Risk assessment and prevention of Venous Thromboembolism (VTE)

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Disclosures for Doyeun Oh

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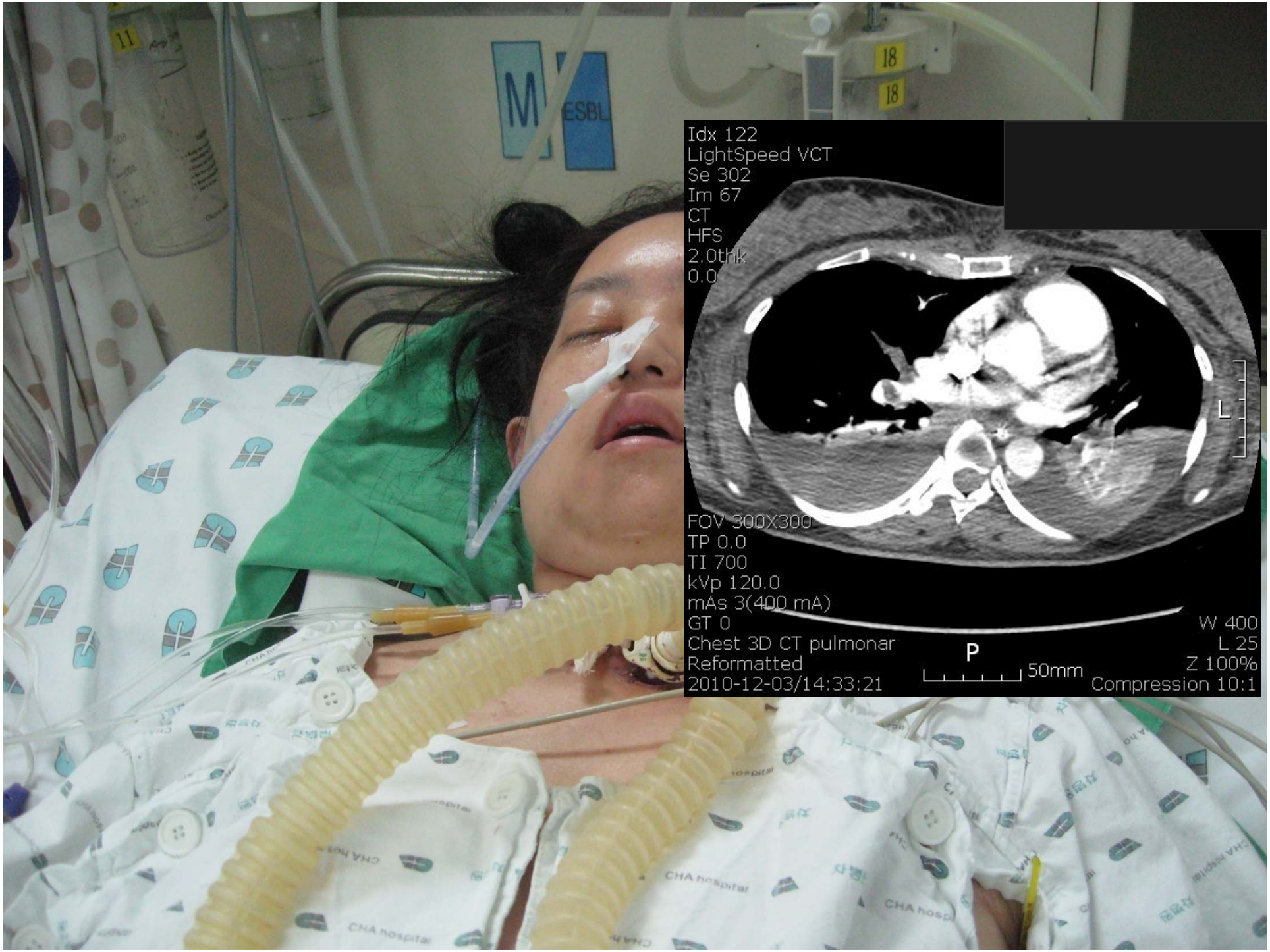
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Contents

- Rationale of thromboprophylaxis
- Risk factors of VTE
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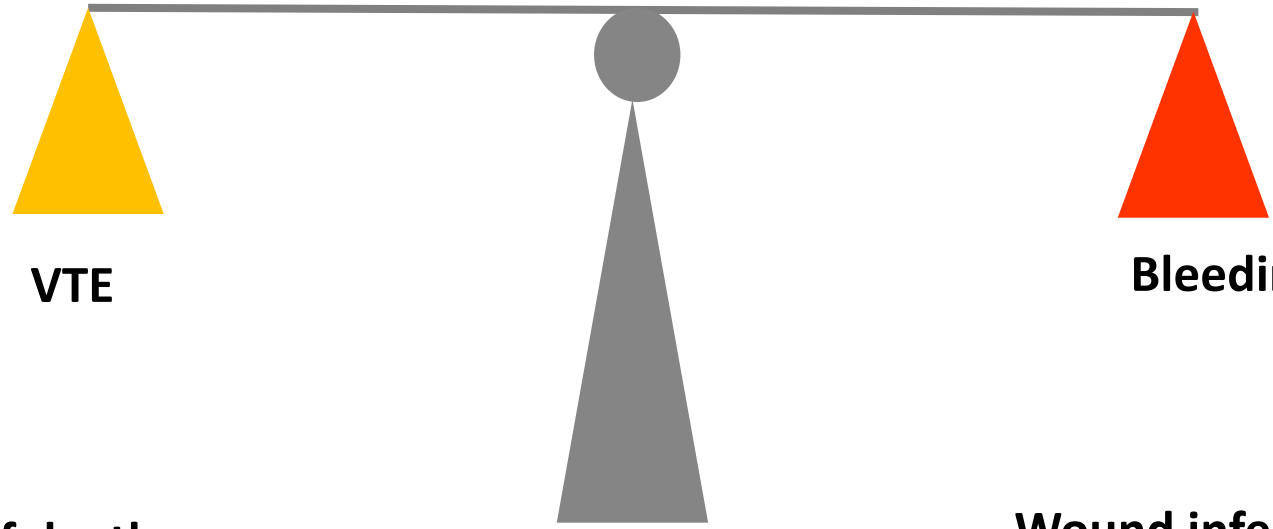
Rationale of thromboprophylaxis

- The high incidence of VTE in hospitalized patients.
- The high mortality of pulmonary embolism without prompt management.
- VTE is a major cause of sudden death in hospitalized patients.
- The difficulty of early diagnosis due to vague symptomatology.
- Pharmacologic prophylaxis reduces the incidence of VTE.
- VTE prophylaxis is cost-effective.

Arch Intern Med 1991;151:933-8
JAMA 1987; 257:203–208
Arch Intern Med 1995; 155:757–764

Risks and Benefits of Thromboprophylaxis



Risk of death or morbidity
Unexpected cost
Malpractice sue

Wound infection
Surgical failure
Adverse effect
Unnecessary cost
Malpractice sue

Risks factors of VTE

- Prior VTE
- Major surgery
- Trauma
- Old age
- Cancer
- Acquired or familial thrombophilia
- Immobilization
- Hormone (estrogen) treatment
- Obesity

Risks factors of bleeding

- Prior bleeding
- Old age
- Cancer
- Renal/liver dysfunction
- Thrombocytopenia
- Peptic ulcer
- Concurrent antithrombotic drug
- Stroke
- Severe hypertension

Process of thromboprophylaxis

- Assess the risk of VTE
- Assess the risk of prophylaxis (bleeding)
- Prescribe appropriate prophylaxis

VTE risk assessment

Approach	Group	Individual
Rationale	Difficult to identify the small population of patients in the various groups who do not require thromboprophylaxis.	An increasing number of patient-specific thrombosis risk factors contribute to the substantial variability in VTE rates.
Advantage	Simple	Precision medicine
Disadvantage	Neglect individual variance	Complex
Evidence	Strong	Few
Example	Orthopedic surgery	General surgery

Geerts Wh, et al. Chest 2008;133(6 Suppl):381S-453S
Falck-Ytter Y, et al. Chest 2012;141:e278S-e325S

