Perioperative Considerations for Direct Oral Anticoagulant Therapy: *The Role of the Hospitalist*

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Learning Objectives

After participating this activity, the participant will demonstrate the ability to:

- **EVALUATE the efficacy, safety and clinical indications of DOACs for hospitalized patients.**
- **DEVELOP anticoagulation treatment regimens using DOACs in patient case scenarios.**

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Perioperative Considerations for Direct Oral Anticoagulant Therapy: *The Role of the Hospitalist*

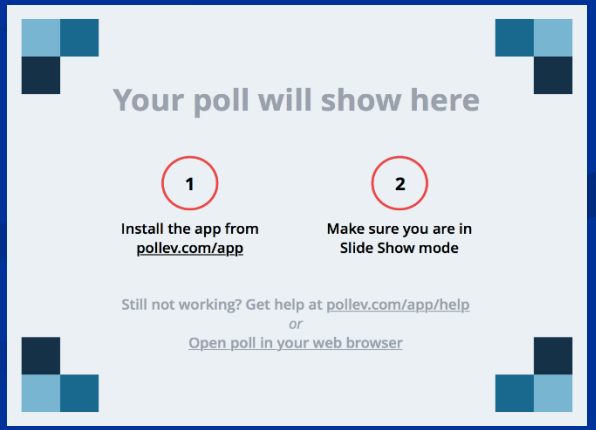
Appropriate Use of DOACs

- Nonvalvular atrial fibrillation (NVAF)
- Acute post-op VTE (DVT and PE)
- DOAC reversal

DOAC = direct oral anticoagulant; DVT = deep vein thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism.

Case

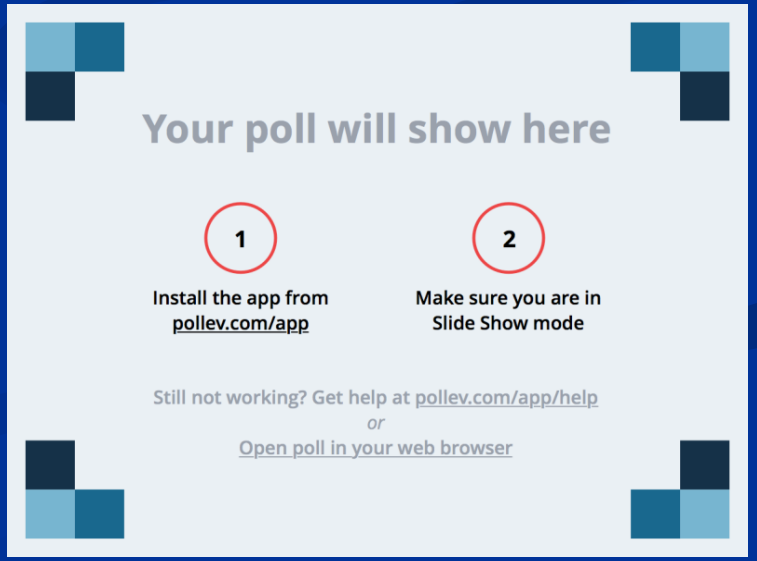
- 68-year-old female 2 days post-op elective knee arthroplasty
- New-onset atrial fibrillation (AF), rate controlled
- Cardiac “workup” negative
- History of HTN and DM, normal renal function, no valvular disease
- Ortho wants to discharge
- What would you do for stroke prevention?
  - A. Begin anticoagulation
  - B. Consult cardiology for anticoagulation
  - C. Punt to outpatient PCP
  - D. Other



DM = diabetes mellitus; HTN = hypertension; PCP = primary care provider.

Case

- 68-year-old female 2 days post-op elective knee arthroplasty
- New-onset AF, rate controlled
- Cardiac “workup” negative
- History of HTN and DM, normal renal function, no valvular disease
- You decide to begin anticoagulation.
- What would you choose?
  - A. Warfarin
  - B. Dabigatran
  - C. Rivaroxaban
  - D. Apixaban
  - E. Edoxaban



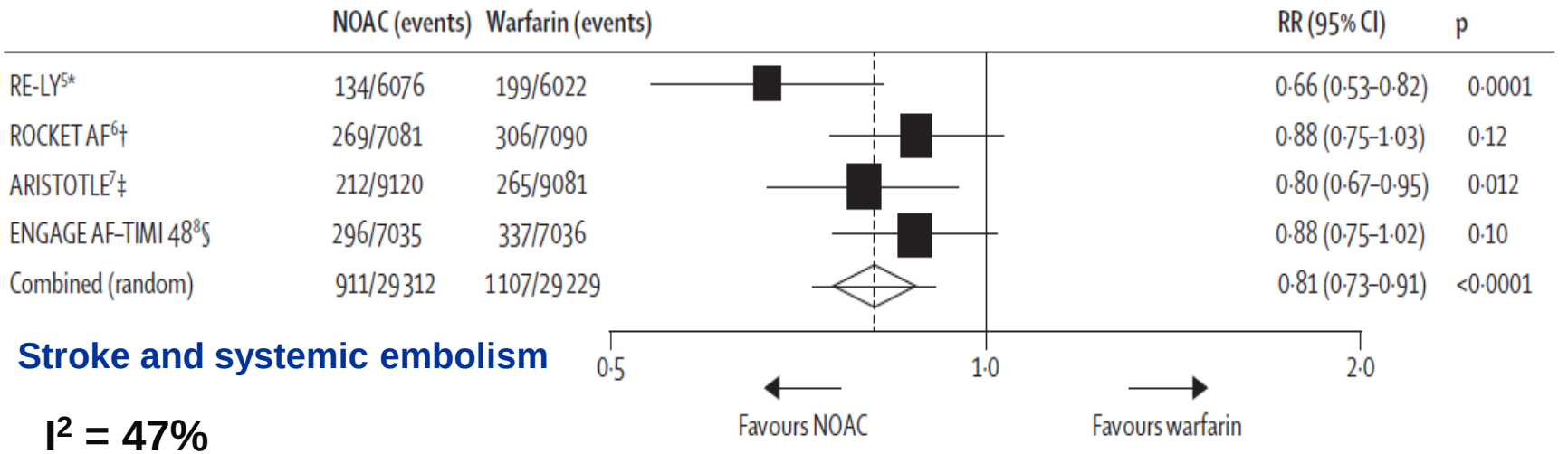
ACC Guidelines (Class I)

- For patients with NVAF with prior stroke, transient ischemic attack (TIA), or a CHA_2DS_2-VASc score of 2 or greater, oral anticoagulants are recommended. Options include:
  - Warfarin (INR 2.0 to 3.0) (171–173) (Level of Evidence: A),
  - Dabigatran (177) (Level of Evidence: B),
  - Rivaroxaban (178) (Level of Evidence: B), or
  - Apixaban (179) (Level of Evidence: B)
- For patients with NVAF unable to maintain a therapeutic INR level with warfarin, use of a direct thrombin or factor Xa inhibitor (dabigatran, rivaroxaban, or apixaban) is recommended. (Level of Evidence: C)

ACC = American College of Cardiology; INR = international normalized ratio.

