Jedi Training 101:

Mind-tricks & Evidence -Based Approaches to Combating Clinical Controversies in Anticoagulation Therapy

Kelly Rudd, PharmD, FCCP, BCPS, CACP
Basset Medical Center, Cooperstown, NY

Learning Objectives

Pharmacist Learning Objectives

- Identify patient populations for whom evidence-based anticoagulation guidelines and literature lack clarity.
- Evaluate available evidence for anticoagulation treatment in special patient populations (eg. patients at extremes of weight, with hypercoaguable states, impaired or variable renal function, etc.)
- Utilize clinical reasoning skills to assimilate anticoagulation recommendations to create a patient-specific treatment plan.

Pharmacy-Technician Learning Objectives

- Identify patient populations for whom evidence-based anticoagulation guidelines and literature lack clarity.
- Identify patient populations who may benefit from anticoagulation therapy.
- Identify patient populations who anticoagulation therapy may be unsafe.
- Utilize clinical reasoning skills to aid in flagging anticoagulated patients who may need further review and care plan assessment.

DISCLAIMERS

Advisory Board: Portola Pharmaceuticals

No other conflicts of interest to disclose.

"These ARE the ~~Droids~~ Guidelines You're Looking For…"

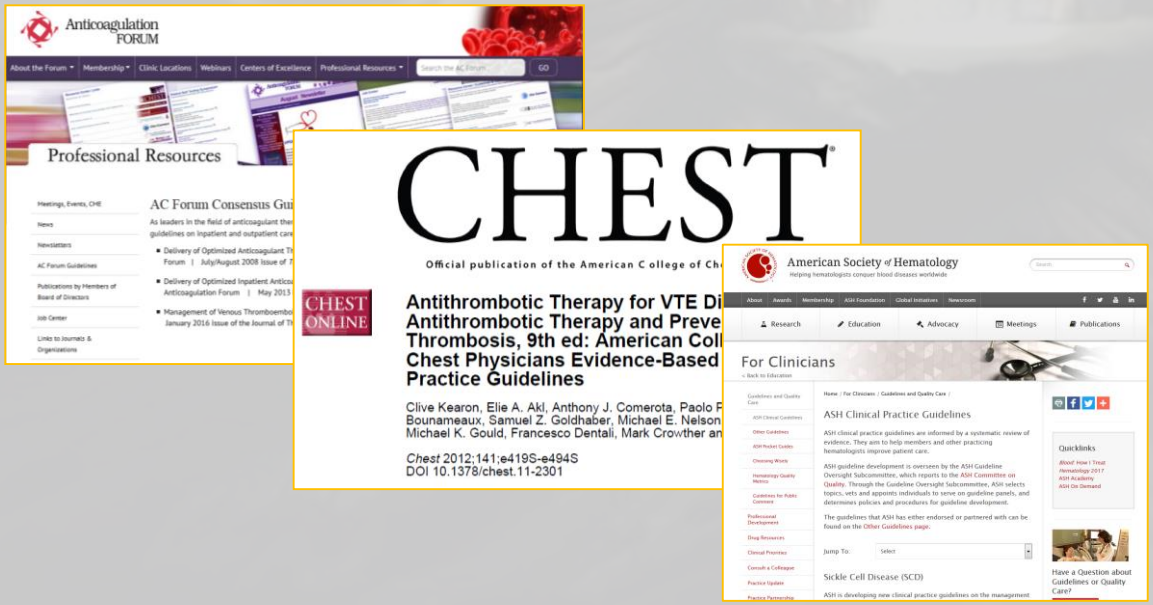
"THESE ARE THE ~~DROIDS~~ GUIDELINES YOU'RE LOOKING FOR…"

Management of Venous Thromboembolism: Clinical Guidance from the Anticoagulation Forum. Journal of Thrombosis & Thrombolysis Volume 41, Issue 1, January 2016. https://link.springer.com/journal/11239/41/1/page/1.

Antithrombotic Therapy and Prevent of Thrombosis, 9th Ed:
American College of Chest Physicians Evidence-Based Clinical Practice Guidelines 2012; Chest 141(2) (Suppl).

Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report.
CHEST 2016; 149(2):315-352. https://doi.org/10.1016/j.chest.2015.11.026

The American Society of Hematology Clinical Practice Guidelines.
http://www.hematology.org/Clinicians/Guidelines-Quality/Guidelines.aspx



"These ARE the ~~Droids~~ Guidelines You're Looking For…"

What's missing?

- extremes of weight
- impaired or variable renal function
- the elderly
- (potentially) active cancer
- how/when do you monitor DOAC therapy

What do we know?

Martin K, et al. *J Thromb Haemost* 2016; 14: 1308-13

What do we know?

- Apixaban is the only DOAC to have specific considerations for weight.
- Large, well controlled randomized trials have not been done to evaluate the safety and efficacy of DOACs in the obese population
- Modest numbers of patients were included in the Phase III clinical trials
- Definitions of obesity varied widely from trial to trial and not all trials conducted formal safety and efficacy evaluations in the obese population
- None of the trials report the number of patients with BMI > 40 kg/m^2

Martin K, et al. *J Thromb Haemost* 2016; 14: 1308-13

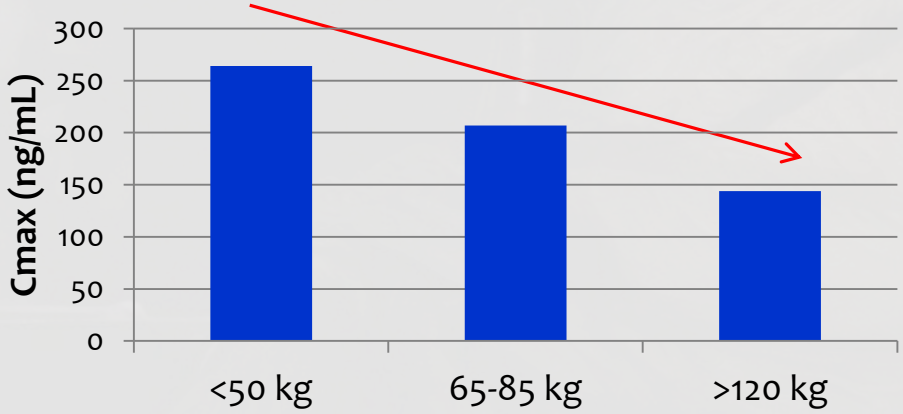
Weight distribution in phase III trials

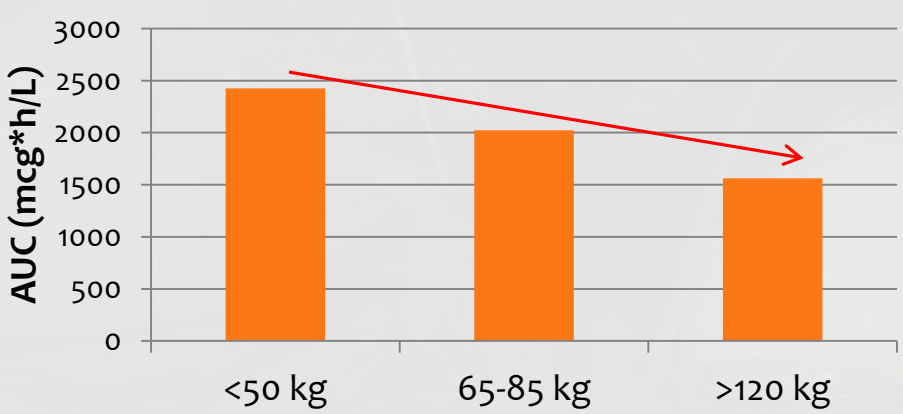
Medication	Clinical Trial	Weight Classifications	Number (%)
Dabigatran	RE-COVER 1	≥ 100 kg BMI ≥ 35	502/2539 (20) 306/2539 (12)
	RE-COVER 2	> 100 kg BMI > 35	438/1280 (34.2) 302/1280 (23.6)
	RE-LY	≥ 100 kg	3099/18,113 (17.1)
	RE-MEDY	≥ 100 kg	299/1430 (20.9)
	RE-SONATE	≥ 100 kg	122/681 (17.9)
Rivaroxaban	EINSTEIN DVT	> 100 kg	245/1731 (14.2)
	EINSTEIN PE	> 100 kg	345/2419 (14.3)
	EINSTEIN EXTENSION	> 100 kg	85/602 (14.1)
	ROCKET-AF	> 90 kg BMI > 35	2035/7131 (28.5) 972/7131 (13.6)
Apixaban	AMPLIFY	≥ 100 kg BMI > 35	522/2691 (19.4) 349/2691 (13.0)
	ARISTOTLE	BMI ≥ 40	1006/17,913 (5.6)*
Edoxaban	HOKUSAI VTE	> 100 kg	611/4118 (14.8)

Connolly SJ, et al. N Engl J Med 2009;361:1139-51; Schulman S et al. *N Engl J* Med 2009; 361: 2342-52. Schulman S et. al. Circulation. 2014; 129: 764-72. Schulman S et. al. *N Engl J Med.* 2013 Feb 21;368(8):709-18; Einstein Investigators. *N Engl J Med.* 2010;363:2499-2510. Einstein-PE Investigators. *N Engl J Med.* 2012;366:1287-87. Agnelli G et al. *N Engl J* Med 2013; 369:799-808. Patel MR et al. *N Engl J Med.* 2011;365(10):883-891. Sandhu RK, et. a. *European Heart Journal* (2016) 37, 2869–2878, post hoc. HOKUSAI-VTE Investigators et al. *N Engl J* Med 2013; 369: 1406-15.

