La scelta del farmaco e la durata del trattamento anticoagulante nel TEV: gli AVK

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Patients excluded by DOAC VTE trials

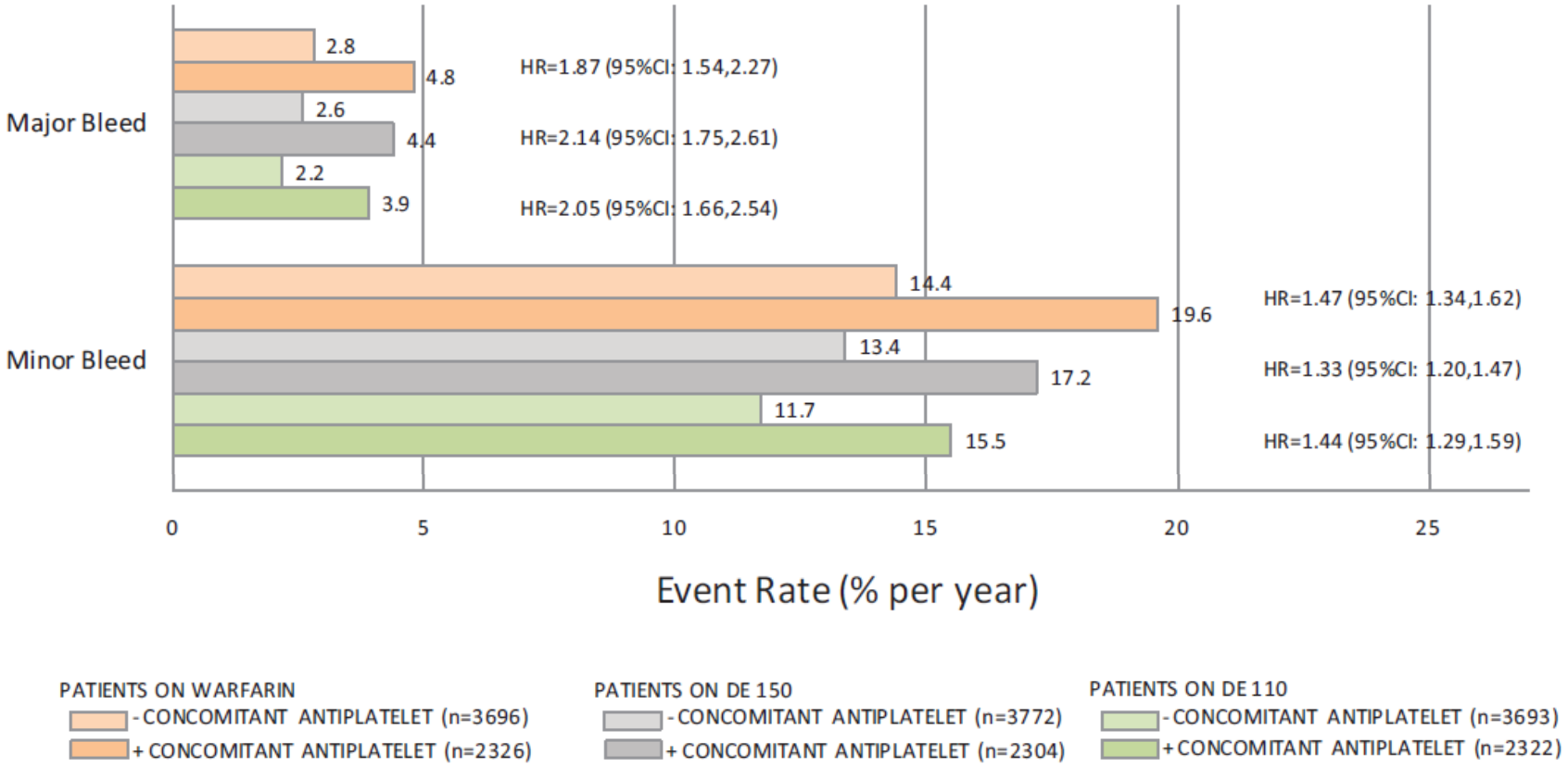
	Rivaroxaban	Dabigatran	Apixaban	Edoxaban
Renal insufficiency	CrCl < 30ml/min	CrCl < 30ml/min	CrCl < 25 ml/min	CrCl < 30ml/min
Hepatic disease	ALT>3xUL, cirrhosis	ALT>2xUL	ALT or AST > 2xUL	ALT>2xUL HBV or HCV +ve
Hypertension (despite anti-hypertensives)	>180 mmHg >110 mmHg	No	>180 mmHg >110 mmHg	> 170 mmHg or > 100 mmHg
Pregnancy/Breastf.	Excluded	Excluded	Excluded	Excluded
Concomitant medication	Strong CYP3A4 inhibitors/inducer ASA>100 mg/day Dual antiplatelet	ASA>100 mg/day	Strong CYP3A4 inhibitors/inducer Dual antiplatelet ASA>165 mg/day	Strong CYP3A4 inhibitors/inducer ASA>100 mg/day Dual antiplatelet
Site	Proximal only	Proximal only	Proximal only	Proximal only
Other	«High bleeding risk»	«High bleeding risk»	«High bleeding risk»	

The Einstein Investigators New England Journal of Medicine, 2010; Agnelli et al. New England Journal of Medicine, 2013; Schulman et al. N Engl J Med, 2009; Hokusai VTE Investigators et al. N Engl J Med, 2013.

