TECHNOLOGY ASSESSMENT REPORT

ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR TREATMENT FOR DIABETIC MACULAR EDEMA

Prepared for:

Medicare Evidence Development & Coverage Advisory Committee (MEDCAC)

Prepared by:

March 5, 2012

Daniel A. Ollendorf, MPH, ARM	Chief Review Officer
Kristen Migliaccio-Walle, BS	Senior Decision Scientist
Jennifer A. Colby, PharmD	Research Associate
Steven D. Pearson, MD, MSc, FRCP	President

Table of Contents

ABOUT ICER

The Institute for Clinical and Economic Review (ICER), based at the Massachusetts General Hospital's Institute for Technology Assessment (ITA), provides independent evaluation of the clinical effectiveness and comparative value of new and emerging technologies.

ICER's academic mission is funded through a diverse combination of sources, including health plans, manufacturers, private foundations, state agencies, and the federal government; funding is not accepted from manufacturers or private insurers to perform reviews of specific technologies.

No funding for this work was received from manufacturers of any product included in this review.

More information on ICER's mission and policies can be found at www.icer-review.org.

ACKNOWLEDGMENTS

ICER wishes to acknowledge the individuals listed below for their expert views on the clinical management of diabetic macular edema as well as their review of the draft report. Despite their input, neither the methods nor the content of the evidence review presented in this report should be taken as a representation of their personal views.

Juan E. Grunwald, MD
Professor of Ophthalmology, Hospital of the University of Pennsylvania and Presbyterian Medical Center
Director, Vivian S. Lasko Ocular Vascular Laboratory, Sheie Eye Institute

Manju Subramanian, MD
Associate Professor of Ophthalmology, Boston University School of Medicine
Vice Chairman, Clinical Services, Boston University Eye Associates, Inc.

Demetrios Vavvos, MD, PhD
Assistant Professor of Ophthalmology, Harvard University Medical School
Joan W. Miller Scholar, Retina
Attending Physician, Massachusetts Eye and Ear Infirmary

ICER would also like to acknowledge Elkan Halpern, PhD, Director of Statistics, Massachusetts General Hospital Institute for Technology Assessment, and Chris Cameron, MSc, Lead, Health Economics, Canadian Agency for Drugs and Technologies in Health, for their assistance on development of the statistical methods employed in this review.

STRUCTURED ABSTRACT

OBJECTIVES: To conduct a systematic review of the evidence on the clinical effectiveness and potential harms of intravitreal agents which inhibit vascular endothelial growth factor (VEGF) in patients with diabetic macular edema (DME).

DATA SOURCES: Databases searched included MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. Searches were conducted using multiple terms and subject headings, were limited to English-language reports, and focused on reports of randomized controlled trials (RCTs) and observational studies published between January 2000 and December 22, 2011. Searches were supplemented by manual reference review. Additional Web searches were conducted to identify relevant data presented at scientific meetings but not yet published in peer-reviewed journals.

REVIEW METHODS: Abstract screening, full-text article evaluation, data abstraction, and quality ratings were all subject to dual review; disagreements were resolved by consensus. Quality ratings were assigned to RCTs and observational studies based on the methods of the U.S. Preventive Services Task Force.

Candidate studies included those analyzing at least one intravitreal anti-VEGF agent (i.e., pegaptanib [Macugen®], bevacizumab [Avastin®], ranibizumab [Lucentis®], or aflibercept [Eylea™]), in comparison to macular laser, sham injection, or other control (single-arm observational studies were also eligible). Outcomes of interest must have included measures of improvement in best-corrected visual acuity (BCVA), expressed in terms of letters of vision gained or converted to such values from other standard formats. Studies evaluating outcomes associated with a one-time anti-VEGF injection were excluded.

Analyses were both qualitative and quantitative. Direct meta-analyses were conducted on BCVA measures for each anti-VEGF agent of interest; indirect comparisons also were performed for each anti-VEGF pair.

RESULTS: A total of 15 RCTs and 8 observational studies were included; 11 of 15 RCTs were rated fair- or good-quality. No RCT directly compared any of the anti-VEGF agents of interest. Patients represented a broad spectrum of those with DME, including duration of diabetes, level of glycemic control, comorbidity, and baseline visual acuity. In contrast to RCTs of the other agents, Avastin studies tended to be small, single-center, and investigator-initiated. Improvement in visual acuity relative to control was seen with all agents; findings were notable for their (1) consistency and stability across multiple timepoints; and (2) similarity across agents, with improvements averaging 4-9 letters. Meta-analyses confirmed qualitative findings, with no statistically-significant and/or consistent differences between agents in the mean difference (relative to control) in the average change in BCVA or the rate ratio of the percentage of patients achieving a gain of ≥10 letters.

No discernible differences in the potential harms of anti-VEGFs, including ocular events (e.g., eye infections, glaucoma), MI, stroke, and other systemic events, as well as death, were noted in the multicenter trials or observational studies of Macugen, Lucentis, and Eylea. Data on harms from Avastin RCTs and observational studies were underreported and lacking in detail when reported. Examination of harms data from RCTs and observational studies directly comparing anti-VEGF agents for neovascular age-related macular degeneration yielded no conclusive evidence of differences in safety.

CONCLUSIONS: Evidence accumulated to date suggests that anti-VEGF therapy improves visual acuity in patients with diabetic macular edema relative to macular laser treatment or sham injection. Our analyses suggest no significant difference in clinical performance among the anti-VEGF agents, however. The systemic side effect profile of Avastin relative to Lucentis or other anti-VEGF agents remains the greatest element of uncertainty.

1. Background

Diabetic macular edema (DME) is a consequence of microvascular changes in the retina that develop as a result of the progression of diabetic retinopathy (Romero-Aroca, 2010, 2011). In DME, weakened capillaries in the eye allow fluid to cross the blood-retinal barrier, which in turn results in retinal thickening and an accumulation of fluid in the retinal tissue of the macula. Patients suffering from DME typically experience blurred vision, floaters and dark areas in the visual field, and/or poor night vision. Untreated, DME causes moderate vision loss in 25-30% of patients, and severe vision loss and blindness in many of these individuals (ETDRS, 1985; Morello, 2007; Wong, 2009; Romero-Aroca, 2010).

Diabetic retinopathy impacts approximately 2 million adults age ≥65 years in the U.S. (The Eye Diseases Prevalence Research Group, 2004). Of these, approximately 15% are estimated to have DME (Lee, 2008; Wong, 2006), and one-half of DME patients may have "clinically significant" disease. Clinically significant macular edema is characterized by retinal thickening or hard exudates close to the macula center, the area most critical for preserving vision, or particularly large zones of retinal thickening within range of the macula center (ETDRS, 1985). DME may also be characterized as "focal", in which disease is caused primarily by microaneurysms and other foci of vascular abnormalities, or "diffuse", in which widespread dilated retinal capillaries are the primary manifestation (Ali, 1997).

Several studies have found that levels of independence and ability to perform activities of daily living such as shopping, meal preparation, and using the telephone decreases as visual acuity worsens (Hazel, 2000; Haymes, 2002; Bibby, 2007). Worsening DME may also affect diabetes self-care, as patients report difficulties with reading nutrition and medication labels, testing blood sugar, and checking feet for wounds or sores (James, 2012). In these studies and others (Brown, 2002), overall quality of life measures have been highly correlated with visual acuity irrespective of disease etiology. For example, studies that employ the National Eye Institute Visual Function Questionnaire (NEI VFQ-25), a vision-specific measure of quality of life and functional ability, have found that improvements in visual acuity correspond to significantly improved perceptions of quality of life (Suñer, 2009; Cahill, 2005; Miskala, 2003; Miskala, 2004).

Beyond decrements in daily functioning and quality of life, clinically significant macular edema has been associated with poorer survival in patients with adult-onset diabetes (Hirai, 2008). Over a 20-year period, the risk of death from all causes among patients with clinically significant macular edema was estimated to be 40%, a rate twice that of patients without the condition (Hirai, 2008).

The economic impact of DME and its treatment is also substantial. Findings from a recent study indicate that patients with DME consume more resources overall than patients with diabetes who do not have DME, resulting in significantly higher direct medical costs to Medicare (Shea, 2008). A diagnosis of DME resulted in expenditures of $11,290 and $33,620 at 1 and 3 years, respectively, a 30% increase over patients without DME when controlling for other factors. Importantly, these data were collected prior to the introduction of expensive biologic agents to treat DME and other ocular disorders (see Section 2). The impact on overall utilization and costs of the introduction of these new agents is unknown.

2. DME Management Alternatives

Treatment for patients with DME focuses on reducing inflammation and halting or slowing fluid leakage into the retinal space, with the ultimate goals of stopping visual loss and potentially restoring vision (Cheung, 2010). The approach to treatment depends on the severity of underlying retinopathy and whether the macular edema is clinically significant. Patients presenting with clinically significant macular edema are candidates for focal laser therapy; intravitreal injections of agents that inhibit vascular endothelial growth factor (VEGF) and/or corticosteroids are also increasingly used in these patients (AAO, 2008). For patients with macular edema that is not clinically significant, ophthalmologists may elect to monitor their patients for progression, treat them with focal or grid laser therapy (particularly in patients with severe non-proliferative or high-risk proliferative retinopathy), or utilize adjunctive agents such as anti-VEGF agents (AAO, 2008).

Input from our clinical experts indicated that the goals of treatment differ by approach. Laser surgery is used primarily to stabilize vision, while the use of anti-VEGF agents is intended to incrementally improve vision. In certain circumstances, experts stated that they would start treatment with laser alone (e.g., DME affecting less than 25% of the retina), but in most other circumstances, treatment with anti-VEGF agents could be initiated first. Patients could receive laser treatment concurrently; alternatively, laser could be used as "rescue" option for patients not responding to anti-VEGF therapy. Our experts also agreed that injections of triamcinolone or other steroids are no longer in favor given their propensity to cause cataracts and glaucoma in a significant percentage of patients.

In terms of decisions regarding which eye to treat, experts estimated that approximately one-third of the patients they see have clinically significant DME in both eyes. If only one eye is affected severely, there was general consensus that the worse-seeing eye would be treated, but there was also acknowledgment that DME, even if currently severe in only one eye, will eventually become bilateral.

In addition to the primary treatments described above, glycemic control along with management of blood pressure and lipid control remain crucial to controlling the rate of progression of diabetic retinopathy and preserving vision (ADA, 2011).

2.1 Laser Photocoagulation

Findings from the Early Treatment Diabetic Retinopathy Study (ETDRS) in the mid-1980s confirmed the role of laser photocoagulation as the gold standard for treatment of DME (Ali, 1997; Cheung, 2010). A large, multicenter trial sponsored by the National Eye Institute (n=3,928), the ETDRS examined patients with varying degrees of diabetic retinopathy at baseline, with or without DME (ETDRS, 1985). DME patients with clinically significant macular edema who received prompt laser therapy exhibited significantly less visual loss than those receiving deferred laser therapy beginning at 8 months of follow-up and continuing through 36 months.

Laser therapy is applied in a focal or diffuse (grid) manner, depending on the clinical presentation of the macular edema and concurrent diabetic retinopathy (Romero-Aroca, 2010). Focal laser therapy targets individual microaneurysms, while grid laser therapy involves the application of laser burns in a grid pattern to areas of diffuse leakage (Romero-Aroca, 2010). Treatment usually involves an initial session, occurring in the doctor's office, with the use of topical anesthesia (Mayo Clinic, 2011; Fraser, 2011). Full effects of therapy may not be seen for up to 6 months following treatment (Ali, 1997).

Response to laser therapy is difficult to predict, but it is often the case that patients who respond to such treatment tend to be those with less visual impairment when therapy is initiated, while those whose vision worsens despite laser therapy tend to have thicker, more edematous retinas (NICE, 2011). Repeated treatment with laser photocoagulation within 2-4 months may be indicated, depending on the level of resolution of the edema and stabilization of vision (AAO, 2008).

Side effects of laser photocoagulation may include transient blurred vision, accumulation of laser scars, neovascularization, and fibrosis (Mayo Clinic, 2011; Fraser, 2011). While laser therapy is effective in halting the progression of vision loss, complete reversal of vision loss and/or improvement in visual acuity are uncommon (Cheung, 2010).

2.2 Anti-VEGF Agents

VEGF is a mediator of vascular permeability known to play a role in abnormal vessel growth and leakage in the eye (Romero-Aroca, 2010; Cheung, 2010). Clinical development efforts have focused on VEGF inhibition as one pathway to improving vision in DME and other ocular conditions. Inhibition of VEGF interferes with the downstream cascade of events that contributes to neovascularization, inflammation and edema (Romero-Aroca, 2010).

Currently, there are 3 anti-VEGF agents approved by regulators in one or more countries for one or more ophthalmologic indications: ranibizumab (Lucentis®, Genentech, Inc.), pegaptanib (Macugen®, Eyetech Inc.), and aflibercept/VEGF Trap-Eye (Eylea™, Regeneron Pharmaceuticals, Inc.). A fourth agent, bevacizumab (Avastin®, Genentech, Inc.), is a cancer chemotherapeutic agent used in several disease states such as colorectal cancer, glioblastoma, and metastatic renal cell carcinoma (Avastin package insert, 2011); it has also seen significant off-label use as an intravitreal injection (Avery, 2006). Regulatory status of each agent in the U.S., Europe, Canada, and Australia can be found on Table 1 on page 11.

Macugen

Macugen is an RNA aptamer that selectively binds $VEGF_{165}$, a particular isoform of VEGF (Macugen package insert, 2011). Macugen was approved by the FDA, HealthCanada, and the European Medicines Agency (EMA) for treatment of neovascular age-related macular degeneration (AMD) in 2004, 2005, and 2006 respectively. In early 2011, Pfizer, Inc., the European distributor of Macugen, submitted an application to EMA for an additional indication of DME. In July 2011, Pfizer withdrew its application, believing that the

recommendation from the internal evaluating committee of the EMA would not provide a favorable risk-benefit assessment for this additional indication (Pfizer Ltd., 2011).

Avastin

Avastin is a recombinant humanized monoclonal antibody to VEGF type A comprised of human and mouse DNA. Avastin was approved for use in the U.S. in 2004 as an intravenous chemotherapeutic agent, and was first used intravenously to treat ocular disease in patients with neovascular AMD by an investigator familiar with the molecule (Steinbrook, 2006). Further studies have been conducted with Avastin administered as an intravitreal injection, and this agent has seen increasing off-label use for multiple ocular conditions including DME (Rosenfeld, 2006). Currently Avastin has not been submitted for regulatory approval for any intraocular use (Table 1, page 11).

Lucentis

Lucentis is an antibody fragment developed from the identical parent antibody as Avastin; both medications are manufactured by Genentech, Inc. Lucentis was approved for neovascular AMD in the U.S. in 2006, and is authorized for multiple ocular conditions in Australia, Canada, and Europe (Table 1). It has a licensed indication for use in DME in Australia, Canada and Europe. A supplemental biologics license application for DME has been submitted to the FDA with a decision expected in late summer 2012.

Avastin and Lucentis differ in two ways. First, Avastin is a much larger molecule, approximately 3 times the size of Lucentis (Wong, 2007). It has been suggested that Avastin's greater molecular weight is associated with increases in both ocular and systemic half-life, which may in turn increase the potential for adverse effects (Lim, 2011; Meyer, 2011). The plasma half-life of intravitreal Avastin has been estimated to be approximately 21 days, vs. 0-5 days for Lucentis (Wong, 2007).

There is also a difference in the cost of these agents. While the cost of intravenous use of Avastin for chemotherapeutic purposes can exceed $4,000 per infusion, the wholesale price of a single 100 mg vial is approximately $500; when compounded into fractional doses for intravitreal use, the cost per injection has been reported to range from $17 - $50 (Rosenfeld, 2006). In contrast, a single 0.5 mg injection of Lucentis has a wholesale price of $1,950 (Steinbrook, 2006).

The similarities between Avastin and Lucentis, as well as uncertainty regarding how the effectiveness and safety of these agents compares, led to the development and conduct of the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT), which randomized patients to 4 groups based on agent (Lucentis vs. Avastin) and dosing regimen (monthly vs. as-needed) (Martin, 2011). One-year results have been released, and suggest equivalent efficacy and similar rates of death and specific adverse events known to be associated with systemic use of Avastin (e.g., myocardial infarction, stroke). However, the proportion of patients with "serious systemic adverse events" was higher with Avastin. This finding was the subject of some controversy, however, as hospitalizations for any cause were included in this definition and excess risks were not seen in organ systems typically associated with systemic anti-VEGF therapy (Rosenfeld, 2011). Detailed safety

findings from the CATT trial are available in Section 7 of this report under "Potential Harms".

Two-year results from CATT are expected to be presented at the Association for Research in Vision and Ophthalmology (ARVO) meeting in May, 2012.

Eylea

Eylea is a fusion protein that binds VEGF-A and placental growth factor, another angiogenic factor (Eylea package insert, 2011). Approved for neovascular AMD in the U.S. in November 2011, Eylea is currently under review for use in central retinal vein occlusion in Europe. It is not currently being considered for any indications in Australia and Canada.

Table 1 Regulatory status of anti-VEGF medications in ocular conditions

	Macugen	Avastin	Lucentis	Eylea
Australia	Not currently under consideration for ocular conditions	Not currently under consideration for ocular conditions	Approved for use in: • Neovascular AMD • DME • ME following CRVO	Not currently under consideration for ocular conditions
Canada	Approved for use in: • Neovascular AMD	Not currently under consideration for ocular conditions	Approved for use in: • Neovascular AMD • DME • ME following CRVO	Not currently under consideration for ocular conditions
Europe	Approved for use in: • Neovascular AMD Application for use in DME withdrawn	Not currently under consideration for ocular conditions	Approved for use in: • Neovascular AMD • DME • ME following CRVO	Under review for: • ME following CRVO
United States	Approved for use in: • Neovascular AMD	Not currently under consideration for ocular conditions	Approved for use in: • Neovascular AMD • ME following CRVO Under review for: • DME	Approved for use in: • Neovascular AMD

AMD: age-related macular degeneration; CRVO: central retinal vein occlusion; DME: diabetic macular edema; ME: macular edema

Administration of the different anti-VEGF agents may be done in an ophthalmologist's office, under aseptic conditions with use of topical anesthesia and appropriate antibiotics. The volume of each injected agent is identical: 0.05 ml. The approved dose of Lucentis is 0.5 mg, given every 4 weeks (Lucentis package insert, 2010). The observed dose of Avastin for intravitreal use is 1.25 mg, also given every 4 weeks. Macugen is dosed as 0.3 mg every 6 weeks (Macugen package insert, 2011), and Eylea is given as 2 mg every 4 weeks for 3 months, and every 8 weeks thereafter. Ophthalmologists observe their patients following the procedure for signs of increased intraocular pressure and infection, and patients typically use antibiotic eye drops for 2-3 days as a prophylactic measure.

As described previously, input from clinical experts indicated that anti-VEGF agents may be used alone or in combination with laser photocoagulation, given before, after, or at the same time as anti-VEGF therapy. Opinions were mixed on the course and number of injections required; our experts reported that between 3 and 6 injections are typically given at 4-6 week intervals before vision is re-evaluated and a decision made about the need for further treatment. The course of treatment is heavily dependent on the level of glycemic control maintained: the poorer the control, the greater the number of injections required.

In terms of the choice of anti-VEGF agent, our experts said that in the clinical practices of which they are aware, Avastin is used as the initial anti-VEGF agent for the majority of patients because it is viewed as equally effective compared to Lucentis and more affordable. Macugen was not used as an initial agent, although there was mention of its occasional use as a maintenance therapy once patients appear to be "leveling off" on other anti-VEGF agents. Eylea was not currently being used because it was viewed as too new an agent on which to form an opinion.

Because Avastin is only commercially-available as a solution to be administered intravenously as a chemotherapeutic agent, it must be compounded and repackaged to be used as an intravitreal injection. In the summer of 2011, 4 clusters of infectious endophthalmitis were identified in patients receiving repackaged Avastin, raising concerns about variability in aseptic technique among compounding pharmacies (Goldberg, 2012). Two of these clusters were at Veteran's Administration (VA) hospitals, prompting the VA to suspend use of Avastin for ocular conditions until further notice (Berkrot, 2011). The VA has since rescinded this order, and both the VA and American Academy of Ophthalmology (AAO) have issued new guidelines requiring the repackaging of Avastin by accredited compounding pharmacies that adhere to U.S. Pharmacopeial Convention (USP) quality standards for aseptic technique (VA National PBM Bulletin, 2011; AAO, 2012).

Patients who should not receive intravitreal anti-VEGF agents are those with ocular or periocular infections, as well as those with hypersensitivities to the medications or their components. Side effect profiles vary among the different agents and include transient eye pain, cataracts, vitreous hemorrhage, retinal detachment, and endophthalmitis (Boscia, 2010; Cheung, 2010; AAO, 2008). Use of intravitreal anti-VEGF agents may also be associated with systemic cardiovascular and/or thrombotic events. For further discussion on this issue see "Potential Harms" in Section 7 of this report.

2.3 Additional Therapies

Although not part of the scope of this assessment, other therapeutic alternatives are available to treat DME, particularly for patients who are refractory to initial treatment.

Vitrectomy
In patients refractory to laser therapy or with macular traction (i.e., tension on the central macular area of the retina, causing blurred or distorted vision), vitrectomy is an alternate approach, involving the removal of fluid and scar tissue from the middle of the eye through a small incision (Mayo Clinic, 2011; Boscia, 2010). Potential benefits of this surgical procedure include a decrease in macular edema and diminished risk of retinal neovascularization (Stefánsson, 2009); associated risks include iris neovascularization, cataract formation, and endophthalmitis (AAO, 2008). Changes in visual acuity with vitrectomy have yet to be confirmed in randomized, placebo-controlled trials, however, and its place in therapy remains undetermined (Boscia, 2010; AAO, 2008).

Intravitreal Corticosteroids
While the intravitreal use of corticosteroids in DME has not received FDA approval, several agents have been investigated as therapeutic alternatives given their anti-inflammatory properties. The primary medication used is triamcinolone acetonide; potential benefits include improved visual acuity and decreased macular edema (Boscia, 2010; Cheung, 2010). Adverse effects, however, are observed frequently with the use of intravitreal triamcinolone, including increased intraocular pressure, cataract progression, development of glaucoma, and endophthalmitis (Boscia, 2010; AAO, 2008). In the era of anti-VEGF agents, many ophthalmologists consider the use of intravitreal corticosteroids as a last-choice alternative. Current studies are investigating triamcinolone and other corticosteroids as adjunctive therapy to laser therapy or other intravitreal injections (Boscia, 2010).

2.4 Ongoing Clinical Studies

(from www.clinicaltrials.gov)

There are 13 ongoing clinical studies of DME treatment for which patient recruitment is complete. Table 2 on the following page summarizes the 7 largest of these studies (>50 patients). One relatively small (n=53) study (IBERA-DME) is a head-to-head trial of Lucentis and Avastin; this study is scheduled to complete in September 2012.

As previously mentioned, while not specific to DME, the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) will release 24-month efficacy and safety data for Lucentis and Avastin at the ARVO Annual Meeting in May 2012.

Table 2 Ongoing studies in DME

NCT ID	Name	Trial Sponsor	Design	Primary Outcomes	Populations	Treatment Arms	Estimated Completion Date
NCT00444600	LRT for DME	Diabetic Retinopathy Clinical Research Network; National Eye Institute (NEI); Allergan; Genentech	Phase III	Δ BCVA with various subgroup analyses Δ OCT; # of Injections in First Year; # of Laser Treatments Received Prior to the 1 Year Visit	n=691 BCVA <= 78 and >= 24; OCT ≥250 microns	Triamcinolone Acetonide 4 mg + laser; Lucentis 0.5 mg + laser; Sham injection + laser; Lucentis 0.5 mg + deferred laser	Mar 2012
NCT00901186	RED-ES	Novartis Pharmaceuticals	Phase II	Δ BCVA 12-month. [Time Frame: 4 weeks]	n=84 HbA1c < 11.0%; CSME in ≥1 eye; BCVA of 78 to 25 letters; OCT >250µm	Lucentis 0.5 mg vs. laser	Jul 2012
NCT01487629	IBERA-DME	University of Sao Paulo; Fundação de Amparo à Pesquisa do Estado de São Paulo	Phase II	Δ BCVA; Δ CSFT	n=53 BCVA ≥ 20/40 and < 20/800; OCT thickness > 300 µm	Avastin 1.5 mg; Lucentis 0.5 mg	Sep 2012

NCT ID	Name	Trial Sponsor	Design	Primary Outcomes	Populations	Treatment Arms	Estimated Completion Date
NCT01171976	RETAIN	Novartis Pharmaceuticals	Phase III	Δ BCVA VFQ-25 and EQ-5D Δ CSFT	n=374 HbA1c ≤ 12.0% BCVA ≥ 39 and ≤ 78 letters	Lucentis 0.5 mg "treat & extend"+ laser; Lucentis 0.5 mg "treat & extend"; Lucentis 0.5 mg PRN	May 2013
NCT00168337 NCT00168389	---	Allergan	Phase III	% with BCVA ≥ 15 Letters from Baseline [Time Frame: Baseline, 36 Months]	n=510 per study Decrease in VA in at least 1 eye; VA in other eye no worse than 20/200	Dexamethasone 700 µg Dexamethasone 350 µg Sham	Jun 2013
NCT01363440	VISTA DME	Regeneron Pharmaceuticals; Bayer	Phase III	Δ BCVA [Time Frame: week 100]	n=466 BCVA of 73 to 24 letters in the study eye	Eylea vs. laser	Nov 2014

BCVA=best corrected visual acuity; CRT=central retinal thickness; CSME=clinically significant macular edema; CSFT=central subfield thickness; HbA1c=glycosylated hemoglobin test; OCT=optical coherence tomography; PRN=as needed;

3. Clinical Guidelines

American Academy of Ophthalmology, 2008
"There is insufficient evidence to make definitive treatment recommendations for intravitreal therapies, but anti-VEGF agents and intraocular corticosteroids show promise in treating diabetic macular edema and neovascularization. The visual gain found in the initial 1 year follow-up is encouraging, but longer follow-up is needed to determine which treatment strategies are most beneficial for patients with DME."
Available at:
http://one.aao.org/CE/PracticeGuidelines/PPP_Content.aspx?cid=d0c853d3-219f-487b-a524-326ab3cecd9a

American Diabetes Association, 2011
"Laser photocoagulation therapy is indicated to reduce the risk of vision loss in patients with high-risk proliferative diabetic retinopathy, clinically significant macular edema, and in some cases of severe non-proliferative diabetic retinopathy." Intravitreal injections with anti-VEGF or other agents are not listed in the treatment recommendations section of this document.
http://care.diabetesjournals.org/content/35/Supplement_1/S11.full

American Optometric Association, 2009
"Intravitreal steroid injections, such as triamcinolone, and intravitreal anti-VEGF injections, such as- Avastin or Lucentis, are sometimes used in clinical practice to treat macular edema, despite the lack of definitive studies on their effectiveness or safety."
http://www.aoa.org/documents/CPG-3.pdf

Joslin Diabetes Center, 2010
"For clinically significant macular edema, focal laser and/or intravitreal Lucentis injection is generally indicated regardless of level of retinopathy. If a patient is receiving intravitreal Lucentis injection, follow-up may be as frequent as monthly. Intravitreal injections of steroids and anti-VEGF agents other than Lucentis are sometimes used in clinical practice to treat macular edema despite limited studies on their effectiveness or safety to date. These modalities are currently under rigorous investigation to further define their role."
http://www.joslin.org/bin_from_cms/Adult_guidelines_-edit_7_2_10.pdf

4. Previous Technology Assessments

Health technology assessment documents evaluating treatment modalities for DME were searched for from agencies in the U.S., Canada, the U.K., Germany, and Australia. No reports were found from the U.S., Germany, or Australia.

Canadian Agency for Drugs and Technologies in Health, 2012
Lucentis has been submitted to the Common Drug Review (CDR) and is currently under review by the Canadian Agency for Drugs and Technologies in Health (CADTH) for use in patients with DME. A recommendation is anticipated in March, 2012.
http://www.cadth.ca/media/cdr/tracking/cdr_tracking_Lucentis.pdf

National Institute for Health and Clinical Excellence, 2011
In final guidance (November 2011) from the National Institute for Health and Clinical Excellence (NICE), Lucentis was not recommended for use in patients with DME. The primary reason for this was that the committee believed there remained too many uncertainties around the assumptions of the economic analysis, thereby concluding that Lucentis is "not an effective use of NHS resources". A new review of the evidence may be considered as early as March 2013.
http://www.nice.org.uk/nicemedia/live/13621/57342/57342.pdf

Scottish Medicines Consortium, 2011
In June 2011 the National Health Service (NHS) in Scotland conducted a single technology assessment of Lucentis use in patients with DME. Despite strong clinical evidence of effect and a positive association with patient reported outcomes, the Scottish Medicines Consortium (SMC) concluded that Lucentis was not recommended for use in patients with DME. The basis for this decision was insufficient evidence justifying the economic impact of Lucentis.
http://www.scottishmedicines.org.uk/files//advice/ranibizumab_Lucentis_FINAL_JUNE_2011_amended_050711_for_website.pdf

5. ICER Systematic Review

5.1 MEDCAC Panel Discussion and Voting Questions

The panel discussion and voting questions are listed below and available at this link. While the listed anti-VEGF questions pertain only to Avastin, Lucentis, and Macugen, Eylea was nevertheless considered for this review because of its anti-VEGF properties and availability of evidence on use in DME.

Outcomes of Interest: CMS is most interested in meaningful changes to beneficiaries' visual function that enable their independent accomplishment of routine daily activities. We also seek the panel's input on the preferred measures for determining progression in clinical trials of DME treatment.

Discussion Question

1. In a 2005 MEDCAC on wet age-related macular degeneration (WAMD), the following commonly used outcomes or intermediate endpoint measures were discussed:
    a. Visual acuity
    b. VFQ 25
    c. Dilated eye exam (to assess retinal damage)
    d. Grade of diabetic retinopathy (DR)
    e. Amsler grid
    f. Extent/progression as measured by retinal photography
    g. Fluorescein angiography (to assess blood flow/leakage in retina and choroid)
    h. Visual fields
    i. Ocular coherence tomography (OCT) (to assess retinal thickening, other damage)

    Please discuss the suitability of these measures for assessing DME treatment-related health outcomes, i.e., benefits and harms.

Voting Questions

For the voting questions, use the following scale identifying level of confidence - with 1 being the lowest or no confidence and 5 representing a high level of confidence.

1 *Low*	*2*	*3* *Intermediate*	*4*	*5* *High*

2. How confident are you that there is adequate evidence to determine whether or not DME management using intravitreal targeted anti-VEGF treatment improves patient health outcomes compared to DME management without intravitreal targeted anti-VEGF treatment?

1 *Low*	*2*	*3* *Intermediate*	*4*	*5* *High*

3. If the result of Question 2 is at least intermediate (mean vote ≥ 2.5), how confident are you that there is adequate evidence to conclude that DME management using intravitreal targeted anti-VEGF treatment improves patient health outcomes compared to DME management without intravitreal targeted anti-VEGF treatment?

1 *Low*	*2*	*3* *Intermediate*	*4*	*5* *High*

4. Please discuss any patient characteristics, treatment regimens, or other factors that may have important impacts on the degree of patient benefit or harm from these treatments.

5. If the result of Question 3 is at least intermediate (mean vote ≥ 2.5), how confident are you that there is also adequate evidence to determine whether or not there are clinically meaningful differences in health outcomes among the available intravitreal targeted anti-VEGF treatments for the management of DME?

1 *Low*	*2*	*3* *Intermediate*	*4*	*5* *High*

6. If the result of Question 4 is at least intermediate (mean vote ≥ 2.5), how confident are you that there is adequate evidence to conclude that there are clinically meaningful differences in the health outcomes when comparing the following available intravitreal targeted anti-VEGF treatments?

1 *Low*	*2*	*3* *Intermediate*	*4*	*5* *High*

   a. Ranibizumab (Lucentis) vs. pegaptanib (Macugen)
   b. Bevacizumab (Avastin) vs. pegaptanib (Macugen)
   c. Ranibizumab (Lucentis) vs. bevacizumab (Avastin)

Please discuss whether your conclusions are based on evidence of:

a. Different benefits with similar harms
b. Similar benefits with different harms
c. Different benefits and different harms

7. How confident are you that the conclusions above are generalizable to:

   a. Medicare beneficiaries?
   b. Community-based settings?

