Incidence of Ketoacidosis in the Danish Type 2 Diabetes Population Before and After Introduction of Sodium–Glucose Cotransporter 2 Inhibitors—A Nationwide, Retrospective Cohort Study, 1995–2014

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The U.S. Food and Drug Administration warns that sodium–glucose cotransporter 2 (SGLT2) inhibitors may lead to diabetic ketoacidosis (DKA). To establish a baseline occurrence of DKA in type 2 diabetes, we used national registries in Denmark to estimate incidence rates of DKA and linked the data to information on filled prescriptions to determine treatment exposure, with special attention paid to SGLT2 inhibitor use.

Patients with filled prescription(s) for antidiabetes medication or a type 2 diabetes diagnosis identified through national registers (1995–2014) (1,2) were included. Patients were followed from the date of diagnosis until an event or censoring due to death or emigration, or by end of study 31 December 2014, whichever occurred first. Events of DKA were defined as a primary or secondary diagnosis in the National Patient Register between 1 January 1995 and 31 December 2014. Patients diagnosed with type 1 diabetes or who had a filled prescription for any antidiabetes drug before the age of 30 years were excluded. Rates of incidence were analyzed with Poisson regression, adjusted for sex, current age, calendar time, and duration of diabetes, with natural splines (5 knots) describing the time effects. The inclusion of calendar time was essential in order to avoid confounding, as SGLT2 inhibitors were first introduced in Denmark in December 2012.

During follow-up, 415,670 patients had 4,045 first events of DKA in 3 million person-years, corresponding to a crude

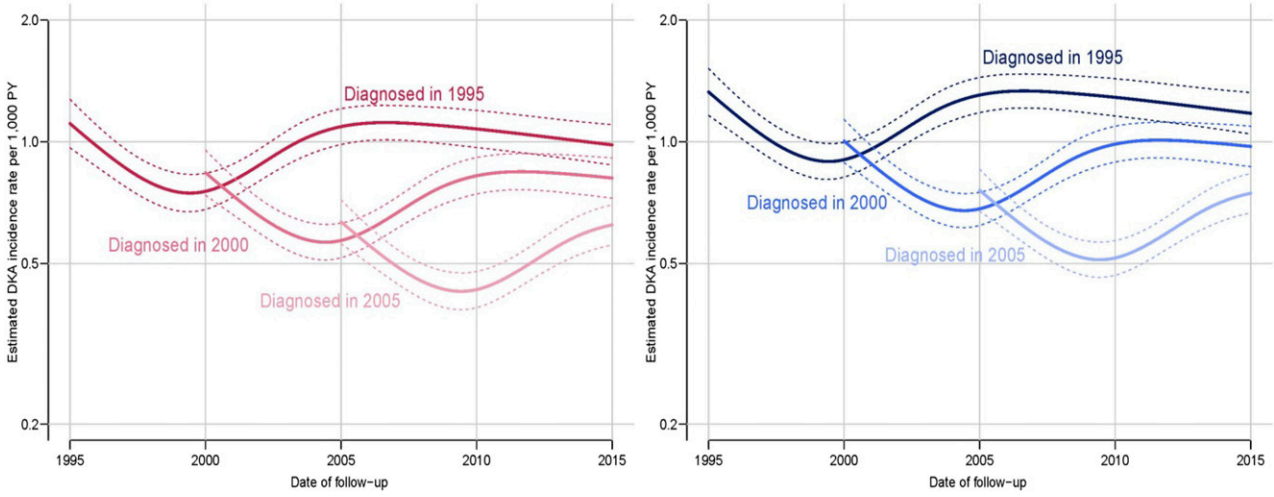

Figure 1—Estimated incidence rates of a first DKA event per 1,000 person-years (PY) among women (left panel) and men (right panel) diagnosed with type 2 diabetes at age 65 years in 1995, 2000, and 2005 and exposed to noninsulin glucose-lowering drugs.

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incidence rate of 1.34 per 1,000 person-years, decreasing by 5.6% (95% CI 5.0–6.2%) per year. Figure 1 shows DKA incidence rates for women and men diagnosed at age 65 years in 1995, 2000, and 2005.

Relative to patients without pharmacological treatment, exposure to noninsulin glucose-lowering drugs carried a hazard ratio for DKA of 1.3 (95% CI 1.2–1.5), insulin monotherapy 6.0 (95% CI 5.3–6.8), and the combination 3.0 (95% CI 2.7–3.4). Importantly, for SGLT2 inhibitor monotherapy, no events of DKA were registered (31 person-years), and in any treatment combination using SGLT2 inhibitors, there were only six events of DKA in a total of 3,811 person-years of observation, corresponding to a nonsignificant hazard ratio of 1.6 (95% CI 0.7–3.5).

This is the first study to estimate nationwide incidence of DKA in type 2 diabetes with 20 years of follow-up and 3 million person-years of observation combined with prescription data. DKA is a rare condition in type 2 diabetes with decreasing incidence. Patients on insulin monotherapy have the highest occurrence, and there were few events among those prescribed SGLT2 inhibitors and only among those concomitantly prescribed other glucose-lowering drugs and insulin. Compared with canagliflozin trials (3), our DKA incidence rates in the SGLT2 inhibitor–treated groups are higher, but the rates presented here indicate what we are likely to face in clinical practice; out of 1,000 people classified as having type 2 diabetes, one will be hospitalized with DKA each year, a potentially life-threatening acute situation, especially in the older population, demanding hospital admission and intensive treatment. The excess risk associated with SGLT2 inhibitor treatment was, however, not significant and is hardly clinically relevant.

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Author Contributions. All authors were involved in the conception and design of the study. M.L.J. performed the analysis. M.L.J. and B.C. were the study statisticians. All authors interpreted the data. M.L.J., F.P., and M.E.J. wrote the first draft. All authors read and approved the final version of the manuscript. M.E.J. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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