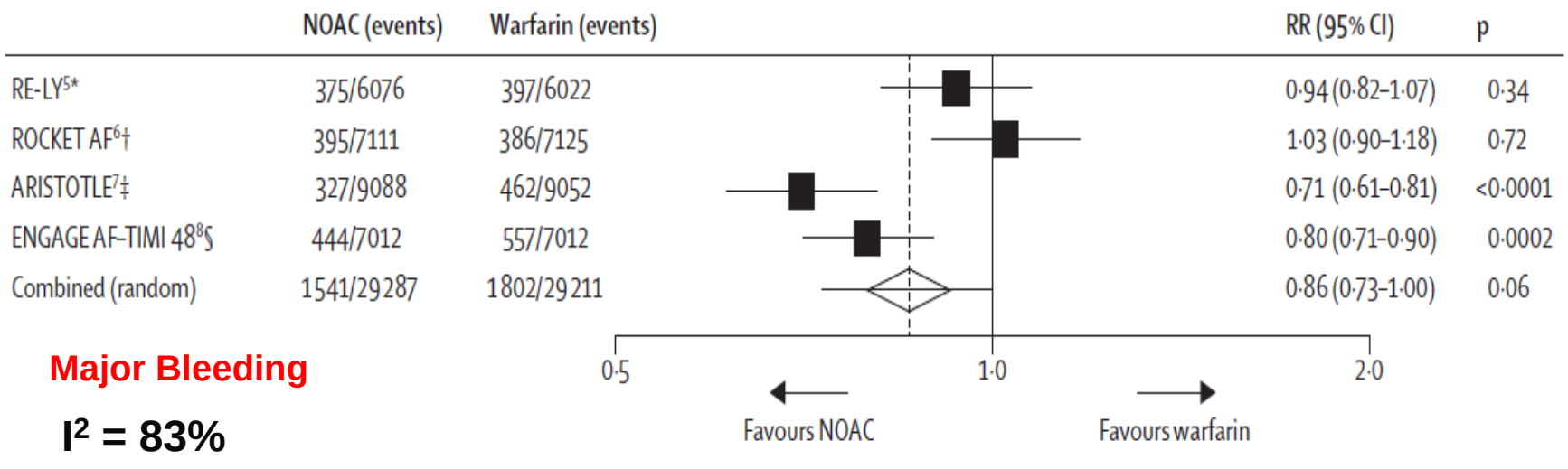
January CT. *J Am Coll Cardiol*. 2014;64:2246-2280; PMID: 24685669.

Systematic Review



Stroke and systemic embolism

I^2 = 47%



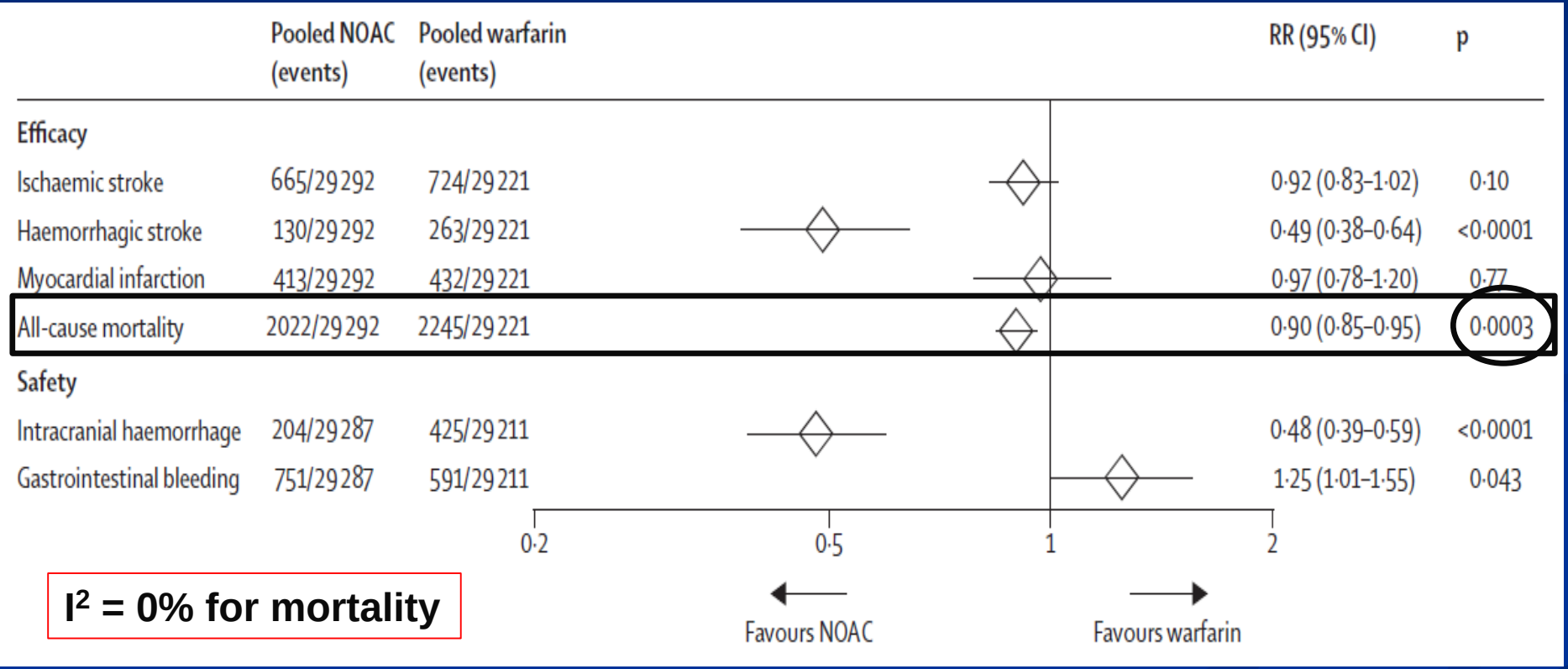
Major Bleeding

I^2 = 83%

ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; CI = confidence interval; ENGAGE = Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48; RE-LY = Randomized Evaluation of Long Term Anticoagulation; ROCKET-AF = Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; RR = risk reduction.

Ruff CT. *Lancet*. 2014;383:955-962; PMID: 24315724. For educational purposes only.

Systematic Review



I^2 = 0% for mortality

Ruff CT. *Lancet*. 2014;383:955-962; PMID: 24315724. For educational purposes only.

