Anticoagulants Old and New!

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GENERAL HEMATOLOGY
OHSU

DISCLOSURE

Relevant Financial Relationship(s)

Speaker Bureau - None

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Author – UpToDate (Iron)

Anticoagulants: 1991

- Aspirin
- Warfarin
- Heparin

Anticoagulants: 2025

- Aspirin
- Clopidogrel
- Prasugrel
- Ticagrelor
- Cangrelor
- Aggrenox
- Heparin
- Enoxaparin
- Tinzaparin
- Dalteparin
- Fondaparinux
- Abciximab
- Tirofiban
- Eptifibatide
- Lepirudin
- Argatroban
- Bivalirudin
- Dabigatran
- Rivaroxaban
- Apixaban
- Edoxaban
- Betrixaban
- Vorapaxar
- Osocimab
- Milvexian
- Abelacimab
- Asundexian

Talk

- Antiplatelets
- Heparin
- Warfarin
- DOAC
- The next generation!

Antiplatelet Therapy


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The Sedative for Coughs,

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Its water-soluble salt.

You will have call for them. Order a supply from your Jobber.

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SELLING AGENTS

Aspirin

- Blocks production of thromboxane A_2
- Effects last life of the platelet
  - Drug has only short half-life
- First line agent for any arterial ischemic disease
- Dose
  - Acute > 162.5 mg
  - Chronic 81 mg/day

Aspirin: 2nd Prevention

- In patients with event the use of aspirin is associated with 22% reduction of future events and 15% reduction in death
- Aspirin is recommended for anyone with a history of a vascular event
- Strongest indication for aspirin

Primary Prevention

- Analysis of recent trials
- Reduction CV events: 0.89
  - Absolute: 0.38%
- Increase in Bleeding: 1.43
  - Absolute: 0.47%
- JAMA 2019;321(3):277-287

Now What?

- Risk in primary prevention of aspirin greater than benefit
- Statins and BP control paramount

Aspirin in Afib

- Limited to no effectiveness
  - Only one positive trial
  - Multiple trials inferior to warfarin/DOAC
- Not effective in older patients
- Not effective in preventing disabling strokes
- Not the safer choice
  - Equal bleeding rates to warfarin/apixaban
- Not recommended by guidelines

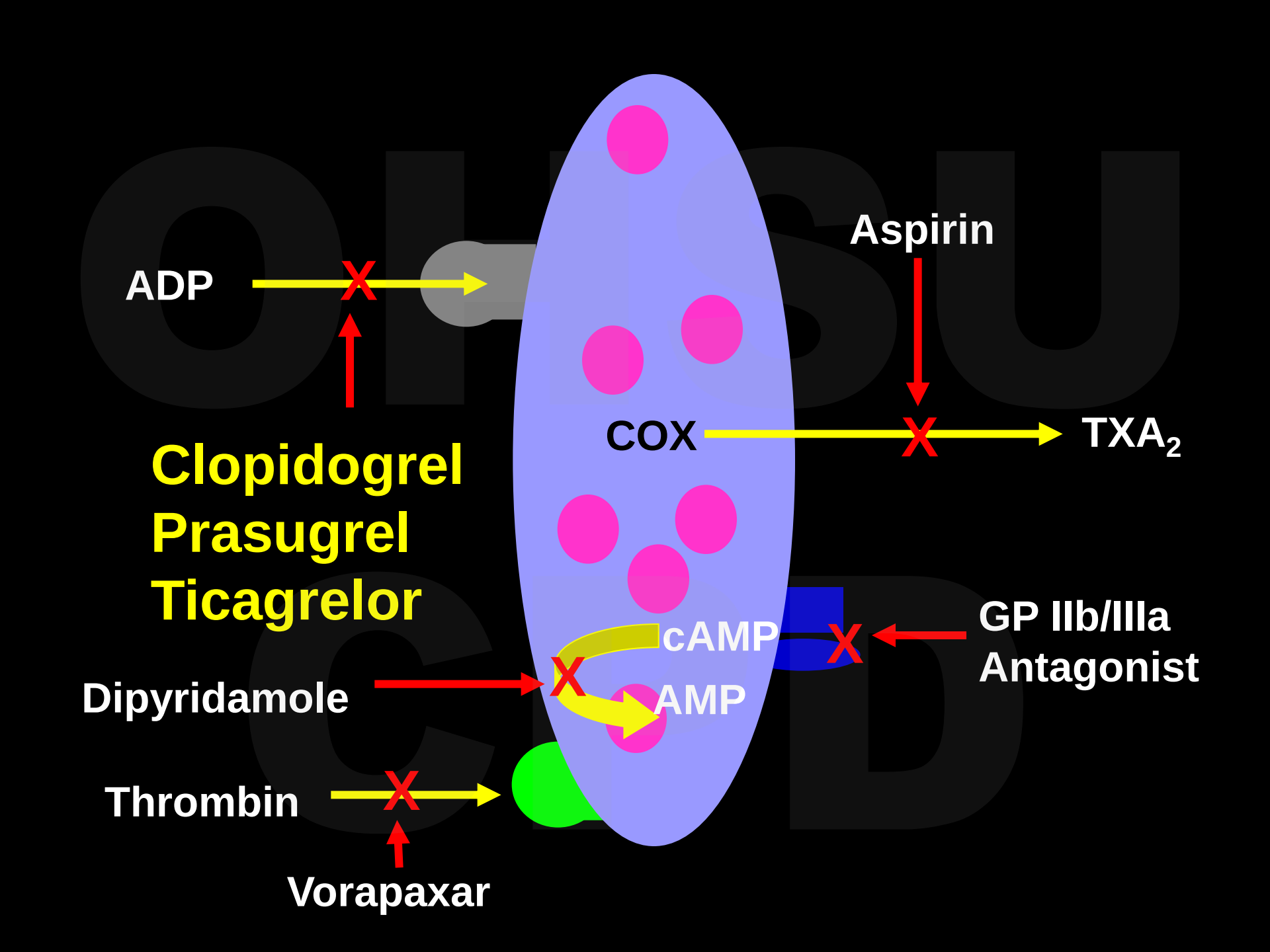

RIP
Aspirin
for
Afib

ASA: Bottom Line

- Secondary Prevention- YES!
- Atrial Fibrillation – NO!
- Primary – No unless
  - Evidence of atherosclerosis

Better Aspirin?

