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Cost-Effectiveness and Formulary Evaluation: Imaginary Worlds and Entresto Claims in Heart Failure

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Abstract

The Program in Social and Administrative Pharmacy at the University of Minnesota recently released its proposed guidelines for formulary evaluation. The guidelines were focused on ensuring that comparative claims made for pharmaceutical products and devices rested on a credible evidence base. The argument was put forward that if value claims for clinical and cost-effectiveness outcomes were to be accepted then they had to be empirically evaluable. The purpose of this commentary is to explore alternative modeled claims for Entresto, an angiotensin receptor neprilysin inhibitor, versus the standard of care with an ACE inhibitor in patients with chronic heart failure. Two models are compared: a lifetime cost-per-QALY model and a 3-year cost and budget impact model. The primary reason for this comparison is the puzzling feature that for a product which is over 120 time as expensive compared to the standard of care (Entresto $380 per month vs. ACE inhibitor $3 per month) the modeled claim can be made that the product is, in willingness to pay terms, cost-effective. The analysis illustrates that, perhaps not surprisingly, different models can generate quite different perspectives on the presumption of 'cost-effectiveness'. In the present case the simple decision model yields a breakeven monthly cost for Entresto of only $23.74. If modeled claims are to be useful for formulary decision making, then we need to eschew 'black box' models with non-evaluable claims in favor of those models that yield credible, evaluable and replicable claims that can support defensible product placement and pricing decisions.

Keywords: heart failure, Entresto, cost-effectiveness, hospitalization costs, ED costs

Introduction

The Program in Social and Administrative Pharmacy at the University of Minnesota recently released its proposed guidelines for formulary evaluation [1]. The guidelines were focused on ensuring that comparative claims made for pharmaceutical products and devices rested on a credible evidence base. The argument was put forward that if value claims for clinical and cost-effectiveness outcomes were to be accepted then they had to be empirically evaluable [2]. The guidelines proposed that all submissions for formulary review be accompanied by a protocol that proposed how the claims were to be evaluated and reported to a formulary committee in a meaningful time frame. The standards proposed were those of normal science: claims had to be credible, evaluable and replicable [3]. Claims from manufacturers, even if based on the results of apparently well conducted randomized clinical trials (RCTs) were not to be taken at face value: they had to be replicated for target patient populations in a real world treating environment. Achieving these goals was seen as a necessary precursor to creating an outcomes based formulary where formulary status, contracting and pricing were consistent with increased accountability for quality and the total cost of care with the focus on population health management [4].

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The purpose of this commentary is to consider as a case study the cost-effectiveness claims made by the Institute for Clinical and Economic Review (ICER) for the angiotensin receptor neprilysin inhibitor Entresto in surviving patients with heart failure [5]. This commentary has been prompted by what may appear to be an odd situation when comparative clinical effectiveness is compared to differences in drug prices. According to the ICER report the monthly cost of Entresto is $380 compared to the monthly cost of Enalapril, an ACE inhibitor, at $3 per month. With a product more than 120 times as costly as the existing monthly cost of the established standard of care, the ICER report claims Entresto to be cost-effective at a 9% price reduction if we accept a willingness to pay benchmark of $50,000 per QALY.

Yet the benefits conferred by Enalapril from the PARADIGM-HF trial appear marginal: (i) a reduction from 14.3% to 12.4 % (absolute reduction 1.9%) in patients with worsening heart failure leading to intensification of outpatient therapy; (ii) a reduction in the number of patients with emergency department visits for heart failure from 208 to 151 from respective index enrollments of patients of 4,212 and 4,187 respectively over some 50 months from first patient randomization (4.9% to 3.6%); (iii) a reduction in the number of patients hospitalized for heart failure from 658 to 537 (15.6% to 12.8%); and (iv) a reduction in the average number of admissions per patient from 1.64 to 1.58 of those hospitalized [6].

In order to illustrate the impact of an alternative model framework to support claims for cost-effectiveness, the results of the ICER reference case model are compared to a simple decision model which attempts to evaluate the comparative clinical claims made in the PARADIGM-HF trial in terms of the direct medical costs likely to be incurred in switching patients from the ACE inhibitor Enalapril to Entresto. This does not mean that alternative cost-per-QALY models could not be constructed; the point at issue is whether the ICER framework meets the standards of normal science for experimentation and replication [7].

The ICER Entresto Model

The ICER Entresto model utilized a Markov framework to assess cost-effectiveness. It was designed to model or simulate the natural history of chronic heart failure in a cohort of 64-year-old-patients with New York Heart Association (NYHA) class II-IV heart failure with reduced ejection fraction based on the PARADIGM-HF trial and other published literature [8]. Entresto was compared to lisinopril standard treatment. Event rates for the probabilities of hospitalization and mortality in the routine care comparison were from the PARADIGM-HF trial. The trial data also supported estimates of the numbers of heart failure hospitalizations, costs, deaths, life years and quality adjusted life years (QALYs). For model purposes outcomes associated with ACE inhibitors were considered equivalent. The model included switching for those intolerant to either Entresto or the ACE-inhibitor.

The model assumed a monthly Markov time cycle with a lifetime horizon. Each month patients were assumed to be at risk for a heart failure hospitalization, angioedema requiring hospitalization, any other non-heart failure hospitalization, an ED visit for heart failure not requiring hospitalization, intolerance to their treatment agent and a cardiovascular or non-cardiovascular death. Where patients were assumed to be intolerant or who suffered an angioedema they were switched to either an ACE inhibitor for those taking Entresto or an ARB if intolerant to an ACE inhibitor. Transition probabilities between Markov states were determined from the events reported in the PARADIGM-HF trial. Probabilities of cardiovascular death were derived from the literature. Event costs were derived from the literature: CHF hospitalization from the AHRQ National Inpatient Sample.

The baseline QALY estimate (0.822; range 0.705-0.938) was from the average EQ-5D measurement during the course of the trial. This estimate has not been published but was based on a personal communication from the manufacturer. The utility increment from receiving Entresto was based on the least squares mean of difference between the changes in baseline in the two arms (0.009; range 0.002-0.016). Exacerbations requiring an ED visit but not hospitalization were assumed to incur two days of disutility; a disutility of one day was estimated for therapy intolerance and two days for an angioedema requiring hospitalization. Disutilities based on the literature were applied for CHF hospitalization and non-CHF hospitalization of approximately three days in a monthly cycler. The model was estimated for all-patients and the then for two sub-groups: NYHA Class II and NYHA Class III/IV patients.

In the all-patients base case the model predicted 6.78 years of survival in the ACE inhibitor arm (from initial entry of 64 years of age) and 0.97 undiscounted CHF hospitalizations per patient. These compared in the Entresto arm to 7.41 years of survival and 0.90 CHF hospitalizations in the Entresto arm. The corresponding QALY estimates were 5.56 for the ACE inhibitor arm with total costs of $123,578 compared to 6.13 QALYs and costs of $152,716 in the Entresto arm. The per patient cost on the Entresto arm was 23.6% higher than for those on the ACE inhibitor for these survival estimates. The modeled cost per QALY gained with Entresto was $50,915. If a willingness to pay threshold of $50,000 was assumed, Entresto would be deemed cost-effective at a price per annum of $4,464 vs. $4,560.

The ICER Entresto model is the standard reference case cost-for quality adjusted life year model that is found in its drug evaluation reports. It is based on the NICE reference case model [9]. Typically, the model is not released for public review which means that, in practical terms, it is impossible to review, modify and replicate. It is the quintessential black box. Previous commentaries in this series have pointed to the limitations of reference case models, the use of QALYs in modeled claims and the impossibility of evaluating these claims to support formulary decisions [10 11]. The point to note is that, irrespective of claims made that reference case models provide a useful correspondence with the real world, they are imaginary constructs. It is assumed, presumably by those who accept this methodology in decision making, that the sufficient correspondence of the model and its assumptions with the natural history of chronic heart failure, necessarily entails the claims for the clinical impact of Entresto in this target population. Similar models could, of course, be built to come to quite different conclusions and, indeed, it would be possible to reverse engineer any reference case or similar model to come to conclusions that favor a particular product.

Reference models or simulations must fail the standards or normal science if they present value claims for products that are neither evaluable nor replicable. In the absence of experimentation the claims are of little use to formulary committees in seeking real world evidence to support formulary listing and pricing. They are best seen as pseudoscience.

Presenting claims based on reference case models puts formulary committees in a quandary. The sheer complexity of lifetime models, their claim to be based on unevaluable model standards that are approved by agencies such as the Academy of Managed Care Pharmacy (AMCP) in their Format for Formulary Submissions and the International Society for PharmacoEconomics and Outcomes Research (ISPOR) together with blanket claims that the particular product is 'cost-effective' is to ask formulary committees to take the claims at face value [12] [13] [14]. A situation that is not helped by the willingness of journal editors to publish modeled yet untestable cost-effectiveness claims for drugs and devices [15].

The risk, as exemplified by the Entresto case, is that claims that the product is 'cost-effective' are taken at face value [16]. This is not helped by the lack of transparency in descriptions of the modeling framework. As a result, integrated health delivery systems, pharmacy benefit management groups and other health systems run the risk of entering into contracts that have the potential to incur significant drug costs for, possibly, minor clinical benefits in the target treating population. Untestable claims generated by imaginary worlds are not a basis for formulary decision making.

An Imaginary Reconfiguration

The most puzzling feature of the ICER assessment of Entresto for heart failure hospitalization is how a product that is over 120 times as expensive as the ACE inhibitor standard of care ($380 vs. $3 per month) in surviving patients with heart failure can be considered to be cost-effective [17]. In order to examine the merits of this claim, a simple decision budget impact model is proposed that evaluates the direct medical costs of emergency room visits and hospitalizations for heart failure over a 3 year time frame. The estimated direct medical costs are compared to the number of emergency room visits and hospitalizations avoided to give a cost per event avoided together with an estimated breakeven monthly cost for Entresto where transitioning patients to the new drug has a zero impact on the overall costs of care. The model is constructed in Excel and a copy of the model is provided as a simple spreadsheet in Appendix A to this commentary.

The model has been configured to reproduce the results for the total number of emergency department visits and hospitalizations (HF Events) reported from the PARADIGM-HF trial, adjusted for 10,000 patients in each of the Entresto and ACE arms over an arbitrary 3-year period. It should be emphasized that the model is concerned with orders of magnitude, not claims that can be defended as valid to the nearest dollar. A number of the assumptions are only considered 'reasonable' as more detail from the Entresto trial are unavailable. Unlike the ICER model the one proposed here includes emergency room visits as well as hospitalization. It also attempts to take account of non-persistence with therapy. It is assumed that adherence is not an issue. The model is not concerned with utility measures, quality of life or willingness-to-pay thresholds as the justification for claiming cost-effectiveness and recommending a price consistent with that threshold.

Six patient groups are modeled for each intervention arm. These are:

- Group A: Patients who are adherent to therapy throughout 3 year forecast period with no heart failure (HF) related events (ED or hospitalizations
- Group B: Patients who were not persistent with therapy (dropped out before end of 3 year period) but who had no HF related events
- Group C: Patients who were adherent to therapy with events before end of 3 year period
- Group D: Patients who were not persistent with therapy who experienced HF related events before dropping out
- Group E: Patients who were persistent with therapy but who and died without HF events
- Group F: Patients who were persistent with therapy but who experienced HF events before death

In all cases, where patients were not persistent or who died (Groups B, D, E and F), this was assumed to occur on average after 18 months of treatment with the respective therapies.

Costs for the HF events were $12,832 for a hospitalization and $1,000 for an emergency room visit. Monthly drug costs were assumed to be $380 for Entresto and $3 for the ACE inhibitor. All costs were assumed to remain unchanged over the 3-year period. Apart from the emergency room costs, these costs are from the ICER model.

Table 1 details for the 6 patient groups assumptions for (i) the number of emergency care and hospitalizations per patient over the 3 year period (Group C) and the 18 months prior to dropout (Groups D and F) for Entresto and the ACE inhibitor arm respectively and (ii) the distribution of patients between the 6 groups at the index prescription for both product arms.

Table 1
Heart Failure Events and Patient Distribution by Drug Utilization Group

Patient Group	Entresto: ER visits/3 years/18 months	ACE: ER visits/3 years/18 months	Entresto: Hospitalizations /3 years/18 months	ACE: Hospitalizations/3 years/18 months	Patient Distribution
A					0.4
B					0.19
C*	0.15	0.24	1.5	1.8	0.08
D**	0.06	0.09	0.4	0.5	0.03
E					0.15
F**	0.06	0.09	0.4	0.5	0.15

Note: *3 year time frame; **18 month time frame; event frequency and patient distribution from Appendix A

Results
The model results are summarized in Table 1 below:

i. Medical Costs: Weighted by the distribution of index patients across the 6 groups the total direct medical costs for an assumed 10,000 index patients are Entresto $126,097,440 and the ACE inhibitor $31,180,080. An increase in costs of $94,917,360 (or $94,917 per patient) or weighted per patient $12,609 and $3,118 respectively
ii. Drug Costs: Drug costs in the Entresto arm account for 80.3% of total costs; in the ACE arm 2.6%
iii. HF Events avoided from switching to Entresto : for the 10,000 index patients are 96 emergency department visits and 420 hospitalizations
iv. Cost per HF hospitalization for 10,000 index patients: Entresto - $65,675; ACE - $13,325
v. Cost per ER visit for 10,000 index patients: Entresto - $488,749; ACE – 88,079
vi. Direct Medical Cost per HF event avoided by switching to Entresto: emergency room visit $998,722 per patient and hospitalizations $225,993 per patient
vii. Cost differential: over the 3 year time horizon the ratio of Entresto to ACE total costs is 4.04
viii. Breakeven price of Entresto when switching yields same total cost as the ACE inhibitor: $23.74 per month

Discussion
A product is cost-effective only if the payer considers it to be cost-effective. Irrespective of the ICER use of reference case cost-per-QALY model and $50,000 cost per QALY thresholds, there are no agree standards for judging whether a cost-per-outcome estimate is meaningful to a payer. The ICER model builds an imaginary reference case cost-per-QALY world to justify its claim for cost effectiveness. In the report on Entresto, ICER judged (on a $50,000 willingness-to-pay threshold) that Entresto would be cost effective for any payer if Novartis reduced price by 9%. The imaginary world analysis above suggests that a price reduction of over 90% might be more appropriate with a monthly breakeven price of $23.75.

The differences in total treatment costs are marked. With an assumed 10,000 patients initiated to therapy on each arm, over 3 years total costs increase from $31.2 million to $126.1 million (just over 4 times). On the event assumptions built into the model for illustrative purposes, to achieve a reduction in 96 ER events and 420 hospitalizations, the cost per event saved in adopting Entresto is $998,722 and $225,993 per event (not per patient) respectively. It is also worth noting that in the ICER model, the direct medical (including pharmacy) costs for Entresto are only 23.6% greater than for the ACE inhibitor while in the 3-year illustrative model the difference is over 304.4% greater. It is not clear from the ICER model why the cost differential is relatively small given the magnitude of the difference in drug costs. If a health system considers these costs acceptable, it should be kept in mind that all decisions to support new products involve opportunity costs, benefits forgone to patients in other disease and therapy areas.

Unevaluable claims based on imaginary worlds should not be a guide to either formulary decisions or contracts for product pay-for-performance. In the absence of value claims for products that are evaluable and replicable, claims should be put to one side until a manufacturer can put forward evaluable claims that are credible and can be reported back to formulary committees in a meaningful time frame. The model presented here is intended as an illustration of a counterpoint to lifetime cost-per-QALY models. It has two

advantages (i) the model is transparent and (ii) all assumptions and predictions are verifiable. Simple spreadsheet models are not new; what is new, unfortunately, is a trend towards the specification of more complex models which are not only a 'black box' to formulary committees but which are incapable of supporting evaluable claims. At the same time these models may embed value benchmarks in their assessments of cost-effectiveness which, like other assumptions built into the models, may be unacceptable to the intended audience.

Conclusions

In the US there are no agreed standards for value benchmarks in modeled claims for cost-effectiveness. Indeed, attempts to put cost-per-QALY benchmarks in place have been excluded for evaluations falling under the umbrella of the *Patient Protection and Affordable Care Act*. While unintended, this decision may be seen in retrospect as eminently sensible as it may act as a brake on the enthusiasm for developing and publishing 'black box' lifetime cost-per-QALY models in order to justify product placement and pricing. Modeled claims which, in probably the overwhelming majority of cases, are put to one side by formulary committees as of limited (if any) application in formulary decision making. After all, if the formulary committee, in the absence of evaluable claims being presented, has no idea whether the claims are right or even if they are wrong, it is then perhaps unsurprising that an independent observer might see these endeavors as a waste of time and resources..

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