

Anticoagulation in Cardiac Diseases Relative Risk and Benefits

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Thrombosis and Thrombolysis: Complex

- Platelet: production, activation, inhibition
- Plaque: formation, rupture
- Coagulation: activation, inhibition
- Thrombolysis
- Platelet Inhibitors
- Anticoagulation
- Non-Infarction related thrombosis

Platelet Production

- **Platelets (Plts):**
 - Formed from Megakaryocytes
 - Thrombopoietin stimulates Megakaryocytes
- **Thrombopoietin(TPO):**
 - Constant low level TPO production
 - TPO binds to platelets ↓ Free TPO
- ↓Plts → ↑TPO → Production Plts ↑
- ↑Plts → ↓TPO → Production Plts ↓

Handin, R. Ch 60 & 117. Harrison's Principles of Internal Medicine. 14th Edition

Normal Platelet Function

- Endothelial Injury: Initiates Plt activation
- Platelet Aggregate on the wall (transient adhere)
- Platelet Adhere to the wall (firm adhere)
- Granules Release:
 - Pro-inflammatory cytokines and chemo-attractants
 - (IL-1B, RANTES) and surface express CD40 ligand (CD40L)
 - Promotes adhesion of leukocytes and extravasations of monocytes

Handin, R. Ch 60 & 117. Harrison's Principles of Internal Medicine. 14th Edition
Haverstick Blood 1985;66:946-952

Thrombocytopenia (Platelet Decrease)

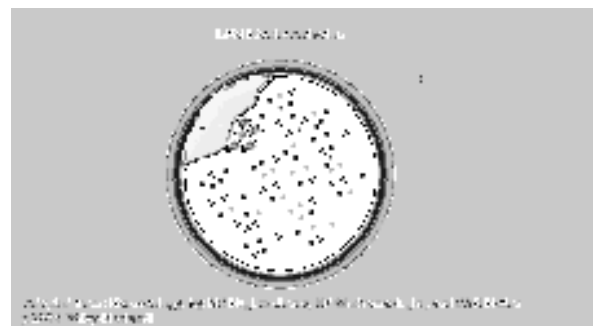
- Decreased Plt Production

Myelosuppression: Doxorubicin	Diuretics: Thiazides
Hormones: Estrogens	OTC Drugs: Ethanol
- Increase Plt Destruction

– Antibiotics: Sulfathiazole	Novobiocin
– Sedatives: Hypnotics	Anticonvulsants
– Digitoxin: Methyldopa	Quinidine,
- ? Increased Plt Destruction

– Aspirin	Chlorothiazide	HCTZ
– Chlorpropamide	Chloroquine	Gold salts
– Insecticides	Sulfadiazide	Food: Beans

Ruptured Plaque: Platelet Activation->Thrombosis



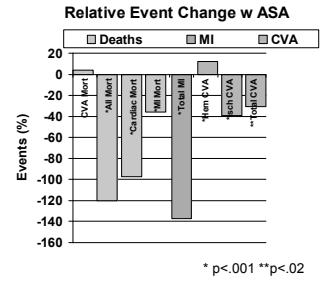
Platelet Inhibitors

- Aspirin: Thromboxane A2 Synth Blocker
- Clopidogrel: ADP receptor blocker:
- ADP-receptor activates: Glycoprotein-IIb/IIIa complex
- Persantine: Not better than ASA alone
- Ticlodipine: ↑ Side effect vs Clopidogrel
- Glycoprotein IIb/IIIa Receptor Blockers

Aspirin

100mg: Thromboxane A2 Synthesis
 ≥100 mg: Endothelial prostacycline Synthesis

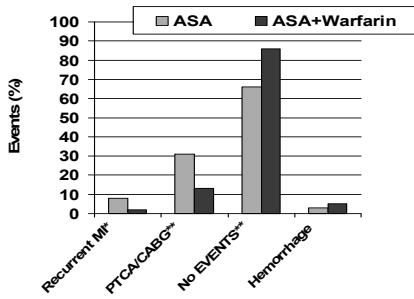
- Meta-analysis 16 Studies
- N = (ASA) 28,570
- (Control) 26,892
- Aspirin Total MI Events Reduced 137/10,000
 CI: 107-167/10,000
- Isch CVA Events Reduced: 39/10,000
 CI: 17-61/10,000
- Hemorrhagic CVA Events Increased: 12/10,000
 CI: 5-20/10,000
- Overall Cardiac Mortality Reduced: 97/10,000
 CI: 59-135



