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# Efficacy and safety of dexamethasone versus intravitreal aflibercept implants for macular edema: a systematic review and meta-analysis

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## Abstract

**Background** Macular edema (ME) is a prevalent complication of diabetic retinopathy (DR) and retinal vein occlusion (RVO) that contributes significantly to vision impairment worldwide. This condition is primarily driven by elevated vascular endothelial growth factor (VEGF) and pro-inflammatory cytokines, resulting in the use of anti-VEGF agents such as aflibercept and corticosteroids such as dexamethasone implants. However, evidence comparing the clinical efficacy and safety of these two modalities remains limited.

**Objectives** This systematic review and meta-analysis aimed to compare the safety and efficacy of intravitreal aflibercept injections and dexamethasone implants in ME associated with DR and RVO.

**Method** The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and registered with PROSPERO (CRD42024577212). A comprehensive search of the PubMed, Cochrane, Web of Science, and Scopus databases was performed until August 30, 2024. Nine studies, involving 572 eyes, were included in the analysis. Key outcomes assessed included Best-Corrected Visual Acuity (BCVA), Central Retinal Thickness (CRT), and Intraocular Pressure (IOP). A random-effects model was applied to the pooled effect size calculations, and heterogeneity was addressed using sensitivity analyses.

**Results** Both treatments showed comparable efficacy in improving BCVA and reducing CRT across follow-up intervals. At 3 months, dexamethasone implants demonstrated statistically significant superiority in BCVA improvement (MD = 1.18, 95% CI [0.89, 1.47], P < 0.001) and CRT reduction (MD = −62.45 µm, 95% CI [−85.67, −39.22], *P* < 0.001) compared to aflibercept. Similarly, at 12 months, dexamethasone implants maintained greater efficacy in CRT reduction (MD = −58.73 µm, 95% CI [−78.12, −39.34], *P* < 0.001). However, dexamethasone implants were associated with an increased IOP at 3 and 6 months (MD = 1.04 mmHg, 95% CI [0.56, 1.52], *P* < 0.001). No significant differences in IOP were observed between treatments at 12 months.

**Conclusion** Intravitreal aflibercept injections and dexamethasone implants are effective modalities for the management of ME, with each presenting distinct advantages. Dexamethasone implants minimize the frequency of treatment, while achieving superior outcomes in terms of BCVA and CRT. However, they are also associated

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with a heightened risk of IOP elevation and cataract formation. Conversely, aflibercept requires more frequent administration, which may result in logistical and financial challenges for patients and health care providers. Therefore, personalized treatment strategies should consider disease severity, comorbidities, and individual preferences. Future research should prioritize patient-centered outcomes, emphasizing quality of life and treatment costs while also investigating condition-specific responses to these therapeutic interventions.

**Keywords** Macular edema, Diabetic macular edema (DME), Diabetic retinopathy (DR), Retinal vein occlusion (RVO), Intravitreal aflibercept, Dexamethasone implants, Visual acuity, Central retinal thickness, Intraocular pressure, Corticosteroids, Anti-VEGF therapy

## Introduction

Retinal vascular diseases pose a significant risk to global vision health, with diabetic retinopathy (DR) and retinal vein occlusion (RVO) being the most prevalent conditions [1]. Macular edema (ME), a secondary complication of DR and RVO, is a common clinical manifestation characterized by the accumulation of fluid and proteins in the extracellular space of the retina [2]. Current estimates indicate that the global prevalence of DR, RVO, branch RVO, and central RVO is approximately 103 million, 16.4 million, 13.9 million, and 2.5 million, respectively [3, 4]. Diabetic retinopathy has emerged as a leading cause of blindness, affecting 100 million individuals worldwide, with projections suggesting that this number may exceed 130 million in the forthcoming six years [5]. Data indicate that ME affects approximately 7 million adults with DR and 3 million individuals with RVO [6]. The pathogenesis of ME is predominantly linked to increased secretion of vascular endothelial growth factor (VEGF) and production of pro-inflammatory cytokines [7, 8]. Consequently, anti-VEGF agents such as aflibercept, along with anti-inflammatory corticosteroid formulations such as dexamethasone intravitreal implants, are regarded as the preferred treatment regimens for ME [9, 10].

Dexamethasone implant (DEX implant; Ozurdex), which was approved by the Food and Drug Administration (FDA) in 2009, utilizes biodegradable polymers for the sustained release of dexamethasone over several months. The mechanism of action of aflibercept involves the inhibition of VEGF-A and placental growth factor, whereas dexamethasone inhibits a broad spectrum of growth factors and multiple inflammatory cytokines. In addition, dexamethasone may cause or worsen cataracts in phakic eyes and induce ocular hypertension with repeated treatment [11, 12].

Although aflibercept is typically a first-line treatment for ME, its specific half-life in comparison to dexamethasone necessitates more frequent administration than dexamethasone implants, which provides a more sustainable alternative by providing prolonged therapeutic effects and reduced treatment burden [2, 5]. These differences underscore the need for comparative evaluation to optimize clinical decision-making in ME management.

Aflibercept and dexamethasone implants have distinct advantages and limitations. Frequent administration of aflibercept can pose a logistical and financial burden for patients, while extended-release of dexamethasone reduces the treatment frequency but carries risks of ocular hypertension and cataract development [13]. Given the need for personalized treatment strategies, comprehensive evaluation of these modalities is necessary. Systematic reviews and meta-analyses comparing the safety and efficacy of aflibercept and dexamethasone implants remain limited. Therefore, this systematic review and meta-analysis was conducted to provide evidence-based insights for clinicians.

Moreover, advancements in imaging techniques, particularly optical coherence tomography (OCT), have significantly enhanced the ability to localize and delineate retinal pathology. OCT is an essential diagnostic tool that aids retinal specialists in accurately diagnosing and monitoring ME and other retinal conditions associated with diabetic complications. The utility of OCT has been highlighted in several studies, which will be briefly discussed in the Discussion section to contextualize its importance in clinical practice [14–25].

## Methodology

This study was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [26]. The results were reported as specified by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [27]. Additionally, this study was registered with PROSPERO under identification number CRD42024577212.

### Information sources and search strategy

The literature search was performed using four electronic databases: Cochrane, PubMed, Web of Science, and Scopus. The search targeted literature from its inception to August 30, 2024. The strategy employed utilized keywords such as “aflibercept,” “dexamethasone,” “retinal

vein occlusion," and "diabetic macular edema," along with their pertinent synonyms. Two researchers performed the searches concurrently and independently.

## Eligibility criteria

### *Inclusion criteria*

The eligibility criteria for this systematic review and meta-analysis were based on the PICO framework, and included studies evaluating human patients diagnosed with macular edema associated with diabetic retinopathy (DR) or retinal vein occlusion (RVO). Studies were eligible if they evaluated the efficacy and safety of intravitreal dexamethasone implants (DEX) compared with intravitreal aflibercept (IVA) [28]. The primary outcomes included safety (e.g., adverse events such as intraocular pressure elevation and cataract progression) and efficacy measured using best-corrected visual acuity (BCVA) and central macular thickness (CMT). Randomized controlled trials (RCTs) and observational studies (e.g., retrospective and prospective cohort studies and non-randomized comparative studies) published in peer-reviewed journals were included, provided that they had a minimum follow-up duration of six months. Only studies published between January 2013 and December 2024 in English were considered.

### *Exclusion criteria*

Studies were excluded if they were case reports, reviews, letters to the editor, conference abstracts, or non-peer-reviewed. Additionally, studies that lacked sufficient data on outcomes or failed to provide details regarding the intervention and comparator were excluded. Non-English language studies were excluded to ensure consistency in data interpretation and analysis.

### *Screening and data management*

The screening process was conducted in two distinct phases. The first phase involved the initial screening of titles and abstracts to identify potentially relevant studies. In the second phase, full-text articles from the selected studies were thoroughly reviewed to confirm their eligibility. Rayyan software was used to facilitate the screening. Two independent reviewers conducted the eligibility assessment and any disagreements were resolved by consulting a third reviewer [29].

### *Additional considerations*

The dosage of IVA administered across the included studies was consistently 2 mg per injection, following the recommended dosing guidelines for intravitreal aflibercept (EYLEA®) injections (Regeneron Pharmaceuticals, Inc., Updated 2023). The studies employed different drug administration regimens based on their protocols, as detailed in Table 1. For BCVA assessment, the studies utilized either Snellen charts (converted to logarithm of the minimum angle of resolution [logMAR]) or Early Treatment Diabetic Retinopathy Study (ETDRS) letter scores, ensuring uniformity in reporting visual acuity outcomes. These methodological considerations enhanced the reliability of the findings and allowed for consistent comparisons across studies.

