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The EMPA-REG study: What has it told us?:

A diabetologist's perspective

Ralph A. DeFronzo [Chief]

Diabetes Division, University of Texas Health Science Center, San Antonio, TX, 78229 USA, Tel.:

+1 210 567 6691; fax: +1 210 567 6554, albarado@uthscsa.edu

EMPA-REG (Zinman et al., 2015) is the first study to conclusively demonstrate that a medication developed to reduce glycemia (Abdul-Ghani, Norton, & DeFronzo, 2011) in patients with type 2 diabetes mellitus (T2DM) decreases cardiovascular events. In 7020 T2DM patients with established cardiovascular (CV) disease, empagliflozin (pooled 10 and 25 mg/day doses) significantly reduced the primary MACE outcome (cardiovascular death, nonfatal MI, nonfatal stroke) by 14% compared to placebo (HR = 0.86, 95% CI = 0.74–0.99, $P = 0.04$ for superiority). It is noteworthy that a striking disconnect was observed between the three MACE components; (i) for nonfatal MI, the HR (= 0.87) decreased slightly but not significantly ($P = 0.22$); (ii) for stroke, the HR (= 1.24) increased slightly but not significantly ($P = 0.22$); (iii) for cardiovascular death, the HR (= 0.62) decreased significantly by 38% ($p < 0.001$). The reduction in CV death (5.9% to 3.6%, $p < 0.001$) was observed across all diagnostic categories (sudden death, 1.6% to 1.1%; worsening heart failure, 0.8% to 0.2%; acute MI, 0.5% to 0.3%; stroke, 0.5% to 0.3%; “other cardiovascular death”, 2.4% to 1.6%). The latter category includes deaths that cannot be explained by any other known cause. The majority of such cases have been shown to result from acute MI or, less commonly, arrhythmias and this category is not as diagnostically sound as the others. Other CV outcomes of interest included a significant reduction in hospitalization for heart failure (HR = 0.65, $p < 0.002$) and no effect on hospitalization for unstable angina (HR = 0.97, $P = 0.97$). Although these results are very exciting and have important implications for all physicians who care for patients with T2DM, they raise a number of questions concerning: (i) the generalizability of the results; (ii) the mechanisms responsible for the reduction in CV mortality; and (iii) whether the beneficial CV effects represent a class effect.

Before discussing the generalizability of results and mechanism of the drug's beneficial effect to reduce CV mortality, it should be emphasized that the EMPA-REG study also confirms the excellent safety profile of the SGLT2 inhibitor (SGLT2i) class of antidiabetic agents. Empagliflozin significantly reduced body weight, waist circumference, A1c, and blood pressure without change in heart rate. There was no increase in the incidence of hypoglycemia, renal impairment, urinary tract infections, volume-related side effects, bone fractures, or thromboembolic events. Given the current reports of diabetic ketoacidosis (Peters et al., 2015) in T2DM patients treated with SGLT2 inhibitors, it was encouraging to see that the incidence of DKA was low (0.035%) and similar to that in the placebo group

(0.020%). Serious adverse events and AEs leading to drug discontinuation were slightly, although not significantly lower in the empagliflozin group. The only AE noted with increased incidence in the empagliflozin group was genital infections, 6.4% vs 1.8%. Thus, physicians should feel comfortable that the benefits of empagliflozin far outweigh the risks in this high CV risk diabetic population and, based upon the mechanism of action of the SGLT2 inhibitors, one would expect a favorable benefit to risk profile even if a reduction in CV events was not observed.

With regard to generalizability, it should be noted that the diabetic population was unique in that a prior CV event was a requirement for entry into the study. Further, the subjects were relatively older (mean age = 63.1 years) and had long duration of diabetes (greater than 10 years in 57% of participants), both of which are major independent risk factors for adverse CV events. Although the results of EMPA-REG clearly support the use of SGLT2i therapy in this high CV risk group, it remains unclear whether empagliflozin would produce similar CV benefits in a younger group of T2DM patients with shorter duration of diabetes and without clinically evident CV disease. Even within the high risk CV group of patients who participated in EMPA-REG, it is unclear whether there is a specific subgroup with unique cardiovascular abnormalities that render them particularly susceptible to the beneficial effects of empagliflozin. Lastly, it will be debated whether the beneficial CV effects observed with empagliflozin are unique to this SGLT2i or represent a class effect. In T2DM patients who are well controlled on other SGLT2 inhibitors and who do not fit the patient characteristics of those in EMPA-REG, it seems reasonable to continue with their current SGLT2i therapy. However, evidence-based results would dictate that T2DM patients with high CV risk characteristics similar to those in EMPA-REG should be switched to empagliflozin, with close follow up to ensure that the level of glycemic control remains unchanged.

