Diabetes medications with cardiovascular protection after HARMONY Outcomes and DECLARE-TIMI 58: could metformin, pioglitazone, SGLT2 inhibitors and long-acting GLP-1 receptor agonists complement each other to save lives by different mechanisms?

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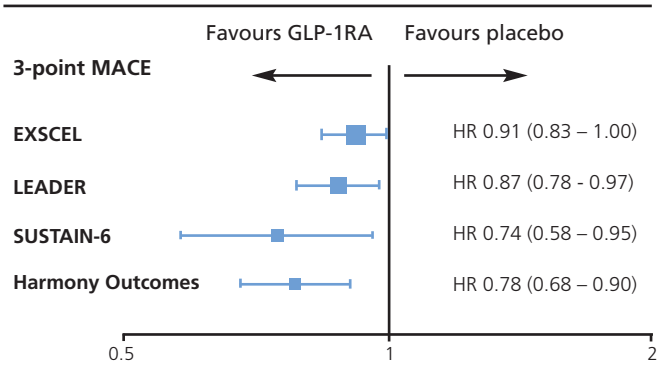
In previous editorials[1-4] we proposed that metformin, pioglitazone, sodium glucose transporter 2 (SGLT2) inhibitors (in particular empagliflozin and canagliflozin) and long-acting glucagon-like peptide-1 (GLP-1) receptor agonists (in particular liraglutide) in combination could complement each other to prevent cardiovascular events and save lives in patients with type 2 diabetes at high cardiovascular risk. Since those editorials, new information has come to light to increase our understanding in the field; in particular, a presentation on 2 October 2018 during the European Association for the Study of Diabetes Congress in Berlin, Germany of the results of the HARMONY Outcomes study[5,6] and, on 10 November 2018 during the American Heart Association, Scientific Sessions in Chicago, USA, the results of the DECLARE-TIMI 58 study.[7,8]

HARMONY Outcomes was a randomised controlled trial of the long-acting GLP-1 receptor agonist (GLP-1RA) albiglutide (which is not commercially available) against placebo in 9,463 patients with type 2 diabetes and established cardiovascular disease.[5,6] In line with previous cardiovascular outcome studies, HARMONY Outcomes assessed as its primary outcome the three-point Major Adverse Cardiovascular Events (3-point MACE: cardiovascular death, non-fatal myocardial infarction and non-fatal stroke). There was a 22% reduction in 3-point MACE (HR=0.78, 95% CI 0.68 to 0.90).[5,6] By 8 months, mean HbA_{1c}, weight and systolic blood pressure decreased by 0.63%, 0.66 kg and 0.65 mmHg, respectively, in the albiglutide group compared with placebo.[5,6] Figure 1 shows side by side the results of the four cardiovascular outcome studies with long-acting GLP-1RAs and is in keeping with a class effect for this group of agents. In making this statement we refer to our previous editorial[4] where we proposed that the difference in outcome between the LEADER (liraglutide) and EXSCEL (exenatide QW) cardiovascular outcome studies with regard to statistical significance might be related to the fact that the LEADER patients were at higher cardiovascular risk and had longer exposure to study medication than the EXSCEL patients due to a high discontinuation rate in EXSCEL.[4] Although only top line results are available, REWIND, which compared dulaglutide against placebo in 9,931 patients with type 2 diabetes who were at high cardiovascular risk or who had a prior cardiovascular event, also demon-

Figure 1. Comparison between the results of the four cardiovascular outcome studies with long acting GLP-1 receptor agonists. The agents studied were exenatide QW (EXSCEL), liraglutide (LEADER), semaglutide (SUSTAIN-6) and albiglutide (HARMONY Outcomes)



MACE, major adverse cardiovascular event. HR, hazard ratio. Adapted from EASD Virtual Meeting (5).

