International Journal of Technology Assessment in Health Care

cambridge.org/thc

Projecting effectiveness after ending a randomized controlled trial: a two-state Markov microsimulation model

Fei Yuan[1], Shrikant I. Bangdiwala[1,2], Wesley Tong[1] and Andre Lamy[1,2,3]

[1]Population Health Research Institute, DBCVSRI, 20 Copeland Avenue, Hamilton, ON L8L 2X2, Canada; [2]Department of Health Research Methods, Evidence and Impact, McMaster University, 1280 Main St W, Hamilton, ON L8S 4L8, Canada and [3]Hamilton Health Sciences, 237 Barton St. East, Hamilton, ON L8L 2X2, Canada

Objective. To investigate the behavior of restricted mean survival time (RMST) and designs of a two-state Markov microsimulation model through a $2 \times 4 \times 2$ full factorial experiment.
Method. By projecting patient-wise 15-year-post-trial survival, we estimated life-year-gained between an intervention and a control group using data from the Cardiovascular Outcomes for People Using Anticoagulation Strategies Study (COMPASS). Projections considered either in-trial events or post-trial medications. They were compared based on three factors: (i) choice of probability of death, (ii) lengths of cycle, and (iii) usage of half-a-cycle age correction. Three-way analysis of variance and post-hoc Tukey's Honest Significant Difference test compared means among factors.
Results. When both in-trial events and post-trial study medications were considered, monthly, quarterly, or semiannually were not different from one other in projected life-year-gained. However, the annual one was different from the others: mean and 95 percent confidence interval 252.2 (190.5–313.9) days monthly, 251.8 (192.0–311.6) quarterly, 249.1 (189.7–308.5) semiannually, and 240.8 (178.5–303.1) annually. The other two factors also impacted life-year-gained: background probability (269.1 [260.3–277.9] days projected with REACH-based-probabilities, 227.7 [212.6–242.8] with a USA life table); half-a-cycle age correction (245.5 [199.0–292] with correction and 251.4 [209.1–293.7] without correction). When not considering post-trial medications, only the choice of probability of death appeared to impact life-year-gained.
Conclusion. For a large trial or cohort, to optimally project life-year-gained, one should consider using (i) annual projections, (ii) life table probabilities, (iii) in-trial events, and (iv) post-trial medication use.

Introduction

Cardiovascular diseases are one of the leading causes of death in recent decades. To reduce the cardiovascular burden in the aging population, many clinical trials and epidemiology studies are ongoing in this area (1–3). To assist policy making, researchers often want to study the long-term health effect of a novel intervention versus a standard care. This is challenging, as there are very few studies that can follow-up with participants for long-term or even life-time. Discrete-time Markov microsimulation models are often used in the field of cardiology to simulate a trial and to project long-term survival (4–6). Such models, especially with multiple states and their complicated mutual relationships, large cohorts, and average survival estimated by the restricted mean survival time (RMST), are computationally demanding. Therefore, a burning methodological question is how to improve the effectiveness of these models. Recent literature discussed various efforts on constructing and expediting models with dramatically complex structures. However, there are scarce discussions about fundamental parameters such as cycle lengths, half-a-cycle age correction and background probabilities (7–18). Moreover, these parameters have been used without justification in many recent implementations and applications of Markov microsimulation models (4–6). Actually, with optimal setup, these parameters can help to accelerate a modeling process too.

First proposed in 2010 (19;20), the measurement of RMST has been becoming popular in medical research for its intuitive interpretation of treatment effects. Especially when the assumption of proportional hazards is violated in the design and analysis of a study with time-to-event outcomes, it is not appropriate to estimate the treatment effect using a single hazard ratio for all time points. In this case, RMST can be an alternative approach (20;21). This makes it meaningful to study the behavior of RMST here.

In this article, we demonstrate how to project "after-a-clinical trial survival" through a two-state Markov microsimulation model and then estimate average survival time using RMST. Moreover, we investigate whether three parameters of the model, cycle lengths,

Method

Abbreviations: ASA, acetyl-salicylic-acid or aspirin; COMPASS, the Cardiovascular Outcomes for People Using Anticoagulation Strategies Study; CAD, coronary artery diseases; CHD, coronary heart diseases; ICER, incremental cost-effectiveness ratio; a modification of the International Society on Thrombosis and Homeostasis (ISTH) criteria for major bleeding (fatal bleeding excluded); MI, myocardial infarction; PAD, peripheral artery diseases; RMST, restricted mean survival time. This measurement is used to measure survivals of two intervention groups (life expectancy) and the incremental survival (life-year-gained) between intervention groups; REACH registry, Reduction of Atherothrombosis for Continued Health Registry; Riva, rivaroxaban.

Cite this article: Yuan F, Bangdiwala SI, Tong W, Lamy A (2020). Projecting effectiveness after ending a randomized controlled trial: a two-state Markov microsimulation model. *International Journal of Technology Assessment in Health Care* **36**, 317–324. https://doi.org/10.1017/S0266462320000446

Received: 31 July 2019
Revised: 19 May 2020
Accepted: 12 June 2020
First published online: 3 August 2020

Key words:
Statistics; Health economics/economic evaluation; Clinical epidemiology; Modeling; Epidemiology

Author for correspondence:
Fei Yuan,
E-mail: yuanf@phri.ca; yuanfeifei@gmail.com

© The Author(s), 2020. Published by Cambridge University Press

CAMBRIDGE UNIVERSITY PRESS

half-a-cycle age correction, and background probabilities, affect the estimated incremental life-year-gained between intervention and control groups and computational performance.

