DR. ANG LI (Orcid ID : 0000-0002-8455-2309)
MR. JOSH CARLSON (Orcid ID : 0000-0001-7664-8370)
DR. JORDAN K SCHAEFER (Orcid ID : 0000-0002-7166-386X)

Article type : Original Article

Cost-effectiveness analysis of low-dose direct oral anticoagulant (DOAC) for the prevention of cancer associated thrombosis in the United States

Running Title: Cost utility analysis for cancer VTE

Ang Li[1], MD, MS, Josh J. Carlson[2], PhD, MPH, Nicole M. Kuderer[3], MD, Jordan K. Schaefer[4], MD, Shan Li[5], PharmD, David A. Garcia[1], MD, Alok A. Khorana[6], MD, Marc Carrier[7], MD, MSc, Gary H. Lyman[8,9], MD, MPH

[1]Division of Hematology, University of Washington School of Medicine, Seattle, WA
[2]The Comparative Health Outcomes, Policy, and Economics (CHOICE) Institute, University of Washington School of Pharmacy, Seattle, Washington
[2]Advanced Cancer Research Group, and Department of Medicine, University of Washington, Seattle, WA
[4]Division of Hematology/Oncology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI
[5]Pharmacy Services, University of Washington Medical Center, Seattle, WA, USA
[6]Department of Hematology and Medical Oncology, Taussig Cancer Institute and Case Comprehensive Cancer Center, Cleveland Clinic, Cleveland, OH

[7]Department of Medicine, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Ontario, Canada
[8]Division of Medical Oncology, University of Washington School of Medicine, Seattle, WA
[9]Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle WA

Corresponding Author:
Gary H. Lyman, MD, MPH
Fred Hutchinson Cancer Research Center
1100 Fairview Ave N
Seattle, WA, United State 98109
Phone: (206) 667-6670, Fax: (206) 667-5977
Email: glyman@fredhutch.org

Funding Support:
Dr. Li reports research support from the Conquer Cancer Foundation Young Investigator Award, Hemostasis and Thrombosis Research Society Mentored Research Award supported by an independent medical educational grant from Shire, and National Hemophilia Foundation Shire Clinical Fellowship Award. Dr. Khorana reports research support from the Sondra and Stephen Hardis Chair in Oncology Research at the Taussig Cancer Institute at Cleveland Clinic, and the Consortium Linking Oncology with Thrombosis (CLOT) of the National Heart, Lung and Blood Institute (U01-HL143402). Dr. Carrier reports research support from the T2 Research Chair in Venous Thromboembolism and Cancer from the Department of Medicine at University of Ottawa.

Conflict of Interest Disclosure:
The current study was conducted without funding from industry. Dr. Li has no relevant financial interests, activities, relationships, or affiliations. Dr. Kuderer reports receiving research consulting fees and travel expense reimbursement for serving on the steering committee of CASSINI from Janssen, and research consulting fees and travel expense reimbursement from Janssen, Pfizer, Bayer, and Halozyme, outside the submitted work potentially related to this topic. Dr. Garcia reports grants from Daiichi Sankyo, personal fees and personal fees and non-financial

support from Alexion, grants and personal fees from Incyte, grants, personal fees and non-financial support from Janssen, personal fees and non-financial support from Seattle Genetics, outside the submitted work. Dr. Khorana reports personal fees and non-financial support from Janssen, personal fees and non-financial support from Bayer, personal fees and non-financial support from Sanofi, personal fees and non-financial support from Parexel, personal fees and non-financial support from Janssen, personal fees and non-financial support from Halozyme, personal fees and non-financial support from Pfizer, personal fees and non-financial support from Seattle Genetics, personal fees from Pharmacyclics, personal fees from Pharmacyte, personal fees and non-financial support from AngioDynamics, personal fees and non-financial support from Leo Pharma, personal fees from TriSalus, personal fees and non-financial support from Medscape/WebMD, grants from Merck, grants from Array, grants from Bristol-Myers Squibb, grants from Leap Pharma, outside the submitted work. Dr. Carrier reports grants and personal fees from BMS, grants and personal fees from Pfizer, grants and personal fees from Leo Pharma, personal fees from Bayer, personal fees from Sanofi, personal fees from Servier, outside the submitted work. Dr. Lyman reports receiving no compensation for serving as co-chair of the Steering Committee of the CASSINI study or chair of the Data Safety Monitoring Committee of the AVERT study and has no personal financial disclosures related to the subject of this study. Dr Lyman reports that his spouse received research consulting fees from Janssen during the conduct of this study and consulting fees from Bayer and Pfizer, outside the submitted work.

Author Contribution:

Dr. Ang Li contributed to the conceptualization, data curation, formal analysis, methodology, and writing (original draft). Dr. Carlson contributed to the formal analysis, methodology, software, and writing (review and editing). Drs. Kuderer, Schaefer, Shan Li, Garcia, Khorana, and Carrier contributed to data curation and writing (review and editing). Dr. Lyman contributed to the conceptualization, methodology, supervision, and writing (review and editing).

Condensed Abstract:

- Low-dose direct oral anticoagulant appears to be cost-effective versus placebo for preventing cancer associated thrombosis

- Patients with the highest risk for thrombosis according to the Khorana score derived the most incremental benefit from a preventive strategy

Abstract:

Introduction: Randomized controlled trials (RCTs) have demonstrated that low-dose direct oral anticoagulant (DOAC), including rivaroxaban and apixaban, may help reduce the incidence of cancer-associated venous thromboembolism (VTE).

Methods: We performed a cost-utility analysis from the health sector perspective using a Markov state-transition model in cancer patients who are at intermediate-to-high risk for VTE. We obtained transition probability, relative risk, cost, and utility inputs from a meta-analysis of the RCTs and relevant epidemiology studies. We calculated the differences in cost, quality-adjusted life year (QALY), and incremental cost-effectiveness ratio (ICER) per patient over a lifetime horizon. One-way, probabilistic, and scenario sensitivity analyses were conducted.

Results: In cancer patients at intermediate-to-high risk for VTE, treatment with low-dose DOAC thromboprophylaxis for 6 months, when compared to placebo, was associated with 32 per 1,000 fewer VTE and 11 per 1,000 more major bleeding over lifetime. The incremental cost and QALY increases were $1,445 and 0.12, respectively, with an ICER of $11,947 per QALY gained. Key drivers of ICER variations included relative risks of VTE and bleeding, as well as drug cost. This strategy was 94% cost effective at the threshold of $50,000/QALY. Selection of patients with Khorana Score 3+ yielded the greatest value with an ICER of $5,794 per QALY gained.

Conclusion: Low-dose DOAC thromboprophylaxis for 6 months appears to be cost-effective in patients with cancer at intermediate-to-high risk for VTE. Implementation of this strategy in patients with Khorana Score 3+ may lead to the highest cost-benefit ratio.

Keywords: Apixaban, Cost-Benefit Analysis, Factor Xa Inhibitors, Neoplasm, Rivaroxaban, Venous Thromboembolism

Word Count: 3708

Text pages: 35

Tables: 5

Figures: 4

Supporting files: 1

Introduction:

Cancer-associated thrombosis (CAT) is often the harbinger of complication or death in ambulatory cancer patients.[1,2] Patients with venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), often experience delay in cancer treatment as well as 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) produce similar clinical outcomes and quality adjusted life years (QALYs) at a lower to similar cost when compared to low-molecular-weight heparins (LMWHs).[4–6] No such economic analysis has been done in the preventive setting.

