

## COMMENTARY

## After Metformin, What Comes Next? Empagliflozin?

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### Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Zinman B, Wanner C, Lachin JM, et al; EMPA-REG OUTCOME Investigators  
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The EMPA-REG OUTCOME trial is part of the new wave of cardiovascular (CV) outcome trials required by the US Food and Drug Administration (FDA) for all new diabetes drugs. Empagliflozin is in the relatively new class of antihyperglycemics known as sodium-glucose cotransporter 2 (SGLT2) inhibitors, which reduce renal glucose reabsorption and thus increase glucose excretion through the urine.

#### Risk or Benefit?

EMPA-REG recruited participants from 42 countries. The investigators randomly assigned 7020 patients with established CV disease to receive 10 mg or 25 mg of empagliflozin or placebo once daily against a background of standard diabetes care. Background glucose-lowering therapy was to remain unchanged for the first 12 weeks after randomization; investigators were then encouraged to adjust glucose-lowering therapy to achieve glycemic control according to local guidelines.

The primary composite outcome was death from CV causes, nonfatal myocardial infarction, or nonfatal stroke, as analyzed in the pooled empagliflozin group vs the placebo group. Secondary outcomes included the primary outcome plus hospitalization for unstable angina, hospitalization for heart failure, and all-cause mortality. Effects on glycemia and other cardiometabolic risk factors were also assessed.

#### A Reduction in Risk

Compared with placebo, the pooled empagliflozin groups had a 38% lower risk for death from CV causes, a 32% lower risk for all-cause mortality, and a 35% lower risk for hospitalization for heart failure (all statistically significant). For independent analyses of the 10-mg dose and the 25-mg dose vs placebo, the risk reduction was virtually identical but did not reach significance because of smaller numbers of events in each dosage group. In addition, the glycated hemoglobin (A1c) level was significantly lower in each empagliflozin dosage group compared with placebo, ranging from -0.60 to 0.24 percentage points at weeks 12 and 206, respectively. Of interest, the dose response of empagliflozin was negligible.

#### Abstract

### Early Glycaemic Control in Metformin Users Receiving Their First Add-On Therapy: A Population-Based Study of 4,734 People with Type 2 Diabetes

Thomsen RW, Baggesen LM, Sogaard M, et al  
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This observational cohort study used electronic databases in Northern Denmark from 2000 to 2012 to assess glycemic control of people who initiated metformin monotherapy and then added another glucose-lowering agent within 3 years. Specifically, the investigators examined attainment of A1c goals (<7.0% and <6.5% among "healthy" patients) within 2 to 6 months following the add-on therapy. They then compared these levels among patients who added one of five categories of second-line agents: sulfonylurea; dipeptidyl peptidase-4 (DPP-4) inhibitors; glucagon-like peptide-1 (GLP-1) receptor agonists; insulin; or other antihyperglycemic drugs (undefined in the study). Analyses used sulfonylurea as the reference category and adjusted for age, sex, preintensification A1c, diabetes duration, complications, and Charlson Comorbidity Index.

#### Do Second-Line Agents Differ in Effectiveness?

Of the 4734 patients in the analysis, 52% added sulfonylurea, 27% added a DPP-4 inhibitor, 7% added a GLP-1 receptor agonist, 8% added insulin, and 6% added something else. Of note, and as one might expect, that distribution was decidedly different depending on when the add-on occurred (eg, between 2000 and 2003 vs from 2010 to 2012).

In any case, the proportion reaching an A1c of <7% was generally similar across therapies (59% for sulfonylurea, 59% for

DPP-4, 62% for GLP-1) although somewhat lower for insulin (42%) and "other" antihyperglycemics (50%). Absolute reductions in A1c were generally similar for each of the drug classes, ranging from -0.8 to -1.3 percentage points, except for insulin (-2.4 percentage points). However, the statistically adjusted relative risk of attaining A1c <7.0% was 6% lower for DPP-4, 10% higher for GLP-1, 12% lower for insulin, and 14% lower for other antihyperglycemics compared with sulfonylureas.

