# Anti-VEGF drugs compared with laser photocoagulation for the treatment of diabetic retinopathy

This document presents additional tables and figures covering:

* Systematic review details
* All meta-analyses and forest plots for PDR
* All network meta-analyses and threshold analyses for PDR
* All analyses of NPDR

# Appendix 1: Systematic review processes

## 1.1: Database search strategies

The aim of the literature search was to identify RCTs on anti-vascular endothelial growth factors, angiogenesis inhibitors and other specific drugs used for the treatment of diabetic retinopathy.

An Information Specialist (HF) designed a preliminary search strategy in Ovid MEDLINE in consultation with the research team. The strategy consisted of terms for the condition (diabetic retinopathy), which were combined with terms for the intervention (anti-vascular endothelial growth factor, angiogenesis inhibitors, or specific drugs used for the treatment of diabetic retinopathy) using the Boolean operator AND. Text word searches for terms appearing in the title and abstracts of database records were included in the strategy alongside searches of relevant subject headings. An RCT study filter was applied using the Boolean operator AND. No date or language limits were applied. The final MEDLINE strategy was adapted for use in all resources searched.

The searches were performed on 27th August 2021. The following databases were searched: Ovid MEDLINE(R) ALL, Embase (Ovid), Science Citation Index Expanded (Web of Science), Conference Proceedings Citation Index Science (Web of Science), Cochrane CENTRAL (Wiley), Cochrane Database of Systematic Reviews (Wiley), DARE (CRD), PROSPERO (CRD), and Epistemonikos. The following trial registries were searched: WHO ICTRP, ClinicalTrials.gov, and the EU Clinical Trials Registry.

Search results were imported into EndNote 20 (Clarivate Analytics, US) and deduplicated. All search strategies are presented in full below.

The searches were updated on 13th July 2022 and again on 26th May 2023 using all the databases and strategies as used previously, except for DARE as this database is no longer updated. For each update search, the results of the databases were deduplicated against each other in a separate EndNote 20 Library before being merged with the results of the original EndNote Library and deduplicated for a second time.

**Ovid MEDLINE(R) ALL**

(includes Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE)

via Ovid <http://ovidsp.ovid.com/>

Date range searched: <1946 to May 25, 2023>

Date searched: 26 May 2023

Records retrieved: 3172

The MEDLINE strategy below includes a search filter to limit retrieval to RCTs using the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); Ovid format.

Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, Noel-Storr A, Rader T, Shokraneh F, Thomas J, Wieland LS. Technical Supplement to Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, Welch VA (eds). *Cochrane Handbook for Systematic Reviews of Interventions* Version 6.2 (updated February 2021). Cochrane, 2021. Available from: [www.training.cochrane.org/handbook](http://www.training.cochrane.org/handbook).

1 (\*Diabetes Mellitus/ or \*Diabetes Complications/) and exp \*Retinal Diseases/ (3199)

2 Diabetic Retinopathy/ (29304)

3 ((diabet\* or DM) adj3 (retinopath\* or vitreoretinopath\* or vitreo-retinopath\* or chorioretinopath\* or chorio-retinopath\* or maculopath\*)).ti,ab,kw. (30685)

4 (((proliferat\* or PDR or pre-proliferat\* or preproliferat\* or non-proliferat\* or nonproliferat\* or NPDR or background) adj3 (retinopath\* or vitreoretinopath\* or vitreo-retinopath\* or chorioretinopath\* or chorio-retinopath\*)) and (diabet\* or DM)).ti,ab,kw. (7895)

5 (new blood vessel\* and diabet\*).ti,ab,kw. (273)

6 (((retin\* or subretina\* or sub-retina\* or interretina\* or inter-retina\* or vitreoretin\* or vitreo-retin\* or chorioretin\* or chorio-retin\* or choroid\* or macula\* or intraocular or intra-ocular or intravitreal or intra-vitreal) adj4 (damage\* or deteriorat\* or degnerat\* or disease\* or edema or oedema or neovasculari?ation\*)) and diabet\*).ti,ab,kw. (13654)

7 ((retinal vein\* adj3 (occlu\* or obstruct\* or clos\* or stricture\* or steno\* or block\* or emboli\*)) and diabet\*).ti,ab,kw. (1473)

8 or/1-7 (44519)

9 exp Vascular Endothelial Growth Factors/ai (9366)

10 exp Receptors, Vascular Endothelial Growth Factor/ai (3393)

11 (anti adj2 VEGF\*).ti,ab,kw. (9210)

12 (anti-VEGF\* or antiVEGF\*).ti,ab,kw. (9455)

13 ((anti vascular or anti-vascular or antivascular) adj2 endothelial growth factor\*).ti,ab,kw. (5745)

14 (((vascular endothelial adj2 growth factor\*) or vasculotropin or VEGF\* or vascular permeability factor\* or VPF) adj2 (trap\* or inhibit\* or antagonist\*)).ti,ab,kw. (11005)

15 (vascular proliferation adj4 inhibit\*).ti,ab,kw. (38)

16 or/9-15 (28125)

17 Angiogenesis Inhibitors/ (28876)

18 exp Angiogenesis Inducing Agents/ai (118)

19 (angiogen\* adj2 (antagonist\* or inhibit\*)).ti,ab,kw. (14831)

20 ((antiangiogen\* or anti angiogen\* or anti-angiogen\*) adj2 (agent\* or drug\* or effect\*)).ti,ab,kw. (10949)

21 (angiostatic adj2 (agent\* or drug\*)).ti,ab,kw. (103)

22 ((neovasculari?ation or vasculari?ation) adj2 inhibit\*).ti,ab,kw. (1243)

23 or/17-22 (45139)

24 Aflibercept\*.ti,ab,kw,rn. (3315)

25 (Eylea or Zaltrap or Ziv-Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005).ti,ab,kw. (316)

26 Bevacizumab/ (14139)

27 Bevacizumab\*.ti,ab,kw,rn. (22533)

28 (Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabev or rhuMAbVEGF or rhuMAb-VEGF or rhuMAb VEGF or "NSC 704865" or NSC704865).ti,ab,kw. (1675)

29 (IVB adj2 inject\*).ti,ab,kw. (316)

30 Ranibizumab/ (4684)

31 Ranibizumab\*.ti,ab,kw,rn. (6307)

32 (Lucentis or "rhuFab V2").ti,ab,kw. (456)

33 (IVR adj2 inject\*).ti,ab,kw. (139)

34 Pegaptanib\*.ti,ab,kw,rn. (671)

35 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838).ti,ab,kw. (140)

36 or/24-35 (28353)

37 8 and (16 or 23 or 36) (4979)

38 randomized controlled trial.pt. (593242)

39 controlled clinical trial.pt. (95314)

40 randomized.ab. (604126)

41 placebo.ab. (238387)

42 drug therapy.fs. (2592996)

43 randomly.ab. (408822)

44 trial.ab. (649200)

45 groups.ab. (2520111)

46 or/38-45 (5663345)

47 37 and 46 (3308)

48 exp animals/ not humans.sh. (5123796)

49 47 not 48 (3190)

50 limit 49 to yr="2000-Current" (3182)

51 remove duplicates from 50 (3172)

**Key:**

/ or .sh. = indexing term (Medical Subject Heading: MeSH)

/ai = indexing term with subheading for antagonists & inhibitors

exp = exploded indexing term (MeSH)

\* or $ = truncation

? = adds up to 1 additional character

ti,ab,kw = terms in either title, abstract or keyword fields

rn = registry number/name of substance

adj3 = terms within three words of each other (any order).

pt = publication type

fs = floating sub-heading

**Embase**

via Ovid <http://ovidsp.ovid.com/>

Date range searched: <1974 to 2023 May 25>

Date searched: 26 May 2023

Records retrieved: 2558

The Embase strategy below includes the Cochrane Embase RCT filter (Ovid format).

Glanville J, Foxlee R, Wisniewski S, Noel-Storr A, Edwards M, Dooley G. [Translating the Cochrane EMBASE RCT filter from the Ovid interface to Embase.com: a case study.](https://www.google.com/url?q=https%3A%2F%2Fwww.ncbi.nlm.nih.gov%2Fpubmed%2F%3Fterm%3DTranslating%2Bthe%2BCochrane%2BEMBASE%2BRCT%2Bfilter%2Bfrom%2Bthe%2BOvid%2Binterface%2Bto%2BEmbase.com&sa=D&sntz=1&usg=AFQjCNH0CofWYrMngcNicVE34LrrrxeXlQ) *Health Info Libr J*. 2019 Jul 22. doi: 10.1111/hir.12269

1 \*diabetes mellitus/ and exp \*retina disease/ (4826)

2 exp diabetic retinopathy/ (53891)

3 ((diabet\* or DM) adj3 (retinopath\* or vitreoretinopath\* or vitreo-retinopath\* or chorioretinopath\* or chorio-retinopath\* or maculopath\*)).ti,ab,kw. (43573)

4 (((proliferat\* or PDR or pre-proliferat\* or preproliferat\* or non-proliferat\* or nonproliferat\* or NPDR or background) adj3 (retinopath\* or vitreoretinopath\* or vitreo-retinopath\* or chorioretinopath\* or chorio-retinopath\*)) and (diabet\* or DM)).ti,ab,kw. (11148)

5 (new blood vessel\* and diabet\*).ti,ab,kw. (391)

6 (((retin\* or subretina\* or sub-retina\* or interretina\* or inter-retina\* or vitreoretin\* or vitreo-retin\* or chorioretin\* or chorio-retin\* or choroid\* or macula\* or intraocular or intra-ocular or intravitreal or intra-vitreal) adj4 (damage\* or deteriorat\* or degnerat\* or disease\* or edema or oedema or neovasculari?ation\*)) and diabet\*).ti,ab,kw. (20734)

7 ((retinal vein\* adj3 (occlu\* or obstruct\* or clos\* or stricture\* or steno\* or block\* or emboli\*)) and diabet\*).ti,ab,kw. (2199)

8 or/1-7 (70501)

9 vasculotropin inhibitor/ (7663)

10 (anti adj2 VEGF\*).ti,ab,kw. (15751)

11 (anti-VEGF\* or antiVEGF\*).ti,ab,kw. (16291)

12 ((anti vascular or anti-vascular or antivascular) adj2 endothelial growth factor\*).ti,ab,kw. (7400)

13 (((vascular endothelial adj2 growth factor\*) or vasculotropin or VEGF\* or vascular permeability factor\* or VPF) adj2 (trap\* or inhibit\* or antagonist\*)).ti,ab,kw. (17346)

14 (vascular proliferation adj4 inhibit\*).ti,ab,kw. (50)

15 or/9-14 (38838)

16 angiogenesis inhibitor/ (20415)

17 (angiogen\* adj2 (antagonist\* or inhibit\*)).ti,ab,kw. (20444)

18 ((antiangiogen\* or anti angiogen\* or anti-angiogen\*) adj2 (agent\* or drug\* or effect\*)).ti,ab,kw. (15734)

19 (angiostatic adj2 (agent\* or drug\*)).ti,ab,kw. (125)

20 ((neovasculari?ation or vasculari?ation) adj2 inhibit\*).ti,ab,kw. (1718)

21 or/16-20 (45260)

22 aflibercept/ (8877)

23 Aflibercept\*.ti,ab,kw,dy,tn. (9141)

24 (Eylea or Zaltrap or Ziv-Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005).ti,ab,dy,tn. (1741)

25 bevacizumab/ (72890)

26 Bevacizumab\*.ti,ab,kw,dy,tn. (75152)

27 (Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabev or rhuMAbVEGF or rhuMAb-VEGF or rhuMAb VEGF or "NSC 704865" or NSC704865).ti,ab,kw,dy,tn. (11007)

28 (IVB adj2 inject\*).ti,ab,kw. (395)

29 ranibizumab/ (12442)

30 Ranibizumab\*.ti,ab,kw,dy,tn. (12826)

31 (Lucentis or "rhuFab V2").ti,ab,kw,dy,tn. (3216)

32 (IVR adj2 inject\*).ti,ab,kw. (197)

33 pegaptanib.dy,tn. (2470)

34 Pegaptanib\*.ti,ab,kw,dy,tn. (2544)

35 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838).ti,ab,kw,dy,tn. (1266)

36 or/22-35 (85594)

37 8 and (15 or 21 or 36) (8778)

38 randomized controlled trial/ (785964)

39 controlled clinical trial/ (469252)

40 Random$.ti,ab,ot. (1968994)

41 randomization/ (99178)

42 intermethod comparison/ (297283)

43 placebo.ti,ab,ot. (366311)

44 (compare or compared or comparison).ti,ot. (604093)

45 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. (2766233)

46 (open adj label).ti,ab,ot. (109016)

47 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab,ot. (274477)

48 double blind procedure/ (210575)

49 parallel group$1.ti,ab,ot. (32223)

50 (crossover or cross over).ti,ab,ot. (124540)

51 ((assign$ or match or matched or allocation) adj5 (alternate or group or groups or intervention or interventions or patient or patients or subject or subjects or participant or participants)).ti,ab,ot. (415063)

52 (assigned or allocated).ti,ab,ot. (489023)

53 (controlled adj7 (study or design or trial)).ti,ab,ot. (450984)

54 (volunteer or volunteers).ti,ab,ot. (282270)

55 human experiment/ (650911)

56 trial.ti,ot. (403295)

57 or/38-56 (6311902)

58 37 and 57 (2810)

59 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$).ti,ot. and animal experiment/ (1227092)

60 animal experiment/ not (human experiment/ or human/) (2577203)

61 59 or 60 (2645661)

62 58 not 61 (2689)

63 limit 62 to yr="2000-Current" (2686)

64 remove duplicates from 63 (2558)

**Key:**

/ or .sh. = indexing term (Emtree Subject Heading)

exp = exploded indexing term (Emtree)

\* or $ = truncation

? = adds up to 1 additional character

ti,ab,kw = terms in either title or abstract fields

dy,tn = drug index terms word or drug trade name fields

adj3 = terms within three words of each other (any order).

pt = publication type

ot = original title

**Cochrane Central Register of Controlled Trials (CENTRAL)**

via Wiley <http://onlinelibrary.wiley.com/>

Date range searched: Issue 5 of 12, May 2023

Date searched: 26 May 2023

Records retrieved: 1825

#1 ([mh ^"Diabetes Mellitus"] or [mh ^"Diabetes Complications"]) and [mh "Retinal Diseases"] 250

#2 [mh ^"Diabetic Retinopathy"] 1934

#3 ((diabet\* or DM) NEAR/3 (retinopath\* or vitreoretinopath\* or chorioretinopath\* or maculopath\*)):ti,ab,kw 4547

#4 (((proliferat\* or PDR or preproliferat\* or nonproliferat\* or NPDR or background) NEAR/3 (retinopath\* or vitreoretinopath\* or chorioretinopath\*)) and (diabet\* or DM)):ti,ab,kw 1326

#5 ("new blood" NEXT vessel\* and diabet\*):ti,ab,kw 32

#6 (((retin\* or subretina\* or interretina\* or vitreoretin\* or chorioretin\* or choroid\* or macula\* or intraocular or intravitreal) NEAR/4 (damage\* or deteriorat\* or degnerat\* or disease\* or edema or oedema or neovasculari?ation\*)) and diabet\*):ti,ab,kw 3457

#7 ((retinal NEXT vein\* NEAR/3 (occlu\* or obstruct\* or clos\* or stricture\* or steno\* or block\* or emboli\*)) and diabet\*):ti,ab,kw 254

#8 {OR #1-#7} 5751

#9 [mh "Vascular Endothelial Growth Factors"/ai] 758

#10 [mh "Receptors, Vascular Endothelial Growth Factor"/ai] 154

#11 (anti NEAR/2 VEGF\*):ti,ab,kw 1610

#12 (antiVEGF\*):ti,ab,kw 1523

#13 ((anti NEXT vascular or antivascular) NEAR/2 "endothelial growth" NEXT factor\*):ti,ab,kw 699

#14 ((("vascular endothelial" NEAR/2 growth NEXT factor\*) or vasculotropin or VEGF\* or "vascular permeability" NEXT factor\* or VPF) NEAR/2 (trap\* or inhibit\* or antagonist\*)):ti,ab,kw 2048

#15 ("vascular proliferation" NEAR/4 inhibit\*):ti,ab,kw 1

#16 {OR #9-#15} 3671

#17 [mh ^"Angiogenesis Inhibitors"] 1681

#18 [mh "Angiogenesis Inducing Agents"/ai] 0

#19 (angiogen\* NEAR/2 (antagonist\* or inhibit\*)):ti,ab,kw 2126

#20 ((antiangiogen\* or anti NEXT angiogen\*) NEAR/2 (agent\* or drug\* or effect\*)):ti,ab,kw 717

#21 (angiostatic NEAR/2 (agent\* or drug\*)):ti,ab,kw 10

#22 ((neovasculari?ation or vasculari?ation) NEAR/2 inhibit\*):ti,ab,kw 37

#23 {OR #17-#22} 2691

#24 Aflibercept\*:ti,ab,kw 1081

#25 (Eylea or Zaltrap or Ziv NEXT Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005):ti,ab,kw 252

