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## Effect of prior anti-VEGF injections on the risk of retained lens fragments and endophthalmitis post cataract surgery in the elderly

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### Abstract

**Objective**—To investigate the effect of prior intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections on surgical and postoperative complication rates associated with cataract surgery in a nationally representative longitudinal sample of elderly persons.

**Design**—Retrospective, longitudinal cohort analysis

**Participants**—203,643 Medicare beneficiaries who underwent cataract surgery from January 1, 2009 to December 31, 2013.

**Methods**—Using the 5% sample of Medicare claims data, the study assessed risks of 3 adverse outcomes following receipt of cataract surgery for beneficiaries with a history of prior intravitreal injections. Risks of these outcomes in beneficiaries with a history of intravitreal injections relative to those without were calculated using the Cox proportional hazard model.

**Main Outcome Measures**—The primary outcome was the risk of subsequent removal of retained lens fragments within 28 days following cataract surgery. Secondary outcomes were a new diagnosis of acute (<40 days) or delayed onset (40+ days) endophthalmitis as well as risk of a new primary open angle glaucoma diagnosis within 365 days following cataract surgery.

**Results**—Prior intravitreal anti-VEGF injections were associated with a significantly increased risk of subsequent retained lens fragment removal within 28 days following cataract surgery (Hazard Ratio (HR): 2.26; 95% Confidence Interval (CI) 1.19–4.30). Prior injections were also associated with increased risk of HR both acute (HR:2.29; 95% CI 1.001 – 5.22) and delayed onset endophthalmitis (HR 3.65; 95% CI 1.65–8.05). Prior injections were not a significant indicator of increased risk of a new primary open angle glaucoma diagnosis.

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**Conclusions**—A history of intravitreal injections may be a risk factor for cataract surgery-related intraoperative complications and endophthalmitis. Given the frequency of intravitreal injections and cataract surgery, increased preoperative assessment, additional intraoperative caution, and postoperative vigilance are recommended in patients with a prior history of intravitreal injections undergoing cataract extraction.

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## INTRODUCTION

Intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents have revolutionized the treatment of retinal diseases, and along with cataract surgery, are the most common ophthalmologic procedures performed in the United States (U.S.).<sup>1</sup> Analyses of anti-VEGF injection-associated adverse events have generally focused on systemic complications, particularly thromboembolic events, and intraocular complications, including endophthalmitis, inflammation, retinal detachment, and elevated intraocular pressure.<sup>2, 3</sup>

There are a few published individual reports of needle penetration into the lens resulting in subclinical as well rapid cataract-inducing lenticular trauma following intravitreal injection.<sup>4-7</sup> A single case of “lens trauma” was reported in the combined Phase 3 data of the pivotal ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD) and MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD) trials following a total of 754 ranibizumab (Lucentis; Genentech, Inc; San Francisco, CA) injections for treatment of neovascular AMD.<sup>8, 9</sup> However, the impact of intravitreal injections on surgical complications associated with cataract surgery has not been rigorously investigated in large studies.

In addition to lenticular trauma, there is evidence that repeated intravitreal injections may be associated with sustained elevation of the intraocular pressure (IOP), which may secondarily increase rates of open angle glaucoma.<sup>10-12</sup> Cataract extraction can result in a decrease in IOP<sup>13</sup> and offset this elevation. Additionally, post-injection antibiotics, which were routinely administered until a recent paradigm shift away from their use after demonstration of a secondary increase in antibiotic-resistant ocular flora,<sup>14, 15</sup> may result in an increase in the rate of post-cataract endophthalmitis in eyes with a history of intravitreal injections. These relationships between intravitreal injections and surgical complications, post-cataract surgery endophthalmitis, and post-cataract surgery incidence of primary open angle glaucoma (POAG) have not been examined in large numbers, which are needed to elicit statistical significance in these rare events.

We used the 5% sample of Medicare claims data to determine the incidence of retained lens fragments requiring subsequent removal (as a surrogate for intraoperative complications), POAG, and both acute (<40 days) and delayed onset (40+ days)<sup>16</sup> endophthalmitis associated with cataract surgery in patients with and without a history of prior intravitreal anti-VEGF injections. We provide evidence suggesting that intravitreal injections may be associated with an increased risk of intraoperative complications and endophthalmitis.

