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Sodium–Glucose Cotransporter-2 Inhibitors and the Risk of Diabetic Ketoacidosis: A Narrative Review

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Abstract

Introduction: Sodium-glucose cotransporter-2 inhibitors, or SGLT2 inhibitors for short, have become a key part of managing type 2 diabetes due to their ability to lower glucose levels and provide cardiovascular and renal benefits. However, as their use has increased, so has the occurrence of rare but serious side effects, including diabetic ketoacidosis (DKA). What's notably concerning is that DKA often presents as euglycemic diabetic ketoacidosis (euDKA), where blood glucose levels are normal or only slightly elevated, which can make it harder to diagnose and treat promptly. This might lead to delays in getting the right treatment, which is a serious issue. It's essential to be aware of this potential risk and to monitor patients attentively to ensure they get the care they need.

Objective: To summarize current evidence on the epidemiology, pathophysiology, clinical presentation, risk factors, prevention, and management of SGLT2 inhibitor-associated DKA.

Results: SGLT2 inhibitor-associated DKA is an uncommon but potentially life-threatening complication. Proposed mechanisms include increased urinary glucose excretion, reduced insulin levels, increased glucagon secretion, enhanced lipolysis, and hepatic ketogenesis. The risk is increased because of factors such as acute illness, surgery, prolonged fasting, low-carb diets, dehydration, excessive alcohol consumption, and insulin deficiency. Although the absolute incidence is low, the relative risk is higher than with several other glucose-lowering therapies, notably in individuals with insulin deficiency or pancreatic disorders. Early recognition, patient education, sick-day management, and temporary discontinuation of SGLT2 inhibitors before surgery or prolonged fasting are key preventive measures.

Conclusion: In the end, the benefits of SGLT2 inhibitors for the heart and kidneys outweigh the small risk of DKA. To achieve the best treatment outcomes and avoid adverse effects, it's vital to select the right patients, follow prevention guidelines, and promptly recognize euDKA.

Keywords: SGLT2 inhibitors; diabetic ketoacidosis; euglycemic ketoacidosis; type 1 diabetes.

Introduction

Type 2 diabetes is a huge problem worldwide, affecting over 590 million adults [1-2]. unfortunately, it's expected to get even worse in the coming years [1-2]. Diabetes mellitus is a major cause of heart disease, kidney disease, and even premature death [2]. Diabetes mellites care is putting a huge strain on medical systems [2]. So, health care providers and researchers are now looking beyond just controlling blood sugar levels. They want to find treatments that can also improve heart and kidney health while making sure they're safe for patients. Sodium glucose cotransporter-2 inhibitors (SGLT2 inhibitors), including empagliflozin, dapagliflozin, canagliflozin, ertugliflozin, and Sotagliflozin, represent one of the most significant advances in diabetes management in recent years [3].

By selectively inhibiting the SGLT2 transporter in the proximal renal tubule, these agents reduce renal glucose reabsorption, promote glycosuria, and lower plasma glucose concentrations through an insulin-independent mechanism [4]. In addition to improving glycaemic control, SGLT2 inhibitors produce modest reductions in body weight and blood pressure while carrying a low intrinsic risk of hypoglycaemia [5]. The benefits of SGLT2 inhibitors go far beyond just lowering blood sugar levels. Several major studies, including EMPA-REG OUTCOME [6], CANVAS [7], and DECLARE-TIMI 58 [8], have shown that these medications may also reduce the risk of heart failure, kidney disease, and death from cardiovascular causes. This is true not just for people with diabetes, but for a wide range of patients. As a result, SGLT2 inhibitors have become a key part of the treatment of type 2 diabetes, heart failure, and kidney disease. Major health organizations, including the American Diabetes Association and the European Society of Cardiology, strongly recommend them [5].

In fact, studies such as DAPA-HF [9], EMPEROR-Reduced [10], and EMPEROR-Preserved [11] have demonstrated the effectiveness of SGLT2 inhibitors in reducing hospitalizations for heart failure and slowing the progression of kidney disease. Additionally, trials like DELIVER (12), DAPA-CKD (13), EMPA-KIDNEY [14], and CREDENCE [15] have further confirmed the importance of SGLT2 inhibitors in the management of these conditions. Overall, the evidence is clear: SGLT2 inhibitors are an important tool in the fight against type 2 diabetes, heart failure, and kidney disease, and should be considered a core part of treatment for these conditions. Health care providers should still be careful about some rare but serious side effects of SGLT2 inhibitors, even though they can be very helpful. Some common problems include genital infections, urinary tract infections, and frequent urination, which can bring about dehydration and low blood pressure [5]. More serious, but less common issues can be Fournier's gangrene [16], needing to amputate a limb which was mostly seen in people taking canagliflozin in a study called the CANVAS Program [7] and diabetic ketoacidosis (DKA).

DKA is especially concerning because it can happen even when blood sugar levels are normal or only a little high, which is called euglyce-

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mic diabetic ketoacidosis (euDKA), this can make it harder to diagnose and treat properly. Health care providers need to watch out for these side effects, especially euDKA, because it can be tricky to spot. If someone has DKA, they might not have the usual high blood sugar symptoms, so it could take longer to figure out what's going on and get them the right treatment. By being more aware of this potential issue, health care providers can help prevent serious problems and ensure their patients obtain the best possible care. Unlike classical DKA, which is characterized by marked hyperglycaemia, SGLT2 inhibitor-associated DKA can develop despite relatively normal glucose concentrations because urinary glucose excretion masks the severity of the underlying metabolic disturbance [17]. The disorder results from a multifaceted interaction of reduced circulating insulin concentrations, increased glucagon secretion, enhanced lipolysis, accelerated hepatic ketogenesis, and alterations in renal ketone handling, creating a pro-ketotic state [17]. Clinical stressors-including acute illness, infection, surgery, prolonged fasting, dehydration, excessive alcohol intake, pregnancy, ketogenic or very-low-carbohydrate diets, and inappropriate reduction or omission of insulin therapy-can further precipitate ketoacidosis, notably in individuals with impaired endogenous insulin secretion [18].

It's been a few years since we started paying closer attention to a complication that can occur when people take a certain kind of medicine to lower their blood sugar. This was back in 2015, when the FDA and the European Medicines Agency sent out warnings about it. They did this because they were getting reports of a condition called diabetic ketoacidosis, or DKA for short, in people who were taking a type of medicine called an SGLT2 inhibitor [19]. Since then, we've conducted studies and analysed data, and we've found that while DKA doesn't happen very often, it's more likely to occur in people taking this kind of medicine than in those taking other medicines that lower blood sugar. The people who are most at risk are those with type 1 diabetes, a type of diabetes that happens in adults but is similar to type 1, people with diabetes who don't make enough insulin, and those with problems with their pancreas. We've also found that certain things can trigger DKA in people who are taking this medicine, like metabolic stress [3]. As more people with diabetes, heart failure, and kidney disease are being treated with SGLT2 inhibitors, it's vital to be conscious of the potential risks. Even if some side effects are rare, they can still have a big impact on public health. To get the most benefit from these medications while reducing risks, health care providers need to carefully choose which patients should take them, ensure patients understand how to use them correctly, and have plans in place to manage side effects. This includes having a plan for when patients are sick, stopping the medication before surgery or fasting, and quickly observing signs of serious problems like ketosis and euDKA. By implementing these steps, we can help ensure that patients get the best possible results from their treatment.

This article looks at the latest research on a serious condition called DKA that can occur in people taking a class of medicines called SGLT2 inhibitors. These medicines are used to help control blood sugar levels in people with diabetes. The article intends to understand how often DKA occurs, why it occurs, what the symptoms are, and how to prevent and treat it. It also reviews studies and guidelines from around the world to help doctors use these medicines safely and effectively while still benefiting from reduced risk of heart and kidney problems. By better understanding DKA, doctors can help people with diabetes use these medicines with lower risk and better results.

Pathophysiological Mechanisms of SGLT2 Inhibitor-Associated Diabetic Ketoacidosis.

Diabetic ketoacidosis (DKA) associated with sodium–glucose cotransporter-2 (SGLT2) inhibitor therapy results from a complex interplay between altered glucose homeostasis, hormonal adaptations, enhanced lipid metabolism, and increased ketone body production (Figure 1) [17]. In contrast to classical DKA, which is characterized by marked insulin deficiency, marked hyperglycaemia, and osmotic diuresis, SGLT2 inhibitor-associated DKA frequently occurs with normal or only mildly elevated plasma glucose concentrations [17]. This atypical presentation, referred to as euglycaemic diabetic ketoacidosis (euDKA), may delay diagnosis because the absence of significant hyperglycaemia may obscure the underlying metabolic disturbance.

