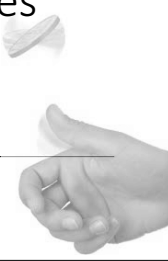


Know Your Chances

AN EVIDENCED BASED APPROACH TO
CLINICAL DECISION MAKING

Jordan Keith, OD, FAAO
Minneapolis, MN



Objectives

Define a structured question

Find the best evidence and apply it clinically

See through hype in medical news and advertisements

Eye Doctor Roles

- Vision
- Pain
- Rehabilitation
- Iatrogenic
- Systemic
- Emotional/Psych



“Science is a way to keep us from fooling ourselves”

-Richard Feynman, PhD

“The most dangerous words in medicine are ‘In my experience’”

-Mark Crislip, MD

Don't believe everything you think

“One has only to review the graveyard of discarded therapies to discover how many patients might have benefited from being assigned to a control group.”

-Thomas Chalmers, MD

Steps of EBM

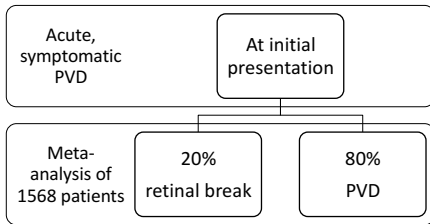
1. Formulate an answerable question
2. Find the best evidence
3. Critically appraise the evidence
4. Apply the evidence

“I see new flashes and floaters”

How often should I expect a RD?

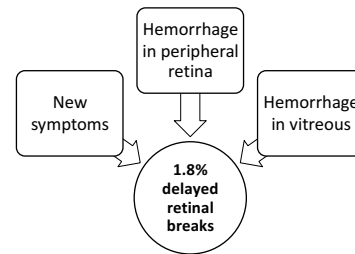
Which patients need further monitoring?

“I see new flashes and floaters”



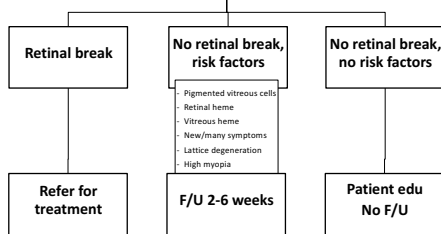
Coffee RE, et al. Am J Ophthalmol 2007;144(3):409-414

Follow-up?



Coffee RE, et al. Am J Ophthalmol 2007;144(3):409-414

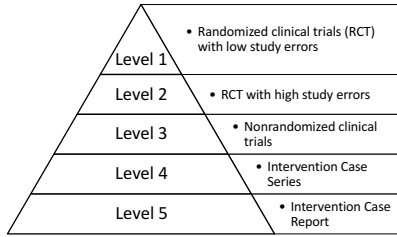
Acute symptomatic PVD



1. Good Questions Lead to Good Answers

- What is my diagnosis?
- What are the threats to vision?
- Are there treatments for this supported by evidence?
- If so, when do we treat?
- What do I do with the patient in my chair now?

2. Find the Best Evidence



3. Critical Appraisal

- Who (where) did the study?
- The goal of the study?
Outcomes used?
- How was the study carried out?
Blind? Double blind? Randomized?
Sample size (N) adequate?
- What did they find out?
- How does this affect us clinically?
Are the benefits greater than the risk?

Discrepancy between Results and Abstract Conclusions in Industry- vs Nonindustry-funded Studies Comparing Topical Prostaglandins

