Optimal Prescribing of Anticoagulants in the Elderly with Atrial Fibrillation: The "Do's" & "Don'ts"

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Dr. M. Hart: No disclosures

 Dr. P. Giancroce: Ontario Trainer, Coaguchek XS, Roche Diagnostics, 2006–2012

Objectives

By the end of this hour you will be able to:

1. Integrate when to use warfarin vs. the new oral anticoagulants with the current guidelines

2. Recognize the challenges in warfarin management and apply optimization strategies in dosing and monitoring

3. Differentiate between the new oral anticoagulants and apply practical recommendations to ensure safe and effective prescribing of each agent

Agenda

- 1. Introduction
- 2. Review of guidelines: CCS 2014
- 3. New OACs vs Warfarin: Efficacy and safety
- 4. Warfarin Management: Challenges and practical tips
- 5. New OAC's: Challenges and practical tips
- 6. Case based summary of Do's and Don'ts

Introduction

Prevalence and Incidence of AF

- Most common sustained cardiac arrhythmia in adults
- Men > Women
- Prevalence increases with age
 - \circ < 1% in those 55–59 years
 - \circ 5–15% in those > 80 years
- Lifetime risk of developing AF after 55 is 24% in men, 22% in women

Prevalence and Incidence

- ► Untreated AF → 5 x more likely risk for thromboembolism, stroke
- Incidence of stroke attributed to AF increases with age
 - -1.5% at age 50-59
 - -23.5% age 80-89

Prevalence and Incidence

- Stroke is the major complication of AF
- Strokes related to AF more severe than strokes from other causes
 - Increased disability
 - Longer in-hospital patient stay
 - Lower rate of discharge home
 - Increased mortality

Decreased Anticoagulation Use with Aging

- 14% reduction in anticoagulation use for each decade after age 75

Decreased Anticoagulation Use with Aging

- New atrial fibrillation guidelines challenging to apply in practice to the elderly
 - -age
 - -CrCl
 - -patient wishes
 - -weight and dosing
 - -falls
 - -nutritional status
 - -risk of bleed
 - -frequent changes in medical status
 - -adherence issues

Case Presentation: Mrs. AF

<u>Case:</u> Mrs. AF comes to see you in your office

- 86 year old female, 55 kg, CrCl 32 mL/min
 PMH:
 - CAD
 - AFib
 - Pacemaker placement in 2004
 - CHF (NYHA II)
 - Right hip # in 2010
 - Osteoporosis
 - CVA 2004
 - Recurrent aspiration pneumonia
 - Recurrent UTIs
 - Partial hysterectomy for fibroids >50 yrs ago.

Mrs. AF's story

- Recent visit to acute care for urosepsis, kidney failure
- On warfarin for Afib, recent changes in her medical status have resulted in unstable INRs, frequent blood tests, warfarin adjustments...
- "Tired of going to emergency departments, does not want her life saved"
- "Tired of having so much blood work and being poked so often"
- Balance more unstable, deconditioned, falling

Review of Guidelines: CCS 2014

Antithrombotic Therapy: Stroke Prevention

- Decision for antithrombotic therapy is individualized by stratifying
 each patient with AF
- Predictors of embolic risk in patients with non valvular AF vs. Predictors of bleeding

 $CHADS_{2} vs. HAS-BLED$ $CHA_{2}DS_{2}-VASc$

Predicting Stroke Risk: CHADS₂

Clinical parameter: P	<u>oints:</u>
Congestive heart failure (CHF)	1
Hypertension	1
Age \geq 75	1
Diabetes mellitus	1
Secondary prevention	2
(prior TIA or ischemic stroke or TE*	*)

Annual stroke rate increasing by about 2.0% for each 1-point increase in $CHADS_2$ score

