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REVIEW

Outcomes of Over 40,000 Eyes Treated for Diabetic Macula Edema in Routine Clinical Practice: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction: We investigated effectiveness and safety outcomes of diabetic macula edema (DME) treatment in routine clinical practice.
Methods: A literature search was conducted of peer-reviewed articles published from January 2011 to September 2021. Studies of DME treatment in real-world practice of at least 6 months with at least 50 eyes at baseline were included. Randomized controlled trials (RCTs) were excluded. The primary outcome for this meta-analysis was change in visual acuity (VA) 12 months after starting treatment.
Results: Of 3034 initially identified studies, 138 met selection criteria, representing more than 40,000 eyes. The mean 12-month VA gain was 4.6 letters (95% CI 3.7, 5.4; baseline 58.6) for vascular endothelial growth factor inhibitors (anti-VEGF), 4.4 (2.5, 6.3; baseline 54.2) for steroids, and 2.1 (− 1.2, 5.3; baseline 63.6) for macular laser. Australian and New Zealand studies had better baseline VA when initiating treatment compared with Asia, Europe, and North America, translating to better VA at 12 months. Fewer anti-VEGF injections were delivered in real-world practice than registrational RCTs. Neither systemic nor ocular safety was consistently reported.

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Conclusions: Intravitreal anti-VEGF or steroids for DME generally led to visual gains in real-world practice but these were less impressive than RCTs, with undertreatment and differences in baseline characteristics likely contributing factors.

Keywords: Diabetic macula edema; Meta-analysis; Observational; Outcomes; Real-world data; Systematic review; Treatment

Key Summary Points

Why carry out this study?

We wished to understand if impressive randomized controlled trial (RCT) results of intravitreal therapy for diabetic macula edema (DME) are replicated in routine clinical practice around the world.

We carried out a systematic review and meta-analysis on data published in the last decade on eyes treated for DME in routine clinical practice globally.

What was learned from the study?

A meta-analysis of over 40,000 eyes treated for DME in routine clinical practice globally identified that intravitreal vascular endothelial growth factor inhibitor or steroid therapy generally led to improved vision at 12 months, but not to the same extent as in RCTs, with undertreatment and differences in baseline characteristics likely contributing factors.

There were significant regional variations in baseline and 12-month visual outcomes with Australia and New Zealand having amongst the best reported outcomes.

The quality of included real-world studies was variable, with considerable heterogeneity and limited safety, quality-of-life, and long-term outcomes data.

INTRODUCTION

Diabetic macula edema (DME) remains a leading cause of visual loss globally [1]. Laser treatment of "clinically significant macula edema" reduced the risk of moderate visual loss by 50% at 3 years but only 17% of eyes gained vision and there was a long-term risk of central vision loss due to enlargement of laser scars [2, 3]. Intravitreal steroids are attractive since they may address the many cytokine networks that are activated in DME [4], but their use is limited by local side effects of raised intraocular pressure and cataract progression [5]. Intravitreal inhibitors of vascular endothelial growth factor (anti-VEGF) have become first-line treatment for center-involving DME [6].

Cochrane reviews of randomized controlled trials (RCTs) have identified strong evidence of benefit of anti-VEGF drugs over macular laser for center-involving DME [7, 8] but called for further research on anti-VEGF drugs to determine "effectiveness under real-world monitoring and treatment conditions and (systemic) safety in high-risk populations" [7]. We investigated whether the efficacy and safety outcomes of macular laser, intravitreal anti-VEGF, and intravitreal steroids reported in RCTs were replicated in routine clinical practice.

METHODS

The MOOSE guidelines for the reporting of meta-analysis of observational studies were followed [9]. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Eligibility Criteria

Only studies reporting effectiveness outcomes for at least one treatment group of interest (laser photocoagulation, intravitreal steroids, or intravitreal anti-VEGF) were included. To improve the reliability of treatment outcome estimates we only included studies with at least 50 eyes with DME at baseline that had at least

6 months (± 2 weeks) of follow-up—these restrictions were not included for safety outcomes.

The primary outcome for this meta-analysis was change in visual acuity (VA) 12 months after starting treatment. Secondary outcomes included the change in VA at 6 and 24 months, change in central subfield thickness (CST) at 6, 12, and 24 months, and number of treatments over 6, 12, and 24 months. Qualitative outcomes included patient-reported outcome measures (PROMs), resource utilization, as well as ocular and systemic adverse events.

Search Methods

A literature search was conducted in the Embase® and MEDLINE® databases on the ProQuest DIALOG search service to include English language peer-reviewed journal articles from 1 January 2011 to 24 September 2021. The search strategy, full search terms and qualification of searchers appear in Electronic Supplementary Material Table S1.

Study Selection

Data was selected and coded according to sound clinical principles using an a priori study protocol (Electronic Supplementary Material Appendix A, PROSPERO registration number 312954).

Data Collection and Risk of Bias Assessment

The list of data collected from each study is included in Electronic Supplementary Material Table S2.

Risk of bias and study quality was assessed using the quality appraisal checklist for case series developed by the Institute of Health Economics (IHE) which is the preferred tool of the National Institute for Health and Care Excellence (NICE) [10]. Criteria for aspects of the checklist were customized for ophthalmology studies similar to the adaptation utilized in Ang et al. [11]. The appraisal checklist is summarized in Electronic Supplementary Material Table S3.

Data Synthesis and Statistical Analysis

Pooled means for primary and secondary outcomes were calculated across all studies weighted according to their total sample size (number of eyes). Additionally, weighted estimates were calculated from random-effects models to account for heterogeneity between studies. The inverse-variance method was used to weight studies in the random-effects estimates. Heterogeneity between studies was measured using the I^2 statistic [12]. VA scores were converted to logMAR letters for consistency [13–16].

Mixed-effects meta-regression models were used to estimate baseline characteristics by continent and treatment group. Additional mixed-effects models were used to compare outcomes by treatment groups with adjustments for mean age, VA, and CST at baseline for estimates of changes in VA and CST. Further details on the estimation of mean, standard deviation, and confidence intervals are available in Electronic Supplementary Material Appendix A.

