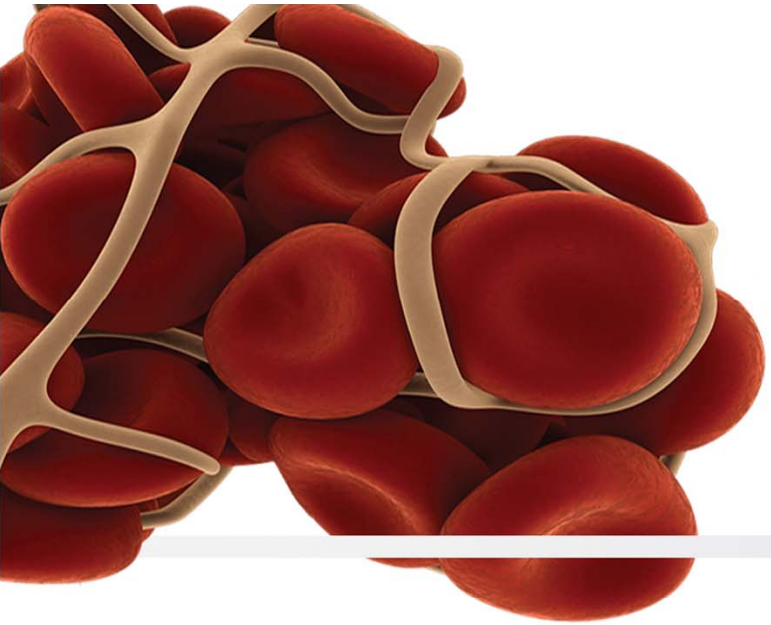

PERSPECTIVE FROM THE ED: REAL WORLD SAFETY AND EFFICACY DATA REFLECTS CLINICAL TRIALS

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The RCT: The Holy Grail

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

Stel Vs, Kid Internatonal (2007) 72, 539–542

Your patient vs. my patient

Jane Johnson

Skinny Jackson

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

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

Major Bleeding in NVAF and DM

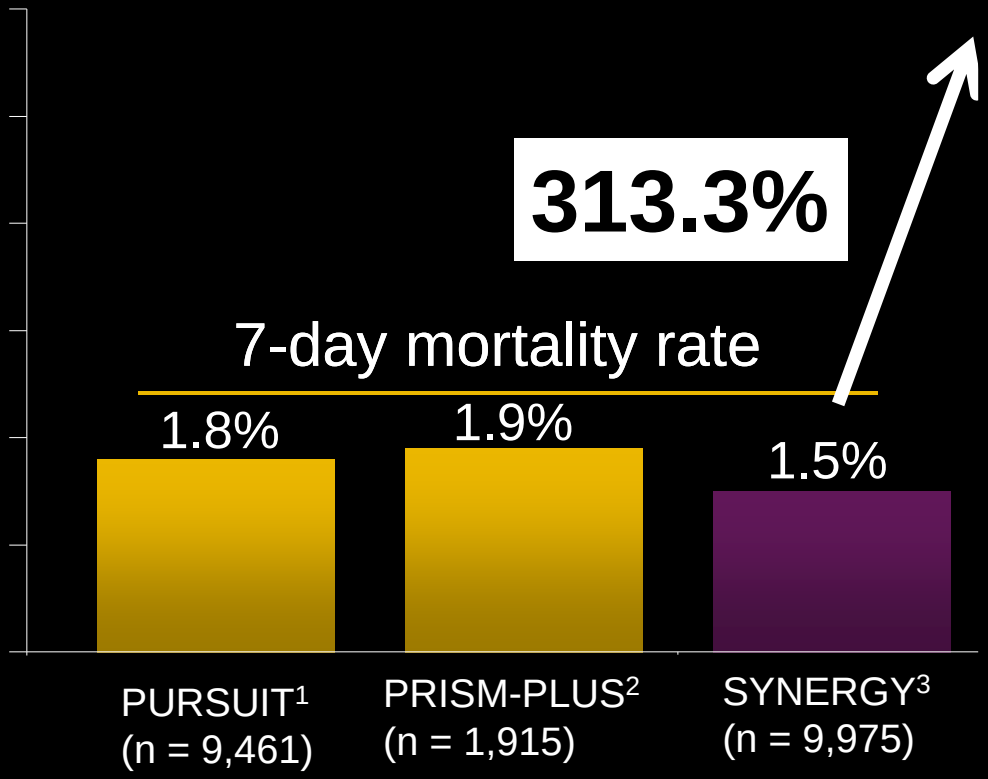
RESULTS		Diabetics		Non-Diabetics	
		MB Cases N=472	Patients without MB N=11,567	MB Cases N=821	Patients without MB N=31,933
Mean Age (SD), years		76.7 (7.7)	75.4 (8.6)	79.9 (7.7)	76.5 (10.5)
Male, *n* (%)		279 (59.1)	7,056 (61.0)	387 (47.1)	17,403 (54.5)
MB Incidence Rate[a] per 100 person-years (95% CI)		3.68 (3.37-4.03)		2.51 (2.34-2.69)	
Gastrointestinal	MB Rate per site, per 100 person-years	n=422	3.30 (3.00-3.63)	n=694	2.12 (1.97-2.28)
Intracranial		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

