Πνευμονική Εμβολή

Αντιπηκτική αγωγή 2018 (και στο μέλλον)

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Disclosures

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Anticoagulation for venous thromboembolism 2018

1) Prolonged primary prevention of VTE in hospitalized medically ill patients: the end of the road?
2) Contemporary anticoagulation for acute VTE: Benefits for all patients, and for specific patient groups
3) Extended anticoagulation for secondary prevention: A change of paradigm

Trials on prolonged VTE prophylaxis for hospitalized patients - 1

Study	EXCLAIM 2010	ADOPT 2011	MAGELLAN 2013	APEX 2016
Drug	**Enoxaprin**	**Apixaban**	**Rivaroxaban**	**Betrixaban**
Primary efficacy outcome	**Asymptomatic proximal DVT and symptomatic VTE** through Day 28 Enoxaparin: 2.5 % Placebo: 4 %	*Idem* through Day 30 Apixaban: 2.7 % Enox/placebo: 3.1 %	*Idem* at d10 and d35 Rivaroxaban: 4.4 % on d35 Enoxaparin/placebo: 5.7 % on d35	*Idem* through d35 Betrixaban: 6.9 % Enox/placebo: 8.5 % (P=0.054 in cohort 1, D-dimers only)
Principal safety outcome	***Major* bleeding** Enoxaparin: 0.8 % Placebo: 0.3 %	Apixaban: 0.5 % *major*, 2.7 % CRNM Enox/placebo: 0.2% *major*, 2.1 % CRNM	Major/*CRNM* bleeding, d35 Rivaroxaban: 4.1 % Enox/placebo: 1.7 %	Major bleeding Betrixaban: 0.7% Enox/placebo: 0.6% (P=0.55 in overall population)
Sample size	5,963	6,758	8,101	6,850

Hull RD, et al. *Ann Intern Med* 2010; 153: 8–18
Goldhaber SZ, et al. *N Engl J Med* 2011; 365:2167–2177
Cohen AT, et al. *N Engl J Med* 2013; 368: 513–523
Cohen AT, et al. *N Engl J Med* 2016;375:534-44

Trials on prolonged VTE prophylaxis for hospitalized patients - 2

	EXCLAIM 2010	ADOPT 2011	MAGELLAN 2013	APEX 2016
Drug	**Enoxaprin**	**Apixaban**	**Rivaroxaban**	**Betrixaban**
Regimen	40 mg o.d.	2.5 mg b.i.d.	10 mg o.d.	80 mg o.d.
Dose ▼ in selected pts	No	No	No	**Yes** (CrCl 15-30 ml/min, P-gp)
Timing of Rx	In hospital	In hospital	In hospital	In hospital
RAM for eligibility	No	No	No	No
D-dimers for eligibility	No	No	No	**Yes**
Treatment duration	28±4 d after initial 10±4 d	30 d	35±4 d	35-42 d
Comparator	Placebo	Enoxaparin ≥6 d	Enoxaparin 10±4 d	Enoxaparin 6-14 d
Double-blind design	Yes	Yes	Yes	Yes

Hull RD, et al. *Ann Intern Med* 2010; 153: 8–18
Goldhaber SZ, et al. *N Engl J Med* 2011; 365:2167–2177
Cohen AT, et al. *N Engl J Med* 2013; 368: 513–523
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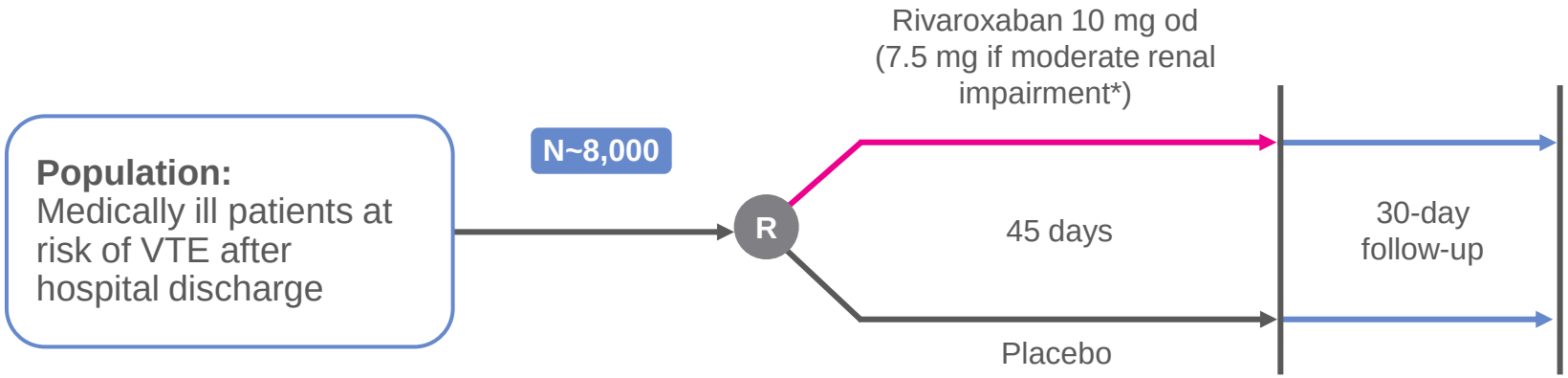
VTE prevention in the medically ill: Rivaroxaban (MARINER)

Official study title: Medically Ill Patient Assessment of Rivaroxaban Versus Placebo in Reducing Post-Discharge Venous Thromboembolism Risk

Objective: efficacy and safety of rivaroxaban in reducing post-discharge VTE risk in high-risk medically ill patients



Short design: Multicentre, prospective, randomized, double-blind, placebo-controlled, event-driven study

Indication: VTEp Med Ill

FPFV: Q2-14
LPLV: Q1-17

*Patients with CrCl 30–49 ml/min
www.clinicaltrials.gov/ct2/show/NCT02111564

Raskob G, et al. *Thromb Haemost* 2016;115:1240-1248

MARINER vs previous VTE prophylaxis studies

- Validated **VTE risk score** for hospitalized patients
- Combination with **D-dimer** levels
- Randomization at hospital **discharge**
- **45-day** treatment period
- Efficacy outcome includes only **symptomatic** VTE
- Rivaroxaban dosage reduction (7.5 mg od) in renal impairment

