# Cost-Effectiveness Analysis of Low-Dose Direct Oral Anticoagulant (DOAC) for the Prevention of Cancer-Associated Thrombosis in the United States

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**BACKGROUND:** Randomized controlled trials (RCTs) have demonstrated that low-dose direct oral anticoagulants (DOACs), including rivaroxaban and apixaban, may help reduce the incidence of cancer-associated venous thromboembolism (VTE). **METHODS:** A cost-utility analysis was performed from the health sector perspective using a Markov state-transition model in patients with cancer who are at intermediate-to-high risk for VTE. Transition probability, relative risk, cost, and utility inputs were obtained from a meta-analysis of the RCTs and relevant epidemiology studies. Differences in cost, quality-adjusted life-years (QALYs), and the incremental cost-effectiveness ratio (ICER) per patient were calculated over a lifetime horizon. One-way, probabilistic, and scenario sensitivity analyses were conducted. **RESULTS:** In patients with cancer at intermediate-to-high risk for VTE, treatment with low-dose DOAC thromboprophylaxis for 6 months, compared with placebo, was associated with 32 per 1000 fewer VTE and 11 per 1000 more major bleeding episodes over a lifetime. The incremental cost and QALY increases were $1445 and 0.12, respectively, with an ICER of $11,947 per QALY gained. Key drivers of ICER variations included the relative risks of VTE and bleeding as well as drug cost. This strategy was 94% cost effective at the threshold of $50,000 per QALY. The selection of patients with Khorana scores ≥3 yielded the greatest value, with an ICER of $5794 per QALY gained. **CONCLUSIONS:** Low-dose DOAC thromboprophylaxis for 6 months appears to be cost-effective in patients with cancer who are at intermediate-to-high risk for VTE. The implementation of this strategy in patients with Khorana scores ≥3 may lead to the highest cost-benefit ratio. ***Cancer* 2020;126:1736-1748**. © *2020 American Cancer Society*.

**KEYWORDS:** apixaban, cost-benefit analysis, factor Xa inhibitors, neoplasm, rivaroxaban, venous thromboembolism.

## INTRODUCTION

Cancer-associated thrombosis (CAT) is often the harbinger of complication or death in ambulatory patients with cancer.[1,2] Patients with venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), often experience a delay in cancer treatment as well as an increase in hospitalization rates and total health care cost.[3] Studies have shown that treatment of CAT with full-dose direct oral anticoagulant drugs (DOACs) produces similar clinical outcomes and quality-adjusted life-years (QALYs) at a lower to similar cost compared with low-molecular-weight heparin (LMWH).[4-6] To our knowledge, no such economic analysis has been done in the preventive setting.

In the year 2019, 2 randomized controlled trials (RCTs) showed that thromboprophylaxis with low-dose DOACs, specifically apixaban and rivaroxaban, could help reduce the incidence of CAT compared with placebo.[7,8] In contrast to prior studies that included patients with heterogeneous risk for VTE,[9,10] those studies only selected patients with cancer who were at intermediate-to-high risk of VTE (approximately 9% by 6 months) based on the Khorana score risk stratification.[11] This patient selection strategy led to a higher absolute risk reduction of VTE than the absolute increase in major bleeding (MB) associated with low-dose DOAC prophylaxis.

Despite these promising results, it remains unclear whether a thromboprophylaxis strategy based on the Khorana score would affect QALYs in patients with cancer, whether it is cost effective from a health sector perspective, and which subgroup of patients would benefit the most from such an approach. In the current study, we performed a cost-utility analysis comparing low-dose DOAC versus placebo for the prevention of CAT in ambulatory patients with cancer.

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Herein, we present our results for the overall population with intermediate-to-high risk for CAT as well as a scenario analysis for patients determined to be high risk based on the Khorana score risk-stratification.

## MATERIALS AND METHODS

### *Target Population and Setting*

We built a Markov state-transition model to evaluate the cost utility of low-dose DOAC, including rivaroxaban and apixaban, versus placebo for the prevention of CAT over a 40-year lifetime horizon. We used a hypothetical cohort ambulatory patients with cancer aged 60 years who were considered at intermediate-to-high risk for venous thromboembolism (VTE) (Khorana score ≥2) without absolute contraindications for thromboprophylaxis. The age was chosen based on the median age of participants in the clinical trials. To estimate the relative proportion of the most common cancer subtypes in this cohort, we pooled patients from both low-dose DOAC RCTs (see Supporting Table 1). We also considered subgroup analyses of patients at the highest risk for VTE (Khorana score ≥3) and those at intermediate risk (Khorana score 2).

### *Model Overview*

The Markov model diagram is shown in Figure 1. The initial transition states for the model included on-prophylaxis (prophylactic dose of DOAC), off-prophylaxis, first PE, first DVT, MB, and clinically relevant nonmajor bleeding (CRNMB). Patients who survived the first PE or DVT were transitioned into an on-treatment state (therapeutic dose of DOAC), which was linked to off-treatment, recurrent PE, recurrent DVT, MB, and CRNMB states. PE, DVT, MB, and CRNMB were temporary states. Additional postcomplication states included postintracranial bleeding (post-ICH) after MB, chronic thromboembolic pulmonary hypertension (CTEPH) after PE, and post-thrombotic syndrome (PTS) after DVT. Finally, there were 3 self-absorbing death states for tracking purposes: PE-related death, MB-related death, and non-PE/non-MB–related (cancer) death. The cycle length was chosen to be 1 month as a clinically meaningful time interval to capture potential transitions and apply the appropriate disutility weights from previous studies. The time horizon of 40 years was chosen as the maximum lifetime for individuals aged 60 years. Three percent yearly discounts for cost and quality were applied based on the US rates.[12]

Our Markov model made several assumptions: 1) patients existed in mutually exclusive states; 2) patients who experienced a first VTE event would transition to treatment with a therapeutic-dose of DOAC and would remain on-treatment unless VTE, bleeding, death, or discontinuation occurred; 3) patients who experienced any bleeding while on prophylaxis would all transition off DOAC after 1 cycle because of low tolerance of adverse effects; 4) patients who experienced a recurrent VTE or CRNMB would return to the same anticoagulant on-treatment state after 1 cycle unless death had occurred; 5) patients who experienced MB would transition to an off-treatment state after 1 cycle unless death had occurred; 6) patients who were still alive after 5 years had similar VTE and mortality rates as the general noncancer population; and 7) patients would suffer from bleeding complications and/or discontinue anticoagulant at a constant rate unrelated to cancer remission or cure.