How to stratify the risk developing VTE ? (group approach)

Level of risk	Calf DVT (%)	Proximal DVT (%)	Clinical PE (%)	Fatal PE (%)
Very low	2	0.4	0.2	0.002
Low	10~20	2~4	1~2	0.1~0.4
Moderate	20~40	4~8	2~4	0.4~1.0
High	40~80	10~20	4~10	0.2~5

Falck-Ytter Y, et al. Chest 2012;141:e278S-e325S

Risk stratification of VTE in surgical patients (group approach)

Table 2—*Levels of Thromboembolism Risk in Surgical Patients Without Prophylaxis

Level of Risk Examples	Calf DVT, %	Proximal DVT, %	Clinical PE, %	Fatal PE, %	Successful Prevention Strategies
Low risk Minor surgery in patients < 40 yr with no additional risk factors	2	0.4	0.2	0.002	No specific measures Aggressive mobilization
Moderate risk Minor surgery in patients with additional risk factors; nonmajor surgery in patients aged 40–60 yr with no additional risk factors; major surgery in patients < 40 yr with no additional risk factors	10–20	2–4	1–2	0.1–0.4	LDUH q12h, LMWH, ES, or IPC
High risk Nonmajor surgery in patients > 60 yr or with additional risk factors; major surgery in patients > 40 yr or with additional risk factors	20–40	4–8	2–4	0.4–1.0	LDUH q8h, LMWH, or IPC
Highest risk Major surgery in patients > 40 yr plus prior VTE, cancer, or molecular hypercoagulable state; hip or knee arthroplasty, hip fracture surgery; major trauma; spinal cord injury	40–80	10–20	4–10	0.2–5	LMWH, oral anticoagulants, IPC/ES + LDUH/LMWH, or ADH

Geerts WH et al., Chest 2001;119:134S

Risk stratification of VTE in surgical patients (individual approach)

Each Risk Factor Represents 1 Point

- ❑ Age 41-60 years
- ❑ Minor surgery planned
- ❑ History of prior major surgery (< 1 month)
- ❑ Varicose veins
- ❑ History of inflammatory bowel disease
- ❑ Swollen legs (current)
- ❑ Obesity (BMI > 25)
- ❑ Acute myocardial infarction
- ❑ Congestive heart failure (< 1 month)
- ❑ Sepsis (< 1 month)
- ❑ Serious lung disease incl. pneumonia (< 1 month)
- ❑ Abnormal pulmonary function (COPD)
- ❑ Medical patient currently at bed rest
- ❑ Other risk factors_____

Each Risk Factor Represents 2 Points

- ❑ Age 60-74 years
- ❑ Arthroscopic surgery
- ❑ Malignancy (present or previous)
- ❑ Major surgery (> 45 minutes)
- ❑ Laparoscopic surgery (> 45 minutes)
- ❑ Patient confined to bed (> 72 hours)
- ❑ Immobilizing plaster cast (< 1 month)
- ❑ Central venous access

Each Risk Factor Represents 5 Points

- ❑ Elective major lower extremity arthroplasty
- ❑ Hip, pelvis or leg fracture (< 1 month)
- ❑ Stroke (< 1 month)
- ❑ Multiple trauma (< 1 month)
- ❑ Acute spinal cord injury (paralysis)(< 1 month)

Each Risk Factor Represents 3 Points

- ❑ Age over 75 years
- ❑ History of DVT/PE
- ❑ **Family history of thrombosis***
- ❑ Positive Factor V Leiden
- ❑ Positive Prothrombin 20210A
- ❑ Elevated serum homocysteine
- ❑ Positive lupus anticoagulant
- ❑ Elevated anticardiolipin antibodies
- ❑ Heparin-induced thrombocytopenia (HIT)
- ❑ Other congenital or acquired thrombophilia

If yes:

Type_____

***most frequently missed risk factor**

For Women Only (Each Represents 1 Point)

- ❑ Oral contraceptives or hormone replacement therapy
- ❑ Pregnancy or postpartum (<1 month)
- ❑ History of unexplained stillborn infant, recurrent spontaneous abortion (≥ 3), premature birth with toxemia or growth-restricted infant

Total Risk Factor Score ☐

Caprini JA. Dis Mon. 2005;51:70–78.

Risk stratification of VTE in medical patients (individual approach)

Risk Factor	Points
Active cancer	3
Previous VTE	3
Reduced mobility	3
Already known thrombophilic condition	3
Recent (≤1 mo) trauma and/or surgery	2
Elderly age (70 y)	1
Heart and/or respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Acute infection and/or rheumatologic disorder	1
Obesity (BMI ≥ 30)	1
Ongoing hormonal treatment	1

In the Padua Prediction Score risk assessment model, high risk of VTE is defined by a cumulative score 4 points.

Kahn SR, et al. Chest 2012;141:e195S-e226S

Risk assessment models of VTE in hospitalized patients (Individual approach)

Model	Year	Risk factors
Caprini	2005	Prior VTE, major surgery, age, cancer, thrombophilia, immobilization, obesity, hormone treatment stroke, trauma, acute spinal cord injury (paralysis), thrombophilia, central venous access, plaster cast , acute myocardial infarction, CHF, varicose veins, Inflammatory bowel disease, sepsis, COPD or abnormal pulmonary function, severe lung disease, pregnancy or postpartum
Kucher	2005	Prior VTE, major surgery, age, cancer, thrombophilia, immobilization, obesity, hormone treatment
Roger	2007	Surgery type, performance status, sex, relative value score, cancer, transfusion, chemotherapy, ventilator dependency, anemia, jaundice, dyspnea, albumin, sodium, wound class, emergency
Padua	2010	Prior VTE, major surgery, age, cancer, thrombophilia, immobilization, obesity, hormone treatment, trauma, CHF, respiratory failure, acute myocardial infarction, stroke, active infection, rheumatologic disease
Improve	2011	Prior VTE, age, cancer, thrombophilia, immobilization, ICU/CCU stay
Geneva	2014	Prior VTE, age, cancer, thrombophilia, immobilization, obesity, hormone treatment CHF, respiratory failure, stroke, myocardial infarction, active infection, acute rheumatic disease, myeloproliferative syndrome, nephrotic syndrome, long travel , chronic venous insufficiency, pregnancy, dehydration
APEX	2014	Prior VTE, age, cancer, thrombophilia, immobilization, obesity, hormone treatment, chronic venous insufficiency, CHF, chronic respiratory failure, rheumatologic disorder, active infection, erythropoiesis stimulating agent

Modified from Stuck AK, et al. Thromb Haemost 2017; 117: 801–808

Prediction of VTE in hospitalized patients (individual approach)

Model	No of items	No of Subjects	VTE (%) at 3m	VTE (%) Low-risk	VTE (%) High-risk
Caprini	39	606	3.46	0	3.38-4
Kucher	8	190,821	3.7-4.5	NA	NA
Roger	26	183,069	0.63	0.103	1.456
Padua	11	1478	2.3	1.1	3.5
Geneva	19	1478	2.3	0.6	3.2
IMPROVE	7	15156	1.2	0.4-0.6	1.5-5.7
APEX	16	7513			0.9 vs 1.5

Modified from Stuck AK, et al. Thromb Haemost 2017; 117: 801–808

Risk assessment model of bleeding in VTE during anticoagulation

Model	Year	Risk factors
Nieuwenhuis HK	1991	WHO performance status, prior bleeding, cardiopulmonary resuscitation, recent trauma or surgery, leukocyte counts, platelet counts, duration of symptoms, and BSA
Kuijer PM	1999	age, female, cancer
Kearon C	2003	age, CVD, prior GI bleeding, renal dysfunction, liver disease, anemia, thrombocytopenia, DM, peptic ulcer, and the use of antiplatelet therapy
RIETE	2008	age, recent bleeding, anemia, cancer, PE, renal dysfunction
IMPROVE	2010	peptic ulcer, prior bleeding, thrombocytopenia, age, hepatic or renal dysfunction, ICU stay, central venous catheter, rheumatic disease, cancer, male.
EINSTEIN	2016	age, black race, anemia, cancer, and antiplatelet or non-steroidal anti-inflammatory therapy
VTE-BLEED	2016	cancer, male, hypertension, anemia, prior bleeding, age, renal dysfunction
ACCP	2016	age, prior bleeding, cancer, renal dysfunction, liver dysfunction, thrombocytopenia, CVD, DM, anemia, antiplatelet therapy, poor anticoagulant control, comorbidity, recent surgery, alcohol abuse, NSAID, frequent falls

