PHARMACOLOGY OPTIONS FOR ORTHOPEDICS

Toral Patel, PharmD, BCPS

Assistant Professor of Clinical Pharmacy

University of Colorado Anschutz School of Pharmacy and Pharmaceutical Sciences

Disclosure

Non-Declaration Statement: I have no relevant relationships with ineligible companies to disclose within the past 24 months. (Note: Ineligible companies are defined as those whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.)

- Pain Management Pharmacology
- Bone Health
- Pharmacological VTE Prophylaxis

Educational Objectives

At the conclusion of this session, participants should be able to:

1. Discuss the risks associated with the use of nonsteroidal anti-inflammatory medications
2. Recommend therapies for the management of osteoporosis
3. Articulate the safety of medications used for clot prevention in orthopedic patients

What pain medications do you commonly prescribe in your practice? Please specify route if relevant

Principles of Pain Management

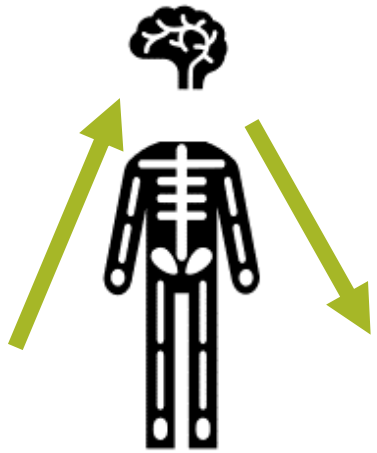
- Assess cause of patient's pain and duration (acute vs chronic (pain greater than 3 months per CDC))
- Optimize non-pharmacologic pain management strategies.
- Goals of Pharmacologic therapy = manage pain while minimizing side-effects of treatment and progression to chronic pain.
- Review patients overall medical status (e.g., renal/ hepatic function, age, cognitive status)
- Utilize a multi-modal pharmacologic approach to pain management
- Optimize non-opioid therapies where possible
  - Evidence lacking for long term benefits of opioids for chronic pain
- Reserve opioids for inadequate control with or contraindications to non-opioid therapies after reviewing benefits/risks

https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm

Pain Pathways

Inhibit Ascending Pain Signals:

- Acetaminophen (APAP)
- Non-steroidal Anti-inflammatory (NSAID)
- Local Anesthetics (e.g., lidocaine)
- Topical capsaicin, menthol
- Opioids



Modulate Descending Pain Pathways:

- Anticonvulsants (e.g., GABA receptor analogs)
- Antidepressants (e.g., Serotonin Norepinephrine Reuptake Inhibitors, Tricyclic Antidepressants)

Adapted from: Pain Pathways Figure from Approach to the management of chronic non-cancer pain in adults - UpToDate (ucdenver.edu)

Over the Counter (OTC) Topical Analgesics

	Pearls for Adult Use
Menthol Salicylate*	• Apply 3-4 times daily to intact skin • Indication: minor pain of muscles and joints • Avoid in pregnancy after 20 weeks gestation
Capsaicin • Lotion • Patch*	• Apply up to 4 times daily to intact skin • Wash hands immediately after application unless utilized for hands (for hand pain, wash hands after 30 min) • Use: neuropathic pain, muscle/ joint pain
Diclofenac (Voltaren®)	• = Non-steroidal anti-inflammatory (NSAID) • Localized effects and minimal side-effects • Apply up to 4 times daily to intact skin • Beneficial in localized pain (e.g., arthritis of the hand, knee, elbow; myofascial pain)

