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CancerCare Manitoba COMMUNITY ONCOLOGY PROGRAM

UPCON Uniting Primary Care and Oncology

FOR Health Professionals

How I use and reverse novel oral coagulants

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Objectives

1. Review properties and uses of the novel oral anticoagulants (NOACs)
2. Discuss reversal strategies for oral anticoagulants
3. Present concepts related to therapeutic monitoring of NOACs

Treatment of atrial fibrillation and VTE has changed!

1970 to 2000

- Warfarin reigned supreme: anticoagulant of choice (afib)
- 6 months was ‘standard’ (VTE)
- Thrombophilia testing was the the rage

2016

- Warfarin no longer the ‘go to’ blood thinner (afib)
- 3 months is ‘standard’ (VTE)
- Thrombophilia testing recognized as unhelpful

Traditional management of VTE

Initial treatment — **5-7 days**

LMWH or UFH*

Long-term therapy — **≥3 months**

VKA (INR† 2.0-3.0)**

*UFH = unfractionated heparin
**VKA = vitamin K antagonist
†INR = international normalization ratio

Conventional Management

Pros

- Effective
- Familiar
- Facilitates outpatient therapy

Cons

- Requires multiple injections
- INR monitoring
- Plus…all the burdens of warfarin

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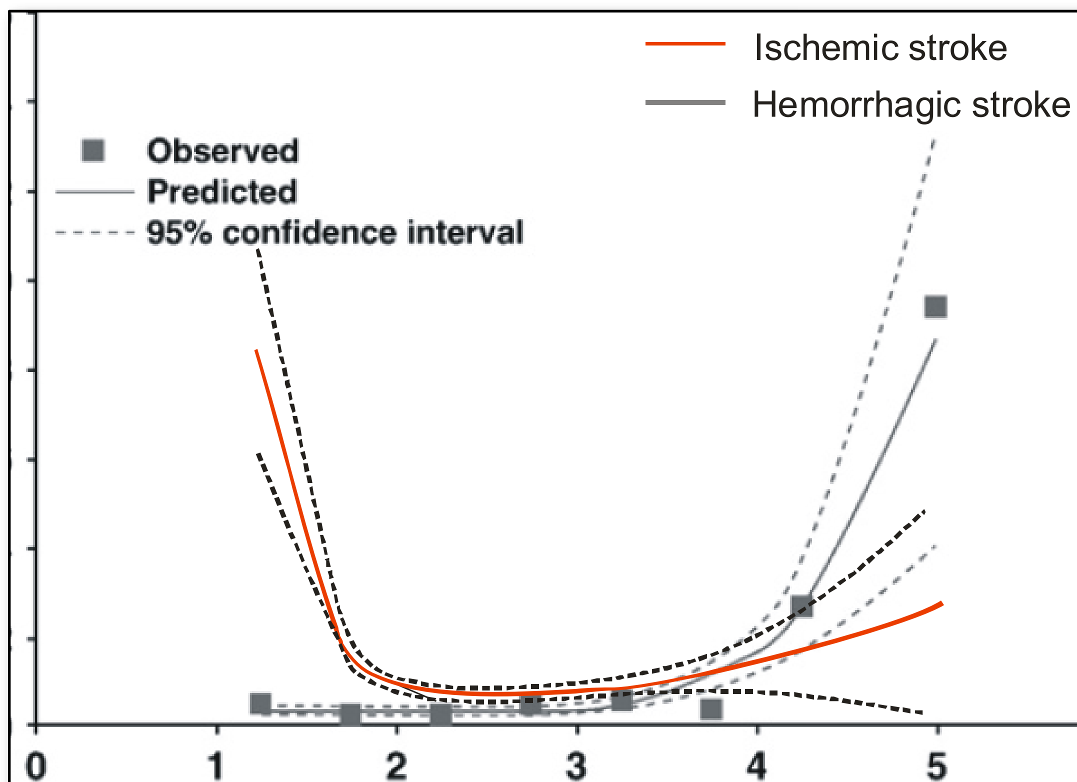
Blood Disorders Day 2016

Why Don Houston likes warfarin

1. Strong evidence base for its use
2. Highly effective anticoagulant in a broad range of indications
3. No significant off-target toxicities
4. Profoundly inexpensive

Why we *dislike* warfarin

1. Brutal pharmacodynamics
2. Unfavourable pharmacokinetics
3. Drug interactions
3. Requirement for monitoring



Novel oral anticoagulants (NOACs)

Direct thrombin inhibitor

Dabigatran (Pradaxa®)

