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CADTH METHODS AND GUIDELINES

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4th Edition

Appendix — Worked Example

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Worked Example: Cost-Effectiveness of Direct Oral Anticoagulants Compared With Warfarin in Preventing Stroke and Other Cardiovascular Events in Patients With Atrial Fibrillation

Context

The following is a worked example of how economic evaluations can be designed and reported, and aligned with the recommendations in the 4th edition of CADTH's *Guidelines for the Economic Evaluation of Health Technologies: Canada*.[1] The case study used is based on a published economic evaluation,[2] modified for illustrative purposes for this example. The analysis has been changed to correspond with the current guidance; however, the decision problem and data inputs remain the same.

1. Decision Problem

A new class of direct oral anticoagulants became available for the prevention of stroke in the treatment of patients with atrial fibrillation. The decision problem relates to whether these new oral anticoagulants should be reimbursed under provincial public drug plans, depending on patients' underlying risk (as assessed by a CHADS2 score) and based on the expected costs and outcomes of therapy. To address this problem, a cost-utility analysis (CUA) was conducted that compared the individual new direct oral anticoagulants available at the time of the analysis (e.g., dabigatran, rivaroxaban, apixaban) with warfarin in patients with non-valvular atrial fibrillation. Patients were stratified into subgroups based on their CHADS2 scores. Given the relevant decision-makers, a CUA over a lifetime horizon was conducted from a health care payer perspective (incorporating the lifetime costs, treatment effects, and the events either prevented or caused by the respective treatments).

2. Types of Evaluations

The reference-case analysis was in the form of a CUA, with outcomes expressed as quality-adjusted life-years (QALYs).

3. Target Population

The target population for the analysis was Canadian patients with non-valvular atrial fibrillation requiring anticoagulation therapy. The analysis was stratified whereby cost-effectiveness was assessed by a CHADS2 score (2, ≥ 3 without previous stroke, ≥ 3 with previous stroke). The stratification was based on an understanding of the disease, the factors associated with an increased risk of subsequent events, and the criteria used for deciding upon interventions. This was based on consultation with clinical experts (i.e., the expert judgment of individuals with clinical expertise).

4. Comparators

Interventions compared in the analysis included the current care option at the time (warfarin) and the newer oral anticoagulants as required by the specific decision problem (dabigatran 150 mg twice daily and 110 mg twice daily, rivaroxaban, and apixaban). Given the decision problem, no other comparators were considered appropriate within the preventive setting.

5. Perspective

As required by the decision problem, the perspective adopted was that of a publicly funded health care payer. No other perspectives were of interest to the decision-maker; therefore, costs and outcomes were restricted to those of relevance to a publicly funded health care payer.

6. Time Horizon

To fully address the decision problem, a lifetime time horizon was adopted for the reference case to capture the lifetime costs and effects of the treatments, and the events either prevented or caused by the respective treatments. Non–reference case analyses adopted alternative time horizons of 20 years, 10 years, and two years (average duration of major clinical trials).

7. Discounting

In the reference case, an annual discount rate of 1.5% was applied to both costs and outcomes. Non–reference case analyses were conducted that explored discount-rate scenarios of 0% and 3%.

8. Modelling

A Markov model was designed that both addressed the decision problem and was justified, based on the temporal nature of the condition and events associated with the condition. Thus, the model was consistent with the current understanding of the clinical and care pathways for atrial fibrillation and the interventions being compared. Furthermore, the model structure was conceptualized, considering existing well-conducted and validated models that appropriately captured the clinical and care pathways for the condition, and reflected all of the components of the decision problem.

Within the Markov model, a population cohort of patients was followed from initiation of treatment (pharmacotherapy) to death, while simulating the incidence of condition-related events associated with the patient population (Figure 1). Events were simulated based on a three-month cycle. For incorporation into the economic model, transition probabilities with respect to warfarin were derived for the three-month cycle using standard methodology.

The specific events modelled were: transient ischemic attack (TIA); stroke (fatal, major, or minor); bleeding (fatal, intracranial hemorrhage [ICH], major non-ICH, and minor); myocardial infarction (MI); pulmonary embolism (fatal or non-fatal); and death without an event. The probability that such events occur is influenced by a number of factors, including treatment and patient characteristics. Patients who experience a stroke, major bleed, or ICH while on treatment were assumed to subsequently receive Aspirin treatment alone. It was assumed that the outcomes of events would not differ by treatment. Given the need for health states to be reflective of events and previous history, there were a total of 173 potential health states in the model. All assumptions made within the model are detailed in Table 2.

The model structure is detailed in Figure 1. A cycle length of three months was adopted.[2]

The face validity of the model in terms of structure, assumptions, and parameters was sought throughout the exercise by seeking the expert judgment of those with related content expertise, and by presenting the final version of the model and inputs for validation. The model was subject to rigorous internal validation involving quality assurance for all mathematical calculations and parameter estimates. A second expert in health economic modelling reviewed the model to validate all coding. Validation checks included varying individual parameters and assessing whether the results changed in the appropriate direction. For example, setting utility values to one and ensuring that, under this scenario, QALYs were equivalent to life-years. In addition, relative effects were set to one to ensure the same outcomes with respect to costs and QALYs, and then varied in each direction to ensure the expected direction of results was found. As previously discussed, cross-validation with other models was also conducted. The external validity of the model was explored by comparing the results of the model with the results of the clinical trials. Calibration was unnecessary, as all data required to populate the model were directly observable.

9. Effectiveness

Information on clinical effectiveness was obtained through a systematic review of the clinical evidence.

Data from the RE-LY randomized controlled trial (RCT) were used for obtaining baseline estimates for the annual rates of clinical events for patients on warfarin and for ascertaining the probability that events were fatal (Table 1). The RE-LY RCT was selected because it had the most comprehensive reporting of data judged to be fit for purpose, credible, and consistent among the various sources. Where pertinent, data were obtained based on the strata identified previously.

Based on the evidence from both the clinical trial and expert judgment, it was assumed there were no differences in event-fatality rates among treatments.

The estimate for the transition probability for each event for patients being treated with dabigatran, apixaban, and rivaroxaban was derived by using the odds ratio for each treatment. This was obtained from a network meta-analysis (NMA) that followed best practices according to guidelines for the conduct of such analyses.[3] A detailed description of the methods and results of the NMA are available elsewhere.[4] Based on the available results, the following events were modelled to vary by anticoagulant: stroke, MI, major bleeds, and ICH. In addition, the model incorporated the same risks of minor bleeds, pulmonary embolism, and TIA for all anticoagulants.

The relative effectiveness of the newer anticoagulants versus warfarin was assumed to continue for the duration of the patient's lifetime while they continue on therapy. A scenario analysis was conducted where the effectiveness of therapy was assumed to decline by a rate of 5% per annum after year two (the typical follow-up in the identified clinical trials), i.e., for each cycle, the percentage decrease or increase in event rates on therapy is weighted by a factor of 0.95^{t-2}.

In addition, the analysis explored the impact of extrapolation on the expected QALY gains from the optimal treatments. Specifically, the proportion of QALY gain off-treatment, and the proportion of QALY gain post the time horizon of the clinical trials, were analyzed.

In the model, patients who have a stroke, ICH, or major bleeding while on warfarin, rivaroxaban, dabigatran, or apixaban will continue on treatment with Aspirin alone. What is therefore of interest is to assess what proportion of the incremental QALY gains from the newer therapies is due to QALY gains while on Aspirin. For all three stratified groups, the incremental QALY gained while on the original treatment compared with warfarin were greater than the overall incremental QALY gained. Thus, the model did not forecast continued QALY gains after treatment discontinuation.

Of further interest is to assess what proportion of the incremental QALY gains from the newer therapies occurs in the period for which there is no clinical trial evidence (i.e., post two years). For patients with CHADS2 = 2, the proportion of the QALY gain for the new therapies compared with warfarin that was observed during the first two years was between 1.9% and 2.2%. For patients with CHADS2 ≥ 3 without previous stroke, the proportion was between 2.4% and 2.6%. For patients with CHADS2 ≥ 3 and previous stroke, the proportion was between 7.0% and 7.9%. Thus, the model suggested that a high proportion of expected QALY gains occurs after the study period with respect to clinical evidence. This would suggest that uncertainty related to time horizon and the waning of treatment effect may be highly relevant to decision-makers although, in this instance, it does not have a differential effect between the new oral anticoagulants.

10. Measurement and Valuation of Health

Utility values were based on both the patient's previous event history (previous MI or stroke) and whether the patient experienced an event in the current cycle. Utility values are detailed in Table 1. Utility values were obtained from the literature through a detailed systematic review and were selected based on their fitness for purpose, credibility, and consistency. Fitness for purpose was assessed based on the contemporaneous nature of the data, the relevance to the specified patient population, and the Canadian context, including preferences reflective of the general population. Credibility was assessed based on the appropriateness of the methodology in terms of demonstrated psychometric properties.

Given the diverse nature of the utility values required to populate the model and the paucity of data in certain instances, alternate sources for values were required — with the values based on different populations and different instruments. As such, there was a degree of inconsistency in the methods adopted among utility values and, in certain instances, data from indirect utility measures were unavailable. This is an identified limitation of the analysis.

11. Resource Use and Costs

Given the design of the Markov model and the perspective of the analysis, costs were required for the treatment comparators and for resource use related to the specific events being modelled, as well as underlying health care management, given the patient's event history. As decision-making is at the provincial level, drug costs were obtained from the Ontario public drug plan formulary. Canadian health care costs related to both the management of the patients' underlying health states and the clinical events were obtained from the published literature through a detailed systematic review of published information. The selection of cost estimates was made based on their fitness for purpose, credibility, and consistency. To ensure the data reflect the jurisdiction of interest, fitness for purpose was weighed more heavily when assessing the relative trade-offs in these criteria among the various sources. Given that global health care costs by health state and clinical event were obtained, details of individual resource use were not required.

Costs were provided for all health states and for all clinical events. Estimates in 2011 Canadian dollars are detailed in Table 1. The year 2011 was an appropriate base year, given the context of the study. Costs that were obtained for a different base year were inflated by the consumer price index using the Bank of Canada Inflation Calculator.

12. Analysis

The expected values of costs and QALYs for each comparator for the different strata based on CHADS2 score were obtained through probabilistic analysis.

The expected values were obtained from a Monte Carlo simulation with 5,000 replications. This was considered sufficient, as a plot of the expected values of incremental costs, QALYs, and cost per QALY gained by number of replications, demonstrated stability (Figure 2). The analysis followed standard methods for defining uncertainty around parameters. Transition probabilities were characterized by beta distributions, and relative risks and odds ratios were characterized by lognormal distributions. Utility values for long-term states were characterized by beta distributions, while utility decrements were characterized by normal distributions. Costs were characterized by gamma distributions. Drug costs were assumed fixed. Probability distributions were parameterized using empirical data. No data on correlation among parameters were available and no correlations were assumed. For event costs where no measures of dispersion were available, it was assumed that the standard error of the mean was 25% of the mean value.

