Apirax®

Apixaban (2.5, 5 mg)

Clinical considerations of Apixaban in VTE

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Rivaroxaban

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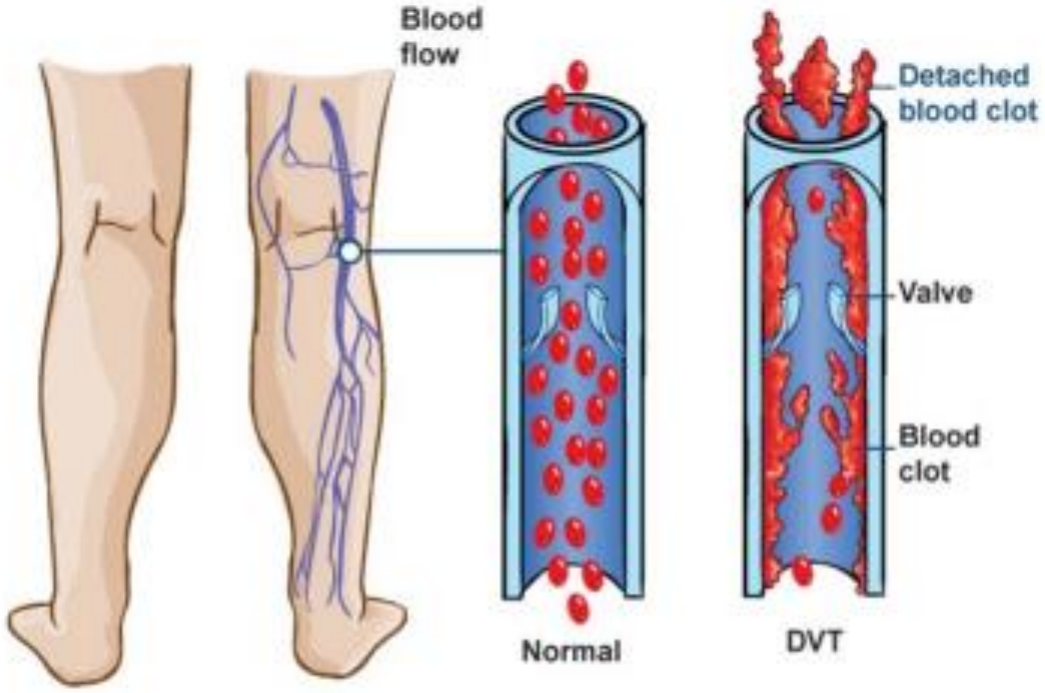
Arena Life Science
Medical Department

Anticoagulation Therapy with Apirax - Indication



Images from NIH MedLine Plus. National Institutes of Health, U.S. Library of Medicine.

Prevention of Venous Thromboembolism

Treatment of Venous Thromboembolism

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Obtain baseline PT/PTT, CBC (for HCT and plts), M7 (for Scr)

Current Inpatient Status

Current Outpatient Status

Determine eligibility for outpatient treatment

ADMIT

Start IV Heparin infusion

YES TO ANY

NO TO ALL

- Medical or social reasons for acute hospitalization
- Creatinine Clearance < 30ml/min
- Severe liver disease
- Severe thrombocytopenia
- If PE is present, sPESI > 0
  [Simplified Pulmonary Embolism Severity Index]

Transition to oral and/or outpatient therapy when medically stable and procedures completed

CRITERIA FOR sPESI	
Age > 80 years	+1
Cancer (active or history)	+1
Heart failure or chronic lung disease	+ 1
Pulse > 110 bpm	+ 1
Systolic BP < 100 mmHg	+ 1
Arterial O2 sat < 90%	+ 1

SELECT TREATMENT OPTION based on patient characteristics, cost, convenience and patients preferences

1.	Rivaroxaban 15mg bid x 3 weeks, then 20mg once daily	• Avoid in patients with CrCl < 30ml/min • Avoid in patients on potentially interacting medications • Limited data in morbid obesity
2.	Apixaban 10mg bid x 7 days, then 5mg bid	• Avoid in patients with CrCl < 30 ml/min • Avoid in patients on potentially interacting meds • Limited date in morbid obesity
3.	Enoxaparin 1mg/kg SQ q12h x 5-10 days, then dabigatran 150mg bid	• Adjust enoxaparin dose if CrCl < 60ml/min • Avoid dabigatran if CrCl < 50 ml/min • Avoid dabigatran in patients on potentially interacting meds • Limited data in morbid obesity
4.	Enoxaparin 1mg/kg SQ q12h + warfarin Stop enoxaparin when INR > 2.0 after a minimum of 5 days of overlap	• Adjust enoxaparin dose if CrCl < 60 ml/min • Start warfarin on same day as heparin/LMWH

Additional Considerations

- **FOR WARFARIN**: Check INR daily (inpatients) or q2-3 days (outpatients) until INR>2
- **FOR HEPARIN/ENOXAPARIN:** check CBC (HCT and plts) daily (inpatients) or q2-3 days (outpatients) for the first 2 weeks of heparin/enoxaparin therapy
- **FOR CANCER-ASSOCIATED THROMBOSIS**: continue enoxaparin alone for 3-6 months
- **FOR PTS WITH HIT**: see *UWMedicine Guidelines for Management of HIT**
- **FOR DURATION OF THERAPY:** see*UWMedicine Recommendations for Duration of Anticoagulant Therapy Following VTE**

* https://depts.washington.edu/anticoag

Arrange outpatient follow-up

For Warfarin/Enoxaparin
Refer to Anticoagulation Clinic or local PCP

For Apixaban/Dabigatran/ Rivaroxaban
See *UWMedicine Management Plan Following Initiation of Direct Oral Anticoagulants**

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Are the Direct Oral Anticoagulants First Line?

Antithrombotic Therapy for VTE Disease

CHEST Guideline and Expert Panel Report

Clive Kearon, MD, PhD; Elie A. Akl, MD, MPH, PhD; Joseph Ornelas, PhD; Allen Blaivas, DO, FCCP; David Jimenez, MD, PhD, FCCP; Henri Bounameaux, MD; Menno Huisman, MD, PhD; Christopher S. King, MD, FCCP; Timothy A. Morris, MD, FCCP; Namita Sood, MD, FCCP; Scott M. Stevens, MD; Janine R. E. Vintch, MD, FCCP; Philip Wells, MD; Scott C. Woller, MD; and COL Lisa Moores, MD, FCCP

