Drug Interaction Cases with Anticoagulation Therapy

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Faculty Disclosure

Jeannette Wick has no relationships with ineligible companies

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Learning Objectives

- **Identify** anticoagulation therapy's clinically significant drug interactions
- **Discuss** drug interactions that patients may ask about, but are generally not clinically significant
- **Analyze** cases to determine if a drug interaction is clinically significant
- **Diminish** the effect of identified drug interactions in simulated cases
- **Describe** monitoring parameters for the identified drug interactions in the simulated cases

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Start with Warfarin

- Widespread use despite the fact that we have new drug entities with fewer "issues"

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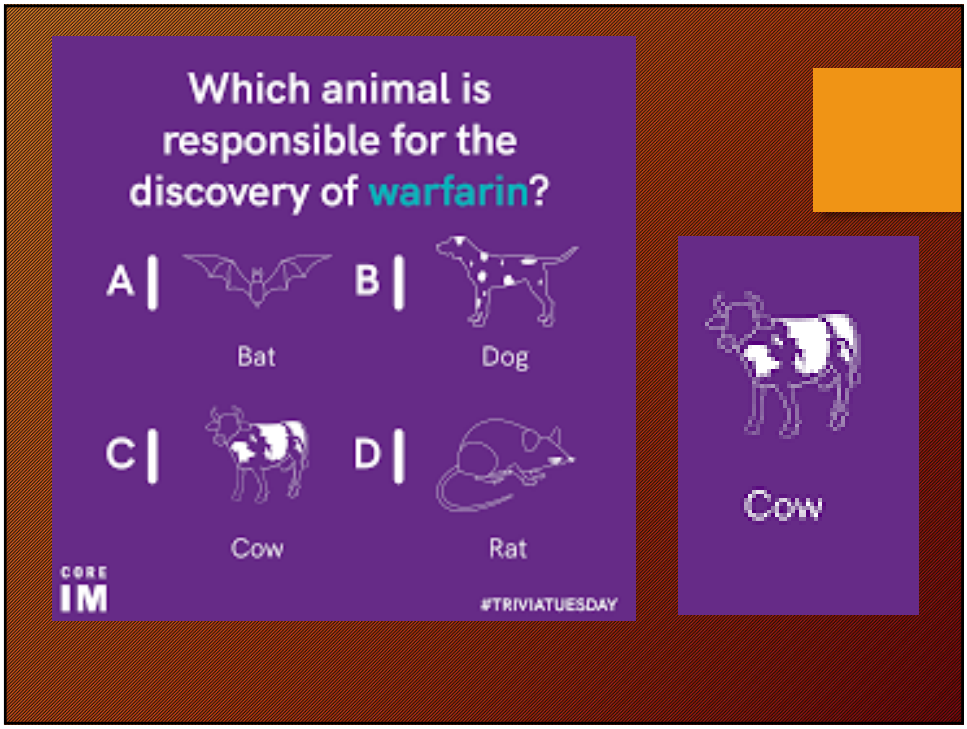

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DDI and Drug Labeling

- The FDA provides recommendations on clinical DDI studies' structure and interpretation
- It asks for strategies for managing DDI risk in all product labeling language
  - Results should be summarized concisely with actionable prevention/management instructions and strategies
- Manufacturers (and clinicians) may extrapolate the presence or absence of clinical DDI risk to other substrates of the tested CYP enzymes or drug transporters
- Labeling language variation may lead to differences in interpretations

Henderson LM, et al. *Clin Ther*. 2021;43(11):2032-2039.

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Magnitude of Warfarin Interactions

- Warfarin prescribing information identifies >300 reported drug interactions
  - Many more should be anticipated
- Clinicians need to monitor all new medication carefully until data is available
- Interactions can be severe (potentially life-threatening)
  - Warfarin has a narrow therapeutic index
- When used properly, warfarin is safe and effective

WARFARIN SODIUM. Complete prescribing information. Warfarin Sodium Tablets, USP for oral useThese highlights do not include all the information needed to use Warfarin Sodium safely and effectively. See full prescribing information for Warfarin Sodium. Warfarin Sodium (Warfarin Sodium) TABLET for ORAL use.Initial U.S . Approval: 1954

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Audience Engagement

A patient arrives at the clinic with a new prescription for bananamycin. How would you determine if bananamycin is likely to interact with warfarin?

a. Check bananamycin's prescribing information
b. Evaluate bananamycin's metabolic characteristics
c. Review case reports through Pubmed or Medline
d. Request information from warfarin's manufacturer
e. All of the above

