

# Anticoagulation Cases in the Hospital 2018

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A microscopic image showing numerous red blood cells (erythrocytes) and a dense network of yellow, thread-like fibrin strands. The red blood cells are mostly spherical and have a reddish-pink hue. The fibrin strands are thin, yellow, and form a complex, interwoven mesh that traps the red blood cells. The overall appearance is that of a blood clot or a highly viscous blood sample.

**No  
Disclosures**

# Objectives

- Properly target at-risk patients for DVT prophylaxis.
- When to use NOACs and which one?
- Bridging therapies
- Reversal agents.





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The Surgeon General's Call to Action  
to Prevent Deep Vein Thrombosis  
and Pulmonary Embolism

2008



U.S. Department of Health and Human Services

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A large US study of more than 5000 patients at 183 medical centers found that the majority of hospitalized patients did not receive any prophylaxis for VTE

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U.S. Department of Health and Human Services



# How Common is DVT in hospitalized medical patients?

ACCP 8<sup>th</sup> 2008

*“Almost all hospitalized patients have at least one risk factor for VTE, and approximately 40% have three or more risk factors.*

*Without thromboprophylaxis, the incidence of objectively confirmed, hospital-acquired DVT is approximately 10 to 20% among medical, 15-40% general surgical patient and 40 to 60% following major orthopedic surgery”*

# Preventing Hospital-Acquired Venous Thromboembolism

A Guide for Effective Quality Improvement

AHRQ 2008

Greg Maynard and Jason Stein

Yet, despite the reality that hospitalized medical and surgical patients routinely have multiple risk factors for VTE, making the risk for VTE **nearly universal** among inpatients, large prospective studies continue to demonstrate that these preventive methods are significantly underutilized.

# Joint Commission

## VTE-1

*“This measure assesses the number of patients who received VTE prophylaxis or have documentation why no VTE prophylaxis was given the day of or the day after hospital admission or surgery end date for surgeries that start the day of or the day after hospital admission”*

No stratification tool offered.

# Stratification Tools



- Caprini
- Geneva
- Kucher
- Padua
- VTE Valourr
- Improve
- Intermountain...



# Offer DVT prophylaxis?

- 55 yo female Hx DM, HTN admitted with UE cellulitis, fever, hyperglycemia.
- Continues to smoke.
- Admitted for IV ABX.

# Who do you Prophylax?

- A. All, if no contraindication  
(therapeutic AC, coagulopathy, bleed, thrombocytopenia).
- B. Bedbound.
- C. Stratification tool.

# Who do you Prophylax?

BJH Medical Floor DVT prophylaxis 2015. 372 patients.

	Pharm prophylaxis	Pharm and /or mechanical prophylaxis
Low risk (n=272)	67%	85%
High risk (n=100)	61%	85%

# Caprini

# Deep Vein Thrombosis (DVT)

## Prophylaxis Orders

(For use in Elective General Surgery Patients)

### Thrombosis Risk Factor Assessment (Choose all that apply)

BIRTHDATE \_\_\_\_\_

NAME \_\_\_\_\_

CPI No. \_\_\_\_\_

SEX M F VISIT No. \_\_\_\_\_

#### Each Risk Factor Represents 1 Point

<input type="checkbox"/> Age 41-60 years	<input type="checkbox"/> Acute myocardial infarction
<input type="checkbox"/> Swollen legs (current)	<input type="checkbox"/> Congestive heart failure (<1 month)
<input type="checkbox"/> Varicose veins	<input type="checkbox"/> Medical patient currently at bed rest
<input type="checkbox"/> Obesity (BMI >25)	<input type="checkbox"/> History of inflammatory bowel disease
<input type="checkbox"/> Minor surgery planned	<input type="checkbox"/> History of prior major surgery (<1 month)
<input type="checkbox"/> Sepsis (<1 month)	<input type="checkbox"/> Abnormal pulmonary function (COPD)
<input type="checkbox"/> Serious Lung disease including pneumonia (<1 month)	
<input type="checkbox"/> Oral contraceptives or hormone replacement therapy	
<input type="checkbox"/> Pregnancy or postpartum (<1 month)	
<input type="checkbox"/> History of unexplained stillborn infant, recurrent spontaneous abortion (≥ 3), premature birth with toxemia or growth-restricted infant	
<input type="checkbox"/> Other risk factors _____	

Subtotal: \_\_\_\_\_

#### Each Risk Factor Represents 5 Points

<input type="checkbox"/> Stroke (<1 month)	<input type="checkbox"/> Multiple trauma (<1 month)
<input type="checkbox"/> Elective major lower extremity arthroplasty	
<input type="checkbox"/> Hip, pelvis or leg fracture (<1 month)	
<input type="checkbox"/> Acute spinal cord injury (paralysis) (<1 month)	

Subtotal: \_\_\_\_\_

#### Each Risk Factor Represents 2 Points

<input type="checkbox"/> Age 61-74 years	<input type="checkbox"/> Central venous access
<input type="checkbox"/> Arthroscopic surgery	<input type="checkbox"/> Major surgery (>45 minutes)
<input type="checkbox"/> Malignancy (present or previous)	
<input type="checkbox"/> Laparoscopic surgery (>45 minutes)	
<input type="checkbox"/> Patient confined to bed (>72 hours)	
<input type="checkbox"/> Immobilizing plaster cast (<1 month)	

Subtotal: \_\_\_\_\_

#### Each Risk Factor Represents 3 Points

<input type="checkbox"/> Age 75 years or older	<input type="checkbox"/> Family History of thrombosis*
<input type="checkbox"/> History of DVT/PE	<input type="checkbox"/> Positive Prothrombin 20210A
<input type="checkbox"/> Positive Factor V Leiden	<input type="checkbox"/> Positive Lupus anticoagulant
<input type="checkbox"/> Elevated serum homocysteine	
<input type="checkbox"/> Heparin-induced thrombocytopenia (HIT) (Do not use heparin or any low molecular weight heparin)	
<input type="checkbox"/> Elevated anticardiolipin antibodies	
<input type="checkbox"/> Other congenital or acquired thrombophilia	
if yes: Type _____	
* most frequently missed risk factor	

Subtotal: \_\_\_\_\_

**TOTAL RISK FACTOR SCORE:** \_\_\_\_\_

#### FACTORS ASSOCIATED WITH INCREASED BLEEDING

Patient may not be a candidate for anticoagulant therapy & SCDs should be considered.

Active Bleed, Ingestion of Oral Anticoagulants, Administration of glycoprotein IIb/IIIa inhibitors, History of heparin induced thrombocytopenia

#### CLINICAL CONSIDERATIONS FOR THE USE OF SEQUENTIAL COMPRESSION DEVICES (SCD)

Patient may not be a candidate for SCDs & alternative prophylactic measures should be considered.

Patients with Severe Peripheral Arterial Disease, CHF, Acute Superficial DVT

Total Risk Factor Score	Risk Level	Incidence of DVT	Prophylaxis Regimen
0-1	Low Risk	2%	<input type="checkbox"/> Early ambulation
2	Moderate Risk	10-20%	Choose the following medication <u>OR</u> compression devices: <input type="checkbox"/> Sequential Compression Device (SCD) <input type="checkbox"/> Heparin 5000 units SQ BID
3-4	Higher Risk	20-40%	Choose <u>ONE</u> of the following medications + / - compression devices: <input type="checkbox"/> Sequential Compression Device (SCD) <input type="checkbox"/> Heparin 5000 units SQ TID <input type="checkbox"/> Enoxaparin/Lovenox: <input type="checkbox"/> 40mg SQ daily (WT < 150kg, CrCl > 30mL/min) <input type="checkbox"/> 30mg SQ daily (WT < 150kg, CrCl = 10-29mL/min) <input type="checkbox"/> 30mg SQ BID (WT > 150kg, CrCl > 30mL/min) (Please refer to Dosing Guidelines on the back of this form)
5 or more	Highest Risk	40-80%	Choose <u>ONE</u> of the following medications <u>PLUS</u> compression devices: <input type="checkbox"/> Sequential Compression Device (SCD) <input type="checkbox"/> Heparin 5000 units SQ TID (Preferred with Epidurals) <input type="checkbox"/> Enoxaparin/Lovenox (Preferred): <input type="checkbox"/> 40mg SQ daily (WT < 150kg, CrCl > 30mL/min) <input type="checkbox"/> 30mg SQ daily (WT < 150kg, CrCl = 10-29mL/min) <input type="checkbox"/> 30mg SQ BID (WT > 150kg, CrCl > 30mL/min) (Please refer to Dosing Guidelines on the back of this form)

☐ Ambulatory Surgery - No orders for venous thromboembolic prophylaxis required

☐ VTE Prophylaxis Contraindicated, Reason: \_\_\_\_\_

Joseph A. Caprini, MD, MS, FACS, RVT  
VTE Risk Factor Assessment Tool

Physician Signature \_\_\_\_\_

Dr. # \_\_\_\_\_

Date \_\_\_\_\_

Time \_\_\_\_\_

Processed By: \_\_\_\_\_

Date/Time: \_\_\_\_\_

White-Medical Record  
Yellow-MIS Pink-Pharmacy

University of Michigan  
Health System

DVT Prophylaxis Regimen



# Kucher

- Prev VTE (3)
- Thrombophilia (3)
- Cancer (3)
- Surgery (<1 mo) ( 2)
- Age >70 (1)
- BMI>30 (1)
- Immobile (1)
- Hormone Rx, OCP (1)

- Computer alert program
- Single center
- Medical and surgical
- Expert consensus
- Lack of validation
- High Cancer rate (80%)

# Padua

- Prev VTE (3)
- Thrombophilia (3)
- Cancer (3)
- Immobile (3)
- Surgery or trauma (<1 mo) (2)
- >70 (1)
- BMI>30 (1)
- CHF (1)
- MI or CVA (<1 mo) (1)
- Hormone Rx (1)
- Sepsis pneumonia RA other acute infection (1)

- Modeled after Kucher
- Single Center
- Low number VTE
- All VTE in patients with Cancer and/or age >70.
- 40% at risk

J Thromb Haemost. 2010;8:2450-2457.



# IMPROVE

- Prev VTE (3)
- Thrombophilia (3)
- Cancer (1)
- >60 (1)

- Multinational registry.
- Good Validation.
- Associative model (ICU days, immobility).

