

Thromboprophylaxis in hospitalized medical and surgical patients

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DISCLOSURES

- Advisory boards: Servier, Portola, Sanofi
- Investigator for Bayer and Sanofi-sponsored clinical trials

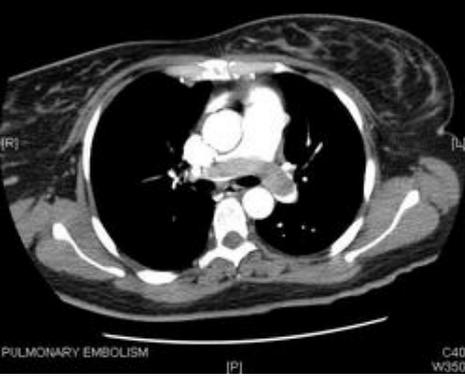
Objectives

- To understand the rationale for and approach to thromboprophylaxis in hospitalized patients (incl. risk assessment)
- To describe the particular approach to thromboprophylaxis in hospitalized patients with cancer
- To be aware of the most recent consensus guidelines on venous thromboembolism (VTE) prevention in hospitalized patients

Objective 1:
Rationale for and approach to
thromboprophylaxis in
hospitalized patients

VTE prophylaxis: *Why is it important?*

- Hospitalization increases risk for VTE
 - 6 to 13-fold increased risk
 - Case-fatality of VTE = 12%
- Absolute risk for VTE with hospitalization (medical patients)
 - 1.7% develop VTE within 3 months after hospitalization
 - 1/3 of VTE patients have prior hospitalization for medical illness
 - 70-80% of fatal PEs occur in medical patients
- High potential for disease prevention
 - VTE often clinically silent, first manifestation may be fatal PE
 - PE most common preventable cause of in-hospital death



