Diabetes medications with cardiovascular protection – what now after LEADER®? Could metformin, pioglitazone, empagliflozin and liraglutide complement each other to save lives?

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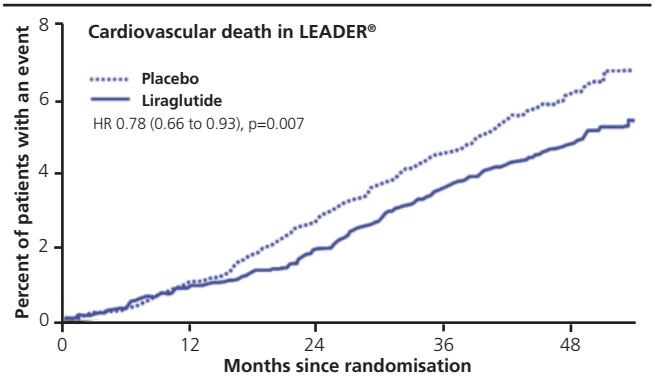
We suggested in a previous editorial that the combination of metformin, pioglitazone and empagliflozin would likely improve cardiovascular outcomes in patients with type 2 diabetes at high cardiovascular risk.[1] This conclusion was 15 years in the making: 7 years between the UK Prospective Diabetes Study (UKPDS) in 1998[2] and the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) study in 2005,[3] and then another 8 years from there to the landmark moment when we saw the results of the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes trial (EMPA-REG OUTCOME™) at the European Association for the Study of Diabetes (EASD) 2015 in Stockholm.[4,5] Against this background, it is remarkable that we needed to wait only another 9 months for a similar moment at American Diabetes Association (ADA) 2016 in New Orleans. This 4th landmark event, when the finding shown in Figure 1 was greeted with loud applause, was the presentation of the results of the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER®) study, which evaluated the effect of the glucagon-like peptide-1 receptor agonist (GLP-1RA) liraglutide on cardiovascular outcomes in people with type 2 diabetes at high cardiovascular risk.[6,7] Once again though, as the results unfolded, we realised that we were to be left with as many questions as answers.

Our previous editorial concluded that the accumulated evidence from multiple studies suggests that pioglitazone (PROactive) probably exerts its beneficial effects by slowing down – or even reversing – the atherosclerotic process.[1] Empagliflozin (EMPA-REG OUTCOME™), which reduced cardiovascular death but not myocardial infarction or stroke, seemed to have an entirely different mechanism, more haemodynamic in nature and involving the combined effects of a decrease in blood pressure (after load reduction) and volume depletion (preload reduction).[1,8] Other hypotheses have now been proposed, including the possibility that empagliflozin, by increasing circulating ketone bodies, provides the failing myocardium with a more efficient fuel source.[9] Further evidence for pioglitazone as an agent of cardiovascular protection has also emerged from a study in an insulin resistant (but non-diabetic) population with recent prior ischaemic stroke or transient ischaemic attack; in this study the risk of recurrent stroke plus myocardial infarction was reduced by 24% in patients who received pioglitazone versus those who received placebo.[10] These mechanisms of cardiovascular benefit are potentially complementary. Accordingly, we proposed that combination therapy with pioglitazone and empagliflozin might provide additive, or even multiplicative, cardiovascular benefits in people with diabetes at high cardiovascular risk compared with either given alone.[1]

Figure 2 shows side-by-side the effects of empagliflozin in EMPA-REG OUTCOME™ and liraglutide in LEADER® on three-

Figure 1. Cumulative incidence of death from cardiovascular causes in the liraglutide group versus placebo group in the LEADER study



Hazard ratios [HR (95%CI)] based on Cox regression analysis
Adapted from reference 6