In year 2019, two randomized controlled trials (RCTs) showed that thromboprophylaxis with low-dose DOACs, specifically apixaban and rivaroxaban, could help reduce the incidence of CAT when compared to placebo.[7,8] In contrast to prior studies that included patients with heterogeneous risk for VTE,[9,10] these studies only selected cancer patients who 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 associated with low-dose DOAC.

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

Method:

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 of 60-year-old ambulatory cancer patients 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 (Supplemental eTable 1). We also considered subgroup analyses of patients at the highest-risk for VTE (Khorana Score 3+) and those at an 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, major bleeding (MB), and clinically relevant non-major 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 post-complication states included post-intracranial bleeding (ICH) after MB, chronic thromboembolic pulmonary hypertension (CTEPH) after PE, and post-thrombotic syndrome (PTS) after DVT. Finally, there were three 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 one 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 60-year-old subjects. A 3% yearly discount 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 therapeutic-dose of DOAC and remain on-treatment unless VTE, bleeding, death, or discontinuation occurs, 3) patients who experienced any bleeding while on prophylaxis would all transition off DOAC after 1 cycle due to 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 rate as the general non-cancer 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 (RR), and confidence intervals (CI) for VTE, bleeding, discontinuation, and mortality outcomes in a meta-analysis of the AVERT and CASSINI RCTs.[7,8,13] RR estimation was performed with 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 that 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-analysis was performed for patients with Khorana Score 3+ and 2 after outcomes were obtained directly from the trial authors.[13] Due to the low case fatality associated with PE, MB, and ICH, pooled estimates were derived from two prophylaxis trials and one 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 extrapolation from the RCTs because VTE incidence decreases significantly over time beyond initial cancer diagnosis and treatment. For the first two years, we estimated the transition probability using the product of cancer-specific VTE incident rate from the epidemiology study and the proportion of cancer subtype from the RCTs (Supplemental eTable 2). The rate was assumed to be constant between second and fifth year. After five years, we used the age-specific VTE incident rate from a United

Kingdom (UK) epidemiology study of non-cancer patients.[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 cancer patients.[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 (SEER) database.[21] For the first 5 years, we estimated the probability using the product of cancer-specific mortality rate from SEER and the proportion of cancer subtype from the RCTs (Supplemental eTable 3). After five years, we used the age-specific mortality rate from the US 2016 life table.[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 cost related to drugs and complications. Unit costs for rivaroxaban 10 mg ($14.93), apixaban 2.5 mg ($7.40), edoxaban 60 mg ($12.12), and enoxaparin 100 mg ($15.00) were based on the wholesale acquisition cost (WAC) from the *Red Book*.[23] Monthly costs (each cycle) were derived from 30 day prescription 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 (FSS) as a sensitivity analysis. Adverse event costs (each cycle) for initial and recurrent VTE events as well as bleeding episodes were obtained from *Preblick et al.* where the cost per stay estimates were derived from the Premier Hospital Database and post-hoc analysis of the DOAC arm of the Hokusai-VTE study.[24] For post-complication 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 cancer patients as the product of cancer-specific utility weight from various studies and the proportion of cancer subtype from the RCTs (Supplemental eTable 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.* 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 quality-adjusted life-years (QALY) were estimated for each treatment over the lifetime time horizon. The incremental cost effectiveness ratio (ICER) was calculated as the difference in cost over the difference in QALY. 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% CI were used if such data were available from literature (Table 2). Otherwise, the variations were assumed to be +/- 20% from the mean value. We performed probabilistic sensitivity analysis (PSA) using Monte Carlo simulation over 1,000 times to generate the cost-effectiveness (CE) plane and the cost effectiveness acceptability curve (CEAC). The distributions assumed for the input parameters were gamma (cost), beta (utility weights and transition probability), and log-normal (RR) (Table 2). The standard errors were derived from the 95% CI and alpha/beta parameters were estimated using 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 (CHEERS) 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 AVERT and CASSINI RCTs are shown in Table 1. For the primary efficacy outcome of first VTE occurrence by 6 months, low-dose DOAC prophylaxis was associated with a RR of 0.56 (0.35-0.89) for VTE. A higher risk reduction with a RR of 0.30 (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 a RR of 1.96 (0.80-4.82) for MB and a RR of 1.28 (0.74-2.20) for CRNMB. Both intervention and placebo arms had similar rates of drug discontinuation unrelated to primary outcomes with a RR of 1.00 (0.84-1.19). The two RCTs had moderate heterogeneity in the mortality outcome reporting and a pooled RR of 0.98 (0.67-1.43); however, this estimate was not used as 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 the subgroup of Khorana Score. In patients with Khorana Score 3+, low-dose DOAC was associated with a RR of 0.47 (0.25-0.89) for VTE and a RR of 1.60 (0.42-6.01) for MB; in those with Khorana Score 2, low-dose DOAC had a RR of 0.60 (0.30-1.19) for VTE and a RR of 1.91 (0.56-6.53) for MB. The proportions of patients that died from PE, MB, or 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. Based on this analysis, PE and MB case fatalities were 13.21% (n=14) and 3.85% (n=3), respectively; 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, and 21 more CRNMB per 1,000 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-month and 5-year time (Supplemental eTable 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 non-adherence/discontinuation factor in the Markov's model, which led to small attenuations of the absolute risk reductions of the primary outcomes. Over lifetime, the intervention group had a mean total cost of $9,899 per person, a life year of 6.51, and a QALY of 4.79. The placebo group had a mean total cost of 8,454 per person, a life year of 6.34, and a QALY of 4.67. Low-dose DOAC prophylaxis was associated with an incremental cost increase of $1,445, an incremental QALY increase of 0.12, and an ICER of $11,947 per QALY.

In one-way sensitivity analyses (Figure 2), variations in the relative risks of PE, DVT, MB along with the cost associated with low-dose DOAC prophylaxis led to the largest differences in ICER. In probabilistic sensitivity analysis (Figure 3 and Table 3), low-dose DOAC prophylaxis was associated with an incremental cost increase of $1,537, an incremental QALY increase of 0.11, and an ICER of $14,330 per QALY. As shown in the cost effectiveness acceptability curve (Figure 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 (ITT) follow-up (Table 4.1). While the ITT estimates preserve the randomization and generally represent unconfounded effects associated with the intervention, the as-treated estimates are more realistic since our Markov model accounts for unintended discontinuation of study drugs. As compared to the primary analysis, low-dose DOACs in this analysis were associated with a similar incremental cost increase, a greater incremental QALY increase (0.14 vs. 0.12), and an ICER of $9,896 per QALY. Second, we examined the effect of assigning patients to 12 months of prophylaxis instead of 6 months (Table 4.2). As compared to the primary analysis, low-dose DOAC in this scenario was associated with a greater incremental cost increase ($2,410 vs. $1,445), 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 year 5 cancer mortality rate instead of US life table would affect the overall outcome. In this sensitivity analysis, the incremental cost difference was similar but the incremental QALY difference was smaller between the DOAC and placebo arm and the resulting ICER was higher at $15,602 per QALY (Table 4.3). Finally, we assessed how differential negotiated drug acquisition cost would affect our outcomes by using the Federal Supply Schedule (FSS) drug pricing instead of the Red Book commercial pricing. In this sensitivity analysis, the lower acquisition drug cost translated into a lower incremental cost difference of $518 and an unchanged incremental QALY difference for the two arms and an ICER of $4,283 per QALY gained over lifetime (Table 4.4).

