Anticoagulation – New, Old, Reversal

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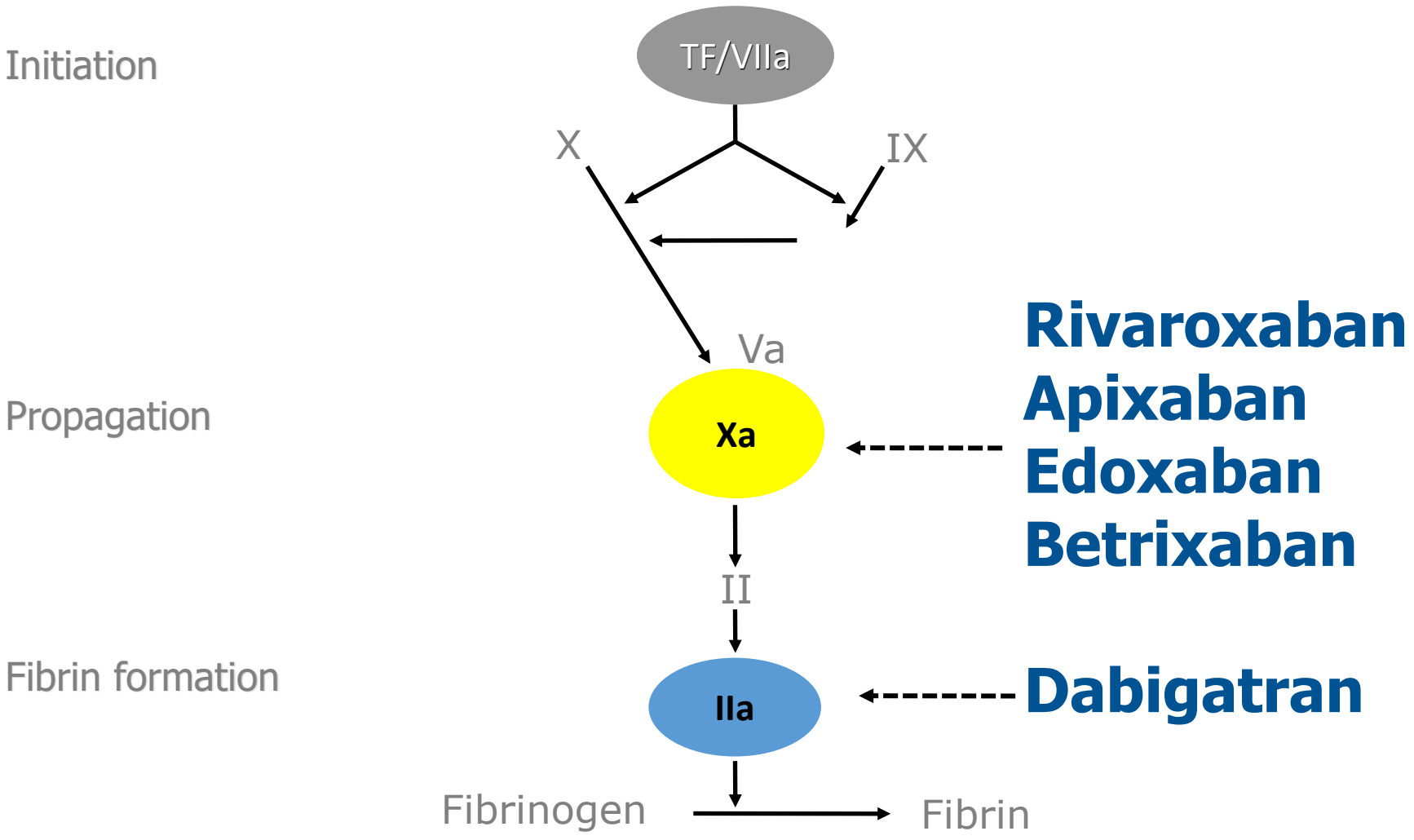
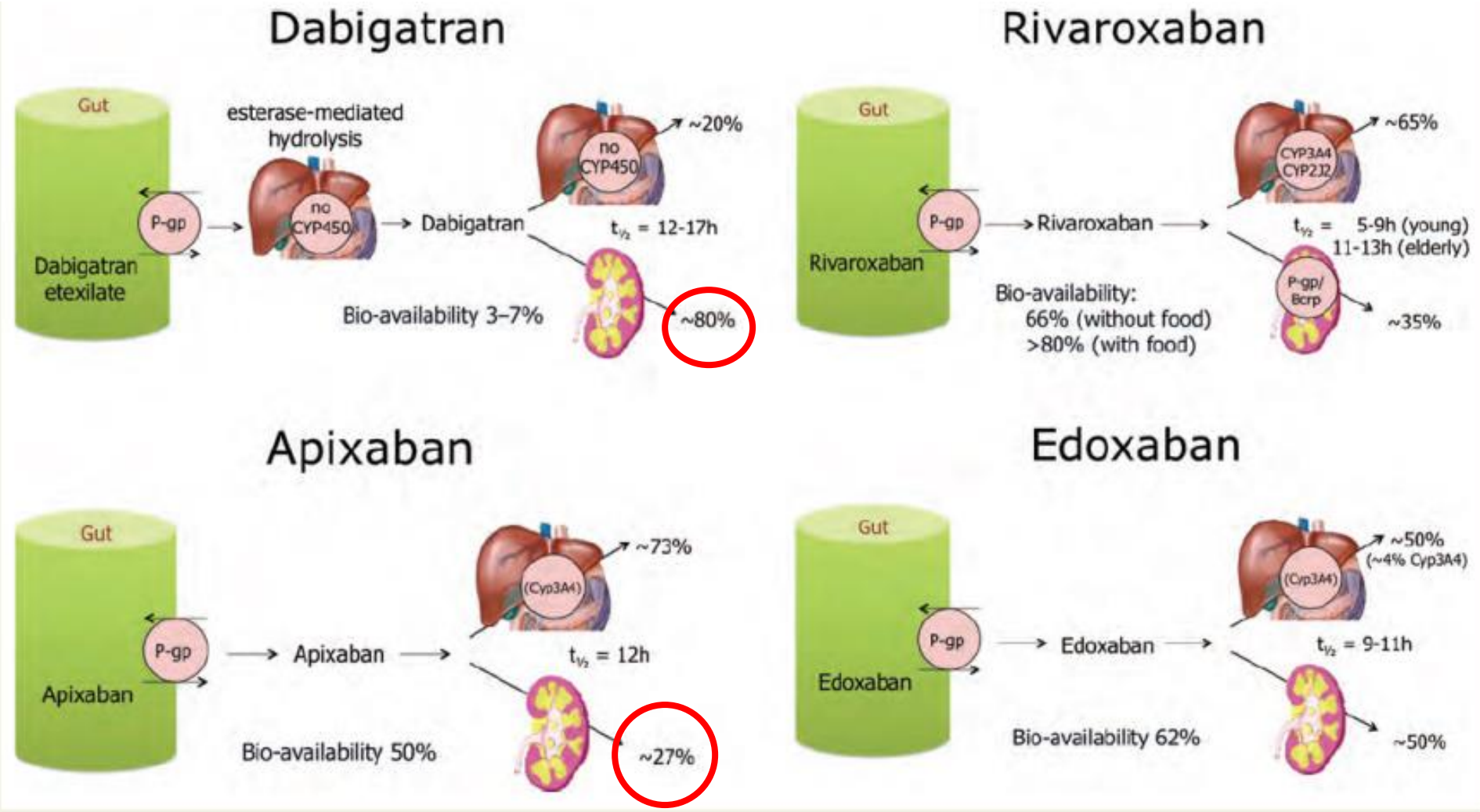
Steps in Coagulation **Coagulation Pathway** **Drugs**



Adapted from Hankey and Eikelboom. Circulation. 2011;123:1436-1450

NOACS DIFFER IN METABOLISM



Heidbuchel H et al. Europace 2013; 15: 625-651

Treatment Options for DVT and PE

Agent	Initial Dosing or Lead In	Maintenance Dosing
Preferred for Renal Insufficiency (<30 mL/min)		
UFH[1]	Weight-based bolus followed by weight-based continuous infusion Fixed subcutaneous: 333 U/kg followed by 250 U/kg BID	
Ideal for Normal Renal Clearance		
LMWH[1]	**Dalteparin:** 200 IU/kg every 24 h or 100 IU/kg BID **Enoxaparin:** 1 mg/kg BID or 1.5 mg/kg every 24 h **Nadroparin:** 86 IU/kg BID or 171 IU/kg every 24 h **Tinzaparin:** 175 IU/kg every 24 h	
Warfarin[1]	Bridge with LMWH or UFH ≥5 d 0.5–10 mg/d	• 0.5–6 mg/d, individualized to INR 2.0–3.0
Apixaban[2]	10 mg BID for 7 d ***Coadministration with strong dual CYP3A4 and P-gp inhibitors:*** For patients receiving apixaban > 2.5 mg BID, reduce the dose by 50% when apixaban is coadministered with drugs that are strong dual inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) (e.g., ketoconazole, itraconazole, ritonavir, clarithromycin)	• 5 mg BID • 2.5 mg BID for secondary prevention
Dabigatran[3]	5–10 d parenteral anticoagulant	• 150 mg BID (CrCL >30 mL/min)
Edoxaban[4]	5–10 d parenteral anticoagulant	• 60 mg/d • 30 mg/d (CrCL 15–50 mL/min, ≤60 kg, or with some P-gp inhibitors)
Rivaroxaban[5]	15 mg BID for 21 d with food	• 20 mg/d with food (CrCL >30 mL/min)

CrCl, creatinine clearance; INR, international normalized ratio; LMWH, low-molecular weight heparin; UFH, unfractionated heparin

1. Wells PS et al. *JAMA*. 2014;311:717-728. 2. Eliquis® (apixaban) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; March 2014. 3. Pradaxa® (dabigatran etexilate mesylate) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc; April 2014. 4. Savaysa® (edoxaban) [prescribing information]. Parisppany, NJ: Daiichi Sankyo, Inc, 2015. 5. Xarelto® (rivaroxaban) [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc; March 2014.

Clinical Case Challenge 1:
Low-risk, Healthy Patient Presents to Emergency Department With DVT

Clinical Case Challenge 1: Low-risk, Healthy Patient With DVT

Presentation

- 62-y-old male
- 4-d history of right calf and thigh pain
- 1 wk prior, traveled to China on business

Current Medications

- Atorvastatin
- Saw palmetto

Labs

- Normal: CBC, PT, PTT, Cr, UA, CXR, ECG

Past Medical History

- Hyperlipidemia
- Benign prostatic hyperplasia

Physical Examination

- BP 110/88, P 80, R 14, POx 100%, T 98.6^{o}, 82 kg
- Right leg +2 edema, warm, tender to palpation, pulses +2

Tests

- Ultrasound revealed a right popliteal vein thrombosis

BP, blood pressure; CBC, complete blood count; Cr, creatinine; CXR, chest X-ray; ECG, echocardiogram; P, pulse; POx, pulse oximetry; PT, prothrombin time; PTT partial thromboplastin time; R, respiration; T, temperature; UA, urinary analysis

Clinical Case Challenge 1: How Would You Handle This Patient?

- Is this patient a candidate for outpatient-only VTE therapy?
  - If so, what are your primary concerns?
- Is his use of saw palmetto a concern?
- When would you direct him to schedule a follow-up?
- Which agent would you prescribe for initial anticoagulation?
  - LMWH, bridge to warfarin
  - NOAC

Which of the following is an acceptable initial treatment choice for JF?

a. Dabigatran
b. Edoxaban
c. Rivaroxaban
d. Warfarin

JF is given an appropriate initial treatment. What of the following would be appropriate sub-acute treatment and secondary prevention of VTE in this case?

a. Apixaban 5 mg daily for 6 months

b. Dabigatran 150 mg once daily for at least 1 year

c. Rivaroxaban 20 mg daily for 3 months

d. Warfarin, INR range 2-3, indefinitely

JF has been taking an appropriate anticoagulant for 2 months. His DVT symptoms have resolved and he has no signs and symptoms of bleeding.
He calls the pharmacist at 11:30 AM.
He states he forgot to take his 8:00 AM dose.
What should JF do?

a. Take morning dose of anticoagulant now
b. Skip morning dose of anticoagulant and take next scheduled dose
c. Take morning dose of anticoagulant now and skip next scheduled dose
d. Stop oral anticoagulant and start subcutaneous LMWH as soon as possible

NOAC Acute Treatment: Study Regimens

Trial	Initial Heparin/Fondaparinux	Duration, mo	Regimen
Apixaban			
AMPLIFY	No	6	BID
Dabigatran			
RE-COVER	Yes	6	BID
RE-COVER II	Yes	6	BID
Edoxaban			
HOKUSAI VTE	Yes	3–12	QD
Rivaroxaban			
EINSTEIN-DVT	No	3, 6, or 12	QD
EINSTEIN-PE	No	3, 6, or 12	QD

Walter JA et al. *Curr Med Res Opin*. 2014;30:1975-1989.

