NEW DRUG UPDATE
A FAST AND FURIOUS FDA

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Objectives

Pharmacist	Technician
■ Recognize the indications of new medications with significant impact to long term care and older adult patients. ■ Recognize new options for new anticoagulation therapy and the use of medication to reverse life threatening bleeding due to rivaroxaban and apixaban. ■ Recognize key practice points on a new medication used to mitigate opioid withdrawal symptoms ■ Recognize the new FDA labeling standards for biosimilar drugs. ■ Recognize key practice points of the new treatment for Tardive Dyskinesia and how to measure efficacy.	■ Identify the reasons for use of new medications with significance for older adult patients. ■ Recognize trends in dosing medications to treat HIV Infections. ■ Recognize the new FDA labeling standards for biosimilar drugs ■ Recognize the potential use of medicinal cannabidiol in treating devastating forms of epilepsy

Pharmaceutical Industry Headlines

- **The CMS spent $174 billion, or 23% of its total budget, on prescription drugs in 2016**
- **Common Antidepressants Are Less Effective at High Altitudes, Rodent Study Suggests**
- **Depression, Money Woes Higher in Heart Patients With Job Loss**
- **Kids With Asthma Need a Flu Shot**
- **HHS IG: Part D Spending Rose 77 percent In Five Years Despite 17 Percent Drop In Prescriptions**
- **Drug makers don't want to cut prices**
- **Cataract Surgery Tied to fewer Care Crashes for Seniors**
- **Dark Chocolate Can Improve Contrast Sensitivity and Visual Acuity; *JAMA Ophthalmology, April 26, 2018***
- ***No Kidding!***

New Drugs Approved in 2018
Non-Cancer Therapies

Avatrombopab (Doptelet®, AkaRx, Inc.)	Thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a medical or dental procedure
Betrixaban, (Bevyxxa®, Portola)	Anticoagulant
Bictegravir/Emtricitabine/Tenofovir alafenamide, (Bictarvy®, Gilead)	HIV Infection
Burosemab (Crysvita®, Ultragenyx)	X-linked hypophosphatemia
Cannabidiol (Epidolex® GW Pharmaceuticals)	Severe Seizures
Coagulation Factor Xa recombinant, (Andexxa®, Portola)	Reversal of anticoagulation for patients treated with rivaroxaban and apixaban ONLY
Erenumab (Aimovig®, Amgen)	Preventative treatment of Migraine Headaches

New Drugs Approved in 2018
Non-cancer Therapies

Estradiol vaginal inserts (Imvexxy®, Therapeutics MD)	Dyspareunia
Fosnetupitant and Palonosetron Infusion (Akynzeo, Helsinn)	Chemotherapy-induced nausea and vomiting
Fostamatinib (Tavalisse®, Rigel Pharm.)	Chronic immune thrombocytopenia
Lidocaine 1.8% topical patch (ZTLido®, Scilex)	Post herpetic neuralgia
Lofexidine HCl (Lofexidine ®, Britannica Pharmaceuticals)	Mitigation of opioid withdrawal
Lokelma (Na Zirconium cyclosilicate)	Hyperkalemia
Pegavaliase-pqpz (Palynziq-pqpz, Biomarin)	Phenylketonuria
Plazomicin (Zemdri,	Complicated Urinary Tract Infection
Plecanatide (Trulance®, Synergy)	Chronic Idiopathic Constipation

New Drugs Approved in 2018
Non-cancer Therapies

Ranibizumab injection (Lucentis, Genentech)	Diabetic macular edema, Diabetic Retinopathy
Safinamide mesylate (Xadago®, Newron)	Parkinson's Disease
Tolvaptan (Jynarque®, Otsuka)	Slows Kidney Function Decline
Tildrakizumab-asmn (Ilumya®, Sun Pharm. Inc.)	Moderate to severe Plaque Psoriasis
Velbenazine tosylate (Ingrezza ®, Neurcrine)	Treatment of Tardive Dyskinesia
Zoster Vaccine recombinant, Adjuvanted (Shingrix®, GSK)	Herpes Zoster prevention

New Cancer Treatments

Abiraterone Acetate (Yonsa, Sun Pharma)	Metastatic castration-resistant prostate cancer • Use with methylprednisolone
Apalutamide (Erleada®, Janssen)	Non-metastatic castration-resistant prostate cancer
Lutetium Lu177 dotatate (Lutathera, Advanced Accelerator Applications)	Gastroenteropancreatic neuro-endocrine tumors
Osimertinib (Tagrisso, Astra Zeneca)	Metastatic non-small cell lung cancer
Rucaparib (Rubraca, Clovis Oncology)	Maintenance treatment of recurrent ovarian cancer

New Biosimilars

Adalimumab-atto (Amjevita, Amgen)	Humira®
Epoetin-alpha-epbx (Retacrit, Hospira)	Procrit®
Infliximab-dybb (Inflectra, Pfizer) Infliximab-abda (Renflexis, Merck) Infliximab-qbtx (Ixifi, Pfizer)	Remicade®
Pegfilgrastim-jmdb (Fulphila, Mylan/Biocon)	Neulasta®

https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm411418.htm

Regulation

- Under section 351(i)(2), "biosimilar" or "biosimilarity" means that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components, and there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity and potency of the product
- Under 351(k)(4), an "interchangeable" biological product is a product that has been shown to be biosimilar to the reference product, and can be expected to produce the same clinical result as the reference product in any given patient. In addition, to be determined to be an interchangeable biological product, it must be shown that for a biological product that is administered more than once to an individual the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch

https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilarsucm411418.htm

Biosimilar Nomenclature

- In January 2017, the FDA released final guidance on naming of biological products. Under this guidance, each originator biologic, related biologic and biosimilar is assigned a nonproprietary name consisting of a core name and a hyphenated suffix made up of four lowercase letters.
- As we know, biosimilars are not an exact copy of the reference biologic, so it is important to distinguish among them. The proper use of the suffix to capture a biologic medicine's full name facilitates accuracy in medical records and allows adverse event data to be immediately associated with the exact drug. It will also help improve pharmacovigilance and clearly differentiate biological products for safe use.

Market Withdrawals

MEDICATION	REASON
Daclizumba (Zinbryta ®, AbbVie)	Relapsing Multiple Sclerosis* Europan Medicines Agency : Urgent review due to encephalitis and/or meningoencephalitis

*Blank, C. MS drug removal leaves patient with fewer options. Drug Topics. March 9, 2018

Betrixaban)Capsules 40 mg and 80 mg (Byvexxa®, Portola)

Indication: Prophylaxis of VTE in hospitalized patients

Once daily dosing 35-42 days

No available reversal agent

Rapid onset, Initial 160 mg single dose, then 80 mg daily

90% of patients in trials ≥ 65 years

Studies compared enoxaparin and placebo: 25% RRR of VTE

Low renal excretion, dose adjustment with SEVERE renal impairment

Major bleeding occurred < 1%

Drug-drug interactions P-gp inhibitors, anticoagulants, antiplatelet, thrombolytics

Bevyxxa Full Prescribing Information, Portola. June 2017

Avatrombopag tablets (Doptelet, AkaRx, Inc.)

- Granted priority review by the FDA
- Used to treat thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a medical or dental procedure
  - *Patients at risk of bleeding*
  - *Safely increases platelet count*
    - May decrease the need for platelet transfusions
- Thrombopoetin receptor agonist; stimulates megakaryocytes in bone marrow
- NOT to be used to normalize platelet counts
  - *Two trials ADAPT-1 and ADAPT-2 – double blinded placebo*
    - 435 patients with chronic liver disease and thrombocytopenia
    - Increased platelet counts and lower platelet transfusions or recue therapy
    - Side effects: fever, abdominal pain, nausea, headache, fatigue, edema of hands and feet
  - *Patients with chronic liver disease and persons with certain blood clotting conditions may have an increased risk of blood clots.*

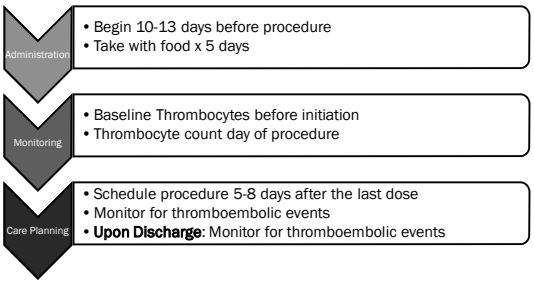
FDA News Release. FDA approves new drug for patients with chronic liver disease who have low blood platelets and are undergoing a medical procedure. May 21, 2018
Doptelet Full Prescribing Information. AkaRx, Inc. Durham, NC May, 2018

Avatrombopag

- Oral Route; Give with food
- Obtain a platelet count prior to administration and on the days of the procedure.
- 5-day course of treatment, beginning 10-13 days prior to procedure
- Peak effect in 10-13 days
- Patients should undergo the procedure within 5 – 8 days after the last dose
- No dose adjustments for age, renal or hepatic function
- Monitor platelet count and for thromboembolic events.
- No antidote for overdose, hemodialysis will not enhance elimination

Platelet Count ($x10^9$/L	Once daily Dose	Duration
< 40	60 mg (3 tablets)	5 days
40 to <50	40 mg (2 tablets)	5 days

Library of Recommendations: Avatrombopag



Valbenazine tosylate (Ingrezza®, Neurocrine)

- Vesicular monoamine transporter inhibitor – inhibits dopamine
  - Classification: Neurologic agent
- Indicated for the treatment of adults with **Tardive Dyskinesia**
- Three randomized double blind placebo-controlled trials
  - 445 patients had schizophrenia, schizoaffective disorder, or a mood disorder
  - AIMS was the primary measure of efficacy (videos)
  - 6 weeks in duration; age range 26-84 years, 54% males
  - QT prolongation may occur during coadministration of a strong CYP2D6 or CYP3A4 inhibitor, or in those who are poor metabolizers of CYP2D6
- Contraindicated with Tetrabenazine and Deutetrabenazine

Dosage Recommendations for Concomitant Strong CYP3a4 Inducers and Strong CYP3A4 or CYP2D6 Inhibitors

Strong CYP3A4 Inducer	Valbenazine NOT RECOMMENDED
Strong CYP3A4 Inhibitors	Reduce the dose of Valbenazine to 40 mg
Strong CYP2D6 Inhibitors	Reduce the dose based on tolerability

Clinical Trials

- The assessment of efficacy of Velbenazine tosylate was primary evaluated in a single, randomized (1:1:1 to Velbenazine tosylate 40 mg, Velbenazine tosylate 80 mg or placebo), parallel-group trial of patients with moderate to severe tardive dyskinesia as determined by clinical observation. Patients had underlying schizophrenia, schizoaffective disorder, or a mood disorder, and 84% of them were receiving antipsychotics. The change from baseline for two fixed doses of Velbenazine tosylate (40 mg or 80 mg) was compared to placebo.
- The primary efficacy endpoint was the mean change from baseline in the AIMS dyskinesia total score at the end of Week 6. The AIMS is a 12-item scale; items 1 to 7 assess the severity of involuntary movements across body regions and these items were used in this trial. The AIMS dyskinesia total score (sum of items 1 to 7) could range from 0 to 28.
- The safety of Velbenazine tosylate was evaluated in three randomized, placebo controlled, parallel-group trials that include the trial described above
- All subjects previous antipsychotics 70% taking atypical; 14% taking typicals; 16% taking no antipsychotic

Items 1-7 on the AIMS Test©

Facial and Oral	• Muscles of facial expression • Lips and perioral Area • Jaw • Tongue
Extremity Movements	• Upper: Arms. Wrist, hands, Fingers • Lower: legs, knees, ankles, toes
Trunk Movements	• Neck, shoulders, hips

Abnormal Involuntary Movement Scale (AIMS); Public Health Service, Alcohol, Drug Abuse and Mental Health Administration, national Institute of Mental Health, 9/2000

Endpoint Efficacy
A negative change indicates improvement

	Treatment Group	Change from Baseline	95% Confidence Interval
Aims Total Score	Valbenazine 40 mg	-1.9	-1.8
	Valbenazine 80 mg	-3.2	-3.1
	Placebo	-.01	

Velbenazine tosylate (Ingrezza®, Neurocrine)

- Titration: 40 mg once daily x 7 days, increase to 80 mg once daily
- 80 mg dose was statistically significantly different from placebo
- Take with or without food
- In the presence of moderate to severe hepatic insufficiency, 40 mg once daily
- No dose modification for age or kidney disease

*Velbenazine tosylate Full Prescribing Information, Neurocrine Biosciences, Inc. April, 2018

Library of Recommendations: Valbenazine

Administration
- 40 mg once a day x 1 week, titrate to 80 mg once a day
- Take with or without food

Monitoring
- Q-T Prolongation
- Somnolence
- AIMS test

Care Planning
- May impair complex motor and mental skills
- Patients to inform their physician if: feel faint, lose consciousness, have heart palpitations
- **Upon Discharge**: Inform prescribers that they are taking Valbenazine before any new drug is added to the regimen; with discontinuation of the drug, movement scores return to baseline.

Coagulation factor Xa (recombinant), inactivated-zhzo (Andexxa®, Portola)

- Granted priority review by the FDA
- Reversal of anticoagulation for patients treated with rivaroxaban and apixaban ONLY
  - *Binds and sequesters rivaroxaban and apixaban*
- Lyophilized Powder for Injection single use vial 100 mg; infusion only
  - *Must be refrigerated. Do not freeze*

Coagulation factor Xa (recombinant), inactivated-zhzo

Dosing Regimens		
Dose	**Initial IV Bolus**	**Follow-on IV Infusion**
Low Dose	400 mg at a target rate of 30 mg/min	4 mg/min up to 120 min
High Dose	800 mg at a target rate of 30 mg/min	8 mg/min up to 120 min

Dose Based on Rivaroxaban or Apixaban Dose			
FXa Inhibitor	**FXa Inhibitor Last Dose**	**< 8 hours or unknown**	**≥ 8 hours**
Rivaroxaban	≤ 10 mg	Low Dose	Low Dose
	> 10 mg/Unknown	High Dose	
Apixaban	≤ 5 mg	Low Dose	
	> 5 mg/Unknown	High Dose	

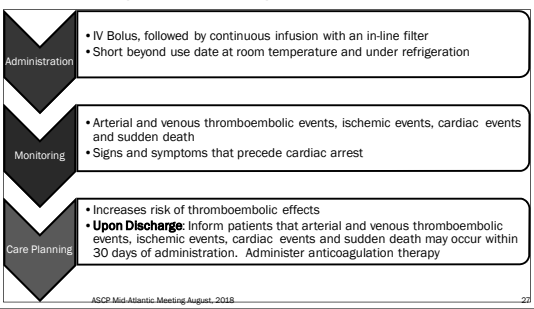
Coagulation factor Xa (recombinant), inactivated-zhzo

- Stability:
  - Vials 8 hrs. room temperature; 24 hours refrigerated
  - In IV bags 8 hrs. room temperature; 16 hours refrigerated
- Reconstitution
  - 3-5 minutes for dissolution
  - Do not shake
  - 250 ml or less IV volume
- Administration
  - Must use a 0.2 or .22 micron in-line filter
  - Start Bolus at 30 mg/min
  - Within 2 minutes following bolus dose, Infuse continuously for up to 125 min
- ADRs
  - UTI, Pneumonia, injection site reaction

Coagulation factor Xa (recombinant), inactivated-zhzo

- Studies
  - 185 subjects
  - 161 were 65 years or older
  - 113 were 75 years or older
  - No overall difference in safety or efficacy

Library of Recommendations: Coagulation factor Xa (recombinant), inactivated-zhzo



FDA Approves Cannabidiol Oral solution (CBD Oil) for Severe Seizures

- Indication: Two devastating forms of Epilepsy
  - Lennox-Gastaut Syndrome
  - Dravet Syndrome
  - Emerge first years of life
  - 20% of patients die by age 20
- Many families had to move where medical or recreational cannabis is legal
- This form of cannabis that does not make patients high
- DEA may have to reschedule CBD Oil
  - *Dronabinol*
  - *Nabilone*

FDA approved Epidiolex® (cannabidiol) [CBD] oral solution 100 mg/ml

- FDA approved Epidiolex (cannabidiol) [CBD] oral solution for the treatment of seizures associated with two rare and severe forms of epilepsy, Lennox-Gastaut syndrome and Dravet syndrome, in patients two years of age and older. This is the first FDA-approved drug that contains a purified drug substance derived from marijuana. It is also the first FDA approval of a drug for the treatment of patients with Dravet syndrome.

  CBD is a chemical component of the Cannabis sativa plant, more commonly known as marijuana. However, CBD does not cause intoxication or euphoria (the "high") that comes from tetrahydrocannabinol (THC).

Comparing Lennox Gastaut and Dravet Syndromes

Dravet Syndrome	Lennox-Gastaut Syndrome
■ Dravet syndrome is a rare genetic condition that appears during the first year of life with frequent fever-related **seizures** (febrile seizures). Later, other types of seizures typically arise, including myoclonic seizures (involuntary muscle spasms). Additionally, status epilepticus, a potentially life-threatening state of continuous seizure activity requiring emergency medical care, may occur. Children with Dravet syndrome typically experience poor development of language and motor skills, hyperactivity and difficulty relating to others.	■ **Lennox-Gastaut** syndrome begins in childhood. It is characterized by multiple types of seizures. People with Lennox-Gastaut syndrome begin having frequent seizures in early childhood, usually between ages 3 and 5. More than three-quarters of affected individuals have tonic seizures, which cause the muscles to contract uncontrollably. Almost all children with Lennox-Gastaut syndrome develop learning problems and intellectual disability. Many also have delayed development of motor skills such as sitting and crawling. Most people with Lennox-Gastaut syndrome require help with usual activities of daily living.

Cannabidiol

- Under the Controlled Substances Act (CSA), CBD is currently a Schedule I substance because it is a chemical component of the cannabis plant. In support of this application, the company conducted nonclinical and clinical studies to assess the abuse potential of CBD.
- The FDA prepares and transmits, through the U.S. Department of Health and Human Services, a medical and scientific analysis of substances subject to scheduling, like CBD, and provides recommendations to the Drug Enforcement Administration (DEA) regarding controls under the CSA. DEA is required to make a scheduling determination.
- The FDA granted Priority Review designation for this application. Fast-Track designation was granted for Dravet syndrome. Orphan Drug designation was granted for both the Dravet syndrome and Lennox-Gastaut syndrome indications

Cannabidiol

- Oral administration
- Titration: 2.5 mg/kg BID x 7 days, then increase to a maintenance dose of 5 mg/kg BID
  - *Maximum recommended dose 10 mg/kg BID*
  - *For patients in need of rapid titration, increase the dose no more than every other day*
- Adverse reaction increase with an increase in dose
- Cannabidiol should be decreased gradually. Abrupt discontinuation may result in increased seizure frequency and status epilepticus.
- Dose reductions are required for hepatic impairment
- Trials did not include patients older than 55 years
  - *Use in the elderly should be cautious, starting at the low range of dosage*

Cannabidiol

- Protein bound
- Half life of 56-61 hours after BID dosing for 7 days
- Metabolism in liver and gut
  - *CYP2C19 and CYP3A4*

Clinical Studies

Lennox-Gastaut Syndrome

- Endpoint of 2 studies: Drop in seizure frequency
- Study 1: N=171 Cannabidiol 20mg/kg with placebo
- Study 2: N=255 Cannabidiol 10mg/kg BID and 20mg/kg BID to placebo
- 4-week baseline, 2-2week titration, 12 week maintenance

Dravet Syndrome

- Study 3 N=120 patients, 2 to 108 years old
- Compared Cannabidiol 20mg/kg to placebo
- 4-week baseline, 2-2week titration, 12 week maintenance

Study Results

Lennox-Gastaut

Study 1	Placebo		20mg/kg/day
	N=85		N=86
% change	-22		-44
			P=0.01
Study 2	Placebo	10mg/kg BID	20mg/kg BID
% Change	-17	-37	-42
		P=<0.01	P=<0.01

Dravet Syndrome

Study 3	Placebo	20mg/kg/day
	N=59	N=61
% change	-13	-39
		P=0.01

Cannabidiol Adverse Reactions (ADRs)

- Somnolence; Sedation
- Suicidal behavior and ideation
- Decrease in appetite
- Hypersensitivity: to cannabis and is strawberry flavored
- Hepatocellular injury:
  - Discontinue with transaminase levels 3 times greater than upper limit of normal
  - Discontinue with bilirubin levels 2 times greater than upper limit of normal
- Decreases in hemoglobin and hematocrit, elevations in Serum Creatinine
- Discontinuation rates due to ADRS, including hypersensitivity:
  - 2.7% of patients taking 10 mg/kg daily
  - 11.8% of patients taking 20 mg/kg daily
- Discontinuation rates due to transaminase elevation:
  - 1.3% of patients taking 10 mg/kg daily
  - 5.9% of patients taking 20 mg/kg daily
- Discontinuation rates due Somnolence, Sedation, and Lethargy
  - 3 % of patients taking 20 mg/kg daily

Cannabidiol Specific drug-drug Interactions

- Clozabam: 3-fold increase in the metabolite of clozabam, reduce the dose of clozabam
- Valproate: Increased liver enzymes, reduction or discontinue use of concomitant cannabidiol and/or valproate

Cannabidiol Storage

- DEA Scheduling
- 100 ml provided in a 105 ml amber bottle
- 2-5 ml calibrated dosing syringes and bottle adapter
- Pharmacy must provide 1 ml calibrated oral syringes when less than 1 ml is prescribed
- Dispense in original bottle upright position at room temperature
- Must be used within 12 weeks of first opening
- Medication Guide

Epidolex Full Prescribing Information, Greenwich Biosciences, Inc. June, 2018

CBD Oil Policy and Procedures

1. EPIDIOLEX (CBD Oil) is indicated only for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older.
   a. EPIDIOLEX should be prescribed by a neurologist
   b. Complete documentation for the indication for use, resident response to the medication, efficacy, and observed side effects should be available in the resident's medical record.
2. Prescriber should obtain serum transaminases (ALT and AST) and total bilirubin levels in all patients prior to starting treatment.
3. The recommended starting dosage is2.5mg/kg taken twice daily (5mg/kg/day). After one week, the dosage can be increased to a maintenance dosageof5 mg/kg twice daily (10 mg/kg/day).
   a. Based on individual clinical response and tolerability, EPIDIOLEX can be increased up to a maximum recommended maintenance dosage of 10 mg/kg twice daily (20 mg/kg/day).
   b. Dosage adjustment is recommended for patients with moderate or severe hepatic impairment.
4. EPIDIOLEX should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus
5. EPIDIOLEX is to be administered orally. Nurse should administer the medication using a calibrated measuring device or one supplied with the medication.

Policy and Procedures

6. Facility staff should monitor the resident for the following potential adverse events:
   a. somnolence;
   b. decreased appetite, weight loss
   c. diarrhea;
   d. transaminase elevations;
   e. fatigue,
   f. malaise, and asthenia;
   g. rash;
   h. insomnia,
   i. sleep disorder, and poor quality sleep; and
   j. infections

7. Discard any unused EPIDIOLEX remaining 12 weeks after first opening the bottle.
   a. Staff should indicate the date the bottle was opened and it beyond-use-date on the medication container.

