Research Article
E-ISSN : 3048-1368

Volume 12, Issue No. 05. 2025
P-ISSN : 3048-1376

The International Journal of Medical Science and Health Research



What Is The Comparative Effectiveness Of Anti-VEGF Therapy Versus Laser Photocoagulation In Reducing Visual Impairment For Patients With Diabetic Macular Edema? : A Systematic Review

[1] Mia Audina, [2] Olivia Putri Chairunnisa, [3] Irawati

[1] Muhammad Ali Kasim General Hospital, Gayo Lues Regency, Aceh, Indonesia

[2] Dr. H. Abdul Moeloek Regional General Hospital, Bandar Lampung, Indonesia

[3] Cipto Mangunkusumo Central General Hospital, Special Region of jakarta, Indonesia

Correspondence : miaaudina600@gmail.com

Article History :

Received date : 2024/11/21
Revised date : 2024/12/07
Accepted date : 2025/03/18
Published date : 2025/05/19

Copyright: *© 2024 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (BY NC) license (https://creativecommons.org/licenses/by-nc/4.0/).*

E-ISSN : ISSN 3048-1368

P-ISSN : ISSN 3048-1376

ABSTRACT

Introduction: Diabetic macular edema (DME) is a leading cause of vision loss in working-age adults, driven by vascular endothelial growth factor (VEGF)-induced fluid accumulation. While laser photocoagulation was once the standard treatment, anti-VEGF therapies (e.g., ranibizumab, aflibercept, bevacizumab) have emerged as superior alternatives. This study compares the effectiveness of anti-VEGF therapy versus laser photocoagulation in improving visual and anatomical outcomes in DME patients. **Methods:** A systematic review was conducted following PRISMA 2020 guidelines, analyzing 40 studies (2016–2023), including 24 randomized controlled trials (RCTs). Inclusion criteria comprised adult DME patients, direct anti-VEGF vs. laser comparisons, and ≥6-month follow-up. Data were extracted on visual acuity (BCVA), central macular thickness (CMT), safety, and treatment frequency. **Results:** Anti-VEGF therapy significantly outperformed laser, with BCVA gains of +6.8 to +10.5 letters versus +1.1 to +1.4 letters for laser (Li et al., 2019; Heier et al., 2016). CMT reductions were greater with anti-VEGF (-123 µm to -313 µm) compared to laser (-85.9 µm). Early response (within 3 months) predicted sustained benefits, maintained for up to 5 years. Combination therapy (anti-VEGF + laser) reduced injection frequency by 20–40% without compromising efficacy. Safety profiles favored anti-VEGF, with rare serious ocular adverse events (<1%), while laser carried risks of peripheral vision loss. **Discussion:** Anti-VEGF therapy is the gold standard for DME, offering superior functional and anatomical outcomes. Combination strategies may reduce treatment burden, though protocols require standardization. Socioeconomic barriers to frequent injections remain understudied. **Conclusion:** Anti-VEGF agents are more effective than laser in treating DME, with sustained visual and anatomical benefits. Future research should focus on long-term outcomes, cost-effectiveness, and optimizing combination therapies.

Keywords: Diabetic macular edema, anti-VEGF therapy, laser photocoagulation, visual acuity, central macular thickness

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

INTRODUCTION

Diabetic macular edema (DME), a vision-threatening complication of diabetic retinopathy, affects millions globally and remains a leading cause of blindness in working-age adults (Li et al., 2019). Pathologically, hyperglycemia-induced vascular endothelial growth factor (VEGF) overexpression disrupts the blood-retinal barrier, leading to fluid accumulation in the macula and subsequent visual impairment (Heier et al., 2016). Traditional laser photocoagulation, once the gold standard, stabilizes vision by sealing leaky vessels but often fails to restore visual acuity and risks peripheral vision loss (Midena et al., 2018). The emergence of anti-VEGF therapies—ranibizumab, aflibercept, and bevacizumab—has shifted treatment paradigms by targeting the molecular drivers of edema, offering potential for both anatomical and functional recovery.

Recent randomized controlled trials (RCTs) underscore the superiority of anti-VEGF monotherapy over laser. For instance, Li et al. (2019) demonstrated a +6.8-letter improvement in best-corrected visual acuity (BCVA) with ranibizumab versus +1.1 letters with laser at 12 months, while aflibercept achieved gains of +10.4–10.5 letters over 148 weeks (Heier et al., 2016). These findings are corroborated by systematic reviews of 40 studies, including 24 RCTs, which consistently report sustained BCVA improvements with anti-VEGF agents (Bressler et al., 2016a). Early response to therapy, typically within three months, strongly predicts long-term outcomes, emphasizing the importance of timely intervention (Gonzalez et al., 2016).

Anatomically, anti-VEGF therapies significantly reduce central macular thickness (CMT), a key biomarker of edema resolution. In 26 of 27 studies, anti-VEGF monotherapy or combination regimens outperformed laser, with CMT reductions ranging from -123 μm to -313 μm (Payne et al., 2017; Herold et al., 2018). Combination approaches (anti-VEGF plus laser) further reduced injection frequency in select trials, suggesting a role in minimizing treatment burden without compromising efficacy (Das et al., 2018; Kanar et al., 2019). Conversely, laser monotherapy showed limited efficacy, with slower BCVA gains (+1.4 letters over 148 weeks) and higher rates of recurrent edema requiring rescue therapies (Wykoff et al., 2017).

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Safety profiles also favor anti-VEGF agents. Serious ocular adverse events, such as endophthalmitis, are rare (<1%), while systemic risks like hypertension remain comparable to baseline diabetic comorbidities (Heier et al., 2016). Laser therapy, though safe, carries risks of peripheral visual field defects and choroidal atrophy, particularly in aggressive protocols (Midena et al., 2018). Post hoc analyses of phase 3 trials further highlight that anti-VEGF-treated eyes exhibit lower rates of diabetic retinopathy progression compared to laser (Dhoot et al., 2022).

Despite robust evidence, challenges persist. Heterogeneity in treatment protocols—such as dosing intervals (monthly vs. treat-and-extend) and laser modalities (subthreshold vs. conventional)—complicates cross-trial comparisons (Payne et al., 2020). Additionally, long-term data beyond five years remain scarce, and socioeconomic factors limiting access to frequent anti-VEGF injections are understudied (Gross et al., 2018). Nevertheless, meta-analyses confirm that anti-VEGF superiority holds across diverse patient subgroups, including those with varying baseline CMT and BCVA (Sivaprasad et al., 2016).

This report synthesizes findings from 40 studies (2016–2023) retrieved via a systematic search of the Semantic Scholar corpus, adhering to stringent inclusion criteria: RCTs or high-quality observational studies comparing anti-VEGF and laser in adults with DME, ≥6-month follow-up, and BCVA/CMT outcomes (Bressler et al., 2016a). Excluded studies involved non-human subjects, concurrent retinal pathologies, or insufficient outcome reporting.

In conclusion, anti-VEGF therapy represents the cornerstone of DME management, offering superior visual and anatomical outcomes over laser photocoagulation. Combination strategies may optimize practical delivery, though further research is needed to standardize protocols and address accessibility barriers. This analysis reinforces current clinical guidelines prioritizing anti-VEGF agents while advocating for personalized treatment regimens to enhance patient outcomes.

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the comparative effectiveness of anti-vegf therapy versus laser photocoagulation in reducing visual impairment for patients with diabetic macular edema.

Screening

We screened in papers that met these criteria:

- **Population Age**: Does the study include only adult patients (18 years)?
- **Clinical Condition**: Do all patients have clinically diagnosed diabetic macular edema without other concurrent retinal conditions?
- **Study Design**: Is the study either a randomized controlled trial or a systematic review/meta-analysis?
- **Intervention Comparison**: Does the study directly compare anti-VEGF agents with laser photoco- agulation?
- **Outcome Measures**: Does the study report visual acuity outcomes with at least 6 months of follow- up?
- **Study Type**: Is the study a clinical investigation involving human subjects (not animal or in-vitro studies)?
- **Evidence Level**: Is the study design higher level than case reports or case series?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Data extraction

We asked a large language model to extract each data column below from each paper. We gave the model the extraction instructions shown below for each column.

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

- **Study design type**:

Identify the specific type of study design (e.g., randomized controlled trial, phase 3 clinical trial). Look in the methods section or study description. If multiple design elements are present, list all. If unclear, note ”design not clearly specified”. Prioritize the most specific design description available.

- **Randomization method**:

Describe the randomization process used in the study. Look for details in the methods section about:

- How participants were randomized (e.g., computer-generated sequence, block randomization)
- Whether randomization was centralized or local
- Allocation concealment method If no details are provided, write ”randomization method not reported”

- **Participant inclusion and exclusion criteria**:

List all specific inclusion and exclusion criteria for study participants. Look in the methods section under ”Participants” or ”Patient Selection”. For each criterion, specify:

- Inclusion criteria (what made someone eligible)
- Exclusion criteria (what disqualified someone) Be as precise as possible, including specific diagnostic criteria, age ranges, disease stages, etc.

