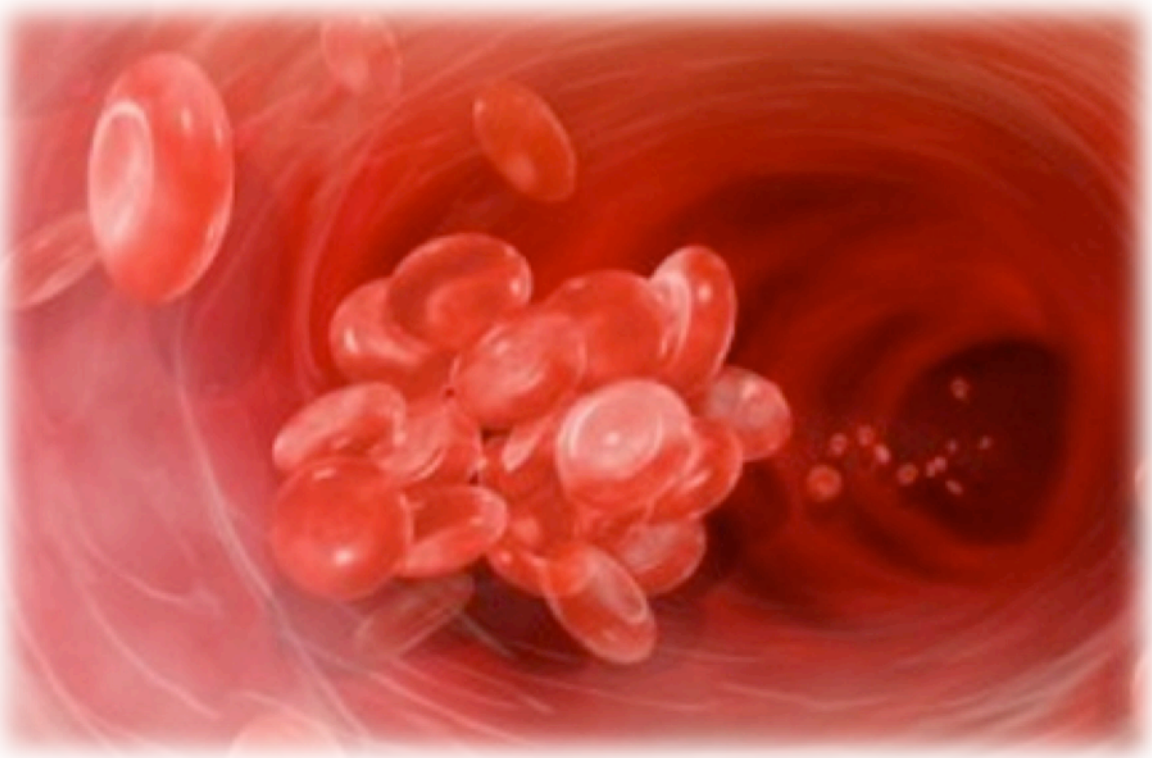
