Semaglutide and Diabetic Retinopathy: an OHDSI Network Study

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Semaglutide and diabetic retinopathy: an OHDSI network study

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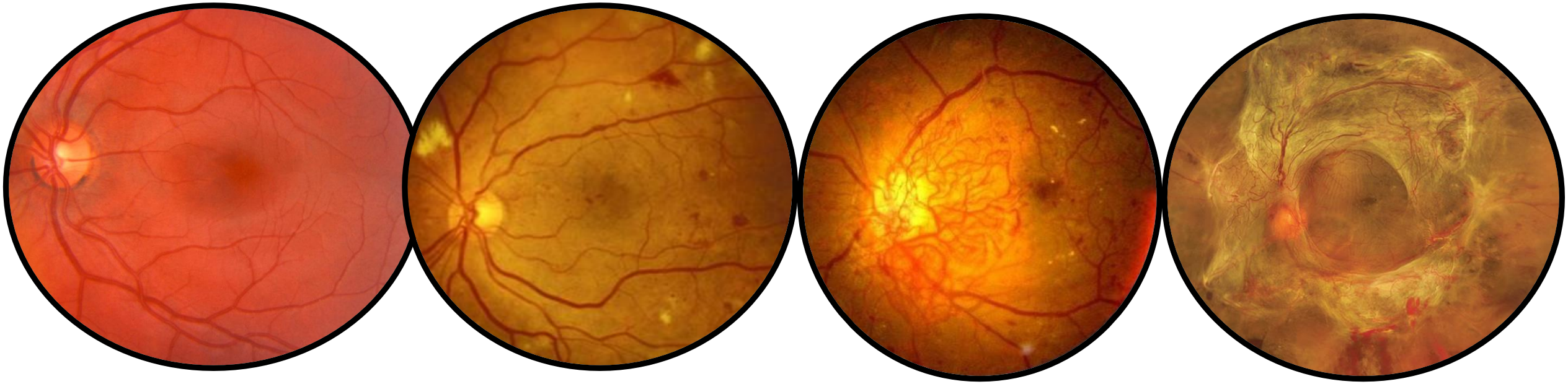
Received 14 July 2025
Accepted 11 October 2025

https://drc.bmj.com/content/13/6/e005424

Diabetic Retinopathy

- Diabetic retinopathy: retinal changes from diabetes
  - Irreversible vision loss in late stages