### *Model Input: Measurement of Effectiveness*

To simulate the impact of thromboprophylaxis over a study period of 6 months, we first estimated the transition probabilities, risk ratios (RRs), and confidence intervals (CIs) for VTE, bleeding, discontinuation, and mortality outcomes in a meta-analysis of the AVERT (Apixaban for the Prevention of Venous Thromboembolism in Cancer Patients; clinicaltrials.gov identifier NCT02048865) and CASSINI (A Study to Evaluate the Efficacy and Safety of Rivaroxaban Venous Thromboembolism Prophylaxis in Ambulatory Cancer Participants; clnicaltrials.gov identifier NCT02555878) RCTs.[7,8,13] RR estimation was performed using the Mantel-Haenszel random effects model (DerSimonian-Laird analysis).[14] Transition probability for the pooled primary efficacy VTE outcome was reported for the overall follow-up and on-treatment study period. The probability for the pooled primary safety outcome was reported for the on-treatment study period only. The probability from on-prophylaxis to off-prophylaxis was estimated using the number of patients who permanently discontinued the study drug for any reason other than VTE, bleeding, or death, as reported in the supplemental material of the studies. Subgroup meta-analyses were performed for patients with Khorana scores ≥3 and 2 after outcomes were obtained directly from the trial authors.[13] Because of the low case fatality associated with PE, MB, and ICH, pooled estimates were derived from 2 prophylaxis trials and 1 treatment trial (Hokusai-VTE Cancer).[15]

### *Model Input: Transition Probability Beyond Study Period*

To estimate the time-varying transition probability for incident VTE beyond the first 6 months, we used data from a US epidemiology study[16] rather than parametric

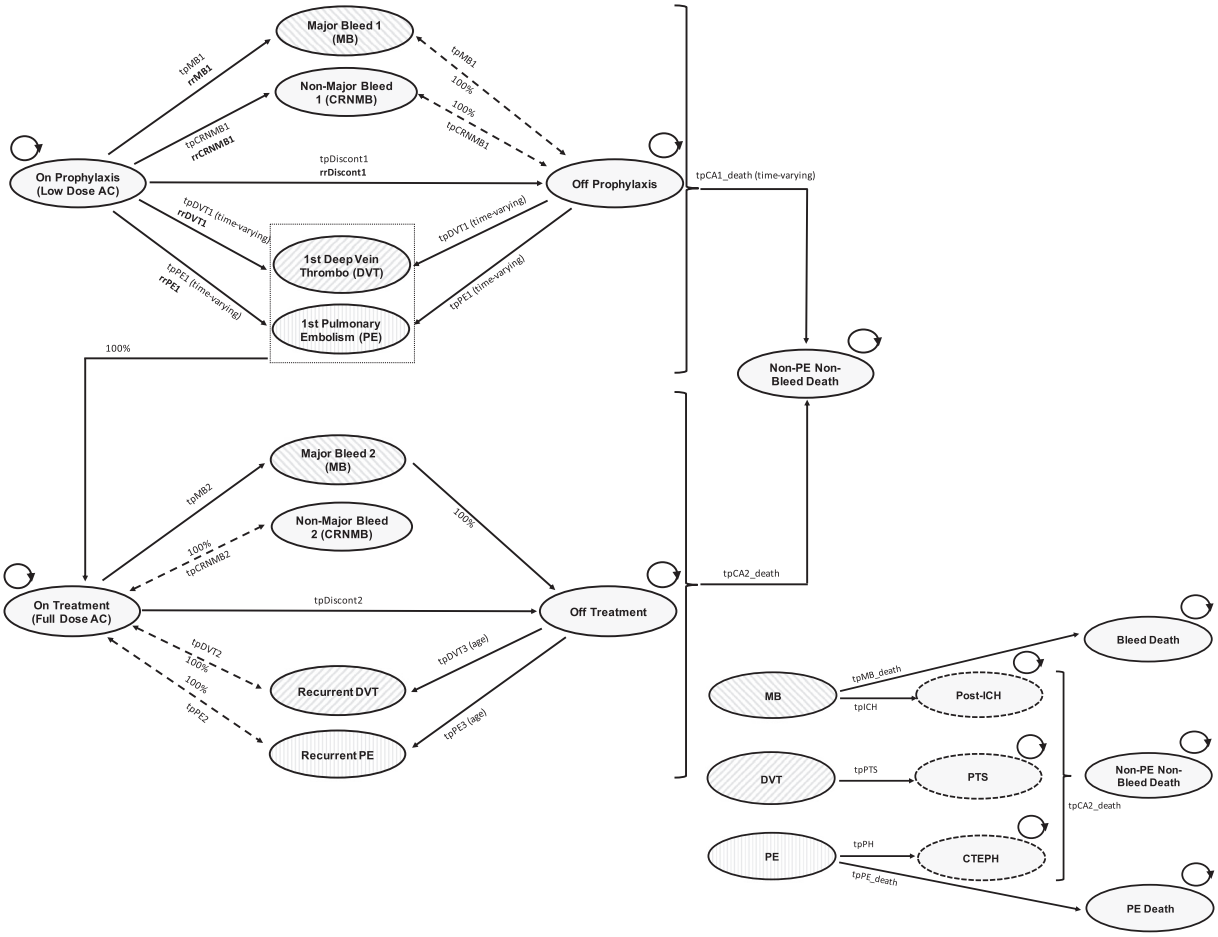


**Figure 1.** The Markov state transition model is shown. AC indicates anticoagulant; CA, cancer-associated; CRNMB, clinically relevant nonmajor bleeding; CTEPH, chronic thromboembolic pulmonary hypertension; Discont, discontinuation; DVT, deep vein thrombosis; ICH, intracranial bleeding; MB, major bleeding; PE, pulmonary embolism; PH, pulmonary hypertension; PTS, post-thrombotic syndrome; rr, relative risk; tp, transition probability.

extrapolation from the RCTs because VTE incidence decreases significantly over time beyond initial cancer diagnosis and treatment. For the first 2 years, we estimated the transition probability using the product of the cancer-specific VTE incident rate from the epidemiology study and the proportion of cancer subtype from the RCTs (see Supporting Table 2). The rate was assumed to be constant between second and fifth years. After 5 years, we used the age-specific VTE incident rate from a UK epidemiology study of patients without cancer.[17] To estimate the probability for recurrent VTE while on-treatment, along with anticoagulant-associated bleeding, discontinuation, and mortality, we used data reported in the DOAC arm of the Hokusai-VTE Cancer RCT.[15] The probability for recurrent VTE while off-treatment was estimated from the age-specific rates from a UK epidemiology study of patients with cancer.[18] Finally, we estimated the probability for PTS and CTEPH from published studies.[19,20]

To estimate the time-varying transition probability for non-PE/non-MB mortality beyond the first 6 months, we used data from the Surveillance, Epidemiology, and End Results database.[21] For the first 5 years, we estimated the probability using the product of the cancer-specific mortality rate from the Surveillance, Epidemiology, and End Results data and the proportion of cancer subtype from the RCTs (see Supporting Table 3). After 5 years, we used the age-specific mortality rate from the US 2016 life-tables.[22] For patients with recurrent VTE, the mortality rate was estimated from the Hokusai-VTE Cancer study.