# Intermountain

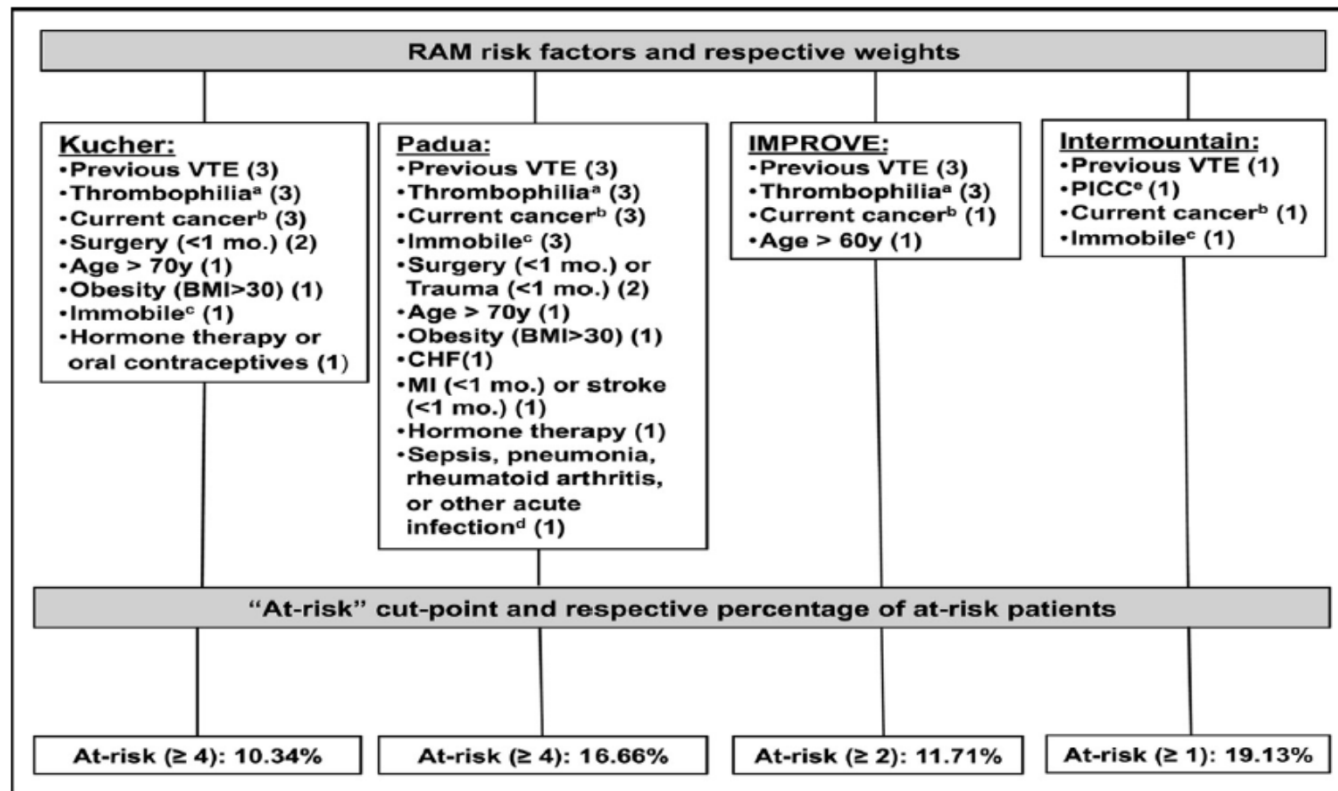
- Prev VTE (1)
- PICC (1)
- Cancer (1)
- Immobile (1)

- Included UE DVT
- 45% Cancer
- Out performed Kucher in validation.
- Use of ICD-9 for DVT may misdiagnose (eg phlebitis).
- 40% at risk.



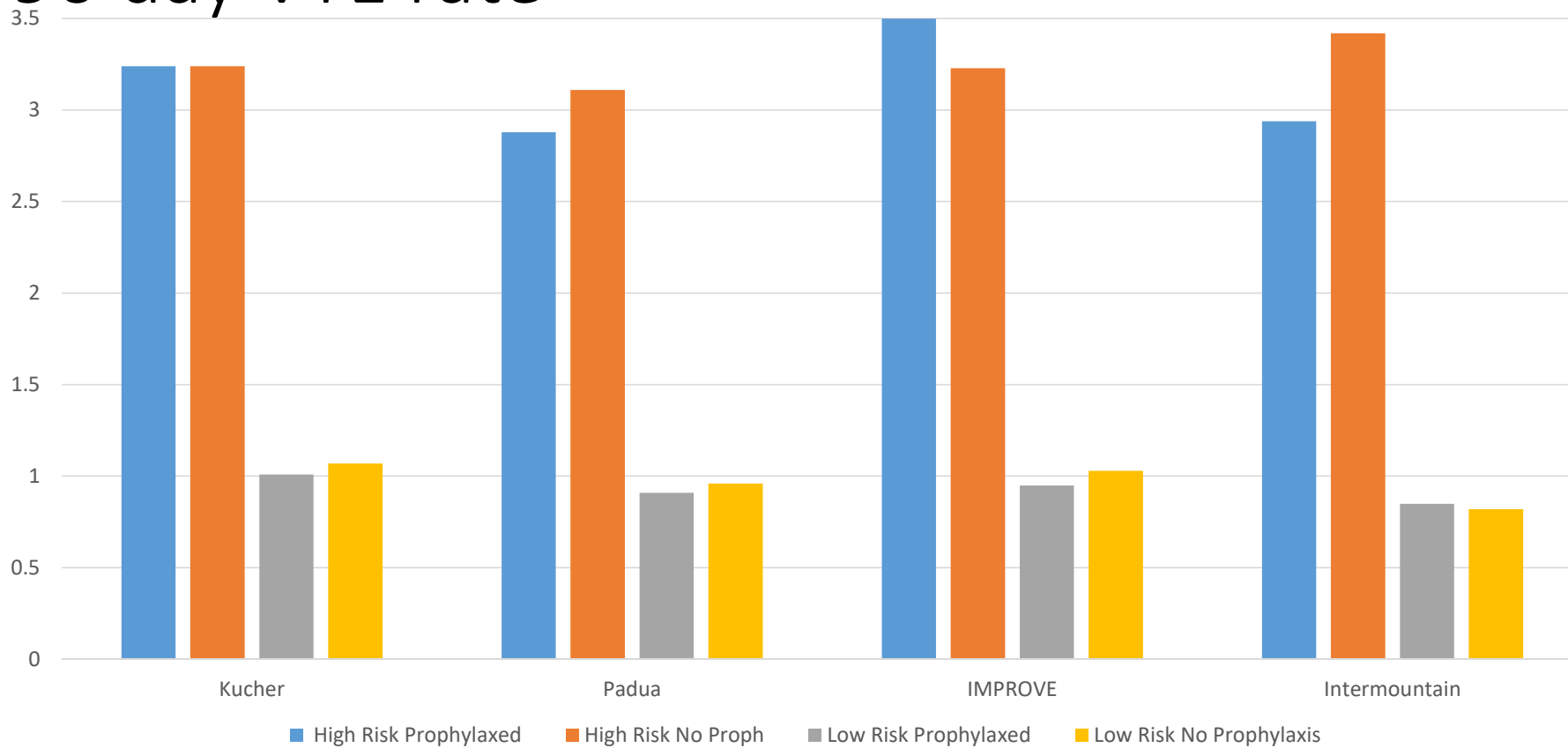
# Looking for Validation

Michigan HMS Consortium-- 63K patients



The American Journal of Medicine (2016) 129, 1001.e9-1001.e18

# 90 day VTE rate



The American Journal of Medicine (2016) 129, 1001.e9-1001.e18

How Common is DVT in hospitalized medical patients? Not.

- Older studies used venograms to detect Asymptomatic DVTs.
- Asymptomatic DVTs 10-30 times more common than symptomatic.
- Exaggerates the success of prophylaxis.

# How well does DVT prophylaxis work?

Meta-analysis Dentali et al.

- Any PE- ARR=0.29%, NNT=345.
- Fatal PE- ARR=0.25%, NNT=400
- Symptomatic DVT- non-signif. reduction.
- Major bleed- non-signif. increase.
- Mortality- No effect.

Ann Intern Med. 2007;146:278-288.

# VTE prophylaxis

- Low rates of VTE in medical patients (~1%)
- Much lower fraction of patients at risk than previously assumed.
- Benefit of pharmacologic prophylaxis is low.
- Bleeds and HIT are real concerns of un-needed prophylaxis.

# I'd ambulate TID for a Camel!



Rothberg JHM 2011

TABLE 1. Patient Characteristics and Their Association With Venous Thromboembolism (VTE)

Variable	Total		No VTE		VTE		P-Value
	N	%	N	%	N	%	
Total	242,738	100	241,686	100.0	1,052	100.0	
Demographics							
Age							0.20
18-49	31,065	12.8	30,952	12.8	113	10.7	
50-64	51,309	21.1	51,083	21.1	226	21.5	
65-74	51,230	21.1	50,993	21.1	237	22.5	
75+	109,134	45.0	108,658	45.0	476	45.2	
Female	142,910	58.9	142,330	58.9	580	55.1	0.01
Race/ethnicity							0.49
White	155,866	64.2	155,189	64.2	677	64.4	
Black	41,556	17.1	41,374	17.1	182	17.3	
Hispanic	9,809	4.0	9,776	4.0	33	3.1	
Other	35,507	14.6	35,347	14.6	160	15.2	
Marital status							0.28
Married/life partner	88,035	36.3	87,627	36.3	408	38.8	
Single	39,254	16.2	39,103	16.2	151	14.4	
Separated/divorced	23,492	9.7	23,394	9.7	98	9.3	
Widowed	58,669	24.2	58,426	24.2	243	23.1	
Other	33,288	13.7	33,136	13.7	152	14.4	
Admission characteristics							
Primary diagnosis							<0.001
Community-acquired pneumonia	81,171	33.4	80,792	33.4	379	36.0	
Septicemia	7,643	3.2	7,568	3.1	75	7.1	
Chronic obstructive pulmonary disease	35,116	14.5	35,027	14.5	89	8.5	
Respiratory failure	7,098	2.9	7,012	2.9	86	8.2	
Congestive heart failure	46,503	19.2	46,336	19.2	167	15.9	
Cardiovascular disease	33,044	13.6	32,931	13.6	113	10.7	
Urinary tract infection	32,163	13.3	32,020	13.2	143	13.6	
Insurance payer							0.93
Medicare traditional	157,609	64.9	156,927	64.9	682	64.8	
Medicare managed care	10,649	4.4	10,597	4.4	52	4.9	
Medicaid	17,796	7.3	17,720	7.3	76	7.2	
Private	44,858	18.5	44,665	18.5	193	18.3	
Self-pay/uninsured/other	11,826	4.9	11,777	4.9	49	4.7	
Admitted from skilled nursing facility	3,003	1.2	2,980	1.2	23	2.2	0.005
Risk factors							
Any VTE prophylaxis	72,558	29.9	72,164	29.9	394	37.5	<0.001
Length of stay ≥6 days	99,463	41.0	98,680	40.8	783	74.4	<0.001
Paralysis	16,764	6.9	16,689	6.9	75	7.1	0.77
Metastatic cancer	5,013	2.1	4,928	2.0	85	8.1	<0.001
Solid tumor without metastasis	25,127	10.4	24,995	10.3	132	12.5	0.02
Lymphoma	3,026	1.2	2,995	1.2	31	2.9	<0.001
Cancer chemotherapy/radiation	1,254	0.5	1,231	0.5	23	2.2	<0.001
Prior venous thromboembolism	2,945	1.2	2,926	1.2	19	1.8	0.08
Estrogens	4,819	2.0	4,807	2.0	12	1.1	0.05
Estrogen modulators	2,102	0.9	2,091	0.9	11	1.0	0.53
Inflammatory bowel disease	814	0.3	803	0.3	11	1.0	<0.001
Nephrotic syndrome	520	0.2	517	0.2	3	0.3	0.62
Myeloproliferative disorder	1,983	0.8	1,973	0.8	10	1.0	0.63
Obesity	16,938	7.0	16,856	7.0	82	7.8	0.30
Smoking	35,386	14.6	35,284	14.6	102	9.7	<0.001
Central venous catheter	14,754	6.1	14,525	6.0	229	21.8	<0.001
Inherited or acquired thrombophilia	114	0.1	108	0.0	6	0.6	<0.001
Steroids	82,606	34.0	82,185	34.0	421	40.0	<0.001
Mechanical ventilation	13,347	5.5	13,167	5.4	180	17.1	<0.001
Urinary catheter	39,080	16.1	38,816	16.1	264	25.1	<0.001
Decubitus ulcer	6,829	2.8	6,776	2.8	53	5.0	<0.001
Statins use	57,282	23.6	57,068	23.6	214	20.3	0.01

