Anticoagulation Cases in the Hospital 2018

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Professor and Chief of Hospital Medicine
Washington University School of Medicine
Objectives

- Properly target at-risk patients for DVT prophylaxis.
- When to use NOACs and which one?
- Bridging therapies
- Reversal agents.
More than 100,000 Americans die each year from VTE.
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More than from breast cancer, traffic accidents, and AIDS combined.
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More than from breast cancer, traffic accidents, and AIDS combined.

American public does not recognize their risk for VTE or know the signs and symptoms. Fewer than 1 in 10 Americans know about DVT and are familiar with its symptoms or risk factors.

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.
How Common is DVT in hospitalized medical patients?

ACCP 8th 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”
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.

<table>
<thead>
<tr>
<th></th>
<th>Pharm prophylaxis</th>
<th>Pharm and /or mechanical prophylaxis</th>
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<tbody>
<tr>
<td>Low risk (n=272)</td>
<td>67%</td>
<td>85%</td>
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<tr>
<td>High risk (n=100)</td>
<td>61%</td>
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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

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

90 day VTE rate

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.

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!
I’d ambulate TID for a Camel!

Rothberg JHM 2011
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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• McLean spent rest of his life fighting for credit.

[Image of a plaque dedicated to Jay McLean.]

In recognition of his major contribution to the discovery of heparin in 1916 as a second-year medical student in collaboration with Professor William H. Howell, this plaque is presented to the Johns Hopkins Medical School at the conference on bleeding in the surgical patient held by the New York Academy of Sciences May 3, 1963.
Making heparin is a dirty job

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$_2$DS$_2$-VASc leads to much higher anticoagulation rates.

Women- 48% to 19% low risk
Men- 75% to 31% low risk

(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\(_2\)R\(_2\) 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.

Chest 2013 144 1555
# NOACs

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
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<td><strong>Half-life (h)</strong></td>
<td>12-17</td>
<td>5-9</td>
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<td><strong>Time to peak activity (h)</strong></td>
<td>1-3</td>
<td>2.5-4</td>
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<td><strong>Interactions</strong></td>
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<td>P-gp, CYP3A4</td>
<td>P-gp, CYP3A4</td>
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<td><strong>Protein bound</strong></td>
<td>35%</td>
<td>95%</td>
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<td><strong>Renal excretion</strong></td>
<td>&gt;80%</td>
<td>33%</td>
<td>27%</td>
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<td><strong>Monitor</strong></td>
<td>TT</td>
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## NOAC Afib Trials

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# NOAC VTE Trials

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<td>Dabig 150 BID</td>
<td>HR=1.09</td>
<td>HR=.73</td>
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<td>Einstein DVT and PE</td>
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<tr>
<td>Rivaroxaban 15 BID 21d, then 20 qD</td>
<td>HR=.89</td>
<td>HR=.54</td>
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<td>AMPLIFY</td>
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<td>Axipaxaban 10 BID 7d, then 5 qD</td>
<td>RR=.84</td>
<td>RR=.31</td>
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<td>HOKUSAI-VTE</td>
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<tr>
<td>Edoxaban 60 mg (30mg if CrCl,50 or &lt;60 kg)</td>
<td>HR=.89</td>
<td>HR=.81</td>
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</table>
65 yo black female with DM, HTN new DVT admitted overnight by ED. Very interested in going home, and avoiding shots and INR monitoring.
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.
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.
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

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

**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: ≤ 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 paO2<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).

Lancet 2011;378:41-48
## OTPE Trial

<table>
<thead>
<tr>
<th>14 day outcome</th>
<th>Outpatient</th>
<th>Inpatient</th>
<th>p value for non inferiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>0</td>
<td>0</td>
<td>.003</td>
</tr>
<tr>
<td>Major Bleed</td>
<td>1.2%</td>
<td>0</td>
<td>.031</td>
</tr>
<tr>
<td>Overall Mortality</td>
<td>0</td>
<td>0</td>
<td>.003</td>
</tr>
</tbody>
</table>

Lancet 2011;378:41-48
Observed in Ontario

- 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.