#26 [mh ^Bevacizumab] 2633

#27 Bevacizumab\*:ti,ab,kw 7386

#28 (Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabev or rhuMAbVEGF or rhuMAb NEXT VEGF or "NSC 704865" or NSC704865):ti,ab,kw 941

#29 (IVB NEAR/2 inject\*):ti,ab,kw 89

#30 [mh ^Ranibizumab] 1049

#31 Ranibizumab\*:ti,ab,kw 2266

#32 (Lucentis or "rhuFab V2"):ti,ab,kw 451

#33 (IVR NEAR/2 inject\*):ti,ab,kw 32

#34 Pegaptanib\*:ti,ab,kw 166

#35 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838):ti,ab,kw 82

#36 {OR #24-#35} 10087

#37 #8 and (#16 or #23 or #36) 1847

#38 (rat or rats or rodent\* or mouse or mice or "mus musculus" or "mus domesticus" or murine or murinae or bovine or sheep or ovine or "ovis aries" or porcine):ti,ab,kw 17188

#39 #37 not #38 with Publication Year from 2000 to 2023, in Trials 1825

**Science Citation Index Expanded**

via Web of Science, Clarivate Analytics <https://clarivate.com/>

Date range searched: 1900 – 26 May 2023

Date searched: 26 May 2023

Records retrieved: 2394

32 #29 NOT #30 2,394 Limited by 2000-01-01 to 2023-05-26

31 #29 NOT #30 2,410

30 TI=(animal or animals or rat or rats or rodent\* or mouse or mice or "mus musculus" or "mus domesticus" or murine or murinae or porcine or pig or pigs or piglet or piglets or sow or sows or minipig or minipigs or sheep or ovine or "ovis aries" or lamb or lambs or ewe or ewes or rabbit or rabbits or leporide or leporidae or kitten or kittens or dog or dogs or puppy or puppies or monkey or monkeys or horse or horses or foal or foals or equine or bovine or calf or calves or cattle or heifer or heifers or hamster or hamsters or chicken or chickens or livestock or alpaca\* or llama\*) 3,259,653

29 #27 AND #28 2,524

28 TS=(random\* or control\* or trial\* or "single blind" or "double blind" or "triple blind" or placebo) 8,083,064

27 #6 AND #26 6,121

26 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 83,065

25 TS=("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838) 142

24 TS=(Pegaptanib\*) 716

23 TS=(IVR NEAR/2 inject\*) 177

22 TS=(Lucentis or "rhuFab V2") 564

21 TS=(Ranibizumab\*) 9,347

20 TS=(IVB NEAR/2 inject\*) 307

19 TS=(Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabev or rhuMAbVEGF or rhuMAb-VEGF or "rhuMAb VEGF" or "NSC 704865" or NSC704865) 3,355

18 TS=(Bevacizumab\*) 36,279

17 TS=(Eylea or Zaltrap or Ziv-Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005) 320

16 TS=(Aflibercept\*) 4,076

15 TS=((neovascularisation or neovascularization or vascularisation or vascularization) NEAR/2 inhibit\*) 1,858

14 TS=(angiostatic NEAR/2 (agent\* or drug\*) ) 105

13 TS=((antiangiogen\* or "anti angiogen\*" or anti-angiogen\*) NEAR/2 (agent\* or drug\* or effect\*) ) 11,802

12 TS=(angiogen\* NEAR/2 (antagonist\* or inhibit\*) ) 19,846

11 TS=("vascular proliferation" NEAR/4 inhibit\*) 44

10 TS=((("vascular endothelial" NEAR/2 "growth factor\*") or vasculotropin or VEGF\* or "vascular permeability factor\*" or VPF) NEAR/2 (trap\* or inhibit\* or antagonist\*) ) 14,540

9 TS=(("anti vascular" or anti-vascular or antivascular) NEAR/2 "endothelial growth factor\*") 5,018

8 TS=(anti-VEGF\* or antiVEGF\*) 10,111

7 TS=(anti NEAR/2 VEGF\*) 10,549

6 #1 OR #2 OR #3 OR #4 OR #5 43,073

5 TS=(("retinal vein\*" NEAR/3 (occlu\* or obstruct\* or clos\* or stricture\* or steno\* or block\* or emboli\*) ) and diabet\*) 1,546

4 TS=(((retin\* or subretina\* or sub-retina\* or interretina\* or inter-retina\* or vitreoretin\* or vitreo-retin\* or chorioretin\* or chorio-retin\* or choroid\* or macula\* or intraocular or intra-ocular or intravitreal or intra-vitreal) NEAR/4 (damage\* or deteriorat\* or degnerat\* or disease\* or edema or oedema or neovasculari?ation\*) ) and diabet\*) 16,980

3 TS=("new blood vessel\*" and diabet\*) 288

2 TS=(((proliferat\* or PDR or pre-proliferat\* or preproliferat\* or non-proliferat\* or nonproliferat\* or NPDR or background) NEAR/3 (retinopath\* or vitreoretinopath\* or vitreo-retinopath\* or chorioretinopath\* or chorio-retinopath\*) ) and (diabet\* or DM) ) 7,763

1 TS=((diabet\* or DM) NEAR/3 (retinopath\* or vitreoretinopath\* or vitreo-retinopath\* or chorioretinopath\* or chorio-retinopath\* or maculopath\*)) 36,053

**Key:**

TS= terms in either title, abstract, author keywords, and keywords plus fields

TI= search in title field

NEAR/3  = terms within three words of each other (any order).

\* = truncation

**Conference Proceedings Citation Index - Science**

via Web of Science, Clarivate Analytics <https://clarivate.com/>

Date range searched: 1990 – 26 May 2023

Date searched: 26 May 2023

Records retrieved: 86

32 #29 NOT #30 86 Limited by 2000-01-01 to 2023-05-26

31 #29 NOT #30 89

30 TI=(animal or animals or rat or rats or rodent\* or mouse or mice or "mus musculus" or "mus domesticus" or murine or murinae or porcine or pig or pigs or piglet or piglets or sow or sows or minipig or minipigs or sheep or ovine or "ovis aries" or lamb or lambs or ewe or ewes or rabbit or rabbits or leporide or leporidae or kitten or kittens or dog or dogs or puppy or puppies or monkey or monkeys or horse or horses or foal or foals or equine or bovine or calf or calves or cattle or heifer or heifers or hamster or hamsters or chicken or chickens or livestock or alpaca\* or llama\*) 295,290

29 #27 AND #28 92

28 TS=(random\* or control\* or trial\* or "single blind" or "double blind" or "triple blind" or placebo) 1,616,551

27 #6 AND #26 458

26 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 8,998

25 TS=("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838) 14

24 TS=(Pegaptanib\*) 39

23 TS=(IVR NEAR/2 inject\*) 1

22 TS=(Lucentis or "rhuFab V2") 29

21 TS=(Ranibizumab\*) 564

20 TS=(IVB NEAR/2 inject\*) 7

19 TS=(Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabev or rhuMAbVEGF or rhuMAb-VEGF or "rhuMAb VEGF" or "NSC 704865" or NSC704865) 196

18 TS=(Bevacizumab\*) 4,659

17 TS=(Eylea or Zaltrap or Ziv-Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005) 60

16 TS=(Aflibercept\*) 577

15 TS=((neovascularisation or neovascularization or vascularisation or vascularization) NEAR/2 inhibit\*) 177

14 TS=(angiostatic NEAR/2 (agent\* or drug\*) ) 6

13 TS=((antiangiogen\* or "anti angiogen\*" or anti-angiogen\*) NEAR/2 (agent\* or drug\* or effect\*) ) 634

12 TS=(angiogen\* NEAR/2 (antagonist\* or inhibit\*) ) 1,209

11 TS=("vascular proliferation" NEAR/4 inhibit\*) 6

10 TS=((("vascular endothelial" NEAR/2 "growth factor\*") or vasculotropin or VEGF\* or "vascular permeability factor\*" or VPF) NEAR/2 (trap\* or inhibit\* or antagonist\*) ) 1,025

9 TS=(("anti vascular" or anti-vascular or antivascular) NEAR/2 "endothelial growth factor\*") 224

8 TS=(anti-VEGF\* or antiVEGF\*) 836

7 TS=(anti NEAR/2 VEGF\*) 869

6 #1 OR #2 OR #3 OR #4 OR #5 5,826

5 TS=(("retinal vein\*" NEAR/3 (occlu\* or obstruct\* or clos\* or stricture\* or steno\* or block\* or emboli\*) ) and diabet\*) 74

4 TS=(((retin\* or subretina\* or sub-retina\* or interretina\* or inter-retina\* or vitreoretin\* or vitreo-retin\* or chorioretin\* or chorio-retin\* or choroid\* or macula\* or intraocular or intra-ocular or intravitreal or intra-vitreal) NEAR/4 (damage\* or deteriorat\* or degnerat\* or disease\* or edema or oedema or neovasculari?ation\*) ) and diabet\*) 2,140

3 TS=("new blood vessel\*" and diabet\*) 29

2 TS=(((proliferat\* or PDR or pre-proliferat\* or preproliferat\* or non-proliferat\* or nonproliferat\* or NPDR or background) NEAR/3 (retinopath\* or vitreoretinopath\* or vitreo-retinopath\* or chorioretinopath\* or chorio-retinopath\*) ) and (diabet\* or DM) ) 642

1 TS=((diabet\* or DM) NEAR/3 (retinopath\* or vitreoretinopath\* or vitreo-retinopath\* or chorioretinopath\* or chorio-retinopath\* or maculopath\*) ) 4,723

**Key:**

TS= terms in either title, abstract, author keywords, and keywords plus fields

TI= search in title field

NEAR/3  = terms within three words of each other (any order).

\* = truncation

**Cochrane Database of Systematic Reviews (CDSR)**

via Wiley <http://onlinelibrary.wiley.com/>

Date range searched: Issue 5 of 12, May 2023

Date searched: 26 May 2023

Records retrieved: 14

#1 ([mh ^"Diabetes Mellitus"] or [mh ^"Diabetes Complications"]) and [mh "Retinal Diseases"] 250

#2 [mh ^"Diabetic Retinopathy"] 1934

#3 ((diabet\* or DM) NEAR/3 (retinopath\* or vitreoretinopath\* or chorioretinopath\* or maculopath\*)):ti,ab,kw 4547

#4 (((proliferat\* or PDR or preproliferat\* or nonproliferat\* or NPDR or background) NEAR/3 (retinopath\* or vitreoretinopath\* or chorioretinopath\*)) and (diabet\* or DM)):ti,ab,kw 1326

#5 ("new blood" NEXT vessel\* and diabet\*):ti,ab,kw 32

#6 (((retin\* or subretina\* or interretina\* or vitreoretin\* or chorioretin\* or choroid\* or macula\* or intraocular or intravitreal) NEAR/4 (damage\* or deteriorat\* or degnerat\* or disease\* or edema or oedema or neovasculari?ation\*)) and diabet\*):ti,ab,kw 3457

#7 ((retinal NEXT vein\* NEAR/3 (occlu\* or obstruct\* or clos\* or stricture\* or steno\* or block\* or emboli\*)) and diabet\*):ti,ab,kw 254

#8 {OR #1-#7} 5751

#9 [mh "Vascular Endothelial Growth Factors"/ai] 758

#10 [mh "Receptors, Vascular Endothelial Growth Factor"/ai] 154

#11 (anti NEAR/2 VEGF\*):ti,ab,kw 1610

#12 (antiVEGF\*):ti,ab,kw 1523

#13 ((anti NEXT vascular or antivascular) NEAR/2 "endothelial growth" NEXT factor\*):ti,ab,kw 699

#14 ((("vascular endothelial" NEAR/2 growth NEXT factor\*) or vasculotropin or VEGF\* or "vascular permeability" NEXT factor\* or VPF) NEAR/2 (trap\* or inhibit\* or antagonist\*)):ti,ab,kw 2048

#15 ("vascular proliferation" NEAR/4 inhibit\*):ti,ab,kw 1

#16 {OR #9-#15} 3671

#17 [mh ^"Angiogenesis Inhibitors"] 1681

#18 [mh "Angiogenesis Inducing Agents"/ai] 0

#19 (angiogen\* NEAR/2 (antagonist\* or inhibit\*)):ti,ab,kw 2126

#20 ((antiangiogen\* or anti NEXT angiogen\*) NEAR/2 (agent\* or drug\* or effect\*)):ti,ab,kw 717

#21 (angiostatic NEAR/2 (agent\* or drug\*)):ti,ab,kw 10

#22 ((neovasculari?ation or vasculari?ation) NEAR/2 inhibit\*):ti,ab,kw 37

#23 {OR #17-#22} 2691

#24 Aflibercept\*:ti,ab,kw 1081

#25 (Eylea or Zaltrap or Ziv NEXT Aflibercept or "AVE 0005" or AVE0005 or "AVE 005" or AVE005):ti,ab,kw 252

#26 [mh ^Bevacizumab] 2633

#27 Bevacizumab\*:ti,ab,kw 7386

#28 (Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabev or rhuMAbVEGF or rhuMAb NEXT VEGF or "NSC 704865" or NSC704865):ti,ab,kw 941

#29 (IVB NEAR/2 inject\*):ti,ab,kw 89

#30 [mh ^Ranibizumab] 1049

#31 Ranibizumab\*:ti,ab,kw 2266

#32 (Lucentis or "rhuFab V2"):ti,ab,kw 451

#33 (IVR NEAR/2 inject\*):ti,ab,kw 32

#34 Pegaptanib\*:ti,ab,kw 166

#35 ("EYE 001" or EYE001 or Macugen or "NX 1838" or NX1838):ti,ab,kw 82

#36 {OR #24-#35} 10087

#37 #8 and (#16 or #23 or #36) 1847

#38 (rat or rats or rodent\* or mouse or mice or "mus musculus" or "mus domesticus" or murine or murinae or bovine or sheep or ovine or "ovis aries" or porcine):ti,ab,kw 17188

#39 #37 not #38 with Cochrane Library publication date Between Jan 2000 and May 2023, in Cochrane Reviews 14

**Key:**

mh = exploded indexing term (MeSH)

mh ^ = unexploded indexing term (MeSH)

/ai = indexing term with subheading for antagonists & inhibitors

\* = truncation or additional characters within a word

? = adds up to 1 additional character

ti,ab,kw = terms in either title or abstract or keyword fields

near/3 = terms within three words of each other (any order)

next = terms are next to each other

**Epistemonikos**

via<https://www.epistemonikos.org/>

Date range searched: Inception - 26 May 2023

Date searched: 26 May 2023

Records retrieved: 1026

((title:((title:(((diabet\* OR proliferat\* OR PDR OR pre-proliferat\* OR preproliferat\* OR non-proliferat\* OR nonproliferat\* OR NPDR OR background) AND retinopath\*)) OR abstract:(((diabet\* OR proliferat\* OR PDR OR pre-proliferat\* OR preproliferat\* OR non-proliferat\* OR nonproliferat\* OR NPDR OR background) AND retinopath\*))) OR (title:((new blood vessel\* AND diabet\*)) OR abstract:((new blood vessel\* AND diabet\*)))) OR abstract:((title:(((diabet\* OR proliferat\* OR PDR OR pre-proliferat\* OR preproliferat\* OR non-proliferat\* OR nonproliferat\* OR NPDR OR background) AND retinopath\*)) OR abstract:(((diabet\* OR proliferat\* OR PDR OR pre-proliferat\* OR preproliferat\* OR non-proliferat\* OR nonproliferat\* OR NPDR OR background) AND retinopath\*))) OR (title:((new blood vessel\* AND diabet\*)) OR abstract:((new blood vessel\* AND diabet\*))))) AND (title:((anti AND VEGF\*)) OR abstract:((anti AND VEGF\*))) OR (title:((anti-VEGF\* OR antiVEGF\*)) OR abstract:((anti-VEGF\* OR antiVEGF\*))) OR (title:((("anti vascular" OR anti-vascular OR antivascular) AND "endothelial growth factor")) OR abstract:((("anti vascular" OR anti-vascular OR antivascular) AND "endothelial growth factor"))) OR (title:((("vascular endothelial growth factor" OR vasculotropin OR VEGF\* OR "vascular permeability factor" OR VPF) AND (trap\* OR inhibit\* OR antagonist\*))) OR abstract:((("vascular endothelial growth factor" OR vasculotropin OR VEGF\* OR "vascular permeability factor" OR VPF) AND (trap\* OR inhibit\* OR antagonist\*)))) OR (title:((angiogen\* AND (antagonist\* OR inhibit\*))) OR abstract:((angiogen\* AND (antagonist\* OR inhibit\*)))) OR (title:(((antiangiogen\* OR "anti angiogen" OR anti-angiogen\* OR angiostatic) AND (agent\* OR drug\* OR effect\*))) OR abstract:(((antiangiogen\* OR "anti angiogen" OR anti-angiogen\* OR angiostatic) AND (agent\* OR drug\* OR effect\*)))) OR (title:((Aflibercept\* OR Eylea OR Zaltrap OR Ziv-Aflibercept OR "AVE 0005" OR AVE0005 OR "AVE 005" OR AVE005 OR Bevacizumab\* OR Avastin OR Mvasi OR Alymsys OR Aybintio OR Equidacent OR Onbevzi OR Oyavas OR Zirabev OR rhuMAbVEGF OR rhuMAb-VEGF OR "rhuMAb VEGF" OR "NSC 704865" OR NSC704865 OR Ranibizumab\* OR Lucentis OR "rhuFab V2" OR Pegaptanib\* OR "EYE 001" OR EYE001 OR Macugen OR "NX 1838" OR NX1838)) OR abstract:((Aflibercept\* OR Eylea OR Zaltrap OR Ziv-Aflibercept OR "AVE 0005" OR AVE0005 OR "AVE 005" OR AVE005 OR Bevacizumab\* OR Avastin OR Mvasi OR Alymsys OR Aybintio OR Equidacent OR Onbevzi OR Oyavas OR Zirabev OR rhuMAbVEGF OR rhuMAb-VEGF OR "rhuMAb VEGF" OR "NSC 704865" OR NSC704865 OR Ranibizumab\* OR Lucentis OR "rhuFab V2" OR Pegaptanib\* OR "EYE 001" OR EYE001 OR Macugen OR "NX 1838" OR NX1838))) OR (title:(((IVB OR IVR) AND inject\*)) OR abstract:(((IVB OR IVR) AND inject\*))))

