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Temporal Trends in the Treatment of Proliferative Diabetic Retinopathy

An AAO IRIS® Registry Analysis

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Purpose: This study examined how treatment patterns for proliferative diabetic retinopathy (PDR) have changed over time using clinical registry data from the AAO IRIS® Registry (Intelligent Research in Sight).

Design: A retrospective cohort analysis using the IRIS Registry database spanning 2013–2017.

Participants: A total of 141 317 patients with newly diagnosed PDR (International Classification of Diseases [ICD], Tenth Revision, codes E08.35, E09.35, E10.35, E11.35, and E13.35 and ICD, Ninth Revision, code 362.02) were included.

Methods: Comparison analyses were conducted using Tukey and chi-square tests, and time-trend analyses were conducted using Mann-Kendall tests and Theil-Sen slopes.

Main Outcome Measures: Patient characteristics including age, gender, and laterality; whether patients received intravitreal anti–vascular endothelial growth factor injections (IVI) only, panretinal photocoagulation (PRP) only, both IVI and PRP (IVI+PRP), or observation; intravitreal drug data; and diabetic macular edema (DME) status were compared.

Results: From 2013–2017, the average age of PDR diagnosis was 59.2 years, with 53.3% of patients being male. Sixty-two thousand one hundred five newly diagnosed PDR patients (43.9%) received IVI, 32 293 patients (27.1%) received PRP, 27 664 patients (19.6%) received IVI+PRP, and 13 255 patients (9.4%) underwent observation. In 2013, more PDR patients undergoing treatment received PRP only (47.5%) than IVI only (37.3%) or IVI+PRP (15.1%). From 2013 to 2017, the percentage of patients treated with PRP only decreased by 5.6% per year ($P = 0.05$) and the percentage of patients treated with IVI only increased by 3.9% per year ($P = 0.05$). By 2017, most patients received IVI only (52.9%). Patients with PDR with DME were more likely than patients without DME to receive IVI only (64.3% vs. 31.5%; $P < 0.001$). Among patients receiving IVI and IVI+PRP, bevacizumab (69.8%) was the most common intravitreal medication given followed by aflibercept (18.4%) then ranibizumab (11.7%).

Conclusions: In this cohort analysis of the IRIS Registry, IVI surpassed PRP as the more common method of treating newly diagnosed PDR from 2013 to 2017, with bevacizumab administered in more than two thirds of IVIs. *Ophthalmology Science 2021;1:100037 © 2021 Published by Elsevier Inc. on behalf of the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Diabetic retinopathy is a leading cause of permanent vision loss in the United States, and its treatment represents an important health care priority to prevent blindness.[1] Among non-Hispanic White, Hispanic, and Black people, diabetic retinopathy ranks as the second most common cause of irreversible legal blindness.[2] Proliferative diabetic retinopathy (PDR)—diabetic retinopathy with neovascularization present—causes up to 24 000 new cases of blindness each year in the United States.[3] Since the publication of the 1981 Diabetic Retinopathy Study, the standard treatment for high-risk PDR—defined as neovascularization of the disc of more than one-fourth to one-third disc area, any neovascularization of the disc with preretinal or vitreous hemorrhage, or neovascularization elsewhere of more than one-half disc area with preretinal or vitreous hemorrhage—had been panretinal photocoagulation (PRP), which reduces the risk of severe vision loss (defined as visual acuity < 5/200) from 25% to 14% over 2 years.[4] In the absence of treatment over a 5-year period, up to half of patients with high-risk PDR may experience severe vision loss.[4] However, PRP may be painful and associated with decreased visual field and night vision and exacerbation of diabetic macular edema (DME).[5–8]

With the advent of anti–vascular endothelial growth factor (VEGF) therapy, an alternative to PRP exists for treating patients with PDR.[9] Recent publications from the Diabetic Retinopathy Clinical Research (DRCR) Retina Network have shown that anti-VEGF therapy given via intravitreal injection (IVI) is a noninferior method for

