AN ECONOMIC EVALUATION OF TICAGRELOR AS COST-EFFECTIVE DRUG FOR ACUTE CORONARY SYNDROMES: Australia Healthcare System Perspective

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Abstract

Background: Ticagrelor, an oral antiplatelet therapy has its function to prevent an atherothrombotic events in acute coronary syndromes (ACS) patients. This drug was registered on Therapeutic Goods Administration (TGA) Australia on 21 June 2011 for use in combination with aspirin (Pharmaceutical Benefits Advisory Committee (PBAC) 2011). Meanwhile, Clopidogrel as the comparator, is the current treatment guidelines for use after recent MI or stroke, in the presence of established arterial disease, and in acute coronary syndrome. The aim of this article is to analyses the current evidence regarding the safety, efficacy and effectiveness of ticagrelor.

Method: Keywords searching through MEDLINE Ovid and EBSCO database and additional references from retrieved articles.

Result: There is statistically significant difference between ticagrelor and clopidogrel [hazard ratio: 0.84 (95% CI: 0.77-0.92)]. The quality of the evidence from the study is reliable considering the validity of data sources used; the provision of sensitivity analysis; the time horizon which is long enough; the complex model use (markov model); the discounting rate recommended by Australian authorities and World Health Organization (WHO); and the PLATO design which is a prospective, randomised, and double-blind trial become an adding value in the quality of evidence. Cost-utility analysis (CUA) is used as economic evaluation of ticagrelor compare with clopidogrel. CUA combine the estimated quality-adjusted life-year (QALY) gains with the estimated difference in resource costs and the result will be described as incremental cost-effectiveness ratio (ICER).

Conclusion: The combination of ticagrelor with aspirin is superior to clopidogrel with aspirin in preventing Myocardial Infarction (MI) and vascular death. The economic evaluation suggest that ticagrelor compared with clopidogrel is likely to represent a cost-effective on preventing the morbidity and mortality to the ACS patients from the Australian health care system context.

Keywords: *Ticagrelor, antiplatelet therapy, cost effectiveness, acute coronary syndromes*.

TICAGRELOR AS THE NEW HEALTH TECHNOLOGY

The potential impacts of ticagrelor on the Australian health budget and costs to consumers are still erratic. Ticagrelor might be used not only in ACS patients but also in any other cases so that it may impact to the high costs to the Australian health budget and to the consumers. Meanwhile, due to the adverse events associated with ticagrelor (an increasing of non-Coronary Artery Bypass Grafting bleeding), the use of ticagrelor probably less than the prediction, hence it may reduce the costs burden of the Australian health budget or costs to consumers.

Ticagrelor is an oral antiplatelet therapy which is used to prevent an atherothrombotic events in acute coronary syndromes (ACS) patients. This drug is a reversible and direct-acting oral P2Y12-receptor antagonist that provide greater and more consistent platelet inhibition than clopidogrel with more rapid onset and offset of action[1,2]. Ticagrelor was registered on Therapeutic Goods Administration (TGA) Australia on 21 June 2011 for use in combination with aspirin (PBAC 2011). As the comparator, Clopidogrel which is an antiplatelet drug, is the current treatment guidelines that has approved indications for use after recent MI or stroke, in the presence of established arterial disease, and in acute coronary syndrome[3,4]. Canon et al. (2010) claimed that patients given ticagrelor had significant and clinically relevant reduction in cardiovascular and total deaths without an increase in risk of major bleeding. While clopidogrel has critical risk of ischaemic events and it does not has benefit of pre-treatment for patients undergoing PCI (Percutaneous Coronary Intervention). According to this finding and other similar studies, it is therefore imperative to assess the cost-effectiveness of the new technology that is ticagrelor, whether this new treatment is cost-effective or not in Australia setting.