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Warfarin (Coumadin)

- Synthesized at University of Wisconsin
- Derived from **W**isconsin **A**lumni **R**esearch **F**oundation and **ARIN** from "heparin"
- Reversibly binds and inhibits enzymes which convert inactive vitamin K to active vitamin K
- Decreases production of vitamin K-dependent clotting factors II, VII, IX, and X
- Decreases production of natural anticoagulants protein C and S

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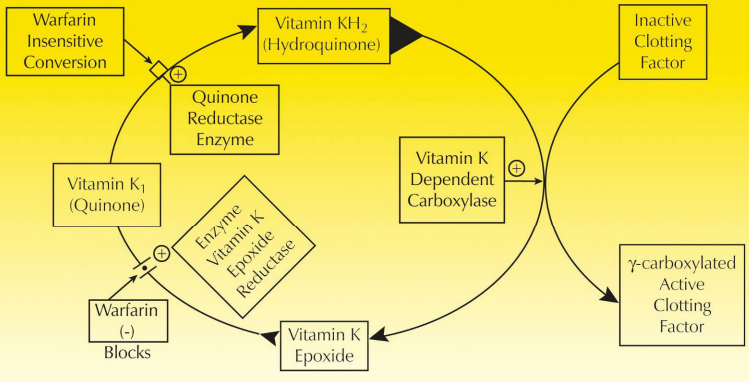
Vitamin K Mechanism of Action



Vitamin K cycle. Warfarin blocks the conversion of vitamin K epoxide to vitamin C.

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Warfarin Pharmacokinetics

- Racemic mixture of *R*- and *S*-warfarin
  - *S*-warfarin 5x more potent, eliminated more rapidly
- Well absorbed (100% bioavailability)
- Highly protein bound to albumin
- Metabolized by
  - *S*-warfarin-2C9
  - *R*-warfarin-1A2, 2C19, 3A4
- Average half-life 36 to 42 hours

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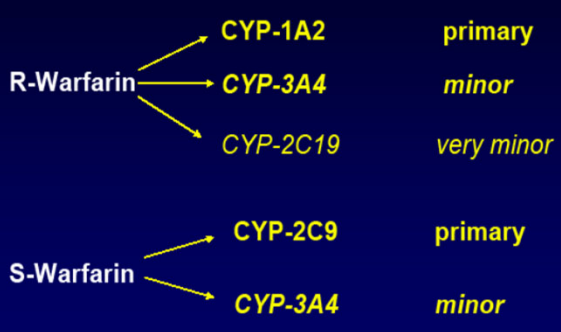
WARFARIN OXIDATIVE METABOLISM



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Mechanisms for Drug Interactions

- **Pharmacokinetic Mechanisms**
  - Altered warfarin plasma concentrations
- **Enzyme inductions or inhibition**
  - Induction: metabolic activity is enhanced
  - Inhibition: metabolic activity is diminished
- **Protein binding**
  - Protein bound drugs are inactive
  - If a second drug displaces warfarin from its binding sites, anticoagulation may be enhanced

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Mechanisms for Drug Interactions

- **Pharmacodynamic Mechanisms**
  - Do not alter warfarin plasma concentration
- **Synergism**: Two drugs when used in combination produce a greater effect than each's individual effect when used alone
- **Antagonism**: One drug's effect is inhibited or reversed by the activity of another drug (i.e., vitamin K and warfarin)

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Pharmacokinetic mechanisms of drug interactions

- Reduced absorption/bioavailability: cholestryramine
- Alterations in protein binding: phenytoin
- Alterations in metabolism
  - Enzyme induction: rifampin, barbiturates, carbamazepine
  - Enzyme inhibition: fluconazole, cimetidine, erythromycin, ciprofloxacin

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Pharmacokinetic mechanisms of drug interactions (cont.)

- Stereoselective alterations in metabolism (*R* or *S* enantiomer)
  - *S* is 5 times more potent
  - Metronidazole (*S*), cotrimoxazole (*S*), omeprazole (*R*), cimetidine (*R*),
  - Amiodarone (*R* & *S*)
- Alterations in plasma clearance or excretion
  - Thyroid hormones (i.e., levothyroxine)

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Pharmacodynamic mechanisms of drug interactions

- **Drug synergism**: increased risk of bleeding
  - Antiplatelet drugs (i.e., clopidogrel)
  - NSAIDS including COX-2 Inhibitors
- **Drug antagonism**: block absorption of warfarin, supplementation of vitamin K
  - Enteral feeds, protein shakes, multivitamins
  - Dietary supplements

