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Efficacy and safety of intraocularly administered vascular endothelial growth factor inhibitors for macular disease

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Efficacy and safety of intraocularly administered vascular endothelial growth factor inhibitors for macular disease
[Effekt och säkerhet vid intraokulär behandling med vaskulär tillväxtfaktorhämmare för makulasjukdom]

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1. Abstract

Background: Age-related macular degenerative disease (AMD) is the most common cause of permanent visual handicap in the Western population. Previous treatment modalities like laser coagulation had very limited effect and the introduction of anti-vascular growth factor (VGEF) inhibitors for intraocular use was therefore a major breakthrough. The idea emanated from the observation in case reports that a VGEF inhibitor used as an anti-tumour agent, bevacizumab, had a positive effect on visual acuity in patients with AMD. Bevacizumab was however never evaluated for intraocular use, instead a new similar substance, ranibizumab, went through the registration process. Ranibizumab was later followed by a third substance, aflibercept. The price for these substances is quite high and use of the considerably cheaper bevacizumab started. There is now an extensive off label use of intraocularly administered bevacizumab on all approved indications for ranibizumab and aflibercept.

Objective: Are there any clinically relevant differences in efficacy or safety between the three anti-VGEF compounds bevacizumab, ranibizumab and aflibercept, when used for intraocular treatment of age-related macular degeneration, diabetic macular edema, retinal vein occlusion or choroidal neovascularization due to pathologic myopia?

Method: After establishing a relevant PICO, a systematic literature search up to March 2016 was conducted in PubMed, Embase and the Cochrane Library. The websites of SBU and Kunnskapssenteret together with reference lists of relevant articles were also searched for additional references. After an exclusion process we identified 13 RCTs (19 publications, 9,122 individuals), 18 cohort studies (n>1.2 M injections) and 3 case series (n>16,000 injections). The outcomes for efficacy were visual function, quality of life and visual acuity (VA). The vast majority of data involved AMD and the comparison bevacizumab vs ranibizumab and the outcome VA (seven RCTs, reported in 10 publications, with 3,235 individuals). For the comparison bevacizumab vs aflibercept, only studies including patients with DME were identified with VA as outcome. The safety outcomes reported were mortality, cardiovascular mortality, myocardial infarction, stroke, endophthalmitis and serious ocular events with the main body of data involving either AMD or mixed indications (presumably also mainly patients with AMD) and the comparison bevacizumab vs ranibizumab.

Results

Efficacy

Visual function: Only data regarding the comparison aflibercept vs ranibizumab, in patients with AMD, was found.

Conclusion: There is little or no difference in the effect on visual function between aflibercept and ranibizumab in patients with AMD (GRADE ⊕⊕⊕⊕).

Quality of life: This outcome was reported in one study performed in patients with AMD, for the comparison bevacizumab vs ranibizumab.

Conclusion: There may be little or no difference in the effect on quality of life between bevacizumab and ranibizumab in patients with AMD (GRADE ⊕⊕◯◯).

Visual acuity: Data from AMD, DME, RVO and PM patients were reported.

Conclusion: There is probably little or no difference between bevacizumab and ranibizumab in the effect on visual acuity in patients with AMD and DME (GRADE⊕⊕⊕◯), and it is uncertain whether there is any difference in the effect of bevacizumab vs ranibizumab in patients with RVO or PM (GRADE ⊕◯◯◯).

For the comparisons bevacizumab vs aflibercept and aflibercept vs ranibizumab we found data from one group of patients with DME presented in two studies. The results differed depending on baseline visual acuity.

For bevacizumab vs aflibercept in patients with poor initial VA, there was a statistically significant larger improvement in the aflibercept group (mean difference in letters) = +6.5 [+2.9, +10.1], p<0.001. In patients with better initial vision, the difference was not statistically significant (p=0.69).
Conclusion: In a subgroup of patients with poor initial visual acuity due to DME, aflibercept probably had a better effect on visual acuity than ranibizumab (GRADE⊕⊕⊕◯).

For the comparison aflibercept vs ranibizumab and the outcome VA, the results were different in patients with AMD and DME. In patients with AMD, no significant differences were seen whereas in patients with DME, there was a larger improvement in basal letter score with aflibercept in the subgroup of patients with poor basal letter score.
Conclusion: There is little or no difference in VA between aflibercept and ranibizumab in patients with AMD (GRADE⊕⊕⊕⊕), and there is probably a slightly larger effect on VA with aflibercept in patients with DME (GRADE⊕⊕⊕◯). Regarding patients with RVO and PM, no evaluable data for this comparison was found.

Safety
Safety variables assessed were mortality, cardiovascular (CV) mortality, myocardial infarction (MI), stroke, endophthalmitis and serious ocular events. Most of the data emanated from the patients with AMD but there were also large registry studies based on mixed diagnoses.
Conclusion: In patients with AMD, there is probably little or no difference regarding mortality, cardiovascular mortality, myocardial infarction, stroke, endophthalmitis, or serious ocular complications, between bevacizumab and ranibizumab (GRADE⊕⊕⊕◯). For patients with DME and the same comparison, there may be little or no difference in the risk for mortality, cardiovascular mortality, myocardial infarction, stroke, or serious ocular complications (GRADE ⊕⊕◯◯), and it is unknown if there is any difference in the risk for endophthalmitis (too few cases for evaluation). For the diagnoses RVO and PM, the number of patients was too low to allow a meaningful analysis.

The risk for endophthalmitis was analysed in a large patient group with mixed diagnoses, probably consisting of mainly patients with AMD. The OR for endophthalmitis was 1.03 [0.69, 1.53], p=0.90, based on data from 13 cohort studies.
Conclusion: There is probably little or no difference in the risk for endophthalmitis between bevacizumab and ranibizumab in patient groups with mixed diagnoses (GRADE⊕⊕⊕◯). It is unknown if this applies also to patients with DME, RVO or PM.

For the comparison bevacizumab vs aflibercept, only data from patients with DME (436+448 patients) was found. The number of events was consistently low and no significant differences were seen for any of the chosen outcomes.
Conclusion: There is probably little or no difference in the risk for mortality, myocardial infarction, stroke, or other serious ocular events in patients with DME (GRADE ⊕⊕⊕◯). Regarding endophthalmitis there were too few events to allow meaningful analysis.

The comparison aflibercept vs ranibizumab was evaluated in patients with AMD and DME. In the AMD material (2 RCTs and in addition one cohort for endophthalmitis) there were no significant differences in the RCT studies for any of the safety outcomes but there was a significantly increased risk for endophthalmitis with aflibercept vs ranibizumab in the cohort study.
Conclusion: In patients with AMD, there is probably little or no difference in the risk for mortality, cardiovascular mortality, myocardial infarction, stroke, or serious ocular events between aflibercept and ranibizumab (GRADE ⊕⊕⊕◯). For endophthalmitis, there may be little or no difference in the risk between aflibercept and ranibizumab (GRADE⊕⊕◯◯). In patients with DME, there may be little or no difference in the risk for mortality, cardiovascular mortality, myocardial infarction, stroke or other serious ocular events (GRADE ⊕⊕◯◯), and it is unknown whether there is any difference in the risk for endophthalmitis (no data).

Summary
The analysis did not identify any clinically relevant differences in efficacy (measured as change in visual acuity) or safety (measured as risk for mortality, cardiovascular mortality, myocardial infarction, stroke, endophthalmitis or serious ocular events) between intraocular bevacizumab, ranibizumab or aflibercept. The degree of certainty of this conclusion varies with indication and outcome, the highest certainty of evidence exist for patients with AMD and for the comparison bevacizumab versus ranibizumab (for most outcomes GRADE⊕⊕⊕◯).

For safety related outcomes, the highest certainty of evidence (GRADE⊕⊕⊕◯) for a lack of clinically relevant difference, is available for the comparison bevacizumab versus ranibizumab for patients with AMD and DME regarding mortality, cardiovascular mortality, myocardial infarction, stroke, serious ocular events, and for the outcome endophthalmitis regarding patients with AMD but not those with DME. A similar certainty of evidence (GRADE⊕⊕⊕◯), regarding safety related outcomes is available for the comparison bevacizumab versus aflibercept for patients with AMD or DME (i.e. mortality, cardiovascular mortality, myocardial infarction, stroke, serious ocular events). For the remaining indications and outcomes, the certainty of evidence is less extensive or somewhat inconsistent, and largely lacking for the indications RVO and PM.

Graphic summary of results:

Comparison	Outcome	AMD	DME	RVO	PM	Mixed diagnoses
	Efficacy					
Bevacizumab-ranibizumab	VF					
	QoL	⊕⊕◯◯				
	VA	⊕⊕⊕◯	⊕⊕⊕◯	⊕◯◯◯	⊕◯◯◯	
Bevacizumab-aflibercept	VF					
	QoL					
	VA		⊕⊕⊕◯ **B<A**			
Aflibercept-ranibizumab	**VF**	⊕⊕⊕⊕				
	QoL					
	VA	⊕⊕⊕⊕	⊕⊕⊕◯ **A>R**			
	Safety					
Bevacizumab-ranibizumab	Mortality	⊕⊕⊕◯	⊕⊕◯◯			
	CVD	⊕⊕⊕◯	⊕⊕◯◯			
	Myocardial infarction	⊕⊕⊕◯	⊕⊕◯◯			
	Stroke	⊕⊕⊕◯	⊕⊕◯◯			
	Endophthalmitis	⊕⊕◯◯	⊕◯◯◯			⊕⊕⊕◯
	Serious ocular AE	⊕⊕◯◯	⊕⊕◯◯	⊕◯◯◯		⊕◯◯◯
Bevacizumab-aflibercept	Mortality		⊕⊕◯◯			
	CVD		⊕⊕◯◯			
	Myocardial infarction		⊕⊕◯◯			
	Stroke		⊕⊕◯◯			
	Endophthalmitis					⊕⊕◯◯
	Serious ocular AE		⊕⊕⊕◯			
Aflibercept-ranibizumab	Mortality	⊕⊕⊕◯	⊕⊕◯◯			
	CVD	⊕⊕⊕◯	⊕⊕◯◯			
	Myocardial infarction	⊕⊕⊕◯	⊕⊕◯◯			
	Stroke	⊕⊕⊕◯	⊕⊕◯◯ **A>R**			
	Endophthalmitis	⊕⊕◯◯				⊕⊕◯◯
	Serious ocular AE	⊕⊕⊕◯	⊕⊕◯◯			

No clinically relevant difference
Superiority
Not studied

Svensk sammanfattning

Bakgrund: Åldersrelaterad makuladegeneration är den vanligaste orsaken till permanent synhandikapp i västvärlden. Tidigare behandlingsmetoder, exempelvis laserbehandling, hade mycket begränsade effekter och introduktionen av vaskulära tillväxtfaktorhämmare för intraokulärt bruk innebar därför ett genombrott. Behandlingsprincipen hade sitt ursprung i fallrapporter om att anti-tumörsubstansen bevacizumab intravenöst hade positiva effekter på synskärpan hos patienter med våt makuladegeneration. Läkemedelsföretaget tog fram en liknande substans, ranibizumab, som sedan genomgick en formell registreringsprocess och godkändes för intraokulär behandling. Ranibizumab följdes senare av en annan substans, aflibercept, som fick samma indikation. Priset för dessa två substanser var betydligt högre än för bevacizumab varför användning av den senare uppstod parallellt. Det förekommer nu en omfattande off label användning av intraokulärt administrerat bevacizumab på alla de indikationer som gäller för de två registrerade substanserna.

Syfte: Finns några kliniskt relevanta skillnader i effekt eller säkerhet mellan de tre vaskulära tillväxtfaktor-hämmarna bevacizumab, ranibizumab och aflibercept, vid användning som intraokulär behandling vid åldersrelaterad makuladegeneration (AMD), diabetesorsakat makulaödem (DME), retinalvensocklusion (RVO) eller choroidal neovaskularisering sekundärt till patologisk myopi (PM)?

Metod: Efter framtagning av relevant PICO genomfördes en systematisk litteratursökning fram till mars 2016 i Pubmed, Embase och Cochrane Library. En genomgång av referenslistor gjordes också. Efter en exklusionsprocess identifierades 13 RCT (19 publikationer, 9122 individer), 18 kohortstudier (>1.2 miljoner injektioner) och tre fallserier (n>16000 injektioner). Valda utfallsmått för effekt var synfunktion, livskvalitet och synskärpa. Största mängden data fanns för AMD, för jämförelsen bevacizumab och ranibizumab, med utfallsmåttet synskärpa (sju RCT, rapporterade i 10 publikationer, med 3235 patienter). För bevacizumab jämfört med aflibercept fann vi bara data gällande DME, även här med synskärpa som utfallsmått. Valda utfallsmått för säkerhet var mortalitet, kardiovaskulär mortalitet, hjärtinfarkt, stroke, endoftalmit och allvarliga ögonbiverkningar.

Resultat per utfallsmått:

Effekt

Synfunktion: Vi fann bara data gällande aflibercept jämfört med ranibizumab hos AMD patienter. Det finns liten eller ingen skillnad i effekten på synfunktion hos patienter med våt makuladegeneration (GRADE⊕⊕⊕⊕).

Livskvalitet: Detta utfallsmått rapporterades i en studie baserad på patienter med AMD, och bevacizumab jämfört med ranibizumab. Det kan föreligga liten eller ingen skillnad vad gäller effekten på livskvalitet i aktuell patientgrupp (GRADE ⊕⊕◯◯).

Synskärpa: Det finns troligen liten eller ingen skillnad i effekterna av bevacizumab jämfört med ranibizumab hos patienter med AMD eller DME (GRADE⊕⊕⊕◯), och det är osäkert huruvida det finns liten eller ingen skillnad hos patienter med grenvensocklusion eller patologisk myopi (GRADE⊕◯◯◯).

För bevacizumab jämfört med aflibercept respektive aflibercept jämfört med ranibizumab fann vi data för patienter med diabetisk makulopati i två studier. Resultaten skilde sig beroende på initial synskärpa. För bevacizumab jämfört med aflibercept sågs hos patienter med svag initial synskärpa en signifikant större förbättring med aflibercept (medelskillnad i ökning av antal bokstäver +6,5 [+2,9, +10,1], p<0,001. Hos patienter med bättre initial synskärpa fanns ingen statistiskt säkerställd effekt (p=0.69). I en subgrupp av patienter med dålig initial synskärpa orsakad av DME, har aflibercept troligen en större effekt än ranibizumab (GRADE⊕⊕⊕◯).

För aflibercept jämfört med ranibizumab och utfallsmåttet synskärpa finns liten eller ingen skillnad i effekten hos patienter med AMD (GRADE⊕⊕⊕⊕) och troligen ingen eller liten skillnad hos patienter med DME (GRADE⊕⊕⊕◯). För RVO och PM återfanns inga data gällande denna jämförelse.

Säkerhet
Utfallsmåtten för säkerhet var mortalitet, kardiovaskulär mortalitet, hjärtinfarkt, stroke, endoftalmit och övriga allvarliga ögonbiverkningar. Även här emanerade den största mängden data från patienter med AMD men det fanns också stora registerstudier baserade på blandade indikationer.

För bevacizumab jämfört med ranibizumab vid AMD finns det troligen liten eller ingen skillnad gällande risk för mortalitet, kardiovaskulär mortalitet, hjärtinfarkt eller stroke (GRADE⊕⊕⊕◯), medan det är osäkert huruvida det finns någon skillnad i risken för endoftalmit eller andra allvarliga ögonkomplikationer (GRADE ⊕◯◯◯). För patienter med DME kan det föreligga liten eller ingen skillnad i risken för mortalitet, kardiovaskulär mortalitet hjärtinfarkt eller stroke (GRADE ⊕⊕◯◯) och det är okänt om det finns någon skillnad i risk för endoftalmit (ej studerat). För diagnoserna RVO och PM är antalet studerade patienter för litet för att dra meningsfulla slutsatser (ej studerat). Vad gäller utfallsmåttet risk för endoftalmit fanns ett stort blandat material, sannolikt i huvudsak patienter med AMD, med en oddskvot av 1,03 [0,69 1,53], p=0,90. Det finns troligen liten eller ingen skillnad i risk för endoftalmit mellan bevacizumab och ranibizumab (GRADE⊕⊕⊕◯).

För bevacizumab jämfört med aflibercept återfanns bara data från DME-gruppen. Antalet händelser var genomgående lågt och inga signifikanta skillnader sågs för något av de valda utfallsmåtten. Det finns troligen liten eller ingen skillnad i risken för mortalitet, kardiovaskulär mortalitet, hjärtinfarkt, stroke, endoftalmit eller allvarliga ögonbiverkningar i DME gruppen GRADE⊕⊕⊕◯). Vad gäller endoftalmit var antalet händelser för lågt för att dra några slutsatser.

Säkerheten för aflibercept jämfört med ranibizumab utvärderades för AMD och DME patienter. I AMD materialet (två RCT och därtill en kohort för endoftalmit) fanns det inga skillnader i RCT-studierna för några av säkerhetsutfallen men det sågs en signifikant ökad risk för endoftalmit med aflibercept jämfört med ranibizumab i kohorten. Vid AMD finns troligen liten eller ingen skillnad vad gäller risk för mortalitet, kardiovaskulär mortalitet, hjärtinfarkt, stroke eller övriga allvarliga ögonbiverkningar GRADE⊕⊕⊕◯). Vad gäller risk för endoftalmit kan det finnas en liten eller ingen skillnad i risk mellan aflibercept och ranibizumab (GRADE⊕⊕◯◯). Vid DME kan det finnas ingen eller liten skillnad i risk för mortalitet, kardiovaskulär mortalitet, hjärtinfarkt, stroke eller övriga allvarliga ögonbiverkningar (GRADE⊕⊕◯◯), och det är okänt om det finns någon skillnad i risken för endoftalmit (inga data).

Sammanfattningsvis identifierade inte litteratursökningen några kliniskt relevanta skillnader, varken i effekt (mätt som synskärpa) eller säkerhet (avspeglat i risk för mortalitet, kardiovaskulär mortalitet, hjärtinfarkt, stroke, endoftalmit eller allvarliga ögonbiverkningar) mellan bevacizumab, ranibizumab eller aflibercept. Graden av säkerhet i slutsatsen varierar något med patientgrupp och utfallsmått och den säkraste slutsatsen finns för AMD och jämförelsen bevacizumab och ranibizumab (för majoriteten utfall GRADE⊕⊕⊕◯). Vad gäller säkerhetsrelaterade utfallsmått förelåg det starkaste underlaget (GRADE⊕⊕⊕◯) för avsaknad av skillnad vid jämförelsen bevacizumab med ranibizumab och indikationerna AMD och DME, och gällande utfallsmåtten mortalitet, hjärtinfarkt, stroke, och andra allvarliga ögonbiverkningar. För endoftalmit gäller detta vid AMD men underlaget är något svagare vid DME. Ett kvalitetsmässigt likartat underlag (GRADE⊕⊕⊕◯) finns vad gäller säkerhetsutfallen mortalitet, hjärtinfarkt, stroke, och övriga allvarliga ögonbiverkningar och för jämförelsen bevacizumab vs aflibercept hos patienter med AMD eller DMA. För övriga indikationer och utfall är evidensstyrkan begränsad eller otillräcklig och tolkbara data saknas i stort sett vad gäller indikationerna CVO och PM.

Sammanfattande tabell

Jämförelse	Utfall	AMD	DME	RVO	PM	Blandade diagnoser
	Effekt					
Bevacizumab-ranibizumab	Synfunktion					
	Livskvalitet	⊕⊕◯◯				
	Synskärpa	⊕⊕⊕◯	⊕⊕⊕◯	⊕◯◯◯	⊕◯◯◯	
Bevacizumab-aflibercept	Synfunktion					
	Livskvalitet					
	Synskärpa		⊕⊕⊕◯ **B<A**			
Aflibercept-ranibizumab	Synfunktion	⊕⊕⊕⊕				
	Livskvalitet					
	Synskärpa	⊕⊕⊕⊕	⊕⊕⊕◯ **A>R**			
	Säkerhet					
Bevacizumab-ranibizumab	Mortalitet	⊕⊕⊕◯	⊕⊕◯◯			
	Hjärtkärldöd	⊕⊕⊕◯	⊕⊕◯◯			
	Hjärtinfarkt	⊕⊕⊕◯	⊕⊕◯◯			
	Stroke	⊕⊕⊕◯	⊕⊕◯◯			
	Endoftalmit	⊕⊕◯◯	⊕◯◯◯			⊕⊕⊕◯
	Allvarlig ögonbiverkan	⊕⊕◯◯	⊕⊕◯◯	⊕◯◯◯		⊕◯◯◯
Bevacizumab-aflibercept	Mortalitet		⊕⊕◯◯			
	Hjärtkärldöd		⊕⊕◯◯			
	Hjärtinfarkt		⊕⊕◯◯			
	Stroke		⊕⊕◯◯			
	Endoftalmit					⊕⊕◯◯
	Allvarlig ögonbiverkan		⊕⊕⊕◯			
Aflibercept-ranibizumab	Mortalitet	⊕⊕⊕◯	⊕⊕◯◯			
	Hjärtkärldöd	⊕⊕⊕◯	⊕⊕◯◯			
	Hjärtinfarkt	⊕⊕⊕◯	⊕⊕◯◯			
	Stroke	⊕⊕⊕◯	⊕⊕◯◯ **A>R**			
	Endoftalmit	⊕⊕◯◯				⊕⊕◯◯
	Allvarlig ögonbiverkan	⊕⊕⊕◯	⊕⊕◯◯			

No clinically relevant difference
Superiority
Not studied

The above summaries were written by representatives from the HTA-centrum. The HTA-report was approved by the Regional board for quality assurance of activity-based HTA. The abstract is a concise summary of the results of the systematic review. The Swedish summary is a brief summary of the systematic review intended for decision makers, and is ended with a concluding summary.

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2. Summary of Findings

Efficacy and safety of intravitreal bevacizumab (B) or ranibizumab (R) injections in patients with age-related macular degeneration (AMD)

Outcomes	Study design Number of studies	Relative effect (95%CI)	Absolute effect	Certainty of evidence GRADE*
Efficacy				
Visual function	Not measured			
Quality of life	RCT, n=1 2 publications		EQ-5D, median (IQR) Baseline: B: 0.85 (0.73, 1.00) R: 0.81 (0.73, 1.00), n.s. One and two years (same values): B: 0.85 (0.73, 1.00) R: 0.85 (0.73 to 1.00) n.s.	Low ⊕⊕◯◯[1, 2]
Visual acuity	RCT, n=8 10 publications (absolute data given in three, mean differences with CIs in four)		Mean difference (95%CI) 0,30 (-2,94 to 2,34) -1,99 (-4,04 to 0,06 1,89 (-1,16 to 4,93) -0,50 (-3,9 to 2,9)	Moderate ⊕⊕⊕◯[3, 4]
Safety				
Mortality	RCT, n=6 9 publications Cohort 1	OR=1.13 (0.80, 1.60), p=0.49 OR=1.01 (0.91, 1.16), p=0.91	B: 71/1,528 R: 65/1,565 B: 1,324/38,718 R: 647/19,026	Moderate ⊕⊕⊕◯[3, 4, 5]
CVD mortality	RCT, n=5 8 publications	OR = 1.21 (0.64, 2.27), p=0.56	B: 21/1,374 R: 18/1,402	Moderate ⊕⊕⊕◯[3, 4, 5]
MI	RCT, n=6 9 publications Cohort, 1	OR = 0.80 (0.43, 1.49), p=0.48 OR = 1.09 (0.91, 1.31), p=0.34	B: 19/1,528 R: 25/1,565 B: 378/38,718 R: 170/19,026	Moderate ⊕⊕⊕◯[3, 4, 5]
Stroke	RCT, n=6 9 publications Cohort, 1	OR = 0.66 (0.34, 1.28), p=0.22 OR = 1.12 (0.98, 1.29), p=0.10	B: 15/1,528 R: 24/1,565 B: 659/38,718 R: 289/19,026	Moderate ⊕⊕⊕◯[3, 4, 5]
Endophthalmitis	RCT, n=6 9 publications	OR = 1.57 (0.53, 4.64), p=0.42	B: 8/1,528 R: 5/1,565	Low ⊕⊕◯◯[3, 4, 6]
Other serious ocular AE	RCT, n=5 7 publications	OR = 1.09 (0.24, 4.84), p=0.91	B: 19/1,502 R: 16/1,536	Low ⊕⊕◯◯[3, 4, 6]

AE = Adverse events, CVD = Cardiovascular death, MI = Myocardial infarction

[1] Imprecision (only one trial). Uncertainly regarding publication bias.

[2] Some uncertainty regarding directness (recruitment unclearly described).

[3] Some study limitations regarding randomisation and blinding.

[4] Serious indirectness (population and recruitment unclearly described)

[5] Indirectness in cohort study (registry data which possible socioeconomic intergroup differences).

[6] Imprecision (few events)

* Certainty of evidence

High certainty ⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty ⊕⊕⊕◯	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty ⊕⊕◯◯	Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty ⊕◯◯◯	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Efficacy and safety of intravitreal bevacizumab (B) or ranibizumab (R) injections in patients with diabetic macular edema (DME)

Outcomes	Study design Number of studies	Relative effect (95%CI)	Absolute effect	Certainty of evidence GRADE*
Efficacy				
Visual function	Not studied			
Quality of life	Not studied			
Visual acuity	RCT, n=2, 3publications Cohort, 1		Basal letter score <69:MD = -2.4, [-5.8, 1.0] p=0.18. Basal letter score 69-78: MD = -1.9 (-4.7 to 0.9) p=0.31	Moderate ⊕⊕⊕◯ [1, 2]
Safety				
Mortality	RCT, n=1 2 publications		B: 13/218 (6.0%) R: 11/218(5.2%), p=0.83	Low ⊕⊕◯◯ [1, 3]
CVD mortality	RCT, n=1 2 publications		B: 8/218 (3.7%) R: 9/218 (4.1%), p=1.00	Low ⊕⊕◯◯ [1, 3]
MI	RCT, n=1 2 publications		B: 3/218 (1.4%) R: 6/218 (2.8%), p=0.50	Low ⊕⊕◯◯ [1, 3]
Stroke	RCT, n=1 2 publications		B: 6/218 (2.8%) R: 11/218 (5.0%), p=0.32	Low ⊕⊕◯◯ [1, 3]
Endophthalmitis	RCT, n=1 2 publications 1 Cohort		B: 1/218 (0.5%) R: 0 /218 (0.0%), p=1.00 B: 0/40 (0.0%), R: 0/32 (0.0%),	Very low ⊕◯◯◯ [1, 4, 5]
Other serious ocular AE	RCT, n=2 3 publications 1 Cohort		B: 25/218 (11.5%) R: 16/218 (7.3%), p=0.19	Low ⊕⊕◯◯ [1, 4, 6]

AE = Adverse events, CVD = Cardiovascular death, MD= mean group difference; MI = Myocardial infarction
[1] Some uncertainty regarding directness (setting and/or recruitment unclearly described).
[2] Serious imprecision (only one sufficiently powered study).
[3] Very serious imprecision (only one study with few events).
[4] In cohort study, diabetic comorbidities skewed. No drop out analysis.
[5] Very serious imprecision (few events, studies under dimensioned for this outcome).
[6] Serious imprecision (few events).

Efficacy and safety of intravitreal bevacizumab (B) or ranibizumab (R) injections in patients with macular edema due to retinal vein occlusion (RVO)

Outcomes	Study design Number of studies	Relative effect (95%CI)	Absolute effect	Certainty of evidence GRADE*
Efficacy				
Visual function	Not studied			
Quality of life	Not studied			
Visual acuity	RCT, n=2 1 Cohort		B: +15.6±4.0 R: +18.1±4.5 p=0.37 B: +0.33±0.45, CI95%: -0.47 to -0.18) R: +0.34±0.33, CI95%: -0.45 to -0.23) p=0.38	Very low [1] ⊕◯◯◯
Safety				
Mortality	Not studied			
CVD mortality	Not studied			
MI	Not studied			
Stroke	Not studied			
Endophthalmitis	Not studied			
Other serious ocular AE	RCT, n=2 2 publications	OR=3.96 [0.76, 20.46], p=0.10	B: 7/38 R: 2/37 B: 0/49 R: 0/49	Very low [1] ⊕◯◯◯

AE = Adverse events, CVD = Cardiovascular death, MI = Myocardial infarction
[1] Open studies. High dropouts, or not specified, in cohort study allocation principle not defined

Efficacy and safety of intravitreal bevacizumab (B) or ranibizumab (R) injections in patients with choroidal neovascularisation in pathologic myopia (PM)

Outcomes	Study design Number of studies	Relative effect (95%CI)	Absolute effect	Certainty of evidence GRADE*
Efficacy				
Visual function	Not studied			
Quality of life	Not studied			
Visual acuity	RCT, n=1		Change in letter scores: B: 54±25 to 55±26 R: 45±22 to 58±21 p=0.78	Very low [1] ⊕◯◯◯
Safety				
Systemic: mortality, CVD mortality, MI, stroke	RCT, n=1 1 publication		No events of severe systemic side effects were recorded	No data
Local: Endophthalmitis	RCT, n=1 1 publication		No events of severe ocular side effects were recorded	No data
Other serious ocular AE	RCT, n=1 1 publication		No events of severe ocular side effects were recorded	No data

AE = Adverse events, CVD = Cardiovascular death, MI = Myocardial infarction
[1] Serious study limitations (Open study, gender heterogeneity), some uncertainty regarding directness (study population and recruitment not described), serious imprecision (underpowered study).