1 *Low*	*2*	*3* *Intermediate*	*4*	*5* *High*

Discussion Questions

7. To what extent are the conclusions above generalizable to the management of other forms of diabetic retinal vascular disease beyond DME?
8. Are there significant gaps in the evidence base on the management of diabetic macula edema?
9. What study designs would support the narrowing or closure of these gaps?

5.2 The Evidence

Type of Evidence Considered

The target population for this appraisal was patients diagnosed with DME. Because study populations varied substantially with regard to severity of visual impairment, duration of diabetes and/or DME, receipt of prior DME therapy, level of glycemic control, and other factors, our entry criteria remained broad to reflect the likely diversity of patients presenting for anti-VEGF treatment.

We considered evidence from published randomized controlled trials (RCTs) and observational studies as well as the grey literature. RCTs were the primary source of data on anti-VEGF effectiveness; harms data were also abstracted from these studies, although it was recognized that most RCTs would have been underpowered to detect differences between treatment groups in adverse events. Observational studies with sample sizes >50 eyes were used primarily for supplemental data on harms; in addition, data on long-term effectiveness and/or durability of benefit were also abstracted from these studies as available. In addition, reports of data presented at scientific meetings but not yet published in the peer-reviewed literature were included to add further context to the review. Neither observational studies nor the grey literature were used in any quantitative synthesis of data, due to concerns regarding selection and other biases for the former, and lack of rigorous peer review for the latter.

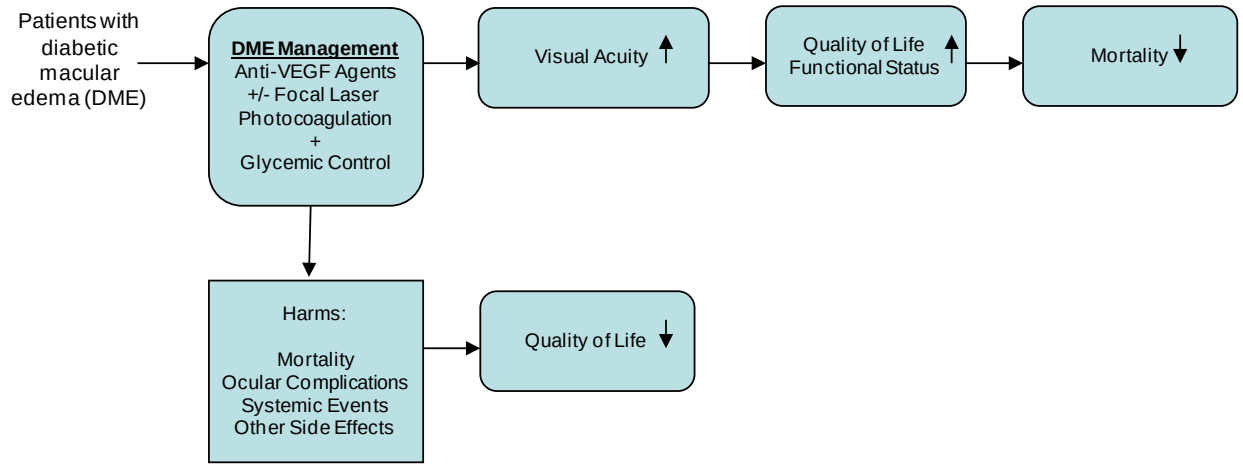
Finally, while not part of the systematic review needed to support discussion of the MEDCAC questions, published studies of the economic impact of the management alternatives of interest are also summarized in this report.

Analytic Framework

The analytic framework for this review is shown in Figure 1 on the following page. Note that the figure is intended to convey the conceptual links involved in evaluating outcomes of anti-VEGF therapy, and are not intended to depict a clinical pathway through which all patients would flow.

There are no data directly demonstrating the impact of anti-VEGF therapies on activities of daily living (e.g., driving), functional status, or mortality, so judgments about the effectiveness of these interventions must rest upon measures of visual acuity and physiologic measurements (see the discussion of outcome measures in Section 6).

Figure 1 Analytic framework: Strategies to improve vision in diabetic macular edema



6. Methods

6.1 Patient Populations

The focus of this technology assessment was on patients with DME. We included studies describing patients with any form of DME, including focal, diffuse, and clinically significant macular edema. We did not employ formal thresholds for DME severity (such as visual acuity or retinal thickness) as entry criteria. We excluded studies of patients with diabetic retinopathy, regardless of severity, unless there was further definition of concurrent macular edema either in all patients or in an identified subgroup with separate measurement of outcomes.

Studies were accepted regardless of prior treatment for DME. We therefore included studies of patients who were completely treatment naïve (no previous therapy for DME), those who had received laser, anti-VEGF, and/or corticosteroid therapy previously, and patients refractory to laser treatment or who were not considered to be good candidates for additional laser sessions. Finally, as described previously, since patients may present for DME treatment at different stages of disease and at different levels of control of underlying diabetes, we did not place limits on studies with respect to age, duration of diabetes or DME, previous DME treatment received, level of glycemic control, or other such factors.

6.2 Interventions

Currently, there are no FDA-approved intravitreal medications for use in DME. Therefore, we evaluated all intravitreal anti-VEGF agents with at least 1 published RCT in a DME population. These included 3 agents that are FDA-approved for use in ocular conditions such as neovascular (wet) AMD and retinal vein occlusion: Lucentis, Macugen and Eylea (note: Lucentis is approved for DME in Europe). Additionally, we included the chemotherapeutic agent Avastin, as it is frequently compounded for intravitreal injection in ocular conditions as previously described (Steinbrook, 2006).

6.3 Comparators

The comparator of primary interest was focal or grid laser photocoagulation, as this is widely considered to be the current gold standard therapy for patients with DME (Cheung, 2010); this was confirmed by expert ophthalmologist input. We accepted any protocol for laser therapy, including randomization to laser as a baseline treatment as well as use of laser as a "rescue" modality for all treatment arms; in this latter instance, use of rescue laser also was abstracted as an outcome of interest (see Section 6.4). Finally, we evaluated data from other comparators in clinical trials, most prominently intravitreal triamcinolone, either as an individual treatment modality or as concurrent therapy.

6.4 Outcomes

Multiple outcome measures to assess the benefits of therapy are available in RCTs of anti-VEGF for DME, including:

- Visual acuity
- Health-related quality of life
- Treatment utilization (need for additional treatment)
- Central retinal thickness (CRT), an indicator of retinal damage
- Extent of retinal leakage
- DME severity

CRT is assessed via optical coherence tomography (OCT), and provides a measure of retinal damage (Virgili, 2007); it has been found to only be modestly correlated with visual acuity changes, however (Browning, 2007). Similarly, fluorescein angiography and fundus photography provide anatomic data—the former to assess the extent of retinal blood flow and leakage, the latter to determine the severity of retinopathy and DME (AAO, 2008; Saine, 2011).

Because CRT, extent of retinal leakage, and DME severity are not directly correlated with changes in vision, the primary measure of effectiveness in anti-VEGF trials, we chose to focus attention in this review on measures of vision change as well as those correlated with visual ability: visual acuity, health-related quality of life, and treatment utilization (i.e., requirements for retreatment as well as rescue laser therapy).

Visual Acuity

Change in visual acuity represents one of the more important outcomes evaluated in clinical trials and in the care for patients with DME (AAO, 2008). Visual acuity refers to how sharp or precise a patient's vision is (Kniestedt, 2003), and is commonly measured as the best-corrected visual acuity (BCVA), an assessment of a person's maximal visual acuity utilizing corrective eyewear. BCVA is reported using a variety of measurements including a count of letters correctly identified on the eye chart, the logarithm of the minimal angle of resolution (logMAR), or in Snellen fractions (Appendix A). Snellen fractions are derived from the Snellen eye chart, a standard clinical tool for evaluating acuity at a distance of 20 feet. A Snellen fraction of 20/20 is considered the reference standard for "normal vision"; for example, a patient who sees at 20/40 is viewing letters at 20 feet that a person with 20/20 sees at 40 feet (Watt, 2003). Visual acuity in patients with DME in available trials ranges from 20/32 – 20/320; within this range, poorer levels of vision are associated with difficulties in "near vision" activities such as reading ordinary newspaper print or finding items on a crowded shelf. Problems with distance vision also occur, such as reading street signs or recognizing faces across a room (Miskala, 2003). Certain aspects of the Snellen chart have been found to lead to imprecise measurements, however, including varying letter size from line to line and different numbers of letters per line (Kniestedt, 2003).

To address these concerns, the ETDRS developed a series of charts to standardize visual acuity evaluation, allowing for accurate and reproducible assessments (Gregori, 2010). Individual line spacing and letter height are geometrically derived to allow for precise mapping to other reporting conventions (Kniestedt, 2003). Each line contains 5 letters; a gain of 10 letters therefore would equal 2 lines of sight, and 15 letters would equal 3 lines.

To reflect the increasing use of ETDRS letters as a standard outcome measure in RCTs, we abstracted visual acuity data (mean change in BCVA) in the form of letters. When studies reported data in logMAR form, we converted baseline and follow-up visual acuity using a standardized conversion equation (Thomson 2005; Holladay, 1997) as follows below:

$$100-(50*\text{logMAR})$$

To convert measures of variance such as standard deviation, we added and subtracted the error measurement to the mean value, obtaining upper and lower ranges of assessed values. We converted logMAR-based figures to letter estimates as described above and divided by 2 to arrive at the distance above or below the mean.

We also abstracted visual acuity data when reported according to specific thresholds of gains or losses of ≥10 or ≥15 letters, which have been designated as representing "clinically significant" changes (Suñer, 2009; Beck, 2007). For example, a person with 20/80 vision is said to have "moderate" vision loss, equivalent to 70 letters on the ETDRS chart (Appendix A). A gain of 15 letters would correspond to 20/40 vision, which is the minimum standard for driver's license renewal in 45 of 50 U.S. states (Shuldiner, 2011).

Health-related Quality of Life (HRQoL)

Generic and vision-specific assessments of HRQoL were abstracted. Outcome scales available for evaluation included the EuroQoL EQ-5D and the National Eye Institute Visual Function Questionnaire (NEI VFQ-25). The NEI VFQ-25 provides vision-specific QoL data within domains such as near vision, driving, and ocular pain, in addition to other more general health domains such as social functioning and mental health (Mangione, 2001). The EQ-5D provides a measure of general health status that can be directly mapped to an estimate of utility using a variety of population norms (Shaw, 2005). All available data were abstracted for any reported domains.

Treatment Utilization

Study protocols varied widely with respect to dosing interval, evaluation for retreatment, and the use of rescue laser therapy. Evaluation of individual treatment utilization provided a benchmark to frame safety and efficacy outcomes. Where available, we abstracted information regarding numbers of injections, numbers of laser treatments and/or proportions of patients receiving rescue therapy and/or retreatment.

Potential Harms

We collected data on adverse events occurring throughout the trials, utilizing the longest recorded follow-up. All events were abstracted regardless of potential attribution to the

study interventions. As described previously, we evaluated serious events that were systemic in nature or specific ocular conditions:

- Endophthalmitis
- Glaucoma
- Stroke
- Myocardial infarction
- Other cardiovascular serious adverse events
- Death

The focus on stroke, myocardial infarction, and all serious cardiovascular events was based on previous documentation of such risks from prior systematic reviews of Avastin as a chemotherapeutic agent (Choueiri, 2011; Galfrascoli, 2010; Geiger-Gritsch 2010; Cao, 2009) as well as its withdrawal from the U.S. market for metastatic breast cancer based on a determination of an unfavorable risk-benefit profile (FDA, 2011). In addition to specific events, we also abstracted data when reported in terms of ***all*** ocular or non-ocular adverse events, as well as numbers of study withdrawals for any reason.

Guidance from our clinical experts suggested that clinicians find the evidence on adverse events from trials of anti-VEGF agents in age-related macular degeneration to be highly relevant for considerations of the safety of these same agents when used for DME. We therefore examined available data from trials directly comparing anti-VEGF agents in neovascular AMD (Martin, 2011; Subramanian, 2010) for additional safety data. Information was also sought from systematic reviews of anti-VEGFs in other ocular conditions to help frame the potential safety issues.

6.5 Timeframes

The timeframe for evaluation of efficacy and safety outcomes differed by study design (see below). Data from included RCTs were appraised at 3-, 6-, 9-, 12-, and 24-month timepoints as available. Safety data were assessed at the latest follow-up timepoint available.

6.6 Study Designs

Data from RCTs and observational studies were considered. RCTs represented the primary source of data on effectiveness and harms and were considered irrespective of sample size. Analyses focused on RCTs where dosing of anti-VEGF therapy reflected that observed in general clinical practice – in other words, patients receive multiple injections before efficacy is evaluated. Several RCTs only evaluated short-term outcomes after a single injection of anti-VEGF therapy; these were typically early experimental studies or those conducted in countries with resource constraints. Such studies were excluded from analyses of effectiveness.

Observational studies were employed to evaluate data on (a) long-term effectiveness and/or durability of clinical benefit, and (b) examination of potential harms. Included

observational studies were limited to those with: evaluation of efficacy outcomes for 1 year or longer, and/or examination of potential harms in studies with sample sizes exceeding 50 eyes and study duration of 6 months or longer. Single-injection RCTs were included in safety analyses only if study duration was at least 6 months. Observational studies were not included in any meta-analysis of data given the likely presence of selection and other attendant biases in these studies.

In addition to published RCTs and observational studies, reports of data presented at scientific meetings but not yet published in the peer-reviewed literature were included in the review. Because these studies were not peer-reviewed, however, findings were only used to provide additional context to qualitative syntheses of study findings, and were not included in any meta-analysis of data.

6.7 Literature Search and Retrieval

We conducted electronic database searches for literature published from January 2000 to December 22, 2011 using MEDLINE, EMBASE and *The Cochrane Central Register of Controlled Trials*, with the precise search criteria listed in Appendix B. Searches were supplemented by manual review of retrieved references. We did not initially place any restrictions on study type. Figure 2 on page 29 provides a flow chart of the search results, in PRISMA format. The major eligibility criteria included:

- Patients with DME/clinically significant macular edema, or identifiable subgroup with separate reporting of outcomes
- Treatment with at least one of the anti-VEGFs of interest, alone or in combination with other therapies
- For RCTs and comparative observational studies, comparison to another anti-VEGF therapy or alternate control
- Studies measuring efficacy/safety outcomes of interest
- English-language only

Study Quality

The quality of all included RCTs was assessed using the framework employed by the U.S. Preventive Services Task Force (USPSTF Procedure Manual, 2008). RCTs were rated "good," "fair," or "poor," using the criteria described below:

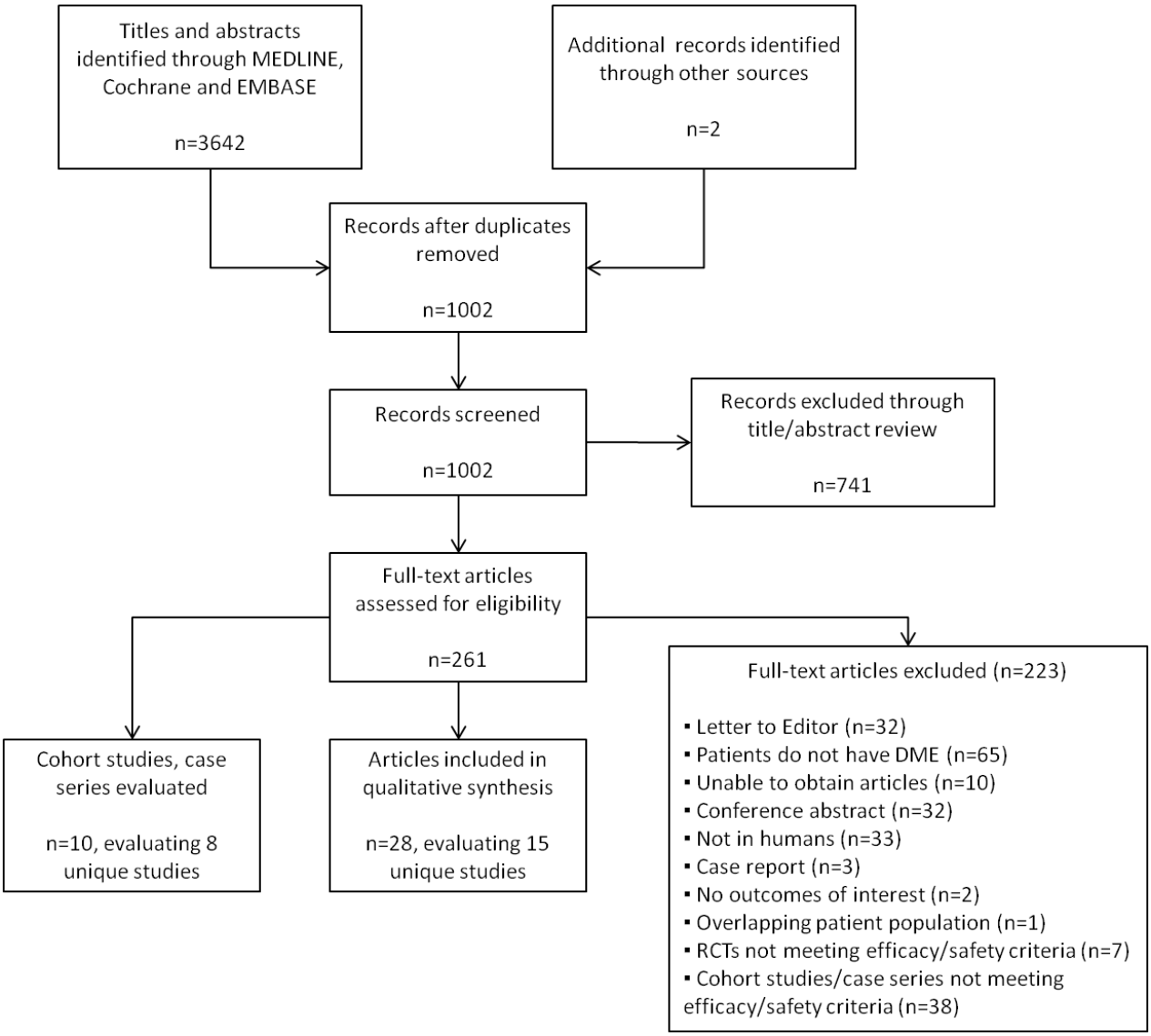
- ***Good:*** Comparable group are assembled initially and maintained throughout the study (follow-up of at least 80%); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention to confounders in analysis. Intention to treat analysis is used.

- ***Fair:*** Generally comparable groups are assembled initially but some question remains whether moderate differences occurred in follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention to treat analysis is done.

- ***Poor:*** Any of the following problems exist: (1) groups assembled initially are not close to being comparable or maintained throughout the study; (2) unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); (3) key confounders are given little or no attention; and (4) intention to treat analysis is *not* conducted.

Ratings of study quality, as well as major quality defects leading to the ratings, were noted in evidence tables. Importantly, poor-quality studies, while given less weight in qualitative discussions of findings, were not explicitly excluded from consideration. These studies were excluded, however, from primary meta-analyses of effectiveness data.

Figure 2 PRISMA style flow chart of included and excluded records



Data Synthesis

Where feasible, estimates of treatment effect were synthesized using meta-analysis, focusing on (a) mean change in BCVA at a common follow-up timepoint; and (b) the percentage of patients gaining ≥10 letters (the most commonly-reported threshold in available RCTs). When direct evidence was deemed to be sufficient, random-effects models were generated based on head-to-head data. Data were deemed to be sufficient if (a) the number of eligible fair or good-quality RCTs was 2 or more; and (b) the measure of interest was reported using uniform methods. The weighted mean difference (WMD) and rate ratio (RR) were the measures of choice for generating pooled estimates of effect for BCVA changes and likelihood of gaining ≥10 letters respectively. Studies rated "poor" were not included in direct meta-analyses, regardless of design. Finally, while cohort and case series studies were not candidates for meta-analyses of treatment effect, qualitative findings from these studies are described for each measure of interest.

Where direct evidence was not available, indirect comparisons were considered. Indirect treatment comparisons were defined as comparisons of 2 or more interventions to a common standard, and were conducted in pairwise fashion using the adjusted indirect comparisons method (Bucher, 1997).

7. Results

A total of 15 RCTs and 8 observational studies were found eligible for review in this assessment. Among these studies none *directly* compared 2 or more anti-VEGF agents. Characteristics of included and excluded studies, including detailed assessments of study quality, are available in Appendix C; full evidence tables with information on clinical benefits and potential harms are available in Appendix D. Detailed summaries of evidence quality and the major RCTs for each anti-VEGF agent are provided in the sections that follow below. Our discussion of the evidence is focused primarily on good- and fair-quality RCTs, but information regarding all included studies is reported in evidence tables.

7.1 Evidence Quality

Of the 15 unique RCTs identified and abstracted, 6 trials (n=2,228) investigated Lucentis, 6 trials (n=625) evaluated Avastin, 2 trials (n=432) assessed Macugen, and 1 trial (n=219) investigated Eylea. While most studies were of fair quality (see Table 3 on the following page), study quality varied somewhat by agent. The RCTs of Lucentis, Macugen, and Eylea, which tended to be large, multicenter studies sponsored by industry or government, were almost exclusively good- or fair-quality trials. While 3 of the 6 RCTs of Avastin were fair quality, all studies were generally smaller, single-center trials, and 3 had flaws serious enough to be judged of poor quality.

Patient inclusion criteria for these trials varied such that a broad range of clinically relevant patient subtypes were evaluated. For example, most RCTs enrolled patients without prior DME treatment (e.g., focal/grid laser, intravitreal steroids) within 3-6 months of study entry, while 2 RCTs enrolled treatment-naïve patients, and 2 RCTs enrolled patients documented as refractory to laser therapy. Across the range of patients enrolled in the RCTs, baseline visual acuity was relatively similar, generally ranging between 55-65 letters on average. These levels correspond to moderate visual impairment (i.e., vision between 20/100 and 20/160), which restricts driving and impairs the ability to read signs and markings, particularly in low light (Dandona, 2006). While some trials excluded patients with relatively poor levels of glycemic control (e.g., HbA1c levels >10-12%), other RCTs did not restrict study entry according to level of glycemic control.

Generally, trial investigators enrolled 1 eye of each eligible patient into the study. In situations where both eyes of a patient were potential candidates, the eye with the worse visual acuity was typically randomized. In 1 study, the eye with the greater central subfield thickness (CST) was selected (Nguyen, 2009). Three studies enrolled both eyes, if eligible, into the study (Lim, 2012; Ahmadieh, 2008; Elman, 2010). Eye selection was left to the discretion of the investigator and patient in 3 other RCTs (Cunningham, 2005; Sultan, 2011; Scott, 2007).

The methods for design of treatment and control arms varied across studies. Most studies included a specific laser treatment protocol as the control arm, whereas other studies had a control arm using laser therapy at the discretion of the treating clinician as a "rescue" option. In most trials, the study drug was used in conjunction with a laser treatment protocol or

rescue laser, but some studies used a study drug alone if the patients being studied were exclusively those who had already received maximal laser treatment.

Masking of patients and investigators was generally well-described. In most studies patients were masked to study treatment through the use of sham interventions (laser or injection). However, some trials did not attempt to disguise the use of laser, and in other reports, it was unclear whether sham or other control injections (e.g., triamcinolone) were given in blinded fashion. Many of the larger RCTs employed a centralized facility for evaluations of visual acuity and retinal thickness, while smaller studies tended to rely on local study staff (some of whom were not completely masked).

Table 3 Study quality of evaluated RCTs

Author	Year	Study Name	Total N	Study Quality
Macugen				
Sultan	2011	Macugen 1013 Study Group	260	Fair
Cunningham	2005	Macugen DR Study Group	172	Fair
Avastin				
Lim	2012	N/A	111	Poor
Michaelides	2010	BOLT	80	Fair
Synek	2010	N/A	60	Poor
Soheilian	2009	N/A	150	Fair
Ahmadieh	2008	N/A	115	Fair
Scott	2007	DRCR.net	109	Poor
Lucentis				
Nguyen	2012	RISE	377	Good
Nguyen	2012	RIDE	382	Good
Mitchell(a)	2011	RESTORE	343	Fair
Elman	2010	DRCR.net	854	Fair
Massin	2010	RESOLVE	151	Fair
Nguyen	2009	READ-2	121	Poor
Eylea				
Do	2011	Da Vinci Study	219	Fair

NOTE: Detailed reporting of study quality assessment available in Appendix C

Study characteristics that were common causes of lower quality ratings included failure to use an intent-to-treat analysis or alternative analytic design to control for study withdrawal; lack of appropriate and documented masking procedures for treatment and outcome assessment; and failure to account for any potential confounders in data analyses. Intent-to-treat analyses were lacking in many RCTs, replaced by "completers-only" analyses or those focusing on a "per-protocol" approach (i.e., subjects with at least 1 injection as well as baseline and at least 1

follow-up assessment). In only a minority of studies were multiple analytic methods applied to evaluate the impact of study attrition on outcomes. Also variable was analysis of visual acuity. While either ETDRS letters or logMAR values were used to track changes, these were evaluated as treatment group effects in some RCTs, as a treatment-by-time interaction in others, and as change from baseline within treatment groups in still others. In addition, some treatment effect estimates accounted for baseline differences in confounders (e.g., baseline visual acuity, HbA1c), while others did not.

7.2 Overview of Major Randomized Controlled Trials

Detailed information on treatment protocols, entry criteria, and other characteristics for all studies can be found in the evidence tables in Appendix D. Below are summaries of the most important trials of each agent, based on considerations of sample size, study quality, and duration of follow-up.

Macugen

Sultan et al. (the "Macugen 1013" study): This was a sham-controlled, double-masked study of 260 patients conducted at 60 centers worldwide that compared Macugen 0.3 mg to sham injection and followed patients for up to 2 years (Sultan, 2011). In the first year, patients received injections every 6 weeks and were candidates for rescue laser therapy beginning at week 18. In the second year, patients were evaluated every 6 weeks for continued injection therapy. Patients were a mean age of 62 years, with a baseline BCVA of approximately 57 letters; the proportion with previous laser therapy was not reported. In a "modified" intent-to-treat analysis (patients with ≥1 baseline VA assessment, ≥1 injection, and ≥1 assessment post-baseline), a significantly greater percentage of Macugen patients gained ≥10 letters relative to sham at 1 year (36.8% vs. 19.7%, p=.0047). Differences in this measure were nonsignificant at 2 years, however, as were changes in the percentage of patients gaining ≥15 letters at either timepoint. Mean BCVA changes favored Macugen at both 1 year (5.2 vs. 1.2 letters, p<.05) and 2 years (6.1 vs. 1.3 letters, p<.01). At 1 year, significantly fewer Macugen patients required laser therapy (23.3% vs. 41.7%, p=.0023); findings were similar at 2 years.

Cunningham et al. (the "Macugen DR" study): In this earlier, double-masked 9-month dose-finding study conducted at 39 centers, 172 patients were randomized to receive Macugen 0.3 mg, 1 mg, or 3 mg, or sham injection every 6 weeks for a minimum of 3 injections (Cunningham, 2005). Rescue laser therapy was allowed after 13 weeks; patients were evaluated for additional injections every 6 weeks. Patients were age 62 years on average and had a mean baseline BCVA of 56 letters; approximately three-quarters of patients had received laser treatment previously. At 9 months, significantly higher percentages of Macugen 0.3 mg patients gained ≥5 (59% vs. 34%, p=.01) and ≥10 (34% vs. 10%, p=.003) letters relative to sham injection. Mean BCVA improved by 4.7 letters in the Macugen 0.3 mg group vs. -0.4 letters in the sham group (p=.04); differences vs. sham were nonsignificant for the other Macugen groups. Significantly fewer patients received laser therapy in the Macugen 0.3 mg group vs. sham (25% vs. 48%, p=.042); again, differences were nonsignificant for the other Macugen groups.

Avastin

Michaelides et al. (the "BOLT" study): BOLT was sponsored by the National Institute for Health Research in the U.K., and was a single-center open-label RCT in which a single eye in 80 patients was randomized to receive Avastin 1.25 mg every 6 weeks for 3 months (followed by evaluation every 6 weeks for retreatment) or macular laser therapy at baseline (followed by evaluation every 4 months for retreatment) (Michaelides, 2010). Patients were retreated with only the therapy to which they were randomized; in other words, Avastin patients were not eligible to receive rescue laser therapy. BOLT was one of 2 available Avastin RCTs with 12-month follow-up. Mean age and BCVA at baseline were 64 years and 55 letters respectively; the proportion of patients receiving prior laser therapy was not reported. The median (IQR) change in BCVA at 12 months was 8 (1, 10) for Avastin as compared to -0.5 (-15, 5) for laser therapy (p=.0002). In addition, while no significant difference was noted in the proportion of patients gaining ≥15 letters, the proportion gaining ≥10 letters did differ significantly in favor of Avastin (31.0% vs. 7.9%, p=.01).

Lim et al.: The other 12-month RCT compared Avastin 1.25 mg alone to Avastin plus triamcinolone 2 mg and triamcinolone alone in a single-center, open-label study of 111 eyes in 105 patients in South Korea (Lim, 2012). Patients in each group received 2 injections at 6-week intervals, and were then monitored for retreatment throughout the remainder of follow-up. Two unique features distinguished this study: first, patients with *any* prior treatment for DME, including intravitreal injections and macular laser therapy, were excluded from the study. Second, retreatment was provided by additional Avastin injections alone, even in the triamcinolone group; laser therapy was not made available at any point in the study. Patients were age 60 years on average at baseline; mean BCVA (converted from logMAR) was 68 letters. At 12 months, BCVA improved substantially in all groups (mean of 7.5-8 letters, converted from logMAR estimates). While improvement differed significantly across groups at earlier timepoints, with findings favoring the Avastin+triamcinolone and triamcinolone alone groups, differences were nonsignificant by 12 months (p=.088).

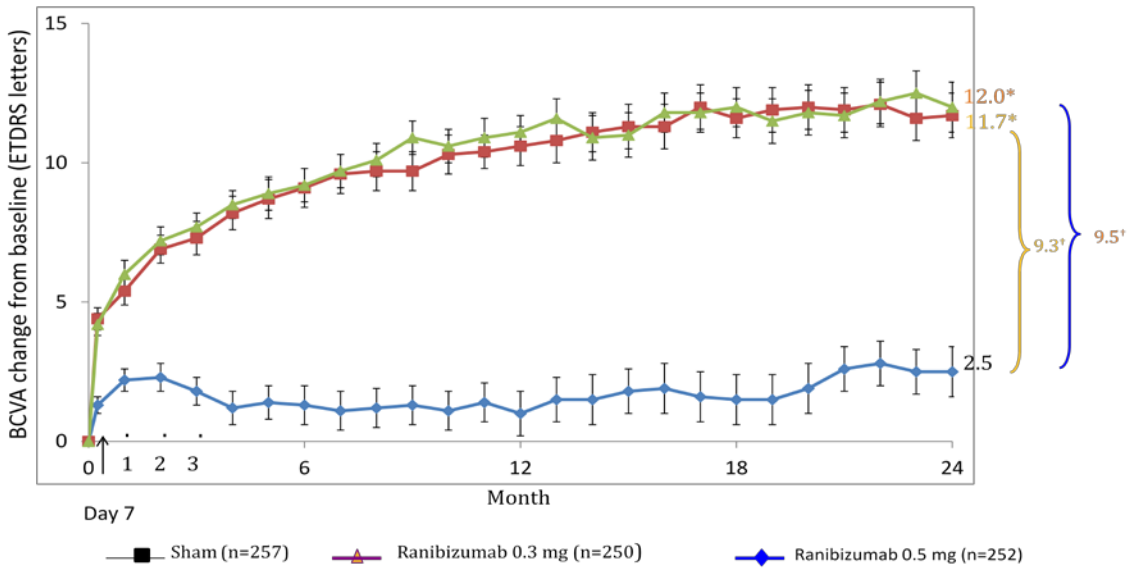
Sohelian et al.: While primary follow-up was limited to 6 months in this single-center RCT conducted in Iran, this study represents the only double-blind RCT of Avastin available in our sample (Sohelian, 2009). A total of 150 eyes in 129 patients were randomized to receive Avastin 1.25 mg plus sham laser, Avastin plus triamcinolone 2 mg plus sham laser, or laser plus sham injection. Patients with previous laser therapy were excluded. A single treatment was given at baseline, and evaluations for retreatment were done every 12 weeks. Mean age at baseline was 61 years; mean BCVA differed by treatment group, ranging from 64 letters for Avastin plus triamcinolone to 73 letters for laser. At 6 months, patients in the Avastin alone group saw an average of 11.5 letters gained (converted from logMAR), versus 3.5 letters in the Avastin + triamcinolone group and 0.05 letters *lost* in the laser group (p=.012 across groups, adjusted for baseline differences). A greater proportion of patients in the Avastin alone group gained >10 letters (31.4% vs. 21.2% and 11.4% for Avastin + triamcinolone and laser respectively), while no patients lost >10 letters (vs. 15.2% and 22.9% in the Avastin + triamcinolone and laser groups respectively); these differences were significant (p=.014). While the magnitude of differences in mean BCVA change and gain/loss of 10 letters was similar at the later, secondary timepoint of 9 months, these differences were not statistically significant, which may have been due to attrition of the sample.

Lucentis

Nguyen et al. (the "RISE" and "RIDE" studies): RISE and RIDE are recently-completed industry-sponsored, multicenter, double-masked studies comparing multiple doses of Lucentis (0.3 and 0.5 mg) to sham injection control (Nguyen, 2012). Patients received monthly injections in a single study eye, and were also evaluated each month for the need for macular laser therapy (which was provided as necessary beginning in month 3). Both studies had a 24-month duration of follow-up, and the primary measure of efficacy was the proportion of patients gaining ≥15 letters on the ETDRS chart.

In RISE, 377 patients were randomized. Patients were age 62 years on average; approximately two-thirds of patients had received laser therapy previously. Mean BCVA ranged from 55-57 letters at baseline. At 24 months, significantly more Lucentis patients gained ≥15 letters compared to sham (44.8% and 39.2% for Lucentis 0.3 and 0.5 mg vs. 18.1% for sham, p≤.0002 for both comparisons). Patient characteristics were comparable in the 382 patients randomized in the RIDE study. Findings from RIDE were also very similar to RISE; the proportions gaining ≥15 letters were 33.6% and 45.7% for Lucentis 0.3 and 0.5 mg vs. 12.3% for sham (p<.0001 for both comparisons). Treatment effects for Lucentis were noted as early as 1 week, as displayed in Figure 3 below for both trials.

Figure 3 Change in best-corrected visual acuity by month, RISE/RIDE studies



Source: Nguyen et al. Ophthalmology 2012 (Epub ahead of print); doi:10.1016/j.ophtha.2011.12.039
*p<.0001 vs. sham; +unadjusted mean differences vs. sham

In both studies, over 24 months of follow-up, substantially more sham patients required laser treatment compared to patients receiving Lucentis (70-74% vs. 20-39% for Lucentis, p<.0001 for all comparisons vs. sham).

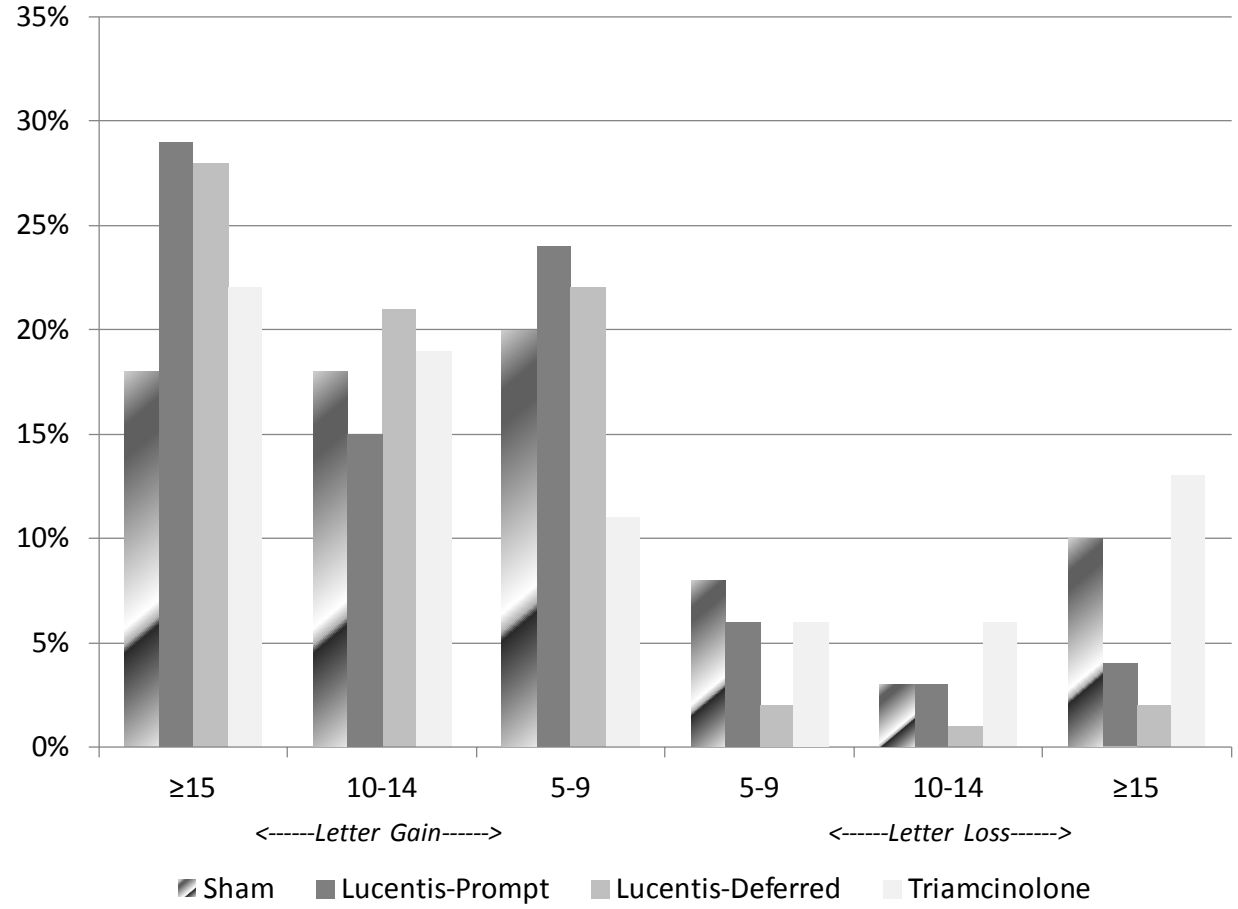
Mitchell et al. (the "RESTORE" study): RESTORE was an industry-sponsored trial conducted at 73 centers in 13 countries (Mitchell(a), 2011). A total of 345 patients were randomized to

receive Lucentis 0.5 mg plus sham laser, Lucentis 0.5 mg plus laser, or sham injection plus laser and were followed for 12 months. Patients were treated monthly for 3 months and then evaluated for retreatment between months 3 and 11. Patients were age 63 years on average, and had a mean baseline BCVA of 64 letters; the proportion of patients with prior laser therapy was not reported. At 12 months of follow-up, mean (SD) changes in BCVA were 6.1 (6.4) for the Lucentis group, 5.9 (7.9) for the Lucentis + laser group, and 0.8 (8.6) for laser alone, ($p<.0001$ vs. laser for both comparisons). While not tested statistically, substantially more patients in the Lucentis treatment arms gained ≥5, 10, or 15 letters relative to those receiving laser, and fewer patients lost ≥10 or 15 letters.

Elman et al. (the "DRCR.net" study): DRCR.net is an NIH-sponsored study being conducted at 52 sites in the U.S. Patients will be followed for up to 3 years; to date, findings at 1 and 2 years have been reported (Elman, 2010; Elman, 2011). A total of 854 eyes of 691 patients were randomized to receive Lucentis 0.5 mg plus prompt laser therapy (3-10 days after initial injection), Lucentis plus deferred laser (given at week 24 or later), triamcinolone 4 mg plus prompt laser, or sham injection plus prompt laser. Injections were given monthly through month 4, and eyes were reevaluated monthly for retreatment thereafter. Mean age at baseline was 63 years; baseline BCVA averaged 63 letters. Approximately 60% of patients had received prior laser therapy for DME. Through 2 years, mean (SD) BCVA changes were 7 (13) and 9 (14) letters for the Lucentis plus prompt and deferred laser groups respectively, both of which were significantly better than sham (difference in mean change 3.7 and 5.8 respectively, $p\leq.03$ for both comparisons). Changes in the triamcinolone group were similar to sham and did not differ statistically.

This study also statistically evaluated the proportions of patients ending the study in different vision states. Significantly greater proportions of eyes in the Lucentis + deferred laser group gained ≥10 or ≥15 letters relative to sham through 2 years, and significantly fewer numbers of eyes in the group lost ≥10 or ≥15 letters (see Figure 4 on the following page). Among eyes in the Lucentis + prompt laser group, significant differences in comparison to sham were only noted in the proportion gaining ≥15 letters.

Figure 4 Proportions of patients in various vision states after 2 years of follow-up, DRCR.net Lucentis study



Source: Elman et al. Ophthalmology 2011;118(4):609-14

Eylea

Do et al. (the "Da Vinci" study): The sole RCT of Eylea in DME was conducted as a double-masked, sham-controlled study of 4 different Eylea doses and regimens vs. macular laser treatment at 39 sites. Patients (n=221) were followed for 6 months and were eligible for retreatment at different timepoints based on the initial regimen received. Patients were age 62 years on average; mean baseline BCVA was approximately 59 letters. The percentage of patients receiving prior focal or grid laser therapy ranged from 48-67% across treatment groups. At 6 months, mean BCVA improved by 8.5 – 11.4 letters in each Eylea group vs. 2.5 letters in the laser group ($p \leq .009$ for all comparisons). Greater numbers of patients in each Eylea group gained ≥10 and ≥15 letters vs. laser, and fewer patients lost ≥15 letters, but these differences were not statistically tested.

7.3 Clinical Evidence

A detailed review of the available evidence from *all* studies (i.e., RCTs, observational studies, and grey literature) is provided in the sections that follow, organized by type of outcome.

Clinical Benefits

Visual Acuity: Qualitative Review

Improvement in visual acuity was presented primarily in terms of the change from baseline in BCVA, either as the number of letters or in logMAR form. A summary of BCVA letter changes relative to control therapy is presented in detail for each anti-VEGF study in Table 4 on the following page. Two elements of these results are important to consider prior to formal pooling and quantitative synthesis:

(1) In studies reporting findings at multiple timepoints, differences in BCVA improvement seen at earlier timepoints remain relatively stable throughout follow-up, suggesting that results from shorter-term studies are relevant for comparison to longer-term trials. For example, the Sohelian and Amadieh trials of Avastin showed similar levels of BCVA improvement at 3, 6, and 9 months of follow-up (Sohelian, 2009; Amadieh, 2008).

(2) While the average gain in vision relative to control ranged between 0 and 14.5 letters across all studies, the magnitude of improvement was similar across anti-VEGF agents. Most improvements were in the 6-9 letter range in studies of Avastin, Lucentis, and Eylea, regardless of differences in study entry criteria, baseline visual acuity, treatment protocol, or duration of follow-up. Level of improvement was slightly lower for Macugen, ranging from 4-5 letters at 9-24 months of follow-up.

Findings for the percentage of patients gaining ≥10 letters are presented for each agent/study of interest in Table 5 on page 41. Findings echoed those of mean BCVA changes; 21-73% of patients receiving Lucentis, Avastin, or Eylea gained ≥10 letters at 6-24 months of follow-up vs. 5-32% of those randomized to laser or sham injection; rates for drug-treated groups were higher than for control therapy in all studies. While the percentage of Macugen patients with a ≥10 letter gain was significantly higher than that for sham (34-37% vs. 10-20%, p≤.003 for both studies), the magnitude of this difference was not as great as in the other studies.

Less frequently reported was the percentage of patients gaining ≥15 letters. The percentage of such gain was significantly higher than sham/laser in all 6 Lucentis RCTs at 6-24 months of follow-up; rates ranged from 22-46% for Lucentis and 8-18% for sham/laser (Appendix D, Table D1). Rates were also higher in the RCTs of other anti-VEGF agents (9-23% vs. 7-15% for sham/laser), but were nonsignificant, in all likelihood due to small sample sizes.

Table 4 Summary of change in BCVA by anti-VEGF agent and clinical study

Study/Author	Publication Date	Control Strategy	Treatment Strategy	Baseline BCVA	Incremental ΔBCVA versus Control			
					3 months	6 months	12 months	24 months
Macugen								
Macugen 1013 Study/ Sultan	2011	Sham injection	PEG 0.3 mg	57.0	2.2	–	4.0	4.8
Macugen DR Study/Cunningham	2005	Sham injection	PEG 0.3 mg	57.1	2.2	–	5.1[b]	--
			PEG 1 mg	55.0	3.0	–	5.1[b]	–
			PEG 3 mg	57.0	1.2	–	1.5[b]	–
Avastin								
Lim	2012	TRI 2 mg	BEV 1.25 mg	69.0	-7.5	-8.5	0	–
			BEV + TRI 2 mg	68.0	0	-4.5	-0.5	–
BOLT/Michaelides	2010	Laser	BEV 1.25 mg	55.7	–	–	8.5[a]	–
Synek	2010	BEV 1.25 mg	BEV 1.25 mg + TRI 2 mg (x1, given as 1 injection)	–	5.0	1.5	–	–
Soheilian	2009	Laser + sham injection	BEV 1.25 mg + sham laser	64.5	11.5	12	14.5[b]	–
			BEV 1.25 mg + TRI 2 mg + sham laser	63.5	6.5	4	2.5[b]	–
Ahmadieh	2008	Sham injection	BEV 1.25 mg	–	6.0	7.5	–	–
			BEV 1.25 mg + TRI 2 mg (x1)	–	9.0	9.0	–	–
DRCR.net/Scott	2007	Laser	BEV 1.25 mg, baseline & 6 weeks	65.0[a]	6.0[a]	–	–	–
			BEV 2.5 mg, baseline & 6 weeks	63.0 [a]	8.0 [a]	–	–	–
			BEV 1.25 mg, baseline & sham at 6 weeks	64.0 [a]	5.0 [a]	–	–	–
			BEV 1.25 mg, baseline & 6 weeks, laser at 3 weeks	66.0 [a]	1.0 [a]	–	–	–

Study/Author	Publication Date	Control Strategy	Treatment Strategy	Baseline BCVA	Incremental ΔBCVA versus Control 3 months	6 months	12 months	24 months
Lucentis								
READ-2/ Nguyen	2009	Laser	RAN 0.5 mg	24.85	5.5	7.7	4.2	2.6
			RAN 0.5 mg + laser	24.87	3.4	4.2	2.4	1.7
RESTORE/Mitchell	2011	Laser + sham injection	RAN 0.5 mg + sham laser	64.8	–	–	5.9	–
			RAN 0.5 mg + laser	63.4	–	–	5.5	–
DRCR.net/Elman	2010	Prompt laser + sham injection	RAN 0.5 mg + prompt laser	66.0 [a]	–	–	6.0	4.0
			RAN 0.5 mg + deferred laser	66.0 [a]	–	–	6.0	6.0
			TRI 4 mg + prompt laser	66.0 [a]	–	–	1.0	-1.0
RESOLVE/Massin	2010	Sham injection	RAN 0.3 mg	59.2	–	–	13.2	–
			RAN 0.5 mg	61.2	–	–	10.2	–
RISE/Nguyen	2012	Sham injection	RAN 0.3 mg	54.7	–	–	–	9.9
			RAN 0.5 mg	56.9	–	–	–	9.3
RIDE/Nguyen	2012	Sham injection	RAN 0.3 mg	57.5	–	–	–	8.6
			RAN 0.5 mg	56.9	–	–	–	9.7
Eylea								
DaVinci/Do	2011	Laser + sham injection	AFL 2 mg+sham laser	59.3	–	6.1	–	–
			AFL 2 mg+sham laser+ sham injection	59.9	–	8.9	–	–
			AFL 2 mg + sham laser + sham injection (PRN)	58.8	–	6.0	–	–
			AFL 2 mg + sham laser (PRN)	59.6	–	7.8	–	–

AFL=Eylea; BEV=Avastin; PEG=Macugen; RAN=Lucentis; TRI=triamcinolone

[a] Median data reported; [b] 9-month data reported

Table 5 BCVA improvement of 10+ letters (% with ≥ 10)

Author	Year	Study Name	Follow-Up	% with Δ BCVA ≥ 10*	
				Sham Injection /Laser	Anti-VEGF
Macugen					
Sultan	2011	Macugen 1013 Study Group	12 months	20%	37%
Cunningham	2005	Macugen DR Study Group	9 months	10%	14-34%
Avastin					
Michaelides	2010	BOLT	12 months	8%	31%
Soheilian	2009	N/A	9 months	25%	20-37%
Scott	2007	DRCR.net	3 months	16-28%†	9-33%
Lucentis					
Nguyen	2012	RISE	24 months	30%	63%
Nguyen	2012	RIDE	24 months	25%	59-65%
Mitchell(a)	2011	RESTORE	12 months	15%	37-43%
Elman	2010	DRCR.net	12 months	—	47-51%
Massin	2010	RESOLVE	12 months	18%	49-73%
Nguyen	2009	READ-2	6 months	5%	30-46%
Eylea					
Do	2011	Da Vinci Study	6 months	32%	43-64%

* indicates ranges of results based on treatment protocol and/or dosing schedule

† laser, baseline (low estimate) and prompt laser with sham injection (high estimate)

Losses of ≥10 or ≥15 letters were reported in 3 Lucentis and 2 Avastin RCTs; the statistical significance of observed differences was reported only in the DRCR.net Lucentis study (Elman, 2010). In this study, the percentage of patients in both Lucentis groups (i.e., plus prompt or deferred laser) losing ≥10 or ≥15 letters was significantly lower at 12 months vs. sham+prompt laser (2-3% vs. 8-13%, p≤.01) (Appendix D, Table D1). At 24 months, however, rates remained significantly lower only for the Lucentis+deferred laser group (2-3% vs. 10-13%, p≤.01). In the 1 double-blind Avastin RCT, Avastin alone had a lower percentage of patients losing ≥10 letters (3.7%) compared to Avastin+triamcinolone (20.8%) or laser+sham injection (18.5%) (Sohelian, 2009), although these rates were not statistically tested. Loss of ≥10 letters did not differ in the DRCR.net Avastin study (Scott, 2007).

Based on baseline levels of visual acuity previously described (i.e., 55-65 letters), the changes described above would move patients into milder vision-loss states and provide meaningful benefit for many. For example, in the RISE and RIDE trials, where baseline visual acuity ranged from 55-58 letters, the proportion of patients achieving 20/40 vision (the threshold for driving in most U.S. states) was evaluated, and was found to be significantly higher for all Lucentis groups in both studies relative to sham (54-63% vs. 35-38% for sham, p≤.0002 for all comparisons) (Nguyen, 2012).

Data on long-term (i.e., >12 months) visual acuity changes from cohorts and case series were limited to 7 studies of Avastin. While changes from baseline BCVA ranged from 3-18 letters over 12-24

months of follow-up, relative benefit was assessed in only 1 study comparing Avastin to triamcinolone (Forte, 2010). Differences were not statistically tested, however, and groups were unbalanced with respect to baseline visual acuity.

Visual Acuity: Quantitative Synthesis

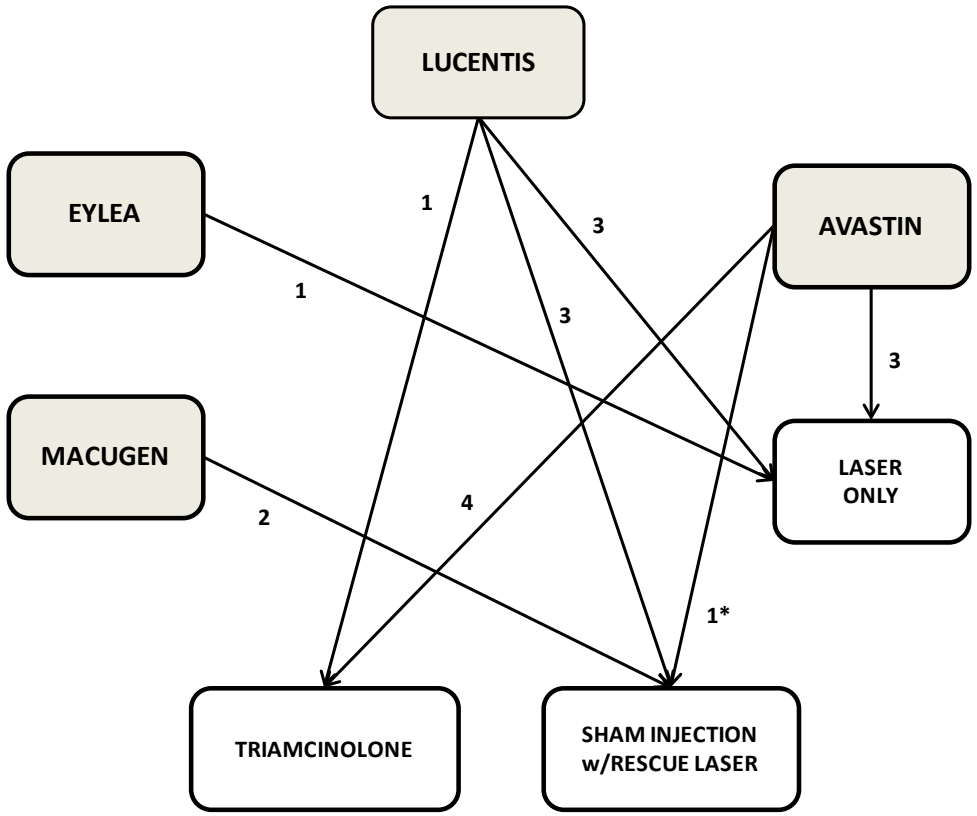
As described earlier, the spectrum of patients enrolled in the anti-VEGF RCTs was broad; this spectrum did not markedly differ when compared across anti-VEGF agents, however. While aspects of study design and outcome measurement did differ across studies, we nevertheless felt that the study populations were sufficiently comparable clinically to attempt quantitative meta-analysis.

The potential evidence network is presented in Figure 5 on the following page. As mentioned previously, there is no direct evidence comparing any of the anti-VEGF agents of interest. While indirect links are available for each anti-VEGF and major comparator, the level of evidence is sparse for several, particularly Macugen and Eylea. As such, we determined that the advantages of employing a sophisticated mixed treatment comparison approach, such as exploration of between-study heterogeneity and adjustment for differences in study characteristics using meta-regression, would be severely limited (Cooper, 2009; Salanti, 2009), and model findings using this approach would be difficult to interpret.

To enhance transparency, we opted to conduct a series of pairwise indirect meta-analyses (Bucher, 1997; Caldwell, 2005; Jansen, 2008). Direct random-effects meta-analyses were first conducted for each individual anti-VEGF agent using the available evidence. Analyses were conducted using RevMan software, version 5.1 (Cochrane Collaboration, 2012). Pooled estimates from these analyses were then input into a program developed by the Canadian Agency for Dugs and Technologies in Health (CADTH) to calculate pairwise indirect comparisons (Wells, 2009). Indirect comparisons were performed alternatively for (a) the mean difference in BCVA change between active and control therapy; and (b) the rate ratio of the likelihood of gaining 10 or more letters of vision. Pairwise comparisons included:

- Lucentis vs. Avastin
- Lucentis vs. Macugen
- Lucentis vs. Eylea
- Avastin vs. Macugen
- Avastin vs. Eylea
- Macugen vs. Eylea

Figure 5 Evidence network for trials of anti-VEGF agents in DME



NOTE: Numbers represent count of RCTs for each treatment-comparator link
*Comparator was sham injection *without* laser; patients were previously unresponsive to laser

In order to focus attention on the set of studies most relevant for clinical practice, primary analyses were limited to those with the following characteristics:

- Control therapy with (a) laser or (b) sham injection with rescue laser available
- Fair or good quality
- Reporting of outcome data at 6-24 months of follow-up

When treatment arms differed by dose, dosage levels were restricted to those considered to be well-established (Macugen 0.3 mg, Avastin 1.25 mg, Eylea 2 mg); 0.3 mg and 0.5 mg doses of Lucentis were pooled, as study results were very similar in RCTs with both dosage levels available. Data from triamcinolone arms and from RCTs with no laser availability were excluded from primary analyses of data. Note that, while data from Eylea treatment arms were pooled, meta-analysis was not performed, as only 1 RCT in DME was available.

While this approach did not allow for full exploration of between-study heterogeneity, we conducted sensitivity analyses to examine the robustness of our findings with respect to changes in the inclusion criteria for studies, including (a) comparison to all controls (i.e., laser, sham, triamcinolone); (b) inclusion of poor-quality studies; and (c) both of these.

Change in BCVA

Meta-analysis findings for the weighted mean difference (treatment vs. laser/sham control) in the change in BCVA are presented in Figure 6 on page 45; *note that, in this analysis, a value of 0 indicates no difference between treatment and control*. A total of 9 RCTs were eligible for this analysis. Pooled results from available Avastin and Lucentis trials indicated a statistically significant treatment effect vs. control, with pooled mean (95% CI) differences of 12.26 (8.05, 16.47) and 7.94 (5.62, 10.27) letters respectively. Data were available only from single trials of Eylea (7.60; 95% CI=5.48, 9.72) and Macugen (5.10; 4.56, 5.64). The recent multicenter Macugen 1013 RCT (Sultan, 2011) could not be used in this analysis, as measures of variance around mean differences were not available or could not be derived.

Indirect comparisons are also presented in Figure 6 (in these analyses, the term "control" refers to the second-listed drug in each comparison). Results from indirect comparisons found no statistically significant differences between Lucentis and Avastin, Lucentis and Eylea, or Avastin and Eylea (as denoted by confidence intervals that crossed 0). While mean changes were significantly greater for each of these agents in comparison to Macugen, definitive interpretation of these findings is highly problematic given the absence of the Macugen 1013 study from the analysis.

Gain of ≥10 Letters

Findings for primary analyses of the rate ratio (treatment vs. laser/sham control) in the percentage of eyes with a gain of 10 or more letters can be found in Figure 7 on page 46; *note that, in this analysis, a value of 1.0 indicates no difference between treatment and control*. A total of 10 RCTs were eligible. Pooled results from available Avastin and Lucentis trials indicated statistically significant treatment effects vs. control, with rate ratios (95% CI) of 3.03 (1.59, 5.79) and 2.14 (1.54, 2.98) respectively. The Eylea RCT also found a statistically significant treatment effect (1.73; 1.09, 2.73), while pooled results from the Macugen RCTs did not (1.88; 0.72, 4.92). Indirect comparisons indicated no statistically significant differences between anti-VEGF agents in the likelihood of achieving a ≥10 letter gain, as all confidence intervals crossed 1.0.

Sensitivity Analyses Using Different Study Inclusion Criteria

Detailed findings from sensitivity analyses with different inclusion criteria for studies and/or study arms can be found in Appendix E. Findings for change in BCVA were similar to those seen in primary analyses when (a) poor-quality studies were included; (b) control arms based on triamcinolone treatment (with or without rescue laser) were included; and (c) both changes were made. These changes did not affect the data included from Macugen or Eylea RCTs, as the RCT count remained the same. The addition of triamcinolone control arms reduced the weighted mean difference (95% CI) for Avastin from 12.26 (8.05, 16.47) to 8.97 (6.20, 11.74); all other changes were small, and indirect analyses remained statistically significant only in comparisons to Macugen.

Likewise, sensitivity analyses with different inclusion criteria produced changes in rate ratios of eyes with a gain of 10 or more letters only for Avastin and Lucentis. Inclusion of poor-quality studies lowered the pooled rate ratio slightly for Avastin (from 3.03 to 2.45) and raised it slightly for Lucentis (from 2.14 to 2.28), while inclusion of additional control arms had minimal effects. Consistent with the findings from our primary analyses, no statistically significant rate ratios were seen in indirect comparisons when performed under the alternative inclusion criteria of any sensitivity analysis.

Figure 6 Meta-analysis and indirect comparisons of mean difference in BCVA change between anti-VEGF therapy and laser/sham control

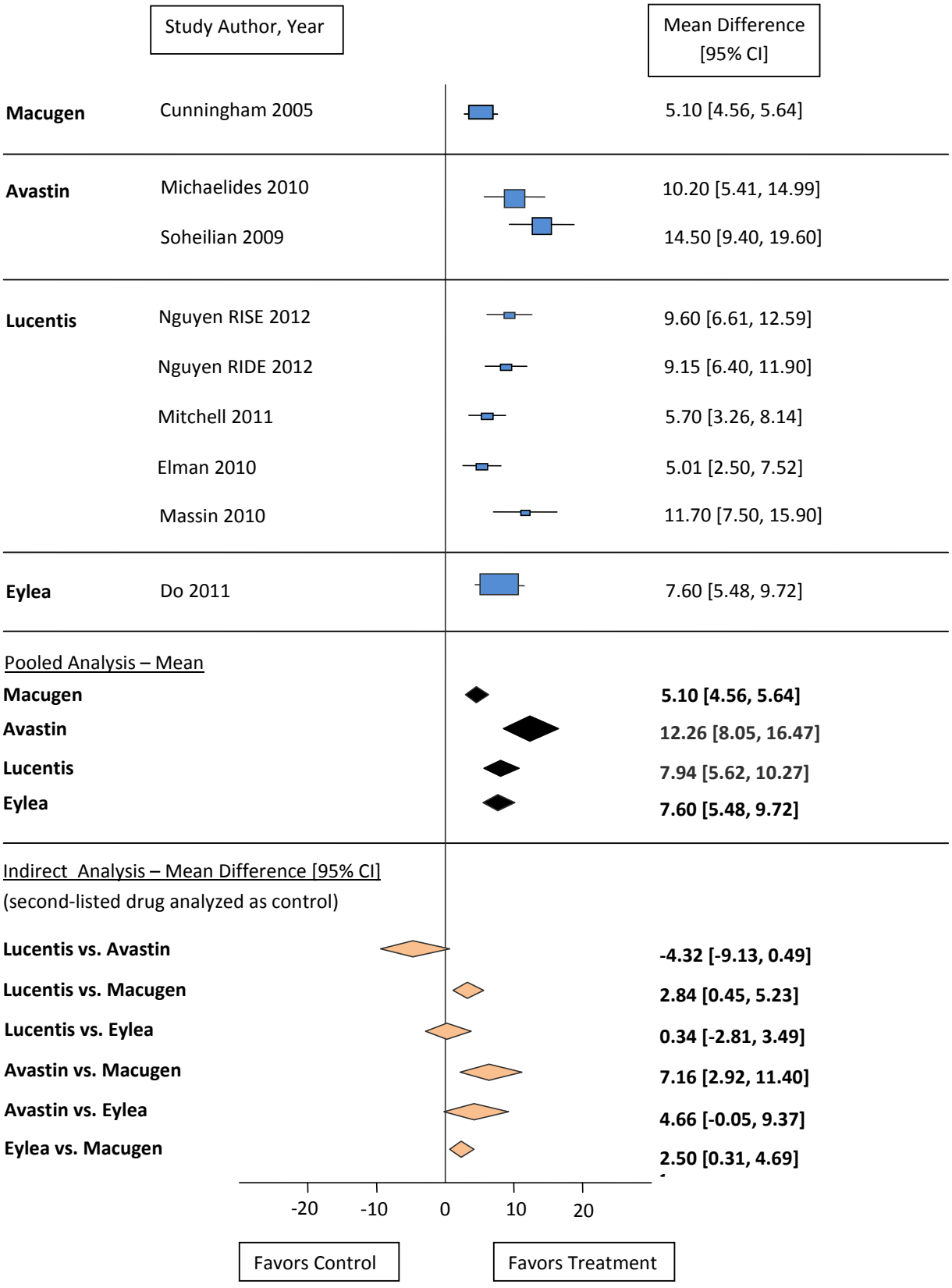
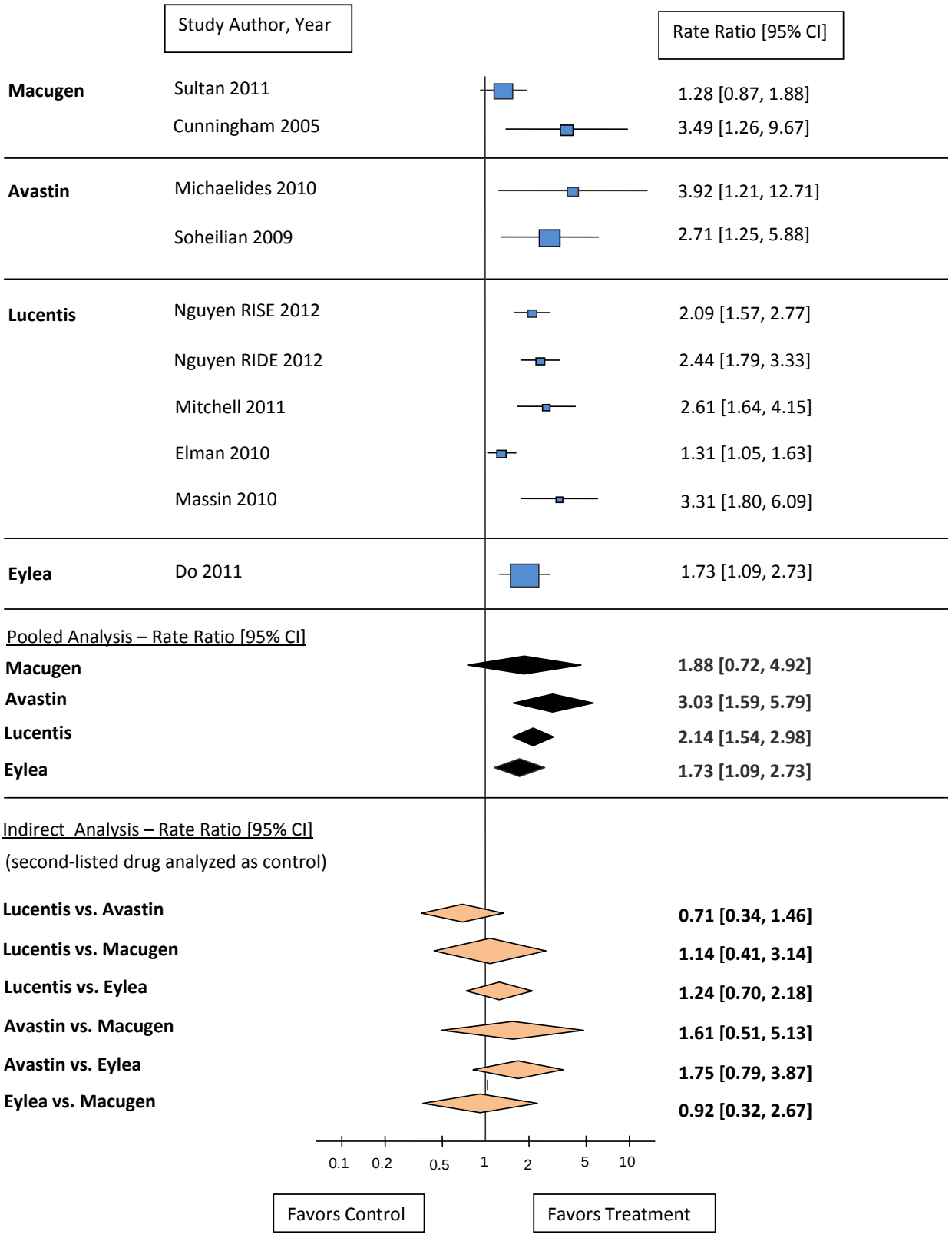


Figure 7 Meta-analysis and indirect comparisons of likelihood of gain of ≥10 letters between anti-VEGF therapy and laser/sham control



Treatment Utilization

Eleven trials reported data on treatment utilization (see Appendix D, Table D4). Across the studies, the mean number of injections in all treatment arms reflected study protocols: patients receiving continued therapy based on retreatment criteria received fewer injections than those with scheduled dosing. For example, in the Macugen 1013 study, patients receiving Macugen every 6 weeks for the first year of the study had a mean of 8.3 injections; patients completing 24 months of follow-up received a mean of 12.7 injections over 2 years (Sultan, 2011).

