Anti-Coagulant
Anti-Thrombotic
Anti-Platelet Drugs
Dental Procedures

- Considered low risk for major bleeding

- High risk procedures:
  - Multiple extractions > 5
  - Surgery lasting more than 45 minutes
  - Head and neck cancer,
  - Extensive oral and maxillofacial surgery in patients with comorbidities

Dental Procedures

• Comorbidities
  • Renal impairment
  • Advanced age
  • Concomitant anti-platelet therapies

ANTICOAGULANT CLASSES

● INHIBITORS OF CLOTTING FACTOR SYNTHESIS
  • WARFARIN (COUMADIN®)
  • Rivaroxaban (Xarelto®)
  • Apixaban (Eliquis)

● INHIBITORS OF THROMBIN
  • HEPARIN, LEPIRUDIN (REFLUDAN™)
  • Dabigatran Etexilate Mesylate (Pradaxa™)

● PREVENTION OF PLATELET AGGREGATION
  • ASA
  • TICLOPIDINE (TICLID™)
  • CLOPIDOGREL (PLAVIX™)
  • TIROFIBAN (AGGRASTAT™)
  • EPTIFIBATIDE (INTEGRILIN™)
  • Prasugrel (Effient™)
  • Ticagrelo (Brilinta®)
Patients at risk of post-op bleeding

- Patients > 75 yo and taking aspirin, long term NSAIDs or clopidogrel or prasugrel

- Surgery dependent factors: dependent upon invasiveness of the surgery and surgical difficulty

ANTICOAGULANTS

• WARFARIN (COUMADIN)
  – ACTS IN LIVER BY INHIBITING REDUCTION OF VIT. K TO A FORM NEEDED FOR SYNTHESIS OF FACTORS VII, IX, X, AND PROTHROMBIN

• HEPARIN
  – POTENTIATES THE ANTICOAGULANT ACTIVITY OF ENDOGENOUS ANTITHROMBIN III
COUMADIN®

• EFFECT IN 24 HRS.

• PEAK 3 – 4 DAYS

• MAY CAUSE SERIOUS HEMORRHAGE
  – ANTIDOTE – VIT. K

  • REQUIRES 12 – 24 HRS.

  – MAY REQUIRE TRANSFUSION
Warfarin

• Outpatient Rx’s 2004 - 31 million

• Ranked 1st in 2003 and 2004 for drug related deaths due to “adverse effects” in therapeutic use

• 10 to 16% of patients will have a major bleed at some point

• No longer acceptable to D/C warfarin routinely!!!
COUMADIN®

- MONITOR WITH INR (INTERNATIONAL NORMALIZED RATIO)

– STANDARDIZES THE VARIOUS LABORATORIES THROMBOPLASTINS (human or rabbit)
Recommended range for oral anticoagulant therapy:

**INR target range 2.0 to 3.0**
- Prophylaxis/treatment of venous thrombosis
- Treatment of pulmonary embolism
- Prevention of systemic embolism
- Recurrent systemic embolism
- Acute myocardial infarction
- Valvular heart disease
- Valvular replacement with tissue
- Atrial fibrillation

**INR target range 2.5 to 3.5**
- Mechanical replacement heart valves
  (High risk)
INTERNATIONAL NORMALIZED RATIO (INR)

INR < 2.0 out of therapeutic range (poorly managed – needs adjustment)

INR 2.0 → 4.0 ok to do surgery with local measures

INR > 4.0 out of therapeutic range – (warfarin dosage needs adjustment)
Warfarin (Coumadin®)

Good
- Continue warfarin therapy
- Hemorrhagic disorders
- Correct INR

Bad
- D/C warfarin therapy
- Malpractice
- Cerebrovascular complications
- Thrombosis formation
Should warfarin be discontinued before a dental extraction?  
A decision-tree analysis

Ben Balevi, BEng, DDS, DipEBHC (Oxford), MSc, Vancouver, Canada

**Objective.** The aim of this study was to determine if warfarin should be withdrawn before a single tooth extraction on a patient with a prosthetic heart valve.

**Study design.** A quantitative decision tree was constructed to assess the expected utility values of 2 typical strategies to manage the dental extraction on a patient currently medicated with warfarin. Probabilities and utilities for a cardiovascular accident and major bleeding from a dental extraction were taken from the literature.

**Results.** The decision slightly favors withholding warfarin: generating an optimal expected utility value of 0.976 utile. This was only 0.02 utile higher than the alternative option of continuing warfarin for a dental extraction.

