Evidence-Based Pharmacotherapy for the Dentist: Anticoagulants and Antibiotics

Kelly W. Jones, PharmD, BCPS
McLeod Family Medicine Center
Florence, South Carolina

kjones@mcleodhealth.org
Disclaimer

- I have no conflict of interest relating to the material covered in our discussion today.
- I do not serve on any speaker bureau.
- I do not have any grants concerning the area of discussion.
Objectives

A Comprehensive, Evidence-Based Review of Anticoagulation for the Dentist.

1. Discuss the different type of research papers that provide outcomes that change the practitioner’s practice of dentistry (Disease-oriented versus Patient-oriented).
2. Comprehensive review of the new anticoagulants, detailing the medications history, pharmacotherapy, pharmacokinetics, side effects, and drug interactions.
3. Discuss low, medium and high risk surgeries and what needs to be done when a patient is on anticoagulation.
4. Briefly describe the concepts of relative risk reduction, absolute risk reduction, number needed to treat (NNT) and number needed to harm (NNH), and how these statistical measures affect data interpretation.
5. Discuss POEMS from clinical research that should change your practice in dentistry.
Objectives

Seek and Destroy: Therapeutic Pearls for Old and New Antibiotics

1. Discuss the various classes of antibiotics, selecting out those antibiotics that are clinically useful today.
2. Discuss the principles used to select an antibiotic empirically for a given infection.
3. Discuss and apply the principle of "Drugs and Bugs" to the antibiotic classes.
4. Discuss the difference dosing regimen duration for different infections.
5. Discuss MRSA and the current treatment for outpatient management.
First thing we have to discuss!

- What is Evidence-Based Medicine (EBM)?
- What is Evidence-Based Dentistry (EBD)?
  - Your profession is embracing the concept of EBD!
  - See www.cebd.org
  - See www.ada.org/276.aspx

- “Evidence-based medicine is the conscientious, explicit, and judicious use of best evidence in making decisions about care of the individual patients.”
  
  David Sackett

- “Evidence-based medicine is the integration of best research evidence with clinical expertise and patient values.”
How do you know what you know?

- The area of study of this question is known as: Epistemology
Epistemology

- Should physician-assisted suicide be allowed in some situations?
- Should it be legal for people to buy organs for transplant, if they would not be able to receive an organ by waiting their turn through a national database?
- A woman has the right to choose an abortion.
- A woman does not have the right to choose an abortion.
- A woman has the right to choose an abortion in certain situations.
Knowing what we know!

- In medicine and dentistry, we utilize several things:
- Experience
- Opinion (although watch out for GOBSAT)
- Empirical evidence
  - we should utilize evidence when we have it
You see a 65 year old postmenopausal woman who has osteoporosis. You want to begin a bisphosphonate (e.g., Fosamax®) in her to prevent a hip fracture. Put these reductions in the order that best reflects what you would like to see for your patient.

Each situation represents the same data.

- A. 1.1% reduction in hip fracture
  Absolute Risk Reduction (ARR)
- B. 50% reduction in hip fracture
  Relative Risk Reduction (RRR)
- C. Treating 91 women just like her would prevent one hip fracture
  Number-needed-to-treat (NNT)
You are responsible!

- Be like “Yoda”
- Your Own Data Analyzer

- The “Force” is not just knowing, it’s in the application
To read POEMS that change your practice!

**DOEs:**

- **Disease-oriented evidence**
  - Pharmacology, pathophysiology, etiology
  - Surrogate markers for disease in medicine
    - Lowering cholesterol, lowering BP or blood glucose, increasing BMD, improved drug bioavailability, etc.
  - Surrogate markers for disease in dentistry
    - Reduction in plaques or bacterial counts (i.e., % Step mutans in plaques), alveolar bone loss, does your toothpaste have fluoride?, fluoride inhibits endolase, bacterial counts on toothbrushes, calcium levels

*JFP. 38(5):505-13, 1994*
POEMs change our practice!

POEMs:

- Patient-oriented evidence that MATTERS
- Morbidity, mortality and quality of life
- Final outcomes of disease
  - Stroke, heart attack, hip fracture, admission to the hospital or SNF, performance of ADLs
  - Dentistry – lower gingivitis, reduce implant failure, fluoride and cavity development

POEMs should result in a change in your practice

*JFP. 38(5):505-13, 1994*
CAST Trial

- CAST evaluated the effect of antiarrhythmic therapy (encainide, flecainide, or moricizine) in patients with asymptomatic or mildly symptomatic ventricular arrhythmia (six or more PVC’s per hour) after myocardial infarction.

- Results
  - 75% reduction in PVC’s
  - Increase total mortality with encainide, flecainide
  - RRI = 60%
  - ARI = 4.7%

NEJM 1989;321:406-12
Which of the following would you expect to be a POEM?