An important confounder was that the proportion of all metformin users who attained A1c targets of <7% after add-on therapy increased from 46% in 2000-2003 to 59% in 2010-2012, a time trend that was associated with decreasing preintensification A1c values over time.

## Abstract

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## Analysis and Commentary

As the number of drug classes available for treating diabetes continues to grow, the decision of what to prescribe and when to prescribe it becomes ever more difficult. Professional organizations have published guidelines for antihyperglycemic therapy,<sup>[1-3]</sup> and scholarly papers also offer advice,<sup>[4,5]</sup> but none of these publications offer a definitive step-by-step algorithm.

From the Danish study presented above, one might gather that the choice of a second-line agent makes little difference, as all provide an approximately equal antihyperglycemic benefit. Yet safety concerns swirl around every option,<sup>[6]</sup> and the newest class of drugs (SGLT2 inhibitors) were not included in Thomsen and colleagues' analysis.

Furthermore, the study may be too confounded by time to draw definitive conclusions. Because the observation period spanned 13 years, some of the drugs analyzed were not available in the earlier years, thus imposing a systematic bias. Moreover, as the authors pointed out, the baseline A1c (before initiation of the second agent) was lower in the later years, and this has been shown to be the single most important predictor of the therapeutic success of several agents.<sup>[7-10]</sup> Although the authors controlled for baseline A1c, a statistical correction may not have been sufficient.

The ongoing GRADE (Glycemic Reduction Approaches in Diabetes) study is a pragmatic clinical trial designed to compare second-line agents in a more systematic fashion.<sup>[11]</sup> GRADE includes four classes of agents added to metformin (sulfonylurea, DPP-4, GLP-1, and insulin) but also does not include an SGLT2 arm. Thus even if a clear "winner" emerges from the four classes studied, it will not be known whether that class is superior to SGLT2 inhibitors.

Since 2008, the FDA has required that new diabetes drugs demonstrate that they pose no excess CV risk, including adjudicated assessment of CV events in phase 2, phase 3, and long-term CVD outcomes trials. Several of these studies have now been completed, including SAVOR (saxagliptin), EXAMINE (alogliptin), TECOS (sitigliptin), and ELIXA (lixisenatide), all of which showed that the agents neither increased nor decreased CV risk.<sup>[12]</sup>

### Empagliflozin Benefits With Caveats

EMPA-REG OUTCOME is the first trial to report on SGLT2 inhibitors and the first to demonstrate a CV benefit. Despite this result, there are several reasons why empagliflozin is not necessarily the next drug to add to metformin monotherapy.

First, the study design consisted of empagliflozin (or placebo) on top of existing and additional therapies. About 75% of participants were on metformin; nearly 50% were already on insulin; over 40% were on a sulfonylurea; and only 30% were on monotherapy of any kind. Thus, this clearly was not intended to test the benefits of the drug as a second-line therapy.

Second, by the end of the trial, a higher proportion of patients in the placebo group were receiving insulin or a sulfonylurea, both of which are suspected of increasing CV risk, although definitive proof is lacking.<sup>[13,14]</sup>

Third, the A1c reduction with empagliflozin was fairly small, although still better than the reduction in the placebo arm, which included any adjustments clinicians deemed necessary to achieve glycemic control. Therefore, if substantial A1c reduction is the goal, empagliflozin may not be the solution.

Finally, the mechanism by which empagliflozin achieved superiority is entirely speculative. The authors offered several possibilities, but supporting these was beyond the scope of the trial.

It should also be noted that other SGLT2s are on the market. Whether the benefits achieved with empagliflozin are drug-specific or a class effect is not known. I would also be remiss not to mention the FDA's warning that SGLT2 inhibitors may cause ketoacidosis. Other potential concerns include elevated risk for urinary tract or genital infections and renal injury. However, rates of these and other adverse events did not differ between the arms in the EMPA-REG study.

So here we are, with much more data to consider but still no closer to an answer on what to add when intensification of metformin monotherapy becomes necessary. For now at least, the guidelines have it right: The best option for this patient may not be the same as for that patient.

That means that we should take a patient-centered approach that considers the specific needs, goals, and health status of each patient. A growing number of options may complicate the clinician's decision-making process, but they should nevertheless benefit patients with diabetes.

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