The availability and utilization of rescue laser therapy varied among the studies (see Appendix D, Table D4). Six studies provided data on patients receiving rescue laser (see Table 6 on the following page). In general, fewer patients receiving anti-VEGF agents were treated with rescue laser therapy, and used less rescue laser therapy than those receiving sham injections. In both RISE and RIDE, significantly fewer patients receiving Lucentis used rescue laser therapy as compared to patients in the sham injection group (19.7 - 39.2% versus 70 – 74%, $p<.0001$). Approximately one-quarter of patients receiving Macugen 0.3 mg in both available trials required rescue laser therapy, vs. 45-48% of those receiving sham ($p\leq.04$). Finally, while not statistically analyzed, fewer patients treated with Lucentis in both the RESOLVE (26.6-63.1% vs. 86.9%) and DRCR.net (4.9% vs. 34.7%) studies received rescue laser as compared to control arms.

Rates of retreatment were compared in the DRCR.net study (Elman, 2010). The fewest number of patients receiving retreatment were those receiving Lucentis plus prompt laser (41.7%). Similar percentages of patients receiving Lucentis plus deferred laser and patients receiving triamcinolone plus prompt laser received retreatment (51.1% and 47.3%, respectively). A greater percentage of patients receiving Lucentis with deferred laser were retreated as compared to those receiving prompt laser (51.1% versus 41.7%).

Quality of Life

Two trial reports provided data on quality of life assessment in patients receiving anti-VEGF agents for treatment of DME (Mitchell(a), 2011; Sultan, 2011) (see detailed results in Appendix D, Table D3). Both trials evaluated general health states using the EQ-5D and both vision-specific and general health benefits with the NEI VFQ-25. Neither study found significant differences among active treatment and control arms with respect to the EQ-5D. As this scale evaluates general health states, there may be decreased sensitivity for assessing changes in vision-related outcomes (Mitchell(a), 2011), despite adequate demonstration of the effects of visual impairment on quality of life and activities of daily living in other studies (Chia, 2004; West, 2002).

Significant treatment effects were observed in both studies with respect to the NEI VFQ-25; these were primarily limited to vision-related domains, however. At 12 months, Lucentis patients in the RESTORE study had significantly better improvement from baseline in scores for general vision (8.0-8.9 vs. 1.1 for laser, $p\leq.001$), near vision activities (9.0-9.1 vs. 1.1, $p\leq.011$), and distance activities (5.3-5.6 vs. 0.4, $p\leq.045$) (Mitchell(a), 2011). Improvements in overall composite score were also significantly better for Lucentis (5.0-5.4 vs. 0.6, $p\leq.014$).

Table 6 Studies reporting use of rescue laser therapy

Author	Year	Comparators	Timepoint (months)	Rescue Laser (%)	p-value (vs. control)
Cunningham Macugen DR Study Group	2005	Macugen 0.3 mg	9	25.0	.042
		Macugen 1 mg	9	29.5	.090
		Macugen 3 mg	9	40.5	.537
		Sham injection	9	47.6	---
Sultan Macugen 1013 Study Group	2011	Macugen 0.3 mg	24	25.2	.003
		Sham injection	24	45.0	---
Nguyen RISE	2012	Lucentis 0.3 mg	24	39.2	<.0001
		Lucentis 0.5 mg	24	35.2	<.0001
		Sham injection	24	74	---
Nguyen RIDE	2012	Lucentis 0.3 mg	24	36	<.0001
		Lucentis 0.5 mg	24	19.7	<.0001
		Sham injection	24	70	---
Elman DRCR.net	2010	Sham injection + prompt laser	24	86.9	Not reported
		Lucentis 0.5 mg + prompt laser	24	63.1	
		Lucentis 0.5 mg + deferred laser	24	26.6	
		Triamcinolone 4 mg + prompt laser	24	73.3	
Massin RESOLVE	2010	Lucentis 0.3 mg + 0.5 mg (pooled)	12	4.9	Not reported
		Sham injection	12	34.7	

*Prompt laser given at baseline; deferred laser given at week 24 or later. Evaluation for retreatment with laser conducted every 13 weeks.

The RESTORE study did not report results for any other NEI VFQ-25 domain, however (general health, ocular vision, social functioning, mental health, role difficulty, dependency, driving, color vision or peripheral vision). RESTORE also evaluated the time tradeoff associated with visual impairment in both treatment arms; improvements in utility did not significantly differ between treatment groups, however.

In the Macugen 1013 study, significant improvements relative to sham in near vision activities (LS mean difference: 5.70, p=.033), distance vision activities (8.50, p=.004) and social functioning (7.99, p=.002) were observed among patients receiving Macugen at 12 months; at 24 months, significant improvements continued only in distance vision activities (9.95, p=.002) as well as social functioning (9.91, p=.002). Mental health was also significantly improved at 24 months in patients receiving Macugen (7.17, p=.040), as well as on the composite score of the NEI VFQ-25 (4.47, p=.038). Nonsignificant improvements were found at 12 and 24 months in all other subdomains.

Finally, while not part of the recent trial publication, NEI VFQ-25 findings from RISE and RIDE have been presented at a national meeting (Bressler, 2011). Three domains were designated *a priori* as secondary efficacy outcomes: near vision activities, distance vision activities and vision-related dependency. At 12 months, statistically significant improvement was seen in both Lucentis doses versus sham injection in distance vision activities in both RISE and RIDE. Significant improvement was also seen with Lucentis 0.5 mg in near vision activities and overall composite score in both studies. However, at 24 months, nearly all differences between Lucentis and sham injections were nonsignificant.

Potential Harms

The incidence of mortality and of serious ocular and non-ocular adverse events is described in further detail in the sections that follow and available in Appendix D, Table D5. Data on ocular and non-ocular adverse events are also summarized in Table 7 on the following page. In addition, as mentioned previously, direct evidence on potential harms available from RCTs, systematic reviews, and observational studies in ocular conditions other than DME is provided for further context.

Ocular Adverse Events

Rates of all serious ocular adverse events ranged from 0-10% across trials. The most frequently-cited serious ocular adverse event was endophthalmitis. The incidence of serious endophthalmitis ranged from 0-2% across all trials (see Table 7 on the following page). Other serious ocular events included cataract, glaucoma, retinal/vitreous hemorrhage, retinal tear, retinal detachment, and uveitis. In most cases, serious ocular events occurred at similar or lower rates for anti-VEGF agents vs. control therapy; for example, rates were higher for sham/laser in available RCTs of Macugen and Eylea. An exception was the RIDE trial, in which serious ocular events occurred in 9.7% of patients randomized to Lucentis 0.5 mg (vs. 3.2% for Lucentis 0.3 mg and 5.5% for sham); differences were manifested primarily in cases of cataract, endophthalmitis, and sudden losses of visual acuity >30 letters (Nguyen, 2012). Statistical significance was not reported; re-analysis of data using a chi-square test indicated that differences were not statistically significant, either across the 3 groups or for each Lucentis group in comparison to sham injection. Rates of serious ocular events were also slightly higher in the RESOLVE study for Lucentis 0.5 mg (5.9% vs. 2% each for Lucentis 0.3 mg and sham), but the absolute number of events was small (3 vs. 1 vs. 1) (Massin, 2010).

Rates of serious ocular events were rarely reported in Avastin trials. Endophthalmitis was not observed in 3 RCTs (Lim, 2012; Michaelides, 2010; Sohelian, 2009); cases of any serious ocular event were reported only in the BOLT trial (2.4% for Avastin vs. 7.9% for laser) (Michaelides, 2010). Rates of serious ocular events were not reported in the remaining 3 RCTs.

Among the 8 available observational studies of anti-VEGF agents, no cases of endophthalmitis were reported, and only 2 cases of any serious ocular adverse event were described (in a cohort of patients receiving triamcinolone plus laser) (Appendix D, Table D7).

Non-Ocular Adverse Events

The incidence of stroke and MI ranged from 0-4% and 0-6% across trials respectively (see Table 7 on the following page). As with serious ocular events, most rates among patients treated with anti-VEGF agents were comparable to those with laser/sham control therapy. The incidence of stroke and MI was slightly higher for patients treated with Lucentis in the RISE study, but this pattern was reversed in the RIDE study (Nguyen, 2012).

Table 7 Data on potential harms of strategies for DME management

DME Strategy	Endophthalmitis	Total Ocular SAEs	Stroke	MI	CV SAEs	Total Non-ocular SAEs
Macugen*	0%	3%	1%	0%	7%	0-22%
Avastin†	0%	0-2%	0%	0%	0%	0-7%
Lucentis‡	0-2%	2-10%	0-4%	0-6%	0-7%	0-41%
Eylea§	0-2%	2-5%	0-2%	0-2%	0-7%	0-7%
Laser/Sham injection	0-0.3%	0-8%	0-3%	0-5%	0-6%	0-35%

SAE: Serious adverse event; CV: cardiovascular
* 1/2 studies reporting outcomes
† 3/6 studies reporting outcomes
‡ 8/9 studies reporting most outcomes
§ 1/1 studies reporting outcomes

Rates of all serious cardiovascular events ranged from 0-7% across RCTs. Rates were higher for patients receiving Lucentis alone (7%) vs. Lucentis+laser (3.3%) and laser+sham injection (3.6%) in the RESTORE trial, primarily as a result of 2 cases of pulmonary embolism and 1 case of arterial thrombosis (Mitchell(a), 2011); rates were also higher in the Macugen 1013 study (6.9% vs. 5.6% for sham), primarily as a result of treatment-emergent coronary artery disease and angina (Sultan, 2011). Rates were not evaluated statistically in either trial, however. Cardiovascular event rates were comparable to laser/sham control in most other trials; however, data were not summarized at the organ system level in the RISE/RIDE trial report (Nguyen, 2012).

Rates of serious non-ocular adverse events in total ranged widely, from 0-41%, which may have been due to variability in the definition of serious non-ocular events and/or lack of rigorous monitoring for such events. The highest rates of serious non-ocular events were observed in the RISE/RIDE trials (28-41% vs. 31-35% for sham). Events were dispersed across many categories; in addition, rates were higher vs. sham in RISE, but lower than sham in RIDE. The authors further note that events potentially related to systemic VEGF inhibition were similar across the Lucentis (6-12%) and sham (9-11%) arms (Nguyen, 2012); as with other RCTs, these rates were not tested statistically.

Rates of stroke, MI, all cardiovascular, and all non-ocular events were rarely observed and/or reported in trials of Avastin for DME. Single cases of stroke and cardiovascular events were described in the 3 RCTs reporting such events, and a total of 10 serious non-ocular events were reported. No data were reported in the remaining 3 RCTs.

Among available cohort and case series studies, single cases of stroke and MI were observed in a series of 139 patients receiving Avastin 1.25 mg or 2.5 mg who were followed for 24 months (Arevalo, 2009).

Mortality

Rates of death from all causes ranged from 0-5% at 6-24 months across available RCTs (see Table D5 in Appendix D); in all studies except 2 of Lucentis, rates did not materially differ between patients treated with anti-VEGF agents and those treated with control therapy. In the recent RISE and RIDE studies, mortality rates were higher in patients receiving Lucentis (2.4-4.8%) vs. sham (0.8-1.6%), but this difference was not statistically evaluated (Nguyen, 2012). We re-analyzed these data using Fisher's exact test; differences were nonsignificant for both RCTs. The authors also point out that in the DRCR.net study, mortality rates were numerically higher in the sham injection+laser group (5.1% vs. 3.2-4.8% for Lucentis) (Elman, 2010).

Evidence on harms of treatment with Avastin for DME is extremely limited in the available RCTs. Mortality was only reported in 3 of 6 available RCTs. A total of 5 deaths were reported; 2 were among patients receiving Avastin in combination with triamcinolone and laser (Sohelian, 2009), and 3 were reported among patients receiving laser/sham treatment (Sohelian, 2009; Ahmadieh, 2008).

There were 3 deaths in the RCT of Eylea, all in treatment groups receiving anti-VEGF therapy; all of these were attributed to underlying diabetic and cardiovascular comorbidity, however (Do, 2011).

Data on mortality were not reported in 8 available observational studies of anti-VEGF agents (7 of Avastin and 1 of Macugen) (Appendix D, Table D7).

Safety Findings from Non-DME Studies

Direct evidence comparing the safety profiles of intravitreal Lucentis and Avastin for neovascular AMD are available from 2 RCTs. The Comparison of Age-Related Macular Degeneration Treatments Trials (CATT), sponsored by the National Eye Institute, randomized over 1200 patients at 44 U.S. centers to receive Lucentis 0.5 mg or Avastin 1.25 mg either monthly or on an "as-needed" basis after the first injection and followed patients for 12 months (Martin, 2011). No statistically-significant differences in rates of death, arteriothrombotic events, or venous thrombotic events were observed across all groups or between Lucentis- and Avastin-treated groups. The rate of systemic adverse events, which included hospitalization for any cause, was significantly higher for Avastin vs. Lucentis (24.1% vs. 19.0%, p=.04); event causes were broadly distributed, with differences primarily manifested in gastrointestinal disorders (e.g. hemorrhage, nausea/vomiting) as well as hospitalizations for pneumonia and urinary tract infection. As mentioned earlier, 2-year efficacy and safety data from CATT are expected to be presented later in 2012.

A second, much smaller RCT of anti-VEGF treatment for age-related macular degeneration was conducted in 22 patients in a single VA hospital who were randomized 2:1 to receive Avastin or Lucentis monthly for 3 months, followed by additional injections on an "as-needed" basis (Subramanian, 2010). Patients were followed for 12 months. Two deaths were reported, both in the Avastin arm; one was due to complications from Merkel cell carcinoma and the other from unknown causes. No major ocular adverse events, stroke, or other systemic adverse events were reported for any subject.

In addition to direct evidence, 2 systematic reviews have compared the safety profiles of Avastin and Lucentis vs. sham injections in neovascular age-related macular degeneration, (Schmucker, 2011; Mitchell(b), 2011). Findings from a Cochrane review indicate that Lucentis was associated with significant increases in the risk of serious ocular adverse events compared to sham injection

(Relative Risk [RR]=3.13; 95% CI=1.10, 8.92) and non-ocular hemorrhage (RR=1.62; 95% CI=1.03, 2.55) (Schmucker, 2011). No conclusions could be drawn from Avastin trial data, however, due to small sample sizes and an apparent lack of rigorous monitoring for adverse events. Similar conclusions were drawn regarding the limitations of Avastin safety data in the second review (Mitchell(b), 2011).

Finally, while subject to attendant selection and other biases, findings from a retrospective claims-based cohort study of nearly 150,000 Medicare beneficiaries treated for neovascular age-related macular degeneration suggested that, after adjustment for differences in baseline characteristics, neither Avastin nor Lucentis was associated with increased risks of mortality, myocardial infarction, bleeding, or stroke relative to Macugen or photodynamic therapy (Curtis, 2010). When Avastin and Lucentis were compared directly, Lucentis was associated with a reduced hazard of mortality (hazard ratio [HR]=0.86; 95% CI=0.75, 0.98) and stroke (HR=0.78; 95% CI=0.64, 0.96) relative to Avastin. However, it was acknowledged that patients with higher socioeconomic status (and therefore possibly better health) may have been more likely to receive Lucentis. A secondary analysis limited only to providers exclusively using Lucentis or Avastin was conducted to address this concern, and showed no differences between groups in the hazard of any event of interest.

8. Economic Evidence

Two published studies evaluated the cost-effectiveness associated with DME treatment in the U.S. (Lin, 2011). Key aspects of study design, primary findings, and major limitations of each study are summarized in Table 8 on page 55.

Sharma and colleagues developed an early cost-utility model comparing immediate grid laser photocoagulation for DME with deferred treatment (Sharma, 2000). This analysis was based on data collected in The Early Treatment Diabetic Retinopathy Study (ETDRS). On a lifetime basis, immediate laser photocoagulation was associated with a gain of approximately 3 months of quality-adjusted life expectancy. The incremental cost of treatment was $733 (expressed in 2000 USD) for photocoagulation yielding a cost per quality-adjusted life year (QALY) gained ranging from $3,101-$3,655, depending on the underlying assumptions.

More recently, Smiddy estimated costs and consequences over 1 year for all current strategies for the management of DME relative to the untreated natural history, including grid laser, intravitreal triamcinolone, dexamethasone intravitreal implant, Avastin, Macugen, Lucentis, and vitrectomy (Smiddy, 2011). Unfortunately, estimates of incremental cost and utility were derived relative to no treatment, rather than laser photocoagulation as the treatment gold standard. We recalculated estimates of cost per QALY gained relative to laser photocoagulation; these are described in more detail below and presented in Table 8.

One-year costs of treatment were reported to range from $1,326 - $21,709. The sample of RCTs used to estimate improvement in visual acuity for anti-VEGF therapies differed from ours, and included 1 Avastin RCT (the PACORES trial) excluded from our sample because it compared 2 Avastin doses and had no control group (Arevalo, 2009). Estimates of improvement in visual acuity were comparable for Lucentis and Avastin; Macugen was slightly inferior to these. Derived estimates of cost per QALY gained were $22,720 for Macugen, $1,227-$3,736 for Avastin (based on the PACORES and BOLT RCTs respectively), and $22,611-$28,747 for Lucentis (based on the READ-2 and DRCR.net RCTs). Corresponding incremental costs per line of vision were $12,397 for Macugen, $772- $1,843 for Avastin, and $13,322-$16,616 for Lucentis.

While not peer-reviewed, findings from a manufacturer-submitted economic model used to estimate the economic impact of Lucentis in the U.K. are publicly-available through the National Institute for Health and Clinical Excellence (NICE, 2011). The cost-utility of Lucentis alone was compared to that of laser photocoagulation alone; no comparisons were made to other anti-VEGF agents, as the manufacturer cited an insufficient base of higher-quality evidence. Data were obtained from the RESTORE and DRCR.net studies to inform this evaluation. An initial incremental cost per QALY gained of £19,075 (~$30,250) for Lucentis was estimated. Several concerns with model structure and assumptions were raised by the NICE Evidence Review Group, however. This group believed that the manufacturer's model underestimated the hazard of mortality associated with DME and made several unrealistic assumptions regarding typical clinical practice (e.g., treatment of worse-seeing eye only vs. first eye to present clinically, halting treatment at arbitrary timepoints and/or BCVA thresholds, etc.). A revised model was submitted addressing these concerns; the primary estimate of cost-utility rose to £30,277 (~$48,000) per QALY.

Table 8 Summary of DME cost-effectiveness studies

Author/Country	DME Strategy	Time horizon	Cost per patient	Lines Saved	QALYs gained	Cost/QALY	Limitations	Comments
Sharma et al. 2000/U.S.	Laser photocoagulation vs. deferred treatment	Lifetime (43 yrs[a])	NR	NR	0.236	U.S.$3,101[b] $3,655[c]	-ETDRS includes only early onset diabetes mellitus -Lifetime impact estimated from 3-year outcomes -Only univariate sensitivity analysis reported	Methods are not fully transparent making it difficult to reproduce estimates
Smiddy 2011[d]/ U.S.	Grid laser therapy	One year	$1,326	0.26	NR	------	-Estimation of costs and benefits variable by expense of modality[f] (p 1828) -Constant incremental utility value of 0.03 ascribed to all patients for each line gained -Assumed lifetime benefit of initial treatment -Incremental benefits relative to natural history, not grid laser -No sensitivity analysis	Methods and assumptions are not fully transparent
	Macugen	One year	$10,500	1.00	NR	U.S. $22,720		
	Avastin	One year						
	-PACORES data		U.S.$2,68	2.02	NR	$1,227		
	-BOLT data		4[e]	2.10	NR	$3,736		
			$4,718					
	Lucentis	One year						
	-DRCR data		$21,265	1.46	NR	$28,747		
	-READ data		$21,709	1.79	NR	$22,611		

[a] 3 years of treatment plus 40 year projection.
[b] costs are based on 1999 Medicare reimbursement data, cost/QALY estimate based on undiscounted QALYs.
[c] costs are based on 1999 Medicare reimbursement data, cost/QALY estimate based on discounted QALYs.
[d] all comparisons made relative to no treatment/natural history.
[e] all costs in Smiddy article estimated based on 2010 Medicare allowable amounts unless otherwise noted.
[f] design of study overestimated benefits and underestimated costs for more expensive strategies; and underestimated benefits and overestimated costs for less expensive strategies.
NA-not applicable; NR-not reported

9. Potential Budgetary Impact

In a 2011 report, the Office of the Inspector General (OIG) for the U.S. Department of Health and Human Services reported that, among patients with neovascular AMD treated with Lucentis or Avastin in calendar years 2008-2009, Medicare Part B paid an average of $1,624 for each Lucentis injection and $43 per Avastin treatment. Out-of-pocket expenditures for patients receiving Lucentis were estimated to be nearly 40-fold higher in comparison to Avastin ($406 vs. $11 per treatment respectively).

Because no similar analysis has been undertaken in a DME population, we first estimated the number of Medicare Part B beneficiaries who would have this condition. Diabetes is estimated to affect approximately 8.3 million adults enrolled in Medicare Part B, based on publicly-available prevalence estimates from CMS (CMS Chronic Conditions, 2011); of these, diabetic retinopathy is expected to be present in one-quarter, or approximately 2.2 million persons. We then used age- and race-based prevalence estimates from a recent epidemiologic study (Wong, 2006) to determine the proportion of Medicare beneficiaries with retinopathy who would also have DME. After adjusting for the distribution of age and race in the Medicare population (CMS Chronic Conditions Warehouse, 2011), we estimated that there are approximately 325,000 Medicare Part B beneficiaries with DME (~15% of persons with diabetic retinopathy).

We also did not have any data on the proportion of DME patients receiving each type of anti-VEGF agent, and so elected to estimate the annual budgetary impact if each Medicare patient with DME received a full year of anti-VEGF therapy. Alternative scenarios were developed assuming 100% of use with each anti-VEGF agent. For these scenarios, we used the labeled dosing schedules for AMD. Lucentis and Avastin were assumed to be injected monthly, Macugen every 6 weeks, and Eylea monthly for the first 3 months, and every other month thereafter. Payments for Lucentis and Avastin were assumed to be identical to those in the OIG report, while payments for Macugen ($1,029 per injection) and Eylea ($1,961 per injection) were based on published Medicare payment rates (CMS Medicare Part B Drug Pricing Files, 2011). We did not assume any difference in patient contribution for this analysis.

Based on these estimates, potential budgetary impact to Medicare Part B if all DME patients were treated with Lucentis was estimated to total $6.3 billion, followed by Eylea ($4.5 billion) and Macugen ($2.7 billion). Total budgetary impact if all such patients were treated with Avastin was estimated to be $167.7 million.

10. Summary

The body of evidence on the use of intravitreal anti-VEGF injections for the treatment of diabetic macular edema includes 15 randomized controlled trials and 8 observational studies conducted in over 4,000 patients worldwide. While available studies differed in terms of entry criteria, treatment protocol, comparators, measurement techniques, and duration of follow-up, the findings of our review suggest that anti-VEGF therapy is associated with sustained improvement in visual acuity and reduced requirements for "rescue" laser treatment over 6-24 months of follow-up. For many patients, improvements in visual acuity were marked and clinically significant (e.g., gains of 10 letters or more); however, the significance of such gains for an individual patient in terms of reduced disability, ability to resume certain daily activities, and other considerations is dependent in large part on the patient's current function, level of visual assistance required, and other non-visual considerations (e.g., comorbidities).

What is less clear is the ability to distinguish the performance of each individual anti-VEGF agent. There have been no head-to-head comparative trials of anti-VEGF agents in patients with DME, and therefore only indirect comparisons are possible. In looking at the RCTs of anti-VEGF agents vs. control, there are differences in patient eligibility, control arm therapy protocols, measurement techniques, and study duration. Nevertheless, mean improvements in BCVA between active agent arms and control arms across all anti-VEGF therapies show great consistency, mostly falling into the range of 4-9 additional letters read at time points between 6 months and 2 years. The qualitative assessment suggesting equivalent visual acuity outcomes is supported by the results of our quantitative meta-analyses. Meta-analyses on the mean difference (relative to laser, sham, or other control therapy) in improvement in BCVA and in the likelihood of achieving a 10-letter or better gain suggest no clinically- or statistically-significant differences in either outcome between Lucentis, Avastin, and Eylea; these conclusions were unchanged in multiple sensitivity analyses allowing for inclusion of additional RCT data. While there is some indication that these agents were associated with greater improvements relative to Macugen, no definitive conclusions could be drawn due to a paucity of available data.

Examination of available information on safety presents greater challenges. There was a marked contrast in the extent, detail, and rigor with which safety data were collected and reported in industry- and government-sponsored trials of Lucentis, Macugen, and Eylea, vs. the primarily small, single-center trials of Avastin. In trials of anti-VEGF agents other than Avastin, rates of serious ocular and non-ocular and/or systemic adverse events were generally comparable to rates for laser/sham control, although there were some discrepant findings in individual trials (e.g., higher rates of stroke/MI with Lucentis vs. sham in RISE, lower rates in RIDE).

In trials of Avastin, reporting of rates of both specific adverse events and serious events as a whole was completely lacking in 3 of 6 RCTs. In the remaining RCTs, the level of detail on the types of events observed was inferior to that in the trial reports for the other anti-VEGF agents. Examination of data from observational analyses failed to shed additional light on

Avastin safety in DME, as reporting frequency and detail were also extremely limited in these studies.

We also examined the available literature on Avastin and Lucentis safety in neovascular AMD, the condition for which Lucentis is approved in the U.S. There is controversy over interpretation of the 1-year results of the CATT trial directly comparing Lucentis and Avastin (Martin, 2011). Whether those data suggest no likely difference in major systemic side effects, or instead herald a true advantage for Lucentis over Avastin, remains a question open to interpretation.

10.1 Limitations

Our review is subject to some important limitations. For one, while efforts were undertaken to reduce publication bias and duplicative research, certain aspects of our search strategy (e.g., exclusion of non-English-language articles) may be subject to residual levels of such bias. For example, because all of these agents are off-label for DME in the U.S. and only Lucentis is currently approved in Europe, the possibility exists that other trials of these agents have been conducted but not published. In addition, our ability to draw conclusions from the Avastin literature, particularly with regard to safety considerations, was limited by small sample sizes, lack of rigor in adverse event reporting, and non-informative observational studies.

10.2 Conclusions

Evidence accumulated to date suggests that anti-VEGF therapy improves visual acuity in patients with diabetic macular edema and provides other clinical benefits relative to macular laser treatment or sham injection. While there are no head-to-head trials of anti-VEGF agents, there are sufficient fair- and good-quality RCTs of individual agents vs. control therapies to allow for qualitative and quantitative indirect comparisons. Despite awareness of differences in patients and study designs that render indirect comparisons challenging, our analyses suggest no significant difference in clinical performance among the anti-VEGF agents. The systemic side effect profile of Avastin relative to Lucentis or other anti-VEGF agents remains the greatest element of uncertainty. Assessment of this issue requires judgment regarding the relevance of data from observational data sources and from comparative RCT data obtained from trials of Avastin and Lucentis for AMD.

References

Ahmadieh H, Ramezani A, Shoeibi N, et al. Intravitreal bevacizumab with or without triamcinolone for refractory diabetic macular edema; a placebo-controlled, randomized clinical trial. *Graefes Arch Clin Exp Ophthalmol*. 2008;246(4):483-489.

Ali FA. A review of diabetic macular edema. *Digit J Ophthalmol*. 1997;3(6):1-7.

American Academy of Ophthalmology (AAO). Preferred practice pattern guidelines: Diabetic retinopathy (2008). http://one.aao.org/ce/practiceguidelines/ppp_content.aspx?cid=d0c853d3-219f-487b-a524-326ab3cecd9a. Accessed December 8, 2011.

American Academy of Ophthalmology (AAO). ONE® Network. Verifying the source of compounded bevacizumab for intravitreal injections. http://onetext.aao.org/CE/PracticeGuidelines/ClinicalStatements_Content.aspx?cid=2409cf9a-7700-4342-a857-a6098e848f6a. Accessed February 13, 2012.

American Diabetes Association (ADA). Standards of medical care in diabetes – 2011. *Diabetes Care*. 2011;34(Suppl. 1):S11-S61.

Arevalo JF, Sanchez JG, Fromow-Guerra J, et al. for the Pan-American Collaborative Retina Study Group (PACORES). Comparison of two doses of primary intravitreal bevacizumab (Avastin) for diffuse diabetic macular edema: results from the for the Pan-American Collaborative Retina Study Group (PACORES) at 12-month follow-up. *Graefes Arch Clin Exp Ophthalmol*. 2009;247(6):735-743.

Arevalo JF, Sanchez JG, Wu L, et al. for the Pan-American Collaborative Retina Study Group (PACORES). Primary intravitreal bevacizumab for diffuse diabetic macular edema. The Pan-American Collaborative Retina Study Group at 24 months. *Ophthalmology*. 2009;116(8):1488-1497.

Arevalo JF, Fromow-Guerra J, Quiroz-Mercado H, et al. for the Pan-American Collaborative Retina Study Group. Primary intravitreal bevacizumab (Avastin) for diabetic macular edema. Results from the Pan-American Collaborative Retina Study Group at 6-month follow-up. *Ophthalmology*. 2007;114(4):743-750.

Avastin® [package insert]. South San Francisco, CA: Genentech, Inc.; 2011.

Avery RL, Pieramici DJ, Rabena MD, et al. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. *Ophthalmology*. 2006;113(3):363-372.

Beck RW, Maguire MG, Bressler NM, Glassman AR, Lindblad AS, Ferris FL. Visual acuity as an outcome measure in clinical trials of retinal diseases. *Ophthalmology*. 2007;114(10):1804-1809.

Berkrot B, Pierson R. VA halts Avastin use for eye disease. http://www.reuters.com/article/2011/09/21/us-roche-va-idUSTRE78K6F520110921. Accessed February 13, 2011.

Bibby SA, Maslin ER, McIlraith R, Soong GP. Vision and self-reported mobility performance in patients with low vision. *Clin Exp Optom*. 2007;90(2):115–123.

Bonini-Filho M, Costa RA, Calucci D, et al. Intravitreal bevacizumab for diabetic macular edema associated with severe capillary loss: one-year results of a pilot study. *Am J Ophthalmol*. 2009;147(6):1022-1030.

Boscia F. Current approaches to the management of diabetic retinopathy and diabetic macular oedema. *Drugs*. 2010;70(16):2171-2200.

Brechner RJ, Rosenfeld PJ, Babish JD, Caplan S. Pharmacotherapy for neovascular age-related macular degeneration: an analysis of the 100% 2008 medicare fee-for-service part B claims file. *Am J Ophthalmol*. 2011;151(5):887-895.

Brennig C, Schöllbauer V, Walter E, Gallagher M, Knudsen MS. Economic evaluation of ranibizumab in the treatment of visual impairment due to diabetic macular edema in Austria. *Value Health*. 2011;14(3):A478.

Bressler NM, Varma R, Lee P, et al. Effects of ranibizumab on patient-reported visual function through 24 months in patients with vision impairment from diabetic macular edema. Presented at: American Society of Retina Specialists, Annual Meeting; August 17, 2011; Boston, MA.

Brooks S. Markov chain Monte Carlo method and its application. *J Royal Stat Soc: Series D*. 1998;47(1):69-100.

Brown MM, Brown GC, Sharma S, Landy J, Bakal J. Quality of life with visual acuity loss from diabetic retinopathy and age-related macular degeneration. *Arch Ophthalmol*. 2002;120(4):481-484.

Browning DJ, Glassman AR, Aiello LP, et al. Relationship between optical coherence tomography-measured central retinal thickness and visual acuity in diabetic macular edema. *Ophthalmology*. 2007;114(3):525-536.

Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol*. 1997;50(6):683-691.

Cahill MT, Stinnett SS, Banks AD, Freedman SF, Toth CA. Quality of life after macular translocation with 360° peripheral retinectomy for age-related macular degeneration. *Ophthalmology*. 2005;112(1):144-151.

Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments combining direct and indirect evidence. *BMJ*. 2005;331(7521):897-900.

Cao Y, Tan A, Gao F, Liu L, Liao C, Mo Z. A meta-analysis of randomized controlled trials comparing chemotherapy plus bevacizumab with chemotherapy alone in metastatic colorectal cancer. *Int J Colorectal Dis*. 2009;24(6):677-685.

Centers for Medicare & Medicaid Services. Chronic Conditions among Medicare Beneficiaries, Chart Book. Baltimore, MD. 2011.

Chen E, Looman M, Laouri M, et al. Burden of illness of diabetic macular edema: literature review. *Curr Med Res Opin*. 2010;26(7):1587-1597.

Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. *Lancet*. 2010;376(9735):124-136.

Chia E-M, Wang JJ, Rochtchina E, et al. Impact of bilateral visual impairment on health-related quality of life: the Blue Mountains Eye Study. *Invest Ophthalmol Vis Sci*. 2004;45(1):71-76.

Choueiri TK, Mayer EL, Je Y, et al. Congestive heart failure risk in patients with breast cancer treated with bevacizumab. *J Clin Oncol*. 2011;29(6):632-638.

CMS Medicare and Medicaid Research Data Chronic Conditions Warehouse. Table 2.3. Medicare Enrollment: Hospital Insurance and/or Supplementary Medical Insurance Enrollees, by Demographic Characteristics, Type of Entitlement, Buy-in Status, and Residence, as of July 1, 2010. http://www.ccwdata.org/summary-statistics/demographics/a1-race-1999-2009.htm Accessed February 21, 2012.

Cooper NJ, Sutton AJ, Morris D, Ades AE, Welton NJ. Addressing between-study heterogeneity and inconsistency in mixed treatment comparisons: application to stroke prevention treatments in individuals with non-rheumatic atrial fibrillation. *Stat Med*. 2009;28(14):1861-1881.

Cunningham ET, Adamis AP, Altaweel M, et al. for the Macugen Diabetic Retinopathy Study Group. A phase II randomized double-masked trial of pegaptanib, an anti-vascular endothelial growth factor aptamer, for diabetic macular edema. *Ophthalmology*. 2005;112(10):1747-1757.

Curtis LH, Hammill BG, Schulman KA, Cousins SW. Risks of mortality, myocardial infarction, bleeding, and stroke associated with therapies for age-related macular degeneration. *Arch Ophthalmol*. 2010;128(10):1273-1279.

Dandona L, Dandona R. Revision of visual impairment definitions in the International Statistical Classification of Diseases. *BMC Medicine* 2006;4:7.

Do DV, Schmidt-Erfurth U, Gonzalez VH, et al. The Da Vinci Study: phase 2 primary results of VEGF Trap-Eye in patients with diabetic macular edema. *Ophthalmology*. 2011;118(9):1819-1826.

Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study Group report number 1. *Arch Ophthalmol*. 1985;103(12):1796-1806.

Elman MJ, Bressler NM, Qin H, et al. for the Diabetic Retinopathy Clinical Research Network. Expanded 2-year follow-up of ranibizumab plus prompt laser or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology*. 2011;118(4):609-614.

Elman MJ, Aiello LP, Beck RW, et al. for the Diabetic Retinopathy Clinical Research Network. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology*. 2010;117(6):1064-1077.

Eylea™ [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; 2011.

Food and Drug Administration (FDA), Department of Health and Human Services. Proposal to withdraw approval for the breast cancer indication for Avastin (bevacizumab) (docket no. FDA-2010-N-0621): Commissioner's decision, Novemebr 18, 2011. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm279485.htm

Forte R, Cennamo GL, Finelli M, et al. Intravitreal bevacizumab vs. intravitreal triamcinolone combined with macular laser grid for diffuse diabetic macular oedema. *Eye*. 2010;24(8):1325-1330.

Fraser CE, D'Amico DJ. Classification and clinical features of diabetic retinopathy. In: UpToDate, Mulder JE (ed.), UpToDate, Waltham, MA, 2011.

Galfrascoli E, Piva S, Cinquini M, et al. Risk/benefit profile of bevacizumab in metastatic colon cancer: a systematic review and meta-analysis. *Dig Liver Dis*. 2011;43(4):286-294.

Geiger-Gritsch S, Stollenwerk B, Miksad R, Guba B, Wild C, Siebert U. Safety of bevacizumab in patients with advanced cancer: a meta-analysis of randomized controlled trials. *Oncologist*. 2010;15(11):1179-1191.

Global Research & Development, Pfizer Limited. Macugen: Withdrawal letter. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/07/WC500109579.pdf. Accessed on February 21, 2012.

Goldberg RA, Flynn HW, Isom RF, Miller D, Gonzalez S. An outbreak of *Streptococcus* endophthalmitis after intravitreal injection of bevacizumab. *Am J Ophthalmol*. 2012;153(2):204-208.

Googe J, Brucker AJ, Bressler NM, et al. for the Diabetic Retinopathy Clinical Research Network. Randomized trial evaluating short-term effects of intravitreal ranibizumab or triamcinolone acetonide on macular edema after focal/grid laser for diabetic macular edema in eyes also receiving panretinal photocoagulation. *Retina*. 2011;31(6):1009-1027.

Goyal S, LaValley M, Subramanian ML. Meta-analysis and review on the effect of bevacizumab in diabetic macular edema. *Graefes Arch Clin Exp Ophthalmol*. 2011;249(1):15-27.

Gregori NZ, Feuer W, Rosenfeld PJ. Novel method for analyzing Snellen visual acuity measurements. *Retina*. 2010;30(7):1046-1050.

Haig J, Lawrence D, Barbeau M, Blouin J, Cruess A. Economic evaluation of ranibizumab for the treatment of diabetic macular edema in Canada. *Value Health*. 2011;14(3):A96-97.

Haymes SA, Johnston AW, Heyes AD. Relationship between vision impairment and ability to perform activities of daily living. *Ophthal Physiol Opt*. 2002;22(2):79–91.

Hazel CA, Petre KL, Armstrong RA, Benson MT, Frost NA. Visual function and subjective quality of life compared in subjects with acquired macular disease. *Invest Ophthalmol Vis Sci*. 2000;41(6):1309–1315.

Hirai FE, Knudtson MD, Klein BE, Klein R. Clinically significant macular edema and survival in type 1 and type 2 diabetes. *Am J Ophthalmol*. 2008;145(4):700-706.

Holladay JT. Proper method for calculating average visual acuity. *J Refract Surg*. 1997;13(4):388-391.

James A, Peters C, Tran I, et al. Impact of diabetic macular edema on the daily lives of diabetic adults – a qualitative study. Abstract accepted by The Association for Research in Vision and Ophthalmology (ARVO) on January 31st, 2012.

Jansen JP, Crawford B, Bergman G, Stam W. Bayesian meta-analysis of multiple treatment comparisons: an introduction to mixed treatment comparisons. *Value Health.* 2008;11(5):956-964.

Javitt JC, Zhou Z, Wilke RJ. Association between vision loss and higher medical care costs in Medicare beneficiaries. *Ophthalmology*. 2007;114(2):238-245.

Kempen JH, O'Colmain BJ, Leske MC, et al. for the Eye Diseases Prevalence Research Group. The prevalence of diabetic retinopathy among adults in the United States. *Arch Ophthalmol*. 2004;122(4):552-563.

Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BE. The Wisconsin Epidemiologic Study of Diabetic Retinopathy XXIII: the twenty-five-year incidence of macular edema in persons with Type 1 diabetes. *Ophthalmology*. 2009;116(3):497–503.

Kniestedt C, Stamper RL. Visual acuity and its measurement. *Ophthalmol Clin North Am*. 2003;16(2):155-170.

Kook D, Wolf A, Kreutzer T, et al. Long-term effects of intravitreal bevacizumab (Avastin) in patients with chronic diffuse diabetic macular edema. *Retina*. 2008;28(8):1053-1060.

Kook PE, Maier M, Schuster T, Feucht N, Lohmann CP. Nine-month results of intravitreal bevacizumab versus triamcinolone for the treatment of diffuse diabetic macular oedema: a retrospective analysis. *Acta Ophthalmol*. 2011;89(8):769-773.

Lee LJ, Yu AP, Cahill KE, et al. Direct and indirect costs among employees with diabetic retinopathy in the United States. *Curr Med Res Opin*. 2008;24(5):1549-1559.

Lim JW, Lee HK, Shin MC. Comparison of intravitreal bevacizumab alone or combined with triamcinolone versus triamcinolone in diabetic macular edema: a randomized clinical trial. *Ophthalmologica*. 2012;227(2):100-106.

Lim LS, Ming C, Cheung G, Mitchell P, Wong TY. Emerging evidence concerning systemic safety of anti-VEGF agents – should ophthalmologists be concerned? *Am J Ophthalmol*. 2011;152(3):329-331.

Lin V, Yeh WS, Kowalski J. Economic evaluations for screening and treatments of diabetic retinopathy and diabetic macular edema: a systematic review. *Value Health*. 2011;14(3):A83.

Loftus JV, Sultan MB, Pleil AM for the Macugen 1013 Study Group. *Invest Ophthalmol Vis Sci*. 2011;52(10):7498-7505.

Lucentis® [package insert]. South San Francisco, CA: Genentech, Inc.; 2010.

Macugen® [package insert]. Palm Beach Gardens, FL: Eyetech Inc.; 2011.

Mangione CM, Lee PP, Gutierrez PR, et al. Development of the 25-item National Eye Institute Visual Function Questionnaire. *Arch Ophthalmol*. 2001;119(7):1050-1058.

Mansourian M, Kazemnejad A, Kazemi I, Zayeri F, Soheilian M. Using skew-symmetric mixed models for investigating the effect of different diabetic macular edema treatments by analyzing central macular thickness and visual acuity responses. *J Res Med Sci*. 2011;16(10):1319-1325.

Martin DF, Maguire MG, Ying GS, et al for the CATT Research Group. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2011;364(20):1897-1908.

Massin P, Bandello F, Garweg JG, et al. Safety and efficacy of ranibizumab in diabetic macular edema (RESOLVE Study). *Diabetes Care*. 2010;33(11):2399-2405.

Mayo Foundation for Medical Education and Research. Diseases and conditions: Diabetic retinopathy. http://www.mayoclinic.com/health/diabetic-retinopathy/DS00447. Accessed November 8, 2011.

Meyer CH, Holz FG. Preclinical aspects of anti-VEGF agents for the treatment of wet AMD: ranibizumab and bevacizumab. *Eye*. 2011;25(6):661-672.

Michaelides M, Fraser-Bell S, Hamilton R, et al. Macular perfusion determined by fundus fluoescein angiography at the 4-month time point in a prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT Study). Report 1. *Retina*. 2010;30(5):781-786.

Michaelides M, Kaines A, Hamilton RD, et al. A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT Study). 12-month data: report 2. *Ophthalmology*. 2010;117(6)1078-1086.

Miskala PH, Bressler NM, Meinert CL. Relative contributions of reduced vision and general health to NEI-VFQ scores in patients with neovascular age-related macular degeneration. *Arch Ophthalmol*. 2004;122(5):758-766.

Miskala PH, Hawkins BS, Mangione CM, et al. for the Submacular Surgery Trials Research Group. Responsiveness of the National Eye Institute Visual Function Questionnaire to changes in visual acuity. Findings in patients with subfoveal choroidal neovascularization – SST Report No. 1. *Arch Ophthalmol*. 2003;121(4):531-539.

Mitchell P (b). A systematic review of the efficacy and safety outcomes of anti-VEGF agents used for treating neovascular age-related macular degeneration: comparison of ranibizumab and bevacizumab. *Curr Med Res Opin*. 2011;27(7):1465-1475.

Mitchell P, Bandello F, Schmidt-Erfurth U, et al. on behalf of the RESTORE study group (a). The RESTORE Study. Ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmology*. 2011;118(4):615-625.

Morello, CM. Etiology and natural history of diabetic retinopathy: an overview. *Am J Health Syst Pharm*. 2007;64(17 Suppl 12):S3–7.

National Eye Institute. Vision problems in the U.S. Prevalence of adult vision impairment and age-related eye disease in America. 2008 Update to the Fourth Edition. Prevent Blindness America, 2008.

National Institute for Health and Clinical Excellence. Final appraisal determination. Ranibizumab for the treatment of diabetic macular oedema. November, 2011.

National PBM Bulletin. Intravitreal bevacizumab (Avastin®) therapy update to interim guidance. Department of Veterans Affairs, Pharmacy Benefits Management Services, October 18, 2011.

Nguyen QD, Brown DM, Marcus DM, et al. on behalf of the RISE and RIDE Research Group. Ranibizumab for diabetic macular edema. Results from 2 phase II randomized trials: RISE and RIDE. *Ophthalmology*. 2012, *in press*.

Nguyen QD, Shah SM, Khwaja AA, et al. for the READ-2 Study Group. Two-year outcomes of the ranibizumab for edema of the macula in diabetes (READ-2) study. *Ophthalmology*. 2010;117(11):2146-2151.

Nguyen QD, Shah SM, Heier JS, et al. for the READ-2 Study Group. Primary end point (six months) results of the ranibizumab for edema of the macula in diabetes (READ-2) study. *Ophthalmology*. 2009;116(11):2175-2181.

Office of Inspector General, D.R. Levinson. Review of Medicare Part B Avastin and Lucentis treatments for age-related macular degeneration. September 2011. A-01-10-00514.

Querques G, Bux AV, Martinelli D, Iaculli C, Noci ND. Intravitreal pegaptanib sodium (Macugen®) for diabetic macular oedema. *Acta Ophthalmol*. 2009;87(6):623-630.

Roh MI, Kim JH, Kwon OW. Features of optical coherence tomography are predictive of visual outcomes after intravitreal bevacizumab injection for diabetic macular edema. *Ophthalmologica*. 2010;224(6):374-380.

Romero-Aroca P. Targeting the pathophysiology of diabetic macular edema. *Diabetes Care*. 2010;33(11):2484-2485.

Romero-Aroca P. Managing diabetic macular edema: the leading cause of diabetes blindness. *World J Diabetes*. 2011;2(6):98-104.

Rosenfeld PJ. Bevacizumab versus ranibizumab for AMD. *N Engl J Med*. 2011;364(20):1966-1967.

Rosenfeld PJ. Intravitreal Avastin: the low cost alternative to Lucentis? *Am J Ophthalmol*. 2006;142(1):141-143.

Saine PJ, Tyler ME. Fundus photography overview. http://www.opsweb.org/?page=fundusphotography. Accessed February 22, 2012.

Salanti G, Marinho V, Higgins JPT. A case study of multiple-treatments meta-analysis demonstrates that covariates should be considered. *J Clin Epidemiol*. 2009;62(8):857-864.

Salman AG. Intravitreal bevacizumab for pediatric exudative retinal disease. *Saudi J Ophthalmol*. 2011;25(2):193-197.

Scott IU, Edwards AR, Beck RW, et al. for the Diabetic Retinopathy Clinical Research Network. A phase II randomized clinical trial of intravitreal bevacizumab for diabetic macular edema. *Ophthalmology*. 2007;114(10):1860-1867.

Scottish Medicines Consortium. Ranibizumab, 10g/mL solution for injection (Lucentis®) SMC No. (711/11). June, 2011. http://www.scottishmedicines.org.uk/files//advice/ranibizumab_Lucentis_FINAL_JUNE_2011_amended_050711_for_website.pdf

Sharma S, Brown GC, Brown MM, Hollands H, Shah GK. The cost-effectiveness of grid laser photocoagulation for the treatment of diabetic macular edema: results of a patient-based cost-utility analysis. *Curr Opin Ophthalmol*. 2000;11(3):175-179.

Shaw JW, Johnson JA, Coons SJ. U.S. valuation of the EQ-5D health states. *Med Care*. 2005;43(3):203-220.

Shea AM, Curtis LH, Hammill BG, et al. Resource use and costs associated with diabetic macular edema in elderly persons. *Arch Ophthalmol*. 2008;126(12):1748-1754.

Shuldiner R. Vision and driving: rules, regulations and policies. http://www.lowvisioncare.com/driving_regulations.html. Accessed February 13, 2012.

Smiddy WE. Economic considerations of macular edema therapies. *Ophthalmology*. 2011;118(9):1827-1833.

Soheilian M, Ramezani A, Obudi A, et al. Randomized trial of intravitreal bevacizumab alone or combined with triamcinolone versus macular photocoagulation in diabetic macular edema. *Ophthalmology*. 2009;116(6):1142-1150.

Soheilian M, Ramezani A, Bijanzadeh B, et al. Intravitreal bevacizumab (Avastin) injection alone or combined with triamcinolone versus macular photocoagulation as primary treatment of diabetic macular edema. *Retina*. 2007;27(9):1187-1195.

Stefánsson E. Physiology of vitreous surgery. *Graefes Arch Clin Exp Ophthalmol*. 2009;247(2):147-163.

Steinbrook R. The price of sight – ranibizumab, bevacizumab, and the treatment of macular degeneration. *N Engl J Med.* 2006;355(14):1409-1412.

Subramanian ML, Abedi G, Ness S, et al. Bevacizumab vs. ranibizumab for age-related macular degeneration: 1-year outcomes of a prospective, double-masked randomised clinical trial. *Eye*. 2010;24(11):1708-1715.

Sultan MB, Zhou D, Loftus J, Dombi T, Ice KS for the Macugen 1013 Study Group. A phase 2/3, multicenter, randomized, double-masked, 2-year trial of pegaptanib sodium for the treatment of diabetic macular edema. *Ophthalmology*. 2011;118(6):1107-1118.

Suñer IJ, Kokame GT, Yu E, Ward J, Dolan C, Bressler NM. Responsiveness of NEI VFQ-25 to changes in visual acuity in neovascular AMD: validation studies from two phase 3 clinical trials. *Invest Ophthalmol Vis Sci*. 2009;50(8):3629-3635.

Synek S, Vojniković B. Intravitreal bevacizumab with or without triamcinolone for refractory diabetic macular edema. *Coll Antropol*. 2010;34(Suppl. 2):99-103.
Thomson D. VA testing in optometric practice. Part 2: Newer chart designs. *Optometry Today.* 2005;45(11):22-24.

U.S. Preventive Services Task Force Procedure Manual. AHRQ Publication No. 08-05118-EF, July 2008. http://www.uspreventiveservicestaskforce.org/uspstf08/methods/procmanual.htm. Accessed January 23, 2012.

Virgili G, Menchini F, Dimastrogiovanni AF, et al. Optical coherence tomography versus stereoscopic fundus photography or biomicroscopy for diagnosing diabetic macular edema: A systematic review. *Invest Ophthalmol Vis Sci.* 2007;48(11):4963-4973.

Watt WS. How visual acuity is measured. Available at: http://www.mdsupport.org/library/acuity.html. Accessed on February 13, 2011.

Wells GA, Sultan SA, Chen L, Khan M, Coyle D. *Indirect Evidence: Indirect Treatment Comparisons in Meta-Analysis.* Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009.

West SK, Rubin GS, Broman AT, et al. How does visual impairment affect performance on tasks of everyday life? The SEE Project. *Arch Ophthalmol*. 2002;120(6):774-780.

Wong TY, Klein R, Islam FMA, et al. Diabetic retinopathy in a multi-ethnic cohort in the United States. *Am J Ophthalmol*. 2006;141(3):446-455.

Wong TY, Liew G, Mitchell P. Clinical update: new treatments for age-related macular degeneration. *Lancet*. 2007;370(9583):204-206.

Wong TY, Mwamburi M, Klein R, et al. Rates of progression in diabetic retinopathy during different time periods: a systematic review and meta-analysis. *Diabetes Care*. 2009; 32(12):2307-2313.

Appendix A – Visual Acuity Ranges and Notations

RANGES (ICD-9-CM)		Equivalent Notations		True Snellen Fractions (numerator = test distance)		Magnification Requirement		Visual Acuity Score (letter count)
		Decimal	US	6m (Britain)	4m (ETDRS)	MAR (1/V)	Log MAR	
(Near-) Normal Vision	Range of Normal Vision	1.6	20/12.5	6/3.8	4/2.5	0.63	-0.2	110
		1.25	20/16	6/4.8	4/3	0.8	-0.1	105
		1.0	**20/20**	**6/6**	**4/4**	**1.0**	**0**	**100**
		0.8	20/25	6/7.5	4/5	1.25	+0.1	95
	Mild Vision Loss	0.63	20/32	6/9.5	4/6.3	1.6	0.2	90
		0.5	20/40	6/12	4/8	2.0	0.3	85
		0.4	20/50	6/15	4/10	2.5	0.4	80
		0.32	20/63	6/19	4/12.5	3.2	0.5	75
Low Vision	Moderate Vision Loss	0.25	20/80	6/24	4/16	4	0.6	70
		0.20	20/100	6/30	4/20	5	0.7	65
		0.16	20/125	6/38	4/25	6.3	0.8	60
		0.125	20/160	6/48	4/32	8	0.9	55
	Severe Vision Loss	**0.10**	**20/200**	**6/60**	**4/40**	**10**	**+1.0**	**50**
		0.08	20/250	6/75	4/50	12.5	1.1	45
		0.063	20/320	6/95	4/63	16	1.2	40
		0.05	20/400	6/120	4/80	20	1.3	35
	Profound Vision Loss	0.04	20/500	6/150	4/100	25	1.4	30
		0.03	20/630	6/190	4/125	32	1.5	25
		0.025	20/800	6/240	4/160	40	1.6	20
		0.02	20/1000	6/300	4/200	50	1.7	15
(Near-) Blindness	Near-blindness	0.016	20/1250	6/380	4/250	36	1.8	10
		0.0125	20/1600	6/480	4/320	80	1.9	5
		0.01	**20/2000**	**6/600**	**4/400**	**100**	**+2.0**	**0**
		---	**---**	---	---	---	---	---
	Blindness	**No Light Perception**						

Adapted from http://www.precision-vision.com
ETDRS: Early Treatment of Diabetic Retinopathy Study; MAR: minimum angle of resolution;
Conversion of logMAR to VAS letter score:
Letter score = **100-(50*logMAR)**
(Thomson 2005, Holladay, 1997)

Appendix B – Search Criteria

Search Strategy for OVID

Databases searched:

- Medline 1996 to Present with Daily Update
- EBM Reviews – Cochrane Central Register of Controlled Trials 4th Quarter 2011

Disease State

1. Diabetic Retinopathy/ or diabetic macular edema.mp
2. Diabetic macular oedema.mp
3. Diabetic blindness.mp
4. Proliferative retinopathy.mp
5. Nonproliferative diabetic retinopathy.mp
6. ("vision loss" and diabetes).mp
7. 1 or 2 or 3 or 4 or 5 or 6

Anti-VEGF Treatment

1. (ranibizumab or lucentis).mp
2. (bevacizumab or avastin).mp
3. (pegaptanib or macugen).mp
4. (aflibercept or eylea or "trap eye").mp
5. Angiogenesis inhibitors/ or angiogenesis inhibitor*.mp
6. Vascular endothelial growth factor.mp or Vascular Endothelial Growth Factor A/
7. Vegf inhibit*.mp
8. (anti adj2 vascular).mp
9. (anti adj3 endothelial).mp
10. 1 or 5 or 6 or 7 or 8 or 9
11. 2 or 5 or 6 or 7 or 8 or 9
12. 3 or 5 or 6 or 7 or 8 or 9
13. 4 or 5 or 6 or 7 or 8 or 9

Combined Terms

1. 7 (from disease state) and 10 (from anti-VEGF treatment)
2. 7 (from disease state) and 11 (from anti-VEGF treatment)
3. 7 (from disease state) and 12 (from anti-VEGF treatment)
4. 7 (from disease state) and 13 (from anti-VEGF treatment)

- Each combined term limited to (English language and humans and yr="2000-current").
- All case reports excluded.

Search Strategy for EMBASE

Disease State

1. 'diabetic retinopathy'/mj
2. 'diabetic macular edema'/mj or 'diabetic macular oedema'/mj
3. 'diabetic blindness'
4. 'proliferative retinopathy'/exp
5. 'nonproliferative diabetic retinopathy'
6. 'vision loss'/de and 'diabetes'/de
7. 1 or 2 or 3 or 4 or 5 or 6

Anti-VEGF Treatment

1. 'ranibizumab'/de or 'lucentis'/de
2. 'bevacizumab'/de or 'avastin'/de
3. 'pegaptanib'/de or 'macugen'/de
4. 'angiogenesis inhibitor'
5. 'vasculotropin'/de
6. 'vegf'/de and inhibitor*
7. 1 or 4 or 5 or 6
8. 2 or 4 or 5 or 6
9. 3 or 4 or 5 or 6

Combined Terms

1. 7 (from disease state) and 7 (from anti-VEGF treatment)
2. 7 (from disease state) and 8 (from anti-VEGF treatment)
3. 7 (from disease state) and 9 (from anti-VEGF treatment)

- Each combined term limited to (English language and humans and [2000-2012]/py).
- All case reports excluded.

Appendix C – Study Characteristics and Quality

Table C1. Study Characteristics and Quality

Author	Year	Study Name	Funding Source	Comparators	Sample Size	Follow-up	Major Inclusion/Exclusion Criteria	Treatment Protocol	Re-treatment Protocol	Rescue Therapy	Study Quality
Ranibizumab											
Nguyen	2012	RISE	Genentech, Inc.	Ranibizumab 0.3 mg	125	24	Inclusion ▪ Study eye: 20/40 - 20/320, Snellen equivalent) ▪ CST ≥ 275 µm Key Exclusion ▪ Active PDR ▪ Prior vitreoretinal surgery ▪ Panretinal or macular laser in study eye w/in prior 3 months ▪ Intraocular corticosteroids or antiangiogenic drugs ▪ Uncontrolled HTN ▪ HbA1c > 12% ▪ CVA or MI w/in prior 3 months	Injections ▪ Given every 4 weeks for 24 months Eye Eligibility ▪ Eye with the worse VA selected for treatment	N/A	▪ Beginning at month 3, all patients were eligible for rescue laser based on study protocol	Good
				Ranibizumab 0.5 mg	125	24					
				Sham injection	127	24					
Nguyen	2012	RIDE	Genentech, Inc.	Ranibizumab 0.3 mg	125	24	Inclusion ▪ Study eye: 20/40 - 20/320, Snellen equivalent) ▪ CST ≥ 275 µm Key Exclusion ▪ Active PDR ▪ Prior vitreoretinal surgery ▪ Panretinal or macular laser in study eye w/in prior 3 months ▪ Intraocular corticosteroids or antiangiogenic drugs ▪ Uncontrolled HTN ▪ HbA1c > 12% ▪ CVA or MI w/in prior 3 months	Injections ▪ Given every 4 weeks for 24 months Eye Eligibility ▪ Eye with the worse VA selected for treatment	N/A	▪ Beginning at month 3, all patients were eligible for rescue laser based on study protocol	Good
				Ranibizumab 0.5 mg	127	24					
				Sham injection	130	24					
Mitchell	2011	RESTORE	Novartis Pharma	Ranibizumab 0.5 mg + sham laser	115	12	Inclusion ▪ Visual impairment due to focal or diffuse DME in at least 1 eye that was eligible for laser therapy ▪ BCVA of 39-78 (Snellen equiv. of 20/32 - 20/160) ▪ HbA1c ≤ 10% Exclusion ▪ Panretinal laser w/in prior 6 months ▪ Focal/grid laser w/in prior 3 months ▪ Treatment with anti-angiogenic drugs in the study eye w/in prior 3 months ▪ Systolic BP > 160 mmHg or diastolic BP > 100mmHg or untreated HTN ▪ Uncontrolled glaucoma in either eye (IOP >24 mmHg on medication) ▪ History of stroke	Injections ▪ Given at baseline and every 4 weeks through month 2 Laser ▪ Given at baseline Eye eligibility ▪ Eye with the worse VA selected for treatment	▪ Evaluations conducted every 4 weeks ▪ Injections given every 4 weeks as needed ▪ Laser therapy given every 3 months if needed	None described	Fair ▪ Analysis approach is not intent-to-treat, but with last observation carried forward
				Ranibizumab 0.5 mg + laser	118	12					
				Laser + sham injection	110	12					
Elman	2010	DRCR.net	National Eye Institute and National Institute of Diabetes and Digestive and Kidney Diseases	Sham inj. + prompt laser	293	24	Inclusion ▪ BCVA score 78 to 24 (20/32 - 20/320) ▪ CST ≥ 250 µm Exclusion ▪ Treatment for DME within prior 4 months ▪ Panretinal laser w/in prior 4 months ▪ Major ocular surgery within prior 4 months ▪ MI, other cardiac events requiring hospitalization, CVA, TIA, or treatment for acute CHF w/in prior 4 months ▪ History of open-angle glaucoma or steroid-induced IOP requiring treatment ▪ IOP ≥ 25 mmHg ▪ Systolic BP > 180 mmHg or diastolic BP > 110mmHg	Injections ▪ Given at baseline and every 4 weeks until week 16 Prompt laser ▪ Given at baseline w/in 3 to 10 days of injection Deferred laser ▪ Given at week 24 or later Eye eligibility ▪ Right eye was randomized such that one eye received sham injection + prompt laser	IVB/IVT/sham injections ▪ Evaluations conducted every 4 weeks with re-treatment given per study protocol Laser ▪ Re-treatment allowed every 13 weeks, per protocol	▪ Beginning at week 24, treatment failures could receive alternative treatments, other than original assigned therapies ▪ At 1 year, all sham injections were discontinued	Fair ▪ Masking procedures not uniform
				Ranibizumab 0.5 mg + prompt laser	187	24					
				Ranibizumab 0.5 mg + def. laser	188	24					
				Triamcinolone 4 mg + prompt laser	186	24					

Author	Year	Study Name	Funding Source	Comparators	Sample Size	Follow-up	Major Inclusion/Exclusion Criteria	Treatment Protocol	Re-treatment Protocol	Rescue Therapy	Study Quality
Massin	2010	RESOLVE	Novartis Pharma	Ranibizumab 0.3 mg Ranibizumab 0.5 mg Sham injection	51 51 49	12 12 12	Inclusion ▪ VA between 20/40 and 20/160 ▪ CRT ≥ 300 µm ▪ HbA1c ≤ 12% ▪ CSME in at least 1 eye Exclusion ▪ Panretinal laser w/in prior 6 months ▪ History of cataract surgery in the study eye w/in 6 months ▪ History of treatment w/systemic corticosteroids w/in 4 months ▪ Grid/central laser ▪ PDR in study eye	Injections ▪ Given once a month for 3 months ▪ After the first month, the dose of injection may be doubled Eye eligibility ▪ Eye with the worse VA selected	▪ Evaluations conducted every month, with re-treatment initiated according to study protocol from months 3 to 11	▪ Laser therapy available beginning at month 3	Fair ▪ Masking procedures not uniform
Nguyen	2009	READ-2	Juvenile Diabetes Research Foundation and Genentech, Inc.	Ranibizumab 0.5 mg‡ Laser‡ Ranibizumab 0.5 mg + laser	41 40 40	24 24 24	Inclusion ▪ VA between 20/40 and 20/320 ▪ CST ≥ 250 µm ▪ HbA1c ≥6% w/in 12 months Exclusion ▪ Focal and/or grid laser therapy w/in prior 3 months ▪ Intraocular injection of steroids within 3 months ▪ Intraocular injection of VEGF antagonist within 2 months	Ranibizumab ▪ Injections given at baseline, and months 1,3 & 5 Laser ▪ Treatment given at baseline Ranibizumab + laser ▪ Injections given at baseline & month 3, with laser given 1 week after each injection Eye eligibility ▪ Eye with the greater CST selected	Ranibizumab ▪Beginning at month 6, evaluations conducted every 2 months Laser ▪ Evaluation conducted at month 3 for re-treatment per study protocol ▪ Beginning at month 6, patients eligible for laser every 3 months Ranibizumab + laser ▪ Beginning at month 6, patients eligible for laser every 3 months and/or ranibizumab every 2 months	Laser ▪ Ranibizumab therapy available every 2 months, per study protocol	Poor ▪ Randomization and masking procedures not described ▪ Analysis approach is not intent-to-treat
Bevacizumab											
Lim	2012	n/a	NR	Bevacizumab 1.25 mg‡ Bevacizumab 1.25 mg + Triamcinolone 2 mg‡ Triamcinolone 2 mg‡	38 36 37	12 12 12	Inclusion ▪ Eyes with CSME ▪ DME with CMT≥ 300µm Exclusion ▪ Any previous treatment for DME ▪ History of vitreoretinal surgery ▪ History of uncontrolled glaucoma ▪ PDR w/active neovascularization ▪ Previous panretinal laser ▪ Presence of vitreomacular traction ▪ History of systemic corticosteroids w/in prior 6 months	Injections ▪ Given at baseline Eye Eligibility ▪ If both eyes eligible, the allocated treatment was applied to the right eye, and the left eye received the other treatment	Evaluations conducted every 6 weeks	Patients in each group eligible for treatment with IVB at 6-week intervals	Poor ▪ Masking procedures not described ▪ Analysis approach is not intent-to-treat
Michaelides	2010	BOLT	Moorfields Special Trustees & National Institute for Health Research UK	Bevacizumab 1.25 mg‡ Laser‡	42 38	12 12	Inclusion ▪ BCVA 35 to 69 (Snellen ≥6/60 or ≤6/12 ▪ CSME w/CMT≥ 270µm ▪ At least 1 prior macular laser therapy ▪ IOP<30 mmHg ▪ Fellow eye BCVA ≥3/60 ▪ Fellow eye received no anti-VEGF treatment w/in prior 3 months Exclusion ▪ Any treatment for DME w/in prior 3 months ▪ Panretinal laser w/in prior 3 months ▪ PDR ▪ HbA1c> 11.0% ▪ History of chronic kidney disease requiring dialysis or transplant ▪ BP > 170/110 mmHg ▪ Any thromboembolic event w/in prior 6 months, UA or evidence of active ischemia on ECG ▪ Major surgery w/in prior 28 days ▪ Systemic anti-VEGF or pro-VEGF treatment w/in prior 3 months ▪ Intraocular surgery w/in prior 3 months ▪ Aphakia ▪ Uncontrolled glaucoma	Laser ▪ Treated at baseline IVB ▪ Given at baseline, 6 & 12 weeks Eye Eligibility ▪ Eye with the worse VA was randomized	Laser ▪ Evaluations conducted every 4 months IVB ▪ At 18 weeks and after, evaluations conducted every 6 weeks	None described	Fair ▪ Patients and study investigators not masked

Author	Year	Study Name	Funding Source	Comparators	Sample Size	Follow-up	Major Inclusion/Exclusion Criteria	Treatment Protocol	Re-treatment Protocol	Rescue Therapy	Study Quality
Synek	2010	n/a	NR	Bevacizumab 1.25 mg	30	6	Inclusion ▪ Eyes w/CSME, unresponsive to previous macular laser therapy ▪ Last laser therapy at least 3 months prior Exclusion ▪ VA = 20/40 ▪ History of cataract surgery w/in prior 6 months ▪ Prior intraocular injection or vitrectomy ▪ History of glaucoma or ocular HTN ▪ PDR w/high-risk characteristics ▪ Vitreous hemorrhage, significant media opacity, or presence of traction on the macula ▪ Monocular patients	IVB ▪ Given at baseline ▪ 2 subsequent injections, interval NR IVB + IVT ▪ Injection of both agents given at baseline ▪ 2 subsequent injections of only IVB given, dosing interval NR Eye Eligibility No data provided	None given	None described	Poor ▪ Only patients masked ▪ Inadequate baseline demographics provided
				Bevacizumab 1.25 mg + Triamcinolone 2 mg (x1, given as 1 injection)	30	6					
Soheilian	2009	n/a	Ophthalmic Research Center, Shahid Beheshti University, Tehran, Iran	Bevacizumab 1.25 mg + sham laser	50	9	Inclusion ▪ Eyes with CSME Exclusion ▪ Previous panretinal or focal laser therapy ▪ Prior intraocular surgery or injection ▪ History of glaucoma or ocular HTN ▪ VA 20/40 to 20/300 ▪ Presence of iris neovascularization ▪ High-risk PDR ▪ Monocular patients ▪ Serum creatinine ≥3 mg/dl ▪ Uncontrolled diabetes	Laser/injections ▪ Given at baseline Eye Eligibility ▪ No data provided on eye eligibility	Evaluations conducted every 12 weeks	None described	Fair ▪ Lack of information on analysis approach
				Bevacizumab 1.25 mg + Triamcinolone 2 mg + sham laser	50	9					
				Laser + sham injection	50	9					
Ahmadieh	2008	n/a	NR	Bevacizumab 1.25 mg	41	6	Inclusion ▪ Patients w/ CSME, previously unresponsive to macular laser therapy ▪ Last laser therapy at least 3 months prior Exclusion ▪ VA = 20/40 ▪ History of cataract surgery w/in prior 6 months ▪ Prior intraocular injection or vitrectomy ▪ History of glaucoma or ocular HTN ▪ PDR w/high-risk characteristics ▪ Vitreous hemorrhage, significant media opacity, or presence of traction on the macula patients ▪ Monocular patients ▪ Serum creatinine ≥3 mg/dl	IVB ▪ Injections given at baseline, 6 & 12 weeks IVB + IVT ▪ Injection of both agents given at baseline ▪ 2 subsequent injections of only IVB given at 6 & 12 weeks Eye Eligibility If both eyes eligible, each eye was individually enrolled in the study	None given	None described	Fair ▪ Inadequate masking of study investigators
				Bevacizumab 1.25 mg + Triamcinolone 2 mg (x1)	37	6					
				Sham injection	37	6					
Scott	2007	DRCR.net	National Eye Institute, National Institute of Diabetes and Digestive and Kidney Diseases, and the Juvenile Diabetes Research Foundation International	Laser‡	19	3	Inclusion ▪ BCVA 24 - 78 (Snellen 20/32 - 20/320) ▪ CST ≥275 µm ▪ Only one study per patient ▪ In fellow eye, BCVA ≥19 (Snellen 20/400 or better) ▪ In fellow eye, no anti-VEGF treatment w/in prior 3 months Exclusion ▪ History of treatment for DME w/in prior 3 months ▪ History of panretinal scatter photocoagulation w/in prior 4 months ▪ History of pars plana vitrectomy ▪ History of major ocular surgery w/in prior 6 months ▪ History of YAG capsulotomy w/in prior 2 months ▪ Aphakia ▪ Uncontrolled glaucoma ▪ Substantial cataract that is likely to be decreasing VA by ≥3 lines ▪ Systemic anti-VEGF or pro-VEGF treatment w/in prior 3 months ▪ Significant renal disease requiring dialysis or transplant ▪ BP >180/110 ▪ Major surgery within 28 days or planned in next 6 months ▪ MI, any other cardiac event requiring hospitalization, stroke, TIA, or treatment for acute CHF within prior 6 months	Laser ▪ Treated at baseline IVB 1.25 mg ▪ Injections given at baseline and 6 weeks IVB 2.5 mg ▪ Injections given at baseline and 6 weeks IVB 1.25 mg + sham ▪ Injection given at baseline and sham given at 6 weeks IVB 1.25 mg + laser ▪ Injections given at baseline and 6 weeks, laser given at 3 weeks Eye Eligibility ▪ Eye selected by the patient and the investigator	▪ Evaluations conducted at 12 and 18 weeks ▪ Treatment given per investigator discretion if not meeting deferral criteria	▪ Patients receiving only laser at baseline were eligible for bevacizumab 1.25 mg at weeks 12 and 18 ▪ At 24 weeks, all groups treated per investigator discretion	Poor ▪ Randomization procedure not described ▪ Inadequate masking of patients and study investigators
				Bevacizumab 1.25 mg*	22	3					
				Bevacizumab 2.5 mg*	24	3					
				Bevacizumab 1.25 mg & sham injection*	22	3					
				Bevacizumab 1.25 mg + Laser	22	3					

Author	Year	Study Name	Funding Source	Comparators	Sample Size	Follow-up	Major Inclusion/Exclusion Criteria	Treatment Protocol	Re-treatment Protocol	Rescue Therapy	Study Quality
Pegaptanib											
Sultan	2011	Macugen 1013 Study Group	Pfizer Inc.	Pegaptanib 0.3 mg	133	24	Inclusion ▪ DME involving the center of the macula not associated with ischemia ▪ Foveal thickness ≥250 µm ▪ BCVA 35-65 (Snellen 20/50 - 20/200) ▪ IOP ≤21 mmHg Exclusion ▪ Atrophy/scarring/fibrosis involving the center of the macula ▪ Subfoveal hard exudates or retinal pigment epithelial atrophy ▪ YAG laser, peripheral retinal cryoablation, laser retinopexy for retinal tears ▪ Focal/grid photocoagulation w/in prior 16 weeks ▪ Panretinal photocoagulation w/in prior 6 months ▪ Any intraoclar surgery in prior 6 months or history of vitrectomy; previous filtering surgery or placement of a drainage device ▪ Pathologic high myopia ▪ Prior radiation in the region of the study eye ▪ History/evidence of severe cardiac disease or PVD ▪ Stroke w/in prior 12 months or any major surgery w/in prior 1 month ▪ HbA1c ≥10% or recent signs of uncontrolled diabetes ▪ Systolic BP >160 mmHg or diastolic BP >100 mmHg	Injections ▪ Given every 6 weeks through week 48 Eye Eligibility ▪ If both eyes eligible, investigators selected one eye; fellow eye was treated according to standard of care (no definition provided)	▪ Evaluations conducted every 6 weeks during year 2	▪ Beginning at week 18, laser permitted every 17 weeks as needed	Fair ▪ Modified intent-to-treat analyses utilized
				Sham injection	127	24					
Cunningham	2005	Macugen DR Study Group	Eyetech Pharmaceuticals, Inc. and Pfizer Inc.	Pegaptanib 0.3 mg	44	9	Inclusion ▪ BCVA of 25-68 (Snellen 20/50 - 20/320) in study eye and at least 35 (20/100) or better in fellow eye ▪ IOP ≤23 mmHg ▪ No clinically relevant abnormalities on an ECG ▪ No clinically meaningful hematological, liver or renal abnormalities Exclusion ▪ History of panretinal or focal photocoagulation, YAG-laser or peripheral retinal cryoablation w/in prior 6 months ▪ Vitreoretinal traction within 1 disc diameter of the fovea ▪ Vitreous incarceration in a previous wound or incision ▪ Any retinal vein occlusion invloving the macula ▪ Atrophy/scarring/fibrosis or hard exudates involving the center of the macula ▪ History of any intraocular surgery w/in prior 12 months ▪ Myopia of ≥8 diopters, axial length of ≥25 mm ▪ Previous therapeutic radiation to the eye, head or neck ▪ HbA1c ≥13% ▪ ≥3 episodes of severe hypoglycemia w/in prior 3 months ▪ ≥2 episodes of ketoacidosis w/in 1 year, or any episode w/in prior 3 months ▪ Evidence of severe cardiac disease, clinically significant PVD, uncontrolled hypertension (treated systolic BP >155 or diastolic BP >95), or stroke w/in prior 12 months	Injections ▪ Given every 6 weeks for 3 injections Eye Eligibility ▪ If both eyes eligible for study, physician and patient selected study eye	▪ Evaluations conducted every 6 weeks beginning at week 18	▪ Laser permitted beginning at week 13	Fair ▪ Incomplete masking of study personnel
				Pegaptanib 1 mg	44	9					
				Pegaptanib 3 mg	42	9					
				Sham injection	42	9					

Author	Year	Study Name	Funding Source	Comparators	Sample Size	Follow-up	Major Inclusion/Exclusion Criteria	Treatment Protocol	Re-treatment Protocol	Rescue Therapy	Study Quality
Aflibercept											
Do	2011	Da Vinci Study	Regeneron Pharmaceuticals, Inc.	VEGF Trap-Eye 0.5 mg + sham laser (Group A) VEGF Trap-Eye 2 mg + sham laser (Group B) VEGF Trap-Eye 2 mg + sham laser + sham injection (Group C) VEGF Trap-Eye 2 mg + sham laser + sham injection (Group D) Macular laser + sham injection (Group E)	44 44 42 45 44	6 6 6 6 6	Inclusion ▪ BCVA 24 to 73 (Snellen 20/40 - 20/320) Exclusion ▪ History of vitreoretinal surgery ▪ Panretinal or macular laser photocoagulation ▪ Use of intraocular or periocular corticosteroids or anti-angiogenic drugs w/in prior 3 months ▪ PDR, unless regressed and inactive ▪ Cataract or other intraocular surgery w/in prior 3 months, or laser capsulotomy w/in prior 2 months ▪ Aphakia ▪ Active iris neovscularization, vitreous hemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula ▪ Visually significant vitreomacular traction or epiretinal membrane ▪ History of idiopathic or autoimmune uveitis ▪ Uncontrolled glaucoma or previous filtration surgery ▪ Infectious blepharitis, keratitis, scleritis or conjunctivitis ▪ Uncontrolled diabetes or hypertension ▪ History of CVA or MI within prior 6 months ▪ Renal failure requiring dialysis or transplant ▪ Only 1 functional eye, even if eye met all other entry criteria ▪ Ocular condition in the fellow eye with a poorer prognosis than the study eye	Group A ▪ Injections given every 4 weeks Group B ▪ Injections given every 4 weeks Group C ▪ Injections given every 4 weeks for 3 injections, and then every 8 weeks ▪ Sham injections given during weeks when active drug was not injected Group D ▪ Injections given every 4 weeks for 3 injections, and then as needed ▪ Sham injections given during weeks when active drug was not injected Group E ▪ Laser given at baseline ▪ Sham laser given at baseline for Groups A - D Eye eligibility ▪ Eye with worse prognosis was selected for inclusion	Group D ▪ Evaluations conducted every 4 weeks Group E ▪ Evaluations conducted every 16 weeks	None described	Fair ▪ Analysis approach is not intent-to-treat, but with last observation carried forward

BCVA: best-corrected visual acuity; BP: blood pressure; CHF: congestive heart failure; CRT: central retinal thickness; CSME: clinically significant macular edema; CST: central subfield thickness; CVA: cerebrovascular accident; DME: diabetic macular edema; ECG: electrocardiogram; HbA1c: glycosylated hemoglobin test; HTN: hypertension; IOP: increased ocular pressure; IVB: intravitreal bevacizumab; IVT: intravitreal triamcinolone; MI: myocardial infarction; N/A: not available; NR: not reported; PDR: proliferative diabetic retinopathy; PVD: peripheral vascular disease; TIA: transient ischemic attack; UA: unstable angina; VA: visual acuity; VEGF: vascular endothelial growth factor; YAG: yttrium-aluminum-garnet

‡ No sham therapies given
* No sham laser given

Table C2. Patient Characteristics for RCTs

Author	Year	Comparators	Mean Age (±SD)		Females n (%)		Diabetes Type 2 n (%)		Mean HbA1c (% ± SD)		Mean time since diagnosis of diabetes (years ± SD)		Mean time since first diagnosis of DME (years ± SD)		Previous laser therapy n (%)		Mean VA, ETDRS (letters ± SD)		Mean CRT (µm ± SD)	
Ranibizumab																				
Nguyen RISE	2012	Ranibizumab 0.3 mg	61.7	8.9	52	41.6	NR	NR	7.7	1.5	15.9	9.9	NR	NR	86	68.8	54.7	12.6	474.5	174.8
		Ranibizumab 0.5 mg	62.8	10	60	48	NR	NR	7.7	1.4	16.3	8.5	NR	NR	90	72	56.9	11.6	463.8	144
		Sham injection	61.8	9.8	53	41.7	NR	NR	7.7	1.5	14.5	9.9	NR	NR	86	67.7	57.2	11.1	467.3	152
Nguyen RIDE	2012	Ranibizumab 0.3 mg	62.7	11.1	52	41.6	NR	NR	7.6	1.3	16	9.8	NR	NR	72	57.6	57.5	11.6	482.6	149.3
		Ranibizumab 0.5 mg	61.8	10.1	47	37	NR	NR	7.6	1.5	15.3	10.1	NR	NR	79	62.2	56.9	11.8	463.8	175.5
		Sham injection	63.5	10.8	64	49.2	NR	NR	7.6	1.4	16.6	10.6	NR	NR	84	64.6	57.3	11.2	447.4	154.4
Mitchell	2011	Ranibizumab 0.5 mg + sham laser	62.9	9.29	43	37.1	103	88.8	NR	NR	15.23	9.91	1.8	1.98	NR	NR	64.8	10.11	426.6	118.01
		Ranibizumab 0.5 mg + laser	64	8.15	48	40.7	102	86.4	NR	NR	14.62	9.84	1.99	3.14	NR	NR	63.4	9.99	416.4	119.91
		Laser + sham injection	63.5	8.81	53	47.7	97	87.4	NR	NR	12.93	9.02	1.58	1.96	NR	NR	62.4	11.11	412.4	123.95
Elman	2010	Sham inj. + prompt laser	63*	57,69	123	42	260	89	7.3*	6.6,8.3	16*	9,22	NR	NR	173	59	65*	56,73	407*	309,505
		Ranibizumab 0.5 mg + prompt laser	62	56,70	85	45	172	92	7.3	6.6,8.4	18	12,24	NR	NR	101	54	66	55,72	371	302,464
		Ranibizumab 0.5 mg + def. laser	64	58,70	78	41	170	90	7.5	6.7,8.4	17	11,22	NR	NR	101	54	66	58,72	382	298,488
		Triamcinolone 4 mg + prompt laser	62	55,70	86	46	166	89	7.4	6.5,8.6	17	11,24	NR	NR	114	61	66	57,72	374	298,463
Massin	2010	Ranibizumab 0.3 mg	63.2	NR	22	43.1	50	98	7.3	NR	14.4	NR	1.2	NR	10	19.6	59.2	10.2	459.5	109.1
		Ranibizumab 0.5 mg	62.8	NR	24	47.1	49	96.1	7.6	NR	13.9	NR	1.1	NR	9	17.6	61.2	9.5	451.3	120.1
		Sham injection	65	NR	24	49	48	98	7.5	NR	15.1	NR	1.4	NR	9	18.4	61.1	9	448.9	102.8
Nguyen	2009	Ranibizumab 0.5 mg	62	NR	28	69	NR	NR	7.39	NR	NR	NR	NR	NR	NR	NR	24.85	NR	NR	NR
		Laser	62	NR	22	55	NR	NR	7.77	NR	NR	NR	NR	NR	NR	NR	28.35	NR	NR	NR
		Ranibizumab 0.5 mg + laser	62	NR	21	52	NR	NR	7.59	NR	NR	NR	NR	NR	NR	NR	24.87	NR	NR	NR
Bevacizumab																				
Lim	2012	Bevacizumab 1.25 mg	61.4	6.7	19	50.0	NR	NR	7.4	1.1	12.4	4.5	NR	NR	NR	NR	69	11.5	447	110
		Bevacizumab 1.25 mg + Triamcinolone 2 mg	58.4	5.9	18	50.0	NR	NR	7.5	1.2	12.5	5.4	NR	NR	NR	NR	68	12.5	458	92
		Triamcinolone 2 mg	59.8	7.9	18	48.6	NR	NR	7.2	1.2	13	5.1	NR	NR	NR	NR	67.5	14	449	106
Michaelides	2010	Bevacizumab 1.25 mg	64.9	9.4	12	28.6	38	90.5	7.6	1.4	13.5	8.3	2*	18-48	NR	NR	55.7	9.7	507	145
		Laser	63.5	8.1	13	34.2	34	89.5	7.5	1.2	14.75	7.9	3	24-55	NR	NR	54.6	8.6	481	121
Synek	2010	Bevacizumab 1.25 mg	NR	NR	NR	NR	NR	NR	9.95	NR	NR	NR	NR	NR	?30	100	NR	NR	NR	NR
		Bevacizumab 1.25 mg + Triamcinolone 2 mg (x1, given as 1 injection)	NR	NR	NR	NR	NR	NR	9.35	NR	NR	NR	NR	NR	30	100	NR	NR	NR	NR
Soheilian	2009	Bevacizumab 1.25 mg + sham laser	60.5	5.9	27	54	NR	NR	NR	NR	10.5	3.2	NR	NR	0	0	64.5	14	341	149
		Bevacizumab 1.25 mg + Triamcinolone 2 mg + sham laser	62.3	6.8	22	44	NR	NR	NR	NR	10.4	2.6	NR	NR	0	0	63.5	14	359	137
		Laser + sham injection	61	5.3	22	44	NR	NR	NR	NR	10.5	2.9	NR	NR	0	0	72.5	13	300	118
Ahmadieh	2008	Bevacizumab 1.25 mg	NR	NR	NR	NR	NR	NR	9.95	NR	NR	NR	NR	NR	41	100	NR	NR	NR	NR
		Bevacizumab 1.25 mg + Triamcinolone 2 mg (x1)	NR	NR	NR	NR	NR	NR	9.35	NR	NR	NR	NR	NR	37	100	NR	NR	NR	NR
		Sham injection	NR	NR	NR	NR	NR	NR	10.06	NR	NR	NR	NR	NR	37	100	NR	NR	NR	NR

Author	Year	Comparators	Mean Age (±SD)		Females n (%)		Diabetes Type 2 n (%)		Mean HbA1c (% ± SD)		Mean time since diagnosis of diabetes (years ± SD)		Mean time since first diagnosis of DME (years ± SD)		Previous laser therapy n (%)		Mean VA, ETDRS (letters ± SD)		Mean CRT (µm ± SD)	
Scott	2007	Laser, baseline	64*	57,72	9	47	18	95	7*	6.5,8.2	17*	13,22	NR	NR	12	63.2	64*	50,70	441*	354,512
		Bevacizumab 1.25 mg, baseline & 6 weeks	63	54,73	6	27	21	95	7.4	5.9,7.8	15	8,22	NR	NR	14	63.6	65	60,70	397	320,538
		Bevacizumab 2.5 mg, baseline & 6 weeks	68	59,75	9	38	21	88	7.3	6.4,8.4	18	12,22	NR	NR	12	50.0	63	57,71	446	342,543
		Bevacizumab 1.25 mg, baseline & sham at 6 weeks	60	54,75	9	41	20	91	6.7	6.3,7.4	17	11,25	NR	NR	17	77.3	64	52,68	406	353,520
		Bevacizumab 1.25 mg, baseline & 6 weeks, laser at 3 weeks	67	60,71	10	45	21	95	7.1	6.2,7.7	20	7,30	NR	NR	15	68.2	66	57,72	389	308,452
Pegaptanib																				
Sultan	2011	Pegaptanib 0.3 mg	62.3	9.3	52	39.1	123	92.5	NR	NR	NR	NR	NR	NR	NR	NR	57	8.9	441.6	148.5
		Sham injection	62.5	10.2	59	46.46	119	93.7	NR	NR	NR	NR	NR	NR	NR	NR	57.5	8.1	464.6	135.5
Cunningham	2005	Pegaptanib 0.3 mg	61.9	10	20	45	42	95.5	7.1	1.2	NR	NR	NR	NR	34	77	57.1	11.5	465.5	NR
		Pegaptanib 1 mg	62.8	10.1	22	50	42	95.5	7.6	1.5	NR	NR	NR	NR	36	82	55	10.5	436.8	NR
		Pegaptanib 3 mg	61.3	9.8	23	55	38	90.5	7.7	1.6	NR	NR	NR	NR	27	64	57	9.1	442	NR
		Sham injection	64	9.3	19	45	38	90.5	7.2	1.4	NR	NR	NR	NR	30	71	55.8	9.5	432.7	NR
Aflibercept																				
Do	2011	VEGF Trap-Eye 0.5 mg + sham laser	62.3	10.7	20	45.5	43	97.7	8.1	1.91	NR	NR	NR	NR	21	47.7	59.3	11.2	426.1	128.3
		VEGF Trap-Eye 2 mg + sham laser	62.1	10.5	17	38.6	41	93.2	8.08	1.94	NR	NR	NR	NR	23	52.3	59.9	10.1	456.6	135
		VEGF Trap-Eye 2 mg + sham laser + sham injection	62.5	11.5	20	47.6	38	90.5	7.85	1.72	NR	NR	NR	NR	28	66.7	58.8	12.2	434.8	111.8
		VEGF Trap-Eye 2 mg + sham laser + sham injection	60.7	8.7	16	35.6	43	95.6	7.97	1.71	NR	NR	NR	NR	26	57.8	59.6	11.1	426.6	152.4
		Macular laser + sham injection	64	8.1	17	38.6	39	88.6	7.93	1.84	NR	NR	NR	NR	22	50	57.6	12.5	440.6	145.4

CRT: central retinal thickness; DME: diabetic macular edema; ETDRS: Early Treatment Diabetic Retionopathy Study; HbA1c: glycosylated hemoglobin test; RCT: randomized controlled trial; VA: visual acuity

* median, IQR

Table C3. Study characteristics for excluded RCTs

Author	Year	Study Name	Funding Source	Comparators	Sample Size	Follow-up	Major Inclusion/Exclusion Criteria	Treatment Protocol	Re-treatment Protocol	Rescue Therapy	Reason for Exclusion
Bevacizumab											
Marey	2011	N/A	NR	Bevacizumab 1.25 mg + sham injection Bevacizumab 1.25 mg + Triamcinolone 2 mg Triamcinolone 4 mg + sham injection	30 30 30	3 3 3	Inclusion ▪ Eyes with CSME Exclusion ▪ Previous laser treatment ▪ Previous intraocular injection ▪ Previous intraocular surgery ▪ History of glaucoma or ocular hypertension	Injections ▪ Given at baseline Eye Eligibility ▪ No data provided on eye eligibility	None given	None described	Baseline treatment only
Cho	2010	N/A	NR	Bevacizumab 1.25 mg + laser Laser Triamcinolone 4 mg + laser	16 14 16	3 3 3	Inclusion ▪ Patients with very severe NPDR to high-risk PDR ▪ Snellen BCVA ≥ 0.3 Exclusion ▪ History of treatment for DME w/in prior 3 months ▪ Previous PRP or focal/grid laser therapy ▪ Previous intraocular surgery ▪ Uncontrolled glaucoma ▪ Previous systemic steroid of anti-VEGF treatment ▪ BP > 180/110 mmHg ▪ HbA1c ≥9.5% ▪ Chronic renal failure ▪ Major surgery w/in prior 1 month	Injections ▪ Given at baseline Laser ▪ Given 1 week following injection, with 2 subsequent treatments at 1-week intervals Eye Eligibility ▪ If both eyes eligible, one eye was randomized to treatment and the other eye received the other procedure	None given	None described	Baseline treatment only
Lanzagorta-Aresti	2009	N/A	NR	Bevacizumab 0.05ml Balanced saline solution 0.05ml	13 13	6 6	Inclusion ▪ Patients with diffuse DME undergoing cataract surgery ▪ Patients with moderate NPDR Exclusion ▪ Previous eye surgery ▪ Patients suffering complications during surgery or in post-operative period	Injections ▪ Given upon completion of cataract surgery Eye Eligibility ▪ Eye with less visual acuity chosen as this was first eye to have cataract surgery	None given	None described	Baseline treatment only
Takamura	2009	N/A	NR	Bevacizumab 1.25 mg No injection‡	21 21	3 3	Inclusion ▪ Macular thickness > 300 µm ▪ Significant lens opacity (> grade 3) ▪ DME occuring w/in prior 3-18 months ▪ ME involving the fovea ▪ BCVA ≤ 20/40 Exclusion ▪ History of ocular surgery and inflammation ▪ Presence of other ocular diseases and intraoperative complications ▪ PDR ▪ Photocoagulation w/in prior 12 months ▪ Previous intravitreal injections	Injections ▪ Given upon completion of cataract surgery Eye Eligibility ▪ No data provided on eye eligibility	None given	None described	Baseline treatment only

Author	Year	Study Name	Funding Source	Comparators	Sample Size	Follow-up	Major Inclusion/Exclusion Criteria	Treatment Protocol	Re-treatment Protocol	Rescue Therapy	Reason for Exclusion
Faghihi	2008	N/A	NR	Laser‡	47	4	Inclusion ▪ BCVA ≤ 20/40 (≤ 0.3 logMAR) ▪ CMT ≥ 250 µm Exclusion ▪ ME related to recent intraocular surgery or other procedures ▪ Vitreous traction ▪ History of any treatment for DR at any time ▪ Uncontrolled glaucoma ▪ Recent history of thromboembolic event ▪ Poorly controlled HTN	Laser/injections ▪ Given at baseline Eye Eligibility ▪ No data provided on eye eligibility	Evaluation at end of study	None described	Baseline treatment only
				Bevacizumab 1.25 mg‡	42	4					
				Bevacizumab 1.25 mg + Triamcinolone 2 mg‡	41	4					
Paccola	2008	IBEME	National Council for Science and Technological Development, and the State of São Paulo	Bevacizumab 1.5 mg	13	6	Inclusion ▪ Refractory DME, defined as CSME persisting despite at least 1 session of macular laser therapy w/in prior 3 months w/diffuse leakage ▪ logMAR BCVA of 0.3 (Snellen 20/40) or worse ▪ CMT ≥ 300 µm Exclusion ▪ Aphakic or pseudophakic eyes ▪ HbA1c >10% ▪ History of glaucoma or ocular HTN (IOP>22 mmHg) ▪ Systemic corticosteroid therapy	Injections ▪ Given at baseline Eye Eligibility ▪ Eye with the worse VA was randomized	None given	None described	Baseline treatment only
				Triamcinolone 4 mg	13	6					
Shimura CCT	2008	N/A	NTT East Japan Tohoku Hospital, Sendai, Miyagi, Japan	Bevacizumab 1.25 mg	14	6	Inclusion ▪ Patients w/bilateral DME ▪ Foveal thickness > 400 µm ▪ VA worse than 0.3 logMAR in both eyes Exclusion ▪ Previous therapies for ME, including grid laser, intravitreal injection of any drugs and/or vitreous surgery	Injections ▪ Given at baseline Eye Eligibility ▪ Eye with the thicker foveal thickness was defined as the primary eye, and the other eye was the secondary eye	None given	None described	Baseline treatment only
				Triamcinolone 4 mg	14	6					

BCVA: best-corrected visual acuity; BP: blood pressure; CMT: central macular thickness; CSME: clinically significant macular edema; DME: diabetic macular edema; DR: diabetic retinopathy; HbA1c: glycosylated hemoglobin test; HTN: hypertension; IOP: increased ocular pressure; logMAR: logarithm of the minimum angle of resolution; ME: macular edema; N/A: not available; NPDR: nonproliferative diabetic retinopathy; NR: not reported; PDR: proliferative diabetic retinopathy; PRP: pan-retinal photocoagulation; RCT: randomized controlled trial; VA: visual acuity; VEGF: vascular endothelial growth factor;

Appendix D – Treatment-Related Outcomes

Table D1. Visual Acuity

Author	Year	Comparators	Timepoint (months)	Mean Change in BCVA (± SD)	Difference vs. Sham or Laser	p-value	Gain of ≥10 letters n(%)	p-value	Gain of ≥15 letters n(%)	p-value	Loss of ≥10 letters n(%)	p-value	Loss of ≥15 letters n(%)	p-value
Ranibizumab														
Nguyen RISE	2012	Ranibizumab 0.3 mg	24	12.5 ± 14.1	9.6	<0.0001	78 (62.4)	<0.0001	56 (44.8)	<0.0001	NR	NR	NR	NR
		Ranibizumab 0.5 mg	24	11.9 ± 12.1	9.4	<0.0001	78 (62.4)	<0.0001	49 (39.2)	0.0002	NR	NR	NR	NR
		Sham injection	24	2.6 ± 13.9	--	--	38 (29.9)	--	23 (18.1)	--	NR	NR	NR	NR
Nguyen RIDE	2012	Ranibizumab 0.3 mg	24	10.9 ± 10.4	8.5	<0.0001	74 (59.2)	<0.0001	42 (33.6)	<0.0001	NR	NR	NR	NR
		Ranibizumab 0.5 mg	24	12 ± 14.9	9.9	<0.0001	82 (64.6)	<0.0001	58 (45.7)	<0.0001	NR	NR	NR	NR
		Sham injection	24	2.3 ± 14.2	--	--	33 (25.4)	--	16 (12.3)	--	NR	NR	NR	NR
Mitchell	2011	Ranibizumab 0.5 mg + sham laser	12	6.8 ± 8.3	NR	<0.0001	43(37)	<0.0001	26(23)	0.0005	4(3)	NR	1(1)	NR
		Ranibizumab 0.5 mg + laser	12	6.4 ± 11.8	NR	0.0004	51(43)	<0.0001	27(23)	0.0037	5(4)	NR	4(3)	NR
		Laser + sham injection	12	0.9 ± 11.4	NR	--	17(15)	--	9(8)	--	14(13)	NR	9(8)	NR
Elman	2010	Sham inj. + prompt laser	12	3 ± 13		--	81 (28)	--	43(15)	--	39(13)	--	23(8)	--
		Ranibizumab 0.5 mg + prompt laser	12	9 ± 11	5.8	<0.001	95(51)	<0.001	57(30)	<0.001	6(3)	<0.001	3(2)	0.009
		Ranibizumab 0.5 mg + def. laser	12	9 ± 12	6.0	<0.001	88(47)	<0.001	52(28)	<0.001	6(3)	<0.001	4(2)	0.01
		Triamcinolone 4 mg + prompt laser	12	4 ± 13	1.1	0.31	61(33)	0.16	39(21)	0.07	27(15)	0.75	15(8)	0.95
		Sham inj. + prompt laser	24	3 ± 15	--	--	75 (36)	--	37 (18)	--	27 (13)	--	21 (10)	--
		Ranibizumab 0.5 mg + prompt laser	24	7 ± 13	3.7	0.03	60 (44)	0.17	39 (29)	0.03	10 (7)	0.12	6 (4)	0.08
		Ranibizumab 0.5 mg + def. laser	24	9 ± 14	5.8	<0.001	68 (49)	0.01	39 (28)	0.01	4 (3)	0.005	3 (2)	0.01
		Triamcinolone 4 mg + prompt laser	24	2 ± 19	-1.5	0.35	58 (41)	0.19	31 (22)	0.18	27 (19)	0.10	19 (13)	0.34
Massin	2010	Ranibizumab 0.3 mg	12	11.8 ± 6.6	13.4	<0.0001	37(73)	<0.0001#	18(35)	0.0001#	0(0)	#	0(0)	#
		Ranibizumab 0.5 mg	12	8.8 ± 11.0	10.6	<0.0001	25(49)	0.001#	15(29)	0.0037#	5(10)	#	3(6)	#
		Sham injection	12	-1.4 ± 14.2	--	--	9(18)	--	5(10)	--	12(25)	#	10(20)	#
Nguyen READ-2	2009	Ranibizumab 0.5 mg	3	3.98	NR	0.01^	NR	NR	NR	NR	NR	NR	NR	NR
		Laser	3	-1.48	NR	--	NR	NR	NR	NR	NR	NR	NR	NR
		Ranibizumab 0.5 mg + laser	3	1.93	NR	0.22ϕ	NR	NR	NR	NR	NR	NR	NR	NR
		Ranibizumab 0.5 mg	6	7.24	NR	0.0001^	17/37(46)	0.00004^	8/37(22)	0.002^	NR	NR	NR	NR
		Laser	6	-0.43	NR	--	2/38(5)	--	0(0)	--	NR	NR	NR	NR
		Ranibizumab 0.5 mg + laser	6	3.8	NR	0.08ϕ	12/40(30)	0.007^	3/40(8)	--	NR	NR	NR	NR
		Ranibizumab 0.5 mg	12	6.61	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		Laser	12	2.39	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		Ranibizumab 0.5 mg + laser	12	4.81	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		Ranibizumab 0.5 mg	24	7.70	NR	NSψ	NR	NR	8/33(24)	NR	NR	NR	NR	NR
		Laser	24	5.10	NR	--	NR	NR	6/34(18)	NR	NR	NR	NR	NR
		Ranibizumab 0.5 mg + laser	24	6.80	NR	--	NR	NR	9/34(26)	NR	NR	NR	NR	NR
Bevacizumab														
Lim	2012	Bevacizumab 1.25 mg	3	4.5	NR	--	NR	NR	NR	NR	NR	NR	NR	NR
		Bevacizumab 1.25 mg + Triamcinolone 2 mg	3	12	NR	0.036‡	NR	NR	NR	NR	NR	NR	NR	NR
		Triamcinolone 2 mg	3	12	NR	0.04‡	NR	NR	NR	NR	NR	NR	NR	NR
		Bevacizumab 1.25 mg	6	2	NR	--	NR	NR	NR	NR	NR	NR	NR	NR
		Bevacizumab 1.25 mg + Triamcinolone 2 mg	6	6	NR	NS	NR	NR	NR	NR	NR	NR	NR	NR
		Triamcinolone 2 mg	6	10.5	NR	NS	NR	NR	NR	NR	NR	NR	NR	NR
		Bevacizumab 1.25 mg	12	8	NR	--	NR	NR	NR	NR	NR	NR	NR	NR
		Bevacizumab 1.25 mg + Triamcinolone 2 mg	12	7.5	NR	NS	NR	NR	NR	NR	NR	NR	NR	NR
		Triamcinolone 2 mg	12	8	NR	NS	NR	NR	NR	NR	NR	NR	NR	NR

Author	Year	Comparators	Timepoint (months)	Mean Change in BCVA (± SD)	Difference vs. Sham or Laser	p-value	Gain of ≥10 letters n(%)	p-value	Gain of ≥15 letters n(%)	p-value	Loss of ≥10 letters n(%)	p-value	Loss of ≥15 letters n(%)	p-value
Michaelides	2010	Bevacizumab 1.25 mg	12	8 (1-10)†	NR	0.0002	13(31)	0.01	5(12)	0.43	NR	NR	NR	NR
		Laser	12	-0.5 (-15-5)	NR	--	3(8)	--	2(5)	--	NR	NR	NR	NR
Synek	2010	Bevacizumab 1.25 mg	3	5 ± 10	3 ± 3	0.994	NR	NR	NR	NR	NR	NR	NR	NR
		Bevacizumab 1.25 mg + Triamcinolone 2 mg (x1, given as 1 injection)	3	10 ± 10	--	--	NR	NR	NR	NR	NR	NR	NR	NR
		Bevacizumab 1.25 mg	6	9 ± 10	1 ± 3	0.999	NR	NR	NR	NR	NR	NR	NR	NR
		Bevacizumab 1.25 mg + Triamcinolone 2 mg (x1, given as 1 injection)	6	10.5 ± 10	--	--	NR	NR	NR	NR	NR	NR	NR	NR
Soheilian	2009	Bevacizumab 1.25 mg + sham laser	3	10.5 ± 9.5	NR	ℓ	18 (36)	NR	NR	NR	0 (0)	NR	NR	NR
		Bevacizumab 1.25 mg + Triamcinolone 2 mg + sham laser	3	5.5 ± 14	NR	ℓ	14 (27)	NR	NR	NR	6 (11)	NR	NR	NR
		Laser + sham injection	3	-1 ± 15.5	NR	ℓ	4 (9)	NR	NR	NR	10 (20)	NR	NR	NR
		Bevacizumab 1.25 mg + sham laser	6	11.5 ± 11	NR	0.003	16 (31)	NR	NR	NR	0(0)	NR	NR	NR
		Bevacizumab 1.25 mg + Triamcinolone 2 mg + sham laser	6	3.5 ± 14	NR	0.033	11 (21)	NR	NR	NR	8(15)	NR	NR	NR
		Laser + sham injection	6	-0.5 ± 18	NR	0.373ж	6 (11)	NR	NR	NR	11 (23)	NR	NR	NR
		Bevacizumab 1.25 mg + sham laser	9	14 ± 12.5	NR	¶	19 (37)	NR	NR	NR	2 (3.7)	NR	NR	NR
		Bevacizumab 1.25 mg + Triamcinolone 2 mg + sham laser	9	2 ± 16.5	NR	¶	13 (25)	NR	NR	NR	10 (20.8)	NR	NR	NR
		Laser + sham injection	9	-0.5 ± 13.5	NR	¶	7 (14.8)	NR	NR	NR	9 (18.5)	NR	NR	NR
Ahmadieh	2008	Bevacizumab 1.25 mg	3	7.5 ± 12	9 ± 3ε	0.013	NR	NR	NR	NR	NR	NR	NR	NR
		Bevacizumab 1.25 mg + Triamcinolone 2 mg (x1)	3	10.5 ± 13.5	12 ± 3	0.001	NR	NR	NR	NR	NR	NR	NR	NR
		Sham injection	3	1.5 ± 9.5	--	--	NR	NR	NR	NR	NR	NR	NR	NR
		Bevacizumab 1.25 mg	6	9 ± 13	10.5 ± 3.5	0.010	NR	NR	NR	NR	NR	NR	NR	NR
		Bevacizumab 1.25 mg + Triamcinolone 2 mg (x1)	6	10.5 ± 9.5	12 ± 3.5	0.006	NR	NR	NR	NR	NR	NR	NR	NR
		Sham injection	6	1.5 ± 12	--	--	NR	NR	NR	NR	NR	NR	NR	NR
Scott	2007	Laser, baseline	3	-1 (-6, +5)†	NR	--	3(16)	NR	1(5)	NR	1(5)	NR	NR	NR
		Bevacizumab 1.25 mg, baseline & 6 weeks	3	5 (1, 12)	NR	0.01λ	7(33)	NR	3(14)	NR	1(5)	NR	NR	NR
		Bevacizumab 2.5 mg, baseline & 6 weeks	3	7 (4, 11)	NR	0.003	6(25)	NR	3(13)	NR	0(0)	NR	NR	NR
		Bevacizumab 1.25 mg, baseline & sham at 6 weeks	3	4 (-3, +7)	NR	--	2(9)	NR	2(9)	NR	2(9)	NR	NR	NR
		Bevacizumab 1.25 mg, baseline & 6 weeks, laser at 3 weeks	3	0 (-5, +8)	NR	--	4(20)	NR	3(15)	NR	2(10)	NR	NR	NR

Author	Year	Comparators	Timepoint (months)	Mean Change in BCVA (± SD)	Difference vs. Sham or Laser	p-value	Gain of ≥10 letters n(%)	p-value	Gain of ≥15 letters n(%)	p-value	Loss of ≥10 letters n(%)	p-value	Loss of ≥15 letters n(%)	p-value
Pegaptanib														
Sultan	2011	Pegaptanib 0.3 mg	12	5.2	NR	<0.05	49(37)	OR 2.38 (1.32, 4.30) p=0.0047	22(17)	OR 1.57 (0.74, 3.34) p=0.2466	NR	NR	NR	NR
		Sham injection	12	1.2	NR	--	25(20)	--	13(10)	--	NR	NR	NR	NR
		Pegaptanib 0.3 mg	24	6.1	NR	<0.01	41 (38)	OR 1.57 (0.83, 2.97) p=0.1729	25 (23)	OR 1.70 (0.80, 3.58) p=0.1582	NR	NR	NR	NR
		Sham injection	24	1.3	NR	--	30 (30)	--	15 (15)	--	NR	NR	NR	NR
Cunningham	2005	Pegaptanib 0.3 mg	3	3.5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		Pegaptanib 1 mg	3	4.3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		Pegaptanib 3 mg	3	2.5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		Sham injection	3	1.3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		Pegaptanib 0.3 mg	9	4.7	NR	0.04	15(34)	0.003	8(18)	0.12	NR	NR	NR	NR
		Pegaptanib 1 mg	9	4.7	NR	0.05	13(30)	NR	6(14)	NR	NR	NR	NR	NR
		Pegaptanib 3 mg	9	1.1	NR	0.55	6(14)	NR	3(7)	NR	NR	NR	NR	NR
		Sham injection	9	-0.4	NR	--	4(10)	--	3(7)	--	NR	NR	NR	NR
Aflibercept														
Do	2011	VEGF Trap-Eye 0.5 mg + sham laser	6	8.6	NR	0.0054	22(50)	NR	15(34)	NR	NR	NR	NR	NR
		VEGF Trap-Eye 2 mg + sham laser	6	11.4	NR	<0.0001	28(64)	NR	14(32)	NR	NR	NR	NR	NR
		VEGF Trap-Eye 2 mg + sham laser + sham injection	6	8.5	NR	0.0085	18(43)	NR	7(17)	NR	NR	NR	NR	NR
		VEGF Trap-Eye 2 mg + sham laser + sham injection	6	10.3	NR	0.0004	26(58)	NR	12(27)	NR	NR	NR	NR	NR
		Macular laser + sham injection	6	2.5	NR	--	14(32)	NR	9(21)	NR	NR	NR	NR	NR

BCVA: best-corrected visual acuity; NR: not reported; OR: odds ratio;

analyzes gain and loss together (Cochran-Mantel-Haenszel test)
^ versus laser
ϕ versus ranibizumab; also NS versus laser alone
ψ Among the 3 groups
‡ versus bevacizumab; at all timepoints, IVB/IVT vs. IVT: NS
† median, IQR
ℓ Pairwise comparisons: NS; among the group: p=0.616
ж versus bevacizumab + triamcinolone
¶ Pairwise comparisons: NS; among the group: p=0.053
ε bevacizumab vs. bevacizumab + triamcinolone: mean difference = 3 ± 3, p=0.994
λ bevacizumab 1.25 mg (x2) vs. bevacizumab 2.5 mg (x2): p=0.82; bevacizumab 1.25 mg (x2) vs. bevacizumab 1.25 mg (x2) + laser: p=NS

Table D2. Central Retinal Thickness

Author	Year	Comparators	Timepoint (months)	Mean Change in CRT (µm) (± SD)	Difference vs. Sham or Laser	P-value
Ranibizumab						
Nguyen RISE	2012	Ranibizumab 0.3 mg	24	-250.6 ± 212.2	-107.9	<0.0001
		Ranibizumab 0.5 mg	24	-253.1 ± 183.7	-119.1	<0.0001
		Sham injection	24	-133.4 ± 209	--	--
Nguyen RIDE	2012	Ranibizumab 0.3 mg	24	-259.8 ± 169.3	-111.8	<0.0001
		Ranibizumab 0.5 mg	24	-270.7 ± 201.6	-132.2	<0.0001
		Sham injection	24	-125.8 ± 198.3	--	--
Mitchell	2011	Ranibizumab 0.5 mg + sham laser	12	-118.7 ± 115.07	-61.5	0.0002
		Ranibizumab 0.5 mg + laser	12	-128.3 ± 114.34	-70.6	<0.0001
		Laser + sham injection	12	-61.3 ± 132.29	--	--
Elman	2010	Sham inj. + prompt laser	12	-102 ± 151	--	--
		Ranibizumab 0.5 mg + prompt laser	12	-131 ± 129	-55	<0.001
		Ranibizumab 0.5 mg + def. laser	12	-137 ± 136	-49	<0.001
		Triamcinolone 4 mg + prompt laser	12	-127 ± 140	-52	<0.001
		Sham inj. + prompt laser	24	-138 ± 149		
		Ranibizumab 0.5 mg + prompt laser	24	-141 ± 155	-31	0.003
		Ranibizumab 0.5 mg + def. laser	24	-150 ± 143	-28	0.01
		Triamcinolone 4 mg + prompt laser	24	-107 ± 145	-10	0.37
Massin	2010	Ranibizumab 0.3 mg	12	-200.7 ± 122.2	-157.3	<0.0001
		Ranibizumab 0.5 mg	12	-187.6 ± 147.8	-152.7	<0.0001
		Sham injection	12	-48.4 ± 153.4	--	--
Nguyen READ-2	2009	Ranibizumab 0.5 mg	12	NR	NR	--
		Laser	12	NR	NR	0.028*
		Ranibizumab 0.5 mg + laser	12	NR	NR	0.027*
		Ranibizumab 0.5 mg	24	NR	NR	--
		Laser	24	NR	NR	0.027*
		Ranibizumab 0.5 mg + laser	24	NR	NR	<0.0001*
Bevacizumab						
Lim	2012	Bevacizumab 1.25 mg	3	-193†	NR	--
		Bevacizumab 1.25 mg + Triamcinolone 2 mg	3	-129	NR	0.02ϕ
		Triamcinolone 2 mg	3	-144	NR	--
		Bevacizumab 1.25 mg	6	-100	NR	NS
		Bevacizumab 1.25 mg + Triamcinolone 2 mg	6	-90	NR	NS
		Triamcinolone 2 mg	6	-120	NR	NS
		Bevacizumab 1.25 mg	12	-199	NR	NS
		Bevacizumab 1.25 mg + Triamcinolone 2 mg	12	-179	NR	NS
		Triamcinolone 2 mg	12	-200	NR	NS

Author	Year	Comparators	Timepoint (months)	Mean Change in CRT (μm) (± SD)	Difference vs. Sham or Laser	P-value
Michaelides	2010	Bevacizumab 1.25 mg	12	-130 ± 122	NR	0.06
		Laser	12	-68 ± 171	NR	--
Synek	2010	Bevacizumab 1.25 mg	3	-70 ± 134	31 ± 27	0.786
		Bevacizumab 1.25 mg + Triamcinolone 2 mg (x1, given as 1 injection)	3	-101 ± 110	--	--
		Bevacizumab 1.25 mg	6	-94 ± 170	-3 ± 42	0.999
		Bevacizumab 1.25 mg + Triamcinolone 2 mg (x1, given as 1 injection)	6	-93 ± 124	--	--
Soheilian	2009	Bevacizumab 1.25 mg + sham laser	3	-37 ± 115	NR	NS
		Bevacizumab 1.25 mg + Triamcinolone 2 mg + sham laser	3	-36 ± 128	NR	NS
		Laser + sham injection	3	4 ± 90	NR	NS
		Bevacizumab 1.25 mg + sham laser	6	-24 ± 103	NR	NS
		Bevacizumab 1.25 mg + Triamcinolone 2 mg + sham laser	6	-14 ± 102	NR	NS
		Laser + sham injection	6	-15 ± 80	NR	NS
		Bevacizumab 1.25 mg + sham laser	9	-56 ± 140	NR	NS
		Bevacizumab 1.25 mg + Triamcinolone 2 mg + sham laser	9	-5 ± 113	NR	NS
		Laser + sham injection	9	-8 ± 67	NR	NS
Ahmadieh	2008	Bevacizumab 1.25 mg	3	-70.6 ± 135.6	65 ± 29	0.079ℓ
		Bevacizumab 1.25 mg + Triamcinolone 2 mg (x1)	3	-102.1 ± 110.9	97 ± 28	0.003
		Sham injection	3	-4.7 ± 57.7	--	--
		Bevacizumab 1.25 mg	6	-95.7 ± 172.5	120 ± 42	0.021л
		Bevacizumab 1.25 mg + Triamcinolone 2 mg (x1)	6	-92.1 ± 125.3	117 ± 45	0.036
		Sham injection	6	34.9 ± 63.9	--	--
Scott	2007	Laser, baseline	3	-40 (-146, +85)‡	--	--
		Bevacizumab 1.25 mg, baseline & 6 weeks	3	-56 (-120, -6)	--	NSψ
		Bevacizumab 2.5 mg, baseline & 6 weeks	3	-47 (-125, -16)	--	NS
		Bevacizumab 1.25 mg, baseline & sham at 6 weeks	3	-5 (-41, +53)	--	--
		Bevacizumab 1.25 mg, baseline & 6 weeks, laser at 3 weeks	3	-40 (-103, +33)	--	--

Author	Year	Comparators	Timepoint (months)	Mean Change in CRT (μm) (± SD)	Difference vs. Sham or Laser	P-value
Pegaptanib						
Sultan	2011	Pegaptanib 0.3 mg	12	NR	NR	NR
		Sham injection	12	NR	NR	NR
Cunningham	2005	Pegaptanib 0.3 mg	9	-50.3	NR	0.205
		Pegaptanib 1 mg	9	-15.9	NR	0.932
		Pegaptanib 3 mg	9	-21.0	NR	0.799
		Sham injection	9	-12.7	NR	--
Aflibercept						
Do	2011	VEGF Trap-Eye 0.5 mg + sham laser	6	-144.6	NR	0.0002
		VEGF Trap-Eye 2 mg + sham laser	6	-194.5	NR	<0.0001
		VEGF Trap-Eye 2 mg + sham laser + sham injection	6	-127.3	NR	0.0066
		VEGF Trap-Eye 2 mg + sham laser + sham injection	6	-153.3	NR	<0.0001
		Macular laser + sham injection	6	-67.9	NR	--

CRT: central retinal thickness; NR: not reported; NS: not significant;

* Laser and combined treatment groups as compared to ranibizumab alone
† Calculated means are approximations only
ϕ Versus bevacizumab; p=0.036 versus triamcinolone; IVB/IVT vs. IVT: NS
ℓ Bevacizumab vs. bevacizumab + triamcinolone: mean difference = -3 ± 42, p=0.999
л Bevacizumab vs. bevacizumab + triamcinolone: mean difference = 31 ± 27, p=0.786
ψ Bevacizumab 1.25 mg (x2) vs. bevacizumab 2.5 mg (x2): p=0.90; bevacizumab 1.25 mg (x2) vs. bevacizumab 1.25 mg (x2) + laser: p=NS
‡ Median, IQR

Table D3. Quality of life

Author	Year	Instrument (Domain)	Ranibizumab + laser		Ranibizumab + sham laser		Laser + sham injection
			Mean change from baseline to Month 12				
Mitchell	2011	***NEI VFQ-25***		*p-value vs. laser*		*p-value vs. laser*	
		Composite score	5.0	0.014	5.4	0.004	0.6
		General vision	8.9	<0.001	8.0	0.001	1.1
		Near vision activities	9.0	0.011	9.1	0.006	1.1
		Distance activities	5.3	0.045	5.6	0.033	0.4
		EuroQol EQ-5D	2.6	NS	4.2	NS	2.4
		Time Tradeoff	0.13	NS	0.032	NS	0.023

<u>Pegaptanib versus sham injection</u>

Author	Year	Instrument (Domain)	12 Months LS Mean Difference (Range)		p-value		24 Months LS Mean Difference (Range)		p-value
Sultan	2011	***NEI VFQ-25***							
		General health	2.68	(-2.95 - 8.30)	0.349		2.84	(-3.43 - 9.10)	0.372
		General vision	0.80	(-3.90 - 5.50)	0.738		0.79	(-4.58 - 6.16)	0.773
		Ocular pain	-2.00	(-7.51 - 3.51)	0.475		4.58	(-2.01 - 11.17)	0.172
		Near vision activities	5.70	(0.48 - 10.91)	0.033		2.24	(-3.98 - 8.46)	0.478
		Distance vision activities	8.50	(2.74 - 14.25)	0.004		9.95	(3.64 - 16.27)	0.002
		Social functioning	7.99	(2.90 - 13.09)	0.002		9.91	(3.65 - 16.18)	0.002
		Mental health	3.07	(-2.43 - 8.57)	0.272		7.17	(0.33 - 14.01)	0.040
		Role difficulty	-0.59	(-8.03 - 6.86)	0.877		2.03	(-6.78 - 10.85)	0.650
		Dependency	-1.10	(-7.97 - 5.77)	0.753		3.02	(-5.28 - 11.33)	0.473
		Driving	6.13	(-0.14 - 12.41)	0.055		3.75	(-3.22 - 10.73)	0.288
		Color vision	1.17	(-4.40 - 6.74)	0.679		-0.36	(-7.74 - 7.01)	0.923
		Peripheral vision	2.91	(-3.55 - 9.36)	0.375		4.53	(-2.76 - 11.82)	0.222
		Composite score	2.92	(-0.32 - 6.16)	0.077		4.47	(0.26 - 8.68)	0.038
		EuroQol EQ-5D	-0.04	(-0.10 - 0.02)	0.186		-0.03	(-0.09 - 0.04)	0.374

LS: least squares; NEI VFQ: National Eye Institute Visual Function Questionnaire; NS: not significant

Table D4. Treatment utilization and use of rescue therapy.

Author	Year	Comparators	Timepoint (months)	Mean Injections (SD)		p-value (vs. control)	Mean Laser Treatments (range)		p-value (vs. control)	Rescue Laser n (%)		p-value (vs. control)	Retreatment n(%)		p-value (vs. control)
Ranibizumab															
Nguyen RISE	2012	Ranibizumab 0.3 mg	24	21.5	6.2	NR	0.8#	1.2	<0.0001	49	39.2	<0.0001	N/A	N/A	N/A
		Ranibizumab 0.5 mg	24	20.9	6.3	NR	0.8	1.3	<0.0001	44	35.2	<0.0001	N/A	N/A	N/A
		Sham injection	24	20	7.5	NR	1.8	1.8	--	94	74	--	N/A	N/A	N/A
Nguyen RIDE	2012	Ranibizumab 0.3 mg	24	20.5	7.2	NR	0.7	1.4	<0.0001	45	36	<0.0001	N/A	N/A	N/A
		Ranibizumab 0.5 mg	24	21.9	5.8	NR	0.3	0.7	<0.0001	25	19.7	<0.0001	N/A	N/A	N/A
		Sham injection	24	20.8	7.1	NR	1.6	1.6	--	91	70	--	N/A	N/A	N/A
Mitchell	2011	Ranibizumab 0.5 mg + laser	12	6.8	3.0	NR	1.7	0.9	NR	--	--	NR	NR	NR	NR
		Ranibizumab 0.5 mg + sham laser	12	7.0	2.8	NR	1.9	1.1	NR	--	--	NR	NR	NR	--
		Laser + sham injection	12	7.3	3.2	NR	2.1	1.0	NR	--	--	NR	NR	NR	NR
Elman	2010	Sham inj. + prompt laser	12	11†	(8-13)	NR	3†	(2-3)	NR	238	86.9	NR	204	69.6	NR
		Ranibizumab 0.5 mg + prompt laser	12	8.0	(6-10)	NR	2	(1-3)	NR	118	63.1	NR	78	41.7	NR
		Ranibizumab 0.5 mg + deferred laser	12	9.0	(6-11)	NR	NR	NR	NR	50	26.6	NR	96	51.1	NR
		Triamcinolone 4 mg + prompt laser	12	8.0	(5-11)	NR	2	(1-3)	NR	129	73.3	NR	88	47.3	NR
		Sham inj. + prompt laser	24	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		Ranibizumab 0.5 mg + prompt laser	24	2.0†*	(1-3)	NR	0.0†*	(0-1)	NR	NR	NR	NR	NR	NR	NR
		Ranibizumab 0.5 mg + deferred laser	24	3.0	(1-7)	NR	0.0	(0-1)	NR	NR	NR	NR	NR	NR	NR
		Triamcinolone 4 mg + prompt laser	24	1.0	(0-2)	NR	1.0	(0-1)	NR	NR	NR	NR	NR	NR	NR
Massin	2010	Ranibizumab 0.3/0.5 mg (pooled)	12	10.2	2.5	NR	NR	NR	NR	5	4.9	NR	NR	NR	NR
		Sham injection	12	8.9	3.5	NR	NR	NR	NR	17	34.7	NR	NR	NR	NR
Nguyen	2009	Ranibizumab 0.5 mg	24	9.3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		Laser	24	4.4	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		Ranibizumab 0.5 mg + laser	24	2.9	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bevacizumab															
Lim	2012	Bevacizumab 1.25 mg	12	2.5	1.8	<0.001	---	---	---	NR	NR	NR	NR	NR	NR
		Triamcinolone 2 mg	12	1.0	1.0	NS	---	---	---	NR	NR	NR	NR	NR	NR
		Bevacizumab 1.25 mg + Triamcinolone 2 mg	12	1.3	1.1	NS	---	---	---	NR	NR	NR	NR	NR	NR
Michaelides	2010	Bevacizumab 1.25 mg	12	9†	(8-9)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		Laser	12	NR	NR	NR	3†	(2-4)	NR	NR	NR	NR	NR	NR	NR

Author	Year	Comparators	Timepoint (months)	Mean Injections (SD)		p-value (vs. control)	Mean Laser Treatments (range)		p-value (vs. control)	Rescue Laser n (%)		p-value (vs. control)	Retreatment n(%)		p-value (vs. control)
Pegaptanib															
Sultan	2011	Pegaptanib 0.3 mg	12	8.3	1.7	NR	NR	NR	NR	31	23.3	0.002	NR	NR	NR
		Sham injection	12	8.4	1.4	--	NR	NR	--	53	41.7	--	NR	NR	--
		Pegaptanib 0.3 mg	24	12.7	4.6	NR	NR	NR	NR	27	25.2	0.003	NR	NR	NR
		Sham injection	24	12.9	4.4	--	NR	NR	--	45	45.0	--	NR	NR	--
Cunningham	2005	Pegaptanib 0.3 mg	9	5.0	1.2	NR	NR	NR	NR	11	25.0	0.042	NR	NR	NR
		Pegaptanib 1 mg	9	5.2	1.0	NR	NR	NR	NR	13	29.5	0.090	NR	NR	NR
		Pegaptanib 3 mg	9	5.0	1.3	NR	NR	NR	NR	17	40.5	0.537	NR	NR	NR
		Sham injection	9	4.5	1.5	--	NR	NR	NR	20	47.6	--	NR	NR	NR
Aflibercept															
Do	2011	VEGF Trap-Eye 0.5 mg + sham laser	6	5.6	(1-6)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		VEGF Trap-Eye 2 mg + sham laser	6	5.5	(1-6)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		VEGF Trap-Eye 2 mg + sham laser + sham injection (2q8)	6	3.8	(1-4)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		VEGF Trap-Eye 2 mg + sham laser + sham injection (PRN)	6	4.4	(1-6)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		Macular laser + sham injection	6	--	--	--	1.7	(1-3)	--	NR	NR	--	NR	NR	--

NR: not reported

Data reported for rescue laser utilization (mean ± SD)
† Median, IQR
*Between 12-month and 24-month visits

Table D5. Adverse Events in RCTs

Author	Year	Comparators	Safety Population	Timepoint (months)	Deaths n (%)		Endophthalmitis n (%)		Total Ocular SAEs n (%)		Stroke n (%)		MI n (%)		CV SAEs n (%)		Total Non-ocular SAEs n (%)		Total ocular AEs n (%)		Total Non-ocular AEs n (%)		Patient WDs n (%)	
Ranibizumab																								
Nguyen	2012	Ranibizumab 0.3 mg	125	24	3	2.4	1	0.0	4	3.2	1	0.8	2	1.6	ϕ	ϕ	46	36.8	ϕ	ϕ	ϕ	ϕ	20	16.0
RISE		Ranibizumab 0.5 mg	126	24	5	4	0	0.0	7	5.6	5	4.0	4	3.2	ϕ	ϕ	52	41.3	ϕ	ϕ	ϕ	ϕ	19	15.1
		Sham injection	123	24	1	0.8	0	0.0	9	7.3	4	3.3	3	2.4	ϕ	ϕ	38	30.9	ϕ	ϕ	ϕ	ϕ	24	19.5
Nguyen	2012	Ranibizumab 0.3 mg	125	24	4	3.2	1	0.0	4	3.2	3	2.4	7	5.6	ϕ	ϕ	35	28.0	ϕ	ϕ	ϕ	ϕ	20	16.0
RIDE		Ranibizumab 0.5 mg	124	24	6	4.8	2	0.1	12	9.7	3	2.4	3	2.4	ϕ	ϕ	39	31.5	ϕ	ϕ	ϕ	ϕ	17	13.7
		Sham injection	127	24	2	1.6	0	0.0	7	5.5	4	3.1	6	4.7	ϕ	ϕ	45	35.4	ϕ	ϕ	ϕ	ϕ	22	17.3
Mitchell	2011	Ranibizumab 0.5 mg + sham laser	115	12	2	1.7	0	0	0	0	1	0.9	1	0.9	8	7.0	23	20.0	49	42.6	67	58.3	14	12.2
		Ranibizumab 0.5 mg + laser	120	12	2	1.7	0	0	2	1.7	0	0	1	0.8	4	3.3	17	14.2	51	42.5	55	45.8	15	12.5
		Laser + sham injection	110	12	2	1.8	0	0	2	1.8	0	0	0	0	4	3.6	15	13.6	43	39.1	68	61.8	13	11.8
Elman	2010	Sham inj. + prompt laser	293	24	15	5.1	1	0.3	ϕ	ϕ	8		4		18		NR	NR	ϕ	ϕ	NR	NR	43	14.7
		Ranibizumab 0.5 mg + prompt laser	187	24	6	3.2	2	1.1	ϕ	ϕ	6ℓ		5ℓ		19ℓ		NR	NR	ϕ	ϕ	NR	NR	26	13.9
		Ranibizumab 0.5 mg + def. laser	188	24	9	4.8	2	1.1	ϕ	ϕ	--		--		--		NR	NR	ϕ	ϕ	NR	NR	24	12.8
		Triamcinolone 4 mg + prompt laser	186	24	5	2.7	0	0.0	ϕ	ϕ	3		5		12		NR	NR	ϕ	ϕ	NR	NR	22	11.8
Massin	2010	Ranibizumab 0.3 mg	51	12	1	2.0	1	2.0	1	2.0	0	0	0	0	0	0	8	15.7	38	74.5	32	62.7	5	9.8
		Ranibizumab 0.5 mg	51	12	0	0	1	2.0	3	5.9	1	2.0	1	2.0	1	2.0	6	11.8	42	82.4	32	62.7	5	9.8
		Sham injection	49	12	0	0	0	0	1	2.0	0	0	1	2.0	2	4.1	8	16.3	28	57.1	32	65.3	9	18.4
Nguyen	2009	Ranibizumab 0.5 mg	41	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2.4	NR	NR	5	12.2
READ-2		Laser	40	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	12.5	NR	NR	4	10.0
		Ranibizumab 0.5 mg + laser	40	6	1	2.5	0	0	0	0	1	2.5	0	0	0	0	1	2.5	3	7.5	NR	NR	2	5.0
Bevacizumab																								
Lim	2012	Bevacizumab 1.25 mg	38	12	NR	NR	0	0	0	0	0	0	0	0	0	0	0	0	0	0	NR	NR	NR	NR
		Bevacizumab 1.25 mg + Triamcinolone 2 mg	36	12	NR	NR	0	0	0	0	0	0	0	0	0	0	0	0	3	8.3	NR	NR	NR	NR
		Triamcinolone 2 mg	37	12	NR	NR	0	0	0	0	0	0	0	0	0	0	0	0	4	10.8	NR	NR	NR	NR
Michaelides	2010	Bevacizumab 1.25 mg	42	12	0	0	0	0	1	2.4	0	0	0	0	0	0	3	7.1	20	47.6	4	9.5	2	4.8
		Laser	38	12	0	0	0	0	3	7.9	1	2.6	0	0	1	2.6	7	18.4	8	21.1	3	7.9	0	0.0
Synek	2010	Bevacizumab 1.25 mg	30	6	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	6	20.0	NR	NR	NR	NR
		Bevacizumab 1.25 mg + Triamcinolone 2 mg (x1, given as 1 injection)	30	6	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	7	23.3	NR	NR	NR	NR
Soheilian	2009	Bevacizumab 1.25 mg + sham laser	NR	9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	NR	NR	NR	NR	NR	NR
		Bevacizumab 1.25 mg + Triamcinolone 2 mg + sham laser	NR	9	2	--	0	0	0	0	0	0	0	0	0	0	0	0	NR	NR	NR	NR	NR	NR
		Laser + sham injection	NR	9	2	--	0	0	0	0	0	0	0	0	0	0	0	0	NR	NR	NR	NR	NR	NR
Ahmadieh	2008	Bevacizumab 1.25 mg	NR	6	0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	10	NR	NR	NR	NR	NR
		Bevacizumab 1.25 mg + Triamcinolone 2 mg (x1)	NR	6	0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	11	NR	NR	NR	NR	NR
		Sham injection	NR	6	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0	NR	NR	NR	NR	NR
Scott	2007	Laser, baseline	19	3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0	0.0
		Bevacizumab 1.25 mg, baseline & 6 weeks	22	3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	1	4.5
		Bevacizumab 2.5 mg, baseline & 6 weeks	24	3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	1	4.2
		Bevacizumab 1.25 mg, baseline & sham at 6 weeks	22	3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0	0.0
		Bevacizumab 1.25 mg, baseline & 6 weeks, laser at 3 weeks	22	3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0	0.0

Author	Year	Comparators	Safety Population	Timepoint (months)	Deaths n (%)		Endophthalmitis n (%)		Total Ocular SAEs n (%)		Stroke n (%)		MI n (%)		CV SAEs n (%)		Total Non-ocular SAEs n (%)		Total ocular AEs n (%)		Total Non-ocular AEs n (%)		Patient WDs n (%)	
Pegaptanib																								
Sultan	2011	Pegaptanib 0.3 mg	144	24	4	2.8	0	0	4	2.8	2	1.4	0	0.0	10	6.9	31	21.5	96	66.7	114	79.2	48	33.3
		Sham injection	142	24	5	3.5	0	0	6	4.2	1	0.7	3	2.1	8	5.6	29	20.4	103	72.5	85	59.9	45	31.7
Cunningham	2005	Pegaptanib 0.3 mg	44	9	0	0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	38	86	40	91	0	0.0
		Pegaptanib 1 mg	42	9	0	0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	34	81	40	95	0	0.0
		Pegaptanib 3 mg	42	9	0	0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	37	88	41	98	3	7.1
		Sham injection	41	9	1	2.4	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	30	73	35	85	6	14.6
Aflibercept																								
Do	2011	VEGF Trap-Eye 0.5 mg + sham laser	44	6	1	2.3	0	0.0	1	2.3	1	2.3	1	2.3	1	2.3	3	6.8	24	54.5	3	6.8	3	6.8
		VEGF Trap-Eye 2 mg + sham laser	44	6	1	2.3	1	2.3	1	2.3	1	2.3	1	2.3	3	6.8	5	11.4	18	40.9	4	9.1	4	9.1
		VEGF Trap-Eye 2 mg + sham laser + sham injection	42	6	1	2.4	0	0.0	2	4.8	0	0.0	0	0.0	0	0.0	0	0.0	23	54.8	2	4.8	4	9.5
		VEGF Trap-Eye 2 mg + sham laser + sham injection	42	6	0	0.0	1	2.4	1	2.4	0	0.0	0	0.0	0	0.0	0	0.0	20	47.6	4	9.5	4	9.5
		Macular laser + sham injection	44	6	0	0.0	0	0.0	3	6.8	0	0.0	0	0.0	0	0.0	0	0.0	15	34.1	3	6.8	4	9.1

AE: adverse event; CV: cardiovascular; MI: myocardial infarction; NR: not reported; RCT: randomized controlled trial; SAE: serious adverse event; WD: withdrawal;

ℓ Data combined for both ranibizumab treatment arms
ϕ Reporting of data precludes comparison to relevant studies; please see text for detailed discussion.

Table D6. Efficacy data from case series and cohort studies

Author	Year	Study Name	Comparators	Study Type	Timepoint (Months)	Number of Eyes	Patient Age Mean ± SD		HbA1c Mean % ± SD		Previous Laser Therapy n, %		Baseline BCVA Mean letters ± SD		Change in BCVA Mean ± SD		p-value	Gain of ≥10 Letters n, %		p-value
Avastin																				
Salman	2011	N/A	Bevacizumab 1.25 mg	Prospective case series	12	16	17.6	0.4	NR	NR	NR	NR	71.5	7.5	17.9	NR	--	NR	NR	NR
Forte	2010	N/A	Bevacizumab 1.25 mg	Retrospective cohort	12	43	68.3	6.1	9.12	0.81	NR	NR	46.5	24.5	10.5	NR	NR	NR	NR	NR
			Triamcinolone 4 mg + Laser		12	96	66.1	8.8	8.47	0.85	NR	NR	54	17	4.5	NR	NR	NR	NR	NR
Roh	2010	N/A	Bevacizumab 1.25 mg	Retrospective case series	12	56	63.29	8.26	NR	NR	22	39.3	NR	NR	2.91	9.96	--	NR	NR	NR
Arevalo	2009	Pan-American Collaborative Retina Study Group	Bevacizumab 1.25 mg	Retrospective cohort	24	74	59.4*	11.1	9.1*	1.86	NR	NR	55*	NR	12	8	NS	47	63.5	NR
			Bevacizumab 2.5 mg		24	65	--	--	--	--	--	--	--	--	12	11	--	25	38.5	NR
Bonini-Filho	2009	N/A	Bevacizumab 1.5 mg	Prospective case series	12	10	59.8	4	8.28	0.97	NR	NR	60.7	19.3	11.4	NR	--	NR	NR	NR
Kook	2008	N/A	Bevacizumab 1.25 mg	Prospective case series	12	126	66.1	23-88	NR	NR	78	22	40.4	20.5	5.1	14.8	--	NR	NR	NR

BCVA: best-corrected visual acuity; HbA1c: glycosylated hemoglobin; N/A: not applicable; NR: not reported

* Baseline characteristics reported for all patients only

Table D7. Adverse Events in Case Series, Cohort Studies and RCTs with Single Treatment Protocols

Author	Year	Comparators	Safety Population	Timepoint (months)	Deaths n (%)		Endophthalmitis n (%)		Total Ocular SAEs n (%)		Stroke n (%)		MI n (%)		CV SAEs n (%)		Total Non-ocular SAEs n (%)		Total ocular AEs n (%)		Total Non-ocular AEs n (%)		Patient WDs
Avastin																							
Kook	2011	Bevacizumab 1.25 mg	30	9	NR	NR	NR	NR	NR	NR	0	0	0	0	0	0	0	0	0	0	0	0	N/A
		Triamcinolone 4 mg	30	9	NR	NR	NR	NR	NR	NR	0	0	0	0	0	0	0	0	1	3.3	0	0	N/A
Forte	2010	Bevacizumab 1.25 mg	43	12	NR	NR	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	N/A
		Triamcinolone 4 mg + Laser	96	12	NR	NR	NR	NR	2	2.1	NR	NR	NR	NR	NR	NR	NR	NR	8	8.3	NR	NR	N/A
Lam	2010	Bevacizumab 1.25 mg	26	6	NR	NR	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	3.8	3
		Bevacizumab 2.5 mg	26	6	NR	NR	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Roh	2010	Bevacizumab 1.25 mg	56	12	NR	NR	0	0	0	0	0	0	0	0	0	0	0	0	3	5.4	0	0	N/A
Solaiman	2010	Bevacizumab 1.25 mg	21	6	NR	NR	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	NR
		Bevacizumab 1.25 mg + Laser	22	6	NR	NR	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	NR
		Laser	19	6	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Arevalo	2009	Bevacizumab 1.25 mg/2.5 mg	139	24	NR	NR	0	0	0	0	1	0.7	1	0.7	1	0.7	2	1.4	13	9.4	1	0.7	N/A
Kook	2008	Bevacizumab 1.25 mg	59	12	NR	NR	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	67*
Lucentis																							
Querques	2009	Pegaptanib 0.3 mg	63	6.7 ± 1.2	NR	NR	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	N/A

AE: adverse event; CV: cardiovascular; MI: myocardial infarction; N/A: not applicable; NR: not reported; RCT: randomized controlled trial; SAE: serious adverse event; W/D: withdrawal

* 126 patients completed 6-month outcomes; 59 completed 12-month outcomes

Appendix E – Quantitative Synthesis: Sensitivity Analysis

Figure E1. Sensitivity Analysis: meta-analysis and indirect comparisons of mean difference in BCVA change between anti-VEGF therapy and laser/sham control studies of good, fair and poor quality.

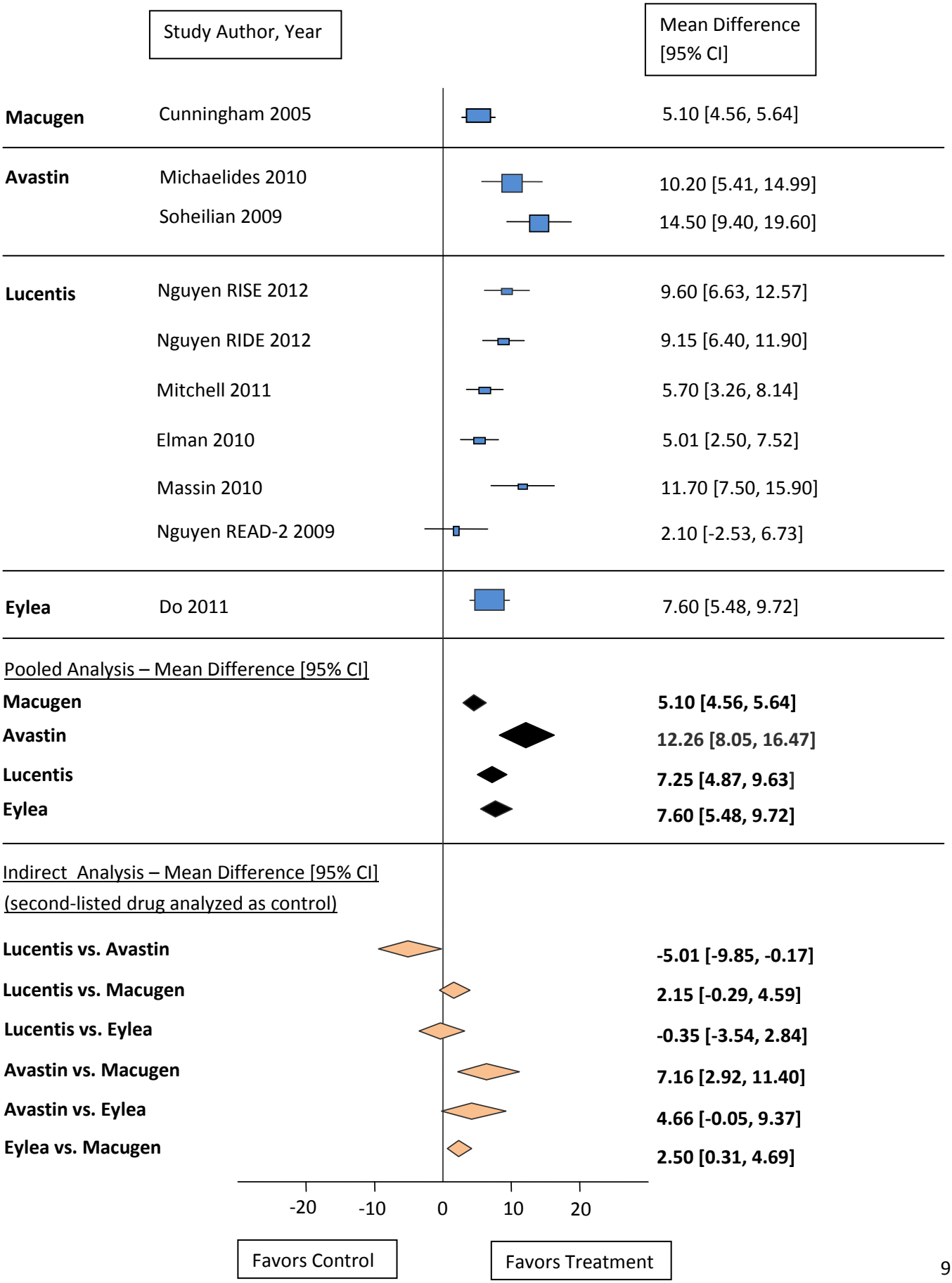


Figure E2. Sensitivity Analysis: meta-analysis and indirect comparisons of mean difference in BCVA change between anti-VEGF therapy and any control.

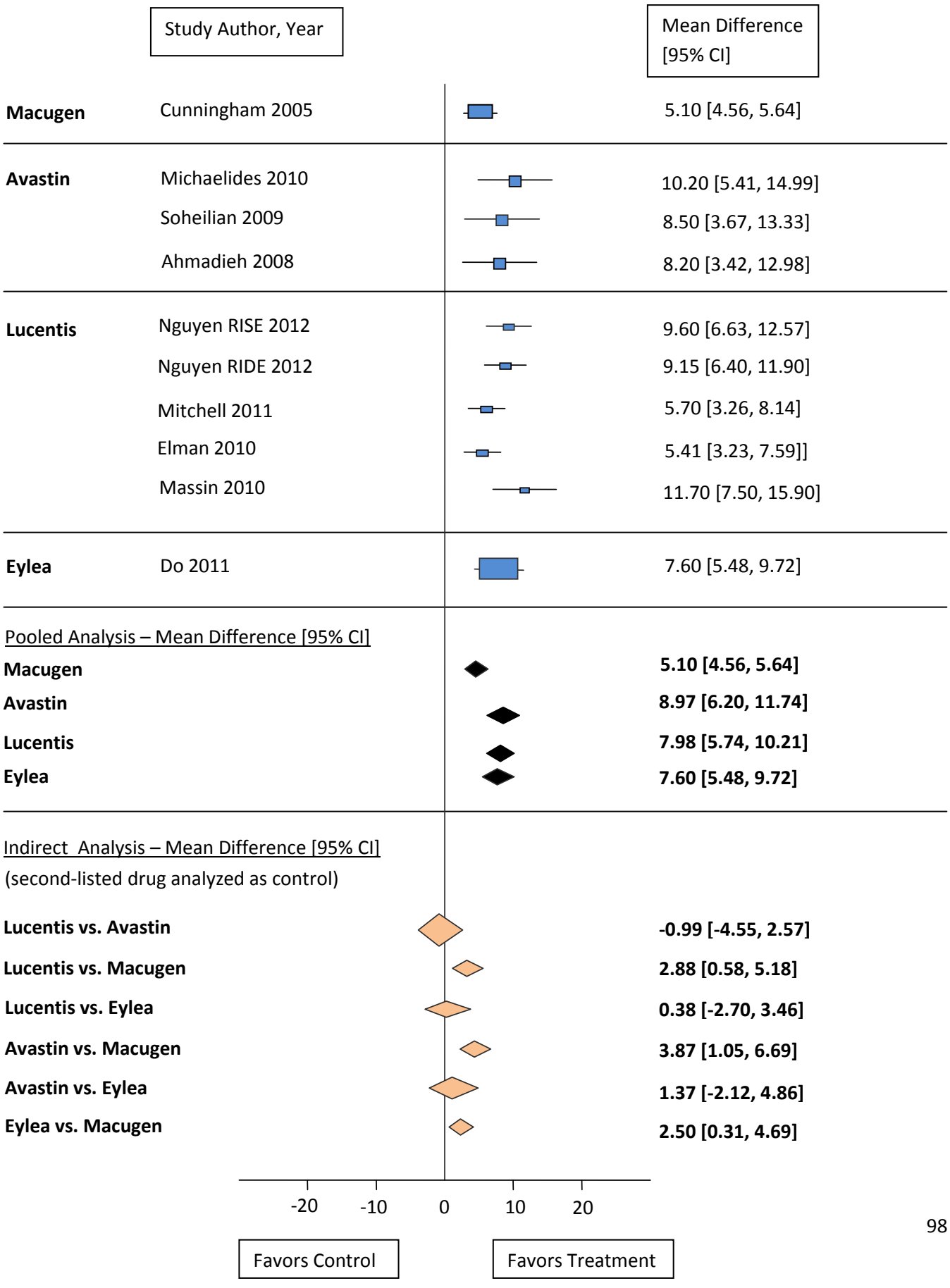


Figure E3. Sensitivity Analysis: meta-analysis and indirect comparisons of mean difference in BCVA change between anti-VEGF therapy and any control in studies of good, fair and poor quality.

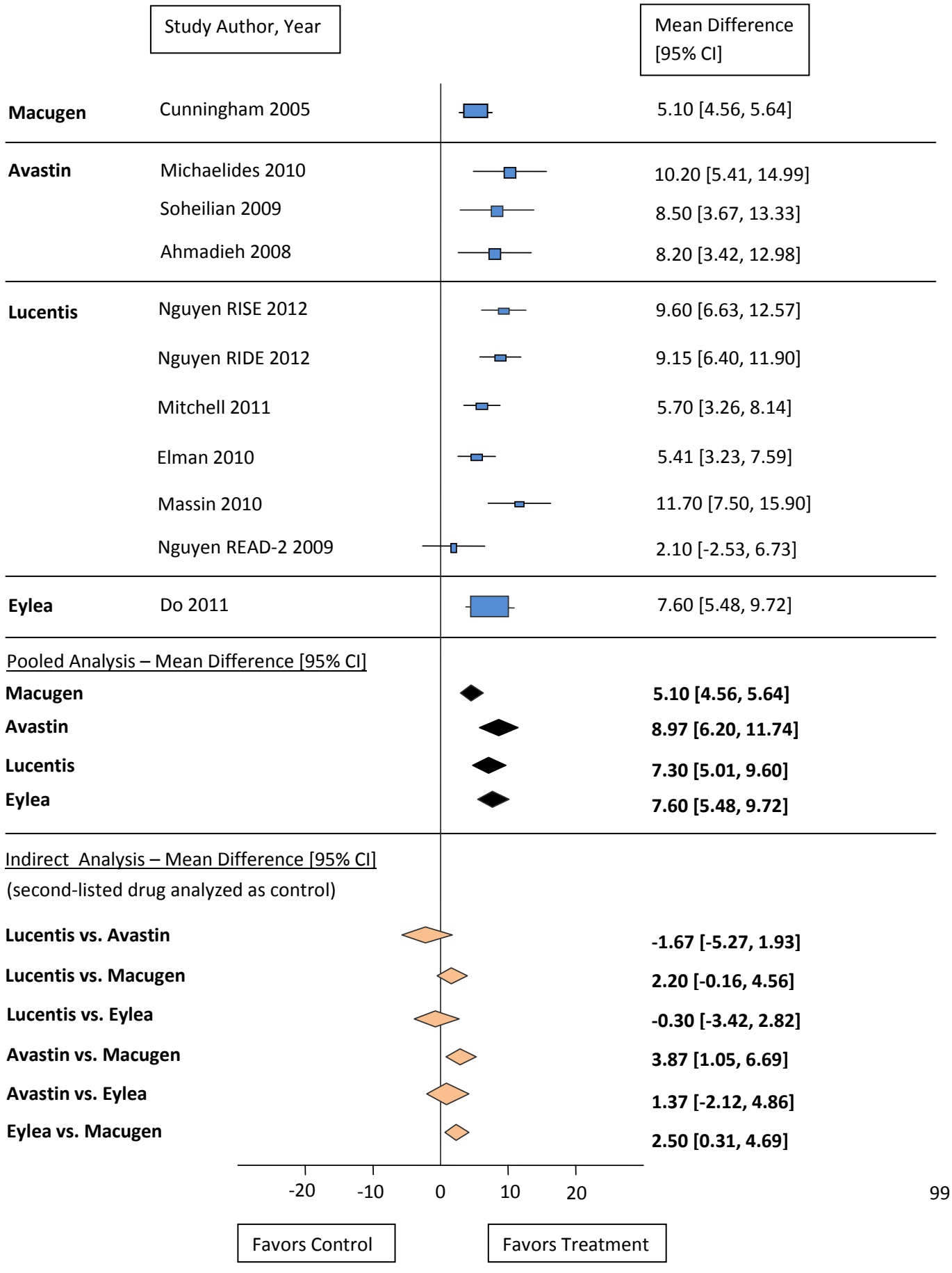


Figure E4. Sensitivity Analysis: meta-analysis and indirect comparisons of likelihood of gain of ≥10 letters between anti-VEGF therapy and laser/sham control in studies of good, fair and poor quality.

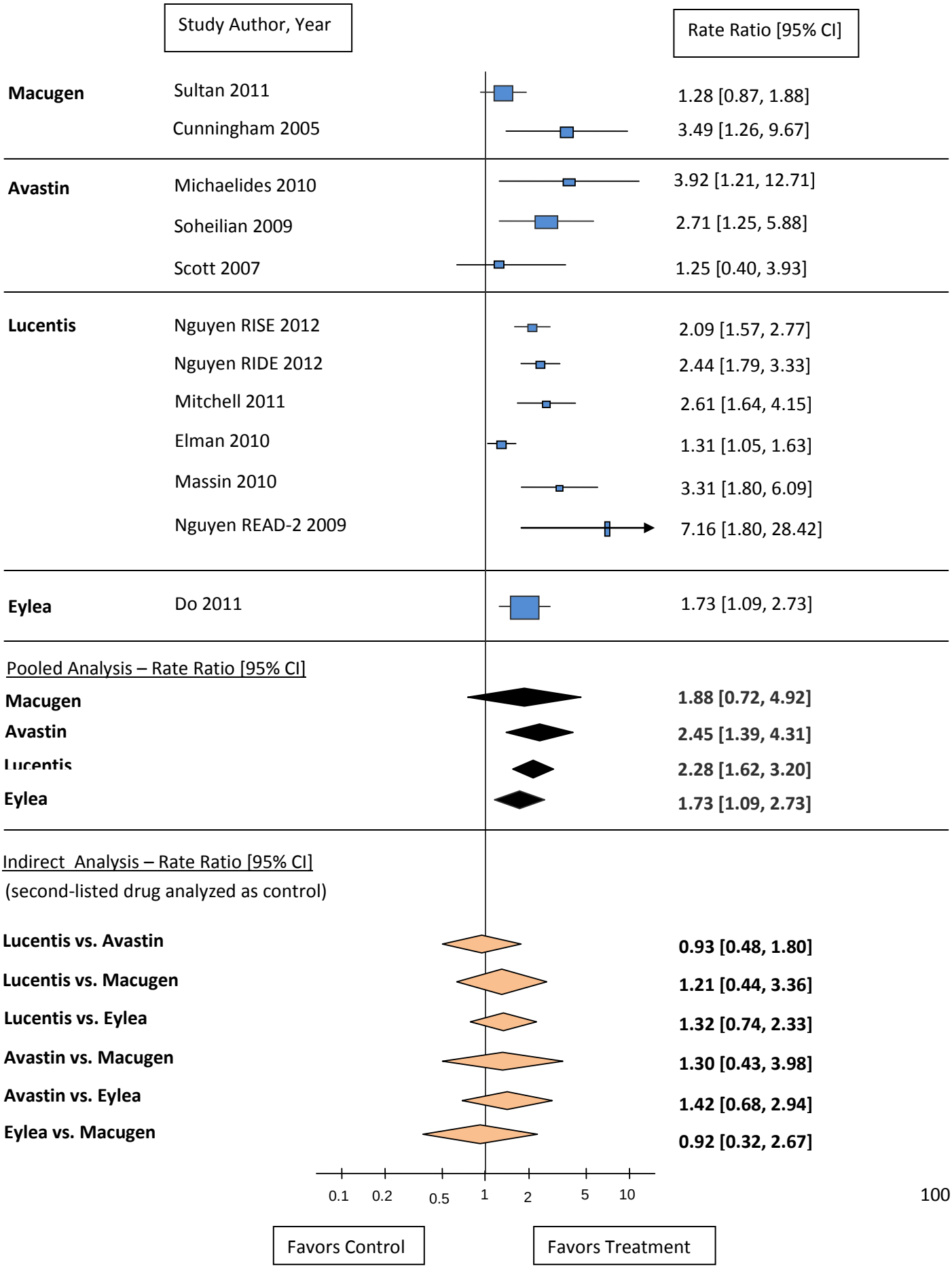


Figure E5. Sensitivity Analysis: meta-analysis and indirect comparisons of likelihood of gain of ≥10 letters between anti-VEGF therapy and any control.

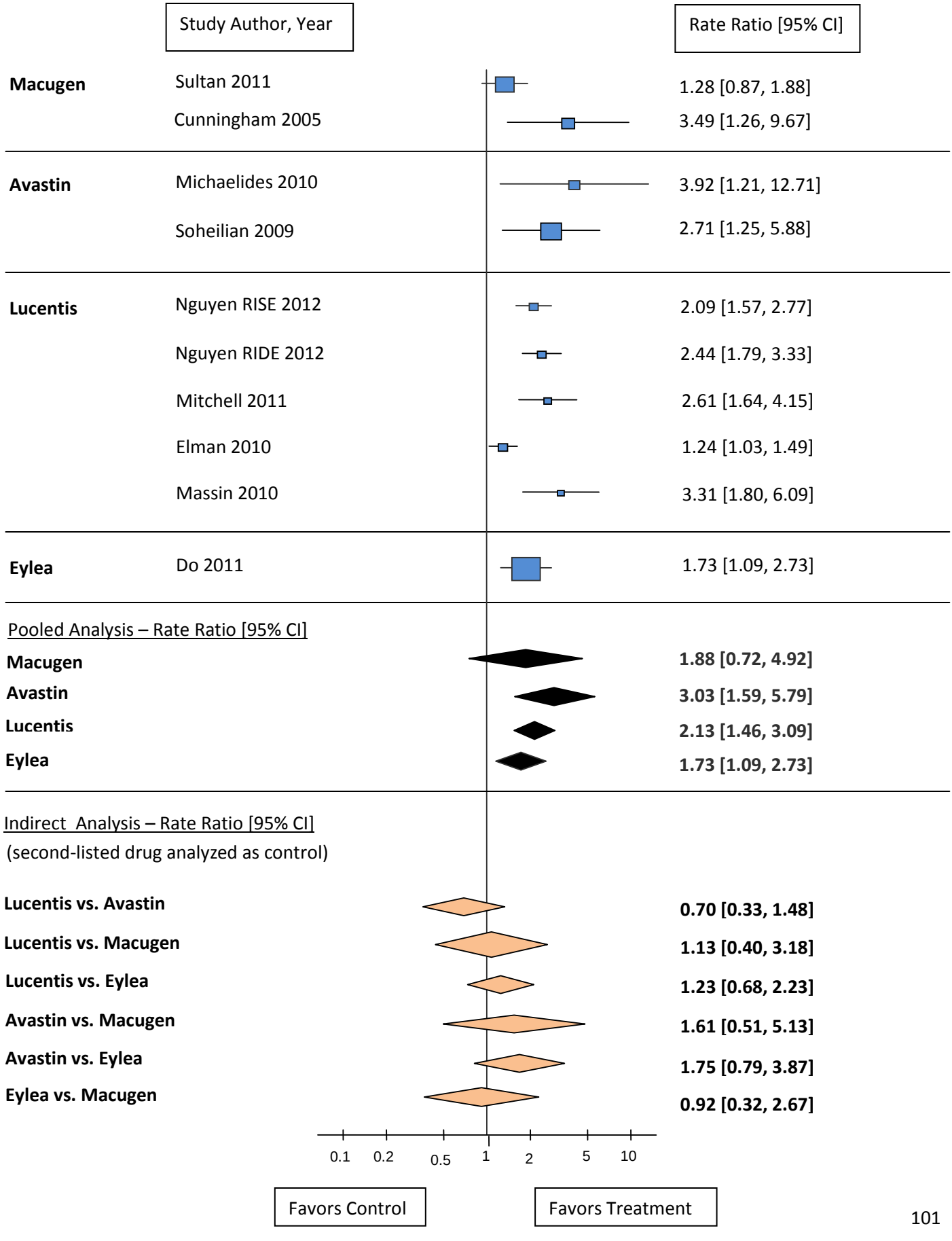


Figure E6. Sensitivity Analysis: meta-analysis and indirect comparisons of likelihood of gain of ≥10 letters between anti-VEGF therapy and any control in studies of good, fair and poor quality