COMPARATIVE CLINICAL AND ECONOMIC EFFECTIVENESS OF ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR AGENTS

Allison Low, BA
Devan Kansagara, MD, MCR
Portland Evidence-based Synthesis Program (ESP)
VA Portland Health Care System

Glenn C. Cockerham, MD
National Program Director, VHA Ophthalmology Service
VA Palo Alto Health Care System

Deborah Khachikian, PharmD
National Pharmacy Benefits Management (PBM) Clinical Pharmacy Program Manager, PBM Services, Department of Veterans Affairs

May 10, 2017

Acknowledgements

Co-authors/Collaborators

- Michele Freeman, MPH (Research Associate)
- Rochelle Fu, PhD (Statistician)
- Kavita Bhavsar, MD (Ophthalmologist)
- Ambar Faridi, MD (Ophthalmologist)
- Karli Kondo, PhD (ESP Investigator)
- Robin Paynter, MLIS (Research Librarian)

Operational Partner

- Glenn Cockerham, MD (National Program Director, VHA Ophthalmology Service)

Technical Expert Panel/Reviewers

- Amy Chomsky, MD (Ophthalmologist; Chair, Ophthalmology Surgical Advisory Board)
- Debbie Khachikian, PharmD (National PBM Clinical Pharmacy Program Manager)
- Loh-Shan B. Leung, MD (Retina Specialist, Stanford)
- Mansi Parikh, MD (Ophthalmologist, Oregon Health & Science University)
- William Gunnar, MD (VA National Director of Surgery)

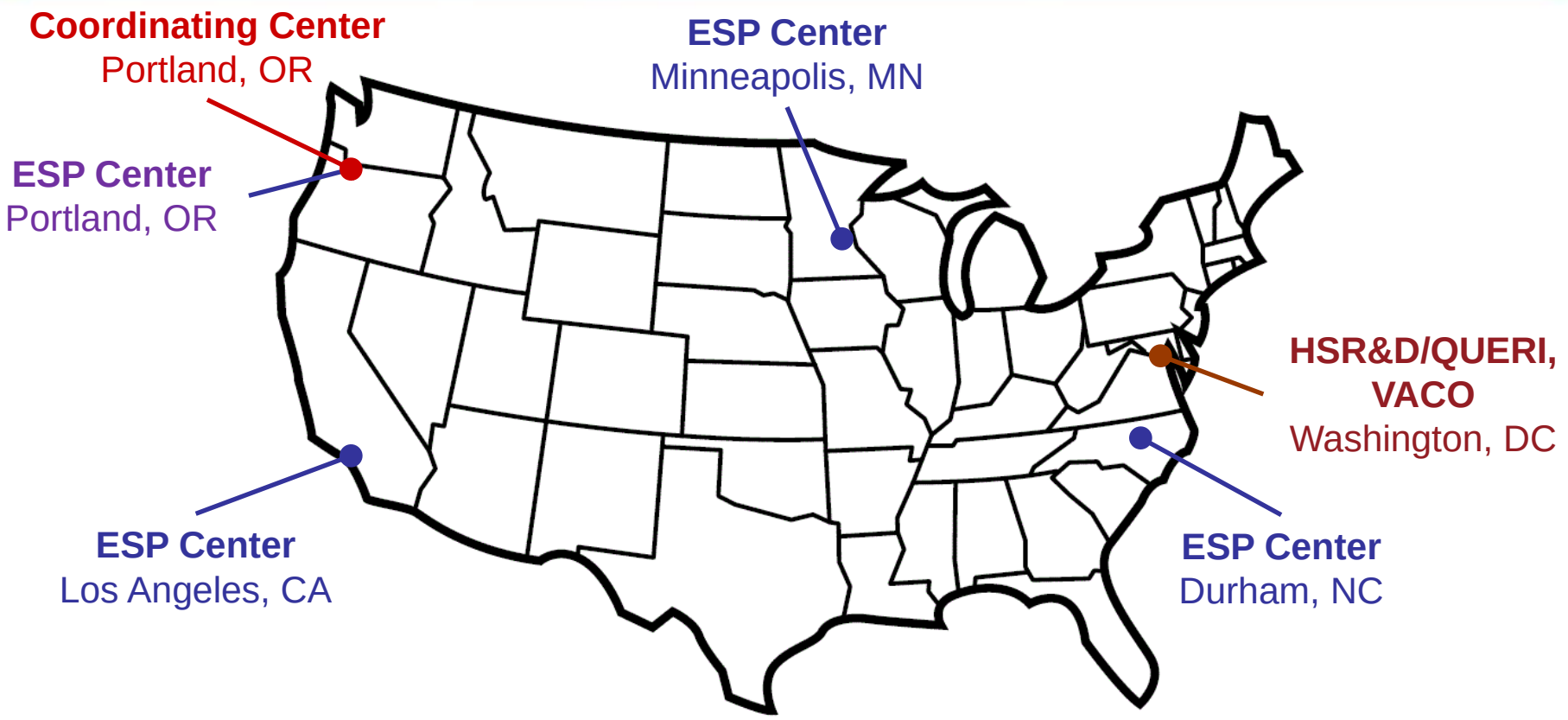
Disclosure

This report is based on research conducted by the Evidence-based Synthesis Program (ESP) Center located at the VA Portland Health Care System, Portland, OR, funded by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative. The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. No investigators have any affiliations or financial involvement (*eg*, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

VA Evidence-based Synthesis Program (ESP) Overview

- Sponsored by VA Office of Research and Development and the Quality Enhancement Research Initiative (QUERI)
- Established to provide timely and accurate syntheses/reviews of healthcare topics identified by VA clinicians, managers, and policy-makers, as they work to improve the health and healthcare of Veterans
- Reports conducted by internationally recognized VA clinician methodologists
- Builds on staff and expertise already in place at the Evidence-based Practice Centers (EPC) designated by AHRQ. Four of these EPCs are also ESP Centers, as shown on the following map.

ESP Center Locations



VA Evidence-based Synthesis Program (ESP) Overview

- Provides evidence syntheses on important clinical practice topics relevant to Veterans. These reports help:
  - develop clinical policies informed by evidence
  - the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures
  - guide the direction of future research to address gaps in clinical knowledge
- Broad topic nomination process – *eg*, VACO, VISNs, field staff – facilitated by the ESP Coordinating Center (Portland) through an online process:

http://www.hsrd.research.va.gov/publications/esp/TopicNominationForm.pdf

Current Report

COMPARATIVE CLINICAL AND ECONOMIC EFFECTIVENESS OF ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR AGENTS

January 2017

Full-length report available on ESP website:
http://www.hsrd.research.va.gov/publications/esp/reports.cfm

Poll #1:

What is your primary role? (Choose one of the following)

- VA clinician
- VA researcher
- VA administrator, manager or policy-maker
- Non-VA clinician
- Other

Poll #2:

For those who do use these anti-VEGF agents, which one do you use *most often*? (Choose one of the following)

- Aflibercept (Eylea®)
- Bevacizumab (Avastin®)
- Ranibizumab (Lucentis®)
- I use all three equally
- NA/I do not use these drugs

Anti-VEGF Agents in Ophthalmology

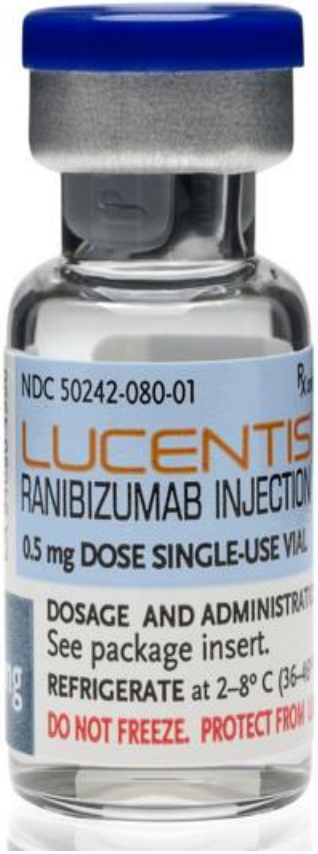
Glenn C. Cockerham, MD
National Program Director
VHA Ophthalmology
VA Palo Alto, CA

Avastin™ (bevacizumab) Genentech/Roche

- FDA approval in 2004 for adenocarcinoma
- Full-length, murine-derived monoclonal IgG1 Ab
- 2 VEGF binding sites
- Theoretically not a good choice for intraocular use, but good results in 2005 in AMD
- Used off label worldwide for intravitreal injections, including VA

Lucentis™ (ranibizumab) Roche/Novartis

- FDA approval in 2006 for age-related macular degeneration, later approved for macular edema, diabetic retinopathy, and myopic choroidal neovascularization
- Bevacizumab (148 kDa) was cleaved into smaller fragment (48 kDa), affinity enhanced
- NIH funded a head-to-head study of Lucentis vs Avastin in 2011 (CATT)



Eylea™ (aflibercept) Regeneron

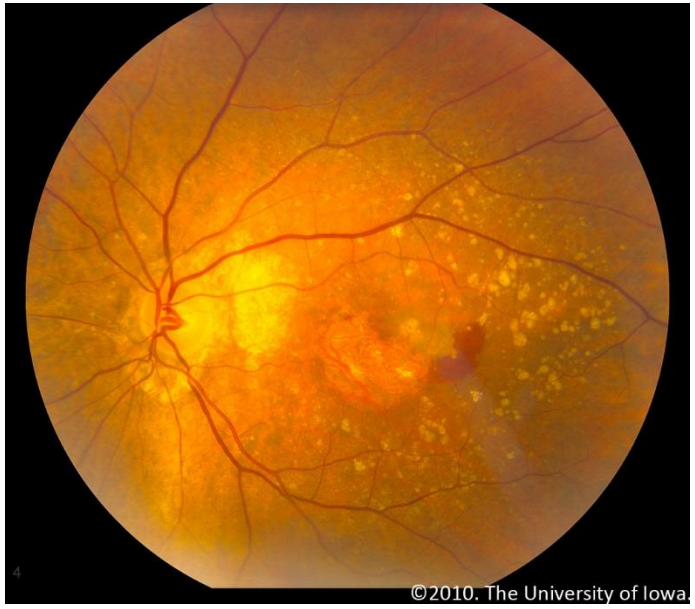
- FDA approval in 2011 for age-related macular edema; later approved for diabetic macular edema and diabetic retinopathy

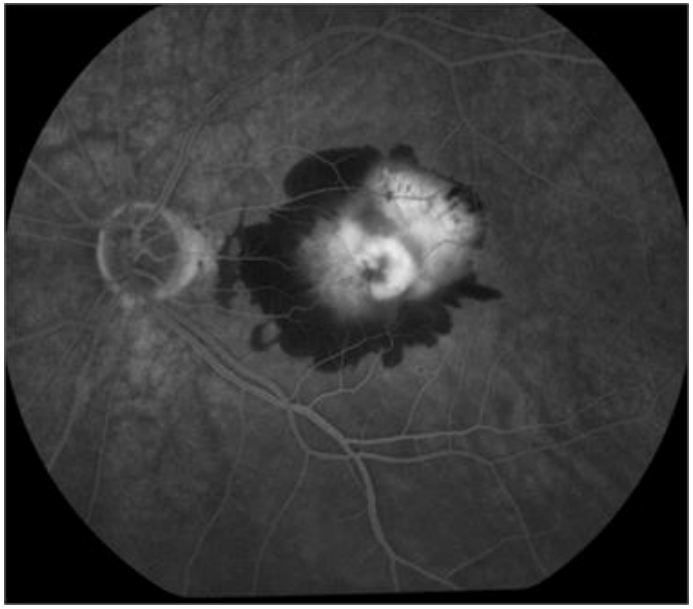
Indications for Anti-VEGF Agents in Ophthalmology

- Conditions that cause blindness due to growth of new blood vessels (neovascularization), bleeding, leakage of fluid (edema) and lipids (exudates)
  - Age-related macular degeneration (AMD)
  - Diabetic retinopathy
  - Retinal vein occlusion

Age-related Macular Degeneration (AMD)

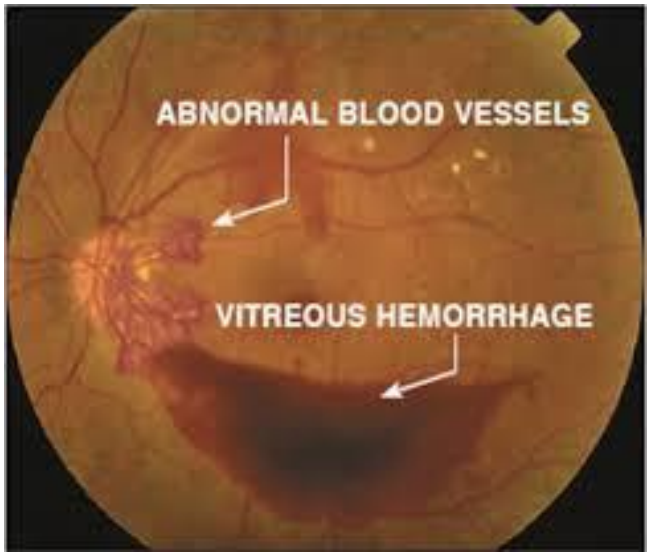
- Most common cause of blindness in adults over 65 years of age
- 10% of patients have neovascular (wet) AMD
- 200,000 new patients in U.S. yearly





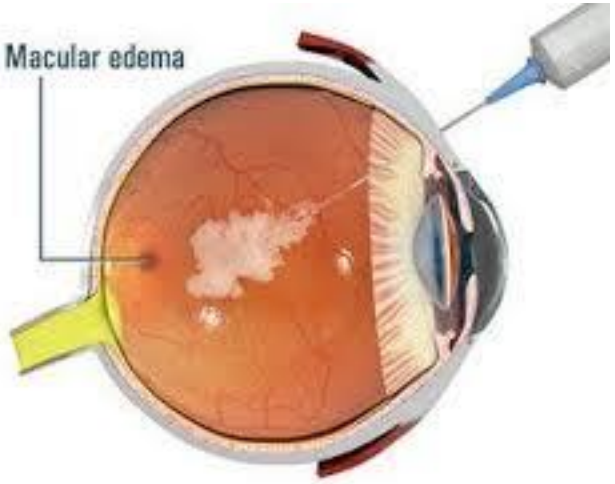
Diabetic Retinopathy

- Most common cause of blindness between ages 20 and 65 years
- Diabetic macular edema
- Proliferative diabetic retinopathy
  - Vitreous hemorrhage
  - Retinal detachments



Route of Administration

- Intravitreal route (into the vitreous cavity)
- Topical anesthesia
- Estimated 5 million injections in 2015



Topic Development

- Topic nominated by Dr. Glenn Cockerham
- Scope and Key Questions developed with help from Technical Experts:
  - Ophthalmologists
  - Retina Specialist
  - Clinical Pharmacy Specialist

Key Questions

- **Key Question 1:** What is the comparative clinical effectiveness of anti-VEGF agents for retinal/choroidal neovascularization and/or macular edema in adults?

- **Key Question 2:** What are the comparative harms of anti-VEGF agents for retinal/choroidal neovascularization and/or macular edema in adults?

- **Key Question 3**: What is the comparative cost-effectiveness of anti-VEGF agents for retinal/choroidal neovascularization and/or macular edema in adults?

Methods: Data Sources

- Search Strategy:
  - Ovid MEDLINE to December 11, 2015
  - PubMed, Elsevier EMBASE, and Ovid EBM to February 2, 2016
- Grey literature sources: trial registries (e.g., ClinicalTrials.gov)
- Requested Scientific Information Packets for unpublished data from manufacturers

Methods: Study Selection

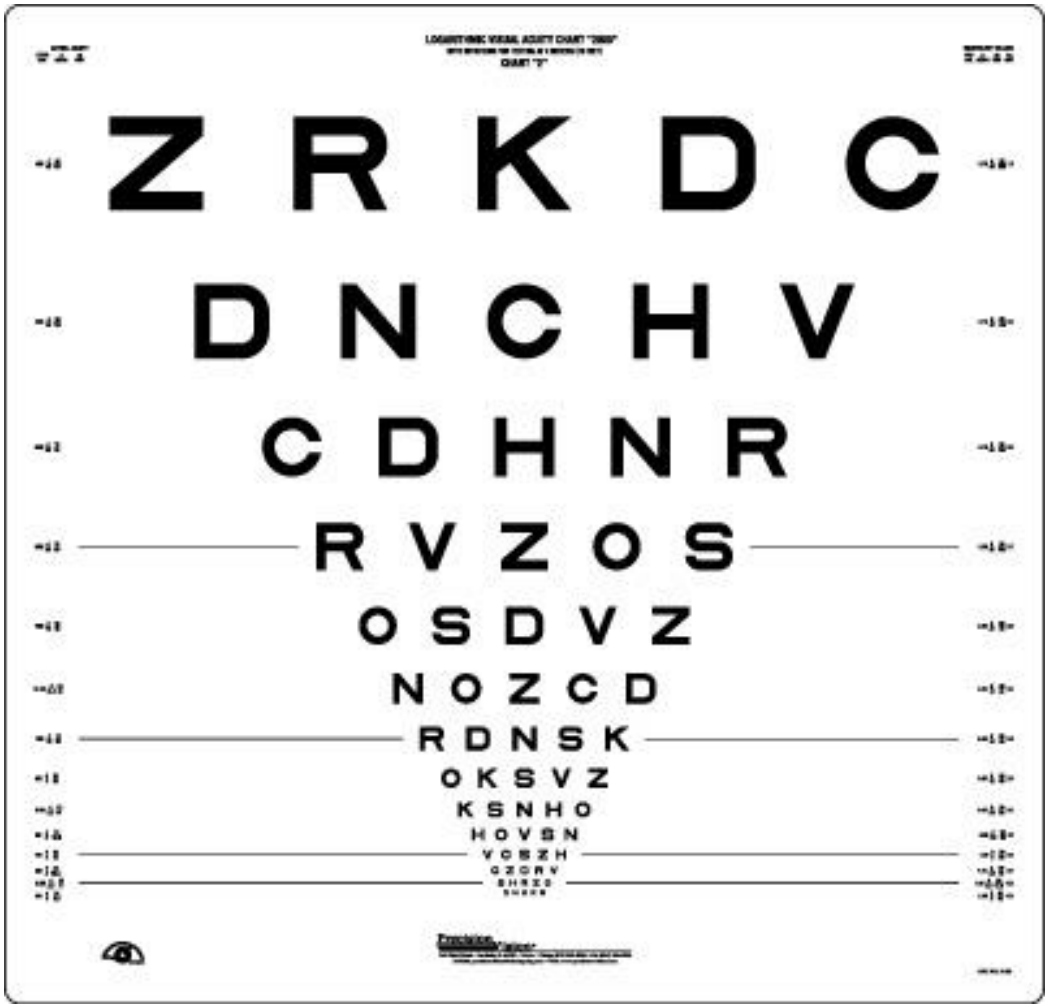
- Population:
  - Diabetic macular edema (DME)
  - Branch or central retinal vein occlusion (BRVO or CRVO)
  - Neovascular age-related macular degeneration (AMD)
  - Vitreous hemorrhage/proliferative diabetic retinopathy/neovascular glaucoma
- Study Designs: only included head-to-head trials
  - Effectiveness and harms: only controlled clinical trials
  - Cost: SRs, cohort studies, validated modeling studies in the US only

Methods: Study Selection

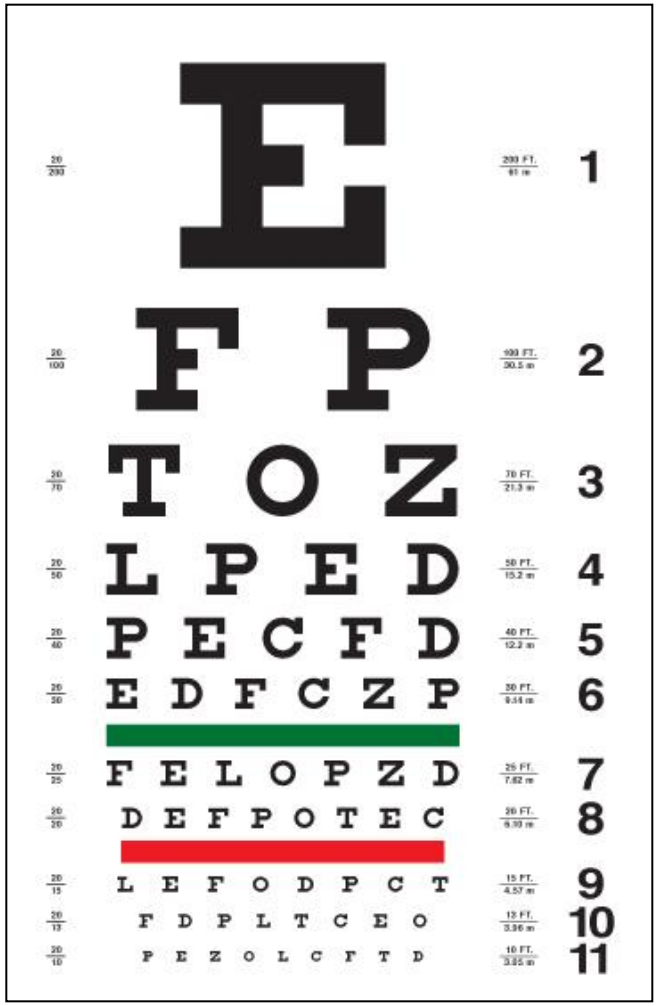
Effectiveness Outcomes

- Visual acuity:
  - Mean change: clinically meaningful difference between groups ≥5 letters
  - % gaining 15 or more letters
    - BCVA: best-corrected visual acuity
    - ETDRS letters: Early Treatment of Diabetic Retinopathy Study chart letters
- Functional status or quality of life
- Intermediate outcomes: e.g., change in central macular/subfield thickness, resolution of subretinal/intraretinal fluid (using OCT)

ETDRS chart



Snellen chart



Methods: Study Selection

Outcomes

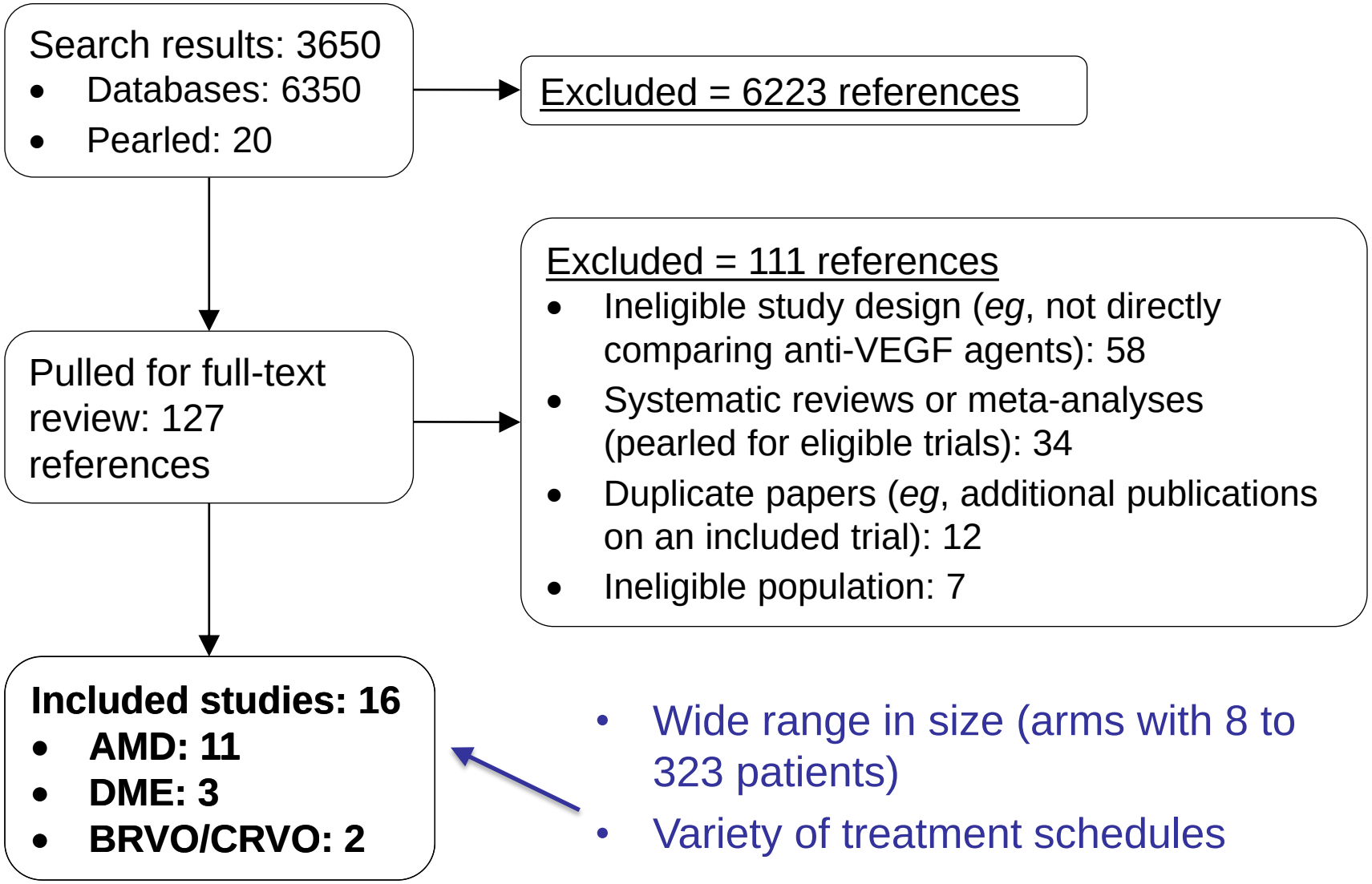
- Harms:
  - Ocular: e.g., endophthalmitis, retinal detachment, glaucoma
  - Systemic: e.g., arterial thrombotic events, GI disorders

- Costs:
  - Cost of drug alone; cost of overall treatment
  - # of injections
  - % needing rescue/co-interventions

Methods

- Quality Assessment: Cochrane Risk of Bias Tool (low, unclear, or high risk of bias)
- Performed meta-analyses when appropriate
- Rating the Body of Evidence: consider consistency, precision, study quality, directness
  - High: Very confident that the estimate of effect lies close to the true effect for the outcome
  - Moderate: Moderately confident; findings are likely to be stable
  - Low: Limited confidence; additional evidence needed before concluding that the findings are stable
  - Insufficient: No evidence or no confidence in the estimate of effect

Literature Flow



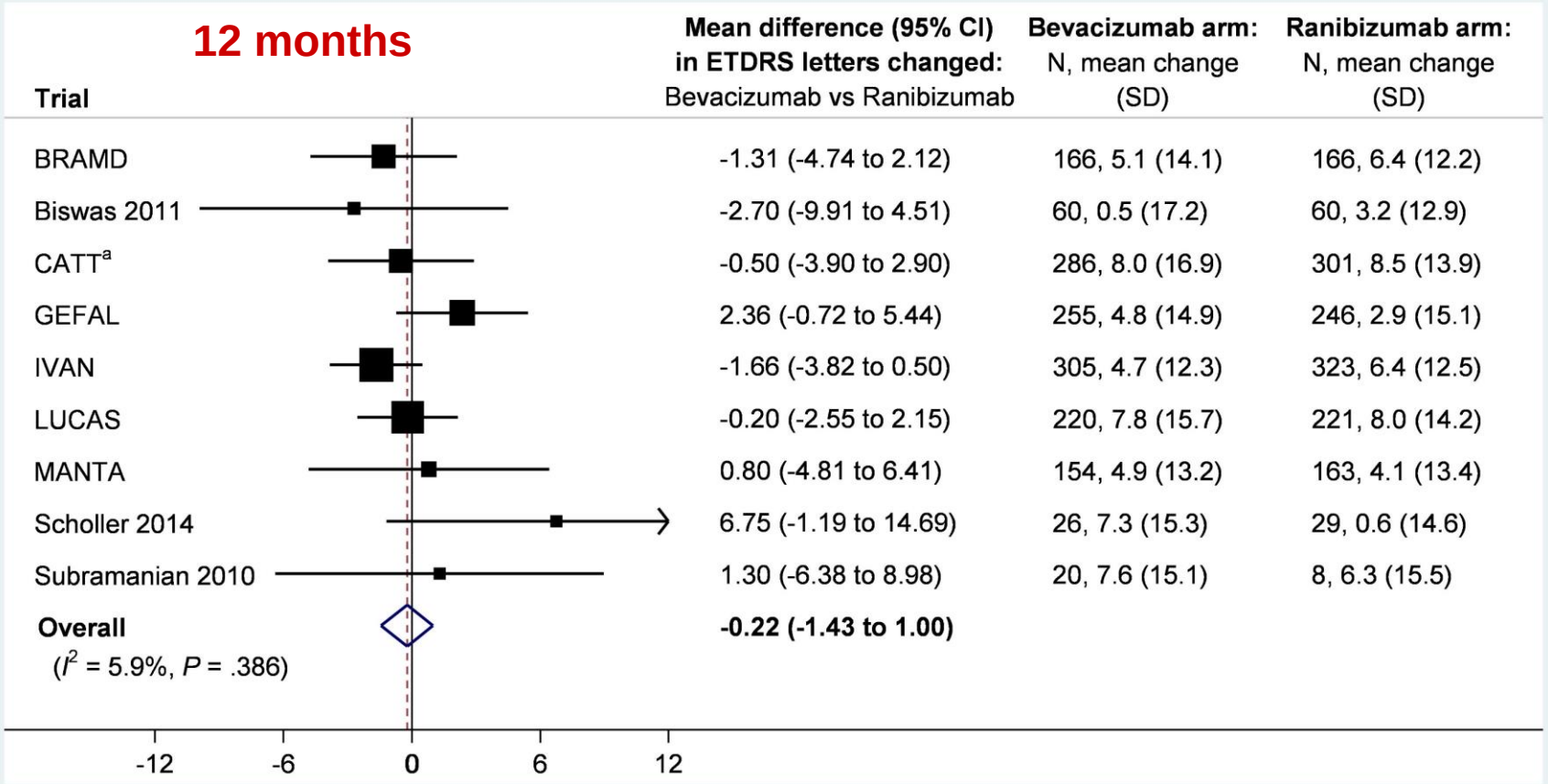
KQ 1: Comparative Effectiveness for AMD

- Patients with AMD: most studied condition (11 trials)
  - Majority of studies:
    - *Pro re nata* (PRN, "as needed") treatment schedules alone or in addition to monthly injections
    - Age in late 70s, baseline 55 to 62 ETDRS letters (moderate vision loss)
    - Most achieved mean BCVA ~65 to 70 letters

Bevacizumab vs Ranibizumab:

- Visual Acuity: no significant difference
- Quality of Life: only reported by IVAN trial, no difference found

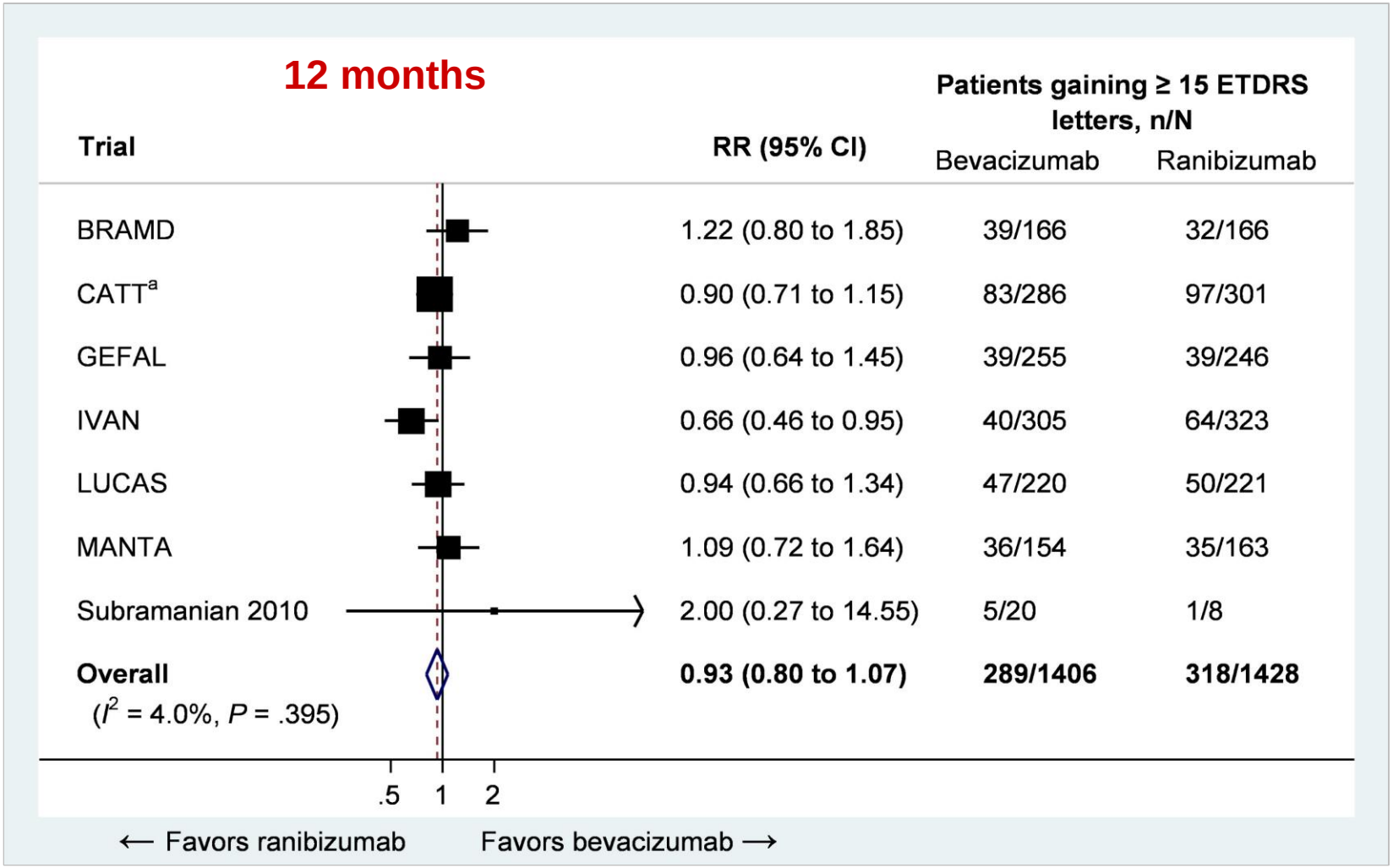
Consistent, high-strength evidence of no difference in mean BCVA improvement



- Similar results at 18 to 24 months (4 trials)

*BCVA = best corrected visual acuity

Moderate-strength evidence of no difference in % gaining ≥15 letters



- Similar results at 18 to 24 months (4 trials)

KQ 1: Comparative Effectiveness for AMD

Aflibercept vs Ranibizumab:

- 2 large sister trials: VIEW 1 and VIEW 2 (~1230 patients per trial)

- Mean change in BCVA: conflicting results, but no clinically meaningful difference at 12 or 22 months (insufficient evidence)
- % gaining ≥15 letters: no significant difference (low-strength evidence)
- No significant differences in visual acuity between *bimonthly* aflibercept and *monthly* ranibizumab (no bimonthly ranibizumab arm)

Aflibercept vs Bevacizumab: no evidence

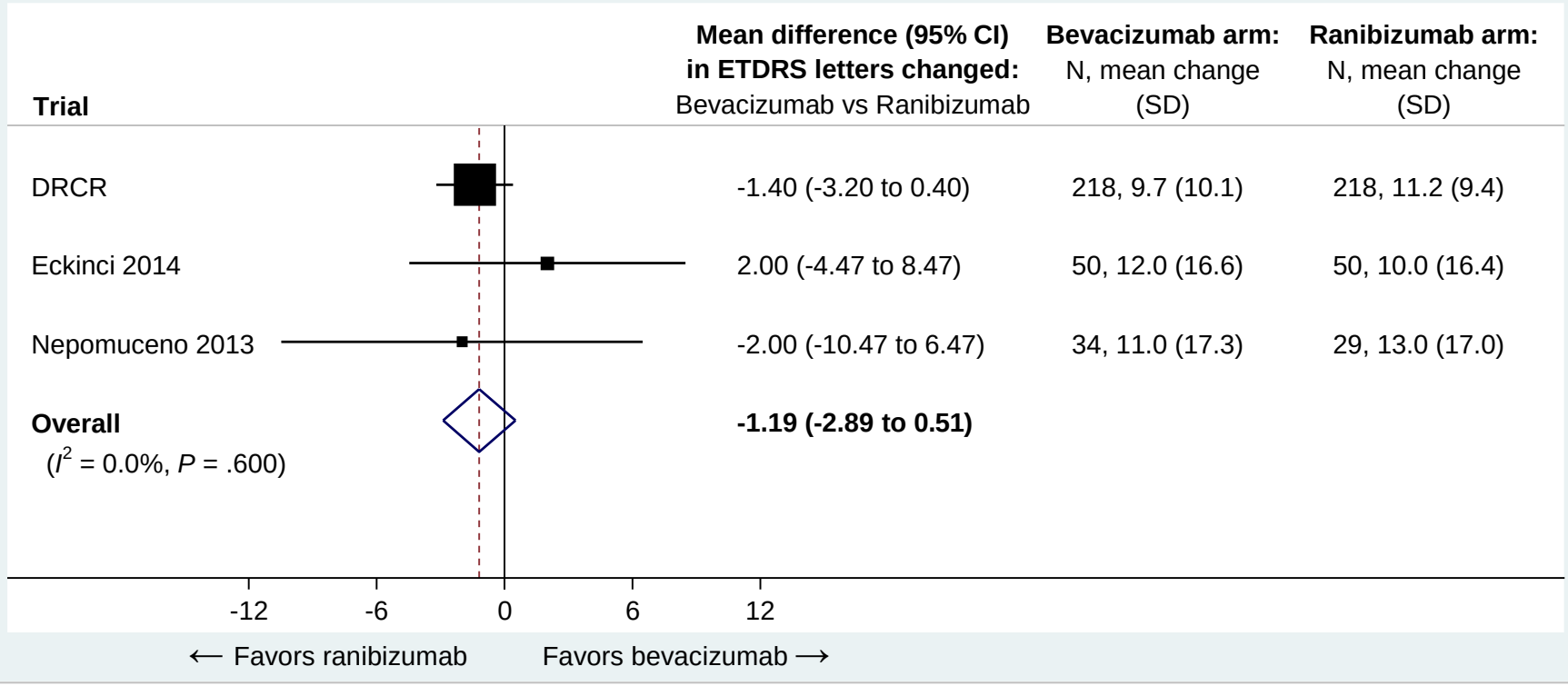
KQ 1: Comparative Effectiveness for DME

- Patients with DME: 3 trials
  - Largest trial: DRCR.net Protocol T, compared all 3 agents

Bevacizumab vs Ranibizumab:

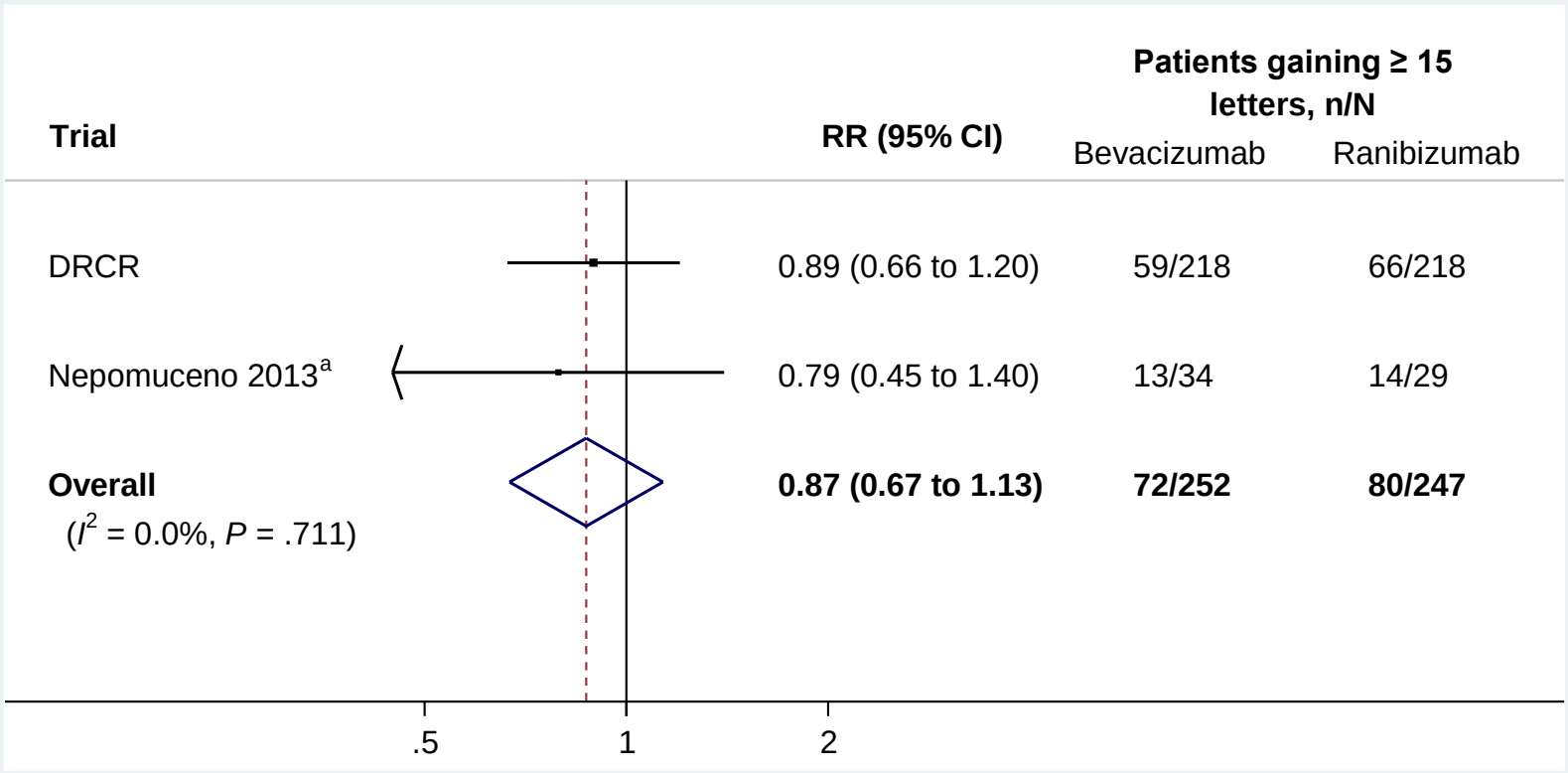
- Visual Acuity: no significant difference (moderate-strength evidence)

Moderate-strength evidence of no difference in mean BCVA improvement at 12 months



*BCVA = best corrected visual acuity

Moderate-strength evidence of no difference in % gaining ≥15 letters at 12 months



KQ 1: Comparative Effectiveness for DME

Aflibercept vs Bevacizumab: DRCR.net Protocol T

- Visual Acuity: some benefit in favor of aflibercept, but difference was not likely clinically meaningful in overall population (low-strength evidence)
  - In subgroup with lower baseline visual acuity, difference was clinically meaningful at 12 months: 6.5 letters (95% CI, 2.9-10.1)
  - Difference slightly smaller by 24 months: 4.7 letters (95% CI, 0.5-8.8)

KQ 1: Comparative Effectiveness for DME

Aflibercept vs Ranibizumab: DRCR.net Protocol T

- Visual Acuity: some benefit in favor of aflibercept in the short-term, but difference was not likely clinically meaningful (low-strength evidence)
  - In subgroup with lower baseline visual acuity, difference more pronounced but still did not reach clinical significance: 4.7 letters (95% CI, 1.4-8.0)

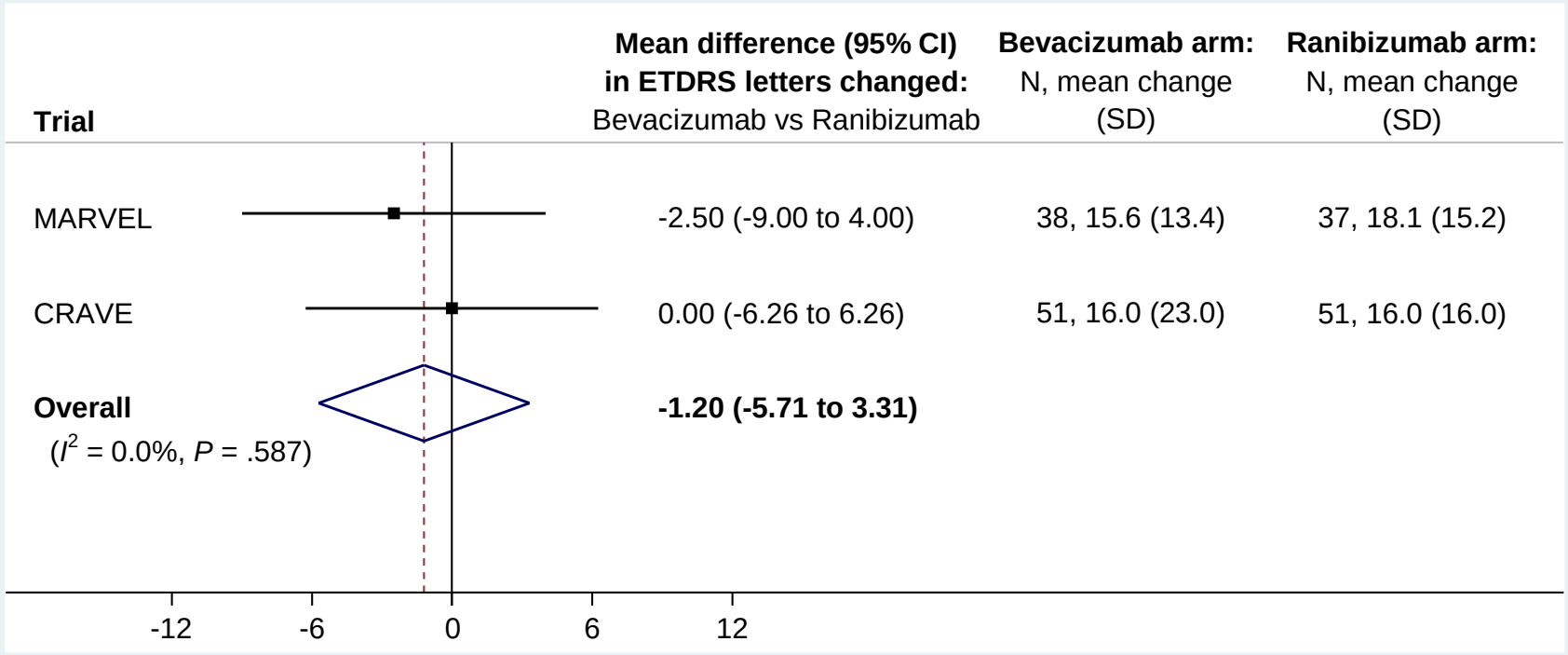
KQ 1: Comparative Effectiveness for RVO

- Patients with RVO:
  - 2 small trials at 6 months (177 patients total)

Bevacizumab vs Ranibizumab:

- Visual Acuity: no difference (insufficient evidence)

No difference in mean BCVA improvement (insufficient evidence)



KQ 2: Comparative Harms

- 12 trials reported harms (9 in patients with AMD)
- *P*-values not reported in many trials
- No trials specifically designed to assess harms (not powered)

AMD:

- Low rate of withdrawals due to adverse events (<1 to 4.5%)
- Serious ocular adverse events: generally low, no significant differences reported between groups (low- to moderate-strength)
  - Endophthalmitis generally occurred in <1% of patients (5 trials), no significant difference between drugs
  - Other serious ocular adverse events very rare (<1% in 5 trials)

KQ 2: Comparative Harms

AMD (continued):

- Systemic adverse events:
  - % with ≥1 serious systemic harms varied widely (10 to 40%)
  - Similar rates reported in most trials
  - CATT had highest rates and was only trial to find significant difference (relative risk [RR] for bevacizumab vs ranibizumab: 1.30)

•*But meaning is unclear*, since most of the difference was in harms not known to be affected by the VEGF pathway

  - Arterial thrombotic events occurred in up to 5% of patients; one trial found higher rates in ranibizumab vs bevacizumab at 12 months, but no difference by 24 months

KQ 2: Comparative Harms

DME:

- Data primarily from DRCR.net Protocol T
- Serious ocular adverse events: no significant differences between drugs
  - Endophthalmitis: only 1 patient (<0.5% of patients) over 24 months (higher rates in 2 smaller trials)
  - Most common were elevated intraocular pressure (15.3% of patients) and vitreous hemorrhage (6.4% of patients)
- Serious systemic adverse events: high rates
  - Ranibizumab had more arterial thrombotic events than aflibercept (*P*=.047) or bevacizumab (*P*=.20) as well as slightly higher rates of hypertension

KQ 2: Comparative Harms

RVO:

- Two small trials provide insufficient data
- Serious ocular adverse events were relatively rare, no instances of endophthalmitis

KQ 3: Comparative Costs

Cost: moderate-strength evidence that ranibizumab and aflibercept are considerably more expensive than compounded bevacizumab and provide no incremental cost-effectiveness benefits

- Two trials: both used compounded bevacizumab
  - CATT: ranibizumab vs compounded bevacizumab for AMD
    - Ranibizumab 35+ times more expensive than bevacizumab (drug only)
  - DRCR.net Protocol T: all 3 agents for DME
    - Total mean costs per participant/year: **$26,000 aflibercept** vs **18,600 ranibizumab** vs **4,100 bevacizumab**
    - Validated model projecting 10-year costs:
      - Lower BCVA at baseline: incremental cost-effectiveness ratios for **aflibercept was $287,000 per QALY vs bevacizumab**

Limitations

- Methodological limitations of included studies
- Limited data on aflibercept, patients with RVO
- Several trials excluded patients with cardiovascular risk factors
- Only one trial stratified by baseline visual acuity
- All evidence on cost used compounded bevacizumab
- Only controlled trials included for effectiveness and harms data
- Examining clinical populations separately limited our power to detect differences

Summary

KQ 1: Comparative Effectiveness

- No clear, consistent, clinically meaningful differences between anti-VEGF drugs were found for the general population (low- to moderate-strength evidence for AMD and DME)
  - Insufficient evidence for RVO
- DME trial: Aflibercept may be superior in patients with lower baseline visual acuity over the short-term
  - Longer-term findings are unclear
  - More trials of aflibercept are needed

Summary

KQ 2: Comparative Harms

- Low rates of serious ocular adverse events
- No clear differences in rates of systemic adverse events

KQ 3: Cost Effectiveness

- Compounded bevacizumab is associated with considerably lower costs than other 2 agents; no data on non-compounded costs

Clinicians should also consider patient preference, individual treatment response, convenience, and distance to treatment facility when choosing amongst these anti-VEGF agents.

VA Costs for Anti-VEGF Agents

- Bevacizumab 4 ml vial $503
- Ranibizumab 0.3 mg (DME) $859
- Ranibizumab 0.5 mg (AMD, RVO) $1437
- Aflibercept 2 mg $1412

- Courtesy of Dr. Debbie Khachikian, Pharmacy Benefits Manager

VA Purchasing Data
April 2016-March 2017

• Aflibercept 2 mg.0.05 ml	$67,730,000
• *Bevacizumab 25 mg/ml, 4 ml	$15,621,000
• Ranibizumab 0.3 mg/0.05 ml	$8,481,000
• Ranibizumab 0.5 mg/0.05 ml	$1,420,000

* Bevacizumab utilized by both Ophthalmology and Oncology

Anti-VEGF Agents in Medicare and VA Costs 2005-2011

- Indication: age-related macular degeneration
- Bevacizumab (Avastin, Genentech/Roche)
  - $50 per dose in Medicare population (multiple doses from vial)
- Ranibizumab (Lucentis, Genentech/Roche)
  - $1000 per dose estimated
- Bevacizumab used more frequently over time in both Medicare and VA
- Incentives in Medicare may influence drug choice:
  - Patient incentive: have lower copays with less expensive drug
  - Physician incentive: higher reimbursement for more expensive drug; CMS pays physician 6% of drug cost as overhead

Pershing S, et al. Treating age-related macular degeneration: comparing the use of two drugs among Medicare and Veterans Affairs Populations. *Health Affairs* 2015;34:229-238.

Potential Cost Savings with Bevacizumab Use

- Medicare savings: $18 billion
- Beneficiary copayment savings: $5 billion
- (Over 10 year period if all patients treated with bevacizumab alone)

- Hutton D, et al. Switching to less expensive blindness drug could save Medicare part B $18 over a ten-year period. Health Affairs 2014;33:931-939.

Questions?

If you have further questions, please feel free to contact:

Allison Low, BA (Report PI): Allison.Low@va.gov

Devan Kansagara, MD, MCR (Portland ESP Director): kansagar@ohsu.edu

Glenn Cockerham, MD (National Program Director, VHA Ophthalmology Service): Glenn.Cockerham@va.gov

Full-length report and cyberseminar available on ESP website:

http://www.hsrd.research.va.gov/publications/esp/