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

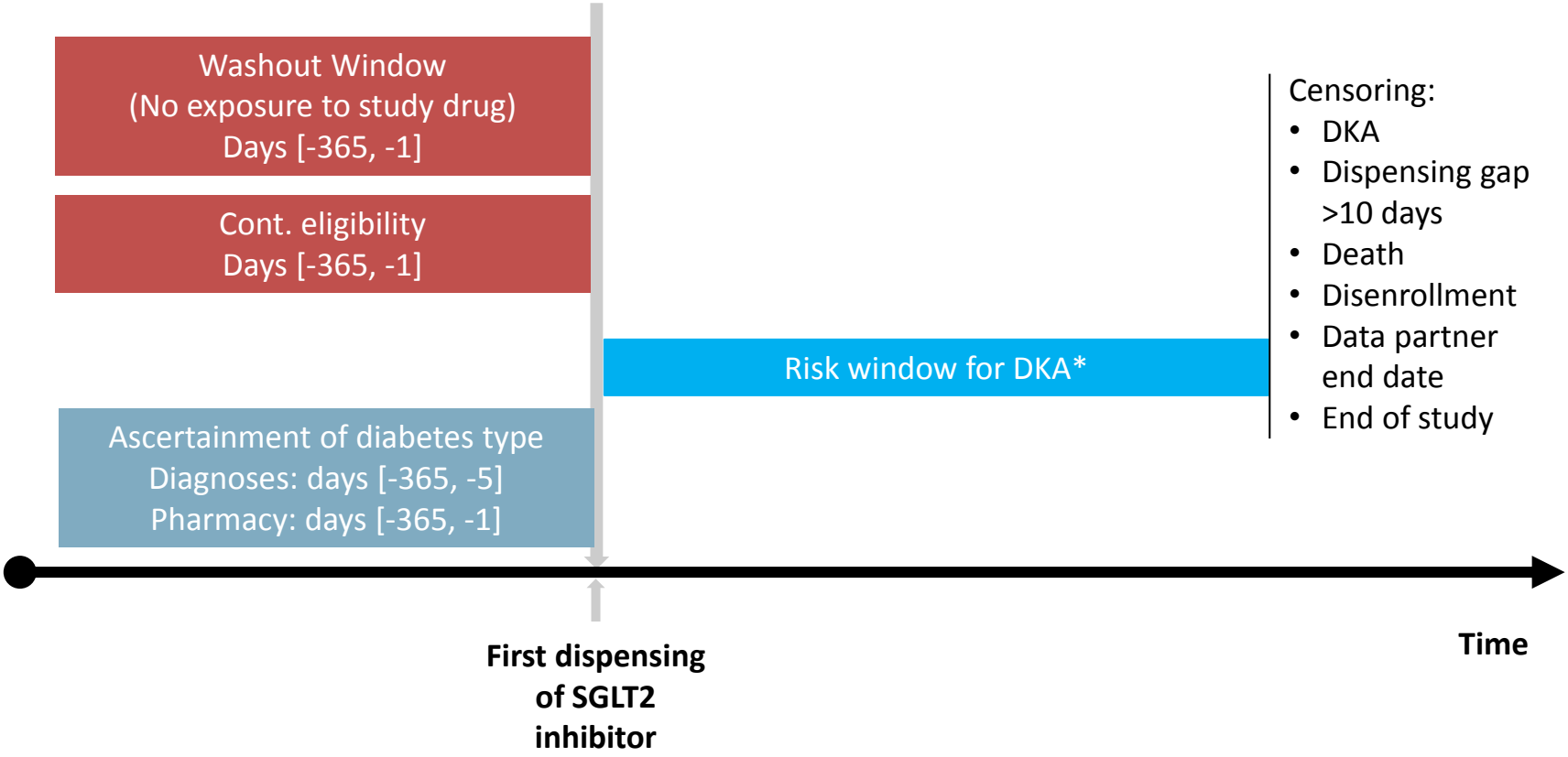
- Sodium-glucose cotransporter (SGLT)-2 inhibitors are indicated for patients with T2DM
- In patients with T1DM, clinical trials of sotagliflozin, an investigational dual SGLT1/2 inhibitor, demonstrated a dose-dependent, increased risk of diabetic ketoacidosis (DKA)
- DKA is a life-threatening complication 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:

- plurality (> 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:

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

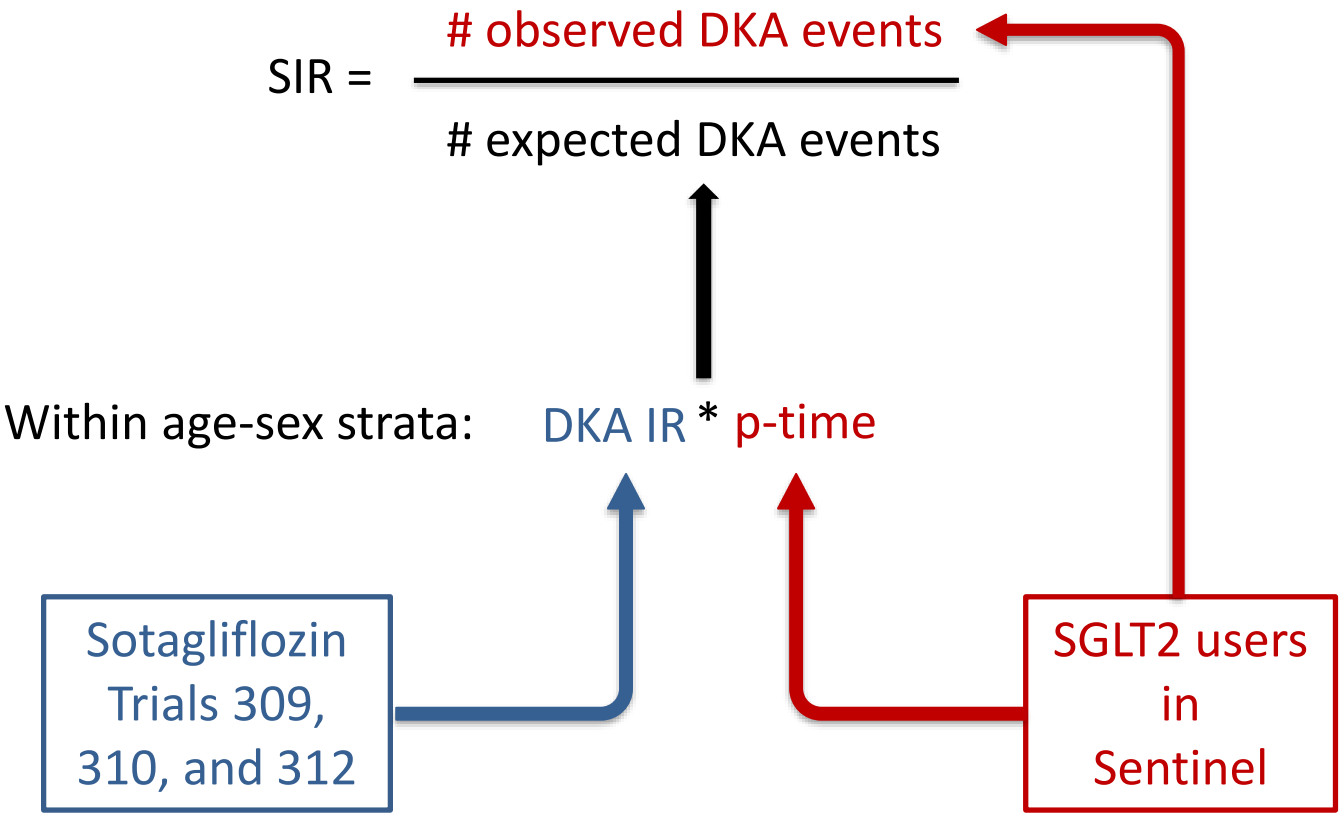
Maximize T1DM sensitivity for analysis of off-label utilization

