Djulbegovic et al. Converting IMPROVE bleeding and VTE risk assessment models into a fast-and-frugal decision tree for VTE prophylaxis

Appendix 0

ICD-10 codes for major bleeding

Intracranial	I60 (Subarachnoid), I61 (intracerebral), I62.0 (subdural), I62.1 nontraumatic extradural), I62.9 (intracranial, nontraumatic, unspecified)
Upper gastrointestinal	K92.0 (haematemesis), K92.1 (melaena), I85.0 (oesophageal varices with bleeding), I98.20 (oesophageal varices in diseases classified elsewhere with bleeding), I98.3 (Oesophageal varices with bleeding in disease classified elsewhere), K22.10 (Ulcer of oesophagus, acute with bleeding), K22.12 (Ulcer of oesophagus, acute with both bleeding and perforation), K22.14 (Ulcer of oesophagus, chronic or unspecified with bleeding), K22.16 (Ulcer of oesophagus, chronic or unspecified with both bleeding and perforation), K25.0 (Gastric ulcer, acute with bleeding), K25.2 (Gastric ulcer, acute with both bleeding and perforation), K25.4 (Gastric ulcer, chronic or unspecified with bleeding), K25.6 (Gastric ulcer, chronic or unspecified with both bleeding and perforation), K26.0 (Duodenal ulcer, acute with bleeding), K26.2 (Duodenal ulcer, acute with both bleeding and perforation), K26.4 (Duodenal ulcer, chronic or unspecified with bleeding), K26.6 (Duodenal ulcer, chronic or unspecified with both bleeding and perforation), K27.0 (Peptic ulcer, acute with bleeding), K27.2 (Peptic ulcer, acute with both bleeding and perforation), K27.4 (Peptic ulcer, chronic or unspecified with bleeding), K27.6 (Peptic ulcer, chronic or unspecified with both bleeding and perforation), K28.0 (Gastrojejunal ulcer, acute with bleeding), K28.2 (Gastrojejunal ulcer, acute with both bleeding and perforation), K28.4 (Gastrojejunal ulcer, chronic or unspecified with bleeding), K28.6 (Gastrojejunal ulcer, chronic or unspecified with both bleeding and perforation), K29.0 (Acute bleeding gastritis), K63.80 (Angiodysplasia of small intestine, except duodenum with bleeding), K31.80 (Angiodysplasia of stomach and duodenum with bleeding)
Lower GI	K55.20 (Angiodysplasia of colon with bleeding), K62.5 (bleeding of anus and rectum), K92.2 (Gastrointestinal bleeding, unspecified)
Other bleeding	N02.0 (Recurrent and persistent haematuria, minor glomerular abnormality) , N02.1 (Recurrent and persistent haematuria, focal and segmental glomerular lesions),

	N02.2 (Recurrent and persistent haematuria, diffuse membranous glomerulonephritis), N02.3 (Recurrent and persistent haematuria, diffuse mesangial proliferative glomerulonephritis), N02.4 (Recurrent and persistent haematuria, diffuse endocapillary proliferative glomerulonephritis), N02.5 (Recurrent and persistent haematuria, diffuse mesangiocapillary glomerulonephritis), N02.6 (Recurrent and persistent haematuria, dense deposit disease), N02.7 (Recurrent and persistent haematuria, diffuse crescentic glomerulonephritis), N02.8 (Recurrent and persistent haematuria, other), N02.9 (Recurrent and persistent haematuria, unspecified), K66.1 (Haemoperitoneum), N93.8 (Other specified abnormal uterine and vaginal bleeding), N93.9 (Abnormal uterine and vaginal bleeding, unspecified), N95.0 (Postmenopausal bleeding), R04.1 (bleeding from throat), R04.2 (Haemoptysis), R04.8 (bleeding from other sites in respiratory passages), R04.9 (bleeding from respiratory passages, unspecified), R31.0 (Gross hematuria), R31.1 (Microscopic hematuria), R31.8 (Other and unspecified hematuria), R58 (bleeding, not elsewhere classified), D68.3 (Haemorrhagic disorder due to circulating anticoagulants), H35.6 (Retinal bleeding), H43.1 (Vitreous bleeding), H45.0 (Vitreous bleeding in diseases classified elsewhere), M25.0 (Haemarthrosis)

Major bleeding ICD 10 Code:

ICD10	Term
K66.1	Hemoperitoneum
I31.0	Chronic adhesive pericarditis
I60.9	Nontraumatic subarachnoid hemorrhage, unspecified (CMS-HCC)
I31.4	Cardiac tamponade
I31.9	Disease of pericardium, unspecified
I61.9	Nontraumatic intracerebral hemorrhage, unspecified (CMS-HCC)
E27.40	Unspecified adrenocortical insufficiency (CMS-HCC)
H44.819	Hemophthalmos, unspecified eye
I62.1	Nontraumatic extradural hemorrhage (CMS-HCC)
I31.8	Other specified diseases of pericardium
I31.1	Chronic constrictive pericarditis
I62.00	Nontraumatic subdural hemorrhage, unspecified (CMS-HCC)
I31.2	Hemopericardium, not elsewhere classified
E27.1	Primary adrenocortical insufficiency (CMS-HCC)
H35.60	Retinal hemorrhage, unspecified eye

I62.9	Nontraumatic intracranial hemorrhage, unspecified (CMS-HCC)
E27.2	Addisonian crisis (CMS-HCC)

Non- Major (clinically significant) bleeding ICD 10 Code:

ICD10	Term
R04.1	Hemorrhage from throat
R58	Hemorrhage, not elsewhere classified
K76.1	Chronic passive congestion of liver
K26.0	Acute duodenal ulcer with hemorrhage
K86.1	Other chronic pancreatitis
K25.6	Chronic or unspecified gastric ulcer with both hemorrhage and perforation
K29.91	Gastroduodenitis, unspecified, with bleeding
K94.09	Other complications of colostomy
I85.01	Esophageal varices with bleeding (CMS-HCC)
R04.2	Hemoptysis
M25.00	Hemarthrosis, unspecified joint
K57.31	Diverticulosis of large intestine without perforation or abscess with bleeding
K29.51	Unspecified chronic gastritis with bleeding
M25.076	Hemarthrosis, unspecified foot
S36.029A	Unspecified contusion of spleen, initial encounter
K31.89	Other diseases of stomach and duodenum
K05.5	Other periodontal diseases
K29.60	Other gastritis without bleeding
K64.5	Perianal venous thrombosis
I85.11	Secondary esophageal varices with bleeding (CMS-HCC)
K28.2	Acute gastrojejunal ulcer with both hemorrhage and perforation (CMS-HCC)
M25.073	Hemarthrosis, unspecified ankle
S36.112A	Contusion of liver, initial encounter
K64.9	Unspecified hemorrhoids
K29.81	Duodenitis with bleeding
K13.70	Unspecified lesions of oral mucosa
K26.4	Chronic or unspecified duodenal ulcer with hemorrhage
K62.5	Hemorrhage of anus and rectum
K27.0	Acute peptic ulcer, site unspecified, with hemorrhage
R47.01	Aphasia
K26.6	Chronic or unspecified duodenal ulcer with both hemorrhage and perforation
K29.41	Chronic atrophic gastritis with bleeding
N00.9	Acute nephritic syndrome with unspecified morphologic changes
K22.6	Gastro-esophageal laceration-hemorrhage syndrome

