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Anticoagulant Therapy for Cancer-Associated Thrombosis:

A Cost-Effectiveness Analysis

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Abstract

Background: Direct oral anticoagulants (DOACs) offer an alternative to low-molecular-weight heparin (LMWH) and warfarin for treating cancer-associated thrombosis (CAT).

Objective: To determine the cost and effectiveness of DOACs versus LMWH.

Design: Cohort-state transition decision analytic model.

Data Sources: Network meta-analysis comparing DOACs versus LMWH.

Target Population: Adult patients with cancer at the time they develop thrombosis.

Time Horizon: Lifetime.

Perspective: Health care sector.

Intervention: Strategies of 1) enoxaparin, 2) apixaban, 3) edoxaban, and 4) rivaroxaban for treatment of CAT.

Outcome Measures: Incremental cost-effectiveness ratio (ICER) in 2022 U.S. dollars per quality-adjusted life-year (QALY) gained.

Results of Base-Case Analysis: In the base-case scenario, using drug prices from the U.S. Department of Veterans Affairs Federal Supply Schedule, apixaban dominated enoxaparin and

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Author contributions are available at Annals.org.

edoxaban by being less costly and more effective. Rivaroxaban was slightly more effective than apixaban, with an ICER of $493246. In a scenario analysis using “real-world” drug prices from GoodRx, rivaroxaban was cost-effective with an ICER of $50053 per QALY.

Results of Sensitivity Analysis: Results were highly sensitive to monthly drug costs. Probabilistic sensitivity analyses showed that at a willingness-to-pay threshold of $50 000 per QALY, apixaban was preferred in 80% of simulations. However, sensitivity analyses also demonstrated that apixaban only remained cost-effective if monthly medication costs were below $530. Above this, rivaroxaban became cost-effective.

Limitations: An assumption was made that patients would continue anticoagulation indefinitely unless they suffered a major bleed. Nonmedical costs such as patient and caregiver loss of productivity were not accounted for, and long-term thrombotic complications were not explicitly modeled.

Conclusion: The 3 DOACs are more effective and more cost-effective than LMWH. The most cost-effective DOAC depends on the relative cost of each of these agents. These are important considerations for treating physicians and health policymakers.

Cancer-associated thrombosis (CAT) results in an almost 2-fold increase in mortality compared with matched patients with cancer without venous thromboembolism (VTE) (1, 2). Compared with others, patients with CAT are at a higher risk for recurrent VTE due to factors such as immobilization, surgery, and systemic therapies (3, 4). Bleeding as a complication of anticoagulant use is also seen at a higher rate in patients with cancer due to coexistent comorbidities, including chemotherapy-induced thrombocytopenia and luminal location of cancer (5). Beyond its detrimental effect on survival and quality of life (QOL), VTE exacts an additional economic burden on patients and the health care system. In a large population-based study, total (all-cause) health care costs were approximately 80% higher in patients with cancer with VTE as compared with a matched cohort of patients with cancer without VTE (U.S. dollars, $74959 vs. $41691) (6).

Heparin and low-molecular-weight heparin (LMWH) formulations such as enoxaparin, dalteparin, and tinzaparin monotherapy have been the cornerstone of prophylaxis and treatment of CAT, based on trial results (7–9). More recently, direct oral anticoagulants (DOACs)—including direct Xa inhibitors (rivaroxaban, apixaban, and edoxaban) and direct thrombin inhibitors (dabigatran)—have come into clinical use. The DOACs were compared with LMWH (dalteparin) in phase 3 clinical trials (10–13). Although these studies lacked the power to demonstrate statistically significant improvements in the efficacy of reducing recurrent VTE risk, a more contemporary network meta-analysis combining DOACs has shown a statistically significant decrease in recurrent VTE risk compared with both LMWH and warfarin (relative risk [RR], 0.75 [95% CI, 0.59 to 0.94], P= 0.020; RR, 0.51 [CI, 0.39 to 0.66], P<0.001) (14).

Here, we explore the cost and effectiveness of the 3 common DOACs (apixaban, edoxaban, and rivaroxaban) and enoxaparin for the treatment of CAT and prevention of recurrent VTE using a Markov state transition decision analytic model. Clinical management decisions ultimately depend on an in-depth discussion about patient values and preferences regarding ease of use, patient comorbidities, and insurance capabilities, which a traditional cost-

effectiveness analysis does not address. This analysis could, however, inform stakeholders (clinicians, patients, and health policymakers) and help them make decisions about using these drugs in the "real-world" clinical setting.

METHODS

Efficacy and Bleeding Risk Data From Randomized Clinical Trials

The clinical trials that led to the incorporation of DOACs in the management of CAT are described in detail in Supplement Table 1 (available at Annals.org). Briefly, the Hokusai VTE Cancer noninferiority trial compared edoxaban with dalteparin (10). At a follow-up of 6 months, the primary outcome of recurrent VTE was lower in the edoxaban group (6.5% vs. 8.6%; hazard ratio [HR], 0.75 [CI, 0.48 to 1.17]). The SELECT-D (Anticoagulation Therapy in Selected Cancer Patients at Risk of Recurrence of Venous Thromboembolism) trial compared rivaroxaban with dalteparin (11). The cumulative probability of VTE recurrence at 6 months was again lower in the rivaroxaban group (4% vs. 11%; HR, 0.43 [CI, 0.19 to 0.99]). Two trials compared apixaban with dalteparin: the ADAM-VTE (Apixaban and Dalteparin in Active Malignancy Associated Venous Thromboembolism) trial with a smaller patient population (n= 287) (12) and the larger phase 3 noninferiority Caravaggio trial (13). The primary efficacy outcome of recurrent VTE in the Caravaggio study was seen in 5.6% versus 7.9% of patients (HR, 0.63 [CI, 0.37 to 1.07]; P< 0.001 for noninferiority).