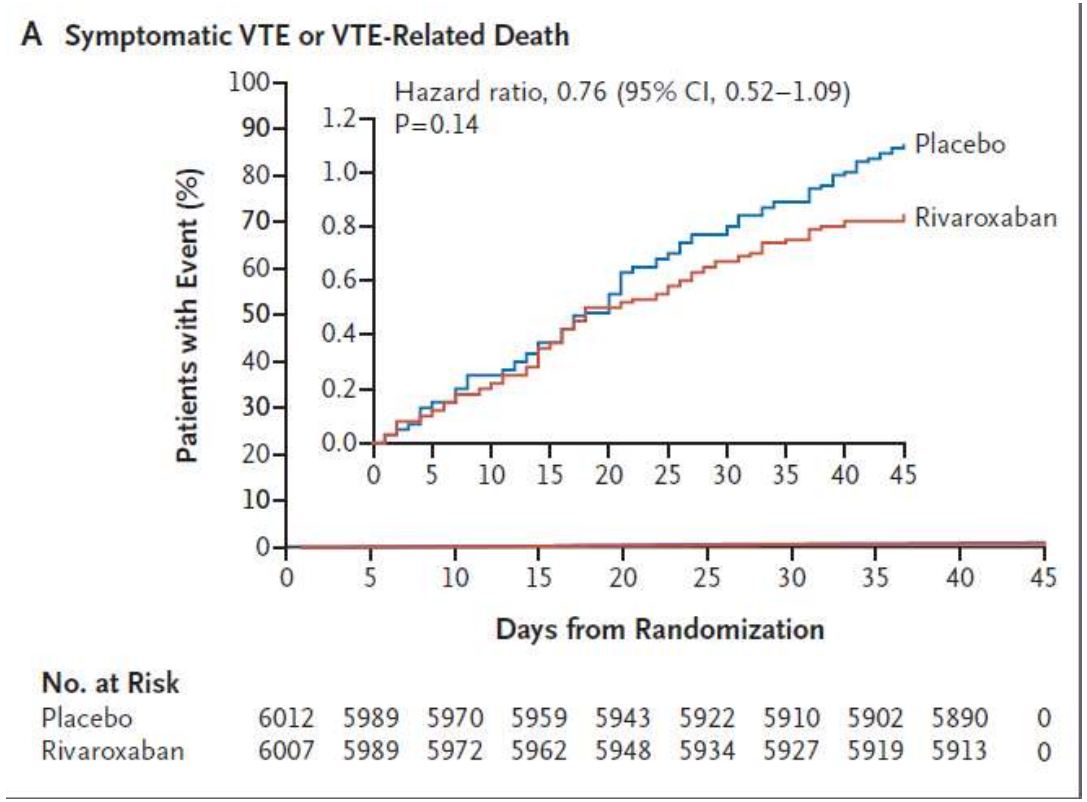
Modified IMPROVE VTE score

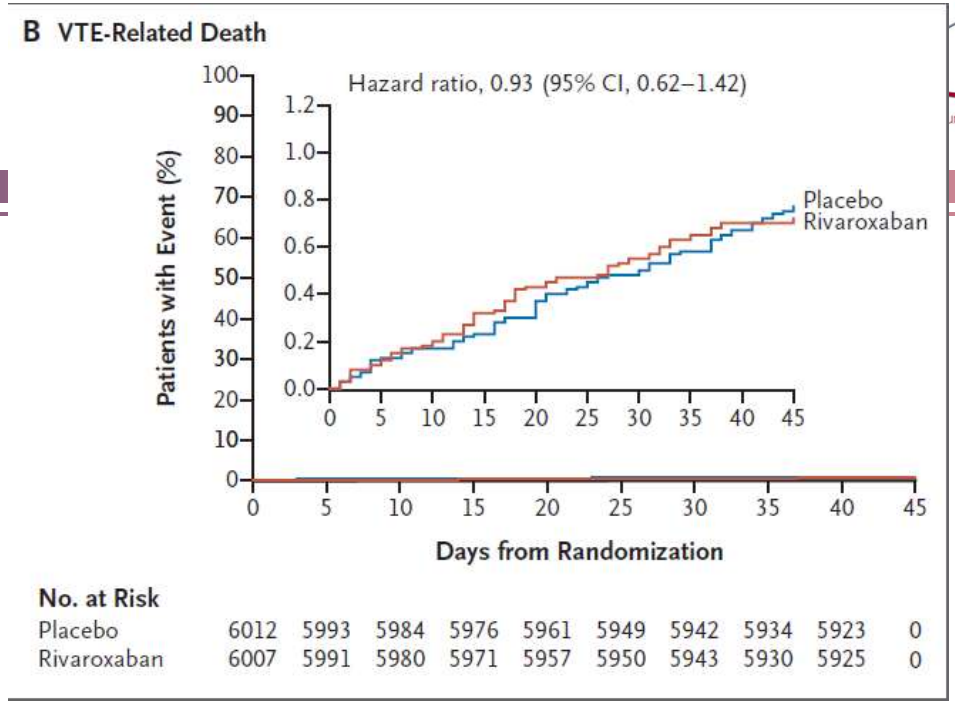
VTE Risk Factor	VTE Risk Score
Previous VTE	3
Known thrombophilia[a]	2
Current lower limb paralysis or paresis[b]	2
History of cancer[c]	2
ICU/CCU stay	1
Complete immobilisation[d] ≥1 day	1
Age ≥60 years	1

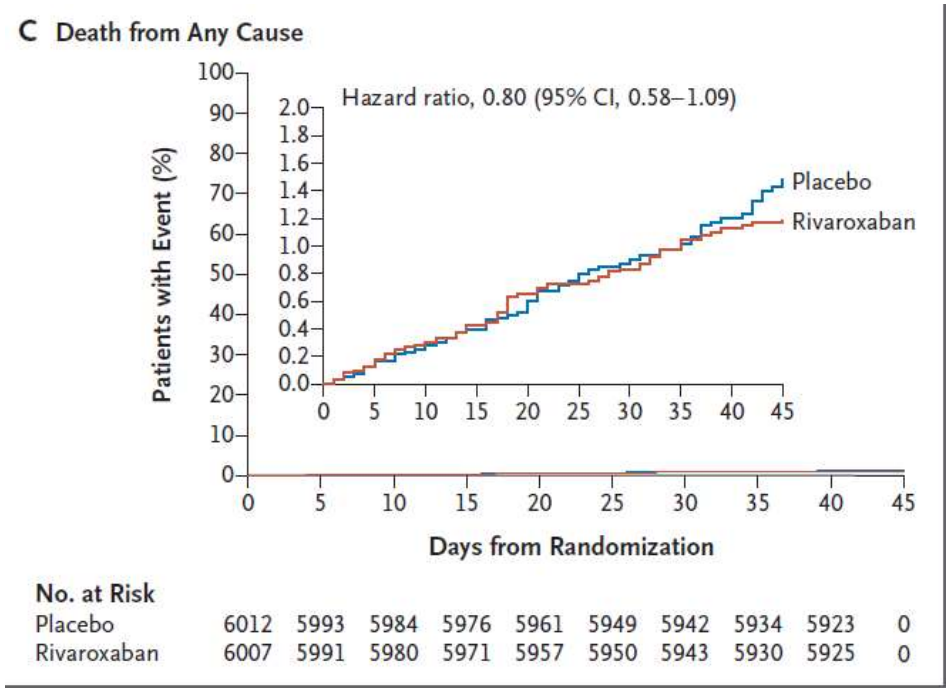
Modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) VTE risk score ≥4, or a score of 2 or 3 plus elevation of D-dimer levels >2x ULN