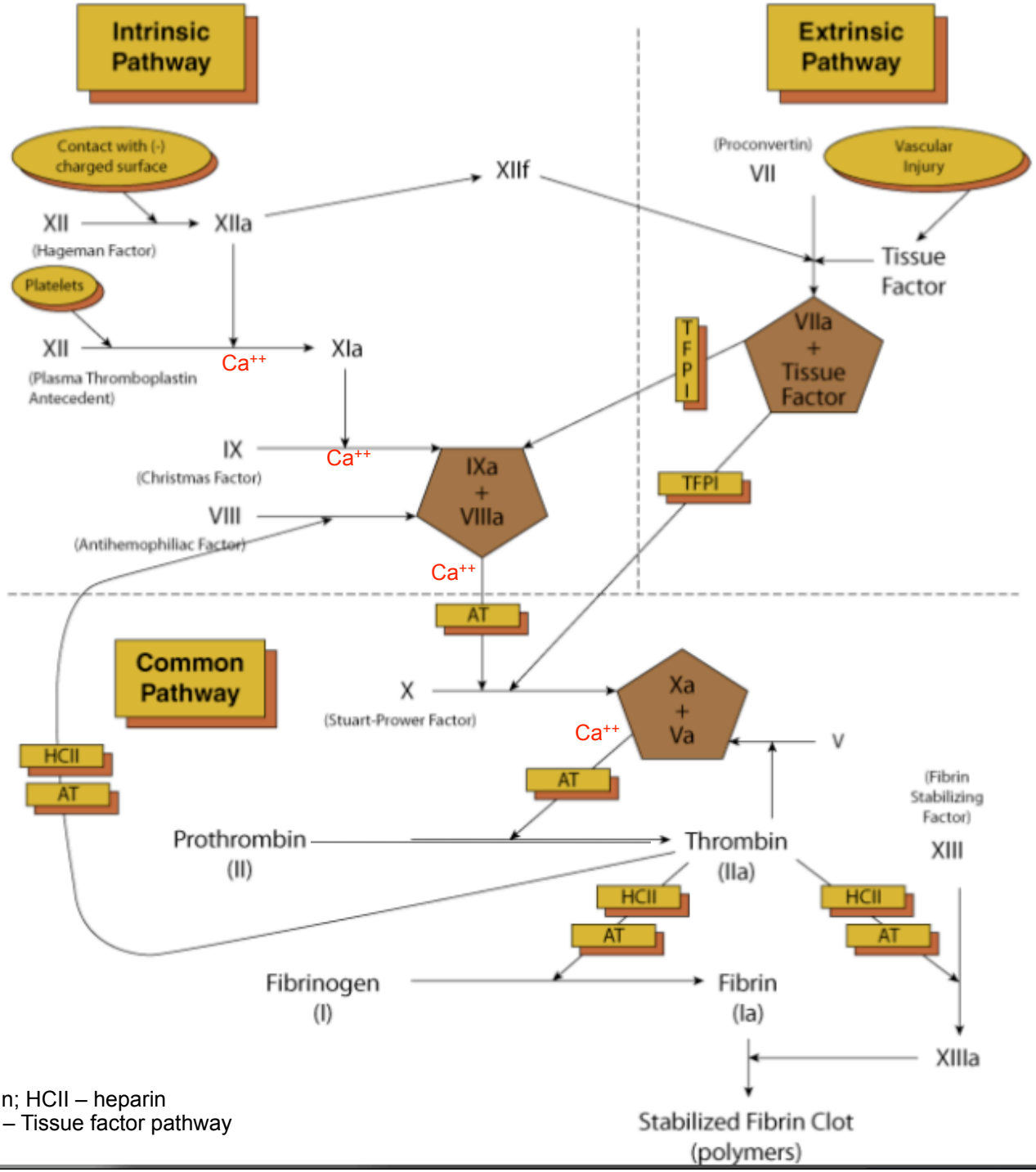


