

**Three Additional Questions For WAMD Dutch
Guidelines
(Searches And Extractions)**



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ABBREVIATIONS

AAO	American Academy of Ophthalmology
AE	adverse events
AMD	Age-related Macular Degeneration
ARVO	Association for Research in Vision and Ophthalmology
BCVA	Best corrected visual acuity
BVZ	bevacizumab
C	control/comparator/classic
C3F8	perfluoropropane
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence Interval
CNV	Choroidal neovascularisation
CRT	central retinal thickness
CTG	Clinical Trials Group
DA	optic disc area
Dex	Dexamethasone
EMBASE	Excerpta Medica Database
ESO	European Society of Ophthalmology
ETDRS	Early Treatment of Diabetic Retinopathy Study
EU	European Union
EUCTR	EU Clinical Trials Register
Euretin	European Society of Retina Specialists
FA	Fluorescein Angiography
GB	Great Britain
GLD	greatest linear dimension (of lesion)
HTA	Health Technology Assessment
I	intervention
ICTRP	International Clinical Trials Registry Platform
ICG/ICGA	indocyanine green angiography
ISRCTN	International Standard RCT Number
ITT	Intention-to-treat
IVT	Intravitreal triamcinolone
IVTA	Intravitreal tiramcinolone acetonide
Log MAR	Logarithm of minimal angle of resolution
MEDLINE	Medical Literature Analysis and Retrieval System Online
m	months/meters
M/F	male to female ratio
mg	Milligram
ml	milli litres
mm	millimeters
LOCF	last observation carried forward
N/a	not applicable
NHS	National Health Service
NIH	National Institutes of Health
NIHR	National Institutes of Health Research
NOG	Nederlands Oogheekundig Gezelschap
NR	Not Reported

OAE	ocular AE
OCT	Optical coherence tomography
OR	Odds Ratio
PCV	polypoidal choroidal vasculopathy
PDT	photodynamic therapy
PED	retinal epithelial detachment
p.r.n.	Pro re nata
RAP	Retinal Angiomatous Proliferation
RBZ	Ranibizumab
RCT	randomised controlled trial
rPDT	reduced Fluence PDT;
RPE	Retinal Pigment Epithelium
RR	Risk Ratio or Relative Risk
SAE	Serious Adverse Events
SD	Standard Deviation
SE	Sweden
SF6	sulfur hexafluoride
SMH	submacular hemorrhage
SOE	Societas Ophthalmologica Europæa
sPDT	standard Fluence PDT
TPA	Tissue Plasminogen Activator
TTT	Transpupillary thermotherapy
ug	micrograms
UK	United Kingdom
USA	United States of America
VA	visual acuity
VAS	visual acuity score
VEGF	Vascular Endothelial Growth Factor
vPDT	verteporfin PDT
vPED	vascularised Pigment Epithelial Detachment
wAMD	wet age-related macular degeneration
WHO	World Health Organisation
Wk(s)	week (s)
Yr(s)	year(s)

1. METHODS

1.1 INCLUSION CRITERIA

Question 1: What are the effects of TPA or gas in patients with both AMD and (sub)macular bleeding?

Patients: patients with both exudative AMD (Age-related Macular Degeneration) and a (sub)macular bleeding

Intervention: urokinase or TPA (Tissue Plasminogen Activator) submacular and/or gas intravitreal (pneumatic displacement)

Comparator: other interventions or no intervention

Outcomes: visual acuity

Study design: randomised controlled trial (RCT), controlled observational studies, case series (single arm studies)

Question 2: What are the effects of PDT alone or combined with anti-VEGF in patients with PCV?

Patients: patients with PCV (polypoidal choroidal vasculopathy) confirmed by ICG (indocyanine green angiography)

Intervention: PDT (Photodynamic Therapy) alone or combination of PDT and anti-VEGF (bevacizumab or ranibizumab)

Comparator: anti-VEGF alone or no treatment

Outcomes: visual acuity

Study design: RCT, controlled observational studies

Question 3: What are the effects of PDT alone or combined with anti-VEGF for RAP (retinal angiomatous proliferation) in patients with PCV?

Patients: patients with PCV (polypoidal choroidal vasculopathy) confirmed by ICG (indocyanine green angiography)

Intervention: PDT (Photodynamic Therapy) alone or combination of PDT and anti-VEGF (bevacizumab or ranibizumab)

Comparator: anti-VEGF alone or no treatment

Outcomes: visual acuity

Study design: RCT

1.2 LITERATURE SEARCHES

Broad search strategies were carried out based on three primary questions:

- 1) What are the effects of TPA or gas in patients with both AMD and (sub)macular bleeding?
- 2) What are the effects of PDT alone or combined with anti-VEGF?
- 3) What is the effectiveness of treatments for RAP (retinal angiomatous proliferation)?

We attempted to identify relevant studies through a comprehensive search of appropriate data sources. The search strategies were developed specifically for each resource and each

primary question, where appropriate an objectively-derived RCT study design filter specific for the target database was used, in combination with population and intervention terms. For these searches, a limit was also incorporated to retrieve studies relevant to humans. Details of the search strategies are listed in Appendices 1 to 3.

Searches were not limited by language or publication date.

Question 1: What are the effects of TPA or gas in patients with both AMD and (sub)macular bleeding?

The following resources were searched:

- Medline (OvidSP) (1946-2013/01/wk1)
- Medline In-Process Citations and Daily Update (OvidSP) (up to 2013/02/15)
- Embase (OvidSP) (1974 – 2013/02/15)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Internet) (Issues 1 of 12:2013)
- Allied and Complementary Medicine (AMED) (OvidSP) (1985-February 2013)
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO) (1981-2013/02/19)

Question 2: What are the effects of PDT alone or combined with anti-VEGF?

The following resources were searched:

- Medline (OvidSP) (1946-2013/01/wk1)
- Medline In-Process Citations and Daily Update (OvidSP) (up to 2013/02/19)
- Embase (OvidSP) (1974 – 2013/02/19)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Internet) (Issue 1 of 12: 2013)
- Allied and Complementary Medicine (AMED) (OvidSP) (1985-February 2013)
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO) (1981-2013/02/19)

Question 3: What is the effectiveness of treatments for RAP (retinal angiomatous proliferation)?

The following resources were searched:

- Medline (OvidSP) (1946 – 2013/01/wk2)
- Medline In-Process Citations and Daily Update (OvidSP) (up to 2013/02/25)
- Embase (OvidSP) (1974 – 2013/02/25)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Internet) (Issue 1 of 12: 2013)
- Allied and Complementary Medicine (AMED) (OvidSP) (1985 – February 2013)
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO) (1981 – 2013/02/08)

Additional searching

Supplementary searches were undertaken for each question to identify grey literature, completed and ongoing trials, on resources such as:

- NIH ClinicalTrials.gov (Internet)
<http://www.clinicaltrials.gov>
- Current Controlled Trials (Internet)
<http://www.controlled-trials.com>
- WHO International Clinical Trials Registry Platform (ICTRP) (Internet)
<http://www.who.int/ictrp/en>

Electronic searches were undertaken for the following conference abstracts:

- American Academy of Ophthalmology (AAO) (<http://www.aao.org/>) (2010-2013) (Internet)
- European Society of Retina Specialists (Euretina) (<http://www.euretina.org/>) (2010-2013) (Internet)
- Association for Research in Vision and Ophthalmology (ARVO) (2010-2012) (Internet)
- European Society of Ophthalmology (Societas Ophthalmologica Europæa (SOE))(2011) (Internet)

1.3 METHODS OF STUDY SELECTION, QUALITY ASSESSMENT AND DATA EXTRACTION

Study selection process

The title/abstract of each reference identified by the literature searches was screened by two reviewers working independently. Where no definitive exclusion criteria were identified, full papers of the references were retrieved. Full papers of the references were retrieved and screened in detail, to assess whether the study fulfilled the inclusion criteria. Full screening was screened by two reviewers working independently.

Any discrepancies between reviewers were resolved through consensus or consultation with a third reviewer. The selection of studies was not limited by language or publication status.

Study quality (risk of bias) assessment

The quality of each included study was assessed using tables provided by NOG (Nederlands Oogheelkundig Gezelschap (Dutch Ophthalmological Society)), shown in Appendix 4. The quality assessments were performed by one reviewer and checked by a second reviewer. Any discrepancies were resolved through consensus or by the involvement of a third reviewer.

Data extraction process

For each included study, data were extracted into tables based on those found in the review Van der Reis "Interventions for neovascular age-related macular degeneration"¹. Later, evidence tables were provided by NOG, (shown in Appendix 4) and these were completed in conjunction with the original tables.

One reviewer extracted the study data and a second reviewer independently reviewed the data against the original paper for completeness and accuracy. Any discrepancies were resolved through consensus or the involvement of a third reviewer.

Each included study was identified by its main publication, using the surname of the first author and year of publication. Multiple publications of the same patient population were considered together and data elements extracted from the paper with the most complete and up-to-date data or relevant follow-up periods. Any relevant additional information presented in the related papers, was added where appropriate.

For each study we extracted the change in visual acuity, measured by either log MAR or ETDRS letters. If this was not possible we extracted other outcome measures of visual acuity. For calculations of logMAR from counting fingers, hand movement or light movement it was assumed that counting fingers = 2, hand movement = 3 and light movement = 4. All other calculations of log MAR were performed as described by Holladay².

2. RESULTS

2.1 QUESTION 1: WHAT ARE THE EFFECTS OF TPA OR GAS IN PATIENTS WITH BOTH AMD AND (SUB)MACULAR BLEEDING?

Literature searches were performed and generated 2,245 records. Figure 1 summarises the flow of studies through the search and screening process. Screening of the titles and abstracts by two independent reviewers identified 47 records (six have yet to be retrieved). These records were examined in full and 31 met the inclusion criteria, whilst 10 were excluded. Due to changes in the Euretina website we were not able to view the abstracts from the Euretina searches, therefore the results were not included in the review but the search results (titles) can be found in Appendix 5.

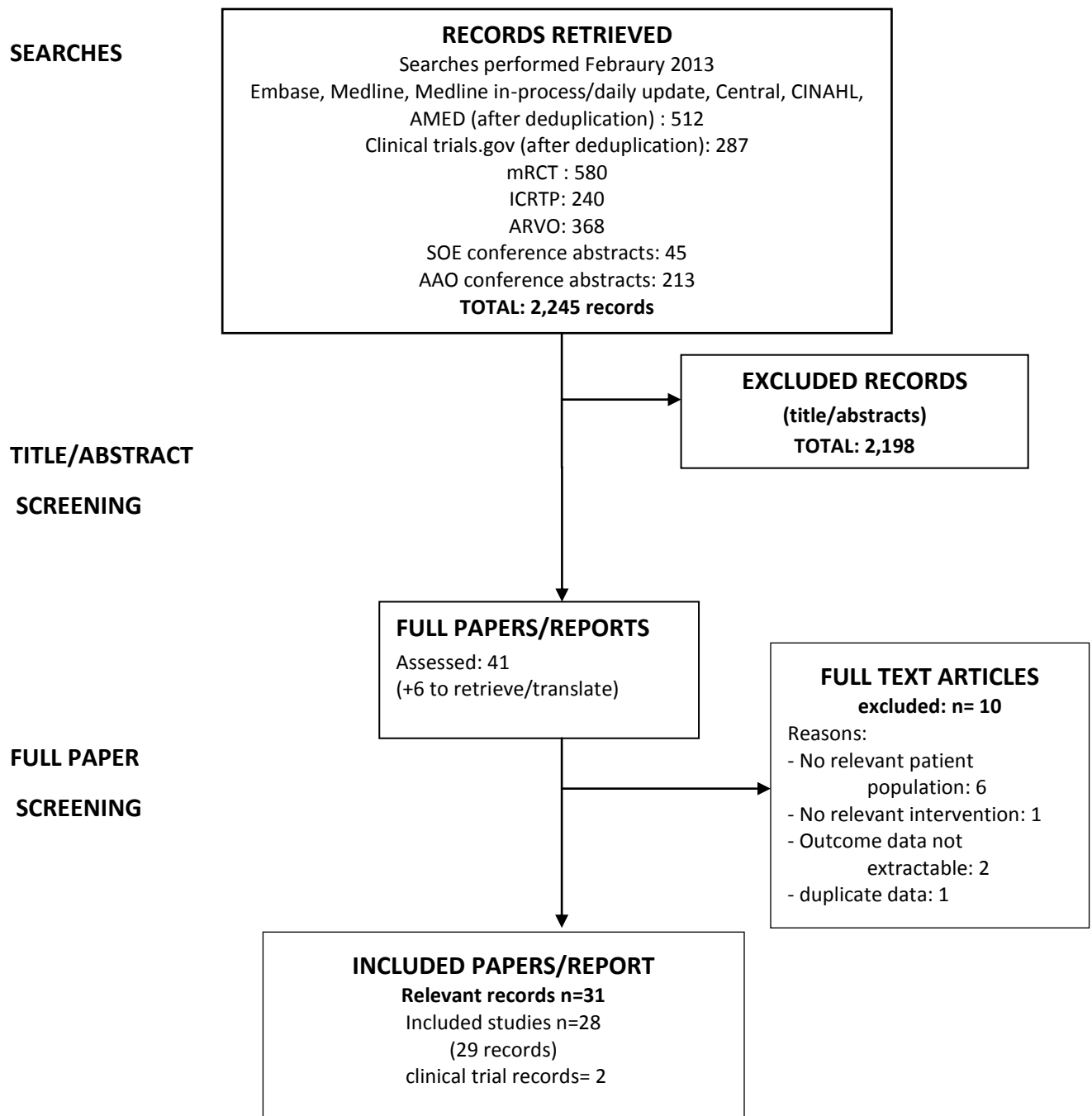
The 31 included records described 28 studies (two records were for one study, therefore 29 total records) and two clinical trial registries.

The baseline characteristics of the 28 included studies are summarised in Tables 1-3, the visual acuity results are summarised in Tables 4-5 and the risk of bias are summarised in Table 6.

Two ongoing trials were identified which met the inclusion criteria and are described in Table 7. One trial was registered in the UK and one in the USA. Neither of the trials had any associated publications.

Reasons for the exclusion of full papers are given in Appendix 6.

Figure 1: Summary searching and inclusion screening for question 1



mRCT = meta register of controlled trials; ICRTP= WHO international clinical trials registry platform; SOE = European Society of Opthamology; AAO = American Academy of Ophthalmology; ARVO = Association for Research in Vision and Ophthalmology; CINAHL =Cumulative Index to Nursing and Allied Health Literature; AMED = Allied and complimentary medicine database.

Table 1: Evidence table for the Research question, 'what are the effects of TPA or gas in patients with both AMD and (sub)macular bleeding?' (Question 1)

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size
Yang 2005 ³	Type of study: Retrospective Case series Setting: Outpatient Country: Taiwan Source of funding: NR	<u>Inclusion criteria:</u> See table 3 <u>Exclusion criteria:</u> See table 3 <u>N patients (eyes) total at baseline:</u> I: 5 (5) AMD C: 13 (13) AMD <u>age ± SD: (years)</u> I: 55.6* ±9.8 (50-73) C: 66.2* ±10.8 (55-80) <u>Sex (M/F):</u> I: 4/1 C: 11/2 <u>Duration of haemorrhage (days):</u> I: 3.6* ±2.1 (1-7) C: 13.5* ±10.4 (3-30) <u>Diameter of haemorrhage (disk area):</u> I: 11* ±10 (5-28) C: 3 to >20 <u>Baseline VA:</u> See table 4 Groups comparable at baseline? n/a	25-33ug TPA + C3F8/SF6 25 to 33 µg of tPA diluted with balanced salt solution up to 0.1 ml was injected into the midvitreal cavity, through a 30-gauge needle introduced 3-4 mm superotemporally posterior to the limbus; this was carried out on eight eyes. After an aqueous tap was used to reduce intraocular pressure, 0.3 to 0.4 ml of perfluoropropane (C3F8) or sulfur hexafluoride (SF6) gas was injected into the vitreal cavity, in a similar fashion.	C3F8/SF6 0.3 to 0.4 ml of C3F8 or SF6 gas.	<u>Length of follow-up (m):</u> I: 19.2* ±7.6 (12-32) C: 13.2* ±6.0 (6-27) <u>Loss-to-follow-up:</u> I: 0 at 6 months C: 0 <u>Incomplete outcome data:</u> Not relevant	Outcome measures and effect size (include 95%CI and p-value if available): See table 4
Thompson 2005 ⁴	Type of study: Retrospective consecutive Case series Setting: Hospital	<u>Inclusion criteria:</u> See table 3 <u>Exclusion criteria:</u> See table 3 <u>N patients (eyes) total at baseline:</u> I: 15	12.5-25 ug tPA + fluid air exchange Vitrectomy was performed with removal of the posterior hyaloid. Then, approx. 0.1 to 0.2 mL of a 12.5 µg/0.1 mL TPA solution was injected into the subretinal immediately before the fluid-air exchange. The eye was	Submacular surgery with removal of neovascular membrane complex	<u>Length of follow-up (yrs):</u> I: 2.30 ± 0.25 C: 2.92 ±0.48 <u>Loss-to-follow-up:</u> NR	Outcome measures and effect size (include 95%CI and p-value if available): See table 4

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size
	Country: USA Source of funding: NR	C: 27 <u>age ± SD: (years)</u> I: 82.5 ±1.5 C: 78.8 ±1.4 <u>Sex (M/F):</u> I: 6/9 C: 8/19 <u>Duration of haemorrhage (months):</u> I: 0.96 ±0.25 C: 0.87 ±0.17 <u>Diameter of haemorrhage (disk area):</u> I: ≥12 C: ≥12 <u>Baseline VA:</u> See table 4 Groups comparable at baseline? Yes	filled about 75% with air, and the patient remained prone 50% of the time for 3 days to encourage displacement of the subretinal blood into the inferior periphery.		<u>Incomplete outcome data:</u> Not relevant	
Sandhu 2010 ⁵	Type of study: Retrospective Case series Setting: Hospital Country: Australia Source of funding: NR.	<u>Inclusion criteria:</u> See table 3 <u>Exclusion criteria:</u> See table 3 <u>N patients (eyes) total at baseline:</u> I: 16 (16) <u>age ± SD:</u> I: 81 (76-88) <u>Sex (M/F):</u> I: 6/10 <u>Duration of haemorrhage (days):</u> I: 15 (3-42) <u>Diameter of haemorrhage (disk area):</u> I: 6 (3-12)	Vitrectomy + 12.5 ug TPA + fluid/air exchange Vitrectomy + 12.5 ug TPA + fluid/air exchange + prn RBZ Subretinal tPA was injected 12.5 ug/ 0.1ml with a 41-gauge needle at 1–4 points over the surface of the SMH away from the fovea. Fluid/air exchange was performed at the end of surgery (no gas). Patient was told to sleep with three pillows on the side of the effected eye at night. RBZ was given prn if ≥logMAR 1.20 (6/96) for x3 doses and then further prn. Subgroup analysis of patients with and without RBZ	None (see subgroup analysis: TPA + fluid/air exchange +RBZ)	<u>Length of follow-up (m):</u> I: 1,6 and 12 <u>Loss-to-follow-up:</u> Intervention: Follow up was available on 16 patients at 1 and 6 months and 10 patients at 12 months (3 died and 3 were lost to follow up). <u>Incomplete outcome data:</u>	Outcome measures and effect size (include 95%CI and p-value if available): See table 4

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size
		<i>Baseline VA:</i> See table 4 Groups comparable at baseline? n/a			Not relevant	
Nourinia 2010 ⁶	Type of study: Interventional case series. Setting: Hospital Country: Iran. Source of funding: NR	<u>Inclusion criteria:</u> See table 3 <u>Exclusion criteria:</u> See table 3 <u>N patients (eyes) total at baseline:</u> I: 2 C: 3 <u>age ± SD: (years)</u> I: 80 ±0 C: 72.7 ±11.7 <u>Sex (M/F):</u> I: NR C: NR <u>Duration of haemorrhage (days):</u> I: 3 and 7 C: 3, 9 and 10 <u>Diameter of haemorrhage (disk area):</u> I: NR C: NR <u>Baseline VA:</u> See table 4 Groups comparable at baseline? Yes	50 ug rtPA + 0.3ml 100% SF6+ 1.25mg bevacizumab Intravitreal injection was performed behind the limbus in phakic and pseudophakic eyes, respectively, using a #30 gauge needle. rtPA, was diluted with balanced salt solution to 1 mg/ml. Then, 0.05 ml, equal to 50 µg rtPA, was injected intravitreally. Subsequently, 0.3 ml of pure sulfur hexafluoride gas was injected into the vitreous cavity. 24hrs later, intravitreal injection of 1.25 mg/0.05 ml bevacizumab was performed in a similar fashion.	0.3ml 100% SF6 + 1.25mg bevacizumab	<u>Length of follow-up (m):</u> I: 12 C: 12 <u>Loss-to-follow-up:</u> NR <u>Incomplete outcome data:</u> Not relevant	Outcome measures and effect size (include 95%CI and p-value if available): See table 4
Tsyanava 2012 ⁷	Type of study: retrospective, non-randomized comparative case study Setting:	<u>Inclusion criteria:</u> See table 3 <u>Exclusion criteria:</u> See table 3 <u>N patients (eyes) total at baseline:</u> I: 64 (64)	50-200 ug tPA + gas	50-200 ug tPA	<u>Length of follow-up (yrs):</u> I: 1-3 wks, 3m, 6m C: 1-3 wks, 3m, 6m <u>Loss-to-follow-up:</u> NR	Outcome measures and effect size (include 95%CI and p-value if available): See table 4

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size
	Hospital Country: Germany Source of funding: NR	C: 46 (46) <u>age ± SD: (years)</u> I: 78.4 ± 6.9 C: 77.7 ± 7 <u>Sex (M/F):</u> I: 21/43 C: 13/33 <u>Duration of haemorrhage, days, median (range):</u> I: 8.0 (1-90) C: 10 (0.5-180) <u>Diameter of haemorrhage, median disk area (range):</u> I: 4.1 (1-42) C: 12.5 (1-38) <u>Baseline VA:</u> See table 4 Groups comparable at baseline? Yes			Incomplete outcome data: Not relevant	
Sacu 2009 ⁸	Type of study: Retrospective pilot Setting: Hospital Country: Austria Source of funding: NR	<u>Inclusion criteria:</u> See table 3 <u>Exclusion criteria:</u> See table 3 <u>N patients (eyes) total at baseline:</u> I: 20 (20) C: 10 (10) <u>age ± SD: (years)</u> I: 75.3±8.5 C: 78.1±6.7 <u>Sex (M/F):</u> I: NR C: NR <u>Duration of haemorrhage (days):</u>	50ug TPA (actilyse)+ SF6 + 1mg BVZ/0.05ml RBZ, then prn 50ug rTPA solution (Actilyse) in a volume of 50 ml was injected into the midvitreous cavity through a 30-gauge needle. After an aqueous tap to reduce IOP, 0.5 ml of 100% SF6 gas was injected into the vitreous cavity. If ocular perfusion was normal and IOP was <20mmHg, an additional injection of an anti-VEGF drug (BVZ, 1.0mg/0.04 ml) or (RBZ, 0.05 ml) was performed. Otherwise, application of an anti-VEGF was performed within 3 days after the initial procedure.	1 mg BVZ, then prn	<u>Length of follow-up (m):</u> I: 4 C: 4 <u>Loss-to-follow-up:</u> NR. <u>Incomplete outcome data:</u> Not relevant	Outcome measures and effect size (include 95%CI and p-value if available): See table 4

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size
		<p>I: 7.1±3.8 C: 12.9±12.6</p> <p><u>Diameter of haemorrhage (disk area):</u> I: 20.2±5.3mm² C: 19.1±5.5mm²</p> <p><u>Baseline VA:</u> See table 4 Groups comparable at baseline? yes</p>				
Guttoff 2011 ⁹	<p>Type of study: Retrospective Cohort</p> <p>Setting: Hospital</p> <p>Country: Germany</p> <p>Source of funding: NR.</p>	<p><u>Inclusion criteria:</u> See table 3</p> <p><u>Exclusion criteria:</u> See table 3</p> <p><u>N patients (eyes) total at baseline:</u> I: 26 (26) C: 12 (12)</p> <p><u>age ± SD:</u> I: 83 ±6.3 C: 81 ±5.2</p> <p><u>Sex (M/F):</u> I: 4/22 C: 5/7</p> <p><u>Duration of haemorrhage (days):</u> I: 10.9 ±8.9 C: 11.25 ±6.2</p> <p><u>Diameter of haemorrhage (disk area):</u> I: 4.96 ±2.48 C: 4.58 ±2.28</p> <p><u>Baseline VA:</u> See table 4 Groups comparable at baseline? Yes</p>	47 (mean) ug rTPA (actilyse) + SF6	1.5 mg BVZ + rTPA + SF6	<p><u>Length of follow-up (m):</u> I: 1 and 7 C: 1 and 7</p> <p><u>Loss-to-follow-up:</u> Intervention: NR Control: NR</p> <p><u>Incomplete outcome data:</u> Not relevant</p>	Outcome measures and effect size (include 95%CI and p-value if available): See table 4

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size
Hohn 2010 ¹⁰	<p>Type of study: Retrospective case series.</p> <p>Setting: Hospital</p> <p>Country: Germany</p> <p>Source of funding: NR</p>	<p><u>Inclusion criteria:</u> See table 3</p> <p><u>Exclusion criteria:</u> See table 3</p> <p><u>N patients (eyes) total at baseline:</u> I: 10 (10)</p> <p><u>Mean age ± SD (range):</u> I: 78.4 ± 6.5 (69-88)</p> <p><u>Sex (M/F):</u> I: 4/6</p> <p><u>Duration of haemorrhage (weeks):</u> I: 1.5 (1-4)</p> <p><u>Diameter of haemorrhage (mm²):</u> I: 9.5 ± 8.12 (0.85-21.7)</p> <p><u>Baseline VA:</u> See table 4</p> <p>Groups comparable at baseline? NA</p>	<p>1.25 mg BVZ + 0.3ml 100% SF6</p> <p>BVZ given in 0.1 ml and then gas.</p>	None	<p><u>Length of follow-up (m):</u> I: Mean = 11.7 (7-20)</p> <p><u>Loss-to-follow-up:</u> Intervention: 0</p> <p><u>Incomplete outcome data:</u> Not relevant</p>	<p>Outcome measures and effect size (include 95%CI and p-value if available): See table 4</p>
Hesgaard 2012 ¹¹	<p>Type of study: Retrospective comparative control case series</p> <p>Setting: Hospital</p> <p>Country: Denmark</p> <p>Source of funding: NR</p>	<p><u>Inclusion criteria:</u> See table 3</p> <p><u>Exclusion criteria:</u> See table 3</p> <p><u>N patients (eyes) total at baseline:</u> I: 8 (8) C: 7 (7)</p> <p><u>age ± SD:</u> I: 84.9 C: 81.2</p> <p><u>Sex (M/F):</u> I: 0/8 C: 3/4</p> <p><u>Duration of haemorrhage (days):</u></p>	<p>C3F8 + 0.5 mg RBZ</p> <p>Injection of pure C3F8 (0.3 ml) into the vitreous cavity through a 30-gauge needle introduced through the pars plana. A prone position was maintained for 48 hr during hospitalization.</p>	0.5mg RBZ	<p><u>Length of follow-up (m):</u> I: 11.7 (8-17) C: 14.9 (8-29)</p> <p><u>Loss-to-follow-up:</u> Intervention: 0 Control: 0</p> <p><u>Incomplete outcome data:</u> Not relevant</p>	<p>Outcome measures and effect size (include 95%CI and p-value if available): See table 4</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size
		<p>I: 6.6 C: 13.3 <u>Diameter of haemorrhage (disk area):</u> I: 4 C: 2.4 <u>Baseline VA:</u> See table 4 Groups comparable at baseline? No</p>				
Treumer ^{12,13}	<p>Type of study: Retrospective Case series</p> <p>Setting: Hospital</p> <p>Country: Germany</p> <p>Source of funding: no specific grant from any funding agency in the public, commercial or not-for-profit sectors.</p>	<p><u>Inclusion criteria:</u> See table 3 <u>Exclusion criteria:</u> See table 3 <u>N patients (eyes) total at baseline:</u> I: 40 (41) <u>age ± SD:</u> I: 77 <u>Sex (M/F):</u> I: 15/25 <u>Duration of haemorrhage (days):</u> I: 4 (1-14) <u>Diameter of haemorrhage (disk area):</u> I: 4.5 (1.5-12) <u>Baseline VA:</u> See table 4 Groups comparable at baseline? n/a</p>	<p>10-20 ug TPA (actilyse) + 1.25mg BVZ + SF6 gas</p> <p>Subretinal injection of 10-20 ug rtPA (Actilyse) dissolved in 0.05-0.1 ml balanced salt solution followed by subretinal injection of 1.25 mg BVZ through a 41-gauge subretinal flexible cannula and fluid-gas exchange with 20% SF6 gas. BVZ was administered for 4 weeks intravitreally and for 8 weeks postoperatively. Thereafter, repeated intravitreal injections of either BVZ or 0.5 mg RBZ were applied.</p>	None	<p><u>Length of follow-up (m):</u> 1, 3, 12</p> <p><u>Loss-to-follow-up:</u> Intervention: 5 Reasons NR</p> <p><u>Incomplete outcome data:</u> Not relevant</p>	Outcome measures and effect size (include 95%CI and p-value if available): See table 4
Meyer 2008 ¹⁴	<p>Type of study: Retrospective consecutive, case series.</p>	<p><u>Inclusion criteria:</u> See table 3 <u>Exclusion criteria:</u> See table 3 <u>N (eyes) total at baseline:</u></p>	<p>50 ug rtPA + 0.3-0.4 ml SF6 + 1.25 mg bevacizumab</p> <p>Each injection was inserted slowly 3.5 mm behind the limbus with a 30 gauge needle</p>	None	<p><u>Length of follow-up (m):</u> 3</p> <p><u>Loss-to-follow-up:</u></p>	Outcome measures and effect size (include 95%CI and p-value if available): See table 4

