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Original Article
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Healthcare Utilization and Treatment Patterns in Diabetic Macular Edema in Korea: a Retrospective Chart Review

Kyu Hyung Park (iD),[1] Yun Young Kim (iD),[2] Young Joon Jo (iD),[3] Jaeryung Oh (iD),[4]
Joo Eun Lee (iD),[5] Ji Eun Lee (iD),[6] Dong Ho Park (iD),[7] Se Woong Kang (iD),[8] Won Ki Lee (iD),[9]
Ha Kyoung Kim (iD),[10] Michael Adena (iD),[11] Jonathan Tan (iD),[12*] and Si Dong Kim (iD)[2]

[1]Department of Ophthalmology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea
[2]Department of Ophthalmology, Daegu Catholic University Medical Center, Daegu, Korea
[3]Department of Ophthalmology, Chungnam National University Hospital, Daejeon, Korea
[4]Department of Ophthalmology, Korea University Anam Hospital, Seoul, Korea
[5]J Eye Center, Busan, Korea
[6]Department of Ophthalmology, Pusan National University Hospital, Busan, Korea
[7]Department of Ophthalmology, Kyungpook National University Hospital, School of Medicine, Kyungpook National University, Daegu, Korea
[8]Department of Ophthalmology, Samsung Medical Center, School of Medicine, Sungkyunkwan University, Seoul, Korea
[9]Department of Ophthalmology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[10]Department of Ophthalmology, Hallym University Kangnam Sacred Heart Hospital, Seoul, Korea
[11]Datalytics Pty Ltd, Canberra, Australia
[12]Allergan Singapore Pte. Ltd, Singapore

Address for Correspondence:
Si Dong Kim, MD, PhD
Department of Ophthalmology, Daegu Catholic University Medical Center, Catholic University of Daegu School of Medicine, 33 Duryugongwon-ro 17-gil, Nam-gu, Daegu 42472, Republic of Korea.
E-mail: sdkim1@cu.ac.kr

*Jonathan Tan was an employee of Allergan Singapore Pte. Ltd. when the study was conducted.

ORCID iDs
Kyu Hyung Park (iD)
https://orcid.org/0000-0002-5516-8121
Yun Young Kim (iD)
https://orcid.org/0000-0002-9929-6635
Young Joon Jo (iD)
https://orcid.org/0000-0002-1542-9841
Jaeryung Oh (iD)
https://orcid.org/0000-0002-1036-6562
Joo Eun Lee (iD)
https://orcid.org/0000-0002-4825-4697
Ji Eun Lee (iD)
https://orcid.org/0000-0002-1820-332X
Dong Ho Park (iD)
https://orcid.org/0000-0001-6911-3765

ABSTRACT

Background: Limited data exist on real-world treatment patterns for diabetic macular edema (DME) in Korea. In this study, we investigated DME treatment patterns from 2009 to 2014 and the impact of baseline treatment on healthcare resource utilization and visual acuity (VA) outcomes.

Methods: A retrospective cohort chart review of DME patients treated at 11 hospital ophthalmology clinics between January 1, 2012 and December 31, 2013 was conducted. We collected data on demographics, healthcare resource utilization (clinic visits, treatment visits, and visits for ocular investigations), distribution of DME treatments, and VA.

Results: Overall, 522 DME patients (men, 55.2%; mean age, 59 years; mean HbA1c [n = 209], 8.4%) with 842 DME eyes were evaluated. For all treatments, healthcare resource utilization was significantly higher during the first 6 months versus months 7–12, year 2, or year 3 ($P \leq 0.001$), but was highest for patients whose first treatment was an anti-vascular endothelial growth factor (VEGF) treatment (visits/quarter; anti-VEGF, 1.9; corticosteroids, 1.7; laser, 1.4). Use of macular laser therapy decreased (44% to 8%), whereas use of anti-VEGF injections increased (44% to 69%) during the study period. However, VA improvement was not commensurate with healthcare resource utilization of anti-VEGF treatment (mean VA gain, 2.7 letters).

Conclusion: A trend toward increasing use of intravitreal anti-VEGF injections for DME treatment was observed in Korea. However, the frequency of dosing and monitoring was lower in clinical practice versus major clinical trials, which may have led to the less-than-favorable improvements in visual outcomes.

Keywords: Anti-VEGF; Clinical Practice Patterns; Intravitreal Injections; Laser Therapy; Visual Acuity; Visual Outcomes

Se Woong Kang
https://orcid.org/0000-0001-8755-3465
Won Ki Lee
https://orcid.org/0000-0001-7039-1762
Ha Kyoung Kim
https://orcid.org/0000-0002-5581-0057
Michael Adena
https://orcid.org/0000-0003-0182-8582
Jonathan Tan
https://orcid.org/0000-0002-0942-8404
Si Dong Kim
https://orcid.org/0000-0002-2038-2961

INTRODUCTION

Diabetes is a global health emergency. One in 11 adults has diabetes, with 5 million diabetes-related deaths having occurred in 2015.[1] In Korea, the prevalence of diabetes has increased drastically from 1.5% in the 1970s to > 10% in the early 2000s.[2] According to the Korea National Health and Nutritional Examination Survey (KNHANES [2013–2014]) results, approximately 4.8 million Koreans (13.7%) aged 30 years or older have diabetes, and nearly 25% of adult Koreans are prediabetic.[3] Diabetes is frequently associated with complications such as retinopathy, renal failure, neuropathy, nephropathy, cardiovascular disease, and amputations.[4] Diabetic retinopathy (DR) is the leading cause of preventable vision loss in working-age adults in developed countries and has a global prevalence of 35.4%.[5,6] According to earlier KNHANES (2008–2011) results, 15.8% of diabetic patients in Korea have DR, 2.8% of whom also have diabetic macular edema (DME), an advanced and severe form of DR.[7,8] The worldwide increase in diabetes coupled with a complex comorbidity profile has resulted in concomitantly increased healthcare utilization, healthcare costs, and lower productivity in this population.[9-11] Furthermore, the incidence of comorbidities and healthcare resource utilization and associated expenditures, including healthcare visits, diagnostic procedures, and treatments requiring frequent monitoring and injections, is higher in diabetic patients with DME versus those without DME.[11-13]

DME was traditionally treated with laser photocoagulation, but treatments have evolved to include intravitreal anti-vascular endothelial growth factors (anti-VEGFs; e.g., ranibizumab, bevacizumab, and aflibercept) and corticosteroid injections (e.g., triamcinolone acetonide).[14-18] In landmark clinical trials, frequent (typically monthly) intravitreal injections of anti-VEGF agents, such as ranibizumab (Lucentis®, Genentech, Inc., South San Francisco, CA, USA)[19-22] and aflibercept (Eylea®, Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA),[20,23,24] were efficacious in improving visual and anatomic outcomes in patients with DME. In these trials, patients received an average of 8 to 12 intravitreal injections per eye in the first year. In more recent trials, a sustained-release dexamethasone intravitreal implant (Ozurdex®, Allergan plc, Dublin, Ireland) demonstrated sustained efficacy for up to 6 months after a single implant.[25,26]

Off-label intravitreal DME treatments, including the anti-VEGF agent bevacizumab (Avastin®, Genentech, Inc.) and various corticosteroid preparations, have been available in Korea for several years. Furthermore, the Ministry of Food and Drug Safety (MFDS) in Korea approved ranibizumab in 2011 and aflibercept and sustained-release dexamethasone intravitreal implant in 2014. However, data on real-world treatment patterns for DME patients and related healthcare resource utilization in Korea are limited.[27] Therefore, we sought to characterize DME treatment patterns in Korea and to examine the impact of treatment on healthcare resource utilization and visual acuity (VA) outcomes.