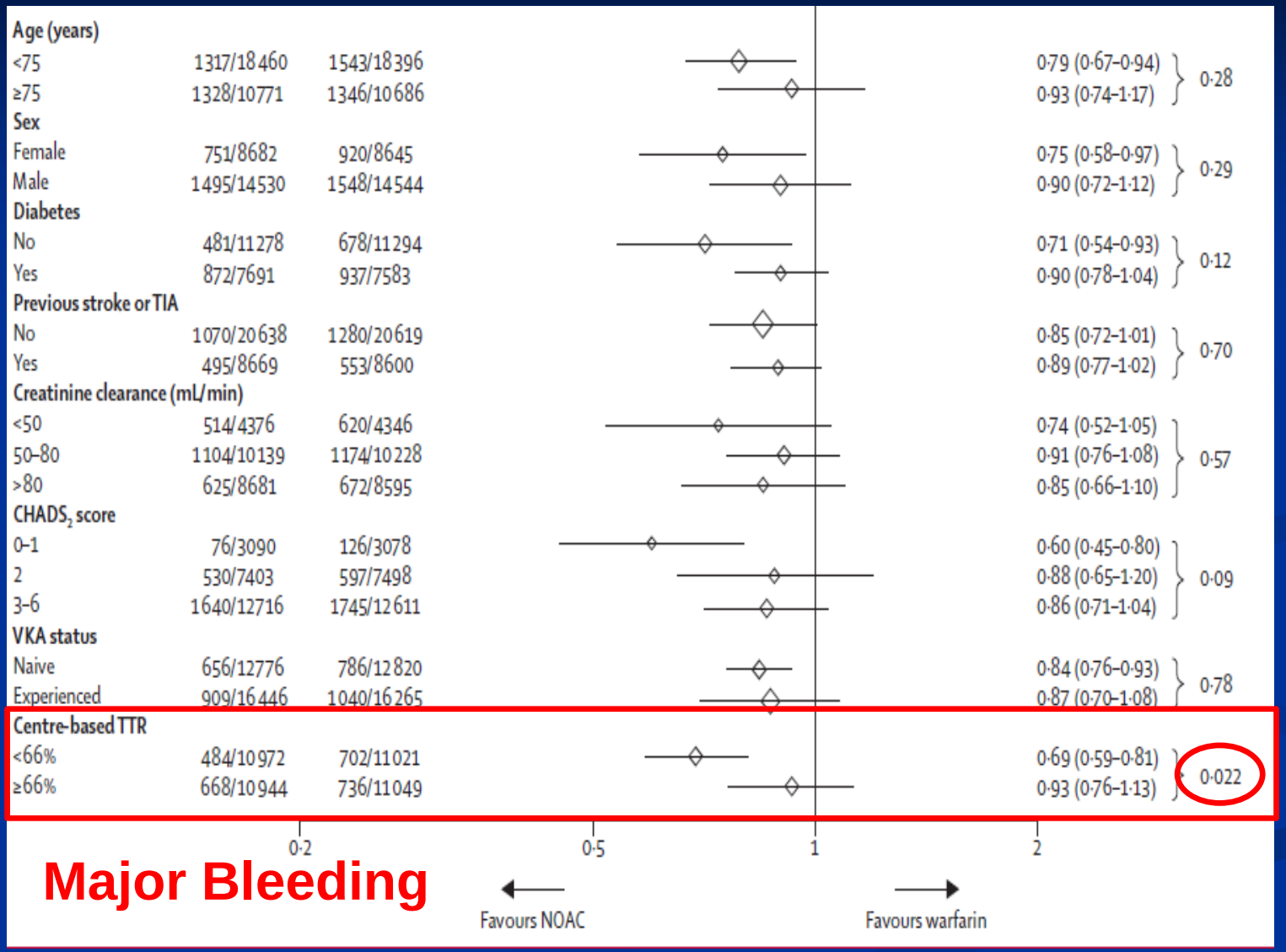
AF Annualized Mortality Rates Warfarin vs DOAC

Trial/DOAC	Warfarin	DOAC	Absolute Difference	NNT	*P* value
RE-LY/Dabigatran (150)	4.13%	3.64%	0.49%	204	.051
ROCKET-AF/Rivaroxaban	4.90%	4.50%	0.40%	250	.15
ARISTOTLE/ Apixaban	3.94%	3.52%	0.42%	238	.047
ENGAGE/Edoxa-ban (high dose)	4.35%	3.99%	0.36%	278	.08

NNT = number needed to treat.

Connolly SJ. *N Engl J Med*. 2009;361:1139-1351; PMID: 19717844; Patel MR. *N Engl J Med*. 2011;365:883-891; PMID: 21830957; Granger CB. *N Engl J Med*. 2011;365:981-992; PMID: 21870978; Giugliano RP. *N Engl J Med*. 2013;369:2093-2104; PMID: 24251359.

Systematic Review



Major Bleeding

VKA = vitamin K antagonist; TTR = time in therapeutic INR range.

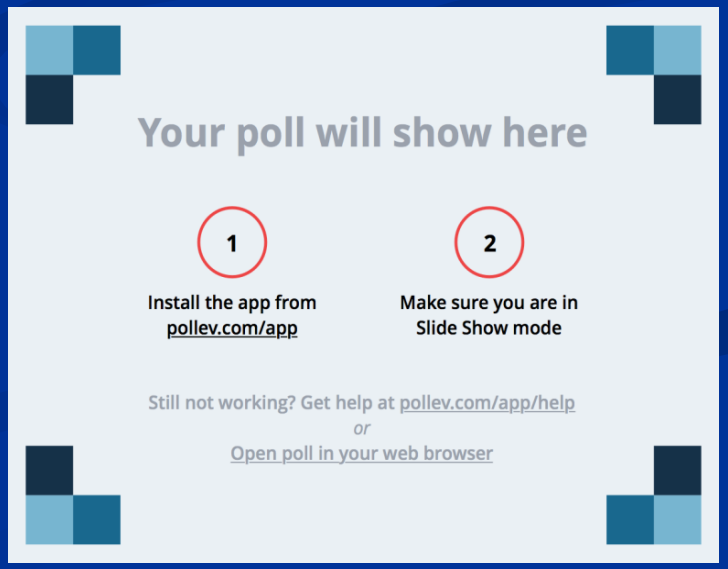
Ruff CT. *Lancet*. 2014;383:955-962; PMID: 24315724. For educational purposes only.

Appropriate Use of DOACs

- NVAF
- Acute post-op VTE (DVT and PE)
- DOAC reversal

Case

- 68-year-old female 2 days postoperative elective knee arthroplasty
- Acute PE
- Hemodynamically stable, low PESI score, normal renal function
- What would you choose?
  - A. Warfarin
  - B. Dabigatran
  - C. Rivaroxaban
  - D. Apixaban
  - E. Edoxaban



PESI = pulmonary embolism severity index.

ACCP Guidelines

In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, it is suggested:

- Dabigatran,
- Rivaroxaban,
- Apixaban, or
- Edoxaban

- **Over VKA therapy (all Grade 2B)**

ACCP = American College of Chest Physicians.

Kearon C. *Chest*. 2016;149:315-352; PMID: 26867832.

ACCP Guidelines

Factor	Preferred Anticoagulant	Qualifying Remarks
Cancer	LMWH	More so if: just diagnosed, extensive VTE, metastatic cancer, very symptomatic; vomiting; on cancer chemotherapy.
Parenteral therapy to be avoided	Rivaroxaban; apixaban	VKA, dabigatran, and edoxaban require initial parenteral therapy.
Once daily oral therapy preferred	Rivaroxaban; edoxaban; VKA	
Liver disease and coagulopathy	LMWH	NOACs contraindicated if INR raised because of liver disease; VKA difficult to control and INR may not reflect antithrombotic effect.
Renal disease and creatinine clearance <30 mL/min	VKA	NOACs and LMWH contraindicated with severe renal impairment. Dosing of NOACs with levels of renal impairment differ with the NOAC and among jurisdictions.
Coronary artery disease	VKA, rivaroxaban, apixaban, edoxaban	Coronary artery events appear to occur more often with dabigatran than with VKA. This has not been seen with the other NOACs, and they have demonstrated efficacy for coronary artery disease. Antiplatelet therapy should be avoided if possible in patients on anticoagulants because of increased bleeding.
Dyspepsia or history of GI bleeding	VKA, apixaban	Dabigatran increased dyspepsia. Dabigatran, rivaroxaban, and edoxaban may be associated with more GI bleeding than VKA.
Poor compliance	VKA	INR monitoring can help to detect problems. However, some patients may be more compliant with a NOAC because it is less complex.
Thrombolytic therapy use	UFH infusion	Greater experience with its use in patients treated with thrombolytic therapy
Reversal agent needed	VKA, UFH	
Pregnancy or pregnancy risk	LMWH	Potential for other agents to cross the placenta
Cost, coverage, licensing	Varies among regions and with individual circumstances	

GI = gastrointestinal; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.

Kearon C. *Chest*. 2016;149:315-352; PMID: 26867832. For educational purposes only.

