LV Prasad Eye Institute

Evidence Based Medicine
An Introduction

Dr. G Chandra Sekhar

L V Prasad Eye Institute

Poll Question 1

What is your position?

1. Ophthalmologist
2. Ophthalmologist-in-training
3. Nurse
4. Ophthalmic Technician / Allied Health
5. Medical Student

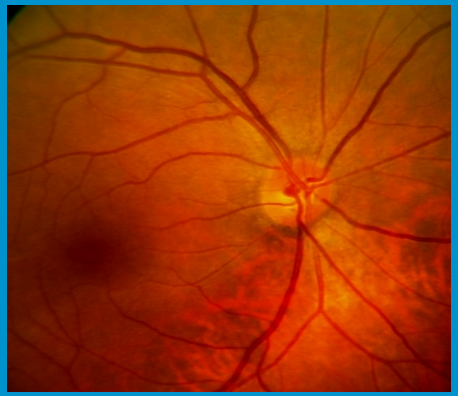
Evidence Based Medicine
An Introduction

- Need for EBM and its definition
- Fallacies in published literature
- Hierarchy of Evidence and its relevance
- Evaluate the data and look for hidden information
- Need to know concepts involved in statistics, the details of the mathematics is optional
    - Confidence intervals
    - Clinical Vs statistical significance
    - Absolute Vs Relative risk

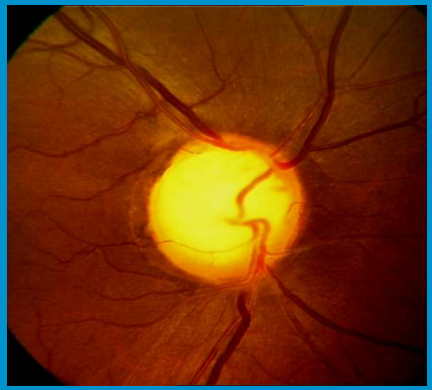
Poll Question 2

Only one of the 4 images is glaucomatous disc. Which one is that?

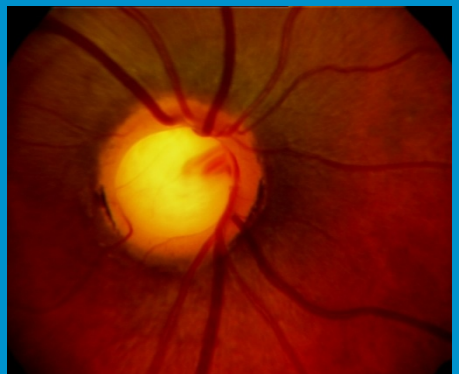
A



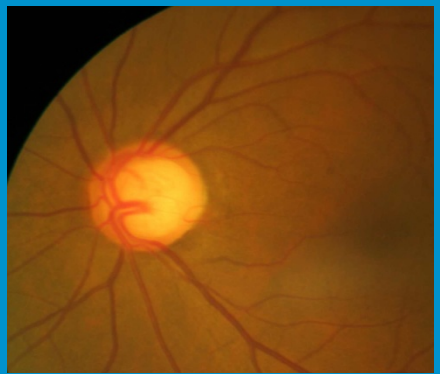
C



B



D



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THE QUALITY OF MEDICAL EVIDENCE: IMPLICATIONS FOR QUALITY OF CARE

by David M. Eddy and John Billings

THE QUALITY OF MEDICAL EVIDENCE: IMPLICATIONS FOR QUALITY OF CARE

David M. Eddy and John Billings

PTA Vs Bypass surgery
Screening for Colorectal cancer
Screening for breast cancer

THE QUALITY OF MEDICAL EVIDENCE: IMPLICATIONS FOR QUALITY OF CARE

David M. Eddy and John Billings

--there is virtually no usable evidence about the effectiveness of medical treatment for glaucoma

An Evaluation of Internal-Mammary-Artery Ligation by a Double-Blind Technic

Leonard A. Cobb, M.D.[†], George I. Thomas, M.D.[‡], David H. Dillard, M.D.[§], K. Alvin Merendino, M.D.[¶], and Robert A. Bruce, M.D.[‖]

N Engl J Med 1959; 260:1115-1118 | May 28, 1959 | DOI: 10.1056/NEJM195905282602204

Evidence based medicine

- Shift in paradigm
- Intuition, unsystematic clinical experience pathophysiologic rationale are insufficient grounds for clinical decision making
- Lower value on authority

Table 1
Combined AAO and Oxford system for rating peer reviewed literature (courtesy of Ophthalmology).

