 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 10 mg daily: 1,127; rivaroxaban 20 mg daily: 1,107; and aspirin: 1,131) with confirmed symptomatic DVT and/or PE who had been treated for 6 to 12 months with anticoagulants. Patients were monitored for up to 12 months, during which symptomatic recurrent VTE and major bleeding were measured.⁵

Cost Analysis Framework

A cost comparison analysis was conducted to compare total health-care direct costs in patients with VTE who received extended treatment with daily rivaroxaban 10 and 20 mg vs daily aspirin 100 mg. Total health-care costs comprised drug cost and clinical event cost and were assessed over a 1-year time horizon and converted to per patient per month (PPPM) costs.

Total health-care cost

= Drug costs + 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 costs for five event types reported in EINSTEIN-CHOICE (recurrent DVT, recurrent PE, major bleeding, clinically relevant nonmajor 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 1-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 health-care insurance claims databases. No amounts representing charges were used as cost estimates in this analysis.

Cost Analysis Inputs

Duration of Treatment: The proportions of patients in the EINSTEIN-CHOICE trial with 6, 9 to 12, and 12 months of 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 (10 and 20 mg) and the aspirin cohort, obtained from EINSTEIN-CHOICE, are presented in Table 1.

Unit Costs: The unit cost of rivaroxaban was estimated on the basis of the 2016 wholesale acquisition cost (WAC) package price from Red Book.⁸ The monthly unit cost was estimated at \$359.61 for a 30-pill package of 10- or 20-mg daily dose rivaroxaban. Since the 100-mg aspirin package price is not available in Red Book, the

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drug price of \$3.67 for a 90-pill package of 81-mg aspirin tablets was used.

The 1-year cost of care for patients with a clinical event compared with patients without an event was determined by conducting a systematic literature review (SLR) in the MEDLINE (via PubMed) database. The search strategy and flowchart (e-Fig 1) of study selection process are available in the online article. The SLR identified 309 studies reporting VTE and bleeding costs, and 36 were considered eligible. After a full-text review of the titles, seven 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 health-care costs associated with recurrent VTE (vs nonrecurrent VTE) estimated in two studies: \$62,181 by Lefebvre et al⁷ and \$59,784 by Lin et al¹ (both in 2016 US dollars). As a result of the SLR, we identified two additional articles, by Amin et al,^{9,10} that reported incremental cost of recurrent VTE and both studies cited findings from Lefebvre et al. The unit cost for a major bleeding event was based on a study assessing the incremental annual total all-cause health-care cost associated with major GI bleeding (vs no

bleeding) among warfarin-treated patients with atrial fibrillation,¹¹ taking into account differences in severity (ie, 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 10 mg, rivaroxaban 20 mg, and aspirin cohorts, respectively. The unit cost for clinically relevant nonmajor bleeding was set at \$364 based on the estimated annual incremental cost associated with minor GI bleeding (vs no bleeding) from the same study.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 was reported as the average cost due to life loss in a VTE population.^{12,13} This human capital method estimates the value of labor taking into account life expectancy, work force composition, earnings by age, and the discount rate. On the basis of the Mahan et al¹² methodology, present value of lifetime earnings was weighted, by sex and age, to reflect a VTE population (ie, 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).