DOACs Compared to LMWH/Warfarin

	Efficacy outcome		
	Recurrent VTE and VTE-related death		
	NOAC, n/N(%)	Warfarin, n/N (%)	ARR, % (95% CI)
Dabigatran[15]	60/2553 (2.4)	55/2554 (2.2)	0.2 (−0.6, 1.0)
Rivaroxaban[27]	86/4130 (2.1)	95/4131 (2.3)	−0.2 (−0.8, 0.4)
Apixaban[18]	59/2609 (2.3)	71/2635 (2.7)	−0.4 (−1.3, 0.4)
Edoxaban[19]	130/4118 (3.2)	146/4122 (3.5)	−0.4 (−1.2, 0.4)

ARR = absolute risk reduction.

Yeh CH. *Blood.* 2014;124:1020-1028; PMID: 24923298. For educational purposes only.

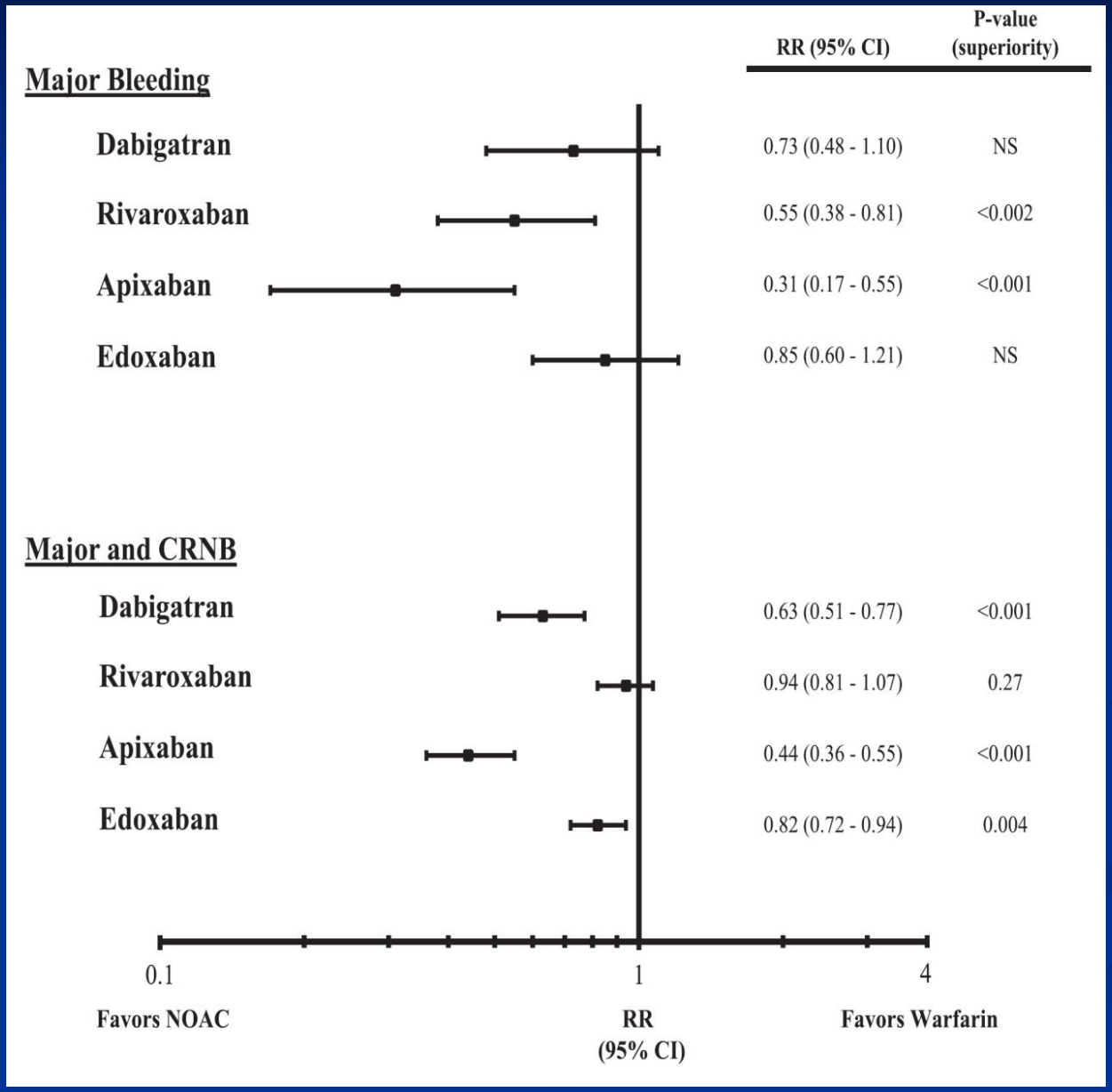
DOACs Compared to LMWH/Warfarin

	Safety outcomes					
	Major bleeding			Major and CRNB		
	NOAC, n/N (%)	Warfarin, n/N (%)	ARR % (95% CI)	NOAC n/N (%)	Warfarin, n/N (%)	ARR % (95% CI)
Dabigatran[15]	37/2553 (1.4)	51/2554 (2.0)	−0.5 (−1.3, 0.2)	136/2553 (5.3)	217/2554 (8.5)	−3.2 (−4.6, −1.8)
Rivaroxaban[27]	40/4130 (1.0)	72/4116 (1.7)	−0.8 (−1.3, −0.3)	388/4130 (9.4)	412/4116 (10.0)	−0.6 (−1.9, 0.7)
Apixaban[18]	15/2676 (0.6)	49/2689 (1.8)	−1.3 (−1.8, −0.6)	115/2676 (4.3)	261/2689 (9.7)	−5.4 (−6.8, −4.1)
Edoxaban[19]	56/4118 (1.4)	66/4122 (1.6)	−0.2 (−0.8, 0.3)	349/4118 (8.5)	423/4112 (10.3)	−1.8 (−3.1, −0.6)

CRNB = clinically relevant nonmajor bleeding.

Yeh CH. *Blood*. 2014;124:1020-1028; PMID: 24923298. For educational purposes only.

DOACs Compared to LMWH/Warfarin



NS = not significant.

Yeh CH. *Blood*. 2014;124:1020-1028; PMID: 24923298. For educational purposes only.

Initial Treatment with DOACs

Trial	Anticoagulant	Initial	# of Days	Major + CRN Bleeding	Major Bleeding
RECOVER	Dabigatran	LMWH	5 days	Less	Similar
RECOVER II	Dabigatran	LMWH	5 days	Less	Similar
EINSTEIN–DVT	Rivaroxaban	15 mg bid	21 days	Similar	Similar
EINSTEIN–PE	Rivaroxaban	15 mg bid	21 days	Similar	Less
AMPLIFY	Apixaban	10 mg bid	7 days	Less	Less
Hokusai-VTE	Edoxaban	LMWH	5 days	Less	Similar

AMPLIFY = Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy; bid = twice a day; CRN = clinically relevant nonmajor; EINSTEIN–DVT = Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep-Vein Thrombosis; EINSTEIN–PE = Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Pulmonary Embolism; RECOVER = Efficacy and Safety of Dabigatran Compared to Warfarin for 6 Month Treatment of Acute Symptomatic Venous Thromboembolism.

Schulman S. *N Engl J Med*. 2009;361:2342-2352; PMID: 19966341; Schulman S. *Circulation*. 2014;129:764-772; PMID: 24344086; Bauersachs R. *N Engl J Med*. 2010;363:2499-2510; PMID: 21128814; Büller HR. *N Engl J Med*. 2012;366:1287-1297; PMID: 22449293; Agnelli G. *N Engl J Med*. 2013;369:799-808; PMID: 23808982; Büller HR. *N Engl J Med*. 2013;369:1406-1415; PMID: 23991658.

