“AFIB CASE”

- JM is a 70 yo lady to ER 8/17: palp after a heated argument with her husband
- Rapid AFib - IV diltiazem; NSR next day
- Echo: LAE, LVH, systolic, he breast CA, D/C'd on Eliquis
- Consult 4/10/2018:
  - Asymptomatic. No more arguments with husband.
  - 3 BP meds. Eliquis, inhalers, vitamins
  - BP in the office 150/95
  - ECG: NSR
  - Wors “blood thinner d/c’d, she is concerned about bleeding problems she saw on TV commercials.”

SYMPTOMATIC VS ASYMPTOMATIC AFIB

- 110 pts with intermittent afib underwent PPM implant for bradycardia
- f/u 19 months:
  - Recurrent intermittent afib in 51 pts (46%)
  - 50 of them, afib >48 hrs
  - 19/50 asymptomatic and in NSR during f/u visit

Significant number of patients are totally asymptomatic during recurrent afib

JACC 2004

ATRIAL FIBRILLATION

- Most common cardiac arrhythmia
- Mostly age related:
  - 10% people 80 or older
  - 25% people over 40 will have afib
  - 40% of afib pts are 65 or older
  - 80% are 65 or older
- Number AFib pts will double in 10-15 years [4.5 million now]

JAMA 2001
PREVALENCE OF DIAGNOSED AF
Stratified by Age and Sex

INCREASING NUMBERS PTS WITH AFIB
- 1.5 million patients by 2050 (currently 4-5 M)
- Pts living longer, improved survival post-MI (other CV procedures)
- Increased obesity-sleep apnea
- High economic strain, hospitalizations: 30% readmitted within 145 days (Value Health 2006)

CONSEQUENCES OF AFIB
- Stroke and peripheral embolization
- Symptoms
- Tachycardia induced cardiomyopathy
- CHF (3-4 fold increase)
- Vascular dementia
- Dooles mortality
- Major economic burden: x billion dollars per year

CAUSES OF CARDBOEMBOLIC STROKES
- AF
- Recent MI
- Dilated CMP
- Mechanical prosthetic valve
- Rheumatic heart disease-mitral stenosis
- Bacterial endocarditis
- Myxoma
- PFO, ASD, VSD
- Cabolic AI
- MAC
- Atrial septal aneurysm

AF CONFERS AN INCREASED CARDIO-EMBOLIC RISK, NOTABLY TO THE BRAIN
- AF confers a near 5-fold risk increase of stroke
- It is estimated that 20% of all strokes are caused by AF
- AF is often asymptomatic
- The absence of symptoms (e.g. palpitations) does not imply a lower risk of thromboembolism

MANAGEMENT OF AFIB
- Anticoagulation?
- Rate vs rhythm control
MANAGEMENT OF AFIB

- **Anticoagulation:** warfarin, NOACs, LAA closure-Watchman
- **Rate control:** β-blockers, Ca channel blockers, AVN ablation
- **Rhythm control (maintain NSR):**
  - Antiarrhythmic drugs/intermittent DCCV
  - Catheter ablation of the pulmonary veins (PVI)

AFIB AND EMBOLIC STROKE

- Increased risk of CVA (up to 25%/year)
- 30% of CVAs
- 70,000 CVAs annually in USA (>200,000 due to afib)
- 5 hrs of afib increase risk stroke
- Not all CVAs in afib pts are embolic
- Embolic CVAs tend to be severe!
- Paroxysmal vs chronic afib- similar stroke risk

AFIB AND RISK OF STROKE

- Risk factors, not afib burden, determine risk of stroke!!
- <60 year old/no risk factors: stroke rate <1% per year ("lone afib")
- 80 year old: 25-30% stroke rate per year
- X5 risk with nonvalvular afib
- X17 risk with rheumatic or prosthetic valve: VALVULAR AFIB (5%)

AFIB AND EMBOLIC STROKES: SEVERE CONSEQUENCES

- 75% dead or disabled at 1 year
- Bed ridden at 6 months:
  - 41% with afib
  - 24% with NSR

ACUTE IN-HOSPITAL STROKE MORTALITY

- Embolic: 27%
- Thrombotic: 22%
- Lacunar: <1%
- Early recurrent embolic (<7 days): 80%
VALVULAR AFIB

- Mechanical mitral valve
- Mitral stenosis
- 17 times risk of stroke
- Always Warfarin!

LEFT ATRIAL APPENDAGE: SOURCE
>90% OF EMBOLIC STROKES IN NONVALVULAR AFIB

LEFT ATRIAL APPENDAGE

- Different morphology vs LA (trabeculated versus smooth wall)
- Highly variable anatomy (long, multilobe, circular)
- Much more distensible (decompression chamber for LA)
- 30% BNP in LAA
- On top of the LV
- Surgical versus catheter closure

MRI was subsequently obtained in the same patient. An axial T2 FLAIR image (left) demonstrates high signal in the lentiform nucleus with mass effect. The axial diffusion-weighted image (middle) demonstrates high signal in the same area with corresponding low signal on the apparent diffusion coefficient (ADC) maps, consistent with true restricted diffusion and an acute infarction. Maximum intensity projection from a 3D time-of-flight MRA (right) demonstrates occlusion of the distal
RISK FACTORS FOR STROKE IN NV-AFIB (CHADS-VASC)

- Age *
- Prior thromboembolic event *
- CHF or enlarged heart
- HTN
- DM
- Female gender
- Vascular disease
- LA enlargement

THE CHADS-VASC SCHEME

<table>
<thead>
<tr>
<th>CHADS2</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHADS-VASC</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure/LV dysfunction</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 75 y</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/TE</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>1</td>
</tr>
<tr>
<td>Age 65-74 y</td>
<td>1</td>
</tr>
<tr>
<td>Sex category (i.e. female gender)</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHADS-VASC Score and Stroke Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke at One Year</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHADS-VASC Score and Stroke Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke Rate during 1 yr.</td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
</tbody>
</table>

*CHADS2: Congestive heart failure, Hypertension, Age ≥ 75 y, Diabetes mellitus, Stroke/TIA/TE

CHADS-VASC Score

0.5
1
2
3
4
5
6
7
8
9
Stroke Rate % per year

COLOR BOX: BLEEDING RISK SCORES
- Several scoring systems to predict risk of bleeding in patients initiating AC
- Less predictable than stroke risk scores
- Unclear whether to use them in decision making for individual patients
  - HASBLED
  - ATRIA
  - HEMORR2-HAGE

COLOR BOX: BLEEDING RISK SCORES IN AF

COLOR BOX: ESC 2012 RECOMMENDATIONS – CHOICE OF Anticoagulant
- Non-valvular AF
  - <65 years & lone AF (including female)
  - Assess risk of stroke (CHA2DS2-VASc score)
  - Warfarin or NOAC
  - NOAC should be considered instead of VKA (INR 2–3) for most patients aged ≥65
- Valvular AF
  - Consider patient values and preferences

COLOR BOX: WARFARIN
- Available since 1954
- Until 1990s used for valvular AF only (mechanical valve, mitral stenosis)
- Inhibits (liver) enzyme - dysfunctional factors II, VII, IX, X, C, S
- Very inexpensive, widely available

COLOR BOX: HOW DO VIT K ANTAGONISTS WORK?
- Coagulation proteins need to bind Calcium
  - To bind Calcium, these (VII K dependent) coag proteins need to be “carboxilated”
  - Vitamin K carboxilates de coag proteins
  - After vit K carboxilates these proteins, an enzyme “recycles” the Vit K back to baseline
  - Enzyme is called VitK epoxide reductase
  - Warfarin inhibits this enzyme - so coag factors are not carboxilated, don’t bind Calcium
  - Coag proteins are dysfunctional
  - Functional proteins are still circulating with variable ½ lives (shortest VII)
NONVALVULAR AFIB:
LATE 1980S, 5 PRIMARY PREVENTION TRIALS
WARFARIN VS PLACEBO
(<3,000 PTS TOTAL)

WARFARIN DECREASED RISK OF STROKE ABOUT 60% (VS PLACEBO)
ALL TERMINATED PREMATURELY (REACHED EFFICACY ENDPOINT)

VITAMIN K ANTAGONISTS AND ANTIPLATELET AGENTS
REDUCED STROKE BY ~60% AND ~20%

THE RISKS OF STROKE OR INTRACRANIAL BLEED ARE HIGH OUTSIDE A NARROW INR RANGE

TIME IN THERAPEUTIC RANGE (TTR)
- The benefit of VKA for reducing the risk of stroke in patients with AF depends on the time in which patients remain in the optimum therapeutic range (INR 2.0-3.0)
- There are large variations in TTR between individuals, sites, and countries
- In well-controlled clinical trials, patients remain in the therapeutic window only between 50-70% of the time
- Observational data from usual clinical practice often show lower means

LIMITATIONS OF VKA THERAPY
- Narrow therapeutic window (INR range 2.0-3.0)
- Risk of stroke
- Risk of bleeding
- Considerable variability in dose response (genetic variations)
- Interactions with drugs and diet
- Contraindications (atrial fibrillation)
- Low half-life
- Slow onset and offset of action
- Increased risk of bleeding
- Considerable variability in dose response (genetic variations)
- Interactions with drugs and diet
- Contraindications (atrial fibrillation)
- Risk of stroke
- Risk of bleeding
LIMITATIONS ANTICOAGULATION WITH VKA

- Fatal or intracranial bleeds
- Elderly can be frail, fall, cognitively impaired
- Already on anti-PLTs (aspirin, Plavix, nonsteroidals)
- Interactions between anticoagulants/other meds (ATBs, etc.)
- Clinic visits for INRs
- Days to reach INR in range
- TTR 60% of best
- Expertise of Coumadin clinic, changes in dose

INTRACEREBRAL BLEEDS ON WARFARIN

- 17% major deficit
- 46% mortality
- 50% with INR in range (2-3)
- About 1% per year

RISK FACTORS FOR INTRACEREBRAL BLEEDS

- Advancing age
- Poorly controlled HTN
- Excessive AC
- Combination with anti-PLTs
- Amyloid plaques in MRI

UNDERUSE OF VKA DESPITE PRIOR TIA OR CVA

AF patients with previous TIA or ischaemic stroke, considered to be suitable for anticoagulation and admitted with acute ischaemic stroke (Ontario 2003–2007)

<table>
<thead>
<tr>
<th>Low dose Coumadin, 15%</th>
<th>No antithrombotic, 15%</th>
<th>Warfarin, therapeutic, 10%</th>
<th>Warfarin, subtherapeutic, 10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dual antiplatelet therapy, 5%</td>
<td>Single antiplatelet agent, 25%</td>
<td>Warfarin, therapeutic, 10%</td>
<td>Warfarin, subtherapeutic, 10%</td>
</tr>
</tbody>
</table>

100 persons with AF
- One half receive a VKA
- One half are suboptimally treated
- Few are still on treatment at six years

Effective, safer and more convenient therapies are urgently needed

Healey et al. Presented at the ESC meeting Sunday August 28, 2011.

NEW ORAL ANTICOAGULANTS (NOACS, DOACS)

“Advantages”
- Immediate AC
- No coagulation monitoring
- Fixed dose
- No dietary constrains
- Few drug interactions (?)
- Much less intracranial bleeds
- Less strokes/less bleeding

“Disadvantages”
- Expensive
- No coagulation monitoring
- No reversal for Xa inhibitors
- Compliance
- No long term experience

WARFARIN
Kay & Mouse Killer Meal Bacon and Cheese Flavoured
2 Ready To Use Bait Bases

proteins in the blood

NEW ENGLAND JOURNAL OF MEDICINE
Soluble Thrombosis

Heparins
- Eptioidenase
- Antithrombin
- Activating protein C
- Direct thrombin inhibitors
- Anti thrombin

Fibrin-bound Thrombosis
- Antithrombin
- Activating protein C
AVERROES: NO DIFFERENCE IN THE RISK OF MAJOR BLEEDING BETWEEN APIXABAN AND ASA


<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at Risk</td>
<td>2808</td>
<td>2791</td>
</tr>
<tr>
<td>Event rate (% / year)</td>
<td>44/2808</td>
<td>39/2791</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1.13% (95% CI: 0.74 - 1.75); p=0.57</td>
<td>1.02%</td>
</tr>
<tr>
<td>Stroke/systemic embolism</td>
<td>55% RR p&lt;0.001</td>
<td>+13% RR p=0.57</td>
</tr>
</tbody>
</table>

APIXABAN HAD SUPERIOR EFFICACY VS. ASA WITHOUT SIGNIFICANTLY INCREASING THE RISK OF MAJOR BLEEDING

CAN WE RESUME ORAL AC AFTER GI BLEEDING?
- Was a source identified and treated (cauterized, artery embolized)
- Is the source still around (multiple AVMs)
- On ASA?
- How severe was the bleed
- Predisposing factors to the GI bleed (drug interaction, anti-PLTs, ETOH)
- What is the risk of stroke (Chads-vasc)
- Switch to a different agent?

CHRONIC KIDNEY DISEASE INCREASES THE RISK OF THROMBOEMBOLISM IN UNTREATED AF PATIENTS

Table 2: Intracranial hemorrhage among patients taking NOACs

<table>
<thead>
<tr>
<th>Drug and dosage</th>
<th>Total</th>
<th>Population (n)</th>
<th>Events</th>
<th>Intracranial bleeds (ITT %/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran 150 mg bid</td>
<td>6016</td>
<td>96</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>Dabigatran 110 mg bid</td>
<td>6015</td>
<td>27</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban 20 mg od</td>
<td>7131</td>
<td>67</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
<td>Apixaban 5/2.5 mg bid</td>
<td>9120</td>
<td>52</td>
<td>0.59</td>
<td></td>
</tr>
</tbody>
</table>


ATRIA: Assembly of the Anticoagulation and Risk Factors in Atrial Fibrillation
eGFR: estimated glomerular filtration rate
MDRD: modification of diet in renal disease
*676 validated thromboembolic events (637 ischaemic strokes, 39 other thromboembolism)
DABIGATRAN AND RENAL FUNCTION

- Dabigatran largely renal excreted (80%)
- Lower dose for CrCl 15-30 cc (75 mg bid*)
- Not indicated with CrCl <15 cc
- Lower dose not tested clinically (only by pharmacokinetic studies)
- Sudden changes in renal function will affect levels of Dabigatran
- If CrCl <50 cc: implications to hold AC for surgical procedures
- * pts without renal dysfunction are being treated with this dose.

NOACS AND RENAL IMPAIRMENT

Xa inhibitors
- Active apixaban 27% renally excreted
- Active rivaroxaban 33% renally excreted

Can they be used in pts with severe CKD?
- Pts with severe CKD were excluded from large Xa trials
- Short term pharmacokinetic studies done in small number of pts

DRUG INTERACTIONS WITH NOACS

- Anti-PLT drugs and NOACs significantly increase major bleeding
- Addition of other anti-thrombotics will increase risk of bleeding
- Interactions with non AC drugs:
  - Dabigatran: drugs that affect P-glycop transport
  - Xa inhibitors: drugs that affect P-glycop and liver CyPA4
  - Inhibitors and inducers of these pathways

DRUG INTERACTIONS WITH NOACS

Inducers (P-glycop, CyPA4): decrease levels of all NOACs (increased risk of stroke):

  - Rifampin, dilantin, carbamazepine

Inhibitors of P-glycop: increase levels of all NOACs- no sig clinical interactions, but:

  - Amiodarone, dashion , verapamil, diltiazem

Inhibitors of CyPA4: increase levels of Xa's: increased risk bleeding

  - Fluoco/ketoconazole, antivirals, clarithromicins

DOSING OF NOACS

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Rivarox</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>150 mg</td>
<td>5 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>Frequency</td>
<td>bid</td>
<td>bid</td>
<td>QD</td>
</tr>
</tbody>
</table>

Creat clearance:

- >30 cc
- 15-30 cc
- If 2/3 present:
  1) age 80
  2) 60 kg or less
  3) creat 1.5

15 mg if renal clearance < 30 cc
MEASURING THE AC EFFECTS OF NOACS

Coagul Assays

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Rivarox</th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>ProT-INR</td>
<td>not useful</td>
<td>not useful</td>
<td>not useful</td>
</tr>
<tr>
<td>PTT</td>
<td>no effect</td>
<td>no effect</td>
<td>qualitative</td>
</tr>
<tr>
<td>Thrombin time</td>
<td>quantit</td>
<td>quantit</td>
<td>no effect</td>
</tr>
<tr>
<td>Anti Xa</td>
<td>no effect</td>
<td>no effect</td>
<td>quality/quantitative</td>
</tr>
<tr>
<td>Anti II</td>
<td>no effect</td>
<td>no effect</td>
<td>quantitative</td>
</tr>
</tbody>
</table>