### *Masking and inter-rater reliability*

Two independent reviewers screened, extracted, and assessed the included studies. Discrepancies were resolved by consensus or by consulting a third reviewer. Although formal masking was not explicitly conducted during the selection process, strict adherence to the PRISMA criteria minimized the bias. Inter-rater reliability was assessed using the intra-class correlation coefficient (ICC), which demonstrated excellent agreement (ICC = 0.89, 95% CI [0.84, 0.92]).

### *Randomization and data digitization*

Data extraction and randomization were digitized using standardized forms in Microsoft Excel. This ensured consistency and traceability during the data analysis. A random-effects model was applied for effect size calculations to account for study heterogeneity.

## Data extraction

The process of searching for full-text articles and subsequent extraction of data were conducted independently by the two authors. Any discrepancies that arose were subjected to further evaluation by an additional author of the manuscript. The information extracted from the published studies encompassed but was not limited to the following elements: the name of the first author, year of publication, geographical location, and design of the study; the characteristics of the participants, including diagnosis, sample size, demographic features, and clinical characteristics, as well as the inclusion and exclusion criteria; detailed descriptions of the interventions, specifying the type and frequency of treatment, dosage of medication, and duration of follow-up; and the outcomes measured, which included BCVA, CST, IOP, and any adverse events reported, as indicated in Tables 1 and 2.

## Risk of bias assessment

Two independent reviewers assessed the risk of bias in the studies included in the analysis. For randomized controlled trials (RCTs), the Cochrane Risk of Bias 2 (ROB2) tool [30] was utilized to assess domains, including the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. Each domain

**Table 1** Summary of the included studies

| Study | Country, year | Design | Drug administered | Methods used for BCVA assessment | Lens status of patients (phakic or pseudophakic) | NOS |
|---|---|---|---|---|---|---|
| Aksoy 2020 [45] | Turkey, 2013–2017 | Retrospective cohort study | IVA: 3 doses post-6 IVR; IVD: single dose post-6 IVR in separate groups | Snellen chart | Not provided | Good |
| Bolukbasi 2019 [46] | Turkey, 2017–2018 | Retrospective cohort study | IA: 3 monthly doses 2 mg; DEX: single implant 0.7 mg | Snellen chart that was converted into a logarithm of the minimum | Out of 25 patients in the IDI group, 10(40%) were phakic and out of 32 patients in the IVA group 23 ( 71.9%) were phakic | Good |
| Comet 2021 [13] | Switzerland, 2016–2017 | Non-RCT | AFL: 3 monthly loading doses, PRN; DXI: 1.4 injections in first 6 months | Early treatment Diabetic Retinopathy Study (ETDRS) charts | Out of 21 eyes of the IDI group, 57% were phakic and out of 20 eyes of the IVA group 59% were phakic | - |
| Hanhart 2017 [40] | Israel, 2013–2016 | Observational retrospective cohort study | IA: 2 mg, DEX: sustained-release 0.7 mg implant, mean injections: DEX = 3.30, IA = 6.50 | Snellen chart | Out of 10 eyes of the IDI group, 8(80%) were phakic and out of 12 eyes of the IVA group, 4( 33.3%) were phakic | Good |
| Kaldirim 2018 [41] | Turkey, 2013–2016 | Observational retrospective cohort study | IA: 3 monthly doses then PRN; DEX: single 0.7 mg dose | Snellen chart that was converted into a logarithm of the minimum angle of resolution (logMAR) | Not provided | Good |
| Ozsaygili 2020 [42] | Turkey, 2017–2018 | RCT | IA: 3 monthly doses then PRN; DEX: single dose 0.7 mg, PRN | ETDRS letters scores | Out of 48 eyes of the IDI group, 29(60.4%) were phakic and out of 50 eyes of the IVA group, 27( 54%) were phakic | - |
| Yucel 2019 [43] | Turkey, 2019 | Observational retrospective cohort study | Aflibercept (IA) 2 mg; Dexamethasone (IDI) 0.7 mg; mean injections: IA = 2.68, IDI = 1.62 over 6 months | Snellen chart that was converted into a logarithm of the minimum | Out of 24 patients in the IDI group, 3(12.5%) were pseudophakic and out of 16 patients in the IVA group 4 ( 25%) were pseudophakic | Good |
| Chakraborty 2024 [44] | India, 2019–2021 | Retrospective comparative case series | IVA: PRN post-ranibizumab loading; DEX preferred pre-Dec 2020, IA post-Dec 2020 | Snellen chart | All of the 84 eyes of 84 patients were pseudophakic | Bad |
| Parca 2024 [39] | Turkey, 2024 | Observational retrospective cohort study | IA: 3 monthly loading doses, PRN; mean injections over 12 months: IA = 4.81, IDI = 1.96 | Snellen chart that was converted into a logarithm of the minimum | Out of 33 patients in the IDI group, 5(15.2%) were pseudophakic and out of 86 patients in the IVA group 17 ( 19.8%) were pseudophakic | Good |

**Table 2** Summary of the included studies' focus and outcomes

| Study | Study focus | Other remarks | Key findings & insights | Outcomes (Abbrev.) | Adverse events |
|---|---|---|---|---|---|
| Aksoy 2020 [45] | Comparison of intravitreal dexamethasone (IVD) and intravitreal aflibercept (IVA) in DME unresponsive to ranibizumab (IVR) | Effective for DME, with changes in retinal thickness observed | Both treatments (IVD and IVA) lead to a reduction in SFCT and CRT in persistent DME. Significant thinning of SFCT was observed in both treatment groups. There was no significant difference at the 3-month mark between treatments. Both treatments effectively managed DME with reduced macular edema and morphological changes | SFCT, CRT, BCVA (functional), multiple time points | Not provided |
| Bolukbasi 2019 [46] | Focus on DME with serous retinal detachment (SRD); no direct data on DR or RVO | Does not provide findings specific to DR or RVO | The study does not specifically address DR or RVO. It compares the efficacy of IVD and aflibercept for treating DME with SRD, looking at visual acuity (BCVA), central macular thickness (CMT), and changes in SRD height | BCVA, CMT, SRD | Not provided |
| Comet 2021 [13] | Overview of DR and RVO | It focuses on the general management of DME but does not directly evaluate the treatment options for DR and RVO | Diabetic Retinopathy (DR): Stages include NPDR and PDR; treatments include anti-VEGF and laser therapy. Retinal Vein Occlusion (RVO): Types are CRVO and BRVO; treatments include anti-VEGF, corticosteroids, and laser therapy. Both DR and RVO lead to DME. This article provides background on the conditions but does not specifically address IVD or aflibercept for DR or RVO | BCVA (M12), CRT, IVI, IOP (M6, M12) | No severe adverse events were reported; no specific numerical data was provided for each event |
| Hanhart 2017 [40] | Focus on RVO-related macular edema | Focuses on RVO-related macular edema and secondary agents post-bevacizumab failure | RVO-related macular edema is the focus, highlighting challenges in managing these cases. The study compares switching treatments for recalcitrant RVO to ranibizumab, aflibercept, and dexamethasone implants. Dexamethasone required fewer injections over 1-year follow-up, and all agents led to substantial improvements in central macular thickness and visual acuity | VA, CMT, IOP, local/systemic complications | No vitrectomy or vitreous hemorrhage; cataract surgeries: 25% in IA, 50% in DEX group; 1 stroke (IA), 1 myocardial infarction (DEX) |

