Clinical Features and C-Peptide Levels Associated With Diabetic Ketoacidosis in Patients With T2D on Dapagliflozin vs. Placebo: Insights From DECLARE-TIMI 58

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Background and Aims

- Diabetic ketoacidosis (DKA) is a serious complication of diabetes mellitus that occurs predominantly in people with type 1 diabetes mellitus (T1D).
- Although rare, DKA can occur with sodium-glucose cotransporter-2 inhibitor (SGLT-2i) use in people with type 2 diabetes mellitus (T2D).
- Due to the rare incidence, a comprehensive understanding of this condition is limited.
- Key clinical and laboratory findings associated with the risk of DKA in people with T2D with or without dapagliflozin treatment were explored.

Methods

- DECLARE-TIMI 58 was a cardiovascular outcome trial of dapagliflozin vs. placebo in people with T2D.
  - Those known or suspected to have type 1 diabetes were excluded.
- A total of 17,143 patients in the on-treatment safety analysis set were included.
- DKA cases were identified using criteria for definite or probable DKA as adjudicated by the TIMI clinical event committee:

DEFINITE DKA

- Clinical manifestation consistent with DKA with the following biochemical evidence:
  - Ketonemia ≥3.0 mmol/L and/or significant ketonuria (>2+ dipstick)
  - At least one of the following criteria suggesting high anion gap metabolic acidosis:
    - Arterial or venous pH ≤7.3
    - Serum bicarbonate ≤18 mEq/L
    - Anion gap [Na – (Cl + HCO3)] >10

PROBABLE DKA

- Does not meet strict criteria for definite DKA due to incomplete biochemical work-up, but clinical setting consistent with DKA and the absence of alternative diagnosis thought to be the primary cause of presentation

Tables and Figures

Figure 1. Risk of DKA by Treatment Arm in DECLARE-TIMI 58

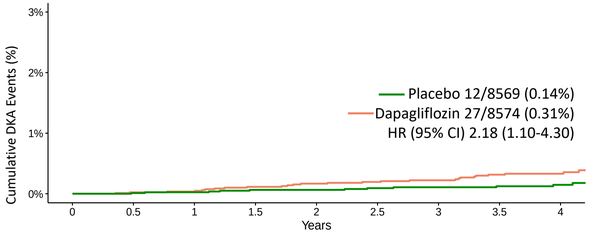


Table 1. Baseline Characteristics of Study Participants by DKA Events

Characteristic*	DKA (n=39)	No DKA (n=17,104)	p-value
Age (yrs)	62 (58 - 69)	64 (60 - 68)	0.68
Male Sex (%)	**43.6**	**62.6**	**0.02**
BMI (kg/m^2)	30.8 (27.0 - 33.8)	31.3 (27.8 - 35.4)	0.41
Weight (kg)	90.0 (72.0 - 100.2)	89.0 (76.3 – 103.0)	0.58
Duration of T2D (yrs)	**14 (10 - 18)**	**11 (6 - 16)**	**0.01**
HbA1c (%)	**9.0 (8.2 - 10.1)**	**8.0 (7.3 - 9)**	**<0.01**
HbA1c>10% (%)	**28.2**	**11.5**	**<0.01**
Insulin (uU/mL)	**9.6 (2.0 - 17.5)**	**18.3 (11.4 - 29.9)**	**<0.01**
C-peptide (nmol/L)	**0.2 (0.0 - 0.6)**	**1.0 (0.7 - 1.4)**	**<0.01**
C-peptide < 0.4 nmol/L (%)	**62.5**	**9.5**	**<0.01**
Serum Glucose (mmol/L)	9.3 (7.3 - 12.3)	9 (7.4 - 11.1)	0.69
Insulin/glucose ratio	**6.2 (1.6 - 12.2)**	**11.1 (6.8 - 18.3)**	**<0.01**
HOMA2-B%	**20.7 (14.1 – 48.0)**	**58.0 (38.5 - 84.5)**	**<0.01**
HOMA2-IR	**0.6 (0.5 - 1.5)**	**2.8 (1.8 - 3.9)**	**<0.01**
eGFR (mL/min/1.73m^2)	91 (76 - 113)	84 (71 - 99)	0.11
Ethnicity			
White	84.6	79.5	
Black	7.7	3.5	0.24
Asian	5.1	13.4	
Other	2.6	3.5	
Insulin use (%)	**82.1**	**40.8**	**<0.01**
Metformin use (%)	**64.1**	**82.0**	**<0.01**
Sulfonylurea use (%)	**12.8**	**42.8**	**<0.01**
DPP-4 inhibitor use (%)	10.3	16.9	0.38
GLP-1 use (%)	0	4.4	0.35
Diuretics use (%)	38.5	40.6	0.91

- **Expressed as median (interquartile range) unless specified otherwise.*
- *All laboratory assessments were performed in a fasting state.*

➢ People who had DKA were more likely to be female and insulin users, and to have longer duration of diabetes, worse HbA1c, and lower insulin and C-peptide levels at baseline.

