Glaucoma: NOT just IOP, Think DPP, OMG!

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I’m a clinician, so let’s talk patients
TWO Patients (a priest and a lawyer) with the same med HX walk into a bar

• 54 Y/O WT M presents for general exam/DM eye evaluation
• FM HX DM, HTN
• FM EYE HX-NEG
• Patient Med HX:
  Type II DM X 5 Yrs-A1-C = 7
  BP controlled with TX = 125/65
  Lipitor for elevated lipids
• No allergies
What is glaucoma?

Just one of many types of Anterior Optic Neuropathy

Definition does not mention IOP-

IS IOP IMPORTANT?

“TOM” says that it is

Live and die by studies—both good and bad: Evidence based GLC management

- OHTS
- EMGT
- AGIS
- ASRANI
- NTG
- LALES

How have they altered our approach to glaucoma?

A NEW standard of care?

The lawyers say yes
The OHT Study - Goals

Evaluate the safety and efficacy of using topical ocular hypotensive medication(s) in preventing or delaying the development of POAG in individuals with elevated IOP

Identify baseline demographic and clinical factors that predict which individuals would develop POAG

OHTS – Study Design

• Patients randomly assigned to one of two groups
  – Treatment or Close Observation
  – Treatment goal to lower IOP at least 20%
• Management
  – Humphrey VF 30-2 every 6 months
  – Annual dilated exam & photos
## OHTS Population

### Entry Criteria
- Age 40 – 80
- Normal visual fields
  - Humphrey 30-2 FT
- Normal optic discs
- Untreated IOP
  - 24 to 32 mm Hg in qualifying eye
  - 21 to 32 mm Hg in fellow eye

### OHTS demographics
- Enrollment complete in 10/96
- Last patient 5 yr. data 11/8/01
- 1,636 subjects at 23 clinical centers
- 1,408 completed 5 yrs.
- 409 (25%) African American

## OHTS Study Design

- 1,636 individuals randomized to Therapy (817) or Observation (819)

- Minimum life of study – 5 years
  - 7 years follow-up for some patients
  - Some individuals dropped out, medication started or withdrawn, died, or lost to follow-up

- 1,408 completed study
  - Observation (706) vs. Therapy (702)
Facts, Fiction and Statistics

KNOW YOUR OHT’s (N = 1636)

- Early TX of ocular hypertension reduced the risk of glaucoma by FIFTY PERCENT
- 9.5% VS 4.4%
- That means that over 90% of UNTREATED ocular hypertensives DO NOT GET GLAUCOMA
- Know your NNT-Number needed to TX
- Need to TX 20-42 to prevent 1 case of glc

OHTS-Conversion to Glaucoma

- Optic nerve changes: 55%
- VF Changes: 35%
- Both: 10%
- WHY? Thank Harry Quigley
Remember, visual fields are a SUBJECTIVE test.

**Significant Baseline Predictive Factors**
from Multivariate Proportional Hazard Models

<table>
<thead>
<tr>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (decade)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
</tr>
<tr>
<td>IOP (per mmHg)</td>
</tr>
<tr>
<td>CCT (per 40 µM decrease)</td>
</tr>
<tr>
<td>PSD (per 0.2 dB increase)</td>
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<tr>
<td>Horizontal C/D Ratio (per 0.1 increase)</td>
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<tr>
<td>Vertical C/D Ratio (per 0.1 increase)</td>
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</tbody>
</table>
POAG Endpoints by Central Corneal Thickness and Baseline IOP (mmHg) in Observation Group*

Baseline IOP (mmHg)
- >25.75: 36%
- >23.75 to ≤25.75: 13%
- ≤23.75: 6%

Central Corneal Thickness (microns)
- ≤23.75: 12%
- >23.75 to ≤25.75: 10%
- >25.75 to ≤555: 7%
- >555 to ≤588: 12%
- >588: 10%

POAG Endpoints by Central Corneal Thickness and Baseline Vertical C/D Ratio in Observation Group*

Vertical C/D Ratio
- ≥0.50: 22%
- >0.30 to <0.50: 16%
- ≤0.30: 4%

Central Corneal Thickness (microns)
- ≤23.75: 17%
- >23.75 to ≤25.75: 9%
- >25.75 to ≤555: 2%
- >555 to ≤588: 22%
- >588: 16%