### *Model Input: Cost and Utility*

Cost estimates were evaluated from a health sector perspective to include direct medical costs related to drugs

and complications. Unit costs for prophylactic doses of rivaroxaban 10 mg ($14.93), apixaban 2.5 mg ($7.40), and therapeutic doses of edoxaban 60 mg ($12.12), and enoxaparin 100 mg ($15.00) were based on the wholesale acquisition cost from the *Red Book*.[23] Monthly costs (each cycle) were derived from 30-day prescriptions of the drugs at the labeled dosing frequency (daily for rivaroxaban and edoxaban, twice daily for apixaban). Additional drug cost analysis was performed using the Federal Supply Schedule as a sensitivity analysis. Adverse event costs (each cycle) for initial and recurrent VTE events as well as bleeding episodes were obtained from the report by Preblick et al, in which the cost-per-stay estimates were derived from the Premier Hospital Database and a post-hoc analysis of the DOAC arm of the Hokusai-VTE study.[24] For postcomplication states, the monthly cost (each cycle) was estimated from the appropriate publications for post-ICH, PTS, and CTEPH.[25-27] All cost estimates were inflated to May 2019 US dollars using the US Consumer Price Index for all urban consumers' medical care.[28]

Utility weights and CI ranges between 0 and 1 were derived from published literature. We first estimated the baseline utility weight for patients with cancer as the product of cancer-specific utility weight from various studies and the proportion of cancer subtype from the RCTs (see Supporting Table 4).[29-33] We then calculated the disutility from general medical patients with VTE, bleeding, ICH, PTS, and CTEPH and subtracted the disutility from the baseline utility weight to determine the adjusted weight for each outcome state.[24,34-36] For the primary utility measures of VTE and bleeding, we used the data published by Hogg et al, who that used a standard gamble method from 216 ambulatory patients with a history of DVT or PE.[34]

### *Base-Case and Sensitivity Analyses*

For the base-case analysis, the cumulative cost and QALYs were estimated for each treatment over a lifetime time horizon. The incremental cost-effectiveness ratio (ICER) was calculated as the difference in cost over the difference in QALYs. Half-cycle correction was not performed given the short cycle length of 1 month. To highlight the model's calibration performance, we also reported clinical events at a time horizon of 6 months to emulate the outcomes reporting from the RCTs.

We performed one-way deterministic sensitivity analyses. The upper and lower bounds of the 95% CIs were used if such data were available the from literature (Table 1).[15-17,19-27,34-36] Otherwise, the variations were assumed to be ±20% from the mean value. We performed probabilistic sensitivity analysis using Monte Carlo simulation over 1000 times to generate the cost-effectiveness plane and the cost-effectiveness acceptability curve. The distributions assumed for the input parameters were γ (cost), β (utility weights and transition probability), and log-normal (RR) (Table 1). The standard errors were derived from the 95% CIs, and α/β parameters were estimated using the method of moments.

Finally, we performed several scenario and sensitivity analyses by varying the duration of intervention (6 vs 12 months), the treatment effect estimate (on-treatment vs intention-to-treat period), and the risk profile of the population (high risk vs intermediate risk). All data analyses in this study were performed in Microsoft Excel for Mac 16.17. We adhered to the Consolidated Health Economic Evaluation Reporting Standards statement in presenting this analysis.[37]

## RESULTS

### *Evidence Synthesis on Effectiveness Measures*

The measurement of effectiveness for low-dose DOAC intervention based on the meta-analysis of the AVERT and CASSINI RCTs are shown in Table 2. For the primary efficacy outcome of first VTE occurrence by 6 months, low-dose DOAC prophylaxis was associated with an RR of 0.56 (95% CI, 0.35-0.89) for VTE. A higher risk reduction with an RR of 0.30 (95% CI, 0.16-0.53) was found for the on-treatment only study period. For the safety outcomes by 6 months, the intervention was associated with an RR of 1.96 (95% CI, 0.80-4.82) for MB and an RR of 1.28 (95% CI, 0.74-2.20) for CRNMB. Both the intervention arm and the placebo arm had similar rates of drug discontinuation unrelated to primary outcomes, with an RR of 1.00 (95% CI, 0.84-1.19). The 2 RCTs had moderate heterogeneity in the mortality outcome reporting and a pooled RR of 0.98 (95% CI, 0.67-1.43); however, this estimate was not used because there is not a biologic rationale for the drug intervention to influence non-PE/non-MB–related mortality. We also performed a meta-analysis of the above outcomes for subgroups according to Khorana score. In patients with Khorana scores ≥3, low-dose DOAC prophylaxis was associated with an RR of 0.47 (95% CI, 0.25-0.89) for VTE and an RR of 1.60 (95% CI, 0.42-6.01) for MB; in those with Khorana scores of 2, low-dose DOAC prophylaxis had an RR of 0.60 (95% CI, 0.30-1.19) for VTE and an RR of 1.91 (95% CI, 0.56-6.53) for MB. The proportions of

