ANTICOAGULATION AND THE EYE
Alyon Wasik, OD, FAAO
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Introduction
• Oral anticoagulant & antiplatelet (AC/AP) medications
  • Indicated for management of several conditions
    • Venous thromboembolism
    • Prevention of stroke in patients w/ atrial fibrillation & MI
    • Review of established & newer therapies
    • Potential ocular & non-ocular complications pertinent in optometry
  • AC/AP medications & ophthalmic surgery
  • Ocular conditions that may require AC/AP use

Goals
• Be familiar with:
  • Commonly used & newer anticoagulants & antiplatelet (AC/AP) therapy
  • Potential ocular complications of AC/AP therapy
  • Potential non-ocular complications of AC/AP therapy pertinent to optometrists

GENERAL INDICATIONS FOR ANTICOAGULATION

Venous Thromboembolism
• Deep Venous Thrombosis
• Pulmonary Embolism

DISCLOSURE STATEMENT
Nothing to disclose
**Atrial Fibrillation (AF)**
- Thromboembolic complications
- Associated with cardiac valve replacement

**Post-Myocardial Infarction**
- Reduce risk of:
  - Death
  - Recurrent myocardial infarction (MI) & systemic embolism
  - Cerebrovascular accident (CVA)

**Drug Description & Mechanism of Action**
- Inhibits vitamin K-dependent coagulation factors

**Warning: dietary changes**

- Zinc
- Magnesium
- Calcium
- Iron
- Vitamin K
- Fatty acids
- Alpha-tocopherol
- Other anticoagulants

**Warning:** Major (fatal) bleeding risk

- Initiation of & intensity of AC therapy
- Age
- Concomitant drug use
- H/O GI bleeding
- High risk of falls or trauma
- Heavy alcohol use
- Kidney failure
- Malignancy
- Cerebrovascular disease
Epidemiology

- % of US population on some form of anticoagulation
- 21 million prescriptions annually as of 2009
- Approximately 2 million users of warfarin at any time

Dosage & Administration

- American College of Chest Physicians evidence-based clinical practice guidelines
- Dosing: initial, maintenance

Pradaxa (dabigatran)

- FDA approved Oct 2010
- Reduce risk of CVA and 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 w/ nonvalvular AF
  - DVT & PE

Aspirin

- 81 vs 325 mg
- 40-50M Americans use for MI prevention

- General mechanism of action

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
  - ↓ 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: SUB-CONJUNCTIVAL HEMORRHAGE

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

INR: 1.2

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

Left Eye and Adnexa

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

Severe ecchymosis of upper lid & lower orbital area

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

Pertinent Exam Results

- Increased to 1.3 – 2.4 over next 6 days
- INR 3.6 19 days prior to presentation

- beige background
Discussion

- Incidence of sub-conjunctival hemorrhages related to long term AC use found to be 1.5-5%\(^1\)
- Risk twice as great in older patients on AC therapy than younger patients\(^2\)

CASE #2: INTRARETINAL HEMORRHAGES

Case History

- 84 year old Caucasian male
- Annual eye exam
- Chief complaint: none
  - Bruises & bleeds easily; bumped arm in waiting room & started bleeding; holding tissue over affected area
- POHx:
  - Chronic intraretinal hemes &/or MAs OU x several years
  - Pseudophakia OU

Case History

- PMHx
  - CAD s/p CAGB 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

Case History

- 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
**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\(^2\)

**CASE #3: VITREOUS HEMORRHAGE**

- 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 History

- 62 yo Caucasian female requests urgent exam
- Chief complaint:
  - 'Streaks of blood' in vision OD x 4 weeks
  - Slowly worsening of vision and symptoms
- Stable F/Fs x 1 week
- POHx:
  - Recurrent vitreous hemes OD x 3/18/08
    - No DM retinopathy OD at LEE when fundus visible
  - Early PDR OS x 2/1/08; did not meet PRP criteria
  - Ocular hypertension OU

PMHx:
- Atrial fibrillation, HTN
- DM x 21 years (HgA1c: 5.9)
- Meds:
  - Warfarin 10mg
    - Take ½ every evening except take 1 on Thurs & Sun
    - INR 3.1
    - Range since onset of VHs: 0.9 – 5.8
  - ASA 81mg

Pertinent Exam Results

- BCVA: OD HM @1 ft (marked reduction)
  OS 20/30
- Pupils: Stable
- EOMs: Full OU
- CF: Full to HM OD / FTFC OS
- SLE: OD no hyphema, no NVI, PCIOL OS stable
- Ta: OD/OS 22/13 mmHg

Fundus View & B-Scan OD

- Hyper-reflectivity in vitreous c/w hemorrhage>inferior
- Retina intact, no masses, no RD/break

Diagnosis & Plan

- Recurrent vitreous hemorrhage OD
  - Reactivated bleed x 1 month
  - Likely from warfarin (h/o very mild NPDR w/ LA1C of 5.9)
  - Consult with retinal specialist
    - In light of past ocular history, recommend to PCP to adjust dosing of warfarin due to recurrence of VHs
- RTC 1 month for follow up
  - Patient educated to avoid heavy lifting & bending over; sleep upright as possible.