**Table 2** (continued)

| Study | Study focus | Other remarks | Key findings & insights | Outcomes (Abbrev.) | Adverse events |
|---|---|---|---|---|---|
| Kaldirim 2018 [41] | Comparison of ranibizumab, dexamethasone implant, and aflibercept for BRVO-related macular edema | Focused on BRVO and not DR or general RVO | Dexamethasone implant showed better visual acuity and SRD height at 3 months. Anti-VEGF drugs (ranibizumab, aflibercept) were more effective at reducing CMT and maintaining visual acuity by the 6-month mark. Dexamethasone had higher intraocular pressure | VA, CMT, SRD height, IOP | No serious adverse events were reported; transient sensation loss in the ranibizumab group; topical anti-glaucomatous agents were needed in the DEX group |
| Ozsaygili 2020 [42] | Diabetic Retinopathy and RVO pathophysiology and treatment options | Provides general background but does not directly compare IVD vs. aflibercept for DR and RVO | Describes the pathophysiology of DR and RVO and their impact on vision. The study emphasizes treatments for diabetic macular edema (DME), focusing on anti-VEGF agents (aflibercept, ranibizumab) and corticosteroids (dexamethasone). Discusses the role of VEGF in DME and edema associated with both DR and RVO | BCVA, CRT, % vision gain, edema resolution, injections, cataract, IOP | Not provided |
| Yucel 2019 [43] | Diabetic Retinopathy and RVO pathophysiology and treatment outcomes | Provides a broader understanding of DR and RVO treatment, but not a direct comparison of IVD vs. aflibercept | Discusses the pathophysiology of DR and RVO, including risk factors like hypertension and diabetes. Emphasizes treatment options, particularly anti-VEGF (aflibercept, ranibizumab) and corticosteroids (dexamethasone). Reports improvements in visual acuity and CMT for both conditions with anti-VEGF and steroid treatments | BCVA, CMT, IOP, cataract incidence | Adverse events were more frequent in the DEX group than in the IA group, but no specific percentages were provided |
| Chakraborty 2024 [44] | Safety and efficacy comparison between aflibercept and dexamethasone for recalcitrant DME | Aflibercept may be preferable for visual improvement, while Dexamethasone may require fewer injections but has a higher IOP | Both IVA and DEX treatments showed comparable visual and CMT improvement, but IVA was associated with more frequent injections. DEX had higher intraocular pressure (IOP), requiring more IOP-lowering medications. Both treatments are effective in managing DME, but Aflibercept offers better visual improvement at the cost of more injections | BCVA, CMT, IOP, IOP-lowering meds, DRIL | 33.3% IOP spikes; no irreversible visual loss or glaucoma; DRIL reduced from 36 to 25% in the DEX group |

**Table 2** (continued)

| Study | Study focus | Other remarks | Key findings & insights | Outcomes (Abbrev.) | Adverse events |
|---|---|---|---|---|---|
| Parca 2024 [39] | Diabetic Retinopathy and RVO pathophysiology and treatment comparison | General review of treatments for DR and RVO but does not offer specific comparison for IVD vs. aflibercept | Highlights shared risk factors (diabetes, hypertension, hyperlipidemia) for both DR and RVO. Discusses anti-VEGF (aflibercept, ranibizumab) and corticosteroids (dexamethasone) for both DR and RVO. The study emphasizes the importance of timely interventions and treatments to prevent vision loss | BCVA, CRT, subgroup by vision (logMAR), complications | No serious ocular/systemic complications; no significant increases in cataracts or IOP observed |

was carefully evaluated and a risk decision (low, some concerns, or high) was made with detailed justifications provided (Fig. 2). For non-randomized studies of interventions, the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) assessment tool was applied [30]. This tool assesses various factors including randomization, allocation concealment, blinding, selective reporting, and additional sources of bias. Based on this comprehensive assessment, the included studies were categorized as having a 'low risk' of bias, 'high risk' of bias, or 'some concerns' (Fig. 2). Robvis [31] was used to generate ROBINS-I and ROB2 figures. For cohort studies, the Newcastle–Ottawa Scale (NOS) for observational and cross-sectional studies was utilized [32]. This tool permits investigators to apply a point-based system to classify studies as 'good,' 'fair,' or 'poor. Any disagreements were resolved through discussion and a third author was consulted when necessary.

### Publication bias

As indicated by Egger et al., the assessment of potential publication bias within this review utilizing Egger's test for funnel plot asymmetry is not feasible when the number of included studies is fewer than ten [33].

### Choice of the meta-analysis model

The DerSimonian and Laird method was employed to calculate the pooled effect size across all the reported outcomes. This random-effects model assigns greater weight to studies with smaller sample sizes, thereby addressing the variability in effect sizes by integrating a larger standard error into the pooled estimate. It is essential to carefully consider any possible inconsistencies in our estimates resulting from this approach[34].

### Calculation of missing data

In instances where data were reported as the median and interquartile ranges (IQR), conversions were performed to obtain the mean (M) and standard deviation (SD) using the equations established by Wan et al. [35]. Furthermore, when the standard deviation was not provided, it was derived from the standard error using the formula for a single sample: $SD = SE^{*}\sqrt{n}$, where (n) denotes the sample size [36].

If the mean change (MC) between the baseline and endpoint data was unavailable, it was calculated from the pre-treatment and post-treatment means using the equation MC = Mpost-treatment—Mpre-treatment. Additionally, in cases where the standard deviation of the mean change was not provided, it was computed from the standard deviations of the pre-treatment and post-treatment samples using the formula: $SD = \sqrt{(SD^2\text{pre-treatment} + SD^2\text{post-treatment})}$ [37]. Effect sizes (d) and effect size correlations (r) were calculated using the following formulas: $d = (Mtreatment—Mcontrol)/SDpooled$, with SDpooled calculated as $\sqrt{[(SD^2\text{treatment} + SD^2\text{control})/2]}$ [22] and $r = d / \sqrt{(d^2 + 4)}$ [38].

### Statistical analysis

Data analysis was performed using Review Manager 5.4 to conduct a statistical comparison of study outcomes. Quality control outcomes were evaluated in terms of best-corrected visual acuity and anatomical measurements, specifically central subfield thickness. Safety measures were defined as the occurrence of any systemic or ocular complication during the treatment period. The analysis employed a random-effects model[34]. Continuous outcomes were assessed using mean differences (MD) with 95% confidence intervals (CIs), whereas categorical outcomes were expressed in terms of risk differences (RD) with 95% CI. Forest plots were generated to illustrate the pooled data.

### Ethical approval

This article is based on previous studies and does not contain any new studies with human participants or animals performed by any of the authors.

### Heterogeneity

A visual inspection of the final forest plots and an assessment using I-square and Chi-Square tests (Cochran's Q test) were conducted to identify the degree of heterogeneity. In case of significant heterogeneity (Chi-Square $P < 0.1$), sensitivity analysis by leaving one out and then leaving two out was performed to resolve heterogeneity, in addition to using the random effects model using RevMan version 5.4.1 for Windows (Cochrane Collaboration, Oxford, UK). [39].

## Results

### Search and screening

Our search yielded 658 potentially relevant publications. After removing 534 duplicates, 124 publications remained for title and abstract screenings. Following this screening process, 20 papers were deemed eligible for a full-text review. Among these, nine studies [13, 40–47] involving 572 eyes were included in the final analysis. A total of 11 publications were excluded; specifically, the outcomes measured in five RCTs did not satisfy the inclusion criteria, five full texts were not accessible, and the remaining publications were found to duplicate the included populations. Additional details are presented in Fig. 1.

