Diabetes medications with cardiovascular protection in the wake of EMPA-REG OUTCOME: the optimal combination may be metformin, pioglitazone and empagliflozin

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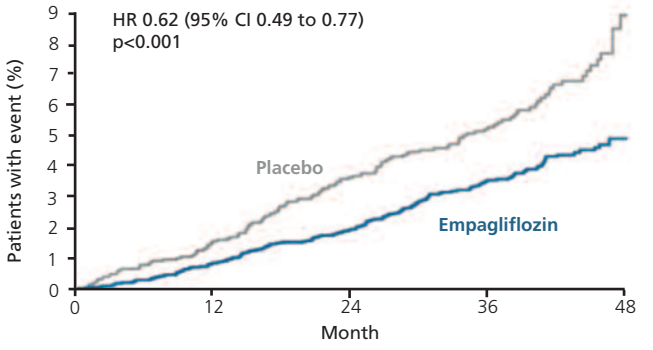
Those of us who were in the huge, packed auditorium when the slide shown in Figure 1 went up on the screen at 17.15 on the 17th September, at the European Association for the Study of Diabetes 2015 congress in Stockholm, were aware that this was one of those landmark moments in the history of diabetes care. There was loud applause. The event was the presentation of the results of the EMPA-REG OUTCOME study, which evaluated the effect of the SGLT2 inhibitor, empagliflozin, on cardiovascular outcomes in people with type 2 diabetes at high cardiovascular risk.[1,2] As the whole story of the results unfolded, however, we realised that we were going to be left with as many questions as answers. In particular it seemed that empagliflozin reduced death from cardiac causes but did not reduce non-fatal myocardial infarction or stroke, a combination of findings which was at first sight difficult to understand. Comparing and contrasting the graphs from EMPA-REG, such as the one shown in Figure 1, with those from other studies is a quick way of getting a feel for the subject of antihyperglycaemic medications that might play a part in reducing cardiovascular risk.

Figure 2 shows the Kaplan-Meier plots for metformin in the 10-year, observational follow-up of the United Kingdom Prospective Diabetes Study (UKPDS),[3] which suggested the value of metformin as a cardioprotective agent seen in the earlier, randomised phase of the study.[4] Intensive glycaemic management with metformin, but not with a sulphonylurea or insulin, reduced cardiovascular outcomes, in comparison with the conventional (mainly diet-based) management of the time, during the original trial.[3,4] The fact that this occurred even though there was less reduction in HbA_{1c} in the metformin group (who were overweight) than the sulphonylurea-insulin group points to a special effect of metformin over and above any effect on glycaemic control.[3,4] It is noteworthy however that it took at least 3 years before the curves shown in Figure 2 for metformin really started to separate with regard to myocardial infarction or death from any cause. The patients in the UKPDS were newly diagnosed and developed their cardiovascular disease over many years. Furthermore, all of the metformin-treated subjects were overweight or obese and the number receiving this treatment (n=342) would be considered small for a cardiovascular outcomes study by today's standards.

Figure 1. The cumulative incidence of death from cardiovascular causes in the empagliflozin group versus placebo group in the EMPA-REG OUTCOME



Hazard ratios (HR) are based on Cox regression analysis. Reproduced with permission from ref 2.

The EMPA-REG OUTCOME study involved patients at high cardiovascular risk, as all had established cardiovascular disease in addition to being older (mean age 63 years at baseline), with a longer duration of diabetes (82% were diagnosed >5 years previously).[1,2] It can now be accepted by most that the status of pioglitazone as an agent of cardiovascular protection in such patients is supported by overwhelming evidence, with objections to this view no longer having credence.[5,6] Figure 3 shows side by side the effects of empagliflozin (EMPA-REG OUTCOME trial[2]) and pioglitazone (PROactive trial[7]) on 3-point major adverse cardiovascular events (MACE; death, myocardial infarction or stroke) in patient populations at high cardiovascular risk. These appear similar at first sight, but closer examination of the data reveals that empagliflozin significantly reduced cardiovascular death, but not myocardial infarction or stroke.[1,2] Also, the curves for cardiovascular death, shown in Figure 1, separate almost immediately (as do the curves in figure 3a; whereas in figure 3b there is a delay). In a meta-analysis of 19 randomised controlled trials, pioglitazone-treated patients had significantly lower rates of