TABLE 1] Base-Case Inputs and Ranges Used in One-Way Sensitivity Analysis

Input Parameter	Base-Case Input	Lower Limit	Upper Limit	Reference(s)
Unit cost (2016 USD)				
Rivaroxaban (10 and 20 mg) cost, monthly	\$359.61	\$287.69	\$431.53	Red Book ⁸
Aspirin cost, monthly	\$1.22	\$0.98	\$1.46	Red Book ⁸
Recurrent DVT	\$60,000	\$48,000	\$72,000	Lin et al ¹ ; Lefebvre et al ⁷
Recurrent PE	\$60,000	\$48,000	\$72,000	Lin et al ¹ ; Lefebvre et al ⁷
All-cause mortality	\$207,862	\$166,290	\$249,435	Mahan et al ¹³ ; Mahan et al ¹²
Major bleeding				
Rivaroxaban 10 mg	\$17,378	\$13,902	\$20,853	Ghate et al ¹¹
Rivaroxaban 20 mg	\$19,411	\$15,529	\$23,293	Ghate et al ¹¹
Aspirin	\$18,594	\$14,876	\$22,313	Ghate et al ¹¹
Clinically relevant nonmajor bleeding	\$364	\$291	\$437	Ghate et al ¹¹
Rate difference/10,000 person-years (rivaroxaban 10 mg vs aspirin) taken from EINSTEIN-CHOICE trial				
Recurrent DVT	-217	-280	-155	Weitz et al ¹⁴
Recurrent PE	-121	-180	-63	Weitz et al ¹⁴
All-cause mortality	-51	-80	-23	Weitz et al ¹⁴
Major bleeding	0	-30	30	Weitz et al ¹⁴
Clinically relevant nonmajor bleeding	-34	-124	56	Weitz et al ¹⁴
Rate difference/10,000 person-years (rivaroxaban 20 mg vs aspirin) taken from EINSTEIN-CHOICE trial				
Recurrent DVT	-198	-266	-130	Weitz et al ¹⁴
Recurrent PE	-123	-174	-72	Weitz et al ¹⁴
All-cause mortality	10	-28	48	Weitz et al ¹⁴
Major bleeding	28	-8	64	Weitz et al ¹⁴
Clinically relevant nonmajor bleeding	29	-61	119	Weitz et al ¹⁴

EINSTEIN-CHOICE = Reduced-Dose Rivaroxaban in the Long-Term Prevention of Recurrent Symptomatic Venous Thromboembolism; PE = pulmonary embolism; USD = US dollars.

Sensitivity Analysis

To account for uncertainties surrounding inputs, a one-way sensitivity analysis was conducted, in which the total health-care 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 SD of rate difference derived from the

corresponding 95% confidence intervals obtained from the EINSTEIN-CHOICE trial (Table 1).¹⁴

Moreover, WAC drug prices are frequently negotiated in the US health-care market with rebates and discounts.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 20-mg cohort (Table 2). Compared with the aspirin cohort, PPPM costs for bleeding events were lower for the rivaroxaban 10-mg cohort, but not for the rivaroxaban 20-mg cohort.

Rivaroxaban users had lower PPPM clinical event costs compared with aspirin users (\$123, \$243, and \$381 for rivaroxaban 10 mg, rivaroxaban 20 mg, and aspirin, respectively). The expected loss of lifetime earnings for 12 months on rivaroxaban 10 and 20 mg was \$1,060 lower and \$208 higher per patient, respectively, compared with the aspirin cohort. The higher drug cost of rivaroxaban vs aspirin made total health-care costs for patients treated with rivaroxaban exceed those treated with aspirin (Fig 1).

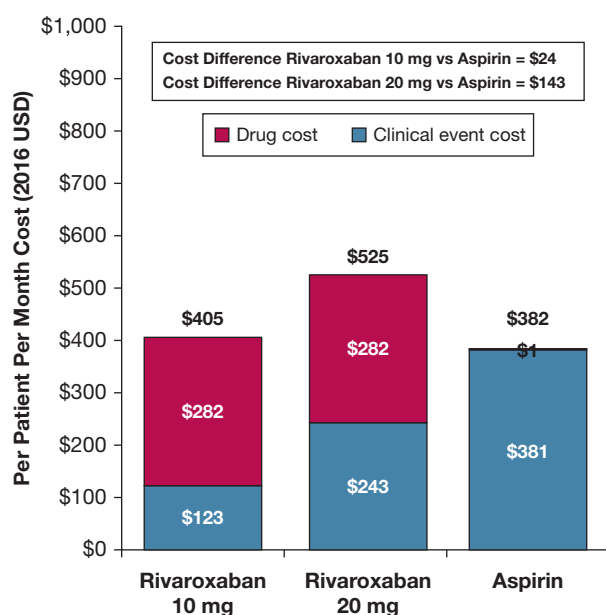
With a 15% discount for rivaroxaban 10 mg, lower clinical events cost for rivaroxaban-treated patients more than fully offset higher drug costs and yielded a \$19 lower PPPM total health-care cost (Fig 2). With a 15% discount for rivaroxaban 20 mg, PPPM total health-care costs remained higher than for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

