Anticoagulants in Renal Impairment

Thrombosis Program
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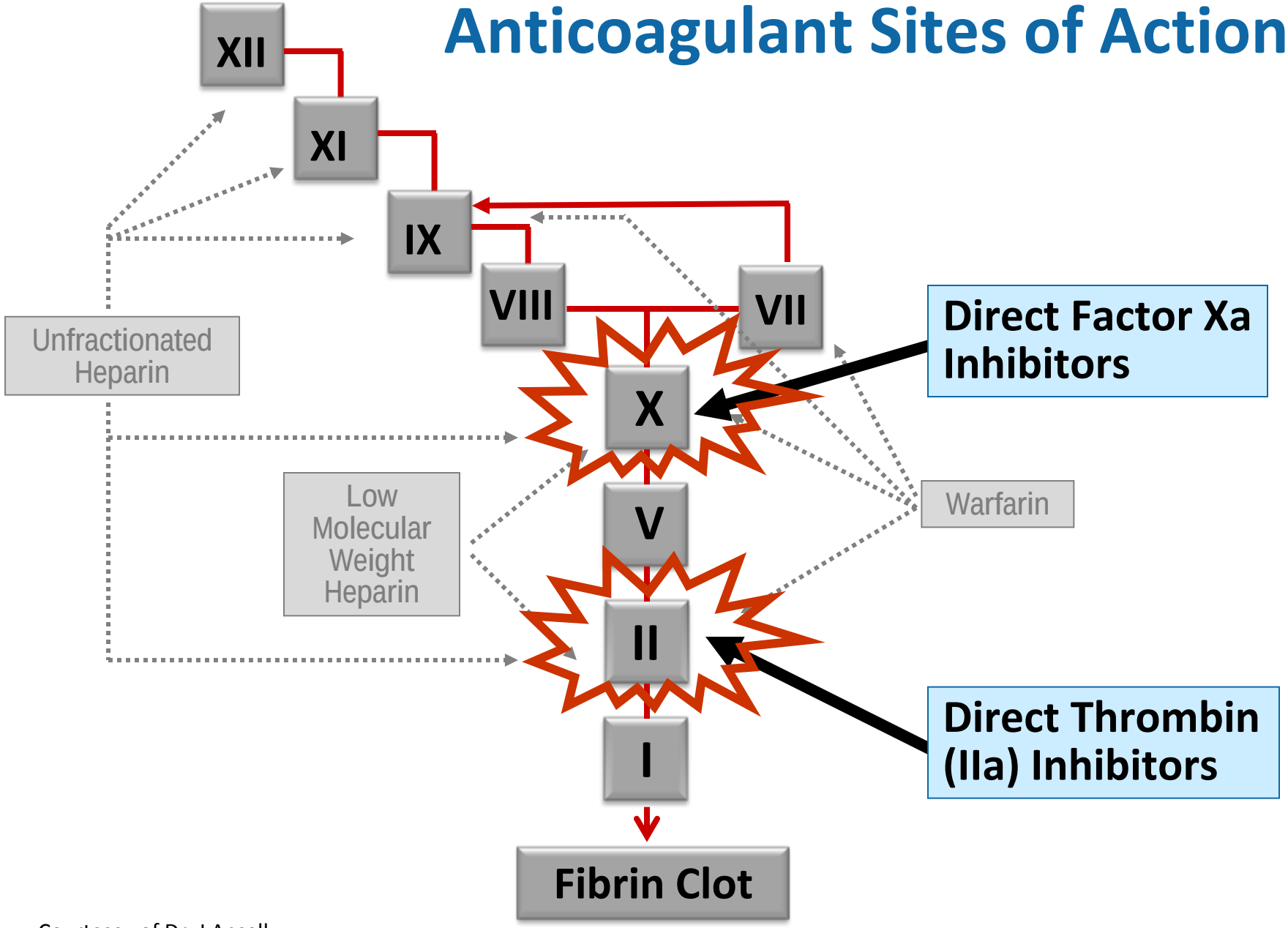
Disclosures

- Bayer
- Boehringer Ingelheim
- Bristol-Myers Squibb
- Daiichi Sankyo
- Eisai
- Laboratory Instruments
- Leo Pharma
- Pfizer
- Sanofi-Aventis

Objectives

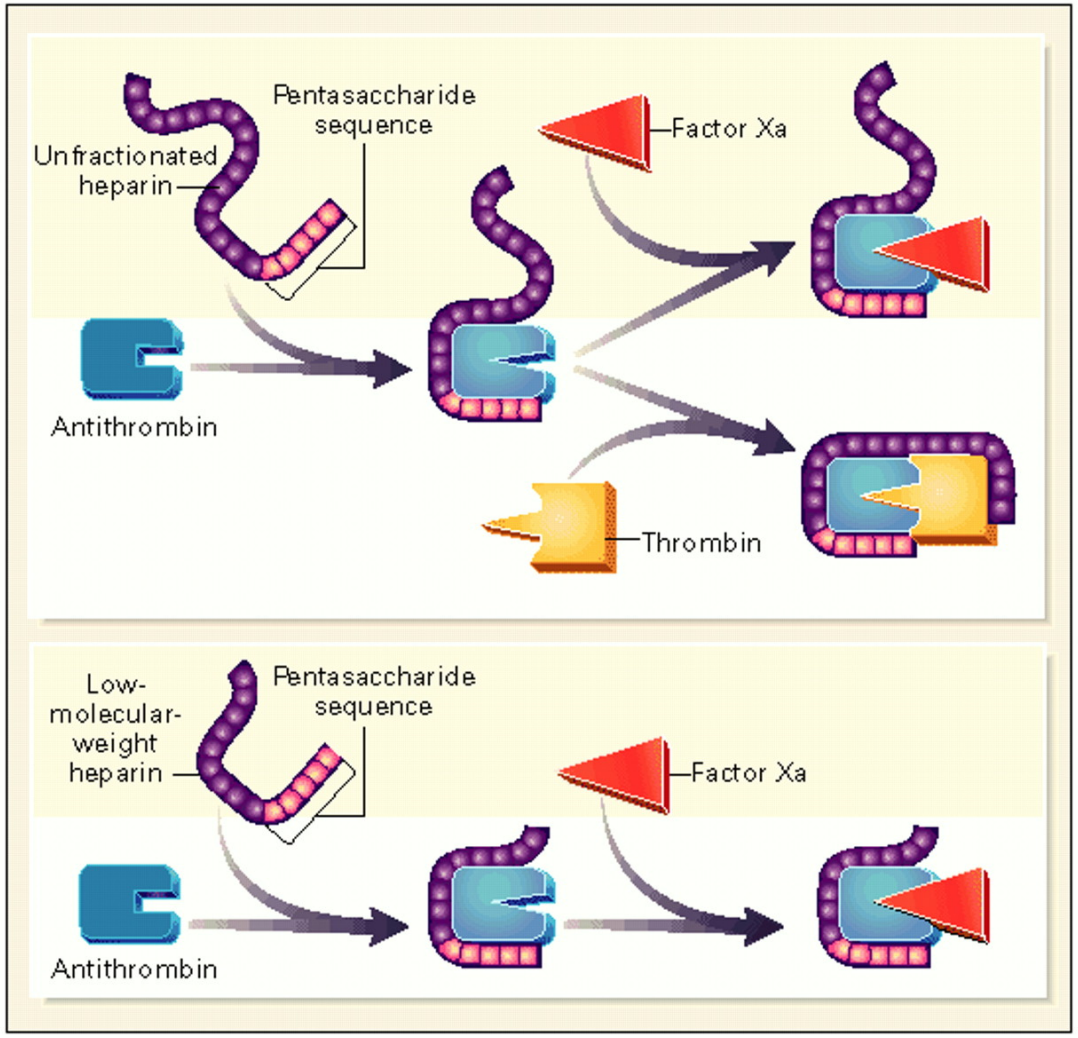
- Review mechanisms of action and routes of clearance of anticoagulants
- Compare and contrast traditional and novel oral anticoagulants
- Summarize clinical data on novel oral anticoagulants
- Outline ACCP guidelines on anticoagulant use in renal impairment

Anticoagulant Sites of Action



Courtesey of Dr. J Ansell.

Heparin and LMWHs



- Pentasaccharide sequence binds to AT and accelerates its inhibitory activity
- UFH inhibits both factor Xa and IIa (thrombin)
- LMWHs have low activity against thrombin because longer chain length is required

Weitz N Engl J Med 1997.