What happens pharmacoKINETICALLY (apixaban)?

Apixaban	<50 kg	65-85 kg	>120 kg
Cmax (ng/ml)	264	207	144
AUC (mcg*h/L)	2424	2024	1561
T ½ (hr)	15.7	12	8.8

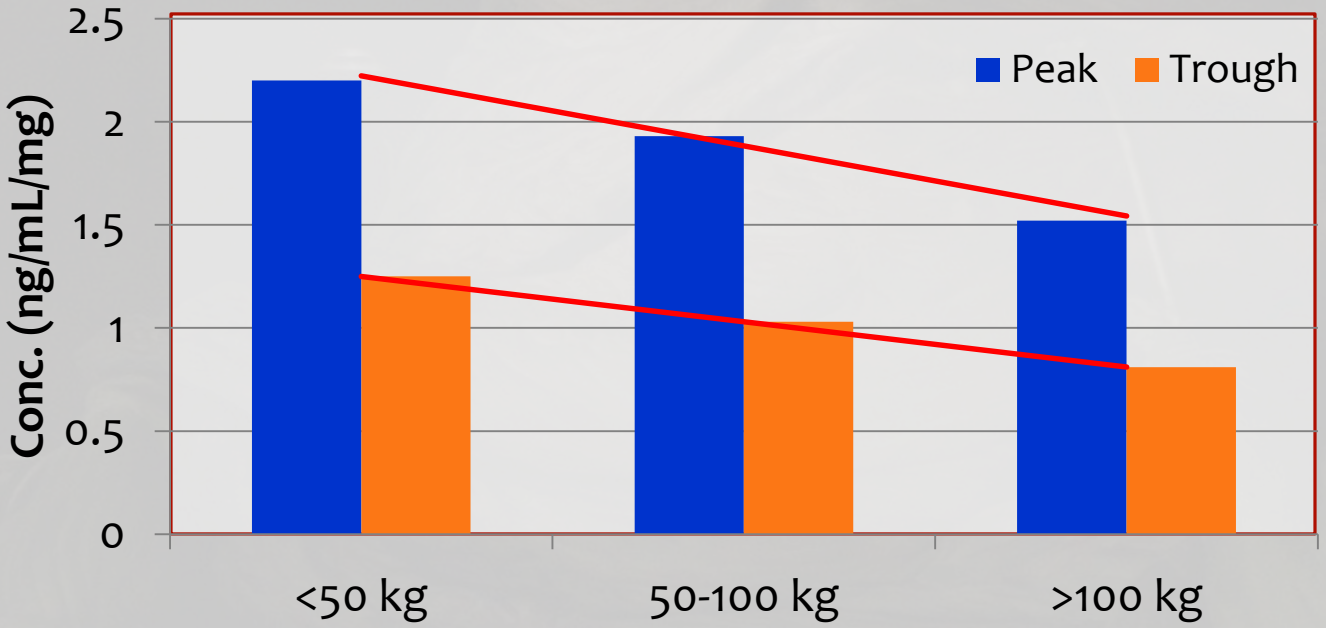




Upreti VV, et al. Br J Clin Pharmacol. 2013;76:908-16.

What happens pharmacoKINETICALLY (dabigatran)?

Dose normalized plasma concentration (ng/mL/mg) of total dabigatran by body weight (kg)



Gulseth MP, et. al. *Pharmacotherapy* 2011;31(12):1232–1249. Reilly PA, et. al. *J Am Coll Cardio* 2014;63:3218-8. Boehringer Ingleheim. Personal Communication. 11/7/14

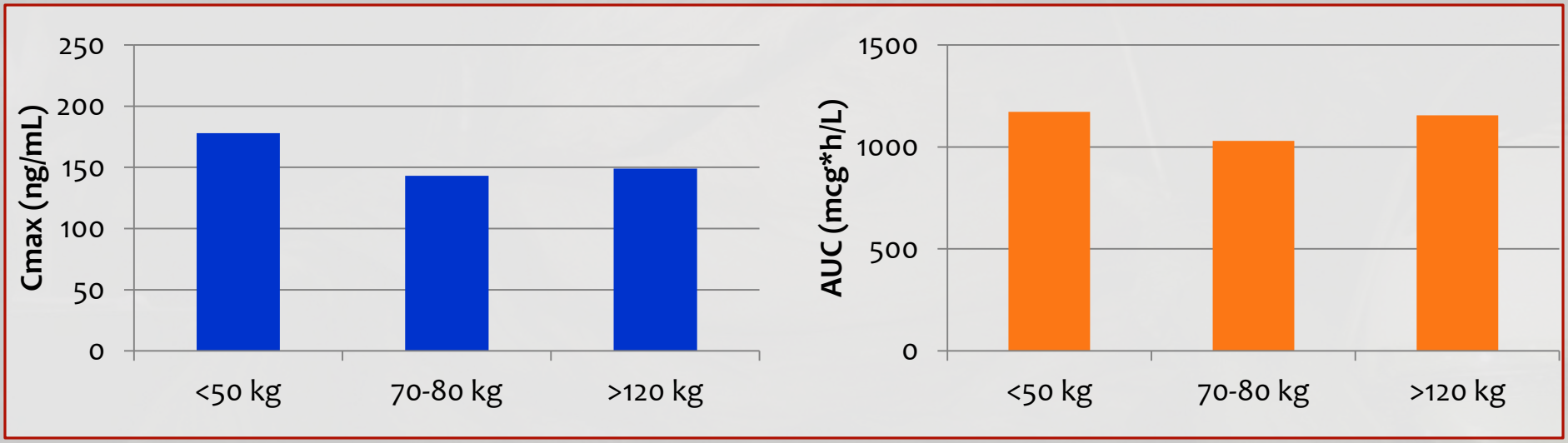
What happens pharmacoKINETICALLY (edoxaban)?

?

(No formal pharmacokinetic studies or data to share)

What happens pharmacoKINETICALLY (rivaroxaban)?

Rivaroxaban	<50 kg	70-80 kg	>120 kg
Cmax (ng/ml)	178	143	149
AUC (mcg*h/L)	1172	1029	1155
T ½ (hr)	9.6	7.2	7.3



Xarelto US Prescribing Information. Janssen Pharmaceuticals; 2015. Kubitza D, et al. *J Clin Pharmacol* 2007; 47: 218-26.

What happens pharmacoKINETICALLY (rivaroxaban)?

Influences of Obesity and Bariatric Surgery on the Clinical and Pharmacologic Profile of Rivaroxaban

Kenneth Todd Moore, MS,[a] Dino Kröll, MD[b]

[a]Medical Affairs – Cardiovascular & Metabolism, Janssen Pharmaceuticals, Inc, Titusville, NJ; [b]Department of Visceral Surgery and Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland.

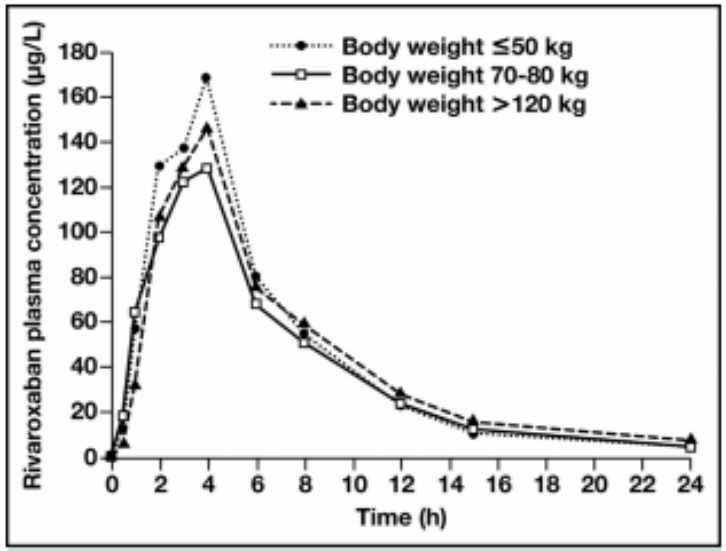
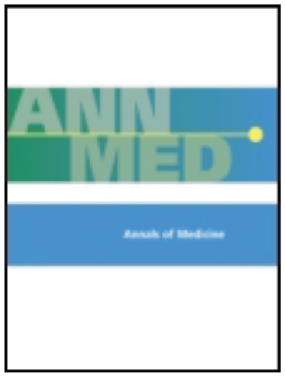


Figure 1 Mean rivaroxaban plasma concentration-time curve after administration of a single 10-mg oral dose. Each weight group included 12 healthy subjects. Reprinted from Kubitza et al (2007).[12]

The American Journal of Medicine, 130:9. September 2017.

What happens pharmacoDYNAMICALLY?