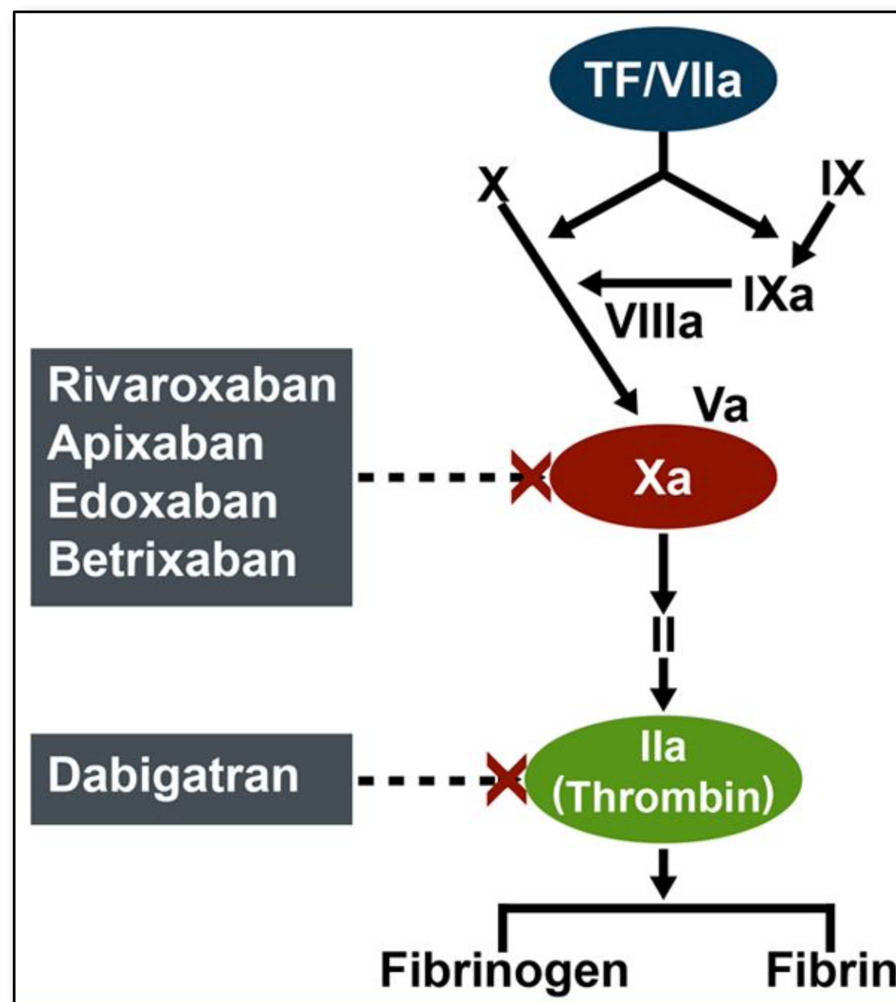
Direct Factor Xa inhibitor

Rivaroxaban (Xarelto®)

Apixaban (Eliquis®)

Edoxaban

Others are coming…



Novel oral anticoagulants (NOACs)

Dabigatran (Pradaxa)

- Oral direct thrombin inhibitor
- little food interaction
- Half life 12-17 hrs

Approved for:

- **DVT prophylaxis in orthopedic surgery**
- **Atrial fibrillation**
- **DVT/PE treatment**

Rivaroxaban (Xarelto)

- Oral direct Factor Xa inhibitor
- little food interaction
- Half-life 5-13 hrs

Approved for:

- **DVT prophylaxis in orthopedic surgery**
- **Atrial fibrillation**
- **DVT/PE treatment**

Apixaban (Eliquis)

- Oral direct Factor Xa inhibitor
- little food interaction
- Half-life ~12 hrs

Approved for:

- **DVT prophylaxis in orthopedic surgery**
- **Atrial fibrillation**
- **DVT/PE treatment**