## METHODS

Under a Duke University Institutional Review Board-approved protocol that adhered to the tenets of the Declaration of Helsinki, this study used data from the 2006–2013 Medicare 5% claims and enrollment files provided by the U.S. Centers for Medicare and Medicaid Services (CMS) on a restricted-access public use basis. This database contains longitudinal information on beneficiary demographic characteristics, diagnoses (International Classification of Diseases, 9th Revision Clinical Modification (ICD-9)), and procedures (Current Procedure Terminology - 4 (CPT-4) from a nationally representative sample of 5% of the total population of Medicare beneficiaries.

The claims files were used to identify Medicare beneficiaries with cataract surgery performed between January 1, 2009 and December 31, 2013 (Table 1). January 1, 2009 was chosen as the earliest date for inclusion in this study to allow a 3-year look-back period, i.e., to 2006, the year when the use of anti-VEGF agents had reached widespread use.<sup>17</sup> For this same reason, beneficiaries had to be at least 68 years of age at baseline. Beneficiaries who enrolled in Medicare Advantage (MA), a private alternative to traditional Medicare, were excluded from the analysis sample since claims data are not available for such Medicare beneficiaries. We also excluded beneficiaries who moved outside the U.S. at any time during the study period. Finally, beneficiaries with diagnoses of traumatic cataract, cataract secondary to ocular disorders, cataract associated with other disorders, infantile/congenital cataract, endophthalmitis, or those with an intravitreal injection of corticosteroids, pars plana vitrectomy, or gas pneumatic retinopexy performed during the look-back period were excluded from the sample. When more than one cataract surgery procedure was performed during the study period, the date of the earliest procedure was chosen as the baseline date while the date of the second procedure was treated as a censoring event as it would not be possible to determine which operation, or which eye was associated with an observed outcome. To be included in the POAG sub-sample an additional restriction of not having a prior diagnosis of glaucoma was imposed. After imposing these restrictions the final sample sizes were: 203,646 for RLF removal/endophthalmitis and 139,656 for POAG (Table 2).

The Cox proportional hazard model as implemented by Stata 11 (StataCorp. 2009. *Stata Statistical Software: Release 11*. College Station, TX: StataCorp LP) was used for the analysis with censoring methods devised for ophthalmologic studies according to the method of Javitt, et. al..<sup>18</sup> Individuals were treated as censored at the earliest of: the date of the second cataract surgery, death, entrance into a MA plan, and the end of the follow-up period (28 days – RLF, 365 days – POAG, <40 days – acute endophthalmitis, 365 days – delayed onset endophthalmitis. Common covariates were: prior history of intravitreal anti-VEGF injections, beneficiary age, male gender, race – black and other (reference group: white race), indicators for the calendar year – 2010, 2011, 2012, and 2013 (reference group: 2009), and a measure of severe co-morbidities represented by the Charlson index.<sup>19</sup> Anti-VEGF injections were specified by the CPT-4 code for intravitreal injection (67028) with a simultaneous claim for Healthcare Common Procedure Coding System (HCPCS) codes for pegaptanib sodium (Macugen; Valeant Pharmaceuticals, Inc., Montreal, CA), bevacizumab (Avastin, Genentech, Inc.), ranibizumab (Lucentis, Genentech, Inc.), aflibercept (Eylea, Regeneron, Inc., Tarrytown, NY), and unclassified biologics (previously reported to be used

almost exclusively for coding of bevacizumab prior to establishment of its HCPCS code<sup>20</sup>). Binary variables for diabetic retinopathy glaucoma, , and pseudoexfoliation at baseline were included as additional covariates in the equation for RLF-removal. Diabetes mellitus was the additional covariate in the POAG analysis.