8. Facility should follow all Federal and State regulations controlled substance policies for prescribing, ordering, receipt, distribution, storage, administration and disposal of EPIDIOLEX

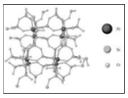
Library of Recommendations: Cannabidiol Oral Solution

Administration
- BID oral Dosing on an empty stomach
- Short beyond use date at room temperature of 12 weeks once opened
- Controlled Substance Management
- Titrated to maintenance
- Clean and dry oral syringe after each use, Water in syringe may cause medication to become cloudy

Monitoring
- Liver function tests: Transaminase, bilirubin; Hemoglobin, hematocrit
- Decrease in frequency of seizures

Care Planning
- Schedule blood tests
- Routine weight and meal monitor
- Fall precautions
- Seizure Precautions
- Mood and suicidal thoughts

Sodium Zirconium Cyclosilicate (Lokelma, Astra Zeneca)



- Indicated for Hyperkalemia in adults
- Non-absorbed zirconium silicate that exchanges potassium for hydrogen and sodium
- Not used in emergencies due to delayed onset of action
- Oral suspension, 5 Grams or 10 Grams per foil lined packet
- Dosage: initial treatment of hyperkalemia: 10 grams 3 times a day for up to 48 hours
  - *10 grams once daily for continued treatment*
- Doses may be adjusted once a week by increments of 5 grams
- Maintenance dose is 5 grams every other day to 15 grams daily
- Decrease the dose or discontinue if serum potassium is below target range

Reconstitution and Administration

- Other oral medications should be taken 2 hours before or 2 hours after other medications
- Empty contents into 45 ml or more water , stir, administer immediately
  - *Repeat adding water until entire dose is taken*
- Avoid use in patients with severe constipation, bowel obstruction, impaction, including post operative motility disorder
- Use with caution with Edema, contains 400 mg Sodium per 5 grams

Clinical Studies

- 1,760 patients
- 652 exposed for 6 months; 507 exposed for at least 1 year
- Placebo controlled trials
- Ages: 22 to 96 years
  - *58% > 65 YEARS*
  - *25% > 75 YEARS*
- Patients had hyperkalemia in association with chronic kidney disease, heart failure, Diabetes Mellitus
- Edema increased with dose
- Most patients were controlled on doses < 15 grams daily
- 4.1% of patients developed HYPOKALEMIA (<3.5 mEq/L) which resolved with a lower dose or discontinuance

Potassium Change from Baseline in 48 hours Study 1

Mean Serum Potassium Change	**Placebo**	**1.25 G TID**	**2.5 G TID**	**5 G TID**	**10 G TID**
All Patients	N = 158	N = 150	N = 137	N = 152	N = 140
	- 0.2	- 0.3	- 0.5	- 0.5	- 0.7
Baseline Serum Potassium > 5.5 mEq/L	N=40	N=40	N=37`	N=29	N=22
	- 0.4	- 0.3	- 0.6	- 0.9	- 1.1

Potassium Change from Baseline in 48 hours Study 2

- Open label
- 2,258 patients with Hyperkalemia received 10 G TID with meals x 48 hours
- Average Potassium level decreased 5.6 to 4.5 mEq mEq/L in acute phase (92% of patients)
- Phase 2: Double blinded randomized trial of those patients who achieved potassium levels of 3.5 to 4.5 mEq/L once a day x 28 days
- Measured mean serum potassium period from day 8 – 29.
- Goal: % patients achieved potassium levels in normal range

Placebo	5 Gm daily	10 Gm daily	15 Gm Daily
N=82	N=45	N=50	N=54
46%	80%	90%	94%

Drug Interactions

- Transient increase in gastric pH
- Can change the absorption of pH dependent solubility
- No dose spacing is needed of concomitant medication does not exhibit pH-dependent solubility
- 39 drugs were tested for interactions
  - *There is an increase systemic exposure to weak acids*
    - Furosemide
    - Atorvastatin
  - *There is a decrease in systemic exposure with weak bases*
    - Dabigatran

Library of Recommendations: Sodium Zirconium Cyclosilicate

Administration
- Used for 48 hours for acute treatment of hyperkalemia
- Separate medications affected by gastric pH 2 hours before and 2 hours after
- Mix in at least 45 ml water and continue to add water until entire dose is take
- Use immediately after preparation

Monitoring
- Serum Potassium
- Serum Sodium
- Manage edema through dose reduction/discontinue medication
- Possible drug-drug interactions with furosemide, atorvastatin, dabigatran

Care Planning
- Schedule blood tests
- Routine weight
- Treat or manage edema
- Manage dietary sodium, if needed

Plazomicin 50 mg/ml (Zemdri, Achaogen, Inc.)

- An intravenous aminoglycoside antibacterial for the treatment of Complicated UTI (cUTI) including Pyelonephritis in adults over 18 years
- Reserved for use in patients who have limited or no alternative options
- Used to treat infections proven or strongly suspected by a susceptible organism.
- Injection available 500 mg/10 ml. Undiluted vial stored under refrigeration
- Box Warning, as with all aminoglycosides
- 40% of patients were 65 years or older
- 17.2% of patients were 75 years or older

Dosage and Administration

- 15 mg/kg Q 24 hours over 30 minutes
- Treatment for 4 to 7 days
- Assess CrCl prior to initiating therapy and DAILY thereafter
- Injection 50 mg/10 ml

CrCl ml/min	Recommended Dose	Dosing interval
≥ 60 - < 90	15 mg/kg	Every 24 hours
≥ 30 - < 60	10 mg/kg	Every 24 hours
≥ 15 - < 30	10 mg/kg	Every 48 hours

Stability of Plazomicin

- Stable at room temperature for 24 hours for concentrations of 2.5 mg/ml to 45 mg/ml once prepared
- Dilute in Normal Saline or lactated Ringers
- 50 ml volume for administration

Antimicrobial Activity and Therapeutic Drug Monitoring

- E. coli
- K. pneumoniae
- P. mirabilis
- Enterobacter cloacae
- Trough plasma concentrations should be below 3 mcg/ml
  - *Q24 hour dose* ⟶ *Q36 hours*
  - *Q48 hour dose* ⟶ *Q72 hours*

Clinical Studies

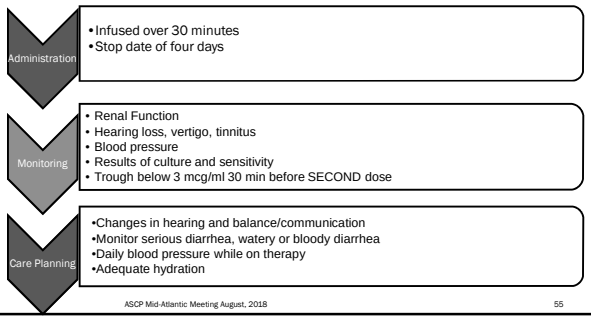
- 609 hospitalized patients, multinational, double blinded, non-inferiority trial comparing meropenem 1 G IV Q8h to plazomicin 15 mg/kg IV Daily
- Demonstrated efficacy a day 5 of therapy
- All pathogens reduced after first dose
- The rate of adverse reactions associated with renal function in patients ≥65 years war 27% vs. 18.9% in meropenem treated patients and 6.6 % vs. 2.8% for adverse reactions associated with renal function

Adverse Drug Reactions Plazomicin

- Do not administer to patients allergic to aminoglycosides
- Nephrotoxicity
- Ototoxicity
- Neuromuscular blockade
- Fetal harm
- C. Difficile associated diarrhea
- Hypertension
- GFR and CrCl closely monitored
- No significant drug-drug interactions

Zemdri Full Prescribing information, Achaogen, Inc., June, 2018

Library of Recommendations: Plazomicin



Lofexidine hydrochloride, Lucemyra ® Britanica)

- First non-opioid Indicated for the mitigation of withdrawal symptoms to facilitate abrupt discontinuation of opioids in adults
  - *Lessens the severity of withdrawal symptoms*
  - *Approved for used only for 14 days*
  - *Not intended to be used for the treatment of opioid use disorder*
  - *Can be used as part of a long-term treatment plan*
- Oral selective 2-adrenergic receptor agonist that reduces the release of norepinephrine
- The FDA is requiring 15 post-marketing studies including newborns with neonatal withdrawal and in children discontinuing opioid therapy

Lofexidine

- The usual Lofexidine dosage is three 0.18 mg tablets taken orally 4 times daily at 5-to 6-hour intervals Lofexidine treatment may be continued for up to14 days with dosing guided by symptoms.
- Discontinue Lofexidine with a gradual dose reduction over 2 to 4 days.
- Store in original container, do not remove desiccant

Dosage Recommendations for Patients with Hepatic Impairment

Recommended dosage adjustments based on the degree of hepatic impairment

Impairment	Child-Pugh Score	Dose
Mild	5-6	3 tablets QID (2.16 mg/day)
Moderate	7-9	2 tablets QID (1.44 mg/day)
Severe	> 9	1 tablet QID (0.72 mg/day)

Dosage Recommendations for Patients with Renal Impairment

Mild or Moderate Impairment	GFR mL/min/1.73 m^2 30-89.9	2 tablets 4 times daily (1.44 mg per day)
Severe Impairment, End-Stage Renal Disease, or on Dialysis	GFR < 30	1 tablet 4 times daily (0.72 mg per day)

Adverse Drug Reactions Lofexidine

- **Risk of QT Prolongation**
  - Lofexidine prolongs the QT interval.
  - Avoid using Lofexidine in patients with congenital long QT syndrome.
  - Monitor ECG in patients with congestive heart failure, bradyarrhythmias, hepatic impairment, renal impairment, or patients taking other medicinal products that lead to QT prolongation (e.g. methadone).
  - In patients with electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia), correct these abnormalities first, and monitor ECG upon initiation of Lofexidine

Risk of Hypotension, Bradycardia, and Syncope

- Syncope: 0.9%, 1.4% and 0% for Lofexidine 2.16 mg/day and 2.88 mg/day and placebo
- Tinnitus: 0.9%, 3.2% and 0% for Lofexidine 2.16 mg/day and 2.88 mg/day and placebo, respectively

Drug Interactions

Methadone Lofexidine and methadone both prolong the QT interval. ECG monitoring is recommended in patients receiving methadone and Lofexidine	**Oral Naltrexone** Coadministration of Lofexidine and oral naltrexone resulted in statistically significant differences in the steady-state pharmacokinetics of naltrexone. It is possible that oral naltrexone efficacy may be reduced if used concomitantly within 2 hours of Lofexidine .
CNS Depressant Drugs Lofexidine potentiates the CNS depressant effects of benzodiazepines and may potentiate the CNS depressant effects of alcohol, barbiturates, and other sedating drugs. Advise patients to inform their healthcare provider of other medications they are taking, including alcohol	**CYP2D6 Inhibitor - Paroxetine** Coadministration of Lofexidine and paroxetine resulted in 28% increase in the extent of absorption of Lofexidine . Monitor for orthostatic hypotension and bradycardia when an inhibitor of CYP2D6 is used concomitantly with Lofexidine

Lucemyra Full Prescribing Information, US Worldwide Meds, June 2018

Library of Recommendations: Lofexidine

Administration
- Store in original Container
- Administered without regard to meals

Monitoring
- Dose based on renal and hepatic function
- Prolongs Q-T Interval
- CNS depression with concomitant use of other CNS depressants

Care Planning
- Monitor Pulse and Blood Pressure
- Fall Precautions due to syncope/hypotension,
- Monitor withdrawal symptoms

Self Test Questions

Which assessment tool is used to measure the efficacy of Valbenazine?

Andexxa reverses the anticoagulation effect of which two medications?

When dispensing CBD Oil is it important to dispense an oral syringe with doses less than or equal to how many milliliters?

What is the recommended stop date for plazomicin?

How does Lucemyra reduce the symptoms of withdrawal from opioids?

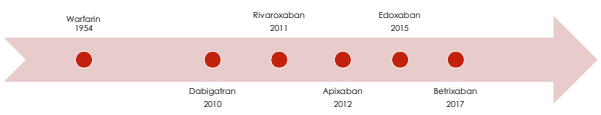
PRACTICAL CONSIDERATIONS FOR THE USE OF DIRECT ORAL ANTICOAGULANTS (DOACS)

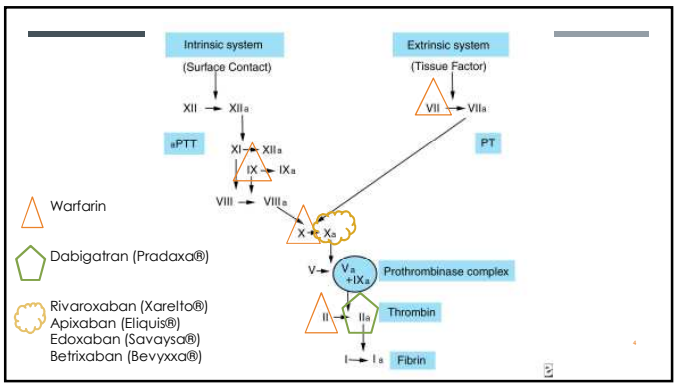
Jessica W. Merrey, PharmD, MBA, BCPS, BCACP, BCGP

OBJECTIVES

- Identify the key considerations in initiating a patient on a direct oral anticoagulant (DOAC)
- Identify data supporting or discouraging the use of each DOAC in special patient populations, including the oldest of the old, renal impairment, hepatic impairment, and obesity
- Recognize the elements of an effective strategy for transitioning a patient to or from a DOAC for maintenance or peri-operative reasons
- Differentiate between the available reversal options for DOACs

REVIEW OF CURRENT ORAL DOACS





INDICATIONS FOR USE

	Indications		
Drug	**VTE Treatment and prophylaxis**	**Nonvalvular AF**	**Post-op VTE prevention**
Dabigatran	X	X	X (hip)
Rivaroxaban	X	X	X (hip/knee)
Apixaban	X	X	X (hip/knee)
Edoxaban	X	X	
Betrixaban	X (prophylaxis only)		

EFFICACY OF DOAC COMPARED TO WARFARIN – A. FIB

Effect	RE-LY Dabigatran 110mg	RE-LY Dabigatran 150mg	ROCKET-AF Rivaroxaban	ARISTOTLE Apixaban	ENGAGE-AF Edoxaban 60mg	ENGAGE-AF Edoxaban 30mg
Reduction of stroke or systemic embolism	Non-inferior	Superior	Non-inferior	Superior	Non-inferior	Non-inferior
Reduction of ischemic stroke	⟷	↓	⟷	⟷	⟷	↑

EFFICACY OF DOAC COMPARED TO WARFARIN - VTE

Effect	RE-COVER Dabigatran	EINSTEIN DVT Rivaroxaban	EINSTEIN PE Rivaroxaban	AMPLIFY Apixaban	HOKUSAI VTE Edoxaban
Reduction of VTE recurrence	Non-inferior	Non-inferior	Non-inferior	Non-inferior	Non-inferior
Major bleeding	⇔	⇔	↓	↓	↓

EFFICACY OF DOAC COMPARED TO LMWH – VTE

Effect	APEX Betrixaban v. enoxaparin	Hokusai VTE Cancer Edoxaban v. dalteparin	SELECT-D Rivaroxaban v. dalteparin
Reduction of VTE-Recurrence	⇔	Non-inferior	↓
Major bleeding	⇔	↑	⇔

INITIATING A NEW PATIENT

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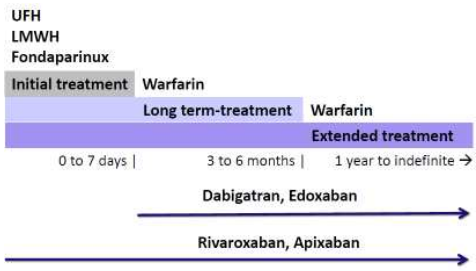
INITIATING A NEW PATIENT

UFH
LMWH
Fondaparinux



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DECIDING BETWEEN DOAC AND WARFARIN

Drug Interactions

- Warfarin
  - Numerous
    - Antimicrobials, CYP 1A and 2C
  - Monitor and manage via INR
- DOACs
  - Less numerous than warfarin
    - P-gp, CYP 3A
  - ? monitoring

Non-adherence

- Warfarin
  - Easily recognized by decrease in INR
  - Long $t_{1/2}$ protective
- DOACs
  - Not seen without evaluating fill history
  - Short $t_{1/2}$ means NO anticoagulation with 1 missed dose

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WHEN TO AVOID DOAC

- Valvular a. fib
- Mechanical heart valve
- Medication non-adherence
- Platelets < 50K
- *Stage 3 or 4 CKD (CrCl < 30mL/min)*
- Severe liver disease
- Pregnancy or lactation
- Recent GI bleed
- Recent major surgery or trauma

Yeh CH, et al. *Blood*. 2014;124(7):1020-1028

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WHEN TO USE DOAC WITH CAUTION

- Thrombosis due to HIT
- *Stage 1 or 2 CKD (CrCl 30-49 mL/min)*
- Chronic use of strong CYP inducers or inhibitors
- Platelets < 100K
- *Active malignancy*
- Low body weight (<50kg)
- High risk hypercoagulable syndromes (APS)

Yeh CH, et al. *Blood*. 2014;124(7):1020-1028

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WHEN TO FEEL COMFORTABLE USING DOAC

- Good record of adherence to other medicines
- High TTR on warfarin
- Routine INR monitoring difficult or inconvenient
- Irregular or inconsistent dietary intake
- Able to afford copays **or** eligible for manufacturer assistance

Yeh CH, et al. *Blood*. 2014;124(7):1020-1028

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MONITORING DOACS

Each Visit
Adherence
Drug-drug interactions
Weight

Renal Function

CrCl > 60 mL/min	Annually
CrCl 30 – 60 mL/min	Every 6 months
CrCl 15 – 30 mL/min Fluctuating	Every 3 months

Liver Function Test

Most patients	Not required
Special population -At risk for (or presence of) hepatic dysfunction	Every 6-12 months

Complete Blood Count

Most patients	Annually
Special population -Low baseline Hgb/Hct -Drug interactions -Age > 75 years	At least every 6 months

Conway S, et al. Pharmacotherapy. 2017;37(2)236-48

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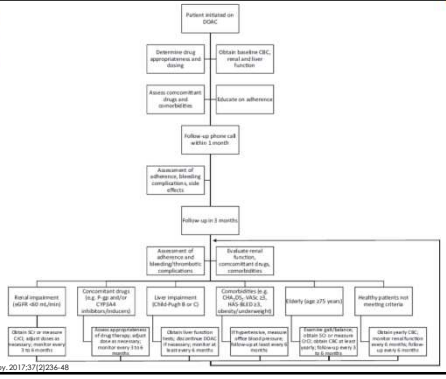
Assay	Direct Thrombin Inhibitors Sensitivity	Utility	Factor Xa Inhibitors Sensitivity	Utility
Activated partial thromboplastin time (APTT)	Low Better than PT	Qualitative, but normal does not rule out effect	Low	Not useful
Chromogenic anti-factor Xa	N/A	N/A	High	Quantitative if calibrated to specific agent
Dilute thrombin time (dTT)	Sensitive	Quantitative	N/A	N/A
Ecarin clotting time (ECT)	Sensitive	Quantitative	N/A	N/A
HepTest	Sensitive	Quantitative	Sensitive	Quantitative
Plasma drug concentration	Sensitive	Quantitative	Sensitive	Quantitative
Prothrombin time (PT)	Low	Not suitable in therapeutic concentrations, qualitative in supratherapeutic doses	Low	Qualitative
Prothrombinase-induced clotting time (PiCT)	Low	TBD	Sensitive except at low doses	TBD
Thrombin time (TT)	Over-sensitive	Qualitative	N/A	N/A

Conway S, et al. Pharmacotherapy. 2017;37(2)236-48

17



Conway S, et al. Pharmacotherapy. 2017;37(2)236-48

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DABIGATRAN (PRADAXA®)

- Indications: A. fib, VTE treatment, VTE extended treatment, VTE prophylaxis s/p THR
- Initial Dosing: Based on indication
  - A. fib – 150mg BID
  - VTE – 150mg BID (after 5-10 days of parenteral anticoagulation)
  - Post-THR VTE prophylaxis – 110mg 1-4 hours after surgery, then 220mg Daily x 28-35 days
- Maintenance Dosing: Unchanged
- Dose Adjustments
  - A.fib – CrCl 15-30 mL/min – reduce to 75mg BID
  - VTE – CrCl <50 and on P-gp – AVOID
- Considerations
  - P-gps
  - Strong 3A4 inducers/inhibitors
  - Must be stored in original bottle for stability, avoid light/moisture (BUD =4 months)

Pradaxa® (package insert). Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2015

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RIVAROXABAN (XARELTO®)

- Indications: A. fib, VTE treatment, VTE extended treatment, VTE prophylaxis s/p THR or TKR
- Initial Dosing: Based on indication
  - A. fib – 20mg daily
  - VTE – 15mg BID x21 days, then maintenance dose
  - Post-TKR/THR prophylaxis – 10mg daily for 12 (TKR) to 35 (THR) days
- Maintenance Dosing: 20mg daily
- Dose Adjustments
  - A.fib - CrCl 15-50 mL/min – reduce to 15mg daily
  - A.fib – CrCl <15 mL/min – AVOID
  - VTE – CrCl <30 mL/min – AVOID
- Considerations
  - P-gp-inhibitors
  - Strong 3A4 inhibitors
  - Must take with food

Xarelto® [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2015

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APIXABAN (ELIQUIS®)

- Indications: A. fib, VTE treatment, VTE extended treatment, VTE prophylaxis s/p THR or TKR
- Initial Dosing: Based on indication
  - A. fib – 5mg BID
  - VTE – 10mg BID x7 days, then 5mg BID x6 months, then maintenance
  - Post-TKR/THR VTE Prophylaxis – 2.5mg BID
- Maintenance Dosing:
  - A. fib – unchanged
  - VTE – 2.5mg BID
- Dose Adjustments
  - 50% dose reduction in CYP 3A4 + P-gp Inhibitor
  - A. fib in special populations

Eliquis® [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2014

21

EDOXABAN (SAVAYSA®)

- Indications: A. fib, VTE treatment, VTE extended treatment
- Initial Dosing:
  - A. fib – 60mg daily
  - VTE – 60mg daily (after 5-10 days of parenteral anticoagulation)
- Maintenance Dosing: Unchanged
- Dose Adjustments:
  - 30mg daily if CrCl 15-50 mL/min
  - VTE – 30mg daily if one of the following
    - Weight <60kg
    - On P-gp inhibitor
- Interactions to Consider
  - AVOID in A. fib patients with CrCl > 95 ml/min

Savaysa® [package insert]. Parsippany, NJ: Daiichi Sankyo, Inc.; 2015

22

BETRIXABAN (BEVYXXA®)

- Indications: VTE prophylaxis in acutely ill
- Initial Dosing:
  - 160mg x1 dose
- Maintenance Dosing:
  - 80mg once daily for 35 – 42 days
- Dose Adjustments:
  - CrCl 15-30 mL/min – 80mg x1 dose then 40mg daily
  - Concomitant P-gp Inhibitor – 80mg x1 dose then 40mg daily
- Considerations
  - Must be taken with food

Bevyxxa® [package insert]. South San Francisco, CA: Portola Pharmaceuticals, Inc.; 2017

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CONCERNS FOR SPECIAL POPULATIONS

Oldest of the old Renal impairment Hepatic impairment Obesity

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PATIENTS >75YO IN PHASE III TRIALS

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
AF	RE-LY 40%	ROCKET-AF 43%	ARISTOTLE 32%	ENGAGE-AF 40%	
VTE	RE-COVER 11%	EINSTEIN-DVT 13% EINSTEIN-PE 17%	AMPLIFY 15%	Hokusai VTE 14%	APEX 62%-74%
ACS	RE-DEEM 13%	ATLAS ACS 9%	APPRAISE 20%		

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OLDEST OF THE OLD: DABIGATRAN