Ruiz-Gimenez, et al. Thromb Haemost 2008;100:26-31
Kuijer PM, et al. Arch Intern Med 1999;159:457-60
Kearon C, et al N Engl J Med. 2003 Aug 14;349(7):631-9
Nieuwenhuis HK, et al Blood. 1991 Nov 1;78(9):2337-43
Decousus H, et al. Chest. 2011;139(1):69-79
Di Nislo M, et al. Thromb Haemost 2016;115:424-32
Klok FA, et al. Eur Respir J 2016;48:1369-76
Riva N, et al. Thromb Haemost 2014;112:511-21

Risk stratification for bleeding (VTE-BLEED)

Risk Factor	Points
Active cancer	2
Prior bleeding	1.5
Renal dysfunction	1.5
Anemia	1.5
Elderly age	1.5
Male with uncontrolled hypertension	1

High risk of bleeding is defined by a cumulative score ≥ 2 points.

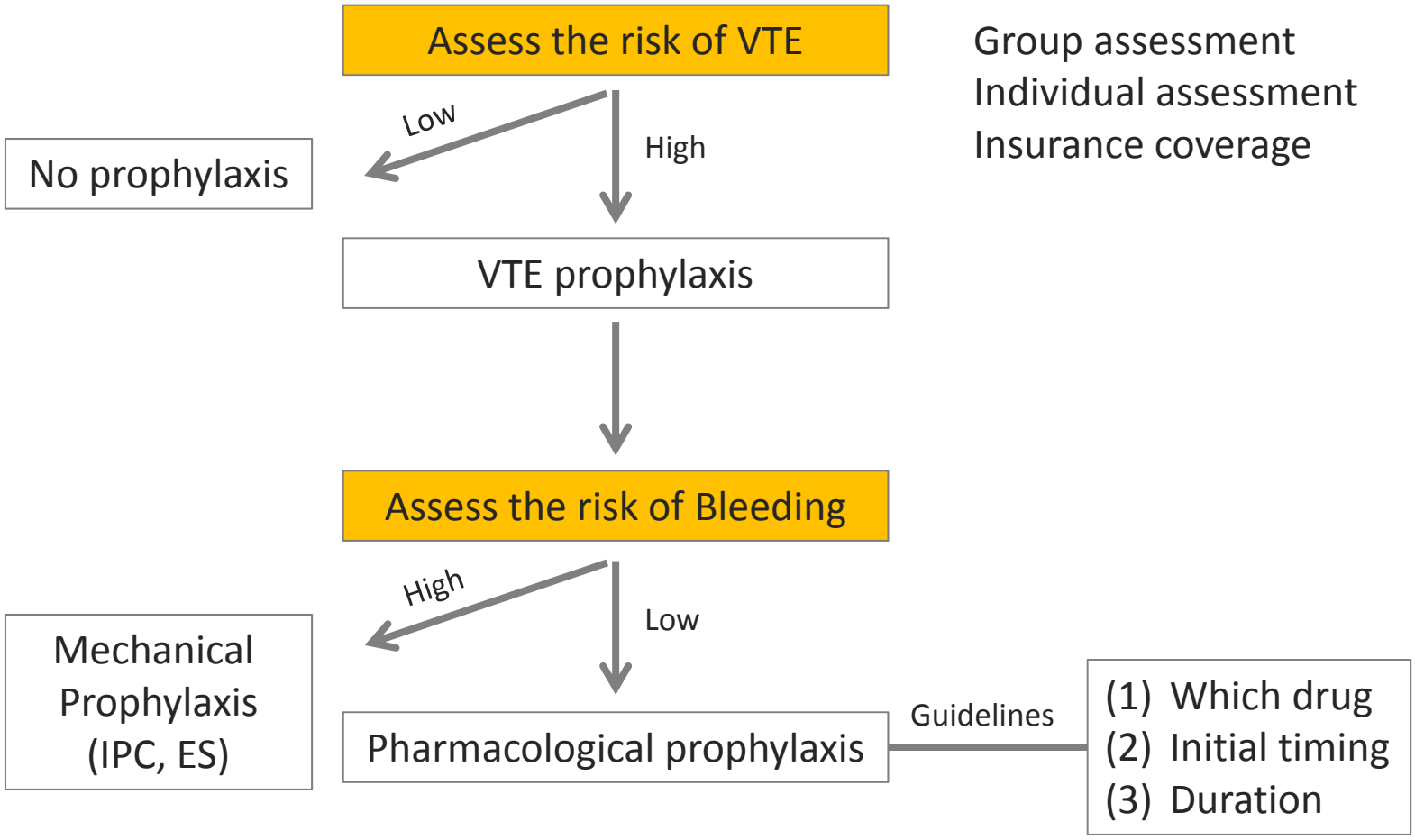
Major bleeding risk in low risk and high risk group was 0.22% vs 1.4% respectively.

Klok FA, et al. Eur Respir J. 2016;48:1369-1376

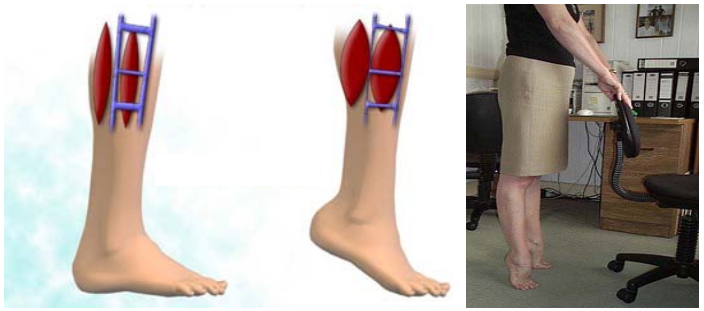
Overall, none of these models is ready for clinical use because management studies or external prospective validation are still needed.

Agnelli G and Becattini C. Hematology Am Soc Hematol Educ Program. 2013:471-7

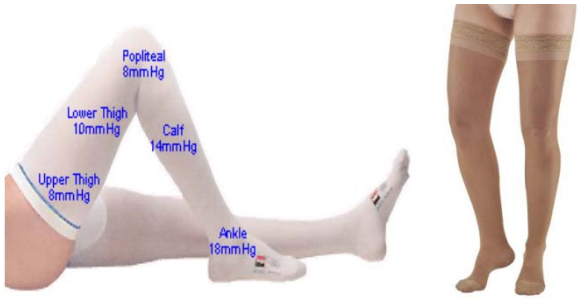
Prescribe appropriate prophylaxis



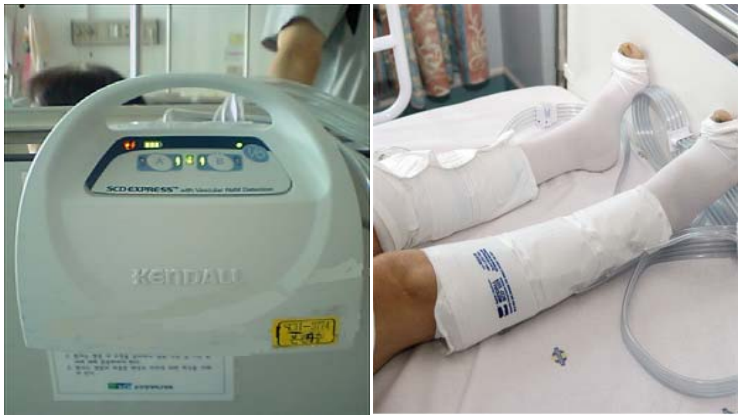
Non-pharmacologic methods



Early ambulation and calf muscle exercise



Graduated compression stocking (GCS)



Intermittent pneumatic compression (IPC)

Pharmacologic methods

- **Injection**
  - Low dose heparin (LDUH)
  - Low molecular weight heparin (LMWH)
  - Fondaparinux