METHODS

Study design

This retrospective chart review of consecutive patients with DME who received treatment between January 1, 2012 and December 31, 2013 (patient selection period) was conducted at 11 hospital ophthalmology clinics across Korea (5 in Seoul and Gyeonggi, 3 in Daegu, 2 in Busan, and 1 in Daejeon). The baseline date was considered to be January 1, 2009, or the

Methodology: Park KH, Kim YY, Oh J, Kang SW, Kim HK, Tan J, Kim SD. Writing - original draft: Park KH, Lee JE,[2] Kang SW. Writing - review & editing: Park KH, Kim YY, Jo YJ, Lee JE,[1] Lee WK, Kim HK, Adena M, Tan J, Kim SD.

Lee JE,[1] Lee Joo Eun; Lee JE,[2] Lee Ji Eun.

date on which the first treatment of the second or only eye was conducted, whichever was later. The pre-index period was from January 1, 2009 to the day before the index date (in 2012 or 2013) and the post-index period was from the day after the index date to September 30, 2014 (chart extraction date), resulting in a total observation period from January 1, 2009 to September 30, 2014 (**Fig. 1**). An electronic database containing medical records of eligible patients was created and all data were de-identified.

Patients

Patients were eligible if they had a clinical diagnosis of DME, received ≥ 1 laser or pharmacotherapy treatment(s) during the patient selection period, and had ≥ 1 follow-up visit. Patients with concurrent progressive retinal disease (e.g., neovascular age-related macular degeneration [AMD] and retinal vein occlusion [RVO]) requiring treatment to prevent vision loss or those participating in a clinical trial were excluded. Patients with concurrent stable retinal disease (e.g., RVO or dry AMD) not requiring treatment to prevent vision loss were included at the investigator's discretion.

Outcomes

Primary outcomes were healthcare resource utilization (defined as clinic visits, DME treatment visits, and visits during which optical coherence tomography [OCT] and fluorescein angiography [FA] were performed), time from diagnosis of DME to treatment, change in distribution of DME treatments over time, and proportion of affected eyes undergoing a treatment switch. All outcomes were assessed from the baseline visit to the end of follow-up.

Secondary outcomes included change in VA (in approximate Early Treatment Diabetic Retinopathy Study [ETDRS] letters), use of FA and OCT in deciding treatment, and safety. VA was originally determined as per the Snellen chart and converted to an ETDRS letter score using a published algorithm.[28] To ensure comparability of the central macular thickness (CMT) measurements across the different OCT machines used, CMT measurements were transformed to Stratus-equivalent values using published algorithms.[29,30]

Data collection

We reviewed eligible patients' charts and extracted data between October 2014 and January 2015. Patient demographics and disease characteristics were collected from baseline. If a characteristic was not recorded at baseline, a search of the 12 months following (preferentially) or preceding the baseline visit was performed. Characteristics not documented during that period were marked as "missing." For each clinic visit, data
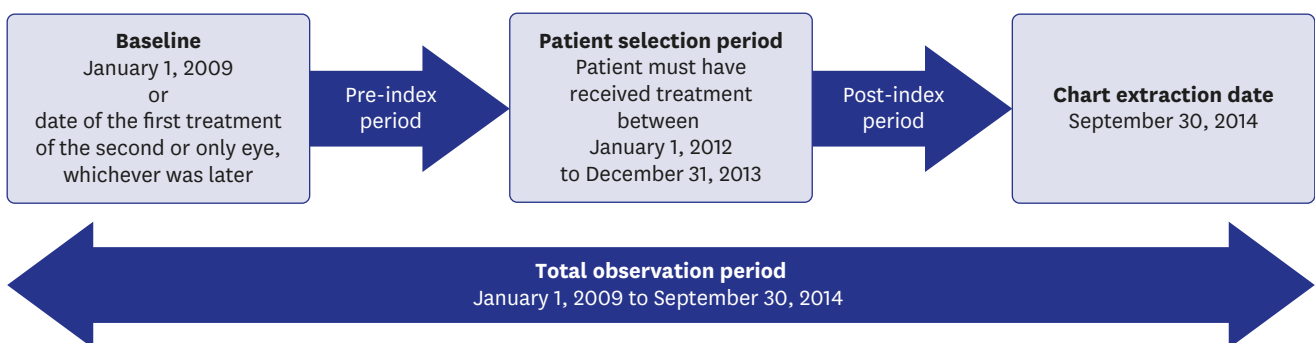

Fig. 1. Study design.

collection included the type of treatment administered (laser photocoagulation, intravitreal corticosteroid [triamcinolone acetonide injection or dexamethasone implant], intravitreal anti-VEGF [ranibizumab or bevacizumab], or other) if applicable, VA of each eye, whether FA was performed, and CMT as measured by OCT. Any treatment received before January 1, 2009 was recorded as medical history. Adverse events (AEs; elevated intraocular pressure, cataract requiring extraction, endophthalmitis, stroke, myocardial infarction, and hospital admissions) occurring from 2009 onward were recorded when available.

Statistical analyses

Descriptive statistics were used for demographic and disease-related data. Chi-squared tests and one-way analysis of variance F-tests were performed to determine the statistical significance of differences between proportions and means, respectively. The standard error of the mean change in VA from baseline was estimated by taking into account multiple post-baseline measurements for each eye. A subanalysis was performed to evaluate the association between anti-VEGF treatment and healthcare resource utilization and patient outcomes. The 95% confidence interval (CI) for each AE rate was calculated by assuming that the number of events followed Poisson distribution. All analyses were performed using the Stata software versions 13, 14 (StataCorp LP, College Station, TX, USA).

Ethics statement

The study protocol was approved by the Institutional Review Board (IRB) of Daegu Catholic University Medical Center (IRB approval No. CR-14-125) at each site and conducted in accordance with the Declaration of Helsinki. Since this was a retrospective chart review, informed consent was waived by the IRB. The sponsor was involved in the study design; collection, analysis, and interpretation of data; writing of the report; and in the decision to submit the article for publication. No honoraria or payments were made for authorship.