Analyses were conducted using R (version 4.1.0). The mice package (version 3.13.0) was used for multiple imputations and the metafor package (version 3.0-2) was used to conduct meta-analyses and random-effects models [17–19].

Assumptions

We included the UK and Turkey in the European region. It is likely there was duplication of patient data between the 2018 (n = 15,608 eyes) and 2021 (n = 28,658) Ciulla et al. publications [20, 21]. We took a conservative approach and reduced the quoted total number of eyes analyzed by 15,608.

RESULTS

Included and Excluded Studies

The literature search identified 3034 articles from 1 January 2011 through 24 September 2021. There were 138 studies that met inclusion criteria (the list of included studies and data extracted is available in Electronic Supplementary Material Appendix B. Reasons for exclusion of articles are available in Electronic Supplementary Material Table S4. A summary of the study selection process is presented in Electronic Supplementary Material Fig. S1 [22]. Intravitreal anti-VEGF therapies were the most widely investigated, representing 65% of treatment groups.

Risk of Bias and Quality of Studies

The quality of studies as assessed using the IHE critical appraisal checklist varied considerably, ranging from 7.0 (lower quality) to 18 (higher quality), with a median score of 13.5 out of 20 (Electronic Supplementary Material Appendix B).

Baseline Characteristics

The mean (95% CI letters) random-effects estimate for baseline VA was 57.9 (56.3, 59.5) and the mean baseline CST (95% CI μm) was 444 (434, 454). The mixed-effects estimate for the mean (95% CI letters) baseline VA for studies in Australia and New Zealand of 66.7 (57.2, 76.3) was better than North America, Asia, Europe, and across multiple continents at 59.7 (53.8, 65.7), 57.5 (54.4, 60.6), 57.6 (55.4, 59.9), and 56.8 (52.1, 61.4), respectively (Table 1). The mixed-effects estimate for mean (95% CI μm) baseline CST of 383 (346, 421) for North America and 410 (346, 474) for Australia and New Zealand was thinner than Asia, Europe, and across multiple continents at 443 (425, 461), 451 (438, 464), and 455 (429, 480), respectively.

In general, patients receiving any combination of steroids only were older than those receiving anti-VEGF only (mixed-effects estimate 66.2 vs. 63.2 years respectively). The mixed-effects mean (95% CI letters) baseline VA for eyes receiving any steroid only combination was worse, 54.2 (51.8, 56.5), than anti-VEGF only eyes 58.6 (56.9, 60.2) and macular laser eyes 63.6 (58.7, 68.4). The mixed-effects mean (95% CI μm) baseline CST was also thicker in eyes receiving any steroid only combination, 469 (453, 485), compared with those receiving anti-VEGF only, 429 (418, 439).

Heterogeneity

The amount of heterogeneity (I^2) for change in VA and CST at 12 months was 93.9% and 92.3%, respectively, indicating substantial heterogeneity. The heterogeneity for numbers of injections was even higher (99.8%).

Visual Acuity Outcomes

The random-effects estimate for the overall mean (95% CI letters) improvement in VA was 5.2 (3.3, 7.1), 4.8 (4.0, 5.6), and 4.6 (3.1, 6.2) at 6 months (23,255 eyes, 22 studies, 38 treatment groups), 12 months (55,988 eyes, 60 studies, 89 treatment groups), and 24 months (19,686 eyes, and 28 studies, 41 treatment groups), respectively. The VA at 12 months was highly correlated with baseline vision (weighted Pearson's correlation coefficient $\rho = 0.95$; Fig. 1).

The mixed-effects mean (95% CI letters) VA improvement was similar between eyes receiving any anti-VEGF only combination and any steroid only combination at 6 months (5.0 [2.8. 7.3] vs. 5.1 [2.2, 8.1], respectively), at 12 months (4.6 [3.7, 5.4], 4.4 [2.5, 6.3], respectively), and at 24 months (4.4 [2.8, 5.9], 5.8 [2.8, 8.8], respectively). The mixed-effects 12-month VA change for each study is summarized in the forest plot (Fig. 2).

Anatomical Outcomes

The mixed-effects mean (95% CI μm) CST change between eyes receiving any anti-VEGF only combination vs. any steroid only combination was − 103 (− 128, − 77) vs. − 113 (− 148, − 79) at 6 months, − 107 (− 118, − 97)

Table 1 Baseline characteristics of eyes included in the meta-analysis

Variable	Number of eyes (studies, treatment groups)	Weighted mean	Random or mixed-effects estimate (95% CI)
Female, %			
Overall	27,339 (109, 135)	42.5	41.4 (39.1, 43.7)
Asia	6263 (34, 45)	41.4	44.0 (39.7, 48.3)
Europe	15,508 (48, 56)	42.2	37.9 (34.6, 41.1)
North America	1049 (9, 11)	46.4	46.0 (37.7, 54.3)
Oceania	723 (3, 3)	50.3	48.5 (36.7, 60.3)
Multi-continent	3796 (15, 20)	42.9	44.1 (38.0, 50.3)
Baseline age			
Overall	86,177 (128, 175)	63.0	64.1 (63.4, 64.9)
Asia	8066 (35, 47)	62.2	61.6 (60.3, 62.9)
Europe	16,997 (60, 79)	65.2	65.9 (64.9, 66.8)
North America	55,530 (13, 21)	62.5	64.9 (62.4, 67.3)
Oceania	978 (3, 3)	58.2	60.4 (56.5, 64.3)
Multi-continent	4606 (17, 25)	63.3	63.2 (61.3, 65.1)
Baseline VA			
Overall	90,049 (131, 189)	58.4	57.9 (56.3, 59.5)
Asia	7416 (36, 47)	58.5	57.5 (54.4, 60.6)
Europe	20,475 (63, 87)	58.0	57.6 (55.4, 59.9)
North America	56,145 (13, 25)	58.2	59.7 (53.8, 65.7)
Oceania	1095 (3, 4)	67.7	66.7 (57.2, 76.3)
Multi-continent	4918 (16, 26)	59.6	56.8 (52.1, 61.4)
Baseline CST			
Overall	23,058 (118, 166)	442	444 (434, 454)
Asia	7109 (34, 45)	447	443 (425, 461)
Europe	9564 (55, 78)	452	451 (438, 464)
North America	1157 (10, 13)	368	383 (346, 421)
Oceania	494 (2, 2)	408	410 (346, 474)
Multi-continent	4734 (17, 28)	438	455 (429, 480)

Weighted means, and mean estimates as estimated by random-effects models (for overall) or mixed-effects models (by continent) for baseline characteristics of studies included in the meta-analysis. Patient eyes that received no treatment were excluded. Patient-level data were reported at the eye level

vs. − 114 (− 138, − 90) μm at 12 months, and − 113 (− 137, − 89) vs. − 104 (− 158, − 50) at 24 months, respectively.

