Welcome Reassurance About GLP-1 Drugs—But They Are Still Young and Not Fully Grown

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An excellent article in this issue of *Diabetes Care* by Yu et al. (1) provides reassurance about the safety of therapies related to GLP-1. This is welcome because of the current uncertainty and anxiety about the use of these agents, which appear very promising yet not without potential risks. To understand the study's relevance at this stage of development of these agents, consider the process of development of new therapies in general.

Like people, therapeutic agents come in families with individual members and a typical life history. A new class of drugs begins as a pathophysiological insight, a gleam in a scientist's eye. A new drug's childhood consists of testing in animal (preclinical) studies and small human (phase 1 and 2) studies. Moving into larger clinical studies (phase 3), an adolescent drug must show consistent therapeutic effects and a lack of alarming side effects over 6 to 12 months of use in a broader population of people. Good results can lead to approval for clinical practice after which further (phase 4) studies and observation of clinical experience may explore specific clinical indications and safety during more prolonged use. Because drugs are, by necessity, launched when young and without long-term experience, there can be distressing surprises that lead to later restriction of usage. Full understanding of any drug's best uses requires years of experience after its introduction.

The family of antidiabetes agents based on the actions of GLP-1 emerged from studies of this hormone that began just over 20 years ago (2,3). About 10 years ago, drugs designed to exploit the metabolic and weight-regulating effects of the native hormone entered clinical evaluation. The first were peptides capable of activating GLP-1 receptors (GLP-1 receptor agonists, or GLP-1RAs) (4–7). These peptide drugs significantly improve glucose control and favor weight loss but require subcutaneous injection and often cause nausea. Drugs that increase blood levels of native GLP-1 by blocking its enzymatic degradation (dipeptidyl peptidase-4 [DPP-4] inhibitors) soon followed (8–10). They are taken orally and do not cause nausea but have less glucose-lowering power and are more inclined to be weight neutral. Protection of β-cells by GLP-1–related drugs has been shown in animals (11), but confirmation of this benefit in human studies is lacking.

At present, five GLP-1RAs (exenatide [Byetta], delayed-release exenatide [Bydureon], liraglutide [Victoza], albiglutide [Tanzeum], and dulaglutide [Trulicity]) and four DPP-4 inhibitors (sitagliptin [Januvia], saxagliptin [Onglyza], linagliptin [Tradjenta], and alogliptin [Nesina]) are approved for use in the U.S. They are vigorously marketed, their use has grown rapidly, and there is some enthusiasm for including them in standard treatment algorithms because their glycemic and metabolic effects compliment the actions of other classes of drugs (12).

But none of the GLP-1–related drugs is fully grown. Subgroups of patients for whom they may be most helpful and perhaps preferred to older and better-studied drugs are not well defined. How medical benefits and risks may differ between GLP-1RAs versus DPP-4 inhibitors and between individual agents within each group is not clear (13). Moreover, specific safety concerns have emerged. An intense debate about the potential for GLP-1 agents to cause pancreatitis or pancreatic or other cancers flared recently (14–17), and while most epidemiological evidence is reassuring, this issue remains incompletely resolved. More recently, two large randomized trials have tested the safety of saxagliptin (18) and alogliptin (19) in people with type 2 diabetes and high cardiovascular risk. Both showed no increase of pancreatitis or cancer and also no cardiovascular harm or benefit in terms of major cardiac events. However, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) found a statistically significant increase of congestive heart failure (CHF) during treatment with saxagliptin compared with placebo (18). This unexpected finding

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was not observed with alogliptin in the Cardiovascular Outcomes Study of Alogliptin in Patients With Type 2 Diabetes and Acute Coronary Syndrome (EXAMINE) (19) and at present has no clear explanation, although inhibition of clearance of a peptide that alters sodium balance is one possibility. The failure to show cardiovascular benefit and the new safety concern with saxagliptin are especially notable because meta-analysis of preceding phase 3 studies had suggested reduced cardiovascular risk relative to placebo or active comparators (20).