RESULTS

Baseline characteristics

Data were extracted from the charts of 522 patients (842 DME eyes) who met the eligibility criteria. Overall, 55.2% of the patients were men, and mean (standard deviation [SD]) age was 59.0 (10.9) years (**Table 1**). Among patients with available diabetes-related data, almost all (96.7% [444/459]) had type 2 diabetes and approximately half (51.3% [214/417]) had the disease for > 10 years. Nearly half (46.4% [97/209]) of the patients had a glycated hemoglobin (HbA1c) value > 8% and 56.32% had bilateral DME. DME was diagnosed within 30 days of the first recorded treatment for 75% of the eyes; of these, 26.4% eyes were pseudophakic. At baseline, 69.4% of eyes had VA between 20 and 70 ETDRS letters (Snellen, 3/60 to 6/12) and 76.2% had CMT ≥ 300 μm. Most patients had their baseline visits in 2012 (38.9%) and 2013 (41.2%).

Table 2 shows the baseline characteristics of patients categorized by the intravitreal DME treatment received during the first 6 months of treatment.

Primary outcomes

Healthcare resource utilization

Overall, 522 patients had a total of 5,311 clinic visits for a total follow-up period of 2,995 person-quarters. The average clinic visit rate was 1.8 per quarter through the study period. In the first year post-baseline, the clinic visit rate was 3.0 in quarter 1, indicating that the

Table 1. Demographics and baseline characteristics

Characteristics	No. (%)
Gender, men (n = 522)	288 (55.2)
Age, yr (n = 522)	
Mean (SD)	59 (10.9)
Type of diabetes (n = 459)	
Type 2	444 (96.7)
Type 1	15 (3.3)
Diabetes duration, yr (n = 417)	
1–5	86 (20.6)
6–10	117 (28.1)
> 10	214 (51.3)
Baseline HbA1c, % (n = 209)	
< 7	63 (30.1)
7–8	49 (23.4)
> 8	97 (46.4)
Year of baseline visit (n = 522)	
2009	16 (3.1)
2010	25 (4.8)
2011	58 (11.1)
2012	203 (38.9)
2013	215 (41.2)
2014	5 (1.0)
CMT ≥ 300 μm, (n = 736 eyes)	561 (76.2)

CMT = central macular thickness, HbA1c = glycated hemoglobin, SD = standard deviation.

baseline visits were most likely the patients' first visits; however, this rate reduced to 1.7 in quarter 2 and halved to 1.5 in quarters 3 and 4 thereafter (**Fig. 2A**).

Results of an analysis of healthcare resource utilization by DME characteristics and treatment received at baseline showed that the clinic visit rate per quarter was higher among patients with non–center-involving DME than those with center-involving DME (2.0 vs. 1.8 per quarter; $P < 0.001$). Of note, patients receiving anti-VEGF treatment at baseline had a higher rate of clinic visits per quarter than patients receiving laser or corticosteroid treatment (1.9, 1.4, and 1.7 visits per quarter, respectively; **Table 3**).

Across all treatment categories (no treatment, intravitreal corticosteroid injection, intravitreal anti-VEGF injection, and both intravitreal corticosteroid and anti-VEGF injections), significantly more clinic visits, treatment visits, and OCT and FA assessments occurred per quarter in the first 6 months post-baseline compared with months 7–12, year 2, or year 3 ($P \leq 0.001$) (**Fig. 2B**). Overall, across the observation period, patients who received anti-VEGF agents (with or without corticosteroid treatment) had the highest number of clinic visits, treatment visits, and OCT assessments per quarter.

Table 2. Baseline characteristics of patients categorized by intravitreal DME treatment received during the first 6 months of treatment

Intravitreal treatment category[a]	Age, yr, mean (SD)	Men, No. (%)	VA, mean (SD), letters	CMT, μm, mean (SD)	Bilateral DME, No. (%)	Pseudophakic, No./No. (%)
Overall (n = 419)	58.4 (10.8)	230 (54.9)	59.0 (19.3)	391.1 (134.9)	236 (56.3)	107/391 (27.4)
None (n = 32)	59.7 (10.5)	17 (53.1)	68.9 (19.1)	328.3 (119.6)	16 (50.0)	4/29 (13.8)
Corticosteroid (n = 29)	63.7 (6.0)	16 (55.2)	53.8 (17.1)	429.2 (128.4)	16 (55.2)	13/28 (46.4)
Anti-VEGF (n = 291)	56.9 (11.1)	158 (54.3)	59.7 (18.7)	377.7 (121.9)	164 (56.4)	65/271 (24.0)
Both (n = 67)	61.9 (9.9)	39 (58.2)	53.1 (20.6)	454.3 (176.7)	40 (59.7)	25/63 (39.7)
P for differences between treatment categories	< 0.001	0.944	< 0.001	0.001	0.838	0.003