Stratified Analysis: Highest Risk vs. Intermediate Risk

To better characterize heterogeneous benefits of low-dose DOAC 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 with the highest risk of thrombosis with Khorana Score 3+ (Table 5.1) had an incremental cost increase of $1,103, an incremental QALY increase of 0.19, and an ICER of $5,794 per QALY. In contrast, those with intermediate risk of thrombosis with Khorana Score of 2 (Table 5.2) had an incremental cost increase of $1,527, 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 cancer patients at intermediate to high risk for CAT in the US. The ICER was considered cost effective 94% of the time using the traditional $50,000 per QALY value threshold. While the exact "threshold" used in cost-effectiveness analyses remains a matter of debate, the $50,000 benchmark serves well as an implied lower boundary.[38] The cost-effectiveness values were particularly high for patients with the highest-risk for VTE (Khorana Score 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 on appropriate patient

selection based on the society's willingness-to-pay threshold, which can in turn help health systems and payers decide whether to implement such a thromboprophylaxis intervention.

CAT is a common complication associated with anti-cancer 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 cost and complications, even if it does not directly reduce cancer-associated mortality. The success of a prophylactic strategy depends on both the baseline rate of VTE occurrence and the relative risk reduction associated with the intervention. In older studies that compared LMWH versus placebo for the prevention of CAT (PROTECHT, SAVE-ONCO), the baseline risk of VTE was only 3-4% by 6 months.[40,41] The two trials included in the current study (AVERT, CASSINI) enrolled patients at intermediate-to-high risk for VTE (Khorana Score 2+) that resulted in VTE rates of approximately 9% by 6 months in the placebo groups.[7,8] The subgroup of patients with Khorana Score 3+ reached rates as high as 12%. As the risk of VTE is the 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. Based on 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 Score 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 (QOL) 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 QOL measurement associated with VTE and bleeding among cancer patients receiving 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 epidemiology studies beyond 6 months during 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 that of the

drug cost would have the largest impact on the ICER estimation. Lastly, we performed our cost-utility analysis over a horizon of lifetime in accordance to the CHEERS 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 due to the impracticality of long-term follow-up.[44] Nonetheless, early differences in key outcomes such as mortality should be evaluated over lifetime for the most accurate estimation of value. To address this issue, we modeled survival using cancer mortality rates and lifetable rates uniformly in both intervention and placebo cohorts. The similarity in clinical outcomes at 6-month, 5-year, and lifetime suggest that the differences in QALY (Supplemental eTable 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 pre-specified discontinuation rate. In reality, some patients (e.g. 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 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 impact on the ICER. Other limitations include the extrapolation of cost and utility data from non-cancer patients to cancer patients. 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 non-medical 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. As the standard of care was LMWH or warfarin in these older studies, future work dedicated to patients with VTE receiving DOAC 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 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 anti-cancer treatment.

References:

1. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. *J Thromb Haemost*. 2007;5(3):632-634. doi:10.1111/j.1538-7836.2007.02374.x
2. Sørensen HT, Mellemkjaer L, Olsen JH, Baron JA. Prognosis of cancers associated with venous thromboembolism. *N Engl J Med*. 2000;343(25):1846-1850. doi:10.1056/NEJM200012213432504
3. Khorana AA, Dalal MR, Lin J, Connolly GC. Health care costs associated with venous thromboembolism in selected high-risk ambulatory patients with solid tumors undergoing chemotherapy in the United States. *Clinicoecon Outcomes Res*. 2013;5(1):101-108. doi:10.2147/CEOR.S39964
4. Li A, Garcia DA, Lyman GH, Carrier M. Direct oral anticoagulant (DOAC) versus low-molecular-weight heparin (LMWH) for treatment of cancer associated thrombosis (CAT): A systematic review and meta-analysis. *Thromb Res*. 2019;173(7):158-163. doi:10.1016/j.thromres.2018.02.144
5. Li A, Manohar PM, Garcia DA, Lyman GH, Steuten LM. Cost effectiveness analysis of direct oral anticoagulant (DOAC) versus dalteparin for the treatment of cancer associated thrombosis (CAT) in the United States. *Thromb Res*. 2019;180(February):37-42. doi:10.1016/j.thromres.2019.05.012
6. Connell NT, Connors JM. Cost-effectiveness of edoxaban versus dalteparin for the treatment of cancer-associated thrombosis. *J Thromb Thrombolysis*. June 2019. doi:10.1007/s11239-019-01903-z
7. Carrier M, Abou-Nassar K, Mallick R, et al. Apixaban to Prevent Venous Thromboembolism in Patients with Cancer. *N Engl J Med*. 2019;380(8):711-719. doi:10.1056/NEJMoa1814468
8. Khorana AA, Soff GA, Kakkar AK, et al. Rivaroxaban for Thromboprophylaxis in High-

Risk Ambulatory Patients with Cancer. *N Engl J Med*. 2019;380(8):720-728. doi:10.1056/NEJMoa1814630

9. Akl EA, Kahale LA, Hakoum MB, et al. Parenteral anticoagulation in ambulatory patients with cancer. *Cochrane database Syst Rev*. 2017;9(12):CD006652. doi:10.1002/14651858.CD006652.pub5
10. Di Nisio M, Porreca E, Candeloro M, De Tursi M, Russi I, Rutjes AW. Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy. *Cochrane database Syst Rev*. 2016;12(2):CD008500. doi:10.1002/14651858.CD008500.pub4
11. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood*. 2008;111(10):4902-4907. doi:10.1182/blood-2007-10-116327
12. Discount Window. Federal Reserve. https://www.frbdiscountwindow.org. Published 2018.
13. Li A, Kuderer NM, Garcia DA, et al. Direct oral anticoagulant for the prevention of thrombosis in ambulatory patients with cancer: A systematic review and meta-analysis. *J Thromb Haemost*. 2019;15(August):jth.14613. doi:10.1111/jth.14613
14. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188. doi:https://doi.org/10.1016/0197-2456(86)90046-2
15. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism. *N Engl J Med*. 2018;378(7):615-624. doi:10.1056/NEJMoa1711948
16. Chew HK, Wun T, Harvey D, Zhou H, White RH. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. *Arch Intern Med*. 2006;166(4):458-464. doi:10.1001/.458
17. Martinez C, Cohen AT, Bamber L, Rietbrock S. Epidemiology of first and recurrent venous thromboembolism: a population-based cohort study in patients without active cancer. *Thromb Haemost*. 2014;112(2):255-263. doi:10.1160/TH13-09-0793
18. Cohen AT, Katholing A, Rietbrock S, Bamber L, Martinez C. Epidemiology of first and recurrent venous thromboembolism in patients with active cancer. A population-based cohort study. *Thromb Haemost*. 2017;117(1):57-65. doi:10.1160/TH15-08-0686
19. Ende-Verhaar YM, Cannegieter SC, Vonk Noordegraaf A, et al. Incidence of chronic

thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature. *Eur Respir J*. 2017;49(2):880-888. doi:10.1183/13993003.01792-2016

