Analysis of SGLT2 inhibitor use in patients with type-1 diabetes mellitus and rates of diabetic ketoacidosis

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Conflict of Interest

The authors report no conflict of interest.

The views expressed are those of the authors and should not be construed to represent views of the FDA or the U.S. government.

Background

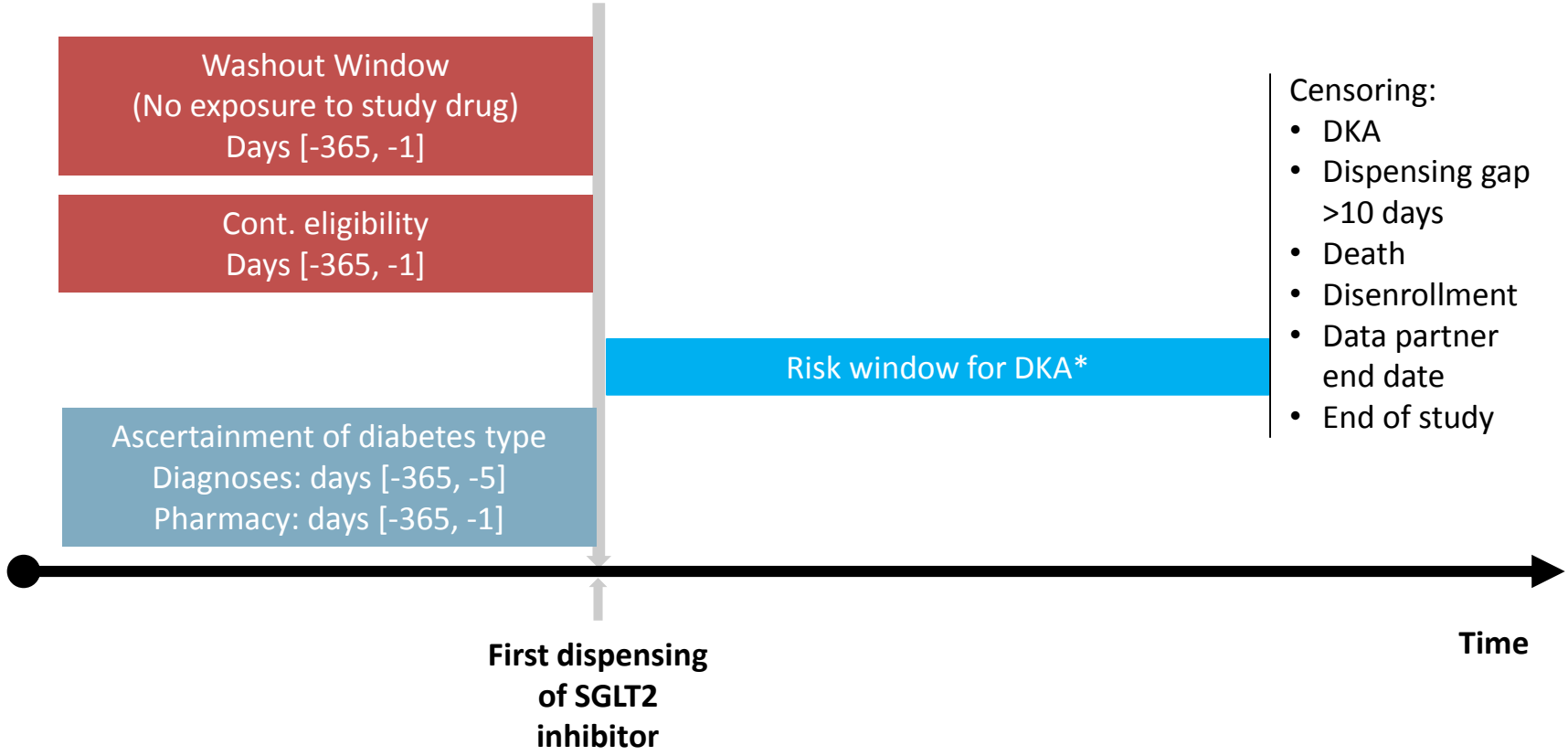
- Sodium-glucose cotransporter (SGLT)-2 inhibitors are indicated for patients with T2DM
- Clinical trials of sotagliflozin, an investigational dual SGLT1/2 inhibitor, demonstrated a dose-dependent, increased risk of diabetic ketoacidosis (DKA) in patients with T1DM
- DKA is a life-threatening complication of diabetes
- Risks and benefits discussed at January 17, 2019, Endocrinologic and Metabolic Drugs Advisory Committee meeting

