Dental relations of heart disorders.

Dr. Laszlo Jakab
Semmelweis University, 3rd Department of Internal Medicine
Topics

• Prophylaxis of infective endocarditis
• Dental management of patients on anticoagulant and antiplatelet drugs
  - Anticoagulant therapy
  - New oral anticoagulants
  - Management of patients who receive anticoagulant therapy
• Antiplatelet agents
• Management of patients who receive antiplatelet therapy
Prophylaxis of infective endocarditis
Epidemiology of infective endocarditis

• 10-20,000 cases per year in the US
• Male:Female ratio 1.7:1
• New trends
  – Mean age was 30 in 1926, now > 50% of patients are over 60
  – Decline in incidence of rheumatic fever
  – More prosthetic valves
  – More nosocomial cases, injected drug use
  – More staphylococcal infection
<table>
<thead>
<tr>
<th>Procedure/Manipulation</th>
<th>Percentage of Positive Blood Cultures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dental</strong></td>
<td></td>
</tr>
<tr>
<td>Dental extraction</td>
<td>18-85</td>
</tr>
<tr>
<td>Periodontal surgery</td>
<td>32-88</td>
</tr>
<tr>
<td>Chewing candy or paraffin</td>
<td>17-51</td>
</tr>
<tr>
<td>Tooth brushing</td>
<td>0-26</td>
</tr>
<tr>
<td>Oral irrigation device</td>
<td>27-50</td>
</tr>
<tr>
<td><strong>Upper Airway</strong></td>
<td></td>
</tr>
<tr>
<td>Bronchoscopy (rigid scope)</td>
<td>15</td>
</tr>
<tr>
<td>Tonsillectomy</td>
<td>28-38</td>
</tr>
<tr>
<td>Nasotracheal suctioning/intubation</td>
<td>16</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
</tr>
<tr>
<td>Upper gastrointestinal endoscopy</td>
<td>8-12</td>
</tr>
<tr>
<td>Sigmoidoscopy/colonoscopy</td>
<td>0-9.5</td>
</tr>
<tr>
<td>Barium enema</td>
<td>11</td>
</tr>
<tr>
<td>Percutaneous needle biopsy of liver</td>
<td>3-13</td>
</tr>
<tr>
<td><strong>Urologic</strong></td>
<td></td>
</tr>
<tr>
<td>Urethral dilation</td>
<td>18-33</td>
</tr>
<tr>
<td>Urethral catheterization</td>
<td>8</td>
</tr>
<tr>
<td>Cystoscopy</td>
<td>0-17</td>
</tr>
<tr>
<td>Transurethral prostatic resection</td>
<td>12-46</td>
</tr>
<tr>
<td><strong>Obstetric/gynecologic</strong></td>
<td></td>
</tr>
<tr>
<td>Normal vaginal delivery</td>
<td>0-11</td>
</tr>
<tr>
<td>Punch biopsy of the cervix</td>
<td>0</td>
</tr>
<tr>
<td>Removal/insertion of IUD</td>
<td>0</td>
</tr>
</tbody>
</table>
Microbiology

- *Staphylococcus aureus* (30-40%)
- Viridans group streptococci (18%)
- Enterococci (11%)
- Coagulase-negative staphylococci (11%)
- *Streptococcus bovis* (7%)
- Other streptococci (5%)
- Non-HACEK Gram negatives (2%)
- HACEK Organisms (2%)
- Fungi (2%)
- “Culture negative” (2-20%)
Risk Factors

• Structural heart disease
  – Rheumatic, congenital, aging
  – Prosthetic heart valves
• Injected drug use
• Invasive procedures (?)
• Indwelling vascular devices
• Other infection with bacteremia (e.g. pneumonia, meningitis)
• History of infective endocarditis

Rick A. Nishimura, Blase A. Carabello, David P. Faxon, Michael D. Freed, Bruce W. Lytle, Patrick T. O'Gara, Robert A. O'Rourke, and Pravin M. Shah

*J. Am. Coll. Cardiol.* 2008;52;676-685; originally published online Jul 28, 2008; doi:10.1016/j.jacc.2008.05.008

This information is current as of May 9, 2009

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://content.onlinejacc.org/cgi/content/full/52/8/676
Risk classification

• Preexisting cardiac disorders
• Procedures
• The AHA Prevention of Infective Endocarditis Committee recommended that prophylaxis be given only to a high-risk group of patients before dental procedures that involve manipulation of either gingival tissue or the periapical region of the teeth or perforation of oral mucosa
• High-risk patients were defined as those patients with underlying cardiac conditions associated with the highest risk of adverse outcome from infective endocarditis, not necessarily those with an increased lifetime risk of acquisition of infective endocarditis.
**Box 76-1: Ranking of Risk for Infective Endocarditis After Dental, Diagnostic, and Therapeutic Procedures Related to Preexisting Cardiac Disorders**