VTE Consequences

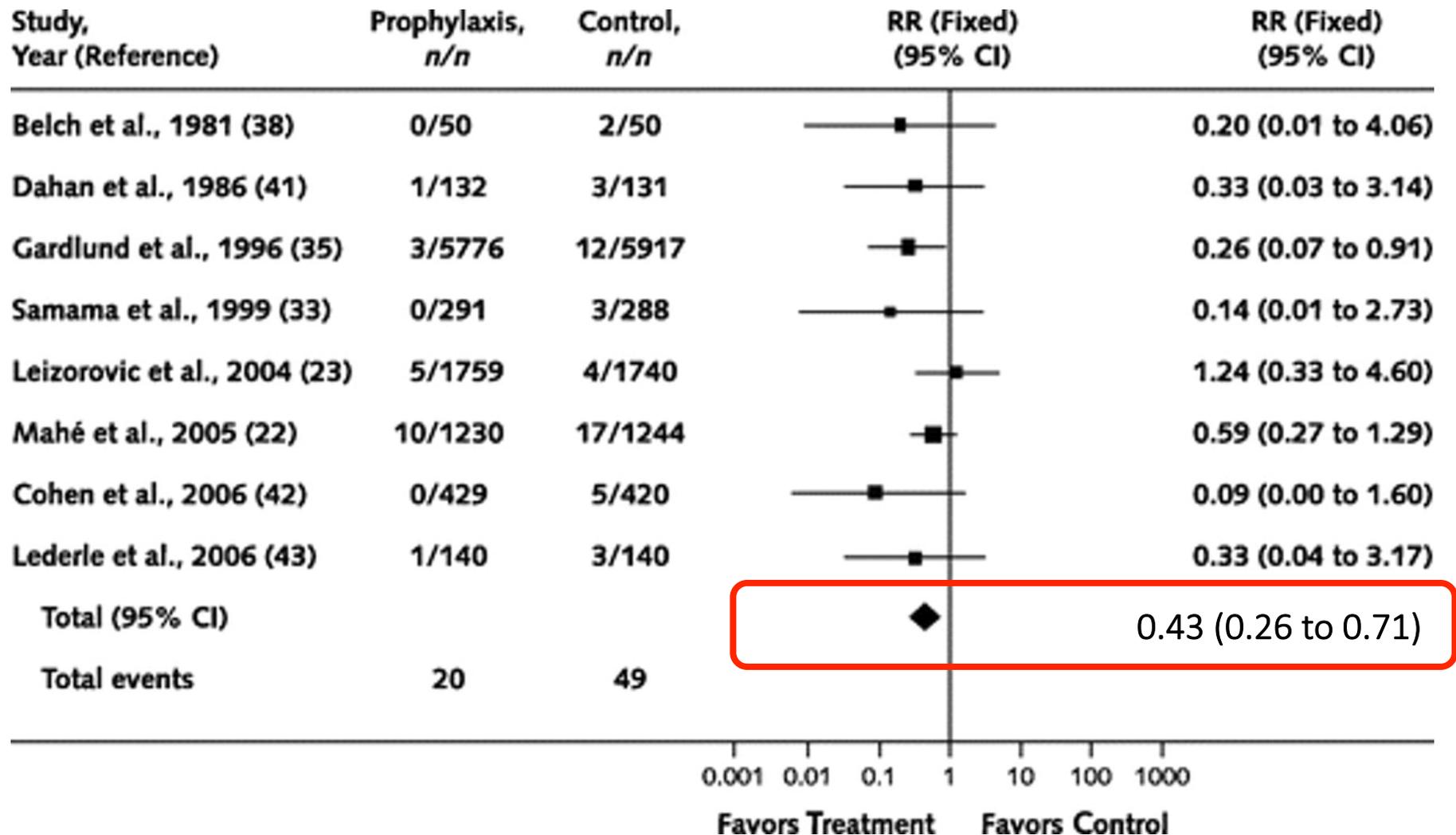


- DVT: Acute leg swelling, discomfort
- PE: Dyspnea, chest pain, hemoptysis, hypoxemia, death (RV failure)
- Extended hospital stay
- Post-thrombotic syndrome (20-30%)
- Chronic thromboembolic pulmonary HTN (~4%)
Pengo et al. *N Engl J Med*. 2004;350:2257-2264.
- Exposure to ≥ 3 months of anticoagulant treatment

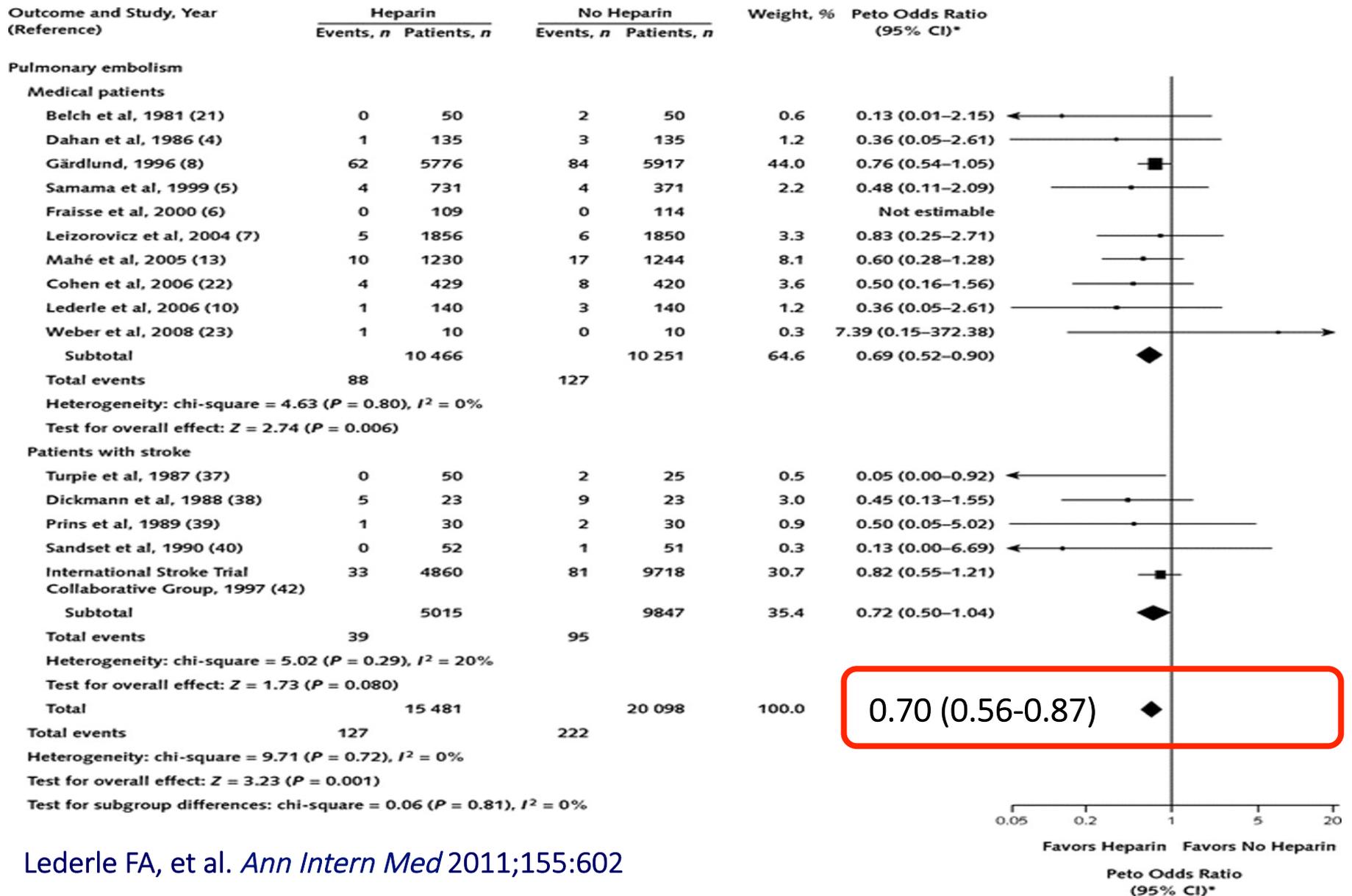
Rationale for VTE prophylaxis

1. High frequency of VTE in many hospitalized patients
2. Numerous adverse consequences of unprevented VTE
3. Thromboprophylaxis is effective, safe and cost-effective

