1 Title Page

Title: Effect of Glucagon-Like Peptide-1 Receptor Agonists on the Risk of Non-Arteritic Anterior Ischemic Optic Neuropathy Among Older Adults with Type 2 Diabetes: A US. Medicare Active-Comparator New-User Cohort Study

Research question and objectives

Question: Among Medicare beneficiaries aged ≥66 years with type 2 diabetes mellitus (T2DMM), does initiation of a glucagon-like peptide-1 receptor agonist (GLP-1RA) increase the risk of non-arteritic anterior ischemic optic neuropathy (NAION) compared with sodium-glucose co-transporter-2 inhibitors (SGLT-2i) and dipeptidyl peptidase-4 inhibitors (DPP-4i)?

Objective: To estimate the comparative effect of initiating GLP-1RA versus SGLT-2i and DPP-4i on the risk of NAION among older adults with type 2 diabetes.

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Contributors

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Study registration

Site: U.S. Medicare Fee-for-Service (Parts A, B, and D)

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Conflict of interest: KH has no conflict of interest to report. TS owns stock in Novartis, Roche, and Novo Nordisk.

2 Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are increasingly prescribed for type 2 diabetes and obesity due to their glycemic, weight-loss, and cardioprotective benefits. Recent safety signals and mixed observational findings have raised concern about a possible association between GLP-1RA therapy and non-arteritic anterior ischemic optic neuropathy (NAION), a sudden and irreversible optic nerve infarction that primarily affects older adults with vascular risk factors. Given the plausible physiologic mechanisms—such as blood pressure lowering, rapid glycemic improvement, and altered nocturnal perfusion—clarifying whether GLP-1RAs influence NAION risk compared with clinical alternatives is an important public health and clinical question.

This study aims to estimate the comparative effect of initiating a GLP-1RA versus alternative second-line glucose-lowering therapies—sodium–glucose cotransporter-2 inhibitors (SGLT-2i) and dipeptidyl peptidase-4 inhibitors (DPP-4i)—on the risk of incident NAION among older adults with type 2 diabetes. We will conduct two parallel active-comparator, new-user cohort studies emulating separate head-to-head target trials. New use will be defined by a 12-month class-specific washout, and eligibility, exposure assignment, and follow-up will be aligned at the first prescription fill to avoid immortal time and ensure proper temporality. Follow-up will proceed under an as-treated framework until treatment discontinuation, switching, outcome occurrence, death, disenrollment, or end of data.

The study will use a 20% random sample of Medicare Fee-for-Service Parts A, B, and D claims, providing large-scale, nationally representative data suitable for evaluating the rare outcome of NAION in older adults. Analyses will estimate absolute and relative risks using standardized morbidity ratio (SMR) weighting to target the average treatment effect in the treated. SMR-weighted Aalen–Johansen cumulative incidence functions will provide adjusted risks accounting for competing mortality, complemented by SMR-weighted Cox models for hazard ratios. Secondary analyses will evaluate as-treated effects conditional on a second refill of the same drug class within days' supply of the index prescription plus a grace period of 30 days, as well as intention-to-treat effects. Finally, sensitivity analyses will address outcome definitions, induction and latency windows, grace-period choices, propensity-score overlap, and unmeasured confounding.

3 Amendments and updates

Amendments and updates				
Version date	Version number	Section of protocol	Amendment or update	Reason

4 Milestones

Table 1:
Milestones

Milestone	Date
Protocol finalization	1/1/2026
Cohort construction	2/1/2026
Primary analysis completed	3/1/2026
Manuscript submission	4/1/2026

5 Rationale and background

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are widely prescribed for type 2 diabetes mellitus (T2DM) and, more recently, obesity, due to their glycemic control and chronic weight loss effects. With some GLP-1RAs having demonstrable cardiovascular benefits in outcome trials, their guideline use continues to expand. However, their rapid uptake has been accompanied by growing efforts to identify long-term safety issues, not least ocular outcomes.[1,2] Safety signals and pharmacovigilance reports have raised concerns about a possible association between semaglutide and other GLP-1RAs and non-arteritic anterior ischemic optic neuropathy (NAION).[3–5]

Ischemic optic neuropathy (ION) is the most common acute optic nerve disorder in adults over 50 years.[6] NAION, the predominant form, has an estimated annual incidence ranging between 2.3 and 10.2 per 100,000 among adults over 50 years and about 82 per 100,000 among patients older than 67 years with T2DM.[7,8] It presents as acute, painless, monocular visual loss with optic disc swelling and is distinct from its arteritic counterpart associated with giant cell arteritis.[9] The exact etiology and pathophysiology of NAION is not established.[9] Putatively, NAION arises from transient hypoperfusion of the optic nerve head, leading to axonal ischemia and swelling within a confined anatomic space. The resultant compartment-like pressure further compromises capillary flow, creating a vicious cycle of ischemia and edema. Histologic and imaging evidence demonstrates disruption of the blood–optic nerve barrier, microvascular ischemia, and secondary inflammatory injury. The condition is strongly linked to atherosclerotic risk factors—hypertension, diabetes, dyslipidemia, and sleep apnea—and to structural susceptibility such as small cup-to-disc ratio or optic disc drusen.[10–12]

Several biologically plausible mechanisms may connect GLP-1RA therapy to NAION risk. GLP-1RAs can lower systemic blood pressure and body weight, potentially precipitating nocturnal hypotension, a recognized precipitant of NAION.[13] Rapid glycemic improvement and osmotic shifts during treatment initiation may transiently alter optic nerve head perfusion, especially in patients with diabetic microvascular disease or impaired autoregulation.[14] Conversely, GLP-1RAs exert anti-inflammatory, antioxidant, and endothelial-protective effects that could plausibly reduce ischemic optic injury.[15] The dual potential for harm and protection underscores the need for rigorous evaluation in real-world data.

Emerging evidence on GLP-1RAs and NAION remains inconclusive and methodologically inconsistent. Analyses using United States electronic health records have yielded conflicting results, ranging from imprecise to moderately positive associations.[16–19] Limitations across prior studies—including prevalent-user inclusion, unvalidated diagnosis algorithms, inconsistent comparator selection, and incomplete

adjustment for confounders—compromise causal estimation and interpretation. Clarifying these risks is essential given the expanding population of GLP-1RA users.

6 Research question and objectives

To estimate the comparative effect of initiating GLP-1RA versus other second-line glucose-lowering therapies—specifically dipeptidyl peptidase-4 inhibitors (DPP-4i) and sodium-glucose co-transporter-2 inhibitors (SGLT-2i)—on the risk of NAION among older adults with T2DM.

Table 2: Research questions and objectives

A. Primary research question and objective

Study element	Specification
Objective:	To estimate the effect of initiating GLP-1RAs versus SGLT-2 inhibitors or DPP-4 inhibitors on NAION incidence
Hypothesis:	GLP-1RA initiation is associated with a higher incidence of NAION compared with alternative add-on therapies SGLT-2i or DPP-4i, albeit a very small absolute risk
Population (mention key inclusion-exclusion criteria):	Inclusion: Medicare Fee-for-Service beneficiaries who: (1) are aged ≥66 years; (2) have continuous Parts A/B/D enrollment during the 12-month baseline period with up to 30-day gaps allowed; (3) have diagnosed type 2 diabetes; (4) have ≥1 baseline ophthalmology or optometry encounter; and (5) are new users of GLP-1RA and SGLT-2i for Cohort I, or GLP-1RA and DPP-4i for Cohort II, after a 12-month class-specific washout. Exclusions: • Diabetes mellitus other than type 2 diabetes • Same-day initiation of both study drug classes • GLP-1RA contraindications including pancreatitis, thyroid cancer, multiple endocrine neoplasia type 2, end-stage renal

A. Primary research question and objective

Study element	Specification
	disease, dialysis dependence or renal replacement therapy • Heart failure for GLP-1RA vs. DPP-4i cohort • Bilateral blindness or legal blindness • Prior ischemic optic neuropathy • NAION mimickers (non-ischemic optic neuropathies • Prior arteritic/systemic vasculitic conditions • Empiric evaluation or treatment for suspected arteritic anterior ION
Exposure:	GLP-1RA initiation
Comparator:	SGLT-2i initiation (Cohort I) DPP-4i initiation (Cohort II)
Outcome:	First incident NAION
Time (when follow up begins and ends):	Follow-up begins 14 days after the index date, defined as the date of the first qualifying dispensing claim for the initiated drug class and continues until NAION, death, disenrollment, end of data, or treatment change (as-treated) or administrative censoring (intention-to-treat)
Setting:	U.S. Medicare Fee-for-Service, national 20% random sample
Main measure of effect:	Average treatment effect in the treated (ATT) • SMR-weighted adjusted cumulative incidence and adjusted risk difference (aRD) from Aalen–Johansen cumulative incidence functions at various durations of treatment/follow-up (6, 12, 24 months) • Adjusted hazard ratio (aHR) from SMR-weighted Cox models

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7 Research methods

7.1 Study design

Research design: We will conduct two parallel active-comparator, new-user (ACNU) cohort studies designed to emulate two separate head-to-head randomized trials of second-line glucose-lowering therapy. Each ACNU cohort will compare new initiators of glucagon-like peptide-1 receptor agonists (GLP-1RA) with new initiators of a clinically relevant alternative: Cohort I will compare GLP-1RA versus sodium–glucose cotransporter-2 inhibitors (SGLT-2i), and Cohort II will compare GLP-1RA versus dipeptidyl peptidase-4 inhibitors (DPP-4i).

