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Determinants in initial treatment choice for diabetic macular edema

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Abstract

Objective: To assess how patient choices (out-of-pocket costs, insurance plan, geographic region) impact initiation of therapy for diabetic macular edema(DME).

Design: Retrospective cohort study using administrative medical claims data from a large, national insurer.

Participants: All patients newly diagnosed with DME from 2013-2016 were observed for 90 days after diagnosis or until first treatment was received.

Methods: Multivariable logistic regression was used to create odds ratios comparing different baseline demographic and patient-related factors.

Outcome measures: The primary outcome was the odds of receiving the different possible initial treatments for DME (anti-vascular endothelial growth factors (anti-VEGF), focal laser, steroids or observation), no treatment and not following up.

Results: Of 6220 new DME patients, 3010 (48.4%) had a follow-up (fu) exam within 90 days of diagnosis. Among those with a fu exam, 1557(51.7%) had no treatment during the observation window. Treatment of the remaining 1453(48.3%) patients was comprised of 614(20.4%) with bevacizumab, 191(6.3%) with ranibizumab or aflibercept(rani/aflib), 560(18.6%) with focal laser, 38(1.3%) with steroid injection and 50(1.7%) with an injection of an unspecified drug. Having a

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Portions of this data will be presented at the International Conference on Pharmacoepidemiology in August 2019

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Brian VanderBeek had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

copay(vs. \$0) lowered the odds of receiving any treatment (OR:0.60, 95%CI:0.51-0.71, $p<0.001$) and of receiving each treatment individually (anti-VEGF treatment OR:0.72, 95%CI:0.59-0.88; bevacizumab OR:0.73, 95%CI:0.59-0.91; rani/aflib OR:0.70; 95%CI:0.49-0.99, focal laser OR: 0.44, 95%CI:0.35-0.55, $p<0.001$). Contrary to having a copay, having a high deductible and type of insurance plan were not associated with initiating treatment ($p>0.41$ for all comparisons). Patients in the Northeast had lower odds of initiating anti-VEGF treatment(OR:0.60, 95%CI: 0.44-0.82, $p<0.001$) and specifically bevacizumab(OR:0.47, 95%CI:0.33-0.67, $p<0.001$). Furthermore, Northeast patients who were treated with anti-VEGF had a higher odds of receiving rani/aflib compared to bevacizumab(OR:2.39, 95%CI:1.31-4.37, $p<0.001$). Southern Midwest patients had a higher odds of treatment (anti-VEGF OR:1.35, 95%CI: 1.02-1.77, $p<0.001$; bevacizumab (OR:1.40, 95%CI:1.04-1.87; focal laser OR:1.39, 95%CI: 1.01-1.89, $p<0.001$).

Conclusion: Patient choices such as copays and where they live are important factors in determining the initial choice in the treatment of DME.

Précis:

While not frequently considered within the patient-doctor relationship, patient choices like copay and geography are significant factors in determining initial treatment for diabetic macular edema.

Keywords

Diabetic macular edema; pharmacoepidemiology; trends; Anti-VEGF; Focal Laser; Steroids

Introduction

Recent advances in the treatment of diabetic macular edema(DME) have established anti-vascular endothelial growth factor (anti-VEGF) agents as the first-line therapy for this vision-threatening disease.¹⁻⁷ Despite this, real world data has shown that many DME patients receive injections less frequently than their clinical trial counterparts, and a substantial proportion are receiving therapies other than anti-VEGF.^{8,9} For decades now, researchers have been trying to understand how and why patients with a disease are treated differently. Across medicine, costs are often attributed as one of the causes of this differential.

While patients cannot always control the amount of medical care they need, they do have control of out of pocket expenses through deductibles and copays. While not necessarily explicit to their decision, patients choose their tolerance for these expenses via the health plan they choose. Typically, different health plans offer a tradeoff between lower premiums and out of pocket costs with increased referral requirements and restrictions on physician availability. Health Maintenance Organizations (HMO) tend to offer the lowest premiums and smallest copays but are also the most restrictive, while these factors invert through Point of Service plans (POS), Exclusive Provider organizations (EPO) up to Preferred Provider plans (PPO) which tend to have the highest premiums and copays, but offer the most freedom to see whichever physician the patient prefers.