ORAL ANTICOAGULANTS

Madeline Stephens and Afshin Taleghani

PharmD Candidates 2011

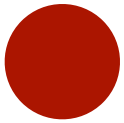
University of Cincinnati



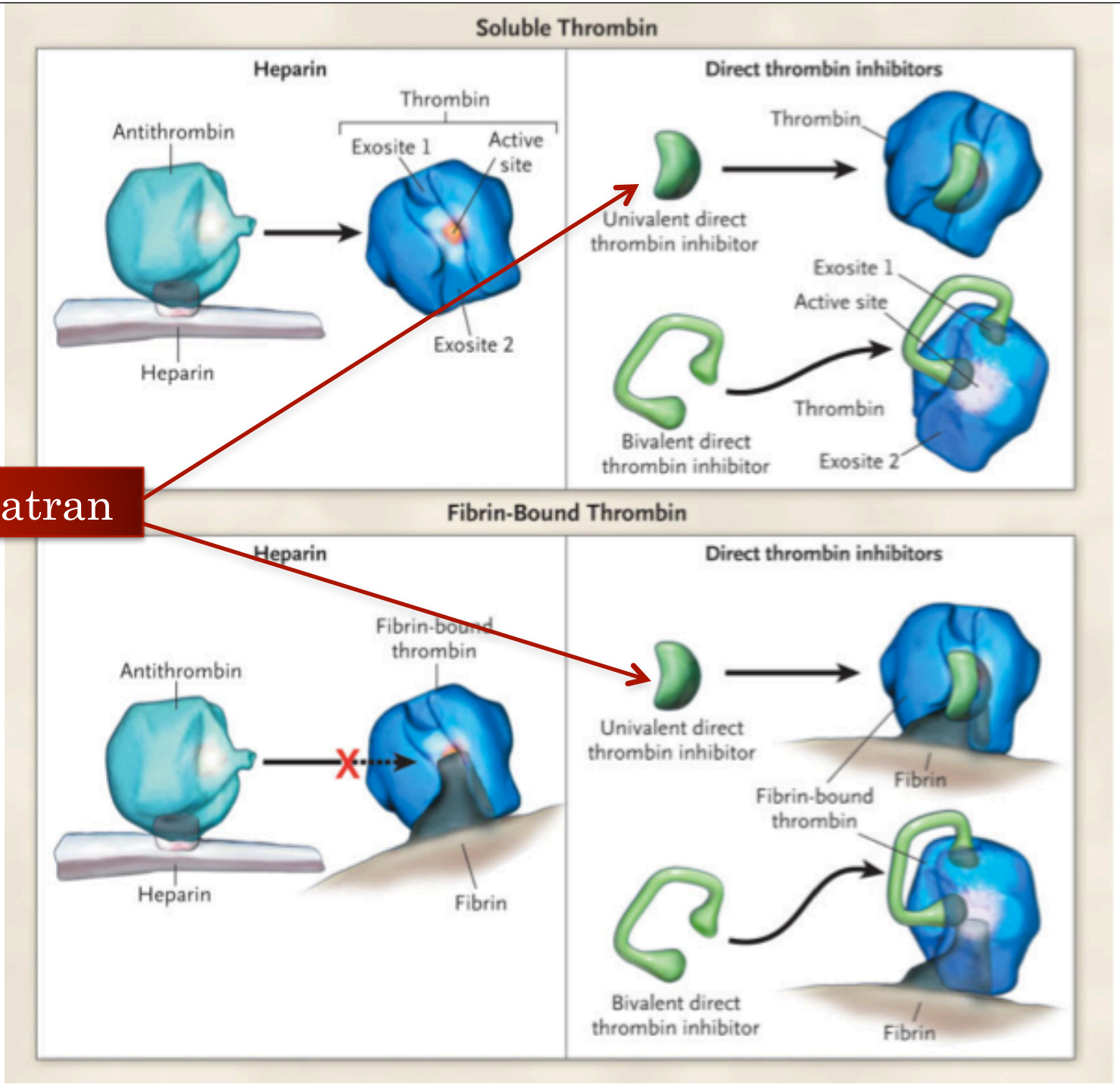
AT – Antithrombin; HCII – heparin cofactor II; TFPI – Tissue factor pathway inhibitor

ORAL ANTICOAGULANTS

- Vitamin K Antagonist
  - Warfarin
- Oral Anti-Xa
  - Rivaroxaban (Xarelto)
    - Not available in U.S.
  - Apixaban
    - Phase III trials
- Oral Direct Thrombin Inhibitors
  - Ximelagatran
  - Dabigatran (Pradaxa)
    - FDA approved

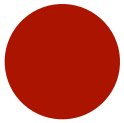


Dabigatran


Soluble Thrombin
Heparin
Thrombin
Antithrombin
Exosite 1
Active site
Exosite 2
Heparin
Direct thrombin inhibitors
Thrombin
Univalent direct thrombin inhibitor
Exosite 1
Active site
Thrombin
Bivalent direct thrombin inhibitor
Exosite 2
Fibrin-Bound Thrombin
Heparin
Fibrin-bound thrombin
Antithrombin
Heparin
Fibrin
Direct thrombin inhibitors
Univalent direct thrombin inhibitor
Fibrin
Fibrin-bound thrombin
Bivalent direct thrombin inhibitor
Fibrin

