


## 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
  - Trukera
  - Allergan
  - B&L
  - Visus
  - M&S Technologies
  - Avellino Labs
  - Peripherex
  - Topcon
  - Sight Science
  - Thea Pharmaceuticals
  - Sydnexis
- 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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## Landmark Glaucoma 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

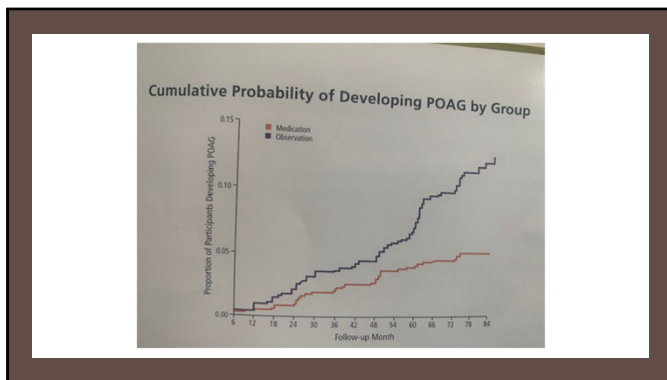
So - lowering IOP in Oc Hx reduced the likelihood of glaucoma by 50% - RIGHT?

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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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### 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”?

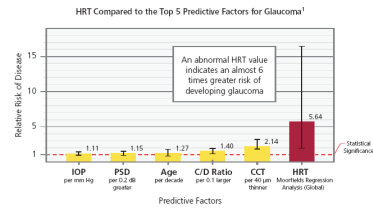
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OHTS – The Nitty Gritty

- 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

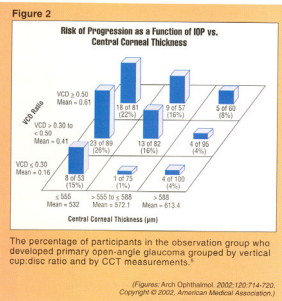
### Juicy Data

- 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 to POAG

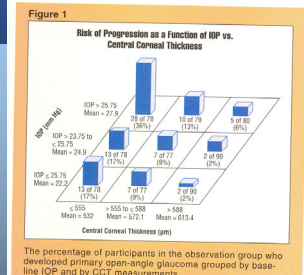
### Juicy Data II

- 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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IOP 30mmHg, CCT 600µ

Glaucoma Risk Estimator						
Age	RIGHT EYE MEASUREMENTS			LEFT EYE MEASUREMENTS		
70	1 <sup>st</sup>	2 <sup>nd</sup>	3 <sup>rd</sup>	1 <sup>st</sup>	2 <sup>nd</sup>	3 <sup>rd</sup>
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 Octopus loss variance (dB)	1.0	1.0		1.0	1.0	

Print Reset

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

Print Reset

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 definitely 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 and IOP measurements

Followed for 5 years

IOP target – individualized per patient based on VF score and baseline IOP

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## CIGTS Results

### IOP Reduction

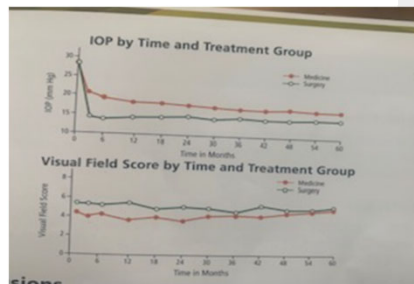
- Medication Arm – 35% Reduction (from baseline of 28mm to 17-18mm)
- Surgical Arm - 48% reduction (from baseline of 27mm to 14mm Hg)

### 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)	<ul style="list-style-type: none"> <li>Objective- to investigate the association between control of IOP after surgical intervention and visual field deterioration</li> <li>The subjects all had POAG that was worsening</li> <li>The essential question in this study was "How low do we need to go?"</li> </ul>
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AGIS Protocol	<ul style="list-style-type: none"> <li>789 eyes (591 pxs)</li> <li>Pxs received ALT first followed by trabeculectomy if needed.</li> <li>Supplemental drops could be used after both procedures if needed.</li> <li>IOP measurements and VF testing performed at least every 6 mths for a minimum of 6 years</li> <li>Most pxs were observed for 8 years</li> <li>IOP goal - &lt; 18mm Hg</li> </ul>
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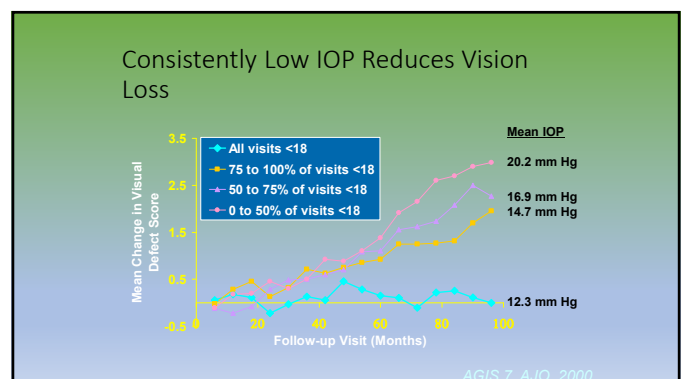
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## AGIS Results

