Wilmer Eye Institute
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# Semaglutide and NAION

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Research

JAMA Ophthalmology | Original Investigation

# Semaglutide and Nonarteritic Anterior Ischemic Optic Neuropathy

Cindy X. Cai, MD, MS; Michelle Hribar, PhD; Sally Baxter, MD, MSc; Kerry Goetz, MS; Swarup S. Swaminathan, MD; Alexis Flowers, MD; Eric N. Brown, MD, PhD; Brian Toy, MD; Benjamin Xu, MD, PhD; John Chen, MD, PhD; Alvin Chen, MD; Sophia Wang, MD, MS; Cecilia Lee, MD, MS; Theodore Leng, MD, MS; Joshua R. Ehrlich, MD, MPH; Andrew Barkmeier, MD; Karen R. Armbrust, MD, PhD; Michael V. Boland, MD, PhD; David Dorr, MD, MS; Danielle Boyce, MPH, DPA; Thamir Alshammari, PhD; Joel Swerdel, PhD, MS, MPH; Marc A. Suchard, MD, PhD; Martijn Schuemie, PhD; Fan Bu, PhD; Anthony G. Sena, BA; George Hripcsak, MD, MS; Akihiko Nishimura, PhD; Paul Nagy, PhD; Thomas Falconer, MS; Scott L. DuVall, PhD; Michael Matheny, MD; Benjamin Viernes, PhD; William O'Brien, MS; Linying Zhang, PhD; Benjamin Martin, PhD; Erik Westlund, PhD; Nestoras Mathioudakis, MD, MHS; Ruochong Fan, MA; Adam Wilcox, PhD; Albert Lai, PhD; Jacqueline C. Stocking, PhD, RN; Sahar Taddouche, MD, MBA; Lok Hin Lee, DPhil; Yangyiran Xie, BS; Izabelle Humes, PT, DPT; David B. McCoy, BA; Mohammad Adibuzzaman, PhD; Raymond G. Areaux Jr, MD; William Rojas-Carabali, MD; James Brash, PhD; David A. Lee, MD, MS; Nicole G. Weiskopf, PhD; Louise Mawn, MD; Rupesh Agrawal, MD; Hannah Morgan-Cooper, Msc; Priya Desai, Msc; Patrick B. Ryan, PhD