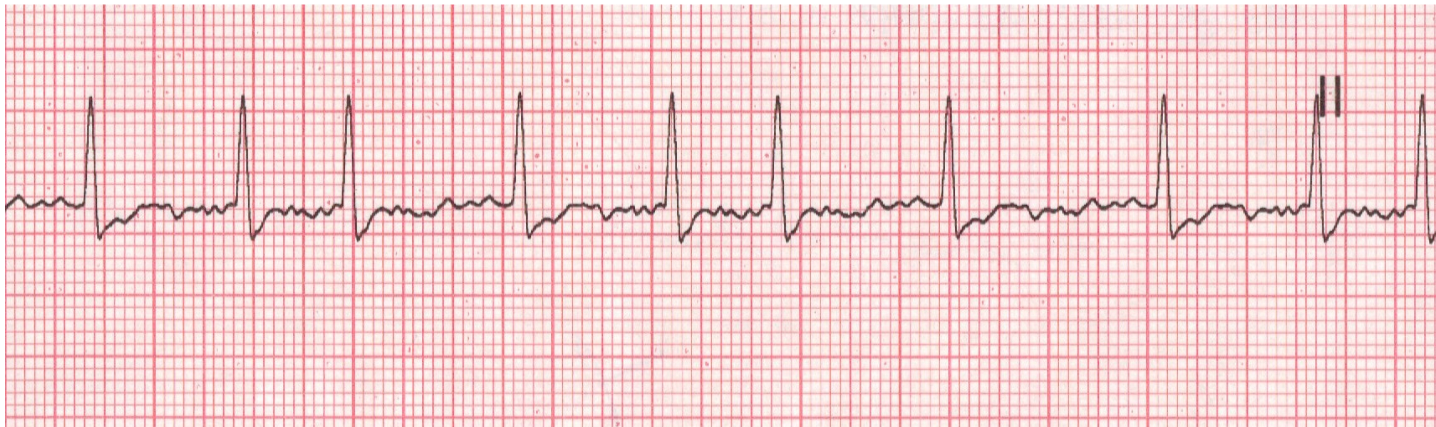
Novel oral anticoagulants (NOACs)

	Dabigatran	Rivaroxaban	Apixaban
Drug Interactions	P-gp	CYP 3A4 & P-gp	CYP 3A4 & P-gp
Renal Elimination	80%	33%	27%

P-gp/CYP 3A4 inhibitors: -azole antifungals, HIV protease inhibitors, tacrolimus, cyclosporine, verapamil, quinidine

P-gp/CYP 3A4 Inducers: rifampin, phenytoin, carbamazepine, St. John's Wart

NOACs in non-valvular atrial fibrillation



NOACs for non-valvuvlar Atrial Fibrillation

Dabigatran (Pradaxa)

- Oral direct thrombin inhibitor
- little food interaction
- Half life 12-17 hrs

- 150 mg BID
- 110 mg BID if at increased risk of bleeding
- CrCl < 30; don't use

Rivaroxaban (Xarelto)

- Oral direct Factor Xa inhibitor
- little food interaction
- Half-life 5-13 hrs

- 20 mg OD

CrCl 30-49 ml/min

- 15 mg OD

CrCl < 30; don't use

Apixaban (Eliquis)