- **Oral**
  - Warfarin
  - Rivaroxaban
  - Dabigatran
  - Apixaban
  - Edoxaban
  - Batrixaban

VTE prophylaxis methods

	Pharmacological	Mechanical
Advantage	Simple, effective	No bleeding
Disadvantage	Bleeding	Less effective
Evidence	Strong	Few

Methods of thromboprophylaxis

Methods	Prescriptions
Mechanical prophylaxis	
Graduated compression stocking (GCS)	Pressure of stocking with 16-20 mmHg
Intermittent pneumatic compression (IPC)	Repeat inflation (11-12 seconds) and deflation (60 seconds)
Pharmacological prophylaxis	
LMWH	0.2-1 mg/kg (20-100U/Kg) SC daily
LDUH	5,000 U SC every 8-12 hr
Warfarin	Dose adjust for PT (INR) of 1.5-2.5
Fondaparinux	2.5 mg SC daily
Rivaroxaban	10 mg PO daily
Dabigatran etexilate	150 mg PO daily
Apixaban	2.5 mg PO every 12 hr
Aspirin	100 mg PO daily

LMWH, low-molecular-weight heparin; LDUH, low-dose unfractionated heparin; SC, subcutaneously; PT, prothrombin time; INR, international normalized ratio; PO, per os.

Guidelines for VTE

- International guidelines

  - 9th ACCP (2012)

  - International consensus statement (2013)

  - NICE

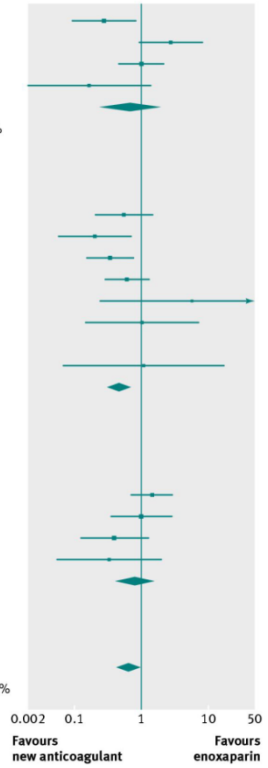
- Guidelines in Asia

  - Japanese, Korean, Asian guidelines

DOAC vs LMWH for the prevention in major orthopedic surgery

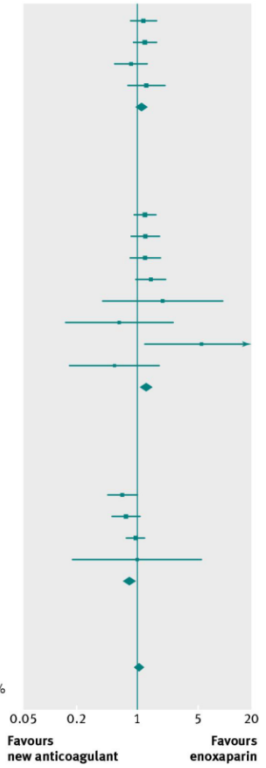
Symptomatic VTE

Trial	Events/total: New anticoagulant	Events/total: Enoxaparin	Weight (%)	Relative risk (95% CI)
Dabigatran				
RE-MODEL[19]	5/1402	9/699	7.5	0.28 (0.09 to 0.82)
RE-NOVATE[20]	22/2331	4/1162	7.7	2.74 (0.95 to 7.94)
RE-MOBILIZE[21]	20/1739	10/876	10.2	1.01 (0.47 to 2.14)
RE-NOVATE II[22]	1/1036	6/1019	3.1	0.16 (0.02 to 1.36)
Subtotal (95% CI)	48/6508	29/3756	28.5	0.71 (0.23 to 2.12)
Test for heterogeneity: τ^2=0.88, χ^2=11.26, df=3, P=0.01, I^2=73%				
Test for overall effect: Z=0.62, P=0.54				
Rivaroxaban				
RECORD 1[23]	6/2266	11/2275	8.2	0.55 (0.20 to 1.48)
RECORD 2[24]	3/1252	15/1257	6.5	0.20 (0.06 to 0.69)
RECORD 3[25]	8/1254	24/1277	9.8	0.34 (0.15 to 0.75)
RECORD 4[26]	11/1584	18/1564	10.3	0.60 (0.29 to 1.27)
PROOF CONCEPT[27]	1/84	0/162	1.5	5.75 (0.24 to 139.71)
ODIXA KNEE[28]	2/102	2/105	3.5	1.03 (0.15 to 7.17)
ODIXA HIP (twice daily)[29]	0/139	0/136		Not estimable
ODIXA HIP (once daily)[30]	1/147	1/160	2.0	1.09 (0.07 to 17.24)
Subtotal (95% CI)	32/6828	71/6936	41.9	0.48 (0.31 to 0.75)
Test for heterogeneity: τ^2=0.02, χ^2=6.34, df=6, P=0.39, I^2=5%				
Test for overall effect: Z=3.22, P=0.001				
Apixaban				
ADVANCE-1[31]	19/1599	13/1596	10.7	1.46 (0.72 to 2.94)
ADVANCE-2[32]	7/1528	7/1529	7.8	1.00 (0.35 to 2.85)
ADVANCE-3[33]	4/2708	10/2699	7.0	0.40 (0.13 to 1.27)
APROPOS[34]	2/310	3/152	4.0	0.33 (0.06 to 1.94)
Subtotal (95% CI)	32/6145	33/5976	29.6	0.82 (0.41 to 1.64)
Test for heterogeneity: τ^2=0.20, χ^2=4.98, df=3, P=0.17, I^2=40%				
Test for overall effect: Z=0.57, P=0.57				
Total (95% CI)	112/19 481	133/16 668	100.0	0.65 (0.43 to 0.99)
Test for heterogeneity: τ^2=0.29, χ^2=27.48, df=14, P=0.02, I^2=49%				
Test for overall effect: z=2.00, P=0.04				
Test for subgroup differences: χ^2=1.73, df=2, P=0.42, I^2=0%				



Clinically relevant bleeding

Trial	Events/total: New anticoagulant	Events/total: Enoxaparin	Weight (%)	Relative risk (95% CI)
Dabigatran				
RE-MODEL[19]	107/1402	46/699	9.0	1.16 (0.83 to 1.62)
RE-NOVATE[20]	141/2331	58/1162	10.0	1.21 (0.90 to 1.63)
RE-MOBILIZE[21]	55/1739	33/876	6.9	0.84 (0.55 to 1.28)
RE-NOVATE II[22]	37/1036	29/1019	5.9	1.25 (0.78 to 2.02)
Subtotal (95% CI)	340/6508	166/3756	31.8	1.12 (0.94 to 1.35)
Test for heterogeneity: τ^2=0.00, χ^2=2.30, df=3, P=0.51, I^2=0%				
Test for overall effect: Z=1.26, P=0.21				
Rivaroxaban				
RECORD 1[23]	105/2266	87/2275	10.6	1.21 (0.92 to 1.60)
RECORD 2[24]	63/1252	52/1257	8.3	1.22 (0.85 to 1.74)
RECORD 3[25]	54/1254	45/1277	7.7	1.22 (0.83 to 1.80)
RECORD 4[26]	66/1584	46/1564	8.1	1.42 (0.98 to 2.05)
PROOF CONCEPT[27]	3/84	3/162	0.8	1.93 (0.40 to 9.35)
ODIXA KNEE[28]	3/102	5/105	1.0	0.62 (0.15 to 2.52)
ODIXA HIP (twice daily)[29]	11/139	2/136	0.9	5.38 (1.22 to 23.83)
ODIXA HIP (once daily)[30]	4/147	8/60	1.3	0.54 (0.17 to 1.77)
Subtotal (95% CI)	309/6828	248/6936	38.6	1.25 (1.05 to 1.49)
Test for heterogeneity: τ^2=0.00, χ^2=7.40, df=7, P=0.39, I^2=5%				
Test for overall effect: Z=2.51, P=0.01				
Apixaban				
ADVANCE-1[31]	46/1599	69/1596	8.2	0.67 (0.46 to 0.96)
ADVANCE-2[32]	53/1528	72/1529	8.6	0.74 (0.52 to 1.04)
ADVANCE-3[33]	131/2708	138/2699	12.1	0.95 (0.75 to 1.19)
APROPOS[34]	4/310	2/152	0.7	0.98 (0.18 to 5.29)
Subtotal (95% CI)	234/6145	281/5976	29.5	0.82 (0.69 to 0.98)
Test for heterogeneity: τ^2=0.00, χ^2=3.10, df=3, P=0.38, I^2=3%				
Test for overall effect: Z=2.17, P=0.03				
Total (95% CI)	883/19 481	695/16 668	100.0	1.06 (0.92 to 1.22)
Test for heterogeneity: τ^2=0.03, χ^2=25.27, df=15, P=0.05, I^2=41%				
Test for overall effect: z=0.75, P=0.45				
Test for subgroup differences: χ^2=11.78, df=2, P=0.003, I^2=83%				



