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Should the Cardiology Guidelines Clarify who Should be Tested for Autoimmune Diabetes before Adding SGLT-2 Inhibitors in Heart Failure Therapy?

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Introduction

Sodium Glucose Cotransporter 2 inhibitors (SGLT2i) are a relatively recent addition to the Heart Failure (HF) treatment guidelines [1,2]. Approved by the FDA in 2014 for the treatment of diabetes mellitus type II (DMII), they were later also approved in 2022 for the treatment of HF based on the DAPA-HF and EMPEROR-REDUCED trials [2-5]. As a result of these breakthrough trials, SGLT2i have become an integral part of heart failure Guideline Directed Medical therapy (GDMT) and are now widely used. As with any medication, there are risks that must be weighed before initiation.

The primary adverse reactions of SGLT2i include skin infections and urinary tract infections. One adverse effect that is now commonly encountered given the widespread use of SGLT2i therapy is diabetic ketoacidosis (DKA) [2]. While SGLT2i are contraindicated in DM1 therapy because of their penchant to cause DKA in this situation, there is a class of diabetes that is sometimes confused with DMII and is harder to recognize at the time of consideration of SGLT2i therapy but physiologically acts similarly to DM1 with respect to SGLT2i DKA risk. Termed latent autoimmune diabetes in adults (LADA) or DM 1.5, it is most often uncovered inside the longitudinal clinical care of DM2 and confirmed with specialized blood tests. Consultants inside episodic patient encounters may overlook this classification and subsequently prescribe an SGLT2i for HF, unknowingly placing the patient at risk for DKA. The American Heart Association and American College of Cardiology Guidelines do not reflect recommendations regarding SGLT2i in LADA. We present a small case series illustrating this risk issue and a diagnostic paradigm for its mitigation.

Case Series, Patient 1

We present a case of a 73-year-old man with presumed DM2 who was hospitalized for Clostridium difficile colitis and progressive dyspnea. Concurrently, he was newly diagnosed with HF with reduced ejection fraction (HFrEF) and was placed on an SGTL2i as part of his GDMT regimen. Shortly after, his medical team performed an extensive review and discovered that he previously had trialed SGLT2i but had experienced the side effect of DKA (and had been hospitalized for that several years prior). His new SGLT2i was promptly discontinued without adverse effect. Workup from his prior DKA revealed positive glutamic acid decarboxylase [GAD] antibodies, diagnosing him with LADA. In hindsight this patient had LADA and was started then stopped on an SGLT2i for his diabetes but later became a candidate for this same class of drug for an entirely new diagnosis (heart failure).

Case series, Patient 2

We additionally present a 73-year-old female with a history of DMII and ischemic cardiomyopathy on GDMT to include SGLT2i

who presented to the emergency room for weakness and falls. Lab work was consistent with DKA, revealing an elevated anion gap metabolic acidosis with severe hyperglycemia. Further medication review revealed her use of the SGLT2i empagliflozin. Her clinical presentation prompted the medical team to check a GAD antibody, which returned with a high titer consistent with LADA. After management of DKA, her SGLT2i was discontinued before discharge.

1.1. How does SGLT2i's work?

The mechanism of action of SGLT2i is by inhibition of a proximal tubule nephron protein called the sodium-glucose cotransporter 2, preventing the kidney from re-absorbing glucose back into the bloodstream. Glucose is then excreted into the urine. By decreasing the amount of sugar in the blood, diabetic patients benefit. Regarding HF, there appears to be additional mechanisms for their benefit [6].

Why does SGLT2i's Help in Heart Failure?

Initially it was postulated that increased excretion of glucose led to a diuretic effect that could potentially help cardiac function. However, it appears the true underlying mechanism for benefit in heart failure may be more complex. This includes downregulation of sympathetic activity, increased erythropoiesis, reduction of inflammation, decrease in cardiac remodeling, decreased oxidative stress, diuretic effects, and decrease in blood pressure [6,7]. These mechanisms require additional research, though in theory do seem to make logical sense. As an example, diuresis is one of the hallmark treatments for both types of heart failure: reduced or preserved ejection fraction. Additionally, lowering blood pressure is one of the independently modifiable risk factors that impacts progression of heart failure.

What is the difference between DMI, DMII, and LADA?