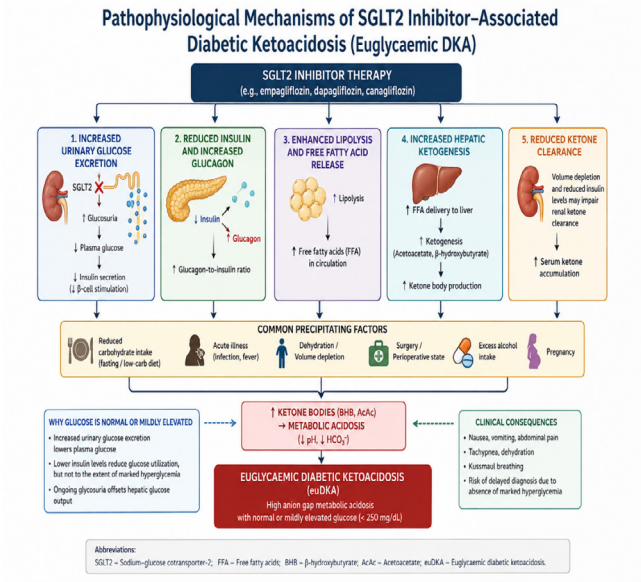

Figure 1: *Pathophysiological Mechanisms of SGLT2 Inhibitor-Associated Diabetic Ketoacidosis.*

Altered Glucose Homeostasis

SGLT2 inhibitors work by blocking a special transporter in the kidneys that helps the body reabsorb glucose. This transporter is like a gate that lets glucose back into the bloodstream, but SGLT2 inhibitors shut this gate, so the glucose gets flushed out in the urine instead. As a result, blood glucose levels decrease, and this occurs without insulin [20]. Normally, when glucose levels are high, the pancreas releases insulin to help cells absorb the glucose. But with SGLT2 inhibitors, the pancreas doesn't get the same signal to release insulin, so less insulin is produced [20]. This can lead to some changes in how the body uses fat for energy. When there's less insulin around, the body starts to break down fat more easily, which can increase the levels of certain fatty acids in the blood [21]. The liver can then use these fatty acids to produce ketones, which serve as an alternative energy source. Overall, SGLT2 inhibitors offer a new way to manage blood sugar levels by modifying how the kidneys handle glucose, rather than relying on insulin.

At the same time, researchers have found that blocking SGLT2 can increase glucagon production, a hormone that raises blood sugar levels [21]. This can happen in two ways: either directly, by affecting the pancreatic cells that produce glucagon, or indirectly, by reducing insulin signalling in the pancreas. As a result, the balance between glucagon and insulin is disrupted, bringing about increased glucose production in the liver, increased fat breakdown for energy, and the formation of ketones [21]. This combination of effects creates an environment in the body that is prone to ketosis, a state in which the body burns fat for fuel instead of carbohydrates.

Enhanced Lipolysis and Hepatic Ketogenesis (Figure 2)

The reduced insulin-to-glucagon ratio is central to the development of SGLT2 inhibitor-associated DKA. Under physiological conditions, in-

sulin suppresses hormone-sensitive lipase within adipocytes, thereby limiting lipolysis [22]. During SGLT2 inhibitor therapy, lower circulating insulin concentrations permit increased mobilization of free fatty acids from adipose tissue [22]. Within hepatocytes, free fatty acids undergo β-oxidation to generate acetyl-CoA [23]. Under normal metabolic conditions, acetyl-CoA enters the tricarboxylic acid (TCA) cycle [23]. However, during relative insulin deficiency and glucagon excess, oxaloacetate is preferentially utilized for gluconeogenesis, limiting TCA cycle activity and diverting acetyl-CoA toward ketogenesis [23]. This process leads to enhanced production of acetoacetate and β-hydroxybutyrate, the principal ketone bodies responsible for metabolic acidosis [23]. Glucagon further increases ketogenesis by stimulating mitochondrial 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) synthase, the rate-limiting enzyme in hepatic ketone body synthesis [23]. Consequently, SGLT2 inhibitors establish a metabolic milieu defined by increased lipolysis, accelerated fatty acid oxidation, and increased ketone production.

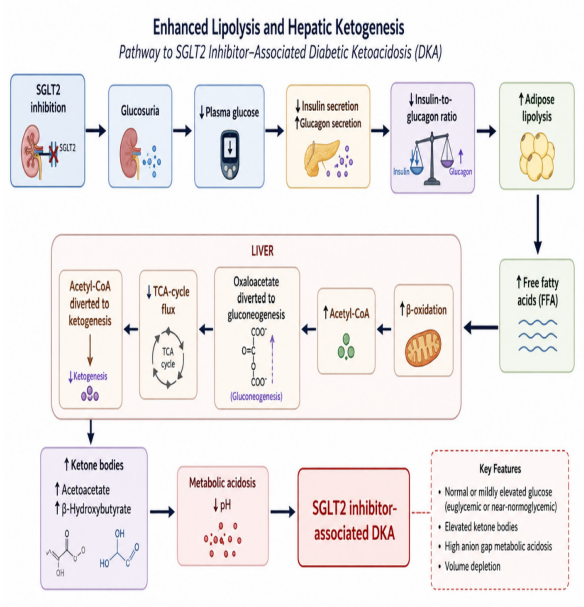

Figure 2: *Enhanced lipolysis and hepatic ketogenesis.*

Altered Renal Ketone Handling

SGLT2 inhibitors don't just boost the liver's ketone production; they may also influence ketosis by altering how the kidneys handle ketones. Research has shown that these inhibitors increase the kidneys' reabsorption of ketone bodies, such as β-hydroxybutyrate and acetoacetate, which means fewer ketones are excreted in urine, and more are circulating in the blood [24]. While we're not entirely sure how much of an impact this has, it's thought that the kidneys' reduced ability to clear ketones amplifies the effects of the liver's increased ketone production, making ketosis more likely. This is an important factor to consider, as it could contribute to the overall pro-ketotic effects of SGLT2 inhibitors.

Euglycemic Diabetic Ketoacidosis [17]

One of the key features of DKA associated with SGLT2 inhibitors is that it doesn't always come with extremely high blood sugar levels. Even though the body is still producing ketones and making glucose, the kidneys continue to remove glucose from the blood in the urine. As a result, many people with this condition have blood glucose levels below 250 mg/dL, which is relatively low compared to what you'd expect with DKA. Despite this, they still meet the criteria for DKA, including having acidic blood, low bicarbonate levels, and high ketone levels. This can make it tricky to diagnose, since the blood sugar levels aren't as high as you'd typically see with DKA. The symptoms of euDKA can be quite vague, making it hard to diagnose. People with this condition may feel sick to their stomach, throw up, have belly pain, and just overall feel unwell and tired. They might also be extremely thirsty, dehydrated, breathe fast, and seem confused or out of it. The problem is, these symptoms can also be signs of many other serious health issues, so it's easy to miss euDKA, especially if blood sugar levels aren't super high. That's why doctors need to be on high alert and check for ketones in the blood right away if someone taking SGLT2 inhibitors comes in with unexplained metabolic acidosis or an acute illness, regardless of their glucose levels. Overall, the development of SGLT2 inhibitor-associated DKA reflects the combined effects of reduced insulin secretion, increased glucagon activity, enhanced lipolysis, accelerated hepatic ketogenesis, altered renal ketone handling, and concurrent physiological stressors. A thorough understanding of these mechanisms is essential for early recognition, appropriate risk stratification, and implementation of preventive strategies that allow patients to derive the substantial cardiovascular and renal benefits of SGLT2 inhibitor therapy while minimizing the risk of this uncommon but potentially life-threatening complication.

Interaction with Precipitating Factors

SGLT2 inhibitors rarely precipitate diabetic ketoacidosis (DKA) in isolation. Rather, DKA typically develops when the metabolic effects of SGLT2 inhibition are superimposed on physiological stressors that additionally impair insulin availability or increase counter-regulatory hormone activity. Reduced carbohydrate intake during prolonged fasting, acute illness, perioperative fasting, or following ketogenic or very-low-carbohydrate diets decreases endogenous insulin secretion and promotes glucagon release, thereby increasing lipolysis and hepatic ketogenesis [3]. Similarly, acute infection, surgery, trauma, and other stress-related conditions increase circulating catecholamines, cortisol, and growth hormone, additionally exacerbating insulin resistance, stimulating hepatic glucose production, and accelerating ketone body synthesis [3]. Concurrent dehydration, resulting from reduced fluid intake, gastrointestinal losses, or the osmotic diuresis associated with SGLT2 inhibitors, may worsen renal hypoperfusion, impair ketone clearance, and aggravate metabolic acidosis.

One of the biggest risks for people with diabetes is when they don't take their insulin as prescribed, or when they stop taking it altogether. This can happen when patients start taking a new type of medication called SGLT2 inhibitors, which help control blood sugar levels [25]. As a result, patients or their doctors might think it's a good idea to reduce the amount of insulin they're taking. But even small reductions in the amount of basal insulin - the kind that's taken regularly, not just when blood sugar is high can be a problem [25]. That's because basal insulin helps prevent the body from breaking down fat for energy, which can lead to a condition called ketoacidosis [25]. This can happen even if blood sugar levels are close to normal, which is why it's so important for patients and doctors to be careful when adjusting insulin doses. These mechanisms work together to explain why a serious condition called DKA, associated with a class of drugs called SGLT2 inhibitors, doesn't occur very often, even though many people take these medications. They also point out the need to identify which patients are at high risk, to have a plan in place for when they get sick, and to ensure they're getting enough insulin to prevent this potentially life-threatening complication [25]. By doing so, we can reduce the risk of DKA and keep patients safe. It's vital to be aware of the possible risks and take steps to minimize them, especially for patients who are already vulnerable.