VKA for treatment of VTE: who

- Patients < 18 years old
- Patients with SVT or distal VTE
- Pregnant/breastfeeding women
- Renal insufficiency (eGFR < 30 ml/min)
- Requiring concomitant antiplatelet treatment (high dose ASA or dual antiplatelet regimen)

Concurrent ASA use increases bleeding risk



Dans et al. Circulation, 2013

DOACs vs. VKA for VTE treatment

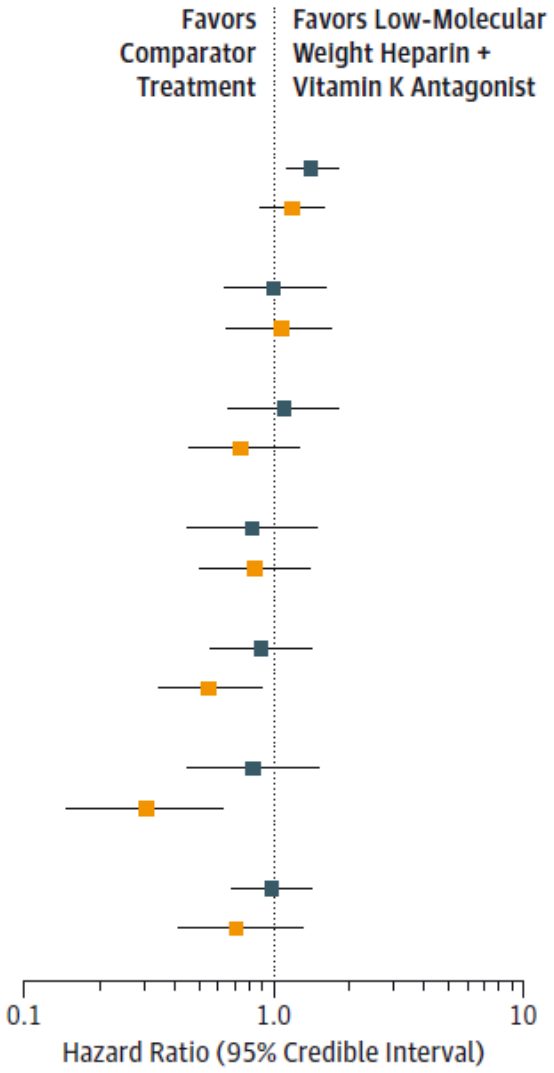
Study name	RE-COVER, RE-COVER II (53, 54)	AMPLIFY (55)	Hokusai-VTE (56)	EINSTEIN DVT, EINSTEIN PE (57, 58)
Study drug	Heparin/dabigatran	Apixaban	Heparin/edoxaban	Rivaroxaban
Comparator	Heparin/warfarin	Enoxaparin/warfarin	Heparin/warfarin	Enoxaparin/VKA
Study design	Double-blind	Double-blind	Double-blind	Open-label, assessor-blind
Number of patients randomised	5,132	5,400	8,292	8,282
Pre-randomisation heparin	–	≤ 36 hours for 77 %	–	≤ 48 hours for 83 %
Heparin lead-in	At least 5 days	None	At least 5 days	None
Study drug treatment regimen	150 mg bid	10 mg bid for 7 days followed by 5 mg bid	60 mg od or 30 mg od[a]	15 mg bid for 21 days followed by 20 mg od
Treatment duration (months)	6	6	3–12	3, 6 or 12
Primary efficacy outcome	Recurrent symptomatic VTE and related deaths	Recurrent symptomatic VTE or VTE-related death	Recurrent symptomatic VTE: composite of DVT or non-fatal or fatal PE	Recurrent symptomatic VTE: composite of fatal or non-fatal PE or DVT
Primary safety outcome[b]	Not defined; safety endpoints included bleeding events, acute coronary syndrome and other adverse events	Major bleeding alone	Clinically relevant bleeding: composite of major and non-major clinically relevant bleeding	Clinically relevant bleeding: composite of major and non-major clinically relevant bleeding
Results for primary efficacy outcome with study drug	Non-inferior	Non-inferior	Non-inferior	Non-inferior
Results for primary safety outcome with study drug	Similar incidence of major bleeding	Significant reduction in major bleeding	Significant reduction in major or clinically relevant non-major bleeding	Similar incidence of major or clinically relevant non-major bleeding

Beyer-Westendorf et al. Thromb Haemost, 2015.