- For > 40 years trying to develop a “better” aspirin
- For most indications aspirin best balance of risk and benefit
- Focus now on dual antiplanet therapy


ADP
Aspirin
COX
TXA_2
Clopidogrel
Prasugrel
Ticagrelor
cAMP
AMP
GP IIb/IIIa
Antagonist
Dipyridamole
Thrombin
Vorapaxar

Stents: Antiplatelet Agents

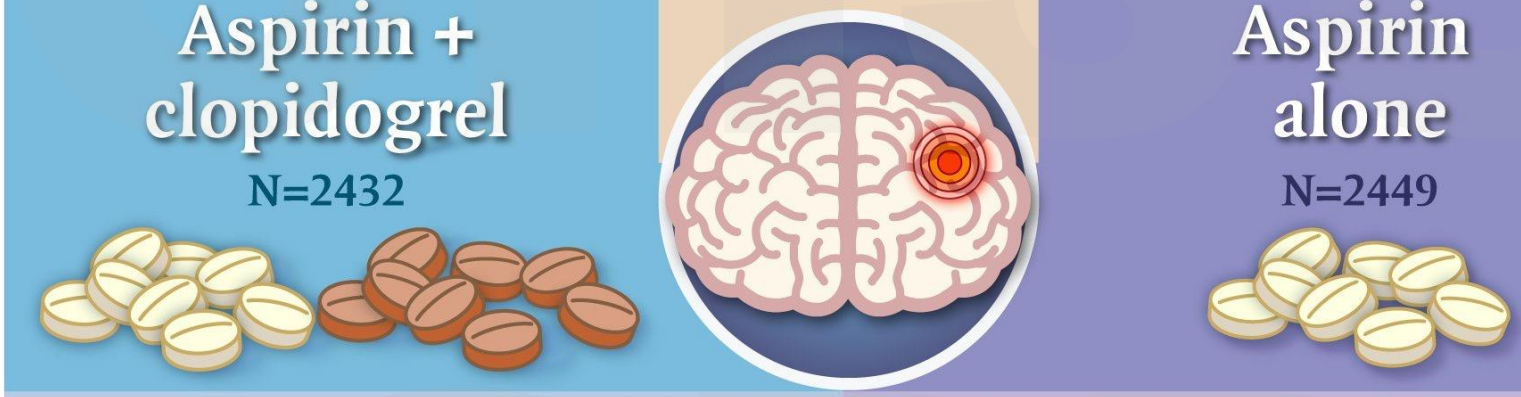
- Bare metal
  - Dual antiplatelet for 4 weeks then ASA
- Drug eluting
  - Long term dual antiplatelet therapy
    - Bleeding risk: 1-3 months
    - Average risk: 6-12 months
    - Ischemic risk: > 12 months

Acute Stroke

- Evidence that short term combination therapy is helpful in acute stroke/TIA

Clopidogrel + Aspirin vs. Aspirin Alone in Acute Ischemic Stroke and TIA

INTERNATIONAL, RANDOMIZED, DOUBLE-BLIND TRIAL



90-Day risk of major ischemic event

Aspirin + clopidogrel		Aspirin alone
5.0%	P=0.02	6.5%
0.9%	Major hemorrhage	0.4%

The NEW ENGLAND JOURNAL of MEDICINE

Johnston et al. 2018

DAPT after Stroke/TIA

- Start within 24 hours
  - Stroke reduced absolute risk reduction 1.9%
  - Increase bleeds 0.2%
  - Most benefit first 10 days and none after 21 days

Dual Antiplatelet Therapy

- Limited indications
  - Coronary stents
  - Acute coronary syndromes
  - Stroke/major TIA

Bottom Line

- Aspirin is Good!
  - Keystone of acute therapy and secondary prevention
- Combination therapy
  - ACS
  - Stents
  - Acute strokes

NSAID and Anticoagulation

- Will raise risk of bleeding
  - Antiplatelet effect
  - GI toxicity
- Options for anticoagulated patients
  - DOAC/PPI plus
  - Celecoxib (does not affect plt function)
  - Meloxicam (does not affect plt function)
  - Other NSAID (accepting risk of bleeding)

Co-administered OACs with NSAIDs and the risk of bleeding

Systematic review & meta-analysis
(PubMed, Embase, Cochrane Library, Web of Science)
Any study with a VKAs/DOACs & NSAIDs arm and a VKAs/DOACs alone arm or with a VKAs & NSAIDs arm and a DOACs & NSAIDs arm

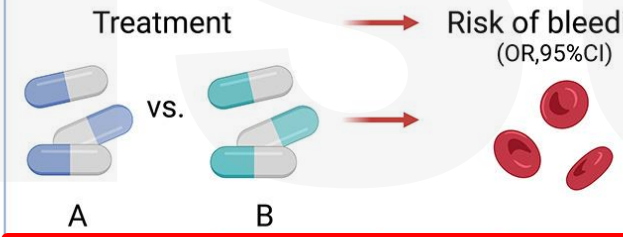
27 studies
(22 observational studies, 5 RCTs)