Raskob G, et al. *Thromb Haemost* 2016;115:1240-1248

MARINER results







Spyropoulos AC, et al. *N Engl J Med* 2018, Aug 26. DOI: 10.1056/NEJMoa1805090

Anticoagulation for venous thromboembolism 2018

1) Prolonged primary prevention of VTE in hospitalized medically ill patients: the end of the road?
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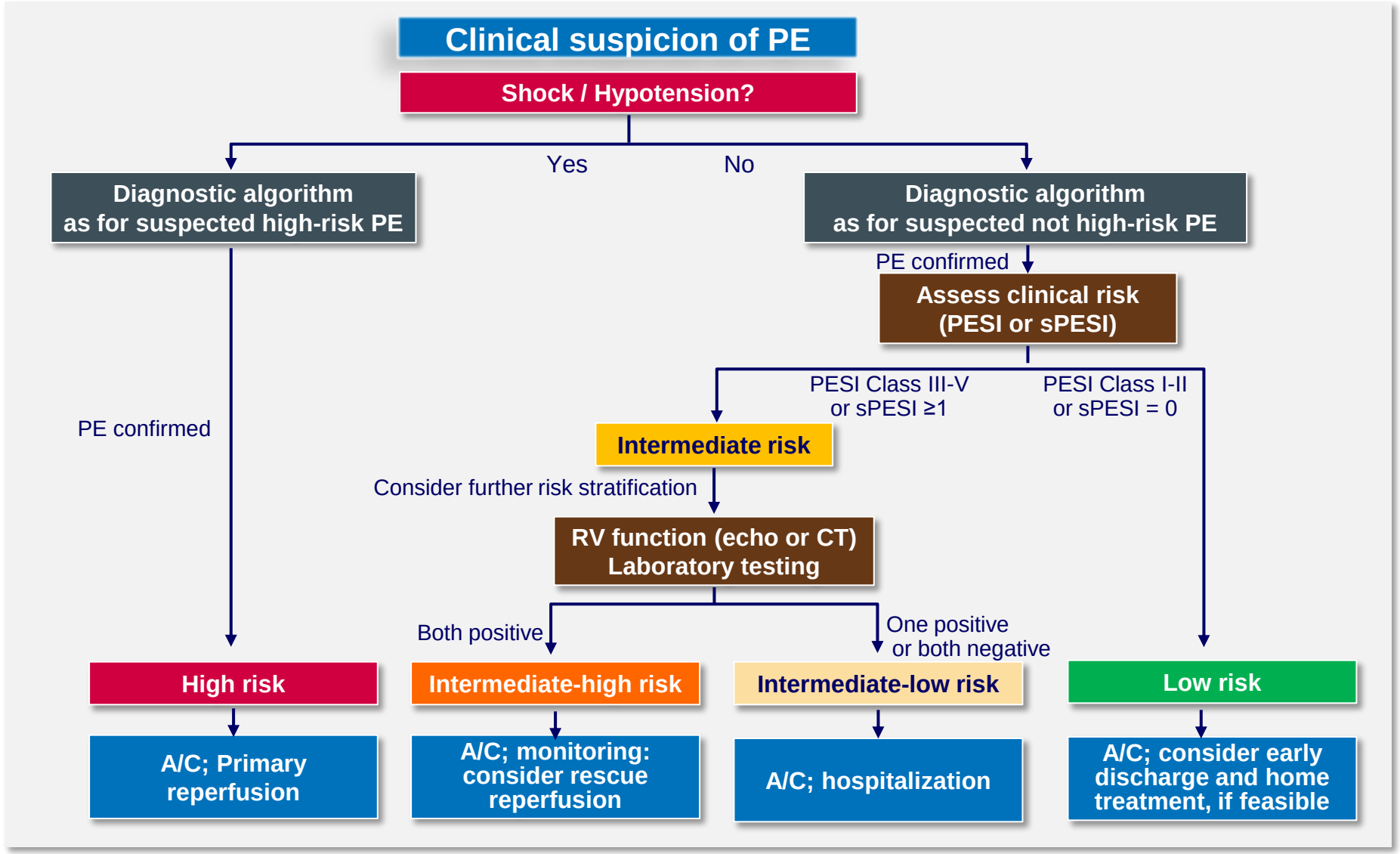
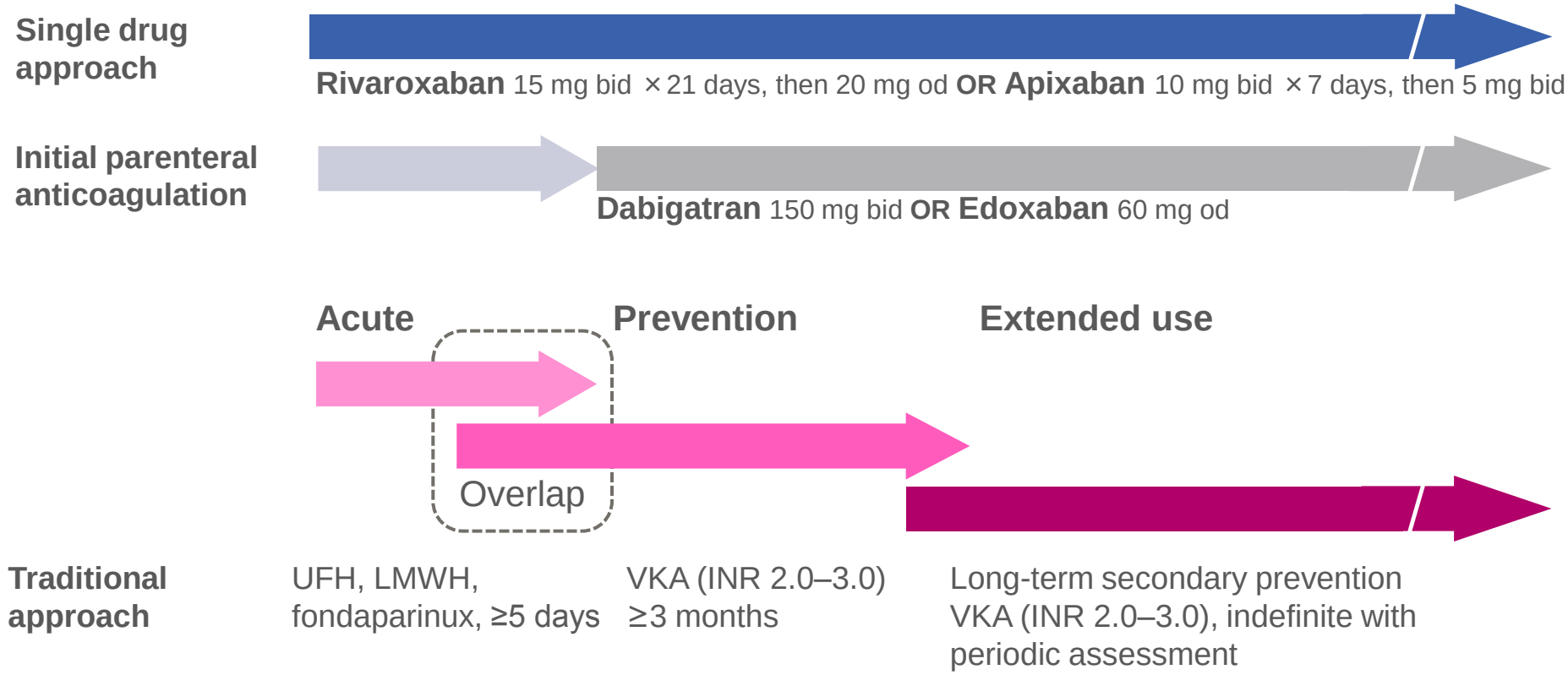
ESC Guidelines 2014: Management algorithm for acute PE



European Heart Journal (2014):doi:10.1093/eurheartj/ehu283

Current (2018) anticoagulation regimens for PE and DVT

Initial treatment schemes with non-VKA oral anticoagulants



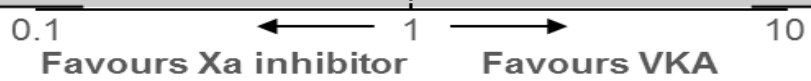
Modified from: Goldhaber SZ *et al, Lancet* 2012; 379:1835–1846
ESC Guidelines, European Heart Journal 2014; doi:10.1093/eurheartj/ehu283

Efficacy and safety of F Xa inhibitors in VTE

Meta-analysis

Efficacy and safety: rivaroxaban/apixaban/edoxaban

	Xa inhibitors n/N (%)	VKA n/N (%)	Risk ratio (95% CI)	RR (95% CI)	*p*
Recurrent VTE	211/10,877 (1.9)	246/10,888 (2.3)		0.86 (0.72–1.03)	0.10
Bleeding					
Major	111/10,924 (1.0)	187/10,927 (1.7)		0.56 (0.36–0.88)	0.01
Intracranial	13/10,924 (0.1)	38/10,927 (0.3)		0.35 (0.19–0.67)	0.001
Fatal	6/10,924 (0.1)	20/10,927 (0.2)		0.32 (0.13–0.82)	0.02
Major GI	48/10,924 (0.4)	61/10,927 (0.6)		0.69 (0.36–1.36)	0.29
Clinically relevant non-major	755/10,924 (6.9)	937/10,927 (8.6)		0.80 (0.59–1.07)	0.13
Net clinical benefit	327/10,877 (3.0)	431/10,888 (4.0)		0.76 (0.65–0.88)	0.0003
All-cause mortality	269/10,924 (2.5)	277/10,927 (2.5)		0.97 (0.81–1.16)	0.71



van Es N, et al. *Blood* 2014;124:1968-1975

Anticoagulants in VTE: 2016 ACCP guidelines

	ACCP recommendation	Grade of recommendation
Initial anticoagulation		
Acute DVT or haemodynamically stable PE and no cancer	**NOAC preferred to LMWH/VKA**	**2B**
	LMWH/VKA preferred to LMWH alone	2C
PE with hypotension	Thrombolytic therapy (systemic rather than catheter-directed unless bleeding risk is high)	2B (2C)
DVT or PE with cancer	LMWH suggested over NOAC or VKA	2C

Kearon C *et al, Chest* 2016;149:315–352

Specific subgroups: Low-risk PE
Single oral drug and early discharge -> home treatment

Haemodynamically stable patient admitted with clinically suspected PE:

☞ **Start parenteral anticoagulation**

↓

☞ **Confirm PE within 24 hours of admission**
(Chest CT, V/Q scan or pulmonary angiogram)

↓

Enrolment after eligibility criteria verified and informed consent

↓

☞ **First dose of rivaroxaban in-hospital**

↓

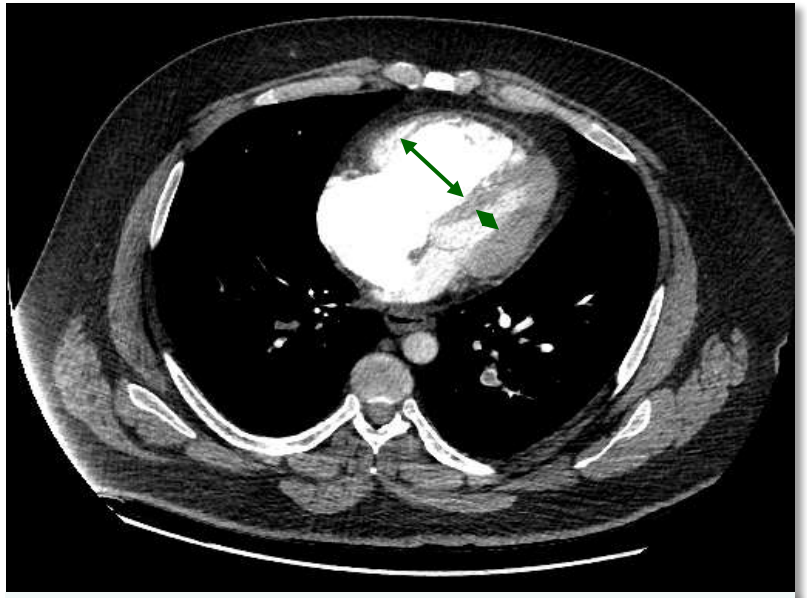
Additional baseline tests (echocardiography, CUS of leg veins)
– recommended, not compulsory