1. Jiang He. JAMA 1998;280:1930 ASA MI+CVA vs Hem CVA
2. Elliott M. Antman. Circ 2008;117:296 2007 Update '04 ACC/AHA ST-Elev MI

ST-Elevation MI:

Fibrinolysis: anistreplase, streptokinase, reteplase, r-TPA
 Heparin 48Hrs + Aspirin ± Warfarin 3 Months



Marc Brouwer. Circ 2002;106:659: Netherlands, <75 Years; anistreplase/streptokinase

Clopidogrel (Plavix)

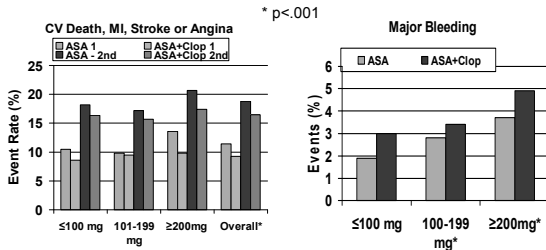
- Direct P2Y₁₂ ADP receptor inhibitor
- Blocks subsequent GP-IIb/IIIa activation
- Prodrug metabolized(CYP50): active form
- Slow onset: 2 hours, effect increased 3-5D

	Clopidogrel +ASA	Placebo +ASA	p-value
Card Dth,MI,CVA	9.3%	11.4%	p<.00009
Above+Ischemia	16.5%	18.8%	p<.00052
CABG or PCI	36%	36%	NS

CURE: ACS(Dec ST seg or Incr Tropl, no MI,

Clopidogrel

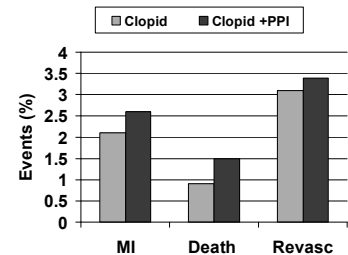
Indication: Acute Coronary Syndrome Dosage: Init: 75/300mg; then 75 mg Daily
 Studied: NonST Elevation Ac Cory Synd w Aspirin (Base Rx) w/wo Clopidogrel
 N: 12,562 1: CVDeath, MI, Stroke; 2nd CVDeath, MI, Stroke or Ref Angina



Ron Peters, Circulation 2003;108:1682-1687, McMaster University, Ont Can – CURE

PPI - clopidogrel interaction

- N = 18,565
- MI/Death RR: 1.22 [0.99-1.51]
- Death RR: 1.20 [0.84-1.70]
- Revasc RR: 0.97 [0.79-1.21]
- Risk of inhibition is clinically unlikely to be more than 20%



2009 Jeremy A. Rassen, Circulation 2009;120:2322-2329

IIb/IIIa Inhibitor: Abciximab (ReoPro®)

- IIb-IIIa receptor Ab inhibitor prevent firm adhesion of platelets to endothelial surface
- Abciximab: Injectable c7E3 Fab
- Plasma T_{1/2}=10 min
- Platelet effect: 48 hrs; high receptor affinity
- Receptor activity decreased 15 days
- 6 mnth: ↓ischemia/revasc (27%vs35.1%*p*<0.01)
- ↑ major bleeds vs heparin (15.4% vs 7%)

1994 Epic Investigators, NEJM330;956

IIb/IIIa Inhib: Eptifibatide (Integrelin®)

- Eptifibatide (Integrelin®) injectable
- Cyclic peptide inhibitor of GP-IIb/IIIa receptor
- T_{1/2} 2.5 Hrs
- Dosage 135 micrograms/kg bolus; 0.75 micrograms/kg/hour
- ↓Emerg Revasc (24 hrs): 5.1% vs 6.8%, *p*<.05)
- ↓Post stent ischemic events

IIb/IIIa Inhib: Tirofiban (Aggrastat®)

- Nonpeptide antagonist of GP- IIb/IIIa receptor mimics fibrinogen
- 335 reduction in refractory ischemia, STΔ's, unstable BP at 24 hours (33% *p*<.007)
- No difference at 30 days vs placebo

New Antiplatelet Agents

- Prasugrel: recently approved for clinical use.
- Cangrelor: Clinical trials stopped, now resumed
- Thromboxane receptor antagonist class of agents are in phase I and II trials (NCX-4016 and S18886).
- Platelet adhesion antagonists: undergoing evaluation for efficacy and risk profile in phase I and II trials.

