Common Drug Review
Pharmacoeconomic Review Report

August 2016

Drug	Ticagrelor (Brilinta)
Indication	Co-administered with low-dose acetylsalicylic acid (ASA: 75-150 mg), is indicated for the secondary prevention of atherothrombotic events in patients with a history of myocardial infarction (MI occurred at least one year ago) and a high risk of developing an atherothrombotic event.
Reimbursement request	Co-administered with low-dose acetylsalicylic acid (ASA: 75-150 mg), is indicated for the secondary prevention of atherothrombotic events in patients with a history of myocardial infarction (MI occurred at least one year ago) and a high risk of developing an atherothrombotic event.
Dosage form(s)	60 mg tablets
NOC date	May 30, 2016
Manufacturer	AstraZeneca Canada Inc.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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ABBREVIATIONS

ADP	adenosine diphosphate
ASA	acetylsalicylic acid
CDR	CADTH Common Drug Review
CV	cardiovascular
ICUR	incremental cost-utility ratio
MI	myocardial infarction
QALY	quality-adjusted life-year
TIMI	Thrombolysis in Myocardial Infarction

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	**Ticagrelor (Brilinta)**
Study Question	What is the cost-effectiveness of ticagrelor 60 mg twice daily plus ASA versus ASA alone for the prevention of atherothrombotic events in adult patients with a history of MI and a high risk of developing an atherothrombotic event?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adult patients with a history of MI and a high risk of developing an atherothrombotic event: the age, gender, and other variables related to risk profile reflected the patient population in the PEGASUS-TIMI 54 trial.
Treatment	Ticagrelor 60 mg twice daily + ASA
Outcome	QALY
Comparator	ASA
Perspective	Canadian public health care system
Time Horizon	Lifetime horizon — 40 years
Results for Base Case (Provided by Manufacturer)	Incremental cost per QALY gained for ticagrelor + ASA versus ASA was $59,724
Key Limitations and CDR Estimates	– Despite the underlying structure of the model and the majority of assumptions made being appropriate, the manufacturer's submission was unduly complex in that it modelled each individual patient within the PEGASUS-TIMI 54 trial rather than a cohort of patients with a specific risk profile. The manufacturer provided a revised model as requested. Once an issue with respect to gender was fixed and the costs of dispensing and markup omitted, the incremental cost per QALY gained was $46,196. – The manufacturer's analysis had only [redacted] of patients with a TIMI major bleed requiring hospitalization with a cost of only 1 bed day applied. The mean length of stay for all patients with a TIMI bleed was [redacted] days for ASA and [redacted] for ticagrelor + ASA. Applying the weighted average length of stay of [redacted] leads to an incremental cost per QALY gained of $49,870. – The analysis was based on 3-year trial data from which the benefit of adding ticagrelor to ASA was extrapolated up to 40 years (lifetime). The results are highly sensitive to the assumption relating to the appropriate time horizon of the analysis. Analysis based on a 40-year time horizon leads to an estimated undiscounted QALY gain of 0.082 (life-year gain of 0.103 or 37.5 days) with ticagrelor. For a time horizon of 3 years (the maximum duration of treatment), the QALY gain was 0.0051 and the life-year gain was 0.006 (2.2 days). Thus, only 6% of the QALY and life-year gains occur during the 3 years of treatment. The incremental cost of ticagrelor was not sensitive to the time horizon. CDR tested a reduction of time horizon down to 10 years, which led to an incremental cost per QALY gained of $85,767. – Addressing the major bleeds issue and reducing the time horizon to 10 years led to an incremental cost per QALY gained of $92,621. – Considering this scenario, to achieve an incremental cost per QALY gained of $50,000, the cost of ticagrelor must be reduced by 47%.

ASA = acetylsalicylic acid; MI = myocardial infarction; QALY = quality-adjusted life-year; TIMI = Thrombolysis in Myocardial Infarction.

EXECUTIVE SUMMARY

Background

Ticagrelor is an oral, direct-acting, selective and reversibly binding $P2Y_{12}$ receptor antagonist that prevents adenosine diphosphate (ADP)-mediated $P2Y_{12}$-dependent platelet activation and aggregation.[1] The proposed new indication is ticagrelor, combined with low-dose (75 mg to 150 mg) acetylsalicylic acid (ASA), for the secondary prevention of atherothrombotic events in adult patients with a history of myocardial infarction (MI) (occurred at least one year ago) and a high risk of developing an atherothrombotic event.[2] The suggested dose is 60 mg twice daily, orally.[1] Ticagrelor should be combined with ASA unless ASA is contraindicated. Treatment with ticagrelor should be continued in patients with a history of MI for as long as the patient remains at high risk of an atherothrombotic event for a duration up to three years.[2] At a submitted price of $1.48 per 60 mg tablet, the daily cost of treatment is $2.96 per patient (or $1,080 annually).[2]

Health Canada recently issued a Notice of Compliance (NOC) (May 30, 2016) for a new dose of ticagrelor (60 mg twice daily), which relates to the use of ticagrelor whereby this dose could be started without interruption after the initial one-year treatment with ticagrelor 90 mg or other ADP receptor antagonist therapy in acute coronary syndromes (ACS) patients at high risk of an atherothrombotic event. Treatment could also be initiated up to two years from the spontaneous myocardial infarction, or within one year after stopping previous ADP receptor antagonist treatment. Treatment with ticagrelor can be continued in patients with a history of MI for as long as the patient remains at high risk of an atherothrombotic event, for a duration up to three years. Efficacy and safety data are insufficient to establish whether the benefits of ticagrelor still outweigh the risks after three years of extended treatment.

