

Diabetic Ketoacidosis Associated with SGLT2 Inhibitors in Type 2 Diabetes Mellitus; A Rapid Systematic Review and Trial-Level Meta-Analysis of Randomised Controlled Trials

Muhammad Asim Rana^{1*}, Mujtaba Hasan Siddiqui², Mubashar Sultan Hashmi³,
Ezaz Yousaf⁴, Rizwan Pervaiz⁵, Muhammad Umar Khan⁶, Basheer Abdelrahman⁷,
Meshal Alharbi⁸, Aseel Mady⁹, Menettallah Mousa⁹

^{1*}Professor of Critical Care Medicine, Amna Inayat Medical College, Sheikhupura, Pakistan; Consultant Physician, Intensive Care Medicine, King Abdullah Specialized Hospital, MNGHA, Qassim, KSA

²Professor of Medicine, Akhtar Saeed Medical and Dental College, Lahore, Pakistan

³Assistant Professor, Critical Care Medicine, Amna Inayat Medical College, Sheikhupura, Pakistan; Consultant Physician, Intensive Care Medicine, Bahria International Hospital, Lahore, Pakistan

⁴Senior Registrar, Medicine, Amna Inayat Medical College, Sheikhupura, Pakistan

⁵Senior Registrar, Critical Care Medicine, Bahria International Hospital, Lahore, Pakistan

⁶Endocrinology Fellow, Bahria International Hospital, Lahore, Pakistan

⁷Pharmaceutical Care Department, King Saud Medical City, Riyadh, KSA

⁸Department of Clinical Pharmacy, King Abdullah Specialized Hospital, MNGHA, Qassim, KSA

⁹Medical Student, Alfaisal University, Riyadh, KSA.

***Corresponding:** Muhammad Asim Rana

Email: drasimrana@yahoo.com

Received: 25-05-2026,

Revised: 19-08-2026,

Accepted: 08-09-2026,

Published: 25-09-2026

ABSTRACT

Background: Sodium-glucose cotransporter-2 (SGLT2) inhibitors reduce cardiovascular and renal events in type 2 diabetes mellitus but are associated with a rare form of diabetic ketoacidosis (DKA), which may occur with only modest hyperglycaemia. This review evaluated the relative and absolute risk of DKA in large placebo-controlled cardiovascular and renal outcome trials and explored whether the signal differed across major trial populations.

Methods: Eight large, placebo-controlled phase 3 cardiovascular or renal outcome trials of empagliflozin, dapagliflozin, canagliflozin, or ertugliflozin that reported arm-level DKA event counts were included. Rare-event data were pooled using the Peto one-step odds ratio, with a Mantel-Haenszel odds ratio as a sensitivity analysis. A prespecified subgroup analysis compared heart-failure trials with the remaining trial populations. Heterogeneity was assessed using Cochran's Q and I². Observational and pharmacovigilance evidence was synthesised narratively and was not pooled with randomised trial data.

Results: Across 55,385 randomised participants, DKA occurred in 74 of 30,245 SGLT2 inhibitor-treated patients (0.245%) and 24 of 25,140 placebo-treated patients (0.095%). The pooled Peto odds ratio was 2.39 (95% CI 1.60-3.57; p<0.0001), while the Mantel-Haenszel sensitivity analysis yielded an odds ratio of 2.66 (95% CI 1.67-4.24). Heterogeneity was moderate (I²=34%). In the two heart-failure trials, the pooled estimate was 1.40 (95% CI 0.45-4.35), compared with 2.58 (95% CI 1.68-3.97) in the remaining six trials; however, the subgroup interaction was not statistically significant (p=0.32). The absolute risk difference was 0.149 percentage points, corresponding to an approximate number needed to harm of 670 over the multi-year trial durations.

Conclusions: In large placebo-controlled outcome trials, SGLT2 inhibitors were associated with an increased relative risk of DKA, while the absolute incidence remained low. The numerically smaller estimate in heart-failure trials should be interpreted cautiously because the subgroup interaction was not statistically significant and event counts were small. Clinicians should maintain a low threshold for checking acid-base status and beta-hydroxybutyrate in patients receiving SGLT2 inhibitors who present with unexplained metabolic acidosis, nausea, tachypnoea, or malaise, even when blood glucose is not markedly elevated.

