Glaucoma Clinical Trials
Key Findings and Practical Implications

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Multicenter Clinical Trials

Advantages
- Careful study design minimizes bias
- Large numbers increase statistical power and generalizability
- DSMB protects patient interests
- More likely to change doctors' habits than several smaller studies published over time

Disadvantages
- Protocol may not mirror "real life" practice
- Protocol may not keep up with changes in clinical practice
- Results may be outdated by time study is completed

modified from Brandt (personal communication 1997)

Justification

Thomas Carlyle (1795 – 1881)
- "A person usually has two reasons for doing something: a good reason and the real reason."
  J. P. Morgan (1837 – 1913)
- "A man always has two reasons for doing anything — a good reason and the real reason."
- "A man generally has two reasons for doing a thing. One that sounds good, and a real one."

Ocular Hypertension Treatment Study (OHTS)*
OHTS Principal Aim
- To evaluate safety and efficacy of topical ocular hypotensive medication in preventing or delaying onset of POAG in moderate-risk ocular hypertensives

Large Glaucoma Treatment Clinical Trials

- Ocular Hypertension Treatment Study (OHTS)*
- Collaborative Normal-Tension Glaucoma Study (CNTGS)†
- Early Manifest Glaucoma Trial (EMGT)*
- Collaborative Initial Glaucoma Treatment Study (CIGTS)*
- Canadian Glaucoma Study (CGS)‡
- Advanced Glaucoma Intervention Study (AGIS)*

OHTS II Principal Aim
- To compare safety and efficacy of earlier vs later treatment in preventing POAG in ocular hypertensives

OHTS Secondary Aim
- To identify risk factors that predict which ocular hypertensives are most likely to develop POAG

THE QUALITY OF MEDICAL EVIDENCE: IMPLICATIONS FOR QUALITY OF CARE
By David M. Hulley and John Millican

"...there is virtually no useable evidence about the effectiveness of medical treatment for glaucoma." Eddy & Billings (Health Affairs 1988;7:19)

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‡Supported by E.A. Baker Foundation of Canadian National Institute for Blind-supported and unrestricted grants from Allergan Canada, Merck Frosst Canada, and Pfizer Canada
Does Treatment of OHT Make Prevent or Delay POAG Development?

Proportion POAG

- Medication: 4.4% @ 5 years
- Observation: 9.5% @ 5 years

5-year absolute risk reduction = 5.1%
Cumulative probability reduction = 60%; HR = 0.40 (95% CI = 0.27 to 0.59; p < 0.0001)

OHTS Primary Outcome: Kass et al. (Arch Ophthalmol 2002;120:701)

OHTS Multivariate Hazard Ratios (95% CI) for Development of POAG (Arch Ophthalmol 2002;120:714)

- Corneal thickness (per 40 μm thinner) 1.71 (1.40-2.09)
- Vertical C/D ratio (per 0.1 larger) 1.32 (1.19-1.47)
- Horizontal C/D ratio (per 0.1 larger) 1.27 (1.14-1.40)
- PSD (per 0.2 dB greater) 1.27 (1.06-1.52)
- Age (per decade) 1.22 (1.01-1.49)
- IOP (per mm Hg) 1.10 (1.04-1.17)

Does Deferring Treatment Make POAG Development More Likely Is There Penalty for Delaying Treatment?

OHTS II Outcome: Kass et al. (Arch Ophthalmol 2010;128:276)

HR = 0.42 med vs obs (95% CI, 0.29 to 0.59; p < 0.001)
HR = 1.06 med vs obs (95% CI, 0.74 to 1.50; p = 0.77)

Need/Desire to Confirm OHTS Risk Model in Large, Independent Sample and to Create Prediction Model Based Solely on Larger Number of Untreated Individuals

- EGPS is randomized clinical trial of 1,077 ocular hypertensives randomized to placebo or dorzolamide
- OHTS & EGPS protocols were
  - Similar enough to test the validity of prediction model after resolution of study differences
  - Different enough in geographic distribution and patient characteristics to test generalizability of OHTS prediction model

