Adherence to Guidelines for Sensitivity Analysis: Cost-effectiveness Analyses of Dual Oral Antiplatelet Therapy

Josephine Mauskopf,[1] Claude Schmitt,[2] Kristina S Boye,[3] Patrick L McCollam,[3] Melissa Juniper,[1] Julie A Birt[3]

[1]RTI Health Solutions, Research Triangle Park, NC, United States;

[2]Eli Lilly and Company Ltd, Windlesham, United Kingdom; [3]Eli Lilly and Company, Indianapolis, IN, United States

ABSTRACT

OBJECTIVES: Cost-effectiveness analyses of new treatments for cardiovascular disease frequently require input parameters whose values are known with uncertainty. The objective of this study is to determine the extent to which published uncertainty analyses adhere to Health Technology Assessment (HTA) guidelines.

METHODS: We performed a systematic review of published cost-effectiveness analyses for an example drug treatment scenario, dual oral antiplatelet therapy compared with aspirin alone following acute coronary syndromes (ACS) and/or percutaneous coronary intervention (PCI). We searched for articles published in English from 1997 to mid-2008 in PubMed, the Cochrane Collaboration, EMBASE, and the Health Economic Evaluation Database (HEED). A total of 191 articles were identified: PubMed, 40; Cochrane Collaboration, 27; EMBASE, 114; HEED, 10. Of these, 106 articles were unique, and 16 were included in this review; all selected articles compared clopidogrel plus aspirin with aspirin alone in patients with ACS and planned PCI. We created evidence tables to show the sensitivity of the cost-effectiveness estimates to changes in the input parameter values, as well as the data sources used for the reference-case and alternative estimates for different input parameter values. We also examined the extent to which the uncertainty analyses adhered to HTA guidelines.

RESULTS: Cost-effectiveness ratios were most sensitive to changes in the efficacy of dual antiplatelet therapy and reference-case model assumptions about costs beyond the trial period. Although the alternative values tested in the uncertainty analyses for some input parameters were based on observed ranges or distributions, the alternative values tested for many other input parameters were assumed without justification.

CONCLUSIONS: The uncertainty analyses of the cost-effectiveness studies of dual oral antiplatelet therapy were not fully adherent with HTA guidelines. In particular, long-term costs and benefits were not always included in the reference case, resulting in varying anchor points for the sensitivity analysis, and the ranges used for the clinical and cost parameters represented different levels of uncertainty about the true value.

BACKGROUND

Guidelines On Uncertainty Analysis

Guidance for uncertainty analyses has been developed by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR),[1] the United Kingdom (UK),[2] and Canada.[3] There are different types of uncertainty analyses, all of which should be completed as part of a cost-effectiveness analysis (Table 1).

Table 1. Characteristics of Different Types of Uncertainty Analysis

Type of Uncertainty Analysis	Description	Recommended Presentation
One-way sensitivity analysis	Changing input parameter values that are estimated with uncertainty one at a time through a range of values	Table or tornado diagram
Multiway sensitivity analysis	Changing input parameter values that are estimated with uncertainty two or more at a time through a range of values	Two-dimensional graph
Probabilistic sensitivity analysis	Changing all input parameter values that are estimated with uncertainty at the same time using random draws from probability distributions for each variable	Scatter plot and cost-effectiveness acceptability curve
Variability analysis	Changing model structure or input parameter values that represent patterns of care or patient characteristics	Table

Dual Antiplatelet Therapy

In 2005 in the United States (US), there were 772,000 ACS discharges as the first-listed diagnosis and 1,413,000 discharges including secondary diagnoses.[4] Drugs that are able to counter the aggregation of platelets are valuable in the treatment of people experiencing an ACS episode.

Recent studies of dual antiplatelet regimens that include clopidogrel plus aspirin[5,6,7] have shown superior efficacy to aspirin alone. Based on the results of the clopidogrel clinical trials, cost-effectiveness analyses have been completed comparing dual oral antiplatelet therapy with aspirin alone.

Including uncertainty analyses as part of the cost-effectiveness analyses of dual oral antiplatelet therapy is important for ensuring that decision makers have the most accurate information possible when making treatment decisions.

METHODS

Overview

In this poster, we present the results of a systematic review of published cost-effectiveness analyses of dual oral antiplatelet therapy compared with aspirin alone following ACS and/or PCI.

The review examines the sensitivity of the cost-effectiveness estimates to changes in the model structure, assumptions, and input parameter values. The data sources used for the reference-case and uncertainty analyses for different input parameter values also are examined.

Based on this review, the extent to which the uncertainty analyses in these studies adhere to HTA guidelines, in particular those from ISPOR, the National Institute for Health and Clinical Excellence (NICE), and the Canadian Agency for Drugs and Technologies in Health (CADTH), is determined. Possible implications of nonadherence to these guidelines also are explored.

Search Strategy

The following medical literature databases were searched: PubMed, Cochrane Collaboration, EMBASE, and HEED. The literature search strategy was limited to articles published in English from 1997 to mid-2008 that reported on studies conducted in humans.

The search strategy included search terms relating to ACS, antiplatelet drugs, and costs and cost-effectiveness analysis. A total of 191 articles were identified: PubMed, 40; Cochrane Collaboration, 27; EMBASE, 114; HEED, 10. Of these, 106 unique articles were unique, and 16 were included in this review.

Included articles compared clopidogrel plus aspirin with aspirin alone for patients presenting with ACS or for whom an elective or urgent PCI was planned.

RESULTS

Clinical Trial Data

All the cost-effectiveness analyses identified were based on the results of one or more of the following clinical trials, all of which compared clopidogrel plus aspirin with aspirin alone:

- The Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial, including the PCI-CURE population subset (those who had a PCI during the trial period) enrolled people presenting with non-ST-segment elevation myocardial infarction (NSTEMI) or unstable angina and followed them for up to 12 months.
- The CLopidogrel as Adjunctive ReperfusIon TherapY (CLARITY) trial enrolled people with ST-segment elevation myocardial infarction (STEMI) and followed them for up to 8 days.[8,9]
- The CIOpidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) study enrolled people with STEMI who did not have a PCI and followed them for up to 4 weeks.
- The Clopidogrel for the Reduction of Events During Observation (CREDO) trial enrolled people with a scheduled PCI or coronary angiogram or symptomatic coronary artery disease with objective evidence of ischemia and followed them for up to 12 months.

Model Structures

The cost-effectiveness models used several different structures, including Markov models, decision-tree analysis, life-expectancy analysis, and combinations of these structures, to extrapolate the trial data to a lifetime time horizon (Table 2).

Table 2. Different Model Structures

Model Structure	Reference and Country
Markov model from ACS episode for remaining lifetime	Germany[10]; the Netherlands[11]; Spain[12,13]; Sweden[14,15,16]; UK[17]; US[18]
Decision tree for first year after ACS episode followed by Markov model for remaining lifetime	Germany, France, Sweden[19]; UK[20]
Decision tree for the first year followed by life-expectancy analysis	Canada[21]; US[22,23,24,25]

Sensitivity Analyses

All the cost-effectiveness analyses included a one-way sensitivity analysis, and about half of them also included a probabilistic sensitivity analysis (PSA). The ranges for the cost-effectiveness ratio estimated in the one-way analyses depended on the reference-case assumptions. The one-way sensitivity analysis results were most sensitive to whether and how costs beyond the trial period were included in the model. However, the PSA results were not sensitive to the cost assumptions. Both types of sensitivity analysis were sensitive to the efficacy assumptions. Two examples of the analyses using data from the CREDO trial are shown in Table 3.

Table 3. Example Sensitivity Analyses Using Data from the CREDO Trial

Country, Trial, Model Structure, Reference	Reference-Case Results	Range in One-Way Sensitivity Analysis	Probability That Regimen is Cost-Effective (Threshold)
US, CREDO, Decision tree + life expectancy[22]	US $4,353/LYG	US $5,411/LYG–US $21,766/LYG	98.9% (US $50,000)
Sweden, CREDO, Markov[16]	€3,022/LYG	€2,388/LYG–€16,295/LYG	70% (€10,000)

LYG = life-year gained.

Variability Analyses

- None of the studies explicitly described a variability analysis and presented it separately from the sensitivity analyses as recommended in the Canadian guidelines.
- Many studies presented estimates of the cost-effectiveness of dual antiplatelet therapy for different patient subtypes (e.g., age, gender, and presence or absence of diabetes).[12, 13, 14, 15, 17, 20, 23]
- Four studies estimated the impact of different treatment durations,[11, 18, 19, 20] and many studies estimated the impact of different discount rates and model time horizons.[10, 11, 12, 14, 15, 16, 19, 20]
- The variability analyses indicated that the cost-effectiveness ratios were very different for different patient subtypes and for different treatment patterns.

Data Ranges/Distributions: Clinical

There were several sources used to estimate the clinical input parameter values (Table 4). Ranges and probability distributions for these inputs were based on 95% confidence intervals or standard deviations from the data source.

Table 4. Sources for Clinical Input Parameter Values

Input Parameter	Data Source
Risk of subsequent events with aspirin only	Clinical trials or Observational data
Relative risk of subsequent events with aspirin plus clopidogrel	Clinical trials – composite endpoint or Clinical trials – individual event endpoints
Event rates beyond clinical trial period	Not included or Observational data
Life expectancy beyond clinical trial period	National life tables or Observational data

Data Ranges/Distributions: Costs

Sources for the cost estimates included the following:

- Observational data
- Diagnosis-related group (DRG) costs
- Assumed treatment algorithms.

Costs included in the different studies varied widely, ranging from only hospital, clopidogrel, and aspirin costs in the first year after the episode to all inpatient and outpatient costs for the patient's remaining lifetime. All studies included acute bleeding costs during the trial period only. Three studies also included additional consumption costs during years of extra life.

The studies varied the costs in the sensitivity analyses by including or excluding different cost categories and/or by using arbitrary percentage increases and decreases. The study conducted by Karnon and colleagues[17] was the only study that used 95% confidence limits from observational data.

DISCUSSION

Reference Case

The range of results obtained in the sensitivity analyses are critically dependent on the results of the reference-case analysis since both the one-way and multiway sensitivity analyses are typically computed using the reference-case estimates as the anchor point.

The HTA guidelines require that the reference-case model structure and input parameter values be based on a systematic review and compilation of all available data sources.[1,2,3]

Yet our review of the cost-effectiveness analyses for dual oral antiplatelet therapy showed that there is a great deal of variability in the model structure, assumptions, and input parameter values used for the reference case.

Data For Sensitivity/Variability Analyses

Several of the articles reviewed included ranges of input parameter values using two methods:

1. In the form of 95% confidence limits from patient-level data
2. In the form of arbitrary percentage increases or decreases from estimated values (e.g., from event costs).

The use of 95% confidence limits for the upper- and lower-bound estimates provides very unlikely worst- and best-case values for the input parameter estimate. For example, the relative risk reduction for clinical events with clopidogrel plus aspirin compared with aspirin alone from the CURE trial is 80%, while the 95% confidence limits are between 0.72 and 0.89.[6] These confidence limits are approximately equal to a 10% increase or decrease in relative risk reduction.

However, a change in event costs of 10%, 20%, or even 50% may not represent the best- and worst-case values for input parameters representing the costs of clinical events.

If these percentage changes are not equally likely to be observed, comparing their impact in a one-way sensitivity analysis or including both parameters in a PSA may provide misleading information to decision makers.

CONCLUSIONS

The reference-case analyses and almost all sensitivity analyses indicated that a dual oral antiplatelet regimen is a cost-effective treatment following an ACS episode or a PCI. However, this review found several areas in which the published cost-effectiveness analyses for dual oral antiplatelet therapy compared with aspirin were not fully adherent with HTA guidelines from ISPOR,[1] NICE,[2] and CADTH.[3]

- The reference-case analysis, which forms the starting point for the sensitivity analyses, varied across studies in critical areas that indicated lack of adherence to HTA guidance.
- The alternative input parameter values used in the sensitivity analyses were sometimes presented without a data source or justification, and possibly did not represent equally likely value ranges.
- Variability analyses looking at the impact on cost-effectiveness of variations in patient characteristics and practice patterns were limited in scope and generally not presented separately from the sensitivity analyses.[3]

REFERENCES

Please refer to the handout.

DISCLOSURE STATEMENT

This research was sponsored by Daiichi Sankyo Company, Limited, and Eli Lilly and Company.

CONTACT INFORMATION

Josephine Mauskopf, PhD
Vice President, Health Economics

RTI Health Solutions
200 Park Offices Drive
Research Triangle Park, NC 27709

Phone: 919-541-6996
Fax: 919-541-7222
E-mail: jmauskopf@rti.org

Presented at: ISPOR 14th Annual International Meeting

May 16-20, 2009
Orlando, Florida
United States

REFERENCES

1. Weinstein MC, O'Brien B, Hornberger J, Jackson J, Johannesson M, McCabe C, et al.; ISPOR Task Force on Good Research Practices-Modeling Studies. Principles of good practice for decision-analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices—Modeling studies. Value Health 2003;6:9-17.
2. National Institute for Health and Clinical Excellence (NICE). Guide to the methods of technology appraisal. 2008. Available at: www.nice.org.uk. Accessed Jan 1, 2009.
3. Canadian Agency for Drugs and Technologies in Health (CADTH). Guidelines for the economic evaluation of health technologies. 2006. Available at: http://cadth.ca/media/pdf/186_EconomicGuidelines_e.pdf. Accessed Jan 2, 2009.
4. Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, et al.; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2008;117:e25-e146.
5. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358:527-33.
6. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494-502.
7. Steinhubl SR, Berger PB, Mann JT 3rd, Fry ET, DeLago A, Wilmer C, et al.; CREDO Investigators. Clopidogrel for the Reduction of Events During Observation: early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002;288:2411-20.
8. Sabatine MS, Cannon CP, Gibson CM, López-Sendón JL, Montalescot G, Theroux P, et al.; CLARITY-TIMI 28 Investigators. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med 2005a;352:1179-89.
9. Sabatine MS, McCabe CH, Gibson CM, Cannon CP. Design and rationale of Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction (CLARITY-TIMI) 28 trial. Am Heart J 2005b;149:227-33.
10. Brüggenjürgen B, Lindgren P, Ehlken B, Rupprecht HJ, Willich SN. Long-term cost-effectiveness of clopidogrel in patients with acute coronary syndrome without ST-segment elevation in Germany (structured abstract). Eur J Health Econ 2007;8:51-7.
11. Heeg BM, Peters RJ, Botteman M, van Hout BA. Long-term clopidogrel therapy in patients receiving percutaneous coronary intervention. Pharmacoeconomics 2007;25:769-82.
12. Badia X, Bueno H, González Juanatey JR, Valentín V, Rubio M. [Short-and long-term cost-effectiveness analysis of adding clopidogrel to standard therapy in acute coronary syndrome patients in Spain]. Rev Esp Cardiol 2005;58:1385-95.
13. Latour-Pérez J, Navarro-Ruiz A, Ridao-López M, Cervera-Montes M. Using clopidogrel in non-ST-segment elevation acute coronary syndrome patients: a cost-utility analysis in Spain. Value Health 2004;7:52-60.
14. Lindgren P, Jönsson B, Yusuf S. Cost-effectiveness of clopidogrel in acute coronary syndromes in Sweden: a long-term model based on the CURE trial. J Intern Med 2004;255:562-70.
15. Lindgren P, Stenestrand U, Malmberg K, Jönsson B. The long-term cost-effectiveness of clopidogrel plus aspirin in patients undergoing percutaneous coronary intervention in Sweden. Clin Ther 2005;27:100-10.
16. Ringborg A, Lindgren P, Jönsson B. The cost-effectiveness of dual oral antiplatelet therapy following percutaneous coronary intervention: a Swedish analysis of the CREDO trial. Eur J Health Econ 2005;6:354-6, 358-62.
17. Karnon J, Bakhai A, Brennan A, Pandor A, Flather M, Warren E, et al. A cost-utility analysis of clopidogrel in patients with non–ST-segment-elevation acute coronary syndromes in the UK. Int J Cardiol 2006;109:307-16.
18. Schleinitz MD, Heidenreich PA. A cost-effectiveness analysis of combination antiplatelet therapy for high-risk acute coronary syndromes: clopidogrel plus aspirin versus aspirin alone. Ann Intern Med 2005;142:251-9.
19. Berg J, Lindgren P, Spiesser J, Parry D, Jönsson B, et al. Cost-effectiveness of clopidogrel in myocardial infarction with ST segment elevation: a European model based on the CLARITY and COMMIT trials. Clin Ther 2007;29:1184-202.
20. Main C, Palmer S, Griffin S, Jones L, Orton V, Sculpher M, et al. Clopidogrel used in combination with aspirin compared to aspirin alone in the treatment of non-ST-segment-elevation acute coronary syndromes: a systematic review and economic evaluation. Health Technol Assess 2004;8: iii-iv, xv-xvi, 1-141. Review..
21. Kolm P, Yuan Y, Veledar E, Mehta SR, O'Brien JA, Weintraub WS. Cost-effectiveness of clopidogrel in acute coronary syndromes in Canada: a long-term analysis based on the CURE trial. Can J Cardiol 2007;23:1037-42.
22. Beinart SC, Kolm P, Veledar E, Zhang Z, Mahoney EM, Bouin O, et al. Long-term cost-effectiveness of early and sustained dual oral antiplatelet therapy with clopidogrel given for up to one year after percutaneous coronary intervention: results from the Clopidogrel for the Reduction of Events During Observation (CREDO) trial. J Am Coll Cardiol 2005;46:761-9.
23. Cowper PA, Udayakumar K, Sketch MH Jr, Peterson ED. Economic effects of prolonged clopidogrel therapy after percutaneous coronary intervention. J Am Coll Cardiol 2005;45:369-76.
24. Mahoney EM, Mehta S, Yuan Y, Jackson J, Chen R, Gabriel S, et al.; CURE Study Investigators. Long-term cost-effectiveness of early and sustained clopidogrel therapy for up to 1 year in patients undergoing percutaneous coronary intervention after presenting with acute coronary syndromes without ST-segment elevation. Am Heart J 2006;151:219-27.
25. Weintraub WS, Mahoney EM, Lamy A, Culler S, Yuan Y, Caro J, et al.; CURE Study Investigators. Long-term cost-effectiveness of clopidogrel given for up to one year in patients with acute coronary syndromes without ST-segment elevation. J Am Coll Cardiol 2005;45:838-45.

Adherence to Guidelines for Sensitivity Analysis:

Cost-effectiveness Analyses of Dual Oral Antiplatelet Therapy

Josephine Mauskopf,[1] Claude Schmitt,[2] Kristina S Boye,[3] Patrick L McCollam,[3] Melissa Juniper,[1] Julie A Birt[3]

[1]RTI Health Solutions, Research Triangle Park, NC, United States;
[2]Eli Lilly and Company Ltd, Windlesham, United Kingdom;
[3]Eli Lilly and Company, Indianapolis, IN, United States

ISPOR 14th Annual International Meeting
May 16-20, 2009
Orlando, Florida, United States

RTI(h)(s)™ RTI HEALTH SOLUTIONS®