Real-World Evidence of Adverse Kidney Outcomes for Intravitreal Use of Vascular Endothelial Growth Factor (VEGF) Inhibitors Among Patients with Diabetic Retinopathy

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Submitted to the Graduate Faculty of the

School of Pharmacy in partial fulfillment

of the requirements for the degree of

Master of Science

University of Pittsburgh

2022

UNIVERSITY OF PITTSBURGH

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2022

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University of Pittsburgh, 2022

Objective: Studies of kidney injury following the use of intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections among patients with diabetic retinopathy have mixed results and are limited by sample size and study design. Our objective was to determine whether intravitreal use of anti-VEGF agents was associated with adverse kidney outcomes compared to treatment with traditional laser photocoagulation. **Methods:** Adult patients with diabetic retinopathy and use of intravitreal anti-VEGF injections or laser photocoagulation were identified from January 2011, through December 2020 in a large nationally representative database of administrative and electronic health record information for commercially insured and Medicare/Medicaid Advantage patients. Outcomes assessed included diagnosis of new chronic kidney disease (CKD) or worsening CKD as primary endpoints, a composite endpoint of overall hospitalization or death, and thromboembolic events as secondary endpoints, and a 40% eGFR reduction within one and two years as exploratory endpoints. We applied inverse probability treatment weighting using propensity scores and adjusted for demographics, comorbidities, and CKD stages at baseline. We performed Cox proportional regression models and accelerated time failure models to assess the study endpoints. **Results:** A total of 2,427 patients met the inclusion criteria, with 1,327 patients receiving intravitreal anti-VEGF injections and 1,100 patients receiving laser photocoagulation. Patients in the anti-VEGF group did not have a statistically significant higher hazard for either newly developed CKD (HR=1.16; 95% CI: 0.99, 1.36) or

worsening of pre-existing CKD (HR=0.88; 95% CI: 0.71, 1.08) compared to patients in the laser group after adjustment. However, patients treated with intravitreal anti-VEGF injections had significantly higher hazards of overall hospitalizations or mortality compared to those treated with laser photocoagulation (HR=1.18; 95% CI: 1.05, 1.33) but there was no difference in the risk of thromboembolic events (HR=1.11; 95% CI: 0.97, 1.27). Our exploratory endpoints showed no significant difference in patients experiencing a 40% eGFR reduction within one year (HR= 1.15; 95% CI: 0.94, 1.40) and within two years (HR=1.24; 95% CI: 0.99, 1.54) . **Conclusions:** While the use of anti-VEGF intravitreal injections was not associated with new or worsening CKD, thromboembolic events, and a significant eGFR reduction compared to laser photocoagulation, patients had a higher risk of hospitalization or death. These results continue to question the effects anti-VEGF injections have on adverse systemic or kidney outcomes.

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Preface

This research aspired to help answer the concern of adverse kidney outcomes from intravitreal anti-VEGF injections using large and real-world data. The research idea came from the review paper written by Dr. Ramy M. Hanna in 2019. As using real-world evidence (RWE) in healthcare-decision making has become a trend, especially addressing long-term safety outcomes which cannot be achieved by randomized clinical trials, I sincerely hope my research provides different aspects to this possible clinical problem.

I wholeheartedly would like to thank my advisors, Dr. Kangho Suh and Dr. Sandra Kane-Gill for their professional guidance in my research. I also would like to appreciate Dr. Levent Kirisci for his insightful advice in my research. As this was my first research, I especially wanted to express my greatest gratitude to Dr. Suh for his teaching and warm encouragement. In addition, I was also grateful to Dr. Inmaculada Hernandez for her invaluable experiences sharing as well as our two data analysts in our program, Jingye Yang and Kerri Freeland, for their kind support to let me work on the Optum database as much as I could.

Furthermore, I sincerely would like to appreciate my friends and my family. I had a difficult time dealing with a work-life balance between my research, Ph.D. application, and my social life in the second half-year of 2021. I want to thank my colleagues, Lanting Yang, and Xiaojiang Guo, for their strong and lovely support during this hard time. I also would like to thank all my friends and my family for always believing me. Without you, I could not come through it.

Lastly, I would like to send my regards to all researchers who have been working in the HEOR (Health Economics and Outcomes Research) field for your excellent work in improving the healthcare setting and decision making.

1.0 Introduction

1.1 Epidemiology of Diabetic Retinopathy

1.1.1 Disease Burden, Disease Pathophysiology, and Impact on the Society

Diabetic retinopathy (DR) is one of the leading causes of blindness among working-age adults worldwide.[1] An estimated 34.6% of people with diabetes have some form of diabetic retinopathy and 10.2% of patients will develop vision-threatening diabetic retinopathy, including proliferative diabetic retinopathy and diabetic macular edema.[2] The latest report from the IDF (International Diabetes Federation) in 2021 showed that almost half of adults (239.7 million) had undiagnosed diabetes globally.[3] The IDF also predicted that adults with diabetes would grow to 578 million by 2030 and 700 million by 2045, owing to sedentary lifestyle, obesity, longer life expectancy, and early detection of the disease.[4] Considering growing risk and improved diagnosis methods for diabetes, a higher prevalence of diabetic eye diseases in the future can be anticipated.

Diabetic retinopathy is a progressive disease.[5] Starting from mild non-proliferative diabetic retinopathy (NPDR) to moderate and severe levels, increased vascular permeability allow fluid leakage, causing retinal edema, retinal hemorrhage, and hard exudates.[5, 6, 7, 8, 9] Moreover, more blood vessels within the retina are occluded, depressing oxygen supply and leading to neovascularization, known as proliferative diabetic retinopathy (PDR).[5, 6, 8, 9] Diabetic macular edema (DME) occurs when the swelling is in the central part of the retina (macula) and it can occur at any stage of diabetic retinopathy, including any severity of NPDR and PDR.[9, 10, 11] Complications of PDR, such as vitreous hemorrhage (VH) and tractional retinal detachment, and

DME are common causes of vision impairment and vision loss.[1, 10] It is a global health issue and requires interventions from a public health perspective.

1.1.2 Approaches to Disease Prevention and Treatments from Public Health Perspectives

Experts in public health and ophthalmology have developed several approaches to minimize the risk of vision loss caused by DR, such as patient education, screening programs, time referral recommendation and the guideline for advanced DR treatments.[5, 6] Screening is considered as cost-effective as most patients are asymptomatic until very late stages of DR.[4, 11] Early intervention can help reduce the rate of disease progression and prevent further vision loss.[4, 11] Nevertheless, without prompt referral to ophthalmologists and accessible treatments, such as intravitreal anti-vascular endothelial growth factor (anti-VEGF) treatments or laser photocoagulation, screening programs will not benefit patients.[5, 12] Patient education involves self-management of blood glucose, blood pressure, and cholesterol level, along with awareness of the importance of routine follow-up regardless of no ocular symptoms.[5, 13]

Despite studies that have corroborated that well glycemic control can reduce DR progression,[13] especially considering many available pharmacological agents to lower blood glucose levels nowadays, DR-induced blindness and visual impairment increased by 27% and 64% from 1990 to 2010, respectively.[14] Risk factors associated with DR include duration of diabetes, hyperglycemia, hypertension, and dyslipidemia.[2, 13] No matter how well control of blood glucose, blood pressure, and lipid level are, patients remain a lifetime risk of diabetic retinopathy and its complication since the diagnosis of diabetes.[5] Severe stages of DR, such as PDR or DME, require urgent interventions to prevent blindness.[5, 6]

1.2 Treatment Options for Diabetic Retinopathy

Interventions for advanced DR include intravitreal use of anti-VEGF agents or corticosteroids, panretinal/grid/focal laser photocoagulation, and vitrectomy.[13] Traditionally, pan-retinal laser photocoagulation (PRP) was the only gold standard for PDR treatment after its introduction in the 1960s.[10] PRP destroys photoreceptors in the retina to reduce the demand for oxygen and further improves the oxygenation from the choriocapillaris.[15] PRP decreases the risk of severe vision loss by 50% or more.[10, 15] Focal/grid laser photocoagulation can be applied to treat clinically significant macular edema (CSME).[5, 9] Study reported that it helped reduce half rates of moderate vision loss in patients with DME over 3 years.[16] Intravitreous injection of corticosteroids (triamcinolone, dexamethasone, fluocinolone) can be considered for patients with pseudophakic eyes or who respond to steroids.[5] Intraocular pressure should be carefully monitored when given corticosteroids intravitreally.[5] Furthermore, there are more frequent side effects of intravitreally-administered steroids, such as cataracts and glaucoma.[5] Vitrectomy is usually given to late stages of DR, such as patients with tractional retinal detachment or with non-clearing retinal hemorrhage due to PDR.[5, 10]

1.2.1 Pharmacological Mechanism of Action of Anti-Vascular Endothelial Growth Factor (Anti-VEGF)

Intravitreal injections of VEGF inhibitors have revolutionized the care for diabetic retinopathy.[17] Neurovascular abnormalities associated with diabetes, involving structural, biochemical, and functional changes in retinal epithelium, may account for pathogenesis of retinopathy and further vision loss.[6] Therefore, treatments including intravitreally-administered

medications, laser photocoagulation, and surgical interventions are intended to manage retinal and neural dysfunction.[9] While intraocular corticosteroids targeting to active microglia cells help alleviate inflammation, laser photocoagulation and vitrectomy manage to reduce the severity of vision loss caused by macular edema and vitreous hemorrhage, VEGF inhibitors aim to regress ocular neovascularization, which occurs due to the occlusions and leakages of retinal capillaries, to reduce disease progression.[6, 13] In addition, intravitreally administered VEGF inhibitors have less adverse effects related to vitreoretinal treatments, such as cataract progression, risk of glaucoma or vitreous hemorrhage owing to injections of corticosteroids.[6, 13] Hence, anti-VEGF agents are now considered the gold standard treatment by limiting angiogenesis for neovascular eye diseases, for example, age-related macular degeneration and diabetic retinopathy.[18] **Table 1** listed the currently approved or commonly used anti-VEGF agents in ophthalmology.[19, 20, 21, 22, 23]

Table 1 Approved or Off-Label Intravitreal Use of Anti-VEGF agents in the U.S.

Generic Name	Trade Name	Initial U.S. Approval	Indications
aflibercept	EYLEA®	2011	• Neovascular (Wet) Age-Related Degeneration (AMD) • Macular Edema Following Retinal Vein Occlusion (RVO) • Diabetic Macular Edema (DME) • Diabetic Retinopathy (DR)
brolucizumab	BEOVU®	2019	• Neovascular (Wet) Age-Related Degeneration (AMD)
bevacizumab	AVASTIN® (firstly approved in 2004)	Off-label use	Mostly used following diseases[24, 25]: • Neovascular (Wet) Age-Related Degeneration (AMD) • Diabetic Macular Edema (DME) • Progressive Diabetic Retinopathy (PDR)
pegaptanib	MACUGEN®	2004	• Neovascular (Wet) Age-Related Degeneration (AMD)
ranibizumab	LUCENTIS®	2006	• Neovascular (Wet) Age-Related Degeneration (AMD) • Macular Edema Following Retinal Vein Occlusion (RVO) • Diabetic Macular Edema (DME)

1.3 Adverse Kidney Outcomes from Intravitreal Anti-VEGF Injections

Regardless of the outstanding clinical effectiveness in ocular diseases, recent studies had reported that intravitreal administration of VEGF inhibitors could lead to decreased renal function.[26] *Shye et al.*[27] reported three cases with stable levels of proteinuria and chronic kidney disease experienced worsening proteinuria and renal function following use of intravitreal anti-VEGF treatments; two cases had sudden deterioration of renal function soon after VEGF blockade. Additionally, *Hanna et al.*[28] reported three cases of thrombotic microangiopathy (TMA) likely related to the intravitreal use of VEGF inhibitors as these three cases were diagnosed with acute kidney injury after treatment with VEGF inhibitors for months to one year. The above findings suggested a possible adverse effect of intravitreal injection of anti-VEGF treatments on renal function.

1.3.1 Biological Plausibility of Anti-VEGF Agents in Adverse Kidney Events

One mechanism by which renal dysfunction is believed to occur is impaired macrovascular and renal microvascular circulation. VEGF plays a crucial role in the systemic circulation as well as in the regulation of renal microvasculature.[29] The decreased free VEGF level in blood dysfunctions vascular endothelium and results in blood vessel constriction, leading to hypertension.[30] Among all VEGF families, VEGF-A, which is mainly produced by podocytes in the glomerulus, is necessary to maintain the normal development of the glomerular silt diaphragm.[31] It has been theorized that altering VEGF-A expression may disrupt the slit diaphragm and the normal function of glomerular filtration.[29] This exact mechanism of the VEGF pathway in renal impairment, however, remains unclear considering insufficient human renal biopsy reports.[32]

1.3.2 Observational Studies that Evaluated the Association between Intravitreal Anti-VEGF Injections and Adverse Kidney Events

Despite several case reports and the plausible explanation for renal impairment after intravitreal injections of VEGF inhibitor, this possible association was not seen from further observational studies. There have been three observational studies aiming to understand the effect of intravitreal use of VEGF inhibitors on kidney outcomes. One single-center, a historical cohort study showed that there was no significant change in estimated glomerular filtration rate (eGFR) following intravitreally-administered anti-VEGF agents (aflibercept, bevacizumab, or ranibizumab) among patients with diabetes and chronic kidney diseases.[33] Another single-center, prospective study found that intravitreal bevacizumab injection did not cause worsening renal function among patients with diabetic nephropathy.[34] Nevertheless, these two studies only assessed short-term outcomes of intravitreal anti-VEGF treatments on renal function. A retrospective cohort study reviewed approximate 2.6 years follow-up period on the long-term renal outcome after the use of aflibercept and ranibizumab.[35] The study concluded that regular long-term use of intravitreal anti-VEGF injections did not significantly alter eGFR and urinary albumin-to-creatinine ratio (UACR) among patients with diabetic kidney disease and without diabetic kidney disease.[35]

1.4 Gap in Evidence

Despite the conclusions drawn from currently observational studies being similar – no significant changes in renal function after intravitreal VEGF treatments, the shared limitations of

these studies were the relatively small sample size and no direct comparison group receiving alternative treatments. Thus, an observational study with larger sample sizes and a well-defined control group was required to further examine the relationship between intravitreal anti-VEGF treatments and the possible adverse kidney outcomes.

2.0 Objective

We aimed to determine whether the exposure of intravitreal use of anti-VEGF agents was associated with adverse kidney outcomes compared to traditional laser photocoagulations, by using real-world data from administrative health claims and electronic health records (EHR). Patients diagnosed with diabetic retinopathy who initiated medical interventions were divided into the study group and the control group – the study group was patients receiving intravitreal use of anti-VEGF agents (aflibercept, bevacizumab, and ranibizumab) only, and the control group were patients receiving laser photocoagulation only.

The primary endpoints were to compare new diagnoses or worsening of chronic kidney disease (CKD) from administrative claims. The secondary endpoints included a composite endpoint (all-cause death or hospitalization) and thromboembolic events. For the composite endpoint, we also performed subgroup analyses for overall death and overall hospitalization as separate endpoints. The exploratory endpoints were a 40% estimated glomerular filtration rate (eGFR) reduction within one year and two years.

3.0 Method

3.1 Study Design and Data Source

This was a retrospective cohort study of the adverse kidney outcomes of intravitreal anti-VEGF injections versus laser photocoagulation in patients with diabetic retinopathy. We used the de-identified Optum Clinformatics Data Mart database (OptumInsight, Eden Prairie, MN), a large nationally representative database for commercially insured and Medicare/Medicaid Advantage patients. The database was composed of integrated electronic health records (EHR) dataset and administrative health claims dataset. The integrated person-linked data from administrative claims and EHR included longitudinal records of diagnoses, hospitalization, procedures, prescriptions, over-the-counter medications, laboratory results, vital signs, and survey data.[36] It provided a comprehensive approach for health analyses using two types of data. The study was exempt from the Institutional Review Board (IRB)'s review of the University of Pittsburgh under 45 CFR 46.104 (IRB number: STUDY21060212).

3.2 Study Population

Patients diagnosed with diabetic retinopathy, defined as at least two or more outpatient visits with at least 30 days apart or listed as a primary diagnosis at a one-time inpatient visit, were eligible to enter the study cohort. We used *International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification* (ICD-9/10-CM) diagnostic codes to identify diseases, *Healthcare*

Common Procedure Coding System (HCPCS) codes, and *Current Procedural Terminology* (CPT) codes to identify medical interventions of interest as well as ways of administration, and *Place of Service* (POS) codes to identify types of visits for the study cohort extraction. **Appendix A** listed all codes used in this study.

We adopted an incident user design – patients who initiated treatments of interest would be considered – to reduce selection biases and confounding factors.[37] Patients identified from the database from January 2011 through December 2020 and met enrollment criteria (Section 3.2.1) were divided into one of the following two groups:

- Study group: anti-vascular endothelial growth factor (anti-VEGF) intravitreal injections (aflibercept, bevacizumab, ranibizumab)
- Control group: laser photocoagulation, including focal/grid and pan-retinal laser photocoagulation

We also used an intent-to-treat design, which meant patients who ever received both anti-VEGF and laser photocoagulation were categorized into the group according to which treatment they received first. Switching to a different anti-VEGF agent was acceptable for patients in the anti-VEGF group.

3.2.1 Enrollment Criteria

We included patients with diabetic retinopathy, aged over 18 years with incident use of intravitreal anti-VEGF injections (defined as the study group) or laser photocoagulation (defined as the control group) from January 1st, 2011, through December 31st, 2020. Intravitreal anti-VEGF agents were limited to aflibercept, bevacizumab, and ranibizumab as they were available and commonly used during our study period. The index date for both groups was the first date of

treatment. Patients were required to have a minimum one-year continuous enrollment (defined as the "pre-index period") prior to the first date of treatments of interest (defined as the "index date") to obtain treatment history for DR and baseline characteristics.

We excluded patients with a history of renal transplantation or receiving any vitreoretinal treatments during the pre-index period, identified by ICD-9/10-CM codes. In addition, patients who had at least two references eGFR within 180 days before the index date showing ≤ 15 ml/min/1.73m^2 with at least 90 days apart[38, 39] or with any ICD-9/10-CM diagnostic codes of end-stage renal disease (ESRD) were excluded. Furthermore, we also excluded patients with only one available reference eGFR taken during sepsis-related hospitalization from the study enrollment, identified by ICD-9/10-CM codes. **Table 2** listed all inclusion and exclusion criteria.

Table 2 Inclusion and Exclusion Criteria

Inclusion Criteria
1. Patients were diagnosed with DR with a diagnosis listed on two or more outpatient visits at least 30 days apart or listed as a primary diagnosis at a one-time inpatient visit.
2. Patients had integrated data in both administrative healthcare claims and EHR.
3. Patients with DR required vitreoretinal interventions, limiting to either intravitreal injections of anti-VEGF agents (aflibercept, bevacizumab, or ranibizumab) or laser photocoagulation (focal/grid/pan-retinal photocoagulation).
4. Patients were aged ≥ 18 years old before the index date.[a]
5. Patients shall have at least one-year of continuous enrollment before the index date.[a]
6. Patients shall have available reference eGFR within 180 days prior to the index date.[a] Definition of available reference eGFR was: i. eGFR value using MCQ equation directly from the database, or ii. calculated eGFR value using MDRD equation from serum creatinine value In addition, extreme serum creatinine values (<0 mg/dL or ≥10 mg/dL) were discarded and were not used for eGFR calculation.
Exclusion Criteria
1. Patients received any vitreoretinal treatments defined as follows during the pre-index period:[b] i. intravitreal anti-VEGF injections (aflibercept, bevacizumab, brolucizumab, ranibizumab, and pegaptanib) ii. focal/grid or pan-retinal laser photocoagulations iii. intravitreal corticosteroids injections, including triamcinolone, dexamethasone, and fluocinolone iv. vitrectomy

Table 2 Continued

2. Patients received any intravenous administration of anti-VEGF agents (aflibercept, bevacizumab, and ranibizumab) during the pre-index period.[b]
3. Patients who were diagnosed with ESRD before the index date.[a] ESRD was defined as: i. at least two reference eGFR $\leq$ 15 ml/min/1.73m^2 with at least 90 days apart, or ii. any diagnosis of ESRD in ICD-9/10-CM codes before the index date.[a]
4. Patients who ever had renal transplantation before the index date.[a]
5. Patients who only had reference eGFR taken during sepsis-related hospitalizations.[c]
6. Patients with the pre-index period[b] of less than one year (who received treatment of interests in 2010).
7. Patients with data clerical errors, were defined as patients with death date earlier than the index date.[a]
8. Patients with unspecified CKD stages during the pre-index period.[b]
9. Patients who did not have eGFR data after the index date[a] (for the exploratory endpoints only).
10. Patients without at least one-year and two-year continuous enrollment after the index date[a] (for the exploratory outcome only).

Abbreviations: DR = diabetic retinopathy; EHR= electronic health records; anti-VEGF = anti-vascular endothelial growth factor; eGFR = estimated glomerular filtration rate; MCQ equation = Mayo Clinic Quadratic equation; MDRD equation = Modification of Diet in Renal Disease (MDRD) equation; ICD-9/10-CM = international classification of diseases, Ninth/Tenth Revision, Clinical Modification; ESRD = end-stage renal disease; CKD = chronic kidney disease.

Note:
[a]The index date was defined as the first date receiving either intravitreal anti-VEGF injections or laser photocoagulations.
[b]The pre-index period was defined as within one year before the index date (the first intervention date of treatments).
[c]Sepsis-related hospitalizations were defined as ICD-9/10-CM codes recorded in any admitting diagnoses.

3.3 Covariates

For patients who met enrollment criteria **(Table 2)**, we then collected baseline data in the pre-index period as covariates, including patient characteristics, clinical characteristics (renal function, comorbidities, concomitant antidiabetic medications), index year, COVID-19 pandemic, and follow-up time.

Chronic kidney disease (CKD) with its severity (stages) and eGFR were presented for renal function at baseline. We used Elixhauser comorbidities[40, 41] with 29 comorbidity categories and medical history of acute kidney injury (AKI) for comorbidity assessment. As our study cohort were patients with diabetic retinopathy and our primary endpoints were new or worsening CKD stages, we did not control for Elixhauser comorbidities of renal failure and uncomplicated diabetes. We reported comorbidities that were accounted for over 5% in our study cohort . As diabetes was one of the leading causes of renal dysfunction,[4] we collected the use of concomitant anti-diabetic medications as surrogates for the control of diabetes. Users of α-glucosidase inhibitors and amylinomimetics agents were less than 1% so we did not control for them. In addition, we did not control for the use of nephrotoxic or renally-excreted medications due to their possible multicollinearity with selected covariates in our study.

We set the year of first treatment as the index year. In addition, we included a COVID-19 pandemic variable, defined as patients receiving their first treatment (the index date) after WHO announced SARS-CoV-2 global emergency on January 31, 2020[42] because it would bias the assessment of overall hospitalization or death in the secondary endpoints. Follow-up time was defined as the time period between the index date and either the date of study endpoints or the end of insurance eligibility date.

The following information was collected in the pre-index period as the baseline characteristics:

- **Demographic characteristics**: sex, age, race (African American, Asian, Caucasian and Other/Unknown), ethnicity (Hispanic, Non-Hispanic, and Unknown), region (Midwest, Northeast, South, West, and Other/Unknown), insurance type (Commercial, Medicaid/ Medicare, and Unknown).
- **Renal function**: CKD including severity (stage 1 to stage 5 without dialysis), eGFR
- **Comorbidities**: acute kidney injury, congestive heart failure (CHF), cardiac arrhythmia, peripheral vascular disorders, hypertension (uncomplicated and complicated), chronic pulmonary disease, diabetes (complicated only), hypothyroidism, malignant neoplasms (lymphoma, solid tumor with and without metastasis), fluid and electrolyte disorders, and depression.
- **Concomitant antidiabetic medications**: biguanides, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide 1 (GLP-1) agonists, insulins, and sulfonylureas.
- **Treatment-related information**: index year, COVID-19 pandemic year, and follow-up time.

3.4 Outcome Measures

3.4.1 Primary Endpoints

The primary endpoints were new diagnoses or worsening CKD stages for patients without CKD and with CKD at baseline from administrative claims, respectively. Considering lower

positive predictive values (PPV) from one CKD diagnosis compared to two CKD diagnoses in administrative claims,[43] we defined the primary outcome as ≥2 new or worsening diagnoses of CKD in administrative claims after the index date compared to the CKD stage at baseline. We used the second diagnosis date as the event date of interest. In addition, we restricted patients with continuous enrollment at 3, 6, 12, and 24 months to evaluate any difference in the number of intravitreal anti-VEGF injections between patients who experienced and who did not experience primary endpoints.

3.4.2 Secondary Endpoints

The secondary endpoints included a composite endpoint of overall hospitalization or death and emergency department (ED) or inpatient visits associated with thromboembolic events. We also evaluated the sub-group data of the composite endpoint – overall death and overall hospitalization. Thromboembolic events included artery thrombosis, deep vein thrombosis, pulmonary embolism, myocardial infarction, and ischemic stroke **(Appendix Table 1)**. Considering higher positive predictive values (PPVs) of thromboembolic events for ED/ hospitalized patients compared to outpatient patients in administrative claims,[44] we identified thromboembolic events only from ED or inpatient visits. We collected ED and inpatient visits data after the index date both from the EHR and administrative claims. Considering duplicate information in both EHR and administrative claims, we allowed ± 3 days gap for the visit dates. For example, if the differences of the admission dates and the discharge dates between EHR and claims data were within this range (± 3 days), we regarded them as the same hospitalization.

We used the first visit (or death) date as the event date of interest. Same as the primary endpoint, we restricted patients with continuous enrollment at 3, 6, 12 and 24 months to evaluate

any difference in the number of intravitreal anti-VEGF injections between patients who experienced and who did not experience secondary endpoints.