- Atrial Fibrillation (RE-LY)
  - No difference in efficacy compared to warfarin
  - Higher rate of major of bleeding vs. warfarin (5.1% v. 4.37%, p<0.001)
- VTE Treatment (RE-COVER)
  - No difference in efficacy compared to warfarin
  - Similar rate of bleeding vs. warfarin (3.5% vs. 3.8%, p=0.83)
- Meta-analysis of all indications
  - More GI bleeding for 150mg (OR 1.78, 95% CI 1.35-2.35) and 110mg (OR 1.4, 1.04-1.9)
  - Less intracranial bleeding with 150mg (0.43, 0.26-0.72) and 110mg (0.36, 0.22-0.61)

Connolly S, et al. N Engl J Med. 2009;361(12)1139-51
Sardar P et al. J Am Geriatr Soc. 2014;62(5):857-64
Geldhof V et al. Thrombosis Journal. 2014;12(21)1-10
Sharma M, et al. Circulation. 2015 Jul 21;132(3):194-204

26

OLDEST OF THE OLD: RIVAROXABAN

- Atrial Fibrillation (ROCKET-AF)
  - Higher stroke and bleeding rates overall compared with younger patients
  - Non-inferior to warfarin in efficacy and safety
- VTE (EINSTEIN-DVT and EINSTEIN-PE)
  - Similar incidence of VTE compared to warfarin
  - Age-dependent increase in recurrence of VTE in warfarin group. This was not seen in rivaroxaban group
    - Overall incidence 2.1% vs. 2.2%
    - >75yo incidence 2.3% vs. 3.7%
  - Lower rates of major bleeding compared to warfarin (1.2% v. 4.5%, p<0.001)

Halperin JL, et al. Circulation. 2014;130(2):138-46
Geldhof V et al. Thrombosis Journal. 2014;12(21)1-10

27

OLDEST OF THE OLD: APIXABAN

- Atrial Fibrillation (ARISTOTLE)
  - Significantly lower risk of stroke and systemic events (OR 0.72, 95% CI 0.54-0.97) compared to warfarin
  - Significantly less bleeding (OR 0.61, 95% CI 0.49-0.76) compared to warfarin
- VTE Treatment (AMPLIFY)
  - Non-significant trend toward a reduction in thromboembolic events (1.8% vs. 3.6%, p=0.13) compared to warfarin
  - Significantly lower risk of major bleeding (1% vs. 4.3%, p=0.009)

Sandar P et al. Am Geriatr Soc. 2014;62(5):857-64
Geldhof V et al. Thrombosis Journal. 2014;12(21)1-10

28

OLDEST OF THE OLD: EDOXABAN

- Atrial Fibrillation (ENGAGE-AF)
  - No statistical difference in rate of stroke and systemic embolism (1.91% vs. 2.31%)
  - No statistical difference in bleeding (4.0% vs. 4.8%)
- VTE Treatment (Hokusai-VTE)
  - Significant reduction in VTE (2.5% vs. 5.0%, p=0.03) compared to warfarin
  - No significant difference in rates of major and clinically relevant bleeding (12.5% vs. 15.1%)

Mavrakanas T et al. Swiss Med Wkly. 2015;145:w14081
Geldhof V et al. Thrombosis Journal. 2014;12(21):1-10

29

OLDEST OF THE OLD: BETRIXABAN

- VTE Prophylaxis
  - Cohort 2 (D-dimer > 2xULN or >75yo) – 73.7% ≥ 75 years of age
    - Significant reduction in rate of systemic embolism (5.3% vs. 7.1%) compared to enoxaparin
    - Significantly more major or clinically relevant nonmajor bleeding (RR 1.64)
  - Cohort 3 (total population) – 70% ≥ 75 years of age
    - Significant reduction in rate of systemic embolism (5.3% vs. 7.1%) compared to enoxaparin
    - Significantly more major or clinically relevant nonmajor bleeding (RR 1.89)
  - No significant difference in major bleeding

Cohen et al. N Engl J Med. 2016;375(6):534-44

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OLDEST OF THE OLD: DOAC SUMMARY

Dabigatran use in age > 75 years:
- Trend toward ↑ extra-cranial bleeding
- ↓ in ICH

Rivaroxaban use in age > 75 years:
- ↑ combination of major and CRNM bleeding
- No difference in ICH

Edoxaban use in age >75 years:
- Greater reduction in VTE but no difference in stroke
- No difference in bleeding

Betrixaban use in age > 75 years:
- ↑ combination of major and CRNM bleeding
- No difference in efficacy

Apixaban use in age 65-75 years and > 75 years:
- Greater net clinical benefit
- **DECREASES** major bleeding and ICH
- Greater reduction in stroke and systemic embolism

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CONCERNS FOR SPECIAL POPULATIONS

Oldest of the old Renal impairment Hepatic impairment Obesity

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CASE: RENAL IMPAIRMENT

- A 77-yo man is admitted to the hospital after a follow-up visit with his PCP (first in 12 months) for progressive renal disease that was found in routine blood tests. He was in his usual state of health until 2 weeks ago, when he starting to feel more fatigued than usual. No chest pain, orthopnea, edema, or dyspnea.
- His PMH is significant for HTN, T2DM, persistent AF, BPH, and CKD with a baseline Cr of 2.0mg/dL (eGFR 34mL/min). He has never been on dialysis in the past.
- His medications include amlodipine, lisinopril, metoprolol, atorvastatin, insulin glargine, and dabigatran 150mg BID.
- Upon hospital admission his vital signs are notable for irregularly regular heart rate 90 BPM, BP 147/89, normal oxygen saturation, BMI 31

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CASE: RENAL IMPAIRMENT

- Laboratory values show: SCr 5.3 mg/dL (eGFR 11.2 mL/min), BUN 105 mg/dL, K+ 7.0 mmol/L, and Hgb 10.5 g/dL. His EKG showed AF with controlled heart rate and peaked T-waves. He is given intravenous calcium gluconate, insulin, and dextrose followed by oral Kayaxelate.
- Remainder of work-up leads the team to determine this is all due to progression of his CKD. He begins hemodialysis after holding dabigatran for 24 hours. No bleeding is noticed post-procedure.
- After tolerating two hemodialysis sessions without complications, he is being prepared for discharge where he will continue dialysis as an outpatient. The team would like to resume anticoagulation for stroke prophylaxis.
- **What is the optimal anticoagulation strategy for this patient?**

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RENAL IMPAIRMENT STUDY EXCLUSIONS

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
AF	RE-LY CrCl < 30mL/min	ROCKET-AF CrCl < 30mL/min	ARISTOTLE CrCl < 25mL/min or SCr > 2.5mg/dL	ENGAGE-AF CrCl < 30mL/min	
VTE	RE-COVER CrCl < 30mL/min RE-MODEL CrCl < 30mL/min	EINSTEIN-DVT CrCl < 30mL/min EINSTEIN-PE CrCl < 30mL/min	ADVANCE-3 CrCl < 30mL/min AMPLIFY CrCl < 30mL/min	Hokusai VTE CrCl < 30mL/min	APEX CrCl < 15mL/min or CrCl 15-30 mL/min with concomitant P-gp inhibitor
ACS	REDEEM CrCl < 30mL/min	ATLAS ACS CrCl < 30mL/min	APPRAISE CrCl < 20mL/min		

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RENAL IMPAIRMENT: DABIGATRAN

- Primarily renally eliminated
  - Risk of bleeding increases with decreasing CrCl
- Prolonged elimination with decreasing CrCl
  - Healthy Individuals $t_{1/2}$: 12-17 hours
  - CrCl 30-50mL/min $t_{1/2}$: 13-23 hours
  - CrCl <30mL/min $t_{1/2}$: 22-35 hours
- Reduce dose to 75mg BID for CrCl 15-30mL/min in A.fib
  - No dose recommendations for VTE prophylaxis in CrCl <30mL/min
- Dialyzable

Liesenfeld KH et al. J Thromb Haemost 2011;9(11)2168-75
Connolly S, et al. N Engl J Med 2009;361:1139-51
Pradaxa® (package insert). Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2015

36

RENAL IMPAIRMENT: RIVAROXABAN

- Reduce dose to 15mg daily for CrCl <50mL/min
  - Similar drug exposure vs. patients with normal renal function receiving 20mg daily
  - Non-inferior to warfarin and LMWH (safety and efficacy) in patients with CrCl <50mL/min
- VTE: Avoid if CrCl <30mL/min
- AF: Avoid if CrCl <15mL/min

Patel M, et al. N Engl J Med 2011;365:883-91
Bauersachs R, et al. N Engl J Med 2010;363:2499-510
Buller H, et al. N Engl J Med 2012;366:1287-97
Xarelto® (package insert). Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2015

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RENAL IMPAIRMENT: APIXABAN

- ARISTOTLE and AMPLIFY both provided sub-group analyses by renal function
  - Similar rates of stroke, systemic embolism, VTE compared to warfarin in CrCl 25-50mL/min
  - Less major bleeding compared to warfarin in atrial fibrillation
- Slightly dialyzable (14%)
- FDA approval for use in ESRD requiring HD
  - 5mg BID
  - 2.5mg BID if patient is >80 years OR <60kg and being treated for a.fib

Granger C et al. N Engl J Med. 2011;365(11):981-92
Agnelli G et al. N Engl J Med 2013; 369:799-808
Wang X et al. Clin Pharmacol Drug Dev 2012;1:4:187

38

RENAL IMPAIRMENT: EDOXABAN

- ENGAGE-AF and Hokusai VTE both had subgroup analyses for various renal function groups
  - Non-inferior to warfarin in CrCl 31-94 mL/min in treatment of AFib
    - Reduced efficacy compared to warfarin in CrCl >95 mL/min in AFib
  - Trend toward improved VTE outcomes compared to warfarin in CrCl 30-50mL/min
- Reduce dose to 30mg daily in CrCl 15-30mL/min
  - 15mg daily in Japanese patients with CrCl 15-30mL/min
- Not recommended in CrCl <15mL/min

Giugliano R et al. N Engl J Med. 2013;369:2093-2104
Hokusai-VTE investigators. N Engl J Med 2013;369:1406-1415

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RENAL IMPAIRMENT: BETRIXABAN

- APEX included subgroup analyses for efficacy and safety in patients dose-reduced for severe renal function
  - No difference in efficacy
  - No difference but trend toward fewer bleeding events in enoxaparin
- If CrCl 15-30 mL/min reduce dose to 80mg first day and 40mg thereafter
- Not recommended in CrCl <15mL/min

Cohen et al. N Engl J Med. 2016;375(6)534-44

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RENAL IMPAIRMENT: SUMMARY

Agent (% renal excretion)	Nonvalvular AF	VTE Treatment or Prophylaxis	Orthopedic VTE Prophylaxis
Dabigatran (80)	CrCl 15-30: 75mg BID CrCl < 15: Avoid	CrCl < 30: Avoid	CrCrl < 30: Avoid
Rivaroxaban (33)	CrCl 15-50: 15mg daily CrCl < 15: Contraindicated	CrCl < 30: Avoid	CrCl < 30: Contraindicated
Apixaban (25)	ESRD on HD: 5mg BID Reduce to 2.5mg BID if >80yo or <60kg	No dose adjustment recommended	No dose adjustment recommended
Edoxaban (35)	CrCl >95: Contraindicated CrCl < 15: Avoid	CrCl < 15: Avoid	
Betrixaban (11)		CrCl <15: Avoid CrCl < 30 and on strong P-gp: Avoid	

Marvakanas TA et al. J Am Soc Nephrol. 2017;28:2241-8

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CONCERNS FOR SPECIAL POPULATIONS

Oldest of the old Renal impairment Hepatic impairment Obesity

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CASE: HEPATIC IMPAIRMENT

- A 71-yo woman with a history of cirrhosis due to fatty liver disease presents to the PCP as a discharge follow-up for hospitalization secondary to a syncopal event at home. Upon ED admission a CT w/contrast revealed bilaterlal pulmonary emboli. Her baseline INR was 2.1 so the team felt uncomfortable initiating warfarin therapy. She was discharged on enoxaparin 80mg (1mg/kg) twice daily.
- She brings her discharge summary to today's appointment. The BMP is WNL with SCr 0.8 mg/dL. Her WBC count is 7 x 10^9/L, Hgb 12 g/dL, and platelets are 95 x 10^9/L. Her AST is 45 IU/L and ALT is 57 IU/L. The remainder of the liver function testing is normal. At today's visit she expresses frustration at the twice daily injection schedule of her enoxaparin.
- **What therapeutic alternative can you offer her?**

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HEPATIC IMPAIRMENT STUDY EXCLUSIONS

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
AF	RE-LY Active liver disease	ROCKET-AF Known liver disease with AST >3x ULN	ARISTOTLE ALT or AST > 2x ULN or Tbili > 1.5x ULN	ENGAGE AF ALT or AST > 2x ULN or Tbili > 1.5x ULN or AlkPhos > 2x ULN	
VTE	RE-COVER Liver disease with AST > 2x ULN	EINSTEIN-DVT Clinically significant liver disease or ALT > 3x ULN EINSTEIN-PE Clinically significant liver disease or ALT > 3x ULN	ADVANCE-3 ALT or AST > 2x ULN or Tbili > 1.5x ULN AMPLIFY ALT or AST > 2x ULN or Tbili > 1.5x ULN	Hokusai VTE Significant liver disease or ALT ≥ 2x ULN or Tbili ≥ 1.5x ULN	APEX Active liver disease, cirrhosis or >3x ULN AST/ALT/ALP or >2x ULN Tbili
ACS	RE-DEEM None	ATLAS ACS Known significant liver disease or ALT > 5x ULN or ALT > 3x ULN + Tbili > 2x ULN	APPRAISE None		

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REAL LIFE DOAC USE IN HEPATIC IMPAIRMENT

	N (69 total)	%
DOAC Indication		
Afib	22 – no SSE	32
DVT/PVT	47 – 38 resolved, 3 progressed	68
Bleeding Events		
Grade 3	8	12
CTP Class A	0	0
CTP Class B	4	50
CTP Class C	4	50
Apixaban	5	63
Rivaroxaban	3	37
Dabigatran	0	0

Kunk PR et al. Blood. 2016;128:3827

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HEPATIC IMPAIRMENT: SUMMARY

- All safe in mild hepatic impairment (CTP A)
- Dabigatran and apixaban are labeled safe for use in moderate hepatic impairment (CTP B)
- Avoid DOACs in severe hepatic impairment (CTP C)
  - Especially rivaroxaban and apixaban based on case studies
- When used in cirrhosis incidence of bleeding is similar to warfarin
- DOACs are not associated with an increased risk of drug-induced hepatic impairment

Graf J, Harder S. Clin Pharmacokinet 2013;52:243-54
Kunk PR et al. Poster Presented At ASH 58th Annual Meeting, December 2016

46

CONCERNS FOR SPECIAL POPULATIONS

Oldest of the old Renal impairment Hepatic impairment Obesity

47

CASE: OBESITY

- A 76-yo woman with PMH of HTN, HPL, and BPD presented to the emergency department with a 4-day history of swelling and pain in her right leg. She denies SOB. After ultrasound of her leg she is diagnosed with an acute occlusive thrombosis of the common femoral vein. She has never had thromboembolism in the past, but her sister has a history of DVT. She denies smoking, trauma/surgery, and recent travel.
- Her weight is 124kg (BMI 53 kg/m^2), SCr 0.93mg/dL, D-dimer >4000 ng/mL
- She was bridged to therapeutic warfarin (INR 2.0-3.0) and now, 2 months into her treatment expresses concern to you, her PCP, during a routine follow-up. She is tired of adhering to vitamin K restrictions and monitoring of warfarin.
- **What DOAC and dose do you recommend?**

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OBESITY IN DOAC TRIALS

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
AF	RE-LY Wt ≥ 100kg 17%	ROCKET-AF Wt. > 90kg 28.5%	ARISTOTLE No details but some obese pts IQR 70-95kg	ENGAGE-AF No details	
VTE	RE-COVER 1 BMI ≥ 35 12% 306/2539 RE-COVER 2 BMI ≥ 35 24%	EINSTEIN-DVT Wt. > 100kg 14.2% EINSTEIN-PE Wt.> 100kg 14.3%	AMPLIFY Wt. ≥ 100kg 19.4%	Hokusai VTE Wt. > 100kg 14.8%	APEX No details

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OBESITY: DABIGATRAN

- RE-LY patients divided into 3 subgroups based on weight
  - BMI > 36, BMI 22.5 – 36, BMI < 22.5
- No difference in stroke rates for BMI > 36 compared to BMI 22.5 – 36
  - High rates in BMI > 36 and BMI 22.5 – 36 than BMI <22.5
- Case reports of morbidly obese patient (BMI 44) receiving dabigatran 150mg BID developing acute ischemic stroke
- Case reports using high dose (220mg BID) in BMI > 30 did not lead to bleeding and had similar VTE rates as non-obese
- Absorbed in upper GI tract – gastrectomy would impact absorption

Ezekowitz ME et al. Eur. Heart J 2014;35:1111
Breuer L et al. N Engl J med 2013;368(25):1440-2
Eriksson BI et al. Throm Res 2012;130(5):818.20

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OBESITY: RIVAROXABAN

- Has the most published reports of use in obese patients
- No differences found in C_{max}, AUC, t_{max}, or $t_{1/2}$ between obese and non-obese patients (mean BMI 43.5)
- Case reports suggest may be safe and effective regardless of weight
- Absorbed in upper GI tract – gastrectomy would impact absorption

Kubitza D et al. J Clin Pharmacol 2007;47(2):218-26
Upreti VV et al. Br J Clin Pharmacol 2013;76(6):908-16
Domienik-Karlowicz and Pruszczyk. Cardiol J 2016;23(1):12-16

51

OBESITY: APIXABAN

- No clinically significant differences in apixaban exposure between obese and non-obese patients (mean BMI > 42.5)
- Only weight-based adjustment is for <60kg (AF only)

Upreti VV et al. Br J Clin Pharmacol 2013;76(6):908-16
Domienik-Karlowicz and Pruszczyk. Cardiol J 2016;23(1):12-16

52

OBESITY: EDOXABAN

- Hokusai VTE showed similar efficacy to warfarin in weight >100kg
- Only weight-based adjustment is for < 60kg (AF only)

Domieniik-Karlowicz and Pruszczyk. Cardiol J 2016;23(1):12-16

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OBESITY: ISTH GUIDANCE

- Recommend standard dosing patients BMI ≤40 and weight ≤120kg
- Suggest **avoid** DOAC in BMI >40 **and** weight >120kg due to limited data and because data that is available suggests ↓ drug exposure, ↓ peak concentration, and ↓ $t_{1/2}$ with increasing weight, raising concern about under-dosing
- Suggest **monitoring** DOAC if using in BMI >40 **or** weight >120kg
  - Anti-Xa: apixaban, rivaroxaban, edoxaban
  - ET or DTT: dabigatran
  - Drug levels

Martin K et al. J Thromb Haemost 2016;14:1308-13
Graves KK, Edholm K, and Johnson SA. JSM Atheroscleresis 2017;2(4):1035

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TRANSITIONING TO/FROM DOAC

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SWITCHING BETWEEN AGENTS

From warfarin to…

- Dabigatran (Pradaxa®)– initiate when INR <2
- Rivaroxaban (Xarelto®) – initiate when INR <3
- Apixaban (Eliquis®) – initiate when INR <2
- Edoxaban (Savaysa®) – initiate when INR ≤2.5

From DOAC to warfarin

- Dabigatran – overlap with warfarin
  - CrCl > 50 mL/min: 3 days
  - CrCl 31-50 ml/Min: 2 days
  - CrCl 15-30 mL/min: 1 day
- Rivaroxaban – start warfarin and parenteral agent at time of next scheduled dose
- Apixaban – start warfarin and parenteral agent at time of next scheduled dose
- Edoxaban – reduce edoxaban by 50% and start warfarin

Pradaxa® [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2015
Xarelto® [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2015
Eliquis® [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2014
Savaysa® [package insert]. Parsippany, NJ: Daiichi Sankyo, Inc.; 2015

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SWITCHING BETWEEN AGENTS

From DOAC to DOAC

- Stop old agent
- Give new agent at the time that the next dose of the old agent would have been given
- If at maintenance dose of 1 product can start at maintenance dose of switched product (ie. dabigatran to rivaroxaban)

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PERIOPERATIVE BRIDGING

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CASE: PERIOPERATIVE BRIDGING

- A 67-yo male attends an appointment with you for his annual physical. He has PMH significant for recurrent pulmonary embolism and DVT s/p IVC filter, HTN, colon polyps, and OA. You identify that he is due for his colonoscopy and send a referral to GI for scheduling. When he had his colonoscopy 5 years ago he had a large polyp resection.
- Current medications include: rivaroxaban 20mg daily, lisinopril, acetaminophen, and loratadine
- **What instructions do you give him regarding his rivaroxaban prior to his colonoscopy?**

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PERIOPERATIVE MANAGEMENT WITH DOACS

- Usually hold 1-2 days prior to procedure

	Dabigatran		Apixaban		Edoxaban*		Rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. ≥12 h or 24 h after last intake)							
	Low risk	High risk	Low risk	High risk	Low risk	High risk	Low risk	High risk
CrCl ≥80 ml/min	≥24 h	≥48 h	≥24 h	≥48 h	No data	No data	≥24 h	≥48 h
CrCl 50–80 ml/min	**≥36 h**	**≥72 h**	≥24 h	≥48 h	No data	No data	≥24 h	≥48 h
CrCl 30–50 ml/min°	**≥48 h**	**≥96 h**	≥24 h	≥48 h	No data	No data	≥24 h	≥48 h
CrCl 15–30 ml/min°	Not indicated	Not indicated	**≥36 h**	**≥48 h**	No data	No data	**≥36 h**	**≥48 h**
CrCl <15 ml/min	No official indication for use							

- Consider heparin or LMWH bridge 24 hours after stopping DOAC if NPO post-procedure or will be extended break from DOAC

Doherty JU et al. J Am Coll Cardiol 2017;69(7):1392-1403

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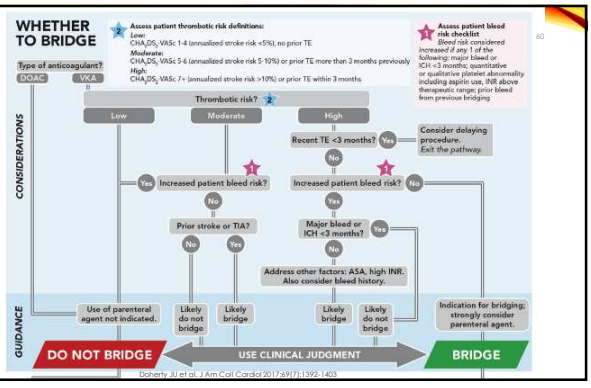
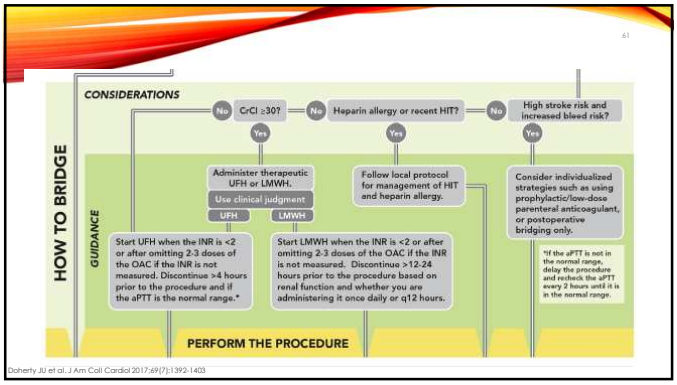


