ANTICOAGULATION AND THE EYE

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Case History

- 78 year old Caucasian male
- Consult for eye exam
- Chief complaint:
  - Broke glasses when fell onto his face and hit right side of head 8 days ago
  - Got black right eye & vision fuzzy OD
  - Did not go to ED or see PCP since incident
- POHx: non-contributory

PMHx:
- Atrial fibrillation
- Peripheral vascular disease
- Meds:
  - Dabigatran 150mg PO every day

Pertinent Exam Results

- BCVA:  OD 20/30 (essentially stable); OS 20/20
- Pupils: PERRL, no APD
- EOMs: No restrictions, no pain, no diplopia
- CF: FTFC OD, OS
- External: Mild ecchymosis around OD; healing abrasion on forehead; no pain or step-offs with orbital rim palpation
- SLE: Unremarkable OU
- IOP: OD/OS 15 mmHg
- DFE: No heme, breaks, RD

CT of Head
Diagnosis & Plan

- Chronic subdural hematoma due to minor head trauma (MHT) after fall
- Long term use of anti-coagulants (dabigatran)
- No ocular sequelae

- Consult with neurosurgery
  - Monitor, repeat CT of head
  - Go to ED for HA, diplopia or other visual changes

Higher risk of intracranial injury when anti-coagulated

- Common practice to image patients after MHT
  - EDs have protocols in place for immediate management as well for observational periods

Venous Thromboembolism

- Deep Venous Thrombosis
- Pulmonary Embolism

Atrial Fibrillation (AF)

- Thromboembolic complications
- Associated with cardiac valve replacement
Post-Myocardial Infarction

- Reduce risk of:

  - Recurrent MI
  - CVA
  - Systemic embolism
  - Death

COUMADIN (WARFARIN)

Inhibits Vitamin K-dependent Coagulation Factors

Clinical Risk Factors for Major Bleeding (%)

- Systolic BP > 160 mmHg
- Kidney failure
- Stroke
- Prior major bleeding
- Age > 65 yrs
- Antiplatelet agent

53.3%

Epidemiology

US Population on some form of anticoagulation in 2009 (millions)

307

21
Dosage & Administration

American College of Chest Physicians evidence-based clinical practice guidelines

Loading Dose Schedule for Warfarin Initiation

Monitoring: narrow therapeutic range

NOVEL ORAL ANTICOAGULANTS

Pradaxa (dabigatran)

FDA approved Oct 2010
Reduce risk of CVA & embolism in atrial fibrillation

Xarelto (rivaroxaban)

• Reduce risk of CVA & embolism in AF
• FDA approved November 2011
• Approved earlier to lower the risk of DVT after hip & knee replacements
• November 2012: also approved to treat DVT & PE; reduction of risk of recurrence

Eliquis (apixaban)

FDA approved Dec 2012
Reduce risk of CVA & embolism in AF
Savaysa (edoxaban)
- FDA approved factor Xa inhibitor for:
  - Prevention of CVA & non-central-nervous-system embolism in patients with nonvalvular atrial fibrillation
  - DVT & PE

ANTIPLATELETS

Aspirin
- 81 versus 325 mg
- 40-50 million Americans use for MI prevention

Plavix (clopidogrel)
- FDA approved Nov 1997
  - Indications: acute coronary syndrome; recent MI/CVA or established peripheral arterial disease
  - DAPT Trial results
  - 30 million prescriptions in 2009

DAPT Trial Results
- Plavix/Effient + ASA vs ASA alone
- \( \downarrow \) risk of stent thrombosis & cardio- & cerebro-vascular events
- Greater bleeding risk & increased death greater in dual group
- FDA: Benefits of Plavix/Effient cont to outweigh potential risks
  - Pts should cont to take drugs as directed to prevent ischemic events
  - Health care providers should not change how they prescribe drugs

OCULAR COMPLICATIONS OF ANTICOAGULANTS / ANTIPLATELETS
CASE 1

Case History

- 82 year old Hispanic male
- Urgent walk-in red eye
- Chief complaint
  - Woke up with blood shot red left eye and bruising under eye yesterday morning
  - No trauma but may have rubbed eye
  - Sleeps on right side

POHx: non-contributory

Significant PMHx
- Pulmonary embolism
- Meds
  - Warfarin 1 mg every evening except take 2 tabs on Mondays, Wednesdays, Fridays
- INR: 1.2
  - Result from 25 days prior to presentation
    - Increased to 1.3 – 2.4 over next 6 days
    - INR 3.6 19 days prior to presentation

Pertinent Exam Results

- BCVA: OD 20/40, OS 20/50 (stable)
- Pupils: PERRL; (-) APD
- EOMs: Full OU
- CF: FTFC OD/OS
- SLE: OD clear
  - OS see next slide
- Ta: OD/OS 15 mmHg

Diagnosis & Plan

- Consult with oculoplastics
  - One of the most dramatic cases he has ever seen!

