Research Article ISSN 2639-9482

Ophthalmology Research

A Comparison of Visual Outcomes Between Patients Treated with Intravitreal Ranibizumab and Bevacizumab for Diabetic Macula Edema in A Real World Setting in Sub-Saharan Africa

Oderinlo Olufemi*, Hassan Adekunle, Oyekunle Idris, Odubela Tolulope and Lateefat Oshunkoya

Eye Foundation Hospital, 27 Isaac John Street GRA Ikeja, Lagos, Nigeria.

***Correspondence:**

Olufemi Oderinlo, Eye Foundation Hospital, 27 Isaac John Street, GRA Ikeja Lagos, Nigeria, Tel: 2348055116376.

Received: 29 Sep 2022; **Accepted:** 05 Nov 2022; **Published:** 10 Nov 2022

Citation: Olufemi O, Adekunle H, Idris O, et al. A Comparison of Visual Outcomes Between Patients Treated with Intravitreal Ranibizumab and Bevacizumab for Diabetic Macula Edema in A Real World Setting in Sub-Saharan Africa. Ophthalmol Res. 2022; 5(1); 1-5.

ABSTRACT

Aims and Objectives: *To report a comparison of visual outcomes between patients treated with intravitreal ranibizumab and bevacizumab for diabetic macula oedema (DME) in a real-world setting in sub-Saharan Africa.*

Methods: *A retrospective review of cases files of patients who were treated with either intravitreal ranibizumab or bevacizumab for diabetic macular edema in Eye Foundation Hospital Ikeja, Lagos, Nigeria between January 2018, and January 2019.*

Results: *A total of 508 injections were received by 138 eyes of 115 patients within the study year and diabetic macular edema accounted for 36 eyes, (26.1%) of the total eyes that received either intravitreal Ranibizumab or Bevacizumab.*

There were 18 males (50%) and 18 (50%) females. Overall, the mean baseline pre injection BCVA was 0.32 ± 0.24 (range:0.05-1.0). One hundred and forty-three total injections of either Bevacizumab or Ranibizumab were received by the 36 eyes of DME participants. Fifteen eyes (41.7%) received Bevacizumab while 21 eyes (58.3%) received Ranibizumab injections.

At 4 months a larger percentage of eyes (47.6%) that received Ranibizumab had better visual acuities compared to (13.3%) eyes that received Bevacizumab. At 6 months, more of the eyes that received Ranibizumab had better visual acuities (26.7%) compared to 23.8% that received Bevacizumab. At 9 months, more of the eyes that received Ranibizumab had better visual acuities (33.3%) compared to (19%) those that received Bevacizumab. However, these differences were not statistically significant.
Compliance to treatment regime was poor, only 7 eyes of the 36 eyes (19.4%) were compliant, 5 eyes (33.3%) form Bevacizumab group and 2 eyes (9.5%) from the Ranibizumab group.

Conclusion: *Despite poor compliance, improvements in best corrected visual acuities was achieved and maintained with the use of either intravitreal bevacizumab or ranibizumab for diabetic macula edema in a real life setting in sub-Saharan Africa. Neither bevacizumab nor ranibizumab showed statistically significant superiority.*

Keywords
Diabetic macula edema, Ranibizumab, Bevacizumab, Real world, Sub-Saharan Africa.

Introduction
Diabetic macula edema (DME) is a leading cause of visual loss in diabetic patients. It is estimated that DME affects about 7% of diabetic patients [1]. The risk factors for DME are like those for diabetic retinopathy and include, duration of diabetes, glycemic control, and associated systemic diseases such as systemic hypertension and dyslipidemia. Dyslipidemia, however, appears to play a more significant rolein DME. Early detection of DR and DME through screening programs and appropriate referral for therapy is important to preserve vision in individuals with diabetes [1].