WARFARIN

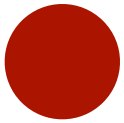
- Indicated for various conditions
- Dosing: Individualized
  - Onset of action: 4 days to reach full anticoagulation
    - (loading dose does not provide more rapid anticoagulation)
  - Elimination: Hepatic
    - No adjustment in renal impairment
- Adverse events: Bleeding and Warfarin-induced skin necrosis
  - Precautions: Category X
- Monitoring: INR, Bleeding (expected vs. severe)
- MANY drug-drug and drug-food interactions
  - What are the major ones?



BRIDGING WARFARIN THERAPY

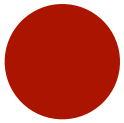
Protein	Half life (hours)
Factor II	**60-100**
Factor VII	**4-6**
Factor IX	20-30
Factor X	24-40
Protein C	**8-10**
Protein S	**40-60**

- When should you start warfarin in a patient on heparin?
- When should you stop the heparin?



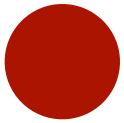
WARFARIN

- Advantages
  - Inexpensive
  - Antidote – Vitamin K
  - Can monitor INR to assess how anticoagulated the patient is
  - Familiarity
- Disadvantages
  - **Interactions** with food and drugs
  - Monthly monitoring
  - Bridge with heparin when initiating warfarin therapy
  - Titrate dose



RIVAROXABAN (XARELTO)

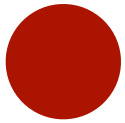
- Approved in Europe for VTE prophylaxis after a knee or hip replacement
  - FDA advisor committee recommended approval in march 2009
- Dosing
  - Knee: 10mg once daily x 14 days (start within 6-10 hours after surgery)
  - Hip: 10mg once daily x 35 days (start within 6-10 hours after surgery)
  - Contraindicated in patients with a CrCl <30mL/min and use caution in patients with a CrCl 30-49mL/min
  - Caution in patients <50kg
- Adverse Events: Bleeding
- Monitoring: No specific guidelines (not done in trials), Bleeding
- Interactions: potentially with P-Glycoprotein and CYP3A4 inducers/inhibitors



Variable	RECORD1	RECORD2	RECORD3	RECORD3
Patients	Post hip replacement	Post hip replacement	Post knee replacement	Post knee replacement
# of Patients (# included in analysis)	4,541 (3,153)	2,509 (1,733)	2,531 (1,702)	3,148 (1,924)
Intervention	Rivaroxaban 10mg/ day or enoxaparin 40mg/day for 33 days	Rivaroxaban 10mg/ day for 35 days or enoxaparin 40mg/day for 14 days	Rivaroxaban 10mg/ day or enoxaparin 40mg/day for 10-14 days	Rivaroxaban 10mg/ day or enoxaparin 30mg twice daily for 10-14 days
Outcome	Composite of DVT, nonfatal PE, or all-cause mortality Safety outcomes included major bleeding, nonmajor bleeding, postoperative wound infection, blood transfusions, and any adverse event			
Results	Primary endpoint -Rivaroxaban 1.1% -Enoxaparin 3.7% - NNT = 38 Secondary endpoint major VTE -Rivaroxaban 0.2% -Enoxaparin 2% - NNT= 56 No significant difference in major bleeding or LFT's	Primary endpoint -Rivaroxaban 2% -Enoxaparin 9.3% NNT= 14 Secondary endpoint major VTE -Rivaroxaban 0.6% -Enoxaparin 5.1% -NNT= 22 No significant difference in major bleeding	Primary endpoint -Rivaroxaban 9.6% -Enoxaparin 18.9% NNT= 11 Secondary endpoint major VTE -Rivaroxaban 1% -Enoxaparin 2.6% -NNT= 63 No difference for major bleeding, but rivaroxaban group	Primary endpoint -Rivaroxaban 6.9% -Enoxaparin 10.1% NNT= 31 Secondary endpoint major VTE -Rivaroxaban 1.2% -Enoxaparin 2% -NNT= 125