Another manner in which out-of-pocket costs are chosen are through the selection of high deductible (HDHP or consumer driven) health plans. This modification is often offered in

conjunction with many of the previously listed forms of health plans and was created to incentivize the patient to be more selective as to when and with whom they would attain care. This is accomplished by shifting the cost sharing heavily to the patient for the first \$2000 or \$2500, encouraging “cost shopping” by the patient themselves. After the deductible is reached, insurance then takes over most of the cost of care. These plans have proven quite popular, with as much as 34% of all US workers enrolled in an HDHP.¹⁰ Although shown to reduce the overall costs of care,^{11–14} this savings may be coming at the expense of necessary services, leading to worse outcomes.¹⁵ This is particularly concerning for diabetic patients who have been shown to utilize fewer outpatient services when covered by an HDHP.¹⁶

Currently, little is understood about how patient’s choices, often made long before care is needed, impacts the initial care they receive for DME. The goal of this study is to assess how factors a patient has control over, namely deductibles (via type of health insurance coverage), copay and geographic location can impact the choice of initial treatment for DME.

Methods

Dataset

Data was abstracted from the de-identified Clinformatics™ Data Mart Database (OptumInsight, Eden Prairie, MN), which contains the medical claims of all beneficiaries from a large insurance network in the United States. Included within the database are all outpatient medical claims (office visits, procedures, ancillary testing performed and medications given), as well as demographic data for each beneficiary during their enrollment in the insurance plan. Due to the relatively recent acceptance of regular anti-VEGF use for DME, the subset of data available for this study included all patients in the database from January 1, 2013 to December 31, 2016. Due to the de-identified nature of the database, the University of Pennsylvania’s Institutional Review Board deemed this study exempt from review. All research was performed in compliance with and adherence to the Declaration of Helsinki.

Patients

All patients 18 years or older with a new diagnosis of DME by an eye care professional after January 1, 2013 were included. The index date was defined as the first date of diagnosis with a ICD9 or ICD10 code for DME in an office visit to an eye care provider in conjunction with history of a diagnosis for ocular or systemic diabetes. For inclusion into the study, individuals had to have at least 2 consecutive years in the plan prior to the index date and 90 days in the plan after the index date.

Individuals were excluded if at any time prior to the index date, they had a diagnosis of DME, any disease state that may be confused for DME, including proliferative diabetic retinopathy (PDR), other proliferative retinopathies, sickle cell disease, vein occlusions, pathologic myopia, retinoschisis, age-related macular degeneration. Patients were also excluded for any history of having a treatment that could be associated with DME or PDR.

Since cystoid macular edema is a common complication of intraocular surgery, all patients with a code for an intraocular surgery within 90 days of index were also excluded. eTable 1 contains all diagnosis, procedure and drug codes used in the study.

Outcomes and Covariates

Once inclusion and exclusion criteria were met, patients were categorized into 1 of 7 groups (5 treatment, 2 with no treatment). All patients were observed for 90 days after and inclusive of the index date. The no treatment categories included patients who were not seen again in the 90-day window (“No follow up”) or saw an eye care provider, but did not receive therapy (“No treatment”). The treatment categories were based on the initial therapy received and included injection with bevacizumab, injection with ranibizumab or aflibercept (combined group due to relative medication costs), injection with steroids or focal laser. Patients who had a procedure code for an injection, but had no associated drug code were categorized as “other.” Use of administrative codes for the detection of diabetic macular edema as well as the treatments for DME have been validated previously.^{17,18}

