

It's a Brave New World: DOACs + PE/AF=DC

30 minutes

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2017 COI Disclosures: W. Frank Peacock, MD, FACEP, FACC

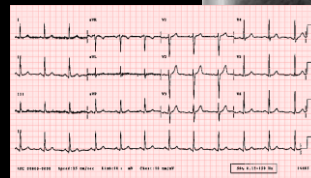
- **Research Grants:**
Abbott, Janssen, Roche, ZS Pharma
- **Consultant:**
Bayer, Beckman, Boehringer-Ingelheim, Instrument Labs
Janssen, Relypsa, Roche, ZS Pharma
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Johnson and Johnson
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Emergencies in Medicine LLC, Ischemia DX, LLC.

Your 72 year old Mom

- Calls you on the phone...
 - She just got back from London after visiting her childhood friend
 - Says her chest hurts
- What do you do?



- HR 94
- BP 122/76
- O2 sat 94%



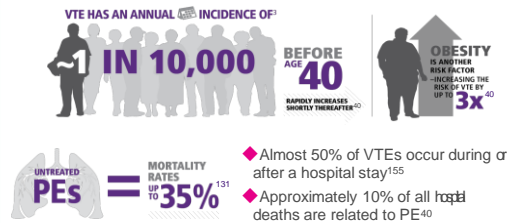
Labs

- Hgb 12.2 g/dL
- BNP 74 pg/mL
- Tnl 0.03 ng/mL
- UCG negative

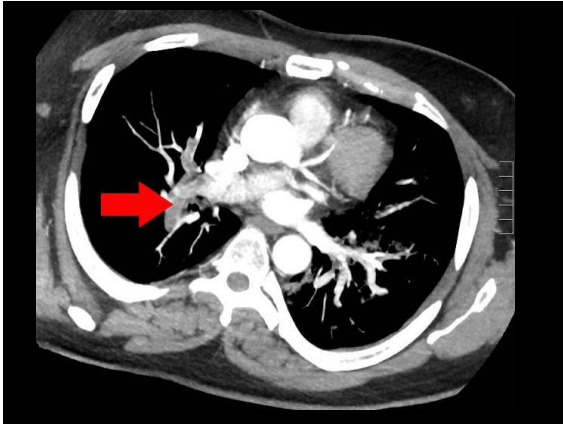
What would you do?

- Nothing?
- Treat vs test?
- If treat, what?
- ~ 90% of ER docs will treat with heparin, even though ultimately treating with a DOAC
 - Mercury data

VTE Is the Leading Cause of Preventable Hospital Death



VTE = venous thromboembolism.



ACCP Recommendations for Anticoagulation Therapy in Patients With DVT/PE⁸⁸

ACCP recommends (Grade 2B) a **NOAC*** over VKA therapy as long-term anticoagulant therapy for patients with:

- ◆ DVT of the leg and no cancer
- ◆ PE and no cancer

◆ Compared with VKA therapy, NOACs appear to have:

- Similar reduction of risk for recurrent VTE
- Less risk of ICH
- No increased risk of a fatal major bleed
- Greater convenience for patients and HCPs

NOAC = non-vitamin K antagonist oral anticoagulant.
*NOACs include rivaroxaban, dabigatran, apixaban, and edoxaban.

Baseline Patient Characteristics in Phase 3 Trials for the Initial Treatment of DVT and PE

	EINSTEIN DVT and PE* (N=8281) ^{2,136,137} XARELTO®	AMPLIFY (N=5395) ^{2,7} Eliquis®	RE-COVER I and II* (N=5107) ^{14,148} Pradaxa®	HOKUSAI (N=8240) ^{15,17} Savaysa®
DVT only, n (%)	3389 (40.9)	3532 (65.5)	3499 (68.5)	4921 (59.7)
PE only, n (%)	3597 (43.4)	1359 (25.2)	1136 (22.2)	2505 (30.4)
Unprovoked index event, n (%)	5255 (63.5)	4845 (89.8)	1817 (35.6)	5410 (65.7)
Recent trauma or surgery, n (%)	1486 (17.9)	Excluded ¹	Did not specify	Did not specify
Cancer at baseline ² , n (%)	462 (5.6)	169 (3.1)	221 (4.3)	209 (2.5)
Elderly ³ , n (%)	1283 (15.5)	749 (13.9)	529 (10.4)	1104 (13.4)
Previous VTE, n (%)	1610 (19.4)	872 (16.2)	1099 (21.5)	1520 (18.4)

◆ These trials were conducted with different designs and evaluated different populations, so direct comparisons of their results cannot be made

*Pooled analysis. ¹Patients defined as having head trauma, other major trauma, or major surgery 1 month prior to randomization were excluded from the trial. ²Hokusai enrolled 771 (9.3%) patients with any history of cancer. ³Elderly patients were aged >75 years for the EINSTEIN and RECOVER trial programs, and aged ≥70 years for AMPLIFY and Hokusai. ⁴Indicated trademarks are registered to their respective owners. Proportion of patients calculated by pooling total patients with noted characteristic in each trial arm.

