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CADTH RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

Anti–Vascular Endothelial Growth Factor Drugs for Retinal Conditions: Comparative Clinical Effectiveness and Guidelines

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Research Questions

1. What is the comparative clinical effectiveness of anti-vascular endothelial growth factor drugs for the treatment of retinal conditions?
2. What are the evidence-based guidelines regarding the use of anti-vascular endothelial growth factor drugs for the treatment of retinal conditions?

Key Findings

One overview of systematic reviews[1],16 systematic reviews (with meta-analyses[2-5,9-13,22,23] and network meta-analyses[8,16,17,20,21]), five meta-analyses[6,7,15,18,19] and one network meta-anaylsis[14] were identified regarding the comparative clinical effectiveness of anti-vascular endothelial growth factor drugs for the treatment of retinal conditions. In addition, one evidence-based guideline was identified regarding the use of anti-vascular endothelial growth factor drugs for the treatment of retinal conditions.

Methods

A limited literature search was conducted by an information specialist on key resources including Ovid Medline, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were anti–vascular endothelial growth factor drugs and retinal diseases. Search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or network meta-analyses, randomized controlled trials or controlled clinical trials or guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2015 and November 6, 2019. Internet links were provided, where available.

Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Table 1:Selection Criteria

Populations	Adult patients with wet age-related macular degeneration, diabetic macular edema, retinal vein occlusion, or choroidal neovascularization due to pathologic myopia
Interventions	Anti-vascular endothelial growth factor drugs
Comparators	Any other anti-vascular endothelial growth factor drug
Outcomes	Q1: Clinical effectiveness (e.g., change in best-corrected visual acuity, vision-related function, mortality, safety [e.g., ophthalmic-related or cardio-thromboembolic adverse events]) Q2: Evidence-based guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, evidence-based guidelines

Results

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by evidence-based guidelines. Additionally, due to the abundance of literature retrieved, randomized controlled trials were not included in this report.

One overview of systematic reviews,[1] 16 systematic reviews (with meta-analyses[2-5,9-13,22,23] and network meta-analyses[8,16,17,20,21]), five meta-analyses[6,7,15,18,19] and one network meta-analysis[14] were identified regarding the comparative clinical effectiveness of anti-vascular endothelial growth factor drugs for the treatment of retinal conditions. In addition, one evidence-based guideline[24] was identified regarding the use of anti-vascular endothelial growth factor drugs for the treatment of retinal conditions.

Additional references of potential interest are provided in the appendix.

Overall Summary of Findings

Overall one overview of systematic reviews,[1] 16 systematic reviews (with meta-analyses[2-5,9-13,22,23] and network meta-analyses[8,16,17,20,21]), five meta-analyses[6,7,15,18,19] and one network meta-anaylsis[14] were identified regarding the comparative clinical effectiveness of anti-vascular endothelial growth factor (anti-VEGF) drugs for the treatment of retinal conditions. Most of these studies concluded that there was no statistically significant difference in clinical effectiveness between anti-VEGF therapies regardless of the population of interest.[3,4,7,8,11-13,19,21-23] However, Nguyen et al., 2018[5] found that intravitreal bevacizumab had a higher rate of serious systemic adverse events compared to intravitreal ranibizumab in patients with age-related macular degeneration. Furthermore, Wang et al., 2018[6] found intravitreal conbercept improved best-corrected visual acuity compared to intravitreal ranibizumab in patients with age-related macular degeneration. Finally, Zhang et al., 2017[9] found that intravitreal aflibercept was significantly more effective than intravitreal ranibizumab in patients with age-related macular degeneration who had initial reduced visual acuity, and Muston et al., 2018[14] found that aflibercept (2 mg bimonthly after 5 initial doses) was significantly more effective than 0.5 mg ranibizumab as-needed but not significantly different from a ranibizumab treat-and-extend regimen in patients with diabetic macular edema. Detailed study characteristics are provided in Table 2.