VTE treatments vs. LMWH+VKA

A Recurrent venous thromboembolism and major bleeding

Comparator Treatment	Hazard Ratio (95% Credible Interval)
Unfractionated heparin + vitamin K antagonist	
Recurrent VTE	1.42 (1.15-1.80)
Major bleeding	1.19 (0.90-1.58)
Fondaparinux + vitamin K antagonist	
Recurrent VTE	1.01 (0.65-1.62)
Major bleeding	1.07 (0.65-1.70)
Low-molecular-weight heparin + dabigatran	
Recurrent VTE	1.11 (0.67-1.80)
Major bleeding	0.74 (0.46-1.26)
Low-molecular-weight heparin + edoxaban	
Recurrent VTE	0.83 (0.46-1.49)
Major bleeding	0.84 (0.51-1.39)
Rivaroxaban	
Recurrent VTE	0.90 (0.57-1.41)
Major bleeding	0.55 (0.35-0.89)
Apixaban	
Recurrent VTE	0.84 (0.46-1.51)
Major bleeding	0.31 (0.15-0.62)
Low-molecular-weight heparin alone	
Recurrent VTE	0.99 (0.70-1.42)
Major bleeding	0.71 (0.42-1.31)



Castellucci et al. JAMA, 2014

VKA for treatment of VTE: who

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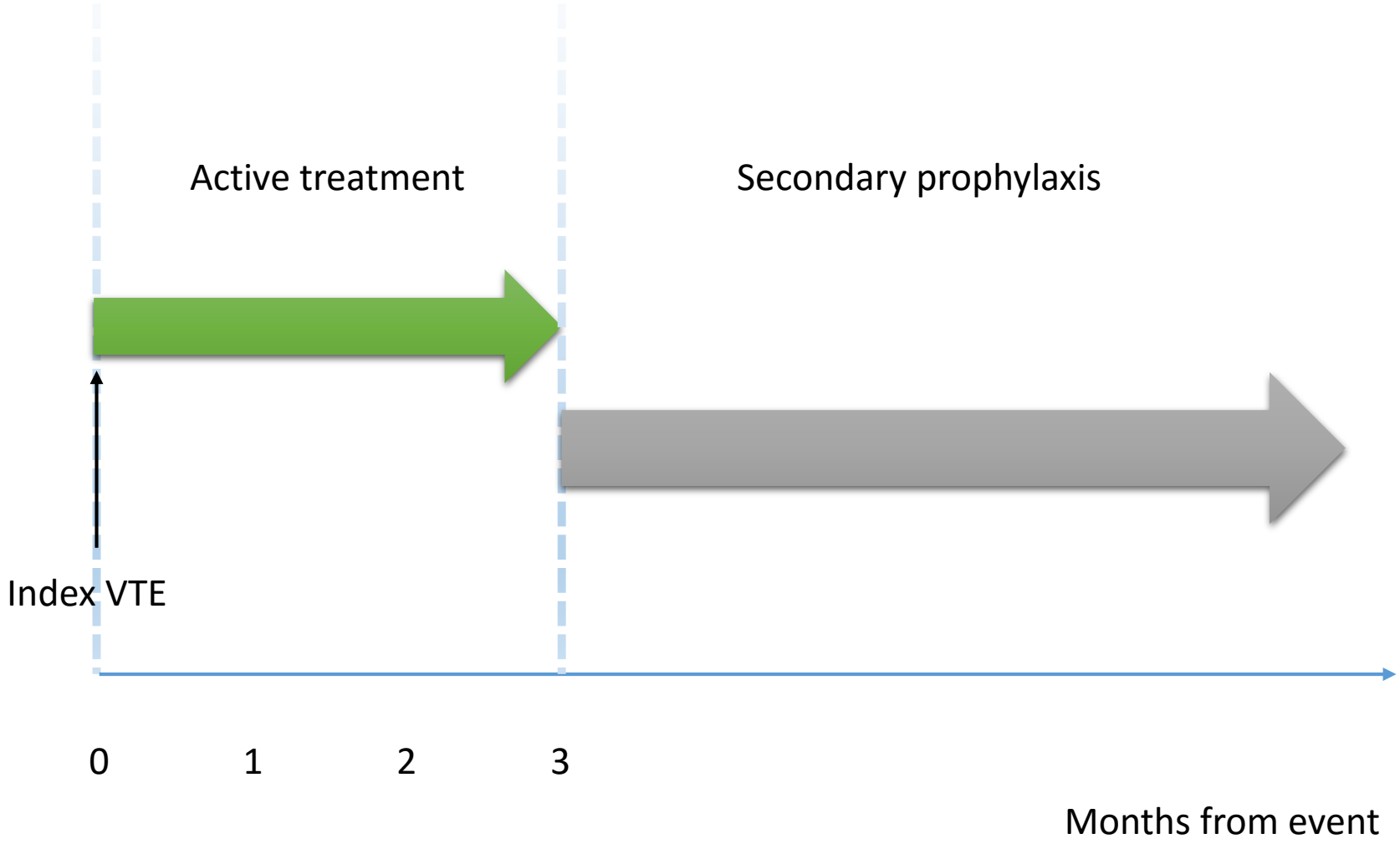
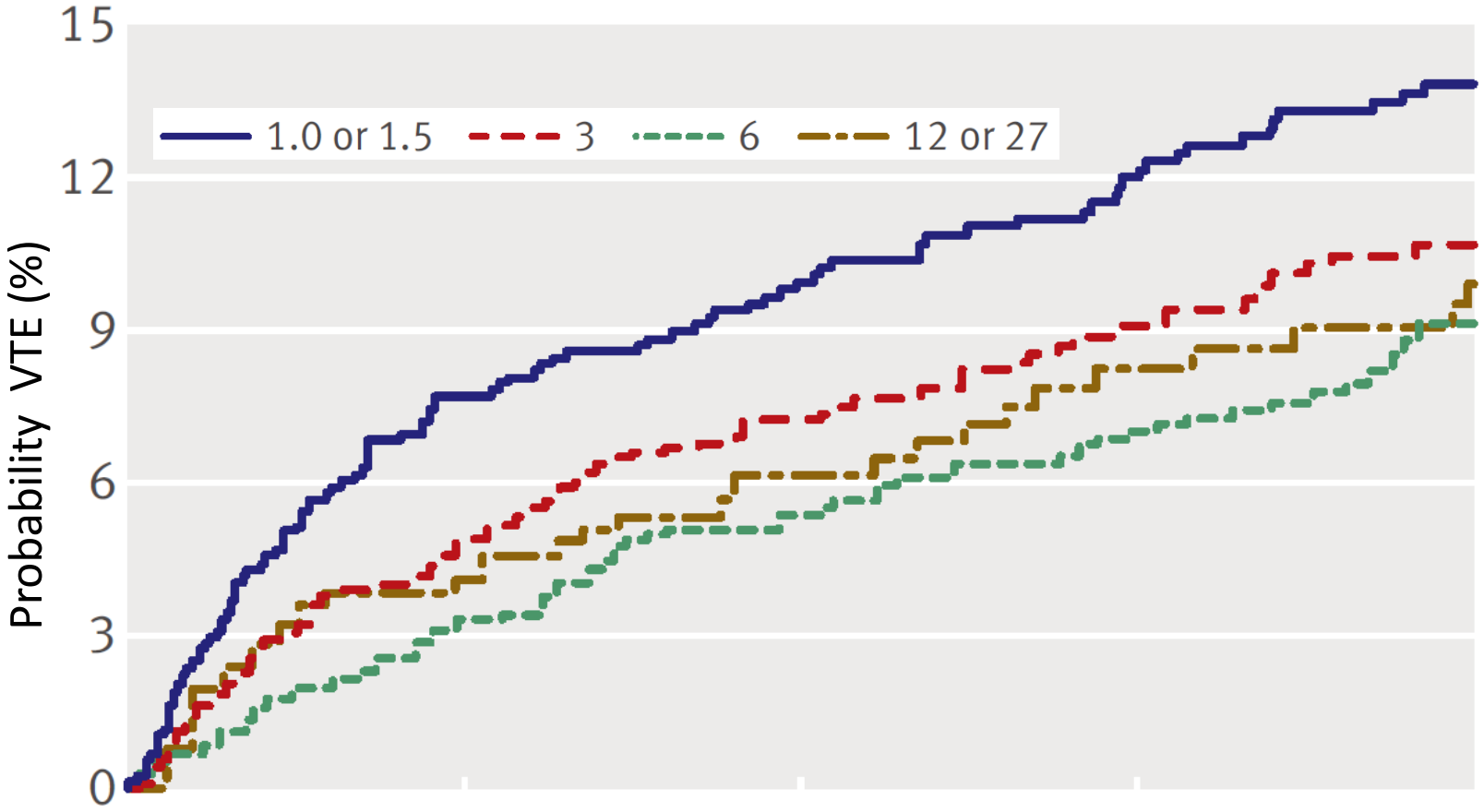
- Patients with SVT or distal VTE
- Pregnant/breastfeeding women
- Renal insufficiency (eGFR < 30 ml/min)
- Requiring concomitant antiplatelet treatment (high dose ASA or dual antiplatelet regimen)
- Patients having a good TTR on VKA do not need to be switched to NOAC

