Prevention and treatment of pulmonary embolism

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Disclosures (last two years)

Speaker bureaux:

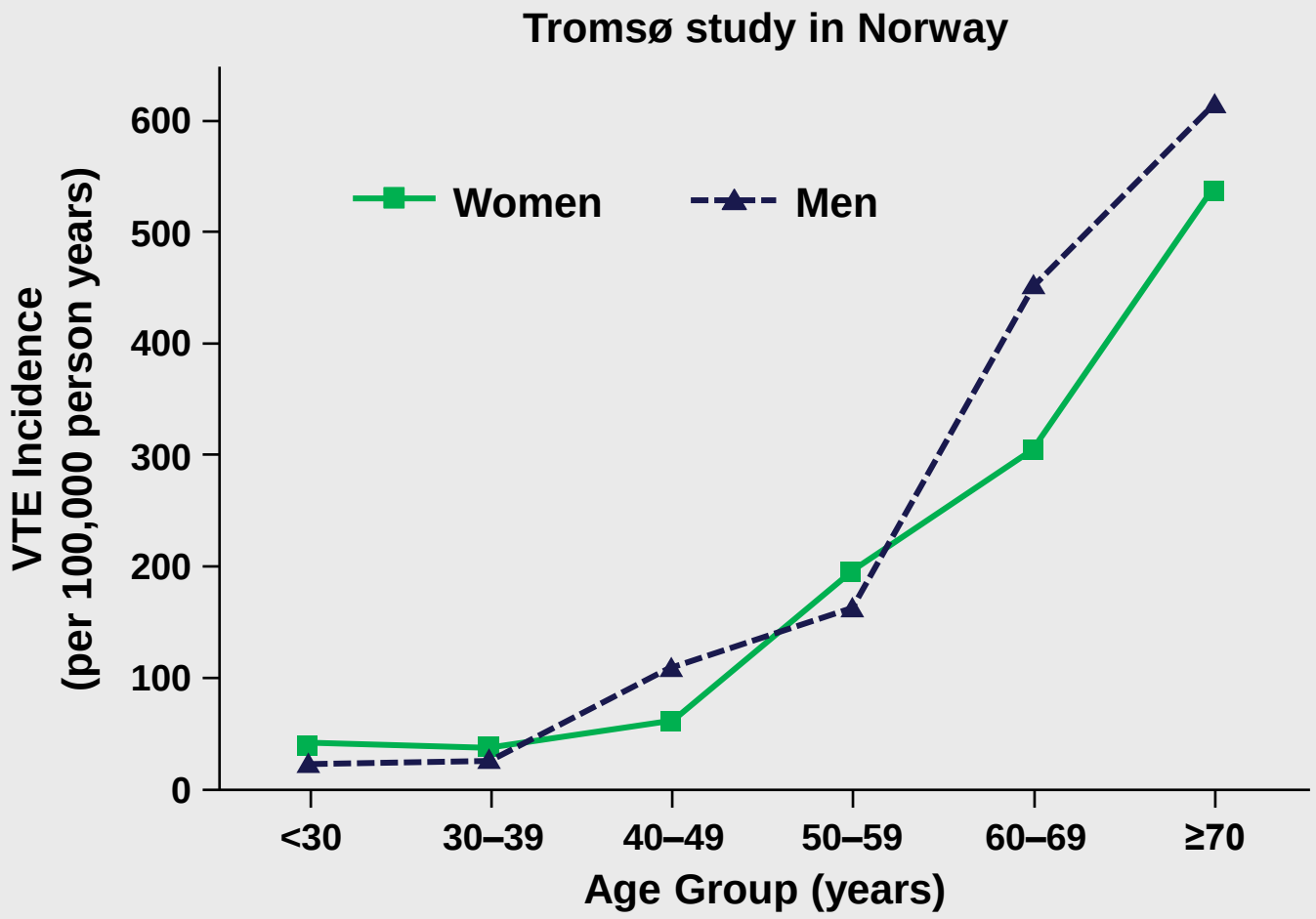
- Bristol-Myers Squibb (Caravaggio)*
- Pfizer (Caravaggio)*

Study steering committees

- Anthos (Aster – Magnolia)*
- BMS - Jansen* (project terminated)
- Daiichi Sankyo (Cope)
- sanofi (Omero)

* with potential implications with this presentation

VTE risk increases with age



Braekkan et al., J Thromb Haemost 2008

Predictors of VTE during the hospitalization in medical patients

	OR (95% CI)
Previous VTE	2.06 (1.10-3.69)
Acute infectious disease	1.74 (1.12-2.75)
Cancer	1.62 (0.93-2.75)
Age > 75 yrs	1.03 (1.00-1.06)

Alikhan et al., Arch Intern Med 2004

My talk today

Recent advances in:

- Prevention of venous thromboembolism
- Treatment of venous thromboembolism*
- Treatment of venous thromboembolism in cancer patients*

* focusing on both efficacy and safety

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Prevention of venous thromboembolism

Clinical settings

Established prophylaxis (routinely used)

Effective prophylaxis (but not commonly used)

Area of uncertainty

Clinical settings with established VTE prophylaxis

- Major orthopedic surgery (extended)
- Surgery for cancer (extended)
- Major abdominal surgery
- High risk medical patients (HF & ARD)

HF: heart failure; ARD: acute respiratory diseases

Clinical settings with effective VTE prophylaxis (but rarely used)

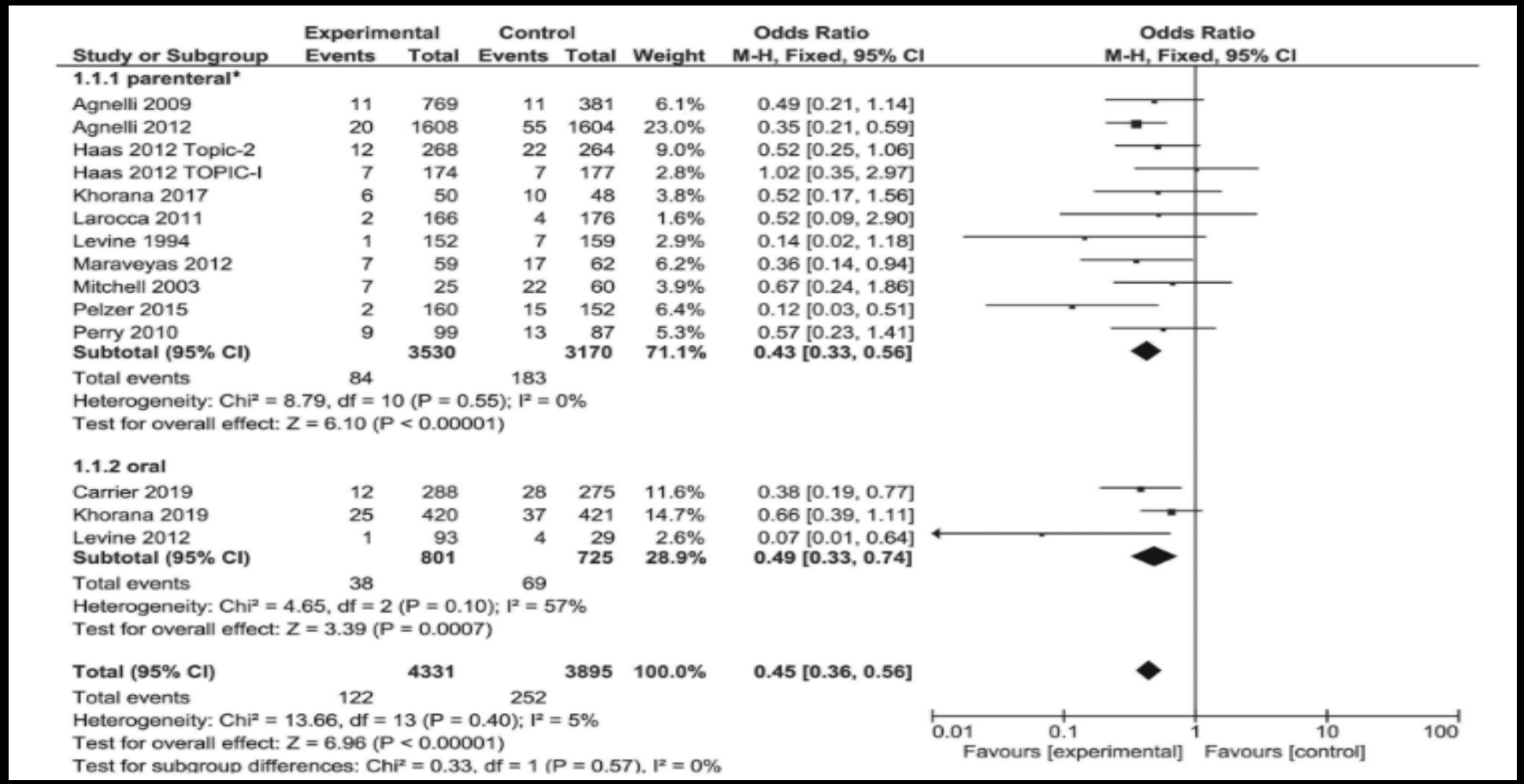
- Arthroscopic surgery
- Ischemic stroke
- Neurosurgery (cancer)
- Thoracic surgery