Doherty JU et al. J Am Coll Cardiol 2017;69(7):1392-1403



Doherty JU et al. J Am Coll Cardiol 2017;69(7):1392-1403

PERIOPERATIVE MANAGEMENT WITH DOACS

Bleeding risk classification and postoperative anticoagulation management

Bleeding Risk Category	Type of surgery or procedure	Suggested postoperative anticoagulation management		
		Warfarin	Low-dose LMWH	Therapeutic-dose LMWH
High (interruption of warfarin therapy recommended)	☐Heart valve replacement ☐Neurosurgical procedure (intracranial or spinal) ☐Prostatectomy or bladder surgery ☐Coronary artery bypass graft ☐Pacemaker or AICD placement ☐Major cancer surgery ☐Major vascular surgery (AAA repair, peripheral artery bypass) ☐Reconstructive plastic surgery ☐Renal or prostate biopsy ☐Bowel polypectomy (may be part of a colonoscopy) ☐Major orthopedic surgery ☐Other, describe:_____	Evening of the day after procedure (24 hrs)	24-48 hours after procedure (If moderate - high thrombotic risk, may start 24 hrs after procedure) (If low thrombotic risk, may start 48 hours after procedure)	48-72 hours after procedure (If moderate - high thrombotic risk, may start 48 hrs after procedure) (If low thrombotic risk, may start 72 hours after procedure)
Moderate (interruption of warfarin therapy recommended)	☐Major intraabdominal surgery ☐Major intrathoracic surgery ☐Other, describe:_____	Evening of the day of procedure (12 hrs)	Evening of the day of procedure (12 hrs)	24-48 hours after procedure (High thrombotic risk 24 hrs, low 48 hrs after)
Low (interruption of warfarin therapy recommended)	☐Most common cutaneous procedures ☐Laparoscopic cholecystectomy or hernia repair ☐Coronary angiography ☐Other, describe:_____	Evening of the day of procedure (12 hrs)	Evening of the day of procedure (12 hrs)	24 hours after procedure

REVERSAL OF DOACS

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NON-LIFE-THREATENING BLEED

- Withhold treatment
  - Hemostasis restored within 12-24 hours
  - Longer in CKD Stages 3-5
- Activated charcoal if within **3 hours** of last dose
- Mechanical pressure
- Surgical hemostasis
- Hemodynamic support
- Hemodialysis possible in dabigatran

LIFE-THREATENING BLEED

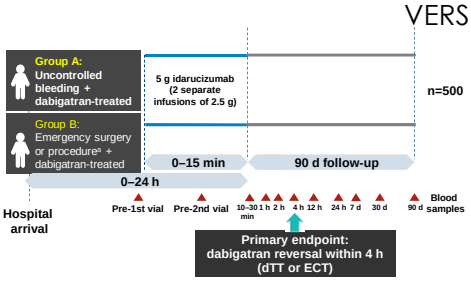
Repletion Agent	Clotting Factors Replaced	Dose(s) for Repletion of Specific OAC			
		Warfarin	Dabigatran	Rivaroxaban/Apixaban	Edoxaban
PCC3	II, IX, and X (inactivated)	25-50 units/kg	…	50 units/kg	
PCC4	II,VII, IX, and X (inactivated)	25-50 units/kg	25-50 units/kg	25-50 units/kg	50 units/kg
aPCC	II, IX, X (inactivated), and VII (activated)	500 units for INR <5 and 1000 units for INR ≥5	Up to 25 units/kg initially with subsequent doses based on response; 80 units/kg	Up to 25 units/kg initially; no data available in patients with active bleeding; 80 units/kg	
Building of PCC4	PCC3: II, IX, and X (inactivated); rFVIIa:VII (activated)	PCC3 50 units/kg (or fixed dose of 4000 units for an 80-kg patient) + rFVIIa 1 mg; if rFVIIa is not available, addition of a small dose of FFP (1-2 units) to PCC3 can be considered	No data available; possibly extrapolate doses from warfarin reversal	No data available; possibly extrapolate doses from warfarin reversal	
rFVIIa	VII (activated)	17.7-53.4 µg/kg	20-120 µg/kg	20-120 µg/kg	

66

AVAILABLE REVERSAL AGENTS

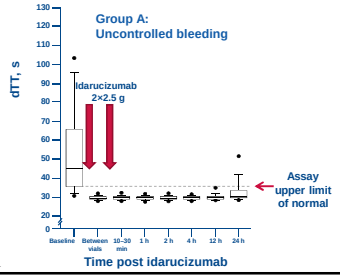
Direct Thrombin (Dabigatran)	Factor Xa (Rivaroxaban, Apixaban)	Universal
Idracizumab (Dabi-Fab) • Approved 2015 • Humanized monoclonal antibody • 350x binding affinity • Immediate onset • Short duration • No ADRs!	Coagulation factor Xa (recombinate),inactivated-zhzo(Andexxa) • Approved 2018 • Recombinant Factor Xa analogue • Binds to antithrombin • Approved for reversal of bleeding from rivaroxaban and apixaban only • Black boxed warning	Ciraparantag (PER 977) • Synthetic small molecule • Binds to DOACs and LMWH • Phase 2 Edoxaban • Phase 3

DABIGATRAN REVERSAL – REVERSE AD



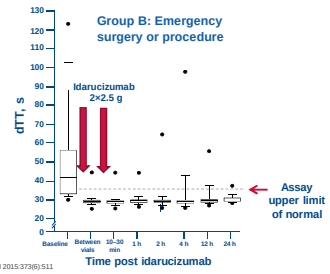
Pollack CV Jr. et al. N. Engl J Med 2015;373(6):511

REVERSE-AD – INTERIM RESULTS



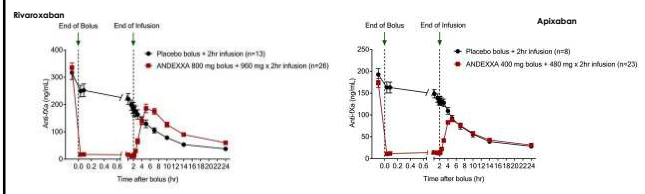
Pollack CV Jr. et al. N. Engl J Med 2015;373(6):511

REVERSE-AD – INTERIM RESULTS



Pollack CV Jr. et al. N. Engl J Med 2015;373(6):511

ANNEXA-R AND ANNEXA-A



https://globenewswire.com/news-release/2018/05/04/1496534/0/en/U-S-FDA-Approves-Portola-Pharmaceuticals-Andexxa-First-and-Only-Antidote-for-the-Reversal-of-Factor-Xa-Inhibitors.html. Accessed June 2018.

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SUMMARY: CHOOSING BETWEEN DOACS

- Advanced age: apixaban, rivaroxaban, edoxaban
- Renal impairment: apixaban if HD, edoxaban
- Liver disease: dabigatran or apixaban
- Obesity: Standard dose of any DOAC unless BMI >40 AND weight >120kg
- Once-daily regimen: rivaroxaban, edoxaban
- High bleeding risk: apixaban
- Concomitant 3A4 + P-gp Inhibitor: dabigatran

PRACTICAL CONSIDERATIONS FOR THE USE OF DOACS

Jessica W. Merrey, PharmD, MBA, BCPS, BCACP, BCGP

DOACs in Special Populations

Renal Impairment:

A 77-yo man is admitted to the hospital after a follow-up visit with his PCP (first in 12 months) for progressive renal disease that was found in routine blood tests. He was in his usual state of health until 2 weeks ago, when he starting to feel more fatigued than usual. No chest pain, orthopnea, edema, or dyspnea. His PMH is significant for HTN, T2DM, persistent AF, BPH, and CKD with a baseline Cr of 2.0mg/dL (eGFR 34mL/min). He has never been on dialysis in the past. His medications include amlodipine, lisinopril, metoprolol, atorvastatin, insulin glargine, and dabigatran 150mg BID. Upon hospital admission his vital signs are notable for irregularly regular heart rate 90 BPM, BP 147/89, normal oxygen saturation, BMI 31. Laboratory values show: SCr 5.3 mg/dL (eGFR 11.2 mL/min), BUN 105 mg/dL, K+ 7.0 mmol/L, and Hgb 10.5 g/dL. His EKG showed AF with controlled heart rate and peaked T-waves. He is given intravenous calcium gluconate, insulin, and dextrose followed by oral Kayaxelate. The remainder of work-up leads the team to determine this is all due to progression of his CKD. He begins hemodialysis after holding dabigatran for 24 hours. No bleeding is noticed post-procedure. After tolerating two hemodialysis sessions without complications, he is being prepared for discharge where he will continue dialysis as an outpatient. The team would like to resume anticoagulation for stroke prophylaxis. **What is the optimal anticoagulation strategy for this patient?**

Hepatic impairment:

A 71-yo woman with a history of cirrhosis due to fatty liver disease presents to the PCP as a discharge follow-up for hospitalization secondary to a syncopal event at home. Upon ED admission a CT w/contrast revealed bilaterlal pulmonary emboli. Her baseline INR was 2.1 so the team felt uncomfortable initiating warfarin therapy. She was discharged on enoxaparin 80mg (1mg/kg) twice daily. She brings her discharge summary to today's appointment. The BMP is WNL with SCr 0.8 mg/dL. Her WBC count is 7 x 10^9/L, Hgb 12 g/dL, and platelets are 95 x 10^9/L. Her AST is 45 IU/L and ALT is 57 IU/L. The remainder of the liver function testing is normal. At today's visit she expresses frustration at the twice daily injection schedule of her enoxaparin. **What therapeutic alternative can you offer her?**

Obesity:

A 76-yo woman with PMH of HTN, HPL, and BPD presented to the emergency department with a 4-day history of swelling and pain in her right leg. She denies SOB. After ultrasound of her leg she is diagnosed with an acute occlusive thrombosis of the common femoral vein. She has never had thromboembolism in the past, but her sister has a history of DVT. She denies smoking, trauma/surgery, and recent travel. Her weight is 124kg (BMI 53 kg/m^2), SCr 0.93mg/dL, D-dimer >4000 ng/mL. She was bridged to therapeutic warfarin (INR 2.0-3.0) and now, 2 months into her treatment expresses concern to you, her PCP, during a routine follow-up. She is tired of adhering to vitamin K restrictions and monitoring of warfarin. **What DOAC and dose do you recommend?**

Perioperative Bridging:

A 67-yo male attends an appointment with you for his annual physical. He has PMH significant for recurrent pulmonary embolism and DVT s/p IVC filter, HTN, colon polyps, and OA. You identify that he is due for his colonoscopy and send a referral to GI for scheduling. When he had his colonoscopy 5 years ago he had a large polyp resection. Current medications include: rivaroxaban 20mg daily, lisinopril, acetaminophen, and loratadine. **What instructions do you give him regarding his apixaban prior to his colonoscopy?**

Laboratory and Clinical Monitoring of Direct Acting Oral Anticoagulants: What Clinicians Need to Know

Susan E. Conway,[1]* Andrew Y. Hwang,[2] Charles D. Ponte,[3] and John G. Gums,[2]
[1]Department of Pharmacy: Clinical and Administrative Sciences, University of Oklahoma College of Pharmacy, Oklahoma City, Oklahoma; [2]Department of Pharmacotherapy and Translational Research, University of Florida College of Pharmacy, Gainesville, Florida; [3]Departments of Clinical Pharmacy and Family Medicine, West Virginia University Schools of Pharmacy and Medicine, Morgantown, West Virginia

The direct acting oral anticoagulants (DOACs), including dabigatran, rivaroxaban, apixaban, and edoxaban, have favorable pharmacokinetic and pharmacodynamic properties and equal or superior efficacy and an improved safety profile compared with warfarin. Noted shortcomings with DOACs are shorter half-lives requiring stricter adherence, lack of standardized laboratory monitoring, lack of anticoagulation reversal agents, and loss of routine coagulation monitoring leading to fewer patient–clinician interactions. This review addresses many of these limitations including monitoring of DOACs for efficacy and toxicity, an assessment of selected qualitative and quantitative tests, and development of monitoring strategies for special populations. Coagulation monitoring is generally recommended only in overdose situations, but once standardized assays are readily available, they could be helpful to ensure efficacy, assess bleeding, and aid in drug selection in a number of other patient scenarios. Coagulation tests that may provide qualitative assessment include activated partial thromboplastin time, prothrombin time, and thrombin time. Methods with potential utility for quantitative assessment of DOACs include plasma drug concentrations, ecarin clotting time, dilute thrombin time, and anti–factor Xa concentrations. Noncoagulation laboratory monitoring should include serum creatinine, liver function tests, and complete blood counts. Clinical monitoring of the DOAC-treated patient should include routine assessment of adherence, bleeding risks, and drug interactions. Frequency of monitoring should be 1–3 months after initiation and then at least every 6 months, with more frequent follow-up (i.e., 3 months) based on patient specific characteristics such as age, renal impairment, hepatic impairment, and concomitant drug therapy. The authors provide a practical tool to assist in DOAC monitoring and recommend that pharmacists collaborate with physicians in selecting appropriate patients and tailoring patient-specific monitoring plans.

Key Words dabigatran, apixaban, edoxaban, rivaroxaban, direct acting oral anticoagulant, monitoring.
(Pharmacotherapy 2017;37(2):236–248) doi: 10.1002/phar.1884

Oral anticoagulation has been the keystone for the management of venous thromboembolism (VTE) and atrial fibrillation (AFib) for decades. The vitamin K antagonist warfarin has been considered the gold standard anticoagulant to manage these conditions since its approval in the United States in 1954. Warfarin remains the most prescribed anticoagulant in the world.[1] Warfarin inhibits vitamin K epoxide reductase, which ultimately inhibits the synthesis of the vitamin K–dependent clotting factors II (FII), FVII, FIX, and FX. Advantages of warfarin include its proven utility and low cost.

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Disadvantages of warfarin include a narrow therapeutic index, numerous drug interactions, interpatient and intrapatient dose variability, and the need for routine international normalized ratio (INR) monitoring and its attendant costs.[2] The efficacy of warfarin is linked to the need to maintain an INR within a narrow therapeutic range of 2–3 for most approved indications. A subtherapeutic INR offers little protection from recurrent thromboembolism, and a supratherapeutic INR (> 4) increases the risk of bleeding. A national assessment of warfarin therapy for stroke prevention in AFib evaluated 138,000 patients in the United States and found the mean time in the therapeutic range was only 53.7%.[3] In a recent multicenter retrospective cohort study of 5062 outpatients with AFib, 72.6% of patients were at high stroke risk (CHA_2DS_2-VASc [congestive heart failure or left ventricular systolic dysfunction; blood pressure consistently >140/90 mm Hg or treated hypertension on medication; age ≥75 yrs; diabetes mellitus; prior stroke or TIA or thromboembolism; vascular disease such as peripheral artery disease, myocardial infarction, aortic plaque; age 65–74 yrs; sex category, i.e., female sex] score > 1), yet only 46.9% of patients were prescribed any thromboprophylaxis (including warfarin and aspirin).[4] These findings are in agreement with a study of warfarin underutilization and the associated economic consequences.[5]

Given the challenges with warfarin dosing and monitoring, the search began for alternative anticoagulants with rapid onset of action, acceptable pharmacokinetic/pharmacodynamic properties, fixed dosing for all patients, fewer drug, disease, and dietary interactions, easy reversibility, a good safety profile, and no requirement for monitoring. The direct acting oral anticoagulants (DOACs), including direct thrombin inhibitors (dabigatran) and FXa inhibitors (apixaban, edoxaban, rivaroxaban), exhibited the characteristics deemed advantageous compared with warfarin. It is well established that DOACs have equal or superior efficacy and an improved safety profile compared with warfarin in the treatment of AFib and VTE.[6] However, ongoing DOAC concerns include their shorter duration of action (requiring strict adherence), limited laboratory monitoring tests, no specific antidote (except dabigatran), dose reduction or avoidance in renal and hepatic impairment, less flexibility in dosing, drug interactions that may preclude use, and higher medication costs. The purpose of this review is to address many of the limitations of DOACs including laboratory and clinical monitoring for efficacy and safety in adult patients as well as to identify monitoring strategies for special populations.

Monitoring the DOACs

An important advantage of the DOACs compared with warfarin is that routine anticoagulation monitoring is not needed due to the DOACs' pharmacodynamics and pharmacokinetic predictability.[7] No routine anticoagulation monitoring is advantageous from both a patient convenience and satisfaction perspective. However, the lack of routine monitoring generally means fewer patient–clinician interactions including compromising routine assessment of anticoagulant adherence.[8] Since most patients on DOACs are not monitored in the anticoagulation clinic setting used for warfarin, DOACs monitoring may be limited to an assessment of adherence on prescription refilling by the community pharmacist and to an assessment of renal function by the prescribing physician. The less stringent monitoring requirements for DOACs may lead to a loss of income for many pharmacist-run anticoagulation clinics that provide warfarin monitoring and management. The inability to gauge a safe and effective anticoagulation dose may result in a loss of peace of mind for both providers and patients.

While routine monitoring is not required, there are many situations when and populations for whom clinicians would like to assess the precise anticoagulant effect for the refinement of treatment decisions.[8] The potential indications for coagulation testing include emergency situations (i.e., trauma), urgent surgery, urgent invasive procedures, major bleeding, overdose/attempted suicide, acute thrombosis, renal failure, liver failure, adherence verification, and potential drug–drug interactions.[8, 9] Coagulation monitoring can be performed to ensure efficacy (e.g., history of nonadherence, drug interactions with cytochrome P450 and p-glycoprotein inducers), assess bleeding potential (e.g., renal failure, overdose), and aid in drug selection decisions (e.g., to determine if drug failure occurred in patients with acute thrombosis). The manufacturers' recommendation is that coagulation monitoring is not required outside of overdose situations.[10–13] However, one author has suggested that unmonitored DOAC therapy should be only for relatively young and healthy patients, whereas patients 75 years of age and

older should have coagulation laboratory monitoring 5–10 times per year.[14] The European Heart Rhythm Association (EHRA) guidelines recommend clinical assessment and noncoagulation monitoring every 1–6 months for patients taking DOACs but do not recommend any monitoring of coagulation assays.[15] The American College of Chest Physicians has not made a recommendation for DOAC monitoring.[16]

The clinical studies of DOACs were conducted with fixed doses and did not evaluate clinical outcomes based on drug concentrations or coagulation assays.[16] No evidence-based recommendations for drug concentration measurements, coagulation tests, assay standardization/calibration, or target therapeutic ranges have been established for DOACs. Therefore, given this lack of clinical data, neither the dose nor dosing interval should be altered at this time in response to changes observed in coagulation tests.[8, 15] In addition, there are no established thresholds for any coagulation tests where surgery or invasive procedures can be safely performed without elevated bleeding risk.[15]

Laboratory Coagulation Monitoring

DOACs have varying effects on coagulation assays (Table 1).[7] The clinical utility of many of the coagulation tests is still being determined. Dose individualization for various populations may occur once high-quality tests with established therapeutic ranges become routinely available. Identification of specific assay thresholds when increased bleeding risk is observed may help guide management, particularly in overdose situations. No studies have evaluated if drug concentration measurement or dose adjustment based on laboratory coagulation parameters affects clinical outcomes (bleeding or thromboembolic complications) during chronic therapy.[15] Information on the clinical utility of coagulation assays largely comes from ex vivo studies using plasma from dabigatran-treated patients or healthy volunteers and in vitro studies with dabigatran added to plasma samples.[17]

The activated partial thromboplastin time (aPTT), prothrombin time (PT), and thrombin time (TT) are widely available tests with rapid turnaround times, but they have poor sensitivity and specificity and lack optimal dose–response relationships for monitoring DOACs.[8, 9] For patients taking DOACs, aPTT, PT, and TT should be used only as qualitative tests to confirm if there is an anticoagulant effect. Plasma drug concentrations, ecarin clotting time (ECT), dilute thrombin time (dTT), and anti-FXa concentrations are generally less accessible and may require specialized laboratories, which would result in slower turnaround time. Yet, ECT, dTT, and anti-FXa concentrations are preferred methods as they have potential utility as quantitative tests to measure DOAC intensity.[9] The dilute PT, HepTest, and prothrombinase-induced clotting time (PiCT) have been used investigationally as quantitative measures of DOAC therapy but are not widely available.[9] When testing is performed, it is important to record when the DOAC was administered relative to the time of the blood draw. The maximum effect on the coagulation test will be at the maximum plasma concentration of the drug.[15] Plasma concentrations are at a peak 2 hours after dabigatran, 2–4 hours after rivaroxaban, 1–4 hours after apixaban, and 1–2 hours after edoxaban ingestion. Trough concentrations occur at 12 hours after ingestion of dabigatran and apixaban and 24 hours after ingestion of edoxaban and rivaroxaban.[15] Specific coagulation laboratory tests and their utility with DOAC monitoring are discussed herein.

Activated Partial Thromboplastin Time

The aPTT measures the activity and presence of FII, FV, and FVIII/FXII, and any anticoagulant that affects these coagulation factors can prolong aPTT.[7]

Direct Thrombin Inhibitors

At therapeutic doses of dabigatran, aPTT is prolonged and provides an approximation of anticoagulation activity.[10] The aPTT is somewhat more sensitive to dabigatran with minimal variability compared with PT.[7, 8] A regression analysis showed an aPTT range of 46–54 seconds corresponded to a therapeutic dabigatran concentration of 90–180 ng/ml. The aPTT demonstrated modest correlation with dabigatran concentration (correlation coefficient of 0.80).[18] In patients receiving chronic dabigatran therapy at therapeutic dosing (150 mg twice/day), the median peak aPTT was approximately 2-fold that of control, and the 12-hour median trough aPTT was 1.5-fold that of control with <10% of patients having aPTT values 2-fold greater than control.[19] Dabigatran affects aPTT in a curvilinear manner with insensitivity at supratherapeutic concentrations.[7] Therefore, the

Table 1. Summary of Laboratory Coagulation Monitoring Tests for DOACs[7–27]

	Direct Thrombin Inhibitors (Dabigatran)		Factor Xa Inhibitors (Apixaban, Edoxaban, Rivaroxaban)	
Assay	Sensitivity	Utility	Sensitivity	Utility
Activated partial thromboplastin time	Low, but better than PT	Qualitative assessment if verify sensitivity, but normal does not rule out effect	Low	Not useful
Chromogenic anti–factor Xa assay	N/A	N/A	High	Quantitative assessment if calibrated to specific anticoagulant
Dilute thrombin time (dTT)	Sensitive	Quantitative assessment	N/A	N/A
Ecarin clotting time (ECT)	Sensitive	Quantitative assessment	N/A	N/A
HepTest	Sensitive	Quantitative assessment	Sensitive	Quantitative assessment
Plasma drug concentration	Sensitive	Quantitative assessment	Sensitive	Quantitative assessment
Prothrombin time (PT)	Low	Not suitable in therapeutic concentrations Qualitative in supratherapeutic doses.	Low	Qualitative assessment if calibrated reagents
Prothrombinase-induced clotting time (PiCT)	Low	Still being determined	Sensitive except at low doses	Still being determined
Thrombin time (TT)	Highly (over) sensitive	Qualitative assessment only	N/A	N/A

aPTT may underestimate high concentrations, posing a significant problem in overdose assessment.[8, 15] When a more sensitive assay (e.g., ECT, dTT) is unavailable, the aPTT may provide qualitative assessment of dabigatran.[9, 15, 20] Because sensitivity of different assays vary, checking the sensitivity of aPTT to dabigatran at each institution is recommended.[15, 18] A normal aPTT does not exclude clinically relevant dabigatran activity.[20]

FXa Inhibitors

All the FXa inhibitors prolong aPTT but at a low sensitivity.[7] The aPTT is affected to a varying extent based on the individual FXa inhibitor and by different reagents.[8] Rivaroxaban has been reported to prolong the aPTT dose-dependently.[11] However, another study has suggested a nonlinear dose response with the most prominent effect at supratherapeutic concentrations.[21] At therapeutic doses, both apixaban and edoxaban caused a small prolongation of aPTT but had a high degree of variability.[12, 13] The aPTT should not be used for any meaningful evaluation (qualitative or quantitative) of FXa inhibitors because of insensitivity, variability of reagents, lack of standardization across laboratories, and paradoxical response at low concentration.[15, 20]

Chromogenic Anti-FXa Assay

For the anti-FXa assay, FXa is added to plasma containing a FXa substrate (e.g., heparin) that is tagged with a chromophore. When the chromophore is cleaved by FXa, a color change results that is directly proportional to the concentration of FXa present in the assay. Each of these standard assays must be calibrated for a specific anticoagulant and cannot be used to assess the anticoagulation effect of other agents not previously calibrated.[7] While the chromogenic anti-FXa assay is commonly available, most health care settings lack a standardized assay calibrated for the individual DOACs.[22]

Direct Thrombin Inhibitors

No effect is expected on the anti-FXa assay from dabigatran based on the mechanism of direct thrombin inhibition.