Multivariate Hazard Ratios Pooled OHTS-EGPS Dataset

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>EGPS</th>
<th>OHTS</th>
<th>Pooled OHTS-EGPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (decade)</td>
<td>1.26 (1.06 to 1.50)</td>
<td>1.26 (1.06 to 1.50)</td>
<td>1.26 (1.06 to 1.50)</td>
</tr>
<tr>
<td>IOP (per mm Hg)</td>
<td>1.09 (1.03 to 1.17)</td>
<td>1.09 (1.03 to 1.17)</td>
<td>1.09 (1.03 to 1.17)</td>
</tr>
<tr>
<td>CCT (per 40 μm decrease)</td>
<td>2.04 (1.70 to 2.45)</td>
<td>2.04 (1.70 to 2.45)</td>
<td>2.04 (1.70 to 2.45)</td>
</tr>
<tr>
<td>Vertical C/D Ratio (per 0.1 increase)</td>
<td>1.19 (1.09 to 1.31)</td>
<td>1.19 (1.09 to 1.31)</td>
<td>1.19 (1.09 to 1.31)</td>
</tr>
<tr>
<td>PSD (per 0.2 dB increase)</td>
<td>1.13 (1.04 to 1.24)</td>
<td>1.13 (1.04 to 1.24)</td>
<td>1.13 (1.04 to 1.24)</td>
</tr>
</tbody>
</table>

Accuracy of Prediction Models for POAG Compared to Framingham Heart Study

- Prediction Models
  - Framingham Heart Study prediction model applied to different studies [D’Agostino et al. (JAMA 2001;286:180)]
  - OHTS observation group
  - EGPS placebo group
  - Pooled OHTS-EGPS sample

C-statistic*
- 0.63 to 0.83
- 0.76
- 0.73
- 0.74

*Accuracy of prediction models in discriminating between patients who do and do not develop disease is measured using C statistic, which ranges from 0.50 (random agreement) to 1.00 (perfect agreement)
How Accurate is OHTS-EGPS Prediction Model for POAG?

![Graph showing accuracy of OHTS-EGPS prediction model for POAG.]

The following example estimates the 5-year risk of developing POAG using the OHTS-EGPS prediction model.

- **55-year-old patient**
  - Ages are right eye: 22, 23, 24, 25, 26
  - Ages are left eye: 21, 22, 23, 24, 25
  - Ages are right eye: 50, 51, 52, 53, 54
  - Ages are left eye: 49, 50, 51, 52, 53
  - Ages are right eye: 0.40 and left eye: 0.40
  - Ages are right eye: 1.0, 2.0, and left eye: 2.0, 2.2

**Benefits of Risk Stratification to Clinicians and Patients**

- Decide on frequency of visits and tests
- Ascertain benefit of early treatment
- Potentially reduce medical costs
  - ≈ 30% to 40% of participants in OHTS/EGPS pooled sample have < 5% 5-yr risk of developing POAG
  - Many of these individuals could be seen and tested annually
  - Treatment is not indicated in most of these individuals

**OHTS-EGPS Prediction Model**

http://ohts.wustl.edu/risk/calculator.html

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**OHTS-EGPS Prediction Model Limitations and Cautions**

- There is no guarantee that predicted risk is accurate for specific patient
- The predictions are more likely to be accurate for patients who are similar to patients studied in OHTS and EGPS, and if your testing protocols for your patients resemble those used in studies
- Model predicts development of early POAG; it is not clear whether model also predicts progression of established disease or development of visual disability
- Model is based on baseline parameters; changes during follow-up will alter risk of developing POAG
OHTS-EGPS Prediction Model
Limitations and Cautions

- Application of prediction models to individual patients must include information outside model
- Predictions are designed to aid but not to replace clinical judgment
- Need to consider factors such as health status, life expectancy, and patient preferences
  - 40-year-old ocular hypertensive with low 5-year risk of developing POAG might be candidate for treatment
  - Seriously ill 65-year-old ocular hypertensive with high 5-year risk of developing POAG might not be candidate for treatment