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treating PDR compared with PRP.[10,11] In the 5-year DRCR Retina Network protocol S results, patients with PDR treated with intravitreal ranibizumab showed a mean change in visual acuity letter score of +3.1 compared with +3.0 in the PRP treatment group, and mean visual acuity was comparable at 20/25. In addition, patient-centered outcomes based on the National Eye Institute Visual Function Questionnaire and the University of Alabama Birmingham Low Luminance Questionnaire were similar between the 2 treatment groups.[11] Given the noninferior results, anti-VEGF therapy can be an appealing alternative to PRP, especially because all 3 commonly used anti-VEGF agents (bevacizumab, ranibizumab, and aflibercept) also are effective at treating DME.[12] But to what extent these findings have created a paradigm shift in the treatment of patients with PDR has not been well characterized. The American Academy of Ophthalmology's (AAO) development of the IRIS Registry (Intelligent Research In Sight), which now contains data from more than 349 million patient visits and 60 million unique patients, creates a unique opportunity to analyze practice trends using clinical registry data.[13] In this study, the IRIS Registry database was used to understand how treatment patterns for PDR have changed over time in the largest clinical registry study of patients with PDR to date.

Methods

This retrospective, cross-sectional analysis of the AAO IRIS Registry included data from 2013 through 2017 (the latest year with data available to our institution) and determined the number of patients with newly diagnosed PDR and the method of treatment in each year during this 5-year period. The data were aggregated in a de-identified manner with methodology mirroring other IRIS Registry-based research.[14] Because the IRIS Registry data are de-identified, no patient-level consent or institutional review board approval were required. All research adhered to the tenets of the Declaration of Helsinki. All patients with a PDR International Classification of Diseases (ICD) diagnosis code (Ninth Revision code 362.02 and Tenth Revision codes E08.35, E09.35, E10.35, E11.35, and E13.35) were included in this study. Of note, the ICD, Ninth and Tenth Revision, codes correspond to the presence of any PDR and not of solely high-risk patients with PDR as defined by the Diabetic Retinopathy Study. Patient characteristics including age, gender, laterality (defined at the time of onset of PDR for the first eye), and the presence or absence of DME (ICD, Ninth Revision, code 362.07 and ICD, Tenth Revision, codes E08.351, E09.351, E10.351, E11.351, E13.351, E08.311, E09.311, E10.311, E11.311, and E13.311) were collected. Treatment method information also was gathered based on Current Procedural Terminology (CPT) codes and whether patients underwent anti-VEGF IVI only (CPT code 67028), PRP only (CPT code 67228), both anti-VEGF IVI and PRP, or observation. To select for newly diagnosed patients with PDR, queries of the IRIS Registry were performed to select only patients for whom a PDR diagnosis code had not been used in the previous 2 years to ensure that this cohort included only incident disease; consequently, all study patients required at least 3 consecutive years of data in the IRIS Registry. For those patients who received anti-VEGF IVI only or both anti-VEGF IVI and PRP, the type of anti-VEGF drug (bevacizumab, ranibizumab, or aflibercept) was identified based on Healthcare Common Procedure Coding System codes.

For the aggregate PDR cohort, comparison analyses of patient characteristics were conducted for each treatment cohort (anti-VEGF IVI, PRP, both anti-VEGF IVI and PRP, or observation). Means were compared using Tukey tests and proportions were compared using chi-square tests. Time-trend analyses were conducted using Mann-Kendall tests, and calculation of Theil-Sen slopes determined the percentage change in each treatment method over time.