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)

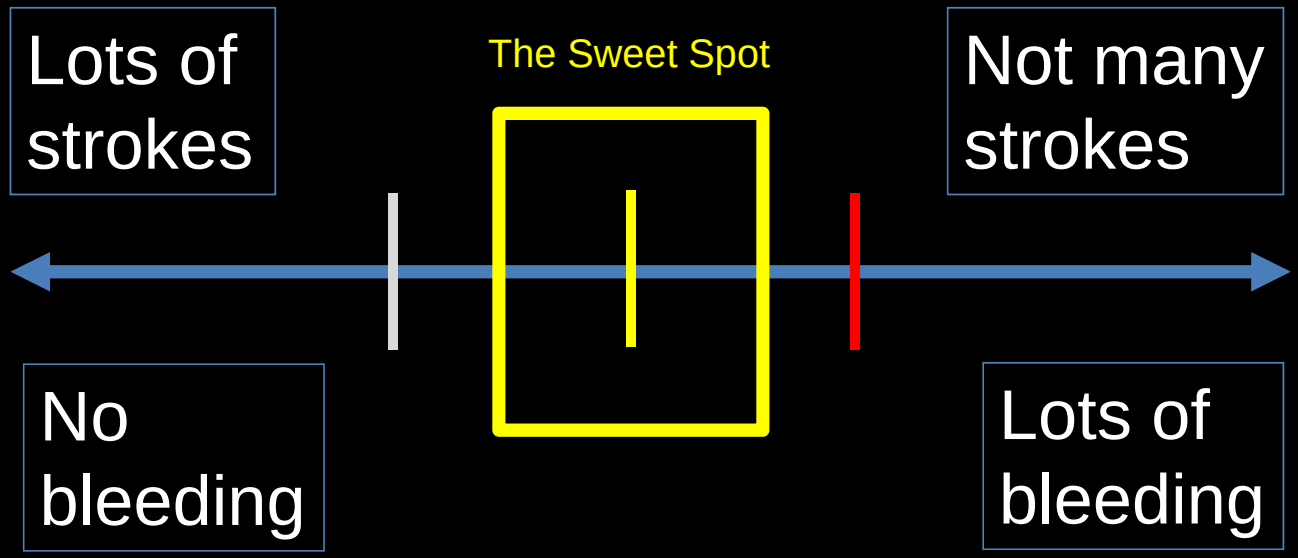
Registration Trials: Safety

	N= k	MB	ICH	GIB	MI
RE-LY (Dabi)	18	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)
ROCKET (Riva)	14	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)
ARISTOTLE (Apix)	18	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)
Vs. Warfarin		2 Similar 1 Less	3 Less	2 More 1 Similar	1 More 2 Similar

Anticoagulants

- If they don't make you bleed, they don't work….
  - That is the point.
  - I can make any anticoagulant safe
    - All I have to do is make it so it doesn't work
- Dr's HATE bleeding, don't mind stroke
  - Act of commission vs an act of god

The Risk:Benefit Continuum



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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

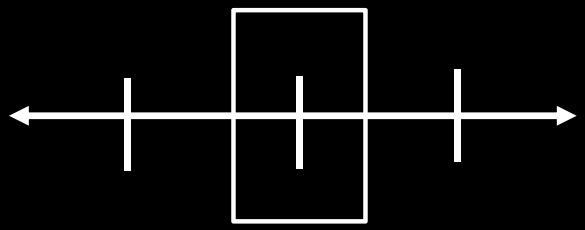
      Correct by multivariate analysis
- Major limitation of observational studies
  - Can't risk adjust for unobserved or unknown confounders
  - May suffer coding errors and missing data.