- Oral direct Factor Xa inhibitor
- little food interaction
- Half-life 12 hrs

- 5 mg BID

2.5 mg BID: If any 2 are present: age ≥80, weight < 60 kg, or creatinine ≥ 133

CrCl 15-24: limited data

CrCl < 15: don't use

ALL AGENTS ARE HEALTH CANADA APPROVED & Part 3 EDS in Manitoba

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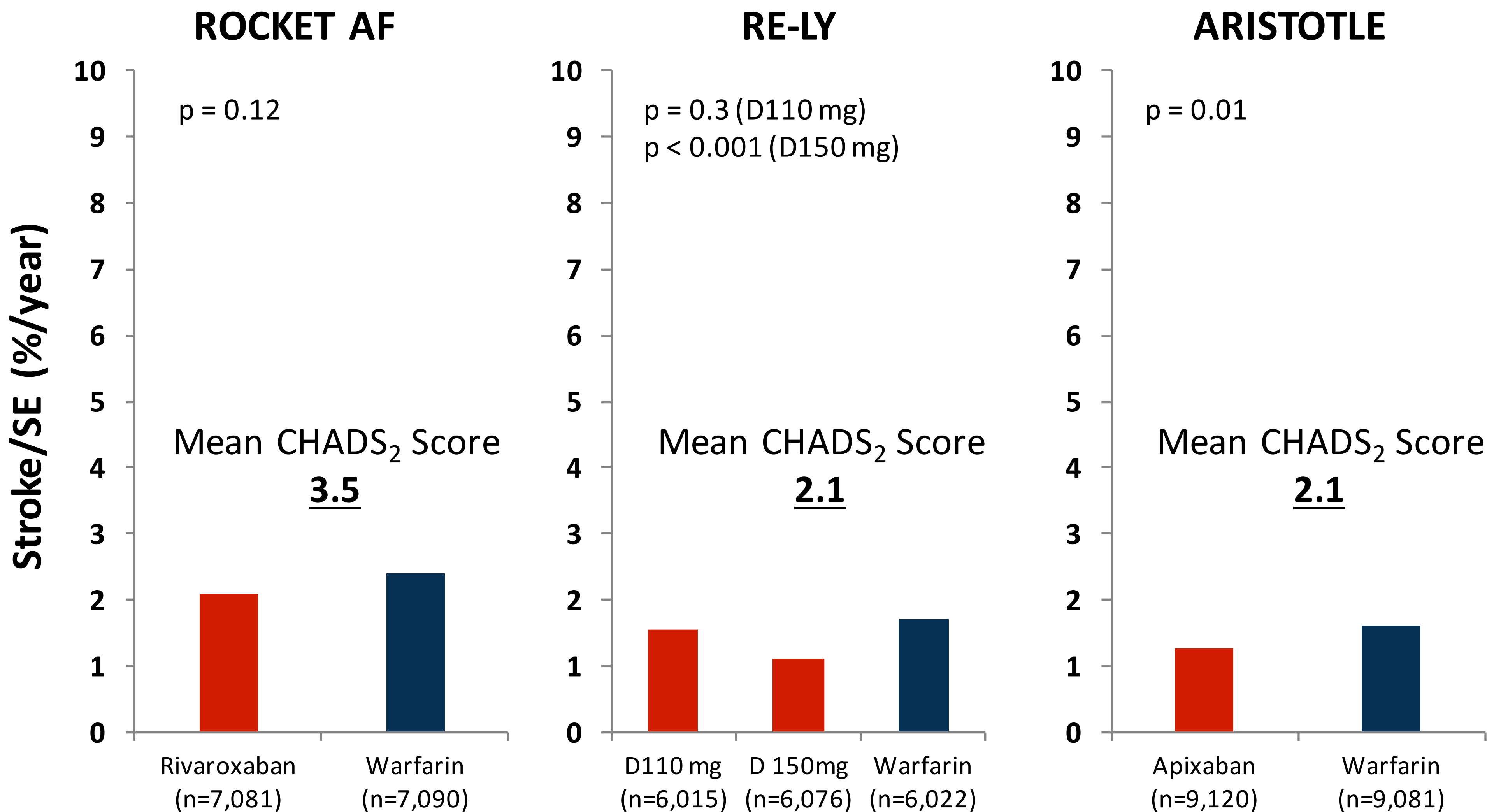
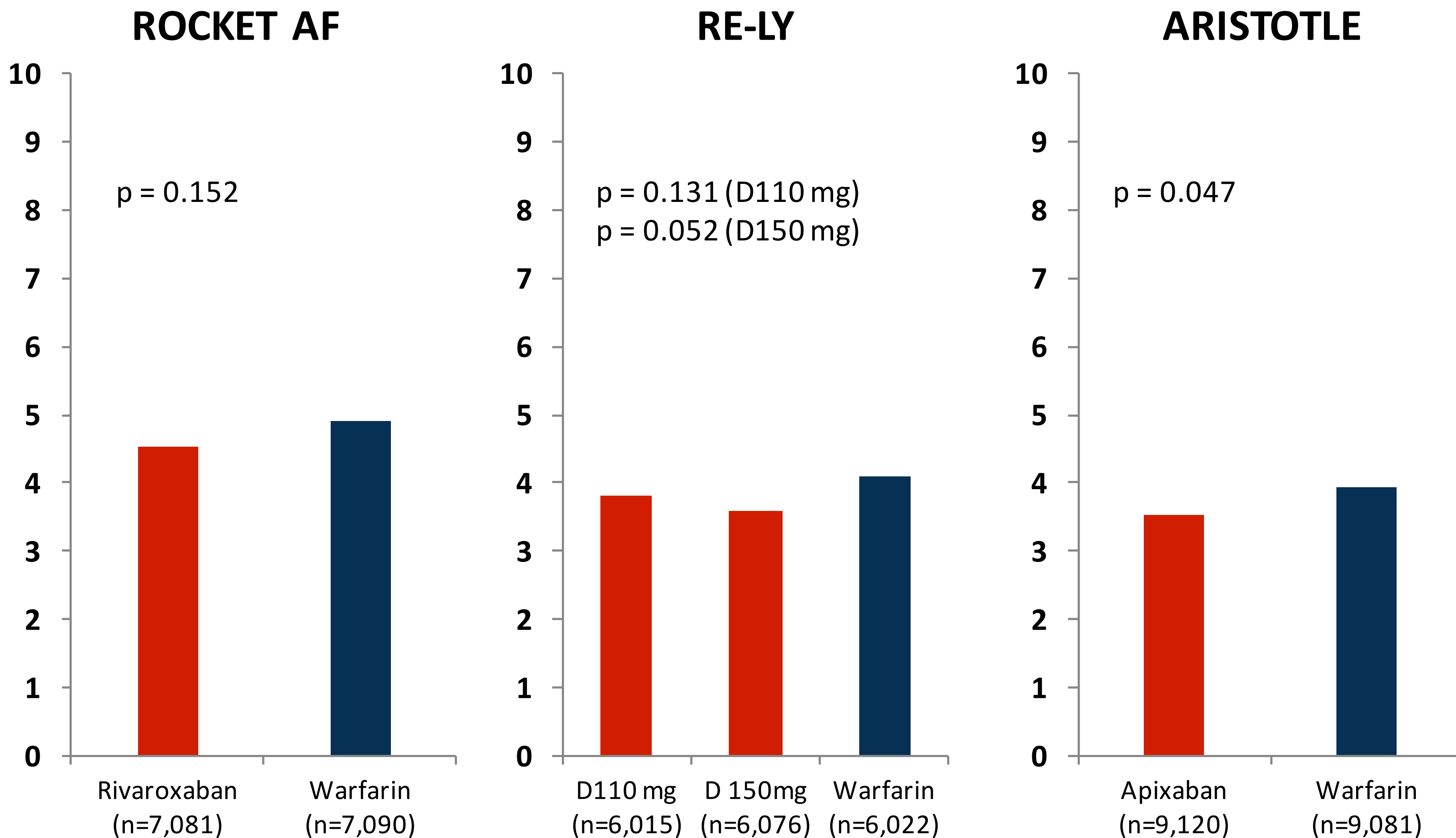
New Anticoagulants vs. Warfarin
Stroke or Systemic Embolism



