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Review Article

Sodium-glucose co-transporter-2 inhibitors as anti-diabetic agents: a review

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ABSTRACT

The incidence and prevalence of Type 2 diabetes mellitus (T2DM) have been increasing worldwide. However, existing therapeutic classes of anti-diabetic drugs are not adequately effective in achieving and maintaining long-term glycemic control in the most patients. The majority of the drugs control blood sugar without addressing the basic pathology of insulin resistance and relative deficiency. Moreover, side effects such as hypoglycemia and weight gain, of both new and established drugs need to be considered prior to treating a patient. An emerging anti-hyperglycemic intervention, the sodium glucose co-transporter 2 (SGLT2) inhibitor acts by a novel mechanism. Under physiological conditions, SGLT2 accounts for 90% of the glucose re-absorption in the kidney, while the SGLT2 inhibitors result in an increase in urinary excretion of glucose and lower plasma glucose levels. Here, the pros and cons of SGLT2 inhibitors are considered, while approaching a patient with T2DM. The basic biochemistry and physiology underlying the mechanisms of SGLT2 inhibitors are discussed alongside its clinical pharmacology, with a focus on metabolic changes associated with urinary glucose loss. Finally, a consideration of Food and Drug Administration safety concerns associated with acidosis due to SGLT2 inhibitor usage is presented, to allow a complete understanding of the utility of these molecules in the light of existing T2DM therapies.

Keywords: Anti-hyperglycemic drugs, Cardiovascular safety, Food and Drug Administration, Hyperglycemia, Renal function, Sodium-glucose co-transporter-2 inhibitors, Type 2 diabetes mellitus

INTRODUCTION

Under normal physiological conditions, most healthy individuals are able to maintain tight glucose homeostasis by regulating glucose production, re-absorption, and utilization. The importance of this homeostatic mechanism is evident from the fact that in spite of extreme variations in glucose intake, only a fraction of individuals develops either diabetes or hypoglycemia.

In healthy adults, about 180 g of glucose is filtered daily by the renal glomeruli and is completely reabsorbed in the proximal convoluted tubule (PCT). This is achieved by passive transport via facilitated glucose transporters (GLUTs), and active co-transport through sodium-glucose co-transporters (SGLTs). There are six identified SGLTs, of which two (SGLT1 and SGLT2) are considered most important.[1]

Here, a review of the role of SGLT2 inhibitors (SGLT2i) in Type 2 diabetes mellitus (T2DM) management, clinical pharmacology including mechanism of action, and the pragmatic placement of these molecules in the existing oral anti-diabetic drug arena is presented.

RENAL REGULATION OF GLUCOSE HOMEOSTASIS

Figure 1 shows kidneys play an important role in the homeostasis of energy metabolites, protein and minerals along with the critical roles of controlling acid base balance, hematopoesis and blood pressure.[2] The role of the kidneys

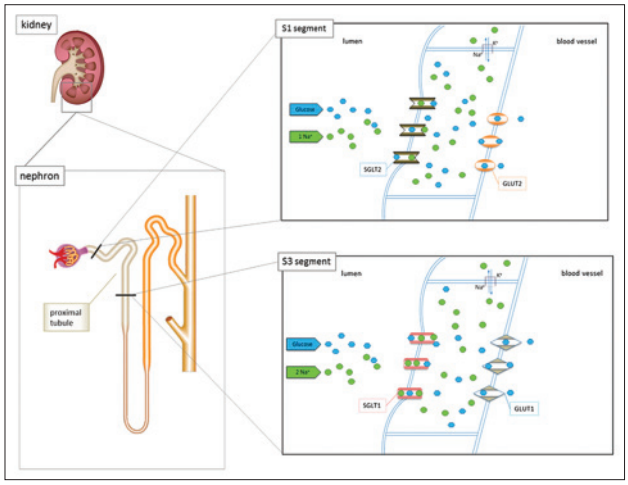

Figure 1: Schematic overview depicting the localization and function of sodium glucose co-transporter (SGLT1) and SGLT2 in the kidneys. SGLT2 reabsorbs glucose in combination with sodium in a 1:1 ratio in the tubular S1 segment, whereas SGLT1 reabsorbs glucose in combination with sodium in a 1:2 ratio in the tubular S3 segment. Both transporters are secondary active and driven by the activity of the Na+/K+-ATPase. Glucose reuptake into blood vessels is facilitated by glucose transporters GLUT1 and GLUT2 (Courtesy: B Haas, N Eckstein, V Pfeifer, P Mayer, M D S Hass; Efficacy, safety and regulatory status of SGLT2 inhibitors; Nutrition & Diabetes (2014) 4, e143; doi:10.1038/nutd.2014.40. http://www.nature.com/nutd/journal/v4/n11/full/nutd201440a.html#tbl1.).

