

Inherited and Acquired Thrombophilia: Advances in Thrombosis and Antithrombotic Therapies

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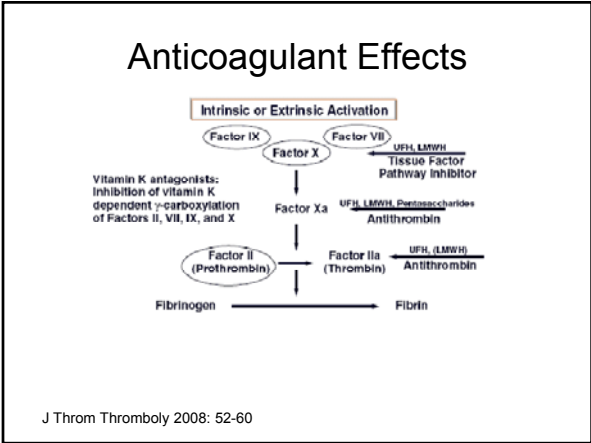
Disclosure Information

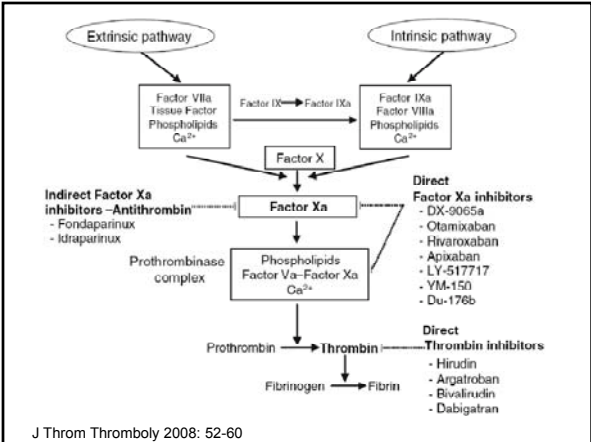
- I have no financial relationships to disclose relevant to the content of this presentation

General Topics

- New Anticoagulant trials
- Treating/Reversing bleeding from anticoagulation
- Specific Hypercoagulable state comments
- Duration of anticoagulation/predictors of VTE recurrence

New Anticoagulant Trials





New Anticoagulants

Name	Class	Dosing	Reversal	T ½	Elimination
Dabigatran Pradaxa®	DTI	Oral	None	12-17 hr	Primary renal
Apixaban	Xa inh	Oral	None	9-14 hr	25% renal 75% fecal
Rivaroxaban	Xa inh	Oral	None	5-9 hr	66% renal 28%bil/fecal
Idrabiotaparinux	Xa inh AT III	SQ	Avidin	120 hr	renal
Fondaparinux Arixtra®	Xa inh AT III	SQ	None	17-24 hrs	renal

See also 2008 ASH Educ Prog p259

Dabigatran-renally impaired

- RE-MODEL and RE-NOVATE ortho trials
- Selected pts: GFR 30-50 mL/min
- 220mg or 150mg dabigatran compared to 40mg Enoxaparin
- VTE: 17.7%; 23.5% and 27.8% respective
- Bleeding: 5.3%; 0%, and 4.7%
- Rec 150mg dabigatran dose for this population

Abstr #981; See also Throm Haem 2007; 5: 2178 and Lancet 2007; 370: 949

Rivaroxaban in TKR

Endpoint	Rivaroxaban 10 mg q d % (n/N)	Enoxaparin 30 mg q 12h % (n/N)	P-value
DVT, non-fatal PE, all cause mortality	6.9% (67/965)	10.1% (97/959)	0.012
Major VTE	1.2% (13/1122)	2.0% (22/1122)	0.124
Symptomatic VTE	0.7% (11/1526)	1.2% (18/1508)	0.187
Major Bleeding	0.7% (10/1526)	0.3% (4/1508)	0.110
Any non-major bleeding	10.2% (155/1526)	9.2% (138/1508)	-
Major and clinically relevant non-major bleeding	3.0% (46/1526)	2.3% (34/1508)	0.179

Abstr #35; See also NEJM 2008, 358:2765-2786 two studies

**Rivaroxaban pooled data:
4 Orthopedic Studies**

Event	Rivaroxaban n-6173	Enoxaparin N=6200	P values
VTE	0.5%	1.0%	0.001
Major bleeding	0.3%	0.2%	0.175
Any bleeding	6.6%	6.2%	0.376