Treatment-Naïve at Baseline

At baseline, there were 63 treatment-naïve groups, 14 pre-treated groups, 31 treatment groups containing a mix, with the remaining treatment groups not clearly providing details.

The random-effects estimate of mean (95% CI letters) VA change at 12 months for any combination of anti-VEGF was 2.3 (− 0.8, 5.4) for pre-treated eyes vs. 5.5 (3.4, 7.5) for treatment-naïve eyes.

Injection Numbers

Eyes treated with any combination of only steroids received a mean (95% CI) of 3.6 (3.1, 4.2) injections at 12 months. In contrast, eyes treated with any combination of only anti-VEGF received a mean (95% CI) of 5.3 (4.9, 5.8) injections at 12 months (Table 2). A similar number of injections of aflibercept, bevacizumab, or ranibizumab monotherapy were given (5.5 [5.1, 5.9], 5.4 [5.0, 5.9], and 5.8 [5.4, 6.3], respectively), which correlated weakly with 12-month VA change across studies (weighted Pearson's correlation coefficient ρ = 0.07; Fig. 3).

The regimen employed when specified varied, but most of the anti-VEGF treatment groups reported some variation of 1–5 monthly injections in a loading phase followed by pro re nata (PRN). We found limited data for treat-and-extend regimens. Dexamethasone or fluocinolone acetonide monotherapy was mostly given PRN.

Fig. 2 Forest plot of mean 12-month change in visual acuity estimated from mixed-effects models. All included studies had at least 50 eyes at baseline and the number of eyes at 12 months is reported. Many studies assessed more than one intervention in different populations and therefore contributed more than one treatment group. Where applicable, the author's name with year of publication is followed by a number indicating multiple treatment groups ▶

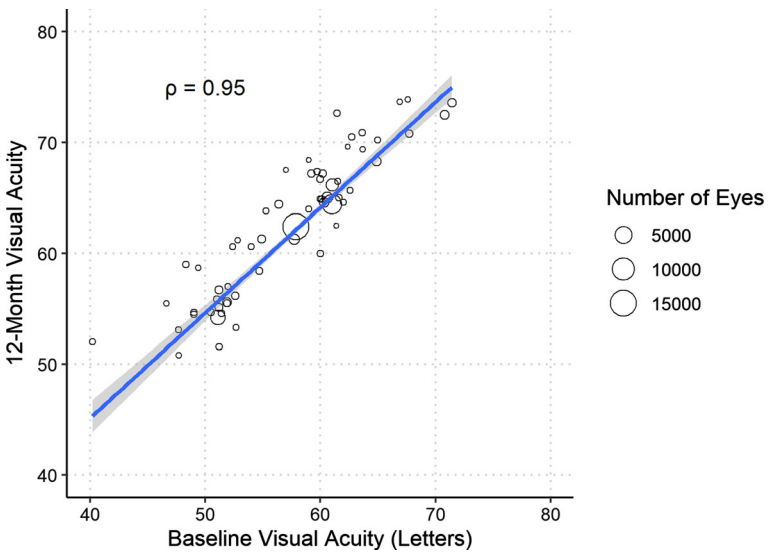
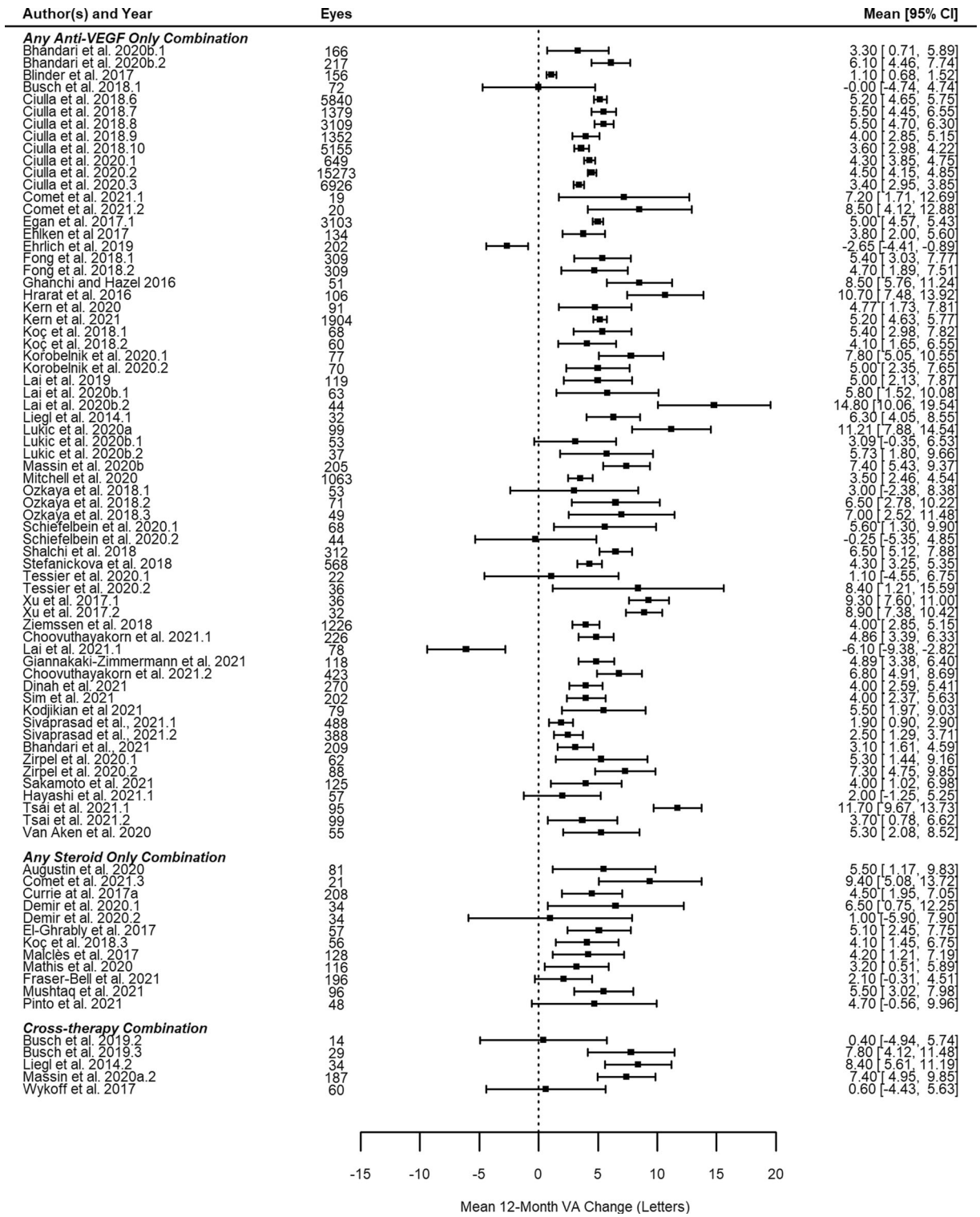