Filter: Publication year 2000-2023

Publication type: Systematic Reviews

= 1026

**Key:**

\* = truncation

title: = searches in title field

abstract: = searches in abstract field

**PROSPERO**

via <https://www.crd.york.ac.uk/prospero/>

Date range: Inception – 26 May 2023

Date searched: 26 May 2023

Records retrieved: 159

#1 MeSH DESCRIPTOR Diabetic Retinopathy 107

#2 ((diabet\* or DM) adj3 (retinopath\* or vitreoretinopath\* or vitreo-retinopath\* or chorioretinopath\* or chorio-retinopath\* or maculopath\*)) 609

#3 (((proliferat\* or PDR or pre-proliferat\* or preproliferat\* or non-proliferat\* or nonproliferat\* or NPDR or background) adj3 (retinopath\* or vitreoretinopath\* or vitreo-retinopath\* or chorioretinopath\* or chorio-retinopath\*)) and (diabet\* or DM)) 110

#4 (new blood vessel\* and diabet\*) 9

#5 (((retin\* or subretina\* or sub-retina\* or interretina\* or inter-retina\* or vitreoretin\* or vitreo-retin\* or chorioretin\* or chorio-retin\* or choroid\* or macula\* or intraocular or intra-ocular or intravitreal or intra-vitreal) adj4 (damage\* or deteriorat\* or degnerat\* or disease\* or edema or oedema or neovascularisation\* or neovascularization\*)) AND diabet\*) 373

#6 ((retinal vein\* adj3 (occlu\* or obstruct\* or clos\* or stricture\* or steno\* or block\* or emboli\*)) and diabet\*) 64

#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 740

#8 MeSH DESCRIPTOR Vascular Endothelial Growth Factors EXPLODE ALL TREES WITH QUALIFIER AI 0

#9 MeSH DESCRIPTOR Receptors, Vascular Endothelial Growth Factor EXPLODE ALL TREES WITH QUALIFIER AI 0

#10 (anti adj2 VEGF\*) 327

#11 (anti-VEGF\* or antiVEGF\*) 327

#12 ((anti vascular or anti-vascular or antivascular) adj2 endothelial growth factor\*) 153

#13 (((vascular endothelial adj2 growth factor\*) or vasculotropin or VEGF\* or vascular permeability factor\* or VPF) adj2 (trap\* or inhibit\* or antagonist\*)) 96

#14 (vascular proliferation adj4 inhibit\*) 0

#15 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 412

#16 MeSH DESCRIPTOR Angiogenesis Inhibitors 40

#17 MeSH DESCRIPTOR Angiogenesis Inducing Agents EXPLODE ALL TREES WITH QUALIFIER AI 0

#18 (angiogen\* adj2 (antagonist\* or inhibit\*)) 74

#19 ((antiangiogen\* or anti angiogen\* or anti-angiogen\*) adj2 (agent\* or drug\* or effect\*)) 145

#20 (angiostatic adj2 (agent\* or drug\*)) 0

#21 ((neovascularisation\* or neovascularization\* or vascularisation\* or vascularization\*) adj2 inhibit\*) 0

#22 #16 OR #17 OR #18 OR #19 OR #20 OR #21 224

#23 (Aflibercept\*) 141

#24 (Eylea or Zaltrap or Ziv-Aflibercept or AVE 0005 or AVE0005 or AVE 005 or AVE005) 22

#25 MeSH DESCRIPTOR Bevacizumab 46

#26 (Bevacizumab\*) 445

#27 (Avastin or Mvasi or Alymsys or Aybintio or Equidacent or Onbevzi or Oyavas or Zirabev or rhuMAbVEGF or rhuMAb-VEGF or rhuMAb VEGF or NSC 704865 or NSC704865) 59

#28 (IVB adj2 inject\*) 0

#29 MeSH DESCRIPTOR Ranibizumab 7

#30 (Ranibizumab\*) 142

#31 (Lucentis or rhuFab V2) 23

#32 (IVR adj2 inject\*) 0

#33 (Pegaptanib\*) 30

#34 (EYE 001 or EYE001 or Macugen or NX 1838 or NX1838) 5

#35 #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 500

#36 #15 OR #22 OR #35 839

#37 #7 AND #36 159

**Key:**

MeSH DESCRIPTOR = indexing term: Medical Subject Heading (MeSH)

QUALIFIER AI = indexing term subheading for antagonists & inhibitors

EXPLODE ALL TREES = exploded indexing term (MeSH)

\* = truncation

adj3 = terms within three words of each other (order specified).

:TI,KW = terms in either title or keyword fields

**ClinicalTrials.gov**

via <https://clinicaltrials.gov/>

Date searched: 26 May 2023

Records retrieved: 286

Two separate searches were used in Advanced Search, retrieving 286 records in total, which were imported into EndNote 20 and deduplicated.

1. **Condition or Disease:** (diabetic retinopathy)

**Other Terms:** (Aflibercept OR Eylea OR Zaltrap OR Bevacizumab OR Avastin OR Mvasi OR Alymsys OR Aybintio OR Equidacent OR Onbevzi OR Oyavas OR Zirabev OR rhuMAb VEGF OR Ranibizumab OR Lucentis OR rhuFab OR Pegaptanib OR Macugen) = **190 hits**

1. **Condition or Disease:** (diabetic retinopathy)

**Other Terms:** ((VEGF OR vascular endothelial growth factor OR vasculotropin OR vascular permeability factor or VPF) AND (anti OR trap or inhibitor or antagonist)) = **96 hits**

**European Union Clinical Trials Register**

via [www.clinicaltrialsregister.eu/ctr-search/search](http://www.clinicaltrialsregister.eu/ctr-search/search)

Date searched: 26 May 2023

Records retrieved: 163

Two separate searches were used, retrieving 163 records in total, which were imported into EndNote 20 and deduplicated.

1. (("diabetic retinopathy") AND (Aflibercept OR Eylea OR Zaltrap OR Bevacizumab OR Avastin OR Mvasi OR Alymsys OR Aybintio OR Equidacent OR Onbevzi OR Oyavas OR Zirabev OR "rhuMAb VEGF" OR Ranibizumab OR Lucentis OR rhuFab OR Pegaptanib OR Macugen)) = **113 hits**
2. (("diabetic retinopathy") AND ((anti OR trap or inhibitor OR antagonist) AND (VEGF OR "vascular endothelial growth factor" OR vasculotropin OR "vascular permeability factor" OR VPF))) = **50 hits**

**WHO International Clinical Trials Registry Platform (ICTRP)**

via <https://trialsearch.who.int/>

Date searched: 26 May 2023

Records retrieved: 198

Two separate searches were used in Advanced Search, retrieving 198 records in total, which were imported into EndNote 20 and deduplicated.

1. Advanced Search

**Condition:** (diabetic retinopathy)

**Intervention:** (Aflibercept OR Eylea OR Zaltrap OR Bevacizumab OR Avastin OR Mvasi OR Alymsys OR Aybintio OR Equidacent OR Onbevzi OR Oyavas OR Zirabev OR rhuMAb VEGF OR Ranibizumab OR Lucentis OR rhuFab OR Pegaptanib OR Macugen)

**Recruitment Status:** ALL = **194 records for 180 trials**

1. Advanced Search

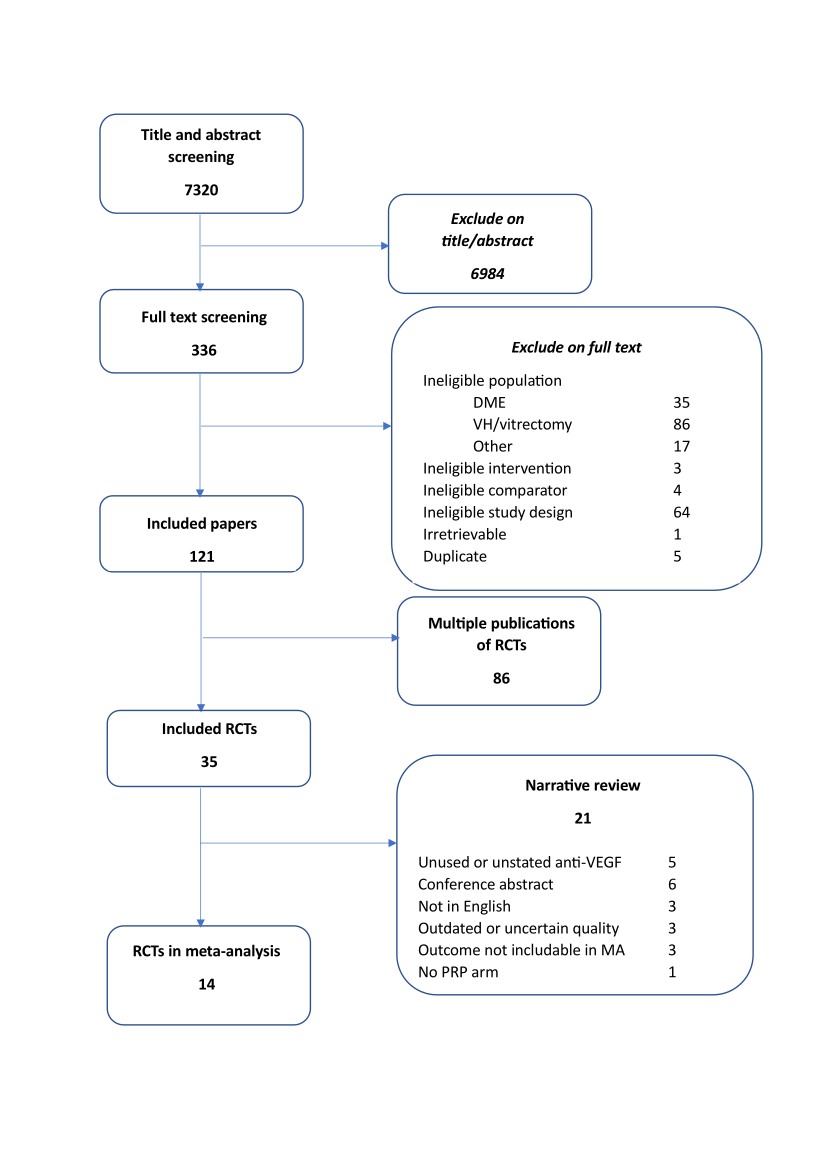
**Condition:** (diabetic retinopathy)

**Intervention:** ((VEGF OR vascular endothelial growth factor OR vasculotropin OR vascular permeability factor or VPF) AND (anti OR trap or inhibitor or antagonist))

**Recruitment Status:** ALL = **23 records for 18 trials**

## 1.2: PRISMA flow chart

Figure 1 PRISMA flow diagram



## 1.3 List of excluded studies

## RCT of DME (35)

Bayer A G. An open-label, randomized, active-controlled, parallel-group, Phase-3b study of the efficacy, safety, and tolerability of three different treatment regimens of 2 mg aflibercept administered by intr.

Braimah I Z, Kenu E and Amissah-Arthur K N; Akafo S ; Kwarteng K O; Amoaku W M;. (2019). Safety of intravitreal ziv-aflibercept in choroido-retinal vascular diseases: A randomised double-blind intervention study. *PLoS ONE [Electronic Resource]*, 14(10), pp.e0223944.

Bressler S B, Qin H, Beck R W; Chalam K V; Kim J E; Melia M ; Wells J A; 3rd ; Diabetic Retinopathy Clinical Research and Network;. (2012). Factors associated with changes in visual acuity and central subfield thickness at 1 year after treatment for diabetic macular edema with ranibizumab. *Archives of Ophthalmology*, 130(9), pp.1153-61.

Bressler S B, Qin H, Melia M ; Bressler N M; Beck R W; Chan C K; Grover S ; Miller D G; Diabetic Retinopathy Clinical Research and Network;. (2013). Exploratory analysis of the effect of intravitreal ranibizumab or triamcinolone on worsening of diabetic retinopathy in a randomized clinical trial. *JAMA Ophthalmology*, 131(8), pp.1033-40.

Bressler S B, Liu D, Glassman A R; Blodi B A; Castellarin A A; Jampol L M; Kaufman P L; Melia M ; Singh H ; Wells J A; Diabetic Retinopathy Clinical Research and Network;. (2017). Change in Diabetic Retinopathy Through 2 Years: Secondary Analysis of a Randomized Clinical Trial Comparing Aflibercept, Bevacizumab, and Ranibizumab. *JAMA Ophthalmology*, 135(6), pp.558-568.

Dep of Ophthalmology and Medical University of Vienna. *A randomized, double-masked study with intraocular Bevacizumab (Avastin®) compared with intravitreal Ranibizumab (Lucentis®) in patients with persistent diabetic macular edema or persistent active*. [online] . Available at: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract\_number:2008-001469-28.

Dhoot D, Hill L and Tarnowski K ; Stoilov I ;. (2018). Baseline factors associated with >= 2-step diabetic retinopathy (DR) severity improvement with ranibizumab (RBZ). *Investigative Ophthalmology and Visual Science. Conference*, 59(9).

Dhoot D S, Hill L F; Ghanekar A and Tarnowski K W; Ali F S;. (2021). Baseline Factors Associated with Diabetic Retinopathy Improvement in RIDE/RISE. *Ophthalmology Retina*, 5(1), pp.101-103.

Dhoot D S, Moini H and Reed K ; Du W ; Vitti R ; Berliner A J; Singh R P;. (2022). Functional outcomes of sustained improvement on Diabetic Retinopathy Severity Scale with intravitreal aflibercept in the VISTA and VIVID trials. *Eye*, 19, pp.19.

Dimitriou E, Theodossiadis P and Chatzirallis A ; Kazantzis D ; Theodossiadis G ; Chatziralli E ;. (2020). Intravitreal ranibizumab alone or in combination with panretinal photocoagulation for the treatment of proliferative diabetic retinopathy with coexistent macular edema: Long-term outcomes in real-life data. *Investigative Ophthalmology and Visual Science. Conference*, 61.

Ekinci M, Ceylan E and Cakici O ; Tanyildiz B ; Olcaysu O ; Cagatay H H;. (2014). Treatment of macular edema in diabetic retinopathy: Comparison of the efficacy of intravitreal bevacizumab and ranibizumab injections. *Expert Review of Ophthalmology*, 9(2), pp.139-143.

Euctr-009909-25-De . (2009). Evaluation of the efficacy and safety of a Macugen monotherapy versus Combined Therapies in the Treatment of Diabetic Retinopathy – a single centre, randomized, prospective Phase II trial. *http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2009-009909-25-DE*

Glassman A R, Stockdale C R; Beck R W; Baker C, Bressler N M; Diabetic Retinopathy Clinical Research and Network;. (2012). Evaluation of masking study participants to intravitreal injections in a randomized clinical trial. *Archives of Ophthalmology*, 130(2), pp.190-4.

Gonzalez V H. (2006). Pegaptanib in Diabetic Retinopathy: improvements in Diabetic Macular Edema, Retinal Neovascularization, and Diabetic Retinopathy Severit. *American academy of ophthalmology*, pp.192.

Gonzalez V H and Wang P W; Ruiz C Q;. (2019). Panretinal Photocoagulation for Diabetic Retinopathy in the RIDE and RISE Trials: Not "1 and Done". *Ophthalmology*, 21, pp.21.

Gonzalez V H and Wang P W; Ruiz C Q;. (2021). Panretinal Photocoagulation for Diabetic Retinopathy in the RIDE and RISE Trials: Not "1 and Done". *Ophthalmology*, 128, pp.1448-1457.

Hassan M, Sadiq M A and Halim M S; Afridi R ; Nguyen N V; Sepah Y J;. (2018). Short-Term Effects of Ranibizumab on Diabetic Retinopathy Severity and Progression. *Ophthalmology Retina*, 2(7), pp.749-751.

Hassan M, Sadiq M A and Halim M S; Afridi R ; Nguyen N V; Sepah Y J;. (2018). Short-term effects of ranibizumab on diabetic retinopathy severity and progression in the ranibizumab for edema of the macula in diabetes - Protocol 3 with high dose (READ-3) study. *Investigative Ophthalmology and Visual Science. Conference*, 59(9).