*Products available in variable strengths

OTC Analgesics

	Adult Dosing:	Pearls for Use
Acetaminophen	325-500 mg Q 6 hours as needed ; 1 g PO TID. Max 4 g/24 hours Limit to 3 g/24 hours for long term scheduled use	• Indicated for mild-moderate pain. • Adjunctive use in more severe pain. • First-line therapy for osteoarthritis (OA) • Scheduled dosing beneficial in OA and low back pain • Limit to max 2 g/day in patients w/ liver dysfunction
Nonsteroidal Anti-inflammatories (NSAIDs) • Ibuprofen (Advil® Motrin®) • Naproxen (Alleve®)	Ibuprofen: OTC: 200 – 400 mg every 4-6 hours as needed. Max 1.2 g/24 hours *Rx: 600 – 800 mg every 6-8 hours as needed. Max 2.4 g - . 3.2 g/24 hours (limit to 2.4 g/24 for chronic use to minimize adverse effects)	• Key treatment for musculoskeletal conditions with inflammation (acute stages; limited efficacy benefit in chronic pain stage with minimal inflammation) • Take w/food to minimize GI upset/irritation • Increases risk of heart attacks, stroke, and heart failure w/ regular use. • Avoid in patients w/ renal dysfunction, Pepcid ulcer disease • May schedule dosing during post-operative period
	Naproxen: OTC: 200 to 400 mg x 1, then 200 mg every 8 to 12 hours as needed; max dose: 400 mg per 8 hour period or 600 mg per 24 hours. *Rx: 500 mg x 1, then 250 - 500 mg every 12 hours as needed **or** 250 mg every 6 - 8 hours as needed; max dose: 1.25 g on day 1, then 1 g/day	

Osteoarthritis Management: Updated Guidelines from the American College of Rheumatology and Arthritis Foundation (aafp.org)

NSAIDs Increase Risk of Heart Attacks, Strokes, and Heart Failure

- Risk of heart attack or stroke can occur as early as the first weeks of NSAID use.
- Risk may ↑ w/ longer NSAID use.
- Greater risk at higher doses.
- Insufficient information to conclude risk difference exists or does not exist between NSAIDs.
- Risk of heart attack or stroke exists in patients with or without pre-existing risk factors for heart attack or stroke.
  - Patients with heart disease or risk factors for heart disease have a greater likelihood of heart attack or stroke following NSAID b/c of higher baseline risk.
- Increased risk of heart failure also possible with NSAID use.

https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-strengthens-warning-non-aspirin-nonsteroidal-anti-inflammatory

Anti-convulsants and Anti-depressants

	Starting Adult Doses	Pearls for Use
GABA analogs	Gabapentin: 100-300 mg PO at bedtime Pregabalin (Lyrica®): 50 mg PO TID or 75 mg PO BID	• Indications: neuropathic pain, perioperative pain • Start low, increase slowly – limited by dizziness and sedation • Case reports of respiratory depression in elderly patients receiving other CNS depressing medications concurrently • Pregabalin is more readily absorbed and rapidly titratable and but may not be first line per insurance and teratogenic in pregnancy.
Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)	Duloxetine (Cymbalta®) Venlafaxine (Effexor®	• Indications: neuropathic pain, musculoskeletal pain (low back pain, osteoarthritis) in acute and chronic phases • Non-sedating*; limited by • Withdrawal possible w/ missed doses – gradually taper when discontinuing therapy • ↑ blood pressure seen, esp. with venlafaxine
Tricyclic Antidepressants (TCAs)	• Amitriptyline- most • Nortriptyline	• Neuropathic pain • Analgesic effect seen at MUCH LOWER doses than antidepressive effect • Amitriptyline most studied for pain • Limited by: ↑QTc, sedation, anticholinergic effects, ↓seizure threshold

Opioids

- MOA = opioid receptor (μ, δ, κ) analog activating INHIBITING central and peripheral pathways
- Indication: moderate-severe pain
- Side-effects: somnolence, respiratory depression, death, tolerance, euphoria, addiction, constipation, urinary retention

CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016 | MMWR

2016 CDC Guideline for Prescribing Opioids for Chronic Pain

- Evidence lacking for long term benefits of opioids for chronic pain (pain > 3 months)
- Should not be routinely used for chronic pain without assessment of risks/benefits.
- Short duration opioids preferred in acute pain
  - May reduce opioid tolerance and dependence
- Reserve longer duration medications (extended release (ER), sustained release (SR), long acting (LA) to chronic pain where "around the clock" dosing is beneficial long term
- Avoid use of combination products (e.g, Lortab (acetaminophen + hydrocodone) in the acute pain phase to minimize overdose and facilitate titration of individual analgesics
- Start w/ lowest effective dose
- Concurrent use with benzodiazepines may put patients at increased risk for harm

https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm

Oral Opioids by Duration

Short-duration Opioids

- Hydrocodone immediate release (IR) products only available in combination (e.g., Lortab®)
- Oxycodone
- Morphine
- Hydrocodone
- Tramadol*