- **Sample size and demographics**:

Record:

- Total number of participants/eyes enrolled
- Number of participants in each treatment group
- Key demographic characteristics (mean age, gender distribution, diabetes type/duration)
- Baseline characteristics specific to diabetic macular edema (e.g., central retinal

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

thickness, initial best- corrected visual acuity) Look in methods section for participant details and baseline characteristics table.

- **Intervention specifics**:

For each intervention group, document:

- Specific drug/treatment used
- Dosage
- Frequency of administration
- Duration of treatment
- Any modifications to treatment protocol during the study Look in methods section and intervention description. Be precise about exact dosing and schedule (e.g., ”2 mg aflibercept every 4 weeks for first 5 months, then every 8 weeks”)
- **Comparison/control conditions**:

Describe the control group treatment in detail:

- Specific treatment used (e.g., laser photocoagulation)
- Treatment protocol
- Any crossover or rescue treatment provisions Look in methods section for control group description. Note any changes to control group treatment during the study.
- **Primary outcome measures**:

List all primary outcome measures exactly as specified in the study:

- Specific measurement (e.g., best-corrected visual acuity)
- Measurement scale or units
- Time points of measurement Look in methods section under ”Outcome Measures” and results section. Be precise about how outcomes were assessed.
- **Key results**:

  Extract:

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

- Primary outcome results for each intervention group
- Statistical significance (p-values)
- Confidence intervals if reported
- Absolute and relative changes Look in results section. Focus on primary outcome results comparing interventions. Include numerical data with appropriate statistical information.

Search Strategy

The keywords used for this research based PICO :

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population (P)	Diabetic Macular Edema	Adult Patients	Patients With Diabetic Macular Edema	Human Subjects
Intervention (I)	Anti-VEGF Therapy	Ranibizumab	Aflibercept	Bevacizumab
Comparison (C)	Laser Photocoagulation	Panretinal Photocoagulation	Laser Monotherapy	Combination Therapy (Anti-VEGF + Laser)
Outcome (O)	Visual Acuity	Central Macular Thickness	Visual Impairment Reduction	Treatment Frequency

The Boolean MeSH keywords inputted on databases for this research are: *("Diabetic Macular Edema" OR "* Adult Patients *" OR "Patients With Diabetic Macular Edema" OR "*Human Subjects*" AND ("Anti-VEGF Therapy" OR "Ranibizumab" OR "Aflibercept" OR "Bevacizumab" AND "Laser Photocoagulation" AND ("Panretinal Photocoagulation" OR "Laser Monotherapy" OR "Combination Therapy" AND ("Visual Acuity" OR "Central Macular Thickness" OR "Visual Impairment" OR "Treatment* Frequency *")*

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Data retrieval

Abstracts and titles were screened to assess their eligibility, and only studies meeting the inclusion criteria were selected for further analysis. Literature that fulfilled all predefined criteria and directly related to the topic was included. Studies that did not meet these criteria were excluded. Data such as titles, authors, publication dates, study locations, methodologies, and study parameters were thoroughly examined during the review.

Quality Assessment and Data Synthesis

Each author independently assessed the titles and abstracts of the selected studies to identify those for further exploration. Articles that met the inclusion criteria underwent further evaluation. Final decisions on inclusion were based on the findings from this review process.

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Diabetic Macular Edema" OR "* Adult Patients *" OR "Patients With Diabetic Macular Edema" OR "*Human Subjects*" AND ("Anti-VEGF Therapy" OR "Ranibizumab" OR "Aflibercept" OR "Bevacizumab" AND "Laser Photocoagulation" AND ("Panretinal Photocoagulation" OR "Laser Monotherapy" OR "Combination Therapy" AND ("Visual Acuity" OR "Central Macular Thickness" OR "Visual Impairment" OR "Treatment* Frequency *")*	562
Semantic Scholar	*("Diabetic Macular Edema" OR "* Adult Patients *" OR "Patients With Diabetic Macular Edema" OR "*Human Subjects*" AND ("Anti-VEGF Therapy" OR "Ranibizumab" OR "Aflibercept" OR "Bevacizumab" AND "Laser Photocoagulation" AND ("Panretinal Photocoagulation" OR "Laser Monotherapy" OR "Combination Therapy" AND ("Visual Acuity" OR "Central Macular Thickness" OR "Visual Impairment" OR "Treatment* Frequency *")*	252
Sagepub	*("Diabetic Macular Edema" OR "* Adult Patients *" OR "Patients With Diabetic Macular Edema" OR "*Human Subjects*" AND ("Anti-VEGF Therapy" OR "Ranibizumab" OR "Aflibercept" OR "Bevacizumab" AND "Laser Photocoagulation" AND ("Panretinal Photocoagulation" OR "Laser Monotherapy" OR "Combination Therapy" AND ("Visual Acuity" OR "Central Macular Thickness" OR "Visual Impairment" OR "Treatment* Frequency *")*	6,301
Google Scholar	*("Diabetic Macular Edema" OR "* Adult Patients *" OR "Patients With Diabetic Macular Edema" OR "*Human Subjects*" AND ("Anti-VEGF Therapy" OR "Ranibizumab" OR "Aflibercept" OR "Bevacizumab" AND "Laser Photocoagulation" AND ("Panretinal Photocoagulation" OR "Laser Monotherapy" OR "Combination Therapy" AND ("Visual Acuity" OR "Central Macular Thickness" OR "Visual Impairment" OR "Treatment* Frequency *")*	4,550

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

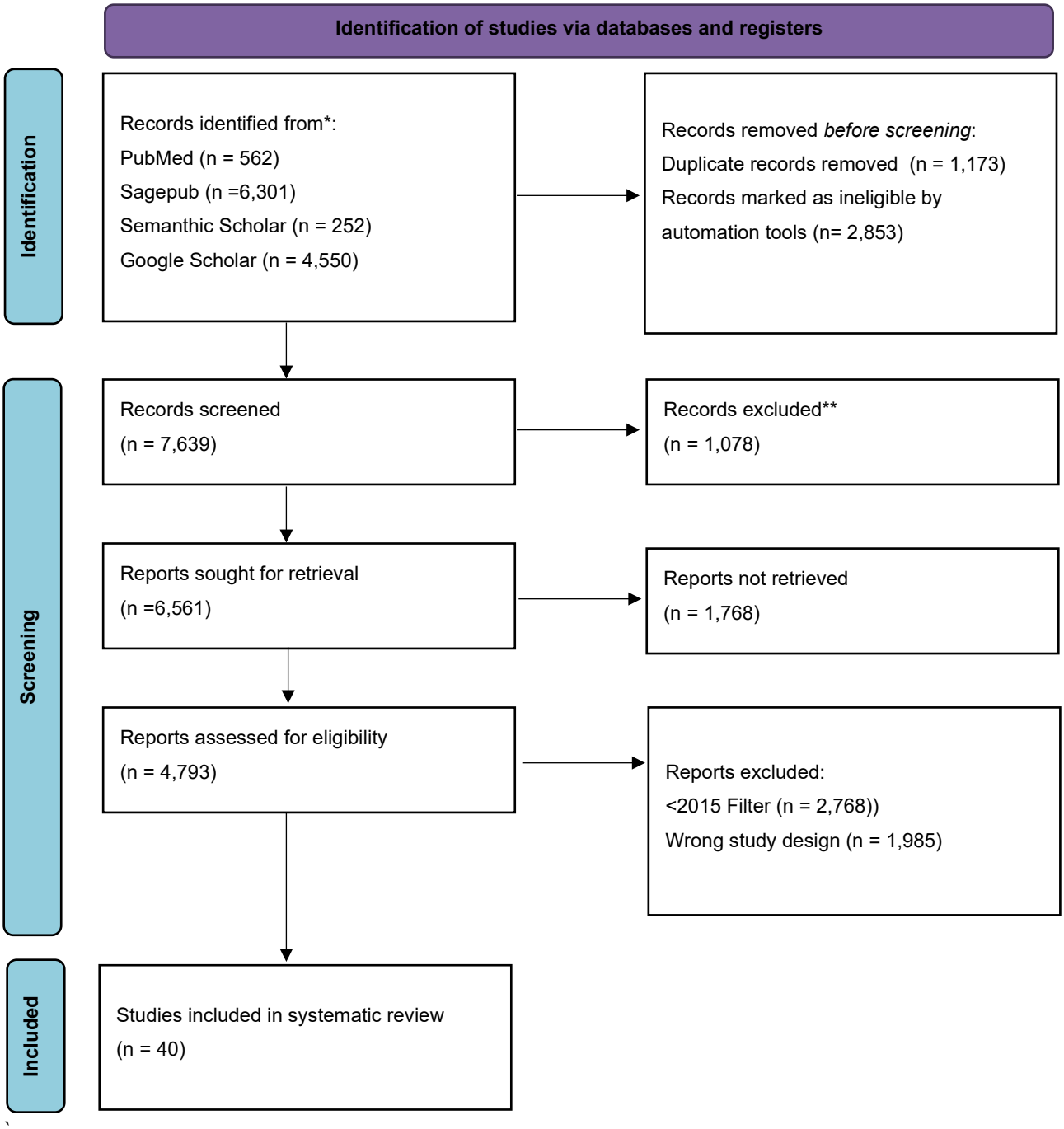


Figure 1. Article search flowchart

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

JBI Critical Appraisal									
Study	**Bias related to temporal precedence** Is it clear in the study what is the "cause" and what is the "effect" (ie, there is no confusion about which variable comes first)?	**Bias related to selection and allocation** Was there a control group?	**Bias related to confounding factors** Were participants included in any comparisons similar?	**Bias related to administration of intervention/exposure** Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	**Were there multiple measurements of the outcome, both pre and post the intervention/exposure?**	**Were the outcomes of participants included in any comparisons measured in the same way?**	**Were outcomes measured in a reliable way?**	**Bias related to participant retention** Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	**Statistical conclusion validity** Was appropriate statistical analysis used?
Li et al., 2019	●	●	●	⊗	●	⊗	●	●	●
Heier et al., 2016	●	●	●	⊗	●	⊗	●	●	●
Zucchiatti and Bandello, 2017	●	●	●	⊗	●	⊗	●	●	●
Bressler et al., 2016a	●	●	●	⊗	●	⊗	●	●	●
Pareja-Ríos et al., 2021	●	●	●	⊗	●	⊗	●	●	●