Based on these values, a sequential analysis of cost-effectiveness was conducted following standard rules for estimating incremental cost-effectiveness ratios, including the exclusion of dominated alternatives. The analysis also reports costs disaggregated in terms of drug therapy costs and costs of treating events. It also reports the net monetary benefit from each therapeutic option based on a threshold value of $50,000 per QALY.

13. Uncertainty

Uncertainty about the value of each parameter included in an analysis, and the impact of this uncertainty on the costs and outcomes for each intervention, were examined explicitly through probabilistic analysis. In addition to the sequential analysis mentioned earlier, results are presented in terms of cost-effectiveness acceptability curves and cost-effectiveness acceptability frontiers.

For illustration, a value-of-information analysis was conducted, with the expected value of perfect partial information for each uncertain parameter estimated for each stratified group. This was conducted assuming a threshold value of $50,000 per QALY, and was chosen for illustrative purposes.

Sources of methodological and structural uncertainty relating to certain assumptions led to the following non–reference case and scenario analyses:

- discount rate of 0%
- discount rate of 3%
- waning of treatment effect after two years
- incorporation of estimates of patients' annual lost productivity due to warfarin-related management (e.g., travel to laboratories) (estimated to be $66.69 per year in 2011 Canadian dollars).[5]

14. Equity

All outcomes were weighted equally. No specific patient characteristics were identified, which may lead to decision-makers to adopt an alternative equity position.

15. Reporting

Given the nature of this report as an illustration of the analysis required to meet the specified guidelines, the focus is on demonstrating the requisite detail in reporting the results of the analysis rather than on the findings themselves and on an interpretation of those results.

Analysis is first presented in disaggregated detail showing total non-discounted and discounted costs, life-years, and QALYs, disaggregated discounted events, and counts of major events reported separately for each comparator for each stratified group (Table 3). All outcomes presented are expected values, that is, they are averages based on outcomes from each of the 5,000 replications within the Monte Carlo simulation. Figure 2 illustrates that with 5,000 simulations, estimates of incremental outcomes are stable.

A sequential incremental analysis was conducted and is presented both in tabular form and as a cost-effectiveness plane for each stratified group (Table 4 and Figure 3).

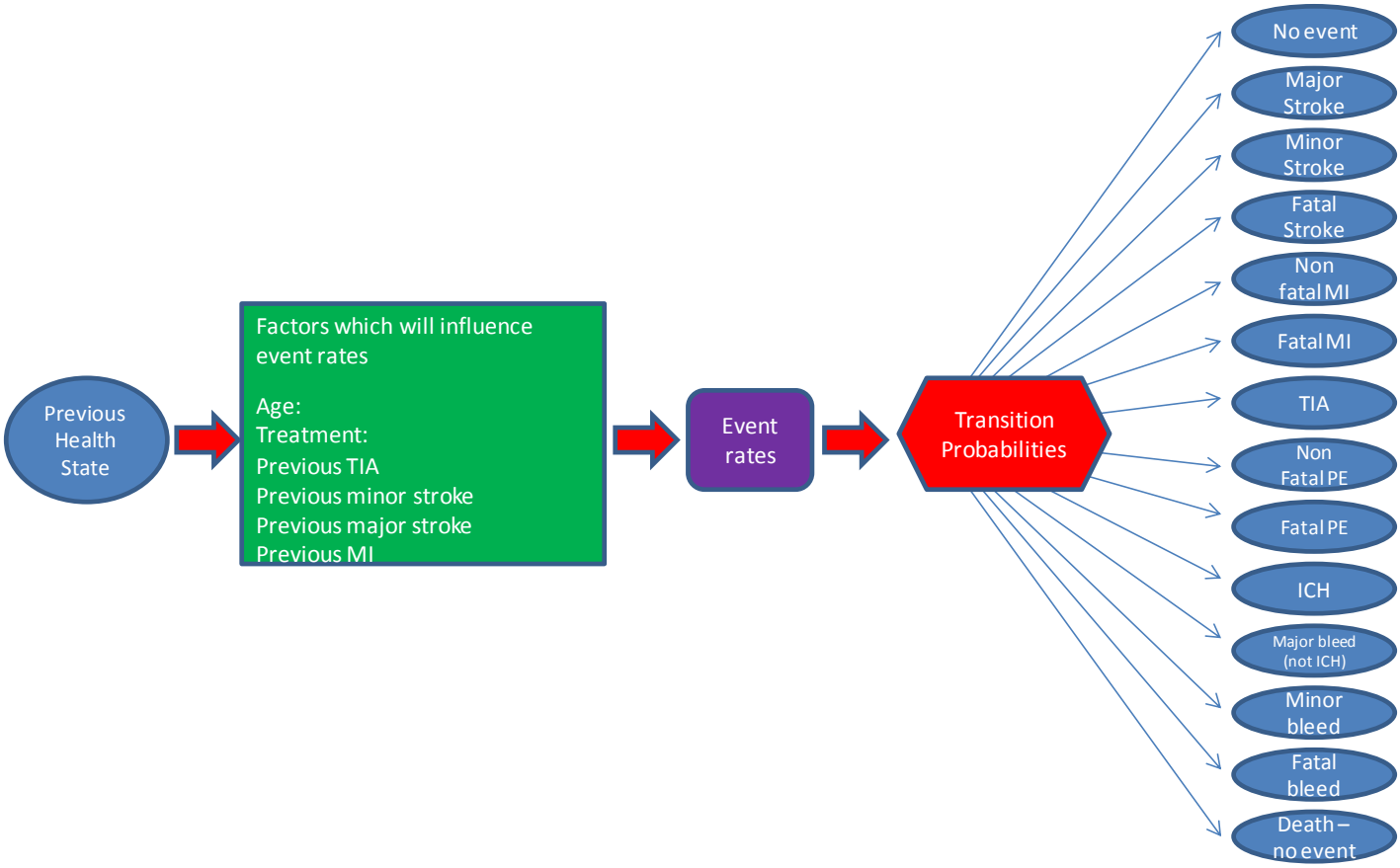
The uncertainty with the model results is presented both through a cost-effectiveness acceptability curve and a cost-effectiveness acceptability frontier for each stratified group (figures 4 and 5).

The contribution of individual parameters to the underlying uncertainty over which treatment is cost-effective is provided in Table 5.

Finally, methodological and structural uncertainty are explored in Table 6, with expected values for each analysis obtained through probabilistic analysis. To aid decision-makers, the impact of uncertainty is reported by identifying optimal treatments for each threshold for each stratified group for the specific analysis explored.

As required by the guidelines, a study disclaimer is needed: this study was funded through a grant from the Canadian Institutes of Health Research Drug Safety and Effectiveness Network. The publication of the study results was not contingent on the sponsor's approval or censorship of the manuscript.

Figure 1: Conceptual Design of Economic Model



ICH = intracranial hemorrhage; MI = myocardial infarction; PE= pulmonary embolism; TIA = transient ischemic attack.

Table 1: Input Parameters

Parameters	Base Estimate	Probability Distribution[a]	Source
Annual rates of events with warfarin			[6]
$CHADS_2$ = 2	0.016	Beta (186, 11 608)	
Stroke	0.008	Beta (99, 11 695)	
TIA	0.008	Beta (90, 11 704)	
ICH	0.033	Beta (386, 11 408)	
Major bleeds	0.164	Beta (1 931, 9 863)	
Minor bleeds	0.006	Beta (66, 11 728)	
MI	0.001	Beta (12, 11 782)	
PE	0.033	Beta (391, 11 403)	
Non-vascular death	0.025	Beta (94, 3 639)	
$CHADS_2 \geq 3$	0.008	Beta (31, 3 702)	
Stroke	0.011	Beta (40, 3 693)	
TIA	0.035	Beta (132, 3 601)	
ICH	0.164	Beta (611, 3 122)	
Major bleeds	0.006	Beta (21, 3 712)	
Minor bleeds	0.001	Beta (4, 3 729)	
MI	0.038	Beta (142, 3 591)	
PE			
Non-vascular death			
Event-related probabilities			
Percentage of first strokes that are fatal	0.237	Beta (44, 142)	[6]
Percentage of non-fatal first strokes that are major	0.333	Beta (39, 78)	[6]
Increased risk of subsequent strokes being fatal	1.570	Lognormal (1.21, 2.03)	[7]
Probability major bleed or ICH is fatal	0.084	Beta (40, 436) Beta (8, 58)	[6]
Probability MI is fatal	0.121	Beta (4, 8)	[6]
Probability PE is fatal	0.333		[6]
Event-rate adjustments			
Increase in stroke for each 10-year age increment	1.50	Lognormal (1.30.1.70)	[8]
Increase in stroke given previous stroke/TIA	2.20	Lognormal (0.78.6.35)	[9]
Increase in MI given previous MI	2.04	Lognormal (1.17, 3.55)	[10]
Increase in bleeding given age greater than 65	2.66	Lognormal (1.33, 5.32)	[11]
Increase in death given previous stroke	2.30	Lognormal (2.00, 2.70)	[12]
Increase in death given AF	1.20	Lognormal (1.04, 1.40)	[13]

Parameters	Base Estimate	Probability Distribution[a]	Source
Relative risks for Aspirin versus warfarin			14
Stroke	1.62	Lognormal (0.99, 2.65)	
MI	1.42	Lognormal (0.84, 2.39)	
ICH	0.51	Lognormal (0.16, 1.60)	
Minor bleed	0.63	Lognormal (0.32, 1.22)	
Major bleed	1.14	Lognormal (0.47, 2.73)	
TIA	1.56	Lognormal (0.86, 2.83)	
Odds ratios for apixaban versus warfarin			4
$CHADS_2$ = 2	0.79	Lognormal (0.65, 0.95)	
Stroke	0.88	Lognormal (0.66, 1.17)	
MI	0.42	Lognormal (0.30, 0.58)	
ICH	0.80	Lognormal (0.68, 0.94)	
Major bleed	0.78	Lognormal (0.63, 0.95)	
$CHADS_2$ ≥ 3	0.88	Lognormal (0.66, 1.17)	
Stroke	0.42	Lognormal (0.3, 0.58)	
MI	0.73	Lognormal (0.62, 0.87)	
ICH			
Major bleed			
Odds ratios for dabigatran 110 mg versus warfarin			4
$CHADS_2$ = 2	0.92	Lognormal (0.74, 1.13)	
Stroke	1.32	Lognormal (0.97, 1.78)	
MI	0.29	Lognormal (0.19, 0.45)	
ICH	0.94	Lognormal (0.93, 1.26)	
Major bleed	0.89	Lognormal (0.71, 1.12)	
$CHADS_2$ ≥ 3	1.32	Lognormal (0.97, 1.78)	
Stroke	0.29	Lognormal (0.19, 0.45)	
MI	0.86	Lognormal (0.73, 1.02)	
ICH			
Major bleed			