Area of uncertainty for VTE prophylaxis

- Clinical settings with unclear (probably low) risk
  (laparoscopic abdominal surgery)
- Clinical settings with a heterogeneous risk in the target population
  (medical in-patients - cancer chemotherapy)
- Clinical settings at high bleeding risk
  (intracranial bleeding)

Antithrombotic prophylaxis in ambulatory cancer patients

22 studies, 11,953 patients. Primary outcome: VTE



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.1 parenteral*						
Agnelli 2009	11	769	11	381	6.1%	0.49 [0.21, 1.14]
Agnelli 2012	20	1608	55	1604	23.0%	0.35 [0.21, 0.59]
Haas 2012 Topic-2	12	268	22	264	9.0%	0.52 [0.25, 1.06]
Haas 2012 TOPIC-I	7	174	7	177	2.8%	1.02 [0.35, 2.97]
Khorana 2017	6	50	10	48	3.8%	0.52 [0.17, 1.56]
Larocca 2011	2	166	4	176	1.6%	0.52 [0.09, 2.90]
Levine 1994	1	152	7	159	2.9%	0.14 [0.02, 1.18]
Maraveyas 2012	7	59	17	62	6.2%	0.36 [0.14, 0.94]
Mitchell 2003	7	25	22	60	3.9%	0.67 [0.24, 1.86]
Pelzer 2015	2	160	15	152	6.4%	0.12 [0.03, 0.51]
Perry 2010	9	99	13	87	5.3%	0.57 [0.23, 1.41]
Subtotal (95% CI)		**3530**		**3170**	**71.1%**	**0.43 [0.33, 0.56]**
Total events	84		183			
Heterogeneity: Chi² = 8.79, df = 10 (P = 0.55); I² = 0%						
Test for overall effect: Z = 6.10 (P < 0.00001)						
1.1.2 oral						
Carrier 2019	12	288	28	275	11.6%	0.38 [0.19, 0.77]
Khorana 2019	25	420	37	421	14.7%	0.66 [0.39, 1.11]
Levine 2012	1	93	4	29	2.6%	0.07 [0.01, 0.64]
Subtotal (95% CI)		**801**		**725**	**28.9%**	**0.49 [0.33, 0.74]**
Total events	38		69			
Heterogeneity: Chi² = 4.65, df = 2 (P = 0.10); I² = 57%						
Test for overall effect: Z = 3.39 (P = 0.0007)						
Total (95% CI)		**4331**		**3895**	**100.0%**	**0.45 [0.36, 0.56]**
Total events	122		252			
Heterogeneity: Chi² = 13.66, df = 13 (P = 0.40); I² = 5%						
Test for overall effect: Z = 6.96 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.33, df = 1 (P = 0.57), I² = 0%						

VTE
Treatment arm =2.4%
Control arm = 5.8%
ARR = 3.4%
NNT = 29

Major bleeding
OR =1.30
95% CI 0.98-1.73

Becattini et al., Haematologica 2020

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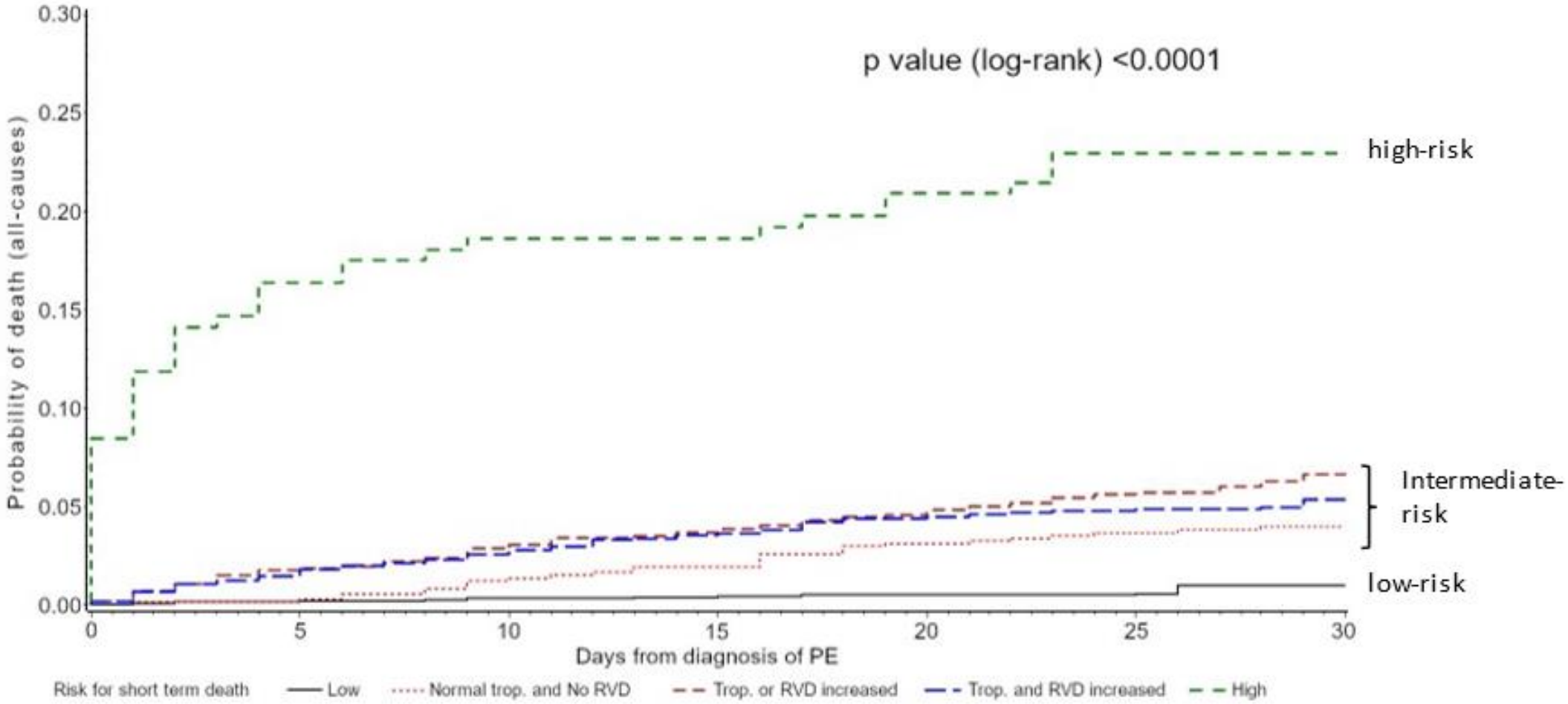
Acute PE: risk stratification according to ESC

Early mortality risk		Indicators of risk			
		Haemodynamic instability	Clinical parameters of PE severity/ comorbidity: PESI III–V or sPESI ≥1	RV dysfunction on TTE or CTPA	Elevated cardiac troponin levels
High		**+**	**(+)**	**+**	**(+)**
Interme-diate	**Intermediate–high**	**-**	**+**	**+**	**+**
	Intermediate–low	**-**	**+**	One (or none) positive	
Low		**-**	**-**	**-**	Assessment optional; if assessed, negative

Konstantinides et al., Eur Heart J 2019

Contemporary clinical course of PE: the COPE study



Becattini et al., Thromb Haemostas 2023

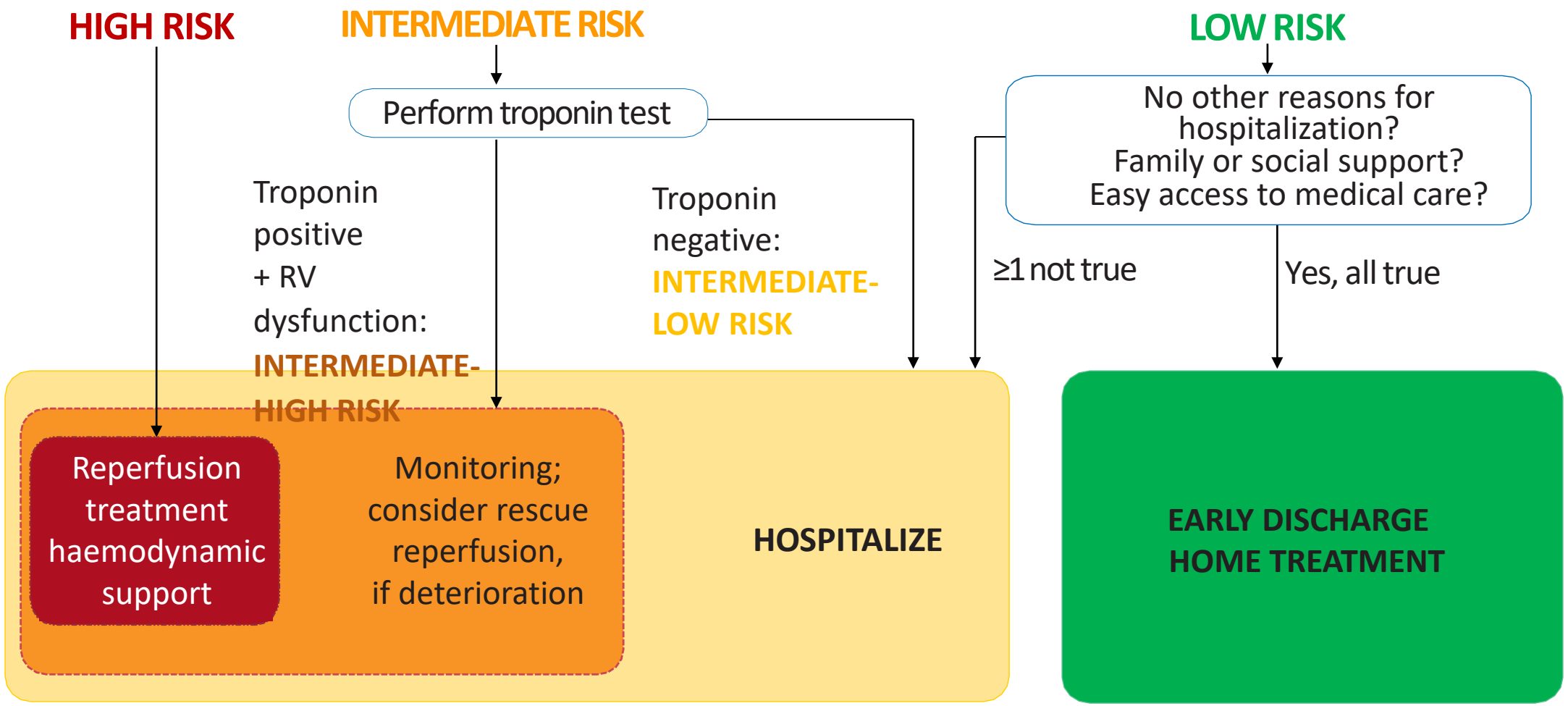
Contemporary clinical course of PE: the COPE study

		In-hospital death			30-day death		
		N (%)	HR (95% CI)	P	N (%)	HR (95% CI)	P
High risk, n=177		20.3	28.10 (13.0-60.7)	<.0001	22.6	51.66 (25.1-106.4)	<.0001
Intermediate	high risk, n=1210	4.3	6.66 (3.2-14.0)	<.0001	5.4	10.41 (5.2-20.9)	<.0001
	low risk, n=1117	4.7	7.35 (3.5-15.5)	<.0001	7.3	14.11 (7.1-28.1)	<.0001
	very low risk*, n=740	1.9	3.13 (1.3-7.5)	0.0102	4.2	8.05 (3.8-16.9)	<.0001
Low risk (sPESI= zero), n=1702		0.5	1	--	0.5	1	--

*sPESI>0, no RVD at echo, no increase in troponin

Becattini et al., 2022 submitted

Figure 5 Risk-adjusted management strategy for acute PE (2)



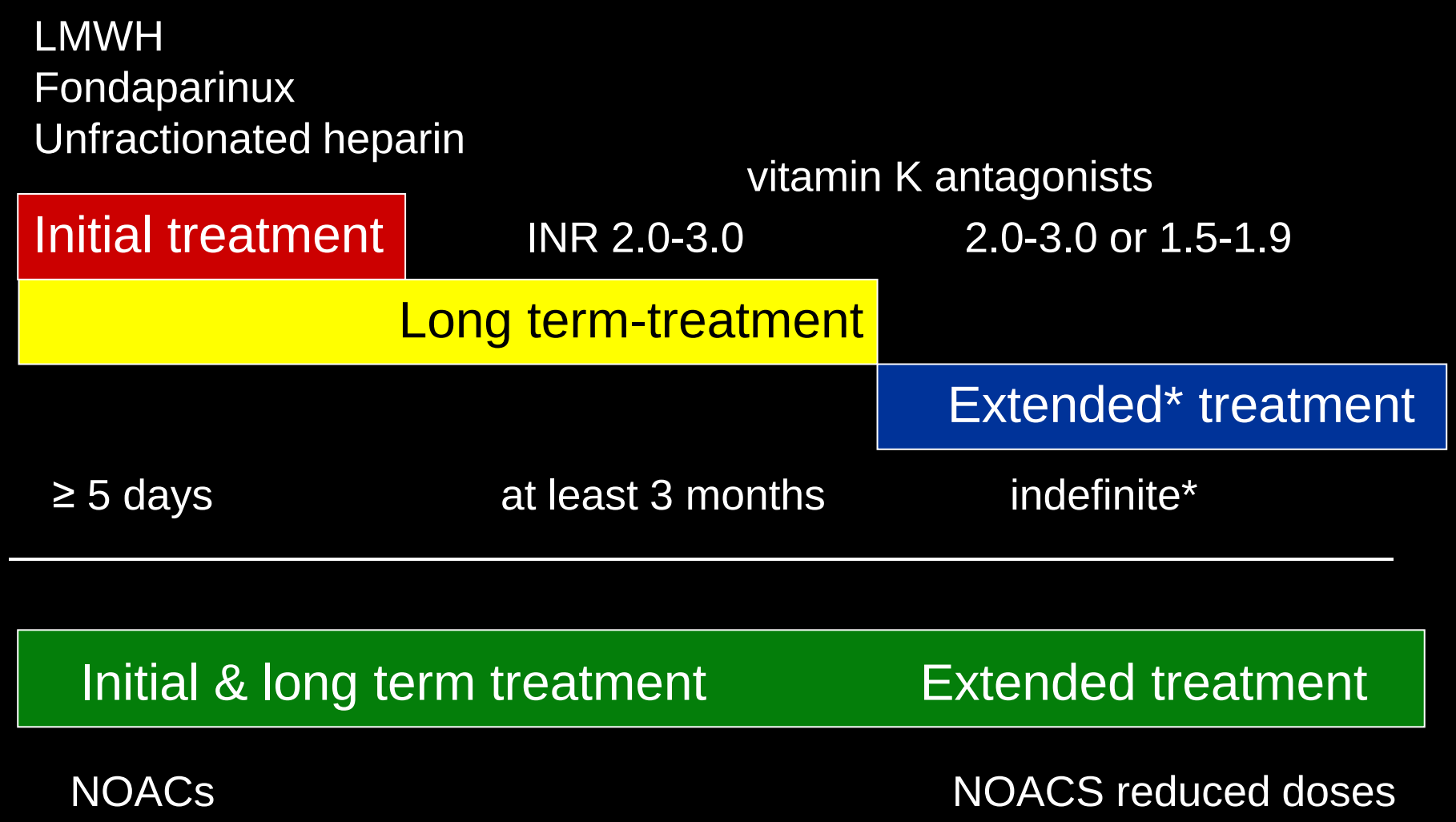
CTPA = computed tomography pulmonary angiography; PESI = Pulmonary Embolism Severity Index; RV = right ventricular; TTE = transthoracic echocardiography.

Thrombolysis for PE: the counterbalance

Outcome of Interest (No. of Studies Reporting)	No. of Events/No. of Patients, Absolute Event Rate (%)		No. Needed to Treat or Harm	*P* Value
	Thrombolytic Group	Anticoagulant Group		
All-cause mortality (16)	23/1061 (2.17)	41/1054 (3.89)	NNT = 59	.01
Major bleeding (16)[a]	98/1061 (9.24)	36/1054 (3.42)	NNH = 18	<.001
ICH (15)	15/1024 (1.46)	2/1019 (0.19)	NNH = 78	.002
Recurrent PE (15)	12/1024 (1.17)	31/1019 (3.04)	NNT = 54	.003
Age >65 y				
All-cause mortality (5)	14/673 (2.08)	24/658 (3.65)	NNT = 64	.07
Major bleeding (5)[a]	87/673 (12.93)	27/658 (4.10)	NNH = 11	<.001
Age ≤65 y				
All-cause mortality (11)	9/388 (2.32)	17/396 (4.29)	NNT = 51	.09
Major bleeding (11)[a]	11/388 (2.84)	9/396 (2.27)	NNH = 176	.89
Intermediate-risk PE				
All-cause mortality (8)	12/866 (1.39)	26/889 (2.92)	NNT = 65	.03
Major bleeding (8)[a]	67/866 (7.74)	20/889 (2.25)	NNH = 18	<.001

Chatterije et al, *JAMA 2014*

Pre-NOACs & current treatment of pulmonary embolism



* With re-assessment of the individual risk-benefit at periodic intervals

NOAC in patients with VTE: 6 studies/24,304 patients

	NOAC	LMWH–VKAs	RR (95% CI)
VTE recurrences	241/12151 2.0%	273/12153 2.6%	0.88 (0.74-1.04)
CRNMB	806/12179 6.6%%	1024/12193 11.3%	0.79 (0.72-0.86)
Major bleeding	131/12197 1.1%	211/12193 1.7%	0.62 (0.50-0.77)

CRNMB: Clinically relevant non-major bleeding

van der Hulle et al., J Thromb Haemost 2014

NOAC in patients with PE: 5 studies/11.539 patients

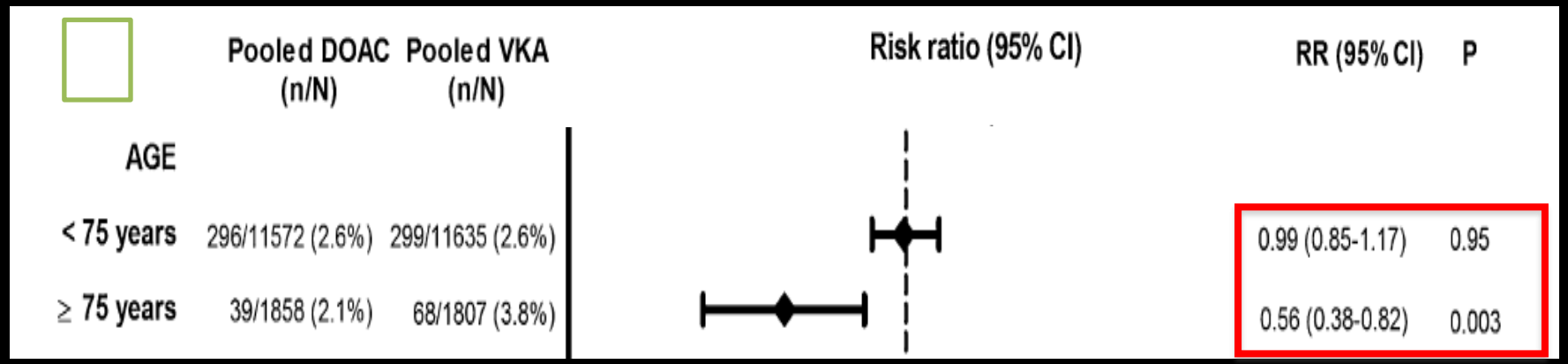
	NOAC	LMWH–VKAs	OR (95% CI)
VTE recurrences	136/5764 2.4%	153/5775 2.6%	0.89 (0.70-1.12)*
CRNMB	415/4062 10.2%	461/4064 11.3%	0.89 (0.77-1.03)
Major bleeding	30/3340 0.9%	77/3307 2.3%	0.30 (0.10-0.95)

CRNMB: Clinically relevant non-major bleeding

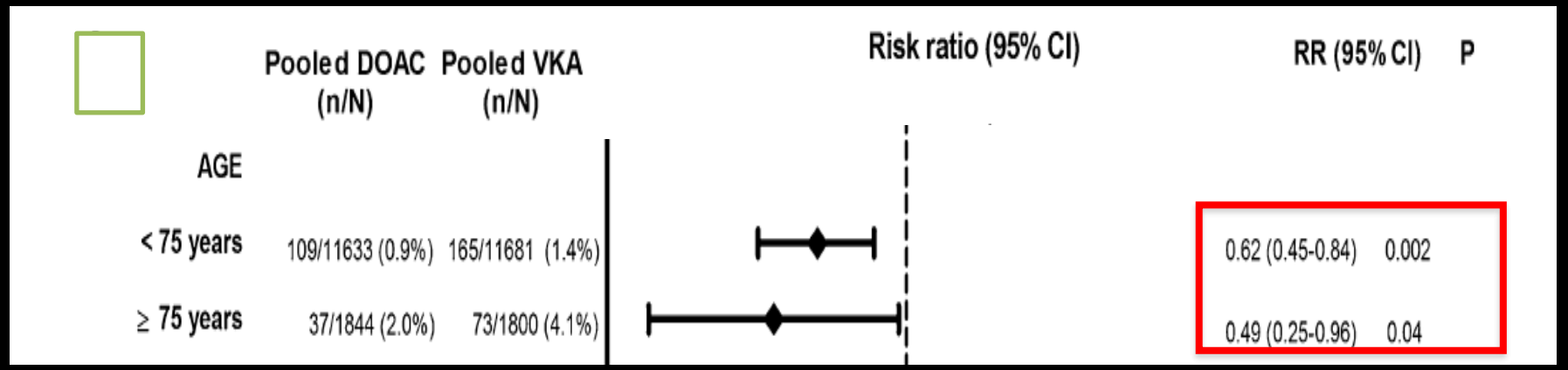
Vedovati et al., Int J Cardiol 2014

Age ≥ 75 years and VTE recurrence in phase III clinical trials

Recurrent VTE

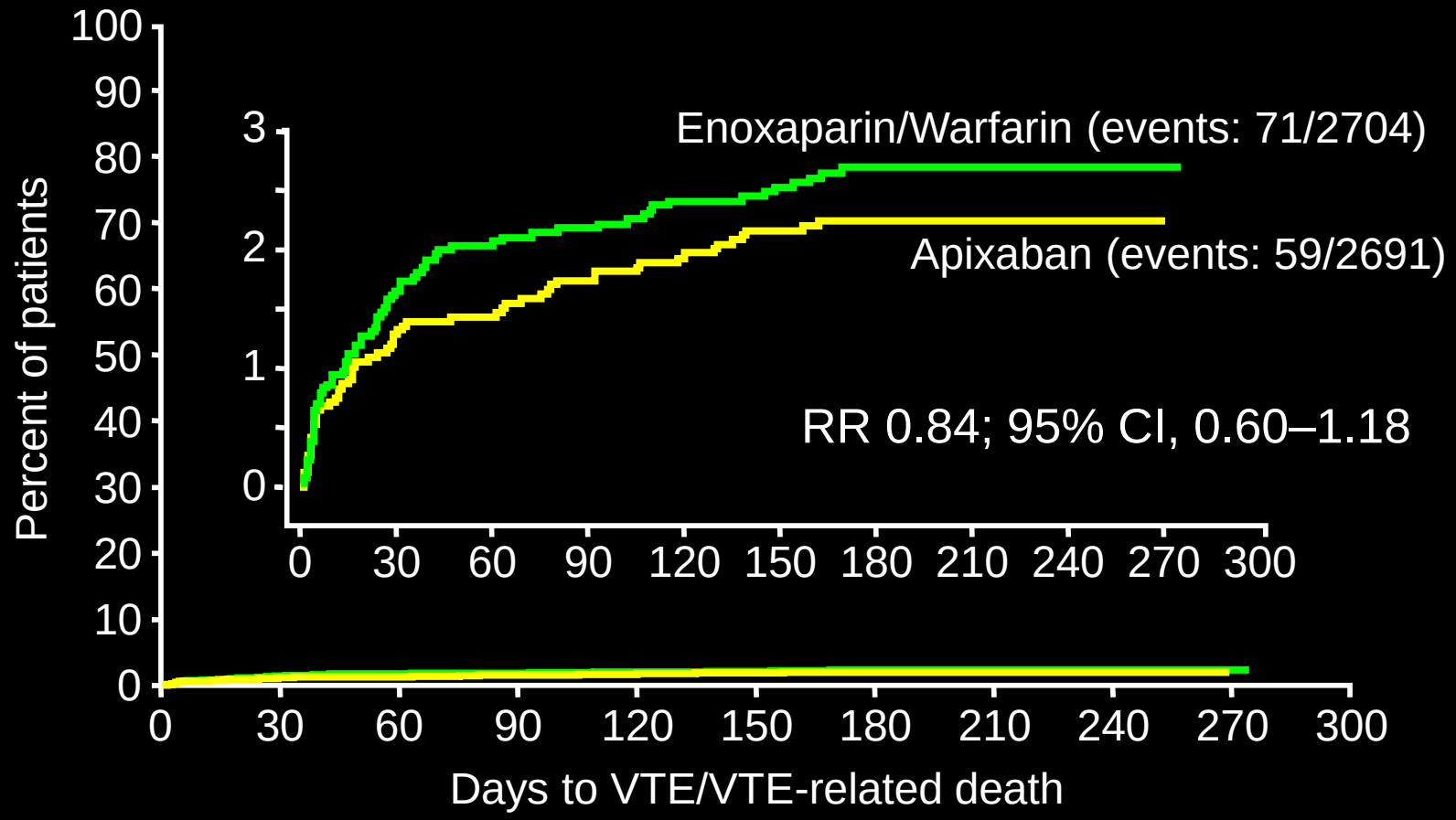


Major Bleeding



Van Es et al Blood 2014

AMPLIFY: recurrent VTE & VTE-related death



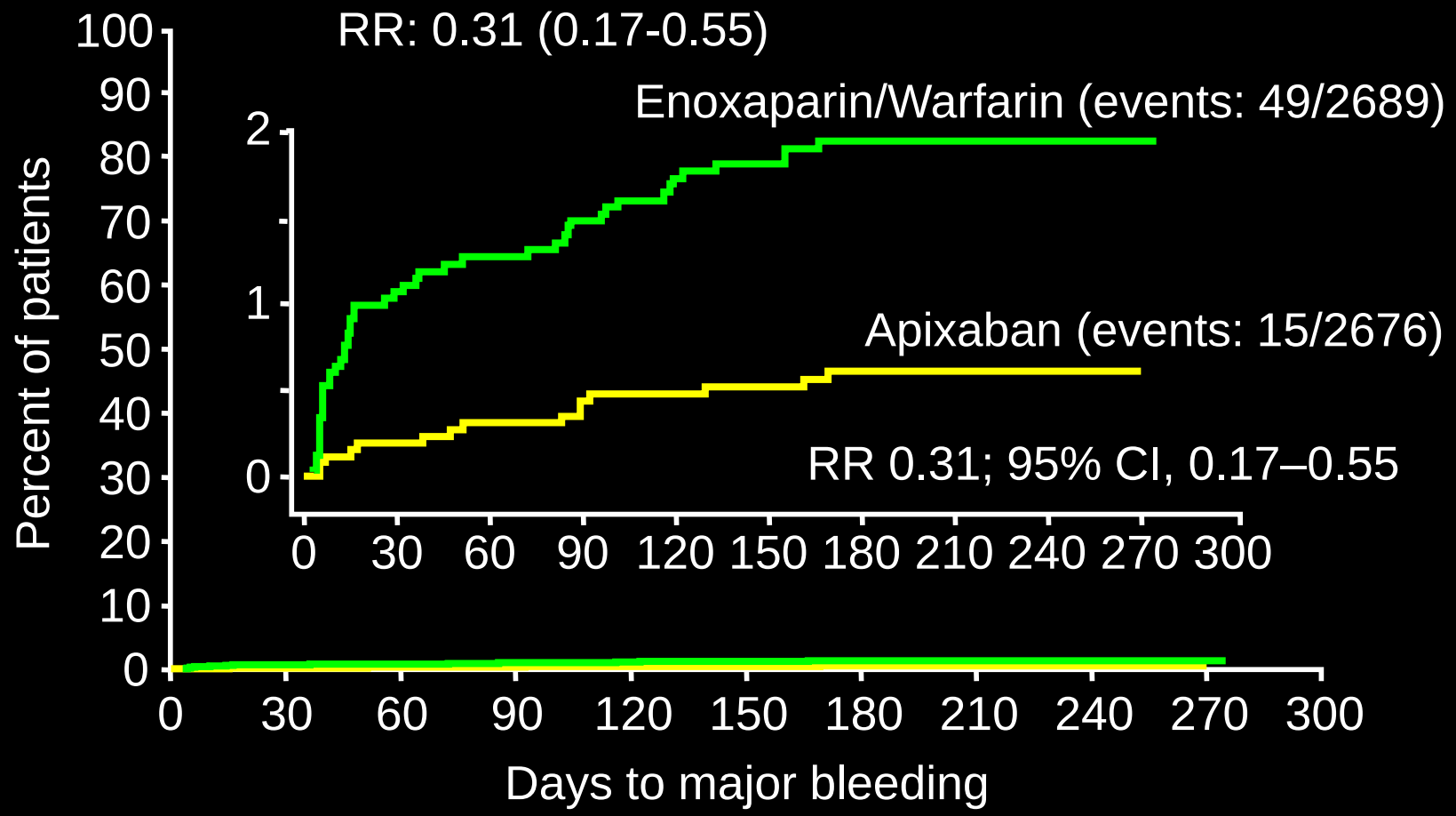
No. of patients at risk

Apixaban	2691	2606	2586	2563	2541	2523	62	4	1	0	0
Eno/War	2704	2609	2585	2555	2543	2533	43	3	1	1	0

TTR, time in therapeutic range.

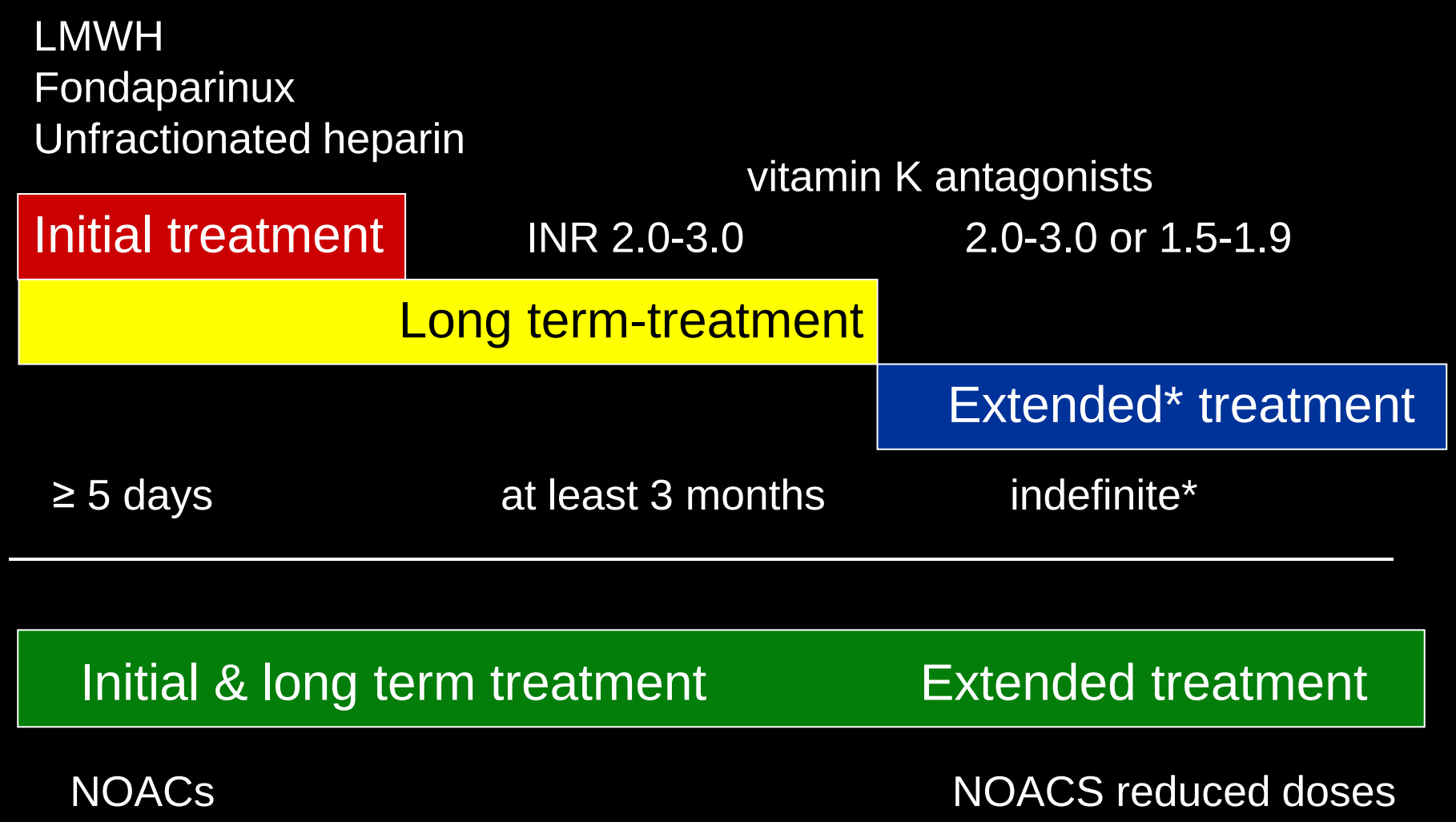
Agnelli et al. N Engl J Med. 2013

AMPLIFY: Major bleedings



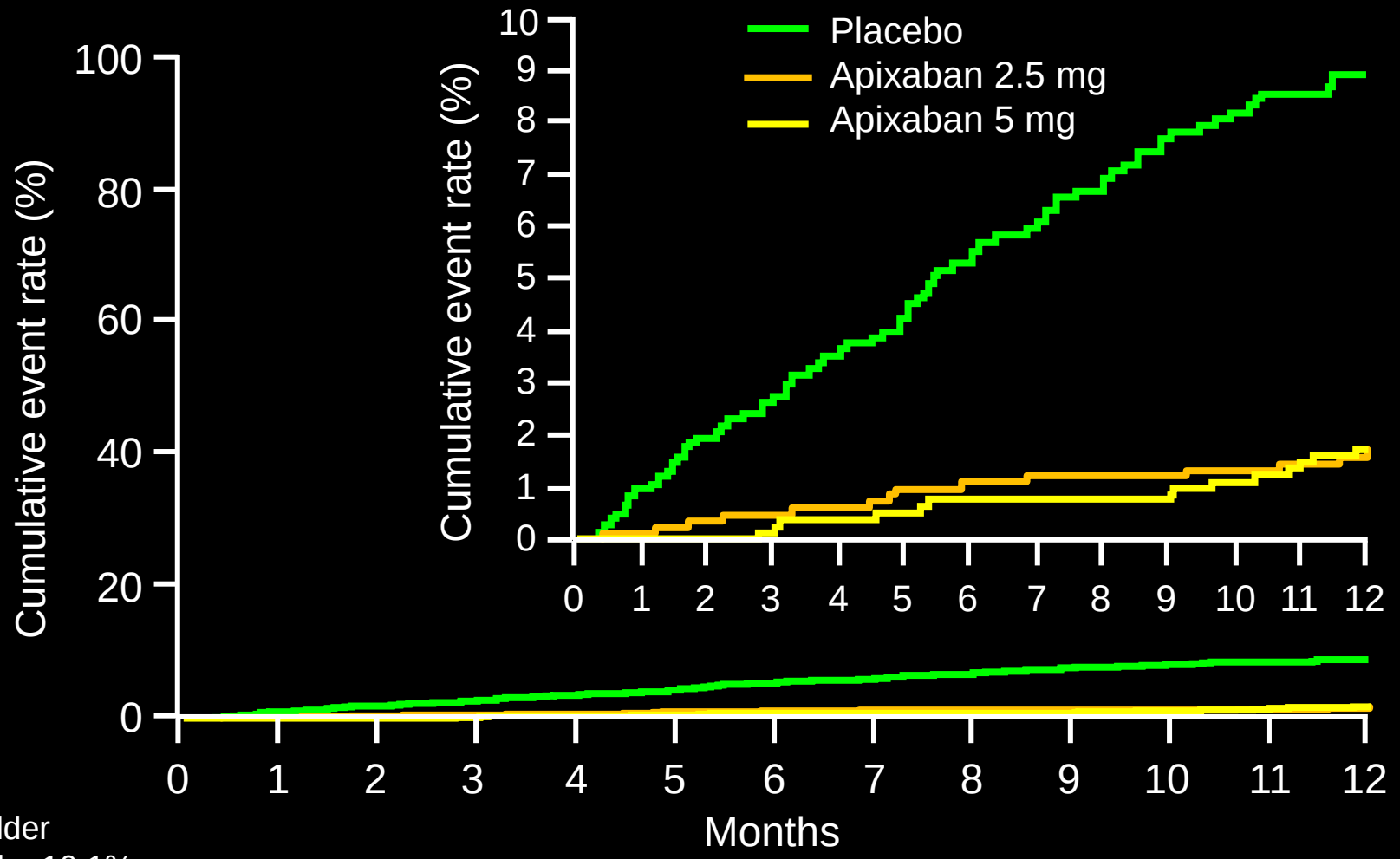
Agnelli et al. N Engl J Med. 2013

Pre-NOACs & current treatment of pulmonary embolism



* With re-assessment of the individual risk-benefit at periodic intervals

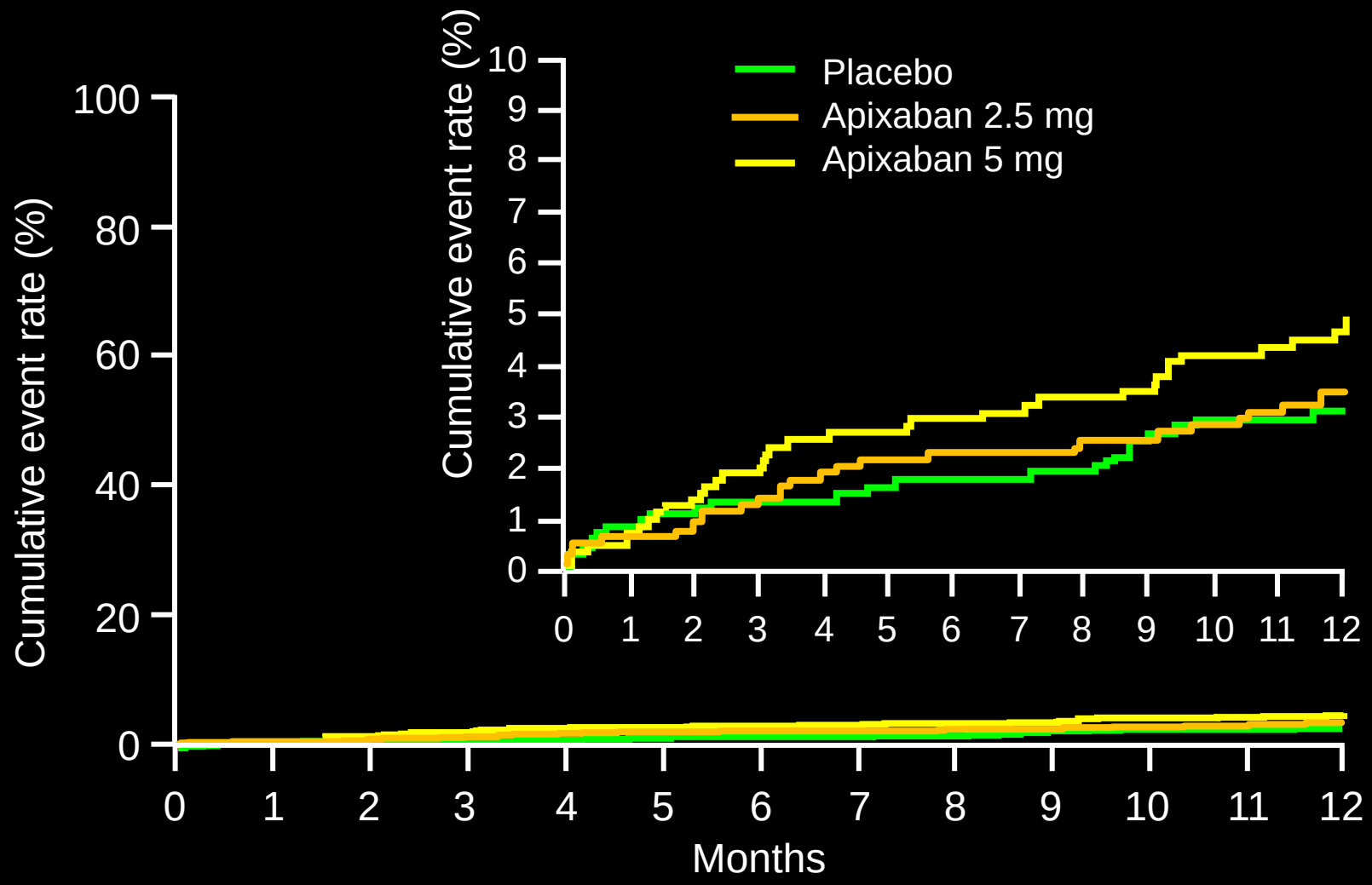
AMPLIFY-Extension: VTE recurrences



Patients aged 75 or older
Apixaban 2.3% Placebo 10.1%
OR: 0.21 (0.07-0.61)

Agnelli et al. N Engl J Med. 2013

Oral anticoagulant treatment for venous thromboembolism



Agnelli et al. N Engl J Med. 2013

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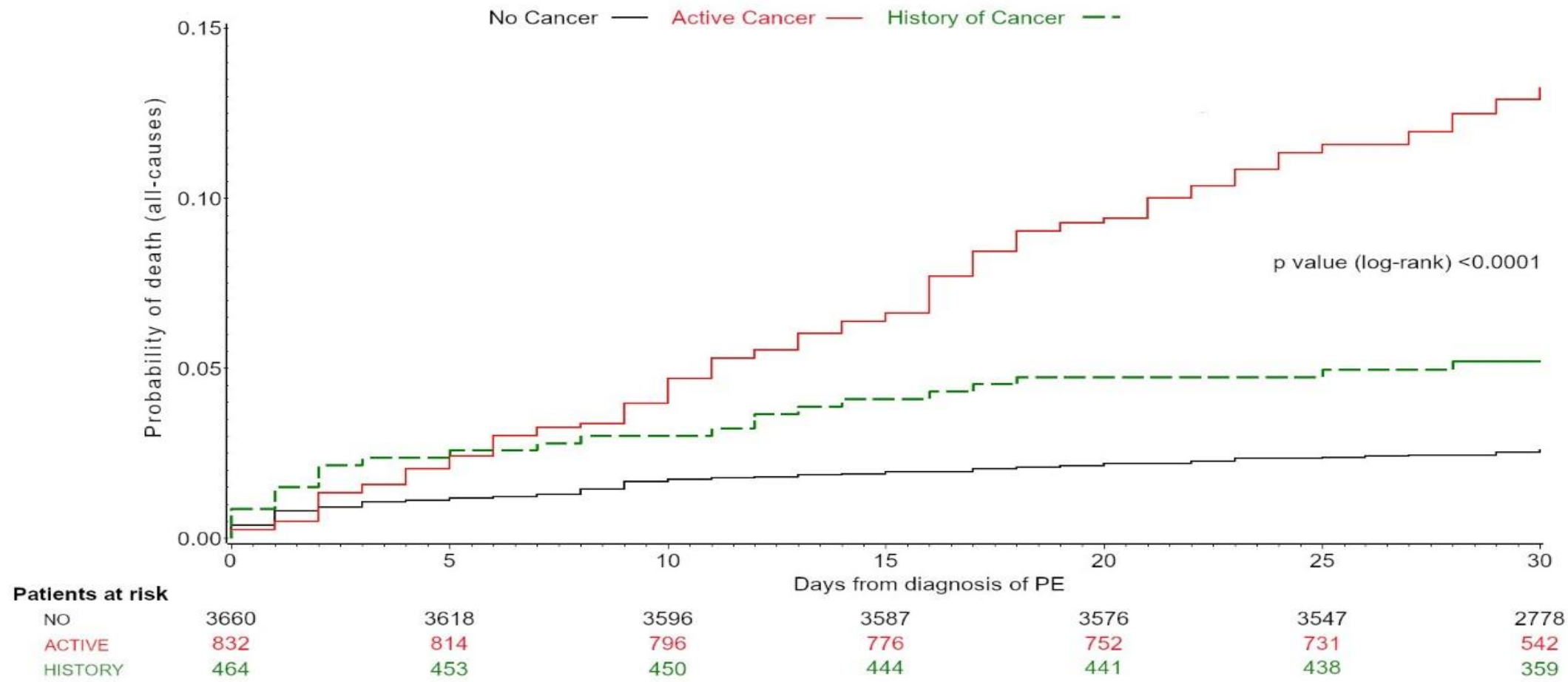
COPE study 30-day mortality in cancer and non-cancer patients



*** COPE: Contemporary pulmonary embolism registry**

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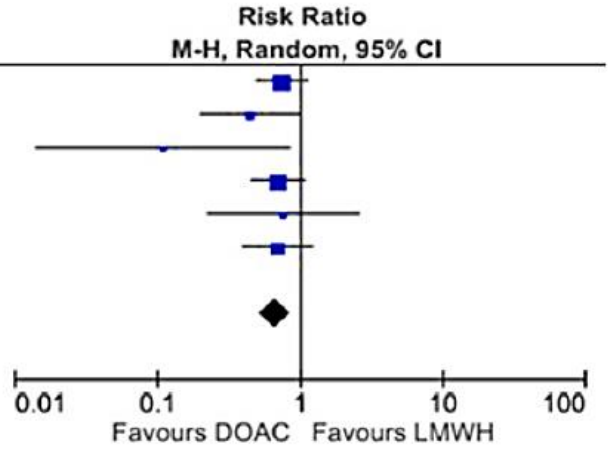
Becattini et al., Clin Res Cardiol 2023

Data from RTCs comparing DOACS and LMWH in CAT

Recurrent VTE

Study or Subgroup	DOAC Events	DOAC Total	LMWH Events	LMWH Total	Weight	Risk Ratio M-H, Random, 95% CI
HOKUSAI-VTE CANCER	34	522	46	524	33.5%	0.74 [0.48, 1.14]
SELECT-D	8	203	18	203	9.3%	0.44 [0.20, 1.00]
ADAM-VTE	1	145	9	142	1.4%	0.11 [0.01, 0.85]
CARAVAGGIO	32	576	46	579	32.0%	0.70 [0.45, 1.08]
CASTA-DIVA	4	74	6	84	4.1%	0.76 [0.22, 2.58]
CANVAS	20	330	27	308	19.6%	0.69 [0.40, 1.21]
Total (95% CI)		**1850**		**1840**	**100.0%**	**0.67 [0.52, 0.85]**
Total events	99		152			

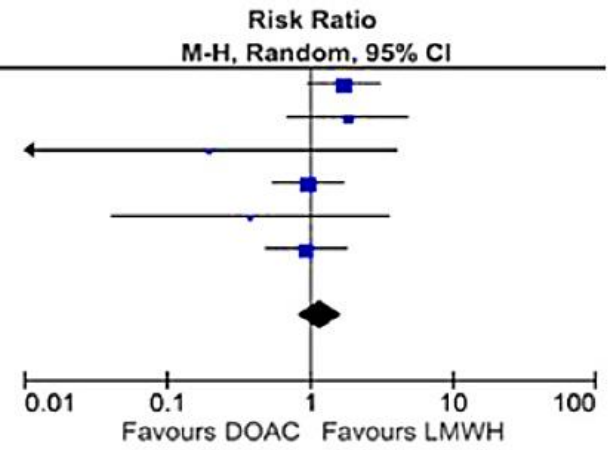
Heterogeneity: Tau² = 0.00; Chi² = 4.36, df = 5 (P = 0.50); I² = 0%
Test for overall effect: Z = 3.22 (P = 0.001)



Major Bleeding

Study or Subgroup	DOAC Events	DOAC Total	LMWH Events	LMWH Total	Weight	Risk Ratio M-H, Random, 95% CI
HOKUSAI-VTE CANCER	29	522	17	524	29.2%	1.71 [0.95, 3.08]
SELECT-D	11	203	6	203	12.2%	1.83 [0.69, 4.86]
ADAM-VTE	0	145	2	142	1.4%	0.20 [0.01, 4.04]
CARAVAGGIO	22	576	23	579	30.3%	0.96 [0.54, 1.71]
CASTA-DIVA	1	74	3	84	2.5%	0.38 [0.04, 3.56]
CANVAS	17	330	17	308	24.5%	0.93 [0.49, 1.80]
Total (95% CI)		**1850**		**1840**	**100.0%**	**1.17 [0.82, 1.67]**
Total events	80		68			

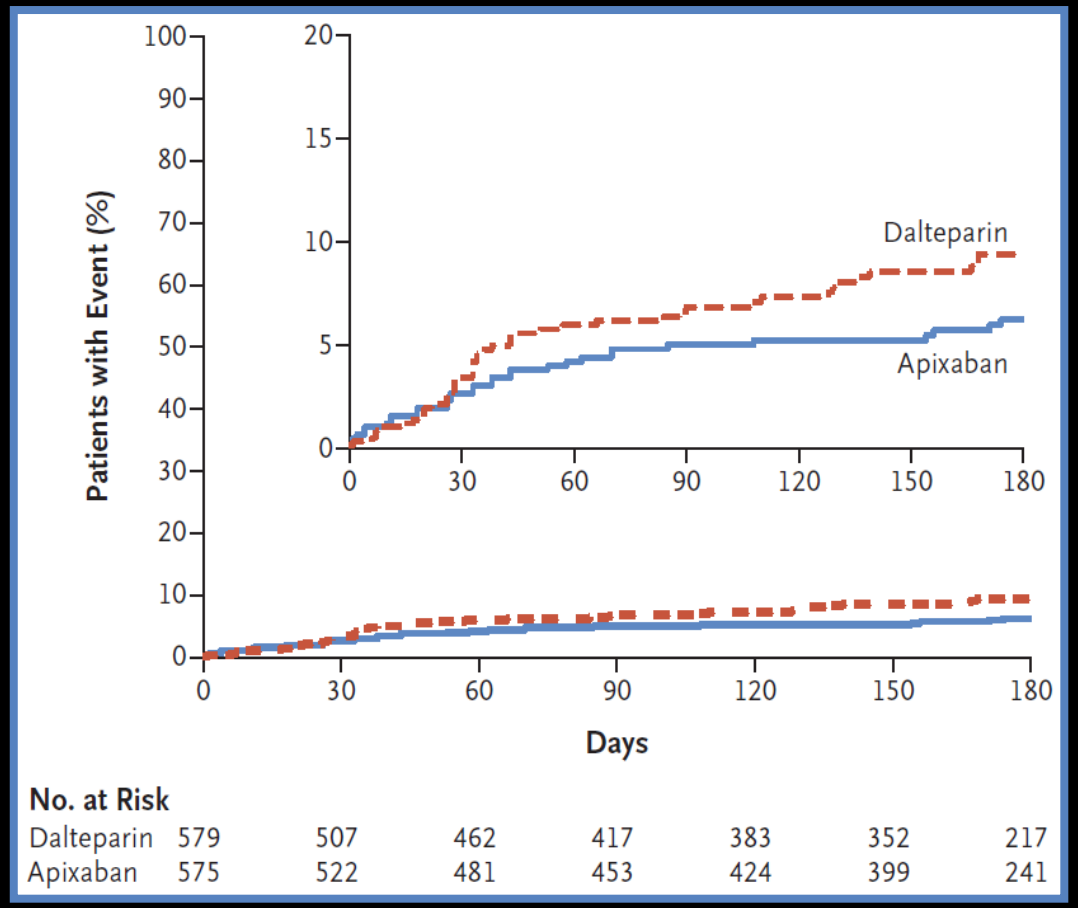
Heterogeneity: Tau² = 0.02; Chi² = 5.66, df = 5 (P = 0.34); I² = 12%
Test for overall effect: Z = 0.85 (P = 0.39)



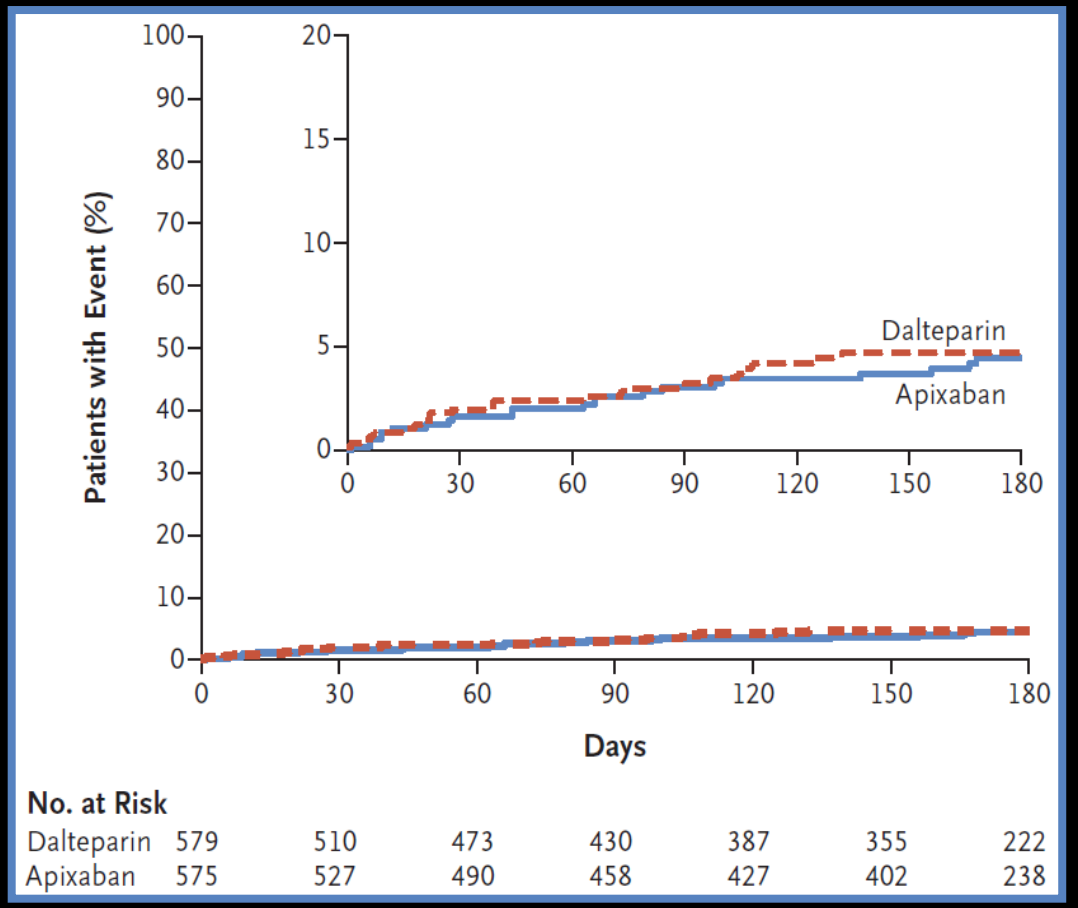
RCT, randomized controlled trial.
Frere C, et al. J Hematol Oncol. 2022;15:69.

Cumulative event rate of VTE recurrences and major bleeding

Recurrent VTE



Major Bleeding



Agnelli et al., N Engl J Med. 2020

Factor XI inhibitors in clinical development

	Abelacimab (MAA868)	Osocimab	FXI-LICA	Asundexian (BAY243334)	Milvexian (BMS986177/ JNJ70033093)
Agent	Monoclonal antibody (fully human)	Monoclonal antibody (fully human)	Antisense oligonucleotide	Small molecule	Small molecule
Mode of action	Dual Factor XI/XIa inhibition	Factor XIa inhibition	Decrease Factor XI synthesis	Factor XIa inhibition	Factor XIa inhibition
Administration	S.C. or I.V.	S.C. or I.V.	S.C.	Oral	Oral
Frequency of dosing*	Monthly, Once	Monthly, Once	Weekly to Monthly	Daily	Daily (QD, BID)
Onset of action	Rapid	Rapid	Slow	Rapid	Rapid
Offset of action	Slow	Slow	Slow	Rapid	Rapid
Renal clearance	No	No	No	Some	Some
Drug-drug interactions	No	No	No	Possible	Possible
Stage of development	Phase 2	Phase 2	Phase 2	Phase 2	Phase 2

Conclusions

LMWH are still largely used in the prophylaxis of VTE and new studies are required in high risk populations

DOACs are effective and safe for the treatment of VTE and are the agents of choice in the large majority of patients.

Reduced dose of DOACs are the strategy of choice for the VTE extended treatment.

NOACS are an effective (and safe) alternative to LMWH for VTE treatment in a large spectrum of patients with VTE and cancer with the advantage of the improved practicality.