3.4.3 Exploratory Endpoints

As eGFR data were available in the study database, we were also interested in whether there were differences in 40% eGFR reduction within one year and two years for patients who had eGFR test results after the index date. National Kidney Foundation (NKF) and Food and Drug Administration (FDA) recommended using 40% eGFR decline as a clinically representative substitute for CKD progression in clinical trials.[45] Compared to 30% eGFR decline, using 40% eGFR decline as a surrogate endpoint decrease the chance of type 1 error and due to acute effect on eGFR.[45] Despite using laboratory values might bring more insightful information for underreporting problems of CKD in administrative claims,[43, 46] selection bias often occurred due to issues of missing data in observational studies.[47] Reasons for missing data might be related to interruptions of health insurance coverage, no routinely scheduled clinic visits, patients' refusal, or loss of follow-up, [48, 49] so eGFR data was certainly not missing completely at random (MCAR).[47] Therefore, we listed them as exploratory endpoints. The percentages of eGFR change were calculated for each post-intervention eGFR test result against the reference eGFR at baseline. We used the first date when 40% eGFR reduction occurred as the event date of interest. We compared the results of the exploratory endpoints with our primary endpoints. We also evaluated any difference in the number of intravitreal anti-VEGF injections between patients who experienced and who did not experience 40% eGFR reduction within one year and two years.

3.5 Data Extraction

Optum Clinformatics Data Mart database (OptumInsight, Eden Prairie, MN) provided two sources of health care data – EHR and administrative claims. To maximize our sample size and generalizability, we explored our patient cohort diagnosed with diabetic retinopathy from these two sources and then only extracted patients who had linked data from EHR and claims. Assuming most of the therapies for diabetic retinopathy were reimbursed, we identified our patients in the study group and control group using the healthcare common procedure coding system (HCPCS) and current procedural terminology (CPT) codes from administrative claims data **(Appendix Table 2 and 3)**. We also used this approach to exclude patients receiving prohibited therapies, such as other vitreoretinal treatments and intravenous anti-VEGF injections in the pre-index period. The number of intravitreal anti-VEGF injections was also calculated to explore the possible dose-outcome relationship. For antidiabetic medications, we used the American Hospital Formulary Service Classification System (AHFSCLASS) codes to identify therapeutic categories **(Appendix Table 4)**.

Comorbidities and primary endpoints were identified using ICD-9/10-CM and place of service (POS) codes from administrative claims **(Appendix Table 5)**. We approached EHR and administrative data to extract hospitalization data for secondary endpoints. Specifically, we extracted the medial history of AKI using hospitalization diagnoses to achieve high specificity.[50] The mortality from Optum was sourced from Social Security Administration Death Master File (DMF).

We collected reference eGFR data within 180 days prior to the index date. Reference eGFR were extracted either from direct eGFR data using Mayo Clinic Quadratic (MCQ) equation[51, 52] from the database or indirect eGFR data using Modification of Diet in Renal Disease (MDRD)

equation[53] from the calculation. Extreme serum creatinine (Scr) values (<0 or ≥10 mg/dL) were excluded.

$$MCQ = 1.911 + \frac{5.249}{Scr} - \frac{2.114}{Scr^2} - 0.00686 \times age - 0.205\ (if\ female)$$

$$MDRD = 175 \times (Scr)^{-1.154} \times (Age)^{-2.203} \times 0.742\ (if\ female) \times 1.212\ (if\ African\ American)$$

eGFR values within 24 hours before the index date were preferred for use. For patients who did not have within 24 hours eGFR, we used either the median of multiple eGFR values or the single eGFR value that was available within 180 days before the index date. In addition, we prioritized eGFR values from outpatient visits to calculate the reference eGFR at baseline to avoid extreme eGFR values taken during hospitalization, such as diabetic complications or infections.

3.6 Statistical Analysis

The unadjusted baseline characteristics for two treatment groups were presented with percentages and means with standard deviation (SD) for categorical and continuous covariates, respectively. We performed χ^2 tests for categorical covariates and Jonckheere-Terpstra tests[54, 55] for continuous covariates. To minimize possible confounding and bias due to differences in baseline characteristics, we applied inverse probability treatment weighting (IPTW) using propensity scores to adjust for demographics, comorbidities, CKD stages at baseline, eGFR, and therapeutic categories of antidiabetic medications. The standardized mean differences (SMD) within ±0.25 and the variance ratio (VR) within 0.5-2 were considered good balance.[56, 57]

Crude Kaplan-Meier survival analysis, Cox proportional hazards regression, and an accelerated failure time (AFT) model were used to determine the association of the study endpoints

and the intravitreal anti-VEGF injections or laser photocoagulation. Sub-group analyses including overall mortality and overall hospitalization were performed as well. Considering death as a competing risk for the primary, thromboembolic events of the secondary endpoints, and exploratory endpoints (non-fatal outcomes), we performed the Kaplan-Meier method with censoring for death and cause-specific hazards regression analyses for these study endpoints. p-values for log-rank tests and 95% confidence interval (CI) for hazard ratios were reported. We also compared the median number of intravitreal anti-VEGF injections with interquartile range (IQR) between patients who experienced events of interest and who did not, using χ^2 tests at 3, 6, 12, and 24 months after the index date.

We selected the listed baseline characteristics in **Table 3** in all regression models and assessed the model assumptions and performance. Reference eGFR was also included as a significant time-varying covariate in the Cox regression models for the primary (a new diagnosis of CKD only) and exploratory endpoints. The proportionality assumption for the main treatment variable was met except for the assessment of a new diagnosis of CKD within two years. An accelerated failure time (AFT) model was used instead. The Cox-Snell residual plots with an exponential distribution showed the overall goodness of fit in most regression models **(Appendix C**). However, the overall model adequacy did not perform well in the regression models for a new diagnosis of CKD within two years, thromboembolic events within two years, and a 40% eGFR reduction within one year and two years with the rest of data points deviating from the reference line. No significant interaction among our covariates was identified. In addition, we assessed the number of intravitreal anti-VEGF injections among all study endpoints using Wilcoxon rank-sum tests. $p<0.05$ was considered statistically significant. All statistical analyses were carried out using SAS version 9.4 (SAS Institute Inc, Cary, NC).

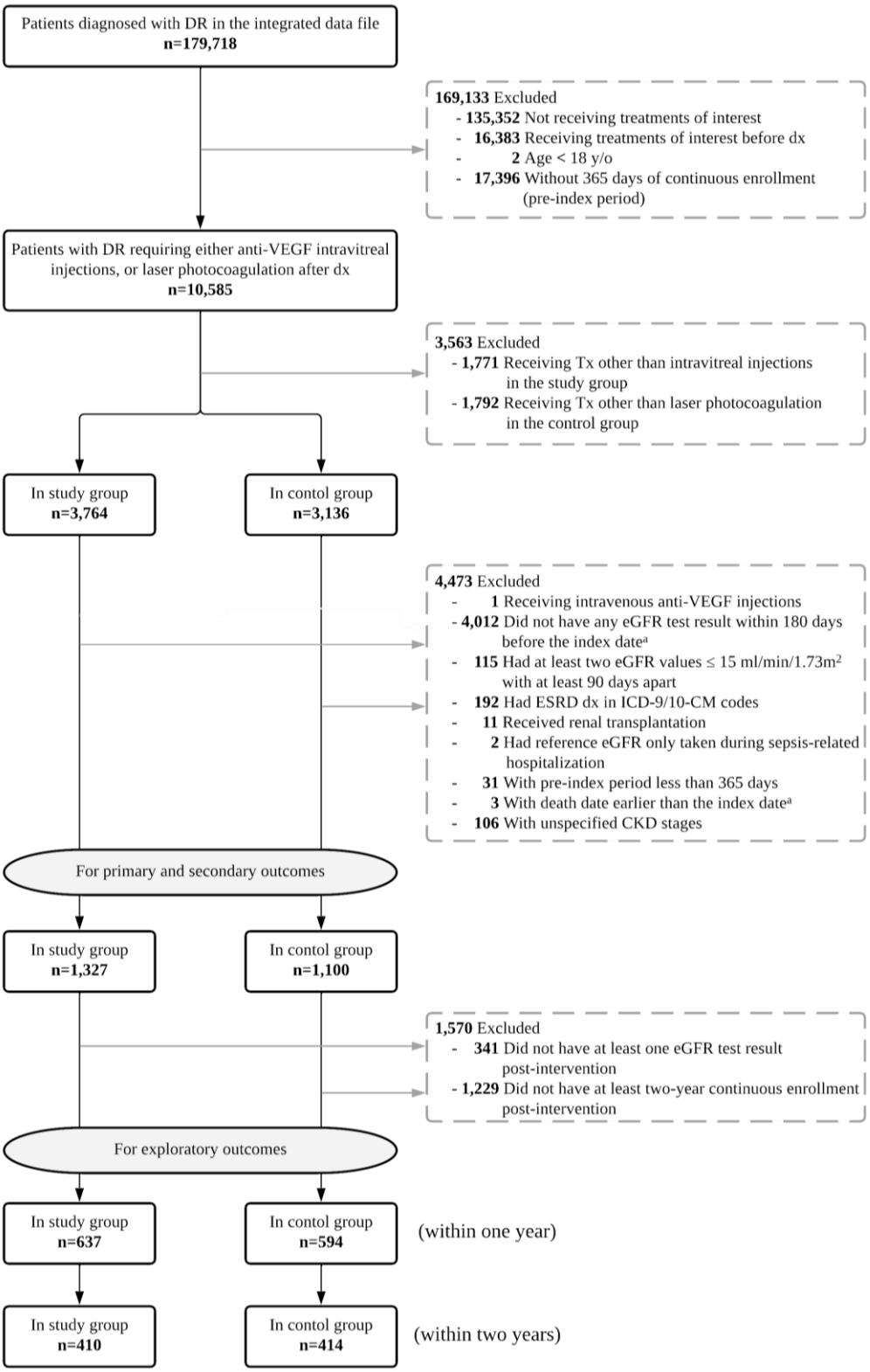
4.0 Results

4.1 Baseline Characteristics

From January 1st, 2011, to December 31st, 2020, a total of 2,427 patients met the enrollment criteria, with 1,327 patients receiving intravitreal anti-VEGF injections (study group) and 1,100 patients receiving laser photocoagulation (control group), shown in **Figure 1**. The median follow-up time was 20.7(±18.60) and 24.5(±21.55) months in the study group and the control group, respectively. Among 1,327 patients in the study group, 84.4% of patients received intravitreal Bevacizumab injection as their first intervention and none of the patients received intravitreal aflibercept injection (**Appendix B Table 6**). Patients in the study group received 5.3(±6.44) intravitreal anti-VEGF injections on average (median=3.0, IQR: 1.0, 7.0). Of 2,427 patients enrolled in the study, there were 1,231 and 824 patients who had available eGFR measurements after the index date for assessments of exploratory endpoints.

Table 3 showed the baseline characteristics of the patients in the study and control group, before and after IPTW adjustment. Before adjustment, patients in the study group were older, likely to have AKI, congestive heart failure (CHF), cardiac arrhythmia, chronic pulmonary disease and had lower eGFR while patients in the control group were likely treated with insulin for diabetes ($p<0.05$). Public health insurance coverage (Medicare/Medicaid) were more prevalent in the study group than the control group. After IPTW adjustment, the mean ages were 65.8 and 65.5 years and the eGFR were 62.1 and 62.6 ml/min/1.73m^2 in the study and the control group, respectively. All covariates were balanced well between the two treatment groups (SMDs: within ±0.25; variance ratios: 0.5-2).

Figure 1 Selection of Patient Cohort, Optum Clinformatics Data Mart 2011-2020



[a]The index date was defined as the first date receiving either intravitreal anti-VEGF injections or laser photocoagulation.

Table 3 Baseline Characteristics of Patients

	Number of Patients		Distribution								
	Study (n=1,327)	Control (n=1,100)	Before IPTW adjustment				After IPTW adjustment				
			Study	Control	P-value	SMD[1]	Study	Control	P-value	SMD[1]	VR[2]
Sex, n (%)					0.4115[3]	0.0335			0.8296[3]	0.0009	1.000
Male	664	532	50.0%	48.4%			49.9%	49.8%			
Female	663	568	50.0%	51.6%			50.1%	50.2%			
Age					<.0001[4]	0.4365			0.0596[4]	0.0243	1.2082
Mean (SD)			68.8 (12.56)	63.3 (12.58)			66.3 (13.42)	66.0 (12.21)			
Median (IQR)			70.0 (61.0, 79.0)	63.0 (55.0, 72.0)			68.0 (59.0, 76.0)	67.0 (59.0, 75.0)			
Race, n (%)					<.0001[3]				<.0001[3]		
Caucasian	925	667	69.7%	60.6%		-0.1912	66.4%	65.7%		-0.0140	0.9905
African American	156	226	11.8%	20.5%		0.2406	15.3%	15.7%		0.0115	0.9781
Asian	19	35	1.4%	3.2%		0.1168	2.1%	2.2%		0.0092	0.9381
Other/Unknown	227	172	17.1%	15.6%		-0.0397	16.3%	16.4%		0.0029	0.9948
Ethnicity, n (%)					<.0001[3]				<.0001[3]		
Non-Hispanic	950	822	71.6%	74.7%		0.0708	73.4%	73.1%		-0.0066	0.9932
Hispanic	136	109	10.2%	9.9%		-0.0113	10.0%	10.5%		0.0178	0.9546
Unknown	241	169	18.2%	15.4%		-0.0750	16.6%	16.4%		-0.0066	1.0120
Region, n (%)					<.0001[3]				<.0001[3]		
Midwest	439	430	33.1%	39.1%		0.1254	36.1%	36.5%		0.0071	0.9960
Northeast	164	247	12.4%	22.5%		0.2687	16.4%	17.0%		0.0162	0.9711
South	481	295	36.2%	26.8%		-0.2040	32.2%	31.3%		-0.0199	1.0156
West	203	88	15.3%	8.0%		-0.2290	12.0%	12.0%		-0.0025	1.0057
Other/Unknown	40	40	3.0%	3.6%		0.0347	3.2%	3.3%		0.0027	0.9856
Insurance Type, n (%)					<.0001[3]				<.0001[3]		
Commercial	536	529	40.4%	48.1%		0.1555	45.0%	45.4%		0.0085	0.9984
Medicaid/Medicare	791	540	59.6%	49.1%		-0.2123	55.0%	53.3%		-0.0345	0.9943
Unknown	0	31	0.0%	2.8%		.	0.0%	1.3%		.	0.0000

	Number of Patients		Distribution								
	Study (n=1,327)	Control (n=1,100)	Before IPTW adjustment				After IPTW adjustment				
			Study	Control	P-value	SMD[1]	Study	Control	P-value	SMD[1]	VR[2]
Index Year, n (%)					<.0001[3]				<.0001[3]		
2011	15	35	1.1%	3.2%		0.1416	2.2%	2.1%		-0.0110	1.0744
2012	78	95	5.9%	8.6%		0.1065	7.5%	7.4%		-0.0070	1.0225
2013	79	109	6.0%	9.9%		0.1468	8.2%	8.1%		-0.0052	1.0157
2014	69	81	5.2%	7.4%		0.0893	6.1%	6.5%		0.0139	0.9515
2015	94	67	7.1%	6.1%		-0.0400	6.7%	6.9%		0.0069	0.9769
2016	100	89	7.5%	8.1%		0.0207	7.9%	7.6%		-0.0086	1.0281
2017	190	166	14.3%	15.1%		0.0218	14.4%	14.3%		-0.0021	1.0043
2018	284	188	21.4%	17.1%		-0.1095	19.3%	19.5%		0.0058	0.9912
2019	231	161	17.4%	14.6%		-0.0756	15.7%	15.6%		-0.0033	1.0062
2020	187	109	14.1%	9.9%		-0.1290	11.8%	12.0%		0.0053	0.9875
COVID-19 Pandemic, n (%)					0.0049[3]	-0.1157			<.0001[3]	0.0019	0.9951
Before	1,160	1001	87.4%	91.0%			89.4%	89.4%			
After	167	99	12.6%	9.0%			10.6%	10.6%			
Reference eGFR					<.0001[4]	-0.2145			0.2946[4]		
Mean (SD)			60.2 (22.22)	65.0 (23.20)			62.2 (22.87)	62.6 (22.40)		-0.0202	1.0425
Median (IQR)			58.0 (45.0, 75.0)	65.0 (50.0, 81.0)			60.5 (47.0, 77.0)	61.0 (46.5, 78.0)			
CKD at baseline, n (%)					0.0012[3]				<.0001[3]		
No CKD	811	760	61.1%	69.1%		0.1679	64.9%	65.1%		0.0042	1.0026
Stage 1	20	18	1.5%	1.6%		0.0104	1.6%	1.8%		0.0146	0.8988
Stage 2	81	56	6.1%	5.1%		-0.0441	5.6%	5.6%		0.0016	0.9940
Stage 3	349	212	26.3%	19.3%		-0.1681	23.2%	22.6%		-0.0135	1.0175
Stage 4	64	53	4.8%	4.8%		-0.0002	4.7%	4.9%		0.0081	0.9658
Stage 5	2	1	0.2%	0.1%		-0.0172	0.1%	0.1%		-0.0078	1.3157
Comorbidities, n (%)											
AKI	212	135	16.0%	12.3%	0.0095[3]	-0.1065	14.3%	13.9%	0.8288[3]	-0.0100	1.0208
Congestive Heart Failure	172	112	13.0%	10.2%	0.0339[3]	-0.0870	12.2%	12.6%	0.6495[3]	0.0113	0.9753
Cardiac Arrhythmia	200	132	15.1%	12.0%	0.0284[3]	-0.0899	13.9%	13.5%	0.8020[3]	-0.0110	1.0235

	Number of Patients		Distribution								
	Study (n=1,327)	Control (n=1,100)	Before IPTW adjustment				After IPTW adjustment				
			Study	Control	P-value	SMD[1]	Study	Control	P-value	SMD[1]	VR[2]
Peripheral Vascular Disorders	131	111	9.9%	10.1%	0.8577[3]	0.0073	10.0%	10.0%	0.9398[3]	-0.0004	1.0011
Hypertension	642	535	48.4%	48.6%	0.8998[3]	0.0051	47.3%	47.6%	0.7221[3]	0.0065	0.9993
Chronic Pulmonary Disease	121	76	9.1%	6.9%	0.0473[3]	-0.0814	8.1%	8.3%	0.8112[3]	0.0048	0.9855
Diabetes Complicated	67	62	5.0%	5.6%	0.5208[3]	0.0261	5.3%	5.4%	0.7645[3]	0.0070	0.9727
Hypothyroidism	90	70	6.8%	6.4%	0.6791[3]	-0.0169	6.4%	6.2%	0.8770[3]	-0.0066	1.0244
Neoplasms	93	84	7.0%	7.6%	0.5536[3]	0.0241	7.3%	7.3%	0.8813[3]	0.0022	0.9928
Fluid and Electrolyte Disorders	78	52	5.9%	4.7%	0.2101[3]	-0.0514	5.0%	4.9%	0.9660[3]	-0.0030	1.0129
Depression	71	62	5.4%	5.6%	0.7580[3]	0.0126	5.4%	5.2%	0.8859[3]	-0.0061	1.0249
Antidiabetic Drugs, n (%)											
Biguanides	462	356	34.8%	32.4%	0.2034[3]	-0.0519	33.2%	33.1%	0.9176[3]	-0.0025	1.0018
DPP-4 Inhibitors	149	124	11.2%	11.3%	0.9725[3]	0.0014	11.2%	11.6%	0.5950[3]	0.0135	0.9680
GLP-1 Agonists	91	103	6.9%	9.4%	0.0234[3]	0.0919	7.4%	7.7%	0.6654[3]	0.0103	0.9662
Insulin	562	535	42.4%	48.6	0.0020[3]	0.1265	44.9%	44.5%	0.9963[3]	-0.0071	1.0015
SGLT-2 Inhibitors	58	49	4.4%	4.5%	0.9203[3]	0.0041	4.0%	4.0%	0.9555[3]	0.0000	1.0000
Sulfonylureas	302	228	22.8%	20.7%	0.2280[3]	-0.0493	22.1%	22.0%	0.9490[3]	-0.0022	1.0030
Follow-up Time (month)					<.0001[4]						
Mean (SD)			20.7 (18.60)	24.5 (21.55)							

[1]SMD: Standardized Mean Difference; [2]VR: Variance Ratio; [3]Chi-Square p-value; [4]Jonckheere–Terpstra p-value
Abbreviations: DPP-4 Inhibitors = Dipeptidyl peptidase-4 inhibitors; GLP-1 Agonists = Glucagon-like peptide-1 receptor agonist; SGLT-2 Inhibitors = Sodium-glucose cotransporter-2 (SGLT-2) inhibitors

4.2 Primary Endpoints

A total of 1,571 patients did not have CKD diagnosis at baseline while 856 patients had CKD diagnosis at baseline for primary endpoints assessment. More than half of patients were censored (new CKD diagnosis: 78.4%; worsening of CKD: 54.8%) and censored patients in the control group had longer follow-up time than in the study group **(Appendix Table 7)**.

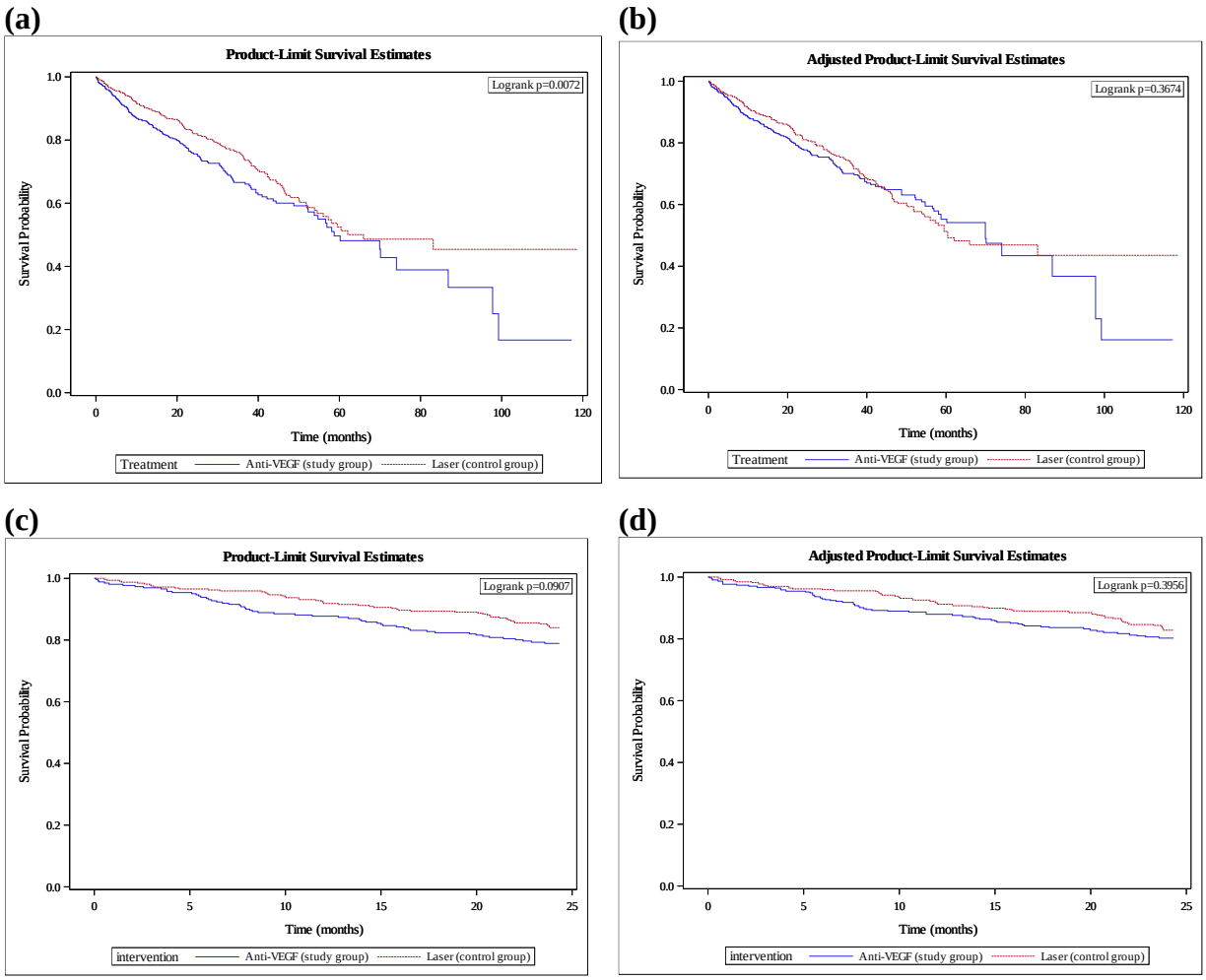
Although patients receiving intravitreal anti-VEGF injections seemed to have a higher risk of developing CKD in the Kaplan-Meier survival analysis (median time to a new CKD diagnosis: 58.1 months vs. 62.07 months; p=0.0072) compared to patients receiving laser photocoagulation **(Figure 2)**, the hazard ratio was not statistically significant (HR=1.16; 95% CI: 0.99, 1.36) after adjustment **(Table 4)**. In addition, patients did not have higher hazards of worsening of pre-existing CKD before and after adjustment (adjusted HR=0.88; 95% CI: 0.71, 1.08) **(Figure 3)**.

In our Cox regression models, females had lower risk while patients with AKI, congestive heart failure, and hypertension had a significantly higher risk of diagnoses of new CKD or worsening of CKD stages. Patients with higher eGFR were less likely to develop new CKD or worsening of CKD. Nonetheless, the possible protective effect of higher eGFR at baseline decreased as time went by in patients who did not have CKD diagnoses at baseline. Although the age effect was not significant in patients without CKD at baseline, we found that older patients with pre-existing CKD had lower risk of CKD deterioration (p=0.03). Among patients with stage 3 or 4 pre-existing CKD, they were more likely diagnosed with worsening CKD stages. Furthermore, our Cox regression models also implied that metformin might have a protective effect on kidneys **(Table 4)**.