Fig. 1 Scatterplot of baseline visual acuity (VA) vs. 12-month visual acuity. Each circle represents a single treatment group with the size of the circle proportional to its sample size. The blue line represents the weighted regression line with the 95% confidence interval shown in gray shading. The weighted Pearson's correlation coefficient, ρ, is reported in the top left


Author(s) and Year
Eyes
Mean [95% CI]
Any Anti-VEGF Only Combination
Bhandari et al. 2020b.1 166 3.30 [0.71, 5.89]
Bhandari et al. 2020b.2 217 6.10 [4.46, 7.74]
Blinder et al. 2017 156 1.10 [0.68, 1.52]
Busch et al. 2018.1 72 -0.00 [-4.74, 4.74]
Ciulla et al. 2018.6 5840 5.20 [4.65, 5.75]
Ciulla et al. 2018.7 1379 5.50 [4.45, 6.55]
Ciulla et al. 2018.8 3109 5.50 [4.70, 6.30]
Ciulla et al. 2018.9 1352 4.00 [2.85, 5.15]
Ciulla et al. 2018.10 5155 3.60 [2.98, 4.22]
Ciulla et al. 2020.1 649 4.30 [3.85, 4.75]
Ciulla et al. 2020.2 15273 4.50 [4.15, 4.85]
Ciulla et al. 2020.3 6926 3.40 [2.95, 3.85]
Comet et al. 2021.1 19 7.20 [1.71, 12.69]
Comet et al. 2021.2 20 8.50 [4.12, 12.88]
Egan et al. 2017.1 3103 5.00 [4.57, 5.43]
Ehlken et al 2017 134 3.80 [2.00, 5.60]
Ehrlich et al. 2019 202 -2.65 [-4.41, -0.89]
Fong et al. 2018.1 309 5.40 [3.03, 7.77]
Fong et al. 2018.2 309 4.70 [1.89, 7.51]
Ghanchi and Hazel 2016 51 8.50 [5.76, 11.24]
Hrarat et al. 2016 106 10.70 [7.48, 13.92]
Kern et al. 2020 91 4.77 [1.73, 7.81]
Kern et al. 2021 1904 5.20 [4.63, 5.77]
Koç et al. 2018.1 68 5.40 [2.98, 7.82]
Koç et al. 2018.2 60 4.10 [1.65, 6.55]
Korobelnik et al. 2020.1 77 7.80 [5.05, 10.55]
Korobelnik et al. 2020.2 70 5.00 [2.35, 7.65]
Lai et al. 2019 119 5.00 [2.13, 7.87]
Lai et al. 2020b.1 63 5.80 [1.52, 10.08]
Lai et al. 2020b.2 44 14.80 [10.06, 19.54]
Liegl et al. 2014.1 32 6.30 [4.05, 8.55]
Lukic et al. 2020a 99 11.21 [7.88, 14.54]
Lukic et al. 2020b.1 53 3.09 [-0.35, 6.53]
Lukic et al. 2020b.2 37 5.73 [1.80, 9.66]
Massin et al. 2020b 205 7.40 [5.43, 9.37]
Mitchell et al. 2020 1063 3.50 [2.46, 4.54]
Ozkaya et al. 2018.1 53 3.00 [-2.38, 8.38]
Ozkaya et al. 2018.2 71 6.50 [2.78, 10.22]
Ozkaya et al. 2018.3 49 7.00 [2.52, 11.48]
Schiefelbein et al. 2020.1 68 5.60 [1.30, 9.90]
Schiefelbein et al. 2020.2 44 -0.25 [-5.35, 4.85]
Shalchi et al. 2018 312 6.50 [5.12, 7.88]
Stefanickova et al. 2018 568 4.30 [3.25, 5.35]
Tessier et al. 2020.1 22 1.10 [-4.55, 6.75]
Tessier et al. 2020.2 36 8.40 [1.21, 15.59]
Xu et al. 2017.1 36 9.30 [7.60, 11.00]
Xu et al. 2017.2 32 8.90 [7.38, 10.42]
Ziemssen et al. 2018 1226 4.00 [2.85, 5.15]
Choovuthayakorn et al. 2021.1 226 4.86 [3.39, 6.33]
Lai et al. 2021.1 78 -6.10 [-9.38, -2.82]
Giannakaki-Zimmermann et al. 2021 118 4.89 [3.38, 6.40]
Choovuthayakorn et al. 2021.2 423 6.80 [4.91, 8.69]
Dinah et al. 2021 270 4.00 [2.59, 5.41]
Sim et al. 2021 202 4.00 [2.37, 5.63]
Kodjikian et al 2021 79 5.50 [1.97, 9.03]
Sivaprasad et al., 2021.1 488 1.90 [0.90, 2.90]
Sivaprasad et al., 2021.2 388 2.50 [1.29, 3.71]
Bhandari et al., 2021 209 3.10 [1.61, 4.59]
Zirpel et al. 2020.1 62 5.30 [1.44, 9.16]
Zirpel et al. 2020.2 88 7.30 [4.75, 9.85]
Sakamoto et al. 2021 125 4.00 [1.02, 6.98]
Hayashi et al. 2021.1 57 2.00 [-1.25, 5.25]
Tsai et al. 2021.1 95 11.70 [9.67, 13.73]
Tsai et al. 2021.2 99 3.70 [0.78, 6.62]
Van Aken et al. 2020 55 5.30 [2.08, 8.52]
Any Steroid Only Combination
Augustin et al. 2020 81 5.50 [1.17, 9.83]
Comet et al. 2021.3 21 9.40 [5.08, 13.72]
Currie at al. 2017a 208 4.50 [1.95, 7.05]
Demir et al. 2020.1 34 6.50 [0.75, 12.25]
Demir et al. 2020.2 34 1.00 [-5.90, 7.90]
El-Ghrably et al. 2017 57 5.10 [2.45, 7.75]
Koç et al. 2018.3 56 4.10 [1.45, 6.75]
Malclès et al. 2017 128 4.20 [1.21, 7.19]
Mathis et al. 2020 116 3.20 [0.51, 5.89]
Fraser-Bell et al. 2021 196 2.10 [-0.31, 4.51]
Mushtaq et al. 2021 96 5.50 [3.02, 7.98]
Pinto et al. 2021 48 4.70 [-0.56, 9.96]
Cross-therapy Combination
Busch et al. 2019.2 14 0.40 [-4.94, 5.74]
Busch et al. 2019.3 29 7.80 [4.12, 11.48]
Liegl et al. 2014.2 34 8.40 [5.61, 11.19]
Massin et al. 2020a.2 187 7.40 [4.95, 9.85]
Wykoff et al. 2017 60 0.60 [-4.43, 5.63]
-15 -10 -5 0 5 10 15 20
Mean 12-Month VA Change (Letters)