*tramadol is a weak opioid agonist

Long-duration Opioids

- Oxycodone sustained release (SR)
- Morphine SR

Tramadol

- MOA: Weak opioid receptor agonist
- Less constipation
- Variations in effective response due to CYP2D6 genetic polymorphisms (i.e, less response noted in "poor metabolizers")
- Decreased seizure threshold
- Contrary to initial beliefs, abuse potential and addiction noted w/ tramadol
- I don't recommend use of tramadol in peri-operative setting

https://cha.com/wp-content/uploads/2020/12/CURE_ACS.CSA_final.pdf

Which of the following statements are TRUE

Steroid medications should be used long-term for the management of pain

Tramadol, a weak opioid agonist, does not have potential for abuse

Opioid products in combination with acetaminophen are optimal for patient convenience, cost, and safety

NSAIDs are associated with cardiovascular effects including heart attacks, strokes, and heart failure

Preventative Therapies for Bone Health

Calcium

- Recommended intake: 1200 mg daily
  - Dietary intake preferable
- Supplement if needed – divided doses of 600 mg by mouth BID

Calcium carbonate	Calcium Citrate
▪Take with food - more GI side effects ▪Absorption interference with proton-pump inhibitors (PPIs)	▪Better tolerated regardless of food ▪No interaction with PPI

Camacho PM. *Endocrine Prac*. 2020;2(Suppl 1):1-46.

Vitamin D

- Sunlight is the main source and is inadequate for many Americans
- Monitor: serum 25-hydroxyvitamin D
- **Goal serum 25-hydroxyvitamin D > 30 ng/mL**

Patients at risk for osteoporosis or who have osteoporosis:

25-hydroxyvitamin D level	Interpretation
< 20 ng/mL	Deficient
20 – 29 ng/mL	Insufficient
30-50 ng/mL	Sufficient

Camacho PM. *Endocrine Prac*. 2020;2(Suppl 1):1-46.

Vitamin D Supplementation

Vitamin D formulation	Insufficiency or Deficiency	Maintenance
Ergocalciferol (D_2)	50,000 units weekly x 8-12 weeks	N/A
Cholecalciferol (D_3)	5,000 units daily x 8-12 weeks*	1,000 to 2,000 units daily

*** Preferred regimen according to 2020 AACE/ACE Guideline**

Camacho PM. *Endocrine Prac*. 2020;2(Suppl 1):1-46.

Pharmacological Treatment for Osteoporosis

- Osteoporosis frequently undertreated
  - Treatment rates decreased by ~20% from 2001 to 2011
  - Men with osteoporosis/fracture are less likely to be treated than women
- Potential causes for undertreatment:
  - Decrease in BMD testing
  - Asymptomatic condition
  - Medication safety concerns among patients and prescribers
    - Adherence to bisphosphonate therapy is poor

Miller PD. *J Clin Endocrinol Metab.* 2016;101:852-859; Reynolds K. *Osteoporos Int* 2013 Sep;24(9):2509-17

Indications for Pharmacologic Treatment of Osteoporosis

- Rule out/address secondary causes of osteoporosis
- Pharmacologic therapy is strongly recommended for:
  - patients with osteopenia or low bone mass and a history of fragility fracture of the hip or spine
  - T-score of –2.5 or lower in the spine, femoral neck, total hip, or 1/3 radius
  - T-score between –1.0 and –2.5 if the FRAX 10-year probability for major osteoporotic fracture is **≥20%** or the 10-year probability of hip fracture is **≥3%** in the U.S. or above the country-specific threshold in other countries or regions

Camacho PM. *Endocrine Prac*. 2020;2(Suppl 1):1-46.