Acute VTE Treatment Trials with DOACs vs LMWH/Warfarin

Table 2. Design and patient characteristics of the trials comparing NOACs with conventional therapy for acute VTE treatment

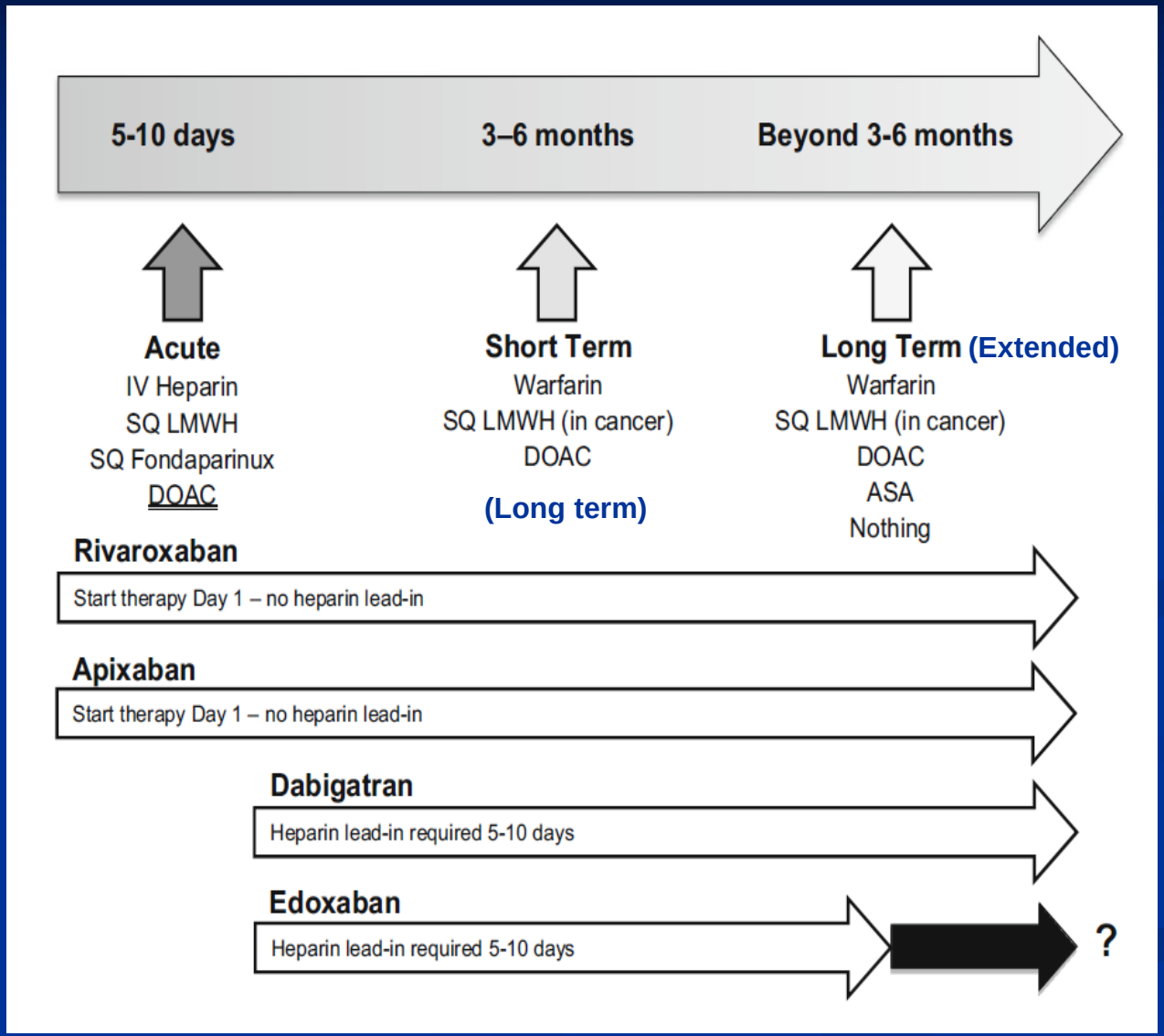
	Dabigatran		Rivaroxaban		Apixaban	Edoxaban
Trial	RE-COVER I & II		EINSTEIN		AMPLIFY	Hokusai-VTE
Indication	VTE		DVT	PE	VTE	VTE
Design	Double-blind		PROBE		Double-blind	Double-blind
Number of patients	2539	2568	3449	4832	5365	8240
Mean age ± SD (y)	54.9 ± 16.0		56.1 ± 16.4	57.7 ± 7.3	57.0 ± 16.0	55.8 ± 16.3
CrCl <30 mL/min, n (%)	22 (0.4)		15 (0.4)	6 (0.1)	29 (0.5)	n/a
Age ≥75 y, n (%)	529 (10)		440 (13)	843 (17)	768 (14)	1104 (13)
Prior VTE (%)	22		19	20	16	18
Unprovoked VTE (%)	35		62.0	64.5	89.8	65.7
Index event PE ± DVT (%)	31		0.7	100	34	40
Noninferiority margin	2.75		2.0		1.8	1.5
Bridge with heparin/LMWH	Yes		No		No	Yes
Treatment protocol	150 mg BID		15 mg BID for 3 wk; then 20 mg OD		10 mg BID for 7 d; then 5 mg BID	60 mg OD; 30 mg OD for those with a creatinine clearance of 30-50 mL/min, weight <60 kg, or taking potent P-gp inhibitors
Duration (mo)	6		3, 6, 12		6	3-12
TTR (%)	60		58	63	61	64

n/a, not available; OD, once daily; BID, twice daily; P-gp, P-glycoprotein; LMWH, low-molecular-weight heparin; PROBE, prospective, randomized, open-label, blinded endpoint; TTR, time in therapeutic range with warfarin.

CrCl = creatinine clearance; SD = standard deviation.

Yeh CH. *Blood*. 2014;124:1020-1028; PMID: 24923298.

DOAC Dosing in Acute VTE

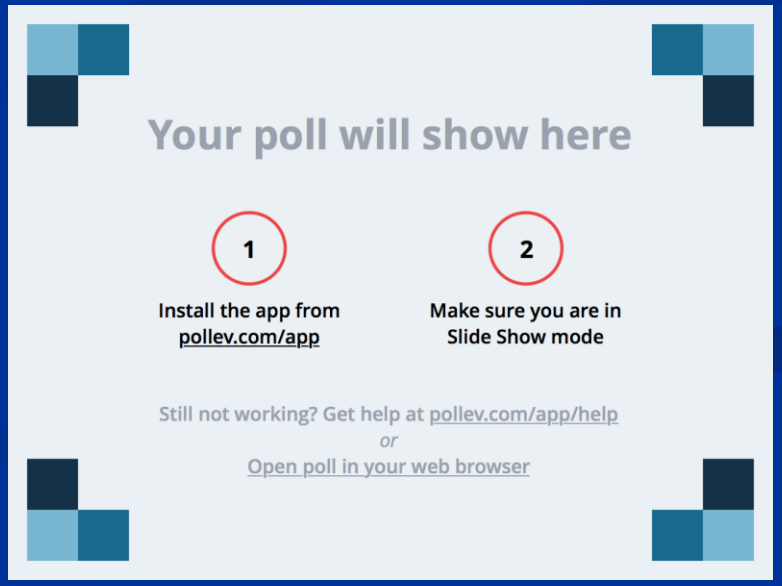


ASA = acetylsalicylic acid; IV = intravenous; SQ = subcutaneous.