No diabetic retinopathy

Non-proliferative diabetic retinopathy

Proliferative diabetic retinopathy

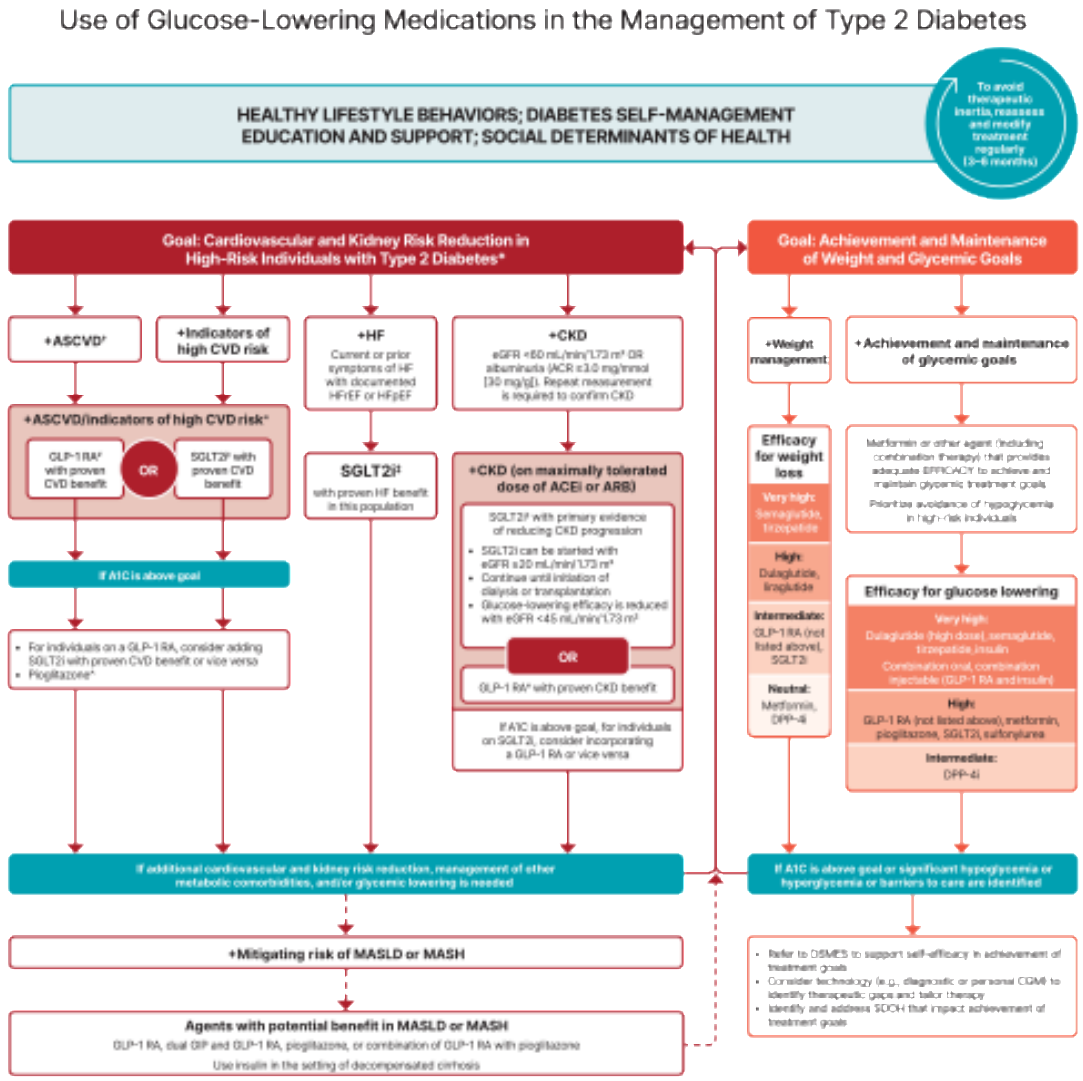
Retinal detachment

Intensive Glycemic Control Can Worsen Diabetic Retinopathy

- 1980s Diabetes Control and Complications Trial (DCCT): studied intensive and conventional treatment among patients with insulin-dependent diabetes
  - Conventional: 1 or 2 daily insulin injections, self-monitoring daily
  - Intensive: ≥3 insulin injections or external pump, self-monitoring 4x daily
- Diabetic retinopathy: assessed by fundus photography
  - Severity graded by Reading Center
- 3-step or more early worsening at 6-months ("early worsening"):
  - 3.5% in intensive group
  - 1.2% in conventional group
  - OR 2.98 (P = .006)
- Magnitude of hemoglobin A1c reduction was an important risk factor
  - Each 1% reduction of A1c from baseline by months 4-5: OR 1.47 (P < .04)

