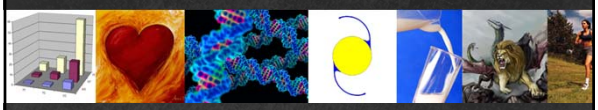
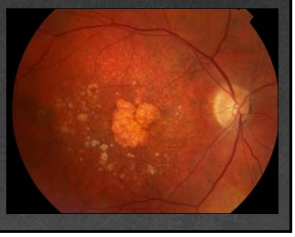


What's New in AMD

Rick Trevino, OD, FAAO
Rosenberg School of Optometry
University of the Incarnate Word

What's New in AMD

- Online notes
  - richardtrevino.net
- Email me
  - rctrevin@uiwtx.edu
- Disclosures
  - None

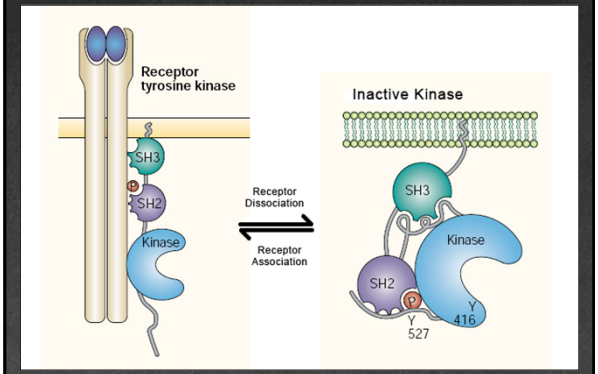


What's New in AMD

10. Drug Pipeline

Topical Pazopanib

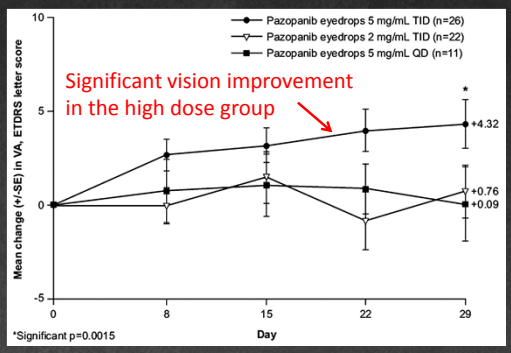
- Topical eye drop for exudative AMD
- Pazopanib is a receptor tyrosine kinase inhibitor that targets VEGF, platelet-derived growth factor, and c-kit receptors
- Used extensively in cancer therapy
- Safety of topical pazopanib has been established in Phase 1 clinical trials



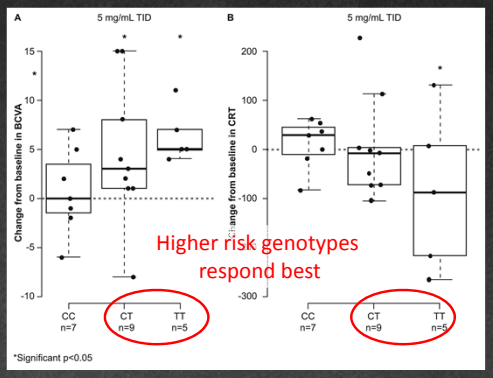
Topical Pazopanib

- Danis (2014)
  - Multicenter phase 2a RCT of 70 patients with subfoveal CNV secondary to AMD
  - Topical pazopanib monotherapy for 28 days
  - Vision improved in the high-dose subgroup and in patients with high-risk genotypes
  - Macular thickness decreased only in patients with high-risk genotypes
  - Conclusion: "Further investigation warranted"

Danis, et al. Br J Ophthalmol. 2014;98:172



Danis, et al. Br J Ophthalmol. 2014;98:172



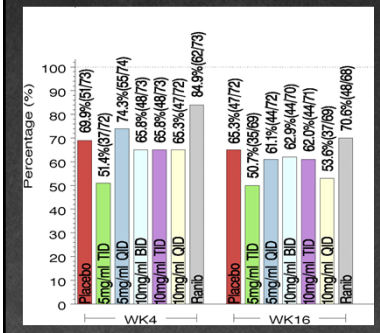
Danis, et al. Br J Ophthalmol. 2014;98:172

Topical Pazopanib

- Csaky (2015)
  - Multicenter, 1yr, Phase 2b RCT of 510 patients with subfoveal CNV secondary to AMD
  - Lucentis given as-needed to patients taking drops
  - Pazopanib did not significantly reduce the need for Lucentis injections (primary outcome)
  - Genotype did not have an effect
  - Conclusion: Pazopanib is not effective in reducing treatment burden of Lucentis

Csaky, et al. Ophthalmology 2015;122:579

Percent of patients receiving an injection at 4 & 16 weeks

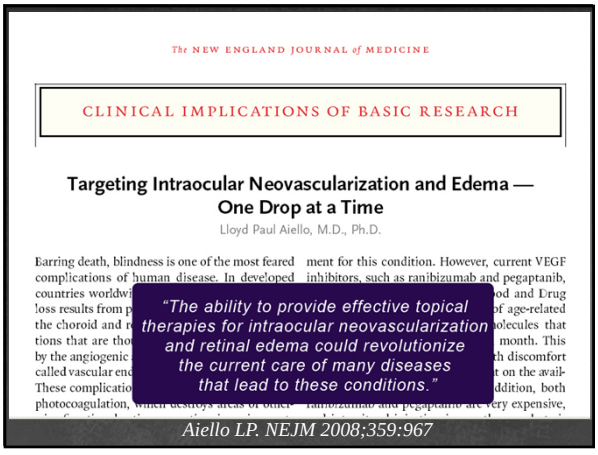


Placebo: Lucentis PRN + saline drops

Ranib: Lucentis PRN

All other bars are Lucentis PRN + pazopanib

Csaky, et al. Ophthalmology 2015;122:579



Aiello LP. NEJM 2008;359:967

What's New in AMD

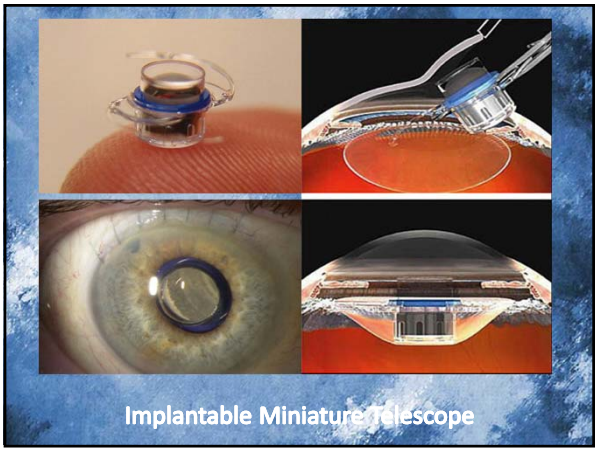
9. Implantable Miniature Telescope
10. Drug Pipeline

Implantable Miniature Telescope

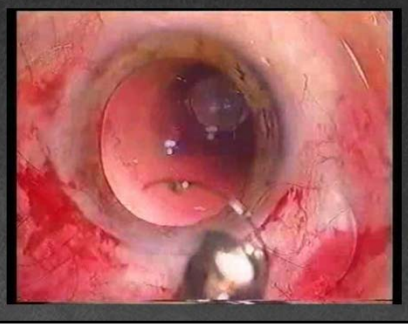
- The FDA approved the Implantable Miniature Telescope (IMT) in 2010 for patients 75yrs and older with stable severe-to-profound vision impairment (20/160 to 20/800) caused by bilateral end-stage AMD
- Marketed as CentraSight

CentraSight
A New Vision for End-Stage AMD

Implantable Miniature Telescope

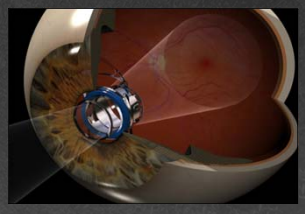


Implantable Miniature Telescope



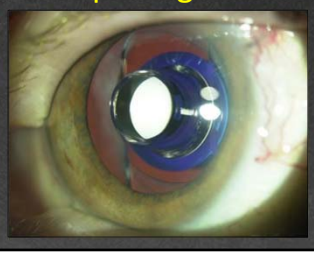
Implantable Miniature Telescope

- Implanted into one eye only (typically the non-dominant or poorer seeing eye)
- Two models available 2.2x or 2.7x
- Generates a 20° to 24° FOV

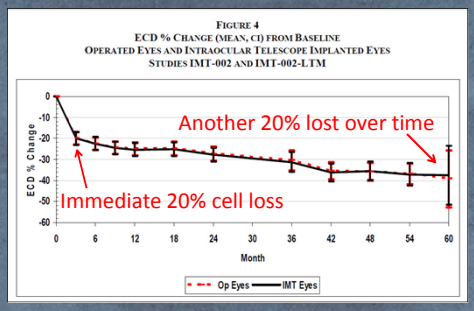


Implantable Miniature Telescope

- Most common adverse event is persistent vision-impairing corneal edema
- 9.2% over 5yrs



Endothelial cell loss following implantation of IMT leads to vision-impairing corneal edema in about 9% of patients

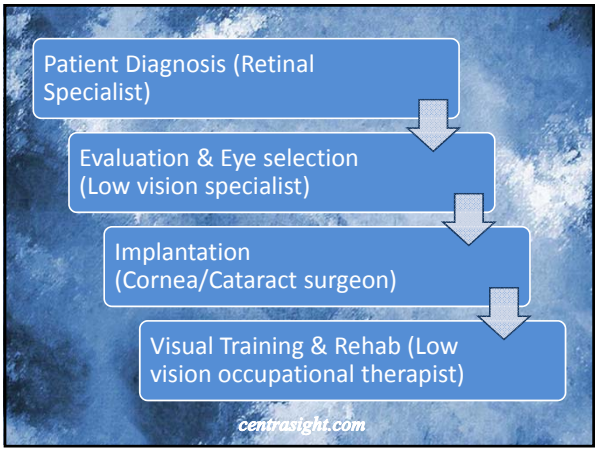


Implantable Miniature Telescope Professional Use Information, FDA-approved product labeling.

Implantable Miniature Telescope

- Partial contraindications list
  - Tx for CNV within the past 6 mos
  - Anterior chamber depth (ACD) <3.0 mm
  - Myopia > 6.0 D or hyperopia > 4.0 D
  - Presence of corneal guttata
  - Failure meet the minimum age (75 yrs), visually significant cataract and endothelial cell density requirements

Implantable Miniature Telescope Professional Use Information, FDA-approved product labeling.



Implantable Miniature Telescope

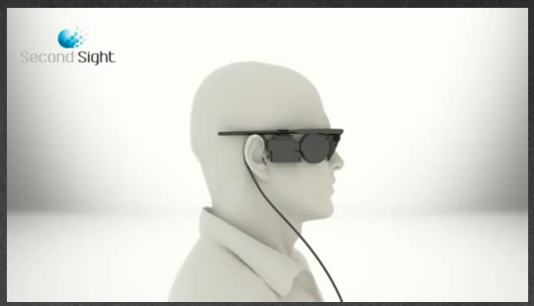
- Key Points
  - Supplements conventional low vision aids for end-stage bilateral AMD
  - Potential for significant surgical complications and post-operative adverse events
  - Success hinges on selection of candidates most likely to succeed with IMT and are at lowest risk of adverse events

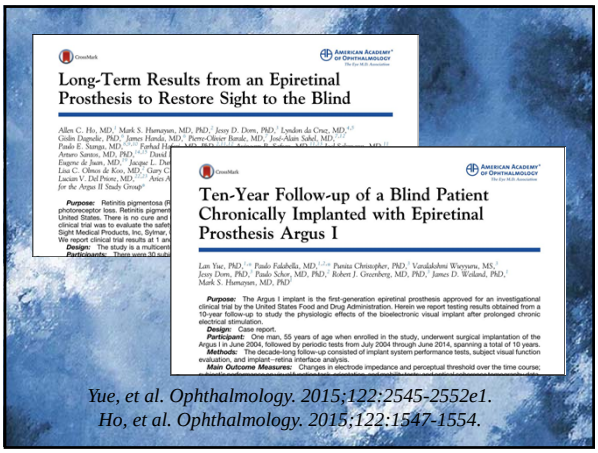
Runner-Up

Retinal Prosthesis

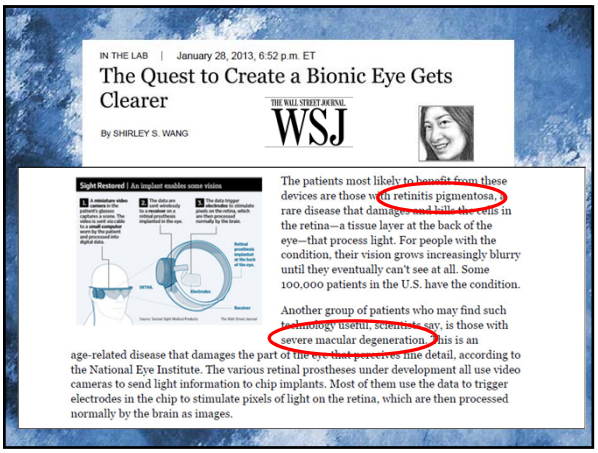
FDA grants Argus II retinal prosthesis from Second Sight, Inc "compassionate use" status for severe end-stage RP

Retinal Prosthesis





Yue, et al. Ophthalmology. 2015;122:2545-2552e1.
Ho, et al. Ophthalmology. 2015;122:1547-1554.



What's New in AMD

8. Aspirin
9. Implantable Miniature Telescope
10. Drug Pipeline

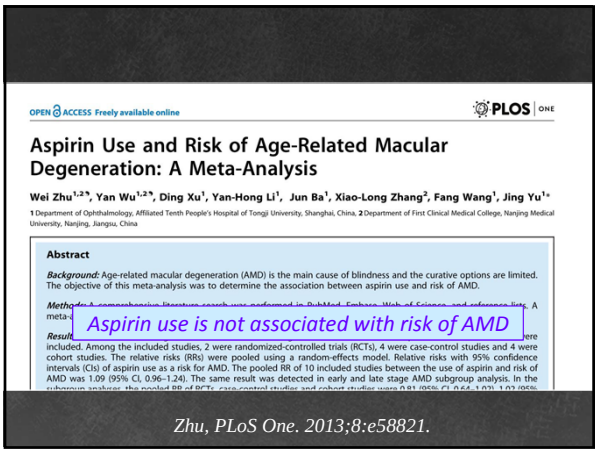
Aspirin & AMD

- Aspirin for the primary prevention of disease
  - Prevent of cardiovascular events, reduce the risk of some cancers, reduced risk of Alzheimer's disease
  - Approximately 36% of adults take aspirin regularly for primary prevention of disease
- Adverse effects of aspirin
  - Gastrointestinal hemorrhage, worsen hypertension, renal failure, aggravate asthma, hemorrhagic stroke
  - Each year 16,500 deaths are related to aspirin and NSAID use

Seshasai SR, et al. Arch Intern Med. 2012;172:209-16

Aspirin & AMD

Harmful Effect	*No Effect*	*Protective Effect*
Feman (1972)	MPS Group (1986)	Christen (2001)
Bloome (1978)	MPS Group (1990)	Christen (2009)
Kingham (1988)	Klein (1991)	
Lewis (1988)	Hirvela (1996)	
AREDS (2000)	Klein (2001)	
Klein (2012)	Douglas (2007)	
de Jong (2012)	Rudnicka (2010)	
Cheung (2013)		
Liew (2013)		



OPEN ACCESS Freely available online

PLOS ONE

Aspirin Use and Risk of Age-Related Macular Degeneration: A Meta-Analysis

Wei Zhu[1,2*], Yan Wu[1,2*], Ding Xu[1], Yan-Hong Li[1], Jun Ba[1], Xiao-Long Zhang[2], Fang Wang[1], Jing Yu[1*]

1 Department of Ophthalmology, Affiliated Tenth People's Hospital of Tongji University, Shanghai, China, 2 Department of First Clinical Medical College, Nanjing Medical University, Nanjing, Jiangsu, China

Abstract

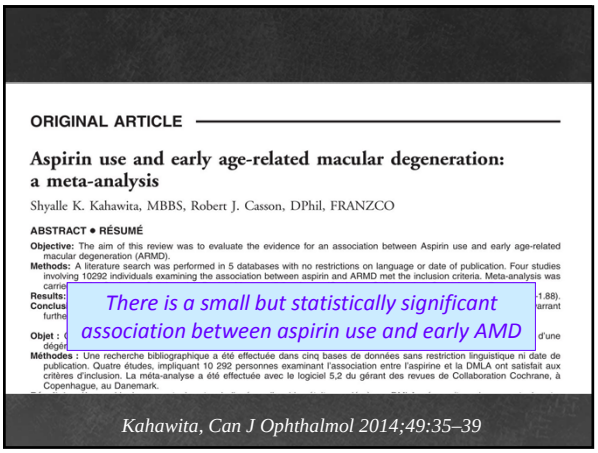
Background: Age-related macular degeneration (AMD) is the main cause of blindness and the curative options are limited. The objective of this meta-analysis was to determine the association between aspirin use and risk of AMD.

Methods: A comprehensive literature search was performed in PubMed, Embase, Web of Science, and reference lists. A meta-

Results: included. Among the included studies, 2 were randomized-controlled trials (RCTs), 4 were case-control studies and 4 were cohort studies. The relative risks (RRs) were pooled using a random-effects model. Relative risks with 95% confidence intervals (CIs) of aspirin use as a risk for AMD. The pooled RR of 10 included studies between the use of aspirin and risk of AMD was 1.09 (95% CI, 0.96–1.24). The same result was detected in early and late stage AMD subgroup analysis. In the subgroup analyses, the pooled RR of RCTs, case-control studies and cohort studies were 0.81 (95% CI, 0.64–1.02), 1.02 (95%

Aspirin use is not associated with risk of AMD

Zhu, PLoS One. 2013;8:e58821.



ORIGINAL ARTICLE

Aspirin use and early age-related macular degeneration: a meta-analysis

Shyalle K. Kahawita, MBBS, Robert J. Casson, DPhil, FRANZCO

ABSTRACT • RÉSUMÉ

Objective: The aim of this review was to evaluate the evidence for an association between Aspirin use and early age-related macular degeneration (ARMD).

Methods: A literature search was performed in 5 databases with no restrictions on language or date of publication. Four studies involving 10292 individuals examining the association between aspirin and ARMD met the inclusion criteria. Meta-analysis was carried

Results:

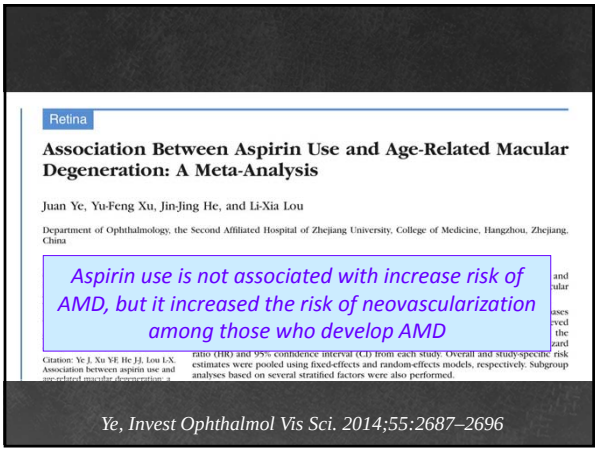
Conclus further

Objet : dégé

Méthodes : Une recherche bibliographique a été effectuée dans cinq bases de données sans restriction linguistique ni date de publication. Quatre études, impliquant 10 292 personnes examinant l'association entre l'aspirine et la DMLA ont satisfait aux critères d'inclusion. La méta-analyse a été effectuée avec le logiciel 5,2 du gérant des revues de Collaboration Cochrane, à Copenhague, au Danemark.

There is a small but statistically significant association between aspirin use and early AMD

Kahawita, Can J Ophthalmol 2014;49:35–39



Retina

Association Between Aspirin Use and Age-Related Macular Degeneration: A Meta-Analysis

Juan Ye, Yu-Feng Xu, Jin-Jing He, and Li-Xia Lou

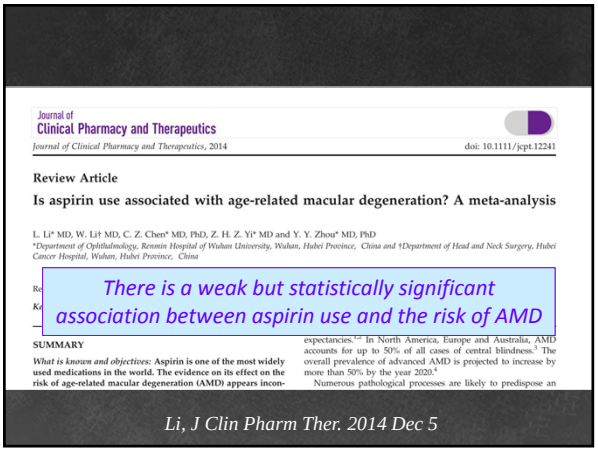
Department of Ophthalmology, the Second Affiliated Hospital of Zhejiang University, College of Medicine, Hangzhou, Zhejiang, China

Aspirin use is not associated with increase risk of AMD, but it increased the risk of neovascularization among those who develop AMD

Citation: Ye J, Xu YF, He JJ, Lou LX. Association between aspirin use and age-related macular degeneration: a

ratio (HR) and 95% confidence interval (CI) from each study. Overall and study-specific risk estimates were pooled using fixed-effects and random-effects models, respectively. Subgroup analyses based on several stratified factors were also performed.

Ye, Invest Ophthalmol Vis Sci. 2014;55:2687–2696



Journal of Clinical Pharmacy and Therapeutics

Journal of Clinical Pharmacy and Therapeutics, 2014 doi: 10.1111/jcpt.12241

Review Article

Is aspirin use associated with age-related macular degeneration? A meta-analysis

L. Li* MD, W. Li† MD, C. Z. Chen* MD, PhD, Z. H. Z. Yi* MD and Y. Y. Zhou* MD, PhD

**Department of Ophthalmology, Renmin Hospital of Wuhan University, Wuhan, Hubei Province, China and †Department of Head and Neck Surgery, Hubei Cancer Hospital, Wuhan, Hubei Province, China*

There is a weak but statistically significant association between aspirin use and the risk of AMD

SUMMARY

What is known and objectives: **Aspirin is one of the most widely used medications in the world. The evidence on its effect on the risk of age-related macular degeneration (AMD) appears incon-**

expectancies.[1,2] In North America, Europe and Australia, AMD accounts for up to 50% of all cases of central blindness.[3] The overall prevalence of advanced AMD is projected to increase by more than 50% by the year 2020.[4]

Numerous pathological processes are likely to predispose an

Li, J Clin Pharm Ther. 2014 Dec 5

Aspirin & AMD

- Key Points
  - Inconsistent link between aspirin and AMD
  - No change recommended for those taking aspirin for secondary prevention of CVD
  - Educate users with strong risk factors for neovascular AMD about risk
  - No evidence that discontinuation of long-term aspirin use will reduce risk of AMD

What's New in AMD

7. Lifestyle
8. Aspirin
9. Implantable Miniature Telescope
10. Drug Pipeline

Lifestyle & Behavioral Factors

What's
Good for the Heart
Is also
Good for the Eye!

Don't smoke
Lose weight
Exercise regularly

Lifestyle & Behavioral Factors

- Smoking
  - Smoking is the most significant modifiable risk factor for AMD
  - Exposure to environmental (second-hand) smoke has not been associated with AMD
  - Gopinath (2015): No significant difference in 10yr smoking cessation rates between smokers with and without AMD (AMD: 25%, non-AMD: 20%)

Gopinath, et al. PLOS One 2015;10:e0122548

Warning label on cigarettes sold in Australia

Smoking Cessation

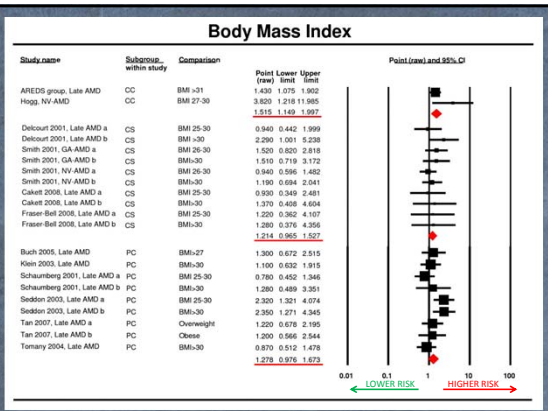
- All physicians, regardless of specialty, are well placed to provide basic information about the harm of smoking, the benefits of cessation and available treatments.
- Very Brief Advice (VBA)
  - Lasting less than 30 s
  - Ask (smoking status), Advise (to stop), Act (offer help)

Raupach, et al. Nicotine Tob Res. 2014:1-4.

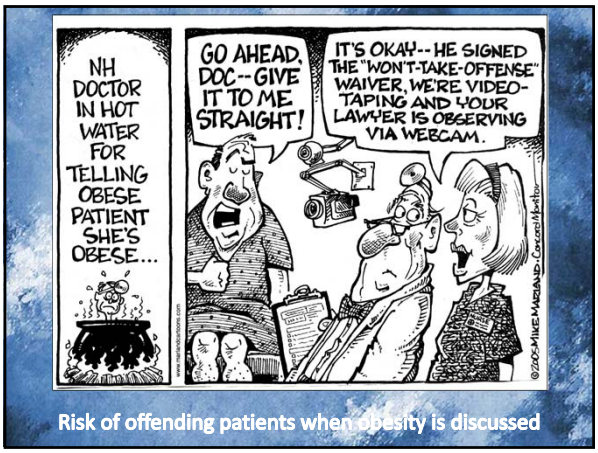
Lifestyle & Behavioral Factors

- Obesity (Munch, 2013)
  - Cross-sectional study of 888 subjects aged 30 to 60 years in Denmark
  - Large waist circumference increased the risk for large drusen in men
  - Average waist circumference reduced these odds in women
  - Being physically active ≥7hrs/wk decreased the risk of large drusen compared to 0-2 hrs/wk

Munch, et al. IOVS 2013;54:3932



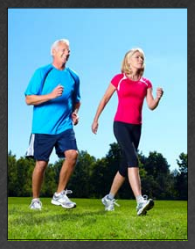
Chakravarthy (2010): Meta-analysis of studies assessing risk of advanced AMD (combined atrophic and exudative) associated with BMI.



Risk of offending patients when obesity is discussed

Lifestyle & Behavioral Factors

- Exercise (Gopinath, 2014)
  - Population-based study of 3654 adults in Australia (BMES)
  - Among persons ≥75yo, the most physically active (top 33%) compared to the least (bottom 33%) were 79% less likely to develop late AMD over 15yrs
  - After adjusting for sex, BMI, smoking, fish consumption, and WBC count, this association was no longer significant



Gopinath, et al. IOVS. 2014;55:7799

Lifestyle & Behavioral Factors

- Wang (2014)
  - Population-based study of 1680 persons in Australia (Australian Heart Eye Study)
  - Severity of coronary stenosis and the presence of stenotic lesions were independently associated with early AMD.
  - Participants in the highest versus lowest tertile of Gensini scores were twice as likely to have early AMD
  - Individuals with CAD are at higher risk for AMD.

Wang, et al. Br J Ophthalmol. 2014;0:1-6 [Epub before print]

Lifestyle & Behavioral Factors

What's
Good for the Heart
Is also
Good for the Eye!

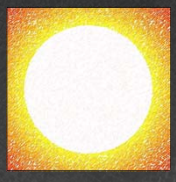
Don't smoke
Lose weight
Exercise regularly

What's New in AMD

6. Sunlight
7. Lifestyle
8. Aspirin
9. Implantable Miniature Telescope
10. Drug Pipeline

Sunlight

- Photochemical damage occurs when low wavelength light is absorbed by photoreactive pigments in the retina, such as lipofuscin, causing release of reactive oxygen species
- Speculate that chronic exposure to low wavelength light may overwhelm normal defense and repair mechanisms
- Inconsistent association with AMD risk



Chalam KV, et al. Eye & Contact Lens. 2011;37:225–232

Sunlight

- Delcourt (2014)
  - Population-based study of 963 residents of France (including former residents of North Africa)
  - Lifetime ambient UV exposure was calculated
  - Individuals with the highest and lowest exposure levels were at increased risk of early AMD compared with medium exposure

Delcourt, et al. IOVS 2014;55:7619

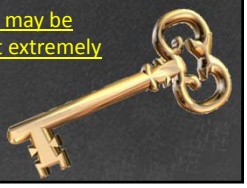
Sunlight

- Klein (2014)
  - Population-based, logintudinal study of 4926 adults in USA over 20yrs
  - Eye and hair color associated with risk of retinal pigment abnormalities (AMD precursor)
    - Gray-blue vs green-brown eyes: HR = 1.36
    - Blond-red vs brown-black: HR = 1.42
  - Conclude that light eye or hair color combined with sunlight exposure is associated with increased risk of developing early AMD

Klein, et al. IOVS 2014;55:5855

Sunlight

- Key Points
  - Strong observational evidence that high sunlight exposure can increase AMD risk
  - Sunlight risk is greatest among persons with light colored hair and eyes
  - Moderate sunlight exposure may be associated with less risk that extremely high or low exposure



Runner-Up

Cataract Surgery

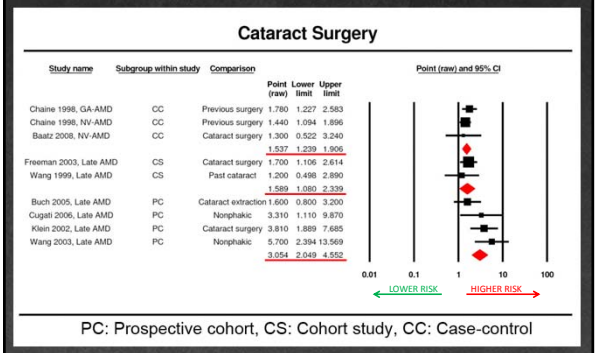
- Cataract Surgery
  - The adult lens absorbs nearly 100% of light below 400nm
  - Cataract surgery results in increased exposure to short-wavelength light and this may increase the risk of photochemical damage to the retina
  - Inconsistent association with AMD risk

Bockelbrink, et al. Surv Ophthalmol 2008;53:359

Cataract Surgery

- Kessel (2015)
  - Meta-analysis of 2 RCT and 2 case-control studies on effect of cataract surgery in pts with existing AMD
  - Surgery significantly improved visual acuity
  - Surgery did not increase risk of progression to wet AMD within 6-12 months
  - Recommend patients with AMD and visually significant cataract are offered cataract surgery

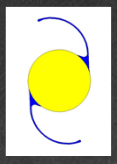
Kessel, et al. Acta Ophthalmol 2015;0:1 [Epub before print]



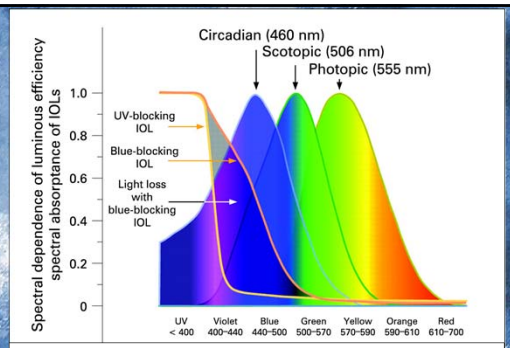
Chakravarthy (2010): Meta-analysis of studies assessing risk of advanced AMD (atrophic and exudative) associated with cataract surgery.

Cataract Surgery

- Blue-blocking IOL Controversy
  - All modern IOLs filter UV radiation below 400nm but most do not filter any visible light
  - Blue-blocking IOLs are designed to simulate transmission characteristics of the adult non-cataractous human lens offering theoretical AMD protection



Wong, et al. Int Ophthalmol. 2011;31:73–82



Concerns have been raised that blue-blocking IOLs attenuate visual performance under scotopic conditions, have undesirable effects on color perception, and disrupt circadian entrainment

Turner (2008): Spectral sensitivity of photopic, scotopic and circadian (melatonin suppression) photoreception

Cataract Surgery

- Lavric (2014)
  - Evaluate visual function in 30pts without AMD with a UV-blocking IOL in one eye and a blue-blocking IOL in fellow eye ≥2yrs prior to study
  - VA was marginally better in the blue-blocker eye
  - No significant difference in color vision, contrast sensitivity, or subjective visual quality (VFQ-25)
  - There were no significant difference in macular status between the IOL groups

Lavric, et al. Optom Vis Sci. 2014;91:1348

Cataract Surgery

- Blue-blocking IOL Controversy
  - There is currently no evidence of any clinically harmful effects of blue-blocking IOLs
  - There is currently no evidence of any clinically beneficial effects of blue-blocking IOLs

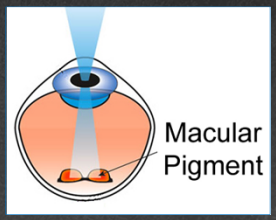
Lai, et al. Cur Opin Ophthalmol 2014;25:35

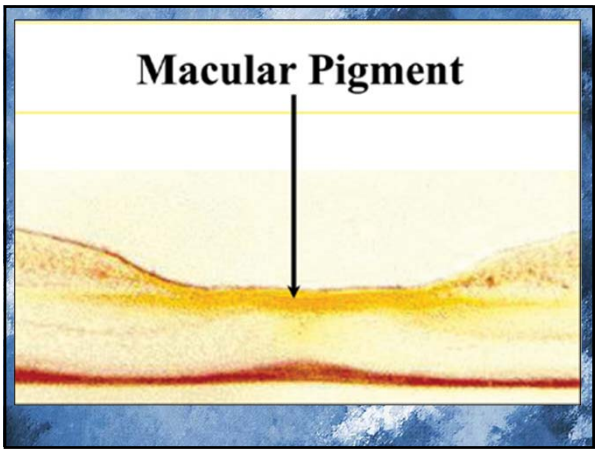
What's New in AMD

5. Lutein
6. Sunlight
7. Lifestyle
8. Aspirin
9. Implantable Miniature Telescope
10. Drug Pipeline

Lutein

- Macular Pigment
  - Lutein and zeaxanthin are the major components of macular pigment
  - Macular pigment may protect the retina from photochemical damage by absorbing blue light and by quenching reactive oxygen species





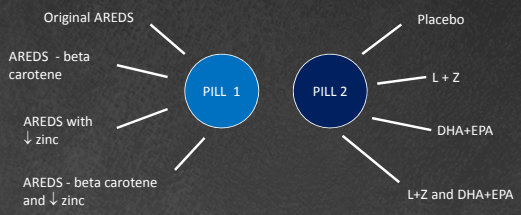
Lutein

- AREDS II (2013)
  - Multicenter, double-masked RCT of AREDS supplement (or a variant of it) plus lutein &/or omega-3 in 4203 participants with intermediate AMD over 5yrs
  - Lutein: lutein (10mg) + zeaxanthin (2mg)
  - Omega-3: DHA (350mg) + EPA (650mg) [ethyl ester]
  - Low-zinc AREDS: 25mg (down from 80mg)
  - No beta carotene AREDS

Chew, et al. JAMA. 2013;309:2005

AREDS-2 Supplement

Double randomization: Every participant was given 2 pills. Each pill was one of 4 possible formulations



Note: Current smokers were never given a pill containing beta-carotene, but former smokers were.

Lutein

- AREDS II Results
  - Addition of lutein and/or omega-3 to the AREDS formula did not further decrease risk of progression
  - Addition of lutein further decreased risk of AMD progression only in persons with the lowest dietary intake
  - Decreasing zinc and eliminating beta carotene had no significant effect on risk of progression

Chew, et al. JAMA. 2013;309:2005

Lutein

- AREDS II Recommendations
  - Substitution of lutein for beta carotene in the AREDS formula increases safety without decreasing efficacy
    - Current and former smokers face increased risk of lung cancer from beta carotene supplementation
  - Further research is needed to determine if an optimal formulation and dosage of DPA+EPA can further decrease the risk of AMD progression

Chew, et al. JAMA. 2013;309:2005

Runner-Up

Meso-Zeaxanthin

- Sabour-Pickett (2014)
  - RCT of 3 different carotinoid formulations in 52 subjects with early AMD
    - Formula 1 (20mg L, 2mg Z)
    - Formula 2 (10mg L, 2mg Z, 10mg MZ)
    - Formula 3 (3mg L, 2mg Z, 17mg MZ)
  - Formulas containing MZ produced the greatest increases in MPOD
  - Formula 3 produced the greatest increase in contrast sensitivity

Sabour-Pickett, et al. Retina. 2014;34:1757

Lutein

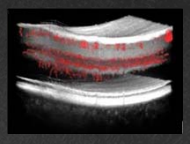
- Key Points
  - Lutein supplementation improves MPOD in patients with low MPOD, and these patients will benefit visually from this intervention
    - Inclusion of meso-zeaxanthin may enhance this effect
  - Lutein supplementation may decrease the risk of AMD progression in persons with low dietary intake
  - Lutein replaces beta carotene in the AREDS supplement to decrease cancer risk in smokers

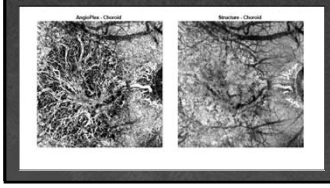
What's New in AMD

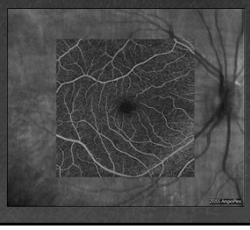
4. OCT Angiography
5. Lutein
6. Sunlight
7. Lifestyle
8. Aspirin
9. Implantable Miniature Telescope
10. Drug Pipeline

OCTA

- Non-invasive flow imaging
- 3D volumetric data
- Structure/Vacular data in tandem





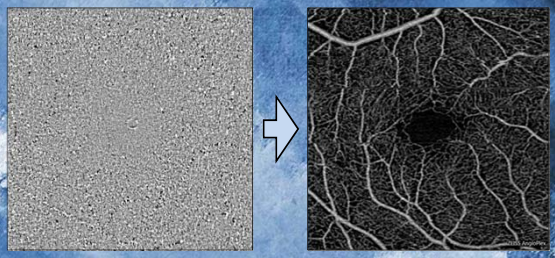


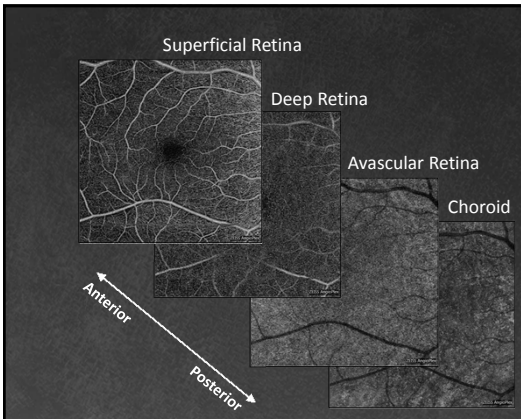
OCTA

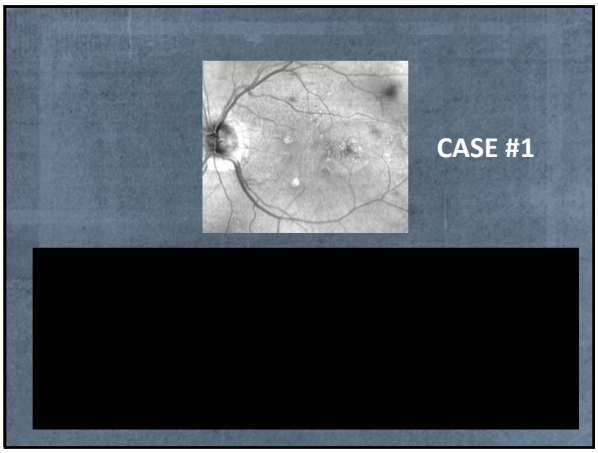
- Zeiss AngioPlex™
  - FDA approved in Sept 2015
  - Cirrus 5000 HD-OCT
- Optovue AngioVue™
  - FDA approved in Feb 2016
  - RTVue XR Avanti SD-OCT

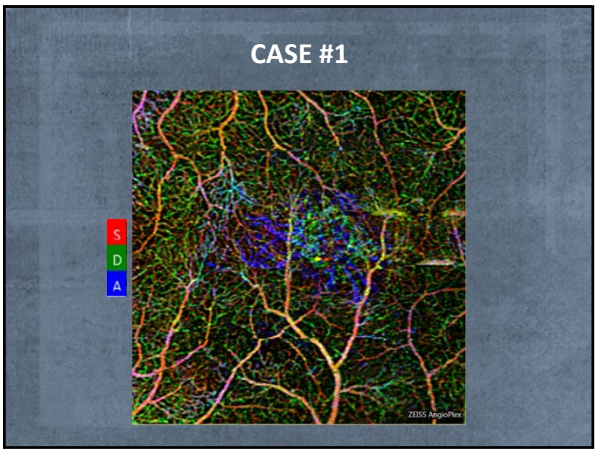
Not FDA Cleared
- Nidek AngioScan ™
- Topcon SS OCT Angio ™
- Canon

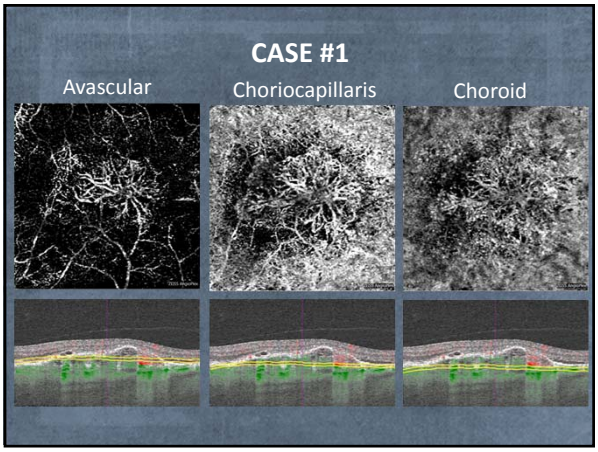
Motion Contrast

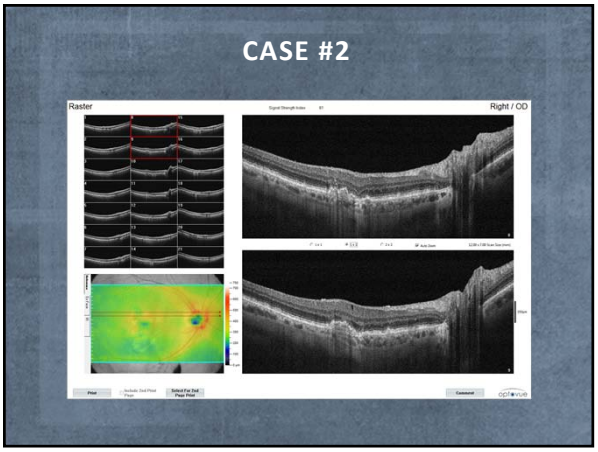


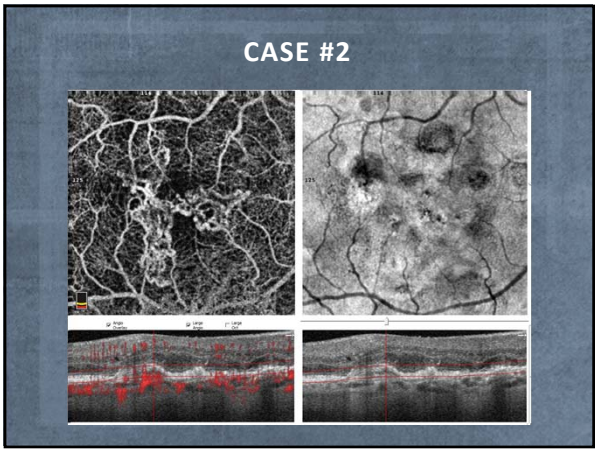


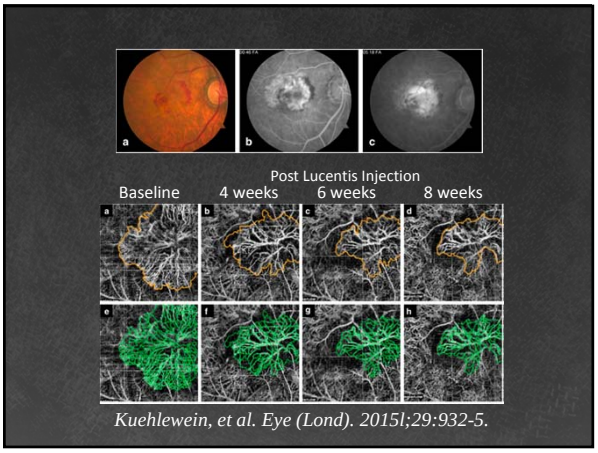

CASE #1


CASE #1
S
D
A


CASE #1
Avascular
Choriocapillaris
Choroid


CASE #2
Raster
Right / OD


CASE #2


a
b
c
Post Lucentis Injection
Baseline
4 weeks
6 weeks
8 weeks
Kuehlewein, et al. Eye (Lond). 2015l;29:932-5.

OCTA

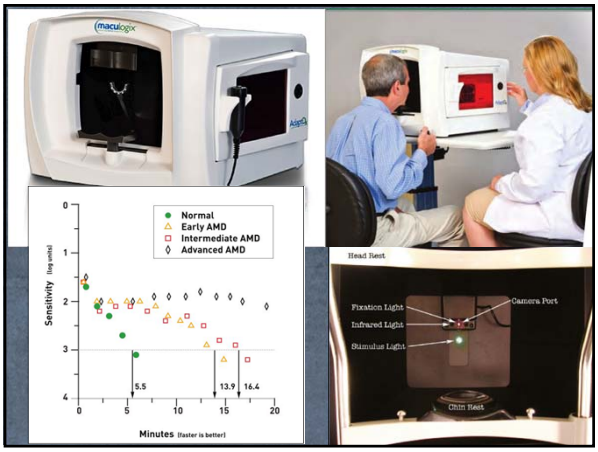
- Key Points
  - Many advantages over fluorescein angiography (non-invasive, higher resolution, quantitative analysis, choroidal imaging, etc)
  - Improved visualization of CNV
  - Rapidly evolving technology
  - Applications outside AMD (retinal vascular disease, glaucoma

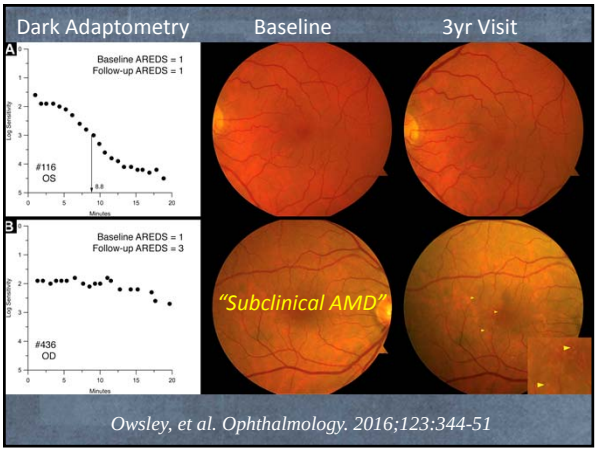
Runner-Up

Dark Adaptometry

- Owsley (2016)
  - Prospective observational study of 325 normal patients over age 65 followed for 3 years
  - Dark adaptometry (DA) was performed at baseline
  - Presence of AMD was assessed at 3yr visit
  - After adjustment for age and smoking, those with abnormal DA at baseline were ~2x more likely to have AMD at 3yrs compared with those who had normal DA at baseline.

Owsley, et al. Ophthalmology. 2016;123:344-51

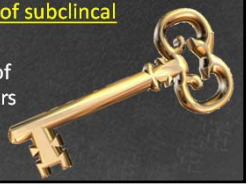




Owsley, et al. Ophthalmology. 2016;123:344-51

Dark Adaptometry

- Key Points
  - About 20%-25% of normal older adults will have abnormal DA
  - Of these, about 20% will develop some AMD over 3yrs (compared to 10% of those with normal DA)
  - Abnormal DA may be a sign of subclincal AMD
  - Consider DA in the context of other known AMD risk factors



What's New in AMD

3. Anti-VEGF medications
4. OCT Angiography
5. Lutein
6. Sunlight
7. Lifestyle
8. Aspirin
9. Implantable Miniature Telescope
10. Drug Pipeline

CATT Study: 5yr Results

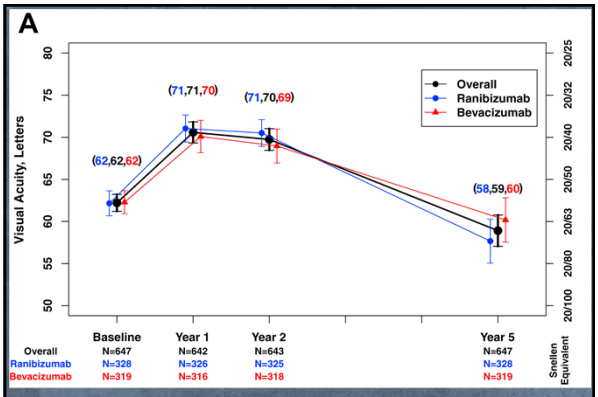
- Methods
  - 1208 patients with neovascular AMD randomly assigned to one of four study groups:
  - Lucentis monthly, Lucentis PRN
  - Avastin monthly, Avastin PRN
  - After 2 years patients released from study and provided with usual and customary care
  - A follow-up visit was performed at 5 years for 914 of the original study participants

Maguire, et al. Ophthalmology 2016;123:1751-61

CATT Study: 5yr Results

- Results:
  - Vision gains during the first 2 years were not maintained at 5 years.
    - 50% of eyes have final VA of 20/40 or better
  - Vision loss primarily related to:
    - Abnormally thin retina (<120 µm)
      - 22% @ 2yrs → 36% @ 5yrs
    - Geographic atrophy
      - 20% → 40%
    - Increase in lesion size

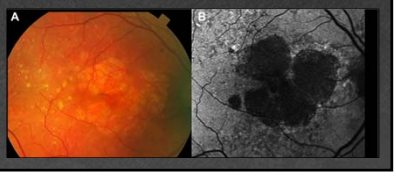
Maguire, et al. Ophthalmology 2016;123:1751-61



CATT 5 year visual acuity results

Anti-VEGF & GA

- A number of studies find that anti-VEGF therapy is associated with progression of geographic atrophy
  - Anti-VEGF drugs may accelerate GA
- *Need to minimize anti-VEGF drug exposure*
- Need to find drugs to combat GA



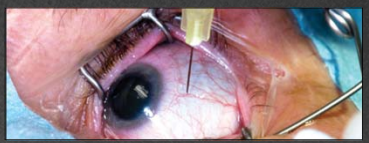
CATT Study: 5yr Results

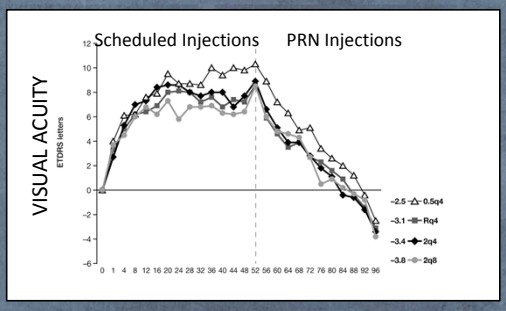
- Key Points
  - 50% of participants retain 20/40 or better vision
  - Mean VA at 5 years was 3 letters worse than at baseline
  - Vision loss while on anti-VEGF therapy largely due to macular atrophy

Runner-Up

Treat & Extend

- "Gold standard" dosing is monthly injections
  - Best visual and anatomic outcomes
- Cost, convenience, and safety factors motivate search for alternative to monthly dosing





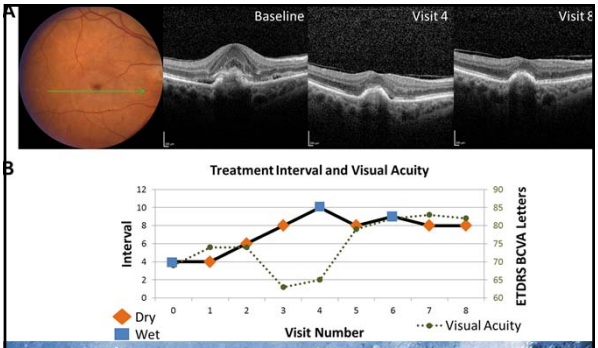
Change in BVA in patients who lost >5 ETDRS letters from weeks 52-96 in the VIEW study.

Richard, et al. Ophthalmol. 2015;122:2497–2503

Treat & Extend

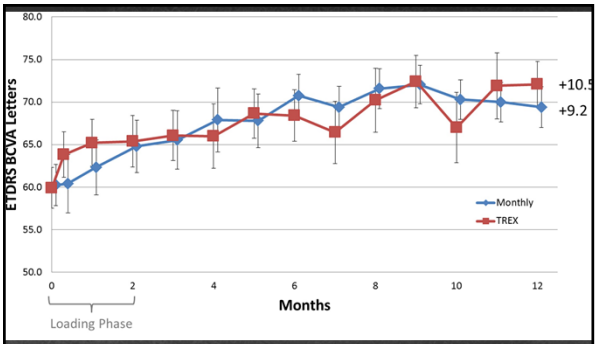
- Wykoff (2015)
  - Phase IIIb, multicenter, randomized, controlled clinical trial of 60 patients with wet AMD treated with Lucentis
  - Randomized to monthly or treat-and-extend (TREX) dosing
  - At 1yr, visual and anatomic gains with TREX dosing were comparable with monthly dosing.

Wykoff, et al. Ophthalmol. 2015;122:2514–2522



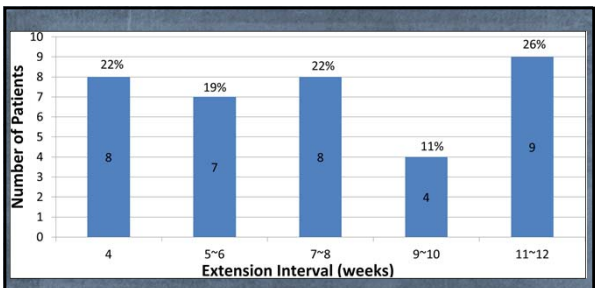
Example of TREX treatment protocol. Patient gets an injection at every visit. If they are dry, the follow-up period is lengthened. If they are wet, the follow-up period is shortened.

Wykoff, et al. Ophthalmol. 2015;122:2514–2522



Visual acuity outcomes for the monthly and TREX study groups

Wykoff, et al. Ophthalmol. 2015;122:2514–2522



Treatment intervals in weeks at 1 year for patients in the TREX study arm. The mean interval was 8.4 weeks.

Wykoff, et al. Ophthalmol. 2015;122:2514–2522

Treat & Extend

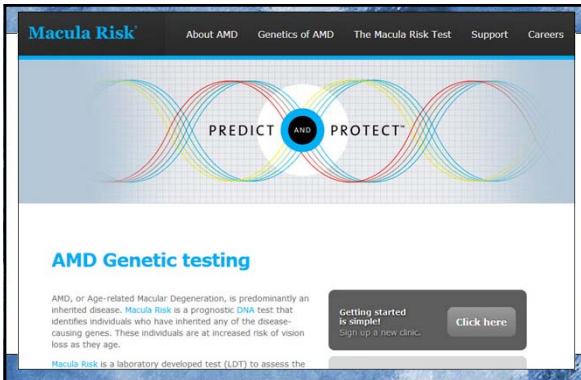
- Key Points
  - PRN dosing is associated with vision loss
  - Treat-and-Extend dosing can deliver outcomes comparable to monthly dosing with significantly fewer injections

What's New in AMD

2. Genetics
3. Anti-VEGF medications
4. OCT Angiography
5. Lutein
6. Sunlight and Cataract Surgery
7. Lifestyle
8. Aspirin
9. Implantable Miniature Telescope
10. Drug Pipeline

Genetics

- Risk modeling
  - Attempts to predict the risk of developing advanced AMD based upon genetic, phenotypic and behavioral factors
- Pharmacogenomics
  - How genetic variations determine response to medication.
  - The ultimate goal is to identify those who respond best and avoid adverse reactions



Genetic testing services use risk models to calculate your risk of contracting various disorders based on genotype

Risk Models

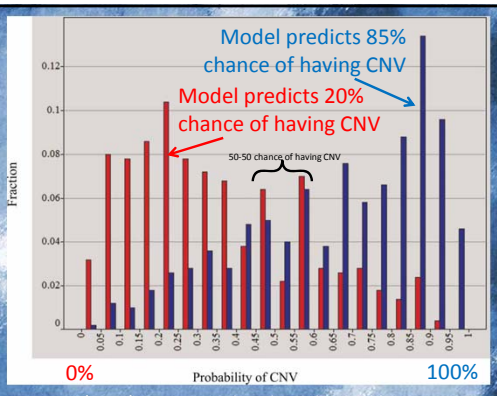
- Genetic only
  - Genetic risk factors are static throughout life
- Genetic plus other factors
  - May include phenotype, behavioral and environmental factors in the model
  - Better short-term risk assessment
  - May reflect change in risk over time (age, smoking behavior, weight loss)

Risk Models

	# Genes	Environment	AUC
Jakobsdottir (2009)	3	No	0.79
AREDS (2009)	6	Yes	0.81
Hageman (2011)	13	No	0.80
Klein (2011)	2	Yes	0.87

The larger the AUC the greater the accuracy of predictions

.90-1 = excellent (A)
.80-.90 = good (B)
.70-.80 = fair (C)
.60-.70 = poor (D)
.50-.60 = fail (F)



Hageman (2011): Genetic-only risk model. Red bars represent controls and blue bars represent patients with CNV.

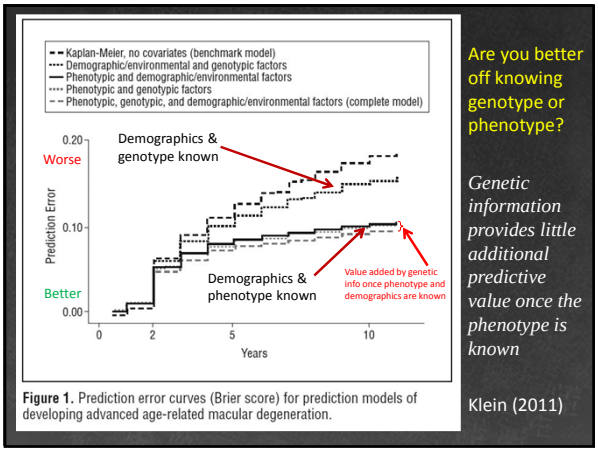
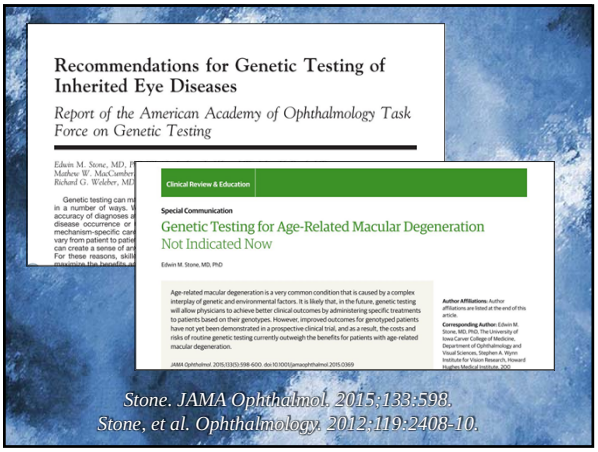


Figure 1. Prediction error curves (Brier score) for prediction models of developing advanced age-related macular degeneration.

Are you better off knowing genotype or phenotype?

Genetic information provides little additional predictive value once the phenotype is known

Klein (2011)



Stone. JAMA Ophthalmol. 2015;133:598.
Stone, et al. Ophthalmology. 2012;119:2408-10.

Risk Models

- Key Points
  - Risk calculators can identify high-risk individuals for more frequent surveillance and clinical interventions.
  - Once phenotype is known, genetic information is of little additional predictive value.
  - May be of greatest value in predicting response to drugs or other therapies

Pharmacogenomics

- Genotype may influence response to drug therapy, with persons responding better or worse depending upon what genes they carry
  - Personalized medicine: Selecting a particular optimized course of therapy based upon genetic testing
- There are reports that response to AMD therapies, including AREDS, vary based on genotype

Gene	Genotype	Disease Treated	Type of Treatment	Results	Reference
HTRA1	rs11200638	AMD	ranibizumab	positive response	McKibbin et al., 2011
CFH	rs106170	AMD	ranibizumab	positive response	McKibbin et al., 2011; Lee et al., 2009
VEGF	rs1413711	AMD	ranibizumab	positive response	McKibbin et al., 2011
ARMS2	rs10490924	AMD	ranibizumab	no response	Teper et al., 2010
CFH	rs106170	AMD	bevacizumab	positive response	Brantley et al., 2007; Nischler et al., 2011
Factor XIII-A	rs5985	AMD	antibody	worsening of CNV	Parmeggiani et al., 2011
ARMS2	rs10490924	AMD	ant-oxidant and zinc	no response	Klein et al., 2008
CFH	rs1061170	AMD	ant-oxidant and zinc	positive response	Klein et al., 2008
CFH	rs1061170*	AMD	PDT	no response	Seitsonen et al., 2007; Feng et al., 2009
CFH	rs1410996/ 2274700	AMD	PDT	positive response	Tsuchihashi et al., 2011
HTRA1	rs11200638*	AMD	PDT	positive response	Tsuchihashi et al., 2011
ARMS2	rs10490924	AMD	PDT	no response	Chowers et al., 2008
CRP	rs2808636 rs876538	AMD	PDT	positive response	Feng et al., 2009
VEGF	rs699947 rs2146323	AMD	PDT	no effect	Immonen et al., 2010
MTHFR	C677T	AMD	PDT	positive response	Parmeggiani et al., 2009
PT	G20210A	AMD	PDT	positive response	Parmeggiani et al., 2007

Shastry BS. Discovery Medicine, Aug 2011

CFH & AREDS

- Klein (2008)
  - Persons homozygous for the CFH high-risk allele (CC) have a smaller treatment response to the AREDS vitamin/mineral supplement than persons homozygous for the CFH low-risk allele (TT)
  - This was among the first pharmacogenetic studies to suggest interaction between genotype and treatment response

Klein ML, et al. Ophthalmology 2008;115:1019–1025

Response to the AREDS supplement is related to CFH genotype

Table 3. Progression from High-Risk to Advanced Age-Related Macular Degeneration (Category 3 to 4, 3 to 5, and 4 to 5) by Treatment Groups and Genotypes, and Assessment of Interactions

			Antioxidants + Zinc vs. Placebo					
			Placebo			Antioxidants + Zinc		
		Genotype	No. Progression	Progression	Proportion That Progress	No. Progression	Progression	Proportion That Progress	P Value for Interaction
CFH Y402H	Low Risk	TT	29	15	0.34	96	24	0.20	0.16
		TC	74	34	0.31	96	24	0.20	
	High Risk	CC	35	27	0.44	93	29	0.24	0.03
LOC387715/ARMS2 A69S		GG	87	17	0.16	96	17	0.15	
		TG	50	41	0.45	93	29	0.24	0.06
		TT	21	21	0.50	20	15	0.43	0.99

23%

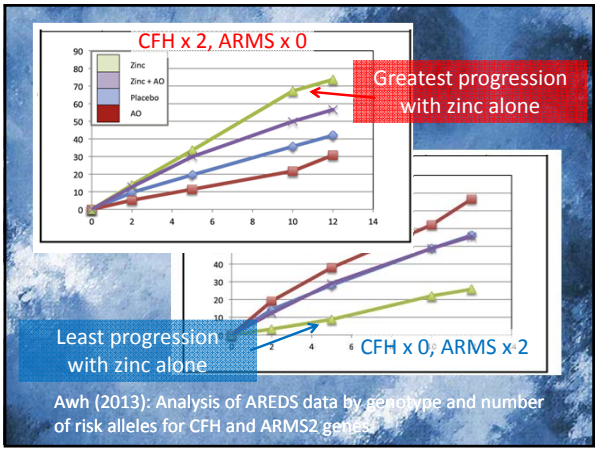
4%

Persons homozygous for the CFH high-risk allele (CC) have a smaller treatment response than persons homozygous for the CFH low-risk allele (TT)

CFH & AREDS

- Awh (2013)
  - CFH: Persons with 1 or 2 CFH risk alleles derived maximum benefit from antioxidants alone
    - The addition of zinc negated the benefits of anti-oxidants in these patients
  - ARMS2: Persons with ARMS2 risk alleles derive maximum benefit from zinc, with a deleterious response to antioxidants
  - Persons with both CFH and ARMS2 risk alleles derive no benefit from the AREDS supplement

Awh, et al. Ophthalmology 2013;120:2317



Awh (2013): Analysis of AREDS data by genotype and number of risk alleles for CFH and ARMS2 genes.

CFH & AREDS

No Clinically Significant Association between *CFH* and *ARMS2* Genotypes and Response to Nutritional Supplements

AREDS Report Number 38

Emily Y. Chew, MD,[1] Michael L. Klein, MD,[2] Traci E. Clemons, PhD,[3] Elvira Agrón, MA,[1] Rinki Ratnapriya, PhD,[4] Albert O. Edwards, MD, PhD,[5] Lars G. Fritsche, PhD,[4] Anand Swaroop, PhD,[4]

The AREDS supplements reduced the rate of AMD progression across all genotype groups. Furthermore, the genotypes at the CFH and ARMS2 loci did not statistically significantly alter the benefits of AREDS supplements.

and baseline AMD severity, were used to examine the influence of genotypes on the response to therapy with 4 randomly assigned arms of AREDS supplement components: placebo, antioxidants (vitamin C, vitamin E, β-carotene), zinc, or a combination.

Chew, et al. Ophthalmology 2014;121:2173

CFH & AREDS

- Awh (2015)
  - Reanalysis of data and confirmation of previous findings.
  - Recommendation to provide nutritional supplementation based upon genotype
- Chew (2015)
  - The results of Awh are a consequence of post-hoc subgroup analysis and selection bias
  - States results similar to Awh could be generated using Zodiac signs rather than genes

Awh, et al. Ophthalmology. 2015;122:162
Chew, et al. Ophthalmology. 2015;122:212

Pharmacogenomics

- Key Points
  - Use of genetic testing in the management of AMD is controversial
    - The evidence supporting treatment based upon genotype is based upon retrospective subgroup analysis, and hence subject to bias
  - Concerns regarding loss of privacy, impact on employment and insurance discrimination.
    - Social, ethical, and economical issues need to be addressed by regulatory agencies.

What's New in AMD

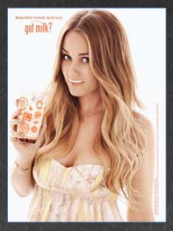
1. Vitamins
2. Genetics
3. Anti-VEGF medications
4. OCT Angiography
5. Lutein
6. Sunlight
7. Lifestyle
8. Aspirin
9. Implantable Miniature Telescope
10. Drug Pipeline

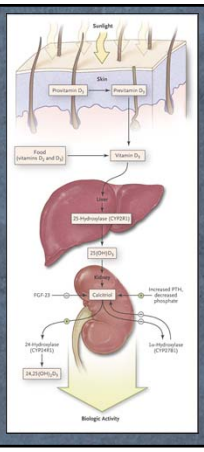
Vitamins

- Vitamin D
  - Has antiangiogenic, antioxidant and anti-inflammatory effects
  - Low vitamin D levels associated with AMD
- B vitamins
  - Capable of significantly lowering serum levels of homocysteine
  - Elevated homocysteine levels are thought to induce vascular endothelial dysfunction, and has been associated with increased risk of AMD

Vitamin D

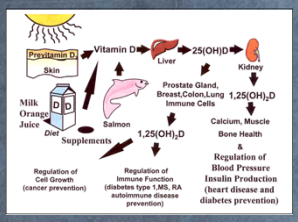
- Vitamin D has many diverse metabolic effects
  - Bone mineralization, regulation of Ca2+ and phosphorus
  - Antiangiogenic, antioxidant and anti-inflammatory effects
  - Role in cellular proliferation, differentiation and apoptosis
- Biologically plausible that vitamin D may influence AMD risk





The 3 major sources of vitamin D are:

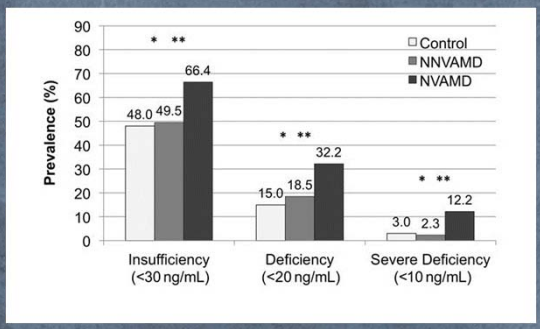
- Sunlight
- Milk
- Supplements



Vitamin D

- Itty (2014)
  - Record review of 362 pts with AMD and 100 matched controls.
  - Mean vitamin D levels were significantly lower among pts with wet AMD than dry AMD and controls
  - Vitamin D deficiency was most common in the wet AMD group
  - The highest quintile of vitamin D levels was protective against AMD (OR: 0.35)
  - Vitamin D deficiency is a potentially modifiable risk factor for the development of wet AMD

Itty, et al. Retina. 2014;34:1779



Itty (2014): Low vitamin D status was significantly more prevalent among patients with wet AMD than among those with dry AMD and normal controls

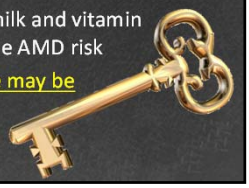
Vitamin D

- Kim (2014)
  - Population-based study of 17,045 adults in Korea
  - The highest quintile of vitamin D levels was protective against AMD (OR: 0.32) in men but not in women

Kim, et al. IOVS. 2014;55:4823

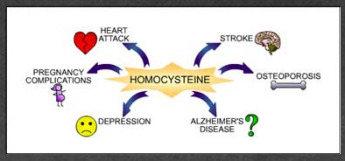
Vitamin D

- Key Points
  - Vitamin D deficiency may be a modifiable risk factor for neovascular AMD
  - Higher serum vitamin D levels associated with reduced risk of AMD
  - Increased consumption of milk and vitamin D supplements may decrease AMD risk
  - Moderate sunlight exposure may be protective against AMD

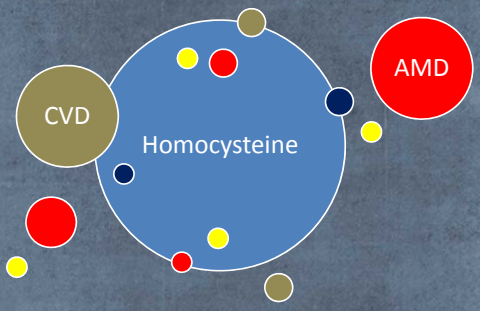


B Vitamins

- Homocysteine is an amino acid that has been found to promote inflammation and oxidative stress in the body
- Among many other effects, B vitamins have the ability to lower serum homocysteine levels
- Elevated homosysteine levels have been associated with higher risk of cardiovascular disease and stroke



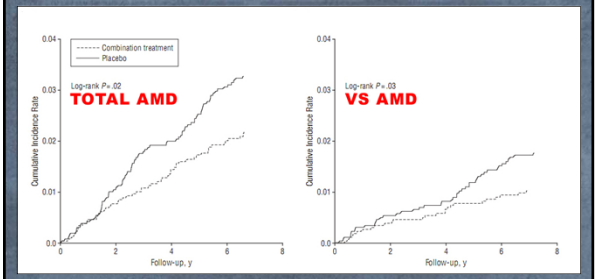
Hypothesis



B Vitamins

- Christen (2009)
  - Women's Health Study: RCT of 5205 women without AMD at baseline randomized to receive folic acid or placebo for 7.3yr
    - 2.5 mg folic acid, 50 mg vitamin B6, 1 mg vitamin B12
  - Women assigned to B vitamin supplementation had a statistically significant 35% to 40% decreased risk of developing AMD

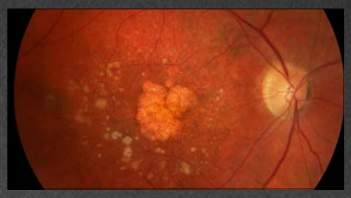
Christen WG. Arch Intern Med. 2009;169:335-341



Cumulative incidence rates of confirmed AMD (left) and visually significant (VS) AMD (right). After an average 7.3 yrs of follow-up those women on treatment had a 35% lower risk of any AMD and a 40% lower risk of visually significant AMD

B Vitamins

- Conclusion
  - *"Folic acid is the first identified means, other than cigarette avoidance, to prevent the onset of AMD"*



Christen WG. Arch Intern Med. 2009;169:335-341

B Vitamins

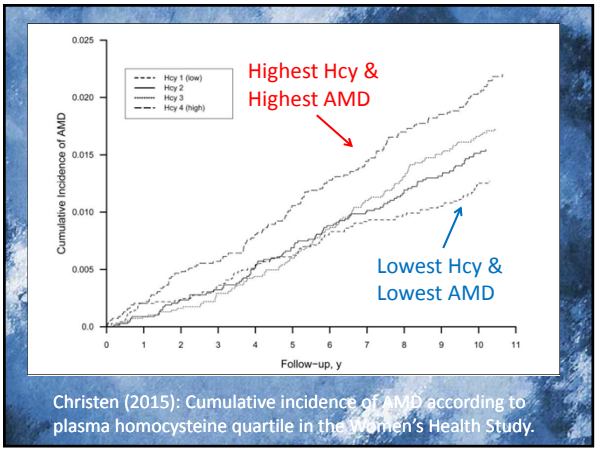
- Gopinath (2013)
  - Population-based study of 3654 adults in Australia followed for 10yrs (BMES)
  - Elevated homocysteine levels associated with increased risk of developing AMD
  - Folate deficiency at baseline associated with 75% and 89% increased risk of developing AMD at 10yrs
  - Taking vitamin B supplements decreased risk of developing AMD by 47%

Gopinath, et al. Am J Clin Nutr 2013;98:129

Vitamin B

- Christin (2015)
  - 27,479 healthy females aged ≥40 years followed prospectively for an average of 10 years
  - 452 cases of AMD occurred during follow-up
  - Women in the highest versus lowest quartile of plasma homocystine had elevated risk of AMD, but this did not achieve statistical significance (hazard ratio: 1.24; 95%CI: 0.95–1.63; p=0.07)
  - *"These data do not support a strong role for homocysteine in AMD occurrence."*

Christen, et al. Ophthal Epidemiol 2015;22:85-93



Christen (2015): Cumulative incidence of AMD according to plasma homocysteine quartile in the Women's Health Study.

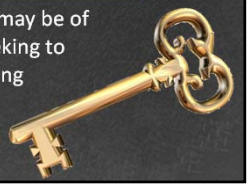
Recommendation

≥200% RDA folic acid

≥100% RDA B12

B Vitamins

- Key Points
  - Elevated serum homocysteine levels associated with increased risk of AMD
  - B vitamin supplements demonstrated to be effective in the primary prevention of AMD
  - B vitamin supplementation may be of value in normal patients seeking to reduce their risk of developing AMD in the future



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