One evidence-based guideline[24] was identified regarding the use of anti-VEGF drugs for the treatment of retinal conditions. The National Institute for Health and Care Excellence (NICE) guideline recommends the use of anti-VEGF drugs for the treatment of eyes with late (wet, active) age-related macular degeneration within a visual acuity range between 6/12 and 6/96.[24] The guideline states that there is no clinically significant difference in effectiveness or safety between ranibizumab, bevacizumab, or aflibercept and recommends the use of ranibizumab or aflibercept as options for the treatment of age-related macular degeneration.[24] On the other hand, NICE recommends against the use of pegaptanib for the treatment of age-related macular degeneration.[24]

Table 2: Study and Patient Characteristics of Included Studies

First Author, Year	Study Characteristics	Population	Intervention vs. Comparator	Relevant Outcomes Assessed	Conclusions
Overview of Systematic Reviews					
Thulliez, 2018[1]	• Overview of SRs and MAs • 11 SRs • N= NR	• Patients with neovascular age-related macular degeneration, diabetic macular edema, or retinal vein occlusion	• Intravitreal bevacizumab vs intravitreal ranibizumab	• Systemic adverse events	• Comparable risk of systemic adverse events with intravitreal bevacizumab and intravitreal ranibizumab
Systematic Reviews and Meta-Analyses of Various Patient Populations					
Low, 2019[2]	• SR and MA • 17 studies • N= NR	• Patients with neovascular age-related macular degeneration, diabetic macular edema, or central/branch retinal vein occlusion	• Intravitreal aflibercept vs intravitreal bevacizumab vs intravitreal ranibizumab	• BCVA • Ocular or systemic adverse events	• No clinically important difference in BCVA (≥5 letters) between intravitreal aflibercept, intravitreal bevacizumab and intravitreal ranibizumab
Pham, 2019[3]	• SR and MA • 19 RCTs • N= 7,459	• Patients with choroidal neovascular age-related macular degeneration, diabetic macular edema, macular edema due to retinal vein occlusion or myopic choroidal neovascularization	• Intravitreal aflibercept vs intravitreal bevacizumab vs intravitreal ranibizumab	• Vision gain • Serious systemic adverse events	• No statistically significant difference in vision gain between intravitreal bevacizumab and intravitreal ranibizumab in patients with choroidal neovascular age-related macular degeneration, diabetic macular edema, macular edema due to retinal vein occlusion or myopic choroidal neovascularization • No statistically significant difference in vision gain between intravitreal bevacizumab and intravitreal aflibercept in patients with choroidal neovascular age-related macular degeneration • Statistically significant increase in vision gain at 12 months, but not 24 months, in patients with diabetic macular edema treated with intravitreal aflibercept

First Author, Year	Study Characteristics	Population	Intervention vs. Comparator	Relevant Outcomes Assessed	Conclusions
					compared to intravitreal bevacizumab and intravitreal ranibizumab
Systematic Reviews and Meta-Analyses- Age-Related Macular Degeneration					
Solomon, 2019[4]	• SR and MA • 16 RCTs • N= 6,347	• Patients with neovascular age-related macular degeneration	• Intravitreal bevacizumab vs intravitreal ranibizumab	• BCVA	• No statistically significant difference in BCVA between intravitreal bevacizumab and intravitreal ranibizumab
Nguyen, 2018[5]	• SR and MA • 15 RCTs • N= 8,320	• Patients with neovascular age-related macular degeneration	• Intravitreal aflibercept vs intravitreal bevacizumab vs intravitreal ranibizumab	• BCVA • Serious systemic adverse events	• No statistically significant difference in BCVA between intravitreal bevacizumab and intravitreal ranibizumab • Intravitreal bevacizumab had a higher rate of serious systemic adverse events compared to intravitreal ranibizumab • Comparable change in BCVA between intravitreal aflibercept and intravitreal ranibizumab
Wang, 2018[6]	• MA • Eight RCTs and four NRS • N= 853	• Patients with neovascular age-related macular degeneration	• Intravitreal conbercept vs intravitreal ranibizumab	• BCVA	• Improved BCVA with intravitreal conbercept compared to intravitreal ranibizumab
Bevacizumab-Ranibizumab International Trials G, 2017[7]	• MA • Five studies • N= 3,052	• Patients with neovascular age-related macular degeneration	• Intravitreal bevacizumab vs intravitreal ranibizumab	• Incidence of serious adverse events • Death • Arteriothrombotic events • Events associated with systemic anti-VEGF therapy	• No significant difference in incidence of serious adverse events, death, arteriothrombotic events, or events associated with systemic anti-VEGF therapy between intravitreal bevacizumab and intravitreal ranibizumab
Danyliv, 2017[8]	• SR and NMA • 23 studies • N= NR	• Patients with neovascular age-related macular degeneration	• Intravitreal ranibizumab treat and extend regimen vs intravitreal ranibizumab via a different regimen vs	• BCVA	• No significant difference in BCVA between intravitreal ranibizumab and intravitreal aflibercept