Efficacy and safety of intravitreal bevacizumab (B) or ranibizumab (R) injections in patient groups with mixed diagnoses

Outcomes	Study design, Number of studies	Relative effect (95%CI)	Absolute effect	Certainty of evidence GRADE*
Efficacy				
Visual function	Not studied			
Quality of life	Not studied			
Visual acuity	Not studied			
Safety				
Systemic: mortality, CVD mortality, MI, stroke	Cohort, n=3 3 publications	No events, except 2 MI	MI events B: 2/2,210 R: 0/1,458	Insufficient data
Local: Endophthalmitis	Cohort, n=13 13 publications (reported per injection)	OR=1.03 (0.69, 1.53), p= 0.90	B: 102/291,461 R: 136/378,060	Moderate [1] ⊕⊕⊕◯
Other serious ocular AE	Cohorts, n=4 4 publications (reported per injection)	OR= 1.37 (0.58, 3.37), p= 0.48	B: 209/18,896 R: 83/5,837	Low [2] ⊕⊕◯◯

AE = Adverse events, CVD = Cardiovascular death, MI = Myocardial infarction
[1] Upgraded for absence of significant difference in event rates in large population
[2] Neither up or downgraded

Efficacy and safety of intravitreal bevacizumab (B) or aflibercept (A) injections in patients with age related macular degeneration (AMD)

This group was not studied.

Efficacy and safety of intravitreal bevacizumab (B) or aflibercept (A) injections in patients with diabetic macular edema (DME)

Outcomes	Study design Number of studies	Relative effect (95%CI)	Absolute effect	Certainty of evidence GRADE*
Efficacy				
Visual function	Not studied			
Quality of life	Not studied			
Visual acuity	RCT, n=1 2 publications		Basal letter score < 69/100: MD: -4.7 (-0.5, -8.8), p=0.02 Basal letter score 69-78: MD: -1.1, (1.1 to -3.4), p=0.51	Moderate [1] ⊕⊕⊕◯
Safety				
Mortality	RCT, n=1 2 publications		B: 13/218(6.0%) R: 5/224(2.0%), p=0.06	Low [1,2] ⊕⊕◯◯
CVD mortality	RCT, n=1 2 publications		B: 8/218(3.7%) R: 3/224 (1.3%), p=0.14	Low [1,2] ⊕⊕◯◯
MI	RCT, n=1 2 publications		B: 3/218 (1.4%) R: 7/224(3.1%), p=0.34	Low [1,2] ⊕⊕◯◯
Stroke	RCT, n=1 2 publications		B: 6/218 (2.8%) R: 2/224(0.9%), p=0.17	Low [1,2] ⊕⊕◯◯
Endophthalmitis	RCT, n=1 2 publications		B: 1/218 (0.5%) R: 0/224 (0.0%), p=0.49	Insufficient data
Other serious ocular AE	RCT, n=1 2 publications		B: 25/218 (11.5%) A: 27/224 (12.1%), p=0.88	Moderate [1] ⊕⊕⊕◯

AE = Adverse events, CVD = Cardiovascular death, MI = Myocardial infarction

[1] Some uncertainty regarding directness (setting /recruitment unclearly described), serious imprecision (only one in sufficiently powered study).

[2] Combined with 1: Very serious imprecision (also including few events).

Efficacy and safety of intravitreal bevacizumab (B) or aflibercept (A) injections in patients with retinal vein occlusion (RVO)

This group was not studied

Efficacy and safety of intravitreal bevacizumab (B) or aflibercept (A) injections in patients with pathological myopia (PM)

This group was not studied

Efficacy and safety of intravitreal bevacizumab (B) or aflibercept (A) injections in patient groups with mixed diagnoses

Outcomes	Study design Number of studies	Relative effect (95%CI)	Absolute effect	Certainty of evidence GRADE*
Efficacy				
Visual function	Not studied			
Quality of life	Not studied			
Visual acuity	Not studied			
Safety				
Systemic : mortality, CVD mortality, MI, stroke	Not studied			
Local: Endophthalmitis	Cohort,n=3 3 publications	OR=0.33 [0.04, 2.88], p=0.32	B: 63/170,277 A: 14/40,564	Low [1] ⊕⊕◯◯
Other serious ocular events	Not studied			

AE = Adverse events, CVD = Cardiovascular death, MI = Myocardial infarction

[1] Some uncertainty regarding directness (setting /selection unclearly described), upgraded for absence of significant difference in event rates in large population.

Efficacy and safety of intravitreal aflibercept (A) versus ranibizumab (R) injections in patients with age related macular degeneration (AMD)

Outcomes	Study design, Number of studies	Relative effect (95%CI)	Absolute effect	Certainty of evidence GRADE*
Efficacy				
Visual function	RCT, n=2 2 publications		General vision mean difference, ±SD VIEW1 A: 10.1±19.0 R: 9.5±18.8 VIEW2 A: 9.1±17.0 R: 9.5±18.1	⊕⊕⊕⊕
Quality of life	Not studied			
Visual acuity	RCT, n=2 2 publications		VIEW 1: A: +6.9±13.4; R: +8.1±15.3 MD=-0.80 [-3.03, +1.43] VIEW 2: A: +9.7±14.1 R: +9.4±13.5 MD = -0.06 (-2.24, 2.12) Week 96 View 1 & 2 pooled change: A: +6.6 R: +7.9	⊕⊕⊕⊕
Safety				
Mortality	RCT n=2 (View 1 and 2, one publication)		A: 41/1,824 (2.2%) R: 11/595 (1.8%), p=0.63	⊕⊕⊕◯ [1]
CVD mortality	RCT n=2 (View 1 and 2, one publication)		A: 24/1,824 (1.3%) R: 3/595 (0.5%), p=0.12	⊕⊕⊕◯ [1]
MI	RCT n=2 (View 1 and 2, one publication)		A: 25/1,824 (1.4%) R: 12/595 (2.0%), p=0.25	⊕⊕⊕◯ [1]
Stroke	RCT n=2 (View 1 and 2, one publication)		A: 13/1,824(0.7%) R: 5/595 (0.8%), p=0.78	⊕⊕⊕◯ [1]
Endophthalmitis	RCT n=2 (View 1 and 2, one publication) Cohort 1		A: 5/1,824 (0.3%) R: 5/595 (0.8%), p=0.07 A: 189 (<0.1%) R: 162 (<0.1%), p<0.0001	⊕⊕◯◯ [1, 2]
Other serious ocular events	RCT n=2 (View 1 and 2, one publication)		A: 65/1,824 (3.6%) R: 26/595 (4.4%), p=0.38	⊕⊕⊕◯ [1]

AE = Adverse events, CVD = Cardiovascular death, MI = Myocardial infarction, 2q4 = 2.0 mg every four weeks, 0.5q4 = 0.5 mg every four weeks, 2q8 = 2 mg every 8 weeks

[1] Imprecision (few events)

[2] Publication bias likely (only one cohort study)

Efficacy and safety of intravitreal aflibercept (A) versus ranibizumab (R) injections in patients with diabetic macular edema (DME)

Outcomes	Study design Number of studies	Relative effect (95%CI)	Absolute effect	Certainty of evidence GRADE*
Efficacy				
Visual function	Not studied			
Quality of life	Not studied			
Visual acuity	RCT, n=1 2 publications		Basal letter score <69 MD: 2.3 (-1.1 to +5.6) p= 0.18 Basal letter score 69-78: MD: 0.7, (-2.9 to +1.5) p=0.51	Moderate [1] ⊕⊕⊕◯
Safety				
Mortality	RCT, n=1 2 publications		A: 5/224 (2.2%) R: 11/218 (5.0%) p=0.13	Low [1,2] ⊕⊕◯◯
CVD mortality	RCT, n=1 2 publications		A: 3/224 (1.3%) R: 9/218 (4.1%) p=0.08	Low [1,2] ⊕⊕◯◯
MI	RCT, n=1 2 publications		A: 7/224 (3.1%) R: 6/218 (2.8%) p=1.00	Low [1,2] ⊕⊕◯◯
Stroke	RCT, n=1 2 publications		A: 2 /224(0.9%) R: 11/218 (5.0%) p=0.01	Low [1,2] ⊕⊕◯◯
Endophthalmitis	RCT, n=1 2 publications		No events reported	No data
Other serious ocular AE	RCT, n=1 2 publications		A: 27/224(12.1%) B: 16/218 (7.3%) p=0.08	Low [1,2] ⊕⊕◯◯

AE = Adverse events, CVD = Cardiovascular death, MI = Myocardial infarction

[1] Some uncertainty regarding directness (setting /recruitment unclearly described), serious imprecision (only in one sufficiently powered study).

[2] Combined with 1: Very serious imprecision (also including few events).

Efficacy and safety of intravitreal bevacizumab (B) or aflibercept (A) injections in patients with retinal vein occlusion (RVO)

This group was not studied

Efficacy and safety of intravitreal aflibercept (A) versus ranibizumab (R) injections in patients with pathological myopia (PM)

This group was not studied

Efficacy and safety of intravitreal aflibercept (A) versus ranibizumab (R) injections in patient groups with mixed diagnoses

Outcomes	Study design Number of studies	Relative effect (95%CI)	Absolute effect	Certainty of evidence GRADE*
Efficacy				
Visual function	Not studied			
Quality of life	Not studied			
Visual acuity	Not studied			
Safety				
Systemic: mortality, CVD mortality, MI, stroke	Not studied			
Local: endophthalmitis	Cohort n= 3	OR=0.99 [0.57, 1.72], p=0.96	A: 14/40,564 R: 109/311,446	Low [1] ⊕⊕◯◯
Other serious ocular events	Not studied			

AE = Adverse events, CVD = Cardiovascular death, MI = Myocardial infarction

[1] Some uncertainty regarding directness (setting /selection unclearly described), upgraded for absence of significant difference in event rates in large population.

3. Abbreviations/Acronyms

Afli = aflibercept

AMD = age-related macular degeneration

Bev = bevacizumab

CVD = cardiovascular death

DME = diabetic macular oedema

MI = myocardial infarction

nAMD = neovascular AMD

OCT = optical coherence tomography

OR = odds ratio

PM = pathological myopia

PRN = pro re nata scheme, treat as needed

Ran = ranibizumab

RVO = retinal vein occlusion

VA = visual acuity

4. Background

Disease/disorder of interest and its degree of severity

Age-related macular degeneration (AMD) is a chronic disease and the leading cause of permanent visual handicap in a Western population. The macula is the central part of the retina where the cone photoreceptors are most tightly packed and the visual resolution is highest. In AMD, pathological changes in the macula disrupt the well-organized cone mosaic leading to image distortion and reduced resolution which usually results in severe deterioration of visual acuity. The majority of patients with AMD suffer loss of central vision which causes difficulty or inability to read text in books and newspapers or watch television but do not become blind. Failure to recognize faces is also a common symptom. Peripheral vision is usually preserved and patients with AMD often have enough visual function to maintain mobility, at least indoors. However, in severe cases of AMD with wide-spread destruction of the retina, functional blindness can occur.

AMD is commonly categorized in a “dry” and a “wet” form. In the dry form, which is the most common form of AMD, cell debris from the photoreceptor outer segments accumulates on the pigment epithelium separating the photoreceptor layer and the choroid. Consequently, the photoreceptor layer becomes disorganized and uneven causing distortion of the image projected onto the retina. Symptoms of AMD, both dry and wet, are therefore image distortion (metamorphopsia) and loss of visual acuity. Currently, there is no treatment for dry AMD.

Wet AMD, also called exudative or neovascular AMD (nAMD), refers to a condition in which the pigment epithelium is penetrated by newly formed vessels from the underlying choroid. The exact mechanism for the outgrowth of choroidal vessels into the retina is currently not known but a complex network of inflammatory mediators including Vascular Endothelial Growth Factor (VEGF) plays a central role in the pathogenesis and progression of nAMD and other diseases associated with ocular neovascularisation. Choroidal vessels are leaky and in the normal eye the pigment epithelium is the barrier preventing fluid from the choroid to reach the photoreceptor layer (the so-called blood-retina barrier). When choroidal vessels penetrate the pigment epithelium this barrier becomes impaired and fluid accumulates under the photoreceptors, causing macular edema and hypoxia. In addition, choroidal vessels bleed easily resulting in hemorrhages under and within the photoreceptor layer, thereby accelerating photoreceptor cell death. In contrast to dry AMD which normally is a very slow process, wet AMD can cause almost instantaneous visual loss when a hemorrhage disrupts the retinal architecture, resulting in irreversible damage of the retina and deterioration of visual acuity. Recent remarkable improvements in ophthalmic imaging techniques, especially in the form of Optical Coherence Tomography (OCT), have made it possible to detect and analyze also very subtle pathological changes in the living eye.

Although AMD is the most prevalent eye disease causing visual loss by newly formed choroidal vessels and/or macular edema, there are several other conditions with a similar pathogenesis. The vascular changes associated with Diabetes Mellitus may result in macular edema. Diabetic maculopathy (DME) is most commonly found in younger diabetic individuals and is the leading cause of blindness among people of working age and may affect persons with both type 1 or type 2 diabetes.

Central retinal vein occlusion (CRVO) is another condition almost always accompanied by macular edema and the subsequent disruption of the retina and deterioration of visual acuity. Branch retinal vein occlusion (BRVO) can cause both macular edema and proliferation of retinal vessels.
Other less common conditions causing proliferation of choroidal vessels include the severe myopia associated with a skin disease called pseudoxanthoma elasticum, but the list can be made much longer. Reduced visual acuity resulting from the aforementioned changes of the macula can indirectly also have negative health consequences, such as reduced life expectancy, depression and increased risk of trauma (Bandello, Lafuma & Berdeaux, 2007).

Prevalence and incidence

AMD is a disease of the elderly with age being the dominating risk factor. The prevalence of AMD is therefore usually stratified into age groups. A number of epidemiological studies, e.g. the Blue Mountain, Beaver Dam, Rotterdam Eye study and others (Joachim et al., 2015; Klein et al., 2014; Buitendijk et al., 2016) give an estimate of the number of patients potentially affected.

In a meta-analysis, the authors found an estimated prevalence of advanced AMD in the various epidemiological studies that ranged from 1-2 percent of people aged 65 till 69 up to 6–12 percent in white people aged over 80 years. Thus in the United States 1.75 million persons had advanced AMD in at least one eye and this number is expected to rise to 2.95 million in 2020. Incidence data has also been published in a number of studies and ranges from a 5 years incidence rate of 0,6% for persons aged 60-69 up to 5,4% for persons over 80 years with late AMD in the Blue Mountain study.

A recent publication deals specifically with the situation in Scandinavia and reports an estimated prevalence in 2012 of persons with late AMD older than 65 years of 5.2% or 187,000 persons. As the number of persons older than 65 is going to increase substantially, a total of 328,000 persons in Scandinavia will be affected by late AMD in 2040, assuming a constant prevalence rate (Lindekleiv & Erke, 2013). Relative numbers for Sweden did not differ from the other Scandinavian countries. The prevalence of AMD in Sweden has recently been estimated to be approximately 100,000 with a yearly incidence rate of 5000 (Kvanta & Lanner, 2016).

The prevalence of Diabetic macular edema (DME) in the diabetic population is approximately 5%, with large variations between settings (Lee, Wong & Sabanayagam, 2015). The 15 year cumulative incidence of branch and central retinal vein occlusion was reported to be 1.8% and 0.5% respectively (Klein et al., 2008). Pathological myopia, finally, has been reported to affect up to 3% of the population (Wong et al., 2014), a substantial proportion of whom develop choroidal neovascularization.

Present treatment

Currently, there is no treatment for dry AMD.
For wet AMD and other diseases causing choroidal or retinal neovascularization and/or macular edema, several treatment options exist. Laser treatment either as a coagulation of choroidal vessels or photodynamic therapy plays a minor role in management of AMD due to side effects like decreased visual acuity, scarring and high recurrence rates. Today the vast majority of patients are treated with intravitreal injections of an anti-VEGF substance, the only therapy that can not only stabilize but also improve visual function. At present, two substances are registered for ophthalmological indications (AMD, DME, RVO and PM); ranibizumab (Lucentis) and aflibercept (Eylea), while a third substance, bevacizumab (Avastin), registered for several malignant conditions, is used off label on ophthalmological indications.

Dosage

A patient eligible for treatment receives 3 initial intravitreal injections of the chosen drug with 4-week intervals. Thereafter, usually 4 weeks after the last injection the need for further treatment and/or follow up is assessed. Treatment is rarely discontinued and the average number of injections during the first, second and third year of treatment is approximately 6-9, 4-6 and 3-4 respectively, depending on the preferred management plan. The number of injections actually administered varies greatly, since the increasing number of patients requiring frequent follow-up visits puts a heavy burden on the health care system that may lead to a significant delay in “actual practice”.
A problematic aspect of the treatment of choroidal or retinal neovascularization and/or macular edema is that current knowledge about long term results duration is scanty or lacking.
Seven year follow up data of patients enrolled for the registration studies showed that the average number of injections 5-7 years after enrollment was still 6.8 injections over the three-year period. It may well be that for some patients, if not all, life-long intravitreal injections are needed.

One advantage of bevacizumab over ranibizumab is its much lower price. Aflibercept is claimed to have a similar or better effect than ranibizumab and to be effective with less frequent injections, but the evidence for this claim is relatively weak. A common feature for all three substances is that to reach sufficient concentration in the back of the eye, they have to be administered by intravitreal injection, which generates a basal substance-independent cost related to the setting required for performing the intravitreal injection.

The normal pathway through the health care system and current waiting time for medical assessment /treatment

Patients experiencing metamorphopsia (disturbed grid vision) or a decrease in visual acuity (mainly while reading) usually seek a general practitioner, optician or an ophthalmologist. In case of suspected wet AMD, patients are referred to the local hospital for further diagnosis and treatment. In the eye clinic, further examinations are performed including fluorescein and indocyanin green angiography and OCT. If treatable macular changes are identified, intravitreal injections are initiated with the drug of choice. Patients are allocated to a treatment plan, either on a "control and treat if necessary" scheme (pro re nata scheme; PRN) or a "treat and extend" scheme where patients get an injection with each visit but intervals between visits are extended according to a fixed schedule. If active nAMD causes a deterioration of visual acuity or retinal morphology despite regular intravitreal injections, the drug used for injection may be changed. Nevertheless, a substantial number of patients are in need of frequent and regular intravitreal injections because treatment is not curative but symptomatic. If visual acuity drops under a certain limit, injections are discontinued since the patient no longer experiences benefit from further injections. In those cases, patients are exempted from the treatment plan.

The time from the first symptoms to the first assessment by an ophthalmologist is highly variable. Ideally, the time from the initial referral to the start of treatment should be as short as possible, and at least not more than 4 weeks. In cases with rapidly declining vision, the waiting time for treatment should be much shorter.

Number of patients per year who undergo the current treatment regimen

Approximately 50,000 intravitreal injections of anti-VEGF are given yearly in Sweden (Kvanta & Lanner, 2016). Based on data from the four treatment centers in the Västra Götaland Region (VGR), an estimated 12,000 injections yearly are given in VGR. Currently, the most commonly used anti-VEGF substances for intraocular use in Sweden are ranibizumab and aflibercept. Tandvårds- och Läkemedelsförmånsverket has compared treatment costs for the two registered drugs (Tandvårds- och Läkemedelsförmånsverket, 2013). Drug cost per injection was about 9,000 SEK for either drug (down to approximately 6,200 SEK with discount in 2015). Other expenses related to the intraocular administration procedure as such added about 5,000 SEK to the total treatment cost. The drug cost for a vial of bevacizumab is about 3,300 SEK and this amount can theoretically be used for 30 injections, i.e. 110 SEK/injection. The cost for preparing bevacizumab must be added to this figure but should not exceed approximately 200 SEK.

Current recommendations from medical societies or health authorities

Ranibizumab and aflibercept are **on label** anti-VEGF treatment options for AMD, DME, RVO and PM, but for reasons related to pricing, bevacizumab has been promoted for off label use by some regions. The use of bevacizumab for intra-ocular indications puts new focus on the debate about off label use of medicinal products (Läkemedelsverket, 2016). Bevacizumab is nevertheless used as first line intraocular anti-VEGF treatment in many parts of Sweden and also in the other Nordic countries.

5. Health Technology at issue: Effects and side effects of intraocular injections of anti-VGEF compounds

Anti-VEGF agents

The introduction of anti-VEGF substances has revolutionized the treatment of choroidal and retinal neovascularization and macular edema during the last decade. The mechanism of action is inhibition of growth of pathological choroidal vessels in the retina and prevention of further destruction of the photoreceptor layer. Furthermore, they may improve vision by reducing the macular edema that frequently accompanies choroidal neovascularization. All three substances bind VEGF, thereby blocking its binding to the VEGF receptor and subsequent receptor-mediated signaling. Bevacizumab consists of the full length anti-VEGF antibody while ranibizumab consists of the antigen binding Fab-fragments (Ziemssen et al., 2016). Aflibercept is a fusion protein with the VEGF-binding portions of the VEGF receptors fused to a portion (the Fc-fragment) of human IgG (Hassan et al., 2016).

The most feared local complication associated with anti-VEGF treatment is infection in the eye, endophthalmitis, caused by the intravitreal injection. It has been argued that the risk for endophthalmitis might be higher after injection of bevacizumab, based on the fact that the syringes in this case must be prepared and handled by the local clinic or pharmacy. In contrast, ranibizumab and aflibercept are distributed in sterile vials for single use. International studies of complications to anti-VEGF treatment are, however, difficult to extrapolate to Swedish conditions due to local differences in injection techniques, facilities etc. For example, some centers perform the injections in an operating theatre under perfectly sterile conditions, while others are administered in a normal out-patient examination room.

6. Objective

Are there any clinically relevant differences in efficacy or safety of the three anti-VGEF compounds bevacizumab, ranibizumab and aflibercept, when used for treatment of age-related macular degeneration, diabetic macular edema, central vein occlusion or choroidal neovascularization due to pathologic myopia?

PICO P= Patients, I= Intervention, C= Comparison, O=Outcome

P	Adults with any of the following disorders: - Impaired vision due to neovascular (wet) age-related macular degeneration (nAMD); - Impaired vision due to diabetic macular edema (DME) - Impaired vision due to macular edema secondary to retinal vein occlusion (central or branch vein) (RVO) - Impaired vision due to choroidal neovascularization secondary to pathological myopia (PM) - Impaired vision due to nAMD or DME or RVO or PM ("mixed diagnoses")
I & C	Intraocular treatment with : I1. bevacizumab (Avastin) C1 ranizumab (Lucentis) I2. bevacizumab (Avastin) C2 aflibercept (Eylea) I3. aflibercept (Eylea) C3 ranizumab (Lucentis)
O	Efficacy outcomes: Critical for decision making: - Visual function Important for decision making: - Visual acuity measured with validated scales[1] - Quality of life - Cost effectiveness (comments only, evidence not graded) Side effects: Critical for decision making - Total mortality - Cardiovascular disease mortality - Myocardial infarction - Stroke - Endophthalmitis - Other serious ocular events Less important for decision making - Other complications

[1]Comment regarding measurement and interpretation of the outcome visual acuity:

- In Sweden it is customary to use a decimal scale to measure visual acuity. Visual acuity is then defined as 1/MAR where MAR stands for minimal angle of resolution, i.e. the smallest angle between two points that could be resolved by the eye. For a young person with very good vision this angle could be as small as 0.5 minutes of arc (1 minute or arc = 1/60 degree). This person's eye therefore has a decimal visual acuity of 1/0.5=2.0. The modern visual acuity charts used in Sweden have a logarithmic scaling. The letters on the rows of the acuity chart represent visual acuities of 0.1, 0.13, 0.16, 0.2, 0.25, 0.3, 0.4, 0.5, 0.65, 0.8, 1.0, 1.3, 1.6, and 2.0. The difference between each row is approximately 1 decibel (dB) or $10*\log_{10}$ (rad x/rad x-1).
- In scientific work, on the other hand, instead of using the reciprocal (visual acuity), MAR is measured and converted to its logarithm logMAR. This way of defining visual acuity has a more solid base in visual physiology and the values are much easier to deal with statistically. With this scale, decimal visual acuity 1.0 corresponds to 0.0 ($\log_{10}$ (1/1)). Decimal acuity 0.1 corresponds to 1 ($\log_{10}$ (1/0.1)). Decimal acuities higher than 1.0 become negative, e.g. decimal acuity 1.5 corresponds to -0.176 ($\log_{10}$ (1/1.5)).
- The most commonly used chart in scientific work is called the ETDRS chart (introduced in the Early Treatment Diabetic Retinopathy Study). It has 5 letters in each row and the scaling between successive rows is 1 dB. If a treatment is said to improve visual acuity by 5 letters, acuity has therefore improved by one line or 1dB. For example, if an eye started with decimal visual acuity of 0.1 and gained 5 letters it has improved to 0.13 after treatment. If another eye started with decimal visual acuity 0.4 and improved 5 letters it has improved 1 line to 0.5 after treatment. Although physiologically equivalent, these two treatment results may have dramatically different implications for the patient. An improvement from 0.1 to 0.13 is hardly noticeable for many persons while an improvement from 0.4 to 0.5 may allow a person to drive a car.
- To convert between logMAR and decimal visual acuity, use the following equation:
visual acuity $=1/(10^{logMAR})$. And for the opposite logMAR= $\log_{10}$ (1/visual acuity).

7. Methods

Systematic literature search (Appendix 1)

During March 2016 two authors (TS, IS) performed systematic searches in PubMed, Medline, Embase and the Cochrane Library. The websites of SBU and Kunnskapssenteret together with reference lists of relevant articles were also searched for additional references. Search strategies, eligibility criteria and a graphic presentation of the selection process are presented in Appendix 1. These authors conducted the literature searches and selected studies. Together with four other reviewers they independently of one another assessed the obtained abstracts and made a first selection of full-text articles for inclusion or exclusion. Any disagreements were resolved in consensus. The remaining articles were sent to all the participants of the project group. All authors read the articles independently of one another and it was finally decided in a consensus meeting which articles should be included in the assessment.

Critical appraisal and certainty of evidence

The included studies, their design and patient characteristics are presented in Appendix 2 a (effects and side effects) and 2b (cost-effectiveness). The excluded studies and the reasons for exclusion are presented in Appendix 3. The included studies have been critically appraised using checklists for assessment of RCTs or cohort studies, modified from SBU by HTA-centrum. The results and the assessed quality of each article have been summarised per outcome in Appendices 4.
Data was extracted by at least two authors independently of each other. Whenever possible and relevant, data was pooled in meta-analyses using RevMan 5.3 and presented as forest plots. Summary result per outcome and the associated certainty of evidence is presented in Summary-of-findings tables. The certainty of evidence was defined according to the GRADE system (Atkins et al., 2004; GRADE Working Group).

High certainty of evidence = (GRADE⊕⊕⊕⊕)
Further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty of evidence = (GRADE⊕⊕⊕◯)
Further research is likely to have an important impact on our confidence in the estimate and may change the estimate.
Low certainty of evidence = (GRADE ⊕⊕◯◯)
Further research is very likely to have an important impact on our confidence in the estimate and is likely to change the estimate.
Very low certainty of evidence = (GRADE ⊕◯◯◯)
Any estimate of effect is very uncertain.

Ongoing research

A search in Clinicaltrials.gov (2016-12-08) was conducted, using the search terms (Aflibercept OR Bevacizumab OR Ranibizumab OR eylea OR lucentis OR avastin) AND ((Polypoidal choroidal vasculopathy or Polypoidal choroidal vasculopathies) OR (Choroidal Neovascularization or Choroid Neovascularization or Choroidal Neovascularizations or Choroid Neovascularizations) OR (Retinal vein occlusion or Retinal vein occlusions or retinal venous occlusion or retinal venous occlusions or retinal vein thrombosis or retinal vein thromboses or RVO or BRVO or CRVO) OR (Diabetic macular edema OR diabetic macular oedema) OR (age-related macula degeneration OR age-related macular degeneration OR age-related macula degenerations OR age-related macular degenerations OR age-related maculopathy OR age-related maculopathies)).