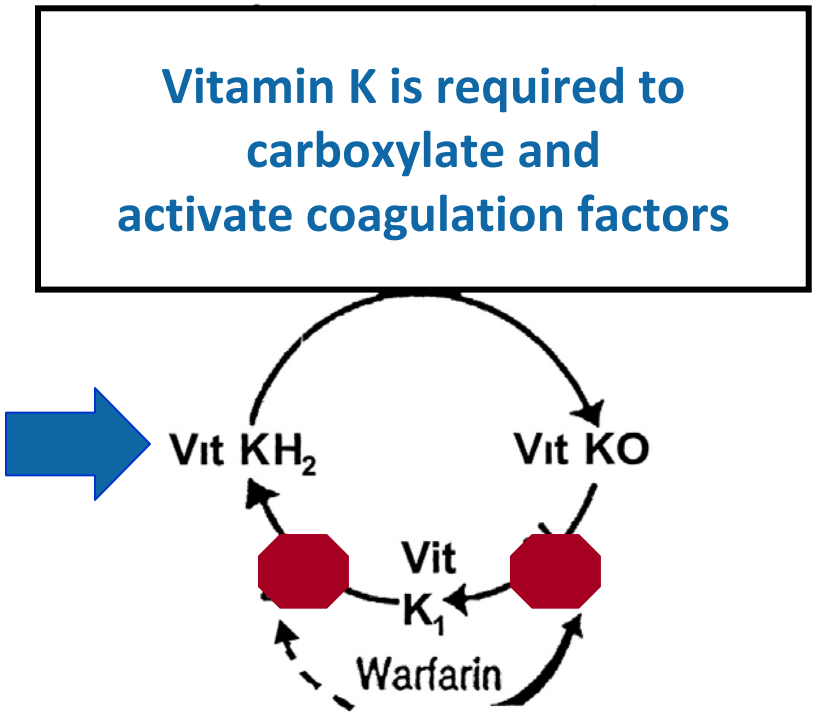
Clearance of UFH and LMWHs

Agent	Average MW (daltons)	AntiXa:IIa Ratio
UFH	15,000	1:1
Tinzaparin	6,500	1.9:1
Dalteparin	5,600	2.0 – 2.7:1
Enoxaparin	4,500	2.7 – 4.1:1
Nadroparin	4,300	3.2 – 3.7:1

- Higher MW chains are cleared by dose-dependent hepatic mechanism
- Lower MW chains are cleared by dose-independent renal route

Pharmacotherapy 2001;21:218-34; Pharmacotherapy 2005; 25:881-5

Vitamin K Antagonists

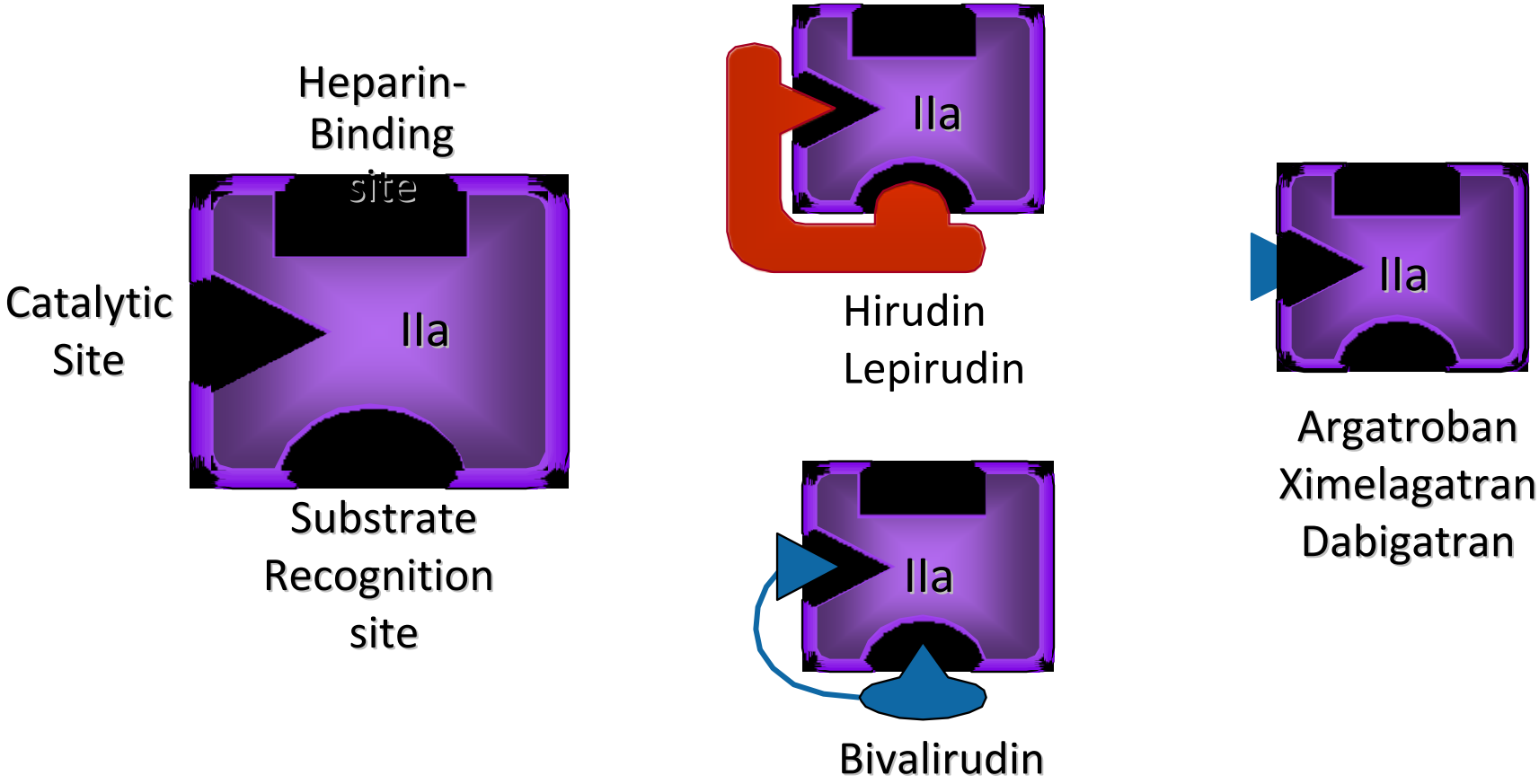


1. KO - reductase - warfarin sensitive
2. K - reductase - relatively warfarin resistant

- Vitamin KH_2 is required for carboxylation and function of vitamin K-dependent factors
- Warfarin interferes with interconversion of vitamin KH_2 and vitamin KO
- Dietary vitamin K bypasses the warfarin blockade
- Anticoagulant effect dependent on half-lives of circulating coagulation factors

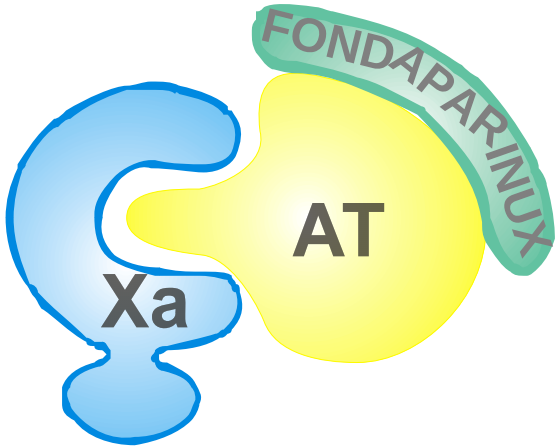
Ansell, J. et al. Chest 2004.

Direct Thrombin Inhibitors



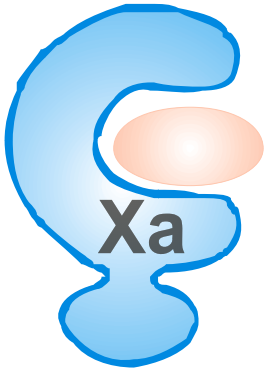
DTIs have key advantages over UFH by their inactivation of clot bound thrombin and fluid phase thrombin