***2. In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (VKA) therapy** (all Grade 2B).

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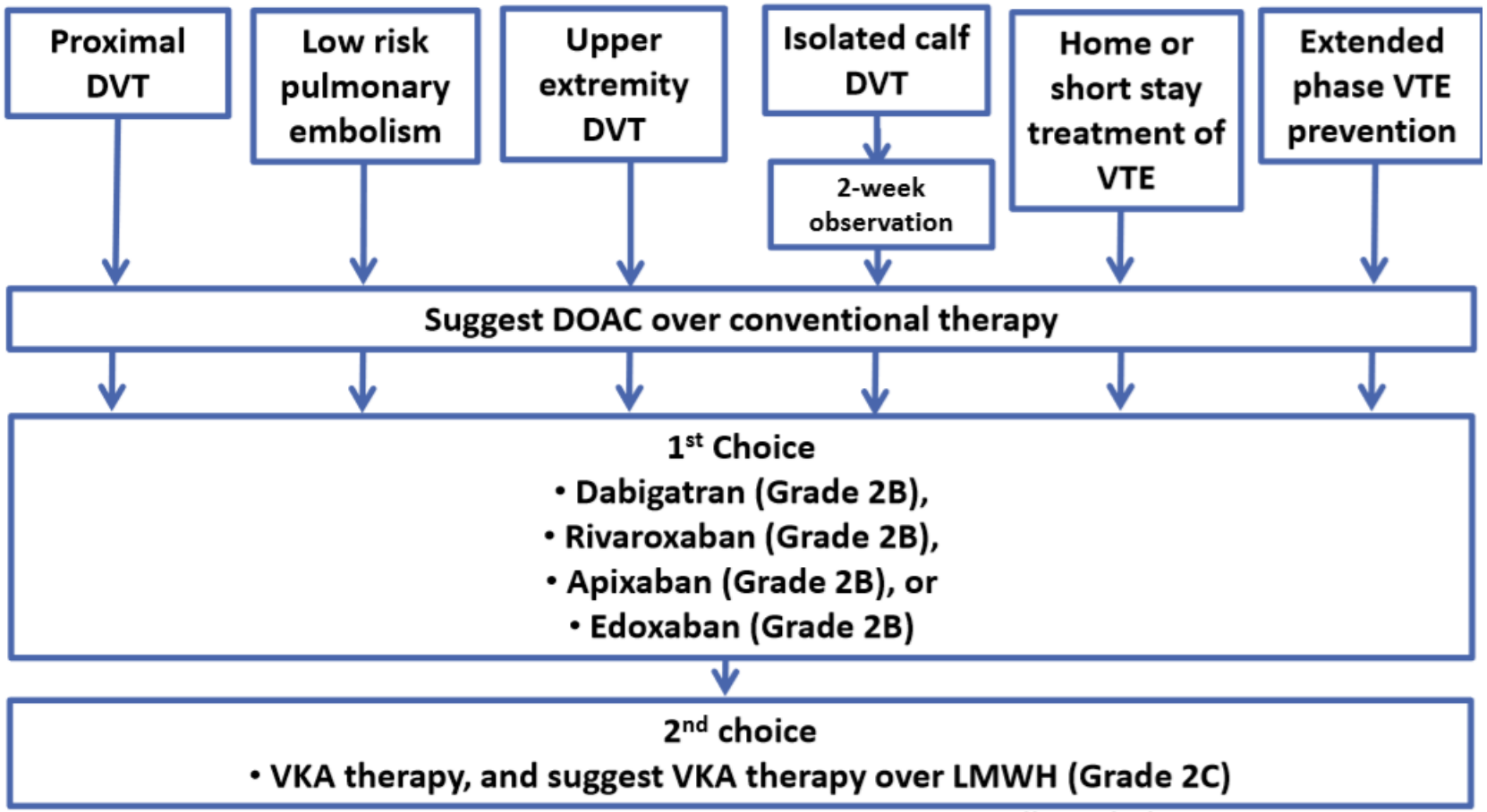
Initiation Phase: VTE Treatment



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

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

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Antithrombotic Therapy for VTE Disease 2016

CHEST Guideline and Expert Panel Report

Factors that influence agent selection for anticoagulation in patients with acute venous thromboembolism

Factor	Preferred Anticoagulant	Qualifying Remarks
Cancer	• LMWH	More supportive if: recent diagnosis, extensive VTE, metastatic cancer, highly symptomatic, vomiting, on chemotherapy
Parenteral therapy to be avoided	• Rivaroxaban • Apixaban	Warfarin, dabigatran and edoxaban require initial parenteral therapy
Once daily oral therapy preferred	• Rivaroxaban • Edoxaban • Warfarin	
Liver disease and coagulopathy	• LMWH	DOA contraindicated if INR elevated due to liver disease. Warfarin difficult to control and INR may not reflect antithrombotic effect.
Renal disease and creatinine clearance < 30 mL/min	• Warfarin	DOAs and LMWH contraindicated with severe renal impairment
Coronary artery disease	• Warfarin • Rivaroxaban • Apixaban • Edoxaban	Coronary artery events appear to occur more often with dabigatran than with warfarin. This has not been seen with the other DOAs, 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	• Warfarin • Apixaban	Dabigatran increased dyspepsia. Dabigatran, rivaroxaban, and edoxaban may be associated with more GI bleeding than warfarin.
Poor compliance	• Warfarin	INR monitoring can help to detect problems. However, some patients may be more compliant with a DOA because it is less complex.
Reversal agent needed	• Warfarin • Unfractionated heparin • Dabigatran	Reversal agents for dabigatran may not be universally readily available.
Pregnancy or pregnancy risk	• LMWH	Potential for other agents to cross the placenta

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TABLE 6] A Simplified Schema to Assist Physician Choice of Anticoagulant (VKA or Individual NOAC) According to Patient Characteristics

Patient Characteristic	Possible OAC Choice	References to RCT Subgroup Data	References to Real-World Data or Indirect Evidence	Comments
• Recurrent ischemic stroke/systemic embolism/TIA despite good anticoagulation control (TTR ≥ 70%). Consider agent with superior efficacy for preventing both ischemic and hemorrhagic stroke	D150	124	127	In general, any NOAC would be recommended, especially where warfarin control suboptimal (TTR < 65%). Ensure good adherence and avoid underdosing
• Moderate-severe renal impairment CrCl 15-49 mL/min	A[a] D[b] E30[d] R15	124	192	All RCTs excluded patients with Cockroft-Gault CrCl < 30 mL/min (< 25 mL/min, for apixaban)
• High risk of GI bleeding	A D110	124	127, 193	
• Major GI symptoms or dyspepsia. Also consider increased risk of bleeding	A R E	194	195, 196	
• High risk of bleeding (HAS-BLED ≥ 3). Consider agent with the lowest bleeding risk	A D110 E	124	127, 128, 193, 197, 198	
• Once-daily dosing or preference to have lower pill burden	E R VKA	[c]	199, 200	
• Asian patients. Consider agents with reduced risk of ICH and major bleed in Asian populations	A D E	134	135, 136, 201	
• Less likely to do well on VKA (SAMe-TT_2R_2 score > 2). Avoid *any* potential "trial" of VKA if possible	NOAC preferred (A D E R)	...	146, 179, 183	VKA with additional education, more regular follow-up, and frequent INR checks

A = apixaban; CrCl = creatinine clearance; D = dabigatran; E = edoxaban; R = rivaroxaban; TIA = transient ischemic attack. See Table 1 and 2 legends for expansion of other abbreviations.

[a]Reduced to 2.5 mg bid with two of three criteria from age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine concentration ≥ 133 μmol/L.

[b]110 mg bid for patients with a CrCl 30 to 49 mL/min (most countries, but not in the United States); in the United States only, 75 mg bid (available in the United States only) for patients with CrCl 15 to 29 mL/min (and only 150 mg bid dose available in the United States for CrCl > 30 mL/min).

[c]Not available.

[d]Dose to be halved if the patient has any of the following: CrCl 15 to 49 mL/min, body weight ≤ 60 kg, or concomitant use of P-glycoprotein inhibitors.