Objectives

1. Estimate the extent of real-world off-label utilization of SGLT2 inhibitors in patients with T1DM
2. Estimate real-world rates of DKA following exposure to SGLT2 inhibitors among patients with T1DM
3. Compare the observed and expected rates of DKA during off-label use of approved SGLT2 inhibitors in patients with T1DM, using data from sotagliflozin clinical trials as the reference

Sentinel analysis

Administrative claims data from 17 Sentinel data partners, from 3/2013-6/2018, new users of SGLT2 inhibitors



*DKA: Inpatient or emergency department diagnosis with an ICD-9-CM code 250.1x or and ICD-10 code E1x.1x

Ascertainment of T1DM

Adaptation of validated algorithms*:

T1DM-narrow:

- majority (> 50%) of diabetes diagnosis codes during the baseline period were specific to T1DM
- at least one prescription for a short- or rapid-acting insulin, and
- no oral antidiabetic drug dispensing (other than metformin) during the baseline period

Maximize T1DM PPV for analysis of DKA rates

T1DM-broad:

- majority (> 50%) of diabetes diagnosis codes during the baseline period were specific to T1DM

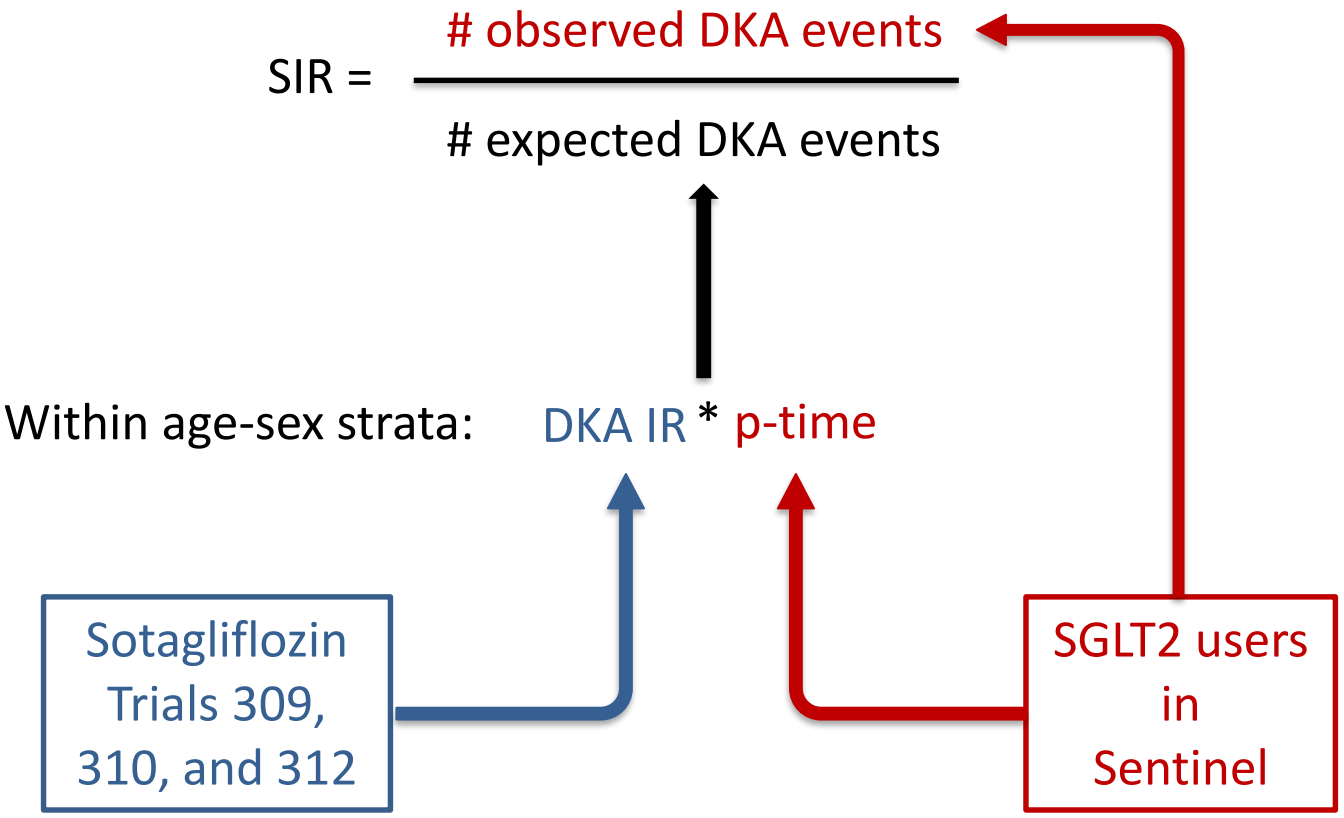
Maximize T1DM sensitivity for analysis of off-label utilization