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size
	Setting: Hospital Country: Germany. Source of funding: NR	I: 19 <u>Mean age ± SD:</u> I: 77 (63-88) <u>Sex (M/F):</u> I: 7/12 <u>Duration of haemorrhage, days:</u> I: 9.3 (1-12) <u>Diameter of haemorrhage, disk area (range):</u> I: 1-4 <u>Baseline VA:</u> See table 4 Groups comparable at baseline? N/a	via a tunnelled sclerotomy into the midvitreal cavity. Firstly, rtPA (Actilyse), was diluted with balanced salt solution to 1 mg/ ml in 0.2 ml aliquots. We injected 0.05 ml, equal to a dose of 50ug. Secondly, 0.3–0.4 ml of pure sulphur hexafluoride (SF6) gas was injected. Thirdly, 0.05 ml (dose rate of 1.25 mg) bevacizumab was injected in each eye.		NR. <u>Incomplete outcome data:</u> Not relevant	
Kemai 1996 ¹⁵	Type of study: Consecutive, case series. Setting: Hospital Country: Japan. Source of funding: NR	<u>Inclusion criteria:</u> See table 3 <u>Exclusion criteria:</u> See table 3 <u>N (eyes) total at baseline:</u> I: 15 (15) <u>Mean age ± SD:</u> I: 72.7 (range 63-83) <u>Sex (M/F):</u> I: 11/4 <u>Duration of haemorrhage, weeks ± SD:</u> I: 4.8 (range 2-10) <u>Diameter of haemorrhage, disk area (range):</u> NR <u>Baseline VA:</u> See table 4 Groups comparable at baseline? N/a	12.5-50 ug tPA + perfluorocarbon liquid + 15-20% SF6	None	<u>Length of follow-up (m):</u> mean = 15 ± 7 (7-31) <u>Loss-to-follow-up:</u> NR. <u>Incomplete outcome data:</u> Not relevant	Outcome measures and effect size (include 95%CI and p-value if available): See table 4
Claes 1996 ¹⁶	Type of study: Prospective,	<u>Inclusion criteria:</u> See table 3	6-36 ug tPA 6-36 + air-fluid exchange	None	<u>Length of follow-up (m):</u>	Outcome measures and effect size (include 95%CI

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size
	consecutive, case series. Setting: Hospital Country: Belgium. Source of funding: NR	<u>Exclusion criteria:</u> See table 3 <u>N (eyes) total at baseline:</u> I: 15 (15) <u>Mean age \pm SD:</u> I: 72.7 (range 63-83) <u>Sex (M/F):</u> I: 11/4 <u>Duration of haemorrhage, weeks \pm SD:</u> I: 4.8 (range 2-10) <u>Diameter of haemorrhage, disk area (range):</u> NR <u>Baseline VA:</u> See table 4 Groups comparable at baseline? N/a			Average = 18.7 \pm 7.8 (5-31) <u>Loss-to-follow-up:</u> NR. <u>Incomplete outcome data:</u> Not relevant	and p-value if available): See table 4
Singh 2006 ¹⁷	Type of study: Consecutive, case series. Setting: Hospital Country: USA. Source of funding: NR	<u>Inclusion criteria:</u> See table 3 <u>Exclusion criteria:</u> See table 3 <u>N (eyes) total at baseline:</u> I: 17 <u>Mean age \pm SD:</u> I: 81.1 \pm 7.1 <u>Sex (M/F):</u> I: 8/9 <u>Duration of haemorrhage, days \pm SD:</u> I: 11.9 \pm 11.6 <u>Diameter of haemorrhage, disk area (range):</u> NR <u>Baseline VA:</u> See table 4 Groups comparable at baseline?	48 ug tPA + partial fluid exchange 32 gauge rigid cannula was used to infuse t-PA (Activase) into the subretinal space. A t-PA dosage of 12 ug/ 0.1 ml was used, with a total dose of 48 ug administered. A fluid-air exchange was then performed to the dome of the macular detachment. All patients were placed for 1 hour face up, and then sat upright overnight.	None	<u>Length of follow-up (m):</u> Average = 17.2 (3-48) <u>Loss-to-follow-up:</u> NR. <u>Incomplete outcome data:</u> Not relevant	Outcome measures and effect size (include 95%CI and p-value if available): See table 4

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size
		N/a				
Sulak 2011 ¹⁸	Type of study: Retrospective clinical case series. Setting: Hospital Country: NR. Source of funding: NR	<u>Inclusion criteria:</u> See table 3 <u>Exclusion criteria:</u> See table 3 <u>N (eyes) total at baseline:</u> I: 9 (9) <u>Mean age:</u> I: NR <u>Sex (M/F):</u> I: NR <u>Duration of haemorrhage, days:</u> I: NR <u>Diameter of haemorrhage, disk area (range):</u> NR <u>Baseline VA:</u> See table 4 Groups comparable at baseline? N/a	TPA + expansile gas (4 patients received BVZ postoperatively)	None	<u>Length of follow-up (m):</u> 19 wks <u>Loss-to-follow-up:</u> NR. <u>Incomplete outcome data:</u> Not relevant	Outcome measures and effect size (include 95%CI and p-value if available): See table 4
Tognetto 2011 ¹⁹	Type of study: Retrospective Case series Setting: Hospital Country: Italy Source of funding: NR.	<u>Inclusion criteria:</u> See table 3 <u>Exclusion criteria:</u> See table 3 <u>N patients (eyes) total at baseline:</u> I: 3 (3) <u>age ± SD:</u> I: 74.3* <u>Sex (M/F):</u> I: 0/3 <u>Duration of haemorrhage (days):</u> I: 1.7* (1-2) <u>Diameter of haemorrhage (disk area):</u>	25ug rTPA + Fluid-air exchange Patients underwent 25 gauge pars plana vitrectomy with posterior hyaloid removal. An injection of 0.2 mL of subretinal rtPA (125 µg/mL) through a 41-gauge flexible translocation microcannula (DORC-dual bore BSS injection needle 0.1 mm tip) followed. The rTPA was injected inferiorly to the SMH in order to create a bullous retinal detachment encompassing the entire blood clot. Finally a fluid-air exchange was performed and patients maintained a supine position for 45 mins followed by a postoperative prone position.	None	<u>Length of follow-up (m):</u> I: 1.0 <u>Loss-to-follow-up:</u> Intervention: 0 <u>Incomplete outcome data:</u> Not relevant	Outcome measures and effect size (include 95%CI and p-value if available): See table 4

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size
		I: 6.11mm ² * (4.15-8.07) reported for 2 patients <u>Baseline VA:</u> See table 4 Groups comparable at baseline? n/a				
Manning 1994 ²⁰	Type of study: Case reports. Setting: Hospital Country: Australia. Source of funding: NR	<u>Inclusion criteria:</u> See table 3 <u>Exclusion criteria:</u> See table 3 <u>N (eyes) total at baseline:</u> I: 3 (3) <u>Mean age:</u> I: 74.7 (range 74-76) <u>Sex (M/F):</u> I: 2/1 <u>Duration of haemorrhage, days:</u> I: 2, 7, and 14 <u>Diameter of haemorrhage, disk area (range):</u> NR <u>Baseline VA:</u> See table 4 Groups comparable at baseline? N/a	12-36 ug tPA + 0.25ml 100% SF6 For case 1: 0.3 ml of TPA solution at 12 ug/O.1 mL was attached to a 30G cannula. The cannula was passed through the retinotomy and 0.1 mL injected directly into the clot. After 30 minutes, balanced saline solution was irrigated through the retinotomy, to clear the haemorrhage. The area of the CNVM on the original FA and the retinotomy site were then treated with argon laser endophotocoagulation and 0.25 mL of 100% SF6 was injected into the vitreous cavity.	None	<u>Length of follow-up (m):</u> 6 wks to 10m <u>Loss-to-follow-up:</u> NR. <u>Incomplete outcome data:</u> Not relevant	Outcome measures and effect size (include 95%CI and p-value if available): See table 4
Moriarty 1995 ²¹	Type of study: Case series. Setting: Hospital Country: Australia. Source of funding: NR	<u>Inclusion criteria:</u> See table 3 <u>Exclusion criteria:</u> See table 3 <u>N (eyes) total at baseline:</u> I: 15 (WAMD= 14) <u>Mean age ± SD:</u> I: 76.9 ± 6.8 <u>Sex (M/F):</u> I: 6/9 <u>Duration of haemorrhage, days:</u>	25 ug tPA + SF6	None	<u>Length of follow-up (m):</u> 11 ± 4.9 (3-18) <u>Loss-to-follow-up:</u> None. <u>Incomplete outcome data:</u> Not relevant	Outcome measures and effect size (include 95%CI and p-value if available): See table 4

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size
		<i>I</i> : 2 days to 8 weeks <u>Diameter of haemorrhage, disk area (range)</u> : NR <u>Baseline VA</u> : See table 4 Groups comparable at baseline? N/a				
Hay 2000 ²²	Type of study: Prospective, case report. Setting: Hospital Country: USA. Source of funding: NR	<u>Inclusion criteria</u> : See table 3 <u>Exclusion criteria</u> : See table 3 <u>N (eyes) total at baseline</u> : <i>I</i> : 1 (1) <u>Mean age ± SD</u> : <i>I</i> : 73 <u>Sex (M/F)</u> : <i>I</i> : 1/0 <u>Duration of haemorrhage, days ± SD</u> : <i>I</i> : 2 <u>Diameter of haemorrhage, disk area (range)</u> : NR <u>Baseline VA</u> : See table 4 Groups comparable at baseline? N/a	tPA + SF6	None	<u>Length of follow-up (m)</u> : 5 (1,2,3,5) <u>Loss-to-follow-up</u> : 0. <u>Incomplete outcome data</u> : Not relevant	Outcome measures and effect size (include 95%CI and p-value if available): See table 4
Krepler 2000 ²³	Type of study: NR, assumed to be prospective. Setting: Hospital Country: Austria	<u>Inclusion criteria</u> : See table 3 <u>Exclusion criteria</u> : See table 3 <u>N (eyes) total at baseline</u> : <i>I</i> : 11 <u>age ± SD</u> : <i>I</i> : 73.8 ± 5.3 (68-83) <u>Sex (M/F)</u> :	25 ug tPA + 0.5 ml SF6	None	<u>Length of follow-up (m)</u> : 1, 3, 6, 9, 12. <u>Loss-to-follow-up</u> : None. <u>Incomplete outcome data</u> :	Outcome measures and effect size (include 95%CI and p-value if available): See table 4

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size
	Source of funding: NR	I: 4/7 <u>Duration of haemorrhage, days (range):</u> I: 7.9 (1-21) <u>Diameter of haemorrhage, disk area (range):</u> I: 7.8* (1-16) <u>Baseline VA:</u> See table 4 Groups comparable at baseline? N/a			Not relevant	
Hattenbach 2001 ²⁴	Type of study: Prospective, case series. Setting: Hospital Country: Germany. Source of funding: NR	<u>Inclusion criteria:</u> See table 3 <u>Exclusion criteria:</u> See table 3 <u>N (eyes) total at baseline:</u> I: 43 (42) <u>Mean age ± SD:</u> I: 74.6 (range 50-91) <u>Sex (M/F):</u> I: 15/27 <u>Duration of haemorrhage, days ± SD:</u> I: 15.4 (range 2-28) <u>Diameter of haemorrhage, disk area (range):</u> Range 0.25-30 <u>Baseline VA:</u> See table 4 Groups comparable at baseline? N/a	50 ug rtPA + 0.5ml SF6 50 ug of rt-PA solution (Actilyse) in 50 ml, was drawn in a tuberculin syringe and injected slowly into the midvitreal cavity through a 30-gauge needle. After an aqueous tap to reduce intraocular pressure, 0.5 ml of 100% sulfur hexafluoride gas was injected into the vitreal cavity. Both injections were administered via the pars plana in the superotemporal quadrant. Patients were then instructed to maintain prone positioning for 72 hours.	None	<u>Length of follow-up (m):</u> Average = 6 ± 3.4 (4-18) <u>Loss-to-follow-up:</u> NR. <u>Incomplete outcome data:</u> Not relevant	Outcome measures and effect size (include 95%CI and p-value if available): See table 4
Steller 2004 ²⁵	Type of study: Case series. Setting: Hospital	<u>Inclusion criteria:</u> See table 3 <u>Exclusion criteria:</u> See table 3 <u>N (eyes) total at baseline:</u>	50 ug rTPA + 0.5ml SF6 SF6 given 24 hrs after TPA, prone positioning for 3 days.	None	<u>Length of follow-up (m):</u> Mean = 14.2 (6-28) <u>Loss-to-follow-up:</u>	Outcome measures and effect size (include 95%CI and p-value if available): See table 4

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size
	Country: Germany. Source of funding: NR	I: 25 (25) <u>Mean age \pm SD:</u> I: 78.6 \pm 7 <u>Sex (M/F):</u> I: NR <u>Duration of haemorrhage:</u> I: \leq 1 week <u>Diameter of haemorrhage, disk area (range):</u> Range 1-10 <u>Baseline VA:</u> See table 4 Groups comparable at baseline? N/a			45 patients treated but only 25 had <6 m follow-up. <u>Incomplete outcome data:</u> Not relevant	
Handwerger 2001 ²⁶	Type of study: Retrospective Case series Setting: Outpatient clinic Country: USA Source of funding: NR	<u>Inclusion criteria:</u> See table 3 <u>Exclusion criteria:</u> See table 3 <u>N (eyes) total at baseline:</u> I: 14 <u>age \pm SD:</u> I: 80.9 \pm 7.5 (71-97) <u>Sex (M/F):</u> I: 7/7 <u>Duration of haemorrhage (days):</u> I: 9 (1-21) <u>Diameter of haemorrhage (disk area):</u> I: 16 (3.5-44) <u>Baseline VA:</u> See table 4 Groups comparable at baseline? N/a	18-50 ug tPA + 0.3-0.4 ml C3F8	None	<u>Length of follow-up (m):</u> Mean 7.7 (range 1-15) <u>Loss-to-follow-up:</u> One patients was lost to follow-up one month after treatment. <u>Incomplete outcome data:</u> Not relevant	Outcome measures and effect size (include 95%CI and p-value if available): See table 4
Kung 2010 ²⁷	Type of study: Retrospective Case series	<u>Inclusion criteria:</u> See table 3 <u>Exclusion criteria:</u>	50 ug TPA + 0.3ml C3F8 TPA administered in 0.1ml injected through	None	<u>Length of follow-up (m):</u> I: 17.6 \pm 17.1 (range	Outcome measures and effect size (include 95%CI and p-value if available):

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size
	<p>Setting: Hospital</p> <p>Country: Taiwan</p> <p>Source of funding: Kaohsiung Veterans General Hospital, Taiwan.</p>	<p>See table 3</p> <p><u>N patients (eyes) total at baseline:</u> I: 27 (28) AMD</p> <p><u>age \pm SD:</u> I: 70.6 \pm9.1*</p> <p><u>Sex (M/F):</u> I: 22/6</p> <p><u>Duration of haemorrhage (days):</u> I: 20.3 \pm17* (1-60)</p> <p><u>Diameter of haemorrhage (disk area):</u> I: 8.6 \pm6.1* (1-19)</p> <p><u>Baseline VA:</u> See table 4</p> <p>Groups comparable at baseline? n/a</p>	<p>pars plana into the vitreous cavity via a 30 gauge needle. 0.3 ml perfluoropropane was injected into the vitreous cavity in a similar fashion.</p>		<p>1-60)</p> <p><u>Loss-to-follow-up:</u> Intervention: 2 patients were excluded due to loss to follow-up after 2 weeks treatment.</p> <p><u>Incomplete outcome data:</u> Not relevant</p>	<p>See table 4</p>
Hesse 1999 ²⁸	<p>Type of study: Consecutive patients.</p> <p>Setting: Hospital</p> <p>Country: Germany.</p> <p>Source of funding: NR</p>	<p><u>Inclusion criteria:</u> See table 3</p> <p><u>Exclusion criteria:</u> See table 3</p> <p><u>N (eyes) total at baseline:</u> I: 11</p> <p><u>Mean age \pm SD:</u> I: 71.5 \pm 4.8</p> <p><u>Sex (M/F):</u> I: 6/5</p> <p><u>Duration of haemorrhage, days:</u> I: 12 hrs to 14 days</p> <p><u>Diameter of haemorrhage, disk area (range):</u> I: Mean 4.9 (2-10)</p> <p><u>Baseline VA:</u> See table 4</p> <p>Groups comparable at baseline? N/a</p>	<p>50 or 100 ug tPA + 0.15-1.0 ml expansile gas (SF6 or C2F6 or C3F8)</p>	<p>None</p>	<p><u>Length of follow-up (m):</u> Mean 4.8 \pm3 (3, 6, 8, 12).</p> <p><u>Loss-to-follow-up:</u> None.</p> <p><u>Incomplete outcome data:</u> Not relevant</p>	<p>Outcome measures and effect size (include 95%CI and p-value if available): See table 4</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size
Ratanasukon 2005 ²⁹	Type of study: Retrospective Case series Setting: Hospital Country: Thailand Source of funding: NR	<u>Inclusion criteria:</u> See table 3 <u>Exclusion criteria:</u> See table 3 <u>N (eyes) total at baseline:</u> I: 15 (AMD) <u>Age, years \pm SD:</u> I: 60.9 (50-80) <u>Sex (M/F):</u> I: 13/2 <u>Duration of haemorrhage (days):</u> I: 13 (3-28) <u>Diameter of haemorrhage (disk area):</u> I: 2 to 3 to >3 <u>Baseline VA:</u> See table 4 Groups comparable at baseline? N/a	50-100 ug/0.1 ml tPA + expansile gas (C3F8 or SF6)	None	<u>Length of follow-up (m):</u> 9.4* (6-19) <u>Loss-to-follow-up:</u> 19 of 24 eyes (79.1%) completed the inclusion criteria. The other five eyes had less than 6 months follow-up and were excluded from the study. 15 of 19 included eyes had wAMD. <u>Incomplete outcome data:</u> Not relevant	Outcome measures and effect size (include 95%CI and p-value if available): See table 4
Daneshvar 1999 ³⁰	Type of study: Prospective, case series. Setting: Hospital Country: N America. Source of funding: NR	<u>Inclusion criteria:</u> See table 3 <u>Exclusion criteria:</u> See table 3 <u>N (eyes) total at baseline:</u> I: 3 (3) <u>Mean age \pm SD:</u> I: NR <u>Sex (M/F):</u> I: NR <u>Duration of haemorrhage, days \pm SD:</u> I: 2, 10 and 28 <u>Diameter of haemorrhage, disk area (range):</u>	0.6ml SF6	None	<u>Length of follow-up (m):</u> At least 6 <u>Loss-to-follow-up:</u> NR. <u>Incomplete outcome data:</u> Not relevant	Outcome measures and effect size (include 95%CI and p-value if available): See table 4

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size
		NR <i>Baseline VA:</i> See table 4 Groups comparable at baseline? N/a				
Ron 2007 ³¹	Type of study: Retrospective Case series Setting: Hospital Country: Israel Source of funding: NR	<u>Inclusion criteria:</u> See table 3 <u>Exclusion criteria:</u> See table 3 <u>N patients (eyes) total at baseline:</u> I: 24 (24) <u>age ± SD: (years)</u> I: 79.9 (range 70-89) <u>Sex (M/F):</u> I: 15/9 <u>Duration of haemorrhage (days):</u> I: 7.8 (range 2-30) <u>Diameter of haemorrhage (disk area):</u> I: ≥3 <i>Baseline VA:</i> See table 4 Groups comparable at baseline? n/a	0.4 ml C3F8 or SF6 Gas given according to surgeons preference.	None	<u>Length of follow-up (m):</u> I: 3 <u>Loss-to-follow-up:</u> NR. <u>Incomplete outcome data:</u> Not relevant	Outcome measures and effect size (include 95%CI and p-value if available): See table 4

A list of abbreviations is given on page 6

* calculated by KSR.

Table 2: Treatment regimens for the Research question, 'what are the effects of TPA or gas in patients with both AMD and (sub)macular bleeding? (Question 1)

Study	Interventions	No. Eyes	PRN/ fixed/ treat & extend	Number of baseline VEGF injections	Time between baseline VEGF injections	Follow-up examinations (wks)	No. final VEGF injections (mean±sd)
Yang 2005 ³	25-33ug TPA + C3F8/SF6	5	fixed	0	-	-	0
	C3F8/SF6	13		0	-	-	0
Thompson 2005 ⁴	12.5-25 ug TPA + fluid/air exchange	15	Fixed	-	-	-	-
	Submacular surgery	27	Fixed	-	-	-	-
Sandhu 2010 ⁵	12.5ug TPA + fluid/air exchange	4	fixed	0	-	-	-
	12.5ug TPA + fluid/air exchange + PRN RBZ	12	PRN	0	-	1 day and 1 week	3.7 (6m), 4.5 (12m, range = 3-8)
Nourinia 2010 ⁶	0.3ml 100% SF6 + 1.25mg PRN BVZ	3	Fixed	-	-	-	-
	50 ug TPA + 0.3ml 100% SF6 + 1.25mg PRN BVZ	2	PRN	1	-	NR	1.8 (range 1-3)
Tsymanava 2012 ⁷	50-200 ug TPA + gas	64	Fixed	-	-	-	-
	50-200 ug TPA	46	Fixed	-	-	-	-
Sacu 2009 ⁸	50ug TPA (actilyse)+ SF6 + 1mg BVZ/0.05ml RBZ, then prn (BVZ/RBZ)	20	PRN	1	-	NR	1.6±0.9
	1 mg BVZ, then prn (BVZ)	10	PRN	1	-	NR	3.0±0.8
Guttoff 2011 ⁹	47(mean)ug TPA (actilyse) + SF6, then prn RBZ/BVZ	26	PRN	0	-	4 (RBZ) or 8 (BVZ)	2.7±1.3 (BVZ), 4.5±1.5 (RBZ).
	TPA + SF6 + 1.5mg BVZ, then prn RBZ/BVZ	12	PRN	1	-	4 (RBZ) or 8 (BVZ)	3.5±0.7 (BVZ), 4.5±1.6 (RBZ).

Study	Interventions	No. Eyes	PRN/ fixed/ treat & extend	Number of baseline VEGF injections	Time between baseline VEGF injections	Follow-up examinations (wks)	No. final VEGF injections (mean±sd)
Hohn 2010 ¹⁰	1.25 mg BVZ + 0.3ml 100% SF6	10	PRN	1	-	4	3.8 ±2.1 (0-6)
Hesgaard 2012 ¹¹	C3F8 + 0.5 mg PRN RBZ	8	PRN	1	NR	NR	5.6
	0.5mg PRN RBZ	7	PRN	1	NR	NR	7
Treumer ^{12, 13}	10-20ug TPA (actilyse) + SF6 + 1.25mg BVZ, then BVZ/RBZ prn	41	PRN	1	NR	NR	4.5 (range 2-9)
Meyer 2008 ¹⁴	50 ug TPA + 0.3-0.4 ml SF6 + 1.25 mg BVZ	19	Fixed	1	-	4, 12	NR
Kemai 1996 ¹⁵	12.5-50 ug TPA + C3F8 liquid + 15-20% SF6 gas	22	Fixed	-	-	-	-
Claes 1996 ¹⁶	6-36 ug TPA + air-fluid exchange	15	Fixed	-	-	-	-
Singh 2006 ¹⁷	48 ug TPA + partial fluid exchange	17	Fixed	-	-	-	-
Sulak 2011 ¹⁸	TPA + expansile gas (4 patients received BVZ postoperatively)	9	NR	NR	NR	NR	NR
Tognetto 2011 ¹⁹	25ug TPA + Fluid-air exchange	3	Fixed	-	-	-	-
Manning 1994 ²⁰	12-36 ug TPA + 0.25ml 100% SF6	3	Fixed	-	-	-	-
Moriarty 1995 ²¹	25 ug TPA + SF6	14	fixed	-	-	-	-
Hay 2000 ²²	TPA + SF6	1	Fixed	-	-	-	-
Krepler 2000 ²³	25 ug TPA + 0.5 ml SF6	11	fixed	-	-	-	-
Hattenbach 2001 ²⁴	50 ug TPA + 0.5ml SF6	43	Fixed	-	-	-	-

Study	Interventions	No. Eyes	PRN/ fixed/ treat & extend	Number of baseline VEGF injections	Time between baseline VEGF injections	Follow-up examinations (wks)	No. final VEGF injections (mean±sd)
Steller 2004 ²⁵	50 ug TPA + 0.5ml SF6	25	Fixed	-	-	-	-
Handwerger 2001 ²⁶	18-50 ug TPA + 0.3-0.4 ml C3F8	14	fixed	-	-	-	-
Kung 2010 ²⁷	50 ug TPA + 0.3ml C3F8	28	Fixed	-	-	-	-
Hesse 1999 ²⁸	50 or 100 ug TPA + 0.15-1.0 ml expansile gas (SF6 or C2F6 or C3F8)	11	fixed	-	-	-	-
Ratanasukon 2005 ²⁹	50-100ug/0.1 ml TPA + expansile gas (C3F8 or SF6)	15	fixed	-	-	-	-
Daneshvar 1999 ³⁰	0.6ml SF6	3	Fixed	-	-	-	-
Ron 2007 ³¹	0.4 ml C3F8 or SF6	24	fixed	-	-	-	-

A list of abbreviations is given on page 6

* calculated by KSR.

Table 3: Study Definitions table for the Research question, 'what are the effects of TPA or gas in patients with both AMD and (sub)macular bleeding? (Question 1)

Study	PRN definition	Inclusion criteria	Exclusion criteria
Yang 2005 ³	NR	Patients who had undergone intravitreal injection of expansile gas, with or without adjunctive commercial tPA solution, for dense submacular hemorrhage; submacular hemorrhage was defined as one causing obvious foveal elevation with an illdefined macular area detectable on stereo fundus photographs. The size of the hemorrhage needed to be at least three disc areas, and the period between symptoms and therapy one month but almost all were within 14 days	Individuals with a bleeding disorder, undergoing anticoagulant therapy or with a history of inflammatory eye disease were excluded from the study. Patients were also excluded if vitreous hemorrhage was present at the initial examination.
Thompson 2005 ⁴	NR	Patients who presented with submacular hemorrhage related to exudative macular degeneration and had surgery. Only patients with relatively recent hemorrhages (<3 months) were treated. The subretinal hemorrhage had to extend to at least the superotemporal or inferotemporal arcade (size >16 disc areas) to be offered surgery in the SRH group. The submacular hemorrhage had to be at least 12 disc areas to be treated with TPA but did not have to reach the temporal arcades. The SRH procedure was favored for eyes presenting with very large submacular hemorrhages outside of temporal arcades.	Patients with white to yellow subretinal hemorrhages from denaturation of haemoglobin.
Sandhu 2010 ⁵	RZB was given to all patients whose vision was logarithm of the minimum angle of resolution (logMAR) 1.20 (6/96) or better at 1 week following initial surgery. The RZB injection was then repeated at monthly intervals until 3 doses had been given. Further RZB was given depending on clinical response as per the National Institute for Health and Clinical Excellence (NICE)/Royal College of Ophthalmologist guidelines.	Consecutive patients with SMH secondary to nAMD; treated if criteria met: a clear history of suddenly reduced vision within 6 weeks; the presence of thick SMH involving the foveal center obscuring the RPE and choroidal patterns and appearing dark red or black with visible elevation; a total extent of blood of at least 3 disc diameters in greatest linear dimension; signs of nAMD in the effected eye and/or in the fellow eye (drusen, pigmentary change or nAMD); patients were unable to comply with the postoperative face down posturing requirements of an expansile gas technique (ie, unable to maintain a face downward position for 48 hours), or who had previously failed displacement using an expansile gas technique.	Patients with a vitreous hemorrhage obscuring the fundus were excluded as were patients with massive hemorrhage measuring more than 12 disc diameters in greatest linear dimension.
Nourinia 2010 ⁶	Patients received reinjection(s) of bevacizumab when recurrent	Patients with SMH due to neovascular AMD. All SMHs were of sufficient thickness to induce significant elevation of the entire neurosensory retina, completely	NR

Study	PRN definition	Inclusion criteria	Exclusion criteria
	CNV was noticed. Recurrence was defined as a decrease in VA associated with new foci of subretinal hemorrhage or intraretinal fluid detected by OCT, and leakage noted by FA.	obscuring the underlying choroidal vascular pattern on biomicroscopic examination.	
Tsymanava 2012 ⁷	NR	To be included in the study, the patients had to meet the following criteria: baseline documentation had to be available before treatment; their medical history had to include information on gender, age, systemic anticoagulation therapy, BCVA (Snellen letters), slit-lamp biomicroscopy, Goldmann tonometry, and funduscopy; and they had to have undergone a minimum follow-up period of 3 weeks. We did not define a minimum or maximum haemorrhage size or duration as inclusion or exclusion criteria. The diagnostic criteria for ARMD, which were based on the Bird et al. (1995), included being age 50 years or older and having haemorrhage associated with macular drusen and / or an alteration of the macular retinal pigment epithelium. If the macular haemorrhage was covering the entire posterior pole, the diagnosis was made by performing a funduscopy of the second eye.	Patients with pathological myopia, diabetic retinopathy, idiopathic retinal or choroidal vasculopathies and history of ocular trauma or vitreoretinal surgery, including intravitreal injections, were excluded from the study.
Sacu 2009 ⁸	Persistent submacular blood or evidence for active CNV on the basis of OCT or FA. In case the patient required repeated injections 1 mg/0.04 ml BVZ or 0.5 mg/0.05 ml RBZ, dependent on the baseline treatment, were applied.	Patients who had had extensive subfoveal haemorrhage secondary to neovascular AMD; submacular haemorrhage was larger than 4 and smaller than 10 disc diameters within the arcades at baseline; subretinal haemorrhage directly beneath the fovea.	NR
Guttoff 2011 ⁹	RBZ or BVZ were given after FA confirmation of CNV at 4 or 8 week intervals, respectively in all patients according to CNV activity.	Acute deterioration of vision in 1 eye in <31 days because of hemorrhage >1 disc diameter directly beneath the fovea, a completed follow up of 7 months and 4 weeks after intravitreal injection, angiographically verified active neovascular lesion because of AMD.	Previous vitreoretinal surgery, intravitreal injections, photodynamic or laser therapy.
Hohn 2010 ¹⁰	NR	Patients with submacular hemorrhage (<28 days) associated with age-related macular degeneration.	Bleeding disorders, submacular haemorrhage of other origins other than WAMD, inflammation