Abstr #36

Apixaban-ADVANCE-1

- 2.5mg orally BID compared to Enoxaparin 30mg SQ BID in 3195 TKR pt
- 8.99% VTE in apix; 8.85% in Enox
- Stats for non-inferiority NOT met
 - Stated enox events fewer than predicted; thus study underpowered to show non-inferiority
- Bleeding 2.88% apix; 4.28% in Enox

Abstr #31

Idrabiotaparinux

- Biotinylated form of idraparinux
- Indirect Xa-inh: needs AT3
- Exceedingly long T $\frac{1}{2}$ ~120 hrs; once weekly dosing; SQ
- Reversibility with Avidin binding and then rapid clearance
- Renal elimination

Idrabiotaparinux-EQUINOX

- DVT treatment study with idraparinix comparator; 757 total pts; 6 mos tx
- Less clin rel bleeding 5.2% v 7.3% with biotinylated form
- Rec VTE similar: VTE 2.3% v 3.2%; PE 1.6% v 1.8%)
- 30 min infusion Avidin reduced anti-Xa activity by 77.8% compared to 2.4% with placebo; effect was sustained; no rebound

Abstr #32

Fondaparinux-Renally impaired

- 8 elderly cancer pts with CrCl 10-29 mL/min
- Dose 2.5 mg q 48 hrs SQ prophylaxis dose
- Fondaparinux levels as measured by anti-Xa assay showed appropriate peaks and troughs

Abstr #3033

Treating/Reversing Bleeding from Anticoagulation

Anticoagulants and Antidotes

Drug	Antidote
Warfarin	Vitamin K1; FFP; PCCs
UFH	Protamine 1 mg/ 100units
LWMHs	Protamine (sort of) 1 mg/1mg or 100 anti-Xa units
Pentasaccharides	None; rVIIa tried
Direct Thrombin inhibitors	None
Direct Xa inhibitors	None

ASH 2008 Educ Prog p266

Xa Inhibitor Antidote?

- Recombinant Factor X protein lacking Gla-domain; not active as protease
- Serves as competitive antagonist for Direct Xa inhibitors
- Mouse model of reversal of Xa inhibition; successful after 1 dose
- Worked with either direct Xa inh or LMWH
- No human data; ??antigenicity

Abstr #983

PCCs and their composition

TABLE 1. PCCs for Warfarin Reversal: Coagulation Factor Composition

	FII	FV	FIX	FX	Indication on label
3-Factor PCCs					
Procoagul* ^a	84 U	-	100 U	84 U	
Konyne ^b	150 U	16 U	100 U	150 U	
Factor 10q ^c	Unavailable	-	Unavailable	Unavailable	
Prothrombinex HT ^d	100 U	-	100 U	100 U	X
Beulster ^e	120 U	13 U	100 U	139 U	
Prothrom 3G ^f	148 U	11 U	100 U	68 U	
CoAct ^g	-75 U	-25 U	100 U	-75 U	
4-Factor PCCs					
Recoagul 4P ^h	108 U	68 U	100 U	112 U	
Prothromplex T ⁱ	100 U	85 U	100 U	100 U	X
Proplex T ^j	50 U	400 U	100 U	50 U	
Octaplex ^k	44-132 U	36-96 U	100 U	72-120 U	
PP2B 4T ^l	100 U	100 U	100 U	100 U	
Unknown					
Prothromplex ^m	Unavailable	Unavailable	Unavailable	Unavailable	

Am J Heme 2008; 83: 137

PCC (Beriplex®) reversal of warfarin

- Dose-finding study to reverse INRs >4.5 with PCC
- In vitro study with spiked plasma
 - Measured INRs and thrombin generation
- 30 units/kg one time dose; successful for all INRs >4.5

Abstr #1985

ASH Evidence-based Guideline

- Warfarin reversal with rVIIa
 - Case reports/series with doses all over the map
 - Rapid INR correction but very little outcome data
 - One randomized; placebo-controlled PK study 28 healthy volunteers
 - Dose as small as 5 µg/kg corrected INR for 12 hrs
- Their conclusion: don't do it; inadequate data to support efficacy

ASH 2008 Educ prog p.36-37

Specific Hypercoagulable State Comments

Plenary Session PROTECT

- Randomized, double blind, placebo-controlled prophylaxis study in Ca pts on chemo; ECOG ≤ 2 ; nadroparin 3800 anti Xa Units daily or placebo
- 1150 pt rec'd drug/placebo
- LMWH 2.1% VTE; placebo 3.9% for RRR 47.2%
- Bleeding: LMWH 0.7%; placebo 0% Major
 - LMWH 7.4%; placebo 7.9% minor bleeding
- Highest clot risk: lung and pancreatic cancer