The Risk of Recurrence Is Higher With Unprovoked VTE After Discontinuation of Anticoagulation¹³⁴

Patients with a first episode of clinically symptomatic proximal DVT and/or PE* (N=1626)

Average of 6 months of anticoagulation treatment

Patients discontinued anticoagulation and were followed for recurrent DVT/PE

Discontinuation of Anticoagulation

— Unprovoked
— Provoked

Cumulative Events (%)

Months After Discontinuation

HR=2.30; 95% CI: 1.82-2.90

*Excluded patients with active cancer, prior VTE, an indication for indefinite anticoagulation, geographic inaccessibility to follow-up, or poor life expectancy.

ACCP Guideline Recommendations for Duration of Anticoagulation for Patients With VTE⁸⁸

Provoked VTE	Unprovoked VTE	VTE and Active Cancer
Treatment with anticoagulation for 3 months (Grade 1B)	Treatment with anticoagulation for at least 3 months (Grade 1B)	Treatment with extended anticoagulation (Grade 1B/2B)
	<p>After 3 months, evaluate for the risk-benefit ratio of extended therapy (no scheduled stop):</p> <p>◆ Extended therapy is:</p> <ul style="list-style-type: none"> ◆ Recommended for second VTE with low bleeding risk (Grade 1B) ◆ Suggested for first VTE with low or moderate bleeding risk or second VTE with moderate bleeding risk (Grade 2B) <p>◆ Only 3 months of therapy is:</p> <ul style="list-style-type: none"> ◆ Recommended for first VTE and high bleeding risk (Grade 1B) ◆ Suggested for second VTE and high bleeding risk (Grade 2B) 	<p>Extended therapy is:</p> <ul style="list-style-type: none"> ◆ Recommended for low or moderate bleeding risk (Grade 1B) ◆ Suggested for high bleeding risk (Grade 2B)
◆ Continuing use of anticoagulation should be reassessed at periodic intervals		

Admit vs Discharge?

- What are the risks?
 - 1) Outpatient risks
 - 2) Inpatient risks
 - 3) Chagrin factor

Inpatient risks vs outpatient risks

Outpatient risks:

- Mortality rates in PE patients who present with shock exceed 30%
- 30-day mortality rate of low-risk PE patients is consistently <1%

— Kasper W, Konstantinides S, Geibel A, et al. Management strategies and determinants of outcome in acute major pulmonary embolism: results of a multicenter registry. *J Am Coll Cardiol.* 1997;30:1165-1171

Hospitalization doesn't change PE outcomes, but increases HAC

Premier Database

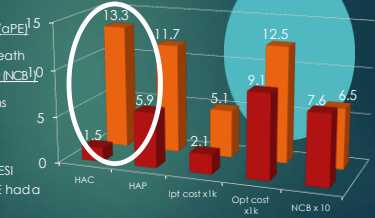
Definitions

- ▶ Short LOS < 2 days
- ▶ Adverse PE events (aPE) = Recurrent DVT, major bleed, or death
- ▶ Net clinical benefit (NCB) = aPE + hospital-acquired conditions (HAC)

6,746 PE

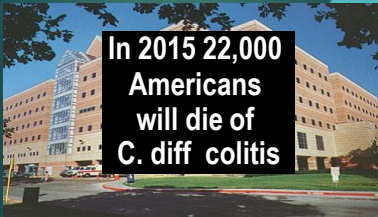
- ▶ 1,918 Low risk by sPESI
- ▶ 688 (35.9%) LRPE had a short LOS
- ▶ After PSM: 784 LRPE patients

No Difference in adverse PE events between Short vs Long LOS (p>0.05)



887% increase in HAC

Ever seen the box where we keep our worst bugs...



Deadly Germs May Lurk In Your Doctor's Clothing

Robert J. Szczerba, MD, MPH
 Infectious Disease Specialist, University of Michigan

"I never go to hospitals, that's where all the sick people are." It's an old joke that's based on some ugly truths. Hospital and other healthcare facilities are dangerous places that can lead to a large number of hospital-acquired infections (HAIs). According to the Centers for Disease Control and Prevention (CDC), about 1 in every 25 inpatients has an infection related to hospital care.