Irct201205029617N . (2012). Efficacy of Macular laser Photocoagulation with or without Intravitreal Injection of Bevacizumab (Avastin) or Triamcinolone Acetonide for Diffuse Diabetic Macular Edema. *http://www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT201205029617N1*

Mehta H, Lim L L and Nguyen V ; Qatarneh D ; Wickremasinghe S S; Hodgson L A. B; Quin G J; McAllister I L; Gillies M C; Fraser-Bell S ;. (2019). Development of New Proliferative Diabetic Retinopathy in the BEVORDEX Trial. *Ophthalmology Retina*, 3(3), pp.286-287.

Mitchell P, McAllister I and Larsen M ; Staurenghi G ; Korobelnik J F; Boyer D S; Do D V; Brown D M; Katz T A; Berliner A ; Vitti R ; Zeitz O ; Metzig C ; Lu C ; Holz F G;. (2018). Evaluating the Impact of Intravitreal Aflibercept on Diabetic Retinopathy Progression in the VIVID-DME and VISTA-DME Studies. *Ophthalmology Retina*, 2(10), pp.988-996.

Nct (2007). Laser-Ranibizumab-Triamcinolone for Proliferative Diabetic Retinopathy. <https://clinicaltrials.gov/show/NCT00445003>

Nct. (2009). Anterior and Posterior Segment Vascular Changes Following Laser and Anti-Vascular Endothelial Growth Factor (VEGF) Treatment of Diabetic Retinopathy.

Nct (2015). Laser Therapy Combined With Intravitreal Aflibercept vs Intravitreal Aflibercept Monotherapy (LADAMO). *https://clinicaltrials.gov/show/NCT02432547*

Novartis Pharma and A G . A 12-Month, 2-Arm, Randomized, Double-Masked, Multicenter Phase III Study Assessing the Efficacy and Safety of Brolucizumab every 4 weeks versus Aflibercept every 4 weeks in Adult Patients with Vis.

Novartis Pharma Gmb and H . A randomized, single-blinded, multicenter, phase IV study to compare systemic VEGF protein dynamics following monthly intravitreal injections of 0.5 mg ranibizumab versus 2 mg aflibercept until stu.

Novartis Pharma and A G . A Two-Year, Three-Arm, Randomized, Double Masked, Multicenter, Phase III Study Assessing the Efficacy and Safety of Brolucizumab versus Aflibercept in Adult Patients with Visual Impairment due to D.

Novartis Pharma and A G . A Two-Year, Two-Arm, Randomized, Double Masked, Multicenter, Phase III Study Assessing the Efficacy and Safety of Brolucizumab versus Aflibercept in Adult Patients with Visual Impairment due to Dia.

Oxurion N V. A Phase 2, randomised, single-masked, active-controlled, multicentre study to evaluate the efficacy and safety of intravitreal THR-317 administered in combination with ranibizumab, for the treatmen.

Quark Pharmaceuticals and Inc . An Open-Label Dose Escalation Study of PF-04523655 (Stratum I) Combined With A Prospective, Randomized, Double-Masked, Multi-Center, Controlled Study (Stratum II) Evaluating The Efficacy and Safety.

Sadiq M A, Hassan M and Soliman M K; Afridi R ; Do D V; Nguyen Q D; Sepah Y J;. (2017). Effects of Two Different Doses of Ranibizumab on Diabetic Retinopathy Severity. *Ophthalmology Retina*, 1(6), pp.566-567.

Sameen M, Khan M S and Mukhtar A ; Yaqub M A; Ishaq M ;. (2017). Efficacy of intravitreal bevacizumab combined with pan retinal photocoagulation versus panretinal photocoagulation alone in treatment of proliferative diabetic retinopathy. *Pakistan Journal of Medical Sciences*, 33(1), pp.142-145.

Sasongko M B, Rogers S and Constantinou M ; Sandhu S S; Wickremasinghe S S; Al-Qureshi S ; Lim L L;. (2020). Diabetic retinopathy progression 6 months post-cataract surgery with intravitreous bevacizumab vs triamcinolone: A secondary analysis of the DiMECAT trial. *Clinical & Experimental Ophthalmology*, 48(6), pp.793-801.

Shahraki T, Arabi A and Nourinia R ; Beheshtizadeh N F; Entezari M ; Nikkhah H ; Karimi S ; Ramezani A ;. (2022). Panretinal photocoaguliation versus intravitreal bevacizumab versus a proposed modified combination therapy for treatment of proliferative diabetic retinopathy: A Randomized Three-Arm Clinical Trial (CTPDR Study). *Retina*, 42, pp.1065-1076.

Yan P, Qian C and Wang W ; Dong Y ; Wan G ; Chen Y ;. (2016). Clinical effects and safety of treating diabetic macular edema with intravitreal injection of ranibizumab combined with retinal photocoagulation. *Therapeutics & Clinical Risk Management*, 12, pp.527-33.

## RCT of vitreous haemorrhage or vitrectomy (86)

Ahmadieh H, Shoeibi N and Entezari S M;. (2008). Intravitreal Bevacizumab for Early Post-vitrectomy Hemorrhage in Diabetics: a Randomized, DoubleMasked Clinical Trial. *American academy of ophthalmology*, pp.181.

Ahmadieh H, Shoeibi N and Entezari M ; Monshizadeh R ;. (2009). Intravitreal bevacizumab for prevention of early postvitrectomy hemorrhage in diabetic patients: a randomized clinical trial. *Ophthalmology*, 116(10), pp.1943-8.

Ahn J, Woo S J and Chung H ; Park K H;. (2011). The effect of adjunctive intravitreal bevacizumab for preventing postvitrectomy hemorrhage in proliferative diabetic retinopathy. *Ophthalmology*, 118(11), pp.2218-26.

Albuquerque T L and Pierozzi G S; Araujo A C. C; Neto N H; Carregal T B; Martins M C; Souza J C; Carlos G A; Bordon A F;. (2014). Comparative, randomized, double blinded study of the use of Anti-VEGF in patients with vitreous hemorrhage or tractional retinal detachment secondary to diabetic retinopathy. *Investigative Ophthalmology and Visual Science*, 55 (13), pp.4391.

Aleman I, Castillo Velazquez and J ; Rush S W; Rush R B;. (2019). Ziv-aflibercept versus bevacizumab administration prior to diabetic vitrectomy: a randomised and controlled trial. *British Journal of Ophthalmology*, 103(12), pp.1740-1746.

Arevalo J F, Lasave A F; Kozak I and Al Rashaed S ; Al Kahtani E ; Maia M ; Farah M E; Cutolo C ; Brito M ; Osorio C ; Navarro P ; Wu L ; Berrocal M H; Morales-Canton V ; Serrano M A; Graue-Wiechers F ; Sabrosa N A; Alezzandrini A A; Gallego-Pinazo R ; Pan-American Collaborative Retina Study; Group ;. (2019). Preoperative Bevacizumab for Tractional Retinal Detachment in Proliferative Diabetic Retinopathy: A Prospective Randomized Clinical Trial. *American Journal of Ophthalmology*, 207, pp.279-287.

Bhavsar A. (2013). A Randomized trial evaluating intravitreal ranibizumab or intravitreal saline for vitreous hemorrhage from proliferative diabetic retinopathy. *Investigative Ophthalmology and Visual Science. Conference*, 54(15).

Bhavsar A R, Torres K and Beck R W; Friedman S M; Glassman A R; Maturi R K; Melia M ; Singer M A; Stockdale C R; Diabet Retinopathy Clin Res; Networ ;. (2013). Randomized Clinical Trial Evaluating Intravitreal Ranibizumab or Saline for Vitreous Hemorrhage From Proliferative Diabetic Retinopathy Diabetic Retinopathy Clinical Research Network. *Jama Ophthalmology*, 131(3), pp.283-293.

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## 1.4: Trials not included in meta-analyses

Table 1 Trials not included in meta-analyses

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Trial** | **Key Paper(s)** | **Anti-VEGF** | **Comparator** | **Location** | **Sample size** | **Population** |
| ***No PRP arm*** | | | | | | |
| **RECOVERY** | Alagorie 2021 | Aflibercept (monthly) | Aflibercept (quarterly) |  | 40 eyes | PDR |
|  |  |  |  |  |  |  |
| ***Conference abstracts*** | | | | | | |
| **Garcia** | Garcia-Aguirre 2008 | Bevacizumab | PRP | Mexico | 10 persons | NPDR, PDR |
| **Ernst** | Ernst 2012 | Bevacizumab | PRP | USA | 10 persons | NPDR, PDR |
| **MEDICARE** | Dufour 2017 | Aflibercept | PRP | France | 20 persons | PDR |
| **Oh** | Oh 2014 CA | Bevacizumab (+PRP) | PRP | South Korea | 125 persons | NPDR, PDR |
| **Ramezani** | Ramezani 2021 | Bevacizumab (+PRP) | PRP | Unknown | 153 eyes | PDR |
| **Tardieu** | Tardieu 2022 | Not stated | PRP | Unknown | 40 persons | PDR |
|  |  |  |  |  |  |  |
| ***Papers in Chinese*** | | | | | | |
| **Bi** | Bi 2020 | Ranibizumab (+PRP) | PRP | China | 120 persons | Unclear |
| **Meng** | Meng 2019 | Ranibizumab (+PRP) | PRP | China | 80 persons | PDR |
| **Zhou** | Zhou W 2017 | Bevacizumab (+PRP) | PRP | China | 30 persons | Unclear |
|  |  |  |  |  |  |  |
| ***Trials from before 2010*** | | | | | | |
| **Cho** | Cho 2009-2010 | Bevacizumab (+PRP) | PRP+Triamcinolone | China | 91 eyes | NPDR, PDR |
| **Mirshahi** | Mirshahi 2008 | Bevacizumab (+PRP) | PRP, Sham injection | Iran | 80 eyes | PDR |
| **Tonello** | Tonelo 2008 | Bevacizumab (+PRP) | PRP | Brazil | 30 eyes | PDR |
|  |  |  |  |  |  |  |
| ***Unused or unspecified anti-VEGFs*** | | | | | | |
| **Chen / Zhou** | Chen 2017 | Unclear | PRP | China | 120 persons | PDR |
| **Gonzalez** | Gonzalez 2007/2009/2014 | Pegaptanib sodium | PRP | USA | 20 persons | PDR |
| **He** | He 2020 | Conbercept (+PRP) | PRP | China | 44 eyes | PDR |
| **Leal** | Leal 2013 | Pegaptanib sodium (+PRP) | PRP | Portugal | 22 persons | PDR |
| **Wang** | Wang 2019 | Conbercept (+PRP) | PRP | China | 64 persons | NPDR, PDR |
|  |  |  |  |  |  |  |
| ***No protocol-specified outcomes*** | | | | | | |
| **Helmy** | Helmy 2023 | Ranibizumab | PRP | Egypt | 50 persons | PDR |
| **Preti** | Preti 2013 | Bevacizumab (+PRP) | PRP | S. America | 42 persons | PDR |
| **Rentiya** | Rentiya 2022 | Ranibizumab (+PRP) | PRP | Brazil | 30 persons | PDR |

## 1.4: Risk of bias assessment

Table 2 Full Risk of Bias assessment- Table A

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Trial** | **Randomization process** | | **Deviations from intended interventions** | | **Missing outcome data** | |
|  | **Judgement** | **Comments** | **Judgement** | **Comments** | **Judgement** | **Comments** |
| Ahmad 2012 | Some concerns | Randomised by "simple lottery". No further details.  No allocation concealment method reported.  No evidence of significant differences in key prognostic factors. | Some concerns | No placebo.  States "the physician did not know which eye has been injected", but the control group did not receive a placebo injection.  No CONSORT diagram, and no reporting of deviation from the intervention due to the trial context.  ITT/mITT not reported.  The risk that the analysis was not based on ITT principles cannot be excluded. | Low | All participants completed the 90 days follow-up. |
| Ali 2018 | Some concerns | States the study is randomised, with allocation by "simple lottery method". No further details.  No information on whether allocation was concealed. | Some concerns | No placebo. Contralateral design.  No CONSORT diagram, and no reporting of deviation from the intervention due to the trial context.  ITT/mITT not reported.  The risk that the analysis was not based on ITT principles cannot be excluded. | Some concerns | No information on loss to follow-up.  No evidence that the result was not biased by any possible missing outcome data.  Likelihood of significant missingness may be limited by relatively short follow-up duration. |
| CLARITY | Low | Computer generated with minimisation. Central allocation by trials unit.  No significant baseline imbalances. | Low | No placebo. "The treating ophthalmologists and participants were not masked." CONSORT diagram reported. No evidence of deviation from intended intervention due to the trial context.  Analyses conducted according to ITT principles. | Low | Available for 91% (211/232) at 52 weeks.  Appropriate sensitivity analyses for missing BCVA data with prespecified alternative scenarios were conducted and showed no evidence of bias. |
| Ferraz 2015 | Some concerns | Described as randomised. No other details.  No details on allocation concealment.  Contralateral design.  No evidence of significant differences in key prognostic factors. | Some concerns | Placebo controlled. Contralateral design. Trial registry entry described as single masked (participants). Masking only reported for outcome assessors ("examiners" and participants), not for carers. No CONSORT diagram, and no reporting of deviation from the intervention due to the trial context.  ITT/mITT not reported. The risk that the analysis was not based on ITT principles cannot be excluded. | Low | 3% (2/60) eyes excluded due to VH in the control arm. It appears that all other randomised eyes were analysed. |
| Marashi 2017 | High | Described as randomised. No other details. No details on allocation concealment. 80% had DME at baseline in the IVB arm, vs. 20% in the control arm. Although the trial is small, the difference is large and considered unlikely to be due to chance alone. No adjustments for baseline imbalance were performed. | Some concerns | No placebo.  No CONSORT diagram, and no reporting of deviation from the intervention due to the trial context.  ITT/mITT not reported.  The risk that the analysis was not based on ITT principles cannot be excluded. | Some concerns | No information on loss to follow-up. Follow-up duration means that the risk of at least some loss to follow-up is high.  No evidence that the result was not biased by any possible missing outcome data. |
| PANORAMA | Low | Patients were randomized according to a central randomization scheme with treatment assignments provided by an interactive voice response system (IVRS)/interactive web response system (IWRS) to the designated study pharmacist (or qualified designee).  Some differences in sex at baseline: higher rate of males in 2q16 (56%) and 2q8 (60%) compared with control (52%), but no other imbalances in reported baseline characteristics. | Low | Placebo controlled. Participants, outcome assessors and study personel were masked throughout the study period, except for study drug administration which was done by an unmasked physician.  Rates of participants not assessed were higher in the control group (73%) at 100 weeks (and 52 weeks) compared with aflibercept arms (84 & 83%), though participants were masked throughout the study period, and there was no evidence of changes from the intended intervention that occured because of the trial context.    All participants analysed. Last-observation carried forward (LOCF) imputation method used. | Low | Rates of participants not assessed were higher in the control group (73%) at 100 weeks compared with aflibercept arms (84 & 83%).  Sensitivity analysis: primary efficacy analysis was also performed using all observed measurements (regardless of whether rescue treatment was given). Protocol also stated that for sensitivity analyses, only true missing values would be imputed using the LOCF procedure, and that baseline values would be carried forward if all post-baseline observations were missing or nongradeable.  Sensitivity analysis results showed similar results to main analyses for DRSS, although all are based on the LOCF principle, and sensitivity analyses were not peformed for BCVA.  The risk that the higher rate of missingness in the control arm is partly due to its true value cannot be excluded. However, due to the size of the difference in missingness, any possible bias arising is likely to be small. |
| PRIDE | Some concerns | A number of differences in baseline characteristics, including key variables, although differences do not clearly favour one arm and may have occurred by chance. Differences in mean age (IVR: 52.5, PRP: 53, IVR+PRP: 55), age distribution (<65y: 86%, 86%, 72%); smoker (14%, 26%, 35%); duration of diabetes (25y, 23, 21), Mean mm2 NVD+NVE: 9.4, 5.4, 4.1; ETDRS: 83.3, 80.5, 80.0. | Low | No masking.   Analyses conducted based on ITT principle, using LOCF. | Some concerns | 23% (25/108) of randomised participants not measured at 12 months.   No significant differences in rates of missingness across groups. |
| PROTEUS | Low | Computer-generated block randomisation. Central allocation implemented through electronic platform.  Large and statistically significant difference in mean age (IVR+PRP: 58.8 yrs (13.3), PRP: 52.0 (11.9)). Non statistically significant difference in sex (31.7% vs. 41.3% female). Difference in time since diagnosis NR.  In a multivariate analysis, "age, HbA1c, and number of PRP treatments did not show a significant association with BCVA difference from baseline to month 12." Re-analysis with IPD provided by trialist suggested low concerns. | Low | CONSORT diagram reported. No evidence of deviation from intended intervention due to trial context.  ITT-principle based primary analysis. | Some concerns |  |
| PROTOCOL-S | Low | Permuted block randomisation. Stratification by site and presence of centrally involved DME. Central allocation concealment with web-based tool from trials unit. No evidence of baseline imbalances. | Low | No placebo. Masking only for outcome assessors.  All eyes randomised received the treatment allocated.  Analyses conducted according to ITT principles. | Low | 83% (382/394) completed 2 year follow-up. Of those, 5% (18/394) died, 12%(48/394) withdrew or missed their visit.  For missing data at 2 years, SAP reports "Markov chain Monte Carlo (MCMC) multiple imputation based on treatment group, the randomization stratification factors, and all available visual acuity data from assessment visits prior to 2 years." |
| PROTOCOL-W | Low | Central, web-based (DRCR network) randomisation, stratified by DR severity level.  No evidence of baseline imbalances | Low | Placebo controlled. Participants masked. Investigators and study coordinators unmasked. CONSORT diagram reported. No evidence of deviation from intended intervention due to trial context.   Analyses conducted according to ITT principles. | Low | 68.5% (137/200, or 74.9% excluding 17 deaths) completed their 4 yr visit in intervention arm, vs. 67.3% (134/199, 73.2% excluding 16 deaths).  Multiple imputation (Markov model) used for missing data (assumes data are missing at random). Model included treatment group, study eye laterality, baseline DRSS, baseline visual acuity, and change in visual acuity from baseline to each protocol assessment visit up to and including 4 years. Missingness documented, balanced between arms and unlikely to depend on its true value. |
| Rebecca 2021 | Some concerns | Described as randomised. No other details.  No details on allocation concealment.  No evidence of significant differences in key prognostic factors. | Some concerns | No placebo.  No CONSORT diagram, and no reporting of deviation from the intervention due to the trial context.  ITT/mITT not reported.  The risk that the analysis was not based on ITT principles cannot be excluded. | Some concerns | No information on loss to follow-up. Follow-up duration means that the risk of at least some loss to follow-up is high.  No evidence that the result was not biased by any possible missing outcome data. |
| Roohipour 2019 | Some concerns | Random block method, but no further details on how allocation sequence was generated. No information on allocation concealment.   No evidence of significant differences in key prognostic factors. | Some concerns | No placebo. Contralateral design.  No CONSORT diagram, and no reporting of deviation from the intervention due to the trial context.  ITT/mITT not reported.  The risk that the analysis was not based on ITT principles cannot be excluded. | Some concerns | Significant loss to follow-up. Only 59% (19 out of 32) completed 10 months follow-up.   No evidence that the result was not biased by missing outcome data.  Reasons for loss to follow-up were NR. The risk that at least some missingness could be due to visual acuity outcomes cannot be excluded. |
| Sao Paulo A | Some concerns | Randomised based on a computer-generated sequence. No further details reported.  There were differences in age (mean PASCAL arm age was 7.5 years older than IVR and 2.2 years older than ETDRS) although they were not statistically significant. | Some concerns | No placebo.  No evidence of deviation from the intervention due to the trial context.  ITT/mITT not explicitly reported. | Some concerns | 13/48 (27%) withdrew. No significant difference in withdrawal between arms.  No evidence that the result was not biased by missing outcome data.  Reasons for loss to follow-up were NR. The risk that at least some missingness could be due to visual acuity outcomes cannot be excluded. |
| Sao Paulo B | Some concerns | Block randomisation (blocks of 2), allocation drawn randomly by technician from one of two identical opaque envelopes. No further information on randomisation and allocation concealment.  No evidence of significant differences in key prognostic factors. | Some concerns | No placebo.  No CONSORT diagram, and no reporting of deviation from the intervention due to the trial context.  ITT/mITT not reported.  The risk that the analysis was not based on ITT principles cannot be excluded. | Some concerns | Only 72.5% (29/40) participants analysed at 48 weeks.   No evidence that the result was not biased by missing outcome data.  Significant loss to follow-up. Reported reasons for loss to follow-up were generally appropriate (incl. 4 deaths and 2 ocular events, 4 did not return for assessment, 1 not specified). No clear imbalances between arms. |

Table 3 Full Risk of Bias assessment - Table B

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Trial | Measurement of the outcome | | Selection of the reported result | | Overall Bias |
|  | **Judgment** | **Comments** | **Judgment** | **Comments** | **Judgment** |
| Ahmad 2012 | High | Snellen chart, converted to logMAR    Participants unmasked (no placebo). No mention of blinding of outcome assessors.  Participants and study personnel may have been influenced by knowledge of the intervention. | Some concerns | Insufficient information about analysis plans. | High |
| Ali 2018 | High | Appears to be ETDRS, standard scale No placebo | Some concerns | No protocol. | High |
| CLARITY | Some concerns | ETRDS, standard scale.  The lack of blinding of participants means raises some concerns, although appropriate steps were taken to mask the optometrists assessing BCVA.  Optometrists "masked to treatment allocation throughout the study. The  optometrists received the participants into the visual acuity lanes with a visual acuity-specific source data worksheet that included the PIN and details of the study eye and non-study eye to be refracted, but with no previous records or case report forms by which the patient’s treatment arm could be identified." | Low | A SAP "was finalised before data lock and agreed with oversight committees." | Low |
| Ferraz 2015 | Low | ETDRS Outcome assessors masked throughout the study period. | Some concerns | Insufficient information about analysis plans. Outcome retrospectively reported in trial registry. | Some concerns |
| Marashi 2017 | High | Snellen scale, converted to logMAR  No placebo  Participants and study personel may have been influenced by knowledge of the intervention. | Low | Protocol registered around time of study start, and prespecified outcome and time point were reported. | High |
| PANORAMA | Low | ETRDS method  Outcome assessors were masked throughout the study period. | Low |  | Low |
| PRIDE | High | ETDRS, standard. No masking of outcome assessors. | Low | SAP not mentioned. Protocol registered before time of study start, and prespecified outcome and time point were reported. | Some concerns |
| PROTEUS | High | Standard ETDRS  No placebo. Participants and outcome assessors were aware of the intervention.  Participants and study personnel may have been influenced by knowledge of the intervention. | Low | No SAP. Outcome and follow-up specified in prospectively registered protocol. | Some concerns |
| PROTOCOL-S | Some concerns | E-ETDRS  Participants unmasked (no placebo), but protocol states that "visual acuity testers [...] will be masked to treatment group at annual visits". | Low | SAP v1.0 is dated March 2015.   Protocol first published December 2011, primary completion dated January 2015.  Outcome specified in prospectively registered protocol. | Low |
| PROTOCOL-W | Low | DRSS  Outcome assessors masked. | Low | SAP reported and finalized before unblinded outcome data were available for analysis. | Low |
| Rebecca 2021 | High | BCVA. Scale not reported, but standard outcome.  No placebo. Participants and outcome assessors were aware of the intervention.  Participants and study personnel may have been influenced by knowledge of the intervention. | Some concerns | Insufficient information about analysis plans. | High |
| Roohipour 2019 | High | BCVA measured using standard Snellen chart  No placebo.  Participants and study personnel may have been influenced by knowledge of the intervention. | Some concerns | SAP not mentioned in protocol or publication. 10 months follow-up assessment was not pre-specified (unlike 6 months). | High |
| Sao Paulo A | High | Standard ETDRS  No placebo. Participants were aware of the intervention. No masking of outcome assessor reported. | Some concerns | No SAP. Outcome and follow-up specified in protocol, but unclear if prospectively registered. | High |
| Sao Paulo B | High | ETDRS, converted to logMA  No blinding of outcome assessor, who performed the interventions.  Participants and study personnel may have been influenced by knowledge of the intervention. | Some concerns | Insufficient information about analysis plans. | High |

# Appendix 2: Proliferative diabetic retinopathy: All BCVA analyses

All figures and tables relate to the trials of proliferative diabetic retinopathy (PDR), excluding the two trials (PANORAMA, PROTOCOL W) of non-proliferative retinopathy. For their results, see Appendix 4.

## 2.1: Figures and forest plots summarising BCVA data

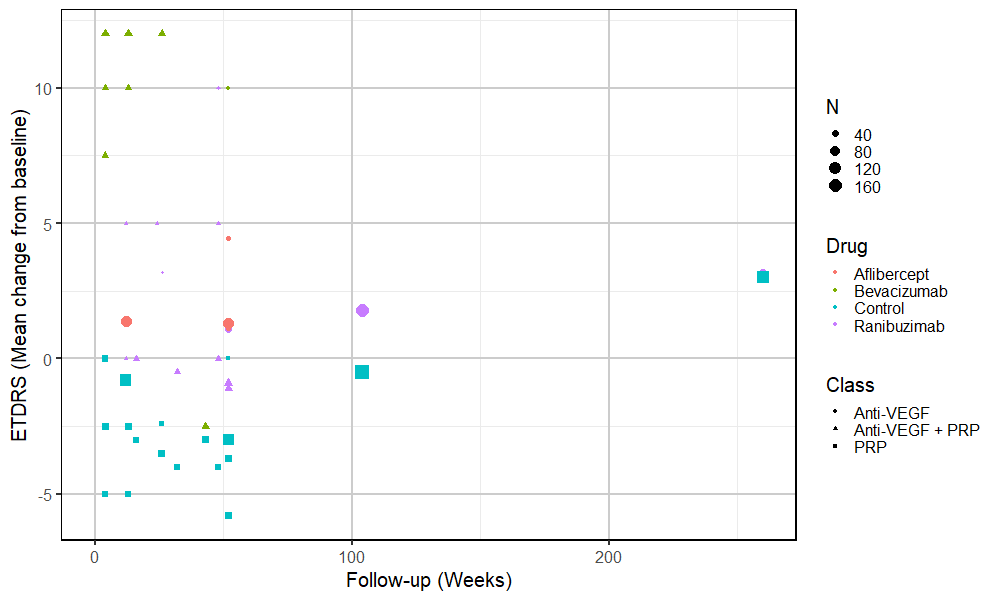


Figure 2 All ETDRS data (as mean change from baseline) by drug and type of intervention

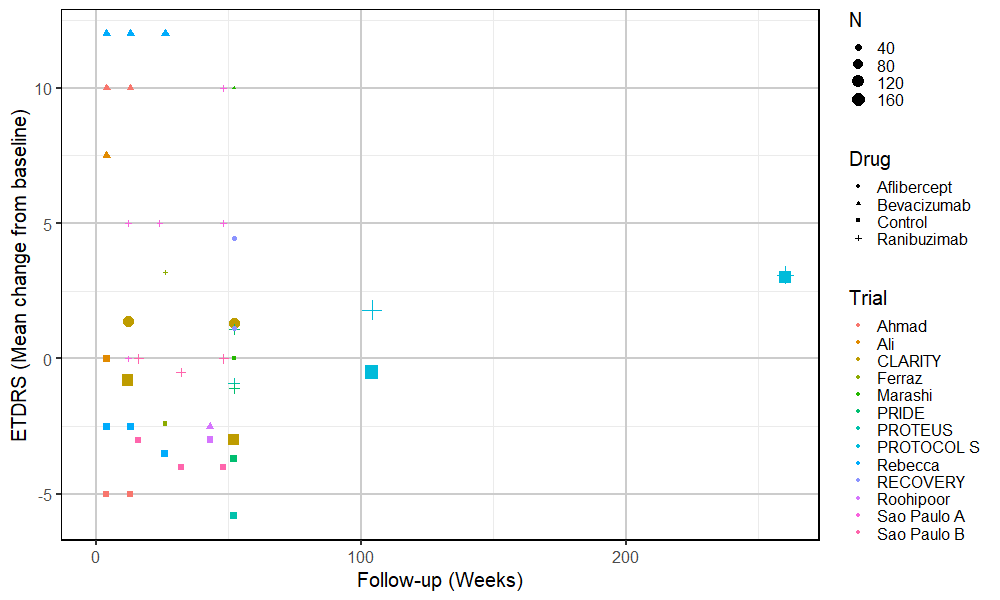


Figure 3 All ETDRS data (as mean change from baseline) by trial and drug type

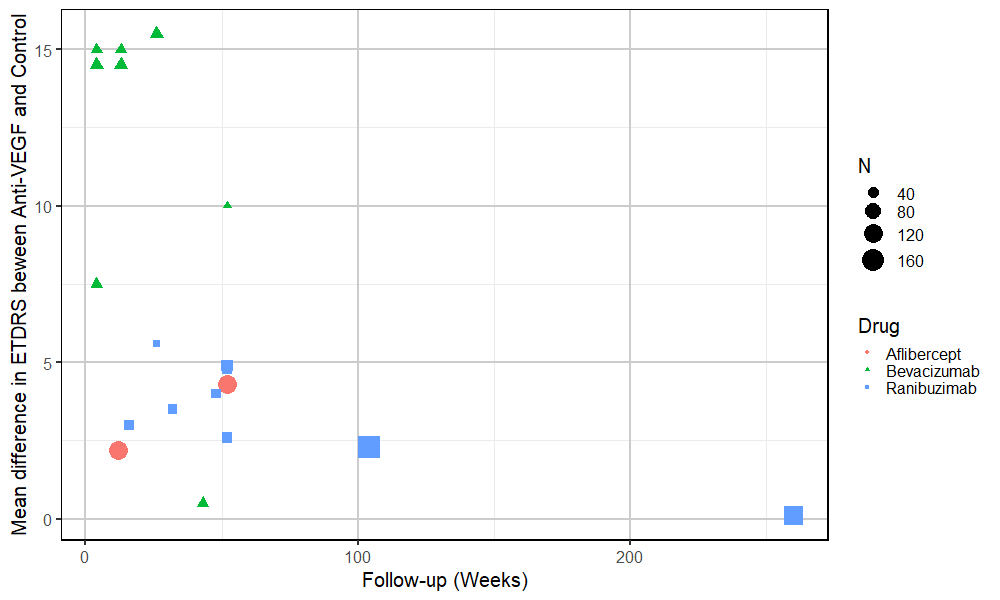


Figure 4 Mean difference in ETDRS between anti-VEGF and control arms over time

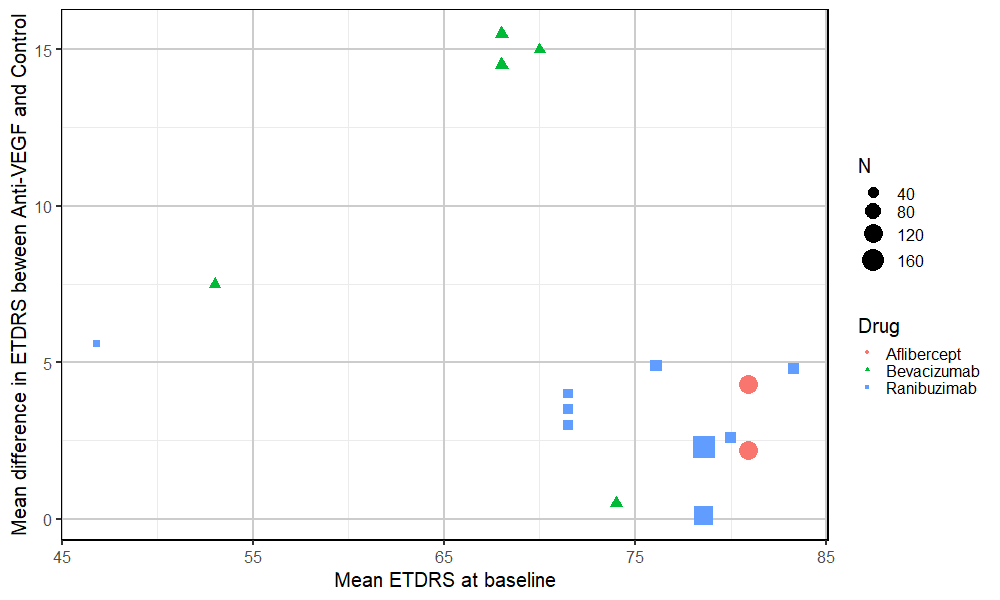


Figure 5 Mean difference between anti-VEGF and control arms by ETDRS at randomisation

Note from these figures that there appears to be a possible decline in benefit to vison over time, and that the benefit of ant-VEGF may be greater in people with poorer initial vision, but these difference may be confounded by differences between types of anti-VEGF.