Other Outcomes

Data on outcomes beyond treatment frequency or VA were lacking. One study reported PROMs and seven studies reported qualitative summaries of cost-effectiveness. Less than 20% of studies reported mean number of visits. Further information can be found in Electronic Supplementary Material Appendix B.

Safety Outcomes

The safety outcomes of each study are available in Electronic Supplementary Material Appendix C. Twenty-seven studies had data on endophthalmitis, of which 24 reported zero cases and the remaining three reported one case each.

Safety outcomes on intraocular pressure (IOP) were more consistently documented, with 44 studies reporting IOP increases requiring therapy, more commonly in eyes treated with intravitreal steroid than other treatment groups. Cataract progression was reported in 25 studies, with 458 individual cases reported out of 2117 eyes, again more commonly in eyes treated with intravitreal steroid.

The systemic AE most commonly reported upon was death. It was not possible to reliably establish rates of myocardial infarction or stroke, particularly in high-risk populations. None of the studies reported on treatment use during pregnancy.

DISCUSSION

This is the largest meta-analysis of real-world outcomes of treatment for DME yet reported, with over 40,000 eyes with 12-month outcomes. Our results provide important insights into DME treatment effectiveness in routine clinical practice with a sample size that would not be possible for an RCT. The phase 3 RISE and RIDE registrational RCTs of ranibizumab for DME enrolled just 759 participants [23].

Anti-VEGF treatment for DME generally improved vision in real-world practice by an average of 5 letters (one line) over 12 months (baseline 59 letters), less than ranibizumab (10 letters, baseline 57 letters) or aflibercept (11 letters, baseline 59 letters) in their registrational RCTs [23, 24]. In the Diabetic Retinopathy Clinical Research network (DRCRnet) Protocol T RCT, the average VA gain at 12 months was 18 letters for aflibercept (baseline 56 letters), 14 letters for ranibizumab (baseline 57 letters), and 12 letters for bevacizumab (baseline 57 letters) [25]. Treatment-naïve eyes gained more vision than previously treated eyes in real-world practice.

Fewer anti-VEGF injections were delivered in the real-world than in registrational RCTs. We found only a weak correlation between intravitreal anti-VEGF injection numbers and 12-month VA gain across studies. This is in contrast to a meta-analysis of real-world outcomes of ranibizumab for neovascular age-related macular degeneration (AMD) [26]. Perhaps undertreatment was so profound in real-world practice (mean 5.3 anti-VEGF injections over 12 months) that a dose–response curve could not be established. The DRCRnet Protocol T RCT had an average of 8 anti-VEGF injections over 12 months. The largest real-world study we included reported VA gains at 1 year generally showed a linear relationship with the mean number of anti-VEGF injections, between 3 and 10 injections [21]. There is an unmet need for longer-acting therapies that may translate RCT results into routine clinical practice more effectively.

The baseline VA when intravitreal anti-VEGF for DME was started was better in Australia and New Zealand than North America, Europe, Asia, and multi-continent studies. The strong correlation between baseline and 12-month VA outcomes identified suggests benefit of earlier treatment.