* through 8 Nov 2001
Back to our ocular hypertensive patient’- (s)

• Guy #1: Pachymetry = 595/600
• Risk of conversion to GLC in 5 years = 2 - 6% monitor

• Guy #2 Pachymetry = 495/501
• Risk = 17 – 36% TREAT
• OHTS Individualizes risk@@@@

The OHTS Lesson

• Treating all ocular hypertensives is not safe/effective or cost effective
• Pachymetry is important
• Conversion best determined by Optic Nerve (Nerve fiber layer) changes HOLD THAT THOUGHT
• TX is optional if risk is acceptable
• IF NFL changes or disc changes TX-DON’T wait for VF changes (thank Harry Quigley again)
How Good are you at judging ON changes?

• Not as good as you think!!

The 3-A’s of Glaucoma Management
Assessment

- Tonometry
- **Optic nerve evaluation**
- Visual fields
- Pachymetry
- NFL analysis

GLAUCOMA is a 3-D DISEASE
**Optic Disc Hemorrhage**
**(Drance Hemorrhage)**

- Usually Superficial In NFL
- Present On Or Adjacent To The Disc
- 70% Located Infra-temporally
- Resolve In One To Three Months
- Often Recurrent

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**Optic Disc Hemorrhage**
**(Drance Hemorrhage)**

- Occurs In 2-23% Of Glaucoma Patients
- More Frequent - Normal Tension Than High Tension Glaucoma
- Indicator Of Early Or Progressive Nerve Damage
- May Precede Optic Nerve And Visual Field Changes
- Warrants Re-evaluation Of Current Treatment

- 6 year study of TX VS non-TX of early glc patients with IOP\(\leq 30\) and minimal VF defect
  \(N = 255\)  
  TX: Betaxolol and ALT-AVG 25% drop in IOP

- TX lowered risk of progression by 10%/mm drop in IOP-

- TX lowered early damage seen in control group

- Risk increased with higher IOP, greater field defects, exfoliation and recurrent disc heme

- First sign of progression VF-86%, Disc change 1%, Both 13% / NNT = 6

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td>55%</td>
<td>38%</td>
</tr>
<tr>
<td>45%</td>
<td>62%</td>
</tr>
<tr>
<td><strong>Mode of progression</strong></td>
<td><strong>Mode of progression</strong></td>
</tr>
<tr>
<td>Visual field only</td>
<td>Visual field only</td>
</tr>
<tr>
<td>Visual field and optic-disc</td>
<td>Visual field and optic-disc</td>
</tr>
<tr>
<td>Optic disc only</td>
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</tbody>
</table>
EMGT (fast) Conclusions

1. Every 1 mm drop in IOP = 10% reduced risk of progression
2. VF's are the best predictor of glaucoma progression in patients with Dx'd Glc
3. TX increased risk of cataract
4. Disc (Drance) hemorrhages predict progression

EMGT: Take Home Messages

- Reducing IOP 25% (about 5 mmHg) prevents the progression of early glaucomatous defects – halves the risk!
- Study about white Swedes with moderately elevated IOPs
- Observations regarding progression in lenticular opacification requires further study
The real story of OHTS VS EMGT (thanks Harry Quigley)

• ON reserve VS ON decompensation
• Don’t wait for VF loss to TX Ocular Hypertensives=save the reserve-monitor disc/NFL with OCT/GDX
• VF’s very sensitive in patient’s that have lost their reserve NFL
• Depend heavily on VF’s in dependable VF takers with pre-existing field loss

OK, OK-The OHT’s and EMGT Study proved that lowering IOP is important in reducing the risk of:

1. Oc. Hypertensives developing GLC
2. Early GLC patients losing Vision (VF)

How low do we go?
ASRANI: Get it low AND KEEP IT LOW ALL DAY
Low IOP during office hours is important, but 24 hour control is the key-Asrani study demonstrates importance of a flat diurnal curve

• Method:
  • 64 patients (105 eyes)
  • Self tonometry 5X / day X 5 days = 25 readings per patient
  • Avg range 10 +/- 2.9mm Hg
  • Risk of progression directly related to degree of fluctuation
  • Caprioli AGIS data confirms importance of dirunal fluctuation as an independent risk factor