**TABLE 1.** Parameter Inputs With a Cycle Length of 1 Month

| Parameter | Reference | Base Case | Lower | Upper | Distribution |
|---|---|---|---|---|---|
| Costs (c), $[a] | | | | | |
| cDOAC_ppx | | 446 | 357 | 535 | γ |
| Apixaban 2.5 mg twice daily | Red Book 2019[23] | 444 | | | |
| Rivaroxaban 10 mg daily | Red Book 2019[23] | 448 | | | |
| cEdoxaban_rx 30-60 mg daily | Red Book 2019[23] | 364 | 291 | 436 | γ |
| cEnoxaparin_rx 100 mg daily | Red Book 2019[23] | 450 | 360 | 540 | γ |
| cPE1 (first) | Preblick 2015[24] | 16,903 | 13,522 | 20,283 | γ |
| cDVT1 (first) | Preblick 2015[24] | 9766 | 7813 | 11,720 | γ |
| cPEr (recurrent) | Preblick 2015[24] | 18,705 | 14,964 | 22,446 | γ |
| cDVTr (recurrent) | Preblick 2015[24] | 8878 | 7103 | 10,654 | γ |
| cMB | Preblick 2015[24] | 19,469 | 15,575 | 23,363 | γ |
| cCRNMB | Preblick 2015[24] | 4880 | 3904 | 5856 | γ |
| cPost-ICH | Lee 2007[25] | 1129 | 903 | 1355 | γ |
| cPTS | Caprini 2003[26] | 235 | 188 | 282 | γ |
| cCTEPH | Kirson 2011[27] | 6814 | 5451 | 8177 | γ |
| Utility weights (u) | | | | | |
| uBase[b] | see Supporting Table 4 | 0.74 | 0.59 | 0.89 | β |
| uPE | Hogg 2013[34] | −0.25 | −0.55 | −0.09 | β |
| uDVT | Hogg 2013[34] | −0.19 | −0.45 | −0.06 | β |
| uMB | Hogg 2013[34] | −0.09 | −0.27 | 0.00 | β |
| uCRNMB | Preblick 2015[24] | −0.35 | −0.85 | −0.14 | β |
| uICH | Lenert & Soetikno 1997[35] | −0.40 | −0.98 | −0.00 | β |
| uPTS | Lenert & Soetikno 1997[35] | −0.05 | −0.21 | −0.00 | β |
| uCTEPH | Ghofrani 2013[36] | −0.34 | −0.83 | −0.00 | β |
| Transition probabilities (tp), % | | | | | |
| tpPE1_1-6mo[c] | see Table 2 | 0.82 | 0.66 | 0.99 | β |
| tpDVT1_1-6mo[c] | see Table 2 | 0.75 | 0.60 | 0.90 | β |
| tpMB1[c] | see Table 2 | 0.17 | 0.14 | 0.21 | β |
| tpCRNMB1[c] | see Table 2 | 0.55 | 0.44 | 0.66 | β |
| tpDiscont1[c] | see Table 2 | 5.36 | 4.29 | 6.43 | β |
| tpCA1_death_1-12mo[c] | see Table 2 | 3.18 | 2.54 | 3.81 | β |
| tpPE1_7-12mo[d] | see Supporting Table 2 | 0.29 | 0.23 | 0.35 | β |
| tpDVT1_7-12mo[d] | see Supporting Table 2 | 0.26 | 0.21 | 0.32 | β |
| tpPE1_13-60mo[d] | see Supporting Table 2 | 0.07 | 0.05 | 0.08 | β |
| tpDVT1_13-60mo[d] | see Supporting Table 2 | 0.06 | 0.05 | 0.07 | β |
| tpPE1_60yo[d] | Martinez 2014[17] | 0.01 | 0.01 | 0.01 | β |
| tpPE1_70yo[d] | Martinez 2014[17] | 0.01 | 0.01 | 0.02 | β |
| tpPE1_80yo[d] | Martinez 2014[17] | 0.02 | 0.02 | 0.03 | β |
| tpPE1_90yo[d] | Martinez 2014[17] | 0.03 | 0.02 | 0.04 | β |
| tpDVT1_60yo[d] | Martinez 2014[17] | 0.01 | 0.01 | 0.01 | β |
| tpDVT1_70yo[d] | Martinez 2014[17] | 0.01 | 0.01 | 0.02 | β |
| tpDVT1_80yo[d] | Martinez 2014[17] | 0.02 | 0.02 | 0.03 | β |
| tpDVT1_90yo[d] | Martinez 2014[17] | 0.03 | 0.02 | 0.03 | β |
| tpCA1_death_13-24mo[e] | SEER Program 2018[21] | 1.96 | 1.57 | 2.36 | β |
| tpCA1_death_25-36mo[e] | SEER Program 2018[21] | 1.12 | 0.90 | 1.35 | β |
| tpCA1_death_37-48mo[e] | SEER Program 2018[21] | 0.73 | 0.58 | 0.87 | β |
| tpCA1_death_49-60mo[e] | SEER Program 2018[21] | 0.58 | 0.46 | 0.69 | β |
| tpCA1_death_60+mo[e] | Arias 2019[22] | Variable | Variable | Variable | β |
| tpPE2 | Raskob 2018[15] | 0.44 | 0.35 | 0.53 | β |
| tpDVT2 | Raskob 2018[15] | 0.23 | 0.18 | 0.28 | β |
| tpMB2 | Raskob 2018[15] | 0.59 | 0.47 | 0.71 | β |
| tpCRNMB2 | Raskob 2018[15] | 1.30 | 1.04 | 1.56 | β |
| tpDiscont2 | Raskob 2018[15] | 1.58 | 1.26 | 1.90 | β |

**TABLE 1.** *Continued*

| Parameter | Reference | Base Case | Lower | Upper | Distribution |
|---|---|---|---|---|---|
| tpCA2_death | Raskob 2018[15] | 3.95 | 3.16 | 4.74 | β |
| tpPE3_60yo[f] | Cohen 2017[18] | 0.44 | 0.36 | 0.54 | β |
| tpPE3_70yo[f] | Cohen 2017[18] | 0.47 | 0.37 | 0.57 | β |
| tpPE3_80yo[f] | Cohen 2017[18] | 0.48 | 0.35 | 0.40 | β |
| tpPE3_90yof[f] | Cohen 2017[18] | 0.57 | 0.16 | 1.46 | β |
| tpDVT3_60yo[f] | Cohen 2017[18] | 0.40 | 0.32 | 0.40 | β |
| tpDVT3_70yo[f] | Cohen 2017[18] | 0.38 | 0.30 | 0.47 | β |
| tpDVT3_80yo[f] | Cohen 2017[18] | 0.33 | 0.22 | 0.47 | β |
| tpDVT3_90yo[f] | Cohen 2017[18] | 0.43 | 0.09 | 1.25 | β |
| tpPE_death (pooled PE fatality %)[c] | see Table 2 | 13.21 | 10.57 | 15.85 | β |
| tpMB_death (pooled MB fatality %)[c] | see Table 2 | 3.85 | 3.08 | 4.62 | β |
| tpMB_ICH (pooled MB to ICH %)[c] | see Table 2 | 10.26 | 8.21 | 12.31 | β |
| tpDVT_PTS | Kahn 2014[20] | 12.70 | 10.16 | 15.24 | β |
| tpPE_CTEPH | Ende-Verhaar 2017[19] | 2.80 | 1.50 | 4.10 | β |
| Relative risk (rr) | | | | | |
| rrPE1[c] | see Table 2 | 0.49 | 0.23 | 1.04 | Log-normal |
| rrDVT1[c] | see Table 2 | 0.64 | 0.37 | 1.11 | Log-normal |
| rrMB1[c] | see Table 2 | 1.96 | 0.80 | 4.82 | Log-normal |
| rrCRNMB1[c] | see Table 2 | 1.28 | 0.74 | 2.20 | Log-normal |
| rrDiscont1[c] | see Table 2 | 1.00 | 0.84 | 1.19 | Log-normal |
| Discounting | | | | | |
| oDR | Federal Reserve 2018[12] | 0.03 | | | |
| cDR | Federal Reserve 2018[12] | 0.03 | | | |

Abbreviations: AC indicates anticoagulant; CA, cancer-associated; cDR, cost discount rate; CRNMB, clinically relevant nonmajor bleeding; CTEPH, chronic thromboembolic pulmonary hypertension; Discont, discontinuation; DVT, deep vein thrombosis; ICH, intracranial bleeding; MB, major bleeding; oDR, outcome discount rate; PE, pulmonary embolism; PH, pulmonary hypertension; ppx, prophylaxis; PTS, post-thrombotic syndrome; yo, years old.

[a]All cost estimates were inflated to 2019 US dollars using the US Consumer Price Index for all urban consumers' medical care.

[b]Baseline utility weight was estimated as the sum of the product of the cancer-specific utility weight and the relative proportion of cancer subtypes from 2 randomized controlled trials (RCTs) (see Supporting Table 4); adverse event utility weights were estimated by subtraction of the disutility from the baseline weight.

[c]The transition probability and relative risk for the first 6 months were derived from the meta-analysis of the 2 RCTs, as shown in Table 2.

[d]The incidence of venous thromboembolism (VTE) beyond first 6 months was estimated as the sum of the product of the cancer-specific VTE rate (Chew 2006[16]) and the relative proportion of the cancer subtype from the 2 RCTs; the incidence of VTE after 60 months (5 years) was estimated using the age-specific VTE incidence rate in the noncancer population (Martinez 2014[17]).

