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The Challenges of Cost-Effectiveness Analyses for the Clinician

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Most clinicians would agree that available resources for the provision of health care are limited. Even a country as wealthy as the United States cannot indefinitely afford to provide all treatments that are considered effective and safe to all individuals who might benefit from them. The question is then, how can we use the available resources to get “the biggest bang for the buck,” to maximize the health benefits for the population under consideration with available budgets? Whether we like it or not, as clinicians we are in a unique position to contribute to the decision among clinical strategies, which inevitably has consequences not only for the health of the individual patient, but also for many other patients that we do not care for directly but who are a part of the broader health care system. If we ignore the cost of diagnostic and treatment strategies when making medical decisions, we may inadvertently direct scarce health care resources away from affordable, effective, and much needed therapies toward expensive therapies that provide little or no health benefit, especially for individuals who cannot afford paying more for health care. In order to make the best use of limited health care resources, clinicians, individuals, and policy makers must weigh both the costs and benefits of the tests and treatments they employ. Economic evaluations help inform cost-benefit decisions by providing formal quantitative methods to compare costs and benefits of alternative strategies.¹

This issue of the *American Journal of Kidney Diseases* includes studies by Shireman et al and Clement et al that utilize a specific type of economic analysis, namely, cost-effectiveness analysis (CEA). Shireman et al examine the cost-effectiveness of treating hyperparathyroidism in dialysis patients with cinacalcet in combination with low-dose vitamin D.² Clement et al examine the cost-effectiveness of using erythro-poietin stimulating agents (ESAs) to achieve several different hemoglobin targets.³

In 1996, a panel of experts published consensus guidelines that helped to define and standardize CEA, which they define as “a method for evaluating the [health] outcomes and costs of interventions designed to improve health.”⁴ As such, CEAs always compare at least 2 competing clinical strategies. Results of CEAs are expressed as the difference in costs divided by the differences in health outcomes between 2 or among several strategies (eg, aspirin vs warfarin vs neither in patients with persistent atrial fibrillation). In order to

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compare cost-effectiveness for different clinical indications (warfarin in patients with persistent atrial fibrillation vs high-dose statin treatment in patients with normal lipids, but elevated C-reactive protein), cost-effectiveness ratios should be expressed in the same units, both for the numerator (costs; eg, currency units) and the denominator (effects; eg, years of life saved). If one strategy is more effective and less costly than its comparator (“dominant”), then one would certainly want to adopt it. But CEAs are most helpful in informing treatment decisions when one strategy is both more effective and more costly than an alternative.

When reading a CEA, it is important to recognize the perspective from which the analysis was conducted. Usually, the choice of perspective affects the costs that are being considered more than it affects the outcomes. For example, an insurance company or public payor will consider their direct costs for treatments, but will disregard patient copayments, or the value of informal caregivers’ time. It has been recommended to conduct CEA from the societal perspective, since only this approach considers all relevant costs and outcomes and avoids the allocation biases that may be introduced by a narrower approach.⁴

The denominator in a cost-effectiveness ratio is the incremental benefit or outcome associated with one clinical strategy over another. Outcomes can be expressed in a variety of ways including life-years gained, quality-adjusted life-years (QALYs) gained, or clinical targets met. The more universal the outcome, the easier it is to compare the results of different studies. For example, the number of life-years gained can be compared between 2 treatment strategies, while the number of clinical targets met cannot be compared between 2 strategies unless the targets are identical. A common outcome used is the QALY, which takes into account the relative value of time spent with certain health conditions. This is useful when clinical strategies affect people’s quality of life, for example, in disability.

Another important aspect of CEA is the choice of time horizon. One may imagine that the relative cost-effectiveness between, for example, kidney transplant and peritoneal dialysis may depend on the follow-up time considered. Kidney transplants have high up-front costs, but lower long-term costs compared with peritoneal dialysis, where costs tend to accrue rather uniformly over time. If one only considers 1 year of follow up, kidney transplant may not be as attractive an option relative to peritoneal dialysis, compared with an approach that considers 10 years of follow up. Guidelines recommend employing a lifetime horizon.

Finally, measurement and valuation of costs and consequences of interventions are adjusted, or discounted, for differences in their timing. This is due to the assumption that people prefer benefits sooner and prefer to postpone costs because of uncertainty about the future.

The studies by Shireman et al² and Clement et al³ represent noble attempts to use CEA to quantify the value of expensive medications used for treating patients with kidney disease. For the reader, appreciation of the differences between these 2 studies demonstrates both strengths and limitations of CEA in the field of nephrology.