4.Clinical Evidence for SGLT2 Inhibitor-Associated Diabetic Ketoacidosis

Large randomized controlled trials have repeatedly demonstrated that diabetic ketoacidosis (DKA) is an uncommon adverse event dur-

ing sodium–glucose cotransporter-2 (SGLT2) inhibitor therapy. Landmark cardiovascular and renal outcome trials, including EMPA-REG OUTCOME [6], DECLARE–TIMI 58 [8], CANVAS (7), CREDENCE (15), DAPA-HF (9), EMPEROR 10-11), and DAPA-CKD [13], reported very low absolute rates of DKA, reflecting careful patient selection, exclusion of individuals with type 1 diabetes mellitus, and intensive clinical monitoring. Nevertheless, DKA occurred more frequently within participants receiving SGLT2 inhibitors than among those receiving placebo, particularly in the CANVAS Program [7], where canagliflozin was associated with a numerically higher incidence of DKA despite an absolute event rate of fewer than 1 case per 1,000 patient-years. Subsequent cardiovascular and renal outcome trials and pooled analyses have consistently established that diabetic ketoacidosis (DKA) remains an uncommon adverse event but occurs more frequently with SGLT2 inhibitors than with placebo or other glucose-lowering therapies. A systematic review and meta-analysis of 39 randomized controlled trials involving 60,580 participants found that SGLT2 inhibitors were associated with approximately a two-fold higher risk of DKA (OR 2.13, 95% CI 1.38–3.27), although the absolute incidence remained low [26].

While DKA is a serious condition, the benefits of SGLT2 inhibitors in reducing heart problems, hospitalizations due to heart failure, and the progression of chronic kidney disease are significant and should be considered when evaluating the risks [6-15]. These benefits have been consistently shown across several trials of SGLT2 inhibitors [6-15], suggesting that the overall advantages of these medications may outweigh the risks for many patients. Evidence from Systematic Reviews and Meta-Analyses Research has shown that there's a link between taking SGLT2 inhibitors and a higher risk of getting diabetic ketoacidosis (DKA). When you look at all the studies together, it seems that people taking these medicines are about twice as likely to get DKA as those who aren't (table), but it's worth noting that DKA remains very rare, even with these medicines. Some people might be more likely to develop DKA than others, and some studies might define DKA a bit differently or follow people for different periods of time, but even with these differences, the results are consistent: SGLT2 inhibitors do seem to increase the risk of DKA.

The good news is that these medicines also confer significant benefits, such as helping with heart and kidney problems. So, for people who are a good fit for these medicines, the benefits are likely to outweigh the small increase in the risk of DKA. It's just something to be aware of, and doctors can help figure out who's a good candidate for these medicines and who might need to be more careful. Overall, the research suggests that SGLT2 inhibitors remain a good choice for many people, as long as they're used carefully and with an eye on possible risks. And that's important, because these medicines can make a big difference in people's health and wellbeing.

4.1. Critical Appraisal of Evidence Evaluating SGLT2 Inhibitor-Associated Diabetic Ketoacidosis

The evidence evaluating sodium–glucose cotransporter-2 (SGLT2) inhibitor-associated diabetic ketoacidosis (DKA) is derived from multiple sources, including randomized controlled trials (RCTs), systematic reviews and meta-analyses, observational cohort studies, and pharmacovigilance analyses. Collectively, these studies exhibit a consistent association between SGLT2 inhibitor therapy and a modest increase in the relative risk of DKA, particularly euglycaemic diabetic ketoacidosis (euDKA). However, interpretation of this association requires examination of several methodological factors, including the rarity of events, limited statistical power, differences in study populations, and the exclusion of high-risk individuals from many clinical trials.

4.1.1. Evidence from Randomized Controlled Trials: Large-scale studies on heart and kidney problems have provided the best information on the safety of SGLT2 inhibitors (Tables 1&2). But these studies mainly looked at how well the treatments worked for heart and kidney problems, not at rare side effects like DKA. So, even though they provide good evidence of the treatment's benefits, they aren't powerful enough to accurately estimate the risk of DKA. This means we need to be careful when interpreting the results, because they might not detect rare but serious side effects. The studies are good at showing us what works, but not always good at showing us what might go wrong. A major study called EMPA-REG OUTCOME [6] looked at how a medication called empagliflozin affected 7,020 people with type 2 diabetes and existing heart disease. The results showed that empagliflozin significantly lowered the risk of death from heart problems, death from any cause, and hospitalization due to heart failure. It's worth noting that a serious condition called diabetic ketoacidosis, or DKA, was rare in this study, which is not surprising given that patients with type 1 diabetes and other high-risk conditions were not included.

The study's design was strong, with many participants, a long follow-up period, and careful assessment of heart-related outcomes. However, because there were so few cases of DKA, it was hard to obtain a precise sense of the risk, and the study's findings might not apply to everyday clinical practice, given the participants' careful selection. Overall, the study suggests that empagliflozin could be a valuable treatment option for people with type 2 diabetes and heart disease. Still, more research is needed to fully comprehend its benefits and risks. The CANVAS [7] Program looked at how well canagliflozin worked in 10,142 patients with type 2 diabetes who were at a higher risk of cardiovascular problems. The study found that canagliflozin was good for the heart and kidneys. Still, it also found that patients taking the drug had a slightly higher chance of getting diabetic ketoacidosis, or DKA. Even though this was still a very rare side effect, it was one of the first signs that SGLT2 inhibitors like canagliflozin might be linked to ketoacidosis. One of the strengths of the CANVAS Program was that it included many patients and followed them for a long time, which made it easier to track side effects. However, because there were so few cases of DKA, it's hard to say for sure how much of a risk it really is.

The confidence intervals were wide, which means the risk estimates could be off by a lot. The DECLARE–TIMI 58 trial [8] evaluated dapagliflozin in 17,160 patients with T2DM across a broad spectrum of cardiovascular risk. The trial demonstrated reductions in heart failure hospitalizations and favourable renal outcomes, with very low rates of DKA. A major strength of DECLARE–TIMI 58 (8) was the inclusion of patients with and without established cardiovascular disease, increasing generalizability compared with earlier cardiovascular outcome trials. However, as with other RCTs, the study excluded many individuals at highest risk of DKA, including those with significant insulin deficiency, thereby limiting the conclusions regarding vulnerable subgroups. Trials investigating SGLT2 inhibitors in heart failure populations, including DAPA-HF [9], EMPEROR-Reduced [10], and EMPEROR-Preserved [11], further expanded understanding of safety beyond diabetes populations. These trials demonstrated that dapagliflozin and empagliflozin reduce heart failure hospitalization and cardiovascular events in patients with and without diabetes. The extremely low frequency of DKA in non-diabetic participants suggests that the risk is strongly related to underlying metabolic susceptibility instead of a direct toxic effect of SGLT2 inhibition. However, because DKA events were rare, these studies were unable to offer definitive risk estimates. Researchers have found that certain medications, known as SGLT2 inhibitors, can really help protect people's kidneys.

This is based on several big studies, including DAPA-CKD [13], EMPA-KIDNEY [14], and CREDENCE [15]. These studies looked at patients with chronic kidney disease, and many of them also had diabetes. One good thing about these studies is that they didn't find many cases of a serious condition called diabetic ketoacidosis, or DKA. The studies were also strong because they included people with significant kidney problems, which occurs frequently in real-life patients. However, there were some limitations to the studies, such as certain inclusion criteria that excluded some patients and insufficient data to fully understand the risk of DKA in patients who are more vulnerable to metabolic problems. Studies have shown that a class of medications called SGLT2 inhibitors can have a significant impact on heart and kidney health. They can really help reduce the risk of serious problems. However, it's worth noting that these studies might not be entirely accurate regarding a specific side effect called DKA. This is because DKA wasn't the primary focus of the studies, and people at high risk of developing it were often excluded. As a result, the actual number of people who get DKA in real-life situations might be higher than what the studies suggest.

