Cost-Effectiveness of Clopidogrel, Prasugrel, and Ticagrelor for Dual Antiplatelet Therapy after Acute Coronary Syndromes: a decision-analytic model

Running title: Cost-effectiveness of prasugrel and ticagrelor

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Abstract

Background: The use of prasugrel or ticagrelor in combination with aspirin after acute coronary syndromes (ACS) improves clinical outcomes relative to clopidogrel. There have been no head-to-head analyses directly comparing the cost-effectiveness of these three agents. Thus, we conducted an economic analysis evaluating one year of treatment with clopidogrel, prasugrel or ticagrelor in patients post ACS.

Methods: We developed a fully probabilistic Markov cohort decision-analytic model using a lifetime horizon, from the perspective of the Ontario Ministry of Health. The model incorporated risks of death, recurrent ACS, heart failure, major bleeds and other adverse effects of therapy. Data on probabilities and utilities were obtained from published literature where available. The primary outcome was quality adjusted life-years (QALYs).

Results: Treatment with clopidogrel was associated with the lowest effectiveness at 7.41 QALYs (95% CI 1.05-14.79) at a cost of $39,601 (95% CI 8,434-111,186). Ticagrelor was associated with an effectiveness of 7.50 QALYs (95% CI 1.13-14.84) at a cost of $40,649 (95% CI 9,327-111,881). The ICER for ticagrelor relative to clopidogrel was $12,205 per QALY gained. Prasugrel had an ICER of $57,630 per QALY gained relative to clopidogrel. Ticagrelor was the preferred option in 90% of simulations at a willingness to pay threshold of $50,000/QALY gained.

Interpretation: Ticagrelor was the most cost effective agent when used as part of dual anti-platelet therapy post ACS. This conclusion was robust to wide variations in model parameters.

Keywords: Cardiac Disease, Coronary cost-effectiveness analysis, myocardial infarction, antiplatelet drugs, prasugrel, health economics, ticagrelor, clopidogrel

Background

Contemporary guidelines recommend dual antiplatelet therapy with acetylsalicylic acid and a P2Y12 antagonist for one year after acute coronary syndrome (ACS)(1-3). The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) Trial demonstrated that clopidogrel reduces adverse cardiovascular events when added to acetylsalicylic acid for twelve months after an ACS(1). However, the individual response to clopidogrel is limited by various factors (4). This has prompted research that culminated in the development of prasugrel and ticagrelor, novel P2Y12 antagonists with superior antiplatelet properties compared to clopidogrel.

The Prasugrel–Thrombolysis in Myocardial Infarction (TRITON– TIMI) 38 trial demonstrated that prasugrel use after an ACS significantly reduced the risk of recurrent ACS, including stent thrombosis, relative to clopidogrel(5). Similarly, the Platelet Inhibition and Patient Outcomes trial (PLATO) demonstrated that ticagrelor reduced the risk of all-cause death after an ACS relative to clopidogrel(6). Both agents increased bleeding rates, with a more prominent increase in risk with prasugrel (5,6). In addition to these clinical tradeoffs, both prasugrel and ticagrelor have substantially higher acquisition costs than clopidogrel (7, 8).

Recent American College of Cardiology/ American Heart Association guidelines emphasize the importance of evaluating the clinical benefits of health care interventions in the context of their costs (9, 10). This enables delivery of the highest quality health care while optimizing scarce resources. While cost-effectiveness analyses have compared clopidogrel individually with prasugrel (11) and ticagrelor (12), none have directly compared all three agents against each other. Decision-analytic modeling is well-suited to

addressing this gap in knowledge, as it provides an explicit framework to integrate all available evidence. Accordingly, we conducted an economic analysis comparing the cost-effectiveness of 12 months of treatment with clopidogrel, prasugrel and ticagrelor in post ACS patients, including both STEMI and NSTE-ACS.

Methods

Overview and Study Design

We developed a fully probabilistic Markov cohort state-transition model, with a life-time horizon. Cycle length was set at one month. The model was analyzed from the perspective of the Ontario Ministry of Health and Long-Term Care. The three alternatives evaluated in the model were treatment with ticagrelor, prasugrel or clopidogrel for 12 months in patients revascularized with percutaneous coronary intervention after an ACS (13-15). Effectiveness was expressed as quality-adjusted life years (QALYs), while costs were adjusted to 2012 Canadian dollars using the general consumer price index.

Incremental-cost effectiveness ratios (ICERs) were calculated by ordering the three strategies from lowest to highest lifetime cost, consistent with economic analysis conventions. We determined the ICER based on the incremental cost and effectiveness compared with the next less expensive treatment strategy. If a strategy was more effective than a more expensive alternative, it was a dominant strategy. If the ICER of a strategy was lower than its less expensive alternative, it extendedly dominated that alternative, as it represented more efficient value per unit cost. Based on guidelines, an alternative was considered to be of value if its ICER was less than $50,000 per QALY gained (1*per capita gross domestic product/GDP) (9, 10). All utilities and costs were discounted at a rate of 5% per year according to current Canadian recommendations (16).

Model structure

A simplified model schematic is presented in Figure 1. Patients in the model progress through cycles of one-month duration. All patients begin with dual antiplatelet therapy with acetylsalicylic acid, combined with one of clopidogrel, prasugrel or ticagrelor, with the objective of completing 12 months of therapy post ACS. We assumed that every patient was successfully revascularized at the time of index PCI for their ACS.

Within any one-month cycle patients could die, develop heart failure or become free of it. Events that occurred within each cycle included recurrent ACS (with possible stent thrombosis), major bleeding, or minor side effects (minor bleeds and ticagrelor-associated bradycardia and dyspnea). Discontinuation of assigned dual antiplatelet strategy was factored into our model using rates derived from clinical trial data.

It was assumed that if patients had to discontinue clopidogrel within the first 12 months post index event, it would be replaced with prasugrel or ticagrelor with a 50% probability of receiving each agent. If patients were initially on one of prasugrel or ticagrelor and had to discontinue it within 12 months of an ACS, they were transitioned to clopidogrel. If patients had to discontinue two P2Y12 antagonists, they were classified as dual antiplatelet intolerant and maintained on single antiplatelet therapy with aspirin. Dual antiplatelet therapy intolerant patients were modeled to have higher risks of recurrent ACS and death for the first 12 months post ACS.

After 12 months of dual antiplatelet therapy without recurrent events, patients were transitioned to single antiplatelet therapy. If an ACS recurred, patients were transitioned to the last dual antiplatelet strategy they tolerated. Patients who were dual antiplatelet therapy intolerant were treated with angioplasty without stenting, and

maintained on acetylsalicylic acid alone. These patients had a higher risk of recurrent ACS for the subsequent six months.

Base Case

The baseline characteristics of our base case were derived from the weighted means of the characteristics of patients enrolled in the TRITON– TIMI 38, the Dose confirmation Study assessing anti-Platelet Effects of AZD6140 vs. clopidogRel in non-ST segment Elevation myocardial infarction (DISPERSE-2) study and the PLATO randomized controlled trials (5, 6, 8, 17). The mean age was 62 years; 61% were male, and 24% were diabetic.

Probabilities

Probabilities were obtained from the published literature and are listed in Table 1. All transition probabilities for death, stent thrombosis, development of heart failure and recurrent ACS were time-dependent based on patient age and time from the most recent ACS event.

a. ACS, stent thrombosis and bleeding

The incidence of recurrent ACS, stent thrombosis, and TIMI major bleeding with clopidogrel was derived from the weighted mean of the event rates in the clopidogrel arm of these trials. The incidence of these events among patients treated with prasugrel or ticagrelor was modeled by multiplying the baseline rate in clopidogrel-treated patients with the corresponding hazard ratio for each event as determined from each agent's Phase III trial data. Rates of minor bleeding and other side effects, as well rates of discontinuation, were determined directly for each agent using the TRITON and PLATO trial data.

b. Probability of death

The baseline risk of death for patients on aspirin monotherapy was derived from age-and sex specific Ontario life tables, and modified by a time-dependent change in the hazard for death based on time since the most recent myocardial infarction (18) and the presence/ absence of heart failure. In each treatment arm, the hazard of death was modified based on the reported hazard ratio for death reported in Phase III trials of prasugrel, ticagrelor and clopidogrel (See Table 2) (4-6, 19).

Costs

Costs and utilities utilized in our study are summarized in Table 3. Costs were reported in 2012 Canadian dollars. Unit costs for medications were obtained from the Ontario Drug Benefits (ODB) Formulary (20). We assumed dispensing fees of once per 3 months (3 months is the maximum time frame that pharmacies prescribe medications under the Ontario Drug Benefit Plan). We employed monthly treatment costs of $20.02 with clopidogrel, $80.96 with prasugrel, and $90.10 for ticagrelor. The Ontario Case Costing Initiative (OCCI) was used to determine hospitalization costs (21). Physician costs were obtained from the 2012 Ontario Schedule of Benefits for Physician Services (22). For each ACS, we assumed there was an emergency physician consultation, a cardiology consultation, and interventional cardiology consultation, a diagnostic angiogram and percutaneous coronary intervention, a transthoracic echocardiogram, and 3 follow up visits by the attending cardiologist.

Utilities

We used previously described utility values for the post MI state, with and without heart failure, as well as for acute coronary syndromes, major and minor bleeding

[16-18,20-24]. The utility of other non-major bleeding related side effects were assumed to be equivalent to those of minor bleeding (19-21, 23-27). The utility of twice a day dosing, which is necessary for ticagrelor, was assumed to be 0.999.

Analysis

The model was fully probabilistic, with all input parameters (probabilities, utilities and costs) expressed as a distribution, with the mean/expected value and confidence intervals derived from the literature (See Tables 1-3). If a confidence interval was not available, we used a conservative estimate of the variance being 1/3 of the mean (28). For probabilities and utilities, we used beta distributions, while gamma distributions were used for costs, and log-normal distributions for hazard ratios. We ran 10,000 simulations of the model, with parameter values in each simulation based on random draws from each of the distributions in the model. Our final outputs are based on the means of the results from the 10,000 simulations. This probabilistic analysis allows for the full incorporation of the uncertainty of the input parameters. In addition, we expressed the degree of uncertainty by plotting a cost-effectiveness acceptability curve, which illustrates the proportion of the 10,000 simulations in which clopidogrel, prasugrel or ticagrelor was the preferred option at different willingness to pay thresholds.

Sensitivity Analyses

We performed one-way sensitivity analyses on all input parameters, to determine the robustness of our model. The ranges of the one-way sensitivity analyses were based on 95% confidence intervals determined by the distributions used for the probabilistic analysis. Given the computation intensity of the probabilistic analyses, one-way sensitivity analyses were conducted deterministically (summarized in Appendix 1).

The model was constructed using TreeAge Pro 2013 (TreeAge Software, Inc., Williamstown, Massachusetts). Computation was conducted using 64 core cloud computing with Amazon Web Services (AWS).

Results

Base case cost effectiveness analysis

Treatment with clopidogrel yielded the lowest effectiveness at 7.41 QALYs (95% CI 1.05-14.79), as well as the lowest cost at $39,601 (95% CI 8,434-111,186). Prasugrel had an effectiveness of 7.43 QALYs (95% CI 1.06-14.79) at a cost of $40,422 (95% CI 9,002-111,881), for an ICER of $57,630 per QALY gained, compared to clopidogrel. Ticagrelor was associated with an effectiveness of 7.50 QALYs (95% CI 1.13-14.84) at a cost of $40,649 (95% CI 9,327-111,881). This translated to an ICER of $3,167 per QALY gained, when compared to prasugrel. Therefore, prasugrel was extendedly dominated by ticagrelor. When compared to clopidogrel, the ICER of ticagrelor was $12,205 per QALY gained (see Table 4). At a willingness to pay (WTP) threshold of $50,000/QALY, 90% of the 10,000 simulations showed that ticagrelor was the preferred agent. When the WTP threshold was $100,000/QALY, 92% of the simulations showed ticagrelor to be the preferred strategy (see figure 2).

One-way sensitivity analyses

Ticagrelor was the most cost effective agent throughout the range of most parameters values in one-way sensitivity analyses. The conclusion was only sensitive to variations in the value of the hazard ratio of death associated with ticagrelor relative to clopidogrel. The ICER associated with ticagrelor relative to clopidogrel exceeded $50,000/ QALY when the hazard ratio was greater than 0.89.

Interpretation

This comparison of clopidogrel, prasugrel, and ticagrelor suggests that ticagrelor is the most cost-effective P2Y12 antagonist for use in combination with acetylsalicylic acid post-PCI after an ACS. This conclusion was relatively robust to variation in the values of important model parameters, with 90% of simulations supporting a preference for ticagrelor.

Prasugrel and ticagrelor are novel P2Y12 receptor antagonists. Prasugrel is a potent antiplatelet agent that substantially reduces the risk of recurrent ACS and stent thrombosis. In fact, an indirect network meta-analysis demonstrates it to be more effective than ticagrelor at reducing stent thrombosis with an estimated OR of 0.635 (95% CI 0.433–0.932)(4). However, this comes at an increased risk of bleeding. The TRITON-TIMI 38 study indicated that the risks for any bleeding, as well as TIMI major bleeds, were higher with prasugrel relative to clopidogrel, with hazard ratios of 1.46 and 1.31 respectively (5). The aforementioned network meta-analysis suggests that this higher bleeding risk persists in comparisons with ticagrelor, with an OR of 1.43 (1.10–1.86) (4). Ticagrelor on the other hand appears to be less potent than prasugrel with respect to reduction of recurrent ACS and stent thrombosis, but is associated with a less substantial increase in bleeding risk. Importantly, it is associated with a significant reduction in all-cause mortality relative to clopidogrel with a hazard ratio of 0.78. This may be a consequence of a more optimal balance between these two competing risks. However, other pleiotropic mechanisms such as promotion of endothelial adenosine activity on the

endothelium have been postulated to explain the survival advantage that is unique to this agent (29).

Traditional cardiovascular treatment guidelines have not incorporated resource utilization and value considerations into their recommendations. However, given the finite available healthcare resources and the increasing costs of providing health services, there has been a recent emphasis on assessment of the cost and value of healthcare interventions. A recent ACC/AHA statement emphasized the importance of considering both cost and value when making healthcare decisions as well as outlining its role in the future of cardiovascular research (9, 10). While prasugrel and ticagrelor, are clearly efficacious, it is currently unclear whether this is offset by their increased cost. The question remains whether or not they provide added value over clopidogrel.

While there have been economic analyses assessing clopidogrel, prasugrel and ticagrelor, none have previously compared all three (11, 12, 30). It is important to determine the most cost-effective option among these three agents, which are all presently available to clinicians and policy makers. ICERs of <100,000/QALY are currently defined as having intermediate values and those with ICERs of <50,000/QALY are thought to provide high value (9, 10). In this analysis, ticagrelor was the most cost effective strategy in 92% and 90% of the simulations at a WTP of 100,000/QALY and $50,000/QALY respectively. This means that the model conclusions are stable to a wide range of variability in the parameters used in the model.

Our conclusions support current NSTE-ACS guidelines that indicate that it is reasonable to consider ticagrelor in preference to clopidogrel for dual antiplatelet therapy (class IIa indication) (31, 32). In contrast, current STEMI guidelines provide no

preference for one agent over another (33, 34). This analysis provides additional cost-effectiveness data to guide decisions by hospitals and third party payers about the adoption of ticagrelor in lieu of clopidogrel. We anticipate that this information will also be useful to authors of future treatment guidelines.

Limitations of our study should be mentioned. First, our model is specific for ACS patients who are treated with PCI; we cannot extrapolate our conclusions to those who are treated medically. Second, we simplified the modeling of adverse effects by assuming that minor bleeding carries a similar utility decrement as ticagrelor-associated bradycardia and dyspnea. Finally, our conclusions are limited to the framework within which we modeled the lifetime course post-ACS and different conclusions may be drawn if this were modeled differently.

Conclusions

This cost-effectiveness analysis indicates that ticagrelor is the most cost-effective P2Y12 antagonist when used in combination with aspirin post ACS. These results may aid decision makers and individual clinicians in both recommending and ultimately selecting the appropriate P2Y12 antagonist in conjunction with aspirin as dual antiplatelet therapy post ACS.

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Disclosures

The authors have no conflicts of interest to declare.

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Figure legends

Figure 1. Simplified schematic of the decision model. This figure illustrates important events and states captured in the model. All patients enter the Markov cohort after percutaneous coronary intervention for myocardial infarction. They are treated with acetylsalicylic acid and one of clopidogrel, prasugrel or ticagrelor with the aim of continuing 12 months of dual antiplatelet therapy. Patients could develop multiple adverse events, the most important of which are recurrent acute coronary syndromes and major bleeds. Patients could transition in and out of heart failure. The model also accounts for risk of death, which is related to age, gender, time since infarction, and presence of heart failure. Less severe adverse events are included in the model but not illustrated in this figure for parsimony.

Figure 2. Cost effectiveness acceptability curve for ticagrelor vs. prasugrel vs. clopidogrel. This figure illustrates the results of the probabilistic analysis based on 10,000 simulations. The graph plots the percentage of iterations (on the Y-Axis) in which clopidogrel, prasugrel, and ticagrelor are cost-effective against different thresholds for willingness to pay in Canadian Dollars (X-Axis).

Figures

Figure 1.

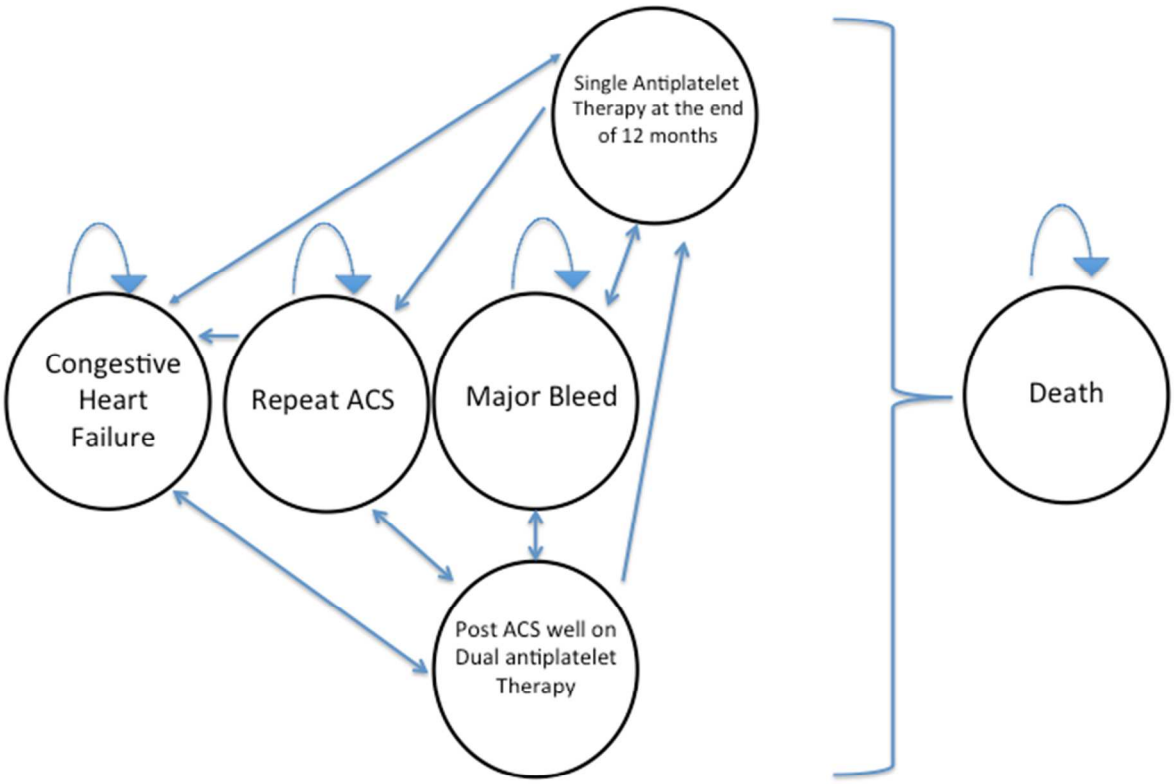
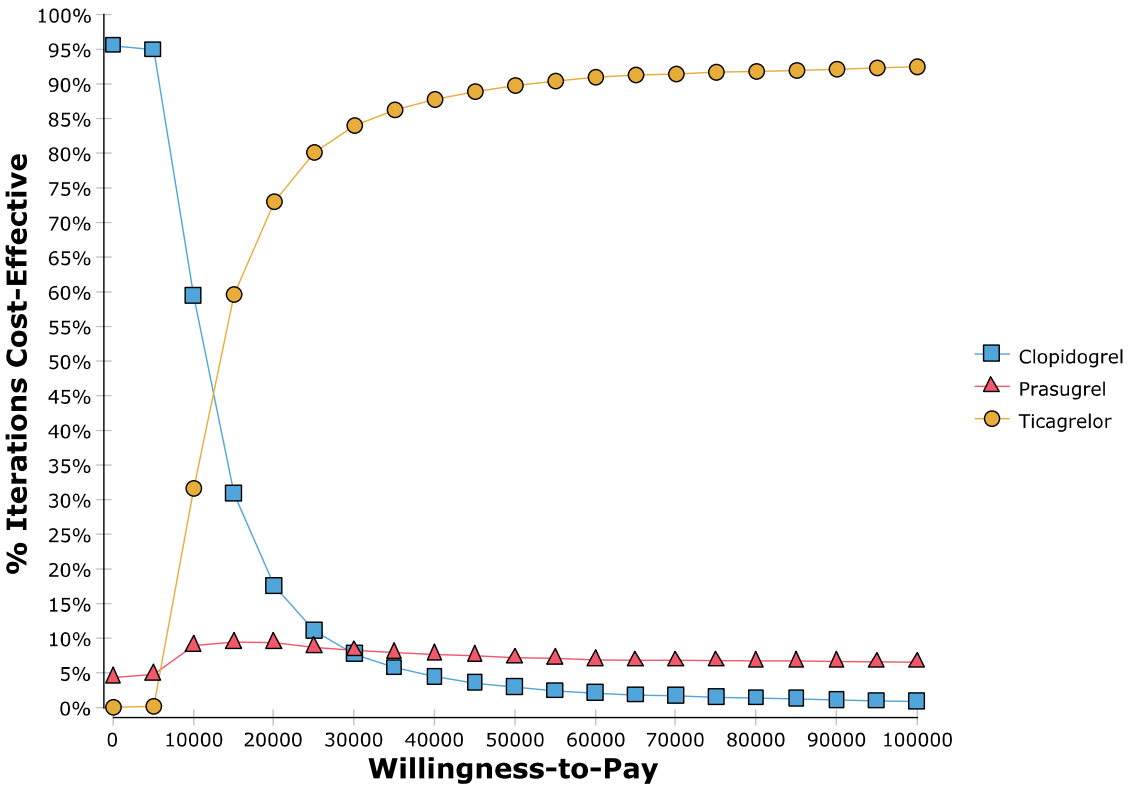


Figure 2.



Tables

Table 1. The rates of important events/ state transitions that were used in the model (ACS – acute coronary syndrome)

Parameter used in model	Value	Low Range of Sensitivity Analyses	High Range of Sensitivity Analyses	Distribution used in probabilistic analysis	Reference
Transition probabilities to and from heart failure					
Monthly incidence of heart failure with no recurrent ACS	0.50 %/23 months	0	0.0006	Beta	(35)
Heart failure incidence in month after ACS without stent thrombosis	4.60%	0.039	0.053	Beta	(35)
Heart failure incidence in month after ACS with stent thrombosis	20%/month	0.155	0.246	Beta	(36)
Probability of transition out of state of heart failure	57.40 %/year	0.488	0.660	Beta	(37)
Incidence of important clinical events					
Incidence of recurrent ACS over one year	7.48 %	0.071	0.079	Beta	(4)(5) (6)
Proportion of recurrent ACS due to stent thrombosis	20%	0	49.70%	Beta	(4)(5) (6)
Incidence of major bleed	3.9 %/year	0	0.255	Beta	(4)(5) (6)
Incidence of discontinuing clopidogrel	12.4 %/year	12.00%	12.80%	Beta	(4)(5) (6)
Incidence of discontinuing prasugrel	14.1 %/year	13.30%	14.90%	Beta	(4)(5)
Incidence of discontinuing ticagrelor	13.9 %/year	13.40%	14.40%	Beta	(4)(6)
Incidence of minor side effects with clopidogrel	14 %/year	13.40%	14.50%	Beta	(4)(5) (6)
Incidence of minor side effects with prasugrel	14.5 %/year	13.70%	15.30%	Beta	(4)(5)
Incidence of minor side effects with ticagrelor	19.8 %/year	19.00%	20.60%	Beta	(4)(6)

Table 2. Hazard/ odds ratios for clinically important events as employed in the model (ACS – acute coronary syndrome, HR – hazard ratio, OR – odds ratio)

Hazard ratios and odds ratios					
Parameter used in model	**Value**	**Low Range of Sensitivity Analyses**	**High Range of Sensitivity Analyses**	**Distribution used in probabilistic analysis**	**Reference**
HR for death post ACS, years 0-5	4.39	1.11	17.39	Log-normal	(18)
HR for death post ACS, years 5-10	3.1	0.93	10.33	Log-normal	(18)
HR for death post ACS, years 10-15	2.25	0.81	6.23	Log-normal	(18)
HR for death post ACS, years 15-20	2.17	0.80	5.88	Log-normal	(18)
HR for death post ACS, years 20-25	2.07	0.79	5.43	Log-normal	(18)
HR for death post ACS, years 25-30	1	N/A	N/A	N/A	Assumption
HR for death in the presence of heart failure relative to its absence	8.22	7.49	9.01	Log-normal	(38)
HR for death with clopidogrel relative to single antiplatelet	0.93 for 12 months	0.79	1.08	Log-normal	(19)
HR for death with prasugrel relative to clopidogrel	0.95	0.78	1.16	Log-normal	(4)(5)
HR for death with ticagrelor relative to clopidogrel	0.78	0.69	0.90	Log-normal	(4)(6)
HR for ACS with aspirin and clopidogrel relative to aspirin alone	0.77 for 12 months post ACS	0.67	0.89	Log-normal	(19)
HR for ACS with prasugrel relative to clopidogrel	0.75	0.66	0.85	Log-normal	(4)(5)
HR for ACS with ticagrelor relative to clopidogrel	0.84	0.74	0.94	Log-normal	(4)(6)
OR for stent thrombosis with single antiplatelet relative to clopidogrel	13.70 for 6 months post ACS	4.04	46.68	Log-normal	(39)
OR for stent thrombosis with prasugrel relative to clopidogrel	0.47	0.35	0.63	Log-normal	(4)(5)
OR for stent thrombosis with ticagrelor relative to clopidogrel	0.74	0.58	0.95	Log-normal	(4)(6)
OR for major bleeding with single antiplatelet relative to clopidogrel	0.88	0.48	1.64	Log-normal	(19)
OR for major bleeding with prasugrel relative to clopidogrel	1.46	1.15	1.85	Log-normal	(4)(5)
HR for major bleeding with ticagrelor relative to clopidogrel	1.09	0.92	1.14	Log-normal	(4)(6)

Table 3. Utilities and costs used in the model

Parameter used in model	Value	Low Range of Sensitivity Analyses	High Range of Sensitivity Analyses	Distribution used in probabilistic analysis	Reference
Utilities					
Utility of post ACS state in absence of heart failure	0.91	0.56	1.00	Beta	(23)
Utility of post ACS state in presence of heart failure	0.55	0	1.00	Beta	(23)
Utility decrement associated with ACS	0.18 for one month	0.10	0.26	Beta	(40)
Utility decrement associated with major bleed	0.16 for one month	0	0.57	Beta	(25)
Utility decrements of minor side effects	0.02	0	0.18	Beta	(40) (25)
Utility decrement associated with twice daily dosing for ticagrelor	0.0001	0	0.04	Beta	Assumption
Costs					
Monthly cost of post ACS state in presence of heart failure	$361.25	$220	$503	Gamma	(41)
Monthly cost of post ACS state in absence of heart failure	$165.25	$100	$230	Gamma	(41)
Hospitalization cost of ACS hospitalization	$9,774	$0	$32,404	Gamma	(21)
Hospitalization cost of major bleed	$10,805	$0	$38,255	Gamma	(21)
Physician billing during ACS hospitalization	$1,461	$1,417	$1,505	Gamma	(22), assumption
Physician billing during hospitalization for major bleed	$588	$560	$616	Gamma	(22), assumption
Monthly cost of clopidogrel	$20.09	$15	$25	N/A	(20)
Monthly cost of prasugrel	$80.96	$70	$92	N/A	(20)
Monthly cost of ticagrelor	$90.10	$79	101	N/A	(20)

ACS= Acute coronary syndrome

Table 4. Summary of cost effectiveness analysis for the base case

Strategy	Cost (95%CI)*	Incremental cost †	Effectiveness in QALYs (95%CI)	Incremental Effectiveness (QALY)	ICER ($/QALY) †
Clopidogrel	39,601 (8,343, 111,186)	-	7.41 (1.05, 14.79)	-	-
Prasugrel	40,422 (9,002, 112,574)	821	7.43 (1.06,14.79)	0.02	57,630 ‡
Ticagrelor	40,649 (9,327, 111, 881)	227	7.50 (1.12, 14.84)	0.07	12,205

* All costs are in 2012 Canadian Dollars
† compared to common reference of clopidogrel
‡ extendedly dominated
QALYs = Quality-adjusted life years; ICER = Incremental Cost-effectiveness ratio

Appendix 1. Summary of the range of parameter values used in the one-way sensitivity analyses, along with the incremental cost effectiveness ratios obtained with the parameters values at the extreme values used in each one-way analysis (* – compared to next less expensive agent. ICER= incremental cost effectiveness ratio; ACS= acute coronary syndrome)

Variable	Low range	ICER *, prasugrel	ICER *, ticagrelor	High range	ICER *, prasugrel	ICER *, ticagrelor
Starting age	37.50	143936	4475	86.50	24887	4056
Proportion of males	0.62	47718	3933	0.64	47529	3932
Transition probabilities to and from heart failure						
Monthly incidence of heart failure in the absence of recurrent ACS	0.00	47640	3917	0.01	47621	4360
Incidence of heart failure within 1 month after ACS without stent thrombosis	0.01	50801	3899	0.10	43568	3976
Incidence of heart failure within 1 month after ACS with stent thrombosis	0.16	49582	3916	0.25	45829	3950
Probability of transition from heart failure to being free of heart failure	0.49	46067	3976	0.66	4927	3895
Incidence of important clinical events						
Incidence of recurrent ACS	0.07	49229	3760	0.08	45934	4120
Incience of recurrent ACS in angioplasty without stenting	0.03	47623	3933	0.07	47623	3933
Proportion of recurrent ACS due to stent thrombosis	0.00	55166	3874	0.50	36609	4065
Incidence of major bleed	0.00	32438	6723	0.26	-13522	13935
Incidence of discontinuing clopidogrel	0.12	47291	3932	0.13	47964	3934
Incidence of discontinuing prasugrel	0.13	47198	3833	0.15	47977	4014
Incidence of discontinuing ticagrelor	0.13	47474	3977	0.14	47772	3887
Incidence of minor side effects with clopidogrel	0.13	47659	3933	0.15	47593	3933
Incidence of minor side effects with prasugrel	0.14	47570	3934	0.15	47677	3932
Incidence of minor side effects with ticagrelor	0.19	47628	3932	0.21	47616	3934
Hazard ratios and odds ratios						
Hazard ratio for death post ACS, years 0-5	1.11	90517	3994	17.40	29914	3843
Hazard ratio for death post ACS, years 5-10	0.93	47357	3822	10.33	47306	3839
Hazard ratio for death post ACS, years 10-15	0.81	47700	3827	6.23	47515	3829
Hazard ratio for death post ACS, years 15-20	0.80	47804	3828	5.88	47547	3828
Hazard ratio for death post ACS, years 20-25	0.79	47828	3828	5.43	47656	3828
Hazard ratio for death in the presence of heart failure relative to its absence	7.49	48680	3932	9.01	46600	3934
Hazard ratio for death with clopidogrel relative to single antiplatelet	0.79	50299	3943	1.08	45125	3923
Hazard ratio for death with prasugrel relative to clopidogrel	0.78	14814	4045	1.16	-3052	10842
Hazard ratio for death with ticagrelor relative to clopidogrel	0.69	52588	3923	0.90	3577	53780
Hazard ratio for recurrent ACS in with aspirin and clopidogrel relative to aspirin	0.67	48605	4336	0.89	47714	3990
Hazard ratio for recurrent ACS with prasugrel relative to clopidogrel	0.66	39491	5321	0.85	57952	2438
Hazard ratio for recurrent ACS with ticagrelor relative to clopidogrel	0.74	48421	2418	0.94	46834	5498
Odds ratio for stent thrombosis with single antiplatelet relative to clopidogrel	4.04	47732	3927	46.68	47547	3936
Odds ratio for stent thrombosis with prasugrel relative to clopidogrel	0.35	46744	3941	0.63	48804	3922
Odds ratio for stent thrombosis with ticagrelor relative to clopidogrel	0.58	47714	3921	0.95	47510	3948

Odds ratio for major bleeding with single antiplatelet relative to clopidogrel	0.48	47663	3768	1.64	47548	4246
Odds ratio for major bleeding with prasugrel relative to clopidogrel	1.15	37647	6212	1.85	60318	1076
Hazard ratio for major bleeding with ticagrelor relative to clopidogrel	0.92	47896	3189	1.14	47295	4826
Utilities						
Utility of post ACS state in absence of heart failure	0.56	78808	6200	1.00	43392	3485
Utility of post ACS state in presence of heart failure	0.01	45993	3927	0.99	49350	3750
Utility decrement associated with ACS	-0.26	47210.41	3939.04	-0.10	48045.55	3927.33
Utility decrement associated with major bleed	-0.57	48682.90	3917.30	0.00	47222.58	3939.43
Utility decrements of minor side effects	-0.18	47743.89	3992.70	0.00	47608.58	3925.88
Utility decrement associated with twice daily dosing for ticagrelor	-0.04	39337.61	9535.17	0.00	47920.45	3866.38
Costs						
Monthly cost of post ACS state in presence of heart failure	220.00	47737.15	3859.10	503.00	47492.26	4018.85
Monthly cost of post ACS state in absence of heart failure	100.00	46903.85	2972.17	230.00	48658.46	4677.67
Hospitalization cost of ACS hospitalization	0.00	60196.03	1859.20	32404.00	18514.24	8735.16
Hospitalization cost of major bleed	0.00	33525.35	6561.80	38255.00	-3280.38	12555.47
Physician billing during ACS hospitalization	1417.00	47841.13	3818.86	1505.00	47727.93	3837.54
Physician billing during hospitalization for major bleed	560.00	47745.90	3835.40	616.00	47823.17	3820.99
Monthly cost of clopidogrel	15.00	51359.88	3934.07	25.00	44019.40	3932.34
Monthly cost of prasugrel	70.00	38591.34	6046.17	92.00	56721.74	1804.79
Monthly cost of ticagrelor	79.00	48453.12	1768.06	101.00	46808.98	6059.31