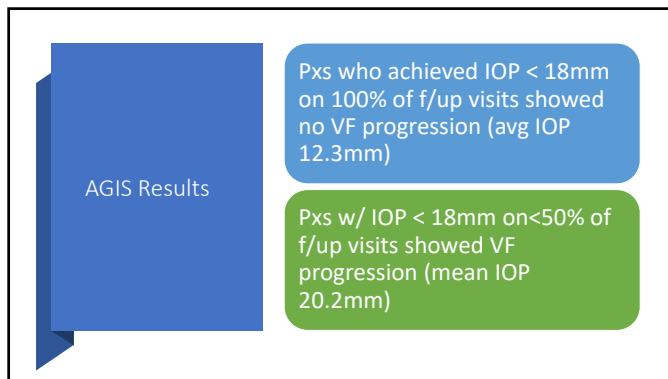
- IOP Results

- 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?

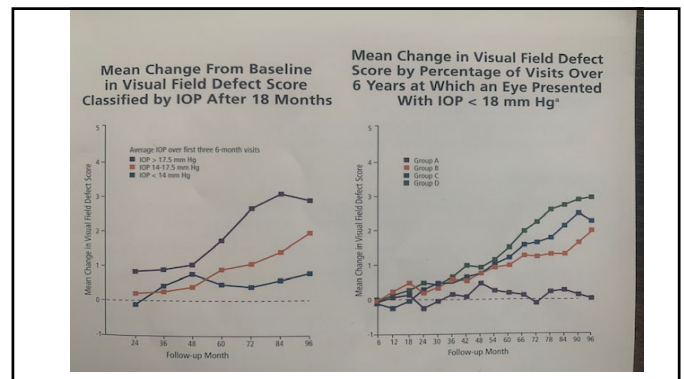
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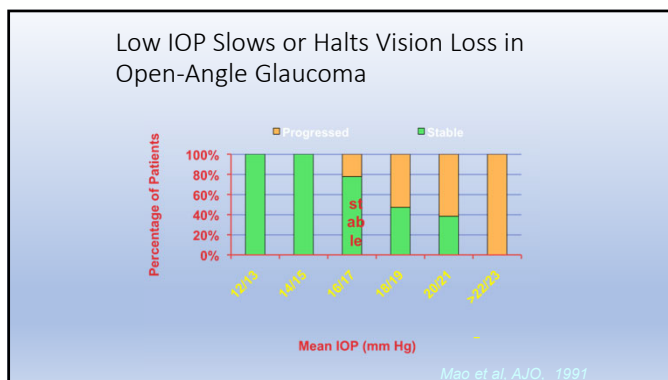
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**Audience Question:**  
Where do you most commonly position SLT in your practice?  
(PLEASE ANSWER IN CHAT FOR YOUR ATTENDANCE QUESTION)

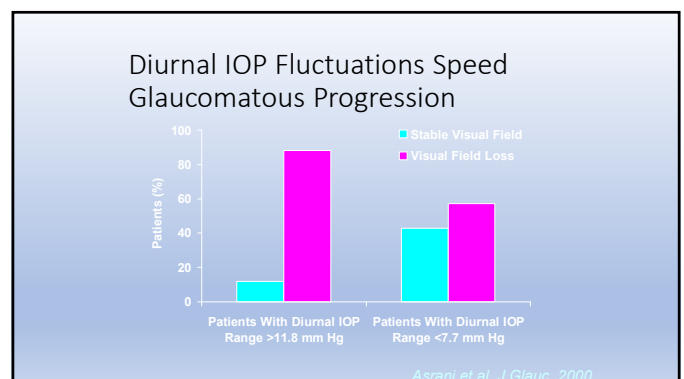
- 1. As 1<sup>st</sup> Line Therapy
- 2. As your first additive therapy
- 3. After 2 drops
- 4. As a last ditch bailout effort to avoid surgery
- 5. Never recommend SLT