**2014 AHA Guidelines added TE

	Condition	Points
С	Congestive heart failure (or Left ventricular systolic dysfunction)	1
A	Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication)	1
A ₂	Age \geq 75 years	2
D	Diabetes Mellitus	1
S ₂	Prior stroke or TIA or thromboembolism (TE) **	2
V	Vascular disease (e.g. peripheral artery disease, myocardial infarction, aortic plaque)	1
Α	Age 65-74 years	1
Sc	Sex category (i.e. female gender)	1

**2014 AHA Guidelines added TE

HAS-BLED

Predict bleeding risk:	Points:
Hypertension	1
Abnormal Renal/Liver Function	1 point each
S troke	1
Bleeding History or Predisposition	1
Labile INR (if on warfarin)	1
Elderly (> 65 Years)	1
Drugs/Alcohol Concomitantly	1 point each

2014 CCS Focused Update

- Advances in oral anticoagulant therapy
- New CCS algorithm
- Optimal approach to peri-operative OAC management
- Updates on rate and rhythm management, catheter ablation

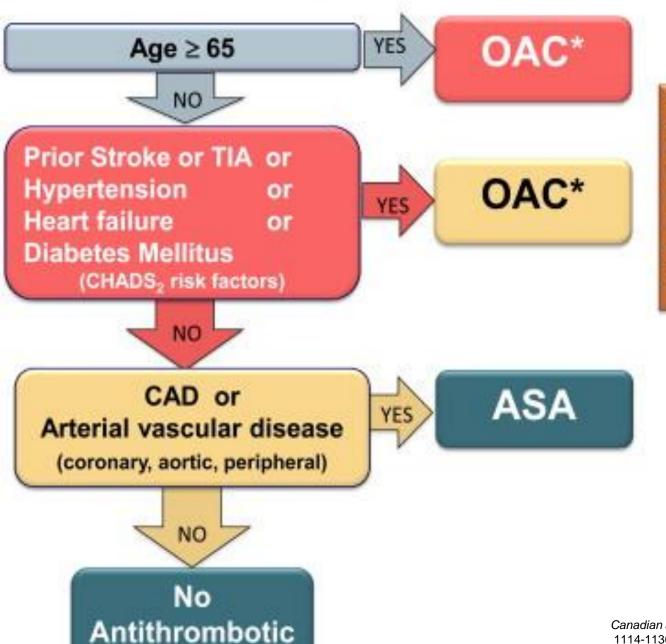
CCS 2014: CHADS₂ and CHA₂DS₂-VASc

- Continue to use CHADS₂ schema to estimate stroke risk
- In some patients, inclusion of CHA₂DS₂-VASc

Anticoagulation

- Dabigatran or Warfarin (INR 2.0-3.0) reduces risk of stroke by 50-68% compared to placebo
- Aspirin reduces risk of stroke by 22–36%

The "CCS Algorithm" for OAC Therapy in AF



Consider and modify (if possible) all factors influencing risk of bleeding during OAC treatment (hypertension, antiplatelet drugs, NSAIDs, excessive alcohol, labile INRs) and specifically bleeding risks for NOACs (low eGFR, age ≥ 75, low body weight).¹



New OACs vs. Warfarin:

Review of evidence comparing efficacy and safety

Oral Anticoagulants

<u>Warfarin</u>

 Inhibits vitamin K-dependent coagulation factors II, VII, IX, X

Four New Oral Anticoagulants (New OACs): Dabigatran, Rivaroxaban, Apixaban, Edoxaban:

- Dabigatran: Factor IIa inhibitor
- Rivaroxaban, Apixaban, Edoxaban: Factor Xa inhibitor

Dabigatran vs. Warfarin: RE-LY

Efficacy: < 75 years old

- Dabigatran 150 mg > Warfarin
- Dabigatran 110 mg ~ Warfarin

<u>Safety/risk of bleeding (< 75 year old)</u>

- Dabigatran 150 mg lower intracranial bleeding
- Dabigatran 110 mg lower major bleeding, but not with Dabigatran 150 mg
- Dabigatran 150 mg higher GI bleeding