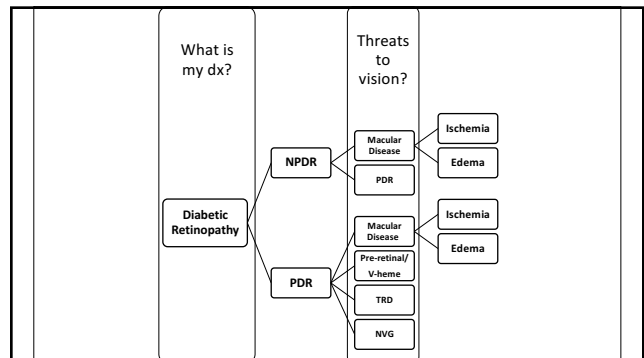
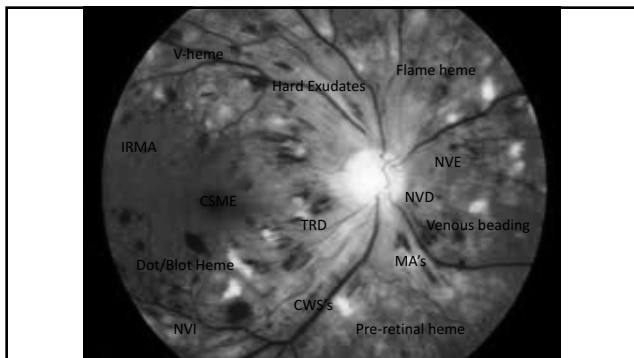
“The published abstract conclusion was not consistent with the results of the main outcome measure in 62% of the industry-funded studies compared with 0% of the nonindustry funded studies.”

“Twenty-four percent of the industry-funded publications had a statistically significant main outcome measure; however, 90% of the industry-funded studies had proindustry abstract conclusions.”

Alasbali T et al. Am J Ophthalmol 2009; 147(1): 33-38

4. Apply the Evidence: Which is Best?

- Treatment A** • Reduced the rate of blindness by 34%
- Treatment B** • Produced an absolute reduction in blindness of 0.06%
- Treatment C** • Increased patients' success rate from 99.82% to 99.88%
- Treatment D** • 1592 patients needed to be treated to prevent 1 case of blindness



Clinically Significant Macular Edema

CSME Retinal thickening within 500 microns of fovea

Exudate within 500 microns of fovea with adjacent thickening

Thickening of at least one disc area any part within one disc diameter of center of fovea

ETDRS. Ophthalmology. 1985; 103:1796-1806 ETDRS. Ophthalmology. 1987; 94: 761-774

Clinically Significant Macular Edema

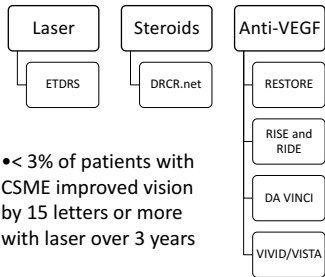
CSME Retinal *thickening* within 500 microns of fovea

Exudate within 500 microns of fovea with adjacent *thickening*

Thickening of at least one disc area any part within one disc diameter of center of fovea

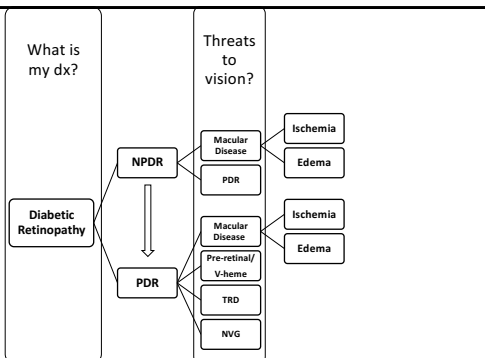
ETDRS. Ophthalmology. 1985; 103:1796-1806 ETDRS. Ophthalmology. 1987; 94: 761-774

Treatments for DME



“In patients with CSME, focal laser reduced the risk of moderate vision loss by 50%...”

ETDRS. Ophthalmology. 1985; 103:1796-1806 ETDRS. Ophthalmology. 1987; 94: 761-774



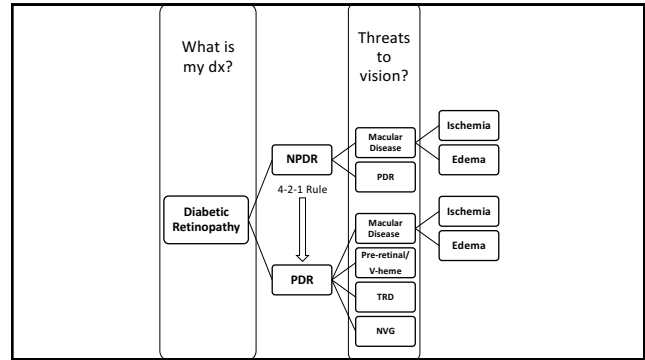
4-2-1 Rule: Raising the (Risk) Bar

- 4 Severe retinal hemorrhages in 4 quadrants
- 2 Venous beading in 2 quadrants
- 1 IRMA in 1 quadrant