FXa Inhibitors

The chromogenic anti-FXa assay for the anticoagulant effects of rivaroxaban, edoxaban, and apixaban is precise, sensitive, and accurate with a concentration-dependent inhibition of FXa activity (correlation coefficient of 0.9669).[7, 11, 12] Low and high plasma concentrations can be

measured with acceptable interlaboratory precision.[15] Clinical trials have shown trough ranges of 6–239 mcg/L for rivaroxaban, 1.4–4.8 IU/ml for apixaban, and 0.05–3.57 IU/ml for edoxaban.[15] Chromogenic anti-FXa assay is a preferred method for quantitative assessment of anticoagulant activity when calibrated to rivaroxaban, apixaban, and edoxaban.[8, 9, 15, 20] In the absence of a calibrated test, a standard chromogenic anti-FXa assay calibrated to unfractionated or low molecular weight heparins may be used for qualitative assessment to measure the presence or absence of anticoagulant effect.[20]

Dilute Thrombin Time

The dTT is a coagulation test that measures coagulation by diluting plasma to make a more useful test than the overly sensitive TT. Various assays are available, including Hemoclot, Technoview, and Hemosil.[9]

Direct thrombin inhibitors

Dabigatran prolongs the dTT in a linear dose relationship and can accurately predict anticoagulation intensity.[15] The dTT demonstrated a high correlation with dabigatran concentrations when used with both in-house and Hemoclot-derived dabigtran calibrators (correlation coefficient of 0.9981 and 0.9982, respectively).[23] When available, the dTT is suitable for quantitative assessment of the magnitude of anticoagulant intensity with dabigatran.[15, 20] A normal dTT indicates no clinically relevant anticoagulation from dabigatran.[16]

FXa Inhibitors

No effect is expected on dTT from this drug class based on the mechanism of direct FXa inhibition.

Ecarin Clotting Time

The ECT directly measures thrombin generation. Coagulation is initiated with ecarin, a type of snake venom, which in turn activates prothrombin to stimulate the thrombin precursor meizothrombin.[7]

Direct thrombin inhibitor

At recommended therapeutic doses, dabigatran prolongs ECT.[10] ECT has a concentration-dependent, linear response in dabigatran-treated patients[7] and is sensitive and precise with a correlation coefficient of 0.92 with dabigatran plasma concentrations.[8, 9] In the RE-LY trial, the median trough ECT was 63 seconds (10th–90th percentile, 44–103) in patients receiving the dabigatran 150 mg twice/day. The ECT is a useful test for quantitative assessment of the magnitude of anticoagulant activity from dabigatran.[10] An ECT near baseline has been associated with no clinically relevant dabigatran effect.[15]

FXa Inhibitors

The mechanism of direct FXa inhibition with this drug class makes ECT an undesirable assay.[7] Rivaroxaban has no effect on ECT.[7, 8]

HepTest (a Clot-Based Anti-FXa Assay)

The HepTest measures the inhibition of exogenous FXa and is based on the ability of heparin to catalyze the inactivation of FXa.[7] The HepTest assay has been used in clinical trials for rivaroxaban and apixaban. A newly developed modified HepTest STAT uses only one incubation step and demonstrated a higher sensitivity to fondaparinux and low molecular weight heparin than the original HepTest.

Direct Thrombin Inhibitors

An ex vivo plasma study on dabigatran-treated patients has an acceptable correlation between dabigatran and the modified HepTest STAT (correlation coefficient of 0.72 and 0.80 for two chromogenic dabigatran assays).[23]

FXa Inhibitors

Rivaroxaban and apixaban prolong the HepTest in a dose-dependent, incremental, and sensitive manner.[7, 11, 23] In patients treated with FXa inhibitors, an ex vivo plasma study found a high correlation of the modified HepTest STAT with rivaroxaban and apixaban (correlation coefficient of 0.95 and 0.93 for rivaroxaban and 0.84 and 0.87 for apixaban on 2 chromogenic assays each).[24] More testing is needed to validate the HepTest.

Plasma Drug Concentrations

Plasma concentrations can be measured for all four DOACs (dabigatran, apixaban, edoxaban,

and rivaroxaban) using liquid chromatography–tandem mass spectrometry.[17]

Direct Thrombin Inhibitors

Based on pharmacokinetic studies, dabigatran 150 mg twice/day is expected to have a median steady state peak and trough concentrations of 184 and 90 ng/ml, respectively.[17] In the PETRO trial, patients receiving dabigatran 150 mg twice/day had a peak dabigatran concentration of 64–443 ng/ml and trough of 31–225 ng/ml (range 5th–95th percentile).[24]

FXa Inhibitors

Based on FXa inhibitor pharmacokinetic studies, the mean peak and trough concentrations at steady state for rivaroxaban 20 mg/day were 274 and 129 ng/ml, respectively, and for and apixaban 5 mg twice/day, 30 and 50 ng/ml, respectively.[17]

Prothrombin Time/International Normalized Ratio

PT is a measure of the activity of the clotting factors FI, FII, FV, FVII, and FX. The INR, which is widely used to monitor warfarin therapy, represents a standardization of the PT used to adjust for the varying sensitivities of the thromboplastin agents through a simple calculation.[7, 8] The INR system cannot be recommended for assessing DOAC therapy because the International Sensitivity Index (ISI) used as a correction factor for thromboplastin was developed specifically for vitamin K antagonists.[8] A determination of an ISI is needed for each individual DOAC.[25]

Direct Thrombin Inhibitors

Dabigatran prolongs PT but has poor sensitivity and response that varies with the thromboplastin used.[7, 9] With clinically relevant doses, little effect has been observed on PT, resulting in a very flat dose–response curve.[15] One study found that INR did not increase above 1.2 at both peak and trough dabigatran concentrations.[26] Therefore, PT is not suitable for quantitative assessment. Supratherapeutic dabigatran concentrations have more pronounced effects on PT. In addition, multiple case studies reported false elevations in the point-of-care INR compared with traditional laboratory findings.[7]

FXa Inhibitors

The different FXa inhibitors affect the PT to varying extents. The FXa inhibitors demonstrate concentration-dependent PT prolongation. At therapeutic doses, rivaroxaban has a relatively weak effect on PT, but there is a more pronounced effect at supratherapeutic concentrations.[15] The sensitivity of the different assays varies greatly depending on thromboplastin reagent, and it is recommended to check the sensitivity of PT at each institution.[7, 15] If more sensitive testing is not available, the PT may provide some qualitative assessment of rivaroxaban anticoagulation, preferably with specific calibrated reagents.[9, 15]However, a normal PT does not exclude a clinically relevant anticoagulant effect.[15, 20] At therapeutic doses of both apixaban and edoxaban, the increase in PT is small and subject to a high degree of variability.[12, 13] Most PT assays are not sensitive for apixaban, and there is a lack of evidence and a presumed insensitivity for edoxaban. Therefore, the PT should not be used for assessing apixaban or edoxaban.[15, 20] The conversion of PT to INR does not correct for this variation.[15] The current INR system is unreliable and not recommended for use with FXa inhibitors.[8, 15, 20] Caution is required in the interpretation of INRs when transitioning from DOACs to warfarin, because values may be increased.[15]

Prothrombinase-Induced Clotting Time

The PiCT assay is composed of FXa, phospholipids, and an enzyme that activates FV on addition of plasma to the assay.[7]

Direct Thrombin Inhibitors

A concentration-dependent relationship has been demonstrated with PiCT and dabigatran but lacks acceptable sensitivity.[27]

FXa Inhibitors

A concentration-dependent relationship and sensitive response has been demonstrated with PiCT and rivaroxaban (correlation coefficient = 0.9663).[7] However, a paradoxical effect (e.g., low doses of rivaroxaban showed an unexpected shortening of the PiCT) suggests some refinements would be necessary before PiCT could be useful for assessing anticoagulant activity.[8] Apixaban and edoxaban have not been

studied with PiCT but may work similarly to rivaroxaban.[7]

Thrombin Time

The TT measures activity of thrombin in plasma.[7]

Direct Thrombin Inhibitors

At recommended therapeutic doses, dabigatran prolongs TT.[10] The TT has a linear, concentration-dependent response with dabigatran (correlation coefficient of 0.86).[7, 9] TT is highly sensitive and may be oversensitive.[8, 9] The TT is not suited for quantitative assessment in the doses expected with clinical use. Because TT is very sensitive to the presence of dabigatran, a normal TT excludes even low concentrations of dabigatran.[15]

FXa Inhibitors

The mechanism of direct FXa inhibition with this drug class makes the TT an undesirable assay. FXa inhibitors have been shown to have no effect on TT.[7]

Additional Coagulation Assays

Diluted PT (dPT) is being investigated as a way to increase sensitivity of PT.[8] Prolongation of dPT in a concentration-dependent manner has been shown for dabigatran, rivaroxaban, and edoxaban in animal models, but more testing is needed to validate the dPT for clinical use.[7] Coagulation assays that are in early-stage clinical testing include thrombin generation assay, activated clotting time, dilute Russell viper venom time, and chromogenic anti-FIIa assay.[7, 8, 15]

Laboratory Safety and Clinical Monitoring

Given the complexities involved with quantitative monitoring of DOACs, monitoring through clinical laboratory methods may offer a more feasible approach to routine follow-up care. Clinical laboratory monitoring involves the routine measurement of serum creatinine (SCr), liver function, or complete blood count (CBC) to guide appropriate anticoagulation therapy and ensure drug safety. Clinicians should also monitor adherence, evaluate comorbid disease states, and analyze potential drug–drug interactions. Appropriate monitoring may provide a surrogate mechanism for assessment of DOAC therapy, thereby bypassing the need for coagulation assays.

The optimal monitoring frequency for DOAC therapy is not known. In phase 3 studies, follow-up visits were relatively frequent, ranging from monthly to every 4 months.[28–31] As such, the majority of patients had routine contact with health care professionals throughout the trials. The EHRA recommends regular follow-up visits (preferably every 3 months) during the initiation of DOAC therapy to assess and review appropriateness of therapy.[15] A recently published practice tool endorsed by Thrombosis Canada, the Canadian Stroke Consortium, the Canadian Cardiovascular Pharmacists Network, and the Canadian Cardiovascular Society suggests follow-up for reassessment of therapy at least every 6 months and every 3–6 months for high-risk patients (e.g., renal and/or hepatic impairment, elderly, concomitant interacting drugs).[32] Importantly, the appropriate monitoring frequency will depend on individual patient-related factors, including renal function, concomitant drug therapy, comorbidities, and age. We provide a practical tool to assist in DOAC monitoring (Figure 1).

Laboratory Safety Monitoring

Dose Adjustment in Renal Insufficiency

Renal impairment is an important risk factor for bleeding,[33] and the incidence of ischemic stroke or VTE may be higher in patients with renal dysfunction (CrCl < 60 ml/min) who are not taking anticoagulation therapy.[34] Thus, routine monitoring of renal function while on a DOAC is necessary to prevent complications from thromboembolism and bleeding. Because all DOACs are partially eliminated through the kidneys, documenting baseline renal function is necessary prior to initiating therapy. Thereafter, the routine monitoring of SCr will ensure appropriate dosing and prevent bleeding complications. Frequency of monitoring for renal function depends on individual patient factors as well as the specific anticoagulant, because the degree of renal elimination varies among the different DOACs.

Of the DOACs, dabigatran has the highest rate of renal elimination; with nearly 80% of the active metabolite eliminated through glomerular filtration.[35] Rivaroxaban (67%), apixaban (33%), and edoxaban (50%) are also eliminated via

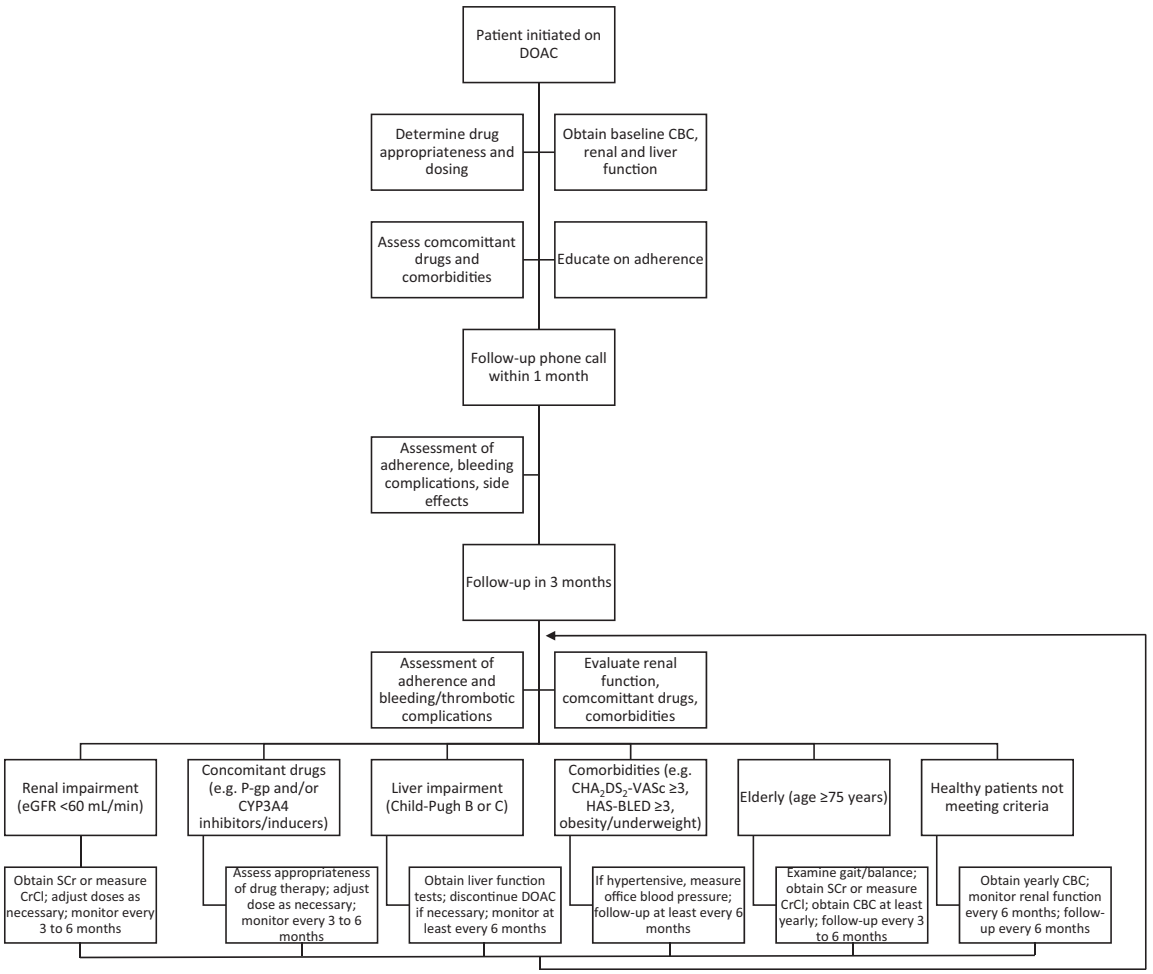

Figure 1. Practical Tool for DOAC Monitoring.

renal mechanisms. Therefore, fluctuations in renal function can potentially lead to substantial bleeding complications. Dosing of DOACs is based on the estimated creatinine clearance (CrCl) or estimated glomerular filtrate rate (eGFR), which is dependent on age, body weight, gender, and SCr. With aging, the measured CrCl tends to worsen and may not closely correlate with estimated eGFR; therefore, increased monitoring and measurement of a 24-hour CrCl in the elderly is recommended.[36] We obtain baseline SCr for all patients beginning a DOAC. A baseline urine analysis may also provide insight into the patient's renal function. Given the high rate of renal elimination of dabigatran, high-risk patients (e.g., elderly or frail individuals) may require more frequent renal function monitoring. Because edoxaban should be avoided in patients with a renal function of CrCl > 95 ml/min due to higher ischemic stroke rates compared with warfarin and lower edoxaban concentrations, baseline renal function may help determine appropriateness of therapy in select patients.

The EHRA recommends frequent assessment of renal function while on DOAC therapy, especially in patients taking dabigatran or those who have a greater likelihood of renal impairment (e.g., elderly, concomitant nephrotoxic drugs).[15] Assessing renal function every 6–12 months may be beneficial in patients who have or are at risk of developing renal impairment.[32, 35] However, limited data exists regarding whether an every 6–12 month frequency has an impact on clinical outcomes. Interestingly, current data indicates that routine monitoring of renal function in clinical practice is rare, suggesting that additional efforts may be required to improve clinician adherence to monitoring renal function.[37] Despite little evidence to support a specific monitoring frequency, we recommend that renal function (SCr and eGFR) should be monitored at least every 6 months. In addition, we recommend renal function monitoring more frequently

(every 3–6 months) in patients with renal impairment (CrCl < 60 ml/min) or during an acute illness that may transiently worsen renal function (e.g., infections, acute heart failure).[15, 32]

Dosing in Hepatic Impairment

With the exception of dabigatran, the DOACs undergo extensive hepatic metabolism. Pharmacokinetic studies with rivaroxaban, apixaban, and edoxaban have shown increased drug exposure in patients with hepatic impairment.[38, 39] Depending on the drug, DOACs are contraindicated in patients with moderate to severe hepatic impairment, defined as Child-Pugh B–C. Therefore, monitoring liver function tests (e.g., aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin, alkaline phosphatase, PT, and INR) and calculation of Child-Pugh scores at baseline are warranted to ensure appropriate initial therapy selection. We suggest periodic monitoring of liver function (e.g., ALT, AST, total bilirubin, and alkaline phosphatase) to monitor for any significant changes in hepatic function. The frequency of testing varies depending on patient-related factors, concomitant medications, and comorbidities. Generally healthy patients may only require measurement of hepatic function yearly; whereas patients at risk for hepatic dysfunction may require more frequent monitoring (every 6 months).

Assessing New Bleeding Risks

Regardless of the choice of anticoagulant, their use has been associated with an increased risk of bleeding. Drug interactions may also place high-risk patients (e.g., elderly, patients with renal dysfunction) at increased bleeding risk. In high-risk patients, the HAS-BLED (hypertension, abnormal renal and liver function, stroke, bleeding, labile INRs, elderly, and drugs or alcohol) risk score may be a useful tool for the evaluation of bleeding risk.[40] An assessment should be performed during every follow-up visit to identify potential risks and avoid bleeding complications. We suggest obtaining a baseline CBC during initiation of the DOAC and at regular intervals (at least yearly) to assess any trends in hemoglobin/hematocrit. In addition, more frequent measurement of the CBC should be considered as necessary, especially in patients with active bleeding symptoms.

Clinical Monitoring

Adherence

Routine assessment of DOAC adherence is important because current coagulation assays may not reliably measure therapeutic anticoagulation, unlike the measurement of the INR with warfarin therapy. Because of the shorter half-life of the DOACs compared with warfarin, missing even one dose may increase the risk of thromboembolic events. Thus, adherence should be evaluated at every follow-up visit. Adherence can be monitored by pill counts, intensive interviewing, and use of an adherence questionnaire (e.g., Morisky Medication Adherence Scale).

Dabigatran and apixaban are administered twice daily, whereas rivaroxaban (except for the initiation of acute VTE treatment) and edoxaban are administered once daily. A once-daily regimen may be associated with higher adherence rates compared with a twice-daily regimen.[41, 42] However, because the half-lives are similar among the various DOACs, the pharmacological impact of one missed dose may be more detrimental with a once-daily regimen than with a twice-daily regimen. Further, one extra dose with a once-daily regimen provides a much higher peak concentration than one extra dose with a twice-daily regimen, potentially increasing the risk of bleeding.[43] We recommend a more stringent assessment of adherence with rivaroxaban and edoxaban compared with dabigatran or apixaban.

Adverse effects tend to affect adherence. The most commonly reported reason for discontinuation of dabigatran was gastrointestinal side effects, which tend to occur early in the course of therapy.[44] We suggest avoiding or cautiously initiating dabigatran in patients with gastroesophageal reflux disease or a history of peptic ulcer disease. Alternatives include rivaroxaban, apixaban, and edoxaban, which are not associated with dyspepsia. Dyspepsia may be alleviated if doses of dabigatran are taken with food or with acid-suppressing therapy (e.g., proton pump inhibitors, H_2-antagonists).

Adherence rates appear to improve with appropriate selection of patients and through pharmacist-led monitoring programs.[45] We encourage pharmacists to collaborate with physicians in selecting appropriate patients for DOAC therapy and tailoring patient-specific monitoring plans. Incorporating DOACs into present-day anticoagulation clinics may be the initial step in

optimizing the pharmacist's role in providing monitoring services in a heterogeneous anticoagulation population.

Assessing Drug–Drug Interactions

Antiplatelet agents, including aspirin, and nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with an increased bleeding risk, and the use of these drugs is an independent risk factor for bleeding events.[46–48] Therefore, avoidance or limiting treatment with these medications is recommended when used concurrently with DOACs. If concurrent therapy must be continued, we suggest closer follow-up and monitoring (every 3–6 months) to minimize the bleeding risk.

Drug–drug interactions should also be considered during therapy with DOACs. All DOACs are substrates of P-glycoprotein (P-gp), and inhibition of this enzyme may increase bleeding risk. In addition, the FXa inhibitors (i.e., rivaroxaban, apixaban, and edoxaban) also undergo metabolism through the cytochrome P450 (CYP) pathway, namely via CYP3A4 (Table 2). In certain cases (i.e., dabigatran and dronedarone for AFib), the dose of the DOAC could be reduced to compensate for the potential interaction, which may especially be important in patients with renal impairment (CrCl 30–50 ml/min). If an interacting medication is necessary, we suggest increased monitoring (at least every 3–6 months) during concurrent use to assess any implications on clinical outcomes. Assessment of any potentially interacting drugs should also be performed at every follow-up visit.

Concomitant Disease States and Drug Therapy

Hypertension, a common comorbidity in patients with nonvalvular AFib, is a significant risk factor for intracerebral hemorrhage. Treatment of hypertension decreases the risk of intracranial bleeding in patients on concurrent therapy with antithrombotics.[49] Thus, we suggest routine measurement of blood pressure during each office monitoring visit. Patients should also be encouraged to regularly monitor blood pressure at home.[32] During follow-up visits, we also suggest regular examination of gait and balance to determine the need for any assistive devices for prevention of falls.[32]

Additional factors have also been associated with an increased risk of bleeding with DOACs, including advanced age, prior stroke, diabetes, and history of gastrointestinal bleeding.[47, 50] These variables are included in the CHA_2DS_2-VASc and HAS-BLED risk scores, which are calculated to assess the risk of thromboembolism and major bleeding, respectively. Several post-hoc analyses have found that higher $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores were associated with major bleeding events with DOACs.[40, 51–53] Patients with high $CHADS_2$ or CHA_2DS_2-VASc scores also generally have high HAS-BLED scores.[40, 53] Therefore, we suggest that patients with CHA_2DS_2-VASc and/or HAS-BLED scores of 3 or higher undergo monitoring at least every 6 months to ensure thromboembolism and bleeding complications are minimized.

