Mortality Reduction in EMPA-REG OUTCOME Trial: Beyond the Antidiabetes Effect

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Two recent large-scale cardiovascular outcome trials, a now common tool in assessing the safety of pharmacological treatments for type 2 diabetes, reported significant reductions in all-cause mortality. In EMPA-REG OUTCOME [BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients], patients who received the SGLT2 inhibitor empagliflozin had a notable reduction of 9.2 deaths per 1,000 per year, while LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long Term Evaluation) found that the patients receiving the GLP-1 receptor agonist liraglutide had a reduction of 3.7 deaths per 1,000 per year. The hypotheses to explain the sizable mortality reduction in EMPA-REG OUTCOME have mainly focused on the potential cardiovascular mechanisms of empagliflozin, but none considered its expected antidiabetes effects. I estimated the portion of the reduction in mortality observed in EMPA-REG OUTCOME expected to be a result of its antidiabetes effects, as measured by glycemic control and the need for additional antidiabetes medication, and contrasted it with LEADER. With use of the mean 0.45% reduction in HbA_{1c} with empagliflozin compared with placebo in EMPA-REG OUTCOME, the rate reduction of 9.2 deaths per 1,000 per year would be expected to be at most 4.5 deaths per 1,000 per year, leaving 4.7 deaths per 1,000 per year otherwise explained. On the other hand, LEADER's rate reduction of 3.7 deaths per 1,000 per year with liraglutide would be expected to be 3.5 by virtue of its effect on HbA_{1c}, leaving 0.2 deaths per 1,000 per year explained otherwise. Similar results were found using the need for additional antidiabetes treatment during follow-up to measure the antidiabetes impact. In conclusion, the expected antidiabetes effects of empagliflozin and liraglutide on the reduction in mortality are important. However, empagliflozin appears to have significant additional effects on survival, possibly due to specific cardiovascular mechanisms, which merit further investigation.

Cardiovascular outcome trials have become common practice in evaluating the risks and benefits of newer pharmacological treatments for type 2 diabetes in terms of major clinical outcomes. Such large-sized trials have been conducted to study the effects of dipeptidyl peptidase 4 inhibitors (DPP4i), glucagon-like peptide 1 receptor agonists (GLP-1a), and sodium–glucose cotransporter 2 inhibitors (SGLT2i) (1–8). Besides their primary composite outcome based on pooling several cardiovascular events into one, these studies also reported the effects of these drugs on all-cause mortality (Table 1). The DPP4i trials did not find any benefit of these drugs on mortality, but LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long Term Evaluation), a trial of the GLP-1a liraglutide, and EMPA-REG OUTCOME [BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients], a trial of the SGLT2i empagliflozin, reported significant reductions in all-cause mortality with these drugs (5,7).

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Table 1—Rates of all-cause mortality and hazard ratios from major randomized cardiovascular outcome trials of medications to treat type 2 diabetes

						All-cause mortality		
						Rate (no. per 1,000 PYs)		
Trial	Year	Study drug	Population	Sample size	Median follow-up (years)	Study drug	Placebo	Hazard ratio (95% CI)
DPP-4i								
SAVOR-TIMI 53 (1)	2013	Saxagliptin	CVD or risk factors	16,492	2.1	24.9*	22.6*	1.11 (0.96–1.27)
EXAMINE (2)	2013	Alogliptin	Post-ACS	5,380	1.5	37.8†	43.0†	0.88 (0.71–1.09)
TECOS (3)	2015	Sitagliptin	CVD	14,671	3.0	24.8	24.5	1.01 (0.90–1.14)
GLP-1a								
ELIXA (4)	2015	Lixisenatide	Recent ACS	6,068	2.1	31.0	33.0	0.94 (0.78–1.13)
LEADER (5)	2016	Liraglutide	CVD or risk factors	9,340	3.8	21.5†	25.2†	0.85 (0.74–0.97)
SUSTAIN-6 (6)	2016	Semaglutide	CVD or risk factors	3,297	2.1	18.2	17.6	1.05 (0.74–1.50)
SGLT2i								
EMPA-REG OUTCOME (7)	2015	Empagliflozin	CVD	7,020	3.1	19.4	28.6	0.68 (0.57–0.82)
CANVAS (8)	2017	Canagliflozin	CVD or risk factors	10,142	2.4	17.3	19.5	0.87 (0.74–1.01)