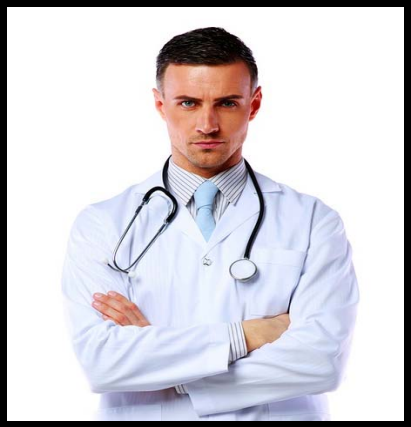
Adamina M. Propensity score and the surgeon. *Br J Surg. 2006.*

	N =k	MB	ICH	GIB	MI	CVA/ SEE
RE-LY (Dabi)	18	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)
US Medicare	38k yrs	HR 0.97 (0.88-1.07)	HR 0.34 (0.26-0.46)	HR 1.28 (1.14-1.44)	HR 0.92 (0.78-1.08)	0.80 (0.67–0.96)
ROCKET (Riva)	14	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)
PMSS	27k pts	IR 2.86 (2.61-3.13)	IR 0.22 (0.15-0.30)	IR 2.53 (2.30-2.78)	NR	NR
ARISTOTLE (Apix)	18	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)
Humedica	27	HR 0.75 (0.63-0.88)	NR	NR	NR	NR

IR = incidence/100 pt yrs

I don’t want to be “that” Dr.





Dr. David “Don’t Blame Me” Jones

I’m really worried about being the doc wrote the Rx that caused a bleed

Dr. Tommy “Treat it to Death” Thompson

I really don’t want to be the doc who let my patient have a stroke

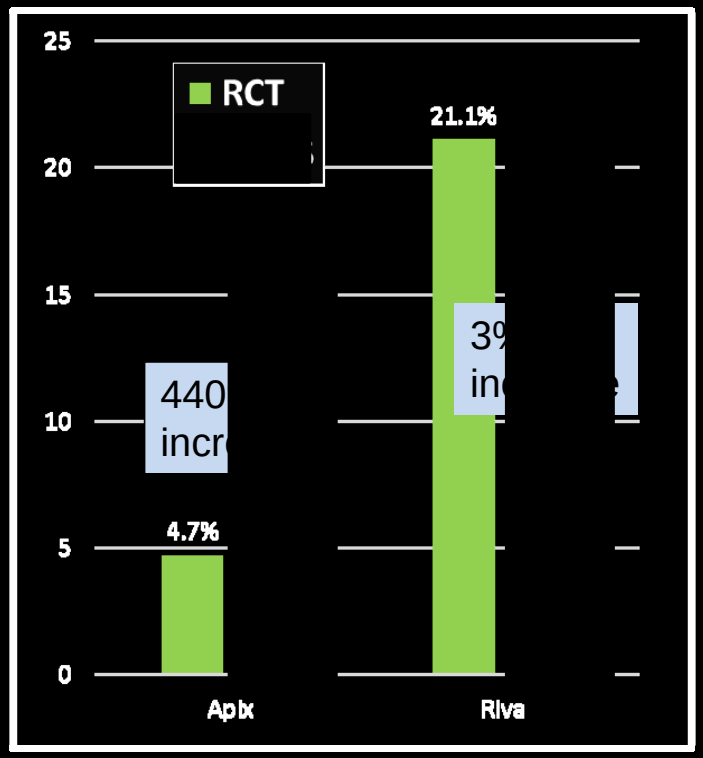
USA Cardiologists & Reduced Dose DOAC

Bleeding sensitive? YES

Stroke?….. Not So Much

- I.M.S. LifeLink dataset
  - 3.6 M Cardiologist's Rx
  - 9/19/14–9/11/15

Dr. David "Don't Blame Me" Jones



Nguyen E, Peacock WF. Current Medical Research and Opinion 32(7):1-13; 2016

Effectiveness & safety of reduced DOAC dose w/o renal impairment.