Once patients were categorized with regards to outcome, numerous analyses were run with multinomial logistic regression, which allows for non-ordered categorical outcomes. HDHP can occur in various forms of insurance types (preferred provider, HMO, etc.) and was categorized as a yes/no variable. This variable was independent of insurance type which was categorized as health maintenance organization, exclusive provider organization, point of service, preferred provider organization and “other.” The database also contains the associated copays for every claim submitted. Frequently when treatment is administered, multiple claims are filed on the same day (i.e. a claim for the visit, a second for the treatment, a third for the drug in the case of injections). To include all care given on the same day, all co-pays for either the day of first treatment or final eye visit after the index date during the observation window were tallied. The copay was then categorized into a binary group of \$0 or >\$0. Next, to help prevent reidentification of de-identified data, the database groups patients in specific states together into larger regions across the United States. Other variables that were studied were age, race, gender, education level, yearly income. Lastly, to control for the systemic diabetic health of the patient the diabetic complications severity index was used.¹⁹ This index is created from six categories of diabetic complications using outpatient diagnosis codes and has been found to predict clinically relevant outcomes more accurately than traditional markers of diabetic severity such as glycosylated hemoglobin and duration of disease.¹⁹

The primary analysis compared the odds of getting each of the treatments to having no treatment. For this analysis, due to a lack of information, patients categorized as “other” or “no follow up” were not included in the analysis. Similarly, the steroid group was not large enough to make meaningful comparisons and was also left out of the treatment analyses. Secondary analyses included a multivariable analysis that grouped both anti-VEGF categories and compared them to no treatment. We also specifically compared bevacizumab to the ranibizumab/aflibercept group. Lastly, we assessed the odds of having any follow up compared to not following up. P-values less than 0.05 were considered significant. Differences in baseline covariates among treatment groups were evaluated with ANOVA

(continuous measures) of chi-squared tests (categorical measures). Statistical analysis was performed using SAS (version 9.4; SAS Institute Inc., Cary, NC).

Results

After all inclusion and exclusion criteria were applied, 6220 new DME patients were evaluated. Of these, 3210 did not have a follow up exam within 90 days of initial diagnosis. Furthermore, 1557 (51.7% of patients who had a follow up) were seen one or more times during the observation window, but did not receive a treatment. Within the treated groups 614(20.4% of those seen) received bevacizumab, 191 (6.3%) had either ranibizumab or aflibercept, 560(18.6%) received a focal laser, 38(1.3%) received a steroid injection and 50(1.7%) patients received an injection that was not further categorized. At baseline differences across the treatment categories were seen in age, race, education level, yearly income, geographic location, diabetic complications severity index, insurance type and copay. (See Table 2 for complete baseline characteristics results.)

Multivariable analysis was performed to determine which factors were associated with not following up within 90 days as compared to patients who were seen in the follow up period. After controlling for all other factors age, race, education level, yearly income, geographic region and HDHP were not associated with following up or not ($p>0.05$ for all comparisons). Patients that scored higher in the diabetes complications severity index had an increased odds of following up (score 4-5 OR:1.20, 95%CI:1.05-1.38; score >5 OR:1.46, 95%CI:1.27-1.68 vs. score of 1-2, $p<0.001$). Insurance type also impacted the odds of following up, with being in a PPO increasing the odds of follow up (OR:1.42, 95%CI: 1.12-1.79, $p=0.02$) compared to patients in an HMO.

Having a co-pay (vs. \$0 copay) was found to have numerous associations through the study. (See TABLE 3 for multivariable model results.) First, it was associated with a significantly decreased odds of a patient following up (OR:0.63, 95%CI:0.56-0.71, $p<0.001$). With regards to initial therapy, it also significantly lowered the odds of receiving any treatment (OR:0.60, 95%CI:0.51-0.71, $p<0.001$). This association remained consistent when any anti-VEGF treatment (OR:0.72, 95%CI:0.59-0.88, $p<0.001$), bevacizumab (OR:0.73, 95%CI:0.59-0.91, $p<0.001$) and rani/aflib (OR: 0.70; 95%CI:0.49-0.99, $p<0.001$) were also compared to no treatment. Having a copay also lowered the odds of receiving a focal laser (OR:0.44, 95%CI: 0.35-0.55, $p<0.001$), but was not associated with receiving bevacizumab as compared to rani/aflib (OR:0.98 95%CI:0.66-1.47, $p=0.94$). Contrary to copays, high deductible out of pocket costs (in the form of HDHP plans) was not associated with initiating or not initiating any specific form of treatment for DME ($p>0.45$ for all comparisons). Similarly, after accounting for copays and other factors, the type of insurance plan was not associated with initiating or not any specific form of treatment ($p>0.41$ for all comparisons).