Risk Stratification for Treatment

Presence of the following factors?

- Advanced age
- Frailty
- Glucocorticoid exposure
- Very low T-score (<-3.0)
- Increased fall risk or history of injurious falls
- Fracture history
- Very high fracture risk probability
  - FRAX scores >30% (major) or >4% (hip)

NO
=
High Risk

YES
=
Very High Risk

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High risk/no prior fractures

Alendronate, denosumab, risedronate, zoledronic acid
Alternate therapy: ibandronate, raloxifene

Reassess yearly for response to therapy and fracture risk

Increasing or stable BMD	BMD decline or fracture
• Consider a drug holiday after 5 years of oral and 3 years of IV bisphosphonate • Resume therapy if a fracture occurs, BMD ↓ beyond the LSC or patient meets initial criteria	• Assess compliance, secondary causes or factors for poor response • Switch to an injectable antiresorptive if on oral • Switch to alternative injectable if on injectable antriresorptive agent

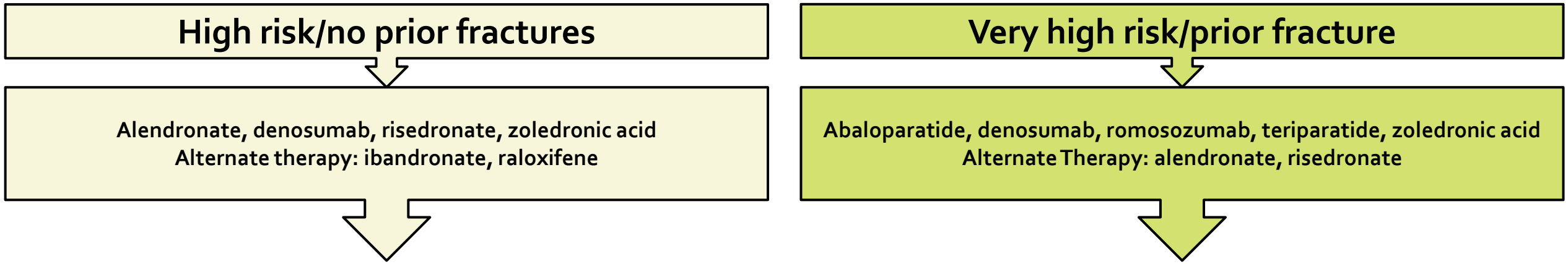
Very high risk/prior fracture

Abaloparatide, denosumab, romosozumab, teriparatide, zoledronic acid
Alternate Therapy: alendronate, risedronate

Reassess yearly for response to therapy and fracture risk

Denosumab	Romosozumab x 1 yr	Anabolic agent x 2 yr	Zoledronic acid
Continue therapy until no longer high risk then use oral agent	Sequential therapy with oral or injectable antiresorptive agent	Sequential therapy with oral or injectable anti-resorptive agent	Continue 6 years; if bone loss, use an anabolic agent or romosozumab

Adapted from: Camacho PM. *Endocrine Prac*. 2020;2(Suppl 1):1-46.


High risk/no prior fractures
Alendronate, denosumab, risedronate, zoledronic acid
Alternate therapy: ibandronate, raloxifene
Very high risk/prior fracture
Abaloparatide, denosumab, romosozumab, teriparatide, zoledronic acid
Alternate Therapy: alendronate, risedronate

Bisphosphonates

Medication	Administration
Alendronate	• PO 10 mg daily or 70 mg once weekly • Available in an effervescent tablet • Strict administration
Risedronate	• PO 5 mg daily or 35 mg once weekly or 150 mg monthly • Available in a delayed-release tablet • Strict administration
Ibandronate	• 150 mg PO once monthly • Strict administration (PO) • 3 mg IV formulation given over 15-30 sec every three months by a health care provider
Zoledronic acid	• 5 mg IV infusion given over at least 15 min once yearly at an infusion center

