Estimating the comparative risk of kidney failure associated with intravitreal anti-vascular endothelial growth factor (anti-VEGF) exposure in patients with blinding diseases

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Background:
Intravitreal anti-vascular endothelial growth factor (anti-VEGF) medications have revolutionized the treatment of blinding diseases.(1,2) While these medications are generally well tolerated, it remains uncertain whether intravitreally administered anti-VEGF medications are toxic to the kidneys and if that risk is different by medication–ranibizumab, aflibercept, and bevacizumab. This uncertainty has led some authors and practitioners to recommend the use of ranibizumab, which has the least suppression of systemic plasma VEGF levels, over the other medications.(3–5) The purpose of this OHDSI network study as part of the Save Our Sisyphus (SOS) Challenge was to fill this gap in knowledge by: A) characterizing the incidence of kidney failure associated with intravitreal anti-VEGF exposure, B) estimating the comparative risk of kidney failure associated with intravitreal anti-VEGF exposure between medications, and C) predicting an individual's risk for kidney failure with intravitreal anti-VEGF use.

Methods:
This was a retrospective cohort study across 12 databases (6 administrative claims, 6 electronic health records) in the OHDSI network standardized to the OMOP CDM.(6) (Table 2) New users (≥18 years) of ≥3 monthly intravitreal anti-VEGF medications (ranibizumab, aflibercept, or bevacizumab) for a blinding disease (diabetic retinopathy, diabetic macular edema, age related macular degeneration, and vein occlusion) with at least 365 days of prior observation were included in the study. Patients with cancer diagnoses (e.g., metastatic colorectal cancer) that could warrant systemic anti-VEGF were excluded. Patients with pre-existing kidney failure were also excluded. The time-at-risk started after the third anti-VEGF exposure until the end of continuous drug exposure, defined as a gap in exposure >180 days, or end of the study. Three anti-VEGF exposures were chosen based on prior studies demonstrating systemic absorption of intravitreal anti-VEGF.(4,5) The outcome of interest was time from cohort entry to kidney failure (needing dialysis or kidney transplant), while on treatment.

All analyses (A: characterization, B: population-level effect estimation, C: patient-level prediction) were performed using the Strategus execution pipeline, which wraps open-source analysis packages developed by the OHDSI community.(7) Analysis A: Summary statistics were used to describe the baseline characteristics of patients in each anti-VEGF exposure cohort by database. These characteristics include demographic information (age, sex, race, ethnicity), Diabetes Comorbidity Severity Index (DCSI) score, and Charlson Comorbidity Index-Romano adaptation (CCI).(8,9) The incidence proportion (standardized to the 2015 US population by age and sex), and incidence rate of kidney failure was provided for each exposure cohort in each database. Analysis B: Only databases that passed the study diagnostics including

minimum detectable relative risk, preference score, attrition fraction, standardized mean difference, and expected absolute systematic error, contributed to the population-level effect estimation. Large-scale propensity score method were used to match patients in each target and comparator exposure cohort comparison (aflibercept versus ranibizumab, bevacizumab versus ranibizumab, and bevacizumab versus aflibercept) using 1:1 propensity score matching.(10) Cox proportional hazards models were used to estimate the risk of kidney failure while on treatment. A meta-analysis was performed to combine each per site hazard ratio estimate into a single network-wide estimate.(11) Analysis C: Only databases that passed the study diagnostics contributed to the patient-level prediction. Machine learning models using an *L1*-regularized logistic regression using 3-fold cross validation auto hyper-parameter selection were trained within each database to predict the risk of kidney failure 6 months to 24 months after the initial 3 monthly intravitreal anti-VEGF medications.(12) The models were trained on 75% of the data and internally validated on the remaining 25%. The performance of each model was evaluated with area under the receiver operating curve (AUC).

Results:
Of the 12 databases evaluated for inclusion in this study, 11 were included in the analysis for A: characterization, 6 for B: population-level effect estimation, and 6 in C: patient-level prediction.

Analysis A: There were 25 to 10051 patients across the databases in the ranibizumab group, 393 to 5626 in the aflibercept group, and 108 to 71916 in the bevacizumab group. Baseline characteristics of patients included in each exposure cohort in the Optum Clinformatics Extended Data Mart - Socio-economic Status (SES) database are presented in Table 1. The number of kidney failure outcomes range from 0 to 317 in each exposure group across all databases. (Table 2) The incidence proportion of kidney failure ranged from 0 to 1.86 with an average of 0.70 per 100 persons. The standardized incidence proportion ranged from 0 to 2.39 across the databases with an average of 0.68 per 100 persons. The incidence rate of kidney failure ranged from 0 to 2.66 per 100 person-years, with an average of 0.74 per 100 person-years.

Analysis B: The hazard ratio (HR) estimates for risk of kidney failure across the databases are shown in Table 3. Comparing aflibercept to ranibizumab, the meta-analysis HR combining the estimates across all databases was 1.01 (95% Confidence Interval (CI) 0.70 to 1.47), p=0.45. Comparing ranibizumab to bevacizumab, the meta-analysis HR estimate was 0.95 (95% CI 0.68 to 1.32), p=0.62, and comparing aflibercept to bevacizumab was 0.95 (95% CI 0.65 to 1.39), p=0.60.

Analysis C: The average AUC of models predicting development of kidney failure in the aflibercept group was 0.91 (range 0.86 to 0.98 across databases), ranibizumab 0.88 (range 0.81 to 0.92), and bevacizumab 0.87 (range 0.77 to 0.93). The most predictive parameters of kidney failure across databases were pre-existing kidney disease including conditions of kidney impairment, chronic kidney disease, chronic disease of genitourinary system, and kidney disease.

Conclusion:
In this large-scale OHDSI network study, we find no difference in the risk of kidney failure between the 3 most commonly used intravitreal anti-VEGF medications. There is no evidence that ophthalmologists treating blinding diseases should preferentially select ranibizumab to avoid inducing kidney failure in patients.

Table 1: Baseline characteristics of patients in each exposure cohort (ranbizumab, aflibercept, and bevacizumab) in the Optum's Clinformatics Extended Data Mart - Socio-economic Status (SES) database (before propensity score matching).

	Ranibizumab N=10051 (%)	Aflibercept N=9817 (%)	Bevacizumab N=71916 (%)
Age Group			
15-19	0 (0)	0 (0)	5 (0)
20-24	3 (0)	7 (0)	29 (0)
25-29	11 (0)	12 (0)	68 (0)
30-34	31 (0)	34 (0)	159 (0)
35-39	42 (0)	48 (0)	312 (0)
40-44	85 (1)	81 (1)	520 (1)
45-49	149 (1)	161 (2)	928 (1)
50-54	274 (3)	240 (2)	1691 (2)
55-59	428 (4)	444 (5)	2696 (4)
60-64	624 (6)	583 (6)	3841 (5)
65-69	1140 (11)	1267 (13)	8205 (11)
70-74	1624 (16)	1741 (18)	12120 (17)
75-79	1977 (20)	1736 (18)	14376 (20)
80-84	1970 (20)	1801 (18)	14352 (20)

85-89	1634 (16)	1609 (16)	12188 (17)
90-94	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)
Unknown	1165 (12)	1409 (14)	11861 (16)
Ethnicity			
Hispanic	750 (7)	923 (9)	8326 (12)
Non-Hispanic	8886 (88)	8408 (86)	60055 (84)
Unknown	415 (4)	486 (5)	3535 (5)
Diabetes Comorbidity Severity Index (DCSI) score	3.8 (N=8504)	3.85 (N=8259)	3.99 (N=61182)
Charlson Index -Romano adaptation	3.29 (N=8319)	3.69 (N=8353)	3.65 (N=60952)
CHADS2	2.59 (N=10051)	2.62 (N=9817)	2.65 (N=71916)

Table 2: The incidence rate of kidney failure in each exposure cohort across all databases.

	Patients at Risk	On Treatment Time (person-years)	Number of Outcomes	Incidence Proportion (per 100 persons)	Standardized Incidence Proportion (per 100 persons)§	Incidence Rate of Kidney Failure (per 100 person-years)
Ranibizumab*						
CCAE[1]	3799	3083.8	40	1.08	0.70	1.30
MDCR[2]	7604	8412.6	48	0.63	0.82	0.57
MDCD[3]	1265	1122.3	17	1.34	2.39	1.52
OptumEHR[4]	2520	2491.0	15	0.60	0.61	0.60
SES[5]	8048	9848.2	65	0.81	0.84	0.66
JMDC[6]	203	133.6	0	0.00	0.00	0.00
JHME[7]	19	12.9	0	0.00	0.00	0.00
NEU[8]	2084	2181.3	14	0.67	0.40	0.64
CUMC[9]	117	114.4	0	0.00	0.00	0.00
VA[10]	3943	2538.6	25	0.63	0.25	0.98
USC[11]	7	9.9	0	0.00	0.00	0.00
Aflibercept						
CCAE	3319	3251.7	56	1.69	1.67	1.72
MDCR	4644	5536.7	23	0.50	0.16	0.42
MDCD	1717	1796.1	32	1.86	1.45	1.78
OptumEHR	3282	4698.5	24	0.73	0.39	0.51

SES	8056	11011.5	72	0.89	1.41	0.65
JMDC	205	190.7	1	0.49	0.33	0.52
JHME	574	656.0	8	1.39	1.83	1.22
NEU	3696	3713.0	17	0.46	0.41	0.46
CUMC	335	466.3	0	0.00	0.00	0.00
VA	6266	6245.2	56	0.89	0.79	0.90
USC	59	89.0	1	1.69	0.32	1.12
Bevacizumab						
CCAE	10508	6777.1	104	0.99	0.68	1.54
MDCR	10625	9050.0	50	0.47	0.11	0.55
MDCD	3845	2632.7	70	1.82	2.20	2.66
OptumEHR	11933	12648.0	69	0.58	1.34	0.55
SES	52642	50615.9	317	0.60	1.07	0.63
JMDC	0	0.0	0	NA	0.93	NA
JHME	286	226.2	2	0.70	0.33	0.88
NEU	8331	6279.9	25	0.30	0.00	0.40
CUMC	74	41.1	0	0.00	0.00	0.00
VA	10037	5930.2	58	0.58	0.30	0.98
USC	27	20.1	0	0.00	0.00	0.00