We all know that once germs are spread through unwashed hands. In a healthcare setting filled with sick patients, these dangers are obviously increased. The incredibly compelling video below by Seema Marwaha, illustrates just how easily a healthcare worker can spread germs through the hospital.



Chagrin Factor

1. My mother
2. Barack Obama
3. Carrie Underwood
- ...
45. My mother -in-law
- ...
1294. Some homeless dude
1295. Your mother -in-law



Treatment of Patients With DVT/PE^{87,88}

Acute DVT⁸⁷

Low-Risk PE⁸⁸

Current guidelines recommend initial treatment at home over treatment in-hospital (Grade 1B)

Current guidelines recommend treatment at home or early discharge over standard discharge (Grade 2B)

These recommendations are contingent on adequate home circumstances, such as:

- ◆ Well-maintained living conditions
- ◆ Strong support network
- ◆ Phone access

- ◆ Patient feeling well enough for home treatment
- ◆ Ability to be promptly rehospitalized

Considerations for Patient Selection for Outpatient Therapy

- 60%-95% of patients with acute, proximal DVT may be eligible for outpatient therapy¹¹
- Exclusion criteria on institutional protocols include^{11,150}:
 - Comorbid illness requiring hospitalization
 - Active or high risk for bleeding
 - Severe hypertension
 - Catheter-associated DVT
 - Recent surgery
 - Morbid obesity
 - Hypercoagulable state
 - Pregnancy

PESI and sPESI: Validated Tools to Identify Low-Risk

Variable	Score	
	PESI	sPESI
Age >80 years	Age in years	1
Male sex	10	0
History of cancer	30	1
History of heart failure	10	
History of chronic lung disease		1*
Pulse ≥110 bpm	20	1
Systolic BP <100 mm Hg	30	1
Respiratory rate ≥30 breaths/min	20	0
Temperature <36°C	20	0
Altered mental status	60	0
SpO ₂ <90% (w or w/o O ₂)	20	1

Old Ca, HF, COPD
Abnl vitals

Classification by Total Score	
PESI	sPESI
Class I ≤65	Low risk=0
Class II 66-85	
Class III 86-105	High risk≥1
Class IV 106-125	
Class V >125	

Jimenez D. Arch Intern Med. 2010;170(15):1383-1389.

Hestia

- ▶ 1. Hemodynamically unstable?
 - ▶ SBP<100, HR>100, BP>180/110, O₂sat >90%
- ▶ 2. Active bleeding or high risk of bleeding?
 - ▶ GIB<2w, CVA<4w, OR<2w, plt<75k
- ▶ 3. Failed anticoagulants?
- ▶ 4. IV pain medication?
- ▶ 5. Med/Soc reason to hospitalize?
- ▶ 6. Renal (eGFR <30) or liver failure?
- ▶ 7. Pregnant?

Any point = admission

Zondag W. J Thrombosis and Haemostasis. 11: 484-492, 2013

External validation of the Hestia criteria for identifying acute pulmonary embolism patients at low-risk of early mortality

Erin R. Weeda, PharmD; Christine G. Kohn, PharmD; W. Frank Peacock, MD, FACEP; Gregory J. Ferrmann, MD; Concetta Crivera, PharmD, MPH; Jeff R. Schein, DrPH, MPH; **Craig I. Coleman, PharmD**

University of Connecticut School of Pharmacy, Storrs, CT, USA; University of Connecticut/Hartford Hospital Evidence-Based Practice Center, Hartford, CT, USA; University of Saint Joseph School of Pharmacy, Hartford, CT, USA; Department of Emergency Medicine, Baylor College of Medicine, Houston, TX, USA; Department of Emergency Medicine, University of Cincinnati, Cincinnati, OH, USA; Janssen Scientific Affairs LLC, Raritan, NJ, USA.