*Klompas, 2013, Schroeder 2018

Secondary analyses

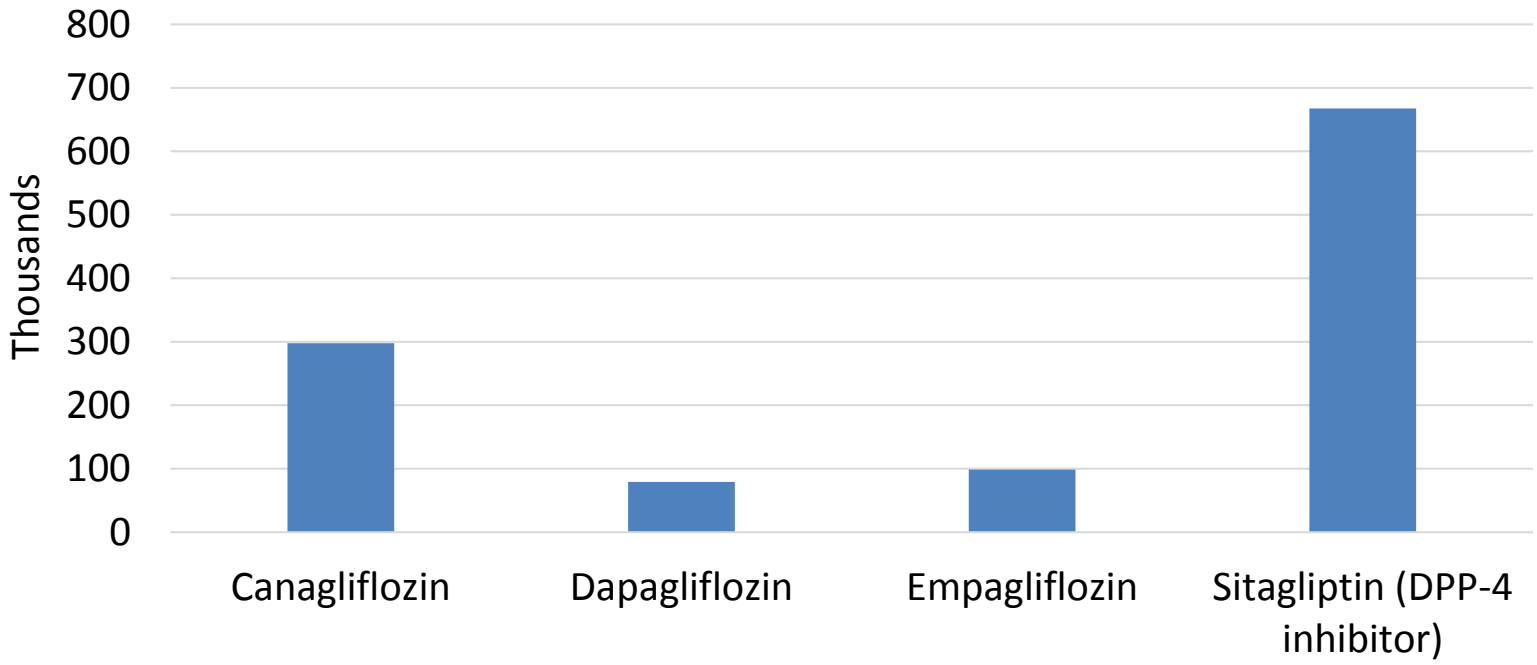
- Repeated analysis with sitagliptin, a DPP-4 inhibitor, primarily to gauge performance of the diabetes algorithms (off-label use for T1DM expected to be low)
- Performed all analyses in patients with T2DM

Standardized incidence ratios



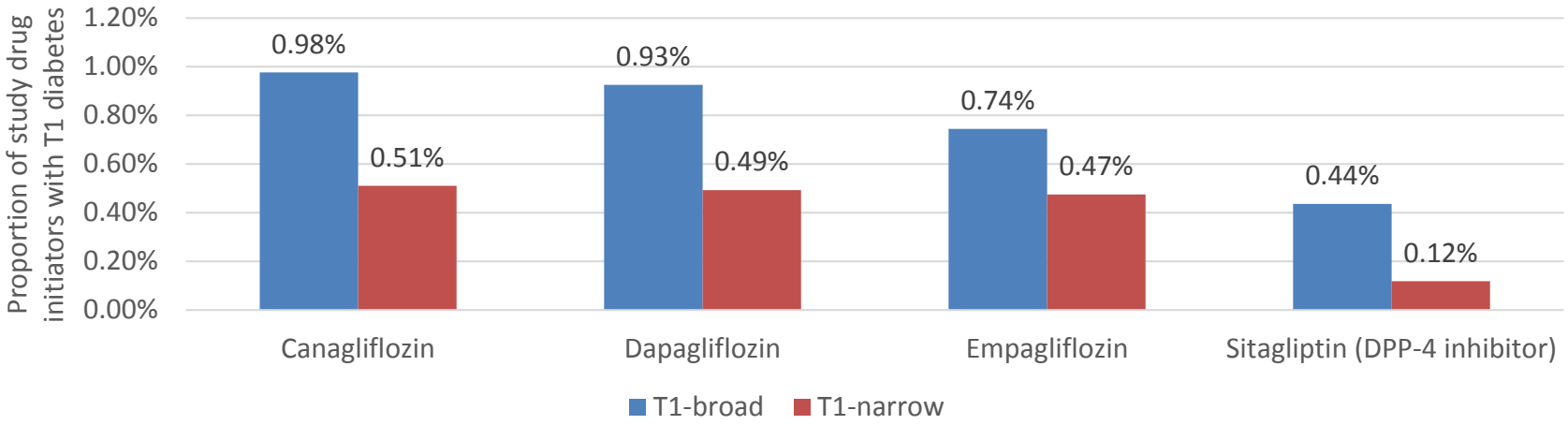
Results

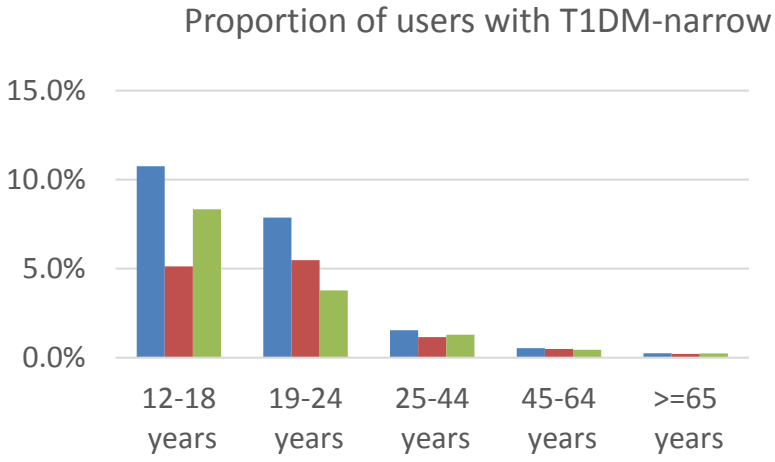
Initiators of study drugs, any diabetes type

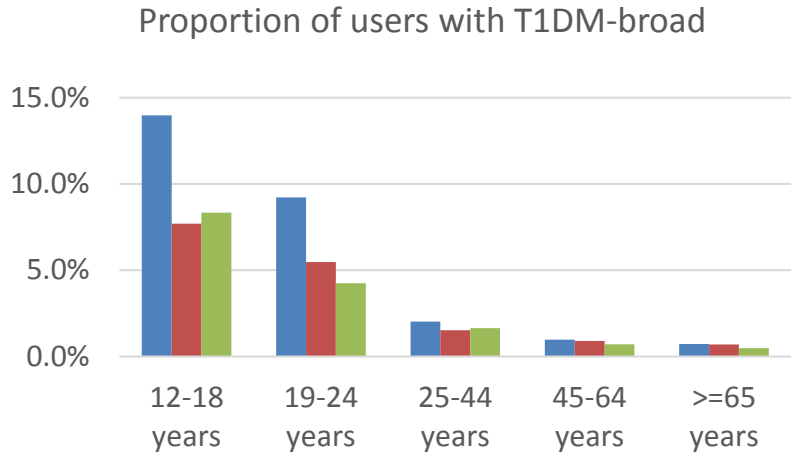


Mean age	61.8	58.9	59.5	67.2
% male	52.1	53.0	56.0	47.9

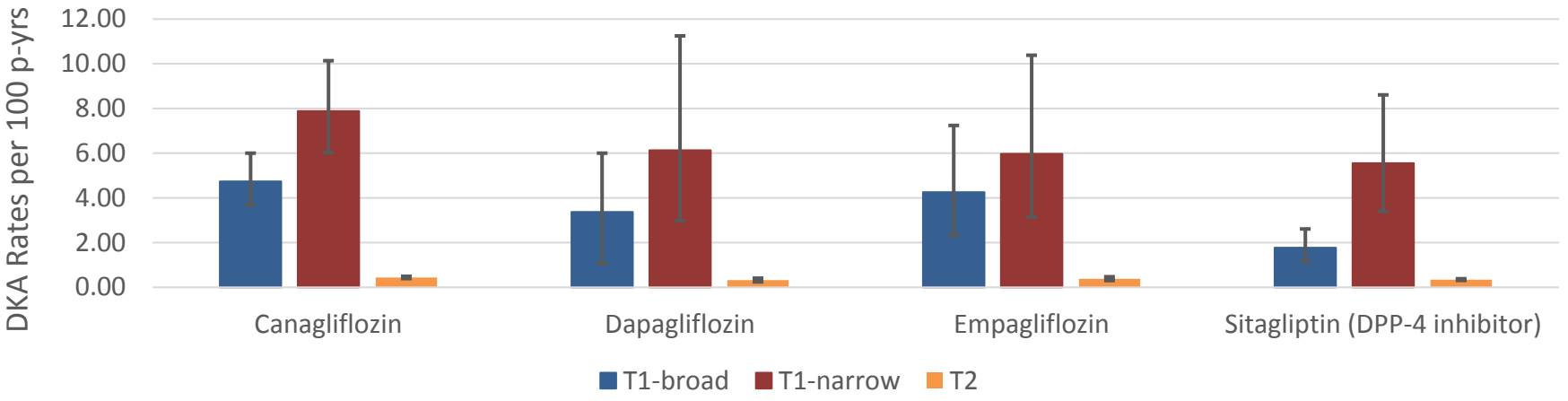
Proportion of SGLT2 inhibitor users with T1DM