↓

☞ **Discharge within 48 hours**

↓

3-month follow-up



++ Absence of RV dilatation/dysfunction
Absence of RA or RV thrombi

CUS, compression ultrasound

HOT-PE

EudraCT Nr. 2013-001657-28

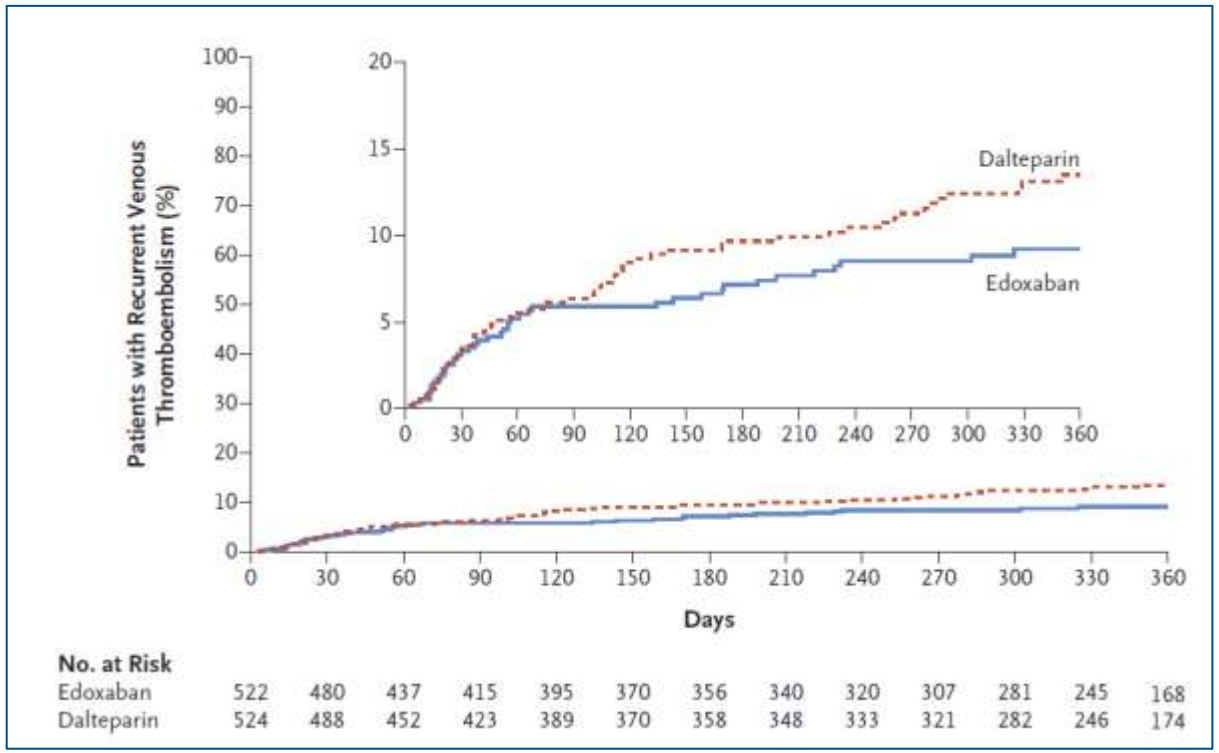
Specific subgroups: PE and cancer (Guidelines)

Recommendations	Class	Level
Incidental PE in patients with cancer should be managed in the same manner as symptomatic PE.	IIa	C
Negative D-dimer levels have the same negative diagnostic value as in non-cancer patients.	IIa	B
For patients with PE and cancer, weight-adjusted subcutaneous LMWH should be considered for the first 3 to 6 months.	IIa	B
For patients with PE and cancer, extended anticoagulation (beyond the first 3 to 6 months) should be considered for an indefinite period or until the cancer is cured.	IIa	C

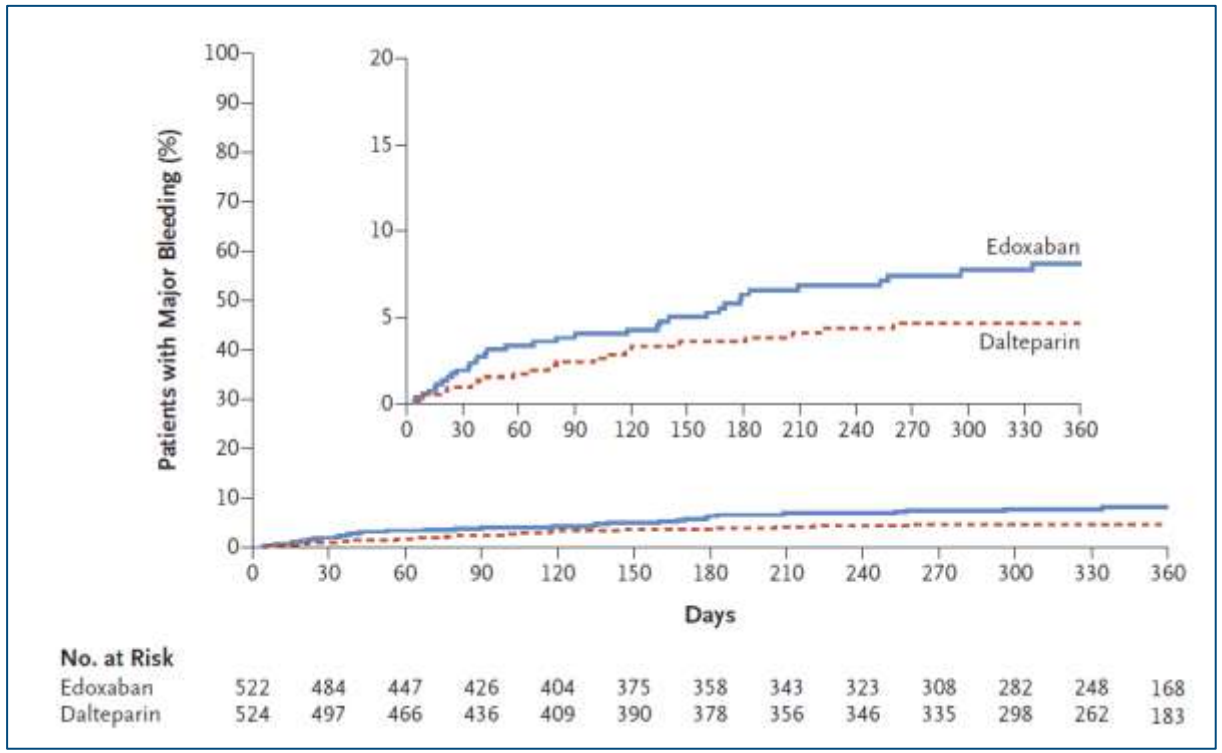
Konstantinides S, et al. *European Heart Journal* (2014):doi:10.1093/eurheartj/ehu283

Specific subgroups: Recent Hokusai VTE Cancer trial

Recurrent VTE (mITT, n=1046)

