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Cost-effectiveness of ticagrelor versus clopidogrel in patients with acute coronary syndromes in Canada

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Background: Ticagrelor demonstrated a significant reduction in major cardiac events in patients with acute coronary syndrome (ACS) compared with clopidogrel in the Platelet Inhibition and Patient Outcomes (PLATO) trial. The objective of this study was to assess the cost-effectiveness of ticagrelor compared with clopidogrel in ACS patients from the perspective of the Canadian publicly funded health care system.

Methods: A two-part model was developed consisting of a 1-year decision tree and a lifetime Markov model. Within the decision tree, patients remained event-free, experienced a nonfatal myocardial infarction, a nonfatal stroke, or death due to vascular or nonvascular related causes based on data from the PLATO trial. The lifetime Markov model followed these patients and allowed for subsequent myocardial infarction, stroke, and death. Patient utility and resource use were derived from the PLATO trial. Transition probabilities and specific Canadian unit costs were derived from published sources. Univariate and probabilistic sensitivity analyses were conducted.

Results: In the base case lifetime analysis, treatment with ticagrelor resulted in more years of life per person (0.097), more quality-adjusted life years per person (QALYs, 0.084), and an incremental cost per QALY gained of $9,745 (Canadian$), assuming a generic cost for clopidogrel. A probabilistic sensitivity analysis demonstrated the robustness of the base case analysis, with a 93% probability of being below $20,000 per QALY gained and a 99% probability of being below $30,000 per QALY gained.

Conclusion: Ticagrelor is a clinically superior and cost-effective option for the prevention of thrombotic events among ACS patients in Canada.

Keywords: acute coronary syndrome, percutaneous coronary intervention, cost-effectiveness analysis, cost-utility analysis, clopidogrel, ticagrelor, antiplatelet therapy

Introduction

Acute coronary syndromes (ACS) are most commonly caused by plaque disruption with exposure of substances that promote platelet activation, adhesion and aggregation, thrombin generation, and thrombus formation leading to partial or complete occlusion of one or more coronary arteries. In Canada, ACS has been estimated to result in 22,000 deaths and 109,000 hospitalizations, of which 77% were due to myocardial infarction (MI) and 23% to unstable angina.[1]

In patients who have ACS with or without ST-segment elevation, clinical practice guidelines at the time of the ticagrelor trials recommended dual antiplatelet treatment with acetylsalicylic acid and clopidogrel.[2] However, the antiplatelet effect of this combination of oral therapies is variable due to interpatient extrinsic or intrinsic

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mechanisms and contributes in part to the recurrence of serious cardiovascular events in approximately 10% of clopidogrel-treated ACS patients.[3–5] Updated guidelines now recommend ticagrelor, a direct-acting oral P2Y12-receptor antagonist that binds reversibly to its receptor, as a better alternative to clopidogrel.[6] Ticagrelor provides greater and more consistent platelet inhibition than clopidogrel, with a more rapid onset and offset of action.[7] Ticagrelor use is supported by the PLATO (PLATelet inhibition and patient Outcomes) trial, an international study of ACS patients (n=18,624) that included 30 Canadian centers. The PLATO trial demonstrated that ticagrelor was superior to clopidogrel for the primary composite efficacy endpoint (a composite of cardiovascular mortality, MI, or stroke; hazards ratio [HR] 0.84; 95% confidence interval [CI] 0.77–0.92, $P<0.001$). Predefined hierarchical testing of secondary endpoints found significant differences in recurrent MI (HR 0.84; 95% CI 0.75–0.95, $P=0.005$) and cardiovascular death (HR 0.79; 95% CI 0.69–0.91, $P<0.001$).[8] The PLATO trial also showed that there was no significant increase in the rate of overall PLATO-defined major bleeding (HR 1.04; 95% CI 0.95–1.13).

The extent to which ticagrelor will be used in Canada depends not only on its relative efficacy but also on its economic value. Cost-effectiveness analyses of ticagrelor versus clopidogrel based on the PLATO trial have found favorable lifetime incremental cost per quality-adjusted life year (QALY) ratios (range US$2728–US$8443) from public payer perspectives in Germany, Singapore, Australia, and the UK,[9–13] and have resulted in coverage by public plans in several countries. A "do not list" recommendation for ticagrelor was made by the Canadian Common Drug Review based in part on the perceived limitations of previously developed cost-effectiveness models.[14] The analysis reported herein assesses the long-term cost-effectiveness of ticagrelor versus clopidogrel in ACS patients from the perspective of the Canadian publically funded health care system and reflects modifications to the originally submitted models. Notably, the current model allows the occurrence of multiple clinical events (eg, stroke and MI) over a lifetime, with the occurrence of future events influenced by previous clinical events. This revised model was used in provincial reimbursement discussions, which have resulted in funding for ticagrelor.[15]

Materials and methods

The economic analysis was based on a two-part cost-effectiveness model, comprised of a decision tree covering the first year following occurrence of ACS, combined with a Markov model to capture costs and outcomes over the remainder of the patients' lifetime. Efficacy and safety data from the PLATO trial were used to inform treatment effectiveness over the first year of the model. The main clinical outcomes of interest were vascular or nonvascular death, nonfatal MI, and stroke. Costs and outcomes were discounted at a rate of 5% per year as per Canadian guidelines.[16] The base case analysis used a lifetime time horizon to capture the short-term and long-term impacts of antiplatelet therapy on death and nonfatal cardiovascular events.

Patient population and treatment

The model was populated with data from the PLATO trial, which included a broad spectrum of ACS patients (ie, ST-segment elevation MI, non-ST-elevation MI, and unstable angina) who were hospitalized within 24 hours of symptom onset. Patients in the trial could undergo invasive management (ie, coronary angiography and percutaneous coronary intervention or coronary artery bypass grafting, where appropriate) or be managed medically (with or without angiography). Baseline patient characteristics included a median age of 62 years, predominantly male sex (72%), and cardiovascular risk factors such as hypertension (65%) and dyslipidemia (47%). Patients in the PLATO trial were randomized to receive a maximum of 1 year of therapy with ticagrelor or clopidogrel, both given in addition to aspirin.[8] Ticagrelor was given in a loading dose of 180 mg followed by a 90 mg dose twice a day. Clopidogrel was given in a loading dose of 300 or 600 mg followed by a 75 mg dose daily.

