



eDiabetes Review VOLUME 2, ISSUE 6

THE NEW AGENTS FOR DIABETES: THE MEANING OF SAFETY



In this Issue...

The GLP-1 receptor agonists, the DPP-4 inhibitors, and the SGLT2 inhibitors are newer treatment choices with proven benefit for managing type 2 diabetes. Yet, as we take advantage of these new treatment options, we must not lose sight of their potential risks.

The assessment of safety of new agents is a continually evolving process. In this issue we present a snapshot of the current (at publication time) knowledge and concerns about the potential adverse effects of these newer glycemic control agents, as well as an explanation of the revised FDA guidance for approval of new diabetes-related agents.

Program Information

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Length of Activity

- 1.0 hour Physicians
- 1.0 contact hour Nurses

Launch Date

January 28, 2016

Expiration Date

January 27, 2018

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Describe the risks and benefits of incretin-based agents.
- Evaluate the benefits and safety issues associated with SGLT2 inhibitors.
- Explain how "safety" of glycemic-control agents should be determined by balancing the longer-term risks of a treatment against its potential benefits.

The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of this CME activity.

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GUEST AUTHOR OF THE MONTH

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Guest Faculty Disclosure

Marc Rendell, MD has indicated that he has received grant/researching funding from AstraZeneca, Boehringer-Ingelheim, Eli Lilly and Company, GlaxoSmithKline, Hanmi, Intarcia Therapeutics, Inc., Merck & Co., Inc., Pfizer and Co., and Sanofi.

Unlabeled/Unapproved Uses

Marc Rendell, MD has indicated that there will be no references to unlabeled/unapproved uses of drugs or products.

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COMMENTARY

The incretin-based agents and the SGLT2 inhibitors have brought great benefits to our management of diabetes. Although their effect in lowering blood glucose varies, their added value — in reducing blood pressure, lack of weight gain, and the absence of significant hypoglycemia — present major advantages that all clinicians should recognize when tailoring glycemic control regimens. The recently released results of the EMPA-REG Study of Empagliflozin in people with diabetes who have significant cardiac risk will cause a strong shift to the use of SGLT2 inhibitors.

At the same time, we must recognize that risks exist that need to be considered when evaluating the new agents. Nowhere is the struggle to assure safety more evident than in the process of the development of new diabetes drugs. Diabetes is a chronic condition that causes many long term problems, including microvascular damage to the retina, kidney, and nervous system, as well as cardiovascular complications — conditions that usually take many years and even decades to progress. In the past, the drug approval process for diabetes agents was based solely on a short-term demonstration that glucose levels were improved by use of an agent. "Safety" was loosely defined as lack of excessive undesirable events in a group treated with the investigational agent compared to placebo for a relatively short time, typically 24 to 52 weeks, followed by nonplacebo-controlled "long term" exposure, usually two years.

This approach to ensuring drug safety was shaken by a series of regulatory mishaps in the thiazolidinedione approval process, including deaths from troglitazone-induced liver failure as well as increased cardiovascular deaths in the muraglitazar program.^{1,2}

The evidence for cardiovascular harm resulting from use of the thiazolidinediones (although the analyses were conflicting) led the FDA in 2008 to issue revised guidance for the evaluation of cardiovascular risk for diabetes drug development.³ The article by Rendell (reviewed herein) describes this new process. The FDA now requests that every submission for approval of a new diabetes drug contain a meta-analysis of all component

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Phase 2 and Phase 3 studies to determine a risk ratio for cardiovascular events. This assumes that the study population includes a sufficient percentage of individuals at risk for cardiovascular mortality, including elderly patients, patients with preexisting cardiovascular disease, and those with diabetic nephropathy. It also assumes that the controlled trials contributing to the meta-analysis be of sufficient duration to allow a meaningful chance for cardiovascular events to occur.

The FDA suggests that the 95% upper bound of the risk ratio for the new agent compared to placebo of less than 1.3 would be considered reassuring. They also stipulate that an upper bound greater than 1.8 would typically require a large cardiac outcomes trial prior to approval. A risk ratio upper bound falling in between 1.3 and 1.8 would allow approval but would require a postmarketing study.