- A/P: Severe sub-conjunctival hemorrhage OS
  - Likely as a side effect of warfarin use
  - Patient education and reassurance on condition
    - Will self resolve in 2-3 weeks
  - RTC next available for comprehensive eye exam
    - No showed for follow up appointments

Left Eye and Adnexa

4++ sub conj heme w/extreme chemosis enveloping limbus & peripheral cornea

Severe ecchymosis of upper lid & lower orbital area
Incidence of subconjunctival hemorrhages related to long term AC use found to be 1.5-5%.

Risk twice as great in older patients on AC therapy than younger patients.

Case History

- 84 year old Caucasian male
- Annual eye exam
- Chief complaint: none
- PMHx:
  - CAD s/p CABG 1994
  - Percutaneous coronary intervention of saphenous vein graft to patent ductus arteriosus in 2012
  - Coronary angioplasty or simply angioplasty, is a non-surgical procedure used to treat the stenotic (narrowed) coronary arteries of the heart found in coronary heart disease
  - Paroxysmal atrial fibrillation
  - HTN, mild anemia but no DM
- Meds:
  - Plavix
  - ASA (325 to 81mg)
    - 325mg initially prescribed but changed to lower dose b/c patient requested to decrease dose
  - Nitroglycerin
  - Declined warfarin for afib b/c ‘intolerant to meds’
    - Standard of care is warfarin x 1 year after stenting but pt refused due to complex dosing & INR monitoring

Pertinent Exam Results

- BCVA: OD 20/25, OS 20/20 (stable)
- Pupils: PERRL; (-) APD
- EOMs: Full OU
- CF: FTFC OD/OS
- SLE: OU PCIOLs
- Ta: OD/OS 19 mmHg
Macula OD

OCT Macular Cube & HD 5 Line Raster

Diagnosis & Plan

- Long standing intraretinal hemes & MAs OU
  - OCT OD mild cystic changes / OS stable
  - HTN, mild anemia but no DM

- RTC next available Retina Clinic
  - Patient educated to continue current medication regiment and maintain regular follow-ups with PCP

Discussion

- Beaver Dam Study
  - Retinal hemes 3x more prevalent in AC patients vs non-AC patients (4.5% vs 1.5%)\(^1\)
    - Non-diabetics
    - ≥65 years old

- Framingham Eye Study
  - 0.9% of eyes had retinal hemes\(^2\)

Discussion

- Risks for retinal hemes\(^3\)
  - Pre-existing ocular disease
    - i.e., retinal vascular disease in fellow eye
  - Hypertension
  - Longer duration, more intense AC, use of concurrent meds
  - Increased age
    - Twice as great in older vs younger patients
    - Beaver Dam: ≥75 years old 9.5x more likely to have hemorrhages

CASE 3
Case History

- 66 yo Caucasian male
- Self made appointment for exam
- Chief complaint:
  - Progressively blurry vision OD x 3 days to the point he can only see outlines and light. Noticed a floater/squiggle a few weeks prior
  - Went to local ER 3 days ago and referred to OMD
    - Told he had ‘bleeding in his eye’
    - Would like to transfer care to VA & 2nd opinion
    - Self d/c Plavix x 3 days ago

Case History

- POHx: non-contributory
- PMHx:
  - CVA vs TIA vs anxiety episode
  - HTN
  - No DM
- Meds:
  - ASA 81mg daily
  - Plavix until 3 days ago

Pertinent Exam Results

- BCVA: OD HM @ 8 feet,
  OS 20/25
- Pupils: ERRL; (-) APD
- EOMs: Full OU
- CF: FTFC OD, OS
- SLE: OD/OS 2+ NSC, ACC
- Ta: OD 15 / OS 12

Vitreous Hemorrhage

- B-scan: Mild vitreous opacity w/ good after-movement
- DFE: PVD, mild preretinal opacity; no tears or detachments