Dabigatran vs. Warfarin (RE-LY)

<u>Efficacy: \geq 75 years old</u>

 Dabigatran (150 or 110 mg) as effective as warfarin

<u>Safety: \geq 75 years old</u>

- Dabigatran (150 or 110 mg) lower ICH
- Dabigatran 110 mg less major bleeding

Dabigatran vs. Warfarin

- Initial RE-LY showed excess of MI with Dabigatran over Warfarin but difference insignificant when additional events considered
- Meta-analysis of a RCT of Dabigatran found statistically significant increase in risk of MI/ACS in patients randomized to Dabigatran, but less total mortality

HAS-BLED

Score 0-2

-Low risk of bleeding

-Warfarin (INR 2-3) or Dabigatran 150 mg bid recommended

Score of ≥ 3

-Dabigatran 110 mg bid may be considered, as it has similar efficacy in the prevention of stroke and systemic embolism but lower rates of intracranial hemorrhage and major bleeding, compared with Warfarin and the 150 mg dose of Dabigatran

Rivaroxaban vs. Warfarin: (ROCKET-AF)

Efficacy:

No difference in reduction of stroke or systemic embolism

<u>Safety:</u>

No difference in risk of major or non-major bleeding

Less fatal bleeding and ICH with Rivaroxaban

 Dose reduction of Rivaroxaban from 20 to 15 mg once daily for renal impairment (CrCl 30 - 49 ml/min)

Apixaban vs. Warfarin: (ARISTOTLE)

Efficacy:

Apixaban 5mg twice daily superior over Warfarin

Safety:

- Apixaban: ↓ major bleeding, ↓ ICH, ↓ mortality rates
- GI bleeding rates the same

Renal Impairment (CPS):

- $CrCl \ge 25 mL/min no dosage adjustment$
- CrCl 15-24 mL/min no dosage recommendations
- CrCl < 15 mL/min use not recommended</p>
- If at least 2 of the following: $CrCl \ge 133$, ≥ 80 yrs, body wt ≤ 60 kg: reduce dose to 2.5 mg twice daily

Edoxaban vs Warfarin ENGAGE AF-TIMI 48 Trial

21,105 patients (mean CHADS₂ = 2.8) randomized double blind to Edoxaban 30 mg once daily, 60 mg once daily, or Warfarin.

Efficacy:

 Non-inferior to Warfarin for both doses, neither was superior, trend toward benefit at higher dose

Safety:

- Bleeding rates significantly lower for both doses
- Intracranial bleeding significantly less with both doses than Warfarin

CAD

- Dabigatran had more MI but lower mortality (RE-LY)
- ROCKET-AF: Non-significant reductions in MI and all-cause mortality with Rivaroxaban (some trend to less MI)
- ARISTOTLE: Non-significant reduction of MI and all-cause mortality

Overall comparison of New OACs vs. Warfarin

- Recent systematic review, meta-analysis (12 phase II and III trials), 2012
- SSE= stroke/systemic embolism in atrial fibrillation or flutter: PE, MI, death, major bleeding
- Statistically significant reductions in SSE, total mortality
- Dabigatran, Apixaban superior in prevention of SSE (Dabigatran 110mg and Rivaroxaban non-inferior)

Summary of New OACs vs Warfarin

- All were non-inferior for outcome of all stroke or systemic embolism
- None caused more major bleeding
- Dabigatran 110 mg and Apixaban cause less major bleeding
- Dabigatran 150 mg and Rivaroxaban do not increase major bleeding
- All were superior for outcome of intracranial bleeding

Summary of New OACs vs. Warfarin

 Comparison of lower-dose regimens with warfarin showed similar rates of SSE, significantly less intracranial bleeding, significantly less mortality

Warfarin Management Challenges and Practical Tips

Challenges of Warfarin

- INRs Patient to lab
 - Blood sample
 - Travel
 - Inaccuracies
 - Variability
 - Timely access
- Dosing Monitoring / Time
 - Changes / Communication / Time
 - Managing missed doses