AAO grade	Oxford level of evidence	Type of study
I	1a	Systematic review (with homogeneity) of RCTs
	1b	Individual RCT (with narrow confidence interval)
	1c	All or none
II	2a	Systematic review (with homogeneity) of cohort studies
	2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)
	2c	"Outcomes" research
	3a	Systematic review (with homogeneity) of case–control studies
	3b	Individual case–control study
III	4	Case series (and poor quality cohort and case–control studies)
	5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Narrative based medicine

Narrative based medicine in an evidence based world

Trisha Greenhalgh

There is a serious danger of reifying that population story—that is, of applying what Whitehead called the fallacy of misplaced concreteness and erroneously viewing summary statistics as hard realities

BECOMING A PHYSICIAN

Level IV Evidence — Adverse Anecdote and Clinical Practice

Alison M. Stuebe, M.D.

I've come to appreciate that the influence of a randomized, controlled trial no matter how well conducted or generalizable — pales in comparison with that of the audible bleeding of a profound postpartum hemorrhage.

NEJM 2011,365;1

Evidence based medicine

- Evidence is alone never sufficient
- Trade the risks and benefits, inconvenience and costs
- Patients' values
- Hierarchy of evidence

Evidence based medicine

The practice of EBM means integrating individual clinical expertise with the best available external clinical evidence.

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EBM

Some (perhaps most) of the published articles belong in the bin and certainly should not be used to inform practice

BMJ 1994,308;283-4

The scandal of poor medical research

What should we think about a doctor who uses the wrong treatment, either willfully or through ignorance, or who uses the right treatment wrongly (such as by giving the wrong dose of a drug)? Most people would agree that such behavior was unprofessional, arguably unethical, and certainly unacceptable.

BMJ 1994;308:283-4

"What, then, should we think about researchers who use the wrong techniques (either willfully or in ignorance), use the right techniques wrongly, misinterpret their results, report their results selectively, cite the literature selectively, and draw unjustified conclusions? We should be appalled. Yet numerous studies of the medical literature, in both general and specialist journals, have shown that all of the above phenomena are common. This is surely a scandal.

BMJ 1994;308:283-4

Quality of Reporting of Key Methodological Items of Randomized Controlled Trials in Clinical Ophthalmic Journals

Timothy Y. Y. Lai,[1] Victoria W. Y. Wong,[1] Robert F. Lam,[1] Andy C. O. Cheng,[1] Dennis S. C. Lam,[1] and Gabriel M. Leung[2]

Table 2. Key methodological items reported in the four selected general clinical ophthalmic journals

Methodological item	All journal articles(n = 67)	American Journal of Ophthalmology(n = 16)	Archives of Ophthalmology(n = 13)	British Journal of Ophthalmology(n = 16)	Ophthalmology (n = 22)
Sequence generation	33 (49.3%)	7 (43.8%)	8 (61.5%)	6 (37.5%)	12 (54.5%)
Restriction	25 (37.3%)	3 (18.8%)	4 (30.8%)	7 (43.8%)	11 (50.0%)
Allocation concealment	24 (35.8%)	4 (25.0%)	4 (30.8%)	7 (43.8%)	9 (40.9%)
Allocation Implementation	24 (35.8%)	5 (31.3%)	7 (53.8%)	5 (31.3%)	7 (31.8%)
Blinding/Masking Status	57 (85.1%)	15 (93.8%)	12 (92.3%)	13 (81.2%)	17 (77.3%)
Flow diagram	17 (25.4%)	2 (12.5%)	6 (46.2%)	4 (25.0%)	5 (22.7%)
Intention-to-treat analysis	48 (71.6%)	10 (62.5%)	12 (92.3%)	11 (68.8%)	15 (68.2%)
Description of withdrawals	51 (76.1%)	11 (68.8%)	12 (92.3%)	12 (75.0%)	16 (72.7%)
Description of adverse events	49 (73.1%)	10 (62.5%)	10 (76.9%)	10 (62.5%)	19 (86.4%)
Sample size calculation	33 (49.3%)	6 (37.5%)	9 (69.2%)	9 (56.3%)	11 (50.0%)
Ethics/informed consent	65 (97.0%)*	15 (93.8%)	13 (100.0%)	16 (100.0%)	21 (95.5%)
Number of items reported					
Mean	6.3	5.4	7.5	6.1	6.5
Median	6.0	5.5	8.0	5.5	6.0
Range	2 to 11	2 to 10	2 to 11	3 to 11	2 to 11
Interquartile range	4 to 8	3 to 8	5.5 to 10	4 to 8	5 to 9

