Landmark Glaucoma Trials- What They Mean Clinically

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Disclosures for Dr Schmidt

- Dr Schmidt is a consultant or advisor for the following:
  - Tarsus
  - Allergan
  - B&L
  - Visus
  - M&S Technologies
  - Avellino Labs
  - Peripherex
  - Topcon
  - Sight Science
- All potential conflicts of interest have been mitigated

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What Is A Landmark Trial?

- Randomized Trials
- NEI Funded
- Multi-Center trials
- Large number of subjects (N)
- Geographically and Demographically diverse
- Comparison Studies
- Definable Outcomes
- Clinically meaningful recommendations

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Glaucoma Landmark Trials

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

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OHTS Objective

- To determine whether early treatment with topical therapy delays or prevents the onset of Open Angle Glaucoma *In Patients With Ocular Hypertension*
- Drops only
- Not the same drops as we now use
- Followed for a minimum of 8 years – *But We Now Have 20 Year Data!*

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OHTS Protocol

- Huge Study (N>1600 pxs)
- None had discernable glaucoma damage (as defined by 1990s understanding)
- IOP between 24mmHg and 32mm Hg in 1 eye. (Could go as low as 21mm Hg in fellow eye)
- Patients randomized to treatment or observation arm
- Treatment was with topical meds; drops could be changed or added to a maximum of 3 drops in order to reach IOP goal
- IOP goal-<24mm Hg and 20% reduction
- IOP and VF q6 mths- FOR A MINIMUM OF 8 YEARS!!!

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OHTS

- Goal of tx – 20% drop in IOP
  - 24mm target IOP

RESULTS: At 5 years

4.4% of tx group developed POAG

9.5% of no tx group developed POAG

So - lowering IOP in Oc Hx reduced the likelihood of glaucoma by 50% - RIGHT?

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OHTS Results

- Treating Ocular Hypertension early more than halved the risk of developing POAG at 5 years.
- What does the data look like at 7 years?
- How about 10 years?

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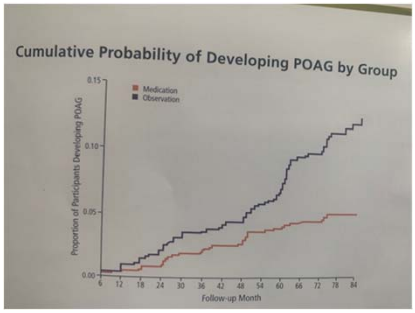

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OHTS Conclusion

Lowering IOP in Ocular hypertensives does slow down the risk of developing POAG

OHTS did not imply that all Ocular Hypertensives should be treated

"For patients with a moderate to high risk of developing POAG, IOP-lowering medications should be considered."

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OHTS – A Closer Look

- 90% of untreated group did not progress
- 95.6% of tx group did not progress
- It proved that ***in those individuals who are going to progress*** to POAG lowering IOP by 22.4% will delay the onset by at least 5 yrs.
- Who are " those individuals at risk"?

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OHTS – The Nitty Gritty

- The most predictive factors for conversion:
  - Older age
    - 22% increase/ decade
  - Larger horizontal and vertical C/D
    - 32% increase/0.1 larger
  - Higher baseline IOP
    - 10% increase/ mm Hg
  - Thinner corneas
    - 71% increase in risk/ 40 microns thinner

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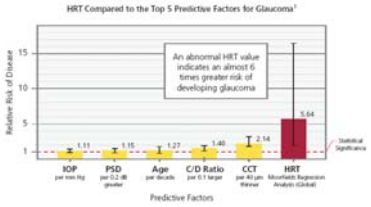
Risk Factors For Conversion



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The pachymetry issue

- Juicy Data
  - 36% of pxs w/ IOP >25.75 AND K thickness < 555 microns developed POAG
  - 6% of pxs w/ same IOP but K thickness > 588 converted toPOAG
- Juicy Data II
  - 15% pxs w/ C/D .3/.3 and K thickness < 555 microns converted but
  - 4% of pxs w/ same disk parameters and K thickness> 588 microns converted

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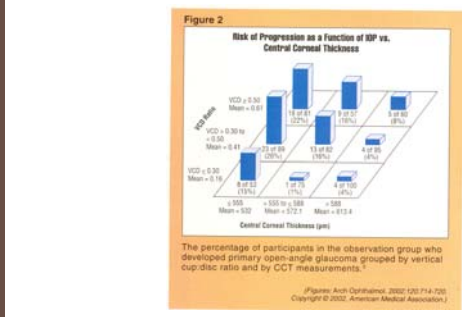

