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HEALTH THROUGH KNOWLEDGE

Chronic Management of Venous Thromboembolic Disease in 2019

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ACC Rockies

Disclosures

- Relationships with commercial interests:
  - Grants/Research Support: Bayer, BI, BMS, Daiichi-Sankyo, Janssen, Pfizer
  - Speakers Bureau/Honoraria: Bayer, BI, BMS, Daiichi-Sankyo, Janssen, Pfizer
- Employment:
  - Hamilton Health Sciences and McMaster University; I work at an anticoagulation clinic
- Government grants:
  - CIHR, HSF, NIF, NHMRC

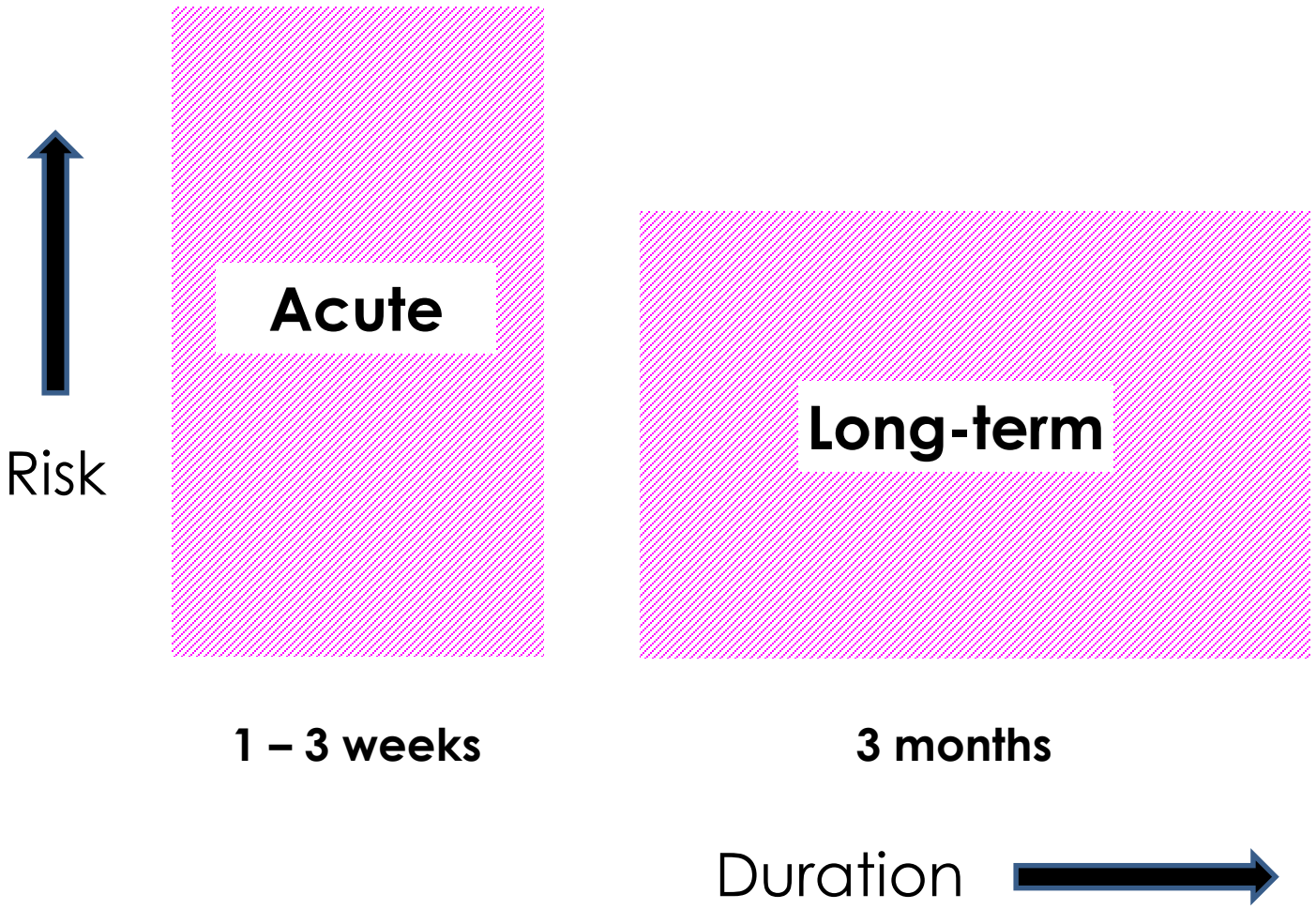
Learning Objectives

Following their participation in this activity, physicians will be in a position to address the following questions:

1. ***Long term anticoagulation for everyone?**
2. Should I be screening my PE patient for CTEPH?
3. How should I manage interruption of anticoagulation for procedures in patients with VTE?

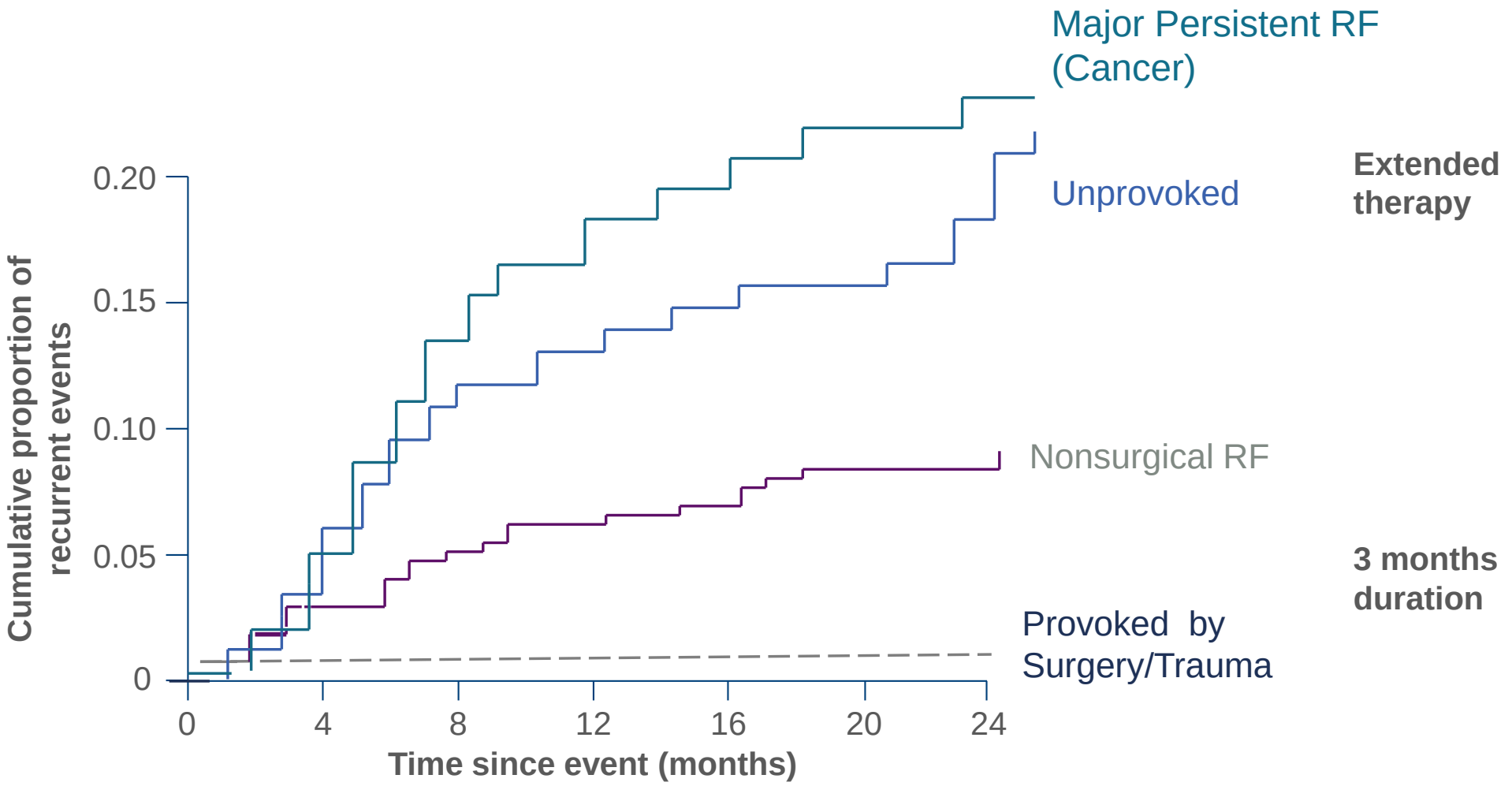
*With grateful acknowledgement of Peter Verhamme who provided a selection of slides on VTE treatment