Table 1: *Comparison of Major Randomized Controlled Trials.*

study	Drug	Population	Sample size
EMPA-REG OUTCOME	Empagliflozin	T2DM with established CVD	7,020
CANVAS Program	Canagliflozin	T2DM with high CV risk	10,142
DECLARE–TIMI 58	Dapagliflozin	Broad T2DM population with/without CVD	17,160
CREDENCE	Canagliflozin	T2DM with diabetic kidney disease	4,401
DAPA-HF	Dapagliflozin	HFrEF ± diabetes	4,744
EMPEROR-Reduced	Empagliflozin	HFrEF ± diabetes	3,730
EMPEROR-Preserved	Empagliflozin	HFpEF ± diabetes	5,988
DAPA-CKD	Dapagliflozin	CKD ± diabetes	4,304
EMPA-KIDNEY	Empagliflozin	CKD ± diabetes	6,609

Table 2: *Studies outcome.*

study	Primary focus	DKA finding	Critical Interpretation
EMPA-REG OUTCOME	Cardiovascular outcomes	Very rare DKA events	Demonstrated major CV benefit; underpowered for DKA risk
CANVAS Program	CV safety and efficacy	Increased DKA signal vs placebo	First major RCT signal suggesting class association
DECLARE–TIMI 58	CV safety and HF outcomes	Very low DKA incidence	Largest diabetes CV trial; better generalizability
CREDENCE	Renal outcomes	Rare DKA events	Demonstrated renal protection; limited DKA assessment
DAPA-HF	HF outcomes	Extremely uncommon DKA	Demonstrated safety beyond diabetes populations
EMPEROR-Reduced	HF outcomes	Very rare DKA	Supports class effect in HF
EMPEROR-Preserved	HF outcomes	Very rare DKA	Confirmed benefit in preserved EF
DAPA-CKD	Renal outcomes	Minimal DKA risk	Supports safety in CKD populations
EMPA-KIDNEY	Renal outcomes	Very low incidence	Expanded evidence to broader CKD population

4.1.2. Evidence from Systematic Reviews and Meta-Analyses: Studies that combine data from many clinical trials have shown that patients taking SGLT2 inhibitors have a higher risk of developing a condition called diabetic ketoacidosis, or DKA, compared to those taking a placebo or other medications to lower blood sugar (Table 3). While the risk is about twice as high, it's still relatively rare. When you combine data from lots of trials, you get more power to spot rare side effects. This is a big plus for meta-analyses. They also show that different drugs in the same class, like SGLT2 inhibitors, tend to have similar effects. But there are some downsides to consider. For one, it's hard to analyse rare events statistically, and different definitions of diabetic ketoacidosis can bias the results, including how long the trials lasted, what other treatments patients were on, and who was included in the trials. Another issue is that individual trials often leave outpatients who are at high risk, so when you pool the data, you might not be getting a complete picture of how these drugs affect the people who are most vulnerable to ketoacidosis. This can make it tough to interpret the results and figure out what they really mean. Despite these limitations, meta-analytic evidence backs the conclusion that SGLT2 inhibitors increase the risk of DKA while continuing a favourable overall clinical benefit profile.

Table 3: Evidence from Systematic Reviews and Meta-Analyses.

Study	Design / Population	Main finding on DKA	Key strength	Main limitation
Liu et al., [26]	Systematic review/ meta-analysis; 39 RCTs, 60,580 participants with T2DM	OR 2.13 (95% CI 1.38–3.27) vs placebo/other therapy	Large RCT dataset; directly evaluates DKA	DKA events were rare; definitions and follow-up varied
Musso et al., [27]	Meta-analysis/meta-regression; 18 RCTs, 7,396 patients with T1DM	RR 2.81 (95% CI 1.97–4.01)	Focused specifically on T1DM, the highest-risk population	Limited sample size and applicability to T2DM
2024 network meta-analysis [28]	Network meta-analysis of RCTs	OR ~1.83 (95% CI 1.35–2.46)	Allows comparison across individual SGLT2 inhibitors	Rare-event estimates remain imprecise
Zelniker et al., [29]	Meta-analysis of cardiovascular outcome trials	Confirmed overall CV/renal benefit; DKA was an uncommon adverse event	Large CVOT evidence base	Not primarily designed to estimate DKA risk
Danne et al., [30]	International consensus	Identifies insulin deficiency, insulin reduction, fasting, dehydration, illness and low-carbohydrate intake as important risk factors	Excellent clinical risk-management framework	Consensus rather than quantitative meta-analysis

4.1.3. Evidence from Real-World Observational Studies (Table 4)
Observational studies provide important complementary evidence because they include broader patient populations than clinical trials, including older adults, individuals with multiple comorbidities, and patients receiving complex treatment regimens [53]. Researchers found that people taking SGLT2 inhibitors were about twice as likely to be hospitalized for diabetic ketoacidosis, or DKA, compared to those taking dipeptidyl peptidase-4 inhibitors. This was discovered in a study that looked at a large group of people, and similar results have been found in big healthcare databases in many parts of the world, including North America, Europe, and Scandinavia [37]. One of the biggest advantages of using real-world evidence is that it can show how safe a medication is when it's being used by patients in everyday clinical practice. This is important because the people in these studies can be very different from those in clinical trials. For example, real-world evidence has identified some significant triggers that can affect medication safety, such as when someone gets sick, has an infection, or undergoes surgery [53].

It also includes things like reducing insulin doses or becoming dehydrated. By looking at how medications work in the real world, we can get a better understanding of how to keep patients safe. There are some problems with studies that just observe people. One issue is that patients who get different treatments often have different risks to start with. This can make it hard to compare them. Also, when we use databases to track patient information, we must rely on codes to diagnose conditions. But these codes can be wrong, which means we might miscount how many people have a condition called DKA. And even when we try to account for all the other factors that could affect the results, like what people eat, how well their bodies make insulin, whether they take their medicine, and how well they understand their condition, there's still a chance that some of these factors will affect the outcome in ways we can't control. So, when we look at observational studies, they can help show that there's a connection between things, but they can't prove that one thing causes another as clearly as randomized trials can.

One of the earliest large population-based studies was conducted by Fralick et al. [31], who evaluated new users of SGLT2 inhibitors compared with dipeptidyl peptidase-4 (DPP-4) inhibitors using a large US administrative claims database. After propensity score matching and adjustment for multiple baseline characteristics, initiation of SGLT2 inhibitors was associated with approximately a twofold increase in the risk of hospitalization for DKA (HR 2.2, 95% CI 1.4–3.6). The use of a new-user design and an active comparator strengthened the study by reducing confounding associated with differences between prevalent users and nonusers. However, the study was limited through its reliance on administrative diagnostic codes, a relatively short follow-up period, and the exclusion of several high-risk groups. Consequently, while the findings provided important early real-world evidence supporting a causal safety signal, their generalizability to patients at particularly high risk of DKA was limited.

A 2018 study by Ueda et al. [33] provided further evidence on this topic. The study examined a large group of people in Sweden and Denmark who were taking either SGLT2 inhibitors or GLP-1RAs. There were 17,213 people in each group, and the researchers found that DKA occurred at a rate of 1.3 events per 1,000 person-years in the SGLT2 inhibitor group, compared with 0.6 per 1,000 person-years in the GLP-1RA group. This means that the risk of DKA was 2.14 times higher in the SGLT2 inhibitor group. The study used a strong method to match the two groups, which helped to make the results more reliable. However, there were not many cases of DKA, which made the results less precise. Also, most participants in the study were taking either dapagliflozin or empagliflozin, so it's unclear whether the results apply to other medications in the same class. Despite these limitations, the study showed that the increased risk of DKA observed in clinical trials was also present in clinical practice. This suggests that doctors and patients should be aware of this potential risk when making treatment decisions. The use of nationwide healthcare registers and an active comparator was a key strength of the study, permitting a more accurate comparison between the two groups. Overall, the study provides important insights into the safety of SGLT2 inhibitors and underscores the need for ongoing monitoring of their potential risks. Researchers took a closer look at how certain medications affect people with diabetes. They compared a class of medications called SGLT2 inhibitors with other commonly used treatments. What they found was that people taking SGLT2 inhibitors had

a higher risk of developing a serious condition called diabetic ketoacidosis, or DKA, compared to those taking other medications. This was true compared with several other classes of medications, including sulfonylureas, DPP-4 inhibitors, and metformin. The study used data from four large databases, which made the findings more reliable. However, when the researchers looked only at people with a specific type of diabetes, the risk of DKA was not as high. This suggests that the type of diabetes a person has can affect their risk of developing DKA, and that some people may be more susceptible to this condition than others. The study highlights the value of understanding how different medications affect people with different types of diabetes, and how the way we define and diagnose diabetes can affect our understanding of the risks and benefits of different treatments. For example, people with type 2 diabetes who take SGLT2 inhibitors may have a higher risk of DKA than those taking other medications, but this risk may be lower if they have a more typical form of type 2 diabetes.

On the other hand, people with a more severe form of diabetes, such as insulin-deficient diabetes, may be at higher risk of DKA regardless of which medication they take. The study's data show that doctors and patients need to carefully consider the potential risks and benefits of different medications, and that more research is needed to better understand how to minimize the risk of DKA in people with diabetes. Overall, the study provides important insights into the potential risks and benefits of SGLT2 inhibitors and highlights the need for meticulous assessment and monitoring when prescribing these medications to people with diabetes. By understanding the potential risks and benefits of different treatments, doctors and patients can work together to develop successful treatment plans that minimize the risk of serious complications such as DKA.