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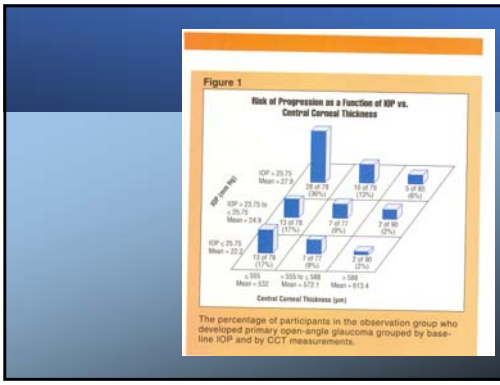

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IOP 30mmHg, CCT 600µ

Glaucoma Risk Estimator

Age 70	RIGHT EYE MEASUREMENTS			LEFT EYE MEASUREMENTS		
	1st	2nd	3rd	1st	2nd	3rd
Untreated Intraocular Pressure (mm Hg)	30	30	30	30	30	30
Central Corneal Thickness (microns)	600	600	600	600	600	600
Vertical Cup to Disc Ratio by Contour	0.55			0.55		
Pattern Standard Deviation (Humphrey (dB) / Octopus loss variance (dB))	1.0	1.0		1.0	1.0	

Print | Reset | 9.1% | The patient's estimated 5-year risk (%) of developing glaucoma in at least one eye.

Glaucoma risk is 9.1%

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IOP 20mmHg, CCT 500µ

Glaucoma Risk Estimator

Age 70	RIGHT EYE MEASUREMENTS			LEFT EYE MEASUREMENTS		
	1st	2nd	3rd	1st	2nd	3rd
Untreated Intraocular Pressure (mm Hg)	20	20	20	20	20	20
Central Corneal Thickness (microns)	500	500	500	500	500	500
Vertical Cup to Disc Ratio by Contour	0.55			0.55		
Pattern Standard Deviation (Humphrey (dB) / Octopus loss variance (dB))	1.0	1.0		1.0	1.0	

Print | Reset | 20.7% | The patient's estimated 5-year risk (%) of developing glaucoma in at least one eye.

Glaucoma risk is 20.7%

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Shortcomings of OHTS ?

- Very conservative IOP reduction goal
- No OCT data
- Antiquated drops
- 24-2 VF tests only
- Did they miss the point?

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The Latest 20 year OHTS Data

- Just released data
- Recommended patience before initiating therapy
- Don't rush to treatment judgement
- Treat them as glaucoma patients but without treatment
- Oh Really?!?!?!

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20 YEAR OHTS DATA

1 in 4 progresses WITHOUT TREATMENT!!

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Early Manifest Glaucoma Trial

Basically this was an early treatment vs delayed treatment study

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EMGT Objective

- To compare the effects of immediately lowering IOP vs no treatment or delayed treatment in POAG patients
  - Randomized into treatment arm or no treatment arm
  - Treatment type was chosen by investigator
  - Progression was determined by investigator (VF worsening)

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EMGT Protocol

- 10 year study
- 255 patients
- EARLY GLAUCOMA – All patients had VF defects!!
- Pxs randomized into either treatment or non-treatment arm
- Treatment was either SLT, drops or both
- IOP goal – no set target. "Maximum possible IOP reduction without causing major side effects."
- Pxs had VF tests performed Q3 Mths, FP Q6 Mths

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EMGT Goal

- Does Early therapy make a difference in how quickly POAG progresses
- If progression occurred in the treatment arm, therapy could be advanced.
- Progression defined as further VF loss

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EMGT Results

- Treated Group – Average IOP reduction of 5.1mm Hg (25%)
  - > Median starting IOP was 20mm Hg
  - > IOP maintained for 6 years
- Untreated group – No change in IOP
- BUT… Both arms showed high rates of progression

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Progression Rates in EMGT Study

Treatment arm- 45% progression rate

Untreated arm – 62% progression rate

- This is very statistically significant

When progression occurred…

- Treatment arm at 66 months
- Non-treatment arm- 48 months

So treatment increased the time to progression by 18 mths

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EMGT Conclusions

- Progression was less frequent in treated pxs as compared to non-treated pxs
- Progression occurred significantly later in the treated arm as compared to the non-treatment arm
- "Early treatment of newly detected glaucoma reduces the risk of progression of visual field loss."

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Let's Talk About This…

- Very high progression rate – Why?
- Was this really early glaucoma?
- What about the low average opening IOP?
- What happened after the 6 year mark?

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EMGT Conclusions

Reducing IOP (by 25%) prevents or slows VF defect and progression

For each 1mm of IOP reduction there is a 10% lower risk of VF loss

Study design and outcome show that these results are only due to IOP reduction (non IOP related factors showed difference between the 2 groups)

Tx effect was equal across age and glaucoma categories

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Eric's spin on the EMGT

- 1-2 extra mm Hg may indeed be important- especially in advanced cases.
- For those pxs who need treatment, aggressive therapy is warranted
- It is defintely better to treat early than late
- You do not need to wait until the VF defects arise before therapy is initiated
- The benefit of treatment does last throughout the lifetime of the px – just remember the risk/benefit

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Collaborative Initial Glaucoma Treatment Study (CIGTS)

- Objective – to assess the effect of initial therapy with either topical medications OR trabeculectomy in newly diagnosed glaucoma patients
- So this is the first randomized surgery vs drops study
- Vast majority of pxs in study had no or minimal VF loss

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CIGTS Protocol

- 607 Patients
- Newly diagnosed with either POAG, Pigmentary Glaucoma or Pseudoexfoliative Glaucoma
- Randomized to either medication (drops) arm or surgery (trabeculectomy) arm
- Type of drops used was investigator choice
- Pxs followed every 6 mths with VF ands IOP measurements
- Followed for 5 years
- IOP target – individualized per patient based onn VF score and baseline IOP

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CIGTS Results

IOP Reduction

- Medication Arm – 35% Reduction (from baseline of 28mm to 17-18mm)
- Surgical Arm - 48% reduction (from baseline of 27mm to 14mm Hg)

Visual Field status

- Mean VF scores were minimal in both arms
- Those remained essentially unchanged FOR 5 YEARS!!!

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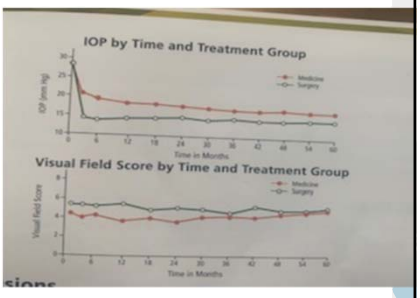
CIGTS Data



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CIGTS Conclusions

- Trabeculectomy lowered IOP on average more than medication(s) alone
- Mean Visual Field Scores were minimal and remained unchanged for 5 years IN BOTH ARMS!!!
- Clearly shows that lowering IOP EARLY and AGGRESSIVELY greatly limits Visual Field advancement

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CIGTS 9 year data

- Confirms the 5 year data
- Medication Arm – Baseline IOP 28mm Hg reduced to and maintained at 17 from years 3-9
- Surgical Arm – Baseline IOP 27mm Hg reduced to and maintained at 13-14 from years 3-9
- Very minimal VF progression in either arm

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CIGTS – So What Do We Think?

- Lowering IOP is essential for preserving visual field
- Reducing IOP by at least 35% greatly slowed the rate of VF loss
- Surgery lowers IOP better than drops, so why not just do surgery first?
- Does this change your idea of how low your target IOP goal should be?

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Advanced Glaucoma Intervention Study (AGIS)

- Objective- to investigate the association between control of IOP after surgical intervention and visual field deterioration
- The subjects all had POAG that was worsening
- The essential question in this study was "How low do we need to go?"

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AGIS Protocol

- 789 eyes (591 pxs)
- Pxs received ALT first followed by trabeculectomy if needed.
- Supplemental drops could be used after both procedures if needed.
- IOP measurements and VF testing performed at least every 6 mths for a minimum of 6 years
- Most pxs were observed for 8 years
- IOP goal - < 18mm Hg

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AGIS Results

- IOP Results
  - 31% had IOP <14mm Hg
  - 39% had IOP 14-17.5mmHg
  - 30% had IOP >17.5mm Hg
  - 24% achieved IOP less than 18 100% of readings
  - 26% achieved IOP less than 18 75-99% of readings
  - 24% achieved IOP less than 18 50-75% of readings
  - 26% achieved IOP less than 18 < than 50% of readings… SO?… SO WHAT?