**Higher Risk**
- Prosthetic heart valves
- Previous infective endocarditis
- Cyanotic congenital heart disease
- Surgically constructed systemic-pulmonary shunts and conduits

**Lower Risk**
- Mitral valve prolapse with regurgitation
- Mitral regurgitation; stenosis; stenosis with regurgitation
- Aortic regurgitation; stenosis; stenosis with regurgitation
- Tricuspid valve disease
- Pulmonary stenosis
- Ventricular septal defect
- Patent ductus arteriosus
- Coarctation of the aorta
- Asymmetric septal hypertrophy
- Calcific aortic sclerosis
- Degenerative valvular disease in elderly patients
- Surgically repaired intracardiac lesions with residual hemodynamic abnormality

**Negligible Risk**
- Mitral valve prolapse without regurgitation
- Minor valvular regurgitation by echocardiography without major structural abnormality
- Isolated atrial septal defect
- Arteriosclerotic plaques and coronary artery disease
- Cardiac pacemakers
- Surgically repaired intracardiac lesions with minimal or no hemodynamic abnormality
Box 76-2 Ranking of Risk for Infective Endocarditis Posed by Various Procedures That Might Cause Bacteremia

**Higher-Risk Procedures**
- Dental procedures that involve the gingival crevice
- Surgical procedures (including biopsies) inside the oral cavity
- Genitourinary tract procedures when bacterial infection is present
- Surgical procedures (including incision and drainage) when bacterial infection is present at the site

**Lower-Risk Procedures**
- Injection of local anesthetic
- Genitourinary tract procedures in absence of active bacterial infection
- Surgery involving gastrointestinal or respiratory mucosa in absence of active bacterial infection
- Skin biopsies and dermatologic procedures using standard antisepsis
- Bronchoscopy with or without biopsy
- Gastrointestinal endoscopy, with or without biopsy
- Cardiac catheterization
- Transesophageal echocardiography
- Esophageal dilatation and sclerotherapy of esophageal varices
- Endotracheal tube insertion
- Tympanostomy tube insertion
- *In the absence of active bacterial infection*: urethral catheterization, laparoscopy, sterilization procedures, vaginal delivery, vaginal hysterectomy, cesarian section, therapeutic abortion, dilation and curettage, insertion or removal of intrauterine devices
Table 76-2. Recommendations for Antibiotic Prophylaxis of Infective Endocarditis, Based on a Matrix Relating Underlying Cardiac Risk Factors (Box 76-1) and Risks Posed by Various Procedures (Box 76-2)

<table>
<thead>
<tr>
<th>Procedures (Box 76-2)</th>
<th>Higher Risk</th>
<th>Lower Risk</th>
<th>Negligible Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher-risk procedures</td>
<td>Prophylaxis recommended</td>
<td>Prophylaxis not recommended, but optional-clinical judgment needed</td>
<td>Prophylaxis not recommended</td>
</tr>
<tr>
<td>Lower-risk procedures</td>
<td>Prophylaxis not recommended, but optional-clinical judgment needed</td>
<td>Prophylaxis not recommended</td>
<td>Prophylaxis not recommended</td>
</tr>
<tr>
<td>Indication</td>
<td>Standard Regimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>For dental procedures; oral or upper respiratory tract surgery, minor gastrointestinal (GI) or genitourinary (GU) tract procedures</td>
<td><strong>Amoxicillin</strong>, $2.0 \text{ g PO } 1 \text{ hr before procedure} \dagger$$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Special Regimens**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral regimens for penicillin-allergic patients (oral and respiratory tract only)</td>
<td><strong>Clindamycin</strong>, $600 \text{ mg PO } 1 \text{ hr before procedure OR}$ \smallskip <strong>Clarithromycin</strong>, $0.5 \text{ g PO } 1 \text{ hr before procedure}$</td>
</tr>
<tr>
<td>Parenteral regimen for high-risk patients; also for GI or GU tract procedures</td>
<td><strong>Ampicillin</strong>, $2.0 \text{ g IM or IV, } 0.5 \text{ hr before procedure}$ \smallskip <strong>Vancomycin</strong>, $1.0 \text{ g IV slowly over } 1 \text{ hr starting } 1 \text{ hr before procedure}$</td>
</tr>
<tr>
<td>Parenteral regimen for penicillin-allergic patients</td>
<td><strong>Vancomycin</strong>, $1.0 \text{ g IV slowly over } 1 \text{ hr starting at induction of anesthesia, then } 0.5 \text{ g IV } 12 \text{ hr later}$</td>
</tr>
</tbody>
</table>