This revised guidance has fundamentally changed the approach to approval of new agents for treatment of diabetes. Several such cardiovascular studies have been completed, finding neither evidence of harm nor of particular benefit. As reviewed in this issue by Tella and Rendell, long-term studies of the DPP-4 inhibitors saxagliptin (SAVOR),⁴ sitagliptin (TECOS),⁵ and alogliptin (EXAMINE),⁶ as well as of the GLP-1 agonist lixisenatide (ELIXA),⁷ all showed nonsignificant cardiovascular differences between those agents and standard medical care.

In contrast to these neutral studies, the EMPA-REG Study is the first of the cardiac-targeted approval studies to show a benefit of treatment of a diabetes agent. The paper by Zinman et al (reviewed in this issue) reported lower rates of death from cardiovascular and all causes, as well as lower rates of hospitalization for heart failure in patients treated with empagliflozin versus placebo.

Yet, as the Rendell article points out, the new approach to assessing cardiovascular risk/benefit (even very clear benefit as demonstrated in the EMPA-REG trial, showing a decrease in cardiovascular events and overall mortality) cannot reassure us of the absence of low-frequency unfavorable events. For example, there exists ongoing concern about GLP-1 receptor agonists and medullary carcinoma of the thyroid. In rats, liraglutide studies demonstrated a clear stimulation of C-cell hyperplasia and an increased incidence of associated C-cell neoplasms. While human studies initially showed an increase in calcitonin levels (although within the normal range) in patients treated with liraglutide over one year, extension of the studies to two years suggests that this effect diminishes with time.⁸ But despite these findings, the suspicion still remains that long-term exposure to GLP-1 RAs may lead to thyroid neoplasms in patients with diabetes.⁹

In late August 2015, the FDA issued a warning that there have been rare cases of DPP-4 inhibitor use associated with intense joint pain.¹⁰ They reported 33 cases, most associated with sitagliptin. On discontinuance of sitagliptin, the pain gradually disappeared. There is as yet no explanation of the possible relationship.

The process of drug and device development requires a constant and ongoing analysis of the benefit obtained from new agents versus the risk arising from those agents. A key (and perhaps the most important) benefit of the incretins and SGLT2 inhibitors compared to alternative agents is minimization of hypoglycemic events. While the ACCORD trial results,¹¹ showing increased mortality in the intensive control group, were initially interpreted as suggesting that glucose levels should not be too tightly controlled, others believe that the ACCORD failure was a demonstration that intensive glycemic control is harmful only when it leads to hypoglycemia.¹² Certainly, one of the contributing factors to the success of empagliflozin in EMPA-REG was the absence of hypoglycemia.

Yet, despite the potential advantages suggested by EMPA-REG for using SGLT2 inhibitors, we should be attentive to the potential risks of these agents, as pointed out by Scheen in his review. Genital and urinary tract infections, dehydration, and loss of bone mineral density are significant considerations. Further, the recent reports of diabetic ketoacidosis in SGLT2 inhibitor-treated patients (described by Peters et al) have also raised concerns.

The challenge we face today is that the risks of new therapy often take a very long time to discover, requiring long duration trials with a large number of subjects to arrive at a statistically valid conclusion. Unfortunately, there is no absolute safety. There is a misconception, among both clinicians and the public, that approval of a treatment is a guarantee of its benefit and absence of risk. Quite to the contrary: the true meaning of "safety" is an ongoing, evidence-based consensus that the balance of benefits of a treatment versus adverse consequences is advantageous.

The incretin agents and the SGLT2 inhibitors represent new options to pursue normalization of glucose levels without precipitating hypoglycemia. We would hope that other studies would follow the empagliflozin path to show significant long-term benefit outweighing unfavorable effects.

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BALANCING GLP-1 BENEFITS AND SAFETY

Tella SH, Rendell MS. Glucagon-like polypeptide agonists in type 2 diabetes mellitus: efficacy and tolerability, a balance. *Ther Adv Endocrinol Metab*. 2015 Jun;6(3):109-34.



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When oral agents fail to control glucose levels in type 2 diabetes, clinicians generally choose between adding an injectable GLP-1 receptor agonist (GLP-1 RA) or long-acting (ie, basal) insulin. This 2015 article discusses the five currently available GLP-1 RAs —



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exenatide, liraglutide, lixisenatide, dulaglutide, and albiglutide — covering their comparative effects and known safety considerations.