NOAC Acute Treatment: Trial Designs

Study Drug	No. of Pts	PE or PE and DVT, n (%)	Isolated DVT, n (%)	Unprovoked, n (%)	Previous VTE, n (%)	TTR on VKA, %
Apixaban						
AMPLIFY	5395	1836 (34)	3532 (65)	4845 (90)	872 (16)	61
Dabigatran						
RE-COVER	2539	786 (31)	1749 (69)	Not reported	649 (26)	60
RE-COVER II	2568	815–819 (32)	1748–1750 (68)	Not reported	(17.5)	57
Edoxaban						
HOKUSAI-VTE	8240	3319 (40)	4921 (60)	5410 (66)	1520 (18)	64
Rivaroxaban						
EINSTEIN-DVT	3449	23 (1)	3405 (99)	2138 (62)	666 (19)	58
EINSTEIN-PE	4832	4832 (100)	0 (0)	3117 (65)	944 (20)	63

Pts, patients; TTR, time in therapeutic range; VKA, vitamin K antagonist

van der Hulle T et al. *J Thromb Haemost*. 2014;12:320-328. Dobesh PP et al. *Drugs*. 2014;74:2015-2032.

NOAC Acute Treatment: Meta-analysis of Efficacy/Safety

NOACs decrease the risk for recurrent VTE and major bleeding compared with VKAs

Outcome	Pooled Abs Risk Difference, % (95% CI)	NNT With NOAC to Prevent 1 Event (95% CI)
Recurrent VTE	-0.24 (-0.60–0.11)	417 (167 to -909)
Fatal PE	0.01 (-0.06–0.08)	10 000 (1667 to -1250)
Overall mortality	-0.10 (-0.47–0.28)	1000 (213 to -357)
Major bleeding	-0.67 (-1.13 to -0.21)	149 (88–476)
Non-fatal bleeding, critical site	-0.38 (-0.65 to -0.10)	263 (153–1000)
CRNM bleeding	-1.77 (-3.40 to -0.15)	56 (29–667)
Non-fatal ICH	-0.14 (-0.31–0.03)	714 (323 to -3333)
Major GI bleeding	-0.16 (-0.42–0.11)	625 (238–909)
Fatal bleeding	-0.09 (-0.17–0.00)	1111 (588–0)

Abs, absolute; CI, confidence interval; CRNM, clinically relevant nonmajor; GI, gastrointestinal; ICH, intracerebral hemorrhage; NNT, number needed to treat

van der Hulle T et al. *J Thromb Haemost*. 2014;12:320-328. Dobesh PP et al. *Drugs*. 2014;74:2015-2032.

NOACs Compared With LMWH and Warfarin

Efficacy

- All 4 NOACs are noninferior to LMWH/VKA for efficacy, regardless of weight, PE versus DVT, chronic kidney disease, and cancer[1]
- Edoxaban: prespecified submassive PE subgroup showed superiority[2]

Safety of NOACs combined (meta-analysis; N=27,023)[1]

- 39% less major bleeding
- 64% less fatal bleeding
- 63% less ICH than LMWH/VKA

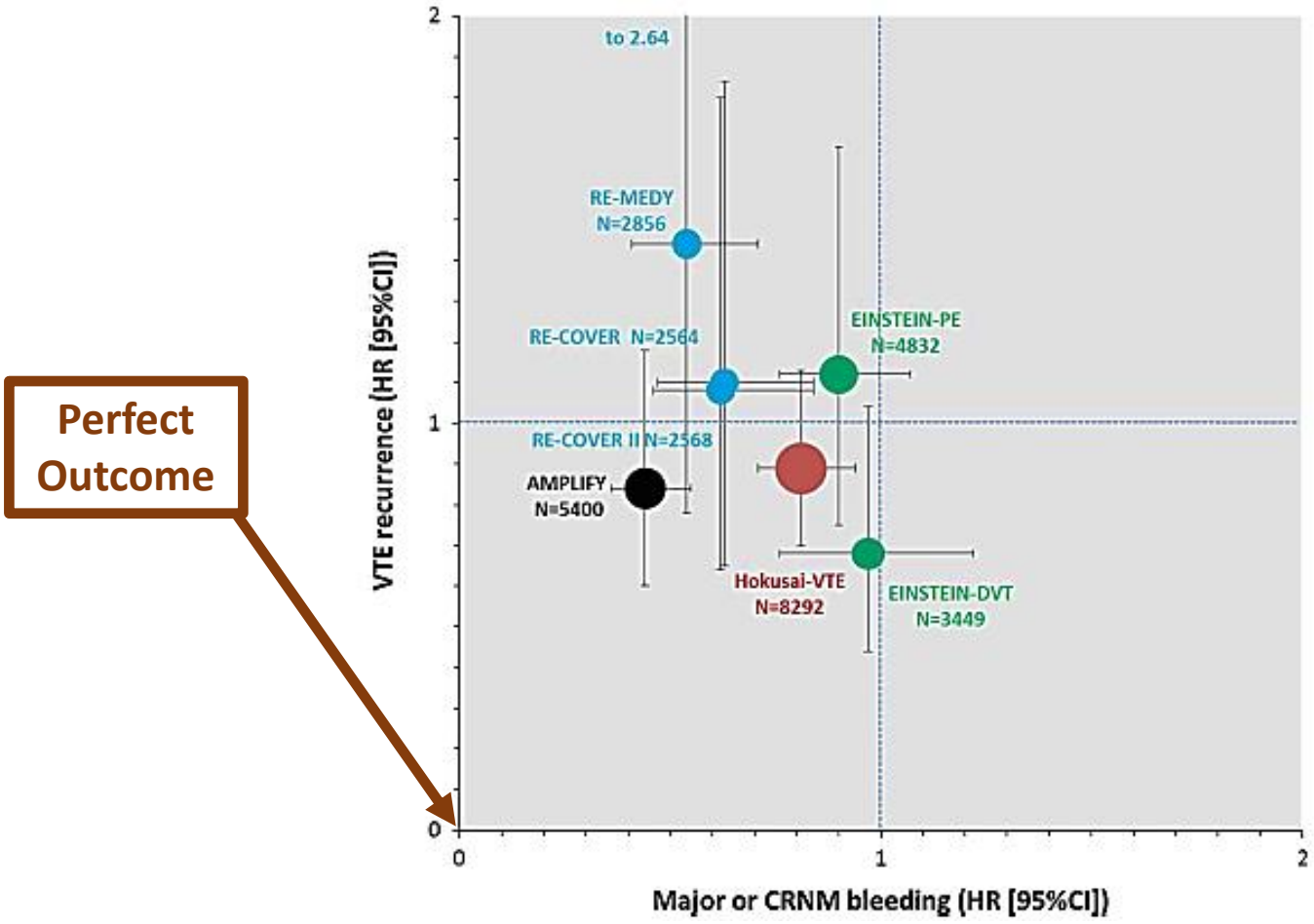
1. van Es N et al. *Blood*. 2014; 124:1968-1975. 2. The Hokusai-VTE Investigators. *N Engl J Med*. 2013; 369:1406-1415.

Which agent would you prescribe?

- LMWH
- LMWH/VKA
- NOAC

Relative Comparison of NOACs

VTE recurrence and rates of major or CRNM bleeding in VTE studies that compared NOACs with either LMWH and VKAs or VKAs



Reproduced with permission from Dr Cohen. Cohen AT et al. *Adv Ther*. 2014;31:473-493.

Take-home Message: Which NOAC?

Characteristic	NOACs	Rationale
Received initial parenteral anticoagulation	Apixaban, dabigatran, edoxaban, rivaroxaban	Allowance of 48–72 h of initial treatment before randomization
Affordability	None; use aspirin or patient preference	NOACs have similar costs
Concurrent clopidogrel	Rivaroxaban	Concomitant use allowed in trial
Chronic NSAID use	Apixaban	Concomitant use allowed in trial
Adherence challenges	Edoxaban, rivaroxaban	Once-daily dosing
Propensity for bleeding	Apixaban, rivaroxaban	Clinical reductions in major bleeding
Multiple concomitant medications with potential drug interactions	Apixaban, edoxaban	Allow for dose reduction

NSAID, nonsteroidal anti-inflammatory drug

Dobesh PP et al. *Drugs*. 2014;74:2015-2032.

Take-home Message: Which NOAC?
(continued)

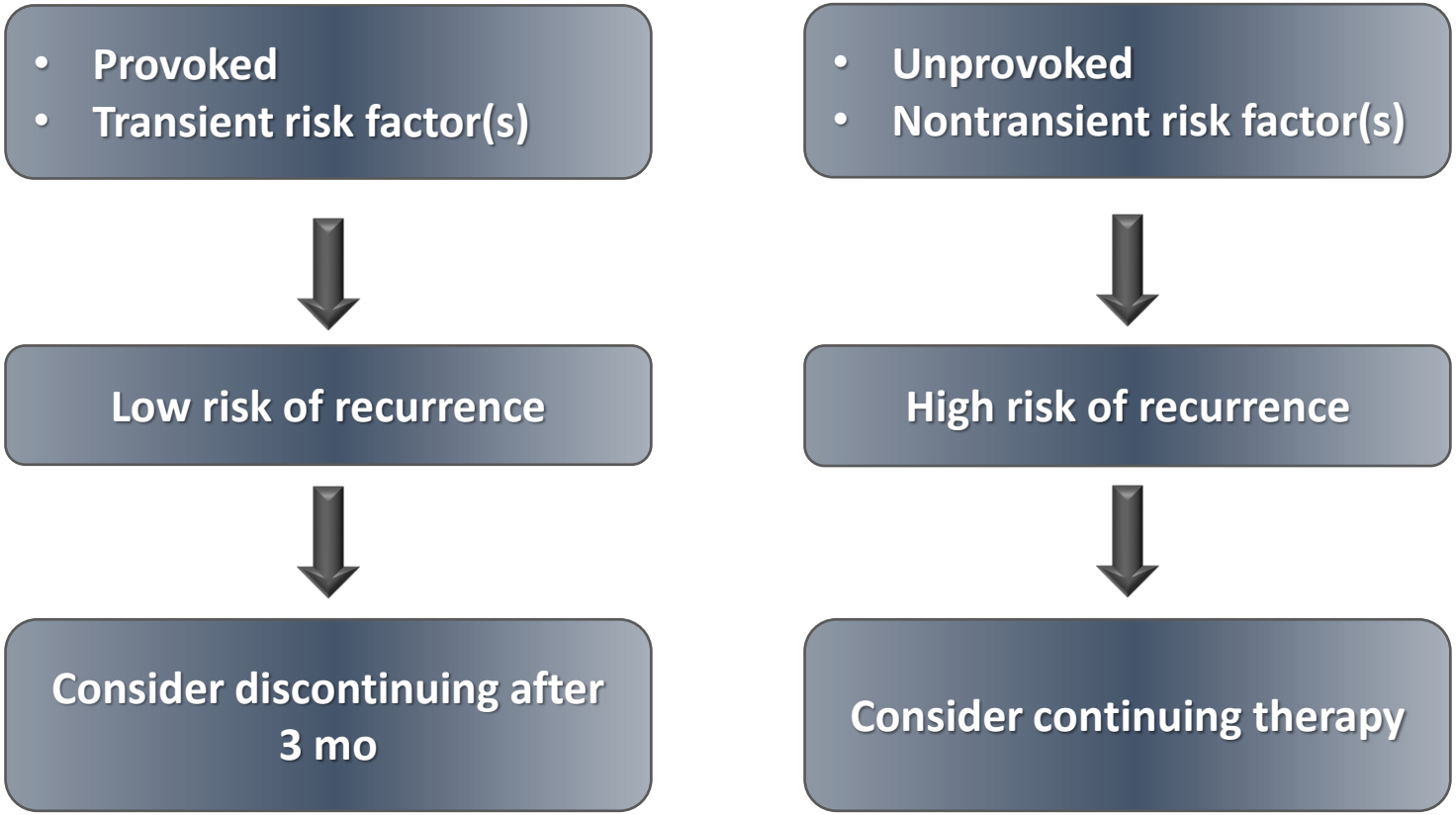
Comorbidity	NOAC	Rationale
Renal dysfunction CrCl ≥25 to ≤30 mL/min	Apixaban	Trial exclusion criteria
PE with elevated biomarkers	Edoxaban	Subpopulations in trial with high-risk features
Prior MI	Apixaban, edoxaban, rivaroxaban	MI events associated with dabigatran
Cancer and thrombophilia	None	Limited data
Low body weight (<60 kg)	Edoxaban	Trial dosing adjustment

MI, myocardial infarction

Dobesh PP et al. *Drugs*. 2014;74:2015-2032.

