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EDITORIAL

Sodium-Glucose Cotransporter 2 Inhibitor-Associated "Ketoacidosis" Versus "Diabetic Ketoacidosis": The Importance of Accurate Terminology

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Late last year, the Australian Product Information for empagliflozin, a sodium-glucose cotransporter 2 inhibitor (SGLT2i), was updated to include the statement that "cases of ketoacidosis have also been reported in patients without diabetes" [1]. Despite being developed for type 2 diabetes, SGLT2i are a major advance in the treatment of heart failure, both with reduced and preserved ejection fraction, and chronic kidney disease, irrespective of the presence of diabetes [2–7]. Having reviewed both the seminal trials that established the role of SGLT2i for people without diabetes who have these conditions, and pharmaceutical Product Information documents from various regions, we note differences in the terminology used to describe the rare but serious adverse effect of ketoacidosis.

In the years following the release of SGLT2i into the pharmaceutical market for type 2 diabetes, there were increasing case reports of diabetic ketoacidosis, a potentially fatal condition [8]. This form of diabetic ketoacidosis differed from that most associated with type 1 diabetes as patients did not necessarily present with hyperglycaemia due to the glycosuric effects of the drug—the reason for this adverse effect being termed "euglycaemic" diabetic ketoacidosis [8]. SGLT2i predispose to ketoacidosis by decreasing the concentration of insulin and the insulin-to-glucagon ratio [9]. Usually, there needs to be other factors in play for this condition to occur, including anorexia, dehydration, and states associated with elevated catecholamines and cortisol, such as surgery [10]. A well-established risk factor for SGLT2i-associated ketoacidosis is insulin deficiency, including off-label SGLT2i use in a person with known type 1 diabetes or with a missed diagnosis of late-onset type 1 diabetes or use in a person with type 2 diabetes with low beta-cell function [10]. There has been debate on whether people without diabetes (and insulin deficiency) could be at risk of developing this adverse effect [11]. However, ketoacidosis (not related to SGLT2i use) is known to occur in normoglycaemic individuals when there is an extreme mismatch between carbohydrate demand and supply such as lactating mothers who are ill and/or on a very low carbohydrate diet [12].

Since 2019, six landmark SGLT2i heart failure and chronic kidney disease outcome trials have been published where the presence of diabetes was not an inclusion factor. The three trials relating to dapagliflozin have referred to the adverse event of interest as "diabetic ketoacidosis", whereas the three empagliflozin trials have termed the adverse event "ketoacidosis" [2–7]. The term "diabetic ketoacidosis" implies that this adverse event is limited to people with diabetes. This is potentially misleading. Indeed, in the EMPA-KIDNEY, one participant without diabetes randomised to empagliflozin experienced ketoacidosis [7].

There are also differences in terminology in current SGLT2i Product Information documents. The Australian, United States and European empagliflozin documents refer to the adverse event as "ketoacidosis" [1, 13, 14]. The warnings sections of the Australian and United States

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dapagliflozin documents contain the heading "ketoacidosis in patients with diabetes mellitus" [15, 16]. The European dapagliflozin Product Information employs the term "diabetic ketoacidosis" [17]. Among the United States, European and Australian empagliflozin Product Information documents, only the Australian version notes that cases of ketoacidosis have occurred in patients without diabetes. Interestingly, the one published case report of SGLT2i-associated ketoacidosis in a person without diabetes was an elderly woman who took dapagliflozin (prescribed for heart failure) on the morning of a scheduled transcatheter aortic valve replacement procedure [18].

Terminology in this context is important for several reasons. First, the difference between "ketoacidosis" and "diabetic ketoacidosis" in clinical trials impacts the case detection of a serious adverse event. Second, the wording of and information contained in Product Information documents are critical for the safety knowledge of health professionals and patients. Additionally, major clinical trials and Product Information documents are key resources for the formulation of clinical practice guidelines such as those relating to the peri-procedural or inpatient management of people taking SGLT2i. For these reasons, we advocate for *accurate and consistent terminology*, especially given the increasing number of patients without diabetes taking these medicines for heart failure and/or chronic kidney disease. We recommend that drug regulatory bodies in each country and/or the World Health Organization, and pharmaceutical companies decide and agree on such terminology that can be reflected in drug information datasheets.

We believe consideration should be given to the employment of two terms, "SGLT2i-associated ketoacidosis in a person with diabetes or pre-diabetes" and "SGLT2i-associated ketoacidosis in a person without diabetes". The use of these two terms would ensure health professionals do not simply exclude the possibility of SGLT2i-associated ketoacidosis in a person without diabetes. Additionally, such a change would be beneficial for pharmacovigilance adverse event monitoring systems, where currently it is very difficult to delineate cases of SGLT2i-associated ketoacidosis in persons with and without diabetes.

Declarations

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