Annals of Medicine

ISSN: 0785-3890 (Print) 1365-2060 (Online) Journal homepage: http://www.tandfonline.com/loi/iann20

Effect of body weight on efficacy and safety of direct oral anticoagulants in the treatment of patients with acute venous thromboembolism: A meta-analysis of randomized controlled trials

Matteo Nicola Dario Di Minno, Roberta Lupoli, Alessandro Di Minno, Pasquale Ambrosino, Antonella Scalera & Francesco Dentali

Ann Med 2015; 47:1, 61-68.

Study Question: What is the effect of extreme body weight on the safety & efficacy of DOACs in acute VTE?

ORIGINAL ARTICLE

Effect of body weight on efficacy and safety of direct oral anticoagulants in the treatment of patients with acute venous thromboembolism: A meta-analysis of randomized controlled trials

Matteo Nicola Dario Di Minno, Roberta Lupoli, Alessandro Di Minno, Pasquale Ambrosino, Antonella Scalera & Francesco Dentali

Pages 61-68 | Received 21 May 2014, Accepted 23 Oct 2014, Published online: 09 Feb 2015

- **Design:** Systematic review & meta-analysis
- **Eligibility criteria:** RCTs of DOAC vs. VKA in treatment of acute VTE
- **Sources:** PubMed, Web of Science, Scopus, EMBASE

- **Outcomes:**

  Efficacy: Recurrent VTE & VTE-related death

  Safety: Major or Clinically Relevant Non-Major Bleeding

Ann Med 2015; 47:1, 61-68.

Study Question: What is the effect of extreme body weight on the safety & efficacy of DOACs in acute VTE?

Study	Low BW	Normal BW	High BW
RECOVER	< 50kg	50-100 kg	> 100kg
EINSTEIN	< 70 kg	70-90 kg	> 90kg
HOKUSAI	< 60 kg	60-100 kg	> 100 kg
AMPLIFY	< 60 kg	60-100 kg	> 100kg

Prevalence of High (> 90-100kg) Body Weight: 15.3 to 28.3%

Prevalence of Low (<50-70kg) Body Weight: 1.1 to 29.5%

Ann Med 2015; 47:1, 61-68.

Extremes of Weight

Efficacy:

High Body Weight

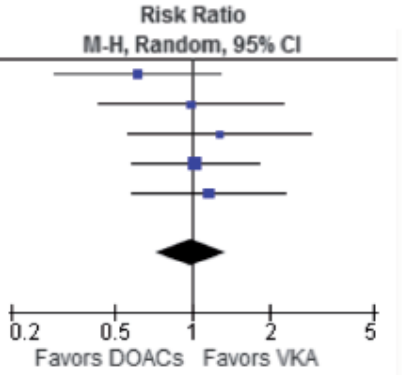
"Normal" Body Weight

Low Body Weight

(A)

Study or Subgroup	DOACs Events	DOACs Total	VKA Events	VKA Total	Weight	Risk Ratio M-H, Random, 95% CI
AMPLIFY	11	509	18	508	18.3%	0.61 [0.29, 1.28]
EINSTEIN-DVT	11	491	11	486	14.7%	0.99 [0.43, 2.26]
EINSTEIN-PE	13	683	10	672	15.0%	1.28 [0.56, 2.90]
HOKUSAI	22	611	23	654	30.5%	1.02 [0.58, 1.82]
RECOVER-I&II	18	438	14	394	21.4%	1.16 [0.58, 2.29]
Total (95% CI)		**2732**		**2714**	**100.0%**	**0.98 [0.72, 1.35]**
Total events	75		76			

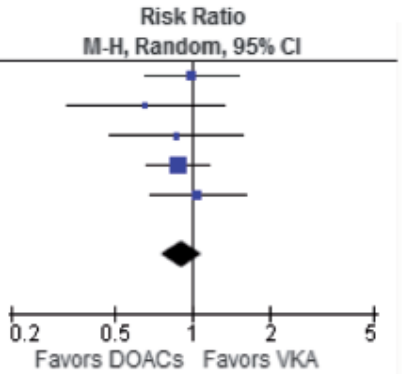
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.23$, df = 4 (P = 0.69); $I^2 = 0\%$
Test for overall effect: Z = 0.10 (P = 0.92)



(B)

Study or Subgroup	DOACs Events	DOACs Total	VKA Events	VKA Total	Weight	Risk Ratio M-H, Random, 95% CI
AMPLIFY	42	1870	43	1892	19.2%	0.99 [0.65, 1.50]
EINSTEIN-DVT	13	740	19	707	7.0%	0.65 [0.33, 1.31]
EINSTEIN-PE	20	1081	24	1119	9.9%	0.86 [0.48, 1.55]
HOKUSAI	93	2971	105	2936	45.2%	0.88 [0.67, 1.15]
RECOVER-I&II	42	2084	41	2127	18.7%	1.05 [0.68, 1.60]
Total (95% CI)		**8746**		**8781**	**100.0%**	**0.91 [0.75, 1.09]**
Total events	210		232			

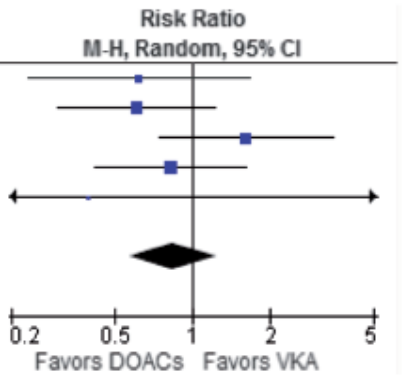
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.53$, df = 4 (P = 0.82); $I^2 = 0\%$
Test for overall effect: Z = 1.05 (P = 0.30)



(C)

Study or Subgroup	DOACs Events	DOACs Total	VKA Events	VKA Total	Weight	Risk Ratio M-H, Random, 95% CI
AMPLIFY	6	225	10	232	14.7%	0.62 [0.23, 1.67]
EINSTEIN-DVT	12	494	21	524	28.9%	0.61 [0.30, 1.22]
EINSTEIN-PE	17	653	10	621	23.9%	1.62 [0.75, 3.50]
HOKUSAI	15	524	18	519	30.9%	0.83 [0.42, 1.62]
RECOVER-I&II	0	26	1	31	1.5%	0.40 [0.02, 9.31]
Total (95% CI)		**1922**		**1927**	**100.0%**	**0.84 [0.57, 1.24]**
Total events	50		60			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 4.18$, df = 4 (P = 0.38); $I^2 = 4\%$
Test for overall effect: Z = 0.88 (P = 0.38)



Ann Med 2015; 47:1, 61-68.

Safety:

High Body Weight

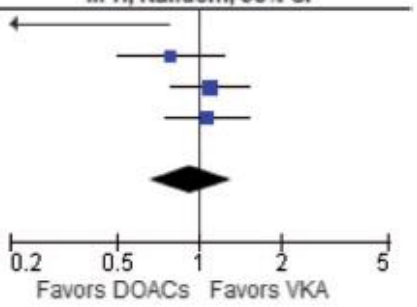
"Normal" Body Weight

Low Body Weight

(A)

Study or Subgroup	DOACs Events	DOACs Total	VKA Events	VKA Total	Weight	Risk Ratio M-H, Random, 95% CI
AMPLIFY	1	521	10	518	2.8%	0.10 [0.01, 0.77]
EINSTEIN-DVT	31	488	39	481	27.9%	0.78 [0.50, 1.23]
EINSTEIN-PE	68	683	61	670	35.7%	1.09 [0.79, 1.52]
HOKUSAI	54	611	54	654	33.6%	1.07 [0.75, 1.54]
Total (95% CI)		**2303**		**2323**	**100.0%**	**0.93 [0.65, 1.32]**
Total events	154		164			

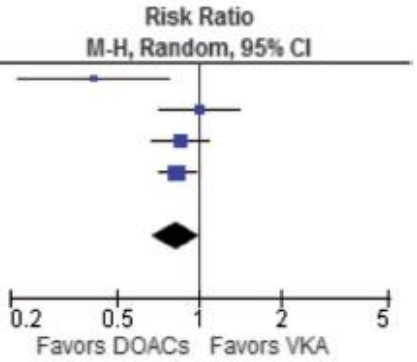
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 6.46$, df = 3 (P = 0.09); $I^2 = 54\%$
Test for overall effect: Z = 0.43 (P = 0.67)



(B)

Study or Subgroup	DOACs Events	DOACs Total	VKA Events	VKA Total	Weight	Risk Ratio M-H, Random, 95% CI
AMPLIFY	13	1920	32	1924	8.2%	0.41 [0.21, 0.77]
EINSTEIN-DVT	59	733	57	708	20.5%	1.00 [0.71, 1.42]
EINSTEIN-PE	110	1078	134	1116	30.7%	0.85 [0.67, 1.08]
HOKUSAI	255	2971	304	2936	40.6%	0.83 [0.71, 0.97]
Total (95% CI)		**6702**		**6684**	**100.0%**	**0.82 [0.67, 1.00]**
Total events	437		527			

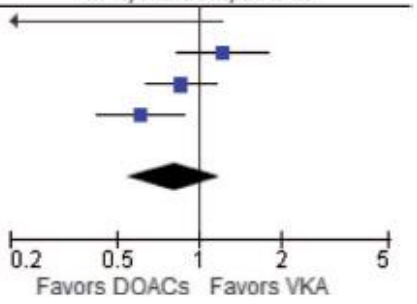
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 5.87$, df = 3 (P = 0.12); $I^2 = 49\%$
Test for overall effect: Z = 1.96 (P = 0.05)



(C)

Study or Subgroup	DOACs Events	DOACs Total	VKA Events	VKA Total	Weight	Risk Ratio M-H, Random, 95% CI
AMPLIFY	1	230	7	243	3.4%	0.15 [0.02, 1.22]
EINSTEIN-DVT	48	492	42	522	30.5%	1.21 [0.82, 1.80]
EINSTEIN-PE	71	649	79	618	34.9%	0.86 [0.63, 1.16]
HOKUSAI	39	524	64	519	31.2%	0.60 [0.41, 0.88]
Total (95% CI)		**1895**		**1902**	**100.0%**	**0.80 [0.54, 1.20]**
Total events	159		192			

Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 8.86$, df = 3 (P = 0.03); $I^2 = 66\%$
Test for overall effect: Z = 1.07 (P = 0.29)



Ann Med 2015; 47:1, 61-68.