Parameters	Base Estimate	Probability Distribution[a]	Source
Odds ratios for dabigatran 150 mg versus warfarin			[4]
$CHADS_2$ = 2	0.64	Lognormal (0.51, 0.81)	
Stroke	1.29	Lognormal (0.95, 1.75)	
MI	0.41	Lognormal (0.28, 0.60)	
ICH	1.08	Lognormal (0.81, 1.10)	
Major bleed	0.66	Lognormal (0.52, 0.85)	
$CHADS_2$ ≥ 3	1.29	Lognormal (0.95, 1.75)	
Stroke	0.41	Lognormal (0.28, 0.6)	
MI	1.01	Lognormal (0.86, 1.19)	
ICH			
Major bleed			
Odds ratios for rivaroxaban versus warfarin			[4]
$CHADS_2$ = 2	0.83	Lognormal (0.68, 1.02)	
Stroke	0.80	Lognormal (0.61, 1.04)	
MI	0.65	Lognormal (0.46, 0.91)	
ICH	1.14	Lognormal (0.97, 1.33)	
Major bleed	0.78	Lognormal (0.64, 0.94)	
$CHADS_2$ ≥ 3	0.8	Lognormal (0.61, 1.04)	
Stroke	0.65	Lognormal (0.46, 0.91)	
MI	1.03	Lognormal (0.89, 1.19)	
ICH			
Major bleed			
Utility values			
Long-term utilities	0.810	Beta (33.82, 7.93)	[15]
AF	0.390	Beta (69.74, 109.08)	[16]
Previous major stroke	0.110	Beta (18.93, 153.16)	[16]
Rankin score of 3 to 4	0.205	Beta (8, 39)	[6]
Rankin score of 5	0.75	Beta (86.69, 28.90)	[16]
Probability of major stroke is a score of 5	0.75	Beta (86.69, 28.90)	[16]
Previous minor stroke	0.012	Normal (0.012, 0.0002)	[15]
Previous ICH	0.00029	Normal (0.00029, 0.00002)	[15]
Previous MI (decrement)			
Decrement per year over 70 years			
Decrements associated with events			
MI	0.125	Normal (0.125, 0.009)	[15]
Major bleeds	0.092	Normal (−0.092, 0.010)	[17]
Minor bleeds	0.013	Normal (−0.013, 0.001)	[17]
PE	0.022	Normal (−0.022, 0.003)	[18]
TIA	0.103	Normal (−0.103, 0.008)	[15]

Parameters	Base Estimate	Probability Distribution[a]	Source
Costs of drug treatment (per annum)			
Warfarin, 5 mg daily	$54.61	Fixed	19
International normalized ratio monitoring	$240.69	Fixed	20
(per annum) for warfarin	$66.69	Fixed	5
Lost productivity associated with warfarin	$39.04	Fixed	19
management	$1,289.44	Fixed	19
Aspirin, enteric-coated, 325 mg daily	$1,289.44	Fixed	19
Dabigatran, 110 mg b.i.d.	$1,147.53	Fixed	19
Dabigatran, 150 mg b.i.d.	$1,289.44	Fixed	19
Rivaroxaban, 20 mg daily			
Apixaban, 5 mg b.i.d.			
Events	$16,800	Gamma (16.0, 1,050.0)	14
Fatal stroke	$16,800	Gamma (16.0, 1,050.0)	14
Minor stroke	$56,864	Gamma (16.0, 3,554.0)	14
Major stroke	$4,296	Gamma (16.0, 268.5)	21
TIA	$16,559	Gamma (16.0, 1,035.0)	14
ICH	$4,392	Gamma (16.0, 274.5)	14
Major bleed	$104	Gamma (6.4, 16.3)	22
Minor bleed	$7,351	Gamma (16.0, 459.5)	14
Fatal MI	$11,380	Normal (11,380.0, 167.0)	23
Non-fatal MI	$7,442	Normal (7,442.0, 7,682.1)	24
PE			
Long-term costs (per annum)			
MI	$3,272	Gamma (190.6, 17.2)	14
Major stroke	$19,069	Gamma (16.0, 1,191.8)	14
Minor stroke	$7,896	Gamma (16.0, 493.5)	23
ICH	$7,896	Gamma (16.0, 493.5)	23

AF = atrial fibrillation; b.i.d. = twice daily; ICH = intracranial hemorrhage; MI = myocardial infarction; PE= pulmonary embolism; TIA = transient ischemic attack.

[a] Transition probabilities were characterized by beta distributions. Relative risks and odds ratios were characterized by lognormal distributions. Utility values for long-term states were characterized by beta distributions, while utility decrements were characterized by normal distributions. Costs were characterized by gamma distributions. Drug costs were assumed to be fixed. For event costs where no measures of dispersion were available, a coefficient of variation of 25% was assumed. Beta distributions are specified by alpha and beta, lognormal distributions are specified by lower and upper limits of the 95% confidence intervals. Gamma distributions are specified by shape and scale parameters. Normal distributions are specified by mean and standard error.

Table 2: List of Study Assumptions

Assumption
The patient population in the warfarin arm of the RE-LY trial is representative of the Canadian atrial fibrillation population.
Patients who have a stroke, ICH, or major bleeding while on warfarin, rivaroxaban, dabigatran, or apixaban will continue on treatment with Aspirin alone.
Patients who have other events (including minor bleeds) continue on their current treatment.
A patient can experience any event within a cycle regardless of their previous history.
A patient can experience only one event within a cycle.
The probability of a patient having a stroke will be greater given a previous stroke or TIA.
The probability of a patient having an MI will be greater given a previous MI.
The probability of stroke will increase with age.
The probability of all-cause mortality will increase with previous stroke.
The probability of bleeding will increase with age.
The disutility from events other than stroke, ICH, or MI is temporary.
The cost of events other than stroke, ICH, or MI is incurred only during the cycle in which the event took place.
There are long-term costs associated with an MI, ICH, and stroke, which continue until death.
The relative efficacy of treatments is assumed to be maintained while patients are on treatment.
The long-term costs and utility for patients with a previous ICH are equivalent to outcomes for a minor stroke.
The costs and disutilities associated with bleeds are the same for all treatments.

ICH = intracranial hemorrhage; MI = myocardial infarction; TIA = transient ischemic attack.

Table 3: Expected Values of Key Outcomes

Outcome	Warfarin	Rivaroxaban	Dabigatran 110 mg	Dabigatran 150 mg	Apixaban
a. $CHADS_2$ = 2					
Non-discounted					
Total cost	$23,573	$27,652	$28,910	$27,623	$27,924
Life-years	10.08	10.31	10.45	10.49	10.51
QALYs	8.28	8.40	8.40	8.49	8.50
Stroke (per 1,000)	242	211	221	190	201
ICH (per 1,000)	61	44	24	31	31
Major bleeds (per 1,000)	298	329	264	301	235
Discounted					
Total cost	$20,558	$24,391	$25,543	$24,400	$24,665
Event costs	$18,264	$15,589	$15,221	$14,142	$14,057
Therapy costs	$2,293	$8,802	$10,322	$10,258	$10,608
Life-years	9.12	9.32	9.44	9.47	9.48
QALYs	7.49	7.59	7.59	7.66	7.67
Net monetary benefit (λ = $50,000)	$354,060	$355,207	$353,928	$358,814	$358,931
b. $CHADS_2$ ≥ 3 Without Previous Stroke					
Non-discounted					
Total cost	$34,061	$36,138	$37,056	$35,091	$35,725
Life-years	9.01	9.33	9.49	9.57	9.58
QALYs	7.39	7.57	7.56	7.71	7.70
Stroke (per 1,000)	454	406	421	370	389
ICH (per 1,000)	84	62	36	46	45
Major bleeds (per 1,000)	371	408	333	378	302
Discounted					
Total cost	$29,951	$31,971	$32,837	$31,053	$31,628
Event costs	$27,985	$24,385	$23,885	$22,088	$22,346
Therapy costs	$1,966	$7,586	$8,951	$8,964	$9,282
Life-years	8.23	8.50	8.64	8.71	8.71
QALYs	6.74	6.90	6.89	7.01	7.00
Net monetary benefit (λ = $50,000)	$307,274	$312,855	$311,657	$319,622	$318,603
c. $CHADS_2$ ≥ 3 With Previous Stroke					
Non-discounted					
Total cost	$82,432	$84,178	$85,862	$83,750	$84,665
Life-years	6.16	6.37	6.42	6.52	6.49
QALYs	4.35	4.51	4.46	4.62	4.57
Stroke (per 1,000)	532	473	497	432	460
ICH (per 1,000)	57	42	25	31	31
Major bleeds (per 1,000)	252	277	227	257	206

Outcome	Warfarin	Rivaroxaban	Dabigatran 110 mg	Dabigatran 150 mg	Apixaban
Discounted					
Total cost	$76,242	$77,877	$79,460	$77,450	$78,312
Event costs	$74,893	$72,587	$73,384	$71,198	$71,987
Therapy costs	$1,350	$5,290	$6,076	$6,252	$6,325
Life-years	5.76	5.94	5.99	6.08	6.05
QALYs	4.08	4.22	4.18	4.32	4.28
Net monetary benefit (λ = $50,000)	$127,614	$133,191	$129,368	$138,641	$135,530

ICH = intracranial hemorrhage; MI = myocardial infarction; TIA = transient ischemic attack.

Table 4: Sequential Cost-Utility Analysis

Treatments	QALYs	Cost	Incremental Cost per QALY Gained Versus Warfarin	Sequential Incremental Cost per QALY Gained
a. $CHADS_2$ = 2				
Warfarin	7.492	$20,558		
Dabigatran 150 mg	7.664	$24,400	$22,350	$22,350
Apixaban	7.672	$24,665	$22,875	$34,694
Dominated Strategies				
Rivaroxaban	7.592	$24,391	$38,487	Dominated by dabigatran 150 mg Subject to extended dominance through warfarin and apixaban
Dabigatran 110 mg	7.589	$25,543	$51,365	Dominated by rivaroxaban, dabigatran 150 mg and apixaban
b. $CHADS_2$ ≥ 3 Without Previous Stroke				
Warfarin	6.744	$29,951		
Dabigatran 150 mg	7.013	$31,053	$4,096	$4,096
Dominated Strategies				
Apixaban	7.005	$31,628	$6,447	Dominated by dabigatran 150 mg
Rivaroxaban	6.897	$31,971	$13,291	Dominated by dabigatran 150 mg and apixaban
Dabigatran 110 mg	6.890	$32,837	$19,850	Dominated by rivaroxaban, dabigatran 150 mg, and apixaban
c. $CHADS_2$ ≥ 3 With Previous Stroke				
Warfarin	4.077	$76,242		
Dabigatran 150 mg	4.322	$77,450	$4,934	$4,934
Dominated Strategies				
Apixaban	4.277	$78,312	$10,364	Dominated by dabigatran 150 mg
Rivaroxaban	4.221	$77,877	$11,336	Dominated by dabigatran 150 mg Subject to extended dominance through warfarin and apixaban

Treatments	QALYs	Cost	Incremental Cost per QALY Gained Versus Warfarin	Sequential Incremental Cost per QALY Gained
Dabigatran 110 mg	4.177	$79,460	$32,362	Dominated by rivaroxaban, dabigatran 150 mg, and apixaban

ICH = intracranial hemorrhage; QALY = quality-adjusted life-year.

