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ALLGEMEINE KINDERHEILKUNDE
DIABETOLOGIE, ENDOKRINOLOGIE,
KLINISCHE FORSCHUNG

ATTD International Consensus on Risk Management of Diabetic Ketoacidosis in Patients with Type 1 Diabetes Treated with Sodium-Glucose Cotransporter (SGLT) Inhibitors

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Disclosure of recent financial relationships

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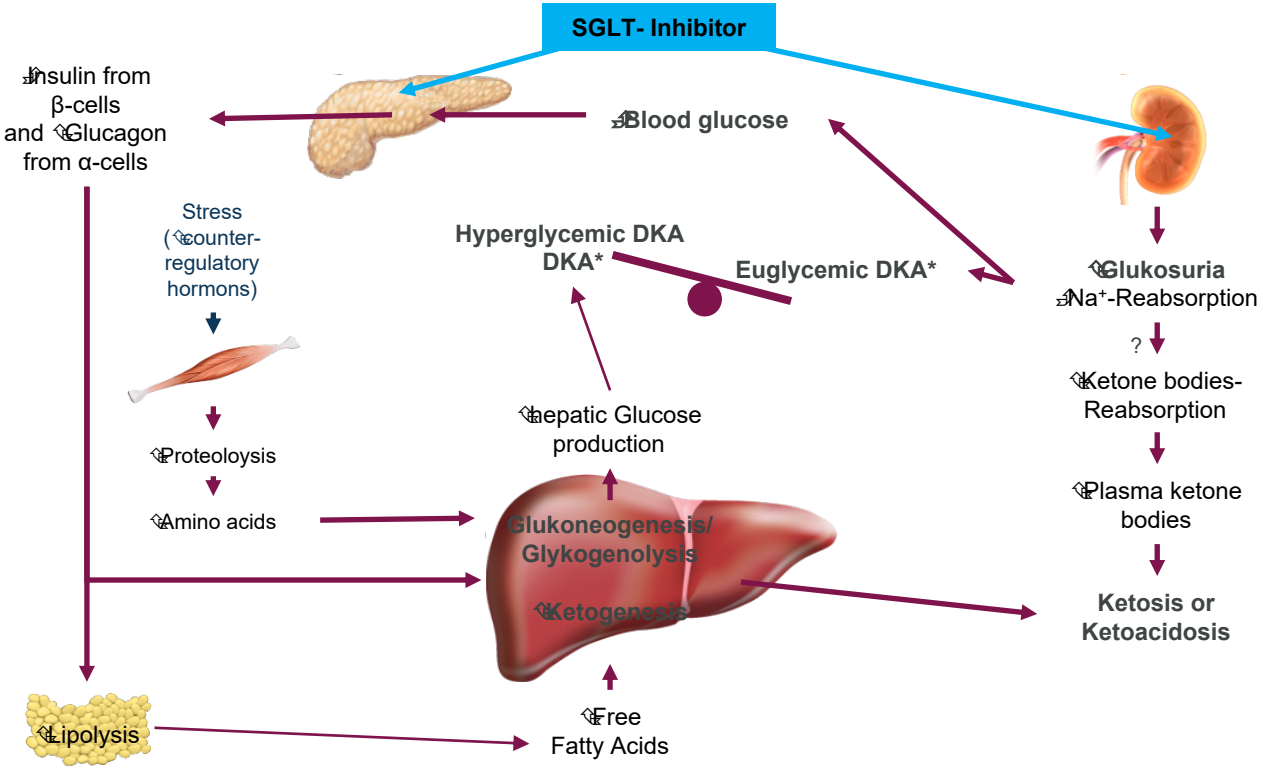
Speaker, advisory panel or research support

AstraZeneca, Bayer, Boehringer, Bristol-Myers Squibb, Dexcom, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Medtronic, Novo Nordisk, Roche, Sanofi, Unomedical, Ypsomed

Stock options/holdings/board of directors

DreaMed Diabetes, Ltd.