Detection & Predictive Value of ODHs in OHTS
Budenz et al. (Ophthalmology 2006;113:2137)

- 8-year cumulative incidence of POAG
  - 3,108 eyes w/o ODH 5.2%
  - 128 eyes w/ ODH 13.6%
- HR 3.7 (2.1 to 6.6, 95% CI) in a multivariate analysis that included baseline factors predictive of POAG
  - NB: ODH was exclusion criterion in OHTS, so risk of POAG associated with ODHs may be underestimated in OHTS

CSLO Results From OHTS
Proportion of Participants Eyes Developing POAG

Collaborative Normal-Tension Glaucoma Study
Am J Ophthalmol 1998;126:487

Principal Aim
- Does reducing IOP* in patients with normal-pressure glaucoma delay or prevent progression of glaucoma?

Collaborative Normal-Tension Glaucoma Study
Am J Ophthalmol 1998;126:498

VF endpoint by four-of-five analysis of progression with censoring of eyes that developed cataracts

- VF or disk change 15% 37%
- Survival time (years) 5.8 ± 0.3 4.0 ± 0.4
  - 3-year 80% 60%
  - 5-year 80% 40%

Collaborative Normal-Tension Glaucoma Study

Risk factors for progression of VF abnormalities in NPG
- Mean ± SE survival time (years)
  - Female 5.1 ± 0.4 6.5 ± 0.4
  - Male 5.3 ± 0.4 6.5 ± 0.4
- M:F risk ratio‡ 0.54 (95% CI 0.28 to 1.04)

* p = 0.0207
† p = 0.0665
‡ p = 0.0622, multivariate survival analysis (Cox proportional hazards) adjusted for baseline median IOP, baseline MD, ↑BP, age, baseline ODH, and migraine
Collaborative Normal-Tension Glaucoma Study

Risk factors for progression of VF abnormalities in NPG
- Mean ± SE survival time (years)
  - All
    - Migraine • 3.3 ± 0.5 • 5.9 ± 0.3
    - Female
      - 3.3 ± 0.6 • 5.3 ± 0.4
    - +/− migraine risk ratio: 2.59 (95% CI 1.32 to 5.07)
- Female
  - 3.3 ± 0.6 • 5.3 ± 0.4
  - +/− ODH risk ratio: 2.72 (95% CI 1.39 to 5.32)

*p = 0.0129
†p = 0.0036
‡p = 0.0058, multivariate survival analysis (Cox proportional hazards) adjusted for baseline median IOP, baseline MD, ↑BP, age, gender, and ODH

Practical Lessons
- If unsure whether findings in NPG likely to be non-progressive or progressive (at least in mild case without threat to fixation), it is reasonable to watch carefully
- Estimated mean time (months) to survival among untreated eyes: 67.2 (SE ± 3.4)

Baseline IOP (mm Hg)
- Control: 20.9 ± 4.1
- Treatment: 20.6 ± 4.1
- “Treated” IOP (mm Hg)
- Control: 20.8 (0%)
  - Reduction
    - 0.0 ± 1.9 (0%)
- Treatment
  - 15.5 (25%)
  - Reduction
    - 4.5 ± 3.4 (22%)
  - IOP ≥ 21: 6.8 ± 3.0 (29%)
  - IOP < 21: 2.7 ± 2.4 (18%)

*at 3-month visit
†through progression or last visit

49% vs 30% 4-year progression rate (19% difference; 95% CI 7% to 23%; p = 0.004)
Multivariate Analyses Evaluating Associations of EMGT Progression with Baseline Factors*  