Ticagrelor is also approved for the secondary prevention of atherothrombotic events (in combination with ASA) in patients with ACS (i.e., unstable angina, non–ST elevation MI, or ST elevation MI) who are to be managed medically and those who are to be managed with percutaneous coronary intervention (PCI) (with or without stent) and/or coronary artery bypass graft (CABG).[1] For this indication, the recommended dose is 90 mg twice daily. Ticagrelor was previously reviewed for this indication and the CADTH Canadian Drug Expert Committee (CDEC) recommended that ticagrelor not be reimbursed for this indication at the submitted price.[3]

The manufacturer submitted a cost-utility analysis to assess the cost-effectiveness of ticagrelor + ASA versus ASA alone in patients with a history of MI (MI occurred at least one year ago) and a high risk of developing an atherothrombotic event.[4] The analysis was based on an individual patient simulation model estimating long-term health care costs and quality-adjusted life-years (QALYs) over a lifetime horizon (40 years), from the perspective of the Canadian public health care payer. The manufacturer reported that ticagrelor + ASA was associated with greater QALYs and higher costs than ASA alone, with an estimated incremental cost per QALY gained of $59,724.

Summary of identified limitations and key results

On the whole, the manufacturer's submitted model was of high quality. The methods for estimating transition probabilities appear appropriate and the model appeared to be without coding errors. There were a number of assumptions that could have been revised but most had little impact on the results.

However, the following key limitations were identified with the model submitted by the manufacturer. The model submitted by the manufacturer lacks transparency. The model simulates individual patient profiles based on the PEGASUS-TIMI 54 trial.[5] This approach made it highly difficult to verify the calculations within the model as the results are obtained directly from a macro rather than being directly visible within the Excel-based model. Furthermore, many of the cells within the model were locked and did not allow the CADTH Common Drug Review (CDR) reviewer to ascertain the impact of the assumptions made. At CDR's request, the manufacturer provided a revised model based on a standard cohort simulation model with all cells unlocked. One minor coding error was identified with the revised model (i.e., coding in relation to mortality led to the underlying mortality rate for females being applied rather than a weighted average based on the proportion of males within the cohort). In addition, the manufacturer's submission included a dispensing fee and pharmacy markup, which is traditionally omitted within CDR analyses. Using the revised model with the issue relating to mortality fixed led to an incremental cost per QALY gained similar to the manufacturer's initial submission of $46,196 per QALY for ticagrelor + ASA compared with ASA alone.

The manufacturer assumes only approximately [redacted] of patients with Thrombolysis in Myocardial Infarction (TIMI) major bleeds would be hospitalized with an average stay per hospitalized patient of one day. However, data from the manufacturer suggest the mean length of stay for all patients with a TIMI major bleed was [redacted] for ticagrelor patients and [redacted] for ASA patients.[6] Using a weighted average length of stay ([redacted] days), the incremental cost per QALY gained was $49,870.

The model did not include any long-term implications from major bleeds. This could not be tested within the CDR reanalysis and it may be likely to favour ticagrelor, given the higher incidence of major bleeds with that treatment comparator.

The results are highly sensitive to the assumption relating to the appropriate time horizon of the analysis. Analysis based on a 40-year time horizon leads to an estimated undiscounted QALY gain of 0.082 (life-year gain of 0.103 or 37.5 days) with ticagrelor. For a time horizon of three years (the maximum duration of treatment), the QALY gain was 0.0051 and the life-year gain was 0.006 (2.2 days). Only 6% of the QALY and life-year gains occur during the three years of treatment. Although it was recognized that avoidance of events from ticagrelor treatment would have a beneficial impact in the long term, the manufacturer's analysis led to additional avoidance of events beyond the trial period for ticagrelor + ASA versus ASA alone, in the absence of any clinical evidence to support it. The model could not be modified to recalibrate the longer-term predictions in events; as such, to try to address this issue, CDR reduced the time horizon down to 10 years. The incremental cost of ticagrelor was not sensitive to the time horizon ($2,090 at three years and $2,075 at 40 years) as the cost of treatment is borne in the first three years of the analysis. With a three-year time horizon, the incremental cost per QALY gained for ticagrelor was $453,690. A 10-year time horizon led to an incremental cost per QALY gained of $85,767.

Combining the 10-year time horizon and the hospitalization data relating to major bleeds, CDR estimated an incremental cost per QALY gained of $92,621. The CDR reanalysis found that with this scenario, a 47% price reduction for ticagrelor resulted in an incremental cost per QALY gained of $50,000.

Based on a manufacturer comment from reviewing the draft report during the review process, a subgroup analysis focusing on patients with the time since previous MI being greater than two years was conducted and found that in this subgroup, ticagrelor + ASA was dominated by ASA alone.

