To Clot or Not
What's New In Anticoagulation?

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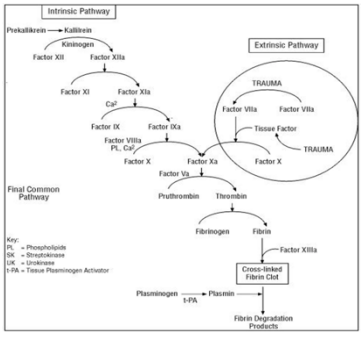
Clotting Cascade



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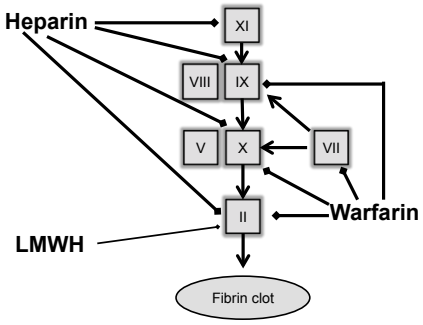
Anticoagulant drug targets



Who Needs Anticoagulation

- **Atrial fibrillation***
- **Venous/arterial thromboembolism**
- **Valvular heart disease**
- **Primary prevention**
- **Post arterial stent**
- **Severe cardiomyopathy**
- **Pulmonary hypertension**
- **LV thrombus**

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Anticoagulation Risks

- 20% increased risk of death.
- The Joint Commission's Sentinel Event Database showed that 7.2% of all adverse medication events from January 1997 to December 2007 were related to anticoagulants.
- #1 drug for hospitalization for adverse drug events on older adults: Warfarin

$CHADS_2$

- **Congestive heart failure = 1**
- **Hypertension = 1**
- **Age = 1**
- **Diabetes = 1**
- **Stroke = 2**

$CHADS_2Vas$

- Congestive heart failure = 1
- Hypertension = 1
- Age over 65 = 1
- Age over 75 = 1
- Diabetes = 1
- Stroke = 2
- Female gender = 1
- Vascular disease = 1

A Fib Anticoagulation Recommendations

- $CHADS_2$ 0-1; calculate $CHADS_2Vasc$ score
- $CHADS_2Vasc$ score of 0-1; ASA
- Score of 2 or more; assess bleeding risk and anticoagulate if possible

Anti Platelet Therapy (APT)

- Acute Coronary Syndrome
- STEMI
- s/p PTCI
- TIA
- Atrial fibrillation/flutter

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APT Drugs

- aspirin
- clopidogrel
- prasugrel
- ticagrelor
- ticlopidine

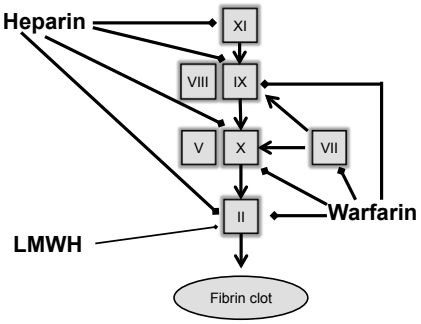
Pearls About APT

- Do not stop for 12 months post PTCI with drug eluding stent
- Do not stop for 1 month post PTIC with bare metal stent
- 7 day “wash out”, life of the platelet treated.
- Genetic testing for clopridrel.
- Cost an issue for prasugrel and ticagrelor

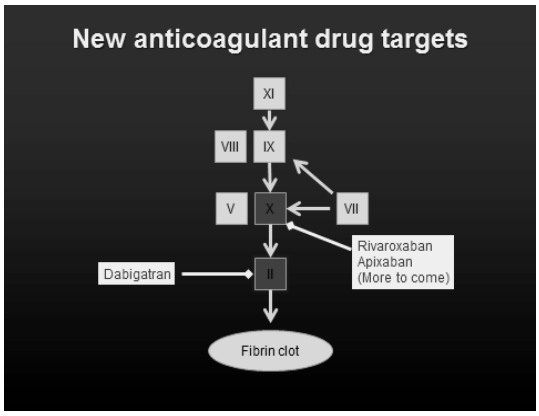
Novel Agents

- Dabigatran (Pradaxa)
- Rivaroxaban (Xarelto)
- Apixaban (Eliquis)
- More to come

Anticoagulant drug targets



New anticoagulant drug targets



Disadvantages of older anticoagulants

- **Warfarin**
  - **Delayed onset of action**
  - **Complex pharmacology (genetics, diet, drug interactions)**
  - **Patient resistance**
  - **Narrow therapeutic window**
  - **Need for monitoring**
- **Heparin**
  - **Variable dose-response, need for monitoring**
  - **Parenteral administration**
  - **Risk of HIT**
  - **Not suitable for long-term treatment**