- 12,593 NVAF. No PI renal indication for dose reduction
  - GOT REDUCED DOSE ANYWAY……
    - 15.4% of Apix, 14.9% of Dabi, 8.2% of Riva

- Reduced dose Apix and Dabi pts:
- More CVA (HR 2.64; 1.01-6.89)
  No MB increase (HR 1.22; 0.67-2.23)

- Reduced Riva: No relationship btwn dosing and stroke or MB risk

Yao X, Value in Health 2016;19:A2.

DOAC PMSS Comparisons

If you can’t compare RCTs, what makes it appropriate to compare more biased evaluations?

Dabigatran vs. Rivaroxaban

- D=52,240, R=66,65

	CVA	ICH	MB	Mort	>75 + CHADS > 2
Riva vs. Dabi	0.81 (0.65-1.01)	1.65 (1.20-2.26)	1.48 (1.32-1.67)	1.15 (1.00-1.32)	1.31 (1.10-1.57)

More Rx of Riva by cardiologists
Less Rx of Riva by Family Practice
What does this mean?

Graham DJ. JAMA Intern Med. doi:10.1001/jamainternmed.2016.5954

Dabi v. Riva

Outcome	Crude (Unadjusted) Incidence Rate per 1000 Person-years (No. of Events)		
	Dabigatran (n = 52 240)	Rivaroxaban (n = 66 651)	
Primary Outcomes			
Thromboembolic stroke	9.7 (150)	7.7 (156)	−1.8 (−3.8 to 0.1)
Intracranial hemorrhage	3.7 (58)	5.8 (118)	2.3 (0.9 to 3.7)
Major extracranial bleeding event	26.6 (413)	39.4 (796)	13.0 (9.2 to 16.7)
Gastrointestinal	23.3 (362)	32.5 (656)	9.4 (6.0 to 12.8)
Mortality	22.2 (346)	24.7 (500)	3.1 (−0.1 to 6.3)
Secondary Outcomes			
All hospitalized extracranial bleeds	39.2 (608)	54.0 (1091)	15.1 (10.7 to 19.6)
Acute myocardial infarction	12.9 (200)	11.0 (223)	−1.7 (−4.0 to 0.6)

Graham DJ. JAMA Intern Med. doi:10.1001/jamainternmed.2016.5954

NVAF: Riva vs Dabi

N=18,249

	Warfarin 9564 (52.4%)	Dabi 5976 (32.7%)	Riva 2709 (14.8%)
MB	3.9 (3.6–4.4)	4.2 (3.7–4.7)	4.1 (3.0–5.3)
ICH	0.71 (0.56–0.90)	0.4 (0.18–0.87)	0.27 (0.10–0.80)
GIB	1.88 (1.62–2.20)	2.98 (2.4–3.5)	2.39 (1.6–3.5)

Conclusion: Similar MB rates with dabi 150 mg & 110 mg, & riva vs W

Ellis MH. EJIM 33 (2016) 55–59

Danish NVAF Study

- Danish registry (2011–15)
- N=43,299 OAC naïve AF
  - VKA (42%), Dabi (29%)
  - Riva (13%), Apix (16%)
    - Mean CHA2DS2-VASc similar (2.9-3.1)
    - 1054 stroke/TE, 261 ICH

1 Yr VKA absolute risk

CVA/TEE 2.01%
(1.80% to 2.21%)

ICH 0.60%
(0.49% to 0.72%)

	Absolute Risk Differences vs. VKA		
	Dabi	**Riva**	**Apix**
Stroke /TE	**0.11%** (-0.16% to 0.42%)	**0.05%** (-0.33% to 0.48%)	**0.45%** (-0.001% to 0.93%)
ICH	**-0.34%** (-0.47% to - 0.21%)	**-0.13%** (-0.33% to 0.08%)	**-0.20%** (-0.38% to - 0.01%)

Staerk, L. EHJ (2016) 0, 1–9

RCT vs Registry Summary

- Need both types of data to understand effect of interventions on outcomes
- Must consider limitations inherent in an RCT and the bias inherent in a PMSS