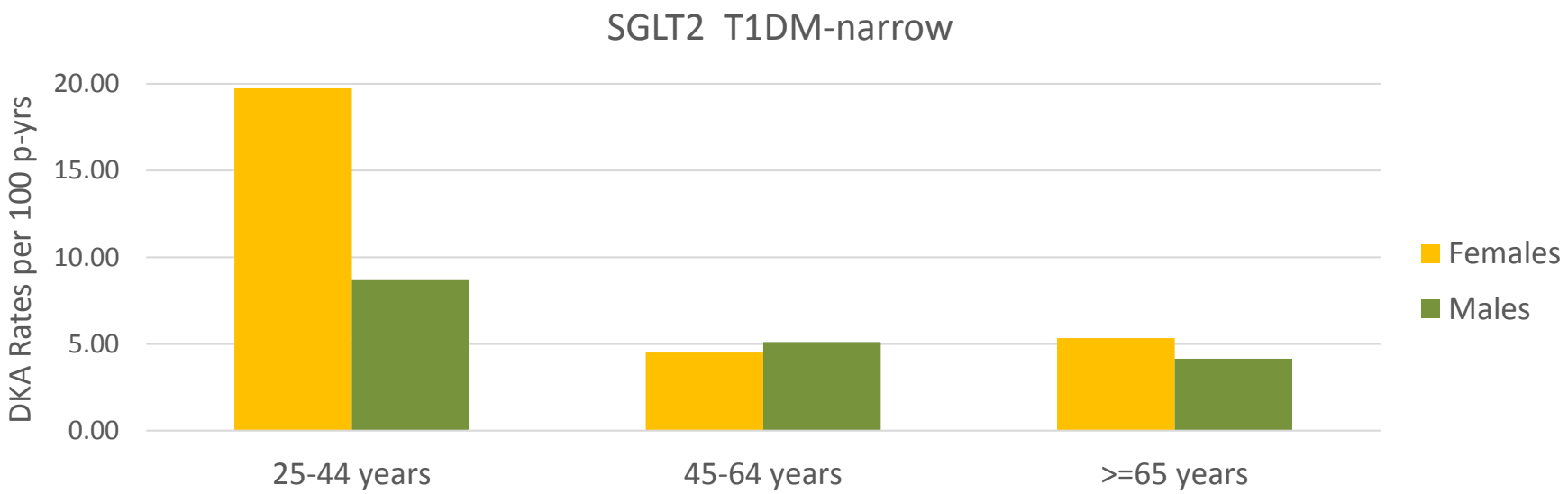




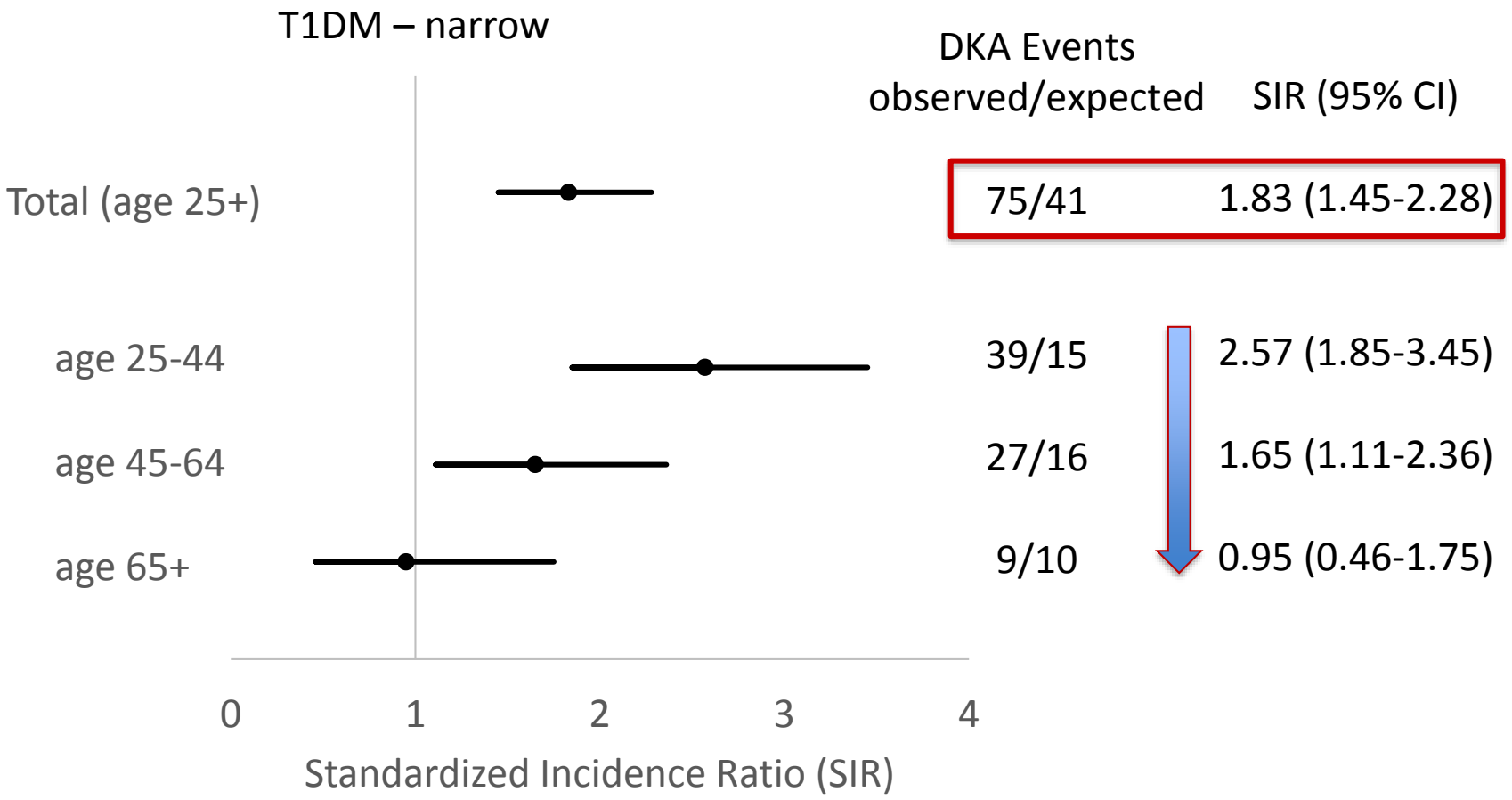


SGLT2 inhibitor DKA rates





Standardized incidence ratios for DKA



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 who met study criteria for 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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Sentinel collaborators