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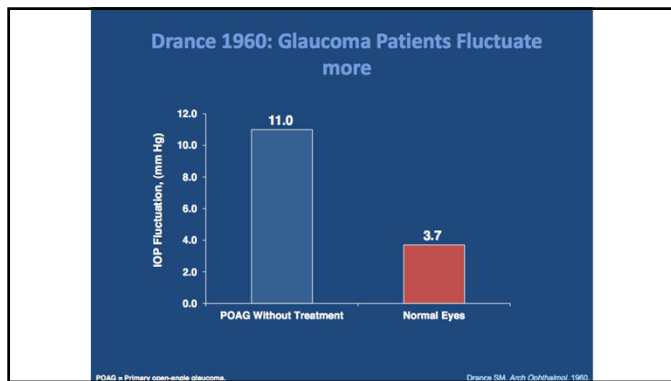
**Secondary AGIS Results**

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

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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**

Diurnal Curve is Real Important  
\* Avg IOP of 15mm with a curve between 13mm – 17mm progresses less than if curve is between 11mm – 19mm

The peak IOP is important

Which tx best affect the diurnal curve?

Also remember risk/benefit ratio

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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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**Collaborative Normal Tension Glaucoma Study (CNTGS)**

Anderson et al, AJO 1998

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## CNTGS Objective

Does Lowering IOP In NTG Delay Glaucomatous Progression

How Did They Define NTG?

- Must Have Fixation Threatened
- Documented VF Progression, or...
- New Disc Hemorrhage

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## Normal Tension Glaucoma Study- Study Design

- 145 Patients Had One Eye Randomized To 30% IOP Reduction (#61) Vs Observation (#79)
- Target IOP 30% Reduction
- Step Therapy With Pilocarpine, ALT And Filter
- No Adrenergic Agents (Beta-blockers, Epinephrine Drug)
- PGAs, Alphagan And Topical CAI's Were Not Available
- Patients Followed With Serial VF's And Optic Disc Photographs For 5 Years
  - Progression defined as either worsening VF or Changes in rim appearance

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## CNTGS Results

- Reducing IOP by 30% Significantly reduced progression
- 12% Of Treated Eyes Versus 35% Of Untreated Eyes Progressed
- Of those who reached a 30% reduction in IOP, 57% did so w/out filtering surgery
- Of those who progressed:
  - 89% showed VF progression
  - 11% showed disk changes
- 48% of all pxs who had surgery developed cataracts
- 23% cataract rate in non-surgical pxs
  - Did that skew the data?

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## Risk Factors For Progression (CNTGS)

- Females
- Migraine HA
- Disk Hemorrhages

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## Normal Tension Glaucoma Study Observations

- SOOOOO MANY CATARACTS!!!
- New Medications May Reduce The Need And Complications Of Filtering Surgery
- Should All NTG Patients Be Treated?
- Is there a benefit to treatment?
- Is earlier treatment advantageous?
- How Low Do You Go??

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## CNTGS Conclusions

- The Collaborative Normal-Tension Glaucoma Study (CNTGS) showed that a 30% reduction of intraocular pressure in patients with normal tension glaucoma slowed the rate of visual field progression compared to eyes in which no effort was made to lower intraocular pressure.
- There are caveats to this though.

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### Further CNTGS conclusions

- 30% IOP reduction is the number
- Pxs who received glaucoma surgery were far more likely to develop cataracts
- The rate of progression without treatment is highly variable, but often slow enough that half of the patients have no progression in 5 years.
- When they do progress, VF loss happens rapidly

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### There are problems with this (awesome) study

1. - SOOOOOO MANY CATARACTS
2. No Baseline IOP was defined
3. Does their definition of NTG match ours currently?
4. Does this diminish the value of this study?

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### Speaking of Normal Tension Glaucoma...

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### Brimonidine and the LoGTS

- Brimonidine was superior at preserving VF over a 3 year period as compared to Timolol 1/2%
- Yet Timolol reduced IOP by 1.5 more mm.
- So?>?>... Does this represent neuroprotection??

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### Treatment Considerations

- What Are We Trying To Achieve?
  - LOOOOW IOP!
  - INCREASE PERFUSION
- Are There Any Medications We Should Avoid?
- What Is The Goal Of Treatment?