GLP-1 RA treatment typically can induce a lowering of HbA1c of 0.5%-1.5% over time. Most patients lose weight (2%-5% of initial weight) with GLP-1 RA treatment and almost all gain weight on insulin. Further, there is evidence that GLP-1 RA therapy opposes the loss of β cells, a key clinical feature of type 2 diabetes. Compared to insulin, GLP-1 RA therapy has a lower incidence of hypoglycemia but a much higher incidence of gastrointestinal complaints.

In fact, the most frequently reported adverse effect of GLP-1 RA treatment is gastrointestinal motility disturbance (one of the modes of action of the hormone), and significant nausea, vomiting, and diarrhea may lead to discontinuation of treatment. The benefits of these agents are in part, but not solely, related to the aversive effect of these gastrointestinal complaints on excess food intake. Albiglutide, which has the fewest associated complaints, does not induce significant weight loss.

Concerns exist that all incretin therapies, including GLP-1 RAs, predispose to pancreatitis and to medullary carcinoma of the thyroid. Early clinical trial results suggesting that liraglutide treatment led to an increase in calcitonin levels, indicating a thyroid effect, did not hold in longer-term treatment. The pancreatitis issue, however, has been a longer-lasting concern (specifics are addressed in the reviewed article by Egan et al describing the FDA/EMA findings).

Although daily injection of GLP-1 agents is successful in helping achieve glycemic control, the development of extended release preparations allows for injection once weekly, and perhaps much longer in the future. The extended release formulations of exenatide and albiglutide tend to have a much lower incidence of associated gastrointestinal disturbance than the daily injections, although both have a significant incidence of injection site reactions.

The use of combined long acting insulin and GLP-1 agonists also promises a major therapeutic change. Combined therapy takes advantage of the benefits of both insulin and GLP-1 agents. Furthermore, direct admixture of both in the same syringe will permit flexible dosing, improvement of glucose levels, and reduction of both the hypoglycemia effects of insulin and the GLP-1 RA gastrointestinal side effects.

The GLP-1 RA agents illustrate well the need for clinicians to balance therapeutic benefits (certainly weight loss and a low incidence of hypoglycemia are major advantages) with likely (GI upset, injection site reactions) and potential (pancreatitis) adverse effects. We await the results of longer-term studies to determine how this balance will translate into overall health consequences.

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THE FDA & EMA INVESTIGATE SAFETY OF INCRETIN-BASED AGENTS

Egan AG, Blind E, Dunder K, et al. Pancreatic safety of incretin-based drugs--FDA and EMA assessment. *N Engl J Med*. 2014 Feb 27;370(9):794-797.



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In this jointly authored review, the FDA and the European Medicine Agency presented their analysis of the entire safety base of the incretin-based agents (GLP-1RAs and DPP-4 inhibitors) to assess risk of pancreatitis and pancreatic cancer. The investigators reevaluated more than 250 toxicology studies conducted in nearly 18,000 healthy animals (15,480 rodents and 2475 nonrodents). Microscopic examinations from these toxicology studies yielded no findings of either overt pancreatotoxic effects or pancreatitis. In addition, drug-induced pancreatic tumors were absent in rats and mice that had been treated for up to two years (their life span) with incretin-based drugs, even at doses that greatly exceed the level of human clinical exposure.

Both the FDA and EMA rereviewed their clinical safety databases, including data from more than 200 trials involving approximately 41,000 participants, more than 28,000 of whom were exposed to an incretin-based drug. Small imbalances in the incidence of pancreatitis were reported in premarketing trials, although the overall number of events was small. Furthermore, a pooled analysis of data from 14,611 patients with type 2 diabetes from 25 clinical trials in the sitagliptin database provided no compelling evidence of an increased risk of either pancreatitis or of pancreatic cancer. Clinical trials in which amylase and lipase levels had been monitored in a systematic manner showed that while incretin-based drugs may increase enzyme levels, the mean levels remained within the normal range. The changes in enzyme levels were not associated with gastrointestinal adverse events (ie, abdominal pain, nausea, and vomiting). The investigations concluded that there is no evidence to implicate incretin agents as a direct cause of pancreatitis.

However, despite this comprehensive analysis, suspicion still exists which is certainly reinforced whenever pancreatitis is diagnosed in a patient treated with incretin.

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DPP-4 INHIBITOR SAFETY CONSIDERATIONS

Tella SH, Rendell MS. DPP-4 inhibitors: focus on safety. *Expert Opin Drug Saf*. 2015. Jan;14(1):127-140.