## RESULTS

The proportion of beneficiaries who received anti-VEGF injections during the look-back period was 1.51% of the RLF-removal/endophthalmitis sub-sample, and 1.38% of the POAG sub-sample (Table 3). The age, gender and racial composition of the 2 sub-samples were similar, and each study year contributed a comparable number of beneficiaries. Within 28 days of cataract surgery, 0.20% of all eligible beneficiaries (0.43% with prior injections and 0.20% without prior injections) underwent subsequent RLF removal. Endophthalmitis was diagnosed within <40 days for 0.08% of all eligible beneficiaries (0.29% with prior injections and 0.08% without prior injections), while within 40–365 days post surgery, 0.04% received a diagnosis of endophthalmitis (0.23% with prior injections and 0.04% without prior injections). Within 1 year of cataract surgery, 0.35% of eligible beneficiaries (0.77% with prior injections and 0.34% without prior injections) were diagnosed with POAG, and 0.20% of eligible beneficiaries (0.75% with prior injections and 0.18% without prior injections) were diagnosed with endophthalmitis.. Beneficiaries who had a history of prior anti-VEGF injections had a higher risk of failure (as shown by the cumulative hazard function) in all parts of the analysis (Figure 1).

A prior history of anti-VEGF treatment was associated with a 126% increase [Hazard Ratio (HR): 2.26; 95% Confidence Interval (CI): 1.19 – 4.30] in the risk of requiring subsequent RLF-removal within 28 days of cataract surgery (Table 4). Men were at increased risk [HR: 1.38; 95% CI: 1.08 – 1.77]. The risk of RLF removal increased slightly with age [HR: 1.03; 95% CI: 1.01 – 1.06].

Prior anti-VEGF treatment was not a significant predictor of increased risk of being diagnosed with POAG within a year of cataract surgery. Male gender [HR: 1.37; 95% CI: 1.17 – 1.65], black race [HR: 3.18; 95% CI: 2.44 – 4.15], other race/ethnicity [HR: 2.02; 95% CI: 1.47 – 2.78], and older age [HR: 1.02; 95% CI: 1.001 – 1.03] were associated with increased risk.

A history of prior anti-VEGF injections was the primary factor associated with increased risk of endophthalmitis up to 40 days [HR: 2.29; 95% CI: 1.001 – 5.22] and 40–365 days [HR: 3.65; 95% CI: 1.65 – 8.05] from the cataract surgery date. The Charlson index was associated with a minor increase in risk [HR: 1.06; 95% CI: 1.02–1.10] in the probability of being diagnosed with endophthalmitis within <40 days only. Of the 171 total endophthalmitis claims within < 40 days (ICD-9 363.0x), the mean (standard deviation) time to diagnosis was 11.10 (11.67) days, and 6.43% (n=11) were coded as chronic endophthalmitis (ICD-9 363.03). Similarly, of the 79 total endophthalmitis claims within 40–365 days of surgery, the mean (standard deviation) time to diagnosis was 68.80 (31.20) days, and 6.3% (n=5) were coded as chronic endophthalmitis.

## DISCUSSION

The relationship between cataract surgery-associated complications and prior intravitreal injections of anti-VEGF agents has not been fully investigated to date. In a retrospective analysis of the pivotal ANCHOR and MARINA Phase 3 trials, Rosenfeld and co-authors concluded that cataract surgery is safe in patients with neovascular age-related macular degeneration (AMD) treated with ranibizumab.<sup>21</sup> Prompting their *post hoc* analysis was longstanding debated concern for progression of AMD following cataract surgery. This study focused on visual outcomes and did not specifically mention analysis of injection-related surgical complications in the 23 injection-treated eyes that underwent cataract extraction. Similarly, in other small retrospective case series, a history of prior intravitreal injections was not found to confer significant risk around cataract extraction of either AMD progression or intraoperative complications.<sup>22–24</sup>