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Go to Setting

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American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients &
CHEST 2018 AF Guideline

9. In patients with prior unprovoked bleeding, warfarin-associated bleeding, or at high risk of bleeding, we suggest using apixaban, edoxaban, or dabigatran 110 mg (where available) as all demonstrate significantly less major bleeding compared with warfarin (Weak recommendation, very low quality evidence).

Remark: In patients with prior gastrointestinal bleeding apixaban or dabigatran 110 mg bid may be preferable as they are the only NOACs associated without an increased risk of gastrointestinal bleeding compared with warfarin.

fibrillation, GI bleeding may be higher with dabigatran, rivaroxaban, and edoxaban than with VKA therapy, although this has not been seen in patients with VTE[27,28,33,41,43]; (7) based on indirect comparisons, the risk of bleeding may be lower with apixaban than with the other NOACs[35,44]; and (8) despite the lack of specific reversal agents for the NOACs, the risk that a major bleed will be fatal appears to be no higher for the NOACs than for VKA therapy.[33,34,45] Based on less bleeding with

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Phases of Treatment for VTE

Apixaban 10 mg BID **Apixaban 5 mg BID** **Apixaban 2.5 mg BID**

Apixaban 10 mg BID x 1 wk, then 5 mg BID

*Trials did not enroll patients with CrCl < 15 mL/min or end-stage renal disease. †No dose reductuion needed for 2.5 mg bid dosing in vascular disease

Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy Initiation of Apirax is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic

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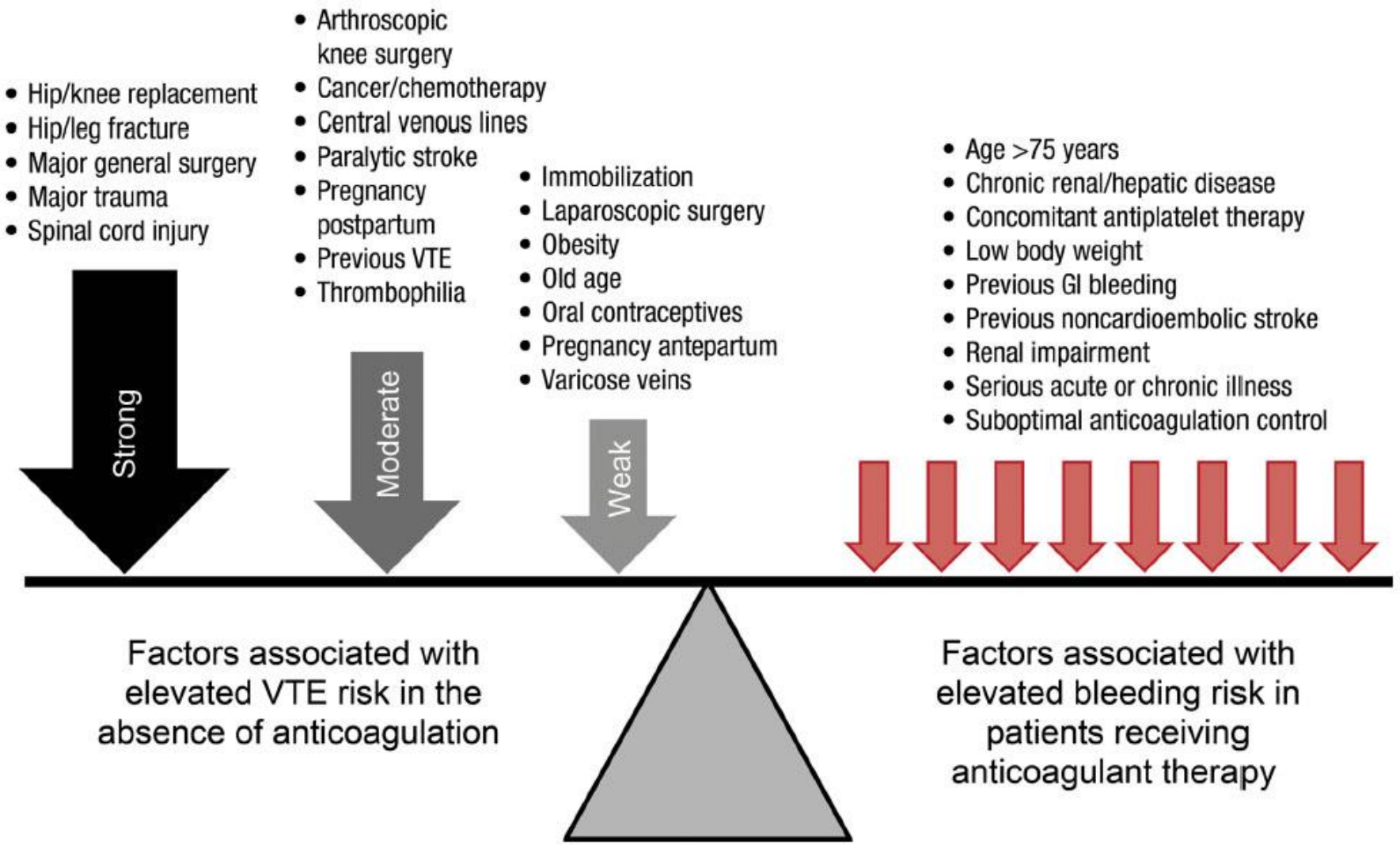

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HAS-BLED

Letter	Clinical Characteristic	Points
H	Hypertension	1
A	Abnormal Liver or Renal Function	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INR	1
E	Elderly (age > 65)	1
D	Drugs or Alcohol	1 or 2
Maximum Score		9