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Oral DPP-4 inhibitors act by blocking the enzyme that degrades GLP-1 in the circulation. The levels of GLP-1 reached with DPP-4 inhibition are lower than with direct administration of GLP-1 receptor agonists. Accordingly, as this 2015 paper points out, the gastrointestinal side effects are minimal and the treatment benefits are less pronounced. In particular, unlike GLP-1 RA therapy, DPP-4 inhibitor treatment does not result in significant weight loss. Five DPP-4 inhibitor agents are now in global use: sitagliptin, vildagliptin, alogliptin, saxagliptin, and linagliptin. Despite the similar effect of these agents on blocking the action of dipeptidyl peptidase 4 on GLP-1, the five agents have substantially different chemical structures. Accordingly, one could possibly expect unique safety issues.

As a group, the DPP-4 inhibitors have few relevant drug interactions. The only exception concerns saxagliptin, which is metabolized to an active metabolite by CYP3A4/5. Therefore, exposure to saxagliptin and its primary metabolite may be significantly modified when saxagliptin is coadministered with specific inhibitors (ketoconazole, diltiazem) or inducers (rifampicin) of CYP3A4/5 isoforms. Linagliptin has primarily enterohepatic excretion, a benefit in patients with renal impairment.

It has been suggested that DPP-4 inhibitors may decrease the degradation of inflammatory peptides such as substance P and bradykinin. As a result, DPP-4 inhibitor use may be associated with a higher incidence of angiotensin converting enzyme inhibitor (ACE-I) related angioedema. In preclinical studies, while there is some evidence that DPP-4 inhibitors may reduce inflammation, no evidence has been presented to date that these agents may reduce the response to infection. Some, but not all the DPP-4 inhibitors, have been associated with a low level frequency of skin reactions. Further, despite lingering uncertainty related to pancreatitis and pancreatic cancer, large, randomized trials have not shown an increased risk with DPP-4 inhibitor treatment.

Several major cardiac safety studies are underway; three have concluded. A major concern arose in the saxagliptin (SAVOR) trial with an increased incidence of congestive heart failure hospitalizations. This issue did not arise in the cardiac trials with either alogliptin (EXAMINE) or sitagliptin (TECOS). None of the three trials showed a higher incidence of major adverse coronary events.

The primary advantage of DPP-4 inhibitors compared to sulfonylureas appears to be a much lower frequency of hypoglycemia, which could translate into a lower incidence of cardiac events in the older population. The results of the CAROLINA trial directly comparing linagliptin and glimepiride on cardiac events (results expected in September, 2018) should shed light on this important question.



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If the CAROLINA trial results are favorable, it is likely that DPP-4 inhibitors will replace sulfonylureas in the treatment of type 2 diabetes.

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SAFETY OF SGLT2 INHIBITORS

Scheen AJ. Pharmacodynamics, efficacy and safety of sodium-glucose co-transporter type 2 (SGLT2) inhibitors for the treatment of type 2 diabetes mellitus. *Drugs*. 2015 Jan;75(1):33-59.



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The SGLT2 inhibitor class of agents — those which reduce hyperglycemia by decreasing the renal glucose threshold and thereby increasing urinary glucose excretion— adds another modality to treat diabetes without the risk of hypoglycemia. Results of numerous placebo-controlled and head-to-head comparison randomized clinical trials lasting up to two years have shown significant reductions in fasting glucose and HbA1c, similar to the results achievable with metformin, DPP-4 inhibitors, and sulfonylureas. However, the risk of hypoglycemia was much lower with SGLT2 inhibitors than with sulfonylureas. Modest weight loss was also achieved, as was a decrease in blood pressure (approaching a systolic reduction of 4-5 mmHg). Moderate renal impairment reduces glucose filtration and accordingly the effect of these agents.

In this 2015 report, Scheen discusses the three agents currently available in the United States and Europe (dapagliflozin, canagliflozin, and empagliflozin), as well as ipragliflozin, which has been released for use in Japan. These agents all have similar pharmacokinetic characteristics, with a rapid oral absorption, a long elimination half-life allowing once-daily administration, an extensive hepatic metabolism mainly via glucuronidation to inactive metabolites, the absence of clinically relevant drug-drug interactions, and a low renal elimination as parent drug.