Diagnosis & Plan

- Hemorrhagic PVD OD
  - Plavix discontinued by prescriber 10 days after initial exam after latest stress test results
- RTC 2 weeks or ASAP if any symptoms of RD
  - Patient educated blood will likely self-resolve
  - Patient educated to avoid heavy lifting & bending over; sleep upright as possible

Discussion

**ORAL ANTICOAGULATION AND THE RISK OF VITREOUS HEMORRHAGE AND RETINAL TEARS IN EYES WITH ACUTE POSTERIOR VITREOUS DETACHMENT**

- Conclusion:
  - “Patients taking ASA, clopidogrel, or warfarin who develop an acute PVD are more likely to present with VH.”

**RETINA 33:621-626, 2014**
Discussion

- AC/SPs generally do not cause VH but may enhance bleeding
  - Early Treatment of Diabetic Retinopathy Study
  - Did not show increased risk of VH among aspirin users

Intraocular Hemorrhage and Novel Oral Anticoagulants

- JAMA Ophthalmol July 2015
  - New oral anticoagulants “…do NOT increase the risk of substantial intraocular bleeding compared to warfarin/Coumadin/heparin.”
  - Rate of serious bleeding events was VERY low <0.4%!

Case History

- 66 y/o WM
- Urgent request for exam
- Chief complaint
  - Transient blurry vision OD x 3+ months
  - Blur lasts a few days then resolves
- PMHx: DM2, HTN
  - Samter’s Syndrome
  - Meds: Glyburide, Metformin, Lisinopril
  - 1.3 grams ASA daily

Ocular History

- CE/PCIOL OU
  - Dislocated IOL OD; surgically retrieved & iris-fixated
  - Macular hole OD s/p PPV & gas bubble
  - Subsequent RD s/p SB & cryotherapy

Pertinent Exam Results

- BCVA: OD 20/60 EV; OS 20/20
- Pupils: (3->2, 4->3)RRL, (-)APD
- SLE OD: see next slide
  - PCIOL decentered inferior w/ sutures at 2:00 & 8:00
- IOP: OD 45, OS 24
- Gonio: Open; no hyphema but hazy view inferior
- DFE: Diffuse ant vit heme; no retinal break
Anterior Segment Findings
3+ swirling RBCs, pigment on inf endo, iridodonesis

B-scan: Diffuse anterior vitreous hemorrhage

Diagnosis & Plan
• Iris-sutured IOL induced Uveitis-Glaucoma-Hyphema+VH (UGH+) complicated by high dose ASA
  • Start IOP lowering medications
  • Rec’d sleeping w/ head elevated
  • Retina consult: No surgical intervention; CPM
  • 2 month follow up visit
    • No changes per pt, notes ‘rebleeds’ occasionally
    • ASA d/c’d due to ineffectively

Discussion
• UGH+
  • Hyphemas reported in patient w/ pre-existing conditions such as iris-fixed IOLs
• Samter’s Syndrome
  • Inflammatory disease of respiratory mucosa
  • Clinical triad:
    • Asthma, ASA sensitivity, nasal/ethmoidal polyposis
  • Tx: ASA desensitization
    • Initially ‘challenged’ w/† doses (650-1300mg/day)

Retina
Sub-sensory
Sub-hyaloid

OTHER OCULAR HEMORRHAGES
Optic Disc

Significant association btw ASA & ODH
Possible association between ODH & generalized vascular disease

Latest study findings

The Association of Aspirin Use With Age-Related Macular Degeneration

Objective: To determine whether regular aspirin use is associated with a higher risk for developing age-related macular degeneration (AMD) by using data from a 15-year prospective cohort study.

Methods: A prospective cohort study. Follow-up data were available on 2,289 participants for 15 years. Aspirin use was defined as daily or nearly daily use of aspirin. The association between aspirin use and geographic atrophy (AMD) and subfoveal choroidal neovascularization (AMD) was assessed using Cox proportional hazards models.

Results: During the 15-year follow-up, 213 individuals (10.1%) developed age-related macular degeneration. The association between aspirin use and incident AMD was weak and not statistically significant. The hazard ratio for AMD associated with aspirin use was 1.05 (95% CI, 0.86-1.27) for subfoveal choroidal neovascularization and 1.32 (95% CI, 0.67-2.61) for geographic atrophy.

Conclusion: Regular aspirin use was not associated with an increased risk of incident AMD, subfoveal choroidal neovascularization, or geographic atrophy. These findings suggest that aspirin use does not increase the risk of incident AMD.


ASA, clopidogrel & warfarin significantly associated with increased risk of intraocular hemorrhage in wet AMD

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ASA use associated with 2-fold increase in wet AMD during 15-year period

Regular ASA use 10 years prior associated with small but statistically significant increase in incident late and wet AMD
Risk Factors for the Incidence of Advanced Age-Related Macular Degeneration in the Age-Related Eye Disease Study (AREDS) AREDS Report No. 19

Age-Related Eye Disease Study Research Group

Abstract

Purpose: To describe the association of demographic, behavioral, medical, and ophthalmic risk factors with the incidence of nonexudative age-related macular degeneration (AMD) and central or geographic atrophy (CAG) in the Age-related Eye Disease Study (AREDS), a randomized trial of antioxidant and zinc supplementation prophylaxis for development of advanced AMD.

Higher incidence of central geographic atrophy weakly associated with ASA use

Low-Dose Aspirin and Medical Record Confirmed Age-related Macular Degeneration in a Randomized Trial of Women


Division of Preventive Medicine, Department of Medicine, Brigham and Women’s Hospital (W.C.G., R.J.G., J.E.B.) and Harvard School of Public Health (E.Y.C.) in Boston, MA, the National Eye Institute, Bethesda, MD (E.Y.C.)

Abstract

Objective: To describe the association of demographic, behavioral, medical, and ophthalmic risk factors with the incidence of nonexudative age-related macular degeneration (AMD) and central or geographic atrophy (CAG) in the Age-related Eye Disease Study (AREDS), a randomized trial of antioxidant and zinc supplementation prophylaxis for development of advanced AMD.

Design: A large-scale, randomized, double-blind, placebo-controlled clinical trial with 10-year follow-up.

Participants:

- 111 cases of AMD in the aspirin group and 111 cases in the placebo group (matched 2:1 by sex, age, race, and smoking status at baseline).

- Men with advanced AMD were excluded.

Results:

- After 2 years of treatment and follow-up, men with advanced AMD were excluded.

Conclusions:

- No association of AC/AP use with hemorrhage except in participants with HTN

Association between Antiplatelet or Anticoagulant Drugs and Retinal or Subretinal Hemorrhage in the Comparison of Age-Related Macular Degeneration Treatments Trials

Guohong Yang, MD; Maurer G. Maguire, MD; H. Bruce Daniel, MD; June E. Groothuis, MD; Chuma Awer, MD; and Donald F. Margo, MD, on behalf of the Comparison of Age-Related Macular Degeneration Treatments Trials Research Group

“Most retinal or subretinal hemorrhages < 1DD

**No association of AC/AP use with hemorrhage except in participants with HTN

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

Wei Zhu,1,2* Yan Xu,1,2 Dong Xu,1,2 Yan-Hong Li,1 Jun Bai,1 Xiao-Long Zhang1,2 Fang Wang1,2 Jing Yu1,2

Department of Ophthalmology, Affiliated Tenth People’s Hospital of Tongji University, Shanghai, China; Department of Ophthalmology, Nantong Medical University, Nantong, Jiangsu, China

Abstract

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

Methods: A comprehensive search of PubMed, EMBASE, Web of Science, and reference lists was performed.

Results: A total of 28 studies were included. Among the included studies, 2 were cohort studies and 26 were case control studies. The relative risk (RR) was pooled using a fixed-effect model. The pooled RR was 0.97 (95% confidence interval 0.92-1.03). The pooled RR was lower in men than in women (RR = 0.97, 95% CI 0.92-1.03). The heterogeneity across studies was low (I^2 = 34%).

Conclusions: The use of aspirin was not associated with the risk of AMD.