Cardiac surgery including implantation of prosthetic valves
Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures

NICE (National Institute of Health and Clinical Excellence, Guidance 64)
Guideline of British Cardiovascular Society

April 2008
Rationale for Antibiotic Prophylaxis

- Standard practise for 50 years
- 10 per 100,000 per annum
- IE life threatening
- IE follows bacteraemia
- Dental procedures cause bacteraemias
- Cases of IE following dental procedures
- IE usually caused by oral organisms
- These organisms sensitive to antibiotics
Patients at Risk of IE

The following patients should be regarded as being at risk of developing infective endocarditis:

• acquired valvular heart disease with stenosis or regurgitation
• valve replacement
• structural congenital heart disease, including surgically corrected or palliated structural conditions but excluding isolated atrial septal defect, fully repaired ventricular septal defect or fully repaired patent ductus arteriosus, and closure devices that are judged to be endothelialised
• previous endocarditis
• hypertrophic cardiomyopathy.
Offer an antibiotic that covers organisms that cause infective endocarditis if a person at risk of infective endocarditis is receiving antimicrobial therapy because they are undergoing a gastrointestinal or genitourinary procedure at a site where there is a suspected infection.

Investigate and treat promptly any episodes of infection in people at risk of infective endocarditis to reduce the risk of endocarditis developing.
## Savings per 100,000 population

<table>
<thead>
<tr>
<th>Recommendations with savings</th>
<th>Savings (£ per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis for patients at risk undergoing a dental procedure</td>
<td>1541</td>
</tr>
<tr>
<td>Prophylaxis for patients at risk undergoing a non-dental procedure</td>
<td>267</td>
</tr>
<tr>
<td><strong>Total net saving of implementing the guideline</strong></td>
<td><strong>1808</strong></td>
</tr>
</tbody>
</table>
The existing evidence does not support the extensive use of antibiotic prophylaxis recommended in previous guidelines.

Prophylaxis should be limited to the highest risk patients (patients with the highest incidence of IE and/or highest risk of adverse outcome from IE).

The indications for antibiotic prophylaxis for IE should be reduced in comparison with previous recommendations.

Good oral hygiene and regular dental review are of particular importance for the prevention of IE.
Highest risk patients

- Patients with a prosthetic valve or a prosthetic material used for cardiac valve repair
- Patients with previous IE
- Patients with congenital heart disease (CHD), in particular those with complex cyanotic heart disease and those who have post-operative palliative shunts, conduits, or other prostheses
Highest risk procedure

• Dental surgery
### Table 6  Recommended prophylaxis for dental procedures at risk

<table>
<thead>
<tr>
<th>Situation</th>
<th>Antibiotic</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>No allergy to penicillin or ampicillin</td>
<td>Amoxicillin or ampicillin*</td>
<td>2 g p.o. or i.v.</td>
<td>50 mg/kg p.o. or i.v.</td>
</tr>
<tr>
<td>Allergy to penicillin or ampicillin</td>
<td>Clindamycin</td>
<td>600 mg p.o. or i.v.</td>
<td>20 mg/kg p.o. or i.v.</td>
</tr>
</tbody>
</table>

Cephalosporins should not be used in patients with anaphylaxis, angio-oedema, or urticaria after intake of penicillin and ampicillin.

*Alternatively cephalxin 2 g i.v. or 50 mg/kg i.v. for children, cefazolin or ceftriaxone 1 g i.v. for adults or 50 mg/kg i.v. for children.
Dental Management of Patients on Anticoagulant and Antiplatelet Drugs
Normal Hemostasis

Following injury to a blood vessel:
1. Vascular retraction (vasoconstriction) to slow blood loss
2. Adherence of platelets to the vessel wall (endothelium) and then to each other to form a platelet plug
3. Initiation of the coagulation cascade resulting in the formation and deposition of fibrin to form a clot
Coagulation Cascade

- Extrinsic pathway: Factor VII is activated by *tissue factor* (phospholipid) that is released by injured perivascular or vascular tissues; very rapid reaction
- Intrinsic pathway: Factor XII is activated by exposure to collagen from vessel wall (endothelium) or blood cell membrane; slower reaction

Each activated factor, in turn, activates the next factor—thus the term “cascade” ultimately resulting in the formation of fibrin
• Anticoagulants:
  – Inhibit the production of clotting factors