Duration of anticoagulation for VTE



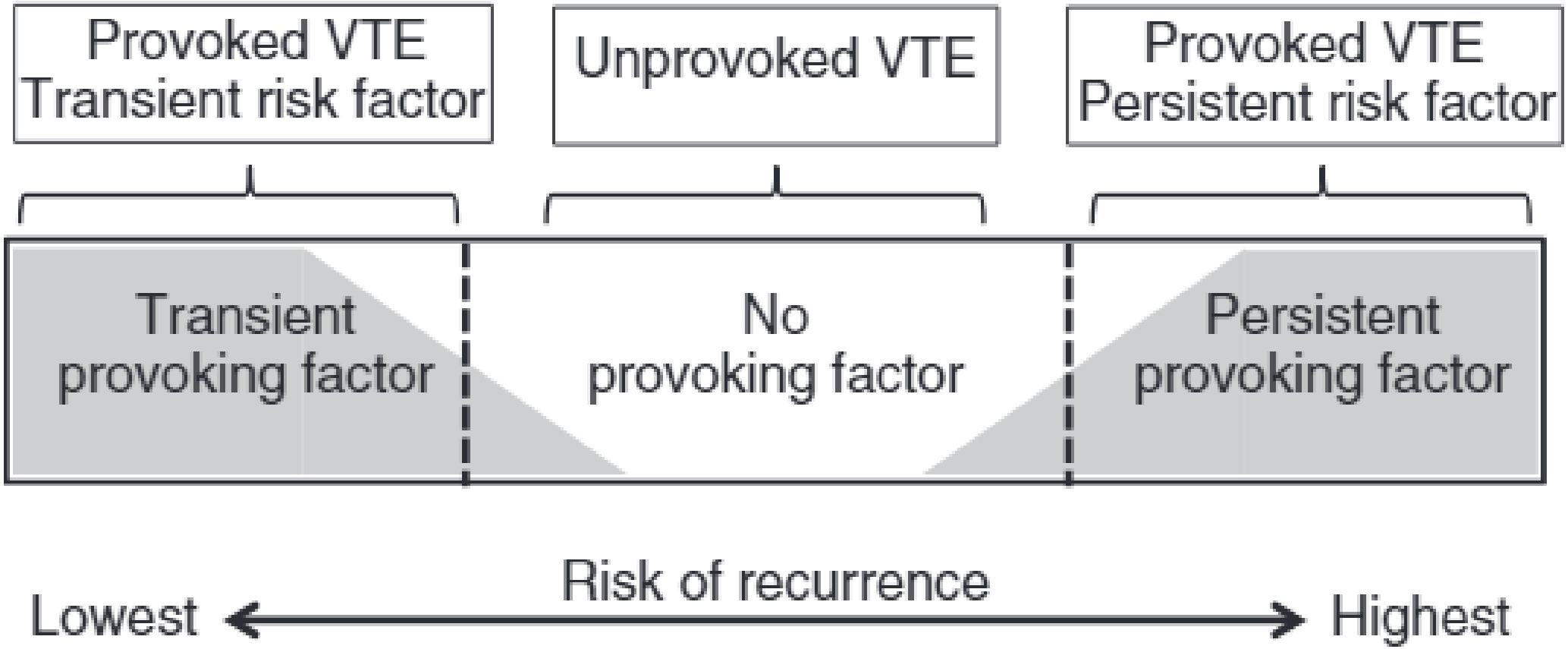
Unprovoked vs. Provoked
Transient vs. Permanent
Minor vs. Major

Risk of VTE recurrence



Baglin T *et al*, *Lancet* 2003; 362: 523–526. Kearon C *et al, Chest* 2016; 149 :315–352

Provoked and unprovoked VTE and risk of recurrence



Kearon C, *et al. J Thromb Haemost* 2016; 14: 1480-3.

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Persistent and transient risk factors: examples

Persistent		Transient	
Major	**Minor**	**Major (≤3 months)**	**Minor (<6 weeks)**
Active cancer	Inflammatory bowel disease	Surgery, GA ≥30 min	Surgery, GA <30 min
	Paralysis	Hospitalized bed rest ≥3 d	Hospitalized bed rest <3 d
	Thrombophilia	Caesarian	Estrogens
			Pregnancy
			Leg injury, ↓ mobility ≥3 d

Kearon C, *et al. J Thromb Haemost* 2016; 14: 1480-3. Prins M, et al. Blood Advances 2018; 2: 788-96.