Instead of individual trials, we used a recently published network meta-analysis of the 4 clinical trials described above, comparing individual DOACs to LMWH (14) to obtain relative hazards and 95% CIs of recurrent VTE, major bleeding (MB), and clinically relevant nonmajor bleeding (CRNMB) for each of the DOACs for the model. Although, when combined, the risk for recurrent VTE was significantly lower with DOACs compared with LMWH (RR, 0.75 [95% CI, 0.59 to 0.94]), individually, none of the DOACs had a significantly lower risk for VTE recurrence (RR for recurrent VTE on apixaban vs. LMWH, 0.66 [CI, 0.42 to 1.02]; RR for recurrent VTE on edoxaban vs. LMWH, 0.79 [CI, 0.55 to 1.12]; RR for recurrent VTE on rivaroxaban vs. LMWH, 0.74 [CI, 0.43 to 1.26]). For MB and CRNMB, there was no difference between DOACs and LMWH. Details of input parameters from the pooled meta-analysis are shown in Table 1. Nevertheless, we used the RRs and 95% CIs from this meta-analysis to inform our decision model, using the described parameter uncertainty to perform probabilistic sensitivity analyses using second-order Monte Carlo techniques.

Overview of Decision Analytic Model

We used Decision Maker software (20) to develop a Markov cohort state transition model to analyze the cost-effectiveness of strategies including apixaban, edoxaban, rivaroxaban, and enoxaparin for the treatment of CAT. We modeled event rates for recurrent pulmonary embolism (PE) and deep venous thrombosis (DVT), MB, and CRNMB relative to rates among patients with cancer receiving LMWH. Event rates for patients receiving LMWH were calculated using weighted average of events. Patients were pooled from the 3 studies (Hokusai, SELECT-D, and Caravaggio (10, 11, 13). We calculated a weighted average for each of the event rates as shown in Supplement Table 2 (available at Annals.org). After

deriving annual event rates from these studies, we calculated 1-month transition probabilities (TP) using theformula: $TP = 1 - e^{-rt}$, where r is the annual event rate and t is (1/12) of a year.

The simulation model contained 4 health states for each patient. The first state included patients 1) otherwise well on anticoagulation (Well_AC). The second and third states included 2) patients after an MB event (anticoagulation was discontinued indefinitely [POST MAJOR BLEED]) and 3) patients who developed a CRNMB episode and entered a 1-month-long temporary state during which anticoagulation was stopped (POST CRNMB); absent further events they returned to the Well_AC state in the next cycle. These patients were transiently assumed to be at a higher risk for developing recurrent VTE and a lower risk for MB due to not receiving anticoagulation. The final state was 4) the terminal health state [DEAD]. These states, along with the model, are shown in the Appendix Figure (available at Annals.org). We used a 1-month cycle length and a lifetime horizon. In each cycle, patients faced chance events, including recurrent VTE, MB, CRNMB, death from recurrent VTE, death from MB, and death from other nonexplicitly modeled causes. We used an annual discount rate of 3% for both costs and effectiveness as recommended by the Second Panel on Cost-Effectiveness in Health and Medicine (21). In addition, the analytic perspective (health care payer rather than societal) to determine which costs and benefits to include in this cost-effectiveness analysis were also based on guidelines from the Second Panel (22). We used the 2022 CHEERS (Consolidated Health Economic Evaluation Reporting Standards) checklist to guide our analysis (see the Supplement Checklist, available at Annals.org) (23).

Model Assumptions

We made several simplifying assumptions. 1) For the base-case scenario analysis, we used enoxaparin rather than dalteparin because this is the more commonly used LMWH formulation in the United States. We assumed enoxaparin had similar efficacy and adverse event profile to dalteparin, as supported by studies such as the RIETE (Registro Informatizado de la Enfermedad TromboEmbólica) CAT study (24). Studies in other noncancer scenarios have yielded similar results (25, 26). 2) We assumed that treatment efficacy and bleeding complications were constant across the lifetime of each patient. Treatment crossovers only occurred after nonfatal MB, when anticoagulant therapy was discontinued indefinitely. The decreased QOL and costs after nonfatal MB and CRNMB were temporary, lasting for a single 1-month cycle. Thus, survivors of MB events and those suffering CRNMB did not face longer-term morbidity or costs after the first month postbleed. 3) We assumed a constant continued risk for recurrent VTE in patients with cancer over time. Although there is limited information about the risks and benefits of anticoagulation beyond 6 months in patients with cancer, there is consensus among experts that this should be considered for select patients (27). In the single-group DALTECAN (Dalteparin Sodium for the Long-Term Management of Venous Thromboembolism in Cancer Patients) trial in which patients with CAT received extended treatment with dalteparin, the risk for recurrent VTE was 5.7% during month 1, 3.4% during months 2 to 6, and 4.1% during months 7 to 12, suggesting that the risk for thrombosis did not decrease over time, despite receipt of anticoagulation (28). 4) We assumed that patients

whose anticoagulant therapy was discontinued after nonfatal MB were no longer at risk for bleeding events but were at risk for developing a recurrent VTE. The RR for recurrent VTE was used from the literature at 2.14 in the model (29, 30). Patients sustaining CRNMB had anticoagulation discontinued for 1 month, and during the 1 month, they were at increased risk for recurrent VTE at the same rate and decreased risk for bleeding. Patients surviving MB had anticoagulation discontinued for the rest of their lives. We assumed that patients whose anticoagulant therapy was discontinued after nonfatal MB were no longer at risk for bleeding events but were at increased risk for developing a recurrent VTE, due to cessation of anticoagulation at the RR just described in this section. They were taken off anticoagulation for the rest of their life given the higher risk versus benefit situation. 5) We assumed CRNMB to be nonfatal; these patients were taken off anticoagulation for a month and then anticoagulation was resumed. 6) We assumed that decrements in QOL were multiplicative (see details in the next section). 7) Finally, we assumed that mortality associated with either recurrent VTE or MB was the same, regardless of the treatment strategy.

