# Empagliflozin reduces albuminuria—a promise for better cardiorenal protection from the EMPA-REG OUTCOME trial

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Nowadays, type 2 diabetes care covers much more than lowering of blood glucose. To prevent and treat both micro- and macrovascular complications, risk factors like blood pressure and dyslipidemia are equally important treatment targets.

Over the last 3 or 4 decades albuminuria has become recognized as both a risk marker and a treatment target in diabetes care, with a strong association to both renal and cardiovascular outcome (1). This has led to albuminuria-lowering treatment as angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) becoming a part of standard treatment in diabetes care, especially following significant clinical studies in patients with microalbuminuria (2) [urinary albumin creatinine ratio (UACR) >30 mg/g] and macroalbuminuria (3,4) (>300 mg/g). In addition, post-hoc analyses from these studies demonstrated higher benefit in patients that achieved the largest reduction in albuminuria, both in relation to renal outcome (5) and cardiovascular outcome (6). Following this, a series of studies investigated different modes of combination treatment seeking to further reduce albuminuria and obtain improved renal and cardiovascular protection (7-9). This approach was however not successful as adverse events as hyperkalemia, hypotension and acute kidney injury offset the benefits of combining two agents blocking the renin-angiotensin system.

In 2015 treatment of type 2 diabetes changed markedly with the publication of the EMPA-REG OUTCOME trial (10), for the first time demonstrating a reduction in cardiovascular outcome in a trial comparing sodium glucose co-transporter (SGLT2) inhibitors to placebo added to standard care.

The SGLT2 inhibitor class lowers blood glucose by blocking the sodium glucose co-transporter on the luminal side of the renal tubuli, thereby causing glucosuria, resulting in up to 70 gram glucose to be excreted daily. It is an oral agent, taken once daily.

It was evident from the EMPA-REG study that the lower occurrence of cardiovascular death and hospitalization for heart failure seen early in the empagliflozin treated group could not exclusively be attributed to lowering of blood glucose levels and several theories regarding the mechanism of effect started to emerge (11-13). Following the primary publication, a secondary analysis of the EMPA-REG OUTCOME trial (14) also found substantial benefit on progression of kidney outcome, with an interesting and apparent protective effect on estimated glomerular filtration rate (eGFR), which displayed a lower rate of decline in the empagliflozin group compared to placebo.

Recently, an EMPA-REG OUTCOME report investigating the effect of empagliflozin on albuminuria levels was published by Cherney *et al.* (15). Of the 7,028 patients included in the study, baseline UACR was available for this post-hoc analysis in 6,953 patients.

Of the treated patients 59% had normoalbuminuria at baseline, 29% had microalbuminuria and 11% had macroalbuminuria. Reductions in UACR of 7%, 25% and 32% were seen after 12 weeks of treatment in the normo-, micro- and macroalbuminuria group, respectively. These reductions were maintained after a median follow-up of 3.1 years. The reduction in UACR in the micro-and macroalbuminuria groups were consistent across strata of changes in $HbA_{1c}$, blood pressure, weight and eGFR. As an interesting exploratory analysis, a group of participants had UACR measured at baseline, at end of treatment and then again at 34–35 days after stopping treatment. In the normoalbuminuria group UACR values returned to baseline levels, but in the micro-and macroalbuminuria group UACR levels in the empagliflozin treated group UACR levels only partly returned to baseline levels. In the microalbuminuria part of the group the albuminuria reduction on empagliflozin was 42% lower versus placebo after 3.1 years, but increased to being 22% lower than placebo after 34 days off treatment, still statistically significantly lower than placebo. For macroalbuminuria the corresponding numbers were 49% and 29%, respectively. This finding indicates that the effect seen after approximately 3 years of treatment is more than just hemodynamic, and that structural changes may also play a role after long term treatment. If the effect on albuminuria was predominately due to hemodynamic effects, UACR levels would be expected to return to baseline levels after a few days. The authors state however that it is difficult to determine whether diabetes-related structural effects as glomerulosclerosis or tubulointerstitial fibrosis could have been attenuated, as there are no human renal biopsy data after SGLT2 treatment available.