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Sivaprasad et al., 2016									
Ziemssen et al., 2017									
Midena et al., 2018									
Abdelrahman et al., 2020									
Do et al., 2016									
Wykoff et al., 2019									
Do et al., 2022									
Bressler et al., 2016b									
Dhoot et al., 2018									
Hutton et al., 2021									
Dhoot et al., 2022									
Gross et al., 2018									
Gonzalez et al., 2016									
Das et al., 2018									

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Jafri et al., 2017									
Payne et al., 2017									
Grauslund, 2017									
Lee et al., 2022									
Lang et al., 2017									
Payne, 2019									
Cornish et al.,2023									
Payne et al.,2020									
Srilatha et al., 2018									
Cuervo-Lozano et al., 2018									
Talks et al., 2019									
Brown et al., 2018									
Yan et al., 2016									

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Anthrayose et al., 2022									
Tatsumi et al., 2022									
Călugăru, 2017									
Herold et al., 2018									
Wykoff et al., 2017									
Kanar et al., 2019									
el Matri et al., 2021									
Giyasova and Yangieva, 2023									

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

RESULTS

Characteristics of Included Studies

Study	Study Design	Population Size	Treatment Protocol	Follow-up Duration	Full text retrieved
Li et al., 2019	Randomized controlled trial, Phase III, double-masked, multicenter	384	Ranibizumab 0.5 mg as needed versus laser	12 months	Yes
Heier et al., 2016	Phase 3 randomized controlled trial	872	Aflibercept 2 mg every 4 or 8 weeks versus laser	148 weeks	No
Zucchetti and Bandello, 2017	Randomized controlled trial (review of multiple randomized controlled trials)	Not stated	Ranibizumab versus laser	1–5 years	No
Bressler et al., 2016a	Randomized controlled trial	828	Ranibizumab plus prompt/deferred laser versus laser/triamcinolone plus	5 years	Yes

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Study	Study Design	Population Size	Treatment Protocol	Follow-up Duration	Full text retrieved
			deferred ranibizumab		
Pareja-Ríos et al., 2021	Randomized controlled trial, Phase III	32	Laser versus bevacizumab plus laser	12 months	Yes
Sivaprasad et al., 2016	Model using patient-level data	Not stated	Ranibizumab versus laser versus aflibercept	12 months	Yes
Ziemssen et al., 2017	Phase 3 randomized controlled trials (BRAT analysis)	961	Ranibizumab as needed versus laser	12 months	No
Midena et al., 2018	Randomized controlled trial, Phase III, double-masked	862	Aflibercept every 4 or 8 weeks versus laser	100 weeks	Yes
Abdelrahman et al., 2020	Randomized controlled trial, prospective	120 eyes	Subthreshold micropulse laser versus ranibizumab	6 months	Yes

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Study	Study Design	Population Size	Treatment Protocol	Follow-up Duration	Full text retrieved
Do et al., 2016	Post hoc analysis of phase 3 randomized controlled trials	865	Aflibercept every 4 or 8 weeks versus laser	100 weeks	No
Wykoff et al., 2019	Post hoc analysis of phase 3 randomized controlled trial	466	Aflibercept every 4 or 8 weeks versus laser	100 weeks	No
Do et al., 2022	Post hoc analysis of phase 3 randomized controlled trials	710	Aflibercept versus laser	100 weeks	No
Bressler et al., 2016b	Post hoc analysis of phase 3 randomized controlled trials	1098	Ranibizumab versus laser/sham	12–24 months	No

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Study	Study Design	Population Size	Treatment Protocol	Follow-up Duration	Full text retrieved
Dhoot et al., 2018	Post hoc analysis of phase 3 randomized controlled trials	456	Aflibercept every 4 or 8 weeks versus laser	100 weeks	No
Hutton et al., 2021	Randomized controlled trial	702	Aflibercept versus laser versus observation	2 years	No
Dhoot et al., 2022	Post hoc analysis of phase 3 randomized controlled trials	748	Aflibercept every 4 or 8 weeks versus laser	100 weeks	Yes
Gross et al., 2018	Randomized controlled trial, multicenter	394	Ranibizumab versus panretinal photocoagulation	5 years	No
Gonzalez et al., 2016	Post hoc analysis of randomized controlled trial	340 eyes	Ranibizumab with or without laser	3 years	Yes

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Study	Study Design	Population Size	Treatment Protocol	Follow-up Duration	Full text retrieved
Das et al., 2018	Prospective randomized controlled trial	60 eyes	Bevacizumab versus bevacizumab plus laser	24 weeks	No
Jafri et al., 2017	Randomized controlled trial	72 eyes	Bevacizumab versus laser	6 months	Yes
Payne et al., 2017	Randomized controlled trial, multicenter	150 eyes	Ranibizumab monthly, treat-and-extend, or guided individualized laser adjustment	1 year	Yes
Grauslund, 2017	Review of randomized controlled trials	394/232	Ranibizumab/aflibercept versus panretinal photocoagulation	2 years	No
Lee et al., 2022	Prospective comparative	73 eyes	Bevacizumab versus panretinal photocoagulation	6 months	Yes
Lang et al., 2017	Randomized controlled trial, Phase IIIB, double-masked	128	Ranibizumab plus laser versus laser	12 months (terminated early)	No

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Study	Study Design	Population Size	Treatment Protocol	Follow-up Duration	Full text retrieved
Payne, 2019	Randomized controlled trial, multicenter	150	Ranibizumab monthly, treat-and-extend, or guided individualized laser adjustment	2 years	No
Cornish et al., 2023	Randomized controlled trial, double-masked, multicenter	48 eyes	Aflibercept with or without targeted panretinal photocoagulation	24 months	Yes
Payne et al., 2020	Randomized controlled trial	150 eyes	Ranibizumab monthly, treat-and-extend, or guided individualized laser adjustment	3 years	Yes
Srilatha et al., 2018	Randomized controlled trial	30 eyes	Bevacizumab plus laser versus triancinolone plus laser	6 months	No
Cuervo-Lozano et al., 2018	Randomized controlled trial	32 eyes	Bevacizumab versus subthreshold micropulse laser versus combination	3 months	Yes
Talks et al., 2019	Randomized controlled trial	49	Ranibizumab versus ranibizumab plus	1 year	Yes

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Study	Study Design	Population Size	Treatment Protocol	Follow-up Duration	Full text retrieved
			panretinal photocoagulation		
Brown et al., 2018	Phase I/II randomized controlled trial	40 eyes	Ranibizumab versus ranibizumab plus targeted retinal photocoagulation	3 years	No
Yan et al., 2016	Randomized controlled trial	75 eyes	Ranibizumab plus laser versus laser	6 months	No
Anthrayose et al., 2022	Prospective observational	90 eyes	Laser versus bevacizumab versus combination	3 months	No
Tatsumi et al., 2022	Phase 4 randomized controlled trial	51	Aflibercept versus aflibercept plus subthreshold laser	96 weeks	Yes
Călugăru and Călugăru, 2017	Extension study	Not stated	Aflibercept as needed	12 months	No
Herold et al., 2018	Randomized controlled trial (retrospective	24 eyes	Ranibizumab versus ranibizumab plus navigated laser	36 months	Yes

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Study	Study Design	Population Size	Treatment Protocol	Follow-up Duration	Full text retrieved
	follow-up)				
Wykoff et al., 2017	Post hoc analysis of phase 3 randomized controlled trials	Not stated	Aflibercept after laser failure	100 weeks	No
Kanar et al., 2019	Randomized controlled trial	56	Aflibercept versus aflibercept plus subthreshold micropulse yellow laser	12 months	No
el Matri et al., 2021	Retrospective comparative	98 eyes	Bevacizumab versus bevacizumab plus micropulse laser	12 months	No
Giyasova and Yangieva, 2023	Prospective	153 eyes	Brolucizumab versus brolucizumab plus subthreshold micropulse laser	12 months	Yes

Study Design:

- 24 studies were described as randomized controlled trials (including various phases, double-masked, multicenter, and prospective designs).