Prasugrel: Platelet Inhibitor (Effient)

- FDA Approved 7/10//2009
- Class: Thienopyridine platelet inhibitor
- Indicated for patients undergoing PCI
- Inhibits platelet aggregation
 - Active metabolites irreversibly binds P2Y₁₂ ADP receptor permanently inhibiting platelet
 - Clinical effect 7 – 10 days (Plts Replaced)
- Renal/Hepatic Impaired: Limited data
- No dose change for modest impairment

Prasugrel: Risks Significant

- Potential Risks: Bleeding
- CVAs and Cardiac Deaths: like clopidogrel
- Contraindications:
 - Patients ≥ 75 years ↑ICB, benefit uncertain
 - Exception diabetic and prior MI Pts ≥ 75 years
 - Prior TIA or Stroke
 - Pts likely to undergo urgent CABG surgery
 - Body Weight ≤ 60 Kgs: ↑ bleeding risk
 - Concomitant medications with ↑ bleeding risk

Prasugrel: Bleeding Risks

- Suspect Bleeding if patients on prasugrel and
 - Hypotensive
 - Recent angiography, PCI, CABG in setting of prasugrel
- Increased risk of MI if prasugrel stopped early post ACS
- In UA and NSTEMI studies, anatomy known before prasugrel or clopidogrel administered

Prasugrel: Why use it?

- Potential Benefit: Decreased MI

	Prasugrel	Clopidogrel	
Non-fatal MI	7.1%	9.2%	p<0.001
STEMI	6.7%	8.8%	p<0.016
STENT Thrombus	0.9%	1.8%	p<0.001
- Indications: Decrease thrombotic cardiac events
 - UA, NSTEMI to be managed with PCI
 - STEMI to be managed with primary or delayed PCI
- Dosage: Load: 60 mg once; then 10 mg Daily with/without food (5 mg if WT< 60 Kg)
- Aspirin 75 – 325 mg Daily should be used
- Avoid: warfarin, non-ASA NSAIDS

Prasugrel: When to Stop it?

Duration of Rx: Unknown

	Prasugrel	Clopidogrel
No past TIA or ICH		
• Thromb CVA	0.7	0.7
• Intracranial Hem	0.2	0.3
• Past TIA or Thrombotic Strike > 3 months		
• Thromb CVA	4.2	1.2
• IC Hemor	2.3	0.0
• Bleeding risk highest first 7 days, but persists		
• Meds D/C'd	7.2%	6.3%
• Fatal Bld	1.0%	0.1%
• D/C: TIA, CVA, TTP, Surg		
• MI Risk increased if D/C'd		

Ticagrelor

(Encouraging but NOT FDA Approved)

- Direct Acting, Oral Platelet ADP P2Y₁₂ receptor inhibitor
- 12months

	Ticagrelor	Clopidogrel	
• MI, CVA, Death	9.8%	11.7%	p<.001
• MI	5.8%	6.9%	p<.005
• Vasc Death	4.5%	5.9%	p<.001
• Bleeds	11.6%	11.2%	NS
• NonCABG Blds	4.5%	3.8%	p=.03

Wallentin NEJM 2009;361:103-1057

Cangrelor

(Under Development but NOT FDA Approved)

- Non-thienopyridine P2Y₂ ADP receptor blocker
- May have role as an IV rapidly reversible blocker in ACS.