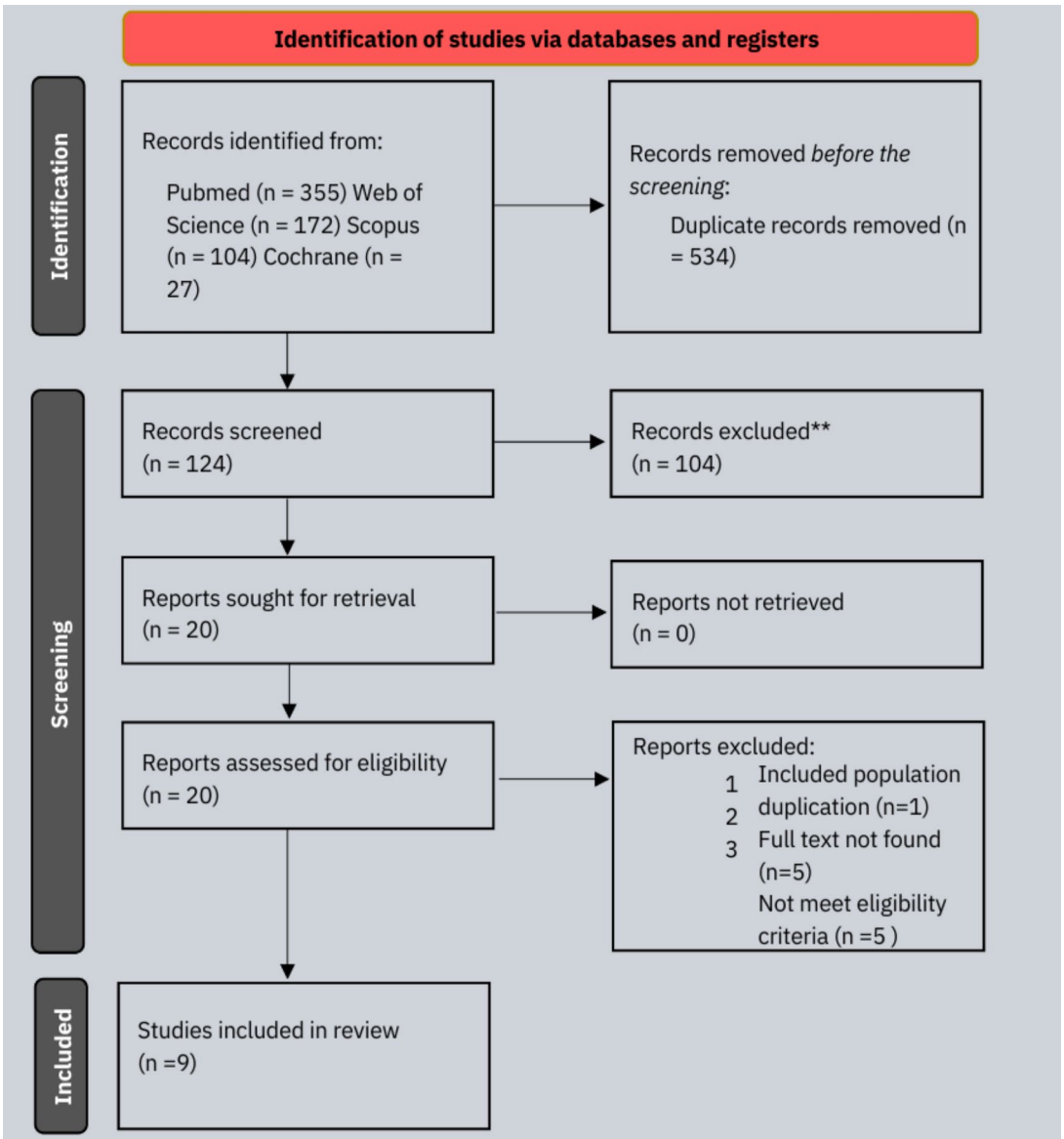


**Fig. 1** PRISMA flow diagram

### Studies characteristics

This review encompasses nine studies published between 2017 and 2024 that examine the comparative efficacy and safety of IVA and DEX in patients diagnosed with DR, DME, or RVO. Seven of the studies utilized a retrospective cohort design, one was an RCT, and one was a non-RCT. The sample sizes varied from 10 to 86 eyes per group, with follow-up durations ranging from 3 to 12 months. Patient demographics varied across the studies, with mean ages ranging from 53.3 to 70.6 years, incorporating both male and female participants (Table 1).

Dosing regimens for IVA generally comprise three monthly loading doses followed by as-needed (PRN) administration. In contrast, DEX was delivered as a single sustained-release implant at different retreatment intervals. The principal outcomes evaluated included BCVA, central retinal thickness (CRT), and IOP, along with additional parameters, such as the resolution of subretinal detachment (SRD), systemic and ocular complications, and occurrences of drug-related adverse events. Reporting of adverse events varied across studies, with some indicating heightened rates of IOP spikes, cataract formation, or systemic incidents, such as stroke or

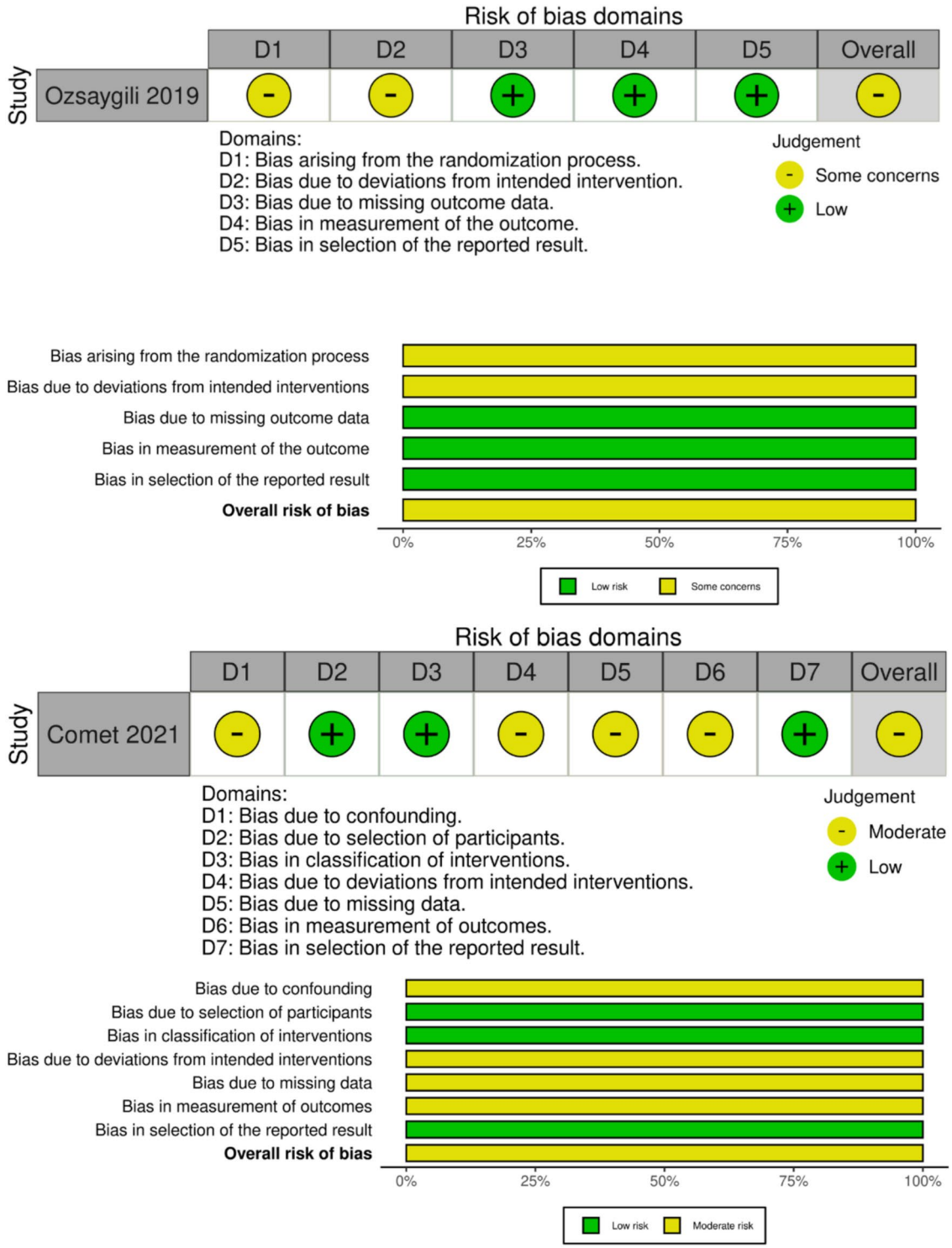


**Fig. 2** Presents a summary of the risk of bias as well as a graphical representation of the risk of bias, following the Cochrane risk of bias assessment tool

myocardial infarction. Nonetheless, it is noteworthy that most adverse events were transient or manageable through medical intervention, and there were no reports of irreversible visual loss.

### Risk of bias assessment

The included studies were assessed for bias using three tools. The RCT [43] was evaluated using the ROB2 tool, demonstrating some concerns, primarily due to unclear allocation concealment and lack of blinding (Fig. 2). The non-randomized study [13] was assessed using the ROBINS-I tool, with a moderate risk of bias due to potential confounding, deviation from intended intervention, and missing data, despite the low risk in other domains (Fig. 2). Six retrospective cohort studies and retrospective comparator case series were evaluated using the Newcastle–Ottawa Scale (NOS). Six cohort studies were rated as good quality [40–42, 44, 46, 47], meeting the criteria for selection, comparability, and outcome assessment. The retrospective comparator case series [45] was rated as poor-quality (Table 1). These assessments reflect a generally robust body of evidence with a clear acknowledgment of the study limitations.

### Lens status of patients

The lens status of the patients across the included studies varied, with both phakic and pseudophakic eyes represented in the intervention groups. In the study by Aksoy (2020), the lens status was not provided. Bolukbasi (2019) reported that 40% of patients in the IDI group and 71.9% of patients in the IVA group were phakic. Similarly, Comet (2021) found that 57% of eyes in the IDI group were phakic compared to 59% in the IVA group. Hanhart (2017) reported a higher percentage of phakic eyes in the IDI group (80%) and a lower percentage in the IVA group (33.3%). Ozsaygili (2020) found that 60.4% of the eyes in the IDI group were phakic, while 54% in the IVA group were phakic. In contrast, Yucel (2019) reported a higher proportion of pseudophakic patients (12.5% in the IDI group and 25% in the IVA group). Chakraborty (2024) included only pseudophakic eyes and all 84 eyes were pseudophakic. Parca (2024) reported that 15.2% of the patients in the IDI group and 19.8% in the IVA group were pseudophakic. While most studies predominantly involved phakic eyes, a few included a significant proportion of pseudophakic eyes, particularly in the Chakraborty (2024) study. It is important to consider that pseudophakic eyes, which have clear media, may yield better outcomes than phakic eyes, as the clarity of the lens reduces optical interference. This distinction should be considered when interpreting the results, as lens status may influence the observed efficacy of the treatments studied.