The “active-treatment” concept

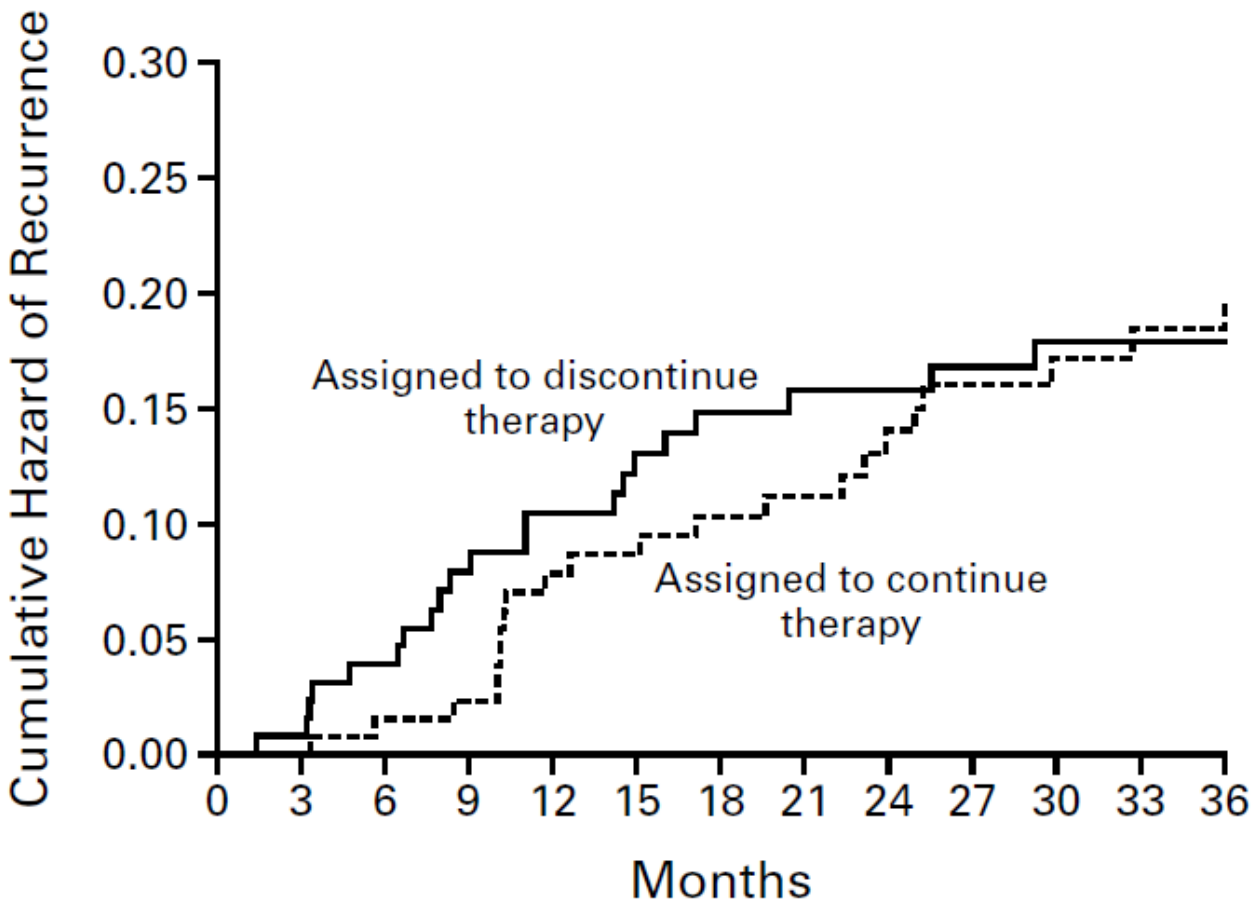


The “active-treatment” concept



Boutitie et al. BMJ, 2011.

3-months vs. 12-months, VTE: no benefit



Agnelli et al. N Engl J Med, 2001.

Treatment or prophylaxis?

- 3 months better than 6 weeks
- 12-18 months not better than 6 months
- *Treatment* is in between 3-6 months

- After 3-6 months: VTE *prophylaxis*
- As per every prophylaxis, benefits should outweigh risks

Benefits of secondary prophylaxis in patients with a previous VTE

- The cumulative risk of recurrence never reaches a plateau
- The recurrence hazard decreases with time
- Annual absolute risk is estimated around 8-10%, but modulated by risk-factors
- Annual absolute risk reduced to 1-3% by anticoagulation
- Case-fatality of recurrent VTE: 3.6%

Carrier et al. Ann Intern Med, 2010.
Linkins et al. Ann Intern Med, 2003.

Risks of secondary prophylaxis in patients with a previous VTE

- Annual absolute bleeding risk is estimated 0.5-4%
- Case-fatality of anticoagulant-bleeding: 9-18%
- Anticoagulant bleeding risk may increase with age and presence of comorbid conditions
- In RCT, the ABR may be low because of selection bias

Ost et al. JAMA, 2005.
Linkins et al. Ann Intern Med, 2003.
Lecumberri et al. Thromb Haemost, 2013.

Benefit, risk and recommendation

Effect on 5-years mortality	Recommendation	Annual Recurrence Risk %	
		Low bleeding risk (0.8%)	High bleeding risk (1.6%)
Increased	3 months only	3-8	3-10
0-1% decrease	Weak for indefinite	9-13	11-16
>1% decrease	Strong for indefinite	>13	>16

Adapted from Kearon et al. Blood, 2014.