	Cang+	Clopid	Clopid
MI, Dth, Revasc(48Hr)	7.5%	7.2%	NS
Major Bleeding(30D)	3.6	2.9%	p=.06

Harrington NEJM 2009 361. 2318-2329

? Platelet Role in Plaque Formation

- Platelet-endothelial adhesion->activates platelets
- Plt-endothelial collagen Ia/Ila receptor
- Plt GP-Iba promotes transient plt adhesion
- Plt GP-IIb-IIIa promotes firm plt adhesion
- Plt Ia/Ila receptors -> subendo collagen-plt adherence
- von Willebrand factor(vWF) stabilizes platelets against shear forces
- vWF link plt receptor GP Ib-IX to collagen

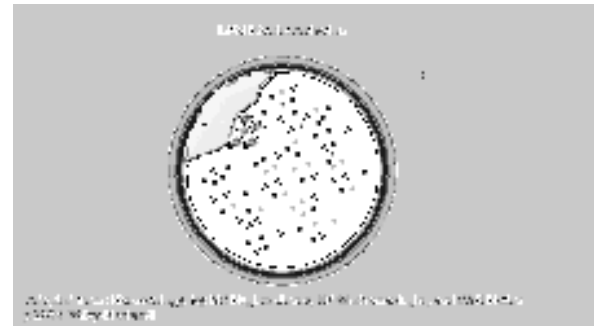
Steffen Massberg et al. J Exp Medicine 2002;196:887 (mice carotid plaques)

Granule Release

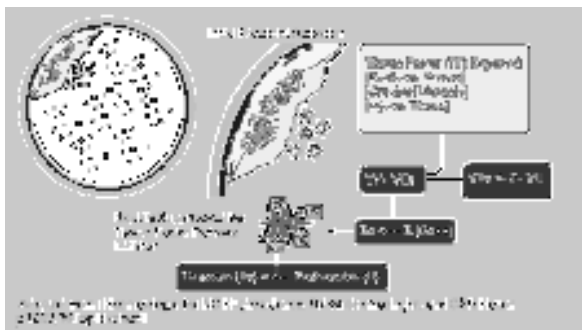
- Pro-inflammatory cytokines and chemo-attractants
- IL-1B and surface express CD40 ligand (CD40L)
- Promotes adhesion of leukocytes and extravasations of monocytes
- Antiplatelet therapy may be beneficial in Atheroma prevention

Steffen Massberg et al. J Exp Medicine 2002;196:887

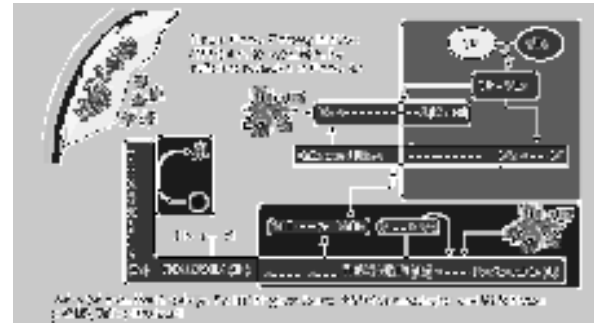
Endothelial and Plaque: Platelet Activation->Inflammation