Our study utilized a large, nationally representative, longitudinal sample of U.S. elderly individuals to investigate these relationships. A key strength of our study is the large, nationally representative sample size, critical for yielding ample statistical power required to detect differences in uncommon outcomes that are likely not detectable with small clinical studies. Given these large number of observations available from the 5% Medicare claims data, we could limit our analysis to injection of anti-VEGF agents, excluding beneficiaries with prior injection of steroids due to potential confounding effects with their well-known association with posterior subcapsular cataract formation, increased intraocular pressure, and glaucoma.<sup>25, 26</sup> A nationwide case-control study in which primary medical records data was obtained to confirm findings generated by the above analytic method confirmed the accuracy of estimates of outcome and proportional hazard despite the second eye ambiguity<sup>27</sup>. We identified an increased risk of subsequent RLF-removal within 28 days following cataract surgery in patients with a prior history of intravitreal anti-VEGF injections. Of note, in 2001, the anterior vitrectomy codes (CPT-4 67005 and 67010) were bundled with the cataract surgery codes (CPT-4 66982 and 66984). As a result of this coding change, identification of patients with intraoperative complications during cataract surgery, such as posterior capsular rupture requiring anterior vitrectomy, was not possible from analysis of claims data. Our finding of 126% increased risk is almost certainly an underestimate of the true risk for posterior capsular rupture, which can often be managed without the need for subsequent RLF-removal. In a large retrospective analysis of cataract surgery performed in the United States Veterans Health Administration system, RLF occurred in 0.20% of veterans, consistent with the overall rate of 0.20% identified in this study, while posterior capsular rupture and/or anterior vitrectomy occurred in 3.5% of veterans.<sup>28</sup> Multivariate analysis confirmed increased risk of RLF in beneficiaries who were male and elderly, consistent with known associations for increased risk of posterior capsular rupture.<sup>29</sup>

Our analysis did not detect an increased risk of POAG following cataract surgery in beneficiaries with a prior history of anti-VEGF intravitreal injections, contrary to recent studies identifying sustained elevation of intraocular pressure with intravitreal injections.<sup>10–12</sup> Further studies, with pathophysiologic and clinic correlations, are warranted to determine if significant IOP elevations are truly associated with intravitreal injections and

if cataract extraction affects this potential risk of POAG, through synergistic or antagonistic effects, in individuals with prior anti-VEGF treatment. Multivariate analysis confirmed increased risk for POAG in beneficiaries who were older, male, black, and of other race, consistent with known associations.<sup>30</sup>

Our analysis revealed an increased risk of endophthalmitis following cataract surgery in beneficiaries with a history of anti-VEGF injections. In the group of endophthalmitis diagnoses within <40 days, the mean time to endophthalmitis was 11 days following cataract surgery, consistent with an association with cataract surgery in the setting of prior injections. In contrast, in both groups of endophthalmitis within <40 days and 40-365 days, only approximately 6% of endophthalmitis claims were coded as chronic endophthalmitis. Furthermore, there was no difference in rate of chronic endophthalmitis between groups, suggesting that the increased risk of endophthalmitis 40-365 days following cataract surgery may not represent chronic endophthalmitis from cataract surgery but rather acute endophthalmitis due to ongoing injections or possibly other procedures. Further analysis of the Medicare claims data is needed to determine if this increased risk of both early-onset and delayed endophthalmitis in beneficiaries with prior anti-VEGF is affected by a history of cataract surgery or simply represents the increased risk inherent in intravitreal injections.

This increased diagnosis of endophthalmitis is unlikely to result from differences in follow up, as the aggressive course of endophthalmitis will invariably prompt immediate evaluation and treatment. Although we excluded those with a prior history of an endophthalmitis Medicare claim, we did not exclude beneficiaries having received prior intravitreal injections of antibiotics. Inclusion of unclassified injections, previously shown to consist almost 100% of bevacizumab,<sup>20</sup> may have inadvertently included beneficiaries incorrectly coded for an injection of antibiotic agents, resulting in selection bias. Further studies are needed to confirm and better understand this relationship. Finally increased risk for the development of endophthalmitis within <40 days of surgery was observed in Medicare beneficiaries with a higher Charlson index<sup>31, 32</sup>

We acknowledge several important study limitations. The Medicare database consists of information collected for billing purposes and not for clinical investigations. Conditions may sometimes have been incorrectly coded. In addition, the database does not include all potentially clinically relevant codes. The Medicare database is limited in its inability to identify which eye has the disease, and it is possible that the associations observed in this study apply to the same individual but in different eyes. By taking only the earliest case of cataract surgery, and censoring the patient should a subsequent cataract surgery occur, any errors in our study due to this limitation are likely to be on the conservative side. Beneficiaries with a history of prior intravitreal injections likely have a chronic eye disease requiring ongoing treatment, and increased diagnoses may have been secondary to differences in follow-up; this possibility is unlikely to affect subsequent removal of lens fragments, which is typically determined at the time of cataract surgery, or diagnosis of endophthalmitis given its aggressive course. Despite these limitations, Medicare claims data have been shown to be able to properly identify clinical phenomena in numerous studies<sup>33-35</sup>. Use of such data in ophthalmology dates back to 1991<sup>36, 37</sup>. Such data have

been used to assess increased risk associated with ancillary procedures that occur at a date following receipt of cataract surgery<sup>38</sup>.

In a separate study (Paul Hahn, Kim Jiramongkolchai, Sandra Stinnett, Terry Kim. Increased rate of intraoperative complications during cataract surgery following intravitreal injections. Manuscript in preparation), Hahn and colleagues investigated clinical data from a review of 10,103 cataract surgeries at the Duke Eye Center from 2005-2012, in which we compared rates of intraoperative complications (posterior capsular rupture and/or anterior vitrectomy and/or unplanned 3-piece intraocular lens placement) during cataract surgery as well as rates of post-cataract surgery glaucoma-related outcomes and endophthalmitis in 197 eyes with prior intravitreal injections compared to a matched control group. In this clinical study, specific cataract surgery-related complications were directly assessed based on review of clinical records, identifying a significantly increased rate in eyes with a prior history of intravitreal injection compared to eyes without a history of injections (3% vs 0%,  $p=0.03$ ). No difference in intraocular pressure or change in glaucoma medication or surgery requirements was noted after excluding steroid-injected patients, and no cases of endophthalmitis were identified in either group. While this clinical study lacked sufficiently large numbers to appropriately power such an analysis of rare events or subtle changes, such clinical records-based data provides complementary evidence to this claims-based analysis, which together suggest that a history of prior intravitreal injections may be a risk factor for cataract surgery-related complications.

As the indications and need for intravitreal injections continue to rapidly grow, the burden of treatment has begun to extend beyond the retina specialist. Inadvertent interaction between the injection needle and the crystalline lens may result in increased rate of cataract surgery-related complications, and we recommend an intimate understanding of intraocular anatomic relationships, particularly of the posterior segment and lens, for practitioners performing intravitreal injections. Practitioners who perform such procedures should be aware of this potential for violation of the posterior capsule and be particularly mindful of these anatomic intraocular relationships, which are often displaced as the eye is intentionally torqued during the injection procedure. Similarly, cataract surgeons should be aware that a history of injections, which is becoming increasingly prevalent, may be an important risk factor for intraoperative complications. A vigilant preoperative assessment of the lens and posterior chamber should be performed with an understanding of surgical procedure modifications that can be performed to minimize intraoperative complications in the setting of a violated posterior capsule.<sup>6</sup> Cataract surgeons should also be aware that a history of prior injections may result in increased risk of postoperative endophthalmitis in addition to risk of intraoperative complications. Further studies are warranted to better explore these interactions.