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Sentinel data partners

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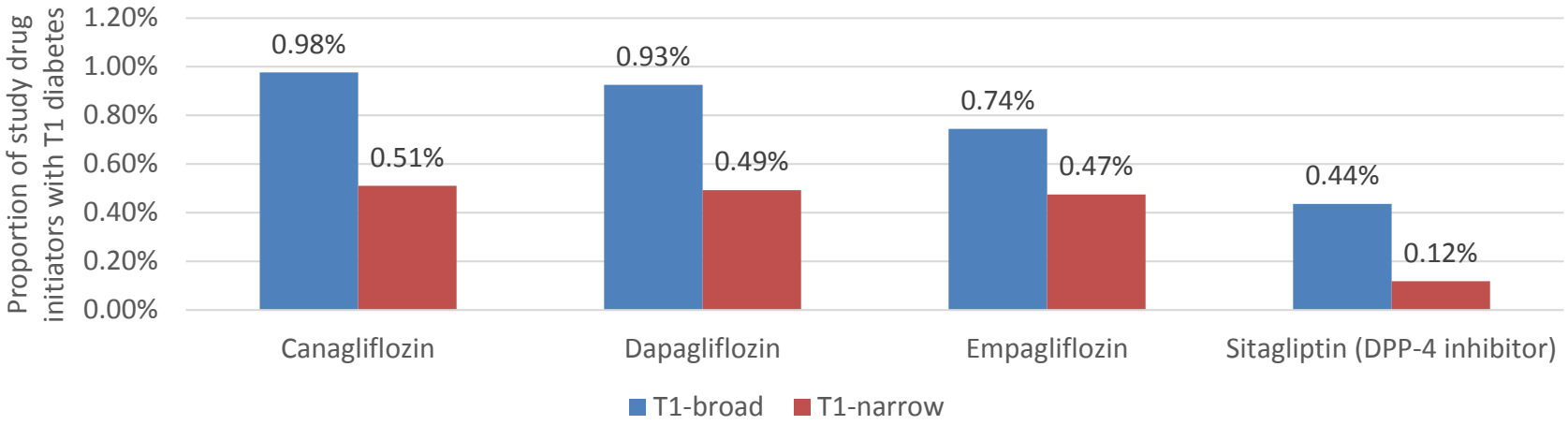
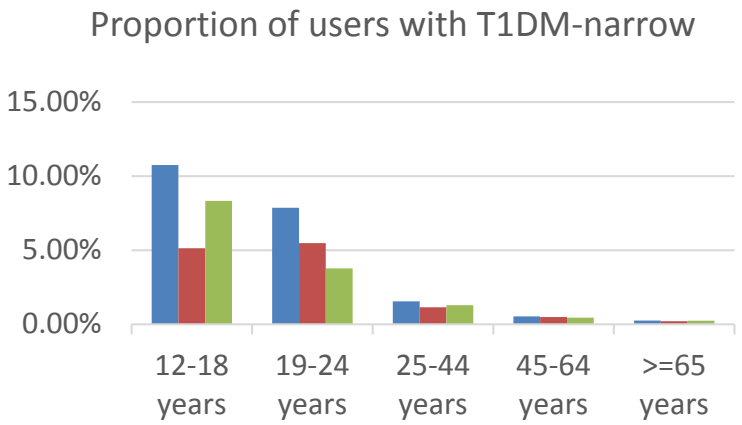
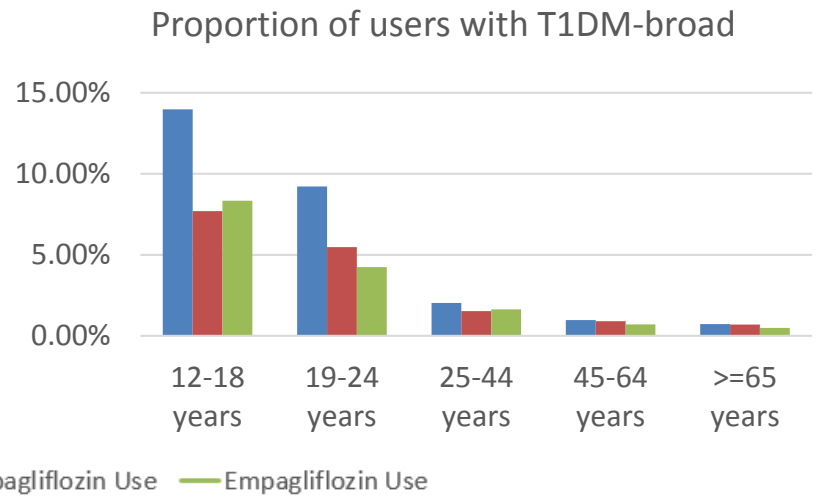
Proportion of SGLT2 inhibitor users with T1DM







Backup

- Add:
- T2 definition
- Demographics

Standardized incidence ratios

Sotagliflozin in Trials 309, 310, and 312:

- Age-and sex-specific follow-up duration and event counts for treatment-emergent, positively adjudicated DKA events, considering the first DKA event within each patient.

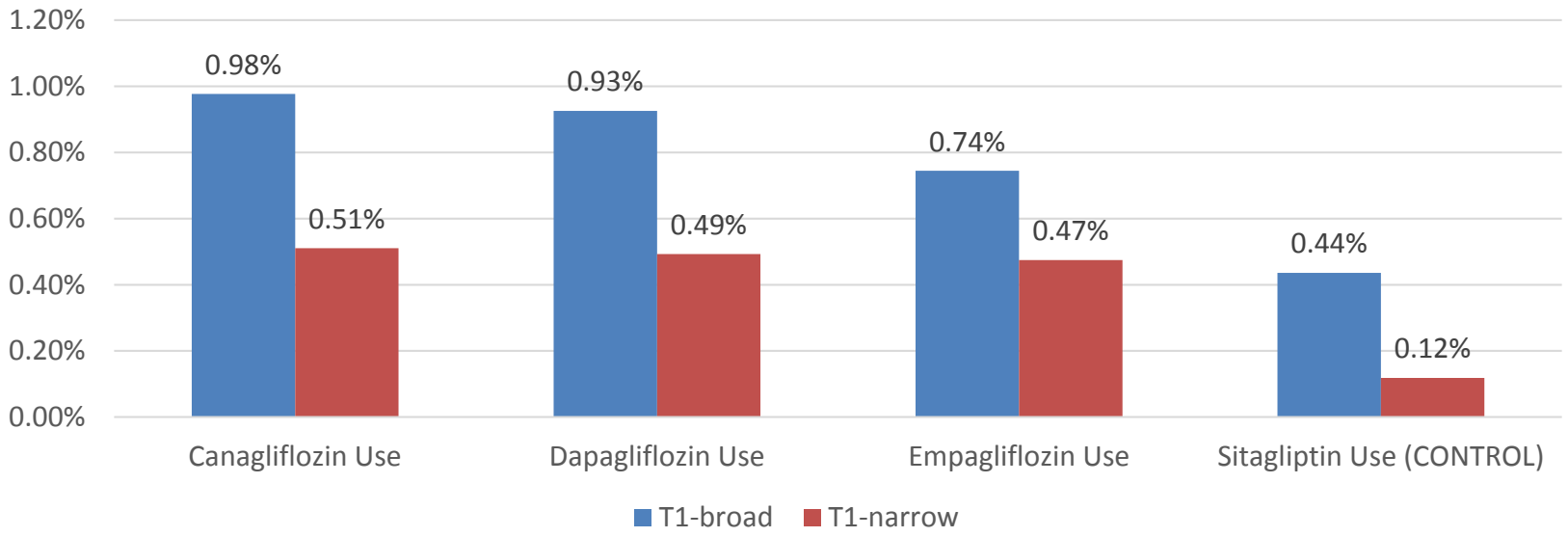
Sentinel:

- Expected age- and sex-specific DKA event counts in Sentinel using the distribution of age- and sex-specific follow-up time in Sentinel and the clinical trials' age- and sex-specific DKA rates.

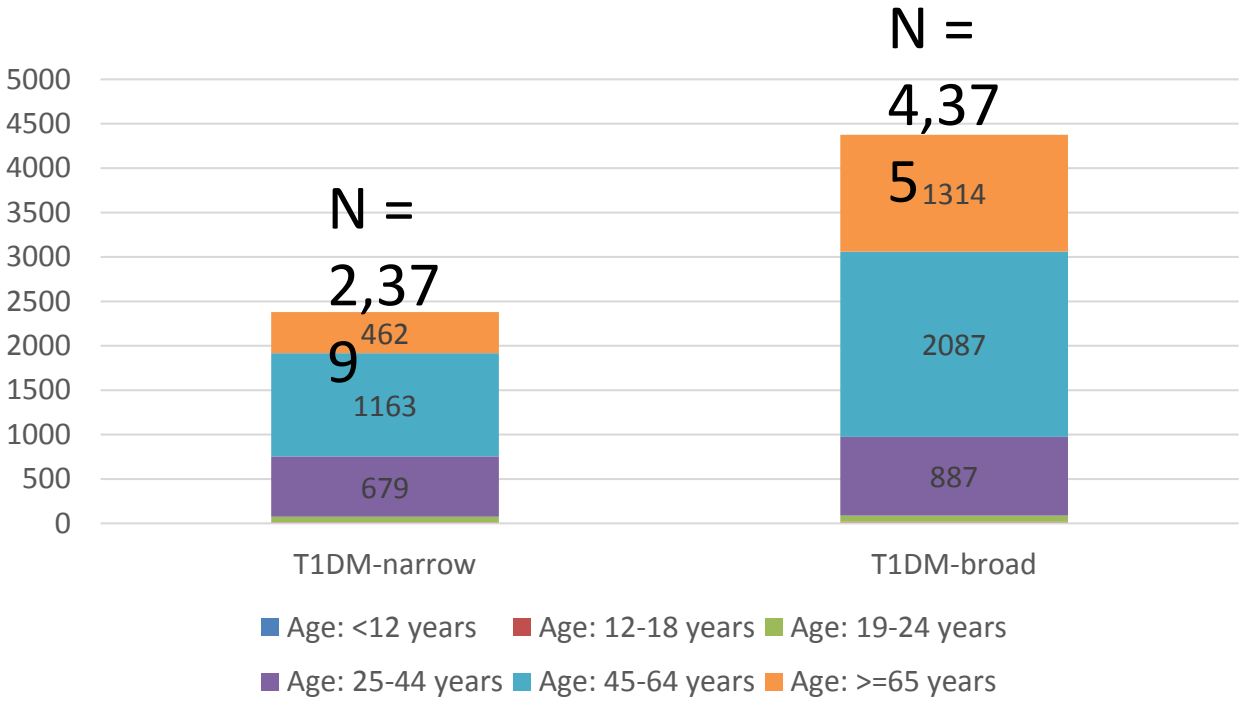
SIR:

- The SIR was calculated as the number of observed events (in Sentinel) divided by the number of events that would be expected if the Sentinel population experienced DKA at the rate observed in the clinical trials.