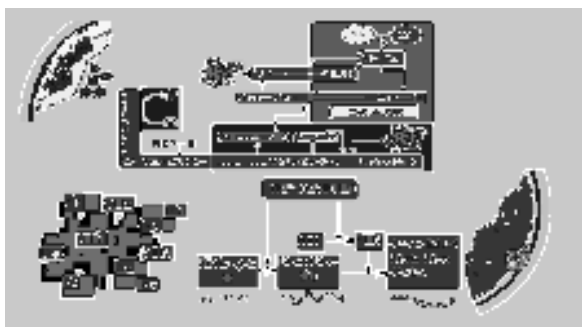
Preliminary Coagulation Pathway



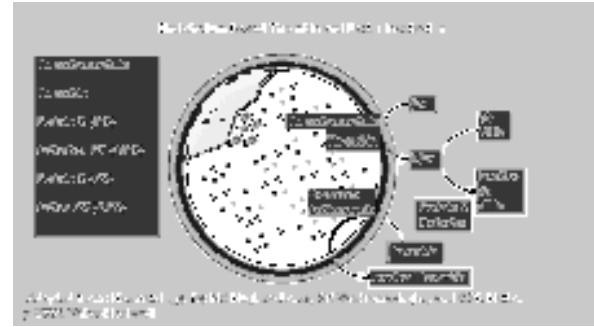
Sustained Coagulation Pathways

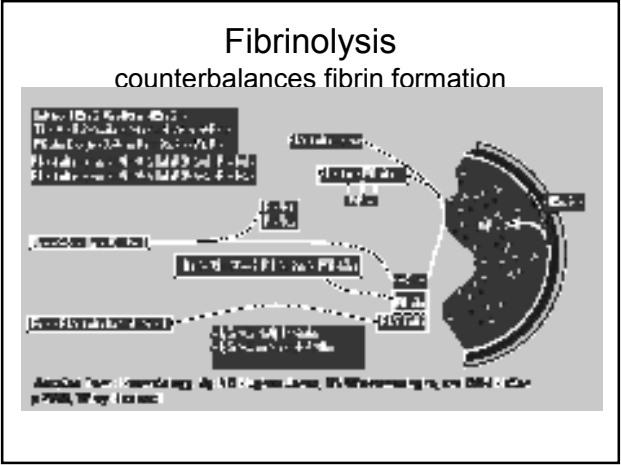


Fibrinogen(I) to Fibrin(Ia) Polymerization Fibrin Cross-Linking with Factor XIIIa

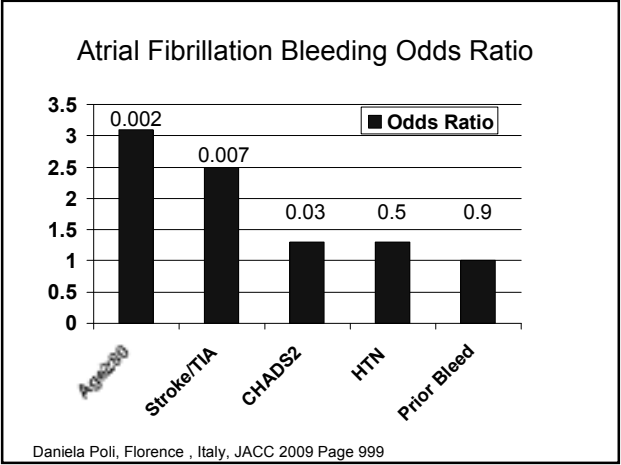
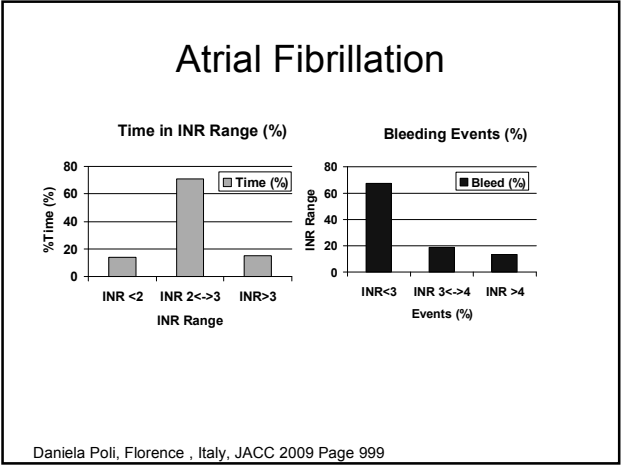
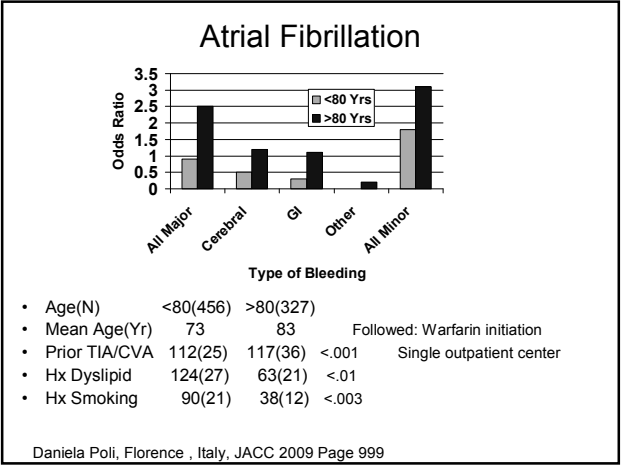