Data and Methods

By using a Markov two-state microsimulation model and a $2 \times 4 \times 2$ full factorial experiment, we examined how three parameters affected the incremental life-year-gained between intervention and control groups. The examination considered either the impacts of in-trial events or that of post-trial medications in the projection. We tested null hypotheses that the projected life-year-gained did not differ by factors. The models were run and analyzed based on the data from the Cardiovascular Outcomes for People Using Anticoagulation Strategies Study (COMPASS).

Data

The data were from the COMPASS trial, which was a randomized, double-blinded, controlled trial with a 3-by-2 partial factorial design. Its study design and main results have been published previously (2;3). To look for optimal strategies of secondary cardiovascular prevention, the trial compared two usages of rivaroxaban and aspirin: (i) rivaroxaban alone (5 mg twice daily) versus aspirin (100 mg once daily), (ii) rivaroxaban-(2.5 mg twice daily)-plus-aspirin (100 mg once daily) versus aspirin (100 mg once daily). There were 27,395 participants with stable atherosclerotic vascular diseases. Compared with aspirin 100 mg once daily, it found that rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily) reduced the risk of a composite outcome of myocardial infarction (MI), stroke, or cardiovascular death in subjects with coronary artery diseases (CAD) or peripheral artery diseases (PAD) (hazard ratio and its 95 percent confidence interval [CI] were .76 [.66–.86], p value <.001) (3). As only rivaroxaban-plus-aspirin was found superior to aspirin, we focused our simulation models and analyses on these two groups of participants. There were 18,278 participants, among which there were 9,152 randomized to the rivaroxaban-plus-aspirin and 9,126 to the aspirin-only groups. The mean age of participants was 68 years old. The mean follow-up was 23 months.

Methods

The projection considered three scenarios: (A) directly using background probability of death without adjustment; (B) assuming impact of three in-trial events on top of the background probability: MI, ischemic stroke, and a modified version of the International Society on Thrombosis and Homeostasis (ISTH) criteria for major bleeding (3); (C) assuming both impacts of in-trial events and post-trial study medications. We investigated three factors: (i) two sets of probability of death: a 2013 USA life table (22), or modified REduction of Atherothrombosis for Continued Health (REACH) registry 20-month risks-based probabilities (23); (ii) four lengths of cycle: monthly, quarterly, semi-annually, or annually, (iii) with or without half-a-cycle correction on age. The effects of three factors on the projection were studied through a $2 \times 4 \times 2$ full factorial experiment with a replicate (whose design table was given in Supplementary Table 1, available with the full text of this article online). In a scenario, there were sixteen subexperiments. In a subexperiment, a two-state Markov simulation model was run for 200 times (Figure 1 in the main text, Supplementary Figures 1–3). As a result, there were 200 RMSTs calculated for an intervention group. The distribution of life-year-gained was shown in Supplementary Figure 4 and Table 2. To stabilize results, the mean of 200 trials was used as the final result of the subexperiment (Figure 2 in the main text, Supplementary Tables 3, 4 and Figures 4, 5).

The two-state Markov simulation model was constructed as follows (Supplementary Table 5). For participants who survived to the end of the trial, to avoid noise of data collected close to the end of the in-trial period, their individual post-trial projection started from two-and-a-half years after their randomization. To directly assess these individual patients' post-trial survival, we considered only two states: life and death (Figure 1). The age- and sex-specific probabilities of death, which would increase with a cycle of projection, were considered as the background probability. Impacts that could affect death would be estimated by background probabilities and various adjustments (Supplementary Figure 3). A possible adjustment was the impact of in-trial events. Time-dependent Cox regression models estimated the effects of in-trial MI, ischemic stroke, and major bleeding. These effects were multiplied to the background probability of all-cause mortality when required. When participants were assumed to take study drugs post-trial, they would continue with a same treatment allocation as that of the in-trial period. In reality, participants were offered the successful intervention at the end of the trial. However, for our projections, we assumed a conservative approach that participants would continue their original study intervention post-trial. Therefore, we adjusted the background probability by a constant drug effect of rivaroxaban-plus-aspirin versus aspirin on all-cause mortality (3). Aspirin alone was not assumed to have an effect on post-trial survival. Participants' life expectancy was projected by cycle, with a half-a-cycle age correction being applied if required. There are various discussions on this correction in the literature (17;18). The half-cycle-correction was applied at the beginning of the projection, considering a transition usually occurring from a state to another in the middle of a cycle.

After the individualized post-trial projection was done in a simulation, RMST was used to estimate life expectancies of two intervention groups. Life-year-gained was the difference in life expectancies between two groups. Kaplan–Meier estimates of survival functions were computed on the combined survival of both in-trial and post-trial periods for an intervention group. Then, RMST was calculated as the area under a survival curve by directly integrating the Kaplan–Meier estimate from the time of zero to mean 17 years (Supplementary Table 5) (21). Given the big sample size of the COMPASS trial, the Kaplan–Meier estimates should be reasonably stable. Moreover, as participants were randomized to two intervention groups (rivaroxaban plus aspirin vs. aspirin), potential confounding factors would be balanced out on average. This was shown on key demographic characteristics in Eikelboom et al. (3). Therefore, there is no further adjustment on covariates applied in the computation of RMST.