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Smoking							
No VTE- 14.6% VTE- 9.7%							
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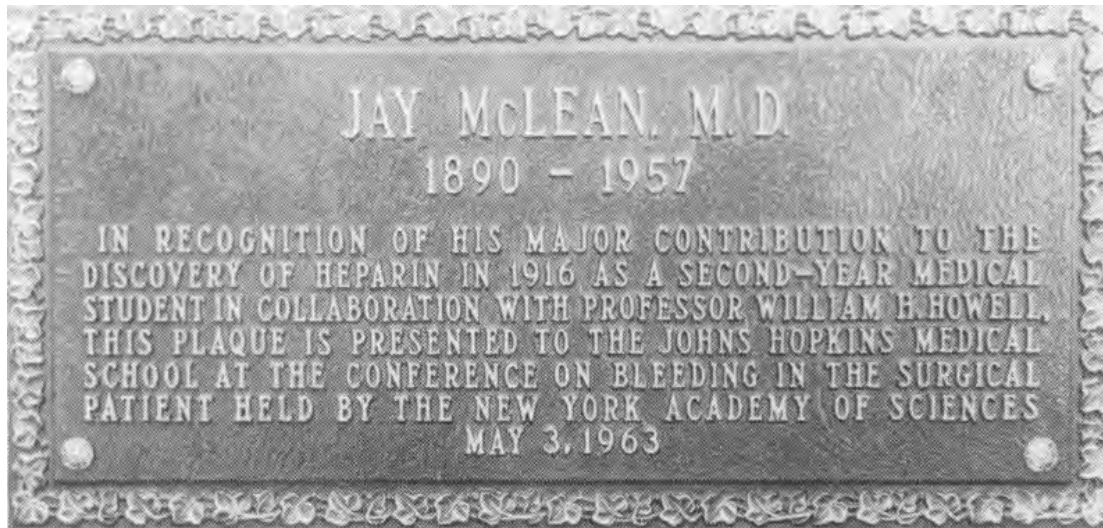
And now, a bit of history





- 1916- Jay McLean, Johns Hopkins medical student credited with discovery of fat-soluble heparin, named for source (liver “hepar”).
- He had been assigned to assess purity of pro-coagulant ‘cephalin’ (brain).
- His boss, William Henry Howell, actually isolated water soluble heparin 1918.
- McLean spent rest of his life fighting for credit.

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# Making heparin is a dirty job

[http://blogs.wsj.com/health/2008/02/21/making-heparin-is-a-dirty-job/?mod=sphere\\_ts&mod=sphere\\_wd](http://blogs.wsj.com/health/2008/02/21/making-heparin-is-a-dirty-job/?mod=sphere_ts&mod=sphere_wd)



Gordon Fairclough

Farmer Ed Carlson drove 200m in blizzard to Madison in a truck with a dead cow in the back, and milk bucket full of non-clotting blood.



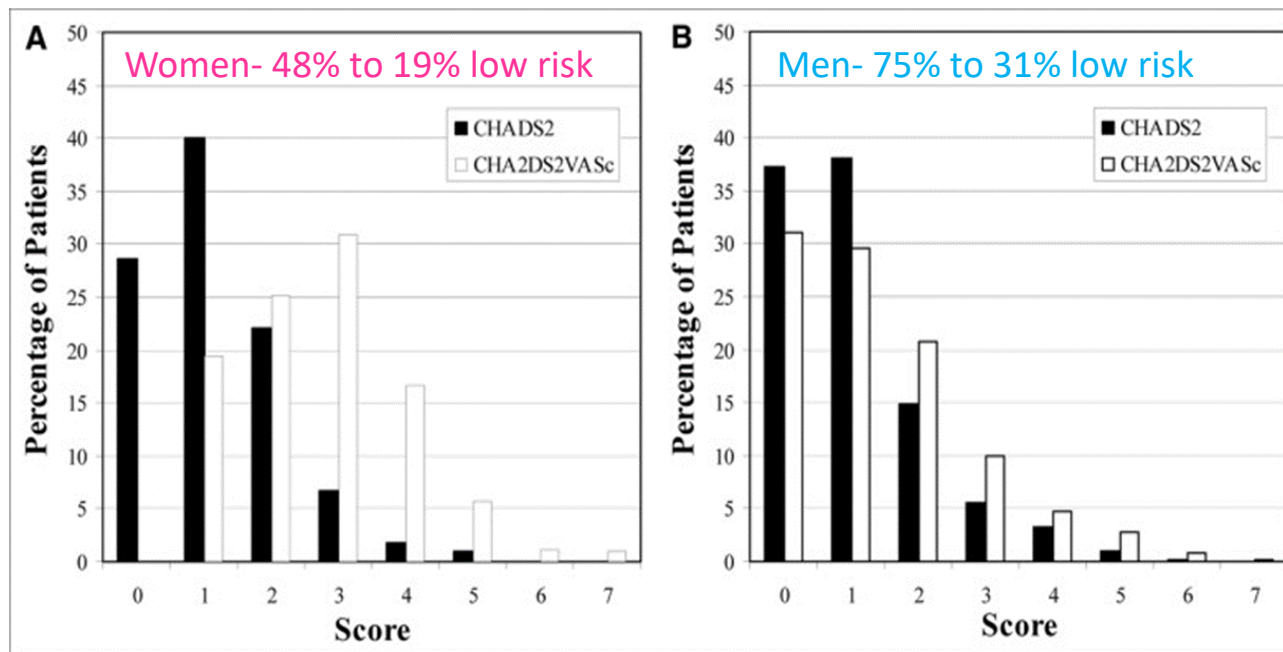
# Warfarin is Underused

- Difficult to maintain therapeutic levels.
- Requires monitoring.
- Numerous food and drug interactions.
- Long half-life, slow onset of action.
- *It's rat poison!*

# Warfarin is Underused

- Underuse (55% ideal candidates with Afib)
- Poor target range when used.
  - Anticoagulation Clinic TTR= .63
  - Community-based TTR= .51
  - Overall TTR= .55
- J Manag Care Pharm 2009 15 244

CHA<sub>2</sub>DS<sub>2</sub>-VASc leads to much higher anticoagulation rates.



Am J Med. 2012.125; 603.

# (Not so) Novel Oral Anticoagulants

- NOAC      Novel
- TSOAC    Target Specific
- DOAC      Direct



# (Not so) Novel Oral Anticoagulants

- NOAC      Novel
- TSOAC      Target Specific
- DOAC      Direct
  
- NOAC      Non VitK antagonist Oral Anti Coag

## NOAC No-No's (Stick with Warfarin)

- Valvular Afib (MS usually 2/2 Rheumatic Fever)
- Prosthetic Valve
- Non-compliance?
- TTR >65%
- SAMe-TT2R2 score = 0-1

## SAMe-TT<sub>2</sub>R<sub>2</sub> Predicts TTR

- Sex (female) 1 pt.
- Age (<60) 1 pt.
- Medical Hx (>2: HTN DM CAD CHF CVA pulm renal liver) 1 pt.
- Treatment (drugs- eg amio) 1 pt.
- Tobacco (within 2 yr) 2 pt.
- Race (non-white) 2 pt.

>2 predicts poor control.

# NOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
<b>Half-life (h)</b>	12-17	5-9	8-15	9-11
<b>Time to peak activity (h)</b>	1-3	2.5-4	3-4	1-2
<b>Interactions</b>	P-gp	P-gp, CYP3A4	P-gp, CYP3A4	P-gp ? CYP3A4
<b>Protein bound</b>	35%	95%	87%	
<b>Renal excretion</b>	>80%	33%	27%	35%
<b>Monitor</b>	TT PTT (qual) ECT	PT (qual) Xa	Xa	Xa

Superior

Trend

NonInferior

Inferior

TRIAL	CVA-SE	Major Bleed	ICH	GI Bleed	Mortality
RE-LY (RR v Warf)					
Dabig 150 BID	.65	.93	.4	1.5	.88
Dabig 110 BID	.9	.8	.31	1.1	.91
ROCKET-AF (HR v Warf)					
Rivaroxaban 20 qD	.88	1.04	.67	1.45	.92
ARISTOTLE (HR v Warf)					
Apixaban 5 BID	.79	.69	.42	.89	.89
AVERROES (HR v ASA)					
Apixaban	.45	1.13	.85	.86	.79
ENGAGE-AF TIMI-48 (HR v Warf)					
Edoxaban 60 qD	.79	.8	.47	1.23	.9
Edoxaban 30 qD	1.07	.47	.3	.67	.87

Superior

Trend

NonInferior

Inferior

TRIAL	CVA-SE	Major Bleed	ICH	GI Bleed	Mortality
RE-LY (RR v Warf)					
Dabig 150 BID	.65	.93	.4	1.5	.88
Dabig 110 BID	.9	.8	.31	1.1	.91
ROCKET-AF (HR v Warf)					
Rivaroxaban 20 qD	.88	1.04	.67	1.45	.92
ARISTOTLE (HR v Warf)					
Apixaban 5 BID	.79	.69	.42	.89	.89
AVERROES (HR v ASA)					
Apixaban	.45	1.13	.85	.86	.79
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Edoxaban 30 qD	1.07	.47	.3	.67	.87



# NOAC Afib Trials

Superior   Trend   Non-Inferior   Inferior

TRIAL	CVA-SE	Major Bleed	ICH	GI Bleed	Mortality
RE-LY (RR v Warf)					
Dabig 150 BID	.65	.93	.4	1.5	.88
Dabig 110 BID	.9	.8	.31	1.1	.91
ROCKET-AF (HR v Warf)					
Rivaroxaban 20 qD	.88	1.04	.67	1.45	.92
ARISTOTLE (HR v Warf)					
Apixaban 5 BID	.79	.69	.42	.89	.89
AVERROES (HR v ASA)					
Apixaban	.45	1.13	.85	.86	.79
ENGAGE-AF TIMI-48 (HR v Warf)					
Edoxaban 60 qD	.79	.8	.47	1.23	.9
Edoxaban 30 qD	1.07	.47	.3	.67	.87

# NOAC VTE Trials

TRIAL	VTE	Major Bleed
RE-COVER I and II		
Dabig 150 BID	HR=1.09	HR=.73
Einstein DVT and PE		
Rivaroxaban 15 BID 21d, then 20 qD	HR=.89	HR=.54
AMPLIFY		
Axipaxaban 10 BID 7d, then 5 qD	RR= .84	RR= .31
HOKUSAI-VTE		
Edoxaban 60 mg (30mg if CrCl,50 or <60 kg)	HR=.89	HR=.81


65 yo black female with DM, HTN new DVT admitted overnight by ED. Very interested in going home, and avoiding shots and INR monitoring.




Warfarin




Dabiga  
tran



Rivaroxaban



Apixaban



Edoxaban

# ACCP Update 2016

- In patients with proximal DVT or PE and no cancer, treatment for three months with dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (VKA) therapy is recommended (all Grade 2B).

65 yo black female with DM, HTN new DVT admitted overnight by ED. Very interested in going home, and avoiding shots and INR monitoring.




Warfarin




Dabiga  
tran



Rivaroxaban



Apixaban



Edoxaban

65 yo black female with DM, HTN new DVT admitted overnight by ED. Very interested in going home, and avoiding shots and INR monitoring.



- No bridge?

65 yo black female with DM, HTN new DVT  
admitted overnight by ED. Very interested in going  
home, and avoiding shots and INR monitoring.




65 yo black female with DM, HTN new PE  
admitted overnight by ED. Very interested in going  
home, and avoiding shots and INR monitoring.




Warfarin




Dabiga  
tran



Rivaroxaban



Apixaban



Edoxaban



# Frequent Asymptomatic Pulmonary Embolism in Patients With Deep Venous Thrombosis

Kenneth M. Moser, MD; Peter F. Fedullo, MD; Judith K. LitteJohn, MD; Rebekah Crawford, MT(ASCP)

(*JAMA*. 1994;271:223-225)

43% of all consecutive patients with DVT and no symptoms suggestive of PE had high probability VQ scans.