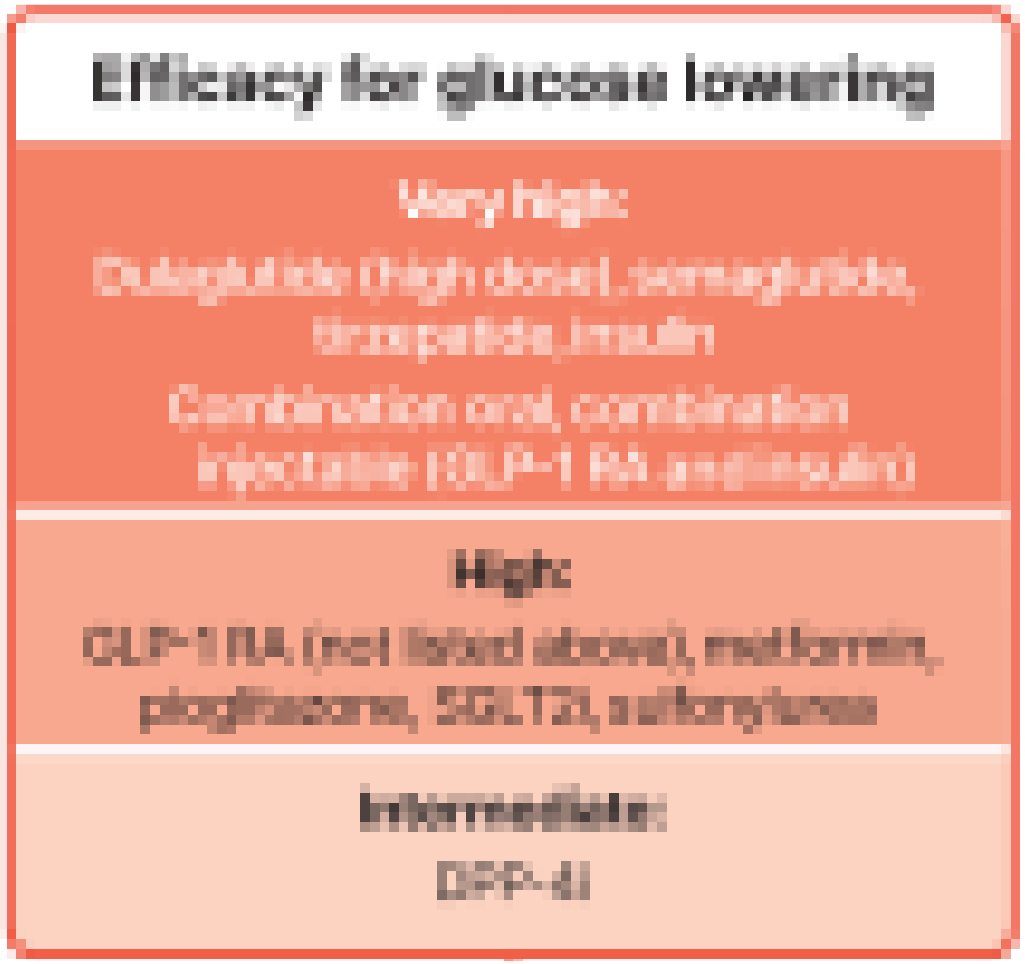
Semaglutide and Glycemic Control

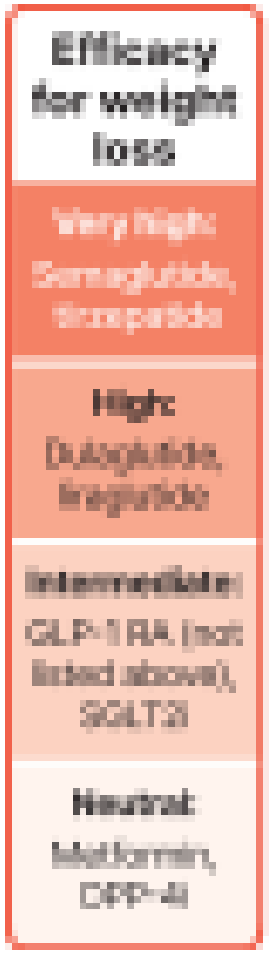
- Glucagon-like peptide 1 receptor agonist (GLP-1 RA)
  - Mimics action of endogenous incretin hormone GLP-1, enhance glucose-dependent insulin secretion, suppress glucagon release, delay gastric emptying, reduce appetite
- Used in treatment of:
  - Type 2 diabetes and obesity management
- Recommended by the ADA as one of the preferred treatments of patients with T2DM and: atherosclerotic cardiovascular disease, chronic kidney disease, or obesity



Committee ADAPP, ElSayed NA, McCoy RG, et al. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2025. *Diabetes Care*. 2024;48(Supplement_1):S181-S206.

Semaglutide Superior to Comparators in Glycemic Control and Weight Reduction





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Signal of Increased Risk of DR Complications Across the Clinical Trials

- SUSTAIN-6 : Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes
  - DR complications: vitreous hemorrhage, blindness, or conditions requiring treatment with an intravitreal agent or photocoagulation
  - Hazards ratio (HR) 1.76 (95% CI 1.11 to 2.78; *P*=.02) when comparing semaglutide to placebo
- PIONEER-6: Cardiovascular Risk with Oral Semaglutide Among Patients with Type 2 Diabetes
  - DR: broad set of DR/DME/VH/RD complications
  - 7.1% with oral semaglutide vs 6.3% placebo

Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsbøll T, SUSTAIN-6 Investigators. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med*. 2016;375(19):1834-1844.

Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, Jeppesen OK, Lingvay I, Mosenzon O, Pedersen SD, Tack CJ, Thomsen M, Vilsbøll T, Warren ML, Bain SC, PIONEER 6 Investigators. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med*. 2019;381(9):841-851.

Conflicting Evidence in Observational Studies

Impact of GLP-1 Agonists and SGLT-2 Inhibitors on Diabetic Retinopathy Progression: An Aggregated Electronic Health Record Data Study

KAREN M. WAI, KAPIL MISHRA, EUNA KOO, CASSIE ANN LUDWIG, RAVI PARIKH, PRITHVI MRUTHYUNJAYA, AND EHSAN RAHIMY

Database: TriNetX
Outcome: PDR or DME
Comparison groups: GLP-1RA, SGLT2i
Higher risk of PDR and DME in GLP-1RA group at various time points
At 1 year: RR 1.26 for PDR, RR 1.24 for DME

AMERICAN ACADEMY OF OPHTHALMOLOGY

Comparative Effectiveness of Glucagon-Like Peptide-1 Receptor Agonists, Sodium-Glucose Cotransporter 2 Inhibitors, Dipeptidyl Peptidase-4 Inhibitors, and Sulfonylureas for Sight-Threatening Diabetic Retinopathy