Note: The numerator represents the number of articles reporting the particular methodological item.
*Two RCTs reported informed consent was obtained but did not mention ethics approval nor of compliance to the tenets of the Declaration of

Quality of Reporting of Key Methodological Items of Randomized Controlled Trials in Clinical Ophthalmic Journals

***Conclusions*: Similar to other specialties, rooms for improvement exist in the reporting of key methodological items of RCTs in clinical ophthalmic journals. Stricter adoption of the CONSORT statement might enhance the reporting quality of RCTs in ophthalmic journals.**

Lai TYY, Wong VWY, Lam RF Ophthalmic Epidemiology Dec 2007

- **As medicine leans increasingly on mathematics no clinician can afford to leave the statistical aspects of a paper to the "experts."**

BMJ 1997;315:364-366

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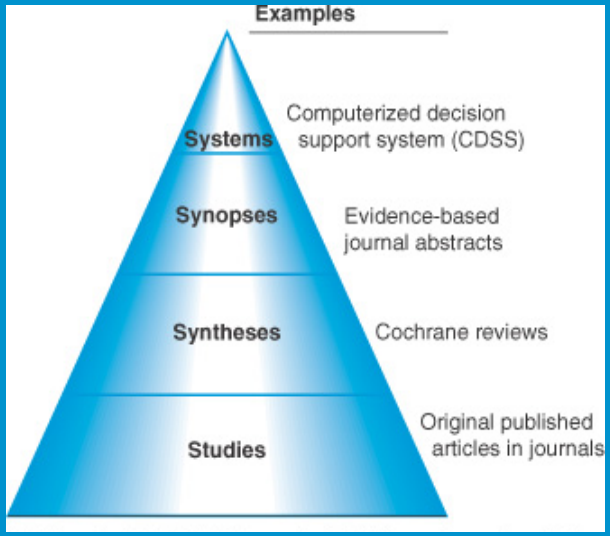
Evidence Based Medicine



Systematic reviews of RCT

Single RCT

N of 1 RCT

Observational study

Case reports

EBM - Caveats

- Methodological limitations of RCT
- Execution limitations of RCT
- Research Vs Clinical experience

RCT and Patient centric care

The paradox of clinical trials is that it is the best way to assess if an intervention works, but arguably is the worst way to assess who will benefit from it.

Mant D Lancet 1999;353:743-46

RCT and Patient centric care

Does it work for most patients?

Does it work for this patient?

Mant D Lancet 1999;353:743-46

RCT and Patient centric care

If the word **homogeneity** describes the goal of randomisation in a clinical trial, then the word **heterogeneity** describes the patient population we see in our practices

Lichter P L Am J Ophthalmol 2003; 136: 136-145

In a perfect world, every clinician would practice only evidence based medicine, but most real world medicine is practiced in areas not covered by clinical trials or meta-analyses.

Dr. Coleman

Personal significance: the third dimension

Kieran G Sweeney, Domhnall MacAuley, Denis Pereira Gray

We argue that doctors conduct an inner consultation with biomedical evidence before deciding how to apply it.