The one-way sensitivity analysis for rivaroxaban 10 mg vs aspirin is illustrated in Figure 3. Inputs at the top have the highest impact on the total health-care cost difference between cohorts. Drug cost was the leading cost driver; the total health-care cost difference became in favor of rivaroxaban 10 mg when lower drug costs or greater rate differences were assessed. Varying other inputs had a smaller impact on total health-care 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 (Fig 4). For the comparison of rivaroxaban 20 mg vs aspirin, the cost

TABLE 2] Drug and Clinical Event Costs in Rivaroxaban and Aspirin Cohorts

Outcome	Event Cost (2016 USD)			Cost Difference (2016 USD)	
	Rivaroxaban 10 mg [A]	Rivaroxaban 20 mg [B]	Aspirin [C]	Rivaroxaban 10 mg vs Aspirin: [A] – [C]	Rivaroxaban 20 mg vs Aspirin: [B] – [C]
Drug cost assessed over a 1-y time horizon					
Total drug cost (per patient)	\$3,389	\$3,387	\$12	\$3,377	\$3,375
Per patient per month	\$282.38	\$282.22	\$0.96	\$281.43	\$281.26
Clinical event cost assessed over a 1-y time horizon					
Primary efficacy (PE or DVT)	\$1,014	\$1,116	\$3,042	–\$2,028	–\$1,926
Recurrent PE	\$492	\$480	\$1,218		
Recurrent DVT	\$522	\$636	\$1,824		
All-cause mortality	\$374	\$1,642	\$1,434	–\$1,060	\$208
Major bleeding	\$78	\$142	\$84	–\$5	\$58
Clinically relevant nonmajor bleeding	\$8	\$10	\$9	–\$1	\$1
Total clinical event cost (per patient)	\$1,475	\$2,910	\$4,569	–\$3,095	–\$1,659
Per patient per month	\$122.88	\$242.52	\$380.78	–\$257.90	–\$138.25

Numbers have been rounded. See Table 1 legend for expansion of abbreviations.



*numbers have been rounded

Figure 1 – Per patient per month costs for 12 months of extended anticoagulation therapy following initial 6 to 12 months of anticoagulation therapy for patients with VTE. Numbers have been rounded.

difference remained in favor of aspirin in the sensitivity analysis across all inputs (data not shown).

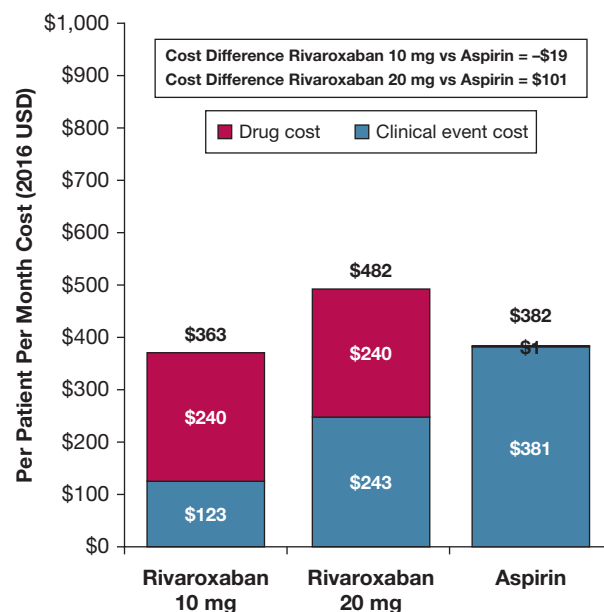
Discussion

In our cost comparison analysis, continued anticoagulation therapy with rivaroxaban 10 and 20 mg in patients with VTE who had completed 6 to 12 months of initial anticoagulation therapy was associated with lower clinical event costs, but higher total health-care costs, compared with 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 health-care cost difference, which became in favor of rivaroxaban 10 mg 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 10 mg had a lower total health-care cost than aspirin after discount.