CMT = central macular thickness, DME = diabetic macular edema, SD = standard deviation, VA = visual acuity, VEGF = vascular endothelial growth factor.
[a]In all treatment categories, patients may have received laser photocoagulation therapy for DME.
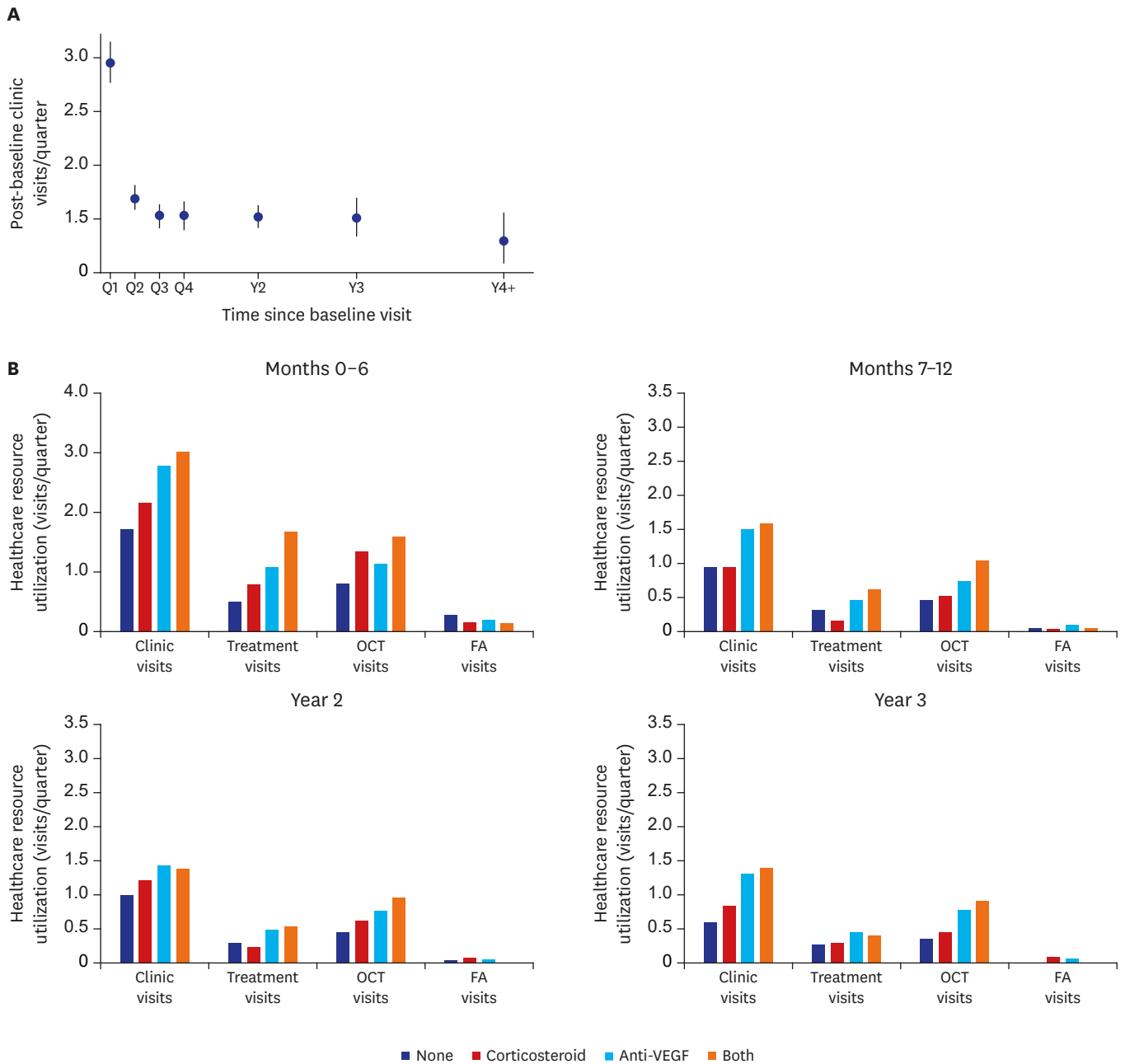
Fig. 2. Healthcare resource utilization for treatment of diabetic macular edema in Korea. (**A**) Overall clinic visit rate and (**B**) Healthcare resource utilization by treatment category over time.
FA = fluorescein angiography, OCT = optical coherence tomography, Q = quarter, VEGF = vascular endothelial growth factor, Y = year.

Time from diagnosis of DME to treatment

The median time from diagnosis of DME to initiation of treatment was 1 week. Three-quarters (75%) of patients were first treated within 30 days of their diagnosis, with an additional 14% and 3% receiving their first treatment in post-diagnosis years 1 and 2, respectively (**Fig. 3**).

Distribution of DME treatments

During the observation period, use of laser photocoagulation therapy reduced considerably

Table 3. Healthcare resource utilization by baseline characteristics of index DME eye and treatment received at baseline

Characteristics	Visits	Quarters at risk	Visits per quarter
Index eye	5,311	2,995	1.8
Type of DME			
Center-involving	3,858	2,204	1.8
Non-center-involving	896	446	2.0
Not recorded	557	345	1.6
Lens status			
Phakic	1,241	762	1.6
Pseudophakic	3,639	1,978	1.8
Not recorded	431	256	1.7
Glaucoma			
No	5,180	2,908	1.8
Yes	96	64	1.5
Not recorded	35	23	1.5
CMT, μm			
< 300	833	489	1.7
≥ 300	3,993	2,298	1.7
Not recorded	485	208	2.3
Baseline treatment with anti-VEGF			
No	1,054	741	1.4
Yes	4,257	2,254	1.9
Baseline treatment with laser			
No	4,540	2,444	1.9
Yes	771	552	1.4
Baseline treatment with IVTA			
No	5,088	2,864	1.8
Yes	223	132	1.7

CMT = central macular thickness, DME = diabetic macular edema, IVTA = intravitreal triamcinolone acetonide, VEGF = vascular endothelial growth factor.

from 57.1% in the first half (H1) of 2009 to 8.7% in the second half (H2) of 2014 (**Fig. 4**). In contrast, use of intravitreal anti-VEGF injections increased from 28.6% in 2009 H1, plateaued at approximately 78% in 2012 and 2013, and decreased to 65.4% in 2014 H2; however, it was consistently the most commonly used treatment (except in 2009 H1). Use of corticosteroid implants increased steadily from 0.2% in 2012 H2 to 7.7% in 2014 H2. Use of intravitreal corticosteroids fluctuated between 2.4% and 18.3% between 2010 and 2014.
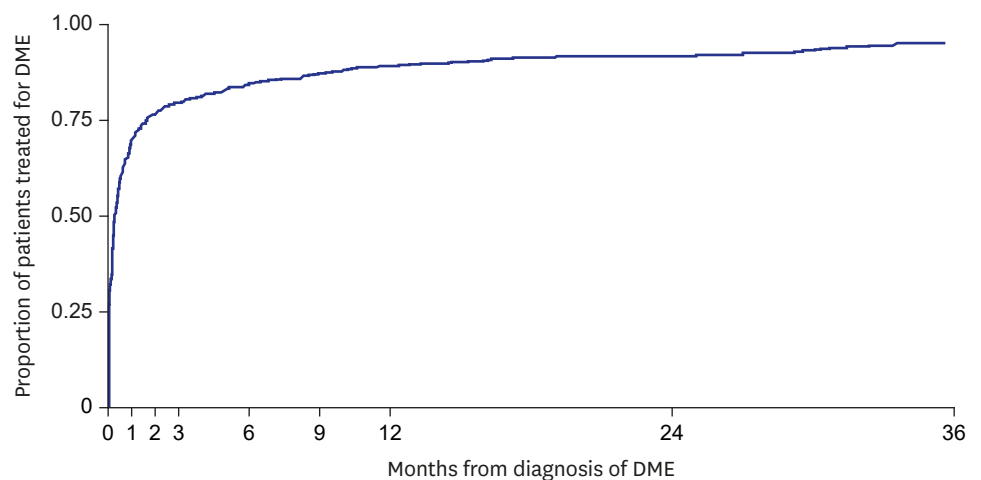

Fig. 3. Time from diagnosis of DME to first treatment.
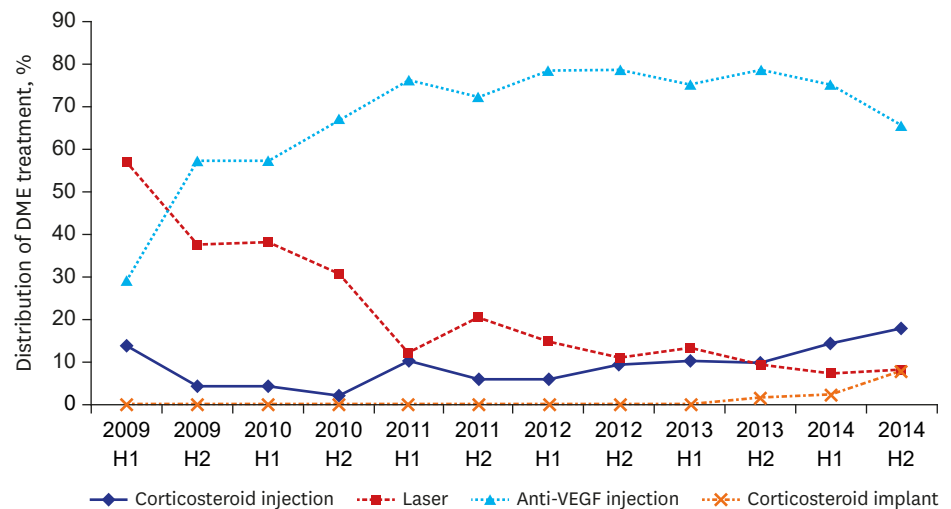DME = diabetic macular edema.