Keywords: Diabetic Ketoacidosis, Diabetes Mellitus, Type 2, Sodium-Glucose Transporter 2 Inhibitors

How to cite this article: Rana MA, Siddiqui MH, Hashmi MS, Yousaf E, Pervaiz R, Khan MU, et al. Diabetic Ketoacidosis Associated with SGLT2 Inhibitors in Type 2 Diabetes Mellitus; A Rapid Systematic Review and Trial-Level Meta-Analysis of Randomised Controlled Trials. IJDDT. 2026;16(85s): 318-326; DOI: 10.25258/ijddt.16.85s.28

INTRODUCTION AND RATIONALE

SGLT2 inhibitors act by blocking glucose reabsorption at the S1 segment of the proximal renal tubule, producing glycosuria, natriuresis, and a reduction in plasma glucose without stimulating endogenous insulin secretion. This insulin-independent mechanism underlies both the drug class's cardiorenal benefit and its principal metabolic liability^{1,2}. By lowering circulating insulin relative to glucagon, SGLT2 inhibition promotes lipolysis and hepatic ketogenesis. Enhanced proximal sodium reabsorption reduces urinary ketone clearance at the same time, and the drug's mild glucosuric effect can mask the degree of ketosis by keeping plasma glucose in a near-normal range. The resulting syndrome, euglycaemic DKA, was first flagged by the FDA in 2015 after 73 post-marketing reports and remains a class-labelled warning today^{3,4}.

This is clinically relevant for critical care practice for three reasons. First, euglycaemic DKA is easy to miss on a standard admission glucose⁵, since bedside teams anchor on hyperglycaemia as the trigger for a ketone or gas check. Second, the indications for this drug class have broadened substantially: current guidelines recommend an SGLT2 inhibitor for defined populations with heart failure with reduced or mildly reduced ejection fraction and for chronic kidney disease meeting specific eGFR and albuminuria thresholds, in each case irrespective of glycaemic control or diabetes status⁶. This is indication-specific guidance rather than a blanket first-line recommendation for every patient with heart failure or CKD, but it does mean a growing proportion of exposed patients do not have diabetes and would not previously have been considered at risk of DKA at all. Third, perioperative and critically ill patients are precisely the group in whom the recognised precipitants of euglycaemic DKA, reduced oral intake, acute illness, surgery, and insulin dose reduction, converge⁷.

The question this review addresses is narrower than the incidence of DKA in unselected clinical practice: what do large placebo-controlled outcome trials show about the relative and absolute risk of DKA across the SGLT2 inhibitor class, and how consistent is that signal across agents and, specifically, across the heart-failure, CKD, and ASCVD trial populations in which the drug class is now used.

METHODS

This rapid systematic review was reported in accordance with the structure of PRISMA 2020 and focused on a single safety outcome: DKA associated with SGLT2 inhibitor use. Consistent with rapid-review methodology, screening and data extraction were performed by one reviewer with verification of extracted values against the cited primary sources. The search was restricted to the large cardiovascular and renal outcome-trial literature rather than a full grey-literature search, and the protocol was not prospectively registered. These methodological limitations are addressed in the Limitations section.

Protocol and Eligibility (PICO)

The unit of eligibility is the individual randomized

controlled trial: a trial was eligible if it enrolled adults with type 2 diabetes mellitus in a randomised, placebo-controlled cardiovascular or renal outcome programme and reported a per-arm DKA count or trial-level hazard ratio. Two heart-failure trials in this synthesis (EMPEROR-Preserved and DAPA-HF) enrolled mixed diabetic and non-diabetic cohorts; both trials were retained because each reported a diabetes-status-stratified breakdown of DKA events in their primary or supplementary safety publications, and only the diabetic-cohort numerator and denominator from that breakdown were extracted into Table 1. No participant without a diagnosis of type 2 diabetes contributes to the numerators, denominators, or person-time in the quantitative pool.

Population: Adults with type 2 diabetes mellitus enrolled in randomised, placebo-controlled cardiovascular or renal outcome trials of an SGLT2 inhibitor, restricted at the trial level to the diabetic-cohort event data as described above.

Intervention: Any licensed SGLT2 inhibitor (empagliflozin, dapagliflozin, canagliflozin, ertugliflozin) at an approved dose.

Comparator: Placebo added to standard background glucose-lowering and cardiorenal therapy.

Outcome: DKA, including euglycaemic DKA, reported as an adjudicated or investigator-identified pre-specified or serious adverse event. The operational definition of DKA varied modestly between trials but generally required the co-occurrence of hyperglycaemia or a history of diabetes, an elevated anion gap or reduced serum bicarbonate consistent with metabolic acidosis, and ketonaemia or ketonuria; trials differed in whether they required a specific pH or bicarbonate threshold and in whether euglycaemic presentations (glucose below the traditional 250 mg/dL or 13.9 mmol/L diagnostic threshold) were captured under the same adverse-event code as hyperglycaemic DKA or flagged separately. Metabolic acidosis without a formal DKA diagnosis was not treated as a separate outcome; where a trial's safety tables listed metabolic acidosis and DKA as distinct adverse-event terms, only events coded as DKA were extracted, to avoid double-counting the same clinical episode. None of the eight included trials publicly reported a definite-versus-probable adjudication split for DKA; this is a genuine limitation of the source data, not an omission in extraction, and is carried forward explicitly into the Limitations and into Table 1's footnote rather than resolved by assumption.

