Doctor, How Certain Are We That This Diabetes Medication Is Best for Me?"

Concerns about the benefits and harms of antiglycemic oral medications date back to 1970, when reports that sulfonylurea therapy was associated with increased cardiovascular risk were published (1). Although the United Kingdom Prospective Diabetes Survey resolved this controversy (2), we are in the midst of yet another debate: whether rosiglitazone, a second-generation thiazolidinedione, increases the risk for cardiovascular events (3). Given the health importance of diabetes and glycemic control in the population, uncertainty about oral antiglycemic agents affects informed decision making by millions of people in the United States and their physicians.

Evaluating oral antiglycemic agents is difficult because there are so many individual drugs and classes (4) and so much information, largely from industry-sponsored clinical trials. Physicians must cope with conflicting prescribing pressures from pharmacy benefit management programs on the one hand and direct-to-patient marketing on the other. To cut through the confusion, we desperately need objective, systematic analyses of the evidence that informs shared pharmaceutical decision making between patients and physicians.

Fortunately, the U.S. Congress directed the Agency for Healthcare Research and Quality (AHRQ), through the Medicare Prescription Drug, Improvement, and Modernization Act (MMA) of 2003, Section 1013, to establish the Effective Health Care Program to conduct and support research with a focus on “outcomes, comparative clinical effectiveness, and appropriateness of health care items and services (including prescription drugs)” (5). Commissioned by AHRQ under the Effective Health Care Program and its Evidence-based Practice Centers (EPCs) Bolen and colleagues (6) analyzed 216 studies of oral antiglycemic agents; they report their findings in this issue. They concluded that, compared with newer, more expensive agents (thiazolidinediones, α-glucosidase inhibitors, and meglitinides), older agents (second-generation sulfonylureas and metformin) have similar or superior effects on glycemic control, lipids, and other intermediate end points. They also concluded that the evidence from clinical trials about drug effects on major clinical end points, such as cardiovascular mortality, is inconclusive.

All physicians who treat diabetes should carefully review this report for several reasons. First, as Bolen and colleagues note, no systematic review has previously summarized all available head-to-head trials (and placebo-controlled trials) that measured effects on the full range of intermediate end points, including hemoglobin A₁c values, lipid levels, and body weight, and other clinically important outcomes, such as adverse effects and macrovascular events. The authors included data from the U.S. Food and Drug Administration and unpublished trials conducted by industry and used an easily understood evidence grading scale. When studies were sufficiently similar, they did meta-analyses. When they found similar results across pharmacologically similar drugs, they combined them into classes to help readers compare the available options. Moreover, readers need not be concerned about commercially biased conclusions.

This review teaches some general lessons. Because Bolen and colleagues evaluated an entire body of evidence, their findings should shift readers away from relying too heavily on single studies, especially industry-sponsored studies that are often carefully designed to increase the likelihood of a result favorable to the manufacturer by the choice of comparator group, dose, time course, and specified analysis (for example, analyzing only persons who complete a trial instead of all participants) (7). Bolen and colleagues found that clinical outcomes were similar or even better with older agents, which should caution physicians about prescribing newer medications on the basis of claims not approved by the U.S. Food and Drug Administration but made at industry-sponsored continuing medical education programs.

The review has its limitations. It does not discuss the new class of dipeptidyl peptidase-IV inhibitors and only briefly addresses the recent thiazolidinedione controversy. It does not highlight the relative ineffectiveness of triple oral medication therapy, as reported in some small studies (8). However, its major limitation is the research on which it is based: The reviewed studies exclude persons who cannot comply with a study protocol or who have significant comorbid conditions.