Fig. 4. Distribution of DME treatments during the observation period (2009–2014).
DME = diabetic macular edema, H = half, VEGF = vascular endothelial growth factor.

To avoid the confounding effects caused by temporal trends and disease progression over time, the distribution of treatment in patients with baseline visits in 2012 and 2013 (i.e., patients initiating treatment around the same time) was analyzed. The relative proportions of treatments over this time period were similar to those from 2009 to 2014.

In the subgroup of patients who did not receive intravitreal treatment during the first 6 months, 26%, 41%, and 57% received intravitreal anti-VEGF or intravitreal corticosteroid treatment during months 7–12, year 2, and year 3, respectively. Of those who received intravitreal corticosteroid treatment during the first 6 months, 0%, 47%, and 33% switched to intravitreal anti-VEGF injections (alone or concurrently) during months 7–12, year 2, and year 3, respectively. Among patients who received intravitreal anti-VEGF injections during the first 6 months, 16%, 23%, and 36% switched to intravitreal corticosteroid therapy (alone or concurrently) during months 7–12, year 2, and year 3, respectively.

Proportion of eyes that switched treatments
Initially, intravitreal anti-VEGF treatment was used for 77% of eyes, and alternative therapies were used for the remaining 23% of eyes. At subsequent visits, treatment was switched for 38% of eyes initiated on intravitreal anti-VEGF treatment and 41% of eyes initiated on an alternative treatment. Overall, 56% of patients received only 1 type of treatment (intravitreal anti-VEGF, laser photocoagulation therapy, or other), 34% received 2 types of treatment, and 10% received all 3 types of treatment.

Secondary outcomes

VA
Overall, mean annual VA improved by 1.4 ETDRS letters from baseline. Although not statistically significant, eyes treated with laser photocoagulation therapy at baseline had worsened VA (1.3 letters worse), while eyes not treated with laser photocoagulation at baseline had improved VA (1.7 letters better). Eyes treated with anti-VEGF at baseline had improved VA (1.5 letters better), which was slightly better than that for eyes not treated with anti-VEGF at baseline (1.0 letter better). Men patients had a greater improvement in

Table 4. Mean change in VA (in letters) after baseline visit by gender and age group

Change in VA	Age group (at baseline), yr											
	< 50		50–59		60–69		70–79		≥ 80		All ages	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Mean	2.2	4.8	0.7	−0.3	1.0	0.6	3.5	−2.0	1.0	4.8	1.5	1.2
SE[a]	1.7	2.3	1.4	1.4	1.2	1.8	2.3	1.7	0.9	3.3	0.8	1.0
Eyes	93	88	168	108	146	110	58	60	3	4	468	370

SE = standard error, VA = visual acuity.
[a]Estimated mean change, controlling for multiple post-baseline measurements for each eye.
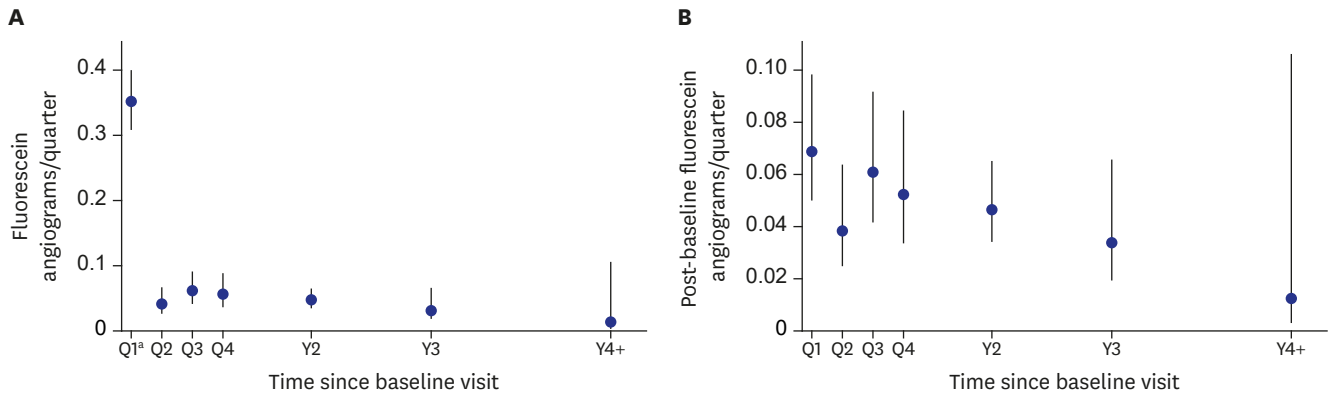
Fig. 5. Quarterly rate of FA procedures. (**A**) Including procedures at or up to 7 days before the baseline visit and (**B**) Ignoring procedures at the baseline visit.
FA = fluorescein angiography, Q = quarter, Y = year.
[a]Q1 count includes fluorescein angiograms within 30 days of the baseline visit.

VA than women patients (mean [standard error (SE)] change in VA from baseline, 1.5 [0.8] versus 1.2 [1.0] letters). In addition, younger patients had greater improvements than older patients (**Table 4**).

Use of FA
Use of FA was highest in the first quarter of year 1 (0.4 visits) and decreased to 0.01 visits per quarter by year 4 (**Fig. 5A**). Most FAs were performed at the baseline visit or in the preceding week. However, eliminating FAs performed at baseline did not alter the trend of FA utilization; 0.1 FAs were performed in quarter 1 of year 1, which decreased to 0.03 per quarter in year 3 and 0.01 per quarter in year 4 (**Fig. 5B**).

Use of OCT
Use of OCT ranged from 1.0 visit in quarter 1 to 0.8 visits in quarter 4 in year 1 post-baseline (**Fig. 6**). OCT use was highest in the first quarter because an OCT was performed at 66% of baseline visits, which then plateaued during years 2 and 3, and decreased to 0.7 in year 4.

Subanalysis in patients receiving anti-VEGF treatment
The association of anti-VEGF treatment frequency with patient outcomes was examined in a subgroup of 213 patients who received anti-VEGF treatment and had at least 12 months of follow-up. These patients had an average of 8.9 clinic visits, received 2.5 anti-VEGF injections, and had a mean VA improvement of 2.7 letters in the first year of follow-up. Overall, 164/291 (56.4%) patients receiving anti-VEGF injections during the first 6 months of treatment had bilateral DME; this could have had an effect on the average number of clinic visits but not on the average number of injections per eye.
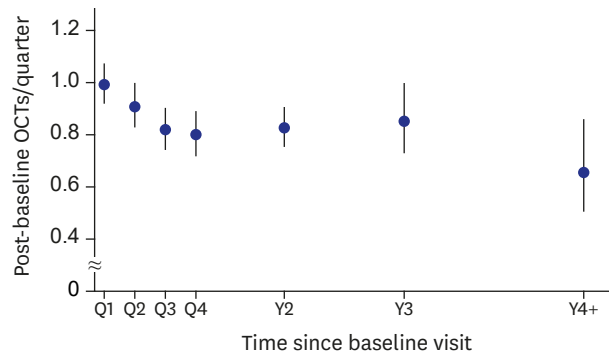
Fig. 6. Quarterly rate of OCT procedures.
OCT = optical coherence tomography, Q = quarter, Y = year.

Table 5. AEs recorded between the baseline date and chart extraction date (522 patients, 749 person-years at risk)

Type of AE	Events			Incidence (events/person-year)	
	Right eye	Left eye	Total	Estimate	95% CI
IOP elevation	22	12	34	0.05	0.03–0.06
Cataract extraction	13	9	22	0.03	0.02–0.04
Endophthalmitis	0	0	0	0.00	0.000–0.004
Myocardial infarction	-	-	1	0.001	0.000–0.005
Stroke	-	-	1	0.001	0.000–0.005
Hospital admission	-	-	39	0.05	0.04–0.07

AE = adverse event, CI = confidence interval, IOP = intraocular pressure.

Safety

The most frequently reported AEs were intraocular pressure elevation (34 cases, 0.05 events per person-year; 95% CI, 0.03, 0.06) and cataract extraction (22 cases, 0.03 events per person-year; 95% CI, 0.02–0.04). Myocardial infarction, stroke, and hospital admissions occurred at rates of 0.001 events per person-year (95% CI, 0.000–0.005), 0.001 events per person-year (95% CI, 0.000–0.005), and 0.05 events per person-year (95% CI, 0.04–0.07), respectively (**Table 5**). There were few hospital admissions, but the associated causes were not available.

DISCUSSION

In Korea, there are limited real-world clinical data available on the patterns of healthcare resource utilization and treatment in diabetic patients with DME. To our knowledge, this is the first multicenter retrospective chart review of a large number of diabetic patients with DME in Korea.

The standard of care for DME treatment used to be laser photocoagulation therapy; however, this paradigm has changed with the results of clinical trials showing benefits with intravitreal anti-VEGF and corticosteroid injections.[14,15,19-24] Studies with intravitreal anti-VEGF agents, such as aflibercept, bevacizumab, and ranibizumab, have consistently demonstrated that these agents are effective and relatively safe for the treatment of DME, which causes vision impairment.[20] Results of the current study confirm this paradigm shift. Use of laser photocoagulation therapy reduced considerably from 57.1% in 2009 H1 to 8.7% in 2014 H2. In contrast, use of intravitreal anti-VEGF injections increased from 28.6% in 2009 H1 to a peak of 78%–79% in 2012 and 2013 and then decreased to 65.4% in 2014 H2. The decrease in the use of intravitreal anti-VEGF injections toward the end of the study period

could be explained by the simultaneous increase in the use of intravitreal corticosteroid injections from 10.0% to 18.3% between 2013 and 2014 and novel alternatives such as the dexamethasone intravitreal implant from 0.2% to 7.7% between 2012 and 2014.

The number of clinic visits, treatment visits, and visits where OCT and FA were performed was the highest for patients receiving intravitreal anti-VEGF injections versus intravitreal corticosteroid injections or no intravitreal treatment. However, across all treatment groups, these numbers were the highest in the first 6 months post-baseline followed by a decline over months 7–12, year 2, and year 3. A variety of reasons could account for this decrease over time. Patients with DME are a difficult-to-treat population given the high number of comorbidities and high treatment burden. This may lead to difficult treatment-decisions for patients between seeking treatment and managing work or personal commitments. Another possible reason may include partial reimbursement or lack of coverage for DME treatment by the national health insurance system. Together, this could lead to poor patient compliance and a dip in the frequency of treatment and monitoring visits.[13] Furthermore, patients in clinical trials and clinical practice are inherently different, and adherence to treatment and monitoring schedules is often less in clinical practice than in clinical trials. For anti-VEGF treatment in particular, the decrease in the frequency of treatment and monitoring can be explained by the findings from recent studies, which demonstrated a lower frequency of treatment and monitoring in patients receiving intravitreal anti-VEGF treatment in clinical practice than in landmark clinical trials such as RISE and RIDE.[22] The disparity between clinical practice and clinical trials indicates under-utilization of anti-VEGF treatment in real-world settings, which can negatively affect treatment outcomes.[18,22,31-33] Although in a real-world study conducted in UK, the mean gain in VA was 6.6 letters (vs. 2.7 in the current study), it is important to note that the mean number of injections received over 12 months was also considerably higher versus the current study (7.2 vs. 2.5).[32]

Previous phase II and phase III studies for intravitreal anti-VEGF injections have suggested a trend toward greater visual benefit associated with more frequent injections. A greater gain in ETDRS letters was observed in studies implementing a more frequent injection regimen (RISE/RIDE[22] and RESOLVE[34]) versus those with a less frequent injection regimen (RESTORE[35] and the Diabetic Retinopathy Clinical Research Network Protocol[36,37]), even though all of them followed a monthly follow-up schedule. This possibly clarifies the findings of this study that although the frequency of treatment and monitoring in patients receiving intravitreal anti-VEGF treatment at baseline was the highest among all treatment types, it may not have been high enough, thereby leading to a small and disproportionate gain in VA (mean, 2.7 letters) versus that reported by major clinical trials.