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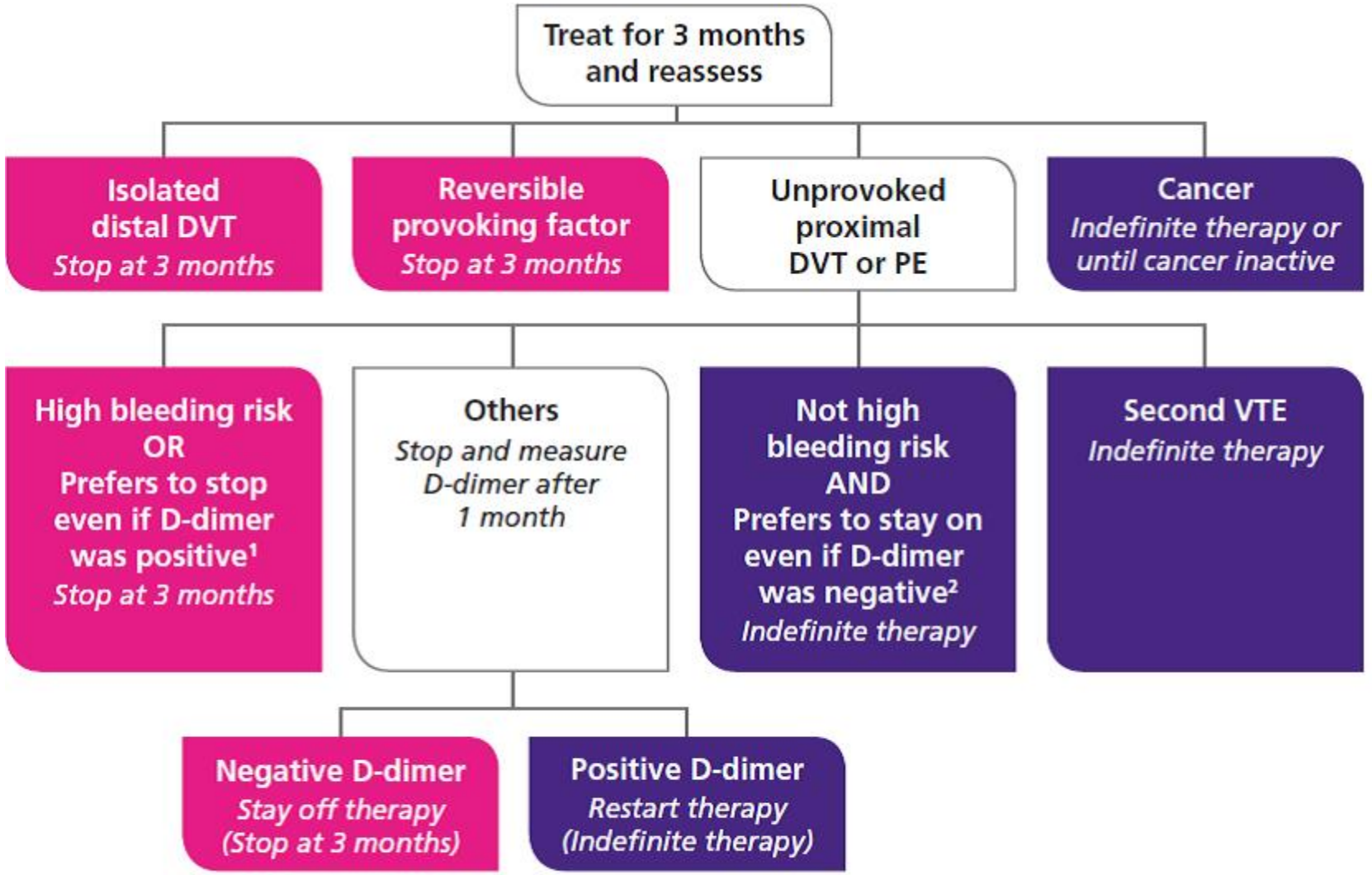

[1] Male would stop even if recurrence risk 16% in first year
Female would stop even if recurrence risk 10% in first year

[2] Male would stay on if recurrence risk 8% in first year
Female would stay on even if recurrence risk 5% in first year

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Rate of VTE recurrence

VTE type	First year	Rate after first year
First episode of unprovoked VTE	10%	5%
Second episode of unprovoked VTE	15%	7.5%
First VTE provoked by surgery	1%	0.5%
First VTE provoked by non-surgical factor	5%	2-5%
Active cancer	Up to 15%	Up to 15%

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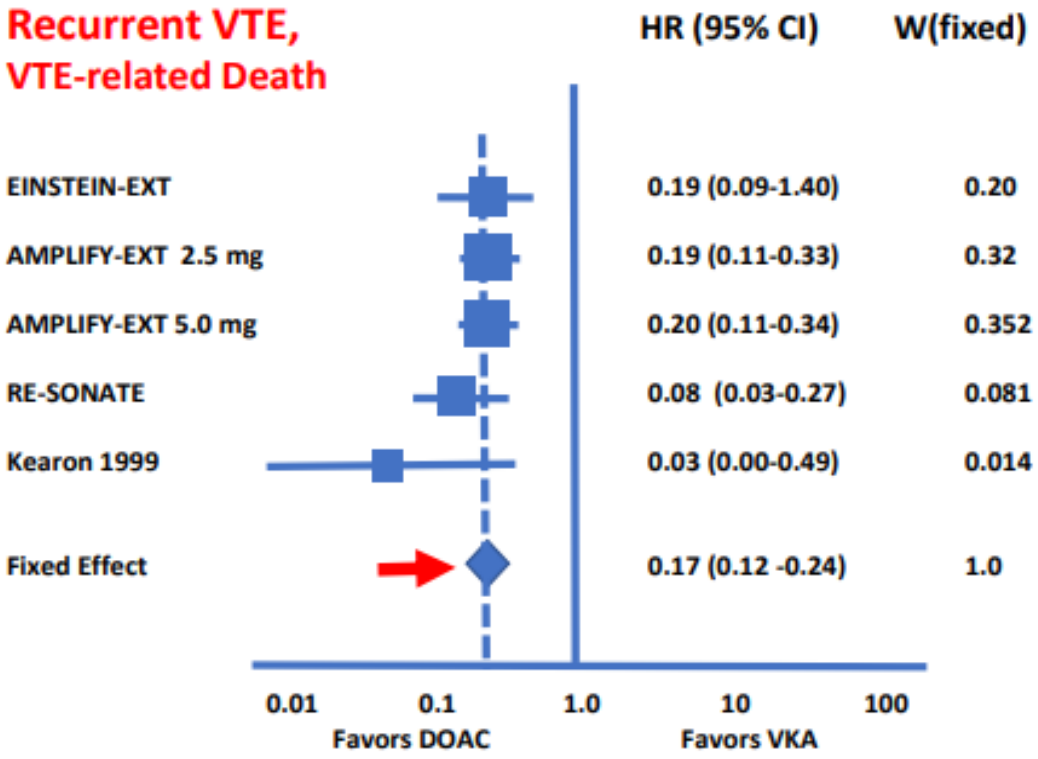
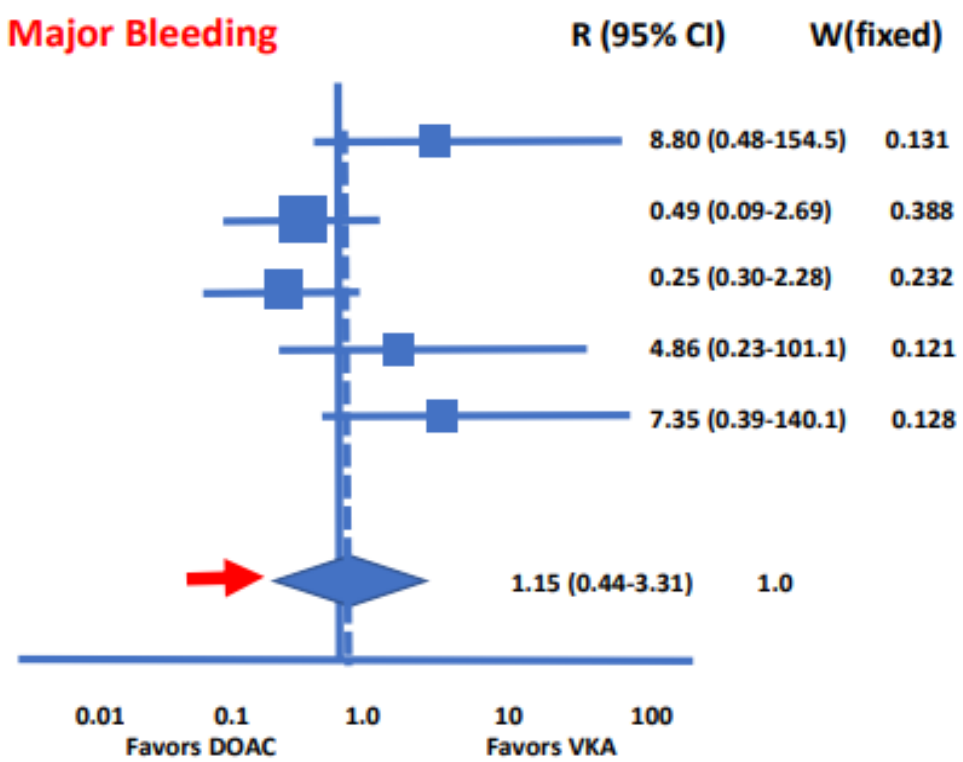
Extended VTE Treatment & DOACs: Outcomes