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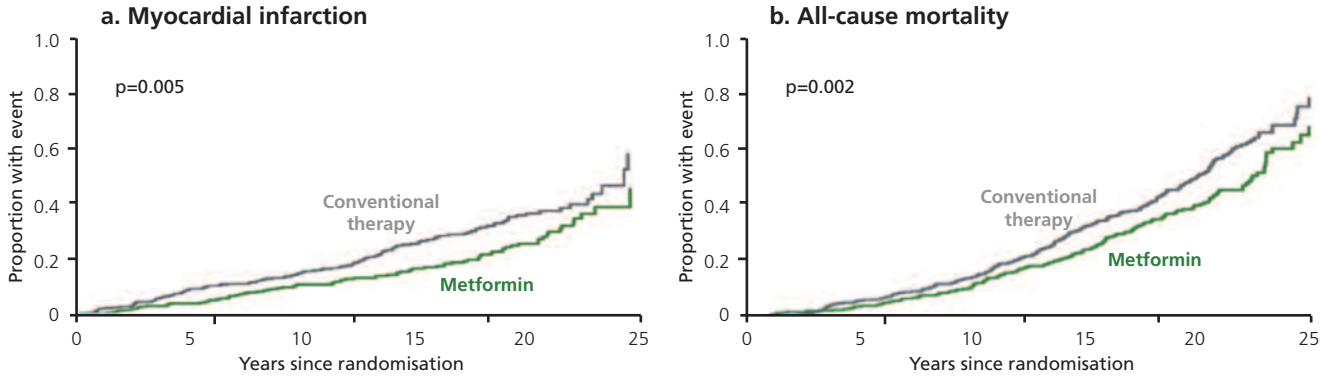
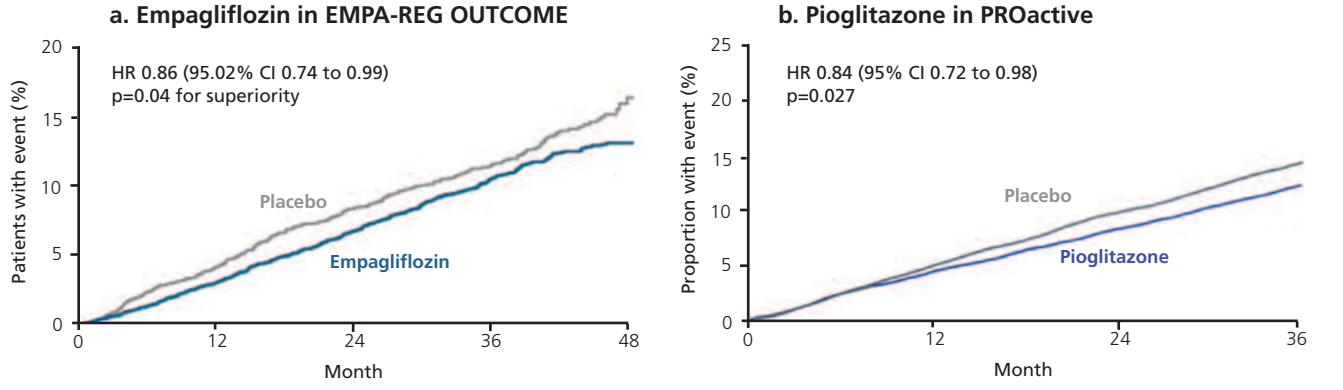
Figure 2. The proportions of patients in the United Kingdom Prospective Diabetes Study who had myocardial infarction (Figure 2a) and death from any cause (Figure 2b) for the metformin group versus the conventional therapy group



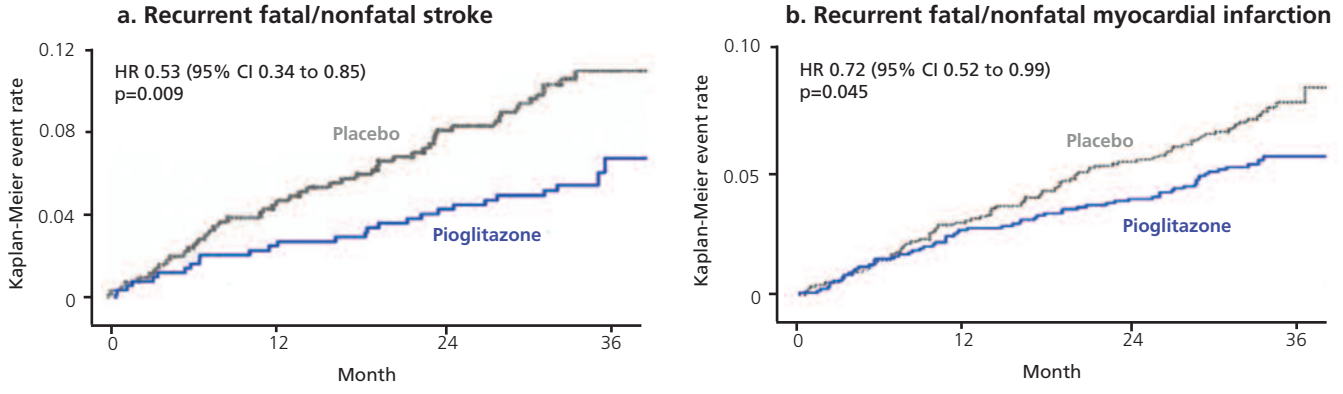
Kaplan-Meier plots show cumulative incidence and log-rank P values are shown at 5-year intervals during a 25 year period from the start of the interventional trial (including randomised treatment followed by observational post-trial follow-up). Reproduced with permission from ref 3.

Figure 3. Side by side comparison of the effects of empagliflozin (EMPA-REG OUTCOME, Figure 3a) and pioglitazone (PROactive study, Figure 3b) on the cumulative incidence of 3-point MACE



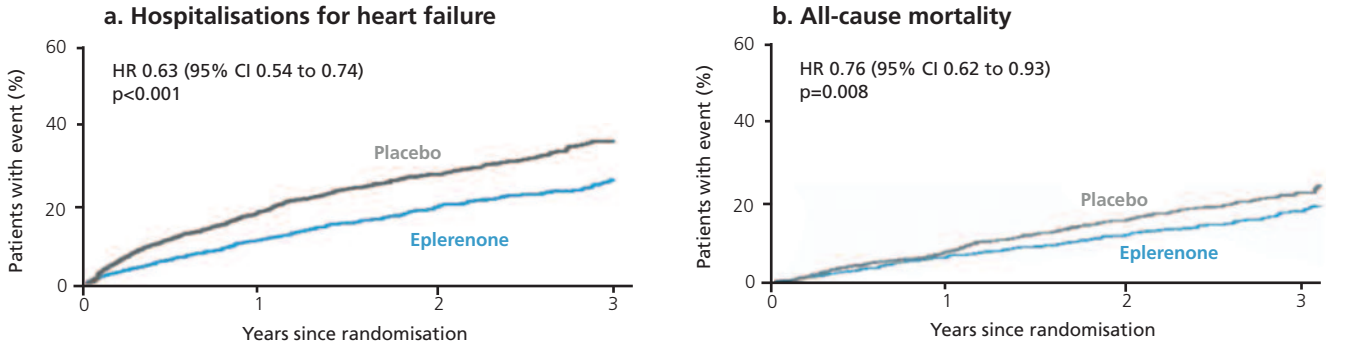
HR: hazard ratio; MACE: major adverse cardiovascular event; 3-point MACE: death, myocardial infarction, or stroke. Reproduced with permission from refs 2 and 7.

Figure 4. Kaplan-Meier curve of the time to fatal stroke/non-fatal stroke in the patients in the PROactive study who had had a previous stroke (Figure 4a) and of time to fatal/non-fatal myocardial infarction (excluding silent myocardial infarction) in patients in the PROactive study who had had a previous myocardial infarction (Figure 4b)



HR: hazard ratio. Reproduced with permission from refs 9 and 10.

Figure 5. Cumulative Kaplan-Meier estimates of rates of hospitalisation for heart failure (Figure 5a) and deaths from any cause (Figure 5b) in the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF)



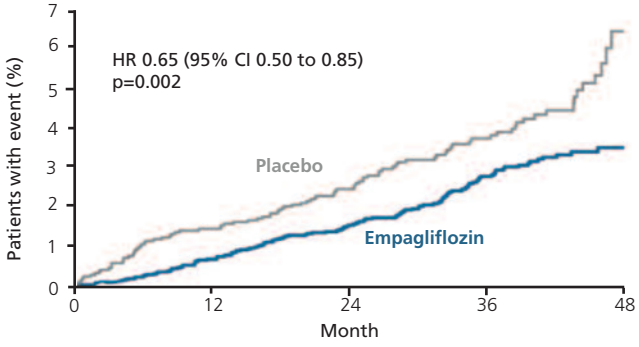
HR: hazard ratio. Reproduced with permission from Ref 13.

death, myocardial infarction and stroke compared with those receiving control therapy.[8] Moreover, pioglitazone reduced the risk of recurrent stroke (Figure 4a) and of recurrent myocardial infarction (Figure 4b).[9,10] This contrasts with the data from EMPA-REG OUTCOME, which suggested that empagliflozin did not reduce the risk of either stroke or myocardial infarction.[1,2]