Table 2. Triggering Factors for DKA by Treatment Arm

Precipitating Events (%)	Dapagliflozin (n=27)	Placebo (n=12)	p-value
Poor Intake of Food or Drink	44.4	50.0	1.00
Dehydration	48.1	50.0	1.00
Severe Illness	40.7	41.7	1.00
Infection	37.0	33.3	1.00
Missed Insulin Dose	37.0	50.0	0.68
Illness	25.9	41.7	0.54
Underdose of Insulin	18.5	16.7	1.00
Reduced Insulin Dose	14.8	8.3	0.97
Surgery	3.7	0	1.00

- *Patients could have had more than 1 triggering factor for DKA*

➢ Poor oral intake, severe illness, infection and missed insulin doses were the common triggering factors in both treatment arms.

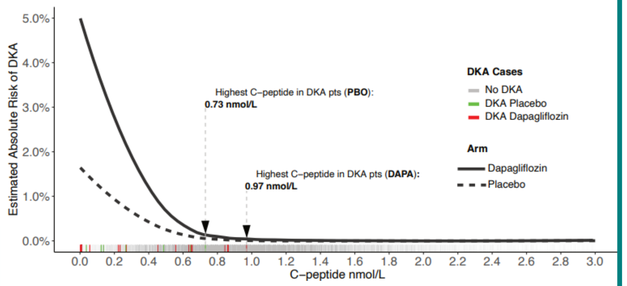
Table 3. Presentation Characteristics During DKA Events

Characteristic (%)	Dapagliflozin Arm (n=27)	Placebo Arm (n=12)	p-value
Median time to onset (weeks)	109 (63 - 169)	121 (62 - 187)	0.83
Euglycemic DKA*	3.7	0	1.00
Hyperglycemic DKA*	92.6	91.7	1.00
Ketonemia ≥3.0 mmol/L	33.3	25.0	0.89
Ketonuria > 2+ in dipstick	55.6	50.0	1.00
Arterial or Venous pH ≤7.3	66.7	66.7	1.00
Serum Bicarbonate ≤18 mEq/L	88.9	91.7	1.00
Anion Gap [Na – (Cl + HCO_3)] >10	59.3	66.7	0.93
Lactate < 2mmol/L	14.8	16.7	1.00
Severity of DKA			
Mild	11.1	33.3	
Moderate	29.6	16.7	0.39
Severe	51.9	41.7	
Not available	7.4	8.3	

- **Euglycemic DKA: DKA with the highest glucose in record <11 mmol/L (<200mg/dL)*
- **Two patients had missing peak glucose values at presentation (1 in each arm)*
- *Severity of DKA :*
  - *Mild: pH 7.25-7.30 and/or serum bicarbonate 15-18 mEq/L*
  - *Moderate: pH 7.00-7.24 and/or serum bicarbonate 10-<15 mEq/L*
  - *Severe: pH <7.00 and/or serum bicarbonate <10 mEq/L*

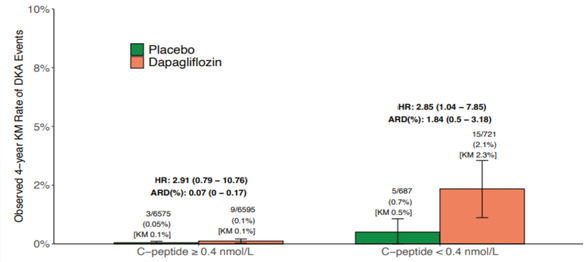
➢ Presentation characteristics were similar in the two arms.

Figure 2. Risk of DKA by Baseline C-peptide Levels



➢ No DKA events occurred in patients with fasting C-peptide > 0.97 nmol/L.

Figure 3. Risk of DKA by Treatment Arm and C-peptide Category



- *KM, Kaplan-Meier; ARD; absolute risk difference*

➢ In patients with fasting C-peptide ≥0.4 nmol/L, the excess in DKA with dapagliflozin was <1/1000 patients/year

Conclusions

- While DKA was more frequently observed with the dapagliflozin use in DECLARE-TIMI 58, the overall incidence remained very low and was mostly confined to participants with insulin deficiency in both treatment arms. Therefore, dapagliflozin can be administered to most people with T2D without significant concerns about DKA.
- Prospective C-peptide testing may help identify a small subset of the T2D population at higher risk of DKA, especially if clinical features indicate potential insulin deficiency (e.g., long duration of diabetes, exogenous insulin use, and poor glycemic control).

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