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Sodium-Glucose Cotransporter 2 Inhibition and Cardiovascular Risk

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Abstract The choice of appropriate therapy for patients with type 2 diabetes is currently based on the effect of available pharmacologic agents on metabolic parameters. Beyond metformin, much uncertainty remains about the cardioprotective properties of several antidiabetic agents. Sodium-glucose cotransporter 2 inhibitors are the latest addition to the therapeutic armamentarium for type 2 diabetes. Apart from effective glycemic control, these agents have also favorable effects on body weight and blood pressure. For dapagliflozin and canagliflozin, large cardiovascular outcome trials are still ongoing whereas for empagliflozin, recent findings show a remarkable reduction in cardiovascular events and all-cause mortality which is probably attributed to osmotic diuresis and the associated volume contraction. Awaiting clarification of the biologic mechanisms that underlie the effects of empagliflozin, future treatment algorithms might need to be revised in order to incorporate this compelling evidence.

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Introduction

Strict glycemic control has been the cornerstone for the management of patients with type 2 diabetes. Nevertheless, too stringent glycemic targets are associated with higher mortality rates [1] leading guideline panels to propose a more conservative approach to hyperglycemia management for frail patients. Beyond glycemic control, a multifactorial intervention including blood pressure control and statin therapy for patients with type 2 diabetes is associated with better outcomes regarding incidence of cardiovascular events and all-cause mortality [2]. In that sense, the latest American Diabetes Association/European Association for the Study of Diabetes position statement published in 2015 puts increased emphasis on cardiovascular risk reduction as the ultimate target of future antidiabetic therapies [3]. Besides that, the US Food and Drug Administration (FDA) requires since 2008 that a detrimental effect on cardiovascular endpoints is excluded for new antidiabetic therapies [4].

Sodium-glucose cotransporter 2 (SGLT-2) inhibitors are a novel class of antidiabetic agents that act in an insulin-independent manner, removing excess blood glucose by inducing glycosuria. Apart from glucose control, these agents have also well-documented benefits on body weight and blood pressure [5]. Empagliflozin is the latest addition to the SGLT-2 inhibitor class, and promising results regarding its effects on cardiovascular morbidity and mortality were recently published [6••]. This review summarizes the available evidence base regarding the impact of SGLT-2 inhibitors on

cardiovascular outcomes and potential underlying mechanisms of action.

Neutral Effects of Dapagliflozin on Cardiovascular Risk

As per the FDA guidance for the assessment of cardiovascular safety of new antidiabetic therapies, a relevant meta-analysis regarding incidence of cardiovascular events in the dapagliflozin clinical development program was submitted to regulatory authorities. Based on this meta-analysis with 145 adjudicated cardiovascular events submitted by the drug sponsor to the European Medicines Agency [7], the hazard ratio (HR) for the composite endpoint including cardiovascular death, myocardial infarction, stroke, and hospitalization for unstable angina was 0.82 (95 % confidence interval (CI) 0.58 to 1.15) [8]. In a subgroup analysis including two studies on patients at high cardiovascular risk, the HR was 1.27 (95 % CI 0.69 to 2.31). This preliminary finding suggests that patients at high cardiovascular risk might be at increased risk for diuresis-related adverse cardiovascular events upon initiation of dapagliflozin. More conclusive evidence is to be expected from DECLARE-TIMI 58, a dedicated cardiovascular outcome trial with dapagliflozin enrolling approximately 17,000 individuals at high cardiovascular risk which is expected to be completed in 2019 [9].

Increased Incidence of Stroke with Canagliflozin

A meta-analysis assessing the cardiovascular safety of canagliflozin found that this SGLT-2 inhibitor was associated with a HR of 0.91 (95 % CI 0.68 to 1.22) for the aforementioned composite endpoint [10]. However, a somewhat higher incidence of stroke was observed in patients initiating treatment with canagliflozin (HR 1.46; 95 % CI 0.83 to 2.58), although not statistically significant. Moreover, an increased number of cardiovascular events with canagliflozin was noted during the first 30 days of the dedicated cardiovascular outcome trial, possibly due to acute changes in volume status upon initiation of canagliflozin. Nevertheless, this imbalance was subsequently reversed. Finally, heart failure-related adverse events were less common with both approved doses of canagliflozin. The Canagliflozin Cardiovascular Assessment Study (CANVAS) to be completed in 2017 has already recruited approximately 4400 participants and will conclusively investigate the effect of canagliflozin on hard cardiovascular endpoints in patients at high cardiovascular risk [11].

Reduction of Cardiovascular Morbidity and Mortality with Empagliflozin

Empagliflozin is the latest addition to the SGLT-2 inhibitor armamentarium for which emerging evidence from a secondary prevention trial suggests a reduction in cardiovascular morbidity and mortality. Findings of the long-awaited event-driven EMPA-REG OUTCOME trial with approximately 7000 patients with established cardiovascular disease showed a beneficial effect of empagliflozin on the primary composite cardiovascular endpoint, which included cardiovascular death and non-fatal myocardial infarction and stroke (HR 0.86; 95 % CI 0.74 to 0.99) [6]. More importantly, empagliflozin was associated with significant reductions in all-cause mortality (HR 0.68; 95 % CI 0.57 to 0.82) and the component of cardiovascular death (HR 0.62; 95 % CI 0.49 to 0.77) as well as a 35 % reduction in rates of hospitalization for heart failure. Findings of the EMPA-REG OUTCOME trial are also in line with a relevant meta-analysis in support of the approval of empagliflozin by regulatory bodies which reported a HR 0.48 (95 % CI 0.27 to 0.85) for the composite endpoint based on seven trials with 3709 patients [12].