The anatomical data reported were limited to CST and sometimes qualitative descriptions such as presence of subretinal fluid. Baseline CST was thinner in North America and Australia, where there were also better 12-month VA outcomes than in Europe, Asia, and multi-continent studies. The UK, where intravitreal anti-VEGF therapy is not reimbursed until CST is greater than 400 μm, was the largest contributor of data to the European region. The impact

Table 2 Visual acuity, central subfield thickness, and injection number outcomes at 12 months

Variable	Number of eyes (studies, treatment groups)	Weighted mean	Random or mixed-effects estimate (95% CI)	I^2 (%)
Female, %				
Overall	27,339 (109, 135)	42.5	41.4 (39.1, 43.7)	93.1
Aflibercept	4921 (13, 18)	36.8	38.3 (32.9, 43.6)	
Bevacizumab	1274 (6, 6)	47.1	45.5 (36.7, 54.4)	
Ranibizumab	9131 (38, 41)	46.6	42.2 (38.6, 45.8)	
Dexamethasone	1535 (14, 15)	39.0	37.1 (31.0, 43.2)	
Fluocinolone acetonide	2147 (11, 11)	43.7	44.1 (37.3, 50.8)	
Macular laser	393 (2, 2)	58.6	46.7 (34.3, 59.0)	
Subthreshold laser	138 (2, 2)	38.3	39.7 (22.8, 56.7)	
Any anti-VEGF only combination	18,948 (70, 85)	43.0	41.6 (39.1, 44.1)	
Any steroid only combination	3682 (25, 26)	41.8	40.2 (35.9, 44.5)	
Any cross-therapy combination	3019 (10, 10)	37.6	41.8 (37.1, 46.5)	
Baseline age				
Overall	85,627 (128, 175)	63.0	64.1 (63.4, 64.9)	97.8
Aflibercept	3136 (16, 19)	63.2	63.2 (62.2, 64.1)	
Bevacizumab	17,137 (10, 10)	61.0	61.3 (60.5, 62.2)	
Ranibizumab	17,368 (39, 42)	64.4	63.7 (62.8, 64.5)	
Dexamethasone	2460 (22, 28)	66.1	65.8 (64.5, 67.0)	
Fluocinolone acetonide	2427 (12, 12)	67.9	68.1 (66.3, 69.8)	
Macular laser	670 (3, 3)	54.7	62.4 (60.1, 64.6)	
Subthreshold laser	190 (2, 2)	65.3	64.5 (60.1, 68.9)	
Any anti-VEGF only combination	74,328 (81, 107)	62.8	63.2 (62.5, 63.9)	
Any steroid only combination	4971 (35, 41)	66.9	66.2 (65.2, 67.2)	
Any cross-therapy combination	3879 (11, 12)	63.1	62.0 (60.9, 63.1)	
Baseline VA				
Overall	89,499 (131, 189)	58.5	57.9 (56.3, 59.5)	99.1
Aflibercept	6133 (18, 24)	63.4	58.2 (56.2, 60.3)	
Bevacizumab	17,752 (10, 14)	57.4	56.0 (54.0, 57.9)	
Ranibizumab	17,774 (42, 45)	58.5	59.1 (57.1, 61.0)	
Dexamethasone	2780 (21, 29)	54.3	54.8 (51.5, 58.0)	
Fluocinolone acetonide	2427 (12, 12)	52.1	52.9 (48.3, 57.4)	

Table 2 continued

Variable	Number of eyes (studies, treatment groups)	Weighted mean	Random or mixed-effects estimate (95% CI)	I^2 (%)
Macular laser	670 (3, 3)	70.8	63.6 (58.7, 68.4)	
Subthreshold laser	190 (2, 2)	72.6	69.7 (58.6, 80.7)	
Any anti-VEGF only combination	78,372 (85, 118)	58.5	58.6 (56.9, 60.2)	
Any steroid only combination	5291 (34, 42)	53.1	54.2 (51.8, 56.5)	
Any cross-therapy combination	4036 (13, 14)	62.2	57.9 (56.0, 59.8)	
ΔVA 1 year				
Overall	55,988 (60, 89)	4.4	4.8 (4.0, 5.6)	93.9
Aflibercept	4249 (14, 17)	4.6	5.6 (4.5, 6.7)	
Bevacizumab	19,918 (7, 8)	4.7	5.2 (3.9, 6.5)	
Ranibizumab	16,328 (25, 28)	4.1	4.6 (3.6, 5.5)	
Dexamethasone	577 (6, 7)	3.5	4.1 (1.3, 6.8)	
Fluocinolone acetonide	442 (4, 4)	5.0	4.8 (1.5, 8.2)	
Macular laser	186 (2, 2)	− 2.6	2.1 (− 1.2, 5.3)	
Subthreshold laser	–	–	–	
Any anti-VEGF only combination	54,111 (44, 65)	4.5	4.6 (3.7, 5.4)	
Any steroid only combination	1075 (11, 12)	4.1	4.4 (2.5, 6.3)	
Any cross-therapy combination	324 (4, 5)	6.0	5.9 (3.4, 8.5)	
Baseline CST				
Overall	22,508 (118, 166)	441	444 (434, 454)	96.6
Aflibercept	2607 (17, 21)	435	441 (427, 455)	
Bevacizumab	968 (5, 5)	464	464 (436, 491)	
Ranibizumab	6443 (39, 42)	433	436 (424, 448)	
Dexamethasone	2908 (22, 31)	474	471 (453, 489)	
Fluocinolone acetonide	1578 (10, 10)	460	460 (433, 487)	
Macular laser	86 (1, 1)	431	–	
Subthreshold laser	190 (2, 2)	367	402 (343, 460)	
Any anti-VEGF only combination	12,803 (75, 98)	434	429 (418, 439)	