First Author, Year	Study Characteristics	Population	Intervention vs. Comparator	Relevant Outcomes Assessed	Conclusions
			intravitreal aflibercept		
Zhang, 2017[9]	• SR and MA • 18 observational studies • N= NR	• Patients with neovascular age-related macular degeneration	• Intravitreal ranibizumab vs intravitreal aflibercept	• Visual acuity	• No statistically significant difference in logMAR between intravitreal ranibizumab and intravitreal aflibercept at 3, 6, 12, and 24 months • Intravitreal aflibercept significantly more effective compared to intravitreal ranibizumab in patients with initial reduced visual acuity
Mikacic, 2016[10]	• SR and MA • 10 RCTs and three observational studies • N= NR	• Patients with age-related macular degeneration	• Intravitreal bevacizumab vs intravitreal ranibizumab or intravitreal pegaptanib	• All-cause mortality • Vascular mortality • Stroke • Transient ischemic attack • Atherothrombotic events • Venous thromboembolism • Hypertension	• Unclear
Sarwar, 2016[11]	• SR and MA • Two RCTs • N= 2,457	• Patients with neovascular age-related macular degeneration	• Intravitreal aflibercept vs intravitreal ranibizumab	• BCVA • Systemic adverse events • Ocular adverse events	• No statistically significant difference in BCVA between intravitreal aflibercept and intravitreal ranibizumab • Comparable safety profiles with intravitreal aflibercept and intravitreal ranibizumab
Szabo, 2015[12]	• SR and NMA • Five trials • N= NR	• Patients with age-related macular degeneration	• Intravitreal aflibercept vs intravitreal ranibizumab	• BCVA	• No statistically significant difference in BCVA between intravitreal aflibercept and intravitreal ranibizumab
Systematic Reviews and Meta-Analyses- Diabetic Macular Edema					
Liu, 2019[13]	• SR and MA • Five RCTs and four NRS • N= 609	• Patients with diabetic macular edema	• Intravitreal conbercept vs intravitreal ranibizumab	• BCVA • Adverse events	• No statistically significant difference in BCVA or adverse events between intravitreal conbercept and intravitreal ranibizumab
Muston, 2018[14]	• NMA • 13 trials • N= NR	• Patients with diabetic macular edema	• Intravitreal aflibercept bimonthly after 5 initial doses	• BCVA	• Intravitreal aflibercept bimonthly after 5 initial doses significantly improved BCVA compared to

First Author, Year	Study Characteristics	Population	Intervention vs. Comparator	Relevant Outcomes Assessed	Conclusions
			vs intravitreal ranibizumab as needed vs intravitreal ranibizumab treat-and-extend vs laser photocoagulation		intravitreal ranibizumab as needed • No statistically significant difference between intravitreal aflibercept bimonthly after 5 initial doses and intravitreal ranibizumab treat-and-extend regimen
Nguyen, 2018[15]	• MA • Four RCTs • N= NR	• Patients with diabetic macular edema	• Intravitreal aflibercept vs intravitreal bevacizumab vs intravitreal ranibizumab	• NR	• NR
Virgili, 2018[16]	• SR and NMA • 24 studies • N= 6,007	• Patients with diabetic macular edema	• Intravitreal aflibercept vs intravitreal bevacizumab vs intravitreal ranibizumab vs intravitreal pegaptanib vs laser photocoagulation	• Visual acuity	• Unclear
Zhang, 2016[17]	• SR and NMA • 21 studies • N= NR	• Patients with diabetic macular edema	• Intravitreal aflibercept vs intravitreal ranibizumab vs intravitreal triamcinolone combined with laser	• BCVA • Adverse events	• Most significant improvement in BCVA at 12 months with intravitreal aflibercept
Systematic Reviews and Meta-Analyses- Retinal Vein Occlusion					
Spooner, 2019[18]	• MA • 22 studies • N= NR	• Patients with macular edema secondary to branch retinal vein occlusion	• Intravitreal aflibercept vs intravitreal bevacizumab vs intravitreal ranibizumab	• BCVA	• Intravitreal aflibercept, intravitreal bevacizumab and intravitreal ranibizumab therapies comparable in safety and efficacy outcomes in patients with macular edema secondary to branch retinal vein occlusion
Zhong, 2019[19]	• MA with relevant subgroup analysis	• Patients with retinal vein occlusion	• Intravitreal aflibercept vs intravitreal ranibizumab	• Cardiovascular events	• No statistically significant difference in cardiovascular events between Intravitreal