Secondary Prevention of VTE: Long-term Anticoagulation

- Should this patient continue on **long-term anticoagulation** (ie, >3 mo)?
  - What are his risk factors for recurrence?



McRae S. *Thromb J.* 2014;12:27-41.

Role of Secondary Prevention of VTE: Risk Factors for Recurrence

Risk Factors	Risk Measure	95% CI
Patient Features		
• Age (per decade increase)	HR, 1.17	1.11–1.24
• Male sex	HR, 1.56	1.22–2.00
Index Event		
• PE	HR, 1.19	0.87–1.63
• Isolated distal DVT	HR, 0.49	0.34–0.71
Risk Factors		
• Surgery	HR, 0.36	0.21–0.62
• Trauma-associated VTE*	HR, 0.51	0.32–0.87
Residual DVT		
• Overall population	OR, 1.50	1.11–2.03
• Unprovoked VTE	OR, 1.24	0.90–1.71
Increased D-dimer	OR, 2.36	1.65–3.36

*Compared with unprovoked VTE

CI, confidence interval; OR, odds ratio; HR, hazard ratio

Table reproduced with permission from the American Society of Hematology.
Agnelli G and Becattini C. *Am Soc Hematol Educ Program*. 2013;1:471-477.

NOAC Extended Treatment: Study Regimens

Trial	Duration, mo	Regimen
Apixaban		
AMPLIFY-EXT	12	BID
Dabigatran		
RE-MEDY	18	BID
RE-SONATE	6	BID
Rivaroxaban		
EINSTEIN-EXT	6 or 12	QDay

Maximum treatment duration before randomization to study drug or placebo: AMPLIFY-EXT: 12 months; RE-MEDY: 12 months; RE-SONATE: 18 months; EINSTEIN-EXT: 12 months.

Walter JA et al. *Curr Med Res Opin*. 2014;30:1975-1989.

NOAC Extended Treatment: Efficacy and Safety

NOACs decrease the risk for recurrent VTE versus placebo or VKA with a low risk of major hemorrhage

Study	No. of Pts	Dose and Comparator	Recurrent VTE, %	Major Hemorrhage	Fatal Bleeds, %
Apixaban					
AMPLIFY-EXT[1,a]	2482	5 mg BID 2.5 mg BID Placebo	1.7* 1.7* 8.8	0.1 0.2 0.5	0 0 0
Dabigatran					
RE-SONATE[2,b]	1343	150 mg BID Placebo	0.4* 5.6	0.3 0	0 0
RE-MEDY[2,b]	2856	150 mg BID Warfarin (INR 2–3)	1.8** 1.3	0.9 1.8	0 1(4)
Rivaroxaban					
EINSTEIN-EXT[3]	1196	20 mg/d Placebo	1.3* 7.1	0.7 0	0 0

[a]Patients had undergone 6 to 12 mo of anticoagulation prior to study entry

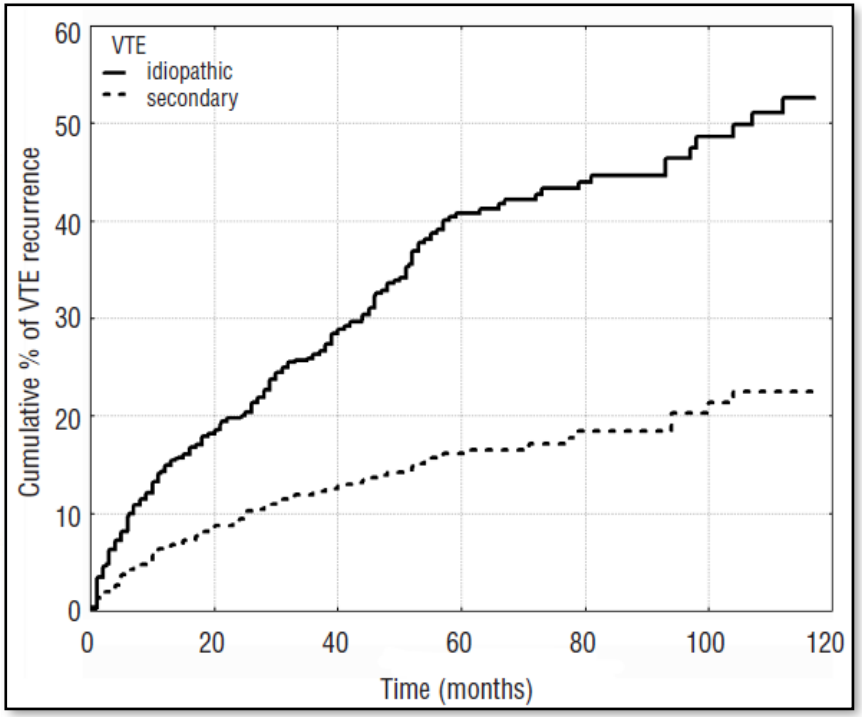
[b]Patients had undergone ≥3 mo of anticoagulation therapy prior to study entry

*$P < .001$; **noninferiority $P = .01$

1. Agnelli G et al; AMPLIFY-EXT Investigators. *N Engl J Med*. 2013;368:699-708. 2. Schulman S et al; RE-MEDY and RE-SONATE Trial Investigators. *N Engl J Med*. 2013;368:709-718. 3. The EINSTEIN-DVT Investigators. *N Engl J Med*. 2010;363:2499-2510.

Role of Prevention of Recurrent VTE

Cumulative Incidence of Recurrent Thromboembolism by VTE Type[1]



Study	Intervention	Recurrent VTE
PREVENT[2,3]	Warfarin, INR 1.5–2 vs placebo	↓64%
ELATE[4]	Warfarin, INR 2–3 vs INR 1.5–2	↓63%
AMPLIFY-EXT[5]	Apixaban vs placebo	↓81%
RE-SONATE[6]	Dabigatran vs placebo	↓93%
RE-MEDY[6]	Dabigatran vs warfarin, INR 2–3	Noninferior
EINSTEIN-DVT[7]	Rivaroxaban vs placebo	↓82%

The figure was obtained from the *Haematologica Journal* website http://www.haematologica.org. Reproduced with permission.

1. Prandoni P et al. *Haematologica.* 2007;92:199-205. 2. Goldhaber SZ et al. *Circulation.* 2011;123:664. 3. Ridker PM et al. *N Engl J Med.* 2003;348:1425-1434. 4. Kearon C et al. *N Engl J Med*. 2003;349:631-639. 5. Agnelli G et al; AMPLIFY-EXT Investigators. *N Engl J Med*. 2013;368:699-708. 6. Schulman S et al; RE-MEDY and RE-SONATE Trial Investigators. *N Engl J Med*. 2013; 368:709-718. 7. The EINSTEIN-DVT Investigators. *N Engl J Med*. 2010;363:2499-2510.

Conclusions

- The 4 NOACs can be used for the treatment of DVT and PE
  - Dabigatran and edoxaban require as per PI, five to 10 days of parenteral anticoagulation
- Dosing is dependent upon renal clearance and drug-drug interactions

Clinical Case Challenge 2:
Assisted Living Resident With PE

Clinical Case Challenge 2: Assisted Living Resident With PE

Presentation

- 85-y-old female
- Transferred from assisted living to ED with increasing SOB
- Fully ambulatory

Past Medical History

- Hyperlipidemia
- Hypertension
- DJD
- Hypothyroid

Current Medications

- Atorvastatin
- Amlodipine
- HCTZ
- Levothyroxine

Physical Examination

- BP 140/78, P 80, R 21, POx 94%, T 98.6º, 50 kg
- Thin

Labs

- Normal CBC, PT, PTT, Cr 1.3, CrCl 46 cc/min, UA, CXR, ECG

Tests

- CTPA: Bilateral lower lobe single segmental defects

CTPA, computed tomography pulmonary angiogram; DJD, degenerative joint disease; ED, emergency department; HCTZ, hydrochlorothiazide; SOB, shortness of breath

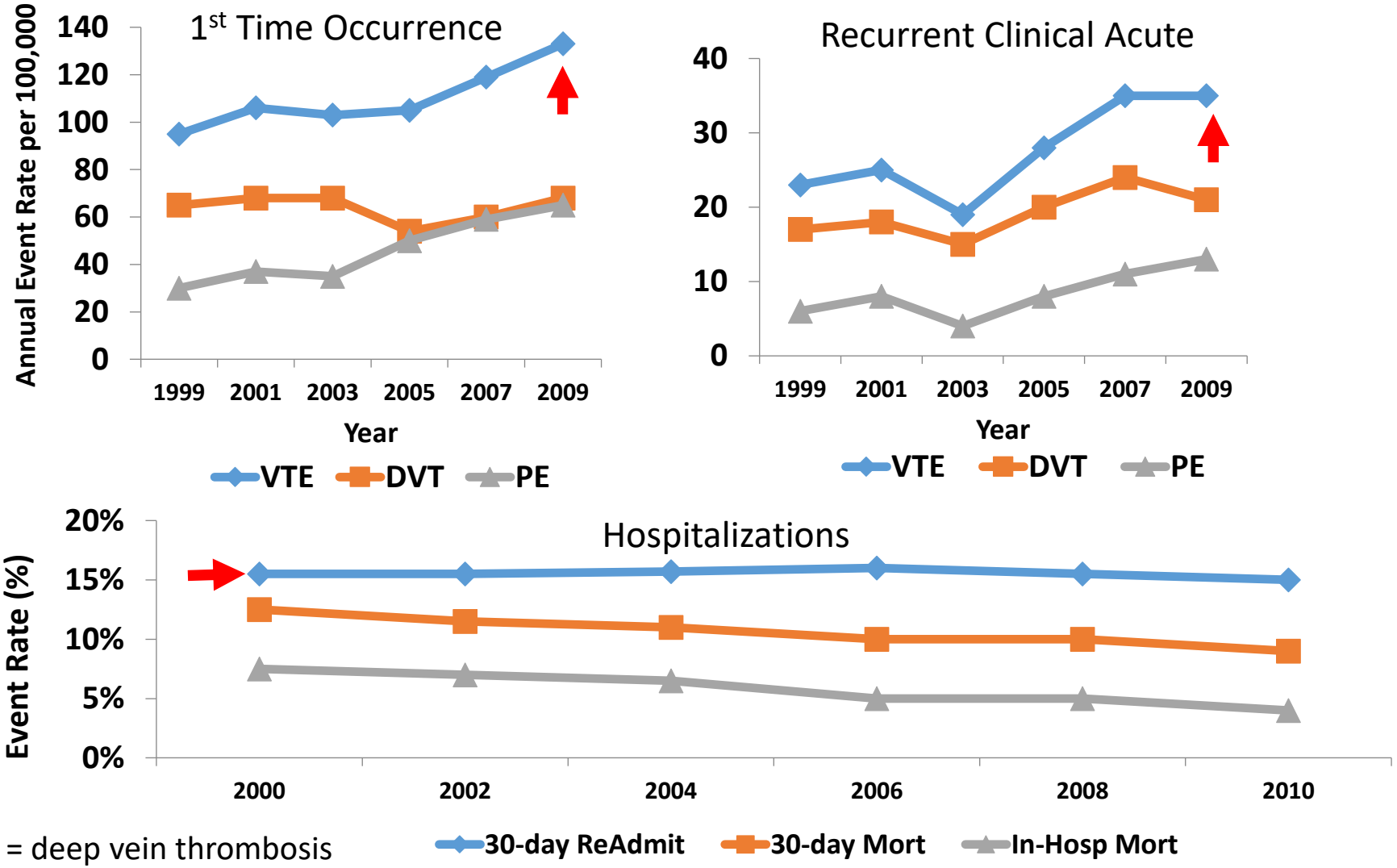
Clinical Case Challenge 2: How Would You Handle This Patient?

- Is this patient a candidate for outpatient-only VTE therapy?
  - If so, what are your primary concerns?
- Is this patient a candidate for observation care?
- How would this patient be managed in your institution today?
- Do you think the standard approach for this patient will change in the near future?

