OHDSI SOS Challenge: Intravitreal Anti-VEGF and Kidney Failure

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~596 million people have vision impairment worldwide

Quality of life
Loss of independence & mobility
Unable to work
Leading Causes of Vision Impairment/Blindness Worldwide

<table>
<thead>
<tr>
<th>Cause</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic retinopathy (DR) / diabetic macular edema (DME)</td>
<td>120 million</td>
</tr>
<tr>
<td>Age-related macular degeneration (AMD)</td>
<td>196 million</td>
</tr>
<tr>
<td>Retinal vein occlusion (VO)</td>
<td>28 million</td>
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</table>

Combined Global Prevalence: 344 million
Leaking Blood Vessels in the Retina

Normal

Diabetic Retinopathy / Diabetic Macular Edema

Vein Occlusion

Age-Related Macular Degeneration
Anti-vascular endothelial growth factor (anti-VEGF) medications

- Aflibercept (Eylea)
- Ranibizumab (Lucentis)
- Bevacizumab (Avastin)

Typically given monthly

CPT Code 67028 intravitreal injection of a pharmacologic agent

>20 million intravitreal injections are given worldwide (estimate from 2016)

https://www.randeye.com/intravitreal-injection/

Intravitreal Anti-VEGF: Side Effects

• Ophthalmic
  – Cataract
  – Retinal detachment
  – Vitreous hemorrhage
  – Endophthalmitis

• Systemic
  – Wound healing complications
  – Hypertension
  – Adjudicated Anti-Platelet Trialists Collaboration defined Thromboembolic events
    • Nonfatal myocardial infarction
    • Nonfatal stroke
    • Vascular death
  – All cause mortality
  – Hospitalization
  – Serious adverse event
Systemic Anti-VEGF and Kidneys

- Systemic administration of anti-VEGF agents have known adverse kidney side effects
  - Acute kidney injury
  - Worsening of proteinuria
  - Hypertension
  - Vascular clotting events
  - Glomerular disease
  - Kidney failure


Intravitreal Anti-VEGF and Systemic Absorption

Detectable/elevated serum drug levels
Decreased plasma concentrations of free-VEGF

Aflibercept > bevacizumab >> ranibizumab
Hospitalized for acute kidney injury after intravitreal anti-VEGF → downward spiral → dialysis
Side Effect: Kidney Failure or End Stage Kidney Disease

- ESKD: kidney transplant recipients and patients treated by dialysis
  - **Prevalent:** ~2.5 million doubling to 5.4 million by 2030
  - **Costly:** $20-100K per person
  - **Deadly:** 2.3-7.1 million adults died prematurely from lack of access to treatment
Gap in Knowledge: Intravitreal anti-VEGF and Kidney Failure

- Not adequately assessed in clinical trials: often lumped under “serious adverse events”
- Existing studies have largely focused on kidney function not the more severe kidney failure
- Kidney failure requires longer follow-up (clinical trials 1-2 years)
- Studies have limited sample size (largest one ~600 patients)
## Comparative Safety Study

<table>
<thead>
<tr>
<th>Analytic use case</th>
<th>Type</th>
<th>Structure</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical characterization</strong></td>
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<tr>
<td>Disease Natural History</td>
<td>Amongst patients who are diagnosed with &lt;insert your favorite disease&gt;, what are the patient’s characteristics from their medical history?</td>
<td>Amongst patients with rheumatoid arthritis, what are their demographics (age, gender), prior conditions, medications, and health service utilization behaviors?</td>
<td></td>
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<tr>
<td>Treatment utilization</td>
<td>Amongst patients who have &lt;insert your favorite disease&gt;, which treatments were patients exposed to amongst &lt;list of treatments for disease&gt; and in which sequence?</td>
<td>Amongst patients with depression, which treatments were patients exposed to SSRI, SNRI, TCA, bupropion, esketamine and in which sequence?</td>
<td></td>
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<tr>
<td>Outcome incidence</td>
<td>Amongst patients who are new users of &lt;insert your favorite drug&gt;, how many patients experienced &lt;insert your favorite known adverse event from the drug profile&gt; within &lt;time horizon following exposure start&gt;?</td>
<td>Amongst patients who are new users of methylphenidate, how many patients experienced psychosis within 1 year of initiating treatment?</td>
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<tr>
<td><strong>Population-level effect estimation</strong></td>
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<tr>
<td>Safety surveillance</td>
<td>Does exposure to &lt;insert your favorite drug&gt; increase the risk of experiencing &lt;insert an adverse event&gt; within &lt;time horizon following exposure start&gt;?</td>
<td>Does exposure to ACE inhibitor increase the risk of experiencing Angioedema within 1 month after exposure start?</td>
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<tr>
<td>Comparative effectiveness</td>
<td>Does exposure to &lt;insert your favorite drug&gt; have a different risk of experiencing &lt;insert any outcome (safety or benefit) &gt; within &lt;time horizon following exposure start&gt;, relative to &lt;insert your comparator treatment&gt;?</td>
<td>Does exposure to ACE inhibitor have a different risk of experiencing acute myocardial infarction while on treatment, relative to thiazide diuretic?</td>
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<tr>
<td><strong>Patient level prediction</strong></td>
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<tr>
<td>Disease onset and progression</td>
<td>For a given patient who is diagnosed with &lt;insert your favorite disease&gt;, what is the probability that they will go on to have &lt;another disease or related complication&gt; within &lt;time horizon from diagnosis&gt;?</td>
<td>For a given patient who is newly diagnosed with atrial fibrillation, what is the probability that they will go onto to have ischemic stroke in next 3 years?</td>
<td></td>
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<tr>
<td>Treatment response</td>
<td>For a given patient who is a new user of &lt;insert your favorite chronically-used drug&gt;, what is the probability that they will &lt;insert desired effect&gt; in &lt;time window&gt;?</td>
<td>For a given patient with T2DM who start on metformin, what is the probability that they will maintain HbA1C&lt;6.5% after 3 years?</td>
<td></td>
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<tr>
<td>Treatment safety</td>
<td>For a given patient who is a new user of &lt;insert your favorite drug&gt;, what is the probability that they will experience &lt;insert adverse event &gt; within &lt;time horizon following exposure&gt;?</td>
<td>For a given patients who is a new user of warfarin, what is the probability that they will have GI bleed in 1 year?</td>
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OHDSI Study:
Intravitreal anti-VEGF and Kidney Failure

• Estimating the comparative risk of kidney failure associated with intravitreal anti-vascular endothelial growth factor exposure in patients with blinding diseases (DR/DME, AMD, VO)
  – Amongst people with blinding diseases, does exposure to ranibizumab increase the risk of kidney failure, relative to aflibercept?
  – Amongst people with blinding diseases, does exposure to bevacizumab increase the risk of kidney failure, relative to aflibercept?
  – Amongst people with blinding diseases, does exposure to bevacizumab increase the risk of kidney failure, relative to ranibizumab?

Hypothesis: in these pairwise comparisons, lower risk of kidney failure in patients with blinding diseases who are exposed to ranibizumab
Implications of Study: Risk of Kidney Failure

• If there is a difference between medications
  — Retina specialist can offer personalized treatment
  — Reduce risk of morbidity/mortality from kidney failure
  — Reduce cost for society

• If there is no difference between medications
  — Important negative study
  — OHDSI network: most robust way of directly evaluating this question
You Can Contribute

• Verification and validation of concept sets

• Data partners
  – No special data elements are required: ICD codes, CPT codes, medications
  – Administrative or EHR data (with ophthalmology department)

Thank You!

Vote for this project: Intravitreal Anti-VEGF and Kidney Failure

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