D-Dimer in prediction models

- Vienna Prediction model:
  - D-Dimer level (quantitative)
  - Proximal/Distal DVT or PE
  - Male sex

- DASH Model
  - D-Dimer (+ve/-ve)
  - Age <50
  - Male sex
  - Use of OC

Eichinger et al. Circulation, 2010.
Tosetto et al. J Thromb Haemost, 2012.

Benefit, risk and recommendation

Effect on 5-years mortality	Recommendation	Clinical setting
Increased	3 months only	Provoked VTE Unprovoked DASH score ≤ 1
0-1% decrease	Weak for indefinite	Unprovoked DASH score ≤ 2 Unprovoked with no RVO or D-Dimer –ve
>1% decrease	Strong for indefinite	Unprovoked DASH score >2 Unprovoked life-threatening (e.g., massive PE, SVT, CVT)

Adapted from Kearon et al. Blood, 2014.

Conclusions

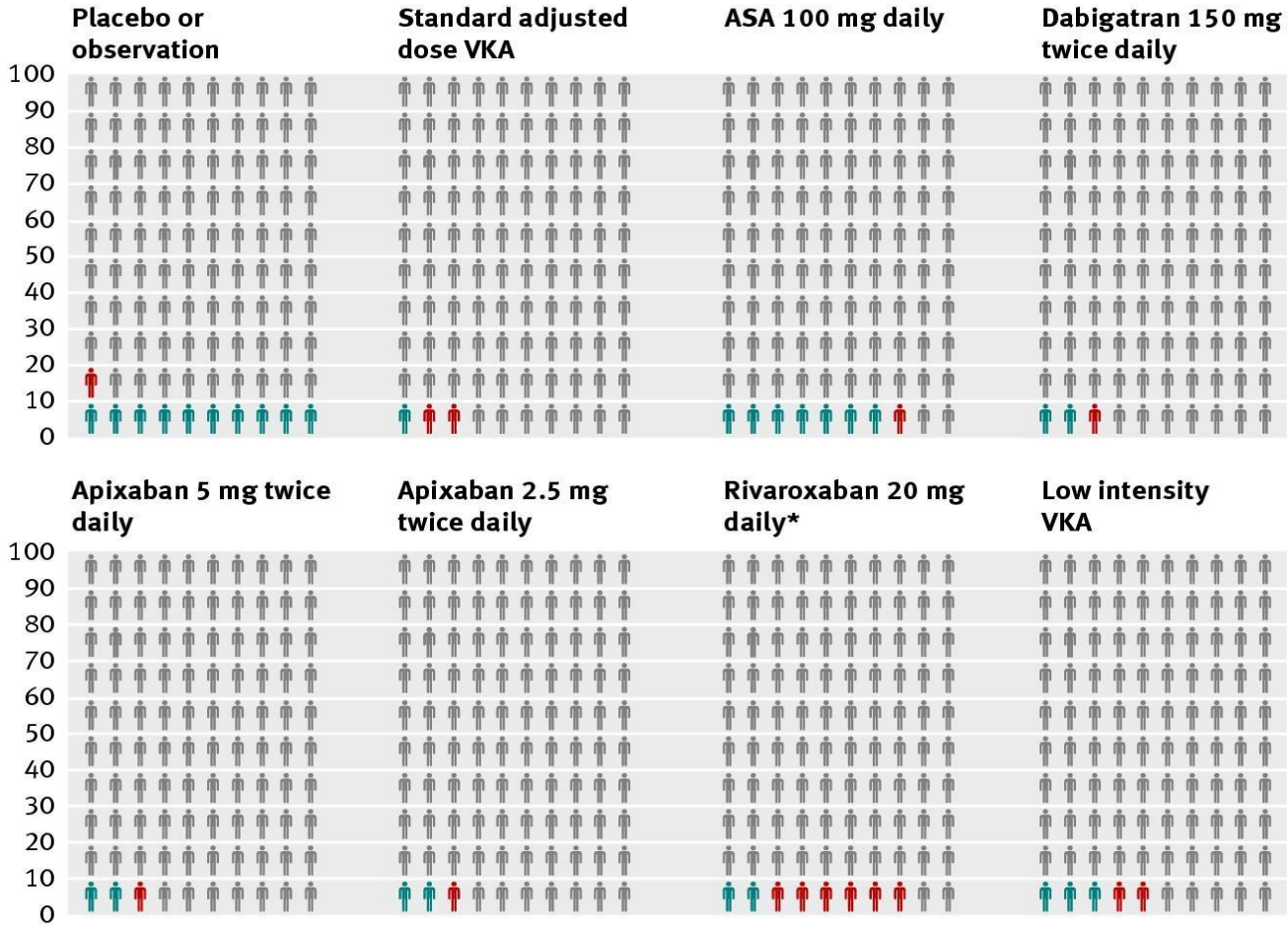
- Consider patient TTR and long-term therapy acceptance
- In patients at high risk of recurrence:
  - Long-term VKA may be acceptable if good TTR and low bleeding risk
  - “Standard-dose” DOACs for long-term therapy in patients at high bleeding risk
- “Low-dose” DOACs may change the scenario for patients at intermediate risk patients, but more real-life data needed