1,182,540 patients
(mean age: 59.3-83 years)

median follow-up:
0.5-14 years

Primary outcome: the risk of bleeding

Results



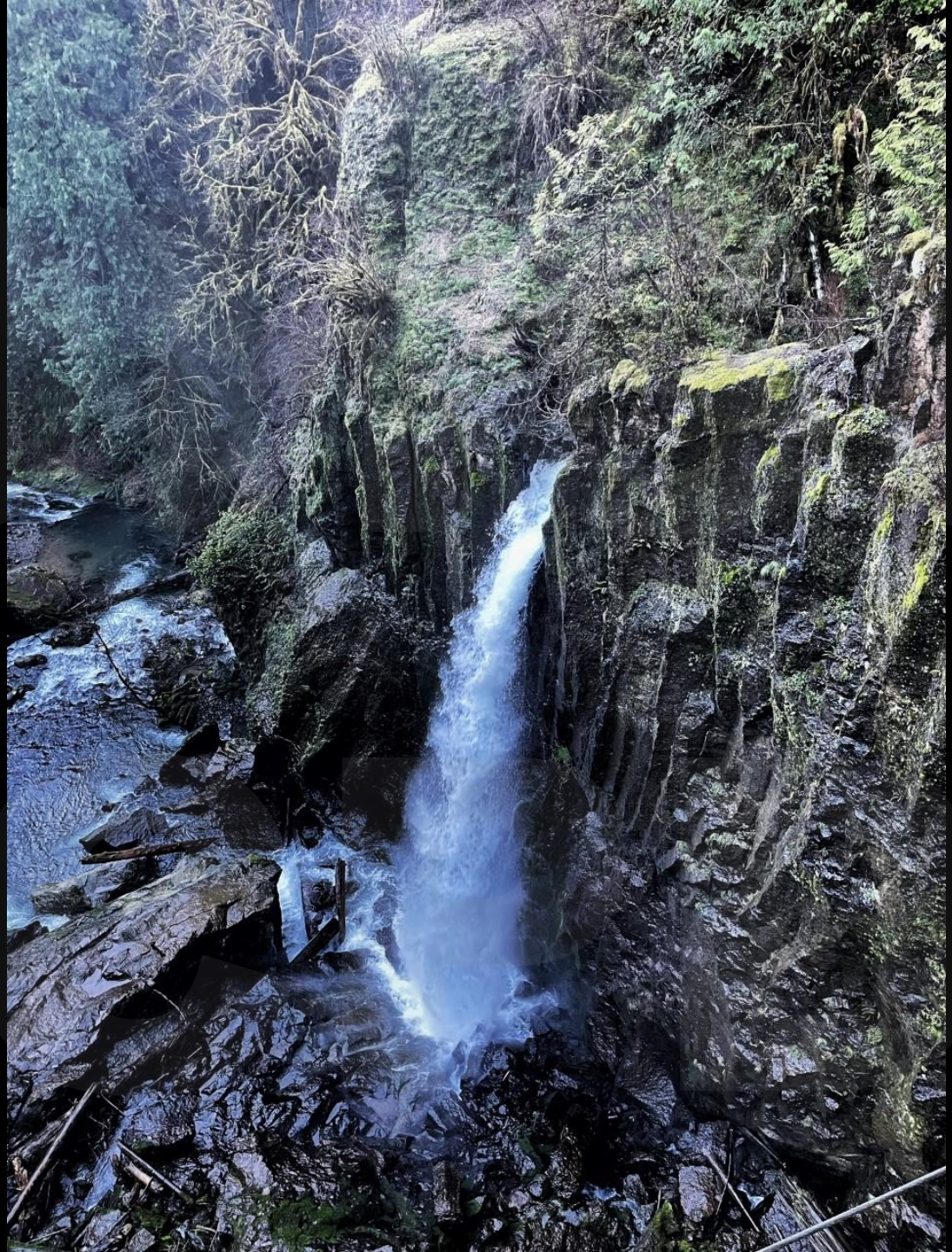
	Any bleeding	GI bleeding	Major bleeding
VKAs & NSAIDs vs. VKAs alone	1.55 [1.21-2.00]	2.66 [1.96-3.62]	1.55 [1.04-2.30]
DOACs & NSAIDs vs. DOACs alone	1.54 [1.33-1.80]	2.18 [1.02-4.69]	1.42 [0.84-2.40]
DOACs & NSAIDs vs. VKAs & NSAIDs	Risk of bleeding: 0.55 [0.34-0.90]		

Conclusions

- Co-administered OACs with NSAIDs significantly increased the risk of any bleeding and GI bleeding.
- Inconsistent results were observed regarding the risk of major bleeding.
- Without considering other confounding factors, DOACs were associated with a lower risk of bleeding compared to VKAs in AF and VTE patients.

DOACs

- DOAC/NSAID combination lower risk of bleeding than warfarin/NSAID
- Risk of adding NSAID worth it if raises patient's quality of life




Standard Heparin

LMWH vs UFH
2017 Cochrane Review

Endpoint	OR
rVTE 1-15	0.69
rVTE 1-90	0.71
Decreased thrombus size	0.71
Major Bleeding	0.69
Death	0.84 (0.7-1.01)