Model Inputs: Costs and Utilities

Patients entered the model at the time they developed CAT. We used a starting age of 63 years for the base-case analysis (as this was the average age of patients included in the network meta-analysis) (14). We used literature to find base-case values for utility weights for patients with cancer and those with cancer and VTE, MB, or CRNMB (Table 1). Patients were assigned a base utility of 0.645, a value adapted from the literature for patients with cancer without distant metastasis residing in the United States (19). We assumed that decrements in QOL were multiplicative. This assumption was based on the recommendation that the multiplicative method for utility adjustment should be used when there is only 1 comorbid condition (31). For instance, although the base-case quality adjustment for cancer with prior VTE was 0.645, those also receiving LMWH had an additional 1% reduction in quality-adjusted life-years (QALYs). Therefore, the adjusted utility for such a patient would be 0.645 × 0.99, or 0.639. Due to the paucity of literature evaluating QOL while taking DOACs, we assumed no decrement in QOL for patients taking any of the DOACs (that is, no relative utility decrement, 0%) (9). Cost estimates were evaluated from a health care sector perspective. These included costs of the anticoagulant medication, costs of complications (MB, CRNMB, recurrent VTE), and the cost of clinic visits, including ancillary laboratory studies. Monthly costs for each cycle were derived from 30-day prescription costs at the labeled dosing frequency (daily for dalteparin, rivaroxaban, and edoxaban, twice daily for apixaban and enoxaparin) and are shown in Supplement Table 3 (available at Annals.org). As recommended by the Second Panel on Cost-Effectiveness in Health and Medicine, we used the U.S. Department of Veterans Affairs Federal Supply Schedule (VA-FSS) to obtain drug costs to reflect the social marginal costs of drugs for base-case analyses (15, 21). We performed an additional scenario analysis using average prices from GoodRx (price averaged across 3 pharmacies) to better reflect real-world costs for each drug (32). The short-term costs of adverse events, such as recurrent VTE and bleeding episodes, were obtained from the literature (16, 17). All cost estimates from the literature were inflated to third-quarter 2022 U.S. dollars using the personal consumption expenditure index for health care (33).

Statistical Analysis

Base Case—Model parameter inputs for the base case are shown in Table 1. As described herein, in our base-case analysis, we determined unit drug costs from the VA-FSS (see Table 1). Relative hazards for the rates of recurrent VTE, MB, and CRNMB, along with their 95% CIs were obtained from a network meta-analysis (14). We evaluated the calibration of our model by comparing the cumulative probability of major outcomes predicted by the model with those from the described clinical trials at 6 and 12 months (Supplement Table 4, available at Annals.org). In each 1-month cycle, patients faced a chance of death from nonexplicitly modeled causes, including their underlying cancer. Patients could proceed through tunnel states, where they could die of nonexplicitly modeled causes or face excess mortality related to the thromboembolic event or bleeding. We used Centers for Disease Control and Prevention (CDC) life tables for the U.S. population to calculate background mortality rates based on age (34). Based on cumulative 5-year cancer mortality of 67% from previously published literature (35), we calculated an excess cancer-specific mortality rate of 0.22 per cycle. The composite mortality rate was calculated by adding the lifetable-based annual mortality rate with the cancer excess mortality rate and then calculating the monthly transition probability as described earlier (Table 1).

We calculated the incremental cost-effectiveness ratio (ICER) as the difference in cost divided by the difference in effectiveness for each increasingly costly strategy. As suggested by the World Health Organization, we used a willingness-to-pay (WTP) threshold of less than 1 times the average per capita gross domestic product to describe a strategy as highly cost-effective and a WTP greater than 3 times the average per capita gross domestic product to denote a strategy as NOT cost-effective (36). This would result in WTP thresholds of roughly $50000 per QALY and $150000 per QALY; we used a WTP threshold of $50000 per QALY, although we realize that this has been noted to be a conservative threshold in the United States (37–39).

Sensitivity Analyses—We performed 1-way deterministic sensitivity analyses to examine the effect of changes in parameter values, including relative hazards of recurrent VTE, MB, and CRNMB for each treatment strategy; QOL on LMWH and oral anticoagulant therapy; cost of LMWH, apixaban, and rivaroxaban; and cost of complications such as recurrent VTE, MB, and CRNMB. We also performed a 2-way sensitivity analysis examining the cost of apixaban and its efficacy (relative hazard for recurrent VTE vs. LMWH) using real-world drug costs from GoodRx. Finally, we performed probabilistic sensitivity analyses (PSAs) to examine the global effect of uncertainty in parameter estimates for both the base-case model and the scenario analysis using real-world prices from GoodRx (see next section). We conducted PSAs using 10000 second-order Monte Carlo simulations, using β and logit distributions for probabilities and utilities, and lognormal distributions for costs and relative hazards. In the PSA using the real-world scenario for drug costs, we used fixed costs based on GoodRx prices, but used distributions for all other parameters, as in the base-case PSA.

Scenario Analyses

We conducted 2 separate scenario analyses. 1) Because drug costs noted in the VA-FSS may not be reflective of real-world costs to patients, we conducted the first alternative scenario analysis using the average costs of enoxaparin and the 3 DOACs from 3 major pharmacies as reported in GoodRx (29). 2) In our second scenario analysis, we used dalteparin as the LMWH strategy because this was the agent used as the comparator group in clinical trials included in the meta-analysis. We conducted 2 subscenarios with dalteparin (VA-FSS and GoodRx costs, respectively).

Role of the Funding Source

No funding was received for this study.

RESULTS

Base-Case Results

We performed our base-case analysis for a 63-year-old patient with CAT using drug costs from the VA-FSS. As shown in Base-case analysis in Table 2, apixaban was the least costly anticoagulant and was more effective than either LMWH or edoxaban. However, rivaroxaban was slightly more effective than apixaban, with an ICER of $493246 per QALY.