- 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

Simplified PESI

Cancer
Age >80
Tachy >110
Cardiopulm
Hypoxia <90
Hypotension <100

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.
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

<table>
<thead>
<tr>
<th>Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN</td>
<td>1</td>
</tr>
<tr>
<td>Abl renal/liver</td>
<td>1 or 2</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>Bleed Hx</td>
<td>1</td>
</tr>
<tr>
<td>Labile INR</td>
<td>1</td>
</tr>
<tr>
<td>Elderly (&gt;65)</td>
<td>1</td>
</tr>
<tr>
<td>Drugs/EtOH</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

2 or less points = low bleed risk

*Chest 2010;138:1093*
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

Chest 2010;138:1093
75 yo white male ESRD, HTN, DM, CHF, CVA with new DVT.

- Warfarin
- Dabigatran
- Rivaroxaban
- Apixaban
- Edoxaban
# Renal Dosing NOACs

<table>
<thead>
<tr>
<th>Renal Function</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl&gt;30</td>
<td>150 BID</td>
<td>CrCl&gt;50</td>
<td>ABC&lt;2</td>
<td>CrCl&gt;50</td>
</tr>
<tr>
<td></td>
<td>20 qPM</td>
<td>5 BID</td>
<td></td>
<td>60 qD</td>
</tr>
<tr>
<td>CrCl=15-30</td>
<td>75 BID</td>
<td>CrCl=15-50</td>
<td>ABC=2 or more</td>
<td>CrCl=15-50</td>
</tr>
<tr>
<td></td>
<td>15 qPM</td>
<td>2.5 BID</td>
<td></td>
<td>30 qD</td>
</tr>
<tr>
<td>CrCl&lt;15</td>
<td>Avoid</td>
<td>CrCl&lt;15</td>
<td></td>
<td>CrCl&lt;15</td>
</tr>
<tr>
<td></td>
<td>Avoid</td>
<td>Avoid</td>
<td></td>
<td>Avoid</td>
</tr>
</tbody>
</table>
Apixaban Renal Dose - A fib.

• The recommended dose is 5 mg twice daily.
• In patients with at least 2 of the following:
  • Age ≥80 years,
  • Body weight ≤60 kg, or
  • Creatinine ≥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.
Advanced Chronic Kidney Disease
(n = 102,504)

Dialysis
(n = 140,918)

Prevalence of Anticoagulant (%)

Jan 10  Jan 11  Jan 12  Jan 13  Jan 14  Jan 15

Apixaban  Rivaroxaban  Dabigatran  Edoxaban

25,000 Dialysis Patients with Afib

Stroke/SE

- Apixaban
- Warfarin

Log-rank $P=0.29$

Major bleeding

- Apixaban
- Warfarin

Log-rank $P<0.001$

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.
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.
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.

- 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.

Dabigatran  
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.
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.**
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. \( \text{CrCl}=100 \).
55 yo female pancreatic cancer with PE.

- Warfarin
- Dabigatran
- Rivaroxaban
- Apixaban
- Edoxaban
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 daltaparin in composite outcome of major bleed and recurrent VTE.

NEJM 2018 378;7
30 yo 20 week gestation with DVT.
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?.
Re-align - terminated early.
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

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Apixaban–Edoxaban–Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl ≥ 80 mL/min</td>
<td>≥ 24 h</td>
<td>≥ 24 h</td>
</tr>
<tr>
<td>CrCl 50–80 mL/min</td>
<td>≥ 36 h</td>
<td>≥ 72 h</td>
</tr>
<tr>
<td>CrCl 30–50 mL/mina</td>
<td>≥ 48 h</td>
<td>≥ 96 h</td>
</tr>
<tr>
<td>CrCl 15–30 mL/mina</td>
<td>Not indicated</td>
<td>Not indicated</td>
</tr>
<tr>
<td>CrCl &lt; 15 mL/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>High risk</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**No important bleeding risk and/or adequate local haemostasis possible:** perform at trough level (i.e. ≥12 or 24 h after last intake).

- **Low risk**
  - CrCl ≥ 80 mL/min: ≥ 24 h
  - CrCl 50–80 mL/min: ≥ 36 h
  - CrCl 30–50 mL/min: ≥ 48 h
  - CrCl 15–30 mL/min: Not indicated
  - CrCl < 15 mL/min: Not indicated

- **High risk**
  - CrCl ≥ 80 mL/min: ≥ 48 h
  - CrCl 50–80 mL/min: ≥ 72 h
  - CrCl 30–50 mL/min: ≥ 96 h
  - CrCl 15–30 mL/min: Not indicated
  - CrCl < 15 mL/min: Not indicated

**Bold values deviate from the common stopping rule of ≥24 h low risk, ≥48 h high risk.**

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

CrCl, creatinine clearance.

*aMany 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. Binnie, 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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Heparin Bridging (N = 338)</th>
<th>Continued Warfarin (N = 343)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically significant hematoma — no. (%)</td>
<td>54 (16.0)</td>
<td>12 (3.5)</td>
<td>0.19 (0.10–0.36)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
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\textsubscript{2}
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.
Stratify the Risk
Annual risk of thromboembolism on no anticoagulation.

- Atrial fibrillation  4-5%
- AVR  4-8%
- MVR  ?
## Risky business

<table>
<thead>
<tr>
<th></th>
<th>Mechanical Valve</th>
<th>Atrial Fibrillation</th>
<th>VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High &gt;10%</strong></td>
<td>Mitral</td>
<td>CHADS2 = 5 or 6</td>
<td>Recent (&lt;3mo) VTE</td>
</tr>
<tr>
<td></td>
<td>Older valve</td>
<td>Recent CVA/TIA</td>
<td>Severe Thrombophilia</td>
</tr>
<tr>
<td></td>
<td>Recent (&lt;6mo) CVA or TIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Moderate 4-10%</strong></td>
<td>Bi-leaflet AoV AND one risk factor: Afib, CVA/TIA, HTN DM, CHF, Age&gt;75</td>
<td>CHADS2 = 3 or 4</td>
<td>VTE 3-12 mo. Non-severe Thrombophilia</td>
</tr>
<tr>
<td><strong>Low &lt;4%</strong></td>
<td>Bi-leaflet AoV With no risk factor</td>
<td>CHADS2 = 0 to 2 and no Hx CVA/TIA</td>
<td>VTE &gt; 12 mo ago And no other risk factors</td>
</tr>
</tbody>
</table>
### Table 3. Study Outcomes.

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

*Significant at the 0.05 level.
†Significant at the 0.01 level.
**BRIDGE Trial**
**NEJM 2015**

<table>
<thead>
<tr>
<th>CHADS$_2$ score</th>
<th>Group A (n=10,714)</th>
<th>Group B (n=10,642)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>2.3±1.03</td>
<td>2.4±1.07</td>
</tr>
<tr>
<td>Distribution — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>1</td>
<td>216 (22.7)</td>
<td>212 (22.7)</td>
</tr>
<tr>
<td>2</td>
<td>382 (40.2)</td>
<td>351 (37.6)</td>
</tr>
<tr>
<td>3</td>
<td>229 (24.1)</td>
<td>232 (24.8)</td>
</tr>
<tr>
<td>4</td>
<td>96 (10.1)</td>
<td>106 (11.3)</td>
</tr>
<tr>
<td>5</td>
<td>23 (2.4)</td>
<td>27 (2.9)</td>
</tr>
<tr>
<td>6</td>
<td>3 (0.3)</td>
<td>5 (0.5)</td>
</tr>
</tbody>
</table>
## Risky business

<table>
<thead>
<tr>
<th></th>
<th>Mechanical Valve</th>
<th>Atrial Fibrillation</th>
<th>VTE</th>
</tr>
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<tbody>
<tr>
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</tr>
<tr>
<td></td>
<td>Recent (&lt;6mo) CVA</td>
<td>Rheum Ht Dz</td>
<td></td>
</tr>
<tr>
<td></td>
<td>or TIA</td>
<td></td>
<td></td>
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<tr>
<td><strong>Moderate 4-10%</strong></td>
<td>Bi-leaflet AoV AND one risk factor: Afib, CVA/TIA, HTN DM, CHF, Age&gt;75</td>
<td>CHADS2= 3 or 4</td>
<td>VTE 3-12 mo. Non-severe Thrombophilia Recurrent VTE Active cancer</td>
</tr>
<tr>
<td><strong>Low &lt;4%</strong></td>
<td>Bi-leaflet AoV</td>
<td>CHADS2= 0 to 2</td>
<td>VTE &gt; 12 mo ago</td>
</tr>
<tr>
<td></td>
<td>With no risk factor</td>
<td>and no Hx CVA/TIA</td>
<td>And no other risk factors</td>
</tr>
</tbody>
</table>

No Bridging required
## Risky business

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

Bridging Required
“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.
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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.