Table 5: Expected Value of Perfect Partial Information per Patient by Stratified Group

	Stratified Group[a]		
	$CHADS_2 = 2$	$CHADS_2 \geq 3$, Without Previous Stroke	$CHADS_2 \geq 3$, With Previous Stroke
EVPI	1,659	2,138	1,309
EVPPI			
Utility Values			
AF	1.52	0.04	0
Minor stroke	0.34	0	0
Major stroke (Rankin score of 3 to 4)	0	0.05	0
Major stroke (Rankin score of 5)	4.97	0	0
Previous ICH	0.34	0	0
Decrement per year over 70 years	2.7	0	0
Decrement from previous PE	0.04	0	0
Decrement from previous TIA	0.07	0	0
Costs			
Major stroke	11.01	0	0
ICH	0.65	0	0
Major bleed	3.26	0.02	0
Minor bleed	2.07	0	0
Fatal MI	11.55	0	0
Long-term costs post MI	0.01	0	0
Long-term costs post minor stroke	25.31	0	0
Event Rates With Warfarin			
Stroke	73.9	2.81	0
ICH	3.7	0	0
Major bleeds	40.17	0.78	0
MI	69.73	0.3	0
Non-vascular death	0.43	0	0
Natural History Parameters			
Percentage of first strokes that are fatal	8.55	0	0
Percentage of non-fatal first strokes that are major	0.95	0	0
Probability of major stroke (Rankin score of 5)	3.47	0	0
Increased risk of subsequent strokes being fatal	0.58	0	0
Probability major bleed or ICH is fatal	18.86	0	0
Probability MI is fatal	58.92	0	0
Probability PE is fatal	2.51	0	0
Increase in stroke for each 10 year age increment	0.13	0	0
Increase in stroke given previous stroke/TIA	4.94	0.11	0
Increase in MI given previous MI	0.05	0	0

	Stratified Group[a]		
	$CHADS_2$ = 2	$CHADS_2$ ≥ 3, Without Previous Stroke	$CHADS_2$ ≥ 3, With Previous Stroke
Increase in bleeding given age greater than 65	0.7	0	0
Increase in death given previous stroke	4.2	0	0
Increase in death given AF	0	0.41	0
Relative Risk of Events: Aspirin Versus Warfarin			
Stroke	143.94	54.76	0
ICH	4.99	0	0
TIA	2.61	0	0
Odds Ratio of Events: Apixaban Versus Warfarin			
Stroke	955.95	1,127.41	446.98
MI	89.93	0	0
ICH	141.82	3.5	0
Major bleed	173.66	18.12	0
Odds Ratio of Events: Dabigatran 110 mg Versus Warfarin			
Stroke	45.39	72.04	30.5
MI	0.11	0	0
ICH	12.53	0	0
Odds Ratio of Events: Dabigatran 150 mg Versus Warfarin			
Stroke	940.32	1,226.29	589.57
MI	132.39	0.35	0
ICH	159.96	35.51	0
Major bleed	229.96	63.59	0
Odds Ratio of Events: Rivaroxaban Versus Warfarin			
Stroke	32.89	17.68	62.02
ICH	9.78	0	0

AF = atrial fibrillation; EVPI = expected value of perfect information; EVPPI = expected value of perfect partial information; ICH = intracranial hemorrhage; MI = myocardial infarction; PE = pulmonary embolism; TIA = transient ischemic attack.

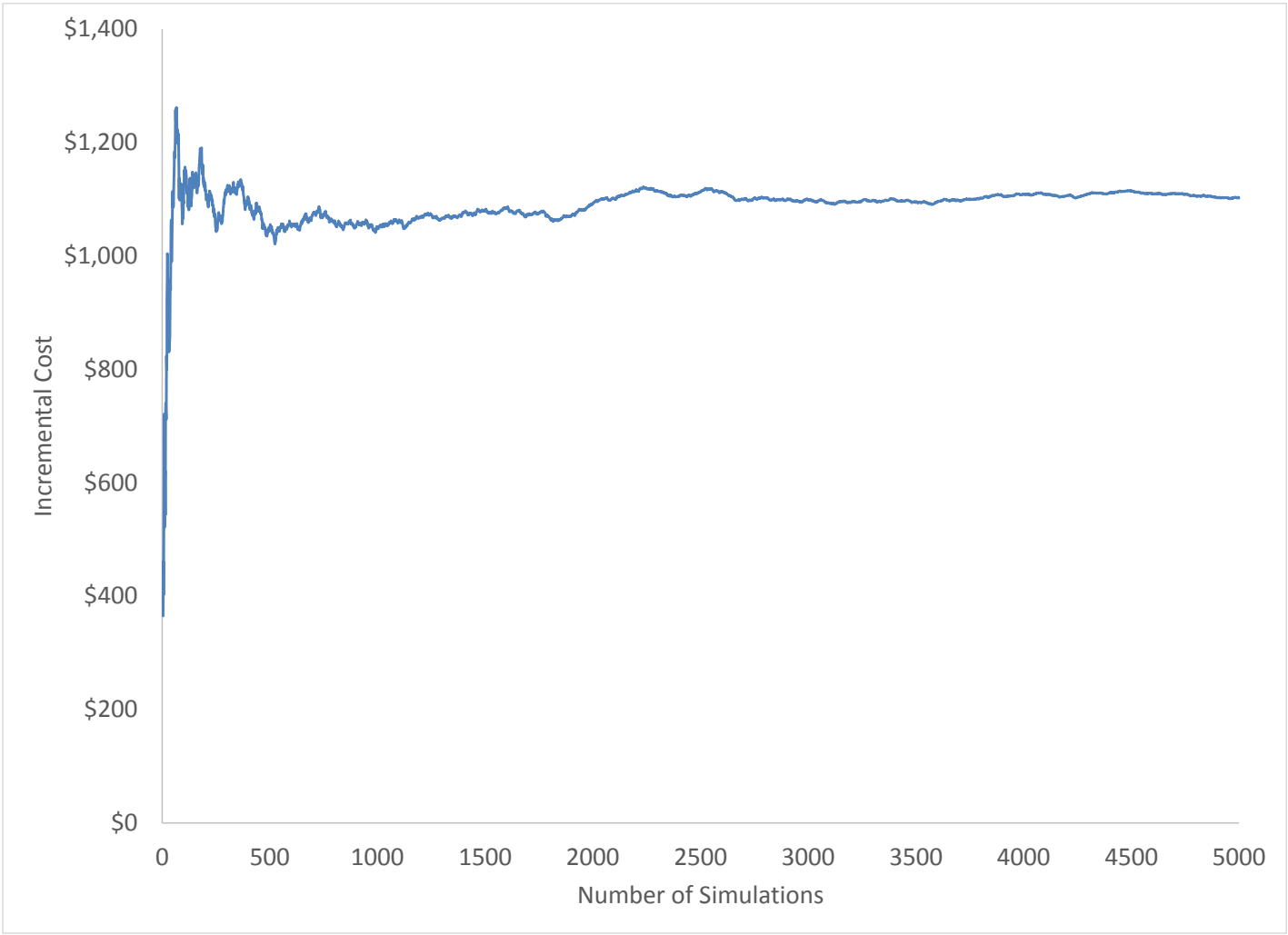
[a] Values are presented only for variables for which the EVPPI is greater than zero for at least one stratified group. Figures in bold represent parameters that were one of the five highest EVPPIs for each stratified group.