Appropriate treatment of VTE and reducing the risk of recurrent VTE constitute an increasing public health

priority.^{16,17} The substantial burden of these events led the US Surgeon General in 2008 to focus on countering the projected VTE trend¹⁸; this continues to be one of 11 core areas of the US Department of Health and Human Services for improving patient safety.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.²⁰ Multiple VTE events are associated with increased risk of chronic complications, including pulmonary hypertension and postthrombotic syndrome,²¹ with burden and costs extending beyond the 1-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.²² Nonetheless, our analyses offer an indication of costs due to all-cause premature death in the VTE population at the 1-year time horizon. Specifically, the study's estimated loss of income for these patients over 1 year of treatment (ie, 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 10 mg, rivaroxaban 20 mg, and aspirin, respectively). Future studies assessing costs over a longer period using alternative economic approaches, such as cost-effectiveness analyses, are warranted.



*numbers have been rounded

Figure 2 – Per patient per month costs for 12 months of extended anticoagulation therapy following initial 6 to 12 months of anticoagulation therapy for patients with VTE, with 15% rivaroxaban discount. Numbers have been rounded.

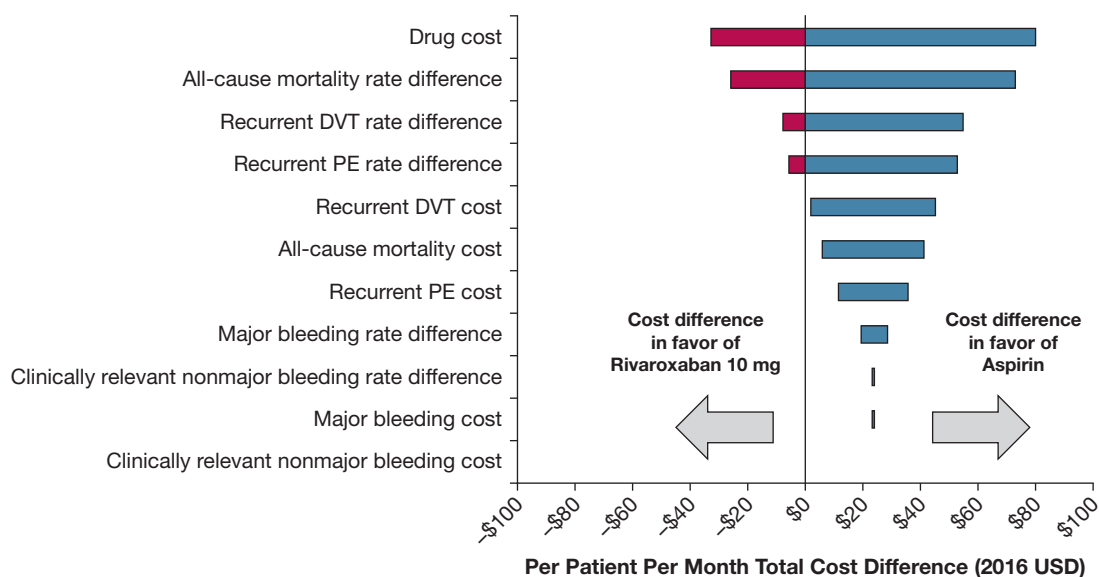


Figure 3 – Total health-care cost difference between patients treated with rivaroxaban 10 mg and patients treated with aspirin, estimated by one-way sensitivity analysis of input parameters. PE = pulmonary embolism.

