Article details: 2015-0056	
Title	Cost-Effectiveness of Clopidogrel, Prasugrel, and Ticagrelor for Dual Antiplatelet Therapy after Acute Coronary Syndromes: a decision-analytic model
Authors	Abdel-Qadir MD, Idan Roifman MD, Harindra C. Wijeysundera MD
Reviewer 1	Dr. Sophia Papadakis
Institution	University of Ottawa Heart Institute
General comments (author response in bold)	This is an excellent paper describing the results of a robust economic evaluation of Clopidogrel, Prasugrel and Trcagrelor. This area of research has important implications to clinical practice and decision makers in the publicly funded Canadian Health Care System. The methods are well described and tables provide excellent detail of main analysis and sensitivity analysis. Please ensure ICER is defined in the abstract. **We thank the Reviewer for this kind assessment of our work. We have now defined ICER in the abstract (see abstract, page 2, line 16):** **"The incremental cost-effectiveness ratio (ICER) for ticagrelor relative to clopidogrel was $12,205 per QALY gained."**
Reviewer 2	**Dr. Narendra Singh**
Institution	
General comments (author response in bold)	Overall a well-designed and thought out paper that adds useful information needed by physicians, patients and payers to make appropriate decisions. **We thank the reviewer for this kind assessment of our work** The event rates in the clopidogrel arm in Triton TIMI 38 has to be considered with caution since the loading dose of 300mg is no longer used and 600mg has become the norm. At least in PLATO the 600mg option was available **We agree with the reviewer and have now added this to our limitations section. Please see our response to the editor's comment #1 for further details.** Figure 1 is confusing and does not help simplify the model. Please redesign to be more informative. Why does death have an arrow on itself? Figure 2 however s very good and illustrates the robustness of the conclusion **We have now modified this figure. Please see our response to copyediting comment #5 above. Please note that death has an arrow onto itself because it is an absorbing state, and patients remain in that state after entering it.** The model is too simple in that not all major bleeds are the same. The more potent P2y12 inhibitors also cause more intracranial bleeding which is a complication on par with death in the minds of many pts and physicians **We agree with Dr. Singh that all major bleeds are not the same, and have different impacts on mortality. We were particularly keen to capture the impact of the different agents on mortality when designing the model. We have done so by incorporating direct estimates of the relative differences in all-cause mortality from the Phase III trials into each stage of the model. This would take into account the contribution to mortality from the competing risks of all the effects for the drugs being studied. Similarly, we could not determine which bleeds would lead to drug discontinuation and which ones would not, so we used estimates of drug discontinuation for any reason into each stage of the model. Thus, the nodes in the model dealing with major bleeds only contributed cost and utility decrements to the cost-effectiveness estimates with overall mortality being accounted for earlier in the model.** **Moreover, the incidence of intracranial bleeds was quite low overall in the Phase III trials. In TRITON-TIMI, the incidence was 0.3% in both the prasugrel and clopidogrel arms, with a hazard ratio of 1.12 (95% CI 0.58–2.15, p-value 0.74). In PLATO, the incidence of intracranial bleeds was 26 events among 9235 patients in the ticagrelor arm (0.3%) versus 14 events among 9186 patients in the clopidogrel arm (0.2%), corresponding to a hazard ratio of 1.87 (95% CI 0.98–3.58, p-value 0.06). This translates to a number needed to harm of 774. We expect the degree of harm due to this absolute difference in risk of intracranial bleeds would be encapsulated within the range that was employed for the sensitivity analysis for the hazard ratios of mortality associated with ticagrelor (best estimate 0.78, range 0.69 - 0.90) and prasugrel (best estimate 0.95, range 0.78 to 1.16). We noted that the benefit associated with ticagrelor would no longer be cost effective if the hazard ratio for mortality with ticagrelor relative to clopidogrel exceeded 0.89.** **That being said, we acknowledge that this is a limitation and have this altered the limitations section to include the following statement:** **(see Page 14, lines 15-18)** **"In addition, we did not explicitly distinguish between different types of major bleeds in the model. However, we did account for their cumulative impact on mortality and discontinuation rates by employing direct estimates of the relative risk of those events from Phase III clinical trials data."** The model determines cost effectiveness in a 62 yr old male. Modelling for younger and older pts would also be useful as I think the benefit will vary **Our model was probabilistic, and as such, the overall primary results were the average of 10,000**

	simulations of the model, with parameters for each iteration obtained from the distribution for the parameter. For age, we used a normal distribution with a mean of 62 years, but a standard deviation of 12.5 years. In addition, the base case population was not exclusively male – 39% of the population were female. As such, the overall results reflect the distribution of patients (by age and sex) in the studies. We have modified the methods to more clearly reflect this. In addition, as requested by this reviewer and the editors, we conducted scenario analyses at different ages. Please see the response to Comment #3 from the editors for further details.
	In the US, the cost differential between clopidogrel and the new agents is significantly greater and therefore the generalizability outside Canada is more limited. Also, prasugrel comes off patent in a year or two which will also impact the conclusions in the future.
	Thank you for bringing up this important limitation in our study. We have added it to the limitations section.
	(see page 14, lines 18-22):
	Finally, our results and conclusions are based on the current price of the three agents in Ontario in 2015. These findings may not be generalizable to other jurisdictions. Further, in the future when the agents come off patent protection there will likely be a significant change in price which would alter our results.
Reviewer 3	**Dr. Jeffrey A Bakal**
Institution	**University of Alberta**
	Overall Abdel-Qadir et al. have assembled a good summary of their cost-effectiveness analysis for Clopidogre1, Prasugrel and Tricagalor. I would suggest a couple modifications to help describe the study better.
	We thank the reviewer for this kind assessment of our work.
	I found the text describing the model easy to understand, Figure one was a little more difficult to work through. Can you add some additional info and restructure it to show clearly where the patient enters, the transitions and then the final state (healthy, HF, Death?)
	We thank the reviewer for these comments. Please see our response to the copy-editor's comments above.
	The description of the results with both cost, QALY and cost per QALY repeated almost verbatim in the Abstract, MS and Table is a little redundant.
	We thank the reviewer for this suggestion to improve our paper. We have edited our Results section to eliminate some of the redundancy.
	(Please see page 10, lines 6-17):
	Clopidogrel treatment resulted in the lowest effectiveness at 7.41 QALYs (95% CI 1.05-14.79) and 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) and a cost of $40,422 (95% CI 9,002-111,881), for an ICER of $57,630 per QALY gained, compared to clopidogrel. Ticagrelor had an effectiveness of 7.50 QALYs (95% CI 1.13-14.84) at a cost of $40,649 (95% CI 9,327-111,881) for an ICER of $3,167 per QALY gained, when compared to prasugrel. Prasugrel was therefore extendedly dominated by ticagrelor. When compared to clopidogrel, the ICER of ticagrelor was $12,205 per QALY gained (see Table 4). 90% of the 10,000 simulations showed that ticagrelor was the preferred agent at a willingness to pay (WTP) threshold of $50,000/QALY. When the WTP threshold was raised to $100,000/QALY, 92% of the simulations showed ticagrelor to be the preferred agent (see figure 2).
	Some additional discussion of the crossovers in willingness to pay, as well as some additional discussion around the impact of sensitivity analyses may be useful, including the baseline risk to an individual patient.
	The reviewer raises a number of important points. In terms of willingness to pay, the probabilistic sensitivity analyses suggests that our results would be robust at a wide range of willingness to pay from $20,000 per QALY gained to $100,000 per QALY gained. This is across the range of willingness to pay that is used by most regulatory agencies. We agree that our estimates were derived from population estimates from trials, and that we did not account for individual patient variability, specifically individual baseline risk. To do so would require a patient-level microsimulation. We have modified the limitations section to acknowledge this limitation.
	(see page 14, line 1-5)
	"Second, our model was a Markov cohort, and therefore applies to the general population of acute coronary syndrome patients undergoing revascularization. We did not account for individual patient variability in terms of baseline risk. Such variability may impact the overall cost-

	effectiveness of an agent. Investigating such subgroups should be a focus for future research.