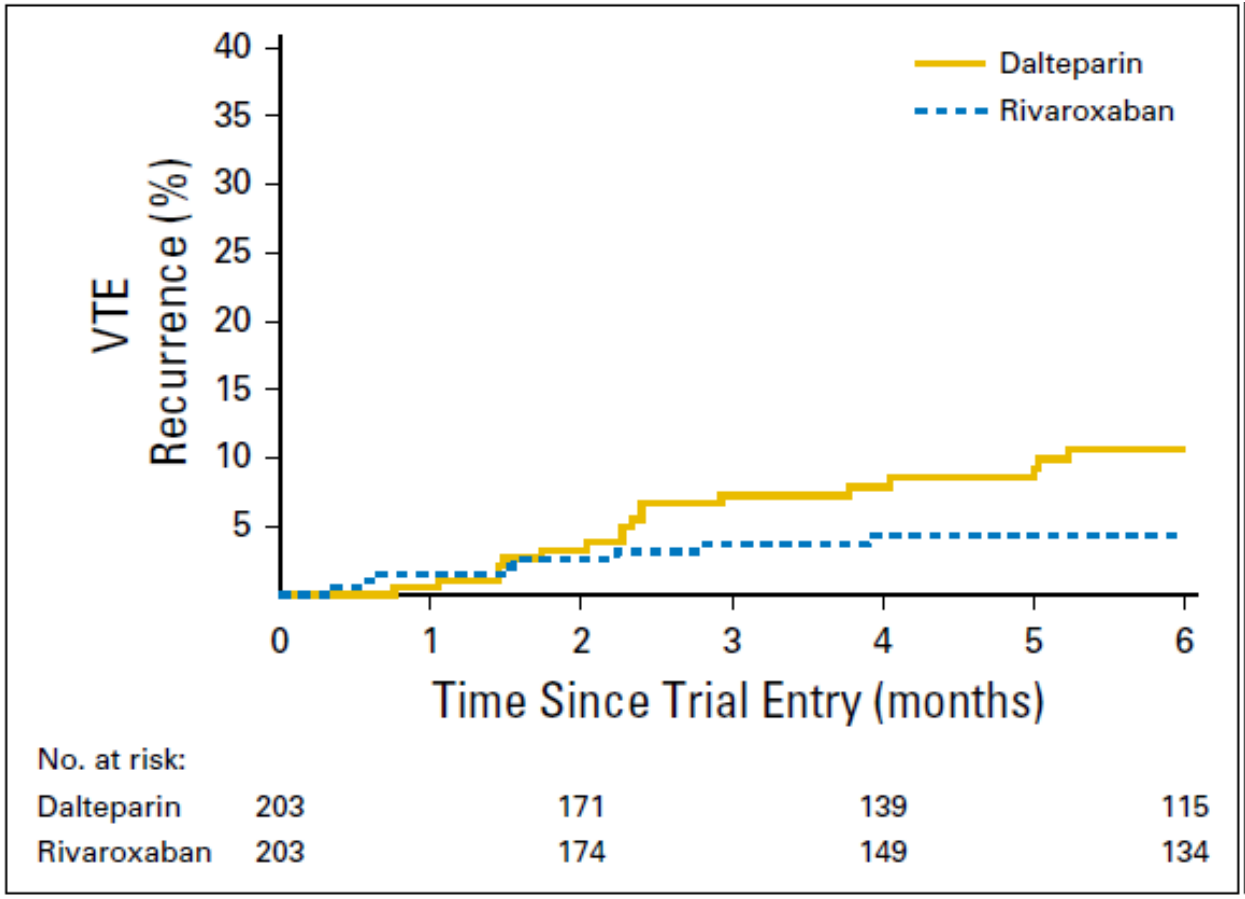


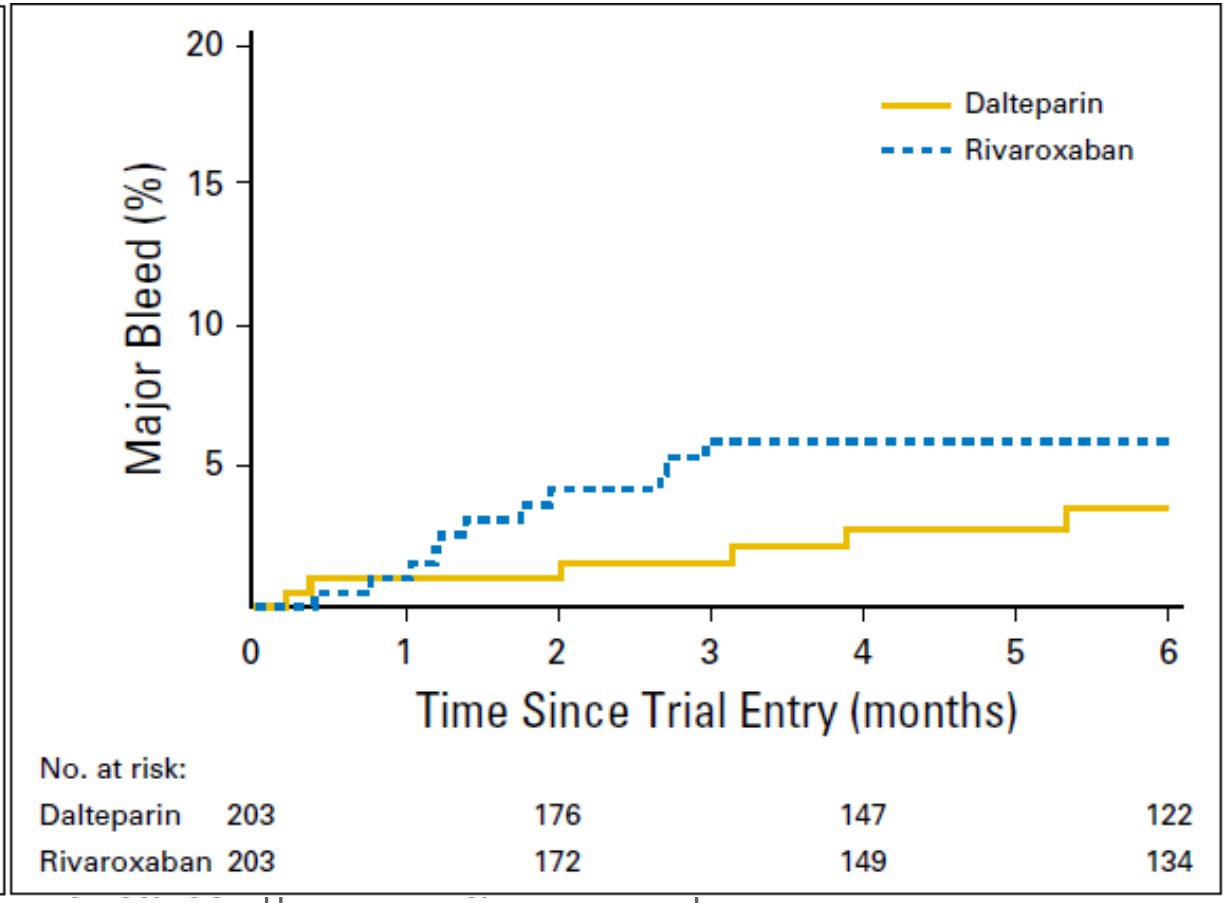
Major bleeding (mITT, n=1046)



Raskob GE *et al*. *N Engl J Med* 2017;378:615-624

Specific subgroups: Recent select-d trial





Young AM, et al. *J Clin Oncol* 2018; Epub ahead of print

*15 mg bid for 21 days followed by 20 mg od; for patients with CrCl 30–49 ml/min dosing recommendations as in rivaroxaban SmPC; if a patient's platelet counts falls to <50,000/mm^3, rivaroxaban should be discontinued until the platelet count recovers to above 50,000/mm^3; #200 IU/kg od for the first 30 days of treatment followed by 150 IU/kg od; if a patient's platelet count falls to 50,000–100,000/mm^3 the daily dose of dalteparin should be reduced by 2500 IU until platelet count returns to ≥100,000/mm^3; if a patient's platelet count falls to <50,000/mm^3, dalteparin should be discontinued until the platelet count recovers to above 50,000/mm^3

IIR, Investigator Initiated Research; FU, follow-up; R, randomization; RVT, residual vein thrombosis

http://www2.warwick.ac.uk/fac/med/research/hscience/ctu/trials/cancer/select-d/; EudraCT number: 20