**Conclusion.** The decision to withhold or continue warfarin before a dental extraction depends more on the relative risk of a major bleeding between the 2 medical management strategies than on the consequences of a cardiovascular accident. *(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;110:691-697)*
CONCLUSION

The decision to withhold or continue warfarin before a dental extraction depends more on the RR of major bleeding between the two medical management strategies than on the consequences of a CVA. For the minimally invasive single tooth extraction, not disrupting the patient’s warfarin protocol and using local adjunctive means of hemostasis is defensible. However, in cases that are significantly invasive and/or involve multiple dental extractions, withholding warfarin may be indicated, because of the risk and thus the negative consequences of major bleeding as perceived by the patient.
I have finished reviewing the OOOOE article on warfarin. Bottom line, there is no statistical weight whatsoever behind the article's recommendation to withhold warfarin. The EUV estimates are separated by only 0.02, and all of the probabilities used to estimate the two EUV values are themselves estimates (from other literature, no less).

This article is in no way a breakthrough or landmark. Would it be okay for me to call you and discuss in more detail my critique of the article? I can call most any time/day this week or next; just let me know.
DRUGS WITH THE POTENTIAL TO AFFECT ANTICOAGULANT THERAPY.

<table>
<thead>
<tr>
<th>MEDICATIONS THAT POTENTIATE THE EFFECT OF COUMARIN</th>
<th>MEDICATIONS THAT OPPOSE THE EFFECT OF COUMARIN</th>
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</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Metronidazole</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Nonsteroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>Chloral hydrate</td>
<td>Penicillins</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Propoxyphene</td>
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<tr>
<td>Diflunisal</td>
<td>Salicylates</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td>Fluconazole</td>
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<tr>
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<td>Barbiturates</td>
</tr>
<tr>
<td></td>
<td>Dicloxacillin sodium</td>
</tr>
<tr>
<td></td>
<td>Nafcillin</td>
</tr>
</tbody>
</table>

Ref. Herman W., et. al., Current Perspectives On Dental Patients Receiving Coumarin Anticoagulant Therapy, JADA March 1997
TAKE-HOME MESSAGE

• MUST HAVE A RECENT INR (WITHIN 30 DAYS IF NO CHANGES IN MEDS)

• IF ANY MED OR DOSAGE CHANGES – THEN MUST REPEAT INR

• BEST IF SAME-DAY FOR MAJOR PROCEDURES!!!
dabigatran (Pradaxa®)
Boehringer Ingelheim

- For prevention of stroke and systemic embolism (blood clots) in patients with atrial fibrillation
- Specific direct thrombin inhibitor
- First replacement for warfarin (Coumadin®) since Coumadin was approved in 1954
dabigatran (Pradaxa®)

• Rapid onset of action (peak plasma level within 0.5 to 4 hours)

• 1/2 life
  • Healthy patient: 12 - 14 hours
  • Elderly patient: 14 - 17 hours
  • Severe renal dysfunction: up to 27 hours

• Wide therapeutic margin

• Few drug interactions

• No significant food interactions
Serine protease
dabigatran (Pradaxa®)  
anticoagulant

- Acts by inhibiting thrombin, an enzyme in the blood that is involved in blood clotting

- Thrombin (serine protease) enables the conversion of fibrinogen to fibrin during the coagulation cascade, its prevention prevents the development of a thrombus.

- Recommended dose is a 150 mg orally once or twice daily

- Warfarin therapy requires patients to undergo periodic monitoring with blood tests
  - INR monitoring not necessary for dabigatran.
dabigatran (Pradaxa®)

- Measure of Effect

  - At therapeutic doses prolongs the activated partial thromboplastin time (aPTT)
  
  - Oral dose of 150 mg twice daily, the median peak aPTT is approximately twice that of control values
  
  - Twelve hours after the last dose, the median aPTT is 1.5x control
  
  - More accurate thrombin clotting time (TT) and ecarin clotting time (ECT)
  
  - INR test is relatively insensitive to the activity of dabigatran and may not be elevated in patients on dabigatran.
dabigatran (Pradaxa®)

- Absorption and Metabolism
  - Minor bleeding event, delay the next dose - consult physician
    - Constantinids et al. BMC Oral Health (2016) 16:5; Managing patients taking novel oral anticoagulants (NOAs) in dentistry: a discussion paper on clinical implications
  - Not metabolized by CYP enzymes
  - After oral administration, dabigatran etexilate is converted to dabigatran through esterase-catalyzed hydrolysis of the molecule in plasma
  - Dabigatran is not a substrate, nor inhibitor, nor inducer of CYP 450 enzymes
Dabigatran and Risk of Bleeding

• ↑ risk of bleeding and can cause significant, and sometimes fatal, bleeding
  • Drugs that can increase the risk of bleeding include antiplatelet agents and chronic use of NSAIDs

• RE-LY trial, life-threatening bleeding occurred at an annualized rate of 1.5% for Pradaxa 150 mg and 1.8% for warfarin.