The SGLT 2 inhibitors are generally well tolerated. The most frequently reported adverse events are female genital infections, as well as a slight increase in urinary tract infections. The diuresis induced by these agents can cause orthostatic hypotension and dehydration — a particular concern in elderly patients. Among the safety issues associated with specific agents:

- Dapagliflozin approval was delayed by FDA concern over a slight excess of cases of breast and bladder cancer reported in the initial studies.
- A nonsignificant trend to increased bone fractures was observed with dapagliflozin and canagliflozin but not with empagliflozin.
- Canagliflozin has a slight crossover effect on SGLT1 and may additionally block intestinal glucose absorption in addition to promoting renal glucose excretion — a potentially significant finding that may make this agent appropriate for type 1 as well as for type 2 diabetes.

The effect of the different SGLT2 inhibitors on the risk of cardiovascular disease is being explored in several large cardiac outcome studies.

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SGLT2 INHIBITORS AND DIABETIC KETOACIDOSIS

Peters AL, Buschur EO, Buse JB, Cohan P, Diner JC, Hirsch IB. Euglycemic Diabetic Ketoacidosis: A Potential Complication of Treatment With Sodium- Glucose Cotransporter 2 Inhibition. *Diabetes Care*. 2015 Sep;38(9):1687-1693.



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Erondu N, Desai M, Ways K, Meininger G. Diabetic Ketoacidosis and Related Events in the Canagliflozin Type 2 Diabetes Clinical Program. *Diabetes Care*. 2015 Sep;38(9):1680-1686.



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The article by Peters et al presents an initial report of 13 episodes in seven patients with type 1 diabetes and two patients with type 2 diabetes. The SGLT2 treatment was clearly used off the labeled indication in the patients with type 1, several of whom used insulin pumps. In all cases, the diagnosis of diabetic ketoacidosis was delayed by deceptively low plasma glucose values. In several cases, rechallenge with the SGLT inhibitor was accompanied by renewed ketosis. The biochemical reason for the onset of diabetic ketoacidosis (DKA) is unclear. Speculation focused on decreased insulin levels related to lower glucose values, dehydration, and hyperglucagonemia induced by the SGLT2 inhibitor treatment.

In a second report in the September 2105 issue of *Diabetes Care*, Erondu et al reviewed the episodes of diabetic ketoacidosis (DKA) reported in the type 2 diabetes population in the canagliflozin preapproval clinical study program.

An analysis of all serious adverse events of DKA and related terms of ketoacidosis, metabolic acidosis, and acidosis was performed using the Janssen database that contained data from 17,596 patients, with nearly 24,000 patient-years of exposure, compiled from completed and ongoing, randomized, controlled clinical studies of canagliflozin. A history of type 1 diabetes or DKA was an exclusion criterion for initial entry in all studies. Through May 11, 2015, 12 patients had 13 unblinded serious adverse events of DKA, ketoacidosis, metabolic acidosis, and acidosis. Eight of the 12 patients had been treated with insulin. Latent autoimmune diabetes of adulthood was diagnosed in six patients. In most but not all cases, blood glucose levels were appropriately elevated.

These reports suggest that much closer surveillance of patients treated with SGLT-2, as well as ketone monitoring, may be required.

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THE COURSE OF APPROVAL OF NEW DIABETES DRUGS

Rendell M. The path to approval of new drugs for diabetes. *Expert Opin Drug Saf*. 2013 Mar;12(2):195-207.



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While the evaluation of effectiveness of agents to lower elevated blood glucose is straightforward and can be done with short-duration studies, it is more difficult to demonstrate the safety of these agents over long periods of clinical use. This article by Rendell addresses that dilemma. A number of large studies have raised questions about the cardiovascular risks of certain drugs such as the thiazolidinediones and have even challenged the wisdom of aggressive attempts to normalize plasma glucose. As a result of this uncertainty, the FDA issued new Guidance to Industry to assess cardiovascular risk. This new approach has markedly increased the burden to achieve approval of new diabetes drugs.

The thiazolidinedione saga shows that certain risks do not clearly manifest in the relatively short duration studies needed to evaluate control of blood sugar levels. Furthermore, the UKPDS and DCCT-EDIC studies show us that the lowering of plasma glucose has a beneficial effect that can only be reliably assessed over a very long time period.