Discussion

- AC/APs 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

Association of Rivaroxaban Anticoagulation and Spontaneous Vitreous Hemorrhage

Brief Report

Judy H. Jin, BSc John C. Hong, MD, MSc
JAMA Ophthalmol. 2015

…risk of heme maybe elevated during transition period when patients are switched from AC to rivaroxaban…
CASE #4: HEMORRHAGIC PVD

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

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 OD

B-scan: mild vitreous opacity w/ good after-movement

Weiss Ring OD

- B-scan:
  - PVD, mild vitreous opacity w/ good after-movement; 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

MATTHEW T. STUMPER, MD, STEVEN M. COHEN, MD

RETINA 33:621-626, 2014

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

Case History

CASE #5: HYPHEMA

- 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
  - 1.3grams 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 centered 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)

Other Retinal Hemorrhages
- Sub-retinal
- Pre-retinal

Optic Disc Hemorrhage
Significant association btw ASA & ODH
Possible association between ODH & generalized vascular disease
AMD & ASPIRIN
Exudative vs Non-Exudative:
Latest study findings

**EPIDEMIOLOGY OF THE ASSOCIATION BETWEEN ANTICOAGULANTS AND INTRAOCULAR HEMORRHAGE IN PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION**

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

**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).

Methods: A prospective analysis was conducted of data from the Beaver Dam Eye Study. Patients were followed for 15 years, and aspirin use was assessed at each visit.

Results: Of 4,209 participants with follow-up data available, 235 individuals (10.6%) were regular aspirin users and 65 of the 2,300 developed neovascular AMD. Persons who were regular aspirin users were more likely to have incident neovascular AMD: the 15-year cumulative incidence was 9.3% in users and 5.8% in nonusers. After adjustment for age, sex, smoking history, body mass index, hypertension, and family history of cardiovascular disease, the hazard ratio for regular aspirin users was 2.01 (95% CI, 1.02-3.94). The association remained significant after multivariate adjustment (hazard ratio, 1.87; 95% CI, 1.00-3.50).

Conclusion: Regular aspirin use is associated with increased risk of incident neovascular AMD, independent of a history of cardiovascular disease and smoking.

**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 nutritional factors with the incidence of neovascular age-related macular degeneration (AMD) and central geographic atrophy (CGA) in the Age-Related Eye Disease Study (AREDS), a randomized trial of antioxidants and zinc supplementation prophylaxis for development of advanced AMD.

Higher incidence of central geographic atrophy weakly associated with ASA use


**The European Eye Study 2012**

Frequent ASA use associated with early & wet late AMD

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

Wei Zha, Yan Wu, Ding Ba, Yan-Hong Li, Jun Bu, Xian-Long Zhang, Fang Wang, Jing Yu
Department of Ophthalmology, Affiliated Tongji Hospital of Tongji University, Shanghai, China. Department of the Clinical Medical College, Fudan University, Shanghai, China.

Abstract

Background: Age-related macular degeneration (AMD) is one of the leading causes of blindness worldwide. Aspirin (ASA) use has been linked to a decreased risk of AMD, but the evidence is limited.

Methods: A comprehensive meta-analysis was performed using data from multiple studies.

Results: Ten studies met the inclusion criteria. Among the included studies, the relative risk of AMD was found to be significantly lower in the aspirin group compared to the control group. The authors concluded that the use of aspirin may be associated with a decreased risk of AMD.

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

Prescribing of Supplements

• AREDS recommended supplements for AMD
• Vitamin E

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 are possible.

Recommendation: Evaluate warfarin response when vitamin E used in combination.

Aspirin Benefits Outweigh Risks in Macular Degeneration
American Society of Retina Specialists (ASRS) 2015 Annual Meeting
Presented July 13, 2015
AC & Ophthalmic Surgery

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

AC & Ophthalmic Surgery

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

- 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 low
  - No intraoperative complications
    - Maintain therapeutic levels of AC during surgery
    - Intravitreal injections
    - No hemorrhagic events; can continue AC safely

PRE-CAUTIONS & OTHER POTENTIAL COMPLICATIONS

Intracranial Injury

- Higher risk for subdural and epidural hematoma when anti-coagulated

CASE REPORT #6: MINOR HEAD TRAUMA
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

Findings:
- Relatively hypodense bilateral subdural fluid collections
- ~0.6cm SDH
- ~1.1cm SDH
- Midline ~1.1cm SDH
- Counter-balancing mass effect w/ ~2 mm net shift to the left

Diagnosis & Plan

- Chronic subdural hematoma due to minor head trauma after fall
- No ocular sequelae
- Consult with neurosurgery
- Monitor, repeat CT of head
- Go to ED for HA, diplopia or other visual changes

Discussion

Common practice to image patients with head CT after even minor head trauma
EDs have protocols in place for immediate management as well for observational periods

Conclusion: If negative initial head CT, recommend 24-hr observation period followed by 2nd CT
**Conclusions:**

Elder patients with head trauma have a higher risk of intracranial injury (SDH/EDH). An occult presentation is more common in elders.

**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
- 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

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

Tx with A/Ps a mainstay of medical therapy

Symptomatic CAS
- Prompt A/P therapy to prevent recurrent TIA
- ASA vs ASA & clopidogrel
- A/C not indicated

Asymptomatic CAS
- ASA only [unless other concomitant condition(s)]

Hollenhorst Plaque/Embolus

Conclusion: Asymptomatic retinal cholesterol embolism is an important risk factor for cerebral infarction…
Retinal Vascular Occlusions

- Often are undiagnosed systemic vascular risk factor & @ risk of systemic ischemic event such as CVA
- CRAO: "ocular analogue of cerebral stroke"
- 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 w/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