Patients who require consideration of extended treatment

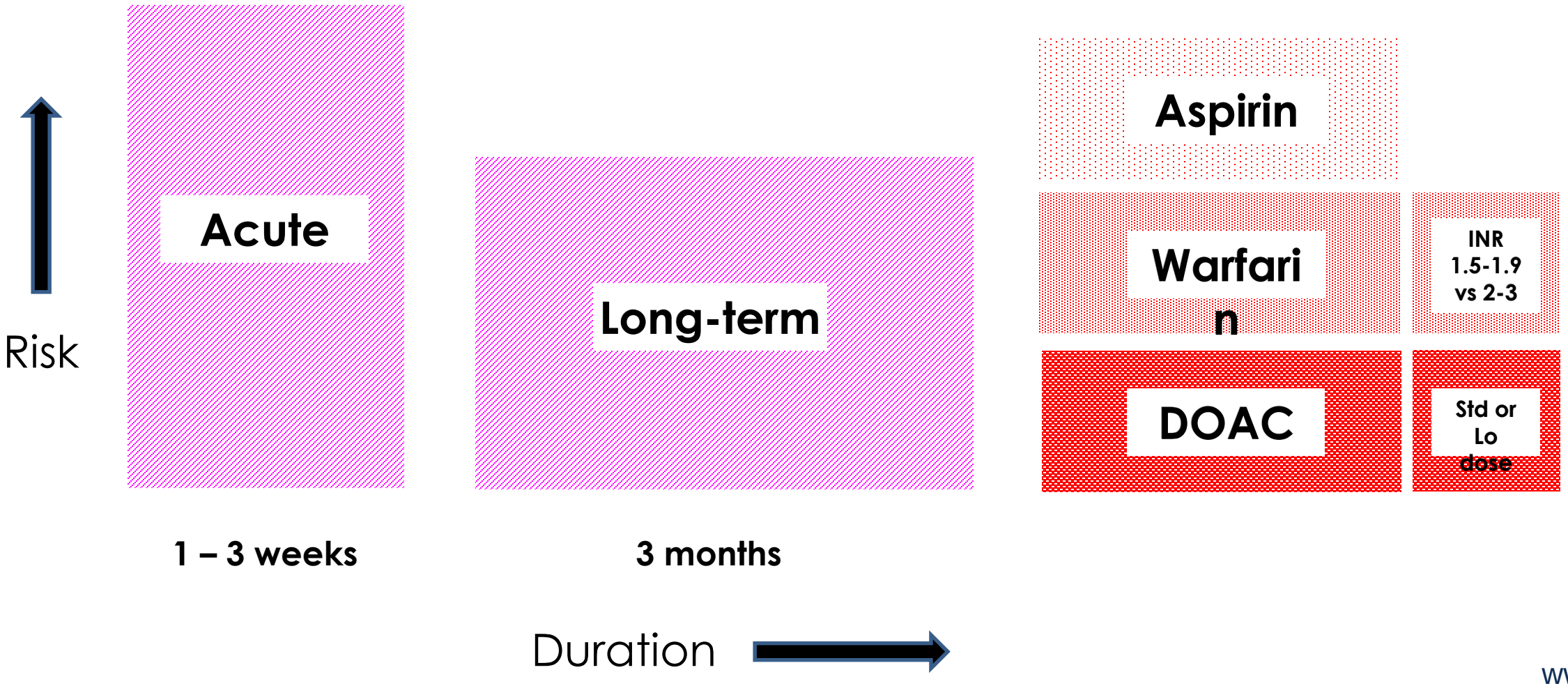
- Unprovoked
- Major persistent risk factor
- Multiple events

Approaches to risk prediction in patients with unprovoked VTE that are of uncertain value

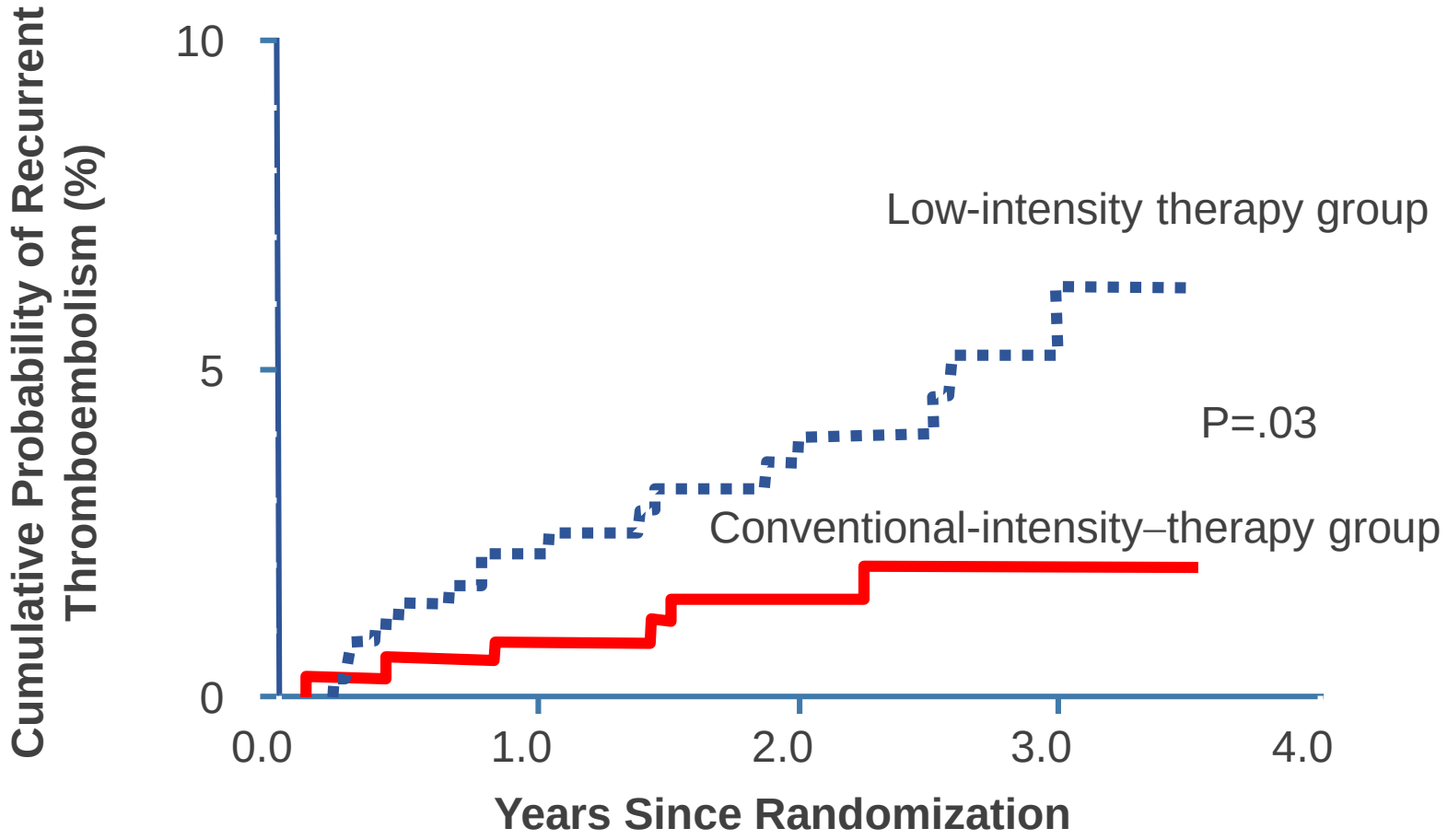
- Male sex
- D-dimer
- Risk scores (e.g., Vienna prediction model, DASH score, HERDOO2)