K64.4	Residual hemorrhoidal skin tags
K25.2	Acute gastric ulcer with both hemorrhage and perforation (CMS-HCC)
K57.11	Diverticulosis of small intestine without perforation or abscess with bleeding
R31.0	Gross hematuria
K66.1	Hemoperitoneum
K57.33	Diverticulitis of large intestine without perforation or abscess with bleeding
K29.61	Other gastritis with bleeding
K06.1	Gingival enlargement
M26.79	Other specified alveolar anomalies
K06.2	Gingival and edentulous alveolar ridge lesions associated with trauma
K76.89	Other specified diseases of liver
K25.4	Chronic or unspecified gastric ulcer with hemorrhage
K28.4	Chronic or unspecified gastrojejunal ulcer with hemorrhage
K29.71	Gastritis, unspecified, with bleeding
M79.81	Nontraumatic hematoma of soft tissue
I88.1	Chronic lymphadenitis, except mesenteric
K64.8	Other hemorrhoids
R31.1	Benign essential microscopic hematuria
R04.89	Hemorrhage from other sites in respiratory passages
K25.0	Acute gastric ulcer with hemorrhage
K29.90	Gastroduodenitis, unspecified, without bleeding
K22.11	Ulcer of esophagus with bleeding
K29.50	Unspecified chronic gastritis without bleeding
K29.00	Acute gastritis without bleeding
K57.13	Diverticulitis of small intestine without perforation or abscess with bleeding
K29.80	Duodenitis without bleeding
K27.4	Chronic or unspecified peptic ulcer, site unspecified, with hemorrhage
R04.9	Hemorrhage from respiratory passages, unspecified
N32.89	Other specified disorders of bladder
I86.8	Varicose veins of other specified sites
K28.0	Acute gastrojejunal ulcer with hemorrhage
K13.79	Other lesions of oral mucosa
I85.10	Secondary esophageal varices without bleeding (CMS-HCC)
K29.40	Chronic atrophic gastritis without bleeding
K29.70	Gastritis, unspecified, without bleeding
K92.0	Hematemesis
K31.82	Dieulafoy lesion (hemorrhagic) of stomach and duodenum
K29.21	Alcoholic gastritis with bleeding
K29.20	Alcoholic gastritis without bleeding

K27.6	Chronic or unspecified peptic ulcer, site unspecified, with both hemorrhage and perforation (CMS-HCC)
N89.8	Other specified noninflammatory disorders of vagina
R31.9	Hematuria, unspecified
K29.01	Acute gastritis with bleeding
M25.069	Hemarthrosis, unspecified knee

Definition of major and clinically relevant bleeding

Major Bleeding Event	Clinically Relevant Non-major Bleeding Events
Contributing to death	Overt non-major GI bleeding
Hemoglobin drop >2 g/dL	Gross hematuria
Transfused >2 units PRBCs	Epistaxis requiring intervention
Bleeding in a critical organ or space	Extensive hematoma >5cm
	Intra-articular
	Menorrhagia/metrorrhagia
	Other bleeding significant enough to be noted in chart

Schulman S, Kearon C on behalf of the subcommittee on control of anticoagulation of the Scientific and Standardization committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. Scientific and Standardization Committee Communication. J Thromb Haemost 2005; 3: 692–4.
Franco L, Becattini C, Beyer-Westendorf J, et al. Definition of major bleeding: Prognostic classification. J Thromb Haemost. 2020;18:2852–2860. https://doi.org/10.1111/jth.15048

ICD-10 code list for VTE

I26.0	Pulmonary embolism with mention of acute cor pulmonale
I26.9	Pulmonary embolism without mention of acute cor pulmonale
I80.1	Phlebitis and thrombophlebitis of femoral vein
I80.2	Phlebitis and thrombophlebitis of other deep vessels of lower extremities
I80.3	Phlebitis and thrombophlebitis of lower extremities, unspecific
I80.8	Phlebitis and thrombophlebitis of other sites
I80.9	Phlebitis and thrombophlebitis of unspecified site
I82.0	Budd-Chiari syndrome
I82.1	Thrombophlebitis migrans
I82.2	Embolism and thrombosis of vena cava
I82.3	Embolism and thrombosis of renal vein
I82.8	Embolism and thrombosis of other specified veins
I82.9	Embolism and thrombosis of unspecified vein
O08.2	Embolism following abortion and ectopic and molar pregnancy
O22.3	Deep phlebothrombosis in pregnancy
O87.1	Deep phlebothrombosis in the puerperium
O88.2	Obstetric blood-clot embolism
I81	Portal vein thrombosis

Cerebral venous thrombosis:
163.6 Cerebral infarction due to cerebral venous thrombosis, non-pyogenic
167.6 Non-pyogenic thrombosis of intracranial venous system
O22.5 Cerebral venous thrombosis in pregnancy

ICD-10 code list for VTE (cont):

ICD10	Term
I82.421	Acute embolism and thrombosis of right iliac vein (CMS-HCC)
I80.203	Phlebitis and thrombophlebitis of unspecified deep vessels of lower extremities, bilateral (CMS-HCC)
I26.92	Saddle embolus of pulmonary artery without acute cor pulmonale (CMS-HCC)
I80.201	Phlebitis and thrombophlebitis of unspecified deep vessels of right lower extremity (CMS-HCC)
I80.209	Phlebitis and thrombophlebitis of unspecified deep vessels of unspecified lower extremity (CMS-HCC)
I82.413	Acute embolism and thrombosis of femoral vein, bilateral (CMS-HCC)
I80.232	Phlebitis and thrombophlebitis of left tibial vein (CMS-HCC)
I82.401	Acute embolism and thrombosis of unspecified deep veins of right lower extremity (CMS-HCC)
I82.411	Acute embolism and thrombosis of right femoral vein (CMS-HCC)
I82.419	Acute embolism and thrombosis of unspecified femoral vein (CMS-HCC)
I82.403	Acute embolism and thrombosis of unspecified deep veins of lower extremity, bilateral (CMS-HCC)
I82.429	Acute embolism and thrombosis of unspecified iliac vein (CMS-HCC)
I26.09	Other pulmonary embolism with acute cor pulmonale (CMS-HCC)
I82.412	Acute embolism and thrombosis of left femoral vein (CMS-HCC)
I82.4Y3	Acute embolism and thrombosis of unspecified deep veins of proximal lower extremity, bilateral (CMS-HCC)
I80.10	Phlebitis and thrombophlebitis of unspecified femoral vein (CMS-HCC)
I80.13	Phlebitis and thrombophlebitis of femoral vein, bilateral (CMS-HCC)
I82.402	Acute embolism and thrombosis of unspecified deep veins of left lower extremity (CMS-HCC)
I82.422	Acute embolism and thrombosis of left iliac vein (CMS-HCC)

I82.423	Acute embolism and thrombosis of iliac vein, bilateral (CMS-HCC)
I82.431	Acute embolism and thrombosis of right popliteal vein (CMS-HCC)
I82.432	Acute embolism and thrombosis of left popliteal vein (CMS-HCC)
I82.433	Acute embolism and thrombosis of popliteal vein, bilateral (CMS-HCC)
I82.4Y2	Acute embolism and thrombosis of unspecified deep veins of left proximal lower extremity (CMS-HCC)
I82.4Y9	Acute embolism and thrombosis of unspecified deep veins of unspecified proximal lower extremity (CMS-HCC)
I26.99	Other pulmonary embolism without acute cor pulmonale (CMS-HCC)
I80.202	Phlebitis and thrombophlebitis of unspecified deep vessels of left lower extremity (CMS-HCC)
I82.409	Acute embolism and thrombosis of unspecified deep veins of unspecified lower extremity (CMS-HCC)
I82.439	Acute embolism and thrombosis of unspecified popliteal vein (CMS-HCC)
I82.4Y1	Acute embolism and thrombosis of unspecified deep veins of right proximal lower extremity (CMS-HCC)
I26.02	Saddle embolus of pulmonary artery with acute cor pulmonale (CMS-HCC)
I80.11	Phlebitis and thrombophlebitis of right femoral vein (CMS-HCC)
I80.12	Phlebitis and thrombophlebitis of left femoral vein (CMS-HCC)
I80.211	Phlebitis and thrombophlebitis of right iliac vein (CMS-HCC)
I80.292	Phlebitis and thrombophlebitis of other deep vessels of left lower extremity (CMS-HCC)

Appendix 1

Converting IMPROVE bleeding and venous thromboembolism (VTE) risk assessment models into a fast-and-frugal decision tree for optimal VTE prophylaxis

A) Best-evidence approach[1, 2]

We simulated a cohort of 1 million people at the risk of developing VTE in-patients per the original IMPROVE report at 0.011 (1.1%).
Using the IMPROVE model, we

1. Divided the patients into three VTE groups[3]:
   Group 1: patients with VTE risk score = 0 or 1: Probability of VTE recurrence = 0.5% (69% of all patients)
   Group 2: patients with VTE risk score = 2 or 3: Probability of VTE recurrence = 1.5%
   Group 3: patients with VTE risk score ≥ 4 : Probability of VTE recurrence = 5.7%
2. Divided the patients into two bleeding groups[4]:
   Group 1: patients with bleeding risk score < 7: Probability of bleeding = 1.5% (90% of all patients)
   Group 2: patients with bleeding risk score ≥ 7: Probability of bleeding = 7.9%

Based on the best evidence as reported in the ASH VTE prophylaxis guidelines, we assumed that the prophylaxis with anticoagulants (e.g., enoxaparin 30 mg bid, or enoxaparin 40 mg qd) will reduce risk of VTE by RRR (relative risk reduction) = 0.41, but at increased risk of major and clinically significant bleeding compared with no prophylaxis by RRI (relative risk increase) = 0.48. We used these estimates to calculate the decision threshold at each cue according to equation 1) shown in the manuscript.
We assumed that VTE and bleeding were independent events.
Using these "best evidence" assumptions, we simulated trajectory and counted the number of patients who experienced bleeding and VTE events according to 10 different VTE prophylaxis strategies as explained in the Method section of the paper and shown graphically in the impact graphs.[5,6]

B) "Learning health system" approach

We performed a similar analysis as above but obtained prognostic score distributions from our MUSC population while assuming the applicability of the best available evidence as per ASH guidelines.

C) "Real-world data" approach

Finally, we conducted the same analysis as above but relied only on the MUSC data.

Appendix 2

Table 1A Categorization of the Intensity of anticoagulation

[prophylactic-, intermediate-, and therapeutic-intensity anticoagulation]
(https://ashpublications.org/bloodadvances/article/5/3/872/475154/American-Society-of-Hematology-2021-guidelines-on)

Table 3. Classification of anticoagulant regimens by intensity

Regimen
Prophylactic*
Apixaban 2.5 mg, PO BID (with intent for VTE prophylaxis)
Bemiparin 3500 U, SC OD
Betrixaban 80 mg, PO OD
Betrixaban 160 mg, PO OD
Dabigatran 220 mg, PO OD
Dalteparin 5000 U, SC OD
Enoxaparin 30 mg (3000 U), SC OD (for GFR 15-30)
Enoxaparin 30 mg (3000 U), SC BID (for BMI ≥40 kg/m^2)
Enoxaparin 40 mg (4000 U), SC OD
Enoxaparin 40 mg (4000 U), SC BID (for BMI ≥40 kg/m^2)
Fondaparinux 2.5 mg, SC OD
Unfractionated heparin 5000 U, SC BID
Unfractionated heparin 5000 U, SC TID
Unfractionated heparin 7500 U, SC BID (for BMI ≥40 kg/m^2)
Nadroparin 2850 U, SC q24h (post-op general surgery)
Nadroparin 5700 U, SC q24h (high-risk medical patients >70 kg)
Nadroparin 3800 U, SC q24h (high-risk medical patients ≤70 kg or post-op hip replacement surgery)
Rivaroxaban 10 mg, PO OD
Tinzaparin 3500 U, SC OD
Tinzaparin 4500 U, SC OD
Tinzaparin 75 U/kg, SC OD
Intermediate*
Enoxaparin 0.5 mg/kg (50 U/kg), SC BID (if CrCl >30 mL/min)
Enoxaparin 0.5 mg/kg (50 U/kg), SC OD (if CrCl <30 mL/min)
Enoxaparin 30 mg (3000 U), SC BID (for BMI <40 kg/m^2)
Enoxaparin 40 mg (4000 U), SC BID (for CrCl >30 mL/min and BMI <40 kg/m^2)
Enoxaparin 60 mg (6000 U), SC BID (for CrCl >30 mL/min and BMI >40 kg/m^2)
Unfractionated heparin 7500 U, SC TID
Dalteparin 5000 U, SC BID
Therapeutic*
Acenocoumarol, PO (target INR 2.0-3.0 or greater)
Apixaban 5 mg, PO BID
Apixaban 10 mg, PO BID
Argatroban, IV to target aPTT therapeutic range as per institutional guidelines
Bemiparin 5000 U, SC OD (if weight ≤50 kg and CrCl >30 mL/min)
Bemiparin 7500 U, SC OD (if weight 50-70 kg and CrCl >30 mL/min)
Bemiparin 10000 U, SC OD (if weight 70-100 kg and CrCl >30 mL/min)
Bemiparin 115 U/kg, SC OD (if weight >100 kg and CrCl >30 mL/min)
Bivalirudin, IV to target aPTT therapeutic range as per institutional guidelines
Dabigatran 75 mg, PO BID (if CrCl 15-30 mL/min)
Dabigatran 110 mg, PO BID (AF: age ≥80 y, or >75 y and 1 or more risk factors for bleeding)
Dabigatran 150 mg, PO BID (if CrCl >30 mL/min)
Dalteparin 100 U/kg, SC BID
Dalteparin 150 U/kg, SC OD
Dalteparin 200 U/kg, SC OD
Edoxaban 30 mg, PO OD (≤60 kg, CrCl 15-50 mL/min)
Edoxaban 60 mg, PO OD (weight ≥60 kg and CrCl >50 mL/min)
Enoxaparin 0.8 mg/kg, SC BID (for BMI >40 and CrCl >30 mL/min)
Enoxaparin 1 mg/kg (100 U/kg), SC BID (for CrCl >30 mL/min)
Enoxaparin 1.5 mg/kg (150 U/kg), SC OD (for CrCl >30 mL/min)
Enoxaparin 1 mg/kg (100 U/kg), SC OD (for CrCl <30 mL/min)
Tinzaparin 175 U/kg, SC OD
Fluindione, PO (target INR 2.0-3.0 or greater)
Fondaparinux 5 mg, SC OD (if weight <50 and CrCl >50 mL/min
Fondaparinux 5 mg, SC OD (if weight 50-100 kg and CrCl 30-50 mL/min)
Fondaparinux 7.5 mg, SC OD (if weight 50-100 kg and CrCl >50 mL/min
Fondaparinux 7.5 mg, SC OD (if weight >100 kg and CrCl 30-50 mL/min)
Fondaparinux 10 mg, SC OD (if weight >100 kg and CrCl >30 mL/min)
Unfractionated heparin, IV to target aPTT therapeutic range as per institutional guidelines or anti-Xa activity 0.3-0.7 IU/mL
Unfractionated heparin 250 U/kg, SC q12h
Nadroparin 86 U/kg, SC q12h (for acute coronary syndrome)
Nadroparin 171 U/kg, q24h (for DVT treatment)
Phenprocoumon, PO (target INR 2.0-3.0 or greater)
Rivaroxaban 15 mg, PO BID
Rivaroxaban 15 mg, PO OD (for GFR 15-50 in AF patients)
Rivaroxaban 20 mg, PO OD
Warfarin, PO (target INR 2.0-3.0 or greater)

AF, atrial fibrillation; aPTT, activated partial thromboplastin time; BID, twice daily; BMI, body mass index; CrCl, creatinine clearance; GFR, glomerular filtration rate; INR, international normalized ratio; OD, once a day; PO, oral; post-op, postoperative; q12h, every 12 hours; q24h, every 24 hours; SC, subcutaneous; TID, 3 times a day.
*Intensity of anticoagulation.

Table 1B antiplatelet combinations without aspirin, heparin flushes and thrombolytics (alteplase) for treatment of thrombotically occluded catheters included in the control arm*

anti-plate-combo/noASA	
	Total
ALTEPLASE 2 MG INTRA-CATHETER SOLUTION	6
ALTEPLASE 2 MG INTRA-CATHETER SOLUTION; CLOPIDOGREL 75 MG TABLET; HEPARIN (PORCINE) 1,000 UNIT/ML INJECTION SOLUTION	1
ALTEPLASE 2 MG INTRA-CATHETER SOLUTION; HEPARIN (PORCINE) 1,000 UNIT/ML INJECTION SOLUTION	4
ALTEPLASE 2 MG INTRA-CATHETER SOLUTION; HEPARIN, PORCINE (PF) 1,000 UNIT/ML INJECTION SOLUTION	1
ALTEPLASE 2 MG INTRA-CATHETER SOLUTION; HEPARIN, PORCINE (PF) 10 UNIT/ML INTRAVENOUS SYRINGE	3
ALTEPLASE 2 MG INTRA-CATHETER SOLUTION; HEPARIN, PORCINE (PF) 100 UNIT/ML INTRAVENOUS SYRINGE	1
CLOPIDOGREL 300 MG TABLET; HEPARIN (PORCINE) 1,000 UNIT/ML INJECTION SOLUTION	1
CLOPIDOGREL 75 MG TABLET	12
HEPARIN (PORCINE) 1,000 UNIT/ML INJECTION SOLUTION; ALTEPLASE 2 MG INTRA-CATHETER SOLUTION	7
HEPARIN (PORCINE) 1,000 UNIT/ML INJECTION SOLUTION; CLOPIDOGREL 75 MG TABLET	1
HEPARIN, PORCINE (PF) 10 UNIT/ML INTRAVENOUS SYRINGE; ALTEPLASE 2 MG INTRA-CATHETER SOLUTION	3
HEPARIN, PORCINE (PF) 10 UNIT/ML INTRAVENOUS SYRINGE; CLOPIDOGREL 75 MG TABLET	2
Grand Total	42

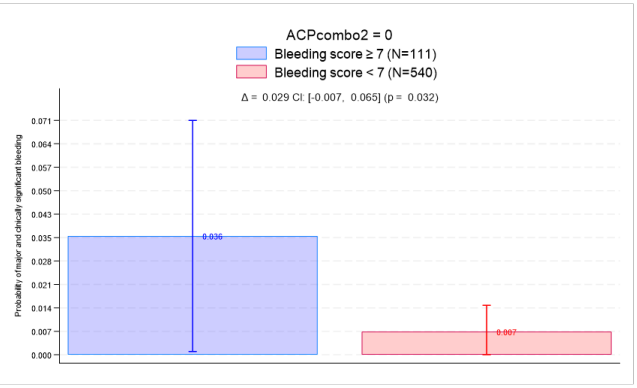
*exclusion of these data did not materially affect the results

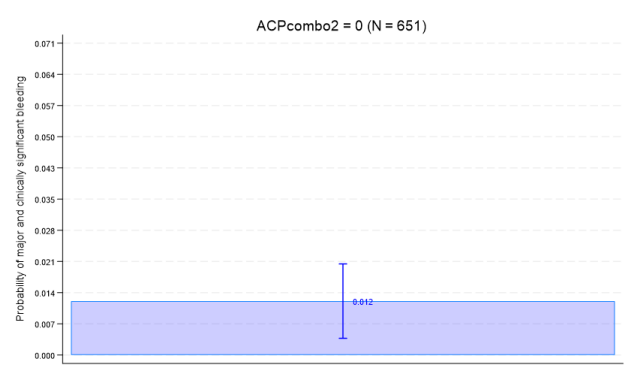
Table 1C. Characteristics of patients according to intensity of anticoagulation*

Predictors	Prophylactic Anticoagulant (%) n=333	Therapeutic Anticoagulant (%) n=601	p-value
Age>60	54.05	57.40	0.323
Current Cancer	15.92	14.98	0.702
Previous VTE	0.30	0.17	0.672
Lower Limb Paralysis	0.60	0.83	0.695
Thrombophilia	0.30	2.16	0.025
ICU Stay (yes)	24.62	32.95	0.008
Immobility >7 days	NA	NA	NA
GFR 30-59	12.61	9.65	0.161
Age 40-84	78.98	80.03	0.701
Rheumatic diseases	6.01	7.65	0.347
Central Venous Catheter	28.83	30.45	0.604
Severe Renal Failure GFR<30	2.40	3.33	0.427
Hepatic failure	1.50	1.00	0.495
Age>=85	6.91	6.66	0.883
Platelet count <50.10^2 cells/L	0.30	0.67	0.464
Bleeding before admission	1.20	2.16	0.292
Male	43.84	56.07	0.000
Active gastro ulcer	0	0	NA
VTE_outcome (yes)	1.53	3.94	0.044
Bleed_outcome (yes)	0.31	1.72	0.067

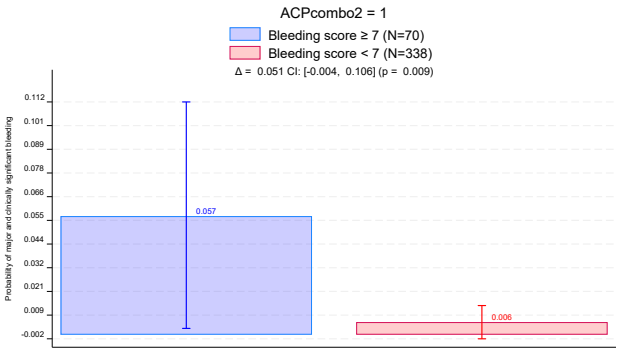
**Table provides supporting evidence for excluding patients admitted to hospital while receiving intermediate/therapeutic anticoagulation. Not surprisingly, the patients on higher intensity anticoagulation were somewhat different from those not receiving anticoagulants on admission. Specifically, the group of patients receiving high-intensity anticoagulation were admitted more often to ICU (33% vs 25%;p=0.008), included more patients with thrombophilia (2.16% vs. 0.3%; p=0.025) and were more often males (56% vs. 44%; p<0.001). As expected, this group- considered at high risk of VTE- also had more VTE events than patients on a prophylactic dose of anticoagulants (3.94% vs. 1.53%; p=0.044) and more bleeding events (1.72% vs. 0.31%;p=0.067).*

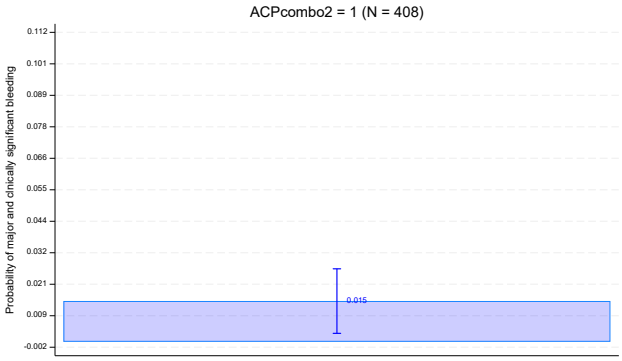
Appendix 3
VTE and bleeding outcomes by prophylactic treatment and IMPROVE prognostic scores.



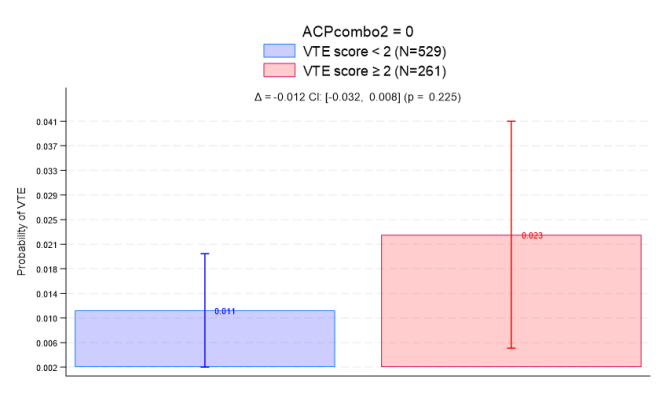


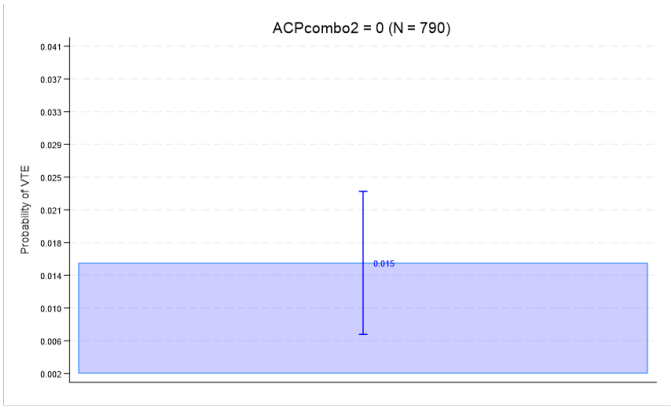
App 3 Fig 1a
[ACPCombo2 = 0, the patients did not receive prophylactic treatment.
Prophylactic treatment is defined as the patients who received prophylactic dose of enoxaparin and/or aspirin- see manuscript for definitions]