Gómez-Outes A, et al. BMJ 2012;344:e3675

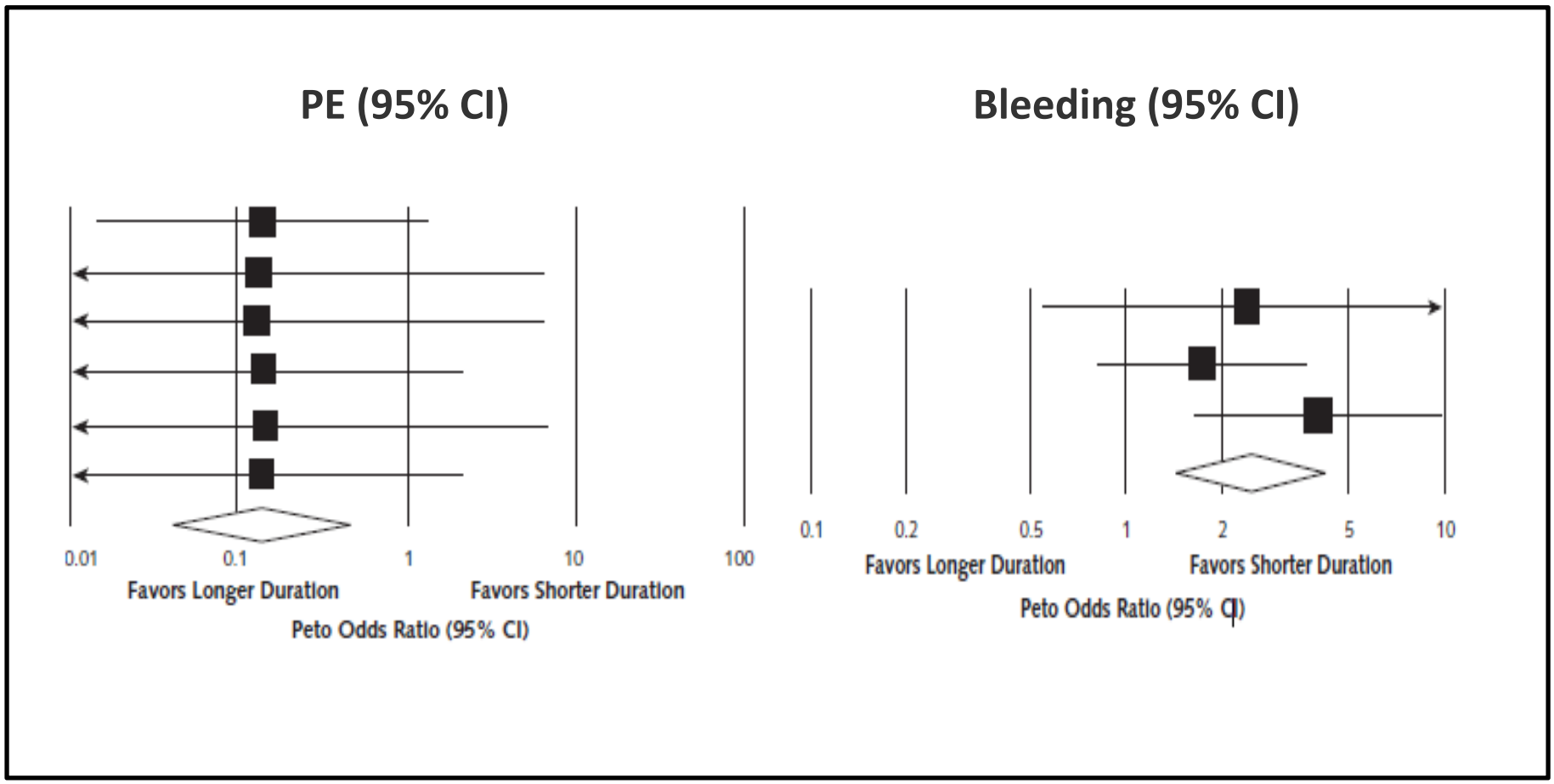
Extended Duration of Anticoagulants

- Extending thromboprophylaxis up to 35 days postoperation compared with 10 to 14 days will result in nine fewer symptomatic VTE per 1,000 without an appreciable increase in major bleeding.

- Extending thromboprophylaxis in the outpatient period for up to 35 days from the day of surgery rather than for only 10 to 14 days (2B)

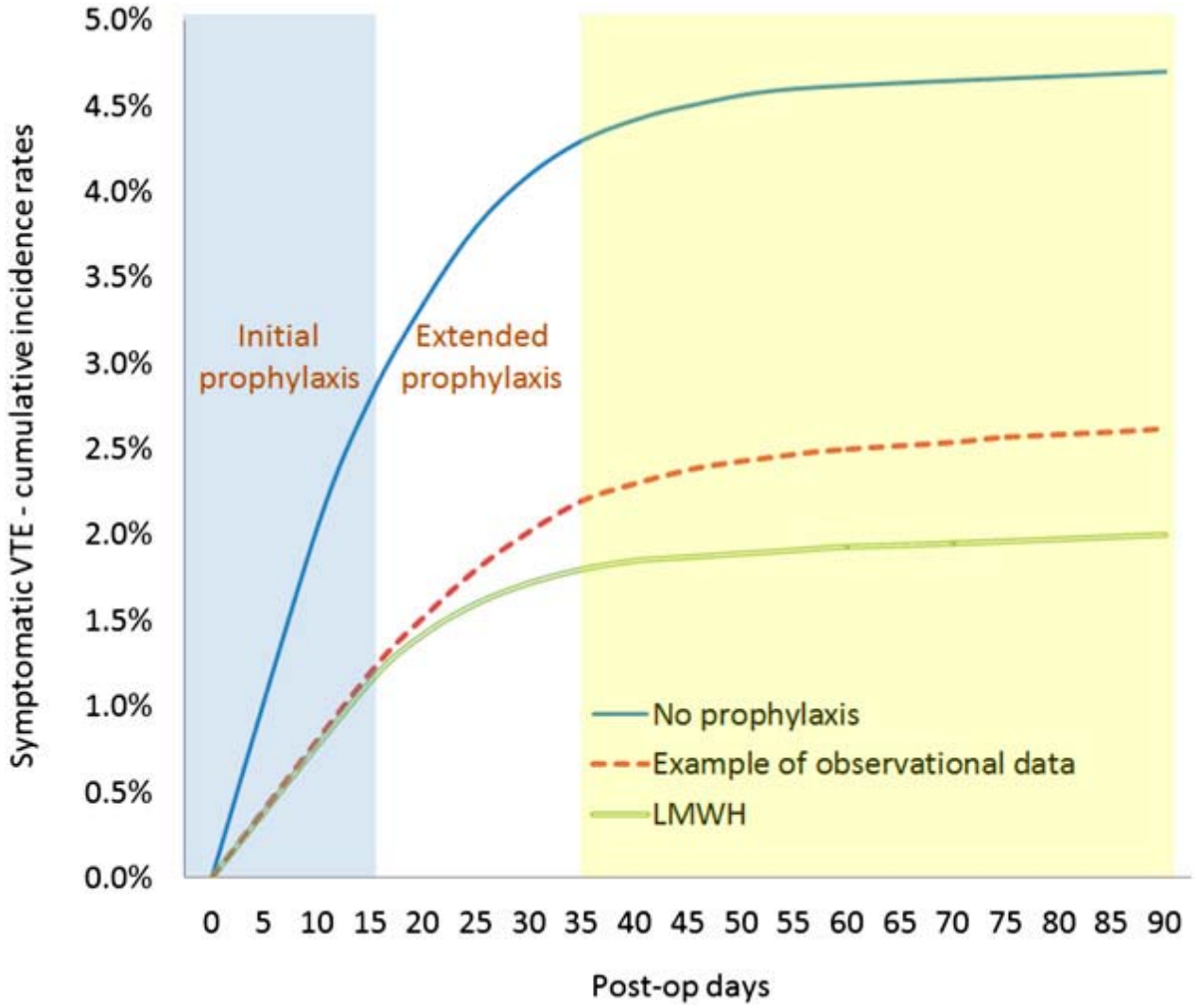
Falck-Ytter Y, et al. Chest 2012;141:e278S-e325S