For the choice of background probability, we compared how a USA life table (22) and the REACH-based-probabilities (23) would affect projection. The USA life table (22) was available online and reflected the risks of death of a general population, while REACH-based-probabilities (23) reflected those of a population with atherothrombosis. As the COMPASS population had stable atherosclerotic vascular diseases, we would also use the REACH-based-probabilities (23) to simulate the potential impact of post-trial cardiovascular burden on the risk of death for this

https://doi.org/10.1017/S0266462320000446 Published online by Cambridge University Press

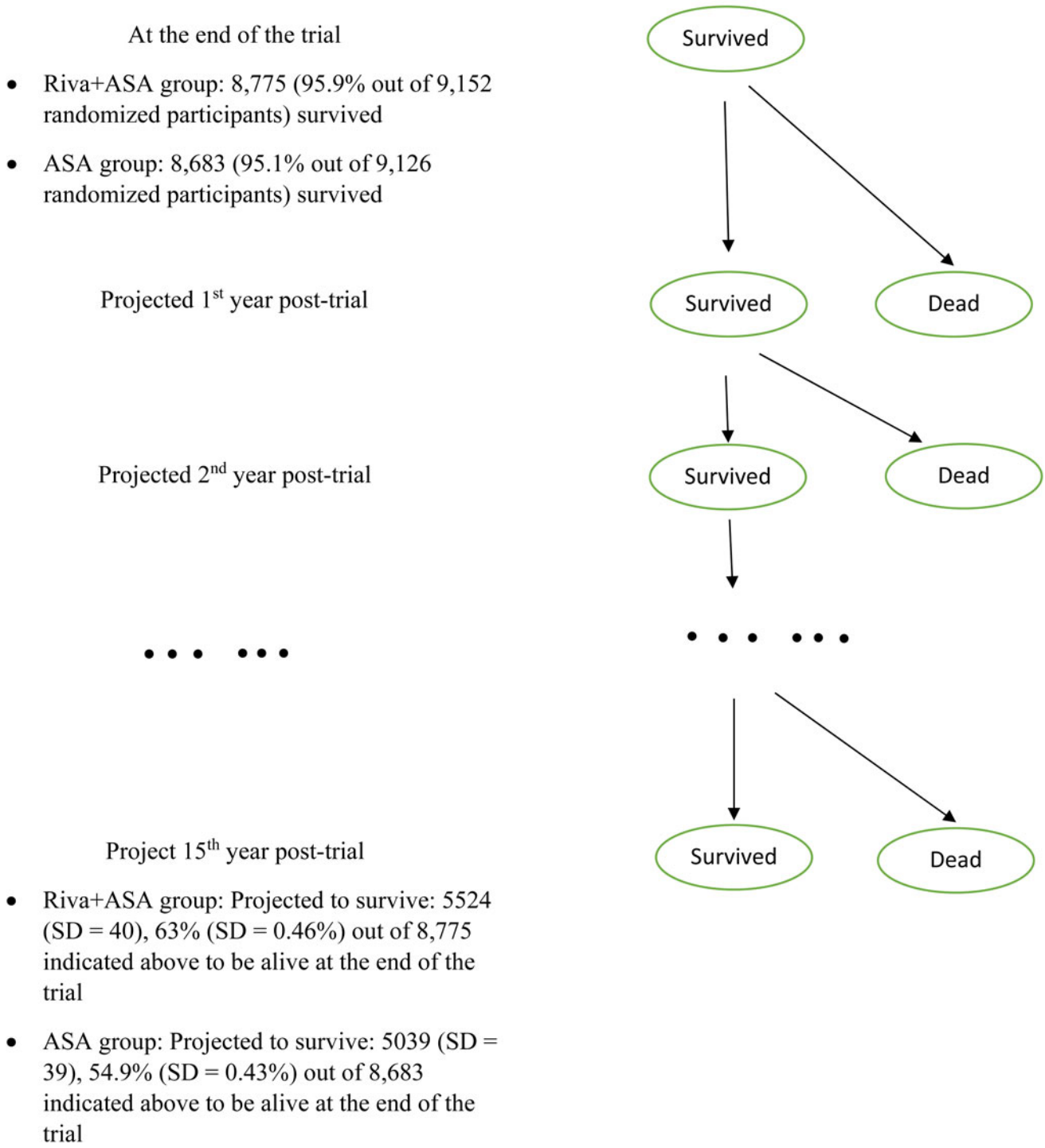


Figure 1. Conceptual diagram of a two-state Markov micro-simulation model with 15-year post-trial projection, assuming that participants continue to take post-trial study medications and in-trial events.

cohort. The REACH registry followed 49,689 outpatients globally for 2 years (23;24). A risk model was established in terms of REACH scores and 20-month risks on two-thirds of the population and validated on the rest one-third (23). It predicted cardiovascular events and death on participants with established atherothrombotic diseases. These factors were considered: sex, age, smoking, diabetes mellitus, BMI <20 kg/m^2, number of vascular beds, cardiovascular events in a past year, congestive heart

https://doi.org/10.1017/S0266462320000446 Published online by Cambridge University Press