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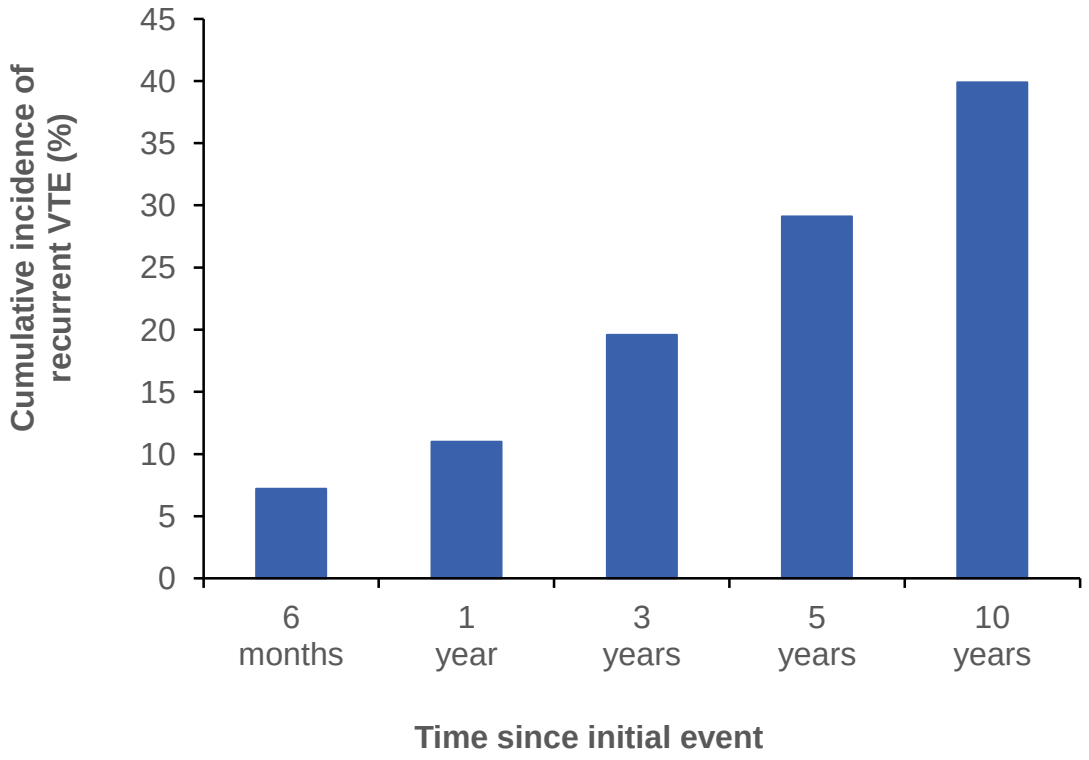
ESC 2014: VTE treatment and secondary prevention

Recommendations	Class	Level
For patients with PE secondary to a transient (reversible) risk factor, oral anticoagulation is recommended for 3 months.	I	B
For patients with unprovoked PE, oral anticoagulation is recommended for at least 3 months.	I	A
Extended oral anticoagulation should be considered for patients with a first episode of unprovoked PE and low bleeding risk .	IIa	B
In patients who receive extended anticoagulation, the risk-benefit ratio of continuing such treatment should be reassessed at regular intervals.	I	C
In patients who refuse to take or are unable to tolerate any form of oral anticoagulants, aspirin may be considered for extended secondary VTE prophylaxis.	IIb	B

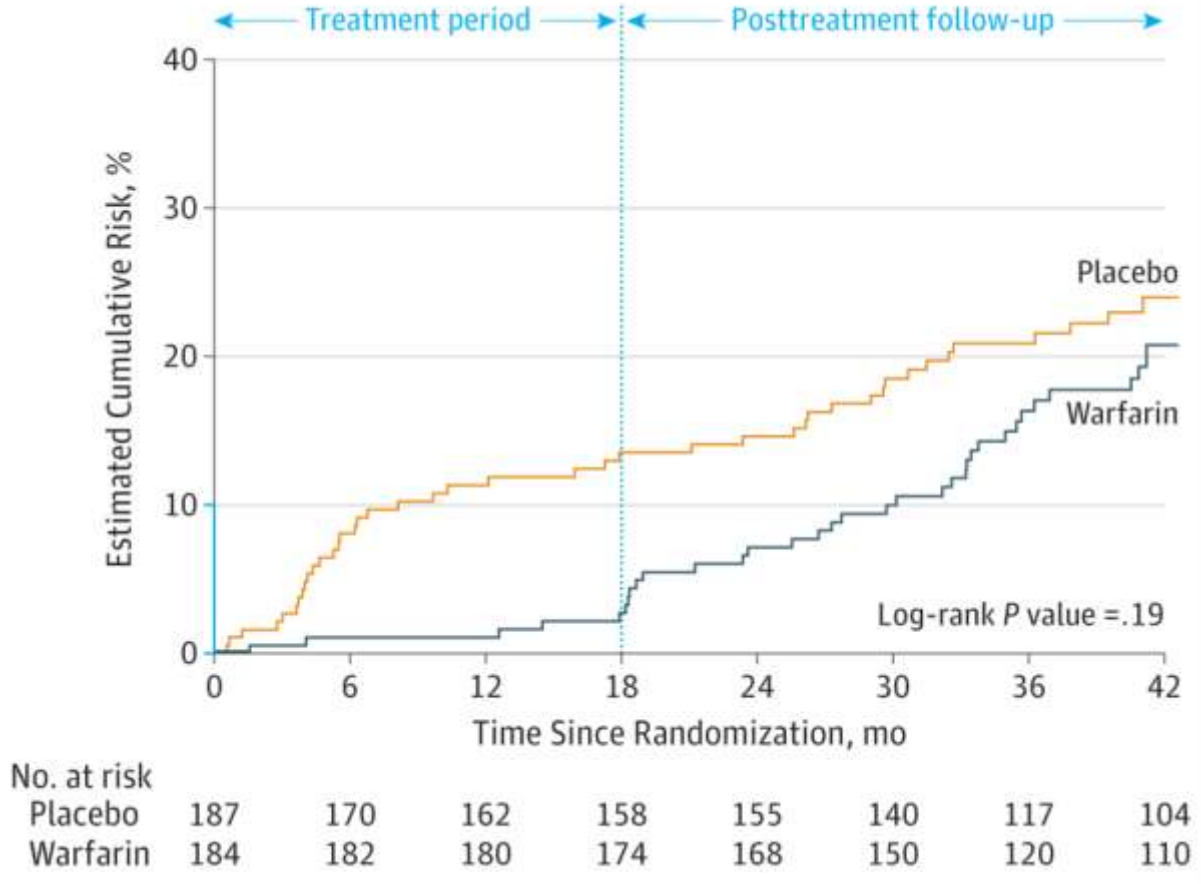
European Heart Journal (2014):doi:10.1093/eurheartj/ehu283

High risk of VTE recurrence – highly effective prevention by VKA

Cumulative incidence of VTE recurrence over time



Prandoni P, et al. *Haematologica* 1997; 82: 423-428
Prandoni P, et al. *Ann Intern Med* 1996;125:1-7



Couturaud F, et al. *JAMA* 2015;314:31-40

BUT: Bleeding frequent and potentially dangerous while on chronic VKA treatment

ARTICLE

Clinical Impact of Bleeding in Patients Taking Oral Anticoagulant Therapy for Venous Thromboembolism

A Meta-Analysis

Lori-Ann Linkins, MD, FRCP(C); Peter T. Choi, MD, MSc, FRCP(C); and James D. Douketis, MD, FRCP(C)