Study design: Eligible studies were large multicentre, double-blind, randomised, placebo-controlled cardiovascular or renal outcome trials with more than 1,000 randomised participants per arm and publicly available peer-reviewed primary or dedicated safety publications. This pragmatic threshold was used to focus the analysis on outcome trials with sufficient exposure and systematic safety reporting for a rare adverse event.

Timeframe: Trial safety data published through 2023 (EMPA-KIDNEY), covering the cardiovascular and renal outcome-trial programmes for the four approved agents that had reported results at the time the search was conducted.

Eligibility criteria

Included: Phase 3 double-blind RCTs with a placebo comparator; DKA reported as an adjudicated or investigator-identified adverse event with a numerator and denominator, or a trial-level hazard ratio.

Excluded studies were open-label extensions; trials without a placebo arm; phase 1 or 2 pharmacology studies without DKA data; case reports and case series; pharmacovigilance or disproportionality analyses; and trials in type 1 diabetes. Active-comparator and observational studies were excluded from the quantitative pool and considered only in the narrative synthesis because they do not provide the same randomised placebo-controlled estimate of treatment-associated risk.

Information Sources and Search

Trials were identified through targeted searches of PubMed/MEDLINE and the general web using each SGLT2 inhibitor name in combination with terms for cardiovascular outcome trials, renal outcome trials, and diabetic ketoacidosis. Reference lists of recent peer-reviewed reviews were hand-searched, and identified studies were verified against their primary trial publications and ClinicalTrials.gov records. The quantitative trial search covered the major cardiovascular and renal outcome programmes available through EMPA-KIDNEY, while later syntheses were used only for contextual comparison in the Discussion.

Data Extraction and the Evidence Ledger

For each eligible trial, the following were extracted from the primary publication or dedicated safety report: trial acronym, drug and dose, population, number randomised per arm, DKA events per arm, and any source-reported effect estimate. Values were not estimated or interpolated. DELIVER was not included in the quantitative pool because consistent arm-level DKA counts could not be confirmed from the prespecified source set. The CANVAS programme was discussed narratively because the primary report provided incidence rates and a hazard ratio rather than raw arm-level event counts, which were required for the odds-ratio meta-analysis.

The quantitative synthesis used peer-reviewed randomised trial publications and did not involve individual-patient-data re-analysis. Observational cohort and pharmacovigilance studies were considered separately in the narrative synthesis because their non-randomised designs and comparator structures were not directly commensurable with the trial-level odds-ratio pool.

Statistical Synthesis

DKA is a rare event, and three of the eight pooled trials have a zero-event arm. Standard inverse-variance methods are unstable under these conditions, and the plain Mantel-Haenszel odds ratio can also become unstable when zero cells are frequent. Consistent with Cochrane Handbook

guidance for meta-analyses of rare binary events¹⁰, the Peto one-step odds ratio was used as the primary pooling method, computed from raw arm-level counts with no continuity correction. A fixed-effect model was used given the mechanistic and pharmacological homogeneity of the class-level question; heterogeneity was nonetheless quantified with Cochran's Q and I².

The Peto method is known to become biased when individual trial effect sizes are large or arm sizes are markedly unbalanced^{11,12}, a concern directly relevant here given the large hazard ratio reported in CREDENCE. As a prespecified sensitivity analysis, the same eight trials were also pooled using the classic Mantel-Haenszel odds ratio, which does not share this specific bias mechanism and tolerates the single-arm zero-event trials in this dataset without requiring a continuity correction (a correction is only necessary when a trial has zero events in both arms simultaneously, which does not occur among the eight included trials). Both estimates, and their concordance, are reported in section 3.2.

A prespecified subgroup analysis compared the two heart-failure trials (EMPEROR-Preserved, DAPA-HF) against the remaining six trials enrolling patients with established cardiovascular disease or chronic kidney disease, using the same Peto method within each subgroup and a chi-squared test for subgroup interaction. This subgroup structure mirrors the population stratification used in a contemporaneous, larger meta-analysis by Wang and colleagues¹³, allowing a direct qualitative comparison of direction and magnitude even though the two analyses draw on different trial sets (see section 5.3).

The absolute risk difference between treatment arms was calculated and converted to a number needed to harm (NNH) as the reciprocal of the risk difference. A 95% confidence interval for the risk difference was derived using the normal approximation.

All meta-analytic calculations were performed directly from the extracted 2×2 trial tables. The computational script used standard Peto and Mantel-Haenszel formulae with the Robins-Breslow-Greenland variance estimator and is available from the corresponding author on reasonable request.

RESULTS

Study and Evidence Characteristics

Eight placebo-controlled outcome trials met the eligibility criteria, comprising 55,385 randomised participants: EMPA-REG OUTCOME, EMPEROR-Preserved, and EMPA-KIDNEY for empagliflozin; DECLARE-TIMI 58, DAPA-HF, and DAPA-CKD for dapagliflozin; CREDENCE for canagliflozin; and VERTIS CV for ertugliflozin. Trial populations included patients with established cardiovascular disease, heart failure, or chronic kidney disease. Extracted DKA event data are presented in Table 1.

Table 1

Trial-level DKA event data included in the quantitative synthesis

Trial (SGLT2i)	Population	SGLT2i events/N	Placebo events/N	Effect estimate (source-reported)	Source
EMPA-REG OUTCOME (empagliflozin 10/25 mg)	T2DM + established CVD	4 / 4,687	1 / 2,333	Not powered for this endpoint; no formal HR reported	14
EMPEROR-Preserved (empagliflozin 10 mg)	HFpEF, diabetic-cohort subset	4 / 1,465	5 / 1,471	No significant between-group difference	15
EMPA-KIDNEY (empagliflozin 10 mg)	CKD, with/without T2DM	6 / 3,304	1 / 3,305	Not formally tested (rare event)	16
DECLARE-TIMI 58 (dapagliflozin 10 mg)	T2DM, CVD or CV risk factors	27 / 8,574	12 / 8,569	HR 2.18 (95% CI 1.10-4.30)	17
DAPA-HF (dapagliflozin 10 mg)	HFpEF, diabetic-cohort subset	3 / 2,373	0 / 2,371	All events occurred in patients with baseline diabetes	18
DAPA-CKD (dapagliflozin 10 mg)	CKD, with/without T2DM	0 / 2,149	2 / 2,149	p = 0.5 (non-significant)	19
CREDENCE (canagliflozin 100 mg)	T2DM + diabetic nephropathy	11 / 2,200	1 / 2,197	HR 10.8 (95% CI 1.39-83.65)	20
VERTIS CV (ertugliflozin 5/15 mg)	T2DM + established CVD	19 / 5,493	2 / 2,745	Not formally powered; descriptive only	21

Values are events/total randomised per arm as reported in the cited primary publication. Where a trial tested more than one dose, doses were combined into a single SGLT2 inhibitor arm for pooling. Effect estimates are as reported in the trial's primary or dedicated safety publication (not a supplementary appendix unless stated). None of the eight trials publicly reported a definite-versus-probable DKA adjudication split; all identified events, regardless of adjudication category, are included in the counts above (see Methods, section 2.1, and Limitations).

Pooled Effect Estimate and Sensitivity Analysis

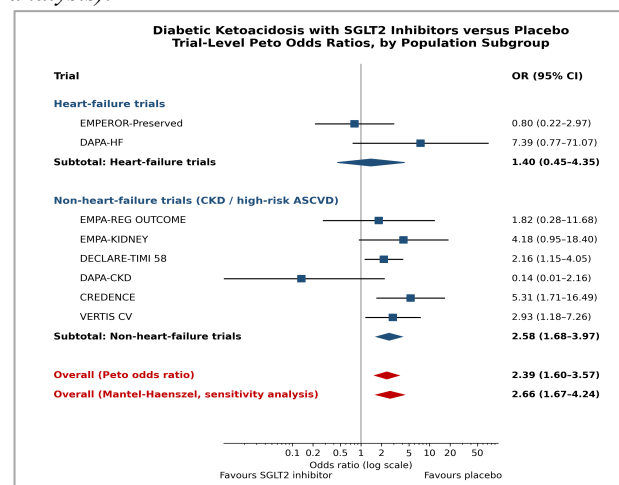
Across the eight pooled trials, DKA occurred in 74 of 30,245 patients randomised to an SGLT2 inhibitor (0.245%) and 24 of 25,140 patients randomised to placebo (0.095%). The pooled Peto odds ratio was 2.39 (95% CI 1.60-3.57; $z=4.24$; $p<0.0001$). The prespecified Mantel-Haenszel sensitivity analysis produced a similar estimate (OR 2.66, 95% CI 1.67-4.24; $z=4.10$; $p<0.0001$). Heterogeneity was moderate (Cochran's $Q=10.6$, $df=7$; $I^2=34\%$).

The absolute risk difference was 0.149 percentage points (95% CI 0.082-0.217), corresponding to an approximate NNH of 670 patients treated over the multi-year duration of the included trials (95% CI approximately 461-1,224).

Figure 1

Forest plot of trial-level Peto odds ratios for diabetic ketoacidosis, SGLT2 inhibitor versus placebo, grouped by heart-failure and non-heart-failure trial subgroups, with subtotal diamonds for each subgroup and overall

pooled estimates (Peto and Mantel-Haenszel sensitivity analysis).



Subgroup Analysis: Heart Failure versus Non-Heart-Failure Trials

A prespecified subgroup analysis compared the two heart-failure trials in the dataset (EMPEROR-Preserved and DAPA-HF) with the remaining six trials because SGLT2 inhibitors are used across populations with differing baseline cardiovascular, renal, and metabolic risk.

In the heart-failure subgroup, the pooled Peto odds ratio was 1.40 (95% CI 0.45-4.35; $z=0.58$; $p=0.56$), not statistically significant. In the remaining six trials, enrolling patients selected for established cardiovascular disease or chronic kidney disease, the pooled odds ratio was 2.58 (95% CI 1.68-3.97; $z=4.32$; $p<0.0001$). The formal test for subgroup interaction was not statistically

significant (chi-square 0.98, 1 df, $p=0.32$), which is unsurprising given that only two small trials, contributing 12 of the 74 SGLT2 inhibitor-arm events, populate the heart-failure subgroup; the test is accordingly underpowered to confirm or refute a true difference in effect by indication.

A larger independent meta-analysis reported a similar directional pattern, with significant increases in DKA risk in CKD and high-risk ASCVD trials and a non-significant estimate in heart-failure trials. Because the subgroup interaction in the present analysis was not significant and only two heart-failure trials contributed to that subgroup, these findings should be considered exploratory rather than evidence of a confirmed difference by indication.

Consistency Across Agents

The direction of effect was generally similar across the major agents, although individual estimates were imprecise because DKA was rare. DECLARE-TIMI 58 reported a trial-level hazard ratio of 2.18 (95% CI 1.10-4.30), close to the Peto odds ratio calculated from its arm-level counts (2.16, 95% CI 1.15-4.05). CREDENCE had the largest point estimate, while EMPEROR-Preserved and DAPA-CKD had confidence intervals that crossed unity. No included trial demonstrated a statistically significant reduction in DKA risk with SGLT2 inhibitor therapy.

Corroborating Real-World Evidence (Narrative Synthesis, Not Pooled)

Because observational studies lack a randomised denominator and often use an active comparator rather than placebo, they were not combined with trial data in the quantitative pool above. They remain relevant to clinical interpretation, and their divergent findings are themselves informative about how outcome definitions shape the apparent signal. A multicentre cohort study using Canadian and UK primary care data²⁴ found SGLT2 inhibitor initiation associated with a near threefold increase in DKA risk compared with DPP-4 inhibitors (2.03 versus 0.75 per 1,000 person-years; HR 2.85, 95% CI 1.99-4.08). A US commercial-claims analysis²⁵ found a similar twofold relative increase compared with DPP-4 inhibitors after propensity matching (HR 2.2, 95% CI 1.4-3.6). Against this, a Scandinavian registry cohort²⁶ found a neutral risk of DKA compared with GLP-1 receptor agonists, a Korean nationwide cohort²⁷ and a Danish national registry study²⁸ did not find a significant increase in DKA hospitalisation, and one large US claims analysis using non-SGLT2-inhibitor comparators broadly²⁹ likewise found no significant difference.

Differences among observational studies may reflect variation in populations, comparator drugs, follow-up, and outcome ascertainment. Registry studies based primarily on administrative coding may identify DKA differently from adjudicated clinical trials, particularly when glucose concentrations are not markedly elevated. These design differences limit direct comparison across data sources and support keeping the observational evidence separate from the randomised quantitative synthesis.

Certainty of the Evidence

Applying GRADE domains narratively to this outcome: the starting point is high certainty, since this is randomised evidence. Risk of bias is not a material concern, since these were large, blinded, placebo-controlled, adjudicated-endpoint trials with low attrition. Inconsistency is moderate ($I^2=34\%$ in the primary pool), with a plausible population-level explanation: the enrichment of CREDENCE for advanced kidney disease, and the directionally weaker, non-significant signal in the heart-failure subgroup described in section 3.3. Indirectness is low for the trial populations actually studied, but the review question, SGLT2 inhibitors and DKA in T2DM, only partially generalises to the growing population of non-diabetic patients now receiving these drugs for heart failure or CKD, and to acutely unwell inpatients, both under-represented or excluded from these outcome trials. Imprecision is the dominant concern: DKA was not a pre-specified primary or key secondary endpoint in any of these trials³¹, absolute event counts are small (fewer than 30 events in every trial except DECLARE-TIMI 58), three of eight trials have a zero-event arm, and the heart-failure subgroup in particular rests on only 12 SGLT2-inhibitor-arm events across two trials. On balance, the certainty of evidence for an increased relative risk of DKA with SGLT2 inhibitors in the trial populations studied is judged moderate, downgraded one level for imprecision and not downgraded further because the effect is directionally consistent across two independent pooling methods, biologically plausible, and corroborated by independent observational data using active comparators. Certainty for the heart-failure subgroup specifically is lower, and is better described as low, given the very small event count and the wide confidence interval that does not exclude a clinically relevant increase.

DISCUSSION

Clinical Interpretation

The pooled relative effect should be interpreted alongside the low absolute event rate. Across the included trials, the absolute excess corresponded to approximately 1.5 additional DKA events per 1,000 treated patients over the multi-year trial durations, with an approximate NNH of 670. Clinical interpretation should therefore consider both the rare but serious nature of DKA and the established cardiorenal benefits of SGLT2 inhibitors in appropriately selected patients.

For intensive care and perioperative practice specifically, three points follow directly from the mechanism and the trial data. First, a normal or only mildly elevated glucose does not exclude DKA in a patient on an SGLT2 inhibitor; an anion gap, venous or arterial blood gas, and beta-hydroxybutyrate, not urine ketones alone, which lag and can be falsely reassuring, should be checked in any such patient with unexplained metabolic acidosis, tachypnoea, nausea, or malaise³². Second, precipitants cluster in exactly the population intensivists see: sepsis, surgery, reduced oral intake, alcohol excess, and abrupt insulin dose reduction. Current perioperative guidance,

drawing on FDA labelling and recent anaesthesia-focused review, recommends withholding SGLT2 inhibitors for approximately three days, or roughly five drug half-lives, before elective major surgery and during acute intercurrent illness with reduced intake, restarting only once the patient is eating normally and the acute issue has resolved³³. A retrospective cohort of patients undergoing surgery while on an SGLT2 inhibitor found the incidence of perioperative euglycaemic DKA was significantly lower among those who discontinued the drug for at least three days beforehand, directly supporting this threshold rather than a shorter one³⁴. Where a three-day holiday is not feasible, as in emergency surgery, mitigation strategies such as preoperative insulin and glucose infusion can reduce the risk of euglycaemic DKA³⁵. Third, once euglycaemic DKA is diagnosed, management is largely conventional: discontinue the drug, start intravenous insulin, and correct volume and electrolytes, but concurrent dextrose infusion is typically required earlier and at a higher rate than in hyperglycaemic DKA, since the insulin infusion needed to switch off ketogenesis will otherwise drive hypoglycaemia^{36,37}.

Population Heterogeneity

The larger point estimate observed in CREDENCE may reflect differences in baseline renal and metabolic risk, but the present trial-level analysis cannot establish the mechanisms responsible for between-study variation. Longer diabetes duration, insulin dependence, and impaired renal function have been proposed as potential risk modifiers in other analyses. The subgroup findings in this review should therefore be considered hypothesis-generating rather than definitive.

Comparison with Existing Meta-Analyses

Two broader analyses provide useful context for the present findings. A 2023 systematic review and network meta-analysis of 36 randomised studies involving 52,264 patients found no statistically significant increase in DKA risk with SGLT2 inhibitors relative to placebo or active comparators. That analysis included many smaller and shorter glycaemic-efficacy trials with very few or no DKA events. Differences in study selection, exposure duration, population risk, and statistical approach may therefore contribute to the different pooled estimates, and neither analysis alone establishes that excess risk is confined to a particular population.

A more recent meta-analysis of 22 trials and 80,235 patients reported an overall relative risk of 2.32 (95% CI 1.64-3.27) and also described higher estimates in CKD and high-risk ASCVD populations than in heart-failure trials. The similarity in overall effect estimates provides external context for the present results, while the differences in trial selection and analytic methods should be considered when comparing the two evidence bases.

Limitations

This review has several limitations. First, it is a rapid, single-outcome synthesis using single-reviewer screening and extraction, without prospective protocol registration, individual patient data, or an exhaustive grey-literature search. Smaller phase 2 and 3 trials with no DKA events in either arm were not systematically retrieved and could influence a broader class-wide estimate. Second, DKA was an adverse-event outcome rather than a primary or key secondary endpoint in the included trials, and event definitions and adjudication procedures were not fully uniform. Third, DELIVER was excluded because consistent arm-level DKA counts could not be confirmed from the prespecified source set. Fourth, fixed-effect Peto pooling assumes a common underlying odds ratio, while moderate heterogeneity was observed. Fifth, active-comparator studies were excluded from the quantitative pool, so this analysis does not estimate comparative DKA risk against other glucose-lowering drug classes. Finally, generalisability is more limited for non-diabetic heart-failure populations and for acutely unwell or perioperative patients, who were under-represented in the outcome trials.

CONCLUSION

Across 55,385 participants in eight large placebo-controlled outcome trials, SGLT2 inhibitor therapy was associated with increased odds of DKA (Peto OR 2.39, 95% CI 1.60-3.57; Mantel-Haenszel OR 2.66, 95% CI 1.67-4.24), while the absolute incidence remained low. The heart-failure subgroup had a numerically smaller and non-significant estimate, but the formal subgroup interaction was not significant, so a true difference by indication cannot be concluded from these data. Clinicians should remain alert to DKA in patients receiving SGLT2 inhibitors who develop unexplained metabolic acidosis or compatible symptoms, including presentations without marked hyperglycaemia.

REFERENCES

1. Brown E, Heerspink HJL, Cuthbertson DJ, Wilding JPH. SGLT2 inhibitors and GLP-1 receptor agonists: established and emerging indications. *Lancet*. 2021;398(10296):262-276. [https://doi.org/10.1016/S0140-6736\(21\)00536-5](https://doi.org/10.1016/S0140-6736(21)00536-5)
2. Peters AL, Buschur EO, Buse JB, Cohan P, Diner JC, Hirsch IB. Euglycemic diabetic ketoacidosis: a potential complication of treatment with sodium-glucose cotransporter 2 inhibition. *Diabetes Care*. 2015;38(9):1687-1693. <https://doi.org/10.2337/dc15-0843>
3. Wheeler DC, James J, Patel D, Viljoen A, Ali A, Evans M, et al. SGLT2 inhibitors: slowing of chronic kidney disease progression in type 2 diabetes. *Diabetes Ther*. 2020;11(12):2757-2774. <https://doi.org/10.1007/s13300-020-00930-x>
4. Blau JE, Tella SH, Taylor SI, Rother KI. Ketoacidosis associated with SGLT2 inhibitor treatment: analysis of FAERS data. *Diabetes Metab Res Rev*. 2017;33(8):e2924. <https://doi.org/10.1002/dmrr.2924>

5. Nasa P, Chaudhary S, Shrivastava PK, Singh A. Euglycemic diabetic ketoacidosis: a missed diagnosis. *World J Diabetes*. 2021;12(5):514-523. <https://doi.org/10.4239/wjd.v12.i5.514>
6. American Diabetes Association Professional Practice Committee. 10. Cardiovascular disease and risk management: Standards of Care in Diabetes-2024. *Diabetes Care*. 2024;47(Suppl 1):S179-S218. <https://doi.org/10.2337/dc24-S010>
7. Mallappa M, Reddy GK, Jayaraman M. Euglycemic diabetic ketoacidosis—a rare cause for delayed extubation: case report. *Indian J Crit Care Case Rep*. 2024;3(3):83-85. <https://doi.org/10.5005/jp-journals-11006-0105>
8. Stevens A, Hersi M, Garritty C, Hartling L, Shea BJ, Stewart LA, et al. Rapid review method series: interim guidance for the reporting of rapid reviews. *BMJ Evid Based Med*. 2025;30(2):118-123. <https://doi.org/10.1136/bmjebm-2024-112899>
9. Yang S, Liu Y, Zhang S, Wu F, Liu D, Wu Q, et al. Risk of diabetic ketoacidosis of SGLT2 inhibitors in patients with type 2 diabetes: a systematic review and network meta-analysis of randomized controlled trials. *Front Pharmacol*. 2023;14:1145587. <https://doi.org/10.3389/fphar.2023.1145587>
10. Deeks JJ, Higgins JPT, Altman DG. Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 6.4. Cochrane; 2023.
11. Bradburn MJ, Deeks JJ, Berlin JA, Localio AR. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. *Stat Med*. 2007;26(1):53-77. <https://doi.org/10.1002/sim.2528>
12. Schwarzer G, Efthimiou O, Rücker G. Inconsistent results for Peto odds ratios in multi-arm studies, network meta-analysis and indirect comparisons. *Res Synth Methods*. 2021;12(6):849-854. <https://doi.org/10.1002/jrsm.1503>
13. Wang Y, Qin Y, Zhang J, Wu A, Qin X, Du L, et al. Sodium-glucose cotransporter-2 inhibitors and diabetic-ketoacidosis in T2DM patients: an updated meta-analysis and a Mendelian randomization analysis. *Clin Pharmacol Ther*. 2025;117(6):1661-1669. <https://doi.org/10.1002/cpt.3615>
14. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-2128. <https://doi.org/10.1056/NEJMoa1504720>
15. Filippatos G, Butler J, Farmakis D, Zannad F, Ofstad AP, Ferreira JP, et al. Empagliflozin for heart failure with preserved left ventricular ejection fraction with and without diabetes. *Circulation*. 2022;146(9):676-686. <https://doi.org/10.1161/CIRCULATIONAHA.122.059785>
16. EMPA-KIDNEY Collaborative Group. Empagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2023;388(2):117-127. <https://doi.org/10.1056/NEJMoa2204233>
17. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347-357. <https://doi.org/10.1056/NEJMoa1812389>
18. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381(21):1995-2008. <https://doi.org/10.1056/NEJMoa1911303>
19. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383(15):1436-1446. <https://doi.org/10.1056/NEJMoa2024816>
20. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380(24):2295-2306. <https://doi.org/10.1056/NEJMoa1811744>
21. Cannon CP, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med*. 2020;383(15):1425-1435. <https://doi.org/10.1056/NEJMoa2004967>
22. Kang YM, Melloni GEM, Cahn A, Raz I, Moura FA, Bhatt DL, et al. 1896-LB: Clinical features and C-peptide levels associated with diabetic ketoacidosis in patients with type 2 diabetes on dapagliflozin vs placebo—insights from DECLARE-TIMI 58. *Diabetes*. 2024;73(Suppl 1):1896-LB. <https://doi.org/10.2337/db24-1896-LB>
23. Neumiller JJ, Kalyani RR. How does CREDENCE inform best use of SGLT2 inhibitors in CKD? *Clin J Am Soc Nephrol*. 2019;14(11):1667-1669. <https://doi.org/10.2215/CJN.05340419>
24. Douros A, Lix LM, Fralick M, Dell'Aniello S, Shah BR, Ronksley PE, et al. Sodium-glucose cotransporter-2 inhibitors and the risk for diabetic ketoacidosis: a multicenter cohort study. *Ann Intern Med*. 2020;173(6):417-425. <https://doi.org/10.7326/M20-0289>
25. Fralick M, Schneeweiss S, Paterno E. Risk of diabetic ketoacidosis after initiation of an SGLT2 inhibitor. *N Engl J Med*. 2017;376(23):2300-2302. <https://doi.org/10.1056/NEJMc1701990>
26. Ueda P, Svanström H, Melbye M, Eliasson B, Svensson AM, Franzén S, et al. Sodium glucose cotransporter 2 inhibitors and risk of serious adverse events: nationwide register based cohort study. *BMJ*. 2018;363:k4365. <https://doi.org/10.1136/bmj.k4365>
27. Kim YG, Jeon JY, Han SJ, Kim DJ, Lee KW, Kim HJ. Sodium-glucose co-transporter-2 inhibitors and the risk of ketoacidosis in patients with type 2 diabetes mellitus: a nationwide population-based cohort study.