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Enzyme Inhibitors P450

CYP1A2	CYP3A4	CYP2C9
Cimetidine	Clarithromycin	Amiodarone
Ciprofloxacin	Fluconazole	Metronidazole
Erythromycin	Erythromycin	SMZ-TMP DS
Fluvoxamine	Itraconazole	Fluconazole
Zileuton	Fluoxetine	Disulfiram

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Enzyme Inducers P450

CYP1A2	CYP3A4	CYP2C9
Barbiturates	Barbiturates	Barbiturates
Carbamazepine	Carbamazepine	Carbamazepine
Cigarette smoke	Griseofulvin	Phyenytoin
Phenytoin	Primidone	Rifampin
Primidone		
Rifampin		

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Drug interactions with OTC's

- Examples:
  - NSAIDS (ibuprofen, naproxen, aspirin)
  - Acetaminophen
  - Omeprazole
  - Cimetadine
  - Bismuth subsalicylate (salicylates)
  - Dietary Supplements (Ensure, Boost)

Bingham AL, et al. *Nutr Clin Pract*. 2013;28(6):766-769. doi:10.1177/0884533613507606; WARFARIN SODIUM. Complete prescribing information. Warfarin Sodium Tablets, USP for oral useThese highlights do not include all the information needed to use Warfarin Sodium safely and effectively. See full prescribing information for Warfarin Sodium. Warfarin Sodium (Warfarin Sodium) TABLET for ORAL use.Initial

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Warfarin interactions with OTCs

- Caution when using NSAIDs with warfarin
  - NSAIDs inhibit platelet aggregation
    - Aspirin – Irreversible inhibition (life of the platelet)
    - Other NSAIDS (ASA, naproxen) – Reversible inhibition
  - NSAIDs can cause GI ulcers
    - Results in bleeding
  - Specific drug-drug interactions may alter PT/INR

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Warfarin-APAP Interactions

- Suggested in case reports
- Verified in clinical trials
- Mechanism: Unknown – possible enzyme inhibition with increased INR
- Comparative to Warfarin-ASA/NSAIDs
  - Inhibit platelet function
  - Injury to GI mucosa

Zhang Q, et al. *Eur J Clin Pharmacol*. 2011;67(3):309-314. doi:10.1007/s00228-010-0975-2; Mahé I, et al. *Haematologica*. 2006;91(12):1621-1627.

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Drug Interactions with Dietary Supplements

- Herbal/Botanical Products
  - Herbal products may affect the coagulation system
  - May enhance or diminish warfarin activity
    - Anticoagulation
    - Platelet actions
  - Few studies have evaluated warfarin-herbal interactions
  - The FDA does not oversee herbal or supplement manufacturing

Hazra S, et al. Safety Issues of Herb-Warfarin Interactions *Curr Drug Metab*. 2024;25(1):13-27.

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Scientific Name	Common Name	Mechanism	Potential Outcome
Aesculus hippocastanum	Horse chestnut	CYP inhibition	↑ bleeding risk
Aloe vera	Aloe	↓ warfarin absorption and/or↑ renal clearance	↓ warfarin effect
Cannabis sativa	**Marijuana**	CYP inhibition	↑ bleeding risk
Glycyrrhiza glabra	Licorice	CYP inhibition	↑ bleeding risk
Harpagophytum procumbens	Devil's claw	CYP inhibition	↑ bleeding risk
Hypericum perforatum	St John's wort	CYP inhibition	↑ bleeding risk
Lycium barbarum	Gogi berry	CYP inhibition	↑ bleeding risk
Plantago ovata Forssk.	**Psyllium**	↓ warfarin absorption and/or↑ renal clearance	↓ warfarin effect
Pueraria lobata	Kudzu	CYP inhibition	↑ bleeding risk
Silybum marianum	Milk thistle	CYP inhibition	↑ bleeding risk

Hazra S, et al. Safety Issues of Herb-Warfarin Interactions *Curr Drug Metab*. 2024;25(1):13-27.

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Factors Affecting Sensitivity to Warfarin

Increase INR

- Hyperthyroidism
- Low vitamin K diet
- Malnutrition
- Age > 75
- Diarrhea/vomiting
- Acute Infection
- Acute alcohol use
- Stress

Decrease INR

- Hypothyroidism
- High Vitamin K diet
- Tobacco (cigarettes)
- Chronic alcohol use

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- Hypothyroidism
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- Tobacco (cigarettes)
- Chronic alcohol use

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Drug Interactions: Patient Considerations

- Consider how the drug works, metabolism, and protein binding
- Intensify monitoring when
  - Starting concomitant drug therapy
  - Discontinuing concomitant drug therapy
- Drug history
  - Prescription meds
  - PRN meds
  - OTC and supplements/herbals

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Drug Interactions: Patient Considerations (cont.)