What anticoagulant regimen is the best choice for FF's initial treatment?

a. Apixaban 10 mg twice daily
b. Dabigatran 150 mg twice daily
c. Edoxaban 30 mg once daily
d. Rivaroxaban 15 mg once daily

- 900,000 patients (1 to 2 per 1,000) afflicted with DVT or PE each year
- 60,000-100,000 Americans die of DVT or PE

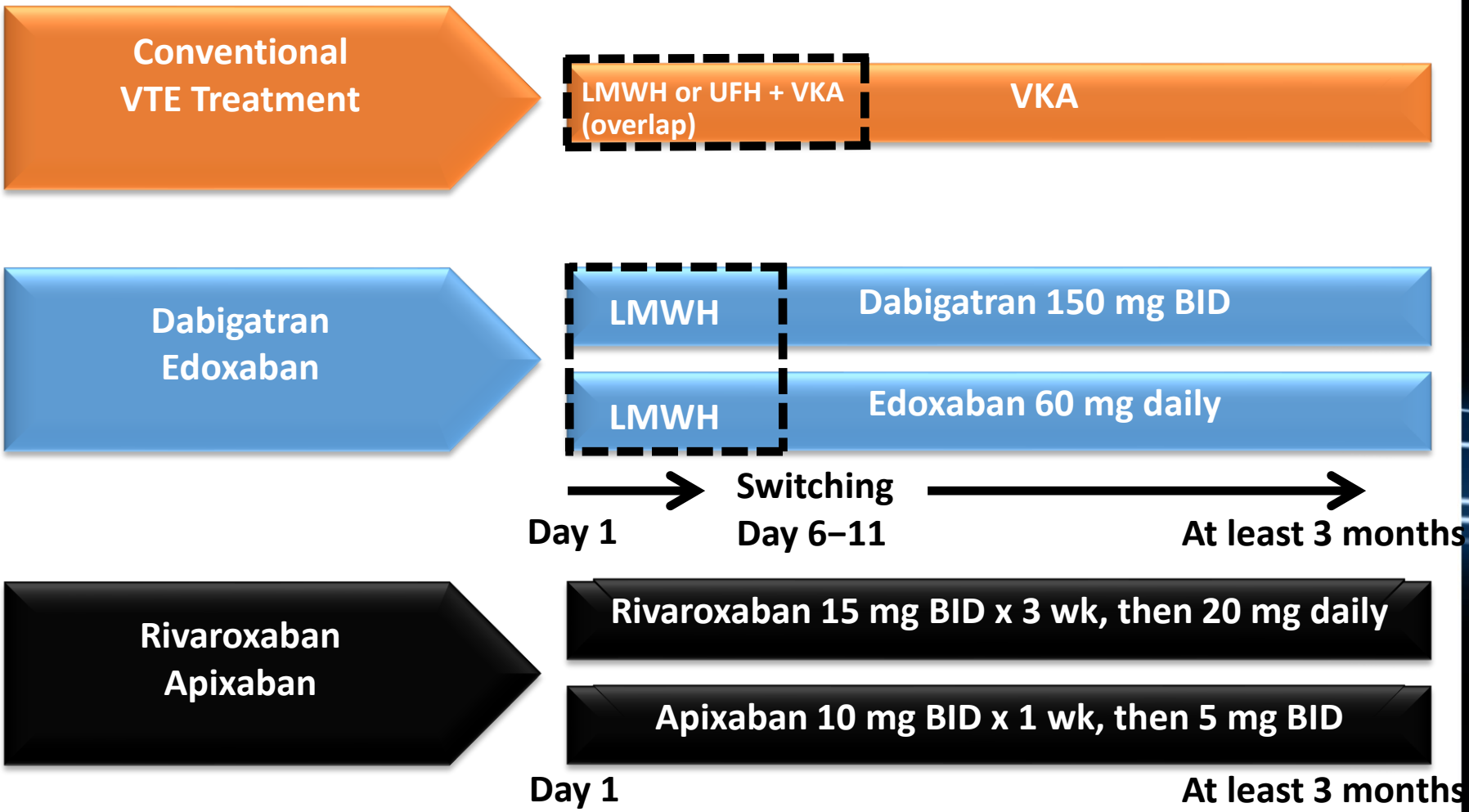


DVT = deep vein thrombosis

PE = pulmonary embolism

Huang W et al. *Am J Med.* 2014; 127: 829-39. Minges KE et al. *Am J Cardiol*. 2015; 116:1436-42. Beckman MG et al. *Am J Prev Med*. 2010; 38:S495-501.

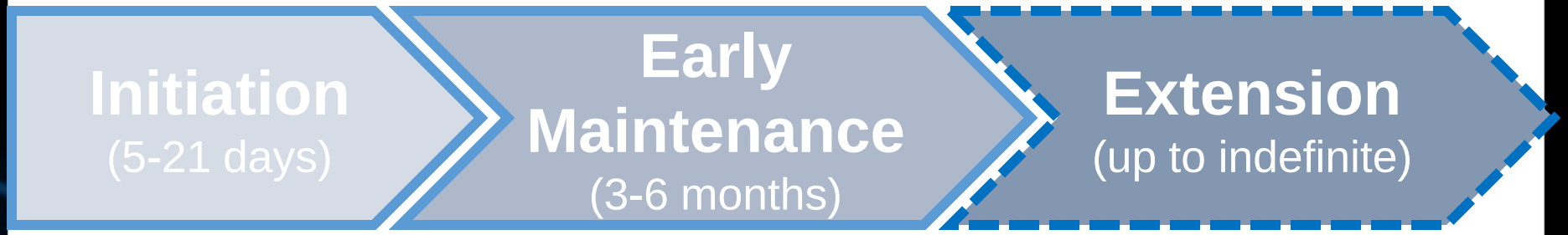
Acute VTE Treatment Options



UFH = unfractionated heparin
LMWH = low-molecular-weight heparin or fondaparinux
VKA = vitamin K antagonists

Streiff MB et al. *J Thromb Thrombolysis*. 2016; 41:32-67

Phases of Treatment for VTE

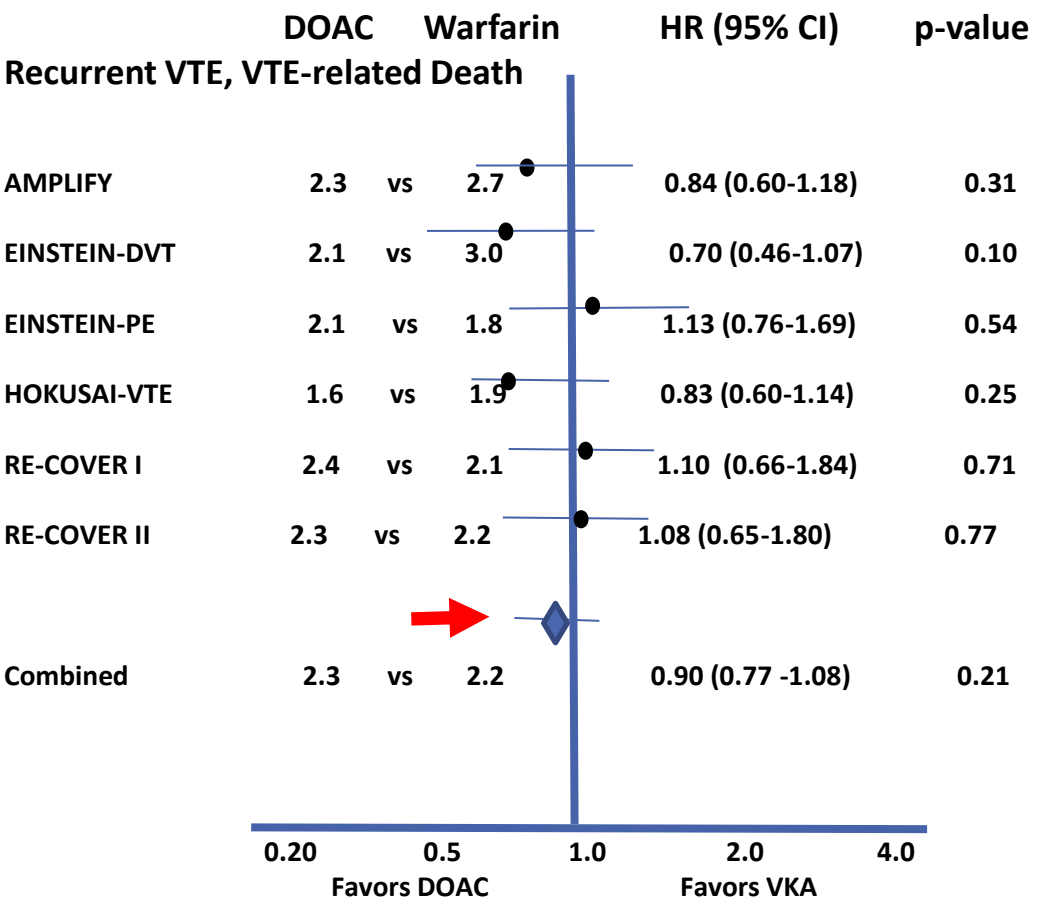


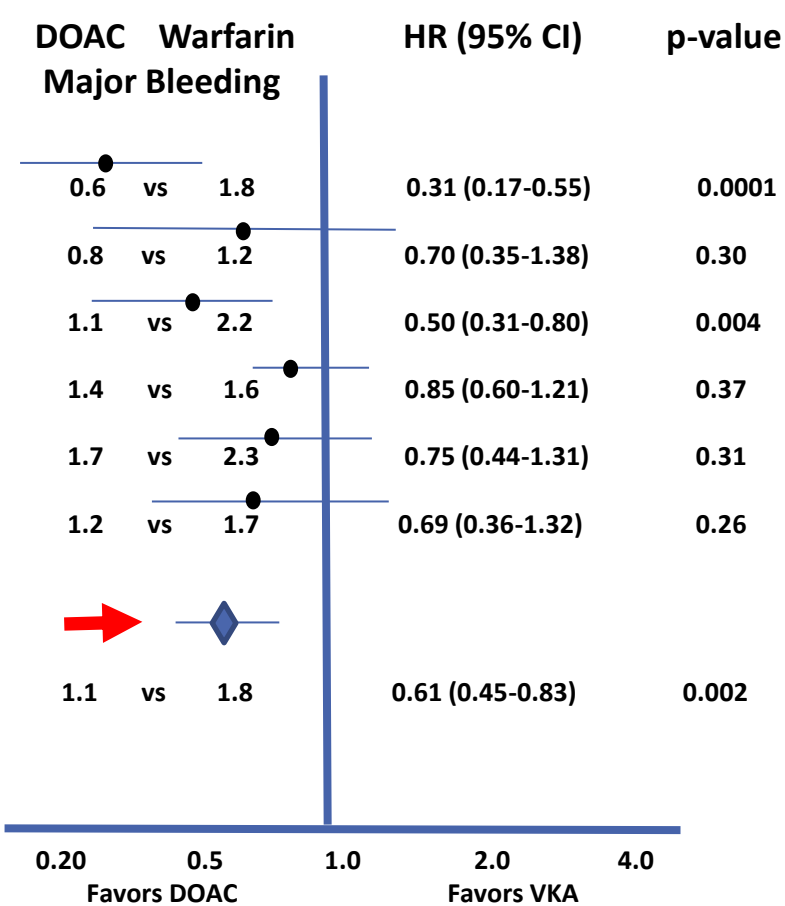
Initiation (5-21 days)	Early Maintenance (3-6 months)	Extension (up to indefinite)
UFH, LMWH, fondaparinux	Warfarin (INR 2.0-3.0)	Warfarin (INR 2.0-3.0)
Rivaroxaban 15 mg BID	Rivaroxaban 20 mg daily	Rivaroxaban 20 mg daily
Apixaban 10 mg BID	Apixaban 5 mg BID	Apixaban 2.5 mg BID
	Dabigatran 150 mg BID	Dabigatran 150 mg BID
	Edoxaban 60 mg daily	----------
		Warfarin (INR 1.5-2.0)
		Aspirin 81 mg daily

Blondon M et al. *Circulation*. 2015; 132:1856-9.