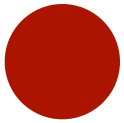
RIVAROXABAN (XARELTO)

- Advantages
  - No monitoring
  - Once daily dosing (no titration) – predicable anticoagulation
  - Less interactions than warfarin
- Disadvantages
  - Cost? – unknown as it is not approved yet but will likely be expensive
  - No antidote



DABIGATRAN (PRADAXA)

- Indicated for reducing the risk of stroke and systemic emoboli in patients with non-valvular A. Fibrillation
  - CrCl >30mL/min: 150mg BID
  - CrCl 15-30mL/min: 75mg BID
    - This dose was NOT studied in the A. Fib trial (RE-LY Study) patients were excluded if they had CrCl <30mL/min
- Adverse events
  - Bleeding (17% of patients in the RE-LY Trial had some type of bleeding)
    - 3% had major bleed
  - GI: dyspepsia and GERD symptoms (30% of patients)
- Drug interactions: p-glycoprotein inhibitors like amiodarone



Trials Involving Dabigatran

Trial	Setting
BISTRO I	THR (dose-escalation study)
BISTRO II	vs enoxaparin in THR/TKR (VTE prophylaxis)
RE-MODEL	vs enoxaparin in TKR (VTE prophylaxis)
RE-MOBILIZE	
RE-NOVATE	vs enoxaparin in THR (VTE prophylaxis)
RE-NOVATE II	vs enoxaparin in THR (VTE prophylaxis)
RELY	vs warfarin in stroke prevention in atrial fibrilliation
RELY-ABLE	extension of RELY: stroke prevention in atrial fibrilliation
REMEDY	vs warfarin in secondary VTE prevention
RESONATE	vs placebo in secondary long-term VTE prevention
RE-DEEM	Phase II: acute coronary syndrome
RECOVER	vs warfarin in acute VTE treatment

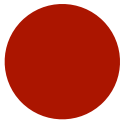
Mehta, Rohtesh S. "Novel oral anticoagulants. Part II: direct thrombin inhibitors." *Expert Review of Hematology* 3.3 (2010): 351+. *Expanded Academic ASAP*. Web. 30 Nov. 2010.

Trial	Setting	Primary Outcome	Result
RE-LY*	**Patients with A. Fib** **Dabigatran 110mg BID, 150mg BID, or Warfarin with target INR 2-3**	**Stroke plus systemic embolism** **Primary Safety outcome major hemorrhage**	**110 mg BID dose was non-*inferior* to Warfarin with fewer bleeding episodes; the** **150 mg BID dose was *superior* to Warfarin with similar bleeding**
REMOBILIZE	Prophylaxis of VTE in patients undergoing unilateral TKR	VTE– Safety Compared to Enoxaparin in TKR	Similar safety profile to enoxaparin 30 mg BID. Noninferior efficacy NOT demonstrated
REMODEL	Dabigatran vs. Enoxaparin for prevention of VTE post unilateral TKR	VTE—Safety Compared to Enoxaparin in TKR	No differences in safety outcomes between two groups
RENOVATE	Efficacy and safety of dabigatran vs. Enoxaparin for prophylaxis of VTE after unilateral THR	VTE—Efficacy/Safety Compared to Enoxaparin in THR	220mg and 150mg doses of Dabigatran were non-inferior to 40mg Enoxaparin ALT elevations seen in Enoxaparin group. Returned to baseline after D/C
RECOVER	Treatment of Acute VTE vs. Warfarin	VTE—Non Inferiority Compared to Warfarin	Non-Inferior to warfarin, lower rate of *major* bleeding, more dyspepsia with Dabigatran