Study	PRN definition	Inclusion criteria	Exclusion criteria
			of the eye, vitreous bleeding, patients unable to lie face down for 48hrs.
Hesgaard 2012 ¹¹	NR	Acute SMH for <4 wks, blood under the fovea, reading vision in the involved eye immediately before the haemorrhage and a follow-up period of at least 8 m.	NR.
Treumer ^{12, 13}	Decrease of BCVA and/or increase in retinal thickness on OCT, central retinal thickness >100 mm) and/or if new leakage on FA and/or if new retinal haemorrhages developed.	Neovascular AMD complicated by SMH involving the fovea, a maximum history of symptoms of 2 wks and a minimum age of 18 yrs.	Other aetiologies of SMH, massive SMH extending beyond the equator and pre-existing macular scar.
Meyer 2008 ¹⁴	NR	Consecutive patients with SRH related to exudative AMD who had undergone intravitreal injection of commercial rtPA solution, expansile gas and bevacizumab; all SRH were of sufficient thickness to induce a significant elevation of the entire neurosensory retina, obstructing completely the underlying choroidal vascular pattern on biomicroscopic examination.	Patients were excluded from the study if the onset of the subretinal bleeding was longer than 3 months prior of the baseline examination or additional vitreous haemorrhages were present at their initial examination.
Kemai 1996 ¹⁵	NR	Patients with submacular hemorrhage associated with age-related macular degeneration that involved a zone of at least one disc diameter centered at the foveola, localized mainly between the neurosensory retina and retinal pigment epithelium. In all cases hemorrhage was thick enough to cause an obvious elevation of the fovea and to completely obscure the choroidalvascular pattern under the hemorrhage.	Subretinal hemorrhage regardless of size that did not involve the macula; submacular hemorrhage thick enough that the choroidal vascular pattern could be seen at the macula; hemorrhage mainly beneath the retinal pigment epithelium; completely organized hemorrhage (appearing as white-yellow clots).
Claes 1996 ¹⁶	NR	Patients with AMD and elevated submacular hemorrhages.	NR
Singh 2006 ¹⁷	NR	Surgical patients with subretinal haemorrhage involving the foveal centre were investigated. All haemorrhages were secondary to age related macular degeneration and did not extend beyond the vasculature arcades.	NR
Sulak 2011 ¹⁸	NR	Submacular hemorrhages in patients with neovascular AMD.	NR

Study	PRN definition	Inclusion criteria	Exclusion criteria
Tognetto 2011 ¹⁹	-	Acute SMH after anti-VEGF injection involving most of the macular region.	NR
Manning 1994 ²⁰	NR	Patients with CNV membranes secondary to AMD and subretinal haemorrhage.	NR
Moriarty 1995 ²¹	NR	Recent history suggestive of bleed (initially within 1 week but a maximum of 8 weeks in 1 case); SMH of >5 disc diameters and also convex with a tenting elevation of the retina, as judged by biomicroscopy, since these have a poorer prognosis than flat haemorrhages if left untreated; A previously good visual acuity, implying little pre-existent macular degeneration, and a current vision of 6/60 or worse; An absence of sub-RPE blood at the fovea.	NR
Hay 2000 ²²	NR	A patient with sudden onset decreased vision in the right eye, with WAMD and subretinal haemorrhage.	NR
Krepler 2000 ²³	NR	Patients with acute subretinal hemorrhage due to suspected AMD (either history of or present signs of AMD, such as drusen or disciform scars in either eye); involvement of fovea, substantial loss of central VA, hemorrhage duration <3 weeks (onset of visual loss within the last 3 wks), history of better visual function before the hemorrhage.	NR
Hattenbach 2001 ²⁴	NR	Consecutive patients with acute (≤ 28 days) submacular hemorrhage secondary to AMD were enrolled. All patients had subretinal hemorrhages centered in or close to the fovea and reading vision in the affected eye before the onset of hemorrhage.	Individuals with bleeding disorders, anticoagulant therapy, or a history of inflammatory eye disease. Patients were excluded whenever vitreous hemorrhage was present at the initial examination.
Steller 2004 ²⁵	-	Patients with AMD and SMH for less than 7 days.	NR
Handwerker 2001 ²⁶	NR	Symptomatic SMH for less than 3 wks, thick blood under the fovea resulting in retinal elevation, hemorrhage of at least 3 DA. Also included patients with thick blood beneath the retinal pigment epithelium.	NR
Kung 2010 ²⁷	-	Patients who received intravitreal injection of tpa and perfluoropropane gas for displacement of submacular hemorrhage and had postoperative follow up of >1 month. All patients had thick SMH between the neurosensory retina and RPE resulting in foveal elevation.	NR
Hesse 1999 ²⁸	NR	Patients presenting with submacular hemorrhage (localized mainly between the neurosensory retina and RPE) causing an obvious foveal elevation.	NR
Ratanasukon	NR	(1) acute onset of bleeding within 1 month, (2) treatment with intravitreal injection	NR

Study	PRN definition	Inclusion criteria	Exclusion criteria
2005 ²⁹		of tPA 50–100 mg/0.1 ml with expansile gas (100% perfluoropropane 0.3 ml or 100% sulphur hexafluoride 0.4 ml), and (3) a follow-up period of at least 6 months; The clinical appearances of soft drusen and retinal pigmentary changes in either eye or the presence of subretinal fluid and exudate associated with drusen and pigmentary changes in patients over =50 years of age suggested the diagnosis of ARMD.	
Daneshvar 1999 ³⁰	NR	Patients with SMH secondary to AMD; pts had sudden onset of decreased vision to the CF level.	NR
Ron 2007 ³¹	NR	Patients with AMD and SMH who underwent intravitreal gas injection.	Patients with SH due to other causes and pts referred more than one months after onset of symptoms, patients who underwent vitrectomy for vitreous hemorrhage concomitant with or immediately after gas injection

A list of abbreviations is given on page 6

Table 4: VA Continuous Results table for the Research question, 'what are the effects of TPA or gas in patients with both AMD and (sub)macular bleeding? (Question 1)

Study	Interventions	Follow-up (months)	No. eyes	Visual acuity results				Visual acuity methods	
				Baseline (mean logMAR)	Follow-up (mean logMAR)	Mean change (logMAR)	Mean change (ETDRS)	Chart	distance
Yang 2005 ³	25-33ug TPA + C3F8/SF6	19.2* ±7.6 (12-32)	5	1.42* ±0.67 (range 0.7 to 2.0)	0.99* ± 0.64 (range 0.17 to 1.3)	-0.43*	NR	Snellen	NR
	C3F8/SF6	13.2* ±6.0 (6-27)	13	1.46* ±0.58 (range 0.48 to 2.0)	0.99* ±0.60 (range 0.3 to 2.0)	-0.47*			
Thompson 2005 ⁴	Submacular surgery	3	27	1.7 (range 0.54-3)	1.5	-0.2	NR	Snellen	NR
		12			1.5	-0.2	NR		
		2.92 ±0.48 yrs			1.5	-0.2	NR		
	12.5-25 ug TPA + fluid/air exchange	3	15	1.4 (range 0.7-2)	1.5	0.1	NR		
		12			1.7	0.3	NR		
		2.3 ± 0.25 yrs			1.7	0.3	NR		
Sandhu 2010 ⁵	12.5 ug TPA + fluid/air exchange	1	4	1.81 (95% CI: 1.38 to 2.24)	1.6*	-0.21*	NR	Snellen	NR
		12			0.58 (95% CI: 0.43 to 0.74)	-1.23*			
	12.5 ug TPA + fluid/air exchange	6	4	1.81 (95% CI: 1.38 to 2.24)	1.82*	0.01*	NR	Snellen	NR
					12	0.69 (95% CI: 0.46 to 0.91)	-1.12*		
	12.5 ug TPA + fluid/air exchange	12	NR	1.81 (95% CI: 1.38 to 2.24)	NR	NR	NR	Snellen	NR
					NR	0.66 (95% CI: 0.46 to 0.87)	-1.15*		
Nourinia 2010 ⁶	50 ug TPA + 0.3ml 100% SF6	12	2	1.25* ±0.4	0.44* ±0.4	-0.81*	NR	Snellen	NR

Study	Interventions	Follow-up (months)	No. eyes	Visual acuity results				Visual acuity methods	
				Baseline (mean logMAR)	Follow-up (mean logMAR)	Mean change (logMAR)	Mean change (ETDRS)	Chart	distance
	+ 1.25mg PRN BVZ 0.3ml 100% SF6 + 1.25mg PRN BVZ	12	3	1.30* ±0.3	0.67* ±0.4	-0.63*			
Tsymanava 2012 ⁷	50-200 ug TPA	1-3 wks	46	Median 1.1 (0.4-2.1)	Median 1.4 (0.4-2.1)	0.3*	NR	Snellen	NR
		3		Median 1.1 (0.4-2.1)	Median 1.8 (0.2-2.1)	0.7*			
		6		Median 1.1 (0.4-2.1)	Median 1.5 (0.2-2.1)	0.4*			
	50-200 ug TPA + gas	1-3 wks	64	Median 1.4 (0.4-2.0)	Median 1.3 (0.4-2.1)	-0.1*			
		3		Median 1.4 (0.4-2.0)	Median 1.4 (0.4-2.1)	0*			
		6		Median 1.4 (0.4-2.0)	Median 1.3 (0.2-2.1)	-0.1*			
Sacu 2009 ⁸	50ug TPA (actilyse)+ SF6 + 1mg BVZ/0.05ml RBZ, then prn (BVZ/RBZ)	4	20	0.82	0.56	-0.26*	NR	Snellen	NR
	1 mg BVZ, then prn (BVZ)	4	10	0.6	0.58	-0.02*			
Guttoff 2011 ⁹	47(mean)ug TPA (actilyse) + SF6, then prn RBZ/BVZ	1	26	0.08 ± 0.09	0.08 ± 0.1	0*	NR	Snellen	NR
	TPA + SF6 + 1.5mg BVZ, then prn RBZ/BVZ		12	0.12 ± 0.13	0.25 ± 0.26	0.13*			
	47(mean)ug TPA (actilyse) + SF6, then prn RBZ/BVZ	7	26	0.08 ± 0.09	0.07 ± 0.06	-0.01*	NR	Snellen	NR
	TPA + SF6 + 1.5mg BVZ, then prn RBZ/BVZ		12	0.12 ± 0.13	0.24 ± 0.35	0.12*			
Hohn 2010 ¹⁰	1.25 mg BVZ + 0.3ml 100% SF6	11.7	10	1.17* ± 0.61	0.73* ± 0.39	-0.44*	NR	NR	NR
Hesgaard	C3F8 + 0.5 mg RBZ	11.7 (8-17)	8	-1.36 (SD 0.37)	-1.33 (SD 0.50)	-0.03*	1.5	ETDRS	NR

Study	Interventions	Follow-up (months)	No. eyes	Visual acuity results				Visual acuity methods	
				Baseline (mean logMAR)	Follow-up (mean logMAR)	Mean change (logMAR)	Mean change (ETDRS)	Chart	distance
2012 ¹¹	0.5mg RBZ	14.9 (8-29)	7	-1.08 (SD 0.44)	-0.87 (SD 0.47)	-0.2*	10		
Treumer ^{12, 13}	10-20 ug TPA (actilyse) + 1.25mg BVZ + SF6 gas	1	41	1.7 (3-0.5)	1.0 (2-0.3)	NR	NR	NR	NR
		3	41		0.8 (1.6-0.2)				
		12	26		0.8 (1.6-0.1)				
Meyer 2008 ¹⁴	50 ug TPA + 0.3-0.4 ml SF6 + 1.25 mg BVZ	1	19	0.82 *	0.63*	-0.19*	2.1 lines	ETDRS	NR
		3			0.57*	-0.25*	3.7 lines		
Kemai 1996 ¹⁵	12.5-50 ug TPA + C3F8 liquid + 15-20% SF6	15 ±7 (7-31)	22	1.56* ±0.8 (range 0.7-4)	0.71* ±0.5 (range 0.97-1.48)	-0.85*	NR	NR	NR
Claes 1996 ¹⁶	6-36 ug TPA 6-36 + air-fluid exchange	18.7 ± 7.8	15	2.44* ± 1 (range 1.08-4)	1.39* ± 0.5 (range 0.15-2.18)	-1.05*	NR	NR	NR
Sulak 2011 ¹⁸	TPA + expansile gas (4 patients received BVZ postoperatively)	4.4	9	1.77	1.05	-0.72*	NR	NR	NR
Tognetto 2011 ¹⁹	25ug TPA + Fluid-air exchange	1.0*	3	3.0* ± 1	0.77 ± 0.23*	-2.23 ± 1.21*	NR	NR	NR
Manning 1994 ²⁰	12-36 ug TPA + 0.25ml 100% SF6	6-8 wks	2	1.52* ±0.7 (range 0.78-2)	0.54* ± 0.1 (range 0.48-0.60)	-0.98*	NR	NR	NR
		4-6	2		1* ± 0	-0.52*			
		9-10	3		0.77*±0.4 (range 0.3-1)	-0.75*			
Moriarty 1995 ²¹	25 ug TPA + SF6	11 ± 4.9 (3-18)	14	2.53 ± 0.8 (range 0.6 to 3)	1.0 ± 0.7 (range 0.18 to 3)	-1.53*	NR	Snellen	6m
Hay 2000 ²²	TPA+SF6	1day	1	1.0	0.54	-0.46*	NR	NR	NR
		1	1		0.54	-0.46*			
		5	1		0.54	-0.46*			

Study	Interventions	Follow-up (months)	No. eyes	Visual acuity results				Visual acuity methods	
				Baseline (mean logMAR)	Follow-up (mean logMAR)	Mean change (logMAR)	Mean change (ETDRS)	Chart	distance
Krepler 2000 ²³	25 ug TPA + 0.5 ml SF6	1 wk	11	1.3* ± 0.88 (range 0.5-3)	0.64* ± 0.36 (range 0.097-1.3)	-0.66*	NR	Snellen	NR
		1			0.8* ± 0.79 (range 0.097-3)				
		3			0.67* ± 0.34 (range 0.097-1.3)				
		6			0.79* ± 0.37 (range 0-1.3)				
		9			0.92* ± 0.44 (range 0-1.3)				
		12			1.07* ± 0.76 (range 0.4-3)				
Hattenbach 2001 ²⁴	50 ug TPA + 0.5ml SF6	Mean 6 ± 3.4 (4-18)	43	1.2* ± 0.6 (range 0.4-3)	1.08* ± 0.6 (range 0.18-3)	-0.12*	NR	Snellen	NR
Steller 2004 ²⁵	50 ug TPA + 0.5ml SF6	14.2	25	1.3* ± 0.6	1.06* ± 0.6	-0.24*	NR	NR	NR
Handwerker 2001 ²⁶	18-50 ug TPA + 0.3-0.4 ml C3F8	0-2 months	14	1.3* ± 0.5 (range 0.7-2.3)	0.91* ± 0.39 (range 0.6-1.5)	-0.39*	NR	Snellen	NR
		>3mo	13		1.35* ± 0.54 (range 0.6-2.3)				
		12	1.07* ± 0.76 (range 0.4-3)						
Kung 2010 ²⁷	50 ug TPA + 0.3ml C3F8	17.6 ± 17.1 (range 1-60)*	28	1.27* ± 0.57 (range 0.3-2)	1.04 ± 0.46* (range 0.3-2)	-0.23*	NR	Snellen	NR
Hesse 1999 ²⁸	50 or 100 ug TPA + 0.15-1.0 ml expansile gas (SF6 or C2F6 or C3F8)	4.8	11	2.25* ± 0.9 (range 0.7-3)	1.17* ± 0.7 (range 0.4-2)	-1.08*	NR	NR	NR
Ratanasukon 2005 ²⁹	50-100 ug/0.1 ml TPA + expansile gas (C3F8 or SF6)	9.4* (6-19)	ARMD 15	1.56* ± 0.86 (range 0.39-3)	1.09* ± 1.10 (range 0.097-3)	-0.47*	NR	ETDRS	NR
Daneshvar	0.6ml SF6	6	3	2.0*	1.18*+/-0.74 (range	-0.82*	NR	NR	NR

Study	Interventions	Follow-up (months)	No. eyes	Visual acuity results				Visual acuity methods	
				Baseline (mean logMAR)	Follow-up (mean logMAR)	Mean change (logMAR)	Mean change (ETDRS)	Chart	distance
1999 ³⁰					0.54 to 2)				
Ron 2007 ³¹	C3F8 or SF6 0.4 ml	3	24	1.81	1.15	-0.66*	NR	Snellen	NR

A list of abbreviations is given on page 6

* calculated by KSR.

Table 5: VA Dichotomous Results table for the Research question, 'what are the effects of TPA or gas in patients with both AMD and (sub)macular bleeding? (Question 1)

Study	Interventions	Follow-up (months)	No. eyes	Visual acuity results – percentage of patients		Visual acuity methods	
				VA at baseline	VA at follow up	Chart	distance
Singh 2006 ¹⁷	48 ug TPA + partial fluid exchange	17.2	17	LP/CF/HM – 47.1% 20/400 – 20/200 – 41.2 % >20/200 – 11.8%	LP/CF/HM -23.5% 20/400 – 20/200 – 23.5% >20/200 -52.9%	Snellen	NR

A list of abbreviations is given on page 6

Table 6: Risk of bias table for intervention studies (observational: non-randomised clinical trials, cohort and case-control studies), for the research question ‘what are the effects of TPA or gas in patients with both AMD and (sub)macular bleeding?’ (Question 1)

Study reference	Bias due to a non-representative or ill-defined sample of patients?	Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?	Bias due to ill-defined or inadequately measured outcome ?	Bias due to inadequate adjustment for all important prognostic factors?
Yang 2005 ³	Unlikely	Likely	Likely	Likely
Thompson 2005 ⁴	Unlikely	Unlikely	Likely	Likely
Sandhu 2010 ⁵	Unlikely	Likely	Likely	Likely
Nourinia 2010 ⁶	Unlikely	Unlikely	Likely	Likely
Tsymanava 2012 ⁷	Unlikely	Unlikely	Likely	Likely
Sacu 2009 ⁸	Unlikely	Unlikely	Likely	Likely
Guttoff 2011 ⁹	Unlikely	Likely	Likely	Likely
Hohn 2010 ¹⁰	Unlikely	Likely	Likely	Likely
Hesgaard 2012 ¹¹	Unlikely	Likely	Likely	Likely
Treumer ^{12, 13}	Unlikely	Likely	Likely	Likely
Meyer 2008 ¹⁴	Unlikely	Unlikely	Likely	Likely
Kemai 1996 ¹⁵	Unlikely	Likely	Likely	Likely
Claes 1996 ¹⁶	Unlikely	Likely	Likely	Likely
Singh 2006 ¹⁷	Unlikely	Likely	Likely	Likely
Sulak 2011 ¹⁸	Unlikely	Unlikely	Likely	Likely
Tognetto 2011 ¹⁹	Unlikely	Unlikely	Likely	Likely
Manning 1994 ²⁰	Unlikely	Unlikely	Likely	Likely
Moriarty 1995 ²¹	Unlikely	Likely	Likely	Likely
Hay 2000 ²²	Unlikely	Unlikely	Likely	Likely
Krepler 2000 ²³	Unlikely	Unlikely	Likely	Likely
Hattenbach 2001 ²⁴	Unlikely	Likely	Likely	Likely
Steller 2004 ²⁵	Unlikely	Likely	Likely	Likely
Handwerger 2001 ²⁶	Unlikely	Unlikely	Likely	Likely
Kung 2010 ²⁷	Unlikely	Likely	Likely	Likely
Hesse 1999 ²⁸	Unlikely	Likely	Likely	Likely
Ratanasukon 2005 ²⁹	Unlikely	Likely	Likely	Likely

Daneshvar 1999 ³⁰	Unlikely	Likely	Likely	Likely
Ron 2007 ³¹	Unlikely	Likely	Likely	Likely

Table 7: Details of relevant ongoing/ incomplete trials for the research question ‘what are the effects of TPA or gas in patients with both AMD and (sub)macular bleeding?’ (Question 1)

Study ID/Name	Design	Comparators	Comments
Nct00161525 http://clinicaltrials.gov/ct2/show/NCT00161525 Pneumatic Displacement of Subretinal Hemorrhage With Perfluorocarbon Gases.	Phase II Non- randomised, open, single group assignment.	0.4 ml of pure C2F6 or 2 injections of 0.2 ml on subsequent days n=25	Funded by Weill Medical College of Cornell University. CTG page last updated 2011. ONGOING
EUCTR2012-004078-24-GB http://apps.who.int/trialsearch/Trial.aspx?TrialID=EUCTR2012-004078-24-GB A clinical trial of a clot dissolving drug and gas, injected into the eye, to treat bleeding associated with wet age-related macular degeneration.	Double blind randomised controlled trial.	intravitreal tissue plasminogen activator (TPA), gas (C3F8) and ranibizumab n=NR	Funded by King's College London. Webpage last updated 2013. ONGOING

A list of abbreviations is given on page 6.

2.2 QUESTION 2: WHAT ARE THE EFFECTS OF PDT ALONE OR COMBINED WITH ANTI-VEGF IN PATIENTS WITH PCV?

Literature searches were performed and generated 404 records. Figure 2 summarises the flow of studies through the search and screening process. Screening of the titles and abstracts by two independent reviewers identified 46 records (one still to be retrieved). These records were examined in full and 17 met the inclusion criteria, whilst 28 were excluded. We were not able to view the abstracts from the Euretina searches, therefore the results were not included in the review but the search results can be found in Appendix 5.

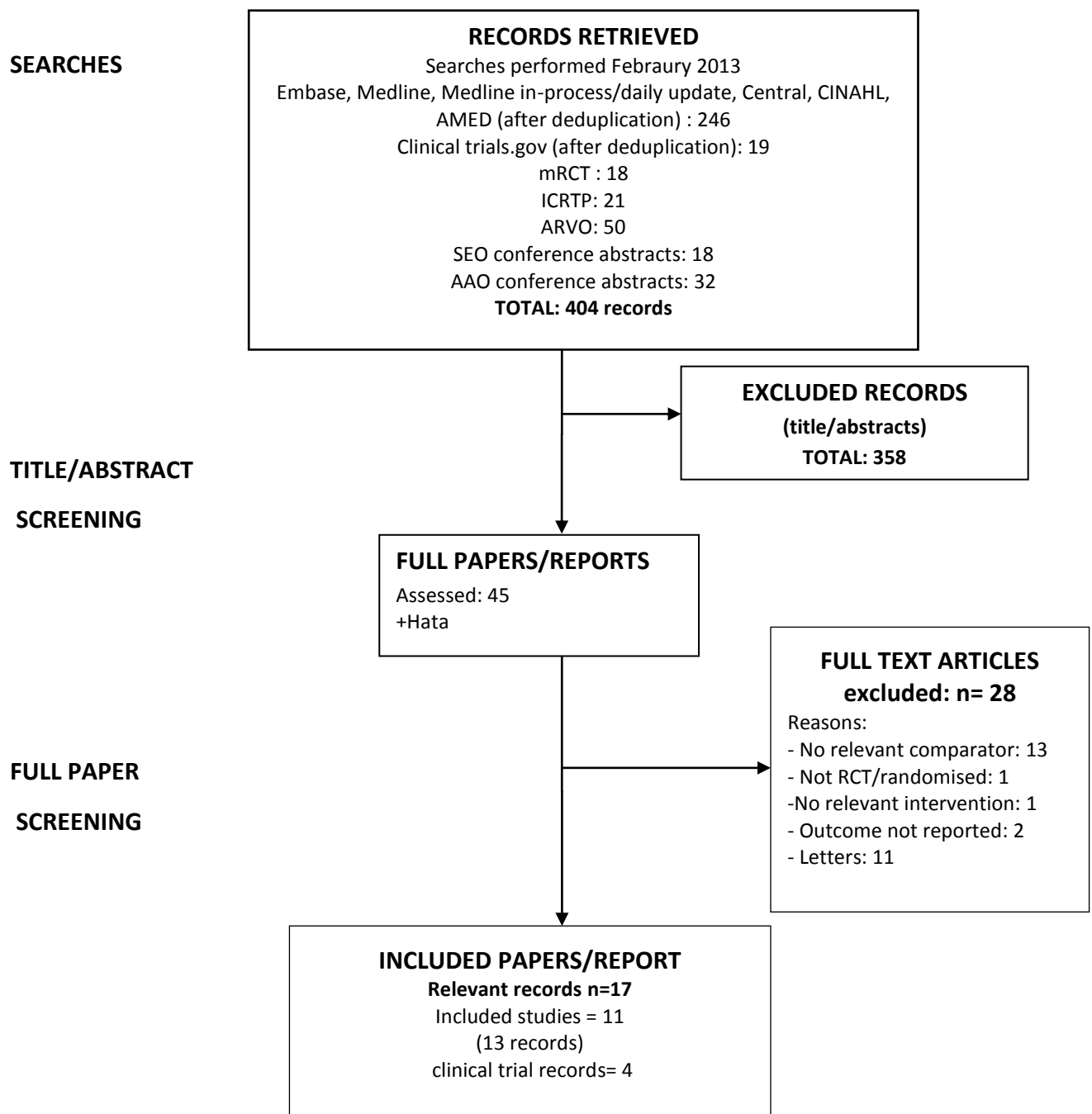
The 17 included records described 11 studies (some studies had more than one record) and four clinical trial registries.

The baseline characteristics of the 12 included studies are summarised in Tables 8-10, the visual acuity results are summarised in Table 11 and the risk of bias was summarised in Tables 12 and 13.

Two ongoing and two completed trials were identified which met the inclusion criteria and are described in Table 14. The EVEREST³² trial was completed and published^{33,34} and was based in several Far Eastern countries. The other trials were all based in Japan and did not have any associated publications.

Reasons for the exclusion of full papers are given in Appendix 7.

Figure 2: Summary searching and inclusion screening for question 2



mRCT = meta register of controlled trials; ICTRP= WHO international clinical trials registry platform; SEO = European Society of Opthamology; AAO = American Academy of Ophthalmology; ARVO = Association for Research in Vision and Ophthalmology; CINAHL =Cumulative Index to Nursing and Allied Health Literature; AMED = Allied and complimentary medicine database; RCT= randomised controlled trial.

Table 8: Evidence table for the Research question, 'what are the effects of PDT alone or combined with anti-VEGF in patients with PCV' (Question 2)

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size
Lai 2008 ³⁵	Type of study: retrospective case series Setting: hospital Country: Hong Kong, China Source of funding: NR	<u>Inclusion criteria:</u> see table 10 <u>Exclusion criteria:</u> see table 10 <u>N total at baseline:</u> I: 7 C: 8 <u>Mean age ± SD:</u> total: 64.5 years (range 55–79 years) <u>Sex (M/F):</u> I: 5/2 C: 6/2 Total: Phakic: eye 80% Pseudophakic eye: 20% Total: PCV associated with retinal or subretinal haemorrhage: 80.0% PCV with exudative retinal detachment without haemorrhage: 20% <u>Baseline VA:</u> See table 11 <u>Groups comparable at baseline?</u> Yes according to VA only.	1.25mg BVZ +PDT +/- BVZ See table 9 for details	1.25mg BVZ x3, then prn or 1.25mg BVZ x3 See table 9 for details	<u>Length of follow-up (m):</u> mean 12.8 (range 9-18) <u>Loss-to-follow-up:</u> I: 0 C: 0 <u>Incomplete outcome data:</u> I: 0 C: 0 N (%)	Outcome measures and effect size (include 95%CI and p-value if available): See table 11
Lee 2008 ³⁶	Type of study: retrospective interventional case	<u>Inclusion criteria:</u> see table 10 <u>Exclusion criteria:</u>	1.25mg BVZ+PDT See table 9 for details	1.25mg BVZ See table 9 for details	<u>Length of follow-up:</u> I: 17wks (12-27) C: 15 wks (13-22)	Outcome measures and effect size

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size
	<p>series</p> <p>Setting: Hospital</p> <p>Country: Korea</p> <p>Source of funding: partially public (Asan Institute for Life and Science Grant)</p>	<p>see table 10</p> <p><u>N total at baseline:</u></p> <p>I: 4 C: 8</p> <p><u>mean age ± SD:</u></p> <p>I: 53 ±7 C: 63±7</p> <p><u>Sex (M/F):</u></p> <p>I: 3/1 C: 8/0</p> <p><u>Lesion:</u></p> <p>I: 4=subfoveal; 2=juxtafoveal; 2=extrafoveal C: NR: 3=subfoveal; 1 = extrafoveal</p> <p><u>Baseline VA:</u></p> <p>See table 11</p> <p><u>Groups comparable at baseline?</u></p> <p>No (sex, lesion, VA)</p>			<p><u>Loss-to-follow-up:</u></p> <p>Not relevant</p> <p><u>Incomplete outcome data:</u></p> <p>Not relevant</p>	<p>(include 95%CI and p-value if available):</p> <p>See table 11</p>
Cho 2009³⁷	<p>Type of study: retrospective observational case series</p> <p>Setting: clinical practice</p> <p>Country: USA</p> <p>Source of funding: Macula Foundation Inc</p>	<p><u>Inclusion criteria:</u></p> <p>see table 10</p> <p><u>Exclusion criteria:</u></p> <p>see table 10</p> <p><u>N total at baseline:</u></p> <p>I: 9 C: 3</p> <p><u>Mean age ± SD:</u></p> <p>total: 75 ±3 (range 56-86)</p> <p><u>Sex (M/F):</u></p> <p>Total: 5/7</p> <p><u>Total Lesion type:</u></p> <p>C: 4</p>	<p>rPDT +RBZ sPDT +RBZ sPDT + BVZ sPDT</p> <p>See table 9 for details</p>	<p>Thermal + RBZ RBZ BVZ</p> <p>See table 9 for details</p>	<p><u>Length of follow-up (m):</u></p> <p>I: rPDT +RBZ 11.6* sPDT +RBZ 10* sPDT + BVZ: 12 sPDT: 7 C: Thermal + RBZ: 9 RBZ: 12 BVZ: 11</p> <p><u>Loss-to-follow-up:</u></p> <p>Not relevant</p>	<p>Outcome measures and effect size (include 95%CI and p-value if available):</p> <p>See table 11</p>

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size
		MC: 1 PC: 1 O: 5 RAP:1 <u>Baseline VA:</u> See table 11 <u>Groups comparable at baseline?</u> No (according to VA only).			<u>Incomplete outcome data:</u> Not relevant	
Mitamura 2010 ^{38,39}	Type of study: Retrospective interventional case study Setting: Hospital Country: Japan Source of funding: no funding	<u>Inclusion criteria:</u> see table 10 <u>Exclusion criteria:</u> see table 10 <u>N total at baseline:</u> I: 49 C1: 18 C2: 22 <u>Mean age ± SD:</u> I: 69.6±7.8 C1: 72.9±5.7 C2: 73.0±8.9 <u>Sex (M/F):</u> I: 42/7 C1: 17/1 C2: 17/5 <u>Foveal thickness (µm)</u> I: 438.5 ± 192 C1: 427.9±190 C2: 438.8±235 <u>GLD (µm)</u> I: 3718±1665 C1: 3366±992 C2: 3651±1833 <u>Baseline VA:</u>	vPDT PRN See table 9 for details	C1: 1.25mg BVZx1 fixed or C2: 1.25mg BVZx3 PRN See table 9 for details	<u>Length of follow-up (m):</u> 3 <u>Loss-to-follow-up:</u> Not relevant <u>Incomplete outcome data:</u> Not relevant	Outcome measures and effect size (include 95%CI and p-value if available): See table 11

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size
		See table 11 <u>Groups comparable at baseline?</u> No significant differences reported				
Song 2011 ⁴⁰	Type of study: retrospective case series Setting: Hospital Country: Korea Source of funding: NR	<u>Inclusion criteria:</u> see table 10 <u>Exclusion criteria:</u> see table 10 <u>N total at baseline:</u> I: 9 C: 15 <u>Mean age ± SD:</u> I: 56.9±12* C: 60.6±10.7* <u>Sex (M/F):</u> I: 9/0 C: 6/9 <u>Lesion type</u> I: 6=subfovea, 3=juxtafoveal C: 11=subfovea, 4 = juxtafoveal <u>Mean CRT um ± sd</u> I: 398.7 ± 138 C: 386 ± 120 <u>Baseline VA:</u> See table 11 <u>Groups comparable at baseline?</u> Sexes are imbalanced.	sPDT + 0.5mg RBZ See table 9 for details	0.5mg RBZ See table 9 for details	<u>Length of follow-up:</u> I: 20.3 +/-7.6mo C: 23.4 +/-8.4 mo <u>Loss-to-follow-up:</u> Not relevant <u>Incomplete outcome data:</u> Not relevant	Outcome measures and effect size (include 95%CI and p-value if available): See table 11
Saito 2011 ⁴¹	Type of study: Retrospective case series Setting: Hospital	<u>Inclusion criteria:</u> see table 10 <u>Exclusion criteria:</u> see table 10 <u>N total at baseline:</u> I: 34	sPDT See table 9 for details	0.5mg RBZ x3, then PRN See table 9 for details	<u>Length of follow-up (m):</u> 6 <u>Loss-to-follow-up:</u> Not relevant	Outcome measures and effect size (include 95%CI and p-value if available):

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size
	Country: Japan Source of funding: NR	C: 25 <u>mean age ± SD:</u> I: 74.8±6.3 C: 75.1±6.4 <u>Sex (M/F):</u> I: 26/8 C: 21/4 <u>Lesion type:</u> I: occult 100% C: occult 100% <u>Mean CRT ± SD um</u> I: 342 ± 178 C: 310 ± 173 <u>Mean GLD ± SD um</u> I: 5010 ± 2055 C: 4549 ± 1692 <u>Serous retinal detachment</u> I: 55.9% C: 64% <u>Edema</u> I: 44.1% C: 48% <u>PED</u> I: 41.2% C: 20% <u>Baseline VA:</u> See table 11 <u>Groups comparable at baseline?</u> Yes			Incomplete outcome data: Not relevant	See table 11
Rouvas 2011 ⁴²	Type of study: Retrospective comparative study	<u>Inclusion criteria:</u> see table 10 <u>Exclusion criteria:</u> see table 10	I1: sPDT or I2: sPDT +0.5mg RBZ x3	0.5mg RBZ x3 then PRN See table 9 for details	<u>Length of follow-up (m):</u> 12	Outcome measures and effect size (include 95%CI)

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size
	Setting: Hospital Country: Greece Source of funding: NR	<u>N total at baseline:</u> I1: 11 I2: 9 C: 10 <u>Mean age:</u> I1: 62.9 I2: 64.7 C: 66.5 <u>Sex (M/F):</u> I1: 5/6 I2: 4/5 C: 4/6 <u>Mean CRT um</u> I1: 304.4; I2: 289 C: 310.9 <u>Peripapillary/macular polyps</u> I1: 54.5%; I2: 33.3% C: 50% <u>Baseline VA:</u> See table 11 <u>Groups comparable at baseline?</u> No significant differences reported but VA was variable.	See table 9 for details		<u>Loss-to-follow-up:</u> Not relevant <u>Incomplete outcome data:</u> Not relevant	and p-value if available): See table 11
Lai 2011 ⁴³	Type of study: Retrospective case series Setting: Hospital Country:	<u>Inclusion criteria:</u> see table 10 <u>Exclusion criteria:</u> see table 10 <u>N total at baseline:</u> I1: 16 I2: 12 C: 7	I1: sPDT + 0.5mg RBZ x3 or I2: sPDT See table 9 for details	0.5mg RBZx3, PRN See table 9 for details	<u>Length of follow-up (m):</u> 12 <u>Loss-to-follow-up:</u> Not relevant <u>Incomplete outcome</u>	Outcome measures and effect size (include 95%CI and p-value if available):

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size
	Hong Kong, China Source of funding: NR	<u>Mean age \pm SD:</u> I1: 71.3 \pm 9.8; I2: 65.6 \pm 11 C: 64.6 \pm 7.9 <u>Sex:</u> I: 8/8 I2: 10/2 C: 4/3 <u>Duration of symptoms (m):</u> I1: 3.1 \pm 3.3 I2: 3.8 \pm 3.7 C: 3.6 \pm 4.1 PCV type Group 2 I1: 37.5% I2: 33% C: 14% Group 3 I1: 62.5% I2: 67% C: 86% <u>Mean GLD \pm um</u> I1: 3490 \pm 1170 I2: 2580 \pm 707 C: 3610 \pm 2240 <u>Baseline VA:</u> See table 11 <u>Groups comparable at baseline?</u> No significant difference reported			data: Not relevant	See table 11
Lim 2012 ⁴⁴	Type of study: Randomized prospective study Setting: Hospital	<u>Inclusion criteria:</u> see table 10 <u>Exclusion criteria:</u> see table 10	PDT + BVZx3 See table 9 for details	1.25mg BVZ x3 See table 9 for details	<u>Length of follow-up:</u> 12 mo <u>Loss-to-follow-up:</u>	Outcome measures and effect size (include 95%CI)

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size
	Country: Korea Source of funding: NR	<u>N total at baseline:</u> I: 5 C: 5 <u>Mean age ± SD:</u> I: 57.8* ±7.9 C: 68.6* ±7.2 <u>Sex (M/F):</u> I: 3/5 C: 5/0 <u>Mean CFT ± sd um</u> I: 213.4 ±53 C: 295.6 ±126 <u>PED present</u> I: 20% C: 80% <u>Baseline VA:</u> See table 11 <u>Groups comparable at baseline?</u> NR			Total: 6 pts lost to follow up (not clear if AMD or PCV) and excluded from analyses <u>Incomplete outcome data:</u> Not relevant	and p-value if available): See table 11
Kagokawa 2012 ⁴⁵	Type of study: retrospective case series Setting: NR Country: Japan Source of funding: NR	<u>Inclusion criteria:</u> see table 10 <u>Exclusion criteria:</u> see table 10 <u>N total at baseline:</u> I: 16 C: 16 <u>mean age ± SD:</u> I: NR C: NR <u>Sex:</u> I: NR C: NR <u>Baseline VA:</u>	PDT + RBZ then PRN See table 9 for details	RBZx3 then PRN See table 9 for details	<u>Length of follow-up (m):</u> 6 and 12 <u>Loss-to-follow-up:</u> Not relevant <u>Incomplete outcome data:</u> Not relevant	Outcome measures and effect size (include 95%CI and p-value if available): See table 11

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size
		See table 11 <u>Groups comparable at baseline?</u> NR				
EVEREST 33,34,32	Type of study: Phase IV, randomized controlled trial Setting: Hospital Country: Singapore, Taiwan, Korea, China, Thailand Source of funding: industry	<u>Inclusion criteria:</u> see table 10 <u>Exclusion criteria:</u> see table 10 <u>N total at baseline:</u> I1: 19 I2: 21 C: 21 <u>Mean age ± SD:</u> I1: 63.8 ± 8.3 I2: 62.2 ± 9.8 C: 69.3 ± 8.3 <u>Sex:</u> I1: 11/8 I2: 15/6 C: 15/6 <u>Mean total lesion area mm² ± SD:</u> I1: 3.58 ± 5.49 I2: 3.25 ± 2.66 C: 3.9 ± 2.2 <u>Mean polyp area mm² ± SD:</u> I1: 0.33 ± 0.45 I2: 0.21 ± 0.14 C: 0.22 ± 0.14 <u>Mean CRT microm ± SD:</u> I1: 334.7 ± 119 I2: 285.3 ± 106 C: 268.5 ± 98 <u>Presence of leakage</u> I1: 100%	I1: sPDT +RBZ 0.5mg x3, PRN or I2: sPDT + sham PRN See table 9 for details	Sham PDT+RBZ 0.5mg x3, PRN See table 9 for details	<u>Length of follow-up (m):</u> 6 <u>Loss-to-follow-up:</u> Intervention: 1 comb; 1 PDT Reasons: BCVA did not meet incl criteria; cancer Control: 0 <u>Incomplete outcome data:</u> Not relevant	Outcome measures and effect size (include 95%CI and p-value if available): See table 11

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size
		<p>I2: 90.5%</p> <p>C: 95%</p> <p><u>Baseline VA:</u> See table 11</p> <p><u>Groups comparable at baseline?</u> The authors say they were well balance, with slight numerical difference in CRT and mean BCVA.</p>				

sPDT = standard verteporfin PDT (6mg/m² verteporfin and 50J/cm² , 600mW/cm² for 83seconds); rPDT = reduced verteporfin PDT (6mg/m² verteporfin and 25J/cm² , 300mW/cm² for 83seconds); C = classic; MC = minimally classic; O = occult; PC = predominantly classic; vPDT = verteporfin +PDT. Other abbreviations are given on page 6. * calculated by KSR.

Table 9: Treatment regimens for the Research question, 'what are the effects of PDT alone or combined with anti-VEGF in patients with PCV' (Question 2)

Study	Interventions	No. Eyes	PRN/ fixed/ treat & extend	Full dose/half dose verteporfin	Full / half fluence laser light	Number of baseline VEGF injections	Time between baseline injections	Number of baseline PDT treatments	Follow-up examinations (wks)	No. final VEGF injections (mean±sd)	No. final PDT treatments (range)
Lai 2008 ³⁵	1.25mg BVZ x3, then prn	6	PRN	-	-	3	Monthly	0	NR, presumed after 3m	6	0
	1.25mg BVZ x3, then vPDT + 1.25mg BVZ	4	PRN	NR	NR	3	monthly	0		6	1
	1.25mg BVZ x3, then vPDTx1	3	PRN	NR	NR	3	montly	0		3	1
	1.25mg BVZ x3	2	fixed	-	-	3	monthly	0		3	0
Lee 2008 ³⁶	1.25mg BVZ	8	PRN	Standard	Standard	1	-	0	1,6, then every 2-3 months	2.25 ±0.9*	0
	1.25mg BVZ+PDT	4	PRN			1	-	1		2.5±1*	1
Cho 2009 ³⁷	rPDT +RBZ	5	NR	Full	Half	NR	NR	NR	NR	NR	NR
	sPDT +RBZ	2		Full	Full					NR	NR
	sPDT + BVZ	1		Full	Full					NR	NR
	sPDT	1		Full	Full					NR	NR
	Thermal + RBZ	1		NR	NR					NR	NR
	RBZ	1		-	-					NR	NR
	BVZ	1		-	-					NR	NR
Mitamura 2010 ^{38,39}	1.25mg BVZx1	18	Fixed	-	-	1	-	-	-	NR	NR
	1.25mg BVZx3	22	PRN	-	-	3	Monthly	-	After 3m		
	vPDT	49	PRN	Full	Full	0	-	1	After 3m		

Study	Interventions	No. Eyes	PRN/ fixed/ treat & extend	Full dose/half dose verteporfin	Full / half fluence laser light	Number of baseline VEGF injections	Time between baseline injections	Number of baseline PDT treatments	Follow-up examinations (wks)	No. final VEGF injections (mean±sd)	No. final PDT treatments (range)
Song 2011 ⁴⁰	sPDT + 0.5mg RBZ	9	PRN	Full	Full	1 (assumed) 1	NR	1 (assumed)	4	4.33±2.8*	1
	0.5mg RBZ	15	PRN	-	-		NR	0	4	4.47 ±2.1*	0
Saito 2011 ⁴¹	sPDT	34	PRN	Full	Full	0	-	1	< 3 m	0	1.4
	0.5mg RBZ x3, then PRN	25	PRN	-	-	3	monthly	0	monthly	3.6	0
Rouvas 2011 ⁴²	sPDT	11	PRN	Full	Full	0	-	1	After 3 m	0	1.82
	0.5mg RBZ x3 then PRN	10	PRN	-	-	3	Monthly	0		6.9	0
	sPDT +0.5mg RBZ x3	9	PRN	Full	Full	3	Monthly	1		5	1.67
Lai 2011 ⁴³	0.5mg RBZx3, PRN	7	PRN	-	-	3	Monthly	0	After 3m	4 (3-6)	0.6 (0-1)
	sPDT + 0.5mg RBX x3	16	PRN	Full	Full	3	Monthly	1		3.4 (3-6)	1.2 (1-2)
	sPDT	12	PRN	Full	Full	0	-	1		0	1.7 (1-4)
Lim 2012 ⁴⁴	1.25mg BVZ x3	5	PRN	0	0	3	6 weeks	0	1,7,13,18,24, 32,48	3 ± 0*	0
	PDT + BVZx3	5		NR	NR	0	-	1		3.6 ± 0.89*	NR
Kagokawa 2012 ⁴⁵	PDT + RBZ then PRN	16	PRN	NR	NR	1	-	1	Every 3m	1.4	1.4
	RBZx3 then PRN	16	PRN	NR	NR	3	monthly	0		4.1	0
EVEREST ^{33,34,32}	sPDT +RBZ 0.5mg x3, PRN	19	PRN	Full	Full	3	Monthly	1	Monthly after 3 months	3.9	1.4
	sPDT + sham PRN	21	PRN	Full	Full	0	-	1		4.2 (Sham)	1.7
	Sham PDT+RBZ 0.5mg x3, PRN	21	PRN	0	0	3	Monthly	0		5.2 (5 m f/up)	1.9 (sham)

sPDT = standard verteporfin PDT (6mg/m2 verteporfin and 50J/cm2 , 600mW/cm2 for 83seconds); rPDT = reduced verteporfin PDT (6mg/m2 verteporfin and 25J/cm2 , 300mW/cm2 for 83seconds); C = classic; MC = minimally classic; O = occult; PC = predominantly classic; vPDT = verteporfin +PDT. Other abbreviations are given on page 6. * calculated by KSR.

Table 10: Study Definitions table for the Research question, 'what are the effects of PDT alone or combined with anti-VEGF in patients with PCV' (Question 2)

Study	PCV definition	PRN definition	Inclusion criteria	Exclusion criteria
Lai 2008 ³⁵	PCV was classified according to the classification by Chan et al which proposed four groups: (1) subclinical asymptomatic polyps; (2) serous neurosensory retinal detachment, serous pigment epithelial detachment, lipid, or hard exudates; (3) subretinal or subretinal pigment epithelial haemorrhage of less than four disc area; and subretinal or subretinal pigment epithelial haemorrhage of four disc area or more. BCVA was measured by certified optometrists using an ETDRS logMAR chart at 4 m or with a standard Snellen chart at 6 m converted to logMAR visual acuity for analysis.	Additional treatments after 3m were performed in eyes with persistent or recurrent exudative macular detachment by OCT evaluation and polypoidal lesions on ICGA. BCVA reduction without any evidence of exudation was not used as a retreatment criterion. The retreatment modality was performed according to the ophthalmologist's discretion which included additional bevacizumab, PDT with verteporfin, or combined BVZ and PDT. PDT was performed under ICGA guidance as described previously.	Age of >18 years or older; PCV as defined by the presence of branching network of choroidal vessels with terminating aneurysmal polypoidal lesions in ICGA; logMAR BCVA of 1.6 or better (Snellen equivalent of 20/800 or better); and follow-up of 6 m or more.	Evidence suggesting that CNV secondary to AMD such as drusens; refractive error of higher than -6 dioptres; previous submacular surgery; and previous PDT within 6 months.
Lee 2008 ³⁶	To confirm the diagnosis of symptomatic PCV, all patients underwent FA, ICGA, OCT analyses.	NR	Patients with new or recurrent subretinal pigment epithelial orange-red vascular lesions associated with exudative changes were included.	NR
Cho 2009 ³⁷	ICGA evidence of a focal well-	NR	Patients with neovascular AMD in	NR

Study	PCV definition	PRN definition	Inclusion criteria	Exclusion criteria
	delineated area of early choroidal vascular hyperfluorescence exhibiting late central hypofluorescence (“wash-out”) and surrounding hyperfluorescence (leakage).		which a poor anatomic response to anti-VEGF therapy was related to PCV. A patient was considered refractory to treatment if clinical examination or imaging studies showed increases in exudation including hemorrhage, intraretinal or subretinal fluid, and lipid deposition and/or when the clinical picture initially improved or stabilized for a period but then worsened with increasing exudation despite continuous anti-VEGF therapy. Patients had to have received continuous treatment for at least 6m with either RBZ (0.5 mg/0.05 ml) or BVZ (1.25 mg/0.05 ml) at regular intervals of no longer than 6 wks.	
Mitamura 2010 ^{38,39}	Based on clinical examination, FA and ICGA. The criteria for a diagnosis of PCV were the presence of reddish-orange lesions, recurrent serosanguinous RPE detachments, and dilated network of inner choroidal vessels with terminal hyperfluorescent aneurysm-like dilatations (polyps) on ICGA. A diagnosis for PCV was made only in the presence of	NR	Japanese patients who had treatment-naïve PCV and subfoveal exudation or hemorrhage, and were treated with BVZ or PDT with verteporfin. All eyes undergoing treatment for PCV between June 2004 and July 2007 were included in this study	NR

Study	PCV definition	PRN definition	Inclusion criteria	Exclusion criteria
	the ICGA features.			
Song 2011 ⁴⁰	Presence of a branching vascular network of choroidal vessels with terminating aneurysmal polypoidal lesions in ICGA	Additional RBZ injections were offered at the discretion of the treating physician if a new hemorrhage was observed on clinical examination or if any sign indicating the recurrence of PCV leakage (diffuse edema, intraretinal cyst, subretinal fluid by OCT, an area of leakage demonstrated by FA or an area of hyperfluorescence suggesting an active polyp on ICGA) was seen on OCT or FA or ICGA examination. Subsequent injections were given at least 4 weeks after the previous injections.	PCV, recent onset of symptoms, follow-up of 1 year or more.	Evidence suggesting CNV secondary to AMD such as drusen or pathological myopia, uncontrolled hypertension, a history of thromboembolic events or tendency of coagulopathy, previous vitrectomy, previous PDT within 6 months.
Saito 2011 ⁴¹	Based on ICGA findings of polypoidal lesions before the initial treatment.	In RBZ group: VA loss of at least 5 letters, with OCT evidence of fluid on the macula, increase in CRT on OCT of >100µm, a new macular hemorrhage, a new area of classic CNV, or evidence of persistent fluid on OCT 1 month after previous injection. In PDT group retreatments were performed if FA showed leakage with evidence of fluid at the macula by OCT.	PCV with complete regression of polypoidal lesions detected by ICGA because of previous PDT applications but recurrent or residual leakage from branching vascular network vessels on FA and evidence of persistent fluid on OCT. All followed for at least 6 months at Fukushima Medical University Hospital.	Previous treatment for PCV (except PDT). Excluded eyes that underwent combined therapy or intravitreal bevacizumab

Study	PCV definition	PRN definition	Inclusion criteria	Exclusion criteria
Rouvas 2011 ⁴²	See inclusion criteria	RBZ retreatment if persistent or recurrent subretinal fluid or intraretinal fluid according to OCT/clinically detectable haemorrhages. PDT retreatment if evidence of leaking polyps.	Macular or temporal peripapillary PCV with baseline VA of 20/30 or worse, identification of polyps & interconnecting vessels on ICG , located in the macula within 1 disk diameter from the centre of the foveal avascular zone, presence of subretinal haemorrhages/ exudation in the macula based on clinical examination.	Previous treatment for PCV; choroidal neovascular secondary to AMD, myopia, or inflammation, presence of retinal vascular disease, systemic contraindication to verteporfin or RBZ, intraocular surgery <2month before entry into study and active intraocular inflammation.
Lai 2011 ⁴³	Presence of branching network of choroidal vessels with terminating aneurismal polypoidal lesions in ICGA.	Eyes with persistent or recurrent polypoidal lesions on ICGA and leakage on FA after 3months.	≥18 years, PCV, BCVA ≥ 0.1-1.6 (logMAR), follow-up of 12 months.	Evidence suggesting CNV secondary to AMD or other causes, refractive error of > -6 diopters, previous submacular surgery, previous PDT within 6 m.
Lim 2012 ⁴⁴	NR	When CFT increased by > 100um, elevated level or newly developed subretinal fluid was detected by OCT or new neovascular AMD was seen on FA.	≥ 50 years, BCVA of 0.6 or worse in study eye.	IVT within 90 days of screening, , PDT within 30 days before screening, history of ocular surgery within 90 days prior to screening, history of vitreous haemorrhage, retinal tear, retinal detachment, macular hole, retinal vein obstruction, severe intraocular inflammation or infections within 30 days before screening, diabetic retinopathy, aphakia, systemic conditions including thromboembolism, previous myocardial infection or prior cerebral vascular accident.
Kagokawa 2012 ⁴⁵	NR	According to VA and OCT.	PCV, VA between 0.1 and 0.5.	NR
EVEREST	Presence of early subretinal	Mainly driven by ICGA-	Patients must give written informed	Women of child-bearing potential who

Study	PCV definition	PRN definition	Inclusion criteria	Exclusion criteria
33,34,32	focal ICGA hyperfluorescence (appearing within first 6min after injection of ICG) and at least on eof the following angiographoc or clinical criteria: (i) association with BVN, (ii) presence of pulsatile polyp, (iii) nodular appearance when viewed stereoscopically, (iv) presence of hypofluorescent halo (in first 6 min), (v) orange subretinal nodules in steresoscopic color fundus photograph (polyp corresponding t ICGA lesions), (vi) association with massive submacular hemorrhage (defined as size of hemorrhage of at least 4 disc areas)	assessed polyp regression considering in addition FA leakage and BCVA, and minimum retreatment interval per label (90d for PDT, 30d for RBZ).	consent before any assessment is performed. Male or Female patients ≥18 yrs of age Patients willing and able to comply with all study procedures. Inclusion criteria for study eye: BCVA letter score between 73-24 (approximately 20/40 to 20/320 Snellen equivalent) using ETDRS visual acuity chart measured at 4 meters. PCV diagnosis confirmed by Central Reading Center. Greatest Linear Dimension of the total lesion area < 5400 μm (~9 Macular Photocoagulation Study Disc Areas)	are not using one or more reliable contraception methods. Pregnant or nursing (lactating) women. History of hypersensitivity or allergy to fluorescein or ICG, clinically significant drug allergy or known hypersensitivity to therapeutic or diagnostic protein products, or to any of the study drugs or their components. Patient with history of porphyria. Systemic medications known to be toxic to the lens, retina, or optic nerve. History of which might affect the interpretation of the results of the study, or renders the patient at high risk from treatment complications. Use of other investigational drugs within 30 days of randomization. Exclusion criteria for study eye: Concomitant conditions/diseases: Presence of angiod streaks, macular fibrosis, presumed ocular histoplasmosis syndrome, pathologic myopia (-8 Diopters or more). Active ocular inflammation or infection. Uncontrolled glaucoma. Ocular disorders that may confound interpretation of study results Prior ocular treatment: verteprofin PDT, external-beam radiation, laser photocoagulation, macular surgery, transpupillary thermotherapy, prior local treatment with pegaptinib,

Study	PCV definition	PRN definition	Inclusion criteria	Exclusion criteria
				<p>ranibizumab, bevacizumab, or other anti-angiogenic compound or any investigational treatment in both eyes or systemic use of bevacizumab within 90 days prior to randomization, History of intraocular surgery including pars plana vitrectomy and intraocular hemorrhage displacement is not allowed with the exception of uncomplicated cataract surgery that is allowed within 60 days prior to screening; Ocular conditions that required chronic concomitant therapy within 90 days prior to randomization with topical, ocular, or systemically administered corticosteroids or any herbal medication known to contain steroid-like components</p>

A list of abbreviations is given on page 6

Table 11: VA Results table for the Research question, 'what are the effects of PDT alone or combined with anti-VEGF in patients with PCV' (Question 2)

Study	Interventions	Follow-up (m)	No. eyes	Visual acuity results					Visual acuity methods	
				Baseline BCVA (meas±sd)	Baseline logMAR (mean ±sd)	Follow-up logMAR (mean ±sd)	Mean change (logMAR)	Mean change (ETDRS)	Chart	Distance (m)
Lai 2008 ³⁵	1.25mg BVZ x3, then prn	11*	6	NR	0.67±0.35*	0.5±0.34*	-0.17*	NR	BCVA was measured by certified optometrists using an ETDRS logMAR chart at 4 m or with a standard Snellen chart at 6 m converted to logMAR visual acuity for analysis.	
	1.25mg BVZ x3, then vPDT + 1.25mg BVZ	12.25*	4		0.7±0.62*	0.45±0.39*	-0.25*			
	1.25mg BVZ x3, then vPDTx1	18*	3		0.6±0.45*	0.73±0.46*	0.13*			
	1.25mg BVZ x3	11.5*	2		0.4±0.14	0.35±0.21*	-0.05*			
Lee 2008 ³⁶	1.25mg BVZ	4*	8*	NR	0.51±0.15*	0.42±0.40*	-0.10*	NR	NR	NR
	1.25mg BVZ+PDT	3.5*	4*		0.62±0.37*	0.35±0.51*	-0.28*			
Cho 2009 ³⁷	Half PDT +RBZ	11.6*	5		0.97±0.27*	1.09±0.39*	0.1*		Snellen	NR
	Full PDT +RBZ	10*	2		1.15±0.21*	0.85±0.21*	-0.3*			
	Full PDT + BVZ	12	1		1.00*	1.00*	0			
	PDT	7	1		0.48*	0.40	-0.08*			
	Thermal + RBZ	9	1		1.3*	1.3*	0*			
	RBZ	12	1		1.00*	1.00*	0			
	BVZ	11	1		0.48*	0.48*	0			
Mitamura 2010 ^{38,39}	1.25mg BVZx1	3	18	NR	0.54±0.37	0.55±0.37	0.01*	NR	Japanese standard Landolt visual acuity chart	NR
	1.25mg BVZx3	3	22		0.53±0.34	0.47±0.37	-0.06*			

Study	Interventions	Follow-up (m)	No. eyes	Visual acuity results					Visual acuity methods	
				Baseline BCVA (meas±sd)	Baseline logMAR (mean ±sd)	Follow-up logMAR (mean ±sd)	Mean change (logMAR)	Mean change (ETDRS)	Chart	Distance (m)
	PDT	3	49		0.54±0.29	0.45±0.34	-0.09*			
Song 2011 ⁴⁰	sPDT + 0.5mg RBZ	12	9	NR	0.93±0.47	0.64±0.27	-0.29±0.23	NR	Snellen	NR
	0.5mg RBZ	12	15		1.06 ±0.44	0.83 ±0.50	-0.24±0.27			
Saito 2011 ⁴¹	sPDT	6	34	NR	0.54* (0 to 1.15)	0.62*	0.08*	NR	Japanese standard decimal VA chart and ETDRS	NR
	0.5mg RBZ x3, then PRN	6	25		0.57* (0.1 to 1.22)	0.39*	-0.18*			
Rouvas 2011 ⁴²	sPDT	12	11	NR	0.53 (0.1-1)	0.28 (0.05-1)	-0.25	NR	Nonstandardised Snellen	NR
	0.5mg RBZ x3 then PRN	12	10		0.79 (0.15-1)	0.75 (0.3-1.3)	-0.04			
	sPDT +0.5mg RBZ x3	12	9		0.81 (0.4-1.3)	0.63 (0.22-1)	-0.18			
Lai 2011 ⁴³	0.5mg RBZx3, PRN	12	7	NR	0.92±0.29	0.61±0.31	-0.31	NR	ETDRS at 4 m or Snellen at 6 m	4 Or 6
	sPDT + 0.5mg RBX x3	12	16		0.70±0.35	0.62±0.35	-0.08			
	sPDT	12	12		0.74±0.41	0.58±0.41	-0.16			
Lim 2012 ⁴⁴	1.25mg BVZ x3	12 [#]	5	NR	0.56 ± 0.24	0.42 ± 0.35	-0.14	NR	NR	NR
	PDT + BVZx3	12	5		0.58 ± 0.43	0.54 ± 0.57	-0.04			
Kagokawa 2012 ⁴⁵	PDT + RBZ then PRN	6	16	NR	0.63	0.44	-0.19	NR	NR	NR
	RBZx3 then PRN		16		0.61	0.32	-0.29			
	PDT + RBZ then PRN	12	16	NR	0.63	0.40	-0.23	NR	NR	NR
	RBZx3 then PRN		16		0.61	0.37	-0.24			
EVEREST ^{33,34,32}	PDT (6mg/m2)+RBZ 0.5mg x3, PRN	6	19	56.6 ±20.9				10.9 ±10.9	ETDRS	4
	PDT (6mg/m2)+ sham PRN	6	21	57.2 ±12.8				7.5 ±10.7		

Study	Interventions	Follow-up (m)	No. eyes	Visual acuity results					Visual acuity methods	
				Baseline BCVA (meas±sd)	Baseline logMAR (mean ±sd)	Follow-up logMAR (mean ±sd)	Mean change (logMAR)	Mean change (ETDRS)	Chart	Distance (m)
	Sham PDT+RBZ 0.5mg x3, PRN	6	21	49 ± 18.1				9.2 ± 12.4		

sPDT = standard verteporfin PDT (6mg/m² verteporfin and 50J/cm² , 600mW/cm² for 83seconds); rPDT = reduced verteporfin PDT (6mg/m² verteporfin and 25J/cm² , 300mW/cm² for 83seconds); C = classic; MC = minimally classic; O = occult; PC = predominantly classic; vPDT = verteporfin +PDT. Other abbreviations are given on page 6. * calculated by KSR. # time assumed to be the same as last visit.

Table 12: Risk of bias table for intervention studies (observational: non-randomized clinical trials, cohort and case-control studies), for the research question ‘what are the effects of PDT alone or combined with anti-VEGF in patients with PCV’ (Question 2)

Study reference	Bias due to a non-representative or ill-defined sample of patients?	Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?	Bias due to ill-defined or inadequately measured outcome ?	Bias due to inadequate adjustment for all important prognostic factors?
Lai 2008 ³⁵	Unclear	Likely	Likely	Likely
Lee 2008 ³⁶	Unclear	Likely	Likely	Likely
Cho 2009 ³⁷	Unclear	Likely	Likely	Likely
Mitamura 2010 ^{38,39}	Unlikely	Unlikely	Likely	Likely
Song 2011 ⁴⁰	Unclear	Unlikely	Likely	Likely
Saito 2011 ⁴¹	Unclear	Unlikely	Likely	Likely
Rouvas 2011 ⁴²	Unclear	Unlikely	Likely	Likely
Lai 2011 ⁴³	Unclear	Unlikely	Likely	Likely
Kagokawa 2012 ⁴⁵	Unclear	Unlikely	Likely	Likely

Table 13: Risk of bias table for intervention studies (randomized controlled trials), for the research question ‘what are the effects of PDT alone or combined with anti-VEGF in patients with PCV’ (Question 2)

Study reference	Describe method of randomisation	Bias due to inadequate concealment of allocation?	Bias due to inadequate blinding of participants to treatment allocation?	Bias due to inadequate blinding of care providers to treatment allocation?	Bias due to inadequate blinding of outcome assessors to treatment allocation?	Bias due to selective outcome reporting on basis of the results?	Bias due to loss to follow-up?	Bias due to violation of intention to treat analysis?
Lim 2012 ⁴⁴	No	Unclear	Unclear	Unclear	Unclear	Unlikely	Unclear	Likely
EVEREST ^{33,34,32}	No	Unclear	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely	Likely

Table 14: Details of trials in patients with PCV, meeting inclusion criteria for question 2

Study ID/Name	Design	Comparators	Comments
EVEREST NCT00674323 http://clinicaltrials.gov/show/NCT00674323 Efficacy and Safety of Verteporfin Added to Ranibizumab in the Treatment of Symptomatic Macular Polypoidal Choroidal Vasculopathy (PCV)	RCT, double blind.	PDT + RBZ Vs RBZ Vs PDT (n=61)	Funded by Novartis, Page last updated 2011. COMPLETED
JPRN-JMA-IIA00028 http://apps.who.int/trialsearch/Trial.aspx?TrialID=JPRN-JMA-IIA00028 Comparison of photodynamic therapy and ranibizumab therapy for the treatment of polypoidal choroidal vasculopathy	Randomized Comparative study.	RBZ Vs PDT (n=124)	Funded by Hyogo macular disease conference, Page last updated 2013. COMPLETED
JPRN-UMIN000008630 http://apps.who.int/trialsearch/Trial.aspx?TrialID=JPRN-UMIN000008630 Long-term Outcome of Intravitreal Ranibizumab Treatment, Compared with Photodynamic Therapy, in Patients with Polypoidal Choroidal Vasculopathy	Observational.	PDT Vs RBZ (n=80)	Funded by Yokohama City University Medical Center, Page last updated 2013. ONGOING
JPRN-UMIN000004845 http://apps.who.int/trialsearch/Trial.aspx?TrialID=JPRN-UMIN000004845 Effect of dose schedule using Ranibizumab and Verteporfin in Japanese Polypoidal Choroidal Vasculopathy Patients (Fuji-san study)	Parallel randomised.	PDT + RBZ Vs RBZ then PDT (n=84).	Funded by Fuji-san study group, Page last updated 2013. ONGOING

A list of abbreviations is given on page 6

2.3 QUESTION 3: RANDOMISED CONTROLLED TRIALS FOR THE TREATMENT OF RAP (RETINAL ANGIOMATOUS PROLIFERATION) IN PATIENTS WITH PCV

Literature searches were performed and generated 229 records. Figure 3 summarises the flow of studies through the search and screening process. Screening of the titles and abstracts by two independent reviewers identified 12 records. These records were examined in full and three met the inclusion criteria, whilst nine were excluded. We were not able to view the abstracts from the Euretina searches, therefore the results were not included in the review, however the the search results can be found in Appendix 5.

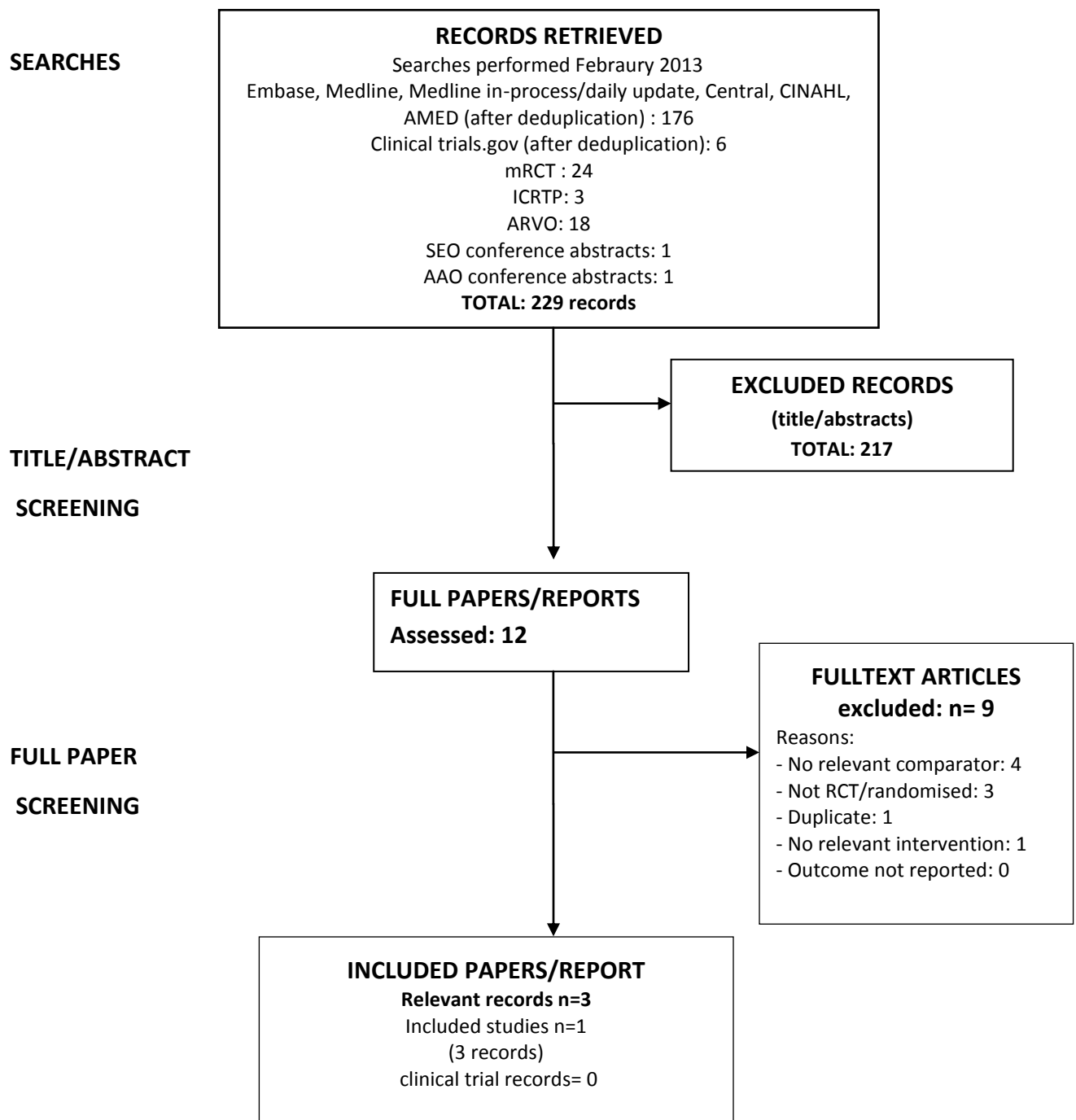
The three included records were all reports of the same trial, ROUVAS 2009 ^{46,47,48}.

The baseline characteristics of ROUVAS 2009 were summarised in Tables 15-17, the visual acuity results were summarised in Table 18 and the risk of bias was summarised in Table 19.

No trials were identified which met the inclusion criteria, however three trials (two complete and one ongoing) were found that were similar to the inclusion criteria and are described in Table 20.

Reasons for the exclusion of full papers are given in Appendix 8.

Figure 3: Summary searching and inclusion screening for question 3



mRCT = meta register of controlled trials; ICRTP= WHO international clinical trials registry platform; SEO = European Society of Opthamology; AAO = American Academy of Ophthalmology; ARVO = Assiation for Research in Vision and Ophthalmology; CINAHL =Cumulative Index to Nursing and Allied Health Literature; AMED = Allied and complimentary medicine database; RCT= randomised controlled trial.

Table 15: Evidence table for the Research question, ' What are the effects of PDT alone or combined with anti-VEGF for RAP (retinal angiomatous proliferation) in patients with PCV' (Question 3)

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size
Rouvas 2009 ^{46,47,48}	Type of study: Prospective, randomised, open label Setting: Hospital Country: Greece Source of funding: NR	<u>Inclusion criteria:</u> See table 17. <u>Exclusion criteria:</u> See table 17. <u>N total at baseline:</u> 0.5 mg RBZ : 13 PDT + 0.5 mg RBZ: 13 PDT + 4mg IVTA: 11 <u>Mean age ± SD:</u> 0.5 mg RBZ : 76.9 PDT + 0.5 mg RBZ: 77.1 PDT + 4mg IVTA: 76.5 <u>Sex (M/F):</u> 0.5 mg RBZ : 5/8 PDT + 0.5 mg RBZ: 4/9 PDT + 4mg IVTA: 5/6 <u>Stage of RAP</u> 0.5 mg RBZ : II (76.9%), III (23.1%), +PED (61.5%) PDT + 0.5 mg RBZ: II (100%), III (0%), +PED (76.9%) PDT + 4mg IVTA: II (100%), III (0%), +PED (63.6%) <u>Baseline VA:</u> See table 12 <u>Groups comparable at baseline?</u> No (see VA data).	Describe intervention: PDT + 0.5 mg RBZ See Table 16 for details.	Describe control: 0.5 mg RBZ or PDT + 4mg IVTA See Table 16 for details.	<u>Length of follow-up:</u> 6 and 36 months <u>Loss-to-follow-up:</u> Intervention: NR Reasons (describe): NR Control: N (%): NR Reasons (describe): NR <u>Incomplete outcome data:</u> Not relevant	Outcome measures and effect size (include 95%CI and p-value if available): See table 16

A list of abbreviations is given on page 6.

Table 16: Treatment regimens for the Research question, 'What are the effects of PDT alone or combined with anti-VEGF for RAP (retinal angiomatous proliferation) in patients with PCV' (Question 3)

Study	Interventions	No. Eyes	PRN/ fixed/ treat & extend	Full dose/half dose verteporfin	Full fluence/ half fluence laser light	Number of baseline VEGF injections	Time between baseline injections	Number of baseline PDT treatments	Follow-up examinations (wks)	No. final VEGF injections (mean±sd)	No. final PDT treatments (range)
Rouvas 2009 ^{46,47,48}	0.5 mg RBZ	13	PRN	-	-	3	Monthly	0	monthly	5.92	0
	PDT + 0.5 mg RBZ	13	PRN	Full	Full	3	monthly	1		3.46	1.15
	PDT + 4mg IVTA	11	PRN	Full	Full	0	-	1		1.63 (IVT)	1.63

Table 17: Study Definitions table for the Research question, 'What are the effects of PDT alone or combined with anti-VEGF for RAP (retinal angiomatous proliferation) in patients with PCV' (Question 3)

Study	PRN definition	Inclusion criteria	Exclusion criteria
Rouvas 2009 ^{46,47,48}	In the case of persistence or recurrence of subretinal fluid or intraretinal fluid (IRF), according to the OCT and/or clinically detectable hemorrhages, x3 RBZ injections were administered to the patients on a monthly schedule/ PDT +RBZ x3/ PDT +IVT every 3 months.	Equal to or older than 50 years with primary or recurrent RAP in the study eye in one of the three vasogenic stages described by Yannuzzi et al, (based on FA and ICG obtained equal or less than 1 week before study Day 0), with total lesion size not exceeding 5,400 um in the greatest linear dimension.	Predominantly classic, occult or minimally classic CNV based on the FA only, vPDT in the preceding 3m (or in the preceding 7d for the non study eye); more than 3 previous PDT sessions in the last yr; juxtafoveal or extrafoveal laser photocoagulation within 2m, previous subfoveal laser photocoagulation, proton beam irradiation, transpupillary thermotherapy at any time; CNV unrelated to AMD, intraocular surgery <2m before entry in the study, active intraocular inflammation, administration of topical or systemic corticosteroids in the previous 2 m. Moreover, patients that had previously received antiangiogenic treatment or other investigational drugs on either eye.

A list of abbreviations is given on page 6

Table 18: VA Results table for the Research question, 'What are the effects of PDT alone or combined with anti-VEGF for RAP (retinal angiomatous proliferation) in patients with PCV' (Question 3)

Study	Interventions	Follow-up (months)	No. patients	Visual acuity results			Visual acuity methods	
				Baseline (mean logMAR)	Follow-up (mean logMAR)	Mean change (logMAR)	Chart	distance
Rouvas 2009 ^{46, 47,48}	0.5 mg RBZ	6	13	0.83 (0.1-1.9)	0.85 (0.1-1.9)	0.02	Nonstandardized Snellen visual acuity	NR
	PDT + 0.5 mg RBZ		13	0.61 (0.05-1.6)	0.63 (0-1.9)	0.02		
	PDT + 4mg IVTA		11	0.92 (0.15-1.6)	0.61 (0.15-1.6)	-0.31		
	0.5 mg RBZ	36	12	0.83 (0.1-1.9)	0.86 (0.3-1.9)	0.03		
	PDT + 0.5 mg RBZ		12	0.61 (0.05-1.6)	0.68 (0.1-1.9)	0.07		
	PDT + 4mg IVTA		9	0.92 (0.15-1.6)	0.63 (0.1-1.3)	-0.29		

A list of abbreviations is given on page 6

Table 19: Risk of bias table for the Research question, 'What are the effects of PDT alone or combined with anti-VEGF for RAP (retinal angiomatous proliferation) in patients with PCV' (Question 3)

Study reference	Describe method of randomisation	Bias due to inadequate concealment of allocation?	Bias due to inadequate blinding of participants to treatment allocation?	Bias due to inadequate blinding of care providers to treatment allocation?	Bias due to inadequate blinding of outcome assessors to treatment allocation?	Bias due to selective outcome reporting on basis of the results?	Bias due to loss to follow-up?	Bias due to violation of intention to treat analysis?
Rouvas ^{46,47,48}	NR	Unclear	Likely	Likely	Likely	Unclear	Unclear	Unclear

Table 20: Details of trials in patients with Retinal Angiomatous Proliferation, but not meeting inclusion criteria for question 3

Study ID/Name	Design	Comparators	Comments
NCT00395707 http://clinicaltrials.gov/show/NCT00395707 Study To Determine Safety/Efficacy of Lucentis For Treatment Of Retinal Angiomatous Proliferation Secondary To Age Related Macular Degeneration.	Phase I randomised controlled trial.	0.3mg RBZ vs 0.5mg RBZ n=20	Funded by The National Retina Institute. CTG page last updated 2009. COMPLETED
NCT00470977 http://clinicaltrials.gov/show/NCT00470977 Treatment of Exudative and Vasogenic Chorioretinal Diseases Including Variants of AMD and Other CNV Related Maculopathy (FVF4140S).	Phase II open single group trial.	0.5mg RBZ n=18	Funded by Manhattan Eye, Ear & Throat Hospital. CTG page last updated 2012. COMPLETED
EUCTR2006-004367-57-AT http://apps.who.int/trialsearch/trial.aspx?trialid=EUCTR2006-004367-57-AT Treatment of retinal angiomatous proliferation lesions due to age-related macular degeneration with ranibizumab (Lucentis®) and photodynamic therapy with verteporfin (Visudyne®) – LUPRA.	Case series.	PDT + RBZ (n=15).	Funded by Department of Ophthalmology, Medical University of Graz, Page last updated 2012. ONGOING

A list of abbreviations is given on page 6

3. REFERENCES

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APPENDIX 1: SEARCH STRATEGY FOR QUESTION 1

What are the effects of TPA or gas in patients with both AMD and (sub)macular bleeding?

Embase (OvidSP): 1974-2013/02/15

Searched 19.2.13

- 1 (WARMD or WAMD).ti,ab,ot,hw. (9)
- 2 exudative macular degeneration/ (228)
- 3 (Wet or Neovascular\$ or Neo-vascular\$ or exudat\$ or moist).ti,ab,ot,hw. (120547)
- 4 (choroidal neovascular\$ or choroidal neo-vascular\$ or CNV).ti,ab,ot,hw. (8537)
- 5 or/2-4 (123430)
- 6 Retina Macula Age Related Degeneration/ (10346)
- 7 (ARMD or AMD).ti,ab,ot,hw. (8610)
- 8 ((degenerat\$ or atroph\$ or hole or lesion\$) adj3 macula\$ adj3 senile).ti,ab,ot,hw. (517)
- 9 ((senile or areolar or guttate) adj3 central adj3 (choroidal or choroid) adj3 (atroph\$ or scleros\$)).ti,ab,ot,hw. (18)
- 10 (macula\$ adj3 (dystroph\$ or degenerat\$)).ti,ab,ot,hw. (20942)
- 11 ((age or Aging or ageing or Senescen\$) adj3 Maculopath\$).ti,ab,ot,hw. (818)
- 12 tays choroiditis.ti,ab,ot,hw. (2)
- 13 or/6-12 (23770)
- 14 5 and 13 (7520)
- 15 1 or 14 (7524)
- 16 Retina-Macula-Hemorrhage/ (598)
- 17 ((central or centralis) adj3 fovea\$ adj3 (h?emorrhag\$ or bleed\$)).ti,ab,ot,hw. (2)
- 18 ((H?emorrhag\$ or bleed\$) adj3 (macula\$ or retina\$)).ti,ab,ot,hw. (8193)
- 19 ((submacula\$ or sub-macula\$) adj3 (H?emorrhag\$ or bleed\$)).ti,ab,ot,hw. (244)
- 20 or/16-19 (8227)
- 21 15 and 20 (590)
- 22 Random\$.tw. or clinical trial\$.mp. or exp health care quality/ (3004565)
- 23 exp case control study/ or case study/ or cohort analysis/ or longitudinal study/ or prospective study/ or follow up/ or case report/ (2914218)
- 24 cohort\$.tw. (321309)
- 25 (case\$ adj3 (control\$ or series or report or study or studies or reports)).tw. (793047)
- 26 clinical study/ or family study/ or retrospective study/ (406711)
- 27 ((follow-up or observational or cross sectional) adj1 (study or studies)).mp. (233644)
- 28 or/22-27 (6014493)
- 29 animal/ or animal experiment/ (3474809)
- 30 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).mp. (5636565)
- 31 or/29-30 (5636565)
- 32 exp human/ or human experiment/ (14260325)
- 33 31 not (31 and 32) (4517674)
- 34 28 not 33 (5818826)
- 35 21 and 34 (450)
- 36 remove duplicates from 35 (443)

37 limit 36 to embase (382)

Trials filter terms based on:

Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. *J Med Libr Assoc* 2006;94(1):41-7.

Observational study terms based on:

Scottish Intercollegiate Guidelines Network. Observational studies search filter: Embase [Internet]. Edinburgh: SIGN, n.d. [accessed 14.1.13]. Available from: <http://www.sign.ac.uk/methodology/filters.html#obs>

Cohort, case-control, case series, and case study terms based on:

Clinical Evidence. Embase cohort, case-control, case series, and case study strategy [Internet]. London: BMJ, n.d. [accessed 14.1.13]. Available from: <http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665076.html>

**Medline (OvidSP): 1946-2013/02/Wk 1
Searched 19.2.2013**

- 1 Wet Macular Degeneration/ or (WARMD or WAMD).ti,ab,ot,hw. (332)
- 2 (Wet or Neovascular\$ or Neo-vascular\$ or exudat\$ or moist).ti,ab,ot,hw. (119445)
- 3 (choroidal neovascular\$ or choroidal neo-vascular\$ or CNV).ti,ab,ot,hw. (7042)
- 4 or/2-3 (121200)
- 5 Macular Degeneration/ (10287)
- 6 (ARMD or AMD).ti,ab,ot,hw. (6191)
- 7 ((degenerat\$ or atroph\$ or hole or lesion\$) adj3 macula\$ adj3 senile).ti,ab,ot,hw. (385)
- 8 ((senile or areolar or guttate) adj3 central adj3 (choroidal or choroid) adj3 (atroph\$ or scleros\$)).ti,ab,ot,hw. (10)
- 9 (macula\$ adj3 (dystroph\$ or degenerat\$)).ti,ab,ot,hw. (14259)
- 10 ((age or Aging or ageing or Senescen\$) adj3 Maculopath\$).ti,ab,ot,hw. (674)
- 11 tays choroiditis.ti,ab,ot,hw. (1)
- 12 or/5-11 (15831)
- 13 4 and 12 (5529)
- 14 1 or 13 (5531)
- 15 Retinal Hemorrhage/ (4229)
- 16 ((central or centralis) adj3 fovea\$ adj3 (h?emorrhag\$ or bleed\$)).ti,ab,ot,hw. (2)
- 17 ((H?emorrhag\$ or bleed\$) adj3 (macula\$ or retina\$)).ti,ab,ot,hw. (5777)
- 18 ((submacula\$ or sub-macula\$) adj3 (H?emorrhag\$ or bleed\$)).ti,ab,ot,hw. (187)
- 19 or/15-18 (5813)
- 20 14 and 19 (296)
- 21 randomized controlled trial.pt. (340350)
- 22 controlled clinical trial.pt. (85196)
- 23 (randomized or placebo).ab. (323971)
- 24 drug therapy.fs. (1579596)
- 25 (trial or randomly or groups).ab. (1415147)
- 26 epidemiologic studies/ or case-control studies/ or exp cohort studies/ (1351947)
- 27 Cross-Sectional Studies/ (150856)

- 28 Epidemiologic Methods/ (28585)
- 29 controlled clinical trial.pt. (85196)
- 30 (case\$ adj3 (control\$ or series or report or study or studies or reports)).tw. (571930)
- 31 cohort\$.tw. (211415)
- 32 ((follow-up or observational or cross sectional) adj1 (study or studies)).ti,ab,ot,hw.
(655493)
- 33 or/21-32 (4415862)
- 34 animals/ not (animals/ and humans/) (3673440)
- 35 33 not 34 (3949628)
- 36 20 and 35 (193)
- 37 remove duplicates from 36 (193)

Trials filter terms based on:

Lefebvre C, Manheimer E, Glanville J. Chapter 6: searching for studies. Box 6.4.c: Cochrane Highly sensitive search strategy for identifying randomized controlled trials in Medline: Sensitivity-maximizing version (2008 version); OVID format. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

Observational study terms based on:

Scottish Intercollegiate Guidelines Network. Observational studies search filter: Medline [Internet]. Edinburgh: SIGN, n.d. [accessed 15.1.13]. Available from: <http://www.sign.ac.uk/methodology/filters.html#obs>

Cohort, case-control, case series, and case study terms based on:

Clinical Evidence. Medline cohort, case-control, case series, and case study strategy [Internet]. London: BMJ, n.d. [accessed 15.1.13]. Available from: <http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665076.html>

Cochrane Central Register of Controlled Trials (CENTRAL): Issue 12:2012 Searched 19.2.2013

- #1 MeSH descriptor: [Wet Macular Degeneration] this term only 19
- #2 (WARMD or WAMD):ti,ab,kw 0
- #3 (Wet or Neovascular* or Neo-vascular* or exudat* or moist):ti,ab,kw 3131
- #4 ((choroidal near/1 neovascular*) or (choroidal near/1 neo-vascular*) or CNV):ti,ab,kw 800
- #5 #3 or #4 3282
- #6 MeSH descriptor: [Macular Degeneration] this term only 576
- #7 (ARMD or AMD):ti,ab,kw 847
- #8 ((degenerat* or atroph* or hole or lesion*) near/3 macula* near/3 senile):ti,ab,kw
33
- #9 ((senile or areolar or guttate) near/3 central near/3 (choroidal or choroid) near/3 (atroph* or scleros*)):ti,ab,kw 0

#10 (macula* near/3 (dystroph* or degenerat*)):ti,ab,kw 1178
 #11 ((age or Aging or ageing or Senescen*) near/3 Maculopath*):ti,ab,kw 68
 #12 (tays near/1 choroiditis):ti,ab,kw 0
 #13 #6 or #7 or #8 or #9 or #10 or #11 or #12 1425
 #14 #5 and #13 815
 #15 #1 or #2 or #14 815
 #16 MeSH descriptor: [Retinal Hemorrhage] this term only 44
 #17 ((central or centralis) near/3 fovea* near/3 (hemorrhag* or haemorrhag* or bleed*)):ti,ab,kw 0
 #18 ((Hemorrhag* or haemorrhag* or bleed*) near/3 (macula* or retina*)):ti,ab,kw 137
 #19 ((submacula* or sub-macula*) near/3 (Hemorrhag* or haemorrhag* or bleed*)):ti,ab,kw 4
 #20 #16 or #17 or #18 or #19 141
 #21 #15 and #20 11

Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO): 1981-2013/02/08

Searched 19.2.2013

S11 s8 and s10 (9)

S10 MH Eye Hemorrhage OR TX (((central or centralis) N3 fovea* N3 (hemorrhag* or haemorrhag* or bleed*))) OR TX (((Hemorrhag* or haemorrhag* or bleed*) N3 (macula* or retina*))) OR TX (((submacula* or sub-macula*) N3 (Hemorrhag* or haemorrhag* or bleed*))) (329)
 S9 MH Eye Hemorrhage (202)
 S8 s1 or s7 (340)
 S7 s2 and s6 (339)
 S6 S3 or s4 or s5 (2,612)
 S5 TX tays N1 choroiditis (0)
 S4 TX (((senile or areolar or guttate) N3 central N3 (choroidal or choroid) N3 (atroph* or scleros*))) OR TX (macula* N3 (dystroph* or degenerat*)) OR TX ((age or Aging or ageing or Senescen*) N3 Maculopath*) (2,431)
 S3 MH Macular Degeneration OR TX ((ARMD or AMD)) OR TX (((degenerat* or atroph* or hole or lesion*) N3 macula* N3 senile)) (2,467)
 S2 TX (Wet or Neovascular* or Neo-vascular* or exudat* or moist) OR TX (choroidal N2 neovascular*) OR TX ((choroidal N2 neo-vascular*) or CNV) (5,923)
 S1 TX WARMD or WAMD (1)

Allied and Complementary Medicine Database (AMED) (OvidSP): 1985-2013/02

Searched 19.2.13

1 (WARMD or WAMD).ti,ab,hw. (0)
 2 (Wet or Neovascular\$ or Neo-vascular\$ or exudat\$ or moist).ti,ab,hw. (357)
 3 (choroidal neovascular\$ or choroidal neo-vascular\$ or CNV).ti,ab,hw. (4)
 4 or/2-3 (361)
 5 (ARMD or AMD).ti,ab,hw. (56)
 6 ((degenerat\$ or atroph\$ or hole or lesion\$) adj3 macula\$ adj3 senile).ti,ab,hw. (2)

- 7 ((senile or areolar or guttate) adj3 central adj3 (choroidal or choroid) adj3 (atroph\$ or scleros\$)).ti,ab,hw. (0)
- 8 (macula\$ adj3 (dystroph\$ or degenerat\$)).ti,ab,hw. (73)
- 9 ((age or Aging or ageing or Senescen\$) adj3 Maculopath\$).ti,ab,hw. (6)
- 10 tays choroiditis.ti,ab,hw. (0)
- 11 or/5-10 (118)
- 12 4 and 11 (1)**

NIH Clinicaltrials.gov (Internet): up to 2013/01/15

<http://www.clinicaltrials.gov/>

Searched 15.01.2013

Advanced search

Terms	Hits
(Eye OR eyes OR ocular OR macula* OR retina* OR choroid* OR sub-macula* OR submacula* OR fovea* OR choroid* OR maculo*) AND (bleed* OR haemorrhag* OR hemorrhag* or neovascula* OR neo-vascula*)	282 (284 when JR searched 20/2/2013)
(ARMD OR AMD OR WAMD OR WARMD OR choroiditis OR CNV) AND (bleed* OR haemorrhag* OR hemorrhag*)	37

mRCT – metaRegister of Controlled Trials (Internet): Up to 20/02/2013

<http://www.controlled-trials.com/>

Searched 20.02.2013

Search terms	Results
(ocular OR macula* OR retina* OR choroid* OR submacula* OR maculo*) AND (bleed* or haemorrhag* or hemorrhag*)	473
(ARMD or AMD or WAMD or WARMD) AND (bleed* or heamorrhag* or hemorrhag*)	107
TOTAL	580

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

<http://www.who.int/ictrp/en/>

Searched 20.02.2013

Advanced search – using condition field as title field produced large result set

Search terms	Results
(eye OR eyes OR ocular OR macula% OR retina% OR choroid% OR submacula% OR maculo%) AND (bleed% or haemorrhag% or hemorrhag% or neovascul%)	48 records for 37 trials
(ARMD or AMD or WAMD or WARMD OR choroiditis OR CNV or macula%)	165 records for 133 trials
(ARMD or AMD or WAMD or WARMD OR choroiditis OR CNV) AND (bleed% or haemorrhag% or hemorrhag% or neovascul%)	27 records for 20 trials
TOTAL	240

Association for Research in Vision and Ophthalmology (ARVO)

<http://www.arvo.org/>

Searched: 20.02.2013

<http://www.iovs.org/search?arvontgsearch=true>

Terms	Hits
ARMD AMD WAMD WARMD	348
Wet macular degeneration	21
Macula degeneration	6
<i>Total</i>	<i>375</i>

European Society of Ophthalmology (Societas Ophthalmologica Europæa [SOE])

<http://www.eur-j-ophthalmol.com/issue/ejo-soe-2011-abstracts>

Searched: 20.02.2013

*only 2011 abstracts in the Journal of Ophthalmology – conferences only every 2 years

Keyword	Hits
AMD	8
Wet	3
WAMD	0
WARMD	0
Submacular	1
CNV	0
Choroidal neovascularization	5
Macular degeneration	28
Macula degeneration	0
Total	45

American Academy of Ophthalmology (AAO)

<http://www.aao.org/>

Searched: 20.02.2013

Program Search and Meeting Archive

Annual meeting 2010-2013

Keyword	Hits
AMD	151
WAMD	0
WARMD	0
CNV	36
Choroidal neovascularization	16
Macular degeneration	10
Macula degeneration	0
Total	213

European Society of Retina Specialists (Euretina)

<http://www.euretina.org/>

Searched: 20.02.2013

Browsed each year's "free posters" and "Free papers" by disease area "**AMD**" 2010-2013

Keyword	Hits
2010	Papers: 29 Posters: 49
2011	Papers: 68 Posters: 62
2012	Papers: 21 Posters: Non available
2013	NA
Total	151

APPENDIX 2: SEARCH STRATEGY FOR QUESTION 2

What are the effects of PDT alone or combined with anti-VEGF?

Embase (OvidSP): 1974-2013/02/19

Searched 21.2.13

- 1 Polypoidal choroidal vasculopathy/ or (Polypoidal choroidal vasculopath\$ or polypoidal choroidal neovascular\$ or polypoidal choroidal neo-vascular\$ or polypoidal CNV or PCV).ti,ab,ot,hw. (4664)
- 2 Photodynamic Therapy/ (13757)
- 3 ((Photodynamic or photo-dynamic) adj1 (Therap\$ or treatment\$ or intervention\$ or course\$ or procedure\$)).ti,ab,ot. (13197)
- 4 (PDT or Photosenti?ation\$ or Photo-senti?ation\$ or photosensiti?ation\$ or photosensiti?ation\$).ti,ab,ot.(11139)
- 5 exp photosensitizing agent/ (29942)
- 6 (photosensiti?er\$ or light sensiti?er\$).ti,ab,ot. (7527)
- 7 (photosensiti?ing adj2 (agent\$ or drug\$ or interven\$ or regim\$ or course\$ or dose\$)).ti,ab,ot. (916)
- 8 (photo-sensiti?ing adj2 (agent\$ or drug\$ or interven\$ or regim\$ or course\$ or dose\$)).ti,ab,ot. (8)
- 9 or/2-8 (40789)
- 10 1 and 9 (202)
- 11 limit 10 to embase (174)**

Medline (OvidSP): 1946-2013/02/wk 1

Searched 21.2.13

- 1 (Polypoidal choroidal vasculopath\$ or polypoidal choroidal neovascular\$ or polypoidal choroidal neo-vascular\$ or polypoidal CNV or PCV).ti,ab,ot,hw. (3455)
- 2 Photochemotherapy/ (11688)
- 3 ((Photodynamic or photo-dynamic) adj1 (Therap\$ or treatment\$ or intervention\$ or course\$ or procedure\$)).ti,ab,ot. (9808)
- 4 (PDT or Photosenti?ation\$ or Photo-senti?ation\$ or photosensiti?ation\$ or photosensiti?ation\$).ti,ab,ot. (8335)
- 5 exp Photosensitizing Agents/ (22928)
- 6 (photosensiti?er\$ or light sensiti?er\$).ti,ab,ot. (5752)
- 7 (photosensiti?ing adj2 (agent\$ or drug\$ or interven\$ or regim\$ or course\$ or dose\$)).ti,ab,ot. (699)
- 8 (photo-sensiti?ing adj2 (agent\$ or drug\$ or interven\$ or regim\$ or course\$ or dose\$)).ti,ab,ot. (10)
- 9 or/2-8 (30934)
- 10 1 and 9 (154)**

Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): Issue 1: 2013

Searched 21.2.13

- #1 ((polypoidal near/1 choroidal near/1 vasculopath*) or (polypoidal near/1 neovascular*) or (polypoidal near/1 choroidal near/1 neo-vascular*) or (polypoidal near/1 CNV) or PCV):ti,ab,kw 240
- #2 MeSH descriptor: [Photochemotherapy] this term only 507
- #3 ((Photodynamic or photo-dynamic) near/1 (Therap* or treatment* or intervention* or course* or procedure*)):ti,ab,kw 689
- #4 (PDT or Photosenti?ation* or Photo-senti?ation* or photosesnsiti?ation* or photosensiti?ation*):ti,ab,kw 499
- #5 MeSH descriptor: [Photosensitizing Agents] explode all trees 355
- #6 (photosensiti?er* or (light near/1 sensiti?er*)):ti,ab,kw 65
- #7 (photosensiti?ing near/2 (agent* or drug* or interven* or regim* or course* or dose*)):ti,ab,kw 365
- #8 (photo-sensiti?ing near/2 (agent* or drug* or interven* or regim* or course* or dose*)):ti,ab,kw0
- #9 #2 or #3 or #4 or #5 or #6 or #7 or #8 1006
- #10 #1 and #9 3

Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO): 1981-2013/02/08

Searched 21.2.2013

S15 s6 AND s14 (51)

- S14 s7 or s8 or s9 or s10 or s11 or s12 or s13 (3,773)
- S13 TX (photo-sensiti?ing N2 (agent* OR drug* OR interven* OR regim* OR course* or dose*)) (6)
- S12 TX (photosensiti?ing N2 (agent* OR drug* OR interven* OR regim* OR course* or dose*)) (542)
- S11 TX photosensiti?er* OR (light n2 sensiti?er*) (193)
- S10 MH Photosensitizing Agents (454)
- S9 TX (PDT OR photosensiti?ation* OR photo-sensiti?ation* OR photosenti?ation* OR photo-senti?ation*) (2,350)
- S8 TX ((photodynamic OR photo-dynamic) N2 (therap* or treatment* or intervention* or course* or procedure*)) (1,305)
- S7 MH Photochemotherapy (572)
- S6 S1 OR S2 OR S3 OR S4 OR S5 (743)
- S5 TX PCV (654)
- S4 TX (polypoidal N2 CNV) (1)
- S3 TX (polypoidal N2 choroidal N2 neo-vascular*) (0)
- S2 TX (polypoidal N2 choroidal N2 neovascular*) (2)
- S1 TX (polypoidal N2 choroidal N2 vasculopath*) (91)

Allied and Complementary Medicine Database (AMED) (OvidSP): 1985-2013/02

Searched 21.2.13

- 1 (Polypoidal choroidal vasculopath\$ or polypoidal choroidal neovascular\$ or polypoidal choroidal neo-vascular\$ or polypoidal CNV or PCV).ti,ab,hw. (18)

- 2 ((Photodynamic or photo-dynamic) adj1 (Therap\$ or treatment\$ or intervention\$ or course\$ or procedure\$)).ti,ab. (23)
- 3 (PDT or Photosenti?ation\$ or Photo-senti?ation\$ or photosensiti?ation\$ or photo-sensiti?ation\$).ti,ab. (17)
- 4 (photosensiti?er\$ or light sensiti?er\$).ti,ab. (3)
- 5 (photosensiti?ing adj2 (agent\$ or drug\$ or interven\$ or regim\$ or course\$ or dose\$)).ti,ab. (2)
- 6 (photo-sensiti?ing adj2 (agent\$ or drug\$ or interven\$ or regim\$ or course\$ or dose\$)).ti,ab. (0)
- 7 or/2-6 (35)
- 8 1 and 7 (0)**

NIH Clinicaltrials.gov (Internet): up to 2013/02/21

<http://www.clinicaltrials.gov/>

Searched 21.02.2013

Advanced search

Terms	Hits
Polypoidal	19
Total	19

WHO International Clinical Trials Registry Platform (ICTRP) (Internet): up to 2013/02/21

<http://www.who.int/ictrp/en/>

Searched: 21.02.2013

Search terms	Results
polypoidal	21
TOTAL	21

mRCT – metaRegister of Controlled Trials (Internet): up to 2013/02/21

<http://www.controlled-trials.com/>

Searched: 21.02.2013

Search terms	Results
polypoidal	10
PCV (screened results by eye to eliminate vaccine results)	8/71

TOTAL	18
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Association for Research in Vision and Ophthalmology (ARVO)

<http://www.arvo.org/>

<http://www.iovs.org/search?arvontgsearch=true>

Searched: 20.02.2013

Terms	Hits
Polypoidal	49
PCV	4
Total	53

European Society of Ophthalmology (Societas Ophthalmologica Europaea [SOE])

<http://www.eur-j-ophthalmol.com/issue/ejo-soe-2011-abstracts>

Searched: 22.02.2013

*only 2011 abstracts in the Journal of Ophthalmology – conferences only every 2 years

Keyword	Hits
polypoidal	4
PCV	0
Total	4

American Academy of Ophthalmology (AAO)

<http://www.aao.org/>

Searched: 21.02.2013

Program Search and Meeting Archive

Annual meeting 2010-2013

Keyword	Hits
PCV	16
Polypoidal	16
Total	32

European Society of Retina Specialists (Euretina)

<http://www.euretina.org/>

Searched: 21.02.2013

Browsed each year's "free posters" and "Free papers" by the following keywords "polypoidal" or "PCV" in all topic areas.

2010-2013

Keyword	Hits
2010	Papers: 1 Posters: 5
2011	Papers: 0 Posters: 3
2012	Papers: 2 Posters: Non available
2013	NA
Total	11

APPENDIX 3: SEARCH STRATEGY FOR QUESTION 3

What is the effectiveness of treatments for RAP (retinal angiomatous proliferation)?

Embase (OvidSP): 1974-2013/02/25

Searched 26.2.13

- 1 rap.ti,ab,ot,hw. (4741)
- 2 (eye or eyes or ophthalm\$ or cornea\$ or retina\$ or oculo\$ or macula\$ or maculo\$ or choroid\$).ti,ab,ot,hw. (683597)
- 3 1 and 2 (215)
- 4 (retina\$ adj3 angiomato\$ adj3 proliferat\$).ti,ab,hw,ot. (207)
- 5 retinal angiomatous proliferation/ (80)
- 6 (retina\$ adj3 anastomosis adj5 lesion\$).ti,ab,hw,ot. (3)
- 7 (type adj1 "3" adj2 neovascular\$).ti,ab,hw,ot. (10)
- 8 or/3-7 (287)
- 9 Random\$.tw. or clinical trial\$.mp. or exp health care quality/ (3006405)
- 10 animal/ (1819167)
- 11 animal experiment/ (1670879)
- 12 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5634584)
- 13 or/10-12 (5634584)
- 14 exp human/ (14267069)
- 15 human experiment/ (309714)
- 16 or/14-15 (14268505)
- 17 13 not (13 and 16) (4517275)
- 18 9 not 17 (2863278)
- 19 8 and 18 (92)
- 20 limit 19 to embase (78)**

Trials filter terms based on:

Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. J Med Libr Assoc 2006;94(1):41-7.

Medline (OvidSP): 1946-2013/02/wk 2

Searched 26.2.13

- 1 rap.ti,ab,hw,ot. (3481)
- 2 (eye or eyes or ophthalm\$ or cornea\$ or retina\$ or oculo\$ or macula\$ or maculo\$ or choroid\$).ti,ab,ot,hw. (548377)
- 3 1 and 2 (171)
- 4 (retina\$ adj3 angiomato\$ adj3 proliferat\$).ti,ab,hw,ot. (158)
- 5 (type adj1 "3" adj2 neovascular\$).ti,ab,hw,ot. (7)
- 6 (retina\$ adj3 anastomosis adj5 lesion\$).ti,ab,hw,ot. (2)
- 7 or/3-6 (222)
- 8 randomized controlled trial.pt. (340350)

- 9 controlled clinical trial.pt. (85196)
- 10 randomized.ab. (243629)
- 11 placebo.ab. (135236)
- 12 drug therapy.fs. (1579596)
- 13 randomly.ab. (174757)
- 14 trial.ab. (250587)
- 15 groups.ab. (1140716)
- 16 or/8-15 (2944179)
- 17 animals/ not (animals/ and humans/) (3673440)
- 18 16 not 17 (2501541)
- 19 7 and 18 (93)**

Trials filter terms based on:

Lefebvre C, Manheimer E, Glanville J. Chapter 6: searching for studies. Box 6.4.c: Cochrane Highly sensitive search strategy for identifying randomized controlled trials in Medline: Sensitivity-maximizing version (2008 version); OVID format. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

**Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): Issue 1: 2013
Searched 26.2.13**

- #1 rap:ti,ab,kw 131
- #2 (eye or eyes or ophthalm\$ or cornea\$ or retina\$ or oculo\$ or macula\$ or maculo\$ or choroid\$):ti,ab,kw 17306
- #3 #1 and #2 7
- #4 (retina* near/3 angiomato* near/3 proliferat*):ti,ab,kw 7
- #5 #3 or #4 9**

**Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO): 1981-2013/02/08
Searched 26.2.13**

S16 S11 OR S15 (57)

- S15 S12 OR S13 OR S14 (31)
- S14 TX (type N2 3 N5 neovascula*) (3)
- S13 TX (retina* N3 anastomosis N3 lesion*) (1)
- S12 TX (retina* N3 angiomato* N3 proliferat*) (29)
- S11 S1 OR S7 OR S10 (55)
- S10 S8 OR S9 (2)
- S9 AB (retina* and anastomosis and lesion*) (1)
- S8 TI (retina* and anastomosis and lesion*) (1)
- S7 S5 AND S6 (11)
- S6 TX (eye or eyes or ophthalm* or cornea* or retina* or oculo* or macula* or maculo* or choroid*) (121,957)
- S5 S2 OR S3 (346)

S4 MW RAP (0)
 S3 AB RAP (222)
 S2 TI RAP (155)
 S1 TX retina* AND angiomato* and proliferat* (46)

Allied and Complementary Medicine Database (AMED) (OvidSP): 1985-2013/02
Searched 26.2.13

- 1 rap.ti,ab. (21)
- 2 (eye or eyes or ophthalm\$ or cornea\$ or retina\$ or oculo\$ or macula\$ or maculo\$ or choroid\$).ti,ab. (1674)
- 3 1 and 2 (0)
- 4 (retina\$ adj3 angiomato\$ adj3 proliferat\$).ti,ab. (0)
- 5 (type adj1 "3" adj2 neovascular\$).ti,ab. (0)
- 6 (retina\$ adj3 anastomosis adj5 lesion\$).ti,ab. (0)

Question 3

NIH Clinicaltrials.gov (Internet): up to 2013/02/25

<http://www.clinicaltrials.gov/>

Searched: 26.02.13

Advanced search

Terms	Hits
(Eye OR eyes OR ocular OR macula* OR retina* OR choroid* OR sub-macula* OR submacula* OR fovea* OR choroid* OR maculo*) AND (RAP)	5
(retina* AND angiomat* AND proliferat*)	0
retinal angiomatous proliferation	3
Total	8

mRCT – metaRegister of Controlled Trials (Internet): up to 06/03/2013

<http://www.controlled-trials.com/>

Searched: 06.03.2013

Search terms	Results
retina* AND angioma* AND prolifer*	17
retina* AND anastomosis	7
TOTAL	24

WHO International Clinical Trials Registry Platform (ICTRP) (Internet): up to 07/03/2013

<http://www.who.int/ictrp/en/>

Searched 07.03.2013

Advanced search – using condition field as title field produced large irrelevant result set

Search terms	Results
(eye OR eyes OR ocular OR macula% OR retina% OR choroid% OR submacula% OR maculo%) AND (RAP)	0
retina% and angiomato% and proliferat\$	3
retina% and anastomosi% and lesion%	0
TOTAL	3

Association for Research in Vision and Ophthalmology (ARVO)

<http://www.arvo.org/>

<http://www.iovs.org/search?arvontgsearch=true>

Searched: 08.03.13

Terms	Hits
Retinal angiomatous proliferation (phrase search)	15
RAP (all)	2
Retinal anastomosis (all)	3
Total	20

Note: For all searches the limit of years used was 2010 – 2012. The first terms were conducted as a phrase search. The other two search term groups were used in a AND search.

European Society of Ophthalmology (Societas Ophthalmologica Europæa [SOE])

<http://www.eur-j-ophthalmol.com/issue/ejo-soe-2011-abstacts>

Searched: 25.02.2013

* only 2011 abstracts in the Journal of Ophthalmology – conferences only every 2 years

Keyword	Hits
Retinal angiomatous	1
RAP	0
Total	1

American Academy of Ophthalmology (AAO)

<http://www.aao.org/>

Searched: 08.03.13

Program Search and Meeting Archive
Annual meeting 2010-2013

Keyword	Hits
Angiomatous proliferation	1
Total	1

European Society of Retina Specialists (Euretina)

<http://www.euretina.org/>

Searched: 08.03.13

Browsed each year's "free posters" and "Free papers" by the following keywords "angiomatous proliferation" or "anastomosis" in all topic areas.

Changes to the Euretina online abstracts meant that links to the retrieved results did not work and only the titles were able to be viewed.

2010-2013

Keyword	Hits
Retinal angiomatous	3
Anastomosis	1
Total	4

APPENDIX 4: RISK OF BIAS AND EVIDENCE TABLES PROVIDED BY NOG

Evidence table for intervention studies (randomised controlled trials and non-randomised *observational* studies [cohort studies, case-control studies, case series])¹

This table is also suitable for diagnostic studies (screening studies) that compare the effectiveness of two or more tests. This only applies if the test is included as part of a test-and-treat strategy – otherwise the evidence table for studies of diagnostic test accuracy should be used.

Research question:

Study reference	Study characteristics	Patient characteristics ²	Intervention (I)	Comparison / control (C) ³	Follow-up	Outcome measures and effect size ⁴	Comments
1st author, year of publication	Type of study: Setting: Country: Source of funding:	<u>Inclusion criteria:</u> <u>Exclusion criteria:</u> <u>N total at baseline:</u> Intervention: Control: <u>Important prognostic factors²:</u> <i>For example</i> <i>age ± SD:</i> <i>I:</i> <i>C:</i> <i>Sex:</i> <i>I: % M</i> <i>C: % M</i> Groups	Describe intervention (treatment/procedure/test):	Describe control (treatment/procedure/test):	<u>Length of follow-up:</u> <u>Loss-to-follow-up:</u> Intervention: N (%) Reasons (describe) Control: N (%) Reasons (describe) <u>Incomplete outcome data:</u> Intervention: N (%) Reasons (describe) Control: N (%)	Outcome measures and effect size (include 95%CI and p-value if available):	

		comparable at baseline?			Reasons (describe)		

Notes:

1. Prognostic balance between treatment groups is usually guaranteed in randomised studies, but non-randomised (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures
2. Provide data per treatment group on the most important prognostic factors [(potential) confounders]
3. For case-control studies, provide sufficient detail on the procedure used to match cases and controls
4. For cohort studies, provide sufficient detail on the (multivariate) analyses used to adjust for (potential) confounders

Risk of bias table for intervention studies (randomised controlled trials)

Research question:

Study reference (first author, publication year)	Describe method of randomisation ¹	Bias due to inadequate concealment of allocation? ² (unlikely/likely/unclear)	Bias due to inadequate blinding of participants to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of care providers to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to inadequate blinding of outcome assessors to treatment allocation? ³ (unlikely/likely/unclear)	Bias due to selective outcome reporting on basis of the results? ⁴ (unlikely/likely/unclear)	Bias due to loss to follow-up? ⁵ (unlikely/likely/unclear)	Bias due to violation of intention to treat analysis? ⁶ (unlikely/likely/unclear)

1. Randomisation: generation of allocation sequences have to be unpredictable, for example computer generated random-numbers or drawing lots or envelopes. Examples of inadequate procedures are generation of allocation sequences by alternation, according to case record number, date of birth or date of admission.

2. Allocation concealment: refers to the protection (blinding) of the randomisation process. Concealment of allocation sequences is adequate if patients and enrolling investigators cannot foresee assignment, for example central randomisation (performed at a site remote from trial location) or sequentially numbered, sealed, opaque envelopes. Inadequate procedures are all procedures based on inadequate randomisation procedures or open allocation schedules..
3. Blinding: neither the patient nor the care provider (attending physician) knows which patient is getting the special treatment. Blinding is sometimes impossible, for example when comparing surgical with non-surgical treatments. The outcome assessor records the study results. Blinding of those assessing outcomes prevents that the knowledge of patient assignment influences the proces of outcome assessment (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.
4. Results of all predefined outcome measures should be reported; if the protocol is available, then outcomes in the protocol and published report can be compared; if not, then outcomes listed in the methods section of an article can be compared with those whose results are reported.
5. If the percentage of patients lost to follow-up is large, or differs between treatment groups, or the reasons for loss to follow-up differ between treatment groups, bias is likely. If the number of patients lost to follow-up, or the reasons why, are not reported, the risk of bias is unclear
6. Participants included in the analysis are exactly those who were randomized into the trial. If the numbers randomized into each intervention group are not clearly reported, the risk of bias is unclear; an ITT analysis implies that (a) participants are kept in the intervention groups to which they were randomized, regardless of the intervention they actually received, (b) outcome data are measured on all participants, and (c) all randomized participants are included in the analysis.

Risk of bias table for intervention studies (observational: non-randomised clinical trials, cohort and case-control studies)

Research question:

Study reference (first author, year of publication)	Bias due to a non-representative or ill-defined sample of patients? ¹ (unlikely/likely/unclear)	Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups? ² (unlikely/likely/unclear)	Bias due to ill-defined or inadequately measured outcome ? ³ (unlikely/likely/unclear)	Bias due to inadequate adjustment for all important prognostic factors? ⁴ (unlikely/likely/unclear)

1. Failure to develop and apply appropriate eligibility criteria: a) case-control study: under- or over-matching in case-control studies; b) cohort study: selection of exposed and unexposed from different populations.

2. Bias is likely if: the percentage of patients lost to follow-up is large; or differs between treatment groups; or the reasons for loss to follow-up differ between treatment groups; or length of follow-up differs between treatment groups or is too short. The risk of bias is unclear if: the number of patients lost to follow-up; or the reasons why, are not reported.
3. Flawed measurement, or differences in measurement of outcome in treatment and control group; bias may also result from a lack of blinding of those assessing outcomes (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has “soft” (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.
4. Failure to adequately measure all known prognostic factors and/or failure to adequately adjust for these factors in multivariate statistical analysis.

APPENDIX 5: RESULTS OF EURETINA SEARCHING

Results For Euretina Searching For Question 1

European Society of Retina Specialists (Euretina)

<http://www.euretina.org/>

2012

Papers

[Audit of Sheffield Lucentis AMD service - effectiveness of the 'virtual review clinic'](#)Presenting Author:H.Abdulkarim United Kingdom

[Neovascular AMD with atrophic areas. Characteristics, evolution of atrophic lesions associated to neovascular AMD treated by series of 3 ranibizumab IVT Protocol, 4 years follow-up](#) Presenting Author:C.Gonzalez France

[Outcomes in the ranibizumab\(Lucentis \) clinic in a district general hospital](#)Presenting Author:S.Awotesu United Kingdom

[Outcomes of the retrospective pooled safety analysis of ranibizumab therapy for neovascular age-related macular degeneration from four European registries and update on the ongoing prospective LUMINOUS study](#)Presenting Author:F.Bandello Italy

[Prediction of individual need for retreatment with ranibizumab for exudative age-related macular degeneration - the results of a treatment regimen 'observe and plan'](#)Presenting Author:I.Mantel Switzerland

[Prospective comparative study of fundus autofluorescence in eyes with an ultraviolet- and a blue light-filtering intraocular lens implantation](#)Presenting Author:T.Yasukawa Japan

[Subgroup analyses of the VIEW 1 and VIEW 2 studies of intravitreal aflibercept injection and ranibizumab for treatment of neovascular AMD](#)Presenting Author:U.Schmidt-Erfurth Austria

[Switch of intravitreal ranibizumab to bevacizumab for the treatment of neovascular age-related macular degeneration - clinical comparison](#)Presenting Author:J.Pinheiro-Costa Portugal

[Systemic beta-blockers may reduce the need for repeated intravitreal injections in patients with wet age related macular degeneration treated by bevacizumab](#)Presenting Author:J.Montero Spain

[Transpupillary thermotherapy as an adjuvant in combination with intravitreal ranibizumab for neovascular age-related macular degeneration: a 24 month prospective randomized clinical study](#) Presenting Author:A.Kvanta Sweden

[Twelve-month efficacy and safety of monthly ranibizumab 0.5 mg in Chinese patients with choroidal neovascularization secondary to age-related macular degeneration - the EXTEND II study](#)Presenting Author:X.Li China

[AMD Atrophic areas. Characteristics, evolution study, and its interest.3 years follow-up](#)Presenting Author:C.Gonzalez France

[Correlation of retinal sensitivity and SD-OCT morphology after one year of monthly ranibizumab in neovascular age-related macular degeneration](#)Presenting Author:F.Sulzbacher Austria

[Effect of bevacizumab/anti-CTGF neutralizing antibody on the production and activity of MMP-2 in human RPE cells](#) Presenting Author:H.Ahmadiéh Iran, Islamic Republic of

[Effect of intravitreal injection of Ranibizumab on the ocular blood flow of wet AMD patients](#)Presenting Author:T.Kiseleva Russian Federation

[En-face OCT imaging for the diagnosis of outer retinal tubulations in age-related macular degeneration](#)Presenting Author:B.Wolff France

[Follow-up study of geographic atrophy patients using adaptive optics retinal imaging](#)Presenting Author:K.Gocho Japan [Multimodal evaluation of foveal sparing in patients with geographic atrophy due to age-related macular degeneration](#)Presenting Author:R.Forte Italy

[Response to ranibizumab in age related macular degeneration patients with vitreomacular traction syndrome . A comparative study](#)Presenting Author:A.Filloy Spain

[Retinal sensitivity is reduced in patients with reticular pseudodrusen in the fellow eye of patients with neovascular age-related macular degeneration](#)Presenting Author:V.Chong United Kingdom

[Score grading system for exudative AMD and clinical evaluation for anti VEGF therapy](#) Presenting Author:S.Donati Italy

[Vitreomacular adhesion may not be a further risk factor for age-related macular degeneration](#)Presenting Author:E.Maggio Italy

2011

Papers

[A phase Ia study in geographic atrophy with FCFD4514S, a novel antigen binding fragment \(Fab\) of a humanized monoclonal antibody directed against complement factor D](#)Presenting Author:DianaDo United States

[Acute endophthalmitis after intravitreal injections](#)Presenting Author:Nil?ferYe?il?rmak Turkey [Adaptive optics imaging in drusen](#)Presenting Author:KiyokoGocho-Nakashima France

[Bevacizumab is able to alter MMP-2, TIMP-1 and TIMP-2 transcription levels in RPE cells](#)
Presenting Author:HamidAhmadiéh Iran, Islamic Republic of

[Comparison of response to first dose versus third dose of ranibizumab injection in neovascular age related macular degeneration \(NVAMD\)](#)Presenting Author:RaebaMathew
United Kingdom

[CTGF neutralizing antibody influences MMP-9 activity and quantity in human retinal pigment epithelial \(RPE\) cell culture](#)Presenting Author:SoheilaSoheili Iran, Islamic Republic of

[Does anti-Vegf treatment alter vitreo retinal adhesion?](#)Presenting Author:GaneshMurthy
United Kingdom

[Does presence or absence of vitreo macular traction \(VMT\) affect the clinical course and treatment outcomes in patients with exudative ARMD ? a comparative study](#)Presenting Author:BalasubramanianRamasamy United Kingdom

[Endophthalmitis associated with intravitreal anti-vascular endothelial growth factor therapy injections in an eye hospital](#)Presenting Author:ManickamThiagarajan United Kingdom

[Evaluation of the clinical efficacy of the Ellex 2RT laser for the treatment of diabetic maculopathy and AMD](#)Presenting Author:JohnMarshall United Kingdom

[Intraocular pharmacokinetics after single intravitreal injection of 1.5 mg versus 3.0 mg bevacizumab in humans](#) Presenting Author:Carsten H.Meyer Germany

[Intravitreal ranibizumab for age-related macular degeneration - optical coherence tomography guided retreatment intervals and their intra- and inter-individual variability](#) Presenting Author:IrmelaMantel Switzerland

[Lesion size comparison of geographic atrophy in blue light vs. green light autofluorescence images](#)Presenting Author:UteWolf-Schnurrbusch Switzerland

[Long-term outcome and treatment frequency until year 4 of flexible ranibizumab AMD treatment](#)Presenting Author:HeinrichGerding Switzerland

[Macular EpiRetinal brachytherapy in treated age related macular degeneration patients \(MERITAGE\) - 12 month results](#)Presenting Author:RobertPetrarca United Kingdom

[Peripheral autofluorescence changes in patients with geographic atrophy secondary to dry ARMD](#)Presenting Author:UteWolf-Schnurrbusch Switzerland

[Pharmacogenetic studies of ranibizumab treatment in neovascular age-related macular degeneration](#)Presenting Author:Jan EEKeunen Netherlands

[Potential predictors of visual acuity response to ranibizumab treatment in patients with age-related macular degeneration of the EXCITE and SUSTAIN trials](#)Presenting Author:UrsulaSchmidt-Erfurth Austria

[Potential safety differences between unlicensed bevacizumab \(Avastin?\) and ranibizumab \(Lucentis?\) in age-related macular degeneration \(AMD\) - a health economic perspective](#)Presenting Author:SanjaySharma Canada

[Randomized, double masked, active controlled phase 3 trial of the efficacy and safety of intravitreal VEGF Trap-Eye in wet AMD- 1 year results from the VIEW-1 study](#)Presenting Author:JeffreyHeier United States

[Ranibizumab in monotherapy and combined with photodynamic therapy for retinal angiomatous proliferation](#)Presenting Author:LuisArias Barquet Spain

[SAVE \(Superdose Anti-VEgf\) trial ? 2.0-mg intravitreal ranibizumab for recalcitrant neovascular age-related macular degeneration](#)Presenting Author:DavidBrown United States

[Status of the external limiting membrane and inner segment–outer segment junction as predictor factor of visual acuity in aged macular degeneration treated with ranibizumab](#)Presenting Author:PaoloCarpineto Italy

[The VIEW-2 study - 1 year results from a randomized, double masked, active controlled phase 3 trial of the efficacy and safety of intravitreal VEGF Trap-Eye in wet AMD](#)Presenting Author:Jean-Fran?oisKOROBELNIK France

[TLR-3 as a novel therapeutic target for age-related macular degeneration](#)Presenting Author:KirstenEibl-Lindner Germany

[A 2 year randomized, double-masked, phase 2/3 trial of pegaptanib sodium in patients with diabetic macular edema](#)Presenting Author:Jan EEKeunen Netherlands

[Acute endophthalmitis after intravitreal injections](#) Presenting Author:N.Ye?il?rmak Turkey

[Assessment of retinal vascular geometry in diabetic retinopathy, and its predictive value in disease progression](#)Presenting Author:MagedHabib United Kingdom

[Causes and incidence of visual impairment in the London borough of Croydon](#) Presenting Author:RamuMuniraju United Kingdom

[Clinical efficacy of image stabilized laser photocoagulation in diabetic macular edema using retinal navigated photocoagulator Navilas?](#)Presenting Author:IgorKozak United States

[Clinical outcome of intravitreal injections comparing with standard care for macular edema secondary to branch retinal vein occlusion](#)Presenting Author:KyungminLee Korea, Republic of

[Comparison of intravitreal bevacizumab and triamcinolone acetone therapies for diffuse diabetic macular edema](#)Presenting Author:GurselYilmaz Turkey

[Cost-effectiveness of the diabetic retinopathy mobile screening in Burgundy](#)Presenting Author:PascaleMASSIN France

[CTGF neutralizing antibody influences MMP-9 activity and quantity in human retinal pigment epithelial \(RPE\) cell culture Presenting Author:S.Soheili Iran](#)

[Cystoid macular edema without macular thickening in diabetic retinopathy Presenting Author:RaimondoForte Italy](#)

[Design and rationale of a 12-month masked phase IV study that compares the safety and efficacy of Ozurdex? versus ranibizumab in patients with branch retinal vein occlusion Presenting Author:FrancescoBandello Italy](#)

[Diabetes as a major risk factor for post-central retinal vein occlusion neovascularisation Presenting Author:MichelPaques France](#)

[Does anti-Vegf treatment alter vitreo retinal adhesion? Presenting Author:G.Murthy UK](#)

[Does presence or absence of vitreo macular traction \(VMT\) affect the clinical course and treatment outcomes in patients with exudative ARMD – a comparative study Presenting Author:B.Ramasamy UK](#)

[Does widefield 200 degree angiography provide additional clinically useful information in patients with insulin dependent diabetes\(IDDM\) with no clinically visible retinopathy Presenting Author:sanjeevnath United States](#)

[Endophthalmitis associated with intravitreal anti-vascular endothelial growth factor therapy injections in an eye hospital Presenting Author:M.Thiagarajan UK](#)

[Evaluation of ranibizumab treatment concept based on stability and deterioration of visual acuity in BRAVO and CRUISE patients Presenting Author:IanPearce United Kingdom](#)

[Exploring parameters that may be associated with the efficacy of response to intravitreal bevacizumab \(ivB\) Presenting Author:SimonaDegli Esposti United Kingdom](#)

[Expression of high-mobility groups box-1 / receptor for advanced glycation end products / osteopontin / early growth response-1 pathway Presenting Author:AhmedAbu El-Asrar Saudi Arabia](#)

[Factors associated with visual acuity outcomes after repeated intravitreal ranibizumab for diabetic macular edema - 12 month results Presenting Author:KatjaHatz Switzerland](#)

[Helicobacter pylori infection, GORD and central serous chorioretinopathy Presenting Author:FarhanZaidi United Kingdom](#)

[Iluvien? \(fluocinolone acetonide intravitreal implant\) in the treatment of diabetic macular oedema - results from phase 3 studies Presenting Author:ClareBailey United Kingdom](#)

[Imaging of intra-retinal morphology following 3 nanoseconds grid laser \(2RT laser system, Ellex\) for the treatment of diabetic macular oedema Presenting Author:LuciaPelosini United Kingdom](#)

[In-vivo morphologic analysis and follow-up of peripheral retinal ischemia secondary to diabetic retinopathy](#) Presenting Author: Christoph Mitsch Austria

[Intraocular pharmacokinetics after single intravitreal injection of 1.5 mg versus 3.0 mg bevacizumab in humans](#) Presenting Author: C. Meyer Germany

[Intravitreal anti-Vegf for severe macular oedema in CRVO \(central retina vein occlusion\) treatment](#) Presenting Author: Maria Caterina Cascella Italy

[Intravitreal bevacizumab versus triamcinolone injection during cataract surgery in patients with diabetic macular edema](#) Presenting Author: Cem Yildirim Turkey

[Lesion size comparison of geographic atrophy in blue light vs. green light autofluorescence images](#) Presenting Author: U. Wolf-Schnurrbusch Switzerland

[Long-term follow-up of myopic choroidal neovascularization treated with ranibizumab](#) Presenting Author: Nuno Franqueira Portugal

[Macular EpiRetinal brachytherapy in treated age related macular degeneration patients \(MERITAGE\) - 12 month results](#) Presenting Author: R. Petrarca UK

[Management of retinal vein obstruction secondary to congenital arteriovenous communication in children](#) Presenting Author: Eva Villota Deleu Spain

[Peripheral autofluorescence changes in patients with geographic atrophy secondary to dry AMD](#) Presenting Author: U. Wolf-Schnurrbusch Switzerland

[Pilot randomized clinical trial of Pascal TargetED retinal versus variable fluence PANretinal \(PETER PAN\) 20-millisecond laser in diabetic retinopathy](#) Presenting Author: Paulo Stanga United Kingdom

[Pooled safety analysis in patients with visual impairment due to diabetic macular edema treated with 0.5mg ranibizumab in the RESOLVE and RESTORE trials](#) Presenting Author: Reinier Schlingemann Netherlands

[Potential predictors of visual acuity response to ranibizumab treatment in patients with age-related macular degeneration of the EXCITE and SUSTAIN trials](#) Presenting Author: U. Schmidt-Erfurth Austria

[Potential safety differences between unlicensed bevacizumab \(Avastin®\) and ranibizumab \(Lucentis®\) in age-related macular degeneration \(AMD\) - a health economic perspective](#) Presenting Author: S. Sharma Canada

[Preoperative intravitreal bevacizumab use as an adjuvant to diabetic vitrectomy-histopathologic findings](#) Presenting Author: Hazem El-Sabagh Saudi Arabia

[Randomized, double-masked, controlled translational study of bevacizumab for severe retinal detachment due to proliferative diabetic retinopathy](#) Presenting Author: Elliott Sohn United States

[Ranibizumab \(Lucentis?\) for diabetic macular edema \(DME\) - 24 month safety and efficacy results of RIDE, a phase III randomized controlled trial](#)Presenting Author:PatricioSchlottmann Argentina

[RaScaL study - results of a pilot study of combination peripheral scatter laser and ranibizumab for diabetic macular oedema associated with peripheral non-perfusion](#)Presenting Author:IvanSuner United States

[The effects of different laser modalities used for the treatment of diabetic macular oedema \(DMO\) - immediate and 4 months follow-up results](#)Presenting Author:RoopaVemala United Kingdom

[Ultra-widefield angiography significantly improves the detection and classification of diabetic retinopathy](#)Presenting Author:Szil?rdKiss United States

[Variations in central macular thickness after panretinal photocoagulation \(PRP\) in patients with proliferative diabetic retinopathy with no maculopathy](#)Presenting Author:RamuMuniraju United Kingdom

[Vitreoretinal interface in central serous choroidopathy -a retrospective case control study](#)Presenting Author:IoannisTheocharis Greece

Posters

[Analysis of VEGFA gene polymorphisms in patients with choroid neovascular membrane](#)Presenting Author:ChikunEkaterina Russian Federation

[Anti-CTGF affects MMP-2 quantity and activity in human retinal pigment epithelial \(RPE\) cell culture](#)Presenting Author:ShahramSamiei Iran, Islamic Republic of

[Anxiety and depression in age related macular degeneration \(AMD\) patients](#)Presenting Author:Maria SaraDias Patricio Portugal

[Bevacizumab in different concentrations affects MMP-2 production and activity in human retinal pigment epithelial cell culture](#)Presenting Author:AbouzarBagheri Iran, Islamic Republic of

[Can the ranibizumab injections in first 6 months predict future retreatment patterns for neovascular AMD](#)Presenting Author:PallaviTyagi United Kingdom

[Cardiovascular risk factors for exudative AMD](#)Presenting Author:AleksandraRadosavljevic Serbia

[Characteristics of fixation in patients with geographic atrophy recorded with the MP-1 microperimeter- follow-up results](#)Presenting Author:Julia-SophieKroisamer Austria

[Characteristics of the population with low intake of Lutein and Zeaxanthin in wet age-related macular degeneration patients](#)Presenting Author:Jose LOlea Spain

[Clinical and OCT results after a 6?24 month variable-dosing regimen of intravitreal ranibizumab in macular degenerationPresenting Author:MarianneWagemans Netherlands](#)

[Clinical assessment and molecular genetics of an autosomal dominant retinitis pigmentosa in a Bulgarian Roma familyPresenting Author:KrassimirKoev Bulgaria](#)

[Clinical characteristics of polypoidal choroidal vasculopathy \(PCV\) in the Scandinavian population of DenmarkPresenting Author:S?renOttosen Denmark](#)

[Clinical evolution of patients with wet age-related macular degeneration treated with ranibizumab- Eye2Eye studyPresenting Author:JavierAraiz Spain](#)

[Combined treatment of photodynamic therapy and bevacizumab for choroidal neovascularization secondary to age-related macular degenerationPresenting Author:ilhanyun Korea, Republic of](#)

[Comparison of efficacy of two surgical procedures with 25 and 27 gauges for macular holesPresenting Author:SergeyAlpatov Russian Federation](#)

[Correlation between functional and anatomical improvement after intravitreal anti-VEGF therapy in wet AMD patientsPresenting Author:KatalinToth-Kovacs Hungary](#)

[Early diagnostics of age-related macular degeneration using new transillumination methodPresenting Author:NataliiaTiashka Ukraine](#)

[Effect of polyunsaturated fatty acids ?-3 on retrobulbar circulation of patients with age-related macula degenerationPresenting Author:TatianaKiseleva Russian Federation](#)

[Efficacy and safety of intravitreal lucentis used for exudative macular degeneration in the first year of service at University Hospital AintreePresenting Author:CLSouthern United Kingdom](#)

[Evaluate the effect of combined photodynamic therapy OR focal laser with intra vitreal injection of anti-VEGF treatment for idiopathic polypoidal choroidal vasculopathy \(IPCV\)Presenting Author:ChiragBhatt India](#)

[Evaluation of two treatment-modalities with ranibizumab for exudative age-related macular degeneration- inject and extend vs PRN \(Pro-re-nata\)Presenting Author:BriceDugas France](#)

[Impact of ranibizumab on quality of life of patients with neovascular age-related macular degeneration in KoreaPresenting Author:HakyounKim Korea, Republic of](#)

[Impact of ranibizumab therapy on optical coherence tomography segmentation error in neovascular age-related macular degenerationPresenting Author:SimonaDegli Esposti United Kingdom](#)

[Influence of haemorheopheresis on drusenoid retinal epithelium detachment in nonvascular age-related macular degenerationPresenting Author:HanaLangrov Czech Republic](#)

[Inhibitory activity of ranibizumab, sorafenib, and pazopanib on light-induced overexpression of PDGF and VEGF Presenting Author: Sarah Thiele Germany](#)

[Intravitreal dexamethasone as a coadjuvant therapy for choroidal neovascularization secondary to age-related macular degeneration Presenting Author: Cristina Marin-Lambies Spain](#)

[Intravitreal ranibizumab for pigment epithelium detachment with subfoveal choroidal neovascularisation in age-related macular degeneration 12 months results Presenting Author: Alessandro Papayannis Italy](#)

[Intravitreal ranibizumab to treat a spontaneous retinal pigment epithelial tear in a patient with age-related macular degeneration Presenting Author: Guillermo Fernandez Sanz Spain](#)

[Long-term results of intravitreal bevacizumab for choroidal neovascularization due to pathological myopia Presenting Author: Yukari Jo Japan](#)

[Macular autofluorescence in patients with neovascular age related macular degeneration \(ARMD\) treated with intravitreal ranibizumab Presenting Author: MYRTOTSAGKATAKI United Kingdom](#)

[Modified ?inject and extend? ranibizumab treatment for exudative age-related macular degeneration associated with pigment epithelium detachment Presenting Author: Athanasios Kotsolis Greece](#)

[More frequent follow-up for patients with wet AMD increases the number of intravitreal ranibizumab injections Presenting Author: Konstantinos Kaprinis Greece](#)

[Morphological changes of the retina according to high definition OCT data in patients with exudative ARMD during treatment with ranibizumab Presenting Author: Igor Malov Russian Federation](#)

[Nutritional factors and exudative AMD Presenting Author: Aleksandra Radosavljevic Serbia](#)

[One year clinical outcome after intravitreal ranibizumab in patients with neovascular age-related macular degeneration- are there differences in responsiveness among subtypes Presenting Author: Caterina Pisano Italy](#)

[Optical coherence tomographic outcomes in the Avastin \(bevacizumab\) for choroidal neovascularization \(ABC\) trial Presenting Author: Pearse Keane United Kingdom](#)

[Optimisation of RIALAB, a drusen quantifying software, in analysing drusen distribution in age-related macular degeneration Presenting Author: Beng Beng Ong United Kingdom](#)

[Optimizing strategies for bevacizumab injections in ARMD- a randomized controlled trial using 4, 6 and 8 weekly injections Presenting Author: Tetyana Lushchyk Netherlands](#)

[Outcome of intravitreal ranibizumab in patients with age related macular degeneration and low visual acuity Presenting Author: Manju Chandran United Kingdom](#)

[Patient satisfaction in one stop macular degeneration treatment centerPresenting Author:TarekEl-khahsab United Kingdom](#)

[Pooled safety analysis in patients with neovascular age-related macular degeneration treated with ranibizumab in clinical trialsPresenting Author:Jean-Fran?oisKOROBELNIK France](#)

[Predictive tomographic factors of retinal pigment epithelium tears in patients with age-related macular degeneration linked serous pigment epithelial detachmentPresenting Author:LARAQUEIROS Portugal](#)

[Preferential hyperacuity perimeter in assessing responsiveness to ranibizumab therapy for exudative age-related macular degenerationPresenting Author:GiuseppeQuerques France](#)

[Ranibizumab injection for neovascular age related macular degeneration in Scotland- a patient satisfaction surveyPresenting Author:MohamedEl-Ashry United Kingdom](#)

[Rapid access wet age related macular degeneration referral network using teleophthalmology and a central image grading centrePresenting Author:PaulGalsworthy United Kingdom](#)

[Rapid unusual reabsorption of drusenoid/lipofuscinic subfoveal lesions in age related macular degeneration \(AMD\) and pseudovitelliform maculopathy \(PM\)Presenting Author:Giorgio FrancescoPacelli Italy](#)

[Recurrence of activity after intravitreal bevacizumab injection in cases of myopic CNVPresenting Author:AhmedSouka Egypt](#)

[Recurrence of CNV after 1 year of 4, 6 and 8 weekly anti-VEGF regimen in age-related macular degenerationPresenting Author:SankhaAmarakoon Netherlands](#)

[Retinal pigment epithelial \(RPE\) tears after intravitreal injection of ranibizumab in a 225 patients case seriesPresenting Author:DavidRodriguez Feijoo Spain](#)

[Safety and tolerability of simultaneous bilateral ranibizumab therapy in AMDPresenting Author:DarioInzerillo United Kingdom](#)

[Serum anti-endothelial antibodies ? new autoantibodies associated with exudative age-related macular degenerationPresenting Author:Dr AgnieszkaKubicka-Trzaska Poland](#)

[Spontaneous detachment of pigmentary epithelium following blunt traumatism of a patient with age-related macular \(AMD\) degenerationPresenting Author:Andrea RominaOle?ik Memmel Spain](#)

[Subretinal neovascularization with atypical localization, a case of difficult diagnosisPresenting Author:Ana LuisaRebelo Portugal](#)

[Sustained ocular hypertension following intravitreal injections of 0, 5 mg /0, 05 ml ranibizumab Presenting Author:ELENILOUKIANOU Greece](#)

[The effect of bevacizumab on MMP-9 production and activity in human retinal pigment epithelial cell culture](#)Presenting Author:[Zahra-SoheilaSoheili Iran, Islamic Republic of](#)

[The protective effect of clodronate against retinal degeneration due to iron-induced oxidative damage in rats](#)Presenting Author:[YulinYao Japan](#)

[The relationship between photoreceptor layer integrity and angiographic, functional and morphological parameters in neovascular age related macular degeneration](#)Presenting Author:[UmitINAN Turkey](#)

[The significance of early treatment of exudative age related macular degeneration ? 12 months results](#)Presenting Author:[BirgitWeingessel Austria](#)

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[Health Economic Evaluation of a PRN treatment schedule with Ranibizumab \(Lucentis?\) in wet AMD](#)
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[Importance of Risk Single Nucleotide Polymorphisms for the Development of Age Related Macular Degeneration in Israel and Its Diagnostic Usefulness.](#)
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[Intra ocular mirror telescopic implant for AMD.](#)
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[Intraoperative detection of the site of entry of an indirect gunshot intraocular foreign body during pars-plana vitrectomy](#)
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[Intravitreal Avastin ? Indications and results, a three-year experience](#)
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[Intravitreal injection of Ranibizumab for AMD: 2 years experience. What determines the outcome?](#)
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[One-year results of a flexible regimen with ranibizumab therapy in macular degeneration: relationship with the number of injections.](#)
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[Pintucci's keratoprosthesis: An interrupted history, a completed path](#)
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[Prevalence of polypoidal choroidal vasculopathy among antiVEGF non-responders with presumed age-related subretinal neovascular membranes](#)
Presenting Author:KatjaHatz Switzerland

[Screening for patient eligibility using fundus autofluorescence in a randomized interventional clinical trial for geographic atrophyPresenting Author:Christian KarlBrinkmann Germany](#)

[SD Optical Coherence Tomography evaluation of Macular Morphology before and after Ranibizumab Treatment of Age-related Macular DegenerationPresenting Author:UgolIntroini Italy](#)

[Sub-Classification of Exudative Age-Related Macular Degeneration Based On Anti-VEGF ResponsePresenting Author:MarkNelson United States](#)

[THE ANALYSIS OF MACULA PIGMENT OPTICAL DENSITY CHANGE BY AGEPresenting Author:NiluferKocak Turkey](#)

[The story of complete posterior vitreous detachment induction: Starring FlutesPresenting Author:A.Das INDIA](#)

[VISUAL PERCEPTIONS INDUCED BY INTRAVENOUS INJECTION OF THERAPEUTIC AGENTSPresenting Author:SofiaCharalampidou Ireland](#)

[Vitreoretinal surgical management of congenital retinoschisisPresenting Author:S.Kaynak TURKEY](#)

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[A survey of physicians knowledge regarding Age Related Macular Degeneration \(ARMD\) and its current management, in Castilla & Leon \(Spain\)Presenting Author:Rosa MariaCoco Spain](#)

[Accurate macular function monitoring in patients with dry age-related macular degeneration.Presenting Author:AllaLisochkina Russian Federation](#)

[Age-related Macular Degeneration ? role of vitreomacular interface and intravitreal antiangiogenic therapeutic efficacyPresenting Author:PedroBorges Portugal](#)

[AMD risk profiling in Estonian high risk families. Study reportPresenting Author:MarisOll Estonia](#)
[AMD when is the right time for reinjection of Lucentis?Presenting Author:OlegFabrikantov Russian Federation](#)

[Angiogenic inhibitors in treatment of wet age-related macular degeneration different stagesPresenting Author:SergeyAlpatov -](#)

[Arterial thromboembolic events in patients with age-related macular degeneration treated with intraocular Bevacizumab or RanibizumabPresenting Author:AngelaCarneiro Portugal](#)

[Assessment of environmental AMD risk factors in a population of patients suffering from stroke and myocardial infarction.Presenting Author:CatherineCreuzot-Garcher France](#)

[Association Analysis of CFH Gene and LOC387715 Gene Polymorphisms in a Brazilian Cohort with Age-related Macular DegenerationPresenting Author:MarcioNehemy Brazil](#)

[Association of risk factors for Age-Related Macular Degeneration with Macular Pigment Optical Density](#)Presenting Author:FilipaRodrigues Portugal

[Case-control study of inflammatory markers in plasma of patients with exudative age-related macular degeneration](#)Presenting Author:AleksandraRadosavljevic Serbia

[Case-control study of systemic antioxidative defense parameters in patients with exudative age-related macular degeneration](#)Presenting Author:AleksandraRadosavljevic Serbia

[CCR3 antagonist suppresses laser-induced choroidal neovascularization in mice](#)Presenting Author:MasayukiAshikari Japan

[Clinical profile of non-progressive Retinitis Pigmentosa without pigment in a family with Autosomal-dominant inheritance](#)Presenting Author:KrassimirKoev Bulgaria

[Combined Photodynamic Therapy With Verteporfin and Intravitreal Ranibizumab for Choroidal Neovascularization in Age-Related Macular Degeneration](#)Presenting Author:JanErnest Czech Republic

[Creating of the experimental model of retinal age-dependent diseases, based on the oxycarotinoid deficiency.](#)Presenting Author:Erika N.Eskina Russia

[Detection of macular changes in AMD using transillumination ophthalmoscopy](#)Presenting Author:MaryiaMorkhat Belarus

[EARLY RESULTS OF RANIBIZUMAB IN PATIENTS WITH CHOROIDAL NEOVASCULARIZATION](#)Presenting Author:NiluferKocak Turkey

[EFEMP1 RETINAL DYSTROPHY \(Dominantly inherited drusen Doyne\) in Serbia](#)Presenting Author:JasminaJaksic Serbia

[EVALUATION OF INTRAVITREAL INJECTIONS IN A CENTRAL HOSPITAL](#)Presenting Author:MariaPicoto Portugal

[EXPERIMENTAL STUDY OF THE EFFECT OF COMBINED THERAPY \(PHOTODYNAMIC THERAPY + ANTIANGIOGENIC DRUG\) ON NORMAL CHOROIDAL VASCULARIZATION.](#)Presenting Author:Maria IsabelLopez Molina Spain

[Gainers and losers after Intravitreal Ranibizumab therapy for Neovascular Age-related Macular Degeneration](#)Presenting Author:RaebaMathew United Kingdom

[Hemorrhagic Complications after Intravitreal Ranibizumab Injection for Polypoidal Choroidal Vasculopathy](#)Presenting Author:HanJooCho Korea, Republic of

[Incidence of spontaneous retinal pigmented epithelium \(RPE\) tears in North Jutland, Denmark](#)Presenting Author:TomasIlginis Denmark

[Interaction of CYP46A1 with CFH, LOC387715 and HTRA1 gene polymorphisms in age-related macular degeneration](#)Presenting Author:DugasBrice France

[Intra ocular mirror telescope for AMD: an additional treatment to all other medical treatments and for all types of AMD.Presenting Author:IsaacLipshitz Israel](#)

[Intraocular VEGF Concentration and Refractive ErrorPresenting Author:JostJonas Germany](#)

[Intravitreal bevacizumab \(Avastin\) and macular thickness in patients with wet AMD - first resultsPresenting Author:VladislavDzinic -](#)

[Intravitreal bevacizumab in age-related macular degeneration as a rescue therapy: two years results.Presenting Author:MontserratGonzalez-Sastre Spain](#)

[Intravitreal bevacizumab in the treatment of retinal angiomatous proliferation \(RAP\): functional outcomes at two years follow-up.Presenting Author:CaterinaPisano Italy](#)

[Intravitreal infliximab in patients with macular degeneration who are nonresponders to anti-vascular endothelial growth factor therapy.Presenting Author:LuisArias Spain](#)

[Intravitreal injection of bevacizumab combined with low fluence verteporfin photodynamic therapy for polypoidal choroidal vasculopathyPresenting Author:WoohyokChang Korea, Republic of](#)

[Intravitreal Ranibizumab vs Bevacizumab in Neovascular Age-Related Macular Degeneration: one-year resultsPresenting Author:LuisMendon Portugal](#)

[Is there a difference in visual outcome between the first and second AMD eyes treated with intravitreal ranibizumab?Presenting Author:KatalinToth-Kovacs Hungary](#)

[One year result of treating Idiopathic neovascularization using intravitreal bevacizumabPresenting Author:GoichiAkiyama Japan](#)

[Optical coherence tomography assessment of retinal nerve fiber layer thickness and optic-disc head changes after ranibizumab in age-related macular degeneration.Presenting Author:JavierBENITEZ Spain](#)

[Pegaptanib in Patients with Small Age-Related Macular Degeneration \(AMD\) Lesions: An Efficacy and Safety StudyPresenting Author:MadinaEstphan France](#)

[Persistent placoid maculopathyPresenting Author:ErbenAlexander Germany](#)

[Photodynamic Therapy with Verteporfin and Anti-VEGF for Polypoidal Choroidal Vasculopathy \(PCV\)Presenting Author:DavorSevsek Slovenia](#)

[Polypoidal Choroidal Vasculopathy Masquerading as Neovascular Age-related Macular Degeneration Refractory to RanibizumabPresenting Author:AlexandrosStangos United Kingdom](#)

[Prevalence of Age-Related Macular Degeneration in Rural Central India. The Central India Eyes and Medical StudyPresenting Author:JostJonas Germany](#)

[Prevalence of age-related macular degeneration in two South East Departments of France.Presenting Author:StephanieBaillif-Gostoli France](#)

[R38X and A69S ARMS2 and Y402H CFH gene variants influence on risk of neovascular age-related macular degeneration in Polish population](#)Presenting Author:SlawomirTeper Poland

[Ranibizumab therapy for choroidal neovascular membrane in angioid streaks.](#)Presenting Author:JavierBENITEZ Spain

[Role of three monthly intra-vitreous bevacizumab \(avastin\) in the management of Idiopathic Choroidal Neo-vascular Membrane: Two year follow up study](#)Presenting Author:AbhishekChandra India

[Short-Term Effects of Intravitreal Bevacizumab \(Avastin?\) on Retrobulbar Hemodynamics in Patients with Wet AMD](#)Presenting Author:YasinToklu Turkey

[The incidence of retinal pigment epithelial tear after intravitreal ranibizumab in the neovascular age-related macular degeneration and visual outcome.](#)Presenting Author:Muhammad AmerAwan United Kingdom

[The Safety and Efficacy of Intra-vitreous Ranibizumab injections for the treatment of Wet Age Related Macular Degeneration.](#)Presenting Author:MariaMilia United Kingdom

[The Treatment of Aged Related Macular Degeneration by the Methods of Acupuncture](#)Presenting Author:AlvinaMusina Russian Federation

[Vision-related quality of life after retinal pigment epithelium tears using NEI VFQ-25](#)Presenting Author:Katja ChristinaSchielke Denmark

Results for Euretina Searching for Question 2

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polypoidal

Papers

[Efficacy and safety of photodynamic therapy with verteporfin and intravitreal injection of anti-vascular endothelial growth factor in patients with symptomatic polypoidal choroidal vasculopathy](#)Presenting Author:M.Bausili Portabella Spain

[A 5-year study of clinical outcomes of polypoidal choroidal vasculopathy \(PCV\) in a multi-ethnic population](#)Presenting Author:C.Tan Singapore

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polypoidal

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Posters

[Clinical characteristics of polypoidal choroidal vasculopathy \(PCV\) in the Scandinavian population of Denmark](#)Presenting Author:S?renOttosen Denmark

[Evaluate the effect of combined photodynamic therapy OR focal laser with intra vitreal injection of anti-VEGF treatment for idiopathic polypoidal choroidal vasculopathy \(IPCW\)](#)Presenting Author:ChiragBhatt India

[Combination treatment with focal laser photocoagulation and ranibizumab \(lucentis\) for polypoidal choroidal vasculopathy](#)Presenting Author:DannyMitry United Kingdom

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polypoidal

Papers

[Prevalence of polypoidal choroidal vasculopathy among antiVEGF non-responders with presumed age-related subretinal neovascular membranes](#)Presenting Author:KatjaHatz Switzerland

Posters

[Hemorrhagic Complications after Intravitreal Ranibizumab Injection for Polypoidal Choroidal Vasculopathy](#)Presenting Author:HanJooCho Korea, Republic of

[Intravitreal injection of bevacizumab combined with low fluence verteporfin photodynamic therapy for polypoidal choroidal vasculopathy](#)Presenting Author:WoohyokChang Korea, Republic of

[Photodynamic Therapy with Verteporfin and Anti-VEGF for Polypoidal Choroidal Vasculopathy \(PCV\)](#)Presenting Author:DavorSevsek Slovenia

[Polypoidal Choroidal Vasculopathy Masquerading as Neovascular Age-related Macular Degeneration Refractory to Ranibizumab Presenting Author:AlexandrosStangos United Kingdom](#)

[Management of Extensive Submacular Haemorrhage in Polypoidal Choroidopathy with Pneumatic displacement, tissue plasminogen activator ranibizumab and focal laser.Presenting Author:OlajumokeAdepegba United Kingdom](#)

Results For Euretina Searching For Question 3

[Ranibizumab in monotherapy and combined with photodynamic therapy for **retinal angiomatous** proliferation](#)
Conference:London 2011 Session: AMD

[Presenting Author:LuisArias Barquet Spain](#)

[Co Author\(s\): :](#)

[Intravitreal bevacizumab in the treatment of **retinal angiomatous** proliferation \(RAP\): functional outcomes at two years follow-up](#)
Conference:Paris 2010 Session: AMD

[Presenting Author:CaterinaPisano Italy](#)

[Co Author\(s\): : Anti-Vascular Endothelial Growth Factor \(VEGF\) therapy for Retinal Angiomatous Proliferation](#)

[Intraoperative laser chorioretinal venous **anastomosis** in treatment of central retinal vein thrombosis](#)
Conference:Milan 2012 Session:

[Presenting Author:OlegKashnan Russian Federation](#)

[Co Author\(s\): :](#)

APPENDIX 6: FULL PAPER EXCLUDES FROM QUESTION 1

[1] Matt G, Sacu S, Stifter E, Prunte C, Schmidt-Erfurth U. [Combination of Intravitreal rTPA, gas and ranibizumab for extensive subfoveal haemorrhages secondary to neovascular age-related macular degeneration]. *Klin Monatsbl Augenheilkd* 2010;227(3):221-5.

No intervention

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Acute diabetic premacular hemorrhage

[3] Vanderbilt University. Prospective Retinal and Optic Nerve Vitrectomy Evaluation (PROVE) Study. 2010. Available from: <http://ClinicalTrials.gov/show/NCT01162356>

Not wAMD/intervention

[4] University Hospital B. Radial Optic Neurotomy in Central Retinal Vein Occlusion : a Randomized Trial. 2011. Available from: <http://ClinicalTrials.gov/show/NCT00379223>

Not wAMD/VA

[5] Duke University, Glenn Jaffe, Bausch , Lomb Incorporated. Fluocinolone Acetonide Implant for Retinal Vein Occlusion (RVO). 2012. Available from: <http://ClinicalTrials.gov/show/NCT00636493>

Not wAMD/VA

[6] Valley Retina Institute, Pfizer. Macugen for Proliferative Diabetic Retinopathy Study With Extended Dosing (M-PDRS ED). 2011. Available from: <http://ClinicalTrials.gov/show/NCT01486771>

Not wAMD/VA

[7] Mizutani T, Yasukawa T, Ito Y, Takase A, Hirano Y, Yoshida M, et al. Pneumatic displacement of submacular hemorrhage with or without tissue plasminogen activator. *Graefes Archive for Clinical and Experimental Ophthalmology* 2011;249(8):1153-1157.

AMD population mixed with another patient population and outcomes were not reported separately.

[8] Hesse L, Kroll P. Successful treatment of acute subretinal hemorrhage in age-related macular degeneration by combined intravitreal injection of recombinant tissue plasminogen activator and gas. *Advances in Therapy* 1997;14(5):275-280.

Units for visual acuity data not clear, nor which eye was treated in patient 1.

[9] Hattenbach LO, Brieden M, Koch F, Gumbel H. Intravitreal injection of rt-PA and gas in the management of minor submacular haemorrhages secondary to age-related macular degeneration. [German]. *Klin Monatsbl Augenheilkd* 2002;219(7):512-518.

Duplicate of Hattenbach 2001.

[10] Ritzau-Tondrow U, Baraki H, Hoerauf H. [Minimally invasive therapy of submacular hemorrhage in exsudative age-related macular degeneration]. *Ophthalmologe* 2012;109(7):670-5.

Patient numbers are inconsistent. Data available for only 22/33 patients, no explanation for missing patients.

APPENDIX 7: FULL PAPER EXCLUDES FROM QUESTION 2

[1] Reduced-fluence PDT may benefit treatment-naïve patients with polypoidal choroidal vasculopathy. *Ocular Surgery News* 2010;28(11):30-30.

Letter of study which did not meet inclusion criteria

[2] PDT plus anti-VEGF effective for treatment-naïve patients with polypoidal choroidal vasculopathy. *Ocular Surgery News* 2012;30(14):12-12.

Control contained PDT

[3] PDT with anti-VEGF temporarily better than PDT alone for polypoidal choroidal vasculopathy... including commentary by Hendrick AM. *Ocular Surgery News* 2013;31(2):30-30.

Letter about Tomita study

[4] Chhablani J. Reduced-fluence photodynamic therapy for polypoidal choroidal vasculopathy. *Am J Ophthalmol* 2010;150(3):443-444.

Letter

[5] Chhablani JK. Photodynamic therapy for polypoidal choroidal vasculopathy... J Ocul Pharmacol Ther. 2010 Feb;26(1):91-5. *Journal of Ocular Pharmacology & Therapeutics* 2010;26(5):529-529.

Letter

[6] Chhablani JK. Disadvantages of photodynamic therapy for polypoidal choroidal vasculopathy... Indian J Ophthalmol. 2010 Jul-Aug;58(4):291-6. *Indian J Ophthalmol* 2010;58(6):552-553.

Letter

[7] Chhablani JK. Photodynamic therapy for polypoidal choroidal vasculopathy. *Am J Ophthalmol* 2010;150(5):754-755.

Letter

[8] Chhablani JK. The long-term data of photodynamic therapy (PDT) for polypoidal choroidal vasculopathy (PCV). *Retina* 2011;31(1):196-7; author reply 197-8.

Letter

[9] Forte R. 1 - year follow-up after intravitreal bevacizumab alone and in combination with photodynamic therapy for AMD and PCV. *Acta Ophthalmol (Oxf)* 2011;89(4):e373.

Letter

[10] Fukushima Y, Gomi F, Ohji M, Tano Y. Massive subretinal hemorrhage after photodynamic therapy for polypoidal choroidal vasculopathy after macular translocation surgery. *Jpn J Ophthalmol* 2007;51(4):307-9.

Not controlled

[11] Gomi F, Sawa M, Wakabayashi T, Sasamoto Y, Suzuki M, Tsujikawa M. Efficacy of intravitreal bevacizumab combined with photodynamic therapy for polypoidal choroidal vasculopathy. *Am J Ophthalmol* 2010;150(1):48-54.e1.

Control contained PDT

[12] Hara R, Kawaji T, Inomata Y, Tahara J, Sagara N, Fukushima M, et al. Photodynamic therapy alone versus combined with intravitreal bevacizumab for neovascular age-related macular degeneration without polypoidal choroidal vasculopathy in Japanese patients. *Graefes Archive for Clinical & Experimental Ophthalmology* 2010;248(7):931-6.

No PCV, both arms PDT

[13] Kim SJ, Yu HG. Efficacy of combined photodynamic therapy and intravitreal bevacizumab injection versus photodynamic therapy alone in polypoidal choroidal vasculopathy. *Retina* 2011;31(9):1827-34.

Control contained PDT

[14] Koh HJ, Kim YM. Long Term Evaluation of Recurrence after Combination of PDT with Anti-VEGF vs. Anti-VEGF Monotherapy for Polypoidal Choroidal Vasculopathy. *ARVO Meeting Abstracts* 2012;53(6):2061.

No VA

[15] Kumar Chhablani J. Photodynamic therapy for polypoidal choroidal vasculopathy. *Graefes Archive for Clinical & Experimental Ophthalmology* 2011;249(5):791; author reply 793.

Letter

[16] Lee MW, Yeo I, Wong D, Ang CL. Photodynamic therapy with verteporfin for polypoidal choroidal vasculopathy. *Eye* 2009;23(6):1417-1422.

No control

[17] Lee WK, Kim KS, Kim W, Lee SB, Jeon S. Responses to photodynamic therapy in patients with polypoidal choroidal vasculopathy consisting of polyps resembling grape clusters. *Am J Ophthalmol* 2012;154(2):355-365.e1.

No control

[18] Lee YA, Yang CH, Yang CM, Ho TC, Lin CP, Huang JS, et al. Photodynamic therapy with or without intravitreal bevacizumab for polypoidal choroidal vasculopathy: two years of follow-up. *Am J Ophthalmol* 2012;154(5):872-880.e2.

Control contained PDT

[19] Mak ST, Wong ACM. Single-session combined photodynamic therapy with verteporfin and intravitreal anti-vascular endothelial growth factor therapy for chronic central serous

chorioretinopathy: A pilot study at 12-month follow-up. *Graefe's Archive for Clinical and Experimental Ophthalmology* 2013;251(1):401-402.

Letter

[20] Mori R, Yuzawa M, Lee Z, Haruyama M, Akaza E. Response to 'photodynamic therapy for polypoidal choroidal vasculopathy'. *Graefe's Archive for Clinical and Experimental Ophthalmology* 2011;249(5):793.

Letter

[21] Pai SA, Shetty R. Sequential therapy with intravitreal bevacizumab and photodynamic therapy for idiopathic polypoidal choroidal vasculopathy. *Acta Ophthalmol (Oxf)* 2009;87(7):806-7.

Case series

[22] Sagong M, Lim S, Chang W. Reduced-fluence photodynamic therapy combined with intravitreal bevacizumab for polypoidal choroidal vasculopathy. *Am J Ophthalmol* 2012;153(5):873-882.e2.

No control, compared to baseline

[23] Sakurai M, Kitahashi M, Yokouchi H, Baba T, Kubota-Taniai M, Yamamoto S. Therapeutic Efficacy of Intravitreal Ranibizumab Combined with Reduced-Fluence Photodynamic Therapy for Polypoidal Choroidal Vasculopathy. *ARVO Meeting Abstracts* 2012;53(6):2062.

No VA for control group

[24] Sato T, Kishi S, Matsumoto H, Mukai R. Combined photodynamic therapy with verteporfin and intravitreal bevacizumab for polypoidal choroidal vasculopathy. *Am J Ophthalmol* 2010;149(6):947-954.e1.

No control, compared to baseline

[25] Tomita K, Tsujikawa A, Yamashiro K, Ooto S, Tamura H, Otani A, et al. Treatment of polypoidal choroidal vasculopathy with photodynamic therapy combined with intravitreal injections of ranibizumab. *Am J Ophthalmol* 2012;153(1):68-80.e1.

Treatment arms are according to previous treatment not current.

[26] Yamashita A, Shiraga F, Shiragami C, Ono A, Tenkumo K. One-year results of reduced-fluence photodynamic therapy for polypoidal choroidal vasculopathy. *Am J Ophthalmol* 2010;149(3):465-71.e1.

No control, compared to baseline

[27] Yamashita A, Shiraga F, Shiragami C, Shirakata Y, Fujiwara A. Two-year results of reduced-fluence photodynamic therapy for polypoidal choroidal vasculopathy. *Am J Ophthalmol* 2013;155(1):96-102.e1.

No control, compared to baseline

[28] Yu H, Kim S. Efficacy of Photodynamic Therapy With or Without Intravitreal Anti-VEGF Injection for the Treatment of Polypoidal Choroidal Vasculopathy. *ARVO Meeting Abstracts* 2010;51(5):900.

Control contained PDT

APPENDIX 8: FULL PAPER EXCLUDES FROM QUESTION 3

[1] Viola F, Mapelli C, Villani E, Tresca Carducci F, Vezzola D, Ratiglia R. Sequential combined treatment with intravitreal bevacizumab and photodynamic therapy for retinal angiomatous proliferation. *Eye* 2010;24(8):1344-1351.

No control group.

[2] Saito M, Shiragami C, Shiraga F, Kano M, Iida T. Comparison of intravitreal triamcinolone acetonide with photodynamic therapy and intravitreal bevacizumab with photodynamic therapy for retinal angiomatous proliferation. *Am J Ophthalmol* 2010;149(3):472-81.e1.

Not an RCT, control = PDT+IVTA

[3] Saito M, Iida T, Kano M. Combined intravitreal ranibizumab and photodynamic therapy for retinal angiomatous proliferation. *Am J Ophthalmol* 2012;153(3):504-514.e1.

Not an RCT, no control

[4] Nakano S, Honda S, Oh H, Kita M, Negi A. Effect of photodynamic therapy (PDT), posterior subtenon injection of triamcinolone acetonide with PDT, and intravitreal injection of ranibizumab with PDT for retinal angiomatous proliferation. *Clinical Ophthalmology* 2012;6:277-82.

Control = PDT, retrospective nonrandomised patients

[5] Bakri SJ, Ekdawi NS. Intravitreal triamcinolone and bevacizumab combination therapy for refractory choroidal neovascularization with retinal angiomatous proliferation. *Eye* 2008;22(7):978-980.

Case study

[6] Atmani K, Voigt M, Le Tien V, Querques G, Coscas G, Soubrane G, et al. Ranibizumab for retinal angiomatous proliferation in age-related macular degeneration. *Eye* 2010;24(7):1193-1198.

No PDT, retrospective nonrandomised

[7] Aa R, Td P, D V, I V, Mm M, A K, et al. Intravitreal ranibizumab, intravitreal ranibizumab with PDT, and intravitreal triamcinolone with PDT for the treatment of retinal angiomatous proliferation: a prospective study. *Retina (Philadelphia, Pa.)* 2009;29(4):536-44.

Duplicate

[8] Department of Health (UK). The impact of indocyanine green (ICG) angiography in multiple diagnostic imaging for the management of exudative age-related macular degeneration (ARMD): a single blind prospective randomised controlled trial of fluorescein angiography vs FA & ICG. 2005. ISRCTN64352175. http://www.controlled-trials.com/mrct/trial/2210783/retina*+AND+angioma*+AND+prolifer*

No treatment

[9] Ahmadi H, Homayouni M, Taei R. Combined Photodynamic Therapy and Intravitreal Bevacizumab With or Without Triamcinolone for Retinal Angiomatous Proliferation. *American Academy of Ophthalmology* 2007:261.

Control contains PDT

APPENDIX 9: GRADE EVIDENCE PROFILES

Author(s):

Date: 2013-10-29

Question: Should bevacizumab be used for neovascular age-related macular degeneration?

Settings:

Bibliography: Lang et al. (2013). Update of Systematic Review by M van der Reis et al. (Interventions for neovascular age-related macular degeneration). KSR Ltd. York, UK.

No of studies	Design	Risk of bias	Quality assessment				No of patients		Effect		Quality	Importance
			Inconsistency	Indirectness	Imprecision	Other considerations	Bevacizumab	Control	Relative (95% CI)	Absolute		
Mean change in number of letters (follow-up 6 months; measured with: ETDRS letters; range of scores: -15-35; Better indicated by higher values)												
72	randomised trials ^{1,2}	serious ³	no serious inconsistency	no serious indirectness	no serious imprecision	none	1288	2721 ^{1,2,4}	-	mean 14.95 higher (12.55 to 17.16 higher) ^{1,2}	⊕⊕⊕○ MODERATE	CRITICAL
Mean change in number of letters (follow-up 12 months; measured with: ETDRS letters; range of scores: -15-35; Better indicated by higher values)												
72	randomised trials ^{1,2}	serious ³	no serious inconsistency	no serious indirectness	no serious imprecision	none	1288	2721 ^{1,2,4}	-	mean 18.49 higher (15.6 to 21.38 higher) ^{1,2}	⊕⊕⊕○ MODERATE	CRITICAL

¹ 72 studies were included in the network analyses, with a total of 14,315 patients.

² For the comparison of treatment effects across treatments a network meta-analysis method was used. The primary outcome measure was a continuous measure of the change in the numbers of letters (measured with visual acuity charts) which was calculated as the mean value at follow-up minus the mean value at baseline. The mean and standard deviation (SD) or standard error (SE) of the change in number of letters was extracted for each treatment group in each study. To perform the meta-analysis the original individual patient dataset was recreated using simulation by sampling from a normal distribution with the mean and SD of the corresponding treatment group within each study. Due to chance, the means and SD of these simulated values will be slightly different to those reported by the study and so they were corrected using a simple linear transformation. A linear regression model was used with the outcome variable being the mean change in the number of letters at six months (using the simulated individual patient data) and the independent variables were the drug and an indicator variable for study (to adjust for differences between patient characteristics and study methods between studies by preserving randomisation). This analysis was repeated for the outcome of mean change in the number of letters at 12 months. The analyses comparing all drugs to placebo are presented in the main report, to enable ranking of the drugs.

³ The pooled result is based on a network meta-analysis including 72 studies which provide direct and indirect evidence for each comparison. Network analyses usually include high levels of heterogeneity. In addition, individual studies were not quality assessed.

⁴ Control includes all control groups: placebo, sham interventions, usual care, etc.

Author(s):

Date: 2013-10-29

Question: Should ranibizumab be used for neovascular age-related macular degeneration?

Settings:

Bibliography: Lang et al. (2013). Update of Systematic Review by M van der Reis et al. (Interventions for neovascular age-related macular degeneration). KSR Ltd. York, UK.

No of studies	Design	Risk of bias	Quality assessment				No of patients		Effect		Quality	Importance
			Inconsistency	Indirectness	Imprecision	Other considerations	Ranibizumab	Control	Relative (95% CI)	Absolute		
Mean change in number of letters (follow-up 6 months; measured with: ETDRS letters; range of scores: -15-35; Better indicated by higher values)												
72 ^{1,2}	randomised trials	serious ³	no serious inconsistency	no serious indirectness	no serious imprecision	none	6986	2721 ^{1,2,4}	-	mean 14.31 higher (12.45 to 16.16 higher) ^{1,2}	⊕⊕⊕○ MODERATE	CRITICAL
Mean change in number of letters (follow-up 12 months; measured with: ETDRS letters; range of scores: -15-35; Better indicated by higher values)												
72	randomised trials ^{1,2}	serious ³	no serious inconsistency	no serious indirectness	no serious imprecision	none	6986	2721 ^{1,2,4}	-	mean 19.16 higher (17.02 to 21.31 higher) ^{1,2}	⊕⊕⊕○ MODERATE	CRITICAL

¹ For the comparison of treatment effects across treatments a network meta-analysis method was used. The primary outcome measure was a continuous measure of the change in the numbers of letters (measured with visual acuity charts) which was calculated as the mean value at follow-up minus the mean value at baseline. The mean and standard deviation (SD) or standard error (SE) of the change in number of letters was extracted for each treatment group in each study. To perform the meta-analysis the original individual patient dataset was recreated using simulation by sampling from a normal distribution with the mean and SD of the corresponding treatment group within each study. Due to chance, the means and SD of these simulated values will be slightly different to those reported by the study and so they were corrected using a simple linear transformation. A linear regression model was used with the outcome variable being the mean change in the number of letters at six months (using the simulated individual patient data) and the independent variables were the drug and an indicator variable for study (to adjust for differences between patient characteristics and study methods between studies by preserving randomisation). This analysis was repeated for the outcome of mean change in the number of letters at 12 months. The analyses comparing all drugs to placebo are presented in the main report, to enable ranking of the drugs.

² 72 studies were included in the network analyses, with a total of 14,315 patients.

³ The pooled result is based on a network meta-analysis including 72 studies which provide direct and indirect evidence for each comparison. Network analyses usually include high levels of heterogeneity. In addition, individual studies were not quality assessed.

⁴ Control includes all control groups: placebo, sham interventions, usual care, etc.

Author(s):

Date: 2013-11-06

Question: Should VEGF trap be used for neovascular age-related macular degeneration?

Settings:

Bibliography: Lang et al. (2013). Update of Systematic Review by M van der Reis et al. (Interventions for neovascular age-related macular degeneration). KSR Ltd. York, UK.

No of studies	Design	Risk of bias	Quality assessment				No of patients		Effect		Quality	Importance
			Inconsistency	Indirectness	Imprecision	Other considerations	VEGF trap	Control	Relative (95% CI)	Absolute		
Mean change in number of letters (follow-up 12 months; measured with: ETDRS letters; range of scores: -15-35; Better indicated by higher values)												
72 ^{1,2}	randomised trials	serious ³	no serious inconsistency	no serious indirectness	no serious imprecision	none	1836	2721 ^{1,2,4}	-	mean 19.07 higher (16.31 to 21.82 higher) ^{1,2}	⊕⊕⊕○ MODERATE	CRITICAL

¹ 72 studies were included in the network analyses, with a total of 14,315 patients.

² For the comparison of treatment effects across treatments a network meta-analysis method was used. The primary outcome measure was a continuous measure of the change in the numbers of letters (measured with visual acuity charts) which was calculated as the mean value at follow-up minus the mean value at baseline. The mean and standard deviation (SD) or standard error (SE) of the change in number of letters was extracted for each treatment group in each study. To perform the meta-analysis the original individual patient dataset was recreated using simulation by sampling from a normal distribution with the mean and SD of the corresponding treatment group within each study. Due to chance, the means and SD of these simulated values will be slightly different to those reported by the study and so they were corrected using a simple linear transformation. A linear regression model was used with the outcome variable being the mean change in the number of letters at six months (using the simulated individual patient data) and the independent variables were the drug and an indicator variable for study (to adjust for differences between patient characteristics and study methods between studies by preserving randomisation). This analysis was repeated for the outcome of mean change in the number of letters at 12 months. The analyses comparing all drugs to placebo are presented in the main report, to enable ranking of the drugs.

³ The pooled result is based on a network meta-analysis including 72 studies which provide direct and indirect evidence for each comparison. Network analyses usually include high levels of heterogeneity. In addition, individual studies were not quality assessed.

⁴ Control includes all control groups: placebo, sham interventions, usual care, etc.

Author(s):
Date: 2013-10-30
Question: Should TPA or gas be used in patients with both AMD and (sub)macular bleeding?
Settings:
Bibliography: Lang et al. (2013). Three Additional Questions For WAMD Dutch Guidelines (Searches And Extractions). KSR Ltd. York, UK.

No of studies	Design	Quality assessment					No of patients		Effect		Quality	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TPA or gas	Control	Relative (95% CI)	Absolute		
Visual Acuity (follow-up 1-35 months; measured with: Measured by either log MAR or ETRDS letters; range of scores: -0.3-1; Better indicated by lower values)												
28	observational studies ¹	very serious ^{1,2}	very serious ²	serious ²	serious ³	none	725 ⁴	-	-	- ⁵	@000 VERY LOW	CRITICAL

¹ case series
² All studies were likely to be biased 'due to ill-defined or inadequately measured outcome' and 'due to inadequate adjustment for all important prognostic factors'.
³ Different inclusion criteria in studies
⁴ Eyes
⁵ Mean change (logMAR)

Author(s):
Date: 2013-10-30
Question: Should PDT alone or combined with anti-VEGF be used in patients with PCV?
Settings:
Bibliography: Lang et al. (2013). Three Additional Questions For WAMD Dutch Guidelines (Searches And Extractions). KSR Ltd. York, UK.

No of studies	Design	Quality assessment					No of patients		Effect		Quality	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PDT alone or combined with anti-VEGF	Control	Relative (95% CI)	Absolute		
Visual Acuity (follow-up 3-23 months; measured with: Measured by either log MAR or ETRDS letters; range of scores: -0.3-1; Better indicated by lower values)												
11	observational studies ^{1,2}	very serious ^{2,3,4,5}	very serious ³	serious ³	serious ⁶	none	379 ⁷	-	-	- ⁸	@000 VERY LOW	CRITICAL

¹ 9 case series and 2 RCTs
² case series
³ All studies were likely to be biased 'due to ill-defined or inadequately measured outcome' and 'due to inadequate adjustment for all important prognostic factors'.
⁴ Bias 'due to a non-representative or ill-defined sample of patients' was unclear in 10 out of 11 studies.
⁵ The two RCTs were of high risk of bias (all quality items scored high risk, except selective outcome reporting).
⁶ Different inclusion criteria in studies
⁷ Eyes
⁸ Mean change (logMAR)

Author(s):
Date: 2013-10-30
Question: Should treatments of RAP (retinal angiomatous proliferation) be used in patients with PCV?
Settings:
Bibliography: Lang et al. (2013). Three Additional Questions For WAMD Dutch Guidelines (Searches And Extractions). KSR Ltd. York, UK.

No of studies	Design	Quality assessment					No of patients		Effect		Quality	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatments of RAP (retinal angiomatous proliferation)	Control	Relative (95% CI)	Absolute		
Visual Acuity (follow-up 36 months; measured with: Measured by log MAR; range of scores: -0.3-1; Better indicated by lower values)												
1	randomised trials	very serious ¹	serious ^{1,2}	no serious indirectness	no serious imprecision	none	12 ^{3,4}	12 ^{3,5}	-	mean 0.07 higher (0 to 0 higher) ^{4,5,6}	@000 VERY LOW	CRITICAL

¹ All quality items scored high risk of bias
² Only one RCT included
³ Eyes
⁴ Intervention = PDT + RBZ
⁵ Control = PDT + IVTA
⁶ Mean change (logMAR)

APPENDIX 10: SUMMARY OF FINDINGS TABLES

bevacizumab for neovascular age-related macular degeneration

Patient or population: patients with neovascular age-related macular degeneration

Settings:

Intervention: bevacizumab

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk Bevacizumab	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Mean change in number of letters ETDRS letters. Scale from -15 to 35. Follow-up: 6 months	The mean mean change in number of letters in the control groups was 2.25 ETDRS letters ^{1,2}	The mean mean change in number of letters in the intervention groups was 14.95 higher (12.55 to 17.16 higher) ^{1,2}		4009 (72 studies ^{1,2})	⊕⊕⊕⊕ ³ moderate ³	
Mean change in number of letters ETDRS letters. Scale from -15 to 35. Follow-up: 12 months	The mean mean change in number of letters in the control groups was 2.09 ETDRS letters ^{1,2}	The mean mean change in number of letters in the intervention groups was 18.49 higher (15.6 to 21.38 higher) ^{1,2}		4009 (72 studies ^{1,2})	⊕⊕⊕⊕ ³ moderate ³	

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ For the comparison of treatment effects across treatments a network meta-analysis method was used. The primary outcome measure was a continuous measure of the change in the numbers of letters (measured with visual acuity charts) which was calculated as the mean value at follow-up minus the mean value at baseline. The mean and standard deviation (SD) or standard error (SE) of the change in number of letters was extracted for each treatment group in each study. To perform the meta-analysis the original individual patient dataset was recreated using simulation by sampling from a normal distribution with the mean and SD of the corresponding treatment group within each study. Due to chance, the means and SD of these simulated values will be slightly different to those reported by the study and so they were corrected using a simple linear transformation. A linear regression model was used with the outcome variable being the mean change in the number of letters at six months (using the simulated individual patient data) and the independent variables were the drug and an indicator variable for study (to adjust for differences between patient characteristics and study methods between studies by preserving randomisation). This analysis was repeated for the outcome of mean change in the number of letters at 12 months. The analyses comparing all drugs to placebo are presented in the main report, to enable ranking of the drugs.

² 72 studies were included in the network analyses, with a total of 14,315 patients.

³ The pooled result is based on a network meta-analysis including 72 studies which provide direct and indirect evidence for each comparison. Network analyses usually include high levels of heterogeneity. In addition, individual studies were not quality assessed.

ranibizumab for neovascular age-related macular degeneration

Patient or population: patients with neovascular age-related macular degeneration

Settings:

Intervention: ranibizumab

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk Ranibizumab	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Mean change in number of letters ETDRS letters. Scale from -15 to 35. Follow-up: 6 months	The mean mean change in number of letters in the control groups was 2.25 ETDRS letters ^{1,2}	The mean mean change in number of letters in the intervention groups was 14.31 higher (12.45 to 16.16 higher) ^{1,2}		9707 (72 studies ^{1,2})	⊕⊕⊕⊕ ³ moderate ³	
Mean change in number of letters ETDRS letters. Scale from -15 to 35. Follow-up: 12 months	The mean mean change in number of letters in the control groups was 2.09 ETDRS letters ^{1,2}	The mean mean change in number of letters in the intervention groups was 19.16 higher (17.02 to 21.31 higher) ^{1,2}		9707 (72 studies ^{1,2})	⊕⊕⊕⊕ ³ moderate ³	

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ For the comparison of treatment effects across treatments a network meta-analysis method was used. The primary outcome measure was a continuous measure of the change in the numbers of letters (measured with visual acuity charts) which was calculated as the mean value at follow-up minus the mean value at baseline. The mean and standard deviation (SD) or standard error (SE) of the change in number of letters was extracted for each treatment group in each study. To perform the meta-analysis the original individual patient dataset was recreated using simulation by sampling from a normal distribution with the mean and SD of the corresponding treatment group within each study. Due to chance, the means and SD of these simulated values will be slightly different to those reported by the study and so they were corrected using a simple linear transformation. A linear regression model was used with the outcome variable being the mean change in the number of letters at six months (using the simulated individual patient data) and the independent variables were the drug and an indicator variable for study (to adjust for differences between patient characteristics and study methods between studies by preserving randomisation). This analysis was repeated for the outcome of mean change in the number of letters at 12 months. The analyses comparing all drugs to placebo are presented in the main report, to enable ranking of the drugs.

² 72 studies were included in the network analyses, with a total of 14,315 patients.

³ The pooled result is based on a network meta-analysis including 72 studies which provide direct and indirect evidence for each comparison. Network analyses usually include high levels of heterogeneity. In addition, individual studies were not quality assessed.

VEGF trap for neovascular age-related macular degeneration

Patient or population: patients with neovascular age-related macular degeneration

Settings:

Intervention: VEGF trap

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk VEGF trap				
Mean change in number of letters ETDRS letters. Scale from -15 to 35. Follow-up: 12 months	The mean mean change in number of letters in the control groups was 2.09 ETDRS letters ^{1,2}	The mean mean change in number of letters in the intervention groups was 19.07 higher (16.31 to 21.82 higher) ^{1,2}		4557 (72 studies ^{1,2})	⊕⊕⊕⊕ moderate ³	

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ 72 studies were included in the network analyses, with a total of 14,315 patients.

² For the comparison of treatment effects across treatments a network meta-analysis method was used. The primary outcome measure was a continuous measure of the change in the numbers of letters (measured with visual acuity charts) which was calculated as the mean value at follow-up minus the mean value at baseline. The mean and standard deviation (SD) or standard error (SE) of the change in number of letters was extracted for each treatment group in each study. To perform the meta-analysis the original individual patient dataset was recreated using simulation by sampling from a normal distribution with the mean and SD of the corresponding treatment group within each study. Due to chance, the means and SD of these simulated values will be slightly different to those reported by the study and so they were corrected using a simple linear transformation. A linear regression model was used with the outcome variable being the mean change in the number of letters at six months (using the simulated individual patient data) and the independent variables were the drug and an indicator variable for study (to adjust for differences between patient characteristics and study methods between studies by preserving randomisation). This analysis was repeated for the outcome of mean change in the number of letters at 12 months. The analyses comparing all drugs to placebo are presented in the main report, to enable ranking of the drugs.

³ The pooled result is based on a network meta-analysis including 72 studies which provide direct and indirect evidence for each comparison. Network analyses usually include high levels of heterogeneity. In addition, individual studies were not quality assessed.

TPA or gas for patients with both AMD and (sub)macular bleeding

Patient or population: patients with both AMD and (sub)macular bleeding

Settings:

Intervention: TPA or gas

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk TPA or gas				
Visual Acuity Measured by either log MAR or ETDRS letters. Scale from -0.3 to 1. Follow-up: 1-35 months	See comment	See comment	Not estimable	725 (28 studies ¹)	⊕⊕⊕⊕ very low ^{1,2,3}	case series; mean ranged from 2.23 lower to 0.7 higher

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ case series

² All studies were likely to be biased 'due to ill-defined or inadequately measured outcome' and 'due to inadequate adjustment for all important prognostic factors'.

³ Different inclusion criteria in studies

PDT alone or combined with anti-VEGF for patients with PCV

Patient or population: patients with PCV

Settings:

Intervention: PDT alone or combined with anti-VEGF

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk PDT alone or combined with anti-VEGF				
Visual Acuity Measured by either log MAR or ETDRS letters. Scale from -0.3 to 1. Follow-up: 3-23 months	See comment	See comment	Not estimable	379 (11 studies ^{1,2})	⊕⊕⊕⊕ very low ^{2,3,4,5,6}	case series; mean ranged from 0.31 lower to 0.13 higher

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ 9 case series and 2 RCTs

² case series

³ All studies were likely to be biased 'due to ill-defined or inadequately measured outcome' and 'due to inadequate adjustment for all important prognostic factors'.

⁴ Bias 'due to a non-representative or ill-defined sample of patients' was unclear in 10 out of 11 studies.

⁵ The two RCTs were of high risk of bias (all quality items scored high risk, except selective outcome reporting).

⁶ Different inclusion criteria in studies

treatments of RAP (retinal angiomatous proliferation) for patients with PCV

Patient or population: patients with PCV

Settings:

Intervention: treatments of RAP (retinal angiomatous proliferation)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk Treatments of RAP (retinal angiomatous proliferation)				
Visual Acuity Measured by log MAR. Scale from: -0.3 to 1. Follow-up: 36 months	The mean visual acuity in the control groups was -0.29 logMAR¹	The mean visual acuity in the intervention groups was 0.07 higher (0 to 0 higher) ^{1,2,3}		24 (1 study)	⊕⊕⊕⊕ very low ^{4,5}	case series; mean ranged from 0.31 lower to 0.13 higher

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Mean change (logMAR)

² Intervention = PDT + RBZ

³ Control = PDT + IVTA

⁴ All quality items scored high risk of bias

⁵ Only one RCT included