Large-scale randomized trial with 10 years of treatment and follow-up, low-dose ASA had no large beneficial or harmful effect on risk of AMD

“We strongly recommend that AMD patients should be on aspirin if it is recommended by their primary physician”

Regular Aspirin Use and Risk of Age-Related Macular Degeneration

Lucia Sorini and Johanna M. Seddon

No change to clinical recommendations

Insufficient evidence for patients with AMD to stop ASA if clinically warranted for secondary prevention of cardiovascular
Prescribing of Supplements

- AREDS recommended supplements for AMD
  - Vitamin E

Recommendation:
Evaluate warfarin response when vitamin E used in combination

Because of warfarin's narrow therapeutic index, AC status should be carefully monitored with use of supplements since serious reactions associated with small changes in INR

Prescribing of Supplements

- Increased AC effect (↑INR) & AP activity
- Decreased AC effect (↓INR)

AC & Ophthalmic Surgery

- Overall, very low risk of hemorrhaging
- Cataract
  - No difference w/ or w/o warfarin use prior to surgery¹
  - Safe with uncomplicated phacoemulsification²
  - Significant increase in minor complications
    - Sharp needle & anesthesia related complications³
  - If ECCE, stop 1 week prior

AC & Ophthalmic Surgery

Glaucoma
- Statistically significant ↑ in hemorrhagic complications¹
  - Patients on AC had significantly higher complication rate than those on AP or no treatment¹

Oculoplastics
- Little data available
- Half of surgeons polled stop warfarin
- Local specialist: stop 1 week prior

AC & Ophthalmic Surgery

- Vitreo-Retinal
  - Most hemorrhagic complications due to manipulation of retina
  - May stop warfarin if thromboembolic risk low¹
  - No intraoperative complications²
    - Maintain therapeutic levels of AC during surgery
    - Intravitreal injections
      - No hemorrhagic events; can continue AC safely²

PRE-CAUTIONS & OTHER POTENTIAL COMPLICATIONS
### Pre-cautions & Other Potential Complications

**Bleeding**

**Tissue necrosis**

**Systemic atheroemboli**
- Microemboli to the feet: “Purple Toe”

**Heparin-induced thrombocytopenia**

**Pregnancy category D**
- If mechanical heart valves otherwise Category X
- Risk of:
  - Warfarin embryopathy (including optic atrophy)
  - Fetal hemorrhage & mortality
- Reproductive potential
  - Discuss pregnancy planning & potential risks to fetus

**Nursing mother**
- Warfarin not detected in human milk

**Renal impairment**
- No dosage adjustment necessary

**Hepatic impairment**
- Can increase effectiveness of response through:
  - Decreased production of clotting factors
  - Decreased warfarin metabolism

**Pediatric use**
- Avoid activity or sport that may traumatic injury
- Dosing varies by age
- Target INR difficult to achieve/maintain so more frequent testing

**Geriatric use**
- ≥60 yo have >expected INR response
- Contraindicated in unsupervised patients w/ dementia
- Consider low initiation and maintenance doses
AC/AP in Primary Eye Care

Key features of Ocular ischemic syndrome (OIS)

Ocular Ischemic Syndrome

- Maybe initial manifestation of carotid occlusive disease in ~70% of patients
- Often have systemic vascular diseases related to atherosclerosis
  - Ischemic heart disease, previous CVA
  - Peripheral vascular disease (DVT)
- Average stroke rate reported to be significantly higher in patients w/ OIS (4% per year) vs 0.49% per year in controls

Hollenhorst Plaque/Embolus

- Antiplatelets: mainstay of medical therapy
  - Symptomatic
    - Prompt A/P therapy to prevent recurrent TIA
    - ASA vs ASA & clopidogrel
    - A/C not indicated
  - Asymptomatic
    - ASA only [unless other concomitant condition(s)]

Hollenhorst Plaque/Embolus

Vascular Outcome in Men with Asymptomatic Retinal Cholesterol Emboli
A Cohort Study

- Concluded: Asymptomatic retinal cholesterol embolism is an important risk factor for cerebral infarction...

Retinal Vascular Occlusions

CRAO: "ocular analogue of cerebral stroke"

Often are undiagnosed systemic vascular risk factor & @ hi risk of systemic ischemic event such as CVA

Event rates for MI similar w/ RVO vs controls; event rate of CVA almost 2-fold vs controls
AC/AP in Primary Eye Care

- Transient visual obscurations (amaurosis fugax)
  - Highlighted in new definition of TIA
  - Greatest risk of stroke (& MI) within 1st few days of event

Conclusion / Clinical Pearls

- Be familiar with traditional & newer AC/AP therapies
- Importance of review of medications, ROS
- AC/AP can affect eye health, ocular surgery, prescription of supplements
- Routine exams/follow-ups not recommended
- Maybe prescribed as a result of an ocular disease which maybe 1st presenting sign for need for AC/AP therapy
- Know potential non-ocular complications of AC/AP therapy such as head trauma

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