Extended Duration of Anticoagulants



Sobieraj DM, et al. Ann Intern Med. 2012;156:720-727

Symptomatic VTE – cumulative incidence rates



Falck-Ytter Y, et al. Chest 2012;141:e278S-e325S

Timing of anticoagulation

- Risk of bleeding complications is closely linked to the timing of thromboprophylaxis around surgery. Perioperative LMWH resulted in major bleeding rates of 5% to 7%, whereas rates were in the 1% to 3% range with preoperative and postoperative administration. The increased risk of major bleeding outweighed any potential benefit of thromboprophylaxis.

- LMWH recommend to start either 12 h or more preoperatively or 12 h or more postoperatively rather than within 4 h or less preoperatively or 4 h or less postoperatively (Grade 1B).

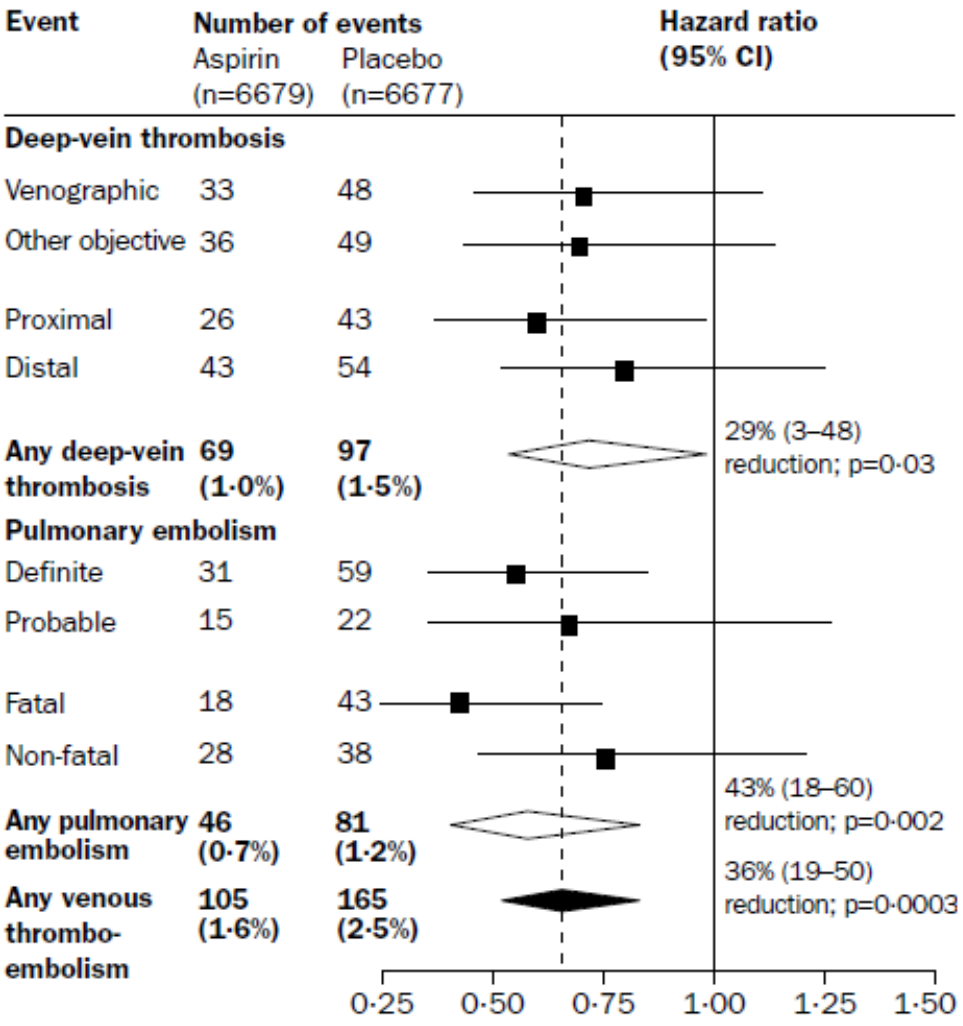
Aspirin

- Low-dose aspirin given before major orthopedic surgery will resulted in seven fewer symptomatic VTE per 1,000 with the expense of three more major bleeding episodes and two additional nonfatal myocardial infarction.

- Aspirin is a new option for the prevention of VTE after orthopedic surgery.

Falck-Ytter Y, et al. Chest 2012;141:e278S-e325S

Aspirin



PEP Trial Collaborative Group. Lancet 2000; 355: 1295–302

Prevention of VTE Hospitalized Medical Patients

Table 2. Components of the Primary and Secondary Efficacy Outcomes.*

Outcome	Cohort 1				Cohort 2				Overall Population			
	Betrixaban (N=1914)	Enoxaparin (N=1956)	Relative Risk (95% CI)	P Value†	Betrixaban (N=2842)	Enoxaparin (N=2893)	Relative Risk (95% CI)	P Value†	Betrixaban (N=3112)	Enoxaparin (N=3174)	Relative Risk (95% CI)	P Value†
	no./total no. (%)				*no./total no. (%)*				*no./total no. (%)*			
Primary end point												
Primary efficacy outcome‡	132/1914 (6.9)	166/1956 (8.5)	0.81 (0.65–1.00)	0.054	160/2842 (5.6)	204/2893 (7.1)	0.80 (0.66–0.98)	0.03	165/3112 (5.3)	223/3174 (7.0)	0.76 (0.63–0.92)	0.006
Asymptomatic proximal deep-vein thrombosis	105	129	NA	NA	128	162	NA	NA	133	176	NA	NA
Symptomatic proximal or distal deep-vein thrombosis	14	19	NA	NA	14	21	NA	NA	14	22	NA	NA
Symptomatic nonfatal pulmonary embolism	5	17	NA	NA	9	18	NA	NA	9	18	NA	NA
Death from venous thromboembolism	12	11	NA	NA	13	13	NA	NA	13	17	NA	NA
Key secondary end points												
Symptomatic venous thromboembolism§	30/2314 (1.3)	44/2313 (1.9)	0.67 (0.42–1.07)	0.09	35/3407 (1.0)	49/3407 (1.4)	0.71 (0.46–1.09)	0.11	35/3721 (0.9)	54/3720 (1.5)	0.64 (0.42–0.98)	0.04
Primary efficacy outcome plus death from any cause¶	232/2014 (11.5)	264/2054 (12.9)	0.89 (0.75–1.05)	0.16	291/2973 (9.8)	329/3018 (10.9)	0.90 (0.77–1.04)	0.15	298/3245 (9.2)	359/3310 (10.8)	0.85 (0.73–0.98)	0.02
Net clinical benefit‖	141/1914 (7.4)	174/1956 (8.9)	0.82 (0.66–1.01)	0.07	174/2842 (6.1)	214/2893 (7.4)	0.82 (0.68–1.00)	0.05	179/3112 (5.8)	233/3174 (7.3)	0.78 (0.65–0.95)	0.01

betrixaban160mg D1, 80mg qd D2-35

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

Prevention of VTE Major Orthopedic Surgery

Surgery type	Pharmacologic	Mechanical
Total Hip Arthroplasty Total Knee Arthroplasty	1B (minimum of 10 to 14 days) (LMWH, fondaparinux, apixaban, dabigatran, rivaroxaban, LDUH, adjusted-dose VKA, aspirin)	1C (IPC)
In THA or TKA, irrespective of the concomitant use of an IPCD or length of treatment, we suggest the use of LMWH in preference to the other agents		
Hip Fracture Surgery	1B (minimum of 10 to 14 days) (LMWH, fondaparinux, LDUH, adjusted-dose VKA, aspirin)	1C (IPC)
In HFS, irrespective of the concomitant use of an IPCD or length of treatment, we suggest the use of LMWH in preference to the other agents		
LMWH recommend to start either 12 h or more preoperatively or 12 h or more postoperatively rather than within 4 h or less preoperatively or 4 h or less postoperatively (Grade 1B)		
Extending thromboprophylaxis in the outpatient period for up to 35 days from the day of surgery rather than for only 10 to 14 days (2B)		
Dual prophylaxis with an antithrombotic agent and an IPCD during the hospital stay (2C)		

