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Protocol for a modelling study to assess the clinical and cost-effectiveness of indefinite anticoagulant therapy for first unprovoked venous thromboembolism

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ABSTRACT

Introduction Deciding whether to stop or extend anticoagulant therapy indefinitely after completing at least 3 months of initial treatment for a first unprovoked venous thromboembolism (VTE) remains a challenge for clinicians, patients and policy makers. Guidelines suggest an indefinite duration of anticoagulant therapy in these patients, yet its benefits, harms and costs have not been formally assessed. The aim of this proposed modelling study is to assess the differences in clinical benefits, harms and costs of stopping versus continuing anticoagulant therapy indefinitely for a first unprovoked VTE.

Methods and analysis We will develop a probabilistic Markov model, adopting a 1-month cycle length and a lifetime horizon, to estimate life-years, quality-adjusted life-years, costs and the incremental cost-effectiveness ratios for a simulated population of patients with a first unprovoked VTE who will receive indefinite duration of anticoagulant therapy versus a population who will not receive extended treatment after completing 3 months of initial anticoagulant therapy. The economic evaluation will adopt a third-party payer perspective relating to a Canadian publicly funded healthcare system. Estimates for the probability of relevant clinical events will be informed by systematic reviews and meta-analyses, while costs and utility values will be obtained from published Canadian sources. Stratified analyses based on sex, age and site of initial VTE will also be performed to identify subgroups of patients with a first unprovoked VTE in whom continuing anticoagulant therapy indefinitely might prove to be clinically beneficial and cost-effective over stopping treatment. We will also conduct sensitivity and scenario analyses to assess robustness of study findings to changes in individual or groups of key parameters.

Ethics and dissemination Ethical approval is not applicable for this study. The results will be disseminated through presentations at relevant conferences and in a manuscript that will be submitted to a peer-reviewed journal.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ To our knowledge, this is the first study designed to compare the clinical benefits, harms and costs of stopping versus continuing anticoagulant therapy indefinitely for a first unprovoked venous thromboembolism (VTE).
⇒ Stratified analyses will address the influence of important patient characteristics (eg, differences in sex, age and site of initial VTE) on study outcomes to potentially help guide an individualised patient-centred approach to long-term management of first unprovoked VTE.
⇒ This study, as with all modelling studies, will be based on necessary assumptions as well as data (associated with uncertainty) derived from various sources, some of which may be limited (eg, outdated, low quality).

INTRODUCTION

Deep vein thrombosis (DVT) and pulmonary embolism (PE), jointly denoted as venous thromboembolism (VTE), represent a major global burden of disease.[1] Anticoagulant therapy is the mainstay of treatment for VTE,[1] and is highly effective in reducing the risk of recurrent VTE (ie, secondary prevention) as long as treatment is continued.[2] Current clinical practice is to stop anticoagulant therapy after 3–6 months of initial treatment in patients with VTE provoked by major transient risk factors (eg, major surgery), and to extend anticoagulant therapy indefinitely in patients with VTE provoked by a persistent risk factor (eg, cancer).[3 4] For patients with a first unprovoked or weakly provoked (ie, associated with minor transient risk factors) VTE, deciding whether to stop or continue anticoagulant therapy indefinitely remains an important challenge for clinicians, patients and policy makers. To justify indefinite duration of anticoagulant therapy, the long-term risk of mortality from recurrent VTE if treatment is stopped should be off-set by

the long-term risk of mortality from major bleeding on extended (beyond the initial 3–6 months) therapy.[5 6]