Absence of evidence is not evidence of absence

There is no such thing as a "typical response" to a drug interaction

Expect variability in

Patient susceptibility	Response magnitude	Time of onset	Duration of effect

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Monitoring Pearls

1. Do not assume an interaction won't occur just because it has not been reported
2. Consider metabolic characteristics of all new drugs and their potential to interact with warfarin
3. Evaluate drug therapy at every visit regardless of INR

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DOACs: Do DDI occur?

- Just because we can't SEE interaction (as in checking INR with warfarin) doesn't mean it's not real
- The number of patients who are on inducing agents with DOACs is crazy
- Many providers say, "Well they haven't had a stroke"-- seriously!
- Little data exists describing dose adjustments in the setting of DDIs for DOACs

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DOAC Drug Interactions

- Most patients taking DOACs are on >5 other medications
- With all potential DOAC DDI, warfarin may have a similar interaction
  - The ability to use INR testing to ensure safe warfarin levels makes it a preferred option for many patients

American College of Cardiology. Drug-Drug Interactions With Direct Oral Anticoagulants. March 19, 2020. https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2020/03/19/14/14/select-drug-drug-interactions-with-direct

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DOAC Drug Interactions

- The most common DOAC drug-drug interactions involve medications mediated by CYP450 and/or the transporter permeability glycoprotein (P-gp)
  - Inhibition → serum concentrations of medication generally increase
  - Induction → serum concentrations generally decline
- CYP3A4 is an important metabolizer for apixaban (~25%) and rivaroxaban (50%) but not the other DOACs
- P-gp is an important mediator for apixaban, ~~betrixaban~~ (removed from market), dabigatran, and rivaroxaban

American College of Cardiology. Drug-Drug Interactions With Direct Oral Anticoagulants. March 19, 2020. https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2020/03/19/14/14/select-drug-drug-interactions-with-direct

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Remember This….

- Drug interaction guidance for dabigatran and edoxaban is different than that for rivaroxaban and apixaban
- The Anticoagulation Forum has an excellent handout on DOAC drug interations
  - It's posted on the web page
  - You can also find it here:
  - https://acforum-excellence.org/Resource-Center/resource_files/-2020-10-08-202155.pdf

Anticoagulation Forum Rapid Resource. -2020-10-08-202155.pdf

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Pharmacokinetic Interaction (Diltiazem, Strong CYP3A4 Inhibitor)

- Retrospective, cohort study examined claims data (N = 204,155 Medicare beneficiaries with AF, mean age 76.9)
  - Started on apixaban or rivaroxaban
  - Also began treatment with diltiazem (53,275) or metoprolol (150,880) for rate control
- Diltiazem n increased the risk for the composite of bleeding-related hospitalization and death with recent bleed [HR; 1.21, 1.13-1.29]
- Initial diltiazem doses **exceeding 120 mg/day** increased the risk for major ischemic or hemorrhagic events [HR; 1.13, 1.04-1.24]

Ray WA, et al *JAMA*. 2024;331(18):1565-1575.

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Pharmacodynamic Interaction (Aspirin & P2Y12 inhibitors)

While aspirin and other antiplatelets do not affect DOAC plasma concentration, concomitant administration increases bleed risk

LOPES (2019)

- Open-label, RCT in patients with AF undergoing coronary revascularization
- Receivied apixaban 5 mg BID or VKA or aspirin or placebo in a 2 x 2 factorial design, P2Y12 inhibitors (P2Y12i) added at prescriber discretion
- P2Y12i + apixaban resulted in lower bleeding than P2Y12i + VKA (10.5% vs. 14.7%) with lower death and rehospitalization rates
- In both arms, adding aspirin increased bleeding without difference in efficacy

PIONEER AF-PCI (2016)

- Open-label, RCT in patients with AF undergoing PCI comparing (1) rivaroxaban 15mg + P2Y12i vs. (2) rivaroxaban 2.5 BID + DAPT and (3) warfarin + DAPT
- Clinically significant bleeding occurred in 16.8% vs. 18.0% vs. 26.7, respectively
- Major bleeding was similar between the three groups

Lopes RD et al. N Engl J Med. 2019;380(16):1509-1524.
Gibson CM, et al. Am Heart J. 2015;169(4):472-8.e5

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Patient Cases

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Case Presentation #1

- Alice is an 86 YO female who has HTN, hypercholesterolemia, T2DM, gout
- Current Rx Meds:
  - Allopurinol 300 mg 1 tab once daily
  - Furosemide 40 mg 1 tab once daily
  - Metoprolol Suc 150 mg 1 tab twice daily
  - Potassium CL 20 mEq once daily
  - Hydralazine 25 mg 1 tab q 8h
  - Novolin 70/30 Insulin 55 units AM & 40 units PM daily
  - Rosuvastatin 5 mg 1 tab every other day
  - Clopidogrel 75 mg 1 tab once daily

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Case #1 (cont.)

