NEWSLETTER 16

SGLT2 Inhibitor Safety Signals in FAERS

Ketoacidosis and other adverse events across 154,476 spontaneous reports

Figure 16. SGLT2 Inhibitor Safety Signals in FAERS — mechanism overview (illustrative; labels added for education).

A June 2026 analysis of the openFDA FAERS database offers a large-scale view of real-world SGLT2-inhibitor safety signals. The extract, dated 2026-06-08, holds 154,476 individual safety reports naming at least one of five SGLT2 inhibitors—empagliflozin, dapagliflozin, canagliflozin, ertugliflozin, and bexagliflozin—covering 2013 to early 2026.[1]

Overall severity is notable: of the class-level reports, 102,173 (66.1%) carry a seriousness flag and 13,310 (8.6%) record a fatal outcome.[1] These proportions reflect reporting biases toward severe events but still merit clinical attention.

Ketoacidosis is the signature signal. The database contains 9,278 reports of diabetic ketoacidosis, 3,108 of euglycaemic DKA, and 2,902 of ketoacidosis—15,288 combined—consistent with the mechanism of urinary glucose loss shifting metabolism toward ketogenesis.[1] The euglycaemic subset is especially important because normal glucose can delay diagnosis.

Other recognised signals appear in expected proportions: lower-limb amputation (4,819), genital mycotic infection (5,385), volume depletion or acute kidney injury (9,162), and the rare but severe Fournier's gangrene / necrotising fasciitis (630).[1]

The comparison with an active-control analysis sharpens the signal: an earlier FAERS study estimated roughly seven-fold higher acidosis reporting for SGLT2 inhibitors versus DPP-4 inhibitors, with most quantifiable cases euglycaemic.[2] That euglycaemic pattern is the practical danger—normal or near-normal glucose can falsely

reassure both patient and clinician while ketoacidosis develops. Set against the class's large, proven cardiorenal benefit, these disproportionality signals argue for structured patient education and sick-day planning, not for abandoning an otherwise foundational therapy.[3]

Interpreting these numbers requires caution. FAERS is a spontaneous-reporting system with no denominator, so counts are not incidence, relative risk, or causal estimates; the FDA first flagged ketoacidosis in a December 2015 Drug Safety Communication.[1] An earlier FAERS analysis estimated a roughly seven-fold higher acidosis risk in type 2 diabetes patients on SGLT2 inhibitors versus DPP-4 inhibitors, with 71% of quantifiable cases euglycaemic—reinforcing vigilance around ketoacidosis in particular.[2] For practice, the message is not to avoid these highly effective drugs but to counsel patients on sick-day rules, hold therapy around surgery or acute illness, and consider ketones whenever an SGLT2-treated patient is unwell, even with normal glucose.

References

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