• New oral anticoagulants

• Antiplatelet Agents:
  – Interfere with the functioning of platelets, thus inhibiting platelet aggregation
Anticoagulant therapy
Anticoagulants
Coumarin Derivitives (acenocoumarol, dicoumarol, warfarin)

Coumarin antagonizes the production of vitamin K
Vitamin K is necessary for the synthesis of four of the coagulation factors (VII, IX, X and prothrombin)
Pharmacologic Properties (warfarin)

- Taken orally
- Metabolized in the liver
- Half-life: 1.5-2.5 days
- Duration of action: 2-5 days (it takes several days for dosage changes to take effect)
- Increased anticoagulant effect when combined with:
  - Antibiotics
  - Aspirin
  - NSAIDs
  - Antifungals
  - Tramadol
  - Tricyclic antidepressants
  - Certain herbals (gingko, ginsing, ginger, garlic)
## Warfarin

<table>
<thead>
<tr>
<th>Kinetics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Oral: Rapid, complete</td>
</tr>
<tr>
<td>Distribution</td>
<td>0.14 L/kg</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic, primarily via CYP2C9; minor pathways include CYP2C8, 2C18, 2C19, 1A2, and 3A4</td>
</tr>
<tr>
<td>Excretion</td>
<td>Urine (92%, primarily as metabolites)</td>
</tr>
<tr>
<td>Half-life</td>
<td>20-60 hours</td>
</tr>
</tbody>
</table>
Warfarin

• Onset of action:
  – 5-7 days
  – May requiring bridging

• Antidote:
  – Vitamin K, FFP, PRBC

• Interactions:
  – Foods with high vitamin K content
Conditions for which coumarin derivates are prescribed to prevent unwanted blood clotting

- Prophylaxis/Treatment of:
  - Venous thrombosis (DVT)
  - Pulmonary embolism
  - Atrial fibrillation
  - Mechanical prosthetic heart valves
  - Recurrent systemic embolism
Co-morbid Conditions That Can Contribute to Increased Bleeding

- Liver disease
- Kidney disease
- Tumor
- Bone marrow failure
- Chemotherapy
- Autoimmune diseases
Laboratory Tests to Monitor the Activity of Coumadin

- Prothrombin Time (PT): time for fibrin formation via the extrinsic pathway-factor VII
  - Test performed by taking a sample of the Pt’s blood and adding a reagent (thromboplastin) and calculating the time required to form a clot; expressed in seconds
- PT Ratio: Pt’s PT/Normal PT
- Normal PT ration = 1
- Problem: There is variation among thromboplastin reagents, therefore the results from lab to lab are not comparable
Solution:
International Normalized Ratio (INR)

- A mathematical “correction” that corrects for the differences in the sensitivity of thromboplastin reagents
- Each thromboplastin is assigned an ISI number which is a sensitivity index
- This correction makes INR values comparable from lab to lab
- Normal INR = 1 (an INR of 2 means that their INR is 2 times higher than normal)
Recommended Therapeutic Range for Oral Anticoagulant Therapy

INR: 2.0-3.0

- Prophylaxis or treatment of venous thrombosis
- Treatment of pulmonary embolus
- Prevention of systemic embolism
- Tissue heart valves
- Atrial fibrillation
Recommended Therapeutic Range for Oral Anticoagulant Therapy

- INR: 2.5-3.5
  - Mechanical prosthetic valves (high risk)
  - Certain patients with thrombosis and the antiphospholipid antibody antibody syndrome (antibodies that interfere with the assembly of phospholipid complexes and thus inhibit coagulation)
There are no uniformly accepted guidelines for managing anticoagulated patients during dental treatment.

Previous AMA/ADA recommendation was that it was safe to perform surgery on a patient if the PT was 1.5-2.5x normal. This, however, is equivalent to an INR of 2.6-5.0 depending on the sensitivity of the various thromboplastins; an average PT of 1.6 = INR of 3!
• This clinical problem is not amenable to a “cookbook” approach
• Each patient must be considered individually and you must take into consideration the risk-benefit of stopping vs continuing anticoagulation (they are on anticoagulants because they are at risk for thromboembolism)
• Your decision depends upon:
  – Medical condition/stability
  – Degree of anticoagulation
  – Magnitude of planned surgery
  – Scientific evidence
• If questionable, decision should be a shared with physician
Conclusions

• It would thus appear that most patients who are on anticoagulant therapy (Coumadin) can **undergo minor dentoalveolar surgery without discontinuance of anticoagulant using local/topical measures if:**
  - INR is within the therapeutic range (<3.5)
  - No assoc aggravating conditions (e.g. antibiotics, liver or kidney disease)
  - Planned surgery is “minor” (extractions, alveoloplasty, biopsy)