- OTC Meds
  Acetaminophen PRN
  Multivitamins
  Green Tea
- Anticoagulation
  Warfarin 5 mg one tablet daily x 1 yr
- The prescriber tells the Anticoagulation Clinic that amiodarone 400 mg bid is being added

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Case #1

How many potential drug interactions can you identify in AT's med list?

a. Two
b. Three
c. Four or more

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Case #1

When should we schedule Alice's next PT/INR visit?

a. Recheck INR in 1 month
b. Recheck INR in 5 to 14 days
c. Recheck INR tomorrow

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Case #2

- Matt, a 67 YO male experiences a recent idiopathic DVT
- PMH: HTN, T2DM, hypercholesterolemia, elevated triglycerides
- Anticoagulation:
  Warfarin 10 mg Tu, 5 mg W, Sa, 7.5 mg X 4 d
- OTC Meds:
  Omega-3 Fatty 1 tab daily
  Multivitamin with calcium 1 tab daily
  Acetaminophen PRN

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Case #2 (cont.)

- Current Rx Meds:
  - Metformin 500 mg 1 tab bid
  - Metoprolol 50 mg 1 tab bid
  - Atorvastatin 80 mg 1 tab daily
  - Lisinopril 40 mg 1 tab bid
  - Fenofibrate 145 mg 1 tab daily
  - Clonidine 0.1 mg 1 tab bid
  - Amlodipine 10 mg 1 tab daily
  - Isosorbide Mon 60 mg 1 tab daily
  - Griseofulvin 500 mg 1 tab daily x 6 weeks

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Case #2 (cont.)

- Primary care informs the Anticoagulation Clinic that his grisofulvin is being discontinued immediately.

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Case #2

How many potential drug interactions can you identify in Matt's med list?

a. Two
b. Three
c. Four or more

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Case #2

When should we schedule Matt's next PT/INR visit?

a. Recheck INR in 5 days
b. Recheck INR in 2 weeks
c. Recheck INR in 1 month

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Case #3

- Jerrilyn is a 57 YO female with AVR
- PMH: HTN, hypercholesterolemia, osteoarthritis
- Anticoagulation:
  Warfarin 7.5 mg Monday and Friday, 5 mg x 5 days
- OTC Meds:
  MVT tab daily
  Calcium 600 mg 1 tab bid
  APAP 1 gm tid

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Case #3 (cont.)

- Current Rx Meds:
  - HCTZ 25 mg 1 tab daily
  - Lisinopril 40 mg 1 tab bid
  - Metropolol 50 mg 1 tab bid
  - Simvastatin 20 mg 1 tab daily

- Jerrilynn decides to decides to self-treat what she suspects is a vaginal yeast infection with miconazole nitrate vaginal cream x 7 days

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Case #3

Should you be concerned about a vaginally administered medication like miconazole with warfarin?

a. Yes
b. No
c. Undecided

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Case #3

When should we schedule Jerrilynn's next PT/INR visit?

a. Recheck INR in 3-4 days
b. Recheck INR in 2 weeks
c. Recheck INR in 1 month

Kovac M, et al. *J Clin Pharm Ther*. 2012;37(1):45-48. doi:10.1111/j.1365-2710.2011.01246.x; Thirion DJ, Zanetti LA. *Pharmacotherapy*. 2000;20(1):98-99. doi:10.1592/phco.20.1.98.34665

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Case #4

- **Josiah, who is 45 YO, presents after having been diagnosed with AFib. His creatinine clearance is 75 mL/min. The prescriber wants you to start a DOAC.**

- Current Rx Meds:
  - HCTZ 25 mg 1 tab daily
  - Verapamil IR 80 mg TID
  - Lisinopril 40 mg bid
  - Metropolol 50 mg bid
  - Simvastatin 20 mg daily

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Case #4

What DOAC would be preferred in this patient?

a. Apixaban
b. Dabigatran
c. Rivaroxiban

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Questions?

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