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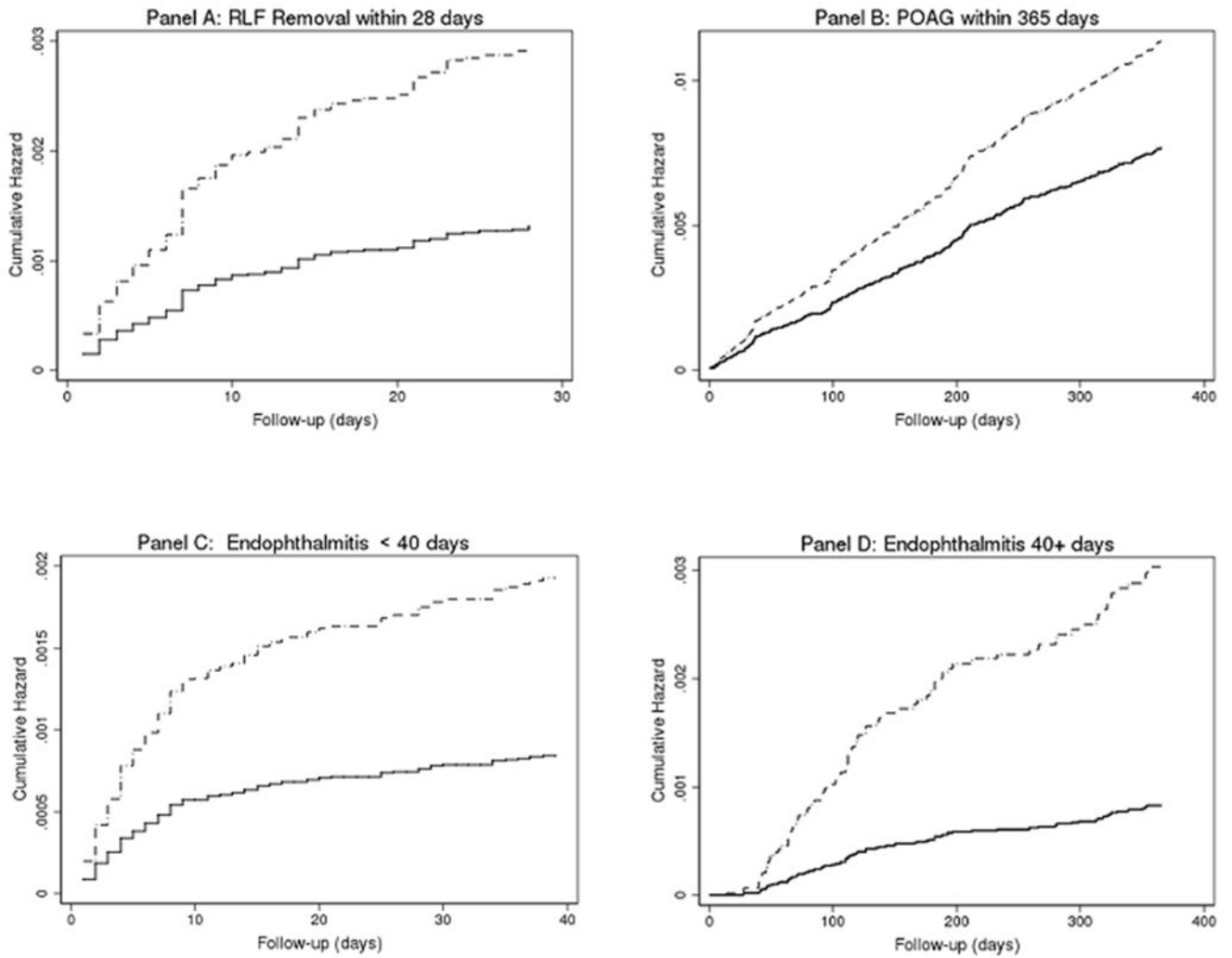
The sponsor or funding organization had no role in the design or conduct of this research

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**Figure 1.**  
Selected Outcomes Following Cataract Surgery  
solid line – No Anti-VEGF Injections; dash-dotted line – Anti-VEGF Injections

**Table 1**

## List of Study Codes

Condition	Administrative Code <sup>†</sup>
Cataract surgery	CPT-4: 66984 66982 67028 with C9399 J3490 J3590 J2503 J9035 Q2024 C9257 C9233 J2778
Intravitreal injection of anti-VEGF agent	CPT-4: Q2046 C9291 on the same claim
Outcomes	
Removal of RLF	CPT-4: 66850
Primary open angle glaucoma	ICD-9: 365.1x
Endophthalmitis	ICD-9: 360.0x
Exclusion restrictions	
Intravitreal injection of corticosteroid	CPT-4: 67028 with J3300 J3301 J3302 J7312 J1100 C9256 J1094 on the same claim
Pars plana vitrectomy	CPT-4: 67036 67038 67039 67040 67041 67042 67043 67108 67112 67113
Gas pneumatic retinopexy	CPT-4: 67110
Traumatic cataract	ICD-9: 366.2x
Cataract 2/2 ocular disorders	ICD-9: 366.3x
Cataract associated with other disorders	ICD-9: 366.4x
Infantile/congenital cataract	ICD-9: 366.0x
Coexisting conditions	
Pseudoexfoliation	ICD-9: 366.11
Diabetes mellitus	ICD-9: 250.xx
Diabetic retinopathy	ICD-9: 362.0x
Other glaucoma <sup>‡</sup>	ICD-9: 365 365.0x 365.2x 365.3x 365.4x 365.5x 365.6x 365.7x 365.8x 365.9x

<sup>†</sup> Codes are drawn from International Classification of Disease, 9th Revision, Clinical Modification (ICD-9), and Current Procedural Terminology (CPT-4).

