Medical Advances and Their Impact on Dental Patient Management: A Historical and Evidence-Based Discussion

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Three Cases

• Antithrombotics and Dental Procedures

• Bone Antiresorptives and Osteonecrosis

• Hypertension in the Dental Chair
Antithrombotics and Dental Procedures

• A case and a dilemma
• Historical perspective & Background
• The Evidence
• Resolution
83 Year-old Male
Chief Complaint: Chronic Lower Left

Medical History significant for Atrial Fibrillation and previous stroke
Diagnosis: Facial Caries #18; Poor Restorative Prognosis

Recommendation: Extract #18
Dilemma

Patient consents to Extraction #18.

Patient states, “I cannot do it today, because my doctor wants me to stop my blood thinners before any surgery.”

Patient had been on Coumadin therapy in the past.
Patient currently is on Xarelto® (Rivaroxaban) and 81 mg Aspirin therapy.
Antithrombotics and Dental Procedures

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Atrial Fibrillation

Manifestations
Often Asymptomatic
Rapid ventricular Rate
Congestive Heart Failure

Causes Stroke
Atrial Fibrillation
Mechanism of Ischemic Stroke
Cardiac Embolism
Warfarin for Atrial Fibrillation

• Vitamin K antagonist isolated from Sweet Clover plant

• Inhibits hepatic synthesis of coagulation factors: II, VII, IX, X

• Prevents 65% of strokes in Atrial fibrillation patients

• 1 to 3% risk of a major bleeding event per year

• Effect on coagulation system monitored by INR
Sep 2009  
RELY (Pradaxa)  
(Rivaroxaban versus Warfarin in Patients with Atrial Fibrillation)

Sep 2011  
ROCKET (Xarelto)  
Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

ARISTOTLE  
Apixaban versus Warfarin in Patients with Atrial Fibrillation
New Anticoagulants

Characteristics
- Do not antagonize Vitamin K
- No dose adjustment
- No routine monitoring
- INR & PTT unreliable measures degree of anticoagulation
- No antidote

Rivaroxaban
Apixaban

Dabigatran
(Thrombin)

Fibrinogen  Fibrin
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Drug</th>
<th>Relative Risk Reduction and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or Systemic Embolism</td>
<td>Dabigatran</td>
<td><img src="image" alt="Relative Risk Reduction" /></td>
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<tr>
<td></td>
<td>Rivaroxaban</td>
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<td>Apixaban</td>
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<td>Ischemic Stroke</td>
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<tr>
<td>Major Bleeding</td>
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<tr>
<td></td>
<td>Apixaban</td>
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<tr>
<td>Intracranial Bleeding</td>
<td>Dabigatran</td>
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<tr>
<td></td>
<td>Rivaroxaban</td>
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<tr>
<td></td>
<td>Apixaban</td>
<td><img src="image" alt="Relative Risk Reduction" /></td>
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<tr>
<td>Gastrointestinal Bleeding</td>
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<td><img src="image" alt="Relative Risk Reduction" /></td>
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<td>Rivaroxaban</td>
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<td><img src="image" alt="Relative Risk Reduction" /></td>
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Relative risk reductions of new antithrombotic regimens compared to dose-adjusted warfarin for various outcomes.
Antithrombotics and Dental Procedures

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Summary of evidence-based guideline: Periprocedural management of antithrombotic medications in patients with ischemic cerebrovascular disease


*Neurology* 2013;80;2065-2069

DOI 10.1212/WNL.0b013e318294b32d
Four Class I Studies re: Dental Procedures


All Randomized Controlled Trials
Dental extractions
Oral Surgery
Clinically Important Bleeding
Risk Difference
Warfarin Recommendations

• Patients taking warfarin should be counseled that warfarin continuation is highly unlikely to increase their risk of important bleeding complications with dental procedures (Level A).

• Given minimal bleeding risks, stroke patients undergoing dental procedures...
Ischemic stroke

Temporary excessive bleeding
Antithrombotics and Dental Procedures

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Surgical Extraction #18
GelFoam + Gut Sutures
Bone Antiresorptives and Osteonecrosis

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Liver cirrhosis; Past smoker w/50 year history

Past bone fractures in ribs, arm, hands, toes

Herniated lower spine discs X 3 from injury 2002
Dilemmas

- Patient has ‘low grade’ prostate cancer
- Patient has infrequent and irregular dental care; poor oral hygiene; limited finances; off and on symptomatic for dental pain
- High fracture risk patient
- Androgen Deprivation Therapy (ADT) has risks for osteoporosis
- Concerns include **timing for surgery** as pt may be future Anti–Resorptive therapy candidate, which has
Bone Antiresorptives and Osteonecrosis