*Klompas, 2013, Schroeder 2018

Secondary analyses

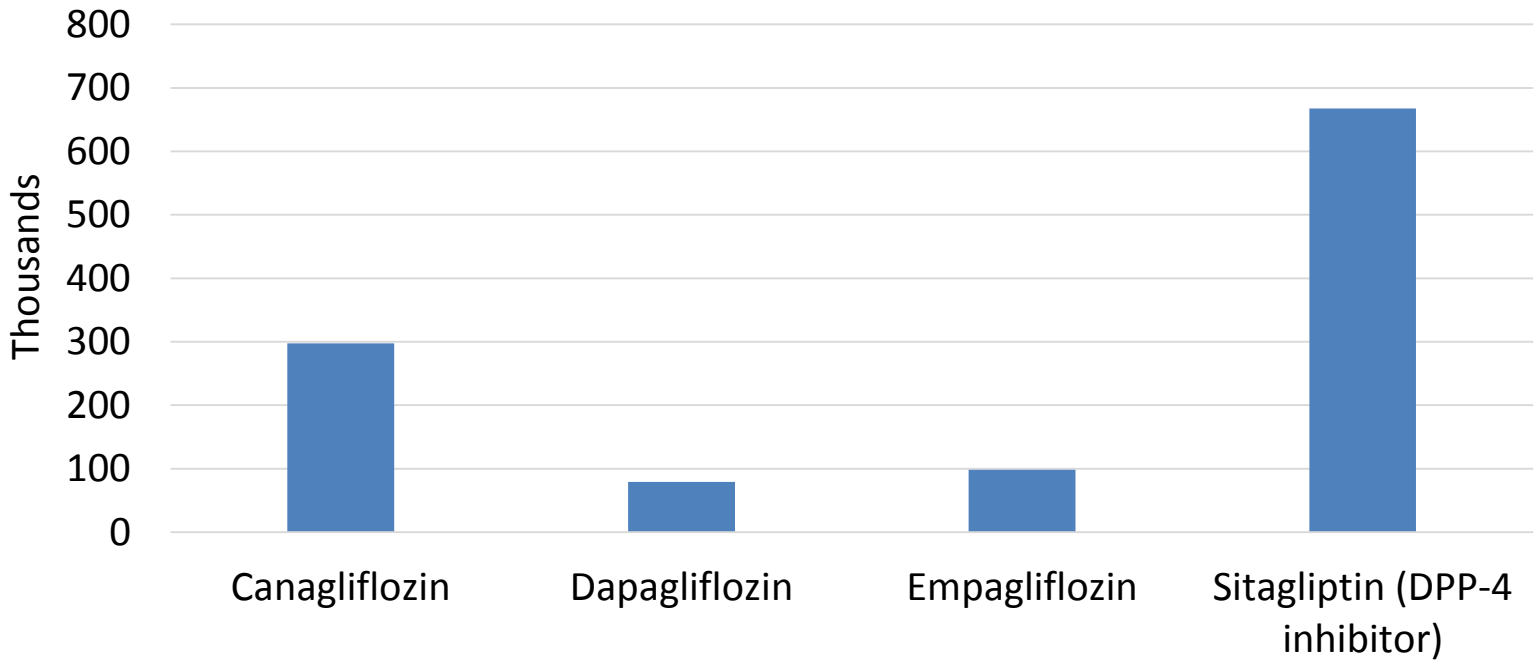
- Repeated analysis with sitagliptin, a DPP-4 inhibitor, primarily to gauge performance of the diabetes algorithms (off-label use for T1DM expected to be low)
- Performed all analyses in patients with T2DM