• If anticoagulant needs to be adjusted (INR>3.5), this is the responsibility of the physician
Major dental surgery

- > 45 min surgical procedure
- Stop Coumarin therapy four days before surgery
- Substitution with 100 IU/kg LMWH (therapeutic dose)
- On the day of surgery miss LMWH morning, but evening continue
- Restart Coumadin in the subsequent days after procedure with LMWH bridging
New oral anticoagulants
Fibrinogen

Common Pathway

New Oral Agents

Apixaban
Rivaroxaban

Xa Blocker

Prothrombin

Thrombin

Fibrinogen

Fibrin

Clot

Dabigatran
Dabigatran

- MOA: direct thrombin inhibitor which inhibits:
  - Both free and fibrin-bound thrombin
  - Cleavage of fibrinogen to fibrin
  - Activation of factors V, VIII, XI, and XIII
  - Thrombin-induced platelet aggregation
# Dabigatran

## Kinetics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Rapid; initially slow postoperatively</td>
</tr>
<tr>
<td>Distribution</td>
<td>$V_d$: 50-70 L</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic; rapidly and completely hydrolyzed to active form by plasma and hepatic esterases</td>
</tr>
<tr>
<td>Excretion</td>
<td>Renal (80%)</td>
</tr>
<tr>
<td>Half-life</td>
<td>12-17 hours</td>
</tr>
</tbody>
</table>
Dabigatran

• Monitoring
  – PTT

• Onset: 1 hour, delayed by food

• Antidote: None

• ADRs
  – Bleeding (8% to 33%; major ≤ 6%)
  – Dyspepsia (11%)
Contraindications
- Hypersensitivity to dabigatran or any component
- Active bleeding

Warnings/Precautions
- Bleeding
- Renal impairment
- Anticoagulants
- Invasive/surgical invasions
- P-gp inducers/inhibitors
Dabigatran

- ISMP Medication Safety Alert: Quarter Watch [01-12-12]

- 932 serious adverse events for 1st quarter of 2011
  - 120 deaths
  - 25 cases of permanent disability
  - 543 cases requiring hospitalization
  - 505 cases involved hemorrhage: elderly patients (Median age of 80)
    - 120 cases of hemorrhagic stroke
Dabigatran

• FDA Drug Safety Communication: [11-02-2012]
  – “… FDA investigated the actual rates of gastrointestinal bleeding and intracranial hemorrhage for new users of [dabigatran] compared to new users of warfarin. The results of this Mini-Sentinel assessment indicate that bleeding rates associated with new use of [dabigatran] do not appear to be higher than bleeding rates associated with new use of warfarin ....”
Dabigatran

  - “A clinical trial in Europe (the RE-ALIGN trial) was recently stopped because [dabigatran] users were more likely to experience strokes, heart attacks, and blood clots forming on the mechanical heart valves than were users of the anticoagulant warfarin. There was also more bleeding after valve surgery in the [dabigatran] users than in the warfarin users [dabigatran] is not approved for patients with AF caused by heart valve problems.”
## Dabigatran

<table>
<thead>
<tr>
<th>May be appropriate</th>
<th>MAY NOT be appropriate</th>
<th>NOT appropriate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ability to comply with twice daily drug regimen</td>
<td>History of non-adherence</td>
<td>Severe renal impairment (CrCl &lt;30 ml/min)</td>
</tr>
<tr>
<td>Unstable INRs on warfarin (unrelated to adherence)</td>
<td>Stable INRs on warfarin</td>
<td>History of GI bleeding or recent ulcers</td>
</tr>
<tr>
<td>Difficulty obtaining regular INRs on warfarin</td>
<td>Advanced age (75-80 yrs and older; consider benefits and risks)</td>
<td>Active liver disease</td>
</tr>
<tr>
<td>Complicated interacting drug regimens on warfarin</td>
<td></td>
<td>Pregnancy, at risk of pregnancy, or lactating</td>
</tr>
<tr>
<td>High risk of intracranial bleed</td>
<td></td>
<td>Need for concomitant treatment with P-gp inducer (e.g., rifampin, St. John’s Wort)</td>
</tr>
<tr>
<td>Medication regimen does not include drugs that interact with dabigatran</td>
<td></td>
<td>Moderate renal impairment (CrCl 30-50 ml/min) and the need for concomitant treatment with the P-gp inhibitors dronedarone or systemic ketoconazole</td>
</tr>
<tr>
<td>Good renal function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No history of GI bleeding or recent ulcers</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
• MOA: selective/reversible direct inhibitor of factor Xa

