Similar Risk of Kidney Failure among Patients with Blinding Diseases Who Receive Ranibizumab, Aflibercept, and Bevacizumab

An Observational Health Data Sciences and Informatics Network Study

Cindy X. Cai, MD, MS,[1] Akihiko Nishimura, PhD,[2] Mary G. Bowring, MPH,[3] Erik Westlund, PhD,[2]
Diep Tran, MSc,[1] Jia H. Ng, MD, MSCE,[4] Paul Nagy, PhD,[5] Michael Cook, BS,[6] Jody-Ann McLeggon, MPH,[7]
Scott L. DuVall, PhD,[8,9] Michael E. Matheny, MD, MPH,[10,11] Asieh Golozar, PhD,[12,13]
Anna Ostropolets, MD, PhD,[12] Evan Minty, MD, MSc,[14] Priya Desai, MS,[15] Fan Bu, PhD,[16] Brian Toy, MD,[17]
Michelle Hribar, PhD,[18,19] Thomas Falconer, MS,[7] Linying Zhang, PhD,[7] Laurence Lawrence-Archer, MSc,[12,13]
Michael V. Boland, MD, PhD,[20] Kerry Goetz, MS,[18] Nathan Hall, MS,[21] Azza Shoaibi, PhD,[21] Jenna Reps, PhD,[21]
Anthony G. Sena, BA,[21,22] Clair Blacketer, MPH,[21] Joel Swerdel, PhD, MPH,[21] Kenar D. Jhaveri, MD,[23]
Edward Lee, BS,[17] Zachary Gilbert, BS,[17] Scott L. Zeger, PhD,[2] Deidra C. Crews, MD, ScM,[24]
Marc A. Suchard, MD, PhD,[8,16] George Hripcsak, MD, MS,[7] Patrick B. Ryan, PhD[21]

Purpose: To characterize the incidence of kidney failure associated with intravitreal anti-VEGF exposure; and compare the risk of kidney failure in patients treated with ranibizumab, aflibercept, or bevacizumab.

Design: Retrospective cohort study across 12 databases in the Observational Health Data Sciences and Informatics (OHDSI) network.

Subjects: Subjects aged ≥ 18 years with ≥ 3 monthly intravitreal anti-VEGF medications for a blinding disease (diabetic retinopathy, diabetic macular edema, exudative age-related macular degeneration, or retinal vein occlusion).

Methods: The standardized incidence proportions and rates of kidney failure while on treatment with anti-VEGF were calculated. For each comparison (e.g., aflibercept versus ranibizumab), patients from each group were matched 1:1 using propensity scores. Cox proportional hazards models were used to estimate the risk of kidney failure while on treatment. A random effects meta-analysis was performed to combine each database's hazard ratio (HR) estimate into a single network-wide estimate.

Main Outcome Measures: Incidence of kidney failure while on anti-VEGF treatment, and time from cohort entry to kidney failure.

Results: Of the 6.1 million patients with blinding diseases, 37 189 who received ranibizumab, 39 447 aflibercept, and 163 611 bevacizumab were included; the total treatment exposure time was 161 724 person-years. The average standardized incidence proportion of kidney failure was 678 per 100 000 persons (range, 0−2389), and incidence rate 742 per 100 000 person-years (range, 0−2661). The meta-analysis HR of kidney failure comparing aflibercept with ranibizumab was 1.01 (95% confidence interval [CI], 0.70−1.47; $P = 0.45$), ranibizumab with bevacizumab 0.95 (95% CI, 0.68−1.32; $P = 0.62$), and aflibercept with bevacizumab 0.95 (95% CI, 0.65−1.39; $P = 0.60$).

Conclusions: There was no substantially different relative risk of kidney failure between those who received ranibizumab, bevacizumab, or aflibercept. Practicing ophthalmologists and nephrologists should be aware of the risk of kidney failure among patients receiving intravitreal anti-VEGF medications and that there is little empirical evidence to preferentially choose among the specific intravitreal anti-VEGF agents.

Financial Disclosures: Proprietary or commercial disclosure may be found in the Footnotes and Disclosures at the end of this article. *Ophthalmology Retina 2024;8:733-743 © 2024 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Supplemental material available at www.ophthalmologyretina.org.

Intravitreal anti-VEGF medications have revolutionized the treatment of blinding diseases.[1,2] However, anti-VEGF agents are known to have adverse kidney effects. Systemic administration of anti-VEGF leads to well-documented proteinuria and acute kidney injury, which are major risk factors for kidney failure.[3-8] Intravitreal administration of anti-VEGF uses 1/150 to 1/400 the medication dose of systemic administration.[9] Despite the lower dose, systemic absorption that differs by medication has been demonstrated after intravitreal administration.[10,11] Comparative studies show that ranibizumab has the shortest systemic half-life of elimination and leads to the least elevation of serum drug levels and suppression of systemic VEGF, as compared with aflibercept and bevacizumab.[10,11]

There is conflicting evidence as to whether intravitreal administration of anti-VEGF medications, similar to systemic administration, are also toxic to the kidneys. Kidney biopsies of patients who have received intravitreal anti-VEGF have demonstrated thrombotic microangiopathy, a pathognomonic finding of systemic VEGF blockade, and associated collapsing focal segmental glomerulosclerosis.[12] Multiple studies have shown worsening hypertension, proteinuria, and kidney disease after intravitreal anti-VEGF.[12,13] However, other retrospective studies and systematic reviews have not shown declines in kidney function or increased risk of kidney disease after intravitreal anti-VEGF medication exposure (*Invest Ophthalmol Vis Sci.* 63:1332-F0166, 2022).[14-17] The concern for kidney toxicity from intravitreal anti-VEGF has led some groups to advocate for the use of ranibizumab, over aflibercept and bevacizumab, in those who are at risk of or have kidney disease.[3,18]

There are only a handful of studies directly comparing the kidney effects of ranibizumab with aflibercept and bevacizumab. The prospective Diabetic Retinopathy Clinical Research (DRCR) Network Protocol T clinical trial identified 26 renal events in the ranibizumab group, 26 in the aflibercept group, and 16 in the bevacizumab group among a total of 218, 224, and 218 patients, respectively, treated for diabetic macular edema; the differences were not statistically significant.[19] The preplanned post hoc analysis from the same study did not identify differences in changes in blood pressure or urine albumin-creatinine ratio in patients treated with any of the 3 anti-VEGF drugs.[20] However, patients enrolled in clinical trials are often younger, with well-controlled diabetes, and may not be generalizable to patients treated with intravitreal anti-VEGF in routine clinical practice. Large-scale studies using routine clinical data comparing the kidney effects of anti-VEGF medications are rare. One study using the United States (US) Food and Drug Administration's Adverse Event Reporting System found no differences in kidney events between drugs but was unable to account for baseline demographic and medical characteristics because of the constraints of the database.[9]

There are major limitations in the adverse kidney effects examined in the existing studies comparing intravitreal anti-VEGF medications. Because of the relatively small sample sizes of the populations studied, many studies examined kidney effects as a group and did not distinguish between severity of kidney events. Specifically, studies have grouped severe conditions such as kidney failure, a leading cause of morbidity and mortality, with transient issues such as acute kidney injury.[9,13,19] There is a need to understand whether there are differences in the severe phenotype of kidney failure between the 3 commonly used intravitreal anti-VEGF medications.

The Observational Health Data Sciences and Informatics (OHDSI, pronounced "Odyssey") network is well poised to address this gap in knowledge. The OHDSI network is an international open-science collaborative centered around the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM).[21] By leveraging the vast data network and standardized analytic pipeline of the OHDSI community, we can assess the risk of kidney failure with intravitreal anti-VEGF exposure across an international population. The purposes of this study were to characterize the incidence of kidney failure associated with intravitreal anti-VEGF exposure and compare the risk of kidney failure in patients treated with ranibizumab, aflibercept, and bevacizumab in the OHDSI network.

Methods

Study Design

This was a retrospective cohort study across 12 databases (6 administrative claims and 6 electronic health records) standardized to OHDSI's OMOP CDM.[22] In this CDM, local clinical concepts (e.g., International Classification of Diseases diagnosis codes or Current Procedural Terminology codes) are mapped to OMOP concepts through an extract-transform-load process. The OMOP CDM normalizes the structure and content of source data, which allows disparate health care databases to be queried in a standardized manner. Database details are included in the appendix (Table S1, available at www.ophthalmologyretina.org). All data partners had local institutional review board approval or exemption for their participation. The study adhered to the tenets of the Declaration of Helsinki and complied with Health Insurance Portability and Accountability Act.

Subjects/Exposure

Adult patients aged $\geq$ 18 years who were newly treated with monthly intravitreal anti-VEGF medications (ranibizumab, aflibercept, or bevacizumab) for $\geq$ 3 months for a blinding disease with $\geq$ 365 days of prior observation were included in the study. Blinding diseases included diagnoses for diabetic retinopathy, diabetic macular edema, exudative age-related macular degeneration, and retinal vein occlusion. The minimum number of anti-VEGF exposures was chosen based on prior studies demonstrating suppression of systemic plasma VEGF levels after 3 monthly intravitreal injections.[10,11] Patients with cancer diagnoses (e.g., metastatic colorectal cancer) that could warrant systemic anti-VEGF were excluded. Patients with preexisting kidney failure (defined further below) were also excluded. If patients switched anti-VEGF medications, only the first exposure was included in the analysis, after which the patients were right-censored from the cohort. Cohorts were created using ATLAS, a publicly available web-based software application developed by the OHDSI community.[23] Details of the cohorts and the codes used to define each phenotype can be found in Tables S2 and S3 (available at www.ophthalmologyretina.org).[24,25]

Time at Risk

Patients were assumed at-risk of kidney failure after the third anti-VEGF exposure until the end of continuous drug exposure or the end of the study period. The end of continuous exposure was defined as a gap of > 180 days between injections. The cutoff of 180 days was chosen because the need for anti-VEGF typically decreases over time. In the DRCR Retina Network's clinical trials for treatment of diabetic macular edema, a median of 8 to 9 ranibizumab injections are given in the first year and that decreases to 2 to 3 in the second year across most studies.[26] The cutoff of 180 days would categorize most patients with diabetic macular edema being treated per the DRCR protocol as having a "continuous" drug exposure in the first 2 years of treatment.

Outcome

The outcome of interest was kidney failure, or end-stage kidney disease in which the operational definitions were based on Kidney Disease Improving Global Outcomes stage 5 chronic kidney disease (CKD) treated with dialysis or kidney transplantation.[27,28] Based on our previous research, we implemented and tested 2 versions of the kidney failure phenotype.[29] The first kidney failure phenotype definition was aligned with Kidney Disease Improving Global Outcomes stage 5 CKD and was defined as having either a condition, observation, or procedure code related to end-stage kidney disease or kidney transplantation, 2 measurements of estimated glomerular filtration rate of < 15 ml/min/1.73m^2 at least 90 days apart, or 2 observation or procedure codes of kidney dialysis spaced at least 90 days apart. Table S2 and S4 (available at www.ophthalmologyretina.org) contain the logic and full list of codes used to represent the definition. The second kidney failure phenotype definition used an administrative code-only limited definition that included the presence of a condition, observation, or procedure related to end-stage kidney disease. (Tables S2 and S4) The sensitivity, specificity, positive predictive value, and negative predictive value of the performance of each kidney failure definition was evaluated on a subset of databases using PheValuator, an R package for evaluating phenotype algorithms.[29,30] In brief, PheValuator uses machine learning to develop predictive models that serve as a probabilistic reference standard, computes the probability of having a disease of interest for each subject in the cohort, and uses that result to determine the rule-based phenotype performance metrics including sensitivity, specificity, positive predictive value, and negative predictive value. Based on the output from PheValuator, it was determined that the second kidney failure phenotype had better positive predictive value with similar sensitivity to the "complex" definition; thus, the simpler kidney failure phenotype was used in this study (Table S5, available at www.ophthalmologyretina.org).

Statistical Analysis

All analyses were performed in R using the Strategus execution pipeline.[31] Strategus is a standardized method to call Health Analytics Data-to-Evidence Suite open-source R packages developed by the OHDSI community for large-scale analytics.[32,33] The prespecified study protocol and end-to-end open executable source code are available on GitHub.[24] We developed an interactive website to promote transparency and allow for sharing and exploration of the results.[34]

(A) Incidence of Kidney Failure

Summary statistics were calculated to describe the baseline characteristics of patients in each anti-VEGF exposure cohort by database. These characteristics included demographic information (age, sex, race, and ethnicity), blinding diseases (retinopathy due to diabetes mellitus, retinal vascular occlusion, age-related macular degeneration, and macular retinal edema), kidney diseases (renal impairment, CKD, chronic disease of genitourinary system, and kidney disease), Diabetes Comorbidity Severity Index score, and Charlson Comorbidity Index-Romano adaptation.[35,36] The baseline characteristics of patients were also stratified by the outcome of kidney failure. Differences between the groups were represented by the standardized mean difference and significant differences reported using a *t* test.[37]

The incidence proportion (number of outcomes divided by the total number of people at risk) and incidence rate (number of outcomes during the time-at-risk divided by the number of total person days) of kidney failure were calculated for each exposure cohort. Only kidney failure events while on treatment contributed to this analysis. Crude incidence proportions for each year were standardized to the 2015 US population by age and sex using direct standardization and then averaged.[38,39]

(B) Comparative Risk of Kidney Failure

A series of study diagnostics were performed and the meta-analysis of comparative risks only included the results from databases that passed all evaluations. The study diagnostics are described in detail elsewhere and the thresholds used in this study are located in the study GitHub.[22,40] We used the large-scale propensity score method to match patients in each target and comparator exposure cohort comparison (aflibercept vs. ranibizumab, bevacizumab vs. ranibizumab, and bevacizumab vs. aflibercept) using 1:1 propensity score matching. The propensity score model included a large number of baseline covariates (e.g., demographic characteristics, preexisting conditions, measurements, and procedures) as potential confounders and used the L_1-regularization technique to avoid model overfitting.[41,42] The outcome was time from cohort entry to kidney failure while on treatment. Cox proportional hazards models were used to estimate the risk of kidney failure while on treatment. A random effects meta-analysis was performed to combine per site hazard ratio (HR) estimates into a single network-wide estimate.[43]

Sensitivity Analysis to Methodological Choices

Analyses were done to test the sensitivity of our design to methodological choices. In the main analysis, only kidney failure events that occurred while the patient was on treatment with intravitreal anti-VEGF contributed to the calculations. As a sensitivity analysis, all calculations were repeated under an intent-to-treat design, in which all kidney failure events after cohort entry contributed to the calculations even if they occurred while the patient was not receiving intravitreal anti-VEGF. There was also no right-censoring; patients who switched anti-VEGF medications were analyzed according to the first anti-VEGF they received. The intent-to-treat sensitivity analysis was chosen for several reasons. Because kidney failure is a long-term outcome, potential adverse kidney impacts of the intravitreal anti-VEGF could be cumulative and manifest years after medication exposure. Furthermore, it is possible that patients who experienced an adverse kidney failure, for example proteinuria, were preferentially switched to another anti-VEGF medication or stopped therapy altogether, thus biasing the main on-treatment study design. Because there was no right-censoring in the sensitivity analysis, patients who switched or stopped anti-VEGF were still included in the intent-to-treat analysis. The sensitivity analysis was performed on a subset of databases (Table S1).

Results

In total, 12 unique databases within the OHDSI network were evaluated for inclusion in this study; data from 11 databases were included in the analysis of the incidence of kidney failure, and data from 6 databases were included in the analysis of the comparative risk of kidney failure (Table S1).

(A) Incidence of Kidney Failure

Across all databases, there were 6 102 794 patients with blinding diseases, among whom 37 189 received ranibizumab, 39 447 received aflibercept, and 163 611 received bevacizumab. These patients contributed a total of 161 724 person-years of treatment exposure time. Baseline characteristics of patients included in each exposure cohort in the Optum's deidentified Clinformatics Data Mart Database: Socioeconomic Status are presented in Table 6 and for all other databases in Table S7 (available at www.ophthalmologyretina.org). Across databases, 3% to 22% of participants in all exposure groups were aged 70 to 74 years, 26% to 97% were men, 45% to 89% were White, 3% to 27% were Black, 1% to 20% were Asian, and 2% to 37% were Hispanic. The average Diabetes Comorbidity Severity Index score ranged from 1.70 to 5.59, and the average Charlson Comorbidity Index-Romano adaptation ranged from 1.37 to 4.98.

The baseline characteristics of patients in the Optum's deidentified Clinformatics Data Mart Database, stratified by whether or not they developed the outcome during the time-at-risk, are shown in Table S8 (available at www.ophthalmologyretina.org). A higher proportion of patients who developed kidney failure across all databases and exposure groups had baseline conditions including CKD, kidney disease, renal impairment, and chronic disease of the genitourinary system. (Fig 1)

The number of kidney failure outcomes range from 0 to 317 in each exposure group across all databases (Table 9). The crude incidence proportion of kidney failure per 100 000 persons ranged from 0 to 1864 across the databases, with an average of 699. The age-sex standardized incidence proportion per 100 000 persons ranged from 0 to 2389 across the databases, with an average of 678. Incorporating person-time, the incidence rate of kidney failure ranged from 0 to 2661 per 100 000 person-years, with an average of 742. Among patients with a blinding disease, whether or not they were exposed to anti-VEGF, the average incidence proportion of kidney failure per 100 000 persons across all databases was 2921, the average standardized incidence proportion per 100 000 persons was 4822, and the average incidence rate was 782 per 100 000 person-years (Table S10, available at www.ophthalmologyretina.org).

In the sensitivity analysis using the intent-to-treat study design, the incidence proportions and rates of kidney failure were higher than the main on-treatment analysis. The average crude incidence proportion of kidney failure among the anti-VEGF exposure groups was 3445 per 100 000 persons, the standardized incidence proportion was 3821 per 100 000 persons, and the incidence rate was 1192 per 100 000 person-years (Table S11, available at www.ophthalmologyretina.org).

(B) Comparative Risk of Kidney Failure

Half of the databases (n = 6) passed study diagnostics for this part of the analysis (Table S1). Results from the study diagnostics are shown in Table S12 (available at www.ophthalmologyretina.org).

The HR estimates for risk of kidney failure across databases are shown in Figure 2. Comparing aflibercept with ranibizumab, the meta-analysis HR combining the estimates across all databases

Table 6. Baseline Characteristics of Patients in Each Exposure Cohort (Ranibizumab, Aflibercept, and Bevacizumab) in the Optum's deidentified Clinformatics Data Mart Database: Socioeconomic Status (Clinformatics)*

	Ranibizumab Number (%)	Aflibercept Number (%)	Bevacizumab Number (%)
Age group (yrs)			
≤ 29	14 (0)	19 (0)	102 (0)
30−49	307 (3)	324 (3)	1919 (3)
50−69	2466 (25)	2534 (26)	16433 (23)
70−89	7205 (72)	6887 (70)	53036 (74)
≥ 90	59 (1)	53 (1)	426 (1)
Sex			
Male	3878 (39)	4012 (41)	28282 (39)
Female	6173 (61)	5805 (59)	43634 (61)
Race			
White	7607 (76)	7109 (72)	52109 (72)
Black	1025 (10)	991 (10)	5956 (8)
Asian	254 (3)	308 (3)	1990 (3)
Ethnicity			
Hispanic	750 (7)	923 (9)	8326 (12)
Non-Hispanic	8886 (88)	8408 (86)	60055 (84)
Diabetes Comorbidity Severity Index score, mean (n)	3.8 (8504)	3.85 (8259)	3.99 (61 182)
Charlson Comorbidity Index, mean (n)	3.29 (8319)	3.69 (8353)	3.65 (60 952)
Retinopathy due to diabetes mellitus	2537 (25)	3202 (33)	20236 (28)
Retinal vascular occlusion	1998 (20)	2056 (21)	14517 (20)
Age-related macular degeneration	6752 (64)	5878 (57)	46496 (61)
Macular retinal edema	2047 (20)	2888 (29)	16488 (23)

*Before propensity score matching. Includes patients who had preexisting kidney failure who were excluded in subsequent analyses.
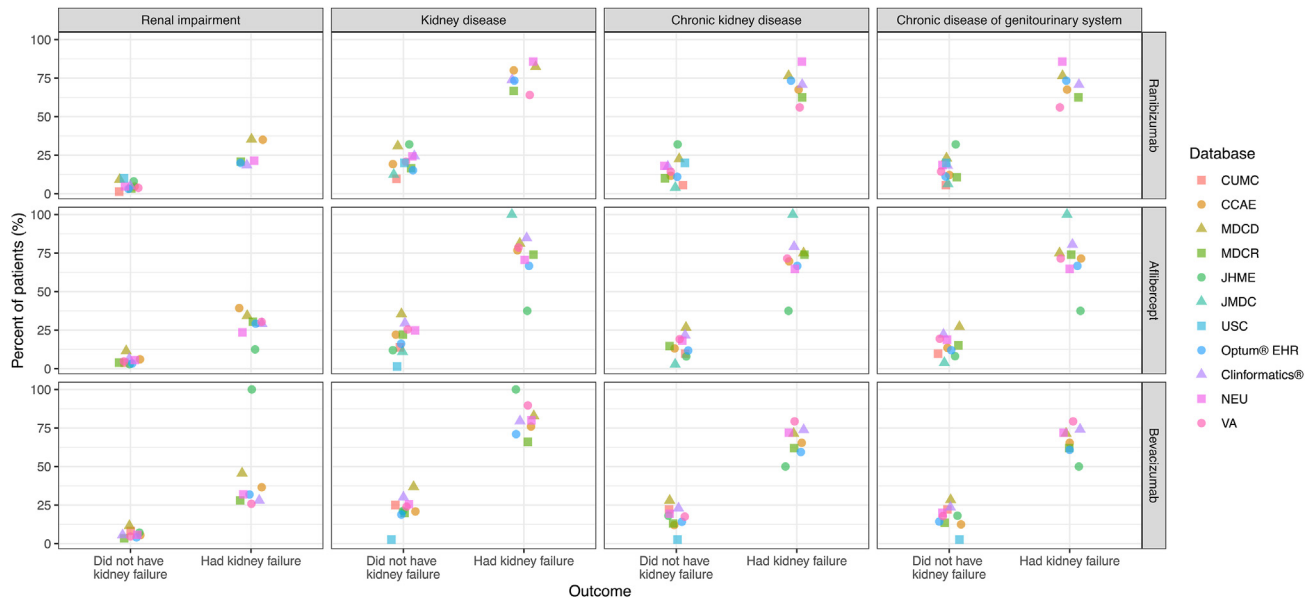
Figure 1. Proportion of patients with baseline kidney diseases comparing those who did and did not develop kidney failure in each exposure group (ranibizumab, aflibercept, and bevacizumab) within each database. CCAE = IBM Health MarketScan Commercial Claims and Encounters Database; Clinformatics = Optum's deidentified Clinformatics Data Mart Database: Socio-economic Status; CUMC = Columbia University Medical Center; JHME = Johns Hopkins Medical Enterprise; JMDC = Japan Medical Data Center; MDCD = IBM Health MarketScan Multi-State Medicaid Database; MDCR = IBM Health MarketScan Medicare Supplemental and Coordination of Benefits Database; NEU = IQVIA PharMetrics Plus for Academics Database; Optum EHR = Optum deidentified Electronic Health Record data set; USC = University of Southern California; VA = Department of Veterans Affairs.

was 1.01 (95% confidence interval [CI], 0.70–1.47; *P* = 0.45). Comparing ranibizumab with bevacizumab, the meta-analysis HR was 0.95 (95% CI, 0.68–1.32; *P* = 0.62), and, comparing aflibercept with bevacizumab, the HR was 0.95 (95% CI, 0.65–1.39; *P* = 0.60).

Results were similar on sensitivity analysis using the intent-to-treat study design. The meta-analysis HR comparing aflibercept with ranibizumab was 1.02 (95% CI, 0.78–1.34; *P* = 0.43), ranibizumab with bevacizumab was 0.90 (95% CI, 0.76–1.07; *P* = 0.89), and aflibercept with bevacizumab was 0.99 (95% CI, 0.80–1.22; *P* = 0.56; Table S13, available at www.ophthalmologyretina.org).

Discussion

In this retrospective cohort study across 12 databases in the OHDSI network evaluating 6.1 million patients with blinding diseases, the overall incidence rate of kidney failure while on treatment among patients who received ≥ 3 monthly intravitreal anti-VEGF was 743 per 100 000 person-years, with a standardized incidence proportion of 678 per 100 000 persons. A greater proportion of patients who developed kidney failure, compared with those who did not, had preexisting kidney disease and impairment. We did not find differences in the risk of developing kidney failure when comparing those who were exposed to intravitreal ranibizumab, aflibercept, and bevacizumab.

The incidence of kidney failure characterized in this study is higher than the overall population. The United States Renal Data System reports a standardized incidence proportion of 36.3 per 100 000 persons in 2020, that peaked

at 43.1 per 100 000 persons in 2006.[44] Among the US databases, we find an incidence of kidney failure of 678 per 100 000 persons in the intravitreal anti-VEGF exposure cohorts, and 4821 per 100 000 persons among patients with blinding diseases. Similar trends were seen in international databases. In Japan, the standardized incidence proportion of kidney failure was estimated at 29.6 per 100 000 persons in 2016, which is again lower than the rates identified in this study using the Japan Medical Data Center.[45] The higher incidence of kidney failure identified in this study is likely due to differences in the underlying study population when compared with the overall population. Patients treated with anti-VEGF are older and often have cardiometabolic risk factors, such as diabetes that put them at higher risk of kidney disease. Although the standardized incidence proportion that we calculate controls for the age and sex of the underlying population, it does not take into account medical risk factors.

Although there is strong evidence for differing suppression of systemic plasma VEGF by the 3 commonly used intravitreal anti-VEGF medications, the estimated risks of kidney failure were not different among the 3 treatment groups. Differences in risk of kidney failure between intravitreal anti-VEGF, if present, are likely to be small. There could be several explanations for not finding a statistically significant difference in the risk of kidney failure between the 3 anti-VEGF medications. In the course of kidney disease progression from kidney damage to kidney failure, death is a major competing risk whereby patients with CKD are more likely to die than to develop kidney failure.[46] Censoring bias from the competing risk of

Table 9. The Crude Incidence Proportion per 100 000 Persons, Age-Sex Standardized Incidence Proportion per 100 000 Persons, and Incidence Rate per 100 000 Person-Years in Each Exposure Cohort across all Databases

	Patients at Risk	On-Treatment Time (Person-Years)	Number of Outcomes	Incidence Proportion per 100 000 Persons	Age-Sex Standardized Incidence Proportion per 100 000 Persons§	Incidence Rate per 100 000 Person-Years
Ranibizumab*						
Total	29 609	29 929.8	224			
CCAE	3799	3081.6	40	1053	682	1298
MDCR	7604	8406.9	48	631	821	571
MDCD	1265	1121.5	17	1344	2389	1516
Optum EHR	2520	2489.3	15	595	611	603
Clinformatics	8048	9841.5	65	808	838	660
JMDC	203	133.5	0	0	0	0
JHME	19	12.9	0	0	0	0
NEU	2084	2179.8	14	672	399	642
CUMC	117	114.3	0	0	0	0
VA	3943	2538.6	25	630	250	980
USC	<10	9.9	0	0	0	0
Aflibercept						
Total	32 153	37 633.3	290			
CCAE	3319	3249.4	56	1687	1659	1723
MDCR	4644	5532.9	23	495	162	416
MDCD	1717	1794.8	32	1864	1447	1783
Optum EHR	3282	4695.3	24	731	394	511
Clinformatics	8056	11 004.0	72	894	1409	654
JMDC	205	190.6	<10	488	335	525
JHME	574	655.6	8	1394	1830	1220
NEU	3696	3710.5	17	460	414	458
CUMC	335	466.0	0	0	0	0
VA	6266	6245.2	56	890	790	900
USC	59	89.0	<10	1695	320	1123
Bevacizumab						
Total	108 308	94 160.8	695			
CCAE	10 508	6772.5	104	990	679	1536
MDCR	10 625	9043.8	50	471	106	553
MDCD	3845	2630.9	70	1821	2203	2661
Optum EHR	11 933	12 639.4	69	578	1341	546
Clinformatics	52 642	50 581.2	317	602	1072	627
JMDC	0	0.0	0	NA	NA	NA
JHME	286	226.0	<5	699	926	885
NEU	8331	6275.6	25	300	328	398
CUMC	74	41.1	0	0	0	0
VA	10 037	5930.2	58	580	300	980
USC	27	20.1	0	0	0	0

CCAE = IBM Health MarketScan Commercial Claims and Encounters Database; Clinformatics = Optum's deidentified Clinformatics Data Mart Database: Socio-economic Status; CUMC = Columbia University Medical Center; JMDC = Japan Medical Data Center; JHME = Johns Hopkins Medical Enterprise; MDCD = IBM Health MarketScan Multi-State Medicaid Database; MDCR = IBM Health MarketScan Medicare Supplemental and Coordination of Benefits Database; NEU = IQVIA PharMetrics® Plus for Academics Database; Optum EHR = Optum deidentified Electronic Health Record data set; USC = University of Southern California; VA = Department of Veterans Affairs.
Only patients who contribute ≥ 1 day to time-at-risk are included in this analysis.
*Standardized to the 2015 United States population by age and sex.

death could be masking differences between intravitreal anti-VEGF medications. Future studies could specifically focus on the outcome of death when comparing intravitreal anti-VEGF medications. Our study design may have impacted our results. For our main analysis, we chose an on-treatment study design where we captured cases of kidney failure while patients were actively receiving intravitreal anti-VEGF. This study design was chosen to best isolate the effects of intravitreal anti-VEGF on the outcome of kidney failure. It is harder to causally link kidney failure events that occur years after exposure to

intravitreal anti-VEGF. However, as a result of the on-treatment study design, patients who switched therapies (e.g., from bevacizumab to ranibizumab) were right-censored and not included in the analysis. It is possible that patients who had experienced an adverse kidney event (e.g., acute kidney injury or proteinuria) were preferentially switched to another intravitreal anti-VEGF or stopped therapy altogether. This would imply that patients who were at higher risk of kidney failure were preferentially excluded from the analysis. We examined this potential source of bias by performing a sensitivity analysis
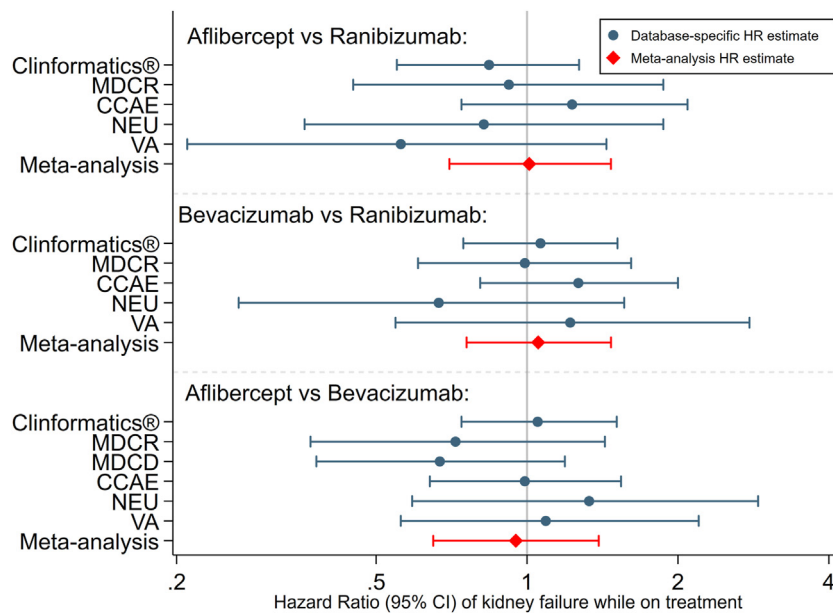
Figure 2. Hazard ratio (HR) estimates for the risk of kidney failure among new users of monthly anti-VEGF medications while on treatment comparing ranibizumab, aflibercept, and bevacizumab. Results from each database are provided as well as the meta-analytic estimates. CCAE = IBM Health MarketScan Commercial Claims and Encounters Database; CI = confidence interval; Clinformatics = Optum's deidentified Clinformatics Data Mart Database - Socio-economic Status; MDCD = IBM Health MarketScan Multi-State Medicaid Database; MDCR = IBM Health MarketScan Medicare Supplemental and Coordination of Benefits Database; NEU = IQVIA PharMetrics Plus for Academics Database; VA = Department of Veterans Affairs.

using an intent-to-treat analysis study design. The intent-to-treat study design captured all cases of kidney failure, whether or not they occurred while on intravitreal anti-VEGF, and did not include any right-censoring. We found similar findings with the intent-to-treat analysis as the on-treatment study design, suggesting that selection bias was not a major driver of our results.

The lack of difference in risk of kidney failure by intravitreal anti-VEGF medication obviates the need to preferentially choose ranibizumab over aflibercept and bevacizumab, as was recommended by prior groups.[3,18] There are several implications for these findings. Because ranibizumab costs nearly 20 times more than bevacizumab, this could represent potential cost savings for the health care system.[47] There are racial and ethnic disparities in intravitreal anti-VEGF medication use. For example, studies have shown that Hispanic patients are less likely to receive ranibizumab and more likely to receive bevacizumab compared with otherwise similar non-Hispanic White patients.[48,49] There are also racial and ethnic disparities in the risk of kidney disease. Minoritized populations, including non-Hispanic Black and Hispanic patients, have nearly fourfold and twofold, respectively, higher prevalences of kidney failure compared with non-Hispanic White populations.[44] By demonstrating that ranibizumab does not lower the risk of kidney failure, this frees the treating physician to choose from any of the anti-VEGF medications and not exacerbate existing health disparities.

There are still many lingering questions, specifically whether the receipt of intravitreal anti-VEGF increases the risk of kidney failure compared with not receiving anti-VEGF. There is both evidence for and against the

increased risk of kidney failure and kidney disease associated with intravitreal anti-VEGF use (*Invest Ophthalmol Vis Sci.* 63:1332-F0166, 2022).[13,50,51] A major challenge in many of these studies is the issue of indication bias; by comparing patients who receive anti-VEGF with patients who do not, it is hard to isolate the effects of the medication compared with the disease itself.[52] By choosing an active comparator design and comparing ranibizumab, aflibercept, and bevacizumab to one another, we mitigated the effects of indication bias. However, we lose the opportunity to specifically address the question of whether receipt of intravitreal anti-VEGF itself increases the risk of kidney failure. The finding that the baseline incidence of kidney failure among patients with blinding disease is similar or even higher to those who receive anti-VEGF suggests there might not be an increased risk. However, more work should be done to definitively address whether intravitreal anti-VEGF increases the risk of kidney failure.

Conducting this study in the OHDSI network allowed us to confidently estimate the comparative risk of kidney failure between intravitreal anti-VEGF medications. The large federated data network of the OHDSI community enabled us to identify 240 247 new users of monthly anti-VEGF, a sample size that would not be feasible in clinical trials or single center retrospective studies. Further, applying the same analytic procedure across different databases allowed us to directly compare results from different centers. Each database reported a different incidence of kidney failure, reflecting the diversity in underlying patient populations. We also found different practice patterns in use of anti-VEGF across our global data partners. For example, there were no instances of intravitreal bevacizumab use for

blinding diseases in the Japan Medical Data Center because that medication has not been approved by Japan's regulatory authority for drugs, Pharmaceuticals and Medical Devices Agency, for intraocular use. The variability of findings across the databases, even when studying the same question, highlights the importance of applying a standard protocol across multiple data sources.[21]

We employed best practices and standardized analytics developed by the OHDSI community. The OHDSI network uses large-scale propensity score estimation,[41,42] adjusting for thousands of variables (after excluding instruments, colliders, and mediators). This has been shown to be superior to manual variable selection,[42,53,54] and superior to attempts to empirically select confounders.[41] We also employed a robust set of study diagnostics to each available database to ensure that valid conclusions were drawn from the comparative effect estimation analysis. Study diagnostics were evaluated with the results masked and only databases that passed diagnostics had the results unblinded. For example, we used a set of negative controls (e.g., epidermoid cyst and impacted cerumen) where no causal effect is believed to exist with intravitreal anti-VEGF to assess potential systematic error.[24,34,55,56] Databases that exhibited potential systematic error were excluded from the population-level effect estimation analysis. Another study diagnostic evaluated baseline covariate balance after propensity score adjustment between the 2 comparative anti-VEGF medication groups. Again, databases that did not have sufficient covariate balance between comparison groups were excluded from the estimation of comparative risk of kidney failure because they are unlikely to produce a scientifically sound result.

There are several limitations to this work. Using data from the Electronic Health Record or administrative claims to define phenotypes is a well-established methodology and we used OHDSI best practices to carefully design and validate these phenotypes. However, the degree to which these phenotypes represent the clinical state of patients is unknown. Although there were many advantages to using best practice analytics developed by the OHDSI community, there are limitations in their application to ophthalmic research. We were unable to consider the dose of medication that any individual received due to limitations in the current standardized analytics pipeline. For example, in our analysis, patients who receive bilateral intravitreal anti-VEGF medications monthly for a year were analyzed in the same way as someone who received unilateral intravitreal anti-VEGF medications despite being exposed to 2 times the amount of medication. We do not believe that this played an important role in the main results because the issue of dosage would be expected to occur in all anti-VEGF comparison groups. Despite these limitations, to our knowledge, this is the largest study examining the association between intravitreal anti-VEGF and kidney failure and the largest application of the OHDSI network to an ophthalmic question to date.

In conclusion, we find an incidence rate of 743 per 100 000 person-years with a standardized incidence proportion of 678 per 100 000 persons of kidney failure, which is higher than the overall population, among patients who are on treatment with intravitreal anti-VEGF medications. The risk of progression to kidney failure is not different when comparing those who received ranibizumab, bevacizumab, or aflibercept. Practicing ophthalmologists should be aware that patients needing intravitreal anti-VEGF medications are at high risk of kidney failure, particularly those with pre-existing kidney disease and impairment, and might benefit from ongoing kidney health monitoring. There is no evidence in this study to support the practice of preferentially selecting ranibizumab over aflibercept and bevacizumab to avoid inducing kidney failure in patients with blinding diseases.

Footnotes and Disclosures

[1] Wilmer Eye Institute, Johns Hopkins School of Medicine, Baltimore, Maryland.

[2] Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland.

[3] Department of Biomedical Engineering, Johns Hopkins School of Medicine, Baltimore, Maryland.

[4] Division of Kidney Diseases and Hypertension, Donald and Barbara School of Medicine at Hofstra/Northwell, New York.

[5] Department of Biomedical Informatics and Data Science, Johns Hopkins School of Medicine, Johns Hopkins University, Baltimore, Maryland.

[6] Johns Hopkins University, Baltimore, Maryland.

[7] Department of Biomedical Informatics, Columbia University, New York, New York.

[8] VA Informatics and Computing Infrastructure, US Department of Veterans Affairs, Salt Lake City, Utah.

[9] Department of Internal Medicine Division of Epidemiology, University of Utah School of Medicine, Salt Lake City, Utah.

[10] VA Informatics and Computing Infrastructure, Tennessee Valley Healthcare System, Nashville, Tennessee.

[11] Department of Biomedical Informatics, Vanderbilt University, Nashville, Tennessee.

[12] Odysseus Data Services, Inc., Cambridge, Massachusetts.

[13] OHDSI Center at the Roux Institute, Northeastern University, Boston, Massachusetts.

[14] O'Brien Center for Public Health, Department of Medicine, University of Calgary, Canada.

[15] Technology / Digital Solutions, Stanford Health Care and Stanford University School of Medicine, Palo Alto, California.

[16] Department of Biostatistics, University of California - Los Angeles, Los Angeles, California.

[17] Roski Eye Institute, Keck School of Medicine, University of Southern California; Los Angeles, California.

[18] National Eye Institute, National Institutes of Health, Bethesda, Maryland.

[19] Casey Eye Institute, Oregon Health & Science University, Portland, Oregon.

[20] Mass Eye and Ear, and Harvard Medical School, Boston, Massachusetts.

[21] Janssen Research and Development, Titusville, New Jersey.

[22] Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, the Netherlands.

[23] Glomerular Center at Northwell Health, Division of Kidney Diseases and Hypertension, Donald and Barbara School of Medicine at Hofstra/Northwell, New York.

[24] Division of Nephrology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland.

References

1. GBD 2019 Blindness and vision impairment collaborators; vision loss expert group of the Global Burden of Disease Study. Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: the Right to Sight: an analysis for the Global Burden of Disease Study. *Lancet Glob Health*. 2021;9:e144−e160.

2. Martin DF. Evolution of intravitreal therapy for retinal diseases-from CMV to CNV: the LXXIV Edward Jackson memorial lecture. *Am J Ophthalmol*. 2018;191:xli−lviii.

3. Hanna RM, Barsoum M, Arman F, et al. Nephrotoxicity induced by intravitreal vascular endothelial growth factor inhibitors: emerging evidence. *Kidney Int*. 2019;96:572−580.

4. Gurevich F, Perazella MA. Renal effects of anti-angiogenesis therapy: update for the internist. *Am J Med*. 2009;122:322−328.

5. Izzedine H, Escudier B, Lhomme C, et al. Kidney diseases associated with anti-vascular endothelial growth factor (VEGF): an 8-year observational study at a single center. *Medicine*. 2014;93:333−339.

6. Iseki K, Ikemiya Y, Iseki C, Takishita S. Proteinuria and the risk of developing end-stage renal disease. *Kidney Int*. 2003;63:1468−1474.

7. Hemmelgarn BR, Manns BJ, Lloyd A, et al. Relation between kidney function, proteinuria, and adverse outcomes. *JAMA*. 2010;303:423−429.

8. Hsu CY, Chinchilli VM, Coca S, et al. Post-acute kidney injury proteinuria and subsequent kidney disease progression: the Assessment, Serial Evaluation, and Subsequent Sequelae in Acute Kidney Injury (ASSESS-AKI) study. *JAMA Intern Med*. 2020;180:402−410.

9. Jiang L, Peng L, Zhou Y, et al. Do intravitreal anti-vascular endothelial growth factor agents lead to renal adverse events? A pharmacovigilance real-world study. *Front Med.* 2023;10:1100397.

10. Avery RL, Castellarin AA, Steinle NC, et al. Systemic pharmacokinetics and pharmacodynamics of intravitreal aflibercept, bevacizumab, and ranibizumab. *Retina.* 2017;37:1847−1858.

11. Avery RL, Castellarin AA, Steinle NC, et al. Systemic pharmacokinetics following intravitreal injections of ranibizumab, bevacizumab or aflibercept in patients with neovascular AMD. *Br J Ophthalmol.* 2014;98:1636−1641.

12. Phadke G, Hanna RM, Ferrey A, et al. Review of intravitreal VEGF inhibitor toxicity and report of collapsing FSGS with TMA in a patient with age-related macular degeneration. *Clin Kidney J.* 2021;14:2158−2165.

13. Zafar S, Walder A, Virani S, et al. Systemic adverse events among patients with diabetes treated with intravitreal anti-vascular endothelial growth factor injections. *JAMA Ophthalmol.* 2023;141:658−666.

14. Kameda Y, Babazono T, Uchigata Y, Kitano S. Renal function after intravitreal administration of vascular endothelial growth factor inhibitors in patients with diabetes and chronic kidney disease. *J Diabetes Investig.* 2018;9:937−939.

15. O'Neill RA, Gallagher P, Douglas T, et al. Evaluation of long-term intravitreal anti-vascular endothelial growth factor injections on renal function in patients with and without diabetic kidney disease. *BMC Nephrol.* 2019;20:478. https://doi.org/10.1186/s12882-019-1650-1.

16. Lees JS, Dobbin SJH, Elyan BMP, et al. A systematic review and meta-analysis of the effect of intravitreal VEGF inhibitors on cardiorenal outcomes. *Nephrol Dial Transplant.* 2023;38:1666−1681.

17. Tsao YC, Chen TY, Wang LA, et al. Acute kidney injury from intravitreal anti-vascular endothelial growth factor drugs: a systematic review and meta-analysis of randomized controlled trials. *BioDrugs*;37:843−854.

18. Hanna RM, Lopez EA, Hasnain H, et al. Three patients with injection of intravitreal vascular endothelial growth factor inhibitors and subsequent exacerbation of chronic proteinuria and hypertension. *Clin Kidney J.* 2019;12:92−100.

19. Diabetic Retinopathy Clinical Research Network, Wells JA, Glassman AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med.* 2015;372:1193−1203.

20. Glassman AR, Liu D, Jampol LM, et al. Changes in blood pressure and urine albumin-creatine ratio in a randomized clinical trial comparing aflibercept, bevacizumab, and ranibizumab for diabetic maculara edema. *Invest Ophthalmol Vis Sci.* 2018;59:11991205.

21. Hripcsak G, Duke JD, Shah NH, et al. Observational Health Data Sciences and Informatics (OHDSI): opportunities for observational researchers. *Stud Health Technol Inform.* 2015;216:574−578.

22. Overhage JM, Ryan PB, Reich CG, et al. Validation of a common data model for active safety surveillance research. *J Am Med Inform Assoc.* 2012;19:54−60.

23. Software tools. https://www.ohdsi.org/software-tools/. Accessed December 21, 2023.

24. GitHub. ohdsi-studies/AntiVegfKidneyFailure. https://github.com/ohdsi-studies/AntiVegfKidneyFailure. Accessed April 22, 2023.

25. Ostropolets A, Ryan P, Hripcsak G. Phenotyping in distributed data networks: selecting the right codes for the right patients. *AMIA Annu Symp Proc.* 2022;2022:826−835.

26. Diabetic Retinopathy Clinical Research Network, Aiello LP, Maturi K, et al. Rationale for the Diabetic Retinopathy Clinical Research network treatment protocol for center-involved diabetic macular edema. *Ophthalmology.* 2011;118:e5−e14.

27. Levey AS, Eckardt KU, Dorman NM, et al. Nomenclature for kidney function and disease: report of a Kidney Disease: Improving Global Outcomes (KDIGO) consensus conference. *Kidney Int.* 2020;97:1117−1129.

28. KDIGO 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl.* 2013;3:1−150.

29. Ostropolets A, Reich C, Ryan P, et al. Adapting electronic health records-derived phenotypes to claims data: lessons learned in using limited clinical data for phenotyping. *J Biomed Inform.* 2020;102:103363. https://doi.org/10.1016/j.jbi.2019.103363.

30. Swerdel JN, Hripcsak G, Ryan PB. PheValuator: development and evaluation of a phenotype algorithm evaluator. *J Biomed Inform.* 2019;97:103258.

31. GitHub. OHDSI/Strategus: [Under development] an R packages for coordinating and executing analytics using HADES modules. https://github.com/OHDSI/Strategus. Accessed April 30, 2023.

32. *The R. Project for Statistical Computing.* https://www.R-project.org/. Accessed December 21, 2023.

33. Suchard MA, Simpson SE, Zorych I, et al. Massive parallelization of serial inference algorithms for a complex generalized linear model. *ACM Trans Model Comput Simul.* 2013;23. https://doi.org/10.1145/2414416.2414791.

34. OHDSI analysis viewer. https://data.ohdsi.org/AntiVegfKidneyFailure/. Accessed August 27, 2023.

35. Glasheen WP, Renda A, Dong Y. Diabetes Complications Severity Index (DCSI)-update and ICD-10 translation. *J Diabetes Complications.* 2017;31:1007−1013.

36. Romano PS, Roos LL, Jollis JG. Adapting a clinical comorbidity index for use with ICD-9-CM administrative data: differing perspectives. *J Clin Epidemiol.* 1993;46:1075−1079. discussion 1081−1090.

37. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med.* 2009;28:3083−3107.

38. Standardized rates of disease. https://sphweb.bumc.bu.edu/otlt/mph-modules/ep/ep713_standardizedrates/ep713_standardizedrates_print.html. Accessed July 14, 2023.

39. United States Census Bureau. Age and sex composition in the United States: 2015. https://www.census.gov/data/tables/2015/demo/age-and-sex/2015-age-sex-composition.html. Accessed July 14, 2023.

40. Suchard MA, Schuemie MJ, Krumholz HM, et al. Comprehensive comparative effectiveness and safety of first-line antihypertensive drug classes: a systematic, multinational, large-scale analysis. *Lancet.* 2019;394:1816−1826.

41. Tian Y, Schuemie MJ, Suchard MA. Evaluating large-scale propensity score performance through real-world and synthetic data experiments. *Int J Epidemiol.* 2018;47:2005−2014.

42. Zhang L, Wang Y, Schuemie MJ, et al. Adjusting for indirectly measured confounding using large-scale propensity score. *J Biomed Inform.* 2022;134:104204. https://doi.org/10.1016/j.jbi.2022.104204.

43. Schuemie MJ, Chen Y, Madigan D, Suchard MA. Combining cox regressions across a heterogeneous distributed research network facing small and zero counts. *Stat Methods Med Res.* 2022;31:438−450.

44. United States Renal Data System. Annual data report. https://adr.usrds.org/. Accessed August 27, 2023.

45. National Institute of Diabetes and Digestive and Kidney Diseases. Annual Data Report. https://www.niddk.nih.gov/about-

niddk/strategic-plans-reports/usrds/prior-data-reports/2018; 2018. Accessed August 16, 2023.

46. Levey AS, Atkins R, Coresh J, et al. Chronic kidney disease as a global public health problem: approaches and initiatives - a position statement from Kidney Disease Improving Global Outcomes. *Kidney Int*. 2007;72:247−259.

47. Ross EL, Hutton DW, Stein JD, et al. Cost-effectiveness of aflibercept, bevacizumab, and ranibizumab for diabetic macular edema treatment: analysis from the Diabetic Retinopathy Clinical Research Network comparative effectiveness trial. *JAMA Ophthalmol*. 2016;134:888−896.

48. Al-Moujahed A, Vail D, Do DV. Racial differences in anti-VEGF intravitreal injections among commercially insured beneficiaries. *Ophthalmic Surg Lasers Imaging Retina*. 2021;52:208−217.

49. Mahr MA, Hodge DO, Erie JC. Racial differences in age-related macular degeneration and associated anti-vascular endothelial growth factor intravitreal injections among Medicare beneficiaries. *Ophthalmol Retina*. 2018;2:1188−1195.

50. Avery RL, Gordon GM. Systemic safety of prolonged monthly anti-vascular endothelial growth factor therapy for diabetic macular edema: a systematic review and meta-analysis. *JAMA Ophthalmol*. 2016;134:21−29.

51. Virgili G, Parravano M, Evans JR, et al. Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis. *Cochrane Database Syst Rev*. 2017;6:CD007419. https://doi.org/10.1002/14651858.CD007419.pub5.

52. VanderBeek BL. Difficulty in assessing the systemic adverse effects of intravitreal anti-vascular endothelial growth factor therapy. *JAMA Ophthalmol*. 2023;141:666−667.

53. Weinstein RB, Ryan P, Berlin JA, et al. Channeling in the use of nonprescription paracetamol and ibuprofen in an electronic medical records database: evidence and implications. *Drug Saf*. 2017;40:1279−1292.

54. Weinstein RB, Ryan PB, Berlin JA, et al. Channeling bias in the analysis of risk of myocardial infarction, stroke, gastrointestinal bleeding, and acute renal failure with the use of paracetamol compared with ibuprofen. *Drug Saf*. 2020;43:927−942.

55. Schuemie MJ, Hripcsak G, Ryan PB, et al. Empirical confidence interval calibration for population-level effect estimation studies in observational healthcare data. *Proc Natl Acad Sci U S A*. 2018;115:2571−2577.

56. Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. *Epidemiology*. 2010;21:383−388.