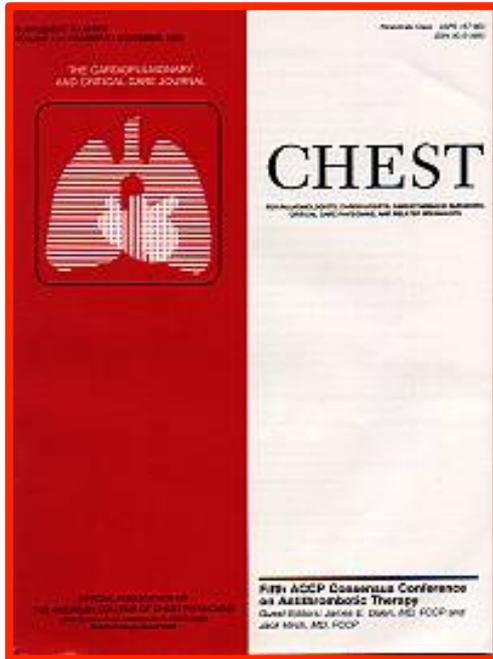
2007 Meta-analysis: Anticoagulant Prophylaxis Prevents Symptomatic (incl. Fatal) PE in Medical Patients



2011 Meta-analysis: Anticoagulant Prophylaxis Prevents Symptomatic PE in Medical and Stroke Patients



ACCP Guidelines: 9th Edition



- NEW: Not all hospitalized medical and surgical patients require thromboprophylaxis
- For chapters on VTE prevention in medical and general (non-orthopedic) surgery patients, shift towards **individualized approach of risk stratifying patients** to apply appropriate thromboprophylaxis strategy

Principles of VTE Risk Determination

- Individual Risk Factors
- Combinations of Risk Factors
 - Risk stratification models (RAMs: risk assessment models)

VTE Risk factors and risk assessment

Virchow's Triad

(born Oct 13th: World Thrombosis Day)

Venous Stasis

Vascular compression
Prolonged bed rest
Hypotension

Vascular Injury

Surgery
Central catheters
Endothelial damage
Chemotherapy

Hypercoagulability

Thrombophilias
Tumor procoagulants
Cytokines
Impaired endothelial
cell defense
Cellular interactions



Rudolph Virchow

Adapted from Joist JH. *Semin Thromb Hemost.* 1990;16:151-157.

VTE Risk Factors

Risk Factor Characteristics	OR
Recent surgery w/ hospitalization	22
Trauma	13
Hospitalization without recent surgery	8
Cancer with chemotherapy	7
Prior central venous catheter or pacemaker	6
Prior superficial vein thrombosis	4
Malignancy without chemotherapy	4
Neurological disease w/ extremity paresis	3

OR: Odds ratio

VTE Risk Factors In Medical Patients

High Risk

- History of VTE
- Family history of VTE
- Acute infection
- Cancer
- Age > 75 years
- CHF
- Stroke
- Immobility > 4 days
- Pregnancy/postpartum
- Acute/chronic lung dis.
- Acute inflammatory dis.
- Shock

Possible Risk

- Paraproteinemia
- Behcet's dis.
- Nephrotic syndrome
- Polycythemia
- PNH
- Myeloproliferative dis.
- Age > 40

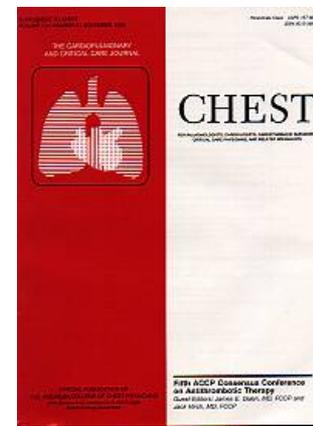
Probable Risk

- High-dose estrogen
- BMI >25
- Varicose veins
- HIT
- Congenital/acquired thrombophilia

An Ideal RAM (Risk Assessment Model): DVT Prophylaxis In Hospitalized Patients

- Enables clinicians to accurately identify patients who meet a threshold risk for DVT in the absence of prophylaxis
- Predicts correct risk level (based on disease state and predisposing risk factors), allowing tailored thromboprophylaxis
- Excludes patients without beneficial risk:benefit ratio
- Evidence based and validated
- Methodologically transparent
- Simple to use in clinical practice

Padua VTE Risk Assessment Model in Hospitalized Medical Patients



Baseline features	Score
Active cancer	3
Previous VTE (excluding superficial phlebitis)	3
Reduced mobility	3
Already known thrombophilic condition	3
Recent (≤ 1 month) trauma and/or surgery	2
Age ≥ 70 yrs	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

Score ≥ 4 =
high risk
of VTE

IMPROVE VTE Risk Assessment Model in Hospitalized Medical Patients: Derivation

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

IMROVE Risk Assessment Model: Validation (n=2326)