1-year decision tree

The 1-year decision tree was modeled based on clinical events (first and subsequent), resource utilization, and utility data collected in the PLATO trial. The model included patient pathways for new non-fatal MI, new non-fatal stroke, or death from vascular or nonvascular causes. Patients not experiencing these events were considered event-free over the 1-year treatment period (Figure 1).[8] The probabilities of a patient in the PLATO trial having a nonfatal MI, nonfatal stroke, or dying from any cause were calculated from published PLATO trial data (Table 1).[12] The majority (89.4%) of patients in the PLATO trial did not experience an event after the initial occurrence of ACS. A further 9.1% of patients experienced only one clinical event (MI, stroke, or death) and approximately 1.5% of the PLATO trial patients had multiple events (MI, stroke, or death). As such, the four health states of the decision tree captured the majority of patient pathways from

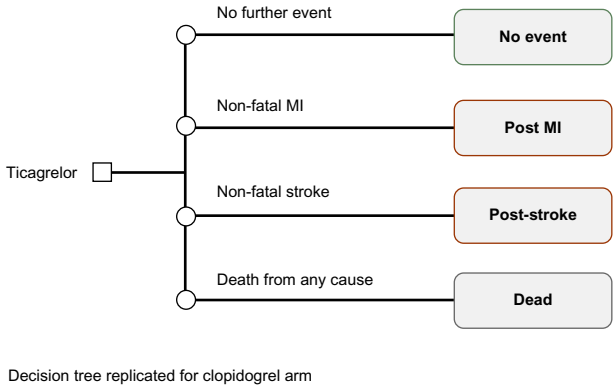

Figure 1 Model diagram of the 1-year decision tree.
Abbreviation: MI, myocardial infarction.

the PLATO trial. Those patients who had an event and died within the first year were included in the dead group for calculating probabilities of events; the remainder were grouped based on the first event experienced. Transition probabilities for ticagrelor patients were calculated by applying the HRs from the PLATO trial to the probabilities for clopidogrel patients, after converting such probabilities to rates.[17]

Lifetime Markov model

At the end of the 1-year decision tree, a Markov state transition model (Figure 2) was used to simulate the natural history of ACS patients from the PLATO trial over their remaining lifetime. Similar to the model structure used in the Canadian Agency for Drugs and Technologies in Health Technology Report on antiplatelet therapy use in ACS,[18] the Markov model states included post-MI/no event, post-stroke, new MI, new stroke, vascular death, or nonvascular death. In this model, patients can have multiple events over time. Specifically, patients entered the Markov model based on the events in the 1-year decision tree. Patients who did not have an event in the 1-year decision tree model entered the post-MI state, as 80% of the PLATO study participants had an MI as their index ACS event. Patients who experienced an MI or stroke in the 1-year decision tree entered the new MI and new stroke states, respectively, in the Markov model. After 1 year in the new MI and new stroke states, patients transitioned to the corresponding post-event state. In each 1-year cycle, patients could experience a new MI, new stroke, vascular death, or nonvascular death, or remain in a post-event state. Patients could not enter the new MI state from the post-stroke state because this would allow stroke patients to transition to a health state characterized by an improved quality of life and lower associated costs.[18] Probabilities for MI, stroke, and vascular death that reflected the history of previous events were based on published logistic and multinomial regression equations (see Supplementary material for values).[18,19] The probabilities of nonvascular death were based on sex-specific Canadian life tables for noncardiovascular-related death.[20] These probabilities were weighted based on the proportion of males to females reported in the PLATO trial.

Table 1 One-year decision tree event probabilities

Clinical Pathway	Clopidogrel n=9,291		Ticagrelor n=9,333	
	N	Proportion	N	Proportion
1. No Events	8,226	0.8854	8,432	0.9035
2. MI	485	0.0522	421	0.0451
3. Stroke	74	0.0080	81	0.0087
4. Dead any cause	506	0.0545	399	0.0428

Abbreviation: MI, myocardial infarction.

Health-related utility values

The utility values used for each of the model health states in the 1-year decision tree were obtained from EuroQol-5D data collected in the PLATO trial and represent the accrued utility over a 12-month period (Table 2).[8] Given that the utility values were not statistically significant between the two treatment groups in the PLATO trial, the mean utility values for all patients in each event state were used. The utility values from the PLATO trial for MI and stroke were also used in the lifetime Markov model. The utility value for post-stroke was assumed to be the same as for new stroke. The utility associated with the post MI/no event state was based on the utility for MI from the trial plus the improvement in utility observed over 1 year after MI as reported by Lacey and Walters.[21] Based on PLATO trial data, patients who died were assigned the accrued utility up to the point at which they entered the dead health state.

Rates of dyspnea were higher in the ticagrelor group than in the clopidogrel group (13.8% versus 7.8%, respectively). However, most reported symptoms of dyspnea were mild to moderate in intensity and presented as a single episode following soon after initiation of treatment. Approximately 30% of episodes resolved within 7 days, and the rate of discontinuation due to dyspnea was 0.9% with ticagrelor versus 0.1% with clopidogrel.[22] As such, the health utility impact of this event was assumed to be minimal and was excluded from the base case analysis but examined in a sensitivity analysis. Similarly, the impact of major bleeding events was not considered in the analysis because no difference in rates of major bleeds was observed in the PLATO trial (11.6% for ticagrelor versus 11.2% for clopidogrel, P=0.43).[8]

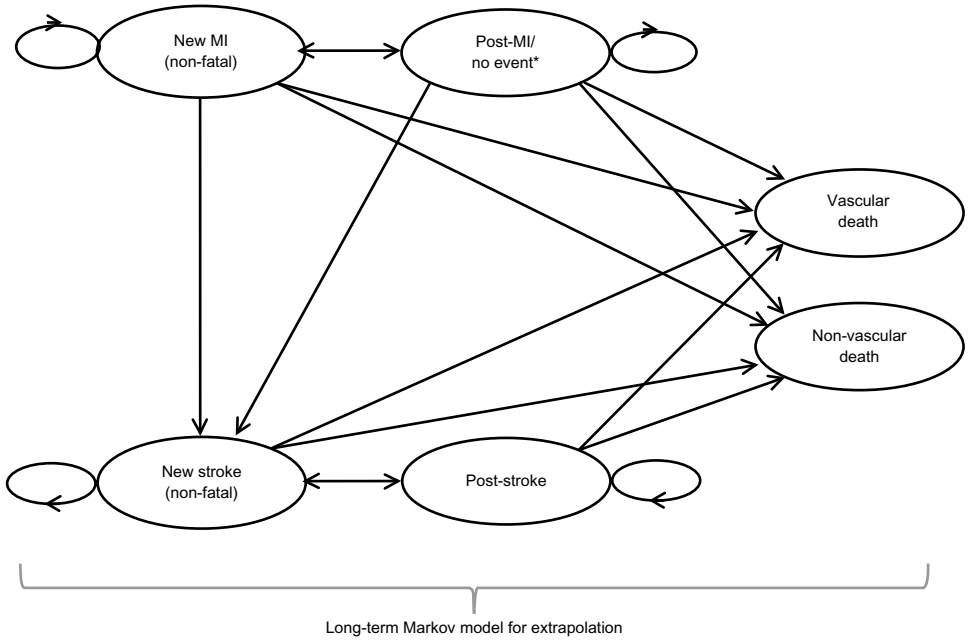

Figure 2 Diagram of the Markov model for post-1-year.
Note: *This state includes patients who had no events within the year after the incident hospitalization for ACS and patients who had an MI in the first year after the ACS event.
Abbreviations: MI, myocardial infarction; ACS, acute coronary syndrome.