Andrew J. Barkmeier, MD,[1] Jeph Herrin, PhD,[2] Kavya Sindhu Swarna, MPH,[3,4] Yihong Deng, PhD,[3,4] Eric C. Polley, PhD,[5] Guillermo E. Umpierrez, MD,[6] Rodolfo J. Galindo, MD,[7] Joseph S. Ross, MD, MHS,[2,8] Mindy M. Mickelson, MA,[3] Rozalina G. McCoy, MD, MS[4,9,10,11]

Database: Optum
Outcome: treatment with intravitreal pharmacotherapy, laser photocoagulation, or vitreoretinal surgery for either DME or PDR
Comparison groups: GLP-1RA, SGLT2i, DPP4i, sulfonylurea
Similar risk of DR outcomes

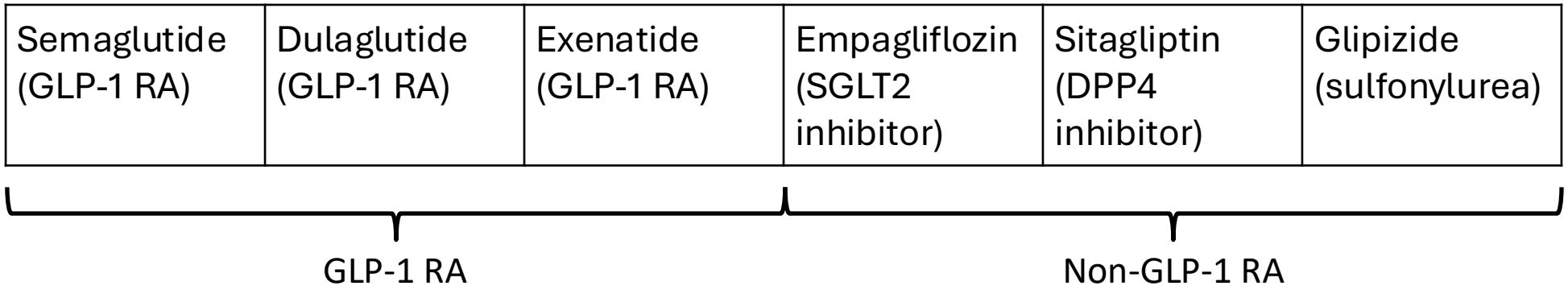
OHDSI Network Study

Analytic use case	Type	Structure	Example
Clinical characterization	**Disease Natural History**	Amongst patients who are diagnosed with **<insert your favorite disease>**, what are the patient's characteristics from their medical history?	Amongst patients with **rheumatoid arthritis**, what are their demographics (age, gender), prior conditions, medications, and health service utilization behaviors?
	Treatment utilization	Amongst patients who have **<insert your favorite disease>**, which treatments were patients exposed to amongst **<list of treatments for disease>** and in which sequence?	Amongst patients with **depression**, which treatments were patients exposed to **SSRI, SNRI, TCA, bupropion, esketamine** and in which sequence?
	Outcome incidence	Amongst patients who are new users of **<insert your favorite drug>,** how many patients experienced **<insert your favorite known adverse event from the drug profile>** within **<time horizon following exposure start>**?	Amongst patients who are new users of **methylphenidate,** how many patients experienced **psychosis** within **1 year of initiating treatment**?
Population-level effect estimation	**Safety surveillance**	Does exposure to **<insert your favorite drug>** increase the risk of experiencing **<insert an adverse event>** within **<time horizon following exposure start>**?	Does exposure to **ACE inhibitor** increase the risk of experiencing **Angioedema** within **1 month after exposure start**?
	Comparative effectiveness	Does exposure to **<insert your favorite drug>** have a different risk of experiencing **<insert any outcome (safety or benefit) >** within **<time horizon following exposure start>**, relative to **<insert your comparator treatment>**?	Does exposure to **ACE inhibitor** have a different risk of experiencing **acute myocardial infarction** while **on treatment**, relative to **thiazide diuretic**?
Patient level prediction	**Disease onset and progression**	For a given patient who is diagnosed with **<insert your favorite disease>**, what is the probability that they will go on to have **<another disease or related complication>** within **<time horizon from diagnosis>?**	For a given patient who is **newly diagnosed with atrial fibrillation**, what is the probability that they will go onto to have **ischemic stroke** in **next 3 years**?
	Treatment response	For a given patient who is a new user of **<insert your favorite chronically-used drug>**, what is the probability that they will **<insert desired effect>** in **<time window>**?	For a given patient **with T2DM who start on metformin** , what is the probability that they will **maintain HbA1C<6.5%** after **3 years**?
	Treatment safety	For a given patient who is a new user of **<insert your favorite drug>,** what is the probability that they will experience **<insert adverse event >** within **<time horizon following exposure>**?	For a given patients who is a **new user of warfarin**, what is the probability that they will have **GI bleed** in **1 year**?