ACS, acute coronary syndrome; CVD, cardiovascular disease; ELIXA, Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 (Lixisenatide); EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; PYs, person-years; SAVOR-TIMI 53, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin. *Estimated using the total person-years of follow-up reported for each group (16,884 for saxagliptin and 16,761 for placebo). †Estimated using the median duration of follow-up for the trial.

While LEADER resulted in a 15% reduction in mortality with liraglutide, EMPA-REG OUTCOME was particularly notable for the magnitude of this effect, namely, a risk reduction of 32% in all-cause mortality with empagliflozin. While this remarkable mortality reduction is undeniable from the robustness of the trial design, these findings have been the subject of several hypotheses on the mechanisms of action of empagliflozin that could explain such sizable reductions. The authors of the trial submitted that the cardiovascular benefits of empagliflozin are multidimensional, involving changes in arterial stiffness, cardiac function, cardiac oxygen demand, and cardio-renal effects, as well as several other cardiovascular-related effects (7). The "diuretic hypothesis" and the "thrifty substrate hypothesis" have also been proposed as potential explanations for this benefit (9,10). Finally, others have also presented several possible mechanisms but prefer to await further data, implying perhaps that the EMPA-REG OUTCOME remarkable risk reductions may, at least in part, be the result of random statistical variation (11). However, a Bayesian analysis demonstrated the statistical robustness of the findings (12). No one has addressed antidiabetes effects on this mortality reduction.

In this article, I use a statistical projection based on epidemiological data to approximate the antidiabetes effect of empagliflozin in comparison with liraglutide. The analysis, a hypothesis-generating simulation, is based on the antidiabetes effects of these drugs, as measured by glycemic control and the need for antidiabetes medications initiated during the trial follow-up.

IMPACT OF DIABETES DISEASE PROGRESSION

Two ways to measure disease progression in diabetes are the increase in glycated hemoglobin (HbA_{1c}) level over time and the need for additional antidiabetes treatment (13). These measures have both been associated with mortality in observational studies. While the more specific cardiovascular mortality end point would have been preferred for this analysis, as it was also shown to be significantly reduced in both EMPA-REG OUTCOME and LEADER, the available epidemiological data did not report on this end point but, rather, on all-cause mortality. Thus, my analyses are based on the broader all-cause mortality end point.

First, in terms of the change in HbA_{1c}, the UK Prospective Diabetes Study (UKPDS) reported that each 1% reduction in mean HbA_{1c} was associated with a significant reduction of 14% (95% CI 9–19) in the rate of death from any cause (14). Therefore, to quantify the expected impact of each drug on mortality from its effect on HbA_{1c}, I applied the UKPDS estimate to the actual mean reduction in HbA_{1c} from LEADER and EMPA-REG OUTCOME. However, since the mean reductions in HbA_{1c} from the trials were likely attenuated by the introduction of other antidiabetes agents, I performed these calculations using simulated reductions 1.5-, 2.0-, and 2.5-fold higher than those actually attained in the trials.