Resources and costs

The mean 12-month resource use for PLATO trial patients was used to calculate health state costs in the first year of the analysis.[12] The PLATO trial provided data on the average days of hospitalization and the number and type of interventions and procedures that occurred in each arm of the trial. Hospital days reflected the initial (index) hospitalization for ACS and hospitalizations for other events (eg, MI, stroke) and procedures (eg, coronary artery bypass grafting). To avoid double counting of the hospital stay, a unit cost was applied to days of hospitalization while only the additional costs beyond hospital stay were applied for each procedure/intervention. Specifically, unit costs from the Ontario Case Costing Initiative and from the Ontario Ministry of Health and Long-Term Care were used to value health care resources consumed during the PLATO trial.[23,24] The 1-year health state costs, calculated from the PLATO trial, were lower in the ticagrelor treatment arm compared with the clopidogrel treatment arm (Table S1). A detailed description of Canadian unit costs is presented in Table S2. In order to be conservative, the 1-year treatment costs were averaged such that no difference in health state costs was modeled between treatments.[12] Costs for the Markov model were obtained from published Canadian estimates.[18] All costs were inflated to reflect 2011 Canadian dollars (Table 3). The exchange rate at the time of preparation was Canadian (CDN)$1 equal to US$0.97.

Total costs of $2.96 and $0.645 for ticagrelor (90 mg twice daily) and generic clopidogrel (75 mg once daily), respectively, were assumed in the base case analysis. Generic clopidogrel

Table 2 Health-related utility values used in the model

State	1-year decision tree*	Markov model**
No further event	0.875	0.854
New MI (nonfatal)	0.812	0.812
New stroke (nonfatal)	0.736	0.736
Post-MI	–	0.854
Post-stroke	–	0.736
All-cause death	0.249	0.0

Notes: *Utilities for 1-year decision represent the average utility values reported in the PLATO trial for ticagrelor and clopidogrel. The utility value for "dead any cause" represents the utility value accrued by the patient before they died. **Data from Banerjee et al.[18] No further event state utilities were assumed to be the same as the post-MI state utilities. New stroke and post-stroke utility values were assumed to be the same as there is no evidence health-related quality of life improves over time.
Abbreviations: MI, myocardial infarction; PLATO, Platelet Inhibition and Patient Outcomes.

Table 3 Resource costs used in the 1-year decision tree and post-1-year Markov model

State	1-year decision tree	Markov model*
No further event	$21,781	$3,151
New MI (nonfatal)	$45,515	$10,961
New stroke (nonfatal)	$55,445	$21,087
Post-MI	–	$3,151
Post-stroke	–	$4,391
All-cause death	$39,630	N/A

Notes: Values inflated to 2011 (Canadian dollars) and rounded for display. *Data from Banerjee et al.[18] No further event state costs were assumed to be the same as the post-MI state costs.
Abbreviations: MI, myocardial infarction; N/A, not applicable.

costs were estimated assuming pricing at 25% of brand name clopidogrel at $2.58. Costs for a 180 mg ticagrelor and 300 mg clopidogrel loading dose were also included. Costs for acetylsalicylic acid were excluded because acetylsalicylic acid is not uniformly listed on all Canadian provincial formularies and the use between treatment arms was similar. The rates of dyspnea were significantly different between ticagrelor and clopidogrel (13.8% versus 7.8%, respectively); however, such events were mild or moderate in intensity.[8] While the utility impact of these events was not explicitly modeled, it was assumed that these patients would require an extra two physician visits for assessment and monitoring purposes ($70.80).[24] This is similar, although more conservative, than an assumption in a recent economic analysis of ticagrelor that assumed dyspnea had no treatment costs.[25]

Other model assumptions

The following assumptions were made for the base case analysis: no treatment effect after year 1 of the model was assumed, because all transition probabilities were the same for both treatment arms; adverse events such as dyspnea had no long-term prognostic impact beyond the duration of the clinical trial; no discontinuation other than due to death was included in the model; and the length of treatment for both ticagrelor and clopidogrel was assumed to be 365 days for those who survived the 1-year trial period. For those patients who died during the year, the length of treatment was assumed to be 183 days, assuming that they died, on average, mid-way through the year.

Subgroup and sensitivity analyses

Analyses were conducted for key subgroups identified in the PLATO trial.[8] Sensitivity analyses were conducted to test the robustness of the cost-effectiveness model and the impact of the input variables on the results. One-way sensitivity analyses were conducted on key parameters such as baseline event rates, costs, QALY values, and age-specific event rates (Table S3). For the majority of the inputs, the 95% CIs were used to inform low and high values. However, in instances where 95% CIs were not available, the input was varied by ±20%. Probabilistic sensitivity analyses were also undertaken (see Table S4 for inputs and distributions). Event rates, HRs, utility values, and resource costs were varied simultaneously using Monte Carlo simulation. Multi-way sensitivity analyses using alternative data sources for costs and utility data were also conducted: a) increased and b) decreased unit costs by 20% to explore the impact of uncertainty and variability in resource costs; c) used costs and utilities for events derived from a Canadian Agency for Drugs and Technologies in Health analysis of antiplatelet agents in the treatment of ACS,[18] because this was considered the most relevant alternative data source for Canadian analysis; discounted rate for costs and outcomes changed to d) 0% and e) 3%; f) changed utility values for post-MI and no event in the Markov model from 0.854 to 0.875 based on alternative utility estimate from the PLATO study; g) the PLATO trial found nonsignificant differences in resource use and health utility between the ticagrelor and clopidogrel arms of the study (these values were used in a sensitivity analysis instead of the pooled values); h) transition probabilities based on a Weibull regression from a published analysis were used;[12] i) treatment-specific data for days of study drug were used (ticagrelor and clopidogrel values were 292 and 299 days for no event patients, 269 and 287 days for MI patients, 189 and 212 days for stroke patients, and 66 and 77 days for dead by any cause patients, respectively).

Results

Base case analysis

The base case analysis demonstrated that ticagrelor is cost-effective compared with generic clopidogrel, with an incremental cost per life year gained of $8,438 and an incremental cost per QALY of $9,745 over a period of 40 years (0.084 QALY gained) due to lifetime gains of 0.097 life years per patient, 0.084 QALYs per patient, and an incremental lifetime cost of $821 per patient. Incremental cost-effectiveness ratios (ICERs) increased with decreasing time horizon, with results remaining under $16,000 per QALY gained even for time horizons as low as 5 years (Table 4).

Subgroup and sensitivity analyses

The mean results from the probabilistic sensitivity analysis (5,000 simulations) indicated that the deterministic results are robust (Table 5, Figures 3 and 4). The univariate analyses indicated that the greatest sensitivity of ICERs was to variability around the HR of death for ticagrelor versus clopidogrel (Figure 5). The cost-effectiveness acceptability curves showed a 93% probability of ticagrelor being cost-effective at a willingness-to-pay of $20,000 per QALY and 99% probability of being cost-effective at a willingness-to-pay of $30,000 per QALY (Figure 4). Univariate and multi-way sensitivity analyses indicated that the ICERs were also robust to plausible changes in the input parameters (Figure 5, Tables S5 and S6). Values for the multi-way sensitivity analyses were a) $8,902, b) $10,586, c) $14,874, d) $8,258, e) $9,138, f) $9,555, g) $4,743, h) $9,907, and i) $7,587. Changes to the HR for death with ticagrelor compared with clopidogrel resulted

Table 4 Summary of discounted cost-effectiveness results for different time horizons

Time horizon	Ticagrelor	Clopidogrel	Incremental	ICER
40 years				
Costs	$52,490	$51,669	$821	
Life-years	8.308	8.211	0.097	$8,438
QALYs	7.016	6.932	0.084	$9,745
20 years				
Costs	$51,393	$50,586	$807	
Life-years	8.041	7.947	0.094	$8,598
QALYs	6.801	6.720	0.081	$9,900
10 years				
Costs	$44,801	$44,079	$722	
Life-years	6.342	6.269	0.072	$9,983
QALYs	5.386	5.322	0.064	$11,329
5 years				
Costs	$36,195	$35,582	$613	
Life-years	4.040	3.996	0.044	$14,046
QALYs	3.442	3.402	0.040	$15,441

Note: All values are in Canadian dollars.
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

in the largest impact ($17,685 per QALY); other analyses produced ICERs below $12,000 per QALY. The ICERs were consistent across all key subgroups (Table S6).

Discussion

The PLATO trial demonstrated a significant reduction in a composite of major cardiac events (cardiovascular death, MI, and stroke) and mortality among ACS patients who were treated for up to 1 year with ticagrelor compared with clopidogrel.[8] The results of the cost-effectiveness analysis and the sensitivity analyses show that for patients with ACS, 12 months of antiplatelet therapy with ticagrelor is highly cost-effective compared with generic clopidogrel in the Canadian health care system, with an incremental cost per QALY gained of $9,745 in the base case scenario. These results strongly support the adoption of ticagrelor for the treatment of ACS patients in Canada, based both on clinical and economic value[26] and have lower ICERs than reported for clopidogrel.[18]

A strength of this analysis includes use of clinical data derived from a large randomized, controlled, head-to-head trial used to compare ticagrelor with the current standard of care, clopidogrel, which has already been established as a cost-effective treatment for ACS.[18] In addition, the PLATO trial included the use of clinically relevant outcomes, such as MI, stroke, and death, as the trial endpoints. In this way, use of data from the PLATO trial avoided the two most common limitations in economic analyses, ie, use of comparators that do not reflect current practice and use of intermediate endpoints that require extrapolation to clinically relevant outcomes.

Within any modeling study, it is critical to test the robustness of the results based on uncertainty in the input parameters. In this regard, extensive sensitivity analyses were conducted using the CIs from the PLATO trial and alternative data inputs based on Canadian data sources wherever possible. The results of the probabilistic analysis, which varied the event rates, costs, and utilities, support the deterministic base case results with a ratio of $9,942 (95% CI $9,764–$10,120) per QALY, with 93% probability of a ratio below $20,000 per QALY gained. These results fall well below commonly quoted acceptable ICER thresholds, so present a strong economic support for adoption. The one-way sensitivity analyses indicated that the results were most sensitive to the CI around the HR for death for ticagrelor relative to clopidogrel; however, in the worst case, the ICER remained strong at $17,685 per QALY.

As in all models, limitations occur due to application of trial findings to real-world clinical practice, data assumptions, and structural choices. The analysis results are primarily driven by the mortality differences observed in the PLATO trial between ticagrelor and clopidogrel. However, to capture the impact of differences in mortality between therapies in the year of treatment, the model had to extrapolate beyond the 12-month follow-up period of the PLATO trial. In this way, the value of deaths prevented in year 1, ie, added years of life, could be captured. Such an approach is common in health economic studies[18] and reflects Canadian health economic guideline recommendations.[16,17] It is noteworthy that most of the benefit is achieved in the first few years of the extrapolation, with the cost per QALY gained for ticagrelor compared with clopidogrel remaining low ($15,441) even with only a 5-year time horizon.

Another limitation of this economic evaluation was the application of Canadian unit costs to resource use from the multina-

Table 5 Probabilistic base case results (40 years) – cost per QALY and LY (5,000 simulations)

	Ticagrelor (95% CI)	Clopidogrel (95% CI)	Incremental (95% CI)	ICER (95% CI)
Costs	$57,697 ($57,055–$58,338)	$56,807 ($56,175–$57,438)	$890 ($879–$901)	–
LYs	8.92 (8.85–8.98)	8.81 (8.75–8.87)	0.105 (0.104–0.106)	$8,482 ($8,302–$8,663)
QALYs	7.43 (7.38–7.48)	7.34 ($56,175–$57,438)	0.090 (0.089–0.090)	$9,942 ($9,764–$10,120)

Note: All values are in Canadian dollars.
Abbreviations: CI, confidence interval; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.

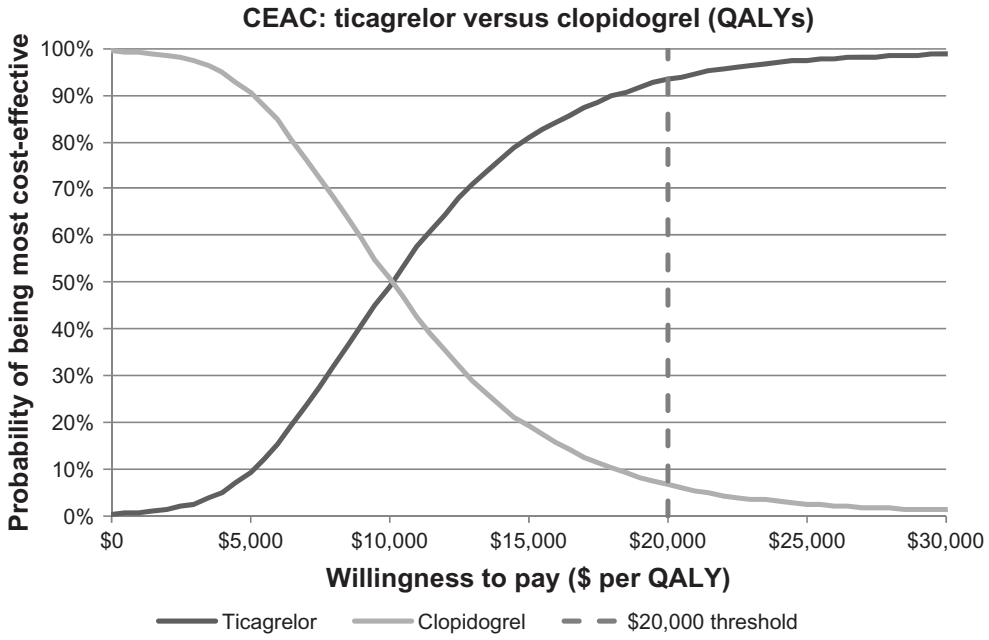

Figure 3 Cost-effectiveness acceptability curve for ticagrelor versus generic clopidogrel.
Note: All values are in Canadian dollars.
Abbreviations: CEAC, cost-effectiveness acceptability curve; QALY, quality-adjusted life year.

tional PLATO study. Canadian participation included 401 patients, or 2.2% of the overall trial population; it is possible that practice patterns in other countries differed from those in Canada. However, sensitivity analyses that used alternative published Canadian health state costs and utility data,[18] instead of the PLATO-derived inputs, also support the cost-effectiveness of ticagrelor, with a ratio below $15,000 per QALY gained. In the absence of long-term data, the model assumed conservatively no extension of treatment benefit beyond 1 year. The approach used to model subsequent events allowed multiple events (as utilized in a paper reported by Banerjee et al),[18] including a simplifying assumption such that the model did not allow patients in year 2 onwards to have a sub-

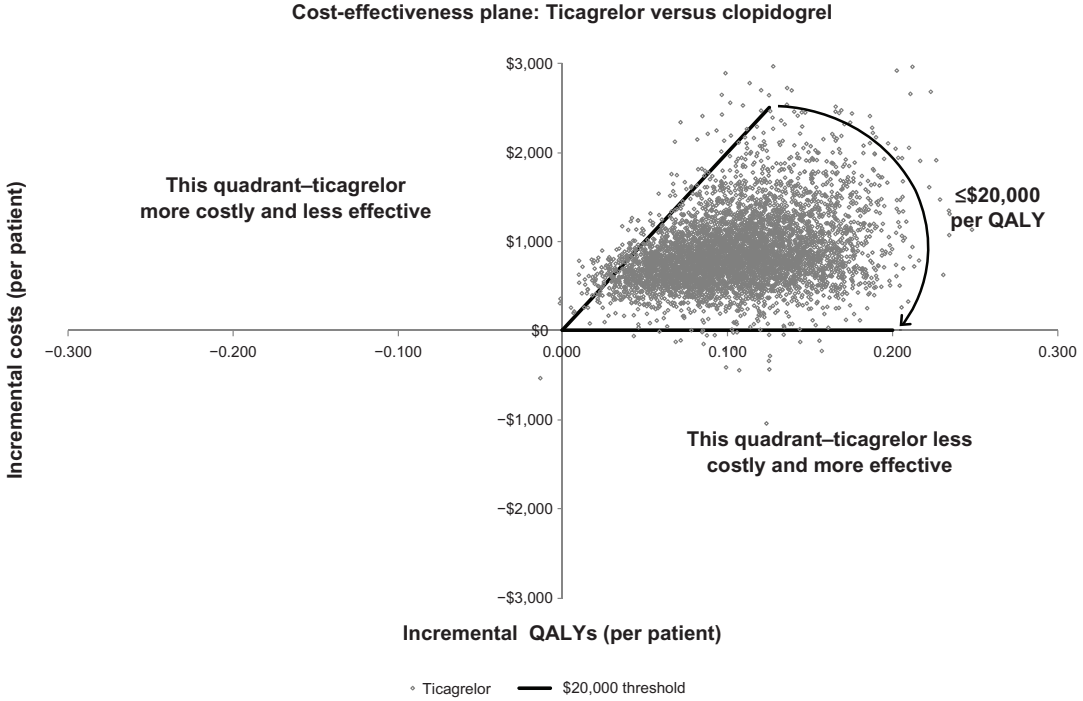

Figure 4 Scatterplot of incremental costs and QALYs for ticagrelor compared to clopidogrel.
Note: All values are in Canadian dollars.
Abbreviations: QALY, quality-adjusted life year.

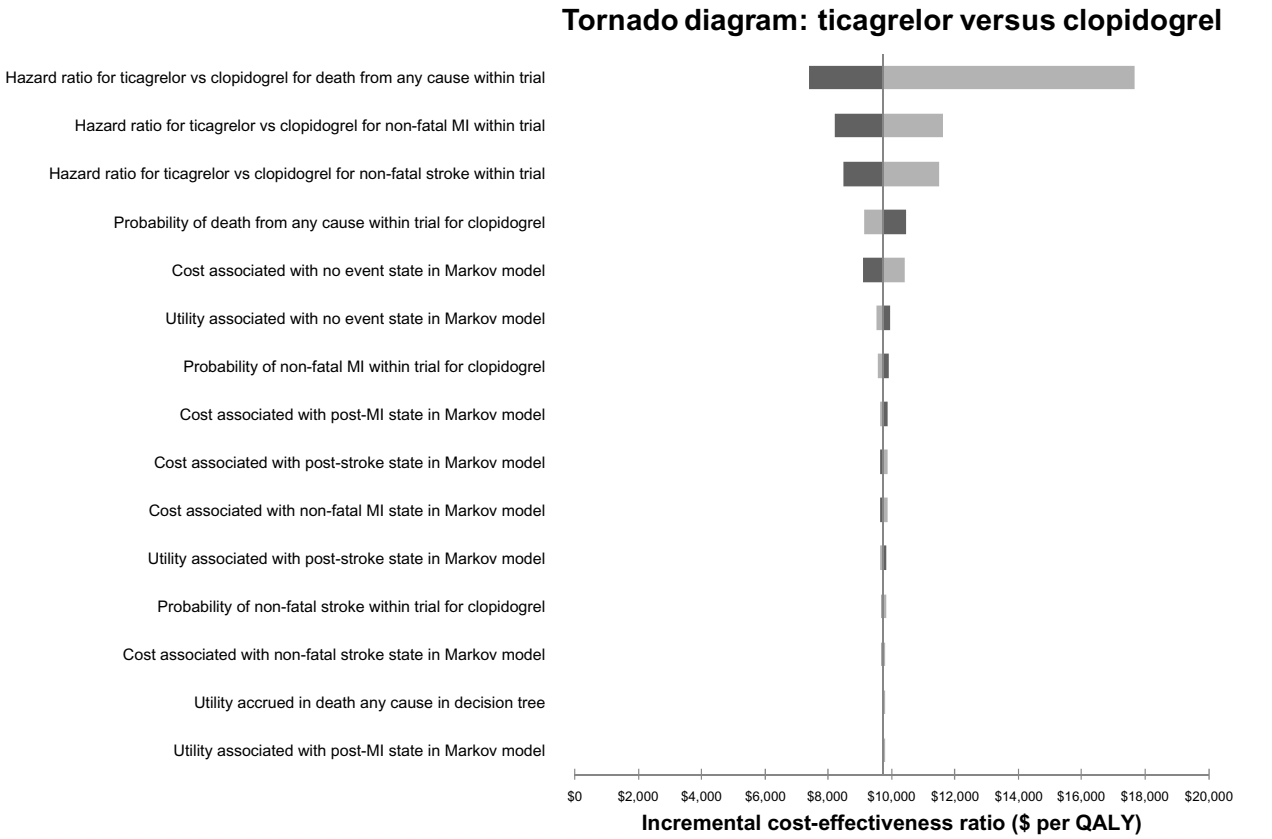

Figure 5 Tornado diagram of one-way sensitivity analyses for ticagrelor versus generic clopidogrel. The light shading represents the higher value for the input and dark shading represents the lower value for the input.
Note: All values are in Canadian dollars.
Abbreviations: MI, myocardial infarction; QALY, quality-adjusted life year; vs, versus.

sequent MI if they had previously had a stroke. This assumption was necessary to ensure that patients would not be considered to transition to a better health state than post-stroke, and is similar to that employed in a previously published model.[18]

To address some of these limitations, conservative assumptions regarding input parameters were used in the base case analyses wherever possible. These included using average health state utilities and costs from the PLATO trial to avoid a potential bias in favor of ticagrelor. For example, therapy-specific resource use and utility values reduced the cost-effectiveness ratio to below $5,000 per QALY gained. In addition, the base case analysis and the majority of sensitivity analyses utilize the generic cost of clopidogrel, which is the lowest cost treatment option available. Use of the brand clopidogrel price resulted in a ratio of $1,523 per QALY gained. Similarly, the mean number of days on study drug from the PLATO trial was not used; instead, 365 days of treatment was assumed in the base case analysis for patients who did not have a fatal event in year 1. Use of the PLATO trial data lowered the cost-effectiveness ratio to approximately $7,600 per QALY gained.

Our findings are consistent with those from published PLATO-based ticagrelor cost-effectiveness studies.[11,12] The current analyses differ from these previous studies by allowing multiple secondary cardiovascular events, adjusting the risk of events for the occurrence of prior events, adjusting the risk of events for age, and utilizing average health state costs and utilities rather than treatment-specific estimates.

Conclusion

The PLATO trial demonstrated significant reductions in the composite endpoint of cardiovascular death, MI, and stroke over a 1-year period with the use of ticagrelor versus clopidogrel in the treatment of ACS patients.[8] The current analyses provides evidence that use of ticagrelor for 12 months in the management of ACS with or without ST elevation in the Canadian health care system is cost-effective compared with the use of brand or generic clopidogrel. The cost per QALY ratio of $9,745 (0.084 QALY gained) versus generic clopidogrel is well below accepted thresholds for cost-effectiveness and consistent with other commonly used and reimbursed cardiovascular therapies in Canada. Overall, this study strongly supports the reimbursement and use of ticagrelor for the treatment of ACS patients in Canada.

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Supplementary material

Costing methodology

The Ontario Case Costing Initiative (OCCI) provides average costs for hospitalizations and average number of hospital days for various hospitalizations such that an average cost per day can be calculated (eg, average cost per day for the treatment of myocardial infarction [MI] patients). Based on 2,089 hospitalizations associated with unstable angina and MI (I200, I201, I2080, I2088, I209, and I219) in the current OCCI database (average of $7,086 per hospitalization in 2008 Canadian dollars for an average of 45 days), an average cost per day of $1,612 (inflated to 2011) was used to cost the number of days spent in cardiac or coronary care units or in the general ward.[1] The PLATO (Platelet Inhibition and Patient Outcomes) trial also collected the number of days spent in the Intensive Care Unit (ICU) which were valued at $3,932/day based on OCCI data.

In the absence of patient-level data, this method of using an average cost per day combined with the average length of stay in hospital for trial patients for various events allows for a more accurate costing of hospitalizations as observed in the clinical trial as opposed to using the average length of stay for patients in the OCCI database. However, OCCI does not capture physician fees billed separately to the Ontario government for minor and major procedures and investigations, and as such these were separately included in the costing analysis. To avoid double counting of the hospital stay, only the additional costs beyond hospital stay were estimated (eg, physician fees) and applied for each procedure and intervention recorded in the PLATO trial.

For each event (no event, MI, stroke, or death), the average cost across the two arms of the study was used in the model (Table S1). This average cost per health event was used instead of treatment-specific costing to avoid artificial differences in health event costs between treatment arms that may be caused by normal heterogeneity in resource use between patients. Further, the Swedish trial-based economic evaluation of the PLATO trial did not show a statistical difference in costs between the treatment groups.[2] The authors mentioned that the PLATO subeconomic study may not have been powered to detect cost differences between treatment arms. As such, random variability in resource use could artificially inflate resource use in one treatment arm. For example, the costs of stroke and death in the clopidogrel arm were substantially higher than in the ticagrelor arm. For these reasons, an average cost per health state was used in the 1-year decision tree. A sensitivity analysis was conducted with treatment-specific health state costs.