Numerous randomised controlled trials have assessed extended anticoagulation versus stopping anticoagulation after 3–6 months initial treatment for secondary prevention of VTE, but no trials have compared stopping anticoagulation with indefinite anticoagulation (maximum duration follow-up in the extended treatment arm was 4 years).[2 7–15] Moreover, these trials were designed to evaluate the efficacy of extended therapy on reducing the risk of recurrent VTE; none were powered to detect a difference in reduction of VTE-related or all-cause mortality. Furthermore, a recent Cochrane systematic review and meta-analysis concluded that there is insufficient evidence to make definitive conclusions regarding effectiveness and safety of extended anticoagulation for the prevention of recurrent VTE in unprovoked VTE patients who have completed initial treatment, and emphasised the need for high-quality randomised controlled trials.[16]

An ideal study design to capture the long-term mortality trade-offs between recurrent VTE and major bleeding in order to provide evidence for or against indefinite anticoagulant therapy would involve randomising unprovoked VTE patients who have completed short-term treatment, to either stop anticoagulation or continue anticoagulation indefinitely. Such a trial, however, is unlikely to be conducted. Reasons for unfeasibility of this hypothetical study include long term, ideally lifelong (ie, until death) follow-up of patients, and the large sample size that would be required to detect the probable small differences in mortality between the two study arms.[6 17] In addition, inconveniences/burdens of medical treatment, patient preferences and costs associated with VTE management may further influence decision about treatment duration at a patient or societal level.[6] Decision analytical modelling, which involves using a specific mathematical model based on best available evidence from the literature, offers an appealing and feasible alternative study design to compare the long-term benefits, harms and costs of stopping versus continuing anticoagulant therapy indefinitely.

Finally, as fewer than half of patients with first unprovoked VTE are expected to have a recurrent VTE within 10 years of stopping anticoagulation,[18] identifying subgroups of patients having a recurrent VTE risk sufficiently low enough or a major bleeding risk sufficiently high enough to justify stopping treatment is a high priority. The International Society on Thrombosis and Haemostasis suggests that in patients with unprovoked VTE, a recurrent VTE risk of 5% (with an upper bound of the 95% CI of 8%) in the first year after discontinuing treatment is low enough to justify stopping anticoagulant therapy.[19] Similarly, given that the case-fatality rate of major bleeding is 2–3 fold higher than that of recurrent VTE,[1 18] experts have proposed that patients with a major bleeding risk of ≥3% per year should be not be considered for indefinite anticoagulant therapy, regardless of their risk of recurrent VTE.[20–22] However, such thresholds lack systematic assessment of the difference in projected long-term risks of mortality. Thus, it is unclear whether these thresholds are reasonable.

Objectives

The objectives of this modelling study will be to estimate life-years, quality-adjusted life-years (QALYs), costs and the incremental cost-effectiveness ratios for a simulated population of patients with a first unprovoked VTE who will receive indefinite duration of anticoagulant therapy versus a population who will not receive extended treatment after completing 3 months of initial anticoagulant therapy. The economic evaluation will be conducted from a third-party payer perspective with a target audience of clinicians, patients and policy makers.

METHODS

An overview of the decision model to be used in this study is described below.

Target population

Patients with first unprovoked VTE aged 55 years (approximate average age in management of VTE trials) who are to be considered for extended anticoagulation beyond completion of 3 months of initial anticoagulant treatment.

Intervention and comparators

The intervention will be anticoagulant therapy with direct oral anticoagulants (DOACs: apixaban, dabigatran, edoxaban, rivaroxaban) extended (beyond the initial 3 months of treatment) indefinitely,[1 4] and the comparator will be no extended anticoagulant therapy.

Form of analysis

A cost–utility analysis will be used, as the recommended approach by the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines for economic evaluations[23] of therapeutic interventions where meaningful differences in the health-related quality of life and health utility between the intervention and the comparator have been demonstrated.

Perspective

The economic evaluation will adopt a third-party payer perspective, relating to a Canadian publicly funded healthcare system as suggested by CADTH guidelines for economic evaluation of health technologies in Canada.[23]

Time horizon

The analysis will adopt a lifetime horizon (ie, until death).