Results

From 2013 through 2017, the IRIS Registry included a total of 141 317 patients with newly diagnosed PDR who met the inclusion criteria (Table 1). The mean age at onset was 59.2 years, with more men (53.3%) than women (46.7%) in this dataset. Among patients with specified laterality, most patients (57.9%) showed bilateral disease. Among patients with specified DME status, 66.3% of patients showed concurrent DME. When segmented by year, mean age at onset exhibited minimal variation (range, 59.1−59.4 years), and in each year, more men received a diagnosis of PDR than women (differential range, 4.8−7.1 percentage points). By treatment cohort, 62 105 patients (43.9%) received anti-VEGF IVI only, 38 293 patients (27.1%) received PRP only, 27 664 patients (19.6%) received both anti-VEGF IVI and PRP, and 13 255 patients (9.4%) underwent observation. Newly diagnosed patients with PDR receiving anti-VEGF IVI only on average were older (mean age, 60.3 years) than patients undergoing both anti-VEGF IVI and PRP (mean age, 57.4 years), PRP only (mean age, 58.4 years), and observation (mean age, 59.7 years; $P < 0.001$). Compared with women, men were more likely to receive both anti-VEGF IVI and PRP (22.5% vs. 20.6%; $P < 0.001$) and less likely to receive PRP only (29.1% vs. 30.8%; $P < 0.001$).

Among newly diagnosed patients with PDR undergoing treatment, from 2013 through 2017, the percentage of patients treated with PRP only decreased by 5.6% per year ($P = 0.05$) and the percentage of patients treated with anti-VEGF IVI only increased by 3.9% per year ($P = 0.05$). In 2013, 47.5% of patients underwent PRP only, 37.3% of patients received anti-VEGF IVI only, and 15.1% of patients underwent both anti-VEGF IVI and PRP; by 2017, 52.9% of patients underwent anti-VEGF IVI only, 22.3% of patients underwent PRP only, and 24.7% of patients underwent both anti-VEGF IVI and PRP ($P < 0.001$; Fig 1). Patients with PDR demonstrating DME were more likely than patients without DME to receive anti-VEGF IVI only (64.3% vs. 31.5%; $P < 0.001$) and both anti-VEGF IVI and PRP (22.1% vs. 19.7%; $P < 0.001$) and were less likely to receive PRP only (13.6% vs. 48.8%; $P < 0.001$). However, similar to the overall trend of increasing anti-VEGF IVI only use, the proportion of patients receiving anti-VEGF IVI only increased in both patients with and without DME from 2013 through 2017: from 25.0% to 65.7% for patients with DME ($P < 0.001$) and from 21.1% to 32.9% for patients without DME ($P < 0.001$).

Among newly diagnosed patients with PDR treated with anti-VEGF IVI only and both anti-VEGF IVI and PRP,

Table 1. Baseline Demographics of Patients with Newly Diagnosed Proliferative Diabetic Retinopathy in the American Academy of Ophthalmology Intelligent Research in Sight Registry, 2013 through 2017 (n = 141 317)

Baseline Demographics	Aggregate Proliferative Diabetic Retinopathy Cohort	2013	2014	2015	2016	2017
Age (yrs), mean ± SD	59.2 ± 12.1	59.4 ± 12.1	59.2 ± 12.4	59.3 ± 12.3	59.3 ± 12.1	59.1 ± 12.1
Sex, no. (%)						
Male	75 192 (53.3)	4515 (52.3)	7234 (53.0)	7390 (52.8)	13 988 (53.0)	42 065 (53.5)
Female	65 837 (46.7)	4102 (47.5)	6388 (46.8)	6569 (46.9)	12 318 (46.7)	36 460 (46.4)
Unspecified	288 (0.2)	20 (0.2)	25 (0.2)	42 (0.3)	81 (0.3)	120 (0.2)
Laterality, no. (%)						
Right	29 050 (20.6)	411 (4.8)	582 (4.3)	856 (6.1)	5575 (21.1)	21 626 (27.5)
Left	31 271 (22.1)	468 (5.4)	600 (4.4)	835 (6.0)	5719 (21.7)	23 649 (30.1)
Bilateral	34 931 (24.7)	589 (6.8)	714 (5.2)	760 (5.4)	5109 (19.4)	27 759 (35.3)
Unspecified	46 065 (32.6)	7169 (83.0)	11 751 (86.1)	11 550 (82.5)	9984 (37.8)	5611 (7.1)
DME status, no. (%)						
With	48 463 (34.3)	35 (0.4)	108 (0.8)	418 (3.0)	8395 (31.8)	39 507 (50.2)
Without	24 629 (17.4)	239 (2.8)	418 (3.1)	621 (4.4)	4922 (18.7)	18 429 (23.4)
Unspecified	68 225 (48.3)	8363 (96.8)	13 121 (96.1)	12 962 (92.6)	13 070 (49.5)	20 709 (26.3)