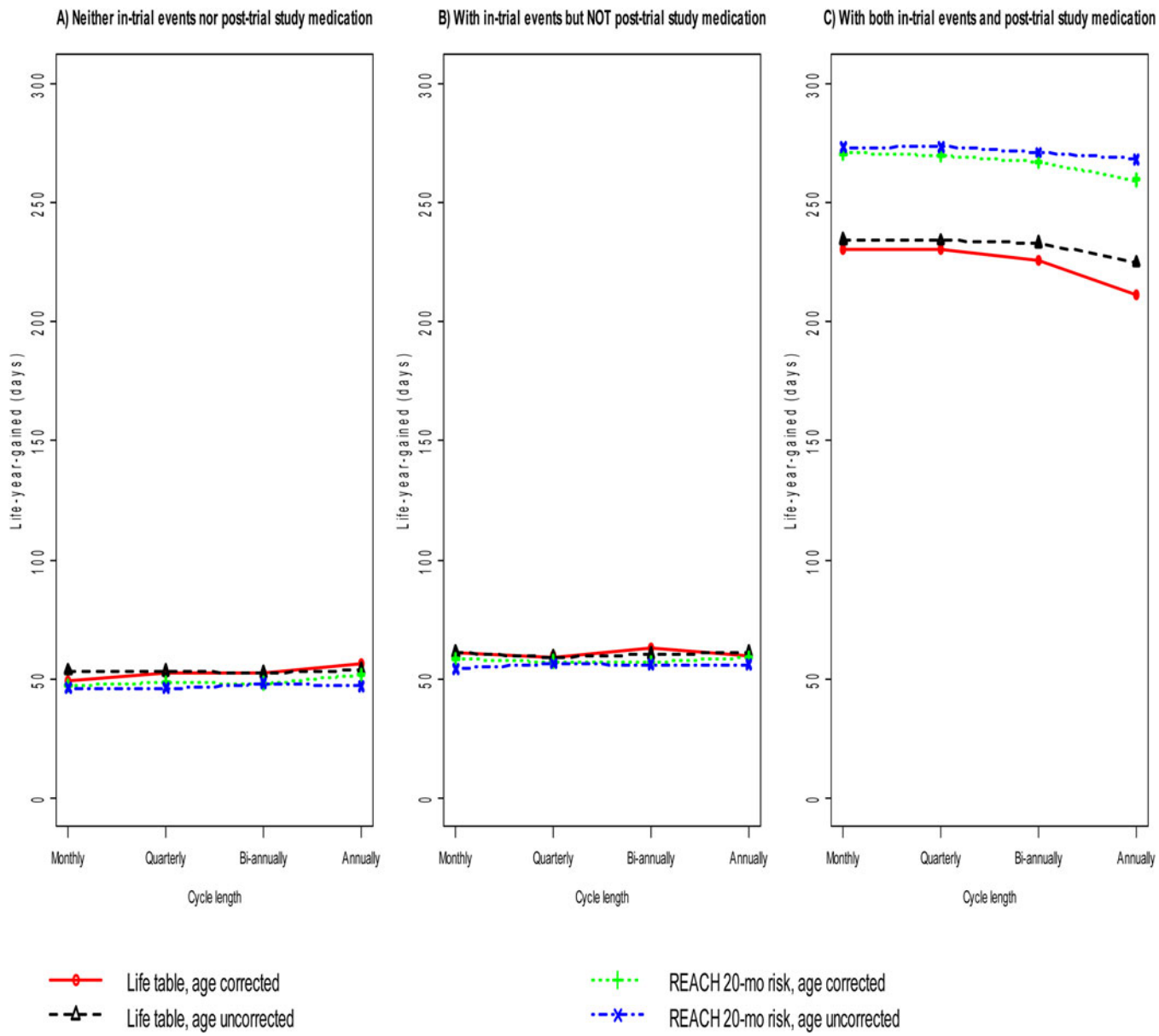


Figure 2. Projection of incremental life-year-gained on all-cause mortality by cycle lengths, half-a-cycle age correction, and background probabilities under three scenarios: (A) neither in-trial events nor post-trial study medications; (B) with in-trial events NOT post-trial study medications; and (C) with in-trial events and post-trial study medications.

failure, atrial fibrillation, statin therapy, aspirin (ASA) therapy, high risk regions (Eastern Europe or Middle East) and low risk regions (Japan or Australia). The middle risk regions, North America or Western Europe, were used as a referenced region of risk. The COMPASS participants were 68.2 years old on average at baseline. Among them, there were 22 percent females, 90.6 percent with CADs, and 27.3 percent with PADs (3). The REACH participants, based on which the REACH model was established, were 68.4 years old on average at baseline. There were 33.1 percent female, 72.4 percent with CADs, and 14.9 percent with PADs (23). Both cohorts were close to each other in terms of these baseline characteristics, even though they investigated different hypotheses. Although the USA life table (22) was comparatively easier to find, it might not sufficiently represent a population with cardiovascular diseases. COMPASS patients might suffer higher risks of mortality than that of the life table. Therefore, we would compare how two sets of background probabilities, either from the USA life table (22) or the REACH-based-probabilities (23), affected the projection.