Scenario Analyses

In the first scenario analysis (using the average costs of enoxaparin and DOACs from 3 pharmacies listed on GoodRx; Real-world scenario analysis in Table 2), rivaroxaban had an ICER of $50053 per QALY. The second scenario analysis used costs for dalteparin instead of enoxaparin. **Panel A of** Supplement Table 5 (available at Annals.org) shows results using costs from the VA-FSS. Apixaban is favored, being the least costly strategy. Although rivaroxaban is slightly more effective, it is not cost-effective, having an ICER of $493246. **Panel B** of Supplement Table 5 shows results using costs from GoodRx. In this analysis, rivaroxaban is favored with an ICER of $50053.

Deterministic Sensitivity Analyses

Results were highly sensitive to monthly anticoagulant costs. As shown in the left panel of Figure 1, in our real-world scenario analysis using drug costs derived from GoodRx, apixaban was cost-effective (ICER ≤ $50000 per QALY) until its monthly cost exceeded $530. Above this cost, rivaroxaban was favored with an ICER of $50053 per QALY. Thus, using real-world monthly costs of apixaban from GoodRx, rivaroxaban is more cost-effective. In the **right panel** of Figure 1, the monthly cost of rivaroxaban is examined. Rivaroxaban is preferred at lower monthly costs, but the ICER exceeds $50000 per QALY at $535. However, it is still more cost-effective than apixaban until rivaroxaban's monthly cost exceeds $570. At this point, apixaban has an ICER of $61791 per QALY. As shown in Figure 2, we performed a 2-way sensitivity analysis to examine the effect of changes in both the monthly cost of apixaban and the efficacy of apixaban (relative hazard of recurrent PE vs. LMWH). For this analysis, we also used the monthly cost of LMWH derived from GoodRx. We examined 3 different thresholds for WTP, $50000 per QALY (highly

cost-effective), $100000 per QALY, and $150000 per QALY (cost-effective). Apixaban is favored in regions where the monthly cost is lower, and the HR of recurrent VTE with apixaban vs. LMWH is low (that is, greater efficacy of apixaban). Using the real-world cost of apixaban, this strategy falls right on the $50000 per QALY WTP threshold line.

Probabilistic Sensitivity Analyses

We performed 2 probabilistic sensitivity analyses using 10000 iterations of a second-order Monte Carlo simulation. The first analysis used the base-case model with drug costs derived from the VA-FSS (top panel of Figure 3). Apixaban was favored across a wide range of WTP thresholds. At WTP thresholds of $50000 per QALY and $150000 per QALY, apixaban was favored in 80% and 64% of simulations, respectively. At a WTP threshold of $150000 per QALY, apixaban was favored 95.9% of the time, whereas LMWH was favored 4.1% of the time. In the second analysis, drug prices were fixed at realworld levels using GoodRx pharmacy prices (bottom panel of Figure 3). At WTP thresholds under $50000 per QALY, edoxaban was favored. At a WTP threshold of approximately $60000 per QALY, edoxaban and rivaroxaban were equally favored in 37% of simulations. At WTP thresholds above this, rivaroxaban was the most cost-effective.

DISCUSSION

We present a cost-effectiveness analysis of the 4 most utilized anticoagulation strategies for CAT. In our base-case analysis, we used HRs of MB, CRNMB, and recurrent VTE (compared with LMWH) from a network meta-analysis of the 4 phase 3 clinical trials (Hokusai, SELECT-D, ADAM-VTE, and Caravaggio) (10–13), thus using the described parameter uncertainty to perform probabilistic sensitivity analyses using second-order Monte Carlo techniques. We used the VA-FSS to obtain drug costs as recommended by the Second Panel on Cost-Effectiveness in Health and Medicine for the base case, which showed that apixaban was favored, being more effective and less costly than either enoxaparin or edoxaban. In this analysis, rivaroxaban was not cost-effective. In a scenario analysis using average prices from GoodRx, reflective of what the typical patient might pay at their local pharmacy, apixaban was no longer cost-effective. If decision makers were unwilling to spend more than $50000 per QALY, edoxaban was favored. However, using the contemporary threshold for societal WTP, rivaroxaban was cost-effective, with an ICER of just more than $50000 per QALY. Deterministic sensitivity analyses of the monthly costs of apixaban and rivaroxaban, using real-world prices for the cost of other anticoagulants, showed that decisions about the most cost-effective treatment were highly sensitive to the monthly cost of either anticoagulant. These findings are important as we notice a stark difference in the cost-effectiveness between the VA-FSS setting and the real-world setting, and this could have implications for value-based price benchmarks in the United States.

Although previous analyses have compared rivaroxaban with dalteparin (40), edoxaban with enoxaparin from a Brazilian payer perspective (41), rivaroxaban and edoxaban with dalteparin (17, 42), and, more recently, DOACs versus enoxaparin from a Chinese payer perspective (43), to our knowledge, this is the first comprehensive cost-effectiveness analysis

of apixaban along with the 2 other DOACs (rivaroxaban and edoxaban) compared with enoxaparin from the perspective of payers in the United States.

Our study has limitations. We performed our analysis over the lifetime of a patient with cancer. We assumed patients would continue secondary prophylaxis with anticoagulation over their entire life, barring MB events leading to discontinuation of anticoagulation. In actual practice, adherence to these regimens may not continue as cancer progresses and care evolves to being focused on comfort rather than prolonging survival. We realize that drug discontinuation may impact both efficacy and side-effect profile data for the drugs. However, there is a lack of precise data in the literature, and hence, we have not reported these rates or included them in the model. This means we may be overestimating the drug costs for DOACs, however, that would be for all of the drugs, as we do believe that discontinuation would be different amongst oral drugs. Moreover, the data we used in this analysis are from clinical trials, which report on an intention-to-treat basis. Thus, the effect of drug discontinuation should be included in the efficacy and bleeding rates presented in the results from clinical trials. Our analysis did not include costs for nonmedical expenditures, such as those associated with transportation or loss of productivity for the patient and his or her caregiver associated with the inability to work. This was because of a lack of specific data on patients with cancer. Also, we have not accounted for costs associated with complications such as severe postthrombotic syndrome and chronic pulmonary hypertension that are associated with recurrent VTE and can contribute tremendously to the cost and deterioration of QOL. These data lower overall costs associated, but the overall cost-effectiveness analysis should not be affected.