Outcome measures

Results for life expectancy will be expressed as both life-years per 1000 persons and life-days per person. Results for quality-adjusted life expectancy will be expressed as bothQALYs per 1000 persons and quality adjusted life-days per person. QALYs will be calculated by multiplying

life-years by utility scores derived from the published literature. Cost-effectiveness will be expressed in terms of the incremental cost per life-years gained, incremental cost per QALYs gained and costs per clinical events (eg, recurrent VTE, major bleeding or death) averted, as per CADTH guidelines for an economic evaluation.[23]

Model structure

A Markov model[24] will be used for the analyses. The model is used to represent random processes which continue over time. Compare to other models (such a decision tree analysis), Markov models are advantageous when a clinical problem, such as deciding the treatment duration for VTE, involves risk that continues over time, when key events may occur more than once, and when the timing of events is important. Using a probabilistic Markov model, with a cycle length of 1 month, long-term outcomes will be assessed for two cohorts of identical patients with a first unprovoked VTE who have completed 3 months of initial anticoagulant therapy—one cohort assigned to stop anticoagulation (termed 'no extended anticoagulation'), and another assigned to continue anticoagulation indefinitely (termed 'indefinite anticoagulation').

The key health states associated with the two treatment strategies in the model will include recurrent DVT, recurrent PE, major bleeding, death as well as long-term outcomes of the post-thrombotic syndrome (PTS), chronic thromboembolic pulmonary hypertension (CTEPH) and post-intracranial hemorrhage (ICH) (figure 1). For both patient cohorts, patients will start and remain in the assigned treatment strategy of 'no extended anticoagulation' or 'indefinite anticoagulation' until the occurrence of any of the specified adverse clinical outcomes.

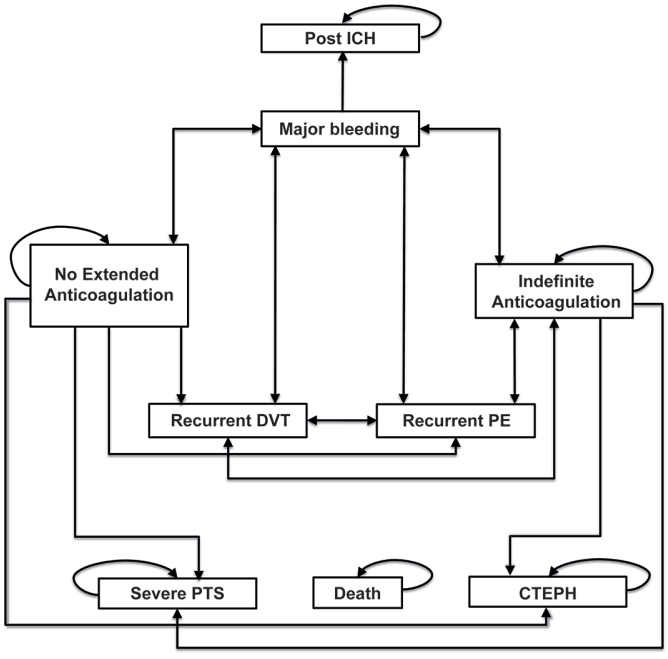

Figure 1 Markov model structure. CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; ICH, intracranial hemorrhage; PE, pulmonary embolism; PTS, post-thrombotic syndrome.

Probability of adverse outcomes

Major bleeding

The annual rate of major bleeding after stopping anticoagulant therapy will be defined as 0.4% per year based on a recent a systematic review and meta-analysis of 8740 patients with a first unprovoked VTE that had completed at least 3 months of initial anticoagulant treatment.[25] The annual rate of major bleeding during extended anticoagulant therapy will be defined as 1.1% per year based on a recent systematic review and meta-analysis of 7220 patients with a first unprovoked VTE that had completed at least 3 months of initial anticoagulant treatment and received extended anticoagulation of up to 1 year with a DOAC.[26] Based on input from clinical experts, for the base case, patients assigned to the 'indefinite anticoagulation' arm that experience a major bleeding event at any point will temporarily interrupt anticoagulation (for 2 weeks),[4] and then restart treatment.

Recurrent VTE

Using data from a recent systematic review and meta-analysis of 7515 patients with a first unprovoked VTE that had completed at least 3 months of initial anticoagulant treatment, the risk of recurrent VTE after stopping anticoagulant therapy will be defined as 10% in the first year, 6% in the second year, 4% in years 3–5 and 3% in the subsequent years.[18] Based on input from clinical expertise, the base-case model will assume that patients in the 'no extended anticoagulation' arm that experience a recurrent VTE at any point, will initiate indefinite treatment and start in the first month of 'indefinite anticoagulation' arm for the subsequent cycle. The annual rate of recurrent VTE during extended anticoagulant therapy will be defined as 1.1% per year based on a recent systematic review and meta-analysis of 7064 patients with a first unprovoked VTE that had completed at least 3 months of initial anticoagulant treatment and received extended anticoagulation of up to 1 year with a DOAC.[27]

Mortality

Age-adjusted and sex-adjusted all-cause death rate will be obtained from Statistics Canada.[28] The case-fatality rate of recurrent VTE will be defined as 4% and the case-fatality rate associated with DOAC-related major bleeding will be defined 10%, as informed by recently published systematic review and meta-analysis.[18 26] In addition, we will incorporate and account for mortality risk for patients with clinical events other than recurrent VTE and major bleeding, including excess risk of death from CTEPH and ICH.

Costs

As we take a perspective of the publicly funded Canada's healthcare system, we will include costs borne to the government. Costs will be adjusted to 2022 Canadian dollars by using the Bank of Canada Inflation

Calculator.[29] The annual costs of drugs to be included in the analysis (apixaban, edoxaban, dabigatran, rivaroxaban and warfarin) will be obtained from the Ontario Drug Benefit formulary[30] or from the drug manufacturer. For each drug therapy, annual drug treatment costs will include a US$7–US$15 prescription fee (every 3 months) and an 8% pharmacist's markup. An additional cost of international normalised ratio (INR) monitoring for warfarin will be added. Costs of drugs will be fixed. Since the cost of individual DOACs will vary, a weighted average cost (unit drug cost weighted by the prevalence of drug use obtained from Canadian sources) will be used in the analysis.

Costs associated with management of clinical events will include costs for hospitalisation, laboratory testing, diagnostics, specialist consultation/follow-up visits, as well as the long-term management costs of ICH, PTS and CTEPH. Estimates for costs including the utilisation rate and unit costs for direct oral anticoagulants will be obtained from the most recently available Canadian sources, including recently published cost-effectiveness literature on anticoagulants for VTE.[31–35]

Utilities

Utility scores will be assigned according to specific health states, in a given cycle. Utility values associated with non-fatal recurrent VTE and major bleeding events, PTS and CTEPH will be derived directly from published data.[31–35] We will consider utility values that are recent, related to our target population of interest and use appropriate methodology as per CADTH guidelines.[23]

Discounting

Future costs and events will be discounted at a rate of 1.5% per annum, according to the CADTH guidelines for economic evaluation.[23]

Stratified analyses

Given that patient characteristics such as sex, age and site of initial VTE influence the risk of recurrent VTE and the risk of bleeding, subgroup analyses will be conducted according to patient's sex, site of initial VTE (isolated proximal DVT, isolated PE and concomitant PE and DVT), as well as age (ie, 35, 50, 65 and 80 years). Results from this stratified analyses will be used to identify subgroups of patients with a first unprovoked VTE in whom continuing anticoagulant therapy indefinitely might be clinically beneficial and cost-effective over stopping treatment.