Standardized incidence ratios



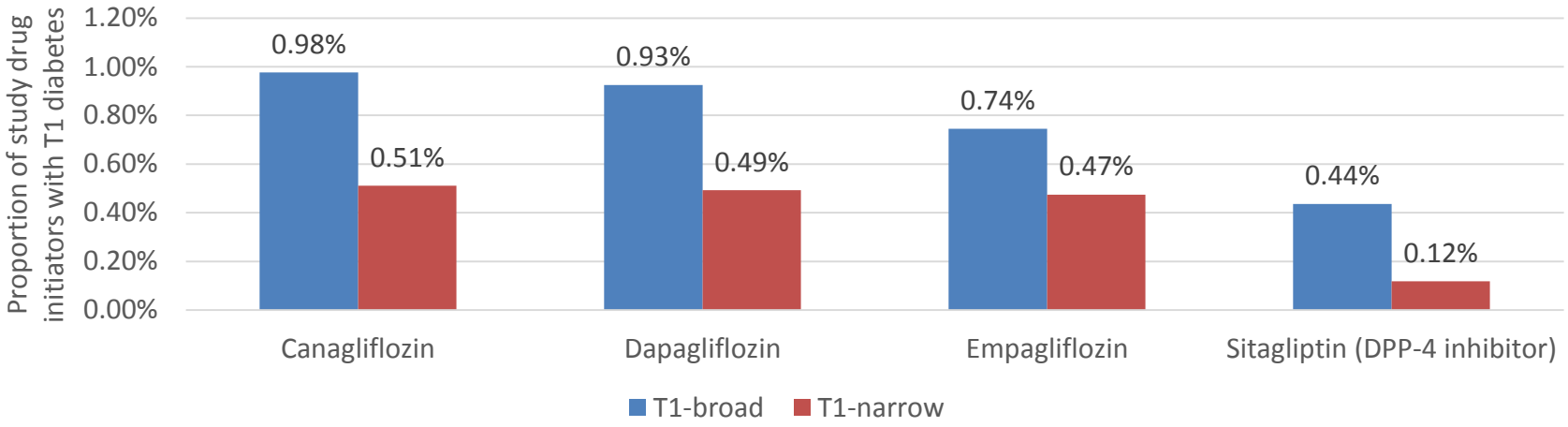
Results

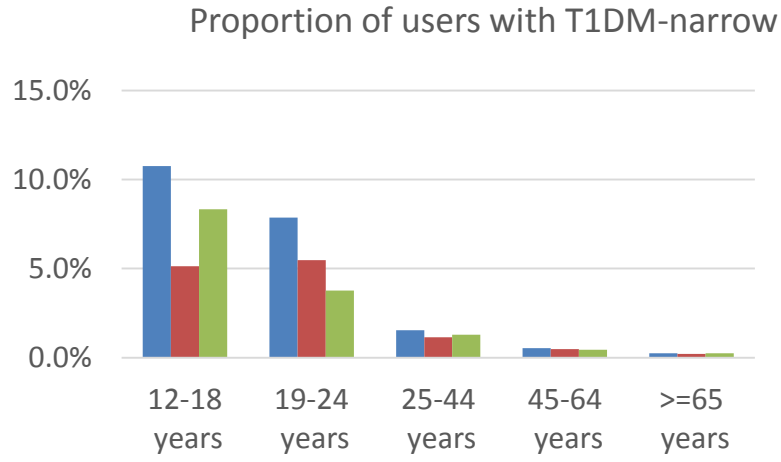
Initiators of study drugs, any diabetes type