Bisphosphonates

- First line therapy
- **MOA:** Inhibit bone resorption (anti-resorptive). Impair osteoclast (OC) development and OC formation of ruffled border. Incorporate into the bone - Long terminal half-life (up to 10 years!)
- **Side-effects:**
  - not recommended for those with creatinine clearance below 30 to 35 mL/min – use denosumab instead
  - Musculoskeletal pain, hypocalcemia,
  - Osteonecrosis of Jaw (ONJ)
- **Contraindications:**
  - patients with esophageal disorders (eg, achalasia, esophageal stricture, esophageal varices, Barrett's esophagus)
  - inability to follow the dosing requirements (eg, stay upright for at least 30 minutes).
  - After certain types of bariatric surgery in which surgical anastomoses are present in the gastrointestinal (GI) tract (eg, Roux-en-Y gastric bypass).
- Oral bisphosphonate preferred unless contraindicated
- **Drug Holiday possible**

Bisphosphonate Drug Holiday

Fracture Risk	Oral Bisphosphonate	IV Bisphosphonate
High risk	Consider drug holiday after 5 years of stability	Consider drug holiday after 3 annual doses
Very high risk	Consider drug holiday after 6-10 years of stability	Consider drug holiday after 6 annual doses

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Denosumab

- **Antiresorptive**
- **MOA**: Fully human monoclonal antibody; binds to RANKL, blocking ability to bind to RANK on osteoclasts → increased osteoclast apoptosis
- **Dose**: 60 mg subcutaneous injection every 6 months
  - Plus calcium 1000 mg once daily and at least 400 IU vitamin D once daily
  - Should be administered by health care provider
- Indication: use in in patients that cannot use bisphosphonates when CrCl <30 ml/min
- Side-effects: ONJ, atypical femur fracture and vertebral column fracture seen after discontinuation of therapy

Prolia. Package insert. Amgen Inc.; 2011.

Osteonecrosis of Jaw

- > 90% of cases have occurred in patients receiving high-dose IV bisphosphonates for cancer
  - Prevalence estimates in patient without cancer range from 0.001%-0.10%
- Risk increases w/ longer durations of use, invasive dental procedures, dental pathologic conditions, and poor dental hygiene
- Cases have been reported with all antiresorptive agents (best described with bisphosphonates and denosumab)
- Dental exam recommended at baseline
  - Delay initiation if significant work is needed
  - No evidence that stopping therapy changes outcome but should be considered

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Raloxifene

- **Antiresorptive**
- **MOA**: Selective estrogen receptor modulator (SERM)
  - The effect of estrogen is to upregulate osteoprotegerin and down regulate RANK-L → Reduced formation of osteoclasts and increase in osteoclast apoptosis
- **Dose**: 60 mg PO once daily
- **Adverse effects**: hot flashes, leg cramps, peripheral edema, 3-fold increase risk VTE
- **Precautions/CI**: Small risk for fatal stroke; CI if history of VTE (black box warning)

Evista. Package insert. Eli Lilly and Company; 2007.

Anabolic Agents

- Teriparatide (Forteo®) and abaloparatide (Tymlos®)
- MOA: Recombinant human PTH
  - Exogenous PTH in low and intermittent doses increases **bone formation** without stimulating bone resorption as endogenous PTH does.
  - Increases bone remodeling, osteoblast number and activity
- Both agents limited to max use 2 years
- **Precautions/CI:** do not use in patients with increased risk of osteosarcoma (black box warning)
- **Monitoring:**
  - Serum calcium, urinary calcium (patients with suspected active urolithiasis or pre-existing hypercalciuria)

Forteo. Package insert. Eli Lilly and Company; 2002.; Tymlos. Package insert. Radius Health, Inc.; 2017.