- The detection of arginine metabolism in dental plaques.
- Escitalopram (Lexapro) is 100X more potent in inhibiting serotonin reuptake than citalopram (Celexa).
- Efficacy of Pneumovax® in preventing pneumonia and improving survival in nursing home residents: double-blinded, randomised and placebo-controlled trial.
- Antibiotics prior to implant placement reduces dental implant failures.
DOEs and POEMs

- **POEM**
  - Often changes daily practice

- **DOE**
  - Does not always change daily practice
  - Ask questions that result in further study
  - A DOE often begets a POEM
  - Sometimes they are misused!
  - For example............
There’s been a murder on Narcotic Row

- Propoxyphene killed by FDA
  - Murder weapon: QT elongation
- Death reports from propoxyphene are primarily due to overdose and suicides
  - Been on the market since 1957
  - 1969 to 2005
  - 472 domestic adverse event reports
  - 91 deaths, 74 linked to multi-drug overdoses (The MJ-PK Effect)
  - Propoxyphene ranks lower than hydrocodone and oxycodone for intentional exposures.

1957 to 2010
Analyzing the POEM!

First we need perspective

RRR vs ARR

Risk vs Benefit

Fracture protection that fits her life

EVISTA reduces first-time vertebral fracture by 55%* vs. placebo
and offers a convenient dosing regimen

Based on results from the MORE (Multiple Outcomes of Raloxifene Evaluation) trial. EVISTA reduces the risk of first-time vertebral fracture in women previously diagnosed with osteoporosis by 55% (absolute risk reduction, 2.4%), and reduces the risk of subsequent vertebral fracture by 30% (absolute risk reduction, 6.1%).

Contraindications — EVISTA is contraindicated in women who are or may become pregnant, as it may cause fetal harm, and in nursing women. EVISTA is also contraindicated in women with active or past venous thromboembolic events (VTEs). Safety and efficacy have not been evaluated in patients with severe hepatic insufficiency.

Adverse Events — EVISTA is associated with an increased risk of VTEs, with the greatest risk for VTEs occurring during the first 4 months of treatment. Common adverse events considered to be drug-related were hot flashes and leg cramps.

Widely accepted risk factors for postmenopausal osteoporosis include: Caucasian or Asian descent, slender body build, early estrogen deficiency, smoking, alcohol consumption, low calcium diet, sedentary lifestyle, and family history of osteoporosis.

Supplemental calcium and/or vitamin D should be added to the diet if daily intake is inadequate.

Please see brief summary of prescribing information on next page for additional information.

For the prevention and treatment of postmenopausal osteoporosis

Proven Protection and Tolerability

Do you understand risk?

- What is the risk of stroke in an elderly patient with atrial fibrillation?
- Warfarin reduces strokes by ~50% in patients with atrial fibrillation
- What’s the risk of a stroke in AF?
  - 5% per year
  - Risk of stroke with warfarin is ~2.5%
- A 50% reduction is really a 2.5% absolute reduction
  - Risk of stroke with aspirin is 4%

BAFTA Trial Lancet 2007; 370: 493-503
Do you understand risk?

- What’s this patient’s risk of a stroke?
- A female age 70 yrs, BP ~174/86
- 44% reduction of stroke when treated
- In the Syst-Eur trial, the risk of having a stroke in this type patient over 4 years was 2.5%
- A 44% reduction is 1.4%

Syst-Eur Study Group. Lancet 1997;350:757-64 (Sept 13)
What’s the risk of a nonfatal MI in this patient?

- male, 60 years of age, white, nonsmoker, BP = 165/95, BMI = 29, glucose = 112, SCr = 1.3, baseline TC = 212, baseline LDL = 130, HDL = 50, diabetes in family
- Lipitor® 10 mg reduces nonfatal MI by 37%
- Risk is ~ 3% over 5 years
- 37% reduction = 3% to 1.9%

ASCOT Trial Lancet 2003;361:1149-58 (April 5)
The Numbers of EBM

- Incidence of hip fracture  (Lancet 1996;348:1535)
- Placebo  2.2%
  - Must always use event rate which is the number of events divided by the total in group (“n”)
- Alendronate  1.1%
- RRR  50%
  - RRR = control - treatment / control (2.2%-1.1%/2.2% = 50%)
- ARR  1.1%
  - ARR = control - treatment (2.2% - 1.1% = 1.1%)
- NNT  91
  - NNT = 1/ARR (100/1.1% = 91)
What about harm?

- The number-needed-to-harm (NNH) is the term for assessing side effects/harm of treatments
- Same type of calculation as NNT
Women Health Initiative

- The Women’s Health Initiative
  - Stopped early because of a 26% increase in risk of breast cancer in women using HT
  - What you saw on the “Today Show”… 26%!!!

- Incidence of the Outcome
  - Placebo Group: 0.30%
  - Hormone Therapy Group: 0.38%

- RRI = 0.38% - 0.30% / 0.30% = 26%
- ARI - 0.38% - 0.30% = 0.08%
- NNH = 100 / 0.08% = 1250
  - Assume 10,000 women - 10,000 / 1250 = 8
Risk/Benefit

- Look at data to weigh the risk-benefit of a treatment.
- We must look at medications based on harm and not just efficacy.
- We weigh risk/benefit every day.
The meaning of risk medicine

*“Risk is basic to medical progress.”*

*“Where risk medicine is abolished, medical advance is also abolished.”*

*“A society which wants good innovations and no risks is asking for the impossible. It is denying the freedom to progress.”*

*“To deny the possibility of failure is to deny the reality of success.”*

RJ Rushdoony, *Roots of Reconstruction*
POEMs and Star Wars?