Factor Xa Inhibitors



Indirect Inhibitors

- Fondaparinux
- Idraparinux



Direct Inhibitors

- Rivaroxaban
- Apixaban
- Edoxaban
- Betrixaban

Comparative Features of Warfarin and New Oral Anticoagulants

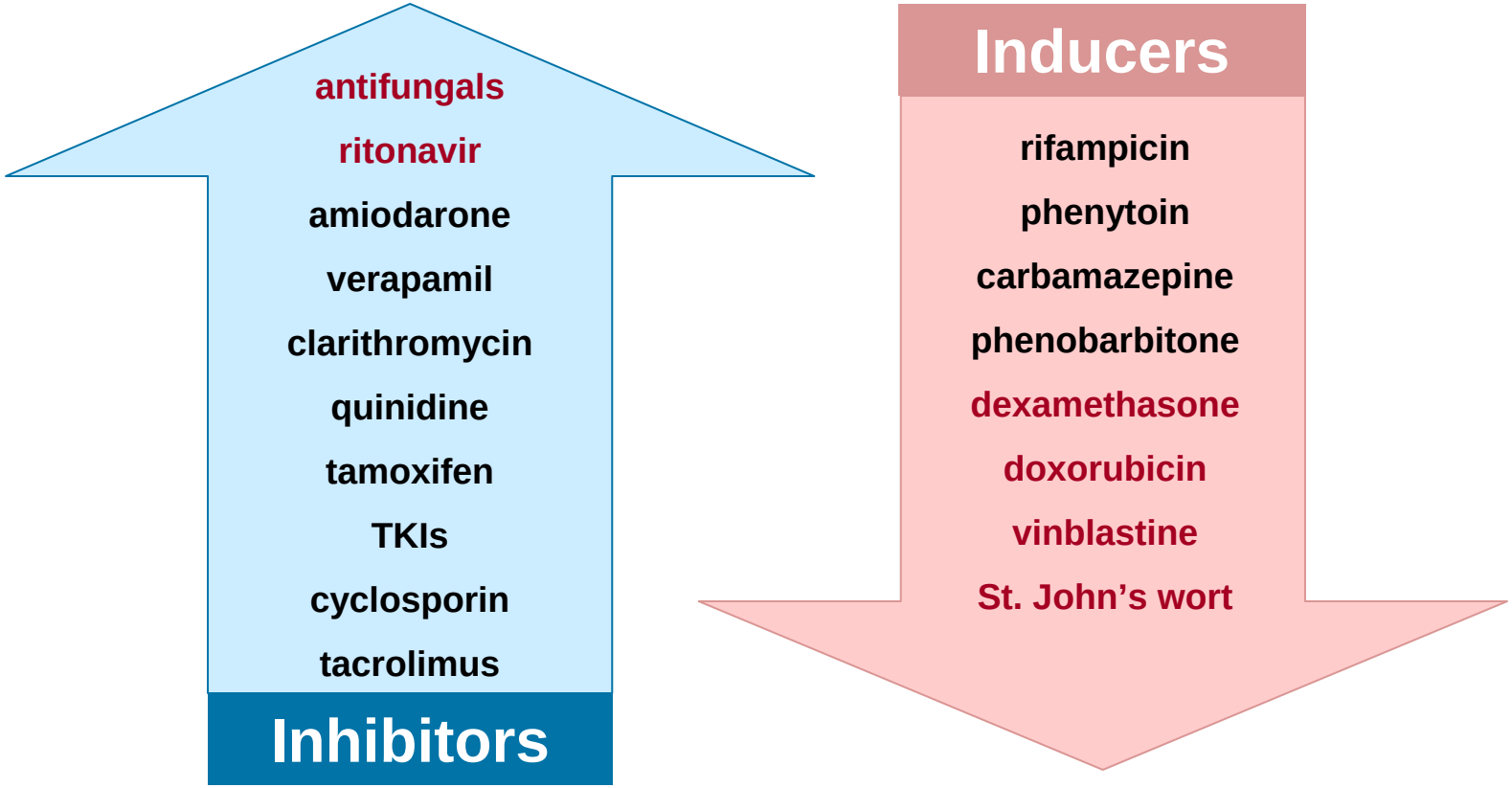
	Warfarin	Dabigatran etexilate	Rivaroxaban	Apixaban
Target	Vit K epoxide reductase	Thrombin	Factor Xa	Factor Xa
Oral bioavailability	99%	6-7%	60-80%	80%
T (max)	72-96 h	2 h	2-4 h	3 h
Half-life	40 h	14-17 h	5-9 h healthy 9-13 h elderly	8-15 h
Monitoring	INR-adjusted	Not needed	Not needed	Not needed
Administration	QD	QD or BID	QD or BID	BID
Metabolism / Elimination	Cytochrome P450	80% renal 20% biliary	66% renal 33% biliary	25% renal 75% biliary
Antidote or treatment of bleeding	Vitamin K + PCC	Standard of care (consider PCC or rVIIa)	Standard of care (consider PCC or rVIIa)	Standard of care (consider PCC or rVIIa)
Coag Assay	PT/INR	TT is extremely sensitive	Not available	Not available
Drug Interactions	CYP 2C9, 1A2, and 3A4	Potent P-gp inhibitors/inducers; PPIs decrease absorp	Potent P-gp inhibitors/inducers; CYP3A4 inhibitors	Potent P-gp inhibitors/inducers; CYP3A4 inhibitors

Advantages and Limitations of NOA

- Advantages
  - Fixed dosing
  - Monitoring of anticoagulant effect not required
  - Fewer drug interactions than warfarin
- Limitations
  - Measurement of anticoagulant effect not available
  - Lack of specific antidote
  - Some drug interactions
  - Dose adjustments required in renal/hepatic dysfunction

Drug Interactions of New Anticoagulants

- Do not inhibit or induce CYP450
- Interactions with inhibitors and inducers of P-glycoprotein +/- CYP3A4



Novel Oral Anticoagulants

Indication	Dabigatran DTI	Rivaroxaban FXa inhibitor	Apixaban FXa inhibitor
Orthopedic Prophylaxis	RE-MOBILIZE RE-MODEL RE-NOVATE	RECORD 1 RECORD 2 RECORD 3 RECORD 4	ADVANCE 1 ADVANCE 2 ADVANCE 3
Stroke Prevention	RE-LY	ROCKET AF	AVERROES (ASA) ARISTOTLE (W)
VTE Treatment	RECOVER REMEDY	EINSTEIN PE EINSTEIN DVT EINSTEIN-EXT	AMPLIFY AMPLIFY-EXT
ACS	RE-DEEM	ATLAS TIMI 46	APPRAISE
Med Prophylaxis		MAGELLAN	ADOPT

Orthopedic Prophylaxis Summary

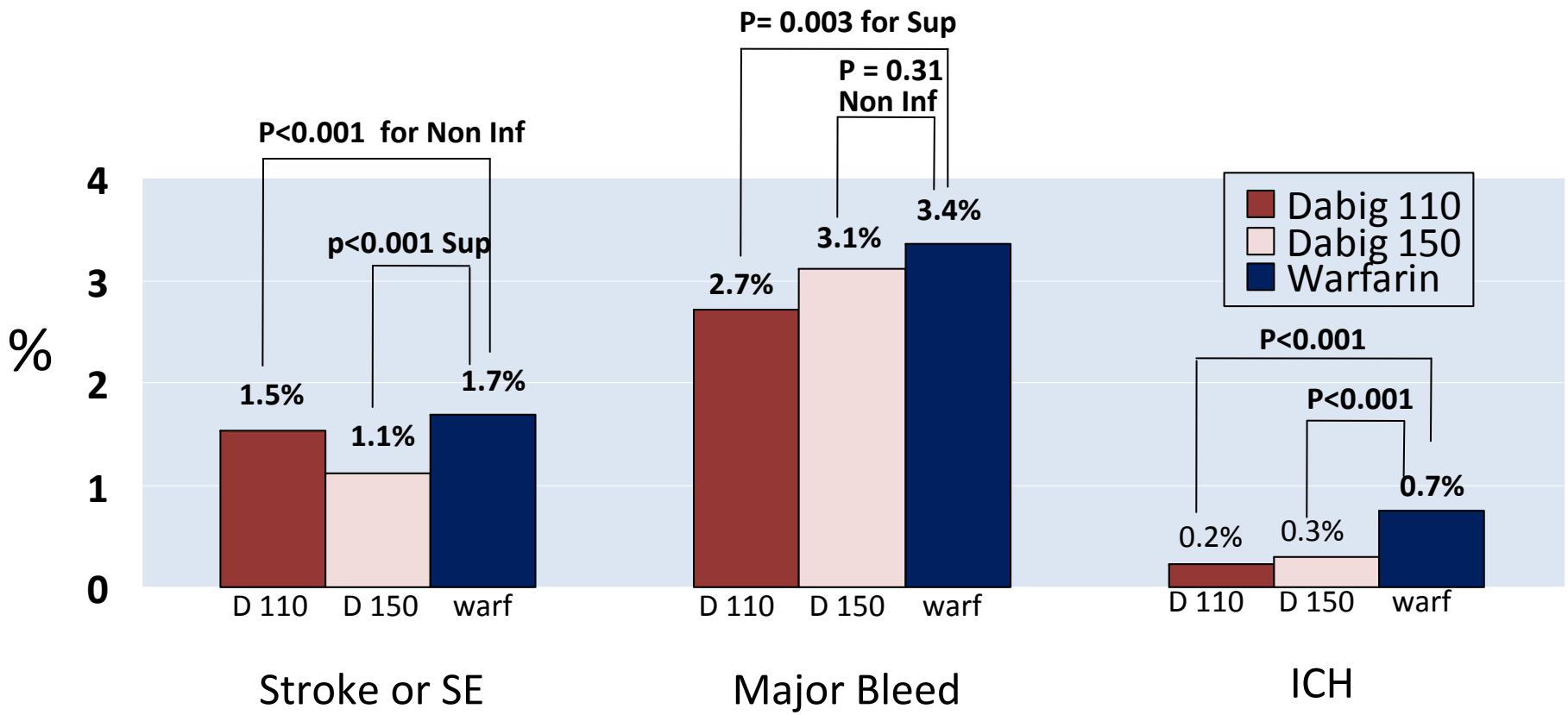
- Novel oral anticoagulants are similar or superior to enoxaparin in efficacy in TKR/THR
  - Dabigatran 220 mg once daily
  - Rivaroxaban 10 mg once daily
  - Apixaban 2.5 mg twice daily