Concomitant drug therapy that increases the risk of renal dysfunction may require more frequent monitoring (every 3–6 months), especially in patients at high risk for renal impairment. The medications potentially impacting renal function include loop diuretics, thiazide-like diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, metformin, and NSAIDs (Table 2). Patients taking concomitant medications that may impart renal function may benefit from closer monitoring of therapy to identify significant changes in renal function. Because DOACs are highly dependent on renal elimination, continual assessment of renal function may help prevent bleeding complications.

Special Populations

Elderly

The incidences of AFib and VTE increase with advancing age.[54, 55] In addition, older patients tend to be at a higher risk for renal and hepatic impairment, which increase the risk of bleeding while on oral anticoagulants. Concomitant medications, dehydration, and variable renal elimination increase bleeding risk in elderly patients treated with DOACs. Because bleeding complications tend to be more detrimental in the elderly population, routine monitoring of DOAC therapy is imperative. Elderly patients (aged 75 years and older) at high risk should have their renal and/or hepatic function monitored regularly and may require more frequent (every 3–6 months) follow-up visits to prevent any potential complications while on DOACs.[32]

Another concern with elderly patients on anticoagulants is the risk of falls, which have been

Table 2. Monitoring Frequency Recommendations for Selected Drug–Drug Interactions

	Mechanism	Direct Thrombin Inhibitor (Dabigatran)	Factor Xa Inhibitors (Rivaroxaban, Apixaban, Edoxaban)
Verapamil, quinidine	P-gp inhibitor	3–6 months; dose adjustment based on renal function	At least 6 months; dose adjustment with edoxaban
Amiodarone	P-gp inhibitor	3–6 months	At least 6 months
Dronederone	P-gp and CYP3A4 inhibitor	3–6 months; dose adjustment based on renal function	3–6 months
HIV protease inhibitors	CYP3A4 inhibitor	6 months	3–6 months; dose adjustment with apixaban
Carbamazepine, phenytoin, phenobarbital	P-gp and CYP3A4 inducer	3–6 months	3–6 months
Antiplatelets, NSAIDs	Pharmacodynamic interaction to increase GI bleeding	At least 6 months	At least 6 months
Loop diuretics, thiazide-like diuretics, ACEI, ARB	Potentially increase risk of renal impairment	3–6 months	3–6 months

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; NSAID, nonsteroidal anti-inflammatory drug; P-gp, P-glycoprotein.

associated with an increased risk of morbidity and mortality.[56] Importantly, patients at high risk for falls are also more prone to higher rates of ischemic events.[57] Avoidance of risk factors for falls is important to prevent devastating complications such as an intracranial hemorrhage. Because elderly patients are often taking multiple medications, a thorough medication review should be performed during follow-up visits to identify and limit drugs that may increase the risk of falls. Close monitoring during DOAC therapy is important, because DOAC-associated bleeding in elderly patients may be more challenging to manage and treat compared with younger patients.[58]

Progressive development of anemia has also been observed in the elderly population during treatment with DOACs.[59] Though the cause is unknown, occult gastrointestinal bleeding could be a contributing factor. Therefore, patients should be advised to avoid medications that increase the risk for gastrointestinal bleeding (e.g., NSAIDs, aspirin). Routine assessment of the CBC (at least yearly) should be performed during follow-visits.[59]

Obesity and Underweight

The prevalence of obesity, defined as a body mass index (BMI) greater than 30 kg/m^2, has steadily increased and thus should be a consideration in selection and dosing of medications.[60] Furthermore, obesity is an independent risk factor for AFib and VTE, which underscores the necessity to understand the safety and efficacy of DOACs in this unique patient population.[61] Conversely, patients who are underweight, generally defined as a BMI less than 18.5 kg/m^2, may have increased exposure to DOACs, thus increasing the risk of bleeding.[62] Phase 3 DOAC trials did not exclude patients on the basis of weight, and subgroup analyses of the relationship between weight and clinical outcomes were inconclusive.[28–31] Pending further investigations, we suggest routine monitoring at least every 6 months in both obese and underweight patient populations to ensure appropriate therapy and to reduce the risk of complications.

Summary

The recent introduction of the DOACs provides safe and effective alternatives to warfarin for prevention and treatment of thromboembolism. Despite a much lower drug interaction potential and reduced bleeding risk, the lack of standardized laboratory monitoring tests and no specific antidote for bleeding (except dabigatran) remain a concern for providers and patients. The concerns related to laboratory monitoring have also sparked research interest in determining which established or newly developed coagulation tests can be used to reliably monitor the DOACs. High-quality specific and sensitive tests will be able to better predict drug efficacy, bleeding risk, and patients likely to respond to therapy.

Based on the available evidence, routine coagulation tests, including the PT, aPTT, and TT, should be used only qualitatively to validate an

anticoagulant effect from the DOACs and not to adjust doses and dosing intervals. The values of these tests are dependent on whether a direct thrombin inhibitor or factor Xa (FXa) inhibitor are being evaluated. The chromogenic anti-FXa assay can be used to quantitatively measure the anticoagulant activity of the FXa inhibitors rivaroxaban, apixaban, and edoxaban. The ECT and dTT assays effectively quantitate the anticoagulant effect from dabigatran. The value of direct measurement of drug plasma concentrations awaits further investigation and cannot be relied on to make therapeutic decisions. The INR test commonly used to measure the effect from warfarin cannot be used to gauge the anticoagulant effects from the DOACs.

Given the shortcomings associated with the utility of coagulation tests to monitor DOACs, qualitative testing methods using surrogates, such as renal function, liver function, and hemoglobin/hematocrit, may prove practical and useful. Specific recommendations include monitoring renal function at baseline and every 6–12 months or more frequently if necessary. Hepatic function in otherwise healthy individuals can be assessed yearly or more frequently in those with hepatic impairment. Monitoring intensity also depends on bleeding risk (e.g., CYP3A4–P-glycoprotein interactions and advanced age) and body habitus (overweight vs underweight). Given the short duration of effect of the DOACs and potential for gastrointestinal side effects, every effort must be made to ensure that patients adhere to their regimen.

Some would argue that the role of the pharmacist and other providers would be lessened with the introduction of the DOACs. Unlike warfarin, the need for monitoring coagulation tests is unnecessary, and the drug interaction potential is much less. However, the pharmacokinetic attributes of these drugs require strict adherence to dosing regimens and careful monitoring/recognition of factors that could adversely affect drug disposition and bleeding risk. As more becomes known about these factors, drug regimens can be designed so that patients can realize the full benefits of these new anticoagulants while minimizing adverse effects.

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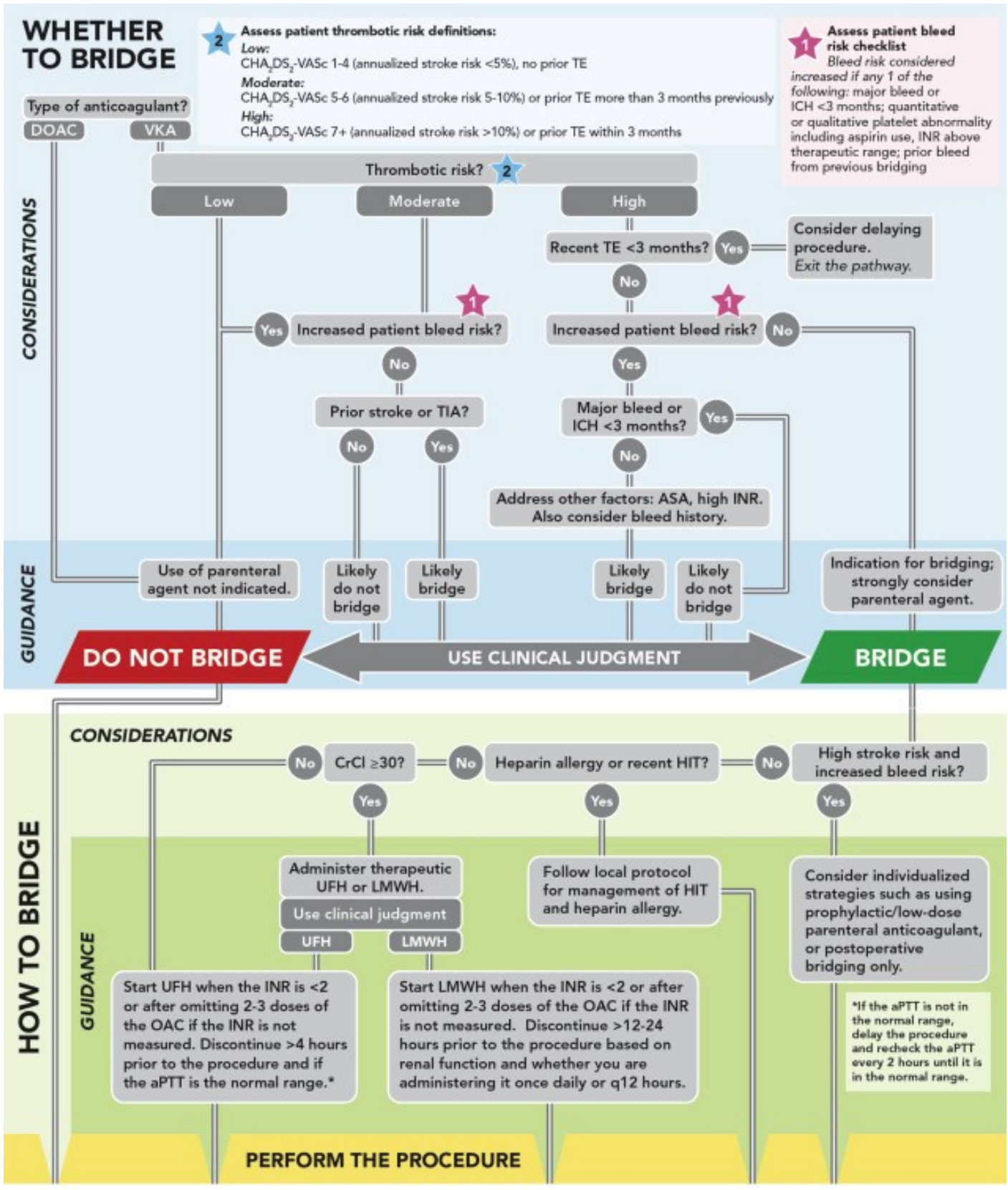


aPTT – activated partial thromboplastin time assay; **ASA** – acetylsalicylic acid (aspirin); **DOAC** – direct oral anticoagulant; **HIT** – heparin-induced thrombocytopenia; **ICH** – intracranial hemorrhage; **INR** – international normalized ratio; **LMWH** – low-molecular-weight heparin; **OAC** – oral anticoagulation; **TE** – thromboembolic event; **TIA** – transient ischemic attack; **UFH** – unfractionated heparin; **VKA** – vitamin K antagonist

Safe Medication Use in Older Adults with Chronic Kidney Disease

Chanel F. Whittaker, PharmD, BCGP, BCPS, FASCP

Pharmacist Session Objectives:

- Recognize the updated global guidelines on CKD management and implications for geriatric care
- Recognizethe geriatric pharmacists role in promoting safe medication use in older adults with CKD
- Given a patient case, identify effective principles of deprescribing to evaluate and adjust the medication regimen of an older adult with CKD

Pharmacy Technician Session Objectives:

- Recognize updated global guidelines on CKD management and implications for geriatric care
- Recognize the pharmacy technician's role in identfying signs and symptoms of medication-related problems in in older adults with CKD
- Given a patient case, identify effective principles of deprescribing to identify high risk medications in an older adult with CKD

How we plan to arrive there…

- Identify common risk factors in older adults with CKD
- Discuss updated KDIGO guidelines in the context of overall diagnosis, classification and management of CKD
- Review key medication management principles in older adults with CKD
- Throughout the presentation, evaluate a patient case scenario and develop a plan to assess medication appropriateness/recommend deprescribing in an older adult with CKD

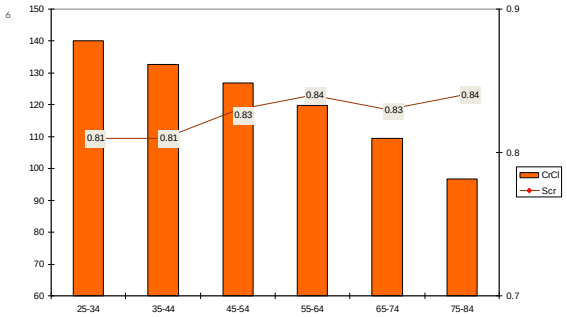
Most older adults with a decline in renal function will develop chronic kidney disease.

A •True

B •False

1

Effect of Age on Creatinine Clearance



Rowe JW, Andres R, Tobin JD, Norris AH, Shock NW. The effect of age on creatinine clearance in men: a cross-sectional and longitudinal study. *J Gerontol*. 1976;31:155-163.

What is the prevalence of CKD in adults over 60?

A	• 1 in 2
B	• 1 in 3
C	• 1 in 4
D	• 1 in 5

2

The JAMA Network

From: **Prevalence of Chronic Kidney Disease in the United States**

JAMA. 2007;298(17):2038-2047. doi:10.1001/jama.298.17.2038

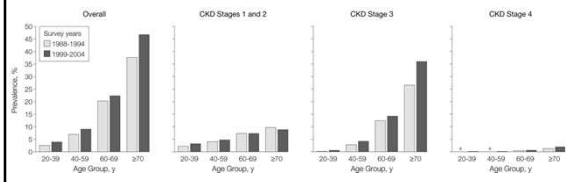


Figure Legend:

NHANES indicates National Health and Nutrition Examination Surveys.aThere were no cases in 1988-1994.

Case: JR 70yo African-American male

- Patient reports to the nephrology pharmacy clinic for evaluation of his medication regimen. PMH is significant for CKD secondary Type 2 DM with nephropathy and neuropathy. JR also has a history of hypertension, atrial fibrillation and gout. Today he is concerned that his blood pressure is becoming uncontrolled. He reports unsuccessful diet control and was started on atenolol last year.

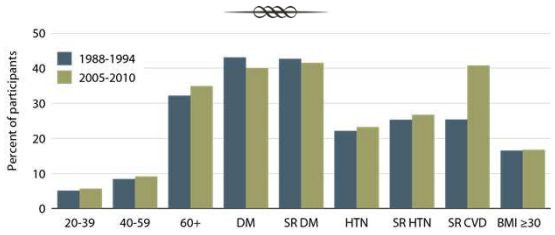
Based on JRs history, which of the following is/are risk factors for chronic kidney disease?

A	• Race/Ethnicity
B	• Gout
C	• History of Hypertension
D	• Both A and C

3

NHANES participants with CKD, by age & risk factor

Figure 1.8 (Volume 1)



NHANES 1988–1994 & 2005–2010 participants age 20 & older; single sample estimates of eGFR & ACR. Diabetes defined as A1c <7 percent, self-reported (SR), or currently taking glucose-lowering medications. Hypertension defined as BP ≥130/≥80 for those with diabetes or CKD, otherwise BP ≥140/≥90, or taking medication for hypertension. eGFR calculated using the CKD-EPI equation.

U.S. Renal Data System, USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2013.

Age-related Risk Factors for CKD: Patient Specific

- Age (> 65)
- Race (African-American, other minorities)
- Family history
- Obesity (BMI ≥ 30)
- Hypertension
- Diabetes
- *Drug induced: NSAIDs; Antibiotics

U.S. Renal Data System, USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2013.

Based on JR's risk factors, how often should JR be screened for CKD?

A	• Every 6 months
B	• Annually
C	• Every 2 years
D	• Only if proteinuria is present

4

Management of CKD in Older Adults

- Kidney Disease Improving Global Outcomes (KDIGO) Guidelines: Goals of Therapy
  - Delay progression
  - Screen/manage complications associated with CKD (Anemia, electrolyte/fluid abnormalities, metabolic bone disorders)
  - Cardiovascular risk reduction (HTN, DM)
  - **Appropriate medication management and patient safety in CKD**

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter., Suppl. 2013; 3: 1–150.

Management of CKD in Older Adults

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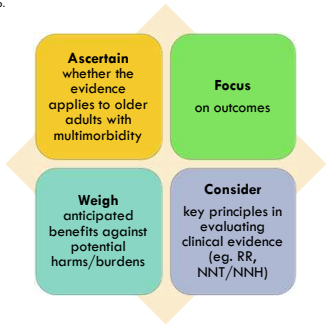
Guiding Principles for the Care of Older Adults with Multimorbidity

American Geriatrics Society Expert Panel on the Care of Older Adults with Multimorbidity. Guiding principles for the care of older adults with multimorbidity: an approach for clinicians. J Am Geriatr Soc. 2012 Oct;60(10):E1-25.

Guiding Principle II: Interpreting the Evidence Domain



"Recognizing the limitations of the evidence base, interpret and apply the medical literature specifically to older adults with multimorbidity"

Relevance of Clinical Practice Guidelines to Older Adults with Multimorbidity

- Key Considerations:
  - Type of patient considered – older adult health status
    - # of comorbidities, cognitive and functional status
  - Potential disease/drug treatment interactions with compliance to guidelines
  - Quality of evidence
  - Specific recommendations for older adults, older adults with multiple conditions
  - Time needed to treat to benefit in the context of life expectancy

Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical Practice Guidelines and Quality of Care for Older Patients With Multiple Comorbid Diseases: Implications for Pay for Performance. *JAMA*. 2005;294(6):716-724. doi:10.1001/jama.294.6.716.

Safe medication use in older adults with CKD: The Pharmacists Role

Drug Dosing in Older Adults with CKD

How should renal function be calculated for drug dosing in in older adults?

MDRD – overestimates, less inaccurate >60ml/min

CKD-EPI – overestimates

Cockcroft Gault – underestimates , less accurate <60 ml/min

24 Hour Urine – collection issues

KDIGO Guidelines: Drug Dosing in CKD

- "A **single tool** to evaluate kidney function for determination of CKD and drug dosing purposes would enable delivery of high-quality care"[1]
  - 1.4.3: We recommend that clinicians: use a GFR estimating equation to derive GFR from serum creatinine…(1B)[2]
  - 4.4.1: We recommend that prescribers should take GFR into account when drug dosing. (1A)[2]
- Other considerations:
  - Equation precision/reliability
  - Consider "range" of function vs. single result
  - Patient characteristics (frailty/obesity)
  - Feasibility

eGFR (creat)

1. Matzke GR, Aronoff GR, et. al. Drug dosing consideration in patients with acute and chronic kidney disease – a clinical update fro Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2011 Dec;80(11):1122-37
2. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter., Suppl. 2013; 3: 1–150.

What is JRs GFR and Albuminuria Category based on KDIGO Classification?

A	•G1, A2
B	•G1, A3
C	•G2, A2
D	•G2, A3

5

Case: JR 70yo African-American male

- Patient reports to the nephrology pharmacy clinic for evaluation of his medication regimen. PMH is significant for CKD secondary Type 2 DM with nephropathy and neuropathy. JR also has a history of hypertension, atrial fibrillation and gout. Today he is concerned that his blood pressure is becoming uncontrolled. He reports unsuccessful diet control and was started on atenolol last year.

JR Objective Data

- **Medications**
  - Atenolol 25mg daily
  - Metformin 500mg BID
  - Dabigatran 150mg BID
  - Losartan 100mg daily
  - OTC Motrin occasionally for migraine headaches
- **Laboratory Data**
  - Serum creatinine (Scr)= 1.0 mg/dL (eGFR=76ml/min/1.73m^2)
  - Blood urea nitrogen (BUN)= 8mg/dL
  - Today's spot protein:creatinine =1.5g/g
  - No electrolyte abnormalities
  - Renal function and protein levels have remained relatively unchanged over the past 2 years

There is an app for that…

- National Kidney Foundation
  - http://www.kidney.org/apps/

KDIGO Guidelines: CKD Definition and Classification

CKD **defined** as abnormalities of kidney structure or function, present for 3 months

CKD **classified** based on cause, GFR category, and albuminuria category (CGA)

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
G1	Normal or high	≥90				
G2	Mildly decreased	60-89				
G3a	Mildly to moderately decreased	45-59				
G3b	Moderately to severely decreased	30-44				
G4	Severely decreased	15-29				
G5	Kidney failure	<15				

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter., Suppl. 2013; 3: 1–150.

What is JRs GFR and Albuminuria Category based on KDIGO Classification?

- A: •G1, A2
- B: •G1, A3
- C: •G2, A2
- D: •G2, A3

Orange zone: High risk of progression to ESRD

Which of the following agent(s) is/are potentially inappropriate based on JR's renal function?

- A: •Metformin
- B: •Atenolol
- C: •Dabigatran
- D: •Ibuprofen

6

Agents to Prescribe with Caution in CKD

Medication Class	Agents	
Antihypertensives/ Cardiac medications	RAAS Antagonists Angiotensin receptor blockers	Beta blockers Diuretics Digoxin
Hypoglycemics	Metformin Sulfonylureas Insulin	DPP4 Inhibitors GLP1 SGLT2 Inhibitors
Pain/Analgesics	Opiods Tramadol	NSAIDs Gabapentin
Anticoagulants	Low-molecular weight heparins	DOACs
Other	Antimicrobials OTC/herbal supplements	Agents for hyperuricemia

Whittaker C, Miklich M, Patel R, Fink, J. (2018). Medication Safety Principles and Practice in CKD. Clinical Journal of the American Society of Nephrology. doi:10.2215/cjn.00580118

Metformin Safety Monitoring based on GFR

eGFR(mL/min per 1.73m^2) and Category	Action
eGFR: $\geq$ 60 Category: G1 – G2	No renal contraindication Monitor renal function annually
eGFR: < 60 and $\geq$ 45 Category: G3a	Continue use Monitor renal function every 3-6 months
eGFR: < 45 and $\geq$ 30 Category: G3b	Prescribe with caution/review use Use lower dose (eg. 50% or half-max dose) Closely monitor renal function every 3 months Do not start new patients on metformin
eGFR: < 30 Category: G4 – G5	Stop metformin
Note: Additional caution in patients at risk for AKI, fluctuations in renal status, based on history, other comorbidities, interacting medications	

1. Lipska KJ, Bailey CJ, Inzucchi SE. Table 1 – Proposed recommendations for use of metformin based on eGFR. Use of metformin in the setting of mild-to-moderate renal insufficiency. Diabetes Care. 2011 Jun;34(6):1431-7
2. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. Kidney inter., Suppl. 2013; 3: 1–150.

Analgesics

Agent	Adverse Effects	Action
NSAIDs	Hyperkalemia, edema, HTN, CHF exacerbation AKI, CKD	*Generally avoid in older adults* Short term use GFR < 60 Avoid: GFR < 30, concomitant use of RAAS Blocker
Opiods (meperidine, morphine, codeine)	Metabolites accumulate, increased risk of adverse effects, CNS/Respiratory depression	Dose reduction: GFR < 60 (according to labelling) Avoid/Caution: GFR <15
Tramadol	Opiod-like adverse effects	*Generally avoid in older adults* Short term use with dose reduction: GFR < 60 (according to labelling) Avoid: extended – release tramadol with CKD

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. Kidney inter., Suppl. 2013; 3: 1–150.

Which of the following agent(s) is/are potentially inappropriate based on JR's renal function?

A	• Metformin
B	• Atenolol
C	• Dabigatran
D	• Ibuprofen

6

Which of the following agents is potentially inappropriate based on JR's renal function?

