APPENDIX A. SEARCH STRATEGIES

SEARCH STRATEGY OVERVIEW

Databases Searched:

- Ovid Medline
- PubMed
- Elsevier Embase (http://Embase.com)
- Ovid EBM Reviews (Cochrane Central Register of Controlled Trials; Cochrane Database of Systematic Reviews; Health Technology Assessment; NHS Economic Evaluation Database)

Clinical Trial Registries:

- ClinicalTrials.gov (https://clinicaltrials.gov/ct2/search/advanced)
- WHO ICTRP (http://apps.who.int/trialsearch/)
- ISRCTN Registry (http://www.isrctn.com/)

Regulatory Agencies:

- FDA
- EMA

Conference Proceedings:

- Association for Research in Vision and Ophthalmology
- American Academy of Ophthalmology
- American Society of Retina Specialists
- COS Conference Papers Index

Scientific Information Packet Requests:

- LUCENTIS ® (ranibizumab); Genentech (Novartis)
- AVASTIN ® (bevacizumab); Genentech (Roche)
- EYLEA® (aflibercept); Regeneron Pharmaceuticals, Inc.

Future Research:

- NIH Reporter (https://projectreporter.nih.gov/reporter.cfm)
- AHRQ Gold (http://gold.ahrq.gov/projectsearch/)

ELECTRONIC SEARCH STRATEGIES

Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1946 to November Week 3 2015,
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 11, 2015
Date Searched: December 11, 2015

1	exp Angiogenesis Inhibitors/	38860
2	Antibodies, Monoclonal, Humanized/	30005
3	Endothelial Growth Factors/	8163
4	exp Vascular Endothelial Growth Factors/	42393
5	((endothelial adj2 growth adj2 factor*) or VEGF or VEGF-A or ((anti* or inhibit*) adj2 VEGF*) or antiVEGF* or anti-VEGF* or VEGF TRAP* or ((anti* or inhibit*) adj2 angiogen*)).tw.	72844
6	(aflibercept* or EYLEA* or bevacizumab* or Avastin* or ranibizumab* or Lucentis*).tw.	12368
7	or/1-6	129921
8	Visual acuity/	62548
9	(visual* or vision or ETDRS or BCVA).tw.	511121
10	or/8-9	530892
11	Diabetic Retinopathy/	20770
12	Glaucoma, Neovascular/	710
13	Macular Degeneration/	12937
14	Macular Edema/	5087
15	Wet Macular Degeneration/	956
16	Choroidal Neovascularization/	4602
17	Vitreous Hemorrhage/	1734
18	Retinal Vein Occlusion/	3355
19	((macula* adj3 (edema* or oedema* or degenerat*)) or (retin* adj3 (angiogenesis* or vein* or occlu* or obstruct* or clos* or stricture* or steno* or block* or embolism*)) or (proliferat* adj3 retinopath*) or (glaucoma* adj4 (neovascular* or haemorrhag* or hemorrhag* or thrombo* or congestive or rubeot*)) or (neovascular* adj2 (retinopath* or retinal* or intraocular* or intravitreal* or glaucoma* or choroidal)) or (vitreous adj2 (haemorrhag* or hemorrhag*)) or new blood vessel* or retinopath* or maculopath* or CME or CSME or CMO or CSMO or DMO or DME or NVG or NVI or BRVO or RVO or AMD or WAMD or CNV).tw.	83310
20	or/11-19	93025
21	and/7,10,20	4393
22	remove duplicates from 21	4166
23	limit 22 to (case reports or comment or editorial or letter or news)	689
24	**22 not 23 (GENERAL SEARCH RESULTS)**	**3477**
25	7 and 20	10749
26	(ae or co or de).fs.	5215408
27	(harm or harms or harmful or safe or safety or side effect* or undesirable effect* or treatment emergent or tolerability or toxic* or adrs or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))).tw.	1331876
28	or/26-27	5972462
29	25 and 28	5489
30	limit 29 to (meta analysis or systematic reviews)	183
31	**30 not 24 (ADVERSE EVENTS/HARMS SEARCH RESULTS)**	**65**

Note: Bevacizumab/ and Ranibizumab/ are new MeSH Terms as of 2016, but currently do not have any results linked to the subject terms, and therefore these were not used in the search. Future search strategies however should include these MeSH terms.

PubMed

Date Searched: February 4, 2016

#14	**Search (#13 OR #7) (ALL SEARCH RESULTS)**	**450**
#13	**Search (#12 NOT #7) (ADVERSE EVENTS/HARMS SEARCH RESULTS)**	**34**
#12	Search (#11 AND english [language])	148
#11	Search (#10 AND #5)	154
#10	Search (#9 AND #8)	795
#9	Search (harm[Title/Abstract] OR harms[Title/Abstract] OR harmful[Title/Abstract] OR safe[Title/Abstract] OR safety[Title/Abstract] OR side effects[Title/Abstract] OR undesirable effect*[Title/Abstract] OR treatment emergent[Title/Abstract] OR tolerability[Title/Abstract] OR toxic*[Title/Abstract] OR adrs[Title/Abstract] OR adverse effect[Title/Abstract] OR adverse effects[Title/Abstract] OR adverse reaction[Title/Abstract] OR adverse reactions[Title/Abstract] OR adverse event[Title/Abstract] OR adverse events[Title/Abstract] OR adverse outcome[Title/Abstract] OR adverse outcomes[Title/Abstract])	1350876
#8	Search (#1 AND #3)	2656
#7	**Search (#6 AND english [language]) (GENERAL SEARCH RESULTS)**	**416**
#6	Search (#4 AND #5)	429
#5	Search ((publisher [sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR inprocess [sb] OR pubmednotmedline [sb] OR pmcbook OR (publisher [sb] AND (pubstatusnihms OR pubstatuspmcsd)))	2783356
#4	Search (#1 AND #2 AND #3)	1826
#3	Search (((macula*[Title/Abstract] AND (edema*[Title/Abstract] OR oedema*[Title/Abstract] OR degenerat*))[Title/Abstract] OR (retin*[Title/Abstract] AND (angiogenesis*[Title/Abstract] OR vein*[Title/Abstract] OR occlu*[Title/Abstract] OR obstruct*[Title/Abstract] OR clos*[Title/Abstract] OR stricture*[Title/Abstract] OR steno*[Title/Abstract] OR block*[Title/Abstract] OR embolism*))[Title/Abstract] OR (proliferat*[Title/Abstract] AND retinopath*)[Title/Abstract] OR (glaucoma*[Title/Abstract] AND (neovascular*[Title/Abstract] OR haemorrhag*[Title/Abstract] OR hemorrhag*[Title/Abstract] OR thrombo*[Title/Abstract] OR congestive[Title/Abstract] OR rubeot*))[Title/Abstract] OR (neovascular*[Title/Abstract] AND (retinopath*[Title/Abstract] OR retinal*[Title/Abstract] OR intraocular*[Title/Abstract] OR intravitreal*[Title/Abstract] OR glaucoma*[Title/Abstract] OR choroidal))[Title/Abstract] OR (vitreous[Title/Abstract] AND (haemorrhag*[Title/Abstract] OR hemorrhag*))[Title/Abstract] OR new blood vessel*[Title/Abstract] OR retinopath*[Title/Abstract] OR maculopath*[Title/Abstract] OR CME[Title/Abstract] OR CSME[Title/Abstract] OR CMO[Title/Abstract] OR CSMO[Title/Abstract] OR DMO[Title/Abstract] OR DME[Title/Abstract] OR NVG[Title/Abstract] OR NVI[Title/Abstract] OR BRVO[Title/Abstract] OR RVO[Title/Abstract] OR AMD[Title/Abstract] OR WAMD[Title/Abstract] OR CNV[Title/Abstract]))	59871
#2	Search ((visual*[Title/Abstract] or vision[Title/Abstract] or ETDRS[Title/Abstract] or BCVA[Title/Abstract]))	515210
#1	Search ((aflibercept*[Title/Abstract] OR EYLEA*[Title/Abstract] OR bevacizumab*[Title/Abstract] OR Avastin*[Title/Abstract] OR ranibizumab*[Title/Abstract] OR	12614

	Lucentis*[Title/Abstract]))	

Elsevier EMBASE.COM

Date Searched: February 3, 2016

#34	**#33 NOT #28 (ADVERSE EVENTS/HARMS SEARCH RESULTS)**	**99**
#33	#30 OR #31 AND ([systematic review]/lim OR [meta analysis]/lim)	202
#32	#30 OR #31	6,445
#31	#29 AND (harm:ab,ti OR harms:ab,ti OR harmful:ab,ti OR safe:ab,ti OR safety:ab,ti OR side:ab,ti AND effect*:ab,ti OR undesirable:ab,ti AND effect*:ab,ti OR treatment:ab,ti AND emergent:ab,ti OR tolerability:ab,ti OR toxic*:ab,ti OR adrs:ab,ti OR (adverse NEAR/2 (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes)):ab,ti)	1,636
#30	#29 AND ('adverse drug reaction'/lnk OR 'complication'/lnk OR 'side effect'/lnk)	5,716
#29	#10 AND #23	18,185
#28	**#25 NOT (#26 OR #27) (GENERAL SEARCH RESULTS)**	**5,131**
#27	#25 AND ([editorial]/lim OR [letter]/lim) 420	420
#26	#25 AND 'case report'/de 910	910
#25	#10 AND #13 AND #23 AND [embase]/lim 6,298	6,298
#24	#10 AND #13 AND #23 6,815	6,815
#23	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 127,711	127,711
#22	(macula* NEAR/3 (edema* OR oedema* OR degenerat*)):ab,ti OR (retin* NEAR/3 (angiogenesis* OR vein* OR occlu* OR obstruct* OR clos* OR stricture* OR steno* OR block* OR embolism*)):ab,ti OR (proliferat* NEAR/3 retinopath*):ab,ti OR (glaucoma* NEAR/4 (neovascular* OR haemorrhag* OR hemorrhag* OR thrombo* OR congestive OR rubeot*)):ab,ti OR (neovascular* NEAR/2 (retinopath* OR retinal* OR intraocular* OR intravitreal* OR glaucoma* OR choroidal)):ab,ti OR (vitreous NEAR/2 (haemorrhag* OR hemorrhag*)):ab,ti OR new:ab,ti AND blood:ab,ti AND vessel*:ab,ti OR retinopath*:ab,ti OR maculopath*:ab,ti OR cme:ab,ti OR csme:ab,ti OR cmo:ab,ti OR csmo:ab,ti OR dmo:ab,ti OR dme:ab,ti OR nvg:ab,ti OR nvi:ab,ti OR brvo:ab,ti OR rvo:ab,ti OR amd:ab,ti OR wamd:ab,ti OR cnv:ab,ti 91,083	91,083
#21	'retina vein occlusion'/exp 6,089	6,089
#20	'vitreous hemorrhage'/de 4,949	4,949
#19	'subretinal neovascularization'/de 7,248	7,248
#18	'wet macular degeneration'/de	520
#17	'macular edema'/exp	12,382
#16	'macular degeneration'/exp	22,598
#15	'neovascular glaucoma'/de	1,724
#14	'diabetic retinopathy'/exp	30,963
#13	#11 OR #12	657,503
#12	visual*:ab,ti OR vision:ab,ti OR etdrs:ab,ti OR bcva:ab,ti	631,128
#11	'visual acuity'/de	85,654
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	528,436
#9	aflibercept*:ab,ti OR eylea*:ab,ti OR 'trap eye':ab,ti OR bevacizumab*:ab,ti OR avastin*:ab,ti OR ranibizumab*:ab,ti OR lucentis*:ab,ti	20,686
#8	'ranibizumab'/de	5,100
#7	'bevacizumab'/de	38,277
#6	'aflibercept'/de	2,484

#5	(endothelial NEAR/2 growth NEAR/2 factor*):ab,ti OR ((anti* OR inhibit*) NEAR/2 vegf*):ab,ti OR antivegf*:ab,ti OR 'anti vegf*':ab,ti OR (vegf NEAR/2 trap*):ab,ti OR ((anti* OR inhibit*) NEAR/2 angiogen*):ab,ti	79,695
#4	'vasculotropin'/de	77,826
#3	'endothelial cell growth factor'/de	2,066
#2	'monoclonal antibody'/exp	391,126
#1	'angiogenesis inhibitor'/exp	102,979

Ovid EBM Reviews

Cochrane Central Register of Controlled Trials December 2015
Cochrane Database of Systematic Reviews 2005 to January 29, 2016
D**atabase of Abstracts of Reviews of Effects** 2nd Quarter 2015
Health Technology Assessment 1st Quarter 2016
NHS Economic Evaluation Database 1st Quarter 2016

Date Searched: February 4, 2016

1	(aflibercept* or EYLEA* or bevacizumab* or Avastin* or ranibizumab* or Lucentis*).tw.	2147
2	(visual* or vision or ETDRS or BCVA).tw.	46966
3	((macula* adj3 (edema* or oedema* or degenerat*)) or (retin* adj3 (angiogenesis* or vein* or occlu* or obstruct* or clos* or stricture* or steno* or block* or embolism*)) or (proliferat* adj3 retinopath*) or (glaucoma* adj4 (neovascular* or haemorrhag* or hemorrhag* or thrombo* or congestive or rubeot*)) or (neovascular* adj2 (retinopath* or retinal* or intraocular* or intravitreal* or glaucoma* or choroidal)) or (vitreous adj2 (haemorrhag* or hemorrhag*)) or new blood vessel* or retinopath* or maculopath* or CME or CSME or CMO or CSMO or DMO or DME or NVG or NVI or BRVO or RVO or AMD or WAMD or CNV).tw.	6283
4	and/1-3	570
5	limit 4 to english language [Limit not valid in CDSR,DARE; records were retained]	434
6	and/1,3	749
7	(harm or harms or harmful or safe or safety or side effect* or undesirable effect* or treatment emergent or tolerability or toxic* or adrs or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))).tw.	194241
8	and/6-7	311
9	limit 8 to english language [Limit not valid in CDSR,DARE; records were retained]	238
10	limit 9 to full systematic reviews [Limit not valid in CCTR,DARE,CLHTA,CLEED; records were retained]	226
11	limit 10 to new reviews [Limit not valid in CCTR; records were retained]	193
12	limit 11 to recently updated reviews [Limit not valid in CCTR,DARE,CLHTA,CLEED; records were retained]	174
13	12 not 5	21
14	13 or 5	455

ClinicalTrials.gov

Date Searched: February 7, 2016

11 studies found for: Interventional Studies | (aflibercept OR EYLEA OR trap-eye) and (bevacizumab OR Avastin) | Adult, Senior | Phase 3, 4
18 studies found for: Interventional Studies | (aflibercept OR EYLEA OR trap-eye) and (ranibizumab OR Lucentis) | Adult, Senior | Phase 3, 4

27 studies found for: Interventional Studies | (bevacizumab OR Avastin) and (ranibizumab OR Lucentis) | Adult, Senior | Phase 3, 4

WHO ICTRP

Date Searched: February 2, 2016

1	diabetic retinopath* OR neovascular* glaucoma OR AMD OR macular degeneration OR macular edema* OR macular oedema* OR vitreous hemorrhag* OR vitreous haemorrhag* OR choroidal neovascularization* OR choroidal neovascularisation* OR retinal vein occlusion*
2	aflibercept OR EYLEA OR trap-eye OR bevacizumab OR Avastin OR ranibizumab OR Lucentis
3	1 AND 2 = 1084 records for 739 trials*
*Of 1084 records, 797 were ClinicalTrials.gov records which were removed from the total number of results, and 287 records were downloaded	

ISRCTN Registry

Date Searched: February 2, 2016

Text Search	aflibercept OR EYLEA OR trap-eye OR bevacizumab OR Avastin OR ranibizumab OR Lucentis	61 results
Limit	Eye Diseases	22 results*
*Of 22 result records, 19 were on specified conditions and downloaded		

Association for Research in Vision and Ophthalmology (-2009 captured in COS Conference Papers Index)

Date Searched: February 8, 2016

2009-present conference content unavailable on Association website.

American Academy of Ophthalmology (-2007 captured in COS Conference Papers Index)

Date Searched: February 8, 2016

aflibercept* OR EYLEA* OR bevacizumab* OR Avastin* OR ranibizumab* OR Lucentis* = 0 results*

*Website conference database was not working correctly on search day, unable to view specific conference programs.