# Risk Stratification of PE- PESI

TABLE 2. INDEPENDENT PREDICTORS OF 30-DAY MORTALITY IN THE DERIVATION SAMPLE AND POINTS ASSIGNED TO THE RISK SCORE

Predictors	$\beta$ -Coefficients (95% CI)	Points Assigned
Demographic characteristics		
Age, per yr	0.03 (0.02–0.03)	Age, in yr
Male sex	0.17 (0.02–0.32)	+10
Comorbid illnesses		
Cancer	0.87 (0.71–1.03)	+30
Heart failure	0.31 (0.14–0.49)	+10
Chronic lung disease	0.30 (0.12–0.47)	+10
Clinical findings		
Pulse $\geq$ 110/min	0.60 (0.44–0.76)	+20
Systolic blood pressure < 100 mm Hg	0.86 (0.67–1.04)	+30
Respiratory rate $\geq$ 30/min	0.41 (0.23–0.58)	+20
Temperature < 36°C	0.42 (0.25–0.59)	+20
Altered mental status*	1.50 (1.30–1.69)	+60
Arterial oxygen saturation < 90%†	0.58 (0.37–0.79)	+20

*Definition of abbreviation:* CI = confidence interval.

A total point score for a given patient is obtained by summing the patient's age in years and the points for each applicable characteristic. Points assignments correspond with the following risk classes:  $\leq$  65 class I, very low risk; 66–85 class II, low risk; 86–105 class III, intermediate risk; 106–125 class IV, high risk; > 125 class V, very high risk.

\* Defined as disorientation, lethargy, stupor, or coma.

† With and without the administration of supplemental oxygen.

# OTPE Trial

- 344 patients diagnosed with acute PE in ED.
- Excluded if: sat <90% or paO<sub>2</sub><60, SBP<100, required IV opioids, high risk bleed, Cr cl <30, >150 kg, Hx HIT, 'barriers to Rx'.
- Class I and II PESI included.
- 30% met eligibility.
- Randomized to outpatient (DC within 24h) or inpatient treatment with enoxaparin and warfarin (open label).

# OTPE Trial

14 day outcome	Outpatient	Inpatient	p value for non inferiority
Recurrent VTE	0	0	.003
Major Bleed	1.2%	0	.031
Overall Mortality	0	0	.003

Lancet 2011;378:41-48

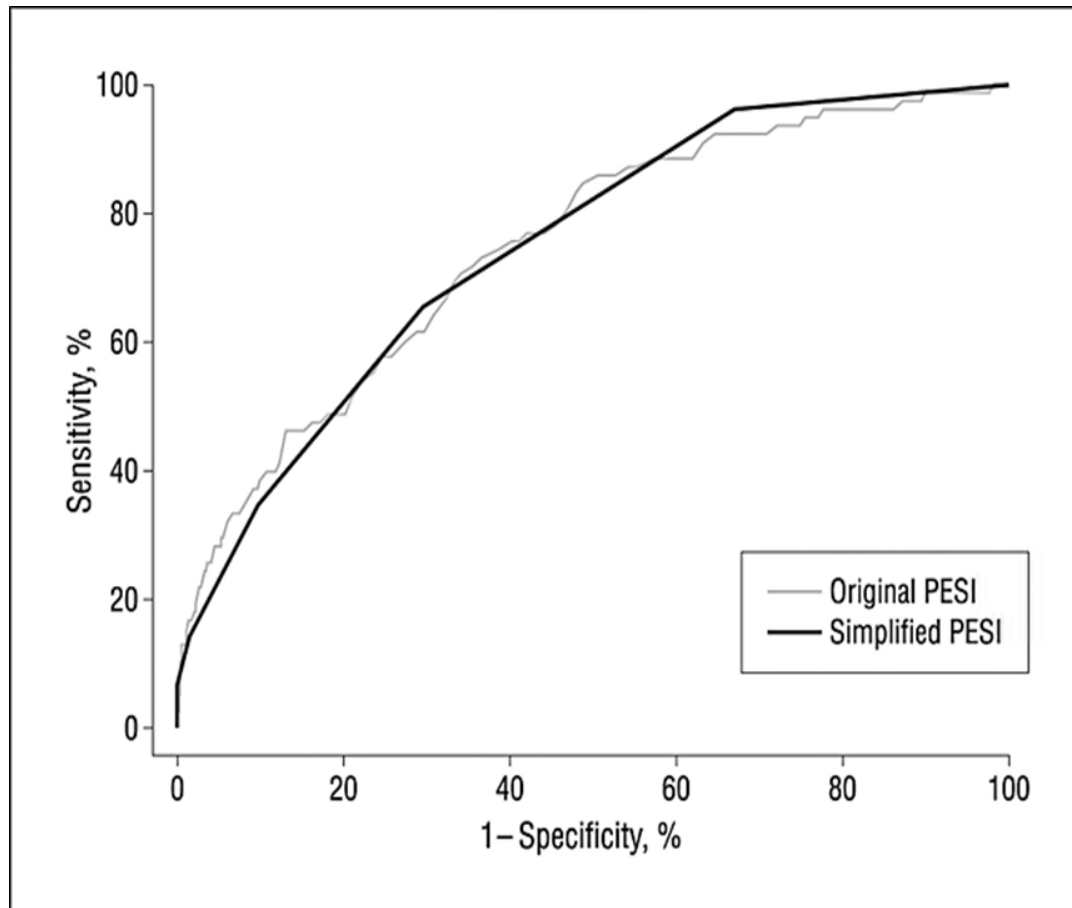
# Observed in Ontario

**Kovacs J Thromb Hemost.  
2010;8:2406-2411.**

- Retrospective consecutive patients with PE. 314 (49%) treated as OPs.
- Eligible if: hemodyn stable, no O2 needs, No IV opioids, Not high risk for bleed.
- No SAE in first 7 days.
- 3 month outcomes same for IP and OP.

**Erkens. J Thromb Hemost.  
2010;8:2412-2417.**

- Retrospective consecutive patients with PE. 260 (55%) treated as OPs.
- Eligible if: SBP > 100, No O2 needs, No contraindication to LMWH (high risk bleed or renal failure).
- One death in first 14 days (readmitted to hospice).
- Low 14d and 90d PE related SAE without difference.



## *Simplified PESI*

Cancer

Age >80

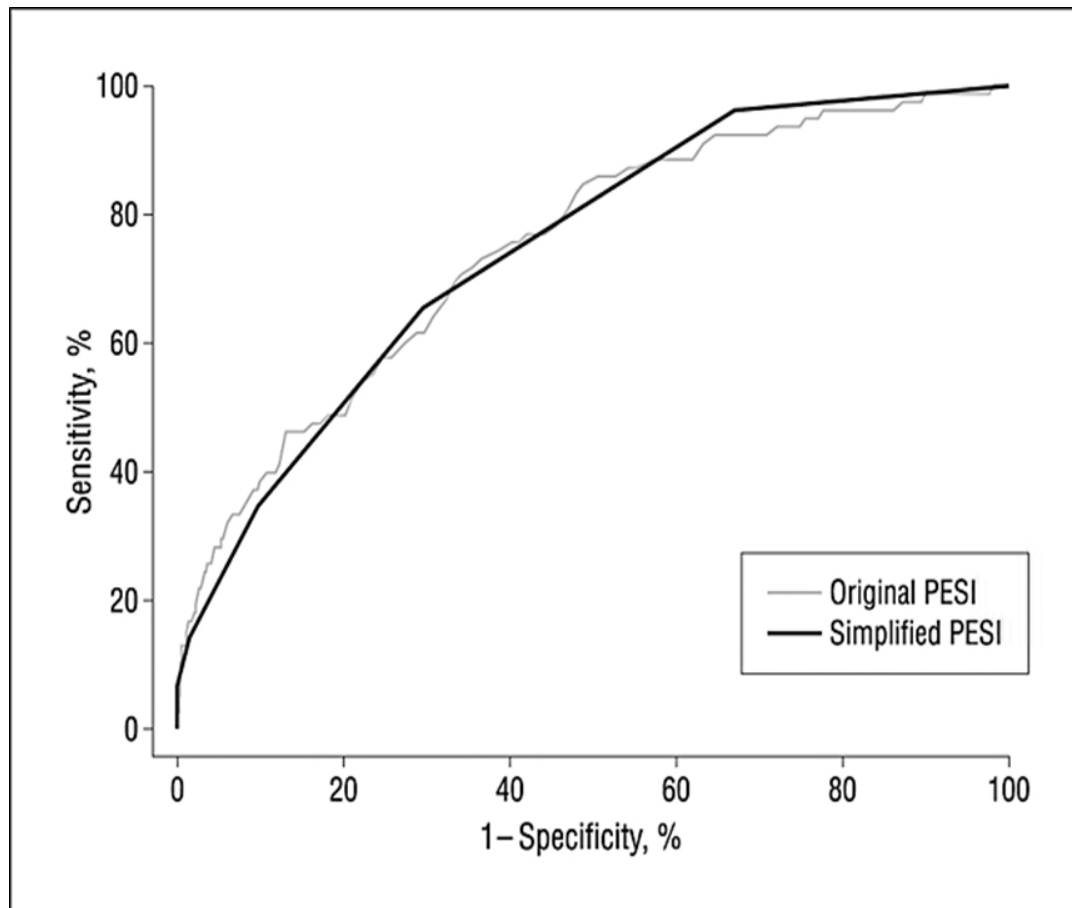
Tachy >110

Cardiopulm

Hypoxia <90

Hypotension <100

Jimenez. et al. Arch Intern Med  
2010;170:1383-1389



## Simplified PESI

Cancer

Age >80

Tachy >110

Cardiopulm

Hypoxia <90

Hypotension <100

Jimenez. et al. Arch Intern Med  
2010;170:1383-1389

# Management of Low-Risk Pulmonary Embolism Patients Without Hospitalization

## The Low-Risk Pulmonary Embolism Prospective Management Study

*Joseph R. Bledsoe, MD; Scott C. Woller, MD; Scott M. Stevens, MD; Valerie Aston, MBA; Rich Patten, MD; Todd Allen, MD; Benjamin D. Horne, PhD, MPH; Lydia Dong, MD, PhD; James Lloyd, BS; Greg Snow, PhD; Troy Madsen, MD; and C. Gregory Elliott, MD*

CHEST 2018; ■(■):■-■



# Intermountain Health Outpatient PE

- 200 consecutive low risk PE patients from 5 EDs
- PESI score <86
- Echo without RV strain
- US no proximal DVT
- Observed in ED 12-24h.

# Intermountain Health Outpatient PE

- 86% DCd on NOAC
  - 0% 90 day mortality,
  - 0% recurrent VTE.
  - 1 major bleed day 61.
- 
- Relatively young, low cancer.

60 yo black female with DM, HTN, Afib with Hx CVA. Interested in transitioning off Coumadin.




Warfarin




Dabiga  
tran



Rivaroxaban



Apixaban



Edoxaban

60 yo black female with DM, HTN, Afib with Hx CVA. Interested in transitioning off Coumadin.



- Best agent for preventing stroke = Dabig 150 BID
- Best data for secondary prevention = Riva, Apixa

# Bleeding Risk? HAS-BLED

• HTN	1	
• Abl renal/liver	1 or 2	
• Stroke	1	
• Bleed Hx	1	2 or less points=
• Labile INR	1	low bleed risk
• Elderly (>65)	1	
• Drugs/EtOH	1 or 2	

# Bleeding Risk? HAS-BLED

• HTN	1	
• Abl renal/liver	1 or 2	
• Stroke	1	
• Bleed Hx	1	2 or less points=
• Labile INR	1	low bleed risk
• Elderly (>65)	1	
• Drugs/EtOH	1 or 2	HTN, Stroke=2 points

75 yo white male ESRD, HTN, DM, CHF, CVA  
with new DVT.