Challenges of Warfarin

Interactions

- Warfarin Drug
- Warfarin Food
- Warfarin Herbal/Natural
- Warfarin Alcohol
- Delay in getting patient therapeutic initially and post procedures

Bleeding

Benefits of Warfarin

- Inexpensive
- Indications: valvular a.fib, a.fib & MI/CHF/hip #
- Long term safety and efficacy data
- Experience e.g. antiplatelet combinations
- Not contraindicated in renal dysfunction
- Test for adherence
- I missed dose unlikely an issue
- Test for assessing safety for emergency surgery
- Reversible (vitamin K, four factor concentrates e.g. Octaplex[®])
- Crushable, Feeding Tube administration

For a cash-paying patient with atrial fibrillation

A) Warfarin and weekly INRsB) Warfarin and weekly point of care (POC)C) New oral anticoagulant

What is the least expensive option?

What is the most expensive option?

Anticoagulation Costs: Cash-paying patient

Options	Components (assuming 4 INRs/month)	~ Cost/month with weekly INRs
A. Warfarin + INRs	Warfarin	\$ 20
	INR (provincially funded)	\$ O
	Gas	\$ 10
	Parking	varies
	Total	\$ 30
B. Warfarin+ POC	Warfarin	\$ 20
	POC device (assuming only 3 yr life)	\$ 15
	POC strips	\$ 33 (\$ 8 if 1 /month)
	Total	\$ 68 (\$ 43 if 1/month)
C. New OAC	Drug	\$ 95-106
	Total	\$ 95-106 (\$1140-1300/yr)

Traditional Venipuncture for INRs: Wastes time and money!



Community Based Anticoagulation: Models of Care across Canada

Level 1			
Physician Prescribes	Level 2		
Certified Pharmacist trains POC	Physician Prescribes	Level 3	
operator	POC testing in pharmacy	Pharmacist co-prescribing	
POC at home (similar to insulin)	Patient chart	POC testing in pharmacy	
	Advanced Patient Counseling	Case Management	
		Comprehensive Patient Counseling	

Practical Tips to Address Challenges: INRs

Challenge	Potential Approaches
Patient to lab	Point of Care, Reinforcement from physician of the importance, Family assistance, Lab come in
Blood sample	Point of Care, butterfly, skill/knowledge level
Travel	Point of Care, copies of results/letter, plan ahead
Pre-analytical inaccuracies	Point of Care, lab with high standards
Variability	Point of Care, consistent lab
Timely access	Point of Care, approve for patient/SDM to get results

Practical Tips to Address Challenges: Interactions

Interaction	Examples	Approach
Drug	Ciprofloxacin, Co-trimoxazole, Metronidazole	Point of Care; Proactively decrease especially if history; Day 3-4 INR
	Phenytoin, Levothyroxine	Point of Care; Day 3-4 INR
Food	Vitamin K rich foods e.g. Broccoli, Spinach	Canada's Food Guide; moderation; Point of Care
Herbal/ Natural	Ginseng, Ginkgo, Ginger, St. John's Wort	Avoid; Check with the pharmacist; Point of Care
Alcohol	Beer, Wine, Spirits	Moderation and Consistency; Point of Care
Disease	Infections	Baseline INR; Point of Care otherwise empiric?

Challenge	Considerations	Potential Approaches
Delay in patient being protected post initiating	Evaluate urgency via CHADS ₂ score	If CHADS ₂ score is low monitor closely with dose adjustment. If higher, consider LMWH to bridge.
Delay in patient being protected post-procedure	As above as well as evaluate risk of VTE post- procedure	Use LMWH if needed to bridge
Missed Doses; Incorrect Doses		Written instructions, Request verbal repeat of changes, work with family or friend/Supervisor, Calendar, Chart, Apps

- Don't wing it!
- Understand pharmacology; indirect MOA (t ½ of factors)
- Monitoring INR/Warfarin form (hard or electronic)
- Review last two weeks INRs/doses at least
- Maintenance Dosing: Change doses by % of weekly dose (typically 5-15 %)

- Computer software; Nomograms
- Confirm first what they have taken in the past two weeks
- Describe new dose using colors, strengths and number to take
- Have them write it down and repeat it back;
 Patient to keep dosing table.

