Technology Assessment: Anti- VEGF Therapy in Diabetic Macular Edema

Presentation to MEDCAC

March 21, 2012

Dan Ollendorf, MPH
Chief Review Officer
ICER

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Outline

- Background on DME/Treatment
- Objectives of Assessment
- Methods
  - Qualitative Review
  - Quantitative Synthesis
- Results
  - Clinical Benefits
  - Potential Harms
- Summary/Conclusions

Background on DME

- Common cause of blindness among persons with diabetes
- Consequence of microvascular retinal changes from diabetic retinopathy
- Characterized by retinal thickening, accumulation of fluid in the retinal center (macula)
- “Clinically significant” disease: high degree of retinal thickening, hard exudates close to macular center
- Affects ~325,000 Americans ≥65

Impact on Vision

Normal Vision

With Retinopathy/DME

Source: National Eye Institute. Facts about Diabetic Eye Disease.
http://www.nei.nih.gov/health/diabetic/retinopathy.asp

DME Treatment

- Laser photocoagulation
  - Established in 1980s as “gold standard” for DME[1]
  - Effective in stabilizing vision; significant *improvement* in vision is rare[2]
- Anti-VEGF agents
  - Vascular endothelial growth factor (VEGF) plays central role in abnormal vessel growth and leakage in eye
  - Intravitreal (“inside the eye”) injections of anti-VEGF agents tested widely and approved for multiple indications
  - May be used alone or before, concurrently with, or after laser

DME Treatment (cont'd)

- Anti-VEGF agents available in U.S.
  - Macugen®: Selective VEGF inhibitor, approved (2004) for wet AMD (~$1,000 per dose); DME application in Europe withdrawn
  - Avastin®: Recombinant antibody to VEGF-A, approved (2004) for metastatic colorectal and other cancers; used off-label for ocular conditions (~$50 per dose)
  - Lucentis®: Antibody fragment derived from identical parent antibody as Avastin; approved (2006) for wet AMD, CRVO; approved for DME in Australia and Europe, under review in Canada and U.S. (~$1,600 per dose)
  - Eylea™: Fusion protein that binds VEGF-A and placental growth factor, approved (2011) for wet AMD (~$2,000 per dose)
- All currently off-label for DME in the U.S.

AMD: age-related macular degeneration
CRVO: central retinal vein occlusion

Project Objective

- To conduct a systematic review of the evidence on the comparative clinical effectiveness and potential harms of intravitreal anti-VEGF agents in patients with DME

Methods

- ***Patients:*** w/DME of any severity or identified subgroup of retinopathy with measurable outcomes
  - Wet AMD studies included for safety evaluation
- ***Interventions:*** All anti-VEGF w/≥1 published RCT in DME
- ***Comparators:*** Laser photocoagulation (as control or "rescue"), sham injection, intravitreal steroids
- ***Timeframes:*** All relevant timepoints (3-24 months)
- ***Study Designs:*** RCTs, observational studies (for safety and long-term effectiveness only)

Outcomes

- "Best corrected" visual acuity (BCVA):
  - Change from baseline (# letters gained/lost)
  - % with "clinically significant" gain (≥10 or 15 letters):
    - E.g. would represent move from 20/80 to 20/40 vision (threshold for driving in nearly all U.S. states)
- Health-related quality of life (QoL):
  - NEI Visual Function Questionnaire (VFQ-25)
  - EuroQol EQ-5D
- Treatment utilization:
  - Number of injections
  - Use of rescue laser
  - Need for retreatment

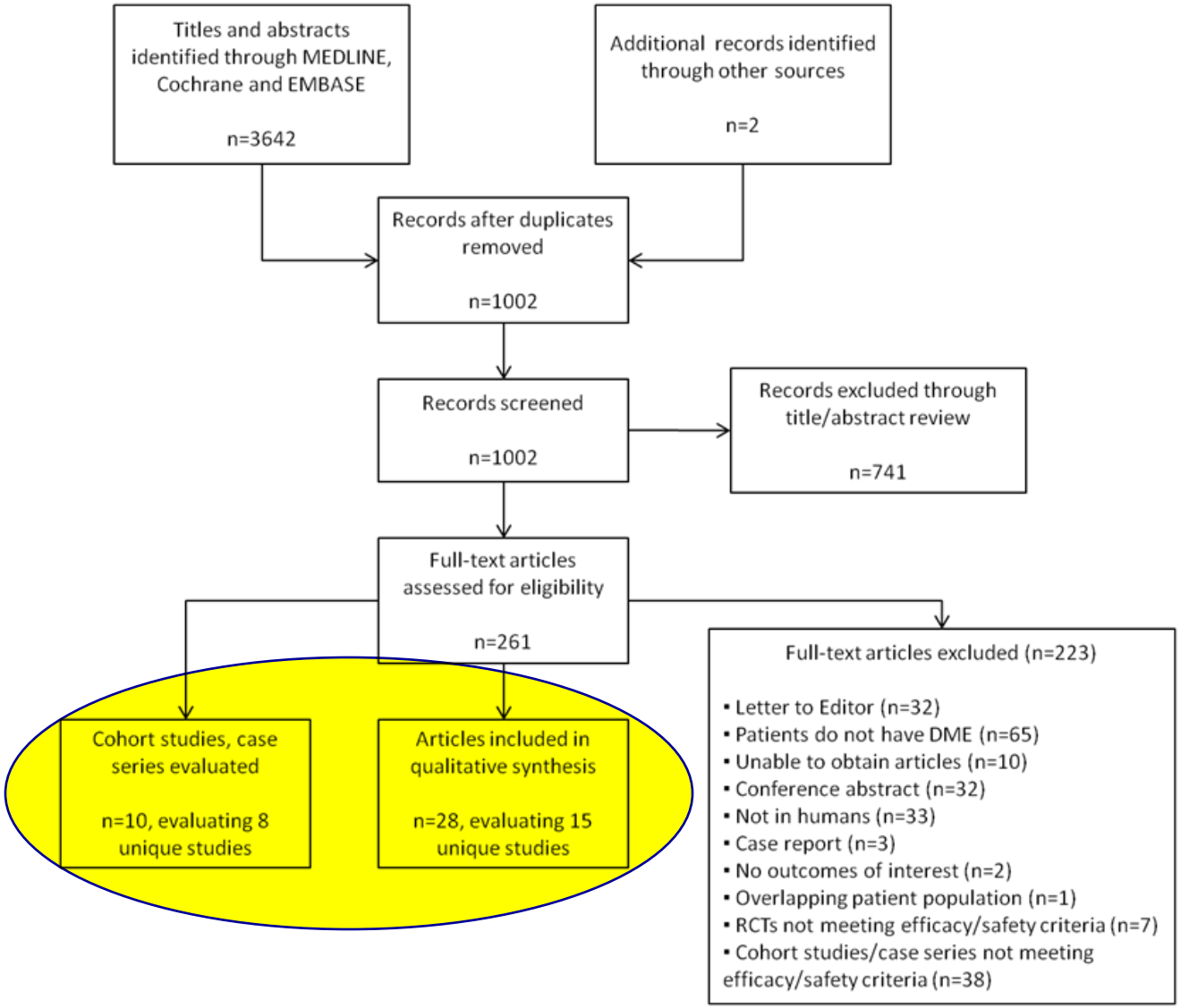
Potential Harms

- Specific ocular and systemic serious adverse events:
  - Endophthalmitis
  - Glaucoma
  - Stroke
  - Myocardial infarction
  - Death
- Also abstracted if reported in summary form:
  - Ocular events
  - Non-ocular events
  - Cardiovascular events

Data Analyses

- Qualitative
- Quantitative
  - All fair-good quality RCTs with outcomes reported at 6-24 months, comparisons to laser control or sham injection + rescue laser
  - Direct meta-analyses for each anti-VEGF
  - Pairwise indirect comparisons[3]
  - Sensitivity analyses:
    - Inclusion of poor-quality studies
    - Inclusion of additional control arms with steroid injections
    - Both changes

Results: PRISMA Flowchart

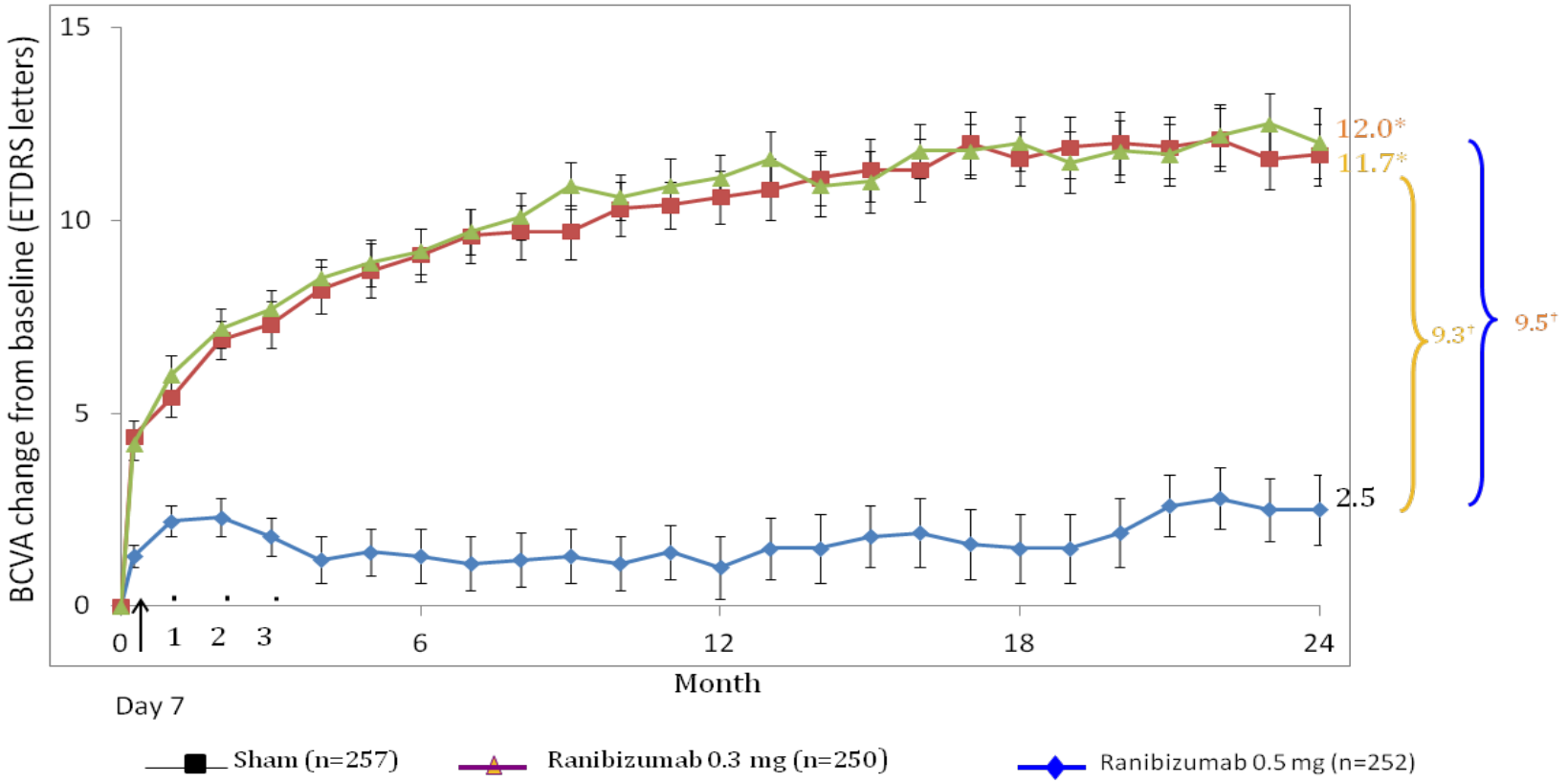


Results: Evidence Quality

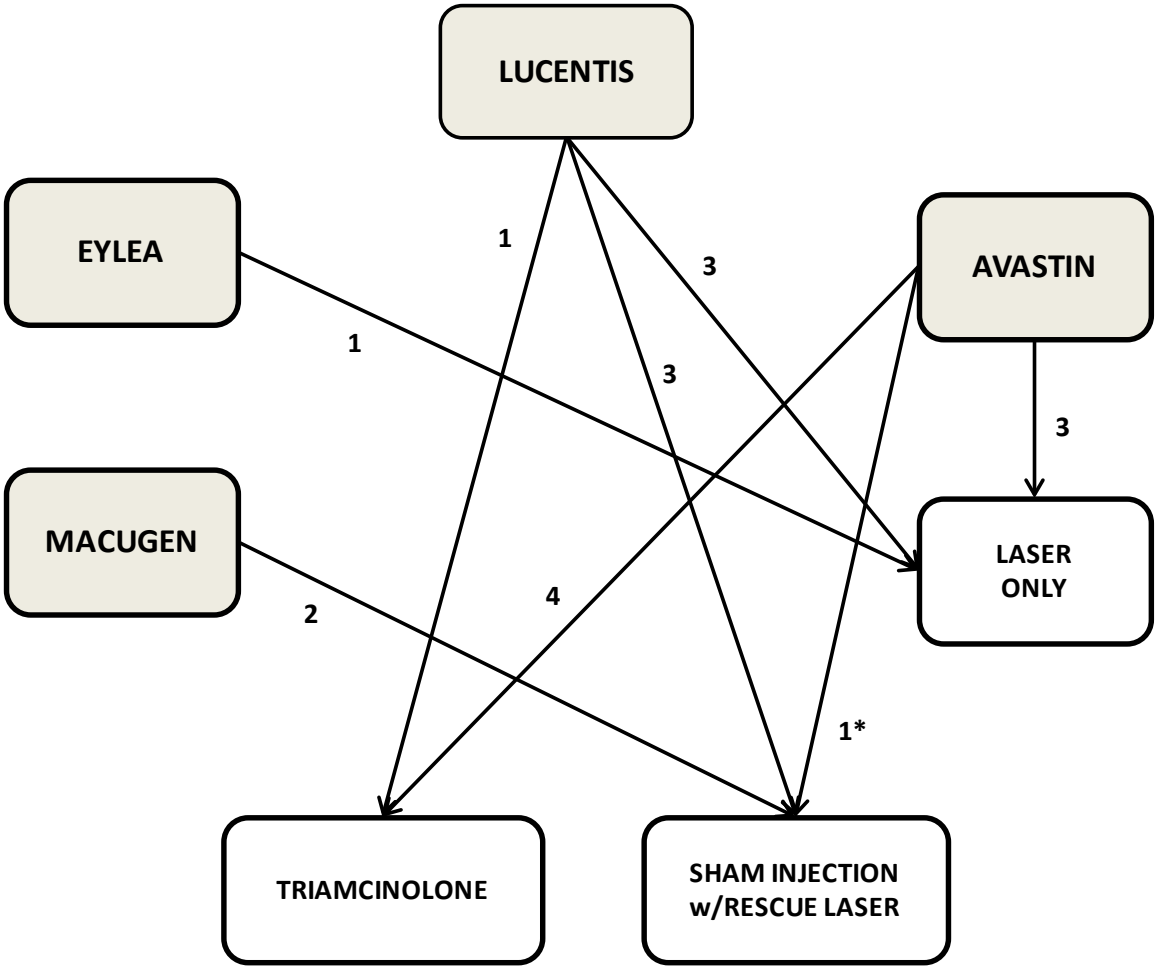
- 11 of 15 RCTs fair- or good-quality
  - 6 each of Avastin & Lucentis, 2 of Macugen, 1 of Eylea
- Large, multicenter, industry- or government-sponsored:
  - Macugen, Lucentis, Eylea
- Small, single-center, investigator-initiated:
  - Avastin
- Broad spectrum of patients enrolled, variability in study design, treatment protocol, follow-up
  - Evidence judged to be sufficiently comparable across anti-VEGF agents to warrant qualitative and quantitative synthesis

Change in Visual Acuity

- Improvements at earlier timepoints remained relatively constant throughout follow-up
- Example from RISE/RIDE studies[4]

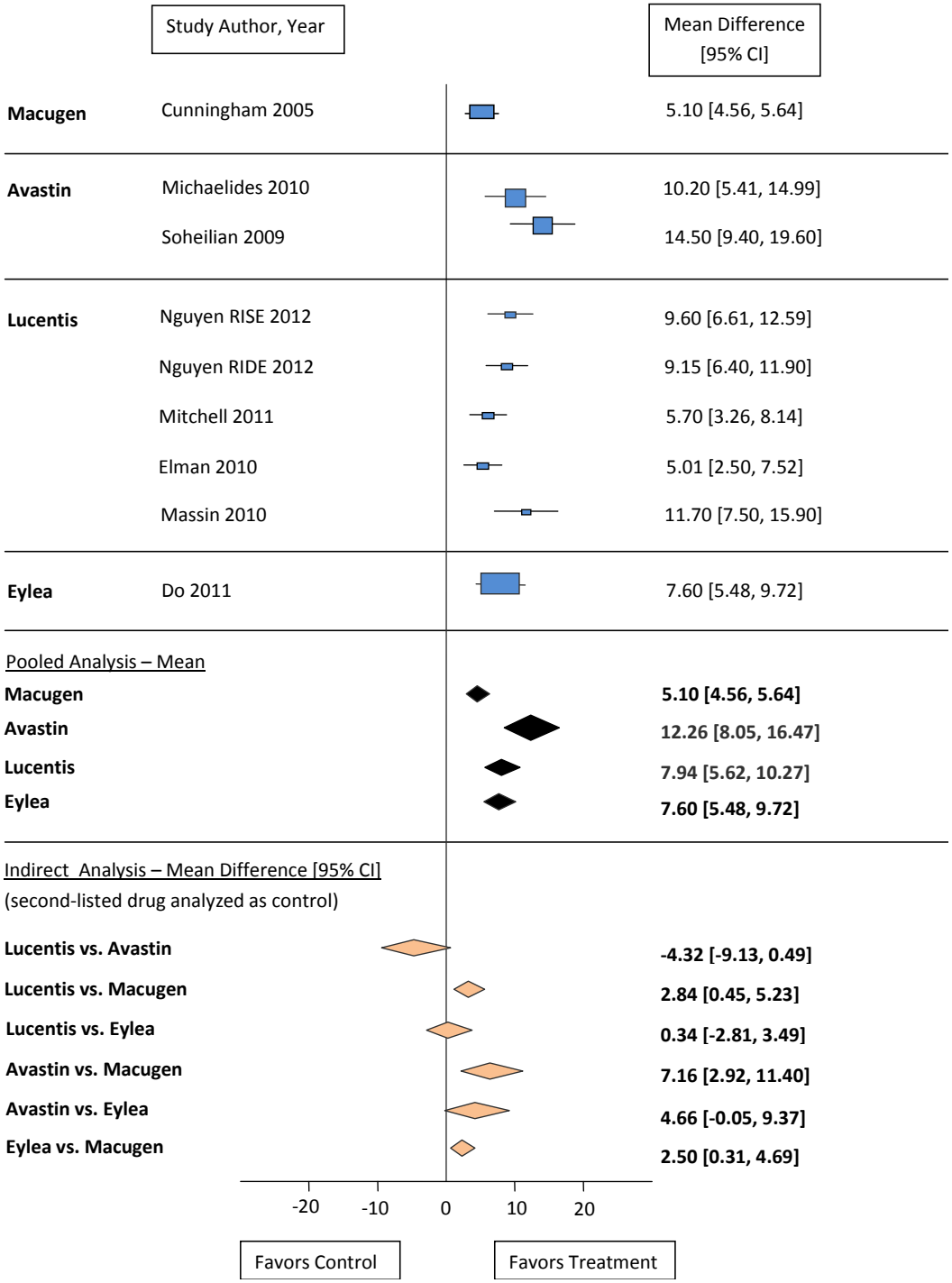


Quantitative Synthesis: Evidence Network



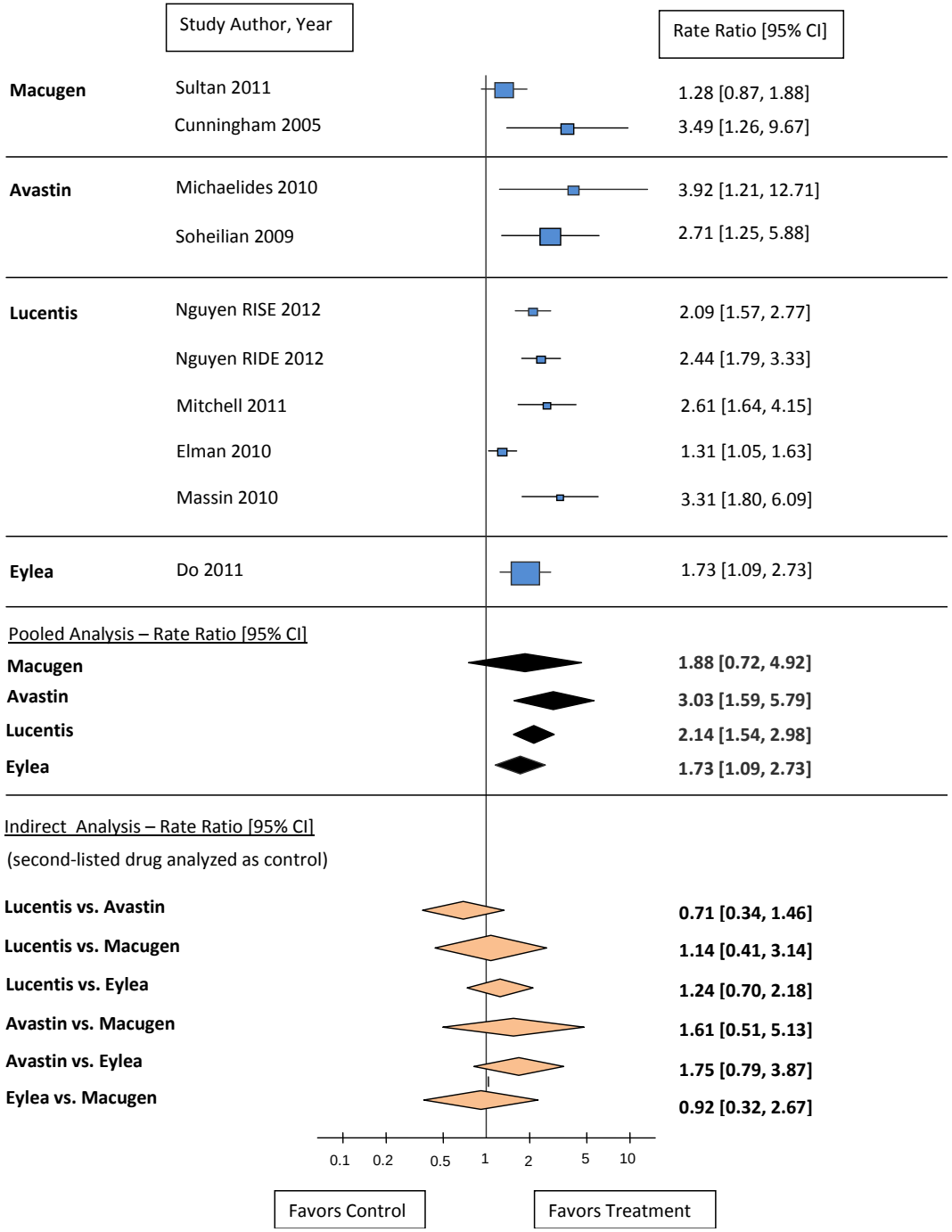
*Comparator was sham injection *without* laser; patients were previously unresponsive to laser

Meta-Analysis on Change in BCVA



CI: Confidence interval

Meta-Analysis on Gain of ≥10 Letters



CI: Confidence interval

Other Outcomes

- QoL:
  - Limited evidence of statistically-significant improvements on vision-related activities in NEI VFQ-25 (single RCTs of Lucentis and Macugen)
  - No significant effects on general domains reported
  - No significant effects on EQ-5D
- Treatment Utilization:
  - Use of injections and retreatment highly dependent on treatment protocol
  - Percentage of patients requiring rescue laser typically substantially lower for anti-VEGF vs. control:
    - Anti-VEGF: 5-41%
    - Control: 35-87%

Potential Harms

- Death rates comparable across anti-VEGF agents
- Other harms:

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

Potential Harms (cont'd)

- 1-year data from head-to-head RCT (CATT[5]) of Lucentis and Avastin:
  - No differences in rates of death or thrombotic events
  - Higher rate of "systemic adverse events" for Avastin (24% vs. 19%, p=.04)
- Retrospective analysis of Medicare claims[6]:
  - Differences in rates of mortality or systemic events between Lucentis vs. Avastin not statistically significant in analyses controlling for selection bias:

Event Type	Original Findings HR (95%CI)	Adjusted for Bias HR (95% CI)
All-cause mortality	0.86 (0.75, 0.98)	1.10 (0.85, 1.41)
Stroke	0.78 (0.64, 0.96)	0.87 (0.61, 1.24)

HR: Hazard ratio; CI: Confidence interval

Summary

- Evidence on anti-VEGF agents in DME includes 15 RCTs and 8 observational studies of >4,000 patients
- Available data suggest that anti-VEGF agents associated with substantial improvement in visual acuity vs. laser/sham control
- Evidence suggests clinically equivalent outcomes among anti-VEGF agents
- Greatest element of uncertainty is lack of rigorous and detailed safety data for Avastin vs. other anti-VEGF agents

References

1. 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.
2. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. *Lancet*. 2010;376(9735):124-136.
3. 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.
4. 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.
5. 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.
6. 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.