Steps of analyses were outlined in Supplementary Table 6. Three-way analysis of variance (ANOVA) and post-hoc Tukey's Honest Significant Difference (HSD) tests compared means of incremental life-year-gained among factors. Assumptions of ANOVA models were checked in the Supplementary Figure 7. The two-way or three-way interactions were considered; however, this experiment, as an initial study, did not have enough degrees of freedom for analysis of these terms. All statistical tests were performed at a two-sided significance level of .05. Statistical analyses were performed using statistical software packages SAS 9.4 on Linux and R 3.5.1 for Windows.

Finally, to understand the computational burden models can cause, we ran the 15-year post-trial projection on various sizes

https://doi.org/10.1017/S0266462320000446 Published online by Cambridge University Press

of simulated cohorts (Supplementary Table 7). Intuitively, projections with or without half-a-cycle correction were supposed to run at a similar speed. Moreover, it would take longer to run a model with the life-table than with the REACH 20-month risks, as patients might die faster with the later ones. Therefore, we focused on studying the computational times needed for projection with half-a-cycle correction and a life-table in three scenarios.

Results

Trends on the Projected Life Expectancies

After projection, rivaroxaban-plus-aspirin group still showed benefit over the aspirin group by its longer life expectancy (Supplementary Figure 6 and Table 3). For both intervention groups, with half-a-cycle age correction, the projected life expectancies were slightly longer than those without correction. Moreover, as the aspirin group was not supposed to take rivaroxaban post-trial, this group had almost the same estimates for the scenarios adjusted on in-trial events and with and without post-trial rivaroxaban. Considering more potential cardiovascular-related risks, the life expectancies projected using REACH-based-probabilities (23) were shorter than those using a USA life table (22).

For the scenario with post-trial study medications and in-trial events and with half-a-cycle age correction, using a USA life table, life expectancies of the rivaroxaban-plus-aspirin group averaged over 200 simulations were 5,019.6 days projected monthly, 5,066.4 days quarterly, 5,133.5 days semiannually, and 5,256.1 days annually. The averaged life expectancies of the aspirin group were 4,789.1 days projected monthly, 4,836.2 days quarterly, 4,908.1 days by semiannually, and 5,045.1 days annually. Using the REACH-based-probabilities (23), the rivaroxaban-plus-aspirin group had a life expectancy of 4,642.5 days projected monthly, 4,668.3 days quarterly, 4,709.3 days semiannually, and 4,789.4 days annually. The aspirin group had a life expectancy of 4,371.8 days projected monthly, 4,398.5 days quarterly, 4,442.0 days semiannually, and 4,529.9 days annually.

Trends on the Projected Life-Year-Gained

Similar to the life expectancy, life-year-gained was also estimated for a subexperiment by averaging over 200 simulations. There were positive mean life-year-gained in all three scenarios (Figure 2 in the main text; Supplementary Figures 4, 5 and Table 4). Among these scenarios, the life-year-gained was the longest with both impacts of post-trial study medications and in-trial events. Based on a USA life table (22) and a half-a-cycle age correction, the life-year-gained was most conservative: 230.5 days (95 percent CI, 184.5–276.4) projected monthly, 230.1 days (95 percent CI, 192.5–267.7) quarterly, 225.4 days (95 percent CI, 182.0–268.9) semiannually, and 211.1 days (95 percent CI, 173.4–248.8) annually. For the remaining scenarios without considering post-trial study medications, the estimated life-year-gained ranged between 45 and 65 days. Projections adjusted for in-trial events were generally shorter than without adjustment. Moreover, adjusted for in-trial events, based on a USA life table (22) and a half-a-cycle age correction, the annual projection (59.7 days, 95 percent CI, 21.8–97.6) was close and comparable to that from using REACH-based-probabilities (58.7 days, 95 percent CI, 10.4–107.1).

Depending on scenarios, the three factors were found to have different effects on the projected life-year-gained. Without the impact of post-trial study medications and in-trial events, only the usage of background probability from a USA life table projected significantly longer life-year-gained than REACH-based-probabilities did (Table 1 and Supplementary Table 4: mean and 95 percent CI, 52.9 [49.3–56.5] days with the life table and 47.9 [49.3–56.5] otherwise). For the scenario without post-trial study medications but with the impact of in-trial events, using half-a-cycle age correction or not was not found to project significantly different (Table 1 and Supplementary Table 4: mean and 95 percent CI, 57.9 [52.8–63.0] days without correction and 59.3 [55.6–62.9] with correction). The background probability was again significant (Table 1 and Supplementary Table 4: mean and 95 percent CI, 60.4 [58.1–62.7] days with the life table and 56.8 [54–59.6] with REACH 20-month risk-based probabilities). With both post-trial study medications and in-trial events, there were main effects for the three factors (Table 1 and Supplementary Table 4): half-a-cycle age correction (mean and 95 percent CI, 245.5 [199.0–292.0] days with correction and 251.4 [209.1–293.7] days without correction), cycle length (mean and 95 percent CI, 252.2 [190.5–313.9] days projected monthly, 251.8 [192.0–311.6] quarterly, 249.1 [189.7–308.5] semiannually, and 240.8 [178.5–303.1] annually), and background probability (mean and 95 percent CI, 269.1 [260.3–277.9] days projected with REACH-based-probabilities and 227.7 [212.6–242.8] days with a USA life table). For scenarios without post-trial study medications, the length of cycle did not affect the projection of life-year-gained (Table 1). However, with both post-trial study medications and in-trial events, annual projection on life-year-gained was significantly different from monthly, quarterly, or semiannual one (Table 2). Projecting annually was 11.4 days shorter than monthly (95 percent CI, −17.4, −5.3), 11 days shorter than quarterly (95 percent CI, −17.0, −4.9), and 8.3 days shorter than semiannually (95 percent CI, −14.3, −2.2). Either monthly, quarterly, or semiannual projection was not found different from one another. The distributions of life-year-gained for subexperiments were shown in Supplementary Figure 4 and Table 2. The distributions shifted higher using REACH 20-month risks than using life tables. They shifted slightly when projecting going from monthly to annually. Age correction did not affect the distributions meaningfully.