DME = diabetic macular edema; SD = standard deviation.

bevacizumab was the most common intravitreal medication given during the study period, with 69.8% of patients receiving this medication, followed by aflibercept at 18.4%, and ranibizumab at 11.7%. Aflibercept use increased from 1.0% of the intravitreal anti-VEGF medications injected in 2013 to 20.4% by 2017, an increase that occurred at the expense of ranibizumab (−10.5 percentage points) more than bevacizumab (−8.9 percentage points) during this same period (Fig 2).

Discussion

During the 5-year study period from 2013 through 2017, the AAO IRIS Registry database included more than 140 000 patients with newly diagnosed PDR. Overall, more patients in this cohort received intravitreal anti-VEGF therapy for PDR treatment than either PRP only or combination therapy with anti-VEGF IVI and PRP. This finding was driven largely by the high percentage of patients with PDR with DME, where anti-VEGF IVI only treatment more than doubled during this 5-year period. Although PRP remained the more common form of treatment for patients with PDR without DME, anti-VEGF IVI only treatment also increased in this group as well, rising by more than one half over the same period.

The shift from PRP to anti-VEGF IVI being the more commonly used treatment method for PDR occurred between 2015 and 2016. In 2015, the DRCR Retina Network published 2-year results of patients with PDR being treated with PRP versus IVI of 0.5 mg ranibizumab. The study group found that the ranibizumab group's mean visual acuity change was noninferior relative to the PRP group.[10] The 5-year study outcomes showed that mean visual acuity was 20/25 in both groups at the end of the study period, and the ranibizumab group showed better visual field testing and less DME compared with the PRP group.[11] Combined with the growing use of anti-VEGF therapy for other retinal conditions, the publication of these results may help to explain the paradigm shift in treatment of patients with PDR seen in the IRIS Registry, which is reflective of national trends in treatment patterns.

During the study period, bevacizumab remained the most commonly used among the 3 anti-VEGF agents for the treatment of newly diagnosed PDR, but aflibercept use increased at the expense of ranibizumab more than bevacizumab. The DRCR Retina Network also published a study in 2015 showing that all 3 medications were effective in improving vision in patients with center-involving DME. However, when the initial visual acuity was 20/50 or worse, patients treated with aflibercept gained 7.1 more letters than patients treated with bevacizumab and 4.7 more letters than patients treated with ranibizumab. Along with Food and Drug Administration approval of aflibercept and ranibizumab for the treatment of PDR, these study results showing improvement in patients with worse initial levels of visual acuity may explain the growing use of aflibercept over bevacizumab and ranibizumab seen in the IRIS Registry over time.