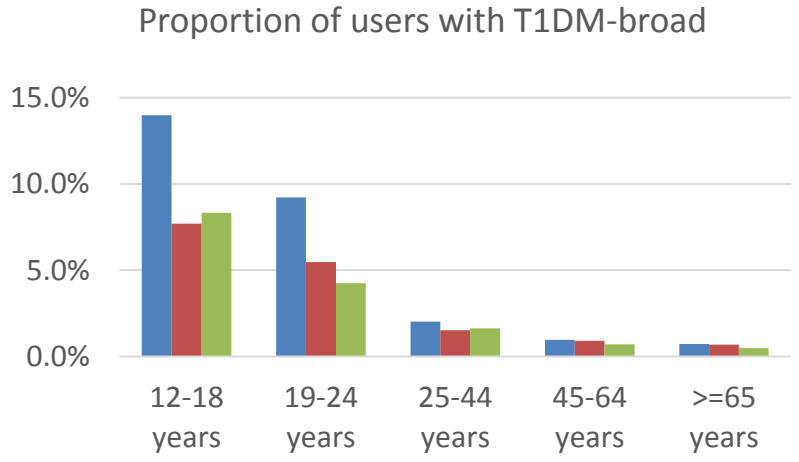


Mean age	61.8	58.9	59.5	67.2
% female	47.9	47.0	44.0	52.1

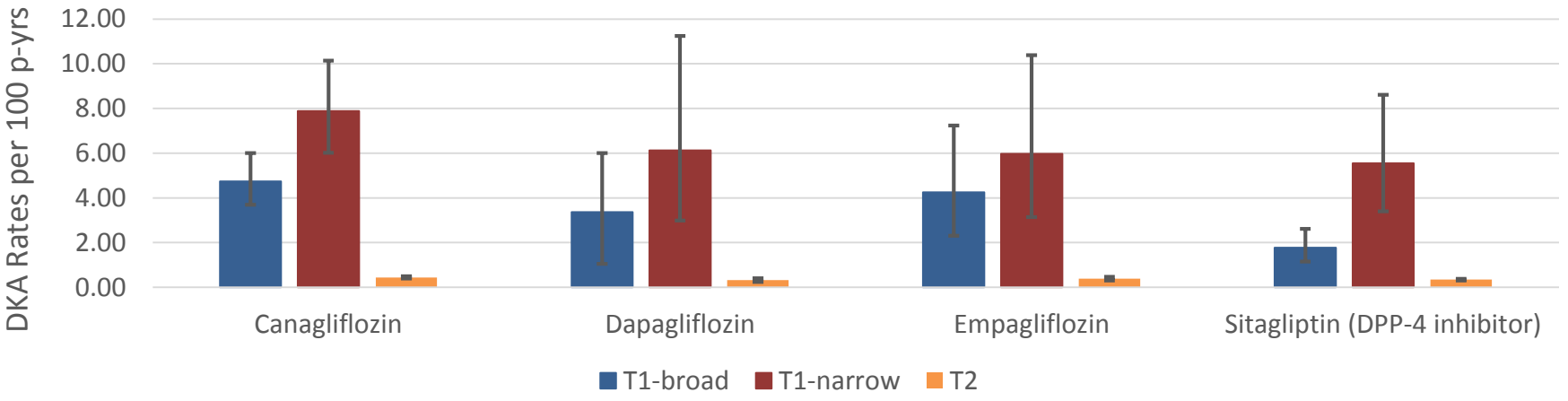
Proportion of SGLT2 inhibitor users with T1DM