Conclusions

Although the manufacturer's analysis was generally of high quality, two specific limitations relating to time horizon and handling of major bleeds were identified. CDR could address these limitations and provided incremental cost per QALY gained up to $92,261 for ticagrelor + ASA compared with ASA alone. Based on this scenario, a 47% price reduction for ticagrelor would lead to an incremental cost per QALY gained to be close to a $50,000 valuation.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer's submission involves a cost-utility analysis (CUA) using a patient-level simulation model comparing ticagrelor plus acetylsalicylic acid (ASA) versus ASA alone.[4] The model incorporates the individual patient profiles from the PEGASUS-TIMI 54 trial.[5] Model cycles are three months. During each cycle, the patient is at risk of various clinical events (myocardial infarction [MI], stroke, fatal cardiovascular [CV] event, fatal other event, and adverse events — dyspnea and bleeds). See Figure 1.

The probabilities of the major clinical events are appropriately modelled through appropriate parametric survival analysis accounting for competing risks.[7] After the initial event, further parametric survival analyses are adopted to model the long-term risk of further events. Each event is associated with costs and utility values. Utility values were derived from panel data analysis of EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire (EQ-5D) data completed within the PEGASUS-TIMI 54 trial.[5,8] Costs were derived from the Ontario Schedule of Fees and Benefits and published literature.[9-12]

2. MANUFACTURER'S BASE CASE

The manufacturer's analysis estimated, over a lifetime horizon, a quality-adjusted life-year (QALY) gain with ticagrelor + ASA versus ASA of 0.038 with incremental costs of $2,296. This leads to an estimated incremental cost per QALY gained of $59,724 (Table 9).

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

A range of sensitivity analyses was included. Analysis appeared most sensitive to assumptions around the functional form for the time to non-CV death and to fatal CV event. However, in the CADTH Common Drug Review (CDR) reanalysis, results were not particularly sensitive to these factors. Other variables had little impact on the results (Table 10).

Analysis for different patient profiles found ticagrelor + ASA to have a similar incremental cost per QALY gained (Table 11).

The manufacturer's probabilistic sensitivity analysis found the probability that ticagrelor + ASA was cost-effective to be 0% at a willingness to pay for a QALY threshold of $20,000 or lower and 96.7% at $50,000.

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

- **Modelling framework:** Although the model submitted by the manufacturer was on the whole of high quality, the complexity incorporated by adopting an individual patient simulation made the model inappropriate for validation purposes. The approach made it highly difficult to verify the calculations within the model as the results are obtained directly from a macro rather than being directly visible within the Excel-based model. Furthermore, many of the cells within the model were

locked and did not allow the CDR reviewer to ascertain the impact of the assumptions made. Given that economic evaluation should be conducted in a homogenous patient population and heterogeneity should be assessed appropriately through stratified analysis, CDR requested that the manufacturer provide a revised model that was a standard cohort simulation model with all cells unlocked.

The manufacturer responded with an appropriately revised model.

One minor problem with the revised model was that the coding in relation to mortality led to the underlying mortality rate for females being applied rather than a weighted average based on the proportion of males within the cohort. This was easily modified by CDR.

In addition, the manufacturer's submission included a dispensing fee and pharmacy markup, which is traditionally omitted within CDR analyses. Again, this was easily modified by CDR.

- **Impact of major bleeds***:* Within the manufacturer's submission, approximately [redacted] of patients with a Thrombolysis in Myocardial Infarction (TIMI) major bleed are assumed to be hospitalized. Data from the manufacturer confirm that the average length of stay for all patients with a TIMI major bleed were [redacted] for patients on ASA and [redacted] for patients on ticagrelor + ASA.[6]
- **Time horizon**: Analysis based on a 40-year time horizon leads to an estimated undiscounted QALY gain of 0.082 (life-year gain of 0.103 or 37.5 days) with ticagrelor. For a time horizon of three years (the maximum duration of treatment), the QALY gain was 0.0051 and the life-year gain was 0.006 (2.2 days). Thus, only 6% of the QALY and life-year gains occur during the three years of treatment. The incremental cost of ticagrelor was not sensitive to the time horizon — $2,090 at three years and $2,075 at 40 years.

5. CADTH COMMON DRUG REVIEW REANALYSES

5.1 CDR reanalyses

A. Revised manufacturer's model

Using the revised model[13] with the issue relating to mortality and drug costs fixed led to an incremental cost per QALY gained similar to the manufacturer's initial submission of $46,197 (Table 12).

B. Major bleeds

CDR reanalysis adopted revised assumptions relating to the average length of stay for patients with a TIMI major bleed. Using the same length of stay ([redacted] days) for both ticagrelor + ASA and ASA patients led to an incremental cost per QALY gained of $49,870 (Table 13).

C. Time horizon

Analysis based on a 40-year time horizon leads to an estimated undiscounted QALY gain of 0.082 (life-year gain of 0.103 or 37.5 days) with ticagrelor. For a time horizon of three years (the maximum duration of treatment), the QALY gain was 0.0051 and the life-year gain was 0.006 (2.2 days). Thus, only 6% of the QALY and life-year gains occur during the three years of treatment.