Patients with VTE and DOACs: Outcomes

Meta-analysis (n=27,235)



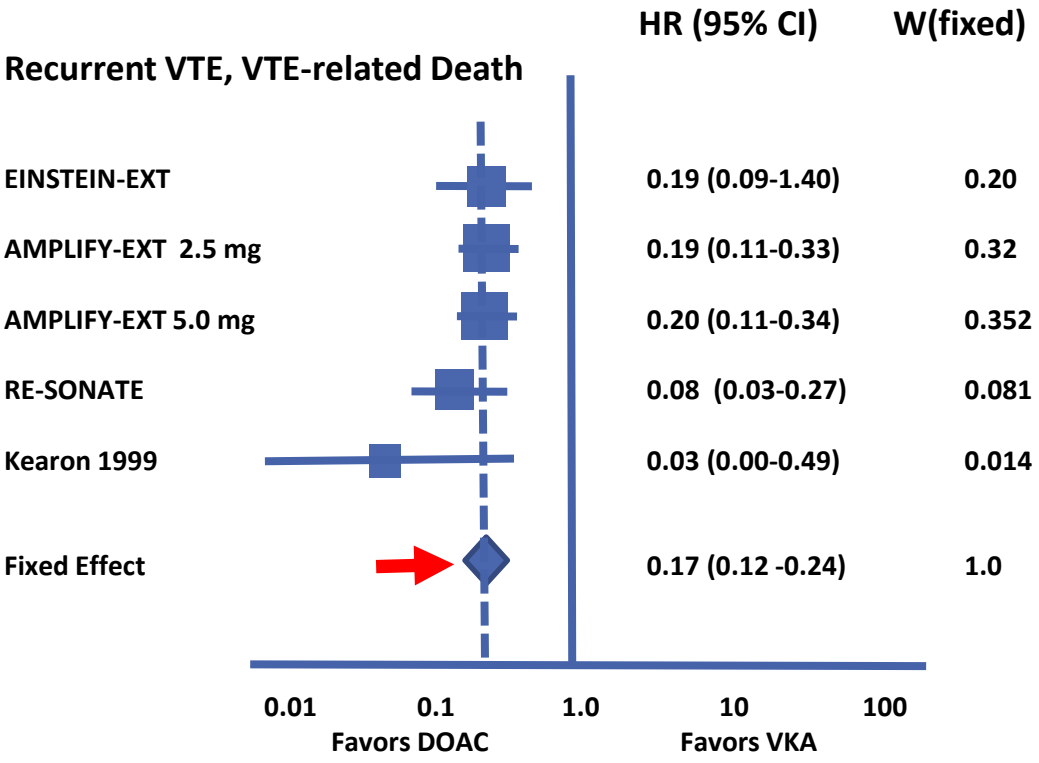


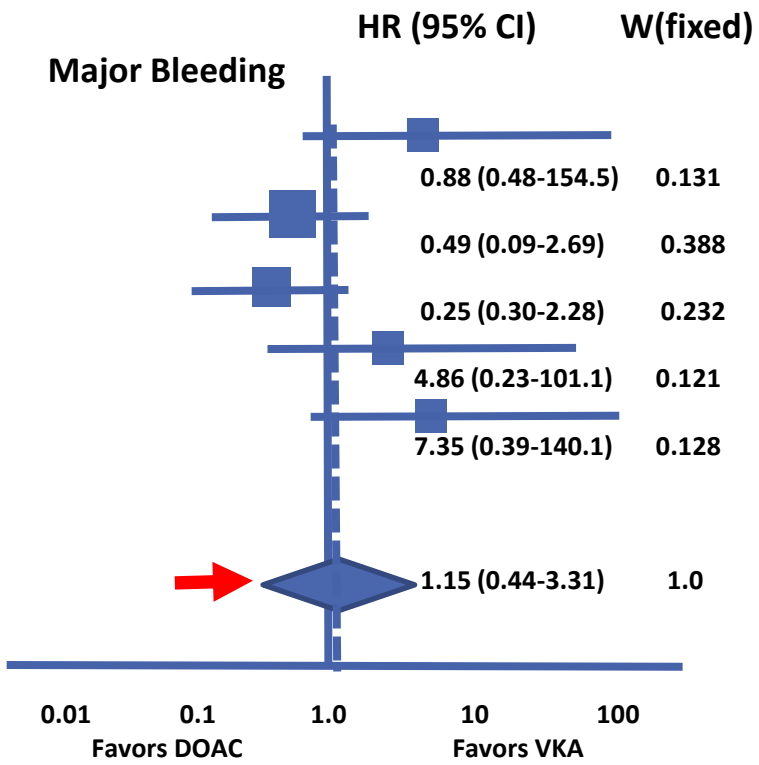
- 39% lower major bleeding
- 64% lower fatal bleeding
- 63% less intracranial hemorrhage vs. vitamin K antagonists

van Es N et al. *Blood*. 2014; 124:1968-75.

Extended VTE Treatment & DOACs: Outcomes

Meta-analysis (n=3,015)





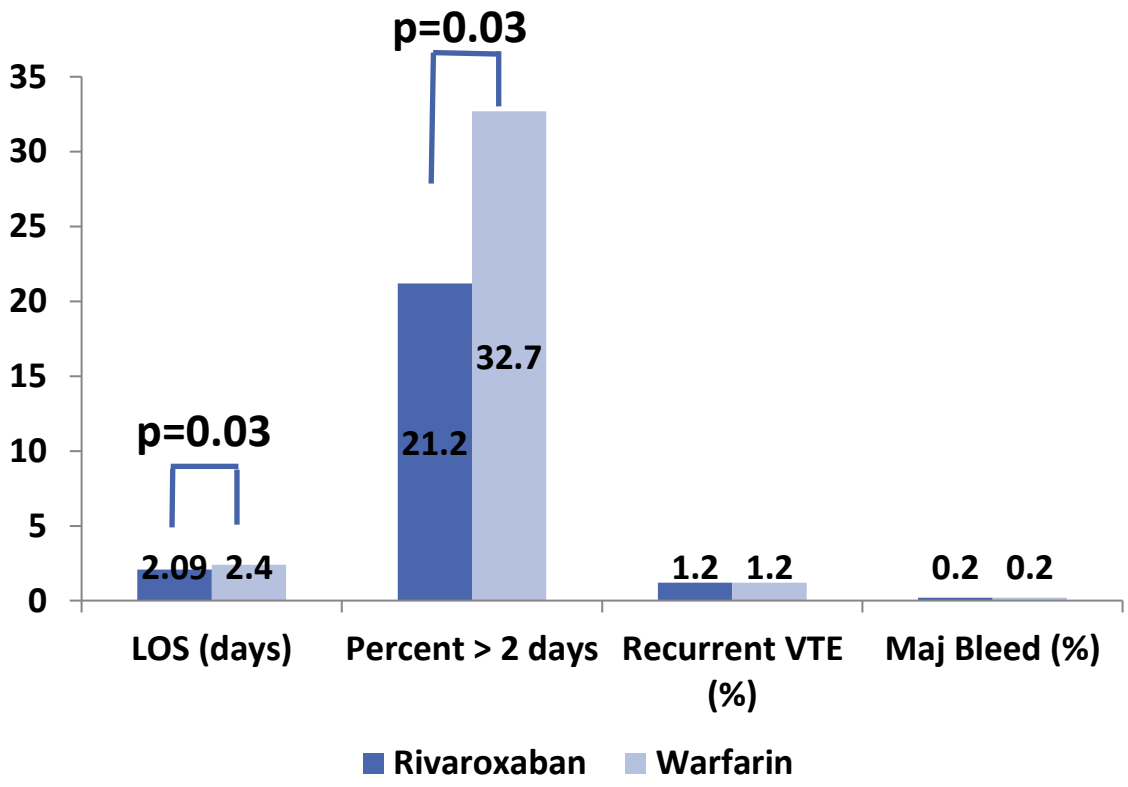
- 83% relative risk reduction of recurrent VTE or VTE-related death (CI: 0.12-0.24, p<0.0001)
- No significant increase in the risk of major bleeding (CI: 0.40-3.31, p=0.38)

W = warfarin

Sindet-Pedersen C et al. *Thromb Res.* 2015; 136:732-8.

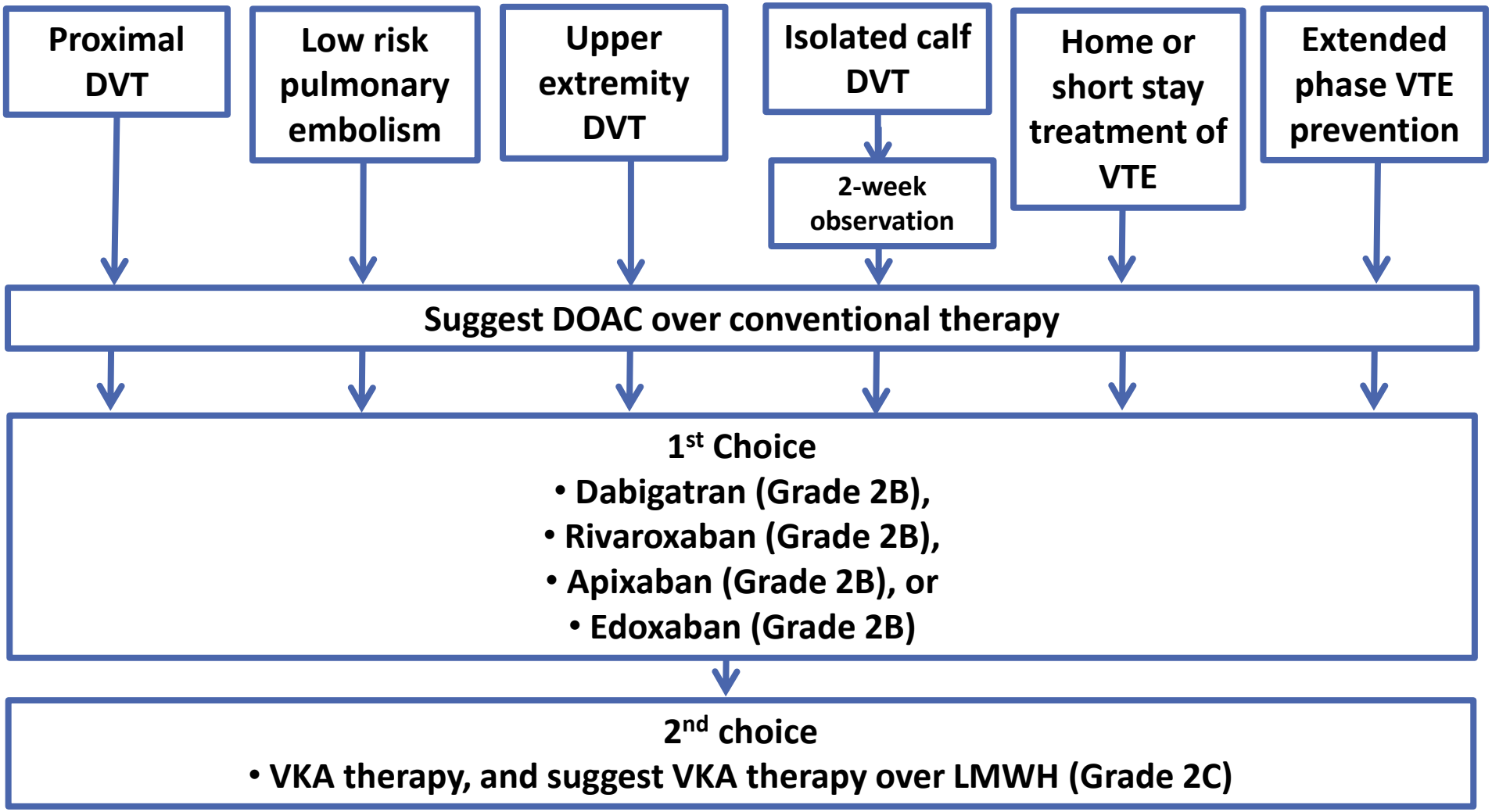
VTE Patients Managed in Observation Status

- Comparison of PE patients managed through observation stays
- Rivaroxaban (n=401) vs. parenterally-bridged warfarin (n=401)
- U.S. claims data 2012-2015 identified PE patients
- Rivaroxaban use associated with
  - Shorter length of stay (-0.25 days)
  - Fewer encounters lasting >2 midnights (21.1% vs. 32.7%)
  - Lower total hospital costs (-$240) (p=0.03 for all)
  - No difference in recurrent VTE and major bleeding requiring readmission