There are two articles that will be analysed in this article regarding the cost-effectiveness of ticagrelor compare with clopidogrel. First article is from Liew et al. (2013) (C*ost-Effectiveness of 12-month treatment with ticagrelor compared with clopidogrel in the management of acute coronary syndromes*), their research was conducted in the contemporary Australian setting and published in Elsevier HS Journals Clinical Therapeutics. While the second article which is derived from European Heart Journal is Nicolic et al. (2013) (*Cost-Effectiveness of treating acute coronary syndrome patients with ticagrelor for 12 months: results from the PLATO study*) which is conducted in Swedish setting in the base-case analysis. These two economic studies are conducted based on PLATO study where it randomised 18,624 ACS patients with or without ST-segment elevation (average age 62 years) to received either ticagrelor or clopidogrel.

THE EVIDENCE FOR THE SAFETY, EFFICACY AND EFFECTIVENESS OF TICAGRELOR

The efficacy and effectiveness of Ticagrelor in ACS was assessed in the PLATO trial which result ticagrelor was associated with a reduction risk of MI, stroke or vascular death with hazard ratio 0.84 [95% CI, 0.77-0.92][4]. Similarly, Nicolic et al. (2013) clarified that ticagrelor compared with clopidogrel significantly reduce the rate of the composite endpoint of death from vascular causes, MI, or stroke without an increase in the rate of overall major bleeding[11]. In terms of safety, Liew et al. (2013) claimed that there is no significant difference in the rates of major bleeding between ticagrelor and clopidogrel groups. Yet there is a report that ticagrelor is associated with a higher rate of major bleeding not related to coronary artery bypass grafting (CABG). Based on those studies, it can be concluded that Ticagrelor is a relatively safety drug which significantly more effective compare with clopidogrel in treating patients with ACS.

THE ECONOMIC EVALUATION USED & THE MODELLING APPROACH

The studies used cost-utility analysis as economic evaluation. It combined between QALYs gain and resources costs. Cost-utility analysis is the appropriate method as it determine what value is adhered to specific health states, hence it enhances the transparency of resource allocation processes[5]. The estimated QALY per patient were 5.754 for ticagrelor and 5.676 for clopidogrel in 10-year model time horizon. While the treatment costs of an ACS patient by using ticagrelor is A$19,132 and A$18,428 for clopidogrel (Australian dollars 2010/2011 prices). Thus, the base case ICER per QALY gained is A$9031. Liew et al. (2013) provided detail calculation in their analysis based on health state and a number of key underlying parameters which tested in sensitivity analyses.

Both Liew et al. (2013) and Nicolic et al. (2013) in their studies were utilised Markov model to simulate the long-term costs and outcomes. Markov model structure in these studies are based on the key clinical outcomes of PLATO (free from further ACS events, MI, stroke, and death). This model is used for 12 months (the duration of PLATO trial) and 10 years to estimate the long-term cost and health outcomes. Within the Markov analysis, the ticagrelor group living longer and have a better quality of life than those in the clopidogrel group.

THE OUTCOME MEASURES IN THE KEY CLINICAL EVIDENCE

By using markov model, the four subjects are assigned a specific utility value for the time they spent in a given health state. Utility value

is 0.880 for the event free-state, 0.811 for (recurrent) MI, and 0.663 for stroke. The QALY derived by multiplying the utility values for each health state or subjects by the time spent in that health state and then summing the result over the 10-year time horizon. The QALY gain will be combined with the estimated costs of ticagrelor and clopidogrel. Subsequently, through CUA it will be translated in the economic evidence as incremental cost-effectiveness ratio (ICER).

THE TYPES OF RESOURCE USE IN THE ECONOMIC EVALUATION

There are four resources use in the economic evaluation of ticagrelor which should be considered in the economic evaluation. First is primary drug intervention which are 180mg/day of ticagrelor (plus aspirin) for 246 days and 75mg/day of clopidogrel (plus aspirin) for 250 days. Second resource is other drug therapies such as statins, beta-blockers, and ACE inhibitors. Third resource is medical services (an annual stress test, cardiologist visit, General Practitioner visit and blood test). The last resource is other cost such as concomitant medications and other ambulatory services. The estimation of all resources costs have been included in the economic evaluation based on the four health states and specifically divided into acute and maintenance therapy. The cost for ticagrelor only is A$1081 and A$506 for clopidogrel, yet the total costs for ticagrelor in ACS management (including all the type of resources) is A$19,132 and A$18,428 for clopidogrel. It is obvious that Liew et al. (2013) has well considered the resources use in the economic evaluation of the new technology.

THE APPLICABILITY OF THE EVIDENCE TO THE AUSTRALIAN CONTEXT

Liew et al. (2013) study is conducted in the contemporary Australia setting so that the study result is applicable to be implemented in Australian context. Moreover, the study used individual patient-level data from the PLATO trial and contemporary Australian-specific estimates of disease cost that allow for more precise estimation of the incidence of ACS as well as the benefit of ticagrelor compare with clopidogrel.

KEY SOURCES OF UNCERTAINTY AND ASSUMPTIONS

Liew et al. (2013) assumed the duration of the treatment is 12 months as per PLATO trial. They assumed that the benefits of ticagrelor ceased once the drug was discontinued, meanwhile there is possibility that some patients will continue consuming ticagrelor more than 12 months. Another limitation is that they also assumed the occurrence of MIs and strokes only count in one cycle and or allowed to occur once during the model time horizon whereas in fact recurrent MIs and strokes are common.

These assumptions may impact to the analysis that underestimated the benefits and the cost-effectiveness of ticagrelor. However, the study has provided sensitivity analysis to explore the impact of potential sources of bias and uncertainty on the results of the economic analysis.

THE FINDINGS IN RELATION TO COST-EFFECTIVENESS OF THE TECHNOLOGY AND THE QUALITY OF THE EVIDENCE

The analysis from Liew et al. (2013) suggest that ticagrelor compared with clopidogrel is likely to represent a cost-effective on preventing the morbidity and mortality to the ACS patients from the Australian health care system context. It can be seen that the QALY gain for ticagrelor is 0.078 higher than clopidogrel and the ICER is A$9031 (base case) and less than A$15,000 per QALY (univariate sensitivity analysis) which represent acceptable cost effectiveness.

The quality of the evidence from the study could be assessed based on several elements that contribute to the outcome. The data provided are sufficient and relevant in order to estimate the QALY and costs. Other elements that should be considered in assessing the quality of the evidence are the provision of sensitivity analysis that strengthen the quality of the economic evaluation; the time horizon which is long enough to capture all relevant differences in future cost and outcomes[6]; the complex model use (markov model); and the discounting rate. Liew et al. (2013) study used 5% discount rate as recommended by Australian authorities, this is in accordance with the WHO (2003) recommendation that the standard practice in most cost-effectiveness studies to discount future health benefits at the same rate as costs, a rate between 3% and 5% per year[7]. Further, the PLATO was a prospective, randomised, and double-blind trial where it is become adding value in the quality of evidence, as randomisation enhances the comparability of the different study groups and provides a valid basis for inferring that the intervention actually caused any observed difference in outcome between the groups[1,8].

POTENTIAL IMPACTS ON THE AUSTRALIAN HEALTH BUDGET AND COSTS TO CONSUMERS

The potential impacts of ticagrelor on the Australian health budget and costs to consumers are still erratic. Ticagrelor might be used not only in ACS patients but also in any other cases so that it may impact to the high costs to the Australian health budget and to the consumers[9]. Meanwhile, it should also be noted that due to the adverse events associated with ticagrelor (an increasing of non-CABG bleeding), the use of ticagrelor probably less than the prediction, hence it may reduce or have no significant impact to the Australian health budget or costs to consumers.

CONCLUSION

It is recommended to use ticagrelor as a drug of choice for the treatment of acute coronary syndrome in combination with aspirin on the basis of acceptable cost-effectiveness compared with the current drug (clopidogrel plus aspirin). The two studies of economic evaluation regarding ticagrelor has met the standard criteria of health economic evaluation as recommended in Consolidated Health Economic Evaluation Reporting Standards (CHEERS)[10]. The economic evaluation used and the modelling approach is reliable and appropriate to evaluate the cost-effectiveness of ticagrelor. Regarding the potential impacts on the Australian health budget, it is necessary to make a collaboration amongst PBAC, department of health and other stakeholders (sponsor, health insurance) regarding the potential use of ticagrelor to non ACS patients.

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