PharmaCare approval
THR 35 days
TKR 14 days

- Serious bleeding similar or marginally higher
- Cost-benefit analyses not available
- Many centres have switched to rivaroxaban in patients with CrCl > 30 mL/min

Dabigatran in Atrial Fibrillation

RE-LY

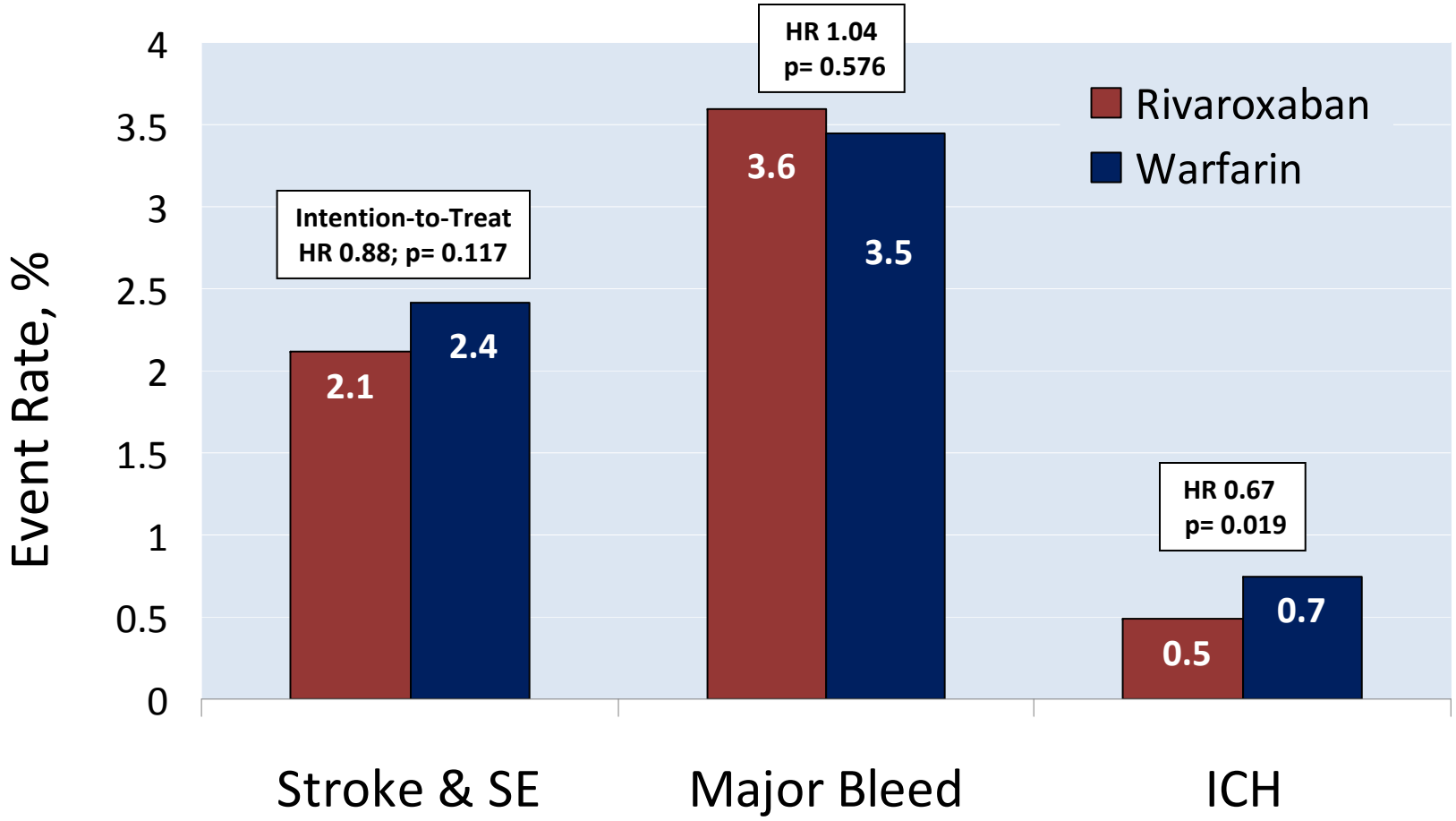


Dabigatran approved for stroke prevention in AF October 2010

Connolly et al. New Engl J Med 2009.

Rivaroxaban in Atrial Fibrillation

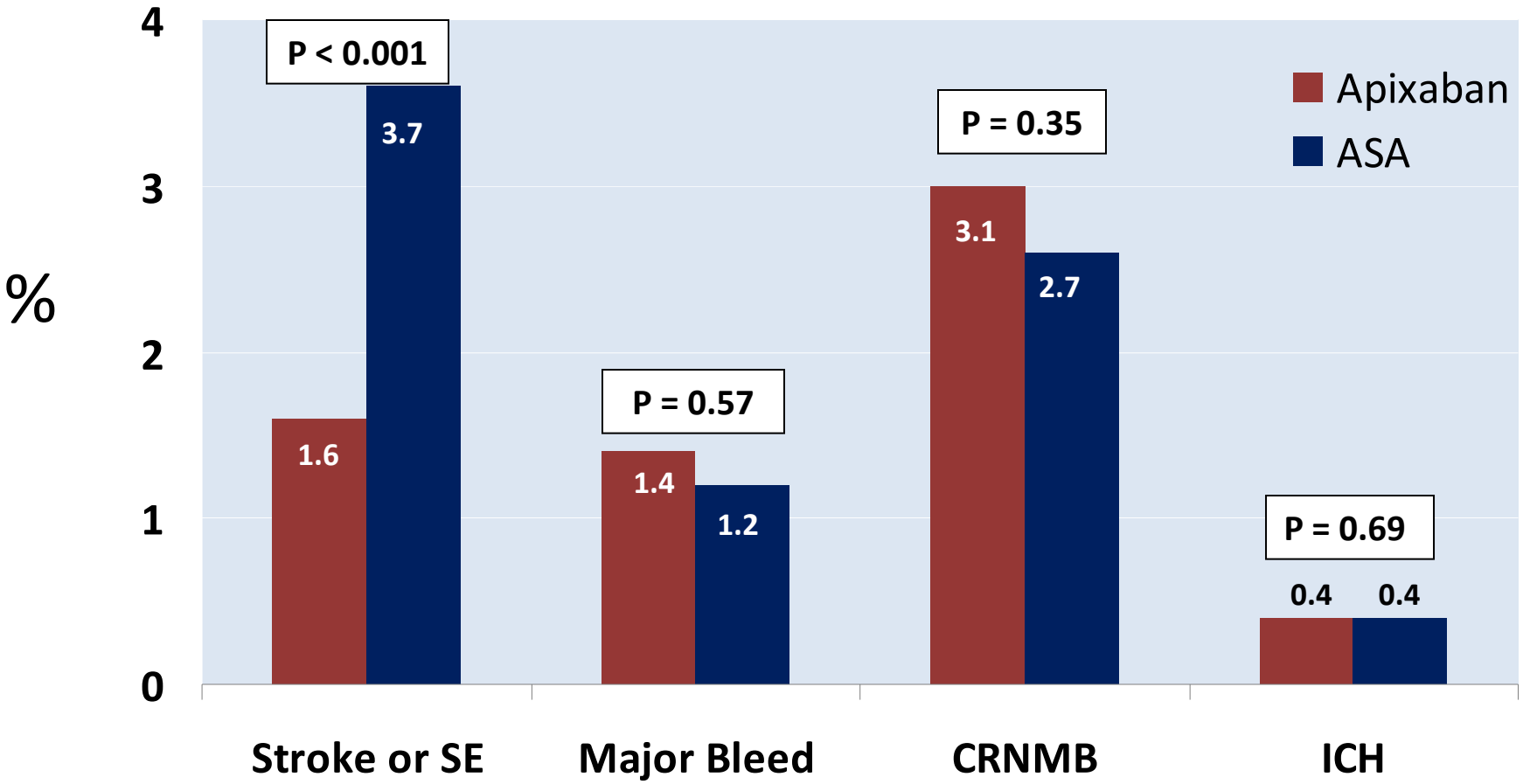
ROCKET AF



Patel et al New Engl J Med 2011.