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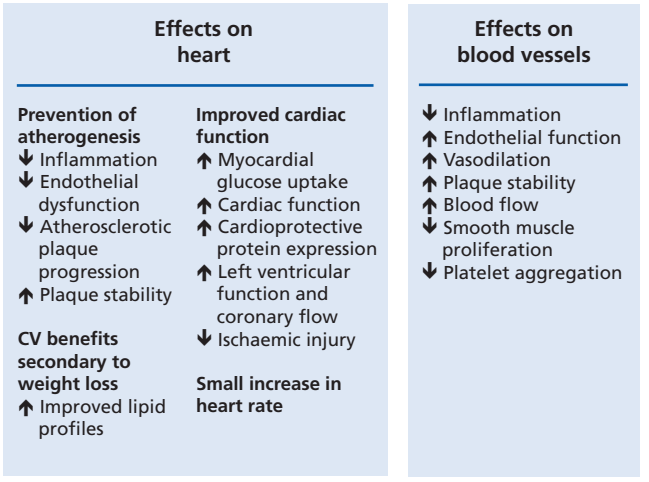
Figure 2. GLP-1 receptor agonists are associated with a number of cardiovascular effects



Evidence for these benefits originates from human and animal studies (11-13). CV, cardiovascular. GLP-1, glucagon-like peptide-1.
Adapted from references 11-13.

strated a significant reduction in 3-point MACE.[9] We await with interest the full presentation of the results at the 79th Scientific Sessions of the American Diabetes Association in June 2019.

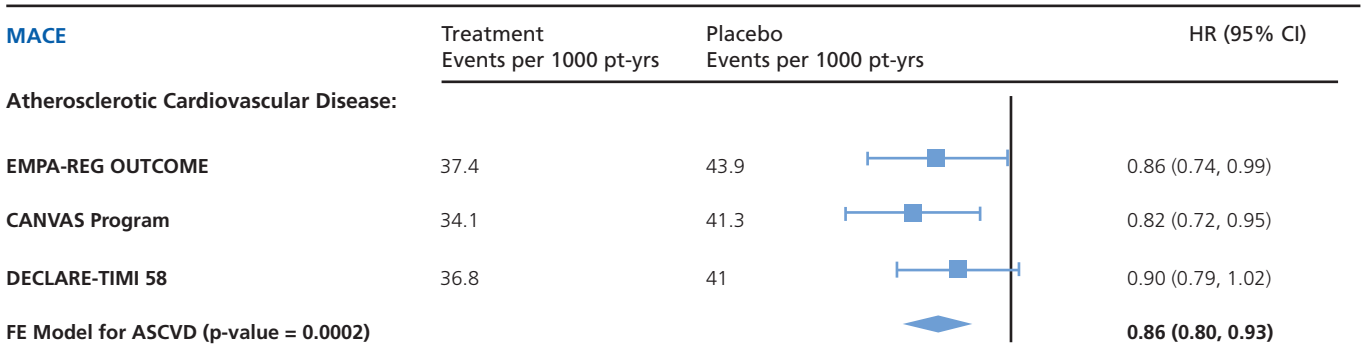
It may be that the results from HARMONY Outcomes increase our understanding with regard to how these agents exert their cardiovascular benefit. It is useful to consider, for example, liraglutide compared with albiglutide. Liraglutide in LEADER achieved a 13% reduction in 3-point MACE,[2] compared with a 22% reduction for albiglutide in HARMONY Outcomes.[5,6] It should be recognised that LEADER and Harmony Outcomes studied populations with different cardiovascular risk and therefore comparison of the results should be undertaken with caution. Nevertheless, it is noteworthy that, in the HARMONY 7 trial[10] which was a head-to-head comparison between liraglutide and albiglutide (but which was not powered for cardiovascular outcomes), the fall in HbA_{1c} for liraglutide was 0.98% compared with 0.79% for albiglutide (p=0.085) whereas the weight decrease was 2.2 kg for liraglutide compared with 0.6 kg for albiglutide (p≤0.0001).[10] Thus, liraglutide may have a lower impact on cardiovascular outcomes than albiglutide despite being associated with a bigger impact on glycaemic control and weight. Looking at changes in key parameters in the phase 3 programme with albiglutide, the fall in HbA_{1c} was 0.6%, in LDL cholesterol was 0.6 mmol/L (2 mg/dL), in systolic blood pressure was 0.6 mmHg, and the weight loss was between 1.5 and 2 kg.[5] Collectively, these results suggest that the considerable impact of albiglutide on cardiovascular outcomes is not related to traditional risk factor improvement (LDL cholesterol, systolic blood pressure, weight) and glycaemic improvement (HbA_{1c}). This raises the possibility that the biological effects of GLP-1RAs other than the effects on traditional cardiovascular risk factors are at play (Figure 2).[11-13]

