# Comparative Effectiveness Research in Action

ICER
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# Case study 1: Lucentis vs. Avastin

- Similar molecules made by the same company, but with different indications and cost
- Difficulty in performing a head-to-head trial
- 1st year CATT results published in NEJM
  - Equivalent visual outcomes
  - 24% vs. 19% serious systemic adverse advents in disease categories not identified in previous studies as areas of concern
- Industry-funded observational analysis of Medicare data showed higher rates of side effects
- VA halts Avastin use
- Manufacturer position
- American Academy of Ophthalmology position

# Questions raised

- Is Lucentis vs. Avastin a good example of a high priority for patient-centered outcomes research?
  - Is it politically sustainable?
- In the future would PCORI or NEI fund this?
- What would PCORI's dissemination effort consist of?

EDITORIALS

# Bevacizumab versus Ranibizumab for AMD

Philip J. Rosenfeld, M.D., Ph.D.

For 5 years, patients and clinicians have wrestled with the choice between two drugs for the treatment of neovascular age-related macular degeneration (AMD), a common cause of irreversible blindness among the elderly worldwide. Vision loss results from the abnormal growth and leakage of blood vessels in the macula, a specialized portion of the retina responsible for the best visual acuity. Without this macular vision, patients become legally blind. Vascular endothelial growth factor (VEGF), the cytokine primarily responsible for blood-vessel growth, is inhibited when anti-VEGF drugs are injected repeatedly into the eye, and blindness is prevented in most patients. The majority of treated patients go on to have some improvement in vision.[1-3]

The two anti-VEGF drugs most commonly used are bevacizumab (Avastin) and ranibizumab (Lucentis), both developed by Genentech.[4] Bevacizumab, a full-length humanized monoclonal antibody, has been approved by the Food and Drug Administration (FDA) for the systemic treatment of certain cancers. Ranibizumab, an antigen-binding fragment, is a smaller molecule that was specifically developed and approved to treat eye diseases and is derived from the same anti-VEGF mouse monoclonal antibody as bevacizumab. Both ranibizumab and bevacizumab bind VEGF at the same position; however, they differ in size, affinity for VEGF, speed of clearance from the eye, and cost.[5] Ranibizumab, the FDA-approved treatment for neovascular AMD, costs approximately $2,000 per dose, whereas bevacizumab, the off-label treatment, costs approximately $50. This cost difference, along with the perceived clinical similarities between these two drugs, has led to the widespread use of bevacizumab in the absence of level I evidence.[6]

In this issue of the *Journal*, Martin and colleagues[7] provide such evidence in their findings from the first year of the Comparison of AMD Treatment Trials (CATT), a large, prospective, multicenter, randomized clinical trial comparing bevacizumab and ranibizumab. Despite formidable obstacles,[8] the investigators successfully compared the two drugs and two different dosing regimens: a monthly regimen versus an as-needed regimen (i.e., drug administration only when signs of exudation are present). A monthly regimen is considered the standard for treatment.[1,2] An as-needed regimen is used less frequently and relies on clinical judgment and imaging techniques to determine when to reinject the drug.[9] The most common imaging method that is used is optical coherence tomography (OCT), a noninvasive technique that identifies fluid leakage from blood vessels. This VEGF-mediated exudate resolves after the injection of ranibizumab or bevacizumab. An OCT-guided as-needed regimen has been shown to result in improved visual acuity,[9] but CATT is the first prospective approach to directly compare a monthly regimen with an as-needed regimen.

Martin et al. found that the monthly use of either bevacizumab or ranibizumab results in the same visual acuity outcome. This finding holds true for the mean visual acuity and the proportion of patients who gain 15 letters (which represents a doubling of the visual acuity), lose 15 letters, or remain stable. Critics will argue that the OCT outcomes suggest differences between these two drugs. Although the OCT retinal thickness measurements favor ranibizumab, this difference

# Case study 2: Metal-on-metal hips

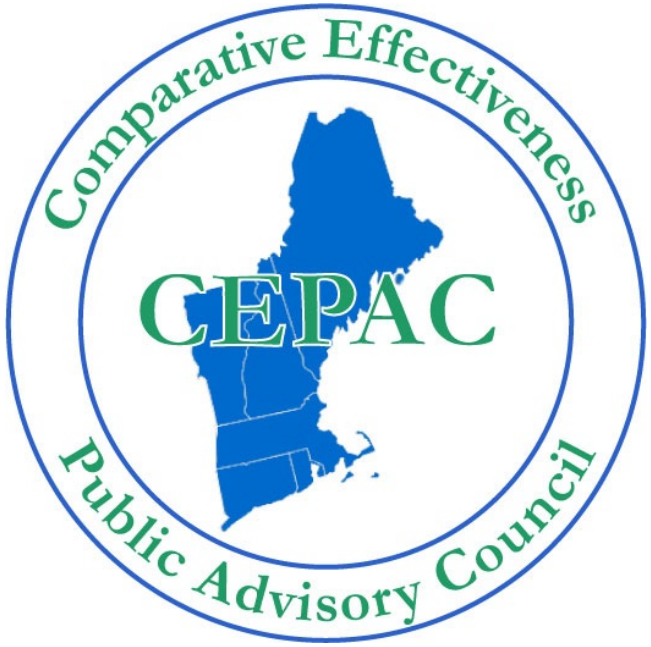
- 500,000 patients in the US
- Some researchers warned of potential health threats of metal debris
- UK national registry:
  - 14% of patients needed joint removed or replaced after 7 years vs. 3% for other types of hips
- 2010 FDA recall of J&J version: UK registry showed 30% needed early replacement
- May 2011 FDA orders all makers of metal-on-metal hips to develop studies to track negative outcomes
- First six months of 2011 more than 5,000 reports of "problems" with all-metal hips, many patients getting blood tests and diagnostic scans

# Questions raised

- Is this an example of regulatory failure?
- Would funding infrastructure for a US registry akin to the UK be a top priority for PCORI?
- How would PCORI coordinate with FDA in post-market surveillance of new devices?

# Case study 3: "Real-world" CER

- "Even after PCORI is up and running, insurers will be left to their own devices."
  - Wellpoint and others using their own data to perform CER
  - Captures adherence and ancillary utilization
- Yale-Medtronic YODA project
- New England Comparative Effectiveness Public Advisory Council (CEPAC)




# The New England Comparative Effectiveness Public Advisory Council

# Case study 3: "Real-world" CER

- New England Comparative Effectiveness Public Advisory Council (CEPAC)
  - Supplements AHRQ reviews with state utilization patterns, budget impact, cost-effectiveness, PMPM, implicit trade-offs
  - Votes and recommendations of CEPAC to support payer and provider policies

# Questions raised

- What relationship should PCORI seek with insurer CER efforts?
- Is an open data access model for CER research good for everyone?
- How will PCORI products be used at the local level to guide policy and practice?

# Conclusions

- CER continues to cast a growing shadow in health care policy
- While PCORI will be a major force, it is clear that the reverberations of CER are being felt across all health care sectors and CER will be led by many rather than few
- One of the many remaining questions:
  - What are the outcomes by which the comparative effectiveness of PCORI and CER will ultimately be judged?