in glucose metabolism is important and includes, in addition to the gluconeogenesis, glucose utilization, glucose filtration and re-absorption.[3]

Plasma glucose enters along with the filtrate into the nephron glomerulus due to its low molecular weight and is reabsorbed at the PCT. This mechanism helps the body avoid catabolism of stored energy reserves by conserving glucose, an important survival mechanism in times of food scarcity. Reabsorption of glucose from the filtrate occurs via sodium-linked GLUT 1 and 2 (SGLT1 and SGLT2), respectively.[4] Table 1 shows these transporters also exist in other organs, such as the intestine, where primarily *SLC5A1* (SGLT1) is expressed. Renal tubules express both *SLC5A1* and *SLC5A2* (SGLT2).[5]

Both SGLT2 and SGLT1 are able to reabsorb glucose, but they show significant differences in their affinities and transport capacity: SGLT2 has a greater transport capacity and reabsorbs glucose in combination with sodium in the ratio 1:1. SGLT1 has a higher affinity for glucose and reabsorbs glucose in combination with sodium in the ratio 1:2.[4,6]

Figure 2 shows different transport properties of GLUT are utilized by kidneys to reabsorb glucose entirely from the

Table 1: Overview of the current regulatory status of selective SGLT2 inhibitors for the treatment of diabetes.

SGLT inhibitor	Daily dose (mg)	Approval/ developmental status
Dapagliflozin	5, 10	Approved by EMA (2012/11), FDA (2014/01), PMDA (2014/03)
Canagliflozin	100, 300	Approved by FDA (2013/03), EMA (2013/11)
Empagliflozin	10, 25	Approved by EMA (2014/05), FDA (2014/08)
Ipragliflozin	25, 50	Approved by PMDA (2014/01)
Tofogliflozin	20	Approved by PMDA (2014/3)
Luseogliflozin	2.5, 5	Approved by PMDA (2014/03)
Ertugliflozin	5, 10	Phase III recruiting

EMA: European Medicines Agency, FDA: Food and Drug Administration, NA: Not applicable, PMDA: Pharmaceuticals and Medical Devices Agency. Japan; source of information: Homepages of the FDA,[47] EMA,[16] PMDA,[48] (www.clinicaltrials.gov), SGLT2: Sodium glucose co-transporter

filtrate. SGLT2 is localized mainly in the first two segments of the proximal tubular system (S1 and S2 segment), and due to its high transport capacity, it is capable of reabsorbing about 90% of glucose from the filtrate, while 10% percent of initially filtered glucose is recovered in the third section of the proximal tubule (S3 segment) by SGLT1 because of its high affinity.[4]

PHYSIOLOGICAL GLUCOSURIA AND RENAL GLUCOSURIA

Glucosuria after an oral glucose challenge depends on the plasma glucose excursion, and is more pronounced in pregnant women generally due to smaller plasma distribution volume.[7] Renal glucosuria, on the other hand, is detected in the absence of any signs of generalized proximal renal tubular dysfunction. An inherited form of this disorder is called familial renal glucosuria, in which mutations in the *SLC5A2* gene are responsible for the majority of cases. Glucosuria with tubular disorder includes Fanconi-de Toni-Debre syndrome, cystinosis, Wilson disease, hereditary tyrosinemia, and oculocerebrorenal osteodystrophy (Lowe syndrome). Renal glucosuria has also been reported in patients with acute pyelonephritis in spite of normal blood glucose level.[8,9]

INCREASED SGLT2 EXPRESSION IN T2DM

Figure 2 shows early clinical studies in patients with Type 2 diabetes showed that the splayed plasma glucose threshold (TmG) is increased by 20-40% in comparison with non-diabetic subjects. Similar findings have been reported in patients with Type 1 diabetes. More recent studies in cultured human renal tubular cells harvested from the urine of diabetic patients have shown that the expression of SGLT2, its protein concentration, and its α-methyl-GLUT capacity are all increased markedly in comparison with non-diabetic subjects. Thus, as a result of chronic hyperglycemia, renal glucose re-absorption appears to be abnormally high in subjects with diabetes.[10-12]

In addition, both transporters are secondarily active owing to their dependence on the activity of the Na^+/K^+-ATPase in the basolateral membrane for the active removal of sodium. GLUT facilitate glucose absorption across the basolateral membrane in the early and more distal regions of the proximal tubule.[4]

DIABETES AND RENAL GLUCOSE REGULATION

Failure of a transporter system in diabetic patients can result in increased glucose excretion in the primary urine as well as increased SLC5A2 expression. This will lead to an increase in the renal threshold for glucose in the final urine, allowing kidneys to retain body glucose under diabetic conditions.[10] Moreover, up-regulation of SGLT2 expression in diabetes has been linked to activation of Ang II AT1 receptors and the transcription factor, hepatocyte nuclear factor HNF-1α that helps in maintaining glucose as an energy source.[13,14]

Figure 3 shows an inhibition of SGLT2 reduces glucose re-absorption in the S1 and S2 segments. This can be compensated only in part by SGLT1 in the S3 segment, and complete re-absorption of glucose does not occur.[15]

HISTORY AND CURRENT REGULATORY STATUS OF SGLT2 INHIBITORS

The new molecules that can inhibit the SGLT transport system result in increased urinary glucose excretion by reducing glucose re-absorption, benefitting patients with T2DM.[16]

The first SGLT2i discovered was phlorizin, which was a naturally occurring compound derived from apple tree bark. Due to its non-selective nature, it caused severe gastrointestinal symptoms, and, this combined with its poor oral bioavailability did not allow research into its development to continue.[17] On the other hand, Table 1 shows drugs which specifically inhibit SGLT2, and thereby avoid gastrointestinal effects related to SGLT1 inhibition, have been developed. These SGLT2 inhibitors, are either currently available or are undergoing clinical development

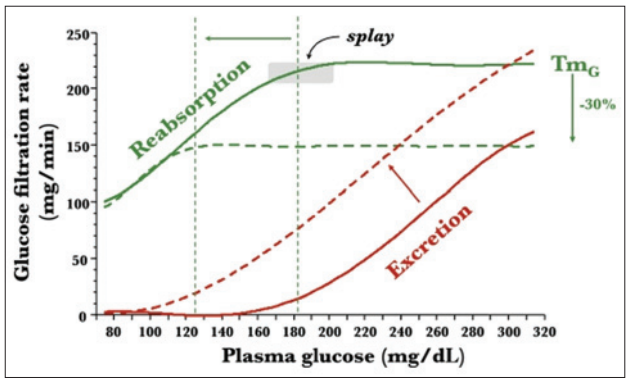

Figure 2: Renal glucose handling. Flux rates (filtration, re-absorption, and excretion) were calculated using a glomerular filtration rate of 120 mL/mins per 1.73 m^2 and a renal threshold of 180 mg/dL (10 mmol/L). To visualize the splay, data were fitted with polynomials. The dotted lines simulate the effect of a 30% reduction in TmG on re-absorption and excretion (TmG=Splayed plasma glucose threshold i.e., normal TmG=180 mg/dL) (Courtesy: Ferrannini E; Learning From Glucosuria; Diabetes. 2011 March; 60(3): 695-696.).