What does your typical initial warfarin prescription for the elderly look like?

Rx: Warfarin 2.5 mg po UD x 3 months?

Pharmacist > 90 tablets of 2.5 mg

Potential doses: 1.25, 2.5, 3.75, 5 mg (etc.)

For those >75 yo consider ...

1 mg tab is the tool to get the dose

NameAddress	
	8
Warfarin 1 mg Tablets	
Mitte 100 (~ 1 month supply)	
Take UD	21
MD	Devited Sun Developments

- Avoid the roller coasters
 - (e.g. "Hold and we'll repeat INR on Monday", Warfarin 4 mg M-F and none S/S, vitamin K minimize use)
- One INR slightly out of range in an otherwise stable patient → recheck INR
- Missed Doses → few hours take it; ½ interval ½ dose; longer ½ extra for next two doses

- Consider delegating to pharmacist
- In motivated/intelligent patients consider providing parameters for them to adjust and provide documentation (like insulin)

Should we switch patients to New OACs?

- Previous experience on warfarin? (TTR?)* If they are stable, why change it?
- Are they just asking if they can have the same without the INRs or is there an issue?
- If getting to the lab is an issue, what about POC?

If challenges can they be addressed?

*TTR=Time in Therapeutic Range

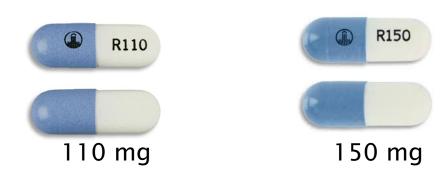
New OACs

Challenges and Practical Tips

Dabigatran (Pradaxa®)



75 mg



Rivaroxaban (Xarelto®)



10 mg



15 mg



20 mg

Apixaban (Eliquis[®])





Considerations when choosing OACs

In addition to effectiveness, risk of bleeding, cost/coverage,

- Indications
- Renal dysfunction
- Liver dysfunction
- Experience with Warfarin/INRs
- Drug interactions
- Non-bleeding Adverse effects
- Dose regimens/Supervision
- Feeding tube, Swallowing issues, Food
- Adherence
- Reversibility Bleeding, Surgical procedures

Indications

New Oral Anticoagulants are NOT indicated for:

- Valvular atrial fibrillation rheumatic valvular disease (especially mitral stenosis)
- Mechanical or bioprosthetic heart valves
- Hip fracture orthopedic surgery prophylaxis
- CHF NYHA Grade III-IV
- Post–MI
- Not all are approved for VTE treatment

Renal Dysfunction

CrCl	Warfarin	Dabigatran	Rivaroxaban	Apixaban
≥ 60 mL/min	Dose adjusted for INR 2.0–3.0	150 mg or 110 mg q12h*	20 mg daily	5 mg q12h (2.5 mg q12h if 2 of 3 of; <u>></u> 80, <u><</u> 60 kg, SCr 133)
50–59 mL/min	Dose adjusted for INR 2.0-3.0	150 mg or 110 mg q12h*	20 mg daily	5 mg q12h (2.5 mg q12h if 2 of 3 of; ≥ 80, <u><</u> 60 kg, SCr 133)
30–49 mL/min	Dose adjusted for INR 2.0-3.0	150 mg or 110 mg q12h*	15 mg daily	5 mg q12h (2.5 mg q12h if 2 of 3 of; <u>></u> 80, <u><</u> 60 kg, SCr 133)
15–29 mL/min (not on dialysis)	No RCT data	Contraindicated	Not recommended	For CrCl 25-29mL/min 5 mg q12h (2.5 mg q12h if 2 of 3 of; ≥ 80, ≤ 60 kg, SCr 133) For CrCl 15-24 mL/min No data available
< 15 mL/min (on dialysis)	No RCT data	Contraindicated	Not recommended	Not Recommended due to lack of data