*low dose ASA was allowed

MORE DETAIL ON THE RE-LY TRIAL

- Median follow up was 2 years
- Primary Outcome (stroke, systemic embolism)
  - Dabigatran 110mg BID: 1.53% (inferior to warfarin)
  - Dabigatran 150mg BID: 1.11% (superior to warfarin)
  - Warfarin: 1.69%
- So you would have to treat 169 patients with dabigatran 150mg BID for one year to prevent one event when compared to warfarin
- Safety
  - Major hemorrhage did not differ
  - Dabigatran 150 BID had more GI bleeding compared to warfarin
  - Dyspepsia was the most common adverse effect
  - Dabigatran was associated with a 0.2%/year risk of MI compared to warfarin (NNH=500)

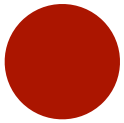


SUMMARY ADVANTAGES/

Drug	Advantages	Disadvantages
Warfarin	•Cost •Easy monitoring •Reversible •Familiarity •Long Term Safety/Efficacy Data	•Frequent monitoring and titration of dose often required •Lots drug and food interactions •Long half-life/slow onset (requires bridging with heparin therapy)
Dabigatran	•No monitoring required •As efficacious as warfarin •Similar/superior safety to warfarin •Rapid onset of action/favorable kinetics	•No monitoring required •Cost (8 dollars/day) •More Bleeding? •BID Dosing •Studies still superficial-long term safety/efficacy not well established
Rivaroxaban	Not approved in US yet	

CONCLUSION

- Dabigatran is the first oral anticoagulant that has been approved in the US since warfarin
  - In addition, there are a couple other oral anticoagulants that could be coming to the US market soon including Rivaroxaban (Xarelto).
- Dabiagatran does have advantages over warfarin the main being less drug interactions and no need for monitoring
- Despite this not all patients on warfarin should be switched to over to Dabigatran



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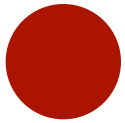


MINI WARFARIN REVIEW IN PATIENTS WITH ATRIAL FIBRILLATION

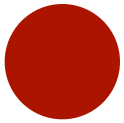
Madeline Stephens

PATIENT DEMOGRAPHICS

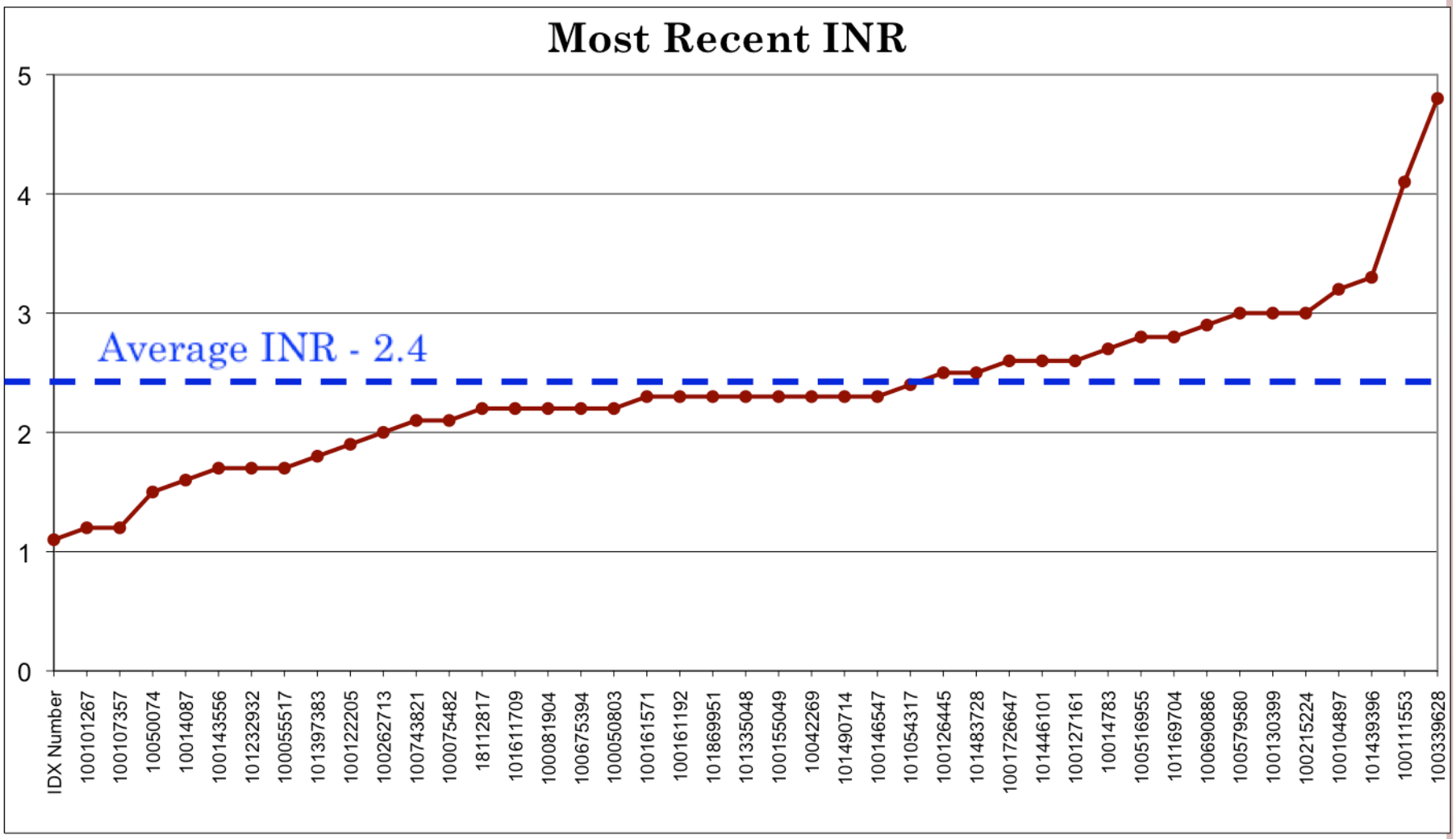
- All patients were being treated with Warfarin secondary to A. Fib and were patients of the Wyoming Family Practice
- Total number of patients: 54
- Percent male: 46% (n=25)
- Average age: 75
  - Age range: 52-90