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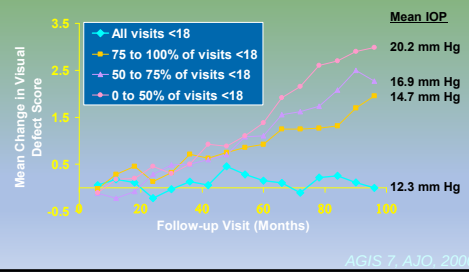
Consistently Low IOP Reduces Vision Loss



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AGIS Results

Pxs who achieved IOP < 18mm on 100% of f/up visits showed no VF progression (avg IOP 12.3mm)

Pxs w/ IOP < 18mm on<50% of f/up visits showed VF progression (mean IOP 20.2mm)

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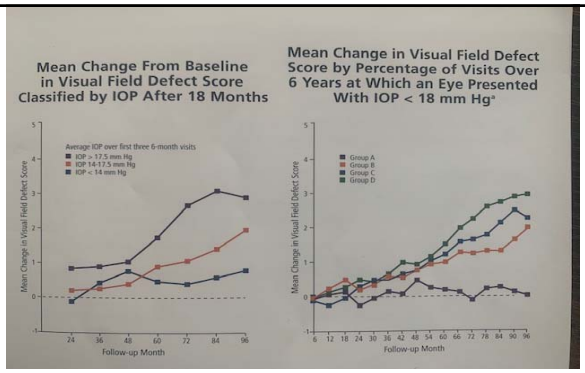

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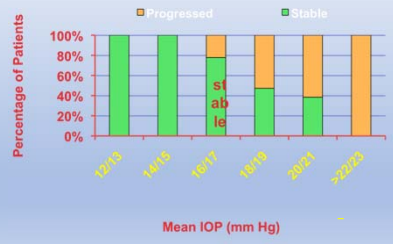
Low IOP Slows or Halts Vision Loss in Open-Angle Glaucoma



Mao et al. AJO. 1991

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Secondary AGIS Results

Intervisit IOP variation was found to be a risk factor for POAG progression

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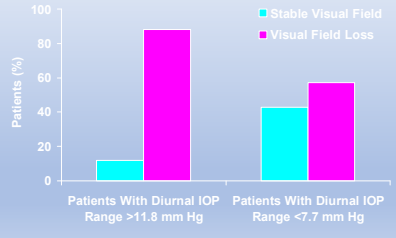
Diurnal IOP Fluctuations Speed Glaucomatous Progression



Asrani et al. J Glauc. 2000

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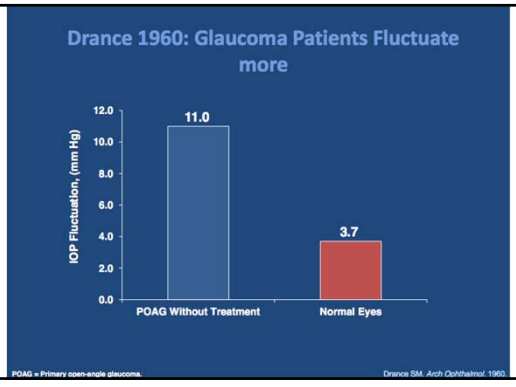

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AGIS Conclusions

- For Progressive Glaucoma:
  - The more times you can get the IOP less than 18mm Hg the better
  - Controlling IOP variability over time is crucial for maintaining VF integrity
  - The lower the IOP, the better
  - The more stable the IOP, the better

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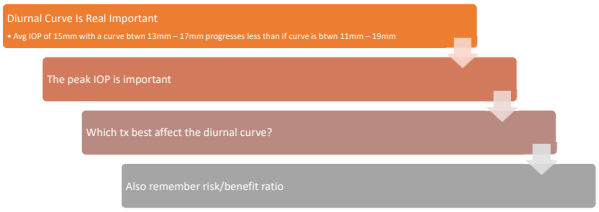
AGIS Conclusions



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2 Magic Numbers From AGIS

<18mm Hg!!

<5mm Hg!!!

The more often you achieve these, the less likely progression is to occur

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Just 1 more slide!

Not all progressing glaucoma pxs need surgery

How do you best detect progression?

How do you really know when to add therapy?

Never let them see you sweat!

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