The costs of the 'no event' state and the other health states include the resource use for the management of the initial ACS: as such, the cost in all these states may be higher than typical costs for a patient with stable cardiovascular disease or an MI patient who did not have ACS in the preceding 12-month period.

Subgroup analysis

In addition to the economic evaluation based on the full PLATO population, a number of subgroup analyses were undertaken, the results of which are shown in Table S6. The subgroups included in the analysis were: 12-month cohort, ST segment elevation myocardial infarction, non-ST segment elevation myocardial infarction, unstable angina, diabetes, no diabetes, patients on low dose acetylsalicylic acid, invasive and medically managed. In all cases, the ratio remained below $11,500 per QALY, further demonstrating the cost-effectiveness of ticagrelor (Table S6).

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Table S1 Health state costs used in the first year of the model (2011 costs)

State	Clopidogrel	Ticagrelor	Average for both treatment groups
No further event	$21,735	$21,828	$21,781
New MI (nonfatal)	$45,205	$45,824	$45,515
New stroke (nonfatal)	$59,133	$51,758	$55,445
Dead any cause	$44,663	$34,597	$39,630

Notes: Values rounded for display, inflated to 2011 costs. All values are in Canadian dollars.
Abbreviation: MI, myocardial infarction.

Table S2 Unit costs (2011 Canadian$)

Cost item	Unit	2011 Cost*	Source
Drugs			
Daily ticagrelor	90 mg twice daily	$2.96	AstraZeneca Canada
Loading dose ticagrelor	180 mg	$2.96	AstraZeneca Canada
Loading dose clopidogrel	300 mg	$10.31 (generic $2.58)	Ontario Drug Benefit Program[3]
Daily clopidogrel	75 mg once daily	$2.58	Ontario Drug Benefit Program[3]
Daily clopidogrel (generic)	75 mg once daily	$0.645	Calculated (25% of brand name)
Daily ASA	75–150 mg	$0	Equivalent between two groups
Hospitalizations			
General ward, cardiac care unit, and coronary care ward	Per day	$1,612	Ontario Case Costing Initiative[1] Based on average cost per day for CCU for UA and MI (1200, 1201, 12080, 12088, 1209, and 1219)
Intensive care unit	Per day	$3,932	Ministry of Health and Long-Term Care[4]
Interventions (physician fees)			
CABG with valve replacement	Per operation	$7,396	Ontario Schedule of Benefits[5]
CABG without valve replacement	Per operation	$6,001	Ontario Schedule of Benefits[5]
Implantable cardiac defibrillator	Per procedure	$1,096	Ontario Schedule of Benefits[5]
Intra-aortic balloon pump	Per procedure	$312	Ontario Schedule of Benefits[5]
Left ventricular assist device	Per procedure	$2,817	Ontario Schedule of Benefits[5]
Pacemaker			
Implantation of single chamber rate-responsive pacemaker	Per procedure	$487	Ontario Schedule of Benefits[5]
PCI without stent	Per procedure	$567	Ontario Schedule of Benefits[5]
PCI with stent	Per procedure	$647	Ontario Schedule of Benefits[5]
Bare metal stent	Per unit	$600	Goeree et al[6]
Drug-eluting stent	Per unit	$1,899	Goeree et al[6]
Investigations (physician fees)			
Coronary angiography	Per procedure	$212	Ontario Schedule of Benefits[5]
CT abdomen	Per procedure	$115	Ontario Schedule of Benefits[5]
CT chest	Per procedure	$92	Ontario Schedule of Benefits[5]
CT extremity			
CT, arm	Per procedure	Assumed all were leg	Ontario Schedule of Benefits[5]
CT, leg	Per procedure	$81	Ontario Schedule of Benefits[5]
CT head/brain			
CT, head	Per procedure	$81	Ontario Schedule of Benefits[5]
CT, brain	Per procedure	Assumed all were head	Ontario Schedule of Benefits[5]
CT helical	Per procedure	Assumed the same as spine	Ontario Schedule of Benefits[5]
CT spine	Per procedure	$115	Ontario Schedule of Benefits[5]
Echocardiography	Per procedure	$140	Ontario Schedule of Benefits[5]
Electrophysiology study	Per procedure	$1,608	Ontario Schedule of Benefits[5]
Holter study	Per procedure	$273	Ontario Schedule of Benefits[5]
MRI abdomen	Per procedure	$78	Ontario Schedule of Benefits[5]
MRI chest	Per procedure	$78	Ontario Schedule of Benefits[5]
MRI extremity	Per procedure	$67	Ontario Schedule of Benefits[5]
MRI, arm	Per procedure	Assumed same as CT extremity	Ontario Schedule of Benefits[5]
MRI, leg	Per procedure	Assumed same as CT extremity	Ontario Schedule of Benefits[5]

(*Continued*)

Table S2 (*Continued*)

Cost item	Unit	2011 Cost*	Source
MRI head/brain	Per procedure	$74	Ontario Schedule of Benefits[5]
MRI, head	Per procedure	Assumed same as CT head/brain	Ontario Schedule of Benefits[5]
MRI, brain	Per procedure	Assumed same as CT head/brain	Ontario Schedule of Benefits[5]
MRI spine	Per procedure	$108	Ontario Schedule of Benefits[5]
Myocardial scintigraphy	Per procedure	$166	Ontario Schedule of Benefits[5]
Pulmonary angiography	Per procedure	$120	Ontario Schedule of Benefits[5]
Stress test	Per procedure	$98	Ontario Schedule of Benefits[5]
Ventilation/perfusion scan	Per procedure	$301	Ontario Schedule of Benefits[5]
Bleeds			
Reoperation due to bleeding	Per operation	$694	Ontario Schedule of Benefits[5]
Unit of fresh frozen plasma	Per unit	$249	Callum and Pinkerton[7]
Unit of packed red blood cells	Per unit	$453	Callum and Pinkerton[7]
Unit of platelets	Per unit	$566	Callum and Pinkerton[7]
Unit of whole blood	Per unit	$453	Callum and Pinkerton[7]
Significant adverse events			
Dyspnea	Physician visits	$35.40 * 2 = $70.80	Ontario Schedule of Benefits[5]

Notes: *In some instances costs were inflated to 2011. All values are in Canadian dollars.
Abbreviations: ASA, acetylsalicylic acid; CABG, coronary artery bypass surgery; CCU, coronary care unit; CT, computed tomography; MI, myocardial infarction; MRI, magnetic resonance imaging; PCI, percutaneous coronary intervention; UA, unstable angina.