Second, in terms of the need for additional antidiabetes treatment, insulin and sulfonylureas have been associated with increased risks of death in several observational studies (15,16). One such study, that included >84,000 patients treated for type 2 diabetes, reported crude rates of all-cause death of 50.7 per 1,000 per year under sulfonylurea monotherapy and 46.0 under insulin compared with 14.9 under metformin monotherapy (17). These correspond to rate ratios of around 3 for the risk of death associated with these drugs. Note that these crude rate differences comparing sulfonylurea and insulin with metformin do not imply that the drugs increase mortality to that extent but, rather, imply that the need for these drugs reflects more severe disease, which itself is associated with higher mortality. Thus, to quantify the expected impact of each drug on mortality from its effect from additional antidiabetes treatments, we can consider that the rate of death in a trial is composed of a weighted average of three rates: the rate under the randomized treatment, the rate under the addition of a sulfonylurea, and the rate under the addition of insulin during follow-up. The approach is thus to

extract from the rates reported in a trial the additional risk due to the introduction of sulfonylurea and insulin treatments during follow-up. As a result, we can obtain corrected rates of death under the study drug and placebo exclusively, free from the effects of these other drugs, and a corresponding "residual" rate difference of death comparing exclusively the study drug with placebo. I simulated these calculations assuming a range of increased risks of death associated with need to add the sulfonylurea and insulin treatments as reported in the observational study, with rate ratios ranging from 1.5 to 3.0 for the association between these drugs and mortality. For simplicity in calculating the weighted average of three rates, I used as weights the proportion of person-time of use of these additional drugs, assuming that the patients who initiated sulfonylurea and insulin treatments during follow-up did so halfway into follow-up. As verification I also considered the hypothetical rate ratio value of 1.0 for the additional effect of these drugs on mortality.

IMPACT ON LEADER AND EMPA-REG OUTCOME

In LEADER, 4,668 patients received liraglutide and 4,672 received placebo, with a median follow-up of 3.8 years. There were 381 deaths from any cause under liraglutide (rate 21.5 per 1,000 per year) compared with 447 deaths under placebo (rate 25.2 per 1,000 per year). During follow-up, among the patients under liraglutide, 349 (7.5%) initiated a sulfonylurea and 1,346 (28.8%) initiated insulin treatment, compared with 505 (10.8%) and 2,019 (43.2%) under placebo, respectively. Moreover, the mean reduction in HbA_{1c} with liraglutide was 0.40% compared with placebo.

In EMPA-REG OUTCOME, 4,687 patients received empagliflozin and 2,333 received placebo, with a median follow-up of 3.1 years. There were 269 deaths from any cause under empagliflozin (rate 19.4 per 1,000 per year) compared with 194 deaths under placebo (rate 28.6 per 1,000 per year). During follow-up, among the patients under empagliflozin, 176 (3.8%) initiated a sulfonylurea and 272 (5.8%) initiated insulin treatment compared with 164 (7.0%) and 268 (11.5%) under placebo, respectively. Moreover, the mean reduction in HbA_{1c} (%) with empagliflozin was 0.45 compared with placebo.

Table 2 shows the impact using the approach based on the reduction in glycemic control. It shows that EMPA-REG OUTCOME attained a mean reduction in HbA_{1c} of 0.45% with empagliflozin, corresponding with an expected HbA_{1c}-related rate reduction of 1.9 deaths per 1,000 per year, leaving 7.3 deaths per 1,000 per year from the trial's actual rate reduction of 9.2 deaths per 1,000 per year. With use of the simulated reductions 1.5-, 2.0-, and 2.5-fold higher than the actual 0.45% attained in the trial, the expected HbA_{1c}-related rate reductions are 2.8, 3.6, and 4.5 deaths per 1,000, respectively.

On the other hand, LEADER's attained mean reduction in HbA_{1c} of 0.40% with liraglutide corresponds with an expected HbA_{1c}-related rate reduction of 1.5 deaths per 1,000 per year, leaving 2.2 deaths per 1,000 per year from the trial's actual rate reduction of 3.7 deaths per 1,000 per year. With use of the simulated reductions 1.5-, 2.0-, and 2.5-fold higher than the 0.40%, the expected HbA_{1c}-related rate reductions are 2.2, 2.9 and 3.5 deaths per 1,000, respectively.

These data comparing EMPA-REG OUTCOME and LEADER are also depicted in Fig. 1. Supplementary Table 1 extends Table 2 to include the expected impact of the attained mean reduction in HbA_{1c} data from SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes) and CANVAS (CANagliflozin cardioVascular Assessment Study), two trials on mortality that did not find an effect of the drugs on all-cause mortality.

Table 3 depicts the impact of additional antidiabetes treatments, with the first row showing this impact assuming no effect (rate ratio of 1) for sulfonylurea and insulin on mortality, corresponding with EMPA-REG OUTCOME's actual reported rate reduction of 9.2 deaths per 1,000 per year with empagliflozin compared with placebo. Table 3 shows that the rate reduction of 9.2 deaths per 1,000 per year decreases gradually to a residual of 4.6 deaths per 1,000 per year as the rate ratio for the effect of sulfonylurea and insulin increases from 1.5 to 3.0. On the other hand, Table 3 shows that for LEADER, the reported rate reduction of 3.7 deaths per 1,000 per year with liraglutide compared with placebo decreases gradually to a residual zero rate reduction with increasing effects of sulfonylurea and insulin. These data are also depicted in Fig. 2.

CONCLUSIONS

I have shown that a portion of the remarkable reduction in mortality observed with

Table 2—Simulation to compute the expected* and residual rate differences of all-cause death from EMPA-REG OUTCOME and LEADER of medications to treat type 2 diabetes from the impact of the study drugs on the HbA_{1c} reduction in the trials

	EMPA-REG OUTCOME				LEADER			
Simulated HbA_{1c} reduction	HbA_{1c} reduction (%)	Observed mortality rate difference (per 1,000 per year)	Expected HbA_{1c}-related mortality rate difference (per 1,000 per year)*	Residual rate difference (per 1,000 per year)	HbA_{1c} reduction (%)	Observed mortality rate difference (per 1,000 per year)	Expected HbA_{1c}-related mortality rate difference (per 1,000 per year)*	Residual rate difference (per 1,000 per year)
Observed (trial)	0.45	−9.2	−1.9	−7.3	0.40	−3.7	−1.5	−2.2
Observed ×1.5	0.67	−9.2	−2.8	−6.4	0.60	−3.7	−2.2	−1.5
Observed ×2	0.90	−9.2	−3.6	−5.6	0.80	−3.7	−2.9	−0.8
Observed ×2.5	1.12	−9.2	−4.5	−4.7	1.00	−3.7	−3.5	−0.2

Computations include simulated HbA_{1c} reductions 1.5-, 2.0-, and 2.5-fold higher than those actually attained in the trials to account for the attenuation resulting from the introduction of hypoglycemic drugs during follow-up. *Expected HbA_{1c}-related mortality rate difference computed using the UKPDS's reported reduction in the rate of death from any cause for each 1% reduction in mean HbA_{1c} (14).