  – Prevents the conversion of prothrombin to thrombin

  – Thrombin both activates platelets and catalyzes the conversion of fibrinogen to fibrin
Rivaroxaban

<table>
<thead>
<tr>
<th>Kinetics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Rapid</td>
</tr>
<tr>
<td>Distribution</td>
<td>$V_{dss}$: $\sim$50 L</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic (33%) via CYP3A4/5 and CYP2J2</td>
</tr>
<tr>
<td>Excretion</td>
<td>Renal (66% primarily via active tubular secretion); feces (28%)</td>
</tr>
<tr>
<td>Half-life</td>
<td>5-9 hours</td>
</tr>
<tr>
<td>Creatine Clearance (mL/min)</td>
<td>&gt;50</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-----</td>
</tr>
<tr>
<td><strong>Atrial fibrillation</strong></td>
<td>20 mg po daily</td>
</tr>
<tr>
<td><strong>Postoperative thromboprophylaxis</strong></td>
<td>10 mg po daily</td>
</tr>
<tr>
<td><strong>Knee:</strong> 12-14 days</td>
<td><strong>Hip:</strong> 35 days</td>
</tr>
<tr>
<td><strong>Treatment of PE/VTE</strong></td>
<td>15 mg twice daily x21 days, then 20 mg po daily</td>
</tr>
<tr>
<td><strong>Secondary Prophaxis for PE/VTE</strong></td>
<td>20 mg po daily</td>
</tr>
</tbody>
</table>
Rivaroxaban

• Monitoring
  – Prothrombin time (PT)
  – CBC with differential
  – Renal/hepatic function

• Onset: 2-4 hours

• Antidote: None
Rivaroxaban

- ADRs
  - Pruritus (2%)
  - Bleeding
    - DVT prophylaxis: 6% [major: <1%]
    - Atrial fibrillation: 21% [major: 6%]
  - Thrombocytopenia (3%)
  - Increase in liver enzymes (7%-3%)
Rivaroxaban

- **Contraindications**
  - Hypersensitivity to rivaroxaban or any component
  - Active bleeding

- **Drug Interactions**
  - P-Gp (ATP dependent efflux transporter) or CYP3A4 inhibitors/inducers
  - Anticoagulants, antiplatelet agents, NSAIDs, salicylates
Apixaban

- MOA: oral direct Xa inhibitor

- Dose: 5mg twice daily
  - Dose reduction to 2.5mg twice daily if 2+ of the following:
    - Age ≥80 years
    - Body weight ≤60kg
    - Scr ≥1.5mg/dl
  - AVOID in CrCl <15 ml/min
# Apixaban

## Kinetics

<table>
<thead>
<tr>
<th>Kinetics</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Rapid; Intestines</td>
</tr>
<tr>
<td>Distribution</td>
<td>$V_d$: 21 L</td>
</tr>
<tr>
<td>Metabolism</td>
<td>15% liver metabolism CYP3A4/5 P-gp</td>
</tr>
<tr>
<td>Excretion</td>
<td>Primarily Biliary/Fecal (46-56%)</td>
</tr>
<tr>
<td></td>
<td>Renal (27%) unchanged</td>
</tr>
<tr>
<td>Half-life</td>
<td>8 to 15 hours</td>
</tr>
</tbody>
</table>
Apixaban

• Monitoring
  – Minimal impact on the PT, INR, or aPTT
  – Factor Xa inhibition

• Onset: 3-4 hours

• Antidote: None
# Comparison of agents

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Factor IIa</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td><strong>FDA Indications</strong></td>
<td>Nonvalvular AF</td>
<td>Nonvalvular AF Ortho VTE Proph Acute Treatment VTE</td>
<td>Nonvalvular AF</td>
</tr>
<tr>
<td><strong>Prodrug</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Twice daily</td>
<td>Daily, with food</td>
<td>Twice daily</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>1-2 hrs</td>
<td>2-4 hrs</td>
<td>3-4 hrs</td>
</tr>
<tr>
<td><strong>Half-life (h)</strong></td>
<td>14–17</td>
<td>7–11</td>
<td>8–14</td>
</tr>
<tr>
<td><strong>Renal Adjustment</strong></td>
<td>↓ 15-29ml/min Avoid &lt; 15 ml/min</td>
<td>Avoid &lt; 30 ml/min</td>
<td>Avoid &lt; 15 ml/min</td>
</tr>
<tr>
<td><strong>Drug Interactions</strong></td>
<td>P-gp</td>
<td>CYP3A4/P-gp</td>
<td>CYP3A4/P-gp</td>
</tr>
</tbody>
</table>
Management of patients on NOAC therapy

• When to stop NOAC treatment before surgery?
  - Patient characteristic: kidney function, age, history of bleeding, etc.
  - Surgical factors: minor/major dental procedure
Minor dental surgery

- Minor dental surgery can be performed at trough concentration of the NOAC (i.e. 12 or 24 h after the last intake, depending on twice or once daily dosing)

- It may be more practical to have the intervention scheduled 18–24 h after the last intake, and then restart 6 h later, i.e. with skipping one dose for BID NOAC
Major dental surgery

• For procedures with a minor bleeding risk, it is recommended to discontinue NOACs 24 h before the elective procedure in patients with a normal kidney function.