Computing Burden Caused by Models

In our computing environment (Supplementary Table 7), to project 15-year post-trial in three scenarios using 200 simulations for 200,000 participants, it took 142.4 minutes to project monthly, 74.7 minutes quarterly, 56.6 minutes semiannually, and 49.2 minutes annually.

Discussion

Markov microsimulation models are popularly used to analyze long-term health benefit for a secondary prevention strategy of cardiovascular diseases and to assist policy decision making. How to verify designs and improve the efficiency of these models, especially with the measurement of RMST, is still not well understood. This article tries to address this problem by evaluating the projecting performance of a two-state Markov microsimulation model with three factors: choice of probability of death, lengths of cycle of projection, and usage of half-a-cycle age correction. We find it projects well by using annual projection and a life table, assuming post-trial study medications and in-trial events,

https://doi.org/10.1017/S0266462320000446 Published online by Cambridge University Press

Table 1. Analyze the effects of half-a-cycle age correction, cycle lengths, and background probabilities on projected of life-year-gained (in days): three-way ANOVA analyses

	Degrees of Freedom	Sum of Squares	Mean Square	*F* Value	*P* Value
Scenario A: Neither in-trial events nor post-trial study medications					
Half-a-cycle age correction	1	1.90	1.90	.810	.39
Cycle length	3	19.25	6.42	2.74	0.099
Background probability	1	100.83	100.83	43.05	<.001
Residuals	10	23.42	2.34		
Scenario B: With in-trial events but NOT post-trial study medications					
Half-a-cycle age correction	1	6.83	6.83	4.520	.06
Cycle length	3	2.25	.75	.497	.69
Background probability	1	53.96	53.96	35.71	<.001
Residuals	10	15.11	1.51		
Scenario C: With both in-trial events and post-trial study medications					
Half-a-cycle age correction	1	139	139	17.70	.002
Cycle length	3	335	112	14.23	<.001
Background probability	1	6,809	6,809	868.10	<.001
Residuals	10	78	8		

Table 2. Tukey's HSD test: pairwise comparisons on projected life-year-gained with various cycle lengths: difference in life-year-gained (in days) and 95 percent confidence intervals

Pairwise-comparisons on projected life-year-gained with cycle lengths	Scenario A: Neither post-trial study medications nor in-trial events	Scenario B: With in-trial events but NOT post-trial study medications	Scenario C: With both post-trial study medications and in-trial events
Quarterly versus monthly	.9 (−2.4, 4.2)	−.6 (−3.3, 2.1)	−.4 (−6.5, 5.7)
Semiannually versus monthly	1.2 (−2.1, 4.5)	.4 (−2.3, 3.1)	−3.1 (−9.1, 3.0)
Annually versus monthly	3.0 (−.3, 6.3)	.2 (−2.5, 2.9)	−11.4 (−17.4, −5.3)
Semiannually versus quarterly	.3 (−3.0, 3.6)	1.0 (−1.7, 3.7)	−2.7 (−8.7, 3.4)
Annually versus quarterly	2.1 (−1.2, 5.4)	.8 (−1.9, 3.5)	−11.0 (−17.0, −4.9)
Annually versus semiannually	1.8 (−1.5, 5.2)	−.2(−2.9, 2.5)	−8.3 (−14.3, −2.2)

if applicable. This finding is very relevant to the current practice of health economic analysis. Even in very recent years, there are various implementations of Markov microsimulation models with usage of these factors that require vigorous justification. For example, Magnuson et al. (4) used a two-state Markov microsimulation model with a USA life table to do monthly post-trial projection on 14,107 patients from the PEGASUS-TIMI 54 Trial. Bress et al. (5) adopted a semiannual microsimulation to project on a hypothetical cohort of 10,000 SPRINT-eligible adults. Kypridemos et al. (6) simulated 29-year experience of cardiovascular diseases prevention for a hypothetical 200 million adults on an annual basis. With the large sample sizes of these cohorts and populations, the computational expense could be heavy. Our work helps to justify and speed up such simulations.

The strength of our study includes a straightforward and efficient structure of the model, usage of individual participants' data instead of aggregated data, and also accounting for the fact that events were measured at discrete time points. We systematically investigated three factors which are key parameters in a Markov microsimulation model, and conducted formal statistical testing on hypotheses and also investigated their computing time. There are a few limitations. First, the projection was adjusted for in-trial nonfatal MI, ischemic stroke, and major bleeding in a scenario. As the in-trial follow-up time was short, there were not too many participants who had these events. Therefore, this adjustment was small. However, the life-year-gained estimated with this adjustment was still slightly higher than those estimated without this adjustment. This also agreed with the in-trial finding on the benefit of the intervention compared with the control in terms of survival. Moreover, the model still needs to be validated on studies with long-term follow-up data. Finally, as COMPASS trial is comparatively large, it is worthwhile to look into the performance of models on smaller data sets in the future.