Thus, we have a family of GLP-1–related agents with attractive physiological effects and limited symptomatic side effects yet no long-term evidence for medical benefit together with potential risks. Fortunately, the article by Yu et al. (1) provides further information regarding this dilemma. In response to concern about CHF associated with saxagliptin in SAVOR-TIMI 53, Yu et al. performed a case-control analysis using a large primary care database. They examined a population of more than 50,000 patients with no prior history of CHF who started treatment with glucose-lowering treatments and were followed an average of 2.4 years. Within this cohort, they identified 1,118 people with newly diagnosed CHF of whom 64 (5.7%) were using GLP-1–related drugs. These "cases" were compared with 17,626 "control" patients without CHF who were matched in other ways, of whom 4,198 were using two or more oral glucose-lowering drugs but no GLP-1 agents. The odds ratio (95% CI) for CHF among people using GLP-1–related drugs, compared with the reference population using two or more oral agents, was 0.98 (0.73–1.33) before and 0.85 (0.62–1.16) after adjustment for covariates. Hence, there was no evidence for increased risk of CHF associated with GLP-1–related therapies. Being aware of the potential for confounding by unmeasured factors or faulty assumptions, the investigators performed five secondary analyses and nine sensitivity analyses that either used different analytical tactics or excluded certain categories of data. None of these materially changed the findings.

This study is well done and has significant strengths. It uses a database that is representative of a large community, and the authors expertly use appropriate statistical methods. But, as the authors acknowledge, the study also has important limitations. The population studied was managed by primary care physicians rather than specialists who might see more high-risk patients, and people with prior CHF were not included. It is plausible that a DPP-4 inhibitor might worsen preexisting myocardial dysfunction but not cause symptoms among people without significant cardiac injury. Also, most of the people using GLP-1–related drugs were taking sitagliptin, and the number using saxagliptin was too low for meaningful statistical analysis. As a result, the findings in the high-risk patients using saxagliptin in SAVOR-TIMI 53 are not directly addressed in the current study. Similarly, patients using a GLP-1RA were too few to provide new information regarding whether these agents have cardiovascular effects that are similar to, or unlike, those of DPP-4 inhibitors.

Despite these concerns, the study provides timely reassurance that—at least for people who are routinely treated in primary care settings—there is little short-term risk of harm from DPP-4 inhibitors. However, the inconsistency of findings from various studies, including meta-analyses of preregistration studies, large randomized trials, and this analysis of a clinical practice database, reminds us that we still do not know in detail how to match GLP-1–related drugs to patients who will derive the greatest benefit with least risk. In terms of clinical experience, both the GLP-1RAs and DPP-4 inhibitors, siblings in this new family, are little more than 10 years old. No conclusive evidence in the short-term for either microvascular or cardiovascular benefit is available, and evidence for long-term benefit or harm can only be accrued through continued observation for another decade or two. Our base of evidence will soon expand with anticipated reports from several other large, randomized trials, notably the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) (21) that is testing the cardiovascular effects of sitagliptin and Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) (22) and Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 (Lixisenatide) (ELIXA) that are evaluating liraglutide and lixisenatide.

For the present, all the approved GLP-1–related drugs can be used with some confidence in individualized settings, based on the clinical judgment of the provider and the personal preferences of the patient. However, routine inclusion in evidence-based algorithms in preference to older and better-tested drugs does not yet seem appropriate, especially given the wide differences in cost. Insulin has actively been used for 90 years and metformin and sulfonylureas for 60 years, and as a result their benefit-to-risk ratios for various kinds of patients are well understood. Of the thiazolidinediones, another relatively young family of drugs, only pioglitazone remains widely available, and after approximately 15 years of experience, its use is generally limited to selected situations. We can look forward to similar maturation of our understanding of the GLP-1 agents with the hope that our high expectations will be validated but also the awareness that patience is required and we have much to learn. These teenaged drugs still need guidance and more experience.

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