[e]The incidence of mortality beyond first 12 months was estimated as the sum of the product of the cancer-specific mortality rate (Surveillance, Epidemiology, and End Results Program 2018[21]) and the relative proportion of cancer subtype from 2 randomized RCTs; the incidence of mortality after 60 months was estimated using US life-tables (Arias 2019[22]).

[f]The incidence of VTE recurrence when off treatment was estimated using the age-specific VTE recurrence rate in the cancer VTE population (Cohen 2017[18]).

patients who died from PE or MB or who developed ICH were too small and heterogeneous for a meaningful meta-analysis. Therefore, we included data from both prophylaxis RCTs and the treatment RCT for pooled estimation. On the basis of this analysis, PE and MB case fatalities were 13.21% (n = 14) and 3.85% (n = 3), respectively, and ICH occurred in 10.26% of patients with MB (n = 8).

### *Base-Case Cost-Effectiveness Analysis*

In the base-case analysis over lifetime (Table 3), low-dose DOAC thromboprophylaxis for 6 months was associated with 20 fewer PEs, 12 fewer DVTs, 11 more MB events, and 21 more CRNMB events per 1000 patients. The distribution of ICH, CTEPH, PTS, and event-related deaths were similar between intervention and placebo arms. A similar pattern of clinical outcomes was observed over 6 months and over 5 years (see Supporting Table 5). The absolute differences in all clinical outcomes, including overall VTE, PE, DVT, MB, CRNMB, and mortality, were all within the 95% CI of previously reported outcomes from the meta-analysis at 6 months.[13] Minor variations in outcomes were likely driven by the inclusion of a drug nonadherence/discontinuation factor in the Markov model, which led to small attenuations of the absolute risk reductions of the primary outcomes. Over a lifetime, the intervention group had a mean total cost of $9899 per person, 6.51 life-years, and 4.79 QALYs. The placebo group had a mean total cost of $8454 per person, 6.34 life-years, and 4.67 QALYs. Low-dose DOAC prophylaxis was associated with an incremental cost increase of $1445, an incremental QALY increase of 0.12, and an ICER of $11,947 per QALY.

In one-way sensitivity analyses (Fig. 2), variations in the relative risks of PE, DVT, and MB along with the

**TABLE 2.** Pooled Measurement of Effectiveness From Direct Oral Anticoagulant Thromboprophylaxis Trials

| Variable | No./Total No. (%) DOAC | No./Total No. (%) Placebo | RR [95% CI] |
|---|---|---|---|
| VTE outcomes on PPX | | | |
| First VTE by 6 mo | 37/711 (5.20) | 65/704 (9.23) | 0.56 [0.35-0.89] |
| PE | 17/711 (2.39) | 34/704 (4.83) | 0.49 [0.23-1.04] |
| AVERT | 5/291 (1.72) | 16/283 (5.65) | |
| CASSINI | 12/420 (2.86) | 18/421 (4.28) | |
| DVT | 20/711 (2.81) | 31/704 (4.40) | 0.64 [0.37-1.11] |
| AVERT | 7/291 (2.41) | 12/283 (4.24) | |
| CASSINI | 13/420 (3.10) | 19/421 (4.51) | |
| First VTE during on-treatment period (sensitivity) | 14/711 (1.97) | 47/704 (6.68) | 0.30 [0.16-0.53] |
| AVERT | 3/291 (1.03) | 20/704 (2.84) | |
| CASSINI | 11/420 (2.62) | 27/421 (6.41) | |
| Bleeding outcomes on PPX | | | |
| MB during on-treatment period | 14/693 (2.02) | 7/679 (1.03) | 1.96 [0.80-4.82] |
| AVERT | 6/288 (2.08) | 3/275 (1.09) | |
| CASSINI | 8/405 (1.98) | 4/404 (0.99) | |
| CRNMB during on-treatment period | 29/693 (4.18) | 22/679 (3.24) | 1.28 [0.74-2.20] |
| AVERT | 18/288 (6.25) | 14/275 (5.09) | |
| CASSINI | 11/405 (2.72) | 8/404 (1.98) | |
| Nonadherence/intolerance on PPX | | | |
| Drug discontinuation unrelated to death/VTE/bleed | 195/693 (28.14) | 191/679 (28.13) | 1.00 [0.84-1.19] |
| AVERT | 88/288 (31.27) | 76/275 (29.68) | |
| CASSINI | 107/405 (26.42) | 115/404 (28.47) | |
| Mortality on PPX | | | |
| Non-PE/non-MB mortality by 6 mo | 117/711 (16.46) | 124/704 (17.61) | 0.98 [0.67-1.43][a] |
| AVERT | 35/291 (12.03) | 27/283 (9.54) | |
| CASSINI | 82/420 (19.52) | 97/421 (23.04) | |
| Subgroup analysis on PPX (Khorana score ≥3) | | | |
| First VTE by 6 mo | 13/239 (5.44) | 25/216 (11.57) | 0.47 [0.25-0.89] |
| AVERT | 6/105 (5.71) | 12/93 (12.90) | |
| CASSINI | 7/134 (5.22) | 13/123 (10.57) | |
| First VTE during on-treatment period (sensitivity) | 7/239 (2.93) | 17/216 (7.87) | 0.38 [0.14-1.07] |
| AVERT | 2/105 (1.90) | 9/93 (9.68) | |
| CASSINI | 5/134 (3.73) | 8/123 (6.50) | |
| MB during on-treatment period | 6/233 (2.58) | 3/211 (1.42) | 1.60 [0.42-6.01] |
| AVERT | 2/105 (1.90) | 0/90 (0.00) | |
| CASSINI | 4/128 (3.13) | 3/121 (2.48) | |
| Subgroup analysis on PPX (Khorana score 2) | | | |
| First VTE by 6 mo | 24/467 (5.14) | 40/485 (8.25) | 0.60 [0.30-1.19] |
| AVERT | 6/186 (3.23) | 16/190 (8.42) | |
| CASSINI | 18/281 (6.41) | 24/295 (8.14) | |
| First VTE during on-treatment period (sensitivity) | 7/467 (1.50) | 30/485 (6.19) | 0.24 [0.08-0.73] |
| AVERT | 1/186 (0.54) | 11/190 (5.79) | |
| CASSINI | 6/281 (2.14) | 19/295 (6.44) | |
| MB during on-treatment period | 8/456 (1.75) | 4/465 (0.86) | 1.91 [0.56-6.53] |
| AVERT | 4/183 (2.19) | 3/185 (1.62) | |
| CASSINI | 4/273 (1.47) | 1/280 (0.36) | |

| Variable | Combined DOAC and Placebo No./Total No. | Percentage | RR [95% CI] |
|---|---|---|---|
| Pooled % estimates for PPX and RX[b] | | | |
| PE case fatality | 14/106 | 13.21 | NA |
| AVERT | 0/21 | 0.00 | |
| CASSINI | 4/30 | 13.33 | |
| Hokusai-VTE cancer study | 10/55 | 18.18 | |
| MB case fatality | 3/78 | 3.85 | NA |
| AVERT | 0/9 | 0.00 | |
| CASSINI | 1/12 | 8.33 | |
| Hokusai-VTE cancer study | 2/57 | 3.51 | |