Does exposure to semaglutide have a different risk of experiencing DR complications while on treatment, relative to other GLP-1 RA and non-GLP-1 RA T2DM medications?

Methods

- T2DM (exclude T1DM)
- Drug Exposures



- Outcomes
  - Proliferative diabetic retinopathy (PDR)
  - Treatment-requiring DR/DME: initiation of intravitreal anti-VEGF, laser photocoagulation, or pars plana vitrectomy

Study Design

- Active-Comparator New-User Cohort Design (primary)
- Self-Controlled Case-Series Analysis (sensitivity analysis)

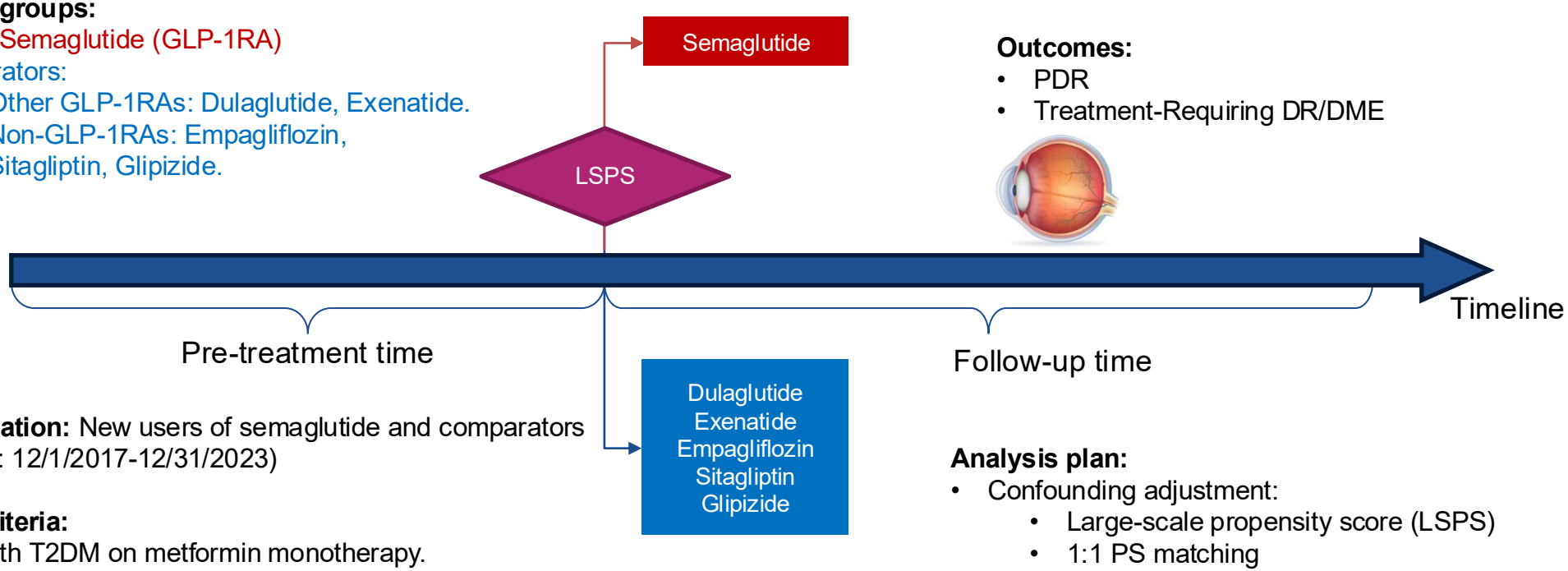
Active-Comparator New-User Cohort Analysis

Objective:

Estimate the risk of PDR or treatment-requiring DR associated with semaglutide use compared to other diabetes medications.

Exposure groups:

- Target: Semaglutide (GLP-1RA)
- Comparators:
  - Other GLP-1RAs: Dulaglutide, Exenatide.
  - Non-GLP-1RAs: Empagliflozin, Sitagliptin, Glipizide.



Outcomes:

- PDR
- Treatment-Requiring DR/DME

Study Population: New users of semaglutide and comparators (study period: 12/1/2017-12/31/2023)

Inclusion Criteria:

- Adults with T2DM on metformin monotherapy.
- At least 1 year of prior observation.
- No prior exposure to comparator diabetes medications.
- No more than 30 days of prior insulin use.