Table 6: Results of Analyses Exploring Methodological and Structural Uncertainty

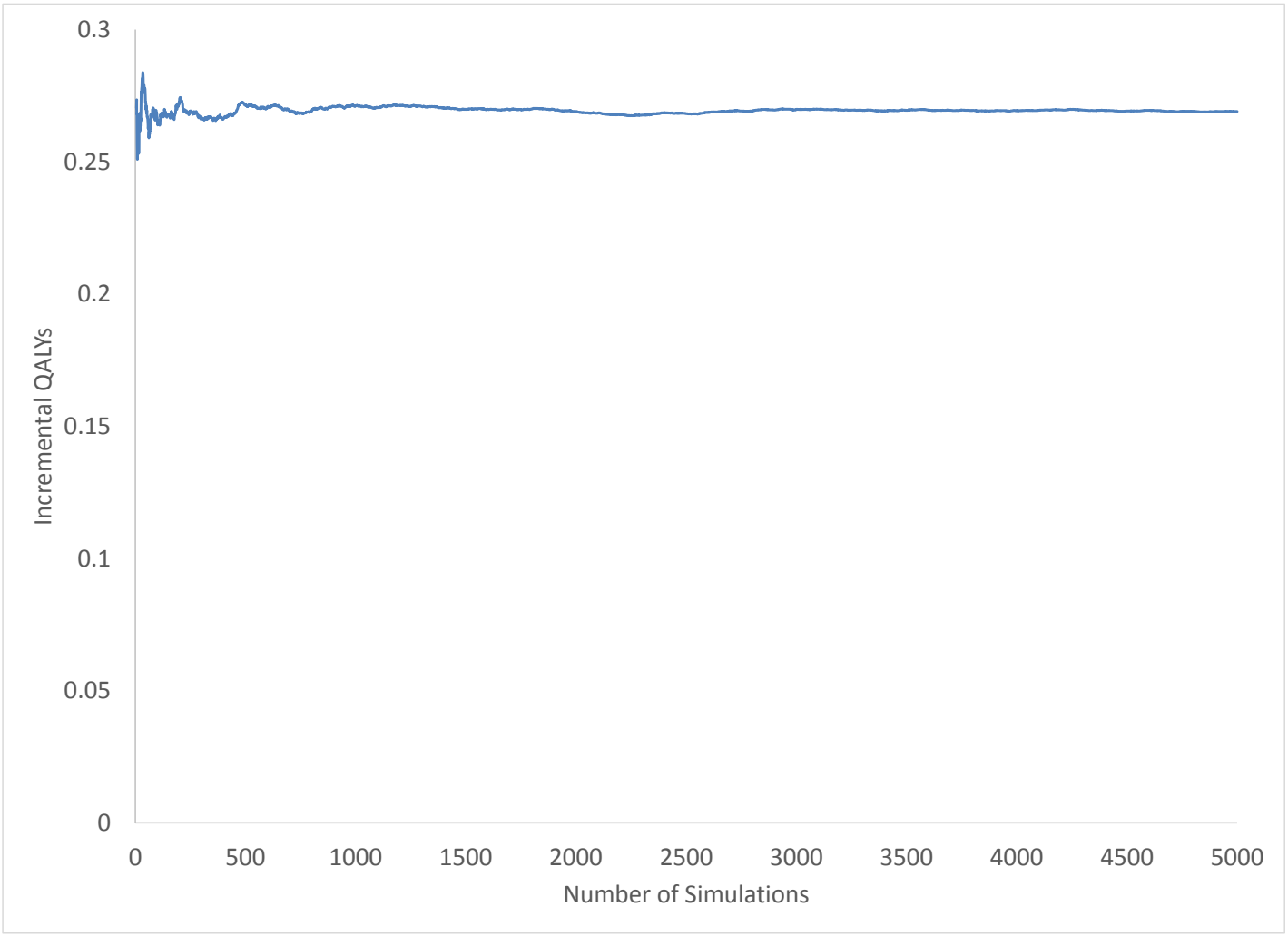
	Stratified Group		
	$CHADS_2$ = 2	$CHADS_2$ ≥ 3 Without Previous Stroke	$CHADS_2$ ≥ 3 With Previous Stroke
Reference case	If λ < $22,350, warfarin is optimal If $22,350 < λ < $34,694, dabigatran 150 mg is optimal If λ > $34,694, apixaban is optimal	If λ < $4,096, warfarin is optimal If λ > $4,096, dabigatran 150 mg is optimal	If λ < $4,934, warfarin is optimal If λ > $4,934, dabigatran 150 mg is optimal
Discount rate of 0%	If λ < $19,647, warfarin is optimal If $19,647 < λ < $34,550, dabigatran 150 mg is optimal If λ > $34,550, apixaban is optimal	If λ < $3,243, warfarin is optimal If λ > $3,243, dabigatran 150 mg is optimal	If λ < $4,833, warfarin is optimal If λ > $4,833, dabigatran 150 mg is optimal
Discount rate of 3%	If λ < $25,146, warfarin is optimal If λ > $25,146, apixaban is optimal	If λ < $3,221, warfarin is optimal If λ > $3,221, dabigatran 150 mg is optimal	If λ < $5,119, warfarin is optimal If λ > $5,119, dabigatran 150 mg is optimal
Waning of treatment effect after two years	If λ < $32,166, warfarin is optimal If λ > $32,166, apixaban is optimal	If λ < $9,033, warfarin is optimal If λ > $9,033, dabigatran 150 mg is optimal	If λ < $7,152, warfarin is optimal If λ > $7,152, dabigatran 150 mg is optimal
Inclusion of lost productivity associated with warfarin management	If λ < $20,049, warfarin is optimal If λ > $20,049, apixaban is optimal	If λ < $2,408, warfarin is optimal If λ > $2,408, dabigatran 150 mg is optimal	If λ < $3,752, warfarin is optimal If λ > $3,752, dabigatran 150 mg is optimal

Figure 2: Impact of Number of Simulations on Expected Values

p. Incremental cost of dabigatran 150 mg versus warfarin for $CHADS_2 \geq 3$ without previous stroke

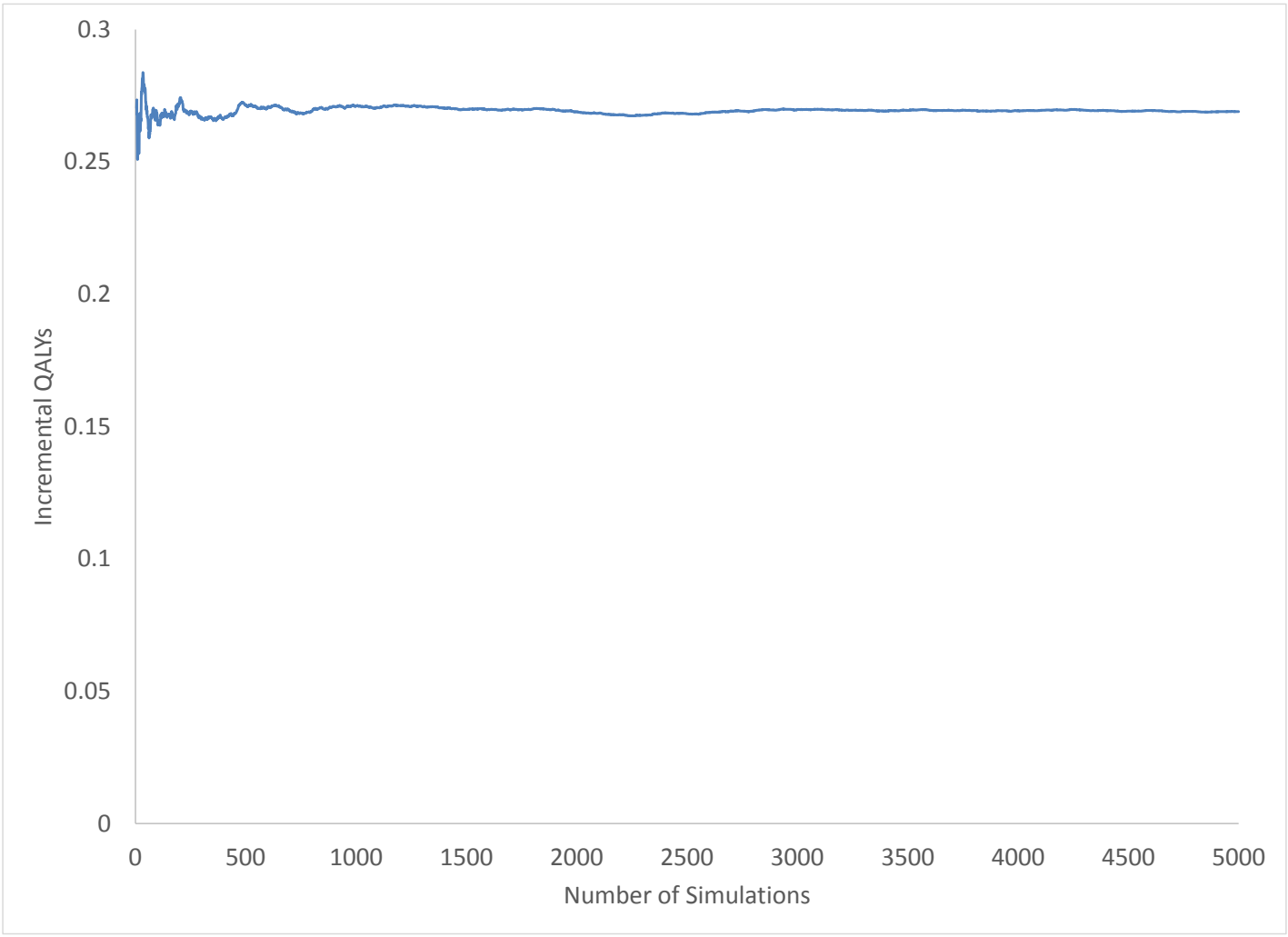


q. Incremental QALYs of dabigatran 150 mg versus warfarin for $CHADS_2 \geq 3$ without previous stroke



QALY = quality-adjusted life-year.

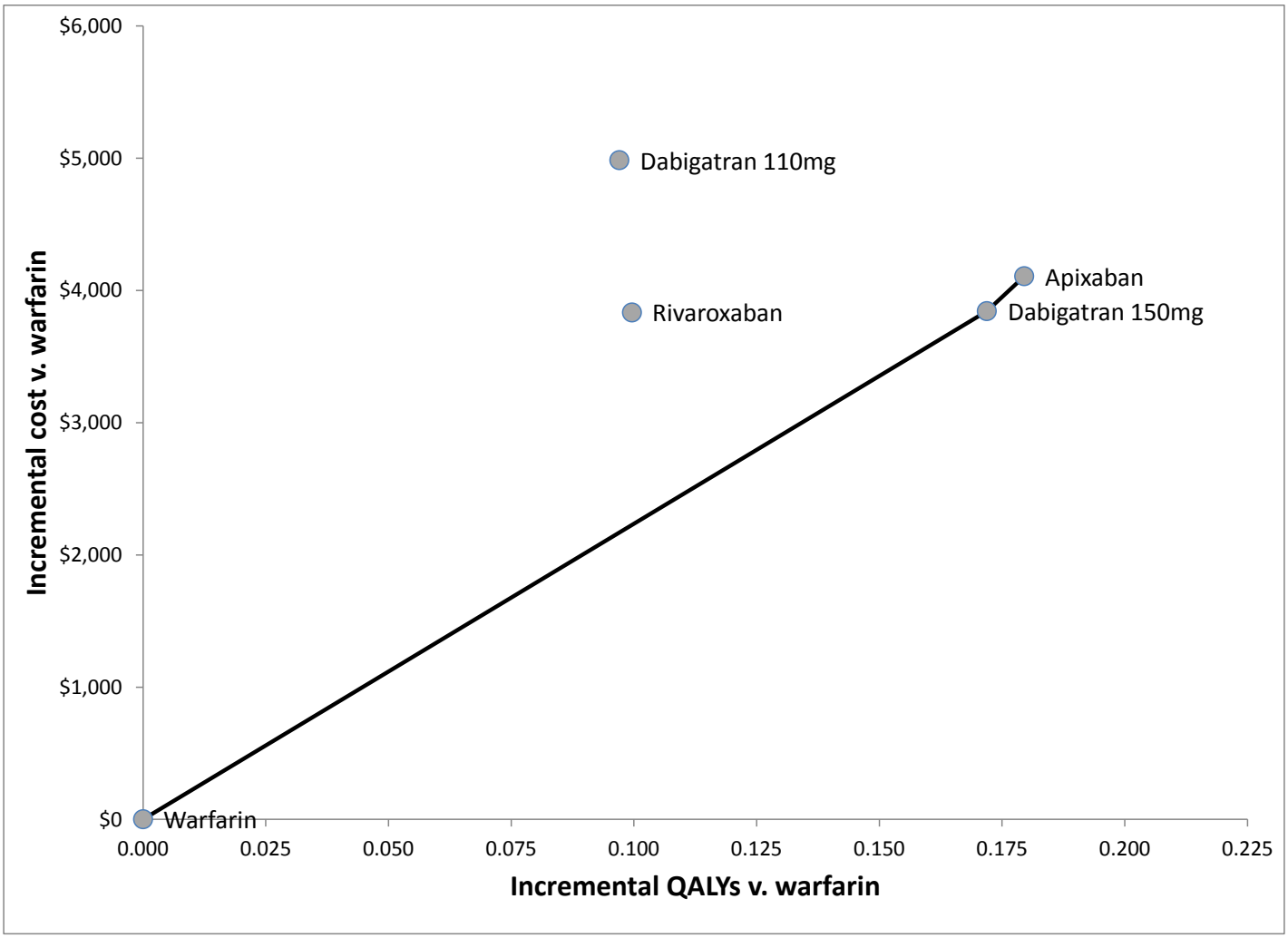
r. Incremental cost per QALY gained for dabigatran 150 mg versus warfarin for $CHADS_2 \geq 3$ without previous stroke



QALY = quality-adjusted life-year.