*Patient values and preferences

Antithrombotic choice for extended treatment



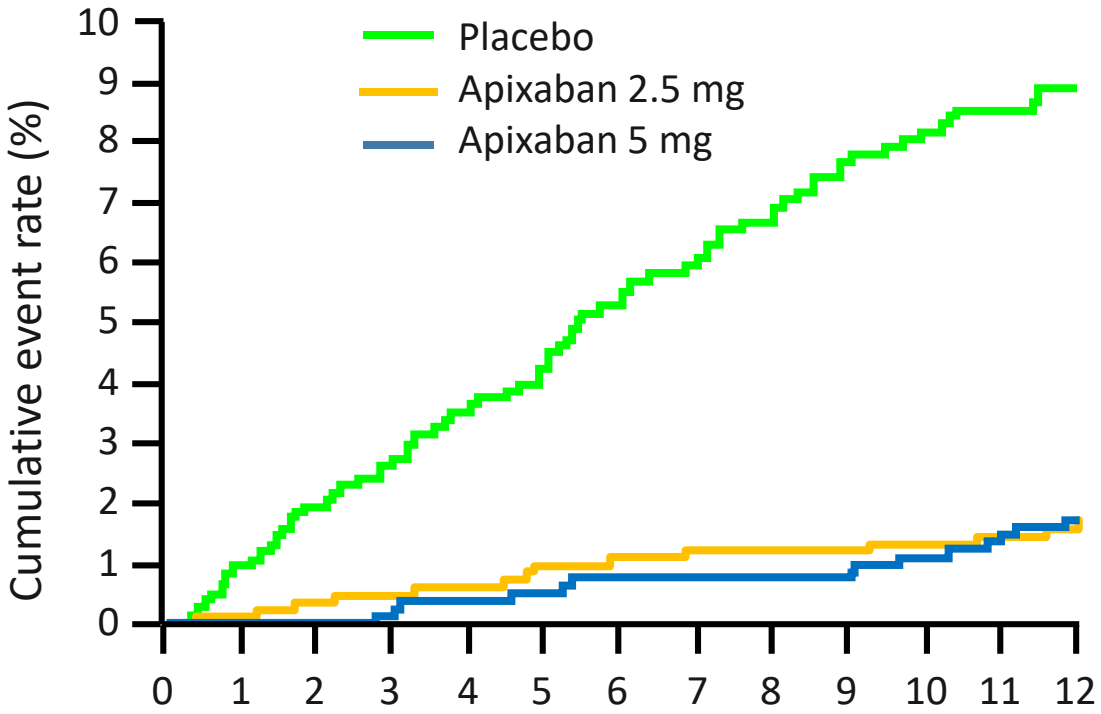
Warfarin INR 1.5-1.9 vs. 2-3 for extended treatment of unprovoked VTE



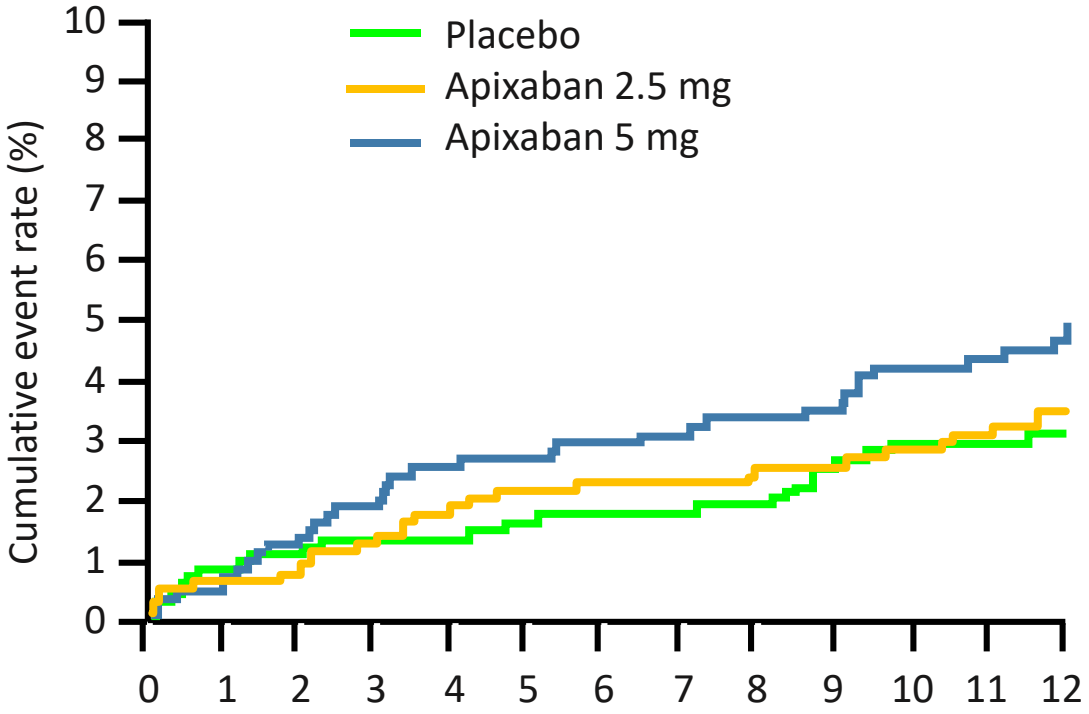
Kearon et al., *N Engl J Med* 2003; 349: 631-9.