A recent study in Korea [32] found something different. It looked at a large group of people, 56,325, who took a type of medicine called SGLT2 inhibitors, and compared them to another group of 56,325 people who took a different type of medicine called DPP-4 inhibitors. The study found no significant difference between the two groups in DKA hospitalization rates. This is important because it shows that what happens in one group of people might not happen in another. However, the study also found substantial uncertainty in the results, so we can't be sure whether there's a real difference. One interesting finding of the study was that people were more likely to develop DKA in the first 30 days after starting SGLT2 inhibitors, suggesting this may be a time when people are more vulnerable. But we need to be careful when interpreting this result because it was based on a small number of events and was an observational study, which means it wasn't a controlled experiment.

New research from 2022 examined the safety of certain medications, comparing data from over 300,000 patients. The study [37] had two main groups: one compared SGLT2 inhibitors with DPP-4 inhibitors, and the other compared SGLT2 inhibitors with sulfonylureas. The results showed that a condition called DKA happened more often in patients taking SGLT2 inhibitors - 6.0 events per 1,000 person-years compared to 4.3 events per 1,000 person-years for DPP-4 inhibitors, and 6.3 events per 1,000 person-years compared to 4.5 events per 1,000 person-years for sulfonylureas. The study found that patients taking SGLT2 inhibitors were about 1.5 to 1.6 times more likely to develop DKA than those taking the other medications. This study is strong because of its large sample size, its design, and the methods used to adjust for between-group differences. However, like all studies that examine insurance claims, it has limitations, including the possibility that some information may be missing or incorrect. Despite these limitations, the study's data indicate a real safety concern with SGLT2 inhibitors. The fact that the results were similar across several comparison groups makes the findings more reliable. Overall, this study provides important information on the safety of these medications, helping doctors and patients make well-informed decisions.

Critical synthesis

Studies (31-38) have shown that people taking SGLT2 inhibitors are more likely to get a serious condition called DKA. This is based on real-world data from many different sources. Most of the studies found that the risk of DKA is 30-120% higher for people taking SGLT2 inhibitors compared to other diabetes treatments (table). The fact that many studies from different countries and using different methods found similar results suggests that this increased risk is real and not just a coincidence. However, one study from Korea [32] did not find an increased risk, suggesting that the risk may vary depending on the population studied, their likelihood of developing DKA, and how the medication is prescribed and outcomes are measured.

When looking at the results, we need to be careful. There are a few things to consider. First, DKA doesn't happen very often, so even with a lot of data, it's hard to get a clear picture. This means that the results might not be as precise as we'd like. Another issue is that we're relying on codes from hospital records or administrative data. This can lead to mistakes in identifying cases and might mean we're more likely to notice the more severe cases. Also, it's hard to completely rule out other factors that could be influencing the results. For example, doctors might be more likely to prescribe certain medications to patients with specific heart, kidney, or metabolic issues. Lastly, how we classify diabetes is important because some people might not realize they have an insulin deficiency, which can greatly increase their risk of DKA. These are all things to keep in mind when interpreting the data.

Importantly, observational studies generally estimate relative risk, whereas the absolute risk remains low in appropriately selected patients with type 2 diabetes. Therefore, the approximately 1.3- to 2-fold relative increase should be interpreted in the context of the established cardiovascular and renal benefits of SGLT2 inhibitors. The observational evidence is best interpreted as showing a clinically relevant but uncommon adverse effect, with risk concentrated among susceptible individuals and under specific precipitating circumstances.

When you look at all the evidence from real-world studies, it backs up what was found in randomized controlled trials (RCTs). This evidence suggests that using SGLT2 inhibitors is linked to a higher risk of diabetic ketoacidosis (DKA) in everyday clinical practice. The fact that both types of evidence point to the same conclusion makes it more likely that there's a cause-and-effect relationship. However, differences among observational studies show the value of selecting the right patients and being aware of factors that can trigger DKA. This evidence supports taking steps to prevent DKA, such as prudently selecting patients, teaching them how to manage their condition when they're sick, eschewing prolonged fasting and excessive carbohydrate restriction, stopping SGLT2 inhibitors before surgery, and promptly checking for euglycemic DKA if symptoms appear.

Table 4: *Major real-world observational studies.*

Study	Setting / design	Population / sample	Comparator	Main DKA finding
Fralick et al., [31]	Population-based cohort; Canada	Adults with T2DM initiating SGLT2i	DPP-4 inhibitor	Approximately 2-fold higher risk of DKA with SGLT2i
Kim YG et al., [32]	Nationwide population-based cohort; South Korea	56,325 SGLT2i users, matched with 56,325 DPP-4i users	DPP-4 inhibitor	No significant increase: HR 0.956 (95% CI 0.581–1.572); early treatment period showed higher incidence
Ueda P et al., [33]	Nationwide register-based cohort; Sweden & Denmark	17,213 SGLT2i users vs 17,213 GLP-1RA users	GLP-1 receptor agonist	DKA: 1.3 vs 0.6/1,000 person-years; HR 2.14 (95% CI 1.01–4.52)
Wang et al., [34]	Four US administrative claims databases	New users of SGLT2i and other antihyperglycaemic drugs	Multiple comparators	Increased DKA risk vs sulfonylureas HR 1.53, DPP-4i HR 1.28, GLP-1RA HR 1.34, metformin HR 1.31
Douros et al., [35]	Population-based cohort; multiple European databases	New SGLT2i users	Other glucose-lowering therapies	Supported increased DKA risk, with differences according to individual drug and population
Pasternak et al.[36]	Scandinavian nationwide observational cohort	SGLT2i users with T2DM	Other glucose-lowering drugs	Evaluated serious adverse events including DKA in routine practice
Nye J [37]	Large US active-comparator new-user cohort	85,125 SGLT2i vs 85,125 DPP-4i; 72,436 SGLT2i vs 72,436 sulfonylureas	DPP-4i and sulfonylureas	DKA incidence 6.0 vs 4.3/1,000 person-years vs DPP-4i and 6.3 vs 4.5/1,000 person-years vs sulfonylureas; adjusted HR 1.63 and 1.56, respectively
Almazrouei R et al. [38]	Retrospective hospital-based study	55 patients with T2DM admitted with DKA	SGLT2i users vs non-users	Characterised clinical presentation and outcomes of DKA among SGLT2i users in a UAE population

4.1.4. Evidence from Pharmacovigilance Studies (Table 5)

Pharmacovigilance analyses were key in identifying SGLT2 inhibitor-associated DKA as a safety concern following widespread clinical use (table). Reports from databases, including the United States Food and Drug Administration Adverse Event Reporting System (FAERS) [41], the European Medicines Agency EudraVigilance [43], and the World Health Organization VigiBase [42], demonstrated disproportionate reporting of DKA among SGLT2 inhibitor users. These reports provided several important clinical observations. First, many cases presented as euDKA, with normal or mildly elevated glucose levels, leading to delayed recognition. Second, most cases occurred in association with identifiable precipitating factors, including surgery, acute infection, prolonged fasting, dehydration, and reduction or discontinuation of insulin therapy. Third, outcomes were generally favourable when the diagnosis was recognized early and appropriate DKA treatment was initiated. One of the main benefits of pharmacovigilance systems is that they can quickly identify rare side effects in many people. But they have some limitations - they can't give us the exact number of people affected because we don't have accurate information about the total number of people taking the medication, and some side effects might not be reported. Also, when there are warnings from regulators, this may lead to more reports, which can be biased. So, while pharmacovigilance data is great for observing potential problems, it's not perfect for estimating the actual risk of a side effect.

Critical interpretation of pharmacovigilance evidence

Pharmacovigilance studies were particularly important because they detected the DKA signal before enough events had accumulated in randomized trials or observational cohorts. Their principal strength is the ability to detect rare and unexpected adverse events across very large populations and to identify unusual clinical phenotypes, such as euglycemic DKA.

These databases have a major limitation - they can't give us a clear picture of how often something happens. This is because we don't know the total number of people exposed to a particular thing, a key piece of information. Also, many cases go unreported, while warnings from regulators can lead to a spike in reports, making it seem like something is happening more often than it really is. Another issue is that the reports we do get commonly lack enough detail, such as the type of diabetes someone has, whether they're taking their medication as prescribed, their insulin doses, how well their kidneys are functioning, what might have triggered the problem, and other possible causes. As a result, when we look at the reports, we might see a pattern showing a safety issue, but it's not enough to prove that one thing causes another or to determine how much risk an individual faces. We use measures such as reporting odds ratios or proportional reporting ratios to identify potential safety signals, but they don't prove causality or quantify individual risk.

5.Evidence in Type 1 Diabetes Mellitus (Table 6)

The risk of SGLT2 inhibitor-associated diabetic ketoacidosis (DKA) is substantially greater among individuals with type 1 diabetes mellitus (T1DM). Several randomized controlled trials have evaluated SGLT2 inhibitors as adjunctive therapy to insulin, demonstrating modest improvements in glycaemic control, body weight, insulin dose requirements, and glycaemic variability. However, these metabolic benefits were consistently accompanied by a clinically significant increase in DKA incidence.