The incremental cost of ticagrelor was not sensitive to the time horizon — $2,090 at three years and $2,075 at 40 years. CDR reanalysis tested a reduction of the time horizon down to 10 years for more reasonable estimates of the long-term impact of treatment with ticagrelor (Table 14).

5.2 CDR estimate

To address concerns regarding the time horizon and the cost associated with TIMI major bleeds, CDR revised the assumption around major bleeds length of stay and reduced the time horizon to 10 years. This led to an incremental cost per QALY gained of $92,621.

TABLE 2: SUMMARY OF RESULTS OF THE CADTH COMMON DRUG REVIEW BEST ESTIMATE

	Ticagrelor + ASA	ASA	Ticagrelor + ASA vs. ASA
Costs (2016 $)	$29,724	$27,514	$2,211
QALYs	5.45	5.43	0.024
Incremental cost per QALY gained			$92,621

ASA = acetylsalicylic acid; QALY = quality-adjusted life-year; vs. = versus.

A probabilistic sensitivity analysis based on the CDR reanalysis found the probability that ticagrelor + ASA was cost-effective was 0% at a willingness to pay for a QALY threshold of lower than $56,000 **(**Figure 3).

5.3 Price reduction scenarios

Reanalysis was conducted assuming alternate prices for ticagrelor. Assuming a 47% price reduction, CDR reanalysis found an incremental cost per QALY gained of approximately $50,000 (Table 15).

5.4 Supplementary analysis

When commenting on the draft CDR Pharmacoeconomic (PE) report, the manufacturer suggested that subgroup analysis conducted based on time since previous MI demonstrated that patients with a previous MI of less than two years ago were found to have greater clinical benefit. CDR reanalysis was based on a cohort of patients representative of the mean characteristics of the patient population in the PEGASUS trial. This equated to a time since previous MI of 660 days (< 2 years); thus, analysis did relate to the patient group with increased clinical benefit. CDR then conducted a further analysis for patients with a time since MI greater than two years (731 days); all other factors remained the same. This analysis found ticagrelor + ASA to be dominated by ASA alone, being more costly and producing fewer QALYs.

6. ISSUES FOR CONSIDERATION

Based on discussions with the CDR clinical expert, the correct selection of patients who would optimally benefit from treatment is associated with important economic implications. The indication of treatment for ticagrelor is for “high-risk” patients; if applied with flexibility in clinical practice, this may cover a wide range of patients and result in large budget spending. Strict and optimal patient selection is associated with improving the cost-effectiveness of the treatment.

7. PATIENT INPUT

Input was received from one patient group: the Heart and Stroke Foundation of Canada, which conducted an online survey of 221 respondents. Respondents indicated that having a heart attack affected their lives by having to take medication at specific times; take medication multiple times a day; make frequent visits to a health care provider; take time off work; and manage their condition with other forms of therapy. Some also reported that it had not affected day-to-day life. Some felt limited in terms of participating in activities of daily living such as doing any strenuous activity, lifting or carrying objects, or walking long distances or uphill. Symptoms experienced as a result of their heart attack included fatigue, angina and/or pain, memory loss and cognitive impairment, swelling and fluid retention, and shortness of breath. The manufacturer accounted for some of these impacts based on health state utility values in its model. Medication-related concerns (e.g., taking medication a number of times per day) were not accounted for and are unlikely to affect the results significantly.

Caregivers were also affected, needing to take time off work, providing care, and/or feeling anxious or overwhelmed. The perspective of the manufacturer's economic analysis (Canadian public health care system) did not take the impact on caregivers into account.

8. CONCLUSIONS

Based on the manufacturer's revised model and minor corrections, CDR calculated the incremental cost-utility ratio (ICUR) for ticagrelor + ASA compared with ASA to be $46,197. However, two key assumptions relating to the cost of major bleeds and time horizon favoured ticagrelor. Addressing these limitations led to a CDR estimate incremental cost per QALY up to $92,621. Based on this scenario, a 47% price reduction for ticagrelor is needed for an incremental cost per QALY to achieve an ICUR of $50,000.

APPENDIX 1: COST COMPARISON

The comparators presented in Table 3 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice, versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified.

TABLE 3: COST-COMPARISON TABLE FOR THE SECONDARY PREVENTION OF ATHEROTHROMBOTIC EVENTS

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Daily Drug Cost ($)	Annual Drug Cost ($)
Ticagrelor (Brilinta)	**60 mg**	**Tab**	**1.4800**[a]	**60 mg twice daily**	**2.96**	**1080**
Clopidogrel (generic)	75 mg	Tab	0.4735	75 mg daily	0.47	173
Acetylsalicylic acid (generic)	80 mg or 81 mg 325 mg 650 mg	Enteric tab	0.0560[b] 0.0280 0.0521	81 mg (or 80 mg) to 325 mg daily	0.03 to 0.06	10 to 20

Drug prices are taken from the Ontario Drug Benefit Formulary (Mar 2015) unless otherwise indicated.
[a] Manufacturer-submitted confidential price.
[b] Régie de l'assurance maladie du Québec Liste des médicaments (Mar 2016).