A	• Metformin – reassess as function declines
B	• Atenolol – reassess as function declines
C	• Dabigatran – no adjustment GFR >30ml/min, caution in elderly (labeling)
D	• Ibuprofen – vasoconstriction, risk of AKI with RAAS Blocker (Losartan)

JR was admitted for AKI related to dehydration. His losartan should be adjusted as follows:

A	• Extend dosing interval to every other day
B	• Decrease dose by 50%
C	• Extend dosing interval and decrease dose
D	• Discontinue Losartan

7

Principles of ACEi and ARB Management in CKD

Serum Creatinine	Interpretation	Action
20-30% "anticipated" rise in serum creatinine	Transient, non-progressive rise in serum creatinine – no structural kidney injury	Not a contraindication, continue therapy, continue to monitor
> 30% rise in serum creatinine	Progressive rise serum creatinine/renal dysfunction	Discontinue agent, investigate renal artery disease, hypoperfusion
Setting of hypoperfusion/loss of counter regulatory mechanism	Increased risk of AKI - Acute azotemic response	Temporary discontinuation of ACEi/ARB. Reinstitute when AKI resolved, correction of precipitating factors

Monitoring: Scr, GFR, potassium
1 weeks after initiation of ACE Inhibitor, ARB or dosing adjustment

1. Schoolwerth AC, Sica DA, et al. Renal considerations in angiotensin converting enzyme inhibitor therapy: a statement for healthcare professionals from the Council on the Kidney in Cardiovascular Disease and the Council for High Blood Pressure Research of the American Heart Association. Circulation. 2001 Oct 16;104(16):1985-91.
2. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. Kidney inter., Suppl. 2013; 3: 1–150.

Use of nephrotoxic and renally eliminated agents in patients with increased risk of AKI

- 4.4.3: Temporary discontinuation of potentially nephrotoxic and renally excreted drugs in people with a GFR < 60 eGFR mL/min per 1.73m^2 (Category: G3a – G5) with **serious intercurrent illness that increase the risk of AKI**

Agents include: RAAS Blockers (ACE inhibitors, Angiotensin receptor blockers, aldosertone inhibitors, direct renin inhibitors), diuretics, NSAIDs, metformin, lithium and digoxin

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter., Suppl. 2013; 3: 1–150.

Deprescribing Principles and Pearls in Older Adults with CKD

Question: is this drug/regimen appropriate/ optimal based on age and renal function?

- Consider acute/long-term changes in health status and renal function
- Consider deprescribing agents:
  - Increased risk of nephrotoxicity/AKI (eg. NSAIDs)
  - Increased risk of ADR as function declines (eg. Insulin, antihypertensives, analgesics)
  - Decreased efficacy as function declines
  - May accelerate progression of CKD/worsening of CKD related complications

Helpful Clinical Tools

- Beers List[1]
  - Identify potentially inappropriate medications (PIMs)
    - Table I: Nitrofurantoin, digoxin, spironolactone, NSAIDs
    - Table II: Kidney/Urinary Tract
    - Table III: Dabigatran
- Geriatric/Drug Databases
  - Geriatrics and renal dosing, ADR, DDIs, contraindications
    - Micromedex
    - Lexicomp

AGS Beers Criteria for potentially inappropriate medication use in older adults. American Geriatrics Society. http://www.americangeriatrics.org/files/documents/beers/PrintableBeersPocketCard.pdf

Summary

Clinical practice guidelines provide goals of therapy to manage CKD but must consider limitations of guidelines/literature in older adults

Nephrotoxicity is not the only reason that a drug may be inappropriate in older adults with CKD

Geriatric pharmacist role to identify medication-related problems using clinical tools along with clinical judgment

Medication regimens should be reassessed and adjusted as renal function declines (toxicity and efficacy)

Putting it into practice

What is one strategy or tool that you can use to help manage older adults with CKD at your practice site?

Please indicate this in the comments section of your evaluation form.

Self-Study Answer Key

- 1 – B
- 2 – B
- 3 – D
- 4 – B
- 5 – D
- 6 – D
- 7 – D

The Road Ahead

ASCP Engagement Issues

Introduction

Chad Worz, PharmD, BCGP

Chad is CEO of the American Society of Consultant Pharmacists

His career included the founding of Medication Managers, LLC and RxConcile.com. He has over 20 years of experience in the management of pharmacy and pharmacist services in the senior care and developmentally disabled populations.

Chad has always been an innovator in consulting pharmacy and was instrumental in the founding of the nation's first full service charitable pharmacy in Cincinnati, Ohio.

Chad has no financial disclosures with regards to this program.

Learning Objectives

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

1. Recognize current legislative and regulatory issues
2. Identify DEA regulatory changes
3. Define the "Triple Aim" concept and "Value based care"
4. Identify opportunities for consultant pharmacists in the current health care environment

Identity

I can…

I have…

I like…

I am…

I remember…

In April 1888, Associated Charities of Cincinnati invited a group of civic leaders to meet and discuss the need for a "home for incurables.

Medical Resort

Changing Identity

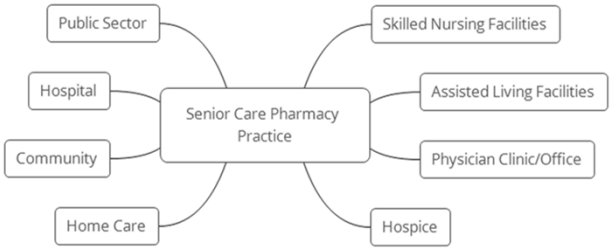
Inception – unconsciously incompetent – Excited
- blissfully ignorant

Deception – consciously incompetent – Fear
- the mind seeks familiar

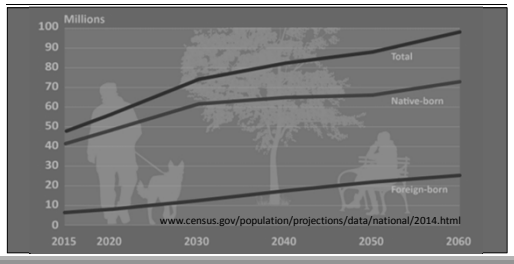
Transformation – consciously competent – Aware
- noticing success

Identity – unconsciously competent
- Who you are

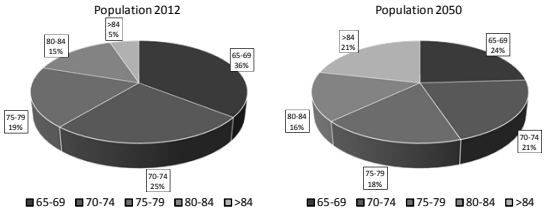
Senior Care Pharmacy Practice



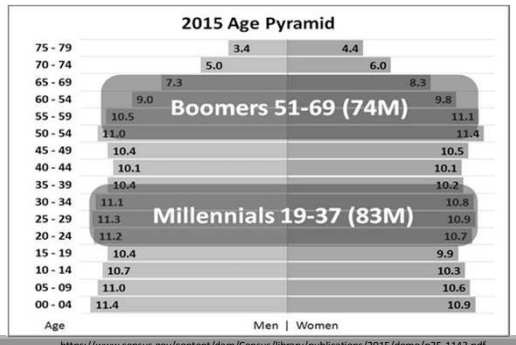
An Aging Nation



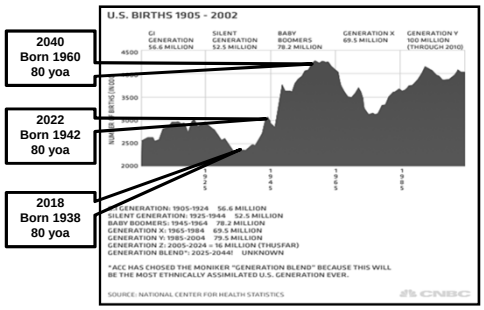
Seniors in America



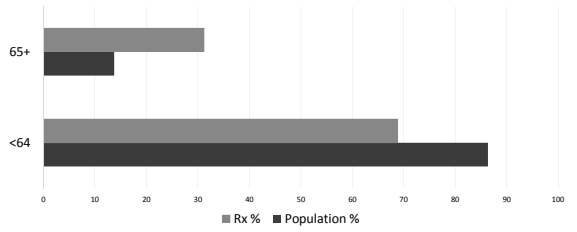
Source: https://www.census.gov/prod/2014pubs/p25-1140.pdf



https://www.census.gov/content/dam/Census/library/publications/2015/demo/p25-1143.pdf

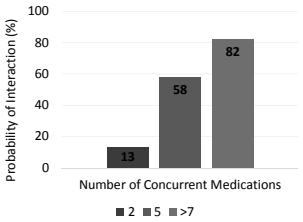


Prescription Use in Seniors



https://www.imshealth.com/files/web/IMSH%20Institute/Reports/US_Use_of_Meds_2013/Percent_population_prescriptions_per_capita.pdf

Polypharmacy and Aging:
Predictors of Potential Drug Interactions



Age

Number of Concurrent Medications

Chronic Disease

Severity of Disease

Mallet L, Spinewine A, Huang A. The challenge of managing drug interactions in elderly people. Lancet 2007;370:185–91.

Variable Influencing Drug Outcomes

Adapted from Hansten. *Science & Medicine.* 1998;5:16-25.

Biosimilars

FDA – Draft Interchangeability Guidance

CMS – Medicare Part B Coding & Reimbursement

State Activity

19

Medicare Advantage & Medicare Part D Proposed Rule

Drug Management Programs	Medication Therapy Management	Benefit Design & Utilization Management
HIT & Data Interoperability	Fraud, Waste, & Abuse	Any Willing Provider

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The "MEGARULE"

Medicare Conditions of Participation (SOM)

DRR/MRR recommendation & action documentation in patient medical record

Antibiotic Stewardship: systems to monitor use; antibiotic protocols

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The "MEGARULE"

Medicare Conditions first published in 1989

Set standards for health care and safety

Proposed rule published July, 2015

Final rule published October 4, 2016

Phased Implementation

- Phase 1 – 11/28/2016
- **Phase 2 – 11/28/2017**
- Phase 3 – 11/28/2019

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The "MEGARULE"

Phase 1 –

- Documentation of DRR recommendations and prescriber response
- Updates definition of medication "irregularity"

Phase 2 -

- Antibiotic Stewardship Program
- Re-defines "psychotropic drugs"
- PRN antipsychotic & psychotropic drug rules (14 days)
- "F-TAGS" RE-NUMBERED

23

The "MEGARULE"

On 11/24/17, just prior to Phase 2 implementation, CMS released a memo to surveyors

- An 18-month temporary moratorium on imposing enforcement remedies for certain Phase 2 requirements, including Behavioral Health Services (F740), Psychotropic Medications (F758), Antibiotic Stewardship Program (F881), as well as 5 other areas of care
- Health Inspection Star Ratings Frozen for one year

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Impact Act 2014

"Improving Medicare Post-Acute Care Transformation Act"

- Bipartisan bill passed on September 18, 2014 and signed into law by on October 6, 2014
- Requires standardized patient assessment data across Post-Acute Care (PAC) settings to enable:
  - Improvements in quality of care and outcomes
  - Comparisons of quality across PAC settings
  - Information exchange across PAC settings
  - Enhanced care transitions and coordinated care
  - Person-centered and goals-driven care planning and discharge planning

IMPACT Act 2014

Standardized patient assessment data across all four PAC settings – Quality Measures Defined by CMS

Defines PAC providers to include : **Home Health Agencies, LTACHs, SNFs and IRFs**

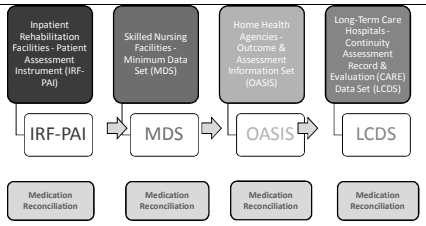
Requires PAC providers to report standardized patient assessment data by 10/2018

Documentation of Medication Reconciliation at Admission & Discharge

Communication of "Med Rec" to

- Patient
- Family
- Primary Care Doc
- Community Pharmacy

IMPACT Act 2014



Standard Data Collection Timeline

Quality Domain	SNF Due Date
Functional Status	October 2016
Skin Integrity	October 2016
Medication Reconciliation	October 2018
Major Falls	October 2016
Patient Preference	October 2018

ASCP DEA Task force

ASCP established its DEA Task Force in 1998 to address ambiguities within the CSA

- Hospital vs. Community vs. LTC Pharmacy
- CSA and the practice standards of LTCPs represented a potential "regulatory compliance risk"
- DEA Task Force - mission of working with the DEA to resolve issues and challenges - Balance patient care vs. regulatory compliance
- Over the years, changes made to DEA regulations such as time required for follow-up written Rx for verbal CII orders and faxing of CII Rx's

ASCP DEA Task force

Task Force – working directly with DEA staff since 2015 on list of issues, focused on Nurse Agency issue.

Resolved: Obtained written clarification from DEA:

- Electronic e-kits: use for 1st dose only **do not** require separate DEA registration (11/30/16).

Comprehensive Addiction & Recovery Act (CARA)

- DEA Clarification: CARA 30-day fill limitation **does not** apply to long-term care and hospice patients (1/13/17)
  - DEA verified, partial-fills for CII prescription medications with up to 60-days to complete.

Current Nurse Agent Overview

Authority of Agent (under current DEA guidance)

- Prepare CII-CV prescription for practitioner to sign
- Transmit CII-CV prescription that is signed by practitioner to pharmacy via fax
- Take a verbal CIII-CV prescription from the physician and communicate that prescription via telephone to the pharmacy

Agents are employed by the authorized prescriber and may be:

- A nurse located in the prescribers office
- A non-licensed receptionist
- Hospital employees (b/c hospitals are DEA registrants)
- **NOT** LTCF Nurses for CDS. Nurses in a facility today remain the agent of the prescriber for non-controlled medications

Current Nurse Agent Overview

October 6, 2010 DEA issues Policy Statement that addressed the nurse as an agent of the prescriber

LTCF employees may become agents but only through a very prescriptive and detailed process that documents such delegation

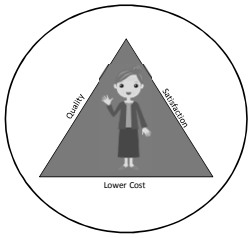
Each Nurse must be contracted with each prescriber and the pharmacy and the facility must maintain records of all contracts

- ASCP DEA-TF Recommended that DEA issue a revised Nurse Agent Policy which specifically addresses an alternative policy approach for the LTC setting
- Continued meetings with DEA in 2018 (Chart Orders, etc)

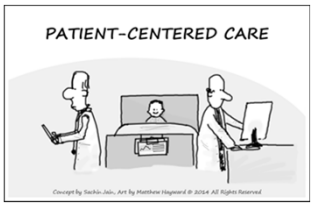
Recent Activity

- Affordable Care Act 2010
- Mega Rule (Medicare Conditions of Participation)
- Impact Act 2014
- Enhanced MTM, CMMI Demonstration
- PPS Revisions, Request for Comments
  - RUGs to RCS to PDPM
- Chronic Care Management Models
  - https://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNProducts/Downloads/ChronicCareManagement.pdf

The Triple Aim



Patient Centered Care



Value Based Reimbursement

Drug Pricing

Some debate continues around the value of drug importation from countries like Canada and Medicare drug price negotiation

Drug price transparency bills targeting both manufacturers and PBMs have limited support

Bipartisan work groups have formed on the issue, though no definitive action has been taken

Chronic Care Act Legislation

Senate Finance Committee Bipartisan Effort

Addresses chronic disease in Medicare

Improves flexibility and predictability to better serve chronically ill beneficiaries by allowing MA plans & ACOs to tailor coordination and benefits to specific patient groups.

Telemedicine- Allows beneficiaries receiving dialysis treatments at home to do their monthly check-in with their doctor via telehealth, rather than travelling to the doctor's office or hospital.

Passed out of Senate and awaiting House movement

Opioid Epidemic

White House Opioid Commission
- President's declaration of state of emergency

Congressional Action
- Committee hearings in House E&C and Senate HELP

Dec. Appropriations Bill Drug Issues in Budget

Implementation of CARA Grants

Action in the States
- State-based initiatives
- State AG, County, City Lawsuits
- Potential for future action

The 2018 Elections: Senate

Senate — 100 Senators — 60 votes important

Senate — 52 current Republican Senators

Senate — 48 current Democratic Senators

2018 Senate election — Democrats overexposed; Majority unlikely to change

Dems defending 25 of the 34 seats up for reelection, including 10 seats in Trump states.

GOP has only one seat up in 2018 in a Clinton state

Dems — Need 3 seats to gain majority

The 2018 Elections: House

All 435 seats up

239 – Current Republican Seats

194 – Current Democratic Seats

2 – Open Seat

Democrats likely to pick up a handful of seats

Narrower majority after 2018 (likely R)

Federal Legislative Advocacy

"Provider Status for Pharmacists" - The Patient Access to Pharmacists' Care Coalition's (PAPCC) mission is to develop and help enact a federal policy proposal that would enable patient access to, and payment for, Medicare Part B services by state-licensed pharmacists in medically underserved communities. Our primary goal is to expand medically-underserved patients' access to pharmacist services consistent with state scope of practice law.

PAPCC – organizations representing patients, pharmacists, pharmacies & interested stakeholders (around 40 groups)

PHARMACISTS CARE

Provider Status in 115th Congress

- **Senate-S.109** introduced in January by Sen. Charles Grassley (R-IA) with **45 co-sponsors**
  - Referred to the Senate Finance Committee
- **House-H.R.592** (same bill number as 114th Congress, but totally new bill) introduced by Brett Guthrie (R-KY) with **226 co-sponsors**.
  - Referred to Energy and Commerce Committee and Ways And Means – Sub-committee on Health

Are there too many pharmacists?

https://pharmacymanpower.com

Why Is it Important?
The Impact of Senior Care Pharmacists

Reduced health care costs

- For every $1 spent on pharmacist intervention, the healthcare system saves $12.[1]
- Pharmacist-provided MTM in Medicare Part D reduced medication costs an average of $840 per patient in year 1 and $1,061 per patient in year 2.[2]

Reduced hospital admissions

- Pindola et al showed a 60% reduction for Dx of bleeding ulcers ($5,000/admission) in patients who received MTM.[2]

1. Isetts BJ, Schondelmeyer SW, Artz MB, et al. Clinical and economic outcomes of medication therapy management services: the Minnesota experience. J Am Pharm Assoc. 2008;48(2):203–11.
2. Pindolia VK, Stebelsky L, Romain TM, Luoma L, Nowak SN, Gillanders F. Mitigation of medication mishaps via medication therapy management. Ann Pharmacother. 2009;43(4):611–20. https://www.pharmacist.com/sites/default/files/EvidenceforPharmacistsSerivces2000-2015.pdf

Why Is it Important?
Opportunities for Senior Care Pharmacists

Medicare is changing payment models from Fee for Service (FFS) to shared risk bundles.

Opportunity for pharmacists to participate in these shared risk models. (ACO, Medicaid, Managed Care).

Self insured employers need to control costs while keeping their employees healthy and productive.

Opportunity for Innovation

Expanding Horizons

MTM

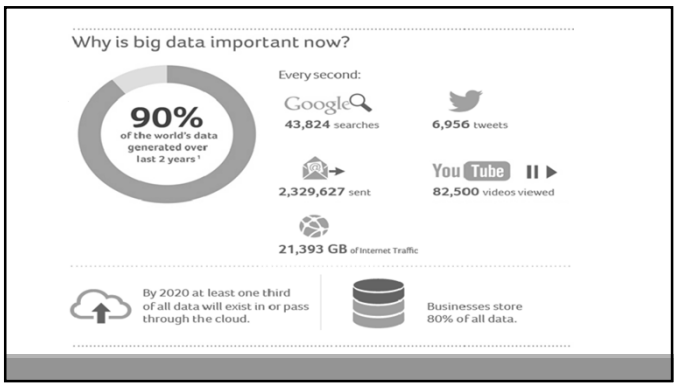
Self Insured Employers

Physician's Offices

Transitions of Care –Hospital Clinics

Industry Consulting

Individuals


Why is big data important now?
90%
of the world's data generated over last 2 years
Every second:
Google
43,824 searches
6,956 tweets
2,329,627 sent
YouTube
82,500 videos viewed
21,393 GB of Internet Traffic
By 2020 at least one third of all data will exist in or pass through the cloud.
Businesses store 80% of all data.


Questions

ASCP and Legislative Update: The Road Ahead
Self-Assessment Questions

1. What is the approximate increase in people over the age of 65 years from now until 2030:
    a. 10 Million
    b. 20 Million
    c. 30 Million
    d. 100 Million

2. What approximate percentage of all prescription medications dispensed do people over the age of 65 consume?
    a. 10%
    b. 20%
    c. 33%
    d. 50%

3. Value Based Care is tied to the number of prescription medications that pharmacists can discontinue
    a. True
    b. False

4. The Triple Aim involves:
    a. Good patient satisfaction
    b. Quality care
    c. Lower cost
    d. All of the above

5. Provider status legislation is now being attached to bills involving what national crisis?
    a. Medical Marijuana
    b. Opioid Management
    c. Tele-pharmacy
    d. DIR Fee elimination

UNIVERSITY of MARYLAND SCHOOL OF PHARMACY
THE PETER LAMY CENTER ON DRUG THERAPY AND AGING

Deprescribing: A Tactic to Meeting the 4 M's in Older Adults

Nicole J. Brandt, PharmD, MBA, BCGP, BCPP , FASCP
Professor, Geriatric Pharmacotherapy, Pharmacy Practice and Science UMB School of Pharmacy
Executive Director, Peter Lamy Center Drug Therapy and Aging
Pharmacist, Center for Successful Aging Good Samaritan Hospital

Joshana K. Goga Pharm.D., BCPP, LSSGB
Clinical Pharmacy Program Manager
Sheppard Pratt Health System
Assistant Professor
University Of Maryland School Of Pharmacy

Objectives

At the end of this presentation, the participant should be able to:

1. Recognize key elements and clinical benefits of deprescribing
2. Identify effective employable tactics to champion deprescribing at your clinical site
4. Using cases, identify practical strategies for rational deprescribing in the care of older adults across multiple practice settings

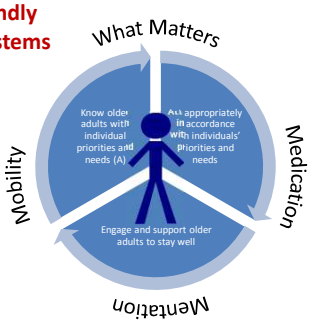
Disclosures

Research Support: **HRSA GWEP, AMCP, IMPAQ**

Consultant: **RAND, IHI, AGS, NCQA GMAP**

3

Vision: Age-Friendly Health Systems



Age-Friendly Health System 4M Bundle

What Matters: Know and act on each older adult's specific health outcome goals and care preferences across settings	Know the health outcome goals and care preferences of older adults for current and future care, including but not limited to end of life
	Align all care and decisions with the older adult's specific health outcome goals and care preferences
Medications: If medications are necessary, use Age-Friendly medications that do not interfere with What Matters, Mentation, or Mobility	Engage the older adult and the health care team in determining whether medications are impacting the older adult's Mobility, Mentation, and/or What Matters; if so, create a shared responsibility to de-prescribe or adjust the dosage
	Make medication decisions in partnership with the older adult, family, and health care team, and identify options that support What Matters, Mentation, and Mobility
Mentation: Identify and manage depression, dementia, and delirium across care settings	Know if an older adult has dementia and/or delirium
	Manage the factors that contribute to delirium
	Treat and manage dementia by understanding the underlying needs of older adults with dementia to keep them safe
	Know if an older adult is depressed, and treat and manage depression
Mobility: Ensure that older adults at home and in every setting of care move safely every day in order to maintain function and do what matters	Create an environment and culture that enables. supports, and encourages mobility
	Identify and treat underlying contributors to immobility and fall injuries

ihi.org/engage/initiatives/age-friendly-health-systems

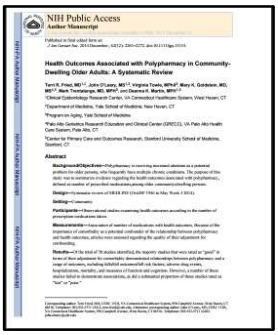
Older Adults and Medication Related Problems

- Medication nonadherence is associated with nearly $290 billion in healthcare costs annually, and it is estimated that half of chronic disease medications are not taken as prescribed.[1]
- Adverse drug events cost the system at least $1.6 billion annually.[2]
- The most common drug classes implicated in leading to ED visits due to ADEs were: anticoagulants, antibiotics, diabetes agents, and opioid analgesics. [3]

[1] *Blue Cross Blue Shield of Rhode Island, Patient Centered Pharmacy Program, http://www.bcbs.com/shop-for-health-insurance/medicare/BCBSRI_MA_RXPRDGRAMv2.pdf.*
[2] *US Department of Health and Human Services, Agency for Healthcare Research and Quality, "Reducing and Preventing Adverse Drug Events to Decrease Hospital Costs," http://archive.ahrq.gov/research/ ndings/factsheets/errors-safety/aderia/ade.html#4.*
[3] Shehab N, Lovegrove MC, Geller AI, Rose KO, Weidle NJ, Budnitz DS. US Emergency Department Visits for Outpatient Adverse Drug Events, 2013-2014. *JAMA.* 2016;316(20):2115-2125. doi:10.1001/jama.2016.16201

Systematic Review

- Adverse drug events
- Falls/Fall outcomes/Fall risk factors
- Hospitalizations
- Mortality
- Declines in Function
- Declines in Cognition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Health Outcomes Associated with Polypharmacy in Community-Dwelling Older Adults: A Systematic Review

Abstract

Fried TR, *et al.*, *JAGS*, 2014

Medication Problems in Patients with Multiple Chronic Conditions

Not feasible	Non-adherence, failure to refill medication
	Cost
	Medication regimen complexity
Lacking benefit	No indication
More than minimal risk of harm	Inappropriate medications
	Polypharmacy
	Excessively tight disease control
	Side effect, serious adverse effect
Not consistent with goals of care	Desired outcome not achieved
	Preventive meds without large enough benefits

Adapted from Fried T *et al. BMC Geriatrics* 2016 16:67

HOW DO YOU DEFINE POLYPHARMACY?