Table 2 continued

Variable	Number of eyes (studies, treatment groups)	Weighted mean	Random or mixed-effects estimate (95% CI)	I^2 (%)
Any steroid only combination	4570 (33, 42)	470	469 (453, 485)	
Any cross-therapy combination	3919 (12, 13)	444	441 (428, 455)	
ΔCST 1 year				
Overall	6262 (36, 52)	− 109	− 110 (− 122, − 97)	92.3
Aflibercept	2197 (11, 14)	− 117	− 127 (− 138, − 115)	
Bevacizumab	692 (3, 3)	− 97	− 66 (− 87, − 44)	
Ranibizumab	1724 (14, 14)	− 112	− 109 (− 120, − 99)	
Dexamethasone	250 (2, 2)	− 93	− 105 (− 133, − 77)	
Fluocinolone acetonide	442 (4, 4)	− 131	− 107 (− 132, − 81)	
Macular laser	86 (1, 1)	− 84	–	
Subthreshold laser	–	–	–	
Any anti-VEGF only combination	5079 (27, 37)	− 111	− 107 (− 118, − 97)	
Any steroid only combination	748 (7, 7)	− 120	− 114 (− 138, − 90)	
Any cross-therapy combination	57 (2, 2)	− 109	− 112 (− 159, − 66)	
Injections over 1 year				
Overall	51,977 (60, 88)	6.2	5.2 (4.6, 5.7)	99.8
Aflibercept	4986 (15, 17)	6.6	5.4 (4.9, 5.9)	
Bevacizumab	20,072 (8, 9)	6.4	5.6 (5.1, 6.1)	
Ranibizumab	17,125 (31, 34)	5.6	5.8 (5.4, 6.3)	
Dexamethasone	321 (5, 6)	1.9	1.4 (0.7, 2.2)	
Fluocinolone acetonide	–	–	–	
Any anti-VEGF only combination	51,128 (54, 74)	6.3	5.3 (4.9, 5.8)	
Any steroid only combination	377 (6, 7)	1.9	3.6 (3.1, 4.2)	

Table 2 continued

Variable	Number of eyes (studies, treatment groups)	Weighted mean	Random or mixed-effects estimate (95% CI)	I^2 (%)
Any cross-therapy combination	281 (3, 3)	4.5	4.4 (3.5, 5.4)	

Weighted outcome means, outcome measures as estimated by random-effects models (for overall outcomes) or mixed-effects models (for treatment-group outcomes), and heterogeneity (I^2) across studies. Dashes indicate no studies (or only 1 for mixed-effects estimates) were available for that treatment group. Moderators for mixed-effects estimates analyzing outcomes by treatment group included age, VA, and CST measured at baseline. Patient-level data were reported at the eye level. Monotherapy groups for conbercept and triamcinolone were excluded from the meta-analysis of monotherapy treatments as only one study was available for each; however, they were included in their respective combination groups, e.g., triamcinolone was included in the analysis of any steroid-only combination. The 6-month and 2-year outcomes are included in Electronic Supplementary Material Table S5

of local reimbursement policies can be better understood by comparing international outcomes.

Visual and anatomical improvements were reported for steroid therapy and combined anti-VEGF/steroid therapy, but studies were of lower quality with limited numbers for the latter. Patients starting intravitreal steroid therapy were generally older, had worse baseline VA and greater CST than those treated with anti-VEGF or macular laser. More intravitreal steroid injections (mean 3.6 over 12 months) were given in real-world practice than in RCTs. The fixed treatment intervals chosen for registrational RCTs of intravitreal steroids for DME were evidently longer than the maximal therapeutic effect [27]. A Cochrane review of RCTs of intravitreal anti-VEGF combined with

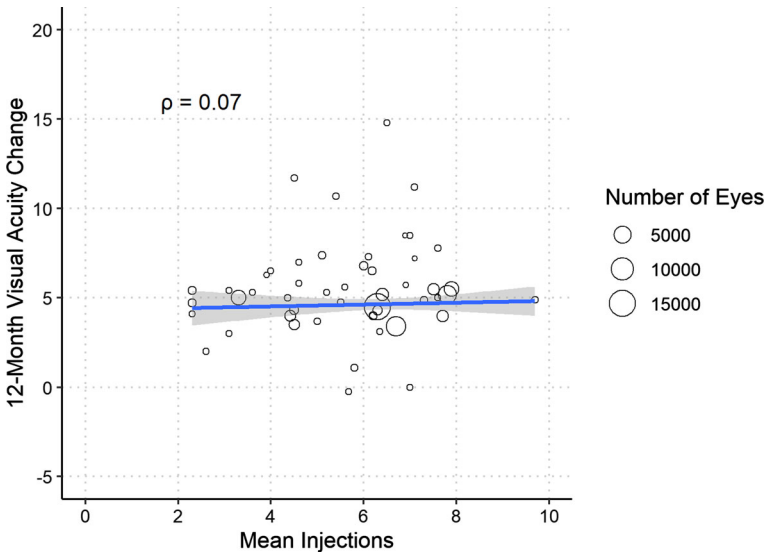


Fig. 3 Scatterplot of mean injections of anti-VEGF over 12 months vs. 12-month change in visual acuity. Only treatment groups utilizing any combination of anti-VEGF only were included. Each circle represents a single treatment group with the size of the circle proportional to its sample size. The blue line represents the weighted regression line with the 95% confidence interval shown in gray shading. The weighted Pearson's correlation coefficient, ρ, is reported in the top left

intravitreal steroid therapy for DME did not identify benefit over monotherapy [28]. Treatment burden includes not only treatments but also visits to manage complications such as raised IOP.

There was likely significant underreporting of the most significant ocular AE associated with intravitreal therapy with only three cases of endophthalmitis reported. A French nationwide study found a crude incidence of endophthalmitis of 0.0245% per intravitreal injection [29]. Moreover, just over a quarter of real-world studies reported any systemic safety data. Greater attention to safety outcomes in real-world studies could improve our understanding of systemic safety beyond RCTs, where patients with recent stroke or myocardial infarction were excluded from anti-VEGF registrational RCTs [30].

There is an urgent need for a minimum, patient-centered treatment outcome set for diabetic retinopathy to facilitate global data collection from real-world practice and make it easier to compare effectiveness, treatment burden, and safety outcomes. The International Consortium for Health Outcomes Measurement (ICHOM) has established such a data set for AMD [31].

Limitations of this analysis include the variable quality of the real-world studies available as measured by IHE criteria. We improved the quality of studies included with a minimum requirement of 50 eyes at baseline and 6 months of follow-up. The use of data from routine clinical practice and the high level of heterogeneity add to the uncertainty of conclusions drawn. Retrospective studies and studies where participants were not recruited consecutively can be prone to selection bias. Studies not reporting loss to follow-up can contribute to attrition bias. We wished to assess real-world outcomes out to 5 years but sparse data was available beyond 2 years. Refracted best-corrected VA is not measured in routine clinical practice and there is no masking. Some studies included patients with both eyes included which may cause bias due to nesting of outcomes. As the granular data on each patient were not available, we were not able to adjust for this.

