Updated clinical models for VTE prediction in hospitalized medical patients

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Disclosures

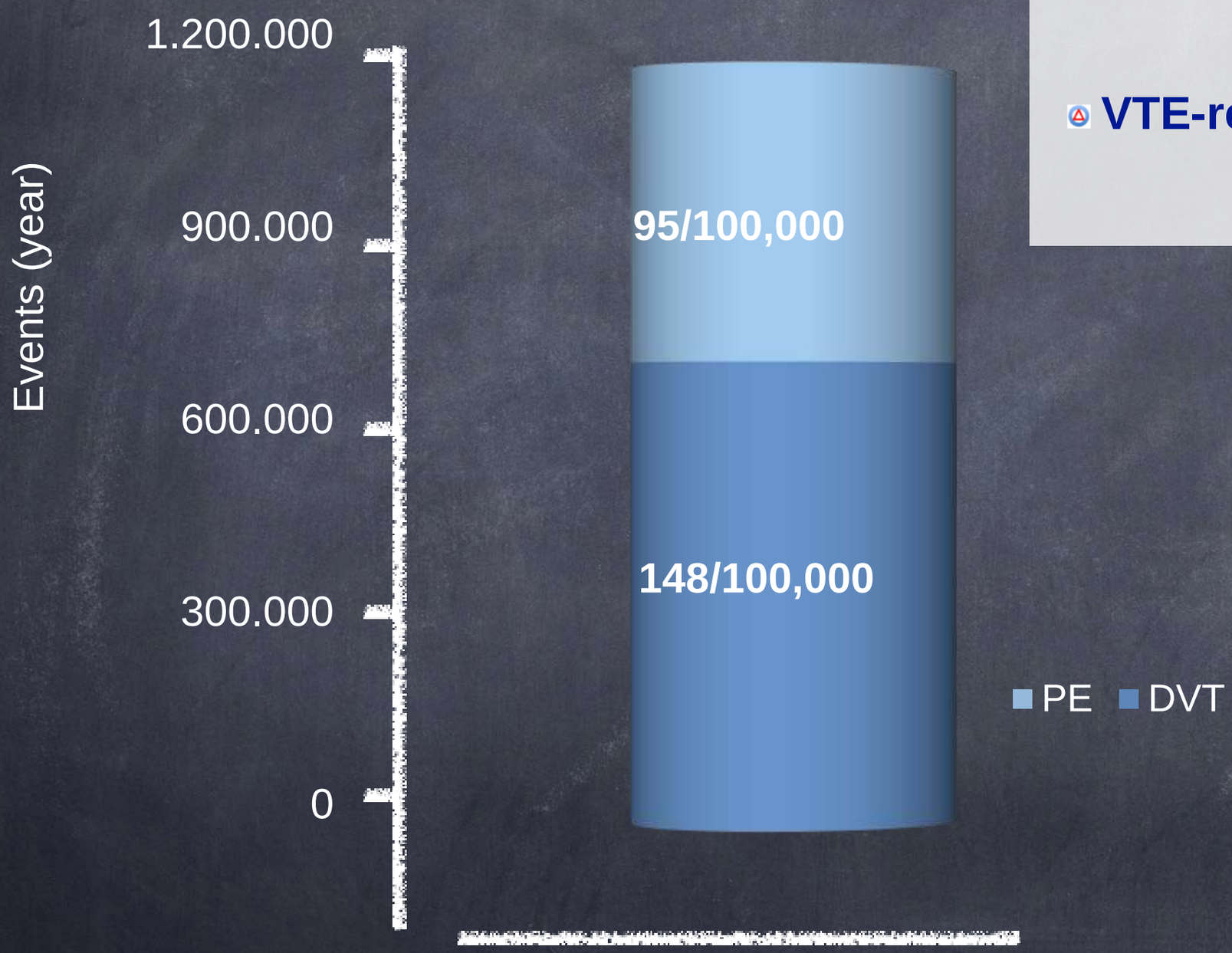
None

Agenda

- Do we need a RAM for VTE in hospitalized medical patients?
- New VTE risk factors in hospitalized acutely ill medical patients
- Performance of RAMs for VTE in hospitalized medical ill patients
- Post-discharge risk of VTE
- Biomarkers in RAM for VTE in acutely ill medical patients
- Conclusions

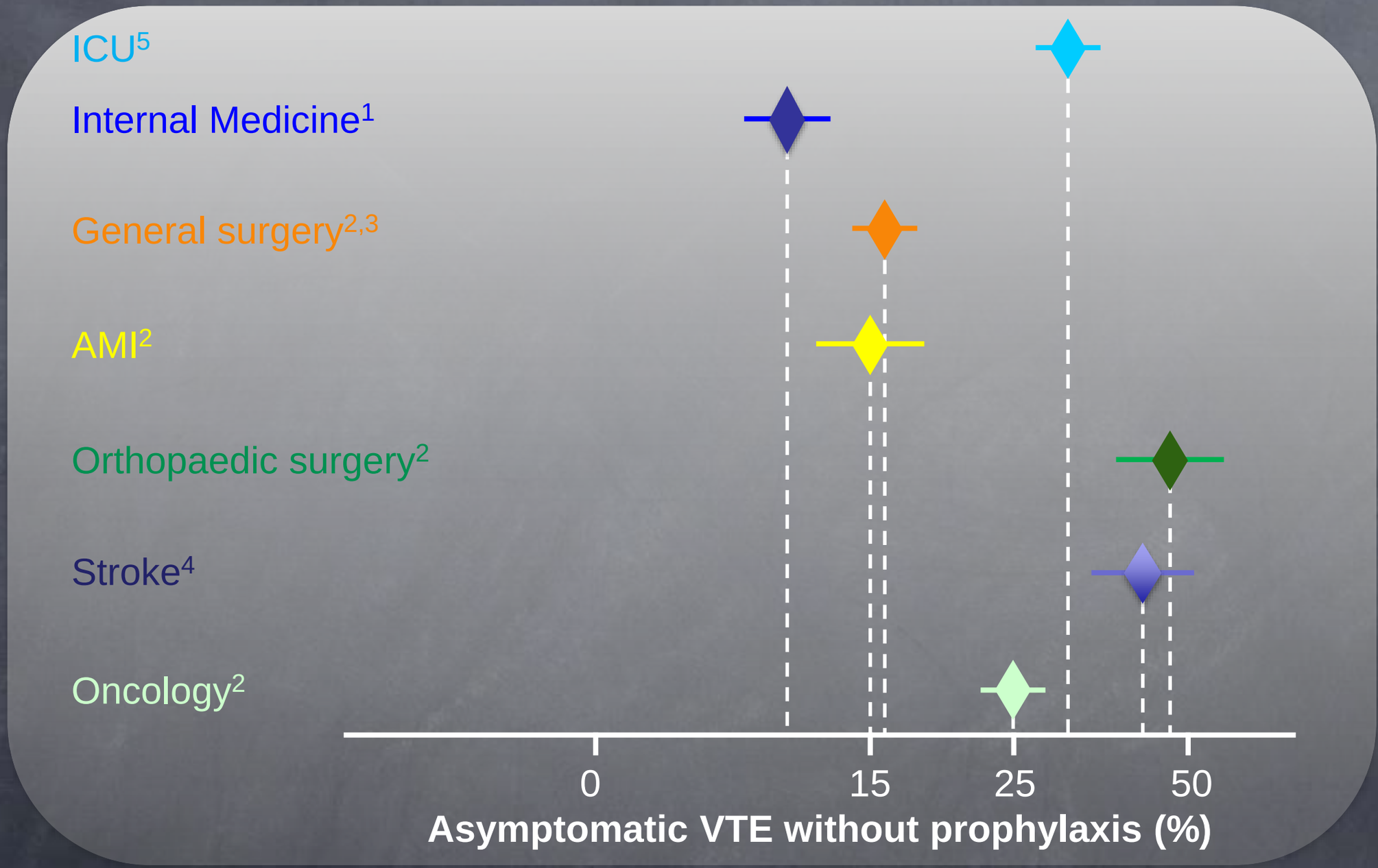
VTE: A nosocomial disease

- **63% of VTE episodes occur during hospitalization**
- **VTE-related deaths are 70% of the in-hospital mortality**



Cohen AT, et al (VITAE). Thromb Haemost 2007; 98: 756–764

Asymptomatic VTE without thromboprophylaxis



AMI = acute myocardial infarction;
ICU = intensive care unit;
VTE = venous thromboembolism.

1. Samama MM, et al. N Engl J Med 1999; **341:**793–800;
2. Geerts WH, et al. Chest 2001; **119:**132S–175S;
3. Collins R, et al. Br Med J 1996; **313:**652–659;
4. Counsell et al. The Cochrane Library 1999:Issue;
5. Cook DJ & Crowther MA. Crit Care Med. 2010; **38:**S76–82. Personal communication.

Hospitalized medical patients had more severe VTE compared to non medical patients

DVT Registry : October 2001 to March 2002

VTE characteristics	Hospitalized medical patients (n=2609)	Hospitalized non medical patients (n=1953)
PE	488 (22%)	241 (15%)*
Proximal & calf DVT	1056 (41%)	589 (30%)*
Proximal DVT without calf involvement	1064 (41%)	708 (36%)*
Calf DVT	335 (13%)	391 (20%)*
Upper extremity DVT	215 (8.3%)	329 (17%)*

*p<0.001

Piazza et al Chest. 200;132:554-61.

Comparison of the inclusion criteria in the three RCT in acutely ill medical patients

	Inclusion criteria	MEDENOX[1]	PREVENT[2]	ARTEMIS[3]
	Acute medical illness	+	+	+
	Projected hospitalisation	> 6 days	> 4 days	> 5 days
	Immobilisation	≤ 3 days	≤ 3 days	
	Patients older than	40 years	40 years	60 years
	Congestive heart failure (NYHA class III or IV)	+	+	+
	Acute respiratory failure not requiring ventilatory support	+	+	+
or one of the following conditions if associated with at least one additional VTE risk factor	Acute infection without septic shock	+	+	+
	Acute rheumatic disorders	+		
	Episode of inflammatory bowel disease	+		+
Additional VTE risk factors	Older than 75 years	+	+	> 60 years
	Cancer	+	+	Not required
	Previous VTE	+	+	
	Obesity	+	+	
	Varicose veins	+	+	
	Hormone therapy	+	+	
	Chronic heart or respiratory failure	+	+	
	Myeloproliferative syndrome	–	+	

1. Samama MM, et al. N Engl J Med 1999; **341:**793–800.
2. Leizorovicz A, et al. Circulation 2004; **110:**874–879.
3. Cohen A, et al. Br Med J 2006; **332:**325-329.

Thromboprophylaxis of medical patients: clear benefits over placebo

Study	RRR (%)	NNT	Prophylaxis	Patients with VTE , n (%)
MEDENOX[1] P < 0.001	63	10	Placebo Enoxaparin 40 mg	43*/288 (14.9) 16*/291 (5.5)
PREVENT[2] P = 0.0015	45	45	Placebo Dalteparin	73†/1,473 (5.0) 42† /1,518 (2.8)
ARTEMIS[3] P = 0.029	47	20	Placebo Fondaparinux	10.5‡ (34/323) 18‡ /321 (5.6)

* VTE between Day 1 and Day 14; † VTE at Day 21;
‡ VTE at Day 15.

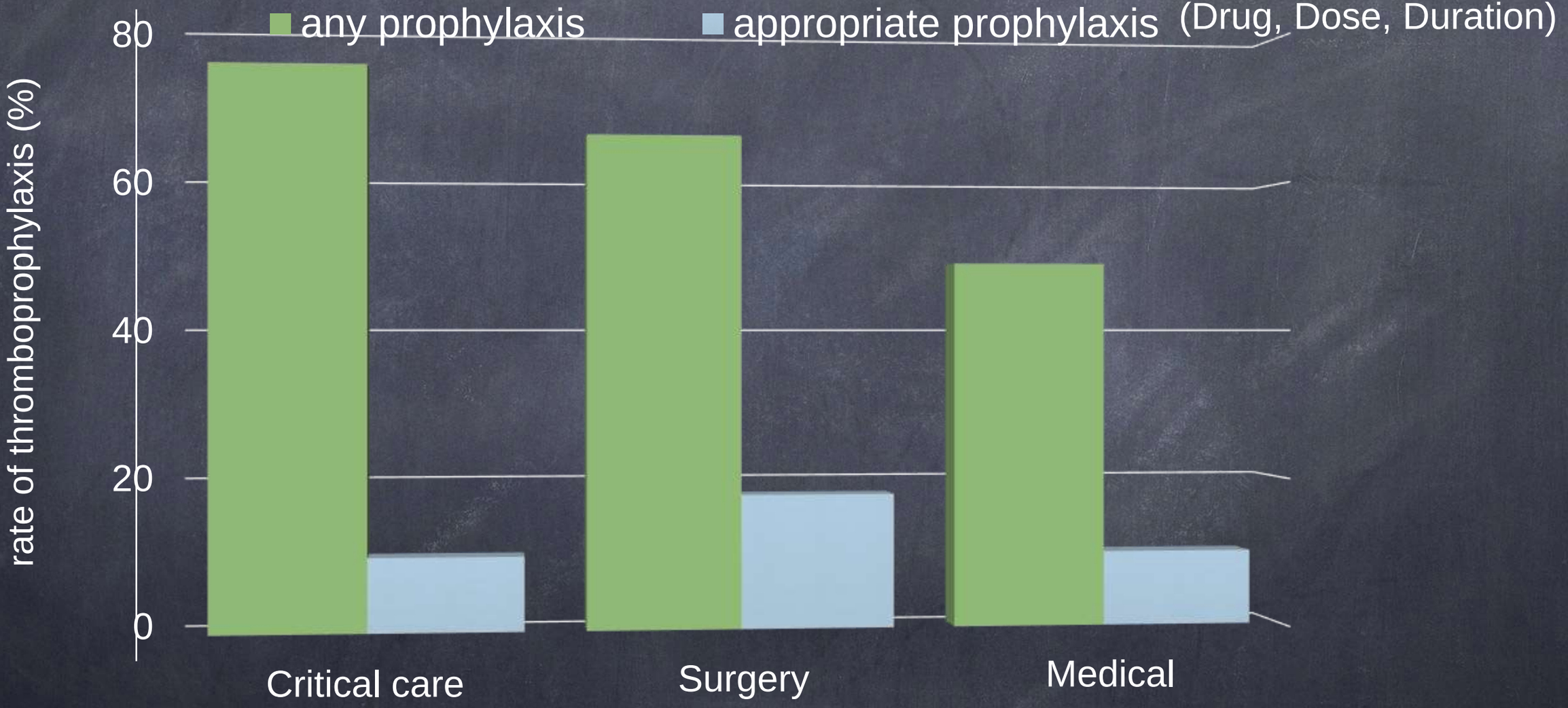
NNT = number needed to treat; RRR = relative risk reduction;
VTE = venous thromboembolism.

1. Samama MM, et al. N Engl J Med 1999; **341:**793–800;
2. Leizorovicz A, et al. Circulation 2004; **110:**874–879;
3. Cohen A, et al. Br Med J 2006; **332:**325–329.

VTE start study

Rates of any and appropriate VTE prophylaxis among patients at risk of VTE (n=68278)

16 acute-care hospitals in USA, from January 2005 to December 2006



Amin et al J Thromb Thrombolysis. 2010;29:326-39

Misuse of pharmacological thromboprophylaxis in hospitalized acutely ill medical patients results from

- Under-estimation of VTE risk
- Low perception that patients included in the trials are actually at risk of thromboembolism
- Confusion regarding the clinical relevance of VTE risk factors
- Heterogeneity of hospitalized acutely ill medical patients
- Fear of treatment related bleeding risk
- Subcutaneous route of administration of pharmacological thromboprophylaxis

Violi et al. Thromb. Haemost. 2013;109:589–595.
Schleyer et al. J. Hosp. Med. 2016;11 (Suppl. 2);S38–S43.

Principal methodology of risk assessment

Triggering risk factor

Appropriate thromboprophylaxis
- Drug
- Dose
- Duration

thrombotic threshold

Predisposing risk factors

Overall risk
- Low
- Moderate
- High

baseline risk

Comorbidities and VTE risk

Risk factors for VTE	Odds ratio	95% CI
Serum albumin levels in chronic kidney disease		
3-3,99 g /dL	1,51	1,01-2,26
2,5-2,99 g/dL	2,24	1,24-4,05
<2,5 g /dL	2,79	1,45-5,37
Sickle cell disease carriers		
VTE	1,78	1,18-2,69
PE	2,27	1,17-4,39
Aortic aneurysms		
VTE	1,88	1,2-2,83
PE	1,90	1,2-2,54
Cardiovascular Risk Factors (CVRF)		
1 CVRF	3	1,44-6,52
2 CVRF	4,33	2,07-9,49
≥3 CVRF	4,58	2,27-9,7

CI: confidence interval; CVRF: cardio-vascular risk factors VTE: Venous ThromboEmbolism; PE: Pulmonary Embolism

Chronic autoimmune/inflammatory diseases and VTE risk

Risk factors for VTE	Odds ratio	95% CI
Celiac disease	1,25	1,02-1,53
Cutaneous lupus erythematosus	1,39	1,10-1,78
IBD and CDI versus IBD without CDI	1,73	1,4-2,2
Psoriasis	2,02	1,42-2,88
Sjogren’s syndrome	2,05	1,86-2,27
Systematic lupus erythematosus	3,32	2,74-4,03
Vasculitis	3,94	1,11-14,01
Immune thrombocytopenic purpura	2,95	2.18-4.00
Polymyositis and dermatomyositis	4,36	2,13-8,95

CI: confidence interval; IBD: inflammatory bowel disease, CDI: clostridium diffcile infection;
HIV: human immunodeficiency virus; HCV: hepatitis C virus.

Infectious diseases and VTE risk

Risk factors for VTE	Odds ratio	95% CI
Hepatitis C virus	1,38	1,08-1,77
Tuberculosis and HIV vs tuberculosis without HIV	8,2	2,9-22,7

CI: confidence interval; IBD: inflammatory bowel disease, CDI: clostridium diffcile infection;
HIV: human immunodeficiency virus; HCV:

Other conditions affecting VTE risk

Risk factors for VTE	Odds ratio	95% CI
Acute kidney injury	1,08	-
Total parenteral nutrition	1,28	-
Acute respiratory failure	1,4	-
Pseudo cyst	1,41	-
Postmenopausal women on antipsychotic drugs versus non-menopausal women	1,9	1,64-2,19
Central venous catheter placement	3,01	-

y bowel disease, CDI: clostridium diffcile infection;
ency virus; HCV: hepatitis C virus.

RAM for VTE in hospitalized medical patients

- Kucher Model[1]
  - e-alert tool with 8 differently weighted predictors
- Padua Prediction Score (PPS)[2]
  - 11 predictors scored with 1, 2 or 3 points
  - Low risk 0–3 High risk >4
- International Medical Prevention Registry on Venous Thromboembolism (IMPROVE-RAM)[3]
  - 7 predictors scored with 1, 2 or 3 points
  - Low risk 0–2 High-risk >3
- Geneva Risk Score[4]
  - 19 predictors which represent the classical VTE risk factors, on a dichotomous analysis (1 or 2).
  - Low risk 0–2; High risk >3

1. Stuck et al, Thromb. Haemost. 2017;117:801–808
2. Barbar and Prandoni, Semin. Thromb. Hemost. 2017;43:460–468
3. Spyropoulos et al Chest 2011;140:706–714
4. Nendaz et al. Thromb Haemost 2014;111:531–53

VTE predictors in VTE RAMs for patients hospitalized fo acute medical illness

VTE predictors	Kucher RAM	Padua Prediction Score [67]	IMPROVE RAM	Geneva score Geneva risk score Low risk 0–2 High risk !3
Personal history of VTE	3	3	3	2
Cancer	3	3	2	2
Hypercoagulability/thrombophilia	3	3	2	1
Age>75 years for Kucher or 70 for PADUA or >60 years IMPROVE, Geneva	3	1	1	1
Obesity (BMI ≥30)	3	1	ni	1
Bed rest (active order for bed rest that was not related to surgery)	3	3	1	2
Hormone replacement treatment or oral contraception	3	1	ni	1
Lower limb paralysis	ni	ni	2	ni
Recent (≤1 month trauma and/or surgery)	ni	2	ni	ni
Heart and/or respiratory failure	ni	1	ni	ni
Acute MI and/or ischemic stroke	ni	1	ni	ni
Acute infection and/or rheumatologic disorder	ni	1	ni	2
ICU/CCU stay	ni	ni	1	ni
Major Surgery (lasting more than 60 min)	3	na	na	na
Cardiac failure	ni	ni	ni	2
Respiratory failure	ni	ni	ni	2
Recent stroke	ni	ni	ni	2
Recent myocardial infarction	ni	ni	ni	2
Acute rheumatic disease	ni	ni	ni	2
Myeloproliferative syndrome	ni	ni	ni	2
Nephrotic syndrome	ni	ni	ni	2
Recent travel (>6 h)	ni	ni	ni	1
Chronic venous insufficiency	ni	ni	ni	1
Pregnancy	ni	ni	ni	1
Dehydration	ni	ni	ni	1

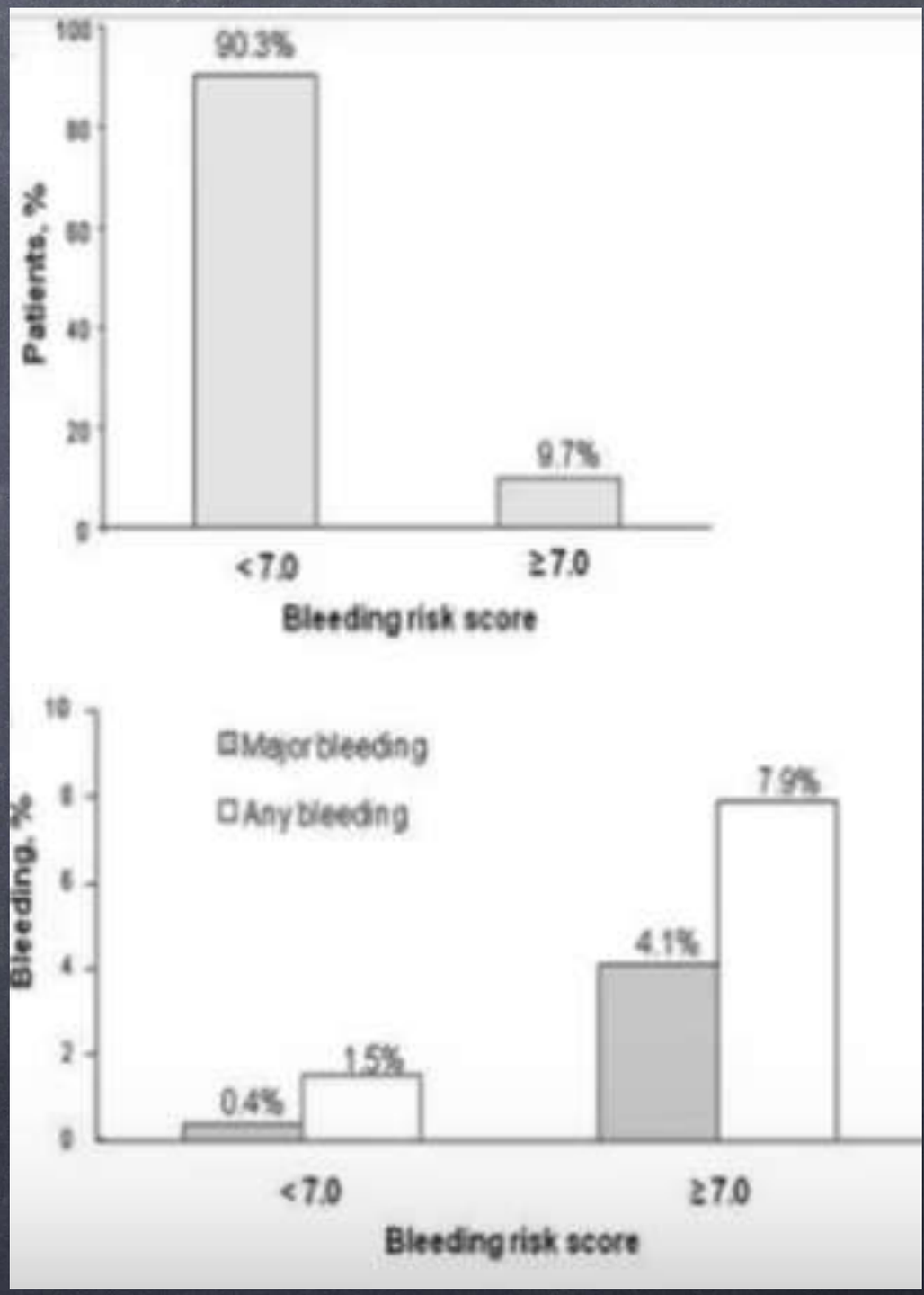
Kucher, PPS and IMPROVE, share a common structure. They share 6 common VTE predictors with different weight in each RAM.

PPS includes more risk factors related to comorbidities, underlying pathologic conditions and co-medications (in regard to hormone treatment),

IMPROVE RAM emphasizes on factors related to immobilization and disease severity.

IMPROVE Bleed Score

Bleeding risk factors	Points
Moderate renal failure GFR 30–59 vs ≥60 ml/min/m2	1
Male vs female	1
Age 40–80 vs <40 years	1.5
Current cancer	2
Rheumatic disease	2
CV catheter	2
ICU/CCU	2.5
Severe renal failure GFR <30 vs ≥60 ml/min/m2	2.5
Hepatic failure (INR >1.5)	2.5
Age ≥85 vs <40 years	3.5
Platelets <50 × 109 cells/l	4
Bleeding in 3 months before admission	4
Active gastroduodenal ulcer	4.5



Decousous et al Chest 2009; 139: 69-79

External validation of RAMs in medical ill patients

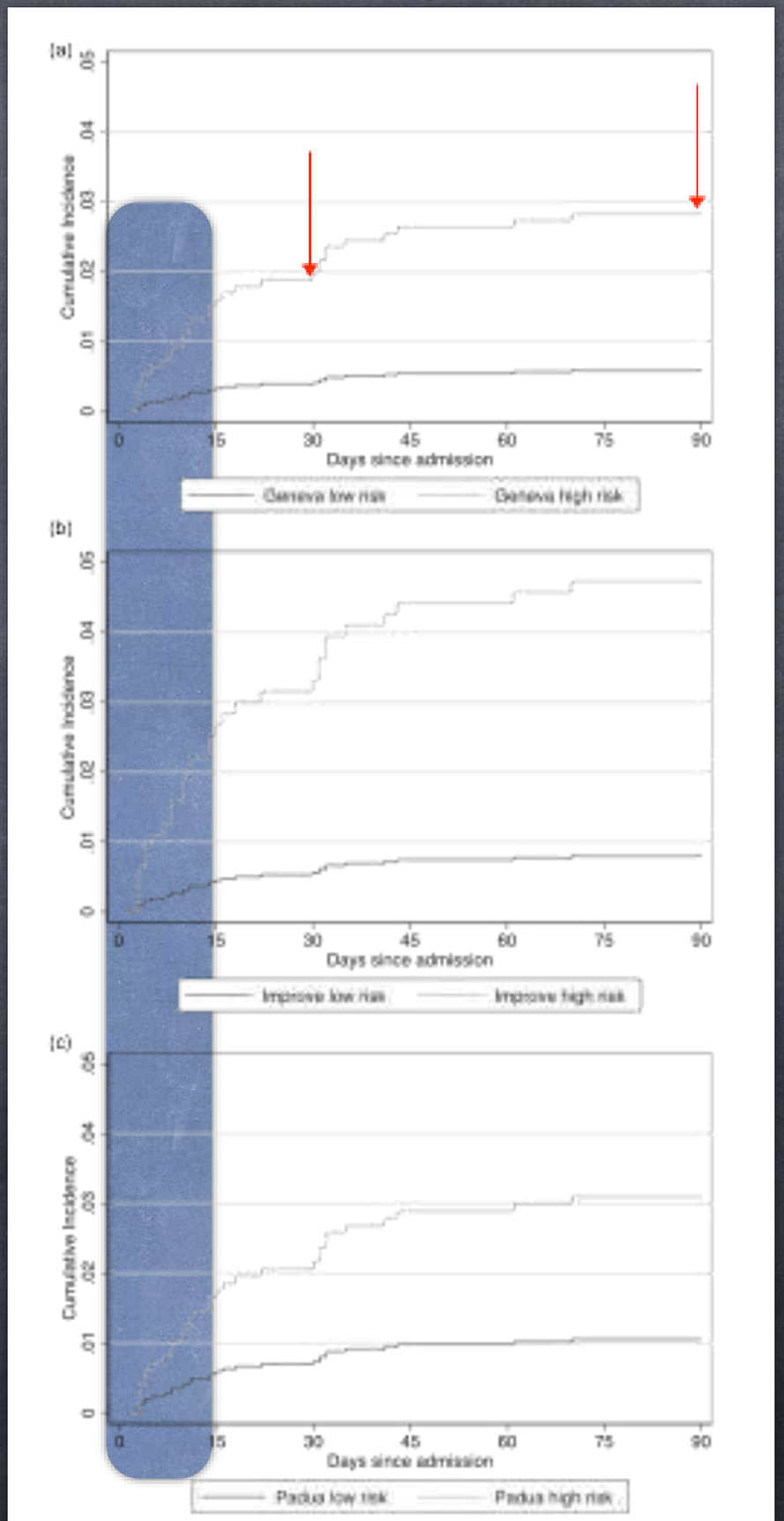
Derivation Population	N	Threshold Score	Symptomatic VTE (~90d)*	Percent Population at Risk	AUC or c-statistic	NPV
Padua VTE	1180	4	7.5%	40%		–
IMPROVE	15,125	2	2.0%	31%	0.69	–
Validation Population						
Padua	1478	4	3.5%	31%	-	98.9%
IMPROVE (NSLIJ)	15,217	3	1.25%	32%	0.70	99.6%
Padua (Michigan)	63,548	4	2.97%	16%	0.60	-
IMPROVE 4 (Michigan)	63,548	2	3.39%	11%	0.57	-

Clinical VTE RAMs suggest that we are over-prophylaxing 50% - 65% of low VTE risk medical patients and likely under-prophylaxing 10%-25% of high VTE risk medical patients

Spyropoulos et al Chest 2010;140:706-714
Barbar et al J Throw Haemost 2010;8:2450-7
Mahan et al Thromb Haemost 2014;112:692-9
Green zt al Am J Med 2016;129:1001
Nendaz M étal Thromb Haemost 2014; 111: 531-38
Rosenberg et al J Am Hear Associ 2011;2

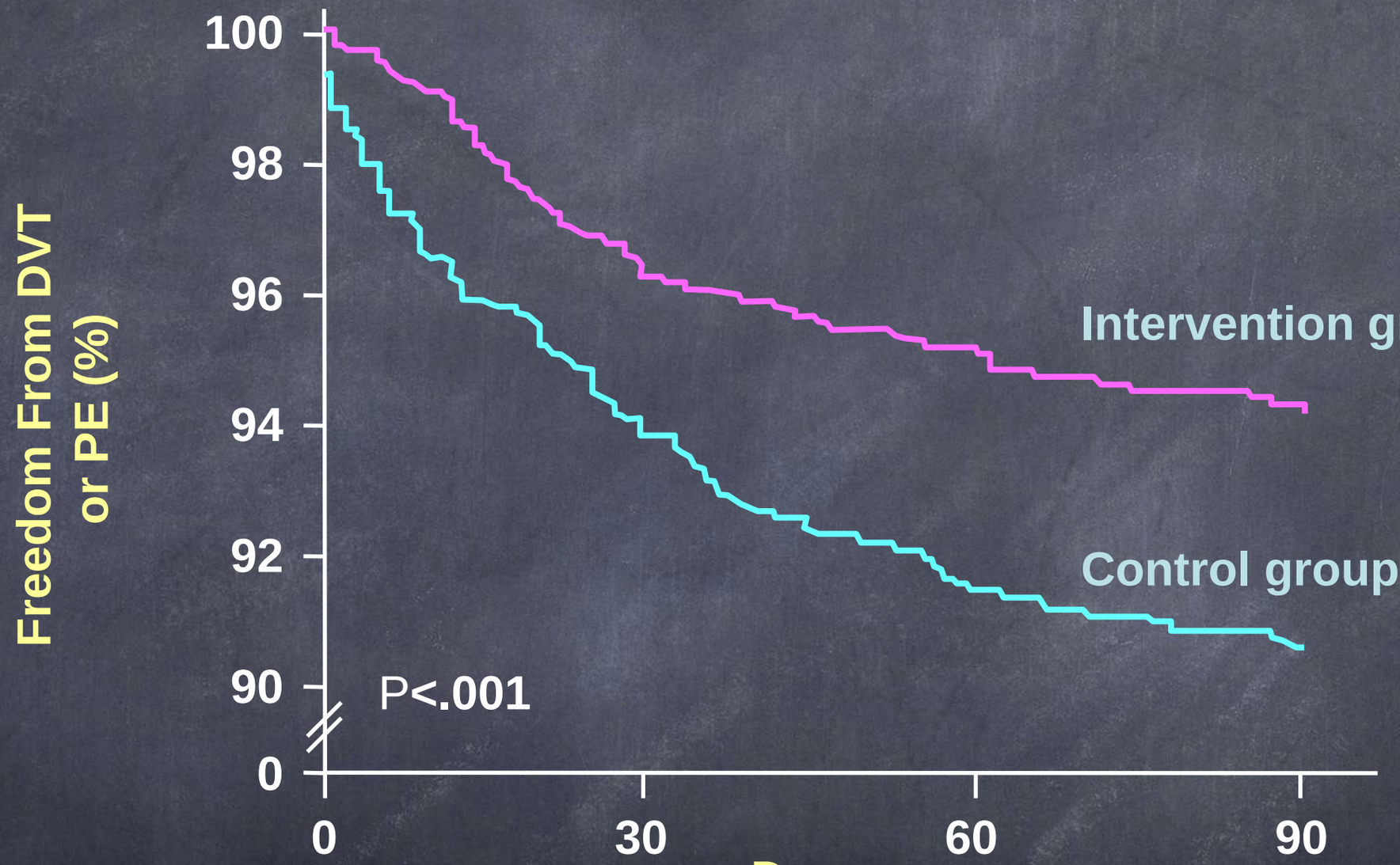
Comparative performance of RAM for VTE in hospitalized medical patients

- 1,478 medical inpatients from eight Swiss hospitals were prospectively followed during 90 days, for symptomatic VTE or VTE-related death
- Study period : December 2010 to November 2011
- Reasons for hospitalization :
  - 24% infection/sepsis
  - 18% cardiovascular events
  - 13% malignancies
- Thromboprophylaxis with LMWHs or fondaparinux: 56%



Blondon et al Thromb Haemost 2018;118:82–89.

Electronic Alerts to Prevent VTE in Hospitalized Patients



No. at Risk

Intervention group	1255	977	900	853
Control group	1251	976	893	839

P<.001 by the log-rank test for the comparison of the outcome between groups at 90 days.

Kucher N, et al. N Engl J Med. 2005;352:969-977.

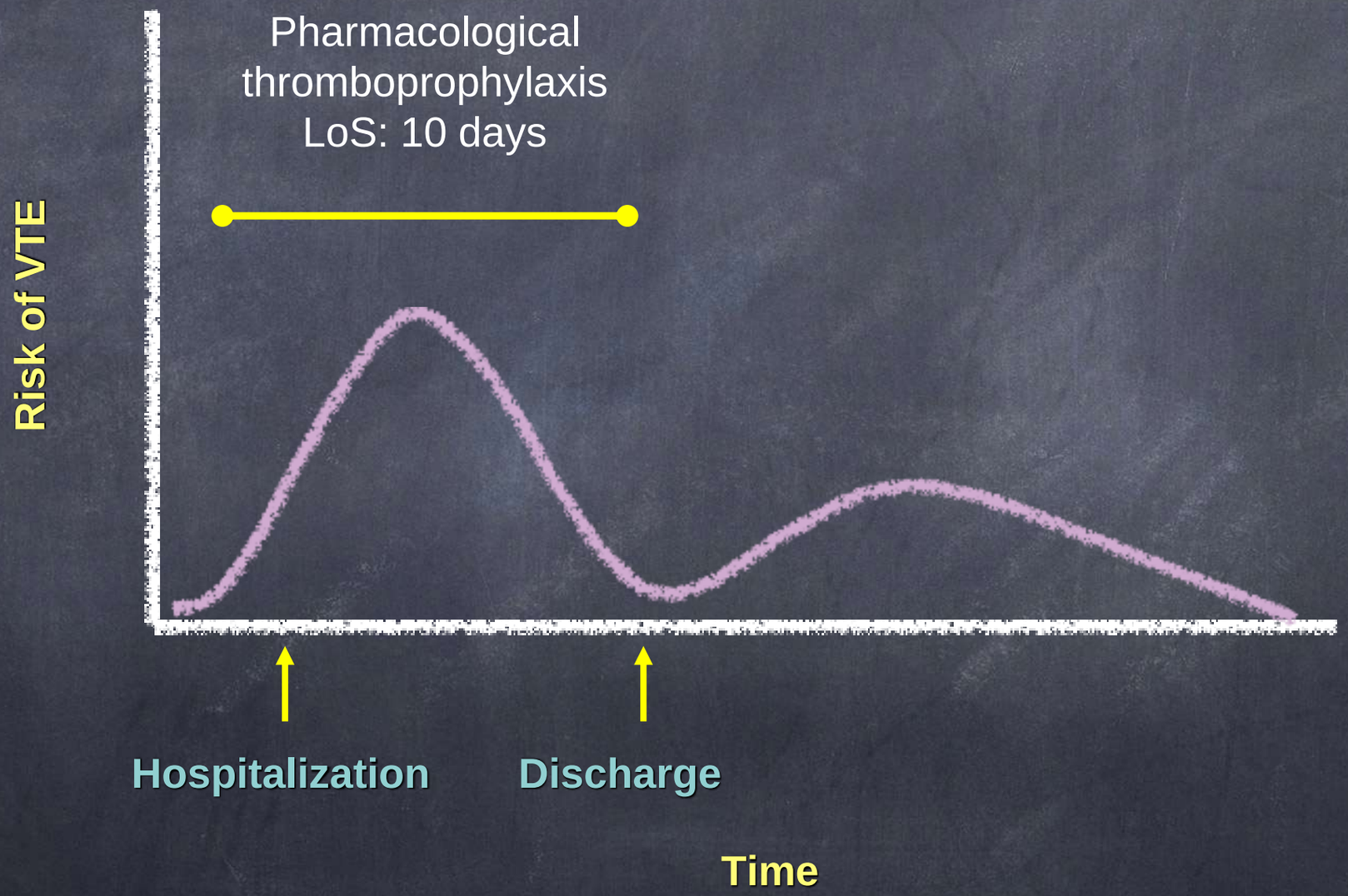
3 scenaria for an actually ill medical patient

50 ys old women; hospitalization for acute pneumonia

- IMPROVE VTE RAM had good discrimination and calibration characteristics when studied in two large external validation studies comprising 40000 patients (ROC AUC = 0.7)
- IMPROVE - BRS was externally validated in 1668 hospitalized acutely ill medical patients. A score ≥7 was associated with major and clinically important bleeding (OR, 2.6; [95% CI: 1.1–5.9]

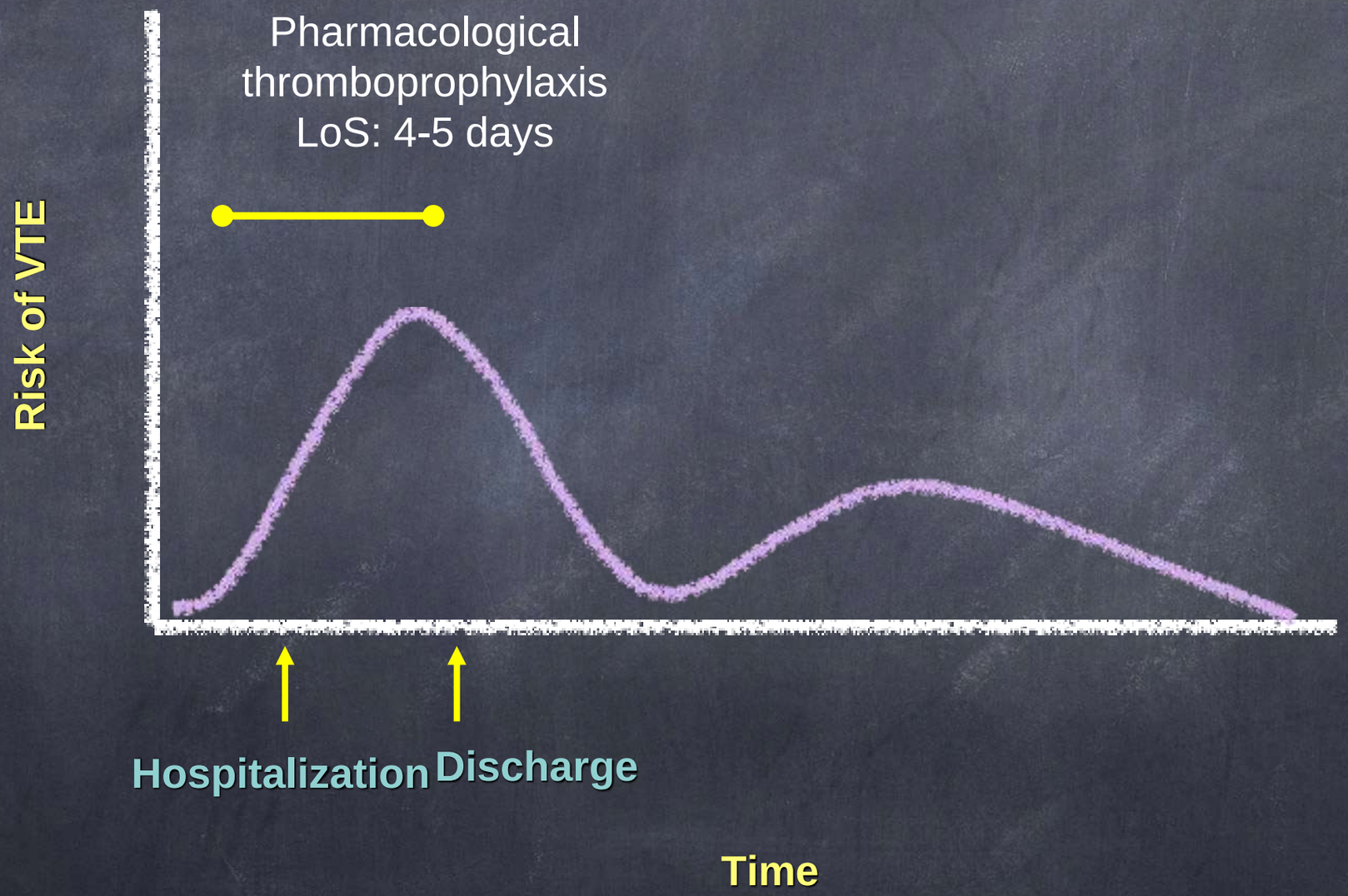
http://www.outcomes-umassmed.org/improve/risk_score/index.html

Time course of VTE risk in hospitalized acutely ill patients



LoS: length of stay

Time course of VTE risk in hospitalized acutely ill patients



LoS: length of stay

Failures of a universal VTE risk assessment strategy in medically ill patients

- Rates of symptomatic VTE vary across unselected medically ill populations
- Thromboprophylaxis with a standardised dose of heparin does not offer the same risk reduction for all patients groups
- Universal thromboprophylaxis without individualised risk assessment may not lead to reduced VTE in medically ill patients
- Beyond inpatient measures, even a 30-day duration of prophylaxis may not be optimal
- Less than 5% of medical inpatients receive post-discharge prophylaxis
- Need for strategies to reduce bleeding risk and improve net clinical outcomes

Alikhan R et al. Blood Coagul Fibrinolyis 2003; 14:341-346
Mahan et al. Thromb Res 2013; 132:520-6

VTE in the Acute Medically Ill

IMPROVE Study (n=15156)			
Days after Hospital Admission	In-Hospital VTE (n=79)	Post-discharge VTE (n=64)	All VTE (N=143)
1-7	42 (53%)	0	42 (29%)
8-30	32 (41%)	24 (38%)	56 (39%)
31-60	5 (6%)	23 (36%)	28 (20%)
61-91	0	17 (27%)	17 (12%)

Spyropoulos AC, et al. Chest 2011;140:706-14
Dobesh PP. Pharmacotherapy. 2009;29:943-53
Heit JA, et al. J Thromb Thrombolysis. 2016;41:3-14

Individualised thromboprophylaxis in hospitalized medically ill patients

Patient-related (predisposing) and Disease specific (triggering) Risk Factors

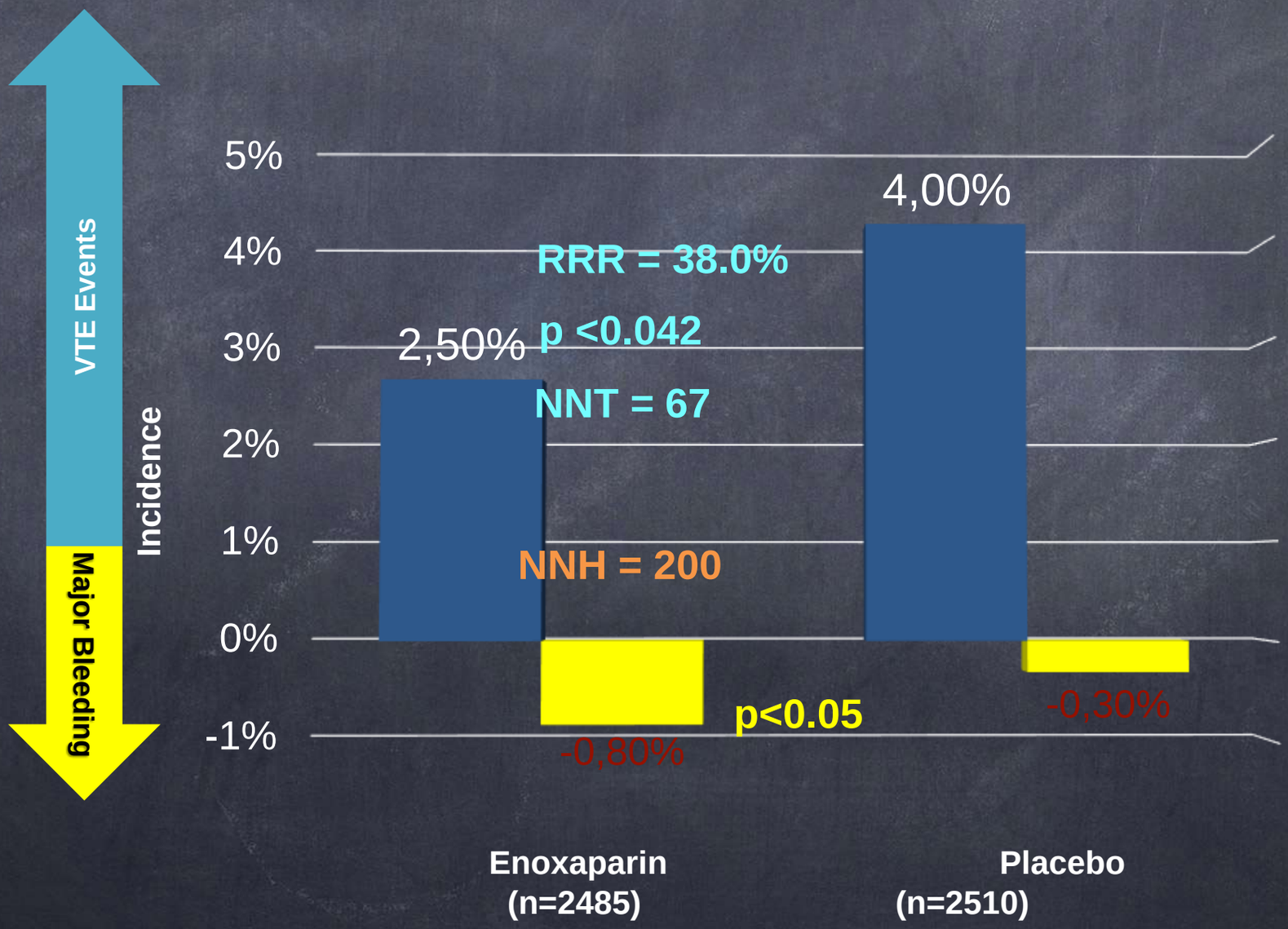
Patient-related (predisposing) and Disease specific (triggering) Risk Factors

Chronic medical illness (+/-predisposing risk factors)

Spyropoulos & Raskob Thromb Haemost. 2017;117:1662-70.

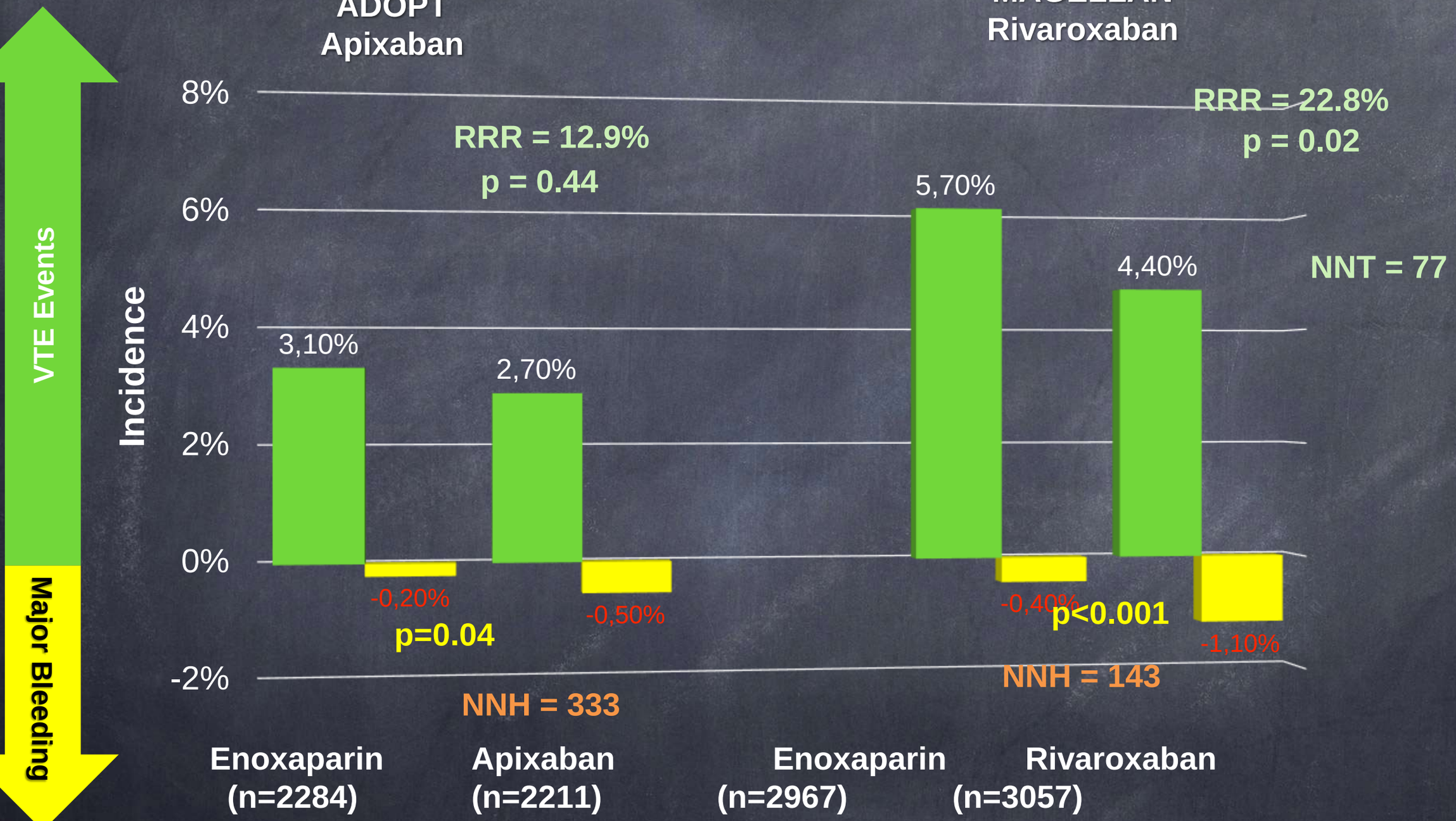
EXCLAIM: Extended-duration Enoxaparin Prophylaxis in High-risk Medical Patients

- Extended-duration enoxaparin 40mg SQ daily vs. placebo x 28-days
- All patients received enoxaparin 40mg daily for 10 + 4 days prior to randomization



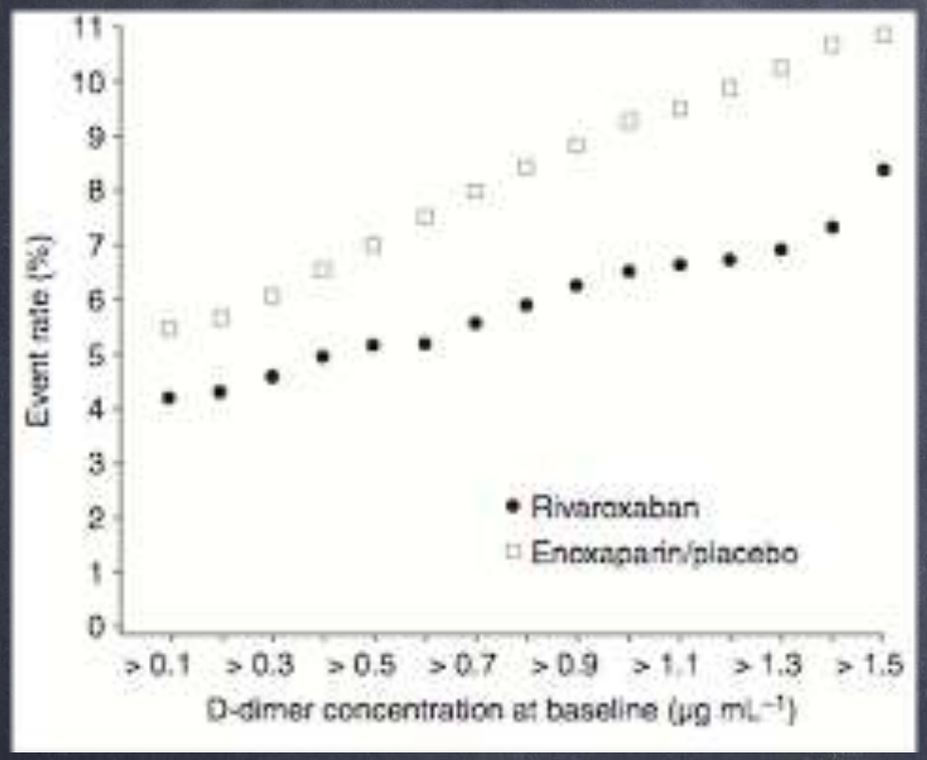
Hull RD, et al. Ann Intern Med. 2010;153:8-18

Extended duration of prophylaxis in medically ill



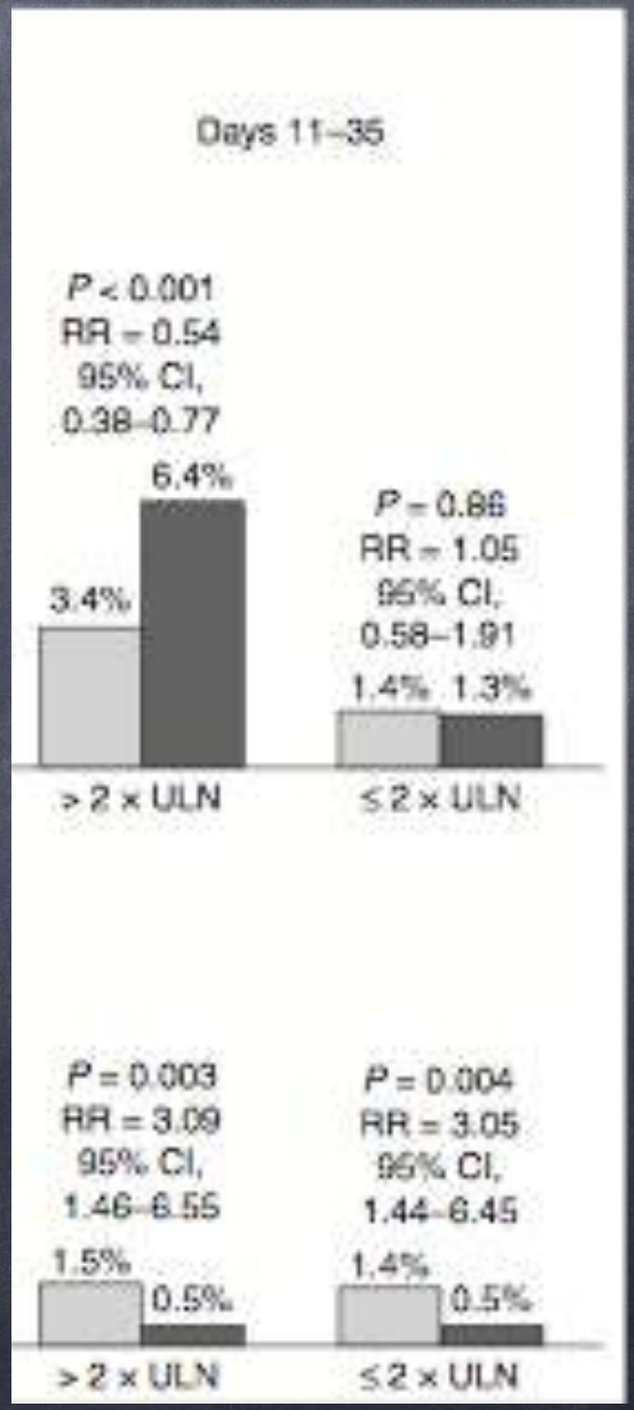
Goldhaber SZ, et al. N Engl J Med. 2011;365:2167-77
Cohen AT, et al. N Engl J Med. 2013;368:513-23

D-dimer as a predictor of venous thromboembolism in acutely ill, hospitalized patients: a subanalysis of the randomized controlled MAGELLAN trial (n=7581)



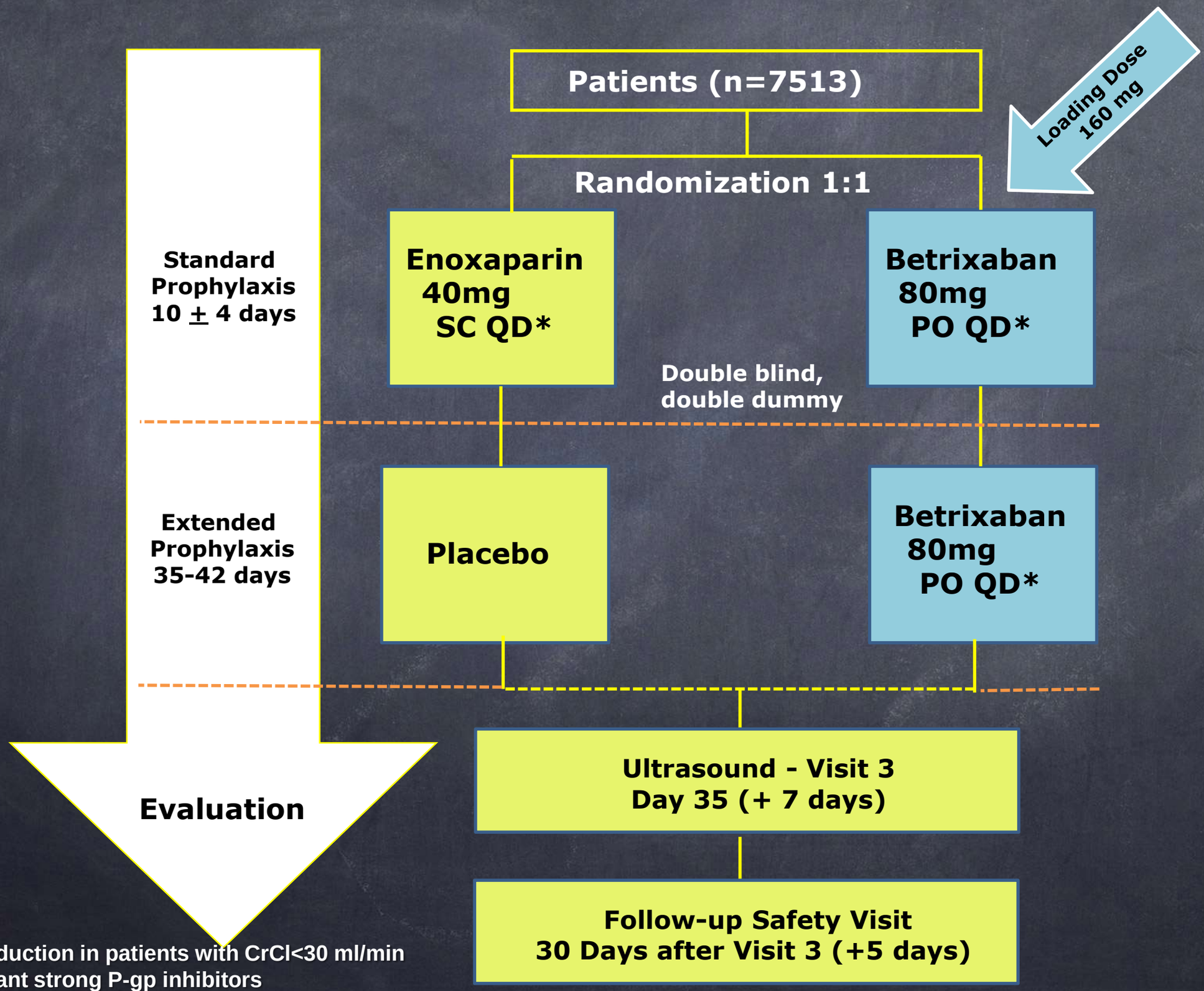
rivaroxaban

enoxaparin/placebo



Cohen et al J Thromb Haemost. 2014;12:479-87.

APEX – Study Design



*50% dose reduction in patients with CrCl<30 ml/min OR concomitant strong P-gp inhibitors

Cohen AT, et al. N Engl J Med. 2016; 375:534-44

APEX: key inclusion criteria

Inclusion Criteria

- Age/Risk Factors:
  - > 75 years old OR
  - 60 – 74 years with D-dimer > 2x ULN OR
  - 40 – 59 years with D-dimer > 2x ULN and a history of either VTE or cancer
- Hospitalized for one of the following acute presentation:
  1. Acute on chronic heart failure decompensation
  2. Acute on chronic respiratory failure
  3. Acute infection without septic shock
  4. Acute rheumatic disorders
  5. Acute ischemic stroke (w/ immobilization)
- Anticipated to be severely immobilized for at least 24 hours after randomization and expected to be severely or moderately immobile for > 3 days
- Anticipated length of hospitalization > 3 days

Cohen et al N engl J Med 2016; 375:534-44

Hierarchical Design

- Cohort 3

Overall Efficacy Population

- Cohort 2

D-Dimer ≥ 2x ULN OR Age ≥ 75

- Cohort 1

D-Dimer ≥ 2x ULN

If p≤0.05, then proceed

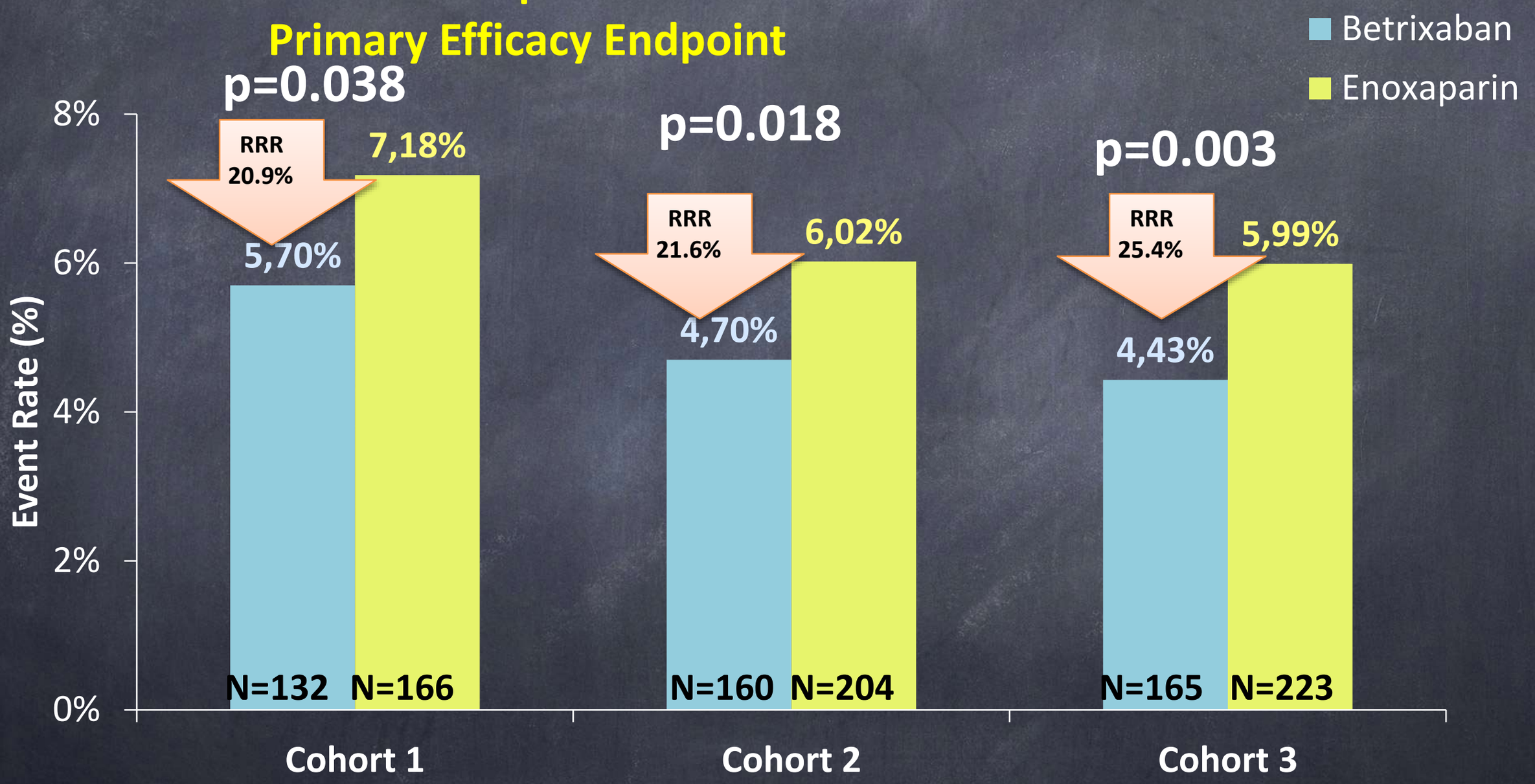
If p≤0.05, then proceed

If p>0.05, then further testing considered exploratory

If p>0.05, then further testing considered exploratory

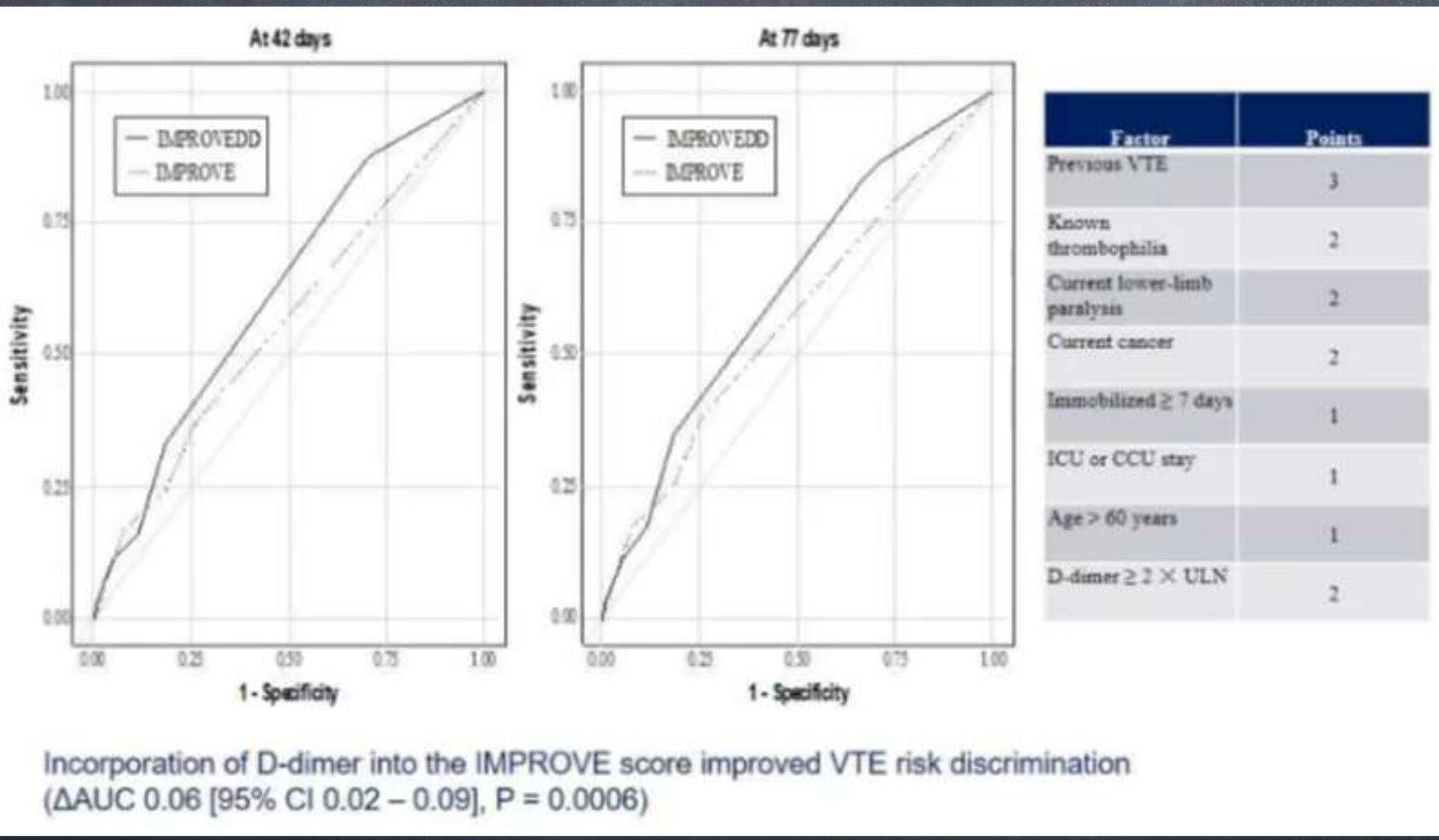
Cohen AT, et al. N Engl J Med. 2016; 375:534-44

APEX - Results



Gibson et. al. ISTH SSC 2016 – May 27, 2016

IMPROVEDD score
APEX substudy

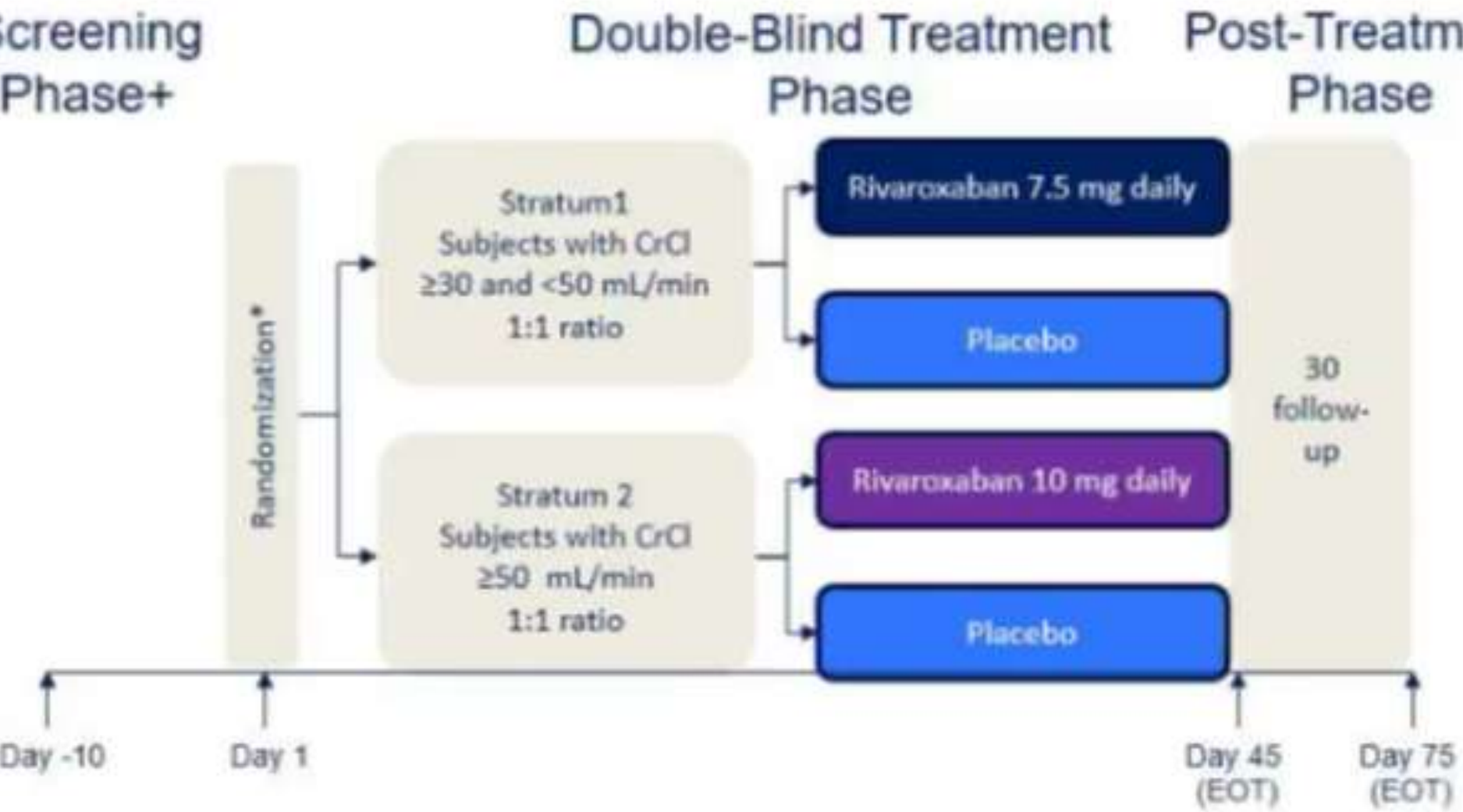


Factor	Points
Previous VTE	3
Known thrombophilia	2
Current lower-limb paralysis	2
Current cancer	2
Immobilized ≥ 7 days	1
ICU or CCU stay	1
Age > 60 years	1
D-dimer ≥ 2 × ULN	2

Incorporation of D-dimer into the IMPROVE score improved VTE risk discrimination
(ΔAUC 0.06 [95% CI 0.02 – 0.09], P = 0.0006)

Gibson et al TH Open 2017; 1:e56

MARINER Study Design



Primary Efficacy Endpoint: Composite of Symptomatic VTE or VTE-Related Death
Secondary Efficacy Endpoint: **VTE-Related Death** (Hierarchical Design)
Primary Safety Endpoint: Major Bleeding (ISTH Definition)

Estimated Sample Size – Event Driven Study

Sample size	Placebo	RRR	Events	Power for superiority	2 sided α
12,000	2.5%	40%	161	90%	5%

Raskob G, Spyropoulos AC, et al. *Thromb Haemost* 2016 Feb 4;115(6):1240-1248

Individualised thromboprophylaxis in hospitalised medically ill patients

Acute hospitalisation - Highest risk
30% - 65% of patients

Post-hospital Discharge - High risk period (up to 45 d)
10% - 25% of patients

Chronic medical illness - Low risk period
<5% of patients

VTE tied to immobility based on disease severity

Period of VTE risk tied to hospital discharge period

Chronic VTE risk tied to medical condition

RAM at admission

RAM at discharge

?

VTE Risk
IMPROVE ≥ 2
Padua ≥ 4
NHS Tool
Bleed Risk
IMPROVE < 7

UFH or LMWH
Fondaparinux
Betrixaban

High VTE Risk
IMPROVE ≥ 4
DD ≥ 2X ULN + IMPROVE 2 to 3
Age > 75 years, history of VTE, cancer or (IMPROVEDD ≥ 4)?

Betrixaban
or
Rivaroxaban?

Patient-related (predisposing) and Disease specific (triggering) Risk Factors

Patient-related (predisposing) and Disease specific (triggering) Risk Factors

Chronic medical illness (+/-predisposing risk factors)

Spyropoulos & Raskob Thromb Haemost. 2017;117:1662-70.

Take home messages

- Patients' "thromboembolic profile" heterogeneity is related to a large spectrum of underlying diseases, comorbidities and patients' intrinsic characteristics.
- The IMPROVE-BRS RAM is a robust risk model which has been externally validated in large cohorts of patients.
- The Geneva Risk Score is based on the concept of several comorbidities evaluation, and external validation results are promising.
- Incorporation of hypercoagulability biomarkers - D-Dimers - into the clinical RAM improve its capacity to identify medical patients at high risk for VTE who might benefit of long term post-discharge thromboprophylaxis