You are responsible!

To read POEMs that change your practice!

So you can make good dental decisions!
Becoming a Jedi

- Putting it all together
- Evidence-based dentistry thinking allows the practitioner to begin making better “dental decision making”

Secrets of the Jedi
1. Patient-focused
2. Efficacy-Safety-Cost
3. NNT-NNH-Cost
Darth Vader: NO!

Data rules, right?

They are just NUMBERS!
Conundrums abound in medicine and dentistry

- What is a conundrum?
- a confusing or difficult problem
- a riddle, especially one whose answer makes a play on words
- Synonym = brain-teaser

- I like to think of it as a TENSION!
Medicine is full of conundrums

- The patient does not have a pulse
- “Hiccups, a medical conundrum”
- Treating RA and Crohn’s disease with a TNF-blocker, increases the risk of psoriasis
- The mobile/medical conundrum
  - Having information at your fingertips vs security issues
  - Patient privacy issues
- Using placebo in medical practice
- Overdiagnosis
- Going to the doctor when you feel well
- Preventative medicine
  - Risk issues
It’s a conundrum!

- More than 6 million patients in the USA take a long-term anticoagulant.
  - Prevention of thromboembolism of atrial fibrillation
  - Placement of mechanical heart-valves
  - Venous thromboembolism (DVT/PE)

- Medications
  - Warfarin (Coumadin®)
  - Dabigatran (Pradaxa®)
  - Rivaroxaban (Xarelto®)
  - Apixaban (Eliquis®)
Conundrum

- Then you got antiplatelet medications
  - Prevention of stroke and MI
  - Secondary prevention of stroke and MI
  - Post-stent placement

- Medications
  - Aspirin
  - Aspirin/dipyridamole (Aggrenox®)
  - Clopidogrel (Plavix®)
  - Prasugrel (Effient®)
  - Ticagrelor (Brilinta®)
Conundrum for YOU!

- What happens to YOU when you need to extract a tooth and the patient is on an anticoagulant or antiplatelet or both?
Dental surgery and anticoagulants!

- professional cleanings, fillings and crowns have not shown to cause a bleeding risk

Dental surgery in anticoagulant patients:
- 30 studies
- based on 2014 surgical procedures in 774 patients on continuous warfarin therapy
- mouth extractions, alveoectomies, surgical extractions
- INR levels were therapeutic

Arch Intern Med 1998;158:1610-16
Recommendations

- 3 control trials found no difference in postoperative bleeding
- more than 98% of patients had no serious bleeding other than minor oozing controlled with local measures
- Local measures: gelfoam, tranexamic acid, biologic adhesive, Surgicel, fibrin sealant, biting on tea bag
- only 12 of 2014 patients had postoperative bleeding not controlled by local measures, but:
  - 5 of 12 had PT above therapeutic levels
Is it OK to withdraw warfarin before dental procedures?

- There have been several documented cases of serious embolic complications, including death
  - 16 papers, 493 patients
  - 5 serious events including 4 deaths
  - 3 occurred within 5 days of the interruption

Arch Intern Med 1998;158:1610-16
Therapeutic Conundrum

- Balance the risk of postprocedural bleeding with continued therapy to prevent thrombotic events.
- “In general a patient undergoing a procedure associated with a low risk of bleeding (low-risk procedure) can safely continue antithrombotic therapy and should do so, particularly if the patient is at risk for a thrombotic event (high-risk patient).”
- Therefore, a low-risk patient undergoing a high-risk procedure can temporarily discontinue antithrombotic agent.
- The challenge is the high-risk patient undergoing a high-risk procedure!
## Atrial Fibrillation Risk

<table>
<thead>
<tr>
<th>CHADS&lt;sub&gt;2&lt;/sub&gt; Risk Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>C Congestive Heart Failure</td>
<td>1</td>
</tr>
<tr>
<td>H Hypertension (consistently &gt; 140/90 mmHg and/or treated with medication)</td>
<td>1</td>
</tr>
<tr>
<td>A Age &gt; 75 years</td>
<td>1</td>
</tr>
<tr>
<td>D Diabetes Mellitus</td>
<td>1</td>
</tr>
<tr>
<td>S&lt;sub&gt;2&lt;/sub&gt; Prior stroke or Transient Ischemic Attack (TIA)</td>
<td>2</td>
</tr>
</tbody>
</table>

Scores 0 to 2  Low risk  
Scores 3 to 4  Moderate risk  
Scores 5 to 6  High risk  
Stroke or TIA, severe valve disease  High risk
## Procedure Risk

### Table S1. Commonly Performed Procedures and Risk Stratification for Bleeding on the Basis of Frequency and/or Clinical Implications