What happens pharmacoDYNAMICALLY?

Journal of Thrombosis and Haemostasis, **15**: 1322–1333 DOI: 10.1111/jth.13701

ORIGINAL ARTICLE

Association of body weight with efficacy and safety outcomes in phase III randomized controlled trials of direct oral anticoagulants: a systematic review and meta-analysis

K. BOONYAWAT,*† F. CARON,‡ A. LI,§ C. CHAI-ADISAKSOPHA,* W. LIM,* A. IORIO,* R. D. LOPES,¶ D. GARCIA** and M. A. CROWTHER*

"In conclusion … in AF and VTE patients treated with DOACs or with warfarin … patients with low body weight had a paradoxical increase in the risk of thromboembolism compared with non-low body weight patients. The subgroup of AF patients with a high bodyweight had a favorable thromboembolic outcome compared with AF patients with a non-high body weight."

RECAP: What do we know?

- Large, well controlled randomized trials have not been done to evaluate the safety and efficacy of DOACs in the obese population

- Meta-Analysis indicate:

  Comparable efficacy to VKA in high & normal for VTE and AF
  Comparable rates to VKA in major & CRNM-bleeding in high & low body-weights

  Analysis based on wide patient weight classes
  "Obesity paradox" is seen in other settings

- Overall:

  Limited information on very extreme body weights: < 40kg & > 150kg, BMI > 30kg/m^2
  Pharmacokinetic alterations have been documented

- Guidelines:

  Consider VKA 1st line if: Weight < 50kg, > 120kg or BMI > 35-40kg/m^2
  Dose Reduction when appropriate (apixaban)

ISTH Statement on Obesity

AC Forum Guidance Statement

J Thromb Thrombolysis (2016) 41: 129-143. Ann Med 2015; 47:1, 61-68. Martin K, et al. *J Thromb Haemost* 2016; 14: 1308-13

"THESE ARE THE ~~DROIDS~~ GUIDELINES YOU'RE LOOKING FOR…"

What's missing?

- ✓ ~~extremes of weight~~
- impaired or variable renal function
- the elderly
- (potentially) active cancer
- how/when do you monitor DOAC therapy

IMPAIRED OR VARIABLE RENAL FUNCTION

What do we know?

Di Lullo L, et al. *Thrombosis Research.* 2017; 38-47.

IMPAIRED OR VARIABLE RENAL FUNCTION

What do we know?

- Warfarin has ***ZERO*** large, randomized clinical controlled trials in the ESRD population
- Warfarin ***IS*** considered the drug of choice in advanced CKD and ESRD patients by the major guidelines when anticoagulation is desired
- Both bleeding and thrombosis rates rise in patients with renal dysfunction, regardless of the treatment
- Having a reversal agent is a plus for anticoagulants in this population

Di Lullo L, et al. *Thrombosis Research.* 2017; 38-47.

What do we know?

Parameter	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Renal clearance	27%	80%	50%	36%
Protein bound	87%	35%	54%	95%
Hemodialysis removal (4 hr)	7%	50-60%	9%	<1%
Specific reversal agent	No	Yes Idarucizumab	No	No
Lowest estimated CrCl in phase III trials	25 ml/min	30 ml/min	30 ml/min	30 ml/min

Di Lullo L, et al. *Thrombosis Research.* 2017; 38-47.

What do we know?

Parameter	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Renal clearance	27%	80%	50%	36%
Protein bound	87%	35%	54%	95%
Hemodialysis removal (4 hr)	7%	50-60%	9%	<1%
Specific reversal agent	No	Yes Idarucizumab	No	No
Lowest estimated CrCl in phase III trials	25 ml/min	30 ml/min	30 ml/min	30 ml/min

Edoxaban US Prescribing Information. Daiichi Sankyo; 2015; Chan KE, et. al. *N Engl J Med* 2013; 369: 2093-2104; Patel MR et al. *N Engl J Med*. 2011;365(10):883-891; Granger CB, et. al. N Engl J Med 2011;365:981-92; Connolly SJ, et al. N Engl J Med 2009;361:1139-51 ; Di Lullo L, et al. *Thrombosis Research*. 2017; 38-47

What happens pharmacoKINETICALLY?

		>80 ml/min	50-80 ml/min	30-50 ml/min	<30 ml/min
Apixaban	Cmax (ng/mL) AUC (ng*h/mL) T ½ (hr)	224 2528 15.1	229 3288 14.6	288 4479 17.6	210 3221 17.3
Edoxaban	AUC (ng*h/mL) T ½ (hr)	- 8.6	32% ↑ -	74% ↑ 9.4	72% ↑ 16.9
Dabigatran	Cmax (ng/mL) AUC (ng*h/mL) T ½ (hr)	85.3 901 13.8	109 1580 16.6	138 2470 18.7	205 6150 27.5
Rivaroxaban	Cmax (ng/mL) AUC (ng*h/mL) T ½ (hr)	172 1247 8.3	217 1863 8.7	206 2068 9.0	232 2228 9.5

Pradaxa PI. Kubitza D. Br J Clin Pharmacol 2010;70:703-12. Ridout G, et al. Journal of Clinical Pharmacology. 2009;49:1124

What happens pharmacoKINETICALLY?

		>80 ml/min	50-80 ml/min	30-50 ml/min	<30 ml/min
Apixaban	Cmax (ng/mL) AUC (ng*h/mL) T ½ (hr)	224 2528 15.1	229 3288 14.6	288 4479 17.6	210 3221 17.3
Edoxaban	AUC (ng*h/mL) T ½ (hr)	- 8.6	32% ↑ -	74% ↑ 9.4	72% ↑ 16.9
Dabigatran	Cmax (ng/mL) AUC (ng*h/mL) T ½ (hr)	85.3 901 13.8	109 1580 16.6	138 2470 18.7	205 6150 27.5
Rivaroxaban	Cmax (ng/mL) AUC (ng*h/mL) T ½ (hr)	172 1247 8.3	217 1863 8.7	206 2068 9.0	232 2228 9.5

Apixaban
Little increase in kinetic parameters

Edoxaban
74% increase in AUC, T ½ doubled

Dabigatran
Significant increase in AUC & t ½

Rivaroxaban
Approximate 50% increase in AUC, little increase in kinetic parameters

Pradaxa PI. Kubitza D. Br J Clin Pharmacol 2010;70:703-12. Ridout G, et al. Journal of Clinical Pharmacology. 2009;49:1124

What happens pharmacoDYNAMICALLY?

- Dose adjustments are recommended for all DOACS
  - Clinical Outcomes data is limited
  - Dabigatran is the most renally cleared, Apixaban the least

Efficacy Vs. Warfarin, CrCl < 50ml/min
(Stroke or Systemic Embolism)

Safety Vs. Warfarin, CrCl < 50ml/min
(Major Bleeding)

Nat Rev Nephrol 2012; 8: 569-78. NEJM 2009; 361:1139. Euro Heart J 2011: 32:2387. NEJM 2011; 365: 981.

What happens in Dialysis?

- Peritoneal Dialysis = ?
- Hemodialysis…
  - **Dabigatran**
    - Dosing recommendations can not be provided
  - **Rivaroxaban**
    - A fib 15 mg po daily
    - *VTE: Avoid use in patients with CrCl <30 ml/min*
  - **Edoxaban**
    - Not recommended in CrCl <15 ml/min
  - **Apixaban**
    - ***No** dose adjustment for patients with ESRD maintained on hemodialysis **unless** they meet other criteria for dose adjustment.*

For all agents, patients with ESRD were not studied in clinical trials…

Package Inserts.

What happens in Dialysis with Apixaban & Rivaroxaban?