Shireman et al provide an example of a CEA based on a single clinical trial, with a limited time horizon and outcomes that have uncertain relevance in the long run. They focus their economic analysis on costs and outcomes from the ACHIEVE (Optimizing the Treatment of

Secondary Hyperparathyroidism: A Comparison of Sensipar and Low Dose Vitamin D vs Escalating Doses of Vitamin D Alone) trial. The ACHIEVE trial was a randomized controlled trial comparing cinacalcet-based therapy with flexible-dose vitamin D for treatment of hyperparathyroidism in dialysis patients. The primary outcome in the ACHIEVE trial was the proportion of individuals who achieved the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) bone mineral targets for parathyroid hormone and calcium-phosphorus product.⁵ While ACHIEVE found no significant difference in primary outcome between the 2 treatment groups, there was a significant difference in achievement of many secondary outcomes, including individual KDOQI bone and mineral targets.

Shireman et al estimate incremental cost-effectiveness ratios associated with reaching the 6 secondary end points for which cinacalcet was more effective than flexible-dose vitamin D. Notably, they estimate a cost to treatment with cinacalcet within the parameters of the study protocol. They found that using an intention-to-treat analysis, a protocol with cinacalcet cost \$1,520 (or 35%) more than a protocol employing flexible-dose vitamin D (\$5,852 vs \$4,332). The estimated incremental cost-effectiveness ratio associated with attaining individual KDOQI targets varied depending on the secondary outcome analyzed.

No attempt was made to translate these intermediate study outcomes and their associated costs into putative long-term outcomes and costs. This may be considered a strength and a weakness—a strength because the authors stayed as close as possible to the available data and avoided making strong assumptions that would have been necessary if they had chosen to extrapolate these findings into long-term outcomes, and a weakness because their findings bear limited relevance to the more important questions of prioritization among competing resource allocation strategies for society in the long run. Their cost only includes the cost incurred during the study period rather than the actual lifetime cost of cinacalcet-based treatment, while it is not clear whether and to what extent achieving individual KDOQI outcomes improves overall health.

By contrast, Clement et al built a more complex decision model in their economic evaluation of ESAs. Their model estimates incremental cost-effectiveness ratios from 4 different ESA strategies: (1) no ESAs with transfusions as needed, (2) low-dose ESA for a hemoglobin goal 9–10.9 g/dL, (3) intermediate-dose ESA with a hemoglobin goal 11–12 g/dL, and (4) high-dose ESA with a hemoglobin goal >12 g/dL. The assumptions they use to construct their model come from 2 large population-based registries and a number of randomized trials and meta-analyses. In multiple instances, where there were no data available to fill in certain model parameters (eg, to indicate how quality-of-life weights differed among treatment groups), the authors had to make assumptions about treatment effects. They estimated an incremental cost-effectiveness ratio of \$96,270 per QALY gained when comparing a strategy without ESAs to a low-dose ESA strategy. On sensitivity analysis, the cost-effectiveness ratio for low-dose ESA use decreased further when accounting for the reduced likelihood of transplant in the no-ESA group. The authors found that high-dose ESA was “dominated” by low-dose ESA since a high-dose ESA strategy was more costly and less effective.

By building a mathematical model that incorporated information from a large number of sources, Clement et al were able to estimate incremental cost-effectiveness ratios that are relevant for clinical decision making. For instance, the dollars/QALY associated with a low-dose ESA strategy can be compared with dollars/QALY associated with other diagnostic and treatment interventions in order to determine whether giving low-dose ESAs represents an optimal allocation of health care resources. However, the price paid for greater applicability and generalizability is the necessity for a complex model that is difficult to understand and critique as well as the necessity for a large number of assumptions that may or may not be valid. For instance, the number of assumptions made in the analysis limited the authors' ability to determine the relative cost-effectiveness of a low vs an intermediate ESA strategy. Applying extensive sensitivity analysis may reveal which assumptions are particularly influential, illustrating that getting these key assumptions wrong may particularly threaten the validity of the CEA.

Comparing these 2 studies demonstrates how the design of a CEA influences how the results can be interpreted. Although both studies reveal important quantitative information about the value of these expensive therapies, they also highlight an unfortunate reality about our care of patients with kidney disease. There is a lack of clinical evidence with meaningful clinical outcomes supporting many of the expensive therapies used to attain preset clinical targets. While CEAs provide important information to ensure that nephrologists provide high-value care, the scope of findings from CEAs will continue to be limited until we know more about how achieving clinical targets involving anemia, bone, and mineral disease affects the overall health of patients with kidney disease.

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