The DECLARE-TIMI 58 study was by far the largest study of an SGLT2 inhibitor with 17,160 randomised patients.[7,8] It included the usual high-risk secondary prevention group with established cardiovascular disease (n=6,974), but also a large primary prevention group (n=10,186) of patients with multiple risk factors: type 2 diabetes and one additional risk factor being dyslipidaemia, hypertension or current tobacco use.[7,8] There were two co-primary endpoints: (1) 3-point MACE; and (2) cardiovascular death or hospitalisation for heart failure. The second primary endpoint was added because, in EMPA-REG OUTCOME, there was greater benefit with respect to cardiovascular death and hospitalisation for heart failure than with respect to 3-point MACE. With regard to the primary endpoint of cardiovascular death plus hospitalisation for heart failure, there was a 17% reduction (HR = 0.83, 95% CI 0.71 to 0.98) in the group with established atherosclerotic cardiovascular disease.[7,8] The reduction in 3-point MACE in this group (HR = 0.90, 95% CI 0.79 to 1.02) did not achieve statistical significance; however, comparing side by side the outcomes with regard to these end points in the three cardiovascular outcome studies with SGLT2 inhibitors (EMPA-REG OUTCOME, CANVAS Program, DECLARE-TIMI 58) and performing meta-analysis, it is clear that there is benefit across the class (Figures 3 and 4).[7] Across all studies combining primary and secondary prevention groups there was a 27% reduction in hospitalisation for heart failure (HR = 0.73, 95% CI 0.61 to 0.88).[7,8] When the multiple risk factor group (ie, those without an established cardiovascular event) was looked at on its own and meta-analysis undertaken with a similar group from CANVAS, the combined end point of cardiovascular death and hospitalisation for heart failure showed a 16% reduction (HR = 0.84, 95% CI 0.69 to 1.01), although this did not quite achieve statistical significance (p=0.06, Figure 4).[7] Further, there was a 24% reduction (HR = 0.76, 95% CI 0.67 to 0.87) in a renal composite end point (≥40% decrease in estimated glomerular filtration rate to <60 ml/min/1.73 m^2 body surface area, new end-stage renal disease or death from renal or cardiovascular causes).[7,8]

Now that we have the data from three SGLT2 inhibitor cardiovascular outcome studies, we can reasonably conclude that the class as a whole has consistent effects on reducing the risk of heart failure and adverse renal outcomes which do not appear to be dependent on baseline atherosclerotic risk or prior heart failure.[7] The benefit of SGLT2 inhibitors on 3-point MACE in patients with established atherosclerotic cardiovascular disease is more moderate than the impact on heart failure. It is noteworthy that none of the SGLT2 inhibitors have shown a significant reduction in developing acute ischaemic events – myocardial infarction or stroke – and, indeed, there is even the possibility of a signal of increased stroke risk in EMPA-REG OUTCOME.[3]

