Trying To Predict the Future for People with Diabetes: A Tough but Important Task

With growing health care costs, policymakers and health care providers need information on the cost-effectiveness of interventions. This issue contains an economic evaluation (1) of a prevention policy for diabetes—a condition that affects more than 18 million persons in the United States at a cost of approximately $132 billion annually.

To assist policymakers, researchers have developed models that simulate the progression of diabetes, expenditures on diabetes care, and effects of interventions. The outputs of these models include costs and health outcomes, such as length of life (often expressed as quality-adjusted life-years [QALYs]), a measure that considers the quality of life in each health state. Two principal types of diabetes models exist. Most researchers use a Markov model, which comprises disease states (for example, normal, impaired glucose tolerance [IGT], and diabetes) represented in a computer program. The computer simulates transitions from one disease state to another as chance events. A second novel type of model, named Archimedes (2, 3), uses object-oriented computer programming and complex differential equations to simulate pathophysiologic processes (for example, hepatic glucose output after a meal) that change over time and can lead to disease. For a technical explanation of the Archimedes model, I refer to the accompanying editorial in this issue (4). My editorial focuses on the clinical and policy aspects of the Archimedes model.

The Archimedes model calculates the changes in costs and quality-adjusted length of life (in QALYs) from implementing the lifestyle intervention of the Diabetes Prevention Program (DPP) study (5) or prescribing metformin to a cohort with IGT like the enrollees in the DPP. Eddy and colleagues (1) took a societal perspective and used time horizons of 10, 20, and 30 years. Compared with no intervention, the cost per QALY of beginning the intensive lifestyle intervention or metformin for IGT was $62 600 and $35 400, respectively, over 30 years (1). The cost per QALY for an intensive lifestyle intervention started after the onset of diabetes was $24 500.

What do these results imply for health care policy? Acceptable cost-effectiveness depends on a society’s willingness to pay. Interventions that cost less than $50 000 per QALY are reasonable to consider for rapid adoption. Thus, the Archimedes model results imply that we should not rush to adopt the DPP lifestyle intervention (6).

Another model, developed by the DPP Research Group (DPPRG), leads to a different conclusion. It used a Markov model, lifetime horizon, and societal perspective to determine the cost-effectiveness of the same interventions for IGT. The cost per QALY was $8800 for the lifestyle intervention and $29 900 for metformin, both less than the $50 000 threshold for rapid adoption (7). Eddy and colleagues critique the model in an online Appendix (1). Speaking as a coauthor of the DPPRG cost-effectiveness analysis, I believe that many of Eddy and colleagues’ criticisms are based on inaccurate descriptions of the DPPRG model. However, my focus is to understand why the 2 models have such different policy implications.

Although these 2 analyses gave different values for cost-effectiveness, several clinically relevant results were similar. First, both analyses predicted that the lifestyle intervention would substantially reduce the proportion of patients at high risk who developed diabetes. Second, both analyses predicted that the lifestyle intervention would delay the onset of diabetes. The Archimedes model predicted that the time required for 50% of patients with IGT to develop diabetes would increase from 7 years to 14 years. The corresponding figures from the DPPRG study were 8 years and 18 years, respectively. Third, both analyses predicted that the lifestyle intervention will lead to fewer complications, longer life, and improved quality of life. Fourth, both analyses suggested that the cost of the lifestyle intervention exceeds the savings from lower rates of diabetes complications.

Why do the 2 studies differ in the cost per QALY of the lifestyle intervention and metformin therapy? This question is crucial because the different costs per QALY lead to different policy recommendations. To facilitate a comparison, I examined the results for the base-case cohorts (Archimedes model, no intervention; DPPRG analysis, standard lifestyle) for both models. The Archimedes’ time horizon (30 years) is shorter than the DPPRG time horizon (the time from IGT diagnosis until death). This difference is important. A shorter time horizon will always be less favorable if some patients benefit only after decades of the intervention, as Eddy and colleagues show by comparing the 10-, 20-, and 30-year time horizon analyses. Because the DPPRG analysis followed the cohort longer but projected roughly the same life expectancy as the Archimedes model (approximately 24 years), one can infer that the Archimedes model projected less morbidity and mortality during its shorter 30-year time horizon. As the complication rate increases, the absolute benefit from an effective intervention increases.

Why are the complication rates higher in the DPPRG model? In the Archimedes model, the microvascular disease cumulative incidence rates were very low. The lifestyle intervention reduced the base-case cohort’s 30-year cumulative incidence of kidney failure from 0.07% to 0.03% and the need for amputation from 0.03% to 0.02%. Comparable rates from the DPPRG were from 1.0% to 0.6% and from 1.9% to 1.3%, respectively. These differences are
probably too large to be due solely to the shorter time horizon used in the Archimedes model.

What accounts for this difference in microvascular disease rates in the 2 studies? One reason is different assumptions for the rates of progression of glycemia. For the base case, the Archimedes analysis modeled the FPG level to increase at a rate of 0.1 to 0.2 mmol/L (2.0 to 3.0 mg/dL) per year from onset of diabetes until it reached 10.0 to 11.1 mmol/L (180.0 to 200.0 mg/dL), taking about 20 to 30 years. This is much longer than the empirical observation of roughly 10 years from onset until clinical diagnosis is made (8–10), which is the assumption used by the DPPRG. Slower rates of glycemic progression imply slower microvascular complication rates. This is consistent with results from a validation study reported by the Archimedes analysis that predicted a substantially lower cumulative incidence of retinopathy than that observed (15% in the Archimedes model vs. 30% in the comparison trial) (see Eddy and colleagues’ Appendix Table 5 [1]).

Assumptions and modeling of cardiovascular outcomes will have a greater effect on life expectancy than microvascular outcome assumptions. Here, the difference between the Archimedes model and the DPPRG analysis was mostly due to the different time horizons. In blinded predictions of the results of the Collaborative Atorvastatin Diabetes Study (CARDS) (11), both models predicted the observed rates reasonably well.

In my editorial, I have tried to dissect the 2 models to show why the cost per QALY was so much higher in the Archimedes model despite the 2 models projecting several similar qualitative conclusions. Different assumptions about the rate of glycemic progression and a different time horizon (which allows a longer time in which events could occur) are probably the principal causes of the differences. The lower rate of complications in the Archimedes analysis means that the interventions will have a smaller effect on the outcomes of complications than in the DPPRG analysis. A smaller effect of the interventions, with roughly the same costs, would translate into lower cost-effectiveness in the Archimedes analysis.

The Archimedes model is a new, novel, and welcome addition to the diabetes care–modeling efforts. However, its inputs and assumptions need more refinement and transparency before we can understand it well enough to use it in setting national diabetes prevention policy. As my editorial shows, understanding why the Archimedes model differs from other models is an exacting and difficult task. However, whoever said that interpreting economic studies would be easy and straightforward? (12, 13). Trying to predicting the future is a tough job—but we should still try to do it and try to do it well.