8. Results

Systematic literature search (Appendix 1)

The literature search identified 4,639 articles after removal of duplicates. After reading the abstracts 4,435 articles were excluded. The remaining 204 articles were sent to all participants of the project group, and 51 articles (13 RCT (19 publications), 18 cohort studies, three case series and 11 cost effectiveness studies) were finally included in the assessment (Appendix 2). In addition, 27 systematic reviews (SR) were commented upon.

The literature searches described above were updated in January 2017, resulting in another 671 references. These are not included in the final assessment, but relevant articles are commented on in the Discussion, section 14.

The characteristics of the identified literature is summarized in Table 1. The most studied comparison was bevacizumab vs ranibizumab, in patients with AMD and with the outcomes visual acuity and adverse events. For the latter outcome, there were also large cohorts based on registry studies in mixed patient groups, presumably mainly patients with AMD.

Table 1. Studied drug comparisons and outcomes (number of studies) across patient groups

Studied Drugs	Studied patient groups				
	AMD	**DME**	**PM**	**RVO**	**Mixed**
Bevacizumab vs. Ranibizumab	VA (8 RCT; 0 CT) HRQoL (1 RCT; 0 CT) AE (6 RCT; 2 CT)	VA (2 RCT; 1 CT) AE (2 RCT; 1 CT)	VA (1 RCT; 0 CT) AE (1 RCT; 0 CT)	VA (2 RCT; 1 CT) AE (2 RCT; 0 CT)	AE (0 RCT; 13 CT)
Bevacizumab vs. Aflibercept	VA (1 RCT; 0 CT) AE (1 RCT; 0 CT)				AE (0 RCT; 3 CT)
Aflibercept vs. Ranibizumab	VA (2 RCT; 0 CT) VF (2 RCT; 0 CT) AE (1 RCT; 3 CT)	VA (1 RCT; 0 CT) AE (1 RCT; 0 CT)			AE (0 RCT; 3 CT)

AMD = age-related macular degeneration, CT = Controlled trial (cohort study), DME =, diabetic macular edema HRQoL = health-related quality of life, PM = pathological myopia, RCT = randomized controlled trial, RVO = retinal vein occlusion, VA = Visual acuity.

General comment regarding presentation of results:
The identified body of literature was large, consisting of totally 19 publications with RCT data (9,122 individuals), 18 cohort studies (n>1.2 M injections, mainly safety data) and 3 case series (n>16,000 injections, safety data only). Among the RCTs, outcome data for the same trial was often reported at different follow up times (e.g. one and two year data) in separate publications.

To present the results in a structured way, we used an indexing system with four positions:

- First position indicates whether efficacy or side effect data
- Second position indicates treatment comparison
- Third position indicates disease group
- Fourth position indicates outcome.

For safety data, the main body of side effect data consists of registry studies where the exact indication for intraocular treatment is not clearly stated. The majority of injections was in most cases AMD but due to the lack of information regarding the other less prevalent indications, safety data has been pooled and presented under the heading “mixed cases”.

Indexing system of the Results section

Table 2: Indexing system of the Results section

In view of the complexity of the material, the results are presented according to the system shown in Table 2. Outcome group (efficacy/safety) is indicated by first position (1./2.), comparison (bevacizumab vs ranibizumab, bevacizumab vs aflibercept and aflibercept vs ranibizumab) is indicated by second position (1.1/1.2./1.3.), patient group (AMD/DME/RVO/PM/mixed) by third position (1.1.1./1.1.2/1.1.3/1.1.4/1.1.5 etc) and outcome by fourth position (1.1.1.1/1.1.1.2. etc).

Comparison	Outcome	AMD	DME	RVO	PM	Mixed diagnoses
	Efficacy					
Bevacizumab-ranibizumab	VF	**1.1.1.1**	**1.1.2.1**	**1.1.3.1**	**1.1.4.1**	**1.1.5.1**
	QoL	**1.1.1.2**	**1.1.2.2**	**1.1.3.2**	**1.1.4.2**	**1.1.5.2**
	VA	**1.1.1.3**	**1.1.2.3**	**1.1.3.3**	**1.1.4.3**	**1.1.5.3**
Bevacizumab-aflibercept	VF	**1.2.1.1**	**1.2.2.1**	**1.2.3.1**	**1.2.4.1**	**1.2.5.1**
	QoL	**1.2.1.2**	**1.2.2.2**	**1.2.3.2**	**1.2.4.2**	**1.2.5.2**
	VA	**1.2.1.3**	**1.2.2.3**	**1.2.3.3**	**1.2.4.3**	**1.2.5.3**
Aflibercept-ranibizumab	**VF**	**1.3.1.1**	**1.3.2.1**	**1.3.3.1**	**1.3.4.1**	**1.3.5.1**
	QoL	**1.3.1.2**	**1.3.2.2**	**1.3.3.2**	**1.3.4.2**	**1.3.5.2**
	VA	**1.3.1.3**	**1.3.2.3**	**1.3.3.3**	**1.3.4.3**	**1.3.5.3**
	Safety					
Bevacizumab-ranibizumab	Mortality	**2.1.1.1**	**2.1.2.1**	**2.1.3.1**	**2.1.4.1**	**2.1.5.1**
	CVD mortality	**2.1.1.2**	**2.1.2.2**	**2.1.3.2**	**2.1.4.2**	**2.1.5.2**
	Myocardial infarction	**2.1.1.3**	**2.1.2.3**	**2.1.3.3**	**2.1.4.3**	**2.1.5.3**
	Stroke	**2.1.1.4**	**2.1.2.4**	**2.1.3.4**	**2.1.4.4**	**2.1.5.4**
	Endophthalmitis	**2.1.1.5**	**2.1.2.5**	**2.1.3.5**	**2.1.4.5**	**2.1.5.5**
	Other serious ocular events	**2.1.1.6**	**2.1.2.6**	**2.1.3.6**	**2.1.4.6**	**2.1.5.6**
Bevacizumab-aflibercept	Mortality	**2.2.1.1**	**2.2.2.1**	**2.2.3.1**	**2.2.4.1**	**2.2.5.1**
	CVD mortality	**2.2.1.2**	**2.2.2.2**	**2.2.3.2**	**2.2.4.2**	**2.2.5.2**
	Myocardial infarction	**2.2.1.3**	**2.2.2.3**	**2.2.3.3**	**2.2.4.3**	**2.2.5.3**
	Stroke	**2.2.1.4**	**2.2.2.4**	**2.2.3.4**	**2.2.4.4**	**2.2.5.4**
	Endophthalmitis	**2.2.1.5**	**2.2.2.5**	**2.2.3.5**	**2.2.4.5**	**2.2.5.5**
	Other serious ocular events	**2.2.1.6**	**2.2.2.6**	**2.2.3.6**	**2.2.4.6**	**2.2.5.6**
Aflibercept-ranibizumab	Mortality	**2.3.1.1**	**2.3.2.1**	**2.3.3.1**	**2.3.4.1**	**2.3.5.1**
	CVD mortality	**2.3.1.2**	**2.3.2.2**	**2.3.3.2**	**2.3.4.2**	**2.3.5.2**
	Myocardial infarction	**2.3.1.3**	**2.3.2.3**	**2.3.3.3**	**2.3.4.3**	**2.3.5.3**
	Stroke	**2.3.1.4**	**2.3.2.4**	**2.3.3.4**	**2.3.4.4**	**2.3.5.4**
	Endophthalmitis	**2.3.1.5**	**2.3.2.5**	**2.3.3.5**	**2.3.4.5**	**2.3.5.5**
	Other serious ocular events	**2.3.1.6**	**2.3.2.6**	**2.3.3.6**	**2.3.4.6**	**2.3.5.6**

FV = Visual function, QoL = Quality of life, VA = Visual acuity, CVD = Cardiovascular death, AMD = Age related macular degeneration, DME = Diabetic mocular adema, RVO = Retinal vein acklusion, PM = Pathological myopia.

Results per comparison, study type, patient group and outcome

1. Efficacy

The efficacy data are summarized in appendices 4.1-4.6

1.1. Comparison bevacizumab versus ranibizumab

1.1.1 Age-related macular degeneration (AMD)

1.1.1.1. Visual function
The outcome was not studied.

1.1.1.2. Quality of life (important for decision-making)
One study reported data on this outcome. The standardized instrument for measuring generic health status, EuroQol five dimensions questionnaire (EQ-5D), was used. At baseline the bevacizumab group had mean (IQR) 0.85 (0.73, 1.00) and the ranibizumab group had 0.81 (0.73, 1.00), n.s. At both one year and two year´s evaluation both bevacizumab and ranibizumab groups had 0.85 (0.73, 1.00).
Conclusion: Intravitreal bevacizumab compared with ranibizumab injections may result in little or no difference in quality of life in patients with age-related macular degeneration (AMD). Low certainty of evidence (GRADE⊕⊕◯◯).

1.1.1.3 Visual acuity (important for decision-making)
The systematic search identified eight RCTs (10 publications) but no cohort studies. Three of the RCT´s (published in: Berg *et al*., 2015, 2016; Chakravarthy *et al*., 2012, 2013; Martin *et al*., 2011, 2012) reported outcome data at different follow up times, after 1 and 2 years. Absolute changes in visual acuity enabling calculation of mean group differences was reported in three studies and similar data (mean difference with confidence interval) was presented in one additional study. The mean group difference (bevacizumab effect minus ranibizumab effect, 1 year data) in the entire available pooled material (4 studies, 2,139 patients) was – 0.23 (Table 3) (range -1.99 to 1.89 letters). The numeric magnitude of group difference was small and in none of the studies was there a significant treatment dependent difference.
Conclusion: There is probably little or no difference in the effect of bevacizumab versus ranibizumab with regard to the outcome improvement in visual acuity. Moderate certainty of evidence (GRADE ⊕⊕⊕◯).

Table 3 Mean difference each after one year in response to bevacizumab and ranibizumab in patients with AMD

Study	Mean difference[1]	lower CI	upper CI	n
Berg 2015	-0,30	-2,94	2,34	441
Chakravarthy 2012	-1,99	-4,04	0,06	610
Kodjikian 2013	1,89	-1,16	4,93	501
Martin 2011	-0,50	-3,9	2,9	587

[1] Difference in magnitude of response in bevacizumab and ranibizumab groups after one year. A positive mean difference indicates a numerically larger (but still in these cases non-significant) effect in the bevacizumab group.

1.1.2 Diabetic macular edema (DME)

1.1.2.1. Visual function and 1.1.2.2. Quality of life (important for decision-making)
The outcomes were not studied.

1.1.2.3. Visual acuity (important for decision-making)

The outcome visual acuity was studied in twoRCTs (three publications). The second RCT was a small study of low quality due to open design, exclusion of patients with side effects and poor precision. None of the studies demonstrated any significant differences between bevacizumab and ranibizumab for DME. Mean difference at two years, in the VA response in the larger RCT was: -2.4, [-5.8, 1.0] (p=0.18) for those with initial basal letter score <69, and MD = -1.9 [-4.7, 0.9] (p=0.31) for those with basal letter score 69-78.
Conclusion: There is probably little or no difference in the effect of bevacizumab and ranibizumab on visual acuity in the DME group. Moderate certainty of evidence (GRADE ⊕⊕⊕◯).

1.1.3. Retinal vein occlusion (RVO)

1.1.3.1. Visual function and 1.1.3.2. Quality of life (important for decision-making)

The outcomes were not studied.

1.1.3.3 Visual acuity (important for decision-making)

The outcome visual acuity for patients with retinal vein occlusion (RVO) was studied in two RCTs (Narayanan, 2015; Rajagopal, 2015) and one cohort study (Yuan, 2014). No significant differences in response between groups were seen (p=0.38 and 0.37 respectively). The quality of the two RCTs was low due to problems with directness (study population and recruitment not described), study design (open studies) and precision.
Conclusion: It is uncertain whether there is little or no difference in the effect of bevacizumab and ranibizumab on visual acuity in RVO patients. Very low certainty of evidence (GRADE ⊕◯◯◯).

1.1.4. Pathologic Myopia (PM)

1.1.4.1. Visual function and 1.1.4.2. Quality of Life (important for decision-making)

The outcomes were not studied.

1.1.4.3. Visual acuity (important for decision-making)

The outcome visual acuity for the rare diagnosis choroidal neovasculazation due to pathologic myopia (PM) was studied in one RCT (Pece, 2015). The study was considered to be of low quality due to baseline differences between groups, an open study design and a low precision. There was no consistent effect in BCVA in the bevacizumab group (54.1 to 54.9 letters) while in the ranibizumab group, BCVA increased from 45.5± 22 to 58.3± 21.2. However, the final BCVA was almost identical in the two groups.
Conclusion: It is uncertain whether there is any difference in the effect of bevacizumab and ranibizumab on visual acuity. Very low certainty of evidence (GRADE ⊕◯◯◯).

1.1.5. Mixed diagnoses

No data was found.

1.2 Comparison bevacizumab versus aflibercept

Outcome data for this comparison was presented in only one RCT, reported in two articles (Wells 2015, 2016), in patients with DME, and with the outcome **Visual acuity (1.2.2.3)**.

1.2.2 Diabetic macular edema (DME)

1.2.2.3 Visual acuity (1.2.2.3)

For patients with a basal letter score of <69, the response in the bevacizumab group was significantly larger than in the aflibercept group, mean difference: -4.7 (-0.5 to -8.8), p=0.02.

However, in patients with somewhat better vision (basal letter score 78-69), the difference was not statistically significant, MD: -1.1, [1.1, -3.4], p=0.51.
Conclusion: In a subgroup of patients with poor baseline vision, aflibercept probably has a larger effect than bevacizumab on VA. Moderate certainty of evidence (GRADE⊕⊕⊕◯).
In patients with somewhat better vision there is probably little or no difference in VA change between aflibercept and bevacizumab. Moderate certainty of evidence (GRADE⊕⊕⊕◯).

1.3 Comparison aflibercept versus ranibizumab

Data for this comparison was presented in two RCTs (four publications) but not in any cohort studies. The two RCTs included patients with AMD with outcomes visual function (**1.3.1.1**) and visual acuity (**1.3.1.3**) as well as DME patients with the outcome visual acuity (**1.3.2.3**). For the remaining efficacy outcomes and patient groups, no data was found.

1.3.1. Age-related macular degeneration (AMD)

1.3.1.1. Visual function (critical for decision-making)

The outcome visual function was evaluated in two patient materials, that were pooled together and reported in two different publications (Yuzawa, 2015; Heier, 2012), i.e. VIEW 1 (North America) and VIEW 2 (outside North America). The main methodological difference between VIEW 1 and VIEW 2 was that visual function (VF) data was collected by telephone in VIEW 1 and face to face in VIEW 2.

Visual function was measured by questionnaire (NEI VFQ-25). In the study by Yuzawa et al, no difference between aflibercept and ranibizumab was detected. In the study by Heier et al, the primary endpoint was defined as the proportion of patients maintaining vision (losing <15 ETDRS letters). Three different dosing regimens for aflibercept were tested; 2q4 (2.0 mg every four weeks), 0.5q4 (0.5 mg every four weeks) and 2q8 (2 mg every 8 weeks). Only one dose was used for ranibizumab; 0.5q4 (0.5 mg every 4 weeks). No difference was detected for any of the dosing regimens between aflibercept and ranibizumab.
Conclusion: There is little or no difference in effect on VF between aflibercept and ranibizumab in patients with AMD. High certainty of evidence (GRADE ⊕⊕⊕⊕).

1.3.1.2. Quality of life

The outcome was not studied.

1.3.1.3. Visual acuity (important for decision making)

In the study by Heier (2012), one year data was presented. No significant difference between the two treatments was reported. VIEW 1: aflibercept +6.9±13.4 (0.5q4) letters; ranibizumab: +8.1±15.3, CI for difference - 0.80 (-3.03 to +1.43), not significant. VIEW 2: aflibercept +9.7±14.1 (0.5q4) letters; ranibizumab: +9.4±13.5, CI for difference - 0.06 (-2.24 to +2.12), not significant.

In the study by Schmidt Erfurdt (2014), two year data from the same patient materials was presented. At week 96 the mean BCVA change for VIEW 1 and 2 pooled was for aflibercept +6.6 letters (CI not stated) and for ranibizumab +7.9 letters (CI not stated). No significance testing was reported.
Conclusion: There is little or no difference in effect on VA between aflibercept and ranibizumab in patients with AMD. High certainty of evidence (GRADE ⊕⊕⊕⊕).

1.3.2 Diabetic macular edema (DME)

1.3.2.1 Visual function and 1.3.2.2. Quality of life (important for decision making)

No data was identified.

1.3.2.3. Visual acuity (important for decision-making)

The comparison was done in 102+101 patients (Wells, 2015, 2016). The results differed depending on base line status. In those with basal letter score < 69, the effect in the aflibercept group was +18.1 ±13.8 and in the ranibizumab group +16.1 ± 12.1. Mean difference: 2.3 (-1.1 to +5.6), p= 0.18. In those with letter score 69-78, there was likewise no significant difference, MD: 0.7, (-2.9 to +1.5) p=0.51.
Conclusion: There is probably little or no difference in the effect of aflibercept and ranibizumab on visual acuity. Moderate certainty of evidence (GRADE⊕⊕⊕◯).

1.3.3. Retinal vein occlusion (RVO)

No data was found.

1.3.4. Pathological myopia (PM)

No data was found.

1.3.5. Mixed diagnoses

No data was found.

2. Safety

The safety data are summarized in appendices 4.7-4.9

2.1. Comparison bevacizumab versus ranibizumab

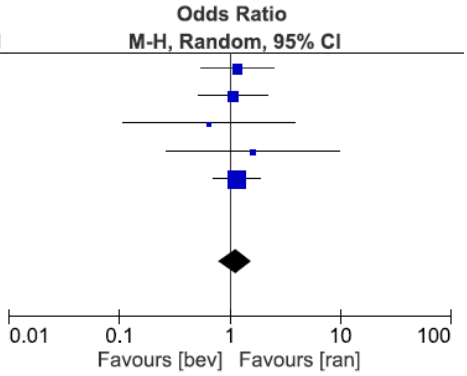
2.1.1. Age-related macular degeneration

2.1.1.1. Mortality

Mortality was reported in six RCTs (nine publications), and one large cohort (Curtis, 2010). In the pooled RCT-material, OR for mortality was 1.13 [0.80, 1.60], p=0.49.

Study or Subgroup	Bev Events	Bev Total	Ran Events	Ran Total	Weight	Odds Ratio M-H, Random, 95% CI
Berg 2016	15	220	13	221	20.4%	1.17 [0.54, 2.52]
Chakravarthy 2013	15	296	15	314	22.3%	1.06 [0.51, 2.22]
Kodjikian 2013	2	246	3	239	3.7%	0.64 [0.11, 3.89]
Krebs 2013	3	154	2	163	3.7%	1.60 [0.26, 9.70]
Martin 2012	36	586	32	599	49.9%	1.16 [0.71, 1.89]
Scholler 2014	0	26	0	29		Not estimable
Total (95% CI)		**1528**		**1565**	**100.0%**	**1.13 [0.80, 1.60]**
Total events	71		65			

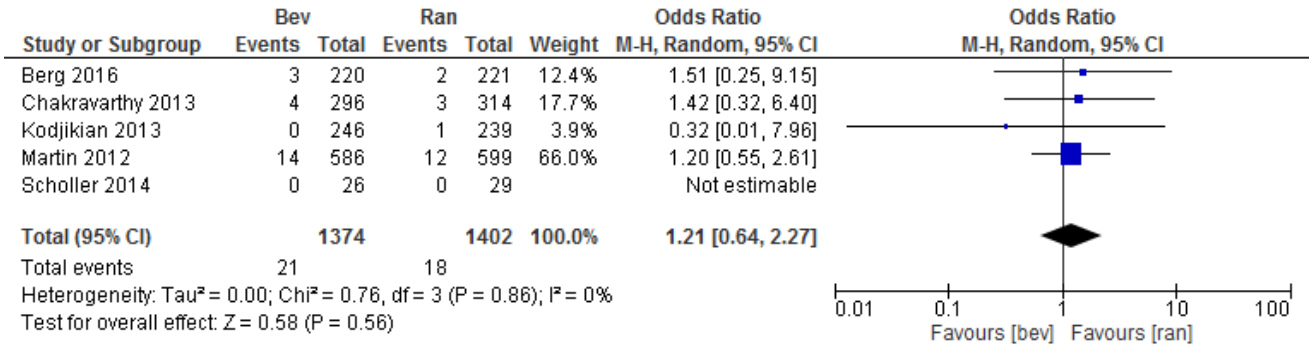
Heterogeneity: Tau² = 0.00; Chi² = 0.56, df = 4 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.68 (P = 0.49)



In the cohort study (n= 38,718 (bevacizumab) + 19,026 (ranibizumab), OR for mortality was 1.01 [0.91, 1.11], p = 0.91.
Conclusion: There is probably little or no difference regarding mortality, cardiovascular mortality, myocardial infarction or stroke between treatment with bevacizumab and ranibizumab. Moderate certainty of evidence (GRADE⊕⊕⊕◯).

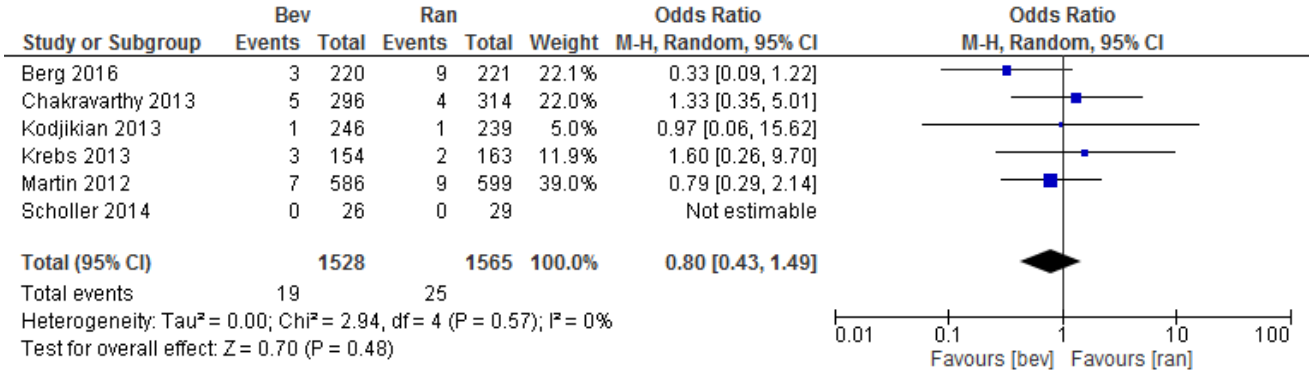
2.1.1.2. Cardiovascular disease mortality

This outcome was studied in five RCTs (eight publications). Mean OR was 1.21 [0.64, 2.27], p=0.56. No cohort data was found.



2.1.1.3. Myocardial infarction

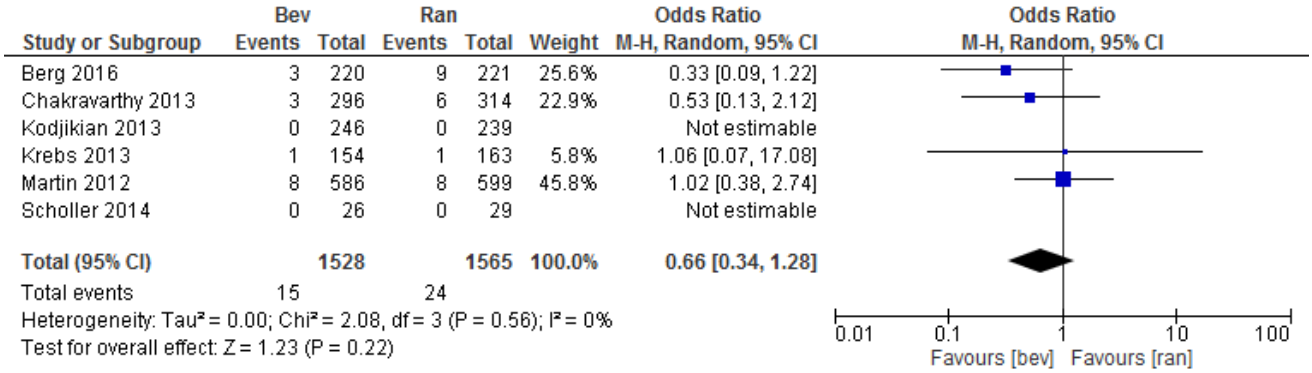
This outcome was studied in six RCTs (nine publications) and one cohort. Mean OR in the RCT material was 0.80 [0.43, 1.49], p=0.48.



In the cohort study (38,718+19,026 patients), the OR was 1.09 [0.91, 1.31], p=0.34

2.1.1.4. Stroke

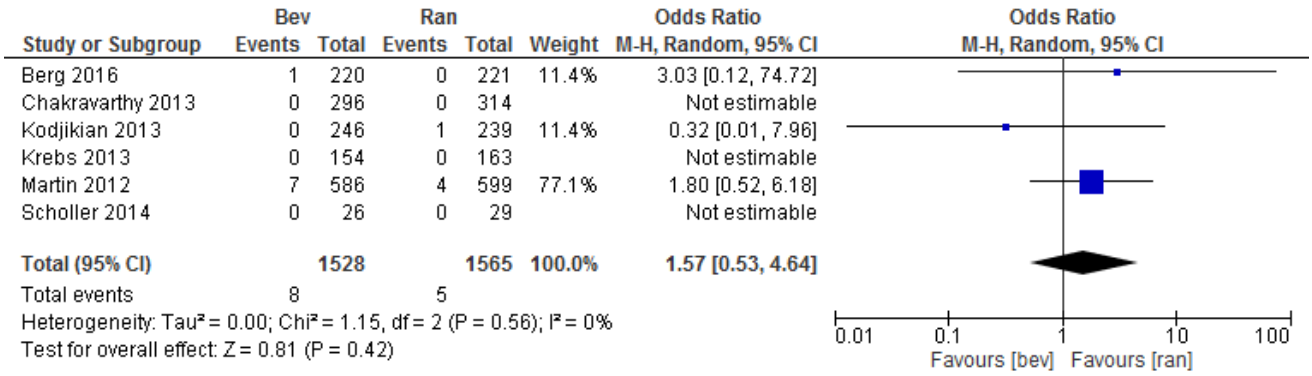
This outcome was studied in six RCTs (nine publications) and one cohort. Mean OR in the RCT material was 0.66 [0.34, 1.28], p=0.22.



In the cohort study (38,718+19,026 patients), the OR was 1.12 [0.98, 1.29], p=0.10.
Conclusion: There is probably little or no difference regarding mortality, cardiovascular mortality, myocardial infarction or stroke between treatment with bevacizumab and ranibizumab. Moderate certainty of evidence (GRADE⊕⊕⊕◯).

2.1.1.5. Endophthalmitis

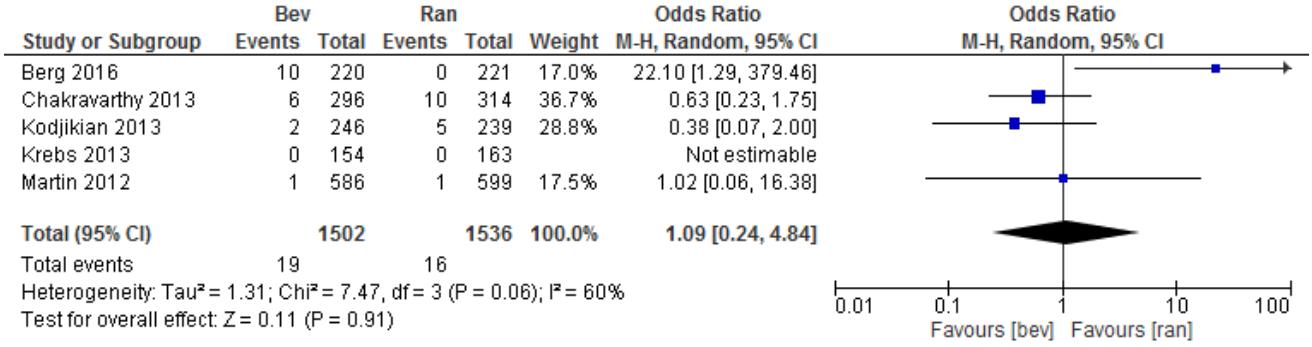
This outcome was studied in six RCTs (nine publications) with very few events. No cohort study was found. Mean OR in the RCT material was 1.57 [0.53, 4.64], p=0.42.