Methods

- Retrospective analysis of consecutive, adult, objectively-confirmed PE patients presenting to the emergency department at Hartford Hospital from 11/11/2010-1/31/2014
- Risk stratification of patients with acute PE using the Hestia criteria
- Ascertained the total number of Hestia criteria met for each patient, calculated the proportion patients categorized as low-risk (Hestia criteria=0) and determined the accuracy of the Hestia criteria for predicting in-hospital and 30-day all-cause mortality
- Mortality status was determined using the Social Security Death Index

Results

Hestia Risk Categories	Patients (n=577) % (95%CI)	In-Hospital Mortality (n=19) % (95%CI)	30-Day Mortality (n=35) % (95%CI)
0	25.8 (22.4-29.6)	0 (0-2.5)	0 (0-2.5)
1	36.2 (32.4-40.2)	0.5 (0.08-2.6)	3.2 (1.6-6.5)
2	19.9 (16.9-23.4)	6.3 (3.2-11.9)	9.5 (5.5-15.8)
3	6.8 (5.0-9.1)	10.6 (4.6-22.6)	17.0 (8.9-30.1)
4-6	5.2 (3.7-7.3)	13.2 (5.8-27.3)	21.1 (11.1-36.4)
Low	25.8 (22.4-29.6)	0 (0-2.5)	0 (0-2.5)
High	74.2 (70.5-77.6)	4.4 (2.9-6.8)	8.2 (5.9-11.2)

In-Hospital & 30-Day Mortality by Hestia Risk Strata

Risk Score Validation In Hospital Mortality (N=861)

	PESI	sPESI	Hestia
Low-Risk Mortality n/N (%)	2/309 (0.6%)	0/250 (0%)	0/211 (0%)
Sensitivity (95%CI)	90.5% (68.2-98.3%)	100% (80.8-100%)	100% (80.8-100%)
NPV (95%CI)	99.4% (97.4-99.9%)	100% (98.1-100%)	100% (97.8-100%)

Risk Score Validation 30 day Mortality (N=573)

	PESI	sPESI	Hestia
Low-Risk Mortality n/N (%)	3/218 (1.4%)	1/177 (0.6%)	0/160 (0%)
Sensitivity (95%CI)	90.9% (74.5-97.6%)	97.0% (82.5-99.8%)	100% (87.0-100%)
NPV (95%CI)	98.6% (95.7-99.6%)	99.4% (96.4-100%)	100% (97.1-100%)

PREMIER: PE Costs and LOS

- Premier data analysis 12/12 to 3/15
- Inclusion
 - hospital encounter for PE (ICD-10=415.1) in the primary position
 - Dx test for PE first 2 days in hospital
 - Tx with rivaroxaban or parenteral anticoagulation/warfarin.
 - 1:1 propensity score matched riva to parenterally bridged warfarin patients.
- Results: N=3466

Coleman C. Clin App Throm Hemo. 2016; 1-8

PREMIER: PE Costs and LOS

- Riva vs Warfarin
 - 1.36-day <LOS (p<0.001)
 - \$2304 <costs (p<0.001)
- Re-admissions similar
 - VTE: 1.7% vs 1.6% (p=0.64)
 - MB: 0.2% vs 0.2% (p>0.99)
- LRPE analyses (n =1551)
 - Riva associated with
 - 1.01-day <LOS (p<0.001)
 - \$1855 <costs (p<0.001)
 - Readmission rates similar (p>0.56 for all)

Coleman C. Clin App Throm Hemo. 2016; 1-8

Mercury

- ▶ RCT, N=114
- ▶ Primary endpoint: Duration of hospitalization
- ▶ RCT: Rivaroxaban vs. SOC
- ▶ Other studies show:
 - ▶ Mean LOS shorter
 - ▶ Costs much less
 - ▶ SAE's similar

Discharge or admit? Emergency department management of incidental pulmonary embolism in patients with cancer: a retrospective study

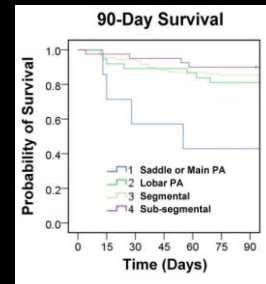
Srinivas R. Banala^{1,2}, Sai-Ching Jim Yeung¹, Terry W. Rice¹, Gielto C. Reyes-Gibby¹, Carol C. Wu³, Knox H. Todd^{1,4}, W. Frank Peacock⁵ and Kumar Alagappan^{1*}

- ▶ Retrospective Review of Incidental PE
- ▶ N= 193 patients;
 - ▶ 135 (70%) discharged, 58 (30%) admitted
- ▶ 189 (98%) ED anticoagulation
- ▶ 170 (90%) LMWH

Banala SR. International J of EM (2017) 10:19

Incidental PE

- The 30-day survival = 92%
 - 99% of D/C'd
 - 76% of admitted
- Dead within 30 days
 - 43% saddle emboli
 - 11% main or lobar
 - 6% segmental
 - 5% subsegmental



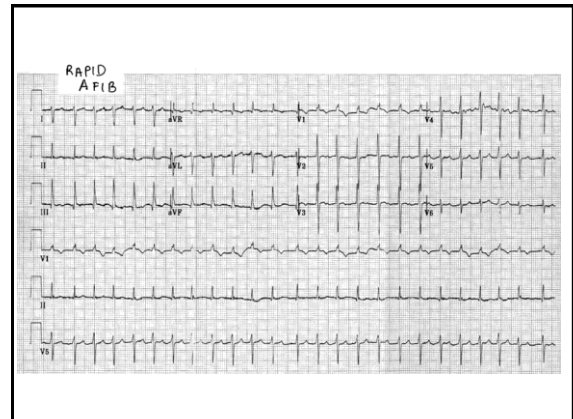
Banala SR. International J of EM (2017) 10:19

CASE 2:

- Sydney Clotier
- 32 years old
- Presents with "fluttering in her chest, SOB, denies CP.
- Started 2hrs PTA while washing dishes
- PMHx: HTN, DM
- SH: Mother of 3, non-smoker

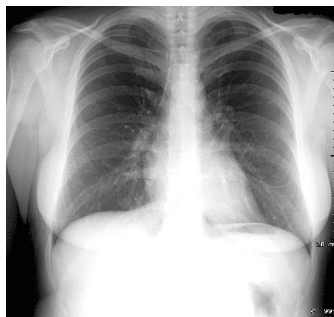


- PE: BP 147/82, HR 147, RR 18, T37, O2 sat 94%
- Neck: No jvd Lungs: CTA
- HR: irreg irreg Ext: No edema



Labs

- K 3.9
- Bicarb 25
- Tnl 0.01
- U/A negative
- WBC 8.0
- Hgb 13.2
- Plt 154k
- D-dimer negative
- INR 1
- TSH normal
- UCG negative

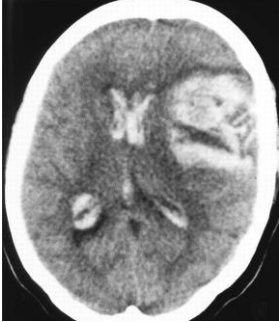


ED Course

- Metoprolol
 - 5mg ivp
 - 10 mins later HR 97bpm
- Anticoagulation
 - Lovenox
 - Started warfarin
- Discussed with internist who will follow up in 5 days
 - Discharged on
 - Warfarin 10 mg/day x 5 days
 - Lovenox 60U subq qd
 - Atenolol 25mg qd



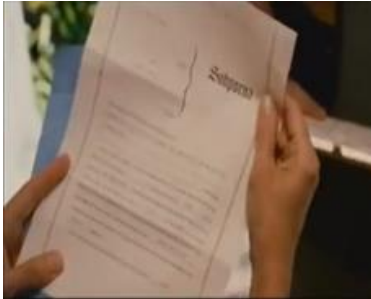

- 4 days later
 - Husband finds his wife unresponsive
 - EMS called
- BP 240/140, HR 117, RR 9, T38
- Neck supple, -jvd
- Lungs CTA
- GCS 5
- Decoriticates to pain
- Head CT orderd



Hospital course

- Intubated
- Receives Kcentra 15 minutes after CT results
 - INR 1.0 reversed at repeat sample 15 minutes later
- Admitted to NICU
 - Unresponsive to therapy
- 3 days later is pronounced dead
- Donates heart, lungs, both kidneys, liver, skin, cornea, and selected bones

1 year later, guess what?

The husband wants to know why you gave his wife rat poison?

Isn't there something safer?

Prosecuting attorney

- The attorney agrees with the necessity of treatment, and the disposition of the patient.
- However, he claims that his client's wife is dead as a result of the emergency physician violation of the standard of care by using a known dangerous drug despite the availability of clearly safer alternatives.
- That the use of this drug was proximal and causal to his clients wife's injury, and asks for 10 million in damages.

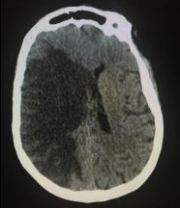
AF Significantly Increases the Risk and Severity of Stroke

AF affects ~2.7 to ~6.1 million Americans, significantly increasing their risk of stroke by ~5-fold^{1,2}

Strokes in patients with AF tend to recur or be more disabling or fatal¹⁰⁰

In the United States:

- ◆ Someone dies of a stroke about once every 4 minutes
- ◆ Stroke is a leading cause of serious long-term disability
- ◆ The direct and indirect cost of stroke was \$33 billion (2011-2012)
- ◆ Admissions for ischemic stroke averaged ~\$1600 per day, while admissions for hemorrhagic stroke averaged ~\$2300 per day



CHADS₂

Parameter	Points
CHF	1
HTN	1
Age > 75y	1
DM	1
H/O CVA/TIA	2

CHADS₂

Risk without anticoagulation

Recommend anticoagulation if score ≥ 2

Points	1 year % CVA risk
1	1.9
2	2.8
3	4
4	5.9
5	8.5
6	12.5

CHA₂DS₂-VASc vs CHADS₂

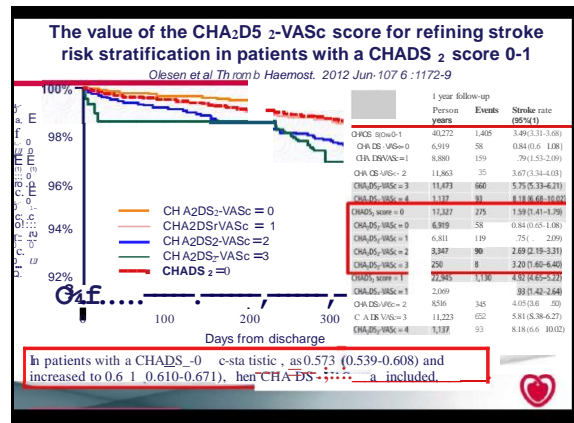
- 73,538 patients with NVAF
 - 23,730 intermediate risk patients by CHADS₂
 - recategorized **92.7%** as high risk by CHA₂DS₂-VASc
- 16,406 low risk by CHADS₂
 - recategorized **39.5%** as intermediate and **21.7%** as high risk by CHA₂DS₂-VASc
- CHA₂DS₂-VASc is much better in measuring stroke risk
 - Found that age, female and vascular disease weighted differently than other risk factors as well

CHA₂DS₂-VASc

* Not a mistake, had less patients in category

Score	% CVA risk/yr
0	0.0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8*	6.7
9	15.2

Vipert et al. European Guidelines



Warfarin-Associated ICH and Major Hemorrhage

- Annual risk of a major bleeding rate is 3.36%
- Annual hemorrhagic stroke rate is 0.38 - 1.0%
- ED visits for hemorrhage-related events from anticoagulants and antiplatelet agents²
 - 60,575 ED visits per year for warfarin
 - 7,654 ED visits per year for antiplatelet agents
- Most events occur at an INR between 2.0 and 3.5 (ie, within the conventional therapeutic range)³

1. Connolly SJ, et al. *N Engl J Med.* 2009;361(12):1139-1151.
2. Shahab N, et al. *Arch Intern Med.* 2010;170(12):1926-1933.
3. Angilleri M, et al. *Mayo Clin Proc.* 2007;82(1):82-92.

NVAF Registration Trials: Safety and Efficacy vs Warfarin

	MB	ICH	GIB	MI	CVA/SEE
RE-LY (Dabig) n=18,113	RR 0.93 (0.81-1.07)	RR 0.40 (0.27-0.60)	RR 1.50 (1.19-1.89)	RR 1.38 (1.00-1.91)	HR 0.66 (0.53-0.82)
ROCKET (Rivaroxaban) n=14,264	HR 1.04 (0.90-1.20)	HR 0.67 (0.47-0.93)	RR 1.46 (p<0.001)	HR 0.81 (0.63-1.06)	HR 0.88 (0.75-1.03)
ARISTOTLE (Apix) n=18,201	HR 0.69 (0.60-0.80)	HR 0.42 (0.30-0.58)	HR 0.89 (0.70-1.15)	HR 0.88 (0.66-1.17)	HR 0.79 (0.66-0.95)

CHADSVASC: CVA & MB Risk

Variable	Score
None	0
CHF	1
HTN	2
Age ≥75	3
DM	4
CVA/TIA	5
Vasc ds	6
Age 65-75	7
Sex	8
All	9

- > 10 million DOD records
- > NVAf, rivaroxaban from 1/1/13 to 6/30/15
- > N = 44,793
- > Overall MB rate = 2.84 (CI 2.69 to 3.00) **per 100 person-years**

Lip YH. Stroke. 2010;41:2731-2738; Peacock WF. Ann EM; 2017:


CHADSVASC: CVA & MB Risk

Variable	SCORE	Annual CVA risk	Annual MB Risk	Annual MB Fatality Risk
None	0	0%	0.003%	0.001%
CHF	1	1.3%	0.007%	0.004%
HTN	2	2.2%	0.010%	0.009%
Age ≥75	3	3.2%	0.018%	0.009%
DM	4	4%	0.032%	0.009%
CVA/TIA	5	6.7%	0.054%	0.001%
Vasc ds	6	9.8%		
Age 65-75	7	9.6%		
Sex	8	6.7%		
All	9	15.2%		

Lip YH. Stroke. 2010;41:2731-2738
Peacock WF. Ann EM; 2017:

FALLS vs Anticoagulation in AF

Risk of TBI/ICH on anticoagulation



Risk of CVA from not being anticoagulated

Equipoise: 295 falls per year

Mon-Don-Hing B. Arch IM 159; 677-85, 1999

ROCKET AF Enrolled a Population at Moderate to High Risk of Stroke

	ROCKET AF: (N=14,264) XARELTO®	ARISTOTLE: (N=18,201) Eliquis®	RE-LY: (N=18,113) Pradaxa®	ENGAGE AF: (N=21,105) Savaysa®
CHADS ₂ score (mean)	3.5	2.1	2.1	2.8
CHF, %	63	35	32	57
Hypertension, %	91	87	79	94
Age ≥75 years, %	44	31	40	40
Diabetes mellitus, %	40	25	23	36
Prior Stroke/TIA/SE, %	55	19	20	28

◆ These trials were conducted with different designs and evaluated different populations, so direct comparisons of their results cannot be made

Randomized Controlled Trial (RCT)

- **Almost unbeatable for determining efficacy**
- **BUT ONLY IF.....** a therapeutic study is feasible
 - No ethical problems
 - Enough patients can be included
 - Affordable
 - Feasible follow-up period

Steil Vs, Kid International (2007) 72, 539-542

Trouble in the RCT world.....

- Entry by strict inclusion & exclusion criteria
 - May be very dissimilar to the real patient population
 - Many RCTs include <10% of all screened patients

Brett W. Card Surg Today;2005;2:43-55

- Commonly exclude very ill, very old, and those with multiple comorbidities (rarely an RCT an all comers study)

- Meta-analyses do not solve this problem
- they are based on the RCTs
- It is not an uncommon for RCT's to be
- Underpowered, use composite endpoints
- Challenged by therapeutic crossover

J Thoracic Cardiovasc Surg 132, (1), 2006, 5-7

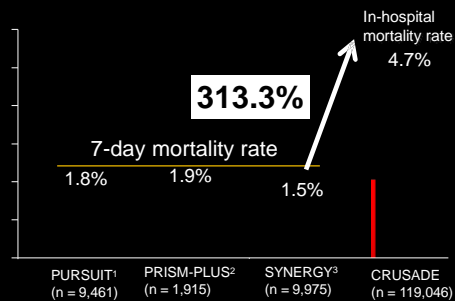
Efficacy vs Efficiency

- Efficacy (RCT)
 - Does it work?
 - Phase 1, 2, and 3 FDA studies
- Efficiency (PMSS)
 - Does it work in REAL LIFE?
 - Mucomyst? Kayexalate?
 - Phase 4 FDA studies
- Is this important?
 - Vioxx, Nesiritide, Glitazone's

What can a registry tell us that an RCT cannot?

- What do we get from a PMSS?
 - True outcomes
 - Get data that is otherwise unobtainable
 - Unethical (delayed in Tx in registry is effectively the placebo arm of an RCT)
 - Data that is otherwise too costly
- Provide feedback for quality improvement

CRUSADE vs. ACS Clinical Trials:



1. The PURSUIT Trial Investigators. N Engl J Med 1998. 2. The PRISM-PLUS Study Investigators. N Engl J Med 1998. 3. The Synergy Study JAMA 2004. CRUSADE cumulative data through 9/04

Why the difference?

- Who gets “less care” than in a RCT?
 - Women (50% of the USA)
 - Elderly (25% of the USA)
 - Underinsured (20% of the USA)
 - Coexistent disease (most of the elderly)
 - Renal failure
 - Diabetics
 - Minorities (becoming the USA majority)

Major Bleeding in NVAF and DM

- ~10 million DOD EMRs
- 1/1/13-6/30/15
- NVAF on Rivaroxaban
- Cunningham algorithm

Tamayo C, Peacock ACC 2016

Post Marketing Surveillance Study

- ▶ 10 million DOD records
 - ▶ NVAF and received rivaroxaban
 - ▶ from January 1, 2013, to June 30, 2015.
 - ▶ Stratified by CHA2DS2-VASc scores
 - ▶ N = 44,793
- Overall major bleeding incidence rate = 2.84 (95% CI 2.69 to 3.00) per 100 person-years

Major Bleeding in NVAF and DM

RESULTS		Diabetics		Non-Diabetics	
		MB Cases N=472	Patients without MB N=11,567	MB Cases N=821	Patients without MB N=31,933
Mean Age (SD), years		76.7 (7.7)	75.4 (8.6)	79.9 (7.7)	76.5 (10.5)
Male, n (%)		279 (59.1)	7,056 (61.0)	387 (47.1)	17,403 (54.5)
MB Incidence Rate ^a per 100 person-years (95% CI)		3.68 (3.37-4.03)		2.51 (2.34-2.69)	
Gastrointestinal		n=422	3.30 (3.00-3.63)	n=694	2.12 (1.97-2.28)
Intracranial	MB Rate per site, per 100 person-years	n=24	0.19 (0.13-0.28)	n=81	0.25 (0.20-0.31)
Other sites		n=26	0.20 (0.14-0.30)	n=46	0.14 (0.11-0.19)
Fatal MB Incidence Rate per 100 person-years (95% CI)		n=11	0.09 (0.05-0.16)	n=30	0.09 (0.06-0.13)

Tamayo C, Peacock ACC 2016

Effectiveness and Safety of Apixaban, Dabigatran, and Rivaroxaban Versus Warfarin in Patients With Nonvalvular Atrial Fibrillation and Previous Stroke or Transient Ischemic Attack

Craig I. Coleman, PharmD; W. Frank Peacock, MD; Thomas J. Bunz, PharmD, PhD; Mark J. Alberts, MD

- Truven MarketScan claims
 - Combined commercial insurance + Medicare
- 170 million covered lives
- Jan 2012 to June 2015

Coleman C, Peacock WF Stroke. 2017. DOI: 10.1161/STROKEAHA.117.017474

Market Scan Analysis

- Entry Criteria
 - Adults newly initiated on OAC
 - ≥2 Dx codes for NVAF
 - Hx/o ischemic CVA/TIA
 - ≥180 d of continuous medical & Rx benefits before anticoagulation initiation

Coleman C, Peacock WF. Stroke. 2017. DOI: 10.1161/STROKEAHA.117.017474

Market Scan Analysis

- 3 analyses, 1:1 propensity score–matched grps
 - apix v warfarin (n=2514)
 - dabi v warfarin (n=1962)
 - riva v warfarin (n=5208)
- Followed till composite end point
 - ischemic CVA, ICH or major bleed
 - Switch or d/c of index OAC
 - insurance disenrollment, or end of follow-up.
- Mean follow-up was 0.5 to 0.6 y

Coleman C, Peacock WF. Stroke. 2017. DOI: 10.1161/STROKEAHA.117.017474

NOAC vs Warfarin

- Primary endpoint (ischemic CVA or ICH):
 - Apix HR 0.70 (95% CI 0.33–1.48)
 - Dabi HR 0.53 (95% CI 0.26–1.07)
 - Riva HR 0.45 (95% CI 0.29–0.72)
- MB:
 - Apix HR 0.79 (95% CI 0.38–1.64)
 - Dabi HR 0.58 (95% CI 0.26–1.27)
 - Riva HR 1.07 (95% CI 0.71–1.61).
- ICH 0.16 to 0.61/100 pt-y
 - No difference for any NOAC vs warfarin

Coleman C, Peacock WF. Stroke. 2017. DOI: 10.1161/STROKEAHA.117.017474

The Trouble with Observational studies

- To compare populations, MUST be similar
 - Must adjust for KNOWN AND RECORDED differences
 - E.G., the propensity of a certain condition to receive a specific treatment
 - Correct by multivariate analysis
- Major limitation of observational studies
 - Can't risk adjust for unobserved or unknown confounders
 - May suffer coding errors and missing data.

Adamina M. Propensity score and the surgeon. Br J Surg. 2006.

Society of Cardiovascular Patient Care AF recommendations for ED discharge

• Patient with AF presents to the ED, may be discharged from the ED if:

- BP stable
- HR controlled (ideally < 100 bpm)
- Strategy in place for prevention of thromboembolism
 - UFH/Lovenox-Warfarin, Dabigatran, Rivaroxaban, Apixabin
- Symptoms managed
- No clinical precipitant requiring inpatient management
- Follow up care established
- Patient education provided

Summary

- Need to consider both RCT AND PMSS data
- DVT = probably discharge
- PE = 1/3 may go home
- AF = consider discharge if rate controlled, AMI ruled out, normal echo and labs, AND appropriately anticoagulated
- If want RCT results, need to use RCT entry criteria and dosing
- Warfarin?
 - Valves and renal failure