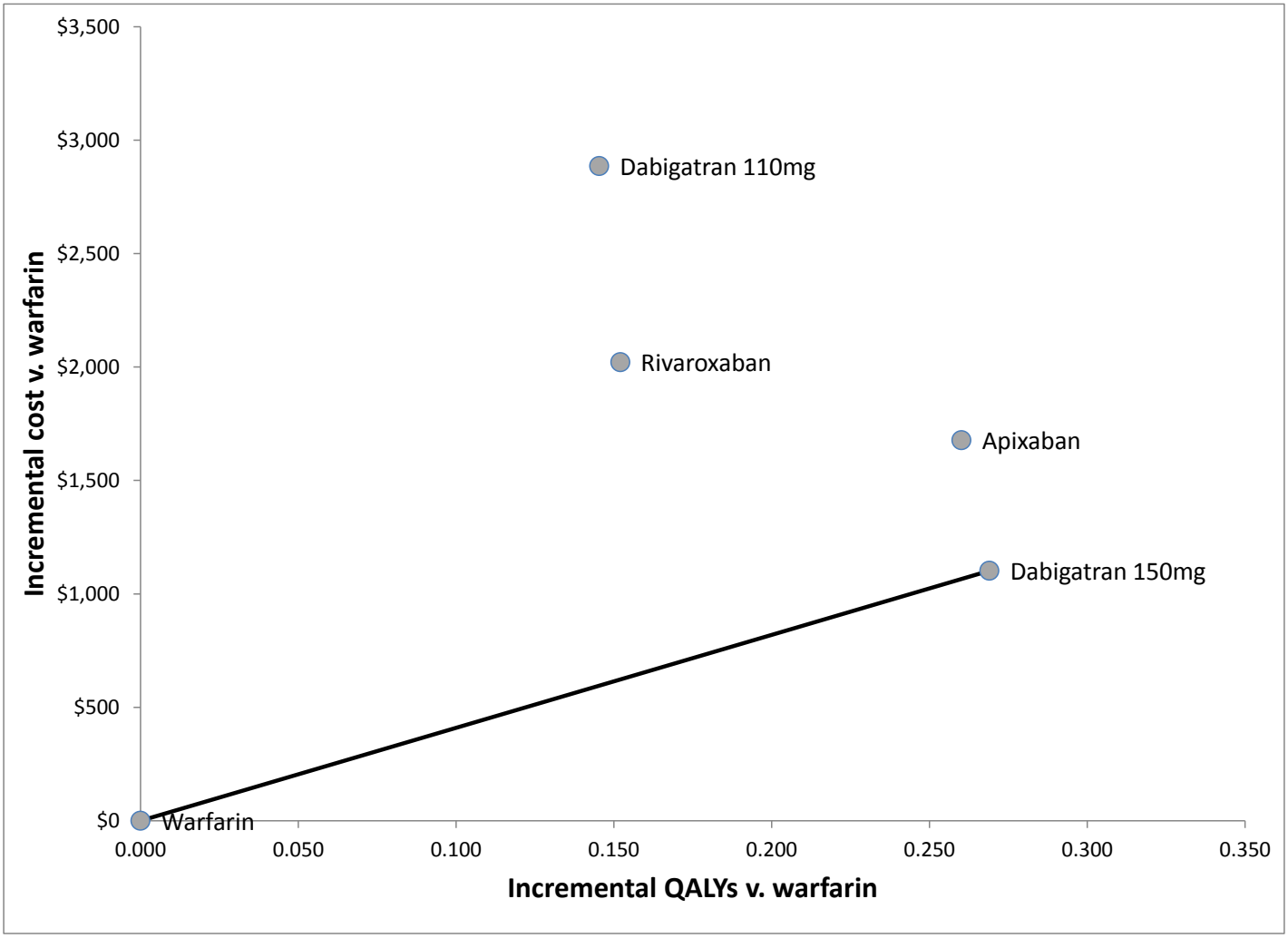
Figure 3: Results Placed on Cost-Effectiveness Plane

a. $CHADS_2 = 2$



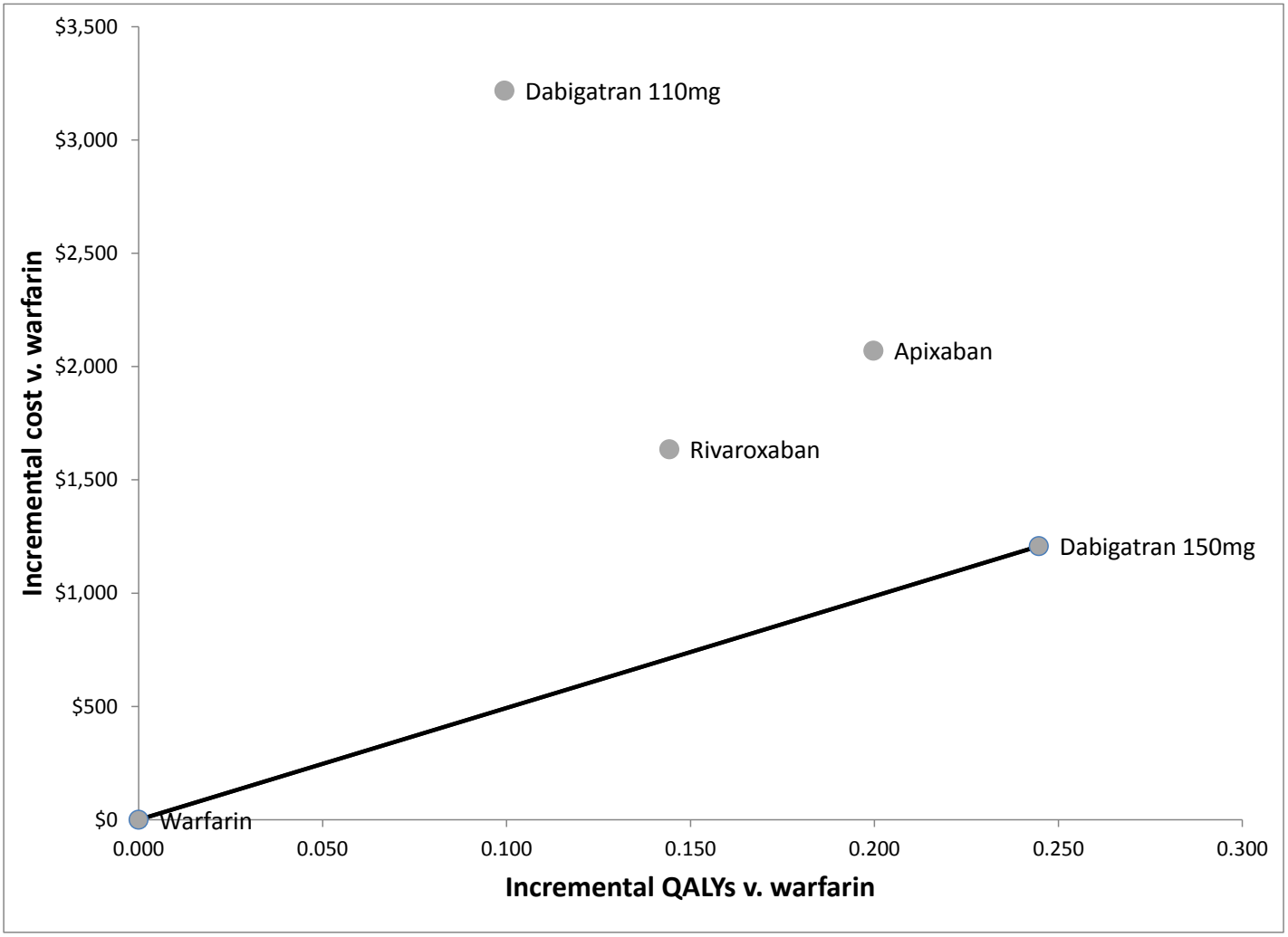
QALY = quality-adjusted life-year; v. = versus.

b. $CHADS_2 \geq 3$ without previous stroke



QALY = quality-adjusted life-year; v. = versus.

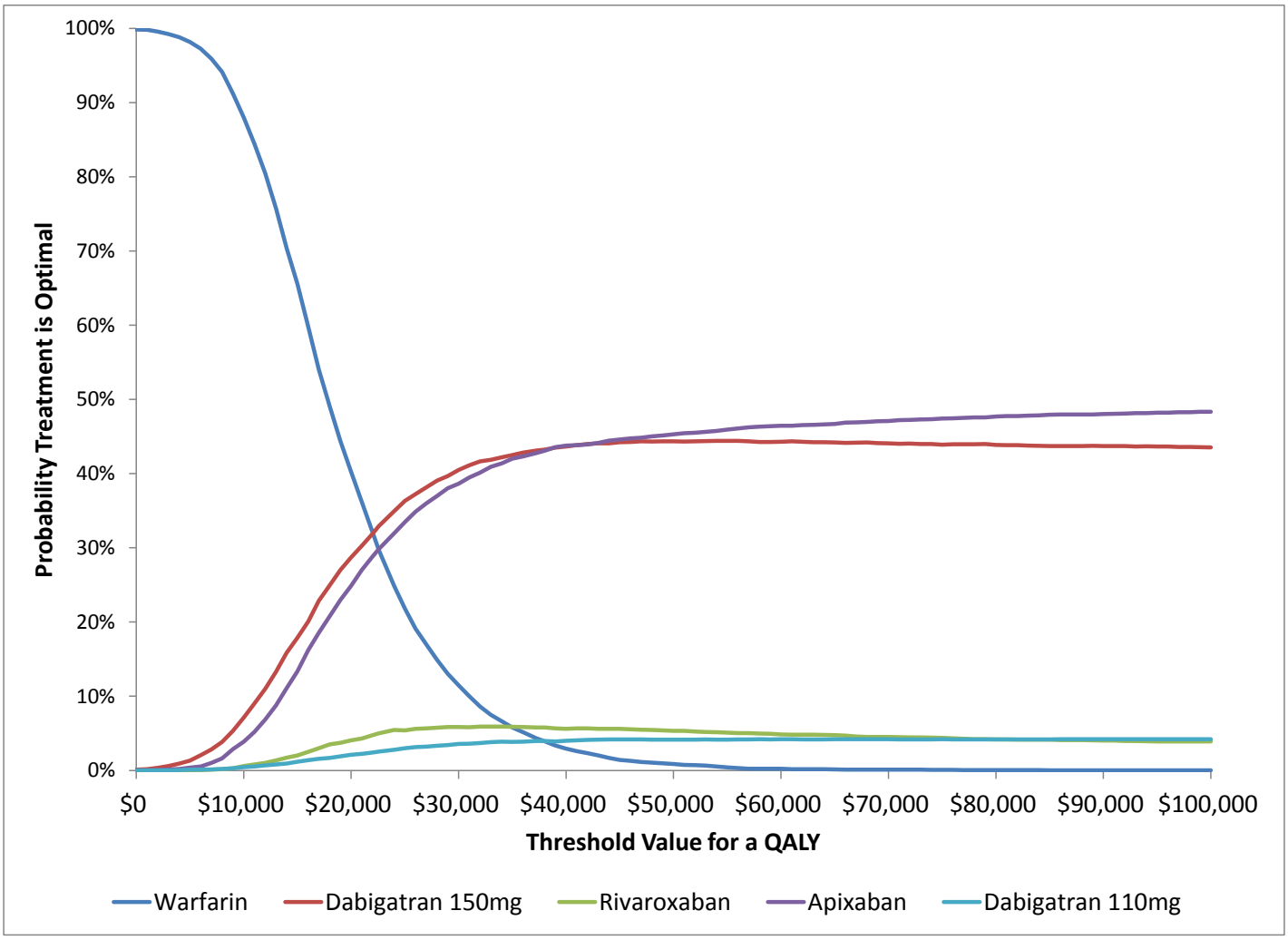
c. $CHADS_2 \geq 3$ with previous stroke



QALY = quality-adjusted life-year; v. = versus.

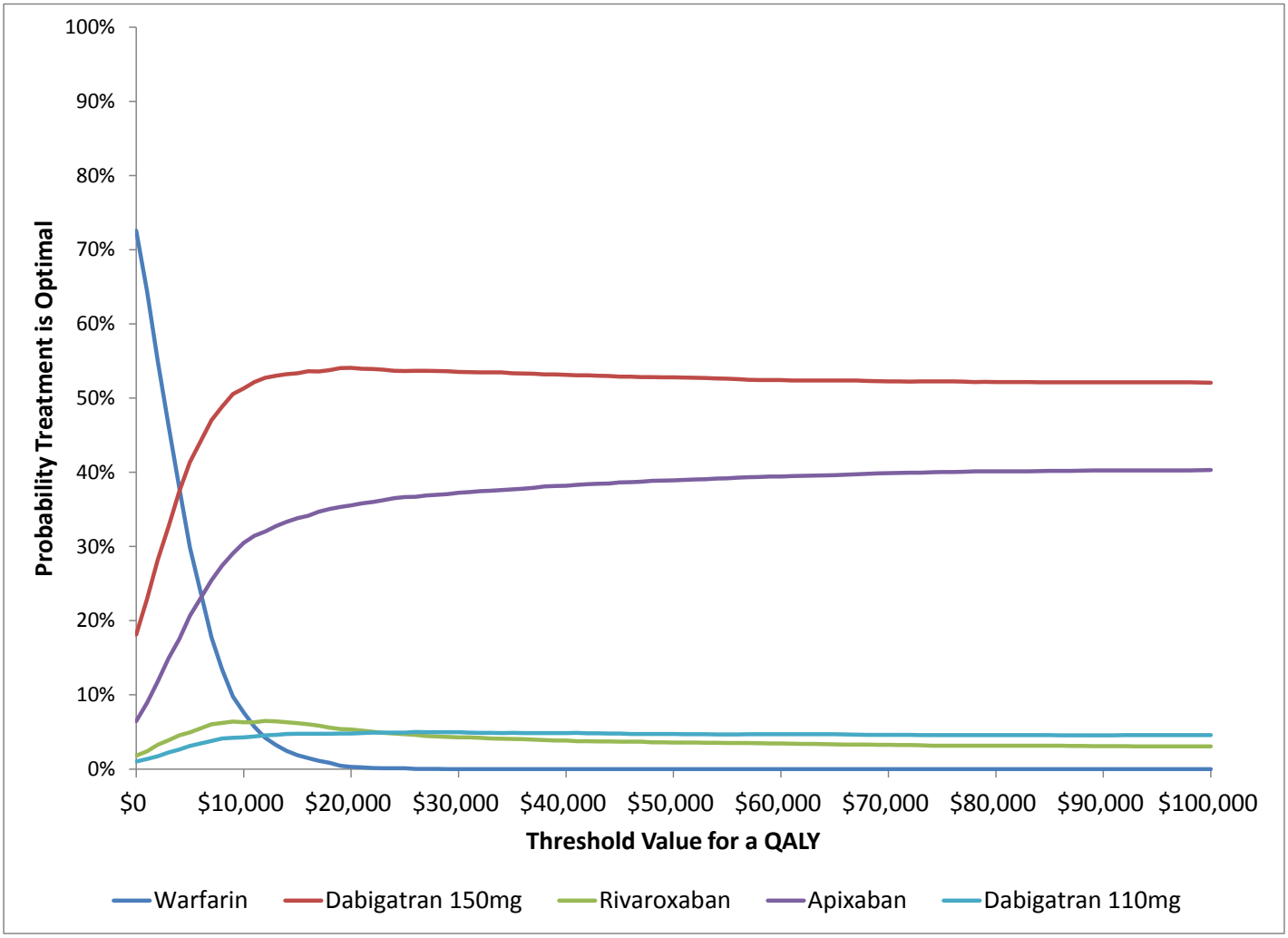
Figure 4: Cost-Effectiveness Acceptability Curve

a. $CHADS_2 = 2$



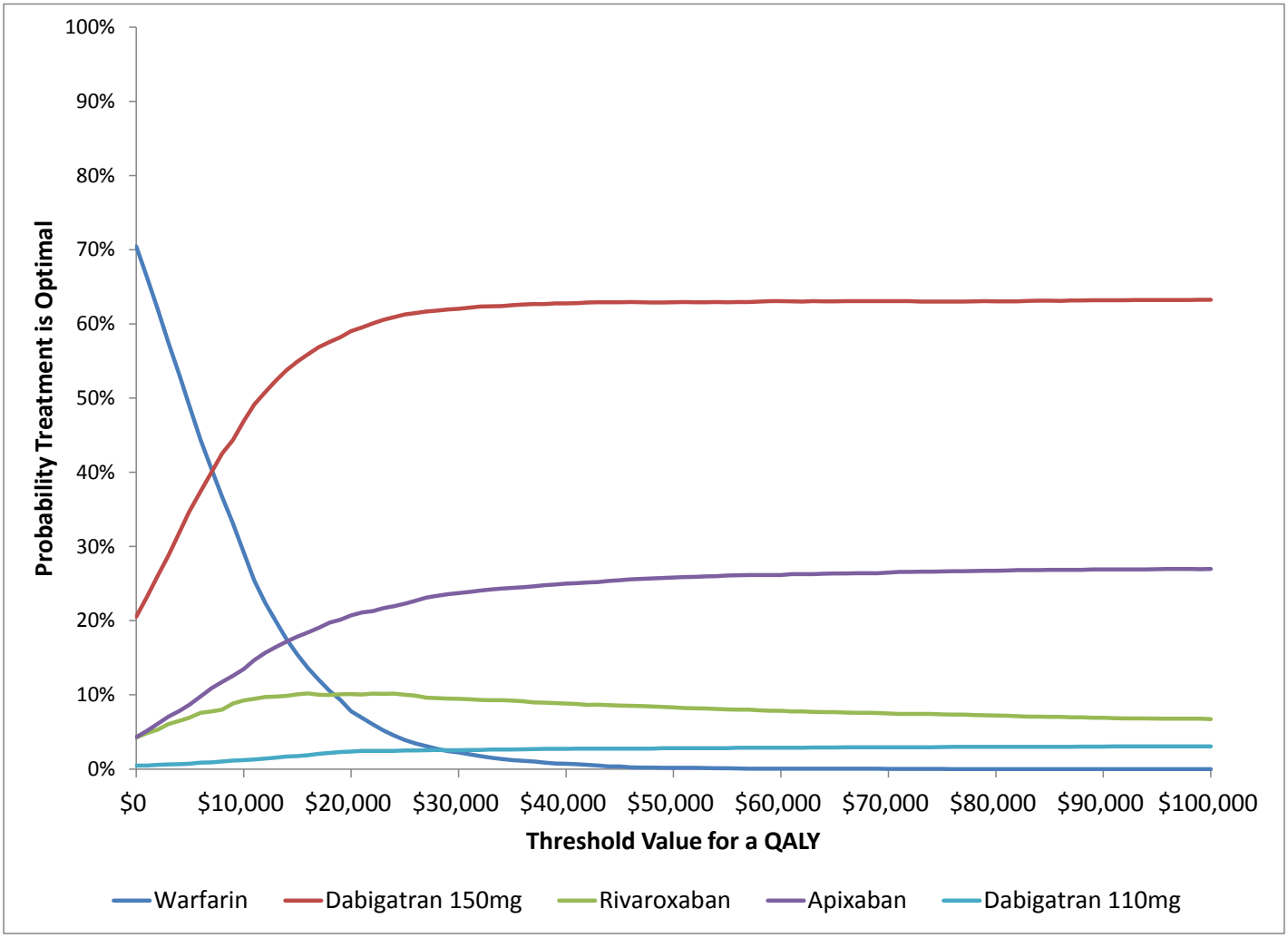
QALY = quality-adjusted life-year.

b. $CHADS_2 \geq 3$ without previous stroke



QALY = quality-adjusted life-year.