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 4: WHEN CONSIDERING ONLY COSTS, OUTCOMES AND QUALITY OF LIFE, HOW ATTRACTIVE IS TICAGRELOR PLUS ACETYLSALICYLIC ACID RELATIVE TO ACETYLSALICYLIC ACID ALONE?

Ticagrelor Versus ASA	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	Manufacturer $59,724 per QALY CDR $92,621 per QALY					

ASA = acetylsalicylic acid; CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year..

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 5: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments *Reviewer to provide comments if checking "no"*	The revised model addressed the CDR reviewer's concerns.		
Was the material included (content) sufficient?		X	
Comments *Reviewer to provide comments if checking "poor"*	None		
Was the submission well organized and was information easy to locate?	X		
Comments *Reviewer to provide comments if checking "poor"*	None		

CDR = CADTH Common Drug Review.

TABLE 6: AUTHORS' INFORMATION

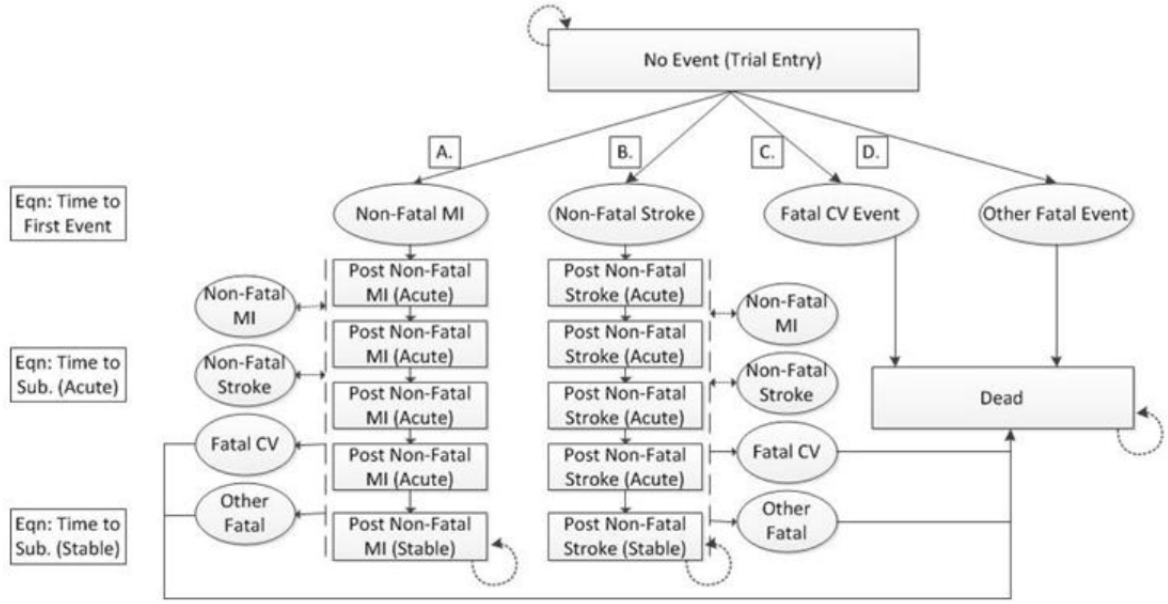
Authors of the Pharmacoeconomic Evaluation Submitted to the CADTH Common Drug Review			
☐ Adaptation of global model/Canadian model done by the manufacturer ☒ Adaptation of global model/Canadian model done by a private consultant contracted by the manufacturer ☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the manufacturer ☐ Other (please specify)			
	Yes	**No**	**Uncertain**
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis		X	

APPENDIX 4: REVIEWER WORKSHEETS

Manufacturer's model structure

Model design

FIGURE 1: MODEL SCHEMATIC



CV = cardiovascular; MI = myocardial infarction.
Source: Manufacturer's pharmacoeconomic submission.[4]

Data inputs

TABLE 7: DATA SOURCES

Main Data Inputs	Description of Data Source	Comment
Patients' baseline characteristics	Taken from the PEGASUS-TIMI 54	Questionable: the clinical expert highlighted that the patients' baseline characteristics from the trial are likely limitedly generalizable to the Canadian setting. However, testing different subgroups with the model resulted in the results not being sensitive to varying this within appropriate ranges.
Impact on CV-related events	Parametric survival analysis based on competing risks using data from PEGASUS-TIMI 54 trial	Appropriate
Health care resource utilization	Taken from the PEGASUS-TIMI 54	Appropriate
Costs of CV events	Canadian literature	Probably appropriate
Cost for other resource utilization	Canadian literature	Probably appropriate

Main Data Inputs	Description of Data Source	Comment
Costs of bleeding	[redacted] of major bleeds require hospitalization of 1 day	Inappropriate
Utility values	Panel analysis of EQ-5D data from PEGASUS-TIMI 54 trial	Appropriate

CV = cardiovascular; EQ-5D = EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire.