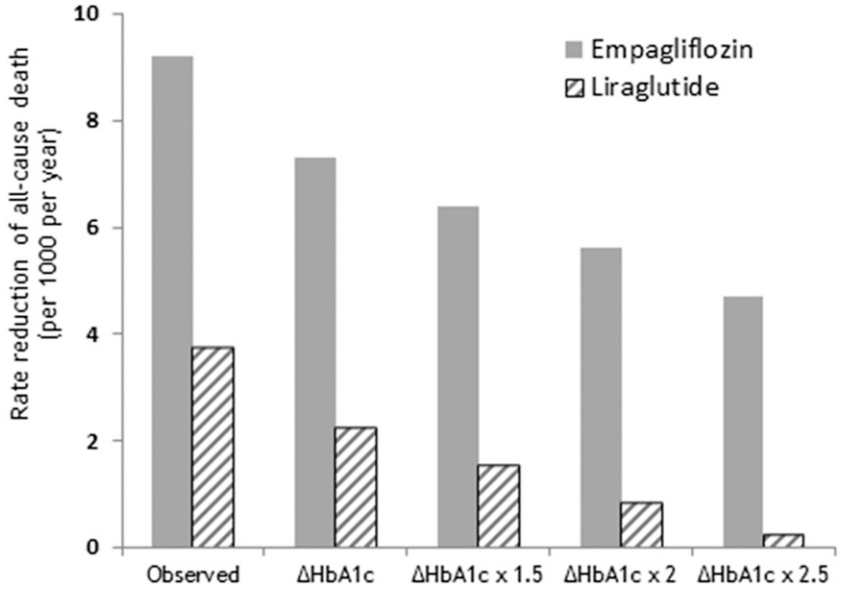

Figure 1—Simulation to compute the residual rate reduction of all-cause death from EMPA-REG OUTCOME and LEADER after accounting for the impact of the drugs on the HbA_{1c} reduction in the trials, with simulated HbA_{1c} reductions 1.5-, 2.0-, and 2.5-fold higher than those attained in the trials.

empagliflozin in EMPA-REG OUTCOME can be expected from the antidiabetes effects of this drug. Indeed, empagliflozin reduced HbA_{1c} and the need for additional antidiabetes treatment. Using data from observational studies, I found that the expected diabetes-related effects on the reduction of 9.2 deaths per 1,000 per year with empagliflozin compared with placebo accounted for at most one-half of this reduction, leaving around half otherwise explained. In contrast, LEADER's reduction of 3.7 deaths per 1,000 per year with liraglutide compared with placebo appears to be accounted for exclusively by the expected antidiabetes effects.

My simulation using the reduction in HbA_{1c} is certainly approximate, as the relationship between reducing HbA_{1c} and mortality cannot be translated directly to randomized trial effects (14). I deemed that the reductions in HbA_{1c} in the two trials were likely affected by the greater introduction of hypoglycemic agents in the placebo group during the trial. As a result, I simulated greater theoretical reductions in HbA_{1c} with the drugs to account for this attenuation in the actual effect on the HbA_{1c}. Nevertheless, using the HbA_{1c} reduction to measure the antidiabetes effects is not itself entirely robust, as most of the other large cardiovascular outcome trials to date, listed in Table 1, showed reductions in HbA_{1c} with the study drugs but no effect on mortality. Certainly, novel research avenues need to be explored to better understand these incongruences.

It is useful to note that, for my simulation based on the need for additional antidiabetes treatment, I used the crude rate ratios of death associated with sulfonylureas and insulin rather than the adjusted ones. The distinction is important because I am claiming that the higher mortality is attributed not to the sulfonylurea or insulin itself, which would be represented by the adjusted rate ratio, but, rather, to the more severe disease in patients requiring these drugs, represented by the crude estimate. This choice of the crude estimates more accurately reflects the trial experience where a selected group of patients with more severe disease (selected based on severity, and not random) is given insulin or sulfonylureas during the course of the trial. My simulation was based on the all-cause mortality end point—not the more specific cardiovascular mortality end point, which would have been preferred for this analysis. Indeed, EMPA-REG OUTCOME and LEADER both showed lower cardiovascular mortality, but the available epidemiological data did not report on this end point, restricting my analysis to the all-cause mortality end point.

None of the hypotheses put forward for the reduction in mortality observed with empagliflozin discussed its expected antidiabetes effects. My calculations, albeit approximate, show that a portion of the reduction in all-cause mortality can be explained by the antidiabetes effects of empagliflozin. Indeed, simulating even

Table 3—Simulation to compute the corrected* and residual rate differences of all-cause death in EMPA-REG OUTCOME and LEADER of medications to treat type 2 diabetes from the impact of initiating other antidiabetes drugs during follow-up