### Outcomes

#### *BCVA (logMAR)*

Seven studies involving 510 participants reported differences in logMAR BCVA between aflibercept and dexamethasone implants at baseline. The analysis indicated no statistically significant difference between aflibercept and dexamethasone at baseline (MD = 0.00, 95% CI [−0.07, 0.08], P = 0.90), as shown in Fig. 3A. Notably, significant heterogeneity was identified among the effect sizes of the included studies (P = 0.04, $I^2$ = 55%), as depicted in Fig. 3A. Sensitivity analysis was performed to address this heterogeneity, excluding one study at a time. Heterogeneity was most effectively resolved by excluding the study by Bolukbasi et al. (P = 0.23, $I^2$ = 27%). However, even after removing this study from the meta-analysis model, the overall mean difference remained statistically insignificant (MD = −0.02, 95% CI [−0.07, 0.04], P = 0.54), as illustrated in Fig. 3B.

All eight studies, encompassing 550 participants, evaluated the differences in BCVA (logMAR) changes between aflibercept and dexamethasone implants at the three-month mark. Six studies with a total of 422 participants investigated the differences in BCVA (logMAR) changes at six-month intervals. The results indicated no statistically significant differences between dexamethasone and aflibercept at both the three-month (MD = −0.00, 95% CI [−0.05, 0.05], P = 0.92) and six-month intervals (MD = 0.03, 95% CI [−0.05, 0.11], P = 0.49), as shown in Fig. 3C, D respectively. Furthermore, no heterogeneity was observed between the effect sizes at both time intervals (P = 0.28, $I^2$ = 19% for three months; P = 0.11, $I^2$ = 45% for six months), as presented in Fig. 3C, D.

Additionally, five studies examined the differences in BCVA (logMAR) changes between aflibercept and dexamethasone implants at the twelve-month interval. The analysis revealed no significant difference between the effect sizes of dexamethasone and aflibercept (MD = 0.09, 95% CI [−0.22, 0.41], P = 0.57). Substantial heterogeneity among the studies could not be resolved by leaving one out of the sensitivity analysis (P < 0.00001, $I^2$ = 91%), as indicated in Fig. 3E. However, heterogeneity was resolved by leaving two out sensitivity analyses excluding the Comet et al. study and Ozsaygali et al. study (P = 0.28, $I^2$ = 21%), although the results remained non-significant (MD = −0.04, 95% CI [−0.11, 0.03], P = 0.24) Fig. 3F.

#### *Central retinal thickness (CRT) (mmHg)*

Changes in CRT measured in mmHg between aflibercept and dexamethasone treatments at baseline were evaluated across five studies, encompassing a total of 355 participants. The analysis revealed no statistically significant difference between the two treatment groups (MD −1.84, 95% CI [−18.96, 15.28], P = 0.83), as illustrated in

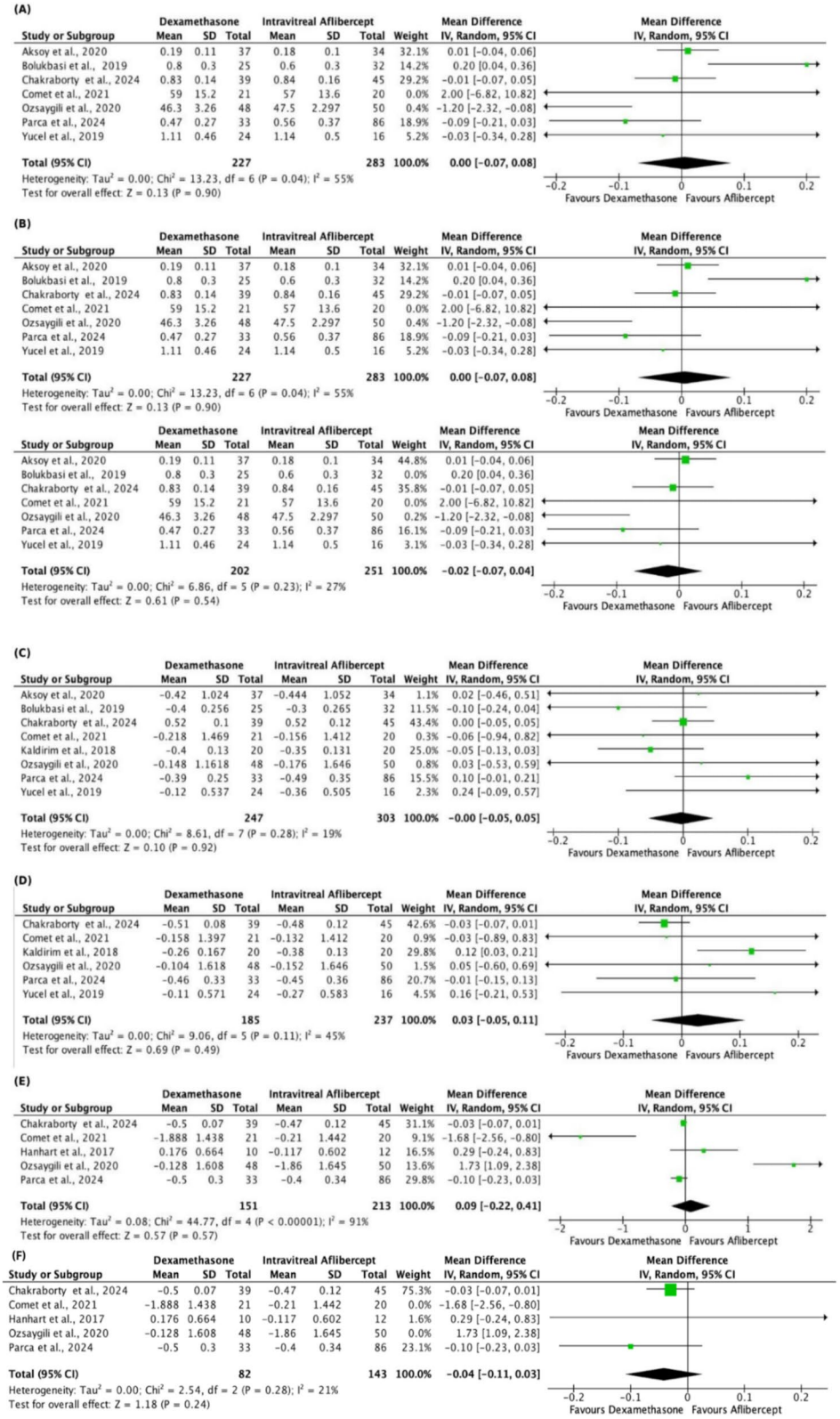


**Fig. 3** Differences in BCVA (logMAR) changes between aflibercept and dexamethasone implant treatment at Baseline **A** before sensitivity analysis **B** after excluding Bolukbasi et al. study, 3mo (**C**), 6mo (**D**), and 12mo **E** before sensitivity analysis and **F** after leaving two out sensitivity analysis. *BCVA* Best-corrected visual acuity, *logMAR* Logarithm of the minimum angle of resolution, *SD* Standard deviation, *CI* Confidence interval