Endothelial Thrombin and Coagulation Inactivation





- ### 2007 AHA/ACC SEMI Recommendations
- Analgesia: Morphine
 - Beta Blockers: <24 Hrs
 - No CHF, Low CO Sn/Sx, or Hrt block
 - If SEMI: Goal total ischemic time <120min
 - PCI <90 min
 - Fibrinolysis <30 min
 - If >24Hrs pMI ASx, then no PCI: Culprit A.
 - Unfractionate Heparin 48 Hrs
 - Clopidogrel 75 mg daily at least 14 days [I rec]
 - Clopidogrel 75 mg possibly 1 year [IIa rec]
- Elliott Anteman Circ 2008;117 296-329



- ### Atrial Fibrillation and Bleeding
- Five times risk as D. Poli
 - 35% had CAD vs 20%
 - ASA use 40% vs 3.5%
 - D. Poli relatively good health in outpatient clinic vs older frail patients
 - CHADS (CHF, Age, Diabetes, Stroke)
- CHECK: EM Hylek, Circulation 2007 115:2689

Atrial Fibrillation

1. Problem: Risk factors for warfarin related bleeding are indications for warfarin use
2. Hx TIA/Stroke is risk for bleeding

1. GY Lip Stroke 2008;39:1406-1408
2. RG Hart Stroke 2005;36:1588-93

Pulmonary Embolism: Bleeding and Thrombosis

- Hypercoagulable Tendencies
 - Immobilized after surgery
 - Chronic CHF
 - Atherosclerotic vascular disease
 - Malignancy
 - Pregnancy

Silve Laporte Circulation 2008; 117:1711-1716
Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) registry

Thrombo-embolism

- RIETE registry: France: Saint Etienne
Spain: Sevilla and Badalona
- N= 15,520 consecutive patients
- Age: 66.3±16.9 yrs; Men: 49.7%
- Sx DVT / No Sx PE: 58.0 % (N=9008)
- Sx DVT / Sx PE: 40.4 % (N=6264)
- Sx Massive PE: 1.6 % (N=248)
- 8.65 % Overall Mortality (3 Months)
- 1.68 % Fatal PE

Silve Laporte Circulation 2008; 117:1711-1716
Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) registry

Therapy

- Heparin: 99.4%
 - Unfractionated
 - Low Molecular Weight:
 - Warfarin (or other vitamin K antagonist)
- IVC Filter: 2.1%
- Fibrinolysis: 1.2%

Silve Laporte Circulation 2008; 117:1711-1716
Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) registry

3 Month Mortality

- Overall: 8.65 %
- Pulm Emb: 1.68 % (19.4% of deaths)
- Sx DVT: 0.55%
- Sx DVT / Sx PE: 2.99%
- Sx Massive PE: 9.27%

Silve Laporte Circulation 2008; 117:1711-1716
Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) registry

Pulmonary Embolism: Mortality Risk

	Odds Ratio	Confidence Interval	p-value
• Any DVT	1		
• Sx DVT	5.66	3.19-9.20	<0.0001
• Massive DVT	17.5	7.45-41.2	
• Neurol Immob	4.90	2.71-8.84	<0.0001
• Age > 75 yrs	2.54	1.58-3.81	<0.0001
• Cancer	2.04	1.29-3.21	0.002
• Cardioresp Dis	1.34	0.84-2.16	0.2
• Recent Surgery	0.54	0.23-1.25	0.15

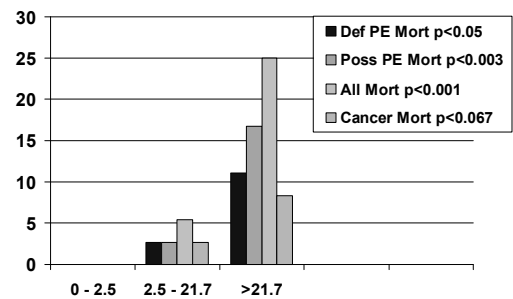
Silve Laporte Circulation 2008; 117:1711-1716
Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) registry

BNP and Pulmonary Embolism

- Inclusion: Objectively confirmed PE
 - Angio, CTA, V/Q, Doppler (L Ext)
- Exclusion:
 - Hemodynamic Instability
 - Renal Insufficiency (↑BNP)
- Follow Up 3 Month Mortality:
 - Due to PE
 - All causes

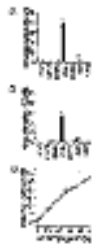
M. Ten Wolde Circulation 2003;107:2082-2084 Erasmus Medical Center, Netherlands

BNP in Pulmonary Embolism may be method to stratify for aggressive Rx



M. Ten Wolde Circulation 2003;107:2082-2084 Erasmus Medical Center, Netherlands

Basic Science: mouse IgG Ab linked to Urokinase
High Affinity for rat lung tissue



Bi-Sen Ding et al, 2003 Circulation;108: Page 2892-2898 Nanjing, China

DVT: Dabigatran vs warfarin (NOT FDA approved in USA)

- Oral Direct Thrombin Inhibitor
- Compared with warfarin in DVT patients
- Dosage 150 mg BID vs warfarin
- Placebo used in each group: double blind
- Prove non-inferiority

Sam Schulman NEJM; 2009;361 2342-2352 DVT

DVT: Dabigatran vs warfarin (NOT FDA approved in USA)

- Trial to prove it is NOT inferior
(ie if significant it is not inferior to warfarin)

	Dabigatran	warfarin	
Recurrent DVT	2.4%	2.1%	p<.001
Major Bleeding	1.6%	1.9%	NS
Any bleeding	16.1%	21.9%	NS
All confidence intervals encompass HR:1.0			

Sam Schulman NEJM; 2009;361 2342-2352 DVT

AF: Dabigatran vs warfarin (NOT FDA approved in USA)

Trial to prove it is NOT inferior in Atrial Fib
(p value for superiority[sup] or not inferior[ninf] to warfarin)

	Dabigatran (110/150mg)	Warfarin (INR2.0-3.0)	
CVA/EMBOL	1.53/1.11%	1.69%	p<.001/.001ninf
Major Bleed	2.71/3.11%	3.36%	p<.003/NS sup
Hem CVA	0.12/0.10%	0.38%	p<.001/.001
Mortality	3.75/3.65%	0.13%	p=0.13/.051
Conclusion: CVA: similar/lower, Bleeds: lower/simil			

Stuart Connolly NEJM; 2009;361 1139-1151 AF

Anticoagulation and Cardiomyopathy

- No long term controlled studies available
- Risk Factors: ↓CO, ↑Stasis, ↓wall motion, AF
- Spodick 1958:
 - Autopsy+CHF: 50% LV Thrombus
- Roberts 1987:
 - Autopsy+myopathy: 37% thromembolus
- Katz 1993:
 - stroke 1.7/100 pt-yrs
- Natterson 1995:
 - transplant candidates: 3% risk of thromboembolism

Anticoagulation and Cardiomyopathy

- Fuster: Cardiomyopathy (p<.05)
 - No warfarin: 3.5 Events/100 patient years
 - Warfarin: 0 Events
- Natterson: Transplant patients (NS)
 - No warfarin 5%
 - Warfarin: 4 %
- V-Heft I (NS) V-Heft II (p<0.01)
 - No warfarin 2.7/100 pt-yrs 2.1/100 pt-yrs
 - Warfarin 2.9/100 pt-yrs 4.9/100 pt-yrs
- If AF, LV Thrombus, prior event: Anticoagulate
- Otherwise: consider aspirin

Pulmonary Hypertension

- Anticoagulation Indicated
- Often associated indications
 - Atrial Fibrillation
 - Prior Pulmonary Emboli
 - DVT
- Warfarin INR 2.0 to 2.5

Aortic Valve Disease

- CLASS I
- B: AVR Bileaf Mech/Medtron Hall 2.0-3.0
- B: Above + RF 2.5-3.5
- B: AVR: Starr-Edwards / disc valves 2.5-3.5
- C: Biologic AVR+RF: 2.0-3.0
- B: AVR Warfarin intolerant: ASA
- B: Mechanical valves add ASA to warfarin
- C: [IIA] AVR(Bio or Mech <3 mnth) 2.5-3.5

Mitral Valve Disease

- C: MVR: Mechanical 2.5-3.5
- C: MVR: Bioprosthesis + RF 2.0-3.0
- C: Biologic MVR: ASA 75-100mg Day
- MVR+Warfarin intolerant: ASA 75-325mg
- C: [IIA] MVR(Bio or Mech <3 mnth) 2.5-3.5

END