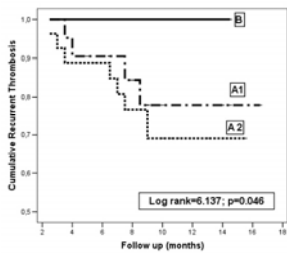
Abstr #6

DACUS Study-Residual Thrombus

- Cancer pts with VTE; Treated with LMWH 1mo full, then reduced 25% for 5 mos and reassessed
- RVT +: randomized to continue (45 pts)
 - or stop LMWH (47 pts)
- RVT -: stop LMWH (42 pts)
- 2 bleeds tx group; 1 each in stopped groups

Abstr #985; See also Blood 2008, 112:511-5

VTE Recurrence-DACUS



- A1 RVT+; continue LMWH
- A2 RVT+; stop LMWH
- B no RVT; stop LMWH

Abstr #985

VTE Prophylaxis in thalidomide-tx Multiple Myeloma

- 539 pts: 40mg Enoxaparin v. 1.25mg warfarin v. 100mg ASA
- 164 pts Controls: non-thalidomide regimens
- Med time onset clots 2-3 mos
- GIMEMA group study

Drug	VTE	Bleeding
Warfarin 1.25mg	3.9%	1.1%
Enoxaparin 40mg	4.5%	0.6%
ASA 100mg	5.5%	3.3%
Control	1.8%	3.7%

Abstr #3017

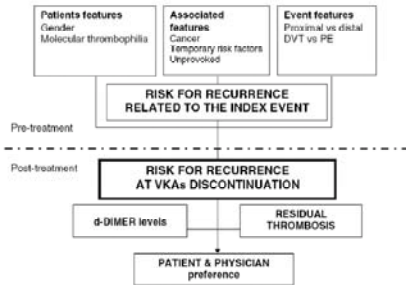
Hydroxychloroquine and APAs

- Basic science study of HCQ effects on protecting the binding of Annexin 5 to phospholipid bilayers from aPL IgG-β2GPI
- Reverses the acceleration of plasma coagulation induced by APAs
- Non-anticoagulant approach to therapy
- Could possibly explain the improvement sometimes seen in HCQ-treated patients

Abstr #404; see also Blood 112(5): 1786, 2008

Duration of Anticoagulation/Predictors of VTE recurrence

Assessing Recurrence Risk



J Throm Thrombol 2008: 37-44; See also Educ Prog ASH 2008 p 252

VTE Recurrence with Reversible Risk Factors

- Duration of anticoagulation dependent upon balancing risks of recurrence with risks of therapy
- What is the risk of recurrence with provoked venous thrombi?
- Evaluation of published literature:
 - 15 studies where rates were reported
- 12 mo recurrence: 4%
- 24 mo recurrence: 6.7%
- Authors conclude: acceptable to stop after 3 mo.

Abstr #3029

Duration of Anticoagulation: Counseling Patients on Bleeding Risk

- Literature review to determine case-fatality rate for DVT/PE
- Published case-fatality rate for bleeding from anticoagulation: 13.4%
- From 30,885 VTE pts: 17,650 DVT; 8801 PE; 4434 DVT or PE
- Could not separate rate by etiology; provoked or unprovoked

Abstr #3032

Case-Fatality Rate for VTE

Initial event	During anticoagulation (% , 95% CI)	After anticoagulation (% , 95% CI)
DVT	10.6 (8.3-13.0)	7.3 (5.0-9.7)
PE	12.3 (5.9-18.7)	12.5 (6.4-28.7)
Any event	10.2 (7.9-12.5)	9.0 (7.3-10.8)

Abstr #3032

There wasn't much on...

- Any new treatments or tests for TTP
- Any new hypercoagulable states
- Validity or value to hypercoagulable state testing (See Blood 2008; 112:4432)
- Any new bleeding disorders or exciting new treatments for bleeding
- No new clotting factor treatment products of any note

Thrombosis Summary 2009

- New anticoagulants may be approved this year or 2010
- Antidotes still a major concern at controlling anticoagulant-related bleeding
- We still don't REALLY know who needs long-term anticoagulation; 3 months may be enough for almost everybody

Questions Anyone?