Warfarin




Dabiga  
tran



Rivaro  
xaban



Apixa  
ban



Edox  
aban

# Renal Dosing NOACs

Dabigatran	Rivaroxaban	Apixaban	Edoxaban
CrCl>30 150 BID	CrCl>50 20 qPM	ABC<2 5 BID	CrCl>50 60 qD
CrCl=15-30 75 BID	CrCl=15-50 15 qPM	ABC=2 or more 2.5 BID	CrCl=15-50 30 qD
CrCl<15 Avoid	CrCl<15 Avoid		CrCl<15 Avoid



## Apixaban Renal Dose- A fib.

- The recommended dose is 5 mg twice daily.
- In patients with at least 2 of the following:
  - Age  $\geq 80$  years,
  - Body weight  $\leq 60$  kg, or
  - Creatinine  $\geq 1.5$  mg/dL,the recommended dose is 2.5 mg orally twice daily.
- Low numbers in trials received low dose:  
AVERROES 6%, ARISTOTLE 4.7%

## Apixaban Renal Dose- VTE.

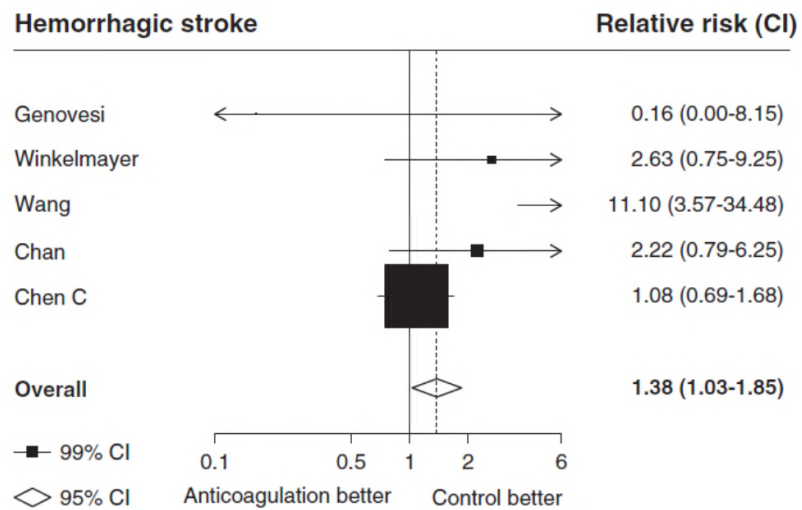
- The recommended dose is 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily.
- No dosing adjustment suggested!

## ESRD and A fib

- KDIGO 2011-

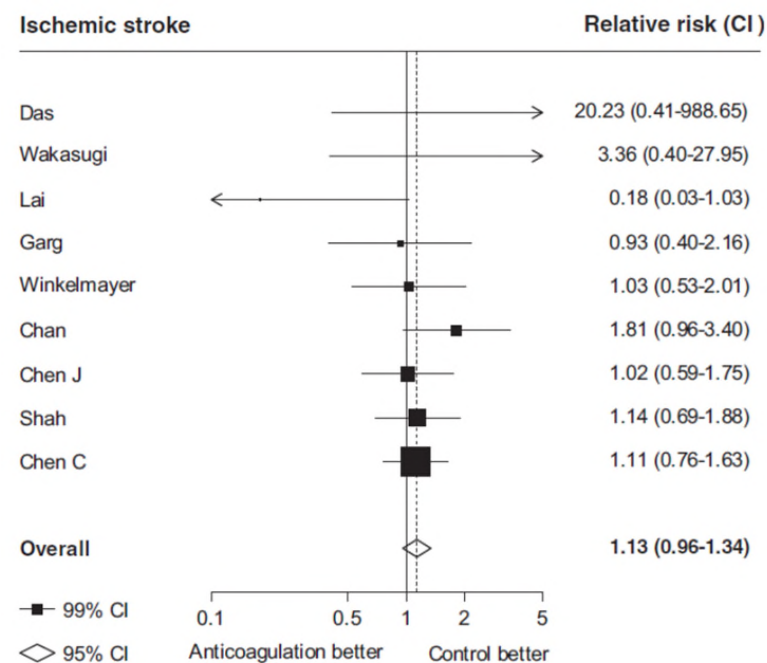
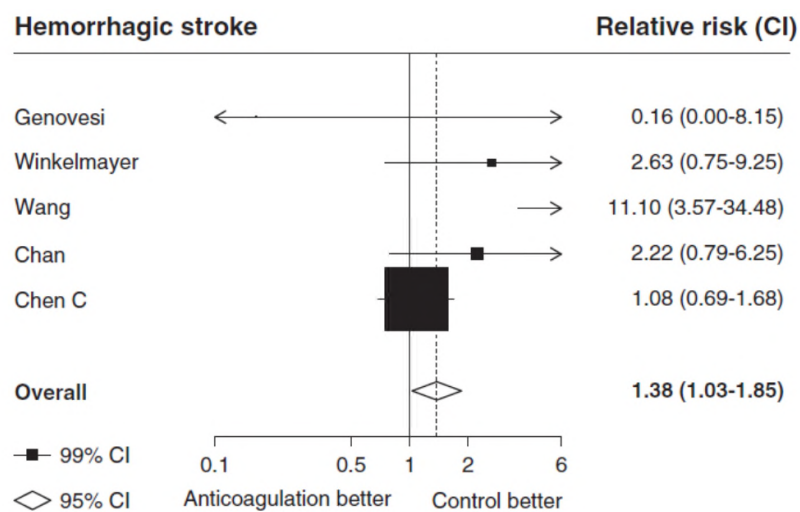
“The benefit of warfarin anticoagulation for primary prevention of stroke in CKD 5D is questionable.”

# ESRD and A fib



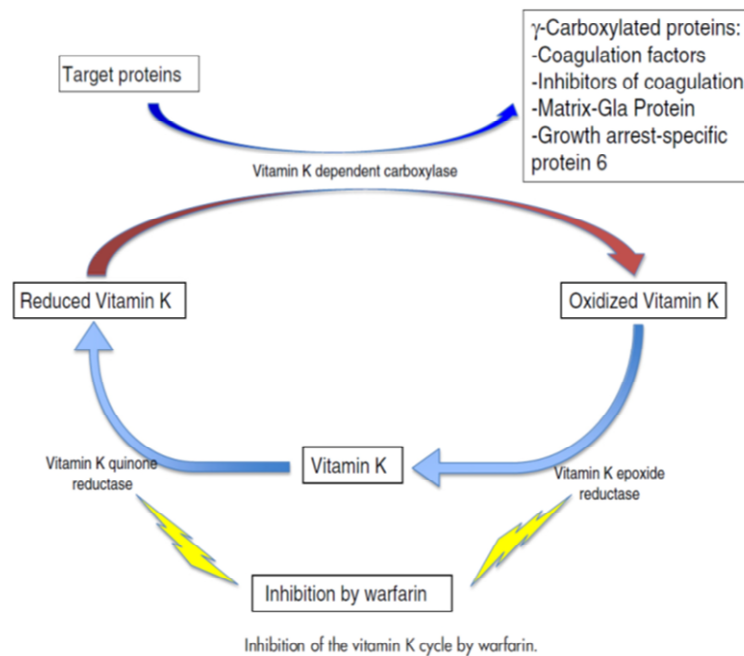
Am J Cardiol 2016;117:1934

# ESRD and A fib

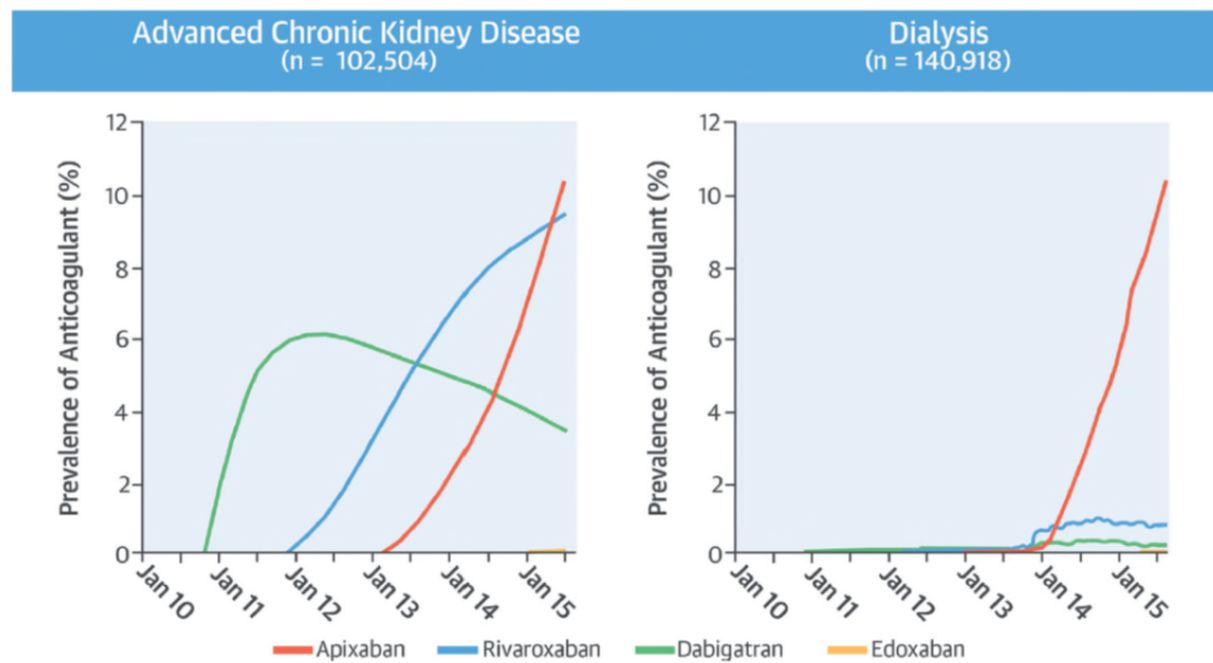


Am J Cardiol 2016;117:1934

# Coumadin leads to vascular calcification

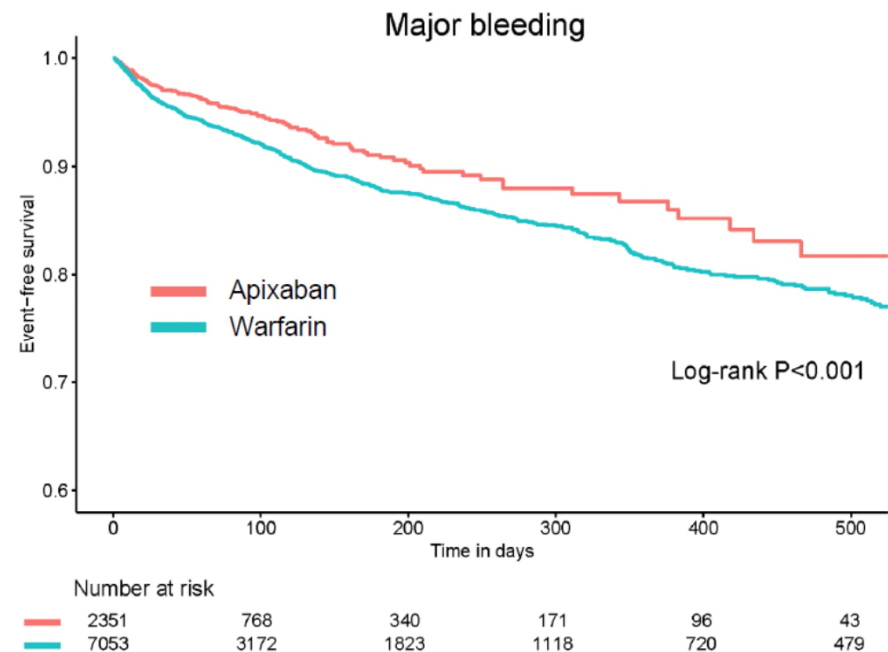
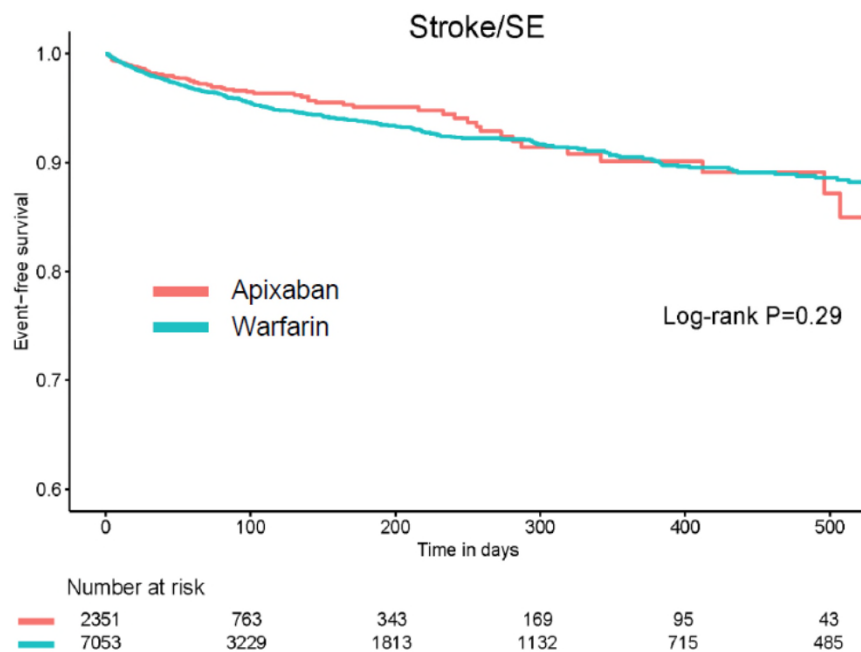


- Matrix-Gla inhibitor of calcification.
- Inhibiting activation leads to less inhibition of calcification.



