# Stop the Revolving Door: What You Need to Know About Postdischarge Prophylaxis for Acutely III Medical Patients

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### Agenda



#### **Presentation**

Understanding the Acutely III Medical Patient

Present Guidelines on VTE Prophylaxis for Hospitalized Medical Patients Postdischarge

Implications of the MAGELLAN and MARINER Trials

Strategies to Improve Uptake of Optimal VTE Prophylaxis

**Questions and Answers** 

Adjourn

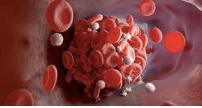




### **Acutely III Medical Patients**

- Mean age 70 years and immobilized for ≥3 days
- CHF (NYHA class III or IV)
- Acute respiratory failure/COPD exacerbation
- Acute infection without septic shock
- Stroke
- Acute rheumatic disorders including acute lumbar pain, sciatica, or vertebral compression (caused by osteoporosis or tumor)
- Acute arthritis of the legs or acute episode of rheumatoid arthritis in the legs
- Inflammatory bowel disease exacerbation

#### Discussion - Patient Case: James



- James is a 75-year-old man with a history of hypertension, hyperlipidemia, and class III heart failure who had been admitted and treated for CHF exacerbation
- After a hospital stay of 5 days, he is now ready to be discharged

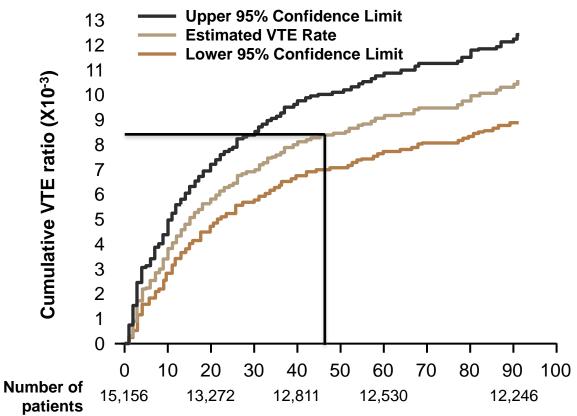
What risks for VTE does James have?



# VTE Risk Extends Beyond Hospitalization in Medical Patients

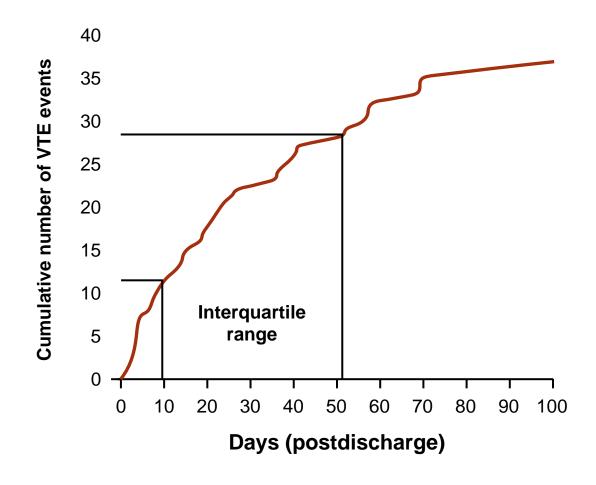


#### **Medically III Patients**



Time from admission (day 0) to VTE, or length of follow-up in days

#### **High-Risk Elderly Medical Patients**





In high-risk elderly medical patients, 80% of VTEs occurred within 6 weeks after discharge.

#### VTE Risk-Assessment Models



#### **Padua**

Baseline Features	Score
Active cancer	3
Previous VTE (with the exclusion of superficial vein thrombosis)	3
Reduced mobility	3
Already known thrombophilic condition	3
Recent (≤1 month) trauma and/or surgery	2
Elderly age (≥70 years)	1
Heart and/or respiratory failure	1
Acute myocardial infarction (MI) or ischemic stroke	1
Acute infection and/or rheumatic disorder	1
Obesity (BMI ≥30 kg/m²)	1
Ongoing hormonal treatment	1

#### **IMPROVE**

VTE Risk Factor	Points for the Risk Score
Previous VTE	3
Thrombophilia	2
Lower limb paralysis	2
Current cancer	2
ICU/CCU stay	1
Immobilization ≥7 days	1
Age >60 years	1

Low risk for VTE = score 0-1 points

Intermediate risk for VTE = 2-3 points

High risk for VTE = ≥4 points

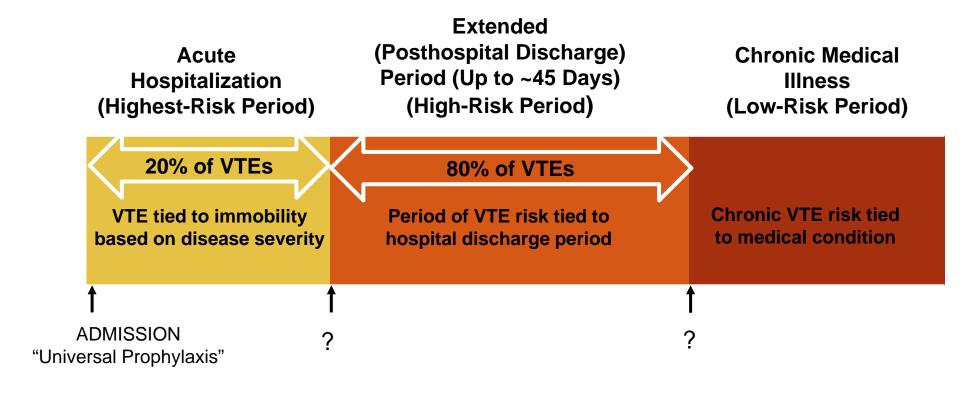
\*IMPROVEDD score with elevated Dd (2 points)