Researchers looked at how well dapagliflozin worked for adults with type 1 diabetes who were already taking insulin. They did two big studies, called DEPICT-1 [44] and DEPICT-2 [45], where they gave patients either 5mg or 10mg of dapagliflozin on top of their insulin. What they found was interesting: patients who took dapagliflozin had lower blood sugar levels, lost some weight, and didn't need as much

insulin each day. However, there was a downside: some patients who took dapagliflozin were more likely to get a serious condition called diabetic ketoacidosis, or DKA for short. This happened to about 3-4% of patients who took the drug every year, which is more often than patients who didn't take it. Overall, the studies showed that dapagliflozin can be a helpful addition to insulin for some patients with type 1 diabetes, but it's not risk-free.

Table 5: *Pharmacovigilance Studies.*

Study	Database / period	Main finding	Relevance
Erondu et al. [39]	Clinical trial reports + post-marketing surveillance	Characterized DKA cases associated with dapagliflozin and highlighted atypical/euglycaemic presentations	Important early description of clinical phenotype
Peters et al. [18]	Case series	**13 cases of euDKA** associated with SGLT2 inhibitors	Important clinical evidence describing delayed recognition and precipitating factors
Blau et al. [40]	FDA FAERS	Markedly increased reporting of DKA with SGLT2 inhibitors compared with other antihyperglycaemic drugs	Important early signal-detection study
Fadini et al. [41]	FDA FAERS	Disproportional reporting of DKA with SGLT2 inhibitors; many cases had relatively modest glucose elevations	Early pharmacovigilance evidence supporting SGLT2i-associated DKA
VigiBase analyses [42]	WHO global pharmacovigilance database	Confirmed disproportionate reporting of DKA/euDKA associated with SGLT2 inhibitors internationally	Provides global pharmacovigilance evidence
EudraVigilance analyses [43]	European Medicines Agency database	Identified disproportionate reporting of DKA, including euDKA, associated with SGLT2 inhibitors	European post-marketing evidence

Researchers examined how well empagliflozin worked in two studies, EASE-2 and EASE-3 [46]. They tested three different doses: 2.5 mg, 10 mg, and 25 mg. The results showed that empagliflozin helped control blood sugar levels, led to weight loss, and reduced the need for insulin. One interesting finding was that the lowest dose, 2.5 mg, had a much lower risk of a serious condition called diabetic ketoacidosis (DKA) compared to the higher doses. This indicates a possible link between empagliflozin dose and the risk of DKA. However, even at the lowest dose, DKA still occurred more often than with a placebo.
Researchers looked at how well a new medicine called sotagliflozin worked for adults with type 1 diabetes. They did three big studies, called inTandem 1 [47], inTandem 2 [48], and inTandem 3 [49]. Sotagliflozin is special because it blocks two things in the body that help control blood sugar levels. The studies showed that people who took sotagliflozin had better blood sugar control, spent more time with their blood sugar levels in a healthy range, lost weight, and needed less insulin. However, there was a problem - some people who took sotagliflozin got a serious condition called diabetic ketoacidosis, or DKA, more often than people who didn't take the medicine. This happened even though the patients were taught how to monitor their ketone levels and were given special instructions to follow. The DKA rate was between 3% and 4% per year, a significant increase.

These studies show that using SGLT2 inhibitors alongside other treatments for type 1 diabetes can improve certain health outcomes. Still, it also raises the risk of a serious condition called diabetic ketoacidosis (DKA) by about three to four times compared to not using these inhibitors. This makes sense because people with type 1 diabetes don't produce much insulin on their own. Even small decreases in circulating insulin can stop the inhibition of lipolysis, leading the liver to produce more ketones and a rapid buildup of these ketone bodies, even when blood sugar levels are relatively normal (figure). This happens because the body's natural balance is disrupted, allowing fat to be broken down more quickly and leading to the production of ketones, which can be harmful if they accumulate. The lack of insulin in type 1 diabetes means that the body can't properly regulate this process, rendering it more vulnerable to DKA when SGLT2 inhibitors are used.

The results of these clinical trials resulted in stricter rules being implemented worldwide. At first, dapagliflozin and sotagliflozin were approved in some parts of Europe for certain adults with type 1 diabetes. Still, this approval was later taken away because the benefits didn't outweigh the increased risk of diabetic ketoacidosis (54). Currently, organizations such as the American Diabetes Association and the European Association for the Study of Diabetes don't recommend using SGLT2 inhibitors for type 1 diabetes unless in a special setting or as part of a clinical trial (55). If they are used, it's vital to carefully select the right patients, educate them thoroughly on what to do when they're sick, monitor their blood ketone levels regularly, ensure they're getting enough insulin, and have them closely supervised by a specialist. This is because the risks associated with SGLT2 inhibitors can be significant, and patients require close monitoring to mitigate them. By taking a careful approach, medical professionals can help ensure that patients with type 1 diabetes obtain the best possible care.

The results of seven key trials involving around 6,328 participants with type 1 diabetes have shed important light on the effects of SGLT2 inhibitor therapy. Across the board, adding SGLT2 inhibitors to existing treatments consistently led to improvements in blood sugar control, weight loss, reduced glycaemic variability, and lower insulin requirements. However, these benefits came at a cost, as the risk of diabetic ketoacidosis (DKA) increased significantly, particularly when higher doses of SGLT2 inhibitors were used. One trial, EASE-3, stood out for its finding that a lower dose of empagliflozin (2.5 mg) was associated with a lower incidence of DKA than higher doses (10 mg and 25 mg), suggesting that the risk of ketoacidosis is closely tied to the dose of SGLT2 inhibitors. This evidence has had a significant impact on regulatory decisions and current guidelines, which now advise

against the routine use of SGLT2 inhibitors in patients with type 1 diabetes, except in specialist care settings.

Table 6: *Major Type 1 Diabetes Trials.*

Trial	Drug	Participants	Main Benefits	DKA Findings
DEPICT-1 [44]	Dapagliflozin	Adults with T1DM (No 833)	↓ HbA1c, ↓ body weight, ↓ insulin dose	Increased DKA (~3–4% annually)
DEPICT-2 [45]	Dapagliflozin	Adults with T1DM (No 813)	Similar metabolic improvements	Increased DKA compared with placebo
EASE-2 [46]	Empagliflozin (10/25 mg)	Adults with T1DM (No 730)	Improved glycaemic control and weight loss Similar efficacy; 2.5 mg maintained benefits	Higher DKA incidence than placebo
EASE-3 [46]	Empagliflozin (2.5/10/25 mg)	Adults with T1DM (No 975)	Similar efficacy; 2.5 mg maintained benefits	Lowest DKA risk with 2.5 mg; dose-dependent increase at higher doses
inTandem 1 [47]	Sotagliflozin	Adults with T1DM (No 793)	↓ HbA1c, ↓ insulin dose, ↑ time-in-range	Increased DKA
inTandem 2 [48]	Sotagliflozin	Adults with T1DM (No 782)	Similar efficacyImproved glycaemic control	Increased DKA
inTandem 3 [49]	Sotagliflozin	Adults with T1DM (No 1402)	Improved glycaemic control	DKA incidence approximately 3–4% annually

Risk Factors for SGLT2 Inhibitor-Associated Diabetic Ketoacidosis DKA, or diabetic ketoacidosis

Risk Factors for SGLT2 Inhibitor-Associated Diabetic Ketoacidosis DKA, or diabetic ketoacidosis, is a serious condition that can happen to people with diabetes. Even though it's rare for people taking SGLT2 inhibitors to get DKA, it can still occur. Usually, it's not just the medication that causes the problem, but rather a combination of the medication's effects and other factors specific to the patient or their treatment. In most cases, there are one or more identifiable risk factors that contribute to the development of DKA, rather than the SGLT2 inhibitor being the sole cause (Figure 3).

Insulin Deficiency: People who don't have enough insulin, either because their body doesn't produce enough or because what they do produce doesn't work properly, are more likely to develop a serious condition called diabetic ketoacidosis (DKA) when they take a class of medicines called SGLT2 inhibitors. This is especially true for people with type 2 diabetes that's advanced, or those whose bodies have trouble making insulin because of problems with their pancreas, like chronic pancreatitis, or because they've had surgery on their pancreas. Some people have a type of diabetes called latent autoimmune diabetes in adults (LADA), which is like a mix of type 1 and type 2 diabetes, and they're also at higher risk. But the people at the highest risk of getting DKA are those with type 1 diabetes - their bodies don't make any insulin at all, which is why we see so many cases of DKA in clinical trials with these patients.

Acute Illness and Infection: When people with diabetes get sick, it can trigger a serious condition called diabetic ketoacidosis, or DKA for short. This often happens when they have infections such as pneumonia, a urinary tract infection, or sepsis, a life-threatening response to infection. Even COVID-19 can cause it. These infections trigger the secretion of stress hormones such as catecholamines, cortisol, and glucagon, which can lead to insulin resistance, in which the body's cells don't respond well to insulin. As a result, the body starts breaking down fat for energy, producing ketones, which can build up to dangerous levels in the blood. If the person isn't eating or drinking enough, or if they stop taking their insulin, it can make things even worse, leading to a metabolic crisis. All the combined factors can increase the risk of DKA in people taking SGLT2 inhibitors, a type of medication used to treat diabetes.