NPDR → PDR in 1 Year

Mild	<ul style="list-style-type: none"> • 5% risk of progression to PDR
Moderate	<ul style="list-style-type: none"> • 15% risk of progression to PDR
Severe	<ul style="list-style-type: none"> • 52% risk of progression to PDR • Meets <u>ONE</u> criteria of 4-2-1 Rule
Very Severe	<ul style="list-style-type: none"> • 75% risk of progression to PDR • Meets <u>TWO</u> criteria of 4-2-1 rule

Klein R, et al. Arch Ophthalmol. 1984;102(4):527-532



High-Risk Characteristics

NVD ≥ ¼ disc area
 Any NVD or NVE with pre-retinal or vitreous heme

DRS. Am J Ophthalmol. 1976; 81:383-369 DRS. Ophthalmology. 1988; 88: 583-600

“In patients with HRC, PRP reduces the risk of profound vision loss by 50%...”

DRS. Am J Ophthalmol. 1976; 81:383-369 DRS. Ophthalmology. 1988; 88: 583-600

What Was the Original Risk?

No Tx	Tx	RRR	ARR	NNT
90%	45%	50%	45%	2
25%	12.5%	50%	12.5%	8
10%	5%	50%	5%	20
2/million	1/million	50%	0.0001%	1,000,000

“In patients with CSME, focal laser reduced the risk of moderate vision loss by 50%...”
 “In patients with HRC, PRP reduces the risk of profound vision loss by 50%...”

Which Treatment is Best?

Treatment A	<ul style="list-style-type: none"> • Reduced the rate of blindness by 34%
Treatment B	<ul style="list-style-type: none"> • Produced an absolute reduction in blindness of 0.06%
Treatment C	<ul style="list-style-type: none"> • Increased patients’ success rate from 99.82% to 99.88%
Treatment D	<ul style="list-style-type: none"> • 1592 patients needed to be treated to prevent 1 case of blindness

Treatment Studies

Relative Risk Reduction (RRR)

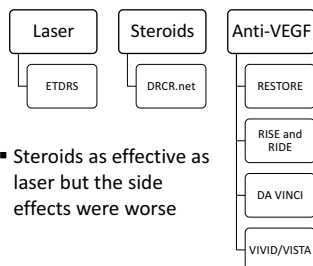
- Efficacy of treatments commonly reported this way in headlines/media/by pharmaceutical companies
- Use caution when reading this stat: can be misleading and commonly overstates the benefit

Absolute Risk Reduction (ARR)

- Much more meaningful clinically
- Tells us what % of patients benefited from the treatment

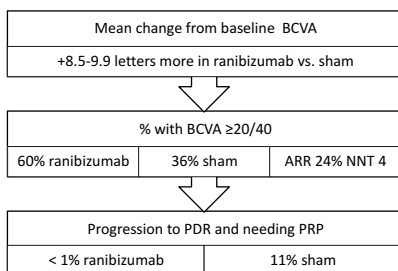
Number Needed to Treat (NNT)

Other Treatments for DME?



DR Clinical Research Network. Ophthalmology 2008;115(9):1447-1459

RISE and RIDE



RISE and RIDE. Ophthalmology 2012; 119: 789-801

Anti-VEGF Iatrogenic?

- Endophthalmitis = 1%
- Transient IOP increase
- Monthly injections

Patient Education

- Answer the question, "Why do I need yearly dilated eye exams?" every year even if they don't ask it.
- Help them understand their vascular disease.
- Encourage them to be intimately aware of their numbers (BS, HbA_{1c}, BP, cholesterol).
- Keep in mind number one indicator of complications is duration.
- You don't "know" how hard it is to control the disease unless you have lived with it.