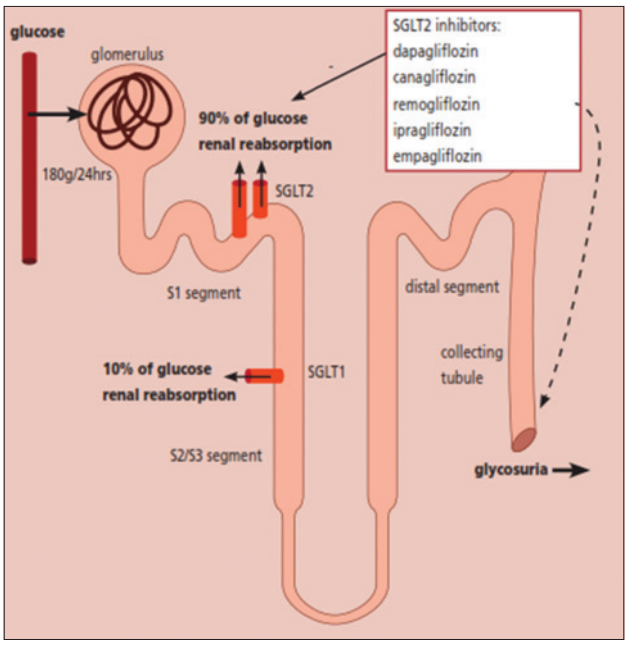

Figure 3: Glucose re-absorption from the kidneys is mediated by sodium glucose co-transporter (SGLT2) (90%) and SGLT1 (10%); inhibitors of SGLT2 lower renal threshold of glucose and increase urinary glucose excretion, therefore reducing circulatory glucose levels (Courtesy: Richard Donnelly; SGLT2 inhibitor for treating Type 2 diabetes; Future prescriber 2013 (14) 1-p 5-8. http://onlinelibrary.wiley.com/doi/10.1002/fps.101/pdf.).

and approval, with a few currently approved by US FDA, as discussed below

SGLT2 INHIBITORS IN GLUCOSE KINETICS OF DIABETIC PATIENTS

SGLT2i are competitive, reversible and highly selective, having 250-fold selectivity toward SGLT2 over SGLT1. These drugs which induce glucosuria of ~70 g per day, resulting in loss of glucose and optimized plasma glucose control.[15,18] The drugs can be used in patients with T2DM to improve glycemic control as monotherapy or in combination with other drugs, when diet and exercise alone do not provide adequate glycemic control.[19]

DAPAGLIFLOZIN

Dapagliflozin was initially rejected by the US Food and Drug Administration (FDA) owing to concerns noted by an Advisory Panel about potential increases in the risk of bladder and breast cancers associated with the drug. However, in November 2012, the first-in-class SGLT2 inhibitor, dapagliflozin, was granted marketing authorization by the European Medicines Agency (EMA).[20,21]

Eventually, in January 2014, FDA granted marketing authorization for dapagliflozin after new safety data on dapagliflozin from ongoing studies were provided. The FDA required to perform several post-marketing studies, in which >17000 patients would be followed for 4-5 years to clarify whether dapagliflozin therapy is associated with increased risks for cardiovascular (CV) events, liver toxicity or cancer. Other post-marketing studies were required by the FDA to further assess bladder cancer risk and dapagliflozin's effect in pediatric patients. Furthermore, an intense pharmacovigilance program to monitor reports of liver toxicity needed to be implemented by the company.[22]

CANAGLIFLOZIN

Canagliflozin was approved by the FDA in March 2013, and in November 2013 by the EMA. Marketing authorizations followed a positive opinion of Advisory Committees, but concerns about the safety of canagliflozin remained, which were addressed in several post-authorization safety studies. In Europe, canagliflozin has been labeled with an inverted black triangle in the package leaflet and the summary of product characteristics (SmPC), indicating that the drug is under additional monitoring by regulatory authorities.[22]

As reflected in the European Public Assessment Report (EPAR) of canagliflozin, depending on the premedication and baseline HbA_{1c} placebo-adjusted reduction, between −0.57% and −0.91% (100 mg dose) and −0.70% and −1.16% (300 mg dose) was observed, respectively. In poorly controlled diabetic patients even a reduction of up to - 2.42% was achieved. The favorable effect on HbA_{1c} values was consistent with an improvement of secondary end points such as fasting plasma glucose. The efficacy of canagliflozin was reduced in patients with moderate renal impairment.[21]

A meta-analysis of all subjects from placebo-controlled Phase III studies with eGFR >30 to <60/ml/min per $1.73m^2$ (1085 subjects) showed a decrease in HbA_{1c} from baseline by −0.47% and −0.38% for canagliflozin 300 and 100 mg, respectively, compared with placebo. This is in line with the mode of action and is reflected in the SmPC as a warning for patients with end-stage renal disease, on dialysis, or with renal impairment and an eGFR <60/ml/min per 1.73m.[2,21,23]