Cohort entry (index date) will be defined as the first qualifying outpatient dispensing claim for a drug within the class of interest. To ensure incident use, we will require a 12-month class-level washout period prior to the index date, during which beneficiaries must have continuous medical and pharmacy enrollment, no dispensing of either comparator drug class, and no prior dispensing whose days' supply plus an allowable grace period extends into the index date (i.e., no overlapping exposure episodes). This approach minimizes inclusion of prevalent users and aligns with established active-comparator, new-user design principles.

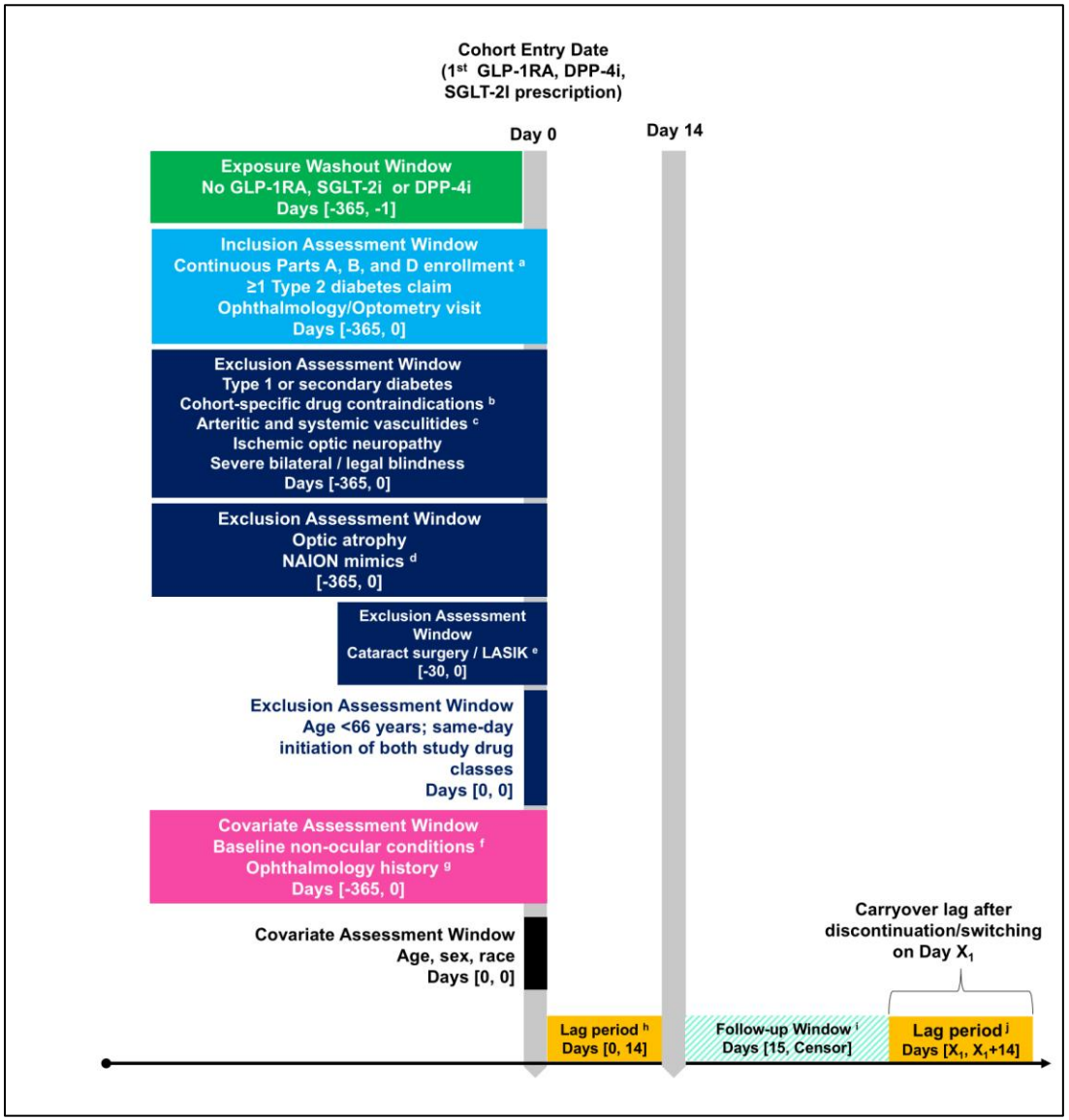
Eligibility assessment and exposure assignment occur at the index date (time zero), and baseline covariates will be measured during the 12-month lookback period prior to index to ensure they preceded treatment initiation. To mitigate reverse causation and early detection bias, a 14-day lag period will be applied following treatment initiation. Outcome follow-up will therefore begin on day 15 after the index date, and events occurring during days 0–14 will not be attributed to exposed risk time. This structure preserves temporal alignment between eligibility and exposure assignment while eliminating immortal time between treatment initiation and risk-set entry. To reduce early-adopter and channeling bias, cohort entry will be restricted to calendar periods after both comparator drug classes are available on the market and after a prespecified stabilization window following market entry. Beneficiaries may contribute more than one treatment episode—either within or across cohorts—provided that all eligibility, washout, enrollment, and stabilization criteria are re-satisfied prior to each new index date.

Under the primary as-treated framework, follow-up will proceed from day 15 after the index date until the earliest occurrence of incident non-arteritic anterior ischemic optic neuropathy (NAION), treatment discontinuation (defined using

dispensing date plus days' supply plus an allowable grace period), treatment switching or augmentation, death, disenrollment from Medicare Parts A, B, or D, or end of data availability. A secondary intention-to-treat analysis will fix exposure at cohort entry and continue follow-up from day 15 until outcome occurrence or administrative censoring.

Rationale for study design choice: The ACNU design is chosen because it minimizes confounding by indication by comparing new initiators of alternative guideline-recommended second-line antihyperglycemic therapies.[20] Restriction to new users ensures appropriate temporality between covariate assessment and treatment initiation and avoids mixing incident and prevalent users. Aligning eligibility, exposure assignment, and follow-up at the index date mirrors the structure of a randomized trial and prevents immortal time bias. Constructing two separate ACNU cohorts allows each comparison to be anchored to the timing of drug approvals and market stabilization, improving treatment overlap and internal validity. Together, these features support a valid emulation of the target trials and enable rigorous estimation of comparative NAION risk.

7.2 Study design diagram



a. Up to 30-day gaps in Medicare Parts A, B, or D enrollment are permitted during the baseline period and follow-up.
b. GLP-1RA contraindications include acute or chronic pancreatitis and personal or family history of multiple endocrine neoplasia type 2 (MEN-2) or medullary thyroid cancer. To enhance clinical comparability and reduce differential prescribing constraints across comparator drug classes, we additionally excluded individuals with end-stage renal disease, dialysis dependence, or renal replacement therapy at baseline. In this population, treatment selection is strongly influenced by renal function–specific labeling and safety considerations, resulting in limited treatment overlap. Moreover, dialysis is associated with hemodynamic instability and intradialytic hypotension, which may independently increase the risk of optic nerve ischemia. Inclusion of such patients would introduce substantial confounding by disease severity and potentially distinct pathophysiologic mechanisms.
c. Arteritic and systemic vasculitides include antineutrophil cytoplasmic antibody (ANCA)–associated and other vasculitides, such as giant cell arteritis, granulomatosis with polyangiitis, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis, Takayasu arteritis, polyarteritis nodosa, Behçet's disease, rheumatoid vasculitis, urticarial vasculitis, Kawasaki disease, IgA vasculitis, and central nervous system vasculitis.
d. NAION mimics include inflammatory or demyelinating optic neuropathies (optic neuritis, multiple sclerosis, neuromyelitis optica, and related demyelinating disorders); papilledema or pseudo-papilledema, including optic disc drusen; compressive or structural optic nerve or visual pathway disorders (optic nerve compression, toxic, nutritional, hereditary optic neuropathies, hemorrhage, hypoplasia; disorders of the optic chiasm, visual pathways, or visual cortex; benign or malignant tumors of the eye, orbit, or brain; metastatic orbital or brain disease); retinal vascular causes of acute vision loss (central or branch retinal artery or vein occlusion); and infectious or inflammatory ocular or orbital disease, including ocular or neurosyphilis.
e. Cataract extraction or laser-assisted in-situ keratomileusis (LASIK) occurring within 30 days prior to the index date were excluded to avoid inclusion of individuals within the acute perioperative period during which transient hypotension may increase NAION risk.
f. Baseline non-ocular conditions include diabetes-related complications (neuropathy, nephropathy, and peripheral angiopathy or foot ulcer, as indicators of advanced diabetes); cardiometabolic conditions (hypertension, dyslipidemia, ischemic/cerebrovascular/peripheral vascular disease, and congestive heart failure); and other systemic conditions (chronic obstructive pulmonary disease, chronic kidney disease [≤stage 4], cancer, and obesity).

g. Ophthalmology history includes age-related macular degeneration, diabetic retinopathy, other macular disorders, retinal detachment and defects, chorioretinal inflammation, cataract, glaucoma, visual disturbance, and other anterior segment disorders.
h. Induction lag period: Days 0–14 after the index date. Follow-up risk time is not accrued during this interval. Beneficiaries must be alive, continuously enrolled, and free of NAION through day 14 to enter follow-up.
i. Follow-up window: Follow-up begins on day 15 after the index date and continues until the earliest occurrence of incident NAION, death, loss of continuous Medicare enrollment, administrative end of the study period, or treatment discontinuation/switching with application of the post-discontinuation carryover period (see i).
j. Carryover period: For as-treated analyses, a 14-day carryover (lag) period is applied following treatment discontinuation or switching. Discontinuation date is the dispensing date plus days' supply plus the allowable grace period. X_1 denotes the first day after discontinuation/switching. The carryover period extends from days [X_1, X_1 + 14]. Censoring due to discontinuation/switching occurs at X_1 + 15.