Although the **doctor's organiser** responds in an analytical, logical way ---,

the doctor's responder will act in a more intuitive manner,----

The responder is sensitive to internal messages determined by the doctor's feelings and emotion, and this affects the interpretation of information in a way that recognizes context, experience, apprehensions, failures, and successes.

Lancet 1998; 351: 134–36

Diode laser transsecleral Cyclophotocoagulation as a primary surgical treatment for primary open angle glaucoma.

Arch. Ophthalmol. 2001; 119: 345-350.

- The treatment as used in this study is free from serious complications, though a new complication of atonic pupil is reported.

- It is a rapid and easy to learn primary surgical procedure for POAG.[1]

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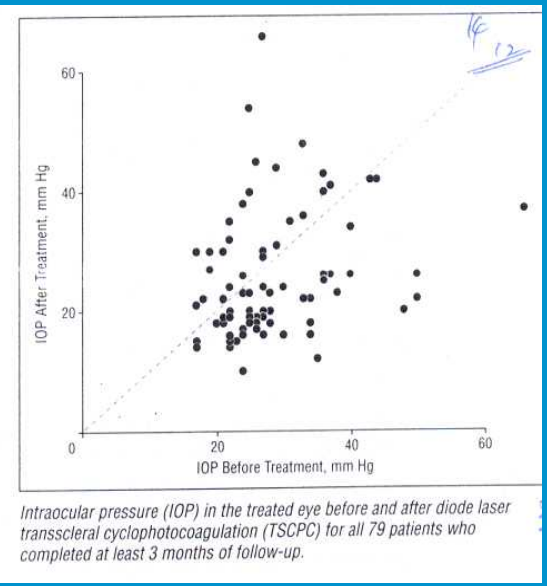

Intraocular pressure (IOP) in the treated eye before and after diode laser transscleral cyclophotocoagulation (TSCPC) for all 79 patients who completed at least 3 months of follow-up.

- The reported success rate is 48% (20% IOP reduction along with medications)
- The IOP increased form the base line in 32.9% (26/79) of the eyes.
- One out of 19 eyes (5%) with a vision better than 20/60 pre-operatively had vision decrease.
- Atonic pupil in 29% reported in this series is a new complication of this procedure

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Role of IOP in glaucoma management

❖ NTG	35% vs 14% 6 years	65%
❖ OHTS	9.5% Vs 4.4% 4 years	89.5%
❖ EMGT	76% Vs 59% 8 years	24%

PROs in Glaucoma in India

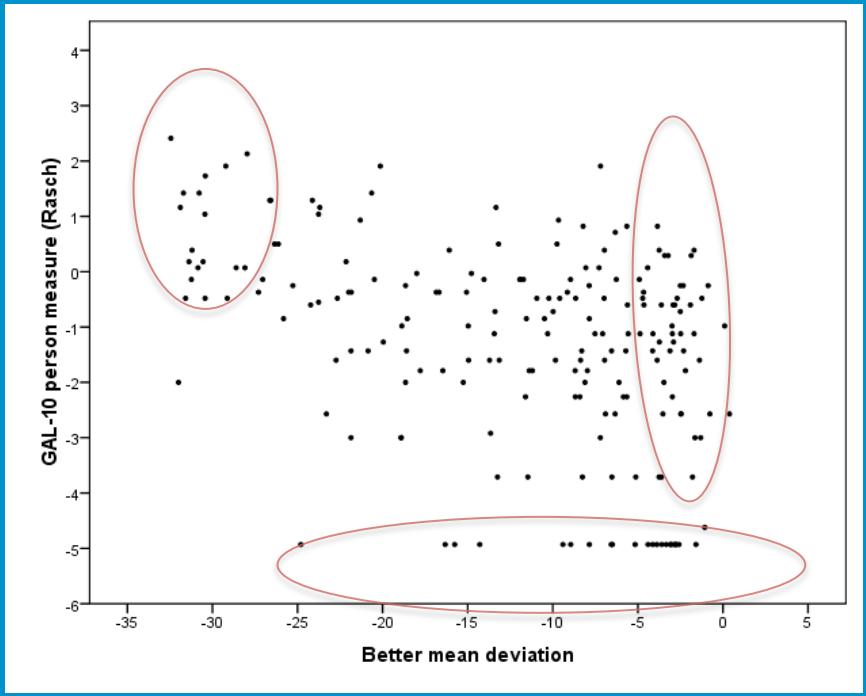
Impact of Glaucoma on Visual Functioning in Indians

