SGTL2 inhibitors and amputations in the US FDA Adverse Event Reporting System

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See Online for appendix

In the CANVAS trial programme, the sodium-glucose co-transporter-2 (SGLT2) inhibitor canagliflozin significantly reduced the risk of cardiovascular events by 14% but doubled the risk of amputation in patients with type 2 diabetes.[1] This unexpected adverse event has not emerged in studies on dapagliflozin or empagliflozin.

We analysed this safety signal in the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS), a useful approach to monitor rare adverse events via assessment of disproportionality,[2] as described in the appendix. Among 9 217 555 adverse event reports in the FAERS up to March 31, 2017, 66 were SGLT2 inhibitor-associated amputations. Most of the available reports (57 [86%] of 66) listed canagliflozin as a suspect or concomitant drug. Average and detailed report information is provided in the appendix. On average, patients were aged about 60 years, and most were men. In 57 (89%) of 64 cases (two reports could not be retrieved for detailed analysis), an SGLT2 inhibitor was the primary suspect and average treatment duration was about 1·5 years. Based on indications, 11% of patients had diabetic foot or wounds, but concomitant adverse events included wound, necrosis, gangrene, or ischaemia in 14 cases, and osteomyelitis or other infections in 15 cases. Cumulatively, in 23 (36%) of 64 cases there was at least one of such features of diabetic foot syndrome. The most common level of amputation was the toe, but there were 13 above-ankle leg or limb amputations, two multiple amputations, one hand amputation, and three fatal cases.

Disproportionality within the FAERS up to Dec 31, 2016, (8 864 346 reports) was analysed with AERSmine[3] (which cannot yet access data for the first quarter of 2017; figure, appendix). The frequency of reports having amputation as an adverse event among all reports listing canagliflozin as suspect or concomitant was 3·4 per 1000 (95% CI 2·6–4·6). The frequency of reports with amputation as an adverse event with canagliflozin was significantly higher than the frequency of amputations in reports filed for non-SGLT2 inhibitor drugs, with a proportional reporting ratio (PRR) of 5·33 (95% CI 4·04–7·04; p<0·0001); by comparison, the PRR for dapagliflozin was 0·25 (0·03–1·76; p=0·163; appendix) and for empagliflozin was 2·37 (0·99–5·70; p=0·054; appendix). Complimentary data showing events per 1000 are shown in the figure.

As SGLT2 inhibitors are indicated for diabetes treatment and diabetes is a major risk factor for amputation, we filtered the search by diabetes indication (appendix). As expected, the frequency of amputations in reports filed for non-SGLT2 inhibitor drugs with the diabetes indication was three times higher than in reports without the diabetes indication. The frequency of amputation reports for canagliflozin in this analysis was still significantly higher than for non-SGLT2 inhibitor drugs, with a PRR of 1·59 (95% CI 1·12–2·30; p=0·009).