Apixaban in Atrial Fibrillation

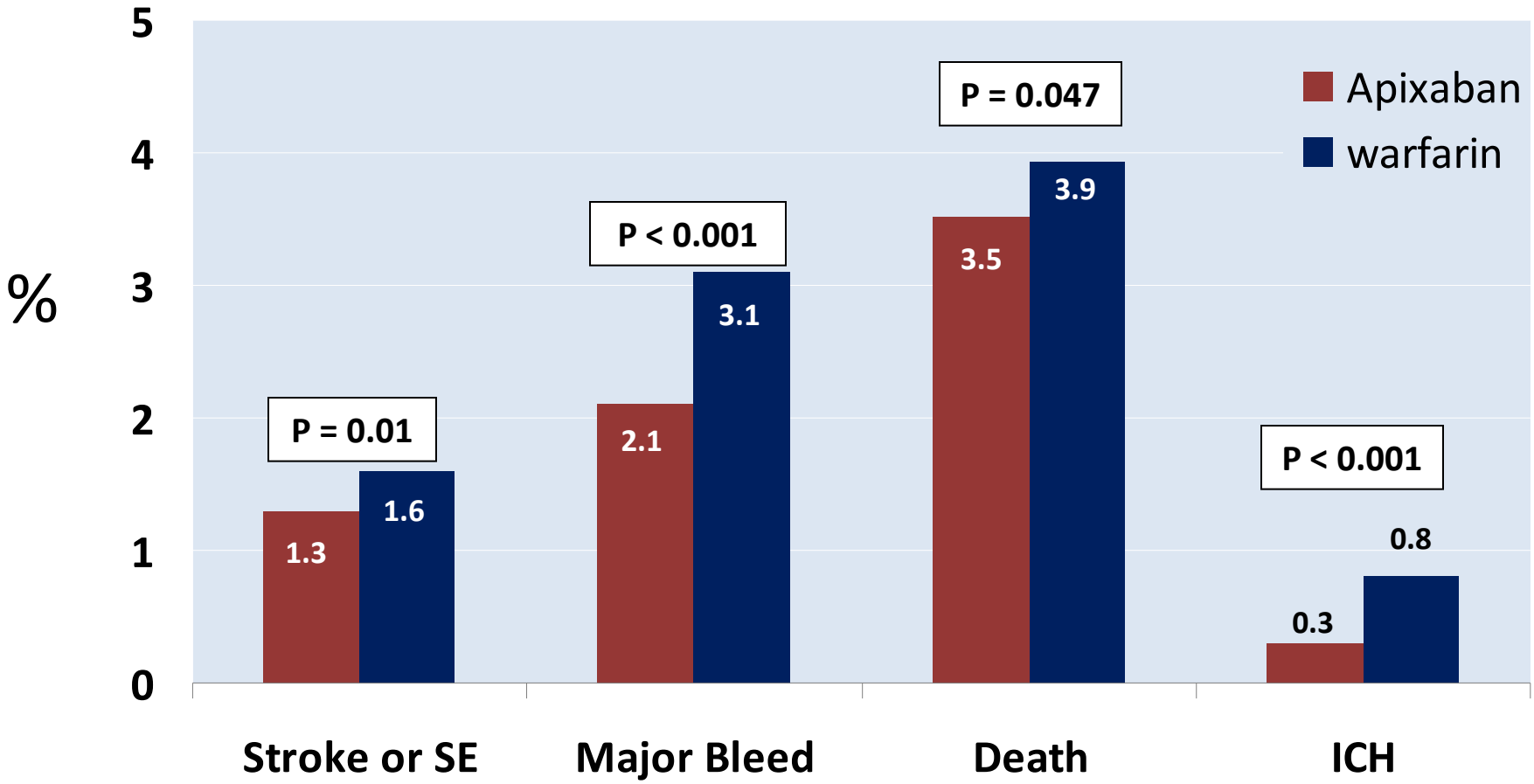
AVERROES



Connolly et al. New Engl J Med 2011.

Apixaban in Atrial Fibrillation

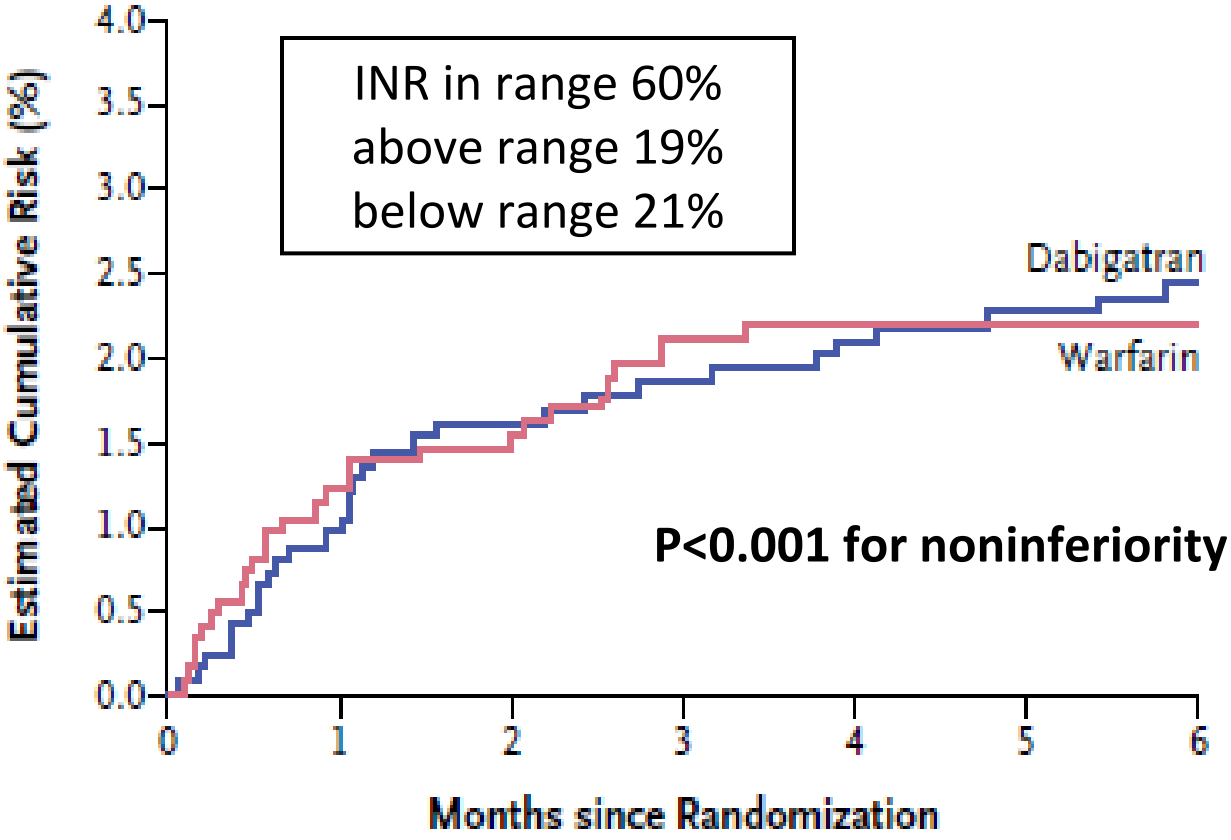
ARISTOTLE



Granger et al. New Engl J Med 2011.