- A phase 1, open-label, parallel, **single-dose** apixaban (5 mg) study assessed the kinetics of apixaban in 8 subjects with end-stage renal disease
  - Apixaban immediately after dialysis
    - C_{max}: no increase vs. healthy subjects
    - **AUC_{0-T}: 36% increase vs. healthy subjects**

- A phase 1, open-label, parallel, **single-dose** rivaroxaban (15 mg) study assessed the kinetics of rivaroxaban in 8 subjects with end-stage renal disease
  - Rivaroxaban 3 hours after dialysis
    - C_{max}: 17% increase vs. healthy subjects
    - **AUC_{0-T}: 56% increase vs. healthy subjects**

Wang X, et al. *J Clin Pharmacol* 2016; 56: 628-636; Dias C, et. al. *Am J Nephrol* 2016; 43: 229-36

IMPAIRED OR VARIABLE RENAL FUNCTION

What we need is more data

Venous Thromboembolism in Renally Impaired Patients and Direct Oral Anticoagulants (VERDICT)

This study is not yet open for participant recruitment. (see Contacts and Locations)

Verified August 2016 by Centre Hospitalier Universitaire de Saint Etienne

Sponsor:
Centre Hospitalier Universitaire de Saint Etienne

Collaborator:
Ministry of Health, France

ClinicalTrials.gov Identifier:
NCT02664155

First received: January 22, 2016
Last updated: August 11, 2016
Last verified: August 2016
History of Changes

Impaired or Variable Renal Function

My Overall Opinion

Moderate Renal - Cr Cl 30-50 mL/min:

All Xa inhibitors are at least as safe as warfarin (Apixaban safer?)

Check package insert for dose adjustments!

Severe Renal - Cr Cl < 30 mL/min:

Avoid all DOACs pending more data

If a DOAC is chosen, get informed consent

It may be too early to assume that warfarin is a safer and more effective alternative – it may just be we are inured to its problems !

- AC Forum Guidance Statement recommends:
  - DOAC renal function monitoring every 3-12 months
  - Dose reduction or avoidance in renal impairment
- There is no high quality data in patients with severe or end stage renal dysfunction or acute renal failure with any of the DOACs
- Renal dysfunction increases the rate of thrombosis and bleeding regardless of the anticoagulant used
- ESRD "approval" is from single dose studies and the LONG-TERM efficacy and safety of DOAC use in this population is not known
- Edoxaban has precautions for *both* excellent and poor renal function
  - Reduce dose if CrCl < 50 ml/min
  - Do not use if CrCr > 95 ml/min (black box warning)

Nat Rev Nephrol 2012; 8: 569-78, NEJM 2009; 361:1139, Euro Heart J 2011: 32:2387. NEJM 2011; 365: 981, Eliquis Package Insert, J Clin Pharmacol. 2016 May; 56(5): 628-36

"THESE ARE THE ~~DROIDS~~ GUIDELINES YOU'RE LOOKING FOR…"

What's missing?

- ✓ ~~extremes of weight~~
- ✓ ~~impaired or variable renal function~~
- the elderly
- (potentially) active cancer
- how/when do you monitor DOAC therapy

What do we know?

What do we know?

- Limited data in age > 75 years

Indication	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
NVAF	40%	31%	38%	41%
VTE	9.9%	13%	16%	14%

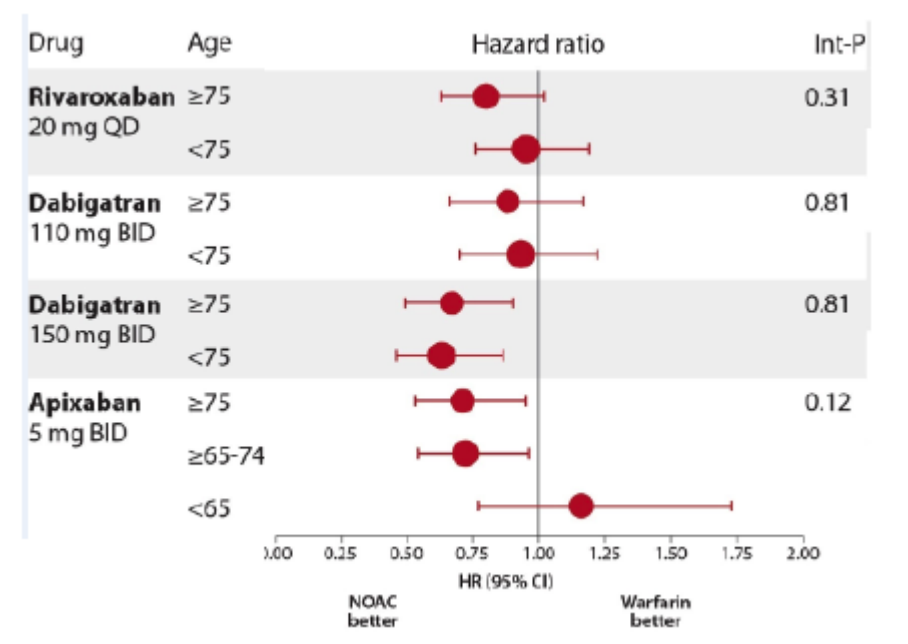
- Little data in age > 85-90 years

Package Inserts.

What do we know?

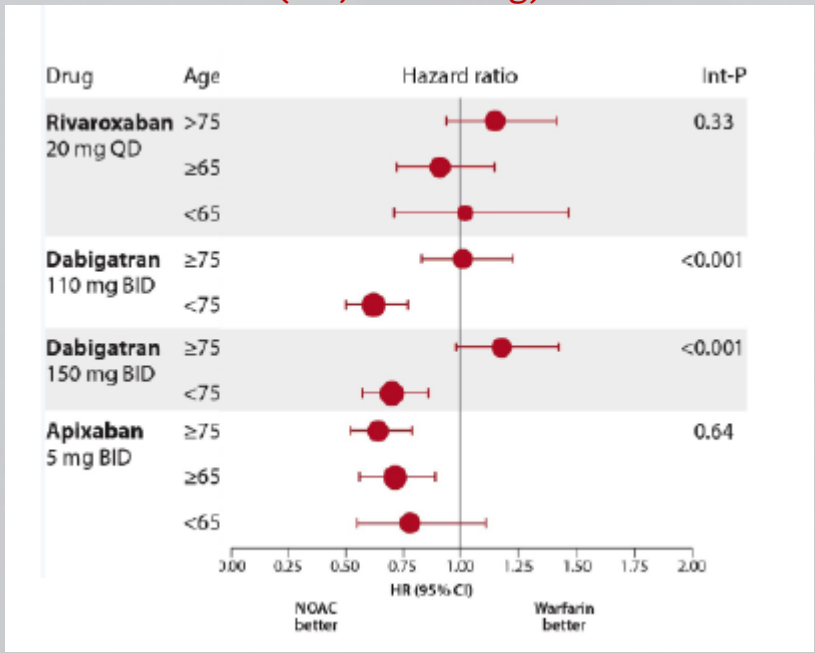
Efficacy Vs. Warfarin

(Stroke or Systemic Embolism)



Safety Vs. Warfarin

(Major Bleeding)



Coppens, M. CMAJ 2013.

What do we know?

Clinical Outcome	<75 yrs HR (95% CI) N=10,855	75-79 yrs HR (95% CI) N=4231	80-84 yrs HR (95% CI) N=2305	≥ 85 yrs HR (95% CI) N=722	P-value
Stroke/Systemic Embolism	0.63 (0.46-0.86)	0.65 (0.42-1.01)	0.67 (0.41-1.10)	0.70 (0.31-1.57)	0.996
Major bleeding	0.70 (0.57-0.86)	1.04 (0.81-1.35)	1.41 (1.02-1.94)	1.22 (0.74-2.02)	0.001
Intracranial major bleeding	0.43 (0.25-0.74)	0.23 (0.09-0.60)	0.55 (0.25-1.21)	0.61 (0.20-1.87)	0.481
Extracranial major bleeding	0.78 (0.62-0.97)	1.22 (0.93-1.61)	1.68 (1.18-2.41)	1.41 (0.80-2.49)	0.001
All-cause mortality	0.77 (0.64-0.93)	0.82 (0.63-1.07)	1.16 (0.87-1.55)	1.15 (0.74-1.79)	0.068

Lauw MN, et. al. *Heart* 2017 Jul;103(13):1015-1023.

What do we know?

Clinical Outcome	<75 yrs HR (95% CI) N=10,855	75-79 yrs HR (95% CI) N=4231	80-84 yrs HR (95% CI) N=2305	≥ 85 yrs HR (95% CI) N=722	P-value
Stroke/Systemic Embolism	0.63 (0.46-0.86)	0.65 (0.42-1.01)	0.67 (0.41-1.10)	0.70 (0.31-1.57)	0.996
Major bleeding	0.70 (0.57-0.86)	1.04 (0.81-1.35)	1.41 (1.02-1.94)	1.22 (0.74-2.02)	0.001
Intracranial major bleeding	0.43 (0.25-0.74)	0.23 (0.09-0.60)	0.55 (0.25-1.21)	0.61 (0.20-1.87)	0.481
Extracranial major bleeding	0.78 (0.62-0.97)	1.22 (0.93-1.61)	1.68 (1.18-2.41)	1.41 (0.80-2.49)	0.001
All-cause mortality	0.77 (0.64-0.93)	0.82 (0.63-1.07)	1.16 (0.87-1.55)	1.15 (0.74-1.79)	0.068

Lauw MN, et. al. *Heart* 2017 Jul;103(13):1015-1023

What do we know?