20. Kahn SR, Shapiro S, Wells PS, et al. Compression stockings to prevent post-thrombotic syndrome: A randomised placebo-controlled trial. *Lancet*. 2014;383(9920):880-888. doi:10.1016/S0140-6736(13)61902-9
21. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database. Incidence - SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2018 Sub (2000-2016), National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2019.
22. Arias E, Xu J, Kochanek KD. United States Life Tables, 2016. *Natl Vital Stat Rep*. 2019;68(4):1-66. doi:10.4135/9781412952484.n432
23. Red Book. Truven Health Analytics: Average Wholesale Price (AWP). http://truvenhealth.com/Products/Micromedex/Product-Suites/Clinical-Knowledge/RED-BOOK. Published 2019.
24. Preblick R, Kwong WJ, White RH, Goldhaber SZ. Cost-effectiveness of edoxaban for the treatment of venous thromboembolism based on the Hokusai-VTE study. *Hosp Pract (1995)*. 2015;43(5):249-257. doi:10.1080/21548331.2015.1099412
25. Lee WC, Christensen MC, Joshi A V., Pashos CL. Long-term cost of stroke subtypes among Medicare beneficiaries. *Cerebrovasc Dis*. 2007;23(1):57-65. doi:10.1159/000096542
26. Caprini JA, Botteman MF, Stephens JM, et al. Economic burden of long-term complications of deep vein thrombosis after total hip replacement surgery in the United States. *Value Health*. 2003;6(1):59-74. doi:10.1046/j.1524-4733.2003.00204.x
27. Kirson NY, Birnbaum HG, Ivanova JI, Waldman T, Joish V, Williamson T. Excess costs associated with patients with pulmonary arterial hypertension in a US privately insured population. *Appl Health Econ Health Policy*. 2011;9(5):293-303. doi:10.2165/11592430-000000000-00000
28. Consumer Price Index, All Urban Consumers, Medical care – Not Seasonally Adjusted. U.S. Department of Labor Bureau of Labor Statistics. http://data.bls.gov/cgi-bin/surveymost?cu. Published 2018.

29. Romanus D, Kindler HL, Archer L, et al. Does health-related quality of life improve for advanced pancreatic cancer patients who respond to gemcitabine? Analysis of a randomized phase III trial of the cancer and leukemia group B (CALGB 80303). *J Pain Symptom Manage*. 2012;43(2):205-217. doi:10.1016/j.jpainsymman.2011.09.001
30. Curran D, Pozzo C, Zaluski J, et al. Quality of life of palliative chemotherapy naive patients with advanced adenocarcinoma of the stomach or esophagogastric junction treated with irinotecan combined with 5-fluorouracil and folinic acid: results of a randomised phase III trial. *Qual Life Res*. 2009;18(7):853-861. doi:10.1007/s11136-009-9493-z
31. Papaioannou D, Rafia R, Rathbone J, Stevenson M, Buckley Woods H, Stevens J. Rituximab for the first-line treatment of stage III-IV follicular lymphoma (review of Technology Appraisal No. 110): a systematic review and economic evaluation. *Health Technol Assess*. 2012;16(37):1-253, iii-iv. doi:10.3310/hta16370
32. Kwon JS, Sun CC, Peterson SK, et al. Cost-effectiveness analysis of prevention strategies for gynecologic cancers in Lynch syndrome. *Cancer*. 2008;113(2):326-335. doi:10.1002/cncr.23554
33. Schünemann HJ, Ventresca M, Crowther M, et al. Use of heparins in patients with cancer: Individual participant data metaanalysis of randomised trials study protocol. *BMJ Open*. 2016;6(4):e010569. doi:10.1136/bmjopen-2015-010569
34. Hogg K, Kimpton M, Carrier M, Coyle D, Forgie M, Wells P. Estimating quality of life in acute venous thrombosis. *JAMA Intern Med*. 2013;173(12):1067-1072. doi:10.1001/jamainternmed.2013.563
35. Lenert LA, Soetikno RM. Automated computer interviews to elicit utilities: potential applications in the treatment of deep venous thrombosis. *J Am Med Inform Assoc*. 1997;4(1):49-56. doi:10.1136/jamia.1997.0040049
36. Ghofrani H-A, D'Armini AM, Grimminger F, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. *N Engl J Med*. 2013;369(4):319-329. doi:10.1056/NEJMoa1209657
37. Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force.

Value Health. 2013;16(2):231-250. doi:10.1016/j.jval.2013.02.002

38. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness--the curious resilience of the $50,000-per-QALY threshold. *N Engl J Med*. 2014;371(9):796-797. doi:10.1056/NEJMp1405158
39. Connors JM. Prophylaxis against Venous Thromboembolism in Ambulatory Patients with Cancer. *N Engl J Med*. 2014;370(26):2515-2519. doi:10.1056/nejmra1401468
40. Agnelli G, George DJ, Kakkar AK, et al. Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. *N Engl J Med*. 2012;366(7):601-609. doi:10.1056/NEJMoa1108898
41. Agnelli G, Gussoni G, Bianchini C, et al. Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study. *Lancet Oncol*. 2009;10(10):943-949. doi:10.1016/S1470-2045(09)70232-3
42. Blom JW, Doggen CJM, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. *JAMA*. 2005;293(6):715-722. doi:10.1001/jama.293.6.715
43. PDQ Adult Treatment Editorial Board. *Financial Toxicity and Cancer Treatment (PDQ®): Health Professional Version*.; 2002.
44. Sculpher MJ, Claxton K, Drummond M, McCabe C. Whither trial-based economic evaluation for health care decision making? *Health Econ*. 2006;15(7):677-687. doi:10.1002/hec.1093

Table 1. Pooled Measurement of Effectiveness from DOAC Thromboprophylaxis Trials

	DOAC	n/N	Placebo	n/N	Relative Risk
VTE outcomes on PPX					
1st VTE by 6 months	5.20%	37/711	**9.23%**	65/704	**0.56 (0.35-0.89)**
(PE)	2.39%	17/711	**4.83%**	34/704	**0.49 (0.23-1.04)**
AVERT	1.72%	5/291	5.65%	16/283	
CASSINI	2.86%	12/420	4.28%	18/421	
(DVT)	2.81%	20/711	**4.40%**	31/704	**0.64 (0.37-1.11)**
AVERT	2.41%	7/291	4.24%	12/283	
CASSINI	3.10%	13/420	4.51%	19/421	
1st VTE during on-treatment period (sensitivity)	1.97%	14/711	**6.68%**	47/704	**0.30 (0.16-0.53)**
AVERT	1.03%	3/291	2.84%	20/704	
CASSINI	2.62%	11/420	6.41%	27/421	
Bleeding outcomes on PPX					
Major bleeding during on-treatment period	2.02%	14/693	**1.03%**	7/679	**1.96 (0.80-4.82)**
AVERT	2.08%	6/288	1.09%	3/275	
CASSINI	1.98%	8/405	0.99%	4/404	
CRNMB during on-treatment period	4.18%	29/693	**3.24%**	22/679	**1.28 (0.74-2.20)**
AVERT	6.25%	18/288	5.09%	14/275	
CASSINI	2.72%	11/405	1.98%	8/404	
Non-adherence/intolerance on PPX					
Drug discontinuation unrelated to death/VTE/bleed	28.14%	195/693	**28.13%**	191/679	**1.00 (0.84-1.19)**
AVERT	31.27%	88/288	29.68%	76/275	
CASSINI	26.42%	107/405	28.47%	115/404	

Mortality on PPX					
Non-PE/non-MB mortality by 6 months	16.46%	117/711	**17.61%**	124/704	**0.98 (0.67-1.43)***
AVERT	12.03%	35/291	9.54%	27/283	
CASSINI	19.52%	82/420	23.04%	97/421	
Subgroup analysis on PPX (Khorana Score 3+)					
1st VTE by 6 months	5.44%	13/239	**11.57%**	25/216	**0.47 (0.25-0.89)**
AVERT	5.71%	6/105	12.90%	12/93	
CASSINI	5.22%	7/134	10.57%	13/123	
1st VTE during on-treatment period (sensitivity)	2.93%	7/239	**7.87%**	17/216	**0.38 (0.14-1.07)**
AVERT	1.90%	2/105	9.68%	9/93	
CASSINI	3.73%	5/134	6.50%	8/123	
Major bleeding during on-treatment period	2.58%	6/233	**1.42%**	3/211	**1.60 (0.42-6.01)**
AVERT	1.90%	2/105	0.00%	0/90	
CASSINI	3.13%	4/128	2.48%	3/121	
Subgroup analysis on PPX (Khorana Score 2)					
1st VTE by 6 months	5.14%	24/467	**8.25%**	40/485	**0.60 (0.30-1.19)**
AVERT	3.23%	6/186	8.42%	16/190	
CASSINI	6.41%	18/281	8.14%	24/295	
1st VTE during on-treatment period (sensitivity)	1.50%	7/467	**6.19%**	30/485	**0.24 (0.08-0.73)**
AVERT	0.54%	1/186	5.79%	11/190	
CASSINI	2.14%	6/281	6.44%	19/295	
Major bleeding during on-treatment period	1.75%	8/456	**0.86%**	4/465	**1.91 (0.56-6.53)**
AVERT	2.19%	4/183	1.62%	3/185	
CASSINI	1.47%	4/273	0.36%	1/280	

Pooled % estimates for PPX and RX**	**Combined**	**n/N**	
PE case fatality %	**13.21%**	**14/106**	**n/a**
AVERT	0.00%	0/21	
CASSINI	13.33%	4/30	
Hokusai-VTE Cancer	18.18%	10/55	
MB case fatality %	**3.85%**	**3/78**	**n/a**
AVERT	0.00%	0/9	
CASSINI	8.33%	1/12	
Hokusai-VTE Cancer	3.51%	2/57	
MB to ICH %	**10.26%**	**8/78**	**n/a**
AVERT	0.00%	0/9	
CASSINI	16.67%	2/12	
Hokusai-VTE Cancer	10.53%	6/57	

PPX: prophylaxis, RX: treatment, VTE: venous thromboembolism, DVT: deep vein thrombosis, PE: pulmonary embolism, MB: major bleeding, CRNMB: clinically relevant non-major bleeding

* The estimate for RR of mortality was not used due to the lack of biologic rationale on DOAC improving survival

** Pooled estimates were derived from multiple DOAC trials due to small event rate in each study arm for individual trials

Table 2. Parameter Inputs with a Cycle Length of 1 Month

	Base Case	**Lower**	**Upper**	**Distribution**
Costs*				
cDOAC_ppx	$446	$357	$535	Gamma

Apixaban (2.5 mg bid) [23]	$444			
Rivaroxaban (10 mg daily) [23]	$448			
cEdoxaban_rx (30-60 mg daily) [23]	$364	$291	$436	Gamma
cEnoxaparin_rx (100 mg daily) [23]	$450	$360	$540	Gamma
cPE1 (first) [24]	$16,903	$13,522	$20,283	Gamma
cDVT1 (first) [24]	$9,766	$7,813	$11,720	Gamma
cPEr (recurrent) [24]	$18,705	$14,964	$22,446	Gamma
cDVTr (recurrent) [24]	$8,878	$7,103	$10,654	Gamma
cMB [24]	$19,469	$15,575	$23,363	Gamma
cCRNMB [24]	$4,880	$3,904	$5,856	Gamma
cPost-ICH [25]	$1,129	$903	$1,355	Gamma
cPTS [26]	$235	$188	$282	Gamma
cCTEPH [27]	$6,814	$5,451	$8,177	Gamma
Utility Weights				
uBase**	0.74	0.59	0.89	Beta
uPE [34]	-0.25	-0.55	-0.09	Beta
uDVT [34]	-0.19	-0.45	-0.06	Beta
uMB [34]	-0.09	-0.27	0.00	Beta
uCRNMB [24]	-0.35	-0.85	-0.14	Beta
uICH [35]	-0.40	-0.98	-0.00	Beta
uPTS [35]	-0.05	-0.21	-0.00	Beta
uCTEPH [36]	-0.34	-0.83	-0.00	Beta
Transition probabilities				
tpPE1_1-6mo ***	0.82%	0.66%	0.99%	Beta

tpDVT1_1-6mo ***	0.75%	0.60%	0.90%	Beta
tpMB1 ***	0.17%	0.14%	0.21%	Beta
tpCRNMB1 ***	0.55%	0.44%	0.66%	Beta
tpDiscont1 ***	5.36%	4.29%	6.43%	Beta
tpCA1_death_1-12mo ***	3.18%	2.54%	3.81%	Beta
tpPE1_7-12mo ^	0.29%	0.23%	0.35%	Beta
tpDVT1_7-12mo ^	0.26%	0.21%	0.32%	Beta
tpPE1_13-60mo ^	0.07%	0.05%	0.08%	Beta
tpDVT1_13-60mo ^	0.06%	0.05%	0.07%	Beta
tpPE1_60yo ^	0.01%	0.01%	0.01%	Beta
tpPE1_70yo ^	0.01%	0.01%	0.02%	Beta
tpPE1_80yo ^	0.02%	0.02%	0.03%	Beta
tpPE1_90yo ^	0.03%	0.02%	0.04%	Beta
tpDVT1_60yo ^	0.01%	0.01%	0.01%	Beta
tpDVT1_70yo ^	0.01%	0.01%	0.02%	Beta
tpDVT1_80yo ^	0.02%	0.02%	0.03%	Beta
tpDVT1_90yo ^	0.03%	0.02%	0.03%	Beta
tpCA1_death_13-24mo ^^	1.96%	1.57%	2.36%	Beta
tpCA1_death_25-36mo ^^	1.12%	0.90%	1.35%	Beta
tpCA1_death_37-48mo ^^	0.73%	0.58%	0.87%	Beta
tpCA1_death_49-60mo ^^	0.58%	0.46%	0.69%	Beta
tpCA1_death_60+mo ^^	variable	variable	variable	Beta
tpPE2 [15]	0.44%	0.35%	0.53%	Beta
tpDVT2 [15]	0.23%	0.18%	0.28%	Beta

tpMB2 [15]	0.59%	0.47%	0.71%	Beta
tpCRNMB2 [15]	1.30%	1.04%	1.56%	Beta
tpDiscont2 [15]	1.58%	1.26%	1.90%	Beta
tpCA2_death [15]	3.95%	3.16%	4.74%	Beta
tpPE3_60yo ^^^	0.44%	0.36%	0.54%	Beta
tpPE3_70yo ^^^	0.47%	0.37%	0.57%	Beta
tpPE3_80yo ^^^	0.48%	0.35%	0.40%	Beta
tpPE3_90yo ^^^	0.57%	0.16%	1.46%	Beta
tpDVT3_60yo ^^^	0.40%	0.32%	0.40%	Beta
tpDVT3_70yo ^^^	0.38%	0.30%	0.47%	Beta
tpDVT3_80yo ^^^	0.33%	0.22%	0.47%	Beta
tpDVT3_90yo ^^^	0.43%	0.09%	1.25%	Beta
tpPE_death (pooled PE fatality %) ***	13.21%	10.57%	15.85%	Beta
tpMB_death (pooled MB fatality %) ***	3.85%	3.08%	4.62%	Beta
tpMB_ICH (pooled MB to ICH %) ***	10.26%	8.21%	12.31%	Beta
tpDVT_PTS [20]	12.70%	10.16%	15.24%	Beta
tpPE_CTEPH [19]	2.80%	1.50%	4.10%	Beta
Relative Risks				
rrPE1 ***	0.49	0.23	1.04	Log-Normal
rrDVT1 ***	0.64	0.37	1.11	Log-Normal
rrMB1 ***	1.96	0.80	4.82	Log-Normal
rrCRNMB1 ***	1.28	0.74	2.20	Log-Normal
rrDiscont1 ***	1.00	0.84	1.19	Log-Normal
Discounting				

oDR	0.03			
cDR	0.03			

* All cost estimates were inflated to 2018 US dollars using the US Consumer Price Index for all urban consumers' medical care

** Baseline utility weight was estimated as the sum of the product of cancer-specific utility weight and relative proportion of cancer subtypes from two RCTs (Supplemental eTable 4); adverse event utility weights were estimated by subtraction of the disutility from the baseline weight

*** Transition probability and relative risk for the first 6 months were derived from the meta-analysis of the two RCTs as shown in Table 1

^ Incidence of VTE beyond first 6 months was estimated as the sum of the product of cancer-specific VTE rate (Chew et al [16]) and relative proportion of cancer subtype from the two RCTs; incidence of VTE after 60 months (5 years) was estimated using age-specific VTE incidence rate in the non-cancer population (Martinez et al [17])

^^ Incidence of mortality beyond first 12 months was estimated as the sum of the product of cancer-specific mortality rate (SEER [21]) and relative proportion of cancer subtype from two RCTs; incidence of mortality after 60 months (60 months) was estimated using the US life table (CDC [22])

^^^ Incidence of VTE recurrence when off treatment was estimated using age-specific VTE recurrence rate in the cancer VTE population (Cohen et al [17])

Table 3. Cost-Utility Analysis Outcomes

Number of Events (per 1000 patients over lifetime)		
	Low-Dose DOAC	**Placebo**
Total PE	73	93
1st event	62	80
Recurrent event	11	13
Total DVT	69	81
1st 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		
	Low-Dose DOAC	**Placebo**
Cost		
Total cost	$9,899	$8,454
Health outcomes		
LY	6.51	6.34
QALY	4.79	4.67
Cost effectiveness		
Δ Cost	$1,445	
Δ LY	0.16	
Δ QALY	**0.12**	
ICER (per QALY)	**$11,947**	
Probabilistic Outcomes		
	Low-Dose DOAC	**Placebo**
Cost		
Total cost	$10,007	$8,470
Health outcomes		

LY	6.44	6.30
QALY	4.81	4.70
Cost effectiveness		
Δ Cost	$1,537	
Δ LY	0.15	
Δ QALY	**0.11**	
ICER (per QALY)	**$14,330**	

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

Table 4. Sensitivity Analyses for Deterministic Outcomes

4.1: transition probability and relative risk (RR) of VTE for low-dose DOAC from on-treatment duration (as-treated) instead of overall follow-up (ITT)

Deterministic Outcomes		
	Low-Dose DOAC	**Placebo**
Cost		
Total cost	$9,448	$8,038
Health outcomes		
LY	6.66	6.47
QALY	4.91	4.76
Cost effectiveness		
Δ Cost	$1,409	

Δ LY	0.19
Δ QALY	**0.14**
ICER (per QALY)	**$9,896**

4.2: 12-month instead of 6-month duration of low-dose DOAC PPX

Deterministic Outcomes		
	Low-Dose DOAC	**Placebo**
Cost		
Total cost	$10,864	$8,454
Health outcomes		
LY	6.54	6.34
QALY	4.82	4.67
Cost effectiveness		
Δ Cost	$2,410	
Δ LY	0.20	
Δ QALY	**0.15**	
ICER (per QALY)	**$16,389**	

4.3: assumption of constant cancer mortality rate from year 5 and beyond instead of using life table extrapolation

Deterministic Outcomes		
	Low-Dose DOAC	**Placebo**
Cost		
Total cost	$8,874	$7,466
Health outcomes		
LY	5.32	5.20
QALY	3.92	3.83
Cost effectiveness		
Δ Cost	$1,409	
Δ LY	0.12	
Δ QALY	**0.09**	
ICER (per QALY)	**$15,602**	

4.4: monthly drug pricing estimates based on Federal Supply Schedule (FSS) instead of Red Book

Deterministic Outcomes		
	Low-Dose DOAC	**Placebo**
Cost		
Total cost	$8,798	$8,280
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)	**$4,283**

Table 5. Cost-Utility Analysis Outcomes Based on Heterogeneous Patient Subgroups

5.1: transition probability and relative risk of VTE for low-dose DOAC limited to high-risk subgroup (Khorana Score 3+)

Deterministic Outcomes		
	Low-Dose DOAC	**Placebo**
Cost		
Total cost	$9,987	$8,884
Health outcomes		
LY	6.47	6.21
QALY	4.76	4.57
Cost effectiveness		
Δ Cost	$1,103	
Δ LY	0.26	
Δ QALY	**0.19**	
ICER (per QALY)	**$5,794**	

5.2: transition probability and relative risk of VTE for low-dose DOAC limited to intermediate-risk subgroup (Khorana Score 2)

Deterministic Outcomes		
	Low-Dose DOAC	**Placebo**
Cost		
Total cost	$9,334	$7,807
Health outcomes		

LY	6.55	6.41
QALY	4.83	4.72
Cost effectiveness		
Δ Cost	$1,527	
Δ LY	0.14	
Δ QALY	**0.11**	
ICER (per QALY)	**$15,118**	

Figure Legends:

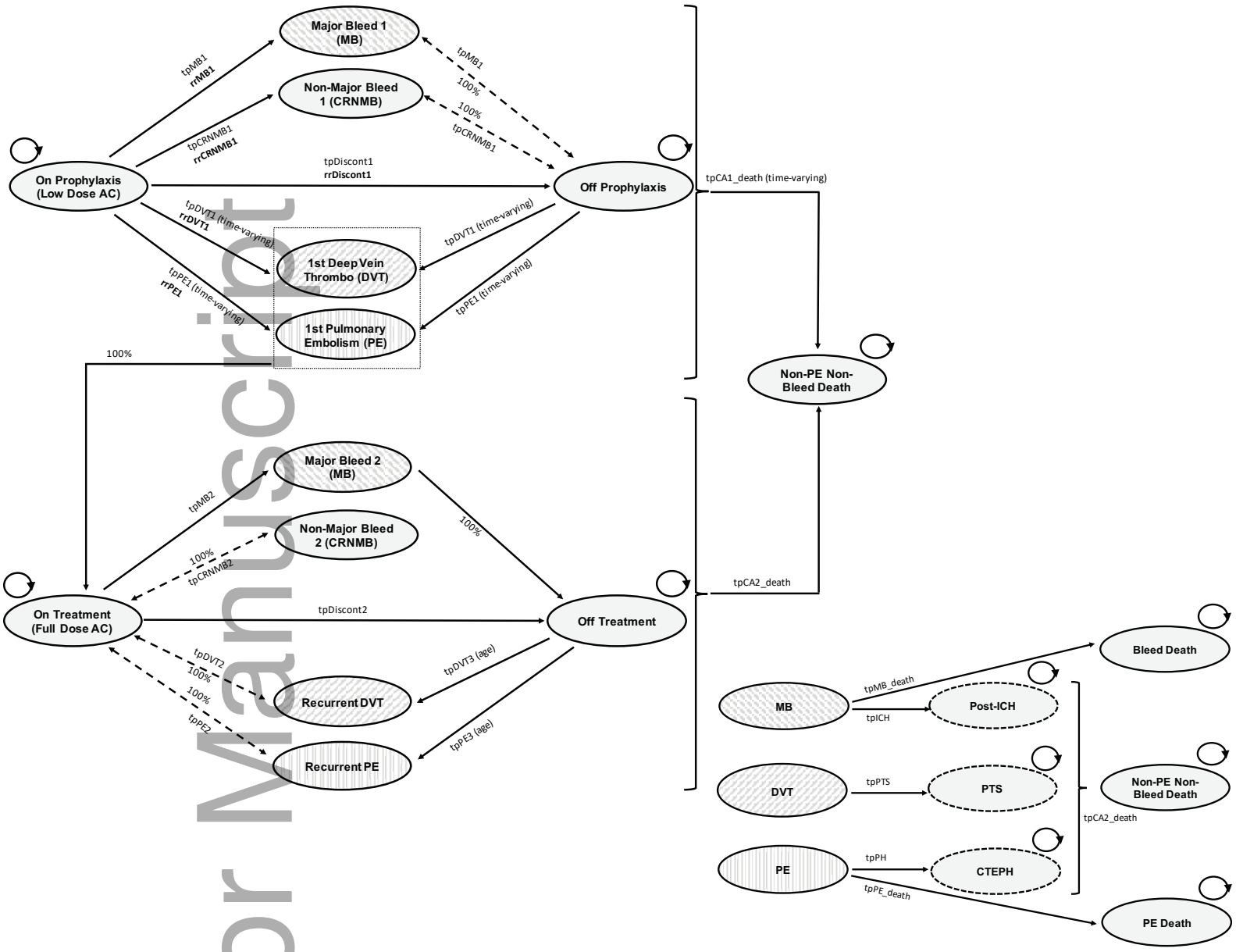
Figure 1. Markov State Transition Model

Figure 2. One Way Sensitivity Analysis (Tornado Diagram)

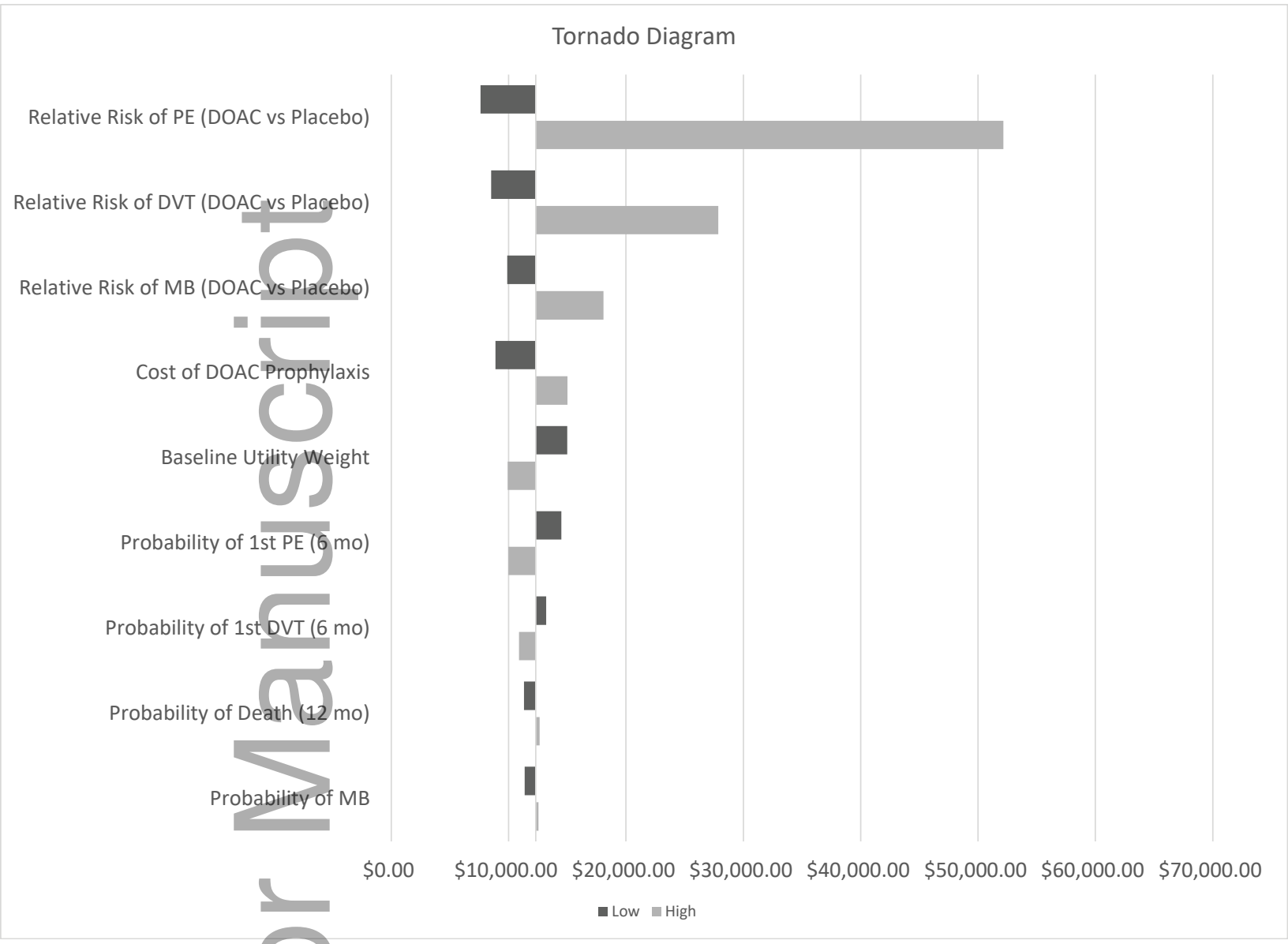
DOAC: direct oral anticoagulant, PE: pulmonary embolism, DVT: deep vein thrombosis, MB: major bleeding, RR: relative risk, TP: transition probability

Figure 3. Probabilistic Sensitivity Analysis

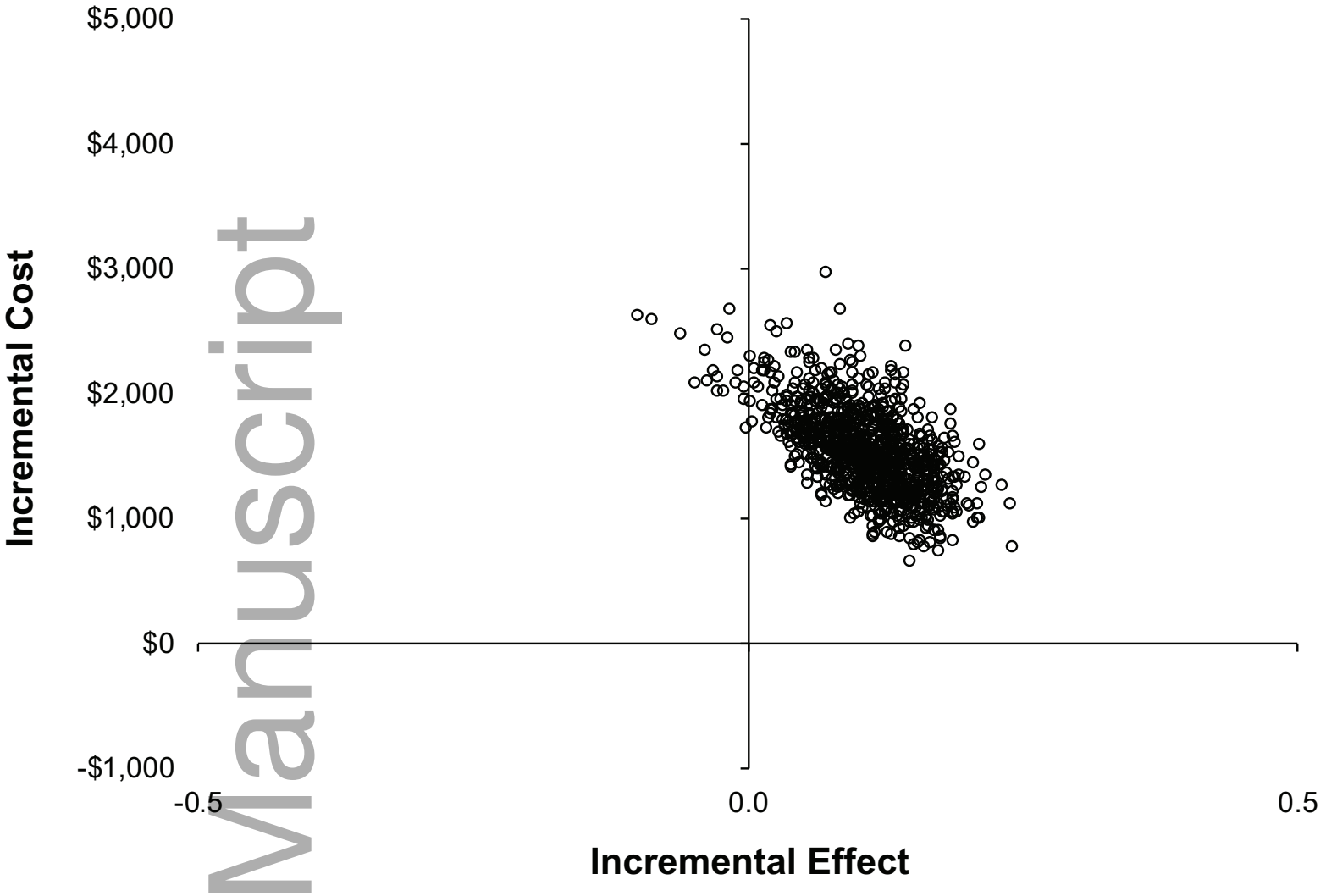
Figure 4. Cost effectiveness acceptability curve



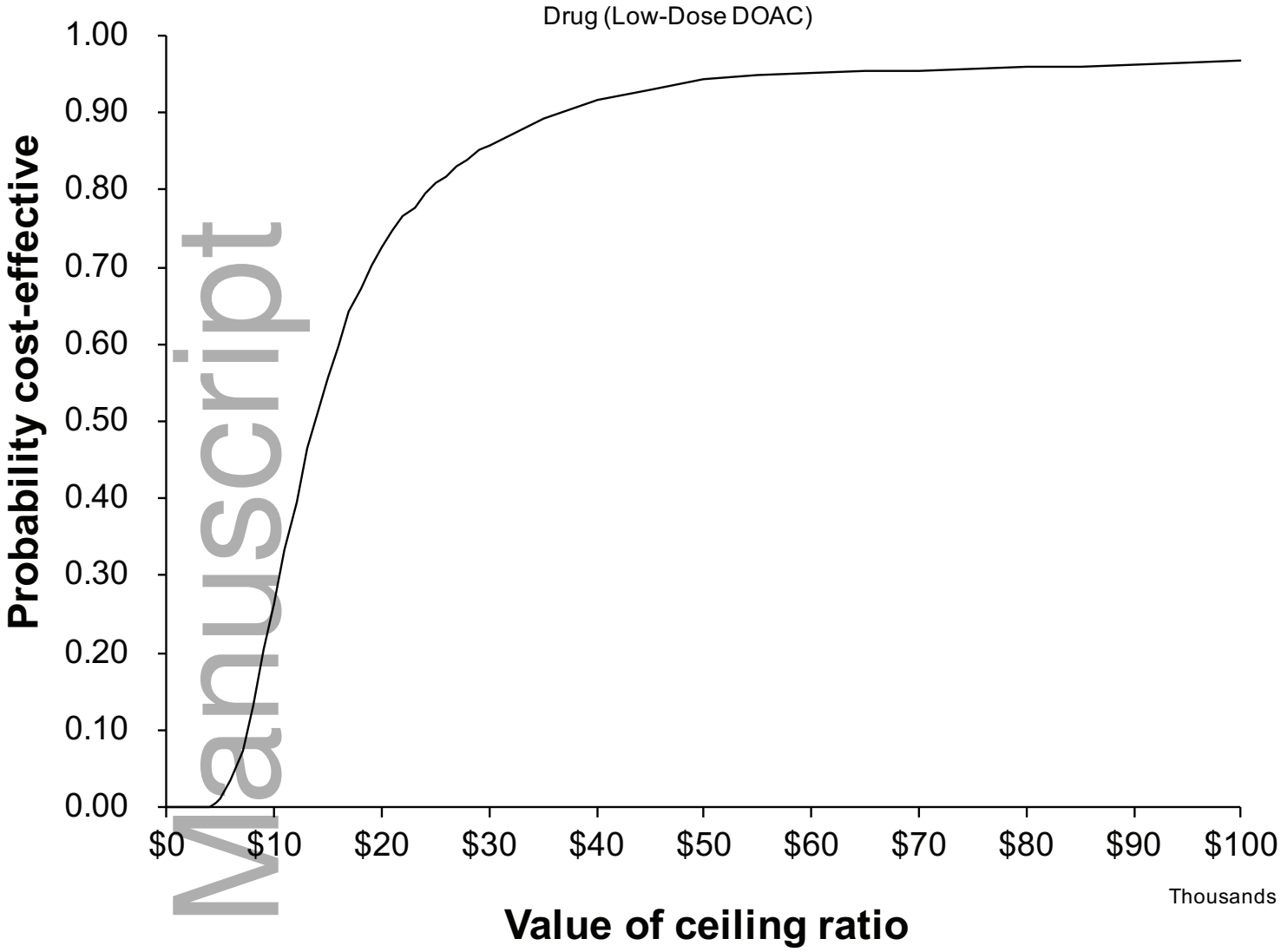
cncr_32724_f1.eps



cncr_32724_f2.eps



cncr_32724_f3.eps



cncr_32724_f4.eps