TABLE 8: MANUFACTURER'S KEY ASSUMPTIONS

Main Assumptions	Comment
The Markov model structure considers 4 health states: non-fatal MI, non-fatal stroke, fatal CV event, other fatal event.	Appropriate
The model incorporates the Public Payers' perspective, using the Ontario Ministry of Health and Long-Term Care as a proxy for all CDR-participating plans.	Appropriate
The model compares ticagrelor + ASA with ASA alone. The placebo arm (i.e., ASA alone) in the PEGASUS-TIMI 54 trial was assumed to represent standard of care for the model.	Likely appropriate
The model accounted for a 40-year time horizon.	Likely highly favourable to ticagrelor as 94% of benefit accumulated after treatment discontinuation
At 3 years, all patients are assumed to discontinue therapy.	Appropriate as aligned with the product monograph
The model used a 3-month cycle length.	Appropriate and aligned with other models in this field of medicine
Assume that on average, patients will move between states halfway through the cycle by employing a half-cycle correction.	Appropriate
[redacted] of major bleeds require hospitalization of 1 day.	Inappropriate

ASA = acetylsalicylic acid; CDR = CADTH Common Drug Review; CV = cardiovascular; MI = myocardial infarction.

Manufacturer's base case

The manufacturer reported the following results for its base-case analysis:

TABLE 9: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE

	Ticagrelor + ASA	ASA	Ticagrelor + ASA Versus ASA
Costs (2016 $)	$44,347	$42,051	$2,296
QALYs	8.17	8.14	0.038
Incremental cost per QALY gained			$59,724

ASA = acetylsalicylic acid; QALY = quality-adjusted life-year; vs. = versus.
Source: Manufacturer's pharmacoeconomic submission.[4]

Manufacturer's sensitivity analyses

Table 10 shows a summary of the manufacturer's sensitivity analyses.

TABLE 10: RESULTS OF THE MANUFACTURER'S SENSITIVITY ANALYSIS

Variable	Base-Case Value	Sensitivity Analysis Value	ICER
ICER from representative patient profile	*NA*	*NA*	$36,214.93
1st Other Death: Gompertz	Log logistic	Gompertz	$59,775.30937
1st CV-Related Death: Weibull	Log logistic	Weibull	$56,616.32
1st CV-Related Death: Gompertz	Log logistic	Gompertz	$21,444.84
Discount rate, Health Outcomes: 0%	5.0%	0.0%	$48,553.62
1st Non-Fatal MI: Weibull	Log logistic	Weibull	$24,045.41
Other Fatal Events: using PEGASUS-derived risks	TRUE	FALSE	$47,999.82
1st Non-Fatal Stroke: Weibull	Log logistic	Weibull	$44,402.41
Discount rate, Health Outcomes: 3%	5.0%	3.0%	$29,743.12
Discount rate, Costs: 0%	5.0%	0.0%	$41,355.55
Base Utilities from: PEGASUS	Population norms	PEGASUS	$40,947.00
1st CV-Related Death: Log normal	Log logistic	Log normal	$33,369.40
1st Non-Fatal MI: Log normal	Log logistic	Log normal	$33,620.26
1st CV-Related Death: Exponential	Log logistic	Exponential	$34,033.66
Discount rate, Costs: 3%	5.0%	3.0%	$38,233.60
Model Subsequent Treatment Effects: Yes	No	Yes	$37,831.17
Discontinuation: Log normal	Piecewise exponential	Log normal	$35,443.91
Discontinuation: Exponential	Piecewise exponential	Exponential	$35,474.94
Discontinuation: Log logistic	Piecewise exponential	Log logistic	$35,588.48
1st Non-Fatal Stroke: Log normal	Log logistic	Log normal	$35,658.71
Discontinuation: Weibull	Piecewise exponential	Weibull	$35,706.07
1st Non-Fatal Stroke: Gompertz	Log logistic	Gompertz	$36,674.79
1st Non-Fatal MI: Gompertz	Log logistic	Gompertz	$35,836.96
Discontinuation: Gompertz	Piecewise exponential	Gompertz	$36,461.40
Sub. CV Death: Gompertz	Log normal	Gompertz	$36,404.20
Sub. CV Death: Exponential	Log normal	Exponential	$36,397.93
1st Non-Fatal MI: Exponential	Log logistic	Exponential	$36,118.09
Sub. CV Death: Weibull	Log normal	Weibull	$36,256.79
Sub. CV Death: Log logistic	Log normal	Log logistic	$36,256.10
Sub. Other Death: Exponential	Weibull	Exponential	$36,176.55
Sub. Other Death: Weibull	Weibull	Weibull	$36,250.91

CV = cardiovascular; ICER = incremental cost-effectiveness ratio; MI = myocardial infarction; sub. = subsequent.
Source: Manufacturer's pharmacoeconomic submission.[4]

Table 11 shows a summary of the scenario analyses conducted by the manufacturer.

TABLE 11: RESULTS OF THE MANUFACTURER'S SCENARIO ANALYSES

Comparator	Total Costs	Incremental Costs	Total QALYs	Incremental QALYs	Incremental Cost per QALY Gained
Patients with diabetes only					
Ticagrelor + ASA	$44,146	$2,320	8.02	0.054	$42,838
ASA	$41,826	NA	7.97	NA	NA
> 1 prior MI					
Ticagrelor + ASA	$43,388	$2,191	7.72	0.054	$40,498
ASA	$41,197	NA	7.66	NA	NA
Multi-vessel CAD					
Ticagrelor + ASA	$45,594	$2,324	8.43	0.040	$58,452
ASA	$43,270	NA	8.39	NA	NA
65+ years of age					
Ticagrelor + ASA	$39,047	$2,130	6.99	0.037	$56,922
ASA	$36,917	NA	6.96	NA	NA
< 2 years from qualifying event					
Ticagrelor + ASA	$44,582	$2,394	8.18	0.057	$42,012
ASA	$42,188	NA	8.12	NA	NA
≤ 12 months from previous anti-platelet therapy					
Ticagrelor + ASA	$44,842	$2,332	8.23	0.045	$51,408
ASA	$42,510	NA	8.18	NA	NA
Renal dysfunction					
Ticagrelor + ASA	$37,294	$1,932	6.46	0.046	$41,895
ASA	$35,362	NA	6.41	NA	NA

ASA = acetylsalicylic acid; CAD = coronary artery disease; MI = myocardial infarction; NA = not applicable; QALY = quality-adjusted life-year.
Source: Manufacturer's pharmacoeconomic submission.[4]

CADTH common drug review analyses

Based on a revised version of the model, provided by the manufacturer,[13] and when correcting for the minor errors, the CADTH Common Drug Review (CDR) calculated the incremental cost-utility ratio (ICUR) for ticagrelor plus acetylsalicylic acid (ASA) compared with ASA alone to be $46,821.

TABLE 12: CADTH COMMON DRUG REVIEW REANALYSIS USING MANUFACTURER'S REVISED MODEL

	Ticagrelor + ASA	ASA	Ticagrelor + ASA vs. ASA
Costs (2016 $)	$45,235	$43,161	$2,075
QALYs	8.34	8.29	0.045
Incremental cost per QALY gained			$46,196

ASA = acetylsalicylic acid; QALY = quality-adjusted life-year; vs. = versus.

To account for the two identified limitations (assumptions regarding major bleeds and the majority of clinical benefits realized long after the treatment period), CDR conducted the following reanalyses:

1) Considering a more appropriate length of stay following major bleed:

TABLE 13: CADTH COMMON DRUG REVIEW REANALYSIS ASSUMING [redacted] BED DAYS PER MAJOR BLEED

	Ticagrelor + ASA	ASA	Ticagrelor + ASA vs. ASA
Costs (2016 $)	$45,977	$43,738	$2,240
QALYs	8.34	8.29	0.045
Incremental cost per QALY gained			$49.870

ASA = acetylsalicylic acid; QALY = quality-adjusted life-year; vs. = versus.

2) Considering a shorter model time horizon (10 years) to reduce the predicted clinical benefits from ticagrelor realized much later in the patient's condition:

TABLE 14: CADTH COMMON DRUG REVIEW REANALYSIS USING MANUFACTURER'S REVISED MODEL AND 10-YEAR TIME HORIZON

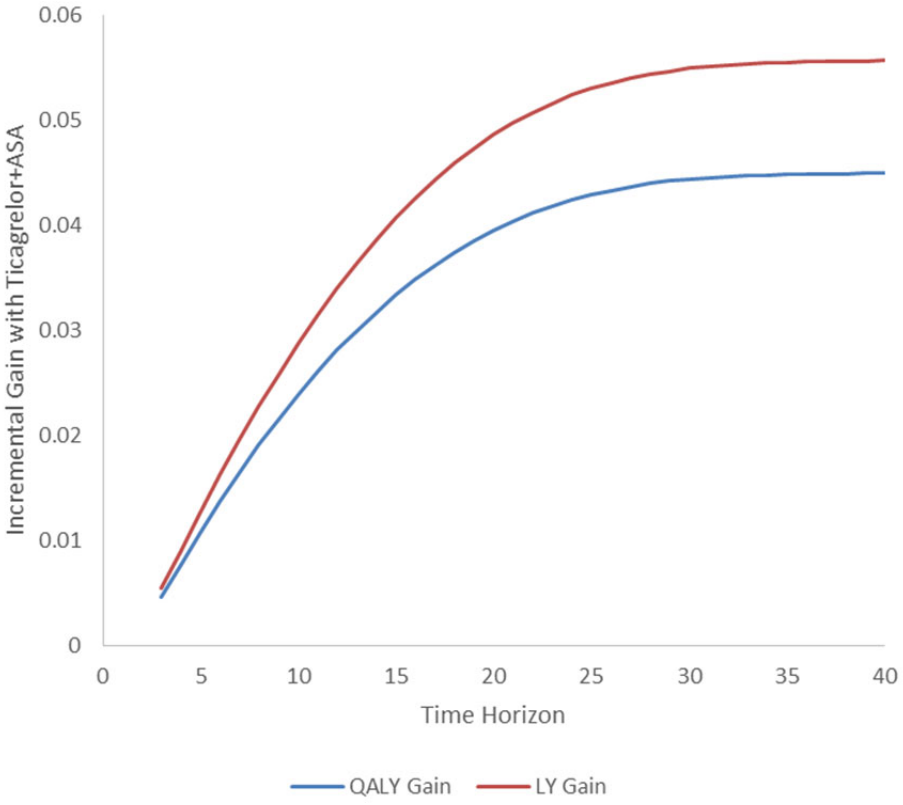
	Ticagrelor + ASA	ASA	Ticagrelor + ASA vs. ASA
Costs (2016 $)	$29,189	$27,142	$2,047
QALYs	5.45	5.43	0.024
Incremental cost per QALY gained			$85,767

ASA = acetylsalicylic acid; QALY = quality-adjusted life-year; vs. = versus.