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Osteonecrosis of the Jaw

Exposed bone in the maxillofacial region for $\geq 8$ weeks

Causes:

• Radiation treatment for cancer of the head/neck

• Medications
  – Bisphosphonates
  – Denosumab
  – Antiangiogenesis
Bisphosphonate History

• 1964: M.D. Francis and J.D. Valent (of P & G) discovered bisphosphonates removed calculus without etching the enamel; concluded that dissolution rate of pure hydroxyapatite crystals was slowed along with blocking hydroxyapatite crystal growth

• 1967: 1st medicinal approach. 16-month patient with myositis ossificans progressiva (MOP), disease that cause calcification of soft tissue. P & G was introduced to try etidronate. It worked to control the pt’s condition

• FDA approval starting mid 1990’s for oral bisphosphonates for osteoporosis and IV Bisphosphonates for metastatic bone disease; more widely used starting in early 2000’s

• Nitrogen containing Bisphosphonates are more potent and therefore more widely used for bone metabolic diseases. Mechanism targets function and survival of mature osteoclasts
Osteonecrosis 1st Report


“36 cases of painful bone exposure in the mandible, maxilla, or both, that were

All had IV Nitrogen containing bisphosphonates [Pamidronate (Aredia) or IV Zoledronate (Zometa)] treatment in common

Dr. Marx urged prudence in therapy to the medical oncology, oral-maxillofacial surgery, and dentistry professions.
Bisphosphonate–Related Osteonecrosis of the Jaw

• Risks for developing Bisphosphonate–Related Osteonecrosis of the Jaw (BRONJ) with IV is 0.8%–12% and with oral it is possibly up to 0.06%. But these percentages may increase due to increased and long term use (>3 years for oral).

• Risks is greater for cancer pts receiving IV bisphosphonates and dentoalveolar surgery.

• Mandible is 2:1 more likely than maxilla.

Denosumab

• Human Monoclonal antibody against RANK ligand, causing suppression of osteoclast formation by targeting pre-osteoclasts

• Route of administration of Denosumab (SQ injection); more convenient and not nephrotoxic compared to IV bisphosphonate

• Subcutaneous injectable
  –Denosumab
    –Prolia (osteoporosis); 60 mg twice a year

    –Xgeva (↓ skeletal related events from cancer metastasis); 120 mg every 4
1st Documented Case
Denosumab related–ONJ

- 60 year old male metastatic prostatic adenocarcinoma
- Phase 3 trial Denosumab vs Zoledronate; pt in Denosumab arm and unblinded and discontinued after oral complication
- Treatment with Amoxicillin and Chlorhexidine Gluconate mouthwash
- Necrotic bone sequestered 12 months later
- Symptom free 15 months post initial presentation
Patient Assessment

• Prostate Cancer
  – Androgen Deprivation Therapy

• Breast Cancer
  – Selective Estrogen Receptor Modulator; Tamoxifen
  – Aromatase Inhibitor (2005) ; Arimidex, Aromasin, Femara

• Osteoporosis
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What is risk for ONJ if given Prolia® 60 mg injections every 6 months for osteoporosis?

Bisphosphonates and Denosumab as Anti-Resorptive therapies are relatively new. Few long-term trials. Much of the ONJ data is incidental in Antiresorptive studies.
Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM)

• 10 year on-going study testing efficacy and safety of Denosumab (Prolia®) 60 mg twice a year injections compared to Placebo

• Ages: 60–90. Women with bone mineral density –2.5 or less; N=7808 at start

• Randomized to Prolia® or Placebo for first three years

• After 3 years, extension phases include all on Prolia®
Adverse Event:

• At two years of use
  – 2/5108 (0.0003%)
  – Both cases healed

• At six years of use
  – 4/1827 (0.002%)
  – “all four cases healed with appropriate treatment”

• Study Design
  – ONJ not an outcome measure; unknown # had oral surgery
Medication–Related Osteonecrosis of the Jaw

• Growing number of cases of osteonecrosis associated with medications other than Bisphosphonates:
  – Antiresorptive (Denosumab)
  – Antiangiogenic therapies

Bone Antiresorptives and Osteonecrosis

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Prostate Cancer Pt case

• Consulted with Urologist; states “possible denosumab therapy a few years down the road”

• Prolia® injections twice a year if pt develops osteoporosis
  – Pt is high fracture risk based on hx of past fractures