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)

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VTE Treatment in Cancer

- Patients with cancer are at an increased risk of thromboembolism compared to the general population
- LMWH shown to be superior to VKA in this setting
- Meta-analyses suggested that DOACs may be superior to LMWH while increasing the risk of bleeding

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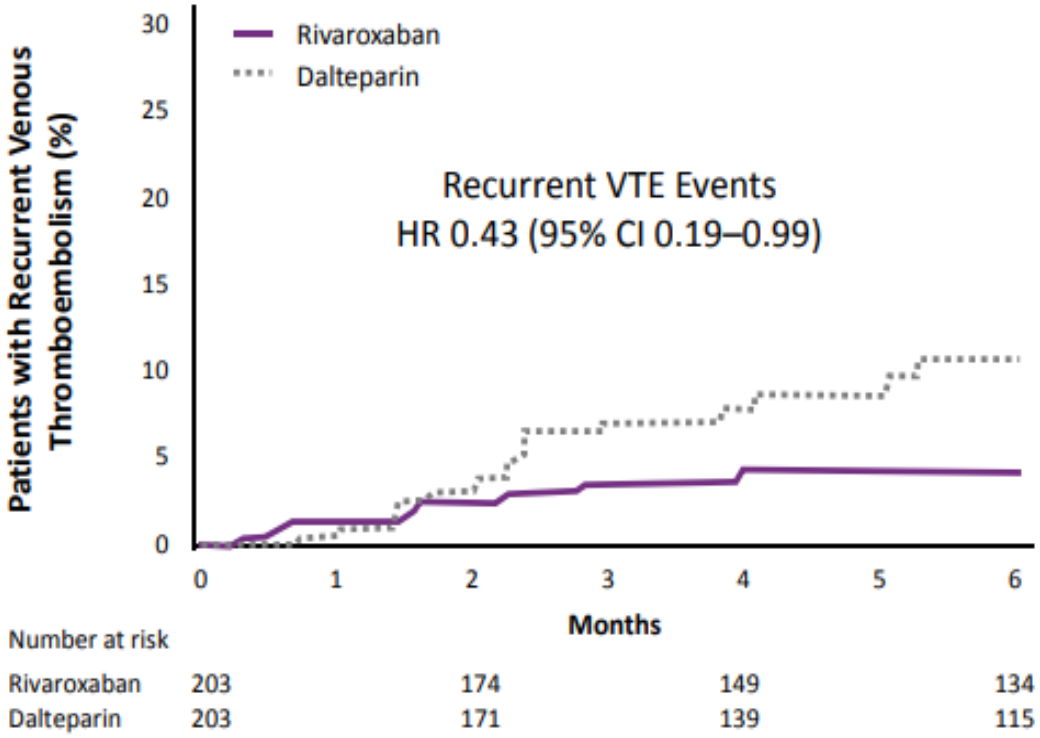
Rivaroxaban vs. Dalteparin

SELECT-D Trial



- No differences in duration of therapy
- Lower risk of VTE events (4% vs. 11%) (see left)
- Numerically higher risk of major bleeding (HR 1.83, 95% CI 0.68-4.69)
- Significantly higher risk of clinically relevant non-major bleeding (HR 3.76, 95% CI 1.63-8.69)

  Defined as bleeding events that were not major but required escalation of care

Abbreviations: CI confidence interval, HR hazard ratio J Clin Oncol. 2018 Jul 10;36(20):2017-2023.

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Apixaban vs. Placebo

AVERT TRIAL

Outcome	CASSINI Trial		AVERT Trial		Cumulative Values				
	Rivaroxaban	Placebo	Apixaban	Placebo	DOACs	Placebo	Relative Risk (95% CI)	Absolute Difference	No. Needed to Treat or Harm†
	number/total number (percent)							*percentage points*	
Primary efficacy outcome									
ITT analysis	25/420 (6.0)	37/421 (8.8)	12/288 (4.2)	28/275 (10.2)	37/708 (5.2)	65/696 (9.3)	0.56 (0.38–0.83)	−4.1	24
Analysis during treatment period	11/420 (2.6)	27/421 (6.4)	3/288 (1.0)	20/275 (7.3)	14/708 (2.0)	47/696 (6.8)	0.29 (0.16–0.53)	−4.8	21
Symptomatic VTE: ITT analysis	15/420 (3.6)	19/421 (4.5)	9/288 (3.1)	22/275 (8.0)	24/708 (3.4)	41/696 (5.9)	0.58 (0.35–0.94)	−2.5	40
Major bleeding	8/405 (2.0)	4/404 (1.0)	10/288 (3.5)	5/275 (1.8)	18/693 (2.6)	9/679 (1.3)	1.96 (0.88–4.33)	1.3	77
Death from any cause	84/420 (20.0)	100/421 (23.8)	35/288 (12.2)	27/275 (9.8)	119/708 (16.8)	127/696 (18.2)	0.92 (0.73–1.16)	−1.4	71

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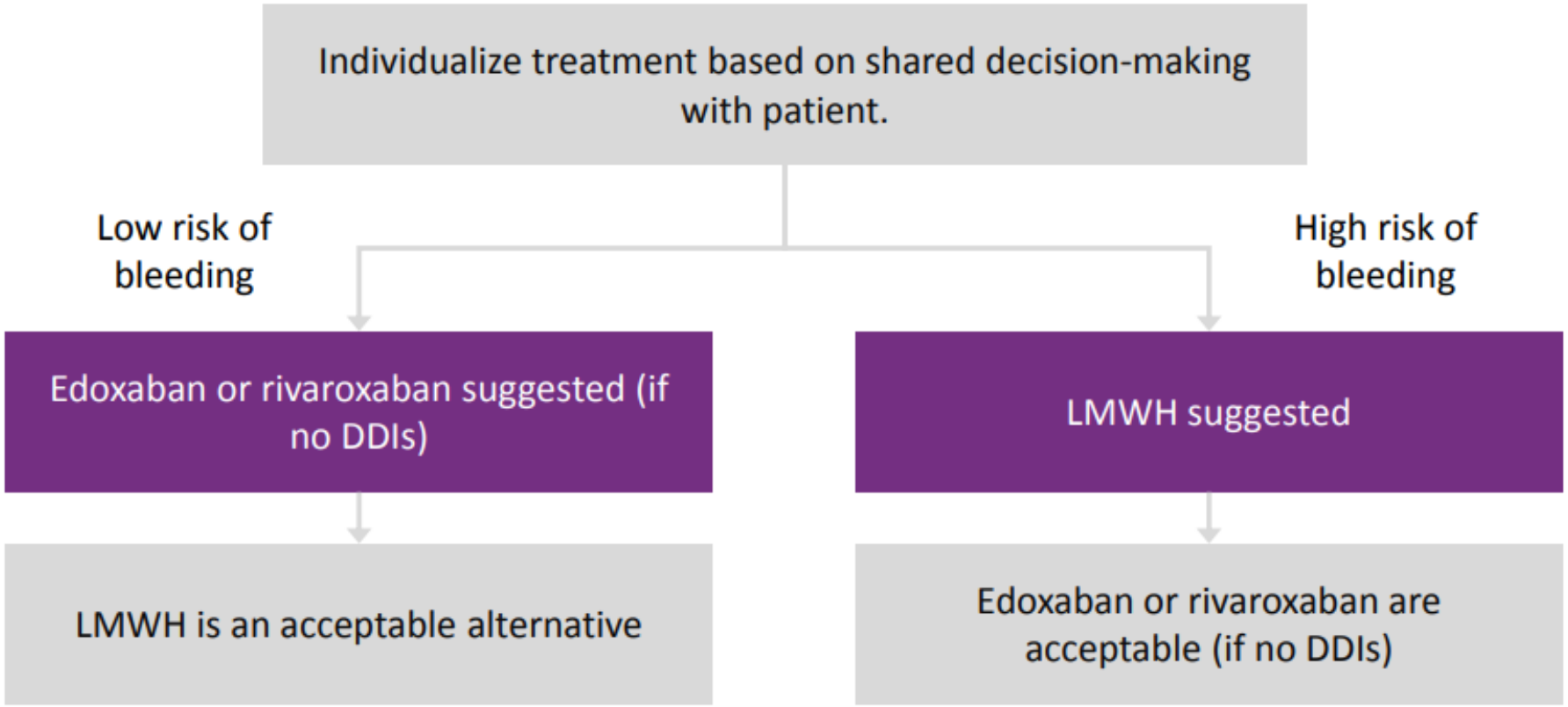
ISTH Recommendations for Cancer VTE