Disadvantages of older anticoagulants

- **LMWH**
  - **Parenteral administration (usually twice daily)**
  - **Risk of HIT (less than UFH)**
  - **Expense (~ 100x warfarin; 100 mg/10 doses = $850.00)**
  - **Difficult to use in renal failure**

Pharmacology of Oral Anticoagulant Drugs

	Warfarin	Dabigatran	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	2.5-4 h	3 h
Half-life	40 h	14-17 h	5-9 h 9-13 h elderly	8-15 h
Metabolism	Cytochrome P450	80% renal 20% biliary	66% renal 33% biliary	25% renal 75% biliary

Ansell, 2011 HTRS meeting

Comparison of Novel Agents

	Dabigatran	Rivaroxaban	Apixaban
Target	Factor IIa	Factor Xa	Factor Xa
FDA Indications	Nonvalvular AF	Nonvalvular AF Ortho VTE Proph Acute Treatment VTE/PE	Nonvalvular AF Ortho VTE Proph
Prodrug	Yes	No	No
Dosing	Twice daily	Daily, with food	Twice daily
Onset	1-2 hrs	2-4 hrs	3-4 hrs
Half-life (h)	14–17	7–11	8–14
Renal Adjustment	↓ 15-29ml/min Avoid < 15 ml/min	Avoid < 30 ml/min	Avoid < 15 ml/min
Drug Interactions	P-gp	CYP3A4/P-gp	CYP3A4/P-gp

Comparison of Safety Results

	RE-LY		ROCKET-AF		ARISTOTLE	
Major bleed	3.1 vs. 3.36%	p=0.31	3.6 vs. 3.4%	p=0.58	2.1 vs. 3.1%	p<0.001 NNT 67
Intracranial bleed	0.3 vs. 0.74%	p<0.001 NNT 116	0.5 vs. 0.7%	p=0.02 NNT 250	0.3 vs. 0.8%	p<0.001 NNT 128
GI bleed	1.5 vs. 1.0%	p<0.001 NNH 100	3.2 vs. 2.2%**	p=0.001 NNH 100	0.76 vs. 0.86%	0.37

Dabigatran Nonvalvular Atrial Fibrillation

- **CrCl >30 ml/min: 150 mg orally, twice daily**
- **Outside US: 110 mg twice daily for age >75 or propensity for GI bleeding**
- **CrCl 15-30 ml/min: 75 mg orally, twice daily**

Converting to/from Dabigratan

Current Anticoagulant	Anticoagulant to be Converted to	Procedure
Warfarin (INR 2-3)	Dabigatran	Discontinue warfarin and start dabigatran when INR <2.0
Dabigatran	Warfarin (INR 2-3)	• CrCl >50 ml/min: start warfarin 3 days before stopping dabigatran • CrCl 31-50 ml/min: start warfarin 2 days before stopping dabigatran • CrCl 15-30 ml/min: start warfarin 1 day before stopping dabigatran • CrCl <15 ml/min: no recommendation
LMWH, heparin	Dabigatran	Start dabigatran 0-2 hours before administration of last heparin/LMWH dose, or at same time as discontinuation of infusional heparin
Dabigatran	LMWH, heparin	• CrCl ≥ 30 ml/min: start 12 hours after last dose of dabigatran • CrCl < 30 ml/min: start 24 hours after last dose of dabigatran

American Society of Hematology

Conclusions with Dabigatran

- Both doses offer advantages over warfarin
- Dabigatran 150 mg is more effective and dabigratan 110 mg has a better safety profile
- Clinical considerations
  - No need for INR monitoring
  - Management of bleeding risks
  - Non-adherence
  - Cost
  - MI/ACS risk
  - Procedure bleeding risks
  - Deterioration when exposed to air.

Rivaroxaban

- FDA approved November 2011
- 20 mg daily for atrial fibrillation if CrCl> 50ml/ min; 15 mg if CrCl 15-50ml/min
- DVT/PE 15 mg BID for first 21 days then 20 mg daily
- Prophy post hip or knee replacement, 10 mg daily
  - Usually dosed in the evening
- Take with food

Rivaroxaban Summary

- Efficiency
  - Non-inferior to warfarin but did not achieve superiority
- Safety
  - Similar rates of bleeding and adverse events
  - Less ICH and fatal bleeding
- Conclusion
  - Potentially viable alternative to warfarin

Apixaban

- FDA approved 2012 for nonvalvular atrial fibrillation
  - Dose 5 mg BID
- Prophy post hip and knee replacement
  - 2.5 mg BID
- Decrease dose to 2.5 mg PO bid in patients w/ at least 2 of the following:
  - >80 yo,
  - <60 kg,
  - or Cr >1.5

Apixaban Summary

Treatment with apixaban vs warfarin in patient with atrial fibrillation and at least one additional risk factor for stroke.