33 studies; 10,757 patients; 4,374 patient-years of OAC

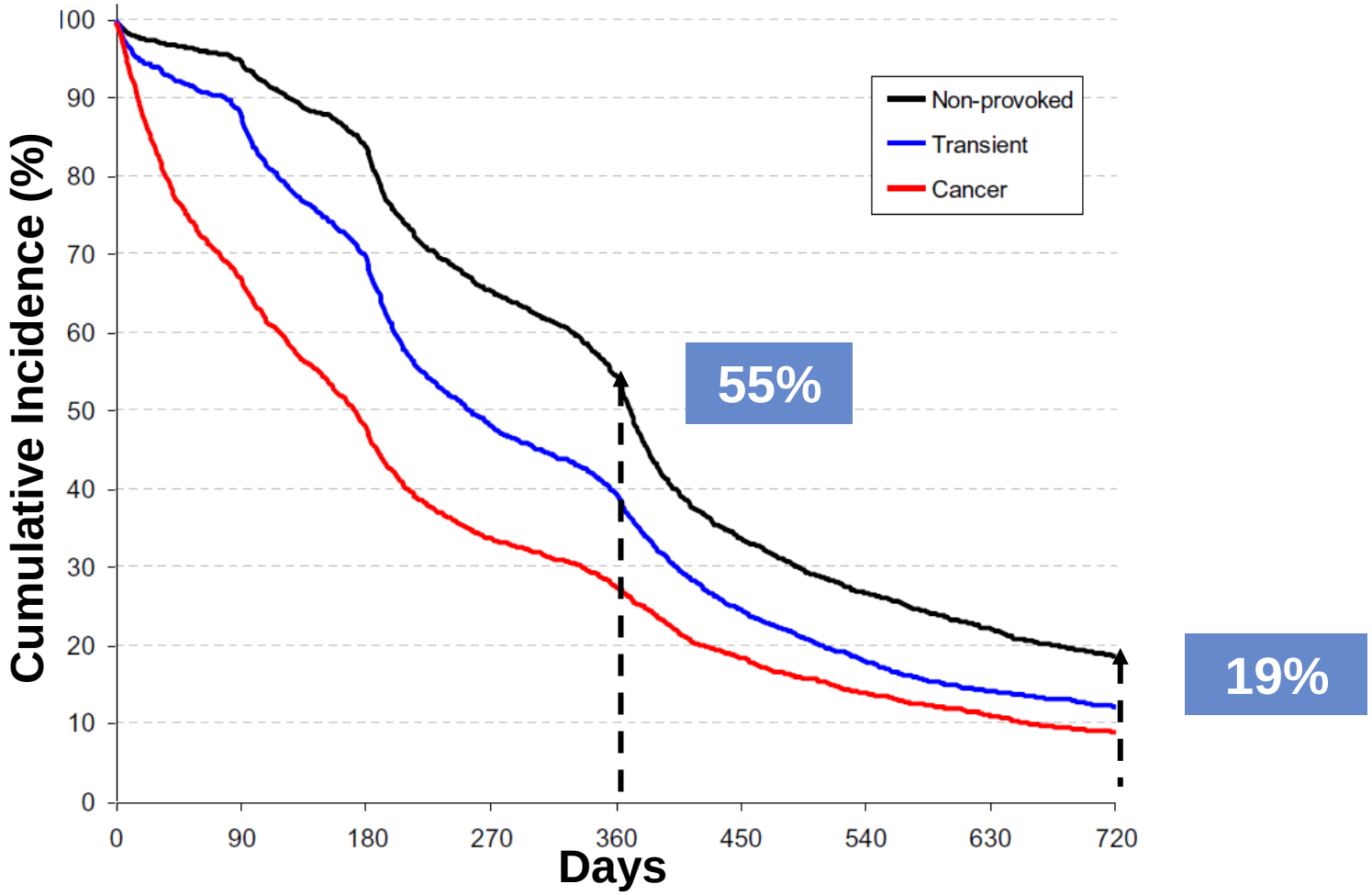
After the first 3 months of OAC:

- Major bleeding rate: 2.74%/yr
- Intracranial bleeding: 0.65%/yr
- Fatal bleeding rate: 0.63%/yr
- Case fatality rate: **9.1%**

Linkins LA, et al. *Ann Intern Med* 2003;139:893-900

Recurrence versus bleeding risk (in the VKA era): What is done in clinical practice?

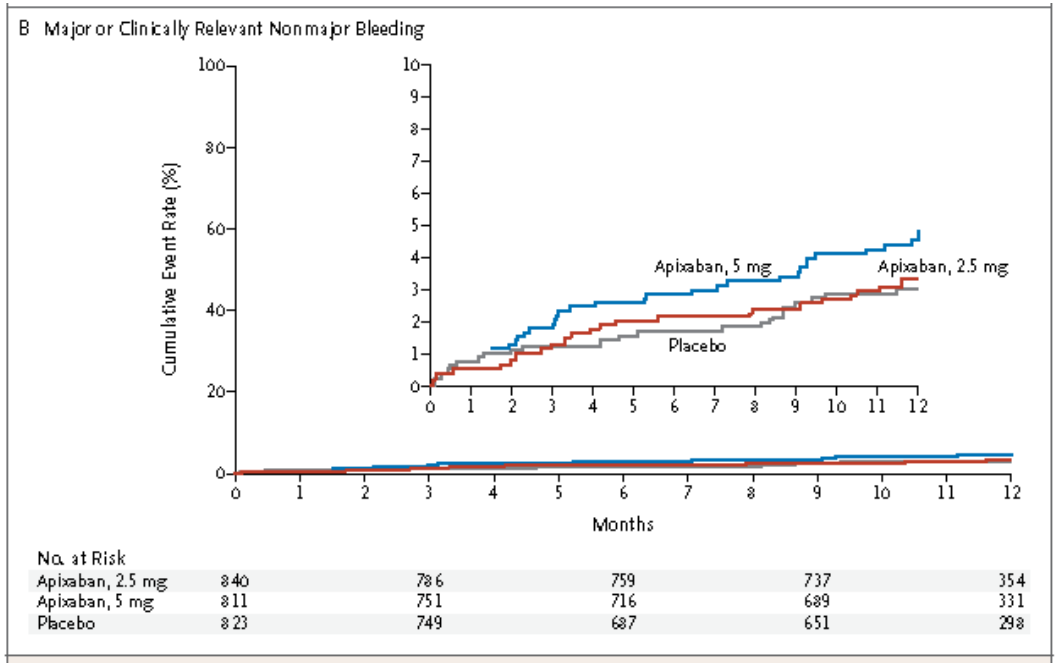
RIETE Registry (N=6944)



Ageno W, et al. *Thromb Res* 2015;135:666–672

Safety and efficacy of extended prophylaxis with *half-dose* apixaban: AMPLIFY-EXT

- Two doses of apixaban (2.5 mg and 5 mg, twice daily) versus placebo
- Pts with VTE who had completed 6-12 months of anticoagulation
- study drugs were given for 12 months
- 2482 pts included in ITT
- **Primary EP**: 8.8% in placebo vs. 1.7% in EACH apixaban dose

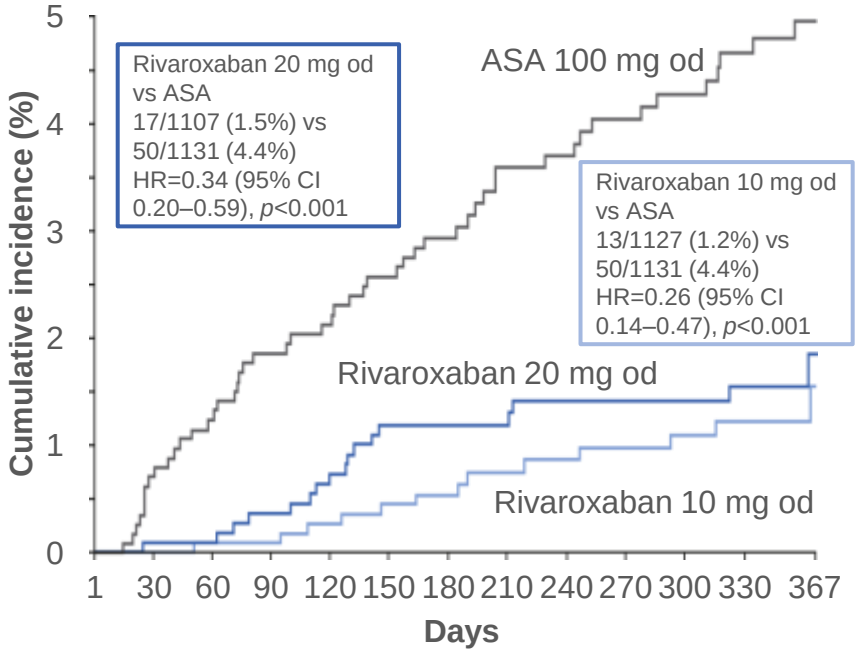


Major / CRNM bleeding:
2.7% vs. 3.2% (2.5 mg) vs. 4.3% (5 mg)

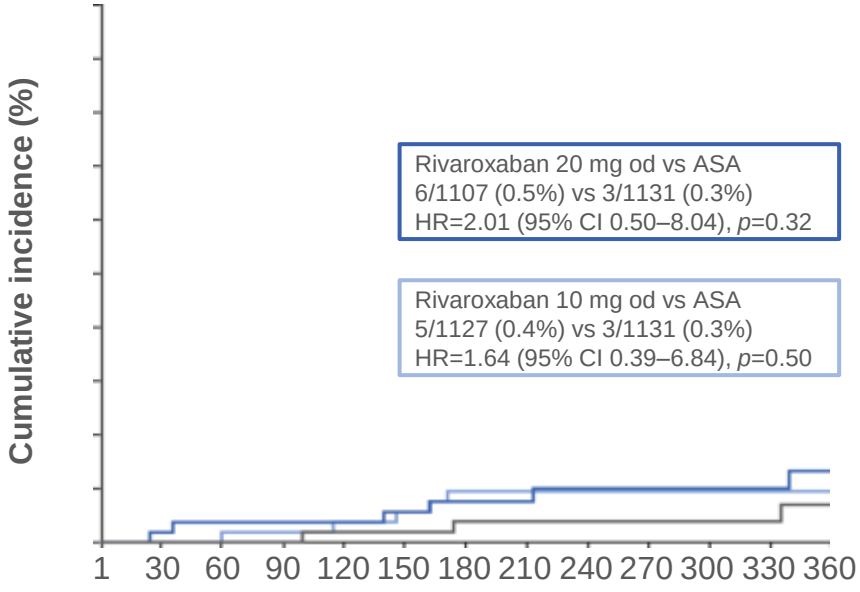
Agnelli G, for the AMPLIFY Investigators. *N Engl J Med* 2013;368:799-808