Falck-Ytter Y, et al. Chest 2012;141:e278S-e325S

Prevention of VTE Non-orthopedic Surgery

Patient type	Pharmacologic	Mechanical
High risk (<6%) (Caprini score >5)	1B (LMWH, LDUH)	
Moderate risk (<3%) (Rogers score > 10; Caprini score, 3-4)	2B (LMWH, LDUH)	2C
Low risk (<1.5%) (Rogers score, <7; Caprini score, 1-2)	X (1B)	2C
Very low risk (<0.5%) (Rogers score, <7; Caprini score, 0)	X (1B)	X (1B)
High risk for VTE + high risk for bleeding		2C (GCS, IPC)
High risk for VTE + Contraindication of LMWH, LDUH	2C Low-dose ASA, fondaparinux	2C (IPC)
Extended-duration phamacologic prophylaxis (4 weeks) with LMWH over limited-duration prophylaxis		1B
Dual prophylaxis with an antithrombotic agent and an IPCD during the hospital stay (2C)		2C

Falck-Ytter Y, et al. Chest 2012;141:e278S-e325S

Prevention of VTE Hospitalized Medical Patients

Acutely Ill Medical Patients	Pharmacologic	Mechanical
increased risk of thrombosis	1B (LMWH, LDUH, fondaprinux) betrixaban	
low risk of thrombosis	X (1B)	X (1B)
high risk for bleeding	X (1B)	
increased risk of thrombosis + high risk for bleeding		2C (GCS, IPC)
Critically Ill Patients		
critically ill patients	2C (LMWH, LDUH)	
high risk for major bleeding		2C (GCS, IPC)

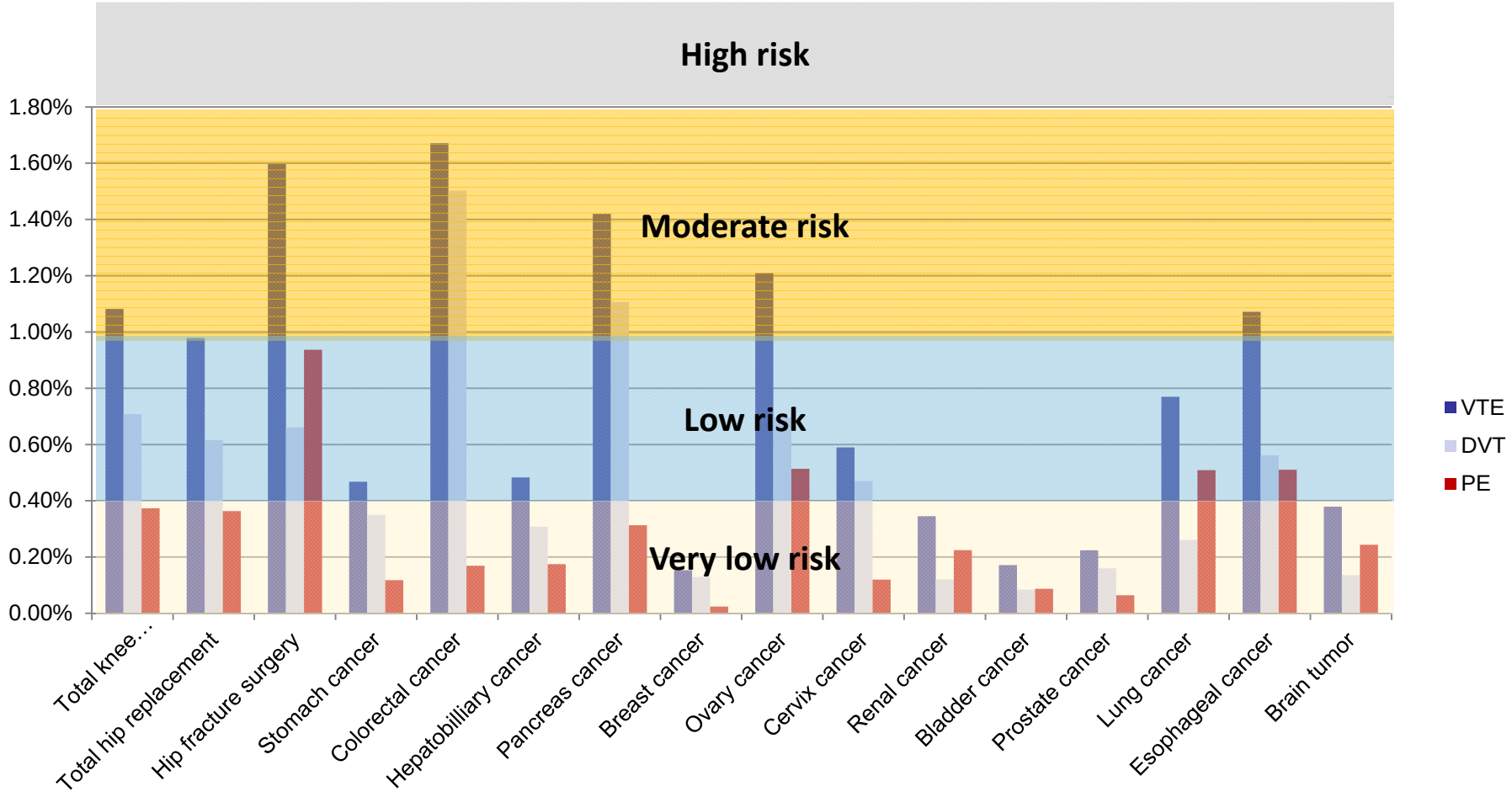
Kahn SR, et al. Chest 2012;141:e195S-e226S
Cohen AT, et al. N Engl J Med 2016;375:534-44

Recent updates of current guidelines

- Risk assessment and stratification of both VTE and bleeding is recommend for the prescription of thromboprophylaxis.
- Patient's value and preference is more emphasized in new guidelines.
- DOAC is preferred in orthopedic surgery over warfarin or LMWH.
- To avoid the risk of post-operative bleeding, recent guidelines recommend starting pharmacologic prophylaxis 12h before or after surgery.
- Extended duration of thromboprophylaxis for up to 35 days after surgery is recommended.
- Aspirin is a new option for the prevention of VTE after orthopedic surgery.
- Batrixaban is known to be effective for the prevention of VTE in acute ill medical patients.

Ethnic differences of VTE Prevention Strategy; the Korean VTE Prevention Guidelines Updates

Stratification of VTE risk is different in Korea



Yhim HY, et al. J Thromb Haemost. 2014;12:1035-43

Proposal of the guidelines according to the levels of VTE risk in Korea

	Types of surgery	Modified risk	Thromboprophylaxis
Orthopedic Surgery	Total knee replacement	moderate	LMWH; fondaparinux; darbigatran, apixaban, or rivaroxaban; UH; warfarin; aspirin; or IPC*
	Total hip replacement	moderate	LMWH; fondaparinux; darbigatran, apixaban, or rivaroxaban; UH; warfarin; aspirin; or IPC*
	Hip fracture surgery	moderate	LMWH; fondaparinux; UH; warfarin; aspirin; or IPC*
Cancer Surgery	Stomach cancer	low	IPC
	Colorectal cancer	moderate	LMWH, UH or IPC*
	Hepatobilliary cancer	low	IPC
	Pancreas cancer	moderate	LMWH, UH or IPC*
	Breast cancer	very low	early ambulation
	Ovary cancer	moderate	LMWH, UH or IPC*
	Cervix cancer	low	IPC
	Renal cancer	very low	early ambulation
	Bladder cancer	very low	early ambulation
	Prostate cancer	very low	early ambulation
	Lung cancer	low	IPC
	Esophageal cancer	moderate	LMWH, UH or IPC*
	Brain tumor	low	IPC

*** for patients with bleeding risk**

Summary

- Current guidelines on VTE is based on Caucasian data
- Incidence of VTE in Korean population is lower than that of Caucasian.
- Several data showed that VTE prophylaxis recommendations in Korea need to be different from those of ACCP guidelines.
- Because Asians are heterogeneous in race and ethnicity, the recommendations may need to be individualized by their own data.