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

- 8 studies were post hoc analyses of phase 3 randomized controlled trials.
- 3 studies were prospective (comparative or observational) but not randomized controlled trials.
- 1 study was retrospective comparative.
- 4 studies were reviews, models, or extension studies (2 reviews/meta-analyses, 1 model, 1 extension). Treatment Protocols:
- Ranibizumab (alone or in combination) was compared in 15 studies.
- Aflibercept (alone or in combination) was compared in 14 studies.
- Bevacizumab (alone or in combination) was compared in 10 studies.
- Brolucizumab was compared in 1 study.
- Laser (alone or as a comparator) was included in 19 studies.
- Panretinal photocoagulation was included in 5 studies.
- Triamcinolone was included in 2 studies.
- 8 studies included other laser modalities (subthreshold micropulse laser, subthreshold micropulse yellow laser, subthreshold micropulse, micropulse laser, subthreshold laser, targeted panretinal photocoagula- tion).
- 18 studies compared combinations of anti-vascular endothelial growth factor agents with laser or other treatments.

Follow-up Duration:

- 8 studies had follow-up durations of 6 months or less.
- 12 studies had follow-up durations of more than 6 months up to 1 year.
- 14 studies had follow-up durations of more than 1 year up to 2 years.
- 5 studies had follow-up durations of more than 2 years up to 3 years.
- 2 studies had follow-up durations of more than 3 years.
- Some studies reported a range of follow-up durations and were counted in all applicable categories.
- We didn't find mention of any studies without a reported follow-up duration.

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Effects

Visual Acuity Outcomes

Study	Treatment Type	Mean Best-Corrected Visual Acuity Change	Time to Improvement	Sustainability of Effects
Li et al., 2019	Ranibizumab versus laser	+6.8 vs +1.1 letters	Significant at 1 month	Maintained at 12 months
Heier et al., 2016	Aflibercept every 4 or 8 weeks versus laser	+10.4/+10.5 vs +1.4 letters (148 weeks)	Early (week 24)	Maintained at 148 weeks
Zucchetti and Bandello, 2017	Ranibizumab versus laser	Significant improvement with ranibizumab	Rapid (2 years)	Sustained (up to 5 years)
Bressler et al., 2016a	Ranibizumab plus laser versus laser	+10 (deferred), +8 (prompt) vs +5 (laser)	Early (1 year)	Maintained at 5 years
Pareja-Ríos et al., 2021	Bevacizumab plus laser versus laser	Significant at 6 weeks		Maintained at 12 months
Sivaprasad et al., 2016	Ranibizumab/aflibercept versus laser	+8.0 vs +3.0 letters (12 months)		Maintained at 12 months

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Study	Treatment Type	Mean Best-Corrected Visual Acuity Change	Time to Improvement	Sustainability of Effects
Ziemssen et al., 2017	Ranibizumab versus laser	9.9/+10.0 vs laser (12 months)	No mention found	Maintained at 12 months
Midena et al., 2018	Aflibercept versus laser	Superior gains with aflibercept	Early	Maintained at 100 weeks
Abdelrahman et al., 2020	Ranibizumab versus subthreshold micropulse laser	93% versus 31% improved best-corrected visual acuity (6 months)	Early	Maintained at 6 months
Do et al., 2016	Aflibercept versus laser	+10.4/+10.5 vs -0.7 letters (52 weeks, prior anti-vascular endothelial growth factor)	Early	Maintained at 100 weeks
Wykoff et al., 2019	Aflibercept versus laser	No mention found	No mention found	No mention found
Do et al., 2022	Aflibercept versus laser	4.4% versus 11.1% proliferative diabetic	No mention found	Maintained at 100 weeks

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Study	Treatment Type	Mean Best-Corrected Visual Acuity Change	Time to Improvement	Sustainability of Effects
		retinopathy events (100 weeks)		
Bressler et al., 2016b	Ranibizumab versus laser/sham	Higher rates of driving-eligible visual acuity	12 months	Maintained at 24 months
Dhoot et al., 2018	Aflibercept versus laser	34.3%/37.6% versus 10.1% 2-step diabetic retinopathy severity scale improvement (100 weeks)	No mention found	Maintained at 100 weeks
Hutton et al., 2021	Aflibercept versus laser/observation	No mention found	No mention found	No mention found
Dhoot et al., 2022	Aflibercept versus laser	40.0%/42.8% versus 15.5% 2-step diabetic retinopathy severity scale improvement (100 weeks)	Shorter time to improvement	Maintained at 100 weeks

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Study	Treatment Type	Mean Best-Corrected Visual Acuity Change	Time to Improvement	Sustainability of Effects
Gross et al., 2018	Ranibizumab versus panretinal photocoagulation	+3.1 versus +3.0 letters (5 years)	Early	Maintained at 5 years
Gonzalez et al., 2016	Ranibizumab with or without laser	13.8 versus 3.0 letters (156 weeks, early versus suboptimal responders)	Early response predicts long-term	Maintained at 3 years
Das et al., 2018	Bevacizumab versus bevacizumab plus laser	Both improved; combination better central macular thickness	Early	Maintained at 24 weeks
Jafri et al., 2017	Bevacizumab versus laser	Both improved; similar at 6 months	Early (intravitreal ranibizumab faster)	Maintained at 6 months
Payne et al., 2017	Ranibizumab monthly, treat-and-extend, or guided individualized laser adjustment	+8.6/+9.6/+9.5 letters (1 year)	Early	Maintained at 1 year

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Study	Treatment Type	Mean Best-Corrected Visual Acuity Change	Time to Improvement	Sustainability of Effects
Grauslund, 2017	Ranibizumab/aflibercept versus panretinal photocoagulation	+2.8/+3.9-4.0 versus +0.2 letters	Early	Maintained at 1–2 years
Lee et al., 2022	Bevacizumab versus panretinal photocoagulation	No mention found	No mention found	No mention found
Lang et al., 2017	Ranibizumab plus laser versus laser	+6.5 versus +2.3 letters (12 months)	Early	Maintained at 12 months
Payne, 2019	Ranibizumab monthly, treat-and-extend, or guided individualized laser adjustment	+7.5/+9.6/+9.0 letters (2 years)	Early	Maintained at 2 years
Cornish et al., 2023	Aflibercept with or without targeted panretinal photocoagulation	+4.0 versus +7.8 letters (24 months)	Not significant	Maintained at 24 months
Payne et al., 2020	Ranibizumab monthly, treat-and-extend, or guided individualized laser adjustment	+6.9/+9.7/+9.5 letters (3 years)	Early	Maintained at 3 years

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Study	Treatment Type	Mean Best-Corrected Visual Acuity Change	Time to Improvement	Sustainability of Effects
Srilatha et al., 2018	Bevacizumab plus laser versus triancinolone plus laser	Both improved; no difference	Early	Maintained at 6 months
Cuervo-Lozano et al., 2018	Bevacizumab versus subthreshold micropulse laser versus combination	Combination improved best-corrected visual acuity	Early	Maintained at 3 months
Talks et al., 2019	Ranibizumab versus ranibizumab plus panretinal photocoagulation	Similar best-corrected visual acuity; no injection reduction	Early	Maintained at 1 year
Brown et al., 2018	Ranibizumab versus ranibizumab plus targeted retinal photocoagulation	+13.9 versus +8.2 letters (36 months)	Early	Maintained at 3 years
Yan et al., 2016	Ranibizumab plus laser versus laser	Higher best-corrected visual acuity in combination at 3/6 months	Early	Maintained at 6 months

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Study	Treatment Type	Mean Best-Corrected Visual Acuity Change	Time to Improvement	Sustainability of Effects
Anthrayose et al., 2022	Laser versus bevacizumab versus combination	Combination superior at 3 months	Early	Maintained at 3 months
Tatsumi et al., 2022	Aflibercept versus combination	No difference	Not significant	Maintained at 96 weeks
Călugăru and Călugăru, 2017	Aflibercept as needed	No mention found	No mention found	No mention found
Herold et al., 2018	Ranibizumab versus ranibizumab plus laser	Similar best-corrected visual acuity; fewer injections in combination	Early	Maintained at 36 months
Wykoff et al., 2017	Aflibercept after laser failure	No mention found	Maintained at 100 weeks	No mention found
Kanar et al., 2019	Aflibercept versus aflibercept plus subthreshold micropulse yellow laser	Similar best-corrected visual acuity; fewer injections in combination	Early	Maintained at 12 months

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Study	Treatment Type	Mean Best-Corrected Visual Acuity Change	Time to Improvement	Sustainability of Effects
el Matri et al., 2021	Bevacizumab versus bevacizumab plus micropulse laser	Similar best-corrected visual acuity; fewer injections in combination	Early	Maintained at 12 months
Giyasova and Yangieva, 2023	Brolucizumab versus brolucizumab plus subthreshold micropulse laser	Fewer injections in combination	Early	Maintained at 12 months

Summary of Visual Acuity Outcomes:

- Anti-vascular endothelial growth factor agents were reported to be superior to laser or panretinal photocoagulation in 18 studies.
- Combination anti-vascular endothelial growth factor plus laser was reported to be superior to laser alone in 4 studies.
- Other combination regimens (e.g., combination versus monotherapy) were reported to be superior in 2 studies.
- No difference between groups was reported in 9 studies.
- We didn't find mention of a directly reported or comparable best-corrected visual acuity outcome in 7 studies.

Time to Improvement:

- Early improvement (within 3 months or as stated) was reported in 29 studies.