Clinical Outcome	<75 yrs HR (95% CI) N=10,855	75-79 yrs HR (95% CI) N=4231	80-84 yrs HR (95% CI) N=2305	≥ 85 yrs HR (95% CI) N=722	P-value
Stroke/Systemic Embolism	0.63 (0.46-0.86)	0.65 (0.42-1.01)	0.67 (0.41-1.10)	0.70 (0.31-1.57)	0.996
Major bleeding	0.70 (0.57-0.86)	1.04 (0.81-1.35)	1.41 (1.02-1.94)	1.22 (0.74-2.02)	0.001
Intracranial major bleeding	0.43 (0.25-0.74)	0.23 (0.09-0.60)	0.55 (0.25-1.21)	0.61 (0.20-1.87)	0.481
Extracranial major bleeding	0.78 (0.62-0.97)	1.22 (0.93-1.61)	1.68 (1.18-2.41)	1.41 (0.80-2.49)	0.001
All-cause mortality	0.77 (0.64-0.93)	0.82 (0.63-1.07)	1.16 (0.87-1.55)	1.15 (0.74-1.79)	0.068

Take Home Points:

- Data is limited, but points to:
  - ICH benefit appears to be maintained in the elderly population for DOACs
  - Dabigatran 150mg is problematic for bleeding as a patient ages
  - Apixaban appears to maintain its bleeding advantage in all age groups
  - Dabigatran, rivaroxaban & edoxaban = increased risk of GI bleeding

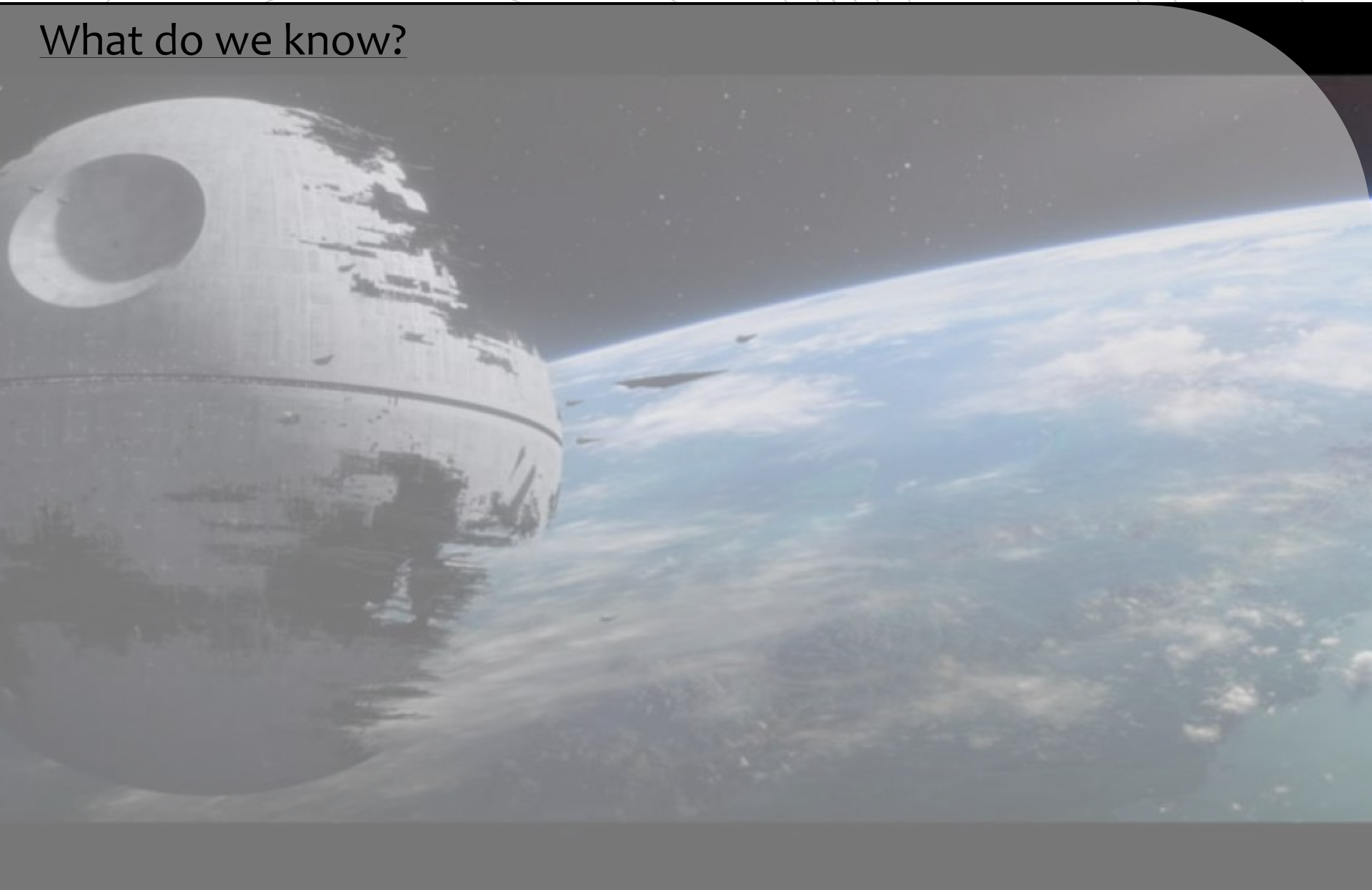
Lauw MN, et. al. *Heart* 2017 Jul;103(13):1015-1023. Eikelboom JW, el al. *Circulation* 2011;123:2363-2372; Prins MH, et al. *Thrombosis Journal* 2013;11:21. http://www.thrombosisjournal.com/content/11/1/21; Granger CB, et. al. N Engl J Med 2011;365:981-92; Agnelli G, et al. *N Engl J Med* 2013; 369: 1406-15 Chan KE, et. al. *N Engl J Med* 2013; 369: 2093-2104; Patel MR et al. *N Engl J Med*. 2011;365(10):883-891; Connolly SJ, et al. N Engl J Med 2009;361:1139-51

"THESE ARE THE ~~DROIDS~~ GUIDELINES YOU'RE LOOKING FOR…"

What's missing?

- ✓ ~~extremes of~~ ~~weight~~
- ✓ ~~impaired or variable~~ ~~renal function~~
- ✓ ~~the~~ ~~elderly~~
- (potentially) active cancer
- how/when do you monitor DOAC therapy

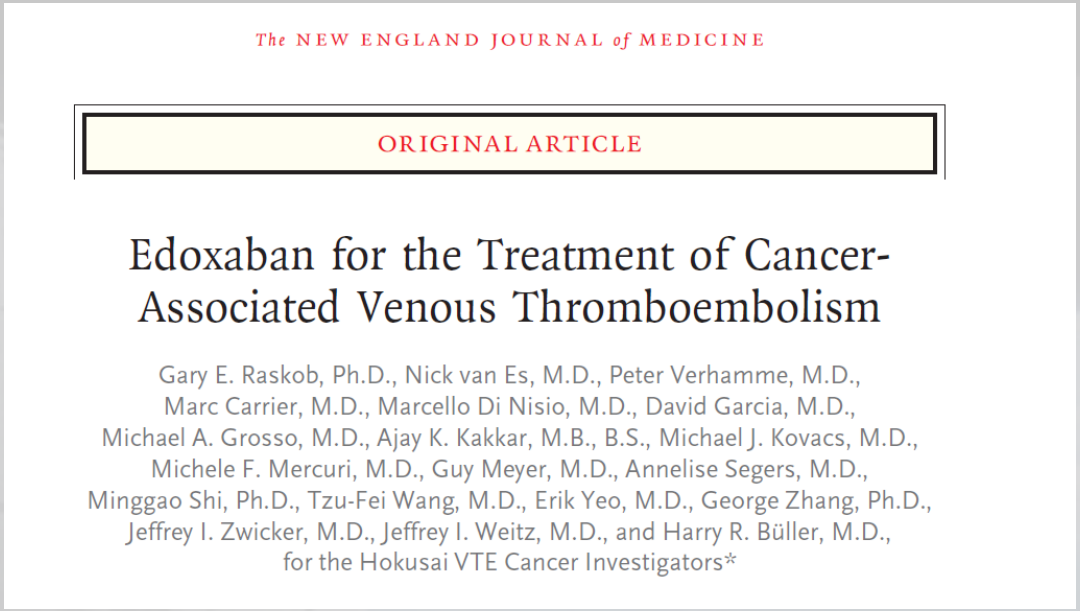
What do we know?



What do we know?

- LMWH is the treatment of choice (0-3 months)
  - Consistent reduction in mortality risk compared to UFH & warfarin
- Active Cancer + VTE = Lifelong AC therapy (or until "cured")
- Cancer patients were included in VTE Trials with all DOACS
  - "Active Cancer" definitions varied
  - Data available is from subgroup analysis
  - **Comparison group was warfarin, not LMWH**

CHEST, ASCO 2013, AC Forum Guidelines. Journal of Thrombosis and Thrombolysis. 2016;41:81-91. Thromb Res. 2014 Dec; 134(6):1214-9. Blood 2015 126:1123. Blood 2016 128:5013



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism

Gary E. Raskob, Ph.D., Nick van Es, M.D., Peter Verhamme, M.D., Marc Carrier, M.D., Marcello Di Nisio, M.D., David Garcia, M.D., Michael A. Grosso, M.D., Ajay K. Kakkar, M.B., B.S., Michael J. Kovacs, M.D., Michele F. Mercuri, M.D., Guy Meyer, M.D., Annelise Segers, M.D., Minggao Shi, Ph.D., Tzu-Fei Wang, M.D., Erik Yeo, M.D., George Zhang, Ph.D., Jeffrey I. Zwicker, M.D., Jeffrey I. Weitz, M.D., and Harry R. Büller, M.D., for the Hokusai VTE Cancer Investigators*

Conclusions:

- Oral edoxaban was **noninferior** to subcutaneous dalteparin with respect to the composite outcome of recurrent venous thromboembolism or major bleeding.