* 110 mg q12h if \geq 80 yo or > 75 yo + bleeding risk factor [antiplatelet, NSAIDs, gP inh (amiodarone, verapamil, quinidine, ketoconazole), CrCl 30-50 mL/min]

Drug Characteristics	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)
Mechanism	Direct Thrombin Inhibitor	Direct Factor Xa Inhibitor	Direct Factor Xa Inhibitor
Bioavailability	3-7 % (may ↑ by 75 % if capsule breached)	$66~\%$ (may \uparrow to 100 % with food)	50 %
Peak level	2-3 hrs	2-4 hrs	3 hrs
Elimination	Renal 80 % Fecal 20 %	Renal 66 % Fecal/Biliary 28 %	Renal 25 % Fecal 55 %
Half life	12-17 hrs (27 hrs if CrCl < 30 mL/min)	7–11hrs (elderly 11–13 hrs)	9–14 hrs
Dosing Interval	q12h	Once daily	q12h
Missed Dose	Half-life > Interval	Half-life << Interval	Half-life= Interval
Dose	150 mg	20 mg with food	5 mg
Dose in Renal Impairment	110 mg q12h if > 80 or >75 +RF Contra < 30 mL/min	15 mg once daily with food if CrCl 30-49 mL/min	2.5 mg q12h If at least 2 of 3; SCr≥ 133, ≥ 80 yo, ≤ 60 kg
Special Considerations	2x Dyspepsia (30 %) No chew, bite, crush, feeding tube. Original package.	levels in renal or hepatic dysfunction.	Okay to chew, bite, crush, feeding tube, with or without food



What's wrong with this picture?

Drug Characteristics	Dabigatran (Pradaxa®) (RE-LY)	Rivaroxaban (Xarelto®) (ROCKET-AF)	Apixaban (Eliquis [®]) (ARISTOTLE)
Prodrug	Yes	No	No
CYP Met	None	32 % CYP 3A4, 2J2	15 % CYP 3A4
P-gp transport	Yes	Yes	Yes
Drug Interactions	Strong P-gp inh/ind (no effect on CYP 450)	Both 3A4 inh + P-gp inh or P-gp inhibitors	Both 3A4 inh + P-gp inh Both 3A4 ind + P-gp ind
	ketoconazole, antacids, amiodarone, verapamil, quinidine, cyclosporine, tacrolimus, clarithromycin, carbamazepine, St. John's Wort, etc.	amiodarone, carbamazepine, phenytoin, pantoprazole, azoles, clarithromycin, phenobarbital fluconazole, St. John's Wort, etc.	azoles, carbamazepine, phenytoin, phenobarbital, St. John's Wort, etc.
Cost Rx (inc DF)	~ \$106/month	~ \$95/month	~ \$106/month
Lab Monitoring	No	No	No
Reversal (Bleed, Sx, MI)	No antidote; Await t ½	No Antidote; Await t ½	No Antidote; Await t½

Drug Characteristics	Dabigatran (Pradaxa [®]) (RE-LY)	Rivaroxaban (Xarelto [®]) (ROCKET-AF)	Apixaban (Eliquis [®]) (ARISTOTLE)
Switching to New OAC	Start when INR < 2	Start when INR <u><</u> 2.5	Start when INR < 2
Switching to Warfarin	Start warfarin 1–3 days before d/c dabigatran depending on CrCl (> 50 mL/min 3 days; 31–50 mL/min 2 days; 15–30 mL/min 1 day)	Start warfarin. Stop rivaroxaban after 2– 4 days of overlapping therapy <u>and</u> once INR <u>></u> 2	Start warfarin, stop apixaban when INR ≥ 2; (Day 3 start INRs & do pre- apixaban dose) OR stop apixaban, start dalteparin (stop when INR > 2) & warfarin.
Discontinuation Rates	Discontinued almost 50 % more often than warfarin in first year.		