With the additional restriction of continuous enrollment post-intervention two years among patients who did not have CKD at baseline (n=580; censored=81.72%), we found that patients

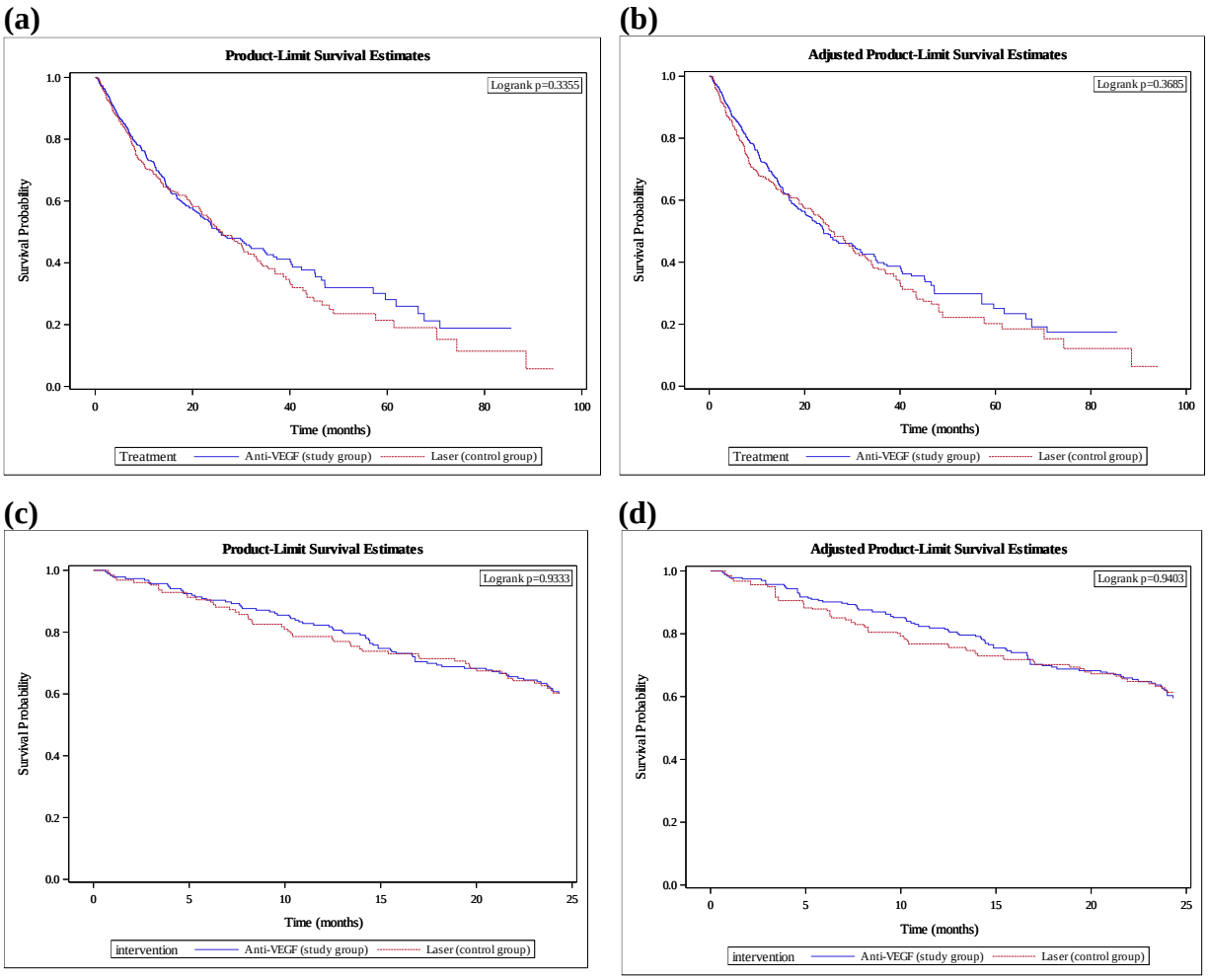
receiving anti-VEGF intravitreal injections had higher hazards in developing CKD than patients receiving laser photocoagulation in the AFT model with an exponential distribution, but the effect was not significant (HR=1.32; 95% CI: 0.98, 1.77) **(Appendix Table 9)**. Patients with new diagnosis of CKD received slightly more injections (median=6.0, IQR: 3.0, 11.0) than patients without new diagnosis of CKD (median=5.0, IQR: 2.0, 9.0) and patients with competing risk of death (median=5.0, IQR: 5.0, 5.0); nevertheless, the p-value was not significant (p=0.40). Likewise, among patients with pre-existing CKD, there were no differences in the risk of worsening of CKD (adjusted HR=0.91; 95% CI: 0.60, 1.38) **(Appendix Table 9)** as well as the number of anti-VEGF intravitreal injections between patients experiencing and not experiencing outcomes of interest. **Figure 4, Figure 5,** and **Appendix Table 8** showed the comparison boxplots and the medians (IQR).

Figure 2 Kaplan-Meier Curves for New Diagnosis of CKD



(a) Unadjusted Kaplan-Meier survival curve for a new diagnosis of CKD (HR=1.16; 95% CI: 0.92, 1.47)
(b) IPTW-adjusted Kaplan-Meier survival curve for new diagnosis of CKD (HR=1.16; 95% CI: 0.99, 1.36)
(c) Unadjusted Kaplan-Meier survival curve for a new diagnosis of CKD within two-year follow-up (HR=1.30; 95% CI: 0.85, 1.99)
(d) IPTW-adjusted Kaplan-Meier survival curve for a new diagnosis of CKD within two-year follow-up (HR=1.32; 95% CI: 0.98, 1.77)

Figure 3 Kaplan-Meier Curves for Worsening of CKD



(a) Unadjusted Kaplan-Meier survival curve for worsening of CKD (HR=0.92; 95% CI: 0.73, 1.16)
(b) IPTW-adjusted Kaplan-Meier survival curve for worsening of CKD (HR=0.88; 95% CI: 0.71, 1.08)
(c) Unadjusted Kaplan-Meier survival curve for worsening of CKD within two-year follow-up (HR=0.85; 95% CI: 0.53, 1.36)
(d) IPTW-adjusted Kaplan-Meier survival curve for worsening of CKD within two-year follow-up (HR=0.91; 95% CI: 0.60, 1.38)

Table 4 Adjusted Cox Proportional Hazards Models for Primary Endpoints

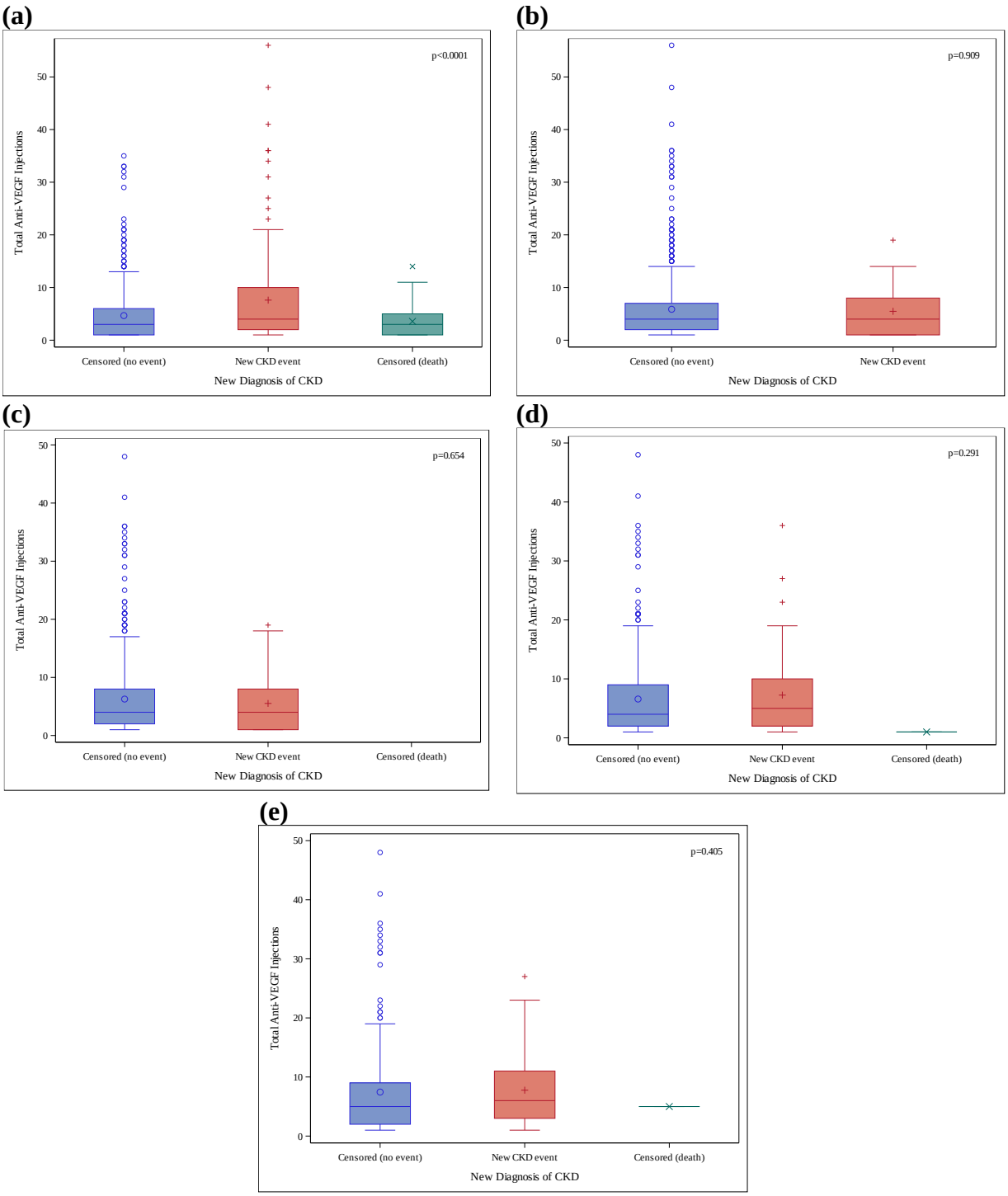
	New Diagnosis of CKD			Worsening of CKD		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Treatment						
Anti-VEGF	1.16	0.99. 1.36	0.07	0.88	0.71, 1.08	0.21
Laser (ref)	-	-	-	-	-	-
Demographic characteristics						
Female	0.52	0.43, 0.61	<0.01*	0.73	0.59, 0.90	<0.01*
Age (every 10 years)	0.94	0.86, 1.02	0.15	0.89	0.79, 0.99	0.03*
Race						
Caucasian (ref)	-	-	-	-	-	-
African American	1.47	1.18, 1.82	<0.01*	1.10	0.81, 1.49	0.53
Asian	1.39	0.85, 2.26	0.19	1.32	0.60, 2.87	0.49
Other/ Unknown	0.92	0.71, 1.21	0.56	0.98	0.71, 1.35	0.89
Ethnicity						
Non-Hispanic (ref)	-	-	-	-	-	-
Hispanic	1.48	1.12, 1.96	<0.01*	1.25	0.88, 1.78	0.21
Unknown	1.00	0.76, 1.32	0.99	0.91	0.65, 1.28	0.59
Region						
Midwest (ref)	-	-	-	-	-	-
Northeast	0.54	0.40, 0.72	<0.01*	0.82	0.56, 1.20	0.31
South	0.89	0.73, 1.09	0.26	1.31	0.99, 1.71	0.05
West	1.12	0.85, 1.47	0.42	1.15	0.81, 1.63	0.45
Other/Unknown	0.54	0.33, 0.87	0.01*	1.24	0.71, 2.15	0.45
Insurance Type						
Commercial (ref)	-	-	-	-	-	-
Medicaid/Medicare	1.49	1.20, 1.84	<0.01*	1.04	0.77, 1.40	0.81
Unknown	2.55	1.03, 6.38	0.04*	1.24	0.38, 4.02	0.72
Renal function						
Stage 1 CKD (ref)	-	-	-	-	-	-
Stage 2 CKD	-	-	-	1.32	0.76, 2.31	0.39

	New Diagnosis of CKD			Worsening of CKD		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Stage 3 CKD	-	-	-	0.53	0.32. 0.89	0.01*
Stage 4 CKD	-	-	-	0.45	0.25, 0.79	<0.01*
Stage 5 CKD	-	-	-	0.33	0.03, 4.36	0.40
eGFR	0.93	0.92, 0.94	<0.01*	0.96	0.95, 0.97	<0.01*
eGFR* log(time)	1.01	1.01, 1.02	<0.01*	-	-	-
Comorbidities						
Acute kidney injury	1.36	1.07, 1.73	0.01*	1.80	1.40, 2.32	<0.01*
Congestive heart failure	1.61	1.26, 2.08	<0.01*	1.49	1.15, 1.94	<0.01*
Cardiac arrhythmia	1.34	1.07, 1.69	0.01*	1.16	0.88, 1.52	0.29
Peripheral vascular disorders	1.04	0.80, 1.35	0.79	1.28	0.94, 1.75	0.11
Hypertension	1.36	1.15, 1.61	<0.01*	1.31	1.06, 1.63	0.01*
Chronic pulmonary disease	1.34	0.99, 1.81	0.05	1.22	0.89, 1.66	0.22
Diabetes complicated	1.95	1.30, 2.92	<0.01*	1.24	0.82, 1.89	0.31
Hypothyroidism	0.54	0.36, 0.81	<0.01*	1.06	0.69, 1.64	0.79
Malignant Neoplasms	1.08	0.77, 1.51	0.67	1.08	0.74, 1.58	0.69
Fluid and Electrolyte Disorders	1.15	0.81, 1.62	0.45	1.51	1.04, 2.18	0.03*
Depression	0.93	0.62, 1.38	0.71	1.19	0.77, 1.82	0.43
Anti-diabetic Drugs						
Biguanides	0.66	0.54, 0.80	<0.01*	0.69	0.52, 0.92	<0.01*
DPP-4 Inhibitors	0.72	0.54, 0.96	0.02*	0.86	0.59, 1.24	0.42
GLP-1 Agonists	1.16	0.82, 1.63	0.40	0.91	0.57, 1.46	0.70
Insulin	1.23	1.03, 1.47	0.02*	1.13	0.90, 1.41	0.30
SGLT-2 Inhibitors	1.33	0.84, 2.10	0.22	0.32	0.12, 0.87	0.02*
Sulfonylureas	1.16	0.93, 1.45	0.18	1.04	0.77, 1.41	0.80

	New Diagnosis of CKD			Worsening of CKD		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Treatment-related information						
Index Year						
2011 (ref)	-	-	-	-	-	-
2012	2.05	1.16, 3.64	0.01*	1.14	0.49, 2.69	0.76
2013	1.80	1.03, 3.14	0.04*	1.25	0.54, 2.91	0.60
2014	2.07	1.15, 3.71	0.01*	1.21	0.53, 2.78	0.65
2015	3.06	1.78, 5.26	<0.01*	1.34	0.57, 3.13	0.50
2016	3.13	1.77, 5.51	<0.01*	1.34	0.59, 3.05	0.48
2017	2.41	1.40, 4.14	<0.01*	1.56	0.70, 3.45	0.28
2018	2.14	1.22, 3.75	<0.01*	1.76	0.81, 3.83	0.16
2019	1.88	1.01, 3.50	0.04*	1.38	0.62, 3.10	0.43
2020	4.56	1.55, 13.46	<0.01*	1.30	0.39, 4.31	0.68
COVID-19	0.66	0.23, 1.91	0.44	0.86	0.30, 2.48	0.77

*indicated statistical significance ($p<0.05$)

Figure 4 Total Anti-VEGF Injections by New Diagnosis of CKD Events



(a) Comparison of total anti-VEGF intravitreal injections by overall new diagnosis of CKD events; the medians (IQR) for each group: censored (median=3, IQR: 1, 6), a new diagnosis of CKD (median=4, IQR: 2, 10), death as the competing event (median=3, IQR: 1, 5); p<0.0001

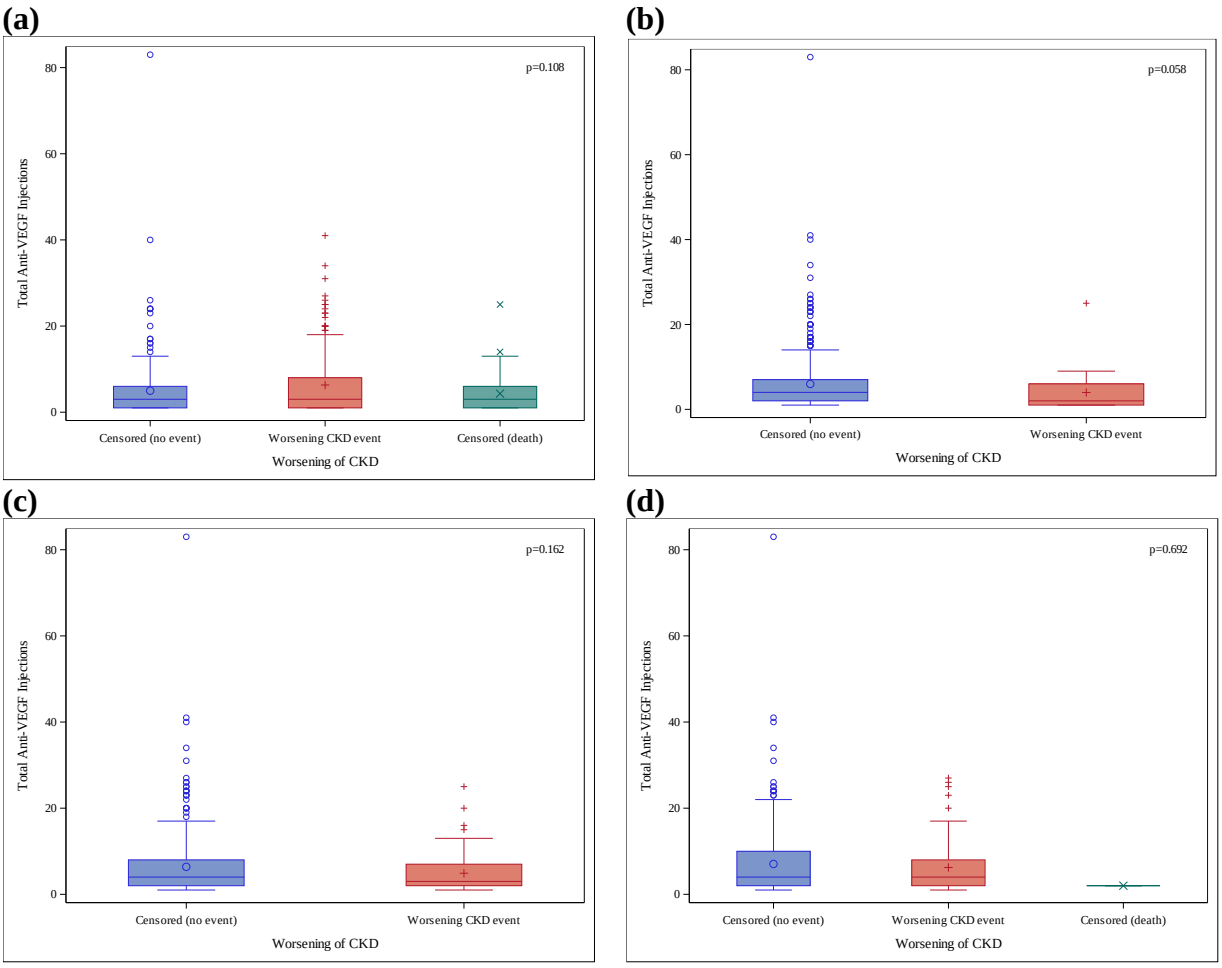
(b) Comparison of total anti-VEGF intravitreal injections by new CKD events within three months; the medians (IQR) for each group: censored (median=4, IQR: 2, 7), a new diagnosis of CKD (median=4, IQR: 1, 8), no death as the competing event; p=0.909

(c) Comparison of total anti-VEGF intravitreal injections by new CKD events within six months; the medians (IQR) for each group: censored (median=4, IQR: 2, 8), a new diagnosis of CKD (median=4, IQR: 1, 8), death as the competing event (median=1, IQR: 1, 1); p=0.654

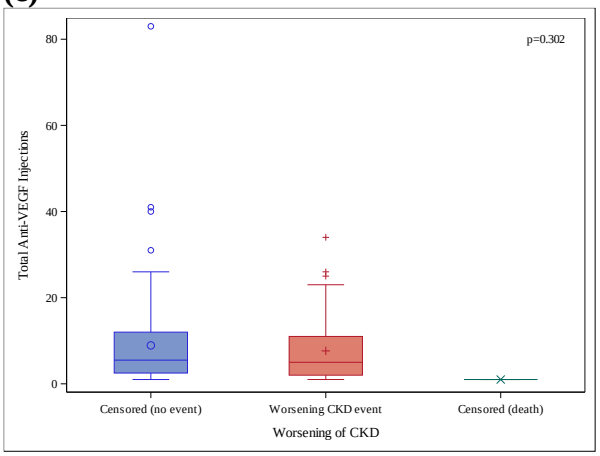
(d) Comparison of total anti-VEGF intravitreal injections by new CKD events within one year; the medians (IQR) for each group: censored (median=4, IQR: 2, 9), a new diagnosis of CKD (median=5, IQR: 2, 10), death as the competing event (median=1, IQR: 1, 1); p=0.291

(e) Comparison of total anti-VEGF intravitreal injections by new CKD events within two years; the medians (IQR) for each group: censored (median=5, IQR: 2, 9), a new diagnosis of CKD (median=6, IQR: 3, 11), death, competing event (median=5, IQR: 15, 5); p=0.405

Figure 5 Total Anti-VEGF Injections by Worsening Diagnosis of CKD Events



(e)



(a) Comparison of total anti-VEGF intravitreal injections by overall worsening CKD events; the medians (IQR) for each group: censored (median=3, IQR: 1, 6), worsening of CKD (median=3, IQR: 1, 8), death as the competing event (median=3, IQR: 1, 6); p=0.108

(b) Comparison of total anti-VEGF intravitreal injections by worsening CKD events within three months; the medians (IQR) for each group: censored (median=4, IQR: 2, 7), worsening of CKD (median=2, IQR: 1, 6), no death as the competing event; p=0.058

(c) Comparison of total anti-VEGF intravitreal injections by worsening CKD events within six months; the medians (IQR) for each group: censored (median=4, IQR: 2, 8), worsening of CKD (median=3, IQR: 2, 7), no death as the competing event; p=0.162

(d) Comparison of total anti-VEGF intravitreal injections by worsening CKD events within one year; the medians (IQR) for each group: censored (median=4, IQR: 2, 10), a new diagnosis of CKD (median=4, IQR: 2, 8), death as the competing event (median=2, IQR: 2, 2); p=0.692

(e) Comparison of total anti-VEGF intravitreal injections by worsening CKD events within two years; the medians (IQR) for each group: censored (median=5.5, IQR: 2.5, 12.0), worsening of CKD (median=5, IQR: 2, 11), death, competing event (median=1, IQR: 1, 1); p=0.302

4.4 Secondary Endpoints

A total of 2,427 patients were evaluated for secondary endpoints, including a composite endpoint (overall hospitalization or death), thromboembolic events, and sub-group analyses of the composite endpoint. 52.6% and 93.7% of patients were censored in the analysis of a composite endpoint and thromboembolic events, respectively. Similar to the primary endpoints, patients in the control group had a longer follow-up time than in the study group **(Appendix Table 7)**.

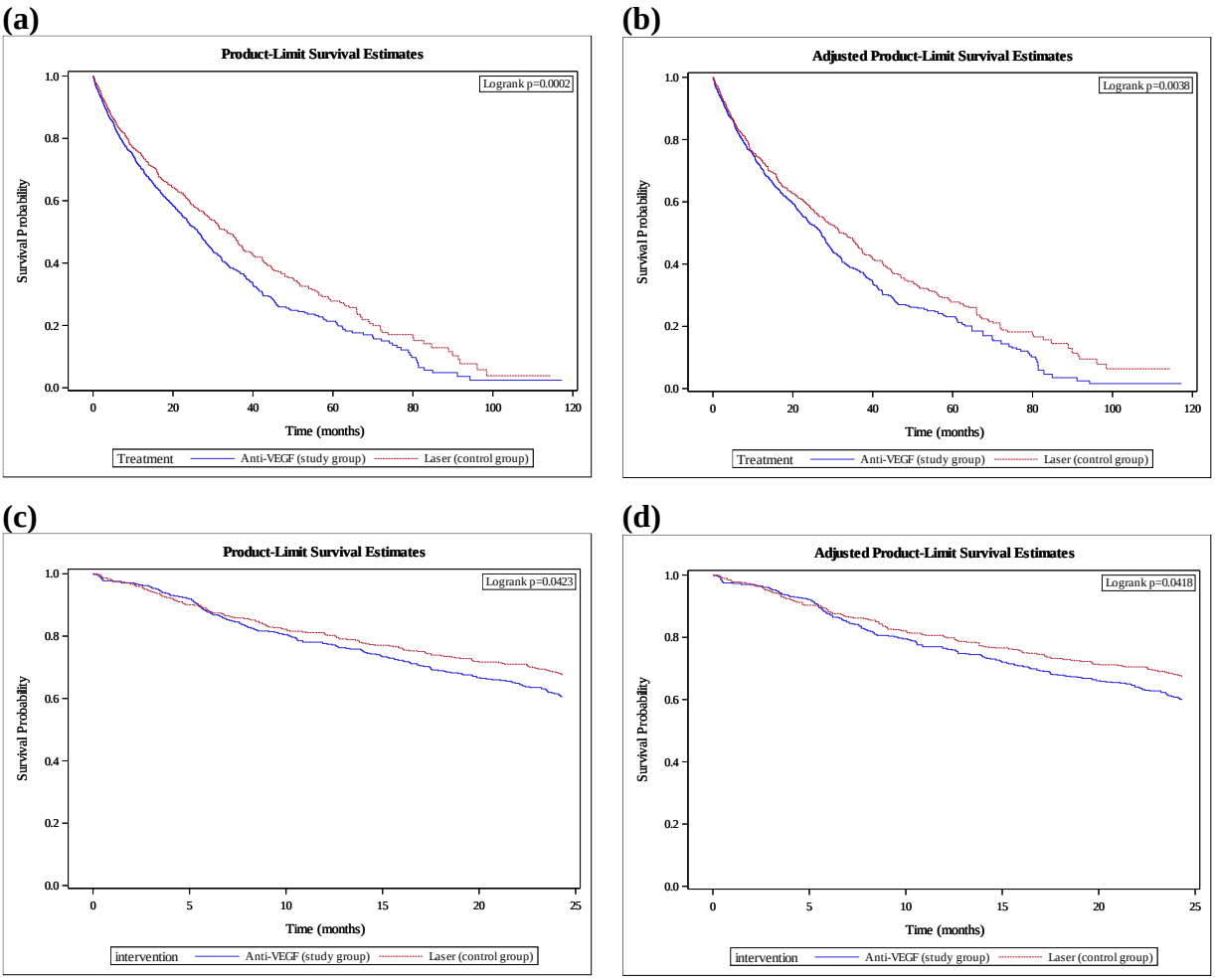
4.4.1 A Composite Endpoint – Overall Hospitalization or Death

Overall, patients receiving intravitreal anti-VEGF injections had a higher risk of hospitalization or death compared to patients receiving laser photocoagulation **(Figure 6)**. After adjustment, the median time to the hospitalization/death in the study group and the control group were 26.93 months and 31.6 months, respectively. The adjusted Cox PH regression model showed that patients in the study group had 1.18 higher hazards (95% CI: 1.05, 1.33) of experiencing hospitalization or death than patients in the control group **(Table 5)**. In addition, non-Hispanic patients and those with AKI, congestive heart failure, cardiac arrhythmia, peripheral vascular disease, hypertension, and depression had a higher risk of all-cause hospitalization and death. Patients with higher eGFR might have better overall outcomes; nevertheless, this effect was not statistically significant.