- "The rate of recurrent VTE was lower with edoxaban."
  - 7.9% vs. 11.3%, NS (CI -7.0 to 0.2)

- "The rate of major bleeding was higher with edoxaban."
  - 6.9% vs. 4.0%, (CI 0.1 to 5.6) = NNH of 35

NEJM 2017. doi:10.1056/NEJMoa1711948

Take home points?

DOACs are not recommended 1st line by ASH or AC Forum.

- The efficacy and safety of DOACs in cancer patients are at least comparable to those of warfarin (at a TTR 55-60%).

- However, the quality of the evidence is low considering that the studies were underpowered to show noninferiority or superiority of DOACs with respect to warfarin in cancer patients.

- DOACs (edoxaban) *may* be an option for carefully selected patients.

- More data is needed:

Future:

Direct Oral Anticoagulants (DOACs) Versus LMWH +/- Warfarin for VTE in Cancer (CANVAS)
Sponsor: Alliance Foundation Trials, LLC
NCT02744092
Currently recruiting participants; Anticipated to close September 2019.

CHEST, ASCO 2013, AC Forum Guidelines. Journal of Thrombosis and Thrombolysis. 2016;41:81-91. Thromb Res. 2014 Dec; 134(6):1214-9. Blood 2015 126:1123. Blood 2016 128:5013. NEJM 2017. doi:10.1056/NEJMoa1711948

"THESE ARE THE ~~DROIDS~~ GUIDELINES YOU'RE LOOKING FOR…"

What's missing?

- ✓ ~~extremes of~~ ~~weight~~
- ✓ ~~impaired or variable~~ ~~renal function~~
- ✓ ~~the~~ ~~elderly~~
- ✓ ~~(potentially) active~~ ~~cancer~~
- how/when do you monitor DOAC therapy

What do we know?

DOAC "MONITORING"

What do we know?

- Routine safety DOAC monitoring should be performed.

- Routine therapeutic DOAC monitoring is not required/recommended.
- No commercial test is available.

DOAC "MONITORING"

What do we know?

- Routine safety DOAC monitoring should be performed.

- Routine therapeutic DOAC monitoring is not required/recommended.
- No commercial test is available.

Gerald is 68 year old man on apixaban 5mg po q12h for Atrial Fibrillation with concurrent hypertension. CHADS2-Vasc score is 2. He presents to your ED unresponsive. Family reports he has not been feeling well for the last several days with the flu, and relays that Gerry had been "off some of his medications." Neurology is consulted and patient is an ideal candidate for TPA. You are consulted. What do you do?

DOAC "MONITORING"

What do we know?

- Routine safety DOAC monitoring should be performed.

- Routine therapeutic DOAC monitoring is not required/recommended.
- No commercial test is available.

Gerald is 68 year old man on apixaban 5mg po q12h for Atrial Fibrillation with concurrent hypertension. CHADS2-Vasc score is 2. He presents to your ED unresponsive. Family reports he has not been feeling well for the last several days with the flu, and relays that Gerry had been "off some of his medications." Neurology is consulted and patient is an ideal candidate for TPA. You are consulted. What do you do?

a) Give TPA regardless of last apixaban dose
b) Do not give TPA due to the risk of bleeding
c) Give Kcentra, followed by TPA
d) Order labs to determine apixaban effect

DOAC "MONITORING"

1 FIRST CHOICE ➡ Test of choice, with "DOAC calibrations"

Medication	2nd Choice	3rd Choice	Never, Ever
Dabigatran	Thrombin Time	aPTT	
Rivaroxaban	Xa	---	
Apixaban	Xa	---	
Edoxaban	Xa	---	

Drug Concentrations to Double PT & aPTT

Test	Dabigatran	Apixaban	Rivaroxaban
Peak Range	100-300 ug/L	200 ug/L	32-215 ug/L
PT	600-1000 ug/L	700-3900 ug/L	Quick: 498-591 ug/L Owren: 1300-1375 ug/L
aPTT	227-285 ug/L	2200-4700 ug/L	389-617 ug/L

ISTH SCC Guidelines. J Thromb Haemst 2013: 11: 756. Thr Haemost 2011: 105: 371. JTH 2011; 9: 133. JTH 2014; 12: 1545.

DOAC "MONITORING"

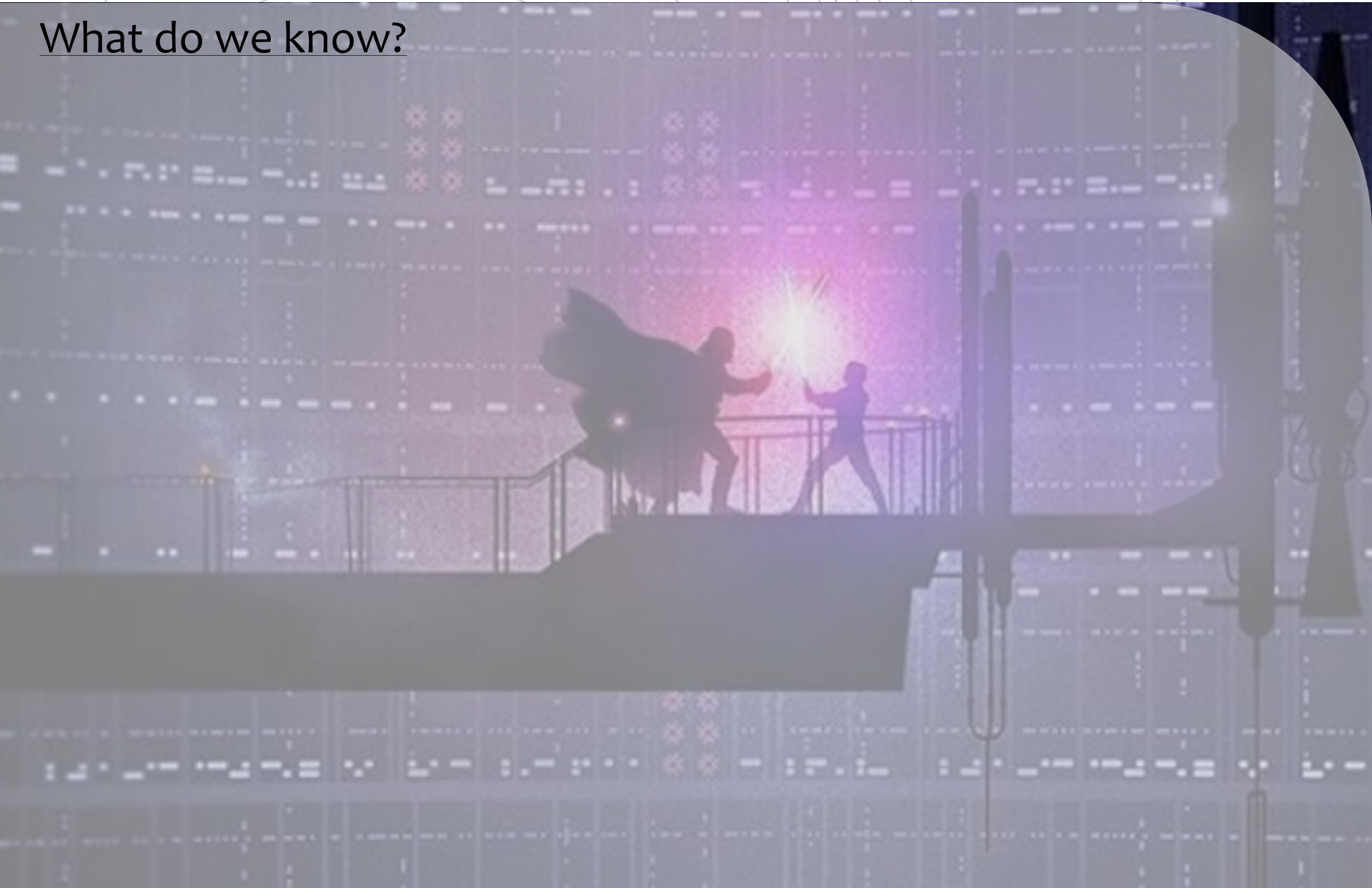
1 FIRST CHOICE ➡ Test of choice, with "DOAC calibrations"

Medication	2nd Choice	3rd Choice	Never, Ever
Dabigatran	Thrombin Time	aPTT	Xa
Rivaroxaban	Xa	---	PT/INR, aPTT
Apixaban	Xa	---	PT/INR, aPTT
Edoxaban	Xa	---	PT/INR, aPTT