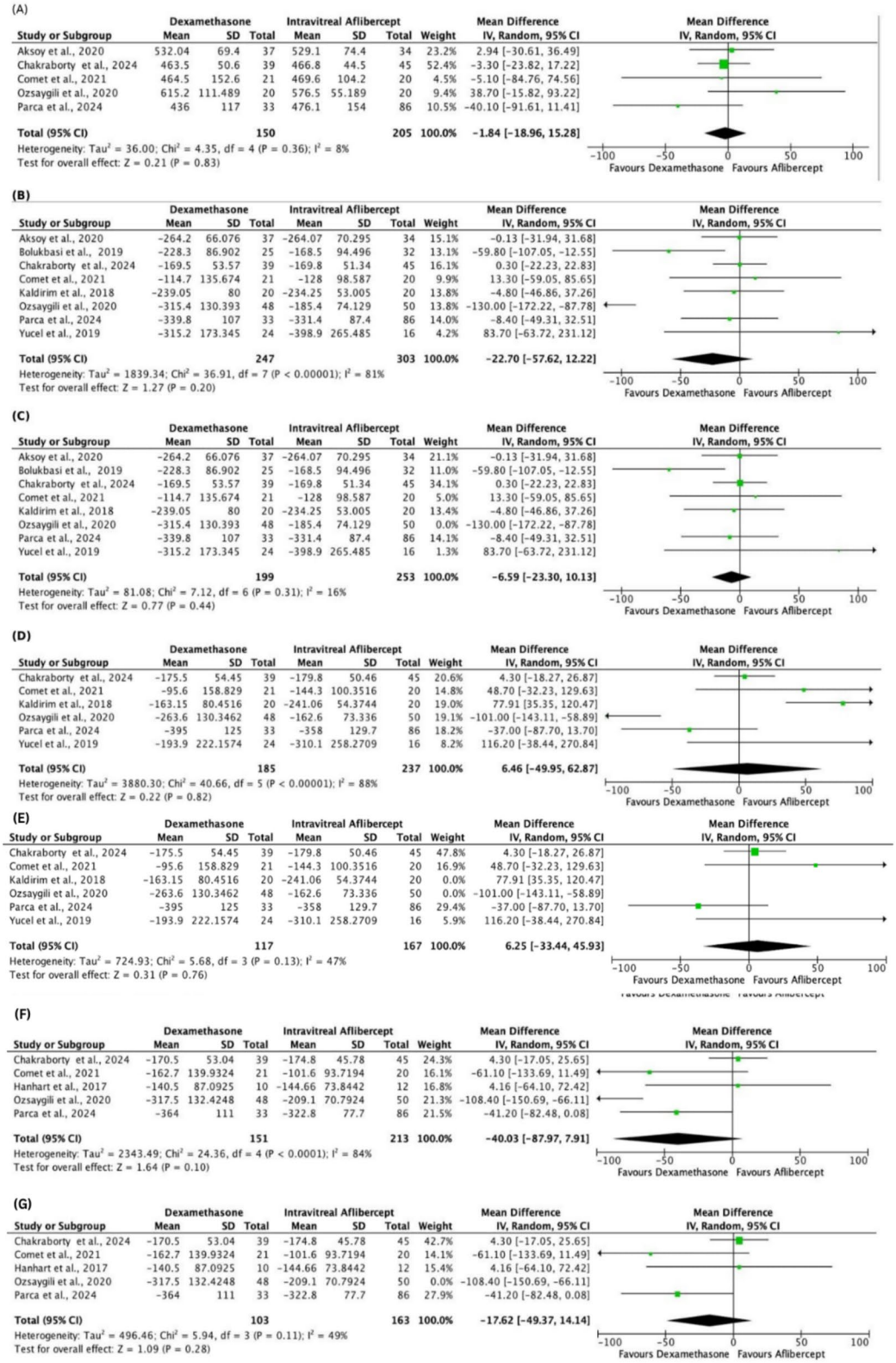


**Fig. 4** Differences in CRT changes between aflibercept and dexamethasone treatment at Baseline(**A**),3mo (**B**) before sensitivity analysis **C** after excluding Ozsaygali et al. study), 6mo (**D**) can't resolve, **E** after leaving out two sensitivity analysis, and 12mo **F** before sensitivity analysis **G** after excluding Ozsaygali et al. study) *CRT* Central retinal thickness, *SD* Standard deviation, *CI* Confidence interval

Fig. 4A. Additionally, the pooled data were homogeneous (P = 0.36, $I^2$ = 8%), as depicted in Fig. 4A.

The effects of aflibercept and dexamethasone on CRT at three-month intervals were analyzed in eight studies involving 550 participants, which also demonstrated no statistically significant variance between the two medications (MD −22.7, 95% CI [−57.62, 12.22], P = 0.20), as shown in Fig. 4B. However, substantial heterogeneity was noted among the studies (P = 0.00001, $I^2$ = 81%) as presented in Fig. 4B. Following a sensitivity analysis excluding the study by Ozsaygali et al., heterogeneity was mitigated (P = 0.31, $I^2$ = 16%), as shown in Fig. 4C, although the results remained non-significant (MD = −6.59, 95% CI [−23.30, 10.13], P = 0.44).

The assessment of CRT changes between aflibercept and dexamethasone at six-month intervals, derived from six studies with 422 participants, also did not show statistical significance (MD 6.46, 95% CI [−49.95, 62.87], P = 0.82), as shown in Fig. 4D. The aggregation of these studies displayed heterogeneity (P = 0.00001, $I^2$ = 88%), as illustrated in Fig. 4D and the considerable heterogeneity among studies could not be resolved by leaving one out in the sensitivity analysis. However, heterogeneity was resolved by leaving two out sensitivity analyses excluding Kaldirim et al.'sstudy and Ozsaygali et al.'sstudy to solve heterogeneity (P = 0.13, $I^2$ = 47%), although the results remained non-significant (MD = 6.25, 95% CI [−33.44, 45.93], P = 0.76) Fig. 4E.

Furthermore, five studies evaluated CRT changes between aflibercept and dexamethasone at 12-month intervals, yielding no statistically significant findings (MD −40.3, 95% CI [−87.97, 7.91], P = 0.10), as depicted **in** Fig. 4F. A significant degree of heterogeneity was detected (P < 0.0001, I2 = 84%) (Fig. 4C. However, sensitivity analysis, which excluded the study by Ozsaygali et al., resolved the heterogeneity (P = 0.11, $I^2$ = 49%), as shown in Fig. 4G. Collectively, these findings indicated that aflibercept and dexamethasone treatments did not significantly affect CRT (mmHg) across any of the evaluated time intervals.

#### *Intraocular pressure (IOP) analysis*

A pooled analysis of six studies involving 315 participants indicated no statistically significant difference between aflibercept and dexamethasone in the treatment of IOP at baseline (MD −0.37, 95% CI, −1.66, 0.91; P = 0.57) (Fig. 5A). Furthermore, substantial heterogeneity was observed across the studies, which could not be resolved by leaving one out of the sensitivity analysis (P < 0.00001, $I^2$ = 86%) (Fig. 5A). Accordingly, by excluding the studies by Chackraborty et al. and Comet et al., heterogeneity was resolved (P = 0.13, $I^2$ = 46%), although the results remained non-significant (MD = −0.26, 95% CI [−1.03, 0.52], P = 0.52) Fig. 5B.

Three studies evaluated the effects of aflibercept and dexamethasone on IOP at three-month intervals. The analysis revealed no statistically significant effect (MD 0.17, 95% CI [−1.26, 1.61], P = 0.81) (Fig. 5C), accompanied by significant heterogeneity (P < 0.002, $I^2$ = 84%) (Fig. 5C). However, following sensitivity analysis under various scenarios and the exclusion of the study by Bolukbasi et al., heterogeneity was resolved (P < 0.31, $I^2$ = 0%) (Fig. 5D), resulting in an overall mean difference that became statistically significant, favoring the aflibercept group (MD 1.04, 95% CI [0.56, 1.52], P < 0.001) (Fig. 5D).

Two studies examined the effects of aflibercept and dexamethasone on IOP at six-month intervals, establishing that aflibercept treatment significantly decreased IOP (MD 1.42, 95% CI [0.99, 1.85], P < 0.00001) (Fig. 5E). No heterogeneity was found in this analysis (P = 0.35, $I^2$ = 0%) (Fig. 5E). For the twelve-month intervals, only two studies showed no statistically significant difference (MD 1.44, 95% CI [−0.31, 3.19], P < 0.11), and significant heterogeneity was noted (P < 0.06, $I^2$ = 73%) (Fig. 5F).