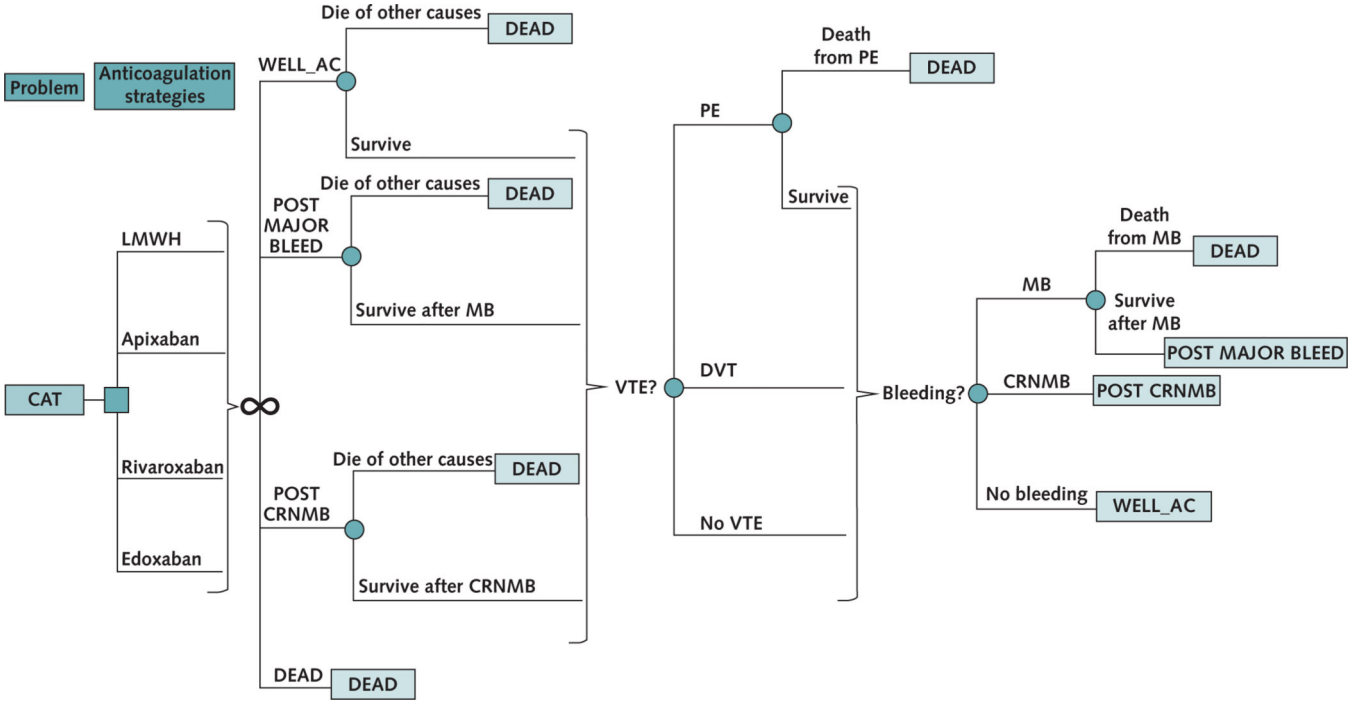
Nevertheless, our analysis is important as the DOACs are unlikely to be compared head-to-head in phase 3 clinical trials. Depending on clinical characteristics, location of cancer, and side effects, patients may be better suited to 1 agent over another in clinical practice and this analysis should help policymakers and clinicians with making these decisions. In terms of cost-effectiveness, the 3 DOACs are more effective and more cost-effective than LMWH. However, the most cost-effective DOAC depends on the relative cost of each of these agents.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

APPENDIX

Appendix



Appendix Figure. Decision tree model.

The Markov state transition model is depicted here, comparing 4 strategies for the treatment of CAT in an adult patient with metastatic cancer, with an average of 63 years. The 4 strategies shown at the square decision include 1) LMWH, 2) apixaban, 3) rivaroxaban, and 4) edoxaban. Round nodes represent chance events. In all 4 strategies, patients enter the Markov state transition model. During each 1-month cycle, they may die of nonexplicitly modeled causes, develop recurrent VTE (either PE or DVT alone), death from PE, or experience bleeding events including MB and subsequent death, or CRNMB. CAT = cancer-associated thrombosis; CRNMB = clinically relevant nonmajor bleeding; DVT = deep venous thrombosis; LMWH = low-molecular-weight heparin; MB = major bleeding; PE = pulmonary embolism; VTE = venous thromboembolism; WELL_AC = otherwise well on anticoagulation.

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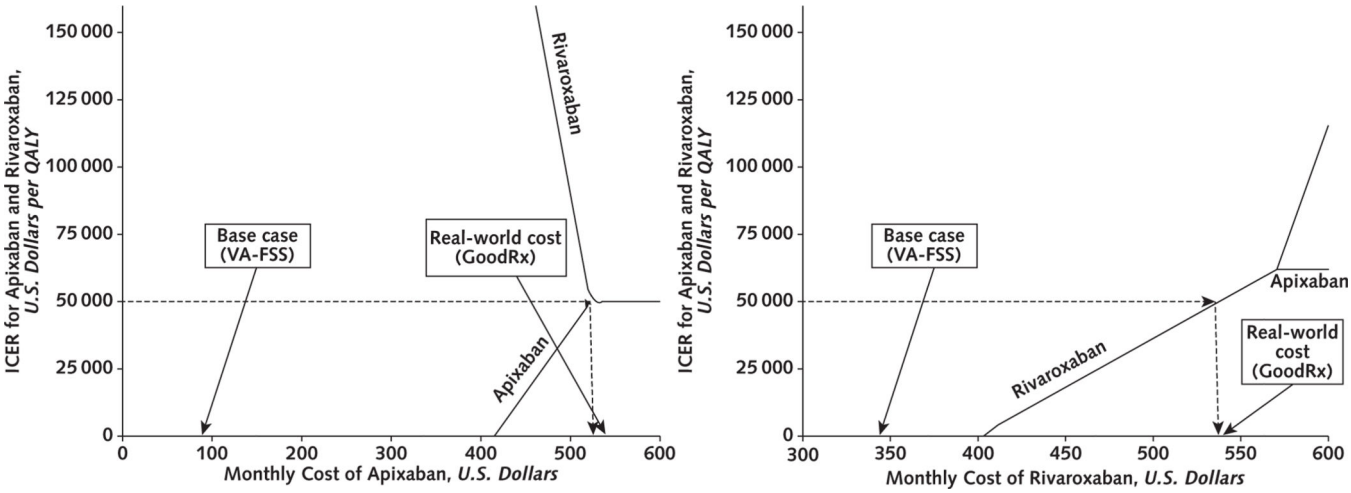