NO reason ever to use UFH in PE patients

Meta-analysis of LMWH inpatient therapy

Recurrent DVT day 1-15

LMWH	SH	
3/365 (0.8)	12/371 (3.2%)	RR 76%

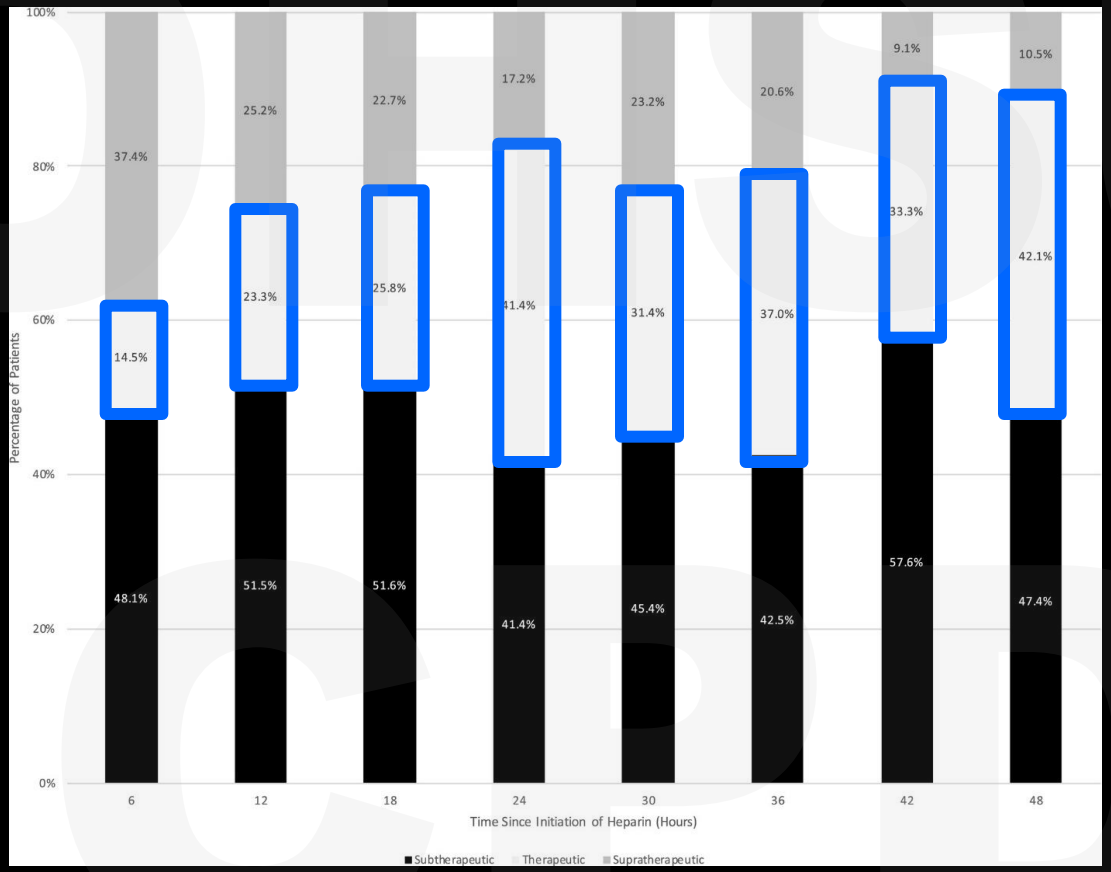
Recurrent DVT day 16 -90

LMWH	SH	
7/365 (1.9%)	12/371 (3.2%)	RR 61%

Bleeding

LMWH	SH	
12/394 (3.0%)	27/402 (6.7%)	RR 58%

Analysis of PTT in Patients With PE First 48 Hours of Anticoagulation With UFH



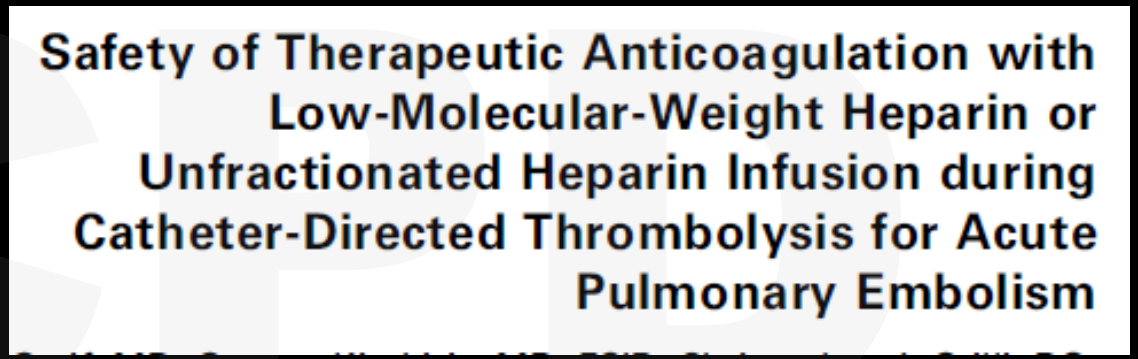
Academic Emergency Medicine, 27: 117-127, 2020

LMWH: Renal Disease

- No increase in bleeding if dose adjusted for renal disease

Procedures

- No issues with IR procedures for PE
- Not that much difference in half-life


Safety of Therapeutic Anticoagulation with Low-Molecular-Weight Heparin or Unfractionated Heparin Infusion during Catheter-Directed Thrombolysis for Acute Pulmonary Embolism

J Vasc Interv Radiol . 2020 Apr;31(4):537-543

PERT Consortium Handbook of PE 2024

	Mortality	Acute recurrent VTE	Late recurrent VTE	Complications
Lensing et al. (1995)	Favors LMWH		Favors LMWH	Favors LMWH
Siragusa et al. (1996)	Favors LMWH	Favors LMWH	Favors LMWH	Favors LMWH
Gould et al. (1999)	Favors LMWH		Nonsignificant	Favors LMWH
Dolovich et al. (2000)	Favors LMWH		Nonsignificant	Nonsignificant
Quinlan et al. (2004)		Nonsignificant	Nonsignificant	Nonsignificant
Castellucci et al. (2014)			Favors LMWH	Nonsignificant
Robertson and Jones (2017)	Nonsignificant	Favors LMWH	Favors LMWH	Favors LMWH

Low molecular weight heparin is preferred due to an increasing body of evidence suggesting lower rates of thromboembolism recurrence and lower rates of hemorrhagic events in patients treated with low molecular weight heparin compared to unfractionated heparin

Heparin

- LMWH was shown in the 90's to be superior to standard heparin
  - Better outcomes
  - Instantly therapeutic
    - > 50% UFH not at goal at 24 hrs
  - No need for the inaccurate PTT
  - Much less HIT
  - Much easier
  - Cheap ~ $20/day
  - Reversible with protamine

Warfarin!

- Still commonly used anticoagulant
- Been around for > 50 years
- Still a tricky drug to use


CAUTION! KEEP OUT OF REACH OF CHILDREN
SEE BACK PANEL FOR ADDITIONAL CAUTIONS
98
Tyler's
cheese
Toss that dirty trap away!
Warfarin
flavored
RAT & MOUSE
KILLER PELLETS
ACTIVE INGREDIENTS: Warfarin [3(a-ac
-4-hydroxycoumarin]
benzyl)
0.025%
INERT INGREDIENTS:
99.975%
NET WEIGHT ONE POUND

Who Must Stay on Warfarin

- Mechanical heart valves
  - DOAC ok for bioprosthetic
- Rheumatic Afib
- Triple positive antiphospholipid
- Extremes of weight

Key of Maintaining an INR of 2-3 Atrial Fibrillation

- Stroke rate increased with INR 1.5-2
- Bleeding NOT reduced
- Even if patients have strokes if there are INR 2-3:
  - Strokes are less severe
  - They are more likely to survive