American Society of Retina Specialists

Date Searched: February 2, 2016

Past conference content unavailable on Society website and conference paper indices.

COS Conference Papers Index

Date Searched: February 8, 2016

(all(aflibercept*) OR all(EYLEA*) OR all(bevacizumab*) OR all(Avastin*) OR all(ranibizumab*) OR all(Lucentis*)) AND (all(Diabetic Retinopath*) or all(neovascular glaucoma) or all(macular degeneration) or all(macular edema) or all(choroidal neovasculari?ation) or all(vitreous haemorrhag*) or all(vitreous hemorrhage*) or all(retinal vein occlusion)) = 426 results

NIH Reporter

Date Searched: February 3, 2016

(aflibercept or EYLEA or bevacizumab or Avastin or ranibizumab or Lucentis) AND ;Search in: Projects AdminIC: All; Fiscal Year: Active Projects = 2 results

AHRQ Gold

Date Searched: February 3, 2016

aflibercept or EYLEA or bevacizumab or Avastin or ranibizumab or Lucentis = 0 results

APPENDIX B. QUALITY ASSESSMENT

CRITERIA USED IN QUALITY ASSESSMENT

Risk of Bias Assessment for Randomized Controlled Trials (RCTs): The Cochrane Collaboration Risk of Bias tool[18]

Overview

Domain	Description	Review authors' judgment
Sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Was the allocation sequence adequately generated?
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of or during enrollment.	Was allocation adequately concealed?
Blinding of participants, personnel and outcome assessors *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Was knowledge of the allocated intervention adequately prevented during the study?
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes).*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Were incomplete outcome data adequately addressed?
Selective outcome reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Are reports of the study free of suggestion of selective outcome reporting?
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Was the study apparently free of other problems that could put it at a high risk of bias?

Specific Criteria Details for Judging Risk of Bias by Domain

SEQUENCE GENERATION **Was the allocation sequence adequately generated? [Short form: *Adequate sequence generation*?]**	
Criteria for a judgment of 'YES' (*ie*, low risk of bias)	The investigators describe a random component in the sequence generation process such as: § Referring to a random number table; using a computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization.* *Minimization may be implemented without a random element, and this is considered

	to be equivalent to being random.
Criteria for the judgment of 'NO' (*ie*, high risk of bias)	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: § Sequence generated by odd or even date of birth; § Sequence generated by some rule based on date (or day) of admission; § Sequence generated by some rule based on hospital or clinic record number. Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgment or some method of non-random categorization of participants, for example: § Allocation by judgment of the clinician; § Allocation by preference of the participant; § Allocation based on the results of a laboratory test or a series of tests; § Allocation by availability of the intervention.
Criteria for the judgment of 'UNCLEAR' (*ie*, uncertain risk of bias)	Insufficient information about the sequence generation process to permit judgment of 'Yes' or 'No'.
ALLOCATION CONCEALMENT **Was allocation adequately concealed? [Short form: *Allocation concealment*?]**	
Criteria for a judgment of 'YES' (*ie*, low risk of bias)	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: § Central allocation (including telephone, web-based, and pharmacy-controlled randomization); § Sequentially numbered drug containers of identical appearance; § Sequentially numbered, opaque, sealed envelopes.
Criteria for the judgment of 'NO' (*ie*, high risk of bias)	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: § Using an open random allocation schedule (*eg*, a list of random numbers); § Assignment envelopes were used without appropriate safeguards (*eg*, if envelopes were unsealed or non-opaque or not sequentially numbered); § Alternation or rotation; § Date of birth; § Case record number; § Any other explicitly unconcealed procedure.
Criteria for the judgment of 'UNCLEAR' (*ie*, uncertain risk of bias)	Insufficient information to permit judgment of 'Yes' or 'No'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgment; for example, if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.
BLINDING OF PARTICIPANTS, PERSONNEL AND OUTCOME ASSESSORS **Was knowledge of the allocated interventions adequately prevented during the study? [Short form: *Blinding*?]**	
Criteria for a judgment of 'YES' (*ie*, low risk of bias)	Any one of the following: § No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding; § Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken; § Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.

Criteria for the judgment of 'NO' (*ie*, high risk of bias)	Any one of the following: § No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding; § Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken; § Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.
Criteria for the judgment of 'UNCLEAR' (*ie*, uncertain risk of bias)	Any one of the following: § Insufficient information to permit judgment of 'Yes' or 'No'; § The study did not address this outcome.
INCOMPLETE OUTCOME DATA **Were incomplete outcome data adequately addressed? [Short form: *Incomplete outcome data addressed*?]**	
Criteria for a judgment of 'YES' (*ie*, low risk of bias)	Any one of the following: § No missing outcome data; § Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); § Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; § For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; § For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; § Missing data have been imputed using appropriate methods.
Criteria for the judgment of 'NO' (*ie*, high risk of bias)	Any one of the following: § Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; § For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; § For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; § 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; § Potentially inappropriate application of simple imputation.
Criteria for the judgment of 'UNCLEAR' (*ie*, uncertain risk of bias)	Any one of the following: § Insufficient reporting of attrition/exclusions to permit judgment of 'Yes' or 'No' (*eg*, number randomized not stated, no reasons for missing data provided); § The study did not address this outcome.
SELECTIVE OUTCOME REPORTING **Are reports of the study free of suggestion of selective outcome reporting? [Short form: *Free of selective reporting*?]**	
Criteria for a judgment of 'YES' (*ie*, low risk of bias)	Any of the following: § The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; § The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

Criteria for the judgment of 'NO' (*ie*, high risk of bias)	Any one of the following: § Not all of the study's pre-specified primary outcomes have been reported; § One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (*eg*, subscales) that were not pre-specified; § One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); § One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; § The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
Criteria for the judgment of 'UNCLEAR' (*ie*, uncertain risk of bias)	Insufficient information to permit judgment of 'Yes' or 'No'. It is likely that the majority of studies will fall into this category.
OTHER POTENTIAL THREATS TO VALIDITY **Was the study apparently free of other problems that could put it at a risk of bias? [Short form: *Free of other bias*?]**	
Criteria for a judgment of 'YES' (*ie*, low risk of bias)	The study appears to be free of other sources of bias.
Criteria for the judgment of 'NO' (*ie*, high risk of bias)	There is at least one important risk of bias. For example, the study: § Had a potential source of bias related to the specific study design used; or § Stopped early due to some data-dependent process (including a formal-stopping rule); or § Had extreme baseline imbalance; or § Has been claimed to have been fraudulent; or § Had some other problem.
Criteria for the judgment of 'UNCLEAR' (*ie*, uncertain risk of bias)	There may be a risk of bias, but there is either: § Insufficient information to assess whether an important risk of bias exists; or § Insufficient rationale or evidence that an identified problem will introduce bias.

QUALITY ASSESSMENT OF INCLUDED STUDIES

Author, Year; Trial name	**Sequence generation:** Was the allocation sequence adequately generated?	**Allocation concealment:** Was allocation adequately concealed?	**Blinding:** Was knowledge of the allocated intervention adequately prevented during the study?	**Incomplete outcome data:** Were incomplete outcome data adequately addressed?	**Selective outcome reporting:** Are reports of the study free of suggestion of selective outcome reporting?	**Other sources of bias:** Was the study apparently free of other problems that could put it at a high risk of bias?	**Overall assessment of potential for bias:** Low/Unclear/High
Choroidal Neovascularization Secondary to Age-Related Macular Degeneration (AMD)Trials							
Biswas 2011[33]	Yes: random number tables.	Unclear: blinding of random number table allocation not reported.	Assessors: Yes. Participants: Unclear. Providers: Yes.	Unclear: loss to follow-up acceptable (16.6% and 10%), but reasons were not reported. Analyses were not ITT.	No: protocol or registration number not provided. Definitions of "minor complications" not reported.	Unclear: effectiveness of randomization is unclear as more men were randomized to bevacizumab (56%) than to ranibizumab (41%).	Unclear
BRAMD; Schauwvlieghe 2016[45]	Yes: computer-generated using TENALEA Clinical Trial Data Management System and stratified by center, BCVA in study eye and fellow eye.	Yes: upon randomization an automatized email notification containing the allocation result was sent to the site's pharmacy.	Assessors: Yes. Participants and providers: Yes.	Yes: ITT analyses reported; acceptable and equal loss to follow-up (19.0%). Missing values imputed using last observation carried forward (LOCF) approach. BCVA at the moment of switch was used for patients who were switched to the other treatment due to non-response.	Unclear: all outcomes pre-specified in the protocol are reported. However, reporting of adverse events was not entirely clear (not separated by ocular vs systemic, just reports "occurrence of serious adverse events") and not all *P*-values reported.	Yes	Low

Author, Year; Trial name	**Sequence generation:** Was the allocation sequence adequately generated?	**Allocation concealment:** Was allocation adequately concealed?	**Blinding:** Was knowledge of the allocated intervention adequately prevented during the study?	**Incomplete outcome data:** Were incomplete outcome data adequately addressed?	**Selective outcome reporting:** Are reports of the study free of suggestion of selective outcome reporting?	**Other sources of bias:** Was the study apparently free of other problems that could put it at a high risk of bias?	**Overall assessment of potential for bias:** Low/Unclear/High
CATT; Martin 2012[41,42]	Yes: computer-generated randomization schedules using a web-based data management system, stratified according to clinical center with the use of a permuted-block method with a randomly chosen block size.	Yes: allocated using a web-based data management system.	Assessors: Yes Participants: No ("Patients were not informed of their drug assignment; however, insurance and billing documents specified ranibizumab but not study-supplied bevacizumab. Therefore, patients may have learned or deduced their assigned drug from these financial documents.") Providers: Yes (although not masked to dosing schedule, monthly or PRN).	Unclear: methods reported using ITT analyses but 1-year outcomes did not include 103 patients (8.6%) lost to follow-up (due to missing data). Three alternative approaches for handling missing data from the 52-week examination were performed as sensitivity analyses.	Yes: all outcomes pre-specified in the protocol are reported.	Yes	Low
GEFAL; Kodjikian 2013[34]	Unclear: randomized using "pre-established lists."	Yes: allocation completed by local hospital pharmacies.	Assessors: Yes. Participants and providers: Yes.	Unclear: 25% lost to follow-up and reasons were reported. Primary analysis was per protocol but ITT analysis also reported, although 97 (19.3%) patients were not included.	Unclear: specific secondary outcomes reported in publication were not reported in ClinicalTrials.gov protocol, and "time before re-injection" from the protocol was not reported in publication.	Unclear: some baseline differences in medical history and total choroidal neovascularization area; however, unlikely to have affected outcomes of interest.	Unclear

Author, Year; Trial name	**Sequence generation:** Was the allocation sequence adequately generated?	**Allocation concealment:** Was allocation adequately concealed?	**Blinding:** Was knowledge of the allocated intervention adequately prevented during the study?	**Incomplete outcome data:** Were incomplete outcome data adequately addressed?	**Selective outcome reporting:** Are reports of the study free of suggestion of selective outcome reporting?	**Other sources of bias:** Was the study apparently free of other problems that could put it at a high risk of bias?	**Overall assessment of potential for bias:** Low/Unclear/High
IVAN; Chakravarthy 2013[27,37,38]	Yes: computer-generated by a third party in blocks and stratified by center.	Yes: concealed using an internet-based system provided by Sealed Envelope Ltd.	Assessors: Yes. Participants and providers: Yes.	Unclear: 18 patients (9 in each group) were excluded from the analyses because they were randomized in error or were not treated, leaving 610 patients who received ≥1 injection. One-year results not reported for 49 (8%) participants and 2-year results not reported for 85 (13.9%). Reasons for withdrawals and missing data thoroughly reported. Multiple imputation using a series of chained regression equations was used to impute missing data.	Yes: all outcomes pre-specified in the protocol are reported.	Yes	Low
LUCAS; Berg 2015[39,40]	Yes: computer-generated with the use of the block method and stratified by center.	Yes: randomization completed by a third party.	Assessors: Yes Participants and providers: Yes	Yes: ITT and per-protocol analyses reported. Attrition was acceptable and even (15%).	Yes: protocol published on ClinicalTrials.gov, all outcomes pre-specified are reported.	Unclear: the patients in the ranibizumab group more often had a history of myocardial infarctions than the patients in the bevacizumab group; increased cardiac events in ranibizumab occurred during trial.	Low
MANTA; Krebs 2013[35]	Unclear: "Randomisation was stratified according to the	Yes: central allocation by members of the	Assessors: Yes. Participants and providers: Yes (injecting physician	Unclear: Efficacy analysis was ITT; last observation carried forward method used to handle missing	Unclear: Data for some measures had to be estimated from graphs.	Yes	Unclear

Author, Year; Trial name	**Sequence generation:** Was the allocation sequence adequately generated?	**Allocation concealment:** Was allocation adequately concealed?	**Blinding:** Was knowledge of the allocated intervention adequately prevented during the study?	**Incomplete outcome data:** Were incomplete outcome data adequately addressed?	**Selective outcome reporting:** Are reports of the study free of suggestion of selective outcome reporting?	**Other sources of bias:** Was the study apparently free of other problems that could put it at a high risk of bias?	**Overall assessment of potential for bias:** Low/Unclear/High
	clinical centre using a permuted block method with a fixed block size of 20," but process of selecting the blocks was not specified.	Department of Clinical Pharmacology at Medical University of Vienna, which was otherwise not involved in the study.	not blinded, but was not involved in the collection of data).	data for 69 (21.4%) patients. Loss to follow-up information not reported.			
Scholler 2014[29]	Yes: computer-generated list of random numbers.	Unclear: not reported.	Assessors: Unclear (not reported). Participants and providers: Unclear (not reported).	No: method of handling incomplete data not reported, unclear whether ITT analysis conducted (reports exclusion of 9 patients, but not whether they were included in analyses), uneven number of exclusions between groups.	No: registration numbers provided appear to be for a different trial. Did not provide mean change calculations for BCVA or anatomic outcomes.	No: Small study and power calculation not reported. Funding source not reported.	High
Subramanian 2010[26]	Unclear: "all subjects were assigned a study number."	Yes: central allocation by research pharmacist.	Assessors: Yes. Participants and providers: Yes.	No: ITT analysis not performed; uneven loss to follow-up (25% vs 13%).	No: adverse events only reported for patients completing 1-year follow-up visit. Data on minor adverse events not reported.	No: not powered to detect differences (original goal sample size was calculated to be 135, while actual enrollment was only 28, with only 22 analyzed).	High
VIEW 1; Heier 2012[43]	Unclear: "Consecutively enrolled patients were assigned to treatment groups on the basis of a	Yes: central allocation by an interactive voice response system.	Assessors: Yes Participants: Yes Providers: No, an unmasked investigator performed the	Yes: acceptable and equal loss to follow-up (7.1%); missing values imputed using last observation carried forward (LOCF) approach. "Full Analysis	Unclear: all outcomes pre-specified in ClinicalTrials.gov protocol; however, confidence intervals	Unclear: funded by manufacturer.	Low

Author, Year; Trial name	**Sequence generation:** Was the allocation sequence adequately generated?	**Allocation concealment:** Was allocation adequately concealed?	**Blinding:** Was knowledge of the allocated intervention adequately prevented during the study?	**Incomplete outcome data:** Were incomplete outcome data adequately addressed?	**Selective outcome reporting:** Are reports of the study free of suggestion of selective outcome reporting?	**Other sources of bias:** Was the study apparently free of other problems that could put it at a high risk of bias?	**Overall assessment of potential for bias:** Low/Unclear/High
	predetermined central randomization scheme with balanced allocation," but unclear what the "randomization scheme" entailed.		injection, but this was unlikely to have introduced bias	set" only included randomized patients who received any study medication and had a baseline and at least 1 post-baseline BCVA assessment; however, 99.4% of randomized patients were included in this analysis.	or *P*-values not reported for all outcomes.		
VIEW 2; Heier 2012[43]	Unclear: "Consecutively enrolled patients were assigned to treatment groups on the basis of a predetermined central randomization scheme with balanced allocation," but unclear what the "randomization scheme" entailed.	Yes: allocation managed by an interactive voice response system	Assessors: Yes Participants: Yes Providers: No, an unmasked investigator performed the injection, but this was unlikely to have introduced bias	Yes: acceptable and equal loss to follow-up (10.2%); missing values imputed using last observation carried forward (LOCF) approach. "Full Analysis set" only included randomized patients who received any study medication and had a baseline and at least 1 post-baseline BCVA assessment; however, 96.9% of randomized patients were included in this analysis.	Unclear: all outcomes pre-specified in ClinicalTrials.gov protocol; however, confidence intervals or *P*-values not reported for all outcomes.	Unclear: funded by manufacturer.	Low
Diabetic Macular Edema (DME) Trials							
DRCR.net (Protocol T); Wells 2016[46,47]	Yes: performed at the DRCR.net study website (computer-generated) in	Yes: central randomization at the DRCR.net study website.	Assessors: Yes. Participants and providers: Yes.	Yes: 7% lost to follow-up (similar between groups). Primary analysis used ITT; used Markov chain Monte Carlo method of multiple	Yes: all outcomes pre-specified in the protocol are reported.	Yes	Low