Ocular HTN

- Threats to vision?
- Treatment?
- When/who do we treat?
 - Everyone?
 - No one?
 - Depends?

“Treating a patient with ocular hypertension reduces the risk of glaucoma by 50%...”

Kass MA et al. OHTS. Arch Ophthalmol. 2002;120:701-713

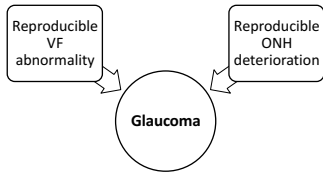
How Effective is Treatment?

No Tx	Tx	RRR	ARR	NNT
90%	45%	50%	45%	2
25%	12.5%	50%	12.5%	8
10%	5%	50%	5%	20
2/million	1/million	50%	0.0001%	1,000,000

“Treating a patient with ocular hypertension reduces the risk of glaucoma by 50%...”

Kass MA et al. OHTS. Arch Ophthalmol. 2002;120:701-713

What Were the Outcomes Used?



Surrogate endpoints vs. clinical endpoints

Kass MA et al. OHTS. Arch Ophthalmol. 2002;120:701-713

How Was Ocular HTN Defined?

- Age 40 – 80
- IOP 24-32 mmHg in one eye and 21-32 mmHg in the other
- Gonioscopically open angles
- 2 normal HVF tests each eye
- Normal ONHs

Kass MA et al. OHTS. Arch Ophthalmol. 2002;120:701-713

Treatment?

Reduction of IOP by 20% or more and reach an IOP of 24 or less

Kass MA et al. OHTS. Arch Ophthalmol. 2002;120:701-713

Treat everyone?

Treat no one?

It depends?

iatrogenic to Treating Everyone?

\$20/bottle x 12 months x 5 years x 20 NNT =

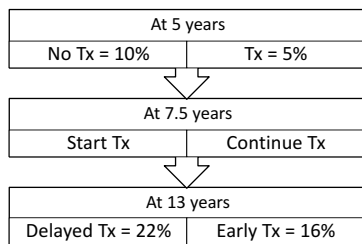
\$24,000

% of patients we didn't help = 95%

% of complication = 100%

Treat no one?

Is there penalty in delaying treatment?

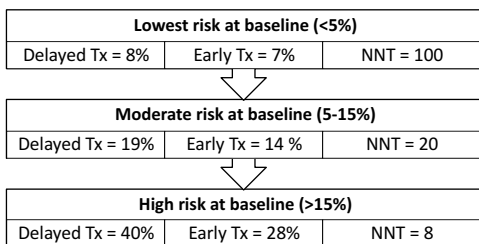


Kass MA et al. OHTS. Arch Ophthalmol. 2002;120:701-713
Kass MA et al. OHTS. Arch Ophthalmol. 2010;128(3):276-287

It Depends?

- Age, health status, patient preference
- Baseline risk determined by OHTS/EGPS calculator?
 - Age
 - IOP
 - CCT
 - PSD
 - C/D

After 13 years % developing glaucoma based on initial risk



Kass MA et al. OHTS. Arch Ophthalmol. 2010;128(3):276-287

What Do I Do With this Patient?

- Assess risk
 - Age, IOP, CCT, C/D
- Testing
 - HVF, ONH/RNFL analysis, stereo ONH photos, gonioscopy, pachymetry

Testing

"Medicine is a science of uncertainty and an art of probability"
 -Sir William Osler, MD

Sensitivity vs. Specificity

Positive Predictive Value vs. Negative Predictive Value

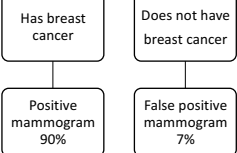


Riddle

Probability of breast cancer = 0.8%

Mammography screening program of 40-50 yo women with no symptoms

What is the probability that a positive mammogram is actually breast cancer?



0.8% with breast cancer
 90% sensitivity
 93% specificity

1000

8 (+) cancer

992 (-) cancer

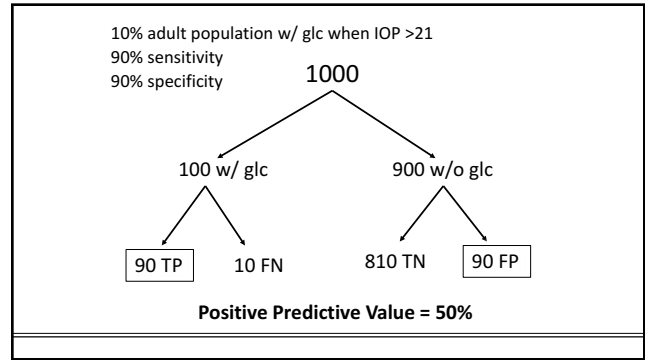
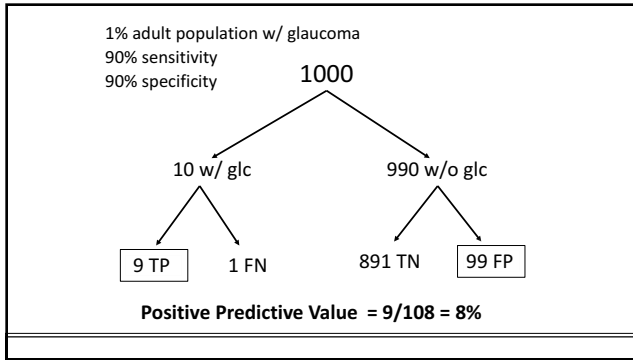
7 TP

1 FN

922 TN

70 FP

Positive Predictive Value = $7/77 = 9\%$

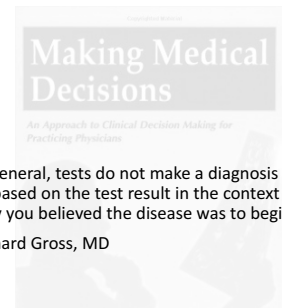


Testing

Sensitivity vs. Specificity

- Efficacy of tests commonly reported this way
- Clinically not valuable information in isolation
- Usefulness of test depends on initial risk of population

More judicious testing leads to fewer false positives and higher positive predictive value



“In general, tests do not make a diagnosis – you do, based on the test result in the context of how likely you believed the disease was to begin with.”

-Richard Gross, MD

“Because there is no need to show that an instrument has any real value in disease detection or management before it is brought to market, we have become enamored with sophisticated analysis algorithms and colorful printouts before we have studies that show what the results of the tests mean. This approach is fueled, of course, by economic interests. Industry is motivated to create product and we [ophthalmologists] provide the key opinion leaders to drive the use of what is developed . . .”

-Paul Lichter, MD

Lichter P. Glaucoma Volume 1: Medical Diagnosis & Therapy. London: Saunders/Elsevier; 2009:506

“. . . Cynical as it seems, these devices belong in the laboratory, before they are marketed as being of value and before billing codes are established for their use, which simply drive up the costs of care without making any impact whatsoever on the critical outcome in glaucoma—preservation of vision related QOL.”

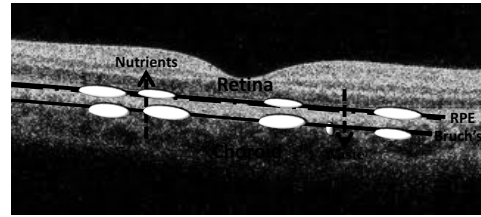
-Paul Lichter, MD

Lichter P. Glaucoma Volume 1: Medical Diagnosis & Therapy. London: Saunders/Elsevier; 2009:506

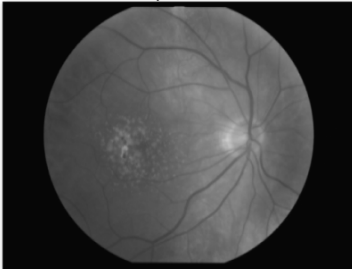
Patient Education

- You don't know your patient's risk for glaucoma.
- Help them understand what the risk is for people like them.
- Empower patients to make the decision to treat or not to treat on their own.
- Acknowledge their fear and help them understand why that won't happen.
- Have a philosophy for treating glaucoma.

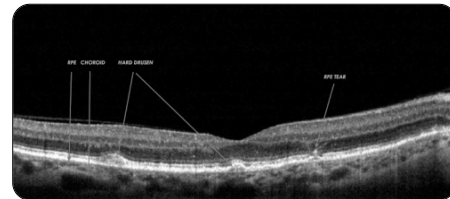
Dry ARMD



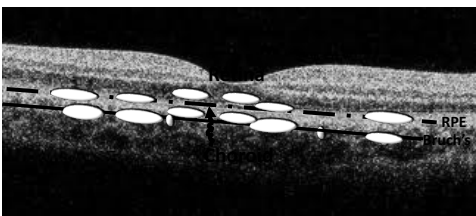
Dry AMD



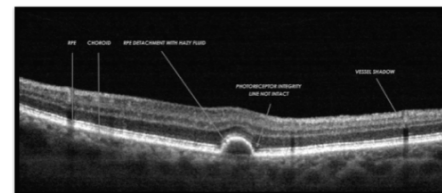
Dry AMD



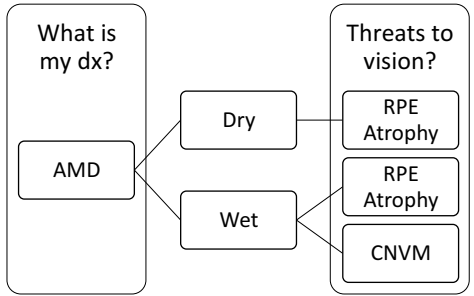
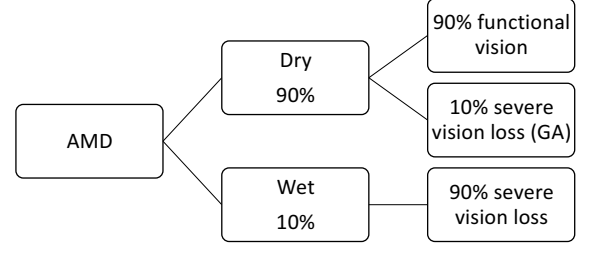
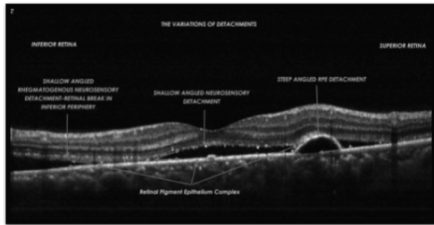
Wet ARMD



Wet AMD



Wet AMD



MARINA for CNVM

20/40 BCVA or better		
Lucentis = 40%	Sham = 11%	NNT = 3.5
↓		
Lost ≤ 3 lines BCVA from baseline		
Lucentis = 94%	Sham = 62%	NNT = 3
↓		
Improved ≥ 3 lines BCVA from baseline		
Lucentis = 30%	Sham = 5%	NNT = 4

Rosenfeld PJ, et al. N Engl J Med 2006;355:1419-31

Iatrogenic?

- Endophthalmitis = 1%
- Transient IOP increase
- Monthly injections

“Despite the lack of convincing evidence, the marketing and use of antioxidants and zinc in eye-targeted formulations has become common practice.”

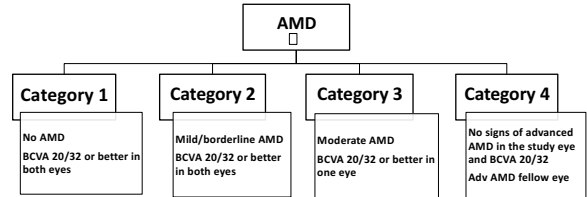
- AREDS I

AREDS Research Group. Arch Ophthalmol. 2001;119:1417-1436

“Taking AREDS I supplements reduces the risk of AMD progression by 25%...”

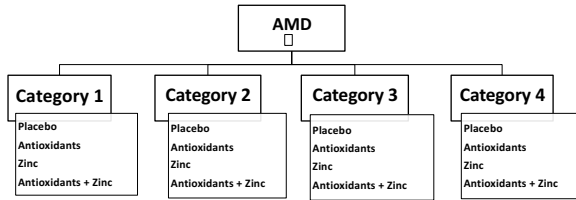
AREDS Research Group. Arch Ophthalmol. 2001;119:1417-1436

AREDS 1



AREDS Research Group. Arch Ophthalmol. 2001;119:1417-1436

AREDS 1



AREDS Research Group. Arch Ophthalmol. 2001;119:1417-1436

Outcome: Progression to ADV AMD at 5 years

Probability by Category			
Category 1	Category 2	Category 3	Category 4
0.004%	1.3%	18%	43%

Probability by Treatment (Placebo vs. Treatment)			
Category 1	Category 2	Category 3	Category 4
Data not evaluated	No sig difference	Data not reported	Data not reported

Combined categories 3 AND 4			
Placebo	Antioxidants + Zinc	ARR	NNT
28%	20%	8%	12.5

AREDS Research Group. Arch Ophthalmol. 2001;119:1417-1436

Outcome: 15-letter decrease from baseline at 5 years

Probability by Treatment (Placebo vs. Treatment)			
Category 1	Category 2	Category 3	Category 4
Data not evaluated	No sig difference	Data not reported	Data not reported

Combined categories 3 AND 4			
Placebo	Antioxidants + Zinc	ARR	NNT
29%	23%	6%	17

AREDS Research Group. Arch Ophthalmol. 2001;119:1417-1436

Iatrogenic?

$$\$142/\text{year} \times 5 \text{ years} \times 17 \text{ NNT} =$$

$$\mathbf{\$12,070}$$

% of patients we didn't help = 92-94%

% of complication = 100%

iatrogenic?

“We do not know the long-term health effects of supplementation with these high doses of vitamins and minerals”

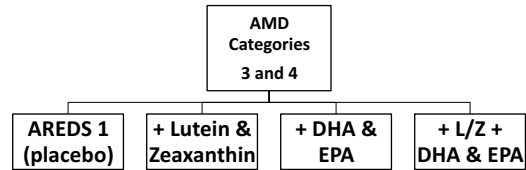
-AREDS I

AREDS Research Group. Arch Ophthalmol. 2001;119:1417-1436

“Taking AREDS 2 supplements reduces the risk of AMD progression by 26%...”

AREDS 2 Research Group. JAMA. 2013;309(19):E1-11

AREDS 2



AREDS 2 Research Group. JAMA. 2013;309(19):E1-11

AREDS 2

Outcome: Progression to ADV AMD at 5 years			
AREDS 1 31%	+ L/Z 29%	+ DHA & EPA 31%	+ L/Z & DHA/EPA 30%
Outcome: Moderate vision loss (≥ 3 lines of acuity) from baseline			
AREDS 1	No additional effect	No additional effect	No additional effect
Subgroup analysis: lowest dietary consumption of Lutein/Zeaxanthin			
HR 0.74 (95% CI, 0.59-0.94; P=(0.01)			

AREDS 2 Research Group. JAMA. 2013;309(19):E1-11

What Do I Do With My Patient?

- Patient Education: this is common and most don't go blind
- Lifestyle changes (diet, smoking)
- Pros/cons supplements vs. no supplements
- Home Amsler grid?



Zaidi FH, et al. Eye 2004;18:503-508

“Even when cure is impossible, healing is not necessarily impossible. While medical science has limits, hope does not.”

-Bernard Lown, MD

“To cure sometimes, to relieve often, to comfort always”

-Edward Trudeau, MD

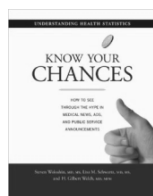
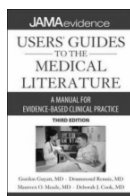
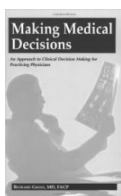
Objectives

Define a structured question

Find the best evidence and apply it clinically

See through hype in medical news and advertisements

Resources



Contact Information
Jordan.Keith@eyecarecenters.net