#AHA22

Universal Electronic Health Record Clinical Decision Support for Prevention of Thromboembolism in Hospitalized Medically-Ill Patients: The IMPROVE-DD VTE Cluster Randomized Trial

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American Heart Association.

Disclosure Page – Alex C Spyropoulos, MD

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Scientific Advisory Board	ATLAS Group

Background

- **The majority of hospital-acquired venous thromboembolism (VTE) occurs in non-surgical (medical) inpatients, including COVID-19 patients**
  - The majority of VTE in this population occurs in the post-discharge period
  - Inpatient thromboprophylaxis reduces VTE by 50 – 60%
  - Extended post-discharge thromboprophylaxis reduces arterial thromboembolism (ATE) and VTE
- **Thromboprophylaxis for medically-ill patients during hospitalization and post-discharge remains underutilized**
  - Approximately 50% to 60% of at VTE risk patients receive thromboprophylaxis
  - Less than 4% of patients receive any post-discharge or extended thromboprophylaxis (25% are high VTE risk)
- **At a health system level, only electronic alerts incorporating VTE risk models or national health system initiatives have been shown to increase appropriate thromboprophylaxis and reduce symptomatic VTE**
  - Alerts are not interoperable across electronic health records (EHRs) and national programs are time and labor intensive, costly, and difficult to apply outside national health systems
- **Our health informatics group developed a novel universal platform integrating clinical decision support (CDS) into any EHR and demonstrated its effectiveness of increasing adoption of evidence-based practice**

Spyropoulos AC et al Thromb Haemost 2020; Hull R et al Clin Appl Thromb Haemost 2013; Mahan CE et al Thromb Res 2014; Kucher N et al NEJM 2005; Piazza G et al Am J Med 2013; Roberts LN et al Brit J Haematol 2017; McGinn T et al JAMA Intern Med 2013; Spyropoulos AC et al J Am Coll Cardiol 2020; Schulman S et al J Thromb Haemost 2022

Inpatient Thromboprophylaxis Trials in Medically Ill Patients

Average duration 7 – 14 days

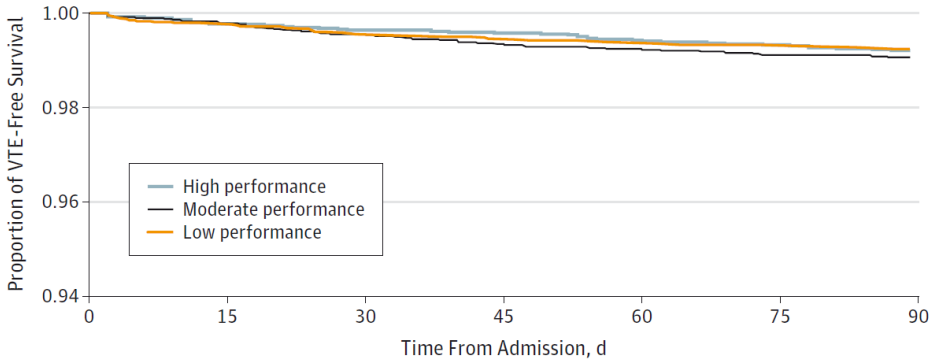
Study	RRR	Thromboprophylaxis	Patients with VTE (%)
MEDENOX[1] N=1102	**63%** p<0.001	Placebo Enoxaparin 40 mg daily	**14.9*** **5.5**
PREVENT[2] N=3706	**49%** p=0.0015	Placebo Dalteparin 5000 IU daily	**5.0*** **2.8**
ARTEMIS[3] N=849	**47%** p=0.029	Placebo Fonda 2.5 mg daily	**10.5†** **5.6**

***VTE at day 14; †VTE at day 15.**
RRR = relative risk reduction.

1. Samama MM, et al. *N Engl J Med*. 1999 2. Leizorovicz A, et al. *Circulation*. 2004 3. Cohen AT, et al. *BMJ*. 2006

No Difference in VTE-free survival by *in-Hospital only* VTE Prophylaxis Performance*

Figure 3. Kaplan-Meier Survival Curve Showing Estimates of Venous Thromboembolism (VTE)–Free Survival by Hospital VTE Prophylaxis Performance



No. (%) at risk							
High performance	5514 (12)	5299 (7)	5220 (3)	5157 (8)	5103 (5)	5072 (24)	5037
Moderate performance	7897 (15)	7623 (19)	7507 (16)	7407 (8)	7338 (9)	7287 (28)	7256
Low performance	7383 (17)	7140 (16)	7032 (6)	6950 (6)	6880 (3)	6841 (24)	6806

*Quality improvement project in 35 Michigan hospitals – rates of pharmacologic thromboprophylaxis in high-, moderate-, and low-performing tertiles was 85.8%, 72.6%, and 55.5%

Flanders SA et al *JAMA Intern Med* 2014

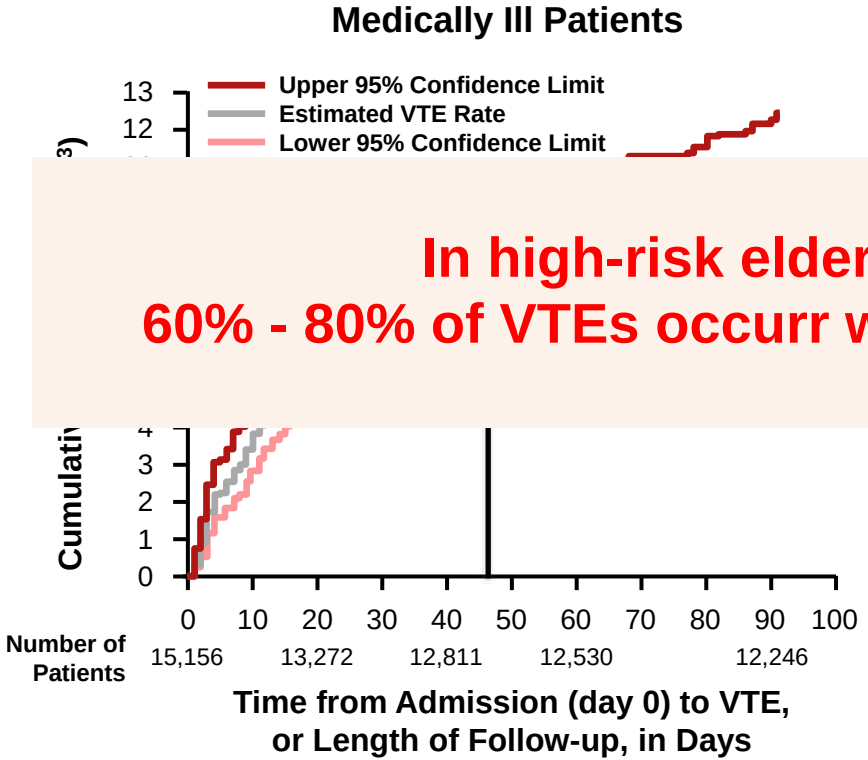
Duration of Inpatient Thromboprophylaxis Has Shortened Compared with Older Hospital Practice Patterns

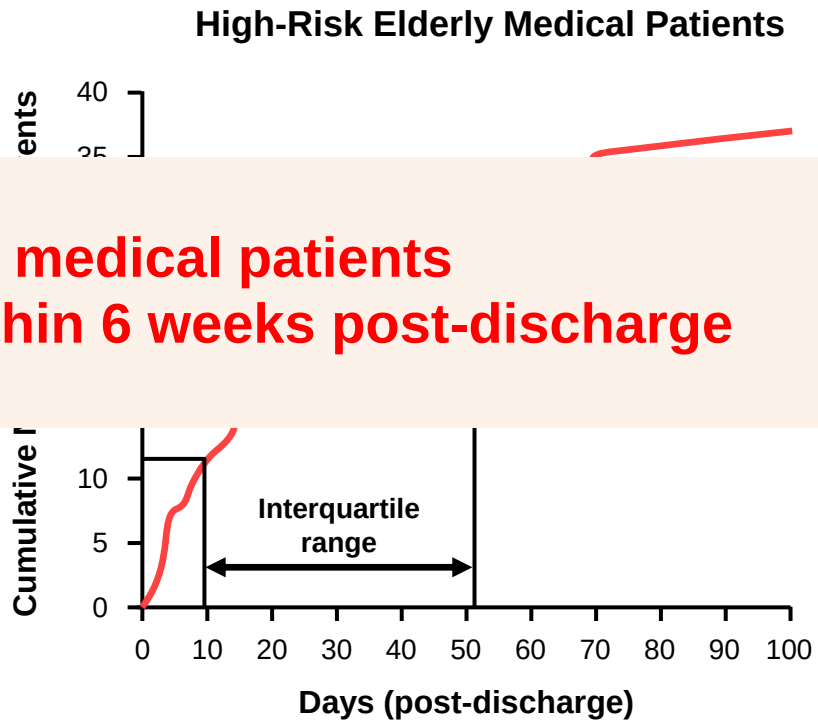
- The shortened hospital length of stay (~4-5 days in the US) and other countries has dampened treatment effects of in-hospital thromboprophylaxis
  - Disease burden of VTE is shifting to the outpatient setting with shorter hospital stays
- Less than 4% of hospitalized medical patients receive post-hospital discharge thromboprophylaxis

Mahan C, et al. *Thromb Res.* 2013;132(5):520-6.

Flanders S et al JAMA Intern Med 2014;174:1577-84

VTE Risk Extends Beyond Hospitalization in Medical Patients

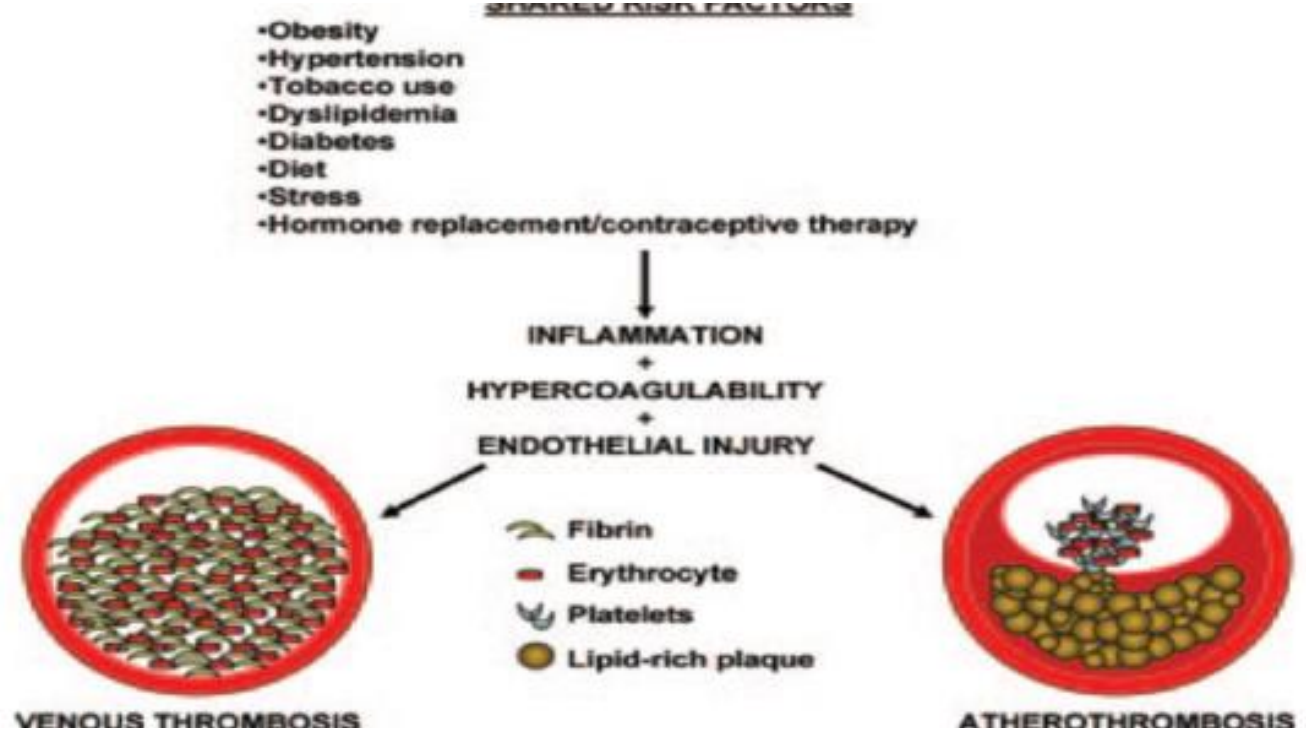




In high-risk elderly medical patients
60% - 80% of VTEs occurr within 6 weeks post-discharge

Spyropoulos AC, et al. *Chest*. 2011
Hull RD et al. *Clin Appl Thromb Hemost*. 2013
Amin A et al *Journal of Hospital Medicine* 2012

The Relationship between Venous Thrombosis and Atherothrombosis



Prandoni P et al *N Engl J Med* 2003

Betrixaban reduces all cause stroke and TIA in APEX

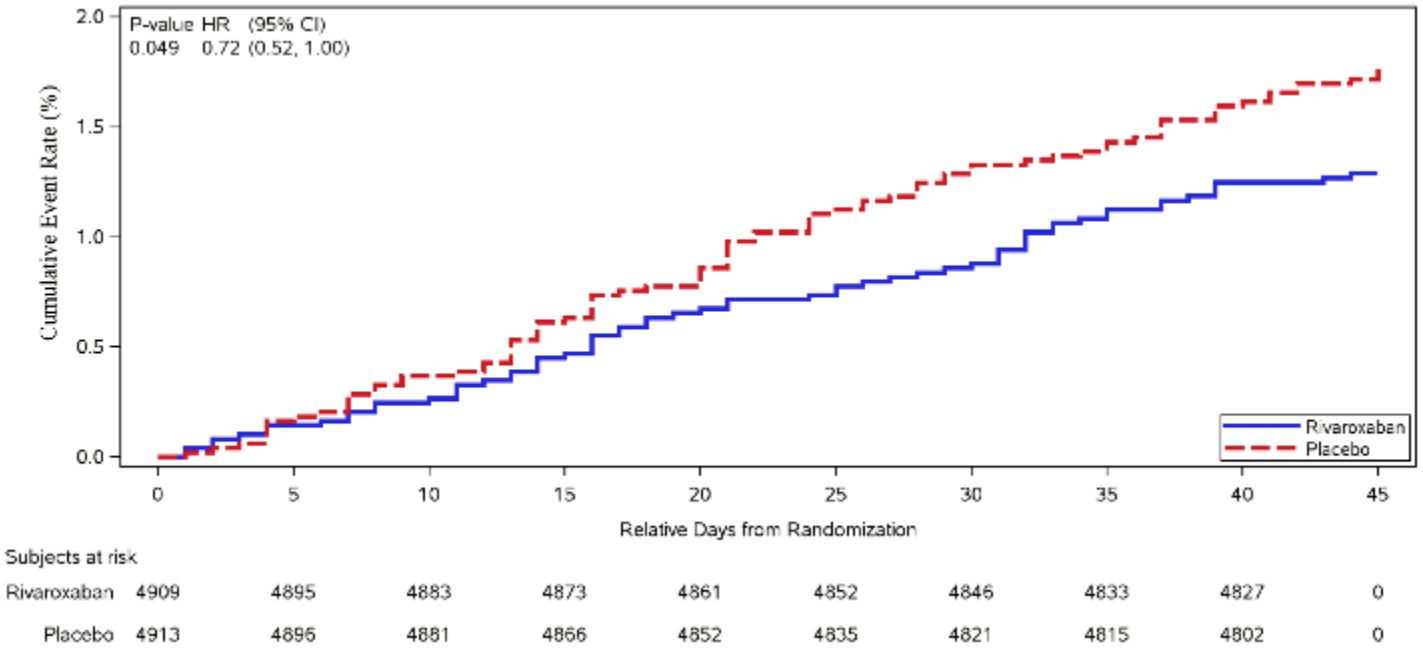
Stroke Type	Betrixaban (n=3716), n (%)	Enoxaparin/Placebo (n=3716), n (%)	RR (95% CI)	*P* Value
All-cause stroke	20 (0.54)	36 (0.97)	0.56 (0.32–0.96)	0.032*
Ischemic	18 (0.48)	34 (0.91)	0.53 (0.30–0.94)	0.026*
Hemorrhagic	1 (0.03)	1 (0.03)	1.00 (0.06–15.98)	1.00
Uncertain type	1 (0.03)	1 (0.03)	1.00 (0.06–15.98)	1.00
TIA	4 (0.11)	5 (0.13)	0.80 (0.22–2.98)	0.74
All-cause stroke or TIA	24 (0.65)	41 (1.10)	0.59 (0.35–0.97)	0.034*

CI indicates confidence interval; RR, relative risk; and TIA, transient ischemic attack. The modified intent-to-treat population includes all subjects who received at least 1 dose of study drug. The analysis was conducted with actual treatment. The *P* values were calculated with the Cochran-Mantel-Haenszel method.

*Significant.

Gibson M et al *Circulation* 2017

Rivaroxaban 10 mg reduces major and fatal vascular events*



***symptomatic VTE, MI, stroke, CV death**

Spyropoulos AC et al *J Am Coll Cardiol* 2020

CV, cardiovascular; MI, myocardial infarction; NNT, number needed to treat; NNH, number needed to harm; PE, pulmonary embolism; VTE, venous thromboembolism.

Objectives

Study hypothesis: Use of a universal, platform agnostic EHR-embedded VTE risk model with integrated CDS would 1) increase rates of appropriate thromboprophylaxis, and subsequently 2) reduce thromboembolism, compared to usual medical care in hospitalized medically-ill patients

Primary Outcome:

- The IMPROVE-DD VTE CDS would improve rate of appropriate thromboprophylaxis for at-risk medical inpatients (score of 2-3) and high risk medical inpatients (score of ≥ 4)

Secondary Outcomes:

- Rates of thromboembolism including:
  - VTE through 30 days post discharge
  - ATE through 30 days post discharge
  - Total TE (VTE + ATE) through 30 days post discharge
- Major bleeding through 30 days post-discharge
- All-cause mortality through 30 days post-discharge
- All-cause readmission or death through 30 days post-discharge
- VTE readmission and death through 30 days post-discharge

Other Outcomes:

- Outcomes with follow-up through 90 days post-discharge
  - VTE
  - ATE
  - Total TE
  - VTE readmission and death

Key Inclusion and Exclusion Criteria

Key inclusion criteria:

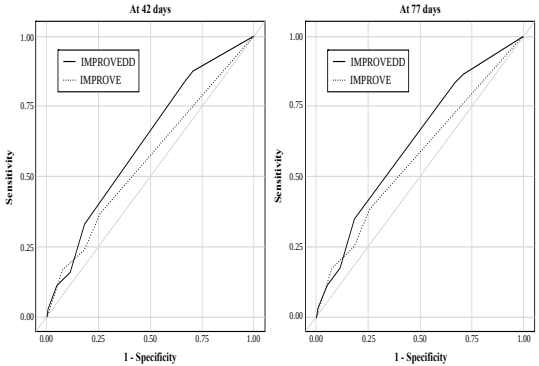
- **Age > 60 years**
- **Hospitalized with one of 5 medical illness diagnoses:**
  - Congestive heart failure exacerbation
  - Acute respiratory insufficiency (including chronic obstructive ling disease and asthma)
  - Acute infectious disease (including COVID-19)
  - Acute inflammatory disease (including rheumatic disease)
  - Acute stroke with or without paralysis
- **Additional risk factors as per the IMPROVE-DD VTE CDS**:
  - Known thrombophilia
  - Intensive care unit (ICU)/coronary care unit (CCU) stay
  - Lower extremity paralysis
  - Cancer
  - Immobilization*
  - Previous VTE history
  - Elevated Dd (> 2 X ULN)

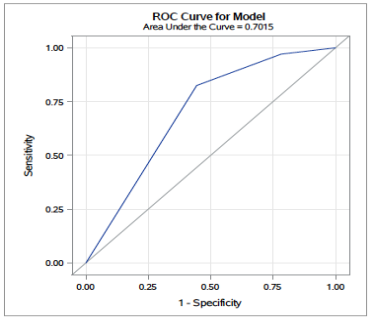
Key exclusion criteria:

- **Home use of anticoagulant medications**
- **In-hospital therapeutic anticoagulants within 24 hours of admission**
- **History of atrial fibrillation**

*It was assumed that all hospitalized patients had immobility criteria

IMPROVE-DD VTE score – derivation and validation



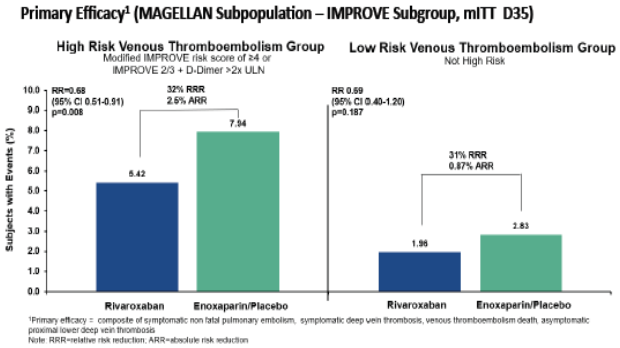


Incorporation of D-dimer into the IMPROVE score improved VTE risk discrimination

(ΔAUC 0.06 [95% CI 0.02 – 0.09], P = 0.0006)

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

Table of IMPROVE_DD by vte			
	vte		
IMPROVE_DD	No	Yes	Total
0-1, Low Risk	1988 99.60	8 0.40	1996
2-3, Moderate Risk	3093 98.72	40 1.28	3133
4-12, High Risk	4052 94.72	226 5.28	4278
Total	9133	274	9407



Gibson M et al 2017 TH Open 2017
Spyropoulos AC et al Res Pract Thromb Haemost 2021
Spyropoulos AC et al TH Open 2020

Appropriate Thromboprophylaxis

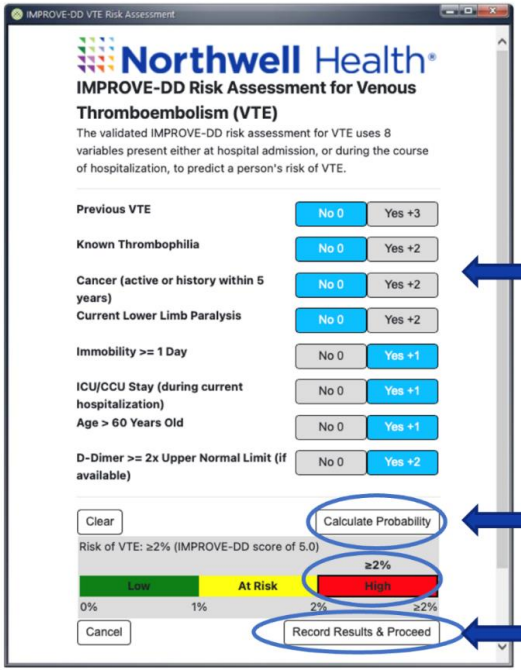
Inpatient: (IMPROVE-DD score of ≥ 2)
UFH SQ any dose (i.e. 5000U BID/TID, 7500U BID/TID, 10,000U BID)
Fondaparinux 2.5mg QD
Enoxaparin SQ <=80 mg QD (i.e. 40mg QD or BID; 30mg QD/BID)
Rivaroxaban 10mg QD

Post-Discharge (ONLY FOR IMPROVE-DD SCORE OF ≥ 4):
UFH SQ any dose (i.e. 5000U BID/TID, 7500U BID/TID, 10,000U BID)
Fondaparinux 2.5mg QD
Enoxaparin SQ <=80 mg QD (i.e. 40mg QD or BID; 30mg QD/BID)
Rivaroxaban 10mg QD

COVID-19 Inpatient: (IMPROVE-DD score of ≥ 2)
UFH SQ any dose (i.e. 5000U BID/TID, 7500U BID/TID, 10,000U BID)
IV UFH continuous
Enoxaparin any dose
Fondaparinux any dose
Rivaroxaban 10mg QD

COVID-19 Post Discharge: (IMPROVE-DD SCORE OF ≥ 4 or DD > 2X ULN)
SQ UFH any dose (i.e. 5000U BID/TID, 7500U BID/TID, 10,000U BID)
Enoxaparin <=80mg QD
Rivaroxaban 10mg QD
Apixaban 2.5mg BID
Fondaparinux 2.5mg QD

Clinical Decision Support Design and Provider Interface of IMPROVE-DD VTE risk tool

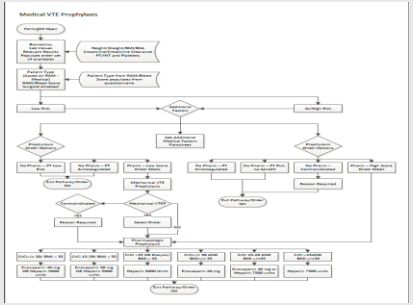


When the IMPROVE-DD tool launches, the answers to the yes/no risk factors are pre-populated based on existing patient-specific data in the EHR.

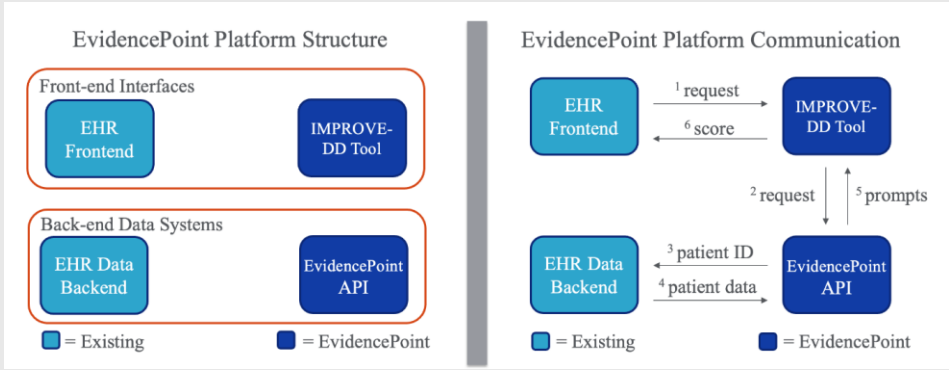
The user is able to manually adjust the individual risk factors as needed.

When the user clicks "Calculate Probably", the IMPROVE-DD score and 3-month VTE risk percentage are displayed.

When the user clicks "Record Results & Proceed", the tool closes, the IMPROVE-DD score is written to the EHR, and an appropriate prophylaxis recommendation is displayed in the EHR.

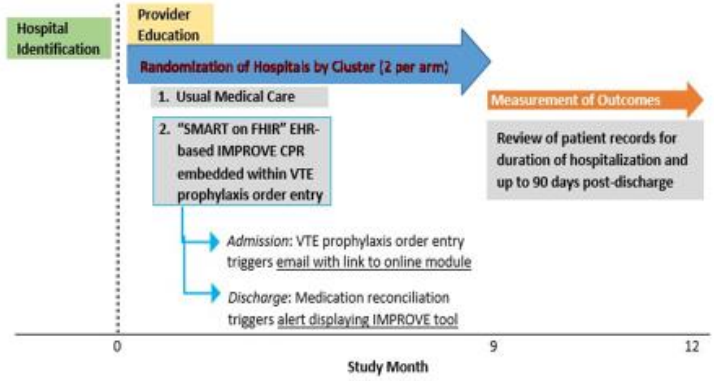


EHR-agnostic, "SMART on FHIR" like CDS platform that can be adapted into any EHR



Study Design

Clustered Randomized Trial at Level of Hospital (4 academic tertiary hospitals)

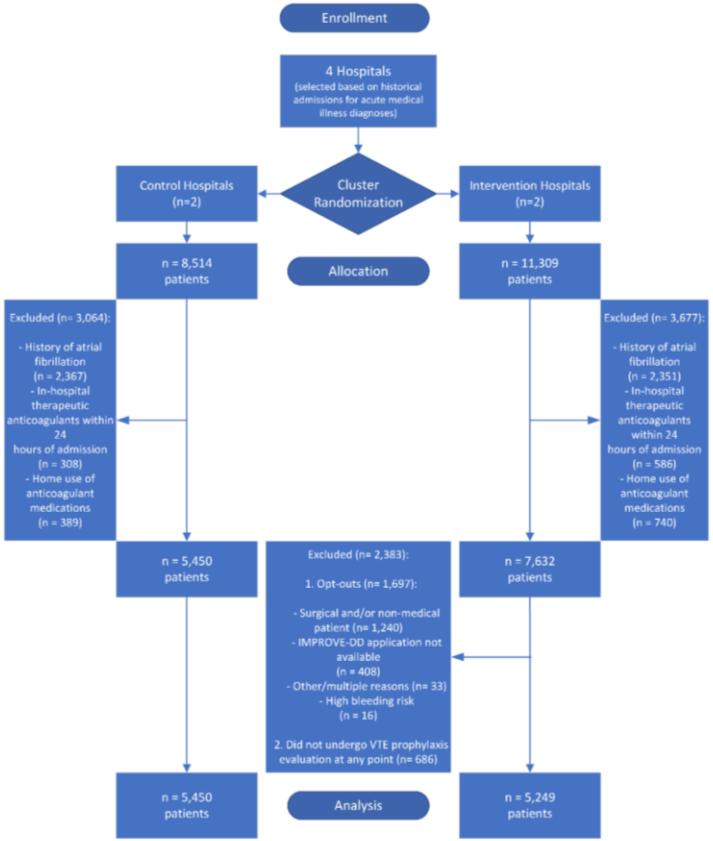


December 21, 2020 to January 21, 2022

Statistical Analysis

- Sample size calculation was based on the rate of VTE (secondary endpoint)
  - Assuming a VTE rate of 1.5% in the control group and 0.9% in the intervention group (40% RRR) a sample size of 5324 per group would achieve 80% power (Chi-square test $\alpha = 0.05$)
- For the primary outcome of rate of appropriate thromboprophylaxis we estimated a rate of 55% in the control based on historical data and assuming an 11% absolute increase in appropriate thromboprophylaxis in the intervention group the calculated sample size would achieve 99% power to detect a significant difference.
- These calculations account for the Design Effect (DE=1.03) introduced by the intra-cluster correlation inherent in the cluster design

CONSORT Flow Diagram



RESULTS

Patient Characteristics

Characteristic	Intervention Group (N = 5249)	Control Group (N = 5450)
Mean age in years (SD)	75.1 (9.9)	74.3 (9.6)
Gender, no. (%)		
Male	2492 (47.5%)	2522 (46.3%)
Female	2757 (52.5%)	2928 (53.7%)
Race, no. (%)		
Caucasian/White	2340 (44.6%)	3743 (68.7%)
African American//Black	1075 (20.5%)	607 (11.1%)
Asian	812 (15.5%)	205 (3.8%)
Other/Multiracial/Unknown	1022 (19.5%)	895 (16.4%)
Ethnicity, no. (%)		
Not Hispanic or Latino	4629 (88.2%)	4725 (86.7%)
Hispanic or Latino	475 (9.0%)	575 (10.6%)
Declined/Unknown	145 (2.8%)	150 (2.8%)
BMI, mean (SD)	27.5 (7.8)	28.2 (8.0)
Acute Medical Illness, no. (%)		
Acute infectious disease/sepsis	2920 (53.6%)	3277 (62.4%)
- COVID-19	1355 (25.8%)	1097 (20.1%)
Heart failure	441 (8.4%)	338 (6.2%)
Severe Lung Disease	1014 (19.3%)	1086 (19.9%)
Ischemic stroke	410 (7.8%)	514 (9.4%)
Inflammatory disease including rheumatic diseases	107 (2.0%)	592 (10.9%)
IMPROVE-DD VTE Risk Factors, no. (%)		
Previous VTE	365 (7.0%)	542 (9.9%)
Known Thrombophilia	44 (0.8%)	43 (0.8%)
Cancer active or history within 5 years	1316 (25.3%)	1543 (28.3%)
Current Lower Limb Paralysis	102 (2.0%)	220 (4.0%)
ICU/CCU Stay during current hospitalization	206 (4.0%)	484 (8.9%)
D Dimer >= 2x Upper Normal Limit if available	588 (11.3%)	751 (13.8%)

IMPROVE-DD VTE risk score, no. (%)	Inttervention Group (N=5249)	Control Group (N=5450)
2 or 3	3183 (60.6%)	2992 (54.9%)
4 or more	2066 (39.4%)	2458 (45.1%)
D-dimer Mean, ng/mL (SD),	998.7 (2861.6)	1196.3 (3994.4)
Hemoglobin Mean, g/dL (SD)	12.1 (2.2)	12.2 (2.1)
Platelet count Mean, K/uL (SD)	242.3 (106.2)	238.1 (96.6)
Creatinine Serum Mean, mg/dL (SD)	1.4 (1.4)	1.3 (1.2)
Mean duration of index hospitalization — days (SD)	8.1 (8.8)	6 (6.6)
Use of Medications, no (%)		
Corticosteroids	2024 (38.6%)	1961 (36.0%)
Antivirals (Remdesivir)	952 (18.1%)	530 (9.7%)
Antiplatelets	2484 (47.3%)	2752 (50.5%)
Aspirin	2345 (44.7%)	2606 (47.8%)
P2Y12 inhibitors*	788 (15%)	886 (16.3%)
Cilostazol	30 (0.6%)	32 (0.6%)

Anticoagulants	Intervention Group (N=5249)	Control Group (N=5450)
Inpatient Thromboprophylaxis, no (%)	4582 (87.3%)	4354 (79.9%)
Enoxaparin	2659 (50.7%)	2656 (48.7%)
UFH	1787 (34.0%)	1609 (29.5%)
Rivaroxaban	48 (0.9%)	14 (0.3%)
Apixaban	88 (1.7%)	75 (1.4%)
Post-Discharge Thromboprophylaxis, no (%)	481 (9.2%)	372 (6.9%)
Enoxaparin	17 (0.3%)	36 (0.7%)
UFH	1 (0.0%)	3 (0.1%)
Rivaroxaban	355 (6.8%)	140 (2.6%)
Apixaban	108 (2.1%)	193 (3.5%)

Primary Outcome

Outcome	Intervention Group (N=5249)	Control Group (N= 5450)	Odds Ratio (95% CI)	P-Value
	No of patients/total no (%)			
Appropriate in-hospital thromboprophylaxis	4203/5249 (80.1%)	3951/5450 (72.5%)	1.52 (95% CI, 1.39 - 1.67)	p<0.001
Appropriate at – discharge extended thromboprophylaxis	331/2433 (13.6%)	195/2588 (7.5%)	1.93 (95% CI, 1.60 - 2.33)	p<0.001

Secondary Outcomes at 30 days

Secondary outcomes	Intervention Group	Control Group	Odds ratio (95% CI)	P-value
VTE	141/5249 (2.7%)	182/5450 (3.3%)	0.80 (95% CI, 0.64 – 1.00)	p=0.048
ATE	13/5249 (0.25%)	38/5450 (0.70%)	0.35 (95% CI: 0.19 - 0.67)	p<0.001
Total TE**	152/5249 (2.9%)	219/5450 (4.0%)	0.71 (95% CI, 0.58 - 0.88)	p=0.002
Major Bleeding	8/5249 (0.15%)	12/5450 (0.22%)	0.69 (95% CI, 0.28 – 1.69)	p=0.42
All-cause mortality	478/5249 (9.1%)	383/5450 (7.0%)	1.32 (95% CI, 1.15 -1.53)	p<0.001
Other secondary outcomes				
All-cause readmission/ death	845/4882 (17.3%)	922/5142 (17.9%)	0.96 (95% CI, 0.86 – 1.06)	p=0.41
VTE-related readmission/ death	136/4882 (2.8%)	114/5142 (2.2%)	1.26 (95% CI, 0.98 – 1.62)	p=0.07

*VTE + ATE

Limitations

- Few number of clusters (n=4)
- Could not ascertain continuous adherence of thromboprophylaxis
- In the intervention group, exclusion of opt-out users
  - Consistent with an impact analysis of the tool's application/performance characteristics

Conclusions

IMPROVE-DD VTE Cluster Randomized Trial

- **Our multicenter cluster randomized trial of hospitalized medically ill patients is the first to show that a universal EHR-integrated CDS tool using a validated VTE risk model (IMPROVE-DD) had a high adoption rate (77%), significantly increased rates of in-hospital appropriate thromboprophylaxis (including at discharge extended thromboprophylaxis), and significantly reduced major thromboembolic events without an increase in major bleeding at 30 days post-discharge compared to usual medical care**
  - An approximate 50% increase in appropriate thromboprophylaxis (72.5% vs 80.1%)
  - An approximate 2-fold increase in appropriate at discharge extended thromboprophylaxis (7.5% vs 13.6%)
  - A 20% reduction in VTE, 65% reduction in ATE, and 29% reduction in total TE (VTE + ATE: 4.0% vs 2.9%)
- **The relatively high baseline rate of appropriate in-hospital and at discharge thromboprophylaxis in academic control hospitals (72.5% and 7.5%) suggests potential for greater benefit in non-academic/community/rural hospitals**
- **30-day mortality was higher in the intervention hospital group**

Acknowledgements

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THANK YOU

American Heart Association.

Scientific Sessions

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