The type 2 diabetes epidemic continues at great human and financial cost (1). Much of the expense that attends diabetes and its care is attributable to the development of long-term complications, such as retinopathy, nephropathy, and neuropathy, which cause more cases of blindness, renal failure, and amputations than any other disease (2). In addition, diabetes is associated with a 2- to 5-fold increase in cardiovascular disease (3), which contributes to premature mortality. Fortunately, diabetes-specific microvascular complications can be reduced substantially by lowering chronic glycemia (4, 5); whether similar reductions decrease cardiovascular disease in type 2 diabetes is not as clear (6, 7). A hemoglobin A1c (HbA1c) level less than 7%, approximately equal to a mean glucose level of 8.3 mmol/L (150 mg/dL) (8), has been widely adopted as a rational goal with the expectation, based on substantial clinical trial data, that microvascular complications will be reduced and health improved (9, 10).

Although the most persuasive trial in type 2 diabetes, the UKPDS (United Kingdom Prospective Diabetes Study) (4–6), used drugs that are now all available in generic formulations and are relatively inexpensive, the need to achieve and maintain low HbA1c levels and the obvious increasing market for diabetes drugs worldwide have spurred the development of 7 new classes of drugs in the past 15 years (11) to complement the 3 older stalwarts: insulin, metformin, and sulfonylureas. Moreover, the progressive decline in β-cell function and accompanying worsening of glycemic control with longer-duration diabetes (12) have made the development of new drugs attractive, if not necessary. The cost of these new drugs has become increasingly problematic. Between 2001 and 2007, the cost of diabetes medications in the United States almost doubled, from approximately $7 billion to almost $13 billion, largely owing to the use of new, more expensive medications (13).

Given the magnitude of the diabetes epidemic, the need to control glycemia effectively over long periods, and the large number of therapeutic choices now available, it is critical to compare therapeutic agents and treatment strategies. The authors of the international consensus algorithm for the treatment of type 2 diabetes decried the paucity of head-to-head drug comparison studies (9). More recently, recognizing the potential public health importance of comparative effectiveness research (CER), the Patient Protection and Affordable Care Act established the Patient-Centered Outcomes Research Institute to assist patients, clinicians, purchasers, and policymakers in making informed health decisions based on CER. More than $1 billion of American Recovery and Reinvestment Act funding has been dedicated to CER, and Francis Collins, director of the National Institutes of Health, has highlighted the need for CER studies (14). The variable effects of the different classes of antidiabetic agents on long-term glycemia and cardiovascular risk factors and the differences in side effect profiles, safety, tolerability, and cost need to be examined and weighed.

Unfortunately, the randomized, controlled clinical trial by Buse and colleagues (15) in this issue, which was designed in concert with and funded by the manufacturer of exenatide, does little to help us understand the relative role of the new drugs and nothing to advance CER. Like many industry-supported and designed trials, the design of this study is safe for the drug under study, the glucagon-like peptide 1 [7-36 amide] receptor agonist exenatide, by virtue of challenging its efficacy only against a placebo control and not using an active comparator (competitor). The investigators combine exenatide, the major effect of which is to stimulate insulin secretion, with insulin, presumably with the intent of positioning exenatide for a new indication to be used with insulin. The study is admirable in that it used a double-blind design and the same protocol for adjusting the insulin dose in both treatment groups. Whether the study could be effectively blind, however, considering the high (probably >50%) prevalence of gastrointestinal side effects with exenatide, is questionable. Moreover, although the higher insulin doses in the placebo group than the exenatide group seem to suggest that the goal-driven insulin algorithm was applied as designed in both groups, one wonders why the basal insulin dose was not adjusted even more aggressively in the placebo group to achieve the target fasting plasma glucose level less than 5.55 mmol/L (<100 mg/dL); the fasting plasma glucose levels achieved were 6.77 mmol/L (122 mg/dL) in the placebo group and 6.27 mmol/L (113 mg/dL) in the exenatide group.

Buse and colleagues (15) note that the current standard of care for type 2 diabetes is to add preprandial insulin to basal insulin when glucose goals are not being achieved. Because they chose a placebo instead of an active comparator, one can only conclude that exenatide added to insulin decreases HbA1c levels by about 0.7% (similar to the effect of exenatide in other combination drug studies [16]) when compared with standard therapy—and at the expense of 2 additional injections per day, very common gastrointestinal side effects, and an estimated additional cost of $3500 per year (17). The study did demonstrate a differential, albeit small, effect on weight: Exenatide was associated with a 1.8-kg weight loss and insulin with a 1.0-kg weight gain, similar to previous studies (18). The study was only 30 weeks in duration, however, limiting its applica-
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The welcome addition of new agents to treat type 2 diabetes must be tempered by a clear understanding of the relative long-term benefits and risks of the new agents and their combinations. The oldest medications—metformin, sulfonylureas, and insulin—which have been recommended as the first tier of care (10), remain more effective in lowering glycemia and are substantially less expensive than the newer agents. Sulfonylurea and insulin are associated with weight gain, albeit modest, and relatively rare severe hypoglycemia. Such studies as the one by Buse and colleagues are not adequate for comparing the effectiveness and cost-effectiveness of the increasingly complex array of medications at our disposal. Long-term comparative effectiveness studies are needed to determine the best treatment approaches for the ongoing epidemic of type 2 diabetes, which shows no sign of relenting.

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References