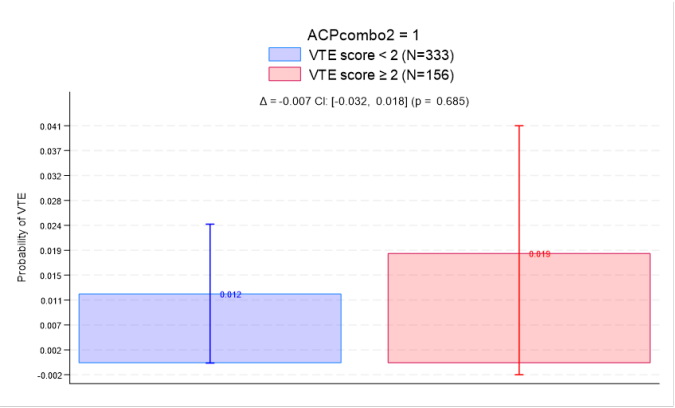
App 3 Fig 1b
[ACPCombo2 = 1, the patients received prophylactic treatment.
Prophylactic treatment is defined as the patients who received prophylactic dose of enoxaparin and/or aspirin- see manuscript for definitions]

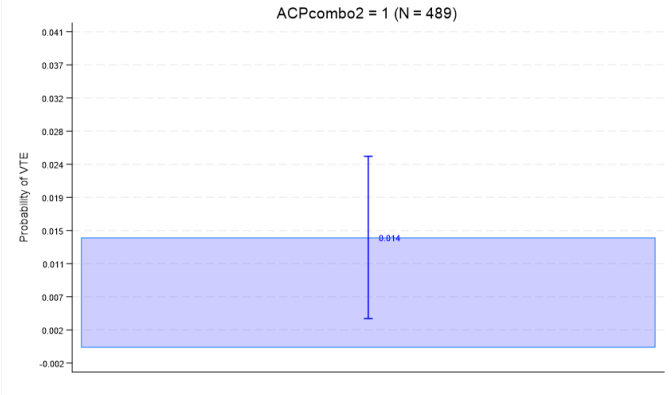




App 3 Fig 1c

[ACPCombo2 = 0, the patients did not receive prophylactic treatment.
Prophylactic treatment is defined as the patients who received a prophylactic dose of enoxaparin and/or aspirin- see manuscript for definitions]



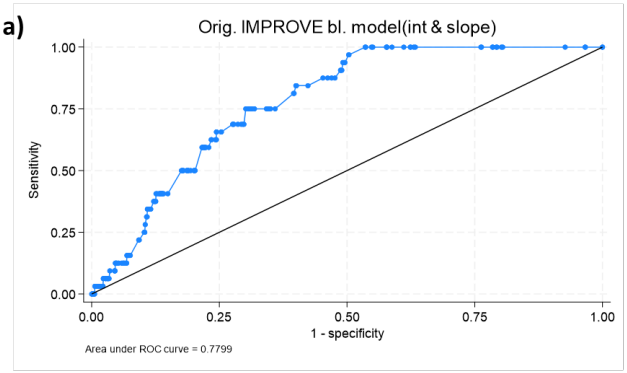


App 3 Fig 1d

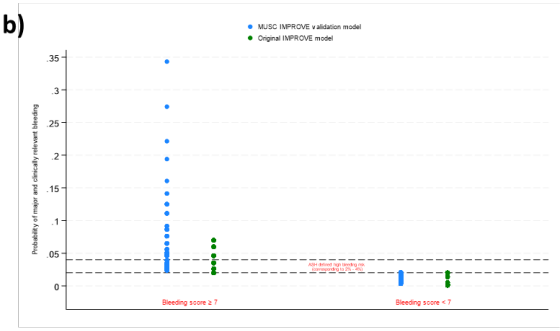
[ACPCombo2 = 1, the patients received prophylactic treatment.
Prophylactic treatment is defined as the patients who received prophylactic dose of enoxaparin and/or aspirin- see manuscript for definitions]

Appendix 4
Validation of IMPROVE risk assessment models

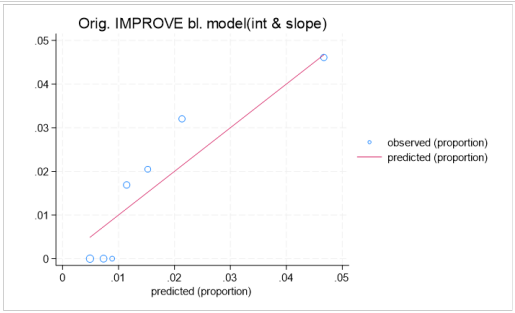
a)



b)



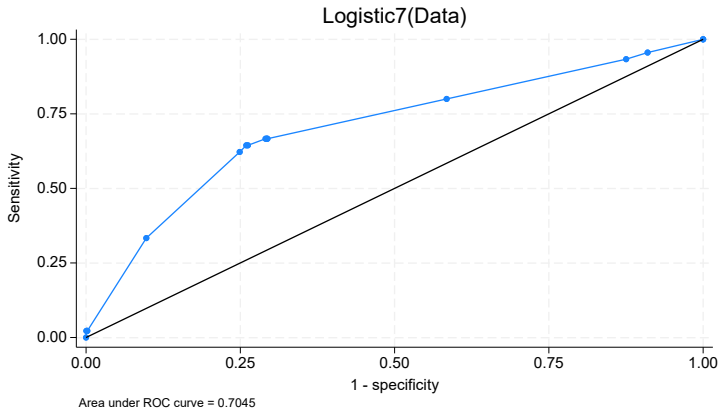
c)

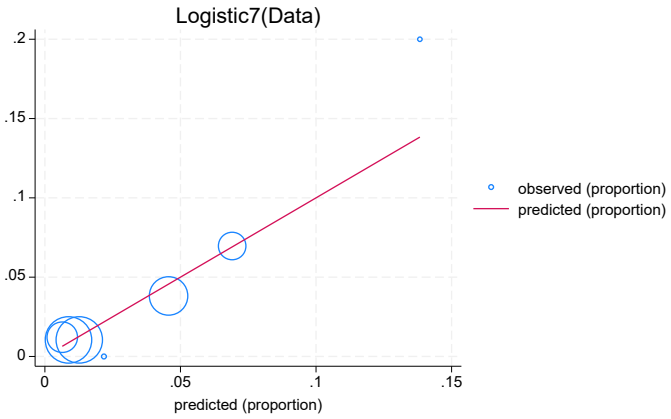


d)

```
==================  UpdatedImproveBleed1  ====================
Group         N       Obs (%)        Exp (%)       Min %     Max %       HL
    1       380     0 (0.0)        1.9 (0.5)         0.3       0.5     1.87
    2       333     0 (0.0)        2.4 (0.7)         0.6       0.8     2.45
    3       162     0 (0.0)        1.4 (0.9)         0.8       0.9     1.45
    4       296     5 (1.7)        3.4 (1.1)         0.9       1.3     0.77
    5       244     5 (2.0)        3.7 (1.5)         1.3       1.7     0.45
    6       281     9 (3.2)        6.0 (2.1)         1.7       2.5     1.54
    7       282    13 (4.6)       13.2 (4.7)         2.5      34.3     0.00
Total      1978    32 (1.6)       32.0 (1.6)         0.3      34.3     8.53

      number of observations =      1978
           number of groups =         7
Hosmer-Lemeshow chi2(7) =         8.53
           Prob > chi2 =          0.2878

                    ROC                    Asymptotic normal
        Obs       area     Std. err.      [95% conf. interval]

      1,978     0.7799     0.0282       0.72459     0.83523
```

Fig 1.1. External validation of IMPROVE bleeding risk assessment model





ModelLRVTE7

Group	N	Obs (%)	Exp (%)	Min %	Max %	HL
1	247	3 (1.2)	1.6 (0.6)	0.6	0.8	1.27
2	575	6 (1.0)	5.0 (0.9)	0.9	0.9	0.20
3	574	6 (1.0)	7.3 (1.3)	1.3	1.3	0.23
4	6	0 (0.0)	0.1 (2.2)	1.6	2.5	0.13
5	393	15 (3.8)	17.9 (4.6)	3.2	4.8	0.50
6	201	14 (7.0)	13.9 (6.9)	6.9	6.9	0.00
7	5	1 (20.0)	0.7 (13.8)	8.7	17.5	0.16
Total	2001	45 (2.2)	46.5 (2.3)	0.6	17.5	2.49

number of observations = 2001
number of groups = 7
Hosmer-Lemeshow chi2(7) = 2.49
Prob > chi2 = 0.9276
(note: graph HLModelLRVTE7 not found)

Obs	ROC area	Std. err.	Asymptotic normal [95% conf.	interval]
2,001	0.7045	0.0430	0.62018	0.78878

Fig 1.2. Internal validation of IMPROVE VTE risk assessment model

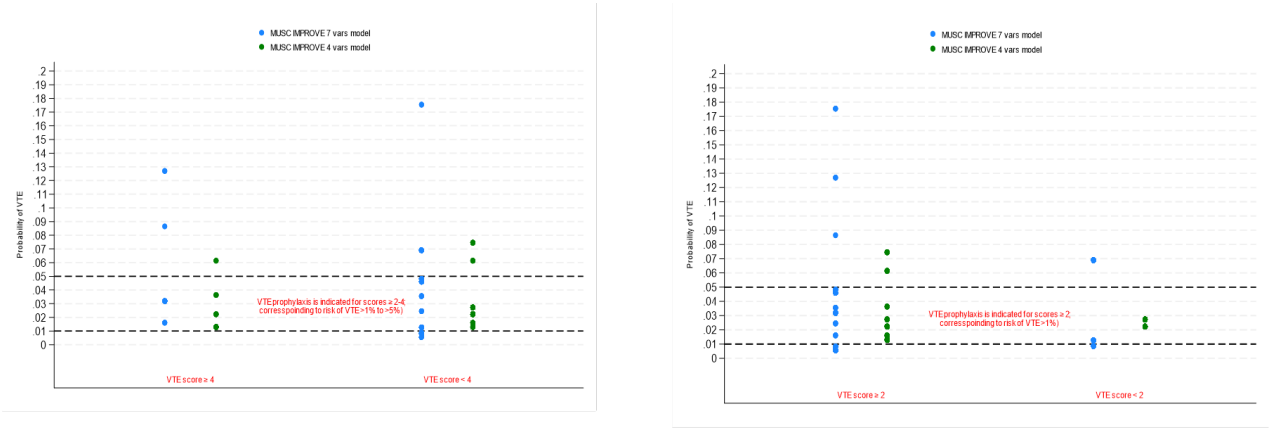


Fig 1.3 Probability of VTE as a function of IMPROVE scores

App 5 Best Evidence Approach Sensitivity Analysis

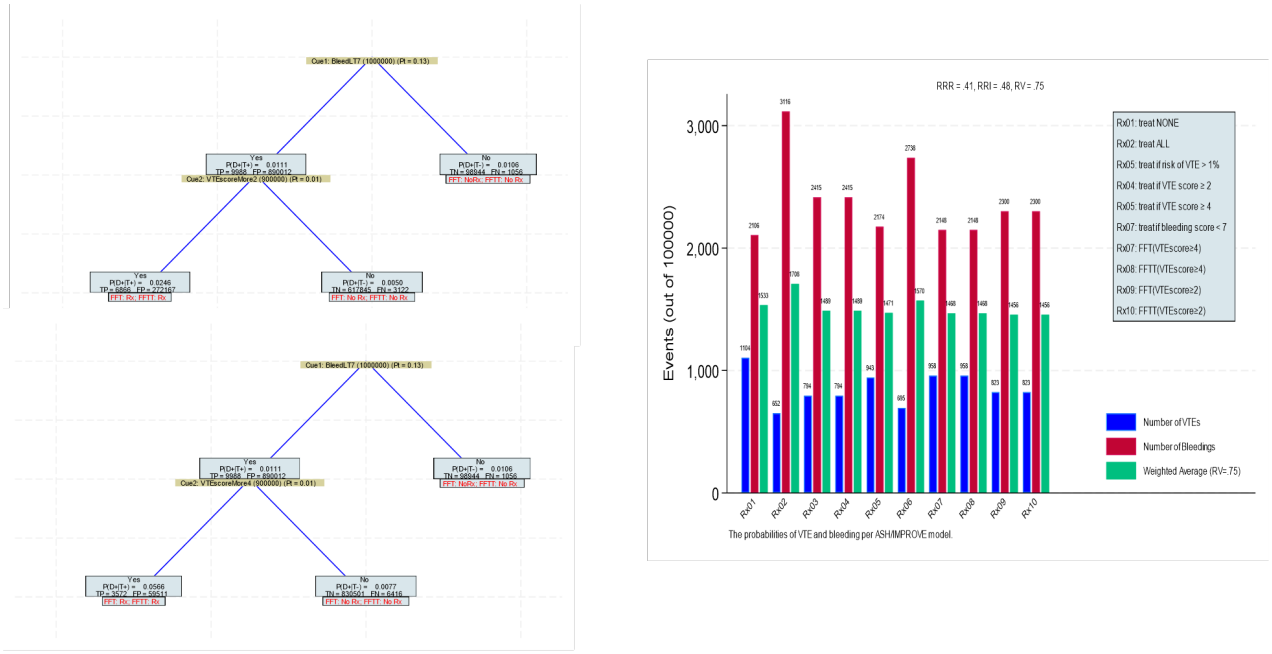


Fig 1.1 Best evidence approach impact analysis: effect of RV=0.75

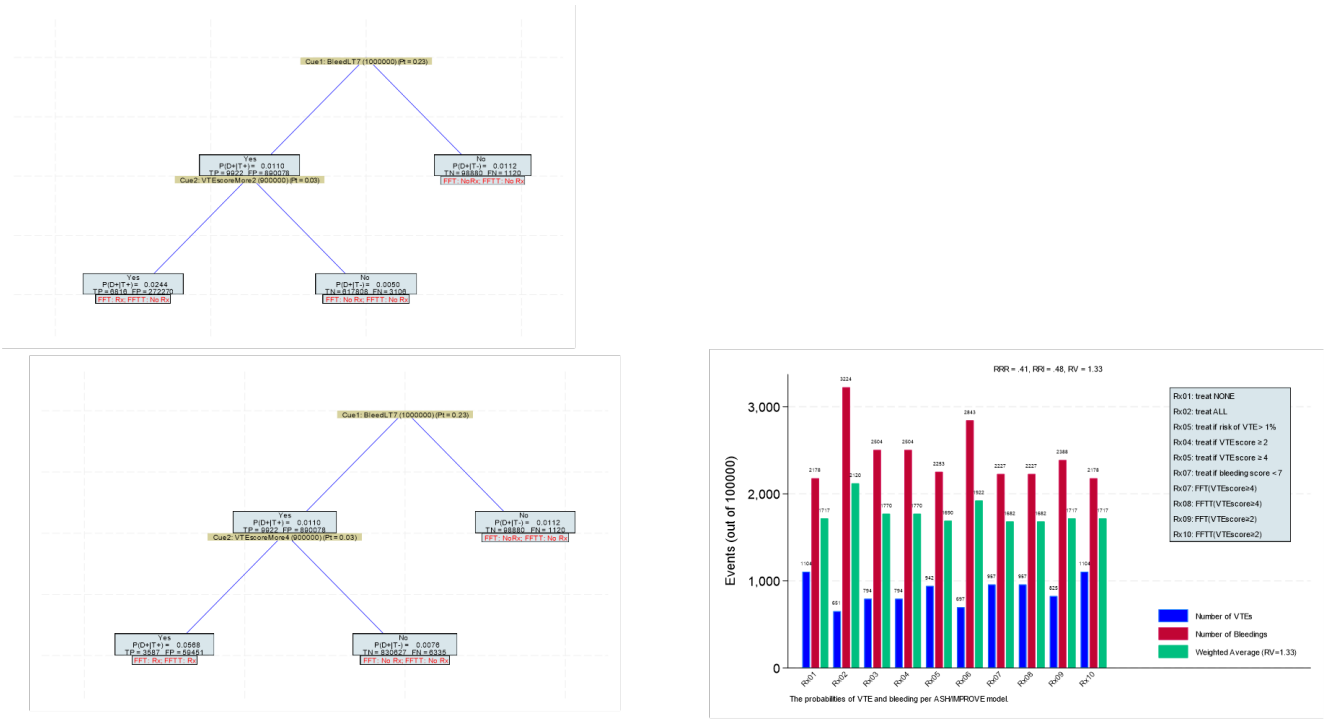
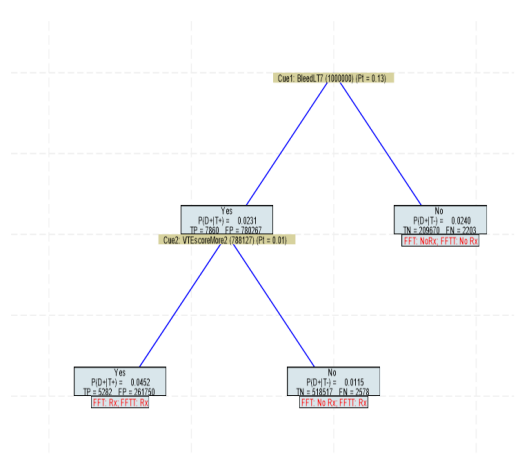


Fig 1.2 Best evidence approach impact analysis: effect of RV=1.33

App 6. Learning health systems [best evidence (ASH)+ MUSC data; probabilities for VTE assumes scores 0 and 1; ≥ 2] sensitivity analyses



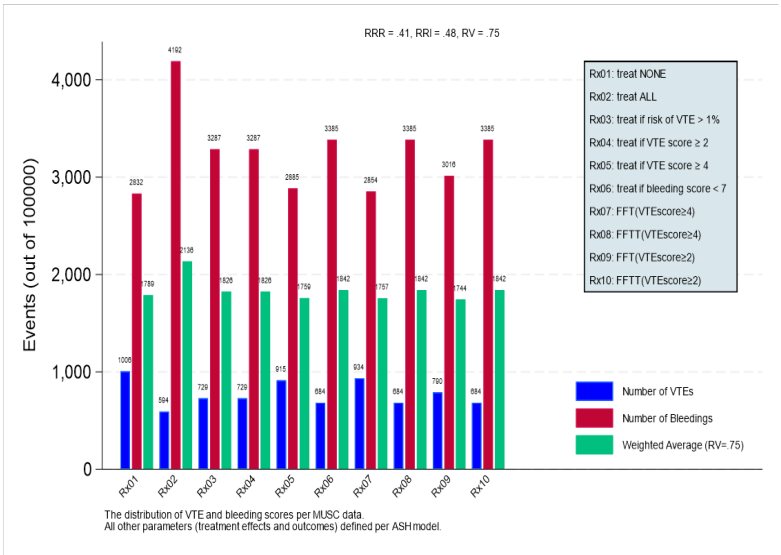
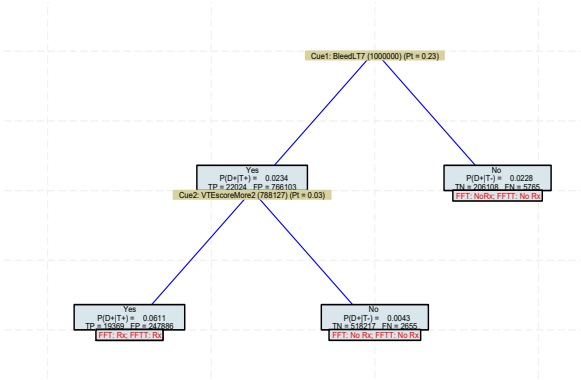


Fig 1.1. Learning health systems approach impact Analysis: effect of RV=0.75



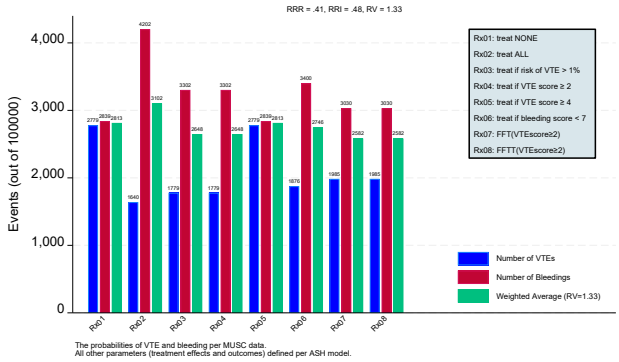


Fig 1.2. Learning health systems approach impact Analysis: effect of RV=1.33

App 7. Real-world MUSC data sensitivity analyses

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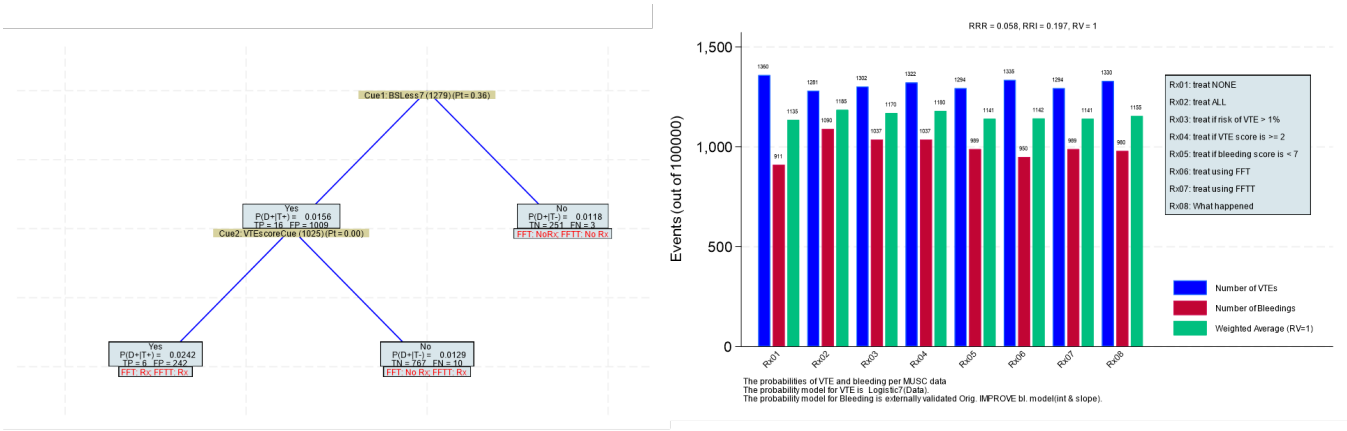
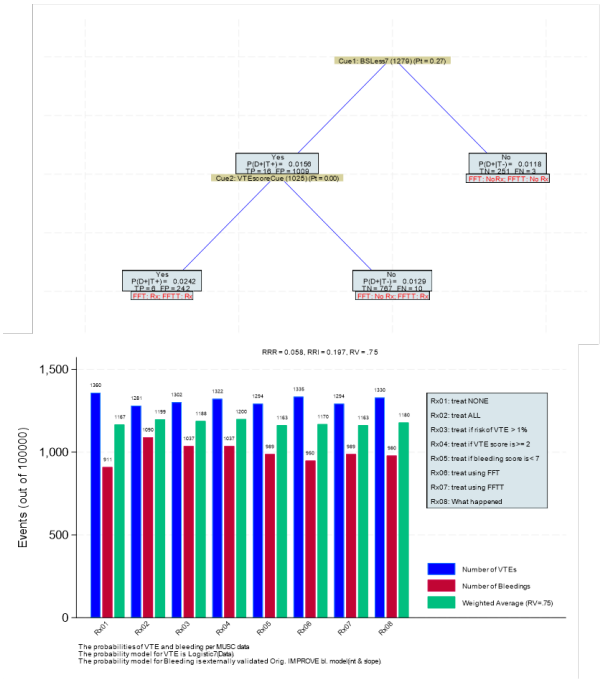


Fig 1.1. Real-world MUSC data sensitivity analyses: effect of RV=1

RV=0.75



RV=1.33

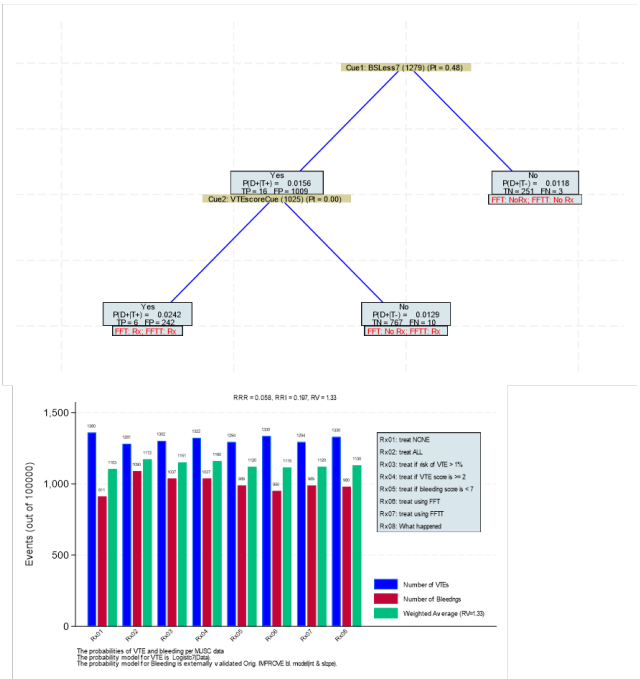
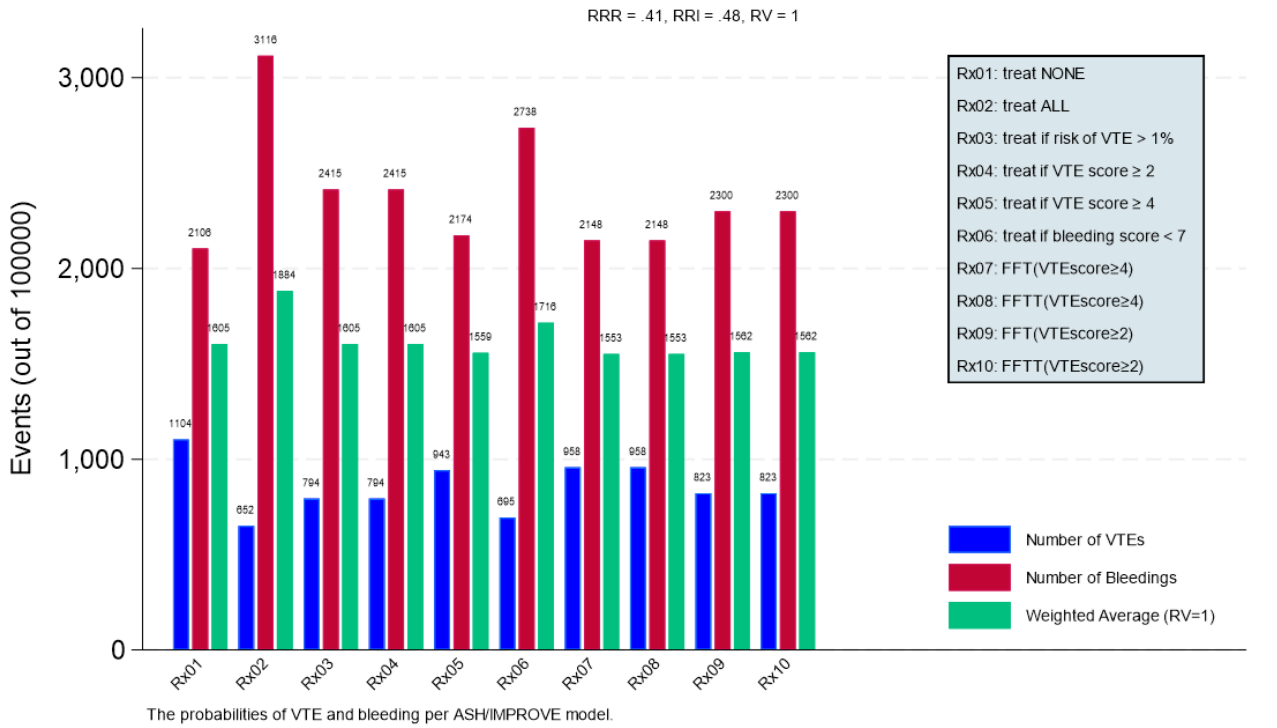


Fig 1.2. Real-world MUSC data sensitivity analyses: effect of RV=0.75 and 1.33

Fig 2 Sensitivity analysis: considering major bleeding only*



*The strategies Rx09 and Rx10 (FFT based on IMPROVE VTE score ≥ 2) are best strategies for VTE prophylaxis if only major bleeding was considered in the analysis

Appendix 8

Calculation of unnecessary costs/wasted resources

We calculated current costs = bleed_outcome14*11,189*1.88 + vte_outcome90*14263*1.42 + VTEprophylaxis*Hosp_stay_days*2.63 + Hosp_stay_days*2511

where 11,189 refers to direct major bleeding costs reported by O'Brien and Caro[7], and 14,263 refers to 30 days VTE-related total medical costs as reported by Lin et al[8]; 1.88 and 1.42 represent inflation conversion factors to January 2024 dollars; $2.63 daily costs of enoxaparin at prophylactic dose; $2,511 represent a daily cost for staying in a hospital in South Carolina (https://www.benzinga.com/money/average-cost-of-hospital-stays-with-and-without-medicare)

We define unnecessary costs as those related to VTE prophylaxis (overuse)= VTE prophylaxis is given for bleeding score ≥7 or VTE score <2, and failure to give VTE prophylaxis (underuse) = VTE prophylaxis is NOT given if VTE score ≥2 and bleeding score <7.

Thus, as shown in the figure, Unnecessary Costs = Current Costs - Required Costs

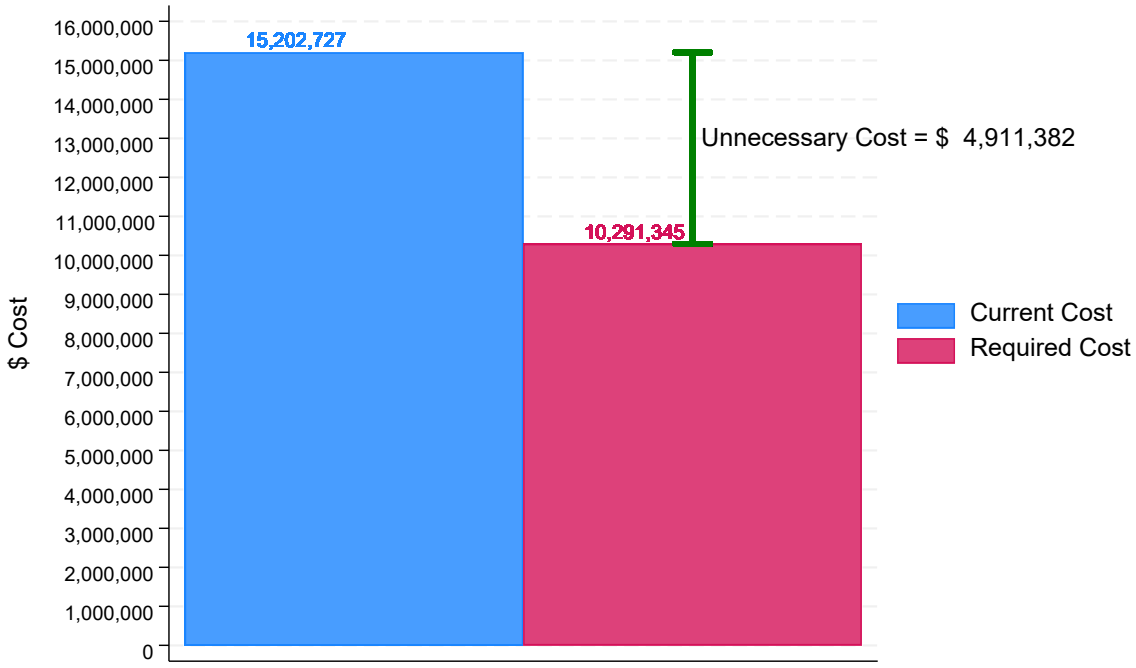


Fig 1. Calculations of unnecessary costs (per year for our MUSC cohort).

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