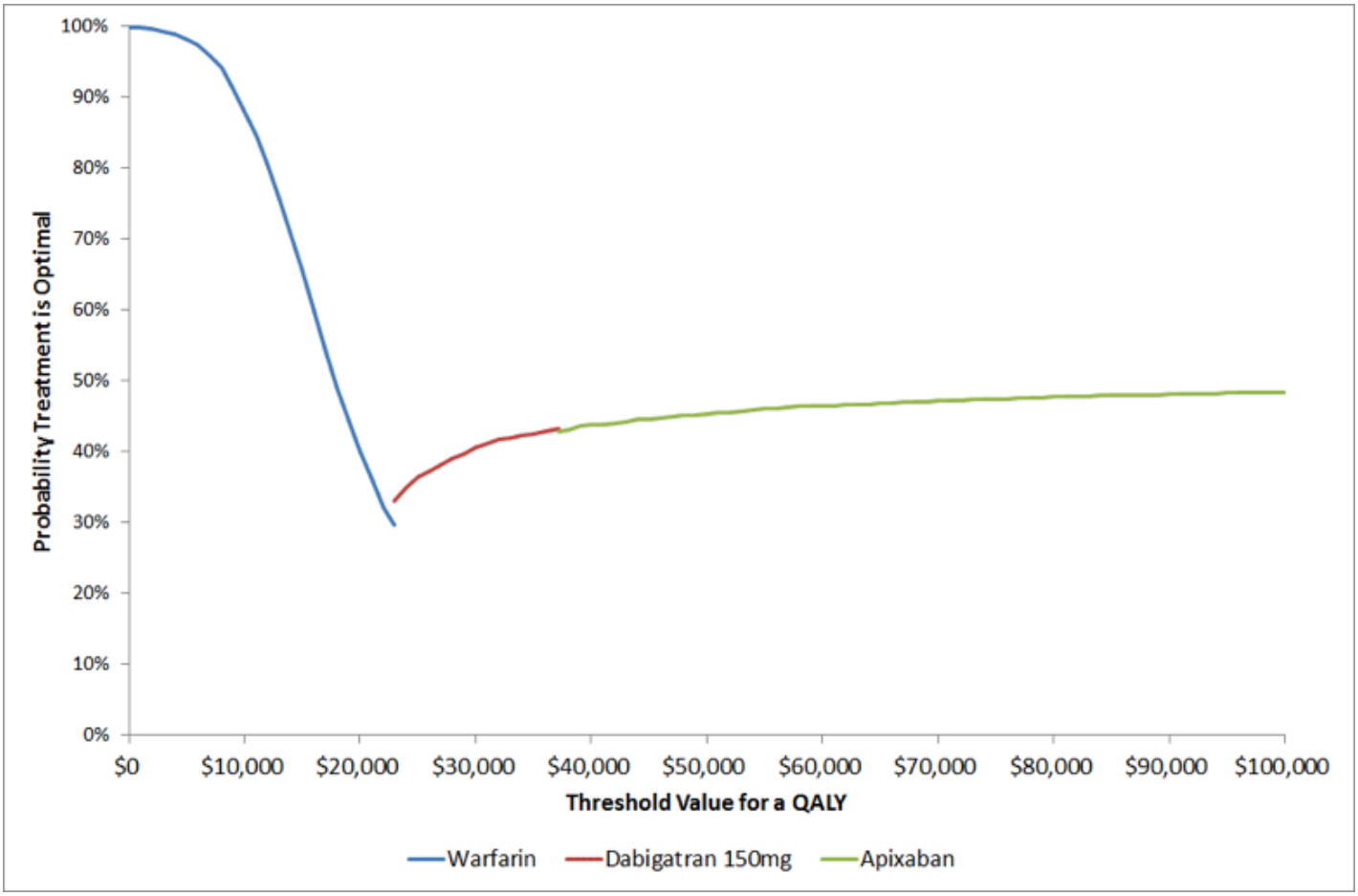
c. $CHADS_2 \geq 3$ with previous stroke



QALY = quality-adjusted life-year.

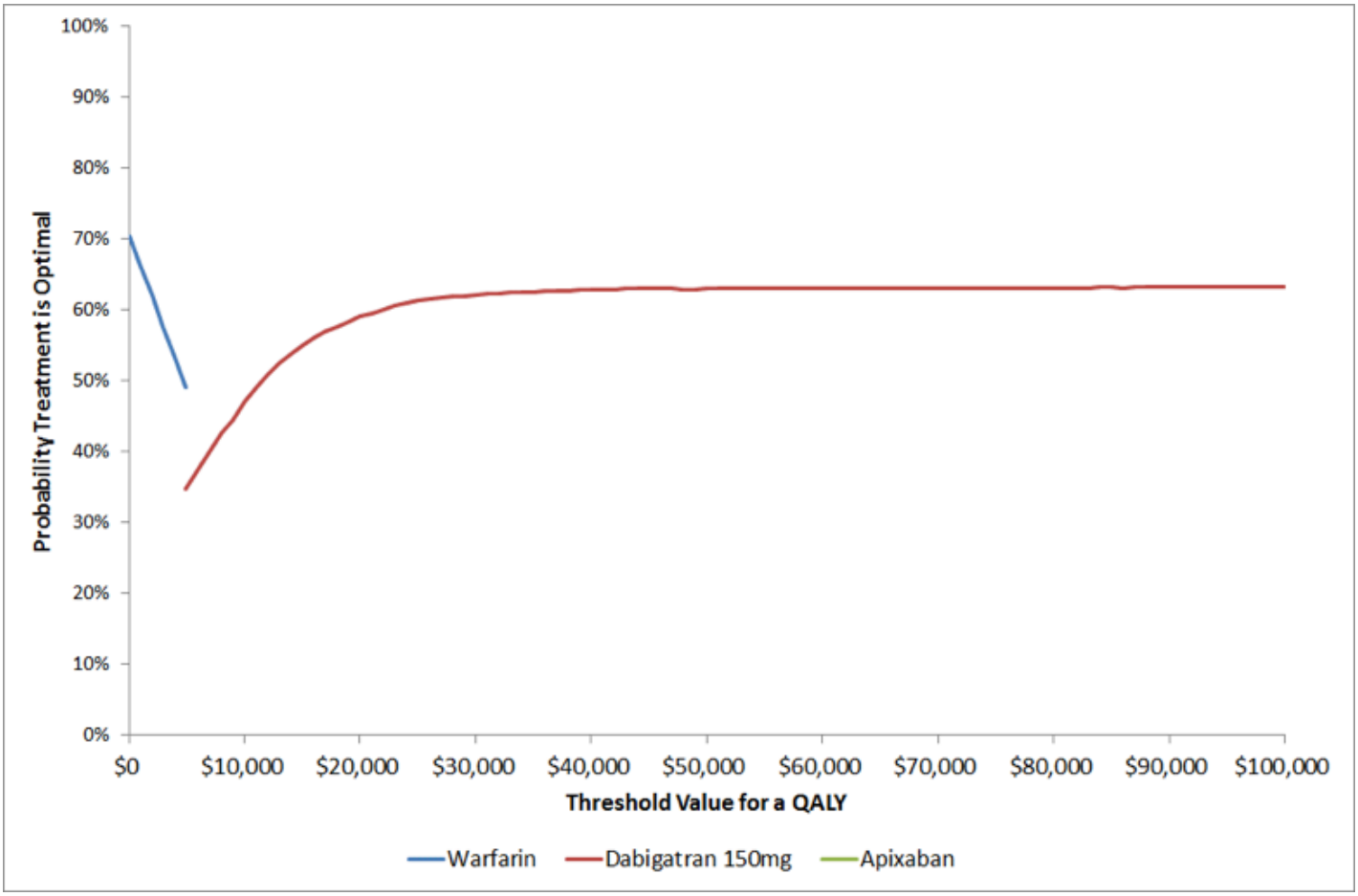
Figure 5: Cost-Effectiveness Acceptability Frontier

a. $CHADS_2 = 2$



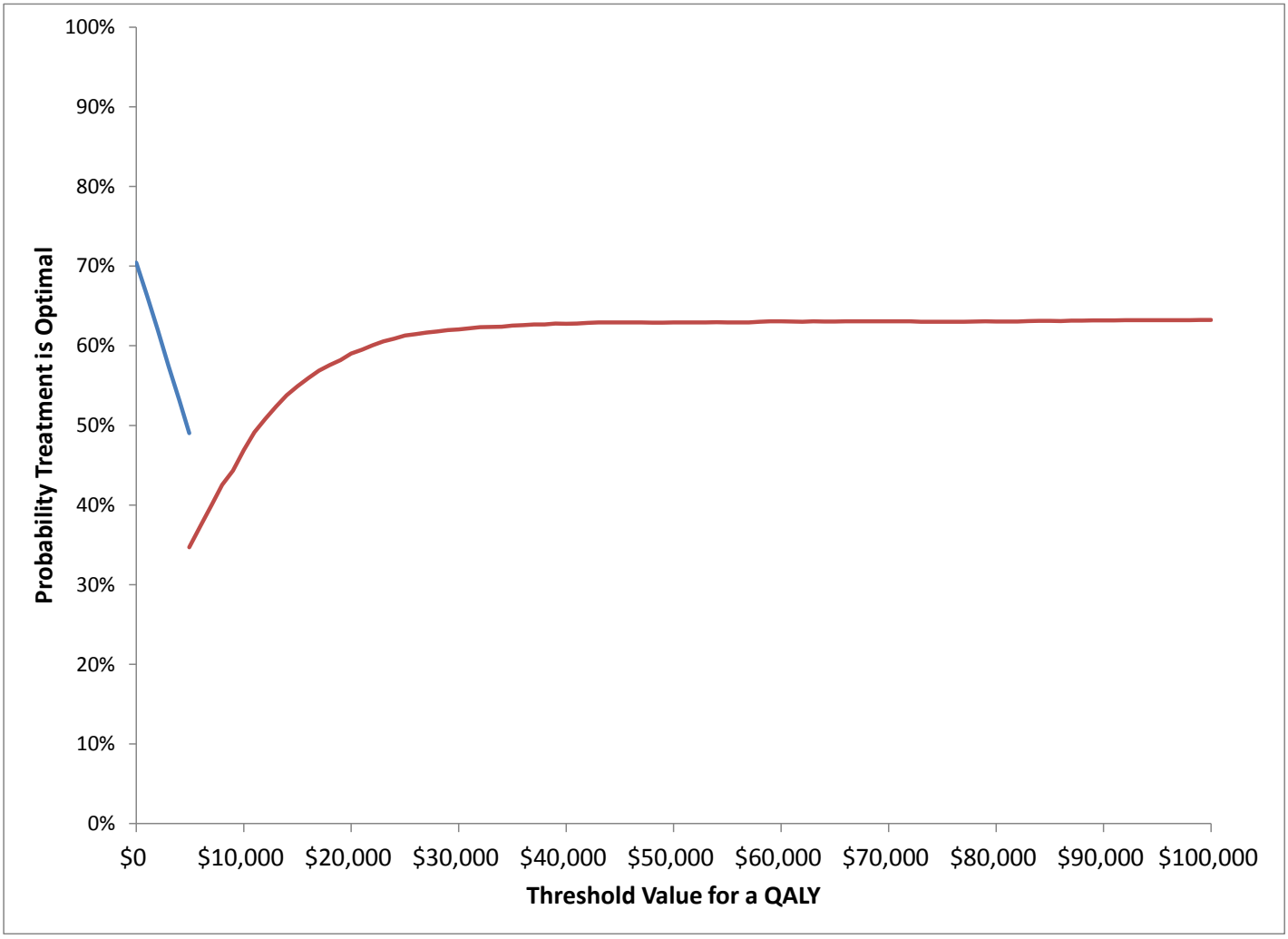
QALY = quality-adjusted life-year.

b. $CHADS_2 \geq 3$ without previous stroke



QALY = quality-adjusted life-year.

c. $CHADS_2 \geq 3$ with previous stroke



QALY = quality-adjusted life-year.

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