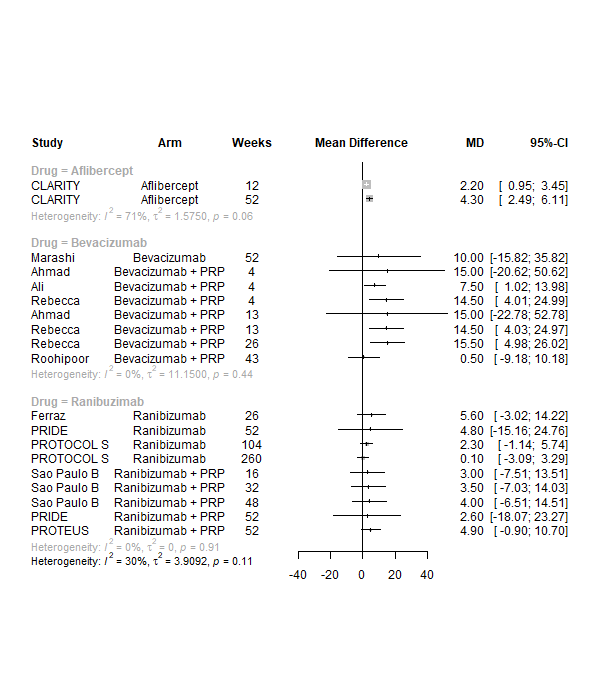


Figure 6 Forest plot of all mean differences in ETDRS between anti-VEGF and control (right side favours anti-VEGF)

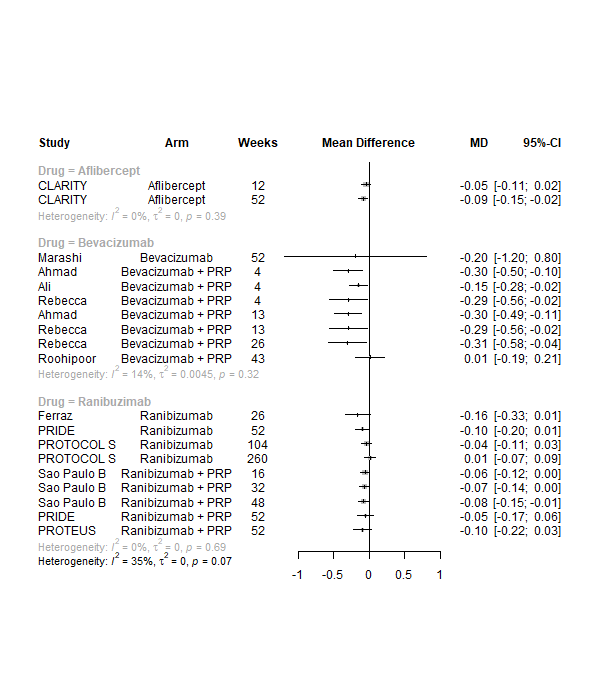


Figure 7 Forest plot of all mean differences in logMAR between anti-VEGF and control (left side favours anti-VEGF)

## 2.2 Forest plots of meta-analyses of BCVA

### 2.2.1 Up to 1 year

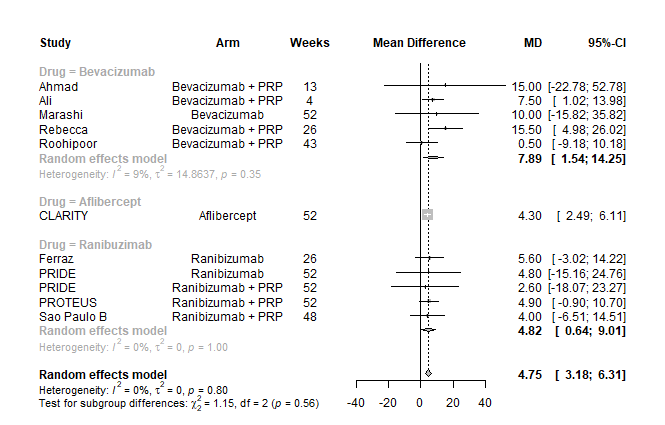


Figure 8 Meta-analysis of mean differences in ETDRS between anti-VEGF and control up to 1 year of follow-up (right side favours anti-VEGF)

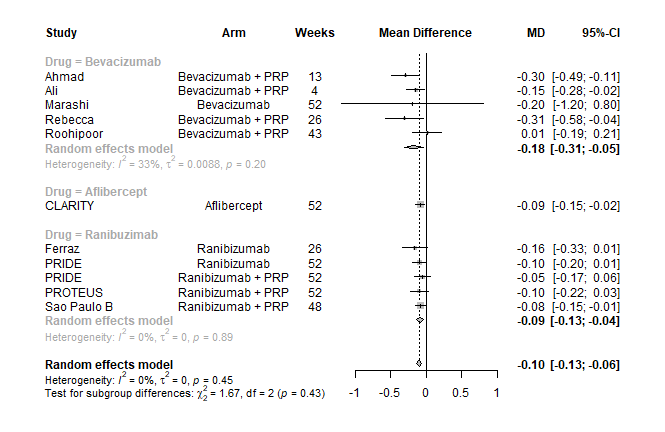


Figure 9 Meta-analysis of mean differences in logMAR between anti-VEGF and control up to 1 year of follow-up (left side favours anti-VEGF)

### 2.2.2 1 to 2 years’ follow-up

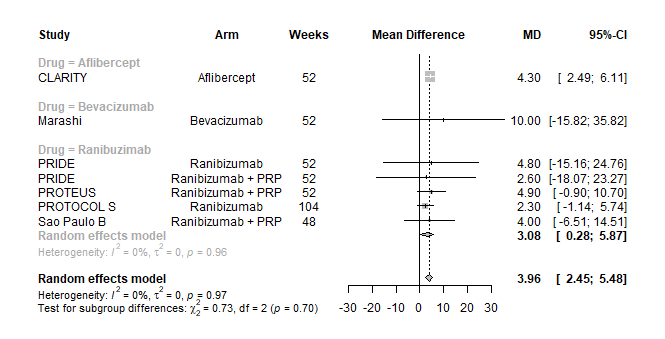


Figure 10 Meta-analysis of mean differences in ETDRS between anti-VEGF and control with 1 to 2 years' of follow-up (right side favours anti-VEGF)

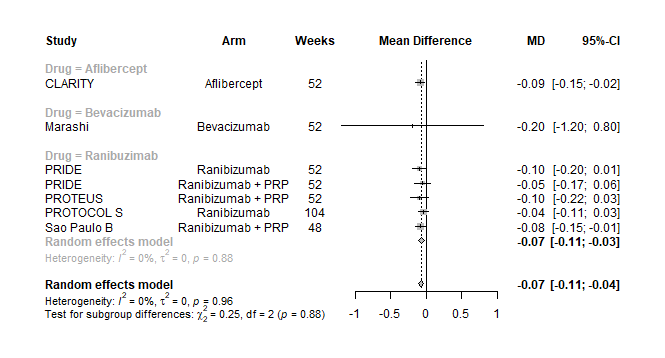


Figure 11 Meta-analysis of mean differences in logMAR between anti-VEGF and control with 1 to 2 years' of follow-up (left side favours anti-VEGF)

### 2.2.3 Maximum follow-up in trial (up to 2 years)

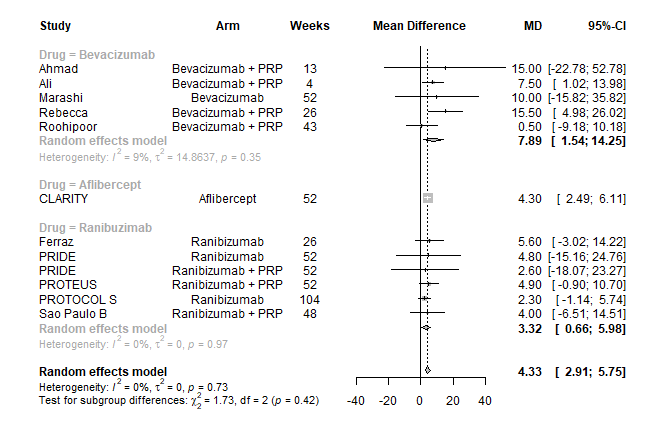


Figure 12 Meta-analysis of mean differences in ETDRS between anti-VEGF and control at end of trial (right side favours anti-VEGF)

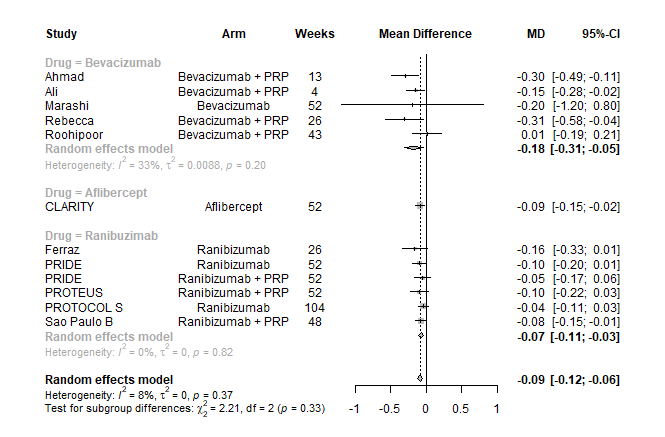


Figure 13 Meta-analysis of mean differences in logMAR between anti-VEGF and control at end of trial (left side favours anti-VEGF)

## 2.3: Network meta-analyses of BCVA (using logMAR)

Note: From this point forward on meta-analyses of BCVA measured using logMAR are presented. Some analyses using ETDRS were performed, but are not included here. Similarly, only random effects analyses are presented for simplicity, as differences between random and fixed effect analyses were minimal.

### 2.3.1 Analyses at up to 1 year of follow-up

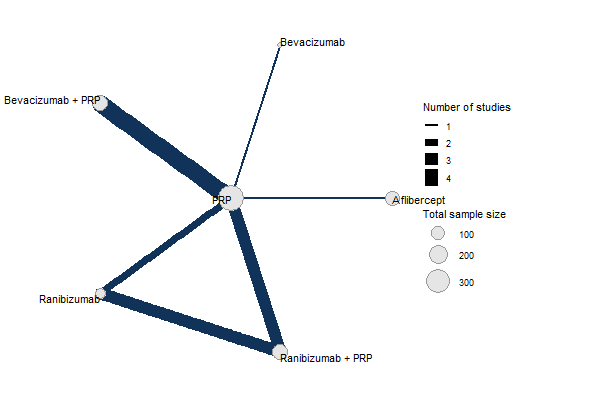


Figure 14 Network diagram of BCVA at up to 1 year of follow-up



Figure 15 All treatment comparisons for 1-year random-effects NMA of logMAR

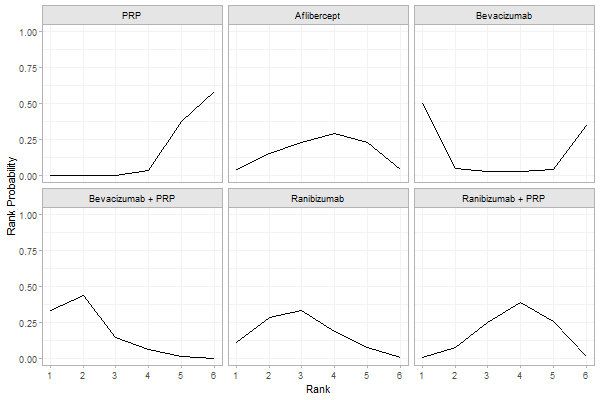


Figure 16 Probability of treatments for 1-year random-effects NMA of logMAR

Table 4 Results of NMA of logMAR up to 1 year - comparisons between treatments

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Intervention** | **Comparator** | **Mean difference** | **95% CI** | |
| Aflibercept | PRP | -0.084 | -0.222 | 0.056 |
| Bevacizumab | PRP | -0.198 | -1.213 | 0.785 |
| Bevacizumab + PRP | PRP | -0.172 | -0.279 | -0.069 |
| Ranibizumab | PRP | -0.121 | -0.233 | -0.006 |
| Ranibizumab + PRP | PRP | -0.078 | -0.165 | 0.013 |
| Bevacizumab | Aflibercept | -0.115 | -1.142 | 0.853 |
| Bevacizumab + PRP | Aflibercept | -0.088 | -0.273 | 0.082 |
| Ranibizumab | Aflibercept | -0.037 | -0.213 | 0.130 |
| Ranibizumab + PRP | Aflibercept | 0.006 | -0.151 | 0.173 |
| Bevacizumab + PRP | Bevacizumab | 0.026 | -0.947 | 1.027 |
| Ranibizumab | Bevacizumab | 0.077 | -0.913 | 1.098 |
| Ranibizumab + PRP | Bevacizumab | 0.121 | -0.867 | 1.151 |
| Ranibizumab | Bevacizumab + PRP | 0.051 | -0.095 | 0.208 |
| Ranibizumab + PRP | Bevacizumab + PRP | 0.094 | -0.040 | 0.236 |
| Ranibizumab + PRP | Ranibizumab | 0.043 | -0.067 | 0.160 |

Table 5 Results of NMA of logMAR up to 1 year – ranking probabilities

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Treatment arm** | **Probability of ranking:** | | | | | |
| **1st** | **2nd** | **3rd** | **4th** | **5th** | **6th** |
| **PRP** | 0.00% | 0.13% | 0.65% | 4.93% | 37.65% | 56.65% |
| **Aflibercept** | 4.33% | 12.65% | 24.65% | 30.48% | 23.10% | 4.80% |
| **Bevacizumab** | 50.73% | 5.05% | 2.38% | 2.63% | 3.83% | 35.40% |
| **Bevacizumab + PRP** | 33.60% | 44.23% | 14.73% | 5.68% | 1.73% | 0.05% |
| **Ranibizumab** | 10.25% | 30.30% | 33.60% | 17.40% | 7.25% | 1.20% |
| **Ranibizumab + PRP** | 1.10% | 7.65% | 24.00% | 38.90% | 26.45% | 1.90% |

### 2.3.2 Analyses at 1 to 2 years’ follow up

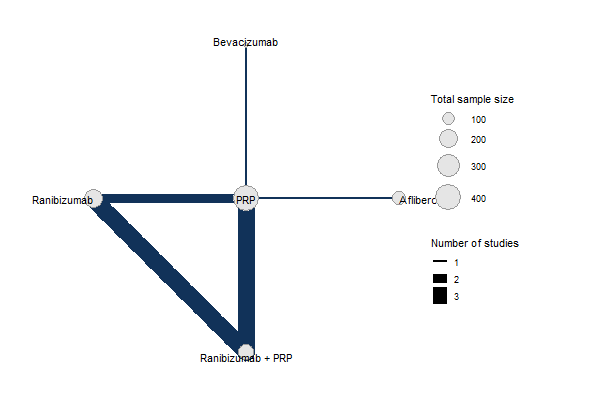


Figure 17 Network diagram of BCVA at up to 1 to 2 years of follow-up



Figure 18 All treatment comparisons for 1 to 2 year random-effects NMA of logMAR

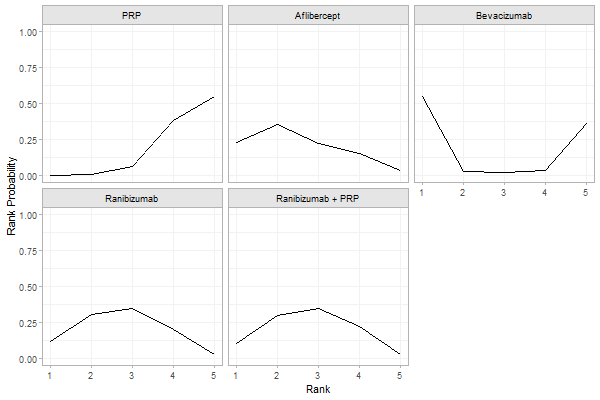


Figure 19 Probability of treatments for 1 to 2 year random-effects NMA of logMAR

Table 6 Results of NMA of logMAR 1 to 2 years - comparisons between treatments

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Intervention** | **Comparator** | **Mean difference** | **95% CI** | |
| Aflibercept | PRP | -0.080 | -0.225 | 0.100 |
| Bevacizumab | PRP | -0.182 | -1.181 | 0.816 |
| Ranibizumab | PRP | -0.072 | -0.171 | 0.017 |
| Ranibizumab + PRP | PRP | -0.068 | -0.152 | 0.020 |
| Bevacizumab | Aflibercept | -0.102 | -1.095 | 0.899 |
| Ranibizumab | Aflibercept | 0.008 | -0.200 | 0.187 |
| Ranibizumab + PRP | Aflibercept | 0.012 | -0.174 | 0.189 |
| Ranibizumab | Bevacizumab | 0.110 | -0.887 | 1.104 |
| Ranibizumab + PRP | Bevacizumab | 0.114 | -0.885 | 1.112 |
| Ranibizumab + PRP | Ranibizumab | 0.004 | -0.100 | 0.114 |

Table 7 Results of NMA of logMAR 1 to 2 years – ranking probabilities

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Treatment arm** | **Probability of ranking:** | | | | |
| **1st** | **2nd** | **3rd** | **4th** | **5th** |
| **PRP** | 0.05% | 1.20% | 6.25% | 37.93% | 54.58% |
| **Aflibercept** | 21.38% | 34.58% | 20.98% | 17.00% | 6.08% |
| **Bevacizumab** | 56.20% | 3.15% | 2.88% | 3.35% | 34.43% |
| **Ranibizumab** | 13.13% | 30.28% | 34.13% | 20.15% | 2.33% |
| **Ranibizumab + PRP** | 9.25% | 30.80% | 35.78% | 21.58% | 2.60% |

### 2.3.3 Analysis at maximum follow-up time (up to 2 years)



Figure 20 All treatment comparisons for end-of-trial random-effects NMA of logMAR

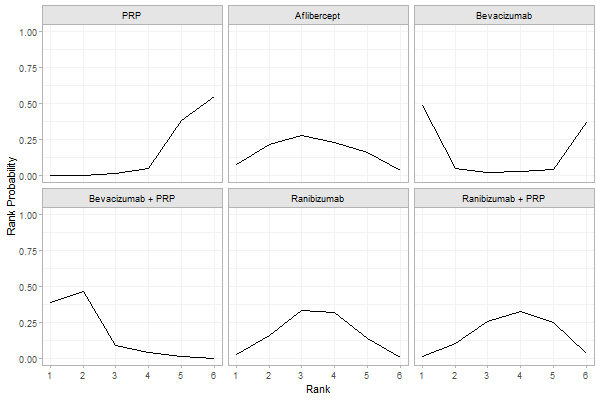


Figure 21 Probability of treatments for end-of-trial random-effects NMA of logMAR