Let’s talk NTG vs Pseudo NTG
Normal IOP Does Not Exclude Glaucoma

- The Baltimore Eye Survey:
- Up to 50% of the Patients Diagnosed With Glaucoma (Based on Optic Nerve and VF) Had an Initial IOP Reading Below 21Mm Hg
- Tonometry Is Not a Glaucoma Test
- Glaucoma Testing Is a Complete Eye Exam
- If You Are Not Diagnosing Glaucoma in Patients With Normal IOP, Then You Are Missing Cases of Glaucoma
- Lowering IOP is Beneficial for Patients with NTG

Collaborative NTG Treatment Trial

- 30% IOP reduction limits VF progression by 2/3
- 140 eyes

Beware of Pseudo NTG:
These studies indicate the need for at least three Baseline IOP Readings Before Starting Glaucoma Treatment

- Helps Uncover Diurnal Fluctuation
- Mix Two Morning Readings With One Afternoon
- Imperative for Setting Target Pressures
- Emphasize the Highest Reading when Setting the Target Pressure
- Allows for Determining the Effectivity of Medications
- A Diurnal study is imperative for NTG suspects
- Pachymetry is now standard of care

LALES Study
C/D Ratio as screening tool

- Los Angeles Latino Eye Study
- Comprehensive evaluation for predictors of eye disease in this population
- 6,357 latinos over 40 Y/O
- Vertical C/D > 0.6 cutoff for glc screening
- 92.3% sensitive for glc
- 95.3% specificity for glc
The 3-A’s of Glaucoma Management

- A- Assessment
- A- Action
- A- Adios
### Treatment goals

- Minimum 20%
- Below 18mm hg
- Minimize diurnal variation

### Available Treatments

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholinergic agonists</td>
<td>Ciliary muscle contraction (facilitating uveoscleral outflow and trabecular outflow)</td>
</tr>
<tr>
<td>$\beta_2$-Adrenergic agonists</td>
<td>Increasing trabecular outflow by a mechanism that is not completely understood</td>
</tr>
<tr>
<td>$\beta_2$-Adrenergic antagonists</td>
<td>Inhibition of aqueous production by the ciliary epithelium</td>
</tr>
<tr>
<td>$\alpha_2$-Adrenergic agonists</td>
<td>Inhibition of aqueous production by the ciliary epithelium ± increasing uveoscleral outflow</td>
</tr>
<tr>
<td>Carbonic anhydrase inhibitors</td>
<td>Inhibition of aqueous production by the ciliary epithelium</td>
</tr>
<tr>
<td>Prostaglandin F$_{2\alpha}$ derivatives</td>
<td>Increased uveoscleral outflow</td>
</tr>
</tbody>
</table>
When combining drugs-go for synergism

- **Reduced Aqueous**
- Beta-blockers
- Alphagan
- Propine/epi
- Azopt/Trusopt/Diamox
- Increased outflow
- Pilo
- Prostaglandins
- Propine/epi

Ocular Beta-Blockers

- 30 years of experience
- Known efficacy
- Known contraindications
Name 8 potentially fatal Beta-blocker Adverse Effects

- Adverse Effects
  1. Asthma
  2. Coronary insufficiency
  3. Heart block/arrhythmia
  4. Depression
  5. Diabetics
  6. Anaphylaxis reversal
  7. Lipid abnormality in coronary artery disease
  8. Impotence (just feel like you want to die)

Are You Short of Breath? @@@@@

- Peak flow testing is “IN”-standard of care-ONLY objective test of lung function
- Check pulse and BP
- AVOID B-BLOCKERS AND THE LAWYERS WILL HATE YOU
Is it safe to use beta blocker topicals and orals together?

- MAYBE
- Probably NOT a good idea
- LOWER EFFICACY-HIGHER SIDE-EFFECTS
- AVOID BETA-BLOCKERS at NIGHT, lower efficacy, reduced perfusion

On-going patient evaluation is critical

- 10% of patients have obvious contraindications to beta-blockers
- 12% of “normals” will develop significant side-effects that will require discontinuation of TX
- Good VS Bad side-effects
Avoid beta-blockers at night?

- Reduction of aqueous production during sleep
- Drop in BP during sleep
- Beta blockers reduce perfusion pressure by vasodilation and decreased cardiac output
- Increased risk of nocturnal hypotensive event

Topical CAI’s - Wonder Drug or Wonder DUD

- **WHEN** it works it works real good: Equivalent to BB: 15-25%
- When it fails it fails real bad
- Poor for monotherapy
- Great with…..
- Note: they are sulfonamides
- The same/but different
Brimonidine: If it don’t make you itchy and red then you’re a winner

- Studies indicate that up to 10-25% will develop allergy

Alphagan - Alpha-2 specificity makes for a better drug

- Alpha-2 Specific
- No tachyphylaxis
- Reduced allergy
- BID dosage if in combination - TID is more appropriate if used alone (diurnal drift)
- Beta blocker equivalent
- Good choice for pulmonary compromised patients
- Neuro-protective? Not in humans yet
- Perfusion pressure
Prostaglandin Derivatives

QUESTION #1: Should prostaglandins be used as first line therapy

- 1. Incredible efficacy
- 2. Minimal systemic side-effects
- 3. Minimal diurnal fluctuation
- 4. Minimal tachyphylaxis
- DUHHHHHHHHHHHH
Use of newer, more expensive glaucoma agents increased, while surgeries decreased.

**Glaucoma Surgery Trend 1994-1999**

- New Rx Products: 25%
- Older Products: -48%
- Surgical Interventions: -46%

**Neuroprotection: Currently NONE, but in the Future**

- Block excitotoxins: Produce cellular damage after ischemia or stress
  - Glutamate
  - Aspartate
  - N methyl-d-aspartate (NMDA)
  - Calcium channel blockade

Source: Bateman 2002, Walt 2002
Treatable Risk Factors For Glaucoma Progression And Their Relationship To Adjunctive Medications

• Treatable
  - Intraocular pressure (IOP)
    - Elevated IOP
    - Variation in IOP
      - 24 hours (diurnal and nocturnal)
  - Ocular Perfusion Pressure


Low ocular perfusion pressure has been shown to be strongly associated with the prevalence of glaucoma progression in multiple population-based surveys

Leske et al. Ophthalmology 114 (11), November 2007

BP – IOP = Ocular Perfusion Pressure (OPP)
(BP is mean arterial pressure, diastolic BP, or systolic BP)
Perfusion Pressures

- Mean arterial pressure (MAP) = \( \frac{2}{3} \) diastolic + \( \frac{1}{2} \) systolic
- Mean Arterial OPP = MAP - IOP
- Systolic OPP = Systolic - IOP
- Diastolic OPP = Diastolic - IOP

Lower Diastolic, Systolic, or Mean Pressure Reduces Perfusion Pressure

Higher IOP Negatively Impacts Perfusion Pressure

Lower Perfusion Pressure Is Associated with Increased Risk for Open Angle Glaucoma

Perfusion Pressure Is a Result of A Delicate Balance Between IOP and Blood Pressure

Ocular Perfusion Pressure and Glaucoma Progression

Hayreh SS. Trans Am Acad Ophthalmol 1974; 79:240-54
OPP and Glaucoma Progression: Population Studies

- **Baltimore Eye Survey (AA and Caucasian)**
  - 6x excess of POAG in subjects with lowest category of Ocular Perfusion Pressure (OPP)

- **Egna-Numarkt Study (Caucasian)**
  - Lower Diastolic Ocular Perfusion Pressure (DOPP) associated with marked, progressive increase in frequency of POAG

- **Barbados 4 yr Eye Study (African-Caribbean)**
  - 4-year risk of developing glaucoma increased dramatically at lower perfusion pressure

- **Proyecto Ver (Hispanic)**
  - Found lower Diastolic Perfusion Pressure (DPP) associated with increased risk of POAG

References:

Ocular Perfusion Pressure and Glaucoma Progression: New Evidence

- Barbados Eye Study 9-year Risk Factor Study
- EMGT Predictors for Long-term Progression
- Thessaloniki Eye Study
- EGPS Inter-current Risk Factors
OPP: Barbados 9-year

- Cohort study of African-Caribbeans residing in Barbados, West Indies
- 9-year risk of developing glaucoma increased dramatically at lower perfusion pressure


POAG Risk Factors 9-year

BES

Figure 1. Risk factors for definite open-angle glaucoma (OMG; n = 1322). Hx = history; PP = perfusion pressure; RR = risk ratio; SBP = systolic blood pressure. *Based on Cox regression model, adjusting for age, gender, intraocular pressure (IOP), and IOP- and blood pressure-lowering treatments; central corneal thickness (CCT) is presented as 4 vs. 4.5 mm, based on logistic regression model as a reference (n = 1022).

Barbados Eye Study
Conclusions

• Correlates indicating increased risk of GLC progression (in order of significance)
  Low mean perfusion pressure
  Family HX of GLC
  Corneal thickness
  Elevated IOP
  Age
  Increased Systolic BP was a protective

Thessaloniki Eye Study

• Performed HRT in 263 subjects
• Excluded those subsequently identified with glaucoma
• Patients with DBP < 90 as a result of systemic anti-HTN treatment had larger C:D ratios and cup areas on HRT compared to normals with DBP < 90 and HTN patients with BP ≥ 90

FINALLY, how does perfusion pressure data affect drug selection and treatment methods?

- What’s happening to IOP at night?
- What drugs work well on a 24 hour cycle (particularly during sleep)?
- Which drugs maximize 24 hour IOP control with minimal effect on BP?
- First, the LIU studies from Weinrebs GLC lab

IOP Is Higher at Night

- Both healthy eyes and eyes with glaucomatous changes showed higher nocturnal supine IOP than diurnal sitting IOP
- Supine IOP is higher than sitting IOP, regardless of time of day

Glaucoma Medications and their effects on Ocular Perfusion Pressure (OPP)

- 27 Patients treated with BID timolol 0.5%, BID brimonidine 0.2%, TID dorzolamide 2% or QHS latanoprost 0.005% for six weeks, followed by a 4-week washout period between different treatments

- 24-hour IOP monitoring in habitual position
- 24-hour systemic blood pressure monitoring

GOAL: Based upon drug effect on IOP and BP find the best mono therapeutic agent and best drug combination

Baseline Timolol Brimonidine Dorzolamide Latanoprost
Mean 24-Hour IOP (mm Hg)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Timolol</th>
<th>Brimonidine</th>
<th>Dorzolamide</th>
<th>Latanoprost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 24-</td>
<td>22.69</td>
<td>17.73</td>
<td>18.32</td>
<td>17.37</td>
<td>16.82</td>
</tr>
</tbody>
</table>

**Diastolic Ocular Perfusion Pressure (DOPP) Results**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Timolol</th>
<th>Brimonidine</th>
<th>Dorzolamide</th>
<th>Latanoprost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 24-Hour Diastolic Ocular Perfusion Pressure (mm Hg)(^1)</td>
<td>50.7</td>
<td>53.0</td>
<td>46.2</td>
<td>55.9</td>
<td>56.4</td>
</tr>
</tbody>
</table>

\(^1\) Reduction in DOPP is a risk factor for glaucoma progression\(^2\)

* Significant reduction in DOPP (p < 0.0001)
* Significant improvement in DOPP vs. baseline (p < 0.0001)

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**Additive effect on IOP of prostaglandin TX PLUS:**

![Additive effect on IOP of prostaglandin TX PLUS](image)

Source: Bateman 2002, Walt 2002
Study Conclusions

- PGA and CAI significantly increased DPP at all time points

- Beta-blocker significantly increased DPP from 4AM to 4PM but had no effect at other times

- Alpha agonist significantly reduced DPP at multiple time points, primarily due to significant decrease in systemic BP


BEST Combinations

• Prostaglandin (+) Topical CAI
• Avoid Alpha agonist (decreases PP) ie lowers BP and least effective agent at night
Relationship between Nocturnal Hypotension and OPP

- Low BP at night, coupled with high IOP in supine position, compromise OPP

- Use systemic BP meds in the AM to minimize nocturnal hypotension

- Use IOP lowering drugs that lower IOP during BOTH the diurnal and nocturnal period (CAI’s and prostaglandins)

- Avoid IOP meds that lower systemic BP at night (beta blockers, alpha agonists)


Think holistically

- Consider measuring perfusion pressures

- Monitor those at greatest risk-low BP/over-aggressive BP control

- Nocturnal hypotension can produce NA-ION

- Talk with PCP
REASONS FOR TREATMENT FAILURE

• Adverse drug effects/ contraindications
• Too many drugs
• Efficacy
• Compliance