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### Treatment Considerations in NTG

- Avoid beta-blockers
- Keep Diurnal Curve Tight!!
- Choose a Low Target and Identify The Peak

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### Disk hemorrhages and Rate of Progression (Medeiros et al)

- Cohort of the DIGS
- Pxs followed for 8 years for VF progression (using the VFI)
- 20% had disk hemorrhage
- Eyes with disk heme had more than double the rate of VF loss
- Eyes w/ more than 1 disk heme showed an even higher rate of VF progression
- Persons with disk heme in general had a more severe glaucoma

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### More New NTG stuff

- Peak IOP in progression group - 17.6mm Hg
- Peak IOP in non-progressors - 15.8mm Hg
- Mean IOP in both groups - ~13.1
- So consistently low IOP is crucial
- Squash the spikes, set a **LOOOW** IOP
- Age of pxs didn't matter

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### 1 MORE THING

NTG PXS TEND TO BE "OVERDIPPERS"  
OVERDIPPERS TEND TO LOSE VF AT A HIGHER RATE

SO HOW DO YOU DETECT OVERDIPPERS?

AND WHAT DO YOU DO ABOUT IT?

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### Audience Question

Where do you most commonly position SLT in your practice?

1. As 1<sup>st</sup> Line Therapy
2. As your first additive therapy
3. After 2 drops
4. As a last ditch bailout effort to avoid surgery
5. Never recommend SLT

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### LiGHT Study (Lasers in Glaucoma and HyperTension)

SLT versus eye drops for first-line treatment of ocular hypertension and glaucoma (LiGHT): a multicenter randomized controlled trial

Gus Gazzard, Eugenias Konstantakopoulos, David Garway-Heath et al

www.thelancet.com Vol 393 April 13, 2019

Pxs had to have mild or moderate glaucoma based on VF criteria

Target IOP reduction 20-30% (depending on severity)

Standard SLT energy protocols

Medicine group - 1<sup>st</sup> line PGA, 2nd Line Beta blocker, 3<sup>rd</sup> line CAI or Alpha agonist

Over 750 eyes, randomly divided

Both groups followed for 36mths

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### LiGHT study outcomes

Both groups showed similar efficacy in lowering IOP

- 16.3mm Hg Drop group, 16.6 mm Hg SLT Group
- 78.2% SLT group required no drops, 12% required 1 drop
- 64.6% drop group controlled on 1 drop, 18.5% required 2 drops
- 0% SLT Group required trab, 3.3% Drop group required trab
- 93% SLT group at target IOP, 91.3% Drop group

SLT Group spent 202 pounds less on care

So what does this mean for us, our clinics and our patients??

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## LiGHT Study – Brand New 6 year data (4/23)

After the initial 3 years of the trial, patients in the SLT arm were permitted a third SLT if necessary;

Patients in the drops arm were allowed SLT as a treatment switch or escalation.

The primary outcome was HRQoL at 6 years; secondary outcomes were clinical effectiveness and adverse events.

Basically the same cohort of patients as the original study

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## 6 Year LiGHT study results

- ❖ No significant difference in QOL scores between the 2 arms
- ❖ No significant difference in IOP reduction between the 2 arms
- ❖ In SLT arm, 69.8% of pxs remained at target IOP w/out further surgery or drops
- ❖ Progression rate drops arm 26.8% vs 19.6% in SLT arm

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## 6 Year Light Study conclusion

"Selective laser trabeculoplasty is a safe treatment for OAG and OHT, providing better long-term disease control than initial drop therapy, with reduced need for incisional glaucoma and cataract surgery over 6 years."

Very Interesting!

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## Does The LiGHT Study...

- 1) Change your impression of the efficacy of SLT?
- 2) Change your impression of when you would recommend SLT for your patients?
- 3) Change your impression on who may be good candidates for SLT?

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## 1 More Study!- ZAP Study

Study Design-

886 pxs diagnosed with PACS – all were asymptomatic

Between ages of 50-70

Random community screening in China

½ of the eyes were prophylactically treated with LPI

½ of the eyes were followed without treatment for 6 years

Primary outcomes were

- 1) Elevated IOP
- 2) Increasing PAS
- 3) Acute angle closure

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## ZAP Results

19 (2%) eyes in LPI group developed acute angle closure

36 (4%) eyes in untreated group developed acute angle closure

So is it worth it to treat narrow angles prophylactically?

When should LPI be performed on these patients?

Why Such A Difference from Previous Studies?

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### ZAP Study Conclusion

"Laser peripheral iridotomy had a modest, albeit significant, prophylactic effect. In view of the low incidence rate of outcomes that have no immediate threat to vision, the benefit of prophylactic laser peripheral iridotomy is limited; therefore, widespread prophylactic laser peripheral iridotomy for primary angle-closure suspects is not recommended."

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### New Therapeutics for Clinical Practice



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