Safety and efficacy of extended prophylaxis with *standard-dose* vs *half-dose* rivaroxaban: EINSTEIN Choice

Efficacy*



Major bleeding#



*Intention-to-treat analysis; #safety analysis; ‡no events after Day 360 up to Day 480

Weitz JI, et al. *N Engl J Med* 2017:doi:10.1056/NEJMoa1700518

Pulmonary embolism 2018: Most patients candidates for extended (**low-dose**) anticoagulation **beyond 6 months**

Centrum für Thrombose und Hämostase Mainz

STOP after 3 months: PE provoked by a strong reversible risk factor

- Major, especially orthopaedic surgery (anaesthesia > 30 min)
- Major trauma with/without surgical treatment
- Immobilisation in hospital for acute severe illness

CONTINUE: All other transient or permanent factors

- More than one VTE event (without strong reversible factor)
- Cancer
- Antiphospholipid syndrome **(only VKA!)**

- Inflammatory bowel disease
- Active autoimmune disease

- Family history of VTE, or major hereditary thrombophilia
- Minor surgery (anaesthesia < 30 min), or (leg) trauma
- Long-haul flight
- Oestrogen contraception or replacement therapy

- Male sex
- Age
- Obesity (BMI > 30 kg/m²)
- Location of index VTE: PE or proximal DVT (not distal DVT)

- **No identifiable risk factor!**

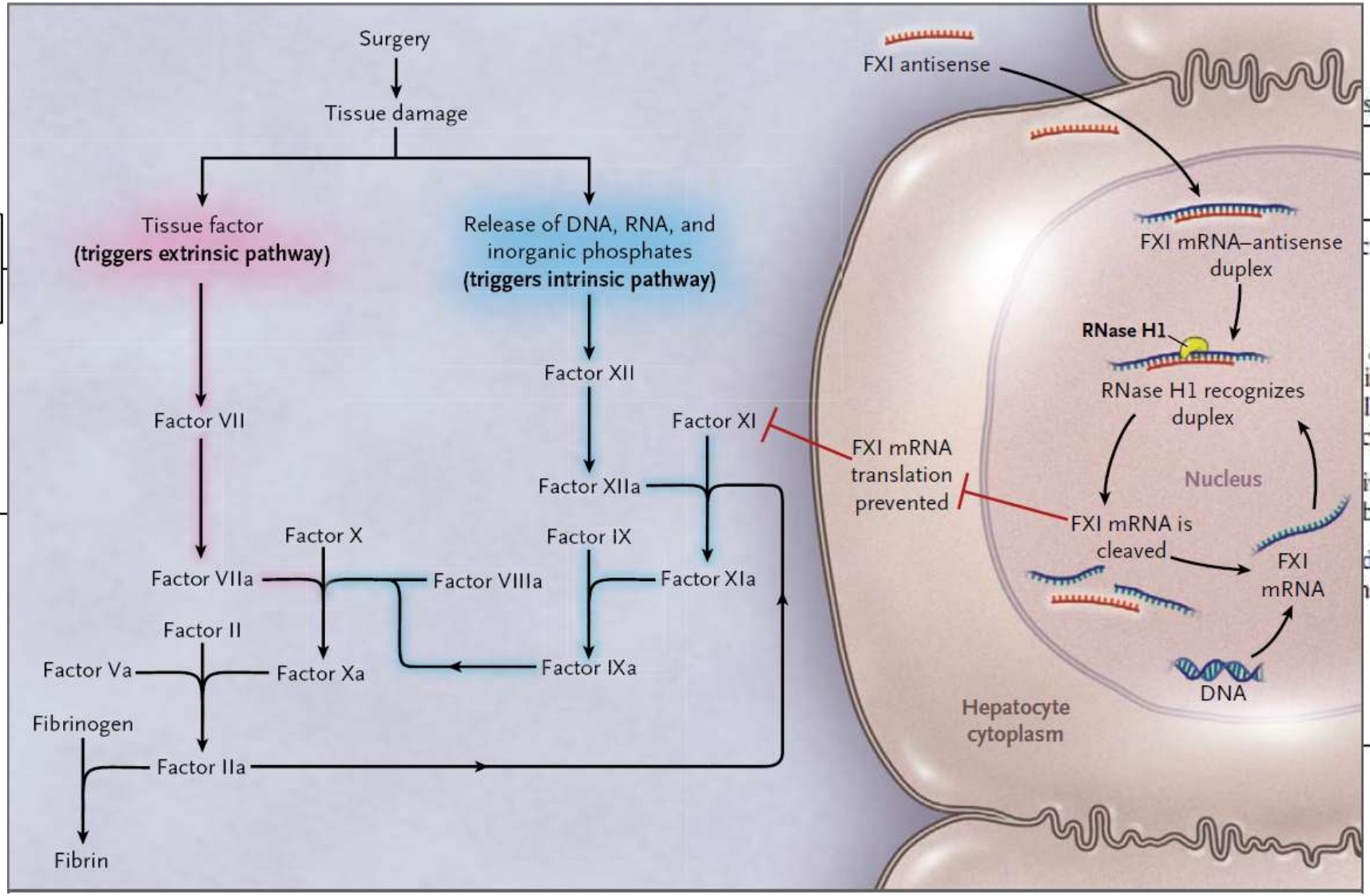
Regular follow-up, assessment of recurrence versus bleeding risk remains necessary!

Recommendations	Class	Level
For patients with PE secondary to a transient (reversible) risk factor, oral anticoagulation is recommended for 3 months.	I	B
For patients with unprovoked PE, oral anticoagulation is recommended for at least 3 months.	I	A
Extended oral anticoagulation should be considered for patients with a first episode of unprovoked PE and low bleeding risk .	IIa	B
In patients who receive extended anticoagulation, the risk-benefit ratio of continuing such treatment should be reassessed at regular intervals.	I	C
In patients who refuse to take or are unable to tolerate any form of oral anticoagulants, aspirin may be considered for extended secondary VTE prophylaxis.	IIb	B

European Heart Journal (2014):doi:10.1093/eurheartj/ehu283

Future targets of anticoagulants?

Targeting coagulation factor XI and XII



Weitz JI. *Thromb Res* 2017;140 (Suppl 2):S40-S45

Büller HE, et al. *N Engl J Med* 2015;372:232-240

Targeting coagulation factor XI

- Patients with congenital F XI deficiency protected from VTE and ischemic stroke
- Subjects with higher levels of F XI at greater risk for VTE and ischemic stroke than those with lower levels
- Levels of factor XI correlate with stroke risk in women taking oral contraceptives

Weitz JI. *Thromb Res* 2017;140 (Suppl 2):S40-S45

- 300 patients for elective primary TKA to of FXI-ASO (200 mg or 300 mg) or 40 mg of enoxaparin once daily
- Tx with FXI-ASO initiated 36 days before surgery: three s.c. doses on days 1, 3, and 5; once-weekly doses on days 8, 15, 22, and 29. On day 36, the day of surgery, one dose 6 hours postoperatively; a final dose on day 39
- Primary efficacy outcome: VTE by mandatory bilateral venography or symptomatic: **27% vs 4% vs 30%**
- Principal safety outcome: major or clinically relevant nonmajor bleeding: **3% vs 3% vs 8%**

Büller HE, et al. *N Engl J Med* 2015;372:232-240

Potential indications for targeting coagulation factor XI or XII

- Elective knee arthroplasty (proof of principle)
- Secondary prevention of venous thromboembolism (safety, convenience)
- Stroke prevention in atrial fibrillation patients with end stage renal disease on dialysis (unmet medical need for efficacy and safety!)
- Extracorporeal membrane oxygenation, left ventricular assist devices or mechanical heart valves -> F XII (unmet medical need in the NOAC era!)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Pulmonary Circulation
& Right Ventricular
Function
ESC Working Group