The annual projection could be a trade-off between accuracy and computing efficiency. For three scenarios, (i) unadjusted, (ii) with only the impact of in-trial events, and (iii) with both impacts of post-trial study medications and in-trial events, life expectancy and life-year-gained, projected monthly, quarterly,

https://doi.org/10.1017/S0266462320000446 Published online by Cambridge University Press

and semiannually, were not found significantly different from one other. The annual projection was significantly different from the other three. Without considering post-trial study medications, the life-year-gained projected annually was numerically close to those by other lengths of cycle. With post-trial study medications, projected life-year-gained was more conservative than other lengths of cycle. This result might be counterintuitive, as the projection would seem to be more accurate with a shorter length of cycle. However, the finding was consistent with Soares and Castro (11), which compared various discrete-time aggregated models with different cycle lengths, instead of microsimulation models, on a simulated data set. Moreover, we argue that given the discrete occurrence of events, a discrete-time Markov microsimulation model, with annual projection, is sufficient to estimate the health benefit of an intervention versus a control by their life-year-gained. Additionally, the time required by the projection by year theoretically reduces to 1/12 of that by month, 1/4 of that by a quarter, 1/2 of that by semiyear. With 200,000 participants and 200 simulations, the savings would be 93.2 minutes from monthly, 25.5 quarterly, and 7.4 semiannually. The saving would be much bigger with a 200-million-participant cohort as that in Kypridemos et al. (6). Thus, the annual projection could be a choice that does not lose too much accuracy but gains computing efficiency. This is especially applicable to a patient-level model running on a large clinical trial or nationwide cohorts.

Next, we assessed the necessity of a half-a-cycle age correction. ANOVA showed that regardless of scenarios and treatments, this correction was found significant to the projection of life expectancy. It was significant to the projected life-year-gained only when post-trial study medications was considered and the intervention group was projected to live considerately longer than the group of control. In this case, the corrected projection, compared with the uncorrected one, estimated slightly longer life expectancy and shorter life-year-gained. The life-year-gained projected annually was about 8–14 days shorter than that of without correction. For the other two scenarios when the post-trial study medications was not considered, the half-a-cycle age correction was not found significant to the projection of life-year-gained. Numerically, there was a difference of about 2–4 days in life-year-gained between corrected and uncorrected projections by various lengths of cycles. This showed that the simulation could be conservative and robust for projecting life-year-gained, regardless using a correction or not. It echoed Barenfiregt (18): even though a half-a-cycle age correction tried to address a situation that a life-to-death transition could occur halfway through a cycle, it was unnecessary because a life table itself had accommodated and provided a better solution. Analysts may be cautious when applying background probabilities without such a built-in correction on midway state-to-state transition.

By comparing with REACH-based-probabilities (23), it seemed conservative to use a USA life table (22) to project life-year-gained. After including the 23-month actual follow-up experience for each individual participant from the COMPASS trial, the model carried these participants' characteristics into post-trial projection. This avoided the complexity of simulating participants' pre- and during-trial experience and allowed a simple structure on post-trial projection. Although we included two states of life and death in the model, we could also consider other states of health to better simulate the reality that patients might experience intermediate cardiovascular burdens. To get a sense of how such burdens affected post-trial survival, we replaced the background probabilities from the life table with REACH-based-probabilities. As expected, the life expectancy projected from the life table was longer than that from the REACH-based-probabilities. Interestingly, shorter life-year-gained was projected with the life table than with REACH risks, if participants were assumed to take study medications post-trial. When not considering post-trial medications, both approaches produced comparable results. This implied that a model could still predict the life-year-gained well when it over-estimated the life expectancy to a similar degree in both treatment arms. This finding was consistent with Gerdtham and Zethraeus (8), although the latter observed a similar phenomenon when comparing the projection of a few parametric survival models. Therefore, it is sufficient to do the projection of life-year-gained based on the life table. This result is especially relevant to the implementation of a Markov microsimulation model. Even though the population of the REACH registry is close to that of the COMPASS trial regarding certain baseline characteristics, they are still different in many aspects. Although there are many other multiple-variable prediction models for cardiovascular outcomes in the literature, one still needs to examine the models for their usefulness and applicability to a certain population (25). So it remains a challenge to accurately estimate the intermediate burden of diseases for a Markov model. Hence, it is a blessing that the life table, which is readily available, can help to project life-year-gained well.

Conclusion

For large trials or cohorts, optimal projections of life-year-gained after a trial has ended should consider using (i) annual projection, (ii) probabilities from a life table, (iii) in-trial events, and (iv) post-trial medication use, if applicable. Our proposed model is easily applied in projecting long-term event-free survival and estimating the effectiveness of a novel intervention versus a control.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0266462320000446.

Acknowledgments. The authors want to acknowledge the investigators of the Cardiovascular Outcomes for People Using Anticoagulation Strategies Study (COMPASS) study for providing access to the data for this investigation. The authors would like to thank the reviewers for their helpful review and suggestions.

Conflict of Interest. The authors declare that they have no conflict of interest.