Apixaban 2.5 vs 5 mg twice-daily for extended treatment

Recurrent VTE



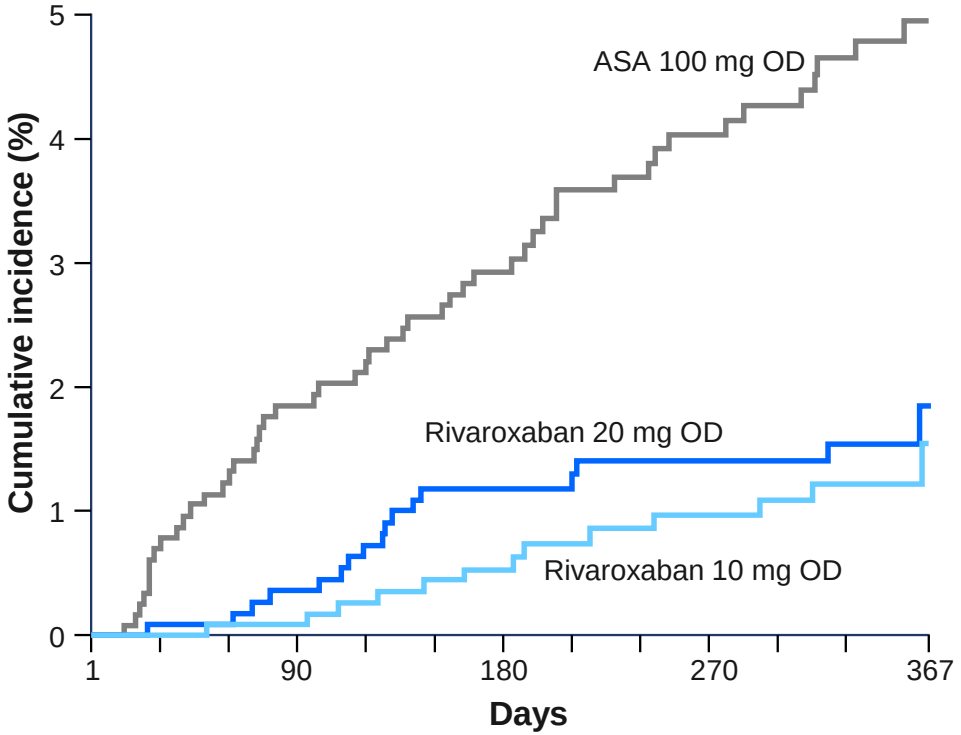
Clinically relevant Bleeding



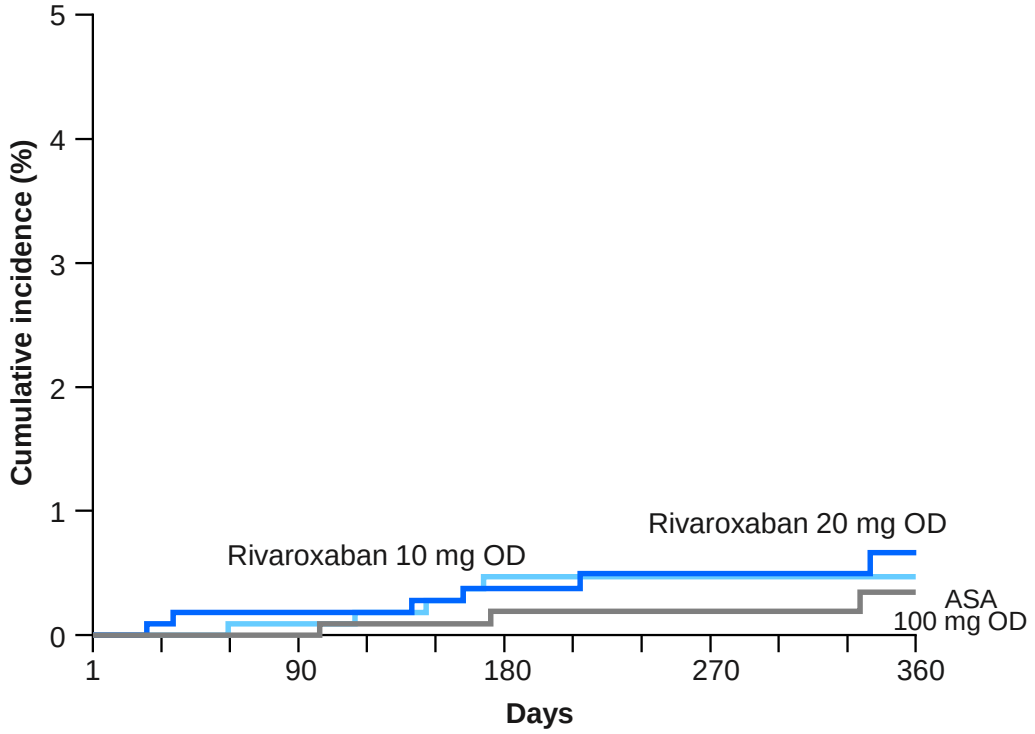
Agnelli G, et al. *N Engl J Med* 2013; 369: 799-808.

Rivaroxaban 10 or 20 mg once-daily for extended treatment

Recurrent VTE

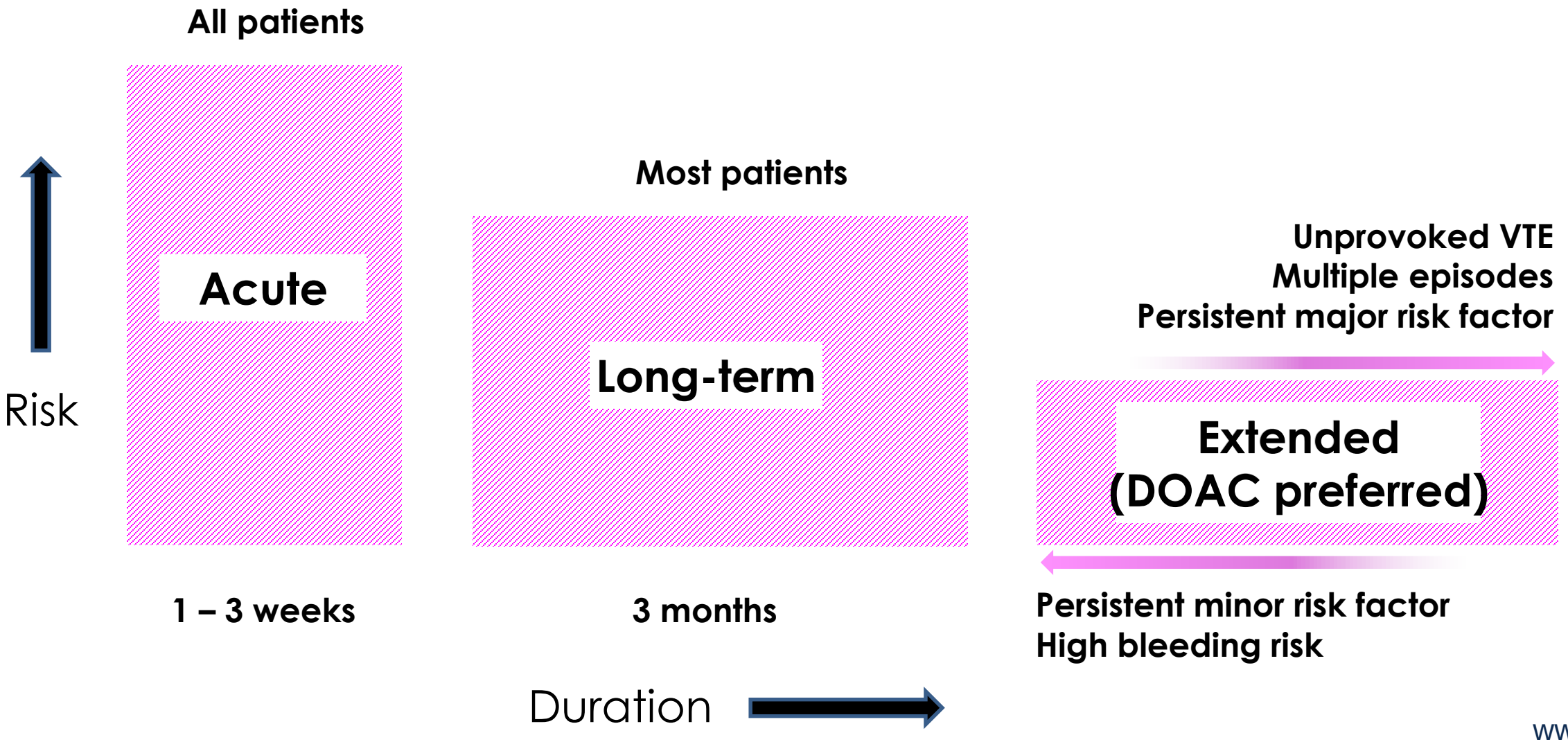


Major bleeding



Weitz JI, et al. *N Engl J Med* 2017; 376:1211–1222.

Recommendations



Question 1: select the correct response

In 2019 extended treatment for prevention of recurrent VTE:

1. Should be used in all patients unless they have contraindications
2. Should be restricted to patients with recurrent events and those with cancer-related thrombosis
3. **The treatment of choice is reduced-intensity NOAC therapy**
4. The treatment of choice is aspirin

Learning Objectives

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1. Long term anticoagulation for everyone?
2. **Should I be screening my PE patient for CTEPH?**
3. How should I manage interruption of anticoagulation for procedures in patients with VTE?

Question 2: select the one that is incorrect

Regarding CTEPH:

1. All patients who present with PE should undergo echocardiography to screen for pulmonary hypertension
2. The recommended test to distinguish CTEPH from other causes of pulmonary hypertension is a V/Q scan
3. Patients with CTEPH require life-long anticoagulation
4. It is not known whether screening for CTEPH in patients with PE is cost-effective

Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

Symptomatic pulmonary hypertension with persistent pulmonary perfusion defects despite adequate anticoagulation for 3-6 months

- 1-5% of PE survivors (100-500 per year in Canada)
- 50-75% have history of PE
- Associated with poor prognosis, high mortality
- Treatable and potentially curable
- Curative success may be improved by early diagnosis

Should I screen my PE patients for CTEPH?

Isabelle O, et al. *Swiss Med Wkly* 2018; 148: w14702. Albani S, et al. *J Cardiovasc Med* 2019; 20: 159-68.

Classical presentation

- Dyspnea on exertion
- Progressive exercise intolerance
- Right heart failure

Isabelle O, et al. *Swiss Med Wkly* 2018; 148: w14702.

Delayed diagnosis

UK survey (n=488):

- 44% of patients diagnosed with CTEPH saw at least 4 doctors before diagnosis was made
- 30% of patients had at least 2 year delay from first consultation to diagnosis

Armstrong I, et al. *BMJ Open* 2012 ;2: doi: http://dx.doi.org/10.1136/Bmjopen-2011-000806.
Armstrong I, et al. *Am J Respir Crit Care Med* 2011; 183: A6130. Isabelle O, et al. *Swiss Med Wkly* 2018; 148: w14702.

Reasons for under-diagnosis and delated diagnosis of CTEPH

- Non-specific clinical presentation
- Unrecognized by clinicians
- Lack of expertise in detecting the disease on CTPA
- Lack of clear guideline recommendations on testing for CTEPH

Isabelle O, et al. *Swiss Med Wkly* 2018; 148: w14702. Kim NH, et al. *Eur Respir J* 2019; 53: 1801915

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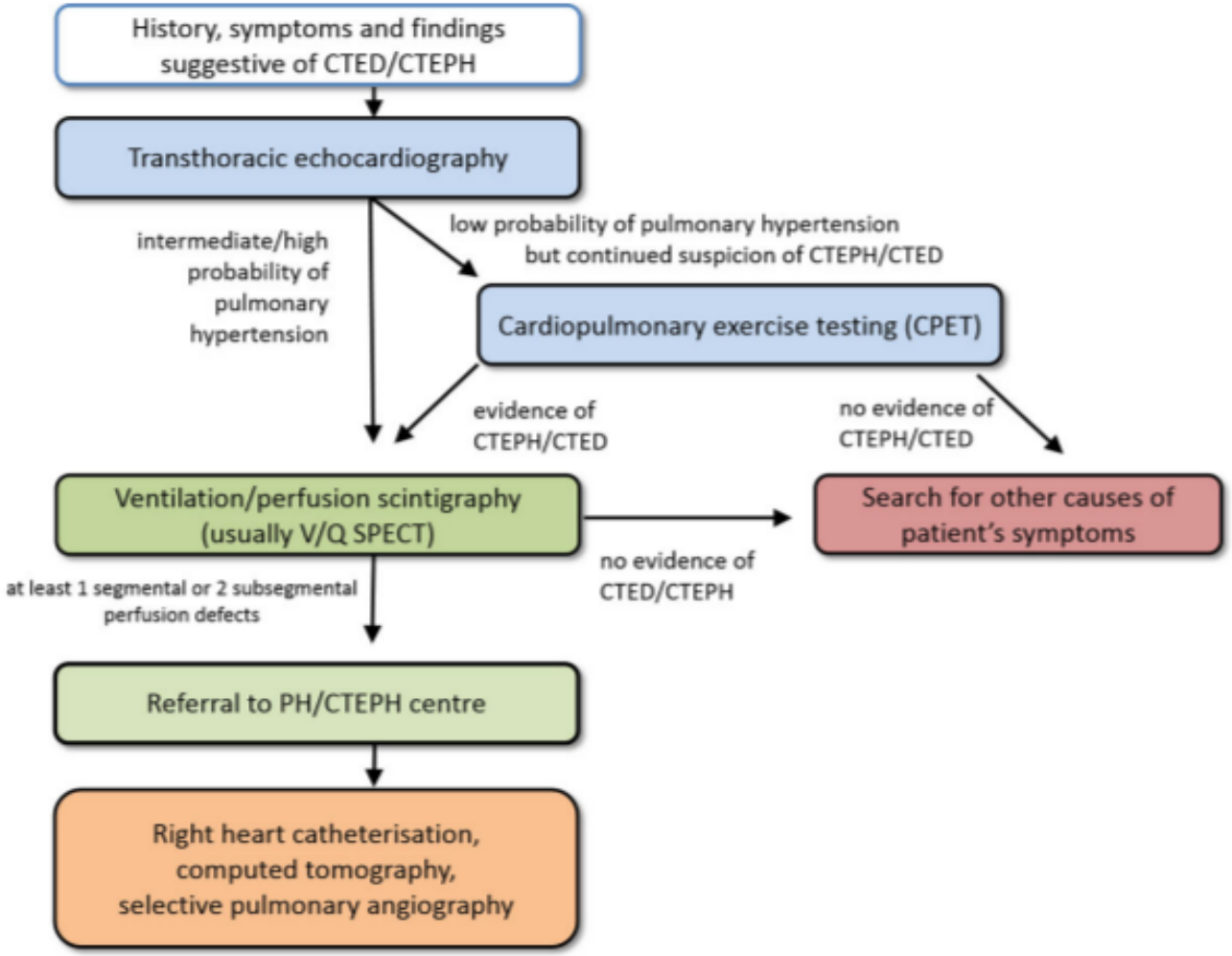
Principles of screening for disease