Patients experiencing the event of interest also received more anti-VEGF intravitreal injections (median=3, IQR: 1, 7) than patients without experiencing the event of interest (median=3, IQR: 1, 6; p=0.009) in the study group. However, there were no differences in the risk of hospitalization or death within two years after the start of the treatments (adjusted HR=1.20;

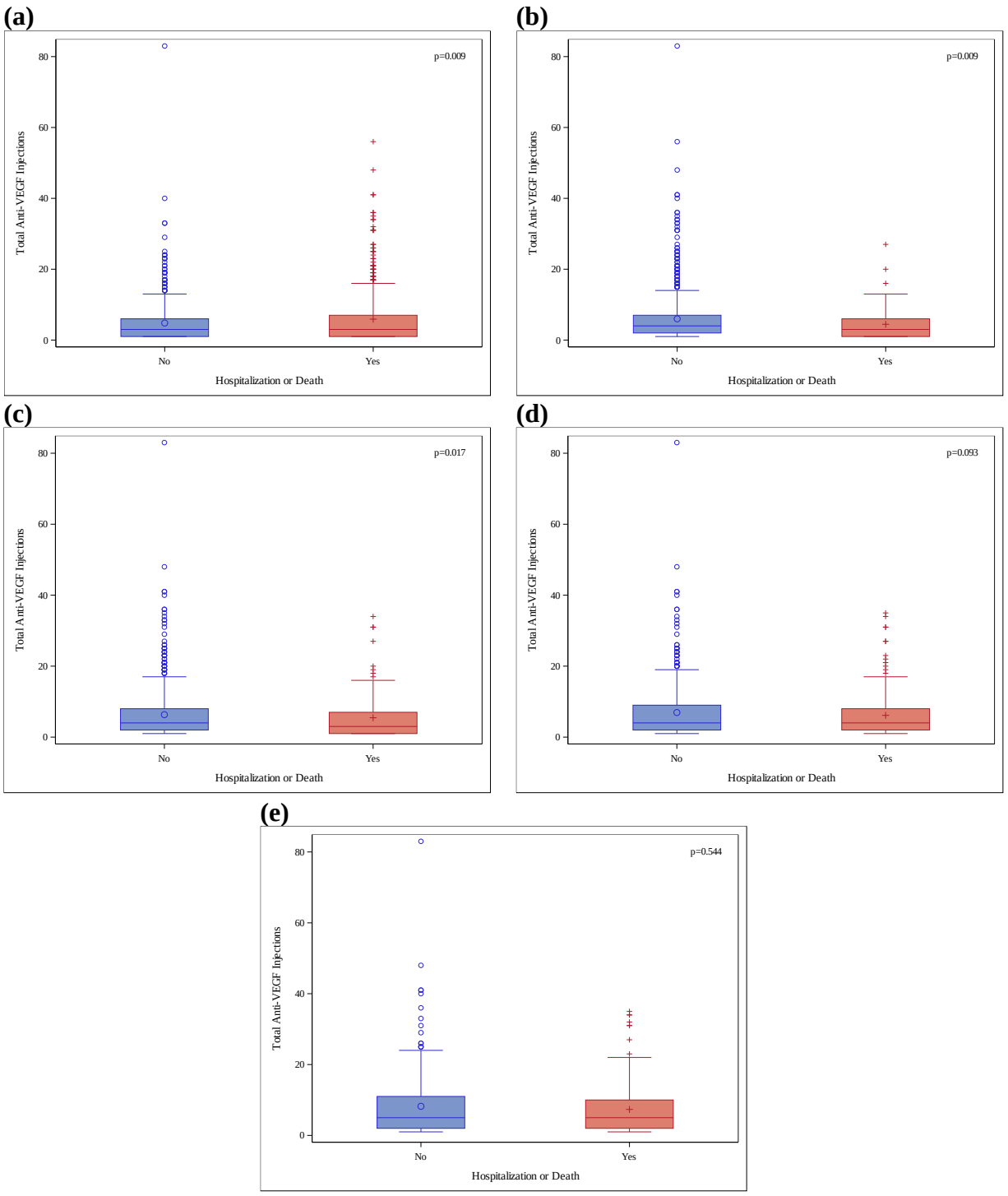
95% CI: 0.95, 1.51) **(Appendix Table 10)**. No difference in the numbers of anti-VEGF intravitreal injections within two years was identified (hospitalization or death: median=5, IQR: 2, 10 vs. censored: median=5, IQR: 2, 11; p=0.54). **Figure 7** and **Appendix Table 8** showed the comparison boxplots and the medians (IQR).

Figure 6 Kaplan-Meier Curves for Overall Hospitalization or Death



(a) Unadjusted Kaplan-Meier survival curve for overall hospitalization or death (HR=1.18; 95% CI: 1.04, 1.34)
(b) IPTW-adjusted Kaplan-Meier survival curve for overall hospitalization or death (HR=1.18; 95% CI: 1.05, 1.33)
(c) Unadjusted Kaplan-Meier survival curve for overall hospitalization or death within two-year follow-up (HR=1.17; 95% CI: 0.91, 1.50)
(d) IPTW-adjusted Kaplan-Meier survival curve for overall hospitalization or death within two-year follow-up (HR=1.20; 95% CI: 0.95, 1.51)

Figure 7 Total Anti-VEGF Injections by A Composite Endpoint



(a) Comparison of total anti-VEGF intravitreal injections by overall hospitalization or death; the medians (IQR) for each group: censored (median=3, IQR: 1, 6), hospitalization or death (median=3, IQR: 1, 7); p=0.009

(b) Comparison of total anti-VEGF intravitreal injections by hospitalization or death within three months; the medians (IQR) for each group: censored (median=4, IQR: 2, 7), hospitalization or death (median=3, IQR: 1, 6); p=0.009

(c) Comparison of total anti-VEGF intravitreal injections by hospitalization or death within six months; the medians (IQR) for each group: censored (median=4, IQR: 2, 8), hospitalization or death (median=3, IQR: 1, 7); p=0.017
(d) Comparison of total anti-VEGF intravitreal injections by hospitalization or death within one year; the medians (IQR) for each group: censored (median=4, IQR: 2, 9), hospitalization or death (median=4, IQR: 2, 8); p=0.093
(e) Comparison of total anti-VEGF intravitreal injections by hospitalization or death within two years; the medians (IQR) for each group: censored (median=5, IQR: 2, 11), hospitalization or death (median=5, IQR: 2, 10); p=0.544

4.4.2 Sub-group Analysis of a Composite Endpoint

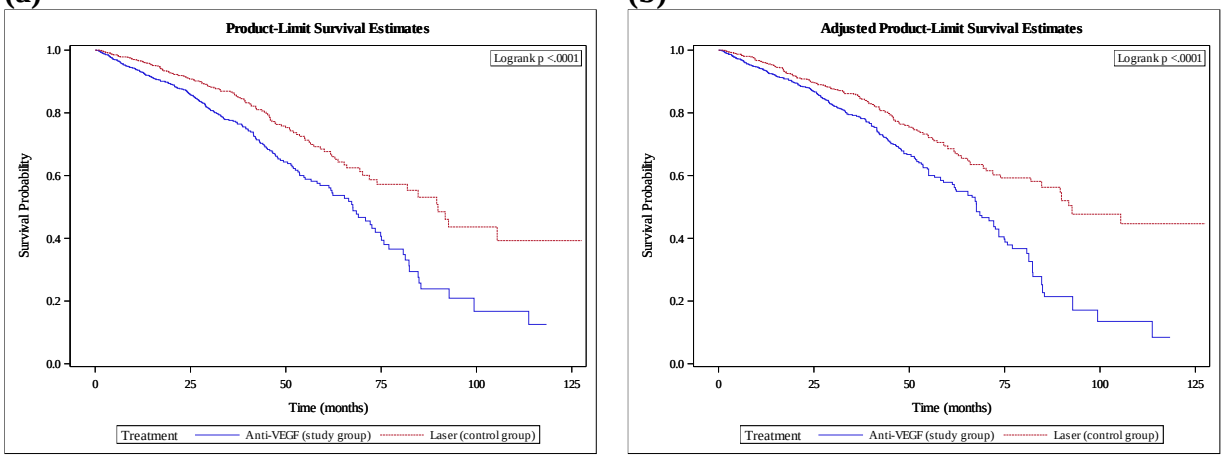
We conducted subgroup analyses for overall death and overall hospitalization. 84.1% of patients and 55.67% of patients were censored in the analyses of overall death and overall hospitalization, respectively. Similar to the analysis of a composite endpoint, we also assessed the outcomes of death and hospitalization within a two-year follow-up. However, we did not assess the association between the total anti-VEGF intravitreal injections and death in the study group due to the very few cases of death **(Appendix Table 8)**.

4.4.2.1 Sub-group Analysis: Overall Death

In the sub-group analysis of overall death, patients in the study group had a 1.36 (95%CI: 1.10, 1.68) higher risk of death than patients in the control group after adjustment. The median time to death in the study group and the control group were 67.57 months and 89.90 months after adjustment, respectively (p<0.0001) **(Figure 8)**. Overall death within two years after the index date was not reported as only 5 deaths occurred among 892 patients who had at least two-year continuous enrollment post-intervention (study group: 3 patients; control group: 2 patients).

Figure 8 Kaplan-Meier Curves for Overall Death

(a) **(b)**



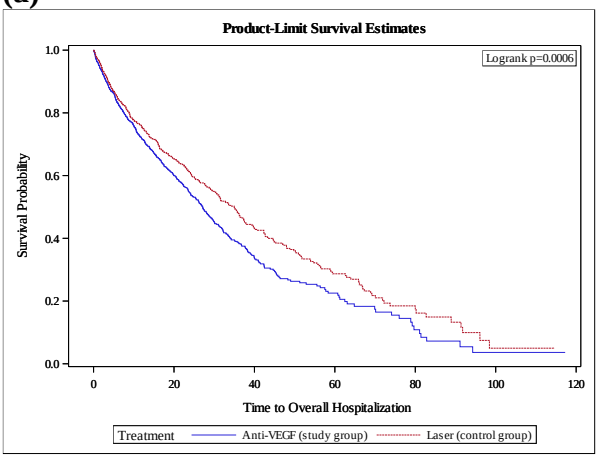
(a) Unadjusted Kaplan-Meier survival curve for overall death (HR=1.32; 95% CI: 1.05, 1.64)
(b) IPTW-adjusted Kaplan-Meier survival curve for overall death (HR=1.36; 95% CI: 1.10, 1.68)

4.4.2.2 Sub-group Analysis: Overall Hospitalization

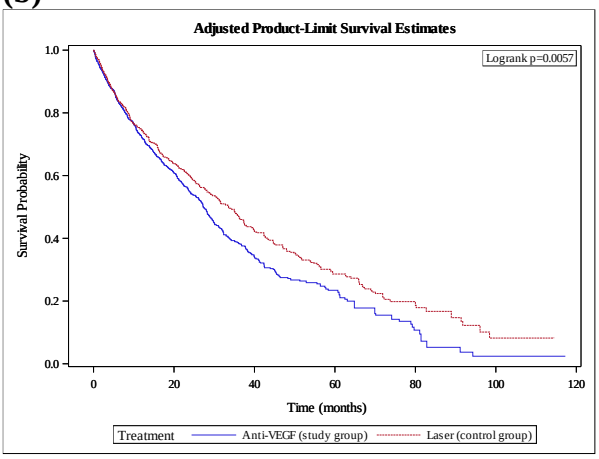
In the sub-group analysis of overall hospitalization, patients in the study group had a 1.18 (95% CI: 1.05, 1.33) a higher risk of experiencing hospitalization than patients in the control group after adjustment. The median time to hospitalization in the study group and the control group was 27.20 months and 33.37 months after adjustment, respectively (p=0.006) **(Figure 9)**. However, with restriction to continuous enrollment for two years to assess the risk of hospitalization within two years after the index date, patients in the study group did not have a significantly higher risk compared to patients in the control group (adjusted HR=1.17; 95% CI: 0.97, 1.41) **(Figure 9)** **(Appendix Table 10)**. No difference in the numbers of anti-VEGF intravitreal injections within two years was identified (hospitalization: median=5, IQR: 2, 10 vs. censored: median=5, IQR: 2, 11; p=0.54) **(Figure 10)**.

Figure 9 Kaplan-Meier Curves for Overall Hospitalization

(a)



(b)



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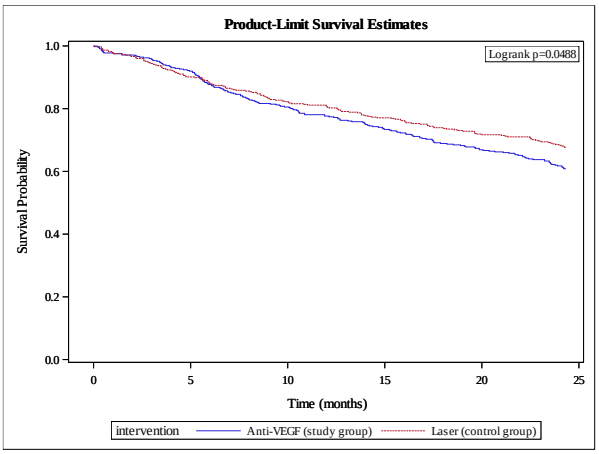
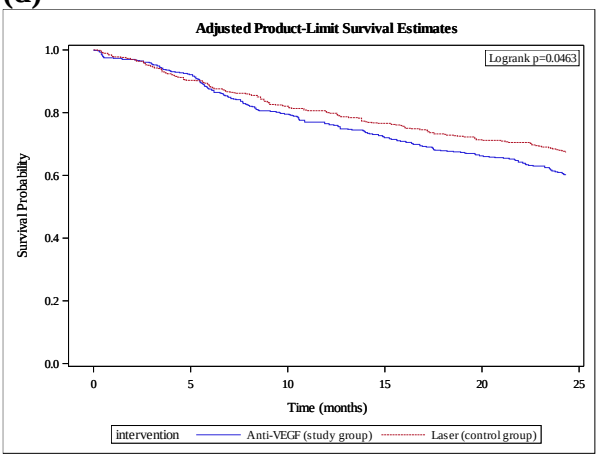


(d)



(a) Unadjusted Kaplan-Meier survival curve for overall hospitalization (HR=1.18; 95% CI: 1.03, 1.34)
(b) IPTW-adjusted Kaplan-Meier survival curve for overall hospitalization (HR=1.18; 95% CI: 1.05, 1.33)
(c) Unadjusted Kaplan-Meier survival curve for overall hospitalization within two-year follow-up (HR=1.16; 95% CI: 0.90, 1.50)
(d) IPTW-adjusted Kaplan-Meier survival curve for overall hospitalization or death within two-year follow-up (HR=1.17; 95% CI: 0.97, 1.41)

Table 5 Adjusted Cox Proportional Hazards Models for a Composite Endpoints and Its Sub-group Analyses

	Composite Endpoint (Overall Hospitalization or Death)			Overall Death			Overall Hospitalization		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Treatment									
Anti-VEGF	1.18	1.05, 1.33	<0.01*	1.36	1.10, 1.68	<0.01*	1.18	1.05, 1.33	<0.01*
Laser (ref)	-	-	-	-	-	-	-	-	-
Demographic characteristics									
Female	0.96	0.85, 1.09	0.54	0.83	0.66, 1.03	0.10	0.98	0.86, 1.12	0.77
Age (every 10 years)	1.00	0.94, 1.06	0.99	1.35	1.20, 1.52	<0.01*	0.99	0.93, 1.06	0.73
Race									
Caucasian (ref)	-	-	-	-	-	-	-	-	-
African American	1.09	0.92, 1.28	0.33	0.80	0.58, 1.10	0.18	1.12	0.94, 1.32	0.20
Asian	0.96	0.62, 1.47	0.85	1.86	0.93, 3.71	0.08	0.92	0.59, 1.45	0.72
Other/ Unknown	1.20	0.98, 1.46	0.07	0.89	0.61, 1.30	0.54	1.20	0.98, 1.46	0.08
Ethnicity									
Non-Hispanic (ref)	-	-	-	-	-	-	-	-	-
Hispanic	0.75	0.60, 0.94	0.01*	0.53	0.34, 0.85	<0.01*	0.75	0.59, 0.94	0.01*
Unknown	0.80	0.66, 0.98	0.03*	0.94	0.65, 1.36	0.75	0.81	0.66, 0.99	0.04*
Region									
Midwest (ref)	-	-	-	-	-	-	-	-	-
Northeast	0.99	0.82, 1.18	0.89	1.14	0.84, 1.54	0.40	1.05	0.87, 1.27	0.60
South	0.92	0.79, 1.07	0.28	1.00	0.77, 1.32	0.97	0.95	0.82, 1.11	0.54
West	0.78	0.63, 0.96	0.02*	0.55	0.37, 0.82	<0.01*	0.81	0.65, 1.01	0.06
Other/Unknown	0.97	0.72, 1.32	0.86	0.99	0.57, 1.69	0.96	1.01	0.73, 1.40	0.94
Insurance Type									
Commercial (ref)	-	-	-	-	-	-	-	-	-
Medicaid/Medicare	1.16	0.99, 1.36	0.06	0.98	0.74, 1.30	0.88	1.11	0.94, 1.30	0.23
Unknown	1.05	0.45, 2.46	0.90	0.42	0.03, 6.73	0.54	1.08	0.46, 2.51	0.87
Renal function									
No CKD (ref)	-	-	-	-	-	-	-	-	-
Stage 1 CKD	1.14	0.73, 1.80	0.57	0.74	0.30, 1.86	0.53	1.18	0.75, 1.86	0.47

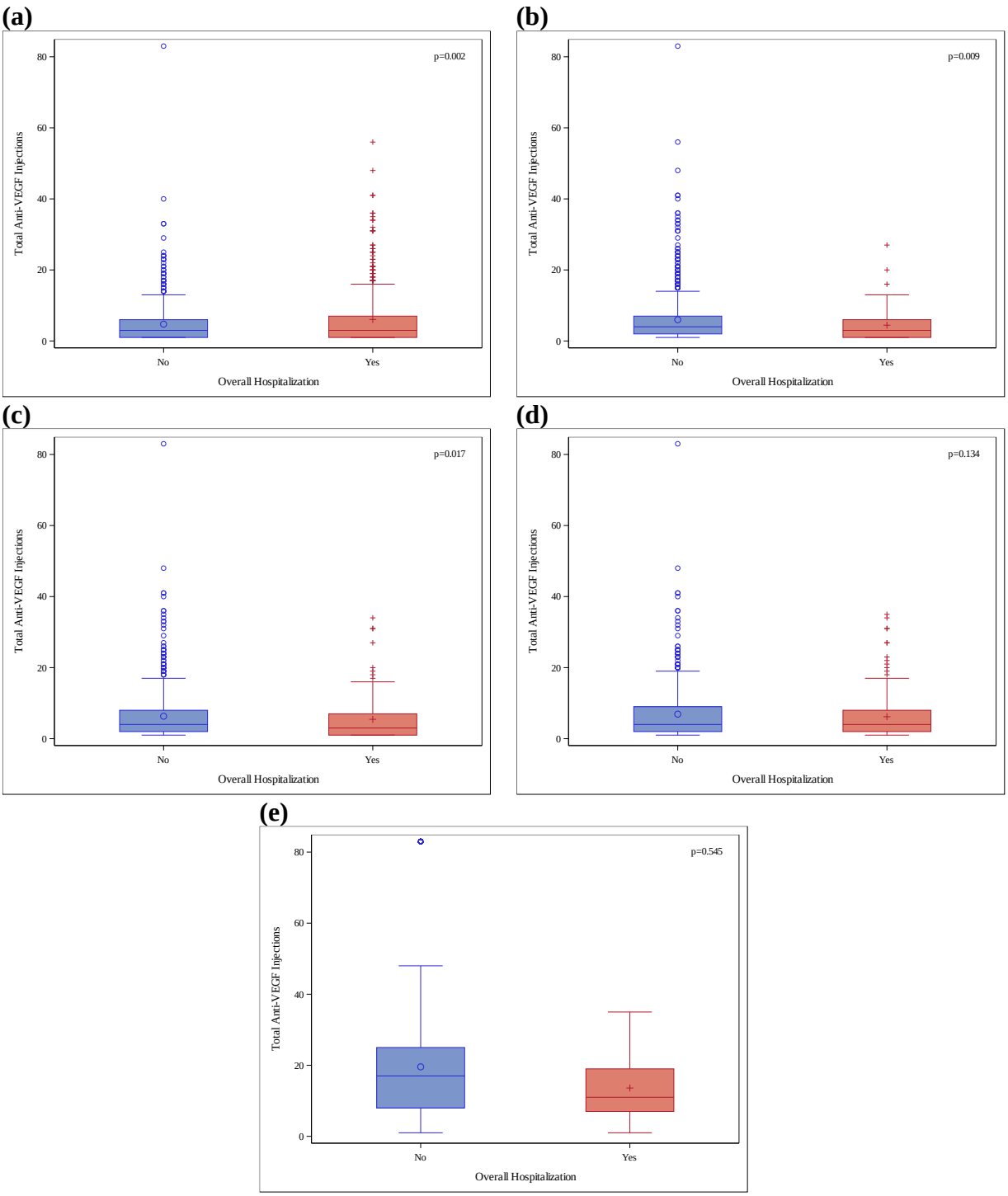
	Composite Endpoint (Overall Hospitalization or Death)			Overall Death			Overall Hospitalization		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Stage 2 CKD	1.00	0.76, 1.30	0.98	1.03	0.62, 1.71	0.90	0.95	0.71, 1.25	0.70
Stage 3 CKD	1.01	0.86, 1.20	0.89	0.99	0.75, 1.31	0.94	1.03	0.86, 1.22	0.77
Stage 4 CKD	1.53	1.16, 2.00	<0.01*	1.47	0.95, 2.27	0.09	1.53	1.15, 2.02	<0.01
Stage 5 CKD	0.42	0.04, 5.08	0.50	2.17	0.17, 27.83	0.55	0.41	0.03, 4.92	0.48
eGFR	0.99	0.99, 1.00	0.03$^{\phi}$	1.00	0.99, 1.01	0.59	0.99	0.99, 0.99	0.02*
Comorbidities									
Acute kidney injury	1.47	1.25, 1.74	<0.01*	1.85	1.39, 2.44	<0.01*	1.47	1.24, 1.75	<0.01*
Congestive heart failure	1.88	1.59, 2.23	<0.01*	2.12	1.62, 2.78	<0.01*	1.95	1.64, 2.32	<0.01*
Cardiac arrhythmia	1.35	1.15, 1.59	<0.01*	1.54	1.19, 1.99	<0.01*	1.34	1.13, 1.59	<0.01*
Peripheral vascular disorders	1.39	1.16, 1.66	<0.01*	1.34	1.00, 1.79	0.04*	1.42	1.18, 1.71	<0.01*
Hypertension	1.26	1.12, 1.43	<0.01*	1.26	1.01, 1.57	0.04*	1.25	1.10, 1.41	<0.01*
Chronic pulmonary disease	1.46	1.21, 1.77	<0.01*	1.11	0.80, 1.55	0.53	1.46	1.20, 1.78	<0.01
Diabetes complicated	1.27	0.96, 1.67	0.09	0.71	0.35, 1.45	0.34	1.31	0.99, 1.73	0.06
Hypothyroidism	1.24	0.98, 1.56	0.07	1.04	0.69, 1.56	0.86	1.22	0.96, 1.56	0.11
Malignant Neoplasms	1.14	0.92, 1.41	0.24	1.42	1.01, 2.01	0.04*	1.16	0.93, 1.44	0.18
Fluid and Electrolyte Disorders	1.03	0.80, 1.32	0.82	0.98	0.65, 1.47	0.93	1.03	0.80, 1.34	0.81
Depression	1.43	1.11, 1.83	0.01*	1.07	0.67, 1.71	0.78	1.37	1.06, 1.76	0.02*
Anti-diabetic Drugs									
Biguanides	0.92	0.79, 1.06	0.24	0.66	0.50, 0.87	<0.01*	0.90	0.77, 1.04	0.15
DPP-4 Inhibitors	0.82	0.67, 1.00	0.05	0.86	0.61, 1.22	0.39	0.89	0.72, 1.09	0.25
GLP-1 Agonists	0.85	0.65, 1.10	0.22	0.65	0.34, 1.25	0.20	0.85	0.65, 1.12	0.26
Insulin	1.21	1.06, 1.37	<0.01*	1.16	0.92, 1.45	0.21	1.25	1.10, 1.43	<0.01*
SGLT-2 Inhibitors	0.65	0.43, 0.98	0.04*	1.36	0.65, 2.84	0.42	0.65	0.42, 0.99	0.04*
Sulfonylureas	1.16	0.99, 1.36	0.07	1.29	0.98, 1.70	0.07	1.19	1.01, 1.40	0.04*

	Composite Endpoint (Overall Hospitalization or Death)			Overall Death			Overall Hospitalization		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Treatment-related information									
Index Year									
2011 (ref)	-	-	-	-	-	-	-	-	-
2012	0.69	0.48, 1.01	0.06	1.04	0.61, 1.77	0.90	0.74	0.50, 1.10	0.13
2013	0.66	0.45, 0.95	0.03*	0.87	0.50, 1.49	0.60	0.71	0.48, 1.05	0.08
2014	0.68	0.47, 1.00	0.05	0.90	0.52, 1.56	0.70	0.75	0.50, 1.11	0.15
2015	0.73	0.50, 1.07	0.10	0.74	0.42, 1.32	0.31	0.78	0.53, 1.15	0.21
2016	0.81	0.56, 1.19	0.28	0.71	0.39, 1.29	0.26	0.84	0.57, 1.25	0.39
2017	0.73	0.51, 1.04	0.09	0.79	0.46, 1.38	0.41	0.78	0.54, 1.13	0.19
2018	0.80	0.56, 1.13	0.21	0.83	0.47, 1.47	0.52	0.81	0.56, 1.18	0.28
2019	0.72	0.49, 1.05	0.06	0.74	0.38, 1.42	0.36	0.71	0.48, 1.05	0.08
2020	0.43	0.18, 1.05	0.06	0.70	0.12, 4.05	0.69	0.46	0.19, 1.12	0.08
COVID-19	1.81	0.75, 4.35	0.18	0.89	0.13, 6.04	0.91	1.78	0.74, 4.29	0.20

*indicated statistical significance ($p<0.05$)

ϕindicated statistical non-significance because the 95% CI included 1.00.