Of note, the EMPA-REG OUTCOME trial utilized an enriched population of patients with type 2 diabetes and high cardiovascular risk, with 92 % of the study population having arterial hypertension and >80 and >75 % using an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker and a statin respectively. Based on findings of the aforementioned trial, empagliflozin used on top of these well-proven non-glucose-lowering interventions was associated with a number needed to treat of 39 to prevent one death for 3 years of follow-up. Nevertheless, uncertainty remains regarding the magnitude of the effect of empagliflozin in patients at lower cardiovascular risk.

Insights into the Cardioprotective Effects of Empagliflozin

Several hypotheses have been suggested to explain the cardiovascular benefits reported in the EMPA-REG OUTCOME trial, based on the favorable effects of empagliflozin on body weight, blood pressure, serum uric acid levels, albuminuria, indices of arterial stiffness, and vascular resistance [13, 14•]. The underlying pathophysiologic mechanism has not been yet elucidated; nevertheless, a rise in endogenous glucose production and enhanced lipid utilization to compensate for the caloric deficit induced by glucosuria have been consistently reported with all SGLT-2 inhibitors including empagliflozin [15]. Accordingly, empagliflozin reduces trunk fat as measured by means of dual-energy X-ray absorptiometry. Magnetic resonance imaging modalities indicate that fat loss is equally accounted for by reductions in amounts of both

visceral and subcutaneous adipose tissue [16]. Finally, it appears that increased glucagon secretion is another unanticipated class effect of SGLT-2 inhibitors [15]. Glucagon is thought to exert direct inotropic and antiarrhythmic actions [17].

Findings of the EMPA-REG OUTCOME trial suggest that empagliflozin prevents cardiovascular events early following exposure to the study drug. Hence, effective control of glycemia and improvements in several metabolic indices with empagliflozin are unlikely to account for the rapid onset of cardiovascular benefits with empagliflozin [18•]. On the other hand, therapy with empagliflozin is associated with a rapid reduction in systolic blood pressure on average by 4 mmHg and an accompanying benefit of approximately 2 mmHg regarding diastolic blood pressure, which are attributed to osmotic diuresis and excess urine output [14]. The effects on blood pressure have also been corroborated in trials using 24-h ambulatory blood pressure monitoring [19], and changes in volume status are accordingly supported by the attendant rise in hematocrit. These benefits pinpoint to volume contraction as the most probable biologic mechanism of action behind the acute effect of empagliflozin on mortality and heart failure rates, potentially combined with amelioration of asymptomatic diastolic dysfunction [18] and concomitant activation of cardioprotective non-classical pathways of the renin-angiotensin-aldosterone system (RAAS) in patients treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers [20•].

Volume Depletion-Related Adverse Events

The possibility that the cardiovascular benefits of empagliflozin are mediated by volume depletion should be placed in context with potential volume-related adverse events. Isolated cases of euglycemic diabetic ketoacidosis have been recently reported in patients treated with SGLT-2 inhibitors, although the overall risk for diabetic ketoacidosis remains unknown. In most cases, relatively low blood glucose levels delayed recognition of the condition and subsequent treatment with insulin [21]. Moreover, acute changes in volume status could probably precipitate orthostatic hypotension, syncope, and dizziness especially in frail patients, including elderly patients with renal impairment or patients treated with thiazide or loop diuretics [12]. Notably, an increased incidence of fractures has been noted with selected SGLT-2 inhibitors such as canagliflozin. Most cases occurred early after initiation of canagliflzin and were related to falls probably due to hypovolemia, although studies have also reported a reduction in bone mineral density and an increase in markers of bone turnover [22, 23].

Conclusions

Predicting the effect of a new drug on hard outcomes based on changes in metabolic parameters is particularly challenging. Several presumptive biologic mechanisms could be quoted a posteriori to support an observed effect on clinical endpoints. The example of empagliflozin reiterates the need for large randomized controlled trials designed to assess cardiovascular outcomes as the only way to conclusively investigate the cardiovascular effects of new antidiabetic drugs. Unlike observational and post-marketing studies, large cardiovascular outcome trials are free from residual confounding and can thus safely prove the existence of a certain biological effect or the lack thereof [24].

Today, the choice amongst existing therapies for type 2 diabetes is still based on their relative merits and harms regarding the effect on metabolic parameters such as blood glucose, body weight and risk of hypoglycemia, and patient preferences [3]. Metformin has shown modest cardiovascular benefits and is therefore considered therapy of choice for type 2 diabetes unless contraindicated for other reasons [25]. EMPA-REG OUTCOME has demonstrated significant cardiovascular benefits for type 2 diabetes patients at increased cardiovascular risk who were treated with empagliflozin, while data from cardiovascular safety trials for other SGLT-2 inhibitors are still pending. This potentially practice-changing observation might facilitate changes in existing guidelines for the management of high-risk patients with type 2 diabetes, although uncertainty remains regarding the cardiovascular benefits of SGLT-2 inhibitors for patients at lower cardiovascular risk.

Compliance with Ethical Standards

Conflict of Interest Drs Liakos, Bekiari, and Tsapas declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the authors.

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- • Of importance
- •• Of major importance

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