Chan, K.E. et al. J Am Coll Cardiol. 2016;67(24):2888-99.

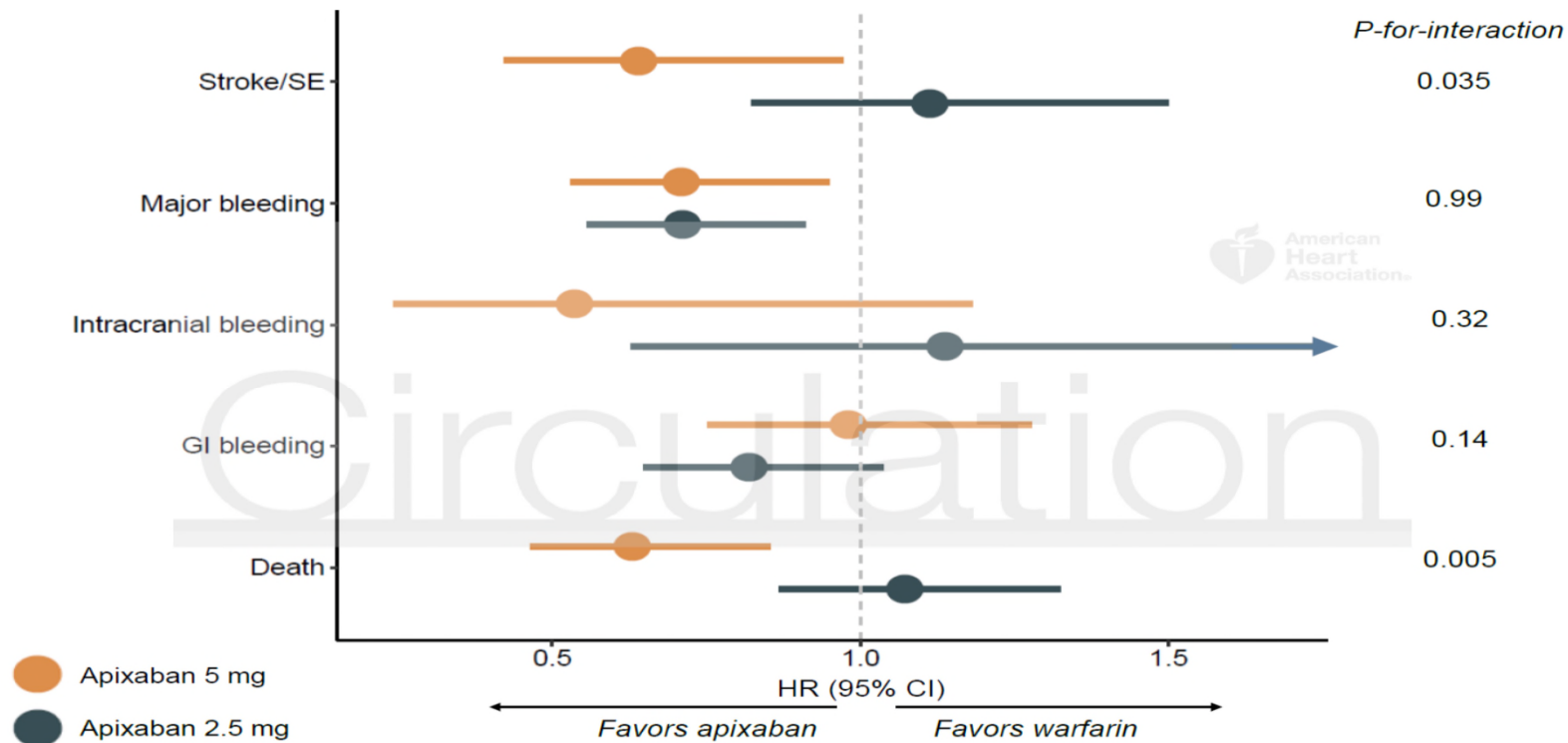
# 25,000 Dialysis Patients with Afib



<http://circ.ahajournals.org/content/early/2018/06/22/CIRCULATIONAHA.118.035418>



# Secondary Dose Specific Analysis



<http://circ.ahajournals.org/content/early/2018/06/22/CIRCULATIONAHA.118.035418>

75 yo white male ESRD, HTN, DM, CHF, CVA  
with new DVT.



Warfarin



Apixa  
ban


50 yo hispanic male new Afib, obesity with poor diet, smoker, alcohol use, HTN, DM, chronic dyspepsia. Adamant takes meds, but misses visits frequently due to work. CrCl=100.




Warfarin




Dabiga  
tran



Rivaroxaban



Apixaban



Edoxaban

50 yo **hispanic** male new Afib, obesity with poor diet, **smoker, alcohol** use, HTN, DM, chronic dyspepsia. Adamant takes meds, but **misses visits frequently** due to work. CrCl=100.



- SAMe-TT2R2 score=5
- High risk for poor INR control.

50 yo **hispanic** male new Afib, obesity with poor diet, **smoker, alcohol** use, HTN, DM, chronic dyspepsia. Adamant takes meds, but **misses visits frequently** due to work. CrCl=100.




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50 yo hispanic male new Afib, obesity with poor diet, smoker, alcohol use, HTN, DM, chronic **dyspepsia**. Adamant takes meds, but misses visits frequently due to work. CrCl=100.



Rivaroxaban



Apixaban



Edoxaban


50 yo hispanic male new Afib, obesity with poor diet, smoker, alcohol use, HTN, DM, chronic dyspepsia. Adamant takes meds, but misses visits frequently due to work.  $\text{CrCl}=100$ .



Rivaroxaban



Apixaban



Edoxaban



# Edoxaban Black Box Warning

- REDUCED EFFICACY IN NVAf PATIENTS WITH CrCl >95 mL/MIN
- SAVAYSA should not be used in patients with CrCl >95 mL/min. In the ENGAGE AF-TIMI 48 study, NVAf patients with CrCl >95mL/min had an increased rate of ischemic stroke with SAVAYSA 60 mg once daily compared to patients treated with warfarin. In these patients another anticoagulant should be used.

50 yo hispanic male new Afib, obesity with poor diet, smoker, alcohol use, HTN, DM, chronic dyspepsia. Adamant takes meds, but misses visits frequently due to work.  $\text{CrCl}=100$ .



Rivaroxaban



Apixaban

55 yo female pancreatic cancer with PE.

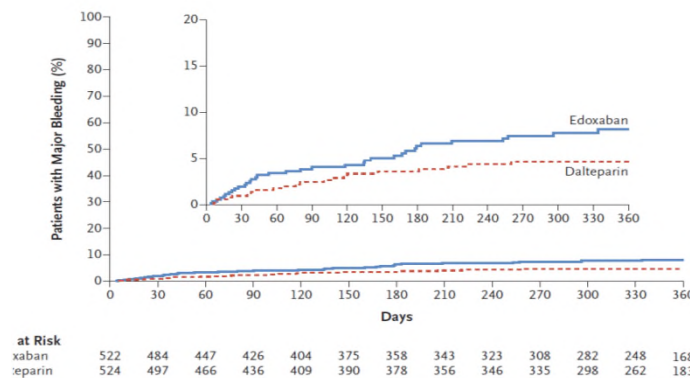
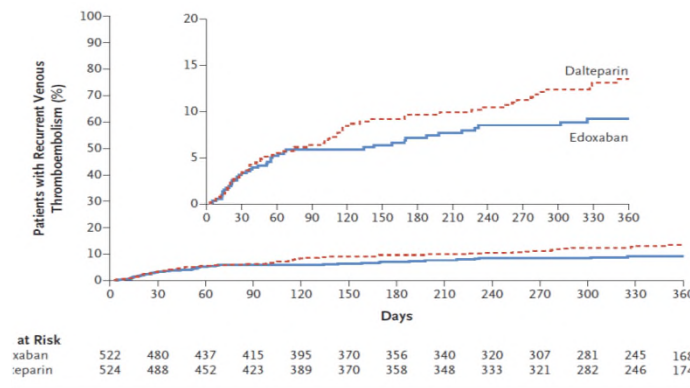


55 yo female pancreatic cancer with PE.

- CLOT study- LMWH for first 6 months.

55 yo female pancreatic cancer with PE.

- **Hokusai VTE-**  
Edoxaban 60 mg  
noninferior to  
dalteparin in  
composite  
outcome of major  
bleed and  
recurrent VTE.



NEJM 2018 378;7



30 yo 20 week gestation with DVT.

Warfarin

Dabiga  
tran

Rivaro  
xaban

Apixa  
ban

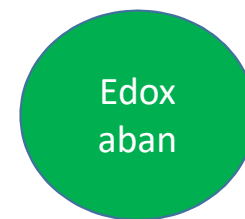
Edox  
aban

30 yo 20 week gestation with DVT.



- NOACs cross placenta.
- Teratogenicity Warfarin

30 yo 20 week gestation with DVT.



- NOACs cross placenta.
- Teratogenicity Warfarin
- If pregnant with a valve; Warfarin still used.



Mechanical valve?.