WARFARIN MANAGEMENT

- Of the 43/54 patients that had documented INR's, 67% (n=29) had an INR between 2-3
  - Of the 14/43 patients not at goal
    - 10 patients had an INR < 2 and 4 patients an INR >3
    - Although, only 5 patients had interventions made in their warfarin dose
- 11/54 patients had no documented INR
- 44% (24/54) of the patients are being monitored monthly
  - 8/24 of these patients were not at goal
    - 4/8 patients had an intervention made on their warfarin dose

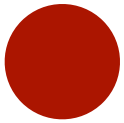


WARFARIN MANAGEMENT



POTENTIAL DABIGATRAN PATIENTS

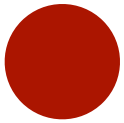
- 65% (35/54) of patients could potentially be good candidates for dabigatran
  - Patients that were noncompliant, not at INR goal, irregular INR monitoring or no INR monitoring
- Of those patients 63% (22/35) had an exclusion to dabigatran therapy?
  - Conditions that increase risk of side effects (15 patients)
    - Renal function: 1
    - **GERD: 6**
    - MI: 3
    - Increased risk for bleeding: 1
    - Poor liver function: 1
    - Heart valve disorder: 4
    - Stroke: 1
  - Potential Drug interactions (20 patients)
    - Amiodarone: 1
    - Verapamil: 3
    - **PPI: 11**
    - H2 antagonist: 1



- Categories to do not add up to 22 because some patients had multiple exclusions and are

POTENTIAL DABIGATRAN PATIENTS

- 13/35 patients had no precautions or contraindications
  - Half of these patients had Medicare
  - The majority of these patients also had another medication that is taken more than once a day which could improve compliance of the twice daily dosing of Dabigatran



CONCLUSION

- In conclusion, this small review of patients being treated with warfarin secondary to A. Fib, showed that the majority of patients may not be good candidates for Dabigatran

- The advantages and disadvantages of Dabigatran should be weighted before initiating therapy