Table S3 Values used in one-way sensitivity analysis

Variable	Parameter	Range		Source
		Low	High	
Event rates for clopidogrel (1-year decision tree)				
Dead any cause	0.0545	0.0500	0.0590	95% confidence intervals
Nonfatal MI	0.0522	0.0477	0.0567	based on PLATO data
Nonfatal stroke	0.0080	0.0062	0.0097	
Hazard ratios for ticagrelor versus clopidogrel (1-year decision tree)				
Dead any cause	0.78	0.69	0.89	95% confidence intervals
Nonfatal MI	0.86	0.76	0.98	based on PLATO data
Nonfatal stroke	1.09	0.80	1.49	
Utilities from PLATO study				
No further event	0.875	0.871	0.879	95% confidence intervals
New MI	0.812	0.792	0.832	based on PLATO HECON
New stroke	0.736	0.662	0.810	substudy
Dead any cause	0.249	0.222	0.276	
New MI (mm)	0.812	0.792	0.832	
Post-MI/no event (mm)	0.854	0.834	0.873	
New stroke (mm)	0.736	0.662	0.810	
Post-stroke (mm)	0.736	0.662	0.810	
Resource cost for the Markov model				
New MI	$10,824	$8,659	$12,989	Costs were varied by ±20%
Post-MI/no event	$3,112	$2,490	$3,734	
New stroke	$20,823	$16,658	$24,988	
Post-stroke	$4,336	$3,469	$5,203	

Note: All values are in Canadian dollars.
Abbreviations: MI, myocardial infarction; PLATO, Platelet Inhibition and Patient Outcomes.

Table S4 Summary of probabilistic sensitivity analysis inputs and distributions

Variable	Value (95% CI)	Distribution	Source
Event rates for clopidogrel (1-year decision tree)			
Dead any cause	0.0545 (0.05–0.059)	Lognormal	Based on the raw data from the PLATO study
Nonfatal MI	0.0522 (0.0477–0.0567)	Lognormal	
Nonfatal stroke	0.008 (0.0062–0.0097)	Lognormal	
Hazard ratios for ticagrelor versus clopidogrel (1-year decision tree)			
Dead any cause	0.78 (0.69–0.89)	Lognormal	Based on the PLATO study
Nonfatal MI	0.86 (0.76–0.98)	Lognormal	
Nonfatal stroke	1.09 (0.80–1.49)	Lognormal	
Event rates (Markov model)			
Subsequent events (MI, stroke, and vascular death)	Various	Normal	Coefficients for the risk equations from Karnon et al[8] were varied around their respective SE
Utility values (decision tree and Markov model)			
No further event	0.875 (0.871–0.879)	Beta	95% confidence intervals based on PLATO study
New MI	0.8120 (0.792–0.832)	Beta	
New stroke	0.7360 (0.662–0.810)	Beta	
Dead any cause	0.2490 (0.222–0.726)	Beta	
Resource costs (decision tree)			
No further event (ticagrelor)	$21,911	Gamma	Based on 95% confidence intervals of individual resource use from the PLATO study
New MI (ticagrelor)	$46,024	Gamma	
New stroke (ticagrelor)	$51,351	Gamma	
Dead any cause (ticagrelor)	$34,387	Gamma	
No further event (clopidogrel)	$21,849	Gamma	
New MI (clopidogrel)	$45,298	Gamma	
New stroke (clopidogrel)	$58,769	Gamma	
Dead any cause (clopidogrel)	$44,391	Gamma	
Resource costs (Markov model)			
New MI	$10,824	Gamma	As no standard error was reported in the original study, we assumed an SE equal to the mean
Post-MI/no event	$3,112	Gamma	
New stroke	$20,823	Gamma	
Post-stroke	$4,336	Gamma	

Note: All values are in Canadian dollars.
Abbreviations: CI, confidence interval; MI, myocardial infarction; SE, standard error; PLATO, Platelet Inhibition and Patient Outcomes.

Table S5 Output of one-way sensitivity analyses: incremental cost per QALY for ticagrelor versus clopidogrel

Parameters	Low value	High value
Hazard ratio for ticagrelor versus clopidogrel for death from any cause within trial	$7,391	$17,685
Hazard ratio for ticagrelor versus clopidogrel for nonfatal MI within trial	$8,209	$11,618
Hazard ratio for ticagrelor versus clopidogrel for nonfatal stroke within trial	$8,465	$11,479
Probability of death from any cause within trial for clopidogrel	$10,467	$9,120
Probability of nonfatal MI within trial for clopidogrel	$9,927	$9,564
Probability of nonfatal stroke within trial for clopidogrel	$9,657	$9,830
Probability of dyspnea whilst on ticagrelor	$9,739	$9,750
Probability of dyspnea whilst on clopidogrel	$9,749	$9,740
Cost associated with no event state in Markov model	$9,090	$10,398
Cost associated with post-MI state in Markov model	$9,865	$9,624
Cost associated with post-stroke state in Markov model	$9,628	$9,861
Cost associated with nonfatal MI state in Markov model	$9,632	$9,857
Cost associated with nonfatal stroke state in Markov model	$9,688	$9,801
Cost of dyspnea in primary care	$9,719	$9,770
Cost of brand clopidogrel	–	$1,523
Cost of generic clopidogrel (20% brand price)	–	$10,293
Utility accrued in no event in decision tree	$9,753	$9,736
Utility accrued in death any cause in decision tree	$9,708	$9,782
Utility accrued in nonfatal MI in decision tree	$9,728	$9,761
Utility accrued in nonfatal stroke in decision tree	$9,751	$9,738
Utility associated with no event state in Markov model	$9,962	$9,536
Utility associated with nonfatal MI state in Markov model	$9,746	$9,743
Utility associated with nonfatal stroke state in Markov model	$9,757	$9,732
Utility associated with post-MI state in Markov model	$9,709	$9,780
Utility associated with post-stroke state in Markov model	$9,839	$9,651
Utility associated with dyspnea (utility reduced by 7% for 7 days[9])	–	$9,849

Note: All values are in Canadian dollars.
Abbreviations: MI, myocardial infarction; QALY, quality-adjusted life year.

Table S6 Summary of subgroup analysis (40-year time horizon)

Subgroup	Incremental cost per QALY gained
12-month cohort	$10,020
STEMI	$10,596
NSTEMI	$7,959
Unstable angina	$11,499
Diabetes	$7,950
No diabetes	$10,285
Low dose ASA	$6,573
Invasive	$11,043
Medically managed	$7,042

Note: All values are in Canadian dollars.

Abbreviations: ASA, acetylsalicylic acid; NSTEMI, non-ST segment myocardial infarction; QALY, quality-adjusted life year; STEMI, ST segment elevation myocardial infarction.