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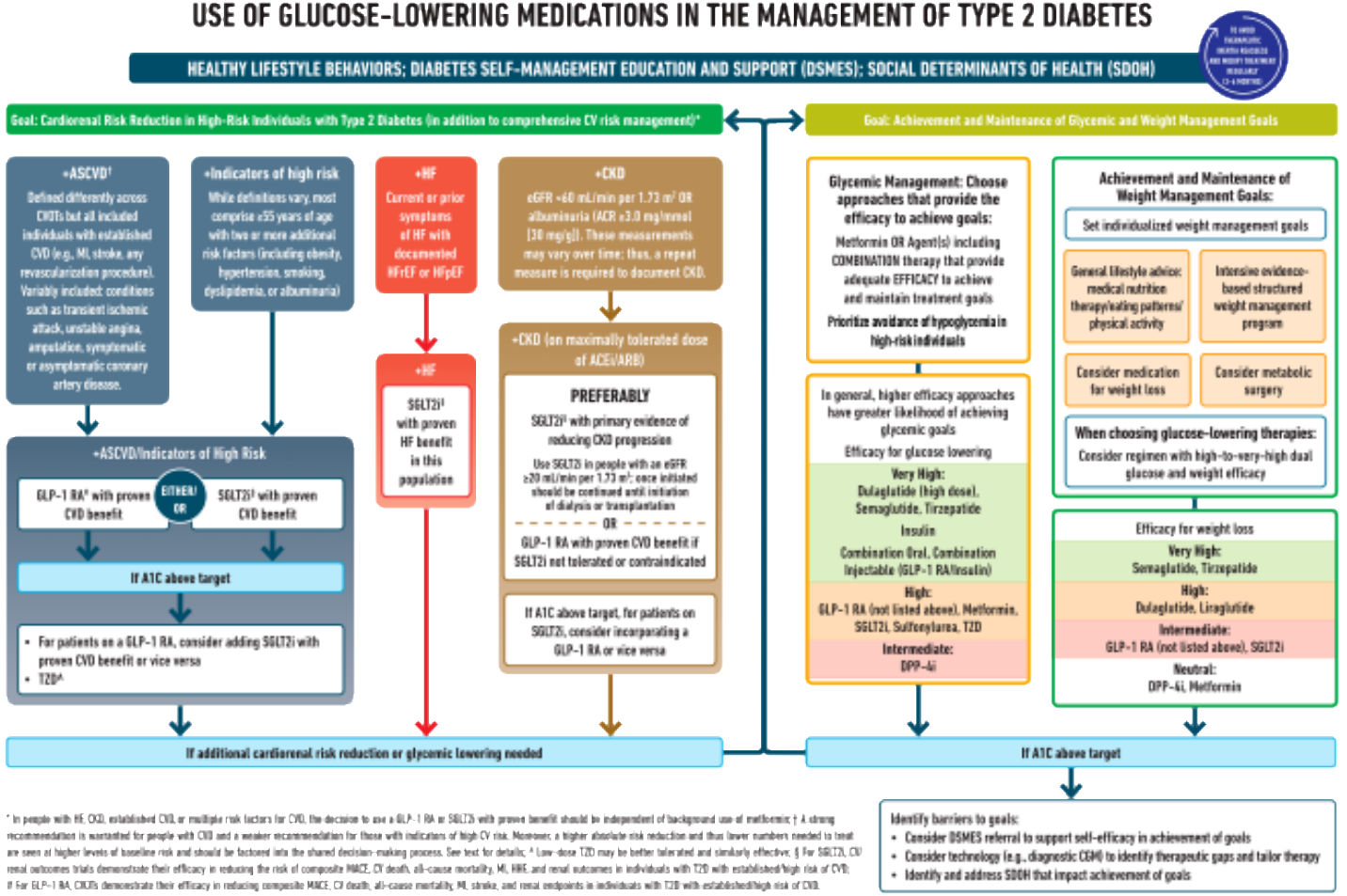
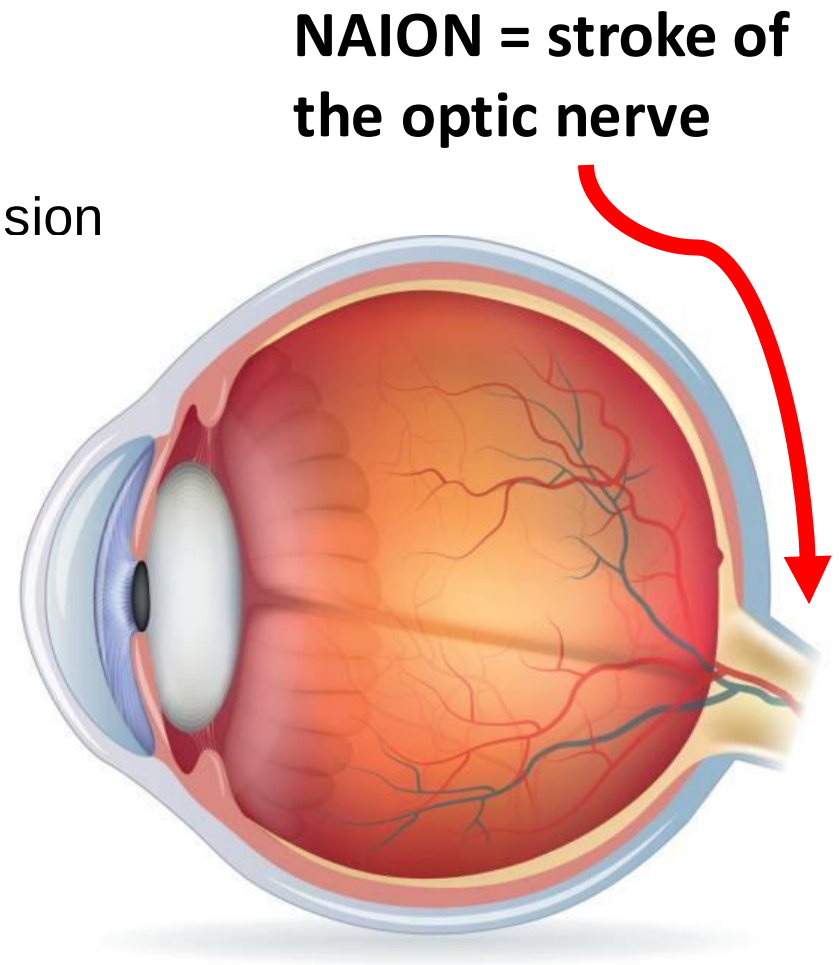
# Semaglutide

- Glucagon-like peptide 1 receptor agonist (GLP-1 RA)
- Benefits in reducing cardiovascular and kidney complications
- Recommended by the ADA as a preferred treatment for T2DM patients with: atherosclerotic cardiovascular disease, chronic kidney disease, or obesity



# Nonarteritic Anterior Ischemic Optic Neuropathy (NAION)

- Leading cause of acute optic neuropathy in the elderly
- Significant cause of blindness:1/4 eyes 20/200 or worse vision
- No definitive treatments



JAMA Ophthalmology | Original Investigation

# Risk of Nonarteritic Anterior Ischemic Optic Neuropathy in Patients Prescribed Semaglutide

Jimena Tatiana Hathaway, MD, MPH; Madhura P. Shah, BS; David B. Hathaway, MD; Seyedeh Maryam Zekavat, MD, PhD; Drenushe Krasniqi, BA; John W. Gittinger Jr, MD; Dean Cestari, MD; Robert Mallery, MD; Bardia Abbasi, MD; Marc Bouffard, MD; Bart K. Chwalisz, MD; Tais Estrela, MD; Joseph F. Rizzo III, MD

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- Cumulative incidence of NAION for the semaglutide and non–GLP-1 RA cohorts over 36 months was **8.9%** (95% CI, 4.5%-13.1%) and 1.8% (95% CI, 0%-3.5%), respectively
- Hazard Ratio of NAION **4.28** (95% CI: 1.62 – 11.29, P < .001) (compared with non-GLP-1 RA)

**Limitations**: single academic institution, major referral center for NAION

"The best approaches to **confirm, refute, or refine** our findings would be to conduct a **much larger, retrospective, multicenter population-based cohort study**; a prospective, randomized clinical study; or a postmarket analysis of all GLP-1 RA drugs."

OHDSI

OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS


Purpose of OHDSI Network Study:

- Characterize NAION incidence
- Association of NAION with semaglutide use
  - Compare the risk of NAION associated with semaglutide use against other GLP-1RAs and non-GLP-1RA drugs
  - Investigate NAION incidence rate during semaglutide exposure compared with non-exposure

https://www.ohdsi.org/wp-content/uploads/2024/10/OurJourney2024.pdf

OHDSI
OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

| Date | |
|---|---|
| July 3, 2024 (Wednesday) | Hathaway et al. study published online in JAMA Ophthalmology |
| July 9, 2024 (Tuesday) | Network Study announce at OHDSI Community Call |
| July 11, 2024 (Thursday) | Discussion at Eye Care and Vision Research WG |
| July 12, 2024 (Friday) | Meeting about Phenotypes |
| July 17, 2024 (Wednesday) | Finalized Protocol |
| August 9, 2024 (Friday) | Deadline for Data Partners to Contribute |

4.5 weeks

# OHDSI Community Infrastructure

- Engaged community members through the Eye Care and Vision Research Work Group
- OHDSI Evidence Network
- Suite of pre-built analytics: HADES

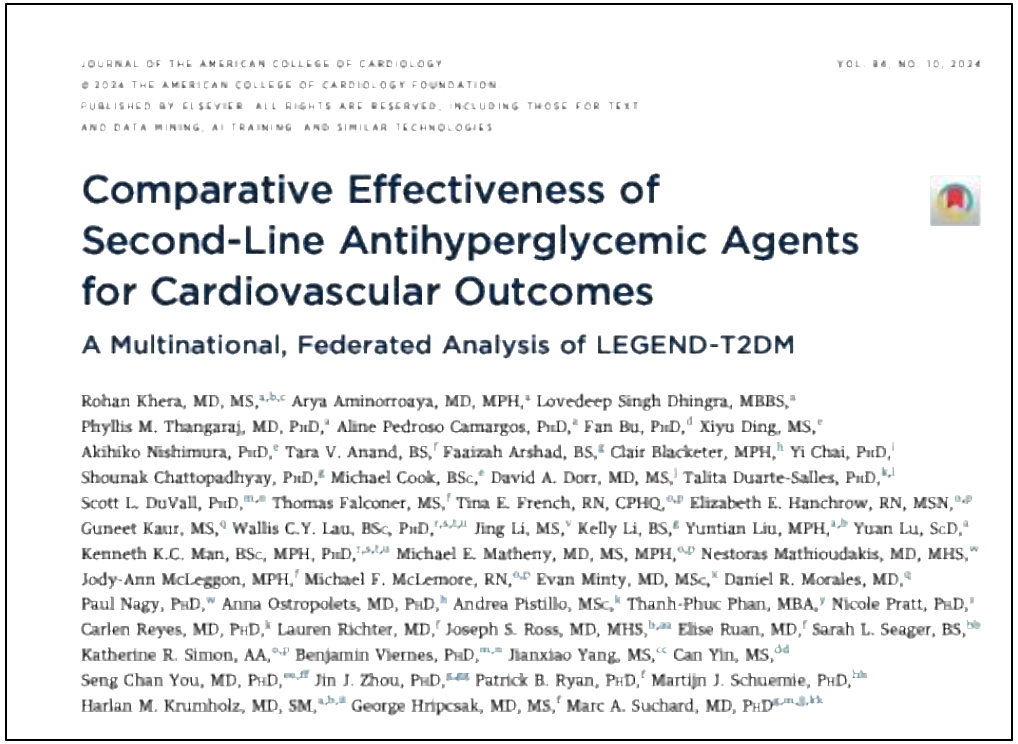
| Analytic use case | Type | Structure | Example |
|---|---|---|---|
| Clinical characterization | Disease Natural History | Amongst patients who are diagnosed with <insert your favorite disease>, what are the patient's characteristics from their medical history? | Amongst patients with rheumatoid arthritis, 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 | progression | disease>, what is the probability that they will go on to have <another disease or related complication> within <time horizon from diagnosis>? | 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? |

**Semaglutide**
**NAION**


| 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) |

# Build upon a prior OHDSI Network Study: LEGEND-T2DM



JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 84, NO. 10, 2024


Comparative Effectiveness of Second-Line Antihyperglycemic Agents for Cardiovascular Outcomes

A Multinational, Federated Analysis of LEGEND-T2DM

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**Indication Cohort:**

-T2DM, exclude T1DM

**Drug exposures:**

| | | | | | |
|---|---|---|---|---|---|
| Semaglutide (GLP-1 RA) | Dulaglutide (GLP-1 RA) | Exenatide (GLP-1 RA) | Empagliflozin (SGLT2 inhibitor) | Sitagliptin (DPP4 inhibitor) | Glipizide (sulfonylurea) |

GLP-1 RA

Non-GLP-1 RA

# Defining NAION

Mobilized the Eye Care and Vision Research Workgroup

- Lack of structured diagnosis codes for NAION
  - 40% of cases coded as ION are not NAION

**Outcome Cohorts (NAION):**

| | |
|---|---|
| “Sensitive” NAION<br>-require 1 ION condition | “Specific” NAION<br>-require 2 ION condition |

ION diagnosis codes, diagnosis date adjustments (visual field defect, optic disc disorder, optic neuritis, optic disc edema), exclude patients with GCA (x2), exclude patients with traumatic optic neuropathy

# Analysis Methods

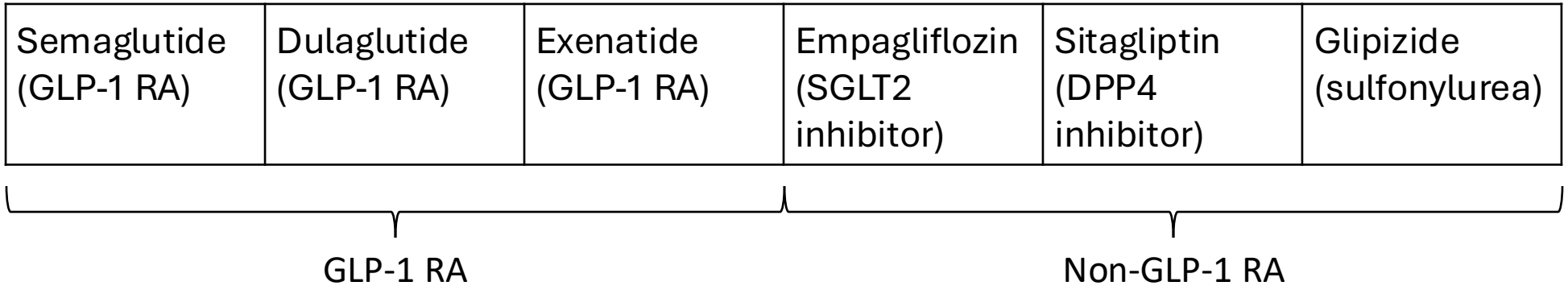
Study start and study end: Dec 2017 to Dec 2023

## New-user active-comparator cohort design

-**New-users** of the second-line medications: prior metformin monotherapy, no other prior comparator diabetes medications, 365 days prior observation period, and at most 30 days of insulin exposure
-Compare HR of NAION between drug exposures
-Large-scale **propensity score** models, groups were 1:1 propensity matched
-**Cox proportional hazards model**

## Self-controlled case-series

-Cases of T2DM and NAION (diagnosed after first 365 days of observation period): **patient serves as their own control**
-Compare **IRR** of NAION between drug exposure versus control time during observation period
-Exposure time: continuous drug exposure
-Control time: observation time when patient had T2DM and excluded first 365 days of observation period
-**Poisson regression model**
-Pre-exposure window: 30 days before exposure




Only databases and comparisons that pass a rigorous set of study diagnostics contribute to HR and IRR estimates

Incidence Proportion and Rate of NAION

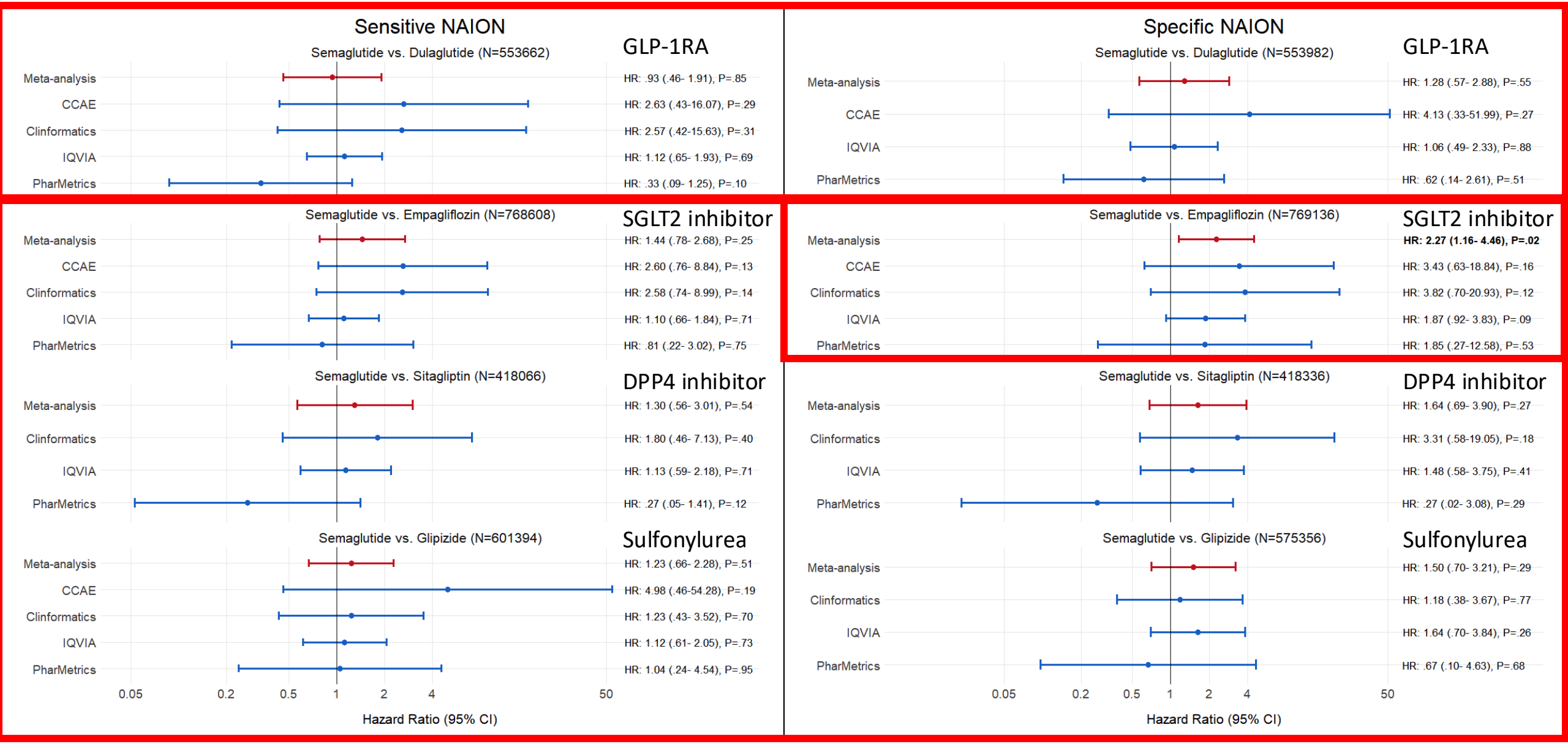
| | T2DM | Semaglutide (GLP-1 RA) | Dulaglutide (GLP-1 RA) | Exenatide (GLP-1 RA) | Empagliflozin (SGLT2 inhibitor) | Sitagliptin (DPP4 inhibitor) | Glipizide (sulfonylurea) |
|---|---|---|---|---|---|---|---|
| Sample Size | 37.1M | 810390 | 326282 | 25936 | 715802 | 493563 | 832295 |
| Incidence Proportion (per 100K persons) | 78.3 / 32 | 7.1 / 4.2 | 7.9 / 3.2 | 0 / 0 | 10.4 / 4 | 12.3 / 4.8 | 18 / 8.7 |
| Incidence Rate (per 100K person-years) | 41 / 16.8 | 14.5 / 8.7 | 13.4 / 4.2 | 0 / 0 | 13.7 / 5.2 | 15.1 / 5.9 | 21.2 / 10.4 |

Sensitive NAION

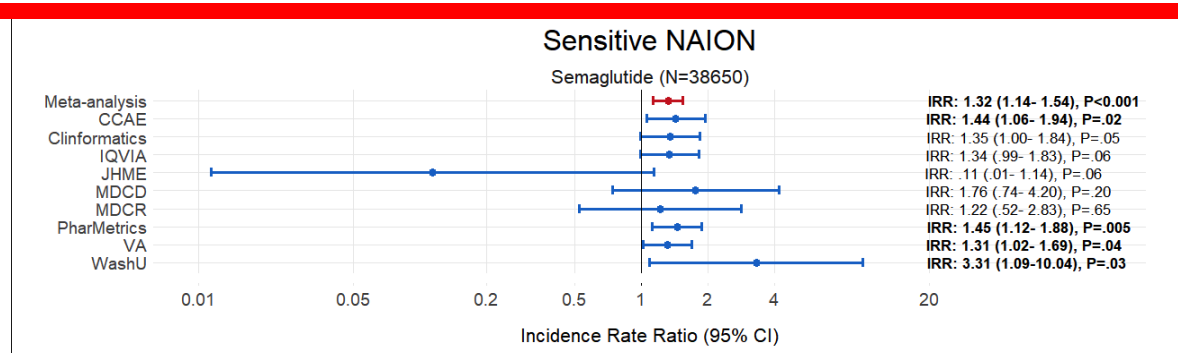
Specific NAION

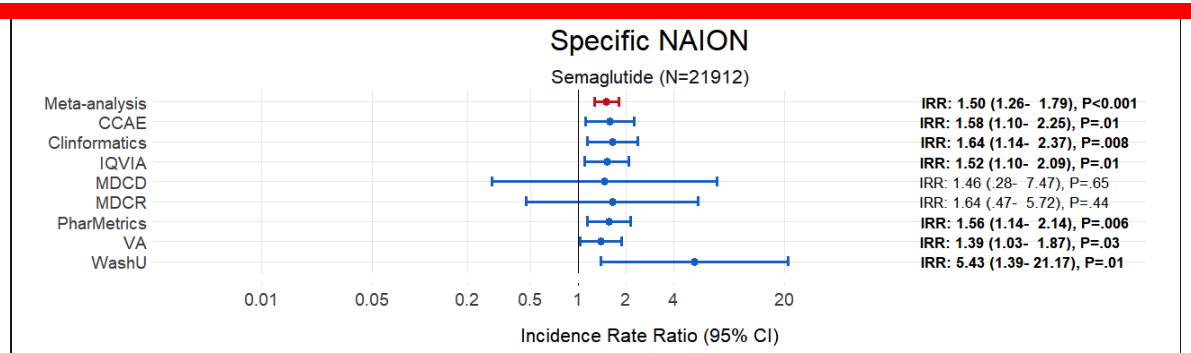
Historically, 2.3 to 11.4 (as high as 82) per 100,000 persons

# New-user active-comparator cohort design



# Self-controlled case-series

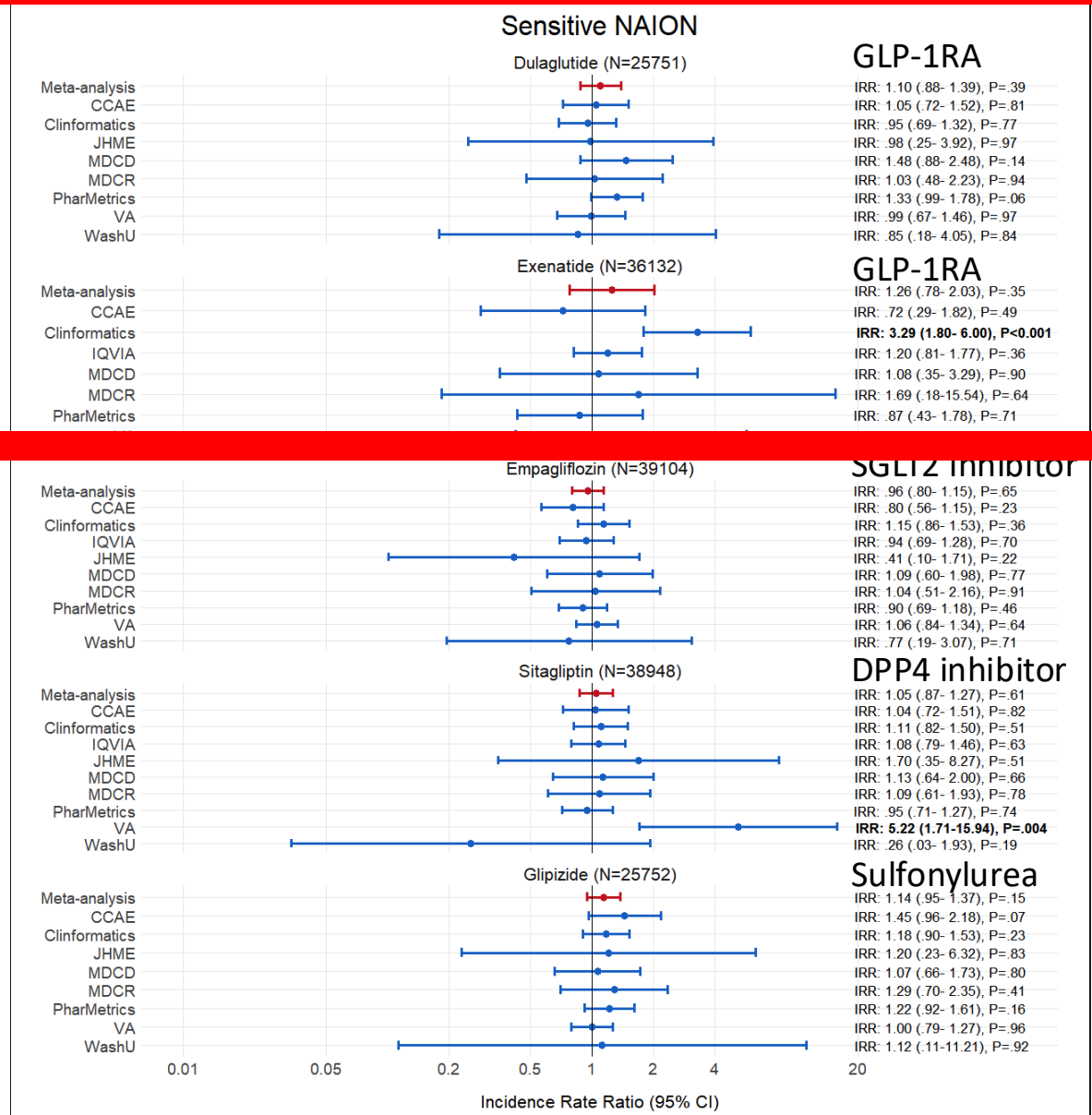


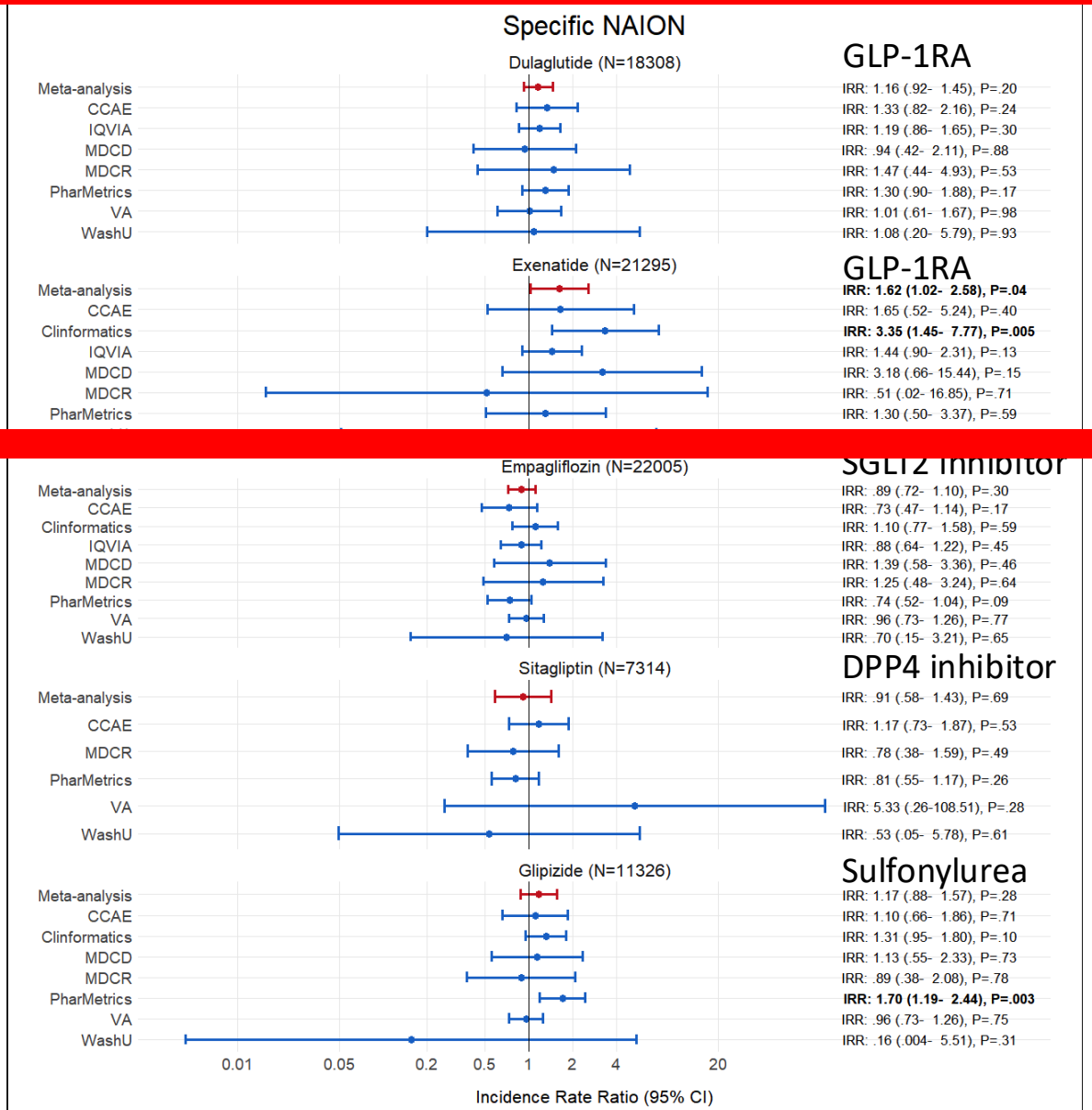




Meta-analysis IRR 1.32

Meta-analysis IRR 1.50

# Self-controlled case-series



# Conclusion

- Small increased risk of NAION among T2DM patients exposed to semaglutide
  - Much smaller than previously reported
- Additional studies should incorporate ophthalmic risk factors (e.g., cup-to-disc ratio)
- Weigh concern for NAION with therapeutic benefits of semaglutide

*Letter to the Editor*

## Real-World Evidence Assessment of the Risk of Nonarteritic Anterior Ischemic Optic Neuropathy in Patients Prescribed Semaglutide

David C. Klonoff, MD, FACP, FRCP (Edin), Fellow AIMBE[1], Gavin Hui, MD[2], and Saurabh Gombar, MD, PhD[2,3]

Journal of Diabetes Science and Technology
1–2

DOI: 10.1177/19322968241268050
journals.sagepub.com/home/dst
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## The Effect of Semaglutide and GLP-1 RAs on Risk of Nonarteritic Anterior Ischemic Optic Neuropathy

NADIA J. ABBASS, RAYA NAHLAWI, JACQUELINE K. SHAIA, KEVIN C. ALLAN, DAVID C KAELBER, KATHERINE E. TALCOTT, AND RISHI P. SINGH

AMERICAN ACADEMY OF OPHTHALMOLOGY

## Association between Semaglutide and Nonarteritic Anterior Ischemic Optic Neuropathy

### *A Multinational Population-Based Study*

*Chien-Chih Chou, MD, PhD,[1,2,3] Ssu-Yu Pan, MD,[1,2] Yi-Jing Sheen, MD, PhD,[1,3,4,5] Jun-Fu Lin, MS,[6] Ching-Heng Lin, PhD,[6,7,8,9] Hui-Ju Lin, MD, PhD,[10,11] I-Jong Wang, MD, PhD,[12,13] Chien-Hsiang Weng, MD, MPH[14,15]*

Research

JAMA Ophthalmology | Original Investigation

## Semaglutide and Nonarteritic Anterior Ischemic Optic Neuropathy Risk Among Patients With Diabetes

Alan Y. Hsu, MD; Hou-Ting Kuo, MD; Yu-Hsun Wang, MS; Chun-Ju Lin, MD; Yi-Ching Shao, MD; Chun-Chi Chiang, MD, PhD; Ning-Yi Hsia, MD; Chun-Ting Lai, MD; Hsin Tseng, MD; Bing-Qi Wu, MD; Huan-Sheng Chen, MD; Yi-Yu Tsai, MD, PhD; Min-Yen Hsu, MD, PhD; James Cheng-Chung Wei, MD, PhD

**RESEARCH** **Open Access**

## Once-weekly semaglutide doubles the five-year risk of nonarteritic anterior ischemic optic neuropathy in a Danish cohort of 424,152 persons with type 2 diabetes

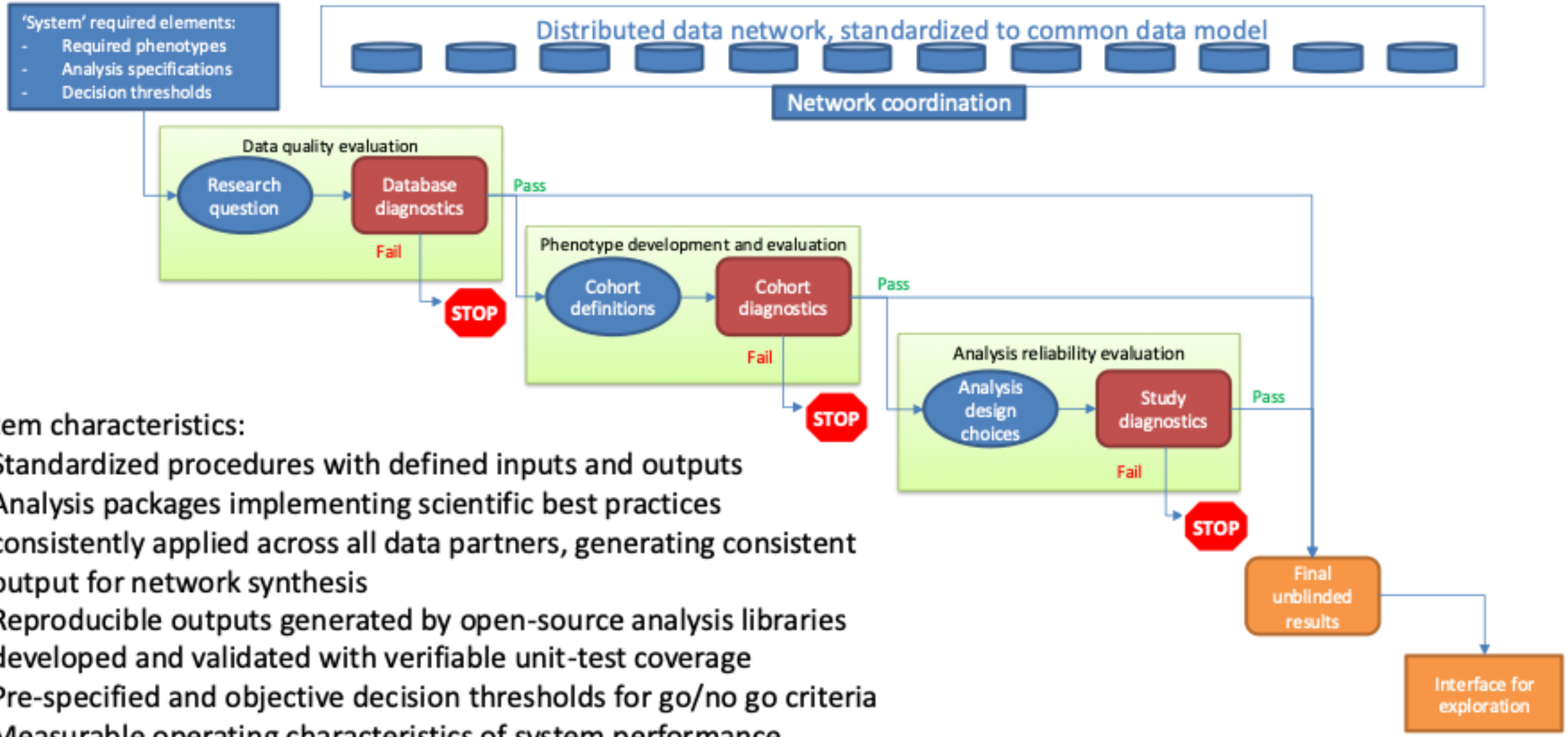
Jakob Grauslund[1,2,3*†], Andreas Abou Taha[1,2†], Laleh Dehghani Molander[1], Ryo Kawasaki[2,4], Sören Möller[2,5], Kurt Højlund[2,3] and Lonny Stokholm[2,5]

ORIGINAL ARTICLE WILEY

## Use of semaglutide and risk of non-arteritic anterior ischemic optic neuropathy: A Danish–Norwegian cohort study

Emma Simonsen MD[1] | Lars Christian Lund PhD[1] |
Martin Thomsen Ernst MSc[1] | Vidar Hjellvik PhD[2] | Laszlo Hegedüs DMSc[3,4] |
Steffen Hamann PhD[5,6] | Øystein Kalsnes Jørstad PhD[7,8] |
Hanne Løvdal Gulseth PhD[2] | Øystein Karlstad PhD[2] | Anton Pottegård DMSc[1]

# Engineering open science systems that build trust into the real-world evidence generation and dissemination process




System characteristics:

- Standardized procedures with defined inputs and outputs
- Analysis packages implementing scientific best practices consistently applied across all data partners, generating consistent output for network synthesis
- Reproducible outputs generated by open-source analysis libraries developed and validated with verifiable unit-test coverage
- Pre-specified and objective decision thresholds for go/no go criteria
- Measurable operating characteristics of system performance

Invited Commentary

# Semaglutide and Risk of NAION—Additional Insights

Joseph F. Rizzo III, MD; Jimena Tatiana Hathaway, MD, MPH

"...**should be congratulated** on conducting a **thoughtful and well-designed study** that advances our knowledge about a relatively small risk associated with semaglutide, at least among patients with T2D."

Research

JAMA Ophthalmology | Original Investigation

# Semaglutide and Nonarteritic Anterior Ischemic Optic Neuropathy

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