Warfarin

Dabiga  
tran

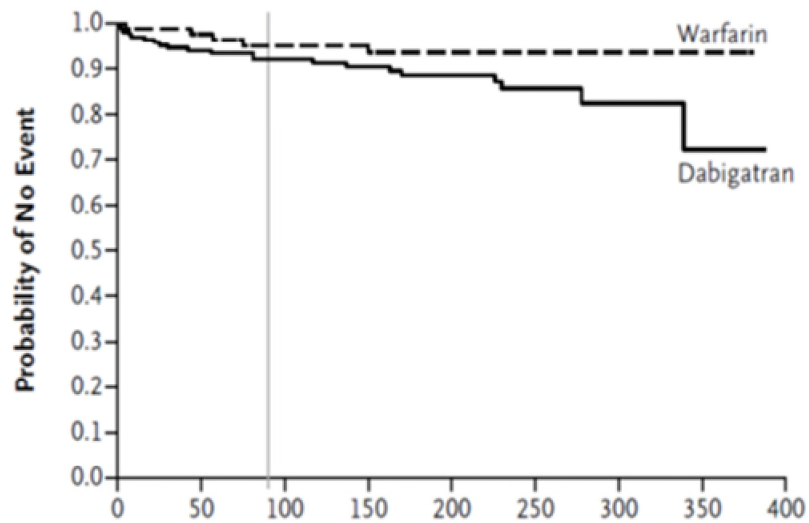
Rivaro  
xaban

Apixa  
ban

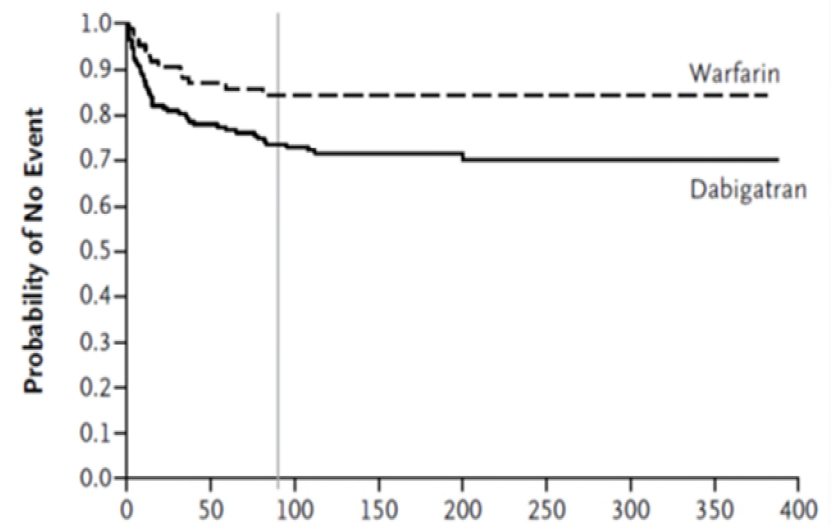
Edox  
aban

Re-align- terminated early.

**A** First Thromboembolic Event



**B** First Bleeding Event



NEJM 2013 369 1206

# When to use 'bridging anticoagulation'.

- NOACs- No need. Stop NOAC

# Know when to hold 'em.

**Table 3** Last intake of drug before elective surgical intervention

	Dabigatran		Apixaban–Edoxaban–Rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. $\geq 12$ or 24 h after last intake)			
	Low risk	High risk	Low risk	High risk
CrCl $\geq 80$ mL/min	$\geq 24$ h	$\geq 48$ h	$\geq 24$ h	$\geq 48$ h
CrCl 50–80 mL/min	$\geq 36$ h	$\geq 72$ h	$\geq 24$ h	$\geq 48$ h
CrCl 30–50 mL/min <sup>a</sup>	$\geq 48$ h	$\geq 96$ h	$\geq 24$ h	$\geq 48$ h
CrCl 15–30 mL/min <sup>a</sup>	Not indicated	Not indicated	$\geq 36$ h	$\geq 48$ h
CrCl $< 15$ mL/min	No official indication for use			
	There is no need for pre-operative bridging with LMWH/UFH			

Bold values deviate from the common stopping rule of  $\geq 24$  h low risk,  $\geq 48$  h high risk.

Low risk: with a low frequency of bleeding and/or minor impact of a bleeding; high risk with a high frequency of bleeding and/or important clinical impact.

CrCl, creatinine clearance.

<sup>a</sup>Many of these patients may be on the lower dose of dabigatran (i.e. 110 mg BID) or apixaban (i.e. 2.5 mg BID), or have to be on the lower dose of rivaroxaban (i.e. 15 mg OD) or edoxaban (i.e. 30 mg OD).

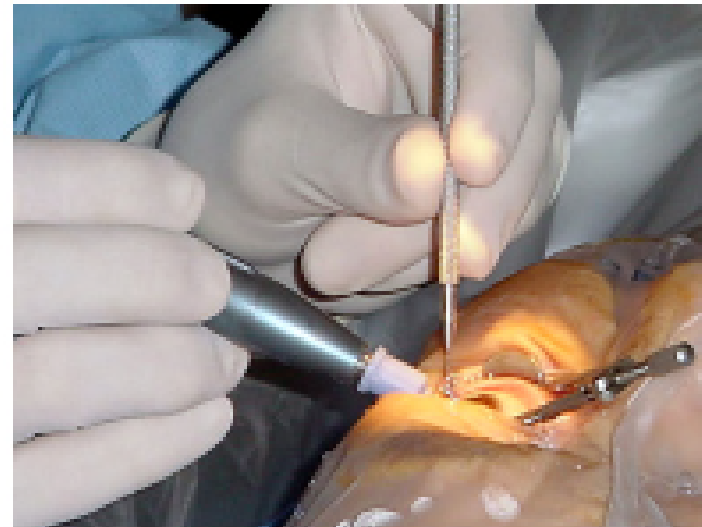
- 60 y.o. with chronic A fib (CHADS2=4) admitted for colonoscopy. Post-procedure management:
- A. IV UFH until INR 2.
- B. Outpatient LMHW bridge.
- C. Resume coumadin without bridge.

- 48 yo woman with bi-leaflet aortic valve is to undergo elective inguinal hernia repair. Post-op management:
- A. IV UFH until INR 2
- B. Outpatient LMHW bridge
- C. Resume coumadin without bridge.

- 70 yo man with a mechanical mitral valve (ball in cage) with a fib, cva, undergoes colectomy. Post-op management:
- A. IV UFH until INR 2
- B. Outpatient LMHW bridge
- C. Resume coumadin without bridge.

# First question--Do you even need to stop Coumadin?

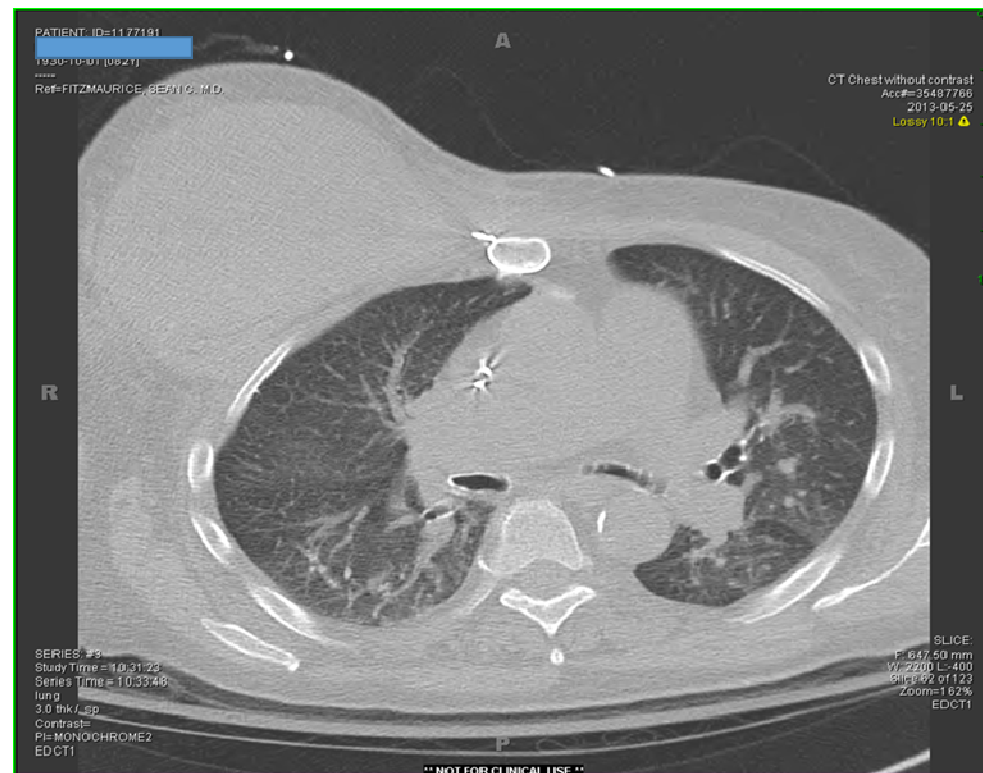
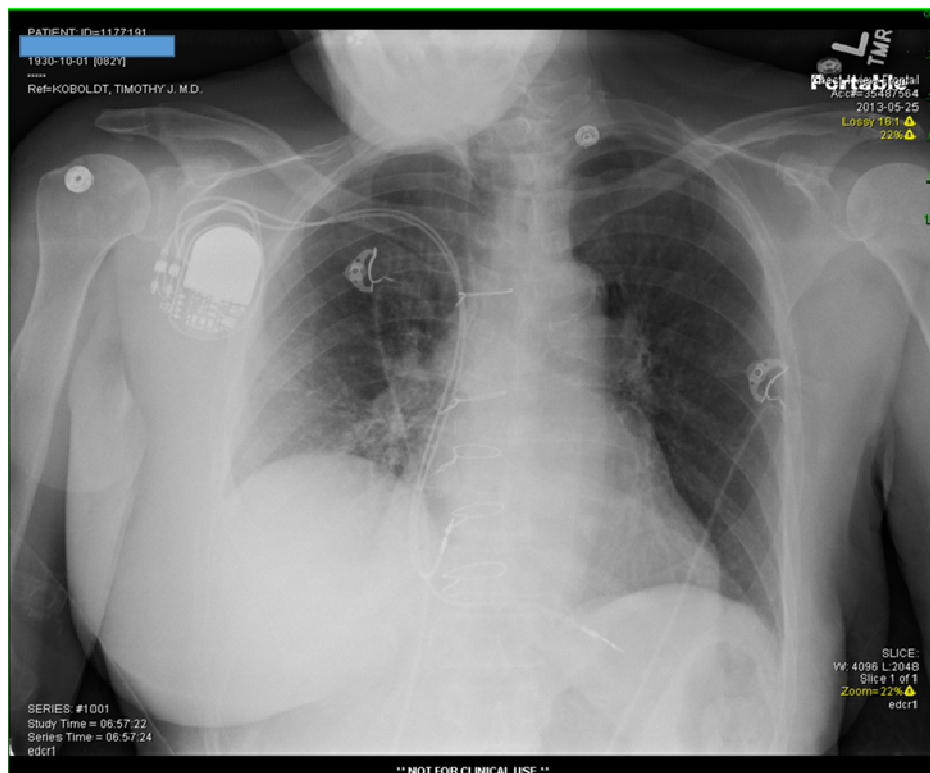
- Dermatologic,
- Cataract,
- Dental procedures,  
are safe with  
therapeutic INR's!



These comprise 20% of all procedures.

Topical agents (tranexamic acid mouthwash) of some value.





# Pacemaker or Defibrillator Surgery without Interruption of Anticoagulation

David H. Birnie, M.D., Jeff S. Healey, M.D., George A. Wells, Ph.D., Atul Verma, M.D.,  
Anthony S. Tang, M.D., Andrew D. Krahn, M.D., Christopher S. Simpson, M.D.,  
Felix Ayala-Paredes, M.D., Benoit Coutu, M.D., Tiago L.L. Leiria, M.D.,  
and Vidal Essebag, M.D., Ph.D., for the BRUISE CONTROL Investigators\*

N ENGL J MED 368;22 NEJM.ORG MAY 30, 2013

Outcome	Heparin Bridging (N=338)	Continued Warfarin (N=343)	Relative Risk (95% CI)	P Value
<b>Primary outcome</b>				
Clinically significant hematoma — no. (%)	54 (16.0)	12 (3.5)	0.19 (0.10–0.36)	<0.001

# When should we not bridge?

- High risk bleed
- CNS, spinal
- CABG
- Major orthopedic
- Recon. Plastic
- Major cancer surgery
- Sessile polyps
- Prostate biopsy

# Stratify the Risk

Annual risk of thromboembolism on no anticoagulation.