Geographic location was consistently associated with the choice of initial therapy for DME. Compared to the Upper Midwest, patients in the Northeast were significantly less likely to receive an anti-VEGF treatment within the initial 90 days after diagnosis (OR:0.60, 95%CI: 0.44-0.82, $p<0.001$). This was also true when the individual comparison was made between bevacizumab (OR:0.47, 95%CI:0.33-0.67) and no treatment, but not for rani/aflib (OR:1.11,

95%CI:0.67-1.82) or focal laser (OR:1.26, 95%CI:0.91-1.74, $p<0.001$ for the location variable as whole). Furthermore, Northeast patients who were treated with anti-VEGF agents had a much higher odds of receiving rani/aflib compared to bevacizumab (OR:2.39, 95%CI:1.31-4.37, $p<0.001$). This is in contrast to the Southern Midwest where patients were more likely to receive an anti-VEGF injection when compared to no treatment (OR:1.35, 95%CI:1.02-1.77, $p<0.001$), which was also true when bevacizumab (OR:1.40, 95%CI:1.04-1.87) and focal laser (OR:1.39, 95%CI:1.01-1.89) were specifically compared to no treatment, but the association did not hold for rani/aflib (OR:1.08, 95%CI:0.64-1.81, $p<0.001$ for location variable as a whole). Patients in the South Atlantic were also found to have a higher odds of initiating rani/aflib (OR:1.60, 95%CI:1.05-2.45, $p<0.001$) and bevacizumab (OR:1.82, 95%CI:1.13-2.96, $p<0.001$) when compared to no treatment.

Discussion

Traditionally, the assumption has been that treatment decisions are made strictly within the confines of the exam room, with the physician being responsible for a larger share of the decision process than the patient. This assumption gives very little consideration to the factors external to the doctor-patient relationship that may impact these decisions. The reality, however is quite different with a myriad of factors influencing the choices made for care. This study found that having a copay and geographic location of where a patient is treated significantly impact the initial choice of therapy.

The central premise behind initiating this study was that the choices patients make long before being seen or diagnosed with DME may impact the type of therapy they initiate. These choices often relate to out-of-pocket costs and involve setting deductible limits through selecting an HDHP, or copays. Having a copay was clearly associated with lowering the odds of receiving treatment and even following up. This was true for anti-VEGFs collectively and individually, as well as for focal laser. Co-pays were not associated with receiving either bevacizumab or rani/aflib when compared with each other. The benefit of treating DME patients with better than 20/40 vision is still being debated, so suggesting all patients who did not receive treatment was done inappropriately would not be correct. However, for this to have influenced these results, patients who are in plans with co-pays would have to have worse DME, which does not seem likely. Cost sharing via copays have been an area of active research for many years and clear evidence has evolved to show increasing copays reduces adherence and worsens outcomes over most fields of medicine.¹⁵ As insurers actively move to a shared risk model²⁰ that forces physicians to be responsible for both costs and outcomes of DME care, future work will be needed to better understand the role copays play in adherence to recommended therapy.

Contrary to copays, high deductibles and type of insurance plans (health maintenance, point of service, exclusive provider or preferred provider organizations) were not associated with initial treatment. Prior to our results it was unknown if, as in other areas of medicine^{15,16}, patients with new DME in HDHP's would be less likely to get treatment (particularly expensive ones) due to the increased initial cost sharing placed on the patient. Fortunately, this impact of HDHP was not seen with regards to treatment choice for DME patients. It is possible that for most diabetic patients in HDHP plans, the cost of diabetic care itself causes

patients to reach their high deductible limit, and that by the time the DME treatment is initiated, the costs are then fully covered.

Some understanding of differential utilization of anti-VEGF agents has been gained via previous insurance-based studies. One recent report demonstrated frequency of injections for DME vary by as much as 34% between patients with private insurance, Medicare, Medicare advantage.²¹ While offering evidence that insurance plan is an important determinant in care, without knowledge of different organizational policies towards anti-VEGF agents, preauthorization requirements, copays and deductibles, discerning where to ascribe the differences seen is difficult at best.