What mechanism(s) is (are) responsible for the impressive reduction in CV death observed in EMPA-REG? It seems unlikely that improved glycemic control (as reflected by A1c) can account for the 38% reduction in CV death for multiple reasons. First, the separation in CV death between empagliflozin- and placebo-treated groups was evident at 2–4 months, was clearly established at 6 months, and progressively widened from years 1 to 3. Second, hyperglycemia is a weak risk factor for CV disease, as evidenced in the UKPDS study (UK Prospective Diabetes Study (UKPDS) Group, 1998), and it took 10 years of follow up to demonstrate a reduction in CV events with improved glycemic control (Holman, Paul, Bethel, Matthews, & Neil, 2008). Third, in ACCORD (Gerstein et al., 2008), ADVANCE (Patel et al., 2008) and VADT (Duckworth et al., 2009) intensive glycemic control failed to decrease CV events despite a significant reduction in microvascular complications. Fourth, the reduction in A1c was quite modest: 0.45% at week 94 and 0.30% at week 204.

The rapid reduction (within 2–4 months) in CV events in the group treated with empagliflozin argues for a hemodynamic mechanism of action. The authors (Zinman et al., 2015) state that empagliflozin “was associated with small reductions in weight and systolic and diastolic blood pressure” and “the mechanisms behind the cardiovascular benefits of empagliflozin are multidimensional”. Although the starting blood pressure (135.5/76.7 mmHg) was reasonably well controlled and the decrease in systolic/diastolic blood pressures

at study end was modest, we believe that this is misleading. Inspection of the supplemental figures demonstrates that the reduction in systolic and diastolic blood pressures is highly significant at 1 month, is maximal at 4 months (~5/2.5 mmHg), and temporarily correlates with both the reductions in CV death and hospitalization for heart failure. With respect to the latter, the reduction in body weight, which reflects both fluid loss and reduced tissue (fat and muscle) mass, was near maximal at month 4 and the persistent increase (by 4.8%) in hematocrit at week 204 suggests that the decrease in intravascular volume persisted until study end. The temporal association between the reductions in blood pressure and intravascular volume versus the decreases in CV death and CHF suggests that these cardiovascular/hemodynamic effects of empagliflozin play a pivotal role in the CV benefits observed with this antidiabetic agent. Further, it should be emphasized that the brachial arterial blood pressure measurement can significantly and consistently underestimate the reduction in central aortic pressure and hemodynamic effects on the heart (Williams et al., 2006). Thus, in the CAFÉ study, despite similar brachial arterial blood pressures, the group treated with amlodipine/perindopril had significantly lower central aortic blood pressures than the group treated with atenolol/thiazide and the reduction in central aortic blood pressure was strongly associated with a reduction in CV events in a post-hoc analysis of 2073 participants. It is reasonable to assume that the central aortic pressure is a better predictor of CV outcomes than brachial arterial blood pressure and it has been shown to be associated with improved cardiovascular remodeling and reduced BNP levels which, unfortunately, were not measured in EMPA-REG. Further, the INTERHEART study (Yusuf et al., 2004) demonstrated that the combination of diabetes and hypertension confers an especially high risk for MI. Thus, we postulate that the beneficial effects of empagliflozin are mediated, in large part, by the hemodynamic/cardiovascular benefits related to the reductions in blood pressure and intravascular volume in the high CV risk diabetic patients with severe, long-standing myocardial dysfunction. With respect to this, it should be noted that empagliflozin has been shown to reduce arterial stiffness in diabetic patients (Cherney et al., 2014). Further, it would be unwise to assume that a similar reduction in CV death and CHF hospitalization will be observed in ongoing trials with other SGLT2 inhibitors, where the diabetic patient population may differ significantly from those in EMPA-REG. In summary, it is likely that the CV benefit of empagliflozin has little to do with its glucose lowering effect.

An important lesson to be learned from EMPA-REG is that we should not let our diabetic patients progress to the stage that they experience a major CV event and, thus, become eligible for participation in a study such as EMPA-REG. Although involving a relatively small number of T2DM patients, the 8 year follow up of the Steno 2 Study (Gaede et al., 2003) has demonstrated that intensive treatment of known cardiovascular risk factors (blood pressure, lipids, A1c, clotting abnormalities, obesity) can markedly reduce, although not completely prevent, cardiovascular (as well as microvascular) events. With respect to the latter, the author believes that combination therapy with low dose pioglitazone (15–30 mg/day) plus empagliflozin may prove to be an extremely effective intervention to reduce CV events in high risk T2DM patients. In PROactive (Dormandy et al., 2005) pioglitazone reduced the MACE endpoint by 16% (HR = 0.84, 95% CI = 0.72–0.98, p = 0.027), although the primary endpoint (MACE plus peripheral vascular disease) did not reach statistical