• For procedures that carry a risk for major bleeding to take the last NOAC 48 h before.
• For procedures with immediate and complete haemostasis, the NOAC can be resumed 6–8 h after the intervention.
• For many surgical interventions, however, resuming full dose anticoagulation within the first 48–72 h after the procedure may carry a bleeding risk.
• One also has to take into account the absence of a specific antidote in case bleeding should occur and/or re-intervention is needed.
When to restart the new oral anticoagulants?

• Initiate a reduced venous thromboprophylactic or intermediate dose of low molecular weight heparins (LMWH) 6–8 h after surgery if haemostasis has been achieved, whereas therapeutic anticoagulation by restarting NOACs is deferred 48–72 h after the invasive procedure.

• There are no data on the safety and efficacy of the post-operative use of a reduced dose of the NOACs
<table>
<thead>
<tr>
<th><strong>Current FDA Approved Indications</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Warfarin</strong></td>
</tr>
<tr>
<td>• Prophylaxis and treatment of venous thrombosis and its extension, pulmonary embolism (PE)</td>
</tr>
<tr>
<td>• Prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement</td>
</tr>
<tr>
<td>• Reduction in the risk of death, recurrent myocardial infarction (MI), and thromboembolic events</td>
</tr>
<tr>
<td><strong>Dabigatran</strong></td>
</tr>
<tr>
<td>• Stroke prevention in patients with non-valvular atrial fibrillation</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
</tr>
<tr>
<td>• Stroke prevention in patients with non-valvular atrial fibrillation</td>
</tr>
<tr>
<td>• Prevention of VTE in patients undergoing hip or knee replacement</td>
</tr>
<tr>
<td>• Acute treatment of DVT/PE</td>
</tr>
<tr>
<td>• Secondary prevention of DVT/PE</td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
</tr>
<tr>
<td>• Stroke prevention in patients with non-valvular atrial fibrillation</td>
</tr>
</tbody>
</table>
Antiplatelet agents
Platelets adhere to the area of injured endothelium (mediated by von Willebrand factor)

Platelets adhere to each other and form a scaffolding for fibrin deposition (von Willebrand factor is a carrier protein for factor VIII)
Uses for Antiplatelet Drugs

- Prevention of heart disease
- During heart attack
- Unstable angina
- Following heart attack
- During or following angioplasty and stenting
- Prevention of stroke or TIA
- Atrial fibrillation (low risk patient)
- Peripheral vascular disease
Antiplatelet Drugs

- Aspirin (irreversible effect for life of the platelet ~ 7-10 days)
- NSAIDs (reversible effect; limited to duration of drug)
  - Cox-1 (renal blood flow, fluid/electrolyte transport, stomach mucosal integrity, vasomotor tone, platelet aggregation)
  - Cox-2 (inflammation)
- Clopidogrel (Plavix)
- Ticlopidine (Ticlid)
- Dipyridamole (Persantine)
Action of Antiplatelet Drugs

Role of Oral Antiplatelet Therapy: Different Mechanisms of Action

- Clopidogrel bisulfate
- Ticlopidine HCl
- Aspirin
- Oral GP IIb/IIIa Inhibitors?
- GP IIb/IIIa (Fibrinogen receptor)
- ADP
- Dipyridamole
- Phosphodiesterase
- Collagen Thrombin TXA2

ADP = adenosine diphosphate, TXA2 = thromboxane A2, COX = cyclooxygenase

Adapted with permission from Tisdale JE. Am J Health-Syst Pharm. 1998;55(suppl 1):S8

*The life of a platelet is about 7-10 days*
Laboratory Tests to Monitor the Effects of Antiplatelet Drugs

- **Ivy Bleeding time**: measures the length of time a patient bleeds after a standardized incision.
  - low reproducibility
  - questionable sensitivity
  - poor correlation to clinical bleeding tendency
  - normal: 1-6 or 7 minutes
  - conventionally, a bleeding time >20 minutes has been considered likely to result in clinically significant bleeding

- **Platelet Function Analyzer (PFA-100)**
  - currently the most widely used autoanalyzer
  - not yet available in all laboratories
  - measures the time it takes to form a platelet plug across the aperture of a capillary tube
  - normals: 60-120 seconds
  - guidelines not currently available for application of PFA-100 results to clinical bleeding probability
Antiplatelet Drugs and Postoperative Bleeding?

