Large-scale evidence generation and evaluation across a network of databases for type 2 diabetes mellitus
LEGEND-T2DM

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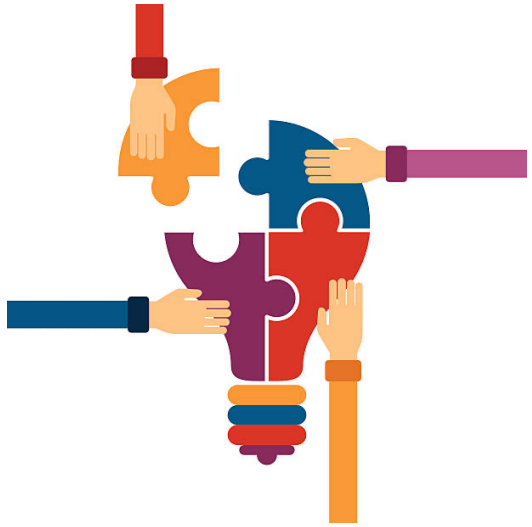
OHDSI
OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

CarDS LAB
YALE SCHOOL OF MEDICINE

Large-scale Evidence Generation



Residual Confounding

P hacking

Publication bias

Generate evidence on the effects of medical interventions using observational health-care databases while addressing the limitations

Schuemie MJ, et al. JAMIA (2020)

LEGEND-T2DM Protocol

Cardiovascular medicine
Protocol

Large-scale evidence generation and evaluation across a network of databases for type 2 diabetes mellitus (LEGEND-T2DM): a protocol for a series of multinational, real-world comparative cardiovascular effectiveness and safety studies

Rohan Khera [1, 2], Martijn J Schuemie [3, 4], Yuan Lu [1, 2], Anna Ostropolets [5], RuiJun Chen [6], George Hripcsak [5, 7], Patrick B Ryan [3, 5], Harlan M Krumholz [1, 2], Marc A Suchard [4, 8, 9, 10]

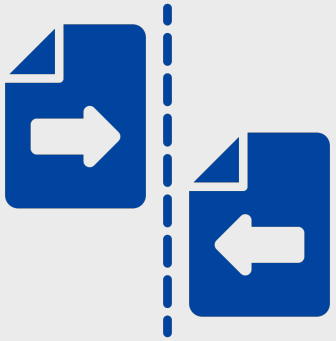
Correspondence to Marc A Suchard; msuchard@ucla.edu

PDF

PDF + Supplementary Material

Knowledge Gaps

No head-to-head comparisons



No direct comparisons within classes

Non cardiovascular outcomes

Limited patient representation in Trials

Khera R, et al. BMJ Open (2021)

LEGEND-T2DM Principles

Journal of the American Medical Informatics Association, 27(8), 2020, 1331–1337
doi: 10.1093/jamia/ocaa103
Perspective

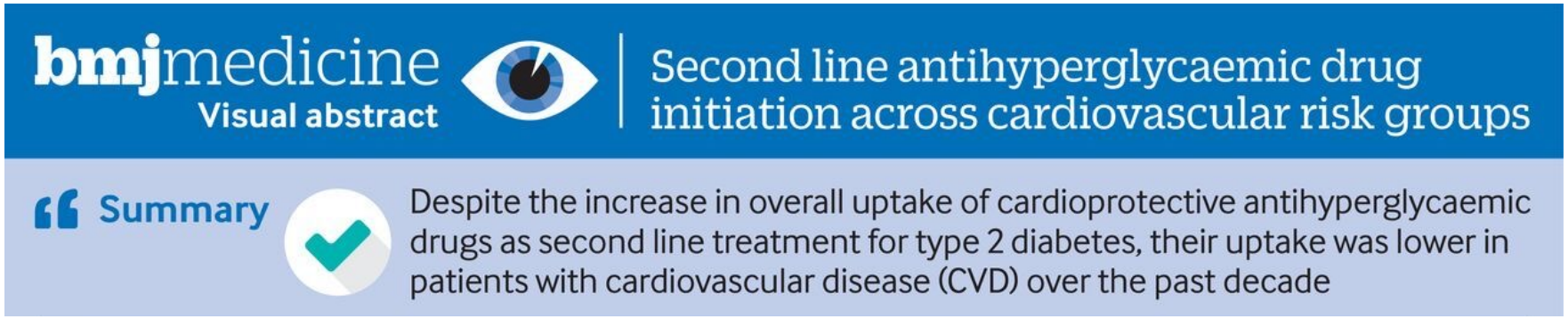
Perspective

Principles of Large-scale Evidence Generation and Evaluation across a Network of Databases (LEGEND)

Martijn J. Schuemie[1,2], Patrick B. Ryan[1,3], Nicole Pratt[4], RuiJun Chen[3,5], Seng Chan You[6], Harlan M. Krumholz[7], David Madigan[8], George Hripcsak[3,9], and Marc A. Suchard[2,10]

1. Large-scale evidence generation
2. Independent dissemination
3. Prespecified analysis design
4. Systematic process
5. Best Practices
6. Empirical evaluation
7. Free open-source software
8. Not to evaluate new methods
9. Network of multiple databases
10. No transfer of patient data

Multinational Uptake of Cardioprotective Antidiabetic Drugs



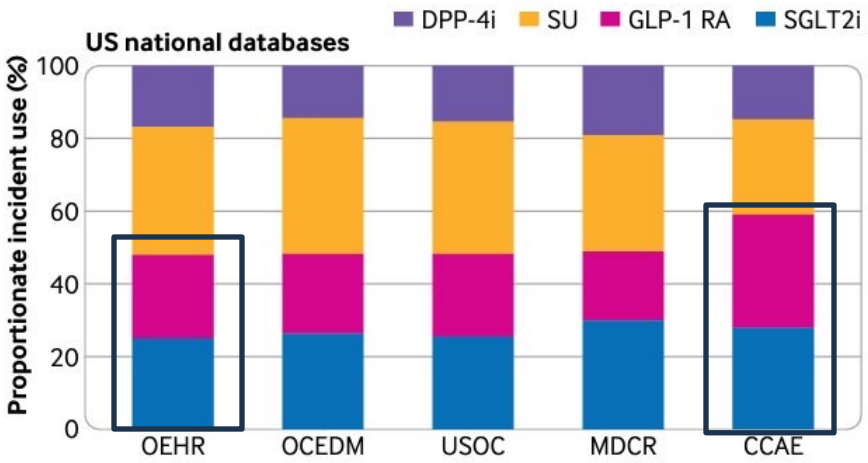
9 Countries

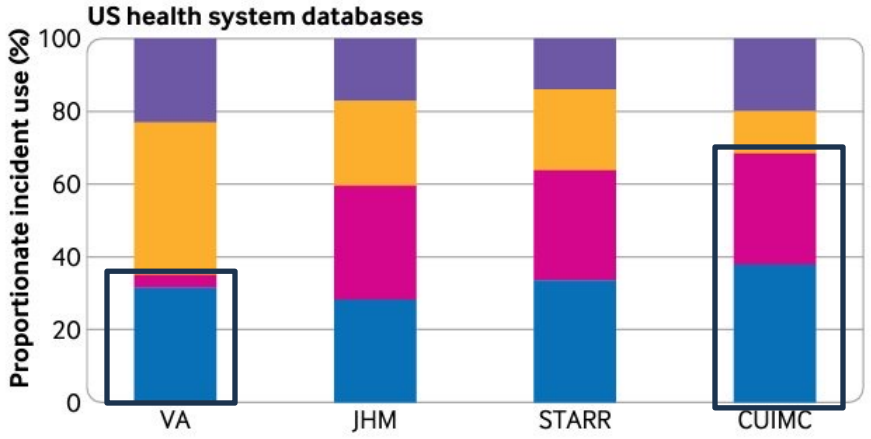
18 Administrative claims & EHR databases (2011-2021)

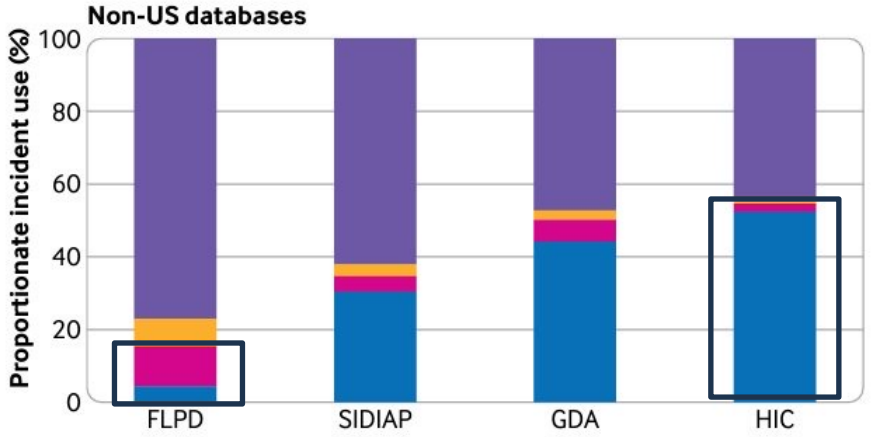
18 Million Participants

Khera R, et al. BMJ Medicine (2023)

Proportional use of second line agents

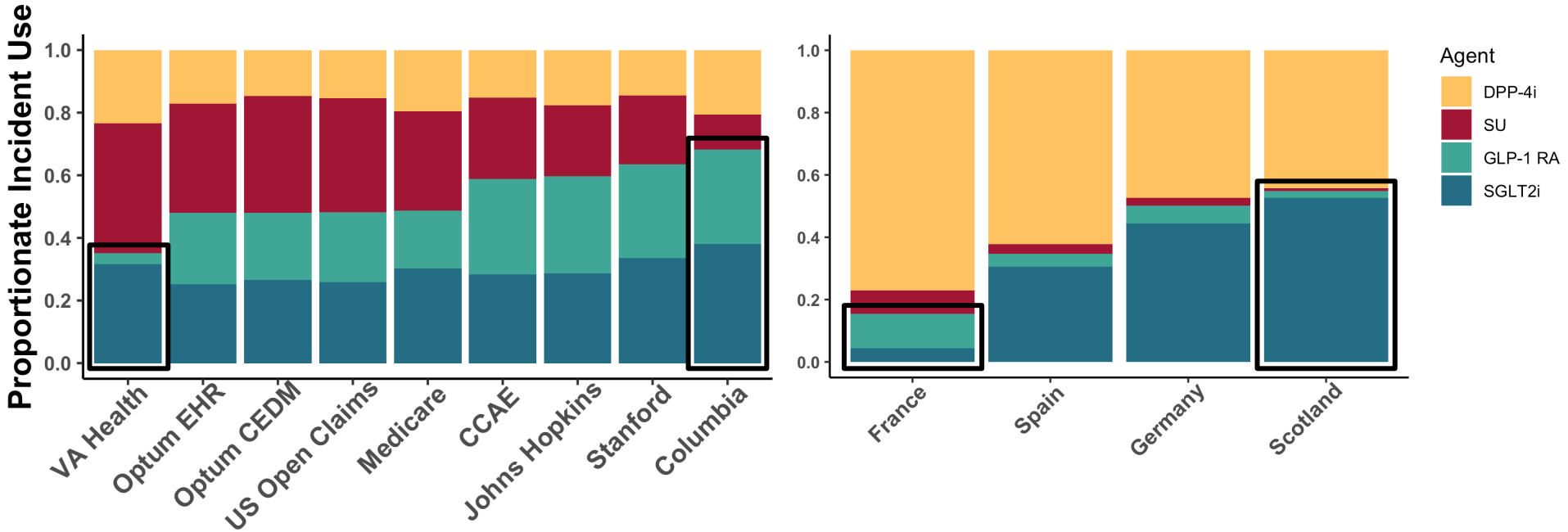




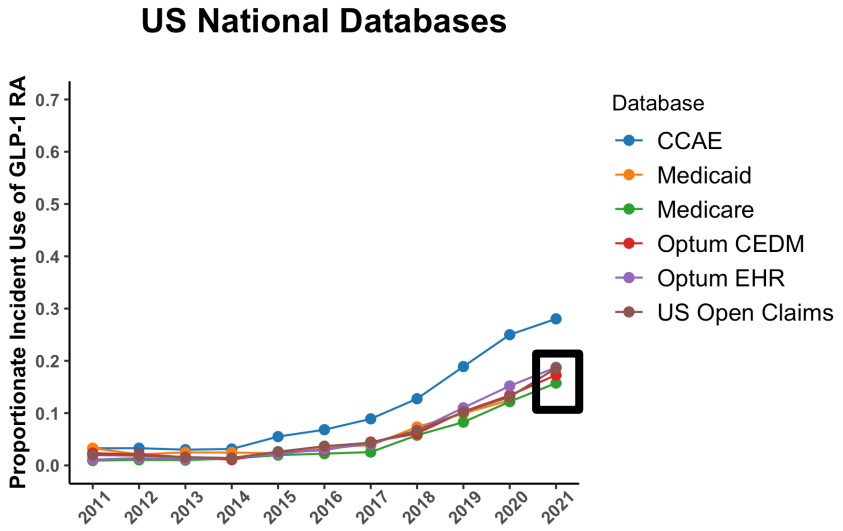


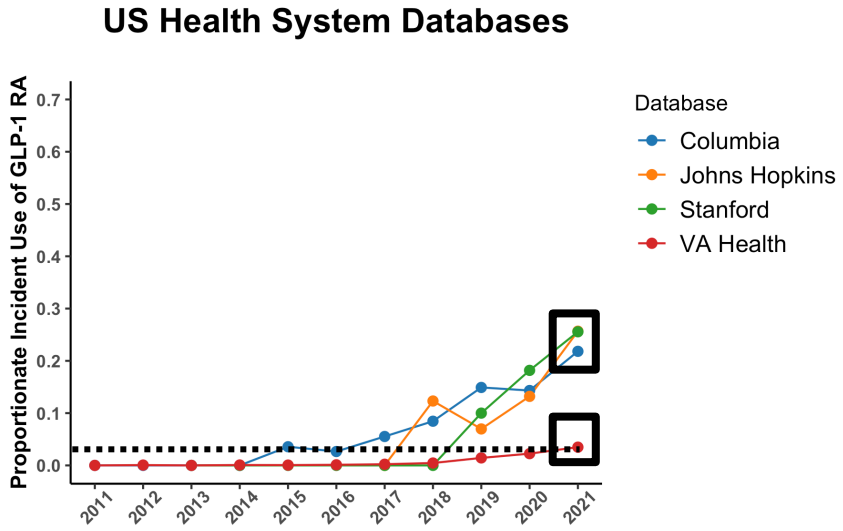
Khera R, et al. BMJ Medicine (2023)

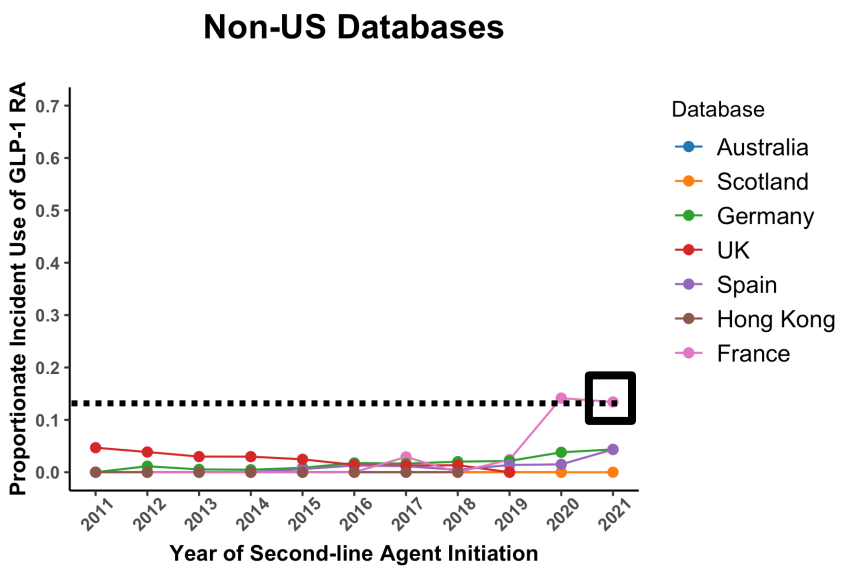
Proportionate Incident Use of Second-line Anti-hyperglycemic Agents in 2021



GLP-1 RA Uptake in Patients with Established CVD

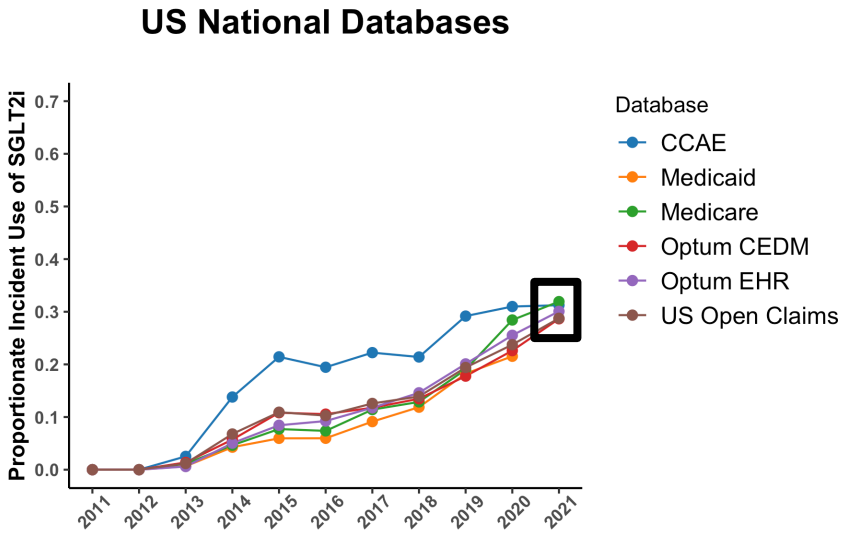


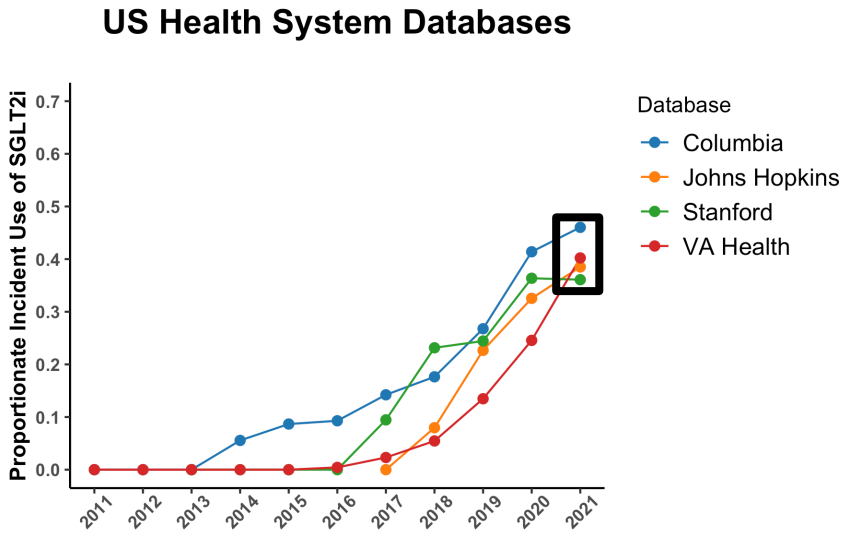


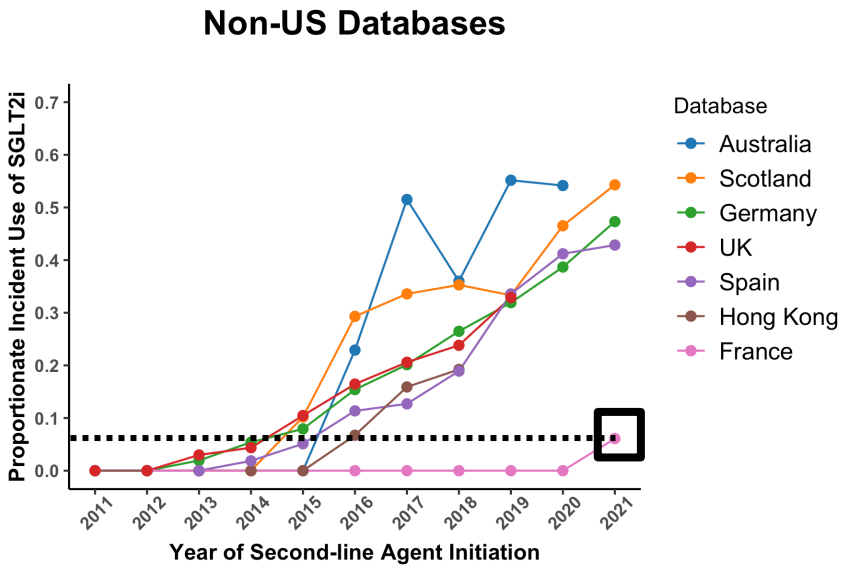


- Initiation of GLP-1 RAs increased to 20-25% across most US populations
- Initiation was <5% in the VA
- Initiation was low across non-US databases, reaching a maximum of 14% in France in 2021

SGLT2i Uptake in Patients with Established CVD







- Initiation of SGLT2is increased to ~35% across US populations
- In the non-US databases, the initiation of SGLT2is was higher in most databases, reaching up to 54% in Scotland in 2021
- In France, the initiation was lower, reaching only to 6% in 2021

Thanks to the OHDSI Community

The LEGEND-T2DM Panel

Comparative Effectiveness of Second-line Antihyperglycemic Agents - *Arya Aminorroaya, Yale University*

Effectiveness of First-line Antihyperglycemic Agents - *Phyllis Thangaraj, Yale University*

Comparative Safety of SGLT2 for Risk of Diabetic Ketoacidosis - *Hannah Yang/Evan Minty, University of Calgary*

Comparative Safety of GLP1-RA and the Risk of Thyroid Tumors - *Daniel Morales, University of Dundee*

Comparative Effectiveness of Second-Line Antihyperglycemic Agents for Cardiovascular Outcomes

A Multinational, Federated Analysis of LEGEND-T2DM

Arya Aminorroaya, MD, MPH
Cardiovascular Data Science Lab | Yale School of Medicine

Clinical Challenge

Patients with T2DM & established CVD
On metformin therapy
Still high blood sugar

Second-line Treatment

	CV Outcome RCTs
SGLT2i	MI, HF, Death
GLP-1 RA	MI, HF, Death
DPP4i	Neutral
SU	Not evaluated

Clinical Challenge

Patients with T2DM & established CVD
On metformin therapy
Still high blood sugar

Second-line Treatment

- SGLT2i
- GLP-1 RA
- DPP4i
- SU

Unknown Comparative Cardiovascular Effectiveness

Clinical Challenge

Patients with T2DM & established CVD
On metformin therapy
Still high blood sugar

SGLT2i

GLP-1 RA

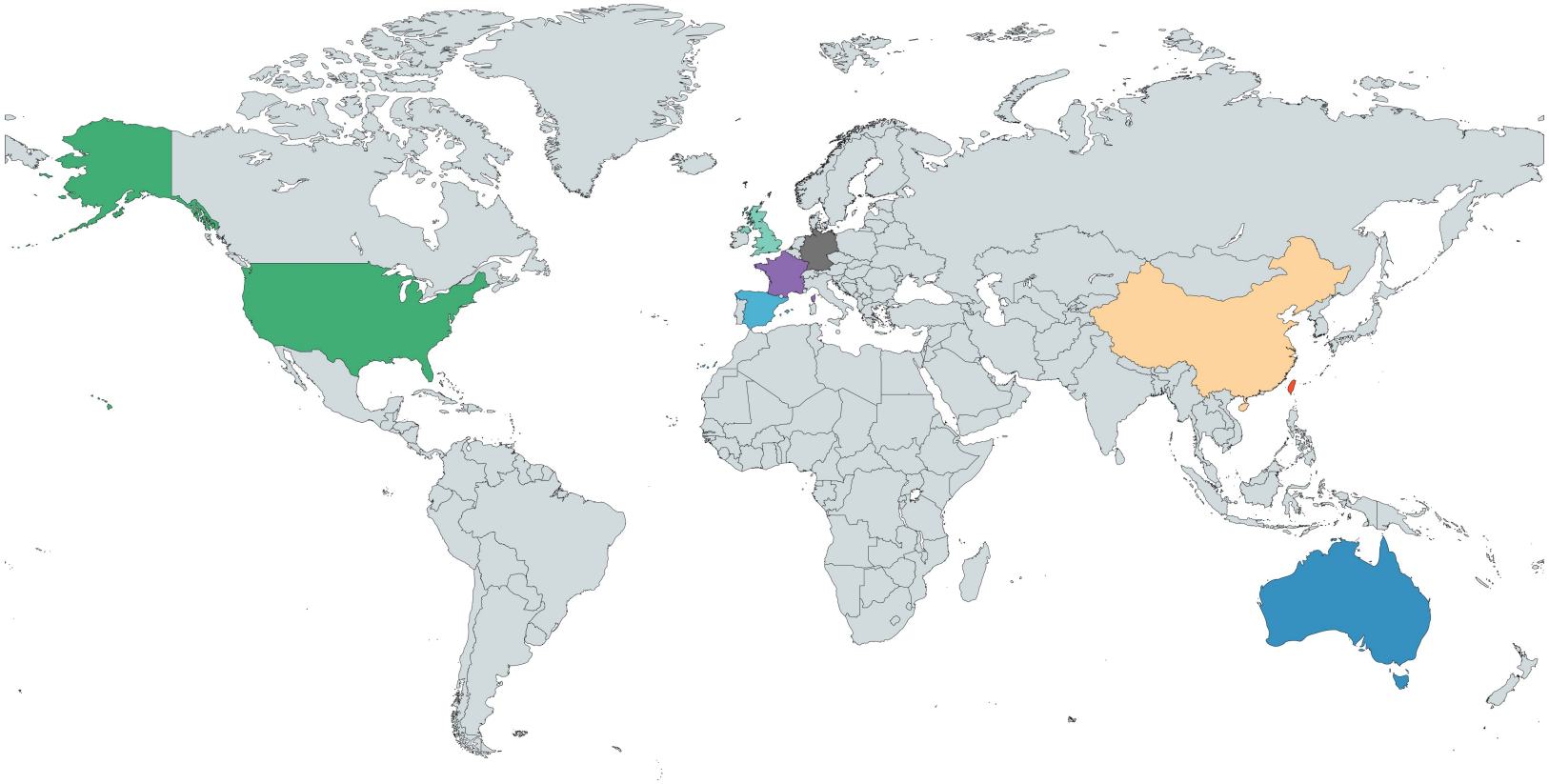
DPP4i

SU

Unknown Comparative Cardiovascular Effectiveness

Multinational Federated Network of LEGEND-T2DM

4.7 million patients with T2DM from
18 real-world data sources,
claims and EHR,
mapped to OMOP CDM
9 countries
1992-2021



Target Trial Emulation

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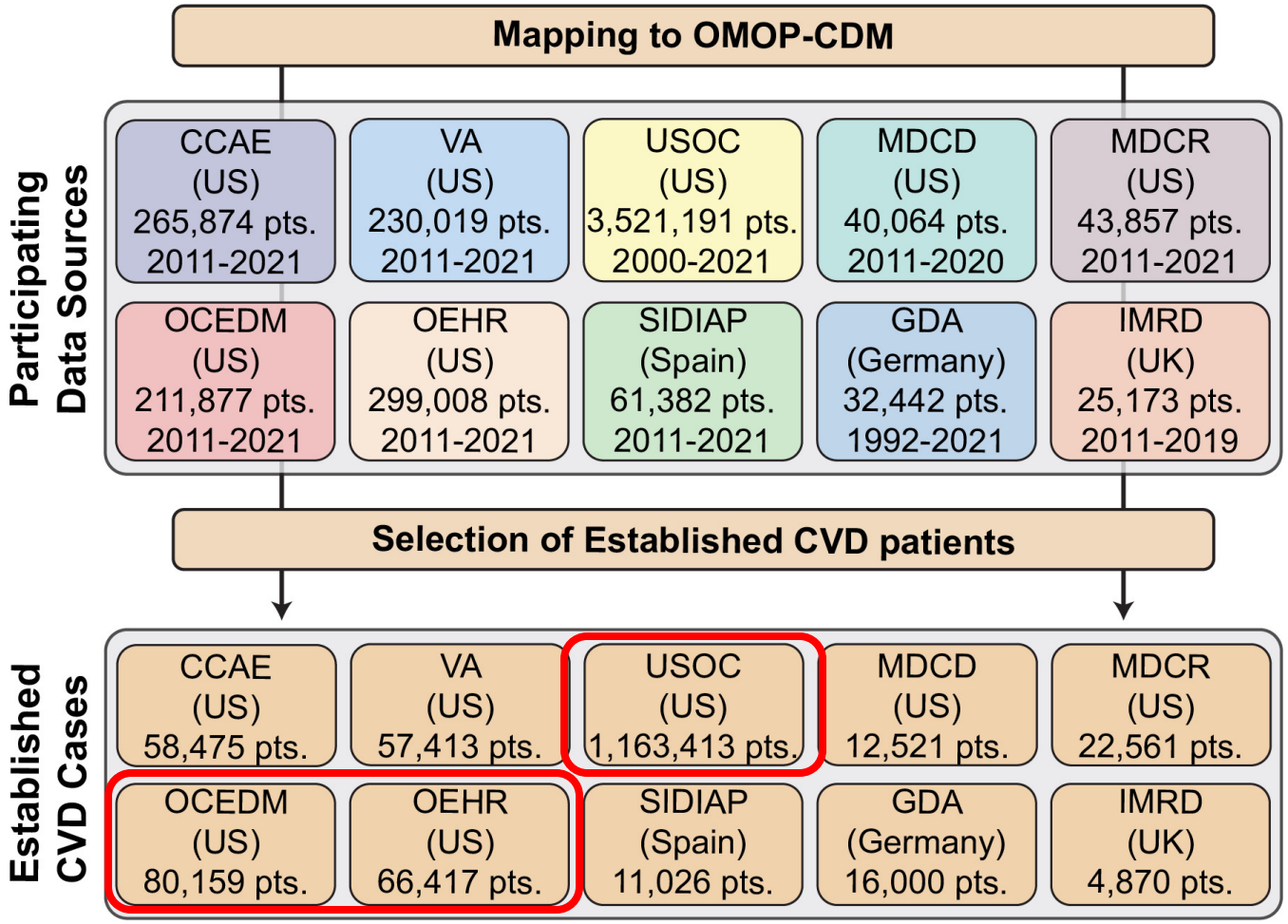
Population	Exposure	Target	Comparator	Outcome	Analysis
T2DM Established CVD ≥90 days on metformin Initiating a 2nd line agent No prior events	New-user cohorts SGLT2i GLP-1 RA DPP4i SU	SGLT2i SGLT2i SGLT2i GLP-1 RA GLP-1 RA DPP4i	GLP-1 RA DPP4i SU DPP4i SU SU	3-point MACE • Acute MI • Stroke • Sudden cardiac death 4-point MACE • 3-point MACE • Hosp. for HF	• On-treatment analysis • No escalation • No insulin

Diagnostics to Ensure Study Power

Eligible Target-Comparator Comparisons Across Data Sources

≥1000 patients per arm	Sufficient Sample Size
PS stratification to achieve SMD <0.15	Covariate Balance
Minimum detectable risk ratio <4	Proxy for Statistical Power
0.3< Preference score <0.7 in 25%	Empirical Equipoise
Negative control calibration	Residual Confounding
Kaplan-Meier plots	HR proportionality assumptions

Study Population



1.5 million patients with T2DM and CVD

SGLT2i 16%

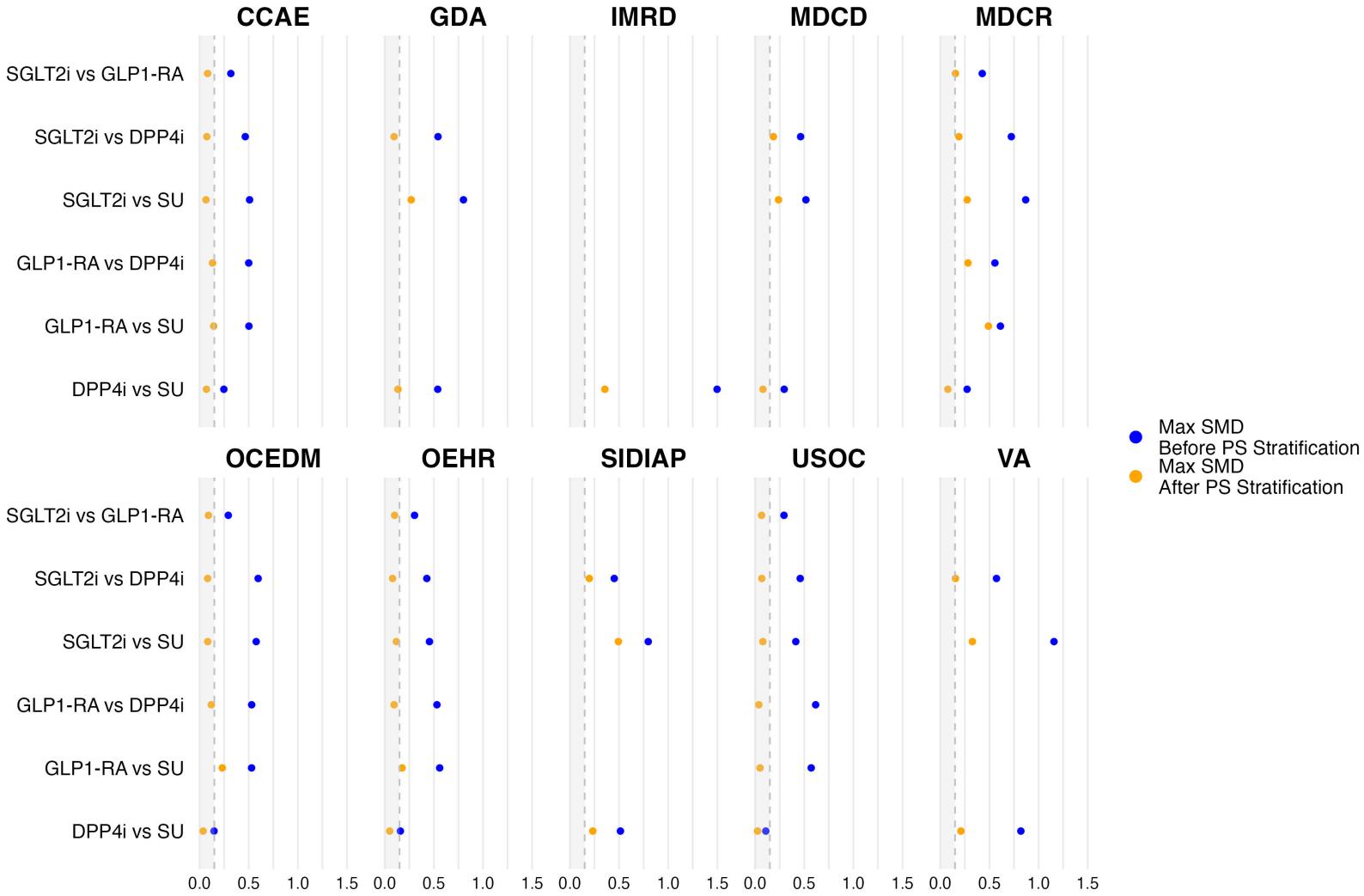
GLP-1 RA 8%

DPP4i 28%

SU 48%

Over 1.4 million patient-years of F/U
25,982 3-pt MACE
41,447 4-pt MACE

Cohort Diagnostics

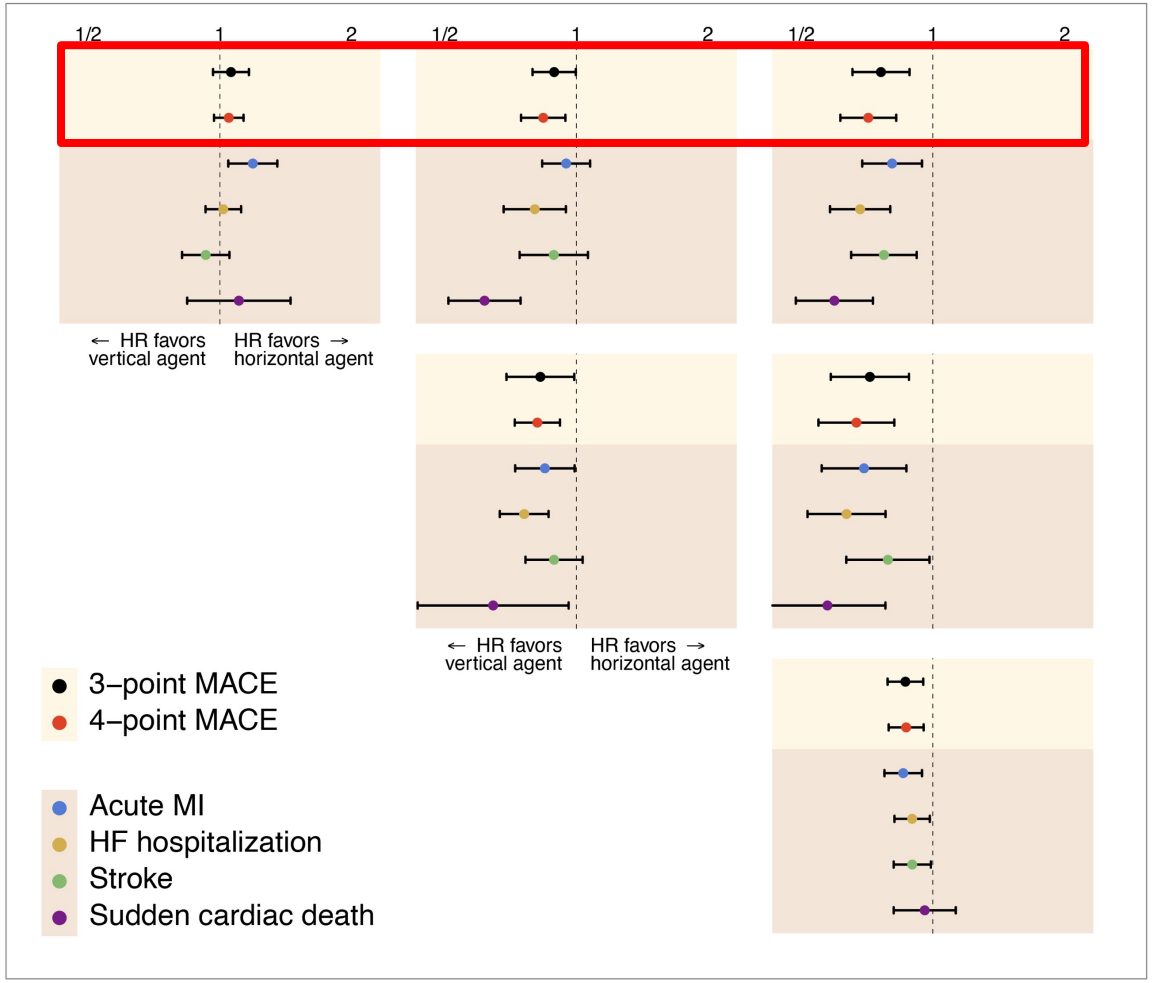


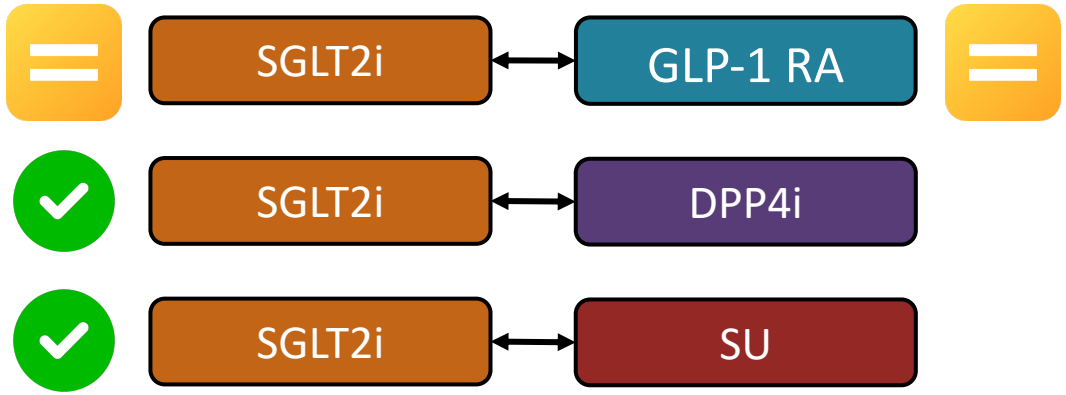
Covariate Balance

Empirical Equipoise

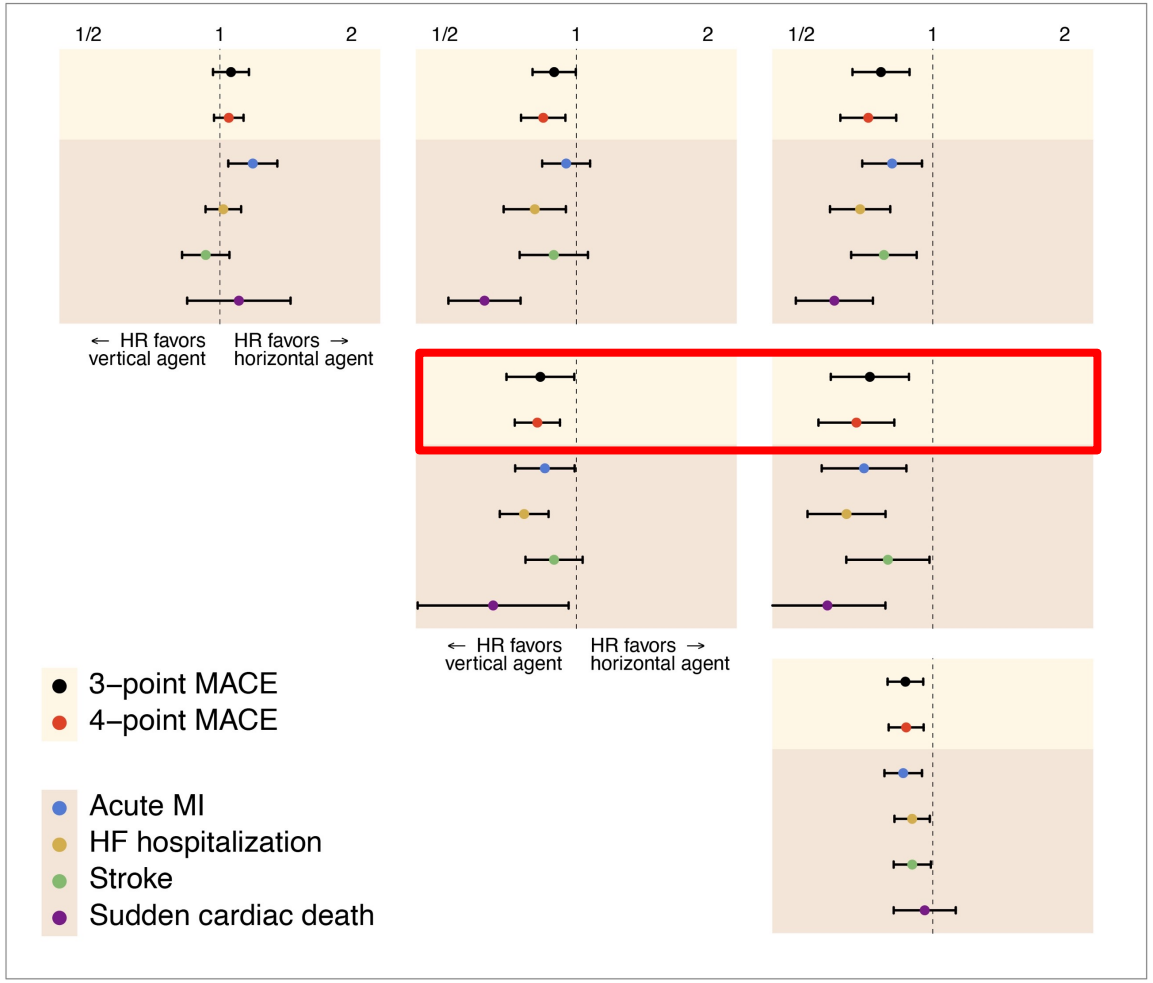
Residual Confounding

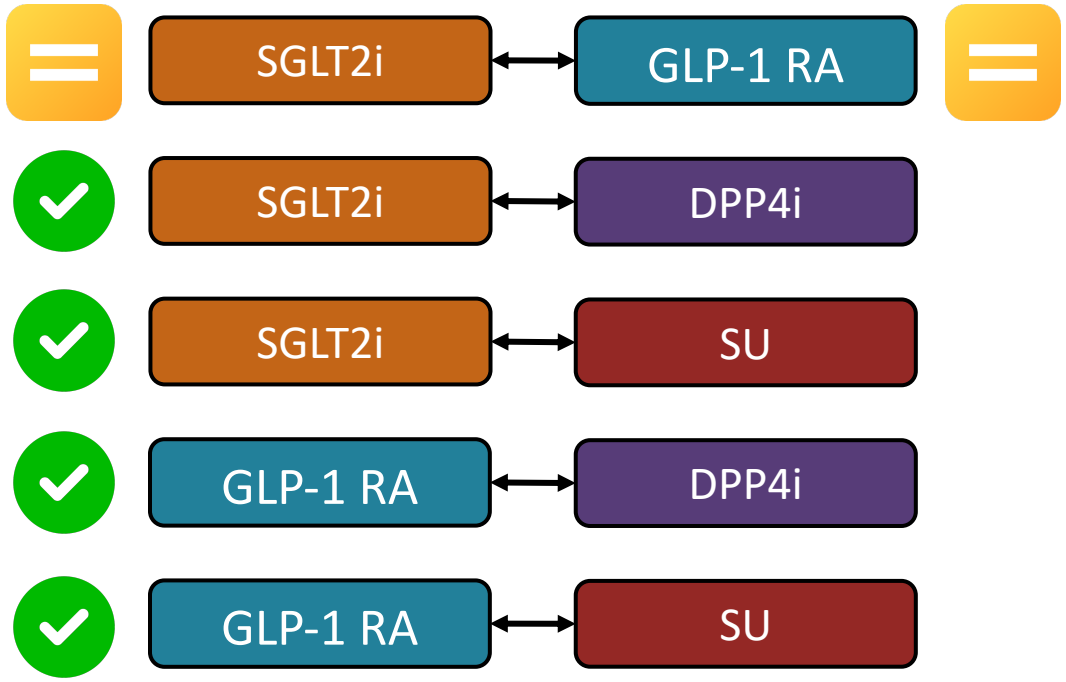
Meta-analytical Calibrated HR Estimates



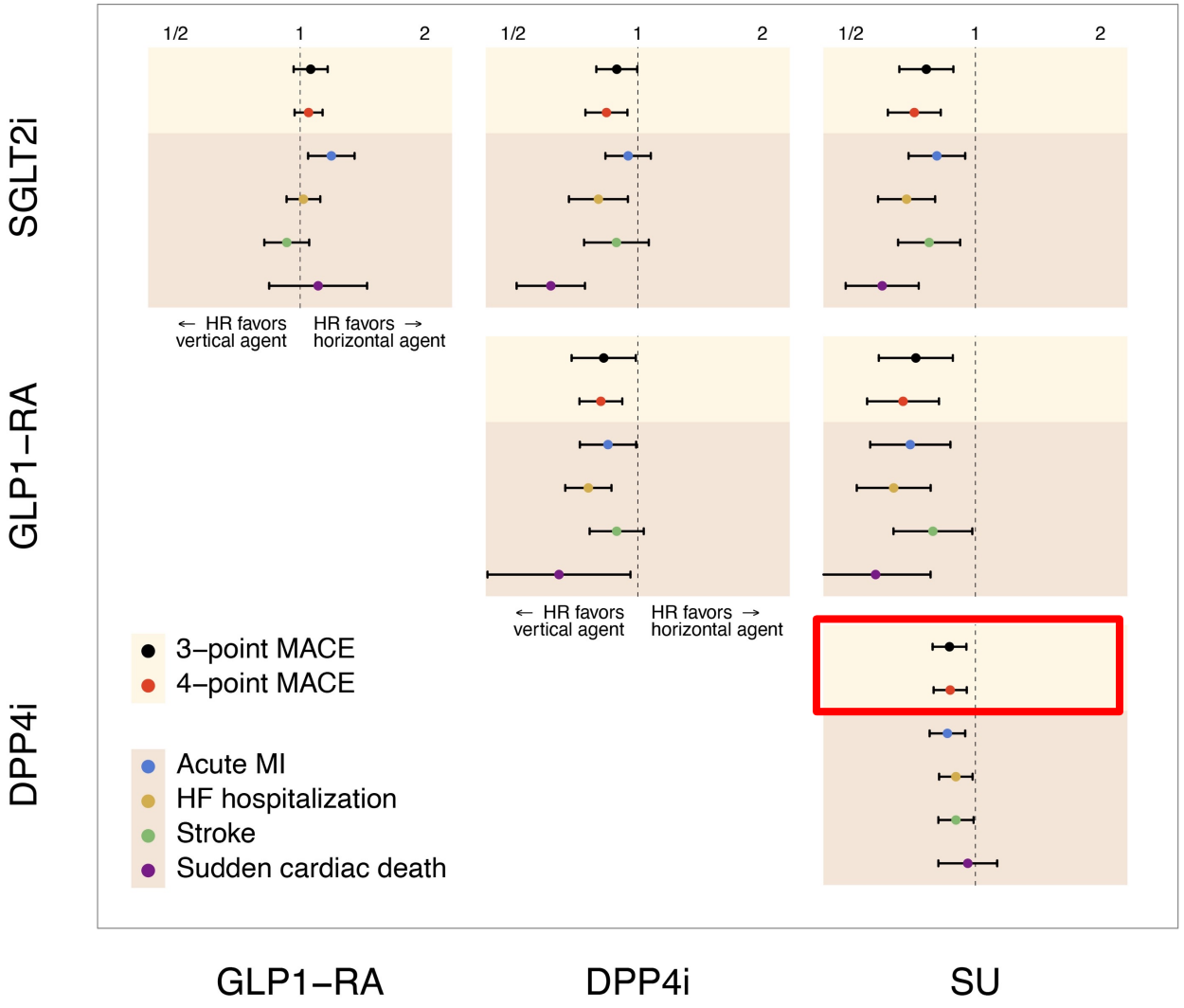


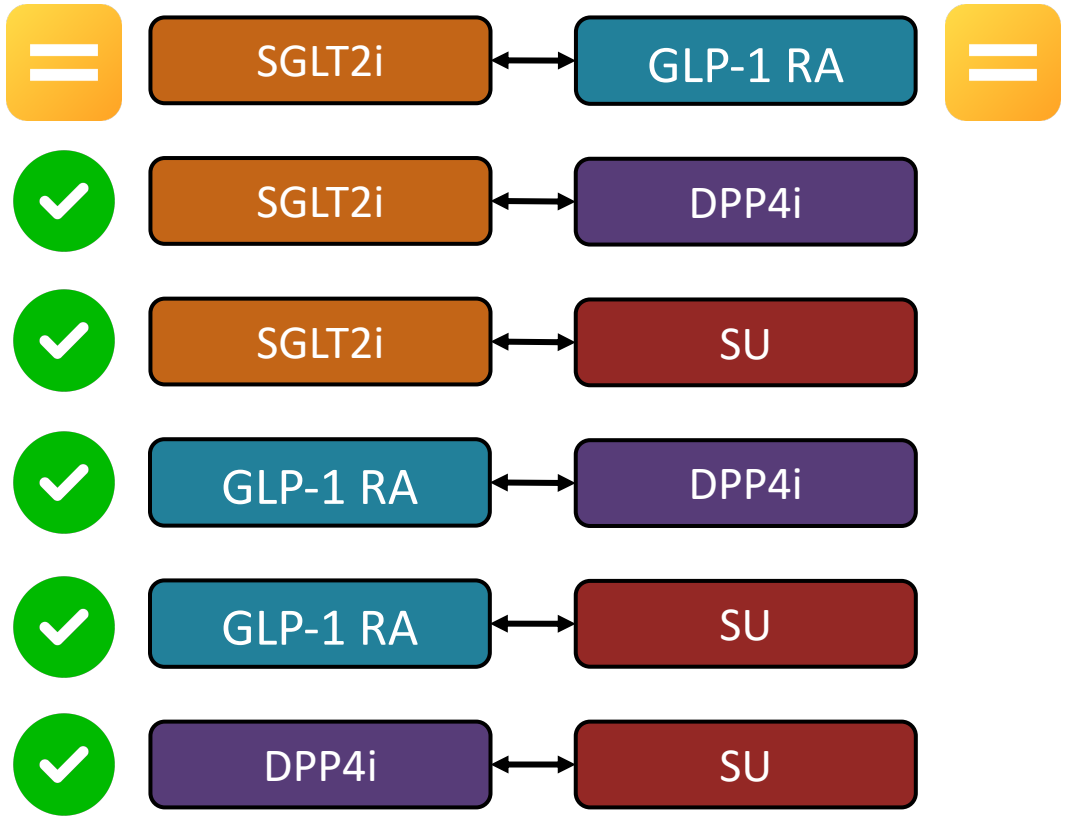
Meta-analytical Calibrated HR Estimates



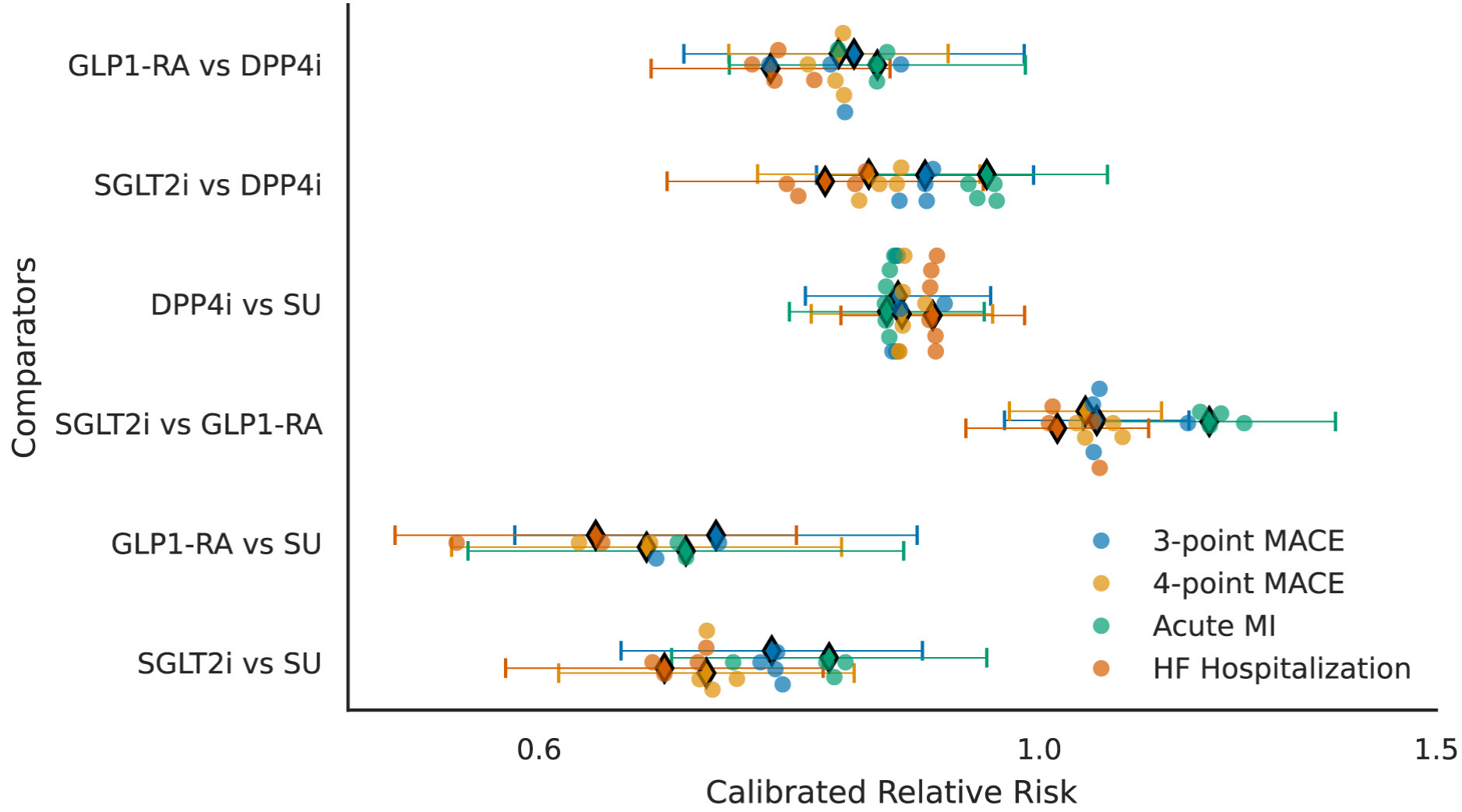


Meta-analytical Calibrated HR Estimates



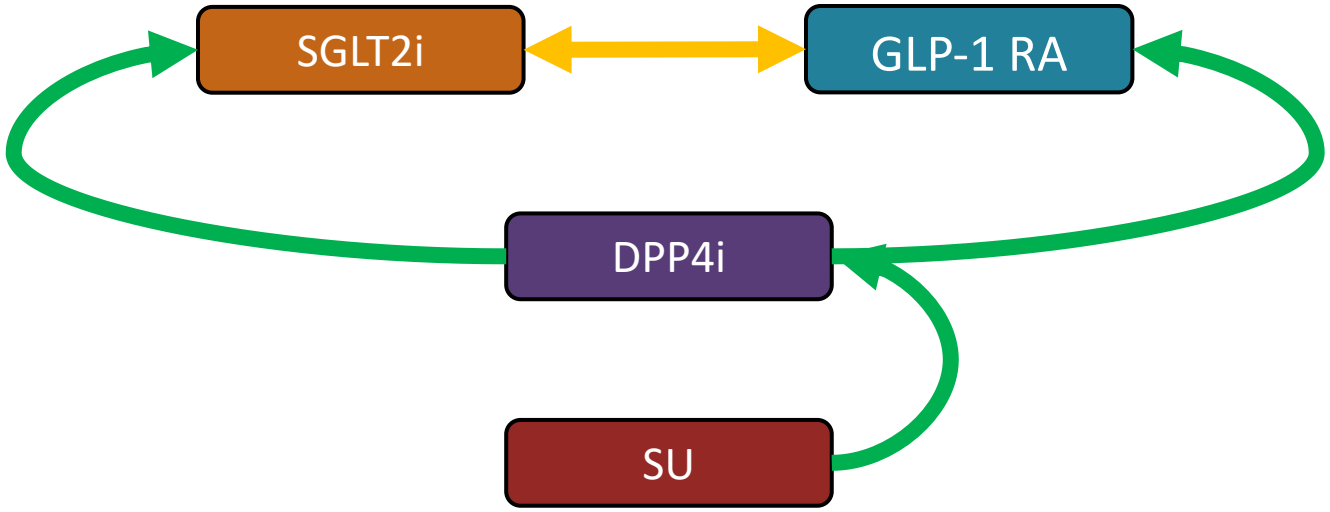


Leave-one-out Meta-analysis



Conclusion

Second-line Treatment



Patients with T2DM & established CVD
On metformin therapy
Still high blood sugar

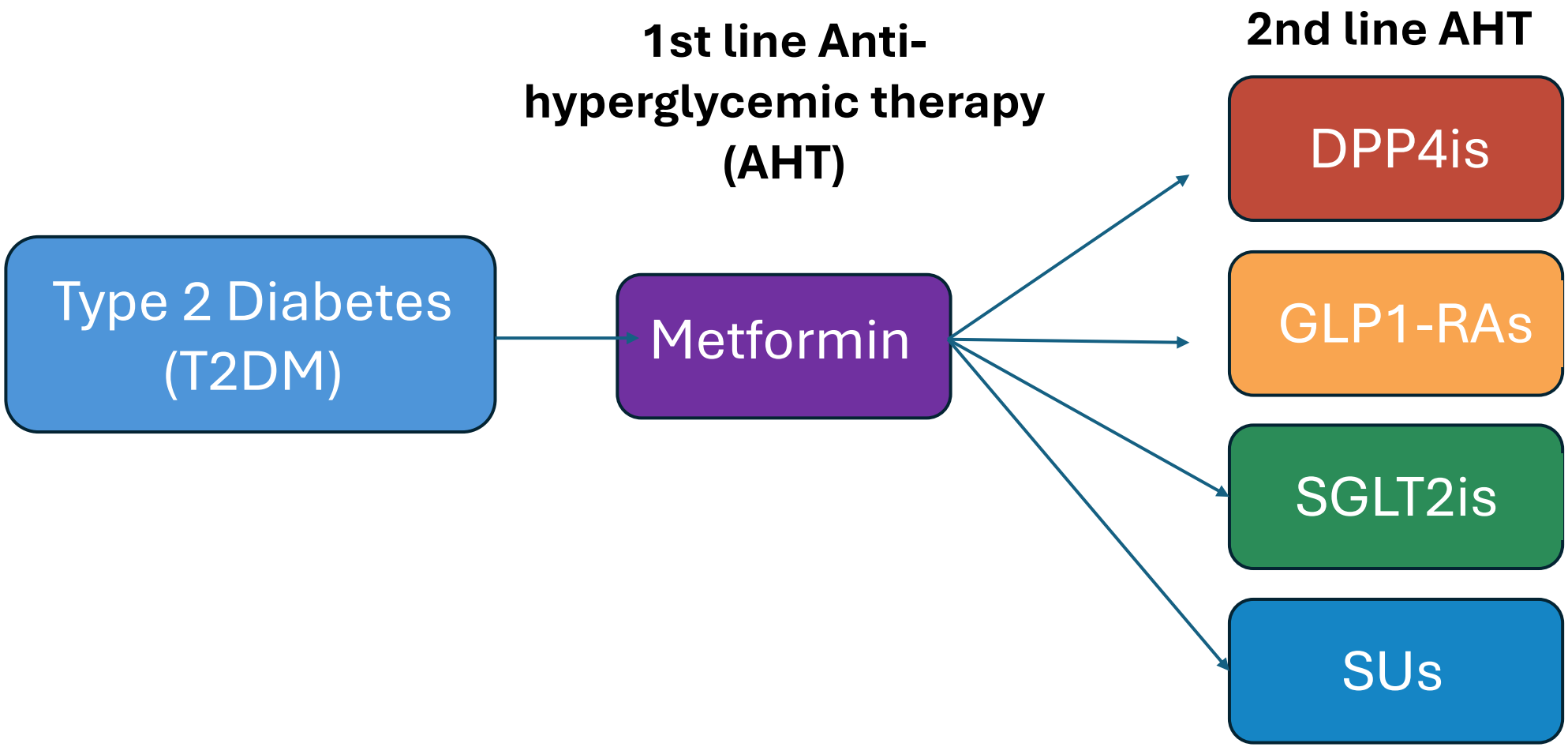
Multinational trends in the use of cardioprotective antihyperglycemic agents as 1st line therapy in patients with T2DM and cardiovascular disease: A LEGEND-T2DM Study

Phyllis Thangaraj, MD, PhD

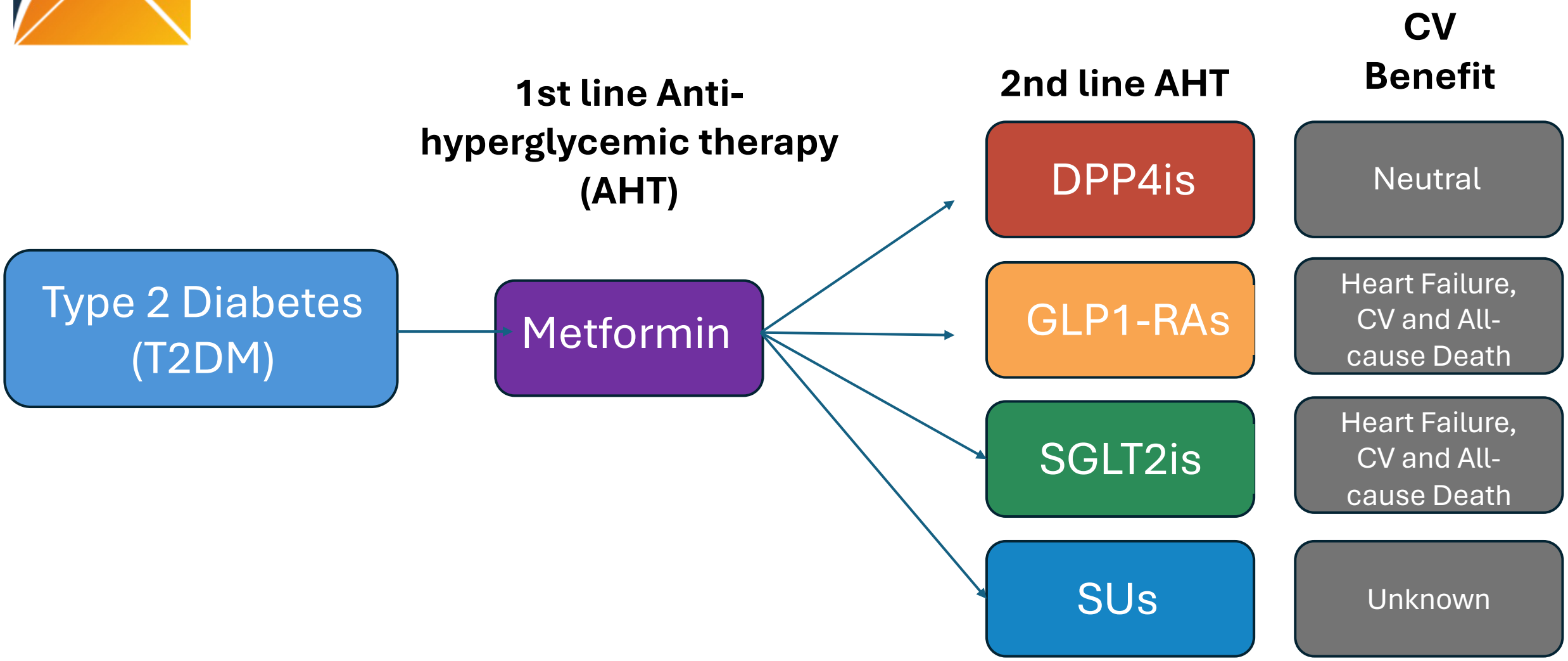
Post-doctoral Fellow in CarDS Lab

Cardiology Fellow at Yale University

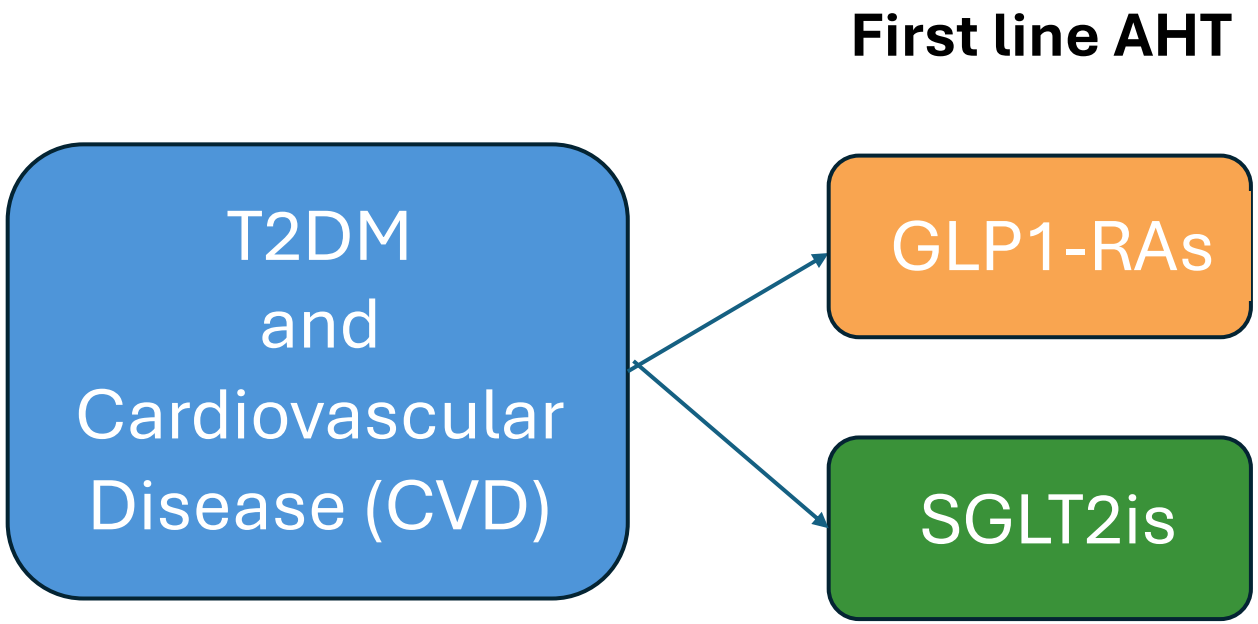
ADA Guidelines Before 2022



ADA Guidelines Before 2022



ADA Guidelines Since 2022



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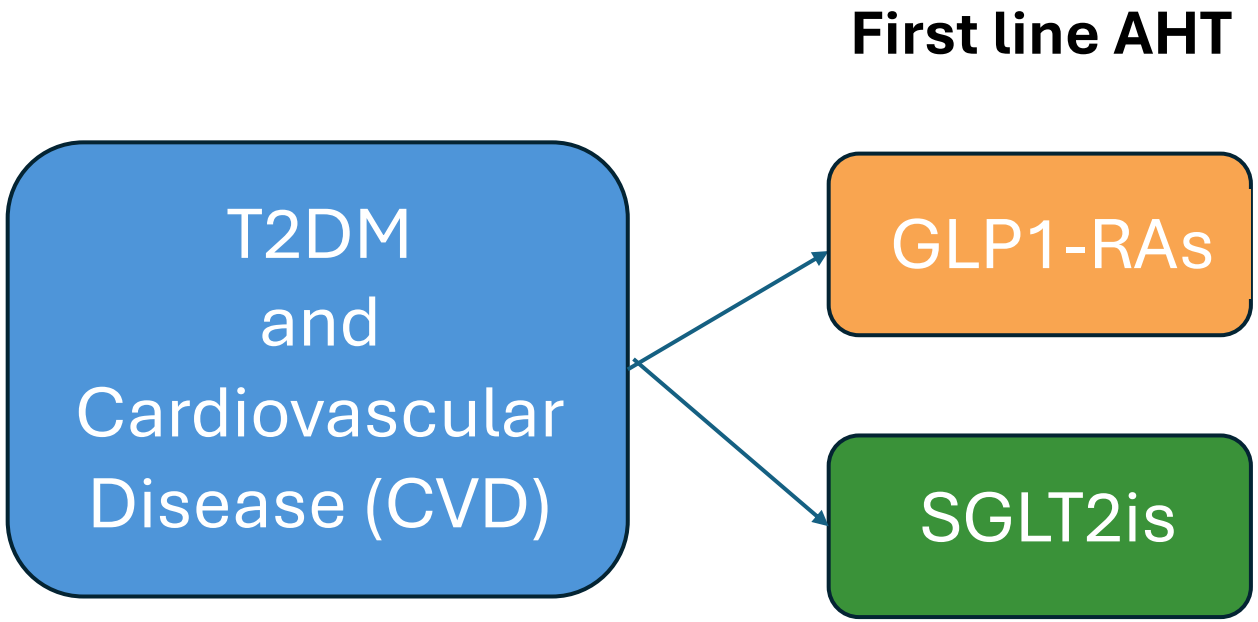
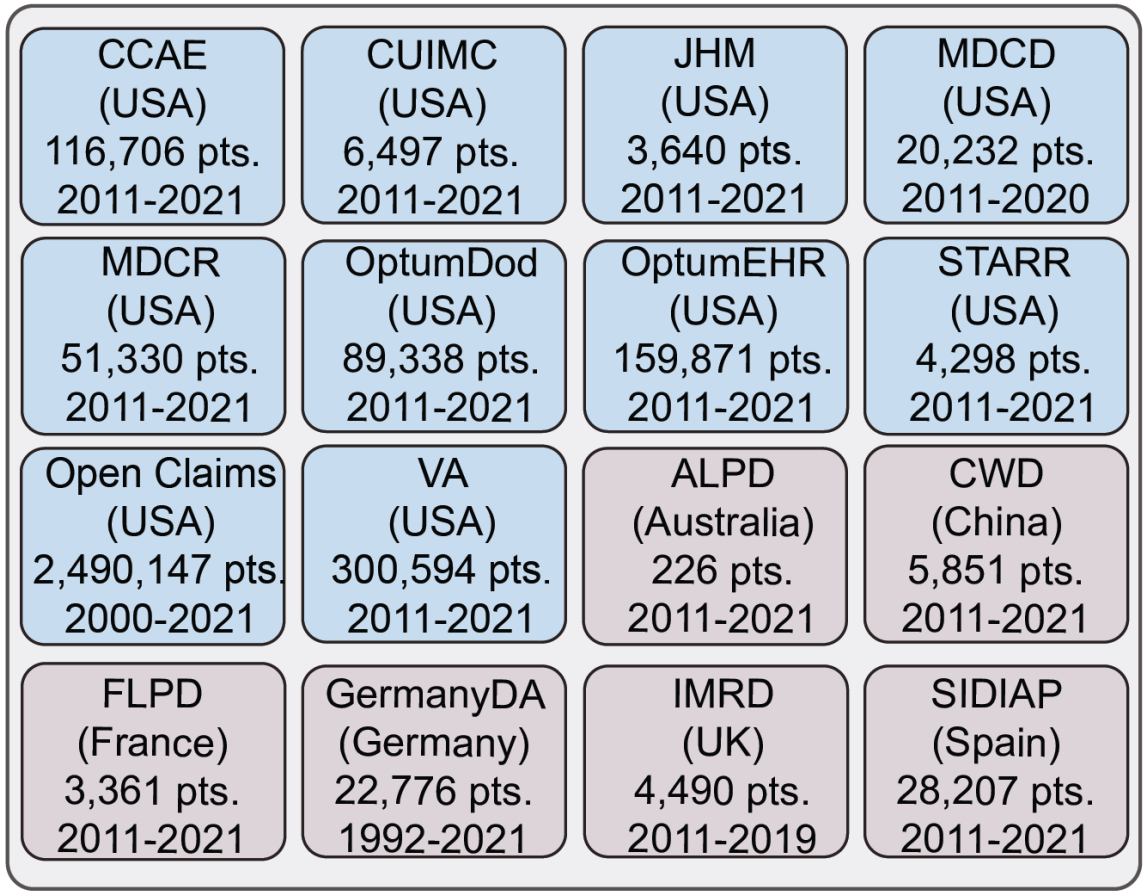


What is the contemporary landscape for this guideline implementation?

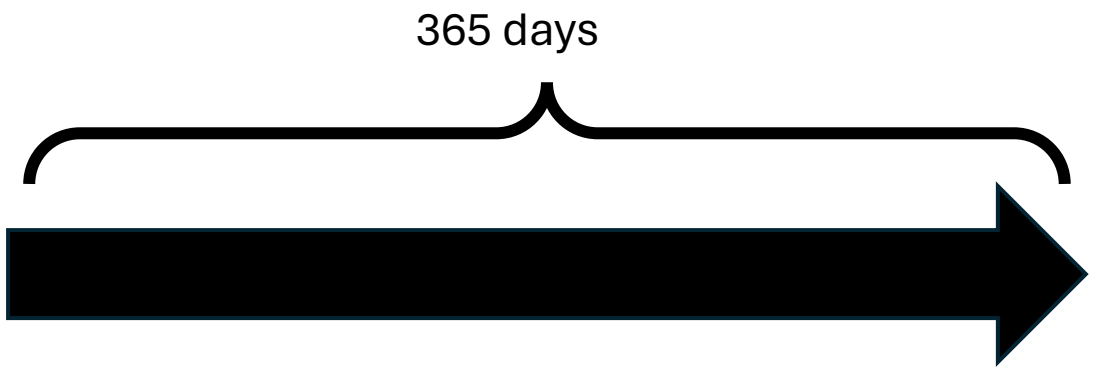
An opportunity with LEGEND-T2DM

3.3 million patients from:

- 6 US National Databases
- 4 US Healthcare Systems
- 6 International Databases



Study Cohort



Cohort Entry:

- >= 18 yo
- T2DM
- CVD
- No prior AHT use

Comparators:

- No CVD
- Prior metformin use

Exposure:

- DPP4is
- GLP1-RAs
- SGLT2is
- SUs

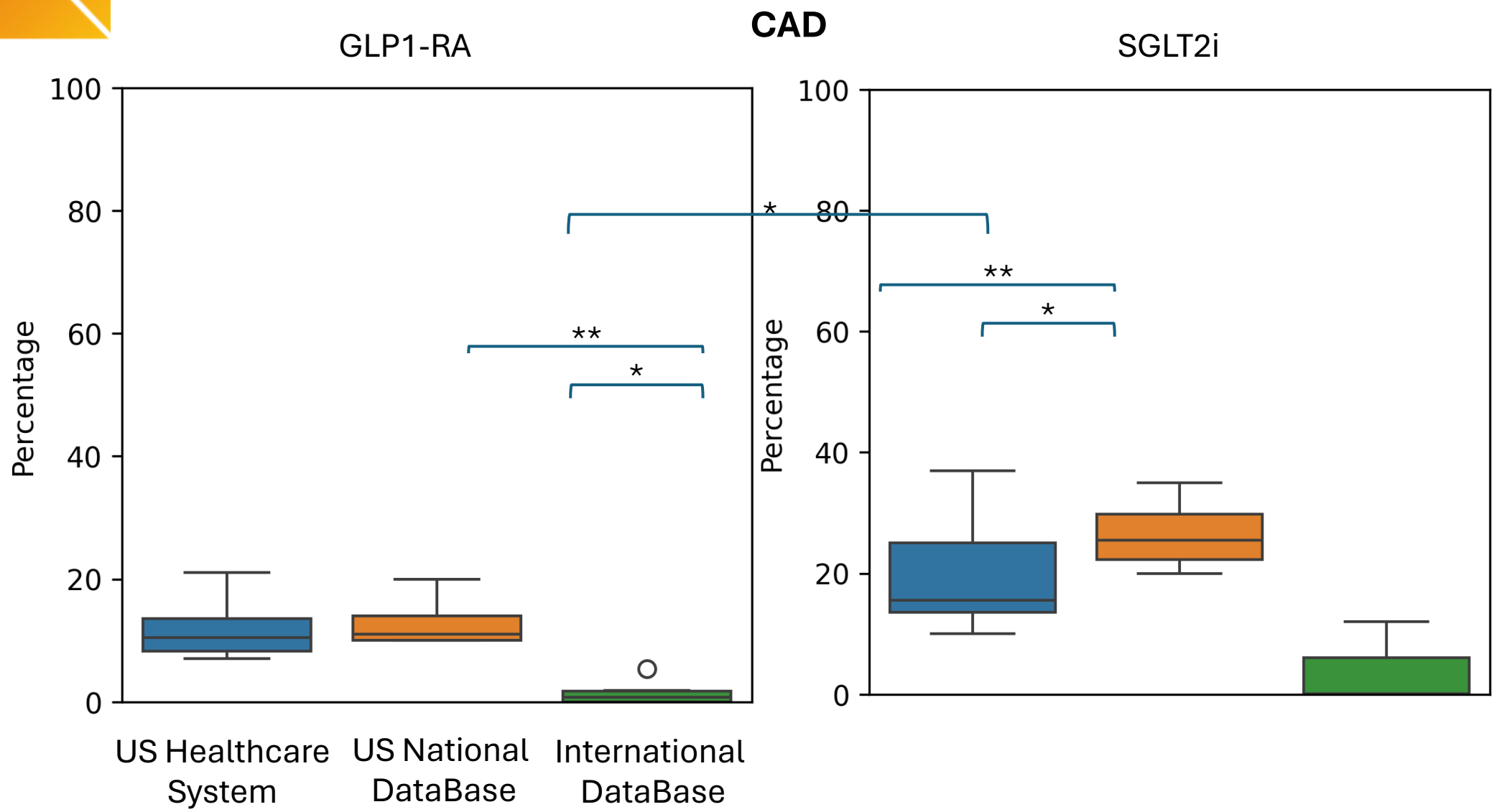
Outcomes:

- Calendar year trends
- Annualized change

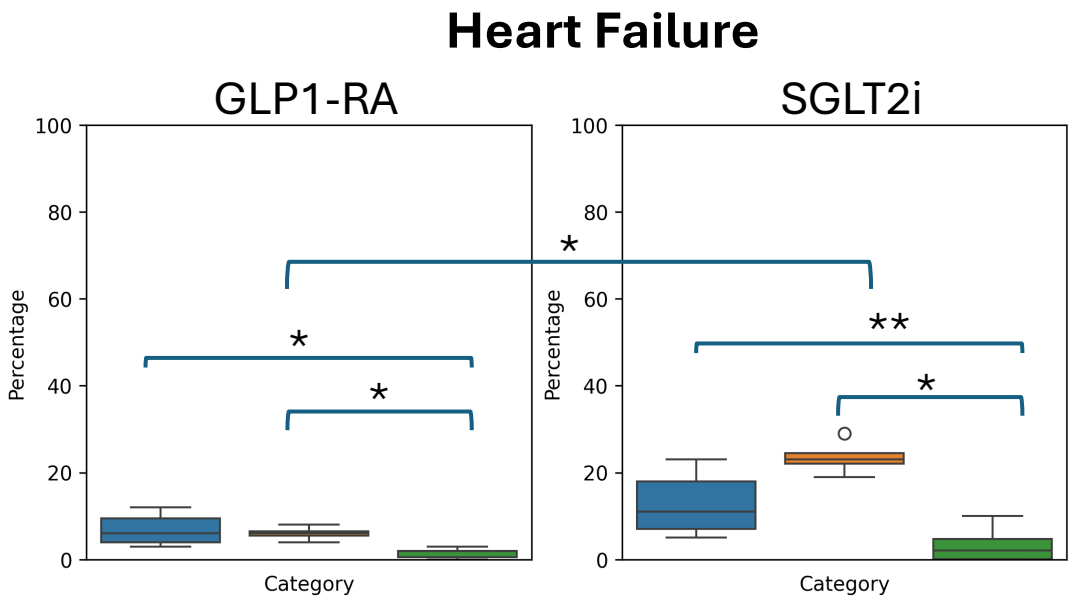
First-line Cardioprotective AHT Patients

GLP1-RA				SGLT2i		
US Healthcare Systems	US National Databases	International Databases		US Healthcare Systems	US National Databases	International Databases
9-57	58-71	46-64	**Female**	4-42	37-61	20-47
35-62	2-95	10-46	**Age >= 65**	51-71	2-96	19-52
18-39	15-43	3-30	**Obese**	15-23	13-36	0-10

First-line Cardioprotective AHT Patients



First-line Cardioprotective AHT Patients



* P<0.05

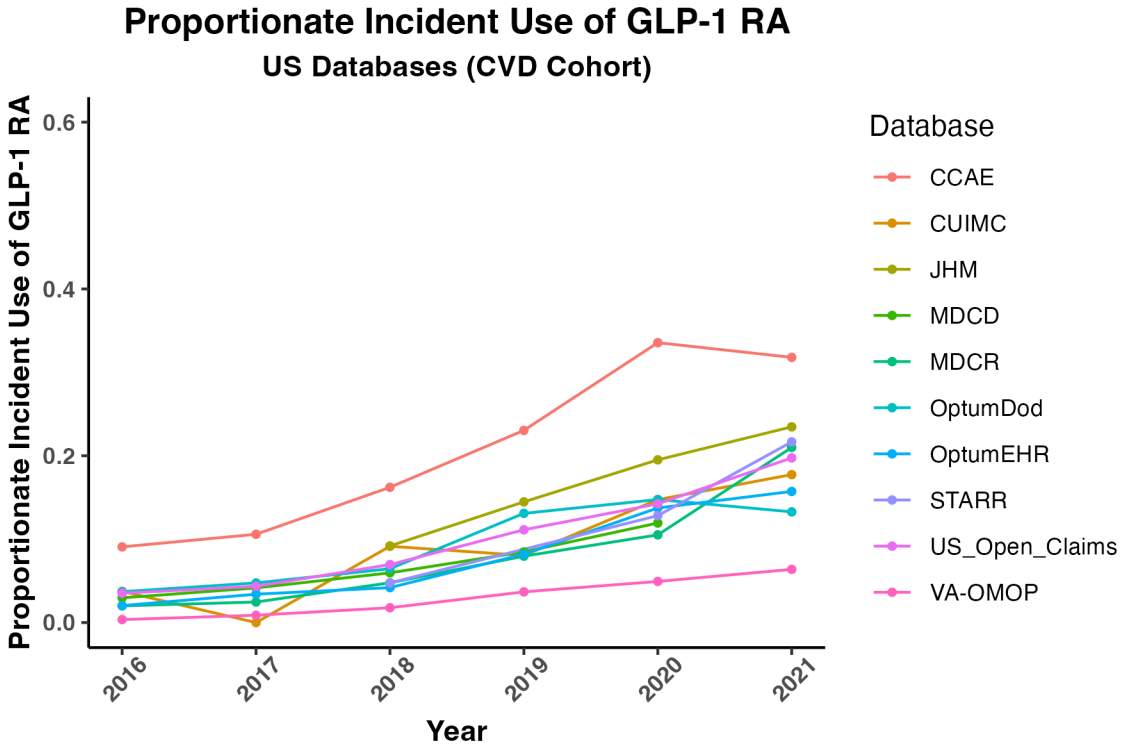
** P<0.01

US National DB

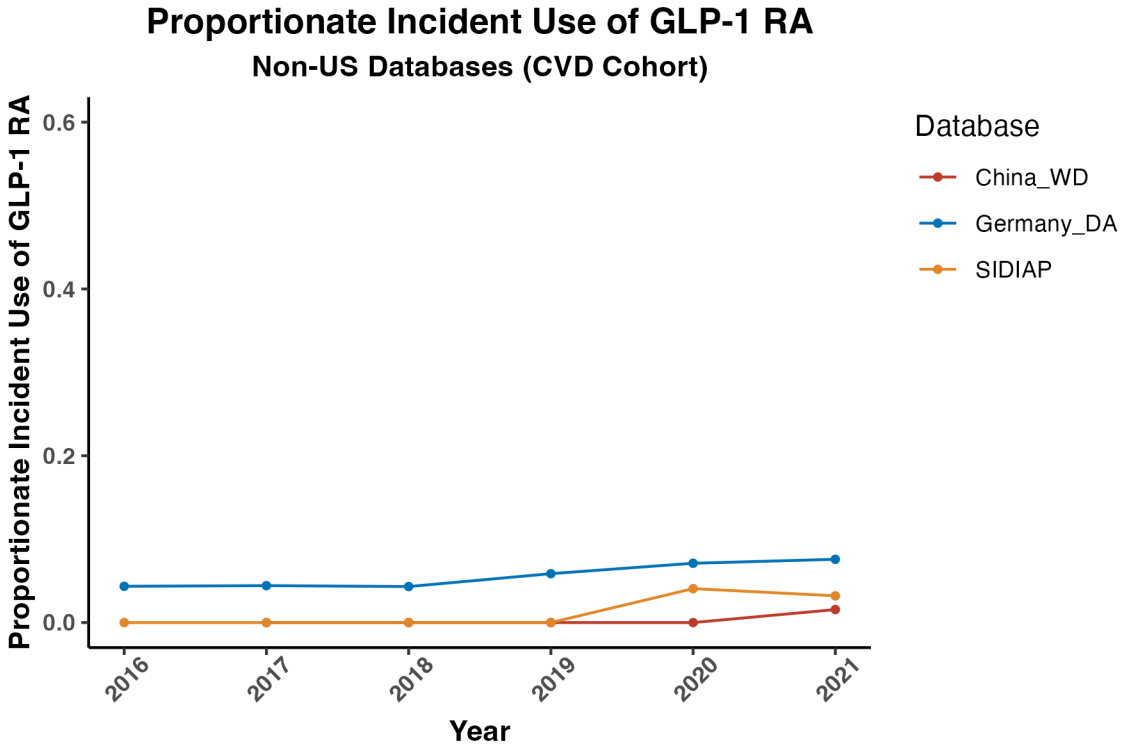
US Healthcare

International DB

Yearly Trends of Proportionate Incident Use of GLP1RAs as 1st line

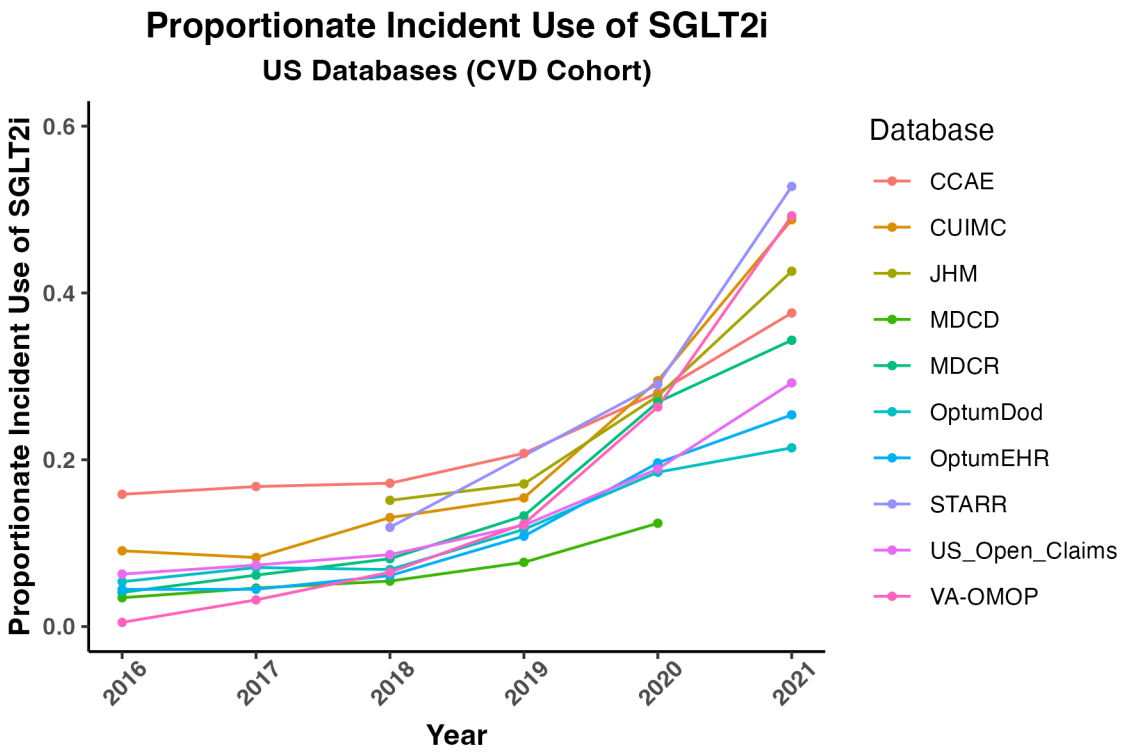


Annual rate of increase 1.3-5.4%

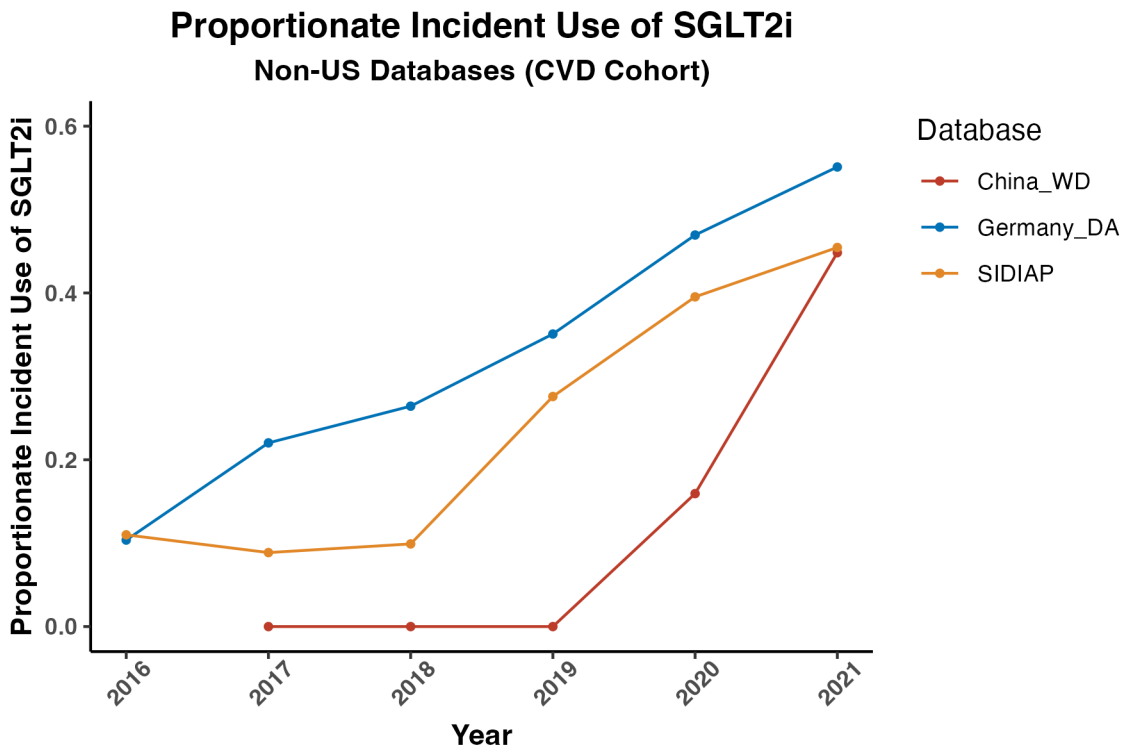


Annual rate of increase 0.3-0.8%

Yearly Trends of Proportionate Incident Use of SGLTis as 1st line



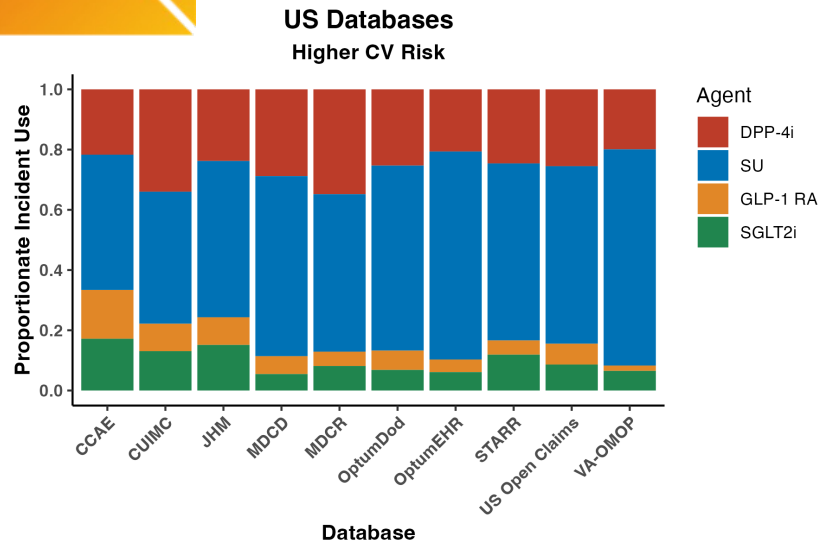
Annual rate of increase 8.1-10.6%

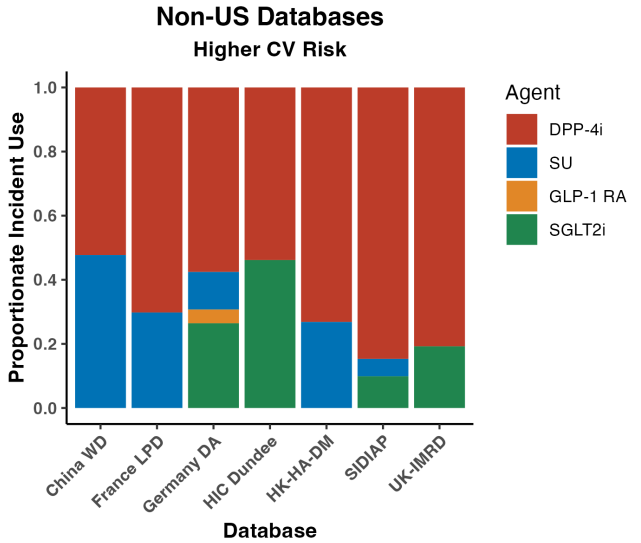


Annual rate of increase 2.1-12.9%

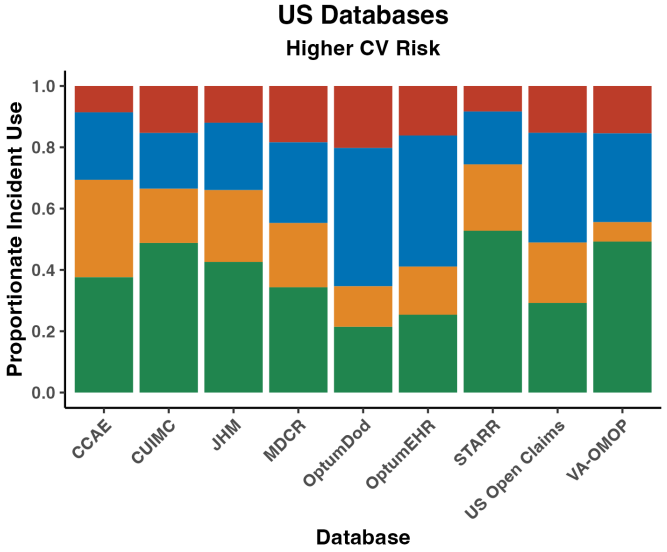
Proportionate Incident Use of 2nd line AHT as 1st line over time

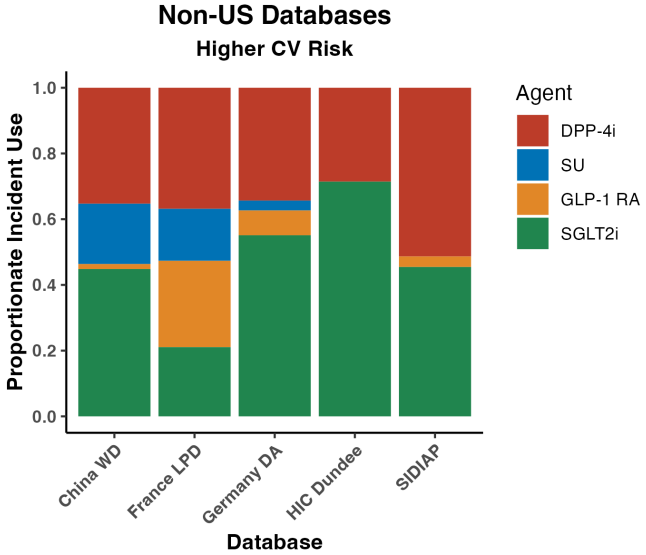
Time





2018





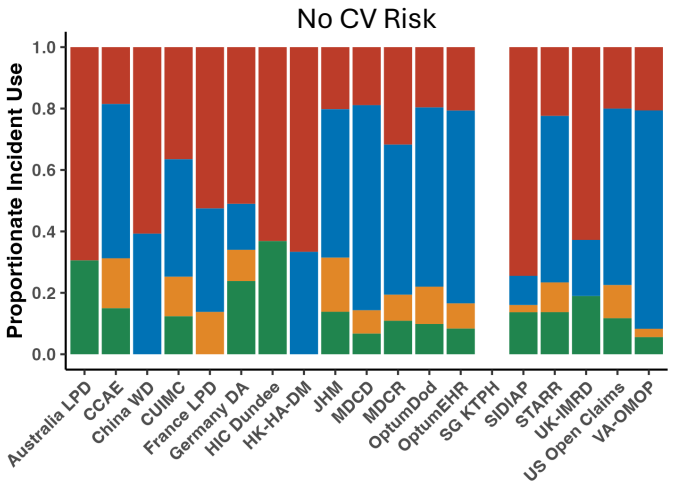
2021

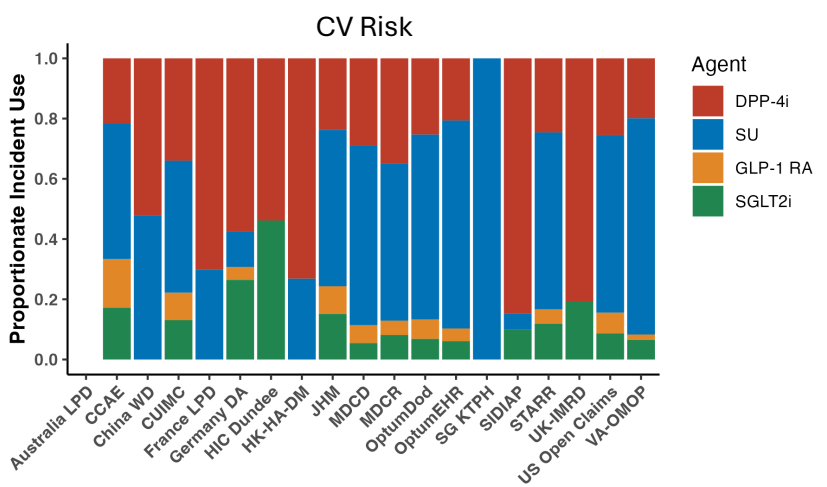
By Database Region

AHT	Time	US	US x Time
SGLTis	↑	—	US < NUS
GLP1RAs	—	—	US >NUS
DPP4is	↓	US<NUS	—
SUs	↓	US>NUS	—

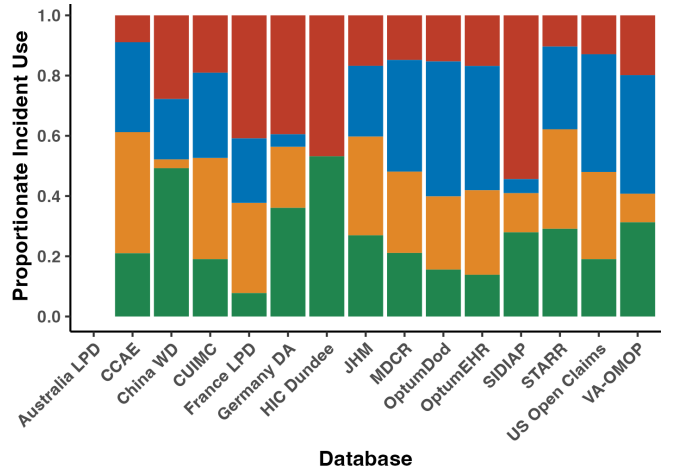
Proportionate Incident Use of 2nd line AHT as 1st line over time

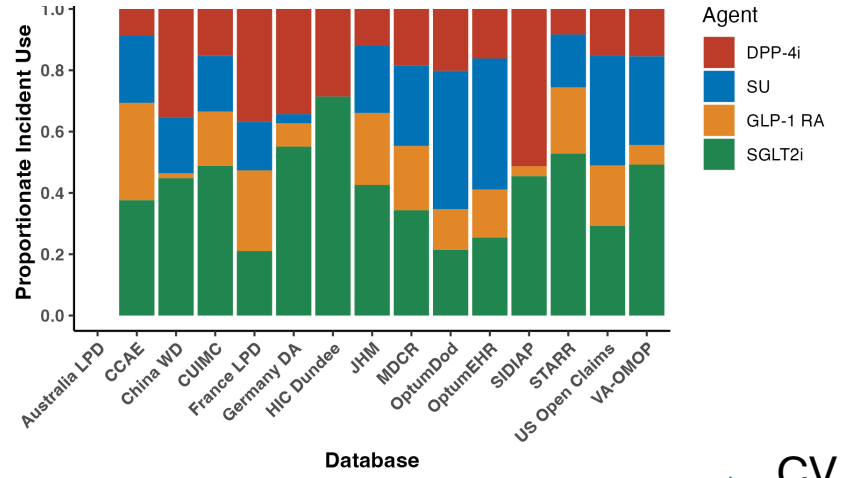
2018





2021





Time

CV Risk

By CV Risk

AHT	Time	CVD	CVD x Time
SGLTis	↑	NCVD > CVD	NCVD < CVD
GLP1RAs	↑	—	NCVD > CVD
DPP4is	↓	—	—
SUs	↓	—	—

Proportionate Incident Use of 2nd line AHT over time

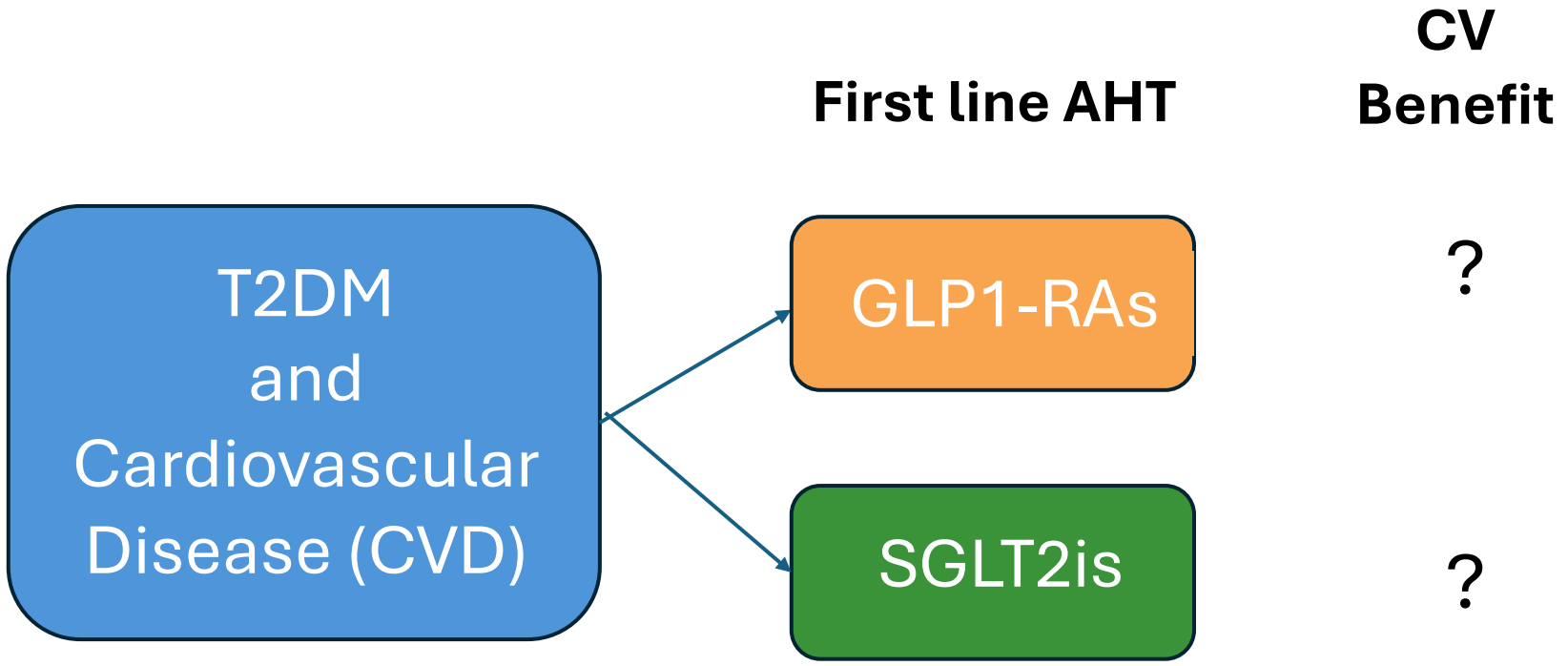
By Database Region and as 1st Line vs 2nd Line

AHT	Time	US	2nd Line	US x Time	US x 2nd Line	2nd Line x Time	US x 2nd Line x Time
SGLTis	↑	—	—	US<NUS	—	1st>2nd	↓
GLP1RAs	↑	US<NUS	—	US>NUS	US>NUS	1st>2nd	↓
DPP4is	↓	US<NUS	1st>2nd	US>NUS	US>NUS	2nd>1st	↑
SUs	↓	US>NUS	1st >2nd	US<NUS	US<NUS	2nd>1st	↑

Conclusions

- Cardioprotective AHT have increased as 1st line over time.
- The rate of increase of SGLTis as 1st line AHT has been greater in non-US databases, while for GLP1RAs, the opposite is true.
- The rate of increase of SGLTis as 1st line AHT has been greater in patients with CVD, while for GLP1RAs, the opposite is true .

After 2022



An Ongoing LEGEND-T2DM CES Study!

Thank you!

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SGLT2 Inhibitors and Diabetic Ketoacidosis:

A study of new users of SGLT2i as second line therapy in Type 2 Diabetes Mellitus

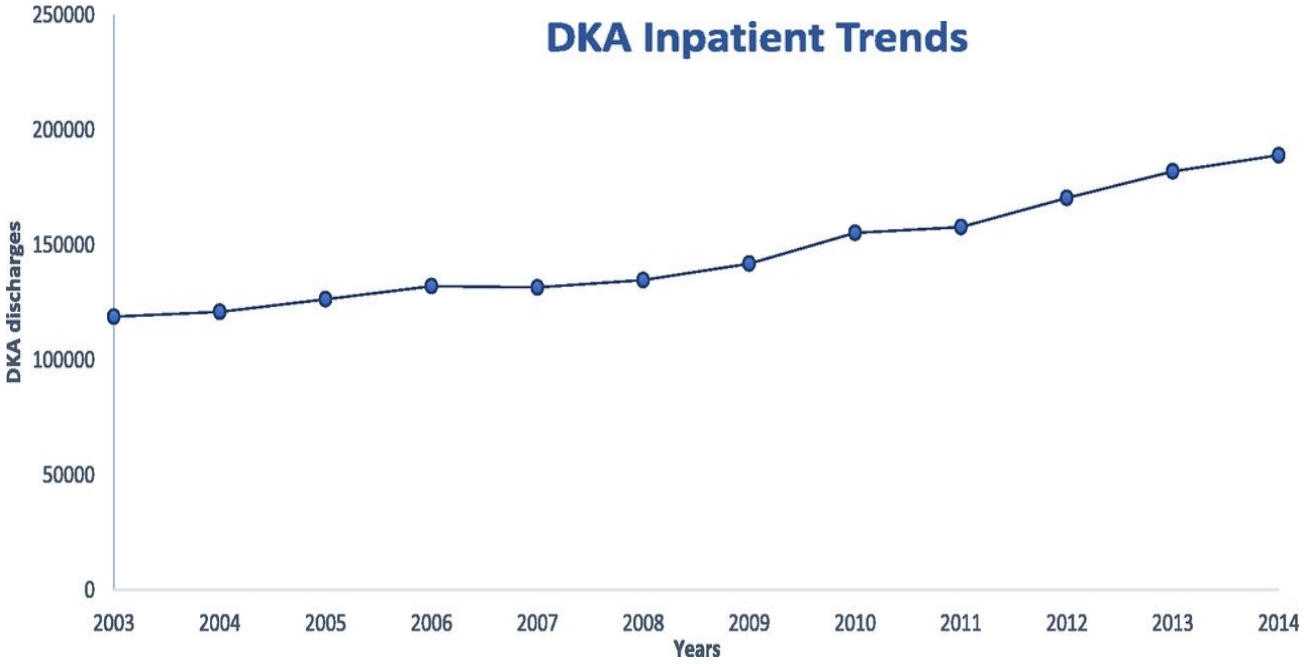
Hannah Yang MD
On Behalf of the LEGEND T2DM Study Group

Acknowledgements

Thank you to Dr. Marc Suchard, Data Partners, and the LEGEND group!

A note on Diabetic Ketoacidosis (DKA)

DKA is a life-threatening complication of diabetes mellitus, more commonly seen in Type 1 Diabetes.



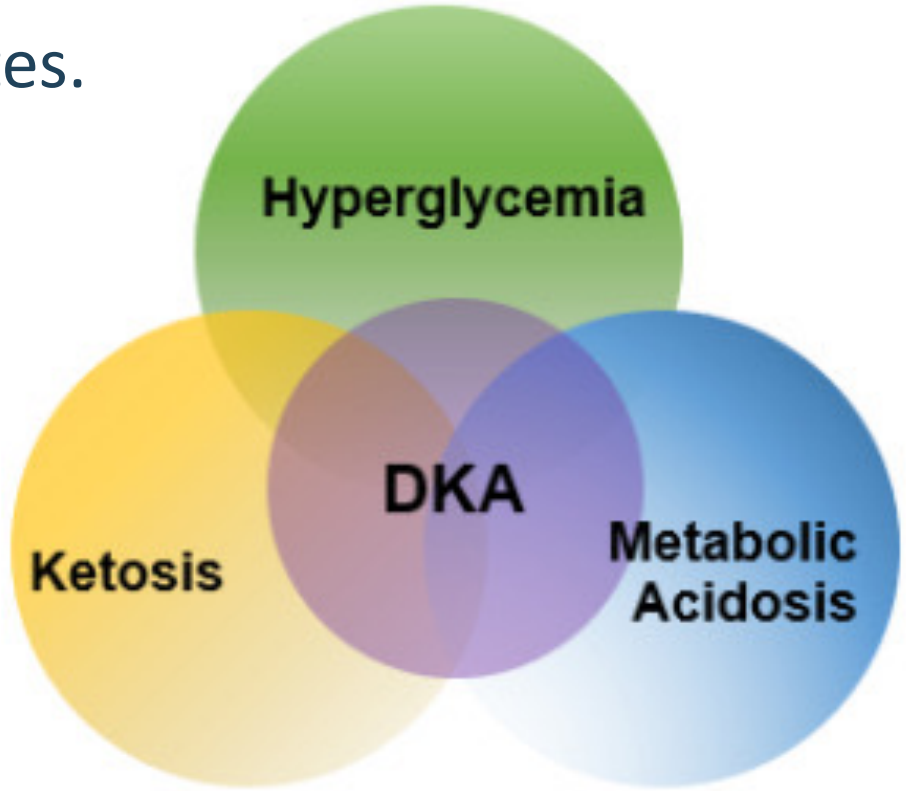
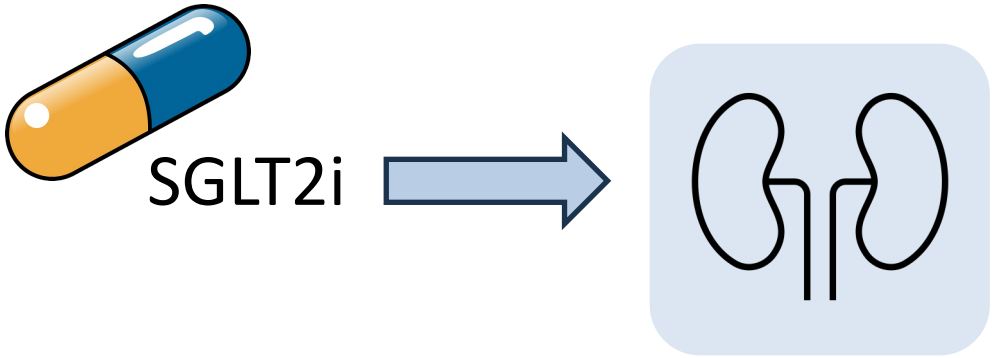


Figure 1. Incidence of DKA from American inpatient data.
Source: *Desai et al., Diabetes Care 2018*

What is the mechanism of SGLT2i’s

SGLT2i

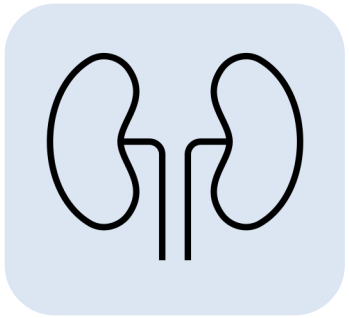
What is the mechanism of SGLT2i's



Glycosuria
Natriuresis

What is the mechanism of SGLT2i's

SGLT2i



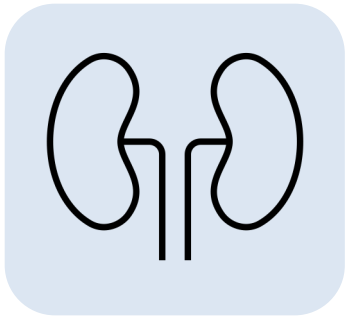
Glycosuria
Natriuresis

Low glucose

↓insulin secretion
↑glucagon

What is the mechanism of SGLT2i's

SGLT2i

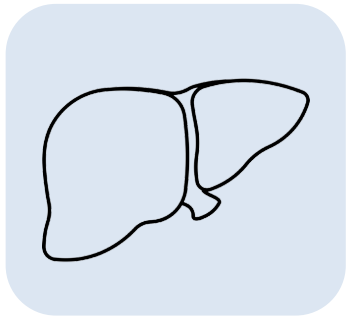


Glycosuria
Natriuresis

Low glucose

↓insulin secretion
↑glucagon

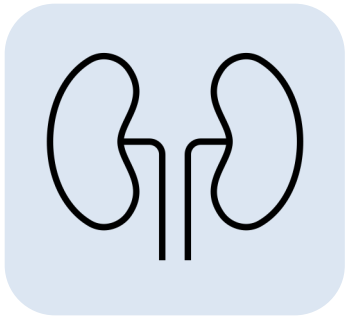
↑lipolysis



Oxidation of FFA's

What is the mechanism of SGLT2i's

SGLT2i

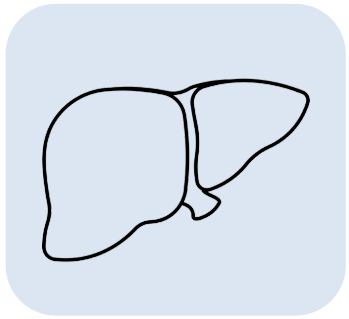


Glycosuria
Natriuresis

Low glucose

↓insulin secretion
↑glucagon

↑lipolysis



Oxidation of FFA's

Ketone Bodies

DKA

A Review of the Literature: RCTs

Table 1. Sample size and number of DKA events observed in the original clinical trial programs for SGLT2i, meta-analysis of randomized controlled trials, and the LEGEND-T2DM study.

	Sample Size	# of DKA Events	
		Total	SGLT2i
Empa-Reg	7020	5	3
Dapa-HF	4744	3	3
CANVAS	17 596	12	10
Meta-analysis of 39 RCTs (Liu et al. 2020)	60 580	85	62
LEGEND-T2DM	**4 290 163**	**3592**	**704**

A Review of the Literature: Cohort Studies

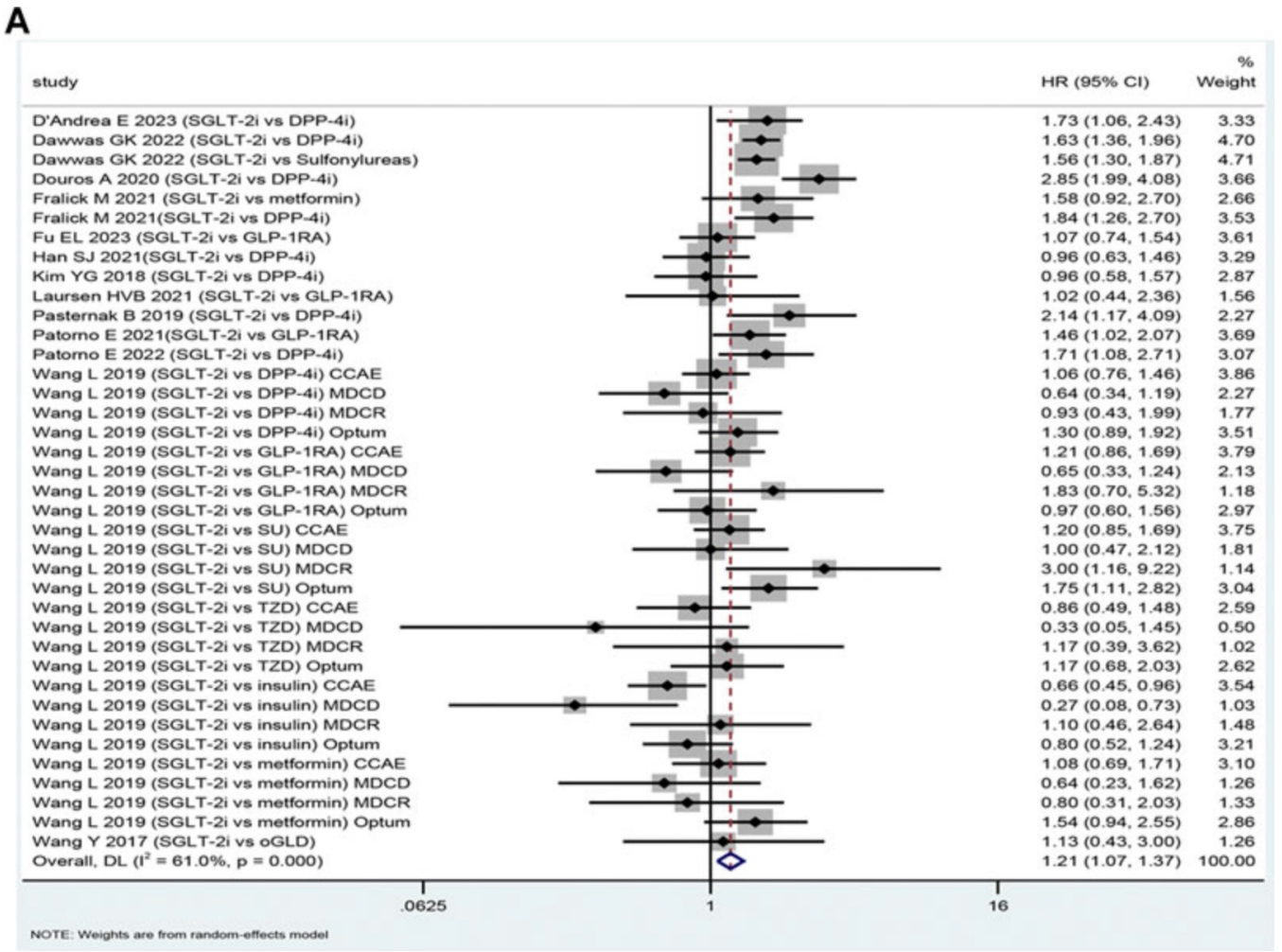


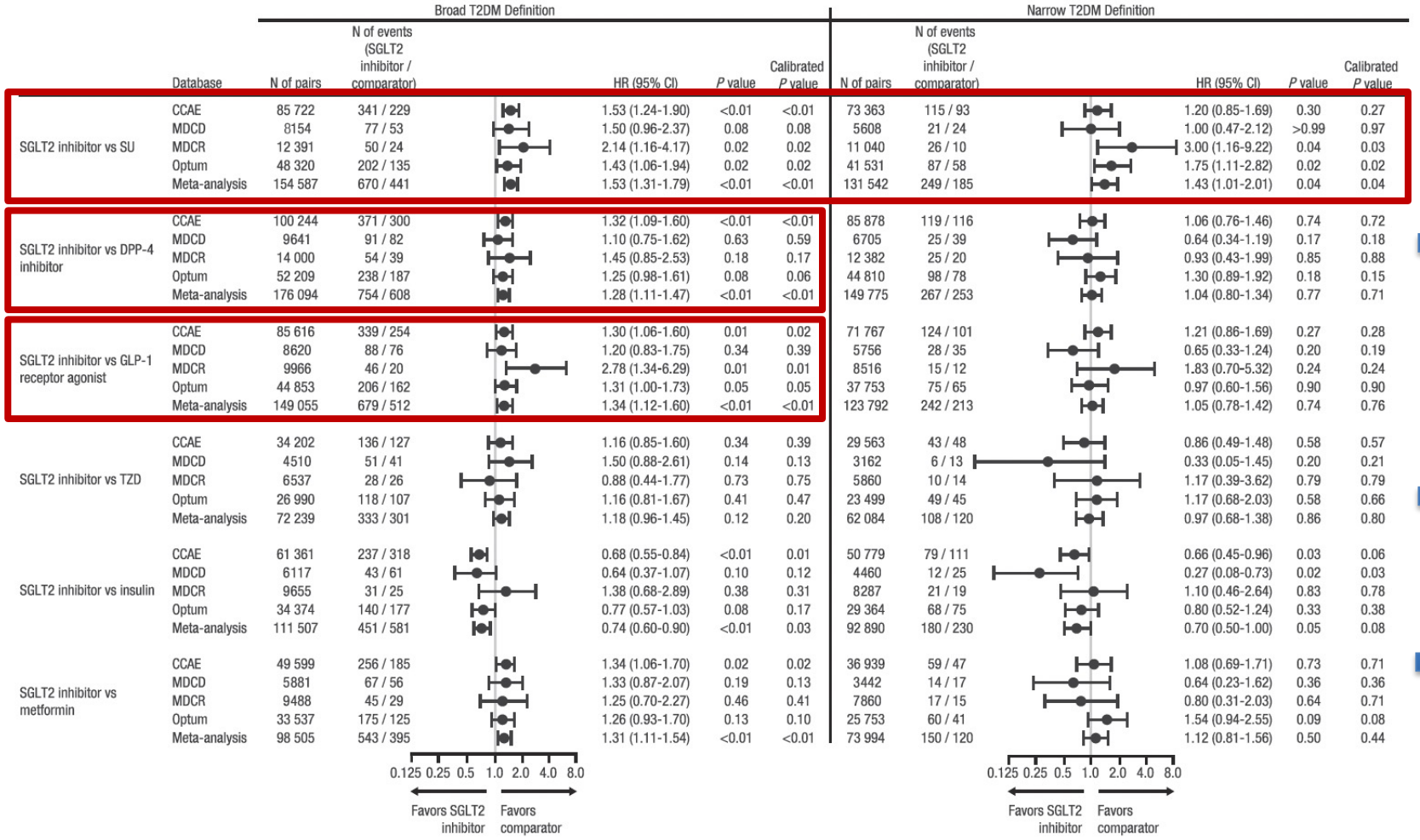
Figure 2. Forest plot of risk of diabetic ketoacidosis generated from meta-analysis of 14 cohort studies. *Source: Li et al. 2023*

A Review of the Literature: Cohort Studies

BROAD DEFINITION

T2DM Dx

No previous T1DM or Secondary Diabetes



	Database	Broad T2DM Definition: N of pairs	N of events (SGLT2 inhibitor / comparator)	HR (95% CI)	P value	Calibrated P value	Narrow T2DM Definition: N of pairs	N of events (SGLT2 inhibitor / comparator)	HR (95% CI)	P value	Calibrated P value
SGLT2 inhibitor vs SU	CCAE	85 722	341 / 229	1.53 (1.24-1.90)	<0.01	<0.01	73 363	115 / 93	1.20 (0.85-1.69)	0.30	0.27
	MDCD	8154	77 / 53	1.50 (0.96-2.37)	0.08	0.08	5608	21 / 24	1.00 (0.47-2.12)	>0.99	0.97
	MDCR	12 391	50 / 24	2.14 (1.16-4.17)	0.02	0.02	11 040	26 / 10	3.00 (1.16-9.22)	0.04	0.03
	Optum	48 320	202 / 135	1.43 (1.06-1.94)	0.02	0.02	41 531	87 / 58	1.75 (1.11-2.82)	0.02	0.02
	Meta-analysis	154 587	670 / 441	1.53 (1.31-1.79)	<0.01	<0.01	131 542	249 / 185	1.43 (1.01-2.01)	0.04	0.04
SGLT2 inhibitor vs DPP-4 inhibitor	CCAE	100 244	371 / 300	1.32 (1.09-1.60)	<0.01	<0.01	85 878	119 / 116	1.06 (0.76-1.46)	0.74	0.72
	MDCD	9641	91 / 82	1.10 (0.75-1.62)	0.63	0.59	6705	25 / 39	0.64 (0.34-1.19)	0.17	0.18
	MDCR	14 000	54 / 39	1.45 (0.85-2.53)	0.18	0.17	12 382	25 / 20	0.93 (0.43-1.99)	0.85	0.88
	Optum	52 209	238 / 187	1.25 (0.98-1.61)	0.08	0.06	44 810	98 / 78	1.30 (0.89-1.92)	0.18	0.15
	Meta-analysis	176 094	754 / 608	1.28 (1.11-1.47)	<0.01	<0.01	149 775	267 / 253	1.04 (0.80-1.34)	0.77	0.71
SGLT2 inhibitor vs GLP-1 receptor agonist	CCAE	85 616	339 / 254	1.30 (1.06-1.60)	0.01	0.02	71 767	124 / 101	1.21 (0.86-1.69)	0.27	0.28
	MDCD	8620	88 / 76	1.20 (0.83-1.75)	0.34	0.39	5756	28 / 35	0.65 (0.33-1.24)	0.20	0.19
	MDCR	9966	46 / 20	2.78 (1.34-6.29)	0.01	0.01	8516	15 / 12	1.83 (0.70-5.32)	0.24	0.24
	Optum	44 853	206 / 162	1.31 (1.00-1.73)	0.05	0.05	37 753	75 / 65	0.97 (0.60-1.56)	0.90	0.90
	Meta-analysis	149 055	679 / 512	1.34 (1.12-1.60)	<0.01	<0.01	123 792	242 / 213	1.05 (0.78-1.42)	0.74	0.76
SGLT2 inhibitor vs TZD	CCAE	34 202	136 / 127	1.16 (0.85-1.60)	0.34	0.39	29 563	43 / 48	0.86 (0.49-1.48)	0.58	0.57
	MDCD	4510	51 / 41	1.50 (0.88-2.61)	0.14	0.13	3162	6 / 13	0.33 (0.05-1.45)	0.20	0.21
	MDCR	6537	28 / 26	0.88 (0.44-1.77)	0.73	0.75	5860	10 / 14	1.17 (0.39-3.62)	0.79	0.79
	Optum	26 990	118 / 107	1.16 (0.81-1.67)	0.41	0.47	23 499	49 / 45	1.17 (0.68-2.03)	0.58	0.66
	Meta-analysis	72 239	333 / 301	1.18 (0.96-1.45)	0.12	0.20	62 084	108 / 120	0.97 (0.68-1.38)	0.86	0.80
SGLT2 inhibitor vs insulin	CCAE	61 361	237 / 318	0.68 (0.55-0.84)	<0.01	0.01	50 779	79 / 111	0.66 (0.45-0.96)	0.03	0.06
	MDCD	6117	43 / 61	0.64 (0.37-1.07)	0.10	0.12	4460	12 / 25	0.27 (0.08-0.73)	0.02	0.03
	MDCR	9655	31 / 25	1.38 (0.68-2.89)	0.38	0.31	8287	21 / 19	1.10 (0.46-2.64)	0.83	0.78
	Optum	34 374	140 / 177	0.77 (0.57-1.03)	0.08	0.17	29 364	68 / 75	0.80 (0.52-1.24)	0.33	0.38
	Meta-analysis	111 507	451 / 581	0.74 (0.60-0.90)	<0.01	0.03	92 890	180 / 230	0.70 (0.50-1.00)	0.05	0.08
SGLT2 inhibitor vs metformin	CCAE	49 599	256 / 185	1.34 (1.06-1.70)	0.02	0.02	36 939	59 / 47	1.08 (0.69-1.71)	0.73	0.71
	MDCD	5881	67 / 56	1.33 (0.87-2.07)	0.19	0.13	3442	14 / 17	0.64 (0.23-1.62)	0.36	0.36
	MDCR	9488	45 / 29	1.25 (0.70-2.27)	0.46	0.41	7860	17 / 15	0.80 (0.31-2.03)	0.64	0.71
	Optum	33 537	175 / 125	1.26 (0.93-1.70)	0.13	0.10	25 753	60 / 41	1.54 (0.94-2.55)	0.09	0.08
	Meta-analysis	98 505	543 / 395	1.31 (1.11-1.54)	<0.01	<0.01	73 994	150 / 120	1.12 (0.81-1.56)	0.50	0.44

NARROW DEFINITION

No T1DM or Secondary Diabetes Dx after index date

No previous insulin monotherapy

Age > 40

Figure 3. Hazard ratio of DKA for new users of SGLT2i versus comparator AHAs. *Source: Wang et al. 2019*

Study Aim

What is the relative risk of DKA amongst second line agents used in T2DM?

Methods

Age > 18 at index

Diagnosis of T2DM

On Metformin > 90d

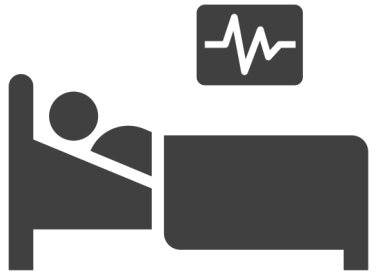
>1 year observation time

No prior Rx with insulin for last 30d

No previous occurrence of T1DM or Secondary DM

No prior treatment with other second-line oral anti-hyperglycemic agents

Primary Outcome



Inpatient or ED visit with occurrence of DKA

Day 0

Initiation of SGLT2i / GLP1-RA / DPP4i / SU for the first time

Statistical Methods

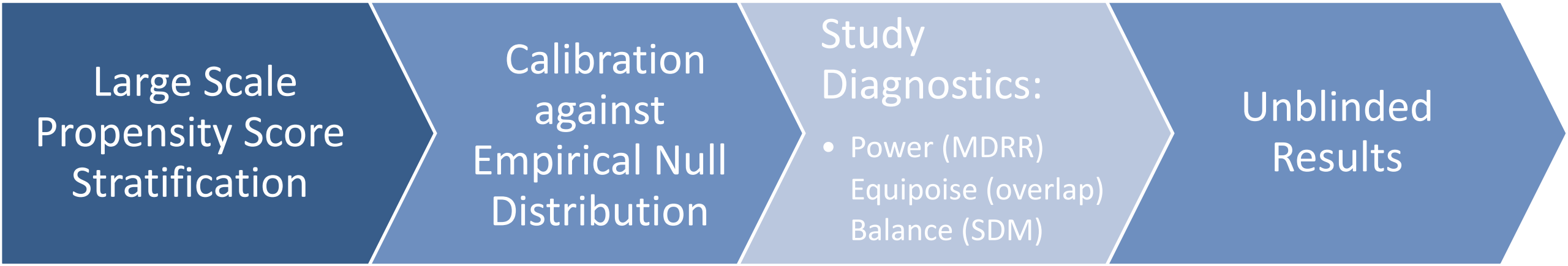
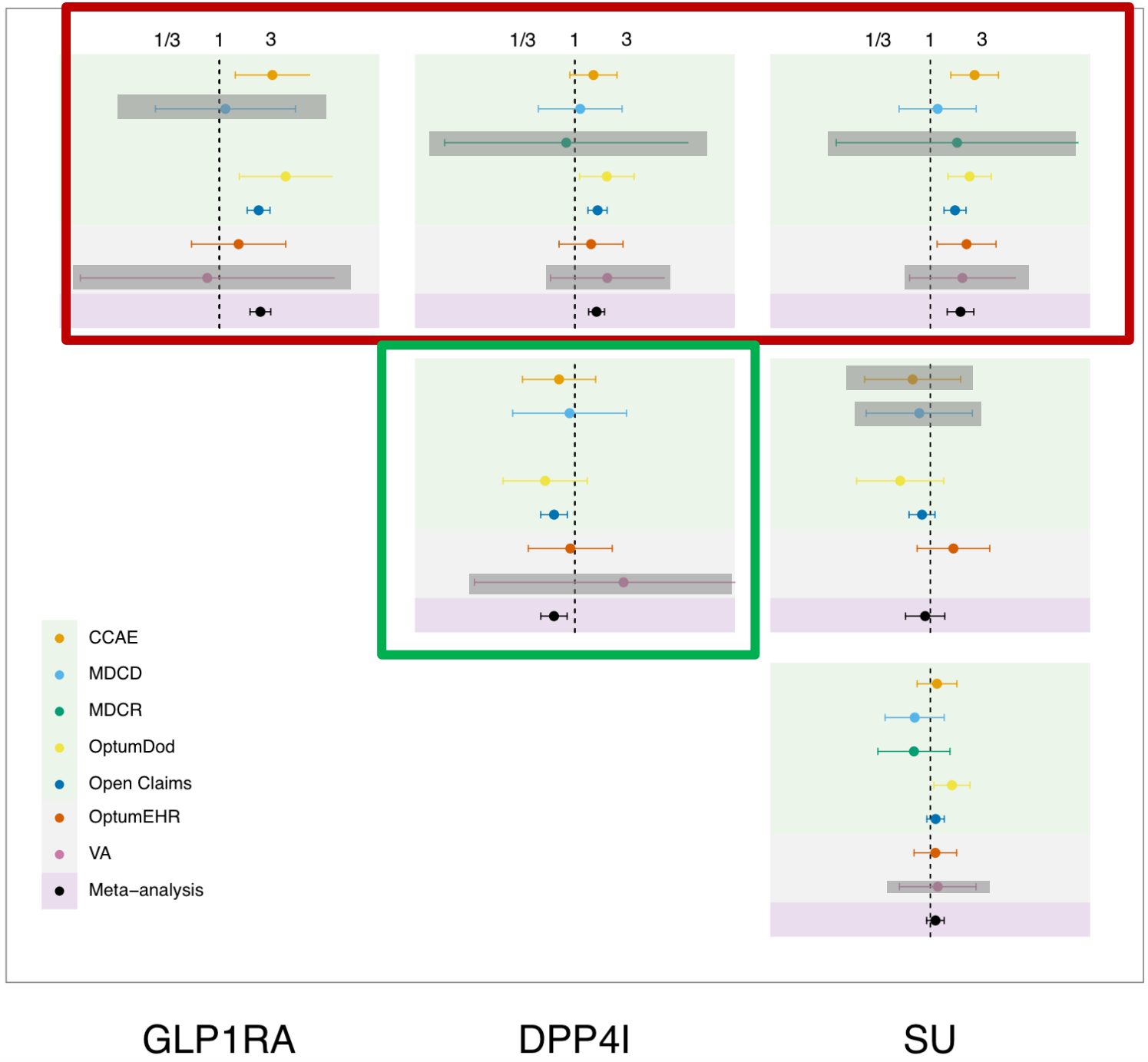


Figure 4. Hazard ratio (HR) estimates and 95% CIs between propensity matched new-user cohorts for DKA.



Comparison to Existing Observational Studies

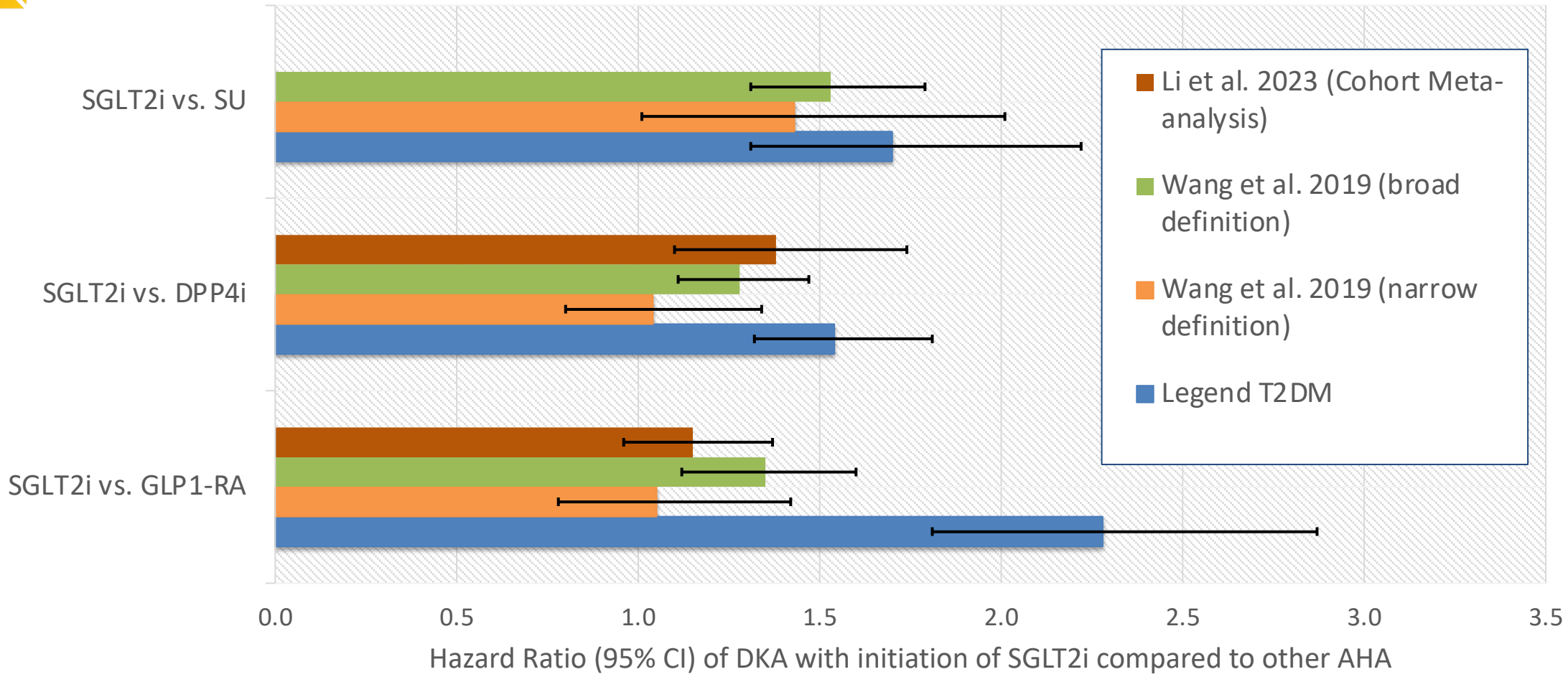


Figure 5. Relative Risk of DKA outcome in users of SGLT2i compared with other Anti-Hyperglycemics

Conclusion

- Findings suggest an increased risk for DKA in new users of SGLT2i compared to other 2nd line agents.

- Clinical emphasis on patient education around sick day management and recognizing DKA signs/symptoms.

GLP-1 Receptor Agonists and Thyroid Tumor:

A study of new users of GLP1-RA as second line therapy in Type 2 Diabetes Mellitus

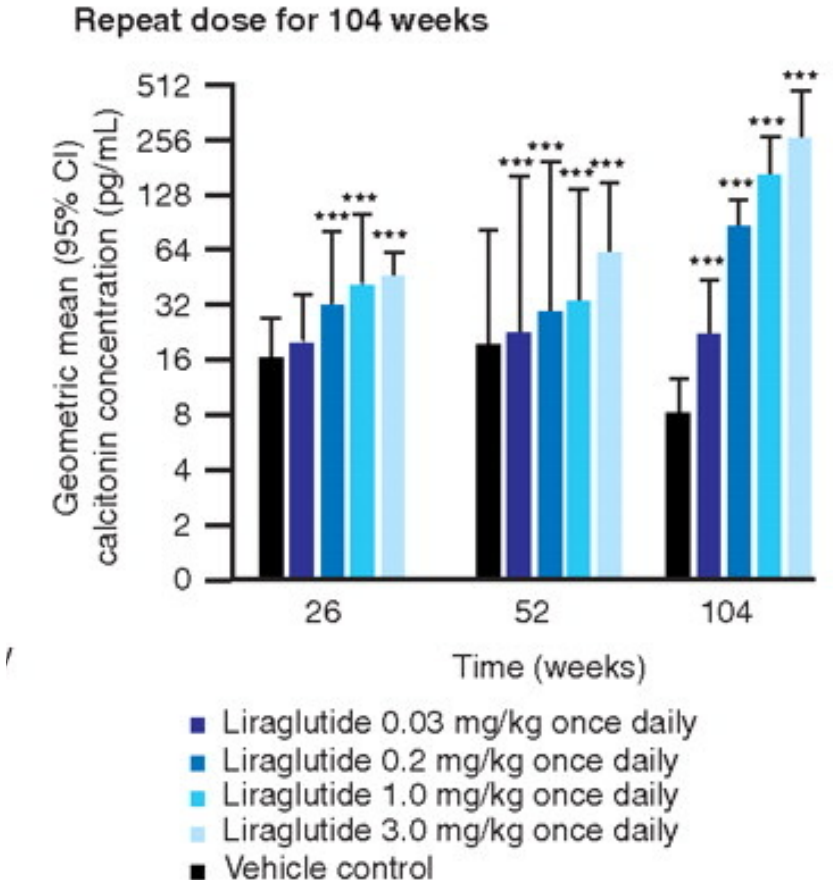
Background on GLP1-RA & thyroid tumor

Non-clinical studies suggest GLP-1 RAs have effects on the thyroid gland, potentially involving the development of thyroid cancers, particularly medullary thyroid cancer (MTC).

In rodents

- Activation of the GLP-1 receptor on thyroid C-cells leads to calcitonin secretion
- Plasma calcitonin is a specific biomarker for increased C-cell number & changes in calcitonin levels are used in the diagnosis of C-cell disease in humans

MTC is an important potential risk in the risk minimization plan (RMP for GLP-1 RAs and monitored in an ongoing PASS.



Endocrinology. 2010;151:1473-86. doi: 10.1210/en.2009-1272.

Background on GLP1-RA & thyroid tumor

TRULICITY (dulaglutide) injection, for subcutaneous use

Initial U.S. Approval: 2014

WARNING: RISK OF THYROID C-CELL TUMORS

See full prescribing information for complete boxed warning.

- **Dulaglutide causes thyroid C-cell tumors in rats. It is unknown whether TRULICITY causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of dulaglutide-induced rodent thyroid C-cell tumors has not been determined (5.1, 13.1).**
- **TRULICITY is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors (4, 5.1).**

FDA

---------- CONTRAINDICATIONS ----------

- Patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (4, 5.1).
- Patients with a prior serious hypersensitivity reaction to TRULICITY or any of the product components (4, 5.4).

---------- WARNINGS AND PRECAUTIONS ----------

- *Thyroid C-cell Tumors:* See Boxed Warning (5.1).

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of safety pharmacology or repeat-dose toxicity.

In a 6 month carcinogenicity study in transgenic mice, there was no tumorigenic response. In a 2 year carcinogenicity study in rats, at ≥ 3 times the human clinical exposure following 4.5 mg dulaglutide per week, dulaglutide caused statistically significant, dose-related increases in the incidence of thyroid C-cell tumours (adenomas and carcinomas combined). The clinical relevance of these findings is currently unknown.

EMA

No warnings or modifications for use

GLP1-RA & thyroid tumor signal assessment

European study published assessing risk of MTC with GLP1-RA leading to EMA signal.

The study included a high proportion of the French population using a case control design.

The adjusted analysis showed that **use of GLP-1 agonists for 1-3 years** was associated with increased risk of **thyroid cancer (HR 1.58; 1.27–1.95**), and **MTC (HR 1.78; 1.04–3.05)**.

GLP-1 receptor agonists and the risk of thyroid cancer

Bezin J., Gouverneur A., Pénichon M., Mathieu C., Garrel R., Hillaire-Buys D., Pariente A., Faillie J-L.

Nationwide population-based study on French SNDS database

3,746,672 individuals with type 2 diabetes treated with second-line antidiabetes drugs between 2006-2018

2,562 cases of thyroid cancers

45,184 matched control subjects

	Case subjects *n* = 2,572	Control subjects *n* = 45,184	Adjusted hazard ratio (95%CI)*
GLP-1 receptor agonists			
No use	2,255 (88.0)	40,836 (90.4)	Reference
Cumulative use ≤1 year	117 (4.6)	1,767 (3.9)	1.22 (0.99 to 1.50)
Cumulative use 1-3 years	112 (4.4)	1,419 (3.1)	1.58 (1.27 to 1.95)
Cumulative use >3 years	78 (3.0)	1,162 (2.6)	1.36 (1.05 to 1.74)
DPP-4 inhibitors			
No use	1,522 (59.4)	27,406 (60.7)	Reference
Cumulative use ≤1 year	333 (13.0)	5,209 (11.5)	1.12 (0.99 to 1.28)
Cumulative use 1-3 years	310 (12.1)	5,918 (13.1)	0.96 (0.84 to 1.10)
Cumulative use >3 years	397 (15.5)	6,651 (14.7)	1.19 (1.04 to 1.35)

*Adjusted for social deprivation index, goiter, hypo- and hyperthyroidism in the last year, and use of other antidiabetes drugs in the last 6 years considered in therapeutic class.

Diabetes Care. 2023;46:384-390. doi: 10.2337/dc22-1148.

GLP1-RA and thyroid tumor

	Target N	Control N	HR (95% CI)	P-value
GLP1-RA vs SGLT2I				
PS matching ITT	369,051	717,707	0.92 (0.77 – 1.10)	0.37
PS stratification ITT	448,528	717,792	0.97 (0.89 – 1.06)	0.55
GLP1-RA vs Sulfonylureas				
PS matching ITT	357,988	2,042,127	1.04 (0.95 - 1.14)	0.42
PS stratification ITT	425,525	2,055,583	1.00 (0.92 - 1.09)	0.96
GLP1-RA vs DPP4I				
PS matching ITT	320,991	1,133,559	0.93 (0.85 - 1.02)	0.12
PS stratification ITT	460,032	1,119,868	0.94 (0.87 - 1.01)	0.11

PS=propensity score. Matching=variable ratio matching. ITT=intention to treat.

New user active comparator federated cohort study comparing GLP1-RA with DPP4I, SU, SGLT2 as second line T2DM therapy.

Different databases, different countries, standardised approach with meta-analysis.

Bea et al. 2023 (South Korea) cohort study. GLP-1RAs was not associated with an increased risk of thyroid cancer (weighted HR 0.98, 95% confidence interval 0.62-1.53) compared with that of SGLT2 inhibitors.

GLP1-RA and thyroid tumor

Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 23-26 October 2023

27 October 2023

News | Human | Pharmacovigilance | Referrals

GLP-1 receptor agonists: available evidence not supporting link with thyroid cancer

EMA's safety committee (PRAC) has concluded that the available evidence does not support a causal association between the Glucagon-Like Peptide-1 Receptor Agonists (GLP-1) - exenatide, liraglutide, dulaglutide, semaglutide, and lixisenatide - and cancer of the thyroid (a small gland in the front and lower part of the neck which makes and releases hormones).

New user activ… …as second line T2DM ther…

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Bea et al. 2023 (South Korea) cohort study. GLP-1RAs was not associated with an increased risk of thyroid cancer (weighted HR 0.98, 95% confidence interval 0.62-1.53) compared with that of SGLT2 inhibitors.

What did we learn?

- Thyroid tumor is rare
- Only US databases contributed to the meta-analysis
- **Generalisability & sample size**

	Patients		Exposure (KYr)		Outcomes		Uncalibrated		Calibrated	
	T	C	T	C	T	C	HR (95% CI)	p	HR (95% CI)	p
PS-matching / on-treatment TAR										
CCAE	33,356	161,935	20.6	130.3	41	178	1.20 (0.79 - 1.77)	0.38	0.99 (0.41 - 2.39)	0.92
GermanyDA	537	3,365	0.5	3.3	0	<5				
OptumDOD	16,631	119,034	9.5	105.5	13	135	0.81 (0.36 - 1.68)	0.60	0.81 (0.37 - 1.76)	0.59
MDCR	2,032	28,785	1.4	28.9	<5	33	1.56 (0.08 - 9.01)	0.71	1.37 (0.13 - 14.3)	0.79
MDCD	2,600	23,268	1.4	15.5	<5	17	1.63 (0.08 - 10.3)	0.69	1.60 (0.14 - 17.8)	0.70
IMRD	206	1,873	0.2	3.1	0	0				
Open Claims	317,049	1,705,918	218.2	1739.2	187	1,340	0.95 (0.77 - 1.16)	0.61	0.97 (0.74 - 1.26)	0.80
OptumEHR	19,676	165,122	5.9	91.9	6	96	1.08 (0.39 - 2.52)	0.87	1.01 (0.40 - 2.55)	0.96
SIDIAP	610	8,136	1.2	21.1	<5	<5	3.10 (0.15 - 26.7)	0.39	2.32 (0.17 - 31.3)	0.53
Meta-analysis	353,356	1,990,074	233.6	1936.6	206	1,571	0.94 (0.78 - 1.15)	0.56	0.95 (0.75 - 1.20)	0.68

GLP1_RA vs SU. Greyed databases/estimates = failed to pass diagnostics

What did we learn?

- Thyroid tumor is rare
- Regulatory focus is on medullary thyroid cancer vs thyroid tumor
- **Phenotyping** & **data quality**

Show 1000 entries

Open Claims

Covariate Name	Start 0 to end 0
All	All
condition_occurrence: Primary malignant neoplasm of thyroid gland (133424)	52.0%
condition_occurrence: Benign neoplasm of thyroid gland (141249)	37.5%
condition_occurrence: Non-toxic uninodular goiter (134898)	13.5%
condition_occurrence: Neoplasm of uncertain behavior of thyroid gland (4317826 ...	11.4%
condition_occurrence: Non-toxic multinodular goiter (136368)	9.5%