Analysis plan:

- Confounding adjustment:
  - Large-scale propensity score (LSPS)
  - 1:1 PS matching
- Hazard ratio estimation:
  - Cox proportional hazards model
- Meta-analysis:
  - Bayesian random-effects model

Study Diagnostics + Meta-Analysis

- Empirical equipoise
  - Assess the similarity between target and comparator groups
- Covariate balance
  - Absolute standardized mean difference (ASMD)
  - Unbalanced covariates -> residual bias
- Expected absolute systematic error (EASE)
  - 97 negative control outcomes
  - Assess residual bias
- Minimum detectable relative risk (MDRR)
- Only databases that passed all diagnostics were included in the Bayesian random effects meta-analysis

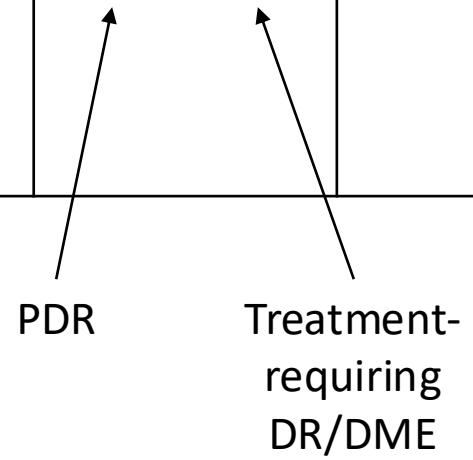
Results

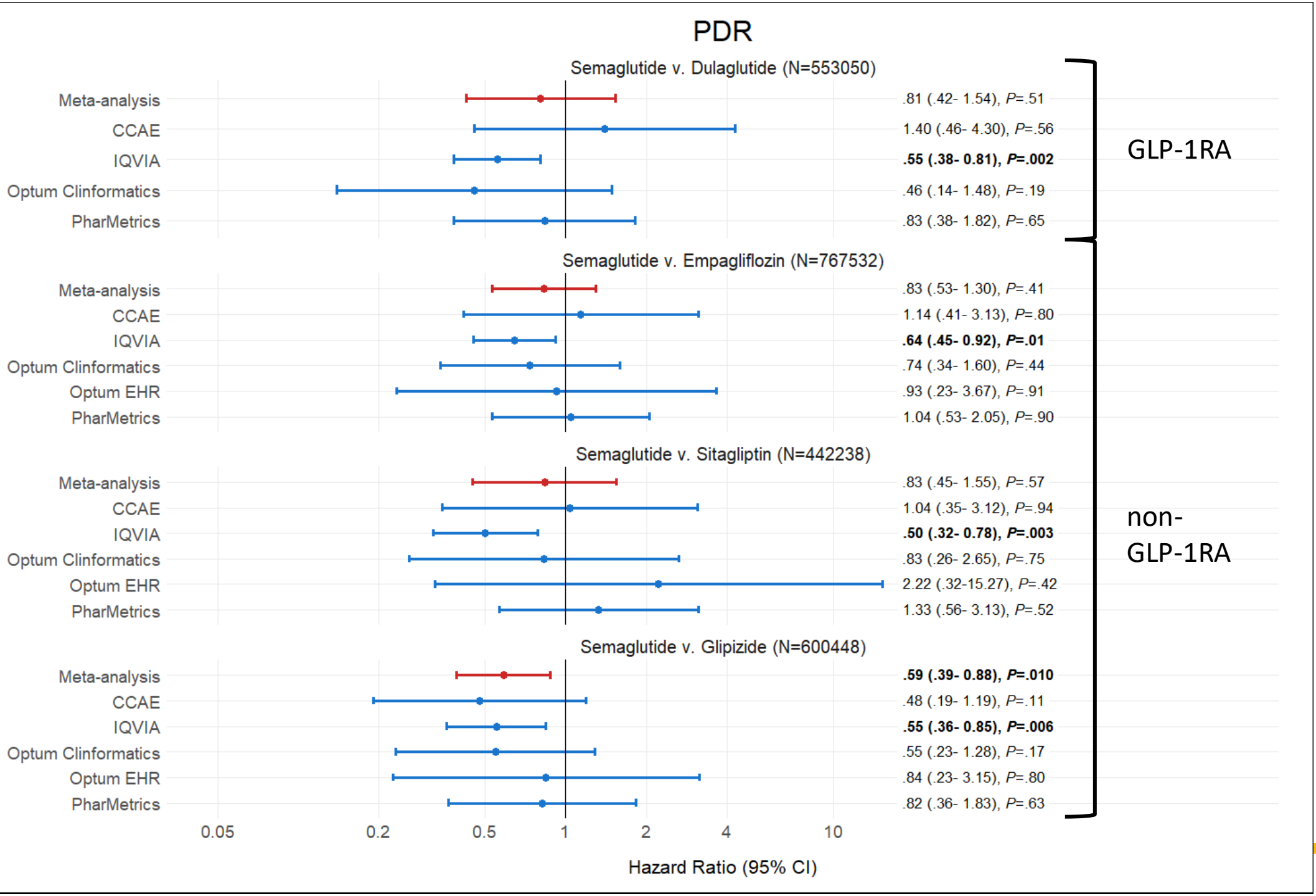
- 14 OHDSI network databases were included

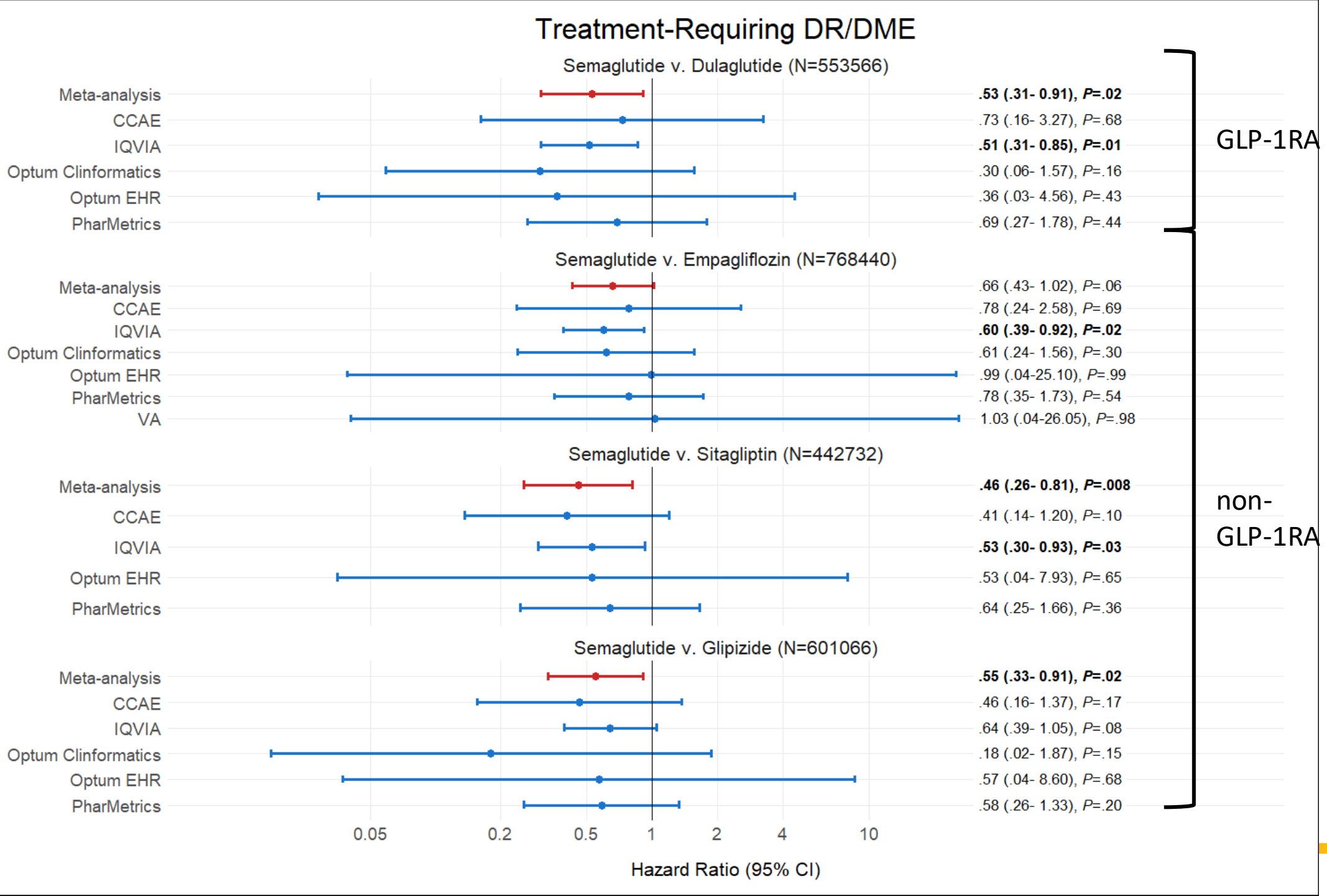
Administrative Claims Databases (6)
Merative MarketScan Medicare Supplemental and Coordination of Benefits Database (MDCR)
Merative MarketScan Commercial Claims and Encounters Database (CCAE)
Merative MarketScan Multi-State Medicaid Database (MDCD)
IQVIA Open Claims (IQVIA)
Optum Clinformatics Data Mart - Extended Data Mart – Socioeconomic Status (Optum Extended SES)
PharMetrics Plus

Electronic Health Record Databases (8)
Optum de-identified Electronic Health Record data set (Optum EHR)
Johns Hopkins Medical Enterprise (JHME)
Department of Veterans Affairs (VA)
Columbia University Medical Center (CUMC)
Keck Medical Center of University of Southern California (USC)
Oregon Health & Science University (OHSU)
Stanford University (STARR)
Washington University (WashU)