Patients with diabetes, especially those with DME, have a considerable pre-existing healthcare burden even before deciding on a treatment for DME.[11] It is therefore important to consider the treatment intensity and monitoring requirements when deciding on a therapy for this population. Monitoring requirements or additional healthcare visits associated with intravitreal treatment may not only affect the patient but also the caregivers and healthcare providers responsible for the coordination of multiple visits.[11,13] A treatment that offers reduced dosing and monitoring frequency without compromising VA might improve patient compliance to treatment and subsequently improve visual outcomes in the real-world clinical setting. The slight increase in the use of sustained-release dexamethasone intravitreal implant in the latter half of 2014 reflects the perceived benefit of this modality that requires a four times lower dosing frequency[25] in comparison to intravitreal anti-VEGF injections that can be burdensome

and uncomfortable for patients. Furthermore, dexamethasone implants are beneficial in patients refractory to anti-VEGF injections; studies have shown that eyes with DME considered refractory to anti-VEGF injections that were switched to dexamethasone implants had better visual and anatomical outcomes than those that were continued on treatment with anti-VEGF therapy.[38,39] A recent study conducted in Korea also demonstrated that dexamethasone implants improved VA and decreased retinal thickness in patients that did not respond to previous treatment including anti-VEGF injections and laser photocoagulation.[40]

We observed a radical shift in treatment patterns over the study period; use of laser photocoagulation drastically reduced, whereas use of anti-VEGF and corticosteroid injections considerably increased. A variety of reasons could account for the change in the distribution of DME treatments over time in Korea. The positive VA improvements demonstrated by intravitreal anti-VEGF injections in landmark clinical trials could have led to their increased and continued use by Korean clinicians in patients with DME. Moreover, multiple studies in Korea demonstrated that the combination of laser photocoagulation and anti-VEGF injections did not yield better visual and anatomical outcomes than anti-VEGF therapy alone in patients with DME[41,42]; this may possibly have discouraged the use of combination treatment in Korea and contributed to the decrease in the use of laser photocoagulation. However, this did not translate to visual outcomes similar to those reported in the major clinical trials. Furthermore, in contrast to the findings from another real-world study, intravitreal anti-VEGF injection use did not entirely eclipse laser photocoagulation therapy in our study.[17] Whether this reflects suboptimal response with intravitreal anti-VEGF injections or raises concerns about their long-term effects or VEGF resistance remains to be investigated in future studies. Of note, use of the dexamethasone implant increased toward the end of the study period. Previous studies in clinical settings in Korea have demonstrated the effectiveness of dexamethasone intravitreal implants in patients with DME, especially in pseudophakic eyes, DME with subretinal fluid, or diffuse type DME.[43]

While this study has several strengths, including length of observation time, some limitations must be acknowledged. A retrospective design can result in selection bias and missing data, necessitating caution when interpreting results. However, our results were consistent with the findings from other real-world studies, which also observed decreased use of laser photocoagulation therapy and increased use of intravitreal anti-VEGF injections.[16-18] The relationship between the type of treatment received and visual outcomes should be more closely examined in future studies.

In conclusion, the results of this study demonstrated that intravitreal anti-VEGF treatment is the most frequently used treatment and accounts for the most healthcare resource utilization in patients with DME in Korea. However, the associated outcomes in real-world clinical settings are not as encouraging as those observed in the landmark clinical trials, possibly because of a lower frequency of treatment and monitoring in real-world clinical settings than in the clinical trials. Alternative treatments with comparable outcomes but reduced frequency of dosing and monitoring need to be explored.

REFERENCES

1. International Diabetes Federation. *IDF Diabetes Atlas*. 7th ed. Updated 2015. Accessed September 19, 2017. http://www.diabetesatlas.org.

2. Kim DJ. The epidemiology of diabetes in Korea. *Diabetes Metab J* 2011;35(4):303-8.
   PUBMED | **CROSSREF**

3. Korean Diabetes Association. *Diabetes Fact Sheet in Korea 2016*. http://www.diabetes.or.kr/bbs/index.html?sub_menu=&code=e_resource&category=1&gubun=&page=1&number=292&mode=view&order=&sort=&keyfield=&key. Updated 2016. Accessed December 7, 2017.

4. Cade WT. Diabetes-related microvascular and macrovascular diseases in the physical therapy setting. *Phys Ther* 2008;88(11):1322-35.
   PUBMED | **CROSSREF**

5. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. *Lancet* 2010;376(9735):124-36.
   PUBMED | **CROSSREF**

6. Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, et al. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care* 2012;35(3):556-64.
   PUBMED | **CROSSREF**

7. Jee D, Lee WK, Kang S. Prevalence and risk factors for diabetic retinopathy: the Korea National Health and Nutrition Examination Survey 2008–2011. *Invest Ophthalmol Vis Sci* 2013;54(10):6827-33.
   PUBMED | **CROSSREF**

8. Lee R, Wong TY, Sabanayagam C. Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. *Eye Vis (Lond)* 2015;2(1):17.
   PUBMED | **CROSSREF**

9. Ramsey S, Summers KH, Leong SA, Birnbaum HG, Kemner JE, Greenberg P. Productivity and medical costs of diabetes in a large employer population. *Diabetes Care* 2002;25(1):23-9.
   PUBMED | **CROSSREF**

10. Hex N, Bartlett C, Wright D, Taylor M, Varley D. Estimating the current and future costs of type 1 and type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs. *Diabet Med* 2012;29(7):855-62.
    PUBMED | **CROSSREF**

11. Kiss S, Chandwani HS, Cole AL, Patel VD, Lunacsek OE, Dugel PU. Comorbidity and health care visit burden in working-age commercially insured patients with diabetic macular edema. *Clin Ophthalmol* 2016;10:2443-53.
    PUBMED | **CROSSREF**

12. Shea AM, Curtis LH, Hammill BG, Kowalski JW, Ravelo A, Lee PP, et al. Resource use and costs associated with diabetic macular edema in elderly persons. *Arch Ophthalmol* 2008;126(12):1748-54.
    PUBMED | **CROSSREF**

13. Wallick CJ, Hansen RN, Campbell J, Kiss S, Kowalski JW, Sullivan SD. Comorbidity and health care resource use among commercially insured non-elderly patients with diabetic macular edema. *Ophthalmic Surg Lasers Imaging Retina* 2015;46(7):744-51.
    PUBMED | **CROSSREF**

14. Chen X, Modjtahedi BS, Young LH. Management of diabetic macular edema: is it time to say goodbye to macular laser? *Int Ophthalmol Clin* 2015;55(4):113-22.
    PUBMED | **CROSSREF**

15. Cheung N, Wong IY, Wong TY. Ocular anti-VEGF therapy for diabetic retinopathy: overview of clinical efficacy and evolving applications. *Diabetes Care* 2014;37(4):900-5.
    PUBMED | **CROSSREF**

16. Jiang S, Barner JC, Park C, Ling YL. Treatment patterns of anti-vascular endothelial growth factor and laser therapy among patients with diabetic macular edema. *J Manag Care Spec Pharm* 2015;21(9):735-41.
    PUBMED | **CROSSREF**

17. Jusufbegovic D, Mugavin MO, Schaal S. Evolution of controlling diabetic retinopathy: changing trends in the management of diabetic macular edema at a single institution over the past decade. *Retina* 2015;35(5):929-34.
    PUBMED | **CROSSREF**

18. Kiss S, Liu Y, Brown J, Holekamp NM, Almony A, Campbell J, et al. Clinical utilization of anti-vascular endothelial growth-factor agents and patient monitoring in retinal vein occlusion and diabetic macular edema. *Clin Ophthalmol* 2014;8:1611-21.
    PUBMED | **CROSSREF**