Over expression of Vascular endothelial growth factor (VEGF) can lead to vision loss due to angiogenesis and vascular hyperpermeability. Anti-VEGF drugs such as bevacizu- mab (off-label) and ranibizumab (licensed) have been widely used by ophthalmologists for treating DME since 2006 [2,3]. More recently, Aflibercept has also become available. All three drugs have similar pharmacokinetics and have been found to be effective and safe for treating DME [4-6]. A major short coming to use, however, is cost. Most patients are unable to afford the clinically approved ranibizumab and aflibercept and as a result, off label use of bevacizumab is very common. Other challenges like poor access to healthcare and shortage of ophthalmologist [7] in sub-Saharan Africa also affect the overall uptake of antivegf medications.

Many clinical trials highlight the effectiveness of intravitreal anti vascular endothelial growth factor (VEGF) medications for treating macula edema [8,9]. Based on recommendations of an expert panel on the use of antivegf for diabetic macula edema, patients are usually advised to continue monthly treatment with antivegf until visual acuity is stable for 3 consecutive months. This leads to patients taking an average of 6 to 7 injections in a year [10]. Patients are then placed on monthly reviews and treatment is resumed if visual acuity (VA) loss is due to macular edema and confirmed by clinical evaluation, optical coherence tomography (OCT) or other anatomic assessments [10].

Better results are seen in clinical trials as they are conducted in well-controlled environments and are usually well-funded with good patient support and counselling [11,12]. These factors are not necessarily available in the real world setting especially in resource challenged areas of the world as is in sub-Saharan Africa. In our study, we seek to report our experience with the use of antivegf for treating diabetic macula edema in a real world setting in sub-Saharan Africa and to compare visual outcomes between the two-antivegf medications most used during the period under review.

Aims and Objectives
To report a comparison of visual outcomes between patients treated with intravitreal ranibizumab and bevacizumab for diabetic macula oedema (DME) in a real world setting in sub-Saharan Africa

Methods
A retrospective review of cases files of patients who were treated with either intravitreal ranibizumab or bevacizumab for diabetic macular edema in Eye Foundation Hospital Ikeja Lagos was done. Only one eye of patients who completed an initial 3-month loading dose were included. Based on recommendations of an expert panel on the use of antivegf for DME, treatment protocol was to continue monthly treatment with antivegf until visual acuity is stable for 3 consecutive months. Included patients received 1.25mg of intravitreal bevacizumab or 0.3 mg intravitreal ranibizumab in the theatre with full sterile procedures observed. Patients were considered compliant if they accepted and received intravitreal antivegf injections according to the protocol (until visual acuity is stable for 3 consecutive months). Visual acuities were expressed as decimal of Snellen acuity values. Eyes that received injections as recommended in the protocol above (monthly injections until visual acuity is stable for 3 consecutive months) were considered compliant.

Comparison of both medications was made based on changes in visual acuity on the Snellen visual acuity chart at 4 , 6 and 9 months after starting antivegf injections. Demographics were expressed as frequencies and percentages. Statistical analyses were performed using IBM SPSS Statistics Version 22 (IBM Corp. Armonk, NY, USA). P values less than 0.05 was considered statistically significant

Results
A total of 508 injections were received by 138 eyes of 115 patients within the study year and diabetic macular edema accounted for 36 eyes, (26.1%) of the total eyes that received either intravitreal Ranibizumab or Bevacizumab.

There were 18 males (50%) and 18 (50%) females. There were more right (22 eyes, 61.1%) than left (14 eyes, 38.9%). The mean age was 63.47 ± 7.6 years, with a range from 43 years to 84 years. The overall mean baseline pre injection BCVA was 0.32 ± 0.24 (range: 0.05-1.0). One hundred and forty-three total injections of either Bevacizumab or Ranibizumab were received by 36 eyes for DME. Fifteen eyes (41.7%) received Bevacizumab while 21 eyes (58.3%) received Ranibizumab injections. Bevacizumab accounted for a total of 69 injections received by patients (48.3%) while 74 (51.7%) Ranibizumab injections were received. The average injection per person per year rate for Bevacizumab was 4.6 (69/15) while for Ranibizumab was 3.5 (74/21). There was an overall significant increase in the mean BCVA following the injections. Mean BCVA at 4 month, 6 month and 9 month post injection was 0.37 ± 0.23 ($p<0.001$), 0.41 ± 0.25 ($p<0.001$), 0.42 ± 0.25 ($p<0.001$) respectively.

