Thromboprophylaxis in critically ill patients; for whom and how

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VTE in medical inpatients

- **Half of VTE** events occur due to hospital admission for surgery (24%) or medical illness (22%)
- Risk factors for VTE in hospital include **cancer, older age, prior VTE, central lines, immobility**
- **40%** of hospitalized patients have 3 or more risk factors for VTE
- Increase in thrombosis risk in medical inpatients persists 45 to 60 days after discharge

Blood Adv (2018) 2 (22): 3198–3225

American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and non-hospitalized medical patients

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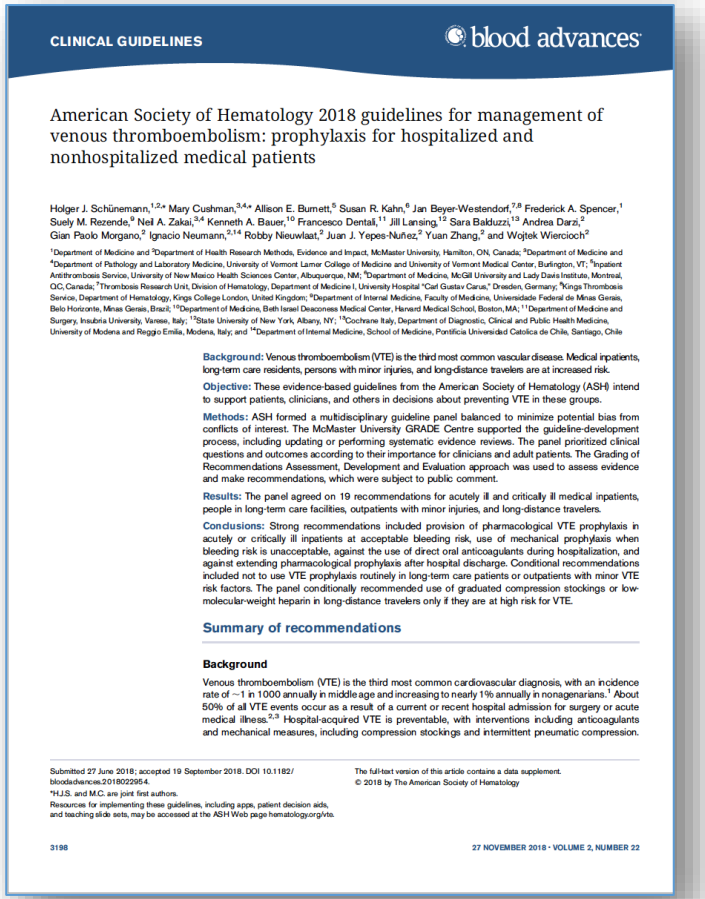

CLINICAL GUIDELINES

blood advances

American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients

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Background: Venous thromboembolism (VTE) is the third most common vascular disease. Medical inpatients, long-term care residents, persons with minor injuries, and long-distance travelers are at increased risk.

Objective: These evidence-based guidelines from the American Society of Hematology (ASH) intend to support patients, clinicians, and others in decisions about preventing VTE in these groups.

Methods: ASH formed a multidisciplinary guideline panel balanced to minimize potential bias from conflicts of interest. The McMaster University GRADE Centre supported the guideline-development process, including updating or performing systematic evidence reviews. The panel prioritized clinical questions and outcomes according to their importance for clinicians and adult patients. The Grading of Recommendations Assessment, Development and Evaluation approach was used to assess evidence and make recommendations, which were subject to public comment.

Results: The panel agreed on 19 recommendations for acutely ill and critically ill medical inpatients, people in long-term care facilities, outpatients with minor injuries, and long-distance travelers.

Conclusions: Strong recommendations included provision of pharmacological VTE prophylaxis in acutely or critically ill inpatients at acceptable bleeding risk, use of mechanical prophylaxis when bleeding risk is unacceptable, against the use of direct oral anticoagulants during hospitalization, and against extending pharmacological prophylaxis after hospital discharge. Conditional recommendations included not to use VTE prophylaxis routinely in long-term care patients or outpatients with minor VTE risk factors. The panel conditionally recommended use of graduated compression stockings or low-molecular-weight heparin in long-distance travelers only if they are at high risk for VTE.

Summary of recommendations

Background

Venous thromboembolism (VTE) is the third most common cardiovascular diagnosis, with an incidence rate of ~ 1 in 1000 annually in middle age and increasing to nearly 1% annually in nonagenarians.[1] About 50% of all VTE events occur as a result of a current or recent hospital admission for surgery or acute medical illness.[2,3] Hospital-acquired VTE is preventable, with interventions including anticoagulants and mechanical measures, including compression stockings and intermittent pneumatic compression.

Submitted 27 June 2018; accepted 19 September 2018. DOI 10.1182/bloodadvances.2018022954.

*H.J.S. and M.C. are joint first authors.

Resources for implementing these guidelines, including apps, patient decision aids, and teaching slide sets, may be accessed at the ASH Web page hematology.org/vte.

The full-text version of this article contains a data supplement.