First Author, Year	Study Characteristics	Population	Intervention vs. Comparator	Relevant Outcomes Assessed	Conclusions
	• Eight trials • N= 2,320				aflibercept and intravitreal ranibizumab
Qian, 2018[20]	• SR and NMA • 11 RCTs • N= 2,060	• Patients with macular edema secondary to central retinal vein occlusion	• Intravitreal aflibercept vs intravitreal bevacizumab vs intravitreal ranibizumab vs dexamethasone	• BCVA	• NR
Sangroongruangsri, 2018[21]	• SR and NMA • 11 RCTs • N= 1,830	• Patients with macular edema secondary to retinal vein occlusion	• Intravitreal aflibercept vs intravitreal bevacizumab vs intravitreal ranibizumab	• BCVA	• No statistically significant difference in BCVA between intravitreal aflibercept, intravitreal bevacizumab and intravitreal ranibizumab
Systematic Reviews and Meta-Analyses- Choroidal Neovascularization Secondary to Pathologic Myopia					
Hu, 2019[22]	• SR and MA • Three RCTs • N= NR	• Patients with choroidal neovascularization secondary to pathologic myopia	• Intravitreal bevacizumab vs intravitreal ranibizumab	• BCVA	• No statistically significant difference in BCVA between intravitreal bevacizumab and intravitreal ranibizumab
Zhu, 2016[23]	• SR and MA • Six studies • N= 594	• Patients with choroidal neovascularization secondary to pathological myopia	• Intravitreal bevacizumab vs intravitreal ranibizumab	• Visual acuity	• No statistically significant difference in visual acuity between intravitreal bevacizumab and intravitreal ranibizumab

Anti-VEGF= anti-vascular endothelial growth factor; BCVA= best-corrected visual acuity; CMT= central macular thickness; DME= diabetic macular edema; logMAR= logarithm of minimum angle of resolution; MA= meta-analysis; NMA= network meta-analysis; NR= not reported; NRS= non-randomized studies; RCT= randomized controlled trial; SR= systematic review.

References Summarized

Health Technology Assessments

No literature identified.

Overviews of Systematic Reviews

1. Thulliez M, Angoulvant D, Pisella PJ, Bejan-Angoulvant T. Overview of systematic reviews and meta-analyses on systemic adverse events associated with intravitreal anti-vascular endothelial growth factor medication use. *JAMA Ophthalmol*. 2018 05 01;136(5):557-566.
PubMed: PM29566105

Systematic Reviews and Meta-analyses

Various Patient Populations

2. Low A, Faridi A, Bhavsar KV, et al. Comparative effectiveness and harms of intravitreal antivascular endothelial growth factor agents for three retinal conditions: a systematic review and meta-analysis. *Br J Ophthalmol*. 2019 Apr;103(4):442-451.
PubMed: PM30409915

3. Pham B, Thomas SM, Lillie E, et al. Anti-vascular endothelial growth factor treatment for retinal conditions: a systematic review and meta-analysis. *BMJ Open*. 2019 May 28;9(5):e022031.
PubMed: PM31142516

Age-Related Macular Degeneration

4. Solomon SD, Lindsley K, Vedula SS, Krzystolik MG, Hawkins BS. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. *Cochrane Database Syst Rev*. 2019 03 04;3:CD005139.
PubMed: PM30834517

5. Nguyen CL, Oh LJ, Wong E, Wei J, Chilov M. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration: a meta-analysis of randomized controlled trials. *BMC Ophthalmol*. 2018 May 30;18(1):130.
PubMed: PM29843663

6. Wang L, Zhang C, Hua R. Clinical effectiveness of ranibizumab and conbercept for neovascular age-related macular degeneration: a meta-analysis. *Drug Des Devel Ther*. 2018;12:3625-3633.
PubMed: PM30464394

7. Bevacizumab-Ranibizumab International Trials Group. Serious adverse events with bevacizumab or ranibizumab for age-related macular degeneration: meta-analysis of individual patient data. *Ophthalmol Retina*. 2017 Sep-Oct;1(5):375-381.
PubMed: PM29038796

8. Danyliv A, Glanville J, McCool R, Ferreira A, Skelly A, Jacob RP. The clinical effectiveness of ranibizumab treat and extend regimen in nAMD: systematic review and network meta-analysis. *Adv Ther*. 2017 03;34(3):611-619.
PubMed: PM28188433

9. Zhang Y, Chioreso C, Schweizer ML, Abramoff MD. Effects of aflibercept for neovascular age-related macular degeneration: a systematic review and meta-analysis of observational comparative studies. *Invest Ophthalmol Vis Sci*. 2017 11 01;58(13):5616-5627.
PubMed: PM29094167

10. Mikacic I, Bosnar D. Intravitreal bevacizumab and cardiovascular risk in patients with age-related macular degeneration: systematic review and meta-analysis of randomized controlled trials and observational studies. *Drug Saf*. 2016 06;39(6):517-541.
PubMed: PM26951234

11. Sarwar S, Clearfield E, Soliman MK, et al. Aflibercept for neovascular age-related macular degeneration. *Cochrane Database Syst Rev*. 2016 Feb 08;2:CD011346. PubMed: PM26857947

12. Szabo SM, Hedegaard M, Chan K, et al. Ranibizumab vs. aflibercept for wet age-related macular degeneration: network meta-analysis to understand the value of reduced frequency dosing. *Curr Med Res Opin*. 2015 Nov;31(11):2031-2042. PubMed: PM26296050

Diabetic Macular Edema

13. Liu WS, Li YJ. Comparison of conbercept and ranibizumab for the treatment efficacy of diabetic macular edema: a meta-analysis and systematic review. *Int J Ophthalmol.* 2019;12(9):1479-1486. PubMed: PM31544046

14. Muston D, Korobelnik JF, Reason T, et al. An efficacy comparison of anti-vascular growth factor agents and laser photocoagulation in diabetic macular edema: a network meta-analysis incorporating individual patient-level data. *BMC Ophthalmol*. 2018 Dec 27;18(1):340. PubMed: PM30591022

15. Nguyen CL, Lindsay A, Wong E, Chilov M. Aflibercept for diabetic macular oedema: a meta-analysis of randomized controlled trials. *Int J Ophthalmol.* 2018;11(6):1002-1008. PubMed: PM29977815

16. Virgili G, Parravano M, Evans JR, Gordon I, Lucenteforte E. Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis. *Cochrane Database Syst Rev*. 2018 10 16;10:CD007419. PubMed: PM30325017

17. Zhang L, Wang W, Gao Y, Lan J, Xie L. The efficacy and safety of current treatments in diabetic macular edema: a systematic review and network meta-analysis. *PLoS ONE*. 2016;11(7):e0159553. PubMed: PM27434498

Retinal Vein Occlusion

18. Spooner K, Hong T, Fraser-Bell S, Chang AA. Current outcomes of anti-VEGF therapy in the treatment of macular oedema secondary to branch retinal vein occlusions: a meta-analysis. *Ophthalmologica*. 2019;242(3):163-177. PubMed: PM31158837

19. Zhong P, He M, Yu H, et al. A meta-analysis of cardiovascular events associated with intravitreal anti-VEGF treatment in patients with retinal vein occlusion. *Curr Eye Res*. 2019 Nov 7:1-8. PubMed: PM31670978

20. Qian T, Zhao M, Wan Y, Li M, Xu X. Comparison of the efficacy and safety of drug therapies for macular edema secondary to central retinal vein occlusion. *BMJ Open*. 2018 12 28;8(12):e022700. PubMed: PM30593547

21. Sangroongruangsri S, Ratanapakorn T, Wu O, Anothaisintawee T, Chaikledkaew U. Comparative efficacy of bevacizumab, ranibizumab, and aflibercept for treatment of macular edema secondary to retinal vein occlusion: a systematic review and network meta-analysis. *Expert Rev Clin Pharmacol*. 2018 Sep;11(9):903-916.
PubMed: PM30071180

Choroidal Neovascularization Secondary to Pathologic Myopia

22. Hu Q, Li H, Du Y, He J. Comparison of intravitreal bevacizumab and ranibizumab used for myopic choroidal neovascularization: a PRISMA-compliant systematic review and meta-analysis of randomized controlled trials. *Medicine (Baltimore)*. 2019 Mar;98(12):e14905.
PubMed: PM30896642

23. Zhu Y, Zhang T, Xu G, Peng L. Anti-vascular endothelial growth factor for choroidal neovascularisation in people with pathological myopia. *Cochrane Database Syst Rev*. 2016 12 15;12:CD011160.
PubMed: PM27977064

Guidelines and Recommendations

24. National Institute for Health Care and Excellence. Age-related macular degeneration. *(NICE guideline NG82)* 2018; https://www.nice.org.uk/guidance/ng82. Accessed 2019 Nov 19
See Section 1.5

Appendix — Further Information

Previous CADTH Reports

25. Acute, sustained, intraocular pressure increases following anti-vascular endothelial growth factor treatment for retinal conditions: a review of clinical evidence and guidelines. *(CADTH Rapid response report: summary with critical appraisal).* Ottawa (ON): CADTH; 2019. https://www.cadth.ca/acute-sustained-intraocular-pressure-increases-following-anti-vascular-endothelial-growth-factor. Accessed 2019 Nov 19.

26. Anti-vascular endothelial growth factor drugs for the treatment of retinal conditions: a review of safety. (*CADTH Rapid response report: summary with critical appraisal)*. Ottawa (ON): CADTH; 2017. https://www.cadth.ca/anti-vascular-endothelial-growth-factor-drugs-treatment-retinal-conditions-review-safety. Accessed 2019 Nov 19.

27. Anti–vascular endothelial growth factor drugs for retinal conditions. *(CADTH Therapeutic Review)*. Ottawa (ON): CADTH; 2016. https://www.cadth.ca/anti-vascular-endothelial-growth-factor-drugs-retinal-conditions. Accessed 2019 Nov 19.

Systematic Reviews and Meta-analyses

Unclear Intervention or Comparator

28. Spooner K, Hong T, Fraser-Bell S, Chang A. Current outcomes of anti-VEGF therapy in the treatment of macular edema secondary to central retinal vein occlusions: a systematic review and meta-analysis. *Asia Pac J Ophthalmol (Phila)*. 2019 May-Jun;8(3):236-246.
PubMed: PM31132002

29. Zhang J, Liang Y, Xie J, et al. Conbercept for patients with age-related macular degeneration: a systematic review. *BMC Ophthalmol*. 2018 Jun 15;18(1):142.
PubMed: PM29902977

30. Arnold JJ. Age-related macular degeneration: anti-vascular endothelial growth factor treatment. *BMJ Clin Evid*. 2016 Feb 24; pii 0701.
PubMed: PM26909890

31. Mohamed QA, Fletcher EC, Buckle M. Diabetic retinopathy: intravitreal vascular endothelial growth factor inhibitors for diabetic macular oedema. *BMJ Clin Evid*. 2016 Mar 16; pii 0702.
PubMed: PM27031563

Randomized Controlled Trials

Age-Related Macular Degeneration

32. Dugel PU, Koh A, Ogura Y, et al. HAWK and HARRIER: phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration. *Ophthalmology*. 2019 Apr 12; pii: S0161-6420(18)33018-5.
PubMed: PM30986442

33. Gillies MC, Hunyor AP, Arnold JJ, et al. Effect of ranibizumab and aflibercept on best-corrected visual acuity in treat-and-extend for neovascular age-related macular degeneration: a randomized clinical trial. *JAMA Ophthalmol*. 2019 Apr 01;137(4):372-379.
PubMed: PM30676617

34. Gillies MC, Hunyor AP, Arnold JJ, et al. Macular atrophy in neovascular age-related macular degeneration: a randomized clinical trial comparing ranibizumab and aflibercept (RIVAL Study). *Ophthalmology*. 2019 Aug 27; pii: S0161-6420(19)31954-2.
PubMed: PM31619357

35. Nunes RP, Hirai FE, Barroso LF, et al. Effectiveness of monthly and fortnightly anti-VEGF treatments for age-related macular degeneration. *Arq Bras Oftalmol*. 2019 May-Jun;82(3):225-232.
PubMed: PM30810619

36. Callanan D, Kunimoto D, Maturi RK, et al. Double-masked, randomized, phase 2 evaluation of abicipar pegol (an anti-VEGF DARPin therapeutic) in neovascular age-related macular degeneration. *J Ocul Pharmacol Ther*. 2018 Nov 09.
PubMed: PM30412448

37. Dugel PU, Jaffe GJ, Sallstig P, et al. Brolucizumab versus aflibercept in participants with neovascular age-related macular degeneration: a randomized trial. *Ophthalmology*. 2017 09;124(9):1296-1304.
PubMed: PM28551167

38. Berg K, Hadzalic E, Gjertsen I, et al. Ranibizumab or bevacizumab for neovascular age-related macular degeneration according to the Lucentis compared to Avastin study treat-and-extend protocol: two-year results. *Ophthalmology*. 2016 Jan;123(1):51-59.
PubMed: PM26477842

39. Holz FG, Dugel PU, Weissgerber G, et al. Single-chain antibody fragment VEGF inhibitor rth258 for neovascular age-related macular degeneration: a randomized controlled study. *Ophthalmology*. 2016 May;123(5):1080-1089.
PubMed: PM26906165

40. Schauwvlieghe AM, Dijkman G, Hooymans JM, et al. Comparing the effectiveness of bevacizumab to ranibizumab in patients with exudative age-related macular degeneration. The BRAMD study. *PLoS ONE*. 2016;11(5):e0153052.
PubMed: PM27203434

Diabetic Macular Edema

41. Bressler NM, Beaulieu WT, Glassman AR, et al. Persistent macular thickening following intravitreous aflibercept, bevacizumab, or ranibizumab for central-involved diabetic macular edema with vision impairment: a secondary analysis of a randomized clinical trial. *JAMA Ophthalmol*. 2018 03 01;136(3):257-269.
PubMed: PM29392288

42. Jabbarpoor Bonyadi MH, Baghi A, Ramezani A, Yaseri M, Soheilian M. One-year results of a trial comparing 2 doses of intravitreal ziv-aflibercept versus bevacizumab for treatment of diabetic macular edema. *Ophthalmol Retina*. 2018 05;2(5):428-440.
PubMed: PM31047323

43. Baghi A, Jabbarpoor Bonyadi MH, Ramezani A, et al. Two doses of intravitreal ziv-aflibercept versus bevacizumab in treatment of diabetic macular edema: a three-armed, double-blind randomized trial. *Ophthalmol Retina*. 2017 Mar - Apr;1(2):103-110. PubMed: PM31047266

44. Fouda SM, Bahgat AM. Intravitreal aflibercept versus intravitreal ranibizumab for the treatment of diabetic macular edema. *Clin Ophthalmol*. 2017;11:567-571. PubMed: PM28356711

45. Jampol LM, Glassman AR, Bressler NM, Wells JA, Ayala AR, Diabetic Retinopathy Clinical Research Network. Anti-vascular endothelial growth factor comparative effectiveness trial for diabetic macular edema: additional efficacy post hoc analyses of a randomized clinical trial. *JAMA Ophthalmol*. 2016 Dec 01;134(12):01. PubMed: PM27711918

46. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial. *Ophthalmology*. 2016 06;123(6):1351-1359. PubMed: PM26935357

Retinal Vein Occlusion

47. Hykin P, Prevost AT, Vasconcelos JC, et al. Clinical effectiveness of intravitreal therapy with ranibizumab vs aflibercept vs bevacizumab for macular edema secondary to central retinal vein occlusion: a randomized clinical trial. *JAMA Ophthalmol*. 2019 08 29. PubMed: PM31465100

48. Pichi F, Elbarky AM, Elhamaky TR. Outcome of "treat and monitor" regimen of aflibercept and ranibizumab in macular edema secondary to non-ischemic branch retinal vein occlusion. *Int Ophthalmol*. 2019 Jan;39(1):145-153. PubMed: PM29274022

49. Scott IU, Oden NL, VanVeldhuisen PC, et al. Month 24 outcomes after treatment initiation with anti-vascular endothelial growth factor therapy for macular edema due to central retinal or hemiretinal vein occlusion: SCORE2 report 10: a secondary analysis of the SCORE2 randomized clinical trial. *JAMA Ophthalmol*. 2019 Oct 10. PubMed: PM31600368

50. Scott IU, VanVeldhuisen PC, Barton F, et al. Patient-reported visual function outcomes after anti-vascular endothelial growth factor therapy for macular edema due to central retinal or hemiretinal vein occlusion: preplanned secondary analysis of a randomized clinical trial. *JAMA Ophthalmol*. 2019 Jun 06. PubMed: PM31169862

51. Lotfy A, Solaiman KAM, Abdelrahman A, Samir A. Efficacy and frequency of intravitreal aflibercept versus bevacizumab for macular edema secondary to central retinal vein occlusion. *Retina*. 2018 09;38(9):1795-1800. PubMed: PM28767552

52. Scott IU, VanVeldhuisen PC, Ip MS, et al. Effect of bevacizumab vs aflibercept on visual acuity among patients with macular edema due to central retinal vein occlusion: the SCORE2 randomized clinical trial. *JAMA*. 2017 May 23;317(20):2072-2087. PubMed: PM28492910

53. Li F, Sun M, Guo J, Ma A, Zhao B. Comparison of conbercept with ranibizumab for the treatment of macular edema secondary to branch retinal vein occlusion. *Curr Eye Res*. 2017 08;42(8):1174-1178.
PubMed: PM28441077

Choroidal Neovascularization Secondary to Pathologic Myopia

54. Pece A, Milani P, Monteleone C, et al. A randomized trial of intravitreal bevacizumab vs. ranibizumab for myopic CNV. *Graefes Arch Clin Exp Ophthalmol*. 2015 Nov;253(11):1867-1872.
PubMed: PM25500986

Clinical Practice Guidelines

Different Population

55. Diabetes Canada Clinical Practice Guidelines Expert Committee, Altomare F, Kherani A, Lovshin J. Retinopathy. *Can J Diabetes.* 2018 Apr; 42 Suppl 1: S210-S216.
PubMed: PM29650099

Unclear Methodology

56. Schmidt-Erfurth U, Garcia-Arumi J, Gerendas BS, et al. Guidelines for the management of retinal vein occlusion by the European Society of Retina Specialists (EURETINA). *Ophthalmologica*. 2019;242(3):123-162.
PubMed: PM31412332

57. Tuuminen R, Uusitalo-Jarvinen H, Aaltonen V, et al. The Finnish national guideline for diagnosis, treatment and follow-up of patients with wet age-related macular degeneration. *Acta Ophthalmol*. 2017 07;95(A105 Suppl):1-9.
PubMed: PM28686003

Correction

In the original report, published November 21, 2019:

1. The Interventions and Comparators sections of Table 1 were listed as “anti-vascular endothelial growth factor drugs (i.e., aflibercept, bevacizumab, and ranibizumab)”. However, this report included any anti-vascular endothelial growth factor drugs compared to any other anti-vascular endothelial growth factor drug identified in the literature search. This has been revised in the selection criteria of Table 1.

2. Significant differences were reported in the conclusions of four studies,[3,6,9,14] but the direction of the effect was not provided. These conclusions were revised to include the direction of the effects for the relevant study[6] in the Overall Summary of Findings section and all four studies[3,6,9,14] in Table 2.

3. The Conclusions section of Table 2 for Liu et al. (2019)[13] indicated that “No statistically significant difference in BCVA or adverse events between intravitreal bevacizumab and intravitreal ranibizumab.” This was revised, according to the information in the abstract by Liu et al. (2019)[13] to “No statistically significant difference in BCVA or adverse events between intravitreal conbercept and intravitreal ranibizumab.”

4. The Conclusions section of Table 2 for Nguyen et al. (2018)[5] indicated that “Intravitreal bevacizumab has less serious systemic adverse events compared to intravitreal ranibizumab”. This was revised, according to the information in the abstract by Nguyen et al. (2018)[5] to “Intravitreal bevacizumab has a higher rate of serious systemic adverse events compared to intravitreal ranibizumab” in both the Overall Summary of Findings section and Table 2.

5. The following statement was included in the Overall Summary of Findings: “Finally, Zhang et al., 2017[9] found a statistically significant difference in visual acuity when comparing intravitreal ranibizumab to intravitreal aflibercept in patients with age-related macular degeneration, whereas Muston et al., 2018[14] had the opposite conclusion when comparing bimonthly intravitreal aflibercept to as needed intravitreal ranibizumab in patients with diabetic macular edema.” This was revised, according to the information in the abstracts by Zhang et al. (2017)[9] and Muston et al. (2018)[14] to “Finally, Zhang et al., 2017[9] found that intravitreal aflibercept was significantly more effective than intravitreal ranibizumab in patients with age-related macular degeneration who had initial reduced visual acuity, and Muston et al., 2018[14] found that aflibercept (2 mg bimonthly after 5 initial doses) was significantly more effective than 0.5 mg ranibizumab as-needed but not significantly different from a ranibizumab treat-and-extend regimen in patients with diabetic macular edema.”