The trend of increasing use of anti-VEGF medications for the treatment of PDR mirrors the findings in a recent publication by Azad et al[15] using a nationally representative claims-based database as opposed to a clinical registry database. Similar to our study, they also found that the rate of anti-VEGF IVI use increased over time at the expense of PRP for treatment of patients with PDR, especially when comparing the prepublication and postpublication periods of the DRCR Retina Network protocol S results. They also were able to stratify their results by DME status and anti-VEGF medication used. Two significant differences between our study and theirs are the number of patients included between the 2 studies and the difference in insurance status. Our study included more than 140 000 patients with newly diagnosed PDR over a 5-year period compared with more than 2500 patients with PDR who met their inclusion criteria. In addition, we also included patients with

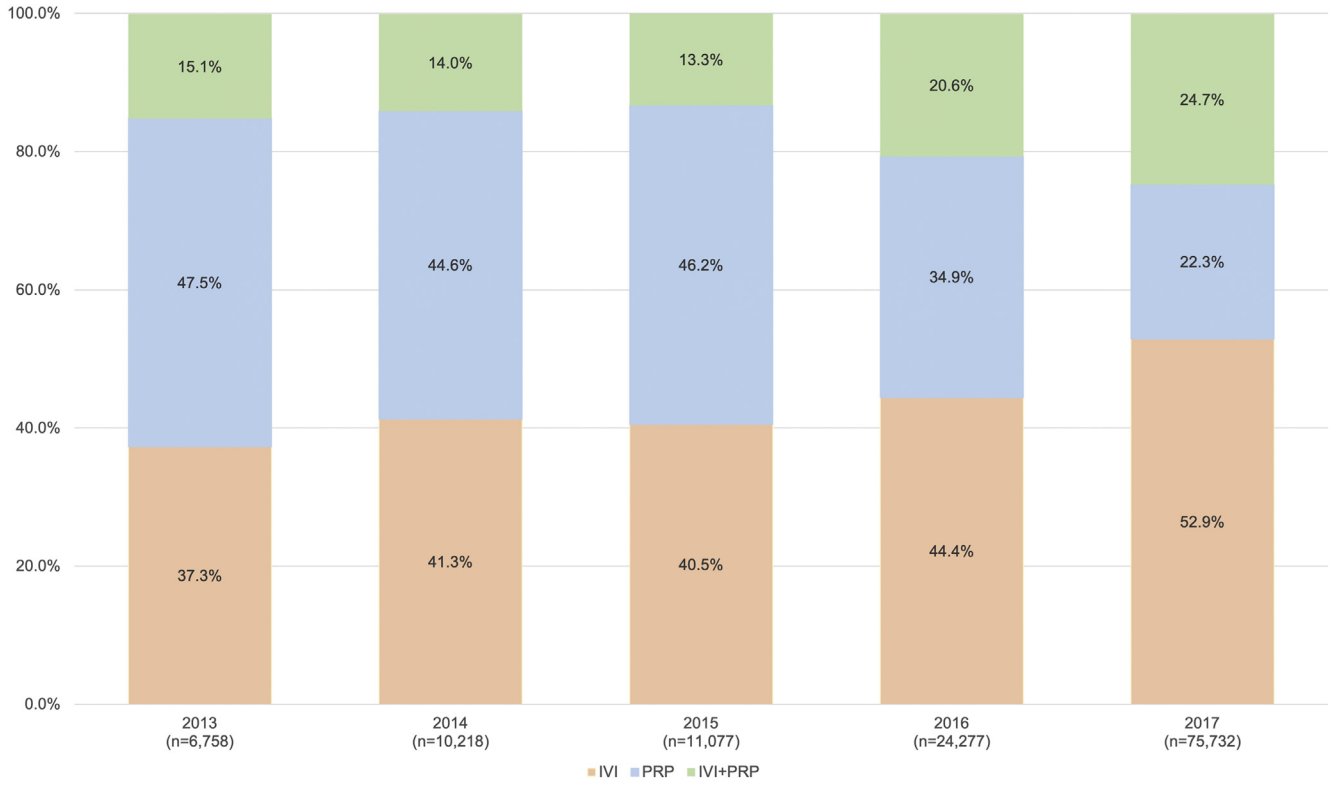

Figure 1. Bar graph showing treatment methods of patients with newly diagnosed proliferative diabetic retinopathy (PDR) in the AAO IRIS Registry by year, 2013 through 2017. IVI = intravitreal injection; PRP = panretinal photocoagulation.

all insurance types including commercial, government, and uninsured patients, as opposed to patients from a single commercial insurance provider.