The present-day approval process is flawed in the basic conception that regulatory agencies can guarantee absolute safety. It is important to acknowledge that the risk/benefit relationship for new agents can only be determined by ongoing, long-term clinical experience and prolonged, longitudinal, controlled studies. It is suggested that the

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increased costs that result from thorough safety evaluations must be defrayed by early initial approval and marketing of new therapeutic agents, and patent lifetimes and marketing exclusivity should be prolonged until results of the long-term studies are finalized.

The success of empagliflozin in the EMPA-REG Trial (see below) has highlighted the importance of the suggestions conveyed in this article.

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SGLT2 INHIBITOR (EMPAGLIFLOZIN) & CARDIOVASCULAR OUTCOMES

Zinman B, Wanner C, Lachin JM, et al; EMPA-REG OUTCOME Investigators. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*. 2015 Sep 17; 373:2117-2128.



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This is the first cardiac study in the new FDA Path to Approval Guidance series to demonstrate a clear and striking cardiovascular benefit of a diabetes drug. A total of 7020 patients were treated with 10 mg or 25 mg of the SGLT2 inhibitor empagliflozin or placebo once daily. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, as analyzed in the pooled empagliflozin group versus the placebo group. The primary outcome occurred in 490 of 4687 patients (10.57%) in the pooled empagliflozin group and in 282 of 2333 patients (12.17%) in the placebo group (hazard ratio in the empagliflozin group, 0.86; 95.027% confidence interval, 0.74 to 0.99; $P = .04$ for superiority; median observation time = 3.1 years), with no significant differences between the 10 mg and 25 mg groups in the rates of myocardial infarction or stroke. In addition, the investigators reported significantly lower rates of death from cardiovascular causes in the empagliflozin patients (3.7%, vs 5.9% in the placebo group; 387% relative risk reduction), hospitalization for heart failure (2.77% and 4.17%, respectively; 357% relative risk reduction), and death from any cause (5.7% and 8.37%, respectively; 327% relative risk reduction).

It is unlikely that improvement in glycemic control alone accounted for the success of empagliflozin in this trial. At 12 weeks of treatment, by which time an outcome difference was already evident, the adjusted mean differences in the HbA1c percentage between empagliflozin and placebo was only -0.547% (957% CI, -0.58 to -0.49) in the 10 mg group and -0.60 percentage points (957% CI, -0.64 to -0.55) in the 25-mg group. By week 206, the HbA1c differences had actually narrowed to -0.24 percentage points (95% CI -0.40 to -0.08) and -0.36 percentage points (957% CI, -0.51 to -0.20). The authors suggest that SGLT2 inhibitor-induced reduction in blood pressure and intravascular volume by osmotic diuresis may be more important contributory factors than glycemic benefit to the large benefit observed.

Analysis of unfavorable side effects was reassuring. There were reductions in overall and severe adverse events in the empagliflozin groups, mainly as a result of improvements in cardiovascular status. The investigators reported a fourfold increase in genital infections in both men and women, and in urosepsis, but not in urinary tract infections. There were no significant differences in volume depletion, heart rate, diabetic ketoacidosis, bone fracture, or thromboembolism. Most reassuring, there were fewer episodes of acute renal failure in the empagliflozin group, and creatinine levels remained stable. Cardiovascular benefits were even seen in patients with decreased renal function.

These impressive cardiovascular results compare favorably to the positive results of treatment in similar large-scale studies of statin drugs and ACE inhibitors — and changes the landscape for diabetes treatment. In addition to providing evidence to support the use of the SGLT2 inhibitors, it constitutes a challenge to other treatment modalities to show equivalent advantages.

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KEY TAKEAWAYS

- The GLP-1 receptor agonists, DPP-4 inhibitors, and the SGLT2 inhibitors have great potential benefit because of reduction in glucose levels, weight loss or avoidance of weight gain, and in particular, minimal association with hypoglycemia.
- There is still controversy over the possible increased risk of pancreatitis with incretin agents, despite a large evidence base to the contrary.
- Empagliflozin has recently been shown to have substantial cardioprotective effects; however, the SGLT2 inhibitors are less beneficial in patients with renal impairment, and there is now concern over possible stimulation of diabetic ketoacidosis.
- Determining the actual "safety" of a diabetes treatment agent goes beyond the initial drug approval process (even with the revised FDA guidance that requires cardiovascular safety testing). In the absence of long-term evidence-based safety data in the general population, clinicians must maintain an awareness of what is currently known about the benefits versus risk of each agent and should contribute their experience as well.

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IMPORTANT CME/CE INFORMATION

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