Sensitivity and scenario analysis

One-way sensitivity analyses will be performed on key parameters (eg, rates of clinical events, costs of management of clinical events, utility associated with health states) included in the decision model over their plausible ranges to determine a 'threshold', that is, a value of a parameter that would result in neither treatment strategy being preferred over the other, and above or below which one treatment strategy provides a survival benefit or is cost-effective over the other. Ranges for adverse outcomes will be derived from either the 95% CIs for event rates from the published literature or based on clinically reasonable values.

Since our base-case model will assume that patients who experience a major bleeding event while receiving anticoagulant therapy will temporarily interrupt anticoagulation (for 2 weeks) and then restart treatment, a scenario analysis will be performed assuming that patients who experience an anticoagulant-related major bleed will discontinue treatment permanently. Given that our base-case analysis will model continuing anticoagulant therapy indefinitely with DOACs, we will conduct a scenario analysis using warfarin (INR range of 2.0–3.0) as the choice of anticoagulant for extended treatment.[4]

A two-way sensitivity analysis will also be performed in order to determine the effect of variation in the rates of recurrent VTE in the first year off anticoagulant therapy and annual rates of major bleeding during extended treatment, on net mortality benefit and cost-effectiveness of indefinite duration of anticoagulant therapy.

For all analyses, the expected values of costs, outcomes and cost-effectiveness ratios will be obtained through second-order Monte Carlo simulations, randomly sampling a distribution of all variables 5000 times. Uncertainty around parameters will be characterised by the following distributions: probabilities (beta); utilities (beta); costs of events (gamma); treatment effects (log normal). In addition, uncertainty over cost-effectiveness will be reported as a cost-effectiveness acceptability curve, which presents the probability that each treatment choice is optimal given different values of willingness to pay for an additional QALY. For our primary analysis, we will assume a willingness-to-pay value of US$50 000 per QALY. We will also perform a value of information analysis to identify parameters, which contribute most to decision uncertainty.

The model will be externally validated by comparing rates of clinical outcomes with those reported in the literature. The Consolidated Health Economic Evaluation Reporting Standards statement will be followed in reporting this economic evaluation.[36] Model creation and analyses will be performed using Microsoft Excel. This study began in September 2021 and is expected to be complete by December 2022.

Patient and public involvement

No patient partners were involved in the research process of our study protocol. We plan on involving patient partners in the CanVECTOR network (www.canvector.ca) along with our network of clinical colleagues in the dissemination and/or knowledge translation activities for final study results. These activities may include developing evidence summaries (concise summary of a published research study written in plain language), and presenting our findings at the annual CanVECTOR conference with patients, clinicians and thrombosis researchers in the audience.

DISCUSSION

Clinicians, patients and policy makers currently lack clear guidance on making decisions regarding the optimal duration of anticoagulant therapy for a first unprovoked VTE. Guidelines suggest considering an indefinite duration of anticoagulant therapy in these patients, but the clinical benefits, harms and costs of this treatment strategy are uncertain. Findings from our proposed modelling study will help inform the uncertainty about whether to stop or continue anticoagulant therapy indefinitely in patients with a first unprovoked VTE who have completed 3 months of initial treatment. Important information will particularly be obtained through our planned subgroup, sensitivity and scenario analyses which will address the influence of important patient characteristics (eg, differences in sex, age and site of initial VTE) and other anticoagulant regimens (eg, reduced-dose DOACs and warfarin) on study outcomes to potentially help guide an individualised patient-centred approach to long-term management of first unprovoked VTE. That is, identify patients in whom indefinite anticoagulation may not be worthwhile so that such patients can be spared the burdens, the costs and harms of lifelong anticoagulation; and identify which patients should continue anticoagulation indefinitely, and with which anticoagulant, in order to maximise health benefits within the available healthcare resources.