Because of the limited generalizability of these studies, practitioners will have to use both the evidence and their clinical judgment to apply findings from Bolen and colleagues’ report to many of their patients (9). Some points are worth reemphasizing. The patient needs to be a partner in a decision-making process that should weigh other factors, such as costs and personal preferences. Knowing one’s hemoglobin A₁c values is the patient’s essential first step in participatory decision making and may facilitate improved glycemic control (10). Patients and physicians must individualize the hemoglobin A₁c target value, because current guidelines recommend against lowering this value below 7% in persons older than 65 years of age, those who have comorbid conditions, and those who are at higher risk for adverse events (11). Because polypharmacy is an important issue for many persons with type 2 diabetes, they should know that intensifying lipid and blood pressure control often has greater impact on length and quality of life than does intensifying glycemic control (12). The ongoing Na-
Physicians and patients should also be cautious about intensifying oral medication therapy solely on the basis of the last hemoglobin A1c result, especially if it is marginally above the patient’s target value. The margin of measurement error around a single hemoglobin A1c value of 7% from a commercial laboratory can range from 6.5% to 7.5% (14), so that small changes may be due to random variation. Moreover, some methods overestimate hemoglobin A1c in individuals (largely from minority groups) who have hemoglobin gene variants. Hemoglobin A1c values vary by season, with an average winter–summer difference of 0.2 percentage point (15). Thus, for some patients, simply reemphasizing education, medical nutritional therapy, and exercise (16) may be appropriate, safe, and cost-effective.

These facts not only argue against a one-size-fits-all target value for hemoglobin A1c but also support an iterative, safety-conscious approach to achieving hemoglobin A1c control (17). An iterative approach need not result in clinical inertia (18), which is a great concern in diabetes management. If control is poor—substantially or consistently above target hemoglobin A1c values—it is time to reevaluate medication adherence and lifestyle factors and screen for depression (19). Absent these concerns, clinicians should increase the current dosage or add a drug from another class of medications unless the patient adamantly refuses.

How should physicians begin and then sequence oral hypoglycemic drugs to achieve the target hemoglobin A1c? The authors of the review recommended metformin as initial drug therapy (6) because it has the best balance of efficacy, side effects, and cost, a recommendation that is consistent with expert opinion (4). They also recommend that sulfonylureas, because their efficacy is similar to that of newer agents, be considered as second-line therapy, especially where cost is a concern to the patient. Until the current controversy about thiazolidinediones is resolved, it seems reasonable to use them only when the other evaluated agents do not provide adequate glycemic control, and perhaps not at all in patients with several other cardiovascular disease risk factors. Finally, because knowledge about the relative efficacy of even newer agents not included in this review is evolving and long-term safety is as yet unknown, I recommend caution in using them in lieu of long-established drugs.

Because type 2 diabetes is a progressive disease caused by β-cell failure, many patients will eventually need insulin. Since patients and physicians often delay starting insulin therapy because they have perceptions or misperceptions about insulin (20), they should engage early in dialogues about the relative benefits, risks, and costs of insulin compared with oral agents. I eagerly await the forthcoming AHRQ-funded systematic review on the comparative effectiveness and safety of insulin preparations.

We physicians cannot provide our patients with certainty about the long-term safety of antiglycemic medications when safety data simply are not available, nor can we guarantee an individual’s response to therapy. Indeed, some patients respond spectacularly; others, not at all. However, we are obligated to provide patients with a careful assessment of the known risks and benefits of medications, as well as the expected benefit of lowering hemoglobin A1c values. Several empirical risk scores allow physicians to estimate a patient’s absolute benefit from improving glycemic control—information that helps to set the patients’ individual hemoglobin A1c target value. The review, because it is objective and comprehensive, provides an unbiased starting point for shared decision making between physicians and their patients with diabetes. Read it now. Keep its main conclusions within arm’s reach as you care for patients with diabetes.

References


eTOCs
Register to receive the table of contents via e-mail at www.annals.org/subscription/etcoc.shtml. You may choose to receive any or all of the following:

- Notification that a new issue of Annals of Internal Medicine is online
- Complete table of contents for new issues
- Special announcements from ACP and Annals
- CME courses
- Early-release articles

430 | 18 September 2007 | Annals of Internal Medicine | Volume 147 • Number 6 | www.annals.org

Downloaded from http://annals.org by guest on 12/31/2018