7.3 Setting

7.3.1 Context and rationale for definition of time 0 and induction lag period for entry to the study population

Time 0 is defined as the date of initiation (first qualifying dispensing) of a GLP-1RA, sodium–glucose cotransporter-2 inhibitor (SGLT-2i), or dipeptidyl peptidase-4 inhibitor (DPP-4i), which serves as the point of entry into the study population. Follow-up for outcome assessment begins after a prespecified 14-day empirical la-time following Time 0.

Table 3: Operational Definition of Time 0 (index date) and induction lag period.

Study population name(s)	Time Anchor Description	Number of entries	Type of entry	Washout window	Care setting	Code type	Diagnosis position	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
GLP-1RA (exposure) vs SGLT-2i (reference) (Cohort I)	Index date (t=0): first qualifying dispensing of GLP-1RA or SGLT-2i	Multiple per individual allowed*	Incident initiation	[-365, -1]	Outpatient pharmacy claims (Part D)	NDC	N/A	Prior use of GLP-1RA or SGLT-2i during the washout period and exposure overlapping the index date	N/A	Investigator review of generic names
GLP-1RA (exposure) vs SGLT-2i (reference) (Cohort I)	Start of follow-up: index date + 14 days (risk time begins day 15)	Mirrors index episodes	Derived (start of risk period)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
GLP-1RA (exposure) vs DPP-4i (reference) (Cohort II)	Index date (t=0): first qualifying dispensing of GLP-1RA or DPP-4i	Multiple per individual allowed*	Incident initiation	[-365, -1]	Outpatient pharmacy claims (Part D)	NDC	N/A	Prior use of GLP-1RA or DPP-4i during the washout period and exposure overlapping	N/A	Investigator review of generic names

Table 3: Operational Definition of Time 0 (index date) and induction lag period.

Study population name(s)	Time Anchor Description	Number of entries	Type of entry	Washout window	Care setting	Code type	Diagnosis position	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
								the index date		
GLP-1RA (exposure) vs DPP-4i (reference) (Cohort II)	Start of follow-up: index date + 14 days (risk time begins day 15)	Mirrors index episodes	Derived (start of risk period)	N/A	N/A	N/A	N/A	N/A	N/A	N/A

* Multiple episodes per individual are permitted provided that continuous enrollment, washout, and eligibility criteria are re-satisfied prior to each new index date.
The washout window of [-365, -1] denotes the 365 days preceding the index date. Incident initiation requires no dispensing of the comparator drug classes during the washout period and no prior dispensing whose exposure episode extends into the index date. An exposure episode is defined using dispensing date and recorded days' supply, allowing for an allowable grace period to account for delayed refills. The induction lag excludes outcome events occurring during days 0–14 after the index date; risk time begins on day 15. Beneficiaries must be alive, continuously enrolled, and outcome-free through day 14 to enter the analytic risk set.
Abbreviations: DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; NDC, National Drug Code; SGLT-2i, sodium–glucose cotransporter-2 inhibitor.

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7.3.2 Context and rationale for study inclusion criteria

We require at least 12 months of continuous medical (Parts A/B) and prescription (Part D) enrollment prior to Time 0, allowing for one or more enrollment gaps of no more than 30 days each. Requiring 12 months of medical and prescription coverage ensures that patients have observable time in the data where contact with the healthcare system will allow capture of clinical codes to measure inclusion-exclusion criteria and baseline covariates. The population is restricted to patients with T2DMM aged at least 66 years at cohort entry (index date).

Table 4: Operational Definitions of Inclusion Criteria

Criterion	Details	Order of application	Assessment window	Care settings	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source of algorithm
Age eligibility	Age ≥66 years at index date to allow ≥12 months of baseline enrollment	At cohort entry date	[0, 0]	Master Beneficiary Summary File	Enrollment variables	N/A	Both ACNU cohorts	N/A	N/A
Continuous Medicare enrollment	Continuous enrollment in Medicare Parts A, B, and D with no HMO coverage. Gap of 30	Before selection of cohort entry date	[-365, -1]	Master Beneficiary Summary File	Enrollment variables	N/A	Both ACNU cohorts	N/A	N/A

Table 4: Operational Definitions of Inclusion Criteria

Criterion	Details	Order of application	Assessment window	Care settings	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source of algorithm
	days allowed.								
Type 2 diabetes mellitus	≥1 inpatient or ≥2 outpatient claims for T2DM	Before selection of cohort entry date	[-365, -1]	Any	ICD-9-CM; ICD-10-CM	Any position	Both ACNU cohorts	N/A	Investigator review of clinical codes
New initiation of study drug class	First dispensing of GLP-1RA or comparator drug following ≥12-month class-specific washout	At cohort entry date	[0, 0]	Outpatient pharmacy (Part D)	NDC; ATC	N/A	Both ACNU cohorts	N/A	Investigator review of generic names
≥1 ophthalmology or optometry visit or diagnostic eye	Improves likelihood of detecting incident	Before or at cohort entry date	[-365, -1]	Outpatient	CPT; HCPCS; specialty codes	N/A	Both ACNU cohorts	N/A	Investigator review of clinical codes

Table 4: Operational Definitions of Inclusion Criteria

Criterion	Details	Order of application	Assessment window	Care settings	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source of algorithm
procedure at baseline	NAION cases								

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225 ### 7.3.3 Context and rationale for study exclusion criteria

Table 5: Operational Definitions of Exclusion Criteria

Criterion	Details	Order of application	Assessment window	Care settings[1]	Code Type[2]	Diagnosis position[3]	Applied to study populations:	Measurement characteristics/ validation	Source of algorithm
Type 1 diabetes	Distinct disease process and treatment pathway compared with Type 2 diabetes (T2DM)	Before or at cohort entry date	[-365, 0]	Any	ICD-9-CM; ICD-10-CM	Any position	Both ACNU cohorts	N/A	Investigator review of clinical codes
Secondary or gestational diabetes	Distinct disease process and treatment pathway compared with T2DM	Before or at cohort entry date	[-365, 0]	Any	ICD-9-CM; ICD-10-CM	Any position	Both ACNU cohorts	N/A	Investigator review of clinical codes

Table 5: Operational Definitions of Exclusion Criteria

Criterion	Details	Order of application	Assessment window	Care settings[1]	Code Type[2]	Diagnosis position[3]	Applied to study populations:	Measurement characteristics/ validation	Source of algorithm
Same-day initiation of both study drug classes	Excluded to minimize exposure misclassification	At cohort entry date	[0, 0]	Pharmacy claims		Any position	Both ACNU cohorts	N/A	Investigator review of generic names
Acute or chronic pancreatitis	Excluded as individuals with history are unlikely to initiate or persist on GLP-1RAs	Before or at cohort entry date	[-365, 0]	Inpatient, outpatient	ICD-9-CM; ICD-10-CM	Any position	Both ACNU cohorts	N/A	Investigator review of clinical codes
Multiple endocrine neoplasia type 2 (MEN-2)	Excluded as long acting GLP-1 RA are contraindicated in this population	Before or at cohort entry date	[-365, 0]	Inpatient, outpatient	ICD-9-CM; ICD-10-CM	Any position	Both ACNU cohorts	N/A	Investigator review of clinical codes
End-stage renal disease (ESRD), dialysis dependence, or renal replacement therapy (RRT)[4]	Excluded. Renal function–based prescribing constraints limit treatment comparability in advanced CKD/dialysis; dialysis-related	Before or at cohort entry date	[-365, 0]	Inpatient, outpatient	ICD-9-CM; ICD-10-CM; CPT/HCPCS	Any position	Both ACNU cohorts	N/A	Investigator review of clinical codes

Table 5: Operational Definitions of Exclusion Criteria

Criterion	Details	Order of application	Assessment window	Care settings[1]	Code Type[2]	Diagnosis position[3]	Applied to study populations:	Measurement characteristics/ validation	Source of algorithm
	hypotension may increase NAION risk.								
Thyroid cancer	Excluded. Only medullary thyroid cancer is a formal contraindication; because claims do not reliably capture histologic subtype, all thyroid cancer is excluded to avoid misclassification	Before or at cohort entry date	[-365, 0]	Inpatient, outpatient	ICD-9-CM; ICD-10-CM; CPT/HCPCS	Any position	Both ACNU cohorts	N/A	Investigator review of clinical codes
Prior ischemic optic neuropathy	Excluded to ensure NAION outcome is incident	Before or at cohort entry date	[-365, 0]	Any	ICD-9-CM; ICD-10-CM	Any position	Both ACNU cohorts	N/A	Investigator review of clinical codes
ANCA-associated and other vasculitides[5]	Excluded to minimize misclassification	Before or at cohort entry date	[-365, 0]	Any	ICD-9-CM; ICD-10-CM	Any position	Both ACNU cohorts	N/A	Investigator review of clinical codes