Dabigatran in VTE Treatment

RECOVER

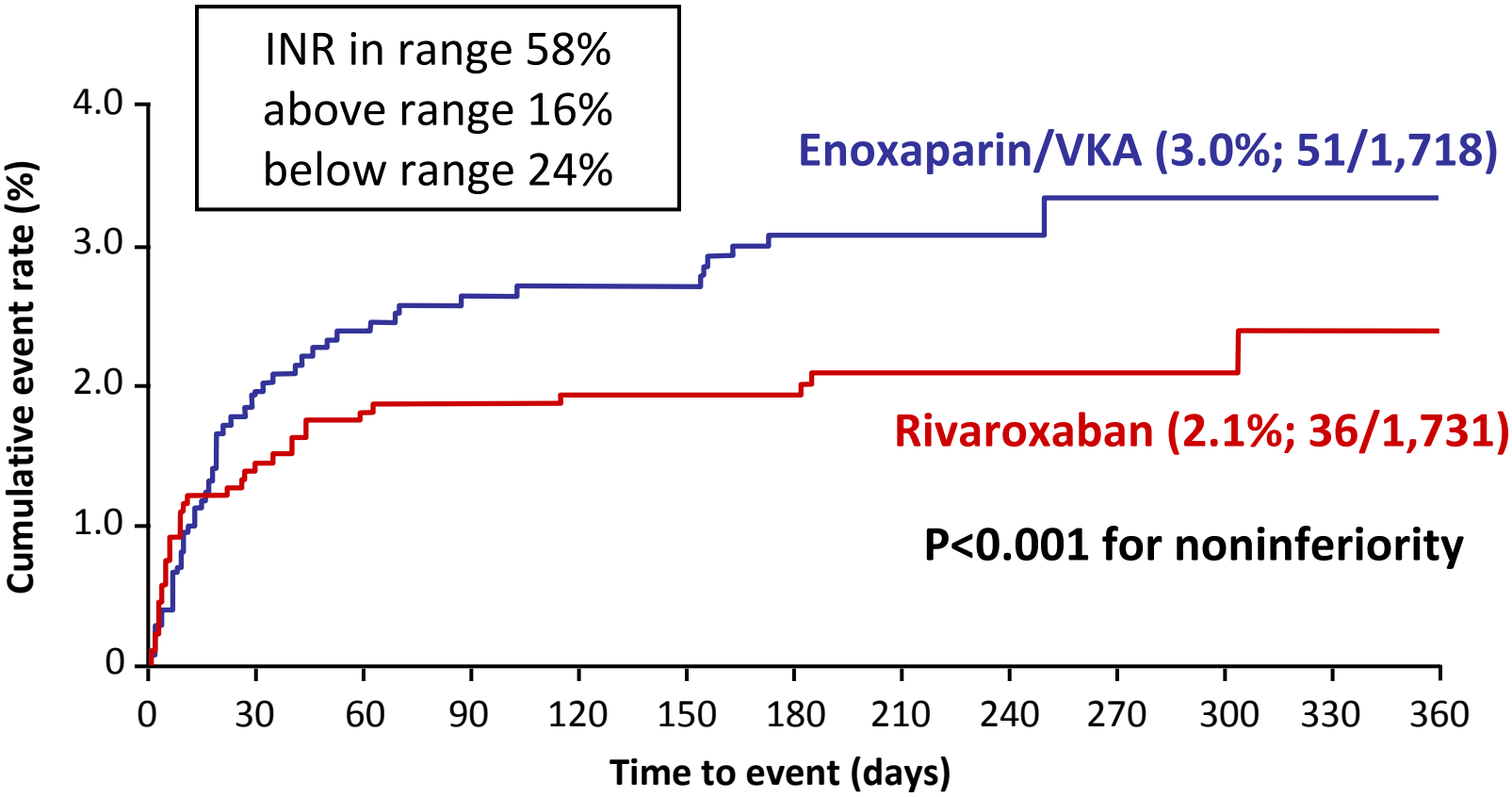


Dabigatran is non-inferior to warfarin for prevention of recurrent or fatal VTE with comparable major bleeding risk (1.6% vs 1.9%)

Schulman et al. New Engl J Med 2009.

Rivaroxaban in DVT Treatment

EINSTEIN



Rivaroxaban is non-inferior to warfarin for prevention of recurrent or fatal VTE with comparable major bleeding risk (0.8% vs 1.2%)

Buller et al. New Engl J Med 2010.

New Oral Anticoagulants Clinical Trials Summary

- novel oral anticoagulants are efficacious alternatives in:

	Dabigatran	Rivaroxaban	Apixaban
Stroke prevention in AF	✓	✓	✓
Prophylaxis in TJR	✓	✓	✓
Treatment of DVT	✓	✓	
Treatment of PE	✓		

✓ Level I evidence

Approval in US+Canada | Canada only | Europe

- Bleeding risk of new agents is similar or slightly better compared to traditional regimens
- Inability to measure anticoagulant effect and lack of specific antidote are major limitations of all new oral anticoagulants

Anticoagulant Options

- Drugs with no significant renal clearance
  - Unfractionated heparin (UFH)
  - Warfarin
  - Direct Thrombin Inhibitors: argatroban
  - Factor Xa inhibitors: apixaban
- Drugs with significant dependence on renal clearance
  - Low molecular weight heparins (LMWHs)
  - Pentasaccharide: fondaparinux
  - Heparinoids: Danaparoid
  - Direct Thrombin Inhibitors: lepirudin, bivalirudin, dabigatran
  - Factor Xa inhibitors: rivaroxaban

Thrombosis in Chronic Renal Disease

- Higher incidence of arterial and venous thrombosis compared to general population
- 6-fold higher risk for PE in dialysis patients
- Renal vein thrombosis and vascular access thrombosis are particularly problematic
- DVT reported in up to 15% of patients with nephrotic syndrome
- Multiple risk factors: inflammation, infection, immobility, reduced levels of endogenous anticoagulants, endothelial dysfunction, rEPO

Pathophysiology of Bleeding in Renal Impairment

	Defect	Mechanism
Platelets	Adhesion Secretion Aggregation	Altered arachidonic acid metabolism Abnormal Ca^{2+} mobilization ↓ ADP, epinephrine, 5-HT production ↓ GPIb, GPIIb-IIIa receptor function ↓ Fibrinogen binding to activated platelets Inhibitor in uremic plasma (e.g. urea, guanidine-succinate)
Platelet-vessel wall interaction	Interaction	↓ vWF activity Inhibitor in uremic plasma ↑ Release of prostacyclin and nitric oxide
RBC hematocrit	Anemia	Altered blood rheology RBCs impact on platelets Reduced clearance of nitric oxide
Other	Medications Comorbid diseases Invasive procedures	Antiplatelet and anticoagulant therapy Iron deficiency, malnutrition, inflammation Post-operative bleeding

Sohal et al Thromb Res 2006. Pavord and Myers Blood Rev 2011.

2008 ACCP Guidelines

- Appropriate dosing of LMWH in patients with severe renal insufficiency is uncertain
- Clearance of the anti-Xa effect of LMWH correlates with CrCl but this varies amongst different LMWHs
- In patients with acute DVT and severe renal failure, we suggest UFH over LMWH (Grade 2C)
- If LMWH is used in patients with severe renal insufficiency for therapeutic anticoagulation, we suggest using 50% of the recommended dose (Grade 2C)

*severe renal insufficiency = CrCl less than 30 ml/min

Hirsh et al and Kearon et al. Chest 2008 8th ACCP Conference on Antithrombotic and Thrombolytic Therapy.

Anti-Xa Monitoring

- Nonstandardized, agent-specific assay
- Measures anticoagulant effect of LMWH
- Weak correlation with efficacy and safety
- “therapeutic” levels defined as peak (4 hr) values:
  - Once daily dosing: 1.0 – 2.0 IU/mL
  - Twice daily dosing: 0.6 – 1.0 IU/mL
- Trough levels are used to detect accumulation:
  - Aim for < 0.5 IU/mL (within 1 hr pre injection)

Kearon et al. Chest 2008 8th ACCP Conference on Antithrombotic and Thrombolytic Therapy.

Anticoagulation in Renal Impairment
Summary

- Bleeding risk is higher in renal impairment, with or without anticoagulation
- Anticoagulant options remain limited in renal impairment
- UFH is preferred over LMWH
- New oral anticoagulants should be used with caution
  - Variable dependence on renal excretion
  - Relatively contraindicated in transplant patients due to drug interactions
  - Inability to measure anticoagulant effect
  - Lack of antidote
  - Not interchangeable

LMWH USE in Renal Impairment - Cases

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Oct 6, 2011

I have no conflicts of interest to declare

Case 1. Long-Term LMWH

A case of Calciphylaxis and Atrial Fibrillation

Anti-Xa Monitoring

(not an exact science)

Measure in patients with renal failue (CrCl < 30 mL/min) or obesity

- Measure peak effect (4 hours)
  - 3-4 hours after twice daily dosing
  - 4-5 hours after once daily dosing
  - Twice daily: **0.6-1** units/mL
  - Once daily: **1-2** units/mL (Tinzaparin 0.6-1.5 U/mL*)
- Trough levels **< 0.5** units/mL

(Semin Thromb Hemost 2001;27:519-22; *Drug Safety 2002;25:725-33)

Mean Peak Anti-Xa Levels
(Normal Renal Function)

Therapeutic Scheme	
80–100 Units/kg Q12H	**175–200 Units/kg daily**
Dalteparin : 0.6	Dalteparin : 1.05
Nadroparin : 0.9	Nadroparin : 1.30
Enoxaparin : 1	Tinzaparin : 0.85