Streiff MB. *J Thromb Thrombolysis*. 2016;41:32-67; PMID: 26780738. For educational purposes only.

Case

- 68-year-old female 2 days post-op elective knee arthroplasty
- Acute PE
- Hemodynamically stable, low PESI score, normal renal function
- How long would you treat?
  - A. 6 weeks
  - B. 3 months
  - C. 6 months
  - D. 12 months
  - E. Indefinitely



ACCP Guidelines

In patients with a proximal DVT of the leg or PE provoked by surgery, we recommend treatment with anticoagulation for 3 months over:

- **(i) Treatment of a shorter period (Grade 1B),**
- **(ii) Treatment of a longer time-limited period (eg, 6, 12, or 24 months) (Grade 1B), or**
- **(iii) Extended therapy (no scheduled stop date) (Grade 1B)**

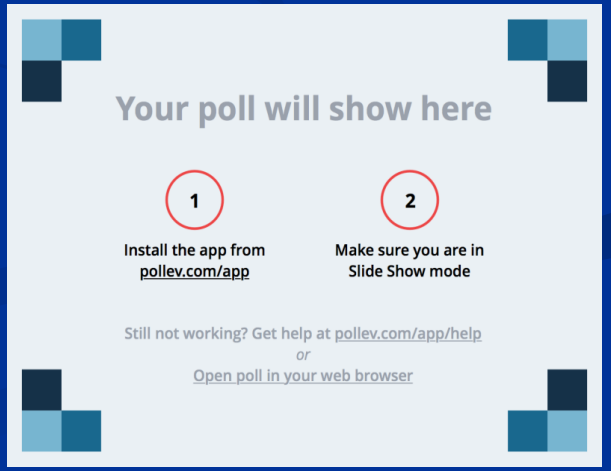
Kearon C. *Chest.* 2016;149:315-352; PMID: 26867832.

Appropriate Use of DOACs

- NVAF
- Acute post-op VTE (DVT and PE)
- DOAC reversal

Case

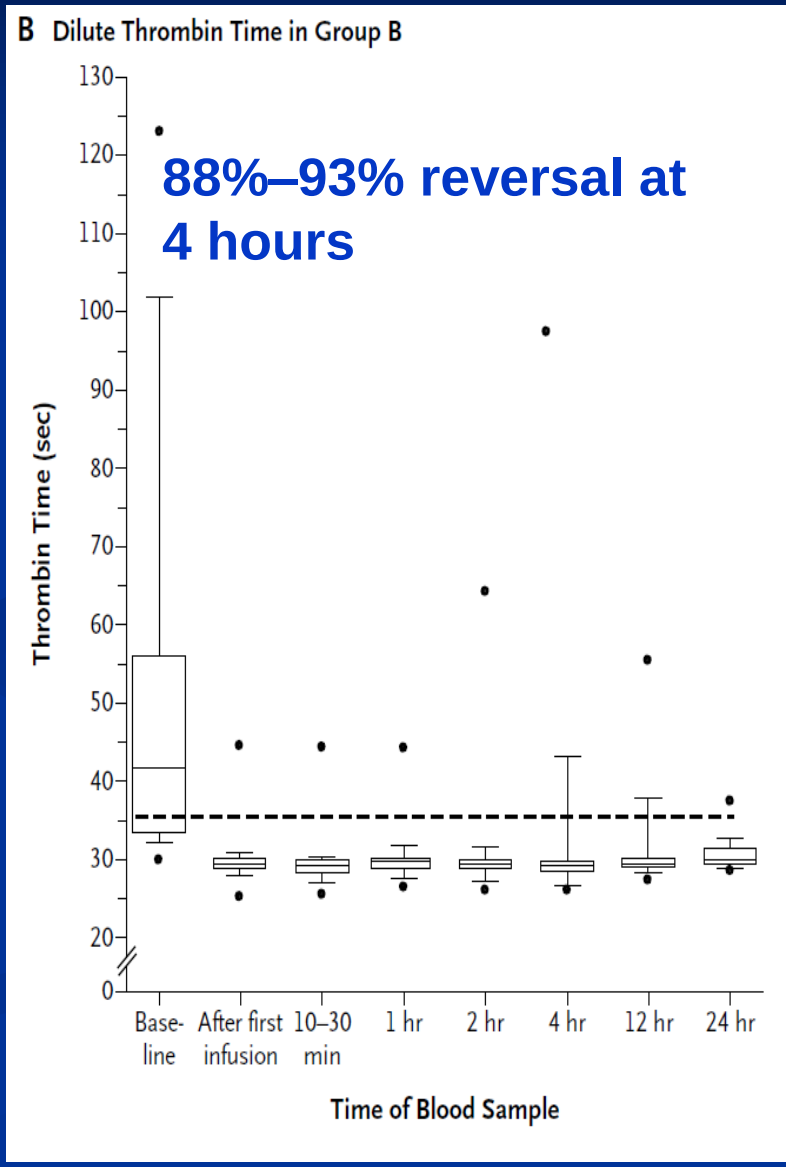
- 78-year-old female with AF, HTN, and peripheral vascular disease
- Admitted with moderate cellulitis and dry gangrene
- Will need BKA in next few days
- On dabigatran, CrCl = 40 mL/min
- What would you do?
  - A. Hold dabigatran for 2 days prior to surgery
  - B. Hold dabigatran for 4 days prior to surgery
  - C. Hold dabigatran for 4 days prior to surgery and bridge with LMWH
  - D. Give idarucizumab and go to surgery now
  - E. Measure aPTT daily and go to surgery when normal



aPTT = activated partial thromboplastin time; BKA = below-knee amputation.

RE-VERSE AD Study

- 39 patients in procedure group
  - 36 underwent a procedure
    - 33 with normal hemostasis
    - 2 mild abnormal hemostasis
    - 1 moderate abnormal hemostasis
- Primary outcome: reversal at 4 hours
  - 93% with dilute thrombin time
  - 88% with ecarin clotting time



RE-VERSE AD = Reversal Effects of Idarucizumab on Active Dabigatran.
Pollack CV Jr. *N Engl J Med*. 2015;373:511-520; PMID: 26095746 . For educational purposes only.

RE-VERSE AD Study

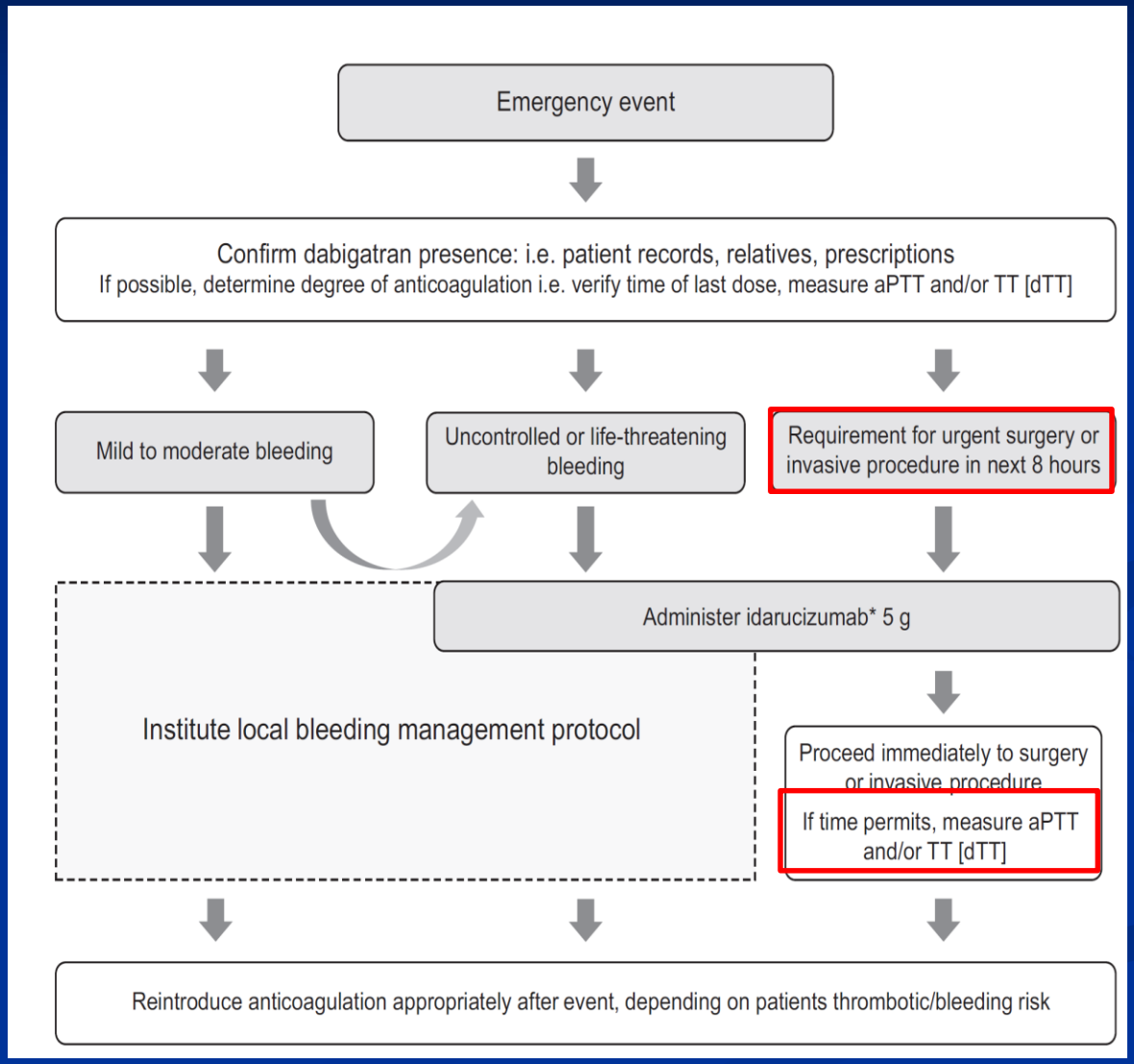
- **Thrombotic complications of all 90 patients post idarucizumab**
- **No patient was receiving anticoagulation**

Thrombotic Event	Time After Idarucizumab
DVT and PE	2 days
DVT	7 days
DVT, PE, and left atrial thrombus	9 days
NSTMI	13 days
Ischemic stroke	26 days

NSTMI = non–ST-segment elevation myocardial infarction.

Pollack CV Jr. *N Engl J Med*. 2015;373:511-520; PMID: 26095746 . For educational purposes only.

Protocol to Reverse Dabigatran with Idarucizumab

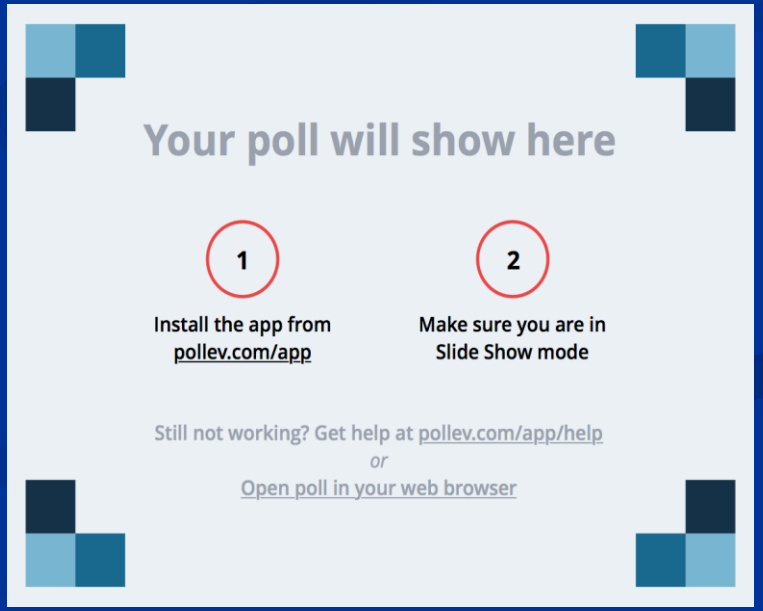


dTT = diluted thrombin time; TT = thrombin time

Eikelboom JW. *Circulation*. 2015;132:2412-2422; PMID: 26700008. For educational purposes only.

Case

- 62-year-old male on indefinite anticoagulation for nonprovoked PE 2 years ago
- Admitted with severe cellulitis and wet gangrene
- Needs urgent BKA for infection source control
- On anti-Xa inhibitor (rivaroxaban or apixaban or edoxaban)
- How would you reverse?
  - A. FFP
  - B. 3 factor PCC (non-activated)
  - C. 4 factor PCC (non-activated)
  - D. FEIBA
  - E. rVIIa



FEIBA = factor eight inhibitor bypass activity; FFP = fresh frozen plasma; PCC = prothrombin complex concentrate; rVIIa = activated recombinant factor VII.

Anticoagulation Forum Guidance

- We suggest hospitals develop evidence-based antithrombotic reversal and bleeding protocols that contain clinical decision support for providers and are easy to access and use in urgent or emergent situations.
- We suggest that general approaches to bleed management be employed for all patients presenting with severe hemorrhage.
- For DOAC patients, clinicians should attempt to rapidly determine time of last DOAC ingestion and patient's renal function to estimate remaining duration of exposure and potential utility of additional interventions.
- Until specific antidotes are available, we suggest clinicians consider use of nonspecific reversal strategies in patients refractory to standard therapies.
  - For direct Xa inhibitors, non-activated 4-Factor PCC 50 U/kg may be considered.

Burnett AE. *J Thromb Thrombolysis*. 2016;41:206-232; PMID: 26780747.

Table 3 Published studies of non-specific agents for reversal of oral factor Xa inhibitor anticoagulant effect in animals and humans

Reversal strategy	Animal studies (factor Xa inhibitor-treated animals)	Ex vivo studies (factor Xa inhibitor-treated volunteer or patient plasma)	Human studies (factor Xa-inhibitor-treated volunteers)
PCC	*Rivaroxaban*	*Rivaroxaban*	*Rivaroxaban*
	Corrected aPTT [48]	Corrected PT [13]	Corrected PT [9]
	Variably corrected PT [48, 49]	Variably corrected TG indices [13, 25]	Corrected PT (4-PCC > 3-PCC) [10]
	No reduction of blood loss in rabbits [48]	No correction of anti-Xa activity [13]	Corrected some TG indices (3-PCC > 4-PCC) [10]
	Reduced bleeding time in rats, but not primates [49]		No effect on aPTT, anti-Xa activity [10]
	Apixaban		*Edoxaban*
	No correction PT [50]		Reversal of prolonged bleeding duration and bleeding volume after punch biopsy (50 IU/kg) dose [11]
	No reduction hepatosplenic blood loss in rabbits [50]		
aPCC	*Rivaroxaban*	*Rivaroxaban*	
	Corrected aPTT [48]	Corrected PT [13]	
	Variably corrected PT [48, 49]	Corrected TG indices [13, 25]	
	No reduction of blood loss in rabbits [48]	No correction of anti-Xa activity [13]	
	Reduced bleeding time in rats and primates [49]		
	Edoxaban		
	Reduced bleeding time in rats [12]		
rVIIa	*Rivaroxaban*	*Rivaroxaban*	
	Corrected PT [49]	Corrected PT [13]	
	Reduced bleeding time in rats, but not primates [49]	Variably corrected TG indices [25]	
	Apixaban	No correction anti-Xa activity [13]	
	Corrected PT [50]		
	No reduction hepatosplenic blood loss in rabbits [50]		
	Edoxaban		
	Reduced bleeding time in rats [12]		