Abbreviations: DDIs drug-drug interactions, LMWH low molecular weight heparin

J Thromb Haemost. 2018 Sep;16(9):1891-1894.

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Pharmacokinetic Data in Obesity

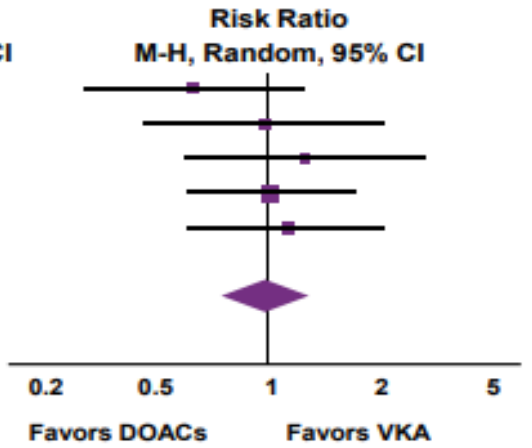
Drug	Data Source	"Obesity"	Findings
Apixaban	Single 10-mg dose in healthy volunteers of reference (n=18) vs. high weight (n=19)[1]	≥ 120 kg	• Decreased C_{max} • Decreased AUC • Decreased $t_{1/2}$

Clinical Data in Obesity

Recurrent Thromboembolic Events in VTE Trials[1]

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			

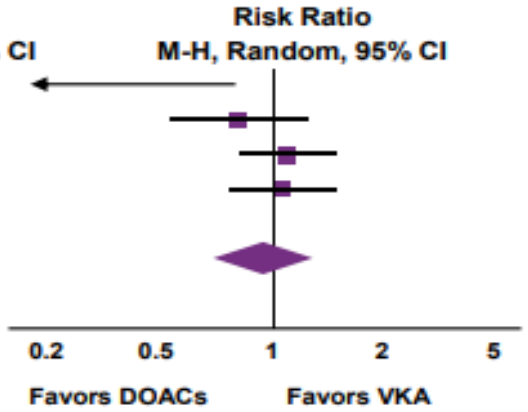
Heterogeneity: $Tau^2 = 0.00$, $Chi^2 = 2.23$, df = 4 (P = 0.69), $I^2 = 0\%$
Test for overall effect: Z = 0.10 (p = 0.92)



Bleeding-Related Outcomes in VTE Trials[1]

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 = d (P = 0.09), $I^2 = 54\%$
Test for overall effect: Z = 0.43 (p = 0.67)



P-gp Inducers	P-gp Inhibitors	P-gp + Strong CYP3A4 Inhibitors	P-gp + Strong CYP3A4 Inducers	P-gp + Moderate CYP3A4 Inhibitors
• Barbiturates • Phenytoin • Carbamazepine • Rifampin • St. John's wort	• Amiodarone • Dronedarone • Diltiazem • Verapamil • Clarithromycin • Grapefruit juice • Cyclosporine • Tacrolimus • Ketoconazole • Itraconazole • Ritonavir	• Barbiturates • Phenytoin • Carbamazepine • Rifampin • St. John's wort	• Clarithromycin • Grapefruit juice • Ketoconazole • Itraconazole • Ritonavir	• Dronedarone • Diltiazem • Verapamil • Azithromycin

Interaction	Apixaban
P-gp inducers	-
P-gp inhibitors	-
P-gp plus strong CYP3A4 inducers	Avoid
P-gp plus strong CYP3A4 inhibitors	Dose-reduce; avoid if already on lower dose
P-gp plus moderate CYP3A4 inducers	

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Periprocedural Holding Recommendations

	Apixaban, Edoxaban, and Rivaroxaban		
CrCl (mL/min)	≥ 30	15-29	< 15
Low bleeding risk	≥ 24 h	≥ 36 h	Consider anti-Xa and/or holding ≥ 48 hours*
Uncertain, moderate, or high bleeding risk	≥ 48 h	Consider anti-Xa and/or holding ≥ 48 hours*	

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Classification of elective surgical interventions according to bleeding risk

Interventions with minor bleeding risk
Dental interventions
Extraction of 1–3 teeth
Paradontal surgery
Incision of abscess
Implant positioning
Cataract or glaucoma intervention
Endoscopy without biopsy or resection
Superficial surgery (e.g. abscess incision; small dermatologic excisions; . . .)

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Classification of elective surgical interventions according to bleeding risk

Interventions with low bleeding risk (i.e. infrequent or with low clinical impact)
Endoscopy with biopsy
Prostate or bladder biopsy
Electrophysiological study or catheter ablation (except complex procedures, see below)
Non-coronary angiography (for coronary angiography and ACS: see Patients undergoing a planned invasive procedure, surgery or ablation section)
Pacemaker or ICD implantation (unless complex anatomical set-ting, e.g. congenital heart disease)

ICD: implantable cardioverter- defibrillator

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Classification of elective surgical interventions according to bleeding risk

Interventions with high bleeding risk (i.e. frequent and/or with high impact)
Complex endoscopy (e.g. polypectomy, ERCP with sphincterotomy etc.)
Spinal or epidural anaesthesia; lumbar diagnostic puncture
Thoracic surgery
Abdominal surgery
Major orthopaedic surgery
Liver biopsy
Transurethral prostate resection
Kidney biopsy
Extracorporeal shockwave lithotripsy (ESWL)
Interventions with high bleeding risk AND increased thromboembolic risk
Complex left-sided ablation (pulmonary vein isolation; some VT ablations)
Cardiac surgeries (CABG/valve replacement)

ERCP: endoscopic retrograde cholangiopancreatograhy

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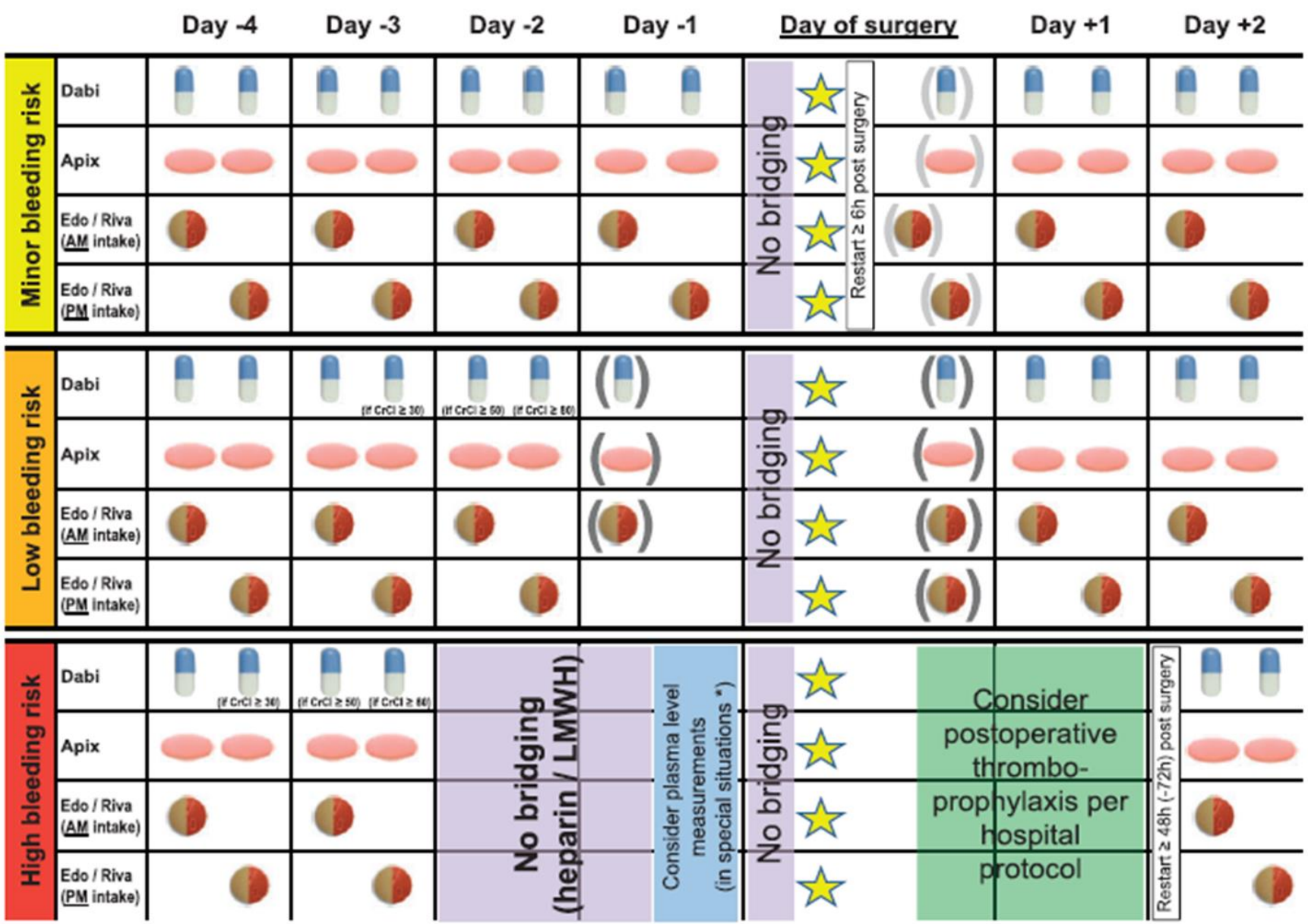

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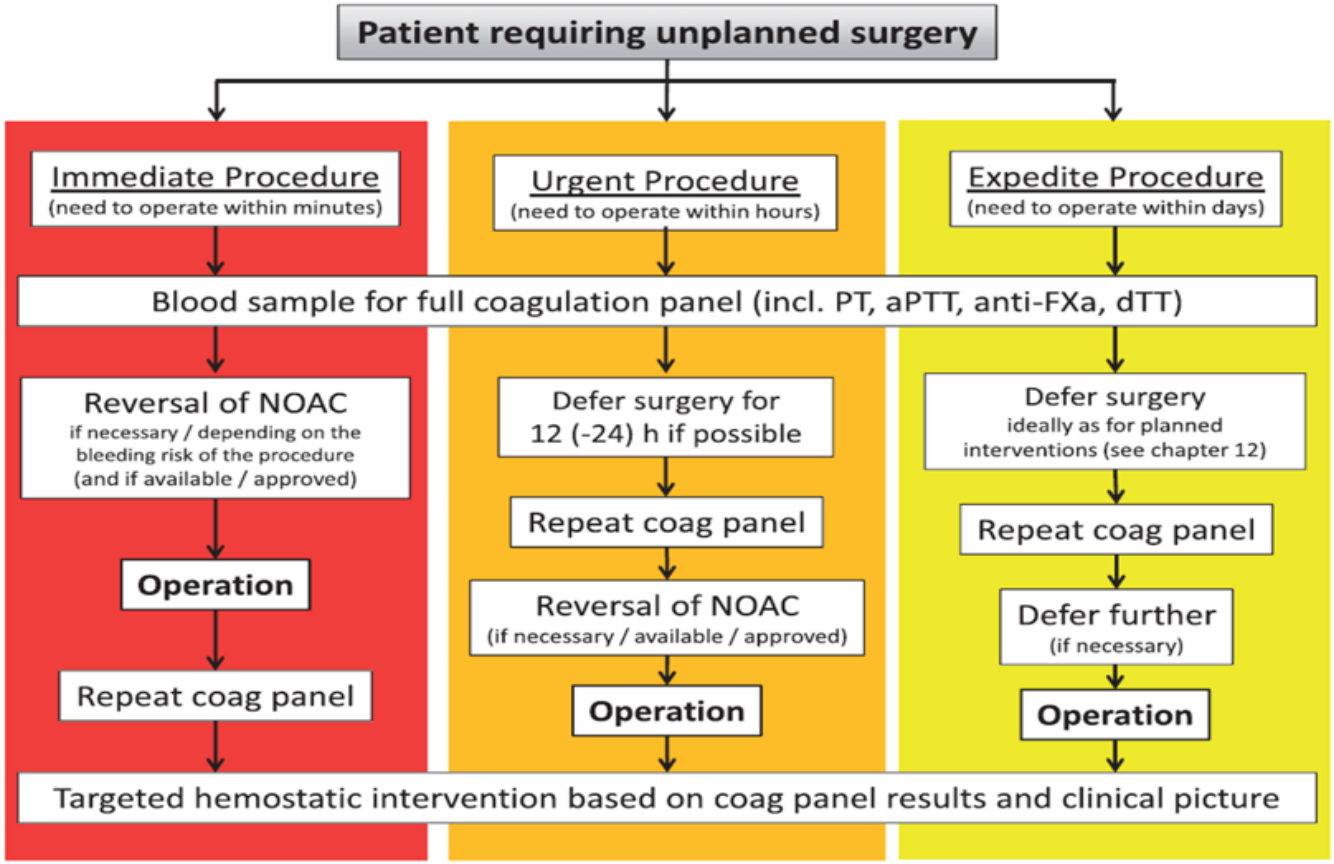
Non-vitamin K antagonist oral anticoagulant management in the setting of unplanned surgery