New Anticoagulants vs. Warfarin

All-Cause Mortality



In Summary:
NOACs vs. warfarin in NV atrial fibrillation

1. NOACs are better than warfarin to prevent stroke in non-valvular atrial fibrillation
2. ~10% reduction in relative risk of death compared to warfarin for all NOACs
3. Lower rate of intracranial bleeding compared to warfarin
4. NOAC is preferred to warfarin as first line therapy

NOACs and VTE (PE/DVT)

NOACs for the treatment of DVT/PE

Dabigatran (Pradaxa)	Rivaroxaban (Xarelto)	Apixaban (Eliquis)
• Oral direct thrombin inhibitor • little food interaction • Half life 12-17 hrs	• Oral direct Factor Xa inhibitor • little food interaction • Half-life 9 hrs	• Oral direct Factor Xa inhibitor • little food interaction • Half-life 12 hrs
• Subcutaneous LMWH x 7 days • Then dabigatran 150 mg BID	• 15 mg BID x 3 weeks • Then 20 mg OD for at least 9 weeks	• 10 mg BID x 7 days • Then 5 mg BID for at least 11 weeks
Use limited due to the need for S/Q injections	• CrCl <30 – don't use • CrCL 30-50; No adjustment	• CrCl <25 – don't use • CrCL 25-50; No adjustment

NOACs for the treatment of DVT/PE

Dabigatran (Pradaxa)

- Oral direct thrombin inhibitor
- little food interaction
- Half life 12-17 hrs

- 1274 patients
- **No difference** in recurrent VTE
- No difference in major bleeding

Rivaroxaban (Xarelto)

- Oral direct Factor Xa inhibitor
- little food interaction
- Half-life 9 hrs

- 8281 patients
- **No difference** in recurrent VTE
- **Decreased major bleeding with NOAC**

Apixaban (Eliquis)

- Oral direct Factor Xa inhibitor
- little food interaction
- Half-life 12 hrs

- 5395 patients
- **No difference** in recurrent VTE
- **Decreased major bleeding with NOAC**

In Summary:
NOACs vs. warfarin for VTE

1. As good as warfarin with less major bleeding

2. No need for multiple ER visits or for dalteparin injections if rivaroxaban or apixaban is used

3. All agents are approved for treatment of DVT and PE in Canada

All great...but what if the patient bleeds!

Bleeding and anticoagulants: **Warfarin**

64 y.o. man on warfarin for atrial fibrillation. Presents with type B dissection.

- Acute renal failure (anuric)
- Hemodynamically stable
- INR 3.4

How would you reverse warfarin?

Pharmacologic treatment/reversal of bleeding on **warfarin**

- 10 mg IV vitamin K
- Prothrombin concentrates
    - Octaplex
    - Beriplex

Dose of Prothrombin Complex

INR <3.0:	40 mL (1000 IU)
INR 3-5:	80 mL (2000 IU)
INR >5:	120 mL (3000 IU)

*Consider dose increase if > 100 kg

**If no bleeding or urgency, then just give 2 mg of vitamin K orally

Prothrombin Concentrates (Octaplex / Beriplex)*

Concentrate of vitamin K dependent factors (II, VII, IX, X)

Appealing features:

- Virus inactivated
- Reconstitute from powder => quicker than thawing/giving FFP
- Small volume to administer
- No blood group matching required
- Cost is comparable

* Contraindicated in HIT

Bleeding and anticoagulants: **Dabigatran**

64 y.o. man on dabigatran for atrial fibrillation. Presents with lower GI bleed.