19. Elman MJ, Qin H, Aiello LP, Beck RW, Bressler NM, Ferris FL 3rd, et al. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: three-year randomized trial results. *Ophthalmology* 2012;119(11):2312-8.
    PUBMED | **CROSSREF**

20. Wells JA, Glassman AR, Ayala AR, Jampol LM, Aiello LP, Antoszyk AN, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med* 2015;372(13):1193-203.
PUBMED | **CROSSREF**

21. Elman MJ, Ayala A, Bressler NM, Browning D, Flaxel CJ, Glassman AR, et al. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: 5-year randomized trial results. *Ophthalmology* 2015;122(2):375-81.
PUBMED | **CROSSREF**

22. Nguyen QD, Brown DM, Marcus DM, Boyer DS, Patel S, Feiner L, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology* 2012;119(4):789-801.
PUBMED | **CROSSREF**

23. Do DV, Nguyen QD, Boyer D, Schmidt-Erfurth U, Brown DM, Vitti R, et al. One-year outcomes of the da Vinci Study of VEGF Trap-Eye in eyes with diabetic macular edema. *Ophthalmology* 2012;119(8):1658-65.
PUBMED | **CROSSREF**

24. Korobelnik JF, Do DV, Schmidt-Erfurth U, Boyer DS, Holz FG, Heier JS, et al. Intravitreal aflibercept for diabetic macular edema. *Ophthalmology* 2014;121(11):2247-54.
PUBMED | **CROSSREF**

25. Gillies MC, Lim LL, Campain A, Quin GJ, Salem W, Li J, et al. A randomized clinical trial of intravitreal bevacizumab versus intravitreal dexamethasone for diabetic macular edema: the BEVORDEX study. *Ophthalmology* 2014;121(12):2473-81.
PUBMED | **CROSSREF**

26. Boyer DS, Yoon YH, Belfort R Jr, Bandello F, Maturi RK, Augustin AJ, et al. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology* 2014;121(10):1904-14.
PUBMED | **CROSSREF**

27. Nozaki M, Suzuma K, Inoue M, Kawasaki R, Kida T, Takamura Y, et al. Preference and trends of treatment for diabetic retinopathy in Korea and Japan. *Nippon Ganka Gakkai Zasshi* 2013;117(9):735-42.
PUBMED

28. Gregori NZ, Feuer W, Rosenfeld PJ. Novel method for analyzing Snellen visual acuity measurements. *Retina* 2010;30(7):1046-50.
PUBMED | **CROSSREF**

29. Bressler SB, Edwards AR, Andreoli CM, Edwards PA, Glassman AR, Jaffe GJ, et al. Reproducibility of Optovue RTVue optical coherence tomography retinal thickness measurements and conversion to equivalent Zeiss Stratus metrics in diabetic macular edema. *Transl Vis Sci Technol* 2015;4(1):5.
PUBMED | **CROSSREF**

30. Bressler SB, Edwards AR, Chalam KV, Bressler NM, Glassman AR, Jaffe GJ, et al. Reproducibility of spectral-domain optical coherence tomography retinal thickness measurements and conversion to equivalent time-domain metrics in diabetic macular edema. *JAMA Ophthalmol* 2014;132(9):1113-22.
PUBMED | **CROSSREF**

31. Campbell J, Cole AL, Almony A, Ingraham H, Holekamp NM, Marks S, et al. Real world vision outcomes in DME treated with anti-VEGF injections - An analysis of EMR data from a large health system. *Invest Ophthalmol Vis Sci* 2014;55(13):3065.

32. Patrao NV, Antao S, Egan C, Omar A, Hamilton R, Hykin PG, et al. Real-world outcomes of ranibizumab treatment for diabetic macular edema in a United Kingdom National Health Service setting. *Am J Ophthalmol* 2016;172:51-7.
PUBMED | **CROSSREF**

33. Dugel PU, Layton A, Varma RB. Diabetic macular edema diagnosis and treatment in the real world: an analysis of Medicare claims data (2008 to 2010). *Ophthalmic Surg Lasers Imaging Retina* 2016;47(3):258-67.
PUBMED | **CROSSREF**

34. Massin P, Bandello F, Garweg JG, Hansen LL, Harding SP, Larsen M, et al. Safety and efficacy of ranibizumab in diabetic macular edema (RESOLVE Study): a 12-month, randomized, controlled, double-masked, multicenter phase II study. *Diabetes Care* 2010;33(11):2399-405.
PUBMED | **CROSSREF**

35. Mitchell P, Bandello F, Schmidt-Erfurth U, Lang GE, Massin P, Schlingemann RO, et al. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmology* 2011;118(4):615-25.
PUBMED | **CROSSREF**

36. Elman MJ, Aiello LP, Beck RW, Bressler NM, Bressler SB, Edwards AR, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology* 2010;117(6):1064-1077.e35.
PUBMED | **CROSSREF**

37. Elman MJ, Bressler NM, Qin H, Beck RW, Ferris FL 3rd, Friedman SM, et al. Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology* 2011;118(4):609-14.
   PUBMED | CROSSREF

38. Sharareh B, Gallemore R, Taban M, Onishi S, Wallsh J. Recalcitrant macular edema after intravitreal bevacizumab is responsive to an intravitreal dexamethasone implant in retinal vein occlusion. *Retina* 2013;33(6):1227-31.
   PUBMED | CROSSREF

39. Busch C, Zur D, Fraser-Bell S, Laíns I, Santos AR, Lupidi M, et al. Shall we stay, or shall we switch? Continued anti-VEGF therapy versus early switch to dexamethasone implant in refractory diabetic macular edema. *Acta Diabetol* 2018;55(8):789-96.
   PUBMED | CROSSREF

40. Unsal E, Eltutar K, Sultan P, Erkul SO, Osmanbasoglu OA. Efficacy and safety of intravitreal dexamethasone implants for treatment of refractory diabetic macular edema. *Korean J Ophthalmol* 2017;31(2):115-22.
   PUBMED | CROSSREF

41. Lee SJ, Kim ET, Moon YS. Intravitreal bevacizumab alone versus combined with macular photocoagulation in diabetic macular edema. *Korean J Ophthalmol* 2011;25(5):299-304.
   PUBMED | CROSSREF

42. Kim K, Kim ES, Kwak HW, Yu SY. Long-term outcomes of diabetic macular edema following initial intravitreal ranibizumab injection based on morphologic pattern. *J Korean Ophthalmol Soc* 2016;57(10):1604-12.
   CROSSREF

43. Moon BG, Lee JY, Yu HG, Song JH, Park YH, Kim HW, et al. Efficacy and safety of a dexamethasone implant in patients with diabetic macular edema at tertiary centers in Korea. *J Ophthalmol* 2016;2016:9810270.
   PUBMED | CROSSREF