Given the growing trend in anti-VEGF IVI treatment for PDR over PRP, one area that requires further exploration in future IRIS Registry studies is how clinical outcomes compare clinical registry data. Follow-up of Diabetic Retinopathy Study patients has shown that long-term durability results for patients with PDR treated with PRP: only 2 of 51 eyes receiving PRP required additional laser treatment over a 15-year period.[16] In contrast, in the DRCR Retina Network protocol S trial, patients in the intravitreal ranibizumab group required an average of 19.2 injections over 5 years.[11] Unfortunately, it was shown previously that loss to follow-up rates for patients with PDR can range from 25.4% to 54.4%, depending on the study population.[17–19] Moreover, patients with PDR receiving anti-VEGF IVI only who were lost to follow-up showed worse anatomic and functional outcomes than those patients who had received PRP, demonstrating vitreous hemorrhage, neovascular glaucoma, and tractional retinal detachments among other complications.[20,21] Thus, the growing trend of anti-VEGF IVI over PRP deserves close scrutiny if in fact this change in clinical practice results in worse clinical results when accounting for differences in durability and outcomes of patients who are lost to follow-up.

The limitations of this study include the following. First, our analysis did not include clinical outcomes such as visual acuity in relationship to treatment, imaging data to document the severity and change in DME in response to treatment, or detailed examination information, including the presence of vitreous hemorrhage or high-risk PDR characteristics. Second, diagnoses and treatment data were based solely on ICD and CPT codes, respectively, which were not confirmed using other sources of information and were subject to the accuracy of patient record documentation and data reporting. Third, our data did not include nonclinical information such as socioeconomic factors, which may contribute to one treatment method being used over another. Prior research has shown that anti-VEGF IVI is more costly and requires more frequent treatment compared with PRP,[22] which may influence physician treatment decisions. Fourth, although the IRIS Registry database now includes more than 60 million unique patients, it does not encompass data from all practices in the United States; in particular, tertiary academic centers and practices without electronic health records are underrepresented, which may limit the generalizability of the observed trends. Fifth, participation in the IRIS Registry rapidly increased from 2013 through 2017, as evidenced by the growing number of new patients with PDR by year in this study. Consequently, the incorporation of new ophthalmology practices with different treatment tendencies may impact the temporal trends in PDR treatment patterns over time. Finally, data in the IRIS Registry given to academic institutions including ours have certain gaps, such as unspecified