	EMPA-REG OUTCOME				LEADER			
Rate ratio of death from initiation of antidiabetes drugs during follow-up	Corrected rate of death (per 1,000 per year)*		Diabetes-related rate difference (per 1,000 per year)*	Residual rate difference (per 1,000 per year)	Corrected rate of death (per 1,000 per year)*		Diabetes-related rate difference (per 1,000 per year)*	Residual rate difference (per 1,000 per year)
	Placebo	Empagliflozin			Placebo	Liraglutide		
1.0 (no effect)	28.6	19.4	−0.0	−9.2	25.2	21.5	−0.0	−3.7
1.5	26.2	18.5	−1.5	−7.7	19.8	18.2	−2.1	−1.6
2.0	24.1	17.7	−2.8	−6.4	16.3	15.8	−3.2	−0.5
2.5	22.4	17.0	−3.8	−5.4	13.8	13.9	−3.8	+0.1
3.0	20.9	16.3	−4.6	−4.6	12.0	12.5	−4.1	+0.4

Simulation is assuming rate ratios ranging from 1.0 to 3.0 for the excess effect from adding sulfonylurea and insulin treatments during follow-up.
*Corrected for diabetes disease progression as measured by need for initiation of antidiabetes drugs during follow-up.

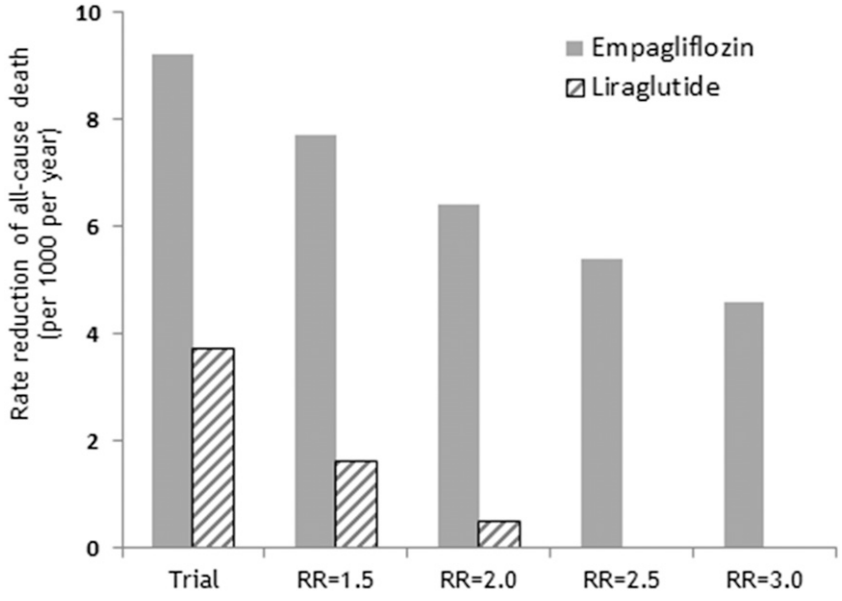

Figure 2—Simulation to compute the residual rate reduction of all-cause death in EMPA-REG OUTCOME and LEADER after accounting for the excess effect of adding sulfonylureas and insulin during follow-up, assuming rate ratios (RR) ranging from 1.0 to 3.0 for the effect of these drugs.

the most extreme antidiabetes effects explains about half the reported rate reduction of all-cause death of 9.2 per 1,000 per year with empagliflozin compared with placebo, leaving half otherwise explained. On the other hand, the most extreme antidiabetes effects explain the entire effect observed with liraglutide in LEADER, the only other cardiovascular outcome trial that reported a significant reduction in all-cause mortality.

My analysis suggests that there possibly remains an important cardiovascular benefit of empagliflozin, which is likely multidimensional, involving several cardiovascular mechanisms, as well as the "diuretic hypothesis" and the "thrifty substrate hypothesis." While recognizing the limitations of this hypothesis-generating statistical projection, my analysis nevertheless provides a complementary perspective into the findings of these cardiovascular outcome trials and stimulates further research. Certainly, further investigation into the cardiovascular properties of empagliflozin could even possibly lead to interesting new avenues in the management of cardiovascular disease.

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