Low risk for VTE = score <4 points

High risk for VTE = ≥4 points

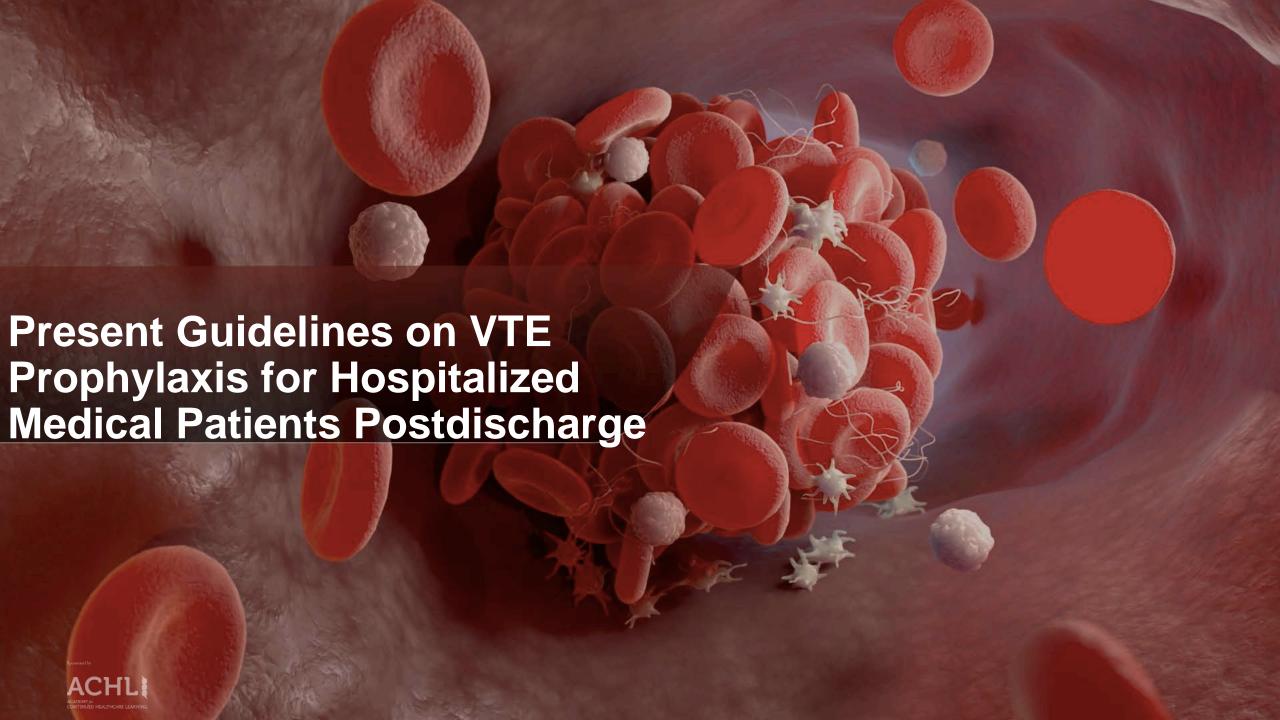
### Periods of VTE Risk in Medically III





- Patient-related (intrinsic) and disease-specific (extrinsic) VTE risk factors
- Patient-related (intrinsic) and disease-specific (extrinsic) VTE risk factors
- Chronic medical illness (+/- intrinsic risk factors)





# Antithrombotic Guideline Recommendations: ETP in Medical Patients

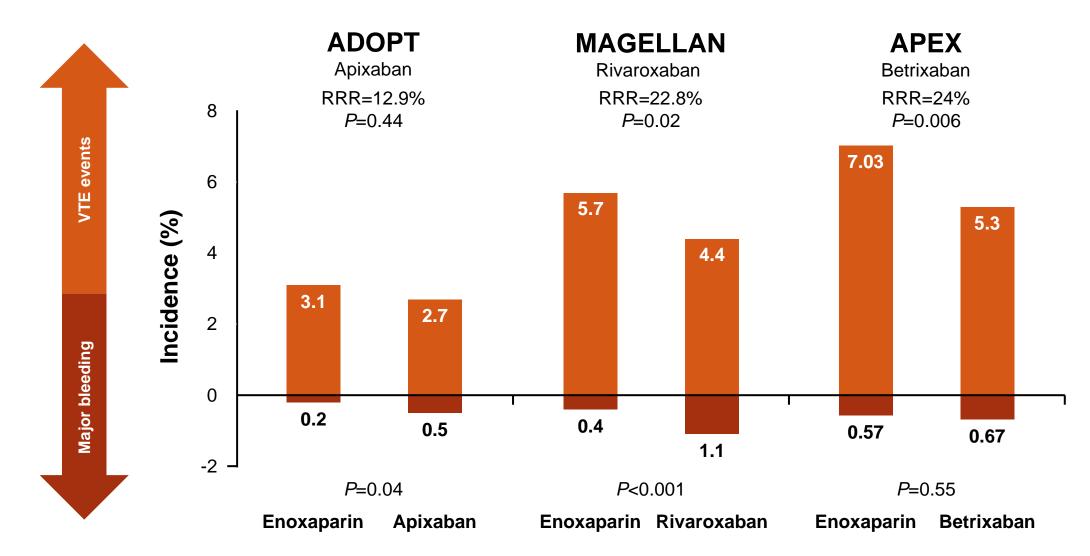


- For acutely ill hospitalized medical patients who receive an initial course of thromboprophylaxis, we suggest against extending the duration of thromboprophylaxis beyond the period of patient immobilization or acute hospital stay (grade 2B)<sup>1</sup>
- Extended duration of thromboprophylaxis may be considered in female patients, patients older than 75 years, or those with severe immobility, but should be determined on an individual basis<sup>2</sup>
- In acutely ill medical patients, [the panel] recommends inpatient over inpatient plus extended-duration outpatient VTE prophylaxis (strong recommendation, moderate certainty in the evidence of effects)<sup>3</sup>