#### Effect of injection frequency on outcomes

The number of injections administered for intravitreal aflibercept (IVA) and dexamethasone (DEX) implants varied significantly across studies, potentially influencing the reported outcomes. For IVA, the dosing regimen typically involves three monthly loading doses followed by pro re nata (PRN) administration, resulting in a higher injection frequency compared to DEX, which is generally delivered as a single sustained-release implant. Studies such as Aksoy (2020) and Bolukbasi (2019) reported that patients receiving IVA underwent three and four injections, respectively, during the study period, whereas patients treated with DEX received only one injection. Similarly, according to Ozsaygili (2020), IVA requires three injections compared with a single DEX injection. In studies by Hanhart (2017) and Chakraborty (2024), the difference in injection frequency became more pronounced, with IVA requiring up to 7–13 injections depending on the follow-up period, while DEX ranged from 3 to 12 injections. Despite the difference in injection frequency, the outcomes in terms of BCVA, central retinal thickness (CRT), and intraocular pressure (IOP) demonstrated no statistically significant differences between the two treatment modalities at most time points. However, the increased frequency of IVA injections may contribute to a higher patient burden and resource utilization, raising concerns about treatment adherence and long-term feasibility. Interestingly, the reduced frequency of DEX injections could partially explain the higher incidence of IOP-related adverse events, because

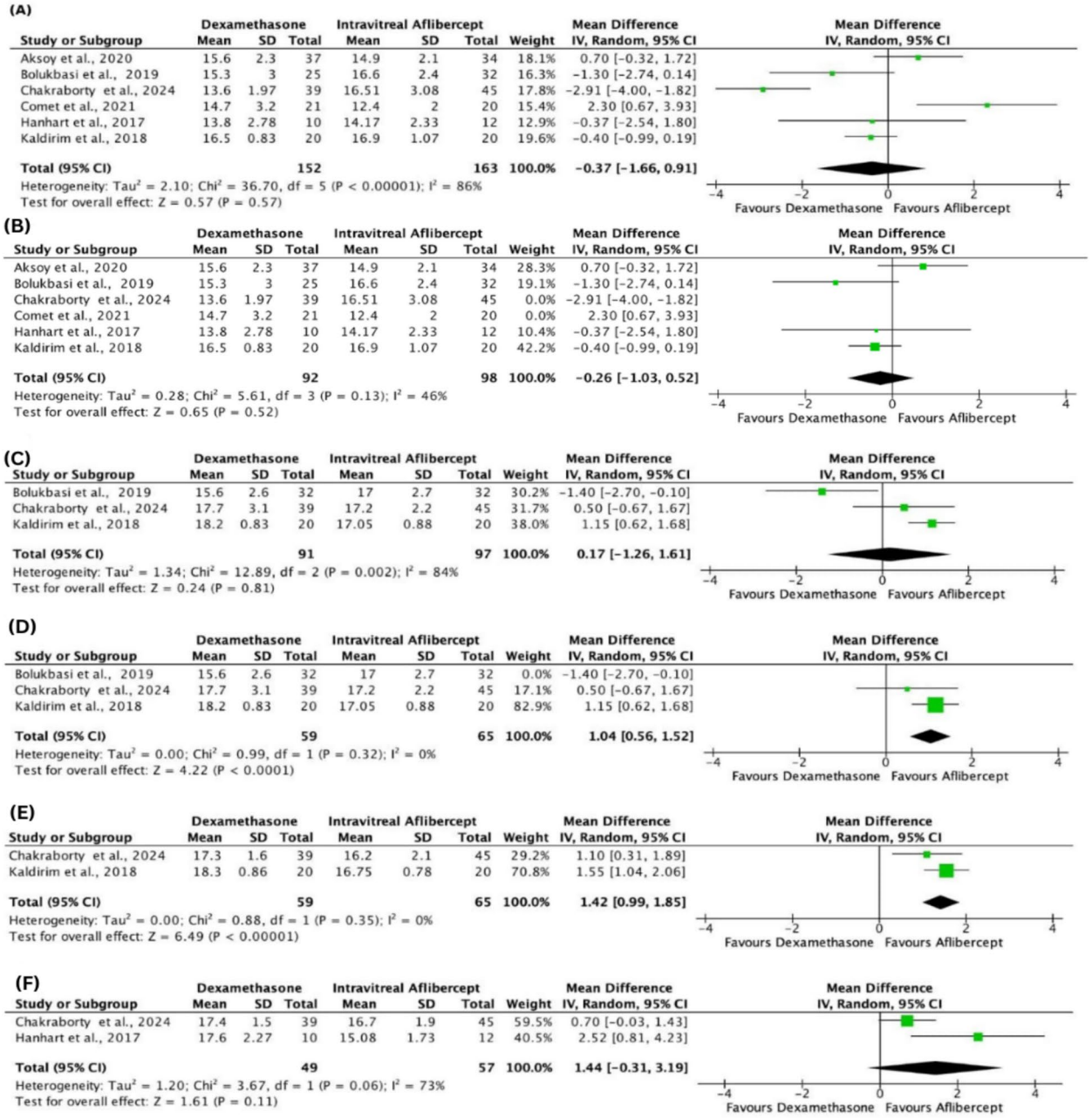


**Fig. 5** Differences in IOP changes between aflibercept and dexamethasone treatment at Baseline (**A**), **B** after leaving out two studies using sensitivity analysis, 3mo **C** before sensitivity analysis **D** after excluding Bolukbasi et al. study, 6mo (**E**), and 12mo (**F**) *IOP* Intraocular pressure, *SD* Standard deviation, *CI* Confidence interval

the sustained-release nature of DEX implants may lead to prolonged corticosteroid exposure in the eye. On the other hand, frequent administration of IVA might offer more consistent control over disease progression but could also increase the risk of cumulative systemic or ocular complications over time. These findings underscore the importance of balancing the efficacy, safety, and patient compliance when considering the injection frequency for IVA and DEX in clinical practice (Table 3).

## GRADE assessment

The quality of evidence for the outcomes assessed in this review was evaluated using the GRADE,,, of Recommendations Assessment Developmentand Evaluation

**Table 3** Summary of the included studies' population

| Study | Disease | Gender (M/F) | | Age (y) | | Eyes (n) | | Injections (n) | | Follow-up (mo) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | IDI | IVA | IDI | IVA | IDI | IVA | IDI | IVA | |
| Aksoy 2020 [45] | DR | 18/19 | 18/16 | 61.3 ± 11.3 | 59.3 ± 10.3 | 37 | 34 | 1 | 3 | 6 |
| Bolukbasi 2019 [46] | DR | 9/16 | 13/19 | 65.1 ± 13.2 | 56.4 ± 13.5 | 25 | 32 | 1 | 4 | 3 |
| Comet 2021 [13] | DR | 12/9 | 11/9 | 66.3 ± 7.8 | 69.6 ± 9.2 | 21 | 20 | 3 | 4 | 12 |
| Hanhart 2017 [40] | RVO | 6/4 | 6/6 | 63.60 ± 7.12 | 62.08 ± 8.87 | 10 | 12 | 3–12 | 7–13 | 12 |
| Kaldirim 2018 [41] | RVO | 12/8 | 13/7 | 70.6 ± 3.9 | 70.45 ± 3.9 | 20 | 20 | 1 | 3 | 6 |
| Ozsaygili 2020 [42] | DR | 15/14 | 20/13 | 64.8 ± 7.9 | 66.4 ± 2.0 | 48 | 50 | 1 | 3 | 12 |
| Yucel 2019 [43] | RVO | NA | NA | 65.4 ± 2.3 | 66.2 ± 3.2 | 24 | 16 | 1–2 | 1–4 | 6 |
| Chakraborty 2024 [44] | DME in pseudophakic eyes | 18/21 | 28/17 | 53.3 ± 4.2 | 55.4 + 4.4 | 39 | 45 | 2,3 and 4 injections in 12,25 and 2 patients respectively | 2,3 and 4 injections in 4, 33, and 8 patients respectively | 12 |
| Parca 2024 [39] | DME | 10/10 | 33/25 | 61.7 ± 6.53 | 61.2 ± 9.71 | 33 | 86 | 1–3 | 3—8 | 12 |

framework. Among the included studies, the certainty of the evidence ranged from high to very low. The primary outcome, best-corrected visual acuity (BCVA), central macular thickness (CMT), and intraocular pressure (IOP) were rated as low due to variation between RCTs and observational studies, heterogeneity, and moderate quality of the studies. Overall, the strength of the evidence highlights the need for further high-quality studies to confirm our findings.

## Discussion

The primary pathophysiological mechanisms associated with DR and RVO involve elevation of VEGF levels and pro-inflammatory reactions. DR induces ischemia and oxidative stress, which subsequently upregulate VEGF expression. This process leads to proliferation of new permeable blood vessels and enhanced vasculogenesis. Furthermore, angiogenesis activates additional inflammatory mediators [48]. Both mechanisms exert a synergistic effect on the pathogenesis of DR and macular edema, underscoring the importance of anti-VEGF pharmacotherapy, such as Aflibercept, Bevacizumab, or Ranibizumab, in its management. Some studies have indicated that aflibercept exhibits a stronger binding affinity for VEGF, thereby resulting in more favorable improvements in BCVA and CRT. Moreover, this medication may offer particular advantages to patients with poorer baseline vision, greater central subfield thickness, and improved glycemic control [28, 49]. Currently, the two principal strategies for treating DR and RVO are intravitreal injection of anti-VEGF agents and the administration of anti-inflammatory steroids. Patients initiating treatment with aflibercept are typically required to receive frequent injections with monthly follow-up during the first year of therapy. This regimen can impose a significant financial burden on many patients, leading to stress due to costs or heightened risk of endophthalmitis [50].