A comparison of visual outcome at 4 months, 6 months and 9 months post injection among patients who had either Bevacizumab or Ranibizumab are below:

For eyes that received Bevacizumab, the mean BCVA at baseline, 4 months, 6 months and 9 months post injection were 0.32 ±

0.16, 0.32 ± 0.17 (p<0.001), 0.40 ± 0.24 (p=0.002), 0.44 ± 0.26 (p=0.029) respectively while in eyes that received Ranibizumab, the mean BCVA at baseline, 4 months, 6 months and 9 months post injection was 0.33 ± 0.29, 0.40 ± 0.26 (p<0.001), 0.43 ± 0.26 (p<0.001), 0.41 ± 0.26 (p<0.001) respectively.

At 4 months, 2 of 15 eyes that received Bevacizumab (13.3%) had better visual acuities, 11 eyes (73.3%) remained the same while 2 (13.3%) had worse visual acuties, while 10 of 21 eyes that received Ranibizumab (47.6%) had better visual acuties , 9 eyes (42.9%) remained the same while 2 (9.5%) had worse visual acuities. This showed that a larger percentage of eyes 47.6% that received Ranibizumab had better visual outcome compared to 13.3% that received Bevacizumab. This difference was not statistically significant (p=0.096) Table 1.

At 6 months, 4 of 15 eyes that received Bevacizumab (26.7%) had better visual acuities, 9 eyes (60%) remained the same while 2 (13.3%) had worse visual acuities while 5 of 21 eyes that received Ranibizumab (23.8%) had better visual acuities, 15 eyes (71.4%) remained the same while 1 (4.8%) had worse visual acuities.

At 6 months, more of the eyes that received Ranibizumab had better visual acuities (26.7%) compared to 23.8% that received Bevacizumab. However, this difference was not statistically significant (p=0.615) Table 1.

At 9 months, 5 of 15 eyes that received Bevacizumab (33.3%) had better visual acuities while 10 eyes (66.7%) remained the same, none had worse visual acuities while 4 of 21 eyes that received Ranibizumab (19%) had better visual acuities, 16 eyes (76.2%) remained the same while 1 (4.8%) had worse visual acuities. Hence, at 9 months, more of the eyes that received Ranibizumab had better visual acuities (33.3%) compared to 19% that received Bevacizumab. However, this difference was not statistically significant (p=0.463) (Table 1).

Only seven eyes of the 36 eyes (19.4%) were compliant. Among eyes that received Bevacizumab injection, 5 eyes (33.3%) were compliant while only 2 eyes (9.5%) in the Ranibizumab group were compliant. This difference was not statistically significant (p=0.075).

Discussion

Diabetic macula edema is a common cause of visual impairment in sub-Saharan Africa, an estimated 14.5% of diabetic patients were found with maculopathy in a recent study [13]. Our study found DME a common indication for use of antivegf, 28.1% (143 out of 508) of injections given within the study period were for DME. Significant overall improvements from baseline BCVA (0.32 ± 0.24 (range: 0.05-1.0) was seen at 4-month, 6 month and 9-month post injection (0.37 ± 0.23 (p<0.001), 0.41 ± 0.25 (p<0.001), 0.42 ± 0.25 (p<0.001) respectively in our study eyes, emphasizing the effectiveness of antivegf medications for DME in our study group. Ranibizumab, bevacizumab and aflibercept, the three main antivegf injections available for use in sub Saharan Africa, differ in their molecular weight, structure and pharmacokinetics. Bevacizumab, was salvaged from proteolytic catabolism and recycled via binding to FcRn in endothelial cells, resulting in a long systemic half-life of approximately 20 days following intravenous infusion while Ranibizumab is a 48 KDa monovalent monoclonal antibody fragment, the antigen-binding Fab without the Fc domain. This structure was designed to prevent FcRn binding and, therefore, shorten its systemic half-life to approximately 2 h after entering systemic circulation from the eye and to facilitate distribution across all retinal layers to the choroidal vasculature [4]. Ranibizumab was specifically designed for intraocular use and is thus approved while bevacizumab is used off label.