This study is subject to some limitations. First, since patient-level health-care utilization data were not collected in the EINSTEIN-CHOICE trial, clinical event costs were estimated on the basis of clinical event rates from the trial and unit costs for events from the literature while real-world costs for treating clinical events may vary across hospitals/centers. However, the one-way sensitivity analysis varying unit cost yielded results consistent with the base-case analysis, suggesting that the study findings of rivaroxaban's association with lower total health-care cost compared with aspirin when

a 15% drug discount is applied are robust across a range of relevant costs. Second, actual costs associated with a major bleed while receiving rivaroxaban are not available and it is possible the costs differ from those of a major bleed while receiving 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 on Thrombosis and Haemostasis definition), intracranial hemorrhage, and death. We chose this in order to be conservative and

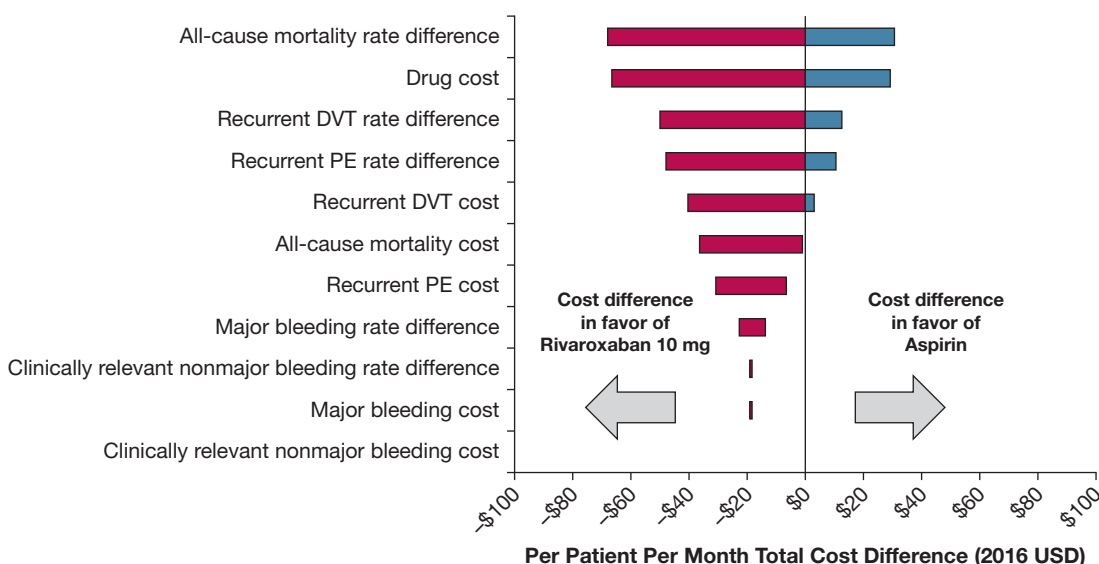


Figure 4 – Total health-care cost difference between patients treated with rivaroxaban 10 mg and patients treated with aspirin, estimated by one-way sensitivity analysis of input parameters, with 15% rivaroxaban discount. See Figure 3 legend for expansion of abbreviation.

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 $\pm 20\%$ 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 (eg, stroke) reported in the EINSTEIN-CHOICE trial as these outcomes were rare and not reported differentially between treatments. Fifth, the assumption of equal health-care costs prior to clinical events may not be true for patients who developed clinical events earlier vs later during follow-up. In addition, 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.²³ A wealth of data has now demonstrated that direct oral anticoagulants are safe, effective, and convenient. The EINSTEIN-CHOICE study demonstrates that 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 cases profoundly.²⁴ 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 in real-world settings patients have more comorbidities and are more susceptible to recurrence, which would increase savings associated with rivaroxaban.²⁵ Finally, although unit cost assumptions in this study were based on the US health-care system, the EINSTEIN-CHOICE trial was conducted in an international setting; differences in health-care systems may have affected the results of this study.

Conclusions

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

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Additional information: The e-Figure can be found in the Supplemental Materials section of the online article.

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