- Blood pressure 90/60 mmHg
- INR 1.4; aPTT 46 sec

How would you manage the bleeding?

Would you reverse dabigatran?

…Do you need to?

Bleeding and anticoagulants: **Dabigatran**

Initiate resuscitation measures:

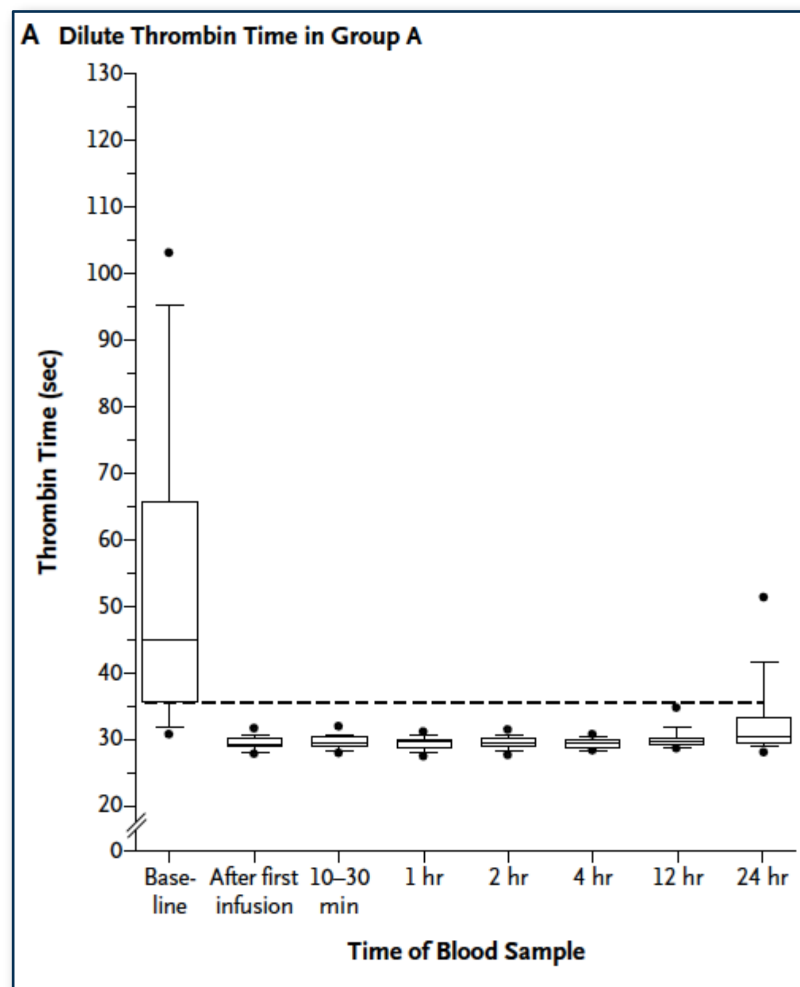
- Bolus isotonic crystalloids
- RBC transfusion (target > 70 g/L)
- Activating Massive Transfusion Protocol if appropriate
- Local hemostatic measures /endoscopy
- Collect baseline labs
- CBC, aPTT, INR

…remember the half life is 12-17 hours

Bleeding and anticoagulants: **Dabigatran**

Idarucizumab

- Monoclonal antibody with 350 X higher affinity over thrombin
- 5 gram dose results in immediate and complete reversal of dabigatran
- No safety concerns yet identified