Table 8 Results of NMA of logMAR at end of trial - comparisons between treatments

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Intervention** | **Comparator** | **Mean difference** | **95% CI** | |
| Aflibercept | PRP | -0.087 | -0.228 | 0.049 |
| Bevacizumab | PRP | -0.209 | -1.176 | 0.782 |
| Bevacizumab + PRP | PRP | -0.171 | -0.284 | -0.064 |
| Ranibizumab | PRP | -0.085 | -0.177 | -0.004 |
| Ranibizumab + PRP | PRP | -0.069 | -0.151 | 0.016 |
| Bevacizumab | Aflibercept | -0.122 | -1.117 | 0.881 |
| Bevacizumab + PRP | Aflibercept | -0.085 | -0.265 | 0.093 |
| Ranibizumab | Aflibercept | 0.002 | -0.167 | 0.151 |
| Ranibizumab + PRP | Aflibercept | 0.017 | -0.139 | 0.180 |
| Bevacizumab + PRP | Bevacizumab | 0.038 | -0.956 | 1.030 |
| Ranibizumab | Bevacizumab | 0.124 | -0.868 | 1.100 |
| Ranibizumab + PRP | Bevacizumab | 0.140 | -0.830 | 1.116 |
| Ranibizumab | Bevacizumab + PRP | 0.087 | -0.054 | 0.225 |
| Ranibizumab + PRP | Bevacizumab + PRP | 0.102 | -0.032 | 0.243 |
| Ranibizumab + PRP | Ranibizumab | 0.015 | -0.086 | 0.128 |

Table 9 Results of NMA of logMAR at end of trial – ranking probabilities

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Treatment arm** | **Probability of ranking:** | | | | | |
| **1st** | **2nd** | **3rd** | **4th** | **5th** | **6th** |
| **PRP** | 0.00% | 0.63% | 4.80% | 35.88% | 58.70% | 0.00% |
| **Aflibercept** | 20.58% | 29.20% | 23.05% | 17.80% | 4.35% | 20.58% |
| **Bevacizumab** | 5.90% | 2.70% | 1.85% | 3.65% | 33.43% | 5.90% |
| **Bevacizumab + PRP** | 46.80% | 9.78% | 3.88% | 1.23% | 0.10% | 46.80% |
| **Ranibizumab** | 17.03% | 31.83% | 31.10% | 16.20% | 0.93% | 17.03% |
| **Ranibizumab + PRP** | 9.70% | 25.88% | 35.33% | 25.25% | 2.50% | 9.70% |

## 2.4: NMAs allowing for interaction with follow-up time and BCVA at randomisation

### 2.4.1 Allowing for variation with follow-up time

Network meta-analyses incorporating all follow-up times (longest in each trial), allowing varying effect of anti-VEGF with follow-up time. Time variation is assumed to be the same for all types of anti-VEGF. A selection of output plots are presented. Results are presented for the predicted effects after 1 year of follow-up.



Figure 22 All treatment comparisons for time-adjusted random-effects NMA of logMAR

Table 10 Results of NMA of logMAR adjusting for time - comparisons between treatments

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Intervention** | **Comparator** | **Mean difference** | **95% CI** | |
| Aflibercept | PRP | -0.086 | -0.221 | 0.045 |
| Bevacizumab | PRP | -0.199 | -1.218 | 0.858 |
| Bevacizumab + PRP | PRP | -0.112 | -0.245 | 0.027 |
| Ranibizumab | PRP | -0.119 | -0.214 | -0.023 |
| Ranibizumab + PRP | PRP | -0.075 | -0.153 | 0.001 |
| Bevacizumab | Aflibercept | -0.112 | -1.135 | 0.945 |
| Bevacizumab + PRP | Aflibercept | -0.026 | -0.216 | 0.163 |
| Ranibizumab | Aflibercept | -0.033 | -0.200 | 0.130 |
| Ranibizumab + PRP | Aflibercept | 0.011 | -0.138 | 0.163 |
| Bevacizumab + PRP | Bevacizumab | 0.086 | -0.957 | 1.127 |
| Ranibizumab | Bevacizumab | 0.080 | -0.973 | 1.105 |
| Ranibizumab + PRP | Bevacizumab | 0.123 | -0.919 | 1.138 |
| Ranibizumab | Bevacizumab + PRP | -0.007 | -0.197 | 0.184 |
| Ranibizumab + PRP | Bevacizumab + PRP | 0.037 | -0.123 | 0.195 |
| Ranibizumab + PRP | Ranibizumab | 0.044 | -0.064 | 0.155 |

Table 11 Results of NMA of logMAR adjusting for time – ranking probabilities

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Treatment arm** | **Probability of ranking:** | | | | | |
| **1st** | **2nd** | **3rd** | **4th** | **5th** | **6th** |
| **PRP** | 0.00% | 0.05% | 0.65% | 5.13% | 38.10% | 56.08% |
| **Aflibercept** | 7.60% | 19.98% | 25.30% | 25.10% | 17.48% | 4.55% |
| **Bevacizumab** | 51.98% | 3.88% | 2.58% | 2.78% | 4.35% | 34.45% |
| **Bevacizumab + PRP** | 18.73% | 30.70% | 17.90% | 17.35% | 12.35% | 2.98% |
| **Ranibizumab** | 19.40% | 34.13% | 25.88% | 14.88% | 5.25% | 0.48% |
| **Ranibizumab + PRP** | 2.30% | 11.28% | 27.70% | 34.78% | 22.48% | 1.48% |

### 2.4.2 Allowing for variation over time and by logMAR at randomisation

Network meta-analyses incorporating all follow-up times (longes tin each trial), allowing for varying effect of anti-VEGF by follow-up duration and varying effect by trial mean logMAR at randomisation. Time and logMAR variation are assumed to be the same for all types of anti-VEGF. A selection of output plots are presented. Results are presented for the predicted effects after 1 year of follow-up and at mean baseline BCVA across trials.



Figure 23 All treatment comparisons for time-adjusted and baseline BCVA adjusted random-effects NMA of logMAR

Table 12 Results of NMA of logMAR adjusting for time and baseline BCVA - comparisons between treatments

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Intervention** | **Comparator** | **Mean difference** | **95% CI** | |
| Aflibercept | PRP | -0.085 | -0.310 | 0.119 |
| Bevacizumab + PRP | PRP | -0.116 | -0.281 | 0.050 |
| Ranibizumab | PRP | -0.117 | -0.247 | 0.011 |
| Ranibizumab + PRP | PRP | -0.073 | -0.187 | 0.041 |
| Bevacizumab + PRP | Aflibercept | -0.031 | -0.287 | 0.228 |
| Ranibizumab | Aflibercept | -0.032 | -0.288 | 0.233 |
| Ranibizumab + PRP | Aflibercept | 0.012 | -0.218 | 0.251 |
| Ranibizumab | Bevacizumab + PRP | -0.001 | -0.239 | 0.225 |
| Ranibizumab + PRP | Bevacizumab + PRP | 0.043 | -0.151 | 0.234 |
| Ranibizumab + PRP | Ranibizumab | 0.044 | -0.112 | 0.203 |

Table 13 Results of NMA of logMAR adjusting for time and baseline BCVA – ranking probabilities

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Treatment arm** | **Probability of ranking:** | | | | |
| **1st** | **2nd** | **3rd** | **4th** | **5th** |
| **PRP** | 0.08% | 0.70% | 4.23% | 19.50% | 75.50% |
| **Aflibercept** | 19.25% | 23.45% | 21.43% | 22.70% | 13.18% |
| **Bevacizumab + PRP** | 38.40% | 23.30% | 18.10% | 15.68% | 4.53% |
| **Ranibizumab** | 36.93% | 30.48% | 19.63% | 10.75% | 2.23% |
| **Ranibizumab + PRP** | 5.35% | 22.08% | 36.63% | 31.38% | 4.58% |

## 2.5: NMAs of reduced networks

### 2.5.1 Assuming anti-VEGF and anti-VEGF+PRP are equivalent

This analysis assumes that anti-VEGF only arms and anti-VEGF+PRP arms have equal effect. To be used to assess differences between anti-VEGF types. A model allowing effect to vary with time and baseline logMAR was used. Results are presented for the predicted effects after 1 year of follow-up and at mean baseline BCVA across trials.



Figure 24 Results from a reduced network to compare anti-VEGFs

Table 14 Results of reduced network to compare anti-VEGFs - comparisons between treatments

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Intervention** | **Comparator** | **Mean difference** | **95% CI** | |
| Aflibercept | PRP | -0.091 | -0.245 | 0.063 |
| Bevacizumab | PRP | -0.126 | -0.261 | 0.007 |
| Ranibuzimab | PRP | -0.094 | -0.173 | -0.023 |
| Bevacizumab | Aflibercept | -0.035 | -0.238 | 0.174 |
| Ranibuzimab | Aflibercept | -0.003 | -0.166 | 0.163 |
| Ranibuzimab | Bevacizumab | 0.032 | -0.142 | 0.200 |

Table 15 Results of reduced network to compare anti-VEGFs - ranking probabilities

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Treatment** | **Probability of ranking:** | | | |
|  | **1st** | **2nd** | **3rd** | **4th** |
| PRP | 0.00% | 0.80% | 11.48% | 87.73% |
| Aflibercept | 25.08% | 32.93% | 33.35% | 8.65% |
| Bevacizumab | 53.60% | 23.33% | 20.18% | 2.90% |
| Ranibuzimab | 21.33% | 42.95% | 35.00% | 0.73% |

### 2.5.2 Assuming all types of Anti-VEGF are equivalent

This analysis assumes that all three anti-VEGF drugs have equal effect. To be used to assess the overall effect of anti-VEGF. A model allowing effect to vary with time and baseline logMAR was used.



Figure 25 Results from a reduced network to compare treatment classes

Table 16 Results of reduced network to compare treatment classes - comparisons between treatments

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Intervention** | **Comparator** | **Mean difference** | **95% CI** | |
| Anti-VEGF | PRP | -0.089 | -0.180 | -0.019 |
| Anti-VEGF + PRP | PRP | -0.108 | -0.192 | -0.039 |
| Anti-VEGF + PRP | Anti-VEGF | -0.019 | -0.126 | 0.083 |

Table 17 Results of reduced network to compare treatment classes - ranking probabilities

|  |  |  |  |
| --- | --- | --- | --- |
| **Treatment** | **Probability of ranking:** | | |
| **1st** | **2nd** | **3rd** |
| PRP | 0.03% | 1.20% | 98.78% |
| Anti-VEGF | 33.05% | 65.88% | 1.08% |
| Anti-VEGF + PRP | 66.93% | 32.93% | 0.15% |

## 2.6: Threshold analyses

***Up to 1 year***

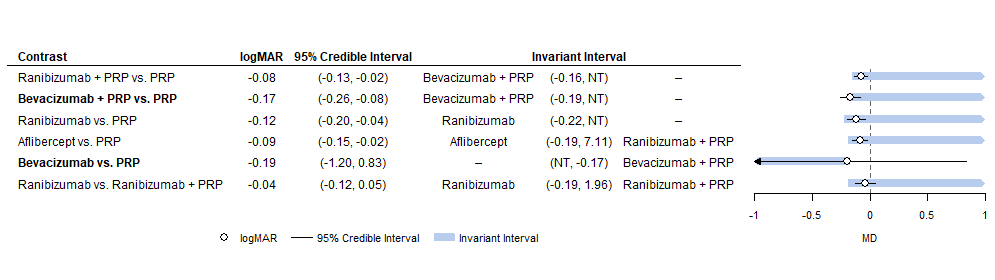


Figure 26 Threshold analyses of data up to 1 year of follow-up

***1 to 2 years***

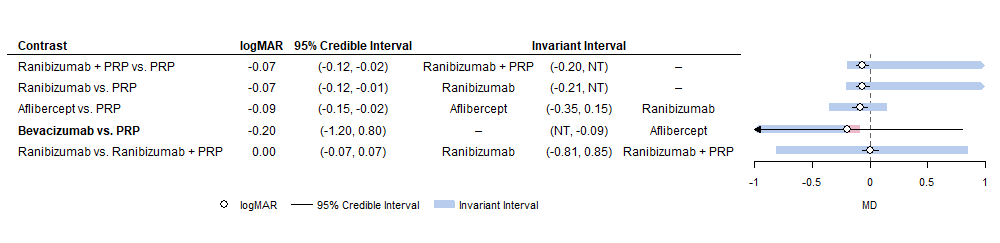


Figure 27 Threshold analyses of data with 1 to 2 years of follow-up

***Maximum follow-up (up to 2 years)***

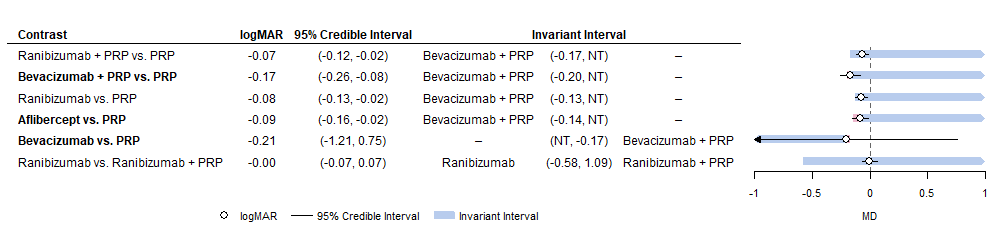
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Figure 28 Threshold analyses of data at end of trial (up to 2 years)

***Allowing for effect variation with time and baseline logMAR***

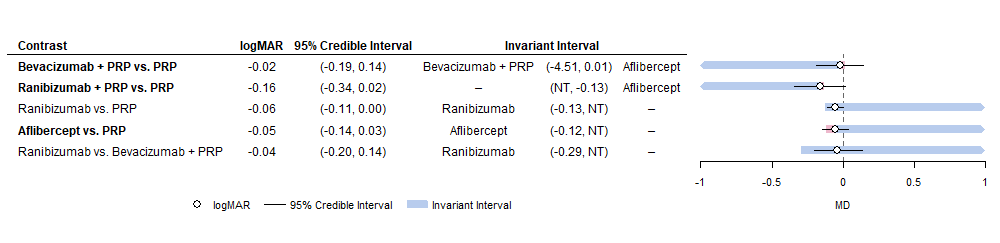


Figure 29 Threshold analyses of model adjusting for effect of time and baseline logMAR

***Reduced network (for comparing anti-VEGFs)***

Adjusted for follow-up time and BCVA at baseline

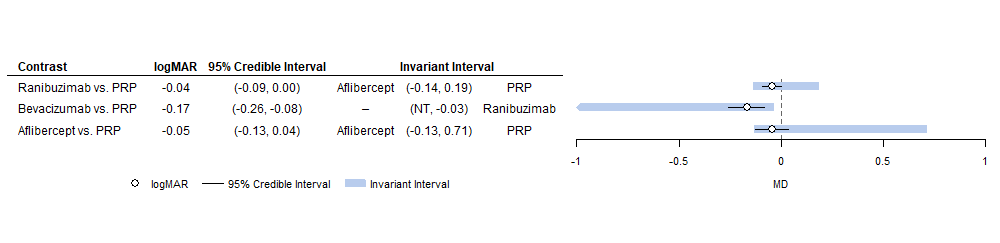
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Figure 30 Threshold analysis of simplified network to compare anti-VEGF types, with time and baseline BCVA adjustment

***Reduced network (comparing anti-VEGF to PRP)***

Adjusted for follow-up time and BCVA at baseline

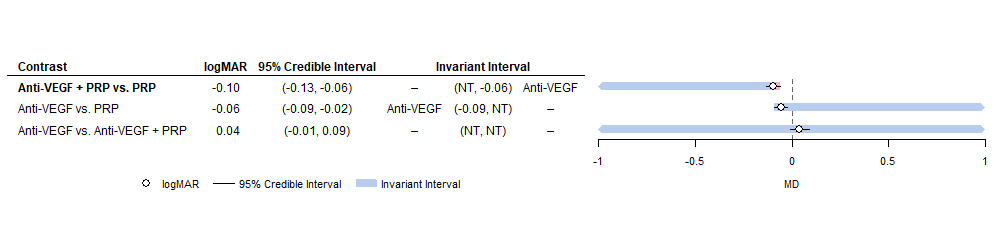


Figure 31 Threshold analyses of simplified network to compare anti-VEGF to PRP, adjusted for follow-up time and baseline BCVA

# Appendix 3: Other outcomes

This appendix presents tables and figures for all analyses, using data from publications of included RCTs for outcomes other than BCVA. These mostly consist of forest plots without meta-analysis, because the evidence was generally too limited in extent, and too diverse in intervention and follow-up times, to justify a full meta-analysis.

As meta-analysis was not possible for most outcomes the forest plots without meta-analysis include trials of proliferative and non-proliferative retinopathy, to aid comparison.

## 3.1: Forest plots of outcomes without meta-analysis

These forest plots show results for all anti-VEGF types, and at all follow-up times. Note that this means some trials appear more than once in a forest plot.

***NVD (neovascularization of the disc)***

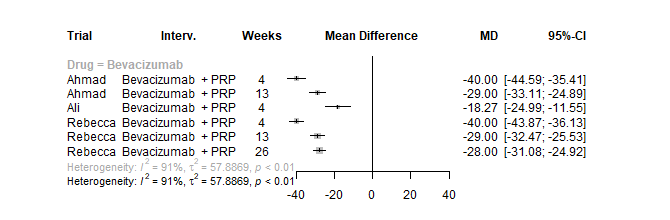


Figure 32 Forest plot of all NVD data (left side favours anti-VEGF)

***NVE (neovascularization elsewhere)***

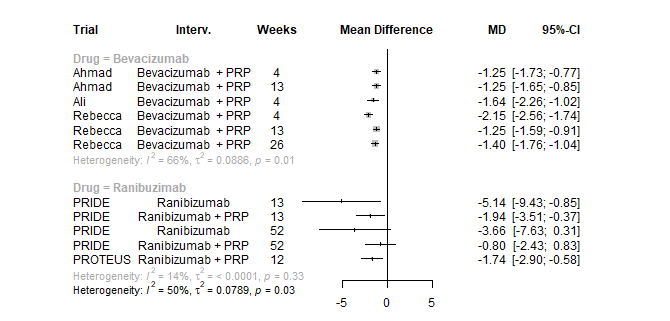


Figure 33 Forest plot of all NVE data (left side favours anti-VEGF)

***Diabetic Macular Oedema (DMO)***

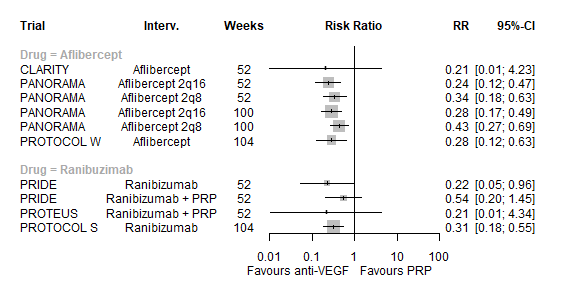
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Figure 34 Forest plot of DME incidence (left side favours anti-VEGF)

***Improvement in diabetic retinopathy severity score (DRSS)***

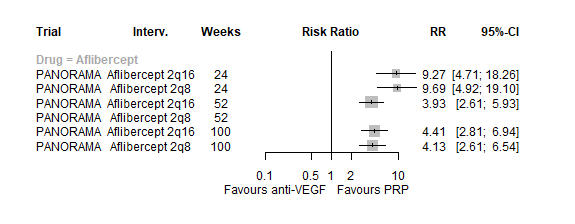


Figure 35 Forest plot of improvement in DRSS severity (right side favours anti-VEGF)

***Proliferative retinopathy incidence***

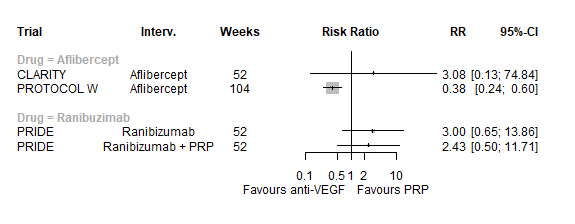
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Figure 36 Forest plot of proliferative DR (left side favours anti-VEGF)

***Regression of neovascularisation***

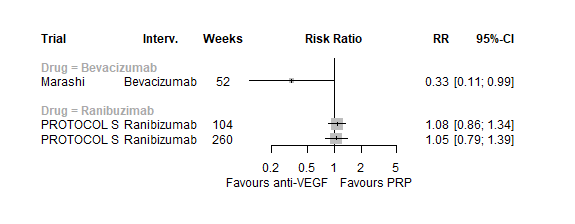
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Figure 37 Forest plot of regressive neovascularisation (left side favours anti-VEGF)

***Use of other treatments***

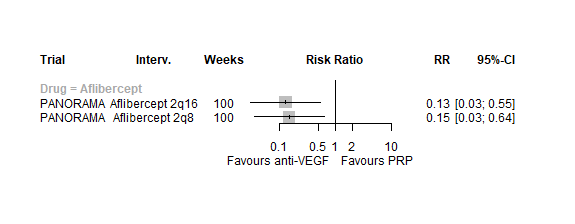
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Figure 38 Forest plot of use of other treatments (left side favours anti-VEGF)

***Vitrectomy***

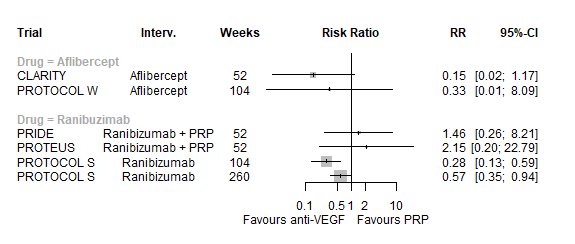
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Figure 39 Forest plot of vitrectomy incidence (left side favours anti-VEGF)

***Vitreous haemorrhage***

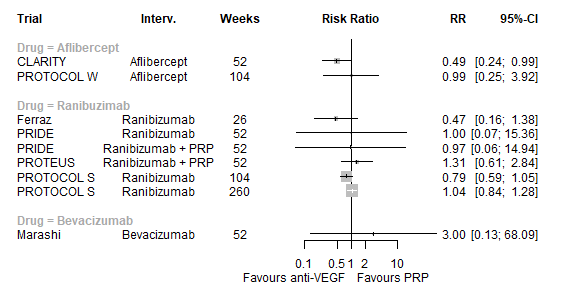


Figure 40 Forest plot of vitreous haemorrhage incidence (left side favours anti-VEGF)

## 3.2: Adverse Event outcomes

These forest plots show results for all anti-VEGF types, and at all follow-up times. Note that this means some trials appear more than once in a forest plot. For simplicity, only adverse event outcomes reported in two or more studies are presented.

***Cataracts***

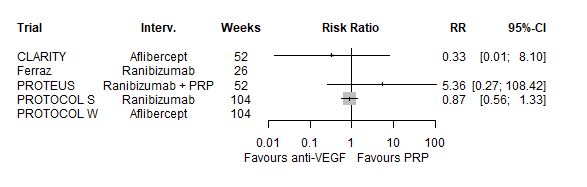


Figure 41 Forest plot of cataracts data (left side favours anti-VEGF)

***Conjunctival haemorrhage***

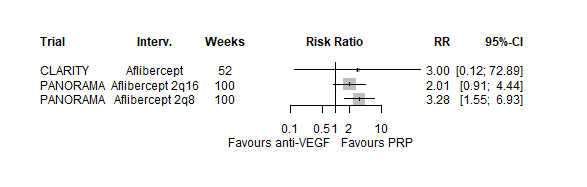


Figure 42 Forest plot of conjunctival haemorrhage data (left side favours anti-VEGF)

***Cardiovascular mortality***

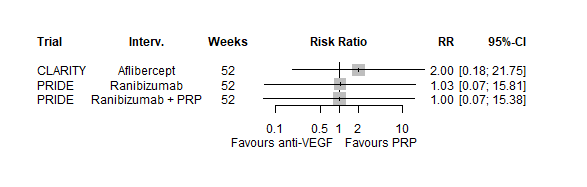
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Figure 43 Forest plot of cardiovascular mortality data (left side favours anti-VEGF)

***Death (all-cause mortality)***

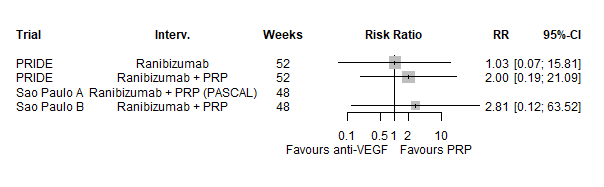
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Figure 44 Forest plot of death data (left side favours anti-VEGF)

***Myocardial infarction***

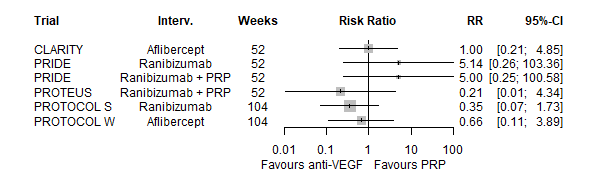
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Figure 45 Forest plot of myocardial infarction data (left side favours anti-VEGF)

***Ocular pain***

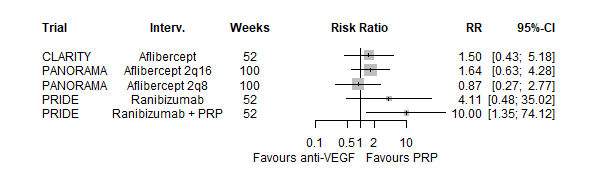
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Figure 46 Forest plot of ocular pain data (left side favours anti-VEGF)

***Raised intraocular pressure***

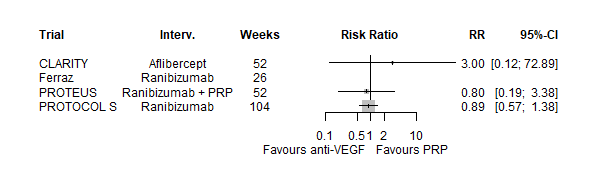
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Figure 47 Forest plot of raised intraocular pressure data (left side favours anti-VEGF)

***Retinal detachment***

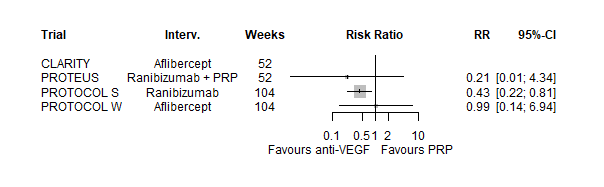


Figure 48 Forest plot of retinal detachment data (left side favours anti-VEGF)

***Retinal tear***

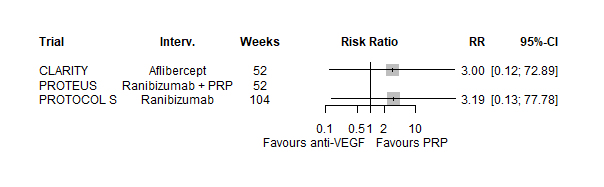


Figure 49 Forest plot of retinal data (left side favours anti-VEGF)

***Serious adverse event (SAE, however defined)***

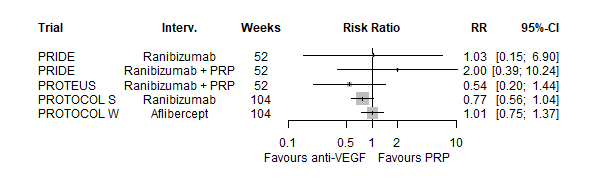
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Figure 50 Forest plot of SAE data (left side favours anti-VEGF)

***Stroke***

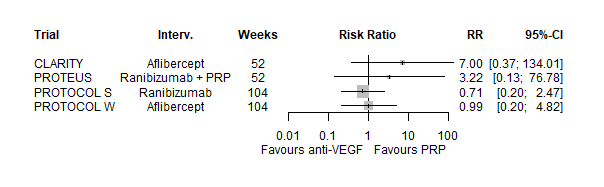


Figure 51 Forest plot of stroke data (left side favours anti-VEGF)

## 3.3: Meta-analyses of other outcomes and adverse events

All meta-analyses presented assumed that the impact of anti-VEGF on outcome (or adverse event) is the same for all types of anti-VEGF (in isolation or combined with PRP), and at all follow-up times. For trials with multiple time points, the longest follow-up was used. For trial with multiple arms only one anti-VEGF arm was used; arms using anti-VEGF alone were preferred.

***NVE***

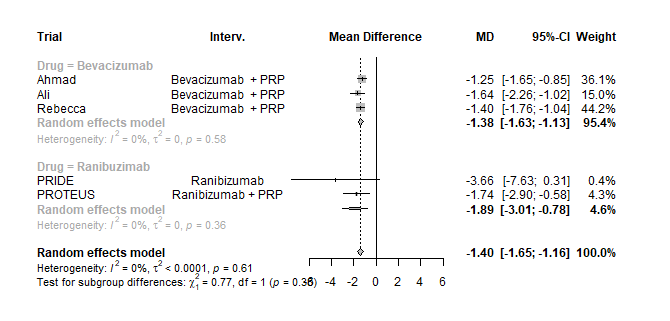


Figure 52 Meta-analysis of NVE (left side favours anti-VEGF)

***NVD***

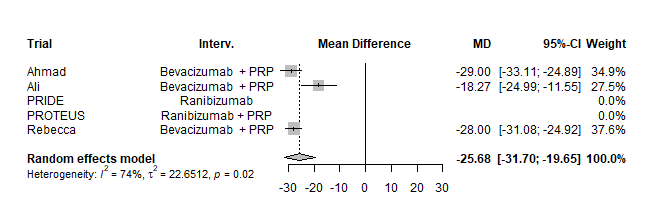
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Figure 53 Meta-analysis of NVD (left side favours anti-VEGF)

***Other non-vison outcomes***

*This forest plot shows the summary results of each meta-analysis (each bar is a meta-analysis result). Meta-analyses are restricted to trials of proliferative retinopathy. Full forest plots for each outcome are not presented.*



Figure 54 Meta-analysis summary for non-vision outcomes in PDR trials (left side favours anti-VEGF)

***Adverse events***

*This forest plot shows the summary results of each meta-analysis (each bar is a meta-analysis result). Meta-analyses are restricted to trials of proliferative retinopathy. Full forest plots for each outcome are not presented.*



Figure 55 Meta-analysis summary for adverse events (left side favours anti-VEGF)

# Appendix 4: Non-proliferative diabetic retinopathy

This section reports the findings of the two trials in non-proliferative retinopathy. As both trials compared aflibercept to sham injection no NMAs were performed. PANORAMA had two aflibercept arms: injections every 8 weeks or every 16 weeks. Only the 16 week arm is analysed here, as that was the schedule used in PROTOCOL W.

**BCVA**

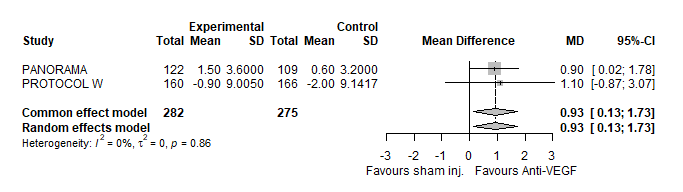


Figure 56 Mean difference in ETDRS after 2 years in NPDR trials

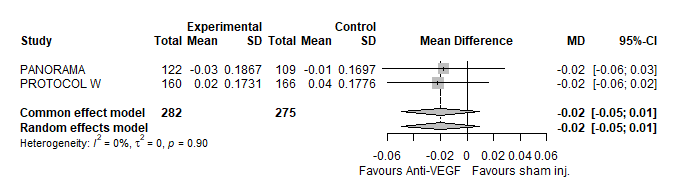


Figure 57 Mean difference in logMAR after 2 years in NPDR trials

***Diabetic macular oedema in non-proliferative retinopathy***

DMO was the only outcome other than BCVA reported in both trials of NPDR.

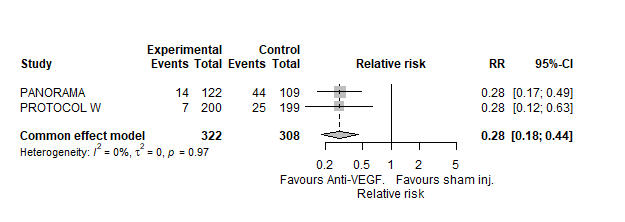


Figure 58 DMO incidence in NPDR trials

**Other outcomes**

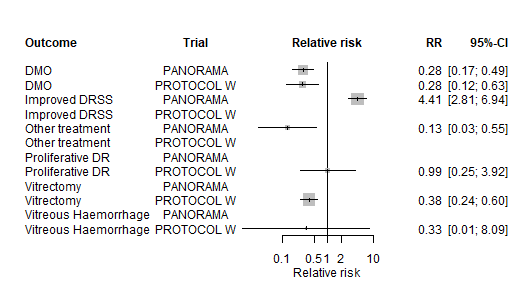


Figure 59 Non-BCVA outcomes in NPDR trials

**Adverse events**

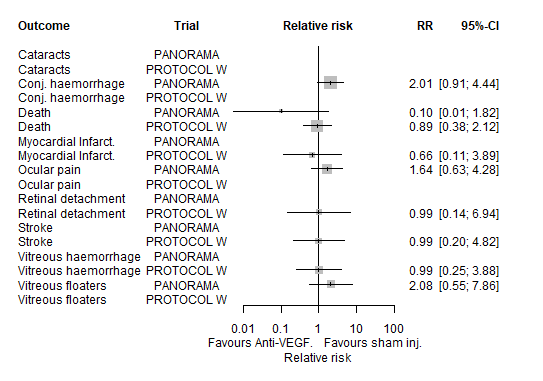
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Figure 60 Adverse event outcomes in NPDR trials