Surgery and Perioperative Fasting: The time before, during, and after surgery is a critical period when people with diabetes are more likely to develop a serious condition called diabetic ketoacidosis (DKA). When we undergo surgery, our bodies react to the stress by releasing hormones such as adrenaline, cortisol, and glucagon, which can raise our blood sugar levels. At the same time, we often must fast before surgery, which means our bodies produce less insulin and start breaking down fat for energy, producing ketones. If we stop taking our insulin or don't drink enough fluids during this time, it can make things even worse. There have been many reports of people developing DKA after surgery, even if their blood sugar levels seemed normal. Because of this, doctors around the world recommend that patients stop taking a certain type of diabetes medication called SGLT2 inhibitors a few days before they have elective surgery.

Reduced Carbohydrate Intake: Prolonged fasting, severe caloric restriction, gastrointestinal illness, ketogenic diets, and very-low-carbohydrate dietary patterns reduce insulin secretion while increasing glucagon-mediated ketogenesis. SGLT2 inhibitors potentiate these bodily adjustments by additionally lowering circulating insulin concentrations and enhancing fat oxidation, thereby heightening susceptibility to ketosis. Caution is therefore warranted when prescribing SGLT2 inhibitors to individuals following carbohydrate-restricted dietary regimens or undergoing prolonged fasting, including religious fasting.

Excessive Alcohol Consumption: Excessive alcohol intake is an established risk factor for ketoacidosis and may further increase the risk during SGLT2 inhibitor therapy. Alcohol suppresses hepatic gluconeogenesis, depletes glycogen stores, promotes ketone body production, and is frequently accompanied by poor nutritional intake and dehydration. These metabolic disturbances may act synergistically with SGLT2 inhibition to precipitate DKA, particularly in susceptible individuals with impaired insulin reserve.

Pregnancy: Pregnancy is characterized by a physiological increase in insulin resistance mediated by placental hormones and an enhanced propensity for ketogenesis during periods of fasting. Although SGLT2 inhibitors are contraindicated throughout pregnancy because of potential foetal toxicity and limited safety data, inadvertent exposure has been associated with cases of severe euglycemic diabetic keto-

acidosis (euDKA). Immediate recognition and immediate discontinuation of SGLT2 inhibitor therapy are therefore essential in pregnant patients presenting with symptoms suggestive of ketoacidosis.

Dehydration: SGLT2 inhibitors can cause the body to lose water and salt, leading to decreased blood volume. This can be a problem if the person is also losing fluids from vomiting, diarrhoea, fever, or excessive exercise, or if they are not drinking enough water, notably in hot weather. If the body loses too much fluid, it may impair kidney function, make it harder to excrete ketones, and increase the risk of metabolic acidosis. So, it's important for people taking SGLT2 inhibitors to drink enough water to stay hydrated and help prevent a serious condition called diabetic ketoacidosis (DKA).

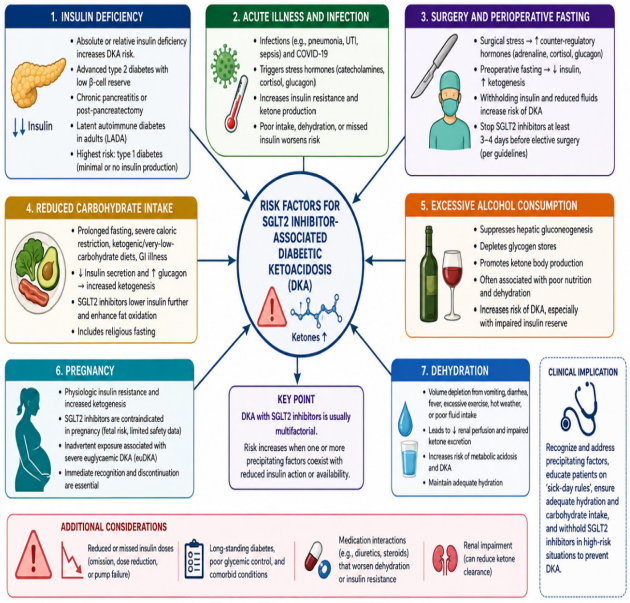

Figure 3: *Risk Factors for SGLT2 Inhibitor-Associated Diabetic Ketoacidosis DKA, or diabetic ketoacidosis.*

Prevention and Clinical Management

To lower the risk of developing a serious condition called DKA when taking SGLT2 inhibitors, it's important to focus on prevention. This entails choosing the right patients for the treatment, teaching them what they need to know, having a plan in place for when they're not feeling well, and catching any signs of ketosis early. By doing these things, we can avoid adverse effects while still getting the well-known benefits of SGLT2 inhibitors for the heart and kidneys. It's all about being careful and prepared to ensure the treatment works well and safely (Figure 4).

Patient Selection: Assessment of individual risk factors before initiating SGLT2 inhibitors is essential. Patients with a history of DKA, type 1 diabetes mellitus, suspected latent autoimmune diabetes in adults (LADA), pancreatic insufficiency, advanced insulin deficiency, previous bariatric surgery, chronic alcohol misuse, eating disorders, recurrent prolonged fasting, or following ketogenic or very-low-carbohydrate diets call for careful evaluation. In individuals with multiple predisposing factors, alternative glucose-lowering therapies or enhanced clinical monitoring should be considered.

Patient Education: Patient education is one of the most successful strategies for preventing SGLT2 inhibitor-associated DKA. Individuals should receive explicit instructions on recognizing early symptoms of ketoacidosis, maintaining adequate hydration, avoiding inappropriate reductions in insulin dose, preserving carbohydrate intake during acute illness whenever feasible, appropriately using blood or urine ketone testing, and identifying situations that warrant temporary discontinuation of SGLT2 inhibitor therapy. Importantly, patients should be informed that DKA may occur despite normal or only mildly elevated blood glucose concentrations.

Sick-Day Management: International diabetes guidelines recommend standardized sick-day management for patients receiving SGLT2 inhibitors. Therapy should be temporarily withheld during acute febrile illness, severe infection, persistent vomiting or diarrhoea, prolonged fasting, inability to keep oral intake, significant dehydration, hospitalization, or major trauma. During these periods, basal insulin should generally be continued, fluid intake should be optimized, and blood ketones should be monitored when possible. Patients who develop ketosis or symptoms suggestive of DKA should seek immediate medical assessment.

Perioperative Management: Surgical procedures that are planned of time can be risky for people taking SGLT2 inhibitors, which are a type of medication. This is because these medicines can increase the chance of getting a condition called diabetic ketoacidosis, or DKA. To stay safe, doctors around the world recommend stopping certain medications, like empagliflozin, dapagliflozin, and canagliflozin, at least three days before surgery. However, for ertugliflozin, it's best to stop taking it 4 days before surgery, as it is eliminated more slowly. After surgery, it's important to wait until the patient is feeling better, eating and drinking normally again, and properly hydrated before restarting the medication. The doctor will also check to ensure the patient's body is no longer producing ketones, which can build up and cause problems. Only when all these conditions are met can the patient safely start taking their SGLT2 inhibitor medication again. This careful approach helps prevent serious complications and ensures the best possible outcome for the patient.

Diagnosis: Early diagnosis of SGLT2 inhibitor-associated DKA requires a high index of clinical suspicion because significant hyperglycaemia may be absent. Patients receiving SGLT2 inhibitors who present with nausea, vomiting, abdominal pain, malaise, dyspnoea, or unexplained metabolic acidosis should be promptly evaluated for DKA irrespective of blood glucose concentration. Diagnostic assessment should include arterial or venous blood gas analysis, serum bicarbonate, anion gap, serum β-hydroxybutyrate, blood glucose, renal function, and serum electrolytes. Early ketone measurement is particularly important, as delayed diagnosis is still a major contributor to morbidity associated with euglycemic DKA.

Treatment: When someone is taking an SGLT2 inhibitor and gets diabetic ketoacidosis, or DKA, we treat it using the same steps we use for regular DKA. First, we stop the SGLT2 inhibitor right away. Then we start giving fluids and insulin continuously through a vein. We also need to fix any electrolyte problems, especially if the patient has low potassium levels, and treat the underlying illness that caused the DKA. It's common for patients with DKA due to SGLT2 inhibitors to have normal or only slightly elevated blood sugar levels. So, we often need to give them dextrose intravenously early in treatment. This helps us keep giving them insulin until their bodies stop producing ketones. We must watch the patient closely, checking their acid-base7 balance, ketone levels, blood sugar, electrolytes, and kidney function throughout treatment. This makes certain that the ketoacidosis goes away completely and doesn't come back. We keep a close eye on these things because it's vital to get the patient all better and prevent the DKA from happening again. By adhering to these steps and monitoring the patient's condition, we can effectively manage SGLT2 inhibitor-associated DKA.