Author, Year; Trial name	**Sequence generation:** Was the allocation sequence adequately generated?	**Allocation concealment:** Was allocation adequately concealed?	**Blinding:** Was knowledge of the allocated intervention adequately prevented during the study?	**Incomplete outcome data:** Were incomplete outcome data adequately addressed?	**Selective outcome reporting:** Are reports of the study free of suggestion of selective outcome reporting?	**Other sources of bias:** Was the study apparently free of other problems that could put it at a high risk of bias?	**Overall assessment of potential for bias:** Low/Unclear/High
	permuted blocks and with stratification according to study site and visual acuity in the study eye.			imputation to impute missing data (sensitivity analyses with different approaches for handling missing data produced similar results). There was no imputation for missing data in secondary analyses.			
Ekinci 2014[30]	Unclear: randomization method not reported.	Unclear: allocation concealment method not reported.	Assessors: Unclear, not reported. Participants and providers: Unclear, not reported.	No: excluded 15 participants after randomization due to adverse events; not reported by randomization group.	Unclear: protocol or registration number not provided.	Yes: either made an error reporting ranibizumab dose, or used an atypical dose (one tenth of typical dose).	High
Nepomuceno 2013[31]	Yes: computer-generated sequence. However, if both eyes were eligible for treatment, one eye received randomized treatment and the contralateral eye received the other anti-VEGF agent.	Unclear: not reported.	Assessors: Yes. Participants and providers: Yes.	Unclear: incomplete data not reported. Analyses were not ITT.	No: change in BCVA was listed as the primary outcome but was not clearly reported for week 48. Outcomes were reported based on at what timepoint there were significant differences.	No: sample size calculation was based on power to detect a difference of 50um between groups in central subfield thickness, and might have been underpowered to detect clinically meaningful differences in BCVA. Also, since 15 patients were treated with both treatments (one in each eye), there was possible crossover that could obscure differences in effects between the drugs.	High

Author, Year; Trial name	**Sequence generation:** Was the allocation sequence adequately generated?	**Allocation concealment:** Was allocation adequately concealed?	**Blinding:** Was knowledge of the allocated intervention adequately prevented during the study?	**Incomplete outcome data:** Were incomplete outcome data adequately addressed?	**Selective outcome reporting:** Are reports of the study free of suggestion of selective outcome reporting?	**Other sources of bias:** Was the study apparently free of other problems that could put it at a high risk of bias?	**Overall assessment of potential for bias:** Low/Unclear/High
Macular Edema due to Central Retinal Vein Occlusion (CRVO) or Branch Retinal Vein Occlusion (BRVO) Trials							
CRAVE; Rajagopal 2015[32]	No: reported using centralized, computer-generated random table for assignments, but an additional 9 patients included in the study who were not randomized to treatment due to financial hardship and were instead assigned to the bevacizumab group.	Unclear: states that "assistance programs were used to defray any financial hardship, but if it could not be eliminated, then the patient was assigned to the bevacizumab arm," which could have introduced bias in allocation.	No: patients, technicians, and examining physicians were not masked to treatment.	Unclear: ITT using LOCF was used for analyses. 25% loss-to-follow-up, but reasons were not reported.	Yes: protocol published on ClinicalTrials.gov, all outcomes pre-specified are reported.	Unclear: power of the study was calculated for anatomical change (their primary outcome) of 50 μm, not BCVA, so it is unknown whether the study was powered to detect differences in BCVA. Original enrollment planned for 150 patients, but only 98 were randomized.	High
MARVEL; Narayanan 2015[36]	Unclear: "randomised...in a 1:1 ratio in block sizes of 6," but process of selecting the blocks was not specified.	Unclear: not reported.	Assessors: Unclear Participants: Unclear Providers: Yes Study is described as "double-masked" but does not specify blinding of outcome assessors (other than at baseline) or patients.	Yes: ITT analyses using LOCF to impute for missing data; 90% completed the study (reasons for not completing NR).	Unclear: a trial registration number was provided but the protocol was unavailable.	Effectiveness of randomization is unclear: *P*-values not reported for baseline characteristics, and the ranibizumab group had a much higher proportion of females (60% vs 32%)	Unclear

APPENDIX C. PEER REVIEW COMMENTS AND AUTHOR RESPONSES

Question Text	Reviewer Number	Comment	Response
Are the objectives, scope, and methods for this review clearly described?	1	Yes	Noted, thank you.
	2	Yes	Noted, thank you.
	3	Yes	Noted, thank you.
	4	Yes	Noted, thank you.
	5	Yes	Noted, thank you.
	6	Yes	Noted, thank you.
Is there any indication of bias in our synthesis of the evidence?	1	No	Noted, thank you.
	2	No	Noted, thank you.
	3	No	Noted, thank you.
	4	No	Noted, thank you.
	5	No	Noted, thank you.
	6	No	Noted, thank you.
Are there any published or unpublished studies that we may have overlooked?	1	No	Noted, thank you.
	2	No	Noted, thank you.
	3	No	Noted, thank you.
	4	No	Noted, thank you.
	5	No	Noted, thank you.
	6	No	Noted, thank you.
Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft report.	2	Excellent report I do have one concern about the DME results and the overall conclusion drawn. Page 32 lines 21-30 shows aflibercept to have statistically significant superiority to bevacizumab with mean improvement in vision at 12 months and still with increased improvement but not statistically significant at 24 months. This was also true for those with lower baseline BCVA for the aflibercept versus ranibizumab on page 33 lines 7-17. These were deemed "not clinically significant" presumably due to the lack of statistical significance at 24 months yet in both the mean visual acuity improvement was still higher in the aflibercept group. The final conclusions on page 69 should likely reflect this consistent superior	We have changed “clinically significant” to “clinically meaningful” throughout the report and have clarified our definition in the Data Synthesis section of the Methods. A clinically meaningful difference often has a greater threshold than statistical significance, as it is related to whether the difference is substantial and noticeable to the patient and relevant to clinical practice. We determined the clinically meaningful difference between drugs to be 5 or more ETDRS letters (i.e., one line) in consultation with our ophthalmologist authors. Since the difference in mean change in BCVA between aflibercept and bevacizumab (and aflibercept and ranibizumab on the following page)

Question Text	Reviewer Number	Comment	Response
		improvement in VA at 12 months for aflibercept and improvement still yet not reaching statistical significance at 24 months. (This is stated in the table on page 62 line 56-60.	was less than 5 letters, this difference was not considered clinically meaningful. However, we revised the language in the paragraph about the subgroup with lower baseline BCVA, since the difference between groups was 6.5 letters. The final conclusion paragraph was also revised slightly to reflect the benefit seen with aflibercept in this study.
	2	In the comparative of cost-effectiveness section, although the literature only shows cost comparison data for multi-dosed vials of bevacizumab to the other two agents, the VA does not multi-dose the vial. Instead it is one 4cc vial per patient. Perhaps this should be mentioned either under this sub-section or in the Research Gaps/Future research section and that there is no cost comparative literature available when bevacizumab is not compounded. The cost-effectiveness will be reduced somewhat with this scenario but still likely superior to the two other agents. This could alternatively be mentioned in the Research Gaps/Future Research section on page 68.	This point was included in the Limitations section (second paragraph), but a sentence was added to the cost-effectiveness section (Key Question 3) as well. A clarification of this point was also added to the Executive Summary.
	3	Findings form this analysis were not unexpected and confirms what is known about this topic	Noted.
	3	p.19 typo regarding bevacizumab dose; should read 1.25mg Trials used standard recommended doses of the drugs unless otherwise indicated (aflibercept 2.0 mg; bevacizumab 0.5 mg; ranibizumab 0.5 mg for AMD and BRVO/CRVO, and 0.3 mg for DME).	Thank you, this has been corrected.
	3	For the tables discussing costs, consider adding a footnote that pricing is based on wholesale costs and not VA costs	The term “compounded” as well as a footnote was added to the Summary of Evidence table when talking about the cost of bevacizumab to clarify that the cost was for compounded bevacizumab, which is not currently available at the VHA.
	4	Although not clearly defined in the key questions, the treatment burden for patients is an important consideration. For example, when comparing aflibercept to bevacizumab in the treatment of AMD, the report mentions the fact that in the fixed interval dosing phase of the VIEW trials, the visual results were comparable between aflibercept given bimonthly and ranibizumab given monthly, although this result is not used in the interpretation of the results. The fact that aflibercept can be given less frequently is an important consideration for both patient and physician.	Thank you, we agree that this is an important consideration. While we had already included a statement to this effect in the Limitations section, we have added some language to the Discussion section to help further address this issue. We also added a brief statement to the Results section about the comparable visual acuity results between these two groups, although the cost implications are unclear since this was not explored by the trial.
	4	The report mentions that in the DRCR.net protocol discussing the	Our definition of a clinical significant or meaningful

Question Text	Reviewer Number	Comment	Response
		treatment of DME, the [*a priori*] subgroup analysis (emphasis mine) of patients with 20/50 or worse vision provides evidence that aflibercept results in better visual outcomes at 12 months than both bevacizumab and ranibizumab (although this improvement is lost at 24 months). This is an important point that should not be glossed over. The difference in visual outcomes in the study overall was driven by the patients with worse vision, at least in part because of a ceiling effect in the group with better starting vision (i.e. vision cannot be better than 20/20). A 7 letter difference between aflibercept and bevacizumab is indeed clinically significant (almost 2 lines of Snellen visual acuity). The conclusion that bevacizumab and aflibercept are equivalent in this context is erroneous. Even when considering the fact that the visual benefit decreases after 24 months, there is an important clinical benefit to having an additional year of better vision, even if this cannot be shown in terms of QALY or cost effectiveness.	difference in mean change in BCVA between drugs was clarified in the Methods section (5 or more ETDRS letters). We also revised this part in the Results to clarify the fact that aflibercept had a significant advantage over bevacizumab and ranibizumab at 12 months in the subgroup of patients with lower baseline BCVA. We added text to the Summary of Evidence table and Summary sections to clarify these findings as well.
	5	The report is comprehensive and includes all major RCTs on this topic. The report questions were adequately addressed.	Noted, thank you.
	6	We had three responses from field ophthalmologists. The points in all three comments are similar and captured in this comment: "The following finding for DME pts should be highlighted a bit more as an important finding: “These differences between aflibercept and both bevacizumab and ranibizumab were slightly more pronounced, but still clinically insignificant, in a subgroup analysis of patients with lower baseline BCVA.”	This statement was clarified in the text to highlight the fact that aflibercept had a clinically meaningful advantage over bevacizumab in this subgroup at 12 months. Similar statements have been added to summary statements throughout the draft.
	6	Also, the following phrase needs to be clarified: “While few differences between agents were seen for most AEs, previous trials and systematic reviews have shown that patients treated with anti-VEGF agents are at higher risk for serious systemic AEs, including death and cerebrovascular accidents.” I assume the latter clause was from the systemic use NOT intraocular use. This needs to be made clearer.	In fact, this sentence is referencing data from systematic reviews comparing intravitreal anti-VEGF agents to sham/placebo or other treatments (such as laser therapy), which show an increased risk for some systemic AEs associated with intravitreal anti-VEGF. The wording in this sentence was revised to clarify this. A more detailed discussion of this evidence can be found in the last paragraph of the “Summary of the Evidence” section in the Discussion (immediately before the Limitations section).

APPENDIX D. DETAILED DATA ABSTRACTION

Abbreviations Used in Appendix D

Abbreviation	Term
AE	Adverse event
AMD	Age-related macular degeneration
B	Bevacizumab
BCVA	Best-corrected visual acuity (represented in ETDRS letters unless otherwise indicated)
BRVO	Branch retinal vein occlusion
CI	Confidence interval
CFT	Central foveal thickness
CMT	Central macular thickness
CNV	Choroidal neovascularization
CRT	Central retinal thickness
CRVO	Central retinal vein occlusion
CST	Central subfield thickness
DME	Diabetic macular edema
EQ-5D	European Quality of Life-5 Dimensions
ETDRS	Early Treatment of Diabetic Retinopathy Study
FA	Fluorescein angiogram
G	Group (G1 = Group 1)
GMR	Geometric mean ratio
HbA1c	Hemoglobin A1c
HR	Hazard ratio
HTN	Hypertension
IOP	Intraocular pressure
IQR	Interquartile range
ITT	Intention-to-treat
logMAR	Logarithm of the Minimal Angle of Resolution
LS	Least squares
MacDQoL	Macular Disease-dependent Quality of Life
MacTSQ	Macular Disease Treatment Satisfaction Questionnaire
MI	Myocardial infarction
N	Number
NCT	National Clinical Trial register number (ClinicalTrial.gov)
NEI VFQ-25	25-item National Eye Institute Visual Functioning Questionnaire
NR	Not reported
NS	Not significant
OCT	Optical coherence tomography
OR	Odds ratio
PDT	Photodynamic therapy
PRN	*Pro re nata* (“as needed”)
QOL	Quality of life

Abbreviation	Term
R	Ranibizumab
PRP	Panretinal photocoagulation
RR	Relative risk
RVO	Retinal vein occlusion
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
TIA	Transient ischemic attack
VEGF	Vascular endothelial growth factor
US	United States

Trials in Patients with Choroidal Neovascularization Secondary to Age-Related Macular Degeneration (AMD)

Study	**Biswas 2011[33]**	**BRAMD; Schauwvlieghe 2016[45]**	**CATT; Martin 2012[41,42]**
• *Follow-up* • *Country* • *NCT or ID number* • *Funding*	• 18 months • India • NR • None ("Source of Support: Nil.")	• 12 months • the Netherlands • Trialregister.nl NTR1704 • The Netherlands Organisation for Health Research and Development; Dutch health insurance companies	• 24 months • US • NCT00593450 • National Eye Institute
Objective	To determine and compare the efficacy and safety of intravitreal ranibizumab and bevacizumab in treatment of choroidal neovascular membrane due to AMD.	To compare the effectiveness of bevacizumab and ranibizumab in the treatment of exudative AMD.	To assess the relative efficacy and safety of ranibizumab and bevacizumab and to determine whether PRN regimen would compromise long-term visual acuity, as compared with a monthly regimen.
Population/ Condition	Choroidal neovascular membrane secondary to AMD.	Primary or recurrent sub- or juxtafoveal CNV secondary to AMD.	Previously untreated active CNV due to AMD
Population Character-istics (baseline)	Age: 63.9 years (SD NR) Male: 48% (B vs R: 56% vs 41%) Mean BCVA: 57.5 (B vs R: 56.80 vs 58.19) Mean CMT: 286.2 μm Occult choroidal neovascular membrane: 44%	Age: 78 years (SD 7) Male: 44% Mean BCVA: 60 (SD 13) Mean CRT: 378 μm (SD 115)	Age: 79.2 years (SD 7.5) Male: 38.2% White: 98.6% Mean BCVA: 60.6 (SD 13.5) Mean foveal thickness: 460 μm (SD 187)
Main Inclusion Criteria	Patients aged more than 50 years; patients with baseline BCVA 35-70; all cases of CNV with classic and occult lesions; all cases of subfoveal and juxtafoveal CNV; cases with active leakage pattern; baseline CMT ≥250 μm.	Age ≥60 years; primary or recurrent sub- or juxtafoveal CNV secondary to AMD; total area of CNV of < 12 disc areas; BCVA 20-78 letters.	Age ≥50 years; presence in the study eye (one eye per patient) of previously untreated active CNV due to AMD (leakage on FA and subretinal or intraretinal fluid on OCT); visual acuity 20/25 to 20/320 on electronic visual-acuity testing; CNV or sequela of the CNV involving the center of the fovea.
Main Exclusion Criteria	Previous treatment for CNV in either eye; macular scarification; coexisting other ocular pathology (like advanced cataract, high myopia, chorio-retinal atrophic	The patient was labelled as a poor-responder and treatment was changed to the other drug if at any visit after the third injection there was a drop in BCVA of >10 letters	Previous treatment in the study eye; previous treatment with intravenous bevacizumab or concurrent use of systemic anti-VEGF agents; any concurrent intraocular condition in the

Study	**Biswas 2011[33]**	**BRAMD; Schauwvlieghe 2016[45]**	**CATT; Martin 2012[41,42]**
	patches, diabetic retinopathy, glaucoma); one-eyed patients; history of ocular surgery within last 6 months; history of cerebrovascular accident and MI.	compared to baseline and there was clear evidence of active CNV or leakage by qualitative OCT and/or FA assessment or at least two of the following signs of leakage on OCT: CRT >300 μm, intraretinal cysts or subretinal fluid any time after the third injection.	study eye (*eg*, cataract or diabetic retinopathy) that could either require medical or surgical intervention during the 2 year follow-up period; active or recent (within 4 weeks) intraocular inflammation; current vitreous hemorrhage in the study eye.
Intervention vs Comparator • *Schedule* • *Co-Intervention/ Rescue Treatment*	**G1:** Bevacizumab 1.25 mg **G2:** Ranibizumab 0.5 mg • **Schedule** (both groups): monthly for 3 months; retreatment afterwards based on OCT or BCVA changes (increase in CMT of >100 μm after the initial 3 injections in or fall in BCVA by >5 letters). • Full aseptic measures on 3 consecutive months	**G1:** Bevacizumab 1.25 mg **G2:** Ranibizumab 0.5 mg • **Schedule** (both groups): Administered monthly.	**G1:** Bevacizumab 1.25 mg monthly **G2:** Ranibizumab 0.5 mg monthly **G3:** Bevacizumab 1.25 mg PRN **G4:** Ranibizumab 0.5 mg PRN • **Schedule**: Monthly regimens were given an injection every 28 days; PRN regimens were given one initial injection and then only when signs of active CNV were present (fluid on OCT, new or persistent hemorrhage, decreased visual acuity as compared with the previous examination, or dye leakage or increased lesion size on FA). Patients in the monthly groups were re-randomized at 12 months to either continue with monthly injections or switch to PRN (study drug not changed). • At the discretion of the investigator, topical antibiotic was used 4 times a day for 3 days (including day of injection).
N	120 G1: 60 (50 analyzed) G2: 60 (54 analyzed)	332 (327 analyzed) G1: 166 G2: 166	1208 (1105 analyzed at 12 months, 1030 analyzed at 24 months) G1: 286 G2: 301 G3: 300 G4: 298
Visual Outcomes (ETDRS chart unless otherwise indicated); Functional Status/QOL Outcomes	**G1 vs G2** • Mean change in BCVA: -12 months: 0.52 vs 3.22; *P*=.463 -18 months: 3.96 vs 3.56; *P*=.563 • Mean BCVA achieved: -12 months: 57.32 vs 61.41 -18 months: 60.76 vs 61.74 • Proportion of participants gaining/losing BCVA letters from baseline: -Gaining >15 letters: 12% vs 26% -Gaining >5 letters: 32% vs 33% -Maintaining BCVA (≤5 letters change): 60% vs 56% -Losing >5 letters: 8% vs 11% -Losing >15 letters: 0% vs 4%	**G1 vs G2** • Mean change in BCVA: 5.1 (SD 14.1) vs 6.4 (12.2); *P*=.37 • Mean BCVA achieved: 65.0 (SD 19.0) vs 66.4 (SD 15.8); *P*=.37 • Proportion of participants gaining/losing BCVA letters from baseline: -Gaining ≥15 letters: 24% vs 19% -Maintaining BCVA (<15 letters change): 65% vs 76% -Losing ≥15 letters: 11% vs 5% • Number of switchers: 6% vs 5%	**G1 vs G2 vs G3 vs G4** • Mean change in BCVA -12 months: 8.0 (SD 16) vs 8.5 (SD 14) vs 5.9 (SD 16) vs 6.8 (SD 13); *P*=.16 ◦Longitudinal regression model, estimated mean change: 7.3 (SE 0.8) vs 7.2 (SE 0.7) vs 6.1 (SE 0.7) vs 6.4 (SE 0.6); *P*=.53 -24 months: 7.8 (SD 15.5) vs 8.8 (SD 15.9) vs 5.0 (SD 17.9) vs 6.7 (SD 14.6); *P*=.21 between drugs ◦Longitudinal regression model, estimated mean change: 0.7 letters (95% CI, -0.9 to 2.3), *P*=.41 • Mean BCVA achieved: -12 months: 68.4 (SD 18.2) vs 68.8 (SD 17.7) vs 66.5 (SD 19.0) vs 68.4 (SD 16.4); *P*=.45 -24 months: 68.2 (SD 16.1) vs 68.5 (SD 18.9) vs 66.0 (SD 19.9) vs 68.5 (15.3); *P*=.17 between drugs

Study	**Biswas 2011[33]**	**BRAMD; Schauwvlieghe 2016[45]**	**CATT; Martin 2012[41,42]**
			• Proportion of participants gaining/losing BCVA letters from baseline: -12 months: ◦Gaining ≥15 letters: 31.3% vs 34.2% vs 28.0% vs 24.9%; *P*=.09 ◦Gaining 5-14 letters: 37.0% vs 31.7% vs 33.2% vs 36.1% ◦Maintaining vision (≤4 letters change): 18.9% vs 21.8% vs 26.3% vs 21.8% ◦Losing 5-14 letters: 6.8% vs 6.7% vs 8.5% vs 8.1% ◦Losing ≥15 letters: 6.0% vs 5.6% vs 8.5% vs 4.6%; *P*=.29 -24 months (patients treated with same dosing regimen for entire 2 years): ◦Gaining ≥15 letters: 31.8% vs 32.8% vs 28.3% vs 30.7% ◦Gaining 5-14 letters: 27.9% vs 36.6% vs 31.5% vs 29.5% ◦Maintaining vision (≤4 letters change): 24.0% vs 16.4% vs 19.5% vs 23.5% ◦Losing 5-14 letters: 8.5% vs 7.5% vs 9.2% vs 9.1% ◦Losing ≥15 letters: 7.8% vs 6.7% vs 11.6% vs 7.2% • Proportion of participants achieving Snellen equivalent of 20/40 or better (>68 ETDRS letters) at 24 months: 60.5% vs 67.9% vs 62.1% vs 63.3%
Anatomic Outcomes (reported in μm unless otherwise indicated)	**G1 vs G2** • Mean change in CMT from baseline: -12 months: -26.44 vs -27.59; *P*=.283 -18 months: -37.96 vs -44.70; *P*=.281 • Percentage of patients showing improvement in CMT: 60% (mean 78.73 μm) vs 63% (mean 96.5 μm) • Percentage of patients showing deterioration in CMT: 40% (mean 41.4 μm) vs 37% (mean 56.6 μm)	**G1 vs G2** • Mean change in CRT: -131 (SD 129) vs -138 (SD 117); *P*=.31 • Subretinal fluid and intraretinal cysts absent on OCT: 44% vs 59%; *P*=.020	**G1 vs G2 vs G3 vs G4** • Mean change in total foveal thickness: -12 months: -164 (SD 181) vs -196 (SD 176) vs -152 (SD 178) vs -168 (SD 186); *P*=.03 -24 months: -180 (SD 196) vs -190 (SD 172) vs -153 (SD 189) vs -166 (SD 190); *P*=.38 between drugs • Fluid absent on OCT: -12 months: 26.0% vs 43.7% vs 19.2% vs 23.9%; *P*<.001 -24 months: 30.2% vs 45.5% vs 13.9% vs 22.3%; *P*=.0003 between drugs
Harms/Adverse Event (AE) outcomes (in study eye)	**G1 vs G2** Minor complications: 11.1% vs 7.3%	**G1 vs G2** • ≥1 serious AE: 21.1% vs 22.3%; *P*=.87 • Number of AEs: 256 vs 299; *P*=.48 *Systemic AEs:* • Death due to serious AE: 0.6% vs 0.6%; *P*=.6818 • Cardiac disorders: 2.5% vs 3.7% • Gastrointestinal disorders: 1.2% vs 1.2%	**G1 vs G2 vs G3 vs G4** *Ocular AEs:* • Endophthalmitis: 1.2% vs 0.7%; *P*=.38 • Pseudo-endophthalmitis: 0.2% vs 0.2%; *P*=1.00 *Systemic AEs:* • ≥1 serious AEs: 39.9% vs 31.7%; *P*=.004; adjusted RR 1.30 (95% CI, 1.07 vs 1.57), *P*=.009 • All-cause death: 6.1% vs 5.3%; *P*=.62 • Arterial thrombotic events: 5.0% vs 4.7%: *P*=.89

Study	**Biswas 2011[33]**	**BRAMD; Schauwvlieghe 2016[45]**	**CATT; Martin 2012[41,42]**
			-Nonfatal stroke: 1.4% vs 1.3%; *P*=1.00 -Nonfatal MI: 1.2% vs 1.5%; *P*=.80 -Vascular death: 2.4% vs 2.0%; *P*=.70 • Venous thrombotic events: 1.7% vs 0.5%; *P*=.054 • HTN: 0.7% vs 0.5%; *P*=.72 • Cardiac disorders: 10.6% vs 7.8%; *P*=.11 • Gastrointestinal disorders: 4.8% vs 1.8%; *P*=.005 • AEs not previously associated with anti-VEGF treatment (*eg*, arterial thrombotic events, systemic hemorrhage, congestive heart failure, venous thrombotic events, HTN, and vascular death): 34.5% vs 28.4%; *P*=.02
Cost and Burden Outcomes	**G1 vs G2** • Mean number of injections: 4.3 vs 5.6	NR	**G1 vs G2 vs G3 vs G4** • Mean number of injections : -12 months (max 13): 11.9 (SD 1.2) vs 11.7 (SD 1.5) vs 7.7 (SD 3.5) vs 6.9 (SD 3.0); *P*=.003 between PRN groups -24 months (max 26): 23.4 (SD 2.8) vs 22.4 (SD 3.9) vs 14.1 (SD 7.0) vs 12.6 (SD 6.6); *P*=.01 between PRN groups • Average cost of drug per patient in US dollars (based on per-dose cost of $50 for bevacizumab and $2,000 for ranibizumab): -12 months: 595 vs 23,400 vs 385 vs 13,800 -24 months: 1,170 vs 44,800 vs 705 vs 25,200
Notes; Subgroup Analyses	• **Subgroup analyses:** -Ranibizumab: Mean change in BCVA at 18 months, whole group vs predominantly classic subgroup: 3.55 vs 5.24 -Bevacizumab: Mean change in BCVA at 18 months, whole group vs predominantly classic subgroup: 3.96 vs 5.4	Non-inferiority trial	• "The data and safety monitoring committee recommended that data for 23 patients at one study center be excluded because of serious protocol noncompliance, so analyses included only the 1185 patients who were enrolled at the remaining 43 centers in the analyses." • At 12 months, treatment decisions by study ophthalmologists were consistent with the retreatment protocol for 2336/3268 examinations (71.5%) in the group assigned to ranibizumab PRN and for 2328/3133 examinations (74.3%) in the group assigned to bevacizumab PRN. • Re-randomization: At 12 months, patients initially assigned to monthly treatment retained their drug assignment but were reassigned randomly to either monthly or as-needed treatment. However, 24-months results recorded here only for patients treated with the same dosing regimen for 2 years.

Study	**GEFAL; Kodjikian 2013[34]**	**IVAN; Chakravarthy 2013[27,37,38]**	**LUCAS; Berg 2015[39,40]**
• *Follow-up* • *Country* • *NCT or ID number* • *Funding*	• 12 months • France • NCT01170767 • French Ministry of Health; French Health Insurance System	• 24 months • UK • ISRCTN 92166560 • UK National Institute for Health Research Health Technology Assessment programme	• 24 months • Norway • NCT01127360 • Oslo University Hospital
Objective	To evaluate the relative efficacy and safety profile of bevacizumab versus ranibizumab intravitreal injections for the treatment of neovascular AMD.	To compare the efficacy and safety of ranibizumab and bevacizumab intravitreal injections to treat neovascular AMD; to estimate the effectiveness of discontinuous versus continuous treatment regimens; and to estimate the cost-effectiveness of the alternative treatment strategies.	To compare the efficacy and safety of bevacizumab versus ranibizumab when administered according to a treat-and-extend protocol for the treatment of neovascular AMD.
Population/ Condition	Active subfoveal neovascular AMD.	Active previously untreated neovascular AMD with neovascular lesion involving the center of the fovea.	Previously untreated active neovascular AMD.
Population Character-istics (baseline)	Age: 79.2 years (SD 7.1) Male: 33.7% Mean BCVA: 55.2 (SD 14.0)	Age: 77.7 years Male: 40% Mean BCVA: 61.4 (SD 15.3) More participants in the bevacizumab group than the ranibizumab group had a history of angina (17% vs 11%).	Age: 78.3 years (SD 7.9) Male: 32.5% Mean BCVA: 61 (SD 13.5) Mean CRT: 364.5 μm History of MI (B vs R): 5.6% vs 11.9%; *P*=.021
Main Inclusion Criteria	Patients aged >50 years with BCVA between 20/32 and 20/320 (Snellen equivalent) measured on the ETDRS chart at a distance of 4 m; active subfoveal neovascular AMD; and total CNV area <12 optic disc areas.	Adults ≥50 years old with previously untreated neovascular AMD in the study eye and BCVA ≥25 letters on the ETDRS chart and a foveal neovascular lesion. Participants without a subfoveal (within 200 μm) neovascular component were eligible if subretinal fluid or serous pigment epithelial detachment was subfoveal.	Age ≥50 years; previously untreated active neovascular AMD in one eye; BCVA between 20/25 and 20/320.
Main Exclusion Criteria	Eyes with subfoveal fibrosis or atrophy; retinal pigment epithelial tear involving the macula; subretinal hemorrhage involving the center of the fovea (>50% of total CNV area); previous treatment with intraocular anti-VEGF or intravenous bevacizumab therapy; history or presence of intraocular inflammation or infection; and uncontrolled systemic HTN despite medical treatment; etc.	Lesions comprising >50% fibrosis or blood (to avoid including inactive or advanced disease); greatest linear diameter >6000 μm; ≥8 diopters of myopia; thick blood involving the center of the fovea; previous treatment (argon laser within 6 months, PDT or a VEGF inhibitor to the study eye); other active ocular disease causing concurrent vision loss.	Pigment epithelial detachments with no associated intraretinal or subretinal edema and lesions comprising more than 50% blood or fibrosis.
Intervention vs Comparator • *Schedule* • *Co-Intervention/ Rescue Treatment*	**G1:** Bevacizumab 1.25 mg **G2:** Ranibizumab 0.5 mg • **Schedule** (both groups): monthly for 3 months; retreatment afterwards based on OCT or BCVA changes (loss of 5 letters from the previous visit with no	**G1:** Ranibizumab 0.5 mg (monthly or PRN) **G2:** Bevacizumab 1.25 mg (monthly or PRN) • **Schedule**: All groups received injections monthly for 3 months. Groups in the monthly regimen were treated monthly thereafter. Participants randomized to the PRN groups were not retreated after 3 months unless prespecified clinical and OCT criteria for	**G1:** Bevacizumab 1.25 mg **G2:** Ranibizumab 0.5 mg • **Schedule** (both groups): A "treat-and-extend" protocol was employed. Patients were examined and injected every 4 weeks until no signs of active AMD were found. If there were no signs of active neovascular disease, a

