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CARDIOPULSE

Braunwald's Corner

SGLT2 inhibitors: the statins of the 21st century

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A relatively small number of drugs have been responsible for major advances in medical practice. The discovery, development, and elucidation of the mechanisms of action of aspirin, penicillin, and statins are remarkable success stories, each with some surprises and each crowned by a Nobel Prize. The sodium glucose co-transporter inhibitors have been proven effective in the treatment of type 2 diabetes mellitus, various forms of heart failure, and kidney failure and represent *the, or one of the*, major pharmacological advances in cardiovascular medicine in the 21st century.

A bit of history

The story begins in 1835, when C. Petersen, a French chemist, isolated phlorizin from the root bark of the apple tree, which was first used in the treatment of malaria. In 1886, von Mering, a German professor of medicine, discovered the glucosuric and consequent plasma glucose lowering effects of phlorizin.[1]

During the first half of the 20th century, it was learned that the glucose that is normally filtered in the glomerulus is almost fully reabsorbed by the proximal renal tubules. In the 1960s, it was demonstrated that this reabsorption requires active transport, and that glucose and sodium are co-transported. It became clear that when the molecule responsible for the reabsorption, i.e. the co-transporter, is inhibited both glucose and sodium are excreted in the urine. In 1962 Alvarado and Crane showed that phlorizin, by that time known to be a glucose molecule attached to two aromatic rings, was a competitive inhibitor of this active transport.[2] Subsequently, it was demonstrated that when injected into diabetic animals phlorizin reduced plasma glucose concentration.[3] Since phlorizin is poorly absorbed from the gastrointestinal tract the search for orally effective inhibitors of the co-transporters was begun. In 1996, investigators at Kyoto University and Tanuba Seiygyu Co. in Japan developed phlorizin analogs, the first chemically engineered sodium glucose co-transporter inhibitors (SGLT2is).[4] In 2000, they developed T-1095, an SGLT2i that reduced hyperglycaemia when given orally to diabetic rats and suggested that it could be useful in the management of persons with type 2 diabetes mellitus (T2DM).[5]

Clinical applications

Between 2012 and 2015, the European Medicine Agency (EMA) and the US Food and Drug Administration (FDA) approved three SGLT2is, dapagliflozin, canagliflozin, and empagliflozin, for reducing plasma glucose in persons with T2DM. Early placebo-controlled trials with these agents showed that in appropriate doses they lowered HgbA1c by an absolute amount of around 0.6%, caused moderate reductions in body weight and blood pressure, and were generally well tolerated. They were considered to be reasonably effective second-tier anti-diabetic agents, and were usually added to metformin or a sulfonylurea.

In 2008, the FDA expressed concern about increased cardiovascular risk of new antidiabetic agents and shortly thereafter the EMA followed suit. The regulators required the sponsors of new anti-diabetic agents to demonstrate cardiovascular safety to gain approval. This was no small task because it required large clinical trials including thousands of patients followed for several years, at great expense.

A surprise

In 2015, the results of the first large placebo-controlled SGLT2i clinical outcome trial, EMPA-REG OUTCOME, in patients with T2DM and cardiovascular disease and reduced ejection fraction was reported.[6] Quite unexpectedly, it showed that empagliflozin resulted in a significant 14% *reduction* of the primary endpoint (cardiovascular death, non-fatal myocardial infarction or stroke). Even more exciting were the 32% reduction in death from any cause, and the 35% reduction in hospitalization for heart failure. Both the cardiovascular and diabetes communities were puzzled by these very favourable results. No one (including myself) could explain them, and many investigators and clinicians simply didn't quite believe them. However, the findings were soon confirmed with canagliflozin and dapagliflozin, leading to the first major paradigm shift affecting clinical practice:

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1. SGLT2 inhibitors are not only glucosuric but also reduce the development and progression of heart failure and prolong life in patients with T2DM and reduced left ventricular ejection fraction.

There followed two trials on patients with a history of heart failure with reduced ejection fraction (HFrEF)—with dapagliflozin[7] and empagliflozin,[8] both of which showed equal benefits in patients with and *without diabetes*. These observations led to the second paradigm shift:

2. *SGLT2 inhibitors improve outcomes in patients with HFrEF irrespective of the presence or absence of T2DM*, thereby greatly expanding the potential target population for these drugs.

At this point the SGLT2 inhibitors were on a winning streak! In 2020 the SOLIST trial demonstrated in patients with T2DM that sotagliflozin reduced heart failure across the full range of ejection fraction, including a small subgroup of patients with heart failure with preserved ejection fraction (HFpEF).[9] In 2021 the EMPEROR Preserved trial extended the improvement in the outcomes in patients with HFpEF to patients without T2DM,[10] leading to the third paradigm shift:

3. *SGLT2 inhibitors appear to be beneficial in patients with chronic heart failure over a wide range of ejection fractions*, again greatly expanding the target population even further.

Patients with T2DM of long duration have a high risk of developing diabetic renal disease. The sodium in the glomerular filtrate that is blocked from reabsorption by SGLT2is acts on the macula densa in the renal tubules, which in turn reduces renin release from the juxtaglomerular cells.[11] This tubuloglomerular feedback causes constriction of the afferent glomerular arterioles and dilation of the efferent arterioles. These changes, in turn, reduce intraglomerular pressure and hyperfiltration, the latter responsible for glomerular fibrosis and diabetic renal dysfunction, and ultimately end-stage renal disease. The above-mentioned trials of SGLT2is in patients with T2DM and HFrEF[6–8] combined with two trials on patients with chronic renal disease that included patients without T2DM,[12,13] exhibited substantial significant renoprotection, leading to a fourth paradigm change:

4. *SGLT2 inhibitors slow the development of end-stage kidney disease in patients with chronic kidney disease*. The benefit of SGLT2i in patients without T2DM but with a variety of chronic kidney diseases is under investigation.

Conclusions

In 1886, phlorizin was found to be glucosuric. Almost a century later, it was shown to be a competitive inhibitor of the active reabsorption of glucose by the proximal renal tubules and to reduce circulating glucose in diabetic rodents. In the 1990s, the first orally active derivatives of phlorizin, the SGLT2is, were developed. The first drugs in this class were approved for control of hyperglycaemia in patients with T2DM in 2012. The first large clinical endpoint trial in T2DM patients with cardiovascular disease was reported in 2015. In the past 6 years, other large clinical endpoint trials on several agents in this class led to four new treatment paradigms. The management of T2DM, of heart failure in patients with and without T2DM, across a wide range of ventricular function, as well as of diabetic renal disease have all been substantially improved by the development of the SGLT2is.

The question recently posed by Freaney *et al* 'Could flozins be the statins for risk-based primary prevention of heart failure?'[14] can now be answered affirmatively!

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