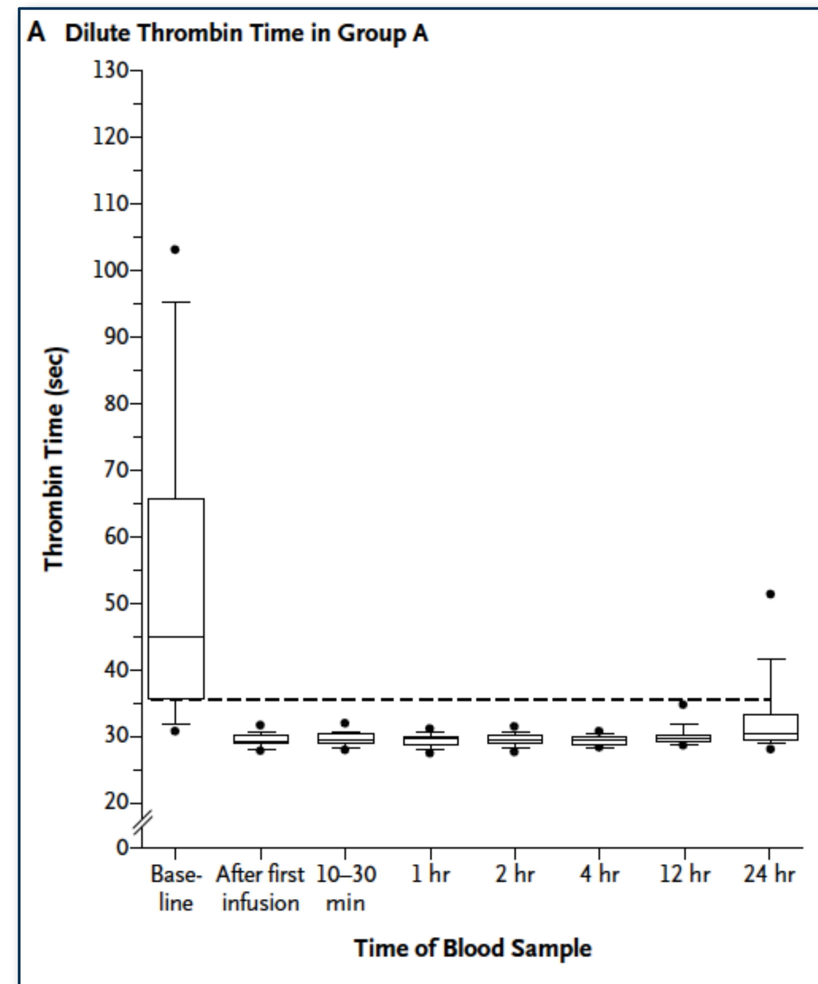


Bleeding and anticoagulants: **Dabigatran**

Idarucizumab

Indications:

1. Emergency surgery/urgent procedures
2. Life-threatening bleeding



Are reversal agents for NOAC the 'cavalry' we've been waiting for?

RE-LY Trial (afib)	**Warfarin**	**Dabigatran**
Mortality from Intracranial bleeding	36% (32/90)	35% (13/37)

You don't have to reverse a bleed that doesn't happen!

Mortality after a major bleeding event: Are NOACs really more dangerous?