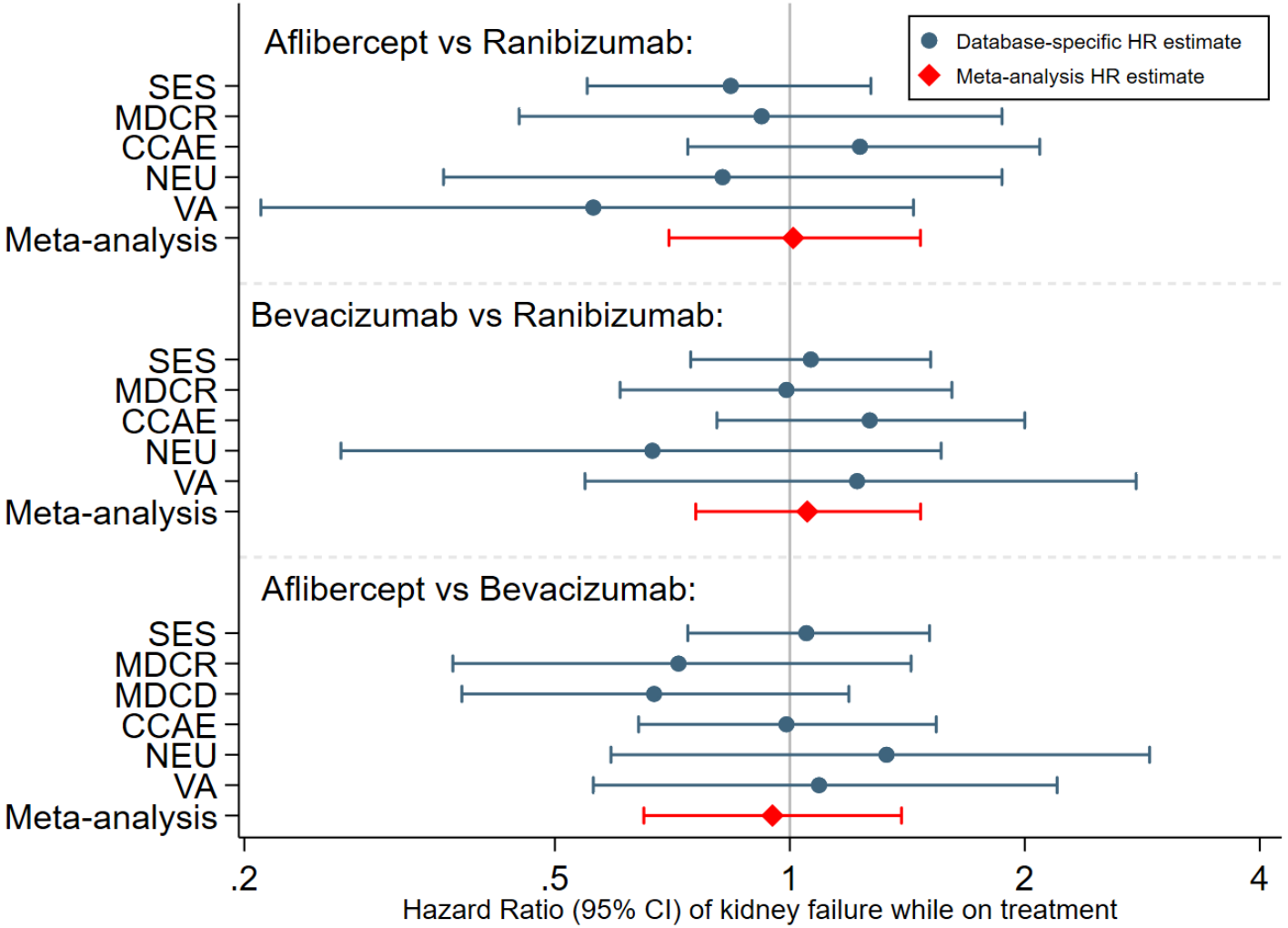
* Only patients who contribute at least 1 day to time-at-risk are included in this analysis.

§ Standardized to the 2015 U.S. Population by age and sex

1 CCAE = IBM Health MarketScan Commercial Claims and Encounters Database, USA commercially insured <65 years

2 MDCR = IBM Health MarketScan Medicare Supplemental and Coordination of Benefits Database, USA commercially insured 65+ years
3 MDCD = IBM Health MarketScan Multi-State Medicaid Database, USA Medicaid enrollees
4 OptumEHR = Optum(R) de-identified Electronic Health Record Dataset, USA combined insured claims and electronic health records
5 SES = Optum's Clinformatics Extended Data Mart - Socio-economic Status, USA commercially insured
6 JMDC = Japan Medical Data Center, Japan insurance claims <65 years
7 JHME = Johns Hopkins Medical Enterprise, USA non-profit academic medical center
8 NEU = PharMetrics Plus, USA commercially insured <65 years
9 CUMC = Columbia University Medical Center, USA non-profit academic medical center
10 VA = Department of Veterans Affairs, veterans in the USA
11 USC = University of Southern California, USA non-profit academic medical center

Figure 1: Hazard ratio 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.



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