Increasing the Methodological Quality and Relevance of Cost effectiveness Analysis

Doug Coyle, MA, MSc, PhD1

1 School of Epidemiology, Public Health and Preventive Medicine, Faculty of Medicine, University of Ottawa, Canada

Address for Correspondence

Doug Coyle

School of Epidemiology, Public Health and Preventive Medicine.

University of Ottawa,

451 Smyth Road,

Ottawa, Ontario,

Canada K1H 8M5

Phone: 613 562-5800 ext 8690

Fax: 613 562-5465

Email: dcoyle@uottawa.ca

Conflict of Interest Statement: The authors report no conflict of interests.

Key words: cost effectiveness, oral anticoagulants

The article by Hernandez and colleagues in this edition of the journal is a good example of a methodologically sound cost effectiveness analysis (1). Given the scarcity of health care resources and that most patients do not pay for health care at the point of consumption, alternative mechanisms are required for making health care resource allocation decisions.

Cost effectiveness analysis provides an analytical framework for assessing the costs and benefits of interventions thus providing information to facilitate such decisions. Cost effectiveness analysis incorporates both concerns for efficiency and concerns for equity, with the assumption that society will value health gains the same irrespective of which individuals accumulate such gains. Through the correct application and interpretation of such analyses, efficient and equitable allocation decisions can be made leading to improved levels of health across our population.

Despite the increasing adoption of these techniques in decision making and the increasing volume of related publications, concerns with the methodology and potential bias within cost effectiveness analysis have been raised (2). This has been particularly pertinent due to the preponderance of industry sponsored studies within the literature, whose result generally favour the sponsor's product. The article by Hernandez and colleagues is independent of industry sponsorship which provides some comfort given the potential biases identified in industry sponsored studies. (3, 4) This is illustrated by the conflicting results within the current paper when compared to a previous study with direct industry sponsorship (5). It should be noted that in the previous study published in the American Heart Journal, although co-authors have industry affiliations, no direct statement of conflict of interest is made highlighting a continued difficulty in assessing the independence of published studies.

The article provides an illustration of the conduct of three methodological developments within the area of cost effectiveness analysis; the conduct of stratified analysis; of probabilistic analysis and of sequential analysis.

Within the paper, results are provided for two patient strata: patients with creatinine clearance between 50 and 95ml/min and patients with creatinine clearance >95ml/min. Results are derived by running the analysis including edoxaban for patients in the former category and excluding edoxaban for patients in the latter category. Stratified cost effectiveness analysis is extremely insightful for decision makers, as cost effectiveness is often not a binary response across an entire patient population (6, 7). Rather it is conditional upon a number of factors relating to the nature of the patient population. Decision-makers have recognized the likely heterogeneity in cost effectiveness by making differential funding decisions within a patient population. Stratified analysis is required which parses a population into smaller, more homogeneous subgroups; with analysis conducted for each distinct subgroup. It provides not only richer information to decision makers but a more precise estimate of cost effectiveness (8)

The present analysis does not assume that parameter values will change across the two subgroups considered. This is not a preferred approach. If stratified analysis is required, it is preferable that where heterogeneity in input parameters is recognised, it should be fully incorporated (7). Heterogeneity may relate to differences in all or merely a subset parameters within the model. In the analysis, there are instances where data is likely to vary across potential subgroups and rather than the heterogeneity recognized through appropriate stratification; data are combined. For example, the annual probability of extracranial bleeding is available for HAS-BLED score 3, 4 and 5. It would have been informative to

conduct analysis based on stratification by HAS-BLED score both to provide richer context to the results and a more precise estimate of the cost effectiveness across the patient population.

The analysis by Hernandez and colleagues incorporates probabilistic sensitivity analysis (PSA). Within a PSA, data parameters are not presented by point estimates but through probability distributions which characterize their underlying uncertainty. Probabilistic analysis is conducted through a Monte Carlo simulation whereby costs and outcomes for each alternative are obtained by re-running the model using random parameter values drawn from each parameter's prescribed probability distribution. This is repeated a number of times (in this example 10,000 times) and the expected values of costs and effects are estimated. (9) The results of the PSA are presented through a Cost Effectiveness Acceptability Curve which graphically presents the probability that each alternative is optimal for different values of a quality adjusted life year (QALY). (9) The methodology adopted by Hernandez and colleagues is of a high standard. The choice of distributions and methods for deriving expected values all meet desired standards.

There are strong arguments that probabilistic analysis should not be relegated to a sensitivity analysis but rather should be the basis for the primary analysis. This is due to the potential likely non-linear relationships between parameters and expected values, leading to the likelihood that probabilistic analysis will give different estimates than a simple deterministic analysis (10). Thus, deterministic analyses can lead to non-optimal decisions (11). Given the characteristics of decision analytic models in health care, especially Markov models, there is potential for discordance between the results of probabilistic models and deterministic models. It is hoped that future cost effectiveness analyses

published within the journal are encouraged to use probabilistic analysis as the basis for the primary results.

To facilitate decision maker`s determination of the optimal therapy, Hernandez and colleagues present their results through a sequential analysis (12). The purpose of cost effectiveness analyses is to allow decision makers to determine which therapy is optimal – that is, to identify which option is the best use of our scarce health care resources. Analyses rarely can definitively determine which therapy is optimal as that is determined by a decision makers threshold in terms of their willingness to pay for a unit of health benefit (i.e. QALY)`- henceforth lambda.

With a sequential analysis, one first removes all dominated (i.e. therapies that are more costly and less beneficial) from consideration. For this analysis, dabigatran and rivaroxaban are removed. Thus, only the following strategies are potentially optimal; warfarin, apixaban and edoxaban. Which is optimal is ultimately a function of lambda. A sequential analysis presents a sequence of incremental cost effectiveness ratios (ICER) for a less costly comparator compared to the next most costly comparator; excluding all dominated comparators. In the analysis for patients with creatinine clearance between 50 and 95 ml/min, the ICER for edoxaban versus warfarin is $77,565 and, for apixaban versus edoxaban, it is $108,631. Thus, the analysis facilitates a decision, in that if the decision maker`s lambda is less than $77,565 warfarin is optimal, if it is greater than $108,631 apixaban is optimal and if it lies in between edoxaban is optimal.

Thus, the interpretation of analyses is highly dependent on a decision maker`s lambda. The valuation of lambda however is a controversial topic. Many authors have cited thresholds of either $50,000 or $100,000 per QALY for US decision makers (13). Recently arguments have been made to increase the threshold based on both the World Health Organization`s stance on this issue and on historical research relating to the value of health gains from medical care (13, 14). These analyses have suggested lambda between $100,000 and $297,000.

Such approaches ignore that health care decisions, whether they are made within a public or private based insurance system, work within a constrained budget. Therefore, lambda should represent; what we forego by funding one technology rather than another; i.e. the opportunity cost of investing in one health care intervention over, another given current rates of expenditure. Thus, to provide efficient and equitable health care, decision makers must actively identify or search for the relevant threshold not as suggested above, set such a threshold as suggested above (15)

Recent work from the UK has attempted to estimate lambda empirically (16). The results from this analysis suggest a value of lambda substantially lower than those suggested above. Based on expenditure in 2008, the value of lambda was £12,936 per QALY. Based on a simple currency conversion for this threshold none of the newer oral anticoagulants can be considered cost effective. Whether such a threshold is a close approximation for an appropriate value of lambda for US decision makers will depend on a variety of factors including the relative efficiency of the health care system and the relative levels of health care expenditure.

Decision makers who are unhappy with the value of a QALY identified by research such as that conducted by Claxton and colleagues must recognise that failure to adopt such thresholds ultimately means that other patients will bear the opportunity costs of such inefficient and inequitable decisions. There is of course a solution to raising the value of lambda; increased health insurance premiums or tax revenue devoted to health care.

In conclusion, the cost effectiveness analysis presented in this issue of the journal is a good contribution highlighting the methodological developments in the area. It is hoped that further research will fully embrace both the use of probabilistic and stratified analyses, whilst further methodological research will help in the search for the true value of a QALY.

References

1. Hernandez I, Smith KJ, Zhang Y. Cost-Effectiveness of non-vitamin K antagonist oral anticoagulants for stroke prevention in patients with atrial fibrillation at high risk of bleeding and normal kidney function. Thrombosis Research.
2. Kassirer JP, Angell M. The Journal's policy on cost-effectiveness analyses. The New England Journal of Medicine. 1994;331(10):669-670.
3. Bell CM, Urbach DR, Ray JG, Bayoumi A, Rosen AB, Greenberg D, Neumann PJ. Bias in published cost effectiveness studies: systematic review.BMJ. 2006 Mar 25;332(7543):699-703
4. Garattini L, Koleva D, Casadei G. Modeling in pharmacoeconomic studies: funding sources and outcomes. Int J Technol Assess Health Care2010;26:330-3.
5. Magnuson EA, Vilain K, Wang K, Li H, Kwong WJ, Antman EM, Ruff CT, Giugliano RP, Cohen DJ; ENGAGE AF–TIMI 48 Trial Investigators. Cost-effectiveness of edoxaban vs warfarin in patients with atrial fibrillation based on results of the ENGAGE AF-TIMI 48 trial. Am Heart J. 2015 Dec;170(6):1140-50.
6. Coyle D, Buxton MJ, O'Brien BJ. Stratified cost-effectiveness analysis: a framework for establishing efficient limited use criteria. Health Economics 2003; 12:421-427.
7. Sculpher M. Subgroups and heterogeneity in cost-effectiveness analysis. Pharmacoeconomics 2008; 26 (9): 799-806 .
8. Zaric GS. The impact of ignoring population heterogeneity when Markov models are used in cost-effectiveness analysis. Med Decis Making. 2003 Sep-Oct;23(5):379-96.
9. Briggs AH. Handling uncertainty in cost-effectiveness models. Pharmacoeconomics. 2000; 17:479-500.

10. Claxton K, Sculpher M, McCabe C, Briggs A, Akehurst R, Buxton M, Brazier J, O'Hagan T. Probabilistic sensitivity analysis for NICE technology assessment: not an optional extra. Health Econ. 2005 Apr;14(4):339-47.
11. Thompson KM, Graham JD. Going beyond the single number: using probabilistic risk assessment to improve risk management. Human and Ecological Risk Assessment 1996;2:1008-1034.
12. Karlsson G, Johannesson M. The decision rules of cost-effectiveness analysis. Pharmacoeconomics. 1996 Feb;9(2):113-20.
13. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness--the curious resilience of the $50,000-per-QALY threshold. N Engl J Med. 2014 Aug 28;371(9):796-7
14. Braithwaite RS, Meltzer DO, King JT Jr, Leslie D, Roberts MS. What does the value of modern medicine say about the $50,000 per quality-adjusted life-year decision rule? Med Care. 2008 Apr;46(4):349-56.
15. Culyer A, McCabe C, Briggs A, Claxton K, Buxton M, Akehurst R, Sculpher M, Brazier J. Searching for a threshold, not setting one: the role of the National Institute for Health and Clinical Excellence. J Health Serv Res Policy. 2007 Jan;12(1):56-8.
16. Claxton K, Martin S, Soares M, Rice N, Spackman E, Hinde S, Devlin N, Smith PC, Sculpher M. Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold. Health Technol Assess. 2015 Feb;19(14):1-503