Figure 10 Total Anti-VEGF Injections by Hospitalization



(a) Comparison of total anti-VEGF intravitreal injections by overall hospitalization; the medians (IQR) for each group: censored (median=3, IQR: 1, 6), hospitalization (median=3, IQR: 1, 7); p=0.002

(b) Comparison of total anti-VEGF intravitreal injections by overall hospitalization within three months; the medians (IQR) for each group: censored (median=4, IQR: 2, 7), hospitalization (median=3, IQR: 1, 6); p=0.009

(c) Comparison of total anti-VEGF intravitreal injections by overall hospitalization within six months; the medians (IQR) for each group: censored (median=4, IQR: 2, 8), hospitalization (median=3, IQR: 1, 7); p=0.017
(d) Comparison of total anti-VEGF intravitreal injections by overall hospitalization within one year; the medians (IQR) for each group: censored (median=4, IQR: 2, 9), hospitalization (median=4, IQR: 2, 8); p=0.134
(e) Comparison of total anti-VEGF intravitreal injections by overall hospitalization within two years; the medians (IQR) for each group: censored (median=5, IQR: 2, 11), hospitalization (median=5, IQR: 2, 10); p=0.545

4.4.3 Thromboembolic Events

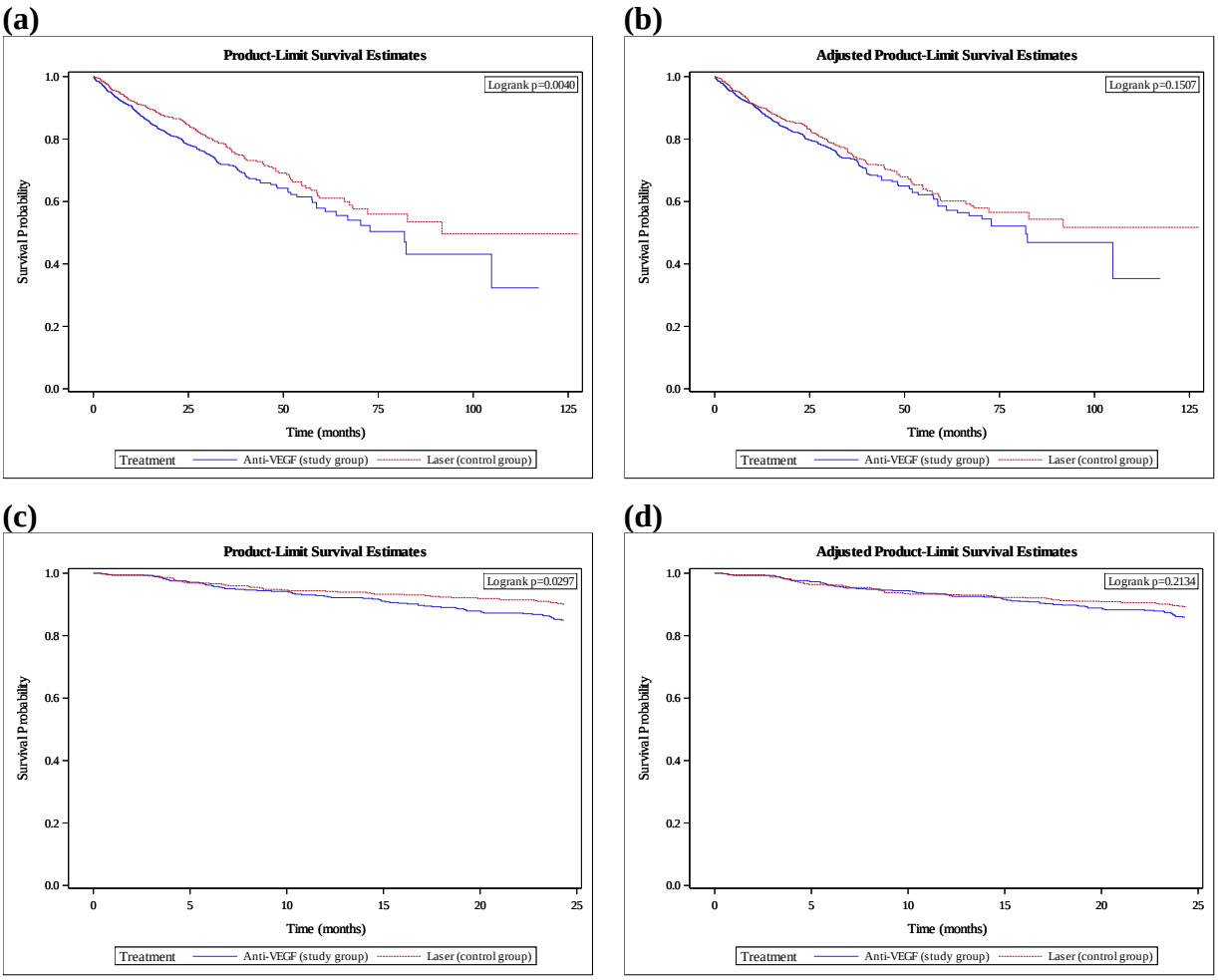
Overall, patients receiving intravitreal anti-VEGF injections did not have a higher risk of thromboembolic events compared to patients receiving laser photocoagulation **(Figure 11)**. 453 patients experienced thromboembolic events among 2,427 patients in our study cohort (study group: 259; control group: 194). Although the Kaplan Meier curve showed that patients in the study group had higher risk of thromboembolic events, they did not have higher hazards than patients in the control group after adjustment (HR=1.11; 95% CI: 0.97, 1.27) **(Table 6)**.

During a two-year follow-up period with the continuous insurance coverage (n=892), 112 (12.56%) patients experienced the event of interest (study group: 67; control group: 45). There was still no difference in the risk of thromboembolic events between the study group and the control group in the adjusted Cox proportional regression model (HR=1.20; 95% CI: 0.90, 1.59) **(Table 6)**. Patients with medical history of acute kidney injury or with pre-existing peripheral vascular diseases in the study group had increased risk of thromboembolic events. In addition, patients with depression might also have higher risk of thromboembolic events; nonetheless, the effect was around the boundary in the Cox regression model with a two-year follow-up.

Among patients with restriction to continuous enrollment for two years, patients in the study group who experienced the events did not received more intravitreal anti-VEGF injections

(median=4, IQR: 2, 9) than patients who were censored, either without experiencing the event (median=5, IQR: 2, 11) or who died (median=5, IQR: 1, 13) in a two-year follow-up period (p=0.380) **(Figure 12)**.

Figure 11 Kaplan-Meier Curves for Thromboembolic Events



(a) Unadjusted Kaplan-Meier survival curve for thromboembolic events (HR=1.15; 95% CI: 0.94, 1.41)
(b) IPTW-adjusted Kaplan-Meier survival curve for overall hospitalization (HR=1.11 95% CI: 0.97, 1.27)
(c) Unadjusted Kaplan-Meier survival curve for overall hospitalization within two-year follow-up (HR=1.30; 95% CI: 0.60, 2.83)
(d) IPTW-adjusted Kaplan-Meier survival curve for overall hospitalization or death within two-year follow-up (HR=1.20; 95% CI: 0.90, 1.59)

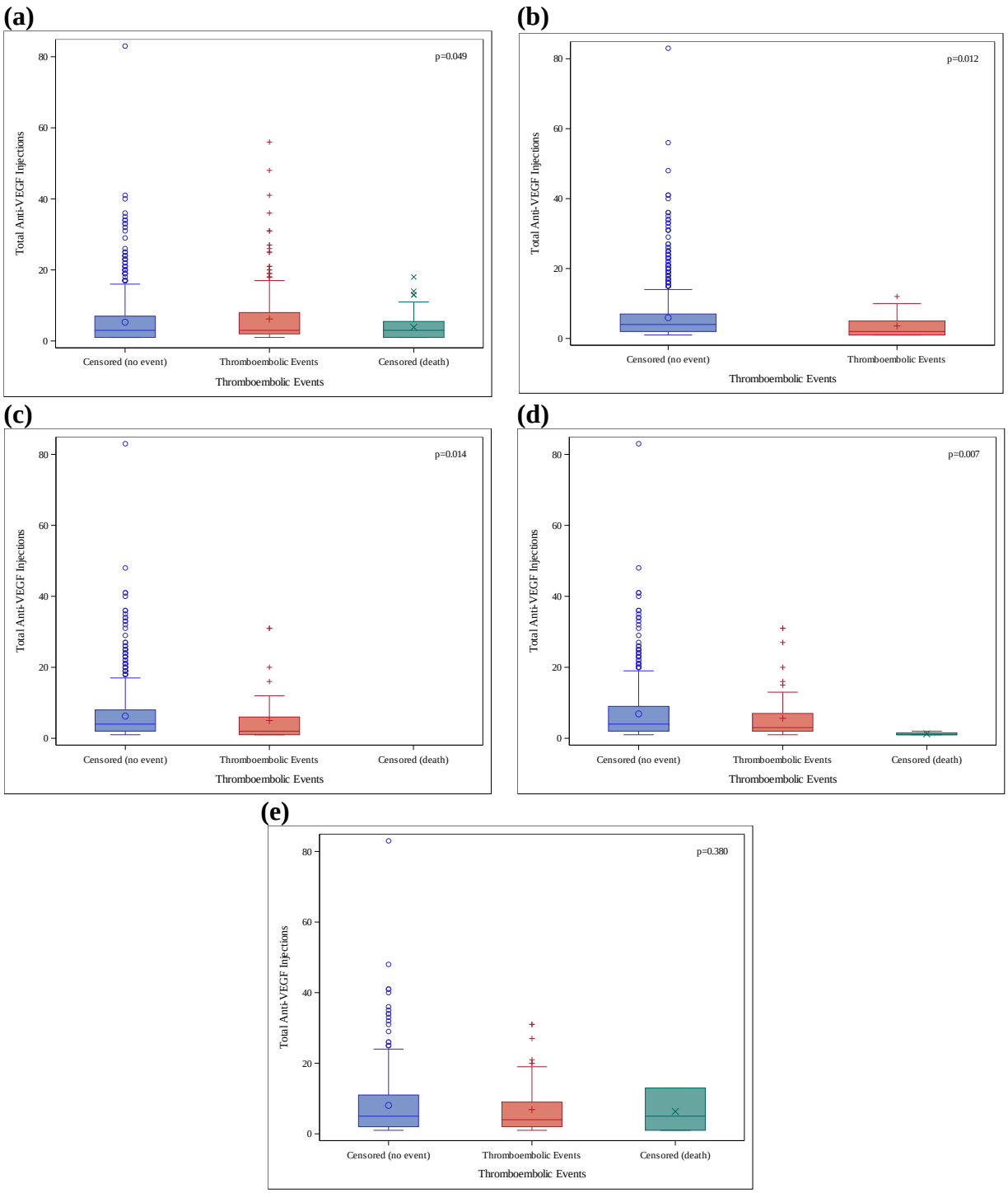
Table 6 Adjusted Cox Proportional Hazards Models for Thromboembolic Events

	Thromboembolic Events			Thromboembolic Events Within a Two-Year Follow-Up		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Treatment						
Anti-VEGF	1.11	0.97, 1.27	0.13	1.20	0.90, 1.59	0.21
Laser (ref)	-	-	-	-	-	-
Demographic characteristics						
Female	0.95	0.83, 1.10	0.50	0.67	0.50, 0.90	<0.01*
Age (every 10 years)	1.27	1.18, 1.37	<0.01*	1.05	0.90, 1.23	0.52
Race						
Caucasian (ref)	-	-	-	-	-	-
African American	1.00	0.83, 1.21	0.99	0.68	0.44, 1.04	0.08
Asian	0.67	0.35, 1.26	0.21	0.42	0.12, 1.55	0.19
Other/ Unknown	0.97	0.78, 1.21	0.80	0.74	0.48, 1.15	0.18
Ethnicity						
Non-Hispanic (ref)	-	-	-	-	-	-
Hispanic	0.74	0.57, 0.97	0.03*	0.86	0.53, 1.39	0.54
Unknown	1.14	0.92, 1.41	0.25	1.17	0.76, 1.79	0.48
Region						
Midwest (ref)	-	-	-	-	-	-
Northeast	1.06	0.86, 1.30	0.58	0.96	0.62, 1.49	0.85
South	1.10	0.92, 1.31	0.28	1.14	0.79, 1.66	0.48
West	0.72	0.57, 0.91	<0.01*	0.92	0.57, 1.48	0.72
Other/Unknown	0.96	0.66, 1.38	0.81	0.50	0.16, 1.55	0.23
Insurance Type						
Commercial (ref)	-	-	-	-	-	-
Medicaid/Medicare	1.05	0.87, 1.27	0.59	1.10	0.75, 1.61	0.63
Unknown	0.98	0.36, 2.65	0.96	1.35	0.18, 10.07	0.77
Renal function						
No CKD (ref)	-	-	-	-	-	-
Stage 1 CKD	0.86	0.49, 1.51	0.59	0.00	0.00, >100	0.97
Stage 2 CKD	1.01	0.74, 1.36	0.97	1.05	0.58, 1.89	0.87
Stage 3 CKD	0.96	0.80, 1.15	0.67	0.62	0.42, 0.91	0.02*
Stage 4 CKD	1.38	1.04, 1.85	0.03*	1.53	0.87, 2.69	0.14
Stage 5 CKD	0.00	0.00, >100	0.96	0.00	0.00, >100	0.99
eGFR	0.99	0.99, 0.99	<0.01*	0.99	0.98, 1.00	0.06
Comorbidities						
Acute kidney injury	1.57	1.31, 1.88	<0.01*	1.91	1.31, 2.80	<0.01*
Congestive heart failure	1.45	1.21, 1.75	<0.01*	1.23	0.79, 1.89	0.39
Cardiac arrhythmia	1.37	1.16, 1.63	<0.01*	1.09	0.73, 1.63	0.68
Peripheral vascular disorders	1.45	1.20, 1.74	<0.01*	1.57	1.04, 2.35	0.03*
Hypertension	1.46	1.27, 1.68	<0.01*	1.01	0.75, 1.34	0.97
Chronic pulmonary disease	1.23	0.99, 1.53	0.07	1.01	0.61, 1.70	0.96

	Thromboembolic Events			Thromboembolic Events Within a Two-Year Follow-Up		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Diabetes complicated	1.19	0.86, 1.64	0.29	0.74	0.35, 1.56	0.43
Hypothyroidism	0.90	0.68, 1.19	0.46	1.13	0.63, 2.02	0.68
Malignant Neoplasms	0.71	0.54, 0.94	0.02*	1.21	0.72, 2.06	0.47
Fluid and Electrolyte Disorders	0.71	0.53, 0.96	0.71	1.13	0.64, 2.00	0.68
Depression	1.64	1.25, 2.14	<0.01*	1.70	0.99, 2.89	0.05
Anti-diabetic Drugs						
Biguanides	0.83	0.71, 0.99	0.03*	1.07	0.77, 1.49	0.68
DPP-4 Inhibitors	0.86	0.68, 1.09	0.22	0.64	0.37, 1.11	0.11
GLP-1 Agonists	1.00	0.73, 1.36	0.97	0.17	0.05, 0.55	<0.01*
Insulin	1.10	0.95, 1.27	0.22	1.08	0.80, 1.46	0.62
SGLT-2 Inhibitors	0.93	0.60, 1.44	0.74	0.28	0.07, 1.18	0.08
Sulfonylureas	1.00	0.83, 1.20	0.99	1.47	1.03, 2.11	0.04*
Treatment-related information						
Index Year						
2011 (ref)	-	-	-	-	-	-
2012	1.12	0.69, 1.83	0.64	1.30	0.40, 4.26	0.66
2013	1.30	0.80, 2.10	0.29	3.11	1.01, 9.57	0.04*
2014	0.98	0.60, 1.63	0.95	1.57	0.49, 5.01	0.45
2015	1.10	0.67, 1.79	0.71	1.37	0.43, 4.34	0.59
2016	1.11	0.68, 1.82	0.67	1.24	0.39, 3.90	0.72
2017	0.84	0.52, 1.36	0.48	1.07	0.35, 3.24	0.92
2018	1.17	0.73, 1.88	0.51	2.64	0.88, 7.88	0.08
2019	1.27	0.78, 2.08	0.34	2.56	0.76, 8.68	0.13
2020	0.43	0.12, 1.53	0.19	-	-	-
COVID-19	2.65	0.77, 9.09	0.12	-	-	-

*indicates statistical significance ($p<0.05$)

Figure 12 Total Anti-VEGF Injections by Thromboembolic Events



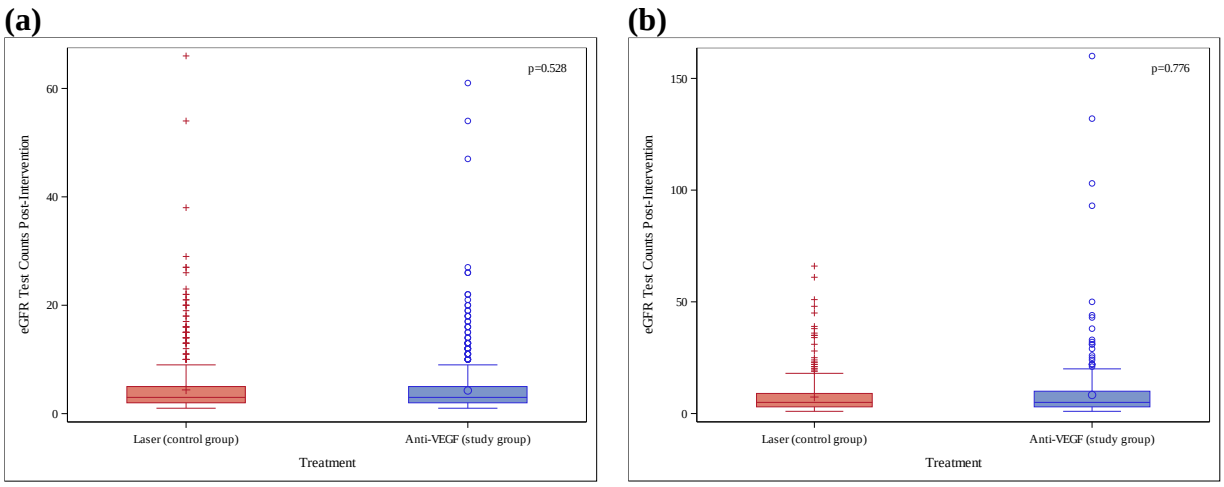
(a) Comparison of total anti-VEGF intravitreal injections by thromboembolic events; the medians (IQR) for each group: censored (median=3, IQR: 1, 7), thromboembolic events (median=3, IQR: 2, 8), death as the competing event (median=3, IQR: 1.0, 5.5); p=0.049

(b) Comparison of total anti-VEGF intravitreal injections by thromboembolic events within three months; the medians (IQR) for each group: censored (median=4, IQR: 2, 7), thromboembolic events (median=2.0, IQR: 1, 5), no death as the competing event; p=0.012
(c) Comparison of total anti-VEGF intravitreal injections by thromboembolic events within six months; the medians (IQR) for each group: censored (median=4, IQR: 2, 8), thromboembolic events (median=2, IQR: 1, 6), no death as the competing event; p=0.014
(d) Comparison of total anti-VEGF intravitreal injections by thromboembolic events within one year; the medians (IQR) for each group: censored (median=4, IQR: 2, 9), thromboembolic events (median=3, IQR: 2, 7), death as the competing event (median=1, IQR: 1.0, 1.5); p=0.007
(e) Comparison of total anti-VEGF intravitreal injections by thromboembolic events within two years; the medians (IQR) for each group: censored (median=5, IQR: 2, 11), thromboembolic events (median=4, IQR: 2, 9), death as the competing event (median=5, IQR: 1, 13); p=0.380

4.5 Exploratory Endpoints

A total of 1,231 patients and 824 patients met additional enrollment criteria (exclusion criteria #9 and #10) for the assessment of 40% eGFR reduction **(Table 2)**. We restricted these patients shall have at least one-year and two-year continuous enrollment to ensure that they had access to have eGFR tests. 40% eGFR reduction and eGFR counts within one year and two years were evaluated (Section 4.5.1 and 4.5.2). On average, eGFR test counts after the index date were not significantly different between the study group and the control group within one year (p=0.53) and within two years (p=0.78), shown in **Figure 13**.

Figure 13 Total eGFR Test Counts After the Index Date by Treatment Groups



(a) Comparison of total eGFR test counts within one year after the index date by treatment groups; median (IQR) for both study group (anti-VEGF) and control group (laser photocoagulation): median=3 (IQR: 2, 5); p=0.528

(b) Comparison of total eGFR test counts within two years after the index date by treatment groups; median (IQR) for both study group (anti-VEGF) and control group (laser photocoagulation): median=5 (IQR: 3, 9); p=0.776

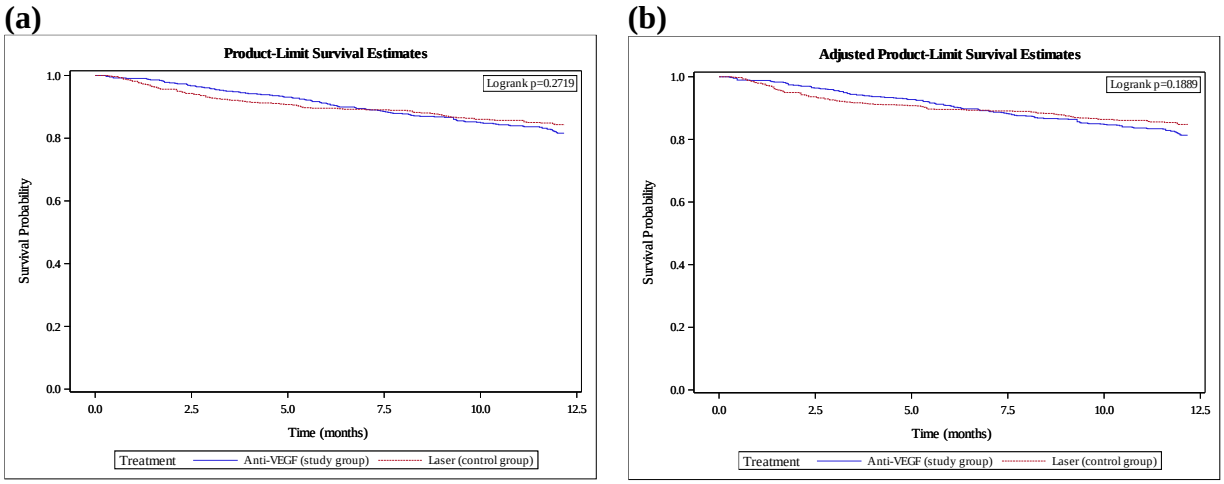
4.5.1 40% eGFR Reduction Within a One-Year Follow-Up

Among 1,231 patients who had at least one-year of continuous enrollment, 637 patients received intravitreal anti-VEGF injections and 594 patients received laser photocoagulation. There was no difference in the numbers of post-intervention eGFR test values in both groups (p=0.53). The median numbers of post-intervention eGFR test values were 3 in both the study group (IQR: 1, 5) and the control group (IQR: 2,5), shown in **Figure 13**.