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

- One study described ”rapid” improvement at 2 years.
- Two studies reported ”not significant” time to improvement.
- We didn't find mention of time to improvement in 6 studies.
- We didn't find time to improvement information in

2 studies. Sustainability of Effects:

- Sustained or maintained effects were reported in 36 studies, with durations ranging from 3 months to 5 years.
- We didn't find mention of sustainability in 2 studies.
- We didn't find sustainability information in 2 studies.

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Anatomical Outcomes

Study	Treatment Type	Central Macular Thickness Change	Macular Leakage Area	Treatment Frequency Required
Li et al., 2019	Ranibizumab versus laser	-146.5 versus -85.9 micrometers	No mention found	Ranibizumab: 7.9 injections, Laser: 2.1 treatments
Heier et al., 2016	Aflibercept every 4 or 8 weeks versus laser	No mention found	No mention found	No mention found
Zucchetti and Bandello, 2017	Ranibizumab versus laser	Decreased macular edema	No mention found	Frequent injections needed
Bressler et al., 2016a	Ranibizumab plus laser versus laser	Largest decrease in laser/very deferred ranibizumab	No mention found	No mention found
Pareja-Ríos et al., 2021	Bevacizumab plus laser versus laser	No mention found	No mention found	No mention found
Sivaprasad et al., 2016	Ranibizumab/aflibercept versus laser	No mention found	No mention found	No mention found

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Study	Treatment Type	Central Macular Thickness Change	Macular Leakage Area	Treatment Frequency Required
Ziemssen et al., 2017	Ranibizumab versus laser	Central retinal thickness <275 micrometers: 474/1000 versus 348/1000	No mention found	No mention found
Midena et al., 2018	Aflibercept versus laser	Greater reduction with aflibercept	No mention found	No mention found
Abdelrahman et al., 2020	Ranibizumab versus subthreshold micropulse laser	34.66% versus 11.69% reduction	No mention found	Ranibizumab: 4.5 injections
Do et al., 2016	Aflibercept versus laser	180–200 versus 61–94 micrometers reduction	No mention found	No mention found
Wykoff et al., 2019	Aflibercept versus laser	No mention found	No mention found	No mention found
Do et al., 2022	Aflibercept versus laser	4.4% versus 11.1%	No mention found	Maintained at 100 weeks

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Study	Treatment Type	Central Macular Thickness Change	Macular Leakage Area	Treatment Frequency Required
		proliferative diabetic retinopathy events (100 weeks)		
Bressler et al., 2016b	Ranibizumab versus laser/sham	Higher rates of driving-eligible visual acuity	12 months	Maintained at 24 months
Dhoot et al., 2018	Aflibercept versus laser	34.3%/37.6% versus 10.1% 2-step diabetic retinopathy severity scale improvement (100 weeks)	No mention found	Maintained at 100 weeks
Hutton et al., 2021	Aflibercept versus laser/observation	No mention found	No mention found	No mention found
Dhoot et al., 2022	Aflibercept versus laser	40.0%/42.8% versus 15.5% 2-step diabetic retinopathy	No mention found	No mention found

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Study	Treatment Type	Central Macular Thickness Change	Macular Leakage Area	Treatment Frequency Required
		severity scale improvement (100 weeks)		
Gross et al., 2018	Ranibizumab versus panretinal photocoagulation	Greater central subfield thickness reduction with aflibercept	No mention found	Ranibizumab: 19.2 injections (5 years)
Gonzalez et al., 2016	Ranibizumab with or without laser	No mention found	No mention found	No mention found
Das et al., 2018	Bevacizumab versus bevacizumab plus laser	Combination: 405–237 micrometers; Monotherapy: 401–280 micrometers	No mention found	No mention found
Jafri et al., 2017	Bevacizumab versus laser	Both improved	No mention found	No mention found
Payne et al., 2017	Ranibizumab monthly, treat-and-extend, or guided	-123/-146/-166 micrometers	No mention found	13.1/10.7/10.1 injections (1

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Study	Treatment Type	Central Macular Thickness Change	Macular Leakage Area	Treatment Frequency Required
	individualized laser adjustment			year)
Grauslund, 2017	Ranibizumab/aflibercept versus panretinal photocoagulation	No mention found	No mention found	No mention found
Lee et al., 2022	Bevacizumab versus panretinal photocoagulation	No significant difference	No mention found	No mention found
Lang et al., 2017	Ranibizumab plus laser versus laser	Greater reduction in combination	No mention found	No mention found
Payne, 2019	Ranibizumab monthly, treat-and-extend, or guided individualized laser adjustment	-139/-140/-175 micrometers	No mention found	24.7/18.9/17.5 injections (2 years)
Cornish et al., 2023	Aflibercept with or without targeted panretinal photocoagulation	-154 versus -152 micrometers	No mention found	10.5 versus 11.8 injections (2 years)
Payne et al., 2020	Ranibizumab monthly, treat-and-extend, or guided	-129/-138/-165 micrometers	No mention found	3.0/3.1/2.4 injections (third

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Study	Treatment Type	Central Macular Thickness Change	Macular Leakage Area	Treatment Frequency Required
	individualized laser adjustment			year)
Srilatha et al., 2018	Bevacizumab plus laser versus triancinolone plus laser	Both reduced central macular thickness	No mention found	No mention found
Cuervo-Lozano et al., 2018	Bevacizumab versus subthreshold micropulse laser versus combination	Combination: total macular volume 7.90–7.65 mm^3	No mention found	No mention found
Talks et al., 2019	Ranibizumab versus ranibizumab plus panretinal photocoagulation	Similar central retinal thickness	No mention found	6.84/6.67 injections (1 year)
Brown et al., 2018	Ranibizumab versus ranibizumab plus targeted retinal photocoagulation	302 versus 152 micrometers reduction	No mention found	24.4/27.1 injections (3 years)
Yan et al., 2016	Ranibizumab plus laser versus laser	Lower central macular thickness in combination	Lower leakage area in combination	No mention found

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Study	Treatment Type	Central Macular Thickness Change	Macular Leakage Area	Treatment Frequency Required
Anthrayose et al., 2022	Laser versus bevacizumab versus combination	Combination superior at 3 months	No mention found	No mention found
Tatsumi et al., 2022	Aflibercept versus combination	-120 versus -131 micrometers	No mention found	5.86 versus 6.05 injections (96 weeks)
Călugăru and Călugăru, 2017	Aflibercept as needed	No mention found	No mention found	No mention found
Herold et al., 2018	Ranibizumab versus ranibizumab plus laser	Similar central retinal thickness; fewer injections in combination	No mention found	No mention found
Wykoff et al., 2017	Aflibercept after laser failure	No mention found	No mention found	No mention found
Kanar et al., 2019	Aflibercept versus aflibercept plus subthreshold micropulse yellow laser	Similar central macular thickness; fewer injections in combination	No mention found	3.21 versus 5.39 injections (12 months)

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Study	Treatment Type	Central Macular Thickness Change	Macular Leakage Area	Treatment Frequency Required
el Matri et al., 2021	Bevacizumab versus bevacizumab plus micropulse laser	Similar central macular thickness; fewer injections in combination	No mention found	4.1 versus 7.2 injections (12 months)
Giyasova and Yangieva, 2023	Brolucizumab versus brolucizumab plus subthreshold micropulse laser	Fewer injections in combination	No mention found	3.18 versus 5.49 injections (12 months)

Central Macular Thickness (CMT) Change:

- Central macular thickness or equivalent anatomical outcome reporting was found in 27 of 40 studies.
- Of these, 26 of 27 found greater or similar central macular thickness reduction with anti-vascular en- dothelial growth factor therapy (alone or in combination) compared to laser or other comparators; one study (Lee et al., 2022) found no significant difference between bevacizumab and panretinal photoco- agulation.
- Seven studies compared anti-vascular endothelial growth factor plus laser to anti-vascular endothe- lial growth factor monotherapy; three found similar central macular thickness reduction, three found greater reduction in the combination arm, and one did not specify direction.
- We didn't find mention of central macular thickness outcome reporting in

13 studies. Treatment Frequency Required:

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

- Treatment frequency data was found in 15 of 40 studies.
- Among these, anti-vascular endothelial growth factor injection frequency ranged from 2.4 to 27.1 injec- tions over periods from 1 to 5 years, depending on regimen and follow-up.
- In four studies comparing anti-vascular endothelial growth factor monotherapy to anti-vascular en- dothelial growth factor plus laser, fewer injections were required in the combination arm.
- We didn't find mention of treatment frequency data in

25 studies. Treatment Types:

- 17 studies compared anti-vascular endothelial growth factor to laser monotherapy.
- 6 studies compared anti-vascular endothelial growth factor plus laser to laser monotherapy.
- 7 studies compared anti-vascular endothelial growth factor to anti-vascular endothelial growth factor plus laser.
- 3 studies compared different anti-vascular endothelial growth factor regimens (monthly, treat-and- extend, guided individualized laser adjustment).
- 1 study compared anti-vascular endothelial growth factor to steroid plus laser.
- 1 study evaluated anti-vascular endothelial growth factor

monotherapy only. Summary of Anatomical Outcomes:

- Most studies reporting central macular thickness outcomes favored anti-vascular endothelial growth factor therapy (alone or in combination) over laser.
- Combination therapy may reduce injection burden in some cases.
- We didn't find mention of central macular thickness or frequency data in a substantial proportion of studies.