Cost considerations and comparable effectiveness are the main drivers of continuous use of Bevacizumab [14-16]. In Nigeria over 190 million Nigerians have no health insurance, as a result 77% of total health spending is out-of-pocket compared with an average of 37% for other African countries and, 18% world average [17]. Hence, like other countries cost is a main driver of the choice of antivegf use. Experts identify absence of mandatory health insurance and systemic corruption as the main reasons for high out of pocket payments. Better funding for health insurance and improvement in health policies can help improve coverage of health insurance for all Nigerians and improve access to antivegf. [17].

Our study compares the outcome of use of either ranibizumab or bevacizumab in a tertiary eye hospital in Lagos Nigeria. Interestingly out of the 36 eyes that met the inclusion criteria 21(58.3%) received the more expensive Ranibizumab compared to 15(41.7%) that received bevacizumab. The average injections per eye in 9 months was 4.6 injections (69/15) for bevacizumab and 3.5 (74/21) for ranibizumab. This number of injections is very low, when compared to pivotal studies like RISE and RIDE phase 3 studies with ranibizumab for DME. More than 20 injections were given per eye over the 24 months of study [18]. The number of injections was low in our study eyes because only 7 eyes of the 36 eyes (19.4%) were compliant. Among eyes that received Bevacizumab injection, 5 eyes (33.3%) were compliant while only 2 eyes (9.5%) in Ranibizumab group were compliant. As stated, earlier our treatment protocol was to continue monthly injections until visual acuity is stable for 3 consecutive months. For our study, we only included eyes that completed the initial 3 consecutive months of injections. The number of injections over a 9-month period in our study was however comparable to a mean of 4.5 injections over a period of 14.1 months reported in a recent open label extension study of the RISE and RIDE phase III trials. Approximately 25% of patients did not require further treatment based on protocol-defined re-treatment criteria and mean BCVA was sustained or improved in these patients through the end of follow-up [19]. Similarly, 95.2% of eyes that received ranibizumab and a 100% of eyes that received bevacizumab were able to at least maintain their vision at 9 months follow up. Figure 1 shows a compliant patient with non-proliferative diabetic