(Semin Thromb Hemost 2001;27:519-22)

Tinzaparin

- Highest MW – May be less dependent upon renal elimination
- Closest anti-Xa:IIa activity compared to heparin

Agent	Average MW (daltons)	AntiXa:IIa Ratio	Dose Adjustment CrCl < 30 mL/min
Heparin	15,000	1:1	No
Tinzaparin	**6500**	**1.9:1**	**No**
Dalteparin	5600	2.0-2.7:1	?
Enoxaparin	4500	2.7-4.1:1	Yes (50%)
Nadroparin	4300	3.2-3.7:1	Yes (no guidelines)

Tinzaparin Full Dose (175 units/kg/day)

Trial	Population	Duration	Outcome
Drug Safety 2002:25:725-33	200 elderly pts with VTE ~25% Cr Cl 20-35 mL/min	Up to 30 d (mean 19 d)	**88% peaks < 1.5 U/mL** (Day 1, qweek) - No correlation to CrCl
Thromb Haemost 2000;84: 800-4	30 elderly VTE pts ~25% CrCl 20-29 mL/min	10 days	**All peaks < 1.1 U/mL** (Days 1,2,7,10) - No correlation to CrCl
Blood 2006; 108:884 (abstract)	78 pts with VTE and varying CrCl including HD	5-7 days	**94% troughs < 0.5 U/mL** (Days 3, 5, 7) -No correlation to CrCl
Thromb Res 2011;128:27-34 (IRIS)	MC, OL, R cf UFH 539 elderly with DVT and CKD (25% pts with CrCl< 30 mL/min)	5-10 days, then warfarin (f/u = 90 d)	-**Study stopped early** due to ↑ mortality in Tinza arm at day 28 (11.9% vs 6.3%, p=0.035) - CA, sepsis in pts ≥ 90 yrs - Imbalance in randomization

Case 1. Calciphylaxis and A Fib

- 79 yo female, 75 kg admitted with calciphylaxis & atrial fibrillation
  - D/C warfarin, daily HD (5/7), hyperbaric unit, sodium thiosulphate, lanthanum
  - Started on tinzaparin 14,000 units SC daily

    (75 kg x 175 units/kg = 13, 125 units)

    Peak Anti-Xa levels (6h):
    - **Day 3 = 0.85 units/mL**
    - **Day 16 = 0.88 units/mL**
    - **Day 37 = 0.78 units/mL**
  - NOTE: Intradialytic heparin discontinued

Case 2. Long-Term LMWH and Triple Anticoagulant Therapy

A case of Anti-phospholipid syndrome and MI

Case 2: 73 yo female, 80kg on HD

PMH: Antiphospholipid antibody syndrome (DVT/PE 2000, IVC filter, warfarin failure, a fib) → Lifelong tinzaparin

Date	Event	Tinzaparin Dose (SC)
Oct-06 to Aug-07	Start HD	14,000 U → 10,000 U → 7000 U daily (Aug 23/07 peak anti-Xa level = 1.03 U/mL)
Aug-09	Seizure (admission)	7000 units daily + Levateracetam (Keppra®)
Aug-09	Pneumonia-ICU NSTEMI x 2	7000 units SC daily + ASA 81mg PO daily + Clopidogrel 75 mg PO daily
Dec-09	Left upper arm hematoma	ASA + Plavix held; Discharged Jan-10 to RN home on triple therapy above
Feb-10	Right upper arm hematoma (readmit); Heme consult	D/C Tinzaparin and Clopidogrel ASA 81mg daily + Heparin 5000 units SC BID
Sept-10	Humerus # - fall	Deceased (?PE vs sudden cardiac death)

Bleed Risk from Single, Dual, or Triple Therapy in Patients with A Fib

Variable	RR (95% CI) non-fatal bleed
Warfarin	1 (reference) Crude Rate = 3.6%
Aspirin	0.84 (0.8-0.89)
Clopidogrel	0.94 (0.76-1.16)
ASA +C	1.64 (1.33-2.03)
W+ASA	1.77 (1.66-1.90)
W+C	3.16 (2.48-4.03)
W+C+ASA	**3.93 (3.05-5.05)**

- Nationwide Danish registry of 82,854 patients with atrial fib discharged on warfarin, ASA, or clopidogrel (Jan 97-Dec 06)
- Analyzed risk hospitalization or death due to bleeding
- 12,191 (10.3%) had non-fatal bleed, primary due to GI

(Arch Int Med 2010;170:1433-41)

Major Bleeding in HD Patients

- Retrospective review of 255 pts from Jan 2002-Jan 2004 (1028 person years of exposure)
- 25/26 major bleeds were upper or lower GI bleed; 1 = CNS

Treatment	# pts	Major Bleed	% Major Bleeds	Hazard Model for Time to First Bleed (95% CI)
None	178	4	0.8%	Reference
Warfarin	89	15	3.1%	3.9 (1.05-14.6)
ASA	107	12	4.4%	5.8 (1.9-18.0)
ASA + Warfarin	50	5	6.3%	8.2 (2.2-30.7)
Total	255	26		

(CJASN 2008;3:105-110)

Cases 3 & 4 Bridge Therapy

Two very high risk patients

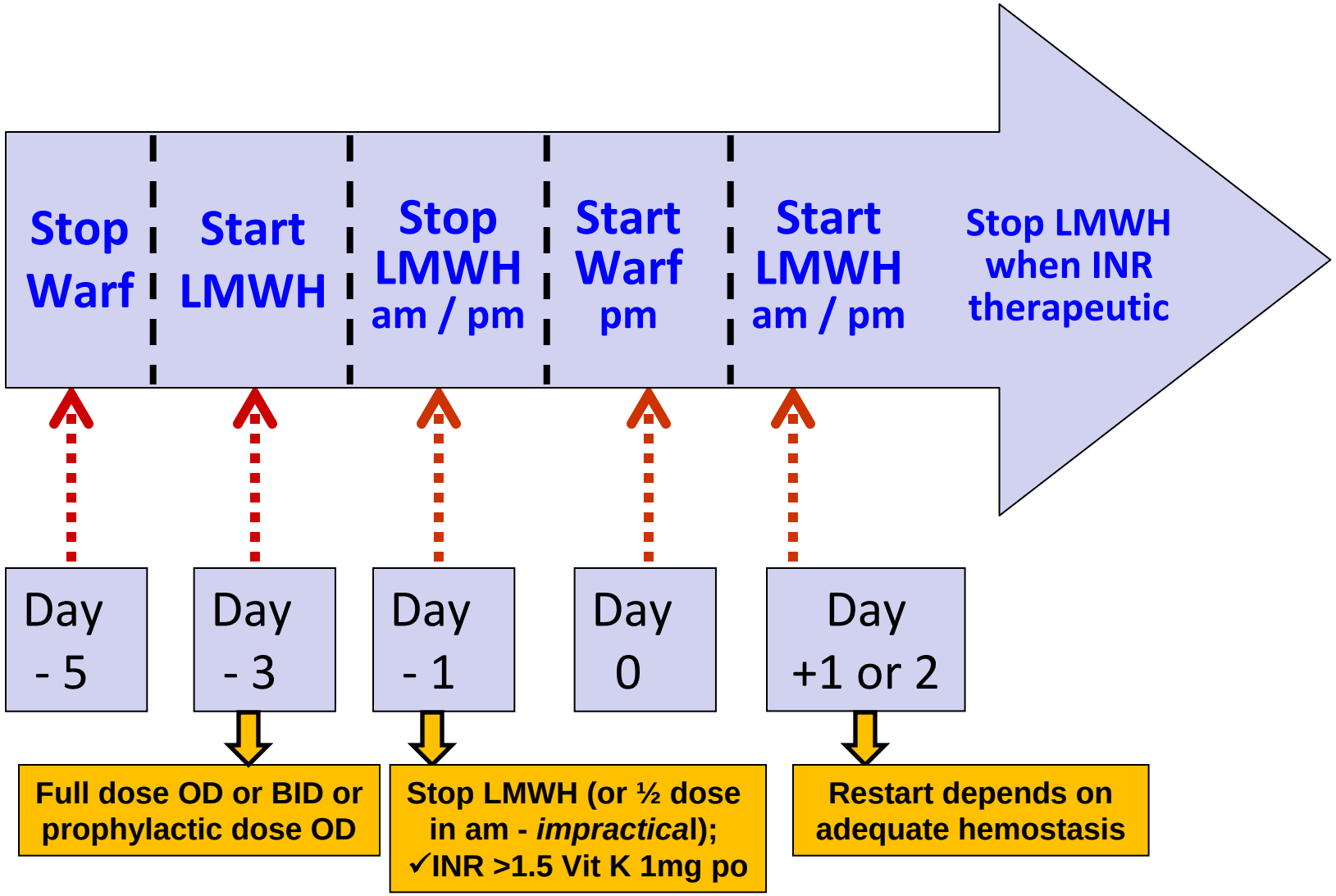
Peri-operative Risk Stratification

(Chest 2008;13:299-335S)