<sup>‡</sup> Excludes Primary open angle glaucoma (ICD-9: 365.1x)

**Table 2**

## Sample Selection Summary

	<b>Sample Size</b>
<b>Initial Sample</b>	<b>278,199</b>
Loss to age restriction (68+)	33,040
Loss to Medicare Advantage membership restriction	12,358
Loss to location restriction	1,188
Loss to medical condition or procedure restriction	27,163
Loss due to prior steroid injection	563
Loss due to endophthalmitis prior to surgery	244
<b>Retained Lens Fragment (RLF) Removal/Endophthalmitis Sample</b>	<b>203,643</b>
Loss due to prior diagnosis of glaucoma	63,987
<b>Primary Open Angle Glaucoma Sample</b>	<b>139,656</b>

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**Table 3**

## Summary Statistics

Variable	Sample	
	RLF Removal / Endophthalmitis	Primary Open Angle Glaucoma
Removal of RLF within 28 days	0.0020	
Endophthalmitis within 39 days	0.0008	
Endophthalmitis 40+ days	0.0004	
Primary open angle glaucoma within 365 days		0.0035
Intravitreal injection of anti-VEGF agent	0.0151	0.0138
Diabetes mellitus	0.4086	0.3944
Diabetic retinopathy	0.0606	0.0562
Any glaucoma diagnosis	0.3142	
Primary open angle glaucoma	0.1393	
Other glaucoma in the absence of primary open angle glaucoma	0.1749	
Pseudoexfoliation	0.0203	0.0120
Charlson Index	4.51 (3.68)	4.39 (3.62)
Male	0.3648	0.3741
White	0.8923	0.9111
Black	0.0586	0.0450
Other	0.0478	0.0427
Age	77.61 (6.01)	77.36 (5.97)
Year 2009	0.2402	0.2477
Year 2010	0.2080	0.2087
Year 2011	0.1938	0.1931
Year 2012	0.1826	0.1808
Year 2013	0.1754	0.1697
N	203,643	139,656

Note: Numbers provided are proportion of sample for categorical variables and sample means with standard deviations in parentheses for continuous variables (Charlson Index, age).

Table 4

## Cox Proportional Hazard Model Results

	Outcome			
	Anterior Vitrectomy HR <sup>†</sup> [95% CI]	Primary Open Angle Glaucoma HR [95% CI]	Endophthalmitis <40 days HR [95% CI]	Endophthalmitis 40 days HR [95% CI]
Intravitreal injection of anti- VEGF agent	<b>2.26*</b> [1.19 4.30]	1.48 [0.88 2.48]	<b>2.29*</b> [1.00 5.22]	<b>3.65**</b> [1.65 8.05]
Diabetes mellitus		1.09 [0.90 1.33]		
Diabetic retinopathy	1.25 [0.78 2.01]			
Glaucoma	1.12 [0.86 1.44]			
Pseudoexfoliation	1.77 [0.93 3.35]			
Charlson index	1.00 [0.96 1.03]	1.00 [0.98 1.03]	<b>1.06**</b> [1.02 1.10]	1.02 [0.96 1.08]
Male	<b>1.38*</b> [1.08 1.77]	<b>1.37**</b> [1.15 1.65]	0.98 [0.72 1.35]	0.83 [0.52 1.33]
Black	1.07 [0.64 1.78]	<b>3.18**</b> [2.44 4.15]	1.63 [0.97 2.75]	1.66 [0.82 3.34]
Other	1.28 [0.77 2.12]	<b>2.02**</b> [1.47 2.78]	1.60 [0.89 2.89]	0.46 [0.11 1.89]
Age	<b>1.03**</b> [1.01 1.06]	<b>1.02*</b> [1.00 1.03]	1.01 [0.98 1.03]	1.01 [0.97 1.05]

<sup>†</sup> Hazard Ratio (HR) and 95% Confidence Interval (CI)

\* p 0.05;

\*\* p 0.01; Hazard ratios significant at these levels are in bold.

Note: Analysis also includes covariates for the year of cataract surgery (not shown). None of the associated hazard ratios are significant at conventional levels.