# Comparison of Direct Oral Anticoagulant Trials of Extended Thromboprophylaxis in Acute Medically III Patients



### MARINER Trial – Results



	Rivaroxaban no. of patients/total no. (%)	Placebo no. of patients/total no. (%)	Hazard Ratio (95% CI)
Primary efficacy outcome Symptomatic VTE or VTE-related death	50/6007 (0.83)	66/6012 (1.10)	0.76 (0.52-1.09) <i>P</i> =0.14
Secondary efficacy outcomes			
VTE-related death	43/6007 (0.72)	46/6012 (0.77)	0.93 (0.62-1.42)
Symptomatic VTE	11/6007 (0.18)	25/6012 (0.42)	0.44 (0.22-0.89)
Symptomatic VTE or death from any cause	78/6007 (1.30)	107/6012 (1.78)	0.73 (0.54-0.97)
Symptomatic VTE, MI, nonhemorrhagic stroke, or CV death	94/6007 (1.56)	120/6012 (2.00)	0.78 (0.60-1.02)
Death from any cause	71/6007 (1.18)	89/6012 (1.48)	0.80 (0.58-1.09)
Safety outcome Major bleeding	17/5982 (0.28)	9/5980 (0.15)	1.88 (0.84-4.23)

### Meta Analysis of ETP in Medically III Patients



Trial	Year	Drug/Dose/Frequency			RR (95% CI)	EDT	No EDT
						n events/N to	tal
Symptomati	c VTE or \	/TE-related death					
EXCLAIM	2010	Enoxaparin 40 mg OD	<del></del>		0.20 (0.08, 0.53)	5/2485	25/2510
ADOPT	2011	Apixaban 2.5 mg BID		-	0.45 (0.19, 1.03)	8/3255	18/3273
MAGELLAN	2013	Rivaroxaban 10 mg OD	<b>⊢</b> ■	1	0.73 (0.50, 1.09)	42/2967	59/3057
APEX	2016	Betrixaban 80 mg OD	<b>⊢</b> ■-		0.65 (0.42, 0.99)	35/3721	54/3720
MARINER	2018	Rivaroxaban 10 mg OD		+	0.76 (0.53, 1.09)	50/6007	66/6012
Subtotal (I-sc	uared=47	.3%, <i>P</i> =0.108)	$\Diamond$		0.61 (0.44, 0.83)	140/18435	222/18572
Major bleedi	ng inclus	ive of fatal bleeding				•	
EXCLAIM	2010	Enoxaparin 40 mg OD			2.51 (1.21, 5.22)	25/2975	10/2988
ADOPT	2011	Apixaban 2.5 mg BID	ŀ		2.53 (0.98, 6.50)	15/3184	6/3217
MAGELLAN	2013	Rivaroxaban 10 mg OD		<b>├─■</b>	2.87 (1.60, 5.16)	43/3997	15/4001
APEX	2016	Betrixaban 80 mg OD			1.19 (0.67, 2.12)	25/3716	21/3716
MARINER	2018	Rivaroxaban 10 mg OD	-		1.89 (0.84, 4.23)	17/5982	9/5980
Subtotal (I-sc	uared=22	.8%, <i>P</i> =0.269)		$\Diamond$	2.04 (1.42, 2.91)	125/19854	61/19902
NOTE: Weigl	hts are fror	m random effects analysis			Reduction of	symptomatic	VTE and V

1.0

10

Favors No EDT --->

0.1

← Favors EDT

BID = twice a day; EDT = extended-duration thromboprophylaxis; OD = once a day; RR = risk ratio

by 40%
RR 0.61, 95% CI: 0.44-0.83, *P*=0.002

2-fold increase in major and fatal bleeding RR 2.04, 95% CI: 1.42-2.91, *P*<0.001

### Key Exclusion Criteria Applied to MAGELLAN



### 5 key risk factors for major bleeding were identified and applied as exclusion criteria to MAGELLAN

- 1. Active cancer
- 2. Dual antiplatelet therapy (DAPT) at baseline
- 3. Any bleeding within 3 months prior to or during hospitalization
- 4. Active gastroduodenal ulcer within 3 months or currently symptomatic
- 5. Bronchiectasis or pulmonary cavitation

80% of the MAGELLAN population had none of the above risk factors for bleeding.

#### **Exclusion Criteria**

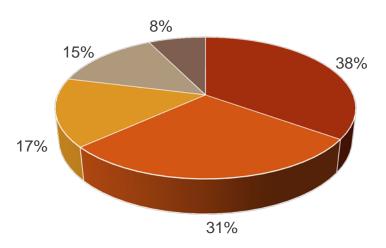
Active cancer

DAPT

Bleeding within 3 months

Active GI ulcer within 3 months

Bronchiectasis/pulm cavitation



Note: Some subjects had more than one exclusion

Safety, efficacy, and benefit-risk analysis were evaluated in this subpopulation.



### MARINER-Like Subpopulation From MAGELLAN Safety

MAGELLAN			MAGELLAN Subpopulation			
Safety Population <sup>*</sup>	Rivaroxaban N=3997	Enoxaparin N=4001	RR (95% CI)	Rivaroxaban N=3218	Enoxaparin N=3229	RR (95% CI)
Rivaroxaban-enoxa	parin/placebo treat	ment phase (day 1	to 35)*			
Clinically relevant bleeding	164 (4.1%)	67 (1.7%)	2.455 (1.854-3.251)	114 (3.5%)	49 (1.5%)	2.345 (1.685-3.264)
Major bleeding	43 (1.1%)	15 (0.4%)	2.867 (1.596-5.149)	22 (0.7%)	15 (0.5%)	1.480 (0.771-2.842)
Clinically relevant nonmajor bleeding	124 (3.1%)	52 (1.3%)		93 (2.9%)	34 (1.1%)	
Fatal bleeding	7 (0.2%	1 (<0.1%)		3 (<0.1%)	1 (<0.1%)	
Rivaroxaban-enoxa	parin treatment pha	ase (day 1 to 10)*				
Clinically relevant bleeding	111 (2.8%)	49 (1.2%)	2.272 (1.628-3.171)	80 (2.5%)	35 (1.1%)	2.306 (1.556-3.418)
Major bleeding	24 (0.6%)	11 (0.3%)	2.181 (1.070-4.445)	13 (0.4%)	11 (0.3%)	1.191 (0.535-2.651)
Clinically relevant nonmajor bleeding	88 (2.2%)	38 (0.9%)		67 (2.1%)	24 (0.7%)	
Fatal bleeding	5 (0.1%)	1 (<0.1%)		1 (<0.1%)	1 (<0.1%)	

The risk of major bleeding associated with rivaroxaban was reduced in both treatment phases in the MAGELLAN subpopulation.

<sup>\*</sup>On treatment + 2 days.

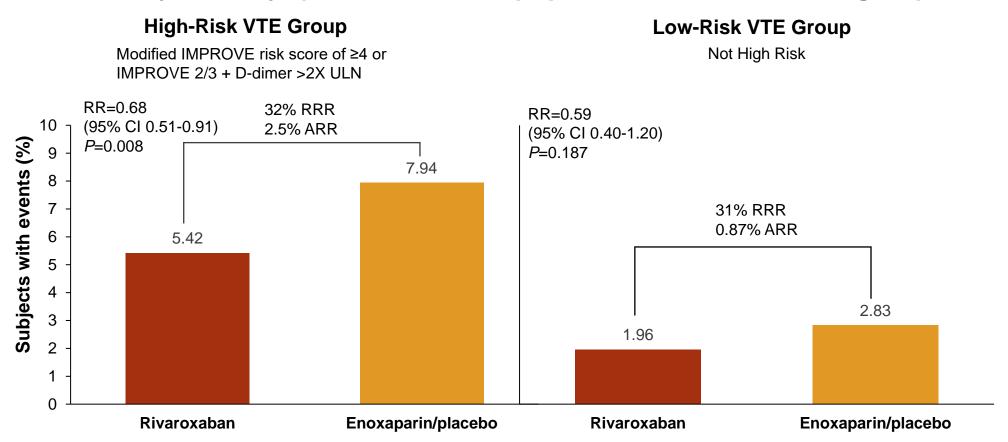


# IMPROVE + DD Subgroup in MAGELLAN Subpopulation



Predicts a nearly 3-fold higher VTE risk group for ET

#### Primary Efficacy\* (MAGELLAN Subpopulation - IMPROVE Subgroup, mITT D35)



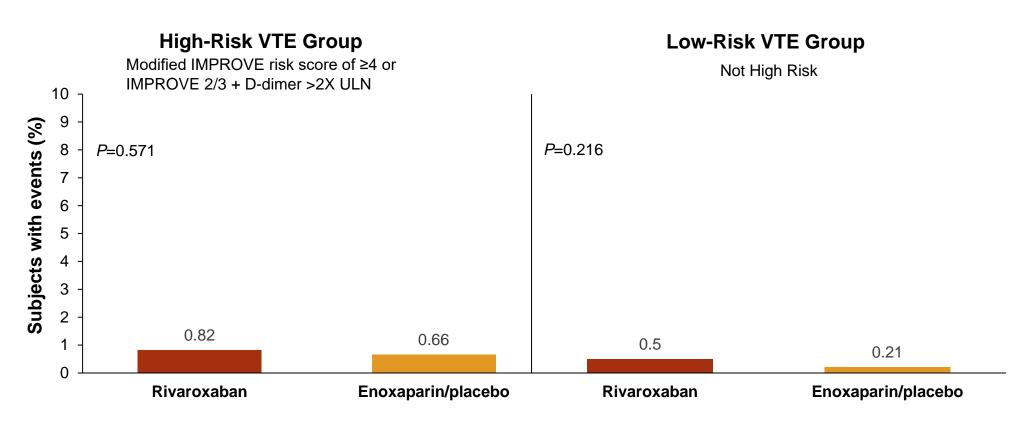
<sup>\*</sup>Primary efficacy = composite of symptomatic nonfatal PE, symptomatic DVT, VTE death, asymptomatic proximal lower DVT.

# IMPROVE + DD Subgroup in MAGELLAN Subpopulation (cont)



Predicts a nearly 3-fold higher VTE risk group for ET

#### ISTH Major Bleeding (MAGELLAN Subpopulation – IMPROVE Subgroup, Safety)

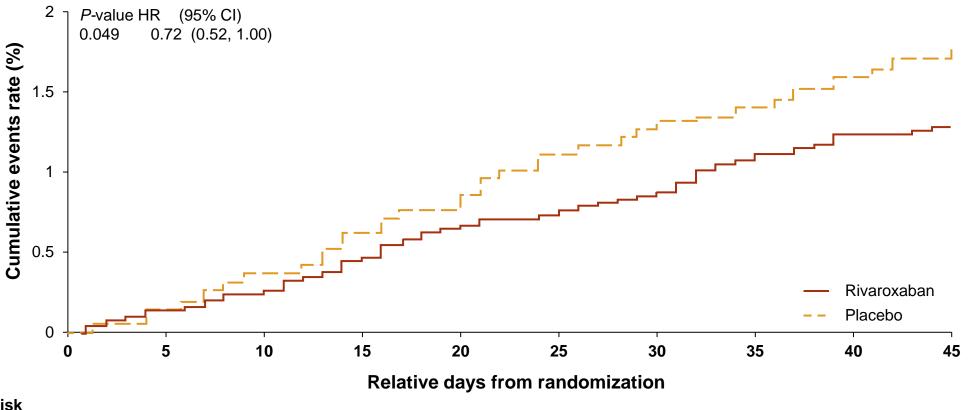


ISTH = International Society on Thrombosis and Haemostasis



# Rivaroxaban 10 mg Reduces Major and Fatal Vascular Events\*





#### Subjects at risk

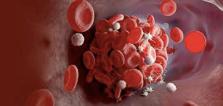
Rivaroxaban	4909	4895	4883	4873	4861	4852	4846	4833	4827	0
Placebo	4913	4896	4881	4866	4852	4835	4821	4815	4802	0

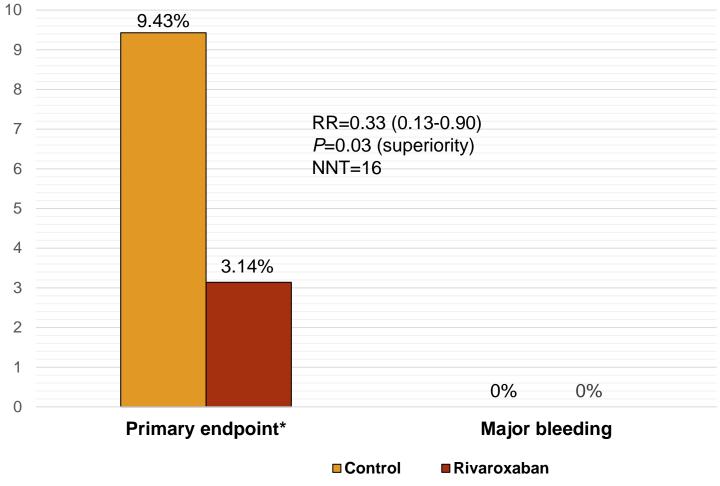
\*Symptomatic VTE, MI, stroke, CV death

Prevented 40 major or fatal vascular events (symptomatic VTE, MI, stroke, CV death) at the cost of almost no critical site/fatal bleeds per 10,000 patients = 24,000 patients (NNT 260/NNH 2000000)

HR = hazard ratio; NNT = number needed to treat; NNH = number needed to harm

### MICHELLE Trial With Extended Rivaroxaban in Hospitalized COVID-19 Patients

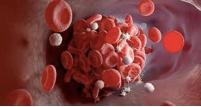




<sup>\*</sup>Composite of symptomatic VTE, VTE-related death, asymptomatic VTE (Doppler and Angio CT scan) and symptomatic ATE, MI, nonhemorrhagic stroke, (MALE), and CV death at day 35.



### **Discussion Topics**



How have the MAGELLAN, MARINER, and MICHELLE trials influenced your clinical practice?

Should we incorporate D-dimer testing into our care of patients with risk of VTE? Why or why not?





# VTE Pharmacy Intervention Management Program: Pharmacist Alert Using a VTE RAM



	Appropriate Prophyla:	xis	Preventable VTE		
2006 vs 2007	Improvement	<i>P</i> -value	Reduction	<i>P</i> -value	
	(95% LCL, UCL)		(95% LCL, UCL)		
Critical care	2.483 (1.668, 3.697)	0.0001	84% (98%,116%)	0.0699	
Surgical	1.582 (1.308, 1.914)	0.0001	89% (18%, 99%)	0.0313	
Medical	2.057 (1.504, 2.814)	0.0001	57% (85%, 123%)	0.1134	
Total discharges	1.839 (1.589, 2.129)	0.0001	74% (44%, 88%)	0.0006	

- Multifaceted intervention reduced incidence of preventable VTE by 74% (P<0.0006)
- Nonsignificant reduction from 10 to 4 "preventable" PEs



# Health Informatics Technology/Electronic Alerts and VTE RAMs in Hospitalized Patients



VTE Prophylaxis at Discharge		
Prophylactic Measures	Alert	Control
Any prophylaxis, n (%)	278 (22)	122 (9.7)
Mechanical prophylaxis, n (%)	46 (3.7)	31 (2.5)
Pneumatic compression device	6 (13)	2 (6.5)
Graduated compression stockings*	29 (63)	7 (23)
Inferior vena cava filter*	13 (28)	22 (71)
Pharmacologic prophylaxis, n (%)*	234 (19)	97 (7.7)
Unfractionated heparin	15 (6.4)	12 (12)
Enoxaparin	130 (56)	52 (54)
Warfarin*	123 (53)	29 (30)
Fondaparinux	8 (3.4)	3 (3.1)

Means are tested with 2-sample t test; medians are tested with the Mann-Whitney U test; proportions are tested with the chi-squared test or Fisher's exact test. Patients could receive more than one type of prophylaxis.  $P \ge 0.05$  unless otherwise noted.

\**P*<0.001.

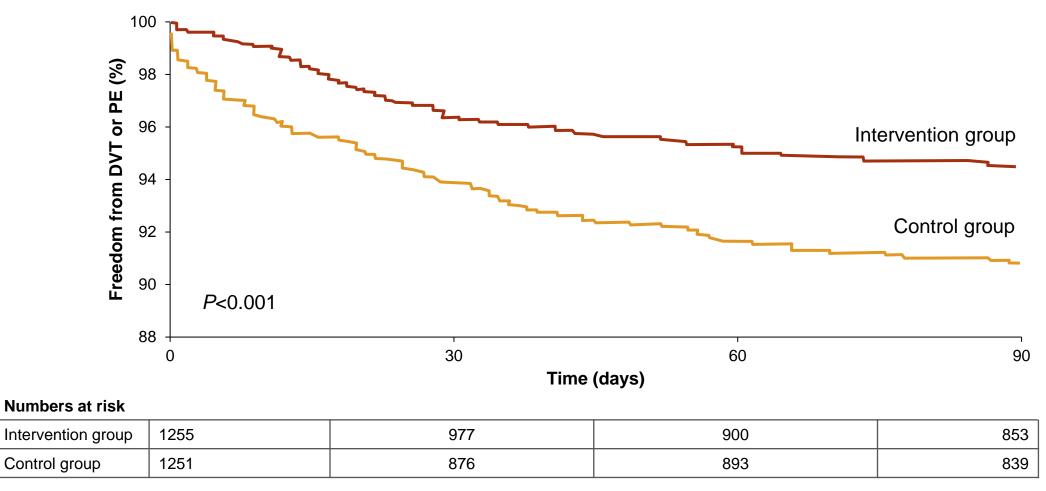
### Physician Alert at Discharge Using VTE RAM

12% increase in rate of pharmacologic prophylaxis (22% vs 9.7%, *P*<0.001)



# Health Informatics and Electronic Alerts to Prevent VTE



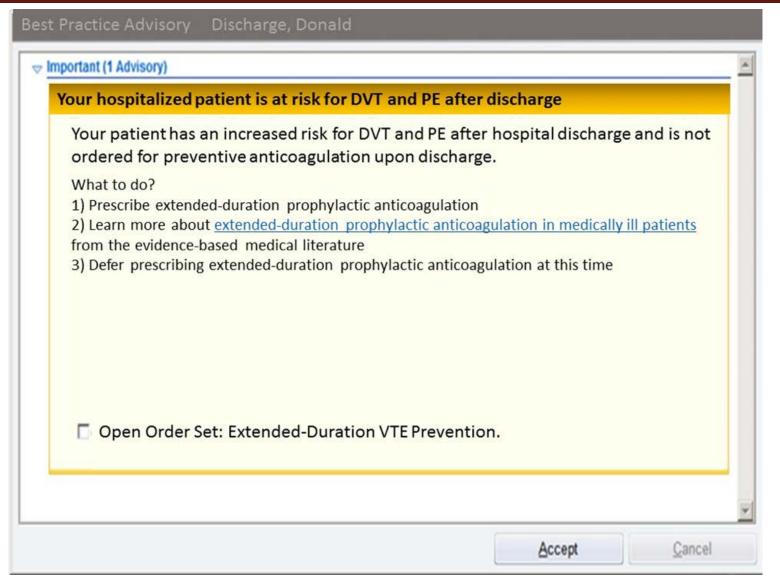


The computer alert system reduced the risk of VTE by 41% during the first 90 days following hospitalization.



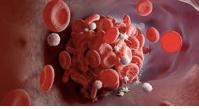
### Example of a Discharge Alert

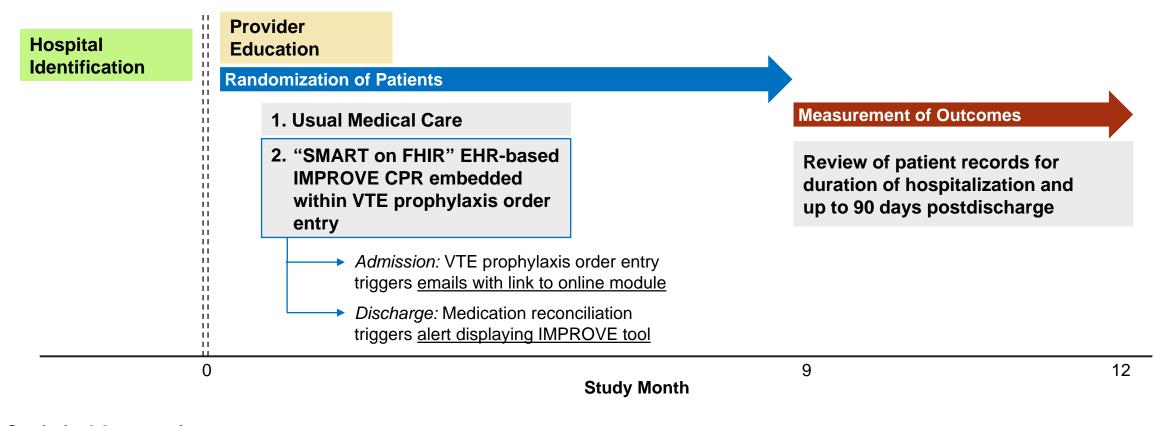






# IMPROVE-DD Study Flow Chart – Cluster Randomization (NT=4 Hospitals) NCT04768036





#### Statistical Assumptions

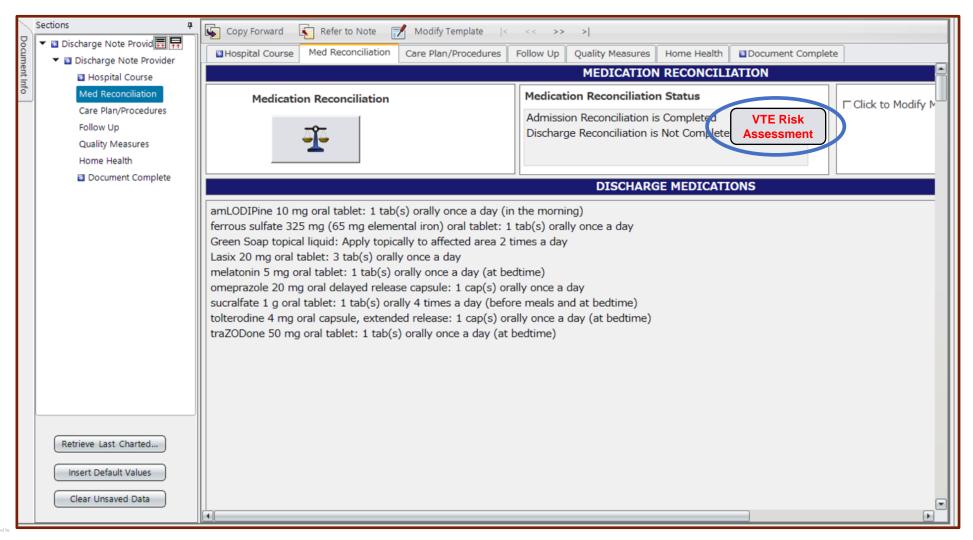
Based on previous published data from Northwell Health hospitals, assuming the VTE event rate to be 1.5% in the control group and 0.9% in the intervention group (a 40% RRR), a sample size of 10930 (5465 per cluster) is needed to achieve 80% power to detect the difference between the 2 groups at a significance level of 0.05 using a 2-sided Chi-squared test.



CPR = computerized patient record; EHR = electronic health record; FHIR = Fast Healthcare Interoperability Resource; RRR = relative risk reduction; SMART = Substitutable Medical Applications and Reusable Technologies; VTE = venous thromboembolism

# IMPROVE-DD Study Discharge VTE Risk Assessment



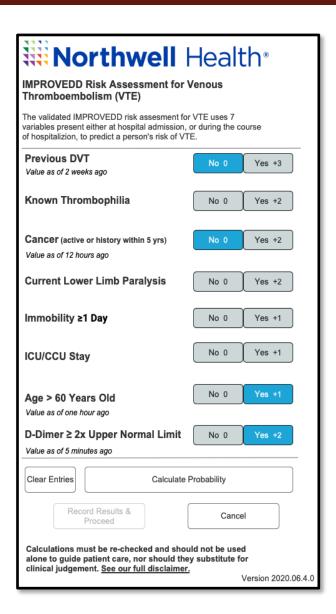


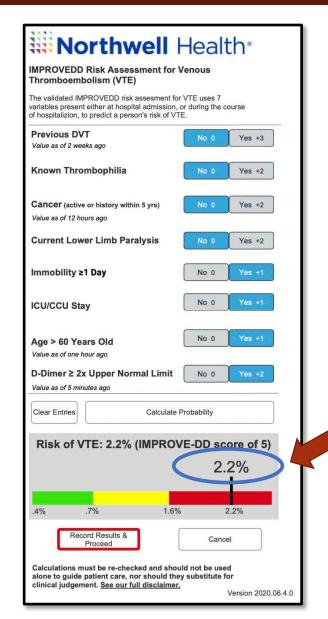


# IMPROVE-DD Study Discharge VTE Risk Assessment (cont)



VTE Risk Assessment





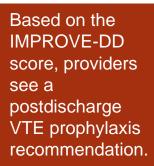
The 42-day VTE risk percentage will display.

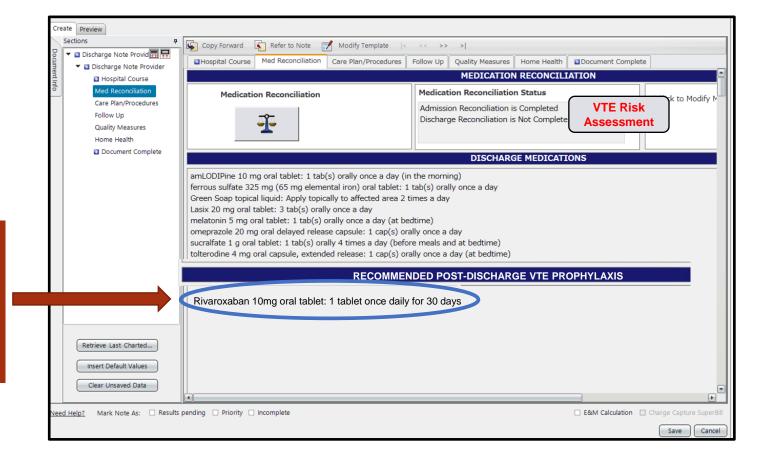
Providers select Record Results and Proceed.



# IMPROVE-DD Study Predischarge VTE Risk Assessment



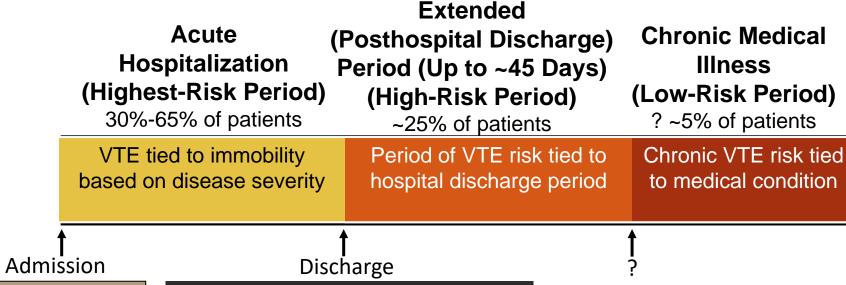






### New Paradigm in Medically III Thromboprophylaxis





VTE Risk
IMPROVE ≥2
Padua ≥4

Bleed Risk
IMPROVE <7

UFH or LMWH Fondaparinux (EU) Rivaroxaban (US) High VTE Risk

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

Rivaroxaban (US)

New paradigm in medically ill thromboprophylaxis: individualized (patient-level) risk adapted approach with clinical decision support/EHR interoperability



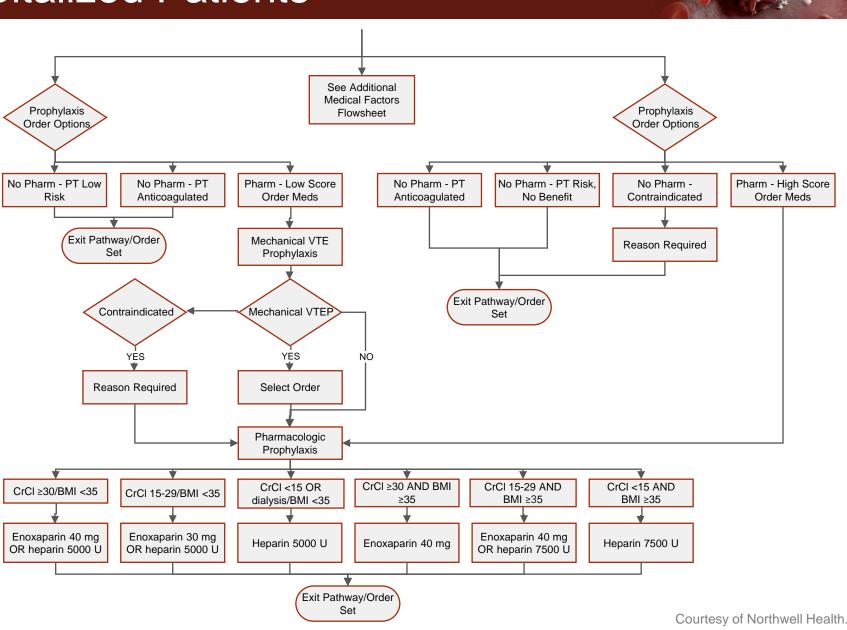
# Health Informatics Technology/Electronic Alerts and VTE RAMs in Hospitalized Patients



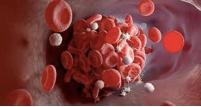
VTE RAM and HL7 and SMART on FHIR Standards (AEHR "agnostic")

AEHR = Academic Electronic Health Record; BMI = body mass index; CrCl = creatinine clearance; FHIR = Fast Healthcare Interoperability Resource; PT = patient; SMART = Substitutable Medical Applications, Reusable Technologies; VTEP = venous thromboembolism prophylaxis





### Discussion Topic



What tactics (if any) has your practice implemented to better ensure optimal VTE prophylaxis in these patients?

What tactics might and might not work in your clinical setting and why?



# Role of the Multidisciplinary Team With Ensuring Optimal Postdischarge Prophylaxis



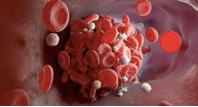
- Patient education
- Multidisciplinary clinical management programs
- Transitions of care
- Long-term care interventions

What are the implications for the hospitalist? Cardiologist? Other clinicians?

How do you work with your multidisciplinary team to ensure continuity of care?



#### Discussion - Patient Case: James



- James is a 75-year-old man with a history of hypertension, hyperlipidemia, and class III heart failure who had been admitted and treated for CHF exacerbation
- After a hospital stay of 5 days, he is now ready to be discharged
  - What strategies are you thinking about for James's postdischarge care and why?
  - How would you work with your multidisciplinary team to ensure optimal postdischarge care for James?





### Action Plan Discussion Topic



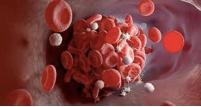
What have been the biggest hurdles for you to ensuring optimal VTE prophylaxis in acutely ill medical patients?

#### Discuss barriers related to:

- Patients
- Interdisciplinary team
- Health system (eg, formulary/insurance)
- Guidelines



### **Action Plan Discussion Topics**



- What changes to do you plan to make to better ensure optimal post-discharge VTE prophylaxis?
  - E.g. incorporation of nurse/pharmacist-led alerts or EHR alerts
- Which team members need to be involved?
- What resources do you need?
- What timelines/benchmarks do you have to be sure to implement these changes?