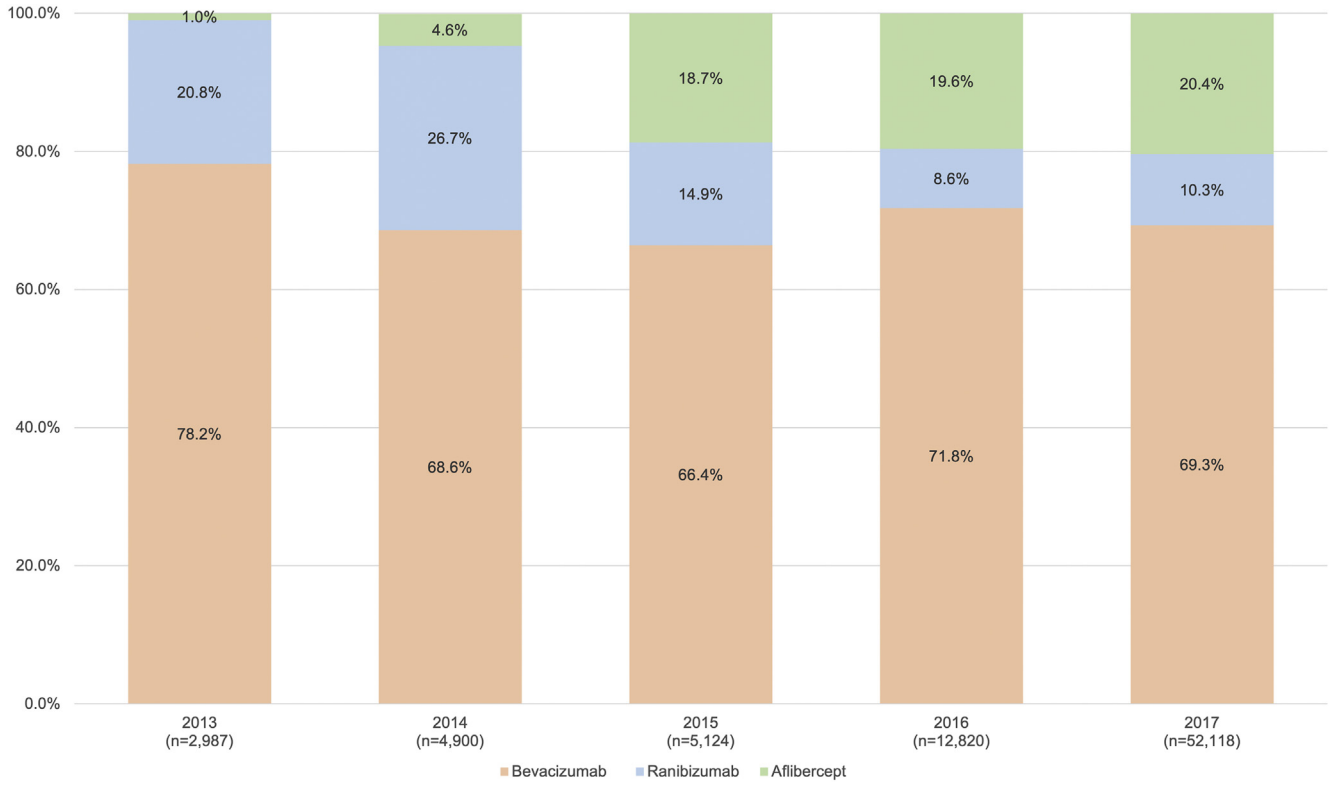

Figure 2. Bar graph showing anti–vascular endothelial growth factor (VEGF) medication use in patients with newly diagnosed proliferative diabetic retinopathy (PDR) in the AAO IRIS Registry by year, 2013 through 2017.

disease laterality and DME status, that limit our analysis; all available and relevant data granted to our institution were included in this study.

This study demonstrated the use of the AAO IRIS Registry enables the inclusion of large populations of study patients to characterize treatment patterns accurately. In this retrospective, cross-sectional analysis, anti-VEGF IVI surpassed PRP as the more common method of treating newly diagnosed PDR from 2013 through 2017. Future studies are needed to determine whether clinical outcomes are impacted by this change in PDR treatment patterns.

Footnotes and Disclosures

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No animal subjects were included in this study.

Author Contributions:

Conception and design: Gong, Hall, Elze, Sobrin, J.W.Miller, Lorch, J.B.Miller

Analysis and interpretation: Gong, Hall, Elze, Sobrin, J.W.Miller, Lorch, J.B.Miller

Data collection: Gong, Hall, Elze, J.B.Miller

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Overall responsibility: Gong, Hall, Elze, Sobrin, J.W.Miller, Lorch, J.B.Miller

Abbreviations and Acronyms:

CPT = Current Procedural Terminology; **DME** = diabetic macular edema; **DRCR** = Diabetic Retinopathy Clinical Research; **ICD** = International Classification of Diseases; **IRIS** = Intelligent Research in Sight; **IVI** = intravitreal injection; **PDR** = proliferative diabetic retinopathy; **PRP** = panretinal photocoagulation; **VEGF** = vascular endothelial growth factor.

Keywords:
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