Summary of A. Fib Elderly - OAC choice

Warfarin if CrCl < 30 mL/min Valvular a.fib, replaced valves, MI, CHF, hip# Funding issues Controlled with warfarin & no concerns Excluded from landmark trials

Otherwise, choice...

Adherence issues \rightarrow not dabigatran / rivaroxaban Borderline renal function \rightarrow not dabigatran / rivaroxaban Crush, chew, bite, feeding tube \rightarrow not dabigatran Lack of consistent food admin \rightarrow not rivaroxaban

Drug interactions \rightarrow choice based on avoiding interacting agents

Case-Based "Do's and Don'ts"

Patient: "I heard that there is a new drug out that is the same as Coumadin but without the blood tests. Would it be good for me?"



In discussing the options with your patient, Do:

- Make patient aware of stroke risk (CHADS₂/CHA₂DS₂VAS_C)
- Discuss the risk of bleeding (HAS-BLED)
- Ensure patient is competent/capable; involve supports
- Assess experience on warfarin (TTR) and ease of INRs
- Identify indications e.g. valvular a.fib, hip#, CHF,valve repl
- Consider POC and other approaches to meet challenges
- Review impact on lifestyle
- Stress adherence requires more than the usual 50 %
- Inform re: lack of reversibility for surgery or bleed
- Discuss cost/coverage
- Recommend Medical Alert
- Check renal function (CrCl) (if < 30 use warfarin)</p>

Renal Function Monitoring

 Depends on age, pre-existing renal function, co-morbidities, other medications, and choice of new OAC

CrCl (mL/min)	Monitoring
> 50	Yearly + with clinical deterioration
30-50	Q 6 months + with clinical deterioration
< 30	Contraindicated

Do:

- Continue to use Warfarin if patient stable on it.
- Continue to use warfarin for valvular a.fib, patients that also have MI, CHF, ortho hip #
- Give Rivaroxaban with food (e.g. evening meal)
- Ask about other drugs, OTC's, herbals etc. => refer to pharmacist
- Avoid Dabigatran unless drug interaction preference
- Reinforce the need for Dabigatran to stay in original packaging

Do:

- Stop prior to surgical procedures (see guidelines)
- Follow instructions when switching
- Inform patient/SDM re: no antidote
- Inform patient re: missed doses
- Consider need for dosage adjustments
- Monitor OAC carefully (similar to Warfarin but without the blood work)
- Look to work in a partnership with a pharmacist with a focus on anticoagulation

Don't:

- Use Vitamin K unless required (exceeds reportable range or bleeding)
- Use Vitamin K IM or SC (use PO; IV for severe life-threatening bleeding)
- Dose Warfarin based only on last INR and increase or decrease to next available strength of tablet.
- Hold Warfarin for days due to an elevated INR until next INR back on Monday

Summary

- Age should not be a deterrent to oral anticoagulant use, but proceed with caution!
- The choice of thrombophylaxis (ASA vs OAC) depends on a patient's stroke risk factors and bleeding risk
- Consider the following factors when guiding decisions regarding which OAC;
 Experience with Warfarin, Renal dysfunction, Indications, Cost, Swallowing, Feeding tube, Adherence, Side effects, Dose regimens, Drug Interactions

What about Mrs. AF?

1) Warfarin vs. new OAC in this patient?

2) If you choose a new OAC- which one, and why?

What about falls in the elderly?

- Risk of falling not a significant factor when deciding on oral anticoagulation therapy
- People taking warfarin must fall ~ 295x/yr "for Warfarin not to be the optimal therapy"
- A patient with a history of falls will have
 1.8 falls/year, on average