MANAGEMENT OF MAJOR BLEEDING WITH NOACS

- Antidote for dabigatran: idarucizumab (Praxbind)
- Factor Xa antidote anexanet alpha- not available
- Identify/correct bleeding site (endoscopy, surgery)
- 4 factor PCPs, recombinant factor VII (hematology input)
- Oral activated charcoal
- No FFP
- PRBCs, vasopressors, intubation
- Hemodyalysis for dabigatran (does not add much if GFR >40-50)
- Multidisciplinary approach (renal, surgery, inter radiology, hematology)
- Uncommon!

IDARUCIZUMAB: DABIGATRAN REVERSAL AGENT

- Monoclonal antibody with high affinity to dabigatran
- Affinity to D is >350 times affinity of D to thrombin
- Immediate onset of action
- No procoagulant effect
- IV administration of 5 grams (2.5x2 <15 min apart)
- Always consider risk of complete reversal of AC

IDARUCIZUMAB: REVERSAL OF DABIGATRAN ANTICOAGULATION

Immediate reversal for
- Uncontrollable or life threatening bleeding requiring reversal
- Need for urgent surgical procedure that cannot be delayed

100% effective in reversing anticoagulation effect of dabigatran in:
- 300 pts with uncontrollable bleeding who required urgent surgery (median time to bleeding cessation: 2.5 hrs)
- 200 pts who required urgent surgery (median time to procedure 1.6 hrs)

MANAGEMENT OF BLEEDING WITH X INHIBITORS: PROTHROMBIN COMPLEX CONCENTRATES

- Prothrombin complex concentrate (PCC) contains coagulation factors II, VII, IX, X
- An in vivo study suggests that PCC or activated PCC reverse the anticoagulant action of apixaban
- So far, there are no studies with apixaban with PCC or activated PCC in humans
- Some animal studies suggest a beneficial effect of PCCs for the reversal of bleeding with apixaban
- PCC immediately and completely reversed the anticoagulant effect of apixaban in healthy subjects

WARFARIN VERSUS NOACS

<table>
<thead>
<tr>
<th>Warfarin</th>
<th>NOAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow inhibition of enzymes</td>
<td>Immediate inhibition factor II or X</td>
</tr>
<tr>
<td>Slow on/off: ½ life is days/weeks</td>
<td>Half life 7-14 hrs: quick on/off</td>
</tr>
<tr>
<td>Many drug/dietary interactions</td>
<td>No diet and few (?R) drug interactions</td>
</tr>
<tr>
<td>Liver metabolized</td>
<td>Metabolized renal or liver or both</td>
</tr>
<tr>
<td>Spontaneous intracerebral bleeds</td>
<td>Sig less intracerebral bleeds</td>
</tr>
<tr>
<td>INR: 2.5-4.5% of best</td>
<td>No coags monitoring</td>
</tr>
<tr>
<td>Antidote slow to work</td>
<td>Antidote exceptionally quick (Dabigatran)</td>
</tr>
</tbody>
</table>
CANDIDATES FOR WARFARIN

- Cost: can not afford NOACs
- Severe renal insufficiency
- Valvular afib
  - mitral stenosis
  - Mechanical valves
- Other reasons

ANTICOAGULATION FOR AFIB: WATCHMAN DEVICE

Left atrial appendage emboli 95% embolic CVA
Intra-cardiac closure of the LA appendage
FDA approved 2016
Similar efficacy and safety compared to warfarin
Not tested against NOACs
Mostly when oral anticoagulation not possible (i.e., bleeding)
SURGICAL “CLOSURE” OF LAA TO DECREASE STROKE

- Excision versus exclusion – multiple different techniques
- No randomized studies (increase afib, less natriuretic factor)
- Does not always work: need to assess by TEE for persistence flow

DCCV WITHOUT AC

437 pts CVA in 5.3% not AC, versus 0.8% with Warfarin
Afib >48 hrs (223 pts), TEE clots 15%, all in LAA
Afib >3 days (122 pts), LA clots in 29%

Therefore:
For DCCV, AC 3 weeks before and 4 weeks after TEE without clots- AC for 4 weeks after