CONCLUSION

Intravitreal anti-VEGF or steroids for center-involving DME generally led to visual gains in real-world practice but these were less impressive than in RCTs, with undertreatment and differences in baseline characteristics likely contributing factors. Macular laser alone did not generally lead to visual gains. Differences were noted in the baseline VA and CST and 12-month outcomes of eyes treated in different parts of the world.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies

and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. The data extracted for the systematic review has been made available in the Electronic Supplementary Material, along with the references of the 138 studies included in this review.

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REFERENCES

1. Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: the Right to Sight: an analysis for the Global Burden of Disease Study. Lancet Glob Health. 2021;9(2):e144–e60.

2. ETDRS. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. Arch Ophthalmol. 1985;103(12):1796–806.

3. Schatz H, Madeira D, McDonald HR, Johnson RN. Progressive enlargement of laser scars following grid laser photocoagulation for diffuse diabetic macular edema. Arch Ophthalmol. 1991;109(11):1549–51.

4. Funatsu H, Yamashita H, Sakata K, et al. Vitreous levels of vascular endothelial growth factor and intercellular adhesion molecule 1 are related to diabetic macular edema. Ophthalmology. 2005;112(5):806–16.

5. Rittiphairoj T, Mir TA, Li T, Virgili G. Intravitreal steroids for macular edema in diabetes. Cochrane Database Syst Rev. 2020;11:CD005656.

6. Biechl AC, Bhandari S, Nguyen V, et al. Changes in real-world treatment patterns for diabetic macular oedema from 2009 to 2019 and 5-year outcomes: data from the Fight Retinal Blindness! Registry Clin Exp Ophthalmol. 2020;48(6):802–12.

7. Virgili G, Parravano M, Menchini F, Evans JR. Anti-vascular endothelial growth factor for diabetic macular oedema. Cochrane Database Syst Rev. 2014;10:CD007419.

8. Virgili G, Parravano M, Evans JR, et al. Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis. Cochrane Database Syst Rev. 2018;10:CD007419.

9. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283(15):2008–12.

10. Moga C GB, Schopflocher D, Harstall C. Institute of Health Economics (IHE) Methodology papers: development of a quality appraisal tool for case series studies using a modified Delphi technique. https://www.ihe.ca/advanced-search/development-of-a-quality-appraisal-tool-for-case-series-studies-using-a-modified-delphi-technique. ISBN: 978-1-926929-04-0. Accessed 08 May 2022.

11. Ang JL, Ah-Moye S, Kim LN, et al. A systematic review of real-world evidence of the management of macular oedema secondary to branch retinal vein occlusion. Eye (Lond). 2020;34(10):1770–96.

12. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539–58.

13. Bailey IL, Lovie JE. New design principles for visual acuity letter charts. Am J Optom Physiol Opt. 1976;53(11):740–5.

14. Ferris FL 3rd, Kassoff A, Bresnick GH, Bailey I. New visual acuity charts for clinical research. Am J Ophthalmol. 1982;94(1):91–6.

15. Mehta H, Tufail A, Daien V, et al. Real-world outcomes in patients with neovascular age-related macular degeneration treated with intravitreal

vascular endothelial growth factor inhibitors. Prog Retin Eye Res. 2018;65:127–46.

16. Beck RW, Moke PS, Turpin AH, et al. A computerized method of visual acuity testing: adaptation of the early treatment of diabetic retinopathy study testing protocol. Am J Ophthalmol. 2003;135(2):194–205.

17. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw. 2010;36(3):1–48.

18. Van Buuren SKG-O. mice: multivariate imputation by chained equations in R. J Stat Softw. 2011;45(3):1–67.

19. Team RC. R: A language and environmental for statistical computing. Vienna: Austria, R Foundation for Statistical Computing; 2021.

20. Ciulla TA, Bracha P, Pollack J, Williams DF. Real-world outcomes of anti-vascular endothelial growth factor therapy in diabetic macular edema in the United States. Ophthalmol Retina. 2018;2(12):1179–87.

21. Ciulla TA, Pollack JS, Williams DF. Visual acuity outcomes and anti-VEGF therapy intensity in diabetic macular oedema: a real-world analysis of 28 658 patient eyes. Br J Ophthalmol. 2021;105(2):216–21.

22. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.

23. Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology. 2012;119(4):789–801.

24. Korobelnik JF, Do DV, Schmidt-Erfurth U, et al. Intravitreal aflibercept for diabetic macular edema. Ophthalmology. 2014;121(11):2247–54.

25. Diabetic Retinopathy Clinical Research Network, Wells JA, Glassman AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med. 2015;372(13):1193–203.

26. Kim LN, Mehta H, Barthelmes D, et al. Metaanalysis of real-world outcomes of intravitreal ranibizumab for the treatment of neovascular age-related macular degeneration. Retina. 2016;36(8):1418–31.

27. Mehta H, Fraser-Bell S, Nguyen V, et al. The interval between treatments of bevacizumab and dexamethasone implants for diabetic macular edema increased over time in the BEVORDEX trial. Ophthalmol Retina. 2018;2(3):231–4.

28. Mehta H, Hennings C, Gillies MC, et al. Anti-vascular endothelial growth factor combined with intravitreal steroids for diabetic macular oedema. Cochrane Database Syst Rev. 2018;4:CD011599.

29. Baudin F, Benzenine E, Mariet AS, et al. Association of acute endophthalmitis with intravitreal injections of corticosteroids or anti-vascular growth factor agents in a nationwide study in France. JAMA Ophthalmol. 2018;136(12):1352–8.

30. Avery RL, Gordon GM. Systemic safety of prolonged monthly anti-vascular endothelial growth factor therapy for diabetic macular edema: a systematic review and meta-analysis. JAMA Ophthalmol. 2016;134(1):21–9.

31. Rodrigues IA, Sprinkhuizen SM, Barthelmes D, et al. Defining a minimum set of standardized patient-centered outcome measures for macular degeneration. Am J Ophthalmol. 2016;168:1–12.