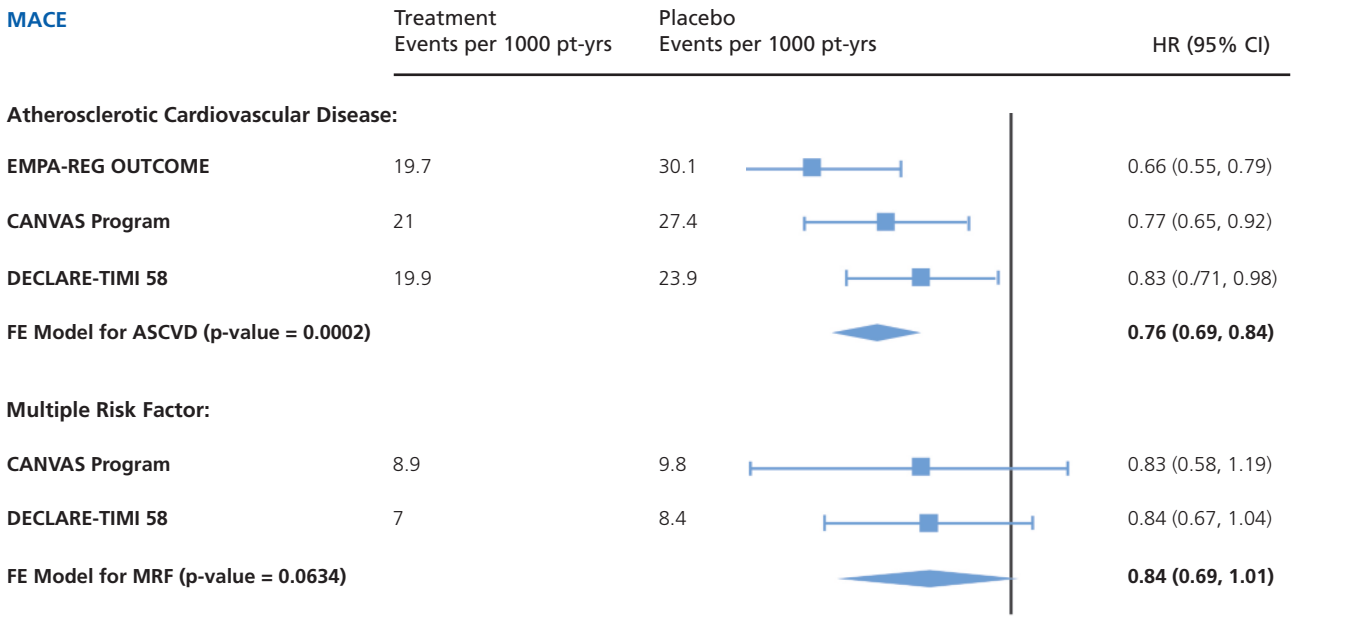
Putting together all of the information we now have from studies of cardiovascular outcomes in patients with type 2 diabetes from UKPDS through to DECLARE-TIMI 58, it is likely that metformin will remain an important first-line drug because of its low cost, safety and modest efficacy, although its cardiovascular benefit remains controversial.[1,14] We have previously documented the evidence that pioglitazone has an important role in reducing 3-point MACE, and the data suggest that it exerts its beneficial effect by slowing down – or even reversing – the atherosclerotic process.[1-3,15,16] The SGLT2 inhibitor class, by contrast, appears to exert its cardiovascular

Figure 3. 3-point MACE results from the three cardiovascular outcome trials with SGLT2 inhibitors shown side by side with result of meta-analysis also shown. The agents studied were empagliflozin (EMPA-REG OUTCOME), canagliflozin (CANVAS), and dapagliflozin (DECLARE-TIMI 58)



MACE, major adverse cardiovascular event. HR, hazard ratio. CI, confidence interval. ASCVD, atherosclerotic cardiovascular disease. FE Model, fixed effects model.
Adapted from reference 7.