Lack of awareness is huddle to implement

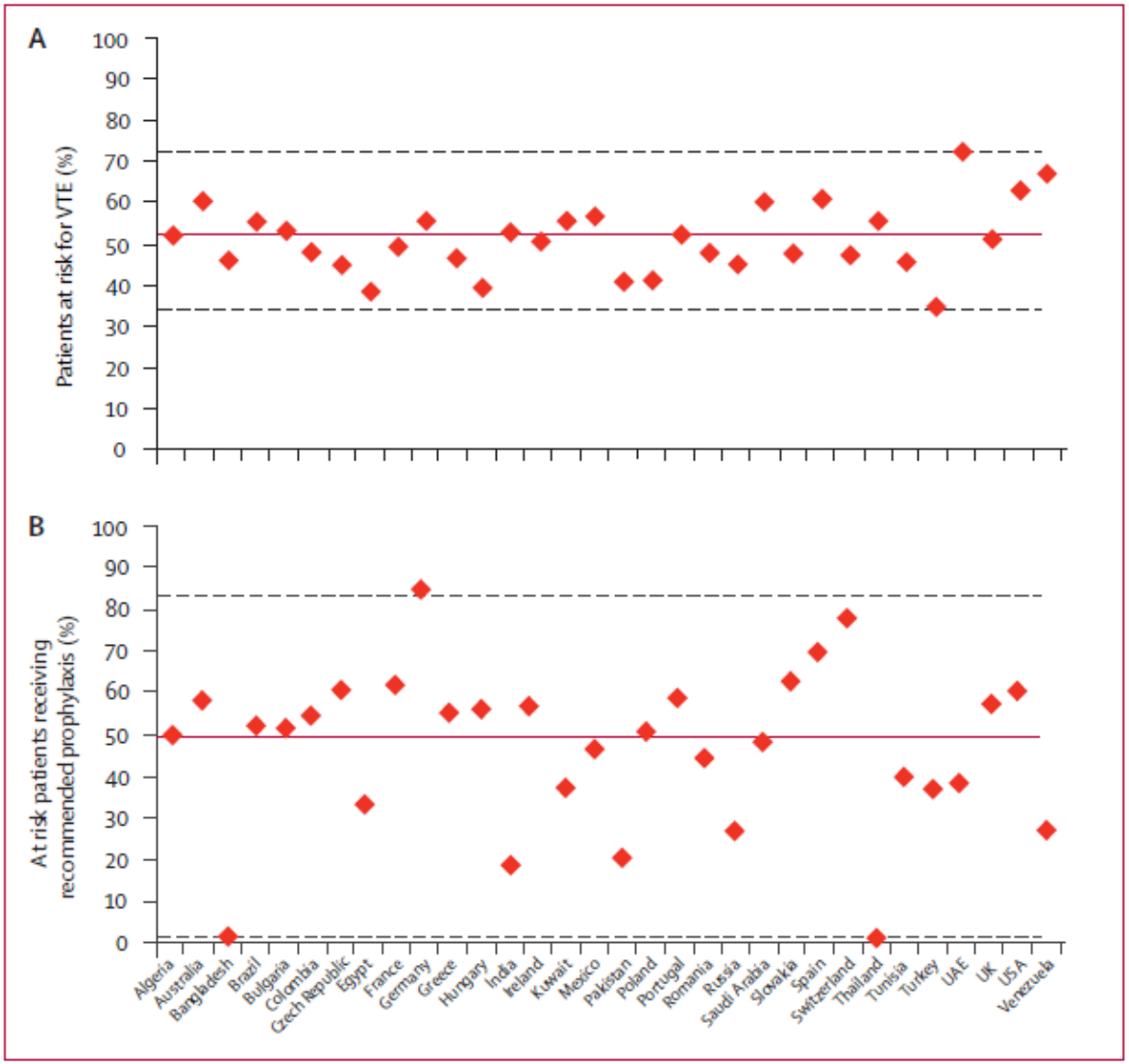


Figure 2: **Proportion of patients at risk for VTE (A) and proportion of at-risk patients receiving recommended prophylaxis (B)**

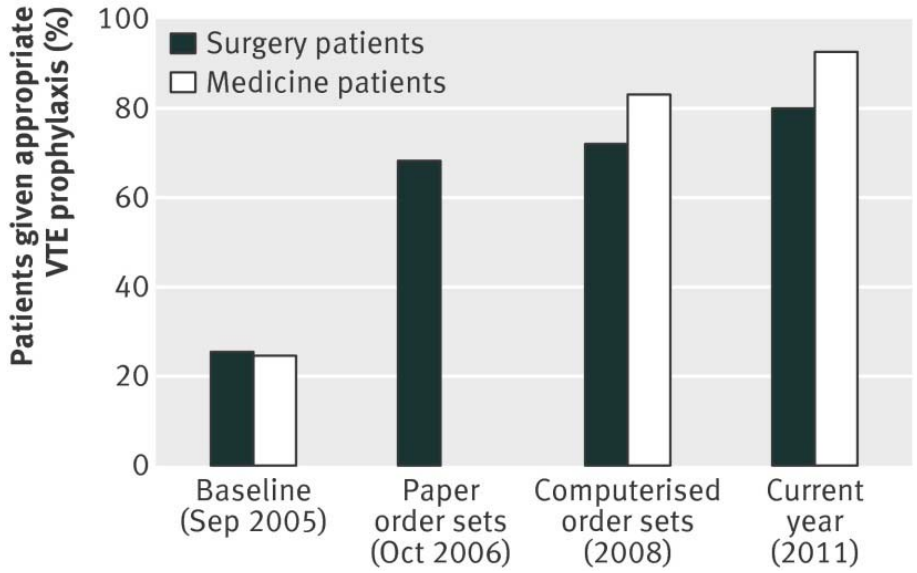
Cohen AT, et al. Lancet. 2008;371:387-394

Implementation of guidelines

- Education
- Mandatory documented risk assessment and order set
- Multidisciplinary team
- Financial sanctions

Lessons from Johns Hopkins VTE Prevention Experience

- The key was a core team of **multidisciplinary professionals** who were willing to work.
- The paper order sets provided standardization of VTE prevention but were labor intensive, lacked a forcing function, and made assessment difficult. These shortcomings were eliminated with **computerized VTE prophylaxis order** sets.



Streiff MB et al. BMJ 2012;344:e3935

Conclusions

- Pharmacologic thromboprophylaxis using warfarin, heparin, low molecular weight heparin (LMWH), fondaparinux or direct oral anticoagulant (DOAC) is recommended as the initial form of prophylaxis.
- Mechanical method using intermittent pneumatic compression (IPC) or compression stockings is indicated in the patient who has contraindication to anticoagulation.
- The VTE risk should be assessed and stratified and pharmacologic prophylaxis is indicated in moderate or high risk patients without risk of bleeding.
- Several risk assessment models for the prevention of individual VTE have been developed but they still need further validation for generalized application.
- Current guidelines in the prevention of VTE are mostly based on the evidence from Caucasian data and there is a limitation to apply it without modification in Asian population and now several Asian guidelines have been developed based on Asian data and expert opinions.
- Awareness of physicians and nurses on the risk assessment of VTE and their active participation in the prevention of VTE is necessary for better thromboprophylaxis in the hospital.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