Starting Dose

- Loading warfarin is not effective!
- Start with predicted daily dose
- Rule of thumb
  - Age under 60 (and albumin >3.5) 10 mg
  - Age 60-75: 5 mg
  - Age > 75: 2.5 mg
- Avoid bridging unless necessary
  - Dramatically increases risk of bleeding

INR Goals

- Target INR of 2.5 with range of 2-3
  - Steady dietary intake of vitamin K
  - Monitor with changes in health or medications
  - Never go longer than one month between INRs
  - Home monitoring

Lack of Dietary Vitamin K

- Even on warfarin patients need some vitamin K to produce coagulation factors
- Lack of vitamin K intake is single leading cause of erratic INRs
- Consistency is important!!!!
- Green salad with meals

Indication for Bridging

Bridge?	Mechanical Valve	Atrial Fibrillation	Venous Thrombosis
YES	Mitral Older valve Non-Bileaflet Aortic Bileaflet Aortic + stroke risk factors	Mechanical or rheumatic valve Recent event	VTE last 3 months Severe thrombophilia Cancer
NO	Bileaflet Valve and NO stroke risk factors	All other atrial fibrillation	VTE > 3 months ago, no other major risk factors

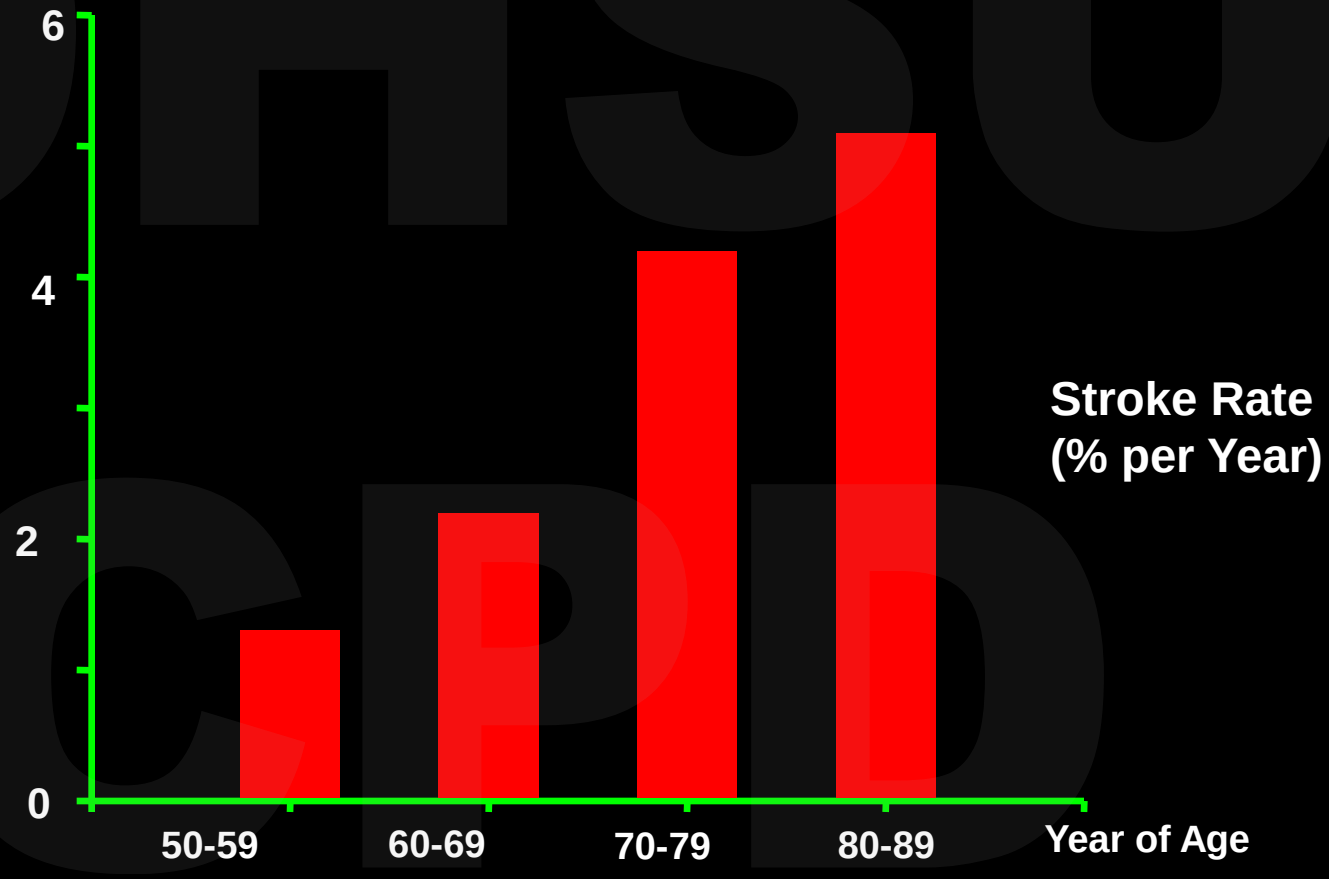
DOACs

- Revolutionized anticoagulation
  - No monitoring!
  - No food interactions!
  - Rare drug interactions!
  - Safer/more effective for many indications!

DOAC: Use

- VTE Prophylaxis
  - Apixaban/rivaroxaban superior
- Atrial Fibrillation
- Venous thromboembolic disease

Atrial Fibrillation and Stroke



Atrial Fibrillation

Drug	Stroke	Bleeding
Apixaban	Better	Safer
Dabigatran	Better	Equal
Edoxaban	Equal	Safer
Rivaroxaban	Equal	Equal

Scared Patients

- Patients fear stroke more than death
- Patients would prefer warfarin if it leads to a > 1% ARR in stroke
  - Baseline risk ~ 2%
- Patients more eager for anticoagulation than most guidelines and doctors!!!

Falls: OK to Anticoagulate!

- Excess bleeding due to falls is markedly overstated
- Patients at risk of falls are those at risk of stroke
- Risk: benefit heavily in favor of treatment esp with DOACs
- Risk of falls is never an excuse to deny patients anticoagulation

Use Right Dose!