- Cardiac
- Vascular
- neurosurgical

(e.g. intervention for acute onset or clinical deterioration of potentially life-threatening conditions, conditions that may threaten the survival of limb or organ, fixation of fractures, relief of pain, or other distressing symptoms)

cholecystectomy

dTT: dilute thrombin time

❖ If specific reversal agents are not available, PCCs or aPCCs should be considered despite the lack of evidence for efficacy and safety

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Contraindications to NOACs

- Extreme BMI (>40)
- CrCl <30
- Significant increased risk of bleeding
- Pregnancy
- Prosthetic mechanical valve

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Oral Apixaban for the Treatment of Acute Venous Thromboembolism

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AMPLIFY

Oral Apixaban for the Treatment of Acute Venous Thromboembolism

- *Randomized, double-blind*
- *5395 patients with acute VTE*

G1: Apixaban	10 mg twice daily	PO bid	first 7 days	2693 patients
	5 mg twice daily	PO bid	after 7 days for 6 months	2707 patients

G2: Subcutaneous enoxaparin 1mg/kg for at least 5 days, ***followed by warfarin*** (INR range 2.0–3.0)

Result

Endpoints	***Apixaban***	***Enoxaparin/Warfarin***
The primary efficacy outcome *recurrent symptomatic venous thromboembolism or death related to venous thromboembolism*	*2.3%* *P<0.001* *For non inferiority*	*2.7%*
The principal safety outcomes *major bleeding alone and major bleeding plus clinically relevant non major bleeding*	*0.6%* *P<0.001* *For superiority*	*1.8%*

Conclusions

A fixed-dose regimen of apixaban alone was noninferior to conventional therapy for the treatment of acute venous thromboembolism and was associated with significantly less bleeding

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TABLE 4] Summary of Findings: Apixaban vs LMWH and VKA for Acute and Long-Term Treatment of VTE[a,b]

Outcomes	No. of Participants (Studies)	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Risk with LMWH and VKA	Risk Difference with Apixaban (95% CI)
All-cause mortality	5,365 (1 study)	⊕⊕⊕⊖ **Moderate**[c] because of imprecision	RR 0.79 (0.53-1.19)	19 per 1,000	4 fewer per 1,000 (from 9 fewer to 4 more)
Recurrent VTE	5,244 (1 study)	⊕⊕⊕⊖ **Moderate**[c] because of imprecision	RR 0.84 (0.6-1.18)	27 per 1,000	4 fewer per 1,000 (from 11 fewer to 5 more)
Major bleeding	5,365 (1 study)	⊕⊕⊕⊕ **High**	RR 0.31 (0.17- 0.55)	18 per 1,000	13 fewer per 1,000 (from 8 fewer to 15 fewer)

The basis for the assumed risk (eg, the median control group risk across studies) is provided in the footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). AMPLIFY = Apixiban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy; PE = pulmonary embolism. See Table 1 legend for expansion of other abbreviations and GRADE Working Group grades of evidence.

[a]Apixaban 10 mg twice daily for 7 days, followed by 5 mg twice daily for 6 mo.

[b]Subcutaneous enoxaparin, followed by warfarin.

[c]CI includes values suggesting no effect and values suggesting either benefit or harm. Bibliography: Agnelli et al[25] (AMPLIFY)

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Apixaban for Extended Treatment of Venous Thromboembolism

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AMPLIFY-EXT

Apixaban for Extended Treatment of Venous Thromboembolism

Description

Method:

- ❑ *A randomized, double-blind clinical trial*
- ❑ *Patients who had been treated for DVT and/or PE for 6 to 12 months with anticoagulation therapy without having a recurrent event, and for whom physicians were uncertain about continuing anticoagulation therapy*

G1: Apixaban	2.5, mg twice daily	for 12 months	840 patients
G2: Placebo		for 12 months	813 patients
G3 : Apixaban	5 mg twice daily	for 12 months	829 patients

Result

Endpoints	*Apixaban 2.5 mg*	*Placebo*	*Apixaban 5 mg*
Primary efficacy outcome: *Recurrent VTE† or all-cause death*	*3.8 %* *P<0.001*	*11.6%*	*4.2%*
Primary safety outcome: *Major bleeding*	*0.2%*	*0.5%*	*0.1 %*

Conclusions	*Extended anticoagulation with apixaban at either a treatment dose (5 mg) or a thromboprophylactic dose (2.5 mg) reduced the risk of recurrent venous thromboembolism without increasing the rate of major bleeding*

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TABLE 10] Summary of Findings: Apixaban vs Placebo for Extended Treatment of VTE[a,b]

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Risk with Placebo	Risk Difference with Apixaban (95% CI)
All-cause mortality	1,669 (1 study) 12 mo	⊕⊕⊕⊖ **Moderate**[c,d] because of imprecision	RR 0.49 (0.2-1.22)	17 per 1,000	9 fewer per 1,000 (from 14 fewer to 4 more)
Recurrent VTE	1,669 (1 study) 12 mo	⊕⊕⊕⊕ **High**	RR 0.19 (0.11-0.33)	88 per 1,000	71 fewer per 1,000 (from 59 fewer to 78 fewer)
Major bleeding	1,669 (1 study) 12 mo	⊕⊕⊕⊖ **Moderate**[c,d] because of imprecision	RR 0.49 (0.09-2.64)	5 per 1,000	2 fewer per 1,000 (from 4 fewer to 8 more)

The basis for the assumed risk (eg, the median control group risk across studies) is provided in the footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). See Table 1 and 4 legends for expansion of abbreviations and GRADE Working Group grades of evidence.

[a]Patients with VTE who had completed 6 to 12 mo of anticoagulation therapy.

[b]Apixaban 2.5 mg twice-daily dose vs placebo.

[c]Significantly wide CIs, including appreciable benefit /harm and no effect line.

[d]Low number of events. Bibliography: Agnelli et al[48] (AMPLIFY-EXT)

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Summery

- A fixed-dose regimen of **oral apixaban** alone was as effective as conventional treatment consisting of **enoxaparin followed by warfarin .**
- **Oral apixaban** was associated with a clinically relevant reduction of 69% in major bleeding.
- These findings add to the evidence that the new oral anticoagulants are simple alternatives to conventional therapy for patients with acute venous thromboembolism

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American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients

1. Should any DOAC extended beyond hospital discharge vs. non-DOAC VTE prophylaxis administered in hospital only be used in acutely ill medical patients?

In acutely ill hospitalized medical patients, the ASH guideline panel recommends inpatient VTE prophylaxis with LMWH only, rather than inpatient and extended duration outpatient VTE prophylaxis with DOACs (strong recommendation, moderate certainty in the evidence of effects).

Travelers

Risk-assessment methods to define travelers at sufficiently high VTE risk to warrant VTE prophylaxis intervention

Large pragmatic trials of interventions to prevent VTE in travelers, particularly those at high VTE risk

Evidence on effectiveness and safety of DOACs to prevent VTE in travelers at risk of VTE

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