**TABLE 2.** *Continued*

| Variable | Combined DOAC and Placebo | | RR [95% CI] |
|---|---|---|---|
| | No./Total No. | Percentage | |
| MB to ICH | 8/78 | 10.26 | NA |
| AVERT | 0/9 | 0.00 | |
| CASSINI | 2/12 | 16.67 | |
| Hokusai-VTE cancer study | 6/57 | 10.53 | |

Abbreviations: AVERT, Apixaban for the Prevention of Venous Thromboembolism in Cancer Patients (clinicaltrials.gov identifier NCT02048865); CASSINI, A Study to Evaluate the Efficacy and Safety of Rivaroxaban Venous Thromboembolism Prophylaxis in Ambulatory Cancer Participants (clnicaltrials.gov identifier NCT02555878); CRNMB, clinically relevant nonmajor bleeding; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; MB, major bleeding; NA, not applicable; PE,: pulmonary embolism; PPX, prophylaxis; RX, treatment; VTE, venous thromboembolism.
[a]Estimates for the RR of mortality were not used because of the lack of a biologic rationale that DOAC improves survival. As the most conservative approach, only pooled incidence estimate from the placebo arms was used for the transition probability of cancer-associated death during the first 12 months.
[b]Pooled estimates were derived from multiple DOAC trials because of the small event rate in each study arm for individual trials.

**TABLE 3.** Cost-Utility Analysis Outcomes

| Outcome | No. of Events per 1000 Patients Over Lifetime | |
|---|---|---|
| | Low-Dose DOAC | Placebo |
| Total PE | 73 | 93 |
| First event | 62 | 80 |
| Recurrent event | 11 | 13 |
| Total DVT | 69 | 81 |
| First event | 62 | 73 |
| Recurrent event | 7 | 8 |
| MB | 195 | 184 |
| CRNMB | 591 | 570 |
| ICH | 20 | 19 |
| CTEPH | 2 | 3 |
| PTS | 9 | 10 |
| PE-related death | 10 | 12 |
| MB-related death | 7 | 7 |
| Non-PE/non-MB death | 982 | 980 |
| Deterministic outcomes | | |
| Cost | | |
| Total cost | $9899 | $8454 |
| Health outcomes | | |
| LY | 6.51 | 6.34 |
| QALY | 4.79 | 4.67 |
| Cost effectiveness | | |
| Δ Cost | $1445 | |
| Δ LY | 0.16 | |
| Δ QALY | 0.12 | |
| ICER (per QALY)$ | $11,947 | |
| Probabilistic outcomes | | |
| Cost | | |
| Total cost | $10,007 | $8470 |
| Health outcomes | | |
| LY | 6.44 | 6.30 |
| QALY | 4.81 | 4.70 |
| Cost effectiveness | | |
| Δ Cost | $1537 | |
| Δ LY | 0.15 | |
| Δ QALY | 0.11 | |
| ICER (per QALY) | $14,330 | |

Abbreviations: CRNMB, clinically relevant nonmajor bleeding; CTEPH, chronic thromboembolic pulmonary hypertension; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; ICER, incremental cost-effectiveness ratio; ICH, intracranial hemorrhage; LY, life-year; MB, major bleeding; PE, pulmonary embolism; PTS, post-thrombotic syndrome; QALY, quality-adjusted life-year.

cost associated with low-dose DOAC prophylaxis led to the largest differences in the ICER. In probabilistic sensitivity analysis (Fig. 3, Table 3), low-dose DOAC prophylaxis was associated with an incremental cost increase of $1537, an incremental QALY increase of 0.11, and an ICER of $14,330 per QALY. As shown in the cost effectiveness acceptability curve (Fig. 4), this strategy would be cost effective 94% of the time if we assume a ceiling ICER of $50,000 per QALY.

### *Sensitivity and Scenario Analyses*

We performed several sensitivity analyses to test the robustness of the model under various assumptions. First, we substituted the transition probability and RR of VTE occurrence with the pooled estimates derived from the as-treated study period instead of the overall intention-to-treat follow-up (Table 4). Although the intention-to-treat estimates preserve the randomization and generally represent unconfounded effects associated with the intervention, the as-treated estimates are more realistic because our Markov model accounts for unintended discontinuation of study drugs. Compared with the primary analysis, low-dose DOAC prophylaxis in this analysis was associated with a similar incremental cost increase, a greater incremental QALY increase (0.14 vs 0.12 QALYs), and an ICER of $9896 per QALY. Second, we examined the effect of assigning patients to 12 months of prophylaxis instead of 6 months (Table 5). Compared with the primary analysis, low-dose DOAC prophylaxis in this scenario was associated with a greater incremental cost increase ($2410 vs $1445), a greater incremental QALY increase (0.15 vs 0.12), and an ICER of $16,389 per QALY. Third, we examined how the extrapolation of mortality rate based on the year-5 cancer mortality rate instead of US life-tables would affect the overall outcome. In this sensitivity

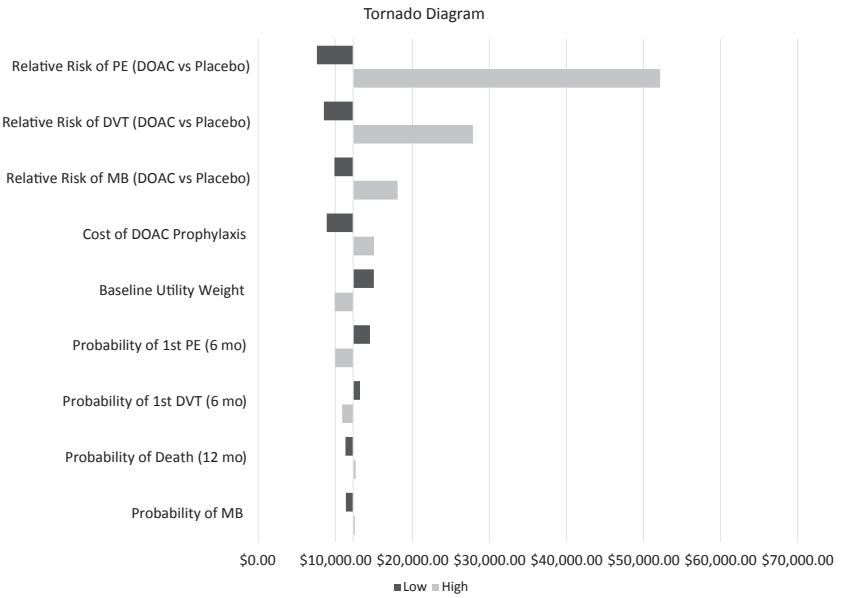


**Figure 2.** A one-way sensitivity analysis (Tornado diagram) is illustrated. DOAC indicates direct oral anticoagulant; DVT, deep vein thrombosis; MB, major bleeding; PE, pulmonary embolism.

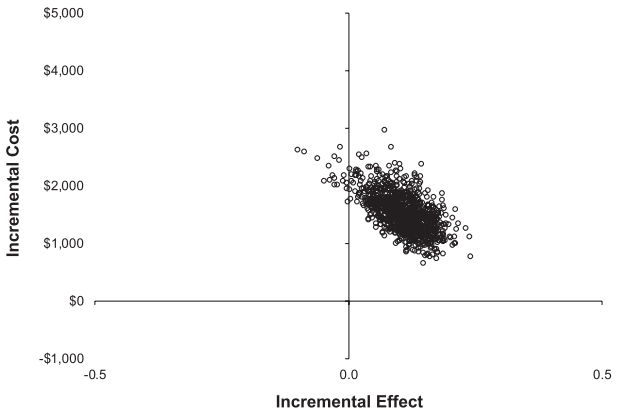


**Figure 3.** A probabilistic sensitivity analysis is illustrated.

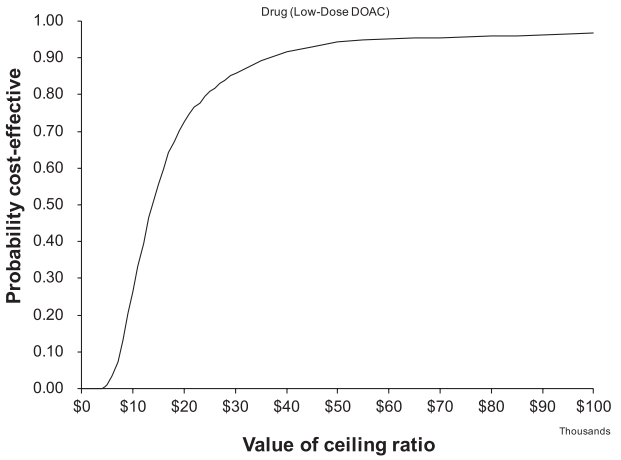


**Figure 4.** A cost-effectiveness acceptability curve is shown. DOAC indicates direct oral anticoagulant.

analysis, the incremental cost difference was similar, but the incremental QALY difference was smaller between the DOAC and placebo arms, and the resulting ICER was higher at $15,602 per QALY (Table 6). Finally, we assessed how differential negotiated drug-acquisition cost would affect our outcomes by using the Federal Supply Schedule drug pricing instead of the Red Book commercial pricing. In this sensitivity analysis, the lower acquisition drug cost for apixaban translated into a lower incremental cost difference of $518, an unchanged incremental QALY difference for the 2 arms, and an ICER of $4283 per QALY gained over a lifetime (Table 7).

### *Stratified Analysis: Highest Risk Versus Intermediate Risk*

To better characterize the heterogeneous benefits of low-dose DOAC prophylaxis in CAT prevention, we explored the cost effectiveness of the intervention after stratification by the Khorana score. As expected, selection of the higher risk group yielded more favorable cost-effectiveness values. Patients who had the highest risk of thrombosis with Khorana scores ≥3 (Table 8) had an incremental cost increase of $1103, an incremental

**TABLE 4.** Sensitivity Analysis #1: Outcomes Based on On-Treatment (As-Treated) Instead of Overall Follow-Up (Intention to Treat) Transition Probability and Relative Risk for VTE

| Outcome | Low-Dose DOAC | Placebo |
|---|---|---|
| Deterministic outcome | | |
| Cost | | |
| Total cost | $9448 | $8038 |
| Health outcomes | | |
| LY | 6.66 | 6.47 |
| QALY | 4.91 | 4.76 |
| Cost effectiveness | | |
| Δ Cost | $1409 | |
| Δ LY | 0.19 | |
| Δ QALY | 0.14 | |
| ICER (per QALY) | $9896 | |

Abbreviations: DOAC, direct oral anticoagulant; ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year.

**TABLE 5.** Sensitivity Analysis #2: Outcomes Based on 12-Months Instead of 6-Month Duration of Drug Prophylaxis

| Outcome | Low-Dose DOAC | Placebo |
|---|---|---|
| Deterministic outcome | | |
| Cost | | |
| Total cost | $10,864 | $8454 |
| Health outcomes | | |
| LY | 6.54 | 6.34 |
| QALY | 4.82 | 4.67 |
| Cost effectiveness | | |
| Δ Cost | $2410 | |
| Δ LY | 0.20 | |
| Δ QALY | 0.15 | |
| ICER (per QALY) | $16,389 | |

Abbreviations: DOAC, direct oral anticoagulant; ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year.

QALY increase of 0.19, and an ICER of $5794 per QALY. In contrast, those who had an intermediate risk of thrombosis with a Khorana score of 2 (Table 9) had an incremental cost increase of $1527, an incremental QALY increase of 0.11, and an ICER of $15,118 per QALY.

## DISCUSSION

In on our cost-utility analysis using the Markov model, we found that low-dose DOAC (rivaroxaban or apixaban) thromboprophylaxis for 6 months was a cost-effective strategy for the prevention of CAT in patients with cancer who were at intermediate-to-high risk for CAT in the United States. The ICER was considered cost effective 94% of the time using the traditional $50,000 per QALY value threshold. Although the exact "threshold" used in cost-effectiveness analyses remains a matter

**TABLE 6.** Sensitivity Analysis #3: Outcomes Based on Constant Cancer Mortality Rate From Year 5 and Beyond Instead of Life-Table Extrapolation

| Outcome | Low-Dose DOAC | Placebo |
|---|---|---|
| Deterministic outcome | | |
| Cost | | |
| Total cost | $8874 | $7466 |
| Health outcomes | | |
| LY | 5.32 | 5.20 |
| QALY | 3.92 | 3.83 |
| Cost effectiveness | | |
| Δ Cost | $1409 | |
| Δ LY | 0.12 | |
| Δ QALY | 0.09 | |
| ICER (per QALY) | $15,602 | |

Abbreviations: DOAC, direct oral anticoagulant; ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year.

**TABLE 7.** Sensitivity Analysis #4: Outcomes Based on Drug Pricing Estimates from the Federal Supply Schedule Instead of the Red Book

| Outcome | Low-Dose DOAC | Placebo |
|---|---|---|
| Deterministic outcome | | |
| Cost | | |
| Total cost | $8798 | $8280 |
| Health outcomes | | |
| LY | 6.51 | 6.34 |
| QALY | 4.79 | 4.67 |
| Cost effectiveness | | |
| Δ Cost | $518 | |
| Δ LY | 0.16 | |
| Δ QALY | 0.12 | |
| ICER (per QALY) | $4283 | |

Abbreviations: DOAC, direct oral anticoagulant; ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year.

of debate, the $50,000 benchmark serves well as a suggested lower boundary.[38] The cost-effectiveness values were particularly high for patients with the highest-risk for VTE (Khorana scores ≥3). As the first formal economic evaluation on the use of low-dose DOACs to prevent CAT, we believe that findings from the current study offer new insight into appropriate patient selection based on society's willingness-to-pay threshold, which, in turn, can help health systems and payers decide whether to implement such a thromboprophylaxis intervention.

CAT is a common complication associated with anticancer therapy; however, controversies exist on the need, duration, and choice of thromboprophylaxis.[39] As shown in our Markov model, appropriate prevention of VTE could help reduce future VTE treatment-associated costs and complications, even if it does not directly reduce cancer-associated mortality. The success of a prophylactic strategy depends both on the baseline rate of

**TABLE 8.** Subgroup Analysis #1: Outcomes Based on the High-Risk Subgroup Patients Only (Khorana Score ≥3)

| Outcome | Low-Dose DOAC | Placebo |
|---|---|---|
| Deterministic outcome | | |
| Cost | | |
| Total cost | $9987 | $8884 |
| Health outcomes | | |
| LY | 6.47 | 6.21 |
| QALY | 4.76 | 4.57 |
| Cost effectiveness | | |
| Δ Cost | $1103 | |
| Δ LY | 0.26 | |
| Δ QALY | 0.19 | |
| ICER (per QALY) | $5794 | |

Abbreviations: DOAC, direct oral anticoagulant; ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year.

**TABLE 9.** Subgroup Analysis #2: Outcomes Based on the Intermediate-Risk Subgroup Patients Only (Khorana Score 2)

| Outcome | Low-Dose DOAC | Placebo |
|---|---|---|
| Deterministic outcome | | |
| Cost | | |
| Total cost | $9334 | $7807 |
| Health outcomes | | |
| LY | 6.55 | 6.41 |
| QALY | 4.83 | 4.72 |
| Cost effectiveness | | |
| Δ Cost | $1527 | |
| Δ LY | 0.14 | |
| Δ QALY | 0.11 | |
| ICER (per QALY) | $15,118 | |

Abbreviations: DOAC, direct oral anticoagulant; ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year.

VTE occurrence and on the relative risk reduction associated with the intervention. In older studies that compared LMWH versus placebo for the prevention of CAT (Prevention of Venous and Arterial Thromboembolism, in Cancer Patients Undergoing Chemotherapy, With a Low Molecular Weight Heparin [PROTECHT; ClinicalTrials.gov Identifier: NCT00951574], Evaluation of AVE5026 in the Prevention of Venous Thromboembolism in Cancer Patients Undergoing Chemotherapy [SAVE-ONCO; clinicaltrials.gov identifier NCT00694382]), the baseline risk of VTE was only 3% to 4% by 6 months.[40,41] The 2 trials included in the current study (AVERT and CASSINI) enrolled patients at intermediate-to-high risk for VTE (Khorana score ≥2), which resulted in VTE rates of approximately 9% by 6 months in the placebo groups.[7,8] The subgroup of patients with Khorana scores ≥3 reached rates as high as 12%. Because the risk of VTE is highest at the time of cancer diagnosis and plateaus over time,[42] a prophylactic strategy focusing on the initial high-risk period may be the most beneficial approach. On the basis of our various sensitivity and scenario analyses, we believe that a health system–wide implementation of limited duration (6 months), low-dose DOAC thromboprophylaxis for patients with Khorana scores ≥3 would lead to the highest incremental quality gained at the lowest incremental cost from a policy implication standpoint. Finally, it is important to consider both the incremental QALY in the context of lower baseline quality-of-life associated with cancer symptoms as well as any incremental cost in light of the very expensive nature of current cancer treatment.[43] Future studies focusing on quality-of-life measurement associated with VTE and bleeding among patients with cancer who are DOACs are needed.

There are several strengths to our current study. The study benefited from a combination of pooled efficacy and safety data from primary RCTs for the first 6 months during intervention and from epidemiology studies beyond 6 months during the follow-up period. The generalizability of the findings was also strengthened by the concordance of various sensitivity and subgroup analyses. The key drivers found in our one-way sensitivity analysis were consistent with our expectation that either more precise estimation of the primary efficacy and safety outcomes or of the drug cost would have the greatest impact on the ICER estimation. Finally, we performed our cost-utility analysis over a lifetime horizon, in accordance with the Consolidated Health Economic Evaluation Reporting Standards guideline, to reflect the long-term consequences of a relatively short (6-month) preventive intervention. Economic evaluations based on RCTs often have truncated time horizons because of the impracticality of long-term follow-up.[44] Nonetheless, early differences in key outcomes such as mortality should be evaluated over a lifetime for the most accurate estimation of value. To address this issue, we modeled survival using cancer mortality rates and life-table rates uniformly in both intervention and placebo cohorts. The similarity in clinical 6-month, 5-year, and lifetime outcomes suggest that the differences in QALYs (see Supporting Table 5) were driven mostly by early preventive effects.

There are also inherent limitations with our study. An assumption worthy of highlighting is that patients would continue the same anticoagulant treatment indefinitely unless they discontinued the drug at a prespecified discontinuation rate. In reality, some patients (eg, those who experience VTE but are alive and cancer-free after 1-2 years) would likely stop anticoagulant treatment.

Those with upper extremity or catheter-associated DVTs also tend to have a shorter duration of treatment. Furthermore, patients often switch the type of anticoagulant during treatment. Such specific scenarios cannot be fully addressed without a patient-level simulation model with tremendous complexity. Another limitation involves the extrapolation of efficacy and safety data beyond 6 months. To mitigate potential errors, we applied the same rates beyond 6 months to both intervention and placebo arms and conducted sensitivity analyses to show that these later rates had little effect on the ICER. Other limitations include the extrapolation of cost and utility data from patients without to patients with cancer. We derived the direct medical cost from a post-hoc analysis of a DOAC trial for medical patients with VTE and did not consider direct nonmedical cost, indirect cost, or individual coupons or cost-assistance programs. We also derived the utility weights from a study of general medical patients with VTE. Because the standard of care was LMWH or warfarin in these older studies, future work dedicated to patients with VTE receiving DOAC prophylaxis are needed to ensure generalizability. Finally, we only performed subgroup analysis for patients with risk stratifications of VTE by Khorana score. Other subgroups, such as patients with different types of cancer, may benefit differently from thromboprophylaxis and would require dedicated analysis in the future.

In conclusion, thromboprophylaxis with low-dose DOAC (rivaroxaban or apixaban) for 6 months appears to be a cost-effective strategy for the prevention of CAT in the United States. Future research should focus on a better understanding of the significance of these adverse events on longer term quality of life and their impact on delays in anticancer treatment.

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## CONFLICT OF INTEREST DISCLOSURES

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## AUTHOR CONTRIBUTIONS

**Ang Li** contributed to the conceptualization, data curation, formal analysis, methodology, and writing–original draft. **Josh J. Carlson** contributed to the formal analysis, methodology, software, and writing–review and editing. **Nicole M. Kuderer**, **Jordan K. Schaefer**, **Shan Li**, **David A. Garcia**, **Alok A. Khorana**, and **Marc Carrier** contributed to data curation and writing–review and editing. **Gary H. Lyman** contributed to the conceptualization, methodology, supervision, and writing–review and editing.

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