Score	Patients, % (n)	3-month Expected VTE Risk, %	Observed VTE rate % (events)	Observed PE rate, % (events)
0	27 (4,029)	0.4	0.4 (14)	0.3 (11)
1	42 (6,350)	0.6	0.6 (33)	0.3 (19)
2	16 (2,420)	1.0	1.5 (31)	0.6 (13)
3	9 (1,335)	1.7	1.6 (18)	0.8 (9)
4	5 (729)	2.9	4.8 (30)	2.8 (17)
5-10	2 (262)	7.2	8.1 (17)	3.8 (7)

- c-statistic = **0.69**
- overall symptomatic VTE rate = **1.0%**
- 3-month VTE rate if **score ≥ 3** :
 - **2.8%** (65/2326) symptomatic VTE
 - **1.4%** (33/2326) symptomatic PE

risk score ≥ 3

score ≥ 4 or 2-3 and +ve D-dimer

MARINER Modified IMPROVE VTE
or

IMPROVE VTE RAM

IMPROVEDD VTE RAM

Risk factor(s)	Risk factor(s)	Points
Previous VTE	Previous VTE	3
Known thrombophilia ^a	Known thrombophilia ^a	2
Lower limb paralysis	Current lower limb paralysis or paresis ^b	2
Cancer	History of cancer ^c	2
Immobilization of ≥ 7 days	Complete immobilization of ≥ 1 day ^d	1
ICU/CCU stay	ICU/CCU stay	1
Age >60 years	Age >60 years	1
	D - dimer > 2 times the upper limit of normal	2

Score ≥ 7 considered high bleed risk

Table 5. Bleeding risk factors and points assigned to each individual factor – the IMPROVE Bleed RAM.^a

Bleeding risk factors	Points
Renal failure GFR 30–59 vs. ≥ 60 mL/min/m ²	1
Male vs. female	1
Age 40–84 vs. <40 years	1.5
Current cancer	2
Rheumatic disease	2
Central venous catheter	2
Intensive care/critical care unit stay	2.5
Renal failure GFR <30 vs. ≥ 60 mL/min/m ²	2.5
Hepatic failure (INR >1.5)	2.5
Age ≥ 85 vs. <40 years	3.5
Platelet count $< 50 \times 10^9$ cells/L	4
Bleeding in 3 months before admission	4
Active gastroduodenal ulcer	4.5

GFR: glomerular filtration rate; INR: international normalized ratio.

A score of ≥ 7 constitutes high bleed risk.

Online IMPROVE calculator for VTE and bleeding risk

http://www.outcomes-umassmed.org/improve/risk_score/index.html

VTE Risk Factors

- Previous VTE
- Thrombophilia
- Lower limb paralysis
- Current cancer
- Immobilization ≥ 7 days
- ICU/CCU stay
- Age > 60 years

Bleeding Risk Factors

- Gastro-duodenal ulcer
- Bleeding prior 3 months
- Admission platelets < 50×10^9
- Hepatic failure
- ICU/CCU stay
- CV catheter
- Rheumatic diseases
- Current cancer

Sex

Age years

GFR mL/min/m²

Reset

Probability of Symptomatic VTE

0.4%

Probability of Bleeding

Major **0.1%** Clinically Important **0.5%**

VTE Risk Stratification in Surgical Patients: Caprini RAM

Deep Vein Thrombosis (DVT)

Prophylaxis Orders

(For use in Elective General Surgery Patients)

Thrombosis Risk Factor Assessment (Choose all that apply)

BIRTHDATE _____

NAME _____

CPI No. _____

SEX M F VISIT No. _____

Each Risk Factor Represents 1 Point

- | | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|
| <input type="checkbox"/> Age 41-60 years | <input type="checkbox"/> Acute myocardial infarction |
| <input type="checkbox"/> Swollen legs (current) | <input type="checkbox"/> Congestive heart failure (<1 month) |
| <input type="checkbox"/> Varicose veins | <input type="checkbox"/> Medical patient currently at bed rest |
| <input type="checkbox"/> Obesity (BMI >25) | <input type="checkbox"/> History of inflammatory bowel disease |
| <input type="checkbox"/> Minor surgery planned | <input type="checkbox"/> History of prior major surgery (<1 month) |
| <input type="checkbox"/> Sepsis (<1 month) | <input type="checkbox"/> Abnormal pulmonary function (COPD) |
| <input type="checkbox"/> Serious Lung disease including pneumonia (<1 month) | |
| <input type="checkbox"/> Oral contraceptives or hormone replacement therapy | |
| <input type="checkbox"/> Pregnancy or postpartum (<1 month) | |
| <input type="checkbox"/> History of unexplained stillborn infant, recurrent spontaneous abortion (≥ 3), premature birth with toxemia or growth-restricted infant | |
| <input type="checkbox"/> Other risk factors _____ | |

Subtotal:

Each Risk Factor Represents 5 Points

- | | |
|--------------------------------------------------------------------------|-----------------------------------------------------|
| <input type="checkbox"/> Stroke (<1 month) | <input type="checkbox"/> Multiple trauma (<1 month) |
| <input type="checkbox"/> Elective major lower extremity arthroplasty | |
| <input type="checkbox"/> Hip, pelvis or leg fracture (<1 month) | |
| <input type="checkbox"/> Acute spinal cord injury (paralysis) (<1 month) | |

Subtotal:

Each Risk Factor Represents 2 Points

- | | |
|---------------------------------------------------------------|------------------------------------------------------|
| <input type="checkbox"/> Age 61-74 years | <input type="checkbox"/> Central venous access |
| <input type="checkbox"/> Arthroscopic surgery | <input type="checkbox"/> Major surgery (>45 minutes) |
| <input type="checkbox"/> Malignancy (present or previous) | |
| <input type="checkbox"/> Laparoscopic surgery (>45 minutes) | |
| <input type="checkbox"/> Patient confined to bed (>72 hours) | |
| <input type="checkbox"/> Immobilizing plaster cast (<1 month) | |

Subtotal:

Each Risk Factor Represents 3 Points

- | | |
|-----------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|
| <input type="checkbox"/> Age 75 years or older | <input type="checkbox"/> Family History of thrombosis* |
| <input type="checkbox"/> History of DVT/PE | <input type="checkbox"/> Positive Prothrombin 20210A |
| <input type="checkbox"/> Positive Factor V Leiden | <input type="checkbox"/> Positive Lupus anticoagulant |
| <input type="checkbox"/> Elevated serum homocysteine | |
| <input type="checkbox"/> Heparin-induced thrombocytopenia (HIT)
(Do not use heparin or any low molecular weight heparin) | |
| <input type="checkbox"/> Elevated anticardiolipin antibodies | |
| <input type="checkbox"/> Other congenital or acquired thrombophilia | |
| If yes: Type _____ | |
| * most frequently missed risk factor | |

Subtotal:

TOTAL RISK FACTOR SCORE:

DVT risk: very low (0-1); low (2); moderate (3-4); high (≥ 5 points)

Objective 2:

To describe the particular approach to thromboprophylaxis in hospitalized patients with cancer

Cancer and medical inpatients

■ Cancer contributes:

- 3 points to Padua VTE score (≥ 4 = high VTE risk)
- 2 points to IMPROVE VTE score (≥ 3 = high VTE risk)
- 2 points to IMPROVE bleeding score (≥ 7 = high bleed risk)

Number of points (not cancer *per se*) [?] helps to determine VTE risk [?] influences decision to give/ not give VTE prophylaxis while hospitalized

Cancer and surgery patients

- Cancer contributes 2 points to Caprini VTE index (3-4 points = moderate risk; ≥ 5 points = high risk)
 - Number of points (not cancer *per se*) [?] helps to determine VTE risk [?] influences decision to give/not give VTE prophylaxis post-operatively
- BUT: Patients undergoing surgery for cancer resection (“surgical cancer patients”) should receive extended VTE prophylaxis post-op

What is the rationale for extended duration (30 days) thromboprophylaxis in surgical cancer patients?

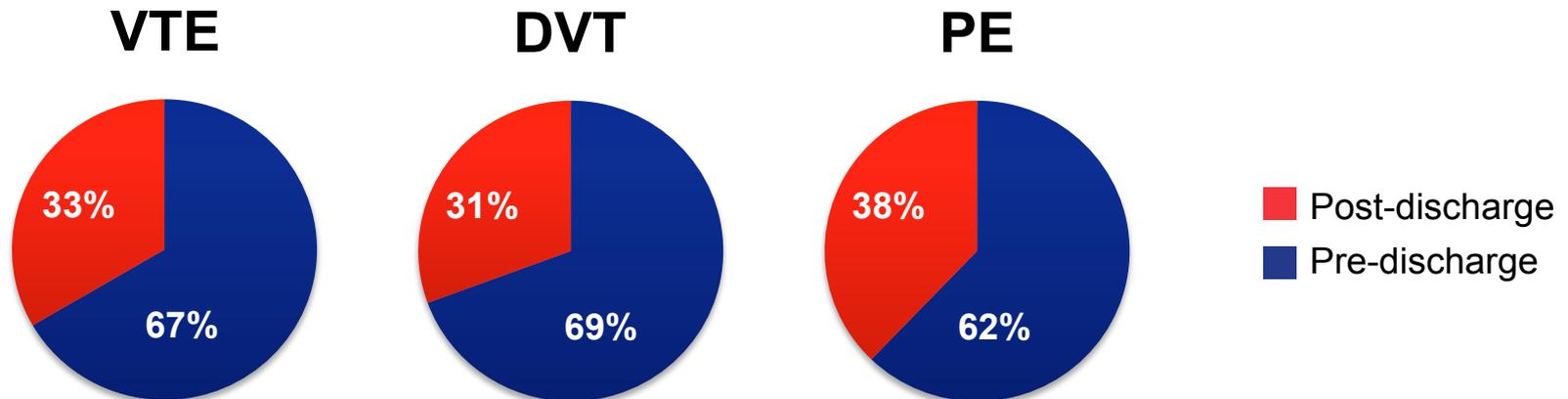
Abdominal and Pelvic Cancer Surgical Patients Continue to have a Significant Proportion of Late VTE Events

- NSQIP 2006-2008
- 211 hospitals, 44,656 pts
- **More than 1/3 of VTE events occurred within 30 day post-discharge**

Post-Discharge Venous Thromboembolism After Cancer Surgery

Extending the Case for Extended Prophylaxis

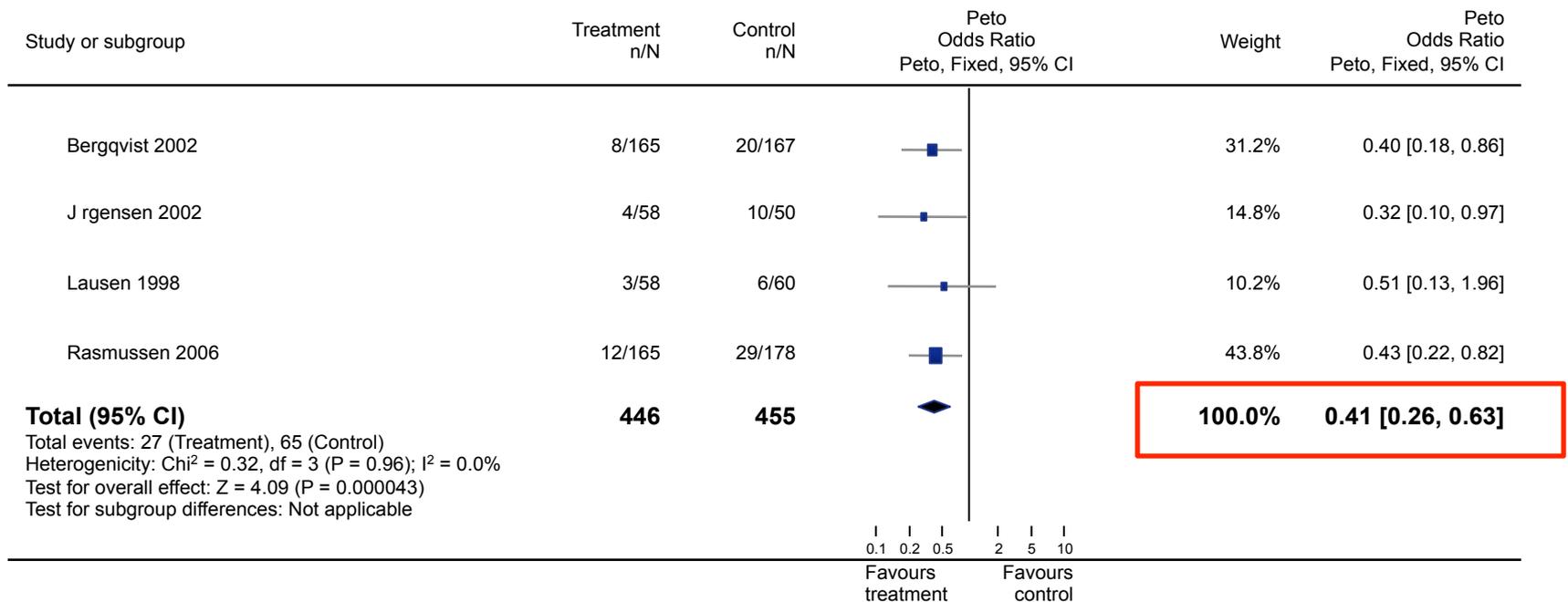
Ryan P. Merkow, MD,†‡ Karl Y. Bilimoria, MD, MS,*‡ Martin D. McCarter, MD,† Mark E. Cohen, PhD,‡
Carlton C. Barnett, MD,† Mehul V. Raval, MD, MS,*‡ Joseph A. Caprini, MD, MS,¶ Howard S. Gordon, MD,§
Clifford Y. Ko, MD, MS, MSHS,‡‡ and David J. Bentrem, MD, MS**



**What is the evidence to support
extended-duration (30-days)
anticoagulant prophylaxis
after abdominal & pelvic
cancer surgery?**

Extended Prophylaxis with Low-Molecular Weight Heparins after Abdominal & Pelvic Cancer Surgery: Cochrane Review: Effect on VTE

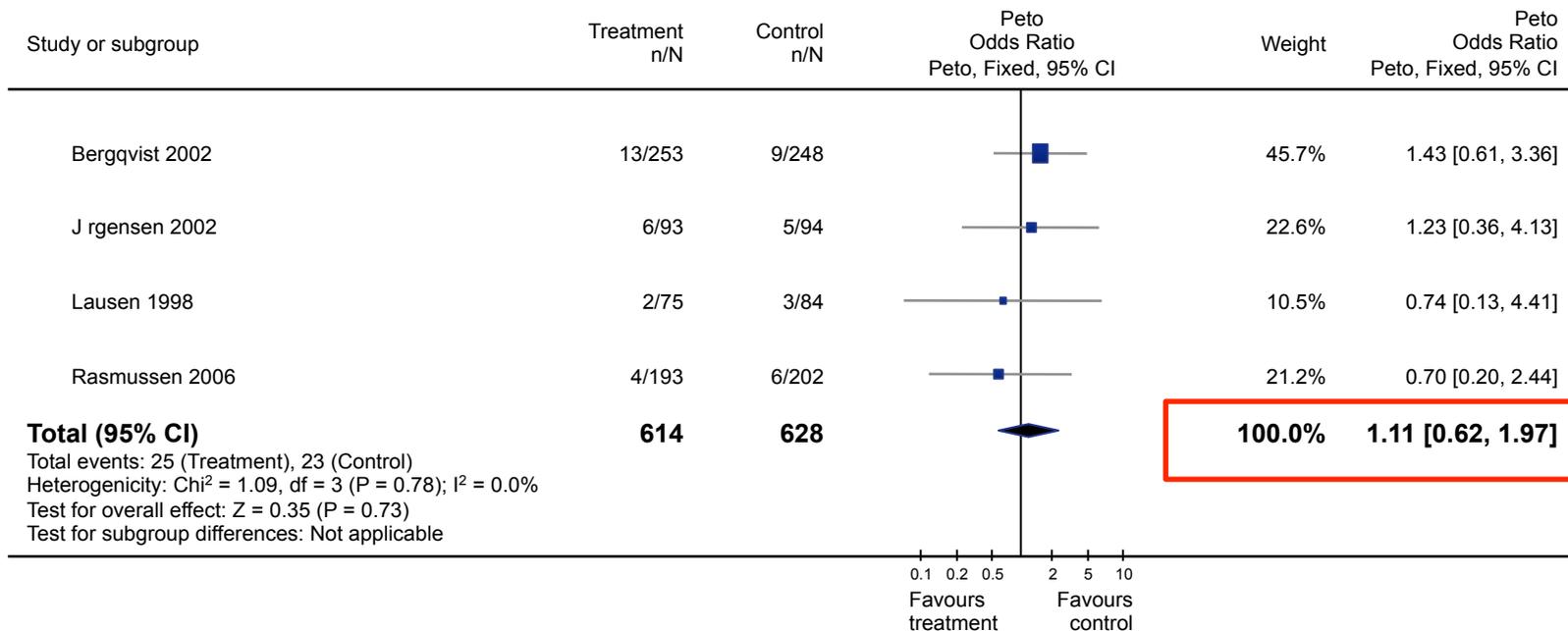
Prolonged thromboprophylaxis with LMWH (**4 weeks compared to usual 5-7 days**) for abdominal or pelvic surgery: Comparison LMWH vs placebo, Outcome **all VTE**



Extended Prophylaxis with Low-Molecular Weight Heparins Post Abdominal & Pelvic Cancer Surgery: Cochrane Review: Effect on Bleeding

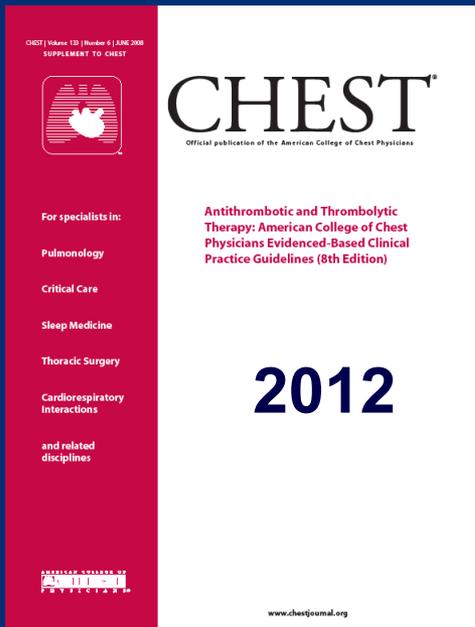
Comparison: LMWH vs. placebo, Outcome **Bleeding complications**

Prolonged thromboprophylaxis with LMWH (**4 weeks compared to usual 5-7 days**) significantly reduces the risk of VTE compared to thromboprophylaxis during hospital admission only, without increasing bleeding complications after major abdominal or pelvic surgery.



Objective 3:

To be aware of the most recent consensus guidelines on venous thromboembolism prevention in hospitalized patients



**ASH Clinical Practice
Guidelines on VTE
Coming in 2018**

Hospitalized medical patient

Stratify risk of VTE (*Padua Prediction score*)

Cancer	(3)	Cardio resp failure	(1)
Previous VTE	(3)	MI or CVA	(1)
Bedrest 3d	(3)	Infection/rheum D.	(1)
Thrombophilia	(3)	Obesity (BMI >30)	(1)
Recent Surg/trauma	(2)	Hormonal therapy	(1)
Age >70y	(1)		

≥ 4 High-risk (~40% of pts; VTE in 11%)

< 4 Low-risk (~60% of pts; VTE in 0.3%)

Hospitalized medical patient: in hospital

High Risk for VTE

Anticoagulants (LMWH, LDUH, fonda)

Grade 1B

If bleeding or high risk for bleeding:

GCS or IPC*

Grade 2C

Low Risk for VTE

No prophylaxis (anticoagulants or mechanical) Grade 1B

* GCS graduated compression stockings; IPC intermittent pneumatic compression

Hospitalized Medical: after discharge

No extended prophylaxis
beyond the period of patient
immobilization or acute hospital stay

Grade 2B

Efficacy and safety of extended thromboprophylaxis for medically ill patients

A meta-analysis of randomised controlled trials

Francesco Dentali¹; Nicola Mumoli²; Domenico Prisco³; Andrea Fontanella⁴; Matteo Nicola Dario Di Minno⁵

Thromb Haemost 2017; 117: 606–617

4 trials (n=28,105) APEX; ADOPT; MAGELLAN; EXCLAIM		
Outcome	OR (95% CI)	NNT (NNH)
DVT	0.50 (0.29, 0.89)	339
PE	0.63 (0.39, 1.03)	N/A
VTE-related death	0.69 (0.45, 1.1)	N/A
Major bleed	2.1 (1.3, 3.3)	(247)

“Results of our meta-analysis did not support a general use of antithrombotic prophylaxis beyond the period of hospitalization in acutely ill medical patients”.

9th ACCP Guideline Recommendations for Standard Surgical Thromboprophylaxis

- Patients undergoing general and abdominal pelvic surgery should receive a risk assessment (e.g. Caprini score) before surgery to predict risk of VTE

General Surgery: in hospital

Very Low Risk (<0.5%)

No Pharmos. **Grade 1B** No Mechanical **Grade 2C**

Low Risk (~1.5%)

No Pharmos. **(not explicit)** Mechanical (IPC) **Grade 2C**

Moderate Risk (~3%)

LMWH, LDUH **Grade 2B** Mechanical (IPC) **Grade 2C**

High Risk (~6%)

LMWH, LDUH **Grade 1B AND** Mechanical (IPC) **Grade 2C**

General Surgery: in hospital, high risk of bleeding

For high-VTE-risk general and abdominal-pelvic surgery patients who are at high risk for major bleeding complications or those in whom the consequences of bleeding are thought to be particularly severe:

- Suggest mechanical prophylaxis, preferably with IPC, over no prophylaxis until risk of bleeding diminishes and pharmacologic prophylaxis can be initiated (Grade 2C).

General Surgery: after discharge

High Risk & Cancer

LMWH (~4 weeks)

Grade 1B

ALSO:

No prophylactic IVC filters

Grade 2C

No ultrasound surveillance

Grade 2C

Dosing Regimens for Extended Duration Thromboprophylaxis VTE in Abdomino-Pelvic Cancer Surgical Patients – Canadian Labeling

Drug	Regimen
Dalteparin	2500 U 2-4 hours preoperatively and 5000 U once daily thereafter <u>or</u> 5000 U 10-12 hours preoperatively and 5000 U once daily thereafter
Enoxaparin	20 mg 2-4 hours preoperatively and 40 mg once daily thereafter <u>or</u> 40 mg 10-12 hours preoperatively and 40 mg once daily thereafter
Tinzaparin	3500 IU SC 2 hours before surgery followed by 4500 IU once daily

Fragmin (dalteparin) Product Monograph; Jan.6, 2014.
Lovenox (enoxaparin) Product Monograph; Dec. 20, 2013.
Innohep (tinzaparin) Product Monograph; Feb. 3, 2011.



Guideline Recommendations for Surgical VTE Prophylaxis: Consistent for ASCO, NCCN, ESMO, ACCP

ASCO 2013	Pharmacological thromboprophylaxis to all patients with malignant disease undergoing major surgical interventions <ul style="list-style-type: none">• Prophylaxis should be commenced preoperatively, should be continued for at least 7 to 10 days.• Extended prophylaxis with LMWH for up to 4 weeks postoperatively should be considered for patients undergoing major abdominal or pelvic surgery for cancer who have high-risk features such as restricted mobility, obesity, history of VTE, or with additional risk factors
NCCN	Out-of-hospital primary VTE prophylaxis is recommended for up to 4 weeks postoperatively (particularly for high-risk abdominal or pelvic cancer surgery patients)
ESMO 2011	Pharmacological thromboprophylaxis to all cancer patients undergoing major cancer surgery <ul style="list-style-type: none">• patients having a laparotomy, laparoscopy, thoracotomy or thoracoscopy lasting >than 30 min, consider s.c. LMWH for at least 10 days postoperatively.• Cancer patients undergoing elective major abdominal or pelvic surgery should receive in hospital and post-discharge prophylaxis with s.c. LMWH for up to 1 month after surgery
ACCP 2012	General and abdominal-pelvic surgery patients for cancer <ul style="list-style-type: none">• High risk for VTE/not at high bleeding risk → extended duration, 4 weeks, prophylaxis with LMWH• LDUH, LMWH or mechanical prophylaxis

No good quality studies have been done using unfractionated heparin for extended duration thromboprophylaxis

Lyman GH, et al. *J Clin Oncol.* 2013;31:2189-204

Streiff MB, et al. *JNCCN* