THE LANDMARK STUDIES IN GLAUCOMA: AN EVIDENCE-BASED REVIEW

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Financial Disclosures

• I have no relevant financial relationships to disclose.

• The content and format of this course is presented without commercial bias and does not claim superiority of any commercial product or service.
Learning Objectives

1. Define evidence-based practice
2. Describe the results of a Randomized Clinical Trial in therapy
3. Appraise landmark studies in glaucoma
4. Feel uncomfortable with what you have learned but appreciate that you are not alone
Outline

• What is evidence-based practice?

• What are the results of RCTs?

• Landmark Randomized Clinical Trials in Glaucoma—review
  1. Ocular Hypertension Treatment study (OHTS) – control group
  2. Early Manifest Glaucoma trial (EMGT) – control group
  3. Advanced Glaucoma Intervention Study (AGIS)
  4. Collaborative Initial Glaucoma Treatment Study (CIGTS)
  5. Collaborative Normal Tension Glaucoma Study (CNTGS) – control group

• Continuing professional education in healthcare
Which drug would you choose?

- Which of the following drugs would you prescribe to treat an ocular condition? Risk of the outcome of interest is 40%

A. One with a relative risk reduction of 50%
B. One with an absolute risk reduction of 20%
C. One with a number needed to treat of 5
Evidence-based practice

- **Evidence-based practice**: The integration of best available evidence with clinical experience and patient values.
Randomized clinical/controlled trial

The Integrated "5S" Levels of Organization of Evidence Pyramid depicts the relationship between the Evidence Hierarchy (the small, inset pyramid) and the "5S" model. The Integrated Pyramid also includes foundational resources that do not have transparent evidence-based methodologies.

The Integrated Pyramid is labeled with resources available at the University of Michigan.
Three questions:

1. Are the results valid?
2. Are the results important?
3. Can I apply the results to my patient?
Lots and lots of research and then the Randomized Clinical Trial

JAMA evidence: Users Guide to the Medical Literature
Understanding the results of a randomized clinical trial

1. How large is the treatment effect?
2. How precise is the treatment effect?
3. Is the treatment effect important to my patient?

Patient oriented outcomes vs Disease oriented outcomes

Paul Glasziou, Centre for Evidence-based Medicine, University of Oxford
# Measures of Association

## The 2 x 2 Table

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

Odds ratio = \( \frac{a/b}{c/d} = \frac{ad}{cb} \)

Relative risk = \( \frac{a/(a+b)}{c/(c+d)} \)

Relative risk reduction = \( 1 - RR = \frac{c/(c+d) - a/(a+b)}{c/(c+d)} \)

Risk difference (RD) = \( \frac{c}{c+d} = \frac{a}{a+b} \)

Number needed to treat = \( 100/(RD \times 100\%) \)

*The exposure may be a putatively beneficial therapy or a possibly harmful agent.*

JAMA evidence: Users Guide to the Medical Literature
## Appendix 1: Formulas for commonly used measures of therapeutic effect

<table>
<thead>
<tr>
<th>Measure of effect</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative risk</td>
<td>(Event rate in intervention group) ÷ (event rate in control group)</td>
</tr>
<tr>
<td>Relative risk reduction</td>
<td>1 – relative risk</td>
</tr>
<tr>
<td></td>
<td>or</td>
</tr>
<tr>
<td></td>
<td>(Absolute risk reduction) ÷ (event rate in control group)</td>
</tr>
<tr>
<td>Absolute risk reduction</td>
<td>(Event rate in intervention group) – (event rate in control group)</td>
</tr>
<tr>
<td>Number needed to treat</td>
<td>1 ÷ (absolute risk reduction)</td>
</tr>
</tbody>
</table>
Fig. 1: Results of hypothetical placebo-controlled trials of a new drug for acute myocardial infarction

Among high-risk patients in trial 1, the event rate in the control group (placebo) is 40 per 100 patients, and the event rate in the treatment group is 30 per 100 patients.

**Absolute risk reduction** (also called the risk difference) is the simple difference in the event rates (40% - 30% = 10%).

**Relative risk reduction** is the difference between the event rates in relative terms. Here, the event rate in the treatment group is 25% less than the event rate in the control group (i.e., the 10% absolute difference expressed as a proportion of the control rate is 10/40 or 25% less).

NNT = 10

Among low-risk patients in trial 2, the event rate in the control group (placebo) is only 10%. If the treatment is just as effective in these low-risk patients, what event rate can we expect in the treatment group?

The event rate in the treated group would be 25% less than in the control group or 7.5%. Therefore, the absolute risk reduction for the low-risk patients (second pair of columns) is only 2.5%, even though the relative risk reduction is the same as for the high-risk patients (first pair of columns).

NNT = 40

What is the modern definition of glaucoma?

• “Primary open-angle glaucoma is a chronic, progressive optic neuropathy in adults in which there is a characteristic acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons. This condition is associated with an open anterior chamber angle by gonioscopy.”

• American Academy of Ophthalmology PPP 2015
What is the modern definition of glaucoma?

• “...glaucoma refers to a group of diseases that manifest as a characteristic progressive optic neuropathy and retinal ganglion cell loss that eventually leads to a permanent loss of visual field”

• Maclver S, MacDonald D, Prokopich CL. Screening, Diagnosis, and Management of Open Angle Glaucoma: An Evidence-Based Guideline for Canadian Optometrists. Can J Optom VOL. 79 Supplement 1, 2017
1. The Ocular Hypertension Treatment Study

- People who had ocular hypertension were randomized to drug treatment to lower IOP or control (no treatment); outcome: onset of glaucoma by VF or disc changes

- Study design considerations
  - Intention-to-treat analysis met – analyzed in the group that they were initially assigned even if crossed over
  - 22 centres: generalizability

- Neither the patients nor doctors were masked to treatment or control
1. The Ocular Hypertension Treatment Study

• Results after 5 years

  • In the treatment group
    • 4.4% of participants got glaucoma
    • 95.6% of participants did not get glaucoma

  • In the control group
    • 9.5% of participants got glaucoma
    • 90.5% of participants did not get glaucoma

Relative risk reduction:
5.1/9.5 = .54 or 54%  Wow that is good!

BUT:

Absolute risk reduction:
9.5- 4.4 = 5.1%

NNT:  20 people to help one
Wow that seems different!
1. The Ocular Hypertension Treatment Study

• Was Anyone Harmed?

• People treated with a prostaglandin analogue
  • Changes in iris colour, darkening of eyelids and growth of eye lashes

In the treatment group
17% of participants had the adverse event

In the control group
7.6% of participants had the adverse event

Number needed to harm

Risk increase: 17 - 7.6 = 9.4%

NNH = 11 people to harm one
1. The Ocular Hypertension Treatment Study

Prospective subgroup analysis (controls): Beware of post-hoc subgroup analysis!

Those at higher risk will have a smaller NNT
2. Early Manifest Glaucoma Trial

- People with early POAG *including pseudo exfoliation* were randomized to either laser trabeculoplasty plus a topical beta blocker or no initial treatment (control); outcome progression by VF or disc changes

- Study design considerations
  - Low loss to follow-up (11%) - loss to follow-up of 20% threatens validity
  - Remote computer randomization
  - Masking limited to readers, stats and other personnel
2. Early Manifest Glaucoma Trial

- Progression in control group was 62% and 45% in the treatment group
  - NNT 62-45=17 1/17 = 6

- Increase in nuclear cataract formation in treatment group 17% and 4% in the control group
  - NNH= 17-4=13 1/13 = 8

- 45% of treated eyes progressed; 38% of untreated eyes did not progress
- Onset of progression was later in the treatment group
2. Early Manifest Glaucoma Trial

- Each 1 mm lowering of IOP was related to a 10% lowering of progression risk

- This is a hazard ratio (HR) that gives the risk per unit of measure

- Initial change in IOP from baseline to 3 months HR of 0.90
- This does not mean that a 10mmHg decrease results in a 100% decrease in risk of progression!
- HR are not additive, there are ceiling effects, assumptions that the IOP risk is linear across the whole IOP range and that IOP reduction is due to treatment alone
2. Early Manifest Glaucoma Study

- CCT was related to progression in patients with higher baseline IOP not lower
- HR 1.42 CI: 1.0 to 1.92 patient with higher IOP

The confidence interval (CI) is the range within which the truth lies
3. Advanced Glaucoma Intervention Study 7

- People with advanced glaucoma were randomly assigned to either argon laser trabeculotomy or trabeculectomy first and then the other second. If needed trabeculectomy was repeated. Outcome: progression of VF damage compared to IOP.

- Loss to follow-up was very high at the end in some subgroups less than half of the patients were remaining this seriously threatens validity
- There were risk differences between the groups
- Post hoc analysis – i.e. not designed as part of the original study
Loss to follow-up

• Sometimes it is possible to do a **simple sensitivity analysis**
  • Recalculate risk based on “best case” scenario where all losses were free of adverse outcome
  • Recalculate risk based on “worst case” scenario where all losses suffered the adverse outcome
  • Compare these recalculation to gauge the potential impact of losses

• This was not done in this study
Differences:

The < 14 mmHg group were more likely to be in the TAT group

The > 17.5 mmHg group were more likely to have diabetes, higher mean reference IOP, lower mean VF score and a lower age compared to the 14 – 17.5 mmHg group

How to deal with this?

1. Adjusted analysis

This was done in this study
Results: Lower IOP reduces progression of VF loss

• Considerations:
  
  • Results are less clear with the adjusted analysis
  • VF were rated on a scale of 0 to 20 with a change of 4 being considered significant
  • Only one VF was done at baseline in a population that has greater fluctuations in VFs so in the lowest IOP group there was no progression on average but individuals worsened by 4 points and improved by 4 points
  • While worsening did occur none of the changes reached the clinical significance of 4 units even after 8 years

Statistically significant does not always equal clinically significant
4. Collaborative Initial Glaucoma Treatment Study

- Newly diagnosed patients with glaucoma were randomized to either medical treatment or trabeculectomy to significantly lower IOP. Outcome measures: VF loss, VA, IOP and cataract.

- Included quality of life measures

- No control group
The VF scores stayed stable in the medicine and surgery groups even though the IOP was lower in the surgery group. Is the relationship between lower IOP and VF stability really there?
What about harms?

- Over 5 years the risk of cataract development in the surgery group was 3 X higher than the medication group.

- Quality of Life
  - The scales used in the study showed very little difference between the two study groups.

Images MD
5. Collaborative Normal-tension Glaucoma Study

- One eye of patients with normal tension glaucoma was randomized to either control or 30% reduction in IOP (medical or surgical). Outcome: VF or cupping progression.

- Intention-to-treat analysis was performed
5. Results

- NNT reported in the initial study was 5
- NNT reported in the intention-to-treat analysis was 17

- Neither the absolute nor the percentage change in IOP over the follow-up period showed any significant association with survival within either group.

- Cataract was a significant factor in the treated group and there was only an effect if the results were terminated when cataract developed

- 85 people were never randomized because they didn’t progress (230 to 145)
Presentation of Evidence in Continuing Medical Education Programs

• Analysis of videotapes and PowerPoint slides of 26 CME presentations, questionnaire survey of CME speakers and learners, and focus groups with learners.

• Data presented
  • General terms (84%)– frequencies, percentages, graphs, p-values with no data
  • Relative terms (19%)
  • Absolute turns (7%)

Presentation of Evidence in Continuing Medical Education Programs

- CME speakers understood relative and absolute terms better than learners.

- 25–35% of speakers
- 45–65% of learners

Could not correctly calculate relative risk reduction, absolute risk reduction, and number needed to treat

- Learners wished to have these terms presented in CME programs in a consistent and easily understood format and requested a brief review of them at the beginning of CME programs.

Odds Ratios vs Risk Ratios

- Race track probabilities
- 4:1 odds is 80%
- When you get down to 10% they are about the same
- Must be used only in case control studies

- Another example of making it seem more important than it is!
Which drug would you choose?

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Thank you