Figure 4. CVD/HHF results from the three cardiovascular outcome trials with SGLT2 inhibitors shown side by side with result of meta-analysis also shown. The agents studied were empagliflozin (EMPA-REG OUTCOME), canagliflozin (CANVAS), and dapagliflozin (DECLARE-TIMI 58). The ASCVD group had established atherosclerotic cardiovascular disease (secondary prevention), whereas the MRF group did not (primary prevention)



CVD/HHF, combination of cardiovascular death and hospitalisation for heart failure. HR, hazard ratio. CI, confidence interval. ASCVD, atherosclerotic cardiovascular disease. FE Model, fixed effects model. MRF, multiple risk factor
Adapted from reference 7.

benefits by improving cardiac homodynamics (simultaneous reduction in preload and afterload) and reduction in heart failure.[1,3,7,8] We have previously pointed out that there is evidence to suggest that SGLT2 inhibitors might mitigate the fluid retention associated with pioglitazone[1,3,17] and, thus, SGLT2 inhibitors and pioglitazone might well work synergistically to improve outcomes in patients at high cardiovascular risk by different mechanisms. The available data strongly support a cardiovascular outcome study of pioglitazone plus SGLT2 inhibitor against each as monotherapy to assess whether this theoretical synergism would translate into real cardiovascular benefit to patients.

With regard to long-acting GLP-1RAs, there are now four contenders (five if dulaglutide is included) with definite or probable cardiovascular benefit (Figure 1), but from these, as 2019 dawns

Key messages

- The considerable benefit of albiglutide on cardiovascular outcomes in the HARMONY Outcome trial despite minimal impact on traditional cardiovascular risk factors points to cardiovascular benefits of long-acting GLP-1 receptor agonists operating through other biological mechanisms
- The results from the DECLARE-TIMI 58 trial with dapagliflozin added to those from EMPA-REG OUTCOME with empagliflozin and CANVAS Program with canagliflozin suggests a class effect for SGLT2 inhibitors on cardiovascular outcomes, mostly related to improvement in cardiac haemodynamic factors and prevention of heart failure
- From the available long-acting GLP-1 receptor agonists, semaglutide might well be the first choice when an agent with cardiovascular benefit is being considered from those available to prescribe
- As pioglitazone, SGLT2 inhibitors and long-acting GLP-1 receptor agonists seem to exert their cardiovascular benefits through entirely separate mechanisms, studies should be undertaken to assess the extent to which these benefits might be synergistic by using the agents in various combinations in patients with high cardiovascular risk

and semaglutide is available to be prescribed in the UK, this GLP-1RA may well be the first choice to be considered. Its 26% reduction in 3-point MACE was the highest from any of the cardiovascular outcome trials (Figure 1).[18] While we must be guarded in concluding that it is the most effective without a head-to-head trial, it is nevertheless noteworthy. Semaglutide has also been shown to have the biggest impact on weight reduction and glycaemic control of the available GLP-1RAs,[18-21] and is therefore likely to be associated with greater improvement in microvascular complications as well as less need for other diabetes medications, in particular insulin. Because the reduction in HbA_{1c} can be considerable and rapid with semaglutide, established diabetic retinopathy may worsen transiently as can happen in many situations where glycaemic control is improved rapidly.[22] If there is concern about this possibility in the patient with active retinopathy, ophthalmologic consultation and appropriate laser therapy of the retinopathy should be instituted. Liraglutide could then be initiated for a time prior to switching to semaglutide in order to reduce the speed of HbA_{1c} reduction.

As GLP-1RAs appear to exert their cardiovascular benefit by mechanisms different from those of both pioglitazone and SGLT2 inhibitors, there would also seem to be a place for a randomised controlled trial comparing a GLP-1RA plus pioglitazone or a GLP-1RA plus SGLT2 inhibitor compared to each monotherapy alone to establish the extent to which extra benefit is accrued with dual or even triple therapy. There also would be interest in undertaking studies with GLP-1RAs such as semaglutide, designed to establish their effect on retardation of the atherosclerosis process along the lines of the studies carried out with pioglitazone,[1-3,12,13] which demonstrated slowing of the progression of carotid artery intima–media thickness[15] and coronary artery atheroma.[16]

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