- Increasing data that under dosing DOACs lead to more thrombosis/stroke <u>without</u> change in bleeding
- Only dose adjust if indicated!
  - Apixaban 2 of 3
    - Age > 80
    - Creat > 1.5
    - Weight < 60

DOACs

- Doses established by clinic trials
- Biggest errors
  - Rivaroxaban (venous disease)
    - Continuing 15 mg bid too long
    - Going to 15 mg daily instead of 20 mg
  - Apixaban (atrial fibrillation)
    - Wrongly going to 2.5 mg bid
      - Renal disease
      - Older patient

Wrong Dosing

	Stroke/Systemic Embolism HR (95% CI)	Bleeding HR (95% CI)
Off-Label UNDER-dose	↑ 22% 1.22 (1.05-1.42)	No difference 0.95 (0.82-1.11)
Off-Label OVER-dose	↑ 26% 1.26 (1.11-1.43)	↑ 30% 1.30 (1.04-1.62)

J Am Heart Assoc 202215;11(6):e024402

DOAC

- Offer to all new Afib patients
- Who to change over
  - Unstable INR
  - Stroke/bleeding on warfarin
  - Osteoporosis

What is a Labile INR?

- In the previous 6 months
  - INR > 5 twice
  - INR > 8 once
  - INR < 2 twice

Venous Thrombosis

- DOAC are first line therapy for most venous thromboembolism

DOAC in VTE

- Recurrent VTE: 0.90 (0.77-1.06)
- Major bleeding: 0.74 (0.59-0.85)
- ICH: 0.37 (0.21-0.68)
- Fatal bleeding: 0.36 (0.15-0.84)

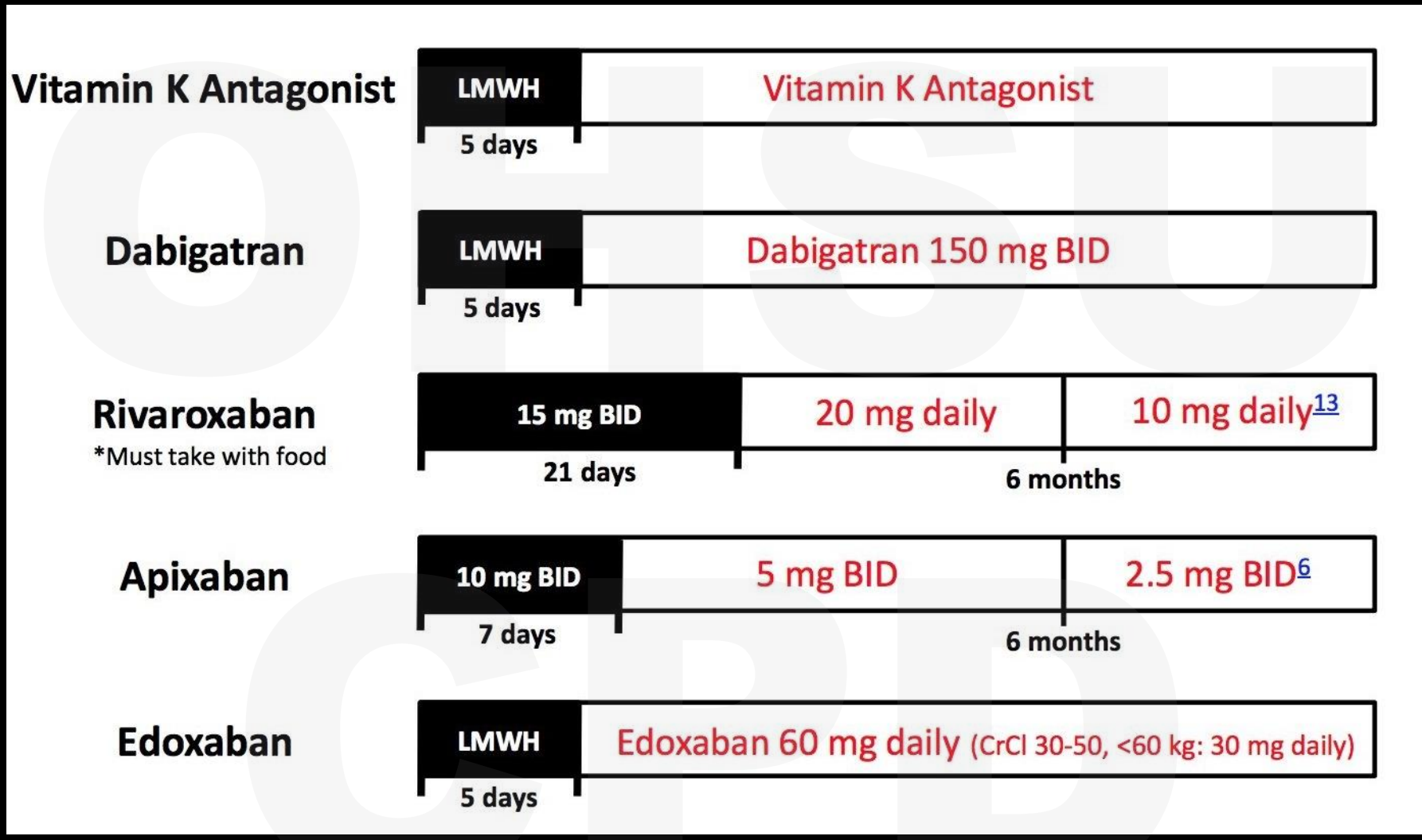
Blood 2014;124(12):1968-1975

Eur J Vasc Endovasc Surg. 2014 Nov;48(5):565-575.

Venous Thrombosis

Drug	Heparin First?	Thrombosis	Bleeding
Apixaban	No*	Equal	Safer
Dabigatran	Yes	Equal	Equal
Edoxaban	Yes	Equal	Safer
Rivaroxaban	No*	Equal	Safer

*Apixaban 10mg bid x 7 days then 5mg BID
*Rivaroxaban 15mg bid x 21 days then 20mg daily


Vitamin K Antagonist
LMWH
5 days
Vitamin K Antagonist
Dabigatran
LMWH
5 days
Dabigatran 150 mg BID
Rivaroxaban
*Must take with food
15 mg BID
21 days
20 mg daily
6 months
10 mg daily[13]
Apixaban
10 mg BID
7 days
5 mg BID
6 months
2.5 mg BID[6]
Edoxaban
LMWH
5 days
Edoxaban 60 mg daily (CrCl 30-50, <60 kg: 30 mg daily)

Lower Dose DOACs?

- Older data for lower doses in chronic therapy of VTE
  - LMWH
  - Ximelagatran
  - Did not work for warfarin

Low Dose DOAC

- Two trials
  - Rivaroxaban 20mg vs 10mg
  - Apixaban 5mg vs 2.5 mg
- Start 6-12 months after VTE
- No difference in VTE or bleeding
  - Trend toward reduce major bleeding

RENOVE Trial

- RCT of patients with thrombosis
- Randomized 6-24 to standard vs low dose anticoagulation
- N = 2768
- Power for bleeding superiority
- Lancet. 2025 Mar 1;405(10480):725-735

RENOVE

	Full Dose N = 1383	Half Dose N = 1385	HR
Recurrent VTE	15 (1.8%)	19 (2.2%)	0.76 (0.4-1.4)
Major Bleeding	38 (4.0%)	15 (2.1%)	0.40 (0.4-1.1)
Clinical Bleeding	107 (12.3%)	84 (10.0%)	0.79 (0.6-1.1)

DOAC in Cancer Patients

- DOAC used in majority of patients
- 4 RCT showing equivalence/superiority with LMWH
  - GI bleeding concern with GI tumors
    - Rivaroxaban/edoxaban
  - Apixaban maybe prefer in patients at risk of GI bleeding
- ASCO Guidelines

API-CAT

- RCT of patients with thrombosis
- Randomized >6 months to standard vs low dose anticoagulation
- N = 1766
- N Engl J Med. 2025

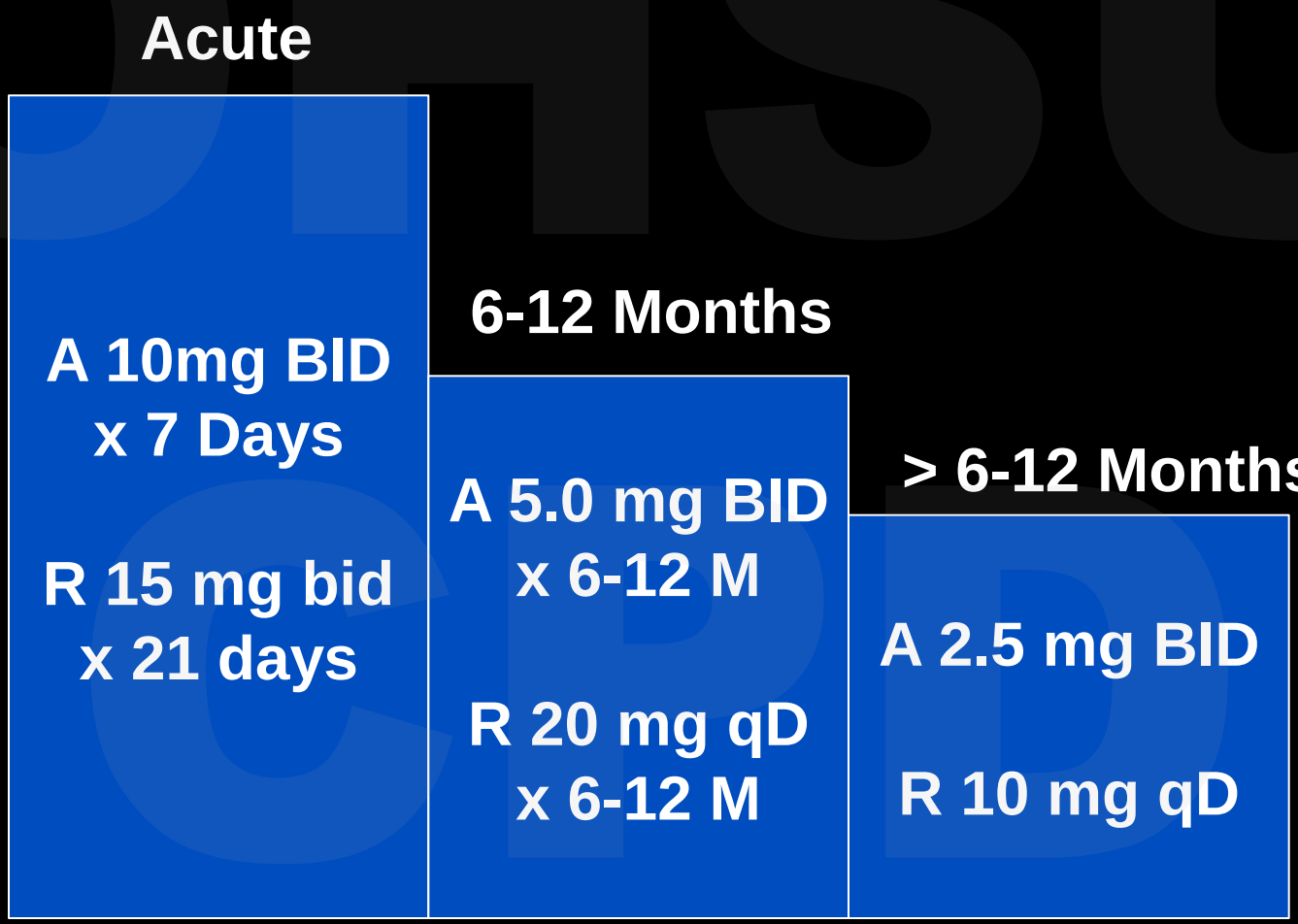
API-CAT

	Full Dose N = 900	Half Dose N = 866	HR
Recurrent VTE	24 (2.8%)	18 (2.1%)	0.76
Major Bleeding	37 (4.3%)	24 (2.9%)	0.66
Clinical Bleeding	154 (15.2%)	96 (9.9%)	0.61 (p <0.5)
Composite	166 (16.5%)	113 (16.7%)	0.67 (p < 0.5)

Lower Dose Therapy

- Only for chronic venous thrombosis!!
- NOT
  - Atrial fibrillation
  - Cancer
  - Bad thrombophilia
  - Visceral vein thrombosis

DOAC VTE Stepped Care



DOACs and Surgery

Drug	Surgery	CrCl	-4	-3	-2	-1	Surgery
Apix	Major				Hold	Hold	Hold
	Minor					Hold	Hold
Dabig	Major	>50			Hold	Hold	Hold
		<50	Hold	Hold	Hold	Hold	Hold
	Minor	>50				Hold	Hold
		<50		Hold	Hold	Hold	Hold
Rivarox	Major				Hold	Hold	Hold
	Minor					Hold	Hold

DOAC

- Issues
  - COST!!!!
  - Drug interactions (rare)
  - Still need to manage anticoagulation


Tell me the truth...I'm...I'm ready
to hear it.


THERE IS A NEW CLASS OF ANTICOAGULANTS

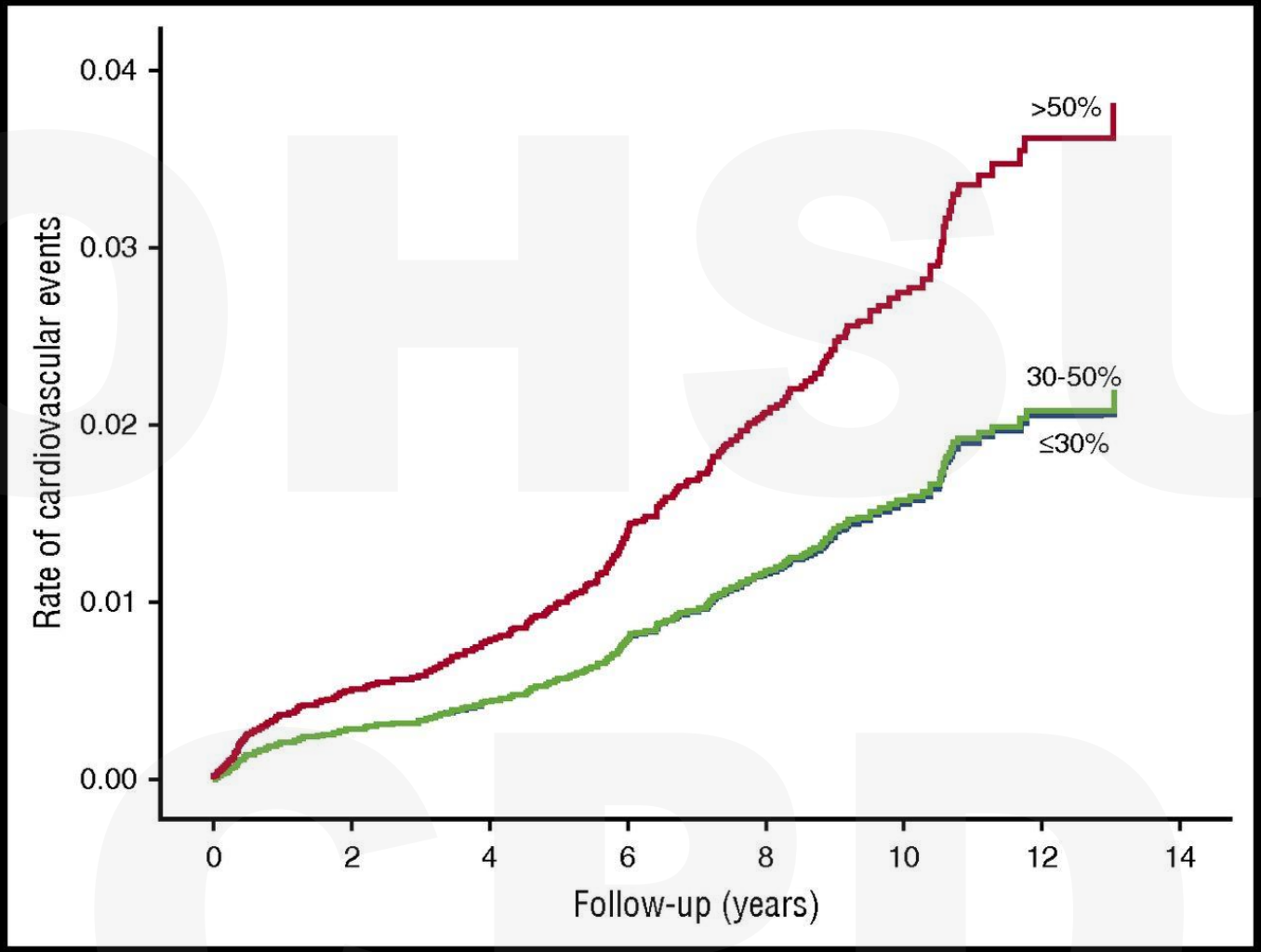

imgflip.com

Contact Pathway

- Part of the coagulation cascade everyone ignores
- Factors 11, 12, prekallikren and HMW Kininogen
- No bleeding with 12, prekallikren and HMW Kininogen deficiency

Factor 11

- Deficient patients often with mild to no bleeding
- Less arterial and venous disease



Factor XI deficiency is associated with lower risk for cardiovascular and venous thromboembolism events

Contact Inhibition

- Contact pathway not need for routine hemostasis
- Blocking pathway in animal models show less thrombosis with no bleeding
- 26 agents in development

Human Trials

- Venous Disease
  - Less thrombosis
  - Less bleeding
- Arterial Disease
  - Less bleeding
  - Thrombosis varible

On Going Trials

- Atrial fibrillation
- Cancer thrombosis
- VTE prophylaxis
- Dialysis
- ECMO

Bottom Line

- Blocking Factor 11
  - Effective
  - Less bleeding
  - Potential for long acting therapy
  - Wide variety of uses
- The next generation!

Talk

- Antiplatelets
- Heparin
- Warfarin
- DOAC
- The next generation!