Ketoacidosis: Biggest Risik for Patients with SGLT inhibitors

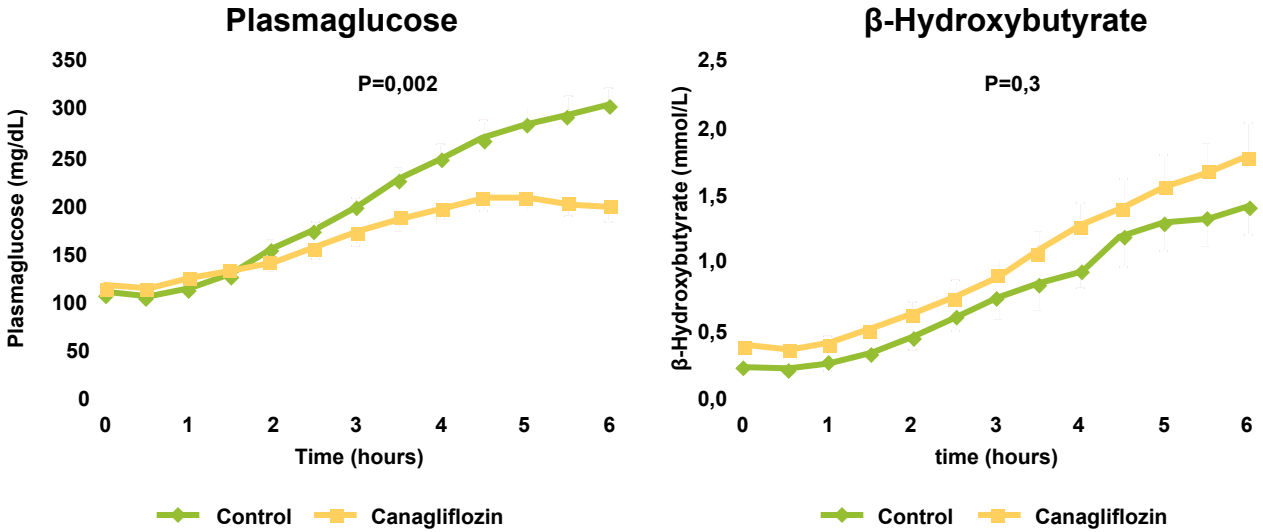


* The balance between hepatic glucose production and glucosuria determines euglycemic or hyperglycemic DKA
DKA, diabetic ketoacidosis

Modified from: Goldenberg RM, et al. Clin Ther 2016; 38:2654-64 e1.

*

Changes in early metabolic decompensation in canagliflozin-treated T1DM patients after basal insulin therapy was discontinued



The increase in β-hydroxybutyrate levels was similar among canagliflozin as in the control group. The gradual increase in plasma glucose with canagliflozin makes it more difficult for patients to detect early metabolic decompensation

T1DM, Typ 1 Diabetes mellitus.

Modified from: Patel NS, et al. Diabetes Technol Ther 2017; 19:618-22.

SGLT- Inhibitors as Add-on to insulin in T1DM DKA

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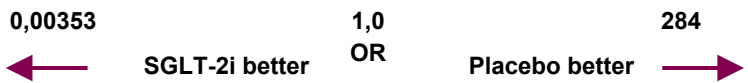
Diabetic Ketoacidosis

Studies	Substance	Phase	N	OR (95 %-KI)	Weight (%)	SGLT-2i (n/N)	Placebo (n/N)
Henry et al.	CANA	2	351	14,00 (0,80; 243,88)	5,40	(7/17)	(0/117)
Sands et al.	SOTA	2	33	4,25 (0,21; 87,34)	4,83	(2/16)	(0/17)
Henry et al.	DAPA	2a	70	0,87 (0,02; 40,68)	2,98	(0/15)	(0/13)
Pieber et al.	EMPA	2	75	1,06 (0,02; 50,43)	2,95	(0/18)	(0/19)
Kuhadiya et al.	DAPA	4	26	2,12 (0,11; 42,19)	4,93	(2/17)	(0/9)
Bode et al	SOTA	3	85	0,49 (0,02; 14,17)	3,89	(0/43)	(1/42)
Buse et al.	SOTA	3	793	16,37 (0,94; 283,52)	5,42	(8/262)	(0/268)
Danne et al.	SOTA	3	782	5,89 (0,30; 116,92)	4,94	(3/263)	(0/258)
Baker et al.	SOTA	2b	141	2,06 (0,07; 59,39)	3,90	(1/35)	(0/36)
Garg et al.	SOTA	3	1.402	5,28 (1,82; 15,30)	38,95	(21/699)	(4/703)
Dandona et al.	DAPA	3	519	1,46 (0,35; 6,07)	21,82	(5/296)	(3/260)
Overall				**3,38 (1,74; 6,56)**	**100,00**	**(49/1781)**	**(8/1742)**



(I^2=0%; Heterogenity p=0,77; Effect p<0,001)

CANA, Canagliflozin; DAPA, Dapagliflozin; EMPA, Empagliflozin; KI, Konfidenzintervall; OR, Odds-Ratio; SOTA, Sotaglilfozin; T1DM, Type 1 Diabetes mellitus.