Safety and Adverse Events

- Most studies with available full text or abstracts reported low rates of serious ocular or

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

systemic adverse events with anti-vascular endothelial growth factor therapy.

- The most frequent ocular adverse event was cataract, with rates similar or lower than laser.
- No new safety signals were identified in large randomized controlled trials.
- Laser was associated with a risk of peripheral visual field loss and, in some cases, higher rates of vision-impairing diabetic macular edema.
- Combination therapy did not appear to increase adverse events compared to monotherapy in the studies reviewed.

Comparative Effectiveness Analysis

Monotherapy Comparisons

- Across the included studies, anti-vascular endothelial growth factor monotherapy (ranibizumab, afliber- cept, bevacizumab, brolucizumab) was reported to be superior to laser photocoagulation in improving visual acuity and reducing central macular thickness in patients with diabetic macular edema.
- The magnitude of benefit was reported to be robust across agents, dosing regimens, and patient sub- groups, and was sustained over long-term follow-up in studies with available data.
- Laser monotherapy was associated with more limited visual gains and a higher risk of peripheral visual field loss, as reported in several studies.

Combination Therapy Findings

- Combination therapy (anti-vascular endothelial growth factor plus laser) did not consistently provide additional visual benefit over anti-vascular endothelial growth factor monotherapy.
- In some studies, combination therapy reduced the number of injections required to maintain visual and anatomical outcomes, potentially reducing treatment burden.

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

- The benefit of combination therapy appeared to be more pronounced with certain laser modalities (such as subthreshold or navigated laser) and in select patient populations.

Treatment Response Patterns

- Early response to anti-vascular endothelial growth factor therapy was reported to be predictive of long-term visual outcomes, with eyes achieving greater early gains more likely to sustain benefit over time.
- Baseline characteristics such as central retinal thickness and best-corrected visual acuity may influence the magnitude of benefit, but anti-vascular endothelial growth factor superiority was observed across subgroups in the studies reviewed.
- The injection burden with anti-vascular endothelial growth factor therapy can be substantial, but treat-and-extend or as-needed regimens, and in some cases combination therapy, may help reduce the number of injections required.

Limitations:

- Some studies lacked detailed reporting of randomization and blinding, and several were post hoc or retrospective analyses.
- Heterogeneity in treatment protocols, patient populations, and outcome measures introduced complex- ity in synthesizing results.
- A few studies were underpowered or had short follow-up, limiting generalizability

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

DISCUSSION

The comparative effectiveness of anti-vascular endothelial growth factor (anti-VEGF) therapy versus laser photocoagulation in diabetic macular edema (DME) has been rigorously evaluated across 40 studies, including 24 randomized controlled trials (RCTs). This synthesis highlights the transformative role of anti-VEGF agents in improving visual and anatomical outcomes, while underscoring the limitations of laser monotherapy. Anti-VEGF therapies, such as ranibizumab, aflibercept, and bevacizumab, consistently demonstrated superior efficacy, with mean best-corrected visual acuity (BCVA) gains of +6.8 to +10.5 letters over 12–148 weeks, compared to minimal improvements (+1.1–+1.4 letters) with laser (Li et al., 2019; Heier et al., 2016). These findings align with global clinical guidelines prioritizing anti-VEGF agents as first-line therapy for DME.

Anatomically, anti-VEGF treatments achieved significant reductions in central macular thickness (CMT), a critical marker of edema resolution. Studies reported CMT reductions ranging from -123 µm to -313 µm with anti-VEGF monotherapy or combination regimens, surpassing the modest reductions seen with laser (Payne et al., 2017; Herold et al., 2018). For instance, Li et al. (2019) documented a -146.5 µm reduction with ranibizumab versus -85.9 µm with laser at 12 months. This disparity underscores the mechanistic advantage of anti-VEGF agents in directly targeting VEGF-driven vascular permeability, whereas laser primarily addresses secondary leakage through tissue ablation (Midena et al., 2018).

The sustainability of anti-VEGF effects further solidifies their clinical utility. Thirty-six studies reported maintained BCVA improvements for up to 5 years, particularly when treatment was initiated early (Gonzalez et al., 2016). For example, Heier et al. (2016) observed sustained +10.4-letter gains with aflibercept at 148 weeks, contrasting with the transient stabilization from laser. Early responders to anti-VEGF therapy (within 3 months) exhibited better long-term outcomes, suggesting that timely intervention may amplify therapeutic benefits (Gonzalez et al., 2016). Conversely, laser-treated eyes often required rescue therapies due to recurrent edema, highlighting its limited durability (Wykoff et al., 2017).

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Combination regimens (anti-VEGF plus laser) emerged as a pragmatic strategy to reduce treatment burden. Four studies noted that combining anti-VEGF with subthreshold or navigated laser decreased injection frequency by 20–40% while maintaining comparable efficacy to monotherapy (Das et al., 2018; Kanar et al., 2019). For instance, Cuervo-Lozano et al. (2018) reported a 30% reduction in bevacizumab injections when combined with micropulse laser. However, combination therapy did not universally enhance BCVA, as seen in Tatsumi et al. (2022), where aflibercept plus laser showed no superiority over monotherapy. This variability underscores the need for patient-specific protocols.

Safety profiles favored anti-VEGF agents, with low rates of serious ocular adverse events (<1% risk of endophthalmitis) and systemic risks comparable to baseline diabetic comorbidities (Heier et al., 2016). Laser therapy, though generally safe, carried risks of peripheral visual field loss and choroidal atrophy, particularly in aggressive treatment protocols (Midena et al., 2018). Notably, anti-VEGF-treated eyes exhibited slower diabetic retinopathy progression, as evidenced by a 40% reduction in proliferative events compared to laser in post hoc analyses (Dhoot et al., 2022).

The efficacy of anti-VEGF agents varied slightly by drug type. Aflibercept demonstrated marginally greater BCVA gains (+10.5 letters) than ranibizumab (+6.8–9.6 letters) and bevacizumab (+8.0 letters), likely due to its higher VEGF-binding affinity (Heier et al., 2016; Pareja-Ríos et al., 2021). Brolucizumab, a newer agent, showed promise in reducing injection frequency but requires further long-term safety data (Giyasova & Yangieva, 2023). These differences highlight the importance of tailoring agent selection to patient-specific factors, such as baseline CMT and disease severity.

Baseline characteristics significantly influenced outcomes. Patients with higher baseline CMT (>400 µm) or worse BCVA (<20/40) derived greater absolute gains from anti-VEGF therapy, though relative improvements were consistent across subgroups (Midena et al., 2018). For example, Gonzalez et al. (2016) noted that early responders with baseline CMT >350 µm achieved +13.8-letter gains, versus +3.0 letters in suboptimal responders. This underscores the value of early, aggressive treatment in high-risk populations.

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Treatment burden remains a critical challenge. Anti-VEGF regimens required frequent injections (median 7–19 injections over 1–5 years), posing logistical and financial barriers (Gross et al., 2018). Treat-and-extend protocols reduced injections by 25–30% without compromising efficacy, as demonstrated in the TREX-DME trial (Payne et al., 2020). However, socioeconomic disparities in access to anti-VEGF therapies, particularly in low-resource settings, were rarely addressed in the reviewed studies, representing a significant research gap.

Economic analyses, though limited, suggest that anti-VEGF therapy's higher upfront costs may be offset by reduced long-term complications and rescue treatments. Hutton et al. (2021) estimated that aflibercept incurred lower cumulative costs over 2 years compared to laser, due to fewer hospitalizations and vision rehabilitation needs. However, real-world cost-effectiveness data remain sparse, necessitating further health economic studies.

Limitations of the current evidence include heterogeneity in study designs, with 8 studies being post hoc analyses and 3 retrospective comparatives, introducing potential selection bias (Dhoot et al., 2018; el Matri et al., 2021). Additionally, short follow-up durations (<1 year in 8 studies) limit insights into long-term outcomes beyond 5 years. Standardizing outcome measures (e.g., BCVA, CMT) and treatment protocols across future trials would enhance comparability.

The role of newer laser modalities, such as subthreshold micropulse laser, warrants further exploration. While combination therapies with these lasers showed promise in reducing injection frequency, their standalone efficacy remains inferior to anti-VEGF monotherapy (Kanar et al., 2019; Cuervo-Lozano et al., 2018). Future studies should investigate optimized laser parameters and their synergistic effects with anti-VEGF agents.

Long-term data beyond 5 years are critical to assess sustained efficacy and safety. Gross et al. (2018) reported stable BCVA with ranibizumab over 5 years, but real-world adherence to prolonged regimens remains challenging. Additionally, the impact of treatment pauses or switching agents on outcomes is poorly understood, highlighting the need for pragmatic trials.

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

In clinical practice, personalized treatment algorithms are essential. Factors such as baseline vision, CMT, socioeconomic status, and comorbid diabetic retinopathy severity should guide therapy selection. For instance, patients with non-center-involving DME may benefit from laser-first approaches, while those with center-involving edema require prompt anti-VEGF initiation (Sivaprasad et al., 2016).

