The Benefits of GLP1RA and SGLT2 Inhibitors for the CV Outcomes: What Is Similar, What Is Different?

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Abstract

In spite of therapeutic advances and progressive decline in cardiovascular (CV) morbidity and mortality, subjects with type 2 diabetes continue to have a 2-fold higher risk than those without diabetes. Intensive glycemic control has been shown to provide marginal benefit though most of the studies addressing the question were based on traditional glucose lowering agents. In the past 20 years, new pharmacologic agents have been introduced and almost all of them have been assessed in dedicated CV outcome trials (CVOT) to test their safety and potential CV benefit in large populations of type 2 diabetic subjects. These trails have provided evidence for CV safety of DPP4 inhibitors and demonstrate superiority of SGLT2 inhibitors (SGLT2i) and GLP1-receptor agonists (GLP1-RAs) in term of risk reduction for major adverse cardiovascular events (3 point MACE: CV mortality, nonfatal myocardial infarction, nonfatal stroke). Therefore, among the currently available classes of glucose lowering agents, two have the potential for reducing CV risk in type 2 diabetic subjects. Nonetheless, some difference between SGLT2i and GLP1-RAs are worth to consider. The first trial to show a beneficial CV effect was EMPA-REG. The trial showed that empagliflozin not only was associated with a significant reduction in the 3-point MACE but also reduced dramatically the risk of hospitalization for heart failure. This effect was then confirmed with the use of canagliflozin (CANVAS program) and dapagliflozin (DECLARE) as well as in real world studies. On the contrary, no such a beneficial effect was detected in the GLP1RA CV outcome trials. This difference has been noted by the extensors of the most recent ADA/EASD consensus for the management of hyperglycemia in type 2 diabetes. The experts of the two organizations first suggested that assessment of the presence of a CV condition is compelling in selecting patient's individualized treatment. If the subject has a prevalent atherosclerotic CV disease a SGLT2i or a GLP1-RA with proven CV effects should be considered upon treatment failure with metformin. On the contrary, if heart failure is the main CV manifestation then a SGLT2i should be preferred.

Of interest, the beneficial effect of SGLT2i appear to occur much earlier than that provided by GLP1RAs. This may suggest that the mechanisms through which these drugs confer CV protection is different. Several potential mechanisms have been postulated, but a main hemodynamic effect seems to be the most likely explanation for the beneficial CV effects of SGLT2i, while an anti-atherosclerotic action may be predominant for GLP1-RAs. The hemodynamic action of the SGLT2i has been interpreted as a direct effect on the target organ of these drugs, i.e the kidney. SGLT2i promotes natriuresis and osmotic diuresis, leading to plasma volume contraction and reduced preload, and decreases in blood pressure, arterial stiffness, and afterload as well, thereby improving subendocardial blood flow in patients with heart failure. SGLT2 inhibition is also associated with preservation of renal function. Of interest the latter seems to be exerted for

all degree of initial renal function as a renal protection has been reported in type 2 diabetic subjects with preserved glomerular filtration rate (eGFR >90 ml/min/1.73 m2) as well as those with impaired (eGFR 60 – 90 ml/min/1.73 m2) and those with reduced eGFR (<60 ml/min/1.73 m2). A renal protective effect has been also observed with GLP1-RAs. However, such an effect seems to be less pronounced as compared to SGLT2i and more apparent in those with albuminuria. In line with this, the recent results of the REWIND trial show a more pronounced reduction of albumin excretion rate than maintenance of eGFR.

EMPA-REG was the first trail suggesting a CV protection for SGLT2i, but it was the trial that, unexpectedly, show no effect of SGT2i on the risk for nonfatal stroke. A similar finding has been observed with the ensuing SGLT2i trials. On the contrary, a consistent reduction in the risk of stroke has been reported with GLP1-RAs.

In summary, both SLT2i and GLP1-RAs provide CV protection, but differences can be identified between the two classes. These differences also extend to the safety profile. SGLT2i may expose to the risk of urinary and genital infection, euglycemic ketoacidosis, fractures and amputations of the extremities of the lower limbs, and Fournier gangrene. GLP1-RAs' most common adverse events remain nausea and vomiting. While it may be important for the physician to keep in mind these differences, they may also be useful for a better positioning of these pharmacological approaches in the treatment algorithm of people with type 2 diabetes. Finally, given the complementarity of the safety/efficacy profiles of the two classes of drugs, one could hypothesize their concomitant use to exploit their cardiorenal protection. This will require, however, had hoc CV outcome trials.