	T2DM	Semaglutide (GLP-1 RA)	Dulaglutide (GLP-1 RA)	Exenatide (GLP-1 RA)	Empagliflozin (SGLT2 inhibitor)	Sitagliptin (DPP4 inhibitor)	Glipizide (sulfonylurea)
Sample Size	37.1M	810390	326282	25936	715802	493563	832295
Incidence Rate (per 100K person-years)	356.9 / 218.8	22.6 / 11.0	38.9 / 26.5	6.3 / 3.9	89.8 / 31.5	91.5 / 40.0	127.3/ 70.9




PDR
Semaglutide v. Dulaglutide (N=553050)
Meta-analysis .81 (.42- 1.54), P=.51
CCAE 1.40 (.46- 4.30), P=.56
IQVIA .55 (.38- 0.81), P=.002
Optum Clinformatics .46 (.14- 1.48), P=.19
PharMetrics .83 (.38- 1.82), P=.65
Semaglutide v. Empagliflozin (N=767532)
Meta-analysis .83 (.53- 1.30), P=.41
CCAE 1.14 (.41- 3.13), P=.80
IQVIA .64 (.45- 0.92), P=.01
Optum Clinformatics .74 (.34- 1.60), P=.44
Optum EHR .93 (.23- 3.67), P=.91
PharMetrics 1.04 (.53- 2.05), P=.90
Semaglutide v. Sitagliptin (N=442238)
Meta-analysis .83 (.45- 1.55), P=.57
CCAE 1.04 (.35- 3.12), P=.94
IQVIA .50 (.32- 0.78), P=.003
Optum Clinformatics .83 (.26- 2.65), P=.75
Optum EHR 2.22 (.32-15.27), P=.42
PharMetrics 1.33 (.56- 3.13), P=.52
Semaglutide v. Glipizide (N=600448)
Meta-analysis .59 (.39- 0.88), P=.010
CCAE .48 (.19- 1.19), P=.11
IQVIA .55 (.36- 0.85), P=.006
Optum Clinformatics .55 (.23- 1.28), P=.17
Optum EHR .84 (.23- 3.15), P=.80
PharMetrics .82 (.36- 1.83), P=.63
0.05
0.2
0.5
1
2
4
10
Hazard Ratio (95% CI)
GLP-1RA
non-GLP-1RA


Treatment-Requiring DR/DME
Semaglutide v. Dulaglutide (N=553566)
Meta-analysis
CCAE
IQVIA
Optum Clinformatics
Optum EHR
PharMetrics
.53 (.31- 0.91), P=.02
.73 (.16- 3.27), P=.68
.51 (.31- 0.85), P=.01
.30 (.06- 1.57), P=.16
.36 (.03- 4.56), P=.43
.69 (.27- 1.78), P=.44
Semaglutide v. Empagliflozin (N=768440)
Meta-analysis
CCAE
IQVIA
Optum Clinformatics
Optum EHR
PharMetrics
VA
.66 (.43- 1.02), P=.06
.78 (.24- 2.58), P=.69
.60 (.39- 0.92), P=.02
.61 (.24- 1.56), P=.30
.99 (.04-25.10), P=.99
.78 (.35- 1.73), P=.54
1.03 (.04-26.05), P=.98
Semaglutide v. Sitagliptin (N=442732)
Meta-analysis
CCAE
IQVIA
Optum EHR
PharMetrics
.46 (.26- 0.81), P=.008
.41 (.14- 1.20), P=.10
.53 (.30- 0.93), P=.03
.53 (.04- 7.93), P=.65
.64 (.25- 1.66), P=.36
Semaglutide v. Glipizide (N=601066)
Meta-analysis
CCAE
IQVIA
Optum Clinformatics
Optum EHR
PharMetrics
.55 (.33- 0.91), P=.02
.46 (.16- 1.37), P=.17
.64 (.39- 1.05), P=.08
.18 (.02- 1.87), P=.15
.57 (.04- 8.60), P=.68
.58 (.26- 1.33), P=.20
0.05
0.2
0.5
1
2
4
10
Hazard Ratio (95% CI)
GLP-1RA
non-GLP-1RA

Conclusions

- There does not appear to be an increased risk for PDR or treatment-requiring DR among patients with T2D exposed to semaglutide compared to other GLP-1 RA and non-GLP-1RAs
- Fundus photography still the gold standard for assessing severity of diabetic retinopathy
- Ongoing FOCUS trial, initiated by Novo Nordisk (A Research Study to Look at How Semaglutide Compared to Placebo Affects Diabetic Eye Disease in People With Type 2 Diabetes)
  - Estimated study completion: 11/2027

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Received 14 July 2025
Accepted 11 October 2025

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