Conclusion: There may be little or no difference regarding risk for endophthalmitis between treatment with bevacizumab or ranibizumab. Low certainty of evidence (GRADE⊕⊕◯◯).

2.1.1.6. Other serious ocular events

This outcome was studied in five RCTs (seven publications). No cohort was found. Mean OR in the RCT material was 1.09 [0.24, 4.84], p = 0.91.



Conclusion: There may be little or no difference regarding risk for serious ocular events between treatment with bevacizumab and ranibizumab. Low certainty of evidence (GRADE⊕⊕◯◯).

2.1.2 Diabetic macular edema (DME)

Safety data for DME patients was found in two studies based on the same material reported after 1 and two years (Wells 2015, Wells 2016).

2.1.2.1. Mortality

In DME patients, the mortality in the bevacizumab group was 13/218 (6.0%) events, compared with 11/218 (5.2%) events in the ranibizumab group (p=0.83).
Conclusion: There may be little or no difference regarding mortality between treatment with bevacizumab and ranibizumab. Low certainty of evidence (GRADE ⊕⊕◯◯).

2.1.2.2. Cardiovascular disease mortality

In DME patients, 8/218 (3.7%) CVD mortalities were reported in the bevacizumab group, compared with 9/218 (4.1%) in the ranibizumab group (p=1.00).
Conclusion: There may be little or no difference regarding cardiovascular mortality between treatment with bevacizumab and ranibizumab. Low certainty of evidence (GRADE ⊕⊕◯◯.

2.1.2.3. Myocardial infarction

3/218 (1.4%) events of myocardial infarction rate was reported in the bevacizumab group, and 6/218 (2.8%) in the ranibizumab group (p=0.50)
Conclusion: There may be little or no difference regarding risk for myocardial infarction between treatment with bevacizumab and ranibizumab. Low certainty of evidence (GRADE ⊕⊕◯◯.

2.1.2.4 Stroke

The stroke rate in DME patients was 6/218 (2.8%) events in the bevacizumab group, and 11/218 (5.0%) events in the ranibizumab group (p=0.32)

Conclusion: There may be little or no difference regarding risk for stroke between treatment with bevacizumab and ranibizumab. Low certainty of evidence (GRADE ⊕⊕◯◯.

2.1.2.5 Endophthalmitis

Only one case of endophthalmitis was reported in in the bevacizumab group (0.5%) and none in the ranibizumab group (p=1.00). There was also a small cohort study (Bakbak, 2013, n=87), with no reported events of endophthalmitis.

Conclusion: It is uncertain whether there is little or no difference in endophthalmitis between treatment with bevacizumab or ranibizumab. Very low certainty of evidence (GRADE ⊕◯◯◯).

2.1.2.6 Other serious ocular events

In the bevacizumab group, 25/218 (11.5%) serious ocular events were reported, compared with and 16/218 (7.3%) events in the ranibizumab group (p=0.19)

Conclusion: There may be little or no difference regarding cardiovascular mortality between treatment with bevacizumab and ranibizumab. Low certainty of evidence (GRADE ⊕⊕◯◯).

2.1.3 Retinal vein occlusion (RVO)

The material consisted of two small RCTs with altogether 75+98 patients followed for 6 months. One study (Narajanan, 2015, n=75) reported only endophthalmitis (n= 0) or other serious ocular adverse events.

In the other study (Rajagopal, 2015), one patient died of pneumonia but treatment in that case was not reported. CVD mortality was not reported, and there were no events of myocardial infarctions, stroke, endophthalmitis or other serious ocular adverse events. No cohort studies were identified.

Conclusion: Too few events occurred in this material to make analysis meaningful.

2.1.4 Pathological myopia

The material consisted of one small RCT with altogether 78 patients followed for 1-2 years. No events of mortality, CVD mortality, MI, stroke, endophthalmitis or other complications occurred in this study.

Conclusion: Too few events occurred in this material to make analysis meaningful.

2.1.5 Mixed diagnoses

In the RCTs, the different patient groups were defined, as presented above. In several large cohort studies, the indication for anti-VEGF treatment was not specified (presumably mainly indication AMD).

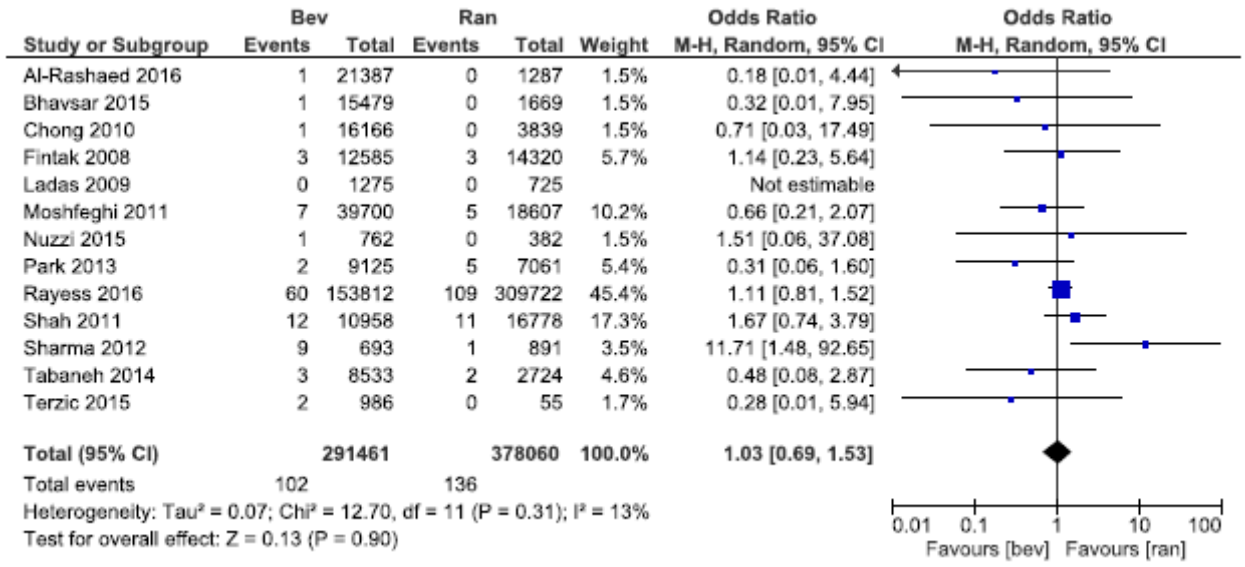
2.1.5.1-2.1.5.4.

Concerning the outcomes mortality, CVD mortality, MI and stroke, no events occurred in the cohort studies Lada, (2009) and Nuzzi (2015) (n=450+1144 patients). In the study by Sharma 2012 (n=524), two events of MI occurred in the bevacizumab group and none in the ranibizumab group (n.s.).

Conclusion: The events were too few for meaningful analysis.

2.1.5.5. Endophthalmitis

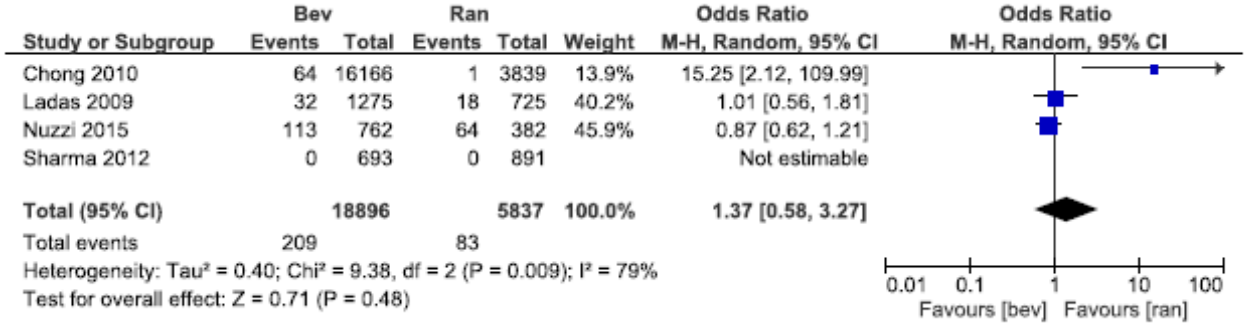
In the case of this particular outcome, injections rather than patient numbers are reported. We identified 13 cohorts with altogether 291,461+378,060 injections. The OR for risk for endophthalmitis was 1.03 [0.69, 1.53], p=0.90.



Conclusion: There is probably little or no difference in the risk of endophthalmitis between bevacizumab and ranibizumab. Moderate certainty of evidence (GRADE ⊕⊕⊕◯).

2.1.5.6. Other serious ocular complications

This outcome was reported in four cohort studies, one large (Chong 2010, 20,005 injections) and three smaller (1,144-2,000 injections). The OR for serious ocular complications was 1.37 [0.58, 3.27], p = 0.48.



Conclusion: There may be little or no difference regarding risk for serious ocular complications between treatment with bevacizumab and ranibizumab. Low certainty of evidence (GRADE ⊕⊕◯◯).

2.2. Comparison bevacizumab versus aflibercept

2.2.1. Age-related macular degeneration (AMD)

Safety data for this comparison was not reported for the AMD group.

2.2.2. Diabetic macular edema (DME)

We found one RCT on systemic safety for the DME group, reported in two publications, with one and two year data (Wells 2015, 2016).

2.2.2.1. Mortality

During two years, 13/218 (6.0%) mortalities had occurred in the bevacizumab group compared with 5/224 (2.0%) events in the aflibercept group (p=0.06).

Conclusion: There may be little or no difference in mortality between aflibercept and bevacizumab. Low certainty of evidence (GRADE ⊕⊕◯◯).

2.2.2.2. Cardiovascular disease mortality

There were 8/218 (3.7%) cases in the bevacizumab group and 3/224 cases (1.3%) in the aflibercept group (p=0.14), during two years.

Conclusion: There may be little or no difference in CVD mortality between aflibercept and bevacizumab. Low certainty of evidence (GRADE ⊕⊕◯◯).

2.2.2.3. Myocardial infarction

During two years, 3/218 (1.4%) MI events were reported in the bevacizumab group, compared with 7/224 (3.1%) events in the aflibercept group (p=0.34).

Conclusion: There may be little or no difference in the risk for myocardial infarction between bevacizumab and aflibercept treatment. Low certainty of evidence (GRADE ⊕⊕◯◯).

2.2.2.4. Stroke

There were 6/218 (2.8%) stroke events in the bevacizumab group, and 2/224 (0.9%) events in the aflibercept group (p=0.17), during two years.

Conclusion: There may be little or no difference in the risk for stroke between bevacizumab and aflibercept treatment. Low certainty of evidence (GRADE⊕⊕◯◯).

2.2.2.5. Endophthalmitis

Only one event of endophthalmitis was reported in the bevacizumab group, and no events in the aflibercept group (p =0.49), during two years of the diabetic retinopathy clinical research network study (Wells, 2016).

Conclusion: There were too few events to make an analysis meaningful.

2.2.2.6. Other serious ocular events

In the bevacizumab group there were 25/218 (11.5%) events in the bevacizumab group compared with 27/224 (12.1%) events in the aflibercept group (p=0.88).

Conclusion: There is probably little or no difference in the risk for serious ocular events rate between aflibercept and bevacizumab treatment. Moderate certainty of evidence (GRADE⊕⊕⊕◯).

2.2.3 Retinal vein occlusion (RVO)

No data was found.

2.2.4 Pathological myopia (PM)

No data was found.

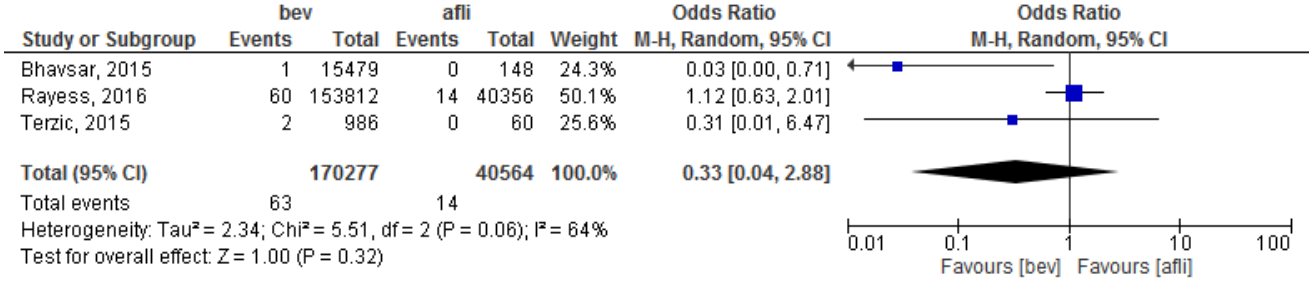
2.2.5. Mixed diagnoses

2.2.5.1 – 2.2.5.4: Mortality, cardiovascular mortality, myocardial infarction, stroke

These systemic adverse events were not studied in the mixed patient group.

2.2.5.5. Endophthalmitis

We found no RCTs but three cohort studies with 210,841 injections in total (15,627+194,168+1,046). Two of the cohorts had too few events to be analysable. The pooled OR was 0.33 [0.04, 2.88], p=0.32.



Conclusion: There may be little or no difference in the risk for endophthalmitis between bevacizumab and aflibercept administration. Low certainty of evidence (GRADE⊕⊕◯◯).

2.3. Comparison aflibercept versus ranibizumab

2.3.1. Age-related macular degeneration (AMD)

2.3.1.1 Mortality

Data from two RCT studies performed in different geographical settings (VIEW 1 and VIEW 2 trial) were reported in each case two different publications (Heier, 2012; Schmidt-Erfurth, 2014).
In the aflibercept group there 41/1,824 (2.2%) deaths, compared with 10/595 (1.8%) deaths in the ranibizumab group (p=0.63), during 96 weeks.
Conclusion: There is probably little or no difference in mortality between aflibercept or ranibizumab administration. Moderate certainty of evidence (GRADE⊕⊕⊕◯).

2.3.1.2. Cardiovascular disease mortality

In the aflibercept group, there were 24/1,824 (1.3%) CV deaths, compared with 3/595 (0.5%) in the ranibizumab group (p=0.12)
Conclusion: There is probably little or no difference in the risk for CVD mortality between aflibercept or ranibizumab administration. Moderate certainty of evidence (GRADE⊕⊕⊕◯).

2.3.1.3 Myocardial infarction

In the aflibercept group, there were 25/1824 (1.4%) MIs, and there were 12/595 (2.0%) MIs in the ranibizumab group (p=0.25).
Conclusion: There is probably little or no difference in the risk for myocardial infarction between aflibercept or ranibizumab administration. Moderate certainty of evidence (GRADE⊕⊕⊕◯).

2.3.1.4 Stroke

In the aflibercept group, there were 13/1,824 (0.7%) stroke events, and in the ranibizumab group there were 5/595 (0.8%) stroke events (p=0.78).
Conclusion: There is probably little or no difference in the risk for stroke between aflibercept or ranibizumab administration. Moderate certainty of evidence (GRADE ⊕⊕⊕◯).

2.3.1.5 Endophthalmitis

This topic was analysed in the RCTs mentioned above and in one large cohort study (Souied, 2016). In the RCTs, there were 5/1,824 (0.3%) events of endophthalmitis n the aflibercept group, and 5/595 (0.8%) events in the ranibizumab group (p=0.07).
In the cohort study (Souied, 2016), 189 (<0.1%) events of endophthalmitis were reported in the aflibercept group, compared with 162 (<0.1%) events in the ranibizumab group (p < 0.0001).
In a sensitivity analysis no significant difference was found between the aflibercept group and ranibizumab group (Souied, 2016, Appendix 4.9).
Conclusion: There may be little or no difference in the risk for endophthalmitis between aflibercept or ranibizumab injections. Low certainty of evidence (GRADE ⊕⊕◯◯).

2.3.1.6 Serious ocular events

Serious ocular events were reported in the two RCTs. In the aflibercept group there were 65/1,824 (3.6%) serious ocular events, compared with 26/595 (4.4%) events in the ranibizumab group (p=0.38).
Conclusion: There is probably little or no difference in the risk for serious ocular events between aflibercept or ranibizumab administration. Moderate certainty of evidence (GRADE⊕⊕⊕◯).

2.3.2. Diabetic macular edema (DME)

2.3.2.1 Mortality

In the RCT (Wells, 2015; 2016), there were 5/224 (2.2%) deaths in the aflibercept group and 11/218 (5.0%) deaths in the ranibizumab group (p=0.13).

Conclusion: There may be little or no difference in risk for mortality between aflibercept or ranibizumab administration in this patient group. Low certainty of evidence (GRADE ⊕⊕◯◯).

2.3.2.2 Cardiovascular disease mortality
Regarding CVD mortality, there were 3/224 (1.3%) deaths in the aflibercept group and 9/218 (4.1%) deaths in the ranibizumab group (p=0.08).
Conclusion: There may be little or no difference in risk for CDV mortality between aflibercept or ranibizumab administration in this patient group. Low certainty of evidence (GRADE ⊕⊕◯◯).

2.3.2.3. Myocardial infarction
There were 7/224 (3.1%) cases of myocardial infarction in patients with aflibercept and 6/218 (2.8%) cases in patients with ranibizumab (p=1.00).
Conclusion: There may be little or no difference in risk for CDV mortality between aflibercept or ranibizumab administration in this patient group. Low certainty of evidence (GRADE ⊕⊕◯◯)

2.3.2.4 Stroke
There were 2/224 (0.9%) stroke events in the aflibercept group, and 11/218 (5.0%) events in the ranibizumab group (p=0.01).
Conclusion: There may be a reduced risk for stroke with aflibercept versus ranibizumab administration in patients with DME. Low certainty of evidence (GRADE ⊕⊕◯◯)

2.3.2.5. Endophthalmitis
No events of endophthalmitis were reported in this patient group.

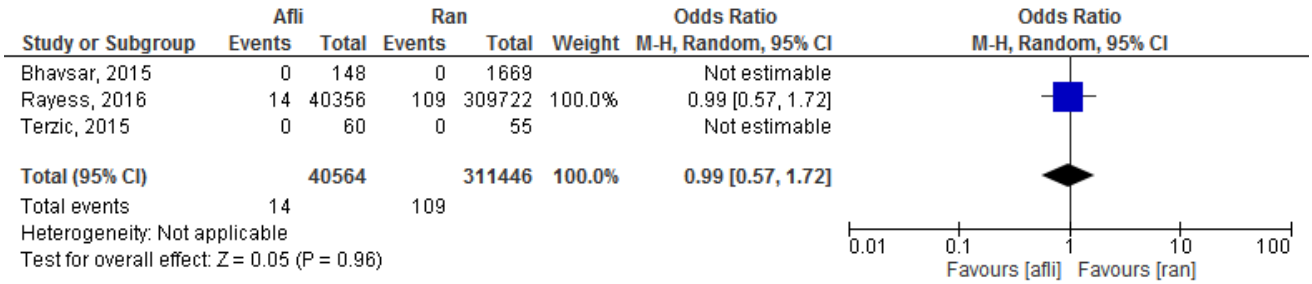
2.3.2.6. Serious ocular events
There were 27/224 (12.1%) cases of serious ocular events in patients with aflibercept and 16/218 (7.3%) cases in patients with ranibizumab (p=0.08).
Conclusion: There may little or no difference in the risk for serious ocular events with aflibercept versus ranibizumab administration in this patient group. Low certainty of evidence (GRADE ⊕⊕◯◯).

2.3.3. Retinal vein occlusion (RVO)
No data was found.

2.3.4. Pathological myopia (PM)
No data was found.

2.3.5 Mixed diagnoses
2.3.5.1 – 2.3.5.4. and 2.3.5.6. For the safety outcomes mortality, CDV mortality, myocardial infarction, stroke and other serious ocular events, no data was found in the mixed patient group.

2.3.5.5. Endophthalmitis
For the mixed patient group, only data regarding endophthalmitis was found. The comparison between aflibercept and ranibizumab was reported in three cohort studies, two of which contained no endophthalmitis events. The relevant material therefore consisted of one large cohort study with 350,078 injections (Rayess, 2016).
There were 14 (<0.1%) cases of endophthalmitis with 40,564 aflibercept injections, and 109 (<0.1%) cases in 311,446 with ranibizumab injections (Rayess, 2016). The pooled OR was 0.99 [0.57, 1.72], (p=0.96).



Conclusion: There may little or no difference in the risk for endophthalmitis with administration of aflibercept versus ranibizumab administration in mixed patient groups. Low certainty of evidence (GRADE ⊕⊕◯◯.

9. Ethical aspects

Lars Sandman, professor of health-care ethics, National Center for Priority Setting in Health-Care, Linköping University; guest professor of care ethics at University of Borås and ethics consultant at Västra Götaland region.

This ethical analysis was not done from a legal perspective and does not take legal aspects into account.

For treatment of wet age-related macular degeneration (AMD), diabetic macular edema (DME), central vein occlusion (RVO) and choroidal neovascularization due to pathologic myopia (PM), there are currently three anti-VGEF compounds available: bevacizumab (Avastin), ranibizumab (Lucentis) and aflibercept (Eylea), with ranibizumab and aflibercept being registered for ophtalmological indications and bevacizumab being used off label for ophtalmological conditions. My interpretation, corroborated by the HTA-centre experts, of the results of this HTA-report is that there are no identified clinically relevant differences regarding efficacy or safety between the three substances. The major difference between the three drugs is the price which is in turn related to the format of the documentation, i.e. whether it has been used for registration on the relevant indication.

Given this background, the central ethical issue is whether the treatment that would be recommended from an equity perspective, can be recommended despite off label status - or whether there are strong ethical reasons against such off label use.

The analysis of this central issue will be made step-wise answering the following questions:

- Which treatment should be recommended from an equity perspective using the Swedish ethical platform for health-care priority setting (= disregarding off label use)?
- Which are the central ethical reasons against off label use of individual drugs?
    - To what extent do they apply to bevacizumab (Avastin)?
    - Are there ethical reasons against off label use from a systems perspective?
    - To what extent do they apply to the use of bevacizumab (Avastin)?
- Conclusions

Which treatment should be recommended from an equity perspective using the Swedish ethical platform for health-care priority setting (disregarding off label use)?

The Swedish ethical platform for priority setting consists of three principles and is part of the Swedish health-care legislation:

- The Human Dignity principle which is a formal equality principle regulating equal rights regardless of race, gender, socioeconomical status, religion, sexual orientation, chronological age, previous life-style etc.

- The Needs-Solidarity principle regulating that the greater the need of patients, the more of the available resources may be used, with the *proviso* that we cannot need what we cannot benefit from.
- The Cost-Effectiveness principle regulating that there should be a reasonable relationship between cost and effect of treatment.

The three principles are ranked implying that what is a reasonable cost of effect depends on the degree of patient need, the larger the need, the less cost-effectiveness is accepted (Prop., 1996/97:60). Normally, in actual priority settings, these principles are operationalized in three different criteria: severity of disease, patient benefit and cost-effectiveness, following the so called National Model for Transparent Priority Setting in Health-Care (Broqvist et al., 2011).

Using these three criteria in the case at hand, we find that since these three treatments are targeting the same conditions and in doing so, have similar efficacy and safety - the only differentiating factor is cost and thereby cost-effectiveness. Even if the ranking order of the three principles above is interpreted in a strict sense, implying that cost-effectiveness only can be used when comparing equally effective treatment for the same condition - the ethical platform would unequivocally support the use of bevacizumab when making priorities at group level.

Thus, in relation to this first question about equity, the Swedish ethical platform would recommend the use of bevacizumab (Avastin) for the indications on which this report is based.

Now, so far the fact that bevacizumab will then be used off label has not been taken into account. Are there conclusive reasons against using Avastin off label in this case thus overturning the recommendation based on equity?

Which are the central ethical reasons against off label use of individual drugs?

New medicinal products are evaluated for efficacy and safety and may be granted marketing authorisation by the European Medicines Agency if a positive balance of patient benefits over risks is attained. The rationale is based on central ethical concerns in health-care which can be related to well-established ethical principles of beneficence, non-maleficence and patient autonomy also found in Swedish health-care legislation (Beauchamp & Childress, 2013; SFS 1982:763).
The balancing of principles of beneficence and non-maleficence puts the responsibility for patient safety with the health-care system. The principle of patient autonomy relates to patient informed consent, for which access for patients and/or health professionals to relevant and unbiased information about the treatment is necessary. For approved medicinal products, documentation of efficacy and safety is available through the approval process, and the assessment made by pharmaceutical authorities is thought to guarantee unbiased information to be available for health care professionals and patients.

Off label use of medicinal products can therefore be an ethical dilemma if the possibility to assess the benefit- risk situation is limited for pharmaceutical authorities, health care professionals and patients.

Are the ethical reasons against off label use of individual drugs applicable to bevacizumab?

The most frequently used route to achieve marketing authorisation is through the centralised procedure. The marketing authorisation is then granted after a scientific evaluation by the European Medicines Agency by the European Commission and valid in all EU member states. The marketing authorisation application is filed by the pharmaceutical company holding the new medicine. Given the results in this HTA-report, it is concluded that the use of bevacizumab for ophthalmological indications has been investigated in RCTs including 4,000 subjects and cohorts including more than half a million patients. Still bevacizumab has not been registered for ophthalmological indications. At face value, there does not seem to be a relevant or a strong ethical reasons against off label use based on patient benefit and safety since bevacizumab shows similar efficacy and safety as the alternative drugs.

Before concluding this, let us first look at whether there are any system-related ethical reasons against off label prescription of drugs.

Are there ethical reasons against off label use from a systems perspective?

From a systems perspective we can identify two different stakeholders here - the pharmaceutical authorities and the pharmaceutical industry. From the perspective of the pharmaceutical authority, important values are to maintain trust in and adherence to the system of licensing and approval. From the perspective of the pharmaceutical industry, an important value is incentives to invest in further innovation within the pharmaceutical area, and to get return on investment in new and innovative drugs is here central. This in turn, is an important concern for patients in need of new and innovative treatments. To promote this, different processes in the market approval system are in place (e.g. patenting, conditional approval, special regulations for orphan and ultra-orphan drugs etc.). However, in a market-based system, this does not imply that the pharmaceutical industry is guaranteed use of developed drugs by the health-care system if the system does not find them valuable enough, given alternative treatment options and price. A central tenet of a market economy is that the market agent takes the calculated economical risk, with the hope of prospective gains in sight. Hence, the pharmaceutical company cannot be guaranteed that the system will use a more expensive drug if there are similarly effective and safe but less costly alternatives.

If there is an existing drug that could be used to treat a new condition (which it was not primarily developed for), the best use of available research resources is to spend these on existing treatment tried for new indications before investing scarce research resources in developing new alternatives.

Are the systems-based reasons against off label use applicable to bevacizumab?

Researchers and in effect also institutional review boards have found it warranted to try bevacizumab to treat AMD and other ophthalmological conditions in patient trials, a decision the pharmaceutical company also could have made. Does trust and adherence in the system of pharmaceutical licensing and approval motivate us to abstain from using bevacizumab off label? Bevacizumab is an exceptional case where there is no identified difference regarding efficacy and safety compared to the competing drugs together with an obvious explanation for why it is has not been filed for licensing and approval for ophthalmological use. Hence, it is unlikely that bevacizumab would set an example for widespread off label use of other drugs.

Summary

Thus, the following criteria related to off label use of bevacizumab have been identified in the present ethical analysis:

- That there is well-documented and strong evidence for efficacy and safety of the drug.
- That the information about the drug is made available and transparent to stakeholders.
- That the decision to recommend off label use and the reasons behind it are transparent to stakeholders.

Ethical conclusions

From the ethical analysis the following conclusions can be drawn:

- That the Swedish ethical platform unequivocally would support the use of bevacizumab before ranibizumab and aflibercept, except in specific individual cases where bevacizumab cannot be used due to lack of effect or serious adverse drug reactions
- That there are no strong ethical reasons against off label use of bevacizumab following the ethical rationales behind pharmaceutical licensing and approval at an indidvidual drug level.

- That there are no strong reasons against using bevacizumab from the perspective of stimulating innovation but rather some reason to use bevacizumab to signal that existing treatment should be tried for new indications before investing scarce research resources in developing new alternatives.
- That there are some reasons to avoid off label use of drugs based on trust and adherence in the system, but that the strict criteria that can be formulated for bevacizumab sets this to be an exceptional case thus minimizing this risk.

Once again, it must be emphasized that this is an ethical analysis and legal requirements might hinder the implementation of what is ethically recommended. For this a legal analysis is needed.

10. Organisational aspects

Time frame for the putative introduction of the new health technology

A change from ranibizumab to bevacizumab can be accomplished rapidly since the dosage regimen is the same (1 injection/month or less). With aflibercept, the standard dosage regimen after the initial treatment period is 1 injection per 2 months, i.e. a change to bevacizumab may theoretically require more injections per unit time which would be a problem if there is a lack of injecting doctors. This issue might delay the switch from aflibercept to bevacizumab. The magnitude of this particular problem varies between hospitals within the region.

Present use of the technology in other hospitals in Region Västra Götaland

Summary of economic aspects

Approximately, 12,500 injections of ranibizumab (Lucentis) and aflibercept (Eylea) were used as treatment to patients with the diagnoses[1] nAMD (75%), DME (11%), RVO (14%) and CNV (0%) during year 2015. The proportion of ranibizumab was approximately 60-70% and aflibercept 40-30%, across all diagnoses. Bevacizumab for intraocular use is off label, making it impossible to determine the extent of current usage.

Consequences of the new health technology for personnel

Off label use of medications is discouraged by the Swedish Medical Products Agency but is allowed “if it is in accordance with science and documented experience”. Since the legal aspects of off label use are unclear, the medical staff is worried particularly about safety issues and the (unlikely) possibility of legal consequences for the individual doctor. These worries may limit the willingness to switch to the new off label technology.

Consequences for other clinics or supporting functions at the hospital or in the Region Västra Götaland

Local off label use in individual hospitals is very difficult to explain to the involved patients. It would therefore be advantageous if the new strategy was introduced simultaneously in all hospitals in VGR.

11. Economic aspects

Summary of economic aspects

The annual cost of injections with the current treatment strategy with ranibizumab (70%) and aflibercept (30%), based on 12,500 injections, was 111 million SEK in the Region Västra Götaland during 2015.

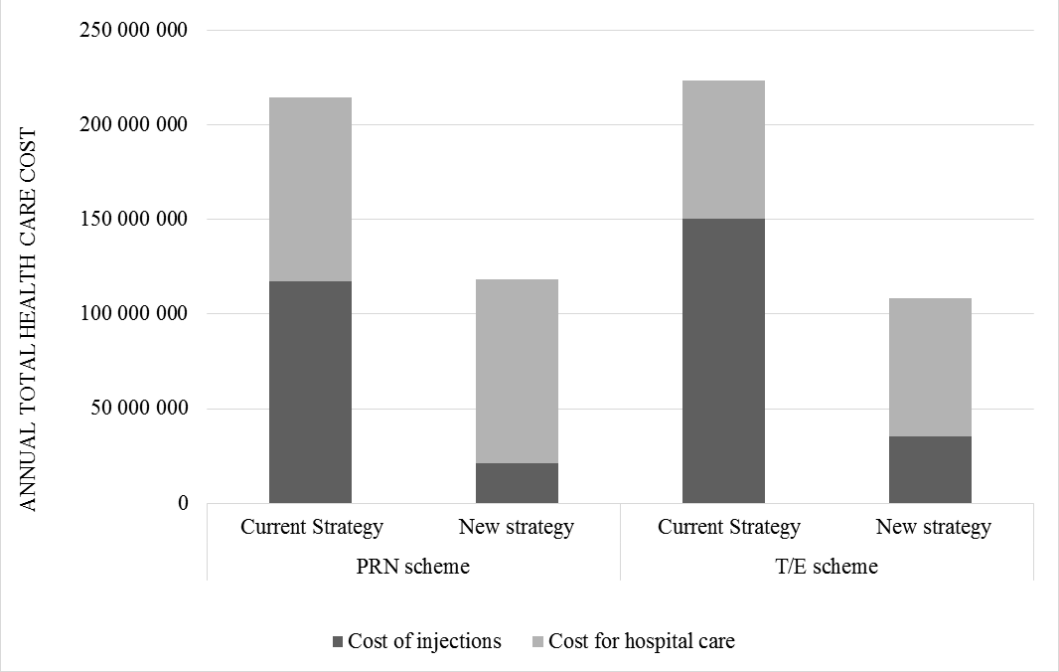
[1] ICD-10 codes: nAMD (ICD-10: H353), DME (ICD-10: H360+E115 and H360+E103), RVO (ICD-10: H348) and CNV (ICD-10: H521+H353 and H442+H353).

If a new treatment strategy of bevacizumab (80%) and aflibercept (20%) would replace the current strategy, the total annual cost was estimated to 26 million SEK. Hence, by switching to bevacizumab when medically appropriate would generate **an annual cost saving of 85 million SEK** in Region Västra Götaland. The price for ranibizumab used in this estimate was 8,909.50 SEK per injection. With a discount of 50% per injection, the expected annual cost saving would instead be 46 million SEK. Another factor that influences the annual cost of injections is the proportion of injections of aflibercept. If the proportion would be 30% instead of 20% with the new treatment strategy, the annual cost saving would be **74 million SEK**.

The total annual health care cost, including injections and other hospital costs, with the PRN scheme for the current strategy was estimated to 214 million SEK, and 118 million SEK with the new treatment strategy. Hence, **by switching to bevacizumab when medically appropriate would generate an annual cost saving of 96 million SEK** in Region Västra Götaland.

Patients diagnosed with nAMD are subjected to treatment plan with either a "control and treat if necessary", called pro re nata scheme (PRN), or a "treat and extend" scheme (T/E). If all patients would be treated according to the T/E scheme, the annual cost saving would be 115 million SEK. With a discount of 50% per injection of ranibizumab, the expected total annual cost saving would be 37.5 with PRN scheme or 75.2 if all patient were treated according to the T/E scheme.

Figure 1. Estimated annual total health care cost with the current treatment strategy (ranibizumab/aflibercept) and new treatment strategy (bevacizumab/aflibercept) in Region Västra Götaland. Costs are presented in SEK (2015).



Present costs of current treatment strategy

Annual cost for injections

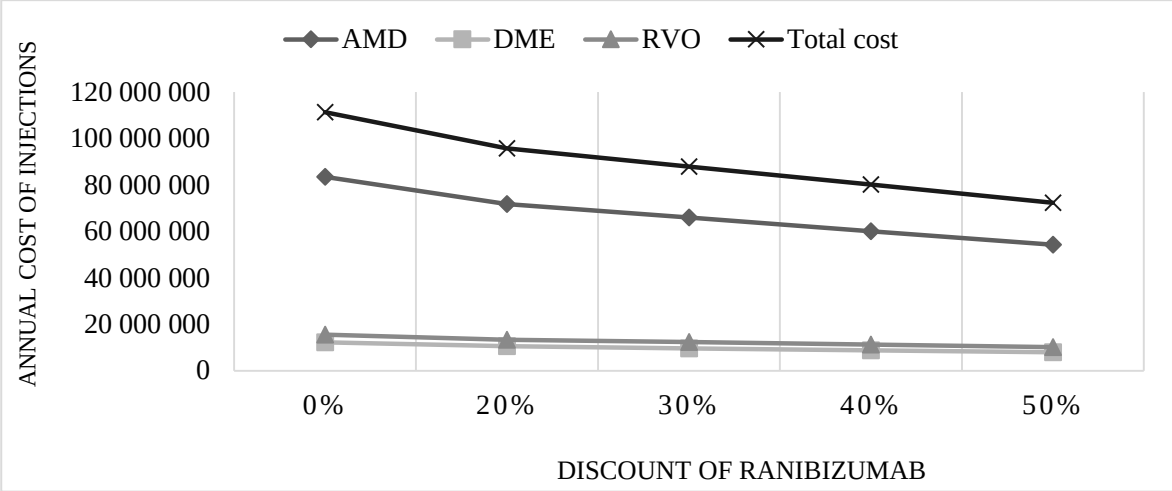
The price per injection of ranibizumab and aflibercept was classified (Läkemedelskommittén i Västra Götalandsregionen, 2016) in Region Västra Götaland at the time when this report was produced. Hence, the estimate of the annual cost was based on prices from The Dental and Pharmaceutical Benefits Agency (TLV); 8,909.50 SEK per injection (0.5mg) of ranibizumab and 8,902 SEK per injection (2mg) of aflibercept (Tandvårds- och Läkemedelsförmånsverket, 2013). The annual cost of injection with ranibizumab (70%) and aflibercept (30%) is estimated to be 111 million SEK in the Region Västra Götaland (Table 4).

To account for a possible discounted price of ranibizumab, sensitivity analyses were provided with a discount of 20%, 30%, 40% and 50%. Hence, in the analyses the discounted prices of ranibizumab were 7,128 SEK, 6,234 SEK, 5,346 SEK, 4,455 SEK (Figure 2).

Table 4. Annual cost of injections of ranibizumab (70%) and aflibercept (30%) in Region Västra Götaland. Costs are presented in SEK (2015).

Diagnosis	Injections	Ranibizumab	Aflibercept	**Total cost**
nAMD	9 375	58 469 000	25 037 000	83 506 000
DME	1 375	8 575 000	3 672 000	12 247 000
RVO	1 750	10914 000	4 674 000	15 588 000
TOTAL	**12 500**	**77 958 000**	**33 383 000**	**111 341 000**

Figure 2. Annual cost of injections of ranibizumab (70%) and aflibercept (30%) in Region Västra Götaland related to degree of discounted prices of ranibizumab. Costs are presented in SEK (2015).



Cost per patient

Patients diagnosed with nAMD are subjected to treatment plan with either a "control and treat if necessary", called pro re nata scheme (PRN), or a "treat and extend" scheme (T/E). With the PRN scheme, during the first year, there is one initial ophthalmic consultation, one visit including an angiography to confirm the diagnosis, six injections and four visits for ophthalmic follow-up. For patients with aflibercept, there is one to two visits less and one injection less. There are three injections and six visits for eye-clinic follow-ups during the second year and two to three injections and four follow-ups during the third year.

With the T/E scheme, the patients' receive one injection with each visit but the intervals between visits are extended according to a fixed schedule. During the first year, there is one initial ophthalmic consultation, one visit with an angiography to confirm the diagnosis and nine injections combined with visits for ophthalmic follow-up. During the second year, there are six injections combined with visits for ophthalmic follow-up. During the third year, there are three to four injections combined with visits for ophthalmic follow-up.

The unit prices in this cost analyses were 2,900 SEK for an ophthalmic follow-up visit (data from VGR), 5,000 SEK for administrations linked to the injections, and 2,300 SEK for an angiography (Tandvårds- och Läkemedelsförmånsverket, 2013). Table 5, presents the annual treatment costs per patient during the first three years. It is seen that from a cost perspective, the two substances are largely identical with a small advantage for aflibercept and the PRN scheme.

Table 5. Cost per patient during the first three years with injections of ranibizumab and aflibercept in Region Västra Götaland. Costs are presented in SEK (2015).

	PRN scheme		T/E scheme	
Cost per year	Ranibizumab	Aflibercept	Ranibizumab	Aflibercept
Year 1	100 300	83 400	130 400	130 300
Year 2	59 100	59 100	83 500	83 400
Year 3	53 300	53 300	55 600	55 600
TOTAL	**212 700**	**195 800**	**269 500**	**269 300**

Total annual health care cost

The exact treatment strategies for the new indications DME, RVO and PM is not yet fully established but in this context we assume a similar scheme for these indications.

The total annual cost estimation was based on 3,125 patients, whereof 10% (Svenska Makularegistret) were newly diagnosed and 45% of the patients were treated during their second year and 45% were treated during their third year.

The total annual cost, including cost of injections and other hospital costs, would be 214 million SEK if all patients were treated accordingly to the PRN scheme, and 223 million SEK if all patients were treated accordingly to the T/E scheme (Table 8).

Expected costs of bevacizumab

Annual cost for injections

Based on information from one of the hospitals in Region Västra Götaland, the price for bevacizumab (Avastin®) was 400 SEK per injection, including administration costs. Table 6 presents the total annual cost if bevacizumab were used as a treatment for 80% of the total number of injections. Since some patients do not respond well to the treatment with bevacizumab (or ranibizumab), approximately 20% of the injections will still be expected to contain aflibercept. If the proportion of injections with aflibercept would instead be 30%, the annual cost of injection was estimated to 36.9 million SEK.

Table 6. Expected annual cost of injections if bevacizumab replaced ranibizumab in Region Västra Götaland. Costs are presented in SEK (2015).

Diagnosis	Total injections	Bevacizumab (80%)	Aflibercept (20%)	**Total cost**
nAMD	9 375	3 000 000	16 691 000	19 691 000
DME	1 375	440 000	2 448 000	2 888 000
RVO	1 750	560 000	3 116 000	3 676 000
TOTAL	**12 500**	**4 000 000**	**22 255 000**	**26 255 000**

Cost per patient

Table 7, presents the expected total annual health care cost, including cost of injections and hospital costs, per patient during the first three years, if bevacizumab replaced ranibizumab.

Table 7. Expected cost per patient during the first three years if bevacizumab replaced ranibizumab in the Region Västra Götaland. Costs are presented in SEK.

	PRN scheme		T/E scheme	
Cost per year	Bevacizumab	Aflibercept	Bevacizumab	Aflibercept
Year 1	49 200	83 400	53 800	130 300
Year 2	33 600	59 100	32 400	83 400
Year 3	27 800	53 300	21 600	55 600
TOTAL	**110 600**	**195 800**	**107 800**	**269 300**

Total annual health care cost

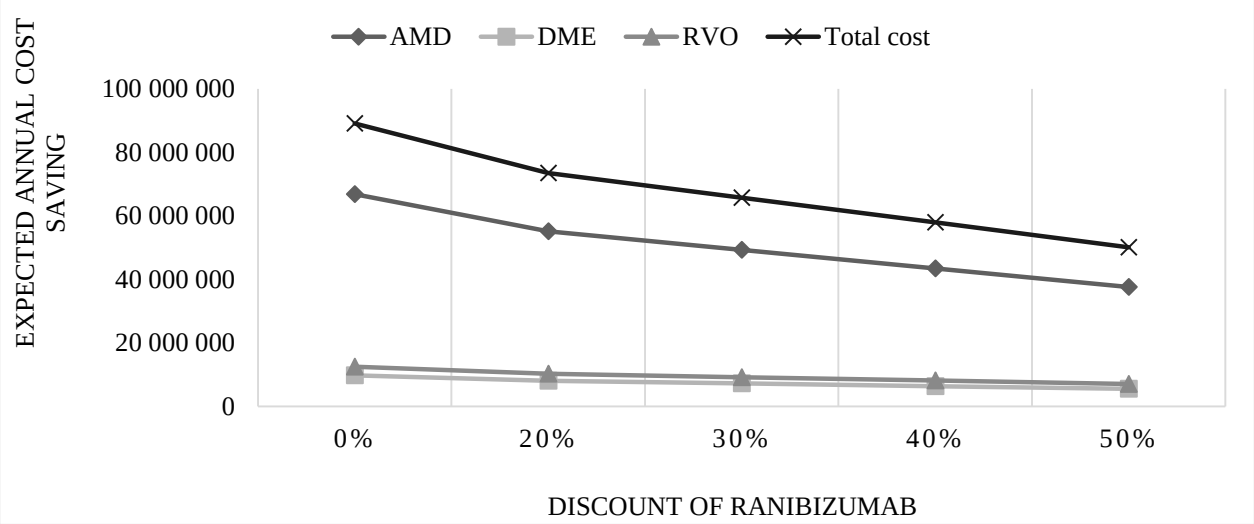
The estimation of the total annual VGR cost was based on 3,125 patients, whereof 10% (Svenska Makularegistret) were newly diagnosed and 45% of the patients were treated during their second year and 45% were treated during their third year. Under this assumption, the total annual cost would be 118 million SEK if all patients were treated accordingly to the PRN scheme, and 121 million SEK if all patients were treated accordingly to the T/E scheme (Table 8).

Total change of cost

If the current treatment strategy with ranibizumab (70%) and aflibercept (30%) would be replaced by the new treatment strategy with bevacizumab (80%) and aflibercept (20%), the annual cost of 12,500 injections would be 26 million SEK compared to 111 million SEK. This corresponds to a cost saving of 85 million SEK.

If the price for ranibizumab was discounted with 30% per injection, the annual cost saving would be 62 million SEK. With a discount of 50% per injection, the annual cost saving would be 46 million SEK instead. Figure 3, illustrates the possible annual cost saving with different discounted prices of ranibizumab.

Figure 3. Expected annual cost saving of injections with treatment strategy of bevacizumab (80%) and aflibercept (20%) compared to ranibizumab (70%) and aflibercept (20%) in Region Västra Götaland with discounted prices of ranibizumab. Costs are presented in SEK (2015).



The total annual cost saving with the new treatment strategy was estimated to 95.9 million SEK with the PRN scheme, and 114.9 million SEK with the T/E scheme. With a discount of 50% per injection of ranibizumab, the expected total annual cost saving would be 37.5 with PRN scheme or 75.2 if all patient were treated according to the T/E scheme (Table 8).

Table 8. Expected total annual health care cost and annual cost saving with the current treatment strategy compared to the new treatment strategy in the Region Västra Götaland. Costs are presented in million SEK.

Cost per year	PRN scheme			T/E scheme		
	Current strategy	New strategy	Annual cost saving	Current strategy	New strategy	Annual cost saving
Total health care cost	214.2	118.2	95.9	223.4	108.5	114.9
Total health care cost with 30% discount of ranibizumab	168.6	118.2	50.4	204.7	108.5	96.2

Total health care cost with 50% discount of ranibizumab	155.7	118.2	37.5	183.7	108.5	75.2

Available economic evaluations

Neovascular age-related macular degeneration (nAMD)

Dakin et al., (2014) conducted a trial-based economic evaluation of ranibizumab in comparison with bevacizumab from a UK National Health Service (NHS) perspective. The result demonstrated a cost-saving of £102 (€160) million per year if patients switched to bevacizumab, with a non-significant change in quality-adjusted life years (QALY). The sensitivity analyses demonstrated that the result were robust to changes in assumptions and methods used to estimate cost and utilities.

Elshout et al., (2013) developed a patient-level, visual acuity-based, 2-eyed model from a Dutch societal perspective over two and five years. The treatment schemes were, aflibercept (1x/2 months), bevacizumab (PRN (ABS study), PRN (CATT study), 1x/month), ranibizumab (PRN, 1x/month) and no treatment, five year costs and QALYs were; €36,030 and 2.15, €19,367 and 2.16, €26,746 and 2.17, €30,520 and 2.15, €45,491 and 2.16, €74,837 and 2.15, €9,530 and 2.15, respectively. In conclusion, aflibercept was a cost-effective treatment over ranibizumab. However, aflibercept was not a cost-effective treatment over bevacizumab.

Patel et al., (2010) conducted a cost-utility analysis using a Markov model to estimate the cost-effectiveness between bevacizumab and ranibizumab from a US payer perspective with a time-horizon of 20 years. According to the model, bevacizumab had a cost of $30,349 and QALYs of 21.60, whereof ranibizumab had a cost of $220,649 and QALYs of 18.12, generating a cost saving of $54,649 per QALY. The probabilistic sensitivity analysis demonstrated a 95% probability of bevacizumab being more cost-effective in comparison to ranibizumab at willingness-to-pay (WTP) threshold of $50 000 per QALY gained.

Stein et al., (2014), conducted a cost-utility analysis using a Markov model with a 20-year time horizon comparing the incremental cost-effectiveness of monthly bevacizumab, as-needed bevacizumab, monthly ranibizumab and as-needed ranibizumab for a cohort of hypothetical 80-year old newly diagnosed patients from a US societal perspective. The expected cost per patient were $65,267, $79,771, $163,694 and $257,496; and QALYs were 6.60, 6.66, 6.64, 6.68. The cost-effectiveness of monthly bevacizumab over as-needed bevacizumab was $242,357 per QALY gained. The cost-effectiveness of monthly ranibizumab over as-needed ranibizumab was $10,708,377 per QALY gained. The probabilistic sensitivity analysis demonstrated that as needed bevacizumab was the preferred alternative in 62% at a WTP threshold of $100,000 per QALY gained, and monthly bevacizumab was the preferred in 18-20% with a WTP of <100,000 per QALY gained.

Macular edema secondary to branch retinal vein occlusion (BRVO)

Adedokun et al., (2016) used a Markov model to simulate the cost-effectiveness of ranibizumab in comparison of aflibercept from a UK healthcare perspective. The life-time cost and QALY gained of ranibizumab was £15,273, 9.668 QALY and £17,347, 9.656 with aflibercept. The cost-effectiveness ratio was £172,833 per QALY gained. The probabilistic sensitivity analysis demonstrated a 62.7% probability of ranibizumab being more cost-effective in comparison to aflibercept at WTP threshold of £20 000 per QALY gained.

Diabetic macular edema (DME)

Regnier et al., (2015) used a Markov model to simulate the cost-effectiveness of ranibizumab in comparison of aflibercept from a UK healthcare perspective. The life-time cost and QALY gained of ranibizumab PRN was £20,019, 8.59 QALY ranibizumab T/E was £22,930, 8.59 QALY and £25,859, 8.54 with aflibercept. The cost-effectiveness of ranibizumab PRN over aflibercept was - £116,820 per QALY gained, and ranibizumab T/E over aflibercept was -£58,600.

The probabilistic sensitivity analysis demonstrated a 79% probability of ranibizumab PRN and 67% probability of ranibizumab T/E being more cost-effective in comparison to aflibercept at WTP threshold of £20,000 per QALY gained.

Conclusion

Previous literature of economic evaluations all provided similar results with extensive differences in costs between bevacizumab in comparison with ranibizumab and aflibercept, meanwhile a small difference in effects, measured with QALYs. The majority of the economic evaluations were undertaken from a UK or US perspective. It is not possible to interpret the results from the UK and US studies into the Swedish settings due to differences in costs in the local health care systems. However, with minor differences in QALYs between the different treatment alternatives the incremental cost-effectiveness ratio (ICER) will be mostly influenced by the costs of the various alternatives. Hence, in this report we provided a cost analysis of the different treatment strategies in the setting of Region Västra Götaland, indicating a major annual cost saving on injections with 85 million SEK by switching to bevacizumab (80%) and aflibercept (20%) compared to the current treatment strategy with ranibizumab (70%) and aflibercept (30%).

12.Discussion

Summary of main results and need for further research

The systematic literature review identified a large RCT material and a very large cohort material that failed to identify any clinically relevant differences in efficacy (bulk of data visual acuity) or safety (mortality, myocardial infarction, stroke, endophthalmitis) between the three substances. The evidence for a non-difference is stronger for the indication AMD than for the smaller patient groups DME, RVO and PM. DME is a special issue since diabetes per se is strongly associated with an increased risk for cardiovascular disease, i.e. the risk profile seen in AMD may not necessarily be applicable in this patient group. Safety data for rare complications in the smaller patient groups RVO and PM are also largely lacking due to low total numbers in the studies.

An issue that is not altogether clear from the literature is the optimal frequency of injections during long term treatment. Eylea is marketed by the argument of the need for a lower injection frequency, but the scientific basis for this statement is relatively weak. Since injection frequency becomes relevant in a situation with a shortage of injecting doctors, this issue needs to be clarified.

The identified data emanates from settings similar to those applying in VGR, i.e. well organized good-hygiene health care. Whether these data apply also in low income countries in less hygienic settings is still not unequivocally settled.

Finally a comment regarding drawing conclusions concerning non-inferiority on the basis of multiple negative superiority studies. With regard to effects on visual acuity, the patient material is very large and in none of the studies a clinically relevant difference between treatment groups was seen. However, in the safety studies and particularly so in DME, there were trends in safety data that might reflect a type II error (underpowered study). Continued attention on safety is therefore warranted in this patient group for all three substances.

Comments regarding off label treatment

The term off label indicates use of a medicinal compound outside of its SPC (summary of product characteristics, i.e. FASS in Sweden). Drug development for use in humans is strictly regulated and involves a number of well-defined steps including animal studies, teratology, toxicology, pharmacodynamics etc. Particularly studies in humans (phase 2 and 3) are very costly, as reflected by the very high price of new compounds that have gone through this process. However, despite being

discouraged by the drug authorities prescription is free in Sweden, for health care professionals (authorised for drug prescription). Thus, off label use is not illegal. However, off label use should take place in accordance with science and proven experience (Swedish: vetenskap och beprövad erfarenhet). Due to lack of documentation of efficacy and safety in paediatric populations, off label use of substances registered for adults is common in paediatric care. Registration is only possible after the drug developer (i.e. the industry) has applied for marketing authorisation. Presently, the Swedish Medical Products Agency discourages the use of medicines off label, except when it is based on science and proven experience (Läkemedelsverket, 2016).

Agreements and disagreements with other studies and reviews

The overall conclusion of this HTA report agrees with that of available systematic reviews as summarized in Table 9. None of these reviews had the same PICO as our current report and most of them were based on older literature.

Table 9. Relevant systematic reviews identified in the literature search (published since 2013)

First author, year	Meta-analysis	Included only RCT	Number of studies	Literature search year	Studied drugs			Studied diagnose groups					Main focus	
					Afli	Bev	Ran	AMD	DME	PM	RVO	Mixed	Efficacy	Safety
Ba, 2015	X	X	12	2014	X	X	X	X					X	
CADTH, 2014		X	2	2014?	X		X	X					X	X
Chen, 2015	X	X	6	2013		X	X	X					X	X
Ford, 2014	X	X	7	2013	X	X	X				X		X	
Jiang, 2014	X	X	8	2013		X	X	X					X	
Kodjikian, 2014	X	X	3	2013		X	X	X					X	X
Loutfi, 2015	X		3	2013		X	X			X			X	
Mikacic, 2016	X		14	2015		X		X						X
Moja, 2014	X	X	9	2014		X	X	X						X
Ollendorf, 2013	X		13	2012	X	X	X		X				X	
Penedones, 2014			95	2013	X		X					X		X
Poku, 2014	X		89	2012		X						X		X
Régenier, 2014	X	X	8	2014	X		X		X				X	
Régenier, 2015	X	X	8	2014	X		X				X		X	X
Sarwar, 2016	X	X	2	2015	X		X	X					X	X
Schmid, 2015	X	X	11	2013	X	X	X	X					X	X
Sigford, 2015			534	2013		X	X					X		X
Solomon, 2014	X	X	11	2014		X	X	X					X	X
Solomon, 2016	X	X	6	2014		X	X	X					X	X
Stuart, 2015	X		16	2014		X	X			X			X	X
Szabo, 2015	X	X	6 (5)	2013	X		X	X					X	X
Thulliez, 2014	X	X	4	2013		X	X	X						X
Wang, 2013	X		3	2012		X	X			X			X	X
Wang, 2014	X	X	4	2013		X	X	X						X
Wang, 2015	X	X	7	2014		X	X	X					X	X
Wu, 2014	X	X	9	2013		X	X					X	X	X
Zhang, 2014	X		15	2012		X	X	X					X	X

Afli = aflibercept, AMD = age-related macular degeneration, Bev = bevacizumab, CT = Controlled trial (cohort study), DME =, diabetic macular edema HRQoL = health-related quality of life, PM = pathological myopia, Ran = ranibizumab, RCT = randomized controlled trial, RVO = retinal vein occlusion, VA = Visual acuity.

13. Future perspective

Scientific knowledge gaps

There is a lack of data regarding effects of changing from ranibizumab or aflibercept to bevacizumab in the individual patient. The evidence regarding effects and safety is also weaker for the smaller patient groups DME, RVO and PM. Long term effects are unknown.

NCT Number	Title (abreviated)	Diagnose groups	Studied drugs*	Status
NCT00682539	Intraocular anti-VEGF compared with intraocular triamcinolone	DME	Bev	Completed (not published?)
NCT02646670	Efficacy of ranibizumab therapy with aflibercept	Mixed	Afli vs. Ran	Completed (not published?)
NCT01014468	Bevacizumab versus ranibizumab	AMD	Bev vs. Ran	Unknown status (not published?)
NCT02036723	Safety and efficacy study of BCD-021 compared to Lucentis®	AMD	Bev vs. Ran	Withdrawn prior to enrollment
NCT01635790	Effectiveness and costs of bevacizumab to ranibizumab	DME	Bev vs. Ran	Recruiting
NCT02130024	Ranibizumab or aflibercept – development of geographic atrophy	AMD	Afli vs. Ran	Recruiting
NCT00593450	Comparison Lucentis-Avastin	AMD	Bev vs. Ran	Active, not recruiting (CATT) Estimated Feb 2018
NCT02363621	Inflammation and Pain Post Injection ranibizumab vs. aflibercept	DME	Afli vs. Ran	Recruiting
NCT01487629	Bevacizumab versus ranibizumab	DME	Bev vs. Ran	Publicerad RCT n=49
NCT00559715	Prevention of vision loss by intravitreal injection	AMD	Bev vs. Ran	Unknown status (not published?)
NCT02591914	Safety, tolerability and development of subfoveal fibrosis	AMD	Afli vs. Bev vs. Ran	Ongoing, not recruiting (estimated 2016)
NCT01918371	A retrospective study of anti-vascular endothelial growth factor	RVO	Anti-VEGF	Completed (not published?)
NCT01170767	French evaluation group	AMD	Bev vs. Ran	Completed (not published?)
NCT01926977	Evaluation of pain and inflammation after injection	AMD	Afli vs. Ran	Completed (not published yet?)
NCT01318941	Effectiveness and safety real life setting	Mixed	Ran	Completed

Ongoing research

The search in the clinicaltrials.gov database resulted in 685 identified studies. Fifteen of these were deemed relevant for the studied question (Table 10).

* Relevant for PICO. Afli = aflibercept, AMD = age-related macular degeneration, Bev = bevacizumab, DME = diabetic macular edema, Ran = ranibizumab, RVO = retinal vein occlusion.

Comments regarding literature published May 2016 to May 2017

Five-year follow-up data from the CATT trial indicate that patients with AMD treated with intravitreal ranibizumab injections, may lose more letters between year two and five than those treated with bevacizumab (group difference - 4 letters, p=0.008), but no other significant differences in VA were found (Maguire et al., 2016).

In a non-inferiority RCT (n=327, BRAMD study) in patients with AMD, bevacizumab was not found to be inferior to ranibizumab regarding best corrected visual acuity (Schauwvlieghe et al., 2016).

14. Participants in the project

The question was nominated by

Regional Advisory Board for priority setting (PPR) by Anders Carlqvist, Pharmaceutical Manager, Corporate Health Care, Gothenburg, Sweden

Participating health care professionals

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Declaration of interest

None of the authors has any conflict of interest to declare.

Project time

HTA was accomplished during the period of 2016-03-01 – 2017-03-29
Literature searches were made in March 2016

Appendix 1, Search strategy, study selection and references

Question(s) at issue:

Are there any clinically relevant differences in efficacy or safety of the three anti-VGEF compounds bevacizumab, ranibizumab and aflibercept, when used for intraocular treatment of age-related macular degeneration, diabetic macular edema, retinal vein occlusion or choroidal neovascularization due to pathologic myopia.

P	Adults with any of the following disorders: - Impaired vision due to neovascular (wet) age-related macular degeneration (nAMD); - Impaired vision due to diabetic macular edema (DME) - Impaired vision due to macular edema secondary to retinal vein occlusion (central or branch vein) (RVO) - Impaired vision due to choroidal neovascularization secondary to pathological myopia (PM) - Impaired vision due to nAMD or DME or RVO or PM ("mixed diagnoses")
I & C	Intraocular treatment with I1. bevacizumab (Avastin) C1 ranizumab (Lucentis) I2. bevacizumab (Avastin) C2 aflibercept (Eylea) I3. aflibercept (Eylea) C3 ranizumab (Lucentis)
O	<u>Efficacy outcomes</u>: Critical for decision making: - Visual function Important for decision making: - Visual acuity measured with validated scales - Quality of life - Cost effectiveness (comments only, evidence not graded) <u>Side effects</u>: Critical for decision making - Total mortality - Cardiovascular disease mortality - Myocardial infarction - Stroke - Endophthalmitis - Other serious ocular events Less important for decision making - Other complications

Eligibility criteria

Study design:

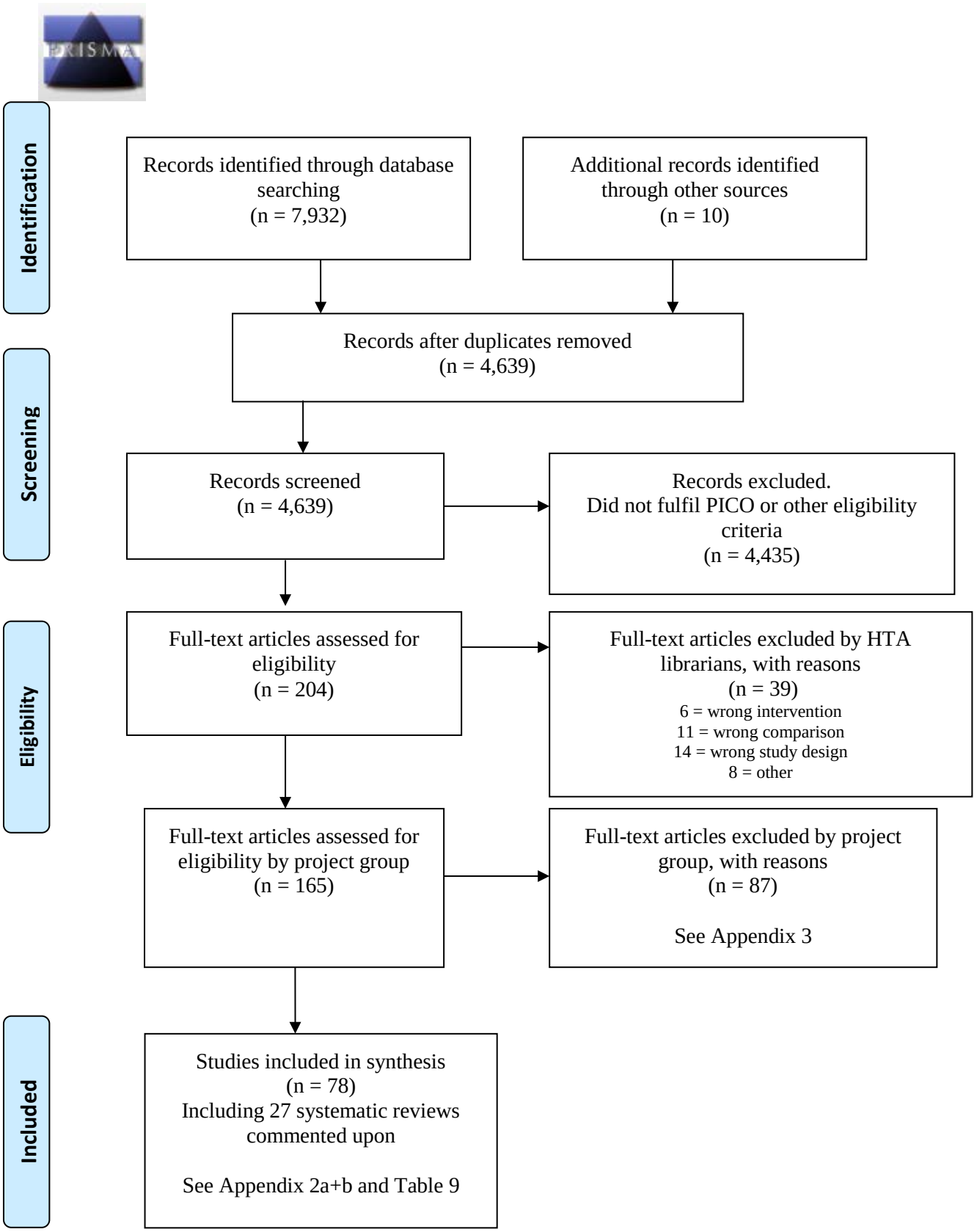
Systematic reviews 2013- (to be commented)
Randomized controlled trials ≥ 25 per study group for AMD (all RCT for other diagnoses)
Non-randomized controlled studies ≥ 25 per study group (controlled studies ≥ 500 for AMD)
Case-series for complications n ≥ 5,000 individuals (across all drugs and diagnoses) or n ≥ 5,000 injections for endophtalmitis (if number of patients ≥500 or number of patients not stated).

Language:

English, Swedish, Norwegian, Danish.

Publication date: 2004-

Selection process – flow diagram



Search strategies

Database: PubMed
Date: 2016-03-10
No of results: 790

Search	Query	Items found
#35	**Search #26 NOT #30 Filters: Swedish; Norwegian; German; English; Danish**	**790**
#31	Search #26 NOT #30	806
#30	Search #27 OR #28 OR #29	7345032
#29	Search animals[ti] OR animal[ti] OR rats[ti] OR rat[ti] OR mouse[ti] OR mice[ti]	1280218
#28	Search ((animals[mh]) NOT (animals[mh] AND humans[mh]))	4185569
#27	Search (Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp] OR case reports[ptyp])	3042433
#26	Search #24 AND #25	832
#25	Search pubmednotmedline[sb] OR inprocess[sb] OR publisher[sb]	2812520
#24	Search #14 AND #23	4372
#23	Search #15 OR #16 OR #17 OR #18 OR #22	33285
#22	Search #21 OR #20	1420
#21	Search Polypoidal choroidal vasculopathy or Polypoidal choroidal vasculopathies	758
#20	Search #18 AND #19	682
#19	Search myopia OR myopic	20503
#18	Search Choroidal Neovascularization or Choroid Neovascularization or Choroidal Neovascularizations or Choroid Neovascularizations	7425
#17	Search Retinal vein occlusion or Retinal vein occlusions or retinal venous occlusion or retinal venous occlusions or retinal vein thrombosis or retinal vein thromboses or RVO or BRVO or CRVO	5603
#16	Search Diabetic macular edema OR diabetic macular oedema	3832
#15	Search age-related macula degeneration OR age-related macular degeneration OR age-related macula degenerations OR age-related macular degenerations OR age-related maculopathy OR age-related maculopathies	24157
#14	Search Aflibercept OR Bevacizumab OR Ranibizumab OR eylea OR lucentis OR avastin OR pegaptanib OR macugen	14470

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present
Date: 2016-03-10
No of results: 2801

#	Searches	Results
1	exp bevacizumab/ or exp ranibizumab/	9098
2	(Aflibercept or Bevacizumab or Ranibizumab or pegaptanib or eylea or lucentis or avastin or macugen).ab,kf,ti.	12606
3	1 or 2	14036
4	macular degeneration/ or exp wet macular degeneration/	13069
5	((age-related or agerelated) adj2 macula$1 adj2 (degeneration$1 or maculopath$3)).ab,kf,ti.	12163
6	4 or 5	17245
7	exp Macular Edema/	4882
8	(diabetic adj2 macular adj2 (edema or oedema)).ab,kf,ti.	2290
9	7 or 8	5648

10	exp Retinal Vein Occlusion/	3237
11	(retinal adj2 (vein or venous) adj2 (occlusion$1 or thrombos$2)).ab,kf,ti.	3876
12	(rvo or crvo or brvo).ab,kf,ti.	1611
13	10 or 11 or 12	4746
14	exp Choroidal Neovascularization/	4349
15	(choroid$2 adj2 neovasculari#ation$1).ab,kf,ti.	5003
16	14 or 15	6361
17	myopi$1.ab,kf,ti.	16203
18	exp Myopia, Degenerative/	752
19	17 or 18	16244
20	16 and 19	618
21	(Polypoidal adj2 choroid$2 adj2 vasculopath$3).ab,kf,ti.	725
22	20 or 21	1323
23	6 or 9 or 13 or 22	26920
24	3 and 23	3743
25	(case reports or comment or editorial or letter).pt.	3044567
26	24 not 25	3013
27	24 not 26	730
28	(animals or animal or rats or rat or mouse or mice or monkey$1).ti.	1316728
29	(animals not (animals and humans)).sh.	4168833
30	28 or 29	4380461
31	26 not 30	2963
32	**limit 31 to (danish or english or german or norwegian or swedish)**	**2801**

Database: EMBASE (OVID SP) 1974 to 2016 March 09
Date: 2016-03-10
No of results: 3555

#	Searches	Results
1	exp aflibercept/ or exp bevacizumab/ or exp ranibizumab/ or exp pegaptanib/	42660
2	(Aflibercept or Bevacizumab or Ranibizumab or eylea or lucentis or avastin or pegaptanib or macugen).ti,ab,tn,kw.	27285
3	1 or 2	43751
4	exp age related macular degeneration/	1884
5	((age-related or agerelated) adj2 macula$1 adj2 (degeneration$1 or maculopath$3)).ab,kw,ti.	14558
6	4 or 5	15017
7	exp diabetic macular edema/	2731
8	(diabetic adj2 macular adj2 (edema or oedema)).ab,kw,ti.	2946
9	7 or 8	3863
10	exp retina vein occlusion/	6060
11	(retina$1 adj2 (vein or venous) adj2 (occlusion$1 or thrombos$2)).ab,kw,ti.	4902
12	(rvo or crvo or brvo).ab,kw,ti.	2094

13	10 or 11 or 12	7175
14	exp subretinal neovascularization/	7189
15	(choroid$2 adj2 neovasculari#ation$1).ab,kw,ti.	5899
16	14 or 15	8515
17	myopi$1.ab,kw,ti.	18983
18	exp degenerative myopia/	141
19	17 or 18	19008
20	16 and 19	760
21	(Polypoidal adj2 choroid$2 adj2 vasculopath$3).ab,kw,ti.	796
22	20 or 21	1536
23	6 or 9 or 13 or 22	26061
24	3 and 23	5202
25	3 and 23	5202
26	(animals or animal or rats or rat or mouse or mice or monkey$1).ti.	1519486
27	(animal not (animal and human)).sh.	1293384
28	26 or 27	2571019
29	25 not 28	5182
30	**limit 29 to (embase and (danish or english or german or norwegian or swedish) and yr="2004 - Current" and (article or conference paper or "review"))**	**3555**

Database: The Cochrane Library
Date: 2016-03-10
No of results: 786
Cochrane reviews 7
Other reviews 27
Technology assessments 37
Economic evaluations 21
Clinical trials 694

ID	Search	Hits
#1	Aflibercept or Bevacizumab or Ranibizumab or eylea or lucentis or avastin or pegaptanib or macugen:ti,ab,kw (Word variations have been searched)	2569
#2	age-related macula degeneration or age-related macular degeneration or age-related maculopathy or age-related maculopathies:ti,ab,kw (Word variations have been searched)	1502
#3	Diabetic macular edema or diabetic macular oedema:ti,ab,kw (Word variations have been searched)	764
#4	Retinal vein occlusion or Retinal vein occlusions or retinal venous occlusion or retinal venous occlusions or retinal vein thrombosis or retinal vein thromboses or RVO or BRVO or CRVO:ti,ab,kw (Word variations have been searched)	414
#5	Choroidal Neovascularization or Choroid Neovascularization or Choroidal Neovascularizations or Choroid Neovascularizations:ti,ab,kw (Word variations have been searched)	711
#6	myopia or myopic:ti,ab,kw (Word variations have been searched)	1612
#7	#5 and #6	47
#8	Polypoidal choroidal vasculopathy or Polypoidal choroidal vasculopathies:ti,ab,kw (Word variations have been searched)	30
#9	#2 or #3 or #4 or #7 or #8	2651
#10	**#1 and #9**	**786**

The web-sites of **SBU** and **Kunnskapssenteret** were visited
2016-08-01
Nothing relevant to the question at issue was found

Reference lists
A comprehensive review of reference lists brought 10 new records.

Reference lists

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Appendix 2a: Characteristics of included studies, listed according to first author and study design

First author, publication year	Study design	Number of participants (unless otherwise stated)	Follow-up period	Diagnose group(-s)	Studied drug(-s)	Age (±SD) (unless otherwise stated)	Men (%)	Outcomes (related to PICO)
Berg, 2016 (LUCAS trial)	RCT	441	2 years	AMD	Bevacizumab Ranibizumab	B: 78.7 (7.6) R: 78.0 (8.2)	B: 62 (29.1) R: 78 (35.8)	Visual acuity Adverse events
Berg, 2015 (LUCAS trial)	RCT	441	1 year	AMD	Bevacizumab Ranibizumab	B: 78.7 (7.6) R: 78.0 (8.2)	B: 62 (29.1) R: 78 (35.8)	Visual acuity Adverse events
Biswas, 2011	RCT	104	1,5 years	AMD	Bevacizumab Ranibizumab	Not reported	Not reported	Visual acuity (Adverse events)
Chakravarthy, 2013 (IVAN trial)	RCT	628	2 years	AMD	Bevacizumab Ranibizumab	B: 77.7 (7.3)* R: 77.8 (7.6)	B: 115 (39) R: 129 (41)	Visual acuity Quality of life Adverse events
Chakravarthy, 2012 (IVAN trial)	RCT	628	1 year	AMD	Bevacizumab Ranibizumab	B: 77.7 (7.2) R: 77.8 (7.6)	B: 115 (39) R: 129 (41)	Visual acuity Quality of life Adverse events
Ekinci, 2014	RCT	100	1 year	DME	Bevacizumab Ranibizumab	B: 68 (9) R: 65 (14)	B: 18 (36) R: 14 (28)	Visual acuity Adverse events
Heier, 2012 (VIEW 1 trial) (VIEW 2 trial)	RCT	2,419	1 year	AMD	Aflibercept Ranibizumab	VIEW 1 A†: 77.7 (7.9) to 78.4 (8.1)† R: 78.2 (7.6) VIEW 2 A: 73.8 (8.6) to 74.7 (8.67)† R: 73.0 (9.0)	VIEW 1 A: 110 (36.2) to 134 (44.5)† R: 132 (43.4) VIEW 2 A: 131 (42.8) to 149 (50.3)† R: 122 (41.9)	Visual acuity Visual function Adverse events
Kodjikian, 2013 (GEFAL trial)	RCT	501	1 year	AMD	Bevacizumab Ranibizumab	B: 79.6 (6.9) R: 78.7 (7.3)	B: 72 (37.7) R: 54 (29.5)	Visual acuity Adverse events

Appendix 2a: Characteristics of included studies, listed according to first author and study design

First author, publication year	Study design	Number of participants (unless otherwise stated)	Follow-up period	Diagnose group(-s)	Studied drug(-s)	Age (±SD) (unless otherwise stated)	Men (%)	Outcomes (related to PICO)
Krebs, 2013 (MANTA trial)	RCT	321	1 year	AMD	Bevacizumab Ranibizumab	B: 76.7 (7.8) R: 77.6 (8.1)	B: 56 (36.4) R: 59 (36.2)	Visual acuity Adverse events
Martin, 2011 (CATT trial)	RCT	1,185	1 year	AMD	Bevacizumab Ranibizumab	Monthly B: 80.1 (7.3) R: 79.2 (7.4) As needed B: 79.3 (7.6) R: 78.4 (7.8)	Monthly B: 106 (37.1) R: 118 (39.2) As needed B: 116 (38.7) R: 113 (37.9)	Visual acuity Adverse events
Martin, 2012 (CATT trial)	RCT	1,185	2 years	AMD	Bevacizumab Ranibizumab	Monthly B: 79.7 (7.5) R: 79.5 (7.4) As needed B: 78.9 (7.4) R: 78.3 (7.8)	Monthly B: 53 (39.3) R: 56 (38.4) As needed B: 104 (38.5) R: 108 (37.6)	Visual acuity Adverse events
Narayanan, 2015 (MARVEL trial)	RCT	75	0.5 years	RVO	Bevacizumab Ranibizumab	B: 50.5 (8.7) R: 52.9 (8.5)	B: 26 (68.4) R: 15 (40.5)	Visual acuity Adverse events
Pece, 2015	RCT	78	1-2 years	PM	Bevacizumab Ranibizumab	B: 61.43 (12.7) R: 56.95 (13.4)	B: 17 (42.5) R: 7 (18.4)	Visual acuity Adverse events

Appendix 2a: Characteristics of included studies, listed according to first author and study design

First author, publication year	Study design	Number of participants (unless otherwise stated)	Follow-up period	Diagnose group(-s)	Studied drug(-s)	Age (±SD) (unless otherwise stated)	Men (%)	Outcomes (related to PICO)
Rajagopal, 2015 (CRAVE trial)	RCT	98	0.5 years	RVO	Bevacizumab Ranibizumab	B: 70.6 (13.0) R: 72.4 (11.1)	B: 20 (40.8) R: 24 (49.0)	Visual acuity Adverse events
Schmidt-Erfurth, 2014 (VIEW 1 trial) (VIEW 2 trial)	RCT	2,457	96 weeks (1.8 years)	AMD	Aflibercept Ranibizumab	A: 75.8 (8.8) to 76.5 (8.5)† R: 75.6 (8.7)	A: 780 (42.9) R: 254 (42.7)	Visual acuity Adverse events
Scholler, 2014	RCT	55	1 year	AMD	Bevacizumab Ranibizumab	B: 80.8 (6.6) R: 79.5 (6.8)	B: 9 (9) R: 7 (6) (Patients who finished the study)	Visual acuity Adverse events
Wells, 2015 (DRCR-network)	RCT	660	1 year	DME	Aflibercept Bevacizumab Ranibizumab	A: 60 (10) B: 62 (10) R: 60 (11)	A: 114 (51) B: 115 (53) R: 124 (57)	Visual acuity Adverse events
Wells, 2016 (DRCR-network)	RCT	660	2 years	DME	Aflibercept Bevacizumab Ranibizumab	A: 60 (10) B: 62 (10) R: 60 (11)	A: 114 (51) B: 115 (53) R: 124 (57)	Visual acuity Adverse events
Yuzawa, 2015 (VIEW 1 trial) (VIEW 2 trial)	RCT	2,457	1 year	AMD	Aflibercept Ranibizumab	VIEW 1 A†: 77.7 (7.9) to 78.4 (8.1)† R: 78.2 (7.6) VIEW 2 A: 73.8 (8.6) to 74.7 (8.67)† R: 73.0 (9.0)	VIEW 1 A: 110 (36.2) to 134 (44.5)† R: 132 (43.4) VIEW 2 A: 131 (42.8) to 149 (50.3)† R: 122 (41.9)	Visual function
Al-Rashaed 2016	Cohort	22,674 injections	Not reported	Not reported	Bevacizumab Ranibizumab	Not reported	Not reported	Endophtalmitis

Appendix 2a: Characteristics of included studies, listed according to first author and study design

First author, publication year	Study design	Number of participants (unless otherwise stated)	Follow-up period	Diagnose group(-s)	Studied drug(-s)	Age (±SD) (unless otherwise stated)	Men (%)	Outcomes (related to PICO)
		(B: 21,387 R: 1,287)						
Bakbak, 2013	Cohort	87	4 weeks	DME	Bevacizumab Ranibizumab	B: 54.31 (12.67) R: 56.01 (13.29)	B: 20 (36.4) R: 12 (37.5)	Visual acuity
Bhavsar, 2015	Cohort	17,296 injections (A: 148 B: 15,479 R: 1,669)	Not reported	Mixed	Aflibercept Bevacizumab Ranibizumab	In the whole study population: 81	In the whole study population: 1,251 (36.2)	Endophtalmitis
Chong, 2010	Cohort	20,005 injections (B: 16,166 R: 3,839)	Not reported	Mixed	Bevacizumab Ranibizumab	Not reported	Not reported	Endophtalmitis
Curtis, 2010	Cohort	57,744	2 years	AMD	Bevacizumab Ranibizumab	B: median (IQR) 81.0 (76.0-86.0) R: median (IQR) 82.0 (77.0-86.0)	B: 14,108 (36.4) R: 6,763 (35.5)	Adverse events
Fintak, 2008	Cohort	26,905 injections (B: 12,585 R: 14,320)	Not reported	Mixed	Bevacizumab Ranibizumab	Not reported	Not reported	Endophtalmitis
Ladas, 2009	Cohort	450 with 2,000 injections (B: 1,275 R: 725)	3-24 months	Mixed	Bevacizumab Ranibizumab	Not reported	Not reported	Adverse events
Moshfeghi, 2011	Cohort	58,307 injections (B: 39,700 R: 18,607)	Not reported	Mixed	Bevacizumab Ranibizumab	Not reported	Not reported	Endophtalmitis

Appendix 2a: Characteristics of included studies, listed according to first author and study design

First author, publication year	Study design	Number of participants (unless otherwise stated)	Follow-up period	Diagnose group(-s)	Studied drug(-s)	Age (±SD) (unless otherwise stated)	Men (%)	Outcomes (related to PICO)
Nuzzi and Tridico, 2015	Cohort	1,144 eyes	Not reported	Mixed	Bevacizumab Ranibizumab	Not reported	Not reported	Adverse events
Park, 2013	Cohort	16,186 injections (B: 9,125 R: 7,061)	Not reported	Mixed	Bevacizumab Ranibizumab	B: 59.1 (11.2) R: 63.4 (12.6)	B: 4,627 (50.7) R: 3,418 (48.4)	Endophtalmitis
Rayess, 2016	Cohort	503,890 injections (A: 40,356 B: 153,812 R: 309,722)	Not reported	Mixed	Aflibercept Bevacizumab Ranibizumab	A: 82 (6.1) B: 75 (12.5) R: 80 (9.2)	Not reported	Endophtalmitis
Schlenker, 2015	Cohort	57,919	1 year	AMD	Bevacizumab Ranibizumab	Not reported	B: 15,663 (46) R: 9,401 (39)	Adverse events
Shah, 2011	Cohort	27,736 injections (B: 10,958 R: 16,778)	≈1.5 year	Mixed	Bevacizumab Ranibizumab	Not reported	Not reported	Endophtalmitis
Sharma, 2012	Cohort	524 (1,584) B: 173 (693) R: 351 (891)	1 month	Mixed	Bevacizumab Ranibizumab	B: 76.9 R: 78.7	B: 73 (42) R: 129 (37)	Adverse events Endophtalmitis
Souied, 2016	Cohort	81,046 with 432,123 injections (A: 179,147 R: 253,647)	Not reported	AMD	Aflibercept Ranibizumab	Not reported	Not reported	Endophtalmitis

Appendix 2a: Characteristics of included studies, listed according to first author and study design

First author, publication year	Study design	Number of participants (unless otherwise stated)	Follow-up period	Diagnose group(-s)	Studied drug(-s)	Age (±SD) (unless otherwise stated)	Men (%)	Outcomes (related to PICO)
Tabandeh, 2014	Cohort	8,210 injections B: 8,533 R: 2,724	Not reported	Mixed	Bevacizumab Ranibizumab	Not reported	Not reported	Endophtalmitis
Terzic, 2015	Cohort	1,101 injections A: 60 B: 986 R: 55	Not reported	Mixed	Aflibercept Bevacizumab Ranibizumab	Not reported	Not reported	Endophtalmitis
Yuan, 2014	Cohort	59	0.5 years	RVO	Bevacizumab Ranibizumab	B: 69.8 (2.2) R: 63.7 (2.9)	Not reported	Visual acuity
Etminan, 2016	Case-series	5,644	Not reported	AMD	Bevacizumab	80.1 (10.1)	4,521 (80.1)	Myocardial infarct. Stroke
Goldberg, 2014	Case-series	5,356 injections	Not reported	Mixed	Aflibercept	Not reported	Not reported	Adverse events
Mason, 2008	Case-series	5,233 injections		Mixed	Bevacizumab	Not reported	Not reported	Endophtalmitis

B = bevacizumab, R=ranibizumab

* As stated in supplementary appendix, Table A1 (Chakravarthy *et al*., 2013), † Age range for groups with different dosing regimens of aflibercept.

Appendix 2b: Characteristics of included studies cost effectiveness, listed according to first author and study design

First author, publication year	Study design	Patient group	n	Study design	Intervention	Comparison 1	Comparison 2
Adedokun 2016	Markov model	BRVO	Virtual cohort		Ranibizumab	Aflibercept	
Chakravarthy 2015	RCT	nAMD	525		Ranibizumab	Bevacizumab	
Dakin 2014	RCT	nAMD	610		Ranibizumab	Bevacizumab	
Elshout 2014	Model-based	nAMD	Virtual cohort		Aflibercept	Bevacizumab	Ranibizumab
Hutton 2014	Markov model	DME	Virtual cohort		Ranibizumab	Bevacizumab	
Nwanze 2012	Markov model	nAMD	Virtual cohort		Bevacizumab	Ranibizumab	
Patel 2012	Markov model	nAMD	Virtual cohort		Bevacizumab	Ranibizumab	
Raftery 2007	Model model	nAMD	Virtual cohort		Ranibizumab	Bevacizumab	
Régnier 2015	Markov model	DME	Virtual cohort		Ranibizumab	Aflibercept	
Stein 2013	Markov model	nAMD	Virtual cohort		Bevacizumab	Ranibizumab	
Stein 2014	Markov model	nAMD	Virtual cohort		Bevacizumab	Ranibizumab	

Appendix 3. Excluded articles

Study (author, publication year)	Reason for exclusion
Abell RG et al, 2012	Not correct PICO (wrong comparison; number of cases not given per drug)
Azar G et al, 2015	Not correct PICO, wrong outcome (only macular hematoma)
Barbazetto I et al, 2010	Not correct PICO (wrong comparison, wrong outcome, case series <5000).
Biagi C et al, 2014	Not correct PICO (wrong study type. Study on adverse events in WHO database- no denominator).
Biarnes M et al, 2011	Not correct PICO (case series n<5000).
Boyer DS et al, 2009	Not correct PICO (case series n<5000).
Bressler NM et al, 2012	Wrong study type (review).
Brown DM et al, 2013	Not correct PICO (wrong comparison; ranibizumab vs placebo; case series n<5000).
Brown DM et al, 2015	Not correct PICO (wrong comparison, aflibercept vs laser, case series n<5000).
Buckle M et al, 2015	Not correct PICO (wrong comparison; number of cases not given per drug).
Busbee BG et al, 2013	Not correct PICO (case series n<5000).
Campbell RJ et al, 2012	Wrong study type. Not correct PICO (wrong comparison).
Carneiro AM et al, 2012	Not correct PICO (AMD; controlled, non-RCT n <500).
Chang TS et al, 2009	Not correct PICO (AMD; controlled, non-RCT n <500).
Cho HJ et al, Korean J Ophtalmol, 2012	Not correct PICO (wrong population).
Cho HJ et al, Eye, 2012	Not correct PICO (wrong population).
Cho HJ et al, 2016	Not correct PICO (wrong population).
Chrapek O et al, 2015	Not correct PICO (wrong intervention).
Daniel E et al, 2014	Not correct PICO (wrong outcome).
Davis RP et al, 2010	Not correct PICO (case series n<5000).
Day S et al, 2011	Not correct PICO (wrong comparison; number of cases not given per drug).
De Bats F et al, 2012	Not correct PICO (AMD; controlled, non-RCT n <500).
Dedania VS et al, 2016	Wrong study type (review).
Dossarps D et al, 2015	Not correct PICO (wrong comparison; number of cases given per drug, but no denominator).
Fischer N et al 2013	Not correct PICO (wrong comparison, case series n<5000).
French DD et al 2011	Wrong design (case-control)
Freund KB et al, 2015	Not correct PICO (wrong outcome, intra-ocular pressure).
Gamulescu MA et al, 2010	Not correct PICO (AMD; controlled, non-RCT, n<500)
Gewaily DY et al, 2014	Not correct PICO (wrong outcome, delayed patchy choroidal filling).
Gillies MC et al, 2014	Not correct PICO (wrong comparison; study design compares effects in “real life” to phase III studies)
Grunwald et al, 2014	Not correct PICO (wrong outcome, only geographic atrophy).
Grunwald et al, 2015	Not correct PICO (wrong outcome, only geographic atrophy).
Ip MS et al, 2012	Not correct PICO (case series n<5000).
Ip MS et al, 2015	Not correct PICO (case series n<5000).

Appendix 3. Excluded articles

Study (author, publication year)	Reason for exclusion
Jaffe GJ et al, 2013	Not correct PICO (wrong outcome, 1-year VA in Martin 2011).
Kelly SP et al, 2011	Wrong study type. Study on patient safety incidents in NHS database- no denominator.
Kemp et al, 2013	Not correct PICO (wrong comparison; outcomes not given per drug).
Kim BJ et al, 2014	Not correct PICO (wrong comparison, wrong outcome; pat with and without sporadic visual loss compared)
Kunavisarut P et al, 2013	No data for comparison (case series n<5000)
Kwon SI et al, 2013	Not correct PICO (wrong comparison (triamcinolone); case series n<5000).
Lazzeri S et al, 2015	Not correct PICO (SR; switching).
Lee AY et al, 2015	Not correct PICO (wrong population; patients with AMD with vision better than 6/12)
Lyall DA et al, 2012	Wrong study type, endophtalmitis case control study- no denominator for endophtalmitis
Maguire MG et al, 2013	Not correct PICO (wrong comparison, wrong outcome; fellow eye studied in CATT).
Meredith TA et al, 2015	Wrong study type. (Endophtalmitis in CATT- no denominator.)
Mozayan A et al, 2013	Not correct PICO (case series n<5000).
Ng WY et al, 2015	Not correct PICO (No relevant comparison data, case series n<5000
Niederhauser N et al, 2013	Article in German.
Ozkaya et al, J of Ocular Pharmacology, 2013	Not correct PICO (AMD; controlled, non-RCT, n<500)
Ozkaya et al, ISRN Ophtalmology, 2013	Not correct PICO (AMD; controlled, non-RCT, n<500)
Ozturk BT et al, 2011	Not correct PICO (DME; controlled, non-RCT, n<25 per study group)
Pratt NL et al, 2014	Not correct PICO (case series n<5000).
Qureshi F et al, 2011	Not correct PICO (case series n<5000).
Rahimy E et al, 2015	Not correct PICO (DME; controlled, non-RCT, n<25 per study group)
Ranchod TM et al, 2011	Not correct PICO (case series n<5000).
Rayess N et al, 2015	Not correct PICO (wrong comparison; outcomes not given per drug).
Richard G et al, 2015	Not correct PICO (wrong comparison; outcomes not given per drug). VIEW 1 & 2 included see Heier and Schmidt-erfurt
Rosenfeld PJ et al, 2006	Not correct PICO (case series n<5000).
Ruiz-Moreno JM et al, 2013	Not correct PICO (PM; controlled, non-RCT, n<25 per study group)
Sarraf D et al, 2014	Not correct PICO (wrong population; patients with AMD and retinal pigment tear)
Sawada O et al, 2016	Non-systematic review.
Schmid MK et al, PLoS ONE, 2015	Wrong outcome
Sharma S et al, 2016	Duplicate. The outcome VA in CATT study included in Martin 2011 and 2012.
Shin HJ et al 2014	Not correct PICO (wrong outcome; retinal nerve fiber layer thickness).
Singer et al., 2013	Not correct PICO (wrong P, combined treatment with cortisone)
Sivaprasad S et al 2016	Wrong study type.
Sophie R et al, 2015	Not correct PICO (wrong comparison (sham); case series n<5000).
Suner IJ et al, 2013	Not correct PICO (wrong comparison (sham); case series n<5000).

Appendix 3. Excluded articles

Study (author, publication year)	Reason for exclusion
Virgili G, 2014	Wrong comparison, laser
Tareen IU et al, 2013	Not correct PICO (case series n<5000).
Tufail A et al, 2014	Not correct PICO (case series n>5000 but no complications).
Van Asten F et al, 2015	Not correct PICO (case series n<5000).
VanderBeek BL et al, 2015	Not correct PICO (wrong comparison; outcomes not given per drug).
Wells JA et al, 2016	Not correct PICO (wrong population; subgroup of patients with DME in Wells studies)
Wiley HE et al, 2016	Wrong study type. (Cross-over design)
Wolf-Schnurrbusch UE et al, 2011	Not correct PICO (wrong comparison; outcomes not given per drug).
Ying GS et al, 2013	VA in subgroup in CATT. Duplicate. The outcome VA in CATT study included in Martin 2011 and 2012.
Ying GS et al, 2014	VA in subgroup in CATT. Duplicate. The outcome VA in CATT study included in Martin 2011 and 2012.
Ying GS et al, 2015	VA in subgroup in CATT. Duplicate. The outcome VA in CATT study included in Martin 2011 and 2012.
Yoon JU et al, 2010	Not correct PICO (wrong comparison (photodynamic therapy, case series n<5000).
Zarranz-Ventura J et al, 2014	Not correct PICO (wrong population; effect in second treated eye). Jmf Tufail
Zhou P et al, 2015	Not correct PICO (wrong population; idiopathic choroidal neovascularization).
Zhu D, 2013	Meta-analysis only including studies with wrong comparison

Ögonläkemedel
Appendix 3b. Excluded articles cost effects

Study author, publication year	Reason for exclusion
Cadth, 2014	Review
Hodge, 2010	Review
Mitchell, 2011	Review
Schauwvlieghe AM et al, 2015	Wrong publication type. Study protocol presented, no data.

* + No or minor problems
? Some problems
- Major problems

Project: Efficacy and safety of intraocularly administered vascular endothelial growth factor inhibitors
Appendix 4:1. Visual acuity for bevacizumab versus ranizumab in Age-related macular degeneration (AMD)

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results		Comments	* Directness	* Study limitations	* Precision
				Intervention Bevacizumab (bev)	Control Ranizumab (ran)				
Berg, 2016, Norway	RCT	441	102	Change letters, mean ±SD: +7.4 ±16.0 Per protocol: 95%CI for mean difference: -4.1 to 2.5, p=0.634 Intention to treat: +7.8 95%CI for mean difference: -3.2 to 2.7, p=0.873	Change letters, mean ±SD: +6.6 ±15.2 Intention to treat: +7.5	Pats > 50 years, VA 20/25-20/320 2 year data	?	+	+
Berg, 2015, Norway	RCT	441	70	Change letters, mean ±SD: +7.9+/-13.4 Per protocol: 95%CI for mean difference: -2.4 to 2.9, p=0.845 Intention to treat: +7.8 95%CI for mean difference:: -2.2 to 2.5, p=0.550	+8.2+/-12.5 Intention to treat: +8.0	Pats > 50 years, VA 20/25-20/320 Treat-and-extend protocol 1 year data	?	+	+
Biswas 2011, India	RCT	120	16	Change letters, mean At 12 months: +0.52 p=0.46 At 18 months: +3.96 p=0.56	Change letters, mean At 12 months: +3.22 At 18 months: +3.56	Pat >50 years, BCVA 35-70 ltrs 18 month data 3,6,12,18 month data Confidence intervals not stated	-	-	-
Chakravarthy, 2013, Multicentre UK	RCT	610	103	Absolute changes not stated Mean difference (95%CI): -1.37 (-3.75 to 1.01) n.s. (favours ran)	Absolute changes not stated	Pats > 50 years, VA>25 ltrs Four arms: (bev/ran, continuous/discontinuous) 2 year data, IVAN study	+	+	+

Project: Efficacy and safety of intraocularly administered vascular endothelial growth factor inhibitors

Appendix 4:1. Visual acuity for bevacizumab versus ranizumab in Age-related macular degeneration (AMD)

* + No or minor problems
? Some problems
- Major problems

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results		Comments	* Directness	* Study limitations	* Precision
				Intervention Bevacizumab (bev)	Control Ranizumab (ran)				
Chakravarthy, 2012, Multicentre UK	RCT	610	67	Absolute values given but absolute changes not stated Mean difference (95%CI): -1.99 (-4.04 to 0.06), p=0.056 (favours ran)		Pats > 50 years, VA>25 ltrs 1 year data, IVAN study	+	+	+
Kodjikian, 2013, France	RCT	501	127 (PP) 97(ITT)	Absolute changes (letters) +5.4±14.4 Mean difference (95%CI): +1.89 (-1.16 to +4.93) p<0.0001 (non-inferiority) favours bev Intention to treat, Mean difference (95%CI): +2.36 (-0.72 to 5.44) p<0.0001 (non-inferiority) favours bev,	Absolute changes (letters) +3.6±14.2	Pats > 50 years, VA 20/32-20/320 1 year GEFAL study	?	?	+
Krebs, 2013, Multicentre Austria	RCT	323	4	BCVA change: +4.9 p=0.78	BCVA change: +4.1	Pats > 50 years, VA 20/40-20/320 1 year MANTA study	?	-	+
Catt research group Martin, 2011, Multicenter US	RCT	1,185	80	Monthly, mean ±SD At 1 year: +8.0 ±15.8 Difference at 1 year: -0.5, CI95%: -3.9 to 2.9 As needed, mean (±SE) At 1 year: 5.9 ±15.7 Difference at 1 year: -0.8, CI95%: -4.1 to 2.4	Monthly, mean ±SD At 1 year: +8.5 ±14.1 As needed, mean (±SE) At 1 year: +6.8 ±13.1	Pats > 50 years, VA 20/25-20/320 1 year data CATT study	?	?	+

* + No or minor problems
? Some problems
- Major problems

Project: Efficacy and safety of intraocularly administered vascular endothelial growth factor inhibitors
Appendix 4:1. Visual acuity for bevacizumab versus ranizumab in Age-related macular degeneration (AMD)

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results		Comments	* Directness	* Study limitations	* Precision
				Intervention Bevacizumab (bev)	Control Ranizumab (ran)				
Martin, 2012, Multicentre USA	RCT	129+134		Mean ±SD At 2 years: +7.8±15.5 n.s.	Mean ±SD At 2 years: +8.8±15.9	Pats > 50 years, VA 20/25-20/320 2 year data Mixed groups, only single monthly dosage one drug only was considered CATT study	?	?	+
Scholler, 2014, Austria	RCT	55	9	Absolute incremental data not stated Mean difference +5.5 ltrs, CI not stated (favours bev), p=0.631		Pats > 50 years, VA 20/40-20/320 1 year	-	-	-

* + No or minor problems
? Some problems
- Major problems

Project: Efficacy and safety of intraocularly administered vascular endothelial growth factor inhibitors
Appendix 4:2. Visual acuity for aflibercept versus bevacizumab versus ranibizumab in diabetic macular edema (DME)

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results			Comments	Directness *	Study limitations *	Precision *
				Aflibercept Within group mean±SD Between groups mean difference, 95% CI	**Bevacizumab** Within group mean±SD Between groups mean difference, 95% CI	**Ranibizumab** Within group mean±SD Between groups mean difference, 95% CI				
Ekinci 2014 Turkey	RCT	100	Not stated	Not evaluated	Basal letter score (Snellen) Mean ±SD: Before: 0.22±0.11 After 0.38±0.12 p<0.01 within group bev vs. ran: n.s.	Basal letter score (Snellen) Mean ±SD: Before: 0.24 ±0.12 After: 0.39±0.11 p<0.01 within group		-	-	-
Wells, 2015, USA	RCT	660	Afli: 16 Bev: 12 Ran:12 Total 40	Basal letter score <69 At 1 year: Mean improvement ±SD: +18.9 ±11.5 Difference (95%CI) afli vs bev: 6.5 (+2.9 to +10.1) p<0.001) afli vs ran: +4.7 (+1.4 to +8.0) p= 0.003 Basal letter score 78-69 At 1 year: Mean improvement ±SD: 8.0 ±7.6 Difference (95%CI) afli vs bev: +0.7, (-1.3 to +2.7) p=0.69)	Basal letter score <69 At 1 year: Mean improvement ±SD: +11.8 ± 12.0 Difference (95%CI) bev vs ran: -1.8, (-4.8 to +1.1) p=0.21 Basal letter score 78-69 At 1 year: Mean improvement ±SD: +7.5 ±7.4 Difference (95%CI) bev vs ran: -1.1 (-3.1 to +0.9) p=0.69	Basal letter score <69 At 1 year: Mean improvement ±SD: +14.2 ± 10.6 Basal letter score 78-69 At 1 year: Mean improvement ±SD: +8.3±6.8	Diabetic Retinopathy Network 1 year data	?	+	+

* + No or minor problems
? Some problems
- Major problems

Project: Efficacy and safety of intraocularly administered vascular endothelial growth factor inhibitors
Appendix 4:2. Visual acuity for aflibercept versus bevacizumab versus ranibizumab in diabetic macular edema (DME)

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results			Comments	Directness *	Study limitations *	Precision *
				Aflibercept Within group mean±SD Between groups mean difference, 95% CI	**Bevacizumab** Within group mean±SD Between groups mean difference, 95% CI	**Ranibizumab** Within group mean±SD Between groups mean difference, 95% CI				
				Difference (95%CI) afli vs ran: -0.4, (-2.3 to +1.5) p=0.69						
Wells, 2016, USA				Basal letter score <69 At 2-years: Mean improvement ±SD: +18.1 ±13.8 Difference (95%CI) afli vs bev: +4.7 (+0.5 to +8.8) p=0.02 afli vs ran: +2.3 (-1.1 to +5.6) p= 0.18 Basal letter score 78-69 At 2-years: Mean improvement ±SD: 7.8 ±8.4 Difference (95%CI) afli vs bev: +1.1, (-1.1 to +3.4) p=0.51 Difference (95%CI) afli vs ran: -0.7, (-2.9 to +1.5) p=0.51	Basal letter score <69 At 2-years: Mean improvement ±SD: +13.3 ± 13.4 Difference (95%CI) bev vs ran: -2.4, (-5.8 to1.0) p=0.18. Basal letter score 78-69 At 2-years: Mean improvement ±SD: +6.8 ±8.8 Difference (95%CI) bev vs ran: -1.9 (-4.7 to 0.9) p=0.31	Basal letter score <69 At 2-years: Mean improvement ±SD: +16.1 ± 12.1 Basal letter score 78-69 At 2-years: Mean improvement ±SD: +8.6±7.0		?	+	+

* + No or minor problems
? Some problems
- Major problems

Project: Efficacy and safety of intraocularly administered vascular endothelial growth factor inhibitors

Appendix 4:2. Visual acuity for aflibercept versus bevacizumab versus ranibizumab in diabetic macular edema (DME)

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results			Comments	Directness *	Study limitations *	Precision *
				Aflibercept Within group mean±SD Between groups mean difference, 95% CI	**Bevacizumab** Within group mean±SD Between groups mean difference, 95% CI	**Ranibizumab** Within group mean±SD Between groups mean difference, 95% CI				
Bakbak, 2013	Cohort	87	0	Not studied	Pretreatment median (range): 39 (14-51) ETDRS letters At 4 weeks median (range): 45 (15-54) ETDRS letters p=0.332 (within group)	Pretreatment median (range): 45 (18-61) ETDRS letters At 4 weeks median (range): 48 (19-63) ETDRS letters p=0.311 (within group)	No p-value stated for intergroup comparison	+	-	-

ETDRS = Early Treatment Diabetic Retinopathy Study chart.

Project: Efficacy and safety of intraocularly administered vascular endothelial growth factor inhibitors

Appendix 4:3. Visual acuity for bevacizumab versus ranizumab in retinal vein occlusion (RVO)

* + No or minor problems
? Some problems
- Major problems

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results		Comments	* Directness	* Study limitations	* Precision
				Intervention Bevacizumab (bev)	Control Ranizumab (ran)				
Naranyan 2015 India	RCT	75	Not stated	Base line, mean ±SD: 56.10±10.01 At 6 months, mean ±SD: 71.66±9.96 (p<0.0001 vs baseline) Mean change (95%CI): +15.6 (+12.0 to +20.5), p<0.0001	Base line, mean ±SD: 52.81±14.41 At 6 months, mean ±SD: 70.89±13.35 (p<0.0001 vs baseline) Mean change (95%CI): +18.1 (+12.8 to +22.6), p<0.0001		?	?	?
Rayagobal 2015 USA	RCT	98	24	Baseline BCVA (log Mar): 0.76±0.38 Mean gain ±SD (95%CI): +0.33±0.45, (-0.47 to -0.18) n.s. p=0.38 for difference between treatment effect in bev vs ran group	Base line BCVA (log Mar): 0.73±0.45 Mean gain ±SD, (95%CI): +0.34±0.33, (-0.45 to-0.23) n.s.	BCVA secondary outcome only	-	-	?
Yuan, 2014	Cohort	59 (eyes)	0	At approximately 1.2 years LogMAR change, mean±SE: -0.29± 0.09 P=0.66 (difference in change)	At approximately 1.2 years LogMAR change, mean±SE: -0.35± 0.08	Mean follow up time for bev: 423 days, for ran: 453 days	?	-	-

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Appendix 4:4. Visual acuity for bevacizumab versus ranizumab in pathological myopia (PM)

* + No or minor problems
? Some problems
- Major problems

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results		Comments	* Directness	* Study limitations	* Precision
				Intervention Bevacizumab (bev)	Control Ranibizumab (ran)				
Pece, 2015	RCT	78		Baseline mean ±SD (range): 54.08 ±24.74 (6-85) Final BCVA letter score, mean ±SD (range): 54.93 ±25.7 (12-85) p bev vs ran = 0.040 at baseline p bev vs ran=0.78 at follow-up	Baseline mean ±SD (range): 45.45 ±22 (13-80) Final BCVA letter score mean ±SD (range): 58.26 ±21.21 (10-85)	No change in absolute values in bev-group, seeming change in ran group, due to group asymmetry. Mean follow up 19 months (SD 2, range 12-24)	?	-	-

* + No or minor problems
? Some problems
- Major problems

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Appendix 4:5. Visual function for aflibercept versus ranizumab in age-related macula degeneration (AMD)

Author, year, country	Study design	Number of participants (n)	With drawals - dropouts	Results		Comments	* Directness	* Study limitations	* Precision
				Intervention Aflibercept (afli)	Control Ranibizumab (ran)				
Heier, 2012 USA+Canada=VIEW1 Europe et al=VIEW2	RCT Non-inferiority	2,419	Afli 2q4: 19 Afli 0.5q4: 31 Afli 2q8:36 Ran: 35	Primary endpoint*, n (%) VIEW 1 2q4: 289/304 (95.1) 0.5q4: 286/301 (95.0) 2q8: 284/301 (94.4) VIEW 2 2q4: 292/309 (94.5) 0.5q4: 282/296 (95.3) 2q8: 292/306 (95.4)	Primary endpoint*, n(%) VIEW 1 0.5q4: 285/304 (93.8) VIEW 2 0.5q4: 276/291 (94.8)	VIEW 1 and 2 similar design but visual function (VF) was collected by telephone in VIEW 1 and face to face in VIEW 2. VF measured by questionnaire. Different dose regimens for aflibercept. *Primary endpoint: proportion of patients maintaining vision defined as losing <15 ETDRS letters.	+	+	+
Yuzawa, 2015 USA+Canada=VIEW1 Europe et al=VIEW2	RCT	2,419	Not stated	VF general vision mean difference ±SD VIEW1 (n=288) 10.1±19.0 VIEW2 (n=297) 9.1±17.0	VF general vision mean difference ±SD VIEW1 (n=296) 9.5±18.8 VIEW2 (n=286) 9.5±18.1	VIEW 1 and 2 similar design but visual function (VF) was collected by telephone in VIEW 1 and face to face in VIEW 2. VF measured by questionnaire NEI VFQ-25.	+	+	+

* + No or minor problems ? Some problems - Major problems

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Appendix 4:6. Visual acuity for aflibercept versus ranizumab in age-related macula degeneration (AMD)

Author, year, country	Study design	Number of patients n=	With drawals - dropouts	Results		Comments	* Directness	* Study limitations	* Precision
				Intervention Aflibercept (afli)	Control Ranizumab (ran)				
Heier 2012 Multicentre	RCT	2,419	Afli: 0.5q4: 31 Ran: 0.5q4 35 (Afli: 2q4: 19 Afli: 2q8: 36)	Mean change ±SD View 1 0.5q4: +6.9 ±13.4 Mean difference (CI95%) afli vs ran: - 0.80 (-3.03 to +1.43), n.s. Mean change ±SD View 2 0.5q4: +9.7 ±14.1 Mean difference (CI95%) afli vs ran: -0.06 (-2.24 to 2.12), n.s.	Mean change ±SD View 1 0.5q4 +8.1±15.3 Mean change ±SD View 2 0.5q4: +9.4±13.5	View 1+2, different populations 1 year data	+	+	+
Schmidt-Erfurt 2014	RCT	2,419	87+125	Week 96 View 1 & 2 pooled change: +6.6 *	Week 96 View 1 & 2 pooled change: +7.9 *	View 1+2, different populations *CI not stated, p not stated	+	+	+

5q4 = 0.5 mg every four weeks

* + No or minor problems
? Some problems
- Major problems

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Appendix 4.7 Adverse events, according to diagnose group and study design, for intravitreal bevacizumab (B) or ranibizumab (R) injections

Author, year, country	Study design	Number of participants (injections within parentheses) in the safety analyses	Follow-up period	Adverse events (AE) n (%)						Comments	Directness *	Study limitations*	Precision *
				All-cause mortality	Cardio-vascular mortality	Myocard. infarction	Stroke	Endophtal-mitis	Other				
Adverse events in patients with age-related macular degeneration (AMD) with intravitreal bevacizumab (B) or ranibizumab (R) injections													
Berg, 2016 (LUCAS trial)	RCT	441 B = 220 R = 221	2 years	B: 15 (6.8) R: 13 (5.9) n.s.	B: 3 (1.4) R: 2 (0.9) n.s.	B: 3 (1.4) R: 9 (4.1) n.s.*	B: 3 (1.4) R: 4 (1.8) n.s.*	B: 1 (0.5) R: 0 (0.0) n.s.	† Serious ocular events: B: 10 (4.5) R: 0 (0.0) p=0.0009	* Non-fatal † Endophthalmitis, pseudoendophthalmitis, macular hemorrhage, retinal tear, pigment epithelial rupture, acute glaucoma; calculated with Fisher's exact test)	?	+	+
Berg, 2015 (LUCAS trial)	RCT	441 B = 220 R = 221	1 year	B: 4 (1.8) R: 7 (3.2) n.s.	B: 1 (0.5) R: 1 (0.5) n.s.	B: 0 (0.0) R: 6 (2.7) n.s.*	B: 2 (0.9) R: 3 (1.4) n.s.*	B: 0 (0.0) R: 0 (0.0) n.s.	† Serious ocular events: B: 5 (2.3) R: 0 (0.0) p=0.03	* Non-fatal † Pseudoendophthalmitis, macular hemorrhage, retinal tear, pigment epithelial rupture; calculated with Fisher's exact test)	?	+	+
Biswas, 2011	RCT	104 B = 50 R = 54	1,5 years	Not reported	Not reported	Not reported	Not reported	Not reported	Minor adverse events: B: (11.1) R: (7.3)		-	-	-
Chakravarthy, 2013 (IVAN trial)	RCT	610 B = 296 R = 314	2 years	B: 15 (5.1) R: 15 (4.8) n.s.‡	B: 4 (1.4) R: 3 (1.0) n.s.‡	B: 5 (1.7) R: 4 (1.3) n.s.‡*	B: 3 (1.0) R: 6 (1.9) n.s.‡*	B: 0 (0.0) R: 0 (0.0) n.s.‡	† Serious ocular events: B: 6 (2.0) R: 10 (3.2) n.s.‡	‡ Calculated with Fisher's exact test * Non-fatal † Uveitis, retinal detachment, pigment epithelial tear, other)	+	+	+
Chakravarthy, 2012 (IVAN trial)	RCT	610 B = 296 R = 314	1 year	B: 5 (1.7) R: 6 (1.9) n.s.‡	B: 0 (0.0) R: 1 (0.3) n.s.‡	B: 1 (0.3) R: 2 (0.6) n.s.‡	B: 0 (0.0) R: 3 (1.0) n.s.‡	B: 0 (0.0) R: 0 (0.0) n.s.‡	Not separated per group †	† Severe uveitits (n=1), traumatic cataract (n=1), retinal epithelial pigment tears (n=3), other ocular events (n=5)	+	+	+

* + No or minor problems
? Some problems
- Major problems

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Appendix 4.7 Adverse events, according to diagnose group and study design, for intravitreal bevacizumab (B) or ranibizumab (R) injections

Author, year, country	Study design	Number of participants (injections within parentheses) in the safety analyses	Follow-up period	Adverse events (AE) n (%)						Comments	Directness *	Study limitations*	Precision *
				All-cause mortality	Cardio-vascular mortality	Myocard. infarction	Stroke	Endophtal-mitis	Other				
Kodjikian, 2013 (GEFAL trial)	RCT	485 B = 246 R = 239	1 year	B: 2 (0.8) R: 3 (1.3) n.s.	B: 0 (0.0) R: 1 (0.4) n.s.	B: 1 (0.4) R: 1 (0.4) [*] n.s.	B: 0 (0.0) R: 0 (0.0) n.s.	B: 0 (0.0) R: 1 (0.4) n.s. [‡]	[†] Serious ocular events: B: 2 (0.8) R: 6(2.5) n.s. [‡]	[*] Fatal [‡] Calculated with Fisher's exact test [†] Amaurosis fugax, retinal artery occlusion, subretinal hematoma, visual acuity reduced, endophthalmitis	?	?	+
Krebs, 2013 (MANTA trial)	RCT	317 B = 154 R = 163	1 year	B: 3 (1.9) R: 2 (1.2) n.s.	Not specified	B: 3 (1.9) R: 2 (1.2) n.s.	B: 1 (0.6) R: 1 (0.6) n.s.	B: 0 (0.0) R: 0 (0.0) n.s.	B: 0 (0.0) R: 0 (0.0) n.s.		?	-	+
Martin, 2011 (CATT trial)	RCT	1,185 B monthly n = 286 R monthly n = 301 B as needed n = 300 R as needed n = 298	1 year	B monthly: 4 (1.4) R monthly: 4 (1.3) B as needed: 11 (3.7) R as needed: 5 (1.7) n.s.	B monthly: 2 (0.7) R monthly: 2 (0.7) B as needed: 5 (1.7) R as needed: 2 (0.7) n.s.	B monthly: 2 (0.7) R monthly: 2 (0.7) B as needed: 1 (0.3) R as needed: 3 (1.0) n.s. [*]	B monthly: 2 (0.7) R monthly: 3 (1.0) B as needed: 2 (0.7) R as needed: 1 (0.3) n.s. [*]	B monthly: 4 (1.4) R monthly: 2 (0.7) B as needed: 0 (0.0) R as needed: 0 (0.0) n.s.	Pseudoend-ophthalmitis: B monthly: 0 (0.0) R monthly: 1 (0.3) B as needed: 0 (0.0) R as needed: 0 (0.0) n.s.	[*] Non-fatal	?	?	+
Martin, 2012 (CATT trial)	RCT	1,185 B = 586 R = 599	2 years	B: 36 (6.1) R: 32 (5.3) n.s.	B: 14 (2.4) R: 12 (2.0) n.s.	B: 7 (1.2) R: 9 (1.5) n.s. [*]	B: 8 (1.4) R: 8 (1.3) n.s. [*]	B: 7 (1.2) R: 4 (0.7) n.s.	B: 1 (0.2) R: 1 (0.2) n.s.	[*] Non-fatal	?	?	+
Scholler, 2014	RCT	55 B = 26 R = 29	1 year	B: 0 (0.0) R: 0 (0.0) n.s.	B: 0 (0.0) R: 0 (0.0) n.s.	B: 0 (0.0) R: 0 (0.0) n.s.	B: 0 (0.0) R: 0 (0.0) n.s.	B: 0 (0.0) R: 0 (0.0) n.s.	Two subretinal bleedings [*]	[*] Data not reported on group level	-	-	-

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Appendix 4.7 Adverse events, according to diagnose group and study design, for intravitreal bevacizumab (B) or ranibizumab (R) injections

Author, year, country	Study design	Number of participants (injections within parentheses) in the safety analyses	Follow-up period	Adverse events (AE) n (%)						Comments	Directness *	Study limitations*	Precision *
				All-cause mortality	Cardio-vascular mortality	Myocard. infarction	Stroke	Endophtal-mitis	Other				
Curtis, 2010	Cohort	57,744 B = 38,718 R = 19,026	1 year	B: 1,324 (3.4) R: 647 (3.4) n.s.‡	Not specified	B: 378 (1.0) R: 170 (0.9) n.s.‡	B: 659 (1.7) R: 289 (1.5) n.s.‡	Not reported	Bleeding:* B: 1,719 (4.4) R: 943 (5.0) p=0.0058‡	* Bleeding defined on the basis of inpatient, outpatient or physician claims with a diagnosis of haemorrhage anywhere in the claim ‡ Calculated with Chi-square test with Yates' correction	?	+	-
Schlenker, 2015	Cohort	57,919 B = 33,917 R = 24,002	1 year	Not reported	Not reported	Not reported per group	Not reported per group	Not reported	Thromboem-bolic events: B=2,136 (6.3) R=1,456 (6.1) n.s. ‡	‡ Calculated with Chi-square test with Yates' correction	?	-	+
Etminan, 2016	Case-series	B = 5,644	Not reported	Not reported	Not reported	B=95 events	Not reported	Not reported	Not reported	The rate of myocardial infarction among B users was 11/1000 person years, and 14.9/1000 person years among nonusers	NA	NA	NA
Adverse events in patients with diabetic macular edema (DME) with intravitreal bevacizumab (B) or ranibizumab (R) injections													
Ekinci, 2014	RCT	100 B = 50 R = 50	1 year	Not reported *	Not reported *	Not reported *	Not reported *	Not reported *	B: 0 (0.0) R: 0 (0.0) n.s. *	* No complications, like intraocular pressure or arterial hypertension was observed in the study as a result of the injections NB: patients with endophtalmitis and stroke, MI, uncontrolled hypertension excluded from study.	-	-	-
Wells, 2015 (DRCR-network)	RCT	436 B = 218 R = 218	1 year	B: 5 (2.3) R: 4 (1.8) n.s. ‡	B: 4 (1.8)± R: 3 (1.4) ± n.s. ‡	B: 1 (0.5) R: 3 (1.4) n.s. ‡,*	B: 4 (1.8) R: 4 (1.8) n.s. ‡, *	B: 0 (0.0) R: 0 (0.0) n.s.	† Serious ocular events: B: 14 (6.4) R: 10 (4.6) n.s. ‡	±Potential vascular cause or unknown cause * Non-fatal ‡ Calculated with Fisher's exact test † Inflammation, retinal detachment or tear, vitreous hemorrhage, injection-related cataract.	?	+	+

* + No or minor problems
? Some problems
- Major problems

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Appendix 4.7 Adverse events, according to diagnose group and study design, for intravitreal bevacizumab (B) or ranibizumab (R) injections

Author, year, country	Study design	Number of participants (injections within parentheses) in the safety analyses	Follow-up period	Adverse events (AE) n (%)						Comments	Directness *	Study limitations*	Precision *
				All-cause mortality	Cardio-vascular mortality	Myocard. infarction	Stroke	Endophtal-mitis	Other				
Wells, 2016 (DRCR-network)	RCT	436 B = 218 R = 218	2 year	B: 13 (6.0) R: 11 (5.0) n.s. ‡	B: 8 (3.7) ± R: 9 (4.1) ± n.s. ‡	B: 3 (1.4) R: 6 (2.8) n.s. ‡, *	B: 6 (2.8) R: 11 (5.0) n.s. ‡, *	B: 1 (0.5) R: 0 (0.0) n.s. ‡	† Serious ocular events: B: 25 (11.5) R: 16 (7.3) n.s. ‡	±Potential vascular cause or unknown cause * Non-fatal ‡ Calculated with Fisher's exact test † Inflammation, retinal detachment or tear, vitreous hemorrhage, injection-related cataract.	?	+	+
Bakbak, 2013	Cohort	87 B = 55 R = 32	4 weeks	Not reported	Not reported	Not reported per group	Not reported per group	B: 0 (0.0) R: 0 (0.0) n.s.	B: 0 (0.0) R: 0 (0.0) n.s. *	* No complications, including endophthalmitis, traumatic lens injury, increased intraocular pressure or retinal detachment, were associated with the injections	+	-	-
Adverse events in patients with choroidal neovascularisation in pathologic myopia (PM) with intravitreal bevacizumab (B) or ranibizumab (R) injections													
Pece, 2015	RCT	78 B = 40 R = 38	1-2 years	B: 0 (0.0) R: 0 (0.0) n.s. *	B: 0 (0.0) R: 0 (0.0) n.s. *	B: 0 (0.0) R: 0 (0.0) n.s. *	B: 0 (0.0) R: 0 (0.0) n.s. *	B: 0 (0.0) R: 0 (0.0) n.s. *	B: 0 (0.0) R: 0 (0.0) n.s. *	* No severe ocular or systemic side effects were recorded.	?	-	-
Adverse events in patients with macular edema due to retinal vein occlusion (RVO) with intravitreal bevacizumab (B) or ranibizumab (R) injections													
Narayanan, 2015 (MARVEL trial)	RCT	75 B = 38 R = 37	0.5 years	Not reported	Not reported	Not reported	Not reported	B: 0 (0.0) R: 0 (0.0) n.s.	† Ocular adverse events: B: 7 (18.4) R: 2 (5.4) n.s. ‡	‡ Calculated with Fisher's exact test † Epiretinal membrane, progression of cataract, raised intraocular pressure.	?	?	?
Rajagopal, 2015 (CRAVE trial)	RCT	98 B =49 R = 49	0.5 years	1 patient died from pneumonia (group not reported)	Not reported	B: 0 (0.0) R: 0 (0.0) n.s.	B: 0 (0.0) R: 0 (0.0) n.s.	B: 0 (0.0) R: 0 (0.0) n.s.	† Serious ocular events: B: 0 (0.0) R: 0 (0.0) n.s.	† No ophthalmic serious adverse events were encountered, including endophthalmitis, non-infectious uveitis, retinal detachment or tear, traumatic cataract.	?	-	?

* + No or minor problems
? Some problems
- Major problems

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Appendix 4.7 Adverse events, according to diagnose group and study design, for intravitreal bevacizumab (B) or ranibizumab (R) injections

Author, year, country	Study design	Number of participants (injections within parentheses) in the safety analyses	Follow-up period	Adverse events (AE) n (%)						Comments	Directness *	Study limitations*	Precision *
				All-cause mortality	Cardio-vascular mortality	Myocard. infarction	Stroke	Endophtal-mitis	Other				
Adverse events in patient groups with mixed diagnoses with intravitreal bevacizumab (B) or ranibizumab (R) injections													
Al-Rashaed 2016	Cohort	(22,674) (B: 21,387) (R: 1,287)	Not reported	Not reported	Not reported	Not reported	Not reported	B: 1 (<0.1) R: 0 (0.0) n.s.	Not reported		-	-	-
Bhavsar, 2015	Cohort	(17,296) (B: 15,479) (R: 1,669)	Not reported	Not reported	Not reported	Not reported	Not reported	B: 1 (<0.1) R: 0 (0.0) n.s.	Not reported		?	+	+
Chong, 2010	Cohort	(20,005) (B: 16,166) (R: 3,839)	Not reported	Not reported	Not reported	Not reported	Not reported	B: 1 (<0.1) R: 0 (0.0) n.s.	* Intraocular inflammation: B: 64 (0.4) R: 1 (<0.1) p=0.0002‡	* 64 intraocular inflammations, of which 44 were true sterile intraocular inflammations, 19 were treated with antibiotics but were culture negative, and 1 culture-proven endophthalmitis. ‡ Calculated with Chi-square test with Yates' correction	+	?	+
Fintak, 2008	Cohort	(26,905) (B: 12,585) (R: 14,320)	Not reported	Not reported	Not reported	Not reported	Not reported	B: 3 (<0.1) R: 3 (<0.1) n.s.‡	Not reported	‡ Calculated with Chi-square test with Yates' correction	?	?	-
Ladas, 2009	Cohort	450 (2,000) (B: 1,275) (R: 725)	3-24 months	B: 0 (0.0) R: 0 (0.0) n.s.	B: 0 (0.0) R: 0 (0.0) n.s.	B: 0 (0.0) R: 0 (0.0) n.s.	B: 0 (0.0) R: 0 (0.0) n.s.	B: 0 (0.0) R: 0 (0.0) n.s.	† Serious ocular events: B: 32 (2.5) R: 18 (2.5) n.s.‡	† Including retinal detachment, uveitis, subconjunctival haemorrhage (< 1 quadrant), elevation of intraocular pressure. ‡ Calculated with Fisher's exact test	-	-	-
Moshfeghi, 2011	Cohort	(58,307) (B: 39,700) (R: 18,607)	Not reported	Not reported	Not reported	Not reported	Not reported	B: 7 (<0.1) R: 5 (<0.1) n.s.‡	Not reported	‡ Calculated with Chi-square test with Yates' correction	?	-	?

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? Some problems
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Appendix 4.7 Adverse events, according to diagnose group and study design, for intravitreal bevacizumab (B) or ranibizumab (R) injections

Author, year, country	Study design	Number of participants (injections within parentheses) in the safety analyses	Follow-up period	Adverse events (AE) n (%)						Comments	Directness *	Study limitations*	Precision *
				All-cause mortality	Cardio-vascular mortality	Myocard. infarction	Stroke	Endophtal-mitis	Other				
Nuzzi and Tridico, 2015	Cohort	1,144 eyes B = 762 eyes R = 382 eyes	2 weeks	B: 0 (0.0) R: 0 (0.0) n.s.	B: 0 (0.0) R: 0 (0.0) n.s.	B: 0 (0.0) R: 0 (0.0) n.s.	B: 0 (0.0) R: 0 (0.0) n.s.	B: 0 (0.0) R: 0 (0.0) n.s.	† Ocular adverse events: B: 115 (15.1) R: 64 (16.8) n.s. ‡ Korr 8/2-17	† Including retinal detachment, infectious uveitis, sub-retinal haemorrhage, elevation of intra-ocular pressure. ‡ Calculated with Fisher's exact test	?	-	-
Park, 2013	Cohort	(16,186) (B: 9,125) (R: 7,061)	Not reported	Not reported	Not reported	Not reported	Not reported	B: 2 (<0.1) R: 0 (<0.1) n.s.‡	Not reported	‡ Calculated with Chi-square test with Yates' correction	?	-	-
Rayess, 2016	Cohort	(503,890) (B: 153,812) (R: 309,722)	Not reported	Not reported	Not reported	Not reported	Not reported	B: 60 (<0.1) R: 109 (0.1) n.s.*	Not reported	*OR B vs. R: 1.11 (CI95%: 0.81 to 1.52)	?	-	+
Shah, 2011	Cohort	(27,736) (B: 10,958) (R: 16,778)	1 year	Not reported	Not reported	Not reported	Not reported	B: 12 (0.1) R: 11 (0.1) n.s.	Not reported		?	-	?
Sharma, 2012	Cohort	524 (1,584) B: 173 (693) R: 351 (891)	1 month	Not reported	Not reported	B: 2 (1.2) R: 0 (0.0) n.s. ‡	Not reported	B: 9 (5.2) R: 1 (0.3) p=0.0008 ‡	† Ocular adverse events: B: 0 (0.0) R: 0 (0.0) n.s.	† Including retinal detachment, infectious endophthalmitis, vitreal haemorrhage. ‡ Calculated with Fisher's exact test	-	-	-
Tabandeh, 2014	Cohort	(11,257 B: 8,533 R: 2,724)	Not reported	Not reported	Not reported	Not reported	Not reported	B: 2 (<0.1) R: 3 (0.1) n.s. ‡ Korr 8/2-17	Not reported	‡ Calculated with Chi-square test with Yates' correction	?	-	-

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- Major problems

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Appendix 4.7 Adverse events, according to diagnose group and study design, for intravitreal bevacizumab (B) or ranibizumab (R) injections

Author, year, country	Study design	Number of participants (injections within parentheses) in the safety analyses	Follow-up period	Adverse events (AE) n (%)						Comments	Directness *	Study limitations*	Precision *
				All-cause mortality	Cardio-vascular mortality	Myocard. infarction	Stroke	Endophtal-mitis	Other				
Terzic, 2015	Cohort	(1,041) (B: 986) (R: 55)	Not reported	Not reported	Not reported	Not reported	Not reported	B: 2 (0.2) R: 0 (0.0) n.s.‡	Not reported	‡ Calculated with Fisher's exact test	?	-	-
Mason, 2008	Case-series	(B: 5,233)	Not reported	Not reported	Not reported	Not reported	Not reported	B: 1 (<0.1)	Not reported		NA	NA	NA

NA = Not applicable for case-series

* + No or minor problems
? Some problems
- Major problems

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Appendix 4 .8 Adverse events, according to diagnose group and study design, for intravitreal aflibercept (B) or ranibizumab (R) injections

Author, year, country	Study design	Number of participants (injections within parentheses) in the safety analyses	Follow-up period	Adverse events (AE) n (%)						Comments	Directness *	Study limitations*	Precision *
				All-cause mortality	Cardio-vascular mortality	Myocard. infarction	Stroke	Endophtal-mitis	Other				
Adverse events in patients with age-related macular degeneration (AMD) with intravitreal aflibercept (A) or ranibizumab (R) injections													
Heier, 2012 (VIEW 1 trial) (VIEW 2 trial)	RCT	2,419[*] A = 1,824[*] R = 595[*]	1 year	A: 16 (0.9)[†] R: 4 (0.7)[†] n.s.[‡]	A: 9 (0.5) R: 2 (0.3) n.s.[‡]	A: 15 (0.8) R: 6 (1.0) n.s.[‡∞]	A: 8 (0.4) R: 2 (0.3) n.s.[‡∞]	A: 3 (0.2) R: 3 (0.5) n.s.[‡]	[≠] Serious ocular events: A: 19 (1.0) R: 11 (1.8) n.s.[‡]	[*] n for safety analysis set includes all dosing regimens for A and R. [†] Deaths as reported in flowcharts in Heier *et al*., 2012. [‡] Calculated with Fisher's exact test. [≠] Endophthalmitis, reduced visual acuity, retinal hemorrhage, posterior capsule opacification [∞] Nonfatal	+	+	+
Schmidt-Erfurth, 2014 (VIEW 1 trial) (VIEW 2 trial)	RCT	2,419[*] A = 1,824[*] R = 595[*]	96 weeks (1.8 years)	A: 41 (2.2) R: 11 (1.8) n.s.[‡]	A: 24 (1.3) R: 3 (0.5) n.s.[‡]	A: 25 (1.4) R: 12 (2.0) n.s.[‡∞]	A: 13 (0.7) R: 5 (0.8) n.s.[‡∞]	A: 5 (0.3) R: 5 (0.8) n.s.[‡]	[≠] Serious ocular events: A: 65 (3.6) R: 26 (4.4) n.s.[‡]	[*] n for safety analysis set includes all dosing regimens for A and R. [‡] Calculated with Fisher's exact test. [≠] Endophthalmitis, cataract, macular degeneration, increased intraocular pressure, macular hole, retinal pigment epithelial tear, reduced visual acuity, retinal hemorrhage, retinal detachment, posterior capsule opacification [∞] Nonfatal	+	+	+
Souied, 2016	Cohort	81,046 (479,123) (A: 179,147 R: 253,647)	Not reported	Not reported	Not reported	Not reported	Not reported	A: 189 (<0.1) R: 162 (<0.1) P=<0.0001 [*] A: 276 (0.2) R: 272 (0.1) n.s. p-value not stated [‡]	Not reported	[*] Primary analysis data [‡] A sensitivity analysis iincluding all claims over time (Nov 2011-Aug 2013).	?	-	+

* + No or minor problems
? Some problems
- Major problems

Project: Efficacy and safety of intraocularly administered vascular endothelial growth factor inhibitors

Appendix 4 .8 Adverse events, according to diagnose group and study design, for intravitreal aflibercept (B) or ranibizumab (R) injections

Author, year, country	Study design	Number of participants (injections within parentheses) in the safety analyses	Follow-up period	Adverse events (AE) n (%)						Comments	Directness *	Study limitations*	Precision *
				All-cause mortality	Cardio-vascular mortality	Myocard. infarction	Stroke	Endophtal-mitis	Other				
Adverse events in patients with diabetic macular edema (DME) with intravitreal aflibercept (A) or ranibizumab (R) injections													
Wells, 2015 (DRCR-network)	RCT	442 A = 224 R = 218	1 year	A: 3 (1.3) R: 4 (1.8) n.s. ‡	A: 2 (0.9) † R: 3 (1.4) † n.s. ‡	A: 4 (1.8) R: 3 (1.4) n.s. ‡,∞	A: 0 (0.0) R: 4 (1.8) n.s. ‡, ∞	A: 0 (0.0) R: 0 (0.0)	≠Serious ocular events: A: 8 (3.6) R: 10 (4.6) n.s. ‡	†Death from potential vascular cause or unknown cause ‡ Calculated with Fisher's exact test ≠ Inflammation, retinal detachment or tear, vitreous hemorrhage, injection-related cataract. ∞ Nonfatal	?	+	+
Wells, 2016 (DRCR-network)	RCT	A = 224 R = 218	2 year	A: 5 (2.2) R: 11 (5.0) n.s. ‡	A: 3 (1.3) † R: 9 (4.1) † n.s. ‡	A: 7 (3.1) R: 6 (2.8) n.s. ‡,∞	A: 2 (0.9) R: 11 (5.0) p=0.0108 ‡, ∞	A: 0 (0.0) R: 0 (0.0)	≠Serious ocular events: A: 27 (12.1) R: 16 (7.3) n.s. ‡	†Death from potential vascular cause or unknown cause ‡ Calculated with Fisher's exact test ≠ Inflammation, retinal detachment or tear, vitreous hemorrhage, injection-related cataract. ∞ Nonfatal	?	+	+
Adverse events in patient groups with mixed diagnoses with intravitreal aflibercept (A) or ranibizumab (R) injections													
Bhavsar, 2015	Cohort	(1,817) (A: 148 R: 1,669)	Not reported	Not reported	Not reported	Not reported	Not reported	A: 0 (0.0) R: 0 (0.0)	Not reported		?	+	+
Rayess, 2016	Cohort	(350,078) (A: 40,356 R: 309,722)	Not reported	Not reported	Not reported	Not reported	Not reported	A: 14 (<0.1) R: 109 (<0.1) n.s.*	Not reported	*OR R vs. A: 1.01 (CI95%: 0.58 to 1.77)	?	-	+
Terzic, 2015	Cohort	(115) (A: 60 R: 55)	Not reported	Not reported	Not reported	Not reported	Not reported	A: 0 (0.0) R: 0 (0.0)	Not reported		?	-	-
Goldberg, 2014	Case-series	(5,356)	Not reported	Not reported	Not reported	Not reported	Not reported	A: 20 (0.4)*	Not reported	* Post injection inflammations	NA	NA	NA

NA = Not applicable for case-series.

* + No or minor problems
? Some problems
- Major problems

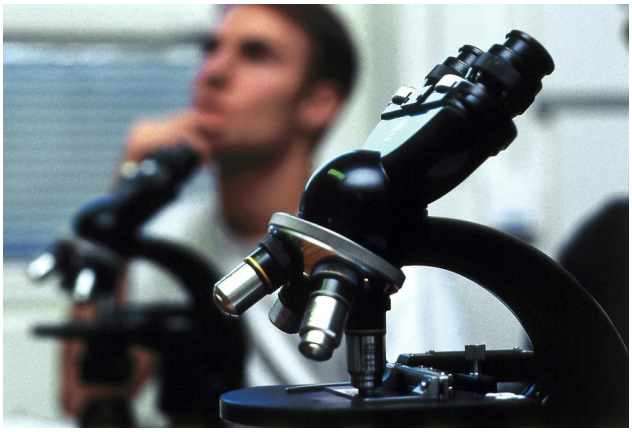
Project: Efficacy and safety of intraocularly administered vascular endothelial growth factor inhibitors

Appendix 4.9 Adverse events, according to diagnose group and study design, for intravitreal bevacizumab (B) or aflibercept (A) injections

Author, year, country	Study design	Number of participants (injections within parentheses) in the safety analyses	Follow-up period	Adverse events (AE) n (%)						Comments	Directness *	Study limitations*	Precision *
				All-cause mortality	Cardio-vascular mortality	Myocard. infarction	Stroke	Endophtal-mitis	Other				
Adverse events in patients with diabetic macular edema (DME) with intravitreal bevacizumab (B) or aflibercept (A) injections													
Wells, 2015 (DRCR-network)	RCT	442 B = 218 A = 224	1 year	B: 5 (2.3) A: 3 (1.3) n.s. ‡	B: 4 (1.8) ± A: 2 (0.9) ± n.s. ‡	B: 1 (0.5) A: 4 (1.8) n.s. *, ‡	B: 4 (1.8) A: 0 (0.0) n.s. *, ‡	B: 0 (0.0) A: 0 (0.0) n.s. ‡	† Serious ocular events: B: 14 (6.4) A: 8 (3.6) n.s. ‡	±Death from potential vascular cause or unknown cause * Non-fatal ‡ Calculated with Fisher's exact test † Inflammation, retinal detachment or tear, vitreous haemorrhage , injection related cataract	?	+	+
Wells, 2016 (DRCR-network)	RCT	442 B = 218 A = 224	2 year	B: 13 (6.0) A: 5 (2.2) n.s. ‡	B: 8 (3.7) ± A: 3 (1.3) ± n.s. ‡	B: 3(1.4) A: 7 (3.1) n.s. *, ‡	B: 6 (2.8) A: 2 (0.9) n.s. *, ‡	B: 1 (0.5) A: 0 (0.0) n.s. ‡	† Serious ocular events: B: 25 (11.5) A: 27 (12.1) n.s. ‡	±Death from potential vascular cause or unknown cause * Non-fatal ‡ Calculated with Fisher's exact test † Inflammation, retinal detachment or tear, vitreous haemorrhage , injection related cataract	?	+	+
Adverse events in patient groups with mixed diagnoses with intravitreal bevacizumab (B) or aflibercept (A) injections													
Bhavsar, 2015	Cohort	(15,627) (B: 15,479) (A: 148)	Not reported	Not reported	Not reported	Not reported	Not reported	B: 1 (<0.1) A: 0 (0.0) n.s.	Not reported		?	+	+
Rayess, 2016	Cohort	(194,168) (B: 153,812) (A: 40,356)	Not reported	Not reported	Not reported	Not reported	Not reported	B: 60 (<0.1) A: 14 (<0.1) n.s. *	Not reported	*OR B vs. A: 1.12 (CI95%: 0.63 to 2.01)	?	-	+
Terzic, 2015	Cohort	(1,046) (B: 986) (A: 60)	Not reported	Not reported	Not reported	Not reported	Not reported	B: 2 (0.2) A: 0 (0.0) n.s. ‡	Not reported	‡ Calculated with Fisher's exact test	?	-	-

Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA



HTA

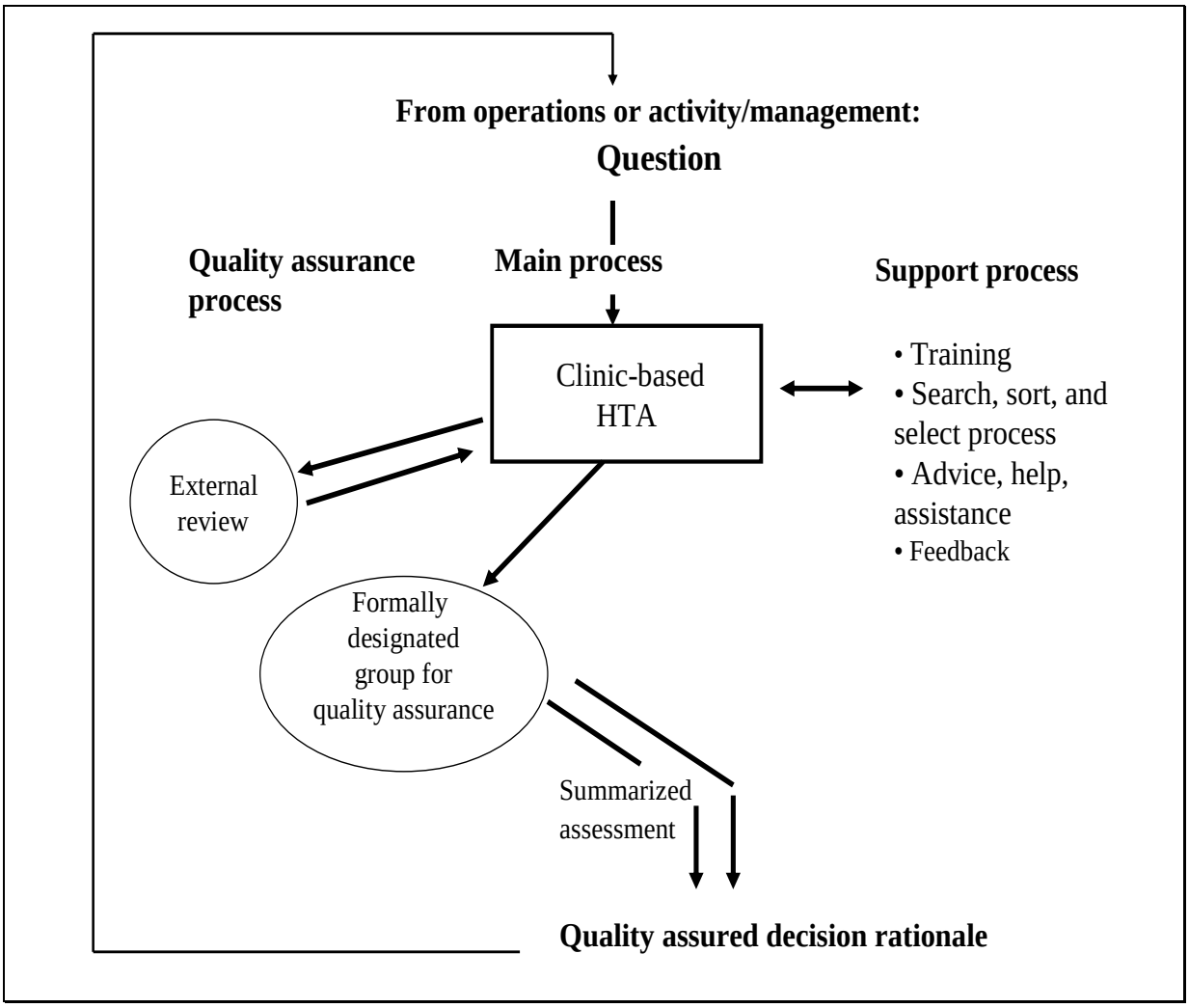
Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the quality of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High quality of evidence	= (GRADE⊕⊕⊕⊕)
Moderate quality of evidence	= (GRADE ⊕⊕⊕O)
Low quality of evidence	= (GRADE ⊕⊕OO)
Very low quality of evidence	= (GRADE ⊕OOO)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

Christina Bergh, Professor, MD.
Head of HTA-centrum


From operations or activity/management:
Question
Quality assurance process
Main process
Support process
Clinic-based HTA
• Training
• Search, sort, and select process
• Advice, help, assistance
• Feedback
External review
Formally designated group for quality assurance
Summarized assessment
Quality assured decision rationale

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