Figure 4: *Management of euDKA.*

Current Guideline Recommendations:

Contemporary international guidelines consistently recognize diabetic ketoacidosis (DKA) as a rare but clinically significant complication of sodium–glucose cotransporter-2 (SGLT2) inhibitor therapy and emphasize risk mitigation rather than avoidance of treatment.

Current guideline recommendations (Figure 5)

The American Diabetes Association (ADA) Standards of Care 2026 [3,50] recommend temporarily discontinuing SGLT2 inhibitors before scheduled surgery, generally for 3 days before surgery and 4 days for ertugliflozin, as well as amid critical illness and prolonged fasting, to reduce the risk of SGLT2 inhibitor-associated diabetic ketoacidosis (DKA), including euglycemic DKA. The ADA additionally emphasizes sick-day planning, recognition of DKA symptoms, and appropriate assessment of blood or urine ketones in individuals at increased risk.

The new guidelines for treating chronic kidney disease, released in 2024 by KDIGO [51], include a warning about a class of medications called SGLT2 inhibitors. These medications might be risky for patients in certain situations, such as when they haven't eaten for a long time, are having major surgery, or are very sick. In these situations, the medication may need to be stopped for a while to prevent a serious condition called diabetic ketoacidosis, or DKA. This is because the medication can cause the body to produce high levels of ketones, which can be toxic. However, when patients are stable and able to eat and drink normally, they can usually continue taking the medication safely. The goal is to evaluate the medication's benefits and potential risks as well as ensure patients are protected from harm. By being cautious and adjusting treatment as needed, doctors can help patients with chronic kidney disease manage their condition successfully and reduce their risk of complications.

The American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) [52] have guidelines for patients taking SGLT2 inhibitors. If a patient has suspected diabetic ketoacidosis (DKA) or is about to have an emergency or invasive procedure, they recommend stopping the SGLT2 inhibitor therapy. They also urge checking ketone levels when necessary. To test for ketones, measuring blood β-hydroxybutyrate is preferable to testing urine ketones, especially when evaluating DKA related to SGLT2 inhibitors.

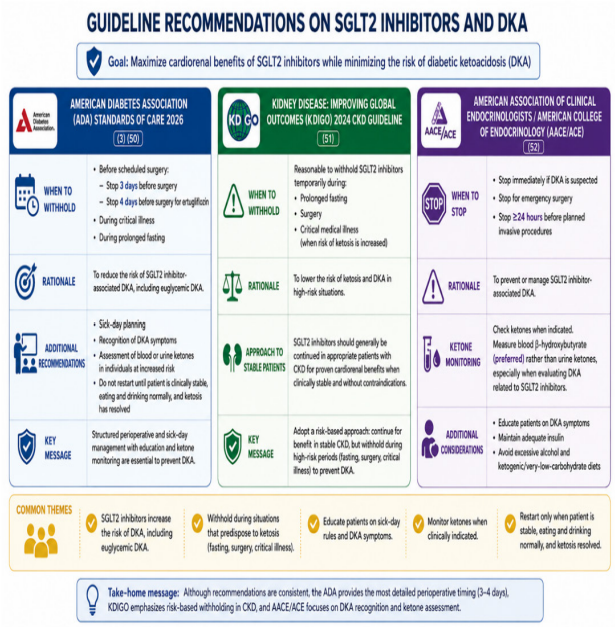

Figure 5: *Comparison between guidelines.*

These guidelines show that most experts agree on one thing: it's a good idea to stop taking SGLT2 inhibitors for a while when the body is under a lot of stress, such as when someone is very sick, hasn't eaten in a long time, or is having surgery. But once the person is feeling better, eating normally again, and their condition is stable, they can usually resume the medicine. This helps prevent a serious condition called diabetic ketoacidosis, or DKA. By temporarily stopping their medicine, people with diabetes can reduce their risk of DKA during periods when their bodies are already under a lot of strain.

These guidelines suggest that health care providers should tailor treatment to each patient's specific needs, considering their risk factors. By doing so, patients can reap the considerable benefits of SGLT2 inhibitors for their heart and kidney health while decreasing the risk of diabetic ketoacidosis. To achieve this, health care providers should carefully assess each patient's risk factors, put preventive measures in place, and quickly identify any signs of ketosis. This strategy allows patients to get the most out of their treatment while reducing potential risks. By being proactive and alert, health care providers can help their patients avoid complications and ensure the best possible outcomes.

Future Directions

Even though we've made significant progress in understanding how SGLT2 inhibitors can cause diabetic ketoacidosis (DKA), there's still much we don't know. To move forward, we need to focus on finding ways to predict which patients are most likely to develop DKA. This means identifying reliable markers in their blood work and medical history that can help us determine their risk. If we can gain a better understanding of how their pancreas functions, how their body handles glucagon and ketones, and what role their genes play, we might be able to customize our treatment approach to each patient and reduce their risk of developing DKA before we even start treatment. Using artificial intelligence and electronic health records can help keep patients safe. It does this by identifying people at high risk, reminding doctors to follow guidelines for discontinuing medications

before surgery, and ensuring patients follow the right plans when they're sick. We also need to do more research to see if regularly checking the blood ketone levels of people at high risk can reduce the bad effects of diabetic ketoacidosis. And we need to find out whether teaching patients in a structured way can help them follow plans to prevent problems and reduce the number of times they need to go to the hospital. This can make a big difference in how well patients do and how safe they are.

By using these new tools and doing more research, we can help patients get better support and remain healthier. As indications for SGLT2 inhibitors continue to expand beyond diabetes to include heart failure and chronic kidney disease in individuals without diabetes, ongoing pharmacovigilance and real-world observational studies will be essential to better define the incidence, clinical characteristics, and risk factors for DKA across these emerging patient populations.

Conclusion

Sodium-glucose cotransporter-2 inhibitors have really changed the way we treat type 2 diabetes, heart failure, and chronic kidney disease. They've been shown to reduce the risk of cardiovascular events greatly, hospitalizations for heart failure, and the progression of kidney disease, as well as lower mortality rates. What's more, they work independently of insulin, have positive effects on metabolism, and provide significant benefits for the heart and kidneys. As a result, this class of drugs has become a key part of modern medical practice. By reducing the risk of these major health issues, sodium-glucose cotransporter-2 inhibitors are helping improve patient outcomes and save lives. Overall, their impact on the management of these diseases has been substantial, and they are now considered an important tool in the fight against type 2 diabetes, heart failure, and chronic kidney disease.

Diabetic ketoacidosis is a rare but serious side effect of SGLT2 inhibitor therapy. What's unusual about this condition is that it often presents as euglycemic diabetic ketoacidosis, with high ketone levels and acidosis, even when blood sugar is normal or only slightly elevated. This can make it harder to diagnose, which is why doctors need to be extra careful when patients taking SGLT2 inhibitors come in with vague symptoms like stomach problems, feeling unwell, or acidosis. It's vital to consider the possibility of diabetic ketoacidosis in these cases, even if the blood sugar levels don't seem that high.

Current evidence indicates that although SGLT2 inhibitors are associated with an increased relative risk of DKA, the absolute incidence remains low. Most episodes occur in the presence of identifiable precipitating factors, including insulin deficiency, acute illness, infection, surgery, prolonged fasting, dehydration, excessive alcohol consumption, ketogenic diets, and inappropriate reduction or omission of insulin therapy. Consequently, safe prescribing calls for careful patient selection, comprehensive patient education, implementation of sick-day management guidelines, temporary discontinuation of therapy during periods of physiological stress, and prompt assessment of ketone status when clinically indicated (Table 7). It's worth noting that even though diabetic ketoacidosis, or DKA, is a rare side effect, it shouldn't distract from the notable benefits that SGLT2 inhibitors have on the heart and kidneys. These benefits have been consistently demonstrated in large clinical trials and real-world studies.

When doctors prescribe these medications according to the newest guidelines and use strategies to prevent complications, SGLT2 inhibitors are among the best ways to reduce the risk of heart and kidney disease. To make these medications even safer and more effective, researchers are working to predict better who is at risk, diagnose problems early, and find the best ways to prevent them. This will help doctors use SGLT2 inhibitors to maximize their benefits while minimizing their risks. By doing so, we can help people with diabetes live longer, healthier lives.

Table 7: key messages.

✓ SGLT2 inhibitors provide substantial cardiovascular and renal benefits in patients with type 2 diabetes, heart failure, and chronic kidney disease, extending beyond their glucose-lowering effects.
✓ SGLT2 inhibitor-associated DKA may occur with normal glucose; suspect it in symptomatic patients and assess ketones promptly.
✓ Major precipitating factors include acute illness, infection, surgery, prolonged fasting, dehydration, excessive alcohol intake, ketogenic diets, insulin deficiency, and inappropriate reduction or omission of insulin therapy.
✓ DKA risk can be reduced through appropriate patient selection, education, sick-day guidance, temporary discontinuation during periods of physiological stress, and timely ketone assessment when clinically indicated.
✓ SGLT2 inhibitor-associated DKA is rare but serious and can occur despite normal glucose levels, demanding prompt recognition and ketone testing.
✓

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