Adapted from [47]. *aPTT* activated partial thromboplastin time, *aPCC* activated prothrombin complex concentrate, *ETP* endogenous thrombin potential, *INR* international normalized ratio, *LT* lag time, *PCC* prothrombin complex concentrate, *PT* prothrombin time, *rVIIa* recombinant activated factor VII, *TEM* thromboelastometry, *TG* thrombin generation, *TP* thrombin potential, *TTP* time to peak

Siegal DM. *J Thromb Thrombolysis*. 2015; PMID: 25586208. For educational purposes only.

Systematic Review of Factor VIIa RCTs

Thromboembolic Event	rFVIIa (N=2583)	Placebo (N=1536)	Odds Ratio (95% CI)*	P Value
	number (percent)†			
All events	264 (10.2)	134 (8.7)	1.17 (0.94–1.47)	0.16
Arterial events	141 (5.5)	49 (3.2)	1.68 (1.20–2.36)	0.003
Venous events	137 (5.3)	88 (5.7)	0.93 (0.70–1.23)	0.61

RCT = randomized clinical trial.

Levi M. *N Engl J Med*. 2010;363:1791-1800; PMID: 21047223. For educational purposes only.

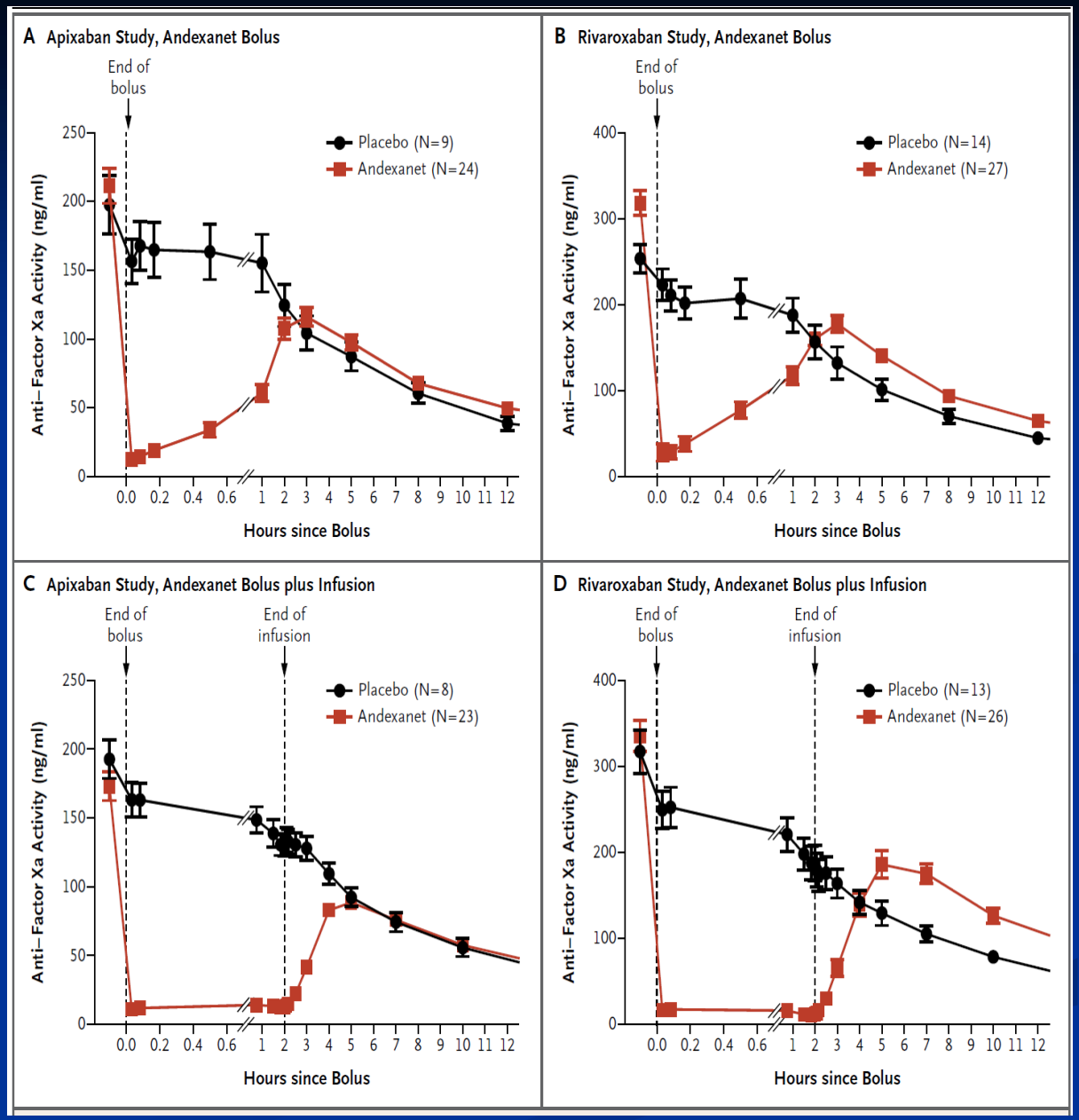
Systematic Review of Nonactivated PCC Cohort Studies

	Rate (95% CI)
TE events	1.4% (0.8–2.1)
Death for all causes	10.6% (5.9–16.6)
TE events in pts treated for bleeding	1.9% (1.0–3.1)
TE events in pts treated before urgent surgery or invasive procedures	0.8% (0.1–2.0)
TE events in pts treated with 4-factor PCCs	1.8% (1.0–3.0)
TE events in pts treated with 3-factor PCCs	0.7% (0.0–2.4)
TE events in high quality studies	2.3% (0.5–5.4)
Viral transmission after PCC administration	1.9% (0.3–4.9)
TE, thromboembolic, pts: patients, PCCs: prothrombin concentrates.	

Dentali F. *Thromb Haemost*. 2011;106:429-438; PMID: 21800002. For educational purposes only.

Andexanet Alpha

- Short duration of action
- Will require bolus + infusion
- Dose different for apixaban and rivaroxaban
- ANNEXA 4 study
  - Only bleeding, not urgent surgery



ANNEXA = Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors.
Siegal DM. *N Engl J Med*. 2015;373:2413-2424; PMID: 26559317. For educational purposes only.

Laboratory Testing of DOACs

Drug	Clinical objective	
	Exclude clinically relevant drug levels	
	Suggested test	Interpretation
Dabigatran	TT	Normal TT excludes clinically relevant levels
Rivaroxaban Edoxaban	None	Normal PT and APTT do not exclude clinically relevant levels
Apixaban	None	Normal PT and APTT do not exclude clinically relevant levels

Cuker A. *J Thromb Thrombolysis*. 2016;41:241-247; PMID: 26386967 For educational purposes only.

Appropriate Use of DOACs

- NVAF
- Acute post-op VTE (DVT and PE)
- DOAC reversal

Thank you for attending!

Please complete and return the evaluations – it really helps us develop quality education

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