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Low Risk Bleeding (&lt;1.5 %)</th>
<th>High Risk Bleeding (&gt;1.5%, or in vulnerable areas)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anesthesiology(^{36,37})</td>
<td>Endotracheal intubation</td>
<td>Spinal and epidural anesthesia*</td>
</tr>
<tr>
<td>Cardiac surgery(^2)</td>
<td>None</td>
<td>All</td>
</tr>
<tr>
<td>Cardiovascular(^2)</td>
<td>Diagnostic coronary angiography (controversial)</td>
<td>Pacemaker or defibrillator placement*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(3.5% on warfarin therapy, 16% with bridging anticoagulation(^{40}))</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coronary intervention</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Electrophysiology testing and/or ablation</td>
</tr>
<tr>
<td>Dental(^7,11)</td>
<td>Tooth extraction</td>
<td>Reconstructive procedures</td>
</tr>
<tr>
<td></td>
<td>Endodontic procedures (root canal)</td>
<td></td>
</tr>
</tbody>
</table>
Oral Surgery Document

- Minor Dental Surgical Procedures
- No need for anticoagulation or antiplatelet changes
  - Extraction up to 3 teeth (bring patient back)
  - Gingival surgery
  - Crown and bridge procedures
  - Supradingival scaling
  - Surgical removal of teeth
Last dose to procedure

- **Warfarin**
  - Stop 1-8 days before procedure depending on INR, goal INR to <1.5 (93% of patients can get to 1.5 in 5 days)

- **Dabigatran, Rivaroxaban, Apixaban**
  - Stop 1-2 days before procedure if patient has good renal function. Stop 3-5 days for patients with CrCl < 50 ml/min.

- **Aspirin or Aspirin/dipyridomole**
  - Stop 7-10 days before procedure

- **Clopidogrel, prasugrel, ticagrelor**
  - Stop 7 days for prasugrel
  - Stop 5 days for the others

NEJM 2013;368(22):2113-24
Statements from ADA

From the American Dental Association

“...it is generally agreed that anticoagulant drug regimens should not be altered prior to dental treatment. A systematic review and meta-analysis found no increased risk of bleeding associated with continuing regular doses of anticoagulant .....for patients undergoing single or multiple tooth extraction.”

The American Academy of Neurology recommend patients undergoing dental procedures continue taking aspirin or warfarin for stroke procedures.

2013 statement Neurology 2013;80:2065-9

For stents – ADA recommends contacting the patients cardiologist

www.ada.org/2526.aspx
Warfarin, Cheese and Green Bay
How do they relate?
Green Bay is not just known for the Packers!

Karl Paul Link was the first to link cattle demise from hay mixed with sweet clover. He worked under the Wisconsin Alumni Research Fund.
Some History on Warfarin

- 1940, Karl Link published the purification and synthesis of dicumarol, the active component of spoiled sweet clover.

- It is derived from the oxidation of coumarin by the action of fungi in the moldy hay.
Some History on Warfarin

- Link assigned the patent rights of this compound to the Wisconsin Alumni Research Foundation (WARF).
Some History on Warfarin

- First clinical study with warfarin was reported in 1955.

- The same year, President Eisenhower was treated with warfarin following a heart attack.
Pharmacology

* the clotting factors are biologically inactive without the carboxylation of glutamic acid

* vitamin K is oxidized and is the cofactor for this carboxylation process
Mechanism of Action

- inhibits the synthesis of vitamin K by 30 to 50%

- clotting factors
  - II
  - VII
  - IX
  - X
  - Protein C
  - Warfarin

- half-life
  - 65-90
  - 4-6
  - 18-30
  - 40-60
  - 4-6
  - 40
## Warfarin Reversal

<table>
<thead>
<tr>
<th>INR range</th>
<th>Vitamin K dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4.5, no bleeding</td>
<td>no vitamin K</td>
</tr>
<tr>
<td>4.5 to 10, no bleeding</td>
<td>no vitamin K</td>
</tr>
<tr>
<td>&gt; 10 and no bleeding</td>
<td>hold dose, 3 to 5 mg oral, should see effect in 24-48 hrs</td>
</tr>
<tr>
<td>Bleeding or &gt; 10</td>
<td>10 mg slow I.V. infusion + FFP, check INR in 6 hours, may repeat every 12 hours</td>
</tr>
<tr>
<td>Life-threatening bleed</td>
<td>replace with 4 factor prothrombin complex + 10 mg vitamin K I.V.</td>
</tr>
</tbody>
</table>

Adapted from: Chest 2012, 141:7S-47S
Bleeding

- frequency of bleeding is related to the intensity of warfarin therapy

- other risk factors:
  - increasing age (>65)
  - hypertension
  - history of strokes
  - atrial fibrillation
  - renal insufficiency
  - anemia
  - history of GI bleed
  - antiplatelet therapy
  - age >75yrs with a. fib.
Warfarin Bleeding Update

- Retrospective analysis of pharmacy and hospital data, 2007-2008, patients > 65 years with AF and taking warfarin