Figure 1. One-way sensitivity analysis examining the effect of monthly drug costs.

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; VA-FSS = U.S. Department of Veterans Affairs Federal Supply Schedule. Left. Monthly cost of apixaban. As the monthly cost of apixaban increases, the ICER increases. Apixaban remains cost-effective (ICER <$50000 per QALY), at monthly drug costs below $530, as shown by the dotted lines on the y-axis and x-axis, respectively. The ICER for rivaroxaban declines as the cost of apixaban increases. Above a cost of $530, rivaroxaban has an ICER of $50053 per QALY. Right. Monthly cost of rivaroxaban. The ICER of rivaroxaban increases as the monthly cost of rivaroxaban increases. Above a cost of $535, its ICER exceeds $50000 per QALY. Above a cost of $571, apixaban becomes more cost-effective, with an ICER of $61791 per QALY.

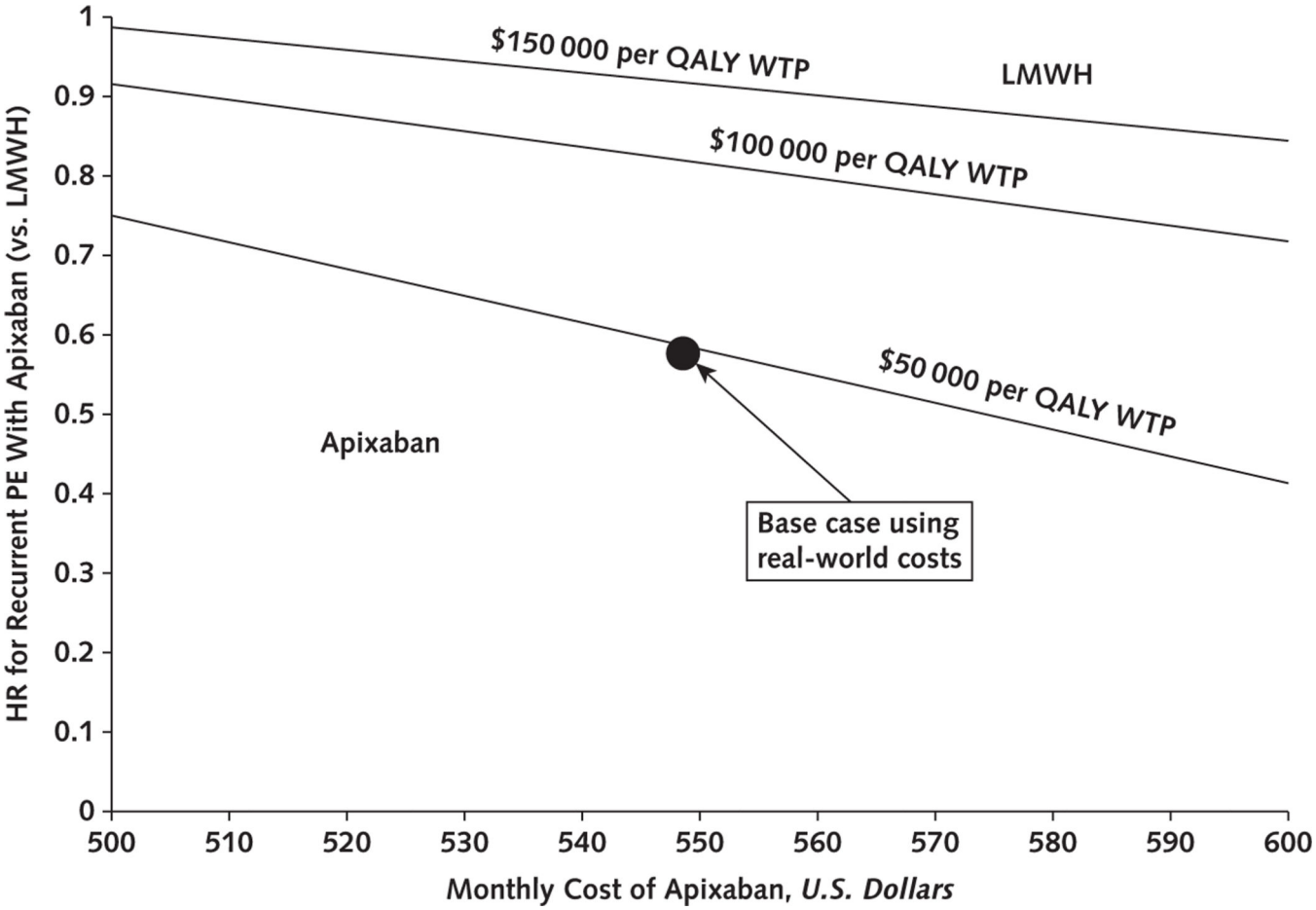

Figure 2. Two-way sensitivity analysis examining the relationship between the monthly cost of apixaban and efficacy (relative hazard for recurrent PTE for apixaban versus LMWH).