- Reduces stroke and systemic embolism by 21%
- Reduces major bleeding by 31%
- Reduces mortality by 11%

Preferences for Agents

- Dabigratan: 10% of patients complain of GI side effects; discard med if open more than 30 days.
- Rivaroxaban: once daily dosing with food
- Apixaban: favorable research findings

Canadian CV Society 2012 Guidelines

- Risk stratify all patients
- $CHADS_2$ = 0 ASA 75-325
- $CHADS_2$ = 1 OAC: ASA or alternative
- $CHADS_2$ = 2 or more OAC
- Where OAC indicated – novel agent preferred

ACC/AHA/HRS 2011

- Dabigatran is an alternative to warfarin for stroke prevention in atrial fibrillation
- 1B recommendation

Concerns with Novel Agents

- Cost…Cost…Cost
- No antidote
- No way to measure anticoagulation
- Proper patient selection
- Patients develop a casual attitude
- Renal function monitoring?

Cost per month of oral anticoagulants

- Rivaroxaban (20 mg/day)
- Apixaban (5 mg bid)
- Dabigatran (150 mg bid)
  - All cost $250-350/month
- Warfarin (7.5 mg/day): $31 plus testing

Anticoagulation and Procedures

- Determine risk of bleeding for dental or medical procedures
  - **Low risk:** Cataract or other ophthalmic surgery, except for major lid or orbital surgery.
  - Skin biopsy or other minor dermatologic procedure. Joint or soft tissue injection.
  - Endoscopy when biopsy is not anticipated.
  - Supragingival scaling.
  - Simple restorations
- Do not stop anticoagulation for low risk procedures.

Anticoagulation and Procedures

- Moderate risk procedures
  - Subgingival scaling.
  - Restorations with subgingival preparations.
  - Single or multiple extractions.
  - Injections of local anesthetic for regional anesthesia (ie, superior alveolar or mandibular nerve block). Gingivoplasty.
- Reversal NOT RECOMMENDED, but topical measures to control bleeding should be used

Anticoagulation and Procedures

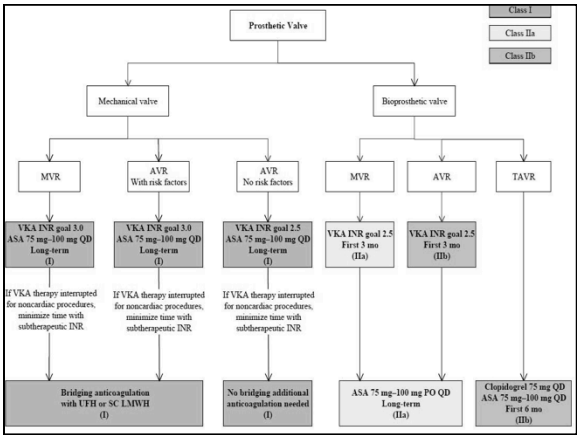
- **High risk procedures:**
  - **Abdominal surgery. Intracranial or spinal surgery.**
  - **Thoracic surgery. Coronary artery bypass or heart valve replacement.**
  - **Endoscopy when intervention is anticipated and the risk of interventionally induced bleeding is high.**
  - **Epidural injections or lumbar puncture.**
  - **Full mouth or full arch extractions.**
  - **Minor or extensive periodontal flap surgery.**
  - **Single or multiple implants.**
- **Anticoagulant reversal recommended**

Anticoagulation Reversal

- **Warfarin**
  - **stop 3-5 days prior; bridge with LMWH when INR subtherapeutic if mechanical valve, history of CVA or high CHADS score. Restart bridging when hemostasis established.**
- **NOAC**
  - **Stop 24-48 hours pre procedure. No bridging. Restart when hemostasis is established.**

A Place for Warfarin

- **Valvular Heart Disease**
  - **Mechanical valves**
- **Affordability**
- **Pre and post ablation**
- **Patient adherence**

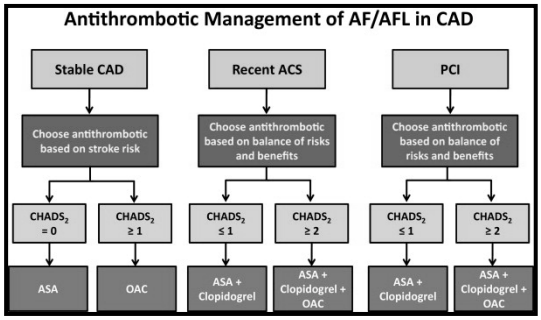


Questions

Thank you

- **Anticoagulation Forum and Centers of Excellence**
- **Heart Rhythm Society**
- **American Heart Association**
- **American College of Cardiology**
- **American Society of Hematology**
- **Canadian Cardiovascular Society**

Canadian CV Society 2012



Canadian CV Society 2012