17% of patients (study group: 117; control group: 93) experienced 40% eGFR reduction within one-year follow-up after the index date and 0.24% of patients experienced a competing risk of death. Patients receiving intravitreal anti-VEGF injections did not have a higher risk of developing 40% eGFR reduction before and after adjustment (adjusted HR=1.15; 95% CI: 0.94,

1.40) **(Figure 14)**. Similar to the findings in the primary endpoints, patients with pre-existing stage 3 or stage 4 CKD, AKI and hypertension had a higher risk of worsening renal function. In contrast, females had a higher risk while patients with higher eGFR or were older at baseline had a lower risk of experiencing a 40% eGFR reduction within one year **(Appendix Table 11)**. Regarding the relationship between the total numbers of intravitreal anti-VEGF injections and the change of renal function, there was also no significant difference in the total intravitreal anti-VEGF injections between patients with 40% eGFR reduction and patients without 40% eGFR reduction in the study group (p=0.28) **(Figure 16)**.

Figure 14 Kaplan-Meier Curves for 40% eGFR Reduction Within a One-Year Follow-Up



(a) Unadjusted Kaplan-Meier survival curve for 40% eGFR reduction within one-year follow up (HR=1.13; 95% CI: 0.83, 1.53)
(b) IPTW-adjusted Kaplan-Meier survival curve for 40% eGFR reduction within one-year follow up (HR=1.24; 95% CI: 0.94, 1.40)

4.5.2 40% eGFR Reduction Within a Two-Year Follow-Up

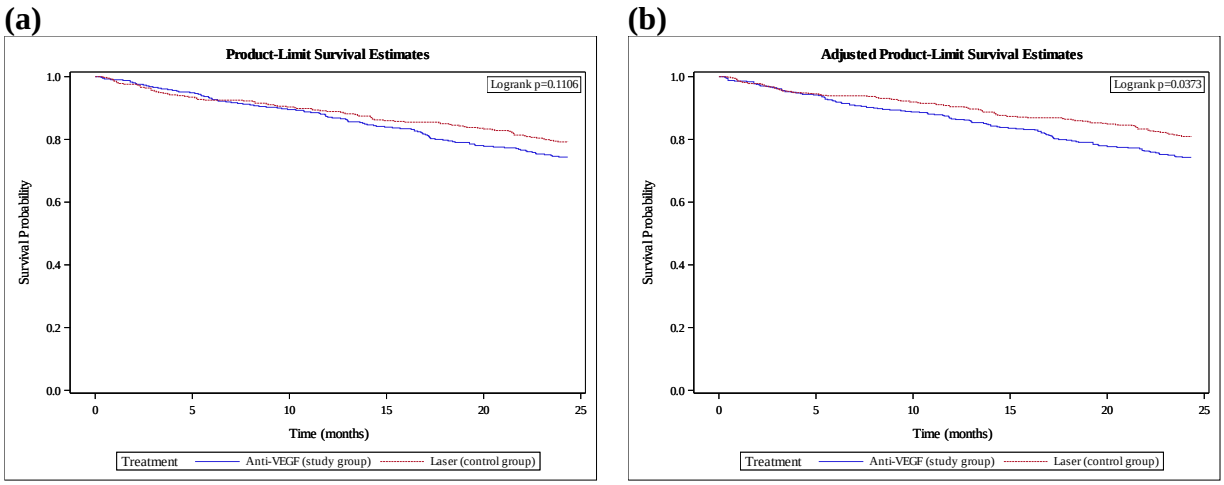
Among 824 patients who had at least two-year continuous enrollment, 410 patients received intravitreal anti-VEGF injections and 414 patients received laser photocoagulation. 23.18% of patients experienced 40% eGFR reduction within two years after the index date and 0.49% of patients experienced a competing risk of death. Similar to the findings for 40% eGFR reduction within a one-year follow-up, there was no difference in the numbers of post-intervention eGFR test values in both groups (p=0.77). The median numbers of post-intervention eGFR test values were 5 in both the study group (IQR: 3, 10) and the control group (IQR: 3, 9), shown in **Figure 13**.

Similar to the finding from a one-year follow-up period, there were no differences in the risk of a 40% eGFR reduction within two years before and after adjustment. The unadjusted HR was insignificant (HR=1.18; 95% CI: 0.86, 1.63). However, apart from the unadjusted findings, the log-rank test from Kaplan-Meier nonparametric analysis showed a significant difference (p=0.04) – 25.73% patients in the study group and 19.07% patients in the control group would experience a 40% eGFR reduction. The adjusted hazard ratio was close to the boundary line (HR=1.24; 95% CI: 0.99, 1.54) but was still not statistically significant **(Figure 15) (Appendix Table 11)**.

We found that patients with pre-existing stage 3 or 4 CKD had a higher risk of worsening renal function within two years, same as the finding in the Cox proportional regression model of a 40% eGFR reduction within one year. Patients with a history of AKI or hypertension had a higher risk as well. In the Cox regression model of patients who had continuous enrollment and available eGFR values within two years, the results also showed that females and patients with higher eGFR at baseline had a higher risk of experiencing 40% eGFR reduction which was the same as the

regression model of patients who had continuous enrollment and available eGFR values within one year **(Appendix Table 11)**, in contrast to the findings of the primary endpoints. There was still also no significant difference in the total intravitreal anti-VEGF injections between patients with 40% eGFR reduction and patients without 40% eGFR reduction in the study group (p=0.94) **(Figure 16)**.

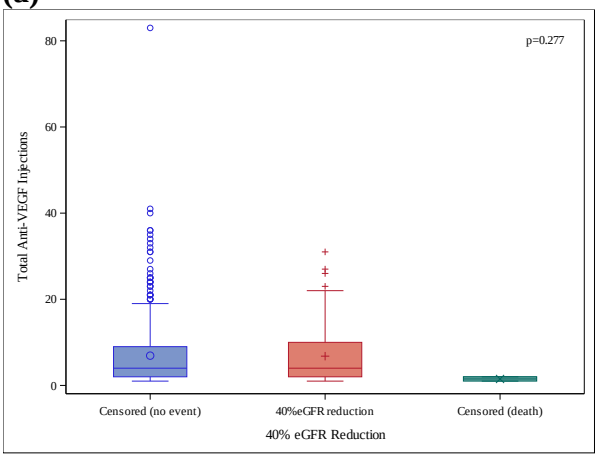
Figure 15 Kaplan-Meier Curves for 40% eGFR Reduction Within a Two-Year Follow-Up



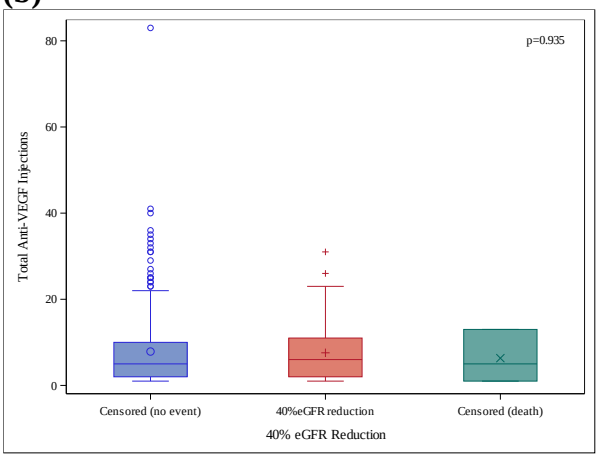
(a) Unadjusted Kaplan-Meier survival curve for 40% eGFR reduction within two-year follow up (HR=1.15; 95% CI: 0.94, 1.40)
(b) IPTW-adjusted Kaplan-Meier survival curve for 40% eGFR reduction within two-year follow up (HR=1.24; 95% CI: 0.99, 1.54)

Figure 16 Total Anti-VEGF Injections by CKD Events and Censored Data

(a)



(b)



(a) Comparison of total anti-VEGF intravitreal injections by 40% eGFR reduction within one year; medians (IQR) for each group: censored (median=4, IQR: 2, 9), new diagnosis of CKD (median=4, IQR: 2, 10), death, competing event (median=1.5, IQR: 1, 2); p=0.277

(b) Comparison of total anti-VEGF intravitreal injections by 40% eGFR reduction within two years; medians (IQR) for each group: censored (median=5, IQR: 2, 10), new diagnosis of CKD (median=6, IQR: 2, 11), death, competing event (median=5, IQR: 1, 13); p=0.935

5.0 Discussion

In this study, we used three different approaches to understand the association of intravitreal anti-VEGF injections and adverse kidney events in a US patient population with diabetic retinopathy. Firstly, we used medical diagnoses with ICD-9/10-CM codes from administrative claims to compare the time to a new diagnosis of CKD or worsening of CKD. Secondly, we assessed clinical long-term outcomes through a composite endpoint of overall hospitalization or death as well as thromboembolic events. Lastly, we used 40% eGFR reduction as a surrogate endpoint for kidney disease progression to compare with the results from the primary endpoint. Although patients receiving intravitreal anti-VEGF injections did not have significantly higher risk of developing new CKD or pre-existing CKD deterioration and thromboembolic events, intravitreal anti-VEGF injections were associated with all-cause hospitalization or death.

In randomized clinical trials (RCT) of aflibercept and ranibizumab, safety was evaluated from 2,980 patients and 949 patients in the aflibercept and ranibizumab trials, respectively.[19, 23] Most common adverse reactions were intraocular events, such as conjunctival hemorrhage, eye pain, and increased intraocular pressure. Non-ocular adverse drug reactions rarely occurred.[17, 21] About 1-4% adverse kidney events were reported in clinical studies and extension studies in patients with DME who were treated with intravitreal aflibercept injection.[58, 59, 60] No severe kidney adverse drug reactions (ADR) were observed in patients with DME in ranibizumab trials (RESOVLE and RESTORE studies).[61, 62] 6% patients experienced chronic renal failure versus 2% patients in the control group among patients with DR, AMD or Retinal Vein Occlusion.[19] However, rare adverse events or adverse events with a latency period are hard to detect in clinical trials.[63] The low occurrence of kidney ADRs reported in trials did not eliminate the possible association

between intravitreal anti-VEGF injections and adverse kidney outcomes because renal insufficiency might not be detected in clinical trials due to its natural progression in the elderly and patients with diabetes.

The systemic effect of intravitreal administration of anti-VEGF agents cannot be fully ruled out.[64] Although very few significant systemic adverse events were reported in clinical trials, higher incidence of thromboembolic events, such as non-fatal myocardial infarction and stroke, were observed in patients receiving intravitreal ranibizumab or aflibercept than patients in the control groups.[19, 23, 65, 66] Nevertheless, no differences in the risk of all serious systemic adverse events (SSAE) in one to two years was found in one network meta-analysis that compared effectiveness and safety between intravitreal anti-VEGF injections (aflibercept, bevacizumab, ranibizumab) and laser photocoagulation.[67] We had similar results in overall hospitalization or death and thromboembolic events within two years in our study. In addition, in the sub-analyses of the composite endpoint, the fatality in the patients who had at least two-year continuous enrollment was about 0.5%, similar to the findings from one systematic review evaluating the systemic safety of bevacizumab versus ranibizumab among patients with neovascular AMD (overall mortality rate about 0.3-0.4% for one or two years).[68] Still, no precise estimates for all-cause death were available due to very few events.

The safety concern for thromboembolic events related to intravitreal anti-VEGF injections is still controversial. In our study, 15% patients treated with intravitreal anti-VEGF injections experienced thromboembolic events within two years compared with 10% patients treated with laser photocoagulation. The occurrence rate of thromboembolic events was higher in our study compared to clinical data reported in the package inserts (aflibercept: 1-6%; ranibizumab: 1-3%).[19, 23] Although the hazard ratios from the Cox regression models in our study showed higher risk of

thromboembolic events with the lower bounds of 95% confidence interval close to one, there was no statistical difference in the risk of thromboembolic events. *Weinstein et al.* reported that patients were more likely to experience stroke two years after the initiation of intravitreal bevacizumab treatment compared with the same patient cohort two years before the treatment, but there were no higher risks of other thromboembolic diseases, such as acute coronary syndrome, deep vein thrombosis, or pulmonary embolism.[69] Still, further systematic reviews and meta-analyses of aggregated clinical trial data concluded no significant difference of adverse thromboembolic events.[68, 70, 71] Besides, the Cox regression models in our study also showed a possibly higher risk of thromboembolism in patients with depression whereof other observational studies found that patients using antidepressants might be associated with venous thromboembolism.[72, 73] Further studies are required to address this question.

Studies have demonstrated systemic VEGF inhibition after intravitreal anti-VEGF injections and serum VEGF levels significantly decreased after intravitreal injections of aflibercept or bevacizumab, whereas no notable reduction was observed in ranibizumab.[74, 75, 76, 77, 78, 79] Data from clinical trials indicated that free aflibercept in the plasma was not detected two weeks after injections[23]; in contrast, several studies found the serum VEGF inhibition remained after 4 weeks in patients receiving intravitreal aflibercept or bevacizumab injections.[74, 75, 78, 79] However, these opposite findings might be related to measurement bias, such as differences in VEGF-binding affinity[74, 80], the selection of the enzyme-linked immunosorbent assay (ELISA) kits,[80, 81] and possible correlations between VEGF and glucose levels in patients with type II diabetes[82] or the severity of diabetic retinopathy.[83] Most importantly, the association between serum VEGF inhibition and systemic adverse events was not yet established,[74, 75, 78] corresponding to our study result which showed no significant difference of total anti-VEGF injections between patients who

experienced and who did not the events of interest. *O'Neill et al.* also concluded no significant association was found in the change of eGFR and the total numbers of intravitreal anti-VEGF injections.[35]

It is still unknown how long adverse impact in the kidney would develop after intravitreal administration of anti-VEGF. Albeit few cases with acute renal dysfunction soon or one month after intravitreal anti-VEGF injections had been reported[84, 85], several cases developed AKI, TMA, or worsening renal function six months to more than one year after treatment initiation.[27, 28, 86, 87, 88] *Kameda et al.*[33] concluded that no significant change in mean eGFR and no AKI event one month after intravitreal administration of aflibercept, bevacizumab and ranibizumab in 69 patients with diabetes and pre-existing CKD. Similarly, the prospective study conducted by *Bagheri et al.*[34] also did not find a significant change in eGFR, serum creatinine (Scr), and urinary albumin-to-creatinine ratio (UACR) one month after the intravitreal bevacizumab injections in 40 patients with proteinuria at baseline. *O'Neill et al.*[35] studied adverse renal effects of intravitreal anti-VEGF injections in 85 patients with 2.6 years of the follow-up period, they found no significant change in eGFR between patients with and without diabetic kidney disease. Although our study also did not find patients who had deteriorating renal function within one-year and two-year follow-up periods, the adjusted hazard ratios increased and the 95% confidence interval was close to one in the Cox regression model with a two-year follow-up compared with the model with a one-year follow-up. This may imply possible accumulation of diminutive effects in the kidney from intraocular administration of anti-VEGF agents and cannot be observed within a short period of time.

The above three observational studies that addressed the concern of short-term and long-term adverse kidney outcomes after intravitreal anti-VEGF treatments used the change of

biomarkers, such as eGFR, Scr, and UACR, as the surrogate endpoints. *Kameda et al.*[33] and *Bagheri et al.*[34] compared before-and-after mean eGFR using paired t-tests while *O'Neill et al.*[35] used linear regression to understand the difference in eGFR slope after the intravitreal anti-VEGF treatments. Direct comparison of the change of mean eGFR or UACR within one month is intuitive and acceptable; however, we may need to question the representative of eGFR slope and UACR slop as surrogate endpoints in kidney disease progression. The time-to-event analysis is a common statistical method in clinical trials that addresses the binary outcome of interest and censored data, but it requires a larger sample size to get the statistical significance than linear regression.[89] Comparing eGFR and UACRs slopes are more appealing because it has larger statistical power that requires less sample size.[90, 91, 92] Nevertheless, FDA commented that this approach increased the risk of type 1 error in eGFR slope and had large variability with very wide confidence intervals in UACR slope.[93] Therefore, we conservatively chose to use 40% eGFR reduction as our exploratory endpoint in our large sample-size study with censored data.

Even though we used different approaches to understand whether there were possible adverse outcomes after intravitreal anti-VEGF injections, our estimates from the regression models in this study shall be interpreted with caution as we did not perform a pairwise selection of covariates to obtain a precise estimation of hazard ratios. Opposite HRs from covariates were identified in our regression models, such as sex, age, and eGFR. While females and higher eGFR had less risk of diagnoses of new CKD or worsening of CKD in the regression models for the primary endpoints, these factors showed an increased risk of 40% eGFR reduction within one or two years. Known factors for CKD included males, the elderly, and some comorbidities or medical history of AKI, diabetes, and cardiovascular diseases.[94, 95] The opposite findings of these covariates from our regression models of the exploratory endpoints might imply that possible bias

and/or uncontrolled confounding existed. Due to a small group of patients (167 patients, 9.0%) identified after COVID-19, this covariate did not provide a statistically significant effect on our study endpoints.

The effects of age in our regression models were also different among our study endpoints. Aging is also a known risk factor for many diseases. Older patients had statistically higher risk of all-cause death and thromboembolic events; however, we found that the elderly with pre-existing CKD had lower risk of CKD progression. Besides, patients had CKD above stage 1 also had less possibility to have worsening CKD stages. Although possible uncontrolled bias and confounding existed, there might be ceiling/floor effects on the assessment of CKD progression. While these patients were older and diagnosed with CKD at baseline, it was possible that the measuring capacity for worsening of CKD attenuated.

Our study had several strengths. Firstly, we used an active comparator (laser photocoagulation) as a control group rather than comparing the before-and-after change of renal biomarkers in the same patients. It reduced biases and confounding to increase the power of the study. Secondly, to enhance the generalizability of our study, we controlled for patients with several comorbidities, such as hypertension and AKI, rather than excluded them. Most clinical trials in assessing the efficacy of intravitreal anti-VEGF injections in patients with AMD and DR excluded patients with uncontrolled diabetes (HbA1c≥ 12%) and hypertension (160/100 mmHg) would limit the extrapolation of the results in real-world patients. Lastly, we compared the finding between the diagnoses from administrative claims and clinical endpoints for lab data. In this approach, we could corroborate the gap of underreporting of CKD diagnosis in administrative claims. [43, 46]

We had a number of limitations related to the use of the secondary database in our study. As AKI is highly associated with increasing mortality and progression to CKD,[96, 97] we only considered AKI diagnosis in inpatient visits rather than including outpatient visits to achieve higher specificity. However, identification of AKI in administrative claims data has very low sensitivity as it is usually underreported.[50] Therefore, we did not have accurate data in AKI to control for in our study and it might have impacts on our outcomes of interests. Similar to inaccurate estimates in patients with AKI history at baseline, it was likely that patients with CKD at baseline were underestimated due to inherent to the use of administrative claims data. Moreover, misclassification of the outcomes existed because we only used ICD-codes diagnoses of CKD in our primary endpoint. Studies have shown a considerable limitation of using ICD codes to identify CKD.[46, 98]

The other problem was that we did not explore which covariates that were actually associated with the treatments of interest (i.e., intravitreal anti-VEGF injections and laser photocoagulation) and the outcomes in our study. We selected covariates that were often considered as potential confounding factors in observational studies. Although this approach penalized the statistical power, increased bias due to colliders or instrumental variables and the possibility of random errors due to overfitting, we could address potential confounding in our regression models.[99, 100] In addition, we did not adjust for diabetes types and other risk factors, such as the severity of diabetes and obesity using hemoglobin A1c (HbA1c) and body mass index (BMI) as incorrect ICD diagnosis and insufficient lab data in our database. Furthermore, mortality information from Social Security Association DMF might be incomplete or with clerical errors.[101, 102] A study showed that the DMF had low sensitivity (10-30%) for both inpatient and outpatient death after 2011[103] and it implied that the mortality might be underestimated in our study.

Although we selected three kinds of anti-VEGF agents as the exposure in the study group, the generalizability was still a concern because 1,120 (84.4%) patients received intravitreal bevacizumab injections, and no patients received intravitreal aflibercept injections as their first intervention in our study. The selection of anti-VEGF agents might be associated with the potency, the treatment regimens, and the costs.[104] Off-label ophthalmic use of bevacizumab requires reformulation by pharmacists but costs less than aflibercept or ranibizumab. We used total injections to find out the possible dose-outcome relationship. Although we did not find the association between total anti-VEGF intravitreal injections and outcomes of interest, this approach might be inaccurate because the recommended dose of intravitreal anti-VEGF injections varied by different pharmacological effects of anti-VEGF agents (structures, binding receptors, affinities, and potencies).[80]

Other than the concern of generalizability, our study might also have selection bias due to types of insurance. Types of insurance affect patients' access to healthcare and further patient outcomes while patients' health and socioeconomic status will affect the selection of insurance.[105, 106] One study which evaluated the self-reported adherence to diabetic retinopathy screening found that patients with private health insurance had higher odds (OR=2.07; 95% CI: 1.70, 2.52) to receive annual eye examination recommended by clinical guidelines compared with patients with public health insurance (OR=1.90; 95% CI: 1.56, 2.31).[107] Among 1,327 patients receiving intravitreal anti-VEGF injections in our study cohort, about 60% were insured by public health insurance (Medicare or Medicaid). These patients might have less favorable socioeconomic and health conditions. In our Cox progression model, people insured by public health insurance were likely to have a new CKD diagnosis ($p<0.01$). Furthermore, it was possibly that these patients

might have limited access to costly anti-VEGF injections[108] and further clinical evaluations. Therefore, our study results might be underestimated.

The use of MDRD equation which takes account of race (Blacks) for adjustment might affect the performance of GFR estimation. *Schwandt et al.* reported that the MDRD equation could provide most accurate eGFR for all CKD stages as well as for elderly among diabetic patients compared with other equations.[109] Nonetheless, a recent study in 2021 from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) reported that algorithms with inclusion of race for eGFR calculation would overestimate eGFR as race is a social construct rather than a biologic attribute.[110] The updated Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation incorporated with cystatin C has omitted race and can provide more accurate eGFR with smaller differences between non-Blacks and Blacks.[110]

Despite of several limitations in our study, our study demonstrated that long-term safety outcomes in kidneys, thromboembolism, and overall all-cause hospitalization or death after intravitreal anti-VEGF injections compared to laser photocoagulation among patients with diabetic retinopathy. We believe that long-term safety is still questionable in patients treated with intravitreal anti-VEGF injections. Further large clinical trials or observational studies with longer follow-up using large real-world data are required.

Appendix A Medical Billing Codes for the Diseases and Procedures

Appendix Table 1 International Classification of Diseases (ICD) Codes

Disease	ICD-9/10-CM codes
Diabetic Retinopathy	• **ICD-9**: 250.50, 250.51, 250.52, 250.31, 362.01, 362.02, 362.03, 362.04, 362.05, 362.06 and 362.07 • **ICD-10**: E08.31x, E08.32x, E08.33x, E08.34x, E08.35x, E08.39, E09.31x, E09.32x, E09.33x, E09.34x, E09.35x, E10.31x, E10.32x, E10.33x, E10.34x, E10.35x, E10.39, E11.31x, E11.32x, E11.33x, E11.34x, E11.35x, E11.39, E13.31x, E13.32x, E13.33x, E13.34x, E13.35x and E13.39
End-Stage Renal Disease (ESRD)	• **ICD-9**: 585.6, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93 • **ICD-10**: N18.6, I12.0, I13.11, I13.2, I13.11, I13.2
Chronic Kidney Disease (CKD)	• **ICD-9**: 585.1, 585.2, 585.3, 585.4, 585.5, 585.9 • **ICD-10**: N18.1, N18.2, N18.3, N18.4, N18.5, N18.9
Deep Vein Thrombosis	• **ICD-9:** 451.1x, 451.2, 451.8x, 451.9, 453.2, 453.4x, 453.5x, 453.6, 453.7x, 453.8x, 453.9 • **ICD-10:** I80.x, I82.2x, I82.4x, I82.5x, I82.6x, I82.7x, I82.Ax, I82.Bx, I82.Cx, I82.8x, I82.9x
Artery Thrombosis	• **ICD-9:** 444.x • **ICD-10:** I74.x
Pulmonary Embolism	• **ICD-9:** 415.11, 415.13, 415.19, 416.2 • **ICD-10:** I26.0, I26.01, I26.02, I26.09
Myocardial Infarction	• **ICD-9:** 410 • **ICD-10:** I21
Ischemic Stroke	• **ICD-9:** 433-434, 436 • **ICD-10:** I63

Disease	ICD-9/10-CM codes
Chronic Heart Failure	• **ICD-9**: 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4, 425.5, 425.7, 425.8, 425.9, 428 • **ICD-10**: I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5, I42.6, I42.7, I42.8, I42.9, I43, I50, P29.0
Cardiac Arrhythmia	• **ICD-9**: 426.0, 426.13, 426.7, 426.9, 426.10, 4261.2, 427.0, 427.1, 427.2, 427.3, 427.4, 427.6, 427.8, 427.9, 785.0, 996.01, 996.04 • **ICD-10**: V45.0, V53.3, I44.1, I44.2, I44.3, I45.6, I45.9, I47, I48, I49, R00.0, R00.1, R00.8, T82.1, Z45.0, Z95.0
Peripheral Vascular Disorders	• **ICD-9**: 093.0, 437.3, 440, 441, 443.1, 443.2, 443.8, 443.9, 447.1, 557.1, 557.9 • **ICD-10**: V43.4, I70, I71, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Hypertension	• **ICD-9**: 401, , 402, 403, 404, 405 • **ICD-10**: I10, I11, I12, I13, I15
Chronic Pulmonary Disease	• **ICD-9**: 416.8, 416.9, 490-496, 500-505, 506.4, 508.1, 508.8 • **ICD-10**: I27.8, I27.9, J40-J47, J60-J67, J68.4, J70.1, J70.3
Hypothyroidism	• **ICD-9**: 240.9, 243, 244, 246.1, 246.8 • **ICD-10**: E00, E01, E02, E03, E89.0
Malignant Neoplasms	• **ICD-9**: 200, 201, 202, 203.0, 238.6, 140-149, 150-159, 160-169, 170-179, 180-189, 190-195 • **ICD-10**: C81, C82, C83, C84, C85, C88, C96, C900, C902, C00-C76, C97
Diabetes (complicated)	• **ICD-9:** 250.4-250.9 • **ICD-10:** E10.2-E10.8, E11.2-E11.8, E12.2-E12.8, E13.2-E13.8, E14.2-E14.8
Fluid and Electrolyte Disorders	• **ICD-9**: 253.6, 276 • **ICD-10**: E22.2, E86, E87

Disease	ICD-9/10-CM codes
Depression	• **ICD-9**: 296.2, 296.3, 296.5, 300.4, 309, 311 • **ICD-10**: F20.4, F31.3, F31.4, F31.5, F32, F33, F34.1, F41.2, F43.2

Appendix Table 2 Healthcare Common procedure Coding System (HCPCS) Codes

Categories	Medication	HCPCS codes
anti-VEGF (ophthalmology)	aflibercept	J0178, Q2046, C9291
	bevacizumab	C9257, S0116, J9035, Q2024, J3490, J3590, C9399, J7999
	brolucizumab	J0179
	pegaptanib	J2503, J9035
	ranibizumab	J2778, C9233
anti-VEGF (oncology)	aflibercept	J0178, Q2046, C9291
	bevacizumab	C9257, S0116, J9035, Q2024, J3490, J3590, C9399, J7999
	ranibizumab	J2778, C9233
corticosteroid	dexamethasone	J7312
	fluocinolone	J7311, J7313, J7314
	triamcinolone	J3300, J3301

Appendix Table 3 Current Procedure Terminology (CPT) codes

Procedure/ Administration	CPT codes
intravitreal injection	67028
intravenous injection	96413, 96415, 96417, 96409, 96411
focal/ grid laser photocoagulation	67210
pan-retinal laser photocoagulation	67228

Appendix Table 4 American Hospital Formulary Service Classification System (AHFCLSS) Codes

Medication	AHFCLSS Codes
biguanides	682004, 68200400
dipeptidyl peptidase-4 (DPP-4) inhibitors	682005, 68200500
glucagon-like peptide 1 (GLP-1) agonists	682006, 68200600
insulin	682008, 68200800
meglitinides	682016, 68201600
sodium-glucose cotransporter-2 (SGLT2) inhibitors	682018, 68201800
sulfonylureas	682020, 68202000

Appendix Table 5 Place of Service Code (POS) for Outpatient Visits

POS	Description
11	Office
17	Walk-In Retail Health Clinic
20	Urgent Care Facility
22	Outpatient Hospital
23	Emergency Room
24	Ambulatory Surgical Center
49	Independent Clinic
62	Comprehensive Outpatient Rehabilitation Facility
65	End-Stage Renal Disease Treatment Facility
71	State or Local Public Health Clinic

Appendix B Supplementary Information of Patient Characteristics and Results

Appendix Table 6 Selection of Intravitreal Anti-VEGF Agents

	Initial Intravitreal Injection of Anti-VEGF Agent	
	Bevacizumab (n=1,120)	Ranibizumab (n=207)
No Treatment Switching		
	1,068	173
Treatment Switching		
Aflibercept	0	2
Bevacizumab	-	33
Ranibizumab	52	-

Appendix Table 7 Median Follow-Up (FU) Time with 95%CI in Censored Patients

Duration of FU Time (months)	Study Group	Control Group	p-value
Primary Endpoints			
New diagnosis of CKD	18.97 (16.97, 20.40)	23.60 (21.13, 26.00)	0.001
Worsening of CKD	22.50 (20.80, 24.93)	23.67 (19.43, 29.67)	0.101
Secondary Endpoints			
Overall Hospitalization or Mortality	23.77 (21.83, 26.60)	28.67 (26.00, 31.00)	0.007
Overall Mortality	20.53 (19.17, 21.80)	22.90 (20.97, 24.83)	0.032
Overall Hospitalization	22.00 (20.47, 23.83)	26.90 (23.60, 28.90)	0.009
Thromboembolic Events	19.63 (18.27, 20.87)	22.97 (20.73, 24.37)	<0.0001

Appendix Table 8 The Number of Intravitreal Anti-VEGF Injections by Events

	No Event, Censored		Event Occurred		Competing Event, Death		
	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	p-value[1]
Primary Endpoint							
New Diagnosis of CKD	549	3 (1, 6)	183	4 (2, 10)	79	3 (1, 5)	<0.0001
New Diagnosis of CKD (Within Three Months)	652	4 (2, 7)	27	4 (1, 8)	0	-	0.909
New Diagnosis of CKD (Within Six Months)	540	4 (2, 8)	46	4 (1, 8)	0	-	0.654
New Diagnosis of CKD (Within One Year)	395	4 (2, 9)	53	5 (2, 10)	1	1 (1, 1)	0.291
New Diagnosis of CKD (Within Two Years)	205	5 (2, 9)	55	6 (3, 11)	1	5 (5, 5)	0.405
Worsening of CKD	254	3 (1, 6)	221	3 (1, 8)	41	3 (1, 6)	0.108
Worsening of CKD (Within Three Months)	432	4 (2, 7)	27	2 (1, 6)	0	-	0.058
Worsening of CKD (Within Six Months)	356	4 (2, 8)	57	3 (2, 7)	0	-	0.162
Worsening of CKD (Within One Year)	247	4 (2, 10)	72	4 (2, 8)	1	2 (2, 2)	0.692
Worsening of CKD (Within Two Years)	112	5.5 (2.5, 12.0)	73	5 (2, 11)	1	1 (1, 1)	0.302
Secondary Endpoint							
Overall Hospitalization or Mortality	686	3 (1, 6)	641	3 (1, 7)	-	-	0.009
Overall Hospitalization or Mortality (Within Three Months)	1,039	4 (2, 7)	99	3 (1, 6)	-	-	0.009

	No Event, Censored		Event Occurred		Competing Event, Death		
	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	p-value[1]
Overall Hospitalization or Mortality (Within Six Months)	853	4 (2, 8)	146	3 (1, 7)	-	-	0.017
Overall Hospitalization or Mortality (Within One Year)	582	4 (2, 9)	187	4 (2, 8)	-	-	0.093
Overall Hospitalization or Mortality (Within Two Years)	271	5 (2, 11)	176	5 (2, 10)	-	-	0.544
Overall Mortality	1,086	3 (1, 7)	241	3 (1, 6)	-	-	0.007
Overall Hospitalization	733	3 (1, 6)	594	3 (1, 7)	-	-	0.002
Overall Hospitalization (Within Three Months)	1,039	4 (2, 7)	99	3 (1, 6)	-	-	0.009
Overall Hospitalization (Within Six Months)	853	4 (2, 8)	146	3 (1, 7)	-	-	0.017
Overall Hospitalization (Within One Year)	584	4 (2, 9)	185	4 (2, 8)	-	-	0.134
Overall Hospitalization (Within Two Years)	272	5 (2, 11)	175	5 (2, 10)	-	-	0.545
Thromboembolic Events	936	3 (1, 7)	259	3 (2, 8)	132	3 (1.0, 5.5)	0.049
Thromboembolic Events (Within Three Months)	1,104	4 (2, 7)	34	2 (1, 5)	-	-	0.012
Thromboembolic Events (Within Six Months)	946	4 (2, 8)	53	2 (1, 6)	-	-	0.014
Thromboembolic Events (Within One Year)	696	4 (2, 9)	69	3 (2, 7)	4	1 (1, 1.5)	0.007

	No Event, Censored		Event Occurred		Competing Event, Death		
	n	**Median (IQR)**	**n**	**Median (IQR)**	**n**	**Median (IQR)**	**p-value[1]**
Thromboembolic Events (Within Two Years)	377	5 (2, 11)	67	4 (2, 9)	3	5 (1, 13)	0.380
Exploratory Endpoint							
40% eGFR Reduction Within One Year	518	4 (2, 9)	117	4 (2, 10)	2	1.5 (1.0, 2.0)	0.277
40% eGFR Reduction Within Two Years	302	5 (2, 10)	105	6 (2, 11)	3	5 (1, 13)	0.899

[1]Wilcoxon rank-sum test

Appendix Table 9 Adjusted Regression Models for Primary Endpoints Within a Two-Year Follow-Up

	New Diagnosis of CKD[1]			Worsening of CKD[2]		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Treatment						
Anti-VEGF	1.32	0.98, 1.77	0.06	0.91	0.60, 1.38	0.65
Laser (ref)	-	-	-	-	-	-
Demographic characteristics						
Female	0.44	0.32, 0.60	<0.01*	0.59	0.38, 0.91	0.02*
Age (every 10 years)	0.86	0.73, 1.01	0.07	0.90	0.73, 1.11	0.32
Race						
Caucasian (ref)	-	-	-	-	-	-
African American	2.35	1.60, 3.43	<0.01*	1.00	0.53, 1.89	0.99
Asian	0.78	0.27, 2.22	0.64	1.44	0.41, 5.10	0.57
Other/ Unknown	0.84	0.53, 1.34	0.47	0.82	0.45, 1.49	0.51
Ethnicity						
Non-Hispanic (ref)	-	-	-			
Hispanic	2.29	1.45, 3.61	<0.01*	1.71	0.91, 3.21	0.09
Unknown	1.18	0.73, 1.92	0.50	0.60	0.29, 1.22	0.16
Region						
Midwest (ref)	-	-	-	-	-	-
Northeast	0.52	0.31, 0.86	0.01*	0.84	0.42, 1.67	0.62
South	0.73	0.50, 1.06	0.10	0.91	0.52, 1.62	0.76
West	1.15	0.70, 1.89	0.57	1.61	0.79, 3.29	0.19
Other/Unknown	0.62	0.20, 1.93	0.41	1.86	0.64, 5.41	0.25
Insurance Type						
Commercial (ref)	-	-	-	-	-	-
Medicaid/Medicare	1.49	0.97, 2.27	0.07	0.83	0.45, 1.54	0.56
Unknown	3.54	0.80, 15.69	0.10	1.64	0.36, 7.60	0.53
Renal function						
Stage 1 CKD (ref)	-	-	-	-	-	-
Stage 2 CKD	-	-	-	1.18	0.34, 4.07	0.80
Stage 3 CKD	-	-	-	0.42	0.12, 1.42	0.16
Stage 4 CKD	-	-	-	0.36	0.09, 1.43	0.15
Stage 5 CKD	-	-	-	0.23	0.01, 4.21	0.32
eGFR	0.95	0.94, 0.96	<0.01*	0.95	0.93, 0.97	<0.01*
Comorbidities						
Acute kidney injury	1.33	0.86, 2.05	0.20	2.00	1.24, 3.23	<0.01*
Congestive heart failure	1.08	0.62, 1.89	0.78	1.38	0.78, 2.44	0.26
Cardiac arrhythmia	1.41	0.88, 2.26	0.15	2.42	1.46, 4.00	<0.01*
Peripheral vascular disorders	1.34	0.81, 2.24	0.26	0.62	0.28, 1.41	0.26
Hypertension	1.16	0.86, 1.56	0.32	1.37	0.89, 2.11	0.15
Chronic pulmonary disease	0.52	0.20, 1.33	0.17	0.88	0.43, 1.81	0.73

	New Diagnosis of CKD[1]			Worsening of CKD[2]		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Diabetes complicated	0.74	0.36, 1.52	0.41	0.60	0.26, 1.37	0.22
Hypothyroidism	0.49	0.22, 1.09	0.08	2.90	1.42, 5.91	<0.01*
Malignant Neoplasms	1.37	0.70, 2.67	0.36	0.55	0.24, 1.29	0.17
Fluid and Electrolyte Disorders	0.54	0.25, 1.19	0.13	1.96	0.99, 3.87	0.05
Depression	1.55	0.85, 2.82	0.15	0.28	0.06, 1.31	0.11
Anti-diabetic Drugs						
Biguanides	0.61	0.43, 0.87	<0.01*	0.86	0.50, 1.50	0.59
DPP-4 Inhibitors	0.48	0.25, 0.92	0.03*	0.68	0.45, 1.64	0.65
GLP-1 Agonists	1.20	0.56, 2.56	0.64	0.78	0.30, 2.00	0.60
Insulin	1.37	0.99, 1.90	0.06	1.52	0.99, 2.32	0.06
SGLT-2 Inhibitors	0.34	0.08, 1.46	0.15	0.08	<0.01, 1.28	0.07
Sulfonylureas	1.25	0.84, 1.86	0.27	1.83	1.10, 3.06	0.02*
Treatment-related information						
Index Year						
2011 (ref)	-	-	-	-	-	-
2012	0.53	0.20, 1.37	0.19	1.67	0.19, 14.30	0.64
2013	0.55	0.21, 1.47	0.23	3.12	0.46, 20.97	0.24
2014	0.87	0.34, 2.22	0.76	1.67	0.25, 11.32	0.60
2015	0.73	0.29, 1.84	0.50	3.53	0.53, 23.70	0.19
2016	0.66	0.25, 1.73	0.39	6.55	1.13, 37.99	0.03*
2017	0.73	0.31, 1.74	0.47	5.84	1.03, 33.06	0.04*
2018	0.49	0.20, 1.23	0.13	7.32	1.29, 41.47	0.02*
2019	0.31	0.07, 1.27	0.10	4.56	0.67, 30.85	0.12
2020	-	-	-	-	-	-
COVID-19	-	-	-	-	-	-

[1]Adjusted accelerated failure time (AFT) models for a new diagnosis of CKD within two years
[2]Adjusted Cox proportional hazard model for worsening of CKD within two years
*indicates statistical significance ($p<0.05$)

Appendix Table 10 Adjusted Cox Proportional Hazards Models for Secondary Endpoints Within a Two-Year Follow-Up

	Composite Endpoint (Overall Hospitalization or Death)			Overall Hospitalization		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Treatment						
Anti-VEGF	1.20	0.95, 1.51	0.13	1.17	0.97, 1.41	0.11
Laser (ref)	-	-	-	-	-	-
Demographic characteristics						
Female	0.76	0.60, 0.98	0.03*	0.91	0.75, 1.11	0.37
Age (every 10 years)	0.92	0.82, 1.04	0.17	0.98	0.89, 1.08	0.69
Race						
Caucasian (ref)	-	-	-	-	-	-
African American	1.41	1.02, 1.94	0.04*	1.32	1.02, 1.72	0.04*
Asian	0.73	0.29, 1.83	0.50	1.16	0.64, 2.09	0.62
Other/ Unknown	1.04	0.73, 1.49	0.83	1.17	0.88, 1.56	0.28
Ethnicity						
Non-Hispanic (ref)	-	-	-	-	-	-
Hispanic	0.88	0.58, 1.34	0.55	0.87	0.63, 1.21	0.42
Unknown	0.96	0.67, 1.38	0.84	0.83	0.61, 1.11	0.21
Region						
Midwest (ref)	-	-	-	-	-	-
Northeast	1.14	0.82, 1.60	0.44	1.02	0.77, 1.35	0.89
South	0.91	0.67, 1.23	0.53	0.93	0.74, 1.19	0.58
West	0.68	0.44, 1.04	0.07	0.74	0.54, 1.03	0.07
Other/Unknown	1.32	0.66, 2.61	0.43	1.39	0.79, 2.45	0.25
Insurance Type						
Commercial (ref)	-	-	-	-	-	-
Medicaid/Medicare	1.26	0.91, 1.73	0.16	1.27	0.98, 1.64	0.07
Unknown	2.07	0.63, 6.75	0.23	1.69	0.57, 4.99	0.35
Renal function						
No CKD (ref)	-	-	-	-	-	-
Stage 1 CKD	0.60	0.19, 1.83	0.36	1.01	0.50, 2.06	0.98
Stage 2 CKD	0.59	0.33, 1.06	0.08	0.75	0.48, 1.18	0.21
Stage 3 CKD	0.89	0.65, 1.22	0.47	0.99	0.77, 1.29	0.96
Stage 4 CKD	1.01	0.59, 1.73	0.97	1.30	0.84, 1.99	0.24
Stage 5 CKD	0.44	0.03, 5.92	0.54	0.39	0.03, 4.98	0.47
eGFR	0.99	0.98, 1.00	0.17	1.00	0.99, 1.00	0.13
Comorbidities						
Acute kidney injury	1.69	1.22, 2.35	<0.01*	1.29	0.96, 1.72	0.09
Congestive heart failure	2.00	1.41, 2.84	<0.01*	1.86	1.37, 2.51	<0.01*
Cardiac arrhythmia	1.51	1.09, 2.08	0.01	1.42	1.09, 1.86	<0.01*

	Composite Endpoint (Overall Hospitalization or Death)			Overall Hospitalization		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Peripheral vascular disorders	1.34	0.93, 1.95	0.12	1.41	1.03, 1.92	0.03*
Hypertension	1.18	0.93, 1.49	0.17	1.15	0.96, 1.39	0.13
Chronic pulmonary disease	1.30	0.87, 1.94	0.19	1.20	0.85, 1.68	0.30
Diabetes complicated	0.99	0.60, 1.63	0.96	1.01	0.65, 1.58	0.96
Hypothyroidism	1.55	0.99, 2.40	0.05	1.33	0.93, 1.90	0.13
Malignant Neoplasms	0.91	0.57, 1.44	0.68	0.69	0.46, 1.03	0.07
Fluid and Electrolyte Disorders	1.31	0.82, 2.07	0.26	1.20	0.80, 1.78	0.38
Depression	0.96	0.58, 1.59	0.86	0.88	0.58, 1.34	0.56
Anti-diabetic Drugs						
Biguanides	1.00	0.76, 1.31	0.97	0.92	0.74, 1.15	0.46
DPP-4 Inhibitors	0.67	0.44, 1.03	0.07	0.78	0.56, 1.08	0.13
GLP-1 Agonists	0.48	0.25, 0.91	0.02*	0.71	0.44, 1.15	0.16
Insulin	1.33	1.04, 1.71	0.02*	1.21	0.99, 1.48	0.06
SGLT-2 Inhibitors	0.72	0.35, 1.50	0.39	0.71	0.38, 1.34	0.29
Sulfonylureas	1.38	1.02, 1.87	0.04*	1.21	0.94, 1.56	0.13
Treatment-related information						
Index Year						
2011 (ref)	-	-	-	-	-	-
2012	0.89	0.38, 2.08	0.78	0.79	0.43, 1.44	0.44
2013	1.21	0.54, 2.72	0.65	0.87	0.48, 1.57	0.64
2014	0.89	0.39, 2.02	0.77	0.77	0.43, 1.39	0.38
2015	0.79	0.35, 1.79	0.56	0.73	0.41, 1.31	0.29
2016	1.03	0.46, 2.29	0.94	0.70	0.39, 1.24	0.22
2017	1.07	0.50, 2.28	0.86	0.63	0.36, 1.09	0.10
2018	1.21	0.57, 2.60	0.62	0.57	0.32, 0.99	0.04*
2019	1.96	0.80, 4.85	0.14	0.67	0.32, 1.38	0.28
2020	-	-	-	-	-	-
COVID-19	-	-	-	-	-	-

*indicates statistical significance ($p<0.05$)

Appendix Table 11 Adjusted Cox Proportional Hazards Models for Exploratory Endpoints

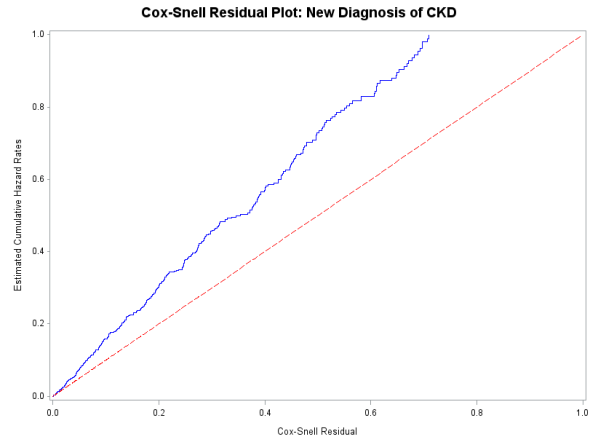
	40% eGFR Reduction Within a One-Year Follow-Up			40% eGFR Reduction Within a Two-Year Follow-Up		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Treatment						
Anti-VEGF	1.15	0.94, 1.40	0.18	1.24	0.99, 1.54	0.06
Laser (ref)	-	-	-	-	-	-
Demographic characteristics						
Female	1.47	1.18, 1.82	<0.01*	1.44	1.14, 1.82	<0.01*
Age (every 10 years)	0.77	0.70, 0.85	<0.01*	0.82	0.73, 0.92	<0.01*
Race						
Caucasian (ref)	-	-	-	-	-	-
African American	0.78	0.59, 1.05	0.10	1.32	0.99, 1.78	0.06
Asian	1.35	0.73, 2.49	0.34	1.48	0.75, 2.89	0.26
Other/ Unknown	0.88	0.63, 1.23	0.45	0.97	0.67, 1.39	0.85
Ethnicity						
Non-Hispanic (ref)	-	-	-	-	-	-
Hispanic	1.28	0.92, 1.79	0.14	1.38	0.98, 1.95	0.07
Unknown	0.85	0.60, 1.20	0.34	0.56	0.38, 0.85	<0.01*
Region						
Midwest (ref)	-	-	-	-	-	-
Northeast	0.64	0.44, 0.93	0.02*	0.70	0.47, 1.03	0.07
South	1.11	0.85, 1.45	0.44	1.04	0.78, 1.38	0.78
West	1.07	0.76, 1.49	0.71	0.86	0.58, 1.26	0.44
Other/Unknown	1.45	0.87, 2.41	0.16	1.41	0.75, 2.63	0.29
Insurance Type						
Commercial (ref)	-	-	-	-	-	-
Medicaid/Medicare	0.94	0.72, 1.24	0.67	1.42	1.05, 1.93	0.02*
Unknown	1.64	0.74, 3.59	0.22	3.51	1.52, 8.10	<0.01*
Renal function						
No CKD (ref)	-	-	-	-	-	-
Stage 1 CKD	1.08	0.58, 2.02	0.81	1.95	0.97, 3.89	0.06
Stage 2 CKD	1.58	1.06, 2.36	0.03*	1.10	0.68, 1.76	0.71
Stage 3 CKD	1.75	1.32, 2.33	<0.01*	1.47	1.09, 1.98	0.01*
Stage 4 CKD	3.00	1.92, 4.68	<0.01*	2.03	1.25, 3.28	<0.01*
Stage 5 CKD	0.00	0.00, 0.00	0.97	0.00	0.00, 0.00	0.96
eGFR	1.02	1.01, 1.03	<0.01*	1.02	1.01, 1.03	<0.01*
eGFR* log(time)	0.99	0.99, 0.99	<0.01*	0.99	0.99, 0.99	<0.01*
Comorbidities						
Acute kidney injury	2.30	1.75, 3.01	<0.01*	2.18	1.62, 2.95	<0.01*
Congestive heart failure	1.32	0.99, 1.76	0.06	1.66	1.18, 2.34	<0.01*
Cardiac arrhythmia	0.86	0.63, 1.17	0.34	1.17	0.86, 1.59	0.33
Peripheral vascular disorders	1.13	0.82, 1.54	0.46	1.16	0.79, 1.69	0.45

	40% eGFR Reduction Within a One-Year Follow-Up			40% eGFR Reduction Within a Two-Year Follow-Up		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Hypertension	1.86	1.50, 2.30	<0.01*	1.28	1.02, 1.59	0.03*
Chronic pulmonary disease	1.40	1.01, 1.94	0.04*	0.82	0.53, 1.27	0.37
Diabetes complicated	0.62	0.37, 1.04	0.07	0.48	0.27, 0.86	0.01*
Hypothyroidism	1.45	0.99, 2.11	0.04*	1.09	0.71, 1.67	0.70
Malignant Neoplasms	1.57	1.11, 2.23	0.01*	1.10	0.74, 1.65	0.64
Fluid and Electrolyte Disorders	1.53	1.06, 2.18	0.02*	0.99	0.61, 1.63	0.98
Depression	1.00	0.66, 1.53	0.99	0.61	0.35, 1.06	0.08
Anti-diabetic Drugs						
Biguanides	1.33	1.04, 1.69	0.02*	0.92	0.71, 1.19	0.53
DPP-4 Inhibitors	0.58	0.39, 0.87	<0.01*	0.53	0.34, 0.82	<0.01
GLP-1 Agonists	0.97	0.64, 1.45	0.87	0.79	0.49, 1.29	0.35
Insulin	0.95	0.77, 1.17	0.63	1.32	1.05, 1.67	0.02*
SGLT-2 Inhibitors	0.68	0.34, 1.34	0.26	1.56	0.89, 2.76	0.12
Sulfonylureas	0.87	0.65, 1.16	0.33	1.17	0.88, 1.55	0.29
Treatment-related information						
Index Year						
2011 (ref)	-	-	-	-	-	-
2012	0.35	0.17, 0.74	<0.01*	0.89	0.35, 2.27	0.81
2013	0.28	0.13, 0.59	<0.01*	0.41	0.16, 1.10	0.08
2014	0.46	0.22, 0.96	0.04*	0.74	0.29, 1.90	0.53
2015	0.45	0.22, 0.94	0.03*	0.71	0.28, 1.81	0.48
2016	0.31	0.15, 0.65	<0.01*	1.14	0.46, 2.78	0.78
2017	0.39	0.20, 0.78	<0.01*	0.83	0.35, 2.00	0.768
2018	0.40	0.21, 0.77	<0.01*	0.81	0.34, 1.97	0.65
2019	0.39	0.20, 0.77	<0.01*	0.59	0.21, 1.69	0.33
2020	0.90	0.28, 2.90	0.86	-	-	-
COVID-19	0.60	0.19, 1.93	0.39	-	-	-