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>0.53 (0.39–0.72)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IOP ≥ 21 mm Hg</td>
<td>1.77 (1.29–2.43)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Pseudoexfoliation</td>
<td>2.12 (1.30–3.46)</td>
<td>0.0026</td>
</tr>
<tr>
<td>Bilateral damage</td>
<td>1.88 (1.35–2.63)</td>
<td>0.0092</td>
</tr>
<tr>
<td>Age ≥ 68 years</td>
<td>1.51 (1.11–2.07)</td>
<td>0.0035</td>
</tr>
<tr>
<td>Systolic PP ≤ 125 mm Hg</td>
<td>1.42 (1.04–1.94)</td>
<td>0.0268</td>
</tr>
<tr>
<td>Mean deviation &lt; -4 dB</td>
<td>1.38 (1.00–1.91)</td>
<td>0.0510</td>
</tr>
</tbody>
</table>

*Leske et al. (Ophthalmology 2007;114:1965); progression analysis with Cox proportional hazard models adjusting for ties in time to progression, after evaluating constancy of hazard ratio (HR) over time; p-values from Wald chi-square statistic.

OHTS, EMGT, & CNTGS  
Number Needed to Treat  

<table>
<thead>
<tr>
<th>Bad Outcome</th>
<th>Good Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Rx</td>
<td>10%</td>
</tr>
<tr>
<td>Rx</td>
<td>2%</td>
</tr>
</tbody>
</table>

• RR (relative risk) = 0.02/0.1 = 0.2 (80% reduction)  
• ARR (absolute relative risk) = 0.1-0.02 = 0.08 (8% reduction)  
• NNT (number needed to treat) = 1/ARR = 1/0.08 = 12.5

OHTS, EMGT, & CNTGS  
Number Needed to Treat

- Ocular Hypertension Study (OHTS): 18.5% net ↓ IOP  
  - 5.1% ARR @ 5 years  
    ⇒ NNT 19.6 pts  
- Early Manifest Glaucoma Trial (EMGT): 22% net ↓ IOP  
  - 19% ARR @ 4 years  
    ⇒ NNT 5.3 pts  
- Collaborative NTG Study (CNTGS): ≥ 30% ↓ IOP  
  - 40% ARR @ 5 years  
    ⇒ NNT 2.5 pts

- OHTS @ 6.0 to 6.5-yr median f/u*  
  = 46.6 patients  
- EMGT @ 6-year median f/u  
  = 31.6 patients  
- CNTGS @ ≥ 6.5 to 5.2-yr mean†  
  = 4.8 patients

*6.0-year African-American median f/u; 6.5-year other subjects’ median f/u; †mean survival on “thinned” data w/o cataract censoring on control & treated subjects, respectively

Collaborative Initial Glaucoma Treatment Study (CIGTS)  
Principal Aim  
- To determine whether patients with newly-diagnosed open-angle glaucomas* are better treated by initial medical treatment or initial trabeculectomy  
Secondary Aims  
- To compare quality of life between treatment groups  

*primary, pigmentary, or pseudoexfoliation

Collaborative Initial Glaucoma Treatment Study (CIGTS)  
Secondary Outcomes  
- First large-scale glaucoma clinical trial to rigorously consider quality-of-life issues  
- Trabeculectomy group reported more symptom impact, but both groups showed decline in symptom impact over time  
- Initial pattern of more local eye symptom impact in trabeculectomy group diminished over time
• Initial treatment w/ either medications or trabeculectomy effectively reduces IOP, and those reductions are sustained through 9 years.

**IOP (mm Hg)**

**Medicine**
- Mean: 17.2 ± 2.7
- Maximum: 21.6 ± 4.7
- SD: 2.6 ± 1.3

**Surgery**
- Mean: 15.0 ± 4.1
- Maximum: 18.8 ± 5.4
- SD: 2.4 ± 1.4

* p < 0.0001; † p < 0.0001; ‡ p = 0.0516

• VF loss was greater with trabeculectomy during the first 3 years, but differences largely disappeared during 4th & 5th years.

• Initial surgery led to less VF progression than initial medicine in subjects with advanced VF loss at baseline.

• Subjects with diabetes had more VF loss over time if treated initially with surgery.

• Three IOP summary measures were significantly associated with ≥3 dB MD worsening (effects were similar in both treatment groups)
  - max IOP (per 5.5 mm Hg) OR = 1.34 (95% CI = 1.09 to 1.64)
  - IOP SD (per 1.5 mm Hg) OR = 1.39 (95% CI = 1.16 to 1.66)
  - IOP range (per 4.5 mm Hg) OR = 1.37 (95% CI = 1.15 to 1.64)

Principal Aim
- To study variety of systemic risk factors for progression of OAG under standardized interventional protocol for IOP control.
Inclusion Criteria
- Newly-diagnosed OAG or previously-diagnosed OAG w/ clinically-defined target IOP
- 6/10 BCVA (ETDRS chart)
- Photographically documented glaucomatous optic neuropathy
- Characteristic glaucomatous VFDs
- Normal, non-occludable angles

Exclusion Criteria
- Significant nonglaucomatous ocular disease (e.g. ARMD, DR)
- Chronic nonglaucoma ocular medication
- Systemic disease with known effects on VF
- Distance refraction > 6 D sphere or > 2.5 D cylinder
- Previous incisional glaucoma surgery

CGS: Risk Factors for Progression
Chauhan et al. (Arch Ophthalmol 2008;126:1030)

- Female gender: HR = 1.94 (95% CI = 1.09 to 3.46)
- Abnormal baseline ACA* levels: HR = 3.86 (95% CI = 1.60 to 9.31)
- Baseline age (per year): HR = 1.04 (95% CI = 1.01 to 1.07)

CGS: Impact of Risk Factors & ↓IOP on Rates of VF Change
Chauhan et al. (Arch Ophthalmol 2010;128:1249)

- Female > Male (p = 0.16, χ² test)
- Positive baseline ACA*

*anticardiolipin antibody; anticardiolipin is one of antiphospholipid antibodies found to have elevated levels in patients with acquired prothrombotic syndromes; ACA levels can also be elevated in miscarriage, systemic lupus erythematosus, ischemic stroke, and myocardial infarction.

CGS: Impact of Risk Factors & ↓IOP on Rates of VF Change
Chauhan et al. (Arch Ophthalmol 2010;128:1249)

- Female > Male (p = 0.16, χ² test)
- Positive baseline ACA*
- weakly associated with increasing baseline age*  
- not associated with mean IOP during follow-up (measurements only up to first endpoint in progressing patients)†
- In patients with one VF endpoint, additional ↓IOP (median 3.1 mm Hg or 20%) resulted in median slope changing significantly (p < 0.02) from −0.36 dB/y to −0.11 dB/y

*Spearman = −0.190; p = 0.005
†Spearman = 0.021; p = 0.76
**Advanced Glaucoma Intervention Study (AGIS)**

**Principal Aim**
- In patients whose glaucoma is worsening despite maximum tolerated medical therapy, which is better next step, trabeculoplasty or trabeculectomy?

**AGIS Cumulative Probability of Failure**
*Ophthalmology* 1998;105:1146

- Adjusted chi-square = 7.2 (p < 0.007)
- Adjusted chi-square = 32.2 (p < 0.001)

**AGIS Cumulative Probability of Sustained Decrease of Vision**
*Ophthalmology* 1998;105:1146

- Adjusted chi-square = 12.1 (p < 0.001)
- Adjusted chi-square = 0.52 (p = 0.470)

**AGIS Target < 18 mm Hg**
*Am J Ophthalmol* 2000;130:429

- 586 (74%) eyes*
  - ≥ 6-year follow-up AND ≤ 2 missed 6-month visits
  - Percentage of visits for which eye had IOP < 18 mm Hg
    - Group A: 100%
    - Group B: 75% to < 100%
    - Group C: 50% to < 75%
    - Group D: 0% to < 50%
  - *180 (23%) eyes had not completed 6-year follow-up; 23 (3%) eyes missed > 2 visits