Funding Statement. This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

References

1. **Wong ND**. Epidemiological studies of CHD and the evolution of preventive cardiology. *Nat Rev Cardiol*. 2014;**11**:276–89.
2. **Bosch J, Eikelboom JW, Connolly SJ, Bruns NC, Lanius V, Yuan F et al.** Rationale, design and baseline characteristics of participants in the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial. *Can J Cardiol*. 2017;**33**:1027–35.
3. **Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O et al.** Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med*. 2017;**377**:1319–30.
4. **Magnuson EA, Li H, Wang K, Vilain K, Shafiq A, Bonaca MP et al.** Cost-effectiveness of long-term ticagrelor in patients with prior

myocardial infarction – results from the PEGASUS-TIMI 54 trial. *J Am Coll Cardiol*. 2017;**70**:527–38.
5. **Bress A, Bellows B, King JB, Hess R, Beddhu S, Zhang Z et al.** Cost-effectiveness of intensive versus standard blood-pressure control. *N Engl J Med*. 2017;**377**:745–55.
6. **Kypridemos C, Collins B, McHale P, Bromley H, Parvulescu P, Capewell S et al.** Future cost-effectiveness and equity of the NHS Health Check cardiovascular disease prevention programme: Microsimulation modelling using data from Liverpool, UK. *PLoS Med*. 2018;**15**:e1002573.
7. **Zafari Z, Bryan S, Sin DD, Conte T, Khakban R, Sadatsafavi M**. A systematic review of health economics simulation models of chronic obstructive pulmonary disease. *Value Health*. 2017;**20**:152–62.
8. **Gerdtham U, Zethraeus N**. Predicting survival in cost-effectiveness analyses based on clinical trials. *Int J Technol Assess Health Care*. 2003;**19**:507–12.
9. **Simpson KN, Strassburger A, Jones WJ, Dietz B, Rajagopalan R**. Comparison of Markov model and discrete-event simulation techniques for HIV. *PharmacoEconomics*. 2009;**27**:159–65.
10. **Reed SD**. Statistical considerations in economic evaluations: A guide for cardiologists. *Eur Heart J*. 2014;**25**:1652–6.
11. **Soares M, Castro L**. Continuous time simulation and discretized models for cost-effectiveness analysis. *PharmacoEconomics*. 2012;**30**:1101–17.
12. **Carvalho TM, Heijnsdijk EAM, Coffeng L, Koning HJ**. Evaluating parameter uncertainty in a simulation model of cancer using emulators. *Med Decis Making*. 2019;**39**:405–13.
13. **Chhatwal J, Jayasuriya S, Elbasha EH**. Changing cycle lengths in state-transition models: Challenges and solutions. *Med Decis Making*. 2016;**36**:952–64.
14. **Saidi O, Flaherty M, Zoghlami N, Malouche D, Capewell S, Critchley JA et al.** Comparing strategies to prevent stroke and ischemic heart disease in the Tunisian population: Markov modeling approach using a comprehensive sensitivity analysis algorithm. *Comput Math Methods Med*. 2019;**2019**:2123079.
15. **Rutter C, Miglioretti D, Savarino J**. Bayesian calibration of microsimulation models. *J Am Stat Assoc*. 2009;**104**:1338–50.
16. **Choi SE, Brandeau ML, Basu S**. Dynamic treatment selection and modification for personalised blood pressure therapy using a Markov decision process model: A cost-effectiveness analysis. *BMJ Open*. 2017;**7**:e018374.
17. **Sonnenberg FA, Beck JR**. Markov models in medical decision making: A practical guide. *Med Decis Making*. 1993;**13**:322–38.
18. **Barenfiregt JJ**. The half-cycle correction: Banish rather than explain it. *Med Decis Making*. 2009;**29**:500–2.
19. **Royston P, Parmar MKB**. The use of restricted mean survival time to estimate the treatment effect in randomized clinical trials when the proportional hazards assumption was in doubt. *Stat Med*. 2011;**30**:2409–21.
20. **Royston P, Parmar MKB**. Restricted mean survival time: An alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome. *BMC Med Res Methodol*. 2013;**13**:152.
21. **Uno H, Tian L, Horiguchi M, Cronin A, Battioui C, Bell J**. Package 'survRM2'. 2017. Available from: https://cran.r-project.org/web/packages/survRM2/survRM2.pdf
22. **Arias E, Heron M, Xu J**. United States life tables, 2013. *Natl Vital Stat Rep*. 2017;**66**:1–64.
23. **Wilson PW, D'Agostino R Sr, Bhatt DL, Eagle K, Pencina MJ, Smith SC et al.** An international model to predict recurrent cardiovascular disease. *Am J Med*. 2012;**125**:695–703.
24. **Ohman EM, Bhatt DL, Steg PG, Goto S, Hirsch AT, Liau CS et al.** The REduction of Atherothrombosis for Continued Health (REACH) registry: An international, prospective, observational investigation in subjects at risk for atherothrombotic events-study design. *Am Heart J*. 2006;**151**:786.e1–786.e10.
25. **Damen JAAG, Hooft L, Schuit E, Debray TPA, Collins GS, Tzoulaki I et al.** Prediction models for cardiovascular disease risk in the general population: Systematic review. *Br Med J*. 2016;**353**:i2416.

https://doi.org/10.1017/S0266462320000446 Published online by Cambridge University Press