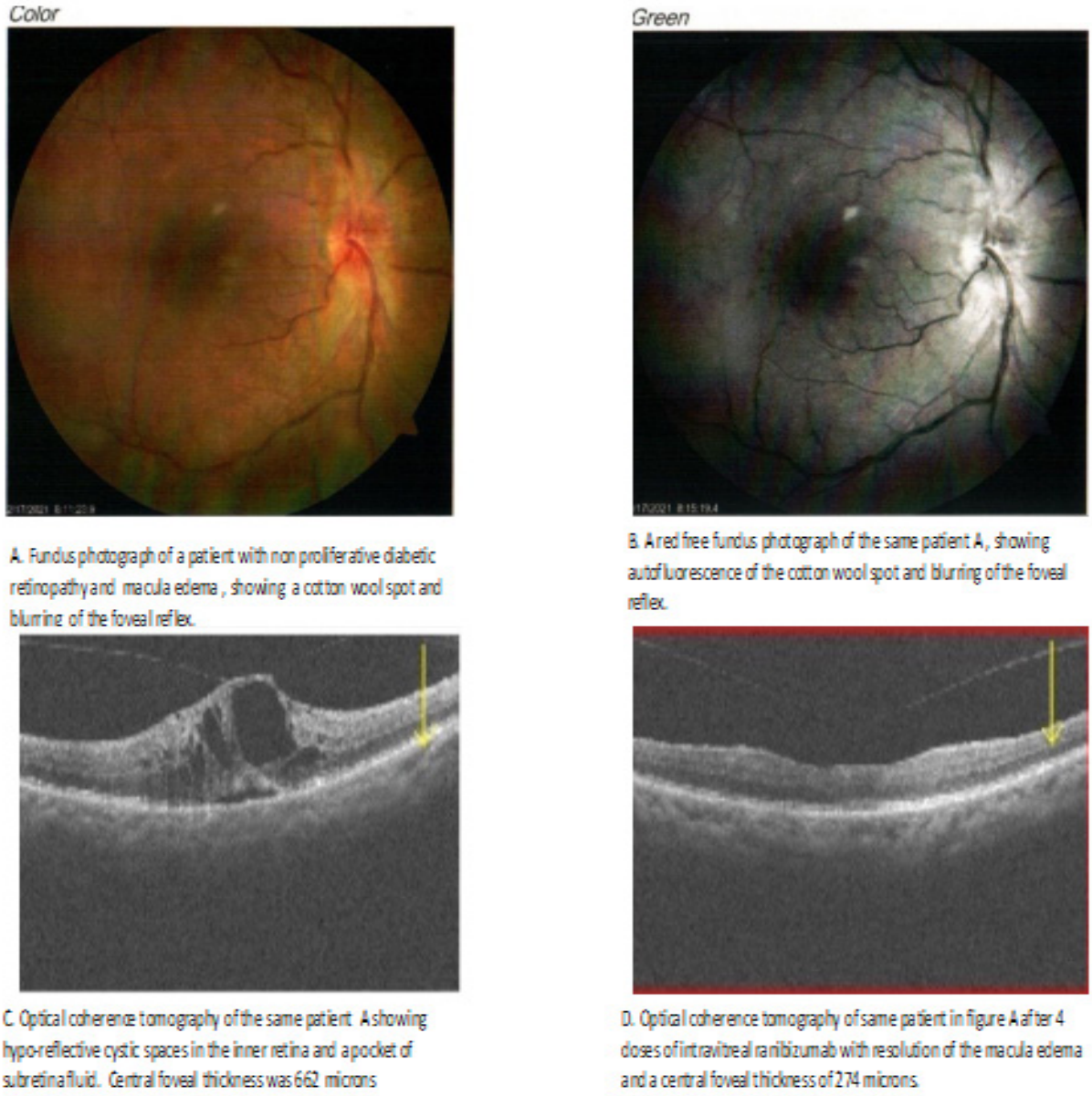

Figure 1: Fundus photographs and optical coherence tomographic scans of a compliant patient with non-proliferative diabetic retinopathy and diabetic macula edema. Patient was managed with intravitreal ranibizumab with resolution of edema.

Table 1: Percentage of study eyes with changes in best corrected visual acuity (BCVA) after intravitreal bevacizumab and ranibizumab.

BCVA	Bevacizumab: ratio of eyes (percentage)	Ranibizumab: ratio of eyes (percentage)	P value
At 4 months post injection			
Better	2/15 (13.3%)	10/21 (47.6%)	P= 0.096
The same	11/15 (73.3%)	9/21 (42.9%)	
Worse	2/15 (13.3%)	2/21 (9.5%)	
At 6 months post injection			
Better	4/15 (26.7%)	5/21 (23.8%)	P= 0.615
The same	9/15 (60.0%)	15/21 (71.4%)	
Worse	2/15 (13.3%)	1/21 (4.8%)	
At 9 months post injection			
Better	5/15 (33.3%)	4/21 (19.0%)	P= 0.463
The same	10/15 (66.7%)	16/21 (76.2%)	
Worse	nil	1/21 (4.8%)	

retinopathy and diabetic macula edema who was managed with intravitreal ranibizumab. Patient had resolution of macula edema after the fourth dose and continued until visual acuity was stable for three months.

Neither ranibizumab nor bevacizumab showed superiority in our group of patients. This is like reports from previous studies. A comparative evaluation of DRCR.net studies evaluating the effectiveness of ranibizumab, bevacizumab and aflibercept for the treatment of DME found all three equally effective for improving visual acuity, only in eyes with "worse visual acuity when initiating therapy was associated with greater visual acuity benefit of aflibercept over bevacizumab or ranibizumab at 1 year after treatment ($P < .001$) [20].

The shortcomings of our study are mainly the small numbers of patients and the retrospective design. Due to the small numbers, treatment effects may be unduly magnified, however, our sample size was due to the uptake of treatment by patients with DME.

Conclusion

Despite poor compliance, improvements in best corrected visual acuities was achieved and maintained with the use of either intravitreal bevacizumab or ranibizumab for diabetic macula edema in a real life setting in sub-Saharan Africa. Neither bevacizumab nor ranibizumab showed statistically significant superiority.