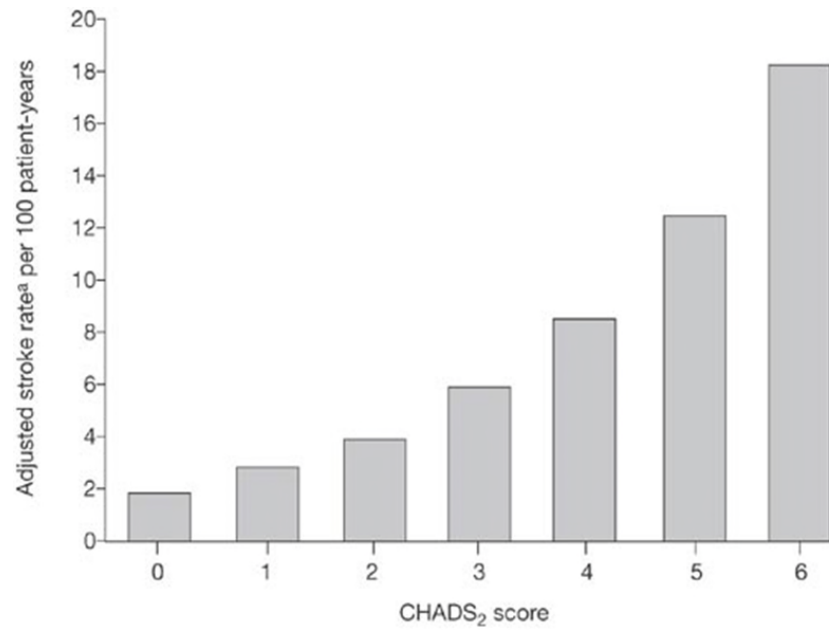
- Atrial fibrillation
- AVR
- MVR

## Stratify the Risk

Annual risk of thromboembolism on no anticoagulation.

- Atrial fibrillation 4-5%
- AVR
- MVR

# CHADS<sub>2</sub>



JAMA 2001;285:2864-70

## Stratify the Risk

Annual risk of thromboembolism on no anticoagulation.

- Atrial fibrillation 4-5%
- AVR
- MVR

## Stratify the Risk

Annual risk of thromboembolism on no anticoagulation.

- Atrial fibrillation 4-5%
- AVR 4-8%
- MVR

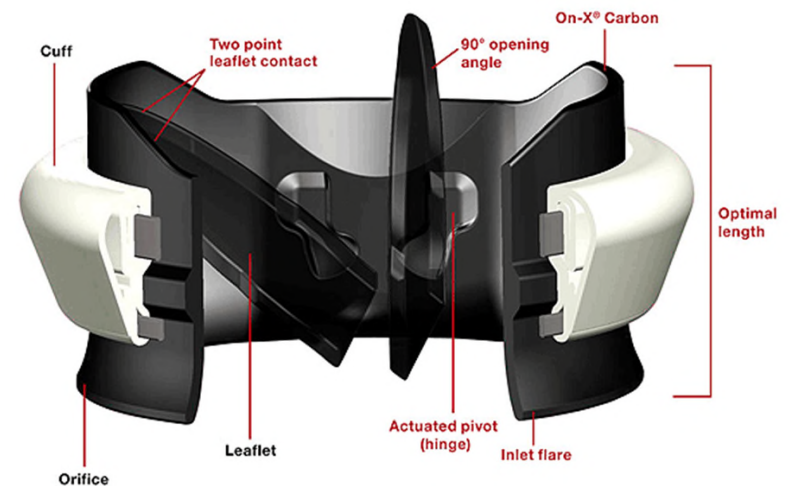


# Evolution of Prosthetic valves.



# PROACT

- Low intensity warfarin (INR 1.5-2) had lower major and minor bleed rates without change in thromboembolism compared to traditional INR.
- DAPT arm terminated for excess thromboembolism.



The unique features of the On-X® Prosthetic Heart Valve are highlighted in red.

# Stratify the Risk

Annual risk of thromboembolism on no anticoagulation.

- Atrial fibrillation 4-5%
- AVR 4-8%
- MVR ?

# Risky business

	Mechanical Valve	Atrial Fibrillation	VTE
High >10%	Mitral Older valve Recent (<6mo) CVA or TIA	CHADS2= 5 or 6 Recent CVA/TIA Rheum Ht Dz	Recent (<3mo) VTE Severe Thrombophilia
Moderate 4-10%	Bi-leaflet AoV AND one risk factor: Afib, CVA/TIA, HTN DM, CHF, Age>75	CHADS2= 3 or 4	VTE 3-12 mo. Non-severe Thrombophilia Recurrent VTE Active cancer
Low <4%	Bi-leaflet AoV With no risk factor	CHADS2= 0 to 2 and no Hx CVA/TIA	VTE > 12 mo ago And no other risk factors

# BRIDGE Trial NEJM 2015

**Table 3. Study Outcomes.**

Outcome	No Bridging (N=918) <i>number of patients (percent)</i>	Bridging (N=895) <i>number of patients (percent)</i>	P Value
<b>Primary</b>			
Arterial thromboembolism	4 (0.4)	3 (0.3)	0.01*, 0.73†
Stroke	2 (0.2)	3 (0.3)	
Transient ischemic attack	2 (0.2)	0	
Systemic embolism	0	0	
Major bleeding	12 (1.3)	29 (3.2)	0.005†
<b>Secondary</b>			
Death	5 (0.5)	4 (0.4)	0.88†
Myocardial infarction	7 (0.8)	14 (1.6)	0.10†
Deep-vein thrombosis	0	1 (0.1)	0.25†
Pulmonary embolism	0	1 (0.1)	0.25†
Minor bleeding	110 (12.0)	187 (20.9)	<0.001†

# BRIDGE Trial

## NEJM 2015

CHADS<sub>2</sub> score†

Mean	2.3±1.03	2.4±1.07
Distribution — no. (%)		
0	1 (0.1)	1 (0.1)
1	216 (22.7)	212 (22.7)
2	382 (40.2)	351 (37.6)
3	229 (24.1)	232 (24.8)
4	96 (10.1)	106 (11.3)
5	23 (2.4)	27 (2.9)
6	3 (0.3)	5 (0.5)

# Risky business

	Mechanical Valve	Atrial Fibrillation	VTE
High >10%	Mitral Older valve Recent (<6mo) CVA or TIA	CHADS2= 5 or 6 Recent CVA/TIA Rheum Ht Dz	Recent (<3mo) VTE Severe Thrombophilia
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No Bridging required			

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Bridging Required



# Risky business

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“The bridging or no-bridging approach chosen is based on an assessment of individual patient and surgery-related factors.”

- 60 y.o. with chronic A fib (CHADS2=2) admitted for colonoscopy. Post-procedure management:
- A. IV UFH until INR 2.
- B. Outpatient LMHW bridge.
- C. Resume coumadin without bridge.

- 60 y.o. with chronic A fib (CHADS2=4) admitted for colonoscopy. Post-procedure management:
- A. IV UFH until INR 2.
- B. Outpatient LMHW bridge.
- C. Resume coumadin without bridge.

- 48 yo woman with bi-leaflet aortic valve is to undergo elective inguinal hernia repair. Post-op management:
- A. IV UFH until INR 2
- B. Outpatient LMHW bridge
- C. Resume coumadin without bridge.

- 48 yo woman with bi-leaflet aortic valve is to undergo elective inguinal hernia repair. Post-op management:
- A. IV UFH until INR 2
- B. Outpatient LMHW bridge
- C. Resume coumadin without bridge.

- 70 yo man with a mechanical mitral valve (ball in cage) with a fib, cva, undergoes colectomy. Post-op management:
- A. IV UFH until INR 2
- B. Outpatient LMHW bridge
- C. Resume coumadin without bridge.

- 70 yo man with a mechanical mitral valve (ball in cage) with a fib, cva, undergoes colectomy. Post-op management:
- A. IV UFH until INR 2
- B. Outpatient LMHW bridge
- C. Resume coumadin without bridge.

# Reversing Anticoagulation

- 60 yo black female with DM, HTN, Afib with Hx CVA. Transitioned from Coumadin to Apixaban 1 month ago present with hematochezia and hypotension.



Reversibility?



# Reversibility?



## Protamine

Fish sperm (milt)

Very basic, high arginine.

Form a stable salt.

Possible allergy

-especially in patients s/p vasectomy, with fish allergies, or who have received NPH insulin.



# Reversibility?



## Protamine

Fish sperm (milt)

Very basic, high arginine.

Form a stable salt.

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-especially in patients s/p vasectomy, with fish allergies, or who have received NPH insulin.



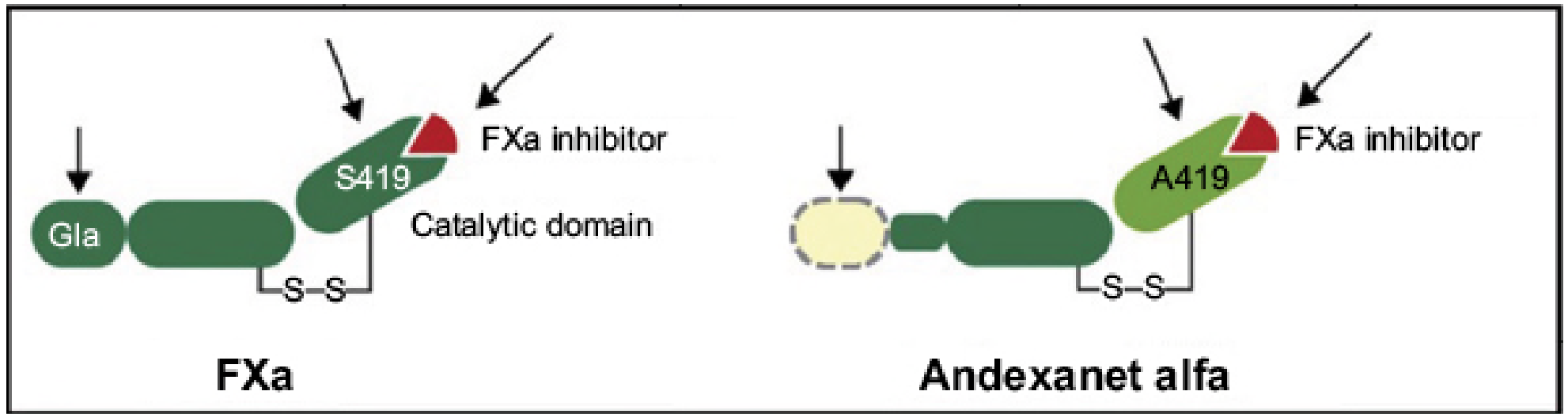
# Labs?

Dabigatran- Thrombin time, aPTT (qualitative), ECT (not in USA)

Xa inhibitors- *calibrated* anti factor Xa level.

# Reversal Agents

- Time
  - Activated Charcoal
  - Dialysis? (Dabigatran)
  - PCC? (only data is healthy volunteers)
- 
- Idarucizumab- Dabigatran
  - Andexanet alpha- all Xa inhibitors.
  - Ciraparantag (in testing) universal?



- Andexanet alpha reverses:
- Heparin (some effect on IIa)
- LMWH
- Pentasacharide
- All Xa-inhibitor NOACs





# Indications for administration of NOAC reversal agents

- **Life-threatening bleeding** in a closed space or critical organ: intracranial hemorrhage, pulmonary hemorrhage, retroperitoneal bleeding, compartment syndrome.
- **Emergency surgery** in patients at high risk of bleeding: cardiovascular or thoracic surgery, hepatic or other major organ surgery, orthopedic neurosurgery.
- **Emergency procedural intervention** in patients at high risk of bleeding: placement of an intracranial pressure-monitoring device, lumbar puncture, placement of vascular access for dialysis.
- **Uncontrollable hemorrhage** despite standard transfusion and clinical management



# Indications for administration of NOAC reversal agents

Reversal agents should not be used for elective surgery or procedural interventions that can be delayed long enough to allow drug clearance, gastrointestinal bleeds that respond to supportive measures, or high drug levels or excessive anticoagulation without associated bleeding.

## In conclusion

- Think about who needs DVT prophylaxis.
- Outpatient PE treatment is safe for low risk patients.
- Stay calm and prescribe NOACs. Reversal agents are available.