- Risk of hemorrhage
  - Overall 4% per year
  - 3% per year 66 – 75 years
  - 5% per year > 75 years
  - Higher CHADS$_2$ score the greater risk
  - Risk is highest in first month
  - Admitted to hospital due to a bleed, NNH = 5 to die
Bleeding

- incidence:
  - 6-39% recipients annually
  - 0.07-0.7% fatal bleeds
  - 0.9-27% severe bleeds
    - intracranial hemorrhage - 2%, mortality 10-68%
    - highest in elderly with INR > 4
    - age > 80
  - bleeding that occurs with INR < 3 are often underlying occult GI or renal lesions
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA</td>
<td>Direct thrombin inhibitor</td>
<td>Factor 10a inhibitor</td>
<td>Factor 10a inhibitor</td>
</tr>
<tr>
<td>Reduce the risk of stroke and embolism with atrial fibrillation.</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>DVT/PE Treatment</td>
<td>+</td>
<td>+</td>
<td>- (has data)</td>
</tr>
<tr>
<td>DVT/PE Prevention</td>
<td>+</td>
<td>+</td>
<td>- (has data)</td>
</tr>
<tr>
<td>Embolism prevention for orthopedic surgery</td>
<td>-</td>
<td>+</td>
<td>- (has data)</td>
</tr>
<tr>
<td>Bleeding issues</td>
<td>Higher risk of GI bleeds vs warfarin (ARI 0.49%/yr, NNH 204)</td>
<td>Bleeding similar to warfarin</td>
<td>Bleeding similar to warfarin</td>
</tr>
</tbody>
</table>

More intracranial bleeding with warfarin (ARI 0.44%, NNH 227)
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Box warning</td>
<td>Do not stop</td>
<td>Do not stop Epidural hematoma</td>
<td>Do not stop</td>
</tr>
<tr>
<td>Unique side effect</td>
<td>MI - NNH 470, Dyspepsia NNH 18</td>
<td>Syncope NNH 200</td>
<td></td>
</tr>
<tr>
<td>Doses</td>
<td>75, 150 mg caps</td>
<td>10, 15, 20 mg tabs</td>
<td>2.5, 5 mg tabs</td>
</tr>
<tr>
<td>Dose adjustment</td>
<td>Dose 15-30, 75 mg &lt; 15, dialysis – do not use</td>
<td>See table</td>
<td>Cut dose to 2.5 mg for any 2 of the three - age &gt; 80; weight &lt; 60 kg; SCr &gt;1.5</td>
</tr>
<tr>
<td>Comments</td>
<td>Must use within 4 mths after opening Do not open or crush</td>
<td>Can be given via NG tube</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>No INR measures</td>
<td>No INR measures</td>
<td>No INR measures</td>
</tr>
</tbody>
</table>
Dabigatran Efficacy in A.Fib

- RE-LY Trial
- Dabigatran versus warfarin in patients with atrial fibrillation
- 2 year trial, n = 18,113
- Drugs: Dabigatran 110 mg or 150 mg twice daily vs adjusted-dose warfarin (INR 2-3)
- Patients: mean age = 71, 64% men, mean CHADS$_2$ score was 2.1 (moderate risk of stroke, 32% high risk), BP 130/77, prior stroke or TIA 20%, HTN 78%, 40% on ASA (allowed by study)
# RE-LY Results

<table>
<thead>
<tr>
<th>% Event per year</th>
<th>Dabigatran 110 mg</th>
<th>Dabigatran 150 mg</th>
<th>Warfarin</th>
<th>Dabigatran 110 mg vs warfarin</th>
<th>Dabigatran 150 mg vs warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke of Embolism</td>
<td>1.53%</td>
<td>1.11%</td>
<td>1.69%</td>
<td>NS, but noninferior</td>
<td>noninferior, ARR 0.58%, NNT 172</td>
</tr>
<tr>
<td>All stroke</td>
<td>1.44%</td>
<td>1.01%</td>
<td>1.57%</td>
<td>NS</td>
<td>noninferior, ARR 0.56%, NNT 178</td>
</tr>
<tr>
<td>MI</td>
<td>0.72%</td>
<td>0.74%</td>
<td>0.53%</td>
<td>NS</td>
<td>P = .048, ARI 0.21%, NNH 476</td>
</tr>
<tr>
<td>PE</td>
<td>0.12%</td>
<td>0.15%</td>
<td>0.09%</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>19.4%</td>
<td>20.2%</td>
<td>20.8%</td>
<td>ARR 1.4%, NNT 71</td>
<td>NS</td>
</tr>
<tr>
<td>Death from CV causes</td>
<td>2.43%</td>
<td>2.28%</td>
<td>2.69%</td>
<td>NS</td>
<td>ARR 0.41%, NNT 244</td>
</tr>
<tr>
<td>All death</td>
<td>3.75%</td>
<td>3.64%</td>
<td>4.13%</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>
## Rivaroxaban Efficacy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Outcome</th>
<th>Rivaroxaban</th>
<th>LMWH</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Record 1</td>
<td>VTE prevention after Hip surgery</td>
<td>1.1%</td>
<td>3.7%</td>
<td>2.6%</td>
<td>38</td>
</tr>
<tr>
<td>Record 2</td>
<td>VTE prevention after Hip surgery</td>
<td>2.0%</td>
<td>8.4%</td>
<td>6.4%</td>
<td>16</td>
</tr>
<tr>
<td>Record 3</td>
<td>VTE prevention after knee surgery</td>
<td>9.7%</td>
<td>18.8%</td>
<td>9.1%</td>
<td>11</td>
</tr>
<tr>
<td>Rocket-AF</td>
<td>Stroke or systemic embolism</td>
<td>1.7%</td>
<td>2.2% vs. warfarin</td>
<td>0.5%</td>
<td>200</td>
</tr>
<tr>
<td></td>
<td>Atrial Fib</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Major bleeding</td>
<td>5.6%</td>
<td>5.4%</td>
<td>0.2%</td>
<td>NS</td>
</tr>
<tr>
<td>ATLAS 5I</td>
<td>Added to standard of care for CAD for death from CV causes, MI and stroke</td>
<td>9.1%</td>
<td>10.7% vs placebo</td>
<td>1.6%</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>2.5 mg bid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All-cause mortality</td>
<td>2.9%</td>
<td>4.5%</td>
<td>1.6%</td>
<td>63</td>
</tr>
</tbody>
</table>
AVERROES Trial