significance because of an increase in leg revascularization. Of particular note, recurrent stroke (HR = 0.53, $p = 0.008$) and recurrent MI (HR = 0.72, $p = 0.045$), which were not reduced in EMPA-REG, both were significantly reduced in PROactive. Pioglitazone has been shown to exert no negative inotropic effects on left ventricular function, to improve diastolic dysfunction, to reduce blood pressure (after load), and to improve endothelial dysfunction (Clarke et al., 2014; Eldor, DeFronzo, & Abdul-Ghani, 2013; Ryder & DeFronzo, 2015). The fluid retention observed with pioglitazone is related to the drug's sodium retentive effect on the kidney. In PROactive, the incidence of CHF in pioglitazone-treated subjects was stated to be increased, but these cases were not adjudicated and overall mortality and cardiovascular events in this group tended to decrease, not increase. Given the natriuretic effect of the SGLT2 inhibitors, one would expect minimal fluid retention with combination therapy, especially if low doses of pioglitazone were used.

In summary, the results of EMPA-REG demonstrate that empagliflozin reduces cardiovascular death in type 2 diabetic patients at high risk for CV disease by 38% with an excellent safety profile. Whether these results are applicable to other patient profiles or represent a class effect remains to be determined. Nonetheless, the SGLT2i class of drugs is certain to move up in the therapeutic algorithm for the treatment of T2DM, not only because of the results of EMPA-REG, but because of: (i) their beneficial effects to reduce A1c, body weight, and blood pressure, (ii) their favorable side effect profile, and (iii) their mechanism of action on the kidney that allows them to be used with any combination of oral or injectable antidiabetic agents.

References

- Abdul-Ghani M, Norton L, DeFronzo RA. Role of sodium-glucose cotransporter 2 (SGLT2) inhibitors in the treatment of type 2 diabetes. *Endocrine Reviews*. 2011; 32:515–531. [PubMed: 21606218]
- Cherney DZ, Perkins BA, Soleymanlou N, Har R, Fagan N, Johansen OE. The effect of empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated type 1 diabetes mellitus. *Cardiovascular Diabetology*. 2014; 29(13):28. [PubMed: 24475922]
- Clarke GD, Molina-Wilkins M, Martinez S, Merovci A, Kincade JR, Solis-Herrera C, DeFronzo RA. Improved left ventricular diastolic function (LVDF) following pioglitazone therapy is strongly related to increased myocardial insulin sensitivity. *Diabetes*. 2014; 63(Suppl. 1):A298.
- Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK. PROactive investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): A randomised controlled trial. *Lancet*. 2005; 366:1279–1289. [PubMed: 16214598]
- Duckworth W, Abaira C, Moritz T, Reda D, Emanuele N, Reaven PD. VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. *NEJM*. 2009; 360:129–139. [PubMed: 19092145]
- Eldor R, DeFronzo RA, Abdul-Ghani M. In vivo actions of peroxisome proliferator-activated receptors: Glycemic control, insulin sensitivity and insulin secretion. *Diabetes Care*. 2013; 36(Suppl. 2):S1627–S1674.
- Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *The New England Journal of Medicine*. 2003; 348(5):383–393. [PubMed: 12556541]
- Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. *NEJM*. 2008; 358:2545–2559. [PubMed: 18539917]
- Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *NEJM*. 2008; 359:1577–1589. [PubMed: 18784090]

- Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Travert F. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *NEJM*. 2008; 358:2560–2572. [PubMed: 18539916]
- Peters AL, Buschur EO, Buse JB, Cohan P, Diner JC, Hirsch IB. Euglycemic diabetic ketoacidosis: A potential complication of treatment with sodium-glucose cotransporter 2 inhibition. *Diabetes Care*. 2015; 38:1687–1693. [PubMed: 26078479]
- Ryder REJ, DeFronzo RA. Rehabilitation of pioglitazone. *The British Journal of Diabetes & Vascular Disease*. 2015; 15:46–49.
- UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998; 352:837–853. [PubMed: 9742976]
- Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D. CAFE Steering Committee and Writing Committee. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: Principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation*. 2006; 113:1213–1225. [PubMed: 16476843]
- Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F. INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. *Lancet*. 2004; 364(9438):937–952. [PubMed: 15364185]
- Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S. EMPA-REGOUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *NEJM*. 2015 <http://dx.doi.org/10.1056/NEJMoa1504720> (Epub ahead of print).