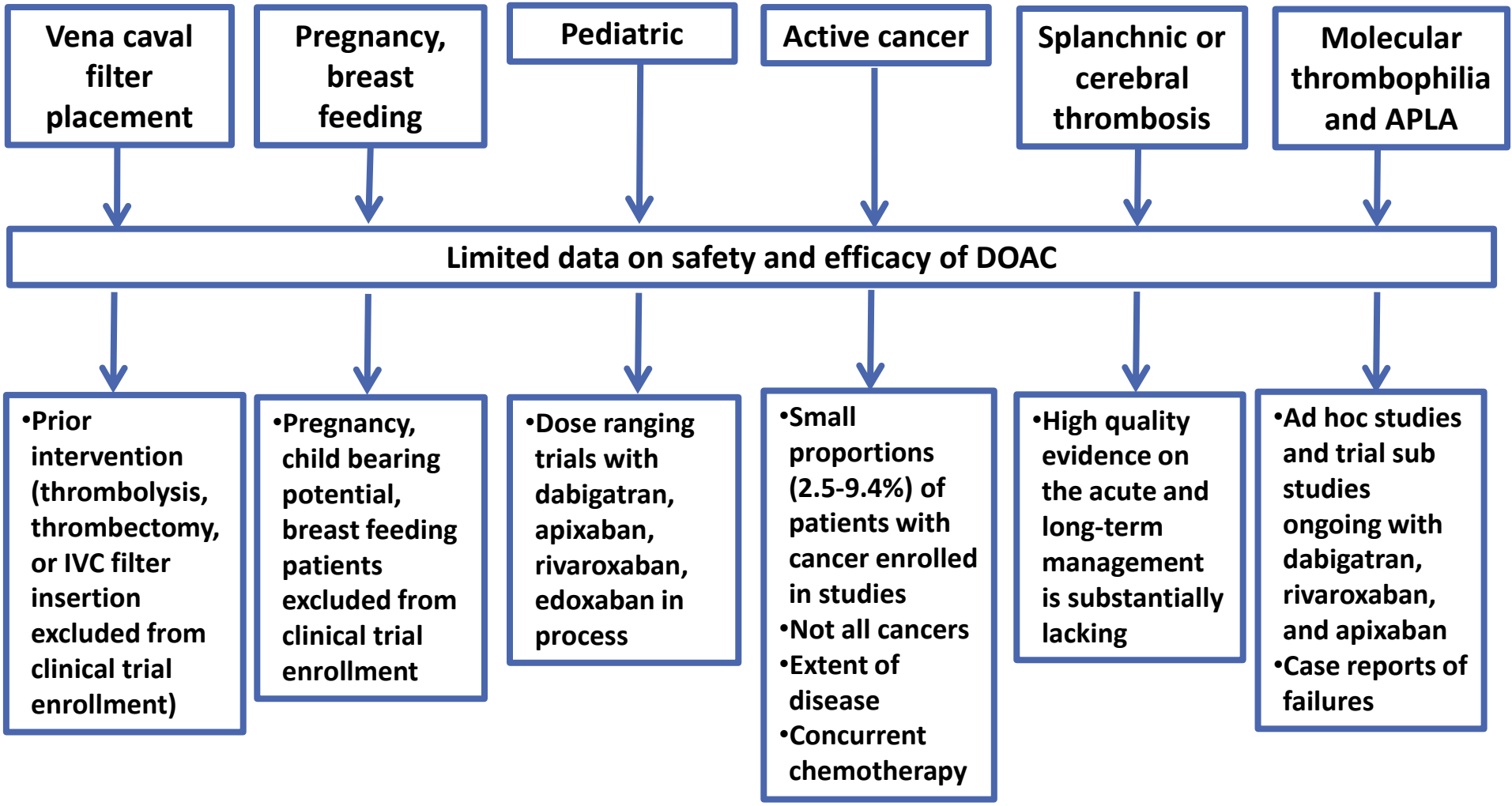
Kohn CG et al. American Society of Hematology Meeting. San Diego, CA; 2016 Dec 3. https://ash.confex.com/ash/2016/webprogram/Paper88809.html (accessed 2017 Mar 22). Abstract 2337.

Initiation Phase: VTE Treatment



Becattini C. *J Am Coll Cardiol*. 2016; 67:1941-55.
Kearon C et al. *Chest.* 2016; 149:315-52.

Initiation Phase: VTE Treatment



APLA = antiphospholipid antibodies

IVC = inferior vena caval filter

Kearon C et al. *Chest*. 2016; 149:315-52.

Becattini C et al. *J Am Coll Cardiol*. 2016; 67:1941-55.

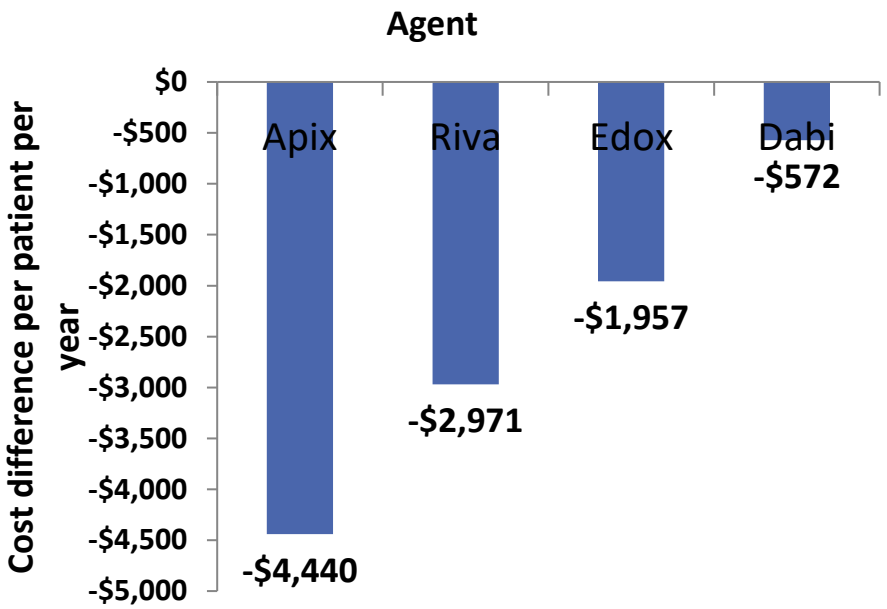
Initiation Phase: Patient Criteria

Characteristic	Drug Choice	Comments
Renal disease (creatinine clearance <30 mL/min)	UFH, VKA	• DOACs and LMWH contraindicated with severe renal impairment • DOAC dosing is unique for each medication and level of renal function
Liver disease and coagulopathy	LMWH	• DOACs contraindicated if elevated baseline INR due to liver disease • VKA difficult to control and INR may not reflect antithrombotic effect
Taking medications known to interact with DOACs	LMWH	• Agents that increase or decrease drug exposure depending on the DOAC being used, including P-glycoprotein (Pgp) and strong CYP3A4 inducers and inhibitors (rifampin, ketoconazole, dronedarone, and itraconazole); depends on the DOAC being used
Coronary artery disease	VKA, rivaroxaban, apixaban, edoxaban	• Coronary artery events appear to occur more often with dabigatran than with VKA • Has not been seen with the other DOACs, and they have demonstrated efficacy for coronary artery disease
Dyspepsia or history of gastrointestinal bleeding	VKA, apixaban	• Dabigatran can cause dyspepsia • Dabigatran, rivaroxaban, and edoxaban may be associated with more gastrointestinal bleeding than VKA
Extremes of weight (e.g. <50kg or >120kg) or BMI >40 kg/m^2	VKA	• Patients at extremes of weight represented a very small proportion of patients in DOAC VTE trials
Parenteral therapy to be avoided	Rivaroxaban, apixaban	• VKA, dabigatran, and edoxaban require initial parenteral therapy

Kearon C et al. *Chest*. 2016; 149:315-52. Burnett AE et al. *J Thromb Thrombolysis*. 2016; 41:206-32. Martin K. *J Thromb Haemost.* 2016; 14:1308-14.

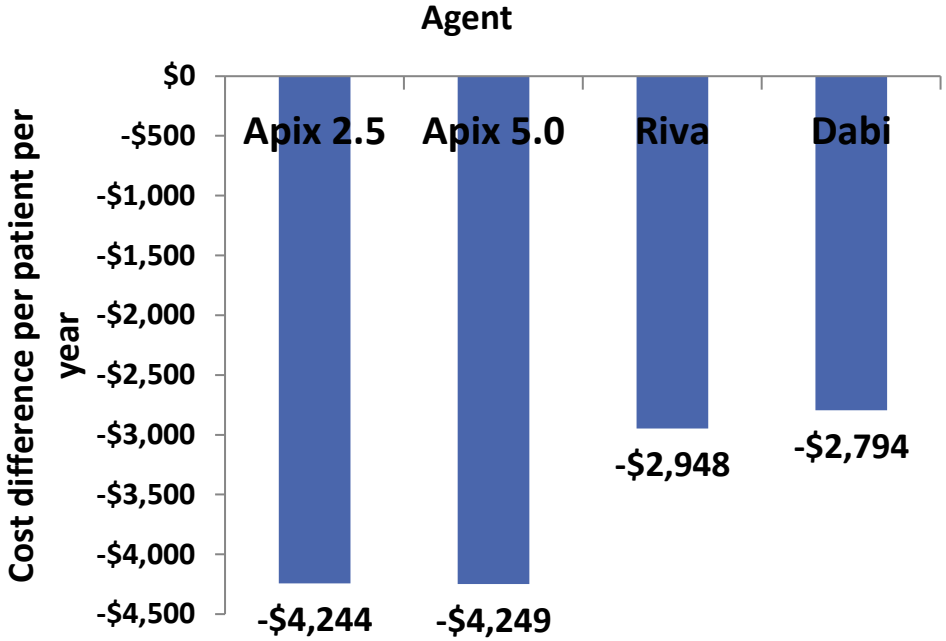
Real World Cost of VTE

Acute VTE Treatment



- Application of clinical trial event rates to U.S. population
- Estimates of annual cost vs. traditional treatment
- Savings generated from reductions in recurrent VTE and bleeding rates