Three different thresholds for WTP are shown: <$50000 per QALY (highly cost-effective), <$100000 per QALY, and <$150000 per QALY (upper limit of cost-effective). Apixaban is favored toward the lower left of the figure, where the monthly cost of apixaban is low, and apixaban is highly efficacious (that is, low HR of recurrent VTE compared with LWMH). The base-case values using real-world costs and an HR of 0.66 fall right on the WTP threshold of $50000. HR = hazard ratio; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; QALY = quality-adjusted life-year; VTE = venous thromboembolism; WTP = willingness to pay.

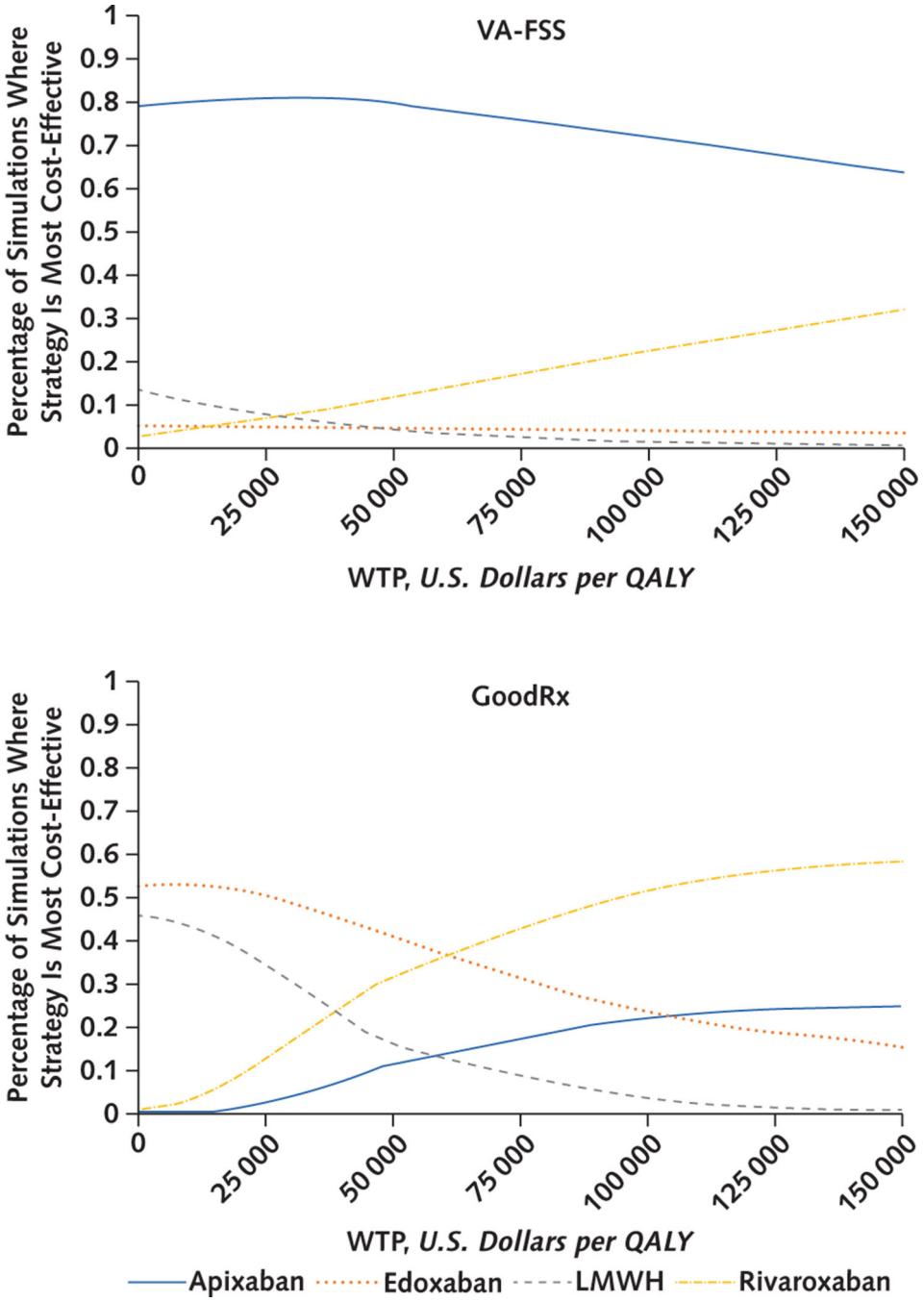

Figure 3. Cost-effectiveness acceptability curves showing results of probabilistic sensitivity analyses using 10000 iterations of a second-order Monte Carlo model.

The curves show the proportion of simulations for which each of the strategies is best (that is, most cost-effective) at a series of willingness-to-pay (WTP) thresholds (x-axis). The curves represent the net monetary benefit (NMB) calculated as $\lambda \times E - C$, where λ represents a series of WTP thresholds per QALY gained, E = total QALYs for each strategy, and C = total lifetime cost of each strategy. LMWH = low-molecular weight heparin; QALY = quality-adjusted life-year. **Top**. Using the basecase model with VA-FSS prices:

apixaban is favored across a wide range of WTP thresholds between $0 and $150 000 per QALY. **Bottom**. Using real-world drug prices from GoodRx: edoxaban is favored at WTP thresholds less than $60 000 per QALY, whereas rivaroxaban is favoured at WTP thresholds above $60 000 perQALY

Table 1.