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Irrational Polypharmacy…..

- Involves using combinations of medications that are:
  - duplicative,
  - antagonistic,
  - No clear indication for use pointless or
  - even deleterious.
- Increases drug costs, complexity of treatment regimens, and risks/side effect burden.

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It is an art of no little importance to administer medicines properly: but, it is an art of much greater and more difficult acquisition to know when to suspend or altogether to omit them.

Philippe Pinel

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HOW DO WE DEFINE DEPRESCRIBING?

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Deprescribing Definition

- "the systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits within the context of an individual patient's care goals, current level of functioning, life expectancy, values, and preferences."

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Patient Centered Deprescribing Process

- Complete a comprehensive patient history
- Identify potentially inappropriate medications
- Determine whether medication can be ceased and prioritization
- Plan and initiate medication withdrawal
- Monitoring, support, and documentation

Reeve, E., Shakib, S., Hendrix, I., Roberts, M. S. and Wiese, M. D. Review of deprescribing processes and development of an evidence-based, patient-centred deprescribing process. Br J Clin Pharmacol. 2014; 78: 738–747

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CASE 1: EVIDENCE BASED MEDICINE

2013 ACC/AHA GUIDELINE ON THE TREATMENT OF BLOOD CHOLESTEROL

BACKGROUND

- This guideline is a collaborative effort by the American College of Cardiology (ACC) and the American Heart Association (AHA) which was released in 2013
- It is designed to replace the previous guideline which was the Adult Treatment Panel (ATP III) which was originally released in 2003 by the National Heart Lung and Blood Institute (NHLBI)
- The NHLBI made a decision to stop producing clinical guidelines and presented its evidence to the ACC and AHA to develop this current guideline.

4 STATIN BENEFIT GROUPS

1. Clinical ASCVD
    a. acute coronary syndromes, or a history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease of atherosclerotic origin
2. LDL-C ≥ 190 mg/dL, Age ≥ 21 years
3. Primary Prevention - ASCVD risk ≥ 7.5%, Age 40-75 years, LDL-C 70-189 mg/dL
4. Primary Prevention - Diabetes, 40-75 years, LDL-C 70-189 mg/dL

PATIENT RISK FACTORS

10 YEAR ASCVD RISK ASSESSMENT

Variables

- Age
- Total Cholesterol
- HDL
- Systolic Blood Pressure
- Receiving medication for blood pressure (Y/N)
- Smoker (Y/N)
- Diabetes (Y/N0

Like previous other risk assessment tools it is flawed

- Use is limited to White Americans and African Americans

PATIENT RISK FACTORS HYPERLIPIDEMIA

- Gender,
- Age older than 55
- Family history, not well defined
- Post menopause

- Diet, managed well at Sheppard Pratt, 1800 calorie (60 gm carbohydrate) with no concentrated sweets
- Weight, BMI 21.4, normal weight
- Medications ?

STATIN TREATMENT RECOMMENDATIONS

1. The panel makes no recommendations for or against specific LDL-C or non-HDL-C targets for the primary or secondary prevention of ASCVD (Grade: N)
2. High-intensity statin therapy should be initiated or continued as first line therapy in women and men less than or equal to 75 years of age who have clinical ASCVD unless contraindicated (Grade:A)
3. Adults ≥21 years of age with primary LDL-C ≥190 mg/dL should be treated with statin therapy (10-year ASCVD risk estimation is not required) (Grade:B)
   a. Use High-intensity statin therapy unless contraindicated
   b. For individuals unable to tolerate high-intensity statin therapy, use the maximum tolerated statin intensity
      - Use high-intensity statin therapy unless contraindicated.
        - For individuals unable to tolerate high-intensity statin therapy, use the maximum tolerated statin intensity

STATIN TREATMENT RECOMMENDATIONS

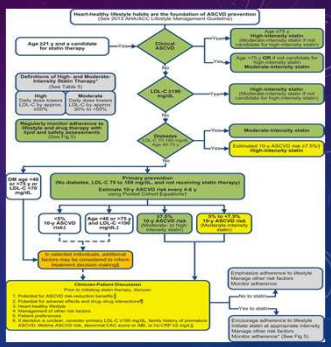
4. Adults 40 to 75 years of age with LDL-C 70 to 189 mg/dL, without clinical ASCVD* or diabetes and an estimated 10-year ASCVD risk ≥7.5% should be treated with moderate- to high-intensity statin therapy. (Grade:A)
5. Moderate-intensity statin therapy should be initiated or continued for adults 40 to 75 years of age with diabetes. (Grade:A)
6. High-intensity statin therapy is reasonable for adults 40 to 75 years of age with diabetes with a ≥7.5% estimated 10-year ASCVD risk unless contraindicated. (Grade:B)

Table. Classification of Statin Therapies

Statin	High-Intensity	Moderate-Intensity	Low-Intensity
	Lowers LDL >50%	Lowers LDL 30% to 49%	Lowers LDL <30%
Atorvastatin	40 mg – 80 mg	10 mg – 20 mg	
Rosuvastatin	20 mg – 40 mg	5 mg – 10 mg	
Lovastatin		40 mg	20 mg
Simvastatin		20 mg – 40 mg	10 mg
Pravastatin		40 mg – 80 mg	10 mg – 20 mg
Fluvastatin (XL)		80 mg	
Fluvastatin		40 mg (twice daily)	20 mg – 40 mg
Pitavastatin		2 mg – 4 mg	1 mg

LDL=low-density lipoprotein.
Source: *Circulation*. 2013;129(25 suppl 2):S1-S45.

TREATMENT ALGORITHM



ROLE OF NON STATIN AGENTS

- Limited evidence to support their use
- Consider their use in the following situations:
  - Adjunct therapy for high-risk patients with less than anticipated response to statin therapy
  - As Monotherapy for patients who are statin intolerant
  - **Patients over 75 years old**
  - Patients with elevated triglycerides (>500)

RISK VS.BENEFIT PRESCRIBING MEDICATION FOR MANAGEMENT OF HYPERLIPIDEMIA

Risk	Benefit

RISK VS.BENEFIT PRESCRIBING MEDICATION FOR MANAGEMENT OF HYPERLIPIDEMIA

Risk	Benefit
• Adverse effects • Pill burden • Increase likelihood of behavioral symptoms	• Possible ASCVD prevention (But uncertain Life Span) **Stroke/TIA**

CASE 2: EVIDENCE BASED MEDICINE

2012 10TH EDITION
MUGS GUIDELINE ON HOSPICE PHARMACIA MEDICATION USE GUIDELINE

HOSPICE

A: All symptoms related to the patient's hospice-qualifying terminal diagnosis as determined by the hospice.

- C: Cancer and HIV/AIDS diagnoses, defined as ICD-9-CM codes 042 or 140-239.
- H: Heart (cardiac) diagnoses, defined as ICD-9-CM codes 391-429 or 440-459.
- L: Lung diagnoses, defined as ICD-9-CM codes 460-519.
- O: Other diagnoses that do not fall into one of the other diagnosis-related inclusion codes (e.g., cerebrovascular disease, defined as ICD-9-CM codes 430-438; cystic fibrosis, defined as ICD9-CM code 277).

HOSPICE –SHEPPARD

- Speech limited to 5 words or less
- Nonambulatory
- Bowel incontinence
- Inability to dress
- Bathe
- Communicate
- 1/6 serious medical conditions in the last year

HOSPICE

HP Medication Paks

1. ComfortPak

Indication	Contents	Quantity	Directions for Use
Pain, Fever	Acetaminophen 650 mg suppository	**6 (six) suppositories**	Insert 1 suppository rectally every 6 hours as needed for mild pain or fever.
Agitation	Haloperidol 2 mg/mL oral concentrate	**15 (fifteen) mL**	Take 0.5 mL (1 mg) by mouth or under the tongue every 6 hours as needed for agitation.
Secretions	Atropine 1% ophthalmic drops	**2 (two) mL**	Place 2 drops under the tongue every 4 hours as needed for secretions.
Anxiety	Lorazepam 1 mg tablet **CIV**	**10 (ten) tablets**	Take 1 tablet by mouth every 6 hours as needed for anxiety.
Pain, Shortness of breath	Morphine sulfate 20 mg/mL oral concentrate **CII prescription for a terminally ill hospice patient**	**15 (fifteen) mL**	Take 0.25 mL (5 mg) by mouth or under the tongue every 4 hours as needed for moderate to severe pain or shortness of breath.
Nausea, Vomiting	Prochlorperazine 10 mg tablet	**6 (six) tablets**	Take 1 tablet by mouth every 6 hours as needed for nausea and vomiting.
Nausea, Vomiting	Prochlorperazine 25 mg suppository	**6 (six) suppositories**	Insert 1 suppository rectally every 12 hours as needed for nausea and vomiting.

HOSPICE

2. Cardiac ComfortPak

Indication	Contents	Quantity	Directions for Use
Edema	Furosemide 40 mg tablet	**10 tablets**	Take as directed by mouth as needed for edema. Contact the prescriber to obtain appropriate dose and instructions. Contact the HP pharmacist to communicate the patient-specific dose and instructions for this medication.
Edema	Furosemide 10 mg/mL solution for injection	**2 x 2 mL (vials)**	Inject intravenously or intramuscularly as directed as needed for edema. Do not exceed a rate of 10 mg/min if given intravenously and the dose is < 120 mg. Contact the prescriber to obtain appropriate dose and instructions. Contact the HP pharmacist to communicate the patient-specific dose and instructions for this medication.

HOSPICE

HP Medication Paks

Agitation	Haloperidol (pediatric) oral solution 1 mg/mL	0.025 mg/kg x _____ kg = _____ mg **OR** 0.05 mg/kg x _____ kg = _____ mg **Consult with an HP pharmacist to select the most appropriate dose between the dosage ranges calculated above.** Remove haloperidol if the patient is **less than** 3 years old. *(Place a line through the item and initial next to the line.)*	**15 (fifteen) mL**	Take _____ mg by mouth or under the tongue divided 3 times daily as needed for agitation.
Insomnia, Itching	Diphenhydramine syrup 2.5 mg/mL	1 mg/kg x _____ kg = _____ mg	**30 (thirty) mL**	Take _____ mg by mouth every 6 hours as need for sleep or itching.
Nausea, Vomiting	Metoclopramide syrup 5 mg/mL	0.1 mg/kg x _____ kg = _____ mg **OR** 0.2 mg/kg x _____ kg = _____ mg **Consult with an HP pharmacist to select the most appropriate dose between the dosage ranges calculated above.**	**15 (fifteen) mL**	Take _____ mg by mouth every 6 hours as needed for nausea and/or vomiting.

NATIONAL HOSPICE AND PALLIATIVE CARE ORGANIZATION

- Defines palliative care as treatment that enhances comfort and improves the quality of an individual's life during the last phase of life
- No specific therapy is excluded from consideration
- The test of palliative care lies in the agreement between the individual, physician(s), primary caregiver, and the hospice team that the expected outcome is relief from distressing symptoms, the easing of pain, and/or the enhancing the quality of life
- The decision to intervene with active palliative care is based on an ability to meet stated goals rather than affect the underlying disease
- An individual's needs must continue to be assessed and all treatment options explored and evaluated in the context of the individual's values and symptoms.
- The individual's choices and decisions regarding care are paramount and must be followed at all times

RISK VS.BENEFIT PALLIATIVE COMFORT CARE

Risk

- Adverse effects
- Pill burden
- Increase likelihood of behavioral symptoms
- Wishes of the family
- Wishes of the patient

Benefit

Take Home Points

- Polypharmacy and Adverse Drug Events are pervasive issues when caring for older adults
- Deprescribing is a tactic to reduce the aforementioned issues.
- Teamwork is needed to improve medication use and safety.

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QUESTIONS?

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Principles for Guiding Deprescribing in Older Adults
Self-Assessment Questions

1) Benefits of deprescribing include the following:
   a. Minimize adverse effects
   b. Reduce pill burden
   c. Engage patient values
   d. All of the above

2) The process of deprescribing begins with
   a. Satisfy the needs of the nursing staff
   b. Consider the risks and benefits of each medication
   c. Ensure patient receives a total of 2 medications
   d. Ensure patient receives only over the counter medications

3) What is the most effective method to facilitate deprescribing at your clinical site?
   a. Implement a policy for all patients to receive no more than 3 medications
   b. Identify champions of deprescribing
   c. Educate family and patient on risks and benefits of medications
   d. b and c
   e. a and b

4) 88 y.o. male with a diagnosis of dementia for the last 10 years complains of urinary retention. He becomes combative when toileting due to the discomfort of retention. Consultant pharmacist asked to review medication list. You recommend the following :
   a. Stop diphenhydramine if patient no longer presenting with seasonal allergies, consider discontinuing olanzapine for management of BPSD
   b. Add ibuprofen for pain management
   c. Stop diphenhydramine and substitute with loratadine
   d. Add lorazepam 0.5mg before toileting

SUBJECTIVE:

EC is an 85-year-old female admitted with a chief complaint of psychosis. She was brought to ER by her daughter. She has been acting abnormally and has been increasingly paranoid. She believes she has connections to Russia and they are going to come to get her through her TV. She ran out of the house because she thought the house was going to explode. Patient's daughter states that psychiatrist had been trying to adjust patient's medications and wean patient off some of the medications. EC has a long history of schizophrenia and has 2 previous suicide attempts. Patient is currently unable to contract for safety in ER and unable to obtain MOLST per ER. Patient was inpatient in 2009 for a suicide attempt.

Allergies:

- Penicillin (hives/hypertension)

Past Medical History:

- Psychosis
- Dementia
- Schizophrenia
- HTN
- Hyperlipidemia
- Diabetes
- Vitamin B12 deficiency

Social History:

Patient is an 85-year-old divorced female who lives in New Jersey and was in Baltimore visiting her daughter. Patient lives in a supported senior high rise in New Jersey and daughters want her move to a more supervised setting such i.e. Assisted Living Facility/Nursing Home. Patient's three children are involved to some extent. Patient was born in Cuba and moved to US at 18 or 19. Patient's preferred language is Spanish, but can speak English.

Review of Symptoms:

General/metabolic: negative

Cardiovascular: positive for hypertension and hyperlipidemia

Genitourinary: Negative

Gastrointestinal: Negative

ENMT: Negative

Neurological: negative

Respiratory: Negative

Endocrine: negative

Skin: negative

Eyes:negative

OBJECTIVE:

Labs

Age: 85 Gender: Female Weight= 54.8 kg, Height= 160 cm

Temperature max= 97.7 F, HR: 89 bpm BP range (sitting)= 146/84 mmHg

CBC: 05/29

WBC= 5.47 k/uL RBC= 4.52 million/UL Hgb= 13.1 gm/dL Hct=40.2 % Platelet= 199 k/uL

Chem-7: 05/14

Na= 138 mmol/L K= 4.1mmol/L Cl= 101 mmol/L CO2= 21.6 mmol/L BUN= 13 mg/dl

Scr= 0.5 mg/dl

Other Relevant Labs:

CrCl= 88 mL/min

TSH: 3.270

Folate: 16.4

Vitamin B12: 249.9

HbA1C 7.8

Cholesterol: 189

Triglycerides: 86

HDL: 53.9

LDL: 135.0

Intake:

07/29: 1680

07/28: 1800

07/27: 1920

07/26: 1680

Glucose levels:

07/30: 06:26 (99)

07/29: 06:18 (102) 16:23 (110)

07/28: 06:28 (95) 16:38 (127)

07/27: 06:45 (116) 16:51 (125)

Diet:

1800 calorie (60 gm carbohydrates); no concentrated sweets

Urinalysis

- 07/24/2018: 10,000-100,000 CFU Pseudomonas aeruginosa

MIC profile:

Pseudomonas aeruginosa
METHOD MIC
---------- ----------
CEFEPIME 4.0 mcg/mL Susceptible
CEFTAZIDIME <=2 mcg/mL Susceptible
CIPROFLOXACIN <=0.5 mcg/mL Susceptible
GENTAMICIN <=1 mcg/mL Susceptible
LEVOFLOXACIN <=1 mcg/mL Susceptible
PIPERACILLIN + TAZOBACTAM 4/4 mcg/mL Susceptible
TOBRAMYCIN <=2 mcg/mL Susceptible

Inpatient Medications:

- Psych
    - Haldol 1 mg q6hr prn agitation
    - Venlafaxine 75 mg qam for depression
    - Mirtazapine 15 mg qhs for insomnia and depression
    - Risperidone 1 mg qhs for psychosis
    - Risperidone 0.75 qam for psychosis
- Chronic diseases:
    - Metformin 500 mg BID for diabetes
    - Lantus 12 units qhs and 5 units qam
    - Lispro 4 units AC
    - Pravastatin 10 mg qhs for hyperlipidemia
    - Losartan 100 mg qam for htn
    - Apixaban 2.5 mg for DVT prophylaxis
    - Levothyroxine 88 mcg q7am for hypothyroidism
    - Clonidine 0.2 mg BID for HTN
    - Acetaminophen 325mg q6 prn for pain
    - Maalox q2hr prn for dyspepsia
    - Milk of magnesia 30 mls q24 hr prn constipation
    - Cyanocobalamin (b-12) 500 mcg qam for b12 deficiency
    - Florastor 1 capsule BID for probiotic
    - Levofloxacin 750 mg qam for UTI (stop after 5 days 08/02)
    - Lactulose 30mL q24 PRN for constipation

Deprescribing Assessment:

Management of Hyperlipidemia

Deprescribing Plan:

SUBJECTIVE:

HPI: GM is a 66 year-old WM who was certified to Sheppard Pratt on 7/29/18 from Howard County General Emergency Room with a chief complaint of aggression and agitation. His ER visit was precipitated by aggression and agitation that was observed by his wife. This past winter, GM suffered from several CVAs (last event 6 months ago) that have resulted in paralysis waist down, vascular dementia, and aphasia. He is unable to dress or bathe himself. He can express his thoughts but cannot complete full sentences. On arrival, patient was agitated, threatening, and verbally abusive, a behavior that has resulted in him being removed from several nursing homes.

GM has not been aggressive or agitated today on the unit. This improvement in behavior has been observed over the past few days. GM reports feeling overwhelmed and frustrated with all the care he needs, not what he wants for his life. He admits all he wants for the end of his life is to be in the comfort of his wife.

Allergies:

- NKDA

Past Medical History:

- Psychotic Disorder, NOS
- Vascular Dementia
- Depressive Disorder, NOS
- Incontinence
- UTI
- DM
- HLD
- HTN
- CAD, s/p CABG
- Hx of CVAs

Social History:

Patient is a 66- year –old male who lives at home with wife who is his primary caretaker. Patient was laid off 4 years ago and was previously employed as corporate credit manager. He filed for bankruptcy and lost his home.

Family History:

Patient is married to current wife for 44 years. They have 3 children – daughter lives with him, sons live in MA. His younger sister died at age 35, suffered from epilepsy, and used psychiatric medications. His mother was an alcoholic

OBJECTIVE:

Labs
Age: 66 Gender: Male Weight= 86.1 kg (190 lbs.), Height= 177.9 cm (70 inches)
Temperature 96.5°F, HR- 76 bpm, RR – 14 breaths/min

Blood pressure

07/20: 08:58 (150/79 mmHg)

07/19: 16:25 (120/60 mmHg)

07/19: 08:40 (149/80 mmHg)

07/18: 16:10 (140/70 mmHg)

07/18: 09:26 (139/75 mmHg)

07/17: 16:37 (160/72 mmHg)

07/17: 11:05 (150/96 mmHg)

07/16: 16:53 (118/78 mmHg)

Glucose levels:

07/20: 11:30 (353)

07/20: 07:00 (144)

07/19: 21:00 (147)

07/19: 17:00 (261)

07/19: 11:45 (297)

07/19: 07:00 (153)

07/18: 21:00 (280)

07/18: 17:00 (174)

07/18: 06:40 (184)

07/17: 21:00 (207)

07/17: 17:00 (204)

07/17: 11:30 (343)

07/17: 05:40 (196)

07/16: 21:00 (193)

Inpatient Medications:

- Psych
    - Risperidone M-Tab 1 mg q6h prn for agitation
    - Lorazepam injection 1 mg IM q6h prn for seizures/agitation
    - Keppra 500 mg BID for seizures
    - Escitalopram 10 mg qAM for depression
    - Quetiapine 25 mg qAM for mood lability
- Chronic diseases:
    - APAP 650 mg QID for pain
    - MgOH/AlOH 1200/mg/1200 mg 30 mL qAM prn for constipation
    - MgOH 30 mL qAM prn for constipation
    - Zolpidem 5 mg qHS prn for insomnia
    - Insulin sliding scale for diabetes
    - Nystatin powder 100,000 units apply BID for 14 days for candida
    - Gabapentin 300 mg qHS for peripheral neuropathy
    - Lisinopril 5 mg qAM for HTN
    - Simvastatin 20 mg qHS for HLD
    - Clopidogrel 75 mg qAM for anticoagulation
    - ASA 325 mg qAM for anticoagulation
    - Phenazopyridine 100 mg qAM for UTI prophylaxis
    - Lantus 14 units SQ qAM for diabetes
    - Multivitamin 1 tablet qAM for supplement
    - Calcium 500 mg BID for supplement
    - Vitamin D 125 IU BID for supplement
    - Fish Oil 1 gm qAM for supplement
    - Vitamin E 200 IU qAM for supplement

Deprescribing Assessment:

Management of Palliative Care

Deprescribing Plan: