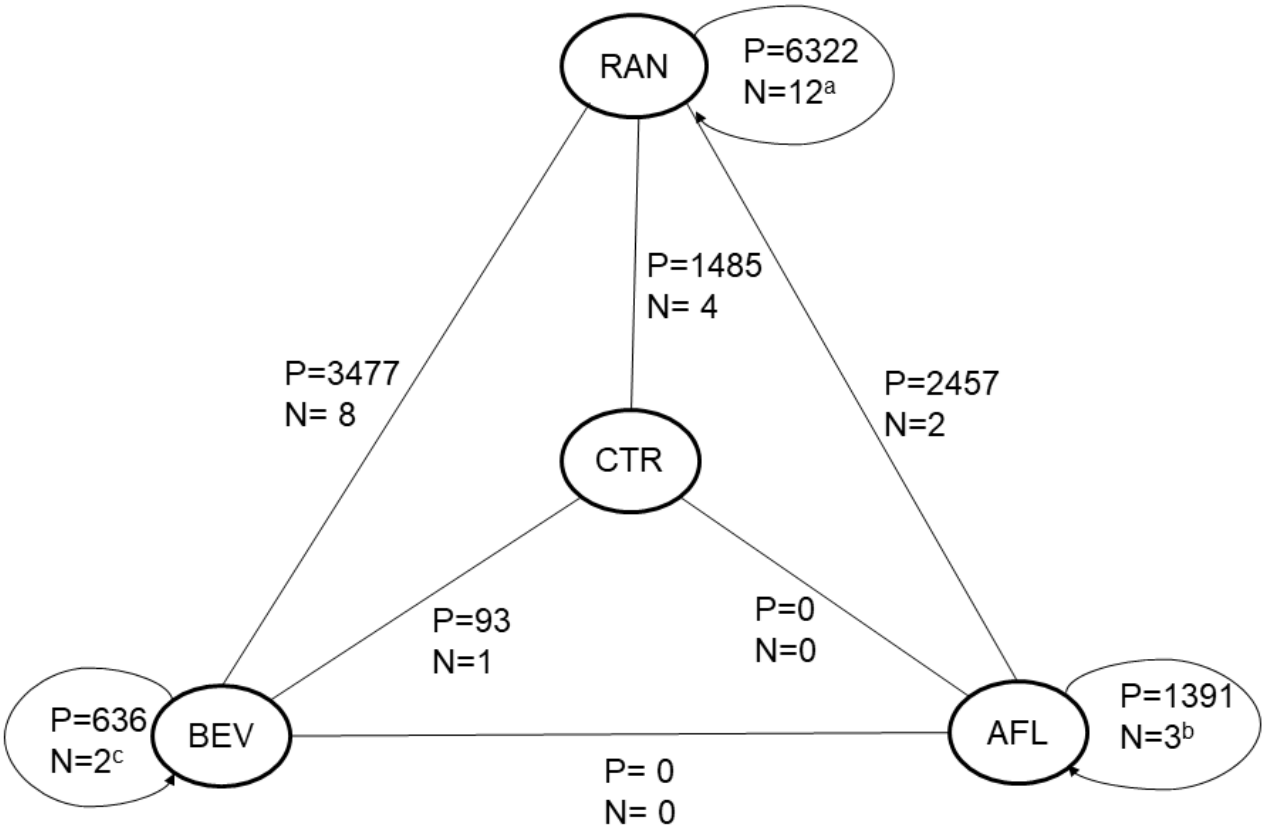
Supplementary Online Content

Ngo-Ntjam N, Thulliez M, Paintaud G, et al. Cardiovascular adverse events with intravitreal anti–vascular endothelial growth factor drugs: a systematic review and meta-analysis of randomized clinical trials. *JAMA Ophthalmol*. Published online April 15, 2021. doi:10.1001/jamaophthalmol.2021.0640

This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Network of anti-VEGF comparisons (anti- VEGF vs control, anti- VEGF vs another anti- VEGF and dose or regimen comparison for the same anti- VEGF) for the 25 included AMD studies.



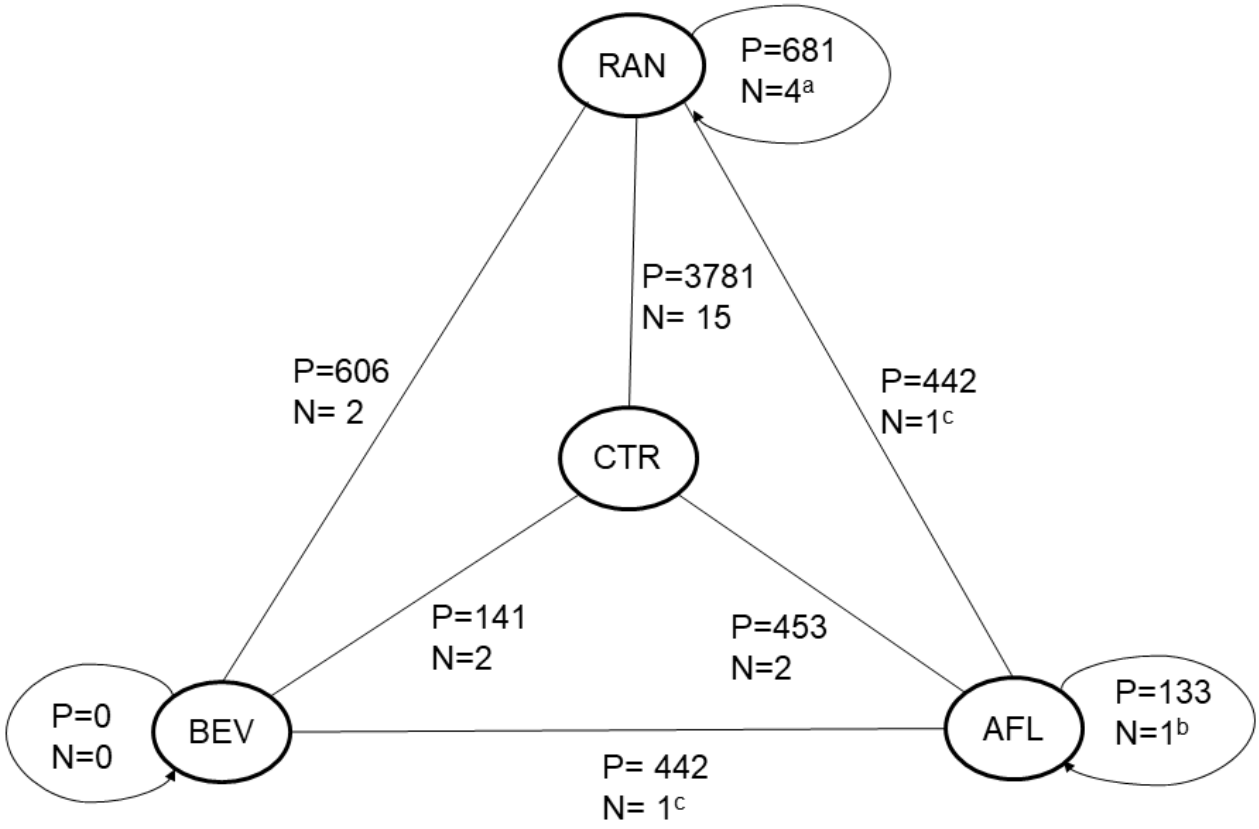
AFL: aflibercept; BEV: bevacizumab; CTR: control; N: number of studies for the comparison (some studies participated in more than one comparison); P: number of patients randomized for the comparison; RAN: ranibizumab.

[a]:studies with RAN vs RAN dose or regimen comparisons; 4 studies participated in other comparisons (3 RAN vs CTR , 1 BEV vs RAN)

[b]:studies with AFL vs AFL dose or regimen comparisons; 2 studies participated in another comparisons (AFL vs RAN)

[c]:studies with BEV vs BEV regimen comparisons, 1 study participated in another comparison (BEV vs RAN)

eFigure 2. Network of anti-VEGF comparisons (anti-VEGF vs control, anti-VEGF vs another anti-VEGF and dose or regimen comparison for the same anti-VEGF) for the 23 included DME/PDR studies



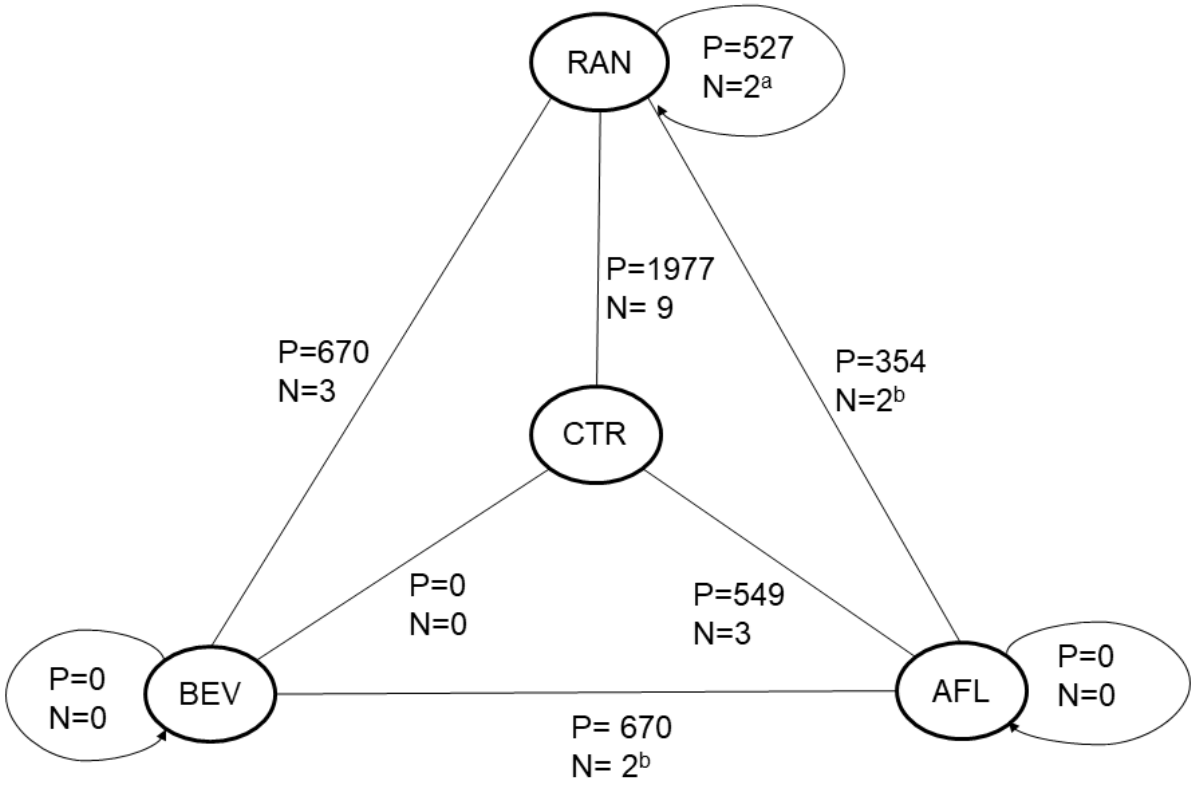
AFL: aflibercept; BEV: bevacizumab; CTR: control; N: number of studies for the comparison (some studies participated in more than one comparison); P: number of patients randomized for the comparison; RAN: ranibizumab.

[a]: Studies with RAN vs RAN dose or regimen comparisons; 2 studies participated in other comparisons (RAN vs CTR)

[b]: AFL vs AFL regimen comparison; the study participated in another comparisons (AFL vs CTR)

[c]: The study participated in another comparison (BEV vs RAN)

eFigure 3. Network of anti-VEGF comparisons (anti-VEGF vs control, anti-VEGF vs another anti-VEGF and dose or regimen comparison for the same anti-VEGF) for the 17 included RVO studies

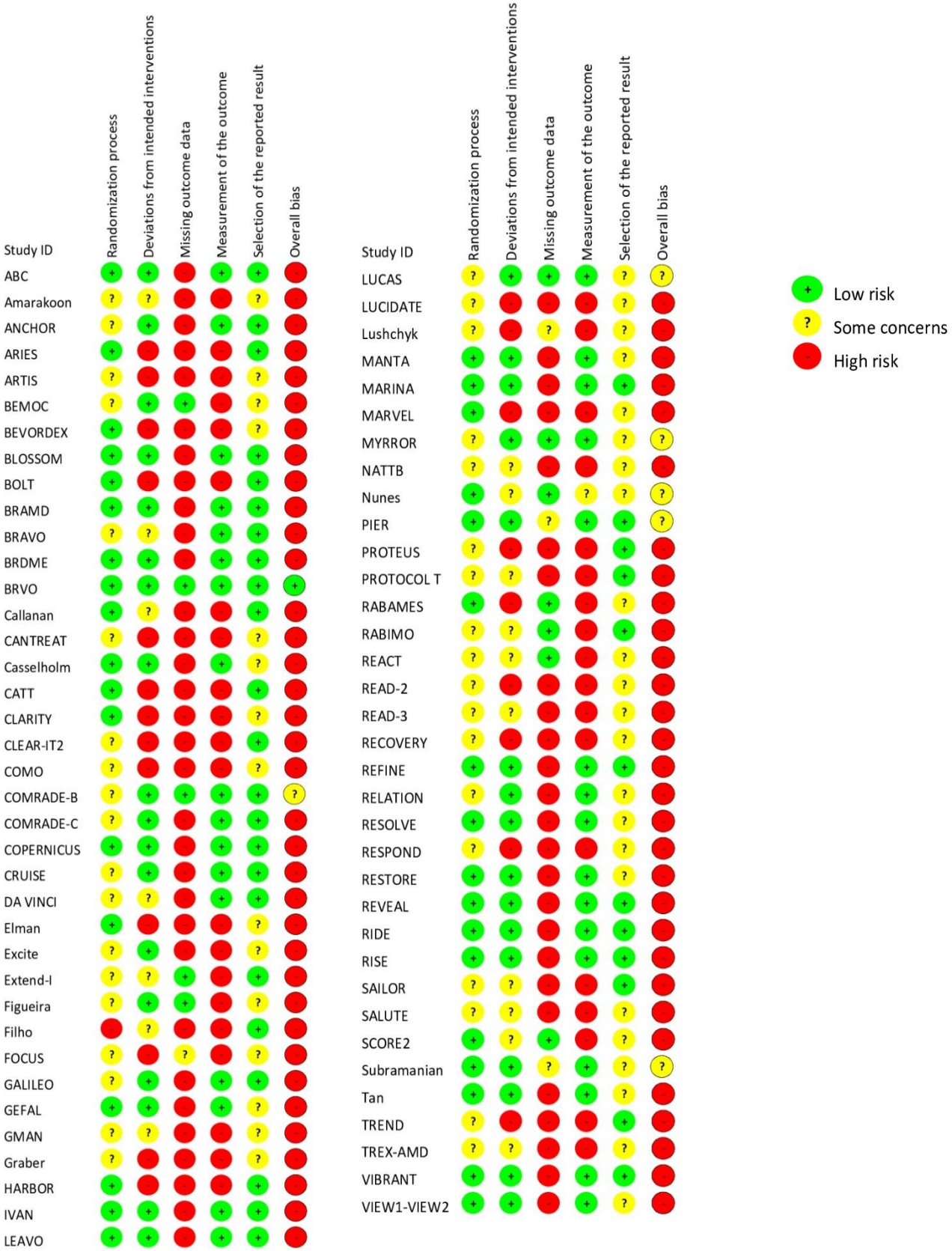


AFL: aflibercept; BEV: bevacizumab; CTR: control; N: number of studies for the comparison (some studies participated in more than one comparison); P: number of patients randomized for the comparison; RAN: ranibizumab.

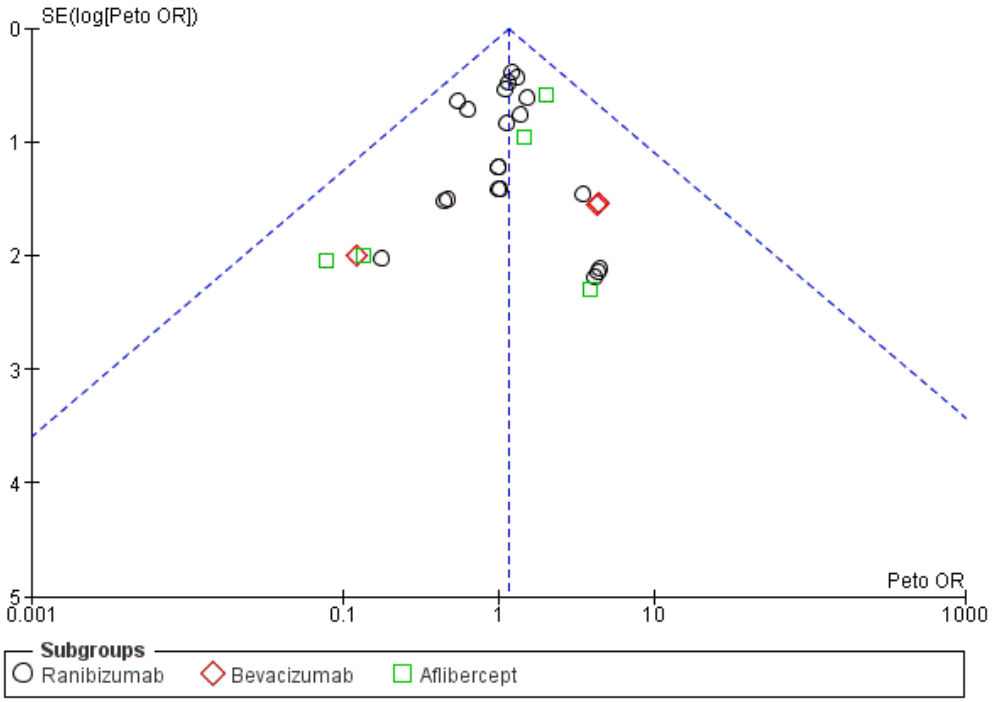
[a]: The 2 studies participated in another comparison (RAN vs CTR)

[d]: One study participated in another comparisons (BEV vs RAN)

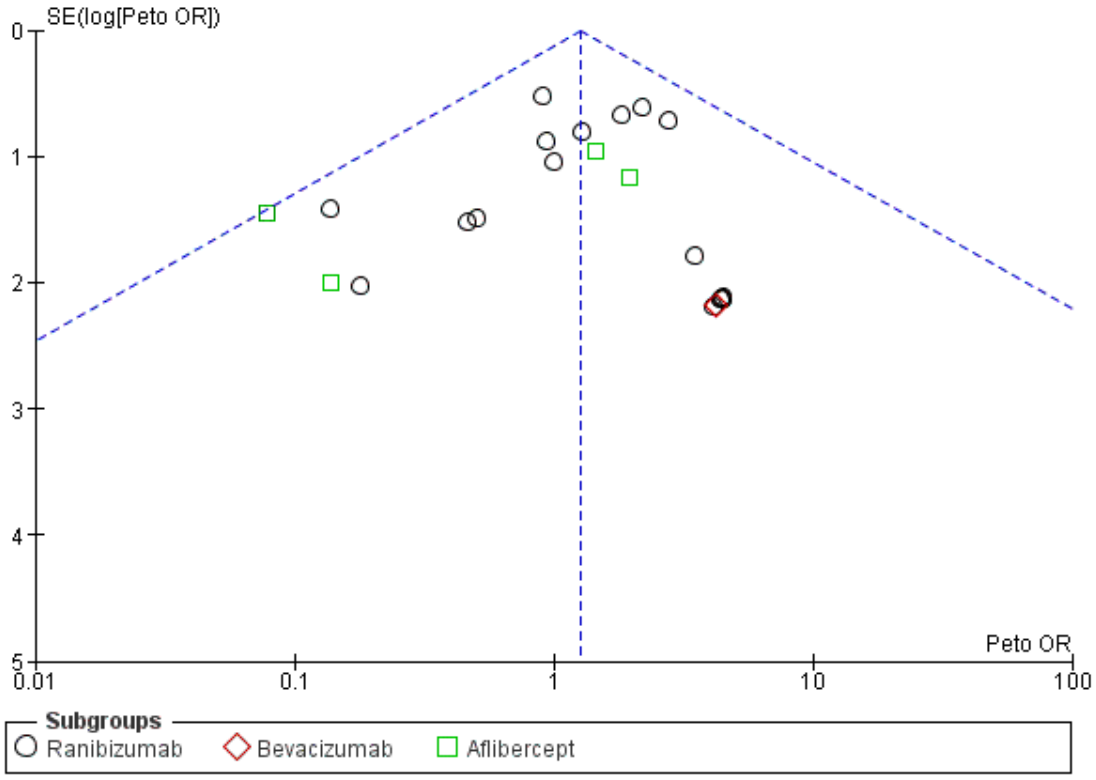
eFigure 4. Risk of bias summary: review authors' judgements about each risk of bias item for each 74 included studies



eFigure 5. Funnel plot for the major adverse cardiovascular events (APTC criteria) outcome, comparison anti-VEGF vs control



eFigure 6. Funnel plot for total mortality outcome, comparison anti-VEGF vs control



eTable 1. Search strategy for Medline and Embase

Date	Database	Search query	articles
07/03/2019, 07/07/2020	Medline	"Search ((((((((((bevacizumab) OR ranibizumab) OR afibercept) OR anti-VEGF) OR anti-vascular endothelial growth factor) OR (""Receptors, Vascular Endothelial Growth Factor/antagonists and inhibitors""[MeSH Terms])) OR ""Neovascularization, Pathologic/drug therapy""[MeSH Terms]) OR vascular endothelial growth factor antagonist) OR vascular endothelial growth factor inhibitor)) AND ((((((((intravitreal) OR ""Injections, Intraocular""[MeSH Terms]) OR intraocular) OR ""Injections, Intraocular""[MeSH Terms]) OR intra-vitreal) OR intra-ocular) OR intravitreous) OR ocular))) AND (((((clinical trial) OR randomized controlled trial) OR randomized) OR randomization) OR randomised)"	2199, 113
07/03/2019	Embase	search (('bevacizumab'/exp OR 'ranibizumab'/exp OR 'vasculotropin receptor'/exp OR 'vasculotropin inhibitor'/exp OR 'neovascularization(pathology)'/exp/dm_dt) AND ('intraocular drug administration'/exp OR intravitrealdrug administration'/exp) AND ('clinical trail'/de OR'controlled clinical trial'/de OR 'randomized controlled trial'/de) AND ([embase]/lim NOT([embase]/lim AND [medline]/lim))	206

eTable 2. Characteristics of included studies: population and interventions

Study	FUP(mo)	Women (%)	Mean Age (Range), y	Active Treatment				Control Treatment			
				Drug	N_t	Dose(mg)/regimen	IVI (mean)	Drug	N_c	Dose(mg)/regimen	IVI (mean)
AMD											
ABC, 2010[83]	12	47	80 (50-85)	BEV	65	1.25/PRN	7	VTP	16	-	-
								SH	12		
Amarakoon et al, 2019[2,a]	12	62	78 (NR)	BEV	60	1.25/8 wks	6	BEV	60	1.25/4wks	9
ANCHOR, 2006[14], 2009[15]	12	50	77(53-97)	RAN	140	0.3/mo	11	VTP	143	-	-
					140	0.5/mo	11				
ARIES, 2019[5, a]	24	57	76 (NR)	AFL	135	2.0/TE[1]	12	AFL	136	2.0/TE[1]	13
ARTIS, 2019[86, a]	12	36	70 (NR)	RAN	54	0.5 /PRN	6	RAN	54	0.5 /PRN + LD	7
BEMOC, 2013[61, a]	12	72	NR (NR)	BEV	50	1.25/6 wks	5	BEV	50	1.25/6wks + LD	6
BRAMD, 2016[73]	12	56	78 (NR)	BEV	166	1.25/mo	NR	RAN	166	0.5/mo	NR
CANTREAT, 2019[49], 2020[50]	24	60	79 (NR)	RAN	287	0.5 /TE	18	RAN	293	0.5 /mo	24
CATT, 2011[59], 2012[58]	24	61	79 (50-90)	BEV	300	1.25/PRN	14	RAN	298	0.5/PRN	13
					286	1.25/mo			301	0.5/mo	
CLEAR-IT2, 2011[39]	12	62	78 (53-94)	AFL	32	2.0/12 wks	4	AFL	32	0.5/12wks	4
					31	4.0/12 wks	4				
					32	0.5/4wks	7				
					32	2.0/4wks	6				
EXCITE, 2011[74]	12	59	75 (50-83)	RAN	120	0.3/qt	6	RAN	118	0.5/qt	6
					115	0.3/mo[2]	11				
EXTEND-I, 2010[82]	12	23	70 (NR)	RAN	35	0.3/mo	11	RAN	41	0.5/mo	11
FOCUS, 2006[40], 2008[3]	24	53	74 (50-93)	RAN + VTP	106	0.5/mo	21	VTP	56	-	-
GEFAL, 2013[51]	12	66	79 (52-98)	BEV	255	1.25/PRN	7	RAN	246	0.5/PRN	7
GMAN, 2015[57, a]	24	61	NR (NR)	BEV	166	1.25/PRN	NR	BEV	165	1.25/12 wks	NR
HARBOR, 2013[17], 2014[43]	24	59	79 (50-98)	RAN	275	0.5/PRN	13	RAN	273	2.0/PRN	11
					276	0.5/mo	21		274	2.0/mo	22
IVAN, 2012[23]	12	60	78 (NR)	BEV	145	1.25/PRN	NR	RAN	155	0.5/PRN	NR
					149	1.25/mo			157	0.5/mo	
LUCAS, 2015[7], 2016[6]	24	68	78 (NR)	BEV	220	1.25/TE	18	RAN	221	0.5/TE	18

Lushchyk et al, 2013[56, a]	12	66	77 (NR)	BEV	64	1.25/8 wks	NR	BEV	64	1.25/4wks	NR
					63	1.25/6 wks					
MANTA, 2013[53]	12	64	77 (NR)	BEV	154	1.25/PRN	9	RAN	163	0.5/PRN	9
MARINA, 2006[72]	24	65	77 (52-95)	RAN	238	0.3/mo	24	SH	238	-	-
					240	0.5/mo	24				
NATTB, 2012[55, a]	12	34	NR (NR)	BEV	94	1.25/12wks	5	BEV	91	1.25/6wks	8
Nunes et al, 2019[68]	12	53	75(NR)	BEV	15	1.25/ mo	14	RAN	15	0.5/mo	11
					15	1.25/2 wks					
PIER, 2008[71], 2010[33]	12	60	78 (54-94)	RAN	60	0.3/mo	NR	SH	63	-	-
					61	0.5/mo	NR				
RABIMO, 2017[32]	12	65	NR (NR)	RAN	20	0.5 /PRN	5	RAN	20	0.5 /2mo	8
SAILOR, 2009[10]	12	59	79 (51-101)	RAN	1169	0.3/PRN	4	RAN	1209	0.5/PRN	6
SALUTE, 2015[30]	12	47	71 (53-87)	RAN	48	0.5 /TE	6	RAN	45	0.5 /PRN	6
Subramanian et al, 2010[80]	12	4	79 (NR)	BEV	20	1.25/PRN	8	RAN	8	0.5/PRN	4
TREND, 2018[78]	12	55	75 (NR)	RAN	323	0.5 /TE	9	RAN	327	0.5 /mo	11
Study	**FUP(mo)**	**Women (%)**	**Mean Age (Range), y**	**Active Treatment**				**Control Treatment**			
				Drug	**N_t**	**Dose(mg)/ regimen**	**IVI (mean)**	**Drug**	**N_c**	**Dose(mg)/ regimen**	**IVI (mean)**
TREX-AMD, 2015[91] , 2017[91], 2017[90]	24	63	77 (59-96)	RAN	40	0.5 /TE	19	RAN	20	0.5 /mo	26
VIEW 1, View 2, 2012[41],2014[74]	24	56	76 (NR)	AFL	615	0.5/4wks	16	RAN	609	0.5/4wks	17
					616	2.0/8wks	11				
					617	2.0/4wks	16				
DME/PDR											
BEVORDEX, 2014[36,b]	12	36	62 (NR)	BEV	15	1.25/PRN	9	DEX	19	-	-
				BEV + DEX	27						
BOLT, 2010[62]	12	31	64 (40-86)	BEV	42	1.25/PRN	NR	LS	38	-	-
BRDME, 2020[84]	6	33	64 (NR)	BEV	86	1.25/ mo	6	RAN	84	0.5/mo	6
Callanan et al, 2017[18]	12	37	64 (24-89)	RAN	182	0.5/mo	9	DEX	181	-	-
CLARITY, 2017[79]	12	33	51 (NR)	AFL	116	2.0/PRN	7	LS	116	-	-
DA VINCI, 2011[26], 2012[27]	12	41	62 (NR)	AFL	45	2.0/PRN	7	LS	44		-
					44	2.0/8wks	7				
					44	0.5/4wks	12				

					44	2.0/4wks	11				
Elman et al, 2010 [31, b]	12	44	63 (55-70)	RAN	372	0.5/PRN	NR	SH / TMC	319	-	-
Figuiera et al, 2016[34]	12	26	NR (45 - 65)	RAN	10	0.5/PRN	NR	LS	13	-	-
				RAN+LS	12		NR				
Filho et al, 2011[35]	12	NR	NR (NR)	RAN+LS	20	0.5/16 wks	NR	LS	20	-	-
LUCIDATE, 2014[25]	11	36	66 (58-75)	RAN	22	0.5/PRN	9	LS	11	-	-
PROTEUS, 2018[33]	12	37	55 (NR)	RAN+LS	41	0.5/PRN	4	LS	46	-	-
Protocol T, 2015[88], 2016[89]	24	47	61 (NR)	AFL	224	2.0/mo[3]	NR	RAN	218	0.3/mo[3]	NR
				BEV	218	1.25/mo[3]	NR				NR
REACT, 2018[29]	12	59	63 (NR)	RAN	12	0.3/TE	10	RAN	15	0.3/mo	11
READ-2, 2009[67]	6	58	62 (NR)	RAN	42	0.5/2 mo	NR	LS	42	-	-
				RAN+LS	42						
READ-3, 2015[28], 2016[77]	24	44	64 (35-87)	RAN	77	0.5/PRN	17	RAN	75	2.0/PRN	18
RECOVERY, 2019[92,a]	12	48	48 (NR)	AFL	20	2.0/qt	4	AFL	23	2.0/mo	11
REFINE, 2019[94]	12	54	59 (NR)	RAN	307	0.5/PRN	8	LS	77	-	-
RELATION, 2018[54]	12	38	64 (NR)	RAN+LS	85	0.5/PRN	5	LS	43	-	-
RESOLVE, 2010[60]	12	46	64 (32-85)	RAN	51	0.3/PRN	NR	SH	49	-	-
					51	0.5/PRN					
RESPOND, 2015[8]	12	40	62 (NR)	RAN	75	0.5/PRN	9	LS	72	-	-
				RAN+LS	73		9				
RESTORE, 2011[63]	12	42	63 (54-72)	RAN+SL	116	0.5/PRN	7	SH	111	-	-
				RAN+LS	118		7				
REVEAL, 2015[48]	12	44	61 (NR)	RAN+SL	133	0.5/PRN	8	LS	131	-	-
				RAN+LS	132		7				
RIDE, 2012[66], 2013[16]	24	43	63 (53-74)	RAN	125	0.3/mo	21	SH	130	-	-
					127	0.5/mo	22				
RISE, 2012[66], 2013[16]	24	44	62 (52-72)	RAN	125	0.3/mo	22	SH	127	-	-
					125	0.5/mo	21				
Study	**FUP(mo)**	**Women (%)**	**Mean Age (Range), y**	**Active Treatment**				**Control Treatment**			
				Drug	**N_t**	**Dose(mg)/regimen**	**IVI (mean)**	**Drug**	**N_c**	**Dose(mg)/regimen**	**IVI (mean)**
RVO											
BLOSSOM, 2020[87]	6	49	60 (NR)	RAN	190	0.5/PRN	5	SH	93	-	-
BRAVO, 2010[21], 2011[11]	6	47		RAN	134	0.3/mo	6	SH		-	-

			66 (26-91)		131	0.5/mo	6		132		
BRVO, 2020[85]	6	66	68 (NR)	BEV	144	1.25/mo	6	RAN	142	0.5/mo	6
Casselholm et al, 2018[22]	18	33	70(NR)	AFL	22	2.0/TE	11	RAN	23	0.5/TE	14
COMO, 2018[4]	12	42	67 (NR)	RAN	153	0.5/PRN	8	DEX	154	-	-
COMRADE-B, 2018[38]	6	55	66 (NR)	RAN	126	0.5/PRN	5	DEX	118	-	-
COMRADE C, 2016[44]	6	40	66 (NR)	RAN	124	0.5/PRN	5	DEX	119	-	-
COPERNICUS, 2012[9], 2013[13],2014[42]	6	43	66 (NR)	AFL	115	2.0/mo	6	SH	74	-	-
CRUISE, 2010[12], 2011[19]	6	43	68 (20-91)	RAN	132	0.3/mo	6	SH	130	-	-
					130	0.5/mo	6				
GALILEO, 2013[45],2014[52],2014[69]	12	44	62 (NR)	AFL	106	2.0/mo	12	SH	71	-	-
Graber et al, 2015[37]	6	32	62 (NR)	RAN	20	0.5/PRN	4	HD	13	-	-
				RAN+HD	11		3				
LEAVO, 2019[46]	24	43	69(NR)	AFL	154	2.0/TE	11	RAN	155	0.5/TE	12
				BEV	154	1.25/TE	12				
MARVEL, 2015[64], 2016[65]	12	45	52 (NR)	BEV	38	1.25/PRN	3	RAN	37	0.5/PRN	4
RABAMES, 2015[70]	6	52	66 (43-82)	RAN	10	0.5	3	LS	10	-	-
				RAN+LS	11	0.5	3				
SCORE 2, 2017[76]	6	69	43 (NR)	AFL	180	2.0/mo	6	BEV	182	1.25/mo	6
Tan et al, 2014[81]	12	53	68 (41-87)	RAN	15	0.5/PRN	8	LS	21	-	-
VIBRANT, 2015[20],2016[24]	6	45	65 (NR)	AFL	91	2.0/4wks	6	LS	92	-	-
mCNV											
MYRROR, 2015[47]	6	76	58 (27-83)	AFL	91	2.0/PRN	4	SH	31	-	-

AFL, aflibercept; BEV, bevacizumab; DEX, dexamethazone; HD, hemodilution; IVI, intravitreal injections; LD, loading dose; LS, active laser; mo,months; wks, weeks; NR,not reported; PRN,pre re nata (as needed); qt=quarterly (every 3 months), RAN=ranibizumab, SH= sham; SL, sham laser; TE ,treat and extend; TMC, triamcinolone; VTP , verteporfine,
[a]comparison not included in the quantitative analysis, [b]studies in which eyes were randomized ,
[1]TE begins at week 16 pour the treatment group and week 48 for the control group, [2]Treatment arm not included in the quantitative analysis, [3]monthly regimen for the first year then TE for the second year
References (1 - 94) of the included studies are listed after etable-3

eTable 3. Methodology and systemic safety of included studies.

Study	Design	Exclusion if CVD history	Main Outcome	Systemic Safety	ROB2
ABC, 2010[83]	Double-masked	yes	Proportion of patients gaining ≥15 letters of VA at 1 y	ATEs specifically assessed at 12 mo	high
Amarakoon, 2019[2]	Open-label	yes	Change in VA between baseline and 1 y	Succinct report of SAEs at 12 mo; Patient questioning, with special emphasis placed on CV events	high
ANCHOR, 2006[14], 2009[15]	Double-masked	no	Patients losing <15 letters from baseline VA at 1 y	Succinct report of SAEs; incidence and severity of SAEs at 12 mo	high
ARIES, 2020[5]	Open-label	no	Change in BCVA as Measured by the ETDRS Letter Score	Succinct report of SAEs	high
ARTIS, 2019[86]	Double-masked	no	Mean change in BCVA between baseline and 1 y	Incidence of ATEs	high
BEMOC, 2013[61]	Open-label	no	Mean change BCVA at 54 wks	succinct report of SAEs at 12 mo	high
BEVORDEX, 2014[36]	Single-masked	yes	Percentage of eyes in which BCVA improved by 10 or more letters at the 48-wks visit, or the 50-wks visit if further treatment had been indicated at 48 wks	Incidence of SAEs at 12 mo; Patient questioning, with special emphasis placed on CV events	high
BLOSSOM, 2020[87]	Double-masked	yes	Change from baseline BCVA to the average level of BCVA	Succinct report of SAEs	high
BOLT, 2010[62]	Open-label	yes	Mean difference in ETDRS BCVA at 12 mo	ATEs specifically assessed; SAEs, including ATEs, BP, and ECG findings, at 12 mo	high
BRAMD, 2016[73]	Triple-masked	no	Change in BCVA in the study eye from baseline to 12 mo	Occurrence of SAEs for 12 mo, Patients questioning , MedDRA Coding system for SAEs. All serious SAEs were reviewed by the principal investigator	high
BRAVO, 2010[21], 2011[11]	Double-masked	yes	Mean change from baseline BCVA letter score at 6 mo	Succinct report of incidence and severity SAEs and serious SAEs at 12 mo; Vital signs, any new sign , symptom , illness, or worsening of any preexisting medical condition was recorded as an AEs	high
BRDME, 2020[84]	Double-masked	no	Difference in BCVA change in the study eye from baseline to month 6	Incidence of SAEs and serious SAEs, MedDRA coding, (secondary outcome)	high

Study	Design	Exclusion if CVD history	Main Outcome	Systemic Safety	ROB2
BRVO, 2020[85]	Double-masked	no	Change in BCVA of the study eye from baseline to 6 months	Incidence of SAEs and serious SAEs, MedDRA coding, (Secondary outcome)	low
Callanan et al, 2017[18]	Single-masked	no	Average change in BCVA from baseline at each visit over 12 mo	Succinct report of SAEs at 12 mo	high
CANTREAT, 2019[49], 2020[50]	Open-label	no	Mean change in BCVA (ETDRS letters) from baseline to month 12	Succinct report of SAEs	high
CATT, 2011[59], 2012[58]	Single-masked	no	Mean change in VA between baseline and 1 y	ATEs as defined by APTC specifically assessed; SAEs through 24 mo; Patient questioning, MedDRA coding, review by a medical monitor	high
Casselholm et al, 2018[22]	Double-masked	no	Number of injections given per patient (18 months)	Succinct report of SAEs	high
CLARITY, 2017[79]	Single-masked	yes	BCVA letter change from baseline to 52 wks	ATEs as defined by APTC specifically assessed; SAEs through 12	high
CLEAR-IT2, 2011[39]	Double-masked	no	Mean change in central retinal/lesion thickness(CR/LT) from baseline to 12 wks	succinct report of SAEs through 12 mo; Clinical laboratory tests, and vital signs	high
COMO, 2018[4]	Open-label	no	Mean change from baseline in BCVA at mo 12	succinct report SAEs through 12 mo	high
COMRADE-C, 2016[44]	Double-masked	yes	Mean average change in BCVA from baseline to mo 1 throught mo 6	Incidence of treatment-emergent SAEs, relationship to the drug or not through 6 mo ; Changes in vital signs (BP and heart rate)	high
COMRADE-B, 2018[38]	Double-masked	yes	Mean average change in BCVA from baseline to mo 1 through mo 6	Incidence of SAEs and serious SAEs, including their relationship to the study treatment and/or ocular injection procedure, during the 6-month study period (seconday outcome); Changes in vital signs, and laboratory evaluations, MedDRA coding	some concern
COPERNICUS, 2012[9], 2013[13] ,2014[42]	Double-masked	yes	Proportion of eyes with a gain of 15 ETDRS letters or more in BCVA from baseline to wks 24	Incidence of SAEs and serious SAEs, SAEs of interest at 6 mo	high
CRUISE, 2010[12], 2011[19]	Double-masked	yes	Mean change from baseline BCVA letter score at 6 mo	Succinct report of AEs; incidence and severity SAEs and serious SAEs at 6 mo	high
DA VINCI, 2011[27], 2012[26]	Double-masked	Yes	Mean change in BCVA from baseline to the wks 24 visit	Succinct report of AEs; incidence and severity of SAEs and serious SAEs through 6 mo	high

Study	Design	Exclusion if CVD history	Main Outcome	Systemic Safety	ROB2
Elman et al, 2010[31]	single-masked	Yes	Mean change in VA at 1 y, adjusted for baseline VA	Succinct report of safety (could be assessed at patient level, and participants with 2 study eyes were assigned to the non sham group) through 12 mo	high
EXCITE, 2011[74]	Double-masked	unclear	Mean change in BCVA at 12 mo	Succinct report of SAEs, serious SAEs, through 12 mo; changes vital signs	high
EXTEND-I, 2010[82]	Open-label	unclear	Mean change from baseline in BCVA score at 6 mo	Succinct report of AEs; incidence of grade 3 targeted AE in study eye and fellow eye up to 6 mo (primary end point) ; Non directive questioning, vital signs, laboratory values	high
Figuiera et al, 2016[34]	Open-label	yes	Regression of neovascularization at 12 mo	Succinct report of SAEs (secondary outcome) through 12 mo	high
Filho et al, 2011[35]	single-masked	yes	Total area (mm2) of fluorescein leakage (FLA) from active NV	succinct report of SAEs through 12 mo	high
FOCUS, 2006[40], 2008[3]	single-masked	unclear	Proportion of patients losing <15 letters at 12 mo	Succinct report of SAEs; incidence and severity SAEs at 24 mo (primary end point)	high
GALILEO, 2013[45],2014[52],2014[69]	Double-masked	no	Proportion of patients who gained ≥15 letters in BCVA at wks 24 compared with baseline	succinct report of SAEs through 12 mo	high
GEFAL , 2013[51]	Double-masked	no	Mean change in BCVA score measured on ETDRS between baseline and final evaluations	Succinct report of incidence and severity SAEs and serious SAEs; MedDRA coding	high
GMAN, 2015[57]	single-masked	yes	Mean BCVA at 92 wks	Succinct report of SAEs through 24 mo	high
Graber et al, 2015[37]	Open-label	yes	Mean change in BVCA in ETDRS letters at 6 mo	succinct report of SAEs through 6 mo	high
HARBOR, 2013[17], 2014[43]	Double-masked	no	Change From Baseline in BCVA at mo 12	ATEs (APTC criteria) specifically assessed, SAEs potentially related to systemic VEGF-A inhibition through 24 mo	high
IVAN, 2013[23]	Double-masked	no	BVCA measured as ETDRS at 2 y	ATEs specifically assessed; occurrence of an ATE or heart failure through 12; MedDRA coding	high
LEAVO, 2019[46]	Double-masked	unclear	change in BCVA letter score from baseline to 100 weeks	Succinct report of SAEs	high
LUCAS, 2015[7], 2016[6]	Double-masked	no	Change in BCVA at 1 y as measured on the EDTRS VA chart	Frequency of ATE	Some concern

Study	Design	Exclusion if CVD history	Main Outcome	Systemic Safety	ROB2
LUCIDATE, 2014[25]	Open-label	yes	Change in retinal function and anatomy at 48 wks compared to baseline	succinct reporting SAEs; BP measurement	high
Lushchyk et al, 2013[56]	Open-label	yes	Change in VA between baseline and 1 y	Succinct report of SAEs through 12 mo; Patient questioning, with special emphasis placed on CV events	high
MANTA, 2013[53]	Double-masked	yes	Mean change in BCVA between baseline and 1 y	Succinct report of SAEs (secondary outcome) through 12 mo ; Patients exploration and documentation in the case record forms	some concern
MARINA, 2006[72]	Double-masked	no	Proportion of patients losing <15 letters at 12 mo	Succinct report of SAEs; incidence and severity of SAEs	high
MARVEL, 2015[64], 2016[65]	Double-masked	no	Change in the BCVA score from baseline at mo 12 versus mo 6	Succinct report of SAEs	high
MYRROR, 2015[47]	Double-masked	yes	Mean change in BCVA from baseline to wks 24	Succinct report SAEs through 6 mo ; Physical examinations, ECG, vital signs, and clinical safety laboratory tests	some concern
NATTB, 2012[55]	Open-label	no	Mean change in VA measurements between baseline and 48 wks	Succinct report of SAEs through 12 mo; Patients questioning	high
Nunes et al, 2019[68]	Double-masked	no	ETDRS BCVA and CMT as measured by SDOCT	Succinct report of SAEs	some concern
PIER, 2008[71], 2010[1]	Double-masked	no	Mean change from baseline to 12 mo in VA score	Succinct report of SAEs; Incidence and severity of SAEs at 12 mo ; changes in vial signs	some concern
PROTEUS, 2018[33]	Open-label	yes	Regression of NV total, on the disc (NVD) plus elsewhere (NVE), defined as any decrease in the area of NV from the baseline to mo 12	Succinct report of incidence and severity of SAEs related to the treatment(secondary outcomes) through 12	high
Protocol T, 2015[88], 2016[89]	single-masked	no	Mean change in visual acuity E-ETDRS at 1 year	Succinct report of SAEs through 24 mo	high
RABAMES, 2015[70]	Open-label	yes	Mean change in BVCA from baseline to 6 mo	SAEs and serious SAEs, evalutaed at each visit through 12 mo	high
RABIMO, 2017[32]	Open-label	no	Impact of the injection frequency on VA development (BCVA after 12 mo in comparison to baseline)	Incidence of SAEs and serious SAEs though 12 mo	high
REACT, 2018[29]	Open-label	no	BCVA from baseline at 6-mo and 12-mo (secondary outcome)	Incidence of SAEs and serious SAEs through 12 mo (primary outcome); Non directive patient questioning, or other means	high
READ-2, 2009[67]	Open-label	unclear	Change from baseline in BCVA at 6 mo	Succinct report of SAEs through 6 mo	high

Study	Design	Exclusion if CVD history	Main Outcome	Systemic Safety	ROB2
READ-3, 2015[28], 2016[77]	Double-masked	no	unclear	Incidence of SAEs and serious SAEs, by changes in vital signs and laboratory parameters through 12 mo	high
RECOVERY, 2019[92]	Open-label	yes	Change in total RNP area from baseline to year 1	Succinct report of SAEs	high
REFINE, 2019[94]	Double-masked	Yes	Mean average change in BCVA from mo 1 to 12 versus baseline	Succinct report of incidence and severity of SAEs and serious SAEs through 12 mo	high
RELATION, 2018[54]	Double-masked	yes	Mean change in BCVA from baseline to mo 12	succinct report of all treatment emergent SAEs (TEAEs) and serious SAEs through 12 mo	high
RESOLVE, 2010[60]	Double-masked	unclear	Mean change in BCVA from baseline to 1 mo through 12 mo	Succinct report of serious SAEs through 12 mo ; BP measurement, Nondirective questioning of patients, physical examination, laboratory test	high
RESPOND, 2015[8]	Open-label	yes	Mean Change From Baseline in BCVA at mo 12	Incidence and severity of SAEs and serious SAEs; MedDRA coding	high
RESTORE, 2011[63]	Double-masked	yes	Mean change in BCVA from baseline to 1 mo through 12 mo and safety	Succinct report of incidence of SAEs and serious SAEs at 12 mo; Vital signs, laboratory parameters	high
REVEAL, 2015[48]	Double-masked	yes	Mean average change in BCVA from baseline to mo 1 through 12	Incidence SAEs and serious SAEs through 12 mo	high
RIDE/RISE, 2012[66] , 2013[16]	Double-masked	yes	Proportion of patients gaining 15 ETDRS letters in BCVA score at 24 mo	Succinct report of SAEs through 12 mo; Vital signs, Non directive questioning, Patient examination, laboratory testing, or other means	high
SAILOR, 2009[10]	single-masked	no	Several efficacy end points including changes in BCVA over time	Succinct report of SAEs; incidence serious SAEs evaluated through 12 mo	high
SALUTE, 2015[30]	Open-label	no	Change in BCVA from baseline to mo 12 in the two treatment groups	Incidence of SAEs and serious SAEs (secondary outcome); Telephone patient questioning, electrocardiogram, vital signs, physical condition	high
SCORE 2, 2017[76]	single-masked	no	Mean change VA letter score (VALS) from the randomization visit to the 6-mo follow-up visit, based on the e-ETDRS VA letters	APTC specifically assessed though 12 mo; MedDRA coding	high
Subramanian et al, 2010[80]	Double-masked	yes	VA and foveal thickness at 1 y	ATEs specifically assessed; SAEs (eg, BP, gastrointestinal, thromboembolic disease) through 12 mo	some concern
Tan et al, 2014[81]	Double-masked	yes	Mean change from baseline BCVA letter score between the ranibizumab group and standard of care groupe at 12 mo	Incidence and severity SAEs (secondary outcome) at 12 mo; Telephone patient questioning	high

Study	Design	Exclusion if CVD history	Main Outcome	Systemic Safety	ROB2
TREND, 2018[78]	single-masked	no	change in BCVA from baseline to 12 mo	Succinct report of incidence and severity of SAEs and serious SAEs at 12 mo; physical examination, vital signs	high
TREX-AMD, 2015[91], 2017[90], 2017[93]	Open-label	no	Mean change ETDRS BCVA change from baseline to (6,12,18,24,30, and 36 mo)	Incidence and severity of SAEs (secondary outcome) through 36 mo	high
VIBRANT, 2015[20],2016[24]	Double-masked	no	Proportion of eyes that gained >= 15 ETDRS letters in BCVA from baseline at wee 4	Incidence SAEs and serious SAEs through 12 mo	high
VIEW 1-View 2, 2012[41,a] ,2014[75'a]	Double-masked	no	Proportion of patients maintaining vision at wks 52 (losing <15 ETDRS letters)	Succinct report of SAEs through 24 mo; Telephone patient questioning	high

ATEs, atherothrombolic events; AEs , adverse events, BCVA, best-corrected visual acuity; CVD, cardiovascular disease; ECG, electrocardiogram; ETDRS, Early Treatment of Diabetic RetiNopathy Study; mo, month; SAEs, serious adverse events VA, visual acuity; wks, weeks, [a] Two studies with the same protocol pooled together in the meta-analysis as a single study , [b] Two studies with the same protocol pooled together in the meta-analysis as a single study.

eReferences

1. Abraham P, Yue H, Wilson L. Randomized, Double-Masked, Sham-Controlled Trial of Ranibizumab for Neovascular Age-Related Macular Degeneration: PIER Study Year 2. American Journal of Ophthalmology. 2010 Sep;150(3):315-324.e1.

2. Amarakoon S, Martinez-Ciriano JP, van den Born LI, Baarsma S, Missotten T. Bevacizumab in age-related macular degeneration: a randomized controlled trial on the effect of on-demand therapy every 4 or 8 weeks. Acta Ophthalmol. 2019 Feb;97(1):107–12.

3. Antoszyk AN, Tuomi L, Chung CY, Singh A. Ranibizumab Combined With Verteporfin Photodynamic Therapy in Neovascular Age-related Macular Degeneration (FOCUS): Year 2 Results. American Journal of Ophthalmology. 2008 May;145(5):862-874.e3.

4. Bandello F, Augustin A, Tufail A, Leaback R. A 12-month, multicenter, parallel group comparison of dexamethasone intravitreal implant versus ranibizumab in branch retinal vein occlusion. European Journal of Ophthalmology. 2018 Nov;28(6):697–705.

5. Bayer Study Director. Managing Neovascular (Known as “Wet”) Age-related Macular Degeneration Over 2 Years Using Different Treatment Schedules of 2 mg Intravitreal Aflibercept Injected in the Eye - Full Text View - ClinicalTrials.gov [Internet]. 2020 [cited 2020 Aug 14]. Available from: https://clinicaltrials.gov/ct2/show/NCT02581891

6. Berg K, Hadzalic E, Gjertsen I, Forsaa V, Berger LH, Kinge B, et al. Ranibizumab or Bevacizumab for Neovascular Age-Related Macular Degeneration According to the Lucentis Compared to Avastin Study Treat-and-Extend Protocol. Ophthalmology. 2016 Jan;123(1):51–9.

7. Berg K, Pedersen TR, Sandvik L, Bragadóttir R. Comparison of Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration According to LUCAS Treat-and-Extend Protocol. Ophthalmology. 2015 Jan;122(1):146–52.

8. Berger A, Sheidow T, Cruess AF, Arbour JD, Courseau A-S, de Takacsy F. Efficacy/safety of ranibizumab monotherapy or with laser versus laser monotherapy in DME. Canadian Journal of Ophthalmology. 2015 Jun;50(3):209–16.

9. Boyer D, Heier J, Brown DM, Clark WL, Vitti R, Berliner AJ, et al. Vascular Endothelial Growth Factor Trap-Eye for Macular Edema Secondary to Central Retinal Vein Occlusion. Ophthalmology. 2012 May;119(5):1024–32.

10. Boyer DS, Heier JS, Brown DM, Francom SF, Ianchulev T, Rubio RG. A Phase IIIb Study to Evaluate the Safety of Ranibizumab in Subjects with Neovascular Age-related Macular Degeneration. Ophthalmology. 2009 Sep;116(9):1731–9.

11. Brown DM, Campochiaro PA, Bhisitkul RB, Ho AC, Gray S, Saroj N, et al. Sustained Benefits from Ranibizumab for Macular Edema Following Branch Retinal Vein Occlusion: 12-Month Outcomes of a Phase III Study. Ophthalmology. 2011 Aug;118(8):1594–602.

12. Brown DM, Campochiaro PA, Singh RP, Li Z, Gray S, Saroj N, et al. Ranibizumab for Macular Edema following Central Retinal Vein Occlusion. Ophthalmology. 2010 Jun;117(6):1124-1133.e1.

13. Brown DM, Heier JS, Clark WL, Boyer DS, Vitti R, Berliner AJ, et al. Intravitreal Aflibercept Injection for Macular Edema Secondary to Central Retinal Vein Occlusion: 1-Year Results From the Phase 3 COPERNICUS Study. American Journal of Ophthalmology. 2013 Mar;155(3):429-437.e7.

14. Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med. 2006 Oct 5;355(14):1432–44.

15. Brown DM, Michels M, Kaiser PK, Heier JS, Sy JP, Ianchulev T. Ranibizumab versus Verteporfin Photodynamic Therapy for Neovascular Age-Related Macular Degeneration: Two-Year Results of the ANCHOR Study. Ophthalmology. 2009 Jan;116(1):57-65.e5.

16. Brown DM, Nguyen QD, Marcus DM, Boyer DS, Patel S, Feiner L, et al. Long-term Outcomes of Ranibizumab Therapy for Diabetic Macular Edema: The 36-Month Results from Two Phase III Trials. Ophthalmology. 2013 Oct;120(10):2013–22.

17. Busbee BG, Ho AC, Brown DM, Heier JS, Suñer IJ, Li Z, et al. Twelve-Month Efficacy and Safety of 0.5 mg or 2.0 mg Ranibizumab in Patients with Subfoveal Neovascular Age-related Macular Degeneration. Ophthalmology. 2013 May;120(5):1046–56.

18. Callanan DG, Loewenstein A, Patel SS, Massin P, Corcóstegui B, Li X-Y, et al. A multicenter, 12-month randomized study comparing dexamethasone intravitreal implant with ranibizumab in patients with diabetic macular edema. Graefes Arch Clin Exp Ophthalmol. 2017 Mar;255(3):463–73.

19. Campochiaro PA, Brown DM, Awh CC, Lee SY, Gray S, Saroj N, et al. Sustained Benefits from Ranibizumab for Macular Edema following Central Retinal Vein Occlusion: Twelve-Month Outcomes of a Phase III Study. Ophthalmology. 2011 Oct;118(10):2041–9.

20. Campochiaro PA, Clark WL, Boyer DS, Heier JS, Brown DM, Vitti R, et al. Intravitreal Aflibercept for Macular Edema Following Branch Retinal Vein Occlusion. Ophthalmology. 2015 Mar;122(3):538–44.

21. Campochiaro PA, Heier JS, Feiner L, Gray S, Saroj N, Rundle AC, et al. Ranibizumab for Macular Edema following Branch Retinal Vein Occlusion. Ophthalmology. 2010 Jun;117(6):1102-1112.e1.

22. Casselholm de Salles M, Amrén U, Kvanta A, Epstein DL. Injection frequency of aflibercept versus ranibizumab in a treat-and-extend regimen for central retinal vein occlusion: A Randomized Clinical Trial. Retina. 2019 Jul;39(7):1370–6.

23. Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Culliford LA, et al. Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. The Lancet. 2013 Oct;382(9900):1258–67.

24. Clark WL, Boyer DS, Heier JS, Brown DM, Haller JA, Vitti R, et al. Intravitreal Aflibercept for Macular Edema Following Branch Retinal Vein Occlusion. Ophthalmology. 2016 Feb;123(2):330–6.

25. Comyn O, Sivaprasad S, Peto T, Neveu MM, Holder GE, Xing W, et al. A Randomized Trial to Assess Functional and Structural Effects of Ranibizumab versus Laser in Diabetic Macular Edema (the LUCIDATE Study). American Journal of Ophthalmology. 2014 May;157(5):960-970.e2.

26. Do DV, Nguyen QD, Boyer D, Schmidt-Erfurth U, Brown DM, Vitti R, et al. One-Year Outcomes of the DA VINCI Study of VEGF Trap-Eye in Eyes with Diabetic Macular Edema. Ophthalmology. 2012 Aug;119(8):1658–65.

27. Do DV, Schmidt-Erfurth U, Gonzalez VH, Gordon CM, Tolentino M, Berliner AJ, et al. The DA VINCI Study: Phase 2 Primary Results of VEGF Trap-Eye in Patients with Diabetic Macular Edema. Ophthalmology. 2011 Sep;118(9):1819–26.

28. Do DV, Sepah YJ, Boyer D, Callana D, Gallemore R, Bennett, M et al, Do DV, Sepah YJ, Boyer D, Callanan D, Gallemore R, et al. Month-6 primary outcomes of the READ-3 study (Ranibizumab for Edema of the mAcula in Diabetes—Protocol 3 with high dose). Eye. 2015 Dec;29(12):1538–44.

29. Ehlers JP, Wang K, Singh RP, Babiuch AS, Schachat AP, Yuan A, et al. A Prospective

Randomized Comparative Dosing Trial of Ranibizumab in Bevacizumab-Resistant Diabetic Macular Edema. Ophthalmology Retina. 2018 Mar;2(3):217–24.

30. Eldem BM, Muftuoglu G, Topbaş S, Çakir M, Kadayifcilar S, Özmert E, et al. A randomized trial to compare the safety and efficacy of two ranibizumab dosing regimens in a Turkish cohort of patients with choroidal neovascularization secondary to AMD. Acta Ophthalmol. 2015 Sep;93(6):e458–64.

31. Elman MJ, Aiello LP, Beck RW, Bressler NM, Bressler SB, Edwards AR, et al. Randomized Trial Evaluating Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular Edema. Ophthalmology. 2010 Jun;117(6):1064-1077.e35.

32. Feltgen N, Bertelmann T, Bretag M, Pfeiffer S, Hilgers R, Callizo J, et al. Efficacy and safety of a fixed bimonthly ranibizumab treatment regimen in eyes with neovascular age-related macular degeneration: results from the RABIMO trial. Graefes Arch Clin Exp Ophthalmol. 2017 May;255(5):923–34.

33. Figueira J, Fletcher E, Massin P, Silva R, Bandello F, Midena E, et al. Ranibizumab Plus Panretinal Photocoagulation versus Panretinal Photocoagulation Alone for High-Risk Proliferative Diabetic Retinopathy (PROTEUS Study). Ophthalmology. 2018 May;125(5):691–700.

34. Figueira J, Silva R, Henriques J, Caldeira Rosa P, Laïns I, Melo P, et al. Ranibizumab for High-Risk Proliferative Diabetic Retinopathy: An Exploratory Randomized Controlled Trial. Ophthalmologica. 2015 Dec 3;235(1):34–41.

35. Filho JAR, Messias A, Almeida FPP, Ribeiro JAS, Costa RA, Scott IU, et al. Panretinal photocoagulation (PRP) versus PRP plus intravitreal ranibizumab for high-risk proliferative diabetic retinopathy. Acta Ophthalmologica. 2011 Nov;89(7):e567–72.

36. Gillies MC, Lim LL, Campain A, Quin GJ, Salem W, Li J, et al. A randomized clinical trial of intravitreal bevacizumab versus intravitreal dexamethasone for diabetic macular edema: the BEVORDEX study. Ophthalmology. 2014 Dec;121(12):2473–81.

37. Graber M, Glacet-Bernard A, Fardeau C, Massamba N, Atassi M, Rostaqui O, et al. Comparison of early management of central retinal vein occlusion with ranibizumab versus hemodilution. J Fr Ophtalmol. 2015 Nov;38(9):815–21.

38. Hattenbach L-O, Feltgen N, Bertelmann T, Schmitz-Valckenberg S, Berk H, Eter N, et al. Head-to-head comparison of ranibizumab PRN versus single-dose dexamethasone for branch retinal vein occlusion (COMRADE-B). Acta Ophthalmol. 2018 Feb;96(1):e10–8.

39. Heier JS, Boyer D, Nguyen QD, Marcus D, Roth DB, Yancopoulos G, et al. The 1-year Results of CLEAR-IT 2, a Phase 2 Study of Vascular Endothelial Growth Factor Trap-Eye Dosed As-needed After 12-week Fixed Dosing. Ophthalmology. 2011 Jun;118(6):1098–106.

40. Heier JS, Boyer DS, Ciulla TA, Ferrone PJ, Jumper JM, Gentile RC, et al. Ranibizumab combined with verteporfin photodynamic therapy in neovascular age-related macular degeneration: year 1 results of the FOCUS Study. Arch Ophthalmol. 2006 Nov;124(11):1532–42.

41. Heier JS, Brown DM, Chong V, Korobelnik J-F, Kaiser PK, Nguyen QD, et al. Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-related Macular Degeneration. Ophthalmology. 2012 Dec;119(12):2537–48.

42. Heier JS, Clark WL, Boyer DS, Brown DM, Vitti R, Berliner AJ, et al. Intravitreal Aflibercept Injection for Macular Edema Due to Central Retinal Vein Occlusion. Ophthalmology. 2014 Jul;121(7):1414-1420.e1.

43. Ho AC, Busbee BG, Regillo CD, Wieland MR, Van Everen SA, Li Z, et al. Twenty-four-Month Efficacy and Safety of 0.5 mg or 2.0 mg Ranibizumab in Patients with Subfoveal Neovascular

Age-Related Macular Degeneration. Ophthalmology. 2014 Nov;121(11):2181–92.

44. Hoerauf H, Feltgen N, Weiss C, Paulus E-M, Schmitz-Valckenberg S, Pielen A, et al. Clinical Efficacy and Safety of Ranibizumab Versus Dexamethasone for Central Retinal Vein Occlusion (COMRADE C): A European Label Study. American Journal of Ophthalmology. 2016 Sep;169:258–67.

45. Holz FG, Roider J, Ogura Y, Korobelnik J-F, Simader C, Groetzbach G, et al. VEGF Trap-Eye for macular oedema secondary to central retinal vein occlusion: 6-month results of the phase III GALILEO study. Br J Ophthalmol. 2013 Mar;97(3):278–84.

46. Hykin P, Prevost AT, Vasconcelos JC, Murphy C, Kelly J, Ramu J, et al. Clinical Effectiveness of Intravitreal Therapy With Ranibizumab vs Aflibercept vs Bevacizumab for Macular Edema Secondary to Central Retinal Vein Occlusion: A Randomized Clinical Trial. JAMA Ophthalmol. 2019 29;

47. Ikuno Y, Ohno-Matsui K, Wong TY, Korobelnik J-F, Vitti R, Li T, et al. Intravitreal Aflibercept Injection in Patients with Myopic Choroidal Neovascularization. Ophthalmology. 2015 Jun;122(6):1220–7.

48. Ishibashi T, Li X, Koh A, Lai TYY, Lee F-L, Lee W-K, et al. The REVEAL Study. Ophthalmology. 2015 Jul;122(7):1402–15.

49. Kertes PJ, Galic IJ, Greve M, Williams RG, Rampakakis E, Scarino A, et al. Canadian Treat-and-Extend Analysis Trial with Ranibizumab in Patients with Neovascular Age-Related Macular Disease: One-Year Results of the Randomized Canadian Treat-and-Extend Analysis Trial with Ranibizumab Study. Ophthalmology. 2019 Jun 1;126(6):841–8.

50. Kertes PJ, Galic IJ, Greve M, Williams G, Baker J, Lahaie M, et al. Efficacy of a Treat-and-Extend Regimen With Ranibizumab in Patients With Neovascular Age-Related Macular Disease. JAMA Ophthalmol. 2020 Mar;138(3):244–50.

51. Kodjikian L, Souied EH, Mimoun G, Mauget-Faÿsse M, Behar-Cohen F, Decullier E, et al. Ranibizumab versus Bevacizumab for Neovascular Age-related Macular Degeneration: Results from the GEFAL Noninferiority Randomized Trial. Ophthalmology. 2013 Nov;120(11):2300–9.

52. Korobelnik J-F, Holz FG, Roider J, Ogura Y, Simader C, Schmidt-Erfurth U, et al. Intravitreal Aflibercept Injection for Macular Edema Resulting from Central Retinal Vein Occlusion: One-Year Results of the Phase 3 GALILEO Study. Ophthalmology. 2014 Jan;121(1):202–8.

53. Krebs I, Schmetterer L, Boltz A, Told R, Vécsei-Marlovits V, Egger S, et al. A randomised double-masked trial comparing the visual outcome after treatment with ranibizumab or bevacizumab in patients with neovascular age-related macular degeneration. Br J Ophthalmol. 2013 Mar;97(3):266–71.

54. Lang GE, Liakopoulos S, Vögeler J, Weiß C, Spital G, Gamulescu M-A, et al. The RELATION study: efficacy and safety of ranibizumab combined with laser photocoagulation treatment versus laser monotherapy in NPDR and PDR patients with diabetic macular oedema. Acta Ophthalmol. 2018 May;96(3):e377–85.

55. Li X, Hu Y, Sun X, Zhang J, Zhang M. Bevacizumab for Neovascular Age-related Macular Degeneration in China. Ophthalmology. 2012 Oct;119(10):2087–93.

56. Lushchyk T, Amarakoon S, Martinez-Ciriano JP, van den Born LI, Baarsma GS, Missotten T. Bevacizumab in age-related macular degeneration: a randomized controlled trial on the effect of injections every 4 weeks, 6 weeks and 8 weeks. Acta Ophthalmologica. 2013 Sep;91(6):e456–61.

57. Mahmood S, Roberts SA, Aslam TM, Parkes J, Barugh K, Bishop PN. Routine versus As-Needed Bevacizumab with 12-Weekly Assessment Intervals for Neovascular Age-Related

Macular Degeneration. Ophthalmology. 2015 Jul;122(7):1348–55.

58. Martin DF, Maguire MG, Fine SL, Ying G, Jaffe GJ, Grunwald JE, et al. Ranibizumab and Bevacizumab for Treatment of Neovascular Age-related Macular Degeneration. Ophthalmology. 2012 Jul;119(7):1388–98.

59. Martin DF, Maguire MG, Ying GS, Grungwald JE, Fine SL, Jaffe GL et al, Martin DF, Maguire MG, Ying G, Grunwald JE, Fine SL, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med. 2011 May 19;364(20):1897–908.

60. Massin P, Bandello F, Garweg JG, Hansen LL, Harding SP, Larsen M, et al. Safety and Efficacy of Ranibizumab in Diabetic Macular Edema (RESOLVE Study): A 12-month, randomized, controlled, double-masked, multicenter phase II study. Diabetes Care. 2010 Nov 1;33(11):2399–405.

61. Menon G, Chandran M, Sivaprasad S, Chavan R, Narendran N, Yang Y. Is it necessary to use three mandatory loading doses when commencing therapy for neovascular age-related macular degeneration using bevacizumab? (BeMOc Trial). Eye. 2013 Aug;27(8):959–63.

62. Michaelides M, Kaines A, Hamilton RD, Fraser-Bell S, Rajendram R, Quhill F, et al. A Prospective Randomized Trial of Intravitreal Bevacizumab or Laser Therapy in the Management of Diabetic Macular Edema (BOLT Study). Ophthalmology. 2010 Jun;117(6):1078-1086.e2.

63. Mitchell P, Bandello F, Schmidt-Erfurth U, Lang GE, Massin P, Schlingemann RO, et al. The RESTORE Study : ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology. 2011 Apr;118(4):615–25.

64. Narayanan R, Panchal B, Das T, Chhablani J, Jalali S, Ali MH. A randomised, double-masked, controlled study of the efficacy and safety of intravitreal bevacizumab versus ranibizumab in the treatment of macular oedema due to branch retinal vein occlusion: MARVEL Report No. 1. Br J Ophthalmol. 2015 Jul;99(7):954–9.

65. Narayanan R, Panchal B, Stewart MW, Das T, Chhablani J, Jalali S, et al. Grid laser with modified pro re nata injection of bevacizumab and ranibizumab in macular edema due to branch retinal vein occlusion: MARVEL report no 2. Clin Ophthalmol. 2016;10:1023–9.

66. Nguyen QD, Brown DM, Marcus DM, Boyer DS, Patel S, Feiner L, et al. Ranibizumab for Diabetic Macular Edema. results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology. 2012 Apr;119(4):789–801.

67. Nguyen QD, Shah SM, Heier JS, Do DV, Lim J, Boyer D, et al. Primary End Point (Six Months) Results of the Ranibizumab for Edema of the macula in Diabetes (READ-2) Study. Ophthalmology. 2009 Nov;116(11):2175-2181.e1.

68. Nunes RP, Hirai FE, Barroso LF, Badaró E, Novais E, Rodrigues EB, et al. Effectiveness of monthly and fortnightly anti-VEGF treatments for age-related macular degeneration. Arq Bras Oftalmol. 2019 Jun;82(3):225–32.

69. Ogura Y, Roider J, Korobelnik J-F, Holz FG, Simader C, Schmidt-Erfurth U, et al. Intravitreal Aflibercept for Macular Edema Secondary to Central Retinal Vein Occlusion: 18-Month Results of the Phase 3 GALILEO Study. American Journal of Ophthalmology. 2014 Nov;158(5):1032-1038.e2.

70. Pielen A, Mirshahi A, Feltgen N, Lorenz K, Korb C, Junker B, et al. Ranibizumab for Branch Retinal Vein Occlusion Associated Macular Edema Study (RABAMES): six-month results of a prospective randomized clinical trial. Acta Ophthalmol. 2015 Feb;93(1):e29–37.

71. Regillo CD, Brown DM, Abraham P, Yue H, Ianchulev T, Schneider S, et al. Randomized, Double-Masked, Sham-Controlled Trial of Ranibizumab for Neovascular Age-related Macular Degeneration: PIER Study Year 1. American Journal of Ophthalmology. 2008 Feb;145(2):239-

248.e5.

72. Rosenfeld PJ, Kaiser PK. Ranibizumab for Neovascular Age-Related Macular Degeneration. n engl j med. 2006;13.

73. Schauwvlieghe AME, Dijkman G, Hooymans JM, Verbraak FD, Hoyng CB, Dijkgraaf MGW, et al. Comparing the Effectiveness of Bevacizumab to Ranibizumab in Patients with Exudative Age-Related Macular Degeneration. The BRAMD Study. Wedrich A, editor. PLoS ONE. 2016 May 20;11(5):e0153052.

74. Schmidt-Erfurth U, Eldem B, Guymer R, Korobelnik J-F, Schlingemann RO, Axer-Siegel R, et al. Efficacy and Safety of Monthly versus Quarterly Ranibizumab Treatment in Neovascular Age-related Macular Degeneration: The EXCITE Study. Ophthalmology. 2011 May;118(5):831–9.

75. Schmidt-Erfurth U, Kaiser PK, Korobelnik J-F, Brown DM, Chong V, Nguyen QD, et al. Intravitreal Aflibercept Injection for Neovascular Age-related Macular Degeneration. Ophthalmology. 2014 Jan;121(1):193–201.

76. Scott IU, VanVeldhuisen PC, Ip MS, Blodi BA, Oden NL, Awh CC, et al. Effect of Bevacizumab vs Aflibercept on Visual Acuity Among Patients With Macular Edema Due to Central Retinal Vein Occlusion: The SCORE2 Randomized Clinical Trial. JAMA. 2017 May 23;317(20):2072.

77. Sepah YJ, Sadiq MA, Boyer D, Callanan D, Gallemore R, Bennett M, et al. Twenty-four–Month Outcomes of the Ranibizumab for Edema of the Macula in Diabetes – Protocol 3 with High Dose (READ-3) Study. Ophthalmology. 2016 Dec;123(12):2581–7.

78. Silva R, Berta A, Larsen M, Macfadden W, Feller C, Monés J. Treat-and-Extend versus Monthly Regimen in Neovascular Age-Related Macular Degeneration. Ophthalmology. 2018 Jan;125(1):57–65.

79. Sivaprasad S, Prevost AT, Vasconcelos JC, Riddell A, Murphy C, Kelly J, et al. Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (CLARITY): a multicentre, single-blinded, randomised, controlled, phase 2b, non-inferiority trial. The Lancet. 2017 Jun;389(10085):2193–203.

80. Subramanian ML, Abedi G, Ness S, Ahmed E, Fenberg M, Daly MK, et al. Bevacizumab vs ranibizumab for age-related macular degeneration: 1-year outcomes of a prospective, double-masked randomised clinical trial. Eye. 2010 Nov;24(11):1708–15.

81. Tan MH, Mcallister IL, Gillies ME, Verma N, Banerjee G, Smithies LA, et al. Randomized Controlled Trial of Intravitreal Ranibizumab Versus Standard Grid Laser for Macular Edema Following Branch Retinal Vein Occlusion. American Journal of Ophthalmology. 2014 Jan;157(1):237-247.e1.

82. Tano Y, Ohji M. EXTEND-I: safety and efficacy of ranibizumab in Japanese patients with subfoveal choroidal neovascularization secondary to age-related macular degeneration. Acta Ophthalmologica. 2010 Feb 16;88(3):309–16.

83. Tufail A, Patel PJ, Egan C, Hykin P, da Cruz L, Gregor Z, et al. Bevacizumab for neovascular age related macular degeneration (ABC Trial): multicentre randomised double masked study. BMJ. 2010 Jun 9;340(jun09 4):c2459–c2459.

84. Vader MJC, Schauwvlieghe A-SME, Verbraak FD, Dijkman G, Hooymans JMM, Los LI, et al. Comparing the Efficacy of Bevacizumab and Ranibizumab in Patients with Diabetic Macular Edema (BRDME): The BRDME Study, a Randomized Trial. Ophthalmol Retina. 2020 Feb 27;

85. Vader MJC, Schauwvlieghe A-SME, Verbraak FD, Dijkman G, Hooymans JMM, Los LI, et al. Comparing the Efficacy of Bevacizumab and Ranibizumab in Patients with Retinal Vein Occlusion: The Bevacizumab to Ranibizumab in Retinal Vein Occlusions (BRVO) study, a

Randomized Trial. Ophthalmology Retina. 2020 Jun 1;4(6):576–87.

86. Wang F, Yuan Y, Wang L, Ye X, Zhao J, Shen M, et al. One-Year Outcomes of 1 Dose versus 3 Loading Doses Followed by Pro Re Nata Regimen Using Ranibizumab for Neovascular Age-Related Macular Degeneration: The ARTIS Trial. J Ophthalmol. 2019;2019:7530458.

87. Wei W, Weisberger A, Zhu L, Cheng Y, Liu C. Efficacy and Safety of Ranibizumab in Asian Patients with Branch Retinal Vein Occlusion: Results from the Randomized BLOSSOM Study. Ophthalmol Retina. 2020;4(1):57–66.

88. Wells JA, AyalaAR, Jampol LM, Aiello LP, Antoszyk AN, Arnold-Bush B. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema. N Engl J Med. 2015 Mar 26;372(13):1193–203.

89. Wells JA, Glassman AR, Ayala AR, Jampol LM, Bressler NM, Bressler SB, et al. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema. Ophthalmology. 2016 Jun;123(6):1351–9.

90. Wykoff CC, Ou WC, Croft DE, Payne JF, Brown DM, Clark WL, et al. Neovascular age-related macular degeneration management in the third year: final results from the TREX-AMD randomised trial. Br J Ophthalmol. 2017 Aug 4;bjophthalmol-2017-310822.

91. Wykoff CC, Croft DE, Brown DM, Wang R, Payne JF, Clark L, et al. Prospective Trial of Treat-and-Extend versus Monthly Dosing for Neovascular Age-Related Macular Degeneration. Ophthalmology. 2015 Dec;122(12):2514–22.

92. Wykoff CC, Nittala MG, Zhou B, Fan W, Velaga SB, Lampen SIR, et al. Intravitreal Aflibercept for Retinal Nonperfusion in Proliferative Diabetic Retinopathy. Ophthalmology Retina. 2019 Dec;3(12):1076–86.

93. Wykoff CC, Ou WC, Brown DM, Croft DE, Wang R, Payne JF, et al. Randomized Trial of Treat-and-Extend versus Monthly Dosing for Neovascular Age-Related Macular Degeneration. Ophthalmology Retina. 2017 Jul;1(4):314–21.

94. Xiaoxin Li, Dai H, Li X, Han M, Li J, Suhner A et al, Dai H, Li X, Han M, Li J, Suhner A, et al. Efficacy and safety of ranibizumab 0.5 mg in Chinese patients with visual impairment due to diabetic macular edema: results from the 12-month REFINE study. Graefes Arch Clin Exp Ophthalmol. 2019 Mar;257(3):529–41.

eTable 4. Summary statistics of anti-VEGF Treatments (aflibercept, bevacizumab, ranibizumab) versus control comparisons for primary and secondary outcomes, and sub-group analyses

Outcome/Subgroup	Studies	Events	Patients	Peto OR [95%CI]	p-Overall	p-Het	I^2	p-Int
Major CV events (APTC)	29	186	7236	1.16 [0.85, 1.58]	0.36	0.99	0	
By anti-VEGF								
Ranibizumab	21	159	6058	1.11 [0.79, 1.55]	0.54	1.00	0	0.78
Bevacizumab	3	5	234	1.90 [0.29, 12.47]	0.50	0.29	18	
Aflibercept	5	22	944	1.40 [0.56, 3.48]	0.47	0.42	0	
By disease								
AMD	5	54	1570	1.20 [0.67, 2.13]	0.54	0.66	0	0.82
DME/PDR	15	118	3974	1.19 [0.80, 1.76]	0.38	0.96	0	
RVO	8	13	1570	0.74 [0.24, 2.30]	0.60	0.80	0	
mCNV	1	1	122	3.82 [0.04, 344.70]	0.56	NA	NA	
By follow up duration								
6 months	7	11	1353	0.90 [0.26, 3.18]	0.88	0.71	0	0.91
12 months	18	90	4259	1.21 [0.77, 1.88]	0.41	0.95	0	
24 months	4	85	1624	1.14 [0.72, 1.82]	0.57	0.85	0	
By study quality								
High risk	27	185	6931	1.15 [0.84, 1.57]	0.38	0.99	0	0.60
some concern	2	1	305	3.82 [0.04, 344.70]	0.56	NA	NA	
By exclusion of patients with CV disease history								
Excluded	21	127	4759	1.21 [0.83, 1.77]	0.32	0.97	0	0.58
Not excluded	6	48	2165	1.19 [0.65, 2.19]	0.57	0.85	0	
No information	2	11	312	0.60 [0.17, 2.13]	0.43	0.83	0	
Total mortality	35	93	8327	1.27 [0.82, 1.96]	0.29	0.85	0	
By anti-VEGF								
Ranibizumab	26	79	6995	1.35 [0.84, 2.17]	0.21	0.92	0	0.56
Bevacizumab	3	1	234	4.18 [0.06, 299.89]	0.51	NA	NA	
Aflibercept	6	13	1098	0.73 [0.21, 2.49]	0.62	0.23	31	
By disease								
AMD	5	27	1570	1.00 [0.45, 2.25]	1.00	0.86	0	0.04
DME/PDR	18	58	4173	1.80 [1.03, 3.16]	0.04	0.99	0	
RVO	11	8	2462	0.27 [0.06, 1.12]	0.07	0.49	0	
mCNV	1	0	122	NE	NA	NA	NA	
By follow up duration								
6 months	10	6	2217	0.58 [0.11, 3.08]	0.52	0.28	21	0.60
12 months	21	47	4486	1.24 [0.66, 2.31]	0.50	0.93	0	
24 months	4	40	1624	1.47 [0.76, 2.86]	0.26	0.47	0	
By study quality								
High risk	32	93	7778	1.27 [0.82, 1.96]	0.29	0.85	0	NA

some concern	3	0	549	NE	NA	NA	NA	
By exclusion of patients with CV disease history								
Excluded	25	5570	62	1.56 [0.91, 2.68]	0.11	0.85	0	0.37
Not excluded	7	2319	27	0.78 [0.35, 1.74]	0.55	0.44	0	
No information	3	438	4	1.49 [0.19, 11.84]	0.71	0.59	0	
Non-ocular hemorrhage	19	135	5547	1.46 [1.01, 2.10]	0.05	0.81	0	
By anti-VEGF								
Ranibizumab	15	130	5033	1.47 [1.01, 2.13]	0.04	0.72	0	0.78
Bevacizumab	2	0	173	NE	NA	NA	NA	
Aflibercept	2	5	341	1.07 [0.12, 9.31]	0.95	0.53	0	
By disease								
AMD	5	95	1570	1.57 [1.01, 2.44]	0.04	0.66	0	0.88
DME/PDR	9	30	2523	1.14 [0.52, 2.48]	0.74	0.51	0	
RVO	4	9	1332	1.37 [0.35, 5.31]	0.65	0.45	0	
mCNV	1	1	122	3.82 [0.04, 344.70]	0.56	NA	NA	
By follow up duration								
6 months	4	7	1151	1.29 [0.27, 6.29]	0.75	0.43	0	0.57
12 months	11	52	2772	1.86 [1.03, 3.34]	0.04	0.93	0	
24 months	4	76	1624	1.24 [0.75, 2.03]	0.40	0.24	29	
By study quality								
High risk	16	124	4998	1.52 [1.03, 2.22]	0.03	0.77	0	0.47
some concern	3	11	549	0.93 [0.26, 3.32]	0.92	0.50	0	
By exclusion of patients with CV disease history								
Excluded	12	3253	32	1.01 [0.48, 2.16]	0.97	0.55	0	0.48
Not excluded	5	1982	90	1.70 [1.09, 2.67]	0.02	0.92	0	
No informatioin	2	312	13	1.19 [0.37, 3.85]	0.78	0.34	0	
CV mortality	33	58	7991	1.21 [0.69, 2.10]	0.50	0.77	0	
By anti-VEGF								
Ranibizumab	24	48	6659	1.33 [0.72, 2.43]	0.36	0.85	0	0.53
Bevacizumab	3	1	234	4.18 [0.06, 299.89]	0.51	NA	NA	
Aflibercept	6	9	1098	0.61 [0.14, 2.58]	0.50	0.22	34	
By disease								
AMD	5	16	1570	0.82 [0.29, 2.34]	0.72	0.47	0	0.27
DME/PDR	17	39	4140	1.60 [0.81, 3.16]	0.17	0.97	0	
RVO	10	3	2159	0.28 [0.03, 2.95]	0.29	0.12	60	
mCNV	1	0	122	NE	NA	NA	NA	
Myocardial infarction	26	91	6803	0.86 [0.55, 1.33]	0.49	0.53	0	
By anti-VEGF								
Ranibizumab	20	78	5930	0.79 [0.49, 1.27]	0.33	0.47	0	0.41

Bevacizumab	3	3	234	4.26 [0.36, 50.22]	0.25	1.00	0	
Aflibercept	3	10	639	1.00 [0.26, 3.76]	1.00	0.32	13	
By disease								
AMD	5	23	1570	0.93 [0.39, 2.24]	0.88	0.07	57	0.97
DME/PDR	16	61	3921	0.82 [0.48, 1.41]	0.48	0.69	0	
RVO	5	7	1312	0.89 [0.19, 4.15]	0.88	0.44	0	
Cardiac failure	17	63	5260	0.93 [0.54, 1.58]	0.79	0.10	32	
By anti-VEGF								
Ranibizumab	14	54	4792	0.77 [0.43, 1.36]	0.36	0.14	30	0.16
Bevacizumab	1	3	61	4.49 [0.37, 53.93]	0.24	NA	NA	
Aflibercept	2	6	407	3.60 [0.48, 27.14]	0.21	NA	NA	
By disease								
AMD	3	14	1294	1.28 [0.42, 3.92]	0.66	0.24	29	0.77
DME/PDR	10	46	2863	0.82 [0.44, 1.54]	0.54	0.05	47	
RVO	4	3	1103	1.24 [0.12, 13.07]	0.86	0.37	0	
Stroke	30	71	7535	1.50 [0.91, 2.48]	0.11	0.57	0	
By anti-VEGF								
Ranibizumab	22	58	6391	1.57 [0.91, 2.73]	0.11	0.66	0	0.93
Bevacizumab	3	3	234	1.16 [0.11, 12.66]	0.90	0.16	50	
Aflibercept	5	10	910	1.23 [0.31, 4.85]	0.76	0.20	34	
By disease								
AMD	5	20	1570	2.35 [0.92, 5.99]	0.07	0.54	0	0.11
DME/PDR	16	41	4100	1.70 [0.88, 3.31]	0.12	0.64	0	
RVO	8	9	1743	0.32 [0.08, 1.26]	0.10	0.64	0	
mCNV	1	1	122	3.82 [0.04, 344.70]	0.56	NA	NA	
VTE/PE	9	14	2249	1.23 [0.40, 3.79]	0.72	0.25	23	0.03
By anti-VEGF								
Ranibizumab	6	13	1857	1.64 [0.52, 5.21]	0.40	0.66	0	
Bevacizumab	2	0	173	NE	NA	NA	NA	
Aflibercept	1	1	219	0.01 [0.00, 0.92]	0.05	NA	NA	
By disease								
AMD	1	0	93	NE	NA	NA	NA	1.00
DME/PDR	6	11	1522	1.23 [0.34, 4.42]	0.75	0.16	40	
RVO	2	3	634	1.23 [0.12, 13.03]	0.86	0.28	14	
Arterial hypertension	28	407	7169	0.94 [0.76, 1.17]	0.58	0.27	13	0.83
By anti-VEGF								
Ranibizumab	21	341	6191	0.93 [0.73, 1.18]	0.53	0.16	24	
Bevacizumab	3	8	234	1.51 [0.32, 7.09]	0.60	0.42	0	
Aflibercept	4	58	744	0.96 [0.54, 1.71]	0.89	0.44	0	

By disease								
AMD	5	158	1570	0.93 [0.65, 1.33]	0.68	0.35	9	0.99
DME/PDR	13	156	3181	0.94 [0.65, 1.35]	0.73	0.50	0	
RVO	10	93	2418	0.96 [0.63, 1.47]	0.86	0.08	41	
Proteinuria	9	7	3589	2.30 [0.47, 11.23]	0.30	0.79	0	
Ranibizumab	9	7	3589	2.30 [0.47, 11.23]	0.30	0.79	0	NA
By disease								
AMD	3	0	1316	NE	NA	NA	NA	NA
DME/PDR	4	7	1488	2.30 [0.47, 11.23]	0.30	0.79	0	
RVO	2	0	785	NE	NA	NA	NA	
All serious SAEs	19	749	4681	0.99 [0.83, 1.18]	0.90	0.79	0	
By anti-VEGF								
Ranibizumab	14	656	3889	1.00 [0.83, 1.20]	0.98	0.67	0	0.63
Bevacizumab	1	6	80	0.44 [0.08, 2.30]	0.33	NA	NA	
Aflibercept	4	87	712	1.01 [0.59, 1.71]	0.98	0.60	0	
By disease								
AMD	2	123	581	0.88 [0.58, 1.34]	0.55	0.88	0	0.70
DME/PDR	10	529	2535	1.02 [0.82, 1.26]	0.89	0.35	10	
RVO	6	94	1443	0.97 [0.64, 1.49]	0.90	0.90	0	
mCNV	1	3	122	3.91 [0.28, 53.74]	0.31	NA	NA	
All SAEs	11	1334	2518	0.93 [0.78, 1.10]	0.39	0.95	0	
By anti-VEGF								
Ranibizumab	9	1238	2255	0.93 [0.77, 1.11]	0.41	0.87	0	0.93
Bevacizumab	1	7	80	1.22 [0.26, 5.72]	0.80	NA	NA	
Aflibercept	1	89	183	0.90 [0.50, 1.60]	0.71	NA	NA	
By disease								
DME/PDR	7	853	1566	0.87 [0.70, 1.09]	0.23	0.83	0	0.41
RVO	4	481	952	1.01 [0.78, 1.32]	0.94	0.93	0	

AE: adverse events; AMD: age related macular degeneration; APTC: antiplatelet trialists' collaboration; CI, confidence interval; CV: cardiovascular; DME, diabetic macular edema; Q, cochrane test; I^2, measure of inconsistency; OR, Odds-ratio; NA, not applicable, NE, not estimable; PE, pulmonary embolism ; RVO, Retinal Vein Occlusion-related edema; SAE, systemic serious adverse events; VEGF, vascular endothelial growth factor; VTE, venous thromboembolism; PDR, proliferative diabetic retinopathy

eTable 5. Sensitivity analysis for primary outcomes by changing methods and models.

Method used for APTC criteria	**Odds Ratio (95%CI)***	**Relative Risk (95%CI)***
Peto, Fixed (95% CI)	1.16 [0.85, 1.58]	/
Mantel Haenszel, Fixed (95% CI)	1.11 [0.82, 1.51]	1.11 [0.82, 1.49]
Mantel Haenszel, Random (95% CI)	1.10 [0.81, 1.51]	1.10 [0.81, 1.49]
Inverse variance, Fixed (95% CI)	1.10 [0.81, 1.51]	1.10 [0.81, 1.49]
Inverse variance, Random (95% CI)	1.10 [0.81, 1.51]	1.10 [0.81, 1.49]
Method used for Total mortality		
Peto, Fixed (95% CI)	1.27 [0.82, 1.96]	/
Mantel Haenszel, Fixed (95% CI)	1.17 [0.76, 1.80]	1.17 [0.76, 1.78]
Mantel Haenszel, Random (95% CI)	1.15 [0.73, 1.83]	1.15 [0.73, 1.80]
Inverse variance, Fixed (95% CI)	1.15 [0.73, 1.83]	1.15 [0.73, 1.80]
Inverse variance, Random (95% CI)	1.15 [0.73, 1.83]	1.15 [0.73, 1.80]

* Studies with zero events in both groups were excluded

eTable 6. Funnel plot asymmetry tests (with continuity correction if necessary) for primary outcomes

Test	z	p-value
APTC criteria		
Rank correlation test of funnel plot asymmetry	-0.4544	0.6495
Linear regression test of funnel plot asymmetry	-0.61516	0.5438
Total mortality		
Rank correlation test of funnel plot asymmetry	0.11279	0.9102
Linear regression test of funnel plot asymmetry	-0.56286	0.5798

eTable 7: Grading of recommendations assessment, development and evaluation (GRADE) evidence table for primary outcomes and non-ocular haemorrhages

							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With control	With any anti-VEGF	Relative effect (95% CI)	Risk with control	Risk difference with any anti-VEGF
Major cardiovascular disease (follow up: range 6 months to 24 months)											
7236 (29 RCTs)	serious [a]	not serious	serious [b]	not serious	none [c,d]	⨁⨁◯◯ LOW	59/2539 (2.3%)	127/4697 (2.7%)	**OR 1.16** (0.85 to 1.58)	23 per 1 000	**4 more per 1 000** (from 3 fewer
Total mortality (follow up: range 6 months to 24 months)											
8327 (35 RCTs)	serious [a]	not serious	serious [b]	not serious	none [c,d]	⨁⨁◯◯ LOW	27/2988 (0.9%)	66/5339 (1.2%)	**OR 1.27** (0.82 to 1.96)	9 per 1 000	**2 more per 1 000** (from 2 fewer to 9 more)
Non-ocular hemorrhage (follow up: range 6 months to 24 months)											
5547 (19 RCTs)	serious [a]	not serious	serious [b]	not serious	none [c,d]	⨁⨁◯◯ LOW	35/1962 (1.8%)	100/3585 (2.8%)	**OR 1.46** (1.01 to 2.10)	18 per 1 000	**8 more per 1 000** (from 0 fewer to 19 more)

CI: Confidence interval; OR: Odds ratio
a. Almost all studies reported lost to follow up patients which could have biased the estimatation of the event rate, especially for rare events, such as adverse systemic events.
b. Almost all studies excluded patients with a history of cardiovascular events (myocardial infarction, stroke) within 3 to 6 months prior to the trial begining, thus selecting a population at lower risk for cardiovascular events and limiting the generalizability of the results.
c. Funnel plot asymmetry tests were not significant
d. We included only randomized controlled trials in our meta-analysis. Randomization produced comparable groups.

eTable 8: Summary statistics of aflibercept vs ranibizumab, aflibercept vs bevacizumab and bevacizumab vs ranibizumab comparison for primary and secondary outcomes

Outcome/Subgroup	Studies	Events	Patients	Peto OR [95%CI]	p-Overall	p-Het	I^2
aflibercept vs ranibizumab							
APTC event	5	130	3213	0.81 [0.55, 1.20]	0.29	0.13	47
Total mortality	5	95	3213	1.01 [0.64, 1.58]	0.98	0.14	46
Non-ocular haemorrhage	3	22	2861	0.98 [0.39, 2.42]	0.96	0.99	0
CV mortality	5	45	3213	1.18 [0.62, 2.24]	0.61	0.05	61
Myocardial infarction	5	55	3213	0.70 [0.39, 1.25]	0.23	0.95	0
Cardiac failure	3	44	2861	0.95 [0.50, 1.80]	0.87	0.81	0
Stroke	4	37	3170	0.59 [0.30, 1.19]	0.14	0.07	62
VTE/PE	3	11	2861	1.35 [0.37, 4.95]	0.65	0.66	0
Arterial hypertension	3	370	2861	0.84 [0.65, 1.07]	0.15	0.99	0
Proteinuria	1	3	442	1.90 [0.20, 18.38]	0.58	NA	NA
All serious SAEs	3	753	2861	0.99 [0.82, 1.20]	0.94	0.65	0
All SAEs	2	1739	2419	1.15 [0.94, 1.41]	0.18	NA	NA
aflibercept vs bevacizumab							
APTC event	3	42	1112	0.89 [0.48, 1.65]	0.71	0.38	0
Total mortality	3	30	1112	0.65 [0.31, 1.35]	0.25	0.22	33
Non-ocular haemorrhage	2	11	804	0.81 [0.25, 2.68]	0.74	0.16	49
CV mortality	3	15	1112	0.65 [0.23, 1.81]	0.41	0.21	36
Myocardial infarction	3	16	1112	0.98 [0.37, 2.64]	0.97	0.21	35
Cardiac failure	2	23	804	1.07 [0.46, 2.46]	0.88	0.32	0
Stroke	3	13	1112	1.15 [0.39, 3.44]	0.80	0.03	72
VTE/PE	2	5	804	1.47 [0.25, 8.50]	0.67	0.36	0
Arterial hypertension	2	74	804	1.41 [0.87, 2.31]	0.16	0.37	0
Proteinuria	1	5	442	0.65 [0.11, 3.78]	0.63	NA	NA
All serious SAEs	1	169	442	1.09 [0.75, 1.61]	0.65	NA	NA
bevacizumab versus ranibizumab							
APTC event	9	166	4231	0.85 [0.62, 1.17]	0.32	0.77	0
Total mortality	12	176	4631	1.16 [0.86, 1.58]	0.33	0.89	0
Non-ocular haemorrhage	4	17	1576	0.53 [0.20, 1.39]	0.20	0.40	0
Mortality CV	8	61	3539	1.11 [0.67, 1.84]	0.69	0.97	0
Myocardial infarction	10	63	4259	0.81 [0.49, 1.34]	0.41	0.43	0
Cardiac failure	5	38	2700	0.82 [0.43, 1.56]	0.54	0.33	13
Stroke	11	68	4304	0.94 [0.58, 1.52]	0.80	0.26	20
VTE/PE	7	22	3465	1.23 [0.53, 2.84]	0.63	0.30	18
Arterial hypertension	8	181	3098	0.69 [0.50, 0.95]	**0.02**	0.59	**0**

Proteinuria	2	72	1621	1.22 [0.76, 1.96]	0.41	0.41	0
All serious SAEs	7	987	3642	1.19 [1.03, 1.39]	**0.02**	0.54	0

AE: adverse event; APTC: antiplatelet trialists' collaboration; CI, confidence interval; CV, cardiovascular, Q, cochrane test; I^2, measure of inconsistency; OR, Odds-ratio; NA, not applicable ; PE, pulmonary embolism ; SAE, systemic adverse events; VTE, venous thromboembolism;

eTable 9. Summary statistics of between doses (ranibizumab 0,5mg vs 2mg; 0,3mg vs 0,5 mg and aflibercept 0,5mg vs 2mg) comparisons for primary and secondary outcomes

Outcome/Subgroup	Studies	Events	Patient	Peto OR [95%CI]	p-Overall	p-Het	I^2
ranibizumab 0,5 vs 2 mg							
APTC event	2	68	1247	0.93 [0.57, 1.52]	0.78	0.67	0
Total mortality	2	50	1247	1.08 [0.61, 1.90]	0.80	0.90	0
Non-ocular Haemorrhage	1	37	1095	0.94 [0.49, 1.81]	0.85	NA	NA
CV mortality	2	31	1247	1.38 [0.68, 2.81]	0.38	0.36	0
Myocardial infarction	2	31	1247	0.71 [0.35, 1.45]	0.35	0.45	0
Cardiac failure	2	29	1247	1.23 [0.59, 2.56]	0.59	0.18	44
Stroke	2	10	1247	0.44 [0.13, 1.54]	0.20	0.33	0
VTE/PE	1	5	1095	0.67 [0.11, 3.85]	0.65	NA	NA
Arterial hypertension	2	83	1247	0.92 [0.59, 1.43]	0.71	0.93	0
All serious SAE	1	106	1095	1.08 [0.72, 1.61]	0.70	NA	NA
ranibizumab 0,3 vs 0,5 mg							
APTC event	9	164	4514	0.91 [0.67, 1.25]	0.58	0.98	0
Total mortality	10	101	4590	0.78 [0.53, 1.16]	0.23	0.49	0
Non-ocular Haemorrhage	10	182	4590	0.89 [0.66, 1.20]	0.43	0.66	0
CV mortality	9	52	4470	1.02 [0.59, 1.76]	0.96	0.89	0
Myocardial infarction	9	75	4514	1.23 [0.78, 1.94]	0.38	0.23	25
Cardiac failure	4	29	1014	0.80 [0.38, 1.69]	0.56	0.07	62
Stroke	10	57	4590	0.55 [0.33, 0.93]	**0.03**	0.43	0
VTE/PE	3	7	737	1.33 [0.30, 5.90]	0.71	NA	NA
Arterial hypertension	10	399	4590	0.87 [0.71, 1.07]	0.20	0.32	14
Proteinuria	7	2	4156	1.01 [0.06, 16.23]	0.99	0.15	51
All serious SAE	7	193	1615	0.70 [0.52, 0.96]	**0.02**	0.76	0
All SAE	2	236	358	0.86 [0.55, 1.36]	0.53	0.95	0
aflibercept 0,5 vs 2 mg							
APTC event	3	44	1365	1.63 [0.89, 2.96]	0.11	0.75	0
Total mortality	3	37	1365	1.20 [0.63, 2.31]	0.58	0.22	34
Non-ocular Haemorrhage	2	7	1302	0.76 [0.17, 3.37]	0.72	0.35	0
CV mortality	3	15	1365	1.16 [0.42, 3.22]	0.77	0.10	63
Myocardial infarction	3	21	1365	2.43 [1.03, 5.75]	**0.04**	0.28	13
Cardiac failure	3	13	1365	0.63 [0.21, 1.88]	0.41	0.23	32
Stroke	3	13	1365	0.63 [0.21, 1.89]	0.41	0.94	0
VTE/PE	2	5	1277	0.68 [0.12, 3.95]	0.67	NA	NA
Arterial hypertension	3	150	1365	1.02 [0.73, 1.43]	0.91	0.13	52
All serious SAE	3	330	1365	1.22 [0.95, 1.56]	0.12	0.87	0
All SAE	1	888	1214	0.96 [0.74, 1.23]	0.74	NA	NA

AE: adverse event; APTC: antiplatelet trialists' collaboration; CI, confidence interval; Q, cochrane test; NA, not applicable; I^2, measure of inconsistency; OR, Odds-ratio; n : number; PE, pulmonary embolism ; RVO, Retinal Vein Occlusion-related edema; SAE, systemic serious adverse events; VTE, venous thromboembolism;

eTable 10. Summary statistics of anti-VEGF drugs (aflibercept, bevacizumab, ranibizumab) as needed (PRN) or treat and extend (TE) regimens vs monthly regimens comparisons for primary and secondary outcomes

Outcome/Subgroup	Studies	Events	Patients	Peto OR [95%CI]	p-Overall	p-Het	I^2
APTC event	9	109	3481	1.02 [0.70, 1.50]	0.91	0.17	30
Total mortality	9	124	3481	1.11 [0.77, 1.59]	0.58	0.33	13
Non-ocular Haemorrhage	4	49	2374	1.14 [0.65, 2.01]	0.65	0.77	0
CV mortality	6	45	2192	1.15 [0.64, 2.07]	0.65	0.08	51
Myocardial infarction	7	41	3414	1.15 [0.62, 2.13]	0.66	0.33	13
Cardiac failure	6	48	2765	1.28 [0.72, 2.27]	0.40	0.89	0
Stroke	9	39	3481	0.95 [0.50, 1.78]	0.87	0.32	14
Arterial hypertension	6	169	2480	1.11 [0.81, 1.52]	0.50	0.34	12
VTE/PE	5	17	3265	0.90 [0.35, 2.33]	0.82	1.00	0
All serious SAE	6	382	2510	1.02 [0.82, 1.27]	0.87	0.30	17
All SAE	3	443	1020	0.84 [0.65, 1.07]	0.16	0.71	0

AE: adverse event; APTC: antiplatelet trialists' collaboration; CI, confidence interval; Q, cochrane test; I^2, measure of inconsistency; OR, Odds-ratio; n : number; PE, pulmonary embolism ; RVO, Retinal Vein Occlusion-related edema; SAE, systemic serious adverse events; VTE, venous thromboembolism;