Type I diabetes mellitus is an autoimmune disease. It is seen in patients younger than 30 years old who develop symptoms of diabetes as their bodies begin to lose their ability to produce insulin. The pancreas is responsible for producing insulin at very specific sites: the beta islet cells. The autoimmune cause of DMI is a self-produced antibody to the beta islet cells of the pancreas, leading to destruction of the body's own ability to produce insulin. In contrast to DMI, type II diabetics are generally able to produce insulin but become resistant to it, resulting in less efficacy over time. Both types of diabetes lead to increased blood glucose ultimately causing a systemic cascade of concomitant illnesses such as diabetic retinopathy, neuropathy, nephropathy, vascular disease, and many more. LADA occurs because of an autoimmune phenomenon directed at the beta-islet cells of the pancreas much like DMI, however it occurs at later stages in life. These same patients may also have insulin resistance. The American Diabetes Association defines LADA using 3 criteria: Onset after age 30, requiring insulin in a rapid period (less than 6 months), and having measurable antibodies related to insulin or its production [8]. Similarly, to DMI, patients with LADA can make relatively little or no insulin. What makes LADA difficult to diagnose is that it often presents similarly to DMII. The current mechanism for SGLT2i induced DKA is thought to be initiated by the euglycemic effect of the SGLT2i which in turn leads to the body's decreased insulin response and subsequent increased glucagon stimulation, ultimately leading to lipolysis and ketogenesis [9,10].

Treatments for the different types of diabetes vary since the pathophysiology behind the diseases is ultimately different. Patients that cannot make insulin should receive insulin as a primary treatment whereas patients that can make insulin are amenable to other regimens such as oral anti-hyperglycemic agents which have both insulin sensitizing and cardiovascular risk reduction benefits. Since SGLT2i does not provide insulin to those with DMI or LADA, they may offer no benefit, or may even cause harm. This potential for SGLT2i harm may be overlooked in LADA as it is a relatively rare form of DM and can go unnoticed. Additionally, medical subspecialty consultant teams with less experience in direct DM management may not be as familiar with a given patient's overall clinical fit for both the presence of LADA and subsequent SGLT2i use. The FDA does specifically recommend that a patient who has pancreatic insulin insufficiency (in the absence of a clarifying mechanism of either insulin under production or beta cell autoimmune destruction or combination thereof) requires careful monitoring when initiating SGLT2i though they are not formally contraindicated [2].

Neither the FDA nor the ACC/AHA describe any discussion of LADA with respect to SGLT2i use though the ACC/AHA does state that a prior history of DKA should prompt more detailed initiation and follow up processes when considering SGLT2i use. In February 2023 the LADA Primary Care Study mentions that SGLT2i should not be used in patients with LADA due to increased risk of DKA, but also acknowledges the difficulty in discerning between DMII and LADA. This study created a clinical score to assess pre-test probability for LADA in patients which are currently undergoing validation [11].

Why is it Important to Consider LADA in Patients with Heart Failure?

It is well established that DMII can increase a patient's risk of HF with up to a 4-fold increase in the incidence of HF in patients with DMII, a risk which appears to be even higher in patients > 60 years old. [12] The advent of SGLT2i treatment in HF for patients with or without diabetes opens an avenue for multi-modality therapy in these patients [12].

As evidenced by the above case series', patients that have an indication for both HF and DM treatment intervention may also harbor an occult contraindication for SGLT2i use given the presence of LADA. Though LADA is relatively rare and there are no established diabetic management guidelines for it, it can be easily

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missed prior to initiation of SGLT2i leading to an elevated risk of DKA [13]. LADA appears to account for 2-12% of all cases of diabetes in the adult population which may be under estimation [12].

Who Should be Screened for LADA?

It is important to keep a high index of suspicion for LADA in patients with diabetes who may present with either hyper or euglycemic DKA and who have recently been started on an SGLT2i. This screening is complicated by both the expense and processing time of diagnostic blood tests. This raises 2 important questions. Should expensive tests with delayed turn-around time be initiated for every HF patient with DM for which an SGLT2i is being considered (potentially delaying GDMT optimization)? Conversely, can close monitoring of new SGLT2i therapy started in diabetics suffice for formal diagnostic testing?

It appears the most reasonable initial approach is to keep a high index of suspicion with clear clinical criteria for who may be at risk for LADA. As mentioned previously, a pre-test probability risk calculator tool is actively being studied for this application through the LADA Primary Care Protocol Study. [11] In addition to the risk calculator tool, some proposals that may lower the threshold for antibody testing include identifying poorly controlled diabetics on oral anti-hyperglycemic medications, a prior autoimmune diabetes diagnosis, labile glycemic levels, and rapidly increasing insulin requirements with no other explanation.

Conclusion: Should This Information be Included in the Heart Failure Guidelines?

Yes. It appears to be an important factor for worldwide heart failure guideline governing bodies to at least address that patients may carry an occult increased risk for DKA with use of SGLT2i's. Further research is needed into the validation of clinical prediction paradigms for LADA in patients with diabetes for whom an SGLT2i is being considered.

Summary Points

i. Sodium Glucose Co-Transporter 2 Inhibitors are an integral part of guideline directed medical therapy for HF in patients with and without diabetes.

ii. DKA is a significant complication of SGLT2i therapy in certain diabetics and its risk may be amplified by unrecognized LADA.

iii. Guidelines should address an approach to the safe initiation of SGLT2i in diabetics with HF.

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