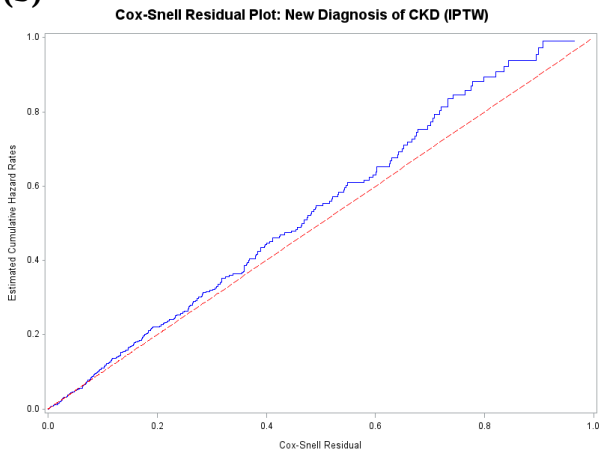
*indicates statistical significance (p<0.05)

Appendix C Cox-Snell Residual Plots of Cox Regression and Accelerated Failure Time Models

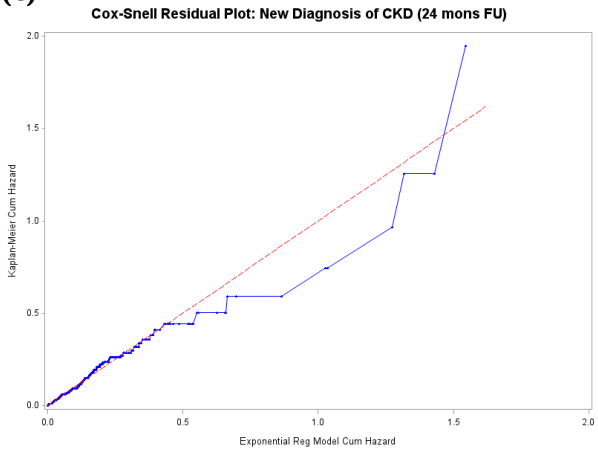
(a)



(b)



(c)



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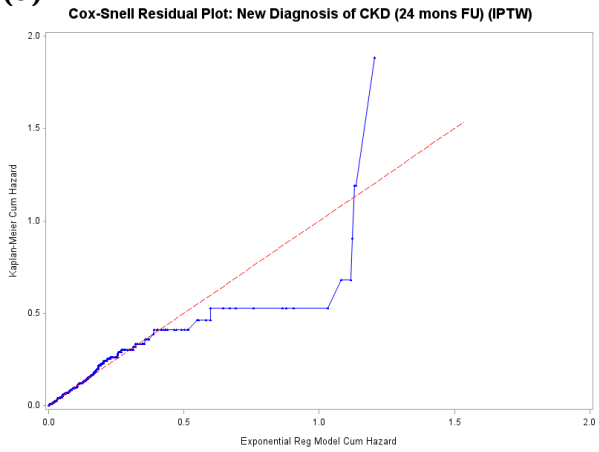

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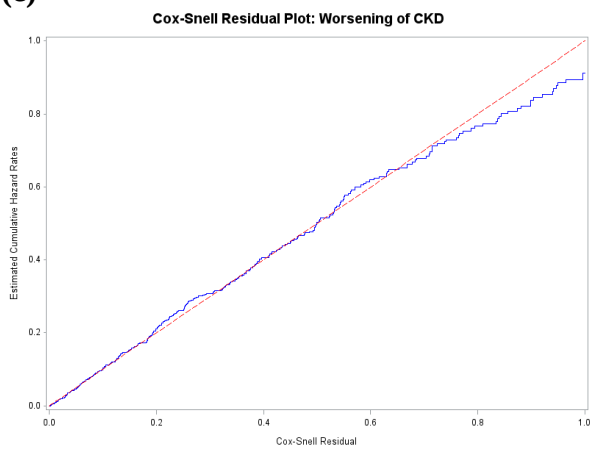

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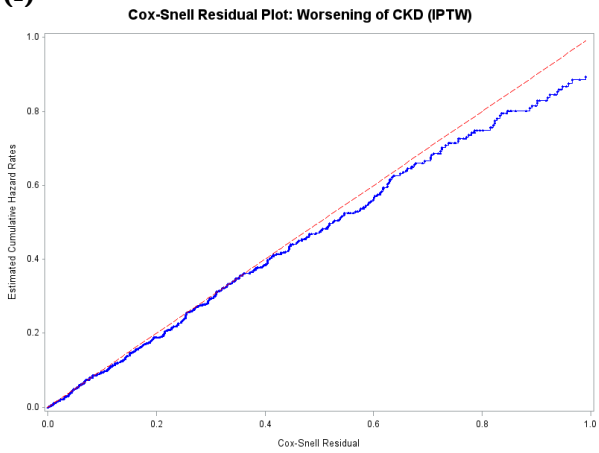

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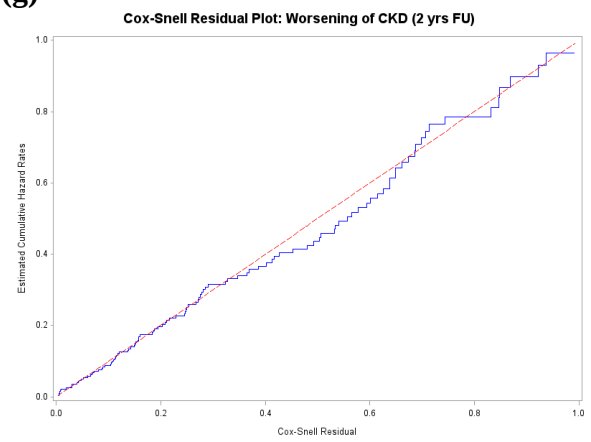
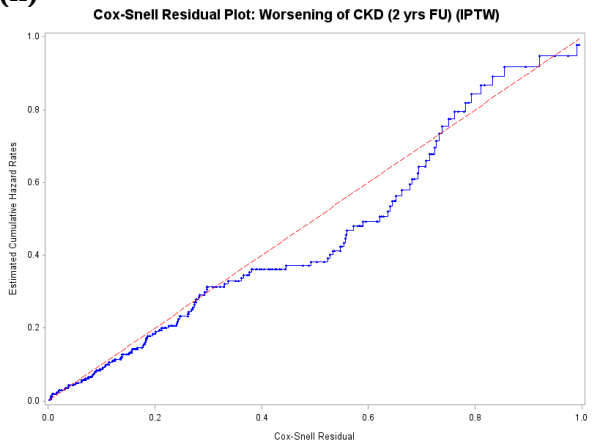
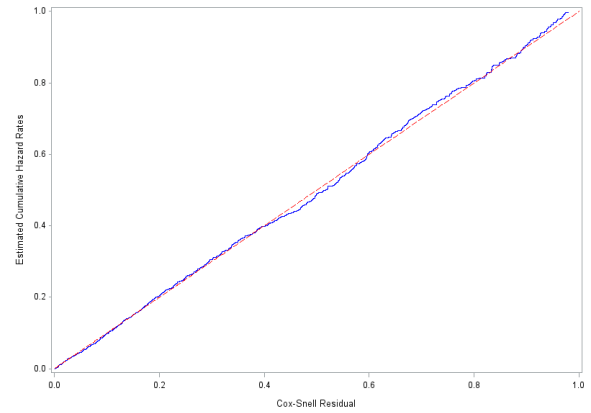

Cox-Snell Residual Plot: Worsening of CKD (2 yrs FU)
Estimated Cumulative Hazard Rates
Cox-Snell Residual
0.0
0.2
0.4
0.6
0.8
1.0

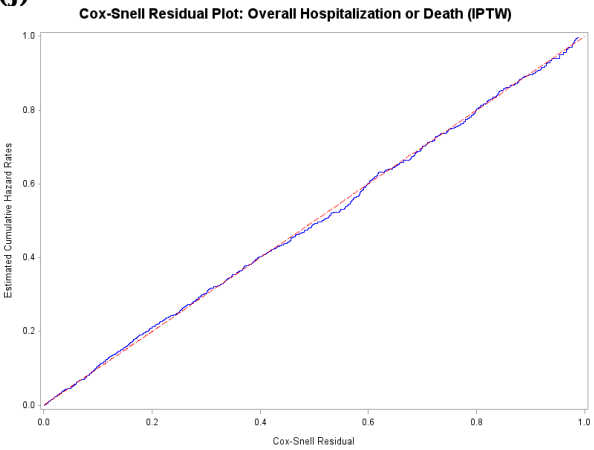
(h)


Cox-Snell Residual Plot: Worsening of CKD (2 yrs FU) (IPTW)
Estimated Cumulative Hazard Rates
Cox-Snell Residual
0.0
0.2
0.4
0.6
0.8
1.0

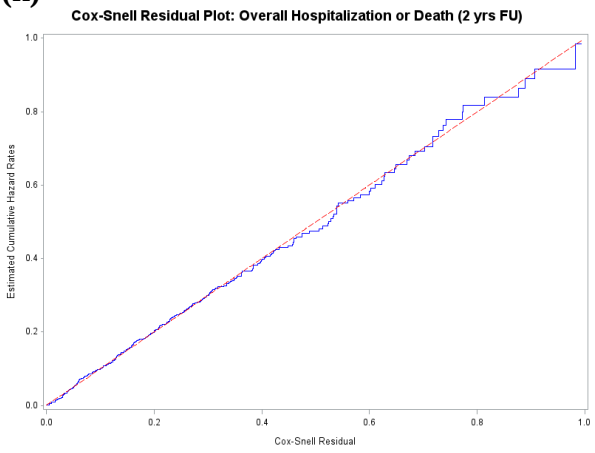
(i)


Cox-Snell Residual Plot: Overall Hospitalization or Death
Estimated Cumulative Hazard Rates
Cox-Snell Residual
0.0
0.2
0.4
0.6
0.8
1.0

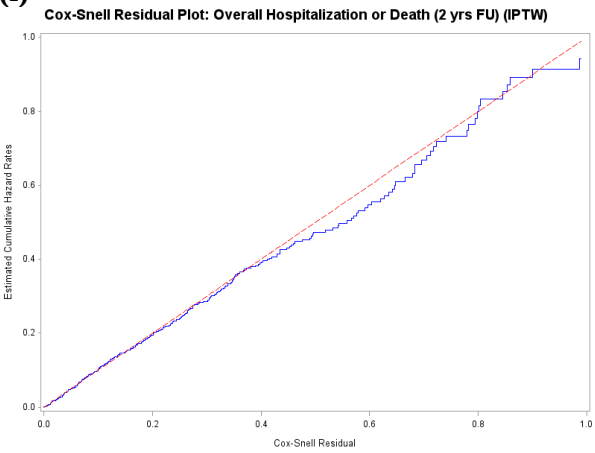
(j)


Cox-Snell Residual Plot: Overall Hospitalization or Death (IPTW)
Estimated Cumulative Hazard Rates
Cox-Snell Residual
0.0
0.2
0.4
0.6
0.8
1.0

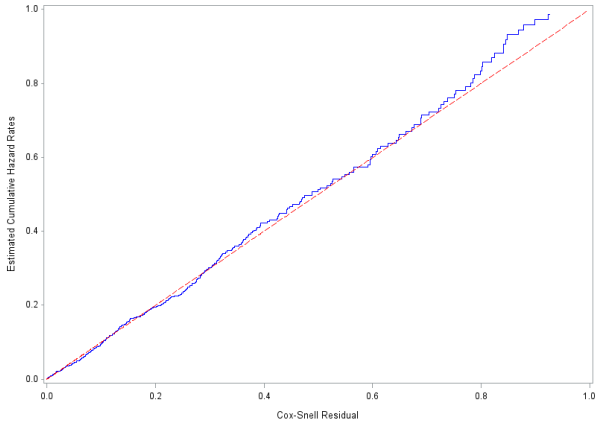
(k)


Cox-Snell Residual Plot: Overall Hospitalization or Death (2 yrs FU)
Estimated Cumulative Hazard Rates
Cox-Snell Residual
0.0
0.2
0.4
0.6
0.8
1.0

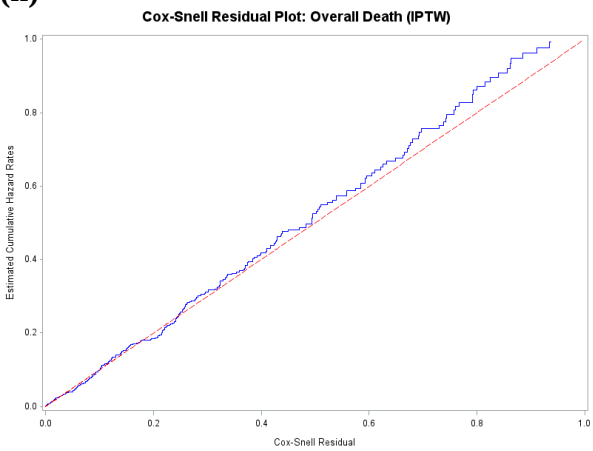
(l)


Cox-Snell Residual Plot: Overall Hospitalization or Death (2 yrs FU) (IPTW)
Estimated Cumulative Hazard Rates
Cox-Snell Residual
0.0
0.2
0.4
0.6
0.8
1.0

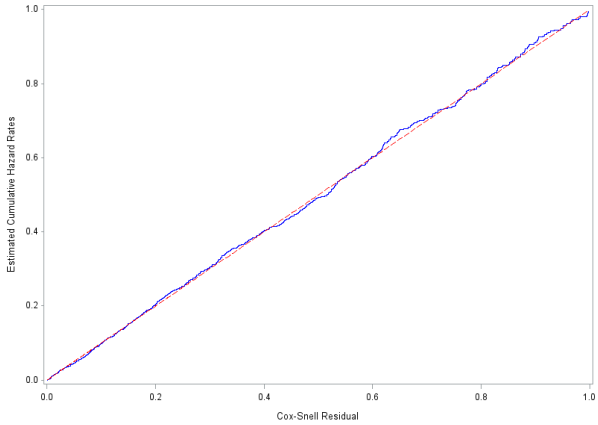
(m)


Cox-Snell Residual Plot: Overall Death
Estimated Cumulative Hazard Rates
Cox-Snell Residual
0.0
0.2
0.4
0.6
0.8
1.0

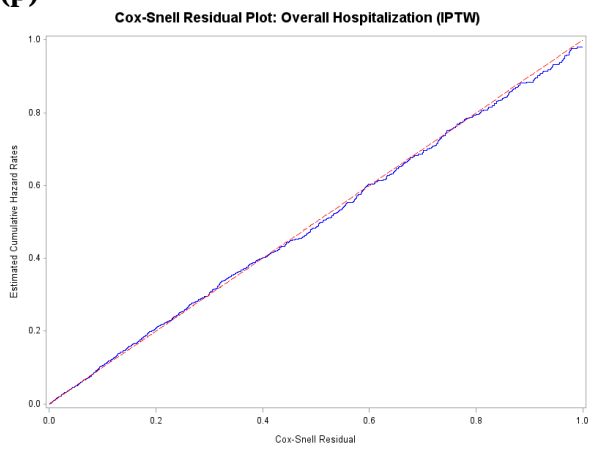
(n)


Cox-Snell Residual Plot: Overall Death (IPTW)
Estimated Cumulative Hazard Rates
Cox-Snell Residual
0.0
0.2
0.4
0.6
0.8
1.0

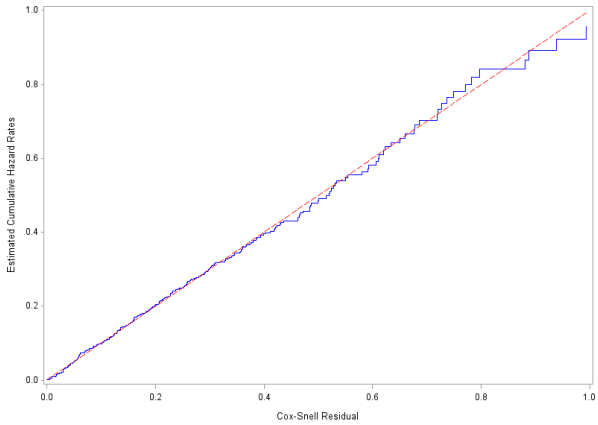
(o)


Cox-Snell Residual Plot: Overall Hospitalization
Estimated Cumulative Hazard Rates
Cox-Snell Residual
0.0
0.2
0.4
0.6
0.8
1.0

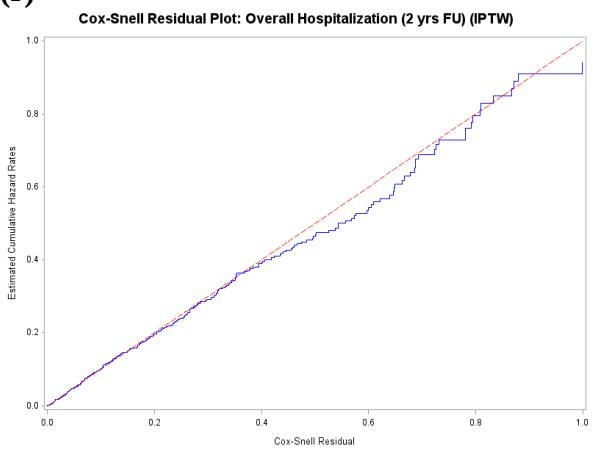
(p)


Cox-Snell Residual Plot: Overall Hospitalization (IPTW)
Estimated Cumulative Hazard Rates
Cox-Snell Residual
0.0
0.2
0.4
0.6
0.8
1.0

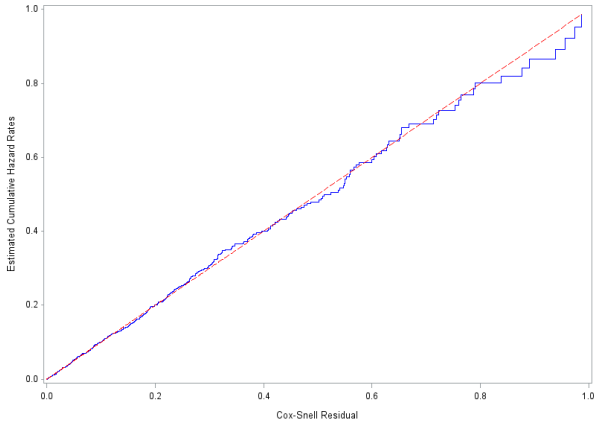
(q)


Cox-Snell Residual Plot: Overall Hospitalization (2 yrs FU)
Estimated Cumulative Hazard Rates
Cox-Snell Residual
0.0
0.2
0.4
0.6
0.8
1.0

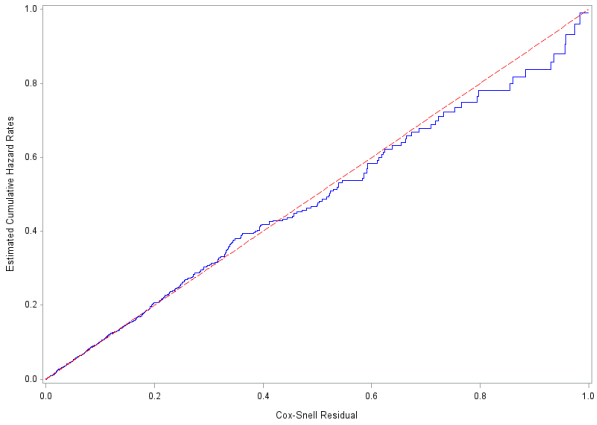
(r)


Cox-Snell Residual Plot: Overall Hospitalization (2 yrs FU) (IPTW)
Estimated Cumulative Hazard Rates
Cox-Snell Residual
0.0
0.2
0.4
0.6
0.8
1.0

(s)


Cox-Snell Residual Plot: Thromboembolic Events
Estimated Cumulative Hazard Rates
Cox-Snell Residual
0.0
0.2
0.4
0.6
0.8
1.0

(t)


Cox-Snell Residual Plot: Thromboembolic Events (IPTW)
Estimated Cumulative Hazard Rates
Cox-Snell Residual
0.0
0.2
0.4
0.6
0.8
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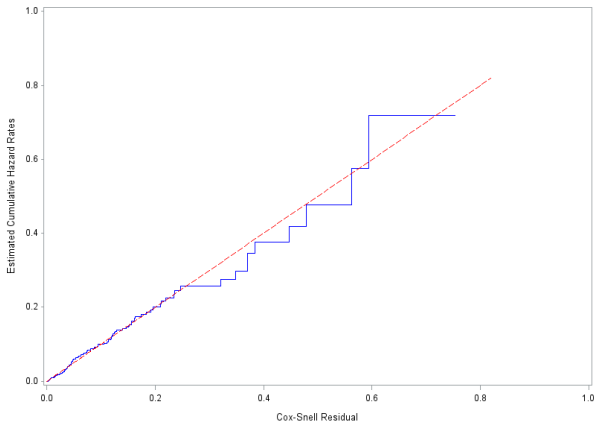
(u)


Cox-Snell Residual Plot: Thromboembolic Events (2 yrs FU)
Estimated Cumulative Hazard Rates
Cox-Snell Residual
0.0
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0.4
0.6
0.8
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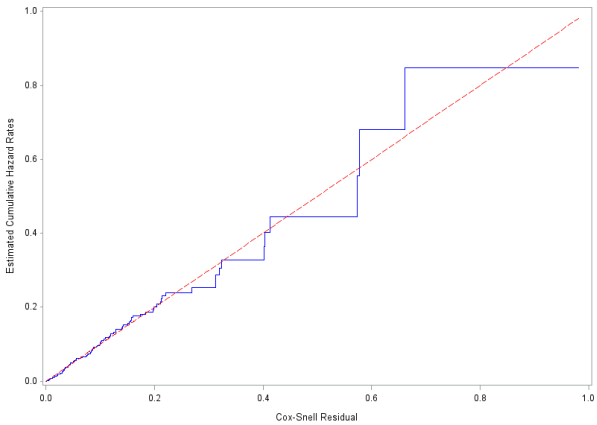
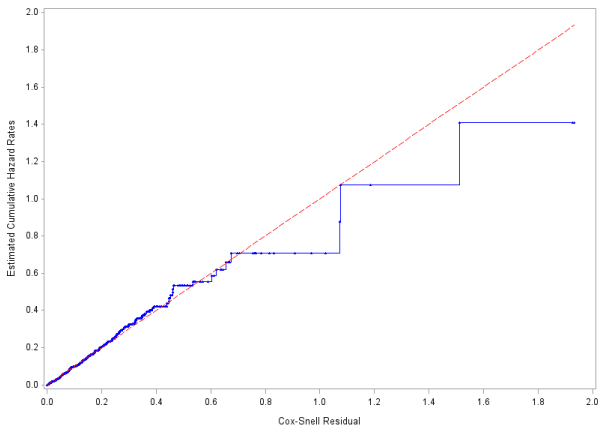
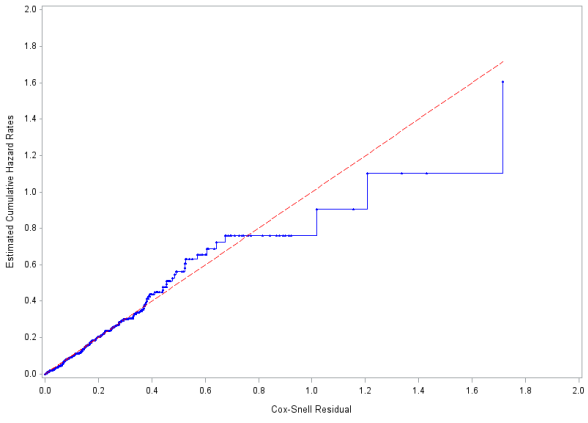
(v)


Cox-Snell Residual Plot: Thromboembolic Events (2 yrs FU) (IPTW)
Estimated Cumulative Hazard Rates
Cox-Snell Residual
0.0
0.2
0.4
0.6
0.8
1.0

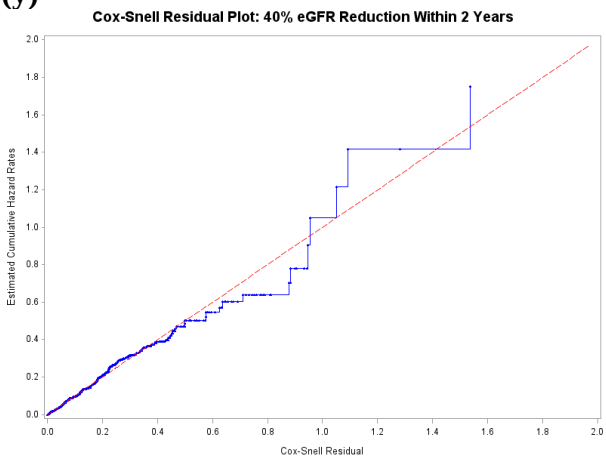
(w)


Cox-Snell Residual Plot: 40% eGFR Reduction within 1 Year
Estimated Cumulative Hazard Rates
Cox-Snell Residual
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0

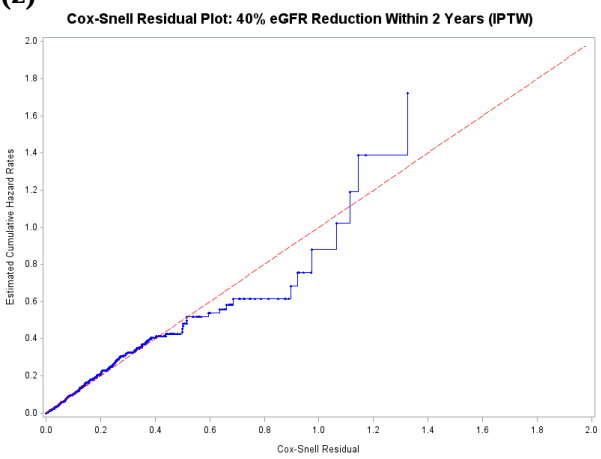
(x)


Cox-Snell Residual Plot: 40% eGFR Reduction within 1 Year (IPTW)
Estimated Cumulative Hazard Rates
Cox-Snell Residual
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0

(y)



(z)



Abbreviations: yrs= years; FU= follow-up; IPTW= inverse prpoensity treatment weighting

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