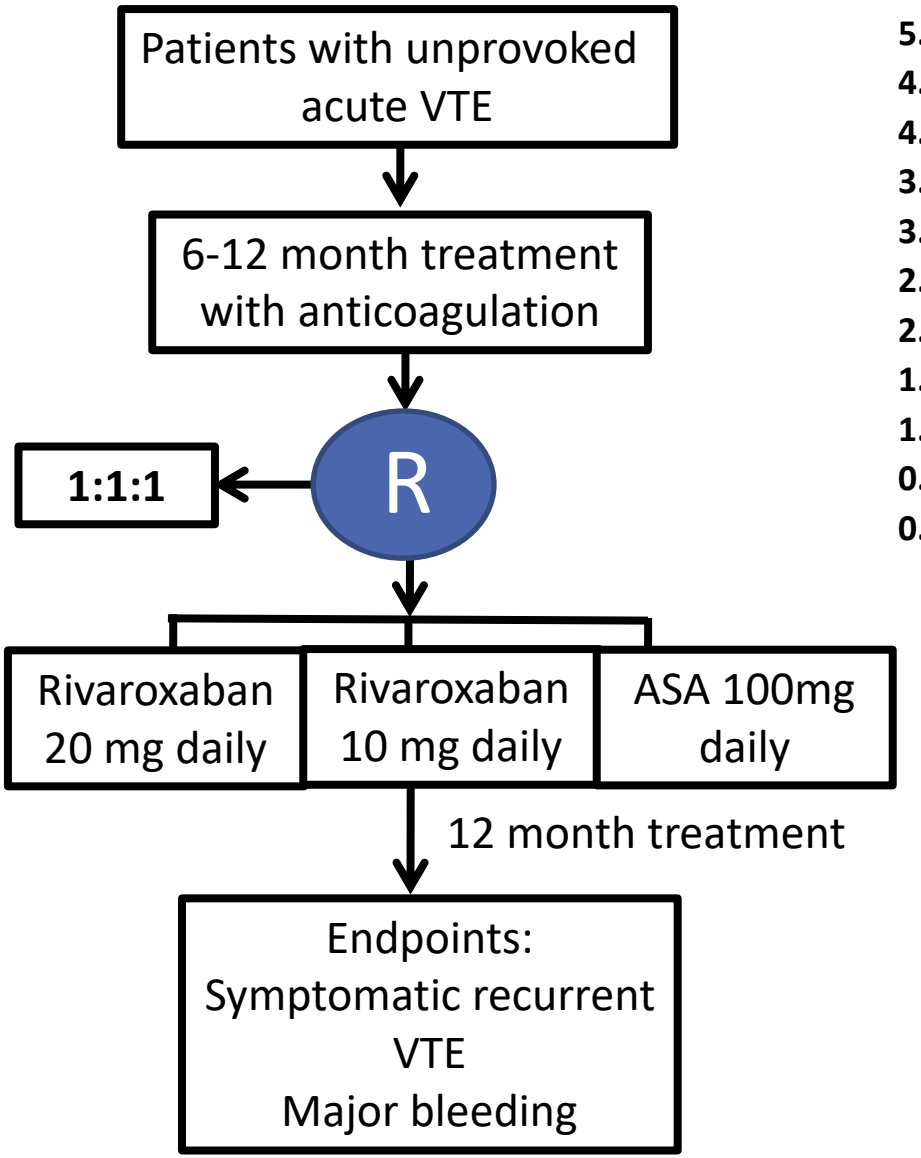
Extended VTE Treatment

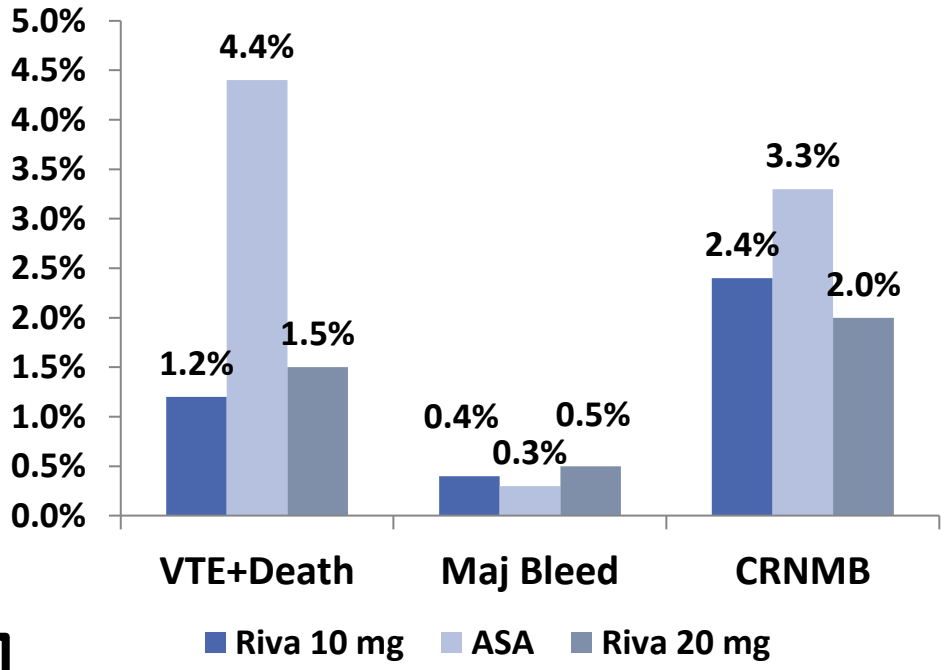


- Annual medical costs among claims database adjusted to 2013 costs
- Comparison of annual cost vs. traditional treatment
- Savings generated from reductions in recurrent VTE and bleeding rates

Amin A et al. *Clin Appl Thromb Hemost.* 2016; 22:5-11.
Amin A et al. *J Thromb Thrombolysis*. 2015; 40; 131-8.

EINSTEIN CHOICE



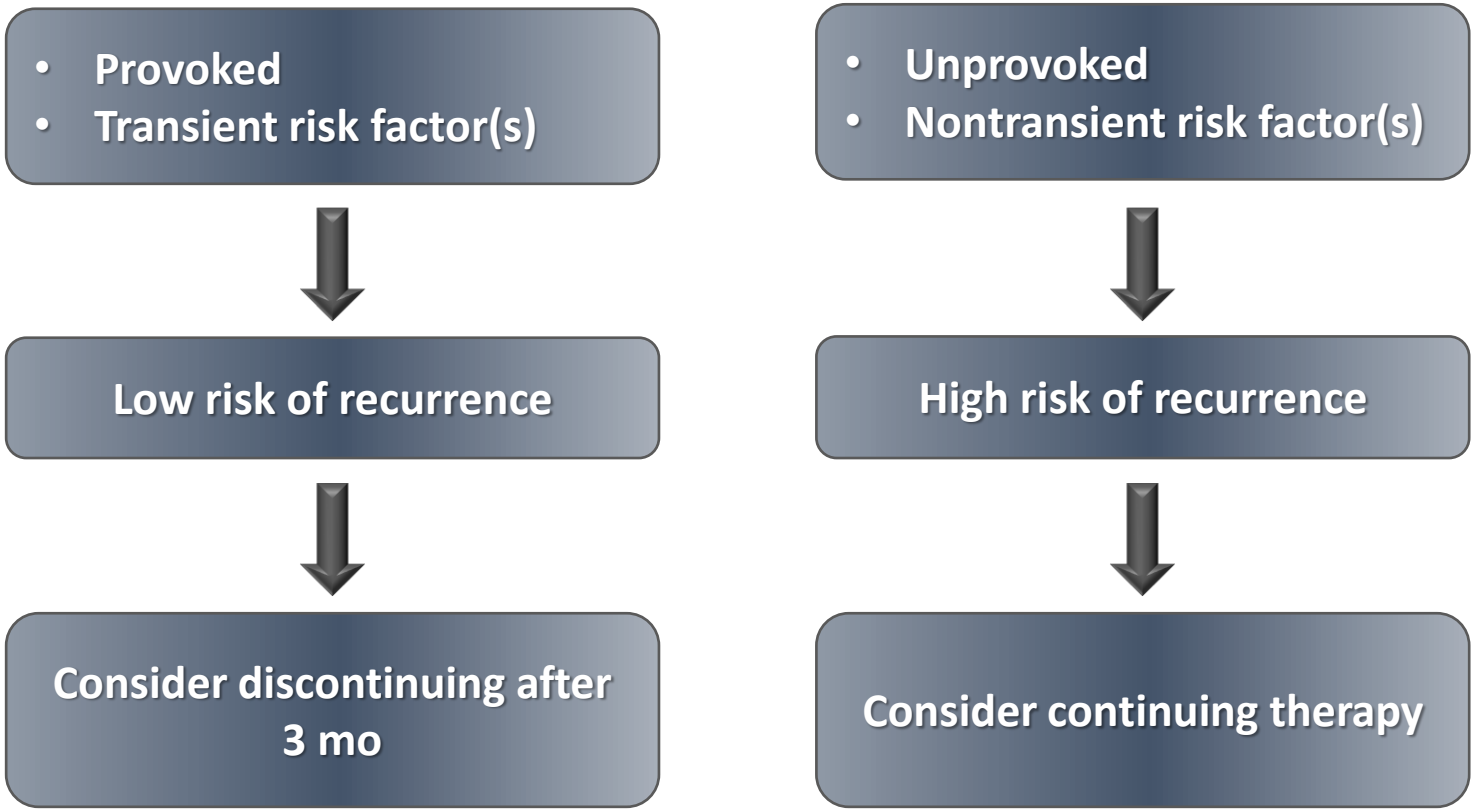


- Compared with aspirin, both rivaroxaban 10 mg and 20 mg reduced the relative risk of recurrent VTE by about 70% (approximately 3 percentage points)
- Rates of major and clinically relevant nonmajor bleeding were low and similar to those with aspirin

Weitz JI et al. *Thromb Haemost*. 2015; 114:645-50. Weitz JI et al. *N Engl J Med.* 2017; 376:1211-22.

Secondary Prevention of PE: Long-term Anticoagulation

- Should this patient continue on **long-term anticoagulation** (ie, >3 mo)?
  - What are her risk factors for recurrence?



McRae S. *Thromb J.* 2014;12:27-41.

Unprovoked PE: Consider Long-term Anticoagulation

- Unprovoked PE plus other risk factor(s)?
  - Older age
- How does low body weight (50 kg) affect treatment?
- Is there a role for NOACs in secondary recurrence of PE in elderly patients?

NOACs for Secondary Prevention in Elderly Patients

Dabigatran[1,2]

- Older age does not alter safety or efficacy compared with warfarin

Rivaroxaban[3]

- Rivaroxaban decreased major bleeding compared with enoxaparin/VKA (1.3 vs 4.5%; HR, 0.27; 95% CI, 0.13–0.54; *P*=.011)

Apixaban[4]

- Older age does not affect efficacy; there is a trend toward increased major and nonmajor clinically relevant bleeding compared with placebo

Edoxaban[5]

- Older age does not alter safety or efficacy (60-mg dose) compared with warfarin

1. Prins MH et al. *Thromob J*. 2013;11:21. 2. Schulman S et al. *Circulation.* 2014;129:764-772. 3. Schulman S et al. ASH 2013;122:2375. 4. Agnelli G et al; AMPLIFY-EXT Investigators. *N Engl J Med*. 2013;368:699-708. 5. Hokusai-VTE Investigators. *N Engl J Med*. 2013;369:1406-1415.

Effect of Low Body Weight (≤60 kg)

t

Agent	Weight (kg)	Dose Adjustment
Apixaban[1]	–	None
Dabigatran[2]	–	None
Edoxaban[3]	≤60	30 mg/d
Rivaroxaban[4]	–	None

Edoxaban requires dose adjustment in patients with low body weigh

1. Eliquis® (apixaban) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; March 2014. 2. Pradaxa® (dabigatran etexilate mesylate) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc.; April 2014. 3. Savaysa® (edoxaban) [prescribing information]. Parisppany, NJ: Daiichi Sankyo, Inc, 2015. 4. Xarelto® (rivaroxaban) [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; March 2014.

Conclusions

- Long-term anticoagulant therapy should be considered in patients with unprovoked VTE
- Older age does not affect efficacy of NOACs
  - No significant difference in bleeding
- Dose adjustment needed with low body weight for apixaban and edoxaban

Summary

- VTE causes substantial morbidity and mortality
- Multiple options are available for initial and long-term anticoagulation for the treatment and secondary prevention of VTE
  - LMWH bridging to warfarin
  - NOACs
- Consider long-term anticoagulation therapy in patients at high risk of recurrence
- Risk of anticoagulant-associated bleeding is very low among patients with VTE

What Is the Risk of AC-associated Bleeding?

- Major bleeding while on a NOAC is associated with increased risk of death and thrombotic events[9]
- AC-associated bleeding occurs less frequently in patients with VTE versus patients with nonvalvular atrial fibrillation (NVAF)
  - NVAF major bleeding, range[1–4]
    - NOACs: 1.61%–3.6%
    - Warfarin: 3.09%–3.43%
  - VTE major bleeding, range[5–8]
    - NOACs: 0.6%–1.4%
    - Conventional therapy*: 1.2%–1.8%

*Conventional therapy included LMWH followed by warfarin

1. Connolly SJ et al. *N Engl J Med*. 2009;361:1139-1151. 2. Granger CB et al. *N Engl J Med*. 2011;365:981-992. 3. Patel MR et al. *N Engl J Med*. 2011;365:883-891. 4. Giugliano RP et al. *N Engl J Med*. 2013;369:2093-2104. 5. Schulman S et al. *Circulation*. 2014;129:764-772. 6. EINSTEIN Investigators. *N Engl J Med*. 2010;363:2499-2510. 7. Agnelli G et al. *N Engl J Med.* 2013;369:799-808. 8. Hokusai-VTE Investigators. *N Engl J Med*. 2013;369:1406-1415. ; [9]Held C et al. Eur Heart J. 2015 36 (20)