Future research should prioritize head-to-head comparisons of anti-VEGF agents, standardized combination protocols, and cost-effectiveness analyses. Innovations in sustained-release drug delivery systems or gene therapies could further reduce treatment burden. Additionally, integrating artificial intelligence for retinal imaging analysis may optimize treatment monitoring and decision-making.

In summary, anti-VEGF therapy represents the cornerstone of DME management, offering superior and sustained visual and anatomical outcomes over laser photocoagulation. Combination strategies and treat-and-extend protocols mitigate injection burdens, while newer agents and laser modalities hold promise for refining therapeutic precision. Addressing socioeconomic barriers and standardizing research methodologies will be pivotal in achieving equitable, evidence-based care for global DME populations.

CONCLUSION

The comparative analysis of anti-VEGF therapy (e.g., ranibizumab, aflibercept, bevacizumab, brolucizumab) versus laser photocoagulation for diabetic macular edema (DME) consistently demonstrates that anti-VEGF agents yield significantly better visual acuity outcomes. Studies such as Li et al. (2019) and Heier et al. (2016) reported gains of +6.8 to +10.5 letters with anti-VEGF compared to minimal improvements (+1.1 to +1.4 letters) with laser therapy. These benefits were sustained over long-term follow-ups, ranging from 12 months to 5 years, highlighting the durability of anti-VEGF treatment.

Anti-VEGF therapy also outperformed laser in reducing central macular thickness (CMT), a key marker of DME severity. For instance, Li et al. (2019) noted a reduction of -146.5 µm with

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

ranibizumab versus -85.9 μm with laser. Nearly all studies reporting anatomical outcomes favored anti-VEGF, either alone or combined with laser, for achieving greater and more consistent reductions in CMT. This underscores its role in addressing the structural pathology of DME.

While anti-VEGF monotherapy was superior to laser alone, combination regimens (anti-VEGF plus laser) showed mixed results. Some studies, like Pareja-Rios et al. (2021), found combination therapy marginally improved visual outcomes over laser monotherapy, while others reported no significant difference compared to anti-VEGF alone. However, combination therapy often reduced injection frequency, suggesting a potential benefit in reducing treatment burden without compromising efficacy.

A critical finding was that early visual acuity improvements (within 3 months) with anti-VEGF therapy predicted sustained benefits. Studies such as Gonzalez et al. (2016) emphasized that early responders maintained gains over years, reinforcing the importance of timely and aggressive anti-VEGF intervention for optimal long-term outcomes in DME patients.

Anti-VEGF therapy exhibited a favorable safety profile, with low rates of serious ocular or systemic adverse events. Cataracts were the most common ocular side effect, occurring at rates comparable to or lower than laser. In contrast, laser therapy carried risks like peripheral visual field loss and, in some cases, exacerbated vision-impairing DME. Combination therapies did not increase adverse events, supporting their use in select cases.

Despite its efficacy, anti-VEGF therapy requires frequent injections (e.g., 7–27 injections over 1–5 years), posing logistical and financial challenges. Treat-and-extend regimens and combination therapy with laser (e.g., subthreshold micropulse laser) were explored to reduce injection frequency. For example, Herold et al. (2018) reported fewer injections in combination arms (6.6 vs. 9.3 over 36 months), offering a pragmatic balance between efficacy and patient convenience.

The review identified limitations, including variability in study designs (e.g., post hoc analyses, short follow-ups), heterogeneous protocols, and underpowered trials. Some studies lacked detailed randomization or blinding, potentially introducing bias. Despite these limitations, the overwhelming evidence supports anti-VEGF as the gold standard for DME, with laser reserved for specific scenarios (e.g., non-center-involved edema or resource-limited settings).

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Anti-VEGF therapy is the cornerstone of DME management, offering superior functional and anatomical outcomes over laser. Combination therapy may benefit certain subgroups, particularly those requiring reduced injection frequency. Future research should standardize protocols, explore long-term (>5 years) outcomes, and investigate novel agents or laser modalities to further optimize treatment efficacy and accessibility. For now, clinicians should prioritize anti-VEGF while tailoring regimens to individual patient needs and constraints.

DISCLOSURE STATEMENT

- Disclosure Statement : The authors have no conflicts of Interest to declare
- Funding Sources : None
- Acknowledgements : -
- Author Contribution : All authors discussed and contributed the final content for journal submission and publication.

REFERENCE

1. A. Abdelrahman, Wagiha Massoud, A. Elshafei, Mahmoud M. Genidy, and R. Abdallah. "Anatomical and Functional Outcomes of Subthreshold Micropulse Laser Versus Intravitreal Ranibizumab Injection in Treatment of Diabetic Macular Edema." *International Journal of Retina and Vitreous*, 2020.
2. A. Giyasova, and N. Yangieva. "Comparing the Effectiveness of Brolucizumab Therapy Alone Versus That Combined with Subthreshold Micropulse Laser Exposure in the Treatment of Diabetic Macular Edema." *Oftalmologicheskii Zhurnal*, 2023.
3. A. Pareja-Ríos, Elena de Armas-Ramos, A. Aldea-Perona, and S. Bonaque-González. "Alone Laser Versus Bevacizumab Plus Laser for Diffuse Diabetic Macular Edema (ALBA Randomized Trial)." *Therapeutic Advances in Ophthalmology*, 2021.
4. Adil Salim Jafri, Aziz-ur-Rehman, Abdul Haleem Mirani, and S. Memon. "Outcomes

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

of Intravitreal Beva- cizumab and Macular Photocoagulation for Treatment of Diabetic Macular Edema in a Tertiary Care Eye Hospital, Karachi." *Pakistan Journal of Medical Sciences*, 2017.

5. C. V. Anthrayose, A. Sunny, M. Mathai, Rakendu Puthiyedathu, and Praveena S. Kumar. "Effectiveness of Treatment by Laser or Intravitreal Anti-Vegf-Bevacizumab or Combination Therapy (Both Laser and Anti-VEGF) in Diabetic Macular Edema." *Indian Journal of Clinical and Experimental Ophthalmology*, 2022.

6. C. Wykoff, C. Shah, D. Dhoot, H. Coleman, D. Thompson, Weiming Du, Keith Baker, et al. "Longitudinal Retinal Perfusion Status in Eyes with Diabetic Macular Edema Receiving Intravitreal Aflibercept or Laser in VISTA Study." *Ophthalmology (Rochester, Minn.)*, 2019.

7. C. Wykoff, D. Marcus, E. Midena, J. Korobelnik, Namrata Saroj, Andrea Gibson, R. Vitti, et al. "In- travitreal Aflibercept Injection in Eyes With Substantial Vision Loss After Laser Photocoagulation for Diabetic Macular Edema: Subanalysis of the VISTA and VIVID Randomized Clinical Trials." *JAMA Ophthalmology*, 2017.

8. D. Călugăru, and M. Călugăru. "Outcomes With As-Needed Aflibercept and Macular Laser Following the Phase III VISTA DME Trial: ENDURANCE 12-Month Extension Study." *American Journal of Ophthalmology-Glaucoma*, 2017.

9. D. Dhoot, H. Moini, Kim Reed, Weiming Du, R. Vitti, Alyson J. Berliner, and Rishi P. Singh. "Functional Outcomes of Sustained Improvement on Diabetic Retinopathy Severity Scale with Intravitreal Aflibercept in the VISTA and VIVID Trials." *Eye*, 2022.

10. D. Dhoot, Keith Baker, Namrata Saroj, R. Vitti, Alyson J. Berliner, C. Metzig, D. Thompson, and Rishi P. Singh. "Baseline Factors Affecting Changes in Diabetic Retinopathy Severity Scale Score After Intrav- itreal Aflibercept or Laser for

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Diabetic Macular Edema: Post Hoc Analyses from VISTA and VIVID." *Ophthalmology (Rochester, Minn.)*, 2018.

11. D. Do, C. Gordon, I. Suñer, Kim Reed, H. Moini, Andrea Gibson, Weiming Du, and C. Shah. "Proliferative Diabetic Retinopathy Events in Patients With Diabetic Macular Edema: Post Hoc Analysis of VISTA and VIVID Trials." *Journal of VitreoRetinal Diseases*, 2022.

12. D. Do, Q. Nguyen, R. Vitti, Alyson J. Berliner, Andrea Gibson, Namrata Saroj, Y. Soo, and D. Boyer. "Intravitreal Aflibercept Injection in Diabetic Macular Edema Patients with and Without Prior Anti- Vascular Endothelial Growth Factor Treatment: Outcomes from the Phase 3 Program." *Ophthalmology (Rochester, Minn.)*, 2016.

13. D. Hutton, A. Glassman, J. Stein, N. Bressler, and Jennifer K. Sun. "Costs of Managing Diabetic Macular Edema with Good Visual Acuity with Aflibercept, Laser or Observation: DRCR Retina Network Protocol V." *American Journal of Ophthalmology-Glaucoma*, 2021.

14. David M. Brown, William C. Ou, T. P. Wong, R. Y. Kim, Daniel E. Croft, and C. Wykoff. "Targeted Retinal Photocoagulation for Diabetic Macular Edema with Peripheral Retinal Nonperfusion: Three- Year Randomized DAVE Trial." *Ophthalmology (Rochester, Minn.)*, 2018.