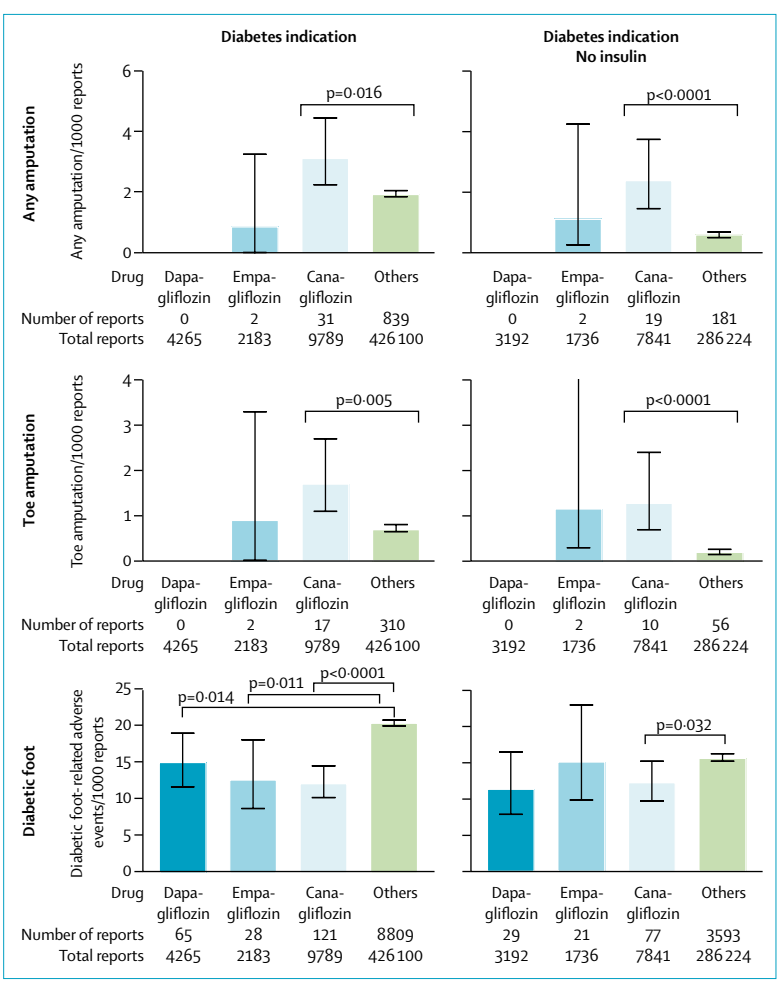

Figure: **Frequencies of any amputation, toe amputation, and diabetic foot-related adverse events associated with SGLT2 inhibitor and non-SGLT2 inhibitor drugs in the FAERS up to up to Dec 31, 2016**
Frequencies of reports are shown along with their 95% CIs. p values from χ^2 test are shown. FAERS=US Food and Drug Administration Adverse Event Reporting System.

A few concomitant drugs occurred more frequently in amputation reports filed for canagliflozin than in those filed for non-SGLT2 inhibitors, especially some oral glucose-lowering drugs, angiotensin-converting-enzyme inhibitors, and anti-thrombotic drugs, whereas insulin occurred less frequently in amputation reports for canagliflozin (appendix). Therefore, we further restricted the analysis to reports not including concomitant insulin therapy, which is associated with amputation risk as a proxy of disease severity.[4] The frequency of amputations in reports filed for non-insulin non-SGLT2 inhibitor drugs with the diabetes indication was similar to that in reports without the diabetes indication and the PRR for amputation associated with canagliflozin was 3·83 (95% CI 2·39–6·14; p<0·0001). A subanalysis limited to toe-level amputation yielded a PRR associated with canagliflozin of 2·38 (95% CI 1·47–3·89; p=0·0005), which increased to 6·52 (3·33–12·78; p<0·0001) after exclusion of reports listing insulin as a concomitant drug (figure, appendix).

Reassuringly, the frequency of more general diabetic-foot related adverse events was significantly lower among reports for SGLT2 inhibitors than among reports for non-SGLT2 inhibitor drugs with the diabetes indication, although this difference was tapered after exclusion of reports listing insulin therapy as a concomitant drug (appendix).

In summary, this pharmacovigilance analysis confirms that use of canagliflozin, but not dapagliflozin or empagliflozin, might be associated with an increased risk of amputations.[1] However, FAERS data analysis has important limitations because there is no definite causal link between drug exposure and adverse event, PRRs do not inform on the true risk in clinical practice, records are often incomplete, and US FDA warnings might result in stimulated reporting. Additionally, we cannot exclude the possibility that some data from patients in the CANVAS trials might not also have appeared in the FAERS dataset (appendix). Further details are provided in the appendix, along with caveats on concluding in favour of a non-class-effect, and notes about potential mechanisms.

No specific prescription guide can be added to the US FDA boxed warning for amputation risk with canagliflozin on the basis of these data, but deciphering predisposing factors and mechanisms of this rare adverse event will be crucial to maximise the benefits of SGLT2 inhibitors in clinical practice.

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Issues with European guidelines for phenylketonuria

Newborn screening and early dietary treatment for phenylketonuria is a major medical success story. More people are screened for phenylketonuria than for any other inherited condition. Since 1970, the outlook for affected individuals has been transformed from severe intellectual disability to fully normal personal, professional, and social lives. Like in many other rare diseases, high quality studies of treatment and outcomes in phenylketonuria are scarce. This scarcity is reflected in the recent key European guidelines for the diagnosis and management of phenylketonuria published in *The Lancet Diabetes & Endocrinology*.[1] We are concerned that these guidelines include opinion-based recommendations that might result in overtreatment, poor compliance, and unnecessary costs to health-care systems. Two recommendations are particularly contentious.

The first is the statement that patients with untreated blood phenylalanine concentrations greater than 360 µmol/L should be treated. Adverse outcomes caused by blood phenylalanine concentrations up to 600 µmol/L (mild hyperphenylalaninaemia) have not been reported;[2] in one study,[3] some children with blood phenylalanine up to 1200 µmol/L were judged as having mild hyperphenylalaninaemia, certainly a misclassification. There is one controlled study,[4] the results of which show that treatment is not required with blood phenylalanine below 600 µmol/L. In their guidelines,[1] Francjan van Spronsen and colleagues object that only seven of 31 patients in that study had phenylalanine concentrations greater than 500 µmol/L, but fail to consider that 18 individuals had concentrations