Some of the more striking findings of this study were how strongly associated geographic location was with initial DME therapy. Our results showed patients in the Northeast states had significantly lower odds of getting an anti-VEGF treatment and were especially unlikely to receive bevacizumab. These patients were both, almost twice as likely to get no treatment compared to bevacizumab, and nearly 2.5 times more likely to receive one of the FDA-approved medications, ranibizumab or aflibercept, as bevacizumab. This is in stark contrast to the southern Midwest where patients had a significantly higher odds of receiving an anti-VEGF agent, most specifically bevacizumab and similarly, focal laser. Geographic region is also a well-known factor to impact ophthalmic care.^{22–27} Specific to anti-VEGF agents, large variations in agent selection as well as injection and reimbursement rates across the US have been reported.²⁸ Disease specific geographic differences have also been shown in anti-VEGF usage for AMD and DME, but neither study accounted for costs to the patient.^{29,30}

Due to potential re-identification of de-identified data, the data vendor will not provide more detailed geographic data than the pre-packaged groups used within this study. While this makes direct comparisons to previous literature discussing geographic variations difficult, one study found that DME patients in the Mid-Atlantic region (which most closely associates with our Northeastern region) were the least likely to use bevacizumab³⁰, which is consistent with our results. Outside of DME, our results also align well with those found in AMD where patients in the Northeast have been shown to be significantly more likely to receive ranibizumab when compared to bevacizumab.²⁹

Additional limitations of this study need to be noted. As discussed above, due to not having chart level data, diagnoses and treatments were unable to be individually verified. In an attempt to reduce the impact of this issue, very strict exclusion criteria were applied such that all patients who have a diagnosis that may be confused with DME or had used a treatment in DME care were removed. Although the codes used to identify DME have been shown to have a high validity^{17,18}, we cannot exclude the possibility that some “rule out” diagnoses were recorded which may have increased the rate of “no follow up” patients.

In addition, the data for this study comes from a single insurer and may not reflect trends for DME patients covered by other insurances or other entities (the Veterans Affairs Health System for example). Nor are we able to rule out the possibility that therapies were paid for by patients in an out-of-pocket manner and not accounted for within the database, but given the high costs of the medications and the fact we evaluated an insured population, we feel

this is very unlikely to represent a significant number of treatments. Similarly, we are unable to account for those patients that had co-pay assistance. Next, we are only able to evaluate therapies given. No manner exists to collect data on patients who were offered one treatment, but declined in preference to another or no treatment. Next, we are unable to comment on the appropriateness of treating or not treating any specific patient. While 52% of patients being untreated seems high, ETDRS reported that over 60% of patients with clinically significant macular edema had vision better than 20/25.³¹ Similarly, although anti-VEGF agents have become the first line therapy for DME,¹⁻⁷ we have no way to determine what percentage of the patients who received focal therapy instead of anti-VEGF where the patients that met the classic definition of clinically significant macular edema criteria (presumably with better than 20/40 vision). Lastly, we assessed only the initial choice of treatment. We did not assess the likelihood of continuing care with an alternative treatment or the factors that would be associated with those changes. Further work will need to be done to assess the ongoing impact of copay with types and rates of treatment after the initial choice is made.

Conclusion

Given the disparate costs of DME therapies, understanding the financial and other baseline characteristics associated with different treatments will allow physicians and health policy creators to better identify who is at risk for receiving suboptimal treatment for DME.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Table 2:

Patient Baseline Characteristics

	Bevacizumab (N=614)	Ranibizumab/Aflibercept (N=191)	Focal Laser (N=560)	Steroid Injection (N=38)	Other (N=50)	No Treatment (N=1557)	No Follow Up (N=3210)	p value
Mean Age (SD)	64.9(11.6)	64.8(10.1)	62.5(10.9)	64.4(10.5)	65.9(10.7)	65.3(12.5)	64.3(12.9)	<0.01
Gender (Female)	257 (42%)	99 (52%)	283 (51%)	18 (47%)	19 (38%)	720 (46%)	1476 (46%)	0.13
Race								0.03
White	366 (60%)	130 (68%)	303 (54%)	19 (50%)	34 (68%)	941 (60%)	1877 (58%)	
Asian	12 (2%)	7 (4%)	21 (4%)	3 (8%)	1 (2%)	73 (5%)	144 (4%)	
Black	92 (15%)	29 (15%)	106 (19%)	6 (16%)	5 (10%)	245 (16%)	518 (16%)	
Hispanic	84 (14%)	18 (9%)	87 (16%)	8 (21%)	7 (14%)	189 (12%)	423 (13%)	
Unknown	60 (10%)	7 (4%)	43 (8%)	2 (5%)	3 (6%)	109 (7%)	248 (8%)	
Education level								0.01
HS Diploma or Less	234 (38%)	83 (43%)	225 (40%)	19 (50%)	17 (34%)	559 (36%)	1140 (36%)	
Less than Bachelor Degree	303 (49%)	90 (47%)	267 (48%)	14 (37%)	26 (52%)	769 (49%)	1605 (50%)	
Bachelor Degree Plus	39 (6%)	13 (7%)	36 (6%)	3 (8%)	6 (12%)	161 (10%)	324 (10%)	
Unknown	38 (6%)	5 (3%)	32 (6%)	2 (5%)	1 (2%)	68 (4%)	141 (4%)	
Yearly Income								0.03
<\$40K	168 (27%)	58 (30%)	139 (25%)	11 (29%)	13 (26%)	422 (27%)	791 (25%)	
\$40K - \$49K	56 (9%)	20 (10%)	57 (10%)	2 (5%)	6 (12%)	115 (7%)	256 (8%)	
\$50K - \$59K	46 (7%)	14 (7%)	54 (10%)	4 (11%)	6 (12%)	127 (8%)	260 (8%)	
\$60K - \$74K	66 (11%)	21 (11%)	57 (10%)	4 (11%)	8 (16%)	139 (9%)	364 (11%)	
\$75K - \$99K	67 (11%)	22 (12%)	72 (13%)	2 (5%)	6 (12%)	212 (14%)	405 (13%)	
\$100K +	110 (18%)	36 (19%)	97 (17%)	8 (21%)	10 (20%)	320 (21%)	730 (23%)	
Unknown	101 (16%)	20 (10%)	84 (15%)	7 (18%)	1 (2%)	222 (14%)	404 (13%)	
Geographic region								0.21
Upper Midwest	166 (27%)	47 (25%)	142 (25%)	12 (32%)	18 (36%)	410 (26%)	768 (24%)	
Southern Midwest	129 (21%)	27 (14%)	116 (21%)	6 (16%)	6 (12%)	232 (15%)	545 (17%)	
Northeast	58 (9%)	35 (18%)	104 (19%)	5 (13%)	8 (16%)	299 (19%)	582 (18%)	
Mountain	67 (11%)	8 (4%)	28 (5%)	3 (8%)	1 (2%)	114 (7%)	247 (8%)	
Pacific	55 (9%)	11 (6%)	29 (5%)	1 (3%)	7 (14%)	120 (8%)	237 (7%)	
South Atlantic	138 (22%)	63 (33%)	141 (25%)	11 (29%)	10 (20%)	379 (24%)	821 (26%)	
Unknown	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (0%)	10 (0%)	
Cohort year								<0.01

	Bevacizumab (N=614)	Ranibizumab/Aflibercept (N=191)	Focal Laser (N=560)	Steroid Injection (N=38)	Other (N=50)	No Treatment (N=1557)	No Follow Up (N=3210)	p value
2013	177 (29%)	41 (21%)	199 (36%)	16 (42%)	10 (20%)	462 (30%)	998 (31%)	
2014	135 (22%)	48 (25%)	159 (28%)	8 (21%)	22 (44%)	368 (24%)	706 (22%)	
2015	152 (25%)	59 (31%)	130 (23%)	10 (26%)	9 (18%)	388 (25%)	770 (24%)	
2016	150 (24%)	43 (23%)	72 (13%)	4 (11%)	9 (18%)	339 (22%)	736 (23%)	
DCSS								<0.01
1-2	174 (28%)	56 (29%)	224 (40%)	10 (26%)	15 (30%)	518 (33%)	1216 (38%)	
3	95 (15%)	26 (14%)	85 (15%)	11 (29%)	8 (16%)	223 (14%)	570 (18%)	
4-5	157 (26%)	45 (24%)	125 (22%)	9 (24%)	15 (30%)	374 (24%)	736 (23%)	
>5	188 (31%)	64 (34%)	126 (23%)	8 (21%)	12 (24%)	442 (28%)	688 (21%)	
High Deductible Insurance	64 (10%)	22 (12%)	76 (14%)	5 (13%)	5 (10%)	158 (10%)	335 (10%)	0.42
Insurance type								0.01
Health Maint Org	123 (20%)	27 (14%)	102 (18%)	2 (5%)	6 (12%)	288 (18%)	609 (19%)	
Point of Service	193 (31%)	64 (34%)	225 (40%)	13 (34%)	17 (34%)	496 (32%)	1087 (34%)	
Exclusive Provid Org	32 (5%)	10 (5%)	33 (6%)	4 (11%)	3 (6%)	74 (5%)	216 (7%)	
Preferred Provid Org	49 (8%)	18 (9%)	38 (7%)	1 (3%)	4 (8%)	133 (9%)	226 (7%)	
Other	217 (35%)	72 (38%)	162 (29%)	18 (47%)	20 (40%)	566 (36%)	1072 (33%)	
Copay								<0.01
No copay	249 (41%)	80 (42%)	288 (51%)	9 (24%)	23 (46%)	530 (34%)	970 (30%)	
\$1 or more	365 (59%)	111 (58%)	272 (49%)	29 (76%)	27 (54%)	1027 (66%)	2240 (70%)	

DCSS= Diabetes Complications Severity Score

Table 3:

Results from Multinomial/Multivariable Logistic Regression[†]

	Any Follow Up vs. No Follow Up [‡] Adj OR (95% CI)	Any Treatment vs. No Treatment [‡] Adj OR (95% CI)	Bevacizumab vs. No Treatment Adj OR (95% CI)	Ranibizumab/ Aflibercept vs. No Treatment Adj OR (95% CI)	Focal Laser vs. No Treatment Adj OR (95% CI)	Any Anti-VEGF vs. No Treatment Adj OR (95% CI)	Ranibizumab/ Aflibercept vs. Becavizumab Adj OR (95% CI)	p- value [*]
DCSS (1-2 ref)								<0.001
3	0.96 (0.83 - 1.12)	1.01 (0.83 - 1.23)	1.29 (0.95 - 1.74)	1.06 (0.64 - 1.75)	0.95 (0.70 - 1.29)	1.23 (0.93 - 1.63)	0.81 (0.46 - 1.42)	
4-5	1.20 (1.05 - 1.38)	0.92 (0.76 - 1.13)	1.21 (0.93 - 1.58)	1.12 (0.73 - 1.71)	0.86 (0.66 - 1.13)	1.19 (0.94 - 1.52)	0.99 (0.62 - 1.61)	
>5	1.46 (1.27 - 1.68)	0.79 (0.63 - 0.97)	1.20 (0.93 - 1.56)	1.35 (0.90 - 2.03)	0.73 (0.55 - 0.96)	1.24 (0.98 - 1.57)	1.14 (0.72 - 1.82)	
Geographic region (Up Midwest Ref)								<0.001
Southern Midwest	0.98 (0.83 - 1.16)	1.30 (1.03 - 1.64)	1.40 (1.04 - 1.87)	1.08 (0.64 - 1.81)	1.39 (1.01 - 1.89)	1.35 (1.02 - 1.77)	0.73 (0.42 - 1.28)	
Northeast	0.86 (0.73 - 1.01)	0.82 (0.64 - 1.05)	0.47 (0.33 - 0.67)	1.11 (0.67 - 1.82)	1.26 (0.91 - 1.74)	0.60 (0.44 - 0.82)	2.39 (1.31 - 4.37)	
Mountain	0.90 (0.72 - 1.11)	1.00 (0.73 - 1.36)	1.47 (1.02 - 2.11)	0.66 (0.30 - 1.46)	0.67 (0.41 - 1.07)	1.34 (0.94 - 1.90)	0.41 (0.18 - 0.94)	
Pacific	1.01 (0.81 - 1.26)	1.05 (0.76 - 1.45)	1.34 (0.90 - 1.98)	1.05 (0.51 - 2.17)	0.72 (0.45 - 1.17)	1.30 (0.90 - 1.88)	0.73 (0.33 - 1.61)	
South Atlantic	0.90 (0.77 - 1.05)	1.03 (0.83 - 1.27)	0.87 (0.66 - 1.16)	1.60 (1.05 - 2.45)	1.06 (0.79 - 1.42)	1.04 (0.81 - 1.34)	1.82 (1.13 - 2.96)	
Unknown	0.43 (0.13 - 1.41)	0.46 (0.05 - 4.48)	0.85 (0.09 - 8.46)	<i>Not calculable</i>	<i>Not calculable</i>	0.77 (0.08 - 7.58)	<i>Not calculable</i>	
High Deductible Ins	0.87 (0.72 - 1.05)	0.84 (0.64 - 1.10)	0.89 (0.62 - 1.28)	0.94 (0.54 - 1.66)	0.76 (0.54 - 1.08)	0.89 (0.63 - 1.24)	0.94 (0.50 - 1.78)	0.15
Insurance type (HMO Ref)								0.02
Point of Service	1.09 (0.91 - 1.30)	1.05 (0.81 - 1.36)	0.96 (0.69 - 1.34)	1.19 (0.68 - 2.09)	0.99 (0.70 - 1.40)	1.04 (0.76 - 1.41)	1.42 (0.75 - 2.70)	
Exclusive Provid Org	0.95 (0.73 - 1.22)	1.25 (0.85 - 1.83)	1.14 (0.69 - 1.90)	1.38 (0.61 - 3.13)	1.10 (0.66 - 1.85)	1.18 (0.74 - 1.87)	1.16 (0.46 - 2.92)	
Preferred Provid Org	1.42 (1.12 - 1.79)	1.18 (0.84 - 1.65)	1.52 (0.98 - 2.35)	1.31 (0.66 - 2.61)	0.87 (0.54 - 1.40)	1.45 (0.97 - 2.15)	0.76 (0.34 - 1.69)	

	Any Follow Up vs. No Follow Up [‡] Adj OR (95% CI)	Any Treatment vs. No Treatment [‡] Adj OR (95% CI)	Bevacizumab vs. No Treatment Adj OR (95% CI)	Ranibizumab/ Aflibercept vs. No Treatment Adj OR (95% CI)	Focal Laser vs. No Treatment Adj OR (95% CI)	Any Anti-VEGF vs. No Treatment Adj OR (95% CI)	Ranibizumab/ Aflibercept vs. Becavizumab Adj OR (95% CI)	p- value [*]
Other	<i>1.18 (1.01 - 1.38)</i>	1.14 (0.91 - 1.43)	1.14 (0.86 - 1.52)	1.29 (0.78 - 2.13)	0.98 (0.72 - 1.34)	1.17 (0.89 - 1.52)	1.00 (0.57 - 1.76)	<0.001
Copay (\$0 ref) \$1 or more	<i>0.63 (0.56 - 0.71)</i>	<i>0.60 (0.51 - 0.71)</i>	<i>0.73 (0.59 - 0.91)</i>	<i>0.70 (0.49 - 0.99)</i>	<i>0.44 (0.35 - 0.55)</i>	<i>0.72 (0.59 - 0.88)</i>	0.98 (0.66 - 1.47)	

[‡]Results of different models are presented in this table with comparison groups designated in the header. Different models are represented by each of the boxed/unboxed columns. All models in addition to the variables listed also controlled for age, gender, race, education level, yearly income and cohort year

[‡]Model also included patients who received steroid injection or an injection with the drug not noted

^{*} p-values represent the lowest value across all models. All significant variables are denoted by *bold Italics* type and normal type denotes insignificant association

DCSS= Diabetic Complications Severity Score