- Important health problem
- Accepted treatment
- Facilities for diagnosis and treatment available
- Recognizable early / latest stage
- Suitable test, acceptable to the population
- Natural history adequately understood
- Agreed policy on who to treat
- Case finding should be ongoing
- Cost-effective

Ende-Verhaar YM, et al. *Thromb Res* 2017; 151: 1-7. Wilson JMG, et al. Principles and Practice of Screening for Disease no. 34, World Health Organization Public health papers, Geneva 1968

CTEPH diagnostic approach: 2016 consensus conference



Isabelle O, et al. *Swiss Med Wkly* 2018; 148: w14702.

Our approach (in the absence of clear guideline recommendations)

Investigate patients (initially with echocardiogram +/- exercise test) at 3-6 months if:

- Risk factors for CTEPH (young age, recurrent PE, large thrombus burden, elevated PA pressure at time of diagnosis [especially if >50 mm Hg)
- Persistent symptoms of dyspnea

Routine screening not recommended at present

Ende-Verhaar YM, et al. *Thromb Res* 2017; 151: 1-7. Isabelle O, et al. *Swiss Med Wkly* 2018; 148: w14702.
Jaff MR, et al. *Circulation* 2011;123(16):1788–830.

Question 2: select the one that is incorrect

Regarding CTEPH:

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Key questions

- Does oral anticoagulation need to be interrupted?
- **If yes, is “bridging” required?**
- When should oral anticoagulation be re-started?

Question 3: select the one that is incorrect

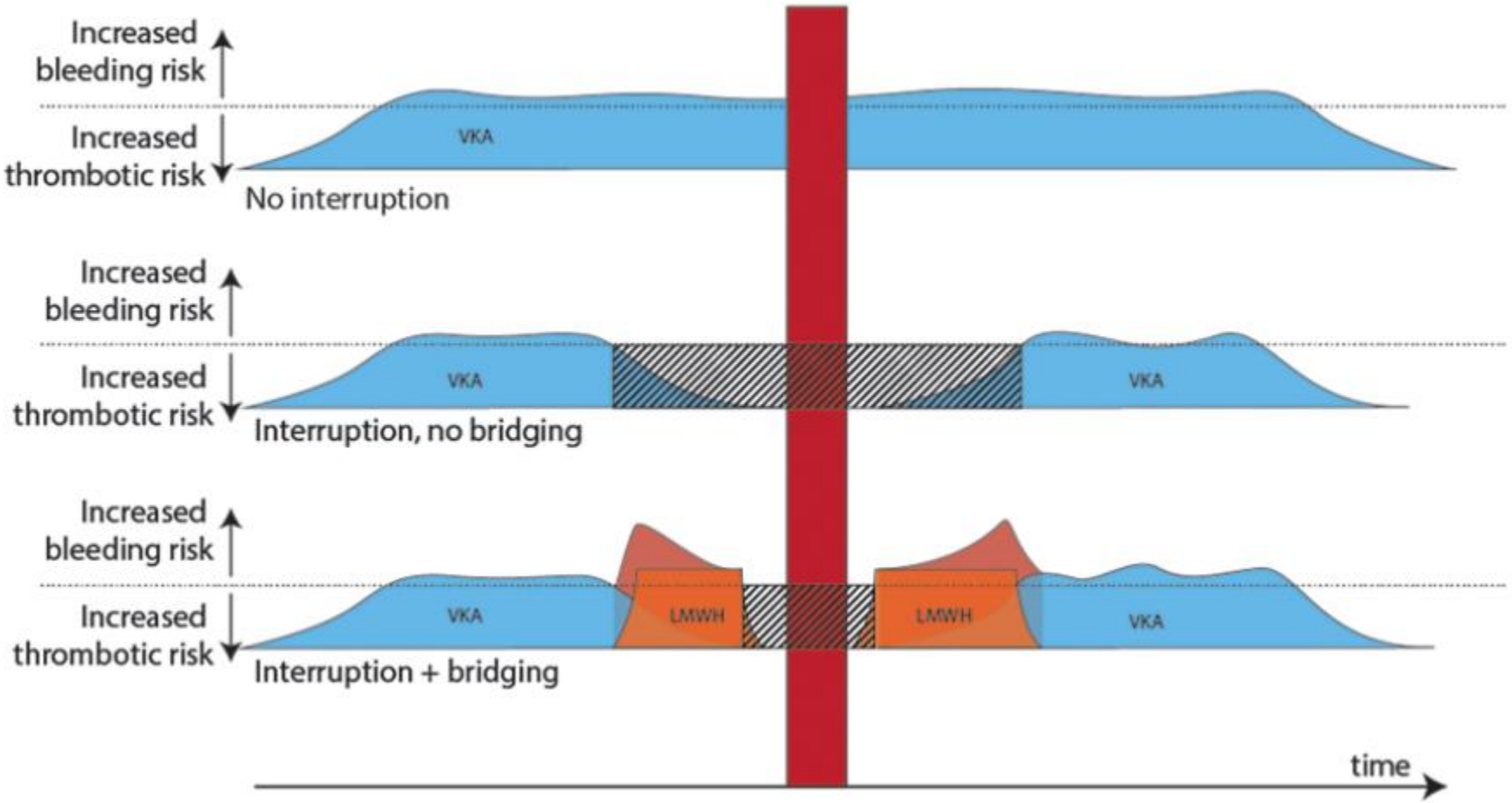
Regarding bridging in VTE patients requiring interruption of anticoagulation for elective surgery:

1. The goal is to minimize the risk of bleeding ad thromboembolism
2. Warfarin-treated patients at low or moderate risk of recurrent VTE do not require bridging
3. Warfarin-treated patients at high risk of recurrent VTE benefit from bridging
4. There is no evidence that monitoring of DOAC drug levels improves outcomes

Rationale for bridging

- Minimize thromboembolic complications by reducing the time off treatment
- Minimize risk of bleeding at the time of the procedure

Interruption of warfarin



Vanassche T, et al. *Eur Heart J* 2014; 28: 1831-3.