The induced glucosuria of 70 g per day additionally leads to an energy deficit of 300 kcal per day, which translates into a body weight reduction of −1.84 and −2.43 kg (100 and 300 mg canagliflozin, respectively). Studies have shown that weight loss stabilizes after a couple of weeks, even so glucosuria persists and calorie loss is maintained.[19,24]

EMPAGLIFOZIN

On March 2014, the EMA recommended granting of a marketing authorization for a third SGLT2 inhibitor empaglifozin. Initially, FDA rejected approval of empagliflozin in March 2014 owing to previously observed deficiencies at a facility where empagliflozin is manufactured, but finally approved it in August 2014. In Japan four SGLT2 inhibitors, namely dapagliflozin, ipragliflozin, tofogliflozin, and luseogliflozin, were approved in 2014.[21,23]

Studies with empagliflozin in streptozotocin-induced diabetic rats and results from a Phase II trial indicate beneficial effects of SGLT2 inhibition on reducing HbA_{1c}, body weight, total daily insulin dose and hypoglycemic events. Further studies with empagliflozin and other SGLT2 inhibitors are currently underway to prove their efficacy and safety in T1DM patients.[25,26]

DISCUSSION

Typical features of T2DM include insulin resistance of various organs such as liver, muscle and adipose tissue, abnormal hepatic glucose production, and reduced glucose-stimulated insulin secretion.[27] This leads to the insensitivity of the insulin receptor and impairment of insulin signaling. In the early stages of developing T2DM, pancreatic insulin production increases to overcome resistance, but eventually, during the progression of T2DM, insulin secretion decreases owing to the depletion of pancreatic β-cells, resulting in absolute insulin deficiency with an increase in plasma glucose levels.[28]

Long-term elevated plasma glucose levels are responsible for the development of microvascular complications, such as retino-, nephro- and neuropathy, and macrovascular

complications, such as atherosclerosis, which are the most common long-term complications of T2DM.[29,30]

Correcting insulin resistance and substituting insulin currently is regarded as the gold standard of diabetes therapy. In addition, several medications are available, which improve glucose utilization and uptake into insulin-sensitive tissue that include metformin and pioglitazone.[31-33] The release of insulin from pancreatic stores is achieved by sulphonylureas,[34] incretin mimetics such as glucagon-like peptide 1 analogues and dipeptidyl peptidase 4 inhibitors.[35]

The major limitation with this type of conventional intervention is that the daily dietary calorie intake usually stays too high and, thus progression of T2DM is supported.[22] In addition, only 50% of patients with T2DM reach their glycemic goal with currently available therapy options. Moreover, the current T2DM treatments have dose-limiting safety or tolerability issues, including hypoglycemia with sulphonylureas, edema with glitazones, weight gain by sulphonylureas or glitazones, and gastrointestinal adverse events by glucagon-like peptide 1 analogues.[36,37]

Therefore, medical need for therapies with fewer side effects, which in addition increase glycemic control, became evident. As per preclinical study, SGLT2 knockout mice and SGLT2 deletion had improved glucose homeostasis and glycemic control. These considerations have led to the clinical development of the new class of anti-diabetic drugs: inhibitors of the renal sodium-linked GLUT 2, which combine two medical needs: glycemic control and reduction of already ingested calories as glucose is secreted unmetabolized.[16]

Among the most important safety aspects of anti-diabetic drug is their low tendency to produce hypoglycemia. Interestingly, during clinical development of SGLT2 inhibitors hardly any hypoglycemia has been shown. This low risk for hypoglycemia can be regarded an advantage of this class of medicines as compared with classical anti-diabetic compounds such as insulin or sulphonylureas.