References

1. Ding J, Wong TY. Current epidemiology of diabetic retinopathy and diabetic macular edema. Curr Diab Rep. 2012; 12: 346-354.
2. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus Verteporfin for Neovascular age-related macular degeneration. N Engl J Med. 2006; 355: 1432-1444.
3. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med. 2006; 355: 1419-1431.
4. Avery RL, Castellarin AA, Steinle NC, et al. Systemic pharmacokinetics following intravitreal injections of ranibizumab, bevacizumab or aflibercept in patients with neovascular AMD. Br J Ophthalmol. 2014; 98: 1636-1641.
5. Brown DM, Schmidt-Erfurth U, Do DV, et al. Intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID studies. Ophthalmology. 2015; 122: 2044-2052.
6. Nguyen QD, Brown DM, Marcus DM, et al. RISE and RIDE Research Group. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology. 2012; 119: 789-801.
7. Resnikoff S, Lansingh VC, Washburn L, et al. estimated number of ophthalmologists worldwide (International Council of Ophthalmology update): will we meet the needs? Br J Ophthalmol. 2020; 104: 588-592.
8. Maturi RK, Glassman AR, Josic K, et al. Effect of intravitreous anti-vascular endothelial growth factor vs sham treatment for prevention of vision-threatening complications of diabetic retinopathy. JAMA Ophthalmology. 2021; 139: 701-712.
9. Brown DM, Wykoff CC, Boyer D, et al. Evaluation of Intravitreal Aflibercept for the Treatment of Severe Nonproliferative Diabetic Retinopathy: Results From the PANORAMA Randomized Clinical Trial. JAMA Ophthalmol. 2021; 139: 946-955.
10. Bandello F, Cunha-Vaz J, Chong NV, et al. New approaches for the treatment of diabetic macular oedema: recommendations by an expert panel. Eye (Lond). 2012; 26: 485-493.
11. Kumluang S, Ingsrisawang L, Sangroongruangsri S, et al. A real-world study of effectiveness of intravitreal bevacizumab and ranibizumab injection for treating retinal diseases in Thailand. BMC Ophthalmol. 2019; 19: 82.
12. Ehlers JP, Wang K, Singh RP, et al. A Prospective Randomized Comparative Dosing Trial of Ranibizumab In Bevacizumab-Resistant Diabetic Macular Edema: The REACT Study. Ophthalmol Retina. 2018; 2: 217-224.
13. Jingi AM, Nansseu JR, Noubiap JJ, et al. Diabetes and visual impairment in sub-Saharan Africa: evidence from Cameroon. J Diabetes Metab Disord. 2015; 14: 21.
14. IVAN Study Investigators, Chakravarthy U, Harding SP, et al. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. Ophthalmology. 2012; 119: 1399-1411.
15. Kodjikian L, Souied EH, Mimoun G, et al. GEFAL Study Group. Ranibizumab versus Bevacizumab for Neovascular Age-related Macular Degeneration: Results from the GEFAL Noninferiority Randomized Trial. Ophthalmology. 2013; 120: 2300-2309.
16. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Martin DF, Maguire MG, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology. 2012; 119: 1388-1398.
17. http://www.nigeriastat.gov.ng
18. Nguyen QD, Brown DM, Marcus DM, et al. RISE and RIDE Research Group. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology. 2012; 119: 789-801.
19. Boyer DS, Nguyen QD, Brown DM, et al. RIDE and RISE Research Group. Outcomes with As-Needed Ranibizumab after Initial Monthly Therapy: Long-Term Outcomes of the Phase III RIDE and RISE Trials. Ophthalmology. 2015; 122: 2504-2513.
20. Jeffrey S Heier, Neil M Bressler, Robert L Avery, et al. Comparative Effectiveness Panel. Comparison of Aflibercept, Bevacizumab, and Ranibizumab for Treatment of Diabetic Macular Edema: Extrapolation of Data to Clinical Practice. JAMA Ophthalmol. 2016; 134: 95-99.