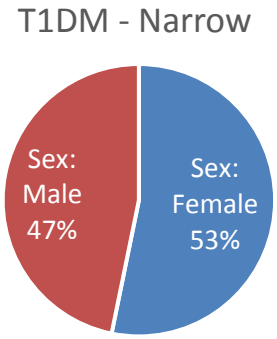
Proportion of SGLT2i users with T1DM

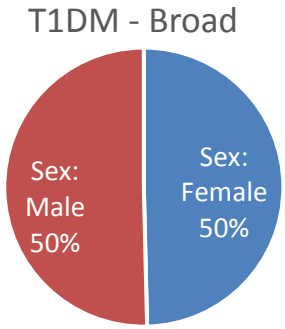


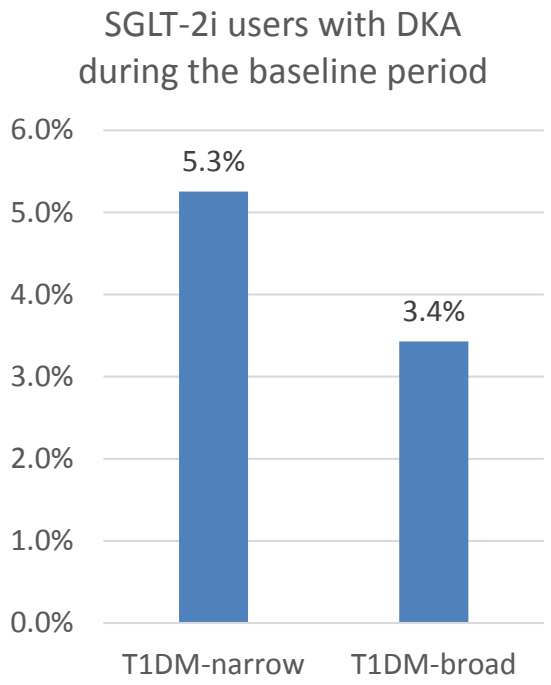
Proportion of SGLT-2i users with T1DM



Patient characteristics - SGLT-2 initiators







Baseline use of non-insulin AD drugs among SGLT2i users

	SGLT-2 inhibitors, pooled		Sitagliptin	
	T1DM-narrow*	T1DM-broad	T1DM-narrow*	T1DM-broad
Acarbose	-	0.5%	-	0.5%
Albiglutide	0.3%	0.4%	0.1%	0.1%
Alogliptin	-	0.3%	-	-
Canagliflozin	-	-	-	2.2%
Dapagliflozin	-	-	-	0.4%
Dulaglutide	1.1%	1.1%	0.3%	0.1%
Empagliflozin	-	-	-	0.2%
Exenatide	2.4%	3.9%	2.0%	1.7%
Glimiperide	-	8.0%	-	11.8%
Glipizide	-	7.2%	-	16.2%
Glyburide	-	3.3%	-	7.8%
Linagliptin	-	2.1%	-	-
Liraglutide	10.6%	11.8%	3.4%	2.6%
Metformin	29.0%	46.6%	40.6%	55.1%
Nateglinide	-	0.8%	-	1.0%
Pioglitazone	-	5.8%	-	6.8%
Repaglinide	-	0.9%	-	1.2%
Saxagliptin	-	3.1%	-	-
Sitagliptin	-	11.2%	-	-

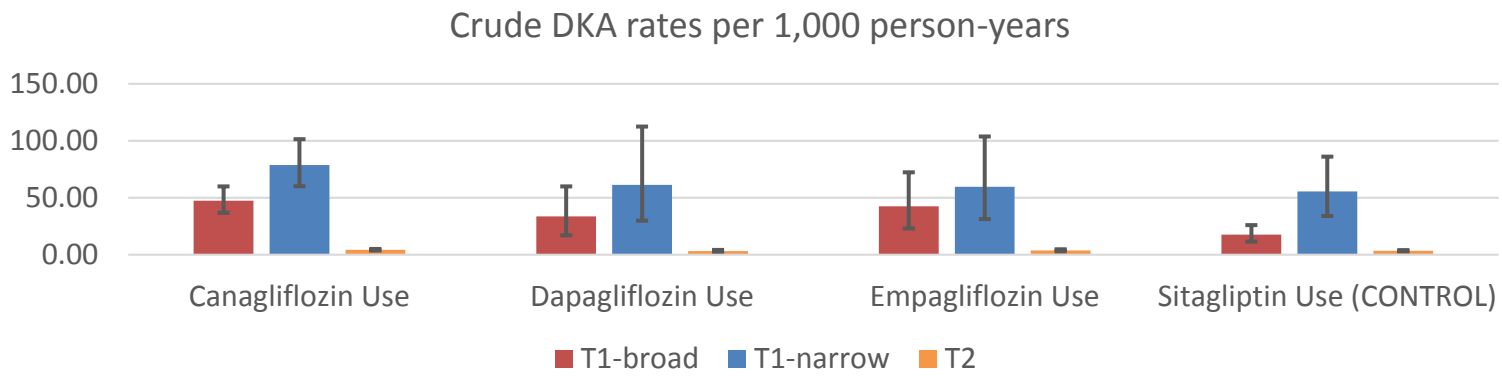
* The narrow T1DM definition excluded patients with baseline oral AD drug use other than metformin

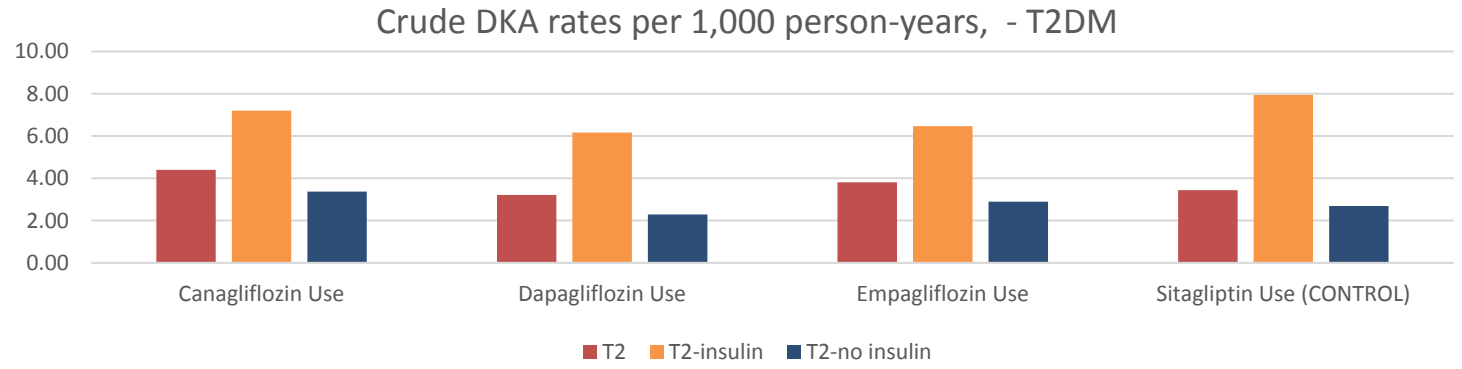
Baseline use of insulin among SGLT2i users

		SGLT-2 inhibitors, pooled		Sitagliptin	
		T1DM-narrow	T1DM-broad	T1DM-narrow	T1DM-broad
short- and rapid-acting	Insulin lispro	54.4%	35.9%	44.5%	16.3%
	Insulin regular, human	7.7%	7.7%	16.8%	10.2%
	Insulin glulisine	7.4%	4.5%	3.2%	1.2%
	Insulin aspart	43.4%	31.6%	51.3%	21.6%
	Insulin lispro protamine	2.6%	2.8%	9.1%	3.6%
long- or intermediate acting	Insulin glargine,human recombinant analog	38.4%	38.9%	54.7%	36.8%
	Insulin NPH human isophane	3.7%	5.3%	9.5%	8.8%
	Insulin detemir	16.5%	18.3%	22.1%	14.8%
	Insulin aspart protamine human	1.6%	3.8%	5.4%	5.0%
	Insulin degludec	1.6%	1.1%	1.0%	0.4%
	Insulin pump	33.7%	19.7%	3.8%	1.6%

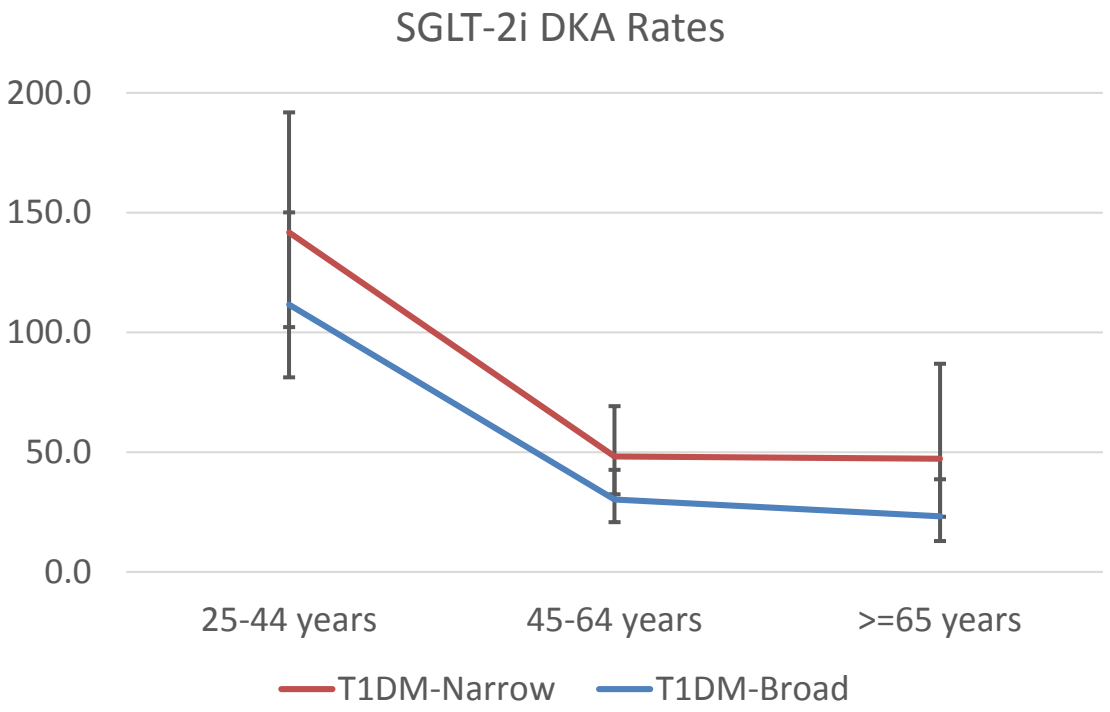
* The narrow T1DM definition required at least one baseline prescription for a short- or rapid-acting insulin

Diabetic Ketoacidosis





SGLT-2i DKA rates by age



Time to first DKA event (days)

	N, events	Mean	Min	Q1	Median	Q3	Max
T1-narrow							
Canagliflozin	57	133	3	25	77	170	572
Dapagliflozin	9	99	5	23	64	197	214
Empagliflozin	11	156	26	93	157	215	273
Sitagliptin (CONTROL)	18	102	3	15	35	120	795
T1-broad							
Canagliflozin	65	136	2	21	73	170	740
Dapagliflozin	10	96	5	23	65	197	214
Empagliflozin	12	144	8	81	144	214	273
Sitagliptin							

Illustration of SIR calculation

Age- and sex-adjusted standardized incidence ratios (SIR) for DKA based on patients age >25 in clinical trials and Sentinel, considering only first event after initiation/randomization.

	Sentinel			Clinical Trials		
Stratum	Person-time [yrs]	Events	Incidence Rate	Person-time [yrs]	Events	Incidence Rate
Females, Age 25-44	100	20	20/100	60	6	10/100

Observed events in Sentinel: 20 events

Expected events in Sentinel: 100 person-years * 10 events/100 p-yrs = 10 events

Illustration of SIR calculation

Age- and sex-adjusted standardized incidence ratios (SIR) for DKA based on patients age >25 in clinical trials and Sentinel, considering only first event after initiation/randomization.

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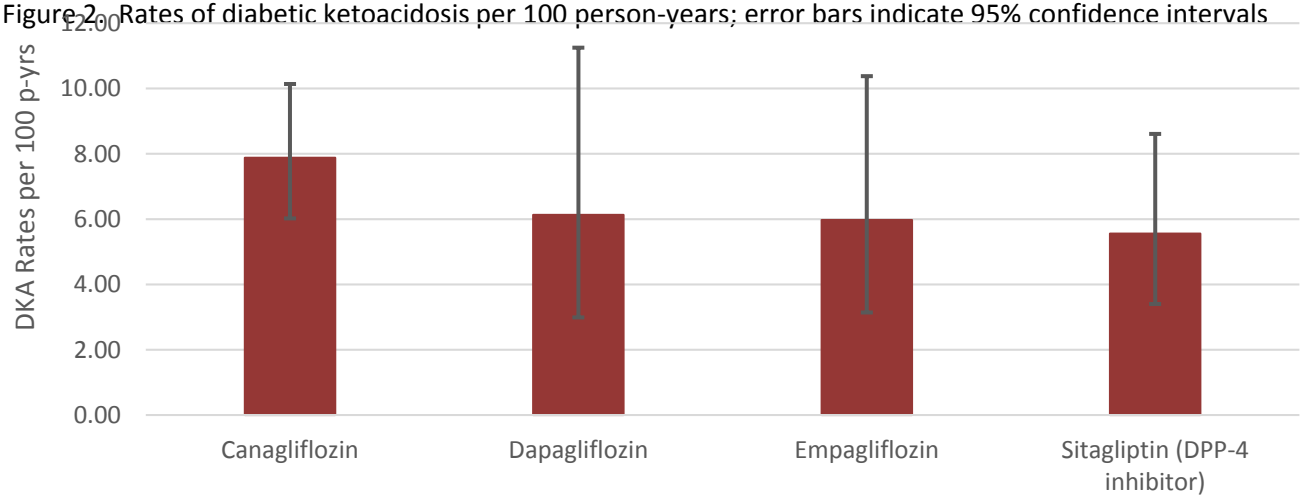
Expected events in Sentinel: 100 person-years * 10 events/100 p-yrs = 10 events

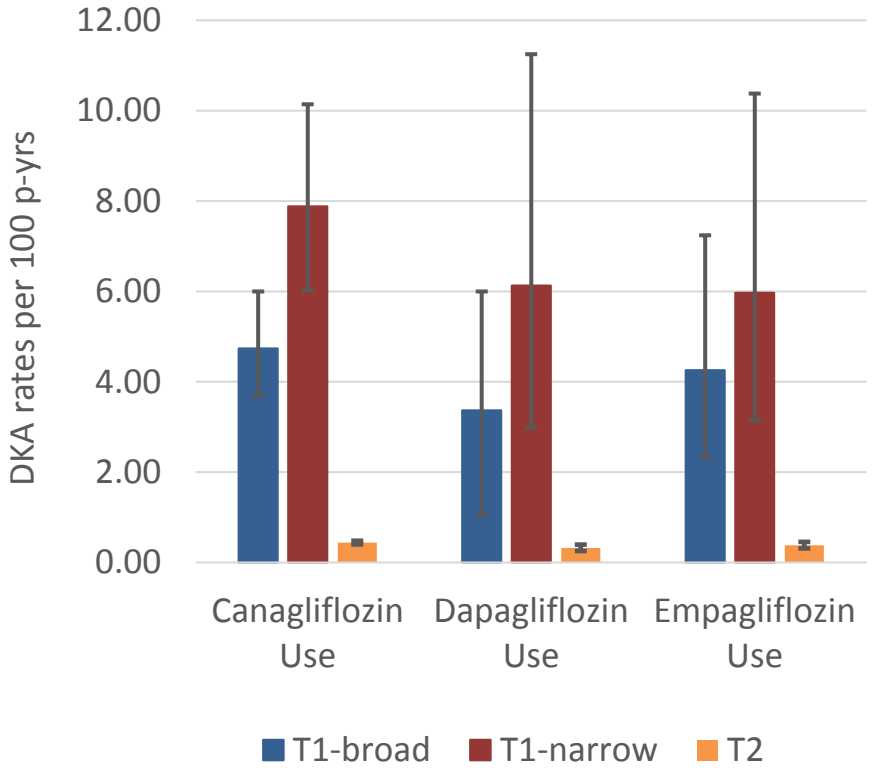
Standardized incidence ratios based on Trials 309, 310, and 312

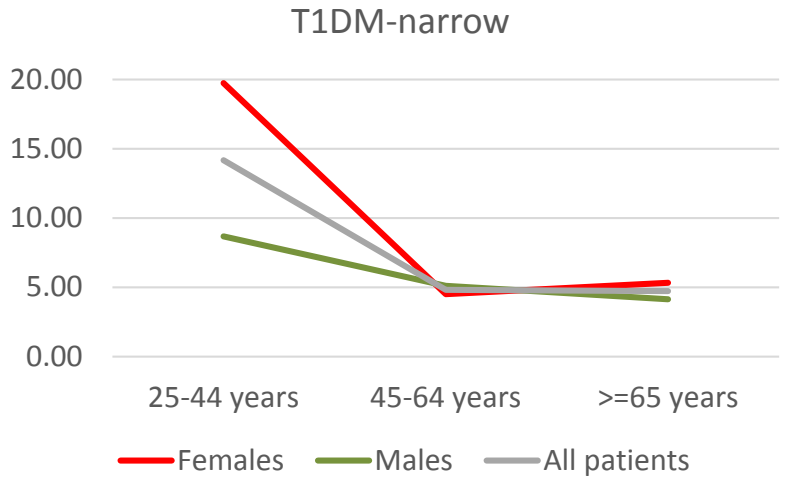
	Age category [years]	DKA events in Sentinel	Expected events	SIR (95% CI)
T1DM-narrow	≥25 (total)	75	41	1.83 (1.45-2.28)
	25-44	39	15	2.57 (1.85-3.45)
	45-64	27	16	1.65 (1.11-2.36)
	≥65	9	10	0.95(0.46-1.75)
T1DM-broad	≥25 (total)	84	78	1.07 (0.86-1.32)
	25-44	41	20	2.03 (1.47-2.72)
	45-64	30	29	1.03 (0.71-1.46)
	≥65	13	29	0.45 (0.25-0.74)

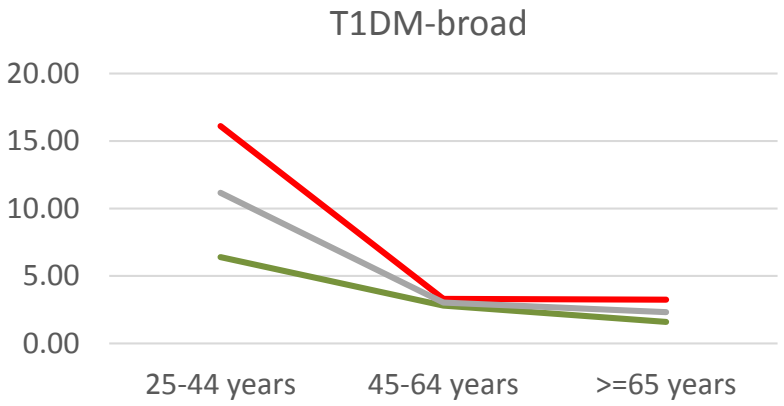
Figure 2. Rates of diabetic ketoacidosis per 100 person-years; error bars indicate 95% confidence intervals



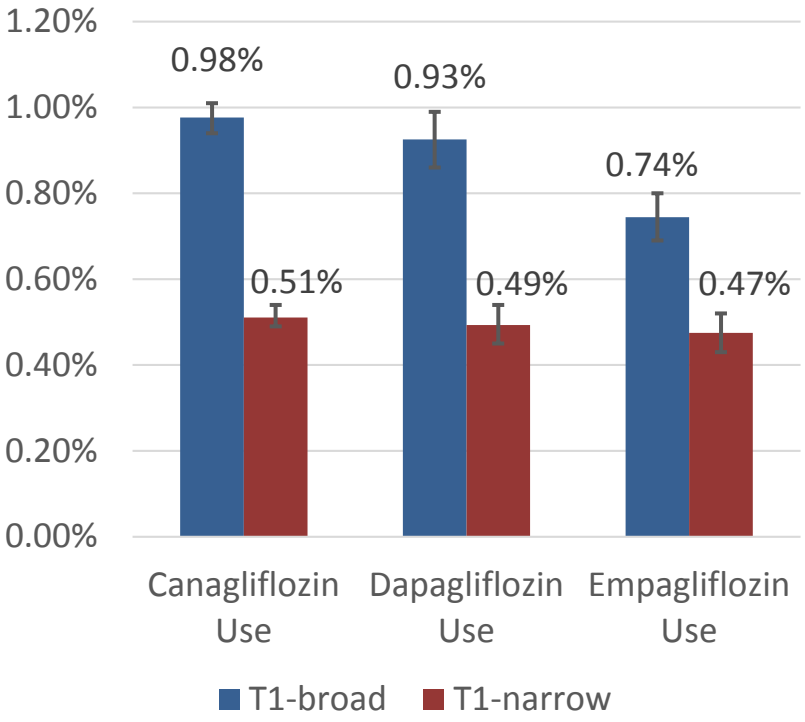
SGLT2 inhibitor DKA rates

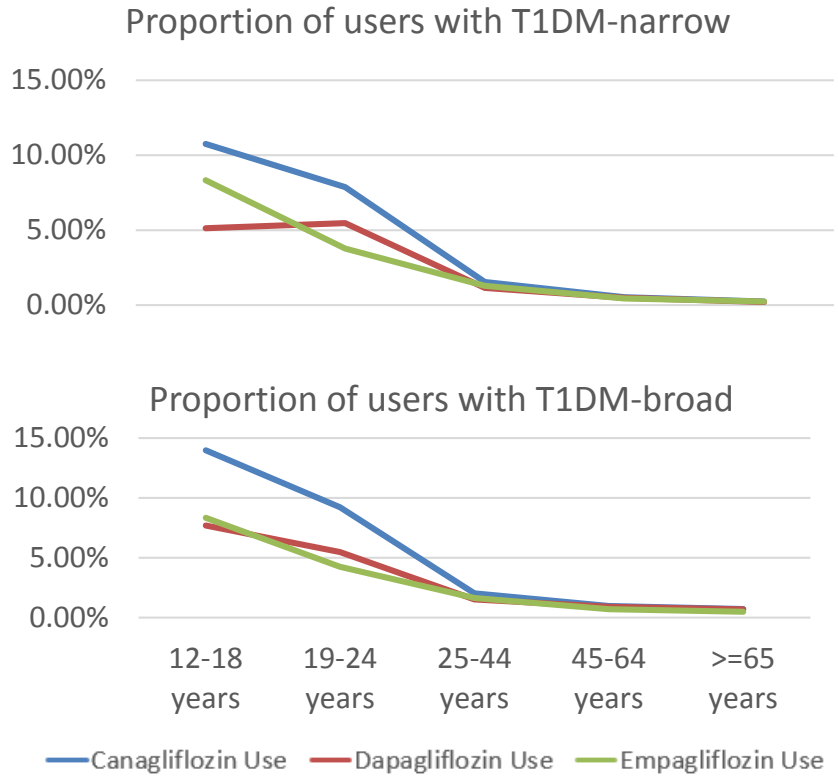




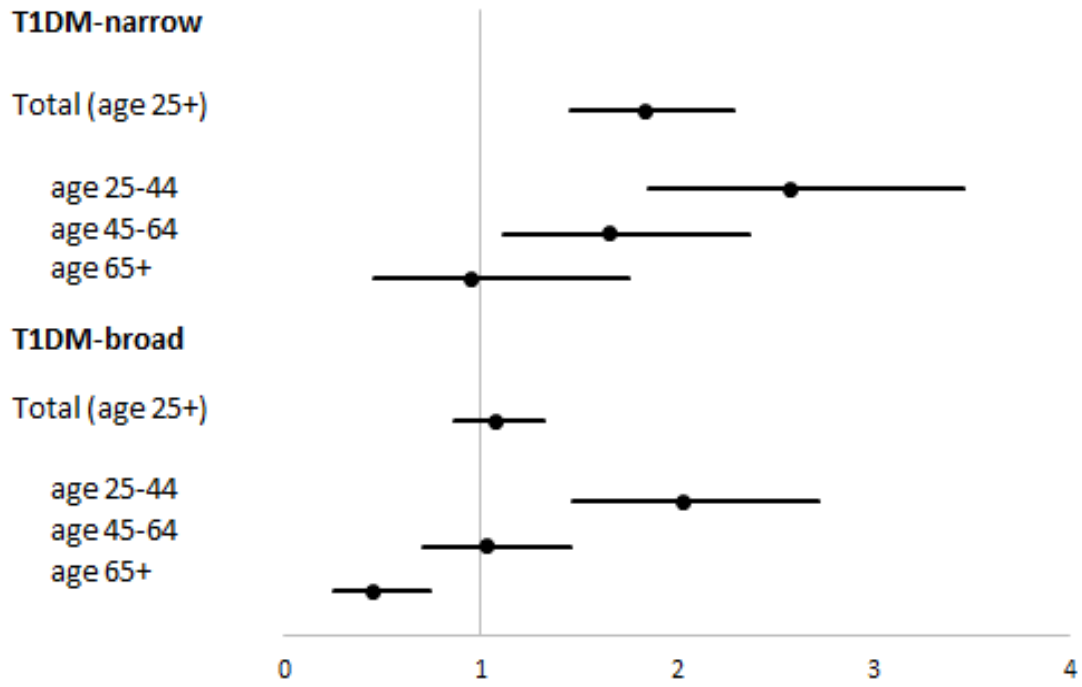


Proportion of SGLT2 inhibitor users with T1DM



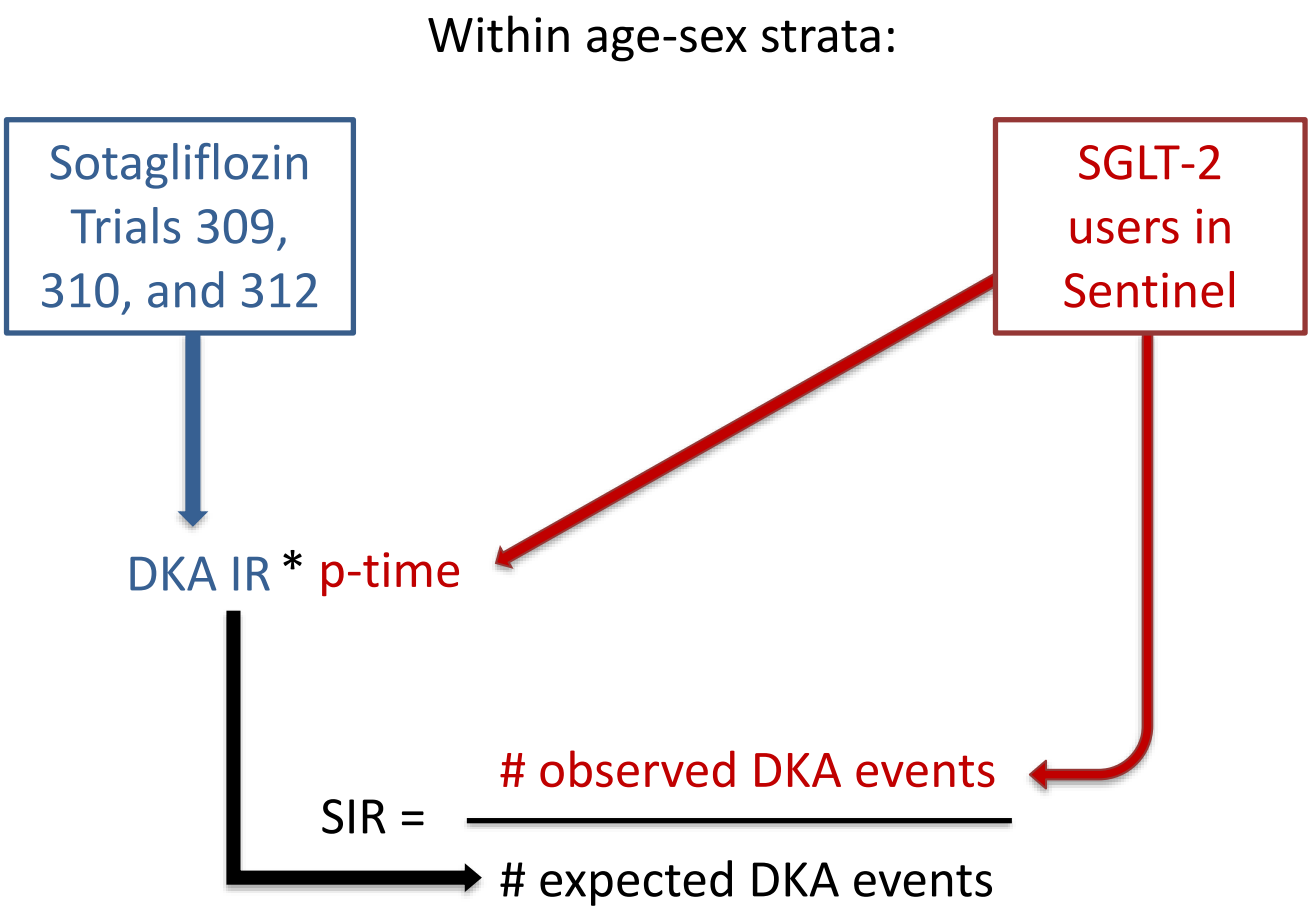


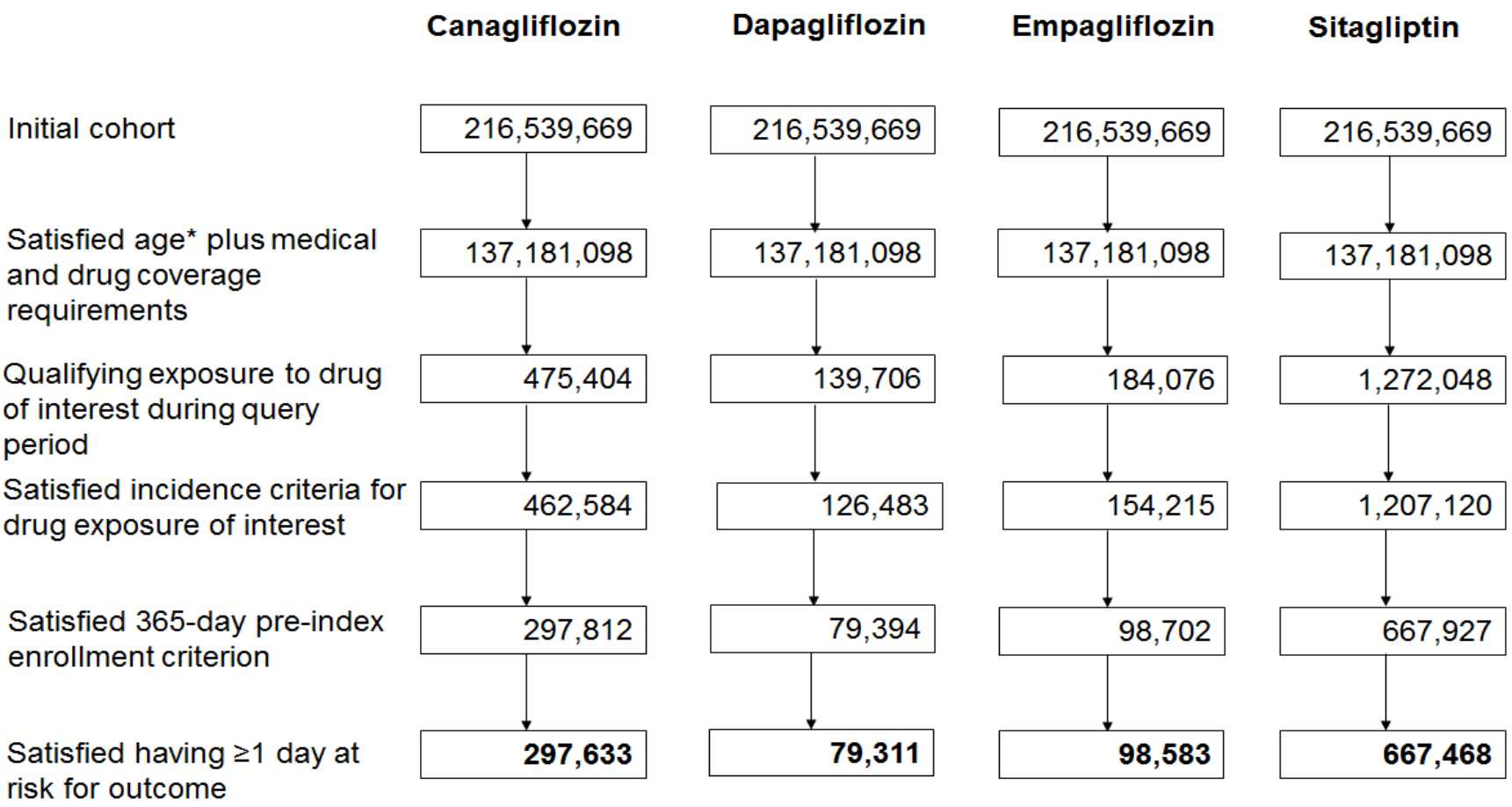
Standardized incidence ratios for DKA



	DKA Events observed/expected	SIR (95% CI)
T1DM-narrow		
Total (age 25+)	75/41	1.83 (1.45-2.28)
age 25-44	39/15	2.57 (1.85-3.45)
age 45-64	27/16	1.65 (1.11-2.36)
age 65+	9/10	0.95 (0.46-1.75)
T1DM-broad		
Total (age 25+)	84/78	1.07 (0.86-1.32)
age 25-44	41/20	2.03 (1.47-2.72)
age 45-64	30/29	1.03 (0.71-1.46)
age 65+	13/29	0.45 (0.25-0.74)

Standardized incidence ratios




Canagliflozin
Dapagliflozin
Empagliflozin
Sitagliptin
Initial cohort
216,539,669
216,539,669
216,539,669
216,539,669
Satisfied age* plus medical and drug coverage requirements
137,181,098
137,181,098
137,181,098
137,181,098
Qualifying exposure to drug of interest during query period
475,404
139,706
184,076
1,272,048
Satisfied incidence criteria for drug exposure of interest
462,584
126,483
154,215
1,207,120
Satisfied 365-day pre-index enrollment criterion
297,812
79,394
98,702
667,927
Satisfied having ≥1 day at risk for outcome
297,633
79,311
98,583
667,468