Pioglitazone also slowed the progression of carotid intima-media thickness (a marker of atherosclerosis) compared with glimepiride,[11] and pioglitazone-treated patients showed a significantly lower rate of progression of coronary atherosclerosis, as assessed using intravascular ultrasonography, compared with glimepiride-treated patients.[12] Thus, the accumulated evidence raises the possibility that pioglitazone might slow down, or even reverse, the atherosclerotic process. With empagliflozin it would seem that something entirely different is going on. Figure 5 shows data from the EMPHASIS-HF heart failure trial, which demonstrated that the mineralocorticoid receptor antagonist, eplerenone, reduced the risk of both death and hospitalisation for heart failure.[13] It is again noteworthy that the graphs separate almost immediately, especially with regard to heart failure. Empagliflozin also reduced the risk of hospitalisation for heart failure in EMPA-REG OUTCOME (Figure 6).[1,2] Comparison of the data on empagliflozin (Figures 1 and 6) with those for eplerenone (Figure 5) suggests similarities between the impact of empagliflozin and this natriuretic and antikaliuretic diuretic agent on these outcome measures. Heart failure may play a part in the mortality of patients with ischaemic heart disease, and reduced risk of death through heart failure may provide at least one mechanism to explain the reduced risk of cardiovascular death with empagliflozin in Figure 1. As an SGLT2 inhibitor, empagliflozin has diuretic properties and also reduces systolic/diastolic blood pressure by 4-5/1-2 mmHg (and thus has the potential to reduce both preload and afterload).[14,15] Whether or not this is a mechanism for the beneficial outcomes observed in EMPA-REG OUTCOME, it does seem that the mechanism underlying these benefits differs from that of pioglitazone.

Putting all of this together raises the possibility that the combination of metformin, pioglitazone and empagliflozin might be additive, or even multiplicative, with regard to reducing, or perhaps even reversing, cardiovascular risk in people with diabetes who are already

Figure 6. The cumulative incidence of hospitalisation for heart failure in the empagliflozin group versus placebo in the EMPA-REG OUTCOME study



Hazard ratios (HR) are based on Cox regression analysis. Reproduced with permission from ref 2.

at high risk. As fluid retention is a side-effect of pioglitazone,[6] the combination of pioglitazone and empagliflozin might well be particularly favourable with empagliflozin mitigating the fluid retention associated with pioglitazone. Indeed, in a study where empagliflozin was added to pioglitazone or pioglitazone and metformin, weight was also reduced along with HbA_{1c} and fasting plasma glucose.[16]

It is perhaps unfortunate that it is less likely that a trial will compare the combination of pioglitazone and empagliflozin and metformin against, say, pioglitazone and metformin alone or empagliflozin and metformin alone, now that pioglitazone is off-patent. We await with interest the results of the cardiovascular outcome studies with canagliflozin (CANVAS)[17] and dapagliflozin (DECLARE-TIMI58).[18] Perhaps the Data Monitoring Committees of those trials might, in the light of EMPA-REG OUTCOME, stop the trials early if it becomes clear that they are heading for a similar result. However, as we famously found out with glitazones and cardiovascular disease, we cannot assume a class effect applies here; while rosiglitazone and pioglitazone were in the same class, the possibility arose that rosiglitazone might cause cardiovascular harm, whilst pioglitazone caused

Key messages

- The UKPDS and its 10-year, observational, follow up, suggested the value of metformin as a cardioprotective agent. The PROactive and EMPA-REG OUTCOME trials show pioglitazone and empagliflozin reducing 3-point MACE: cardiovascular death, myocardial infarction and stroke; but the results are only similar at first sight
- The accumulated evidence suggests pioglitazone reduces cardiovascular death, myocardial infarction and stroke by slowing down, or even reversing, the atherosclerotic process
- The EMPA-REG trial suggests that empagliflozin reduces cardiovascular death but does not reduce either stroke or myocardial infarction, signifying a different mechanism to that of pioglitazone. The EMPA-REG trial data is reminiscent of that from the EMPHASIS-HF heart failure trial with the mineralocorticoid receptor antagonist, eplerenone
- The diuretic properties of empagliflozin, as an SGLT2 inhibitor, may mitigate the fluid retention associated with pioglitazone and the combination of metformin, pioglitazone and empagliflozin would seem to be advantageous for patients with type 2 diabetes at high cardiovascular risk

cardiovascular benefit.[5,6,19] We also await with interest the results of the LEADER study with liraglutide,[20] which may be presented during 2016.

In the meantime, the current data would suggest that the combination of metformin, pioglitazone and empagliflozin would be advantageous for patients with type 2 diabetes at high cardiovascular risk. Given the accumulated evidence in favour of the early use of a combination of metformin, pioglitazone and a GLP-1 receptor agonist as the treatment paradigm of choice for the optimal management of patients with type 2 diabetes,[6,21] it may be that the optimum cocktail in the wake of EMPA-REG OUTCOME now becomes metformin, pioglitazone, empagliflozin, and a GLP-1 receptor agonist.

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