* Modified from: Yamada T, et al. Diabetes Obes Metab 2018; doi 10.1111/dom.13260; [Epub ahead of print].

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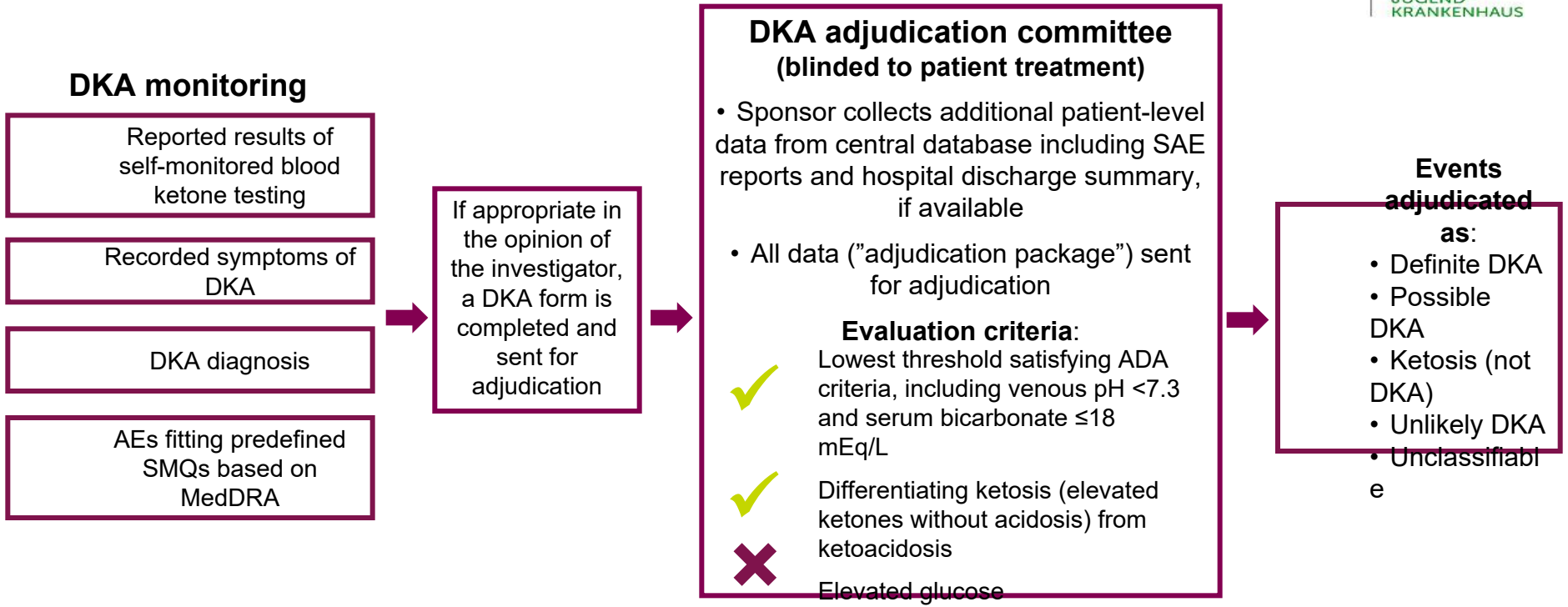
Original Research

International Consensus on Risk Management of Diabetic Ketoacidosis in Patients with Type 1 Diabetes Treated with Sodium-Glucose Cotransporter (SGLT) Inhibitors

Thomas Danne, Satish Garg, Anne L. Peters, John B. Buse, Chantal Mathieu, Jeremy H. Pettus, Charles M. Alexander, Tadej Battelino, F. Javier Ampudia-Blasco, Bruce W. Bode, Bertrand Cariou, Kelly L. Close, Paresh Dandona, Sanjoy Dutta, Ele Ferrannini, Spiros Fourlanos, George Grunberger, Simon R. Heller, Robert R. Henry, Martin J. Kurian, Jake A. Kushner, Tal Oron, Christopher G. Parkin, Thomas R. Pieber, Helena W. Rodbard, Desmond Schatz, Jay S. Skyler, William V. Tamborlane, Koutaro Yokote and Moshe Phillip

Diabetes Care 2019 Feb; dc182316.
https://doi.org/10.2337/dc18-2316

Process for DKA Monitoring and Adjudication in SGLT-Studies



ADA, American Diabetes Association; AE, adverse event; DKA, diabetic ketoacidosis; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; SMQ, standardized MedDRA query.

Danne T, et al. Supplementary Appendix. Online ahead of print. *Diabetes Care* 2019.

Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc18-2316/-/DC1.

Comparisons of DKA in SGLT-inhibitor Trials Cannot Be Made Due to Differences in the DKA Adjudication Processes[1]

	inTandem Program[2-4] (Sotagliflozin)	DEPICT Program[5-7] (Dapagliflozin)	EASE Program[8] (Empagliflozin)
Adjudicated DKA[a]			
Ketosis	**No, unlikely**	**Possible**	**Potential Ketosis**
No DKA or further limitations	**No, with certainty** **Unclassifiable** **Insufficient data**	**Unlikely**	**Unlikely** **Unclassifiable**

[a]As defined in each protocol.

DKA, diabetic ketoacidosis; SGLT, sodium-glucose cotransporter.

1. Danne T, et al. Online ahead of print. Diabetes Care 2019. 2. Buse JB, et al. Diabetes Care 2018; 41:1970-80; 3. Danne T, et al. Diabetes Care 2018; 41:1981-90; 4. Garg SK, et al. N Engl J Med 2017; 377:2337-48; 5. Dandona P, et al. Lancet Diabetes Endocrinol 2017; 5:864-76; 6. Mathieu C, et al. Diabetes Care 2016; 39:1702-10; 7. Dandona P, et al. Online ahead of print. Diabetes Care 2018; 8. Rosenstock J, et al. Online ahead of print. Diabetes Care 2018.

DKA in pivotal Sotagliflozin Trials (inTandem Program)

Supplementary Table 2. Incidence of reported DKA from Tandem1 and Tandem2

A. Diabetic ketoacidosis at 24 weeks inTandem1 and inTandem2

	inTandem1[1]			inTandem2[2]		
Dose	PBO	SOTA 200 mg	SOTA 400 mg	PBO	SOTA 200 mg	SOTA 400 mg
N	268	263	262	258	261	263
Patients with ≥1 Certain DKA event	0	3	8	0	2	3
Patients with ≥1 Probable DKA event	0	0	0	0	0	1
Certain + Probable DKA	0	3	8	0	2	4
% Patients with ≥1 Certain+ Probable DKA	0	1.1	3.1	0	0.8	1.5
% difference versus placebo in patients with Certain+ Probable DKA*	N/A	1.1	3.1	N/A	0.8	1.5

DKA=diabetic ketoacidosis; PBO=placebo; SOTA= sotagliflozin

B. Diabetic ketoacidosis at 52 weeks inTandem1 and inTandem2

	inTandem1[1]			inTandem2[2]			Total inTandem1 & 2[3]		
Dose	PBO	SOTA 200 mg	SOTA 400 mg	PBO	SOTA 200 mg	SOTA 400 mg	PBO	SOTA 200 mg	SOTA 400 mg
N	268	263	262	258	261	263	526	524	525
Patients with ≥1 Certain DKA event	0	9	11	0	5	8	0	14	19
Patients with ≥1 Probable DKA event	1	0	0	0	1	1	1	1	1
Certain + Probable DKA	1	9	11	0	6	9	1	15	20
% Patients with ≥1 Certain+ Probable DKA	0.4	3.4	4.2	0	2.3	3.4	0.2	2.9	3.8
% difference versus placebo of patients with Certain+ Probable DKA*	N/A	3.0	3.8	N/A	2.3	3.4	N/A	2.7	3.6

DKA=diabetic ketoacidosis; PBO=placebo; SOTA= sotagliflozin

References: 1. Buse B, et al. Diabetes Care 2018;41:1970–80 & Supplementary Appendix; 2. Danne T, et al. Diabetes Care 2018;41:1981–90 & Supplementary Appendix. 3. Garg SK et al. *N Engl J Med.* 2017;377:2337–2348.

Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc18-2316/-/DC1.

DKA in pivotal Dapagliflozin Trials (DEPICT Program)

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A. Diabetic ketoacidosis at 24 weeks in DEPICT-1 und DEPICT-2

	DEPICT-1[1]			DEPICT-2[2]		
Dose	**PBO**	**DAPA 5 mg**	**DAPA 10 mg**	**PBO**	**DAPA 5 mg**	**DAPA 10 mg**
N	260	277	296	272	271	270
Patients with ≥1 Definite DKA	3	4	5	0	7	6
Patients with ≥1 Possible DKA	1	5	7	2	6	4
Patients with ≥1 Unlikely DKA	3	8	8	7	8	4
% Patients with DKA as defined in the protocol (definite DKA)*	**1.2**	**1.4**	**1.7**	**0**	**2.6**	**2.2**
% difference versus placebo of patients with DKA as defined in the protocol (definite DKA)*	**N/A**	**0.2**	**0.5**	**N/A**	**2.6**	**2.2**

DKA=diabetic ketoacidosis; PBO=placebo; DAPA= dapagliflozin

B. Diabetic ketoacidosis at 52 weeks in DEPICT-1

	DEPICT-1[1]		
Dose	**PBO**	**DAPA 5 mg**	**DAPA 10 mg**
N	260	277	296
Patients with ≥1 Definite DKA	5	11	10
Patients with ≥1 Possible DKA	2	8	9
Patients with ≥1 Unlikely DKA	3	9	11
% Patients with DKA as defined in the protocol (definite DKA)*	**1.9**	**4.0**	**3.4**
% difference versus placebo of patients with DKA as defined in the protocol (definite DKA)	**N/A**	**2.1**	**1.5**

DKA=diabetic ketoacidosis; PBO=placebo; DAPA= dapagliflozin

References: Dandona et al. Lancet Diabetes Endocrinol. 2017 Nov;5(11):864-876; Mathieu C et al. DEPICT-2 Investigators. Diabetes Care. 2018 Sep;41(9):1938-1946. Dandona et al. Diabetes Care. 2018 Oct 23. pii: dc181087. doi: 10.2337/dc18-1087.

Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc18-2316/-/DC1.

DKA in pivotal Empagliflozin Trials (EASE Program)

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Supplementary Table 4. Diabetic ketoacidosis at 26 and 52 weeks: EASE-2 and EASE-3

	EASE-2 & -3 pooled* (EASE-2 up to 52 Weeks; EASE-3 up to 26 Weeks)			EASE-3 26 Weeks	
Dose	**PBO**	**EMPA 10 mg**	**EMPA 25 mg**	**PBO**	**EMPA 2.5 mg**
N	484	491	489	241	241
Patients with ≥1 Certain** DKA (n/%)	6 (1.2)	16 (3.3)	21 (4.3)	3 (1.2)	2 (0.8)
Patients with ≥1 Potential*** DKA (n/%)	6 (1.2)	13 (2.7)	15 (3.1)	1 (0.4)	3 (1.2)

DKA=diabetic ketoacidosis; PBO=placebo; DAPA= empagliflozin

Results from adjudication based on broad trigger search criteria (1. Investigator reported terms indicative of DKA; 2. All BHB readings >1.5 and < 3.8 mmol/l and clinical manifestations suggestive of ketoacidosis; 3. Any BHB reading ≥3.8 mmol/l). *Definition certain ketoacidosis: Acidosis and ketosis present; ** Definition potential ketoacidosis: Acidosis or ketosis with clinical manifestations suggestive of ketoacidosis

Reference: Rosenstock J, Marquard J, Laffel LM, et al. Empagliflozin as adjunctive to insulin therapy in type 1 diabetes: The EASE Trials. Diabetes Care. 2018;41(12):2560-2569.

Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc18-2316/-/DC1.

International Consensus on Risk Management of Diabetic Ketoacidosis in Patients with Type 1 Diabetes Treated with SGLT-inhibitors

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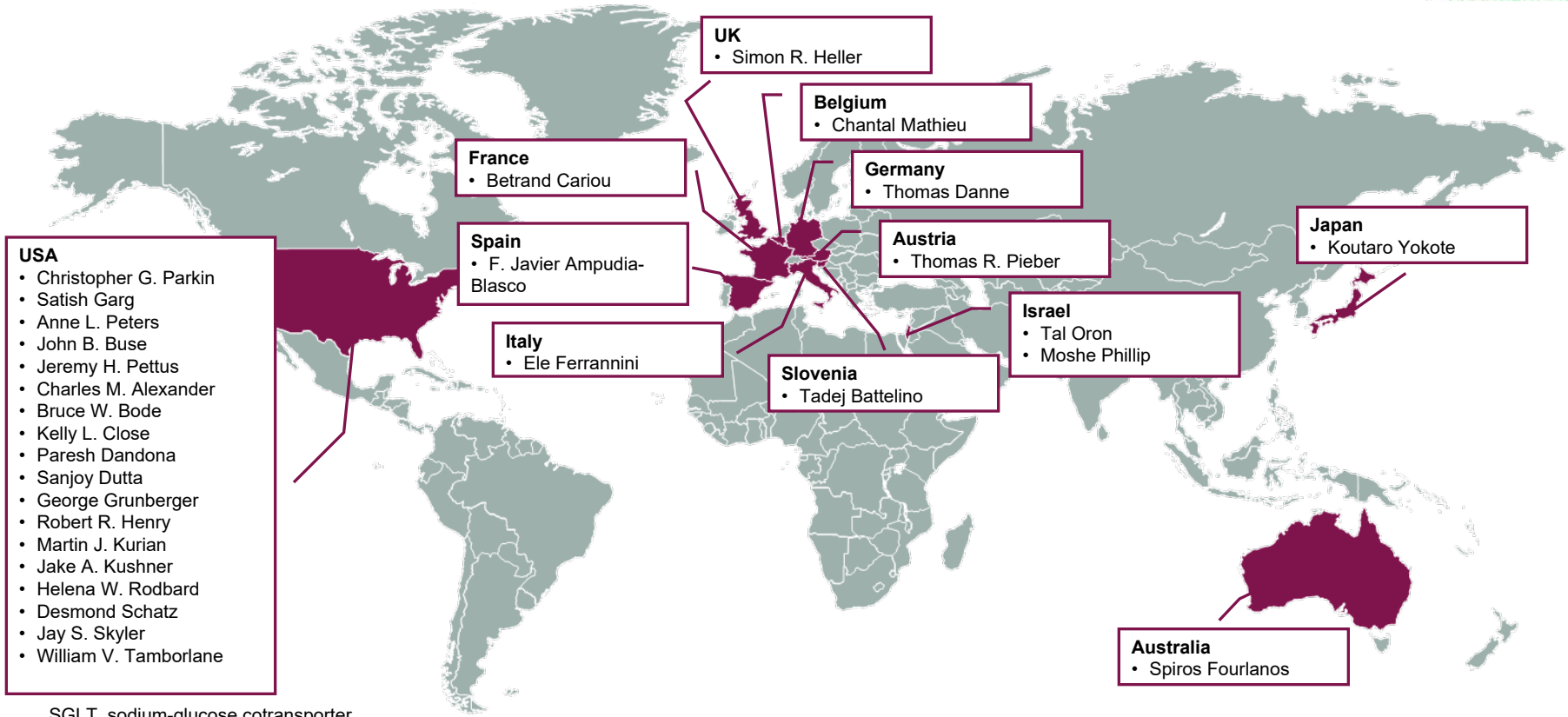

USA
- Christopher G. Parkin
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- Helena W. Rodbard
- Desmond Schatz
- Jay S. Skyler
- William V. Tamborlane

SGLT, sodium-glucose cotransporter.

Danne T, et al. Online ahead of print. *Diabetes Care* 2019

Patient Criteria for SGLT-inhibitor Therapy

- >18 years of age
- Adherent to prescribed diabetes regimen
- Willing/able to perform all prescribed diabetes self-management tasks
- Performs blood glucose monitoring or uses CGM as prescribed
- Willing/able to perform ketone testing as prescribed
- Has received education/training in ketone testing and interpreting/acting upon test results
- Has access to ketone testing materials
- Has immediate access to a clinician if blood or urine ketone levels are elevated
- No or moderate use of alcohol; no use of illicit drugs
- Unimpaired cognition
- Not pregnant or wanting to become pregnant

CGM, continuous glucose monitoring; SGLT, sodium-glucose cotransporter.

* Danne T, et al. Online ahead of print. *Diabetes Care* 2019.

Educational Components of a Risk Mitigation Strategy when Introducing SGLT-Inhibitors for Type 1 Diabetes

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Patient Education

All patients initiating SGLT-inhibitor therapy should receive thorough training/education in the following areas:

- DKA causes and symptoms
- Euglycemic ketoacidosis
- Importance of ketone monitoring
- Use of ketone monitoring – training in testing procedure, proactive monitoring, situations when monitoring is indicated
- Treatment protocol for addressing ketosis
- Guidance in when to seek medical attention

Clinician Education

All prescribing clinicians should acquire full understanding of the safe use and risks associated with SGLT-inhibitor therapy:

- Criteria for patient selection – baseline ketone level, demographic/behavioral considerations
- Training/educational needs of patients – detection (ketone levels, symptoms), prevention strategies, treatment
- Potential for missed DKA, euDKA
- Treatment strategies – STICH protocol recommended

Risk Communication

- Product labelling, Website
- HCP Education
- Medication Guide, Patient Alert Card

DKA, diabetic ketoacidosis; euDKA, euglycemic diabetic ketoacidosis; HCP, health care professional; SGLT, sodium-glucose cotransporter; STICH, Stop SGLT inhibitor, Insulin administration, Carbohydrate consumption and Hydration.

Danne T, et al. Online ahead of print. *Diabetes Care* 2019.

Risk Factors for DKA Associated with SGLT-inhibitor Therapy

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Moderate / High

- Reduced basal insulin by more than 10 to 20%
- Insulin pump or infusion site failure
- Reduced or inconsistent carbohydrate intake
- Excessive alcohol use
- Use of illicit drugs
- Volume depletion/dehydration
- Acute illness of any sort (viral or bacterial)
- Vomiting

Low / Moderate

- Vigorous or prolonged exercise
- Reduced prandial insulin dose by more than 10 to 20%
- Travel with disruption in usual schedule/insulin regimen
- Insulin pump use

Minimal / Low

- Low BMI (<25 kg/m^2)
- Inconsistent caloric intake
- Moderate alcohol use[a]
- Female sex

[a]If ketone levels increase from baseline.

BMI, body mass index; DKA, diabetic ketoacidosis.

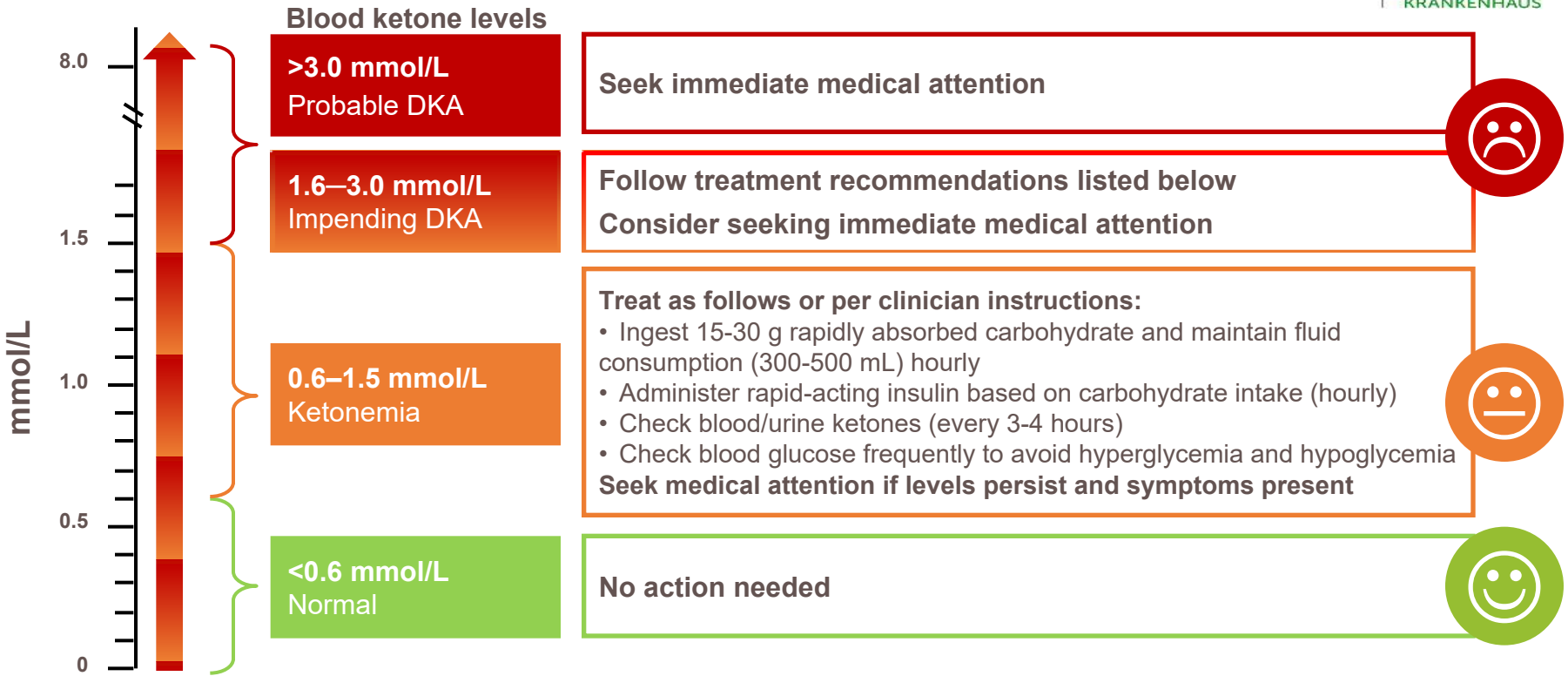
* Danne T, et al. Online ahead of print. Diabetes Care 2019.

Proposed DKA Risk Mitigation Strategy for SGLT-inhibitors

SGLT-inhibitor dosing	▪ Start with lowest dose ▪ Do not start if BHB > 0.60 mmol/L or urine ketones >2+
History of recent or recurrent DKA	▪ Do not start treatment in patients with history of DKA (1 episode in the past 3 months or more than 1 episode in the past 6 months)
Insulin pump use	▪ Patients well trained on pump use ▪ Review strategies to identify and mitigate suspected insulin interruptions ▪ Ketones should be checked prior to insulin interruption ○ Consider ketone check with every pump set change
Ketone monitoring	▪ Ability to test ketones & compliance with monitoring prior to starting ▪ Do not start if > 0.60 mmol/L ▪ Ketone monitoring prior to initiation and individualized monitoring thereafter ▪ Ketone checks in high risk situations (e.g. signs/symptoms of DKA, acute illness), despite minimally elevated glucose, with management of elevated ketones per Sick Day rules
Insulin dosing	▪ Optimize insulin prior to starting therapy and during therapy

BHB, β-hydroxybutyrate; DKA, diabetic ketoacidosis; SGLT, sodium-glucose cotransporter.
Danne T, et al. Online ahead of print. *Diabetes Care* 2019.

Cut-points for DKA and corresponding remedial actions



DKA, diabetic ketoacidosis.

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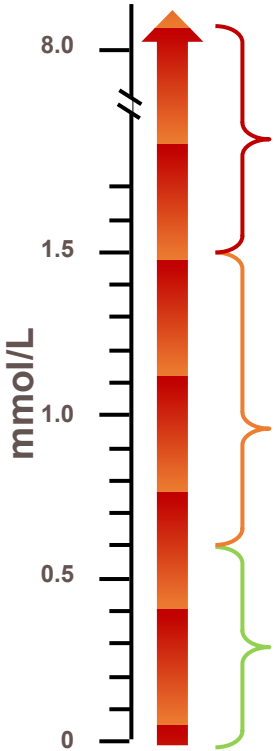
Cut-points for DKA and corresponding remedial actions



Blood ketone levels	Urine ketone levels[a]	
>3.0 mmol/L Probable DKA	**Large to very large** +++ / ++++	**Seek immediate medical attention**
1.5–3.0 mmol/L Impending DKA	**Moderate** ++	**Follow treatment recommendations listed below** **Consider seeking immediate medical attention**
0.6–1.5 mmol/L Ketonemia	**Trace or small** +	**Treat as follows or per clinician instructions:** • Ingest 15-30 g rapidly absorbed carbohydrate and maintain fluid consumption (300-500 mL) hourly • Administer rapid-acting insulin based on carbohydrate intake (hourly) • Check blood/urine ketones (every 3-4 hours) • Check blood glucose frequently to avoid hyperglycemia and hypoglycemia **Seek medical attention if levels persist and symptoms present**
<0.6 mmol/L Normal	**Negative**	**No action needed**

[a]Urine ketone concentrations are dependent on hydration and other factors; these values do not closely correlate with blood BHB levels.
DKA, diabetic ketoacidosis; BHB, β-hydroxybutyrate.
Danne T, et al. Online ahead of print. *Diabetes Care* 2019.

STICH Protocol – Recommended Treatment Strategies

ST

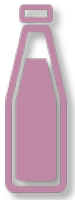
- **STop SGLT-inhibitor for a few days**

I

- **Insulin administration**

C

- **Carbohydrate consumption**



H

- **Hydration with suitable drink** (e.g. water or non-caloric athletic drink with balanced electrolytes)

DKA, diabetic ketoacidosis; SGLT, sodium-glucose cotransporter.

Garg S, et al. Diabetes Technology & Therapeutics Sep 2018.ahead of print http://doi.org/10.1089/dia.2018.0246

Danne T, et al. Online ahead of print. *Diabetes Care* 2019.

Conclusions

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As observed in clinical trials, the rate of DKA in the placebo arm is substantially less than incidence rates from latest registries where the incidence of DKA with SGLT inhibitor therapy is relatively low.

The absolute risk increase in SGLT inhibitor treated patients vs placebo-treated patients was in the range of 4% per year, and in these clinical patients, it was lower than reported in general practice but still higher than seen with placebo.

The potential benefits of SGLT inhibitors for people with T1D appear clinically meaningful. Thus, strategies for mitigating DKA risk are vital to the adoption and safe use SGLT- inhibitors in all diabetes populations particularly those requiring insulin.

Our goal is to provide a starting point for the safe use of SGLT-inhibitor therapy in this population and to encourage additional investigations that will provide more comprehensive, evidence-based- guidance for clinicians and patients

Greetings from the Hannover Team!

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