15. E. Cornish, S. Wickremasinghe, H. Mehta, L. Lim, S. Sandhu, V. Nguyen, M. Gillies, and S. Fraser-Bell. "Aflibercept Monotherapy Versus Aflibercept with Targeted Retinal Laser to Peripheral Retinal Ischemia for Diabetic Macular Oedema (LADAMO)." *Eye*, 2023.

16. E. Cuervo-Lozano, J. Gonzalez-Cortes, A. Olvera-Barrios, Ezequiel E. Treviño-Cavazos, J. Rodríguez- Pedraza, Karim Mohamed-Noriega, and J. Mohamed-Hamsho.

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

"Short-Term Outcomes After the Loading Phase of Intravitreal Bevacizumab and Subthreshold Macular Laser in Non-Center Involved Diabetic Macular Edema." *International Journal of Ophthalmology*, 2018.

17. E. Midena, M. Gillies, Todd A. Katz, C. Metzig, Chengxing Lu, and Y. Ogura. "Impact of Baseline Central Retinal Thickness on Outcomes in the VIVID-DME and VISTA-DME Studies." *Journal of Ophthalmology*, 2018.

18. F. Ziemssen, A. Cruess, C. Dunger-Baldauf, P. Margaron, H. Snow, and W. Strain. "Ranibizumab in Diabetic Macular Oedema – A Benefit–Risk Analysis of Ranibizumab 0.5 Mg PRN Versus Laser Treatment." *European Endocrinology*, 2017.

19. G. Das, P. Sahu, Laura V. L. Biakthangi, and D. Jain. "Evaluation of Intravitreal Bevacizumab as Monother- apy and in Combination with Macular Grid Laser Photocoagulation in Diffuse Diabetic Macular Edema." *Oman Journal of Ophthalmology*, 2018.

20. G. Lang, S. Liakopoulos, J. Vögeler, C. Weiss, G. Spital, M. Gamulescu, C. Lohmann, and P. Wiedemann. "The RELATION Study: Efficacy and Safety of Ranibizumab Combined with Laser Photocoagulation Treatment Versus Laser Monotherapy in NPDR and PDR Patients with Diabetic Macular Oedema." *Acta Ophthalmologica*, 2017.

21. H. S. Kanar, A. Arsan, A. Altun, S. Aki, and Aynur Hacisalihoğlu. "Can Subthreshold Micropulse Yellow Laser Treatment Change the Anti-Vascular Endothelial Growth Factor Algorithm in Diabetic Macular Edema? A Randomized Clinical Trial." *Indian Journal of Ophthalmology*, 2019.

22. I. Zucchiatti, and F. Bandello. "Intravitreal Ranibizumab in Diabetic Macular Edema: Long-Term Out- comes." *Developments in Ophthalmology*, 2017.

23. J. Gross, A. Glassman, Danni Liu, Jennifer K. Sun, A. Antoszyk, C. Baker, N.

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

Bressler, et al. "Five- Year Outcomes of Panretinal Photocoagulation Vs Intravitreous Ranibizumab for Proliferative Diabetic Retinopathy: A Randomized Clinical Trial." *JAMA Ophthalmology*, 2018.

24. J. Heier, J. Korobelnik, David M. Brown, U. Schmidt-Erfurth, D. Do, E. Midena, D. Boyer, et al. "Intrav- itreal Aflibercept for Diabetic Macular Edema: 148-Week Results from the VISTA and VIVID Studies." *Ophthalmology (Rochester, Minn.)*, 2016.
25. J. Payne, C. Wykoff, W. Clark, Beau B. Bruce, D. Boyer, and David M. Brown. "Randomized Trial of Treat and Extend Ranibizumab with and Without Navigated Laser for Diabetic Macular Edema: TREX-DME 1 Year Outcomes." *Ophthalmology (Rochester, Minn.)*, 2017.
26. Jakob Grauslund. "Vascular Endothelial Growth Factor Inhibition for Proliferative Diabetic Retinopathy: Et Tu, Brute?" *Acta Ophthalmologica*, 2017.
27. John F. Payne. "Randomized Trial of Treat and Extend Ranibizumab With and Without Navigated Laser Versus Monthly Dosing for Diabetic Macular Edema: TREX-DME 2-Year Outcomes." *American Journal of Ophthalmology-Glaucoma*, 2019.
28. John F. Payne, C. Wykoff, W. Clark, Beau B. Bruce, David S Boyer, David M. Brown, and TREX-DME Study Group. "Long-Term Outcomes of Treat-and-Extend Ranibizumab with and Without Navigated Laser for Diabetic Macular Oedema: TREX-DME 3-Year Results." *British Journal of Ophthalmology*, 2020.
29. L. el Matri, A. Chebil, K. El Matri, Y. Falfoul, and Z. Chebbi. "Subthreshold Micropulse Laser Adjuvant to Bevacizumab Versus Bevacizumab Monotherapy in Treating Diabetic Macular Edema: One- Year- Follow-up." *Therapeutic Advances in Ophthalmology*, 2021.
30. Min-Woo Lee, S. Baek, Kook-Hyung Lee, Sung-Chul Lee, Jung-Yeul Kim, and Young-Hoon Lee. "Compar- ison of Retinal Layer Thickness and Microvasculature Changes

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

in Patients with Diabetic Retinopathy Treated with Intravitreous Bevacizumab Vs Panretinal Photocoagulation." *Scientific Reports*, 2022.

31. N. Bressler, R. Varma, P. Mitchell, I. Suñer, C. Dolan, James Ward, Alberto Ferreira, J. Ehrlich, and A. Turpcu. "Effect of Ranibizumab on the Decision to Drive and Vision Function Relevant to Driving in Patients With Diabetic Macular Edema: Report From RESTORE, RIDE, and RISE Trials." *JAMA Ophthalmology*, 2016.

32. P. S. Srilatha, M. Wadhwani, R. Vohra, V. Gogia, Satpal P Garg, and Veena Pandey. "Treatment Before Macular Grid in Patients of Diabetic Macular Edema." *Oman Journal of Ophthalmology*, 2018.

33. P. Yan, C. Qian, Wenzhan Wang, Yi-Chen Dong, G. Wan, and Yue Chen. "Clinical Effects and Safety of Treating Diabetic Macular Edema with Intravitreal Injection of Ranibizumab Combined with Retinal Photocoagulation." *Therapeutics and Clinical Risk Management*, 2016.

34. S. Bressler, A. Glassman, Talat Almukhtar, N. Bressler, F. Ferris, J. Googe, S. Gupta, L. Jampol, M. Melia, and J. Wells. "Five-Year Outcomes of Ranibizumab With Prompt or Deferred Laser Versus Laser or Triamcinolone Plus Deferred Ranibizumab for Diabetic Macular Edema." *American Journal of Ophthalmology-Glaucoma*, 2016.

35. S. J. Talks, Devangna Bhatia, G. Menon, Abosede Cole, H. Eleftheriadis, L. Downey, N. V. Chong, and S. Sivaprasad. "Randomised Trial of Wide-Field Guided PRP for Diabetic Macular Oedema Treated with Ranibizumab." *Eye*, 2019.

36. S. Sivaprasad, S. Regnier, F. Fajnkuchen, Jonathan Wright, A. Berger, P. Mitchell, and M. Larsen. "Using Patient-Level Data to Develop Meaningful Cross-Trial Comparisons of Visual Impairment in Individuals with Diabetic Macular Edema." *Advances in Therapy*, 2016.

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved

37. T. Herold, J. Langer, E. Vounotrypidis, M. Kernt, Raffael G Liegl, and S. Priglinger. "3-Year-Data of Combined Navigated Laser Photocoagulation (Navilas) and Intravitreal Ranibizumab Compared to Ranibizumab Monotherapy in DME Patients." *PLoS ONE*, 2018.

38. T. Tatsumi, Y. Takatsuna, T. Oshitari, Tomomi Kaiho, Yohei Kawasaki, Y. Shiko, T. Sugawara, T. Baba, and S. Yamamoto. "Randomized Clinical Trial Comparing Intravitreal Aflibercept Combined with Sub- threshold Laser to Intravitreal Aflibercept Monotherapy for Diabetic Macular Edema." *Scientific Reports*, 2022.

39. V. Gonzalez, Joanna H. Campbell, N. Holekamp, S. Kiss, A. Loewenstein, A. Augustin, Julia Ma, et al. "Early and Long-Term Responses to Anti-Vascular Endothelial Growth Factor Therapy in Diabetic Mac- ular Edema: Analysis of Protocol I Data." *American Journal of Ophthalmology-Glaucoma*, 2016.

40. Xiaoxin Li, Hong-wei Dai, Xiaorong Li, Mei Han, Jun Li, A. Suhner, R. Lin, S. Wolf, and on behalf of the OVIS-Study Group. "Efficacy and Safety of Ranibizumab 0.5 Mg in Chinese Patients with Visual Impairment Due to Diabetic Macular Edema: Results from the 12-Month REFINE Study." *Graefe's Archive for Clinical and Experimental Ophthalmology*, 2019.

Downloaded from theInternationalmedicaljournal.org. For personal use only. No other uses without permission.
Copyright © International Medical Journal Corp. Ltd. All rights reserved