• Though urged to have dental surgery sooner than later, the timeline for risk of ONJ due to
Anti-Resorptive Summary

• Aromatase Inhibitors becoming a standard for post-menopausal Estrogen-Sensitive Breast Cancer patients, in early and late stages; AI associated with moderate enhancement of BMD loss compared to SERM therapy (Tamoxifen)

• Denosumab (Zgeva®) as an alternative to IV bisphosphonates for cancer therapy

• Denosumab (Prolia®) injections as an alternative to Bisphosphonate for osteoporosis and fracture Risks

• Cases of ONJ being associated with Denosumab,
Hypertension in the Dental

• A case and a dilemma
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Case

• 79 year old female patient is treatment planned for Maxillary extractions X 10 & maxillary alveoloplasty.

• BP readings are 160’s systolic range, 99–108 diastolic range in multiple appointments.

• Patient is being followed by a M.D. and is on antihypertensives.

• At surgery appointment, the patient feels well. BP: 164/1

• **Should the procedure proceed?**
Hypertension in the Dental

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Hypertension

- 100+ years ability to measure BP
- 1940’s–50’s Insurance companies recognize high BP as a risk factor for cardiovascular disease
- Epidemiological studies confirm risks of HTN
- VA cooperative study demonstrates large benefit of treating very severe HTN

Overdiagnosed HG Welch et al, Bacon Press, Boston, Jan 2011
## JNC–7 Classification of BP

<table>
<thead>
<tr>
<th>Class</th>
<th>SBP</th>
<th>DBP</th>
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<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
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<tr>
<td>Pre-HTN</td>
<td>120–139</td>
<td>80–89</td>
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<tr>
<td><strong>Stage I HTN</strong></td>
<td><strong>140–159</strong></td>
<td><strong>90–99</strong></td>
</tr>
<tr>
<td>Stage II HTN</td>
<td>&gt;160</td>
<td></td>
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</tbody>
</table>

*JAMA 2003; 289:2560–72*
HTN: Chronic Complications

- Stroke
- Myocardial Infarction
- Congestive heart failure
- Renal disease
- Peripheral vascular disease
Acute Complications: Hypertensive Emergency

• Brain
  – Headache
  – Delirium
  – Stroke symptoms

• Acute heart failure
  – Chest pain
  – Dyspnea

• Acute renal failure

BP almost always > 180/120
Usually systolic > 200
Threshold very dependent on patient’s usual BP
Hypertension in the Dental

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JNC–8 Evidenced-Based Recommendations

- vs Recommendations based on Consensus (JNC 7)
- Did not address definitions of HTN or pre-HTN, though presented thresholds for pharmacologic treatment
- Age 60 or older, systolic threshold for treatment 150 mmHg vs 140 mmHg for those < 60 years
- Changes in recommended initial drug classes to treat

**JAMA, 2014; 311(5): 507–520**
Benefit of Treatment in preventing chronic complications

<table>
<thead>
<tr>
<th>Diastolic BP Range</th>
<th>Risk</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>115–129</td>
<td>72%</td>
<td>1.4</td>
</tr>
<tr>
<td>105–114</td>
<td>26%</td>
<td>4</td>
</tr>
<tr>
<td>90–104</td>
<td>9%</td>
<td>11</td>
</tr>
<tr>
<td>90–100</td>
<td>6%</td>
<td>18</td>
</tr>
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</table>

Modified from Overdiagnosed HG Welch et al, Bacon Press, Boston, Jan 2011
Screening during Dental Visits identifies patients with

- 30% to 40% with SBP > 140 mmHg

- > 80% undiagnosed

Dental Clinics of North America 2012; 731–45
Potential Reasons Not to

• They are at increased risk of stroke or MI in the chair

• Might precipitate a hypertensive crisis
Moderate HTN is not an independent risk factor for perioperative cardiovascular

• Moderate Hypertension: SBP ≤ 180 mm Hg ; DBP ≤ 110 mm Hg

• SBP > 180 mm Hg or DBP > 110 mm Hg

• SBP 180–209 mm Hg or DBP 110–119 mm Hg AND acute target-organ damage

J Am Dent Assoc. 2004 May;135(5): 576–84;
Epinephrine used in typical doses will not precipitate a

• Typically epinephrine exposure increases heart rate and decreases BP.

• In hypertensive patients undergoing dental procedures there is no significant difference in change in mean arterial pressure in those

• Two to three cartridges of lidocaine with 1:100,000 epinephrine is considered safe in patients with CVD

• Avoid epinephrine-impregnated cords

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• Should the procedure proceed?
Proceed with procedure
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