- Purpose: used apixaban to prevent strokes in those with a.fib that are not candidates for warfarin
- Double-blinded RCT, n = 5599
- Duration: 1.1 years
- Apixaban 5 mg twice daily vs aspirin 81 to 324 mg
- Patients: 70 yrs, SBP 132, BMI 28, 58% male, 14% prior stroke or TIA, 86% HTN, 40% HF (7% class IV), mean CHADS$_2$ - 2.1
- Inclusion: 50 years old, A. Fib per EKG, and at least one risk factor for CVA
### AVERROES Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Apixaban</th>
<th>Aspirin</th>
<th>p-Value</th>
<th>ARR</th>
<th>NNT/yr</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1º Outcome:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke or systemic embolism</td>
<td>1.6%</td>
<td>3.7%</td>
<td>&lt;.001</td>
<td>2.1%</td>
<td>48</td>
</tr>
<tr>
<td>Stroke or systemic embolism or death</td>
<td>4.6%</td>
<td>7.2%</td>
<td>&lt;.001</td>
<td>2.6%</td>
<td>38</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.6%</td>
<td>3.4%</td>
<td>&lt;.001</td>
<td>1.8%</td>
<td>56</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.2%</td>
<td>0.3%</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic Embolism</td>
<td>0.09%</td>
<td>0.1%</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cause mortality</td>
<td>3.5%</td>
<td>4.4%</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1º Safety Outcome:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>Apixaban</td>
<td>Aspirin</td>
<td>p-Value</td>
<td>ARI</td>
<td>NNH</td>
</tr>
<tr>
<td></td>
<td>1.4%</td>
<td>1.2%</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>0.4%</td>
<td>0.4%</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI bleeds</td>
<td>0.4%</td>
<td>0.4%</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization from CV</td>
<td>12.6%</td>
<td>15.9%</td>
<td>&lt;.001</td>
<td>3.3%</td>
<td>NNT 30</td>
</tr>
</tbody>
</table>

All bleeding was not significant

## Transitioning from other anticoagulants

<table>
<thead>
<tr>
<th>Converting from warfarin</th>
<th><strong>D/C warfarin and start dabigatran once INR &lt; 2.0</strong></th>
</tr>
</thead>
</table>
| **Converting to warfarin** | CrCL >50 mL/min: start warfarin 3 days before stopping dabigatran  
CrCL 31–50 mL/min: start warfarin 2 days before stopping dabigatran  
CrCL 15–30 mL/min: start warfarin 1 day before stopping dabigatran  
CrCL <15 mL/min: no recommendations can be made |
| **Converting to parenteral anticoagulation** | Wait 12 hours if CrCl ≥30 mL/min or 24 hours if CrCL < 30 mL/min after the last dose of dabigatran before starting parenteral anticoagulation |
| **Converting from parenteral anticoagulation** | Start dabigatran 0 to 2 hours before the time that the next dose of parenteral drug was to be given or at the time of D/C of a continuously administered parenteral drug (e.g. UFH) |
| **Surgical/invasive interventions** | D/C dabigatran 1 to 2 days (CrCL ≥50 mL/min) or 3 to 5 days (CrCL <50 mL/min) before an invasive procedure; longer times should be considered for patients undergoing major surgery or those receiving spinal puncture/epidural catheter  
Measure ECT (ecarin clotting time) if available |

Dabigatran

- **Price**
  - Capsules
  - 75 mg, 150 mg
  - $250 for #60, 150 mg

- **Simplicity**
  - not that simple, but simple
  - Assess renal function yearly in those with
  - CrCl<50 and > 75 years of age
  - 150 mg twice a day
    - t/2 = 12 to 17 hrs
  - Can be given with or without food
  - Do not break, chew, open capsule
  - Do not double dose if missed
  - more than 6 hours should exist between doses
  - 80% clearance in urine
    - Change dose based on kidney function
      - CrCl 15 – 30 – 75 mg twice daily
      - CrCl < 30 or dialysis - not recommended