**AGIS Target < 18 mm Hg**
*Am J Ophthalmol* 2000;130:429

- Mean IOP over 6-year follow-up
  - Group A: 12.3 mm Hg
  - Group B: 14.7 mm Hg
  - Group C: 16.9 mm Hg
  - Group D: 20.2 mm Hg

- Estimated VFDS Δ (95% CI)*:
  - Group A: 1.00 (0.07-1.92)
  - Group B: 2.05 (0.99-3.12)
  - Group D: 1.93 (0.82-3.05)

*adjusted for race, assigned intervention sequence, age, diabetes, gender, reference IOP, and reference VFDS score

**Variation**
*Caprioli & Coleman (Ophthalmology 2008;115:1123)*

- 301 AGIS patients
  - ≤ 16 AGIS VF score
  - ≥ 3-year follow-up (7.2 ± 2.2)
  - ≥ 7 VF reliable exams
  - only 1 surgical intervention
  - VF progression occurred in 26% of randomly-selected eyes

*threshold change < -1.00 dB/yr & p < 0.01 in at least two test locations within same Glaucoma Hemifield Test cluster on pointwise linear regression analysis
*defined as SD of IOP after initial AGIS surgery (per mm Hg)
Intraocular Pressure (IOP) Variation

Caprioli & Coleman (Ophthalmology 2008;115:1123)

Summary:
OHTS

- Approximately 20% ↓ IOP reduced 5-year incidence of POAG in moderate-risk OHT participants from 9.5% in Observation Group to 4.4% in Medication Group with little evidence of safety concerns
- No apparent penalty for delaying treatment

Risk/predictive factors for OHT to POAG conversion
- Age
- IOP
- CCT
- Vertical C/D ratio
- PSD
- Incident disc hemorrhages
- GPA or MRA ONL on CSLO

Summary and Practical Implications: CNTGS

- Treatment of normal-pressure glaucoma is effective
  - However, observation of non-progressive patients without threat to central fixation may be appropriate
- Risk/predictive factors for progression
  - Migraine/peripheral vasospasm
  - Disc hemorrhage
  - Perhaps female gender
Glaucoma Clinical Trials: Key Findings and Practical Implications: EMGT

- Treatment of manifest OAG reduced 4-year progression risk from 49% to 30%
- 1 mm Hg lower mean follow-up IOP → hazard ratio 0.89 (95% CI=0.86-0.93)*
- Combined ALT and betaxolol treatment increases nuclear cataract

*p < 0.001 Wald chi-square statistic

Risk/predictive factors for progression
- Higher baseline (≥ 21 mm Hg) and mean follow-up IOP
- Pseudoexfoliation
- Bilateral damage
- Older age (≥ 68 years)
- Lower systolic PP (≤ 125 mm Hg)
- Thinner CCT
- Incident disc hemorrhages
  ? Worse mean deviation (< – 4 dB)

Glaucoma Clinical Trials: Key Findings and Practical Implications: CIGTS

- Both medical treatment and trabeculectomy are effective initial glaucoma treatment
- Trabeculectomy may be better initial option for non-diabetic patients with more advanced damage (MD < – 10 dB)
- IOP maximum, SD, and range were significantly associated with ≥ 3 dB MD worsening over 3- to 9-year period

Glaucoma Clinical Trials: Key Findings and Practical Implications: CGS

- OAG patients w/ mean F/U IOPs > 17.0 mm Hg had higher cumulative progression than those < 15.0 mm Hg
- Women, patients w/ abnormal baseline ACA levels, and older patients at great risk of progression
- Additional ↓IOP (median 3.1 mm Hg or 20%) after one VF endpoint significantly changed median slope (from −0.36 dB/y to −0.11 dB/y)

Clinical Trials Observations/Caveats

- Patients who enroll in clinical trials tend to be healthier, better educated, and better motivated (typical Lake Wobegone citizens)
- Care (and parking!) is often provided at no cost
- Study coordinators provide invaluable encouragement to patients, improving adherence with study protocol and follow-up visits

"The nurses and technicians did all they could—I just wasn’t into it."