- Diabetes Obes Metab. 2018;20(8):1852-1858. <https://doi.org/10.1111/dom.13297>
28. Jensen ML, Persson F, Andersen GS, Ridderstråle M, Nolan JJ, Carstensen B, et al. 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. *Diabetes Care*. 2017;40(5):e57-e58. <https://doi.org/10.2337/dc16-2793>
29. Wang Y, Desai M, Ryan PB, DeFalco FJ, Schuemie MJ, Stang PE, et al. Incidence of diabetic ketoacidosis among patients with type 2 diabetes mellitus treated with SGLT2 inhibitors and other antihyperglycemic agents. *Diabetes Res Clin Pract*. 2017;128:83-90. <https://doi.org/10.1016/j.diabres.2017.04.004>
30. Sridharan K, Sivaramakrishnan G. Risk of diabetic ketoacidosis associated with sodium glucose cotransporter-2 inhibitors: a network meta-analysis and meta-regression. *J Clin Med*. 2024;13(6):1748. <https://doi.org/10.3390/jcm13061748>
31. Vaduganathan M, Docherty KF, Claggett BL, Jhund PS, de Boer RA, Hernandez AF, et al. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. *Lancet*. 2022;400(10354):757-767. [https://doi.org/10.1016/S0140-6736\(22\)01429-5](https://doi.org/10.1016/S0140-6736(22)01429-5)
32. Lau A, Bruce S, Wang E, Ree R, Rondi K, Chau A. Perioperative implications of sodium-glucose cotransporter-2 inhibitors: a case series of euglycemic diabetic ketoacidosis in three patients after cardiac surgery. *Can J Anaesth*. 2018;65(2):188-193. <https://doi.org/10.1007/s12630-017-1018-6>
33. Doroba O, Czapryniak L, Sanfilippo F, Andruszkiewicz P, Zawadka M. New therapeutic agents for type 2 diabetes: anaesthetic considerations. A narrative review. *Anaesthesiol Intensive Ther*. 2025;57(1):e231-e238. <https://doi.org/10.5114/ait/208895>
34. Takemura M, Ikemura K, Okuda M. Factors and preventive strategies for perioperative euglycemic diabetic ketoacidosis in patients with type 2 diabetes receiving sodium-glucose cotransporter 2 inhibitors: a retrospective study. *J Pharm Health Care Sci*. 2025;11:79. <https://doi.org/10.1186/s40780-025-00487-6>
35. Cardona Z, Friedman JG, Kamal N, Oakes DJ, Wallia A, Aleppo G, et al. Developing a protocol for management of euglycemic diabetic ketoacidosis. *Curr Diab Rep*. 2025;25(1):48. <https://doi.org/10.1007/s11892-025-01604-3>
36. Goudra B, Merli GJ, Green M. Glucose-lowering agents developed in the last two decades and their perioperative implications. *Pharmaceuticals (Basel)*. 2025;18(1):4. <https://doi.org/10.3390/ph18010004>
37. Fu EL, D'Andrea E, Wexler DJ, Paterno E, Paik JM. Safety of sodium-glucose cotransporter-2 inhibitors in patients with CKD and type 2 diabetes: population-based US cohort study. *Clin J Am Soc Nephrol*. 2023;18(5):592-601. <https://doi.org/10.2215/CJN.0000000000000115>