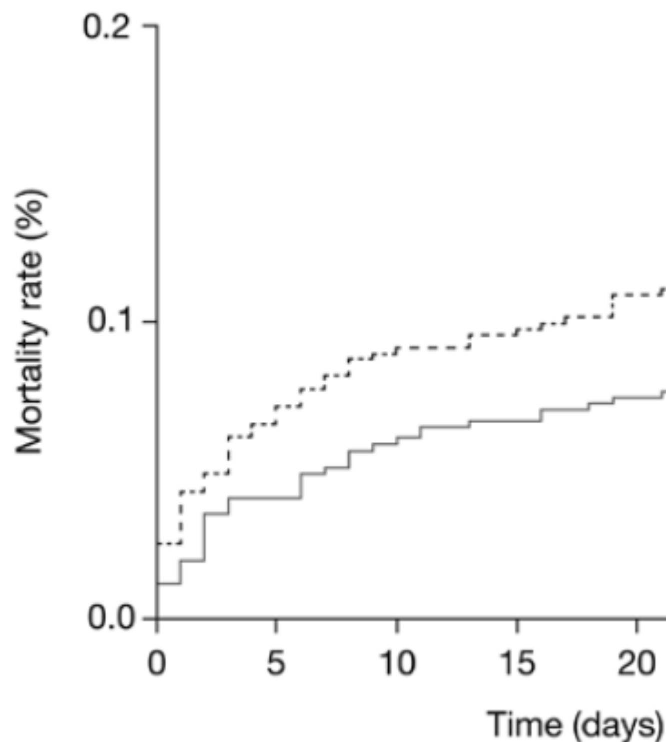


Figure. Thirty-day mortality rate after a ma

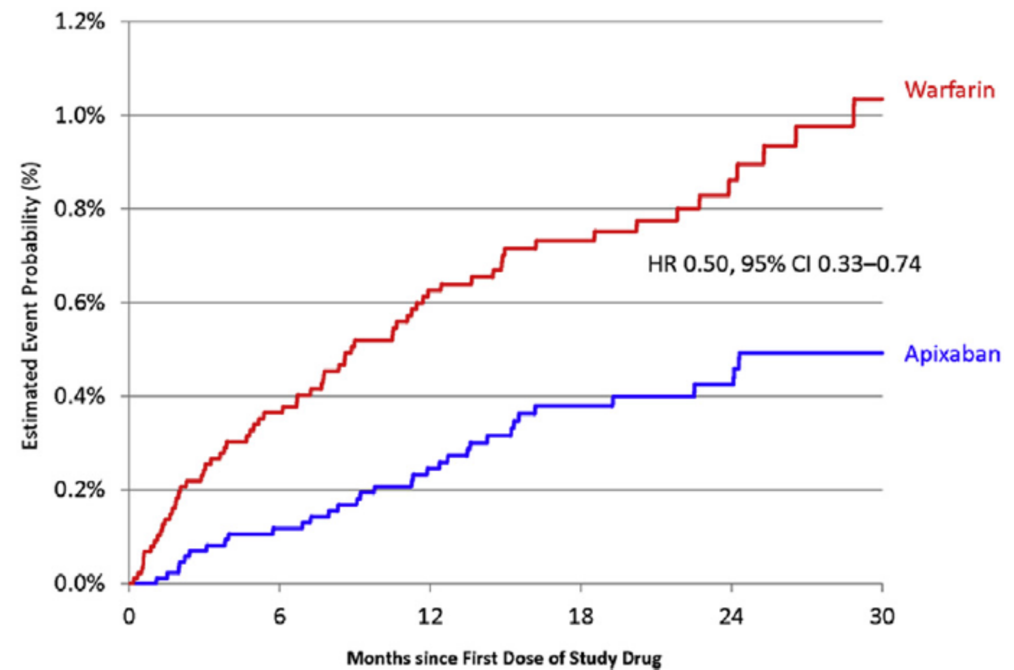


Figure 1 Major Bleeding Following by Death Within 30 Days

CI = confidence interval; HR = hazard ratio.

Mortality after a major bleeding event: Are NOACs really more dangerous?

Goodman *et al.*
Major Bleeding Events in the ROCKET AF Trial

JACC Vol.
March 11

Table 1 Event Rates and HRs and 95% CIs for Bleeding Events

	Events (Rate)			
	Rivaroxaban (n = 7,111)	Warfarin (n = 7,125)	HR (95% CI)	p Value
Principal safety endpoint	1,475 (14.91)	1,449 (14.52)	1.03 (0.96–1.11)	0.442
Major	395 (3.60)	386 (3.45)	1.04 (0.90–1.20)	0.576
Hemoglobin/hematocrit drop	305 (2.77)	254 (2.26)	1.22 (1.03–1.44)	0.019
Transfusion	183 (1.65)	149 (1.32)	1.25 (1.01–1.55)	0.044
Critical organ bleeding	91 (0.82)	133 (1.18)	0.69 (0.53–0.91)	0.007
Death	27 (0.24)	55 (0.48)	0.50 (0.31–0.79)	0.003
Nonmajor clinically relevant	1,185 (11.80)	1,151 (11.37)	1.04 (0.96–1.13)	0.345
Minimal	258 (2.35)	226 (2.03)	1.16 (0.97–1.39)	0.102

Event rates/100 patient-years.

Bleeding and anticoagulants: **Rivaroxaban / Apixaban**

REVERSAL AGENTS are coming very soon. (Andexanet alpha)

Until such agents are available:

- Can you wait it out? (half life 9-12 hours)
- **Prothrombin concentrates recommended** based on non-clinical, laboratory outcomes of uncertain relevance
  - **Dose:** 50 units/kg based on in vitro studies
- Consider tranexamic acid
  - 1 g IV bolus, then 1 gram over 8 hours

In Summary:
Antidotes for NOACs

Idarucizumab (Praxbind)
- Dabigatran specific inhibitor
- **Available – June 2016**

Andexanet alfa
- Direct and indirect FXa inhibitor (e.g. heparins, fondaparinux, apixaban, rivaroxaban)
- *NOT available yet*

Aripazine (PER977)
- The 'universal reverser…'
- FXa inhibitor & oral direct thrombin inhibitor
- Very groovy indeed
- *Still in development*

Take Home Messages

1. In non-valvular atrial fibrillation, NOACs are preferred to warfarin (reduced stroke, mortality, and intracranial hemorrhage)

2. In VTE management, NOACs (rivaroxaban/apixaban) are as effective as warfarin and associated with less major bleeding

3. Reversal agent for dabigatran has arrived. Consider using for:
   - Life-threatening bleeding
   - Very urgent procedures

   The net clinical benefit of reversal agents remains uncertain

Questions?

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4. **A 75 y.o. female with HTN, diabetes and non-valvular atrial fibrillation. Creatinine 130 mmol/L. Estimated creatinine clearance is 34 ml/min. Weight 65 kg**

What agent should you use to treat her atrial fibrillation?

A. Warfarin (INR 2-3)
B. Rivaroxaban 20 mg OD
C. Rivaroxaban 15 mg OD
D. Apixaban 5 mg BID
E. Apixaban 2.5 mg BID

4. **A 75 y.o. female with HTN, diabetes and non-valvular atrial fibrillation. Creatinine 130 mmol/L. Estimated creatinine clearance is 34 ml/min. Weight 65 kg**

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