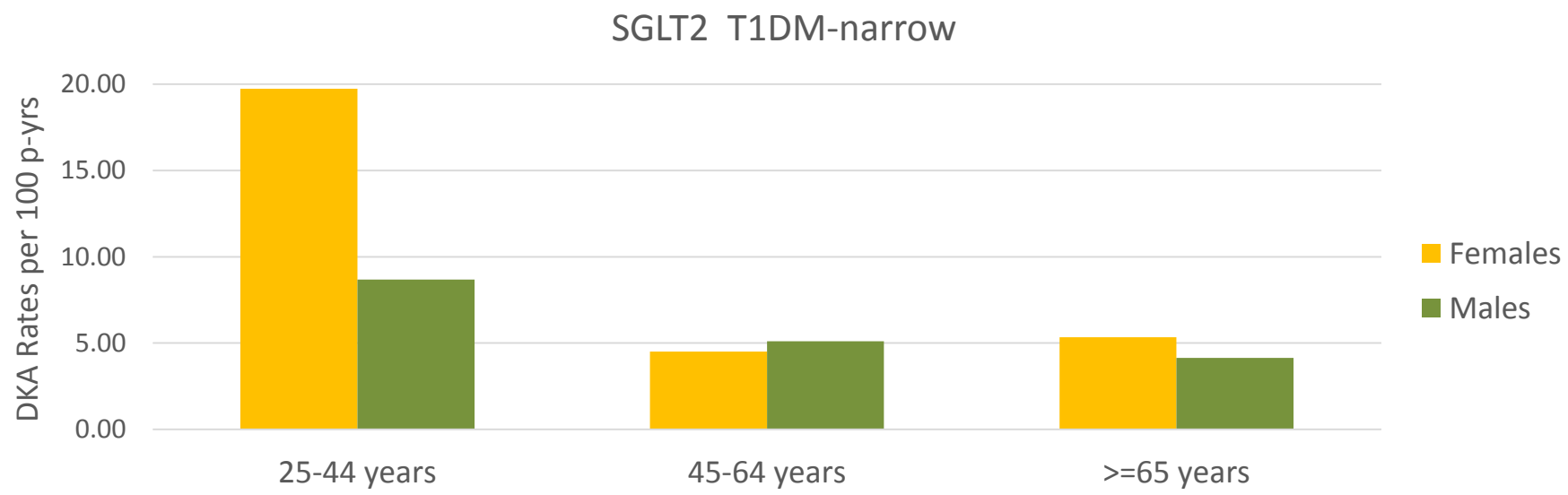




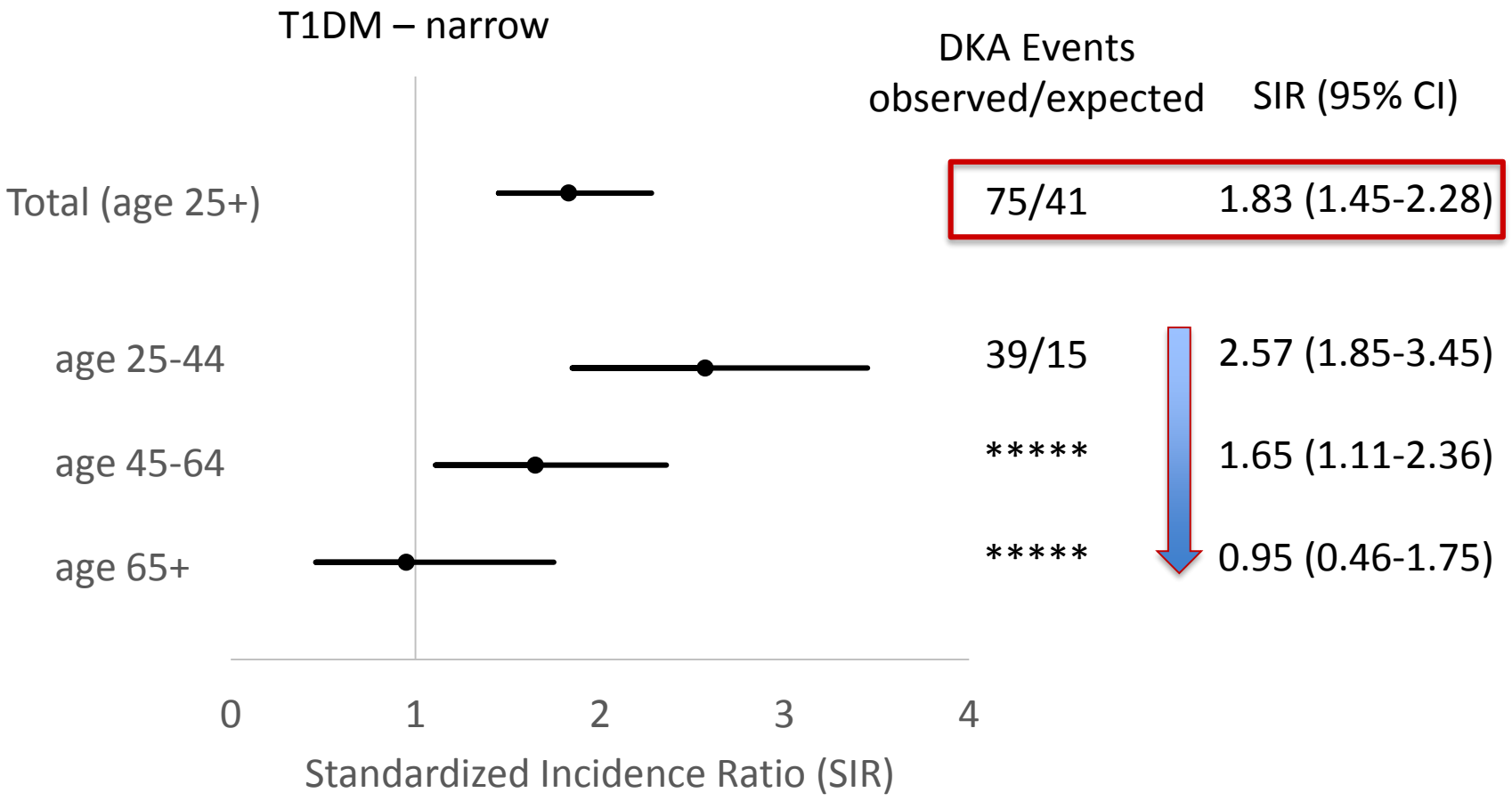


SGLT2 inhibitor DKA rates





Standardized incidence ratios for DKA



***** Data are not presented due to a small sample size or to assure a small cell cannot be recalculated through the cells presented.

Strengths and Limitations

- Sentinel:
  - Large, diverse database
  - Represents commercially insured, Medicare
  - Underrepresents Medicaid, uninsured
- T1DM-narrow may have missed patients with T1DM -> underestimated T1DM exposure rates
- T1DM-broad may have missed patients with T1DM to a lesser degree, but may have included some T2DM patients
- Study is descriptive – does not support causal inference

Comparison of clinical trial with Sentinel data

Some factors may have led to **higher or lower DKA rates** in Sentinel compared with clinical trials:

- Event definition and adjudication procedures
- Trial subjects educated on how to prevent DKA
- Differences in DKA risk between the approved SGLT2 inhibitors and sotagliflozin
- Samples: inclusion/exclusion criteria, international vs. US, etc.

Summary

- Off-label use of SGLT2 inhibitors in patients with T1DM was relatively infrequent.
- Among patients who used SGLT2 inhibitors off-label, the risk for DKA was notable, and higher among patients under the age of 45, especially females.
- DKA rates observed in Sentinel were higher than expected based on the sotagliflozin clinical trials.

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