- Very limited literature on this topic
- Most of the studies deal with aspirin
- Little information available on the other antiplatelet drugs
- Most of the recommendations are based upon clinical experience, case reports and expert opinion
• Medline review and analysis of all articles from 1966-2002 on surgery and bleeding complications due to aspirin
• No clinically relevant bleeding complications were reported for cardiovascular, vascular, or orthopedic surgery, or epidural anesthesia; there was an increase in clinically non-relevant bleeding induced by aspirin
• Conclusion: There is no scientific evidence to support the withdrawal of aspirin in patients prior to surgery

The general consensus of opinion from this survey suggests that most vascular surgeons do not stop antiplatelet drugs preoperatively.
Clinical experience, expert opinion, anecdotal reports and available studies suggest that for most patients undergoing dentoalveolar surgery, it is not necessary to discontinue the use of aspirin or other antiplatelet agents if used alone. The use of these agents is not usually associated with significant (serious) operative or postoperative bleeding.

If two agents are used together (e.g. aspirin and clopidogrel), the risk for bleeding is likely increased, and depending upon the extent of the surgery, should be discussed with the physician.
Summary
IE Prophylaxis

• Only in high risk patients (prosthetic heart valve, previous infective endocarditis, congenital heart disease)

• Only in high risk procedures = dental surgery

<table>
<thead>
<tr>
<th>Situation</th>
<th>Antibiotic</th>
<th>Single dose 30–60 minutes before procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Adults</td>
</tr>
<tr>
<td>No allergy to penicillin or ampicillin</td>
<td>Amoxicillin or ampicillin*</td>
<td>2 g p.o. or i.v.</td>
</tr>
<tr>
<td>Allergy to penicillin or ampicillin</td>
<td>Clindamycin</td>
<td>600 mg p.o. or i.v.</td>
</tr>
</tbody>
</table>

Cephalosporins should not be used in patients with anaphylaxis, angio-oedema, or urticaria after intake of penicillin and ampicillin.

*Alternatively cephalexin 2 g i.v. or 50 mg/kg i.v. for children, cefazolin or ceftriaxone 1 g i.v. for adults or 50 mg/kg i.v. for children.
Management of patients on oral anticoagulants

Minor **dental surgery** (extractions, alveoloplasty, biopsy):

- no need to stop OAC, when INR is in the therapeutic range (between 2-3),
- except for conditions that can lead to bleeding complications (liver, kidney disease, antibiotic therapy)
Management of patients on oral anticoagulants

Major dental surgery

- Consultation with physician!!!
- Stop Coumadin therapy four days before surgery
- Substitution with 100 IU/kg LMWH (therapeutic dose)
- On the day of surgery miss LMWH morning, but evening continue
- Restart Coumadin in the subsequent days after procedure with LMWH bridging
Management of patients on antiplatelet therapy

• For most patients undergoing dentoalveolar surgery, it is not necessary to discontinue the use of aspirin or other antiplatelet agents if used alone. The use of these agents is not usually associated with significant (serious) operative or postoperative bleeding.

• If two agents are used together (e.g. aspirin and clopidogrel), the risk for bleeding is likely increased, and depending upon the extent of the surgery, should be discussed with the physician.
Management of patients on NOAC therapy

- Minor dental surgery can be performed at trough concentration of the NOAC (i.e. 12 or 24 h after the last intake, depending on twice or once daily dosing)

- It may be more practical to have the intervention scheduled 18–24 h after the last intake, and then restart 6 h later, i.e. with skipping one dose for BID NOAC
Major dental surgery

• For procedures with a minor bleeding risk, it is recommended to discontinue NOACs 24 h before the elective procedure in patients with a normal kidney function
• For procedures that carry a risk for major bleeding to take the last NOAC 48 h before.
When to restart the new oral anticoagulants?

- For procedures with immediate and complete haemostasis, the NOAC can be resumed 6–8 h after the intervention.
- When postoperative bleeding risk exists, initiate a reduced venous thromboprophylactic or intermediate dose of low molecular weight heparins (LMWH) 6–8 h after surgery if haemostasis has been achieved, whereas therapeutic anticoagulation by restarting NOACs is deferred 48–72 h after the invasive procedure.