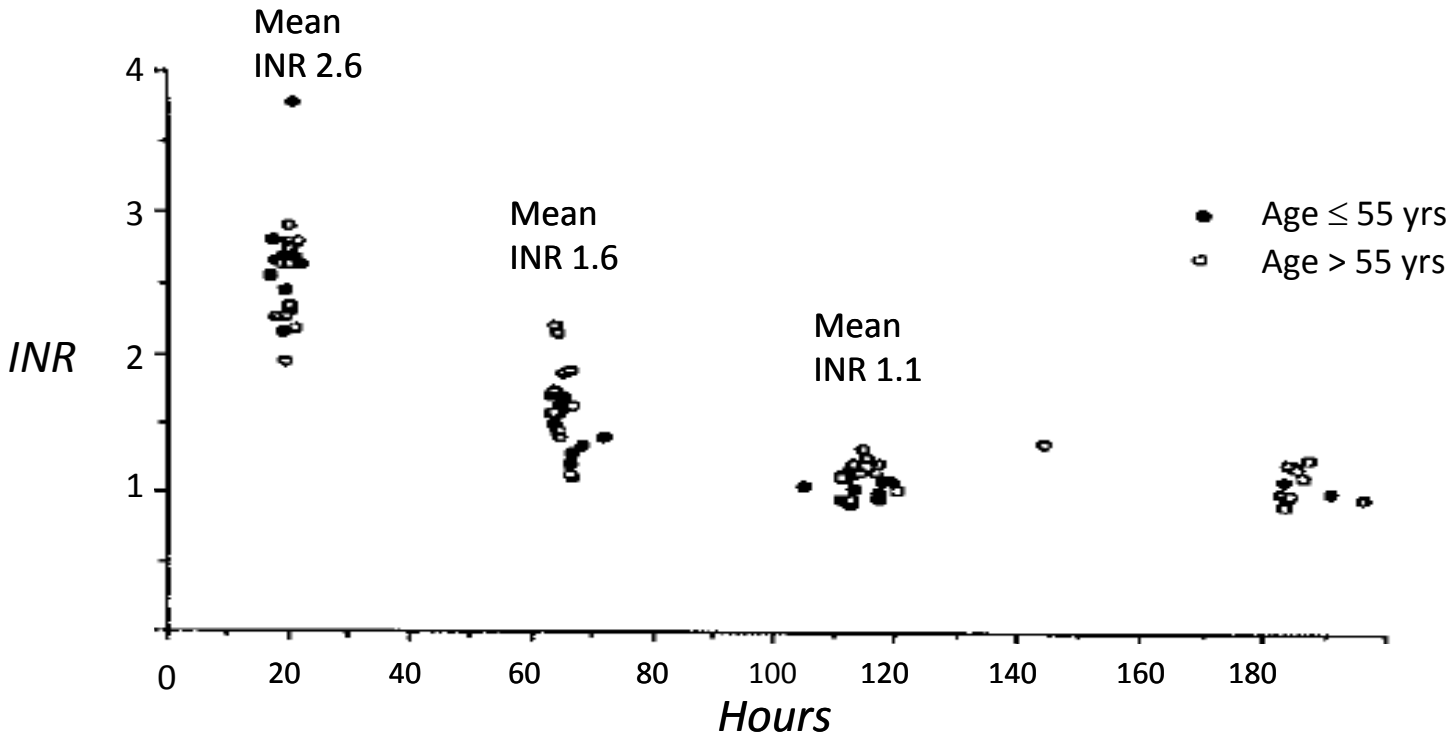
Thrombosis Risk	Mechanical Heart Valve	Atrial Fibrillation	VTE	Bridge
HIGH	•Mitral Valve •Older aortic valve (tilting disc) •Recent (< 6 mo) stroke or TIA	•$CHADS_2$ 5-6 •Recent (< 3 mo) stroke or TIA •Rheumatic valvular HD	• VTE < 3 mo •Severe thrombophilia	**Yes** (1C) LMWH preferred over heparin (2C)
MODERATE	•Bileaflet aortic valve + one of: a fib, stroke, TIA, HT, DM, CHF, > 75	•$CHADS_2$ 3-4	•VTE 3-12 mo •Recurrent VTE •Active cancer	Full dose or Prophylactic dose or No bridge (2C)
LOW	•Bileaflet aortic valve & no risk factors for stroke	•$CHADS_2$ 0-2	•VTE > 12 mos and no other risk factors	**No bridge** or Prophylactic LMWH (2C)

How to Bridge with LMWH

(Circulation 2004;110:1658-63)



Temporary Discontinuation of Warfarin: INR Decay with Target Range 2-3



- N= 22 patients; serial INRs done at 2.7 and 4.7 days after D/C

(Ann Intern Med 1995;122:40-2)

Case 3: 72 yo, 91 kg male

- Recent bilateral PE July 4/11; Hx of PE and DVT x 2
- Pt had been off warfarin AMA prior to recent event
- Requires fistuloplasty July 19/11

Date	Day	Action
July 14	Day - 5	Stop Warfarin (INR = 2.7)
July 15-17	Day - 4 to - 2 (low dose ID heparin)	Start Tinzaparin 14,000 units qpm (175 units x 91kg = 15,925 units)
July 18	Day - 1	No Tinzaparin; INR = 1.0
July 19	Day 0 (if okay by vascular)	Restart Warfarin in evening Restart Tinzaparin in evening
July 27	Day + 8 (end of 10 day Pharmacare coverage)	Last dose Tinzaparin (INR = 1.9)

Case 4: Accidental Overdose

- 74 yo, 58 kg male with PE July 27/10;
- Hx of pulmonary fibrosis

Date	Event	Tinzaparin Dose
Aug 6	Discharged INR = 1.2	10,000 units daily
Aug 7-9	Patient error with dose; was dispensed 3 x 20,000 unit/mL vial (instead of 10,000 unit syringe)	20,000 units daily x 3
Aug 10	Ran out of Tinzaparin	None
Aug 11	INR = 1.3; error discovered; Anti-Xa level ordered (43 h post)	5000 units
Aug 12	Anti-Xa Level = 0.26 units/mL	10,000 units
Aug 13	INR = 2.1	Discontinue tinzaparin

Case 5. LMWH Prophylaxis

A paraplegic patient

Dalteparin Prophylaxis Trial: DIRECT

(Arch Intern Med 2008;168:1805-12)

- 138 ICU patients, CrCl < 30mL/min (mean 18.9mL/min)
  - 9.4% on dialysis
- Dalteparin 5000 U SC daily ≤ 30 days (median 7 days)
- Trough anti-Xa levels on days 3, 10, 17

Results:

- All trough anti-Xa levels < 0.4 units/mL
- No evidence of accumulation
- DVT = 5.1%
- Major bleeding = 7.2%
  - Risk Factors: ASA use, ↑ INR

VTE Prophylaxis Guidelines: VCH/PHC

- Dalteparin 5000 units SC daily (eGFR ≥ 10 mL/min)
  - If patient has eGFR 10-30 mL/min and therapy to extend beyond 10 days, consider switch to heparin Q12H
- Heparin 5000 units SC Q12h (eGFR < 10 mL/min)

Weight Range	**Dalteparin (eGFR ≥ 10mL/min)**	**Heparin (eGFR < 10 mL/min)**
40 kg or less	2500 units SC daily	2500 units SC Q12H
41 kg to BMI 40 kg/m^2	5000 units SC daily	5000 units SC Q12H
BMI > 40 kg/m^2	5000 units SC Q12H	5000 units SC Q8H

Case 5: Dalteparin Prophylaxis

- 57 yo male, 95 kg, paraplegic

Date	Event	Anticoagulation
Apr 2, 2010	Admitted for ↓ LOC – ICU intubation x 2 weeks CKD 2° diabetic nephropathy	Heparin 5000 units SC Q8H
Apr 22	Dialysis initiated – R IJ inserted - radiologist noted incidental finding of R IJ vein thrombosis (from previous ICU catheter)	Heparin 5000 units SC Q8H
May 1	Heme consult Doppler R neck negative	Dalteparin 5000 units SC daily
June 2	Anti-Xa Level > 2 units/mL (13 h post dose)	Hold x 24 h, then Dalteparin 2500 U SC OD
June 5	Patient discharged	