• Discontinuing Pradaxa for surgery places the patient at an ↑ risk of stroke
  • If anticoagulation must be temporarily discontinued for any reason, therapy should be restarted as soon as possible.

• Dental patients who may have a high risk of bleeding if taking Pradaxa include those over 75 years of age, or are taking aspirin, or long term NSAIDs, or clopidogrel (Plavix®) or prasugrel (Effient®).

Dabagatran life threatening bleed

- Administration of prothrombin complex concentrates
- Administration of idarucizumab: Rx - Praxind - (monoclonal antibody)
- Rapidly (within minutes) reverses bleeding effects of dabagatran
Dabigatran Dental Treatment

• Discontinuing for elective surgery places patients at an increased risk of stroke and if discontinued restart as soon as possible
  
  • Wynn, TL. New antiplatelet and anticoagulant drugs. Gen Dent. 2012;608-11

• Risk of post-op bleeding is similar to those patients who take warfarin with an INR of 2 to 3
  

• Perform surgery as late as possible after the most recent dose of dabigatran
Dabigatran dental treatment

- For aggressive oral surgical procedures - get consult on discontinuation of drug

- TT or aPTT performed 6 to 12 hours prior to surgery

- Restart dabigatran once a stable clot has formed (24 - 48 hours) following surgery


- Use acetaminophen or narcotics for analgesia

- Avoid dexamethasone
Rivaroxaban (Xarelto®)

- Mechanism: Factor Xa inhibitor
  - In coagulation cascade factor X → Xa (produces fibrin)
Rivaroxaban (Xarelto®)

- Prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE) in pts undergoing knee or hip replacement surgery
- 10 mg once daily
- 5 - 6% pts have “a bleeding event”
Rivaroxaban (Xarelto®)

• Measurement of Effect
  – Prolongs prothrombin time (PT) and activated partial thromboplastin time (aPTT)
  • Predictive treatment values not established
  – No data on INR use
  – Hip replacement - 35 days
  – Knee replacement - 12 days
Rivaroxaban (Xarelto®)

- Rapid onset (peak plasma level 2.5 - 4 hours)
- 1/2 life 5.7 to 9.2 hours
- patients >75 yo = 12 to 13 hours
Rivaroxaban (Xarelto®)

• Dental considerations
  • ↑ bleeding occurs with 10mg/day
  • Consult (?) for simple surgery
  • No reports of interactions with amoxicill, cephalexin, cefazolin, ampicillin, & clindamycin
  • No interruption for simple surgery
Rivaroxaban (Xarelto®)

- Dental considerations
  - Complex oral surgery or patients at increased risk for bleeding (especially severe renal impairment) discontinue 24 hours in advance
  - Get consult
  - Restart within 24 to 48 hours
  - Analgesia use acetaminophen
Rivaroxaban (Xarelto®)

• Drug interactions
  – Inhibitors of CYP3A4
    • Ketocanazole (antifungal)
    • Clarithromycin (Biaxin®)
    • Erythromycin
  – NSAIDS
  – Opioids
Apixaban (Eliquis)

- Direct anti-coagulant
- Rapid onset - bioavailability 60%
- Peak plasma level 1-3 hours
- 1/2 life 12 hours
- No Reversal agent
Apixaban (Eliquis)

- If post-op bleeding - delay subsequent dose
- Did not stop for oral surgery - be reasonable
THROMBOGENESIS

- PLATELET AGGREGATION

- COAGULATION
ARTERIAL COAGULATION

– CASCADE TO FIBRIN STRANDS

• ARTERIES
  – PLATELETS ADHERE TO DAMAGED VESSEL WALLS
  – AGGREGATE
  – CORE FOR FIBRIN STRANDS
  – OCCLUDE ARTERIAL FLOW
  – ISCHEMIA OF LOCAL TISSUES
VENOUS THROMBESI

- FIBRIN STRANDS

- EMBOLIZE GREAT DISTANCES

- LODGE IN PULMONARY ARTERIES
THROMBOGENESIS

• LOCALIZED RESPONSE
  – INITIATED BY SUBSTANCES RELEASED FROM PLATELETS AND ENDOTHELium
  – LIMITED BY LOCALIZED ANTICOAGULANT MECHANISMS
• ANTITHROMBIN II
ANTIPLATELET DRUG

• ASPIRIN
  – TX: PREVENTION OF MI & THROMBOTIC STROKE
  – 81 mg/day
  – LITTLE RISK FOR DENTAL SURGERY
ANTIPLATELET DRUG

• DIPYRIDAMOLE (PERSANTINE)
  – PREVENTS PLATELET ADHESION TO ENDOTHELIAL SURFACES
  – MIXED WITH ASA
    • ENHANCES ANTITHROMBOTIC ON ARTIFICIAL SURFACES
      – VALVULAR & CARDIAC PROSTHESES
  – DIALATES CORONARY ARTERIES
PLAVIX® - CLOPIDOGREL

• BLOCKS THE ADP RECEPTOR WHICH PREVENTS THE BINDING OF FIBRINOGEN TO THAT SITE

• DOES NOT ALTER THE RECEPTOR

• REDUCES # OF FUNCTIONAL ADP RECEPTORS
PLAVIX® - CLOPIDOGREL

- MONITOR WITH PLATELET AGGREGATION
- INITIAL 2 TO 4 WEEKS MAY CAUSE THROMBOCYTOPENIA – CHECK PLATELETS
- RARELY NECESSARY TO D/C
- SURGERY IF MULTIPLE SITES OR EXTENSIVE? – get consultation
  - DISCONTINUE 7 DAYS PRIOR TO PROCEDURE (RARELY NECESSARY!)
• 30% of population has a genetic variant in liver metabolizing enzymes that affect efficacy of clopidogrel - no effect at all

  — CYP2C19 converts clopidogrel to an active metabolite.

  — Genes which encode and express liver enzymes responsible for metabolism exist in several polymorphic states (CYP2C19 has 4 variants with reduced function)

  — Relative reduction of 32% in active metabolite

  — 53% higher risk for primary efficacy outcome of death from cardiovascular causes, MI, stroke

  — Stent thrombosis in carriers 3 X that of non-carriers

Prasugrel (Effient™)

- Antiplatelet agent and aggregation inhibitor

- For ↓ thrombotic cardiovascular events
  (stent thrombosis)

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Prasugrel (Effient™)

• Pro-drug

• Irreversibly blocks P2Y12 component of adenosine diphosphate (ADP) receptors on platelets for their lifespan
  –↓ platelet activation and platelet aggregation
  –Normal platelet activity does not return (new platelets in 5 to 9 days after D/C
  –Loading dose 60 mg followed by maintenance dose of 10 mg daily.
  –Should take with ASA 75 to 325 mg daily
Prasugrel (Effient™)

- Genetic variants in liver metabolizing enzymes do not affect efficacy
  - Undergoes rapid intestinal and serum metabolism via esterase-mediated hydrolysis to a thiolactone (inactive metabolite), which is then converted, via CYP3A4 & CYP2B6 enzyme oxidation, to the active metabolite designated as R-138727.
Ticagrelor (Brilinta®)

• Reduce rate of thrombotic cardiovascular events in pts with acute coronary syndrome (ACS): unstable angina, non-ST elevation MI, ST elevation MI

• More effective than clopidogrel
Ticagrelor (Brilinta®)

• Drug interactions
  – Inhibitors of CYP3A4
  – Ketocanazole
  – Itaconazole
  – Voriconazole
  – Clarithromycin (Biaxin®)
  – Erythromycin

• NSAIDs
Ticagrelor (Brilinta®)

• Mechanism: An active, reversible platelet inhibitor

• CYP3A4 converts ticagrelor to another active reversible platelet inhibitor - which is the major active metabolite

• Act at the ADP-receptor

• Loading dose 180 mg then 90 mg BID
  – Give with loading dose ASA 325 mg then 75 - 100 mg. Daily
  – ASA doses above 100 mg/day reduce effectiveness of ticagrelor and should be avoided
Ticagrelor (Brilinta®)

- Dental considerations
- Do NOT D/C without consultation
- Expect bleeding and echymosis
- Patients often have SOB
- No coagulation parameters suggested
Ways to stop bleeding

1. Pressure
2. Local Anesthesia with epinephrine on gauze
3. Suture
4. Bone wax
5. Collagen

6. PRP
7. PPP
8. PRF
9. I-PRF
10. Stop Bleed
Ways to stop bleeding

11. Surgicel (oxidized celluler polymer)
12. Avitene (microfilbular collagen)
13. Laser
14. Bovie (high-temperature cautery)
15. Bovine Thrombin

16. Hemostat (clamp)
17. Injecting local anesthesia with epinephrine
18. Ice packs
19. Burnish bone
20. Ligate vessel
21. Periacryl (gel)
Bovie - Salvin

Portable Electrocautery System For Coagulation

Complete Kit Includes:
- Handle & Batteries
- 2 Fine Tips & 2 Loop Tips
- 10 Sterile Handle Sheaths

#CAUT-KIT-DEL-1 . . . . . . . . . . . . . . . 99.50 KIT

Replacement “Fine” Tips
Box Of 10 Single Use “Fine” Tips With Sterile Handle Sheaths
#CAUT-FINE-H101 . . . 64.90 BOX OF 10

Replacement “Loop” Tips
Box Of 10 Single Use “Loop” Tips With Sterile Handle Sheaths
#CAUT-LOOP-H103 . . . 64.90 BOX OF 10