Given the pivotal role of inflammation in both DR and RVO, drugs, such as dexamethasone, are utilized for their anti-inflammatory properties. Dexamethasone implants have been shown to decrease the frequency of required intravitreal injections while effectively improving BCVA and CRT, thus alleviating financial strain and enhancing patient compliance [5]. However, some studies have noted adverse effects associated with dexamethasone, including cataract formation, elevated intraocular pressure, foreign body sensation, ocular pain, pruritus, conjunctival hyperemia, conjunctival edema, and conjunctival hemorrhage [50].

This systematic review and meta-analysis incorporated nine clinical studies involving 572 participants to evaluate the safety and efficacy of intravitreal aflibercept injections versus dexamethasone implants in terms of BCVA, CRT, and IOP. The findings from our meta-analysis suggest that intravitreal aflibercept injections and dexamethasone implants exhibit comparable levels of clinical efficacy. No significant differences were observed between the two treatments in terms of BCVA and CRT at baseline or at the 3-, 6-, and 12-month follow-up intervals. Statistical analysis confirmed that intravitreal aflibercept injection did not demonstrate significant superiority over dexamethasone implants in terms of clinical outcomes. Notably, dexamethasone implants demonstrated superior efficacy in both short-term (three-month) and long-term (twelve-month) outcomes while requiring fewer injections, thus enhancing patient compliance.

Conversely, the IOP results indicated some limitations associated with dexamethasone when compared to aflibercept. Specifically, Dexamethasone implants resulted in increased IOP at three- and six-month intervals, which may necessitate management with anti-glaucoma medications. However, no significant differences were noted between the two treatments at the twelve-month interval, illustrating the equivalence of aflibercept injections and dexamethasone implants in terms of long-term effects.

Significant heterogeneity was detected among the effect sizes of the studies reporting differences in BCVA changes between Aflibercept and Dexamethasone implants ($P < 0.04$, $I^2 = 55\%$), which was resolved by excluding the study by Bolukbasi et al. ($P = 0.23$, $I^2 = 27\%$). Similarly, heterogeneity was identified in five studies assessing CRT changes, which was resolved through the exclusion of the Ozsaygali et al. study. Additionally, three studies compared the effects of Aflibercept and Dexamethasone on IOP levels, and the exclusion of the study by Bolukbasi et al. led to a statistically significant difference favoring the aflibercept group (MD 1.04, 95% CI [0.56, 1.52], $P < 0.001$).

Optical Coherence Tomography (OCT) devices are crucial for detecting and monitoring diabetic macular edema (DME), providing high-resolution, non-invasive retinal imaging for both qualitative and quantitative analyses. Spectral-domain OCT (SD-OCT) offers superior resolution, whereas swept-source OCT (SS-OCT) allows for deeper retinal and choroidal penetration. Enhanced Depth Imaging (EDI-OCT) improves the visualization of the deeper layers. Despite these advances, the detection of subtle retinal changes remains challenging. Enhancements such as integrating AI algorithms for automated measurements, standardizing scan protocols, and combining OCT with other imaging methods, such as fundus photography or fluorescein angiography, could improve diagnostic accuracy and clinical decision-making [14–25].

These findings further demonstrate that dexamethasone implants provide enhanced effectiveness compared to aflibercept in terms of visual acuity gain and retinal thickness reduction, both at three-month and twelve-month follow-up assessments. Although Dexamethasone treatment requires less frequent injections, it is accompanied by an increased risk of elevated intraocular pressure and cataract formation. Therefore, when determining the most appropriate treatment strategy, healthcare providers should consider the severity of the disease, patient preferences, and a comprehensive evaluation of the respective advantages and disadvantages of each treatment option. Before treatment selection, it is imperative to provide patients with essential information to facilitate informed decision-making.

## Limitations of the study

The meta-analysis was conducted using open-access data, primarily derived from retrospective studies, which inherently lack randomization and, therefore, preclude the establishment of causal relationships. The included studies varied significantly in design, patient characteristics, and treatment motivations, which contributed to inconsistent findings. In addition, the small number of studies included in certain subgroup analyses constrained the outcomes.

Another key limitation is the exclusion of non-English studies, which might have introduced selection bias and limited the generalizability of our findings. Moreover, no publication bias assessment tools were employed because of the small number of included studies, and this absence must be acknowledged as a limitation. The small sample size of the included studies further restricted the strength of the conclusions drawn. Furthermore, critical real-world factors, such as patients' quality of life and treatment-associated costs, were not assessed, which are important considerations for clinical decision-making.

This meta-analysis combined data from patients with diabetic retinopathy (DR) and retinal vein occlusion (RVO), conditions with distinct pathophysiology, in the same treatment comparisons. While both conditions result in macular edema, their underlying mechanisms differ. DR is characterized by retinal microangiopathy due to chronic hyperglycemia, whereas RVO is caused by vascular occlusion. These differences likely influenced treatment response. For instance, aflibercept has demonstrated superior visual outcomes in DR-related diabetic macular edema but requires more frequent injections, whereas dexamethasone implants may provide faster improvement in RVO but are associated with side effects such as elevated intraocular pressure. Pooling data from these two conditions may obscure condition-specific responses and lead to generalized conclusions. Stratifying the analysis by DR and RVO could offer more precise insights into the efficacy and safety of each treatment, thereby allowing for tailored therapeutic strategies.

Lastly, the heterogeneity of lens status (phakic vs. pseudophakic) and methods used for best-corrected visual acuity (BCVA) assessment across studies could have influenced the outcomes, further complicating direct comparisons.

## Conclusion

Both intravitreal aflibercept injections and dexamethasone implants effectively improve Corrected Visual Acuity (BCVA) and reduce Central Retinal Thickness (CRT) in macular edema secondary to diabetic retinopathy (DR) and retinal vein occlusion (RVO). Dexamethasone implants offer superior short- and long-term outcomes, with the added benefit of requiring fewer injections and enhancing patient convenience. However, this advantage is counterbalanced by the increased risk of intraocular pressure (IOP) elevation and cataract formation. In contrast, aflibercept significantly improves visual and anatomical outcomes, albeit with the disadvantage of requiring frequent injections, which can present both financial and logistical challenges for patients. Given the distinct advantages and drawbacks of each treatment modality, a personalized treatment approach informed by patient characteristics, preferences, and comorbidities is essential. Future research should prioritize head-to-head randomized controlled trials (RCTs) comparing aflibercept and dexamethasone implants across diverse patient populations. Additionally, greater emphasis on patient-centered outcomes, such as quality of life, treatment costs, and adherence, will provide valuable guidance for clinical decision-making.

This study is particularly relevant for patients with diabetic macular edema (DME) as it underscores the therapeutic benefits of dexamethasone implants, which provide superior improvements in BCVA and CRT in both short- and long-term assessments. These findings suggest that dexamethasone implants may be an optimal treatment for patients requiring less frequent interventions, making them ideal for those with limited access to healthcare or those seeking reduced clinic visits. This approach could alleviate the burden on both patients and the healthcare system.

For ophthalmologists, this systematic review and meta-analysis offers critical insights into the efficacy profiles and safety considerations of intravitreal aflibercept and dexamethasone implants. The evidence presented here can inform clinical decision making and encourage personalized treatment strategies based on individual patient needs. Furthermore, recognition of IOP elevation risks with dexamethasone implants emphasizes the

need for careful monitoring and follow-up. Overall, these findings highlight the importance of a patient-centered approach for managing macular edema, enabling more informed and effective therapeutic choices.

**Abbreviations**

| | |
|---|---|
| IA | Intravitreal Aflibercept |
| IDI | Intravitreal Dexamethasone Implant |
| DEX | Dexamethasone |
| AFL | Aflibercept |
| DXI | Dexamethasone Implant |
| IVA | Intravitreal Aflibercept |
| IVR | Intravitreal Ranibizumab |
| BCVA | Best Corrected Visual Acuity |
| CMT | Central Macular Thickness |
| CRT | Central Retinal Thickness |
| IOP | Intraocular Pressure |
| VA | Visual Acuity |
| SRD | Serous Retinal Detachment |
| PRN | Pro Re Nata (as needed) |
| DRIL | Disorganized Retinal Inner Layers |

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**Author contributions**
K.M. contributed to the conceptualization, methodology of the study, and project administration. T.S., A.M., I.S., and A.S. were responsible for investigation and data curation. A.S., A.A., I.S., and K.M. conducted formal analyses. All the authors collaborated to draft the original manuscript. A.H.M. and T.G. oversaw the writing and reviewing of the draft. I.S. is involved in the conceptualization, writing, and review processes, as well as correspondence. All authors participated in writing, reviewing, and editing the manuscript. Each author read and approved the final manuscript.

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**Availability of data and materials**
All data generated or analyzed during this study are included in the published article.

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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