Parameter Inputs With a Cycle Length of 1 Month

Parameter	Base Case	Lower	Upper	Distribution Parameters	Parameters for Distribution	Distribution	References
Monthly drug costs, *U.S.* dollars				LnMu	LnSigma		
Apixaban 5 mg twice daily	90.45	90	600	4.5048	0.9654	LogNormal	VA-FSS (15)
Rivaroxaban 20 mg daily	342.30	340	540	5.8357	0.2326	LogNormal	VA-FSS (15)
Edoxaban 60 mg daily	276.28	270	410	5.6214	0.2014	LogNormal	VA-FSS (15)
Enoxaparin 60 mg twice daily	218.76	210	400	5.3880	0.3079	LogNormal	VA-FSS (15)
Dalteparin, 10 000 U (= 1 mL/d)	1500.66	-	-	-	-	-	VA-FSS (15)
Event costs, *U.S.* dollars							
Recurrent PE	19685.97	14627	21 941	9.8877	0.1515	LogNormal	Preblick et al and Li et al (16, 17)
Recurrent DVT	9343.60	6943	10 415	9.1425	0.1515	LogNormal	Preblick et al and Li et al (16, 17)
MB	20490.04	15226	22 838	9.9277	0.1515	LogNormal	Preblick et al and Li et al (16, 17)
CRNMB	5135.93	3816	5724	8.5440	0.1516	LogNormal	Preblick et al and Li et al (16, 17)
Cost of clinic visit	222.27	-	-	-	-	-	CMS (18)
Cost of ancillary laboratory tests	18.33	-	-	-	-	-	CMS (18)
Utilities: Patient with				LogitMu	LogitSigma		
Cancer with VTE	0.645	0.616	0.672	0.597603264	0.063774925	Logit	Lloyd et al (19)
Cancer with MB	0.593	0.461	0.693	0.381885324	0.274593292	Logit	Lloyd et al (19)
Cancer with CRNMB	0.6222	0.568	0.669	0.500191606	0.115559069	Logit	Lloyd et al (19)
Cancer with recurrent VTE	0.57	0.485	0.641	0.283541639	0.175285535	Logit	Lloyd et al (19)
VTE treated with LMWH	0.99	-	-	-	-	-	Marchetti et al (9)
VTE treated with DOAC	1	-	-	-	-	-	Assumption
Probabilities				Bsuccess	Bfailure		
Death from recurrent PE	0.2000	0.12	0.28	19	76	β	Raskob et al, Young et al, Agnelli et al (10, 11, 13)
Death from MB	0.0535	0.12	0.09	6	106	β	Raskob et al, Young et al, Agnelli et al (10, 11, 13)
Rates *							
Excess annualmortality fromcancer	0.22	-	-	-	-	-	Li et al (17)
Annual rate of recurrent PE with LMWH	0.096	-	-	123	1183	β	Raskob et al, Young et al, Agnelli et al (10, 11, 13)
Annual rate of recurrent DVT with LMWH	0.077	-	-	99	1207	β	Raskob et al, Young et al, Agnelli et al (10, 11, 13)

Parameter	Base Case	Lower	Upper	Distribution Parameters	Parameters for Distribution	Distribution	References
Annual rate of major bleeding with LMWH	0.0717	-	-	92	1214	β	Raskob et al, Young et al, Agnelli et al (10, 11, 13)
Annual rate of CRNMB with LMWH	0.1345	-	-	170	1136	β	Raskob et al, Young et al, Agnelli et al (10, 11, 13)
Relative hazards							
Apixaban				LnMu	LnSigma		Ueyama et al meta-analysis (14)
Recurrent PE	0.58	0.28	1.21	−0.5447	0.3715	LogNormal	-
Recurrent DVT	0.70	0.29	1.67	−0.3567	0.4495	LogNormal	-
MB	0.81	0.39	1.66	−0.2107	0.3729	LogNormal	-
CRNMB	1.42	0.88	2.3	0.1823	0.2898	LogNormal	-
Edoxaban							Ueyama et al meta-analysis (14)
Recurrent PE	0.97	0.47	2.01	−0.0305	0.3697	LogNormal	-
Recurrent DVT	0.54	0.25	1.18	−0.6162	0.3929	LogNormal	-
MB	1.74	0.87	3.5	0.5539	0.3536	LogNormal	-
CRNMB	1.1	0.61	1.97	0.0953	0.3008	LogNormal	-
Rivaroxaban							Ueyama et al meta-analysis (14)
Recurrent PE	0.44	0.12	1.59	−0.8210	0.6629	LogNormal	-
Recurrent DVT	0.43	0.10	1.82	−0.8440	0.7442	LogNormal	-
MB	0.94	0.43	2.09	−0.0619	0.3990	LogNormal	-
CRNMB	1.66	0.86	3.22	0.5068	0.3355	LogNormal	-

CRNMB = clinically relevant nonmajor bleeding; DOAC = direct oral anticoagulant; DVT = deep venous thrombosis; LMWH = low-molecular-weight heparin; MB = major bleeding; PE = pulmonary embolism; VA-FFS = U.S. Department of Veterans Affairs Federal Supply Schedule; VTE = venous thromboembolism.

* One-month transition probabilities (TP) were calculated from the annual rate using the formula $TP = 1 - e^{-rt}$, where r is the annual event rate and t is (1/12) of a year. One-month transition probabilities: recurrent VTE with LMWH, 0.0146; MB with LMWH, 0.006; CRNMB with LMWH, 0.0111.

Table 2.

Results From the Base-Case and Real-World Analyses

Strategy	Cost, *U.S. Dollars*	Effectiveness, *QALYs*	Incremental Cost, *U.S.* Dollars	Incremental Effectiveness, *QALYs*	ICER, *U.S. Dollars per QALY*
Base-case analysis *					
Apixaban	20 246	2.3171	—	—	—
Enoxaparin	26 569	2.2301	6323	−0.0870	Dominated
Edoxaban	28 207	2.2405	7962	−0.0765	Dominated
Rivaroxaban	29 845	2.3365	9600	0.0195	493 246
Real-world scenario analysis †					
Edoxaban	31 868	2.2405	—	—	—
Enoxaparin	32 334	2.2301	465	−0.0104	Dominated
Apixaban	36 598	2.3171	4730	0.0765	Extended dominance
Rivaroxaban	36 674	2.3365	4805	0.0960	50 053

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

*Results from the base-case analysis (using the U.S. Department of Veterans Affairs Federal Supply Schedule [VA-FSS] drug costs and using relative hazards from the Ueyama et al network meta-analysis [14]).

†Real-world scenario analysis (using drug prices from GoodRx [and using relative hazards from the Ueyama et al network meta-analysis (14)]).