On analyzing the adverse events observed with gliflozin, almost no organ toxicities were found during pre-clinical development; only in long-term rat studies toxicities in terms of excessive bone growth (hyperostosis) and renal tubular tumors were observed, probably caused by undesired SGLT1 inhibition in the gastrointestinal tract and subsequent carbohydrate malabsorption in the rat.[20]

SGLT2 inhibition can lead to urinary tract infections, as glucose serves as nutrient for bacteria, as was indeed observed in regulatory safety trials. Specifically, gliflozin-related increases in female mycotic genital infections were noted, but they were not serious in nature and were easy to treat. However, patients and prescribers should be aware of it. The other reported side effect of gliflozin treatment is osmotic diuresis and subsequent water loss, which need to be taken care of in tropical countries especially during summer season. However, unlike that observed during classical osmotic diuresis, where sodium is retained, SGLT2 inhibition causes sodium loss as sodium is co-transported with glucose by SGLT2.[38]

Gliflozin leads to a decrease in blood pressure and hemoconcentration, reflected by increased hemoglobin and hematocrit, but does not trigger thirst due to lack of notable hypernatremia. The latter may explain why, in particular, elderly patients do not develop sufficient thirst to compensate for water loss and consequently tend to have dehydration, unstable blood pressure or syncope.[39,40]

A sharp decrease in blood pressure can particularly occur at the beginning of therapy; later on, counter-regulatory mechanisms like reduction in glomerular perfusion minimize diuresis and blood pressure reduction. In order to avoid hemodynamic problems in vulnerable patients, gliflozin therapy should be initiated with the lower dose, and concomitant use of gliflozin and loop diuretics is not recommended.[21]

Regarding renal function, gliflozin might damage kidneys, especially when kidney function is already impaired by diabetic nephropathy.[20] Moreover, hemoconcentration observed under gliflozin therapy also leads to an increase in serum creatinine, which is usually a marker of renal damage, which was fully reversible after cessation, so that renal damage can be excluded which require proper evaluation.[41,42]

In Phase III studies with the first SGLT2 inhibitor for which marketing authorization was requested, there had been a discussion of possible cancer risk. However, no increase in bladder cancer was found subsequently with approved SGLT2 inhibitors.[38] Moreover, there is a need to prove clinical efficacy of SGLT2 inhibitors in patients with isolated renal glucosuria. As per preclinical studies, canagliflozin caused renal tubular tumors in rats, but mechanistic studies revealed that off-target inhibition of SGLT1 in these animals was the underlying mechanism.[20,23]

For canagliflozin, a long-term cardiovascular safety study (CANVAS) was originally planned to demonstrate CV safety in patients with increased risk for CV events.[43] According to the present knowledge from a meta-analysis of clinical trials interim analysis of the CANVAS study provided in the EPAR of canagliflozin, it has not shown to increase the overall CV risk.[20,23]

Precaution statement on safety of SGLT2i by U.S. FDA

As per the U.S. FDA safety report, "T2DM canagliflozin, dapagliflozin, and empagliflozin may lead to ketoacidosis, a serious condition where the body produces high levels of blood acids called ketones that may require hospitalization. FDA is continuing to investigate this safety issue and will

determine whether changes are needed in the prescribing information for this class of drugs, called SGLT2 inhibitors.

Patients should pay close attention for any signs of ketoacidosis and seek medical attention immediately if they experience symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue or sleepiness. Moreover, patients should not stop or change your diabetes medicines without first talking to the prescriber. Healthcare professionals should evaluate for the presence of acidosis, including ketoacidosis. In patients experiencing these signs or symptoms; discontinue SGLT2 inhibitors if acidosis is confirmed; and take appropriate measures to correct the acidosis and monitor sugar levels."[44]

On the other hand, considering safety of drug, risk of development of fracture and osteoporosis by measuring bone density[45] and percentage increase in the risk of heat stroke in summer season in tropical countries need to be evaluated in clinical trials or future post marketing surveillance.[46]

CONCLUSIONS

Overall, the SGLT2 inhibitors represent a novel class of drugs which will certainly help a large number of people with diabetes, to achieve the goal of blood sugar in a safe and well-tolerated manner. As compared to existing drugs, they exhibit a different mechanism of action for glycemic control that is complemented with a low risk of hypoglycemia. Moreover, due to reduction of weight and blood pressure, physicians can make it an attractive choice as an add-on therapy for blood sugar not controlled with other medications.

On the other hand, there is a need of long-term renal safety data, cardiovascular risk reduction, and mortality benefit with vigilance on incidence of newer case of tumor after initiating SGLT2 inhibitors. Moreover, precaution should be exercised in patients with a tendency to develop acidosis, dehydration, recurrent urinary tract infections, reduced renal function, and patients living in tropical climates during summer season - especially in special populations like elderly patients.

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