3) Combining the reanalyses mentioned above led to an incremental cost per QALY gained of $92,621. Using a time horizon of 20 years instead led to an incremental cost per QALY gained of $56,325.

Figure 2 illustrates the impact of the time horizon on the estimated QALY and life-year gains.

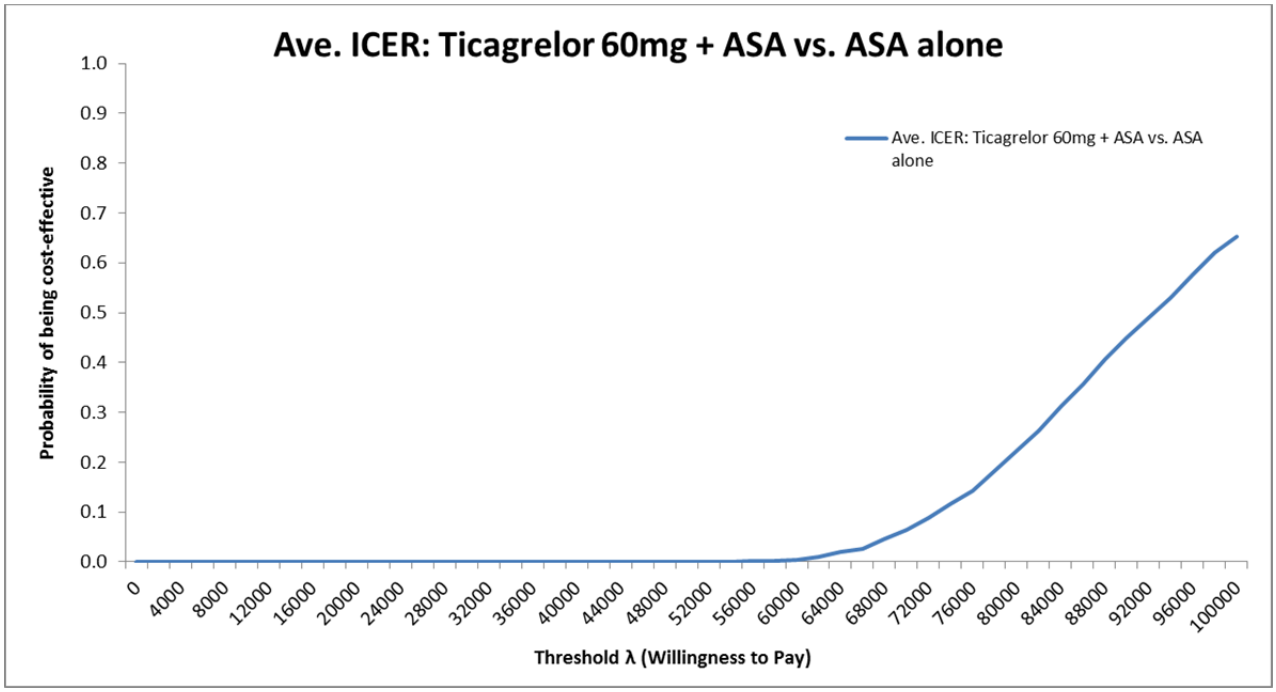
FIGURE 2: IMPACT OF TIME HORIZON



ASA = acetylsalicylic acid; LY = life-year; QALY = quality-adjusted life-year.

A probabilistic sensitivity analysis based on the CDR reanalysis found the probability that ticagrelor + ASA was cost-effective was 0% at a willingness to pay for a QALY threshold of lower than $56,000 (Figure 3).

FIGURE 3: CADTH COMMON DRUG REVIEW BEST ESTIMATE — COST-EFFECTIVENESS ACCEPTABILITY CURVE



ASA = acetylsalicylic acid; ICER = incremental cost-effectiveness ratio; vs. = versus.

Based on price reduction analyses using the CDR best estimate, a 47% price reduction would be required to achieve an ICUR of approximately $50,000 per QALY:

TABLE 15: CADTH COMMON DRUG REVIEW REANALYSIS PRICE REDUCTION SCENARIOS

ICERs of Submitted Drug Versus Comparator	
Price	**CDR best estimate**
Submitted	$92,621
10% reduction	$83,549
20% reduction	$74,477
30% reduction	$65,405
40% reduction	$56,333
50% reduction	$47,261
60% reduction	$38,189
70% reduction	$29,117

CDR = CADTH Common Drug Review; ICER = incremental cost-effectiveness ratio.

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