Limitations

As with all modelling studies, our proposed study will be based on necessary assumptions, as well as data (associated with uncertainty) derived from various sources, some of which may be limited (eg, outdated, low quality). However, we will perform extensive scenario analyses, including alternate assumptions, to establish the robustness of study findings. We acknowledge the limitation regarding the lack of memory of Markov models—that is, the probability of transitioning between states in a given cycle does not depend on events occurred in the previous cycles. To overcome this limitation, we will use time-varying transition probabilities for certain clinical events (eg, probability of death increases with age, probability of recurrent VTE decreases with time spent off anticoagulant therapy).

Ethics and dissemination

Ethical approval and patient consent are not required since this is a modelling study based on the use of secondary data from the published literature and publicly available sources. The study findings will be submitted for presentation at relevant national and international conferences, and for publication in a peer-reviewed journal.

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Contributors FK, KT, DC, MAR and DAF conceived the idea and design for this modelling study. FK, KT and DC developed the methodology for this study protocol. The contents of this manuscript were drafted by FK, KT, DC and DAF with input from SvK, TT, BH, GLG, and MAR. The manuscript was reviewed by FK, KT, DC, SVK, TT, BH, GLG, MR and DAF for important intellectual content. FK, KT, DC, SvK, TT, BH, GLG, MR and DAF read and approved the final manuscript.

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Competing interests None declared.

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REFERENCES

1 Khan F, Tritschler T, Kahn SR, *et al*. Venous thromboembolism. *Lancet* 2021;398:64–77.
2 Couturaud F, Sanchez O, Pernod G, *et al*. Six months vs extended oral anticoagulation after a first episode of pulmonary embolism: the PADIS-PE randomized clinical trial. *JAMA* 2015;314:31–40.
3 Kearon C, Akl EA, Ornelas J, *et al*. Antithrombotic therapy for VTe disease: chest guideline and expert panel report. *Chest* 2016;149:315–52.
4 Ortel TL, Neumann I, Ageno W, *et al*. American Society of hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv* 2020;4:4693–738.
5 Wells PS, Forgie MA, Rodger MA. Treatment of venous thromboembolism. *JAMA* 2014;311:717–28.
6 Kearon C, Akl EA. Duration of anticoagulant therapy for deep vein thrombosis and pulmonary embolism. *Blood* 2014;123:1794–801.
7 Kearon C, Gent M, Hirsh J, *et al*. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. *N Engl J Med* 1999;340:901–7.
8 Agnelli G, Prandoni P, Santamaria MG, *et al*. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. *N Engl J Med Overseas Ed* 2001;345:165–9.
9 Agnelli G, Prandoni P, Becattini C, *et al*. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. *Ann Intern Med* 2003;139:19–25.
10 Ridker PM, Goldhaber SZ, Danielson E, *et al*. Long-Term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. *N Engl J Med* 2003;348:1425–34.
11 , Bauersachs R, Berkowitz SD, *et al*, EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010;363:2499–510.
12 Schulman S, Kearon C, Kakkar AK, *et al*. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *N Engl J Med* 2013;368:709–18.
13 Agnelli G, Buller HR, Cohen A, *et al*. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med* 2013;368:699–708.
14 Raskob G, Ageno W, Cohen AT, *et al*. Extended duration of anticoagulation with edoxaban in patients with venous thromboembolism: a post-hoc analysis of the Hokusai-VTE study. *Lancet Haematol* 2016;3:e228–36.
15 Weitz JI, Lensing AWA, Prins MH, *et al*. Rivaroxaban or aspirin for extended treatment of venous thromboembolism. *N Engl J Med* 2017;376:1211–22.

16 Robertson L, Yeoh SE, Ramli A. Secondary prevention of recurrent venous thromboembolism after initial oral anticoagulation therapy in patients with unprovoked venous thromboembolism. *Cochrane Database Syst Rev* 2017;12:CD011088.
17 Rodger M, Carrier M, Gandara E, *et al*. Unprovoked venous thromboembolism: short term or indefinite anticoagulation? balancing long-term risk and benefit. *Blood Rev* 2010;24:171–8.
18 Khan F, Rahman A, Carrier M, *et al*. Long term risk of symptomatic recurrent venous thromboembolism after discontinuation of anticoagulant treatment for first unprovoked venous thromboembolism event: systematic review and meta-analysis. *BMJ* 2019;366:l4363.
19 Kearon C, Iorio A, Palareti G, *et al*. Risk of recurrent venous thromboembolism after stopping treatment in cohort studies: recommendation for acceptable rates and standardized reporting. *J Thromb Haemost* 2010;8:2313–5.
20 Rodger MA, Le Gal G. Who should get long-term anticoagulant therapy for venous thromboembolism and with what? *Blood Adv* 2018;2:3081–7.
21 Kimpton M, Rodger MA, Exclusive W. Web Exclusive. Annals for Hospitalists Inpatient Notes - Can I Withdraw Anticoagulants in This Patient With Prior Venous Thromboembolism? *Ann Intern Med* 2020;172:HO2–3.
22 Kearon C, Kahn SR. Long-Term treatment of venous thromboembolism. *Blood* 2020;135:317–25.
23 Guidelines for the economic evaluation of health technologies. *Canadian agency for drugs and technologies in health*. 3rd. Ottawa,Canada, 2017.
24 Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Med Decis Making* 1993;13:322–38.
25 Khan F, Rahman A, Tritschler T, *et al*. Long-Term risk of major bleeding after discontinuing anticoagulation for unprovoked venous thromboembolism: a systematic review and meta-analysis. *Thromb Haemost* 2022;122:1186–97.
26 Khan F, Tritschler T, Kimpton M, *et al*. Long-Term Risk for Major Bleeding During Extended Oral Anticoagulant Therapy for First Unprovoked Venous Thromboembolism : A Systematic Review and Meta-analysis. *Ann Intern Med* 2021;174:1420–9.
27 Khan F, Tritschler T, Kimpton M, *et al*. Long-Term risk of recurrent venous thromboembolism among patients receiving extended oral anticoagulant therapy for first unprovoked venous thromboembolism: a systematic review and meta-analysis. *J Thromb Haemost* 2021;19:2801–13.
28 Statistics Canada. Death and mortality rates by age group. Available: https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310071001 [Accessed 10 May 2021].
29 Bank of Canada Inflation Calculator. :. In: . Ottawa, Canada: Bank of Canada, 2021.
30 Ontario drug benefit Formulary/Comparative drug index. Available: https://www.formulary.health.gov.on.ca/formulary/
31 Coleman CI, Limone BL, Bookhart BK, *et al*. Cost-Effectiveness analysis of extended duration anticoagulation with rivaroxaban to prevent recurrent venous thromboembolism. *Thromb Res* 2014;133:743–9.
32 Klarenbach S, Lee K, Boucher M. Direct Oral Anticoagulants for the Treatment of Venous Thromboembolic Events: Economic Evaluation [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health, 2016. Available: https://www.cadth.ca/sites/default/files/pdf/TR0005_DOACS_for_DVT_and_PE_Report.pdf
33 Hogg K, Kimpton M, Carrier M, *et al*. Estimating quality of life in acute venous thrombosis. *JAMA Intern Med* 2013;173:1067–72.
34 Coyle D, Coyle K, Cameron C, *et al*. Cost-Effectiveness of new oral anticoagulants compared with warfarin in preventing stroke and other cardiovascular events in patients with atrial fibrillation. *Value Health* 2013;16:498–506.
35 Bamber L, Muston D, McLeod E, *et al*. Cost-Effectiveness analysis of treatment of venous thromboembolism with rivaroxaban compared with combined low molecular weight heparin/vitamin K antagonist. *Thromb J* 2015;13:20. l.
36 Husereau D, Drummond M, Petrou S, *et al*. Consolidated health economic evaluation reporting standards (cheers) statement. *BMJ* 2013;346:f1049.