Teraparatide

- **Dose:** 20 mcg SC injection daily
- Requires special storage and administration:
  - Inject daily into abdomen or thigh
  - Discard 28 days after first use
  - Store refrigerated at 36-46 °F at all times
  - Special airline travel issues
- **Adverse Effects**: hypercalcemia (2-11%),hypercalciuria, orthostasis, dizziness, leg cramps, arthralgias, nausea, pain

Abaloparatide

- **Dose:** 80 mcg SC injection daily
  - **Not FDA approved for use in men**
- Improved storage instructions
  - Inject daily into preumbilical region
  - Store refrigerated at 36-46 °F up until 1st use, then store up to 30 days at room temp (68-77 °F)
- **Adverse Effects:** hypercalcemia (3%) hypercalciuria, orthostasis, dizziness, nausea, headache, palpitations, fatigue, upper abdominal pain

Forteo. Package insert. Eli Lilly and Company; 2002.; Tymlos. Package insert. Radius Health, Inc.; 2017.

Osteoporosis Combination Therapy

- Generally, combination therapy is not recommended
  - Lack of data to support efficacy
  - Increased cost of medications
  - Increased risk of side effects
- Instead, transitional therapy is recommended

Camacho PM. *Endocrine Prac*. 2020;2(Suppl 1):1-46.

Which of the following statements are TRUE?

There are no injectable options for bisphosphonate medications

Bisphosphonates are frequently associated with the development of osteonecrosis of the jaw (ONJ)

Americans intake sufficient calcium from dietary sources

Vitamin D screening for bone health is recommended in patients over the age of 50 years

Pharmacological VTE Prophylaxis in Patients Undergoing Orthopedic Procedures

Thromboembolic Prophylaxis

- Orthopedic procedures put patients at risk for thromboembolic events.
  - Most cases of venous thromboembolism (VTE) occur after hospital discharge.
- Incidence of symptomatic VTE incidence post total hip arthroplasty (THA):
  - ~2-3% in patients post w/o pharmacologic prophylaxis.
  - ~1 – 1.2% in patients w/ pharmacologic prophylaxis
- Guidelines recommend extended pharmacologic prophylaxis (28-35 days) after major orthopedic surgery.
- Rates of VTE are decreasing after major orthopedic surgery – may see adjustments to duration of pharmacologic prophylaxis in future.

Res Pract Thromb Haemost. 2020 Mar; 4(3): 366–376.

2019 American Society of Hematology (ASH) Guidelines on Prevention of VTE in Surgical Hospitalized patients

- For patients undergoing THA or TKA, these guidelines suggests using either aspirin or anticoagulants for VTE prophylaxis.
- The studies were small and of low quality – higher quality studies needed.
  - No statistically significant differences between aspirin and various anticoagulant comparators for symptomatic proximal DVT (relative risk [RR], 1.49; 95% CI, 0.51-4.34), symptomatic PE (RR, 1.49; 95% CI, 0.37-6.09), major bleeding (RR, 2.63; 95% CI, 0.64-10.79), or death (RR, 2.32; 95% CI, 0.15-36.90).

Blood Adv. 2019;3(23):3898–944.

Risks Associated with pharmacologic VTE Prophylaxis

- All of these medications are included in the list of medications for potential to cause significant harm per the Institute of Safe Medicine Practices (ISMP)

		Antidote; Half-life
Aspirin		None; Irreversible effects on platelets for 5-7 days
• Apixaban • Dabigatran • Rivaroxaban	• Increased risk of hemorrhage (elderly, renal/hepatic dysfunction, recent GI bleed, drug interactions, concurrent use of medications w/ increased bleed risk(e.g., clopidogrel)) • Spinal hematoma esp. patients w/ neuraxial anesthesia or spinal puncture- REFER TO ANESTHESIOLOGY RECOMMENDATIONS	• Andexanet alfa (apixaban, rivaroxaban) • Idaracizumab (dabigatran) *These agents may not be readily available.* • Half-life (increased in renal impairment and elderly): apixaban ~12 hrs;dabigatran 12-17 hrs; rivaroxaban 5-9 hrs
• Enoxaparin • Dalteparin • Fondaparinux		• Protamine • Half-life: 4.5-7 hrs
Warfarin		• Vitamin K • Half-life: 20-60 hrs

Which of the following agents use for VTE prophylaxis after orthopedic procedures does NOT have an antidote

- Enoxaparin
- Warfarin
- Aspirin
- Rivaroxaban
- None of the above

Conclusion