In a categorical analysis the authors also looked at "class shifts", i.e., the progression from normo- to micro-or macroalbuminuria, indicating a worse cardiorenal prognosis, or the regression to normoalbuminuria from the other classes which is associated with improved prognosis. Progression was less frequent in empagliflozin treated participants and a greater proportion of patients in the empagliflozin group experienced regression. In all three groups of albuminuria and eGFR was stable over the course of the study, while it displayed a decline in the placebo group. This difference was most prominent in the macroalbuminuria group.

This paper is indeed of special interest as it adds to understanding of the multifactorial potential of SGLT2 inhibition, as the treatment also lowers blood pressure,

weight, blood glucose and can stabilize kidney function. It also represents evidence that empagliflozin has a clear albuminuria lowering potential, probably by increased sodium delivery to the macula densa, which leads to vasoconstriction of the afferent arteriole followed by a reduction in intraglomerular pressure resulting in a reduced filtration of albumin (11).

The two other major compounds in the SGLT2 inhibitor class, canagliflozin and dapagliflozin, have also demonstrated this potential. Canagliflozin was recently found to lower albuminuria and delay progression of albuminuria (class shift) in the CANVAS program (16), as a secondary outcome. In the ongoing CREDENCE (NCT02065791) study, canagliflozin is investigated in relation to a renal primary endpoint, and this will provide further evidence regarding the compound. Dapagliflozin has demonstrated similar potential in pooled analyses of trials as well as in a study in patients with type 2 diabetes and renal impairment. The ongoing DECLARE-TIMI-58 study (NCT01730534), a cardiovascular outcome trial, will also include a secondary renal analysis. Furthermore, the recently initiated DAPA-CKD study (NCT03036150) investigates dapagliflozin in relation to renal outcome in patients with albuminuria and impaired renal function, including both patients with type 2 diabetes and non-diabetic patients with proteinuria. A similar study in heart failure has been initiated, and both these studies will explore the potential of SGLT2 inhibition outside diabetes.

## Why is it important to lower albuminuria?

The general hypothesis is that a reduction of albuminuria following an intervention is primarily reflecting a reduction in intraglomerular pressure, thereby decreasing filtration of large proteins such as albumin (17). This in turn leads to a reduction in inflammation, endothelial dysfunction, oxidative stress and fibrosis, leading to less long-term damage to the kidney. Although renin-angiotensin system blockade is thought to dilate the efferent arterioles and SGLT2 inhibition leads to vasoconstriction of the afferent arteriole, these and other albuminuria lowering compounds are often referred to as having other local structural effects in the kidney, i.e., anti-fibrotic or anti-inflammatory effects, although complicated to demonstrate in vivo. In a large metanalysis, Heerspink *et al.* (18) explored available clinical trials on albuminuria lowering in relation to hard renal outcome and concluded that for each 30% reduction in albuminuria, ESRD risk is reduced by 24%, an association

that is consistent regardless of drug class used.

## Other antidiabetic treatment and albuminuria

Not all glucose-lowering treatments have the potential to lower albumin excretion. However, treatment with glucagon-like peptide 1 (GLP-1) agonists, have shown reduction in albuminuria (19). So far, only liraglutide has shown renal benefit in a large outcome trial. In a secondary analysis of the LEADER trial (20), a lower proportion of liraglutide treated patients displayed progression to macroalbuminuria, making up the major part of the combined renal endpoint which occurred in 15 versus 19 patients per 1,000 patient-years of observation in the liraglutide and the placebo group, respectively.

For the widely used dipeptidyl peptidase IV (DPPIV) inhibitor class, there are conflicting results as to potential to lower albuminuria. The recently published MARLINA study (21), displayed a placebo-adjusted 6% reduction with linagliptin, which was not statistically or clinically significant, but a secondary analysis of the large saxagliptin study SAVOR-TIMI-53 (22) did report a significant reduction in UACR, however without influencing renal or cardiovascular outcome. More studies investigating the renoprotective potential in the DPPIV class are ongoing.

For now, SGLT2 inhibitors seem to be the obvious addition to standard renin-angiotensin system blocking treatment with the potential to lower residual albuminuria and enhance protection of the kidney and the heart in high risk patients. The EMPA-REG OUTCOME albuminuria analysis discussed here is indicating the potential, and the forthcoming studies will provide the answers needed. In addition, it is expected that global treatment guidelines will change in the coming years considering the recent developments in evidence.

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## Footnote

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