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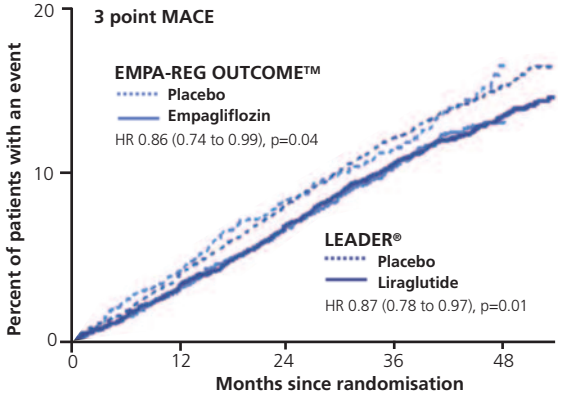
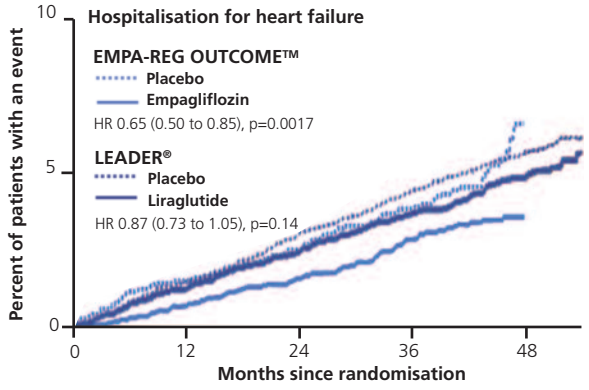
Figure 2. Side-by-side comparison of the effects of empagliflozin (EMPA-REG OUTCOME™) and liraglutide (LEADER®) on the cumulative incidence of three-point major adverse cardiovascular events (MACE)



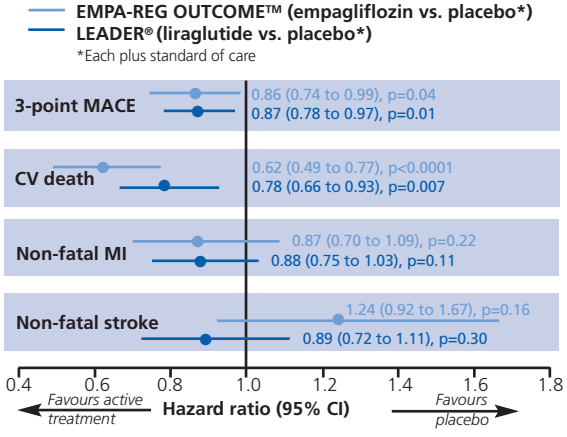
Hazard ratios [HR (95%CI)] based on Cox regression analysis
EMPA-REG graphs adapted from reference 4, LEADER graphs adapted from reference 6

Figure 4. Side-by-side comparison of the effects of empagliflozin (EMPA-REG OUTCOME™) and liraglutide (LEADER®) on the cumulative incidence of hospitalisation for heart failure



Hazard ratios [HR (95%CI)] based on Cox regression analysis
EMPA-REG graphs adapted from reference 4, LEADER graphs adapted from reference 6

Figure 3. Comparison of the effects of empagliflozin (EMPA-REG OUTCOME™) and liraglutide (LEADER®) on the risk of three-point major adverse cardiovascular events (MACE) and its components. Hazard ratios [HR (95%CI)] based on Cox regression analysis



CV, cardiovascular; MI, myocardial infarction
Adapted from references 4 and 6

point major adverse cardiovascular events (MACE: cardiovascular death, myocardial infarction and stroke).[4-7] In Figure 3 the individual components of the three-point MACE endpoint, in addition to the primary composite outcome, are shown side-by-side for the two studies.[4,6] The improvement in three-point MACE in EMPA-REG OUTCOME™ was clearly driven by the reduction in cardiovascular death. This is less striking for LEADER®, although it is noticeable that the greatest benefit is once again on cardiovascular death. Moreover, empagliflozin markedly reduced the risk of hospitalisation for heart failure in EMPA-REG OUTCOME™, while liraglutide did not in LEADER® (Figure 4).[4-7] As only empagliflozin reduced heart failure but both empagliflozin and liraglutide reduced cardiovascular death, it is possible that liraglutide acted, at least in part, by different mechanisms to those of pioglitazone and empagliflozin. An extensive list has been put forward as to what these different mechanisms might be,[8,9,11] and hopefully future research will narrow this down. In the meantime, we have the intriguing possibility that pioglitazone, empagliflozin and liraglutide might work synergistically to improve cardiovascular outcomes by different mechanisms in patients with type 2 diabetes at high cardiovascular risk.

The Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With Lixisenatide (ELIXA) study did not show cardiovascular benefit for the GLP-1RA lixisenatide.[12] However, the ELIXA patients were a less broad-based high cardiovascular risk group than the LEADER® patients as they had all had an acute coronary event in the last 180 days and the trial was of shorter duration. Further, lixisenatide is short-acting (4–6 hours) and patients are thus not covered by the drug for the majority of the day. At present it is unclear whether other longer acting GLP-1RAs will demonstrate a similar cardiovascular benefit to that observed in LEADER®. However, the preliminary dissemination of the top-line results for Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6) indicate that treatment with once-weekly semaglutide for 2 years was associated with a statistically significant reduction in cardiovascular risk.[13]

When considering the combination of pioglitazone and em-

Key messages

- The PROactive, EMPA-REG OUTCOME™ and LEADER® trials show pioglitazone, empagliflozin and liraglutide respectively, all reducing three-point MACE (cardiovascular death, myocardial infarction and stroke), but the results are only similar at first sight
- The accumulated evidence suggests that pioglitazone reduces cardiovascular death, myocardial infarction and stroke by slowing down, or even reversing, the atherosclerotic process. The EMPA-REG OUTCOME™ trial suggests that empagliflozin reduces cardiovascular death but does not reduce either stroke or myocardial infarction, signifying a different mechanism to that of pioglitazone, more hemodynamic in nature
- The LEADER® trial again shows a bigger impact of liraglutide on cardiovascular death than on stroke and myocardial infarction but, in contrast to empagliflozin, no impact on heart failure. This suggests a different mechanism for liraglutide to that of both pioglitazone and empagliflozin
- The combination of metformin, pioglitazone, empagliflozin and liraglutide now appears to be the optimum cocktail of medications for improving both glycaemic control and cardiovascular outcomes for people with type 2 diabetes at high cardiovascular risk. The evidence we have today suggests that these agents in combination could complement each other to prevent cardiovascular events and save lives

pagliflozin, we proposed the possibility that sodium-glucose cotransporter-2 (SGLT2) inhibitors might mitigate the fluid retention associated with pioglitazone,[1] and clinical evidence for such an effect of SGLT2 inhibitors has recently emerged.[14] When considering the combination of pioglitazone and liraglutide, the weight gain associated with pioglitazone might be mitigated by the weight loss associated with liraglutide, as well as with an SGLT2 inhibitor. Indeed, the Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes (EDICT) study showed that a combination of metformin, pioglitazone and exenatide resulted in overall weight loss.[15] As exenatide and liraglutide have similar weight-reducing effects in people with type 2 diabetes,[16] it is likely that the same would apply to liraglutide in such a combination. Meanwhile, evidence is accumulating to support the early use of a triple-therapy combination of metformin, pioglitazone and a GLP-1RA as optimal initial antidiabetic therapy.[15] This approach achieved lower HbA_{1c}, weight loss and much less hypoglycaemia compared with the traditional approach of sequential escalation through metformin, sulphonylurea and insulin; the traditional approach also led to weight gain.[15] In the wake of EMPA-REG OUTCOME™ and LEADER®, a combination of metformin, pioglitazone, empagliflozin and liraglutide now appears to be the optimum cocktail of medications for improving both glycaemic control and cardiovascular outcomes for people with type 2 diabetes at high cardiovascular risk. The evidence we have today suggests that the agents in this combination could complement each other to prevent cardiovascular events and save lives.

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