**Revise label:** Once opened, the product must be used within 4 mths
Rivaroxaban

**PRICE**
- Tablets, 10 mg (light red), 15mg (red) and 20mg (dark red)
- ~$245 / #30

**SIMPLICITY**
- Take with or without food (orthopedic thromboprophylaxis)
- Take WITH food (evening meal) for A. fib indication and DVT/PE treatment indications
- No need for INR monitoring
- Do not use with other anticoagulants at this time
- Avoid in patients with renal dysfunction (specific dosing)
- Can be given via feeding tube
Apixaban (Eliquis®)

- Price and Simplicity
- 2.5 mg, 5 mg tablets
- Price - $4.00/tab, so ~$250/mth
- Recommended dose is 5 mg twice daily
- Lower dose to 2.5 mg in patients with at least 2 of following:
  - Age > 80; weight < 60 kg; SCr > 1.5

- Conversions
  - Discontinue 48 hrs before high risk bleeding surgery
  - Discontinue 24 hrs before low risk bleeding surgery
  - Switching from warfarin: let INR get below 2
  - Switching to warfarin: DC apixaban, give LMWH + warfarin at the next dose due of apixaban
Seek and Destroy:

General Principles and Antibiotic Choices in Treating Dental Infections
Two types of antibiotics

- **Time-dependent killers**
  - Penicillin, cephalosporin, imipenem
  - clindamycin, macrolides, TMP/SMX, tetracyclines
    - Accumulation at the site of infection is important at inhibiting bacterial growth

- **Concentration-dependent killers**
  - Quinolones (really fluoroquinolones), Aminoglycosides, Metronidazole
  - “qAm”
Time-dependant Killers

- Vancomycin
- Cephalosporin
- Macrolides
- Clindamycin
- Tetracycline
- Penicillin
- MIC
Concentration-dependant Killers

- Quinolones
- Aminoglycosides
- Metronidazole

MIC
Dosing Issues

- Three times a day and four times a day dosing is a set up for adherence problems.
- Use total daily dose twice a day.
- Cephalexin (Keflex®)
  - 250 mg capsule (#30 cost $4)
  - 500 mg capsule (#30 cost $4)
  - 750 mg capsule (#30 cost $126)
  - 125 mg/5 ml; 250 mg/5 ml each in 100 and 200 ml
    - Each of these are ~$15

For cost information: Good Rx
Dosing Issues

- Keflex® 750 mg is branded drug.
- Why?
- Has indication for BID use or as JCAHO wants you to write: twice daily use.
- Therefore write:
  - Cefalexin 500 mg capsules, take 2 capsules twice daily.
  - You can do this with Penicillin
Know how to price meds!
Get the App!!

GoodRx

Convenient, affordable prescription drugs
Find the lowest prices at local and online pharmacies
Save 20-80% even if you have insurance

Drug Name
e.g. Lipitor

Your Location
New York, NY

FIND A BETTER PRICE

GoodRx contains more than a million prices for every major US pharmacy chain - Walgreens, CVS, CostCo, WalMart and many more.
You may be wondering?

- Why can you give an antibiotic that is a time-dependent killer less often?
- Pharmacokinetic principle:
  - As you increase the dose and the serum concentration, you can stay above the MIC until the next dose - dose dependent.
Time-dependant Killers

Cephalexin 1 gm

2\textsuperscript{nd} dose

12 hours
The industry understands!

- The concept has made it to market.
- Amoxicillin (Moxatag®)
  - Once-daily form, for Strep pharyngitis and tonsillitis
  - Pulsys delivers staccato pulses (3) over 6 hrs
  - 775 mg tablet
    - 1 immediate release, 2 delay-release
  - 10 day course is $160
Dosing Issues: Concentration Killers

- **“qAm”**
- **More is better!**
  - **Examples: Fluoroquinolone**
    - Levofloxacin
    - 250 mg (#10 cost $10)
    - 500 mg (#10 cost $10)
    - 750 mg (#10 cost $15)
      - 5 day therapy for CAP
  - **Metronidazole for trichomonas infection**
    - 2 gram single dose is better than 500 mg bid for 7 days
Administration Principle

- **IV**
  - 100% bioavailable
  - Best for the sickest patient, they often poorly absorbs oral drugs

- **PO**
  - Several classes of drugs have excellent bioavailability similar to their IV dose
  - TMP/SMX, FQ, metronidazole
How to select an antibiotic!

- CSI-like
- Where is the infection?
- What are the bugs?
  - Guess the organism based on epidemiology research
- What is the best antibiotic?

- Initial antibiotic choice is always empiric therapy
Where is the infection?

- Mouth
  - Reversible pulpitis
  - Irreversible pulpitis
  - Abscess
  - Cellulitis
  - Pericoronitis
  - Periodontal Disease

- Antibiotic are best utilized in situations of regional spread
What are the bugs?

- Dominant isolates are anaerobic bacteria.
  - *Streptococcus mutans*
    - are thought to cause initial caries infection
  - Alpha-hemolytic streptococci, a.k.a. *Streptococcus viridans*
    - Can coexist with staph
  - *Streptococcus anginosus*
What are the bugs?

- **Aerobes**
  - **Gram +:**
    - Peptostreptococci
  - **Gram negative:**
    - *Bacteroides*
      - *Prevotella* (*Bacteroides melaninogenicus*)
      - *Porphyromonas*
    - *Fusobacterium nucleatum*
    - *Porphyromonas gingivalis*

- Infections through the fascial planes usually are polymicrobial (average 4-6 organisms).
Common Oral Dental Antibiotics

- Penicillin (Pen-Vee K®)
- Amoxicillin (Amoxil®)
- Amoxicillin/clavulanate (Augmentin®)
- Clindamycin (Cleocin®)
- Cephalexin (Keflex®)
  - What about cefdinir?
- Erythromycin/Azithromycin/Clarithromycin
- Metronidazole (Flagyl®)
- IV
  - Ampicillin/Sulbactam (Unasyn®)
Common Oral Dental Antibiotics

- Penicillin (Pen-Vee K®)
  - Gram +, no staph, anaerobes
- Amoxicillin (Amoxil®)
  - Gram +, no staph, anaerobes, adds basic gram neg
- Amoxicillin/clavulanate (Augmentin®)
  - Gram +, anaerobes, adds basic gram neg
  - Adds beta-lactamase stability (gets staph)
- IV
  - Ampicillin/Sulbactam (Unasyn®)
  - IV form of Augmentin®
Common Oral Dental Antibiotics

- **Clindamycin (Cleocin®)**
  - Like penicillin BUT gets staph, including community MRSA
  - Gram +, anaerobes

- **Cephalexin (Keflex®)**
  - Gram + only
  - What about cefdinir (Omnicef®)? – adds gram neg, not good for anaerobes
  - Some consider drug of choice for general cellulitis
  - Some use ceftriaxone IM

- **Erythromycin/Azithromycin/Clarithromycin**
  - Gram +, not MRSA, Basic gram neg, good atypical abx

- **Metronidazole (Flagyl®)**
  - Anaerobes only
For dosing – get Epocrates
Or how about Lexicomp®?
Methicillin-resistant Staph Aureus

- 95% of staph was resistant to penicillin by 1953
- MRSA was first isolated in 1968
  - Methicillin was developed in 1960
- Incidence of infection
  - MRSA has risen from < 10% of all infecting staph aureus infections in the hospital in 1983 to 64% in 2004 to 70% in the intensive care units in 2008
- MRSA is prevalent
  - High risk in community dwellers – nursing home, diabetics, those with chronic renal failure, those on dialysis
  - Reduction rates in are higher for hospital than community
MRSA

- Drugs for treatment of community-acquired MRSA
  - Tetracycline 500 mg qid
  - Doxycycline 100 mg bid
  - Minocycline 100 mg bid
  - TMP/SMX 320 mg bid of trimethoprim
    - 2 DS bid
  - Clindamycin 300 to 450 mg tid
  - Linezolid 600 mg bid

- You can always add a second antibiotic:

- Synergy with:
  - Rifampin 300 mg twice daily
  - $65 for 30 caps
Prevention - opinions are plentiful

- Add \( \frac{1}{4} \) cup of Clorox to bath water
- Shower with Hibiclens
- Mupirocin nasal for 5 day
  - Use under nails
- For children, soak toys in Clorox
- Hand hygiene
- DO NOT share personal items
- Keep draining wounds covered
SBE Prophylaxis - In who?

- ACC/AHA Task Force Update 2008
- Prosthetic cardiac valve
- Previous infective endocarditis
- Congenital heart disease (CHD)
- Unrepaired cyanotic CHD, including palliative shunts and conduits
- Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure
- Prosthetic material for valve repair
- Cardiac transplantation recipients who develop cardiac valvulopathy
SBE Prophylaxis - Dental Procedure?

- Dental procedures that involve manipulation of the gingival tissue
- Periapical region of the teeth
- Perforation of the oral mucosa
- No longer required for:
  - Routine anesthetic injections
  - X-ray
  - Bleeding from trauma to the lips or oral mucosa
SBE Prophylaxis - With what?

- **Adults**
  - amoxicillin 2 g PO 1 hour before procedure.

- **Children**
  - amoxicillin 50 mg/kg
  - If by IV, administer ampicillin 2 g for adults and 50 mg/kg for children within 30 minutes before the procedure.

- **For patients allergic to penicillin**
  - Adult - Clindamycin 600 mg PO/IV 1 hour before the procedure. Children - Clindamycin 20 mg/kg PO/IV.
  - Alternatively, azithromycin or clarithromycin 500 mg PO 1 hour before the procedure may be administered for adults and 15 mg/kg PO may be administered for pediatric patients.
The End

E-mail questions:
kjones@mcleodhealth.org
Or
PharmReach.org

Master Yoda