Absolute and relative risks vs. no treatment

	Risk of recurrent VTE OR (95% CrI)	VTE Absolute risk difference, 100 pt/year (95% CrI)	Risk of major bleeding OR (95% CrI)	Major bleeding episode Absolute risk difference, 100 pt/year (95% CrI)
Adjusted dose VKA	0.07 (0.03 to 0.15)	-8.8 (-8 to -9.9)	5.24 (1.78 to 18.25)	+1.3 (0.2 - 5)
Dabigatran 150 mg td	0.09 (0.04 to 0.21)	-8.6 (-7.3 to -9.2)	2.79 (0.79 to 11.69)	+0.6 (0.1 - 3.2)
Apixaban 5 mg td	0.18 (0.08 to 0.38)	- 7.7 (-5.6 to -8.7)	0.19 (0.01 to 1.78)	+0.26 (0.32 - 0.2)
Apixaban 2.5 mg td	0.17 (0.08 to 0.36)	- 7.8 (-5.8 to -8.8)	0.46 (0.05 to 2.82)	-0.2 (-0.3 - 0.6)
Rivaroxaban 20 mg od	0.17 (0.06 to 0.41)	- 7.8 (-5.3 to -8.9)	20.79 (1.31 to 14 230)	+5.7 (0.1 - 62.1)

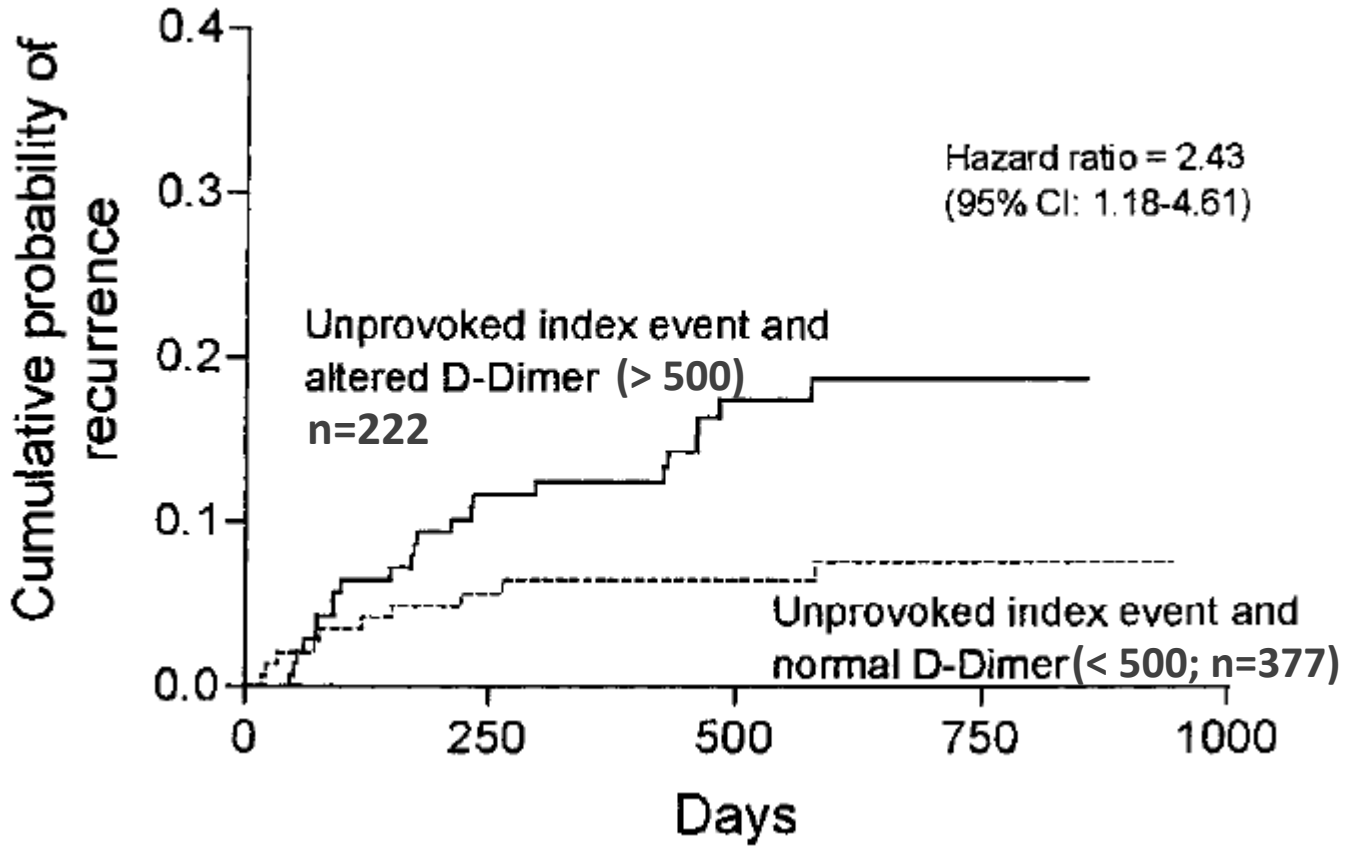
Castellucci et al. BMJ, 2013.