MINIMIZE BLEEDING RISKS

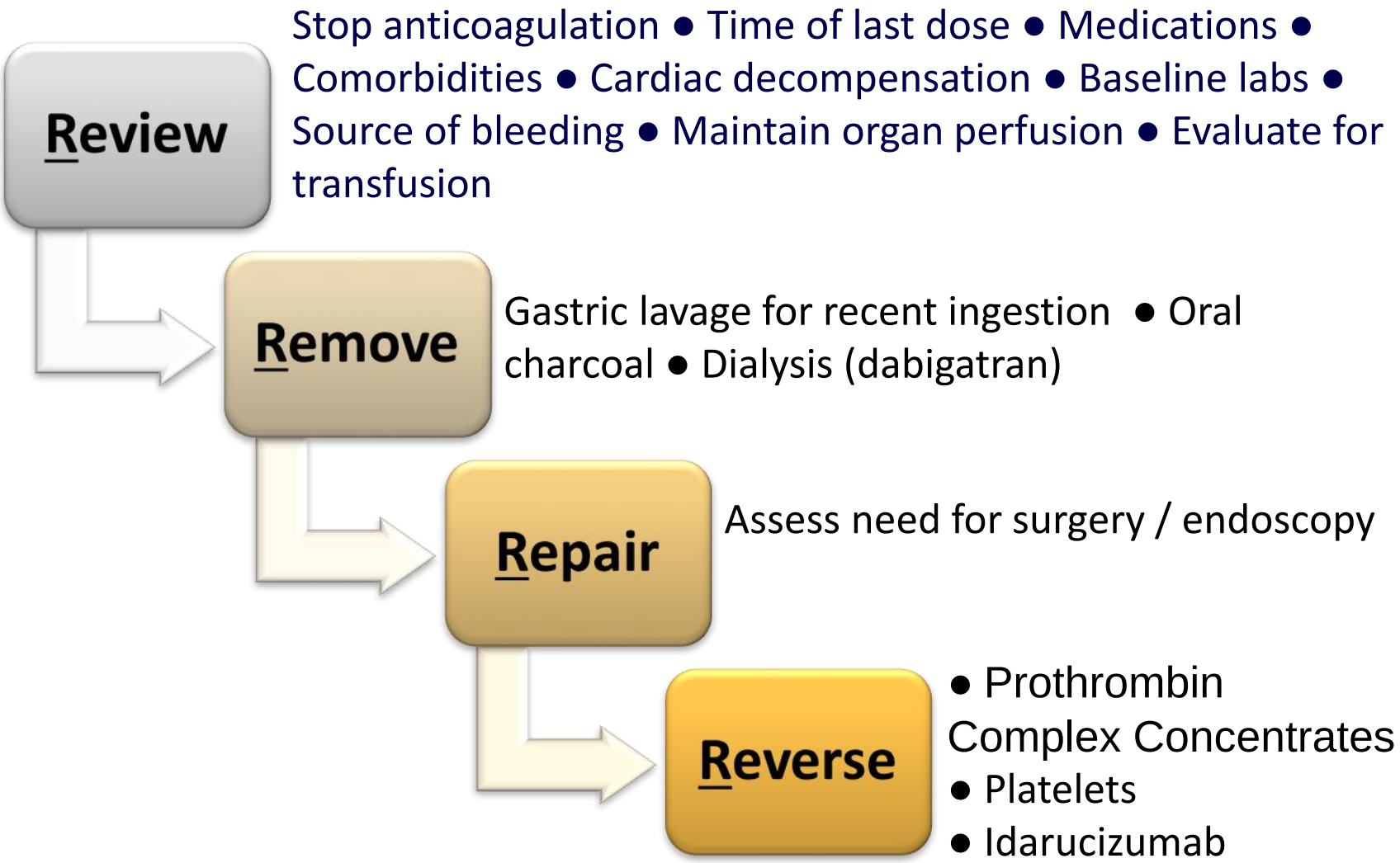
1. Identify and treat modifiable bleeding risk factors
2. Shorten duration of concomitant antiplatelet or NSAID therapy.
3. Moderate alcohol use.
4. Treat and normalize anemia.

Atar D, Benussi S, and Kirchof P. European Heart J 2016; 37: 2853

Renal function and novel drugs

- RE-LY, ROCKET, ARSITOTLE, and ENGAGE excluded patients with eGFR<25-30
- Dabigatran is 80% renally eliminated, edoxaban 50%, rivaroxaban and apixaban are around 30%
- Renal impairment is independent risk factor for stroke, for bleeding, for death
- 150 mg bid of dabigatran should be used cautiously in the elderly (>80 y/o) and with renal impairment (< ~ 40-50 ml/min)
- Rivaroxaban should be used at 15 mg/d with CrCl <50
- Apixaban should be used at 2.5 mg bid with 2 of 3: age ≥80, weight ≤ 60 kg, creatinine ≥ 1.5
- Edoxaban should be used at 30 mg/d with CrCl ≤ 50.
- Edoxaban should NOT be used with CrCl >=95ml/min

Managing NOAC Bleeding: The 4Rs



Kovacs RJ et al. JACC 2015;65:1340-1360

Managing NOAC Bleeding Events

Based on risk stratification

- ***Minor bleeding*** (eg, epistaxis, ecchymosis, or menorrhagia)
  - Withdraw TSOA for ≥1 d; provide definitive interventions
  - Restart TSOA at lower dose for short period of time
- ***Moderate bleeding*** (eg, upper or lower GI bleeding)
  - Stop anticoagulant and monitor carefully
  - Consider activated charcoal if bleeding detected within 2 h of TSOA ingestion
  - Identify and definitively treat bleeding source
  - Consider extended TSOA withdrawal period
    - Consider low-dose parenteral anticoagulant for patients at particularly high risk of thrombosis to allow healing
  - Provide transfusion therapy with red blood cells for symptomatic anemia
  - Ensure renal function is stable

hulman S et al. *Blood.* 2012;119:3016-3023. van Ryan et al. *Thromb Haemost;* 103:1116-1127

Managing NOAC Bleeding Events

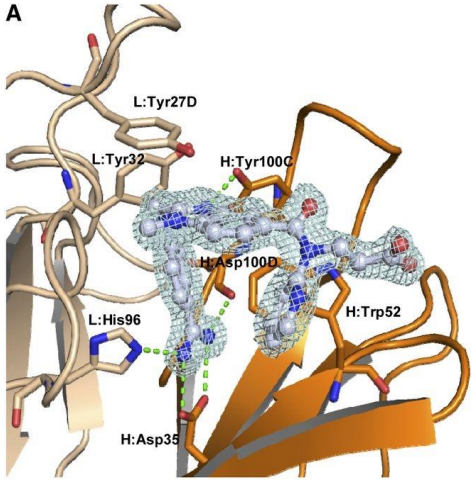
Major and life-threatening bleeding[1,2]

- Immediate withdrawal of anticoagulant and antiplatelet drugs
  - Verify timing of last dose
  - Consider activated charcoal if bleeding detected within 2 h of TSOA ingestion
  - Consider offset of anticoagulant effect and renal function
- Aggressive clinical monitoring
- Transfuse packed red blood cells in response to proven/anticipated severe anemia
- Prior to administration of PCC or rVIIa, consider documenting presence of drug effect via PT for direct factor Xa inhibitors or aPTT for dabigatran; if values normal, do not institute these therapies
- Aggressive interventions to identify and treat the bleeding source
  - Endoscopy, interventional radiology, and/or surgery
- Life-saving therapies
  - Eg, inotropes, ventilation, and ICU admission as needed
- Consider 4-factor PCC replacement therapy

ICU, intensive care unit; PCC, prothrombin complex concentrate

1. Schulman S et al. *Blood.* 2012;119:3016-3023. 2. Weitz JI et al. *Circulation*. 2012:126;2428-2432.

ANTIDOTES TO NOACS

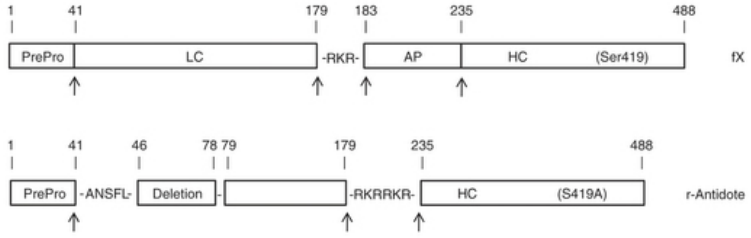


NEJM 2015; 373: 511-520

Idarucizumab

Target: Dabigatran

Structure: Humanized antibody fragment (FAb) to dabigatran; FDA approved in October 2015



Andexanet alpha

Target: FXa inhibitors

Structure: FXa lacking catalytic & binding activity;

This decoy looks like FXa. Antidote for rivaroxaban, apixaban, edoxaban

DOAC Antidote: andexanet alfa

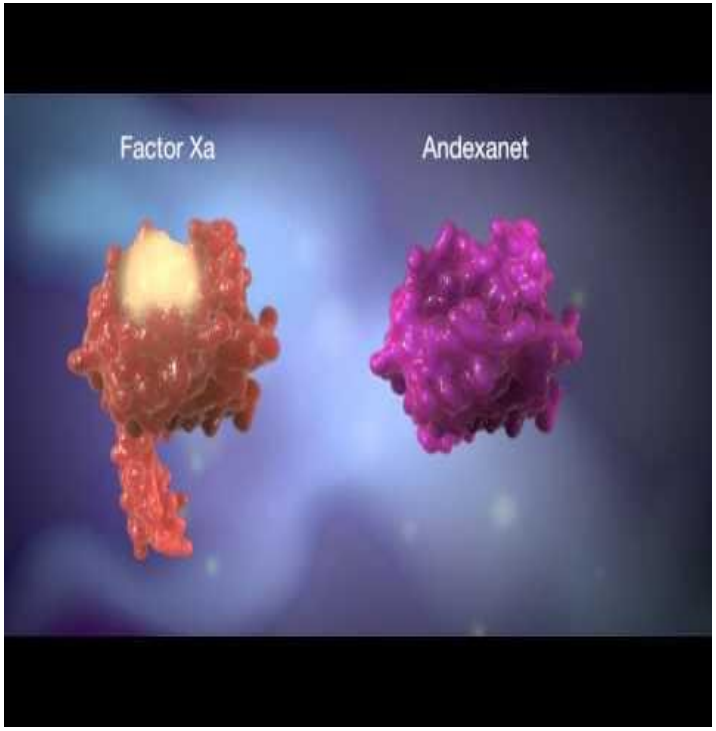
AndexXa = andexanet alfa

- "decoy" recombinant **FXa** molecule with mutation in catalytic site, lacks Gla domain

- "universal" FXai antidote

- Human volunteer studies demonstrate reversal of anticoagulation:
  - apixaban
  - betrixaban
  - edoxaban
  - rivaroxaban

- Not yet approved for use



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

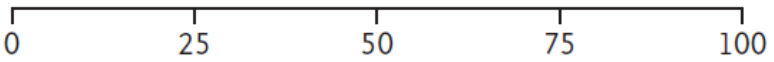
Stuart J. Connolly, M.D., Truman J. Milling, Jr., M.D., John W. Eikelboom, M.D., C. Michael Gibson, M.D., John T. Curnutte, M.D., Ph.D., Alex Gold, M.D., Michele D. Bronson, Ph.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Peter Verhamme, M.D., Ph.D., Jeannot Schmidt, M.D., Saskia Middeldorp, M.D., Alexander T. Cohen, M.D., Jan Beyer-Westendorf, M.D., Pierre Albaladejo, M.D., Jose Lopez-Sendon, M.D., Shelly Goodman, Ph.D., Janet Leeds, Ph.D., Brian L. Wiens, Ph.D., Deborah M. Siegal, M.D., Elena Zotova, Ph.D., Brandi Meeks, B.Eng., Juliet Nakamya, Ph.D., W. Ting Lim, M.Sc., and Mark Crowther, M.D., for the ANNEXA-4 Investigators*

Interim analysis of 67 patients

NEJM August 30 2016

HEMOSTATIC EFFICACY at 12h

Subgroup	No. of Patients	Percent Adjudicated as Excellent or Good Hemostasis (95% CI)
All patients with efficacy analyses	47	79 (64–89)
Drug		
Rivaroxaban	26	81 (61–93)
Apixaban	20	75 (51–91)
Enoxaparin	1	100
Sex		
Male	24	71 (49–87)
Female	23	87 (66–97)
Site of bleeding		
Gastrointestinal	25	84 (64–96)
Intracranial	20	80 (56–94)
Other	2	0
Age		
<65 yr	7	71 (29–96)
65–75 yr	9	89 (52–100)
≥75 yr	31	77 (59–90)
Andexanet dose		
Low	42	76 (61–88)
High	5	100 (48–100)
Anti–factor Xa <75 ng/ml or <0.5 IU/ml	17	82 (57–96)



ANDEXANET vs CIRAPARANTAG

Anticoagulant	Andexanet	Ciraparantag
FXa		
Apixaban	✓	✓
Edoxaban	✓	✓
Rivaroxaban	✓	✓
FIIa		
Dabigatran	—	✓
Heparin		
UFH	✓	✓
LMWH	✓	✓
ATIII-FXa		
Fondaparinux	Unknown	✓
VKA		
Warfarin	—	—

(Am J Med 2016; 129: S80-S88)

1. Indications:
   A. Life-threatening bleeding.
   B. Emergency surgery.
   C. Delayed clearance and bleeding.

2. Contraindications
   A. Surgery that can be delayed.
   B. Abnormal coagulation tests but no bleeding.
   C. Bleeding managed with routine supportive care.