Acutely or Critically ill medical patients: Pharmacological vs None

- Recommends using UFH or LMWH (strong, moderate)
- Suggests using LMWH over UFH (conditional, moderate)

	Outcomes	Relative effect: RR (95% CI)	Anticipated absolute effects (95% CI)	
			Risk with UFH	Risk difference with LMWH
⇨	🔴 Mortality	**0.90** (0.75 to 1.08)	243 per 1,000	**24 fewer deaths per 1,000** (61 fewer to 19 more)
	🔴 PE	**0.80** (0.44 to 1.46)	11 per 1,000	**2 fewer PE per 1,000** (6 fewer to 5 more)
	🟠 Symptomatic proximal DVT	**0.87** (0.60 to 1.25)	25 per 1,000	**3 fewer DVT per 1,000** (10 fewer to 6 more)
⇨	🟠 Major bleeding	**0.98** (0.76 to 1.27)	53 per 1,000	**1 fewer bleeds per 1,000** (13 fewer to 14 more)
⇨	🟠 Heparin-induced thrombocytopenia	**0.42** (0.15 to 1.18)	6 per 1,000	**4 fewer episodes per 1,000** (5 fewer to 1 more)

Quality of Evidence (GRADE): Low 🔴 Moderate 🟠 Strong 🟢

Blood Adv (2018) 2 (22): 3198–3225

Acute or Critically ill medical patients: Mechanical vs Pharmacological

- Suggests pharmacological VTE prophylaxis over mechanical prophylaxis (conditional, very low)

Outcomes	Relative effect: RR (95% CI)	Anticipated absolute effects (95% CI)	
		Risk with pharmacologic prophylaxis	Risk difference with mechanical prophylaxis
Mortality	**0.95** (0.42 to 1.13)	18 per 1,000	**1 fewer death per 1,000** (11 fewer to 21 more)
PE	**1.54** (0.48 to 4.93)	1 per 1,000	**1 more PE per 1,000** (1 fewer to 4 more)
Symptomatic proximal DVT	**2.20** (0.22 to 22.09)	2 per 1,000	**2 more DVT per 1,000** (1 fewer to 38 more)
Major bleeding	**0.87** (0.25 to 3.08)	28 per 1,000	**4 fewer bleeds per 1,000** (21 fewer to 58 more)

Quality of Evidence (GRADE): Low Moderate Strong

Blood Adv (2018) 2 (22): 3198–3225

Acute or Critically ill medical patients: Mechanical vs Combination

- Suggest pharmacological or mechanical prophylaxis alone over combination (conditional, very low)

Outcomes	Relative effect: RR (95% CI)	Anticipated absolute effects (95% CI)	
		Risk with pharmacologic prophylaxis alone	Risk difference with combined prophylaxis
Mortality	**0.50** (0.05 to 5.30)	8 per 1,000	**4 fewer deaths per 1,000** (8 fewer to 34 more)
PE	**0.35** (0.05 to 2.22)	1 per 1,000	**1 fewer PE per 1,000** (1 fewer to 1 more)
Symptomatic proximal DVT	**0.13** (0.04 to 0.40)	2 per 1,000	**2 fewer DVT per 1,000** (2 fewer to 1 fewer)
Major bleeding	**2.83** (0.30 to 26.70)	28 per 1,000	**51 more bleeds per 1,000** (20 fewer to 720 more)

Quality of Evidence (GRADE): Low Moderate Strong

Blood Adv (2018) 2 (22): 3198–3225

Acute or Critically ill medical patients: Mechanical vs none

In whom do not receive pharmacological prophylaxis, suggest using mechanical VTE prophylaxis over no prophylaxis (conditional, moderate)

Blood Adv (2018) 2 (22): 3198–3225

Acutely ill hospitalized medical patients: LMWH vs DOACs

- Recommends using LMWH over DOACs (strong, moderate)

Outcomes	Relative effect: RR (95% CI)	Anticipated absolute effects (95% CI)	
		Risk with prophylactic LMWH	Risk difference with any DOAC
● Mortality	**0.64** (0.21 to 1.98)	1 per 1,000	**0 fewer deaths per 1,000** (1 fewer to 1 more)
● PE	**1.01** (0.29 to 3.53)	1 per 1,000	**0 fewer PE per 1,000** (1 fewer to 3 more)
● Symptomatic proximal DVT	**1.03** (0.34 to 3.08)	2 per 1,000	**0 fewer DVT per 1,000** (1 fewer to 4 more)
● Major bleeding	**1.70** (1.02 to 2.82)	2 per 1,000	**2 more bleeds per 1,000** (0 fewer to 4 more)*

Quality of Evidence (GRADE): Low ● Moderate ● Strong ●

Blood Adv (2018) 2 (22): 3198–3225

Acutely ill hospitalized medical patients: need for extended therapy?

- Recommends inpatients over inpatients plus extended duration outpatient VTE prophylaxis (strong, moderate)

Outcomes	Relative effect: RR (95% CI)	Anticipated absolute effects (95% CI)
		Risk difference with extended prophylaxis
Mortality	**1.00** (0.89 to 1.12)	**0 fewer deaths per 1,000** (5 fewer to 5 fewer)
PE	**0.63** (0.39 to 1.03)	**1 fewer PE per 1,000** (3 fewer to 0 fewer)
Symptomatic proximal DVT	**0.54** (0.32 to 0.91)	**3 fewer DVT per 1,000** (4 fewer to 1 fewer)
Major bleeding	**2.09** (1.33 to 3.27)	**4 more bleeds per 1,000** (1 more to 8 more)

Quality of Evidence (GRADE): Low Moderate Strong

Blood Adv (2018) 2 (22): 3198–3225

Prevention of VTE in Korea

Table 6. Levels of VTE risk in medical patients

Risk groups	Medical illness
Very low	Acute exacerbation of COPD without mechanical ventilation
Low	Long term immobilization Non-metastatic active cancer Central venous catheterization Nephrotic syndrome Inflammatory bowel disease Thalidomide treatment
Moderate	Acute exacerbation of COPD with mechanical ventilation Sepsis, MI, CHF (NYHA grade III or IV) Metastatic cancer with immobilization Admitted to intensive care unit
High	Severe medical illness with previous VTE or thrombophilia Cerebral stroke complicated with paralysis

VTE, venous thromboembolism; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; CHF, congestive Heart failure; NYHA, New York Heart Association.

- Recommends repeated assessment of VTE risk and bleeding risk
- For acutely ill medical patients with one or more risk factors, recommend pharmacological or mechanical prophylaxis

J Korean Med Sci 2014; 29: 164-171

Risk of VTE vs Risk of bleeding

- Critically ill patients are at high risk for venous thromboembolism and bleeding.

- Balancing the dual risks of DVT and bleeding is difficult.

- Optimal care of ICU patients is to administer anticoagulant prophylaxis for reducing VTE while simultaneously minimizing bleeding.

Curr Opin Pulm Med 2009; 15: 455-462

Venous thromboembolism risk factors in ICU

General VTE risk factors	ICU-acquired VTE risk factor
Age	Sepsis
Past history of VTE	Vasopressor use
Past history of cancer	Respiratory or cardiac failure
Immobilization	Pharmacologic sedation
Obesity	Mechanical ventilation
Pregnancy	Central venous catheter
Trauma, spinal cord injury	End-stage renal failure
Recent surgery	
Stroke	

Critical Care (2015) 19:287

Risk Assessment: Padua Prediction Score

- [ ] Cancer: Active or treated with chemotherapy and or XRT within the last 6 months (3 points)
- [ ] History of venous thrombotic disease (not to include superficial thromboses) (3 points)
- [ ] Impaired/reduced mobility of at least 3 days duration (3 points)
- [ ] Preexisting hypercoaguable state (3 points)
- [ ] Trauma or surgery within 1 month (2 points)
- [ ] Age ≥70 years old (1 point)
- [ ] Heart or respiratory failure (1 point)
- [ ] Stroke or acute MI (1 point)
- [ ] Acute infectious disease or rheumatic disease (1 point)
- [ ] Obesity with a body mass index ≥30 kg/m^2 (1 point)
- [ ] Intercurrent hormone replacement treatment (1 point)

- Low-risk patients (score <4): 0.3%
- High-risk patients (score ≥4):

2.2% (receiving adequate in-hospital thromboprophylaxis)

11% (not receiving adequate in-hospital thromboprophylaxis)

N Engl J Med. 2005;352(10):969

Risk Assessment: modified IMPROVE risk score

VTE risk factor	VTE risk score
Previous VTE	3
Known thrombophilia [a]	2
Current lower limb paralysis or paresis [b]	2
History of cancer [c]	2
ICU/CCU stay	1
Complete immobilization [d] ≥ 1 d	1
Age ≥60 y	1

- 0 or 1: 0.4-0.6% at 42days
  0.5-0.7% at 77days
- 2 or 3: 0.8-1% at 42days
  1-1.2% at 77days
- 4 or 5: 1.6-1.9% at 42days
  2.2-2.7% at 77days
- 6 or 7: similar risk as a score of 4 or 5

TH Open. 2020;4(1):e59.

Risk Assessment: Geneva risk score

Item	Points
Cardiac failure	2
Respiratory failure	2
Recent stroke	2
Recent myocardial infarction	2
Acute infectious disease (incl. sepsis)	2
Acute rheumatic disease	2
Malignancy	2
Myeloproliferative syndrome	2
Nephrotic syndrome	2
History of venous thromboembolism	2
Known hypercoagulable state	2
Immobilization (<30 min walk per day) for 3 days or more	1
Recent travel (>6 h)	1
Age >60	1
Obesity (BMI >30)	1
Chronic venous insufficiency	1
Pregnancy	1
Hormonal therapy (contraceptive or substitutive)	1
Dehydration	1

- Low-risk patients (score <3):
  0.6% (thromboprophylaxis +)
  0.8% (thromboprophylaxis-)
- High-risk patients (score ≥3):
  3.2% (thromboprophylaxis +)
  3.5% (thromboprophylaxis-)

Thromb Haemost. 2014 Mar;111(3):531-8

Risk Assessment: simplified Geneva risk score

Table 3

Incidences of VTE and their association with the Geneva, Improve and Padua risk scores

Scores		VTE risk[a]			
	N (%)	Sensitivity	At 30 d	At 90 d	Subdistribution HR (95% CI)[b]
Geneva score					
Low risk (<3)	518 (35%)		0.4%	0.6%	ref.
High risk (≥3)	960 (65%)	90% (27/30)	2.0%	2.8%	5.1 (1.5–16.6)
Improve score					
Low risk (<3)	1,009 (68%)		0.6%	0.8%	ref.
High risk (≥3)	469 (32%)	73% (22/30)	3.6%	4.7%	6.1 (2.7–13.5)
Low-risk (<2)	690 (47%)		0.4%	0.6%	ref.
Intermediate-risk (2–3)	545 (37%)	87% (26/30)	1.5%	2.2%	3.8 (1.2–11.8)
High risk (≥4)	243 (16%)		4.1%	5.8%	10.3 (3.4–30.0)
Padua score					
Low risk (<4)	764 (52%)		0.7%	1.0%	ref.
High risk (≥4)	714 (48%)	73% (22/30)	2.2%	3.1%	3.0 (1.3–6.7)
Simplified Geneva score					
Low risk (<3)	489 (33%)		0.4%	0.6%	ref.
High risk (≥3)	989 (67%)	90% (27/30)	1.9%	2.8%	4.6 (1.4–15.2)
Low-risk (<3)	489 (33%)		0.4%	0.6%	ref.
Intermediate-risk (3–6)	800 (54%)	90% (27/30)	1.2%	1.8%	3.0 (0.8–10.4)
High risk (≥7)	189 (13%)		5.0%	7.1%	12.3 (3.6–42.8)

Low risk 0–2 **High risk ≥3**	
Previous VTE	3
Hypercoagulable state	2
Cancer or myeloproliferative syndrome	2
Cardiac or respiratory failure	2
Acute infection or rheumatic disease	2
Immobilization	2
Age >60 y	1
BMI >30 kg/m^2	1
Recent stroke or myocardial infarction	1

Thromb Haemost 2018;118:82–89

Table 2. Risk of Hospital-Acquired Venous Thromboembolism in High-Risk vs Low-Risk Groups Based on Each Risk Assessment Model

Risk assessment model	Unadjusted SHR (95% CI)	*P* value	Adjusted SHR (95% CI)[a]	*P* value
Simplified Geneva score	2.16 (0.88-5.31)	.09	2.04 (0.83-5.05)	.12
Original Geneva score	2.38 (0.91-6.26)	.08	2.26 (0.86-5.98)	.10
Padua score	1.98 (0.91-4.29)	.08	2.03 (0.94-4.37)	.07
IMPROVE score	1.53 (0.72-3.26)	.27	1.52 (0.72-3.23)	.28

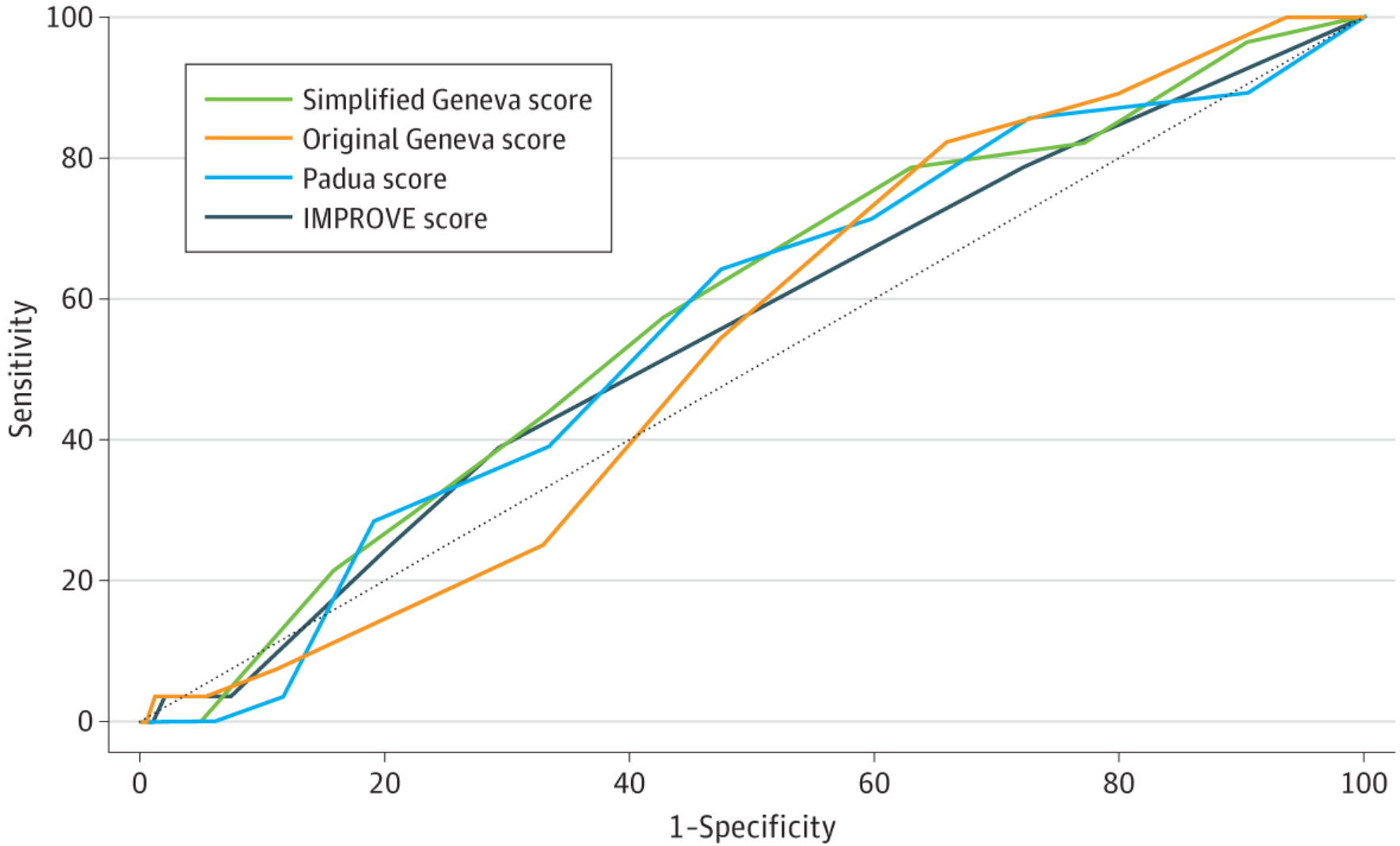
Abbreviations: IMPROVE, International Medical Prevention Registry on Venous Thromboembolism; SHR, subhazard ratio.

[a] Adjusted for site and use of pharmacologic thromboprophylaxis as a time-varying covariate.

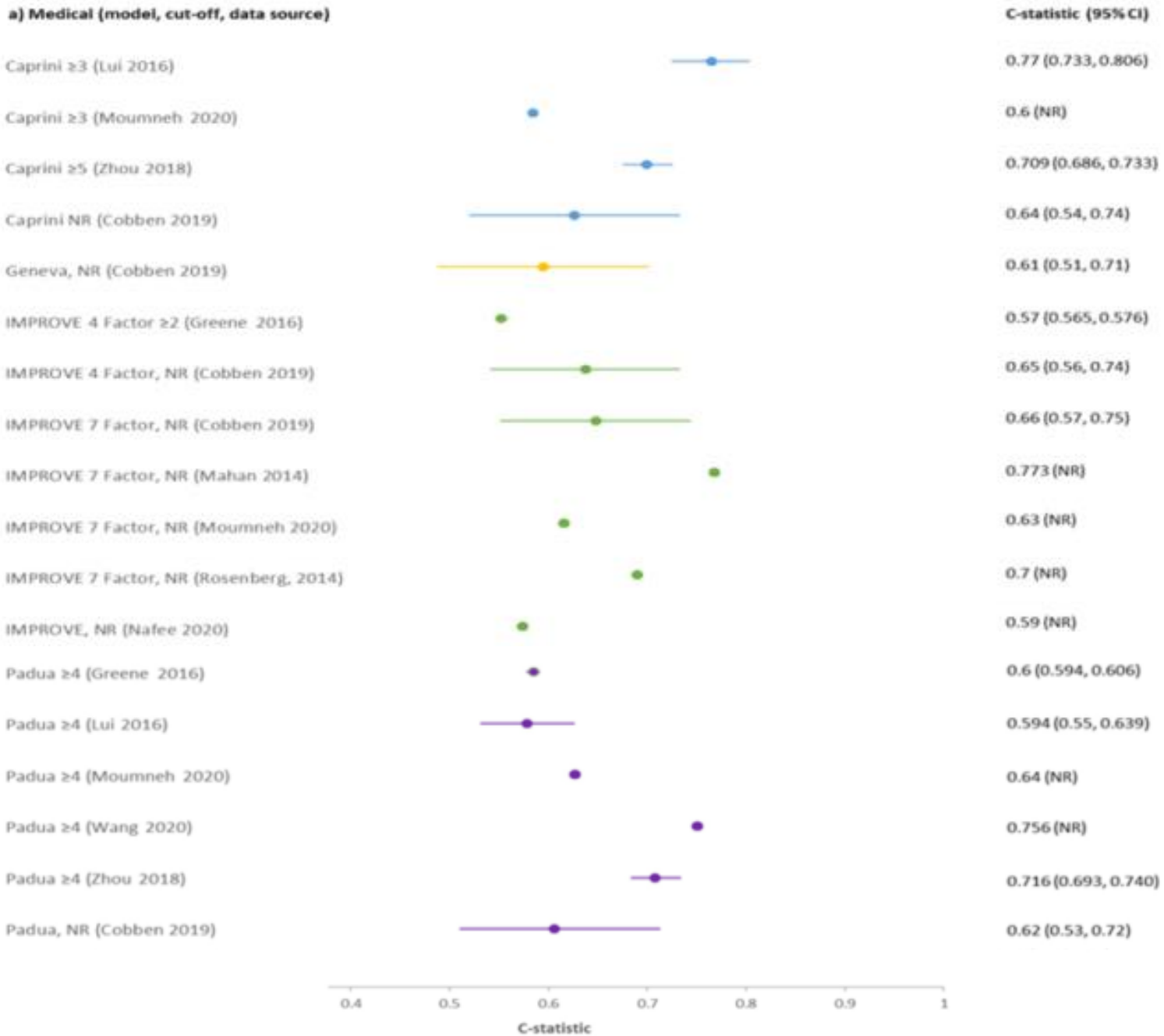
Table 3. Predictive Accuracy of Each Risk Assessment Model for Hospital-Acquired Venous Thromboembolism

	% (95% CI)				LHR (95% CI)	
Risk assessment model	Sensitivity	Specificity	PPV	NPV	Positive	Negative
Simplified Geneva score	78.6 (60.5-89.8)	37.2 (34.6-39.8)	2.6 (1.7-3.9)	98.8 (97.4-99.4)	1.25 (1.03-1.52)	0.58 (0.28-1.18)
Original Geneva score	82.1 (64.4-92.1)	34.3 (31.8-36.9)	2.6 (1.7-3.8)	98.9 (97.5-99.5)	1.25 (1.05-1.49)	0.52 (0.23-1.16)
Padua score	64.3 (45.8-79.3)	52.6 (49.9-55.2)	2.8 (1.8-4.4)	98.6 (97.4-99.2)	1.36 (1.02-1.80)	0.68 (0.41-1.12)
IMPROVE score	39.3 (23.6-57.6)	70.4 (67.9-72.8)	2.7 (1.5-4.8)	98.2 (97.1-98.9)	1.33 (0.83-2.12)	0.86 (0.64-1.16)

Abbreviations: IMPROVE, International Medical Prevention Registry on Venous Thromboembolism; LHR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.



JAMA Netw Open. 2024;7(5):e249980



BMJ Open 2021;11:e045672

Bleeding Risk Assessment: IMPROVE Bleeding Risk Score

IMPROVE bleeding RAM: score ≥7 indicates high bleeding risk¶	
Renal failure (GFR 30-59 vs ≥60 mL/min per m^2)	1
Male vs female	1
Age 40-80 vs <40 y	1.5
Current cancer	2
Rheumatic disease	2
Central venous catheter	2
ICU/Critical Care Unit stay	2.5
Renal failure (GFR <30 vs ≥60 mL/min per square meter)	2.5
Hepatic failure (INR > 1.5)	2.5
Age ≥85 y vs <40 y	3.5
Platelet count $<50 \times 10^9$/L	4
Bleeding in 3 mo before admission	4
Active gastroduodenal ulcer	4. 5

CHEST 2011; 139(1):69–79

Bleeding Risk Assessment: IMPROVE Bleeding Risk Score

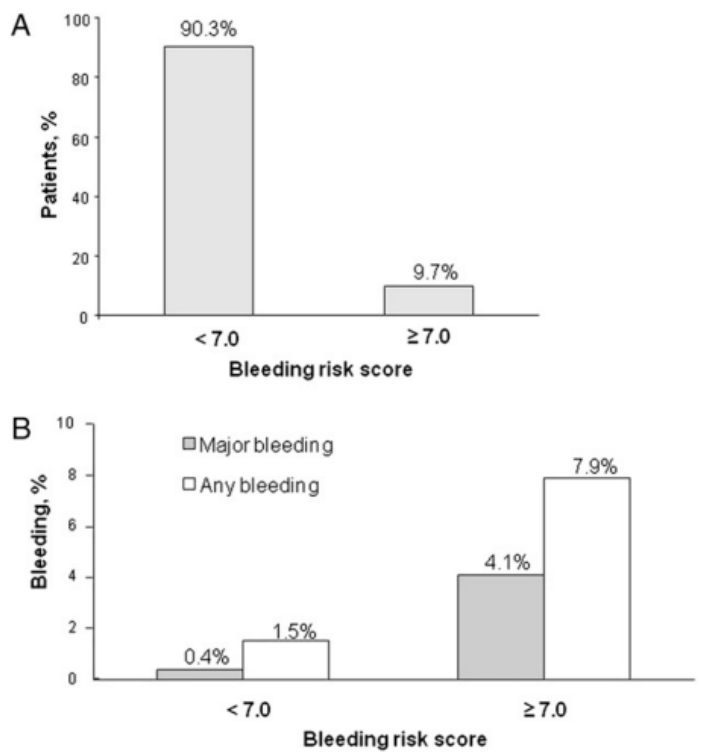


FIGURE 5. Implications of bleeding risk score for clinical decision making. A, Proportion of patients with risk score of < 7.0 and ≥ 7.0 points. B, Rates of major bleeding and any bleeding (defined as major or nonmajor but clinically relevant bleeding) according to the risk score cutoff of 7.0 points.

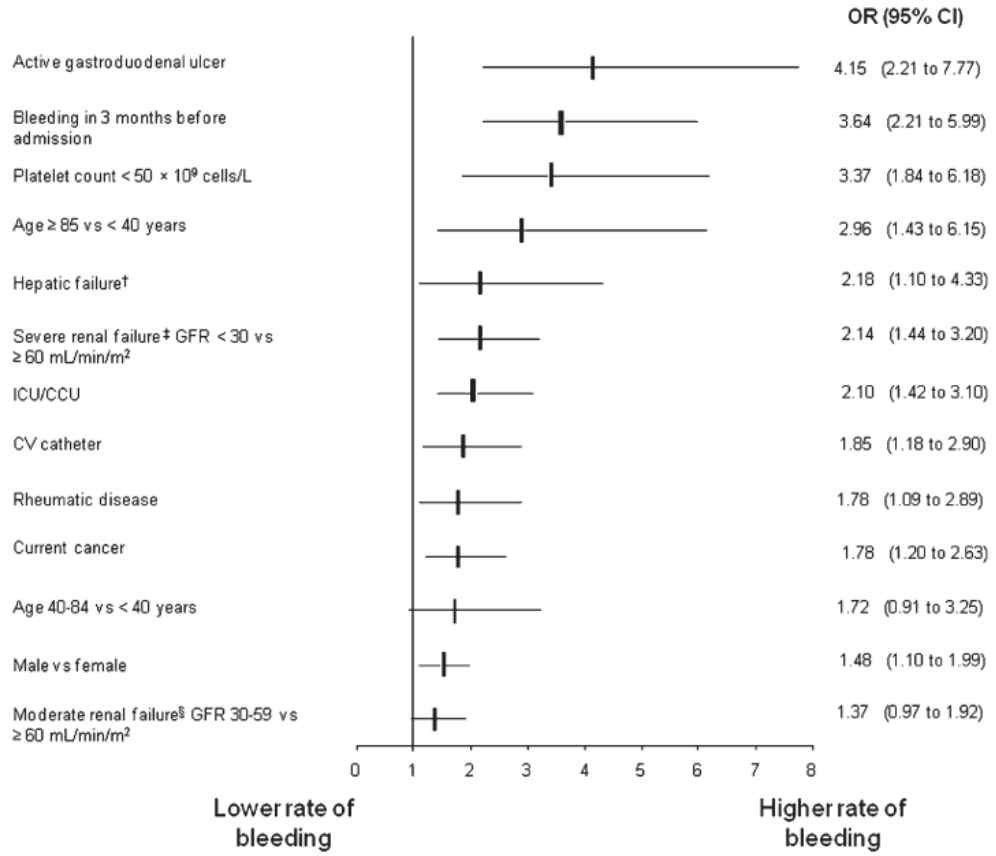
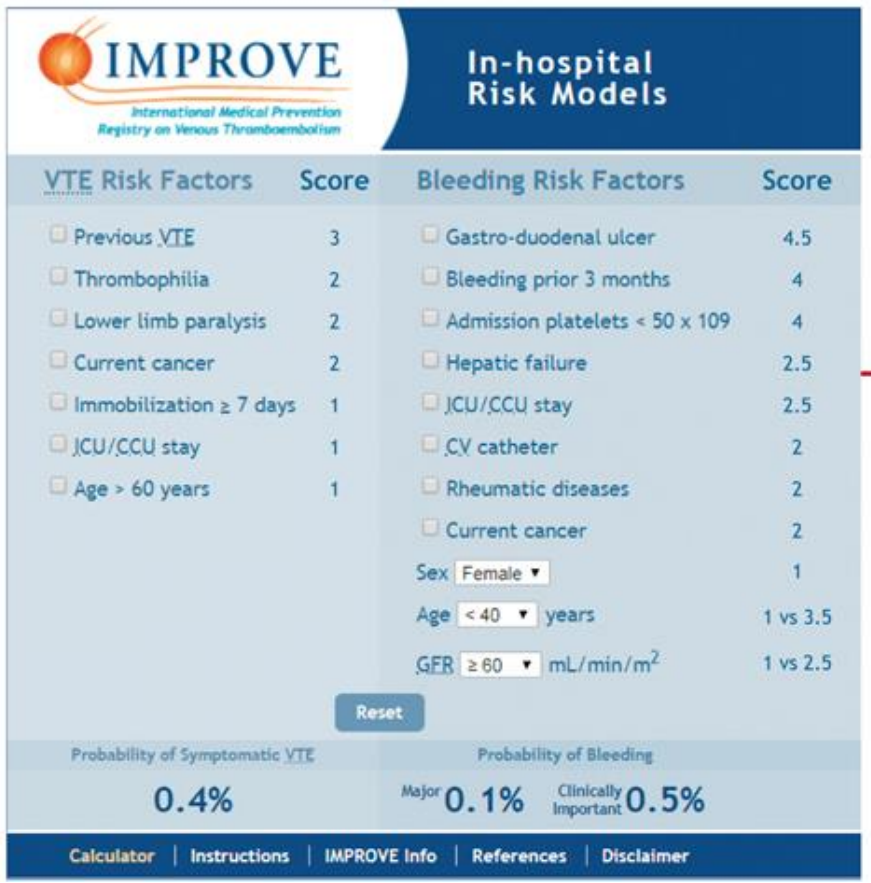
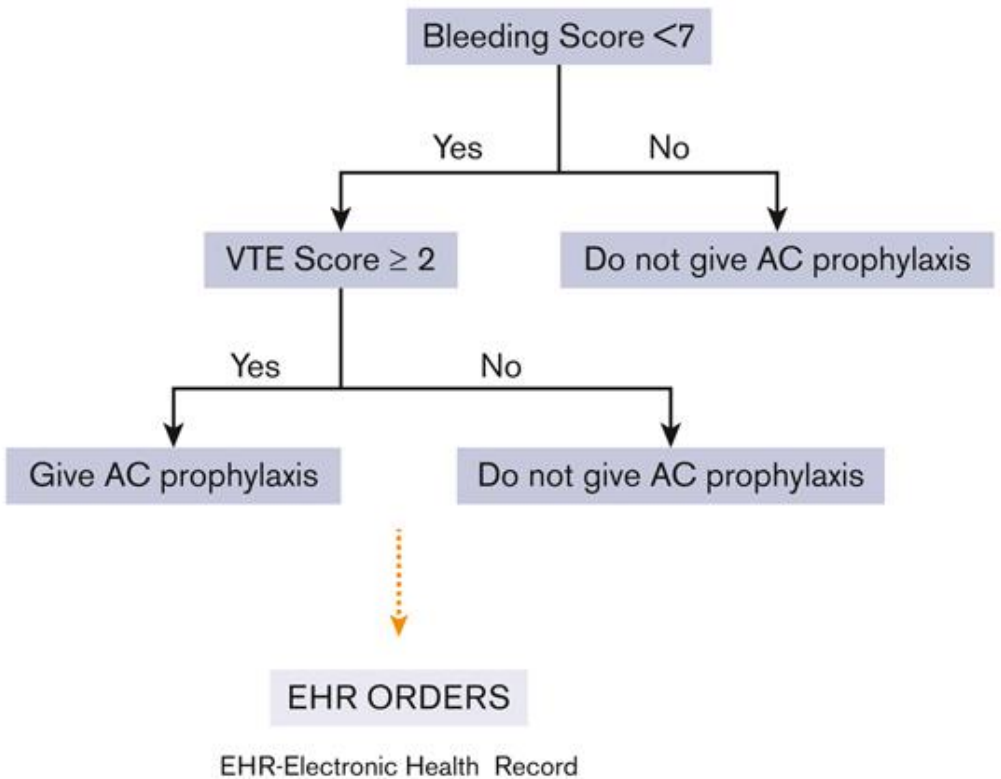


FIGURE 3. Multiple logistic regression model results for characteristics at admission independently associated with in-hospital bleeding in acutely ill medical patients in IMPROVE (9,388 patients with complete data, 198 with in-hospital bleeding within 14 days of admission). Note that 1,478 patients had no covariates observation to be included in the analysis. †Hepatic failure defined as an international normalized ratio > 1.5. ‡Severe renal failure defined as GFR < 30 mL/min/m². §Moderate renal failure defined as GFR 30 to 59 mL/min/m². CCU = coronary care unit; CV = central venous; GFR = glomerular filtration rate. See Figure 1 legend for expansion of other abbreviation.

CHEST 2011; 139(1):69–79

Converting IMPROVE bleeding and VTE predictive models into FFT (T) for implementing most optimal hospital VTE prophylaxis at the point of care





Blood Adv (2024) 8 (12): 3214–3224

Table 1. VTE baseline characteristics and outcomes

Predictors N = 2072	%
Age >60	56.2
Current cancer	16.8
Previous VTE	0.7
ICU (yes)	30.2
Lower limb paralysis	0.8
Thrombophilia	1.0
Immobility >7 days	NA
VTE_Outcome (yes)	2.2

NA, not available.

Table 2. Bleeding baseline characteristics and outcomes

Predictors N = 2072	%
GFR 30-59	14.4
Male	49.6
Age 40-84	77.6
Current cancer	16.8
Rheumatic diseases	7.4
Central venous catheter	34.5
ICU (yes)	30.2
Severe renal failure GFR <30	11.7
Hepatic failure	2.4
Age >85	8.3
Platelet count $<50.10^2$ cells/L	0.9
Bleeding before admission	2.8
Active gastro ulcer	0.0
Bleed_outcome (yes)	1.6

GFR, glomerular filtration rate.

Blood Adv (2024) 8 (12): 3214–3224

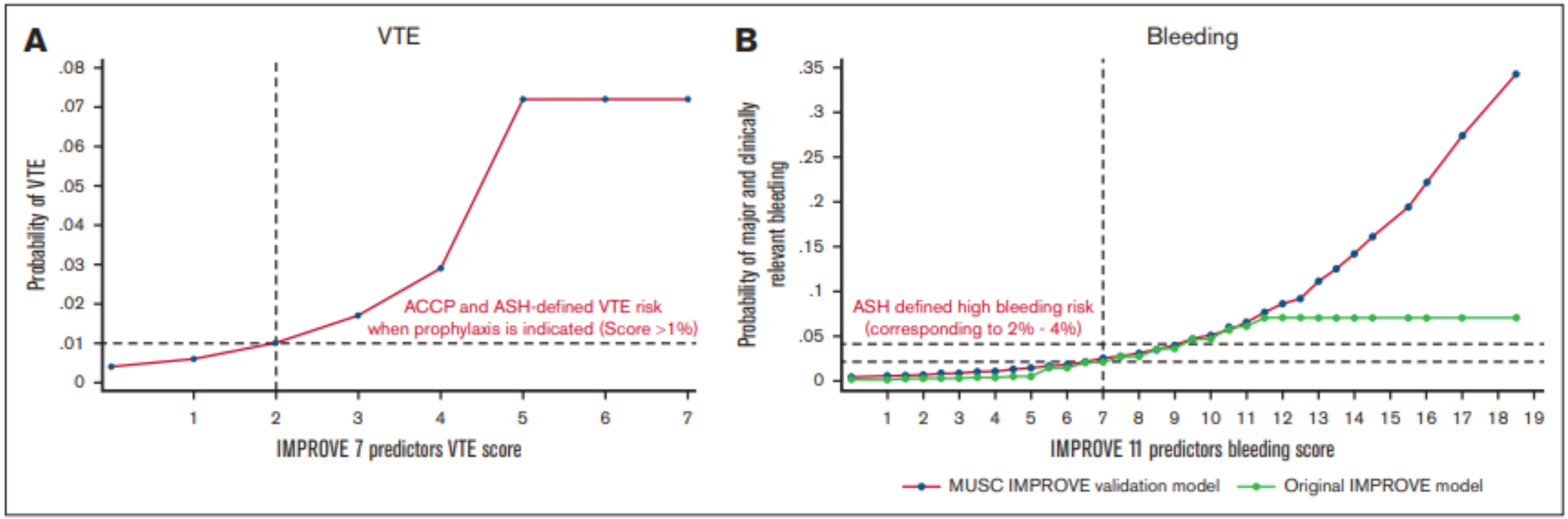
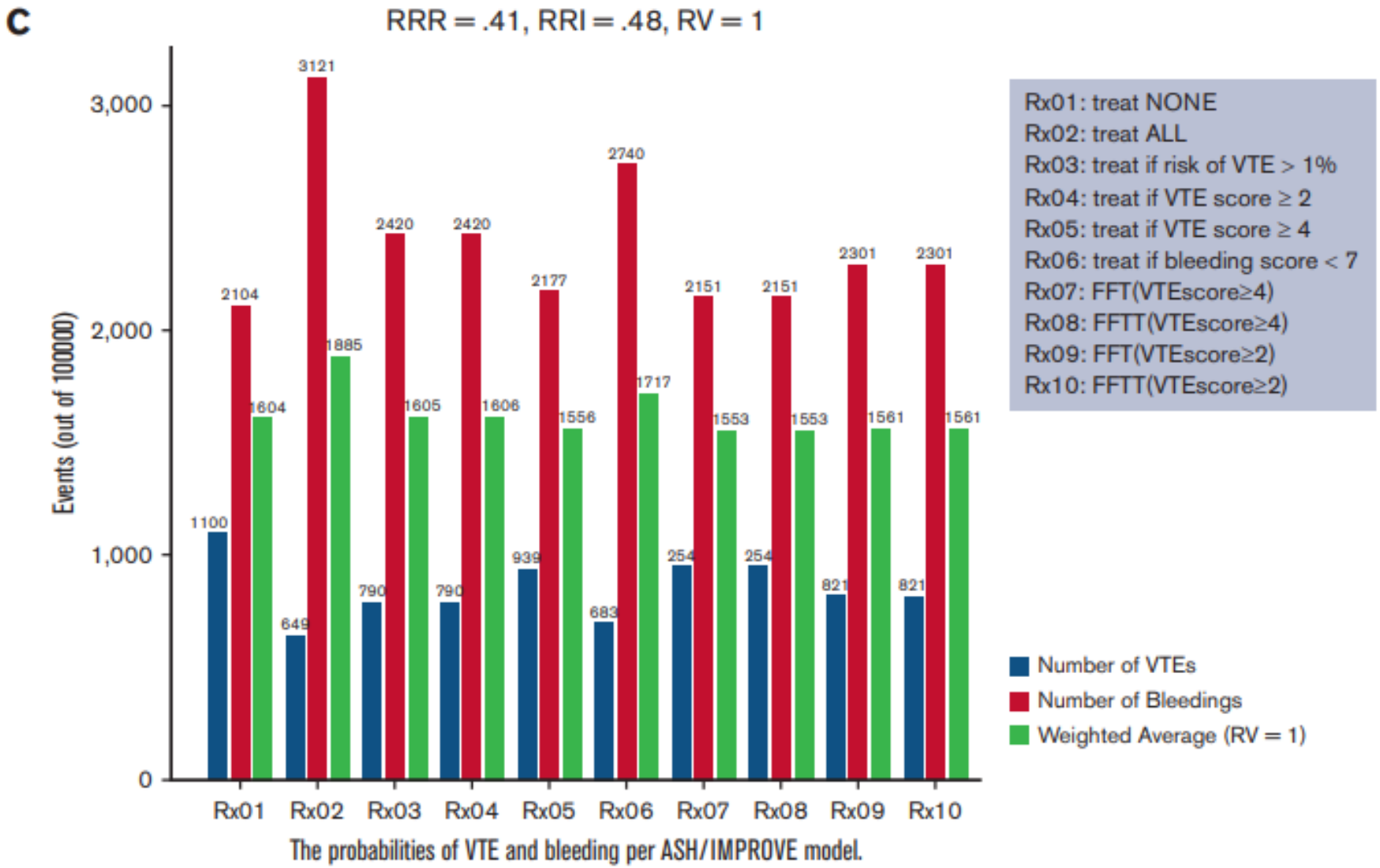


Figure 4. Relationship between IMPROVE VTE scores (A) and bleeding scores (B) and the probability of VTE and bleeding (major and clinically relevant).

Blood Adv (2024) 8 (12): 3214–3224



Blood Adv (2024) 8 (12): 3214–3224