Bridging warfarin treated patients: the evidence

Systematic review: 34 studies (1 randomized); 12,278 patients
Poor quality, substantial heterogeneity

	TE	Major Bleeding	Any Bleeding	Mortality
Bridging (n=7,118)	0.9%	4.2%	13.1%	0.3%
No Bridging (n=5,160)	0.6%	0.9%	3.4%	0.1%

Siegal D, et al. *Circulation* 2012; 126: 1630-9.

Warfarin interruption: systematic review

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Low quality, substantial heterogeneity

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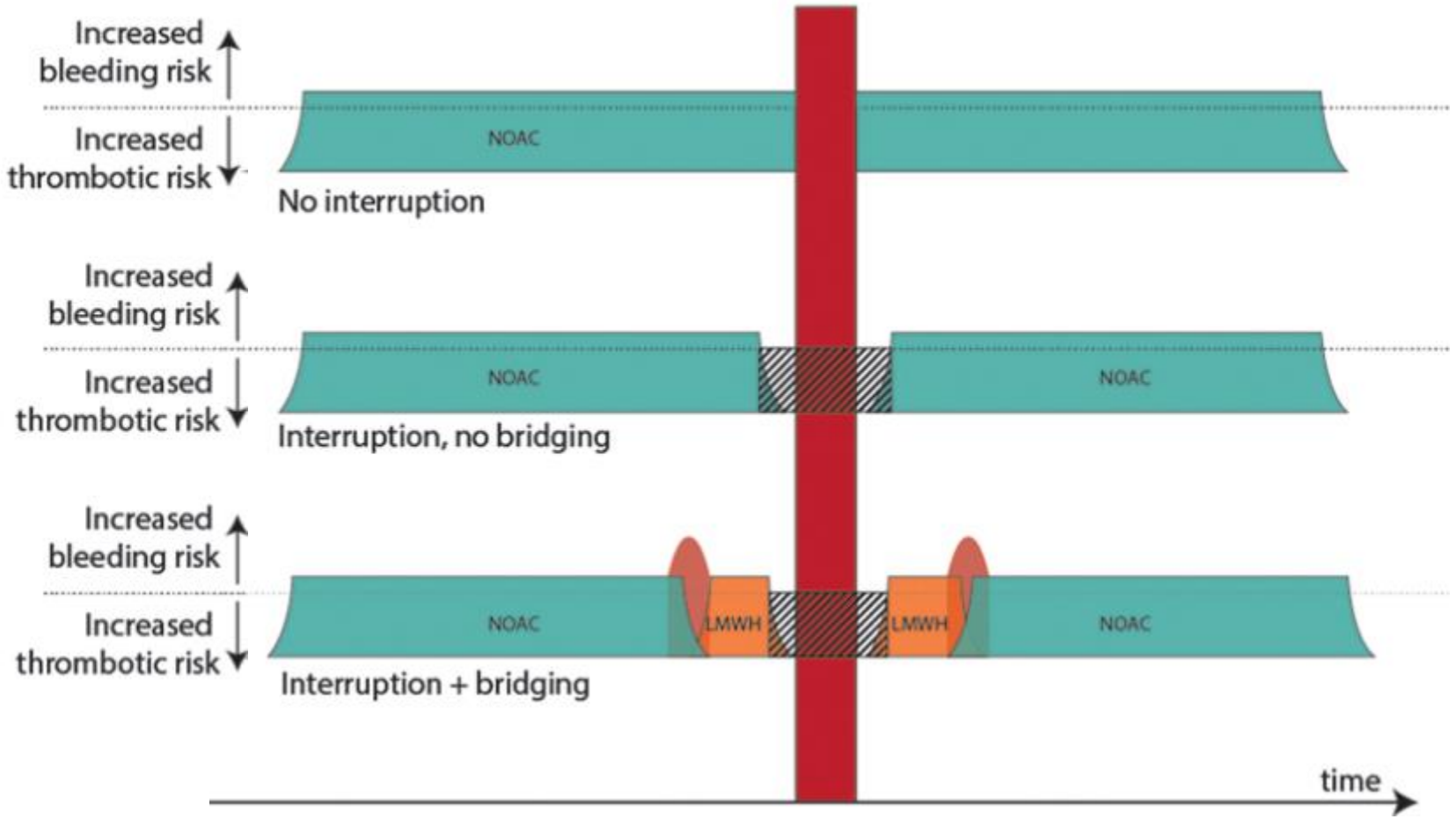
Bridge trial: warfarin in atrial fibrillation

1,884 patients
Mean CHADS2 score 2.3 vs 2.4 (CHADS2 score 5/6: n=58)

	Bridging (n=918)	**No Bridging (n=895)**	**P-value superiority**
Arterial thromboembolism	0.4%	0.3%	0.73
Major bleeding	1.3%	3.2%	0.005
Minor bleeding	12.0%	20.9%	<0.001
Mortality	0.5%	0.4%	0.88

Douketis J, et al. *New Engl J Med* 2015; 373: 823-33.

Interruption of DOACs



Vanassche T, et al. *Eur Heart J* 2014; 28: 1831-3.

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DOAC interruption: systematic review

8 studies; 14,446 patients
Moderate quality

	Event rates At 30 days
Thromboembolism	0.4%
Major bleeding	1.1%
Minor bleeding	3.1%
Mortality	0.7%

No evidence that perioperative measurement of drug levels improves outcome

Shaw JR, et al. *Res Pract Thromb Haemost* 2018; 2: 82-90.

Recommendations

- Do not bridge patients at low or moderate risk of recurrent venous thromboembolism who interrupt warfarin therapy
- Do not routinely perform laboratory testing in patients interrupting DOAC therapy for procedures
- Less certainty about the evidence for bridging warfarin in patients at high risk for recurrent venous thromboembolism (or high risk of thromboembolism in patients taking warfarin for other indications)

Witt DM, et al. *Blood* 2018; 2: 3257-91.

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CTEPH versus chronic thromboembolic disease

Diagnostic criteria	CTEPH	CTED
Symptoms	Exercise dyspnoea	Exercise dyspnoea
PH	*Present at rest*	*Absent at rest*
RHC at exercise		*mPAP/CO slope >3 mmHg·L^{-1}·min^{-1}*
***V/Q* scan**	Any mismatched perfusion defect	Any mismatched perfusion defect
Angiography (CTPA or DSA)	Typical findings of CTEPH	Typical findings of CTEPH
CPET		*Excluding ventilatory limitation, deconditioning*
TTE		*Excluding left ventricular myocardial or valvular disease*
Anticoagulation	At least 3 months	At least 3 months

RHC: right heart catheterisation; *V/Q*: ventilation/perfusion; CTPA: computed tomography pulmonary angiogram; DSA: digital subtraction angiogram; CPET: cardiopulmonary exercise test; TTE: transthoracic echocardiogram; mPAP: mean pulmonary arterial pressure; CO: cardiac output.

Kim NH, et al. *Eur Respir J* 2019; 53: 1801915