Study	**GEFAL; Kodjikian 2013[34]**	**IVAN; Chakravarthy 2013[27,37,38]**	**LUCAS; Berg 2015[39,40]**
	obvious atrophy or subretinal fibrosis and fluid on OCT; active exudation on OCT [subretinal fluid unless stable since the last 3 monthly injections, macular edema with intraretinal fluid, or increase in CST of ≥50 µm compared with the previous examination]; increased CNV area or persistence of leakage on angiography since previous visit; or new or persistent subretinal or intraretinal macular hemorrhage).	active disease were met (any subretinal fluid, increasing intraretinal fluid, or fresh blood; uncertainty about these criteria and BCVA had drop of ≥10 letters; or fluorescein leakage >25% of the lesion circumference or expansion of CNV). If retreatment was needed, a further cycle of 3 doses delivered monthly was delivered.	new injection was given and the period to the next treatment was extended by 2 weeks at a time, up to a maximum interval of 12 weeks. Recurrent disease was defined as any fluid on OCT, new or persistent hemorrhage or dye leakage, or increased lesion size on FA. If examination showed any sign of recurrence, the interval was shortened by 2 weeks at a time, until the disease was considered to be inactive. • The protocol allowed for withdrawal of patients defined as nonresponders, with the intention of offering patients alternative treatments if available.
N	501 G1: 191 G2: 183	628 (610 analyzed) G1: 323 (314 analyzed) G2: 305 (296 analyzed)	441 (431 analyzed) G1: 220 (213 analyzed) G2: 221 (218 analyzed) Patients who developed wet AMD in the nonstudy eye received the same drug in both eyes (31 patients in G1 and 25 patients in G2).
Visual Outcomes (ETDRS chart unless otherwise indicated); Functional Status/QOL Outcomes	**G1 vs G2** • Mean change in BCVA: 4.82 (SD 14.85) vs 2.93 (SD 15.09); *P*=.4200 • Mean BCVA achieved: 59.44 (SD 18.52) vs 58.70 (SD 19.82); *P*=.8632 • Proportion of participants gaining/losing BCVA letters from baseline: -Gaining ≥15 letters: 20.4% vs 21.3%; *P*=.8318 -Gaining ≥5 letters: 54.5% vs 49.7%; *P*=.3607 -Losing ≥5 letters: 20.9% vs 24.6%; *P*=.4001 -Losing ≥15 letters: 8.9% vs 9.8%; *P*=.7562	**G1 vs G2** • Mean change in BCVA -12 months: 6.4 (SD 12.8) vs 4.7 (SD 12.5); weighted mean difference -1.66 (95% CI, -3.83 to 0.50) -24 months: 4.9 (SD 15.0) vs 4.1 (SD 13.5); weighted mean difference -0.80 (95% CI, -3.26 to 1.66) • Mean BCVA achieved: -12 months: 69.1 (SD 15.7) vs 66.2 (SD 17.1) -24 months: 67.8 (SD 17.0) vs 66.1 (SD 18.4); mean difference -1.37 (95% CI, -3.75 to 1.01); *P*=.26 • Proportion of participants gaining/losing BCVA letters from baseline: -12 months: ◦Gaining ≥15 letters: 23% vs 16% ◦Gaining 5-14 letters: 33% vs 31% ◦Losing 5-14 letters: 10% vs 14% ◦Losing ≥15 letters: 5% vs 4% -24 months: ◦Gaining ≥15 letters: 24% vs 16% ◦Gaining 5-14 letters: 32% vs 34% ◦Losing 5-14 letters: 12% vs 12% ◦Losing ≥15 letters: 9% vs 9% • Bailey-Love Near Word Visual acuity chart, logMAR: -Mean at 12 months: 0.57 (SD 0.38) vs 0.62 (SD 0.41); GMR 0.92 [95% CI, 0.84 to 1.00]; *P*=.058	**G1 vs G2** • Mean change in BCVA (ITT analysis): -12 months: 7.8 vs 8.0; mean difference 0.2 (95% CI, -2.2 to 2.5), *P*=.550 -24 months: 7.8 vs 7.5; mean difference -0.3 (95% CI, -3.2 to 2.7), *P*=.873 • Mean BCVA achieved: -12 months: 67.2 (SD 17) vs 69.6 (SD 15.1); *P*=.148 -24 months: 68.0 (SD 17.0) 67.2 (SD 19.1); *P*=.690 • Proportion of participants gaining/losing BCVA letters from baseline: -12 months: ◦Gaining ≥15 letters: 25.5% vs 26.7% ◦Gaining ≥5 letters: 36.4% vs 40.6% ◦Maintaining vision (<4 letters change): 25.5% vs 23.0% ◦Losing ≥5 letters: 8.7% vs 5.3% ◦Losing ≥15 letters: 3.8% vs 4.3% -24 months: ◦Gaining ≥15 letters: 29.9% vs 29.1% ◦Gaining 5-14 letters: 34.7% vs 34.3% ◦Maintaining vision (≤4 letters

Study	GEFAL; Kodjikian 2013[34]	IVAN; Chakravarthy 2013[27,37,38]	LUCAS; Berg 2015[39,40]
		-Mean at 24 months: 0.55 (SD 0.39) vs 0.61 (SD 0.42); GMR 0.94 (95% CI, 0.85 to 1.04), *P*=.23 • Median change from baseline on Belfast Reading Speed chart: -Median at baseline: 36.9 (IQR 15.6 to 65.3) vs 35.0 (IQR 14.0 to 69.6) -Median at 12 months: 57.5 (IQR 23.4 to 94.4) vs 51.8 (IQR 11.5 to 94.6) -Median at 24 months: 50.9 (IQR 22.8 to 93.7) vs 52.5 (IQR 9.7 to 90.6); mean difference -1.34 (95% CI, -8.29 to 5.61), *P*=.70 • Pelli-Robson Contrast Sensitivity chart (letters): -Mean change from baseline at 12 months: 2.1 (SD 4.9) vs 2.1 (SD 5.0) -Mean change from baseline at 24 months: 1.5 (SD 5.9) vs 1.7 (SD 5.1); mean difference 0.21 (95% CI, -0.62 to 1.04), *P*=.62. • Median months from randomization to first treatment failure: 4.9 (IQR 3.2 to 14.0) vs 5.1 (IQR 3.7 to 16.8); HR 1.13 (95% CI, 0.94 to 1.36); *P*=.18. • EQ-5D Utility Index (higher score = better utility): -Median change at 12 months: -0.12 (IQR -0.24 to 0.00) vs -0.13 (IQR -0.26 to 0.00) -Median change at 24 months: -0.15 (IQR -0.27 to 0.00) vs -0.15 (IQR -0.27 to 0.00); score of 1 (“perfect health”) OR 0.89 (95% CI, 0.64 to 1.25), *P*=.51 • MacDQoL [disease-specific QOL index] (lower score = less impact on QOL): -Median at 12 months: -1.27 (IQR -2.76 to -0.36) vs -1.18 (IQR -3.14 to -0.39) -Median at 24 months: -1.45 (IQR -2.77 to -0.27) vs -1.39 (IQR -2.73 to -0.41); GMR 1.05 (95% CI, 0.78 to 1.42), *P*=.74 • MacTSQ treatment satisfaction index (higher score = higher treatment satisfaction): -Median at 12 months: 66.00 (IQR 61.00 to 69.00) vs 66.00 (IQR 59.50 to 69.00) -Median at 24 months: 66.00 (IQR 61.50 to 70.00) vs 65.00 (IQR 60.00 to 69.00); OR 0.79 (95% CI, 0.54 to 1.16), *P*=.23	change): 18.0% vs 19.2% ◦Losing 5-14 letters: 9.6% vs 7.0% ◦Losing ≥15 letters: 7.8% vs 10.5%
Anatomic Outcomes (reported in µm unless otherwise indicated)	**G1 vs G2** • Intraretinal and subretinal fluid absent on OCT: 50.5% vs 58.2%; *P*=.14 • Change in CST from baseline: -94.96 (SD 132.78) vs -107.23 (SD 103.25); *P*=.27 • Pigment epithelial	**G1 vs G2** • Mean change in total thickness at the fovea at 24 months: -146.9 (SD 177.4) vs -133.8 (SD 205.0); GMR 0.96 (95% CI, 0.90 to 1.03), *P*=.24 • Fluid absent on OCT at 24 months: 50% vs 41%; OR 0.72 (95% CI, 0.50 to 1.02), *P*=.065	**G1 vs G2** • Mean change in CRT plus subfoveal fluid: -12 months: -108 (SD 102) vs -111 (SD 96); mean difference 3 (95% CI, -16 to 22); *P*=.265. -24 months: -111 (SD 116) vs -112 (SD 105); mean difference 1 (95% CI , -22 to 20), *P*=.923

Study	**GEFAL; Kodjikian 2013[34]**	**IVAN; Chakravarthy 2013[27,37,38]**	**LUCAS; Berg 2015[39,40]**
	detachment on OCT: 33.2% vs 30.6%; 0.596		• Fluid absent on OCT (intraretinal or subretinal): -12 months: 47.0% vs 65.2%; *P*<.001 -24 months: 55.1% vs 72.1%; *P*<.001
Harms/Adverse Event (AE) outcomes (in study eye)	**G1 vs G2** • ≥1 serious AE: 12.6% vs 12.1%; *P*=.8757 • Withdrawn due to AE: 2.8% vs 2.9% *Ocular AEs:* • Eye disorders: 0.8% vs 2.1%; *P*=.2791 • Amaurosis fugax: 0% vs 0.4% • Retinal artery occlusion: 0.4% vs 0% • Subretinal hematoma: 0.4% vs 0.8% • Vitreous hemorrhage: 0% vs 0.4% • Endophthalmitis: 0% vs 0.4% • Retinal detachment: 0% vs 0% • Traumatic cataract: 0% vs 0% *Systemic AEs:* • ≥1 systemic serious AE: 12.2% vs 10.0%; *P*=.4510 • Death: 0.8% vs 1.3%; *P*=.6818 • Arterial thrombotic events: -MI: 0.4% vs 0.4%; *P*=1.0 -Stroke: 0% vs 0%; *P*=1.0 • Venous thrombotic events: -Pulmonary embolism: 0.4% vs 0.0%; *P*=1.0 -Phlebitis: 0% vs 0%; *P*=1.0 • TIA: 0% vs 0%; *P*=1.0 • HTN: 0.4% vs 0.8%; *P*=.6189 • Gastrointestinal disorder: 2.3% vs 2.3%; *P*=.994	**G1 vs G2** • ≥1 serious AE: 28.3% vs 27.7% • Withdrawals due to serious AEs: 1.3% vs 1.9% *Ocular AEs:* • ≥1 ocular AE: 2.0% vs 2.5% • Endophthalmitis: 0% vs 0% • Retinal detachment: 0% vs 0.3% • Retinal hemorrhage: 0% vs 0.3% • Retinal pigment epithelial tear: 0.3% vs 1.0% • Traumatic cataract: 0.3% vs 0.3% • Vitreous hemorrhage: 0.3% vs 0% • RVO: 0% vs 0.3% • Uveitis: 0.3% vs 0% • Infection: 0.3% vs 0.0% *Systemic AEs:* • ≥1 serious systemic AE: 27.0% vs 25.8%; OR 0.96 (95% CI, 0.66 to 1.39), *P*=.82 • All-cause death: 5.1% vs 4.8%; OR 0.96 (95% CI, 0.46 to 2.02), *P*=.91 • Any vascular event, heart failure, or all-cause death: 9.5% vs 12.1%; OR 1.36 (95% CI, 0.80 to 2.29); *P*=.25 • Arterial thrombotic event: 3.4% vs 4.1%; OR 1.24 (95% CI, 0.53 to 2.86) -Non-fatal MI: 1.4% vs 1.3% -Non-fatal stroke: 1.0% vs 1.9% -Vascular death: 1.4% vs 1.0% • Heart failure: 0.7% vs 2.2% • Arterial thrombotic event or heart failure: 4.1% vs 6.4%; OR 1.69 (95% CI, 0.80 to 3.57), *P*=.16 • Venous thrombotic events: 1.4% vs 1.0% • TIA: 0.3% vs 0.3% • Hospitalized for angina: 1.0% vs 2.2% • Cardiac disorders: 6.4% vs 6.4% • Gastrointestinal disorders: 3.0% vs 1.0%; OR 0.31	**G1 vs G2** • Withdrawal due to AE: 7.3% vs 4.1% *Ocular AEs:* • Endophthalmitis: 0.5% vs 0%; *P*=.499 • Pseudo-endophthalmitis: 1.4% vs 0%; *P*=.123 • Macular hemorrhage: 1.4% vs 0.0%; *P*=.123 • Retinal tear: 0.5% vs 0%; *P*=.499 • Pigment epithelial rupture: 0.5% vs 0%; *P*=.499 • Acute glaucoma: 0.5% vs 0%; *P*=.499 *Systemic AEs:* • ≥1 serious systemic AE: 29.1% vs 30.3%; *P*=.778 • All-cause death: 6.8% vs 5.9%; *P*=.687 • Arterial thrombotic events: 4.1% vs 6.3%; *P*=.289 -Nonfatal MI: 1.4% vs 4.1%; *P*=.080 -Nonfatal stroke: 1.4% vs 1.8%; *P*=1.0 -Vascular death: 1.4% vs 0.9%; *P*=.685 • Venous thrombotic events: 0% vs 1.4%; *P*=.248 • TIA: 1.4% vs 0%; *P*=.123 • HTN: 0.9% vs 0.9%; *P*=1.0 • Cardiac disorder: 5.5% vs 8.6%; *P*=.197 • Gastrointestinal disorder: 3.2% vs 5.0%; *P*=.341
Cost and Burden Outcomes	**G1 vs G2** • Mean number of injections: 6.8 (SD 2.7) vs 6.5 (SD 2.4); *P*=.39 • Patients requiring monthly injections: 4.2% vs 1.6%; *P*=.14	**G1 vs G2** • Median number of treatments: 18 (IQR 11 to 23) vs 19 (IQR 12 to 23)	**G1 vs G2** • Mean number of injections: -12 months: 8.9 (SD 2.6) vs 8.0 (SD 2.3); *P*=.001 -24 months: 18.2 vs 16.0; mean difference 1.2 (95% CI, -3.4 to -1.0), *P*≤.001 Average treatment interval in weeks: 6.5 vs 7.6 • Proportion of patients receiving

Study	GEFAL; Kodjikian 2013[34]	IVAN; Chakravarthy 2013[27,37,38]	LUCAS; Berg 2015[39,40]
			injections at treatment interval: -4 weeks: 27% vs 20%; *P*=.002 -12 weeks: 10% vs 17%; *P*=.002
Notes; Subgroup Analyses	Non-inferiority trial	4 exclusions (3 patients wrong drug injected; 1 patient was not treatment naïve). • **Subgroup Analyses:** No statistically significant differences were found for the drug or treatment regimen comparisons (*P*≥.26) for the following subgroup analyses: baseline BCVA in fellow eye, baseline retinal angiomatous proliferation, baseline lesion, baseline CNV size, baseline BCVA, hemorrhage was present at baseline, study eye ≥5 letters better than in the fellow eye at baseline.	• Non-inferiority study • All 9 patients from 1 study center were excluded because of serious protocol violations, and 1 patient was excluded after a serious retinal and vitreous hemorrhage a few days after inclusion.

Study	**MANTA; Krebs 2013[35]**	**Scholler 2014[29]**	**Subramanian 2010[26]**
• *Follow-up* • *Country* • *NCT or ID number* • *Funding*	• 12 months • Austria • NCT00710229 • Austrian Ophthalmologic Society, Ludwig Boltzmann Institute of Retinology and Biomicroscopic Lasersurgery	• 12 months • Austria • Unclear (registration numbers provided appear to be for a different trial) • NR	• 12 months • US • ISRCTN 73359806 • VA Boston Healthcare System
Objective	To examine whether bevacizumab is inferior to ranibizumab with respect to maintaining/improving visual acuity.	To evaluate the number of needed injections within one year of treatment.	To compare bevacizumab to ranibizumab for treatment of AMD in terms of visual and anatomic outcomes.
Population/ Condition	Active primary or recurrent subfoveal lesion with CNV secondary to AMD.	Active previously untreated neovascular AMD	Symptomatic CNV affecting the foveal center secondary to AMD
Population Character-istics (baseline)	Age: 77.2 years (SD 8.0) Male: 36.3% Mean BCVA: 56.7 (SD 13.3)	Age: 80.1 years (SD 6.7) Male: 29.1% Mean BCVA: 58.0 (SD 11.7) Mean CRT: 422 μm (SD 124)	Age: 78.6 years Male: 95% Caucasian: 100% Mean BCVA (B vs R): 34.9 (range 12-60) vs 32.7 (range 4-66); *P*=.80 Classic or predominantly classic CNV (B vs R): 20% vs 14%
Main Inclusion Criteria	Treatment naive patients >50 years with active primary or recurrent subfoveal lesion with CNV secondary to AMD; BCVA using ETDRS 20/40 to 20/320. If both eyes were eligible for inclusion in the present study, the eye that showed more progression (loss of distance acuity) based on the local investigator's assessment was included.	Age ≥50 years; neovascular AMD verified by fluorescence angiography; BCVA between 20/40 and 20/320.	Age >50 years; presence of a symptomatic CNV (confirmed by intravenous fluorescein angiogram and OCT) affecting the foveal center; baseline BCVA ≥20/400.
Main Exclusion Criteria	Prior treatment with any intravitreal drug or verteporfin PDT in the study eye; prior treatment with systemic bevacizumab or any intravitreal drug; subfoveal fibrosis or atrophy in the study eye >50%; active intraocular inflammation; acute or recurrent infectious conjunctivitis; history of MI and/or stroke.	Previous AMD treatment; previous systemic bevacizumab treatment; vision impairing cataract or other ophthalmologic disease like glaucoma, active inflammation, diabetic retinopathy, etc.	Previous treatment for wet AMD within the past year; presence of subretinal hemorrhage >50% of the size of the lesion on FA; presence of advanced glaucoma; history of malignant or uncontrolled HTN, intraocular inflammation, or history of thromboembolic phenomena.
Intervention vs Comparator • *Schedule* • *Co-Intervention/ Rescue Treatment*	**G1:** Bevacizumab 1.25 mg **G2:** Ranibizumab 0.5 mg • **Schedule** (both groups): monthly for 3 months; retreatment afterwards based on OCT or BCVA changes (BCVA loss of ≥5 letters with OCT or fluorescein angiographic evidence of fluid in the macula; an increase in CRT ≥100 μm; new macular hemorrhage; new area of classic CNV; or evidence of persistent fluid on OCT ≥1 month after the previous injection).	**G1:** Bevacizumab 1.25 mg **G2:** Ranibizumab 0.5 mg • **Schedule** (both groups): monthly for 3 months; retreatment afterwards based on OCT or BCVA changes (loss of BCVA of ≥5 letters with OCT evidence of fluid in the macula; increase in CRT of ≥100 μm; new area of AMD; new macular hemorrhage; persistent fluid on OCT ≥1 month after the previous injection).	**G1:** Bevacizumab (dose not reported) **G2:** Ranibizumab (dose not reported) • **Schedule** (both groups): monthly for 3 months; retreatment afterwards based on OCT or BCVA changes and clinical examination (qualitative increase in intraretinal or subretinal fluid by OCT; if any significant worsening of visual acuity or increase in fluid or hemorrhage present on clinical examination, a repeat FA was administered with possible re-injection based on the results). • Patients were treated with topical antibiotics for 4 days after injection.
N	317 G1: 154 G2: 163	55 (number analyzed unclear) G1: 29 G2: 26	28 (22 analyzed) G1: 20 (15 analyzed) G2: 8 (7 analyzed)

Study	**MANTA; Krebs 2013[35]**	**Scholler 2014[29]**	**Subramanian 2010[26]**
Visual Outcomes (ETDRS chart unless otherwise indicated); Functional Status/QOL Outcomes	**G1 vs G2** • Mean change in BCVA: 4.9 vs 4.1; *P*=.78 • Mean BCVA achieved: 62.2 (95% CI, 60.1 to 64.3) vs 60.7 (95% CI, 58.7 to 62.8) • Proportion of participants gaining/losing BCVA letters from baseline (all estimated from graph): -Gaining ≥15 letters: 23% vs 21%; *P*=.42 -Gaining ≥5 letters: 58% vs 53%; *P*=.31 -Losing ≥5 letters: 21% vs 21%; *P*=.11 -Losing ≥15 letters: 5% vs 6%; *P*=.23	**G1 vs G2** • Mean BCVA achieved: 64.75 (SD 17.03) vs 59.12 (SD 16.64); mean difference 5.5, *P*=.631 • Proportion of participants losing ≥15 letters from baseline: 6.9% vs 7.7%	**G1 vs G2** • Mean change in BCVA: 7.6 vs 6.3; *P*=.74 • Mean BCVA achieved: 42.5 (SD 13.7) vs 39.0 (SD 10.1); *P*=.5 • Proportion of participants gaining/losing BCVA letters from baseline: -Gaining ≥15 letters: 33% vs 14% -Gaining ≥5 letters: 60% vs 57% -Losing ≥5 letters: 27% vs 14% -Losing ≥15 letters: 0% vs 14% *NOTE: BCVA measured using ETDRS at 2 m instead of recommended 4 m; vision was recorded in the same, consistent fashion for all study subjects.
Anatomic Outcomes (reported in μm unless otherwise indicated)	**G1 vs G2** • Mean change in CRT (corrected values): -86.3 vs -89.9; *P*=.81	**G1 vs G2** • Mean CRT: 350.47 (SD 102.84) vs 315.67 (SD 65.86); *P*=.088	**G1 vs G2** • Mean change in CMT: -50 vs -91; *P*=.29
Harms/Adverse Event (AE) outcomes (in study eye)	**G1 vs G2** • Total number of AEs: 19 (12.3%) vs 15 (9.2%); *P*=.37 *Ocular AEs:* 0 (0%) vs 0 (0%); *P*=1.0 *Systemic AEs:* • Death: 3 (1.9%) vs 2 (1.2%); *P*=.61 • Vascular disorders: -Heart attack: 3 (1.9%) vs 2 (1.2%); *P*=.61 -Stroke: 1 (0.6%) vs 1 (0.6%); *P*=.94 -Mesenteric artery occlusion: 1 (0.6%) vs 0 (0%); *P*=.30 • Non-vascular disorders: -Infection: 3 (1.9%) vs 3 (1.8%); *P*=.94 -Injury or procedural complication: 2 (1.3%) vs 3 (1.8%); *P*=.70 -Surgical or medical procedure: 1 (0.6%)vs 0 (0%); *P*=.30 -Any system organ class: 3 (1.9%) vs 2 (1.2%); *P*=.61	**G1 vs G2** *Ocular AEs:* • Subretinal bleeding: 0% vs 7.7% *Systemic AEs:* • TIA: 0% vs 3.8%	No major ocular AEs or systemic AEs reported in any subjects who completed the one-year follow-up visit. Minor AEs (*eg*, subconjunctival hemorrhage, transient post-injection pain, and elevated IOP) data not reported. No reports of anterior chamber inflammation, vitreous hemorrhage, retinal detachment, endophthalmitis, or systemic AEs in patients completing one-year follow-up.
Cost and Burden Outcomes	**G1 vs G2** • Mean number of re-treatments: 6.1 (SD 2.8) vs 5.8 (SD 2.7); *P*=.26	**G1 vs G2** • Mean number of injections: 5.80 (SD 2.28) vs 5.00 (SD 1.67); *P*=.084	**G1 vs G2** • Mean number of injections: 8 (range 3-8) vs 4 (3-6); *P*=.001
Notes; Subgroup Analyses	Non-inferiority approach (power calculated assuming 7 letter increase in BCVA with ranibizumab and no change in BCVA with bevacizumab). The study was not powered to determine AEs of statistical significance.		• VA Boston Healthcare System Hospital. • Inclusion criteria amended from BCVA 20/40 to 20/200, to BCVA ≥20/400. • BCVA measured at 2 m instead of recommended 4 m because of exam room size; vision was recorded in the same, consistent fashion for all study subjects.

Study	**VIEW 1; Heier 2012[43]**	**VIEW 2; Heier 2012[43]**	**VIEW 1 and VIEW 2 combined 96-week results; Schmidt-Erfurth 2014[44]**
• Follow-up *• Country* *• NCT or ID number* *• Funding*	• 12 months • US and Canada • NCT00509795 • Regeneron Pharmaceutical and Bayer HealthCare	• 12 months • Europe, the Middle East, Asia-Pacific, and Latin America • NCT00637377 • Regeneron Pharmaceutical and Bayer HealthCare	•22 months • US, Canada, Europe, the Middle East, Asia-Pacific, and Latin America • NCT00509795 and NCT00637377 • Regeneron Pharmaceutical and Bayer HealthCare
Objective	To compare monthly and every-2-month dosing of intravitreal aflibercept injection with monthly ranibizumab in patients with neovascular AMD.	To compare monthly and every-2-month dosing of intravitreal aflibercept injection with monthly ranibizumab in patients with neovascular AMD.	To compare monthly and every-2-month dosing of intravitreal aflibercept injection with monthly ranibizumab in patients with neovascular AMD.
Population/ Condition	Active subfoveal CNV lesions or juxtafoveal lesions with leakage affecting the fovea, secondary to AMD.	Active subfoveal CNV lesions or juxtafoveal lesions with leakage affecting the fovea, secondary to AMD.	Active subfoveal CNV lesions or juxtafoveal lesions with leakage affecting the fovea, secondary to AMD.
Population Character-istics (baseline)	Age: 78 years (SD 8.0) Male: 41.2% White: 96.6% Baseline BCVA: 55.1 (SD 13.1) Predominantly classic lesion: 26.5%; Minimally classic lesion: 34.1%; Occult lesion: 38.3%	Age: 73.9 years (SD 8.7) Male: 44.5% White: 72.8% Baseline BCVA: 52.4 (SD 13.9) Predominantly classic lesion: 25.8%; Minimally classic lesion: 35.3%; Occult lesion: 38.4%	Age: 75.9 years (SD 8.6) Male: 42.8% White: 84.7% Baseline BCVA: 53.8 (SD 13.6)
Main Inclusion Criteria	Age ≥50 years; active subfoveal CNV lesions (any subtype) secondary to AMD, or juxtafoveal lesions with leakage affecting the fovea; CNV comprising ≥50% of total lesion size; BCVA between 73 and 25 letters (20/40 to 20/320 Snellen equivalent).	Age ≥50 years; active subfoveal CNV lesions (any subtype) secondary to AMD, or juxtafoveal lesions with leakage affecting the fovea; CNV comprising ≥50% of total lesion size; BCVA between 73 and 25 letters (20/40 to 20/320 Snellen equivalent).	Age ≥50 years; active subfoveal CNV lesions (any subtype) secondary to AMD, or juxtafoveal lesions with leakage affecting the fovea; CNV comprising ≥50% of total lesion size; BCVA between 73 and 25 letters (20/40 to 20/320 Snellen equivalent).
Main Exclusion Criteria	Prior treatment for AMD (including investigational agents or anti-VEGF therapy) in study eye.	Prior treatment for AMD (including investigational agents or anti-VEGF therapy) in study eye.	Prior treatment for AMD (including investigational agents or anti-VEGF therapy) in study eye.
Intervention vs Comparator *• Schedule* *• Co-Intervention/ Rescue Treatment*	**G1:** Aflibercept 2.0 mg every 4 weeks **G2:** Aflibercept 0.5 mg every 4 weeks **G3:** Aflibercept 2.0 mg every 8 weeks (after 3 initial doses every 4 weeks) **G4:** Ranibizumab 0.5 mg every 4 weeks **• Schedule**: Patients were seen every 4 weeks and given either active treatment or a sham injection depending on randomization group (*ie*, G3 received sham every other visit).	**G1:** Aflibercept 2.0 mg every 4 weeks **G2:** Aflibercept 0.5 mg every 4 weeks **G3:** Aflibercept 2.0 mg every 8 weeks (after 3 initial doses every 4 weeks) **G4:** Ranibizumab 0.5 mg every 4 weeks **• Schedule**: Patients were seen every 4 weeks and given either active treatment or a sham injection depending on randomization group (*ie*, G3 received sham every other visit).	**G1:** Aflibercept 2.0 mg every 4 weeks for first 52 weeks, capped PRN thereafter **G2:** Aflibercept 0.5 mg every 4 weeks for first 52 weeks, capped PRN thereafter **G3:** Aflibercept 2.0 mg every 8 weeks (after 3 initial doses every 4 weeks) for first 52 weeks, capped PRN thereafter **G4:** Ranibizumab 0.5 mg every 4 weeks for first 52 weeks, capped PRN thereafter **• Schedule** for follow-up phase (weeks 52-96): required a switch of all regimens from fixed monthly or every 2 months regimen to a variable regimen requiring at least quarterly dosing (capped PRN); interim injections allowed based on an assessment of anatomic and visual parameters.
N	1217 G1: 304 G2: 304	1240 G1: 313 G2: 311	2457 G1: 617 G2: 615

Study	**VIEW 1; Heier 2012[43]**	**VIEW 2; Heier 2012[43]**	**VIEW 1 and VIEW 2 combined 96-week results; Schmidt-Erfurth 2014[44]**
	G3: 303 G4: 306	G3: 313 G4: 303	G3: 616 G4: 609
Visual Outcomes (ETDRS chart unless otherwise indicated); Functional Status/QOL Outcomes	**G1 vs G2 vs G3 vs G4** • Mean change in BCVA: 10.9 (SD 13.8) vs 6.9 (SD 13.4) vs 7.9 (SD 15.0) vs 8.1 (SD 15.3); LS mean difference: G1 vs G4: 3.15 (95% CI, 0.92 to 5.37), *P*=.0054; G2 vs G4: -0.80 (95% CI, -3.03 to 1.43), *P*=.4793; G3 vs G4: 0.26 (95% CI, -1.97 to 2.49), *P*=.8179 • Proportion of participants gaining/losing BCVA letters from baseline: -Maintaining BCVA (losing <15 letters, LOCF): 95.1% vs 95.0% vs 94.4% vs 93.8% -Gaining ≥0 letters (losing no letters): 83.6% vs 78.1% vs 79.7% vs 78.9% -Gaining ≥15 letters: 37.5% vs 24.9% vs 30.6% vs 30.9%; LS mean difference: G1 vs G4: 6.58 (95% CI, -0.98 to 14.14), *P*=.1042; G2 vs G4: -6.00 (95% CI, -13.17 to 1.16), *P*=.1037; G3 vs G4: -0.36 (95% CI, -7.74 to 7.03), *P*=.93 • Proportion achieving BCVA 20/40 or better: 45.7% vs 34.9% vs 37.9% vs 34.5% • Mean change in total NEI VFQ-25 score: 6.7 (SD 13.5) vs 4.5 (SD 11.9) vs 5.1 (SD 14.7) vs 4.9 (SD 14.0); LS mean difference: G1 vs G4: 1.28 (95% CI, -0.73 to 3.28), *P*=.2090; G2 vs G4: -0.67 (95% CI, -2.69 to 1.35), *P*=.5128; G3 vs G4: -0.60 (95% CI, -2.61 to 1.42), *P*=.5579	**G1 vs G2 vs G3 vs G4** • Mean change in BCVA: 7.6 (SD 12.6) vs 9.7 (SD 14.1) vs 8.9 (SD 14.4) vs 9.4 (SD 13.5); LS mean difference: G1 vs G4: -1.95 (95% CI, -4.10 to 0.20), *P*=.076; G2 vs G4: -0.06 (95% CI, -2.24 to 2.12), *P*=.955; G3 vs G4: -0.90 (95% CI, -3.06 to 1.26), *P*=.4131 • Proportion of participants gaining/losing BCVA letters from baseline: -Maintaining BCVA (losing <15 letters): 94.5% vs 95.3% vs 95.4% vs 94.8% -Gaining ≥0 letters (losing no letters): 78% vs 83.1% vs 81.7% vs 79% -Gaining ≥15 letters: 29.4% vs 34.8% vs 31.4% vs 34.0%; LS mean difference: G1 vs G4: -4.57 (95% CI, -12.02 to 2.88), *P*=.229; G2 vs G4: 0.78 (95% CI, -6.91 to 8.46), *P*=.843; G3 vs G4: -2.65 (95% CI, -10.18 to 4.88), *P*=.490 • Proportion achieving BCVA 20/40 or better: 32.7% vs 32.4% vs 27.5% vs 35.7% • Mean change in total NEI VFQ-25 score: 4.5 (SD 15.0) vs 5.1 (SD 13.7) vs 4.9 (SD 14.7) vs 6.3 (SD 14.8); LS mean difference: G1 vs G4: -2.79 (95% CI, -4.90 to -0.68), *P*=.0097; G2 vs G4: -0.93 (95% CI, -3.07 to 1.20), *P*=.3917; G3 vs G4: -1.95 (95% CI, -4.07 to 0.17), *P*=.0717	**G1 vs G2 vs G3 vs G4** • Mean change in BCVA at 22 months: 7.6 vs 6.6 vs 7.6 vs 7.9 • Proportion of participants gaining/losing BCVA letters from baseline: -Maintaining vision (losing <15 letters): 92.2% vs 91.5% vs 92.4% vs 91.6% -Gaining ≥15 letters : 31.2% vs 28.1% vs 33.4% vs 31.6%
Anatomic Outcomes (reported in μm unless otherwise indicated)	**G1 vs G2 vs G3 vs G4** • Mean change in CNV area (mm^2): -4.6 (SD 5.5) vs -3.5 (SD 5.3) vs -3.4 (SD 6.0) vs -4.2 (SD 5.6); LS mean difference: G1 vs G4: -0.33 (95% CI, -1.04 to 0.38), *P*=.3575; G2 vs G4: 0.71 (95% CI, -0.01 to 1.42), *P*=.0507; G3 vs G4: 0.86 (95% CI, 0.15 to 1.58), *P*=.0173. • Mean change in CRT: -116.5 (SD 98.4) vs -115.6 (SD 104) vs -128.5 (SD 108.5) vs -116.8 (SD 109) • Proportion with dry retina (no	**G1 vs G2 vs G3 vs G4** • Mean change in CNV area (mm^2): -6.0 (SD 6.1) vs -4.2 (SD 6.1) vs -5.2 (SD 5.9) vs -4.2 (SD 5.9); LS mean difference: G1 vs G4: -1.18 (95% CI, -1.98 to -0.38); G2 vs G4: -0.17 (95% CI, -0.63 to 0.97); G3 vs G4: -0.73 (95% CI, -1.53 to 0.07) • Mean change in CRT: -156.8 (SD 122.8) vs -129.8 (SD 114.8) vs -149.2 (SD 119.7) vs -138.5 (SD 122.2) • Proportion with dry retina (no	**G1 vs G2 vs G3 vs G4** • Mean change in CRT at 22 months: -128 vs -113 vs -133 vs -128 • Proportion with retinal fluid absent on OCT: 54.4% vs 44.6% vs 50.1% vs 45.5%

Study	**VIEW 1; Heier 2012[43]**	**VIEW 2; Heier 2012[43]**	**VIEW 1 and VIEW 2 combined 96-week results; Schmidt-Erfurth 2014[44]**
	cystic intraretinal edema or subretinal fluid on OCT): 64.8% vs 56.7% vs 63.4% vs 63.6%	cystic intraretinal edema or subretinal fluid on OCT): 80.3% vs 63.9% vs 71.9% vs 60.4%	
Harms/Adverse Event (AE) outcomes (in study eye)	**G1-3 (all aflibercept groups) vs G4** • Withdrawal due to AE: 12 (1.3%) vs 4 (1.3%) *Ocular AEs:* • Patients with ≥1 serious ocular AE: 16 (1.8%) vs 10 (3.3%) • Endophthalmitis: 3 (0.3%) vs 3 (1.0%) • Retinal hemorrhage: 2 (0.2%) vs 2 (0.7%) • Increased IOP: 41 (4.5%) vs 22 (7.2%) • Treatment-emergent serious retinal detachment: 1 (0.1%) vs 0 (0%) • Treatment-emergent serious cataract: 1 (0.1%) vs 0 (0%) *Systemic AEs:* • Serious systemic or nonocular AEs: 141 (15.5%) vs 57 (18.8%) • Any arterial thrombotic event: 15 (1.6%) vs 5 (1.6%) -Vascular death: 5 (0.5%) vs 1 (0.3%) -Nonfatal MI: 6 (0.7%) vs 4 (1.3%) -Nonfatal stroke: 4 (0.4%) vs 0% • HTN: 82 (9.0%) vs 29 (9.5%) • Venous thromboembolic event: 1 (0.1%) vs 1 (0.3%) • Congestive heart failure: 4 (0.4%) vs 2 (0.7%) • Gastrointestinal perforation or fistula: 0 (0%) vs 0 (0%) • Nonocular hemorrhagic event: 7 (0.7%) vs 1 (0.3%)	**G1-3 (all aflibercept groups) vs G4** • Withdrawal due to AE: 23 (2.5%) vs 2 (0.7%) *Ocular AEs:* • Patients with ≥1 serious ocular AE: 20 (2.2%) vs 9 (3.1%) • Endophthalmitis: 0% vs 0% • Retinal hemorrhage: 4 (0.4%) vs 1 (0.3%) • Increased IOP: 54 (5.9%) vs 19 (6.5%) • Treatment-emergent serious retinal detachment: 2 (0.2%) vs 1 (0.3%) • Treatment-emergent serious cataract: 2 (0.2%) vs 1 (0.3%) *Systemic AEs:* • Serious systemic or nonocular AEs: 111 (12.2%) vs 26 (8.9%) • Any arterial thrombotic event: 17 (1.9%) vs 5 (1.7%) -Vascular death: 4 (0.4%) vs 1 (0.3%) -Nonfatal MI: 9 (1.0%) vs 2 (0.7%) -Nonfatal stroke: 4 (0.4%) vs 2 (0.7%) • HTN: 81 (8.8%) vs 29 (10.0%) • Venous thrombotic events: 0 (0%) vs 0 (0%) • Congestive heart failure: 1 (0.1%) vs 1 (0.3%) • Gastrointestinal perforation or fistula: 2 (0.2%) vs 0 (0%) • Nonocular hemorrhagic event: 3 (0.3%) vs 0 (0%)	**G1-3 (all aflibercept groups) vs G4** • Withdrawal due to AE by 22 months: 75 (4.1%) vs 16 (2.6%) *Ocular AEs:* • ≥1 serious ocular AE: 65 (3.6%) vs 26 (4.4%) • Endophthalmitis: 5 (0.3%) vs 5 (0.8%) • Retinal detachment: 3 (0.2%) vs 3 (0.5%) • Retinal hemorrhage: 13 (0.7%) vs 4 (0.7%) • Retinal pigment epithelial tear: 4 (0.2%) vs 1 (0.2%) • Cataract: 11 (0.6%) vs 1 (0.2%) • Increased IOP: 3 (1.6%) vs 1 (0.2%) • Any intraocular inflammatory response: 15 (0.8%) vs 9 (1.5%) • Posterior capsule opacification: 0 (0%) vs 2 (0.3%) *Systemic AEs:* • ≥1 serious systemic or nonocular AE: 437 (24.0%) vs 146 (24.5%) • Arterial thrombotic event: 60 (3.3%) vs 19 (3.2%) ◦Nonfatal MI: 25 (1.4%) vs 12 (2.0%) ◦Nonfatal stroke: 13 (0.7%) vs 5 (0.8%) ◦Vascular death: 24 (1.3%) vs 3 (0.5%) • Congestive cardiac failure: 16 (0.9%) vs 5 (0.8%) • Coronary artery disease: 8 (0.4%) vs 5 (0.8%) • Atrial fibrillation: 23 (1.3%) vs 5 (0.8%) -TIA: 17 (0.9%) vs 1 (0.2%) -Cerebrovascular accident: 14 (0.8%) vs 4 (0.7%) -Death: 52 (2.8%) vs 16 (2.7%)
Cost and Burden Outcomes	NR	NR	**G1 vs G2 vs G3 vs G4** • Mean number of injections at week 96: 16.0 (SD 3.2) vs 16.2 (SD 4.0) vs 11.2 (SD 2.9) vs 16.5 (SD 2.7) • Mean number of injections from week 52-96 (PRN schedule): 4.1 (SD 1.8) vs 4.6 (SD 2.2) vs 4.2 (SD 1.7) vs 4.7 (SD 2.2); *P*<.0001 G1 vs G4; *P*<.0001 G3 vs G4
Notes; Subgroup Analyses	Non-inferiority study. Not powered to detect differences in rare but serious intraocular complications (*eg*, endophthalmitis).	Non-inferiority study. Not powered to detect differences in rare but serious intraocular complications (*eg*, endophthalmitis).	

Trials in Patients with Diabetic Macular Edema (DME)

Study	**DRCR.net (Protocol T); Wells 2016[46-48]**	**Ekinci 2014[30]**	**Nepomuceno 2013[31]**
• *Follow-up* • *Country* • *NCT or ID number* • *Funding*	• 24 months • US • NCT01627249 • National Institutes of Health. Regeneron Pharmaceuticals provided the aflibercept at no cost, and Genentech provided the ranibizumab at no cost for the study.	• 12 months • Turkey • NR • NR ("The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter")	•11 months (48 weeks) • Brazil • NCT01487629 • São Paulo Research Foundation, Fundação de Apoio ao Ensino, Pesquisa e Assistência do Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo
Objective	To compare intravitreal aflibercept, bevacizumab, and ranibizumab for the treatment of DME involving the center of the macula and causing vision impairment.	To compare the effects of bevacizumab and ranibizumab on visual acuity and foveal thickness in macular edema due to diabetic retinopathy.	To compare visual acuity and spectral-domain OCT outcomes associated with intravitreal bevacizumab versus ranibizumab for the management of DME.
Population/ Condition	DME involving the macular center	Clinically significant DME	DME with central involvement
Population Character-istics (baseline)	Age: 60.6 years (SD 10) Male: 54% White: 65% Black/African American: 16% Hispanic: 16% Mean BCVA: 64.8 (SD 11.3) Type 2 diabetes: 90.6% (mean duration 17 years) Mean HbA1c: 7.7 Mean CST: 412 μm (SD 130)	Age: 66.5 years (SD 11.5) Male: 36% Mean BCVA, B vs R (Snellen chart): 0.22 (SD 0.11) vs 0.24 (SD 0.12) Mean foveal thickness, B vs R: 483.8 (SD 126) vs 489.8 (SD 141) Mean duration of diabetes: 15.5 years (SD 3.3) Mean HbA1c level: 7.3 (SD 0.6)	Age: 63.8 years (SE 8.9) Male: 45% White: 70% Mean BCVA (logMAR, B vs R): 0.63 (SE 0.06) vs 0.60 (SE 0.05); *P*=.680 Baseline CST (B vs R): 451 μm (SE 22) vs 421 μm (SE 23); *P*=.406 Mean duration of DME: 3.1 years Mean duration of diabetes: 16 years Mean HbA1c: 8.6 (SD 1.6) Moderate or severe nonproliferative diabetic retinopathy: 60% Diabetic retinopathy treated with PRP ≥6 months before enrollment: 40%
Main Inclusion Criteria	≥18 years of age; type 1 or 2 diabetes; at least one eye with a BCVA letter score of 78 to 24 and center-involved DME on clinical examination and OCT according to protocol-defined thresholds; and received no anti-VEGF treatment within the previous 12 months.	Clinically significant DME (CMT >300 μm), as found through FA and OCT evaluations and dilate fundus examination, after 1-year follow-up period.	Center-involved DME, defined as a CST >300 μm on OCT, despite ≥1 session of macular laser photocoagulation performed at least 3 months previously; BCVA between 0.3 logMAR (Snellen equivalent: 20/40) and 1.6 logMAR (Snellen equivalent: 20/800).
Main Exclusion Criteria	Substantial cataract; significant renal disease; unstable medical status including blood pressure, cardiovascular disease, and glycemic control; MI, other acute cardiac	Patients who received intravitreal treatment at another center; PRP, grid	Vitreomacular traction on OCT; history of glaucoma or ocular HTN; systemic

Study	**DRCR.net (Protocol T); Wells 2016[46-48]**	**Ekinci 2014[30]**	**Nepomuceno 2013[31]**
	event requiring hospitalization, stroke, TIA, or treatment for acute congestive heart failure within 4 months of randomization.	or focal laser photocoagulation application within 6 months; intraocular surgery within 6 months; acute ocular infection, stroke, MI, uncontrolled HTN, pregnancy, renal failure and cataract formation during the follow-up period.	corticosteroid therapy; any condition that might preclude follow-up throughout the study period; last anti-VEGF or steroid treatment >6 months before enrollment.
Intervention vs Comparator • *Schedule* • *Co-Intervention/ Rescue Treatment*	**G1:** Aflibercept 2.0 mg **G2:** Bevacizumab 1.25 mg **G3:** Ranibizumab 0.3 mg • **Schedule** (all groups): Administered every 4 weeks unless visual acuity was 20/20 or better with a CST below the eligibility threshold and there was no improvement (≥5 letters or ≥10% decrease in thickness) or worsening in response to the past two injections. • The use of pre-injection or post-injection antibiotics was at the investigator's discretion. Laser photocoagulation therapy (focal, grid, or both) was initiated at or after the 24-week visit for persistent DME. Treatment for DME other than the randomly assigned anti-VEGF agent or laser therapy was permitted if a study eye met the criteria for treatment failure.	**G1:** Bevacizumab 1.25 mg **G2:** Ranibizumab 0.05 mg* (*possible reporting error, as typical dose is 0.3 mg) • **Schedule** (both groups): Administered monthly for 3 months. An additional 3 monthly injections were applied if the CMT was >275 µm or if there was an increase in BCVA of ≥3 letters compared with baseline. After the 6th intravitreal injection, if the CMT >275 µm or if there was an increase in BCVA of ≥2 letters, additional intravitreal injections were performed until stable visual acuity was obtained. • Topical antibiotics 4 times daily for 1 week.	**G1:** Bevacizumab 1.5 mg **G2:** Ranibizumab 0.5 mg • **Schedule** (both groups): Administered monthly if CST was >275 µm. -Randomization of both eyes: If both eyes were eligible for treatment and the patient agreed to treat both eyes with anti-VEGF therapy, 1 eye received the randomized treatment and the contralateral eye received the other anti-VEGF agent on the next day. • Focal/grid laser photocoagulation could be used as rescue therapy (at the discretion of ophthalmologist) after 3 injections if there was not a reduction in CST of ≥10% or an increase in BCVA of ≥5 letters compared with baseline; or patient could receive injections for an additional 3 consecutive visits. • Patients were instructed to instill 1 drop of 0.3% ciprofloxacin into the injected eye 4 times daily for 1 week after the procedure.
N	660 G1: 224 G2: 218 G3: 218	100 G1: 50 G2: 50	48 (63 eyes); 45 (60 eyes) analyzed G1: (32 eyes) G2: (28 eyes) *15 patients with bilateral DME received bevacizumab in one eye and ranibizumab in the other eye.
Visual Outcomes (ETDRS chart unless otherwise	**G1 vs G2 vs G3** • Mean change in BCVA -12 months: 13.3 (SD 11.1) vs 9.7 (SD 10.1) vs 11.2 (SD 9.4); *P*<.001 for G1 vs G2, *P*=.03 G1 vs G3, *P*=.12 G2 vs G3	**G1 vs G2** • BCVA achieved (Snellen chart): 0.38 (SD 0.12) vs 0.39 (SD 0.11); *P*=NS	**G1 vs G2** • Mean BCVA improvement at 48 weeks (logMAR): 0.23 (SD 0.02) vs 0.29 (SD 0.04) • Mean BCVA achieved

Study	**DRCR.net (Protocol T); Wells 2016[46-48]**	**Ekinci 2014[30]**	**Nepomuceno 2013[31]**
indicated); Functional Status/QOL Outcomes	-24 months: 12.8 (SD 12.4) vs 10.0 (SD 11.8) vs 12.3 (SD 10.5); *P*=.02 for G1 vs G2, *P*=.47 G1 vs G3, *P*=.11 G2 vs G3 • Proportion of participants gaining/losing BCVA letters from baseline: -12 months: ◦Gaining ≥15 letters: 42% vs 29% vs 32%; *P*=.028 for G1 vs G2, *P*=.068 G1 vs G3, *P*=.51 G2 vs G3 ◦Gaining ≥10 letters: 63% vs 52% vs 59%; *P*=.021 for G1 vs G2, *P*=.25 G1 vs G3, *P*=.15 G2 vs G3 ◦Losing ≥10 letters: 2% vs 3% vs 1%; *P*=.83 for all comparisons ◦Losing ≥15 letters: 1% vs 1% vs 1%; *P*=.98 for all comparisons -24 months: ◦Gaining ≥15 letters: 39% vs 35% vs 37%; *P*=.70 for all comparisons ◦Gaining ≥10 letters: 62% vs 54% vs 59%; *P*=.22 for G1 vs G2, *P*=.51 G1 vs G3, *P*=.50 G2 vs G3 ◦Losing ≥10 letters: 4% vs 6% vs 2%; *P*=.49 for G1 vs G2, *P*=.39 G1 vs G3, *P*=.15 G2 vs G3 ◦Losing ≥15 letters: 2% vs 3% vs 2%; *P*=.84 for all comparisons • Mean BCVA achieved: 77.8 (SD 11.5) vs 74.6 (SD 14.5) vs 77.1 (SD 12.4) • *Mean change in BCVA according to baseline visual acuity, see Notes; Subgroup Analyses row below*		(logMAR): 0.36 (SE 0.05) vs 0.34 (SE 0.04); *P*=.1886 • Proportion of participants gaining BCVA letters from baseline: -Gaining ≥15 letters: 39% vs 48%; *P*=NS -Gaining ≥10 letters: 61% vs 68%; *P*=NS
Anatomic Outcomes (reported in µm unless otherwise indicated)	**G1 vs G2 vs G3** • Mean change in CST: -12 months: -169 (SD 138) vs -101 (SD 121) vs -147 (SD 134); *P*<.001 for G1 vs G2, *P*=.036 G1 vs G3, *P*<.001 G1 vs G2 -24 months: -171 (SD 141) vs -126 (SD 143) vs -149 (SD 141); *P*<.001 for G1 vs G2, *P*=.08 G1 vs G3, *P*<.001 G2 vs G3	**G1 vs G2** • Mean foveal thickness: 342.3 (SD 121) vs 339.3 (SD 121); *P*=NS	**G1 vs G2** • Mean CST at 48 weeks: 329.7 (SE 19.3) vs 280.9 (SE 12.6); *P*=.4865 • Maximum mean CST reduction: -126 (SE 25) at week 48 vs -136 (SE 23) at week 44; *P*=NS
Harms/Adverse Event (AE) outcomes (in study eye)	**G1 vs G2 vs G3** *Ocular AEs:* • Endophthalmitis: 0 (0%) vs 1 (0.5%) vs 0 (0%); *P*=.66 • Inflammation: 6 (2.7%) vs 3 (1.4%) vs 4 (1.8%); *P*=.69 • Retinal detachment: 2 (0.9%) vs 2 (0.9%) vs 1 (0.9%); *P*=1.0 • Retinal tear: 1 (0.4%) vs 1 (0.5%) vs 1 (0.5%); *P*=1.0 • Vitreous hemorrhage: 15 (6.7%) vs 17 (7.8%) vs 10 (4.6%); *P*=.37 • Injection-related cataract: 3 (1.3%) vs 2 (0.9%) vs 0 (0%); *P*=.38 • IOP elevation: 39 (17.4%) vs 27 (12.4+V12%) vs 35 (16.5%); *P*=.31 *Systemic AEs:* • Serious AE: 88 (39.3%) vs 81 (37.2%) vs 82 (37.6%); *P*=.90 • Vascular events: 12 (5.4%) vs 17 (7.8%) vs 26 (11.9%); *P*=.047	• "Patients with acute ocular infection (endophthalmitis after intravitreal injection, n=3), stroke, MI (n=2), uncontrolled HTN (n=4), renal failure (n=1) and cataract formation during follow-up period (n=4) were excluded from the study." (not reported by group) • "No complications, like IOP rise or arterial HTN was observed in patients in the study as a result of intravitreal bevacizumab and ranibizumab injections."	**G1 vs G2** (percentages based on number of eyes) • Clinically significant cataract progression: 1 (3%) vs 0 (0%) • Transient vitreous hemorrhage after an acute posterior vitreous detachment: 1 (3%) vs 0 (0%) • Endophthalmitis: 0 (0%) vs 2 (7%) • Increased blood pressure: 0 (0%) vs 1 (4%) • Transient worsening of renal function: 1 patients receiving both treatments

Study	**DRCR.net (Protocol T); Wells 2016[46-48]**	**Ekinci 2014[30]**	**Nepomuceno 2013[31]**
	-Nonfatal MI: 7 (3.1%) vs 3 (1.4%) vs 6 (2.8%) -Nonfatal stroke: 2 (0.9%) vs 6 (2.8%) vs 11 (5.0%) -Vascular death (from any potential vascular or unknown cause): 3 (1.3%) vs 8 (3.7%) vs 9 (4.1%) • All-cause death: 5 (2%) vs 13 (6%) vs 11 (5%); *P*=.12 • Hospitalization: 77 (34.4%) vs 71 (32.6%) vs 73 (33.5%); *P*=.93 • Gastrointestinal: 67 (29.9%) vs 64 (29.4%) vs 60 (27.5%); *P*=.85 • Renal and urinary disorder events: 50 (22.3%) vs 46 (21.1%) vs 35 (16.1%); *P*=.22 • HTN: 39 (17.4%) vs 27 (12.4%) vs 44 (20.2%); *P*=.08		
Cost and Burden Outcomes	**G1 vs G2 vs G3** • Median number of injections: -12 months: 9 (IQR 8 to 11) vs 10 (IQR 8 to 12) vs 10 (IQR 8 to 11); *P*=.045 for overall comparison -24 months: 15 (IQR 11-17) vs 16 (IQR 12-20) vs 15 (IQR 11-19); *P*=.08 for overall comparison • Laser photocoagulation performed at least once: -12 months: 37% vs 56% vs 46%; *P*<.001 for overall comparison -24 months: 41% vs 64% vs 52%; *P*<.001 for G1 vs G2, *P*=.04 G1 vs G3, and *P*=.01 G2 vs G3	**G1 vs G2** • Mean number of injections: 5.1 (SD 0.74) vs 6.5 (SD 0.85); *P*<.05	**G1 vs G2** • Mean number of injections: 9.84 (SEM 0.55) vs 7.67 (SEM of the mean 0.60); *P*=.005 • Rescue therapy: -Eyes meeting rescue therapy criteria: 9 vs 4; *P*=.042 -Patients receiving rescue laser therapy: 1 (1 eye) vs 1 (1 eye) -Patients receiving rescue anti-VEGF therapy: 8 (8 eyes) vs 3 (3 eyes)
Notes; Subgroup Analyses	When the other (nonstudy) eye required anti-VEGF treatment (129 participants in the aflibercept group [58%], 122 participants in the bevacizumab group [56%], and 121 participants in the ranibizumab group [56%]), the agent that was used was the same as that used for the study eye. • **Subgroup Analyses: G1 vs G2 vs G3** Subgroup analyses based on baseline visual acuity (<69 vs 69-78 letters) -Patients with letter score <69 at baseline: ◦Mean change in BCVA at 12 months (n=102 vs n=102 vs n=101): 18.9 (SD 11.5) vs 11.8 (SD 12.0) vs 14.2 (SD 10.6); *P*<0.001 for G1 vs G2, *P*=.003 G1 vs G3, *P*=.21 G2 vs G3 ◦Mean change in BCVA at 24 months (n=98 vs n=92 vs n=94): 18.1 (SD 13.8) vs 13.3 (SD 13.4) vs 16.1 (SD 12.1); *P*=.02 for G1 vs G2, *P*=.18 G1 vs G3, *P*=.18 G2 vs G3 -Patients with letter score 78-69 at baseline: ◦Mean change in BCVA at 12 months (n=106 vs n=104 vs n=105): 8.0 (SD 7.6) vs 7.5 (SD 7.4) vs 8.3 (SD 6.8); *P*=.69 for all comparisons ◦Mean change in BCVA at 24 months (n=103 vs n=93 vs n=97): 7.8 (SD 8.4) vs 6.8 (SD 8.8) vs 8.6 (SD 7.0); *P*=.51 for G1 vs G2, *P*=.51 G1 vs G3, *P*=.31 G2 vs G3 The relative treatment effect on CST also varied according to initial visual acuity (*P*<0.001).	Excluded patients with certain AEs during follow-up (acute ocular infection, stroke, MI, uncontrolled HTN, pregnancy, renal failure and cataract formation)	If both eyes were eligible for treatment and the patient agreed to treat both eyes with anti-VEGF therapy, 1 eye received the randomized treatment and the contralateral eye received the other anti-VEGF agent on the next day; thus, if an eye was randomized to the ranibizumab group, the contralateral eye was allocated to the bevacizumab group. • **Subgroup Analyses:** A multivariate analysis comparing BCVA and CST outcomes between the bevacizumab and ranibizumab groups, taking into account number of injections, baseline BCVA, and CST, demonstrated a statistically significant influence of baseline BCVA on follow-up BCVA (*P*<.001) but no other significant differences between groups (*P*=.051) across follow-up time (*P*=.490) regarding these 2 outcomes.

Trials in Patients with Macular Edema due to Central Retinal Vein Occlusion (CRVO) or Branch Retinal Vein Occlusion (BRVO)

Study	**CRAVE; Rajagopal 2015[32]**	**MARVEL; Narayanan 2015[36]**
• *Follow-up* • *Country* • *NCT or ID number* • *Funding*	• 6 months • US • NCT01428388 • Barnes Retina Institute	• 6 months • India • CTRI/2012/ 01/003120 (Clinical Trials Registry-India) • Brian Holden Eye Research Center, L.V. Prasad Eye Institute, Hyderabad, India
Objective	To compare efficacy of monthly treatment with bevacizumab or ranibizumab for macular edema due to RVO.	To assess the efficacy and safety of intravitreal bevacizumab compared with ranibizumab in the treatment of macular edema due to BRVO.
Population/ Condition	Macular edema secondary to RVO (60% of patients with branch RVO or hemi-RVO, 40% with central RVO)	Center-involving macular edema due to BRVO
Population Characteristics (baseline)	Age: 71.5 years (SD 8.6) Male: 44.9% Mean BCVA (logMAR): 0.745 (SD 0.42)	Age: 51.7 years (SD 8.6) Male: 54.6% (B vs R: 68.4% vs 40.5%) Mean BCVA: 54.4 (SD 12.2) Mean CRT: 469 μm (SD 138)
Main Inclusion Criteria	Age ≥50 years; diagnosis of RVO in the past 9 months, BCVA of 20/40 to 20/320 (Snellen) in study eye (regardless of relative afferent pupillary defect); and CFT >250 μm on OCT.	Age ≥18 years; center-involving macular edema due to BRVO of <9 months duration; minimum CRT of 250 μm in the central subfield on spectral domain OCT); BCVA of 20/40 to 20/320 (73 to 24 letters) in the study eye.
Main Exclusion Criteria	History of intraocular surgery in the study eye including pars plana vitrectomy (but not including uncomplicated cataract surgery) within 60 days; any intravitreal injections within 12 weeks; prior RVO; history of PRP within 3 months of study onset or anticipated within 4 months after study onset; history of cerebrovascular event or MI within 3 months.	Prior episode or bilateral manifestation of RVO; previous panretinal laser photocoagulation or macular laser photocoagulation in the study eye; decrease in BCVA due to causes other than BRVO; history or presence of AMD (dry or wet form); use of intraocular or periocular corticosteroids in the study eye within the previous 3 months; previous treatment with anti-VEGF drugs in the study eye.
Intervention vs Comparator • *Schedule* • *Co-Intervention/ Rescue Treatment*	**G1:** Bevacizumab 1.25 mg **G2:** Ranibizumab 0.5 mg • **Schedule** (both groups): Patients received monthly injections for 6 months • Patients were eligible for rescue therapy with focal/grid laser or steroid at any point in the study, at the physician's discretion. Enrolled patients could receive PRP when needed at the discretion of the treating physician	**G1:** Bevacizumab 1.25 mg **G2:** Ranibizumab 0.5 mg • **Schedule** (both groups): Injection at baseline followed by PRN (met one of following retreatment criteria: >50 μm increase in CRT compared with the thinnest previous measurement; new or persistent cystoid retinal changes or sub-retinal fluid on OCT; loss of ≥5 letters from the best previous BCVA measurement in conjunction with any increase in CRT; increase in BCVA of ≥5 letters between the current and months recent visits). • Subjects were eligible to receive modified macular grid laser photocoagulation at 12 weeks if the following prespecified criteria were met: >50 μm increase in CRT compared with the thinnest previous measurement, and persistent diffuse edema ≥250 μm in CRT. Whenever laser photocoagulation was performed, an anti-VEGF injection was also administered
N	98* G1: 49* G2: 49 *Includes 9 patients who were not randomized but were assigned to bevacizumab for financial reasons.	75 G1: 38 G2: 37
Visual Outcomes	**G1 vs G2**	**G1 vs G2**

Study	**CRAVE; Rajagopal 2015[32]**	**MARVEL; Narayanan 2015[36]**
(ETDRS chart unless otherwise indicated); Functional Status/QOL Outcomes	• Mean change in BCVA (logMAR, using Snellen chart): 0.33 (SD 0.45) vs 0.34 (SD 0.33); *P*=.38 • Proportion of participants gaining ≥0.3 logMAR units from baseline: 71.4% vs 70.6%; *P*=.94	• Mean change in BCVA: 15.55 vs 18.08; mean difference: -2.5 letters (95% CI, -8.0 to 5.0), *P*=.74 • Mean BCVA achieved: 71.7 (SD 10.0) vs 70.9 (SD 13.4) • Proportion of participants gaining ≥15 letters from baseline: 57.8% vs 59.4%; *P*=1.0 • Proportion of participants achieving BCVA >20/40 (Snellen equivalent): 68.4% vs 62.2%
Anatomic Outcomes (reported in μm unless otherwise indicated)	**G1 vs G2** • Mean change in CFT: -212.6 (SD 234.8) vs -243.8 (SD 204.2); *P*=.72 • Proportion of participants achieving CFT <275 μm (estimated from graph): 65% vs 67%; *P*=1.0 • Fluid absent on OCT: 56.3% vs 51.4%; *P*=.81	**G1 vs G2** • Mean change in CRT: -212.7 (SD 234.8) vs -177.1 (SD 204.2); *P*=.34
Harms/Adverse Event (AE) outcomes (in study eye)	"No instances of ophthalmic serious AEs including endophthalmitis, noninfectious uveitis, retinal detachment, retinal tear, or traumatic cataract were encountered. Injection site pain and irritation were the most AEs. One patient died from complications of pneumonia. No patients suffered MI or cerebrovascular accident during the study."	**G1 vs G2** *Ocular AEs:* • Epiretinal membrane: 7.9% vs 0% • Progression of cataract: 7.9% vs 5.4% • Elevated IOP: 2.6% vs 0% • Developed a BRVO in the fellow eye: 0% vs 2.7% • Endophthalmitis: 0% vs 0% *Systemic AEs:* • Systemic arterial HTN: 5.3% vs 8.1% • Hospitalization (for fractured foot and fever): 0% vs 5.4%
Cost and Burden Outcomes	NR	**G1 vs G2** • Mean number of injections: 3.0 (SD 1.4) vs 3.2 (SD 1.5) • Received rescue grid laser photocoagulation: 21.0% vs 10.8%; *P*=.34 • Received sector laser photocoagulation due to the development of neovascularization in retina: 2.6% vs 5.4%
Notes; Subgroup Analyses	• "Assistance programs were used to defray any financial hardship, but if it could not be eliminated, then the patient was assigned to the bevacizumab arm (9 patients)." • "No patient departed from the protocol to receive rescue therapy, and none required PRP." It is unclear if this means that no patients received rescue therapy with focal/grid laser or steroid according to the protocol. • **Subgroup Analyses:** No differences between treatment groups were observed among BRVO or CRVO subsets in CFT changes (BRVO: *P*=.37; CRVO: *P*=.92) or change in BCVA (BRVO: *P*=.15; CRVO: *P*=.73).	Non-inferiority trial