Table 5: Operational Definitions of Exclusion Criteria

Criterion	Details	Order of application	Assessment window	Care settings[1]	Code Type[2]	Diagnosis position[3]	Applied to study populations:	Measurement characteristics/ validation	Source of algorithm
	of arteritic AION as NAION								
Severe bilateral visual impairment or legal blindness	Excluded as no at-risk eye remains for incident NAION	Before or at cohort entry date	[-365, 0]	Any	ICD-9-CM; ICD-10-CM	Any position	Both ACNU cohorts	N/A	Investigator review of clinical codes
Optic atrophy*	Excluded as optic atrophy is a long-term sequela of prior optic nerve infarction and may indicate unobserved prior NAION	Before or at cohort entry date	[-365, 0]	Any	ICD-9-CM; ICD-10-CM	Any position	Both ACNU cohorts	N/A	Investigator review of clinical codes
Inflammatory or demyelinating optic neuropathies[6]*	Excluded. Non-ischemic optic neuropathies that can be miscoded as ION or coexist with ambiguous optic nerve findings, thus	Before or at cohort entry date	[-365, 0]	Any	ICD-9-CM; ICD-10-CM	Any position	Both ACNU cohorts	N/A	Investigator review of clinical codes

Table 5: Operational Definitions of Exclusion Criteria

Criterion	Details	Order of application	Assessment window	Care settings[1]	Code Type[2]	Diagnosis position[3]	Applied to study populations:	Measurement characteristics/ validation	Source of algorithm
	threatening outcome specificity								
Structural or compressive optic-nerve disorders[7]*	Structural lesions can cause optic disc pallor and visual field defects indistinguishable from NAION	Before or at cohort entry date	[-365, 0]	Any	ICD-9-CM; ICD-10-CM	Any position	Both ACNU cohorts	N/A	Investigator review of clinical codes
Retinal vascular causes of vision loss[8]*	Excluded. Retinal vascular events can be miscoded as NAION	Before or at cohort entry date	[-365, 0]	Any	ICD-9-CM; ICD-10-CM	Any position	Both ACNU cohorts	N/A	Investigator review of clinical codes
Papilledema or optic disc drusen*	Excluded as they may mimic NAION	Before or at cohort entry date	[-365, 0]	Any	ICD-9-CM; ICD-10-CM	Any position	Both ACNU cohorts	N/A	Investigator review of clinical codes
Cataract surgery / Laser assisted-in-situ	Excluded as they may precipitate NAION	Before or at cohort entry date	[-30, 0]	Any	CPT/HCPCS	Any position	Both ACNU cohorts	N/A	Investigator review of clinical codes

Table 5: Operational Definitions of Exclusion Criteria

Criterion	Details	Order of application	Assessment window	Care settings[1]	Code Type[2]	Diagnosis position[3]	Applied to study populations:	Measurement characteristics/ validation	Source of algorithm
keratomileusis (LASIK)*									

[1]Care setting including inpatient, outpatient, or emergency department
[2]See Appendix for list of clinical codes for each study parameter
[3]Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)
[4]ESRD indicate chronic kidney failure requiring ongoing renal replacement therapy (chronic dialysis or kidney transplant)
[5] ANCA- associated and other vasculitides include giant cell arteritis, granulomatosis with polyangiitis/Wegener's granulomatosis, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis, Behçet's disease, urticarial vasculitis, Kawasaki disease, central nervous system vasculitis, rheumatoid vasculitis, polyarteritis nodosa, Takayasu arteritis, IgA vasculitis (Henoch-Schönlein purpura)
[6]Inflammatory or demyelinating optic neuropathies include optic neuritis, multiple sclerosis-related optic neuropathy, neuromyelitis optica, other demyelinating diseases
[7]Structural or compressive optic-nerve disorders include optic nerve compression, tumors, hereditary or toxic optic neuropathies
[8]Retinal vascular causes of vision loss include central or branch retinal artery or vein occlusion
*Risk-set entry restriction: In addition to baseline (pre-index) assessment, beneficiaries must be free of these diagnoses during days 0–14 after the index date to enter follow-up on day 15.

7.4 Variables

7.4.1 Context and rationale for exposure(s) of interest

We examine new initiators of GLP-1 receptor agonists, SGLT2 inhibitors, and DPP-4 inhibitors, which represent commonly used glucose-lowering therapies at comparable decision points in the management of type 2 diabetes. Restricting to incident new users with a 12-month class-specific washout reduces prevalent-user bias and aligns patients at a similar

stage of therapeutic escalation. This approach supports exchangeability across exposure groups and enables valid comparison of safety outcomes following treatment initiation.

Algorithm to define duration of exposure effect: We will define exposure duration using pharmacy dispensing dates and days' supply. Continuous exposure is defined as sequential fills with ≤30-day allowable gaps (i.e., refill within days supply + 30 days grace period). Exposure episodes end on the earliest of treatment discontinuation, switching to the comparator class, initiation of the alternate study drug class, disenrollment, death, or end of data. For as-treated analyses, risk time is attributed to the observed exposure episode; for intention-to-treat analyses, exposure is fixed at cohort entry. NAION follow-up begins after a 14-day induction lag period and ends 14 days after discontinuation or switching/augmenting (latent period).

Table 6: Operational Definitions of Exposure

Exposure group name(s)	Details	Washout window	Assessment window	Care settings	Code Type	Diagnosis position	Applied to study populations:	Incident with respect to...	Measurement characteristics/ validation	Source of algorithm
GLP-1RA	Exposed group	[-365, -1]	[1, censor]	N/A	NDC	N/A	Exposed group in both ACNU cohorts	Incident new GLP-1RA use after ≥12-month washout	N/A	Investigators review of generic names
SGLT-2i	Comparator group in Cohort I	[-365, -1]	[1, censor]	N/A	NDC	N/A	Comparator group in Cohort I	Incident new use after ≥12-month washout	N/A	Investigators review of generic names

Table 6: Operational Definitions of Exposure

Exposure group name(s)	Details	Washout window	Assessment window	Care settings	Code Type	Diagnosis position	Applied to study populations:	Incident with respect to...	Measurement characteristics/ validation	Source of algorithm
DPP-4i	Comparator group in Cohort II	[-365, -1]	[1, censor]	N/A	NDC	N/A	Comparator group in Cohort II	Incident new use after ≥12-month washout	N/A	Investigators review of generic names

Abbreviations: DPP-4i - dipeptidyl peptidase-4 inhibitor. GLP-1RA - glucagon-like peptide-1 receptor agonist. SGLT-2i - sodium–glucose cotransporter-2 inhibitor.

7.4.2 Context and rationale for outcome(s) of interest

Non-arteritic anterior ischemic optic neuropathy (NAION) is an acute optic nerve ischemic event characterized by sudden, painless monocular vision loss. It is the most common acute optic neuropathy in adults and has hypothesized vascular mechanisms that may plausibly relate to glucose-lowering medications. NAION is rare, and ischemic optic neuropathy (ION) codes do not distinguish arteritic from non-arteritic forms. Therefore, we will use a structured, multi-component claims algorithm to approximate NAION and to minimize misclassification of arteritic anterior ischemic optic neuropathy, as well as other eye conditions that mimic or could represent sequelae of prior unobserved NAION.

The primary outcome (NAION – Algorithm 1) will be defined as ≥1 inpatient or outpatient diagnosis of ION (ICD-9-CM 377.41; ICD-10-CM H47.01x) accompanied by an ophthalmology or optometry encounter within ±30 days of the diagnosis, with exclusion of arteritic or systemic vasculitis codes in the −180 to +14-day window around the ION event. This definition is adapted from a Sentinel Initiative algorithm that has demonstrated a positive predictive value of approximately 75% for ICD-10-CM H47.01 when combined with specialty confirmation, and it is intended to balance

clinical specificity (through specialist confirmation and arteritic exclusion) with adequate sensitivity for detecting NAION in older adults.

Since claims-based outcome algorithms inevitably involve trade-offs between sensitivity and specificity, we will implement a series of prespecified sensitivity outcome definitions that systematically vary key components of the primary algorithm. These alternative definitions are designed to evaluate the robustness of the findings to different assumptions about misclassification, including reliance on specialty confirmation, the breadth of arteritic exclusion, and the presence of clinical mimickers or empiric arteritic treatment.

Sensitivity outcome 1 will remove the requirement for an ophthalmology or optometry visit within ±30 days of the ION diagnosis. This will create a higher-sensitivity, lower-specificity definition that captures ION diagnoses recorded in settings where eye-care specialists may not be coded (e.g., emergency or inpatient settings), thereby testing how strongly results depend on documented specialty confirmation.

Sensitivity outcome 2 will define a high-specificity NAION phenotype by further excluding ION diagnoses with co-occurring optic nerve or retinal conditions that may mimic NAION (e.g., non-ischemic optic neuropathies, papilledema/pseudo-papilledema, demyelinating disease, retinal vascular occlusions, optic atrophy) recorded from −180 to +14 days; severe systemic shock or hypoperfusion within ±3 days; cataract or LASIK procedures within the 30 days before the ION diagnosis (to minimize misclassifying peri- or post-operative ischemic optic neuropathy); or empiric arteritic evaluations,

defined as new systemic corticosteroid courses or temporal-artery biopsy within ±14 days. This outcome will prioritize clinical specificity by removing events likely driven by alternative pathophysiology or work-up for suspected arteritic disease.

Together, these outcome definitions will provide a structured framework to examine how sensitive the comparative NAION risk estimates are to alternative claims-based algorithms that span a spectrum from higher sensitivity (broader, less restrictive outcome definitions) to higher specificity (narrower phenotypes excluding mimickers and empirically treated arteritic cases).

Table 7: Operational definitions of Outcome

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care settings	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source of algorithm
NAION – Algorithm 1	Defined as ≥1 ICD-9-CM (377.41) or ICD-10-CM (H47.01x) coded visit with an ophthalmology or optometry specialist encounter +/- 30 days. Arteritic/vasculitic causes are excluded if any qualifying vasculitis code appears −180 to +14 days around the ION diagnosis	Yes	Time-to-event	Any time prior to cohort entry	Any	ICD-9-CM, ICD-10-CM, ophthalmology or optometry specialist codes	Any ION diagnosis position	Both cohorts	Positive predictive value of 75.8% for ICD-10-CM-only algorithm	Sentinel Initiative protocol (adapted)
Sensitivity 1 – No specialty encounter confirmation	Algorithm 1 without the requirement for ophthalmology/optometry encounter within ±30 days of ION diagnosis	No	Time-to-event	Any time prior to cohort entry	Any	ICD-9-CM, ICD-10-CM	Any ION diagnosis position	Both cohorts	Tests dependence of NAION identification on specialist confirmation	Investigator-defined (variant of primary algorithm
Sensitivity 2 – Algorithm 1 AND NOT: optic atrophy, optic neuritis, mimicking optic neuropathies, retinal vascular events, demyelinating	Algorithm 1 plus exclusion of: (i) optic nerve/retinal mimickers, including optic atrophy, optic neuritis, non-ischemic optic neuropathies,	No	Time-to-event	Any time prior to cohort entry	Any	ICD-9-CM, ICD-10-CM; NDC; CPT/HCPCS	Any ION diagnosis position	Both cohorts	Higher specificity for true NAION by removing cases likely evaluated/treated as arteritic ION	Investigator-defined (variant of primary algorithm

Table 7: Operational definitions of Outcome

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care settings	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source of algorithm
disease, severe systemic shock/hypoperfusion, cataract/LASIK perioperative ischemic risk, OR empiric arteritic treatment	papilledema/pseudo-papilledema, demyelinating disease, and retinal artery/vein occlusion (−180 to +14 days); (ii) severe systemic shock/hypoperfusion (±3 days); (iii) cataract or LASIK procedures (−30 to 0 days); or (iv) empiric arteritic evaluations, defined as new systemic steroids or temporal-artery biopsy within ±14 days									

7.4.3 Context and rationale for follow up

Vision loss in NAION typically presents acutely, often upon awakening, consistent with the hypothesized role of nocturnal hypotension. Ischemic injury to the optic nerve head is believed to occur abruptly, with clinical manifestations emerging shortly thereafter rather than over prolonged periods.[9,21,22] Accordingly, the biological latent period between optic nerve ischemia and vision loss is assumed to be very short (likely ≤24 hours), although formal clinical diagnosis may occur later depending on patterns of care-seeking and evaluation.

Despite the acute nature of NAION, implementation of a short induction lag period is warranted for several epidemiologic reasons. First, protopathic bias (reverse causation) may occur if early visual symptoms prompt medication intensification

prior to formal NAION diagnosis. Second, heightened healthcare utilization around treatment initiation may increase diagnostic intensity, leading to earlier detection of pre-existing or evolving optic neuropathy. Third, although biologic latency for NAION is brief, the temporal window linking initiation of glucose-lowering therapy to clinically manifest ischemia remains uncertain, particularly given short-term hemodynamic effects (e.g., blood pressure reduction or volume shifts) that may unfold over days to weeks.

To mitigate these potential biases and define a conservative exposure attribution window, we apply a 14-day induction lag period following treatment initiation. This induction period is an analytic design choice and does not reflect an assumed biological latency for NAION. Rather, it serves to exclude early outcome events that are unlikely to be causally related to the initiated therapy and that may reflect pre-existing or evolving disease processes. Accordingly, follow-up begins 14 days after the index date, defined as the first qualifying dispensing claim for the initiated drug class. In as-treated analyses, follow-up under a given exposure continues until the earliest of incident NAION, death, disenrollment, end of available data, or 14 days after treatment discontinuation, switching, or augmentation. The 14-day post-discontinuation window reflects the possibility of short-term residual pharmacodynamic effects (e.g., persistent hemodynamic changes), while minimizing misclassification of subsequent exposure periods. In intention-to-treat analyses, exposure is fixed at cohort entry and follow-up begins after the same 14-day induction period and continues until outcome occurrence or administrative censoring.

Table 8: Operational Definitions of Follow up

Time point	Select all that apply	Specify
Follow up start	Day X following index date	Day 15 after cohort entry (index date = first dispensing of cohort-defining drug). A 14-day induction lag period is applied during which NAION events are not attributed to exposure. Applies to both as-treated and intention-to-treat (ITT) analyses
Follow up end	Date of outcome Date of death End of observation in data Day X after exposure discontinuation/switch	Earliest of: • First qualifying NAION event, • Death, • Disenrollment from Medicare Parts A/B/D (allowing 45-day gaps), • End of available data; or

Table 8: Operational Definitions of Follow up

Time point	Select all that apply	Specify
		• Completion of 14-day latent period after exposure ends (only relevant to as-treated analyses)
Date of outcome	Yes	Date of first qualifying NAION event meeting the defined algorithm
Date of death	Yes	Date of death recorded in Medicare denominator files
End of observation in data	Yes	End of the Medicare data window: December 31, 2019, or the earlier loss of continuous enrollment in Parts A, B, or D. Data are available from January 1, 2007, through December 31, 2019
Day X following index date	Yes	Day 15 marks the start of risk attribution for NAION
End of study period	Yes	December 31, 2019; individuals still at risk are censored at this date
End of exposure	Yes (as-treated analysis only)	End of an exposure episode is defined as the last day of days' supply of the final dispensing in that episode, allowing up to a 30-day refill gap. For as-treated analyses, NAION risk under that exposure stops 14 days after this date (latent period)
Date of add to/switch from exposure	Yes (as-treated analysis only)	Date of first dispensing of another study drug class (e.g., switching from GLP-1RA to SGLT2i or DPP-4i, or adding a second study drug class). For as-treated analyses, follow-up under the prior exposure continues through a 14-day latent period; the new exposure class begins its own 14-day induction period (risk counted from Day 15 of the new exposure)
Other date	N/A	N/A; no additional follow-up anchors are used.

7.4.4 Context and rationale for covariates (confounding variables and effect modifiers, e.g. risk factors, comorbidities, comedications)

Covariates will be selected based on subject-matter knowledge of NAION pathophysiology, diabetes treatment selection, and established predictors of treatment allocation and optic-nerve ischemic events. These variables will include demographics, diabetes severity measures, traditional vascular risk factors, comorbidities that may influence treatment

selection, ophthalmic conditions that may reflect patterns of eye-care utilization, and concomitant medications that may be related either to treatment selection or NAION risk. All covariates will be measured during the 12-month baseline period preceding cohort entry to ensure appropriate temporality relative to exposure initiation, minimize reverse causation, and align with new-user design principles. Claims-based definitions will rely on validated algorithms when available; otherwise, covariates will be defined using standard Medicare coding conventions and clinical review.

Table 9: Operational Definitions of Covariates

Characteristic	Details	Type of variable	Assessment window	Care settings	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source of algorithm
Demographics									
Age		Continuous	[0, 0]	Enrollment	Enrollment data	N/A	Both cohorts	N/A	Investigator review of codes
Sex		Binary	[0, 0]	Enrollment	Enrollment data	N/A	Both cohorts	N/A	Investigator review of codes
Race/ethnicity		Categorical	[0, 0]	Enrollment	Enrollment data	N/A	Both cohorts	N/A	Investigator review of codes
Index calendar year		Categorical	[0, 0]	N/A	N/A	N/A	Both cohorts	N/A	Investigator review of codes
Low-income subsidy		Binary	[-365, -1]	N/A	N/A	Any	Both cohorts	N/A	Investigator review of codes
Eye disorders									

Age-related macular degeneration	Any type	Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Retinal detachment / defects	Breaks, tears, detachments	Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Chorioretinal inflammation	Uveitis, chorioretinitis	Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Other retinal disorders		Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Cataract		Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Glaucoma		Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Visual disturbance	Blurred vision, scotoma	Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Other anterior segment disorders	Keratitis, corneal disorders, disorders of the conjunctiva, eyelid disorders,	Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes

	disorder of lacrimal system, disorder of the iris or ciliary body								
Orbital disorders	Infections, inflammation	Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Diabetes-related conditions									
Diabetic retinopathy		Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Diabetic kidney disease		Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Diabetic neuropathy		Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Eye exams/diagnostic testing									
Intermediate eye exam, new patient		Binary	[-365, -1]	Any	CPT	Any	Both cohorts	N/A	Investigator review of codes
Intermediate eye exam, established patient		Binary	[-365, -1]	Any	CPT	Any	Both cohorts	N/A	Investigator review of codes
Comprehensive eye exam, new patient		Binary	[-365, -1]	Any	CPT	Any	Both cohorts	N/A	Investigator review of codes

Comprehensive eye exam, established patient	Binary	[-365, -1]	Any	CPT	Any	Both cohorts	N/A	Investigator review of codes
eye exam with anesthesia, complete	Binary	[-365, -1]	Any	CPT	Any	Both cohorts	N/A	Investigator review of codes
eye exam w/ anesthesia, limited	Binary	[-365, -1]	Any	CPT	Any	Both cohorts	N/A	Investigator review of codes
Gonioscopy	Binary	[-365, -1]	Any	CPT	Any	Both cohorts	N/A	Investigator review of codes
Optical coherence tomography	Binary	[-365, -1]	Any	CPT	Any	Both cohorts	N/A	Investigator review of codes
Scanning computerized ophthalmic diagnostic imaging	Binary	[-365, -1]	Any	CPT	Any	Both cohorts	N/A	Investigator review of codes
Ophthalmoscopy, extended w/ retinal drawing, initial	Binary	[-365, -1]	Any	CPT	Any	Both cohorts	N/A	Investigator review of codes
Ophthalmoscopy, extended w/ retinal drawing, subsequent	Binary	[-365, -1]	Any	CPT	Any	Both cohorts	N/A	Investigator review of codes
Fluorescein angioscopy	Binary	[-365, -1]	Any	CPT	Any	Both cohorts	N/A	Investigator review of codes
Fluorescein angiography	Binary	[-365, -1]	Any	CPT	Any	Both cohorts	N/A	Investigator review of codes

Indocyanine-green angiography	Binary	[-365, -1]	Any	CPT	Any	Both cohorts	N/A	Investigator review of codes
Fundus photography	Binary	[-365, -1]	Any	CPT	Any	Both cohorts	N/A	Investigator review of codes
Ophthalmoscopy/dynamometry	Binary	[-365, -1]	Any	CPT	Any	Both cohorts	N/A	Investigator review of codes
B-scan ultrasonography	Binary	[-365, -1]	Any	CPT	Any	Both cohorts	N/A	Investigator review of codes
Consult eye codes*	Binary	[-365, -1]	Any	CPT	Any	Both cohorts	N/A	Investigator review of codes
Evaluation/Management for established patients involving eye exams*	Binary	[-365, -1]	Any	CPT	Any	Both cohorts	N/A	Investigator review of codes
Evaluation/Management for new patients involving eye exams*	Binary	[-365, -1]	Any	CPT/HCPCS	Any	Both cohorts	N/A	Investigator review of codes
Macular exam	Binary	[-365, -1]	Any	CPT/HCPCS	Any	Both cohorts	N/A	Investigator review of codes
Fluocinolone intravitreal	Binary	[-365, -1]	Any	HCPCS	Any	Both cohorts	N/A	Investigator review of codes
Dexamethasone intravitreal	Binary	[-365, -1]	Any	HCPCS	Any	Both cohorts	N/A	Investigator review of codes

Implant eye drug system		Binary	[-365, -1]	Any	CPT	Any	Both cohorts	N/A	Investigator review of codes
Injection eye drug		Binary	[-365, -1]	Any	CPT	Any	Both cohorts	N/A	Investigator review of codes
Comorbidities									
Hypertension		Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Hyperlipidemia/Dyslipidemia		Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Coronary/Ischemic heart disease	Stable/unstable coronary artery disease, acute myocardial infarction, coronary revascularization	Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Atrial/ventricular arrhythmia		Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Cardiomyopathy		Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Cerebrovascular disease	Stroke, transient ischemic attack	Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes

Peripheral vascular disease		Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Heart failure		Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Carotid artery dissection		Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Obesity		Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Primary hypercoagulable state	Antiphospholipid antibody syndrome, Protein C or S deficiency, Factor V Leiden, and Hyperhomocysteinemia.	Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Chronic obstructive pulmonary disease		Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Asthma		Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Cancer		Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes

Acute kidney injury	Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Chronic kidney disease (Stage 1-2)	Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Chronic kidney disease (Stage 3-4)	Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Obstructive sleep apnea	Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Migraine	Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Orthostatic / symptomatic hypotension	Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Falls	Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Alzheimer’s disease	Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Parkinson’s disease	Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Other dementia types	Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes

Depression	Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Other mood disorders	Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Psychotic disorders	Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Combined comorbidity score	Continuous	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Frailty score	Continuous	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Health behaviors								
Tobacco use	Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Alcohol use	Binary	[-365, -1]	Any	ICD-9-CM, ICD-10-CM	Any	Both cohorts	N/A	Investigator review of codes
Comedications								
Metformin – past use	Binary	[-365, -1]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
Metformin – current use	Binary	[0, 0]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes

Sulfonylureas – past use	Binary	[-365, -1]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
Sulfonylureas – current use	Binary	[0, 0]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
Thiazolidinediones – past use	Binary	[-365, -1]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
Thiazolidinediones – current use	Binary	[0, 0]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
Long-acting insulin – past use	Binary	[-365, -1]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
Long-acting insulin – current use	Binary	[0, 0]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
Alpha-glucosidase inhibitors – past use	Binary	[-365, -1]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
Alpha-glucosidase inhibitors – current use	Binary	[0, 0]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
Meglitinides – past use	Binary	[-365, -1]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
Meglitinides – current use	Binary	[0, 0]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes

Angiotensin-converting enzyme inhibitors	Binary	[-365, -1]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
Angiotensin II receptor blockers	Binary	[-365, -1]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
Beta-blockers	Binary	[-365, -1]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
Calcium-channel blockers	Binary	[-365, -1]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
Thiazides diuretics	Binary	[-365, -1]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
Loop diuretics	Binary	[-365, -1]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
Potassium-sparing diuretics	Binary	[-365, -1]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
Digoxin	Binary	[-365, -1]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
Statins	Binary	[-365, -1]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
Fibrates	Binary	[-365, -1]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes

Ezetimibe		Binary	[-365, -1]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
Antithrombotic medications		Binary	[-365, -1]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
Antiplatelets	Aspirin, clopidogrel, ticagrelor	Binary	[-365, -1]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
Anticoagulants	warfarin, direct oral anticoagulants	Binary	[-365, -1]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
Antiarrhythmics		Binary	[-365, -1]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
Systemic steroids	Oral/parenteral	Binary	[-365, -1]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
Amiodarone	Associated with NAION	Binary	[-365, -1]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
Interferon-alpha	Associated with NAION	Binary	[-365, -1]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
Phosphodiesterase-5 inhibitors	Associated with NAION	Binary	[-365, -1]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
Healthcare Utilization									

Hba1c test	Categorical	[-365, -1]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
Lipid test	Binary	[-365, -1]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
LDL-cholesterol	Categorical	[-365, -1]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
Diastolic pressure	Categorical	[-365, -1]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
Systolic pressure	Categorical	[-365, -1]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
Flu shot	Binary	[-365, -1]	Any	NDC	Any	Both cohorts	N/A	Investigator review of codes
Number of hospitalizations – any reason	Continuous	[-365, -1]	Any	CPT	Any	Both cohorts	N/A	Investigator review of codes
Number of hospitalizations due to diabetes	Continuous	[-365, -1]	Any	CPT	Any	Both cohorts	N/A	Investigator review of codes
Number of ED visits – any reason	Continuous	[-365, -1]	Any	CPT	Any	Both cohorts	N/A	Investigator review of codes
Number of ED visits due to any reason	Continuous	[-365, -1]	Any	CPT	Any	Both cohorts	N/A	Investigator review of codes

Number of office/outpatient visits	Continuous	[-365, -1]	Any	CPT	Any	Both cohorts	N/A	Investigator review of codes

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7.5 Data analysis

7.5.1 Context and rationale for analysis plan

The analysis plan is designed to estimate the comparative risk of NAION under each active treatment strategy while addressing confounding, selection bias, and competing risks inherent to real-world data. Baseline characteristics will be described for each exposure group using counts and percentages for categorical variables and means (standard deviations) or medians (interquartile ranges) for continuous variables, measured during the 12 months before cohort entry. Baseline covariates will include demographics, calendar time, diabetes severity and control, comorbidities, comedications, ocular history, healthcare utilization, and socioeconomic indicators, as previously defined. These descriptive summaries will provide context for clinical interpretation and support evaluation of baseline comparability between groups.

To account for measured confounding, we will estimate propensity scores (PS) separately for each pairwise exposure comparison (GLP-1RA vs SGLT-2i; GLP-1RA vs DPP-4i) using multivariable logistic regression models that include all baseline covariates, modeled flexibly where appropriate (e.g., age splines, categorized bands). Estimating PS separately for each contrast will preserve exchangeability within each comparison. Our primary estimand is the average treatment effect in the treated (ATT), representing the causal effect of initiating a GLP-1RA among patients who actually initiated a GLP-1RA. Accordingly, we will apply standardized morbidity ratio (SMR) weighting to the comparator group using the PS odds weight, $PS/(1-PS)$.[23] SMR weighting is chosen because it targets the clinically relevant GLP-1RA-treated population. We will examine PS and weight distributions and assess covariate balance using standardized absolute mean differences, with a threshold of <0.10 indicating satisfactory balance.[24] Pre- and post-weighting balance tables will be presented in supplementary materials. If diagnostics indicate poor overlap or extreme weights, we will first consider refining the PS model (e.g., alternative functional forms) and, if needed, trim non-overlapping regions to improve comparability and reduce reliance on extrapolation.

For each pairwise comparison, we will then estimate both absolute and relative measures of effect. Crude incidence rates of NAION (events per 100,000 person-years) will first be calculated with exact Poisson 95% confidence intervals. In the SMR-weighted pseudo-population, adjusted cumulative risks at 6, 12, 24, and 36 months will be estimated using Kaplan–Meier methods, and adjusted risk differences (aRDs) will be calculated by subtracting the comparator risk from the GLP-1RA risk. Five-year estimates may be estimated depending on data availability. Ninety-five percent confidence intervals for adjusted risks and risk differences will be obtained using 1,000 bootstrap replicates or robust variance estimation, depending on model stability.

Adjusted hazard ratios (aHRs) and 95% confidence intervals will be estimated using SMR-weighted Cox proportional hazards models with days since index date as the time scale and robust (sandwich) variance estimators. Proportional hazards assumptions will be evaluated using Schoenfeld residuals and time-interaction terms; if violated, we will report time-stratified HRs and/or fit flexible parametric survival models.

Because death is not uncommon among older adults with diabetes and is a competing event for NAION, we will explicitly account for competing risks using the Aalen–Johansen (AJ) estimation framework.[25,26] The AJ estimator extends the Kaplan–Meier approach by jointly modeling cause-specific hazards for NAION and for death, yielding cumulative incidence functions that reflect the probability of NAION in the presence of competing mortality. Within our SMR-weighted analytic population, cause-specific hazards for NAION and death will be estimated at each event time, incorporating stabilized inverse probability of treatment weights and inverse probability of censoring weights to address confounding and informative censoring, respectively. The resulting SMR-weighted cumulative incidence functions will provide adjusted absolute risks of NAION under each treatment strategy, with 95% confidence intervals obtained via nonparametric bootstrap using 1,000 replicates. This framework is chosen because it preserves the ATT interpretation, appropriately handles competing death, and produces clinically interpretable absolute risk estimates that complement the hazard ratios from Cox models.

Secondary analyses will evaluate the robustness of the primary findings under alternative follow-up strategies that reflect different causal questions regarding GLP-1RA exposure. First, we will conduct an as-treated analysis restricted to beneficiaries who refill the same drug class within the index dispensing days' supply plus a grace period of 30 days after the first prescription. Because treatment persistence reflects patient adherence and clinical continuation decisions, this analysis estimates the effect of sustained exposure among users who remain on therapy beyond the initial fill. Follow-up will begin after applying the 14-day induction period to the date of the second fill, and all primary analysis models will be repeated in these treatment-persistent sub-cohorts.

Second, we will conduct an intention-to-treat (ITT) analysis in which follow-up begins 14 days after the index prescription and continues regardless of treatment discontinuation, switching, or augmentation. This analysis provides the effect of initiating therapy while minimizing bias related to informative censoring due to changes in treatment over time. The ITT analyses will repeat all crude and SMR-weighted models from the primary analysis, allowing direct comparison of "assignment-type" and "use-based" causal effects. Together, these secondary analyses will help quantify the degree to which primary results are sensitive to assumptions about treatment continuity and exposure misclassification.

A series of sensitivity analyses will assess the robustness of the findings to variations in outcome definitions, exposure operationalization, and analytic assumptions. To evaluate sensitivity to outcome measurement, we will repeat the analysis using (1) a lower-specificity definition that removes the requirement for ophthalmology or optometry encounters within ±30 days of diagnosis, and (2) a higher-specificity definition that excludes optic-nerve mimickers, demyelinating disease, peri-operative ischemic triggers, hypoperfusion events, and empiric arteritic evaluations. These analyses will assess the dependence of study findings on the specificity versus sensitivity of NAION classification.

We will additionally vary key exposure-timing parameters in as-treated sensitivity analyses, including the induction lag at treatment initiation and the post-discontinuation exposure-attribution window (evaluated symmetrically as 0/0 days, 7/7 days, and 30/30 days), as well as the treatment discontinuation grace period used to define continuous exposure (15 days and 60 days instead of 30 days). These analyses will examine the influence of biologic assumptions regarding onset and carry-over of drug effects and the impact of censoring due to gaps in medication supply. To evaluate sensitivity to extreme treatment channeling and lack of PS overlap, we will implement asymmetric propensity score trimming (1%, 2.5%, and 5%), and we will descriptively compare early NAION events among persistent versus non-persistent initiators to explore potential selection into treatment continuation.

To assess the potential influence of residual confounding by factors not observable in Medicare claims (e.g., nocturnal hypotension, optic-disc crowding), we will conduct a quantitative bias analysis using a confounding-curve approach. Specifically, we will construct a two-dimensional grid that varies the assumed strength of association between a single unmeasured confounder and (a) treatment initiation and (b) NAION risk difference. For each combination of these assumed associations, we will compute bias-adjusted effect estimates and identify the set of values that would attenuate the observed association to the null. These “confounding curves” will be compared with the observed associations of measured strong confounders (e.g., smoking-related diagnoses, markers of diabetes severity, ophthalmology utilization) to provide empirical benchmarks for plausibility. Results will be presented graphically and interpreted as the magnitude of unmeasured confounding that would be required to fully explain the study findings.

433 **7.5.1.1 A. Primary analysis**

434 **Table 10: Primary, secondary, and subgroup analysis specifications**

(a)

A. Primary analysis

Analysis element	Specification
Hypothesis:	Among Medicare beneficiaries ≥66 years with T2DMM, GLP-1RA initiation is associated with a higher risk of NAION compared with initiation of (I) SGLT-2i and (II) DPP-4i
Exposure contrast:	Cohort I: GLP-1RA vs SGLT-2i Cohort II: GLP-1RA vs DPP-4i
Outcome:	Time to incident NAION defined by Algorithm 1
Analytical software	SAS 9.4; R (version ≥4.3)
Model(s):	Measures of effect Crude measures: (1) Crude incidence rates (events per 100,000 person-years) with exact Poisson 95% CIs (2) Crude 5-year unweighted Kaplan-Meier cumulative incidence curves Adjusted measures: (1) Primary: SMR-weighted 5-year Aalen-Johansen cumulative incidence curves, accounting for competing risk of all-cause death (2) Supplementary: SMR-weighted 5-year Kaplan–Meier cumulative incidence curves Measures of association Crude measures: (1) Crude 5-year unweighted Kaplan-Meier risk difference curves Adjusted measures: (1) SMR-weighted 5-year adjusted risk differences (aRDs) based on Aalen–Johansen cumulative incidence functions, with 95% CIs from 1,000 bootstrap replicates or robust variance estimation, as appropriate

(a)
A. Primary analysis

Analysis element	Specification
	(2) SMR-weighted 5-year Kaplan–Meier risk difference curves (supplementary to AJ-based risk differences) (3) SMR-weighted Cox proportional hazards models to estimate hazard ratios and 95% CIs, using days since index date as the time scale robust (sandwich) variance estimators. Proportional hazards will be assessed using Schoenfeld residuals and time-by-exposure interactions, with time-stratified HRs or flexible parametric models used if violations are detected.
Confounding adjustment method	Propensity scores will be estimated separately for each cohort using logistic regression including all baseline covariates with flexible functional forms where appropriate. To target the average treatment effect in the treated (ATT), GLP-1RA initiators receive weight = 1 and comparator users receive the SMR weight PS/(1−PS). Covariate balance evaluated using standardized absolute mean differences (<0.10). If poor overlap or extreme weights are observed, PS model refinement or trimming will be applied.
Missing data methods	Claims-based covariates are expected to have low missingness. For categorical claims-based variables with missing values, we will include a “missing/unknown” category. For continuous claims-based covariates with ≤5% missingness, we will use median imputation with a corresponding missingness indicator in the primary analysis to avoid loss of sample size. If any continuous claims-based covariate exhibits >5–10% missingness and is considered clinically important, we will either exclude it from the primary propensity score model or explore multiple imputation for that covariate in prespecified sensitivity analyses. Laboratory values captured via LOINC will be summarized descriptively where available but will not be included in propensity score models or outcome models; no imputation will be performed for laboratory variables.

(a)

A. Primary analysis

Analysis element	Specification
Subgroup Analyses	(1) Time-window analyses: separate hazard ratios for 0-6 months, 6-12 months, and after 12 months (2) Sex (3) Number of antihypertensive classes (≥3 vs. <3) (4) Diabetes severity (0 vs ≥1 microvascular complications – retinopathy, angiopathy, neuropathy, nephropathy)

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(b)

B. Secondary analysis

Analysis element	Specification
Hypothesis:	Among Medicare beneficiaries ≥66 years with T2DMM, GLP-1RA initiation is associated with a higher risk of NAION compared with initiation of (I) SGLT-2i and (II) DPP-4i, under alternative follow-up strategies (treatment-persistent as-treated and intention-to-treat).
Exposure contrast:	Cohort I: GLP-1RA vs SGLT-2i Cohort II: GLP-1RA vs DPP-4i
Outcome:	Time to incident NAION defined by Algorithm 1
Analytical software	SAS 9.4; R (version ≥4.3)
Model(s):	Treatment-persistent as-treated analysis • Restricted to initiators who obtain a second fill of the same class within the index dispensing's days' supply + 30 days. • Follow-up begins after applying the 14-day induction window to the date of the second fill • Repeat primary analysis models in these treatment-persistent sub-cohorts, including: (1) Crude incidence rates and crude Kaplan–Meier curves (2) SMR-weighted Aalen–Johansen cumulative incidence curves (primary adjusted absolute risks) (3) SMR-weighted adjusted risk differences (aRDs) (4) SMR-weighted Cox proportional hazards models for hazard ratios (HRs). Intention to treat analysis • Follow-up begins 14 days after the index prescription and continues regardless of discontinuation, switching, or augmentation. • Repeat all primary analysis models under the ITT regime, including: (1) Crude incidence rates and crude Kaplan–Meier curves

(b)

B. Secondary analysis

Analysis element	Specification
	(2) SMR-weighted Aalen–Johansen cumulative incidence curves (primary adjusted absolute risks) (3) SMR-weighted adjusted risk differences (aRDs) (4) SMR-weighted Cox proportional hazards models for hazard ratios (HRs).
Confounding adjustment method	Propensity scores will be estimated separately for each cohort using logistic regression including all baseline covariates with flexible functional forms where appropriate. To target the average treatment effect in the treated (ATT), GLP-1RA initiators receive weight = 1 and comparator users receive the SMR weight PS/(1−PS). Covariate balance evaluated using standardized absolute mean differences (<0.10). If poor overlap or extreme weights are observed, PS model refinement or trimming will be applied.
Missing data methods	Claims-based covariates are expected to have low missingness. For categorical claims-based variables with missing values, we will include a “missing/unknown” category. For continuous claims-based covariates with ≤5% missingness, we will use median imputation with a corresponding missingness indicator in the primary analysis to avoid loss of sample size. If any continuous claims-based covariate exhibits >5–10% missingness and is considered clinically important, we will either exclude it from the primary propensity score model or explore multiple imputation for that covariate in prespecified sensitivity analyses. Laboratory values captured via LOINC will be summarized descriptively where available but will not be included in propensity score models or outcome models; no imputation will be performed for laboratory variables.
Subgroup Analyses	None

Table 11:
Sensitivity analyses – rationale, strengths and limitations

Analysis	What is being varied?	Why (expected learning)?	Strengths of the sensitivity analysis compared to primary	Limitations of the sensitivity analysis compared to primary
Sensitivity outcome 1	Outcome definition: remove requirement for ophthalmology/optometry encounter within ±30 days of ION diagnosis	Evaluates whether NAION identification depends on specialist access, documentation, or coding variability	Increases sensitivity of case capture; tests robustness to documentation variability	Reduced specificity; greater likelihood of including non-NAION diagnoses
Sensitivity outcome 2 – High-specificity exclusion set	Outcome definition: exclude optic nerve/retinal mimickers, demyelination, shock/hypoperfusion, peri-operative ischemic triggers, and empiric arteritic treatment)	Evaluates whether results persist under a stricter, high-specificity case definition	Stronger specificity; minimizes contamination with non-NAION conditions	Reduced event counts and precision; potential over-exclusion of true NAION
Varying induction and post-exposure latency (0/0-day, 7/7-day, 30/30-day)	Exposure timing: Vary lengths of induction period and post-exposure carryover window	Evaluates sensitivity to biologic assumptions about onset and offset of drug effects and potential reverse causation	Identifies whether early events disproportionately influence estimates; enhances causal interpretation	Extreme windows may be clinically implausible; may increase exposure misclassification

Table 11:
Sensitivity analyses – rationale, strengths and limitations

Analysis	What is being varied?	Why (expected learning)?	Strengths of the sensitivity analysis compared to primary	Limitations of the sensitivity analysis compared to primary
Varying treatment discontinuation grace period (15 and 60 days)	Exposure discontinuation grace period	Tests robustness of discontinuation rules and assesses whether censoring at medication gaps influences findings	Identifies sensitivity to exposure definition; reduces risk of misclassifying short gaps as discontinuation	Longer grace periods may overestimate exposure duration; shorter periods may censor true continuers
Propensity score trimming	Asymmetric trimming at 1%, 2.5%, and 5% in PS tails)	Evaluates impact of extreme treatment channeling and poor overlap on effect estimates	Improves overlap; reduces influence of extreme weights; increases robustness of SMR weighting	Trimming removes part of the target population; may alter ATT interpretation
Second-fill landmark	Requiring refill within index days' supply + 30-day grace; redefine time zero at second fill; apply 14-day induction period from second fill	Evaluates sensitivity to exposure misclassification from transient initiators and estimates effect among early persisters	Reduces dilution from very short exposure; approximates sustained-use effect; improves biologic alignment for vascular outcomes	Changes estimand by restricting to early persisters; potential selection bias from conditioning on post-initiation persistence

Table 11:
Sensitivity analyses – rationale, strengths and limitations

Analysis	What is being varied?	Why (expected learning)?	Strengths of the sensitivity analysis compared to primary	Limitations of the sensitivity analysis compared to primary
Pre-second fill events	Compare early NAION events among persistent vs non-persistent initiators	Evaluates whether early selection into treatment persistence may bias primary as-treated results	Identifies early-event patterns and selection mechanisms	Descriptive only
Quantitative bias analysis	Unmeasured confounding: Vary strength of unmeasured confounder associations with exposure and outcome	Estimates magnitude of unmeasured confounding necessary to nullify observed associations	Provides interpretable bounds; situates potential bias relative to observed covariates	Exploratory; relies on unverifiable assumptions

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7.6 Data sources

7.6.1 Context and rationale for data sources

Reason for selection: Medicare Fee-for-Service (FFS) Parts A, B, and D claims will be used because they provide a large, nationally representative population of older adults in whom both GLP-1RA and comparator antihyperglycemic agents are routinely prescribed. NAION predominantly affects individuals aged ≥50 years, and Medicare beneficiaries managed for diabetes represent a clinically relevant population for evaluating real-world risks of optic-nerve ischemic events. The Medicare dataset allows longitudinal capture of diagnoses, procedures, inpatient/outpatient encounters, and prescription drug dispensing needed to measure exposures, outcomes, and covariates within a new-user, active-comparator design.

Strengths of data source(s): The 20% random sample of all Medicare fee-ro-service beneficiaries with concomitant parts A, B, and D coverage during at least one month captures millions of older adults with diabetes, enabling robust estimation of rare outcomes such as NAION. Part A, B, and D claims provide comprehensive longitudinal data on hospitalizations, outpatient encounters, specialty visits, ophthalmic procedures, and prescription fillings. Long observation periods (2008–2019) allow adequate washout windows, market-stabilization periods, and multi-year follow-up needed for target-trial emulation.

Limitations of data source(s): Medicare claims have limited direct clinical information such as laboratory values, vital signs, visual field testing, optic nerve imaging, or inflammatory markers, which limits the ability to distinguish arteritic from non-arteritic optic neuropathy based on clinical criteria alone. The absence of laboratory and physiologic measures also restricts detailed characterization of diabetes severity, lipid control, renal function, or blood pressure beyond coded diagnoses and medication proxies. Diagnostic miscoding is possible for NAION, vasculitic conditions, and several exclusion diagnoses, necessitating the use of validated claims-based algorithms and multiple sensitivity definitions. Ophthalmic imaging results and clinical examination findings are not available, which may lead to outcome misclassification or incomplete ascertainment of subtle optic nerve pathology.

Data source provenance/curation: The Medicare data used for this study are obtained under a Data Use Agreement through the University of North Carolina, representing a 20% random national sample of FFS beneficiaries aged ≥65 years with Parts A/B/D enrollment. Once beneficiaries enter the sample, all subsequent claims remain included. Data are curated and maintained by the UNC Research Computing and Epidemiology cores, processed according to CMS standards, and updated annually. Claims include service dates, ICD-9/10 diagnosis codes, ICD-9/10-PCS and CPT/HCPCS procedure codes, NDC-identified prescription dispensing, care settings,

and provider specialty codes. The dataset is de-identified and will be exempted from UNC Institutional Review Board review, with the study expected to qualify as non-human subject research.

Data element	Data
Data Sources:	Medicare Fee-for-Service (FFS) 20% random national sample (Parts A, B, and D)
Study Period:	January 1, 2007 – December 31, 2019 (latest available data cut)
Eligible Cohort Entry Period:	January 1, 2008 – December 31, 2018 (allows 12-month baseline lookback)
Data version (or date of last update):	CMS annual FFS claims files, updated through the most recent release available to UNC at analysis time
Data sampling/extraction criteria:	20% random sample of Medicare beneficiaries aged ≥65 years with concurrent Part A, Part B, and Part D enrollment for ≥1 month; once sampled, all subsequent claims retained
Type(s) of data:	Inpatient, outpatient, carrier/physician claims (ICD-9/10, CPT/HCPCS, revenue center codes), Part D prescription drug event (PDE) files (NDC), beneficiary demographics and Master Beneficiary Summary File
Data linkage	Internal linkage across CMS FFS files using unique beneficiary identifiers; no external linkages performed
Conversion to CDM:	N/A
Software for data management:	SAS

7.7 Data management

All data management will be within the secure UNC Research Computing environment using SAS (v9.4 or later). Medicare Parts A, B, and D claims files will be imported, merged, and formatted using standardized UNC Medicare data processing templates. Data cleaning steps will include verification of enrollment continuity, validation of dates and coding formats, removal of duplicate claims, and harmonization of ICD-9-CM to ICD-10-CM transitions where required. Cohort construction will follow a prespecified, reproducible programming workflow, using modular SAS macros for defining exposures,

outcomes, covariates, washout periods, and follow-up time. Intermediate datasets and logs will be version-controlled, with complete audit trails documenting any updates. Analytic files will be derived only after all inclusion/exclusion criteria, exposure assignments, and variable definitions have been fully validated.

7.8 Quality control

Quality control procedures will be applied at each step of the data pipeline and analysis. Coding algorithms for exposures, outcomes, and covariates will undergo structured internal review for clinical and analytic plausibility. Cohort counts, inclusion and exclusion flows, and key descriptive statistics will be examined for internal consistency and face validity, with discrepancies investigated as needed. Propensity score models will undergo diagnostics for covariate balance, weight distribution, and overlap. Outlier or implausible values (e.g., negative lengths of stay, non-monotonic dates) will be flagged and addressed using prespecified rules. Analytic code and output tables will be reviewed internally prior to finalization of results. All programs will be archived to ensure reproducibility.

7.9 Study size and feasibility

To be decided.

8 Limitation of the methods

To be decided.

9 Protection of human subjects

This study will use de-identified Medicare administrative claims data accessed under a CMS Data Use Agreement. No direct patient contact or identifiable personal information will be involved. The study is expected to be determined “not human subjects research” by the University of North Carolina Institutional Review Board. All data will remain on the secure UNC Research Computing infrastructure, with strictly controlled access, encryption, and auditing. Results will be reported in aggregate to ensure that no individual beneficiary can be identified**.**

10 Reporting of adverse events

Not applicable

11 References

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