Absolute and relative risks vs. no treatment



Castellucci et al. BMJ, 2013.

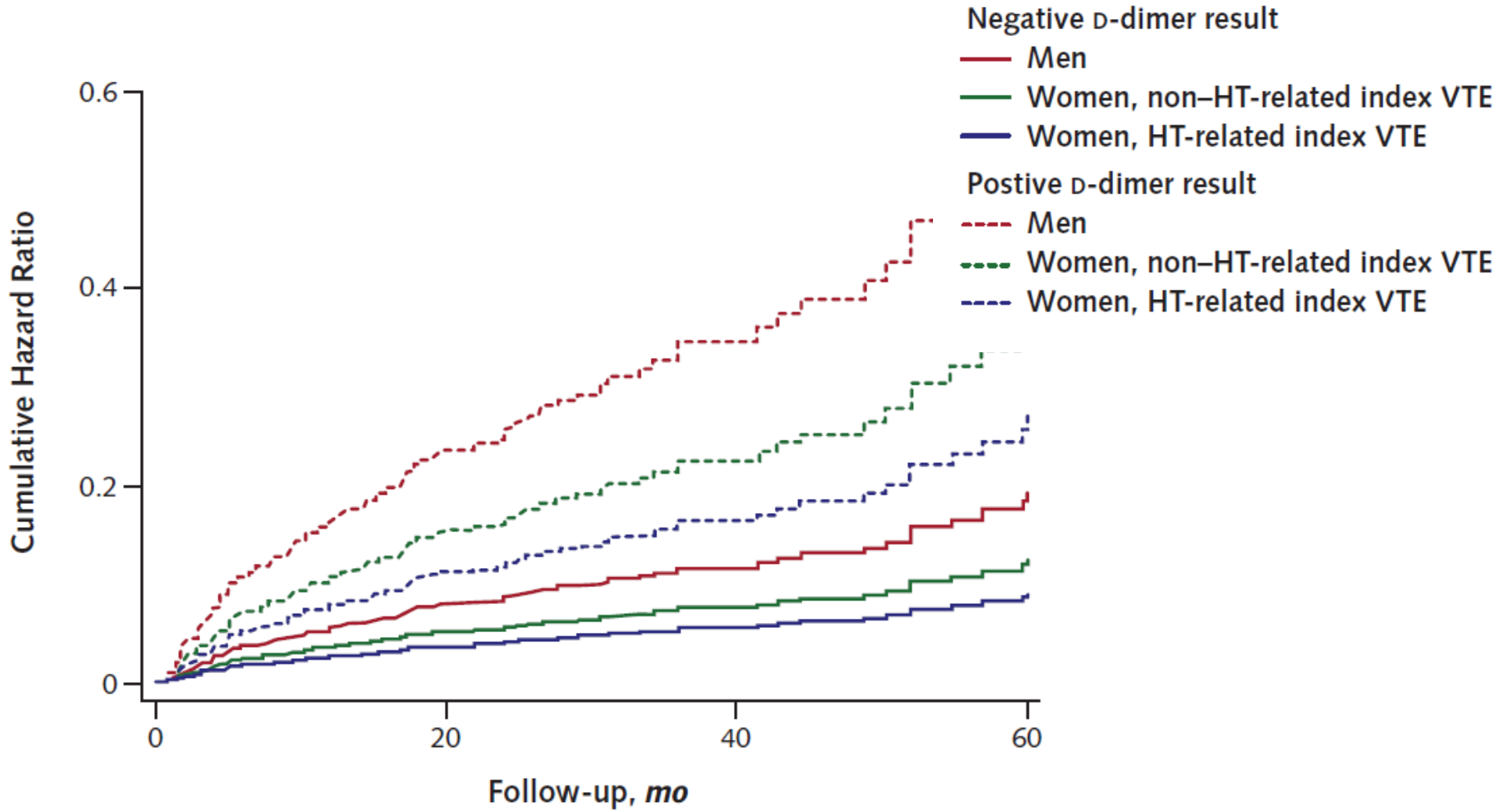
Risk of Recurrence



Palareti et al, Circulation 2003

D-Dimer and VTE recurrence

IPD meta-analysis of 6 studies



Douketis et al, Ann Int Med 2010