- "Normal" TT/Xa indicates very low drug levels (qualitative)
- Do not be alarmed by the Xa levels if drug is present
  - Remember: this is "calibrated" for Heparin/LMWH
- Do NOT perform mixing studies or *functional* hypercoaguable tests while on DOAC therapy

ISTH SCC Guidelines. J Thromb Haemst 2013: 11: 756

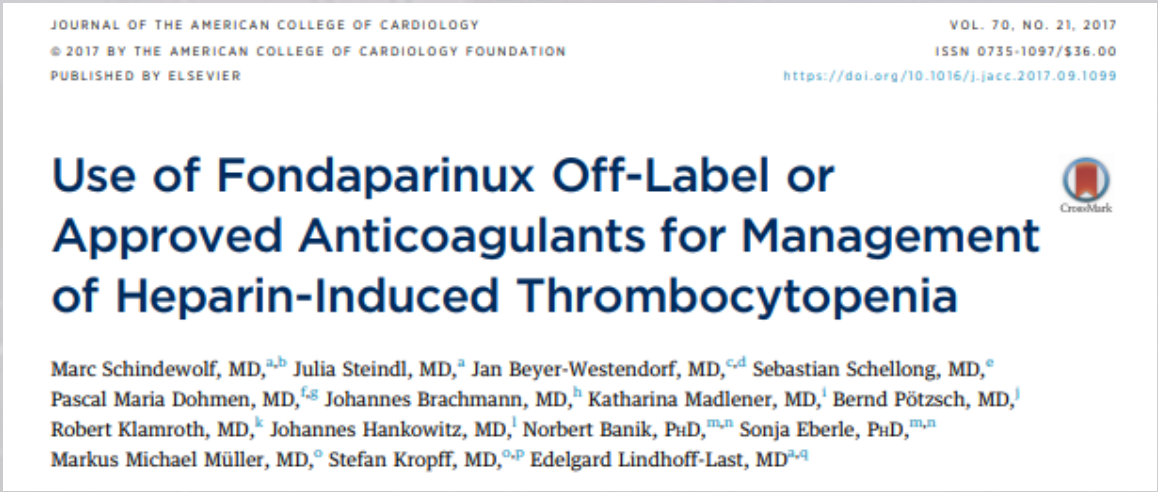
What do we know?



What do we know?

- **Rules of the game**
  - Confirm diagnosis using objective testing
  - Avoid all heparin-like anticoagulants
  - Reverse warfarin if platelets less than 150
  - Ensure patients are aware of need to avoid heparins in future

- **Drugs available and indications**
  - Argatroban: Renal failure, requiring therapeutic anticoagulation
  - Bivalirudin: Hepatic disease, requiring therapeutic anticoagulation
  - Fondaparinux: Has become agent of choice in many circumstances



JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 70, NO. 21, 2017

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER
https://doi.org/10.1016/j.jacc.2017.09.1099

Use of Fondaparinux Off-Label or Approved Anticoagulants for Management of Heparin-Induced Thrombocytopenia

Marc Schindewolf, MD,[a,b] Julia Steindl, MD,[a] Jan Beyer-Westendorf, MD,[c,d] Sebastian Schellong, MD,[e] Pascal Maria Dohmen, MD,[f,g] Johannes Brachmann, MD,[h] Katharina Madlener, MD,[i] Bernd Pötzsch, MD,[j] Robert Klamroth, MD,[k] Johannes Hankowitz, MD,[l] Norbert Banik, PhD,[m,n] Sonja Eberle, PhD,[m,n] Markus Michael Müller, MD,[o] Stefan Kropff, MD,[o,p] Edelgard Lindhoff-Last, MD[a,q]

What about DOACs?

jth journal of thrombosis and haemostasis™

ISTH International Society on Thrombosis and Haemostasis

Explore this journal >

Brief Report

Rivaroxaban for treatment of suspected or confirmed heparin-induced thrombocytopenia study

L. A. Linkins ✉, T. E. Warkentin, M. Pai, S. Shivakumar, R. A. Manji, P. S. Wells, C. Wu, I. Nazi, M. A. Crowther

First published: 10 May 2016 Full publication history

DOI: 10.1111/jth.13330 View/save citation

View issue TOC
Volume 14, Issue 6
June 2016
Pages 1206–1210

Outcomes:

Rivaroxaban appears to be effective for treating patients with confirmed HIT, although the small number of patients (n=22) *enrolled limits precision.*

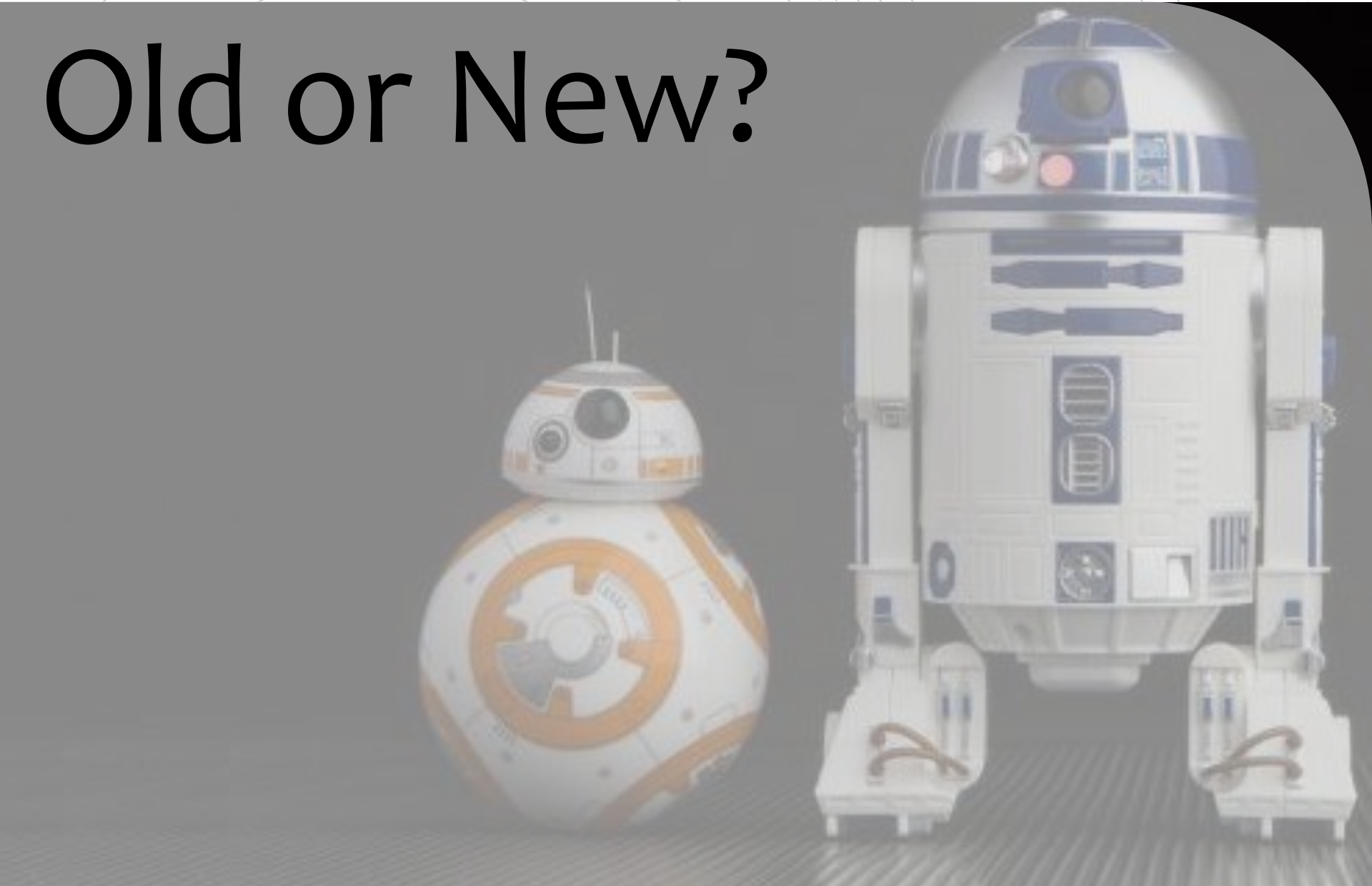
HIT summary

Don't kill the messenger

I stole this slide from Mark Crowther…

- Fondaparinux is now, probably, the "standard" in those patients who are eligible for it.
  - Argatroban, Bivalirudin have important roles in subsets of patients
  - DOACs will likely evolve into an important role, initially replacing warfarin's current role in HIT management

Old or New?



Purely (my) Opinion

The DOACs have changed the way that we deal with anticoagulants BUT the LMWHs, warfarin and other older anticoagulants still have an important role to play.

The ability to monitor and adjust warfarin & enoxaparin provide them with a great deal of flexibility, especially in special populations.

Anticoagulation is a "high-risk" activity and thus we have to have a great deal of familiarity with agents before we use them.

Jedi Training 101:

Mind-tricks & Evidence -Based Approaches to Combating Clinical Controversies in Anticoagulation Therapy

NYSCHP New York State Council of Health-system Pharmacists 60 YEARS

Kelly Rudd, PharmD, FCCP, BCPS, CACP
Basset Medical Center, Cooperstown, NY
kelly.rudd@bassett.org