Vijaya K. Gothwal,[1] Shailaja P. Reddy,[1] Seelam Bharani,[1] Deepak K. Bagga,[1] Rebecca Sumalini,[1] Chandra S. Garudadri,[2] Harsha L. Rao,[2] Sirisha Senthil,[2] Vanita Pathak-Ray,[2] and Anil K. Mandal[2]

Investigative Ophthalmology & Visual Science, September 2012, Vol. 53, No. 10

Glaucoma and Activity limitation
(GAL-10)

++ Activity limitation - -



Rasch person measure (r .0.40; P < 0.0001).

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  - Confidence intervals
  - Clinical Vs statistical significance
  - Absolute Vs Relative risk

- Confidence intervals
- Clinical Vs statistical significance
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Poll Question 3

Rate of serious complications for a new surgical procedure is 3.33% (1/30), compared to 13.33% (4/30) with the current standard of care Which of the following would you agree with.

A. I will adopt the new procedure as the complications are low.
B. I will adopt the new procedure, but would consider the increased costs.
C. May be the competence of the surgeons is not the same in both groups.
D. I feel that the differences are not significant

Uncertainty

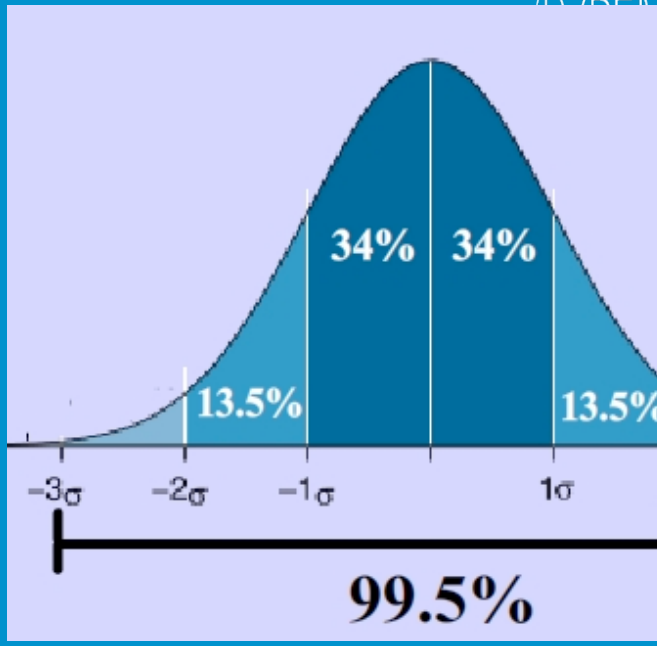
- We can never be absolutely certain
- We can "quantify" uncertainty
- Ask the question :
  - Is this uncertainty acceptable ?
- Confidence Intervals

Confidence Intervals

IOP in a group of patients: Mean

Success of a new surgical procedure: Proportion

95% CI = Mean ±1.96 * SD/ √n



Mean - 1 SD & mean + 1 SD will include about 68 % of the sample values

Mean – 2 SD& Mean + 2 SD will include about 95 % of the sample values

Mean – 3 SD & mean + 3 SD will include about 99 % of the sample values

95% CIs

Denominator	0% Compilation
10	26
25	11
50	6
75	4
100	3

If the complication rate is 1 in "n", you need to have a sample of 3n to encounter one complication

95% CIs

Denominator	0% Compilation	100% Success
10	26	74
25	11	89
50	6	94
75	4	96
100	3	97

If the complication rate is 1in "n", you need to have a sample of 3n to encounter one complication

95% CIs

Proportion	%	95% CI
1/10	10	1.7-40
1/15	6.6	1-30
1/20	5	0.9-24
1/25	4	0.7-20
1/30	3.3	0.5-15

Rate of serious complications for a new surgical procedure is 3.33% (1/30), compared to 13.33% (4/30) with the current standard of care

- Confidence intervals
- Clinical Vs statistical significance
- Absolute Vs Relative risk

Poll Question 4

The final IOP with medication A is statistically significantly (P=0.001) lower than that with medication B.
Which of the following would you agree with.

A. I will use the new drops in my practice.
B. I will use the new drops in my practice, but would consider the increased costs.
C. I need to worry about the side effects.
D. I need more information on the mount of pressure reduction

Example

- Study Hypothesis: Drug A lowers the Intraocular pressure more than Drug B (Timolol)
- Null Hypothesis: The IOP reduction by Drug A and Drug B are same

Experiment 1

- The final IOP with drug A is 14 mm Hg (P=0.01) and that with drug B is 17 mm Hg.
- There is 1 in 100 chance that the 3 mm Hg greater reduction by A as compared to B is by chance

Experiment 2

- The final IOP with drug A is 14 mm Hg (P=0.1) and that with drug B is 17 mm Hg
- There is 1 in 10 chance that the 3 mm HG greater reduction by A as compared to B is by chance

Experiment 3

- **The final IOP with drug A is statistically significantly (P=0.001) lower than that with drug B**
- **The final IOP with drug A is 14.5 mm Hg (P=0.001) and that with drug B is 15.25 mm Hg**
- ***There is 1 in 1000 chance that the 0.75 mm Hg greater reduction by A as compared to B is by chance***

P value

P value measures the "uncertainty" in the observation being reported. We need to know the "significance" of the observation as well as the "chance" or uncertainty involved in its measurement

- Confidence intervals
- Clinical Vs statistical significance
- Absolute Vs Relative risk

Poll Question 5

Ocular Hypertension Treatment Study (OHTS) reported a 50% risk reduction with medical treatment. Early manifest Glaucoma Trial (EMGT) reported a 17% risk reduction of medical treatment.
Which of the following would you agree with.

A. OHTS results show better protection as the risk reduction is more.
B. EMGT results show better protection as the subjects included had glaucoma
C. Cannot comapre as the inclusion criteria are different
D. EMGT results are better as the NNT is lower

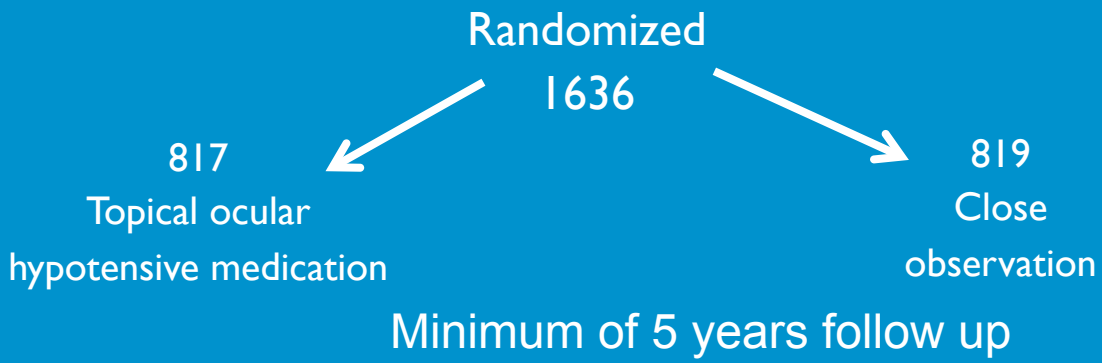
CLINICAL SCIENCES

The Ocular Hypertension Treatment Study

ARCHIVES EXPRESS

A Randomized Trial Determines That Topical Ocular Hypotensive Medication Delays or Prevents the Onset of Primary Open-Angle Glaucoma

Michael A. Kass, MD; Dale K. Heuer, MD; Eve J. Higginbotham, MD; Chris A. Johnson, PhD; John L. Keltner, MD; J. Philip Miller, AB; Richard K. Parrish II, MD; M. Roy Wilson, MD; Mae O. Gordon, PhD; for the Ocular Hypertension Treatment Study Group



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- Conversion to POAG: 9.5% Control group
- Conversion to POAG: 4.4 % Treated Group
- Risk reduction: 5.1%

Factors for Glaucoma Progression and the Effect of Treatment

The Early Manifest Glaucoma Trial

M. Cristina Leske, MD, MPH; Anders Heijl, MD, PhD; Mohamed Hussein, PhD; Bo Bengtsson, MD, PhD; Leslie Hyman, PhD; Eugene Komaroff, PhD; for the Early Manifest Glaucoma Trial Group

Total: 225

Treatment group: 129

Control group: 126

Factors for Glaucoma Progression and the Effect of Treatment

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M. Cristina Leske, MD, MPH; Anders Heijl, MD, PhD; Mohamed Hussein, PhD; Bo Bengtsson, MD, PhD; Leslie Hyman, PhD; Eugene Komaroff, PhD; for the Early Manifest Glaucoma Trial Group

Progression in control group: 62%

Progression in treated group: 45%

Risk reduction: 17%

CLINICAL SCIENCES

The Ocular Hypertension Treatment Study

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- Conversion to POAG: 9.5% Control group
- Conversion to POAG: 4.4 % Treated Group.
- Absolute Risk Reduction: 5.1 %
- Relative RR > 50%
- NNT: 20

Factors for Glaucoma Progression and the Effect of Treatment

The Early Manifest Glaucoma Trial

M. Cristina Leske, MD, MPH; Anders Heijl, MD, PhD; Mohamed Hussein, PhD; Bo Bengtsson, MD, PhD; Leslie Hyman, PhD; Eugene Komaroff, PhD; for the Early Manifest Glaucoma Trial Group

Progression in control group: 62%

Progression in treated group: 45%

ARR: 17% (4.6 to 28.4)

RRR: 27.5%

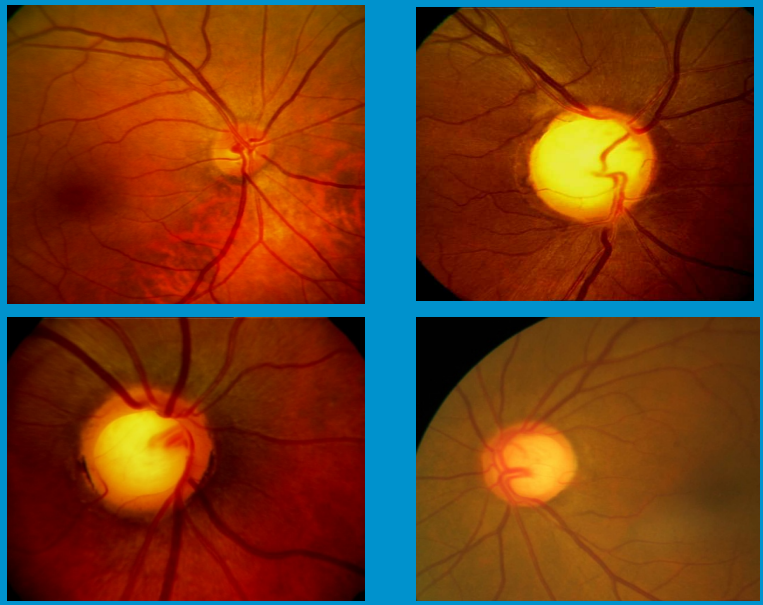
NNT: 6

Relative Risk vs Absolute Risk

- Treatment A mortality is 1%
- Treatment B mortality is 0.5%
- ARR = 1-0.5 = 0.5%
- RRR = 1-0.5/1 = 50%
- RRR could be 50% for (100 to 50; 50 to 25; 25 to 12.5)

Number Needed to Treat (NNT)

- 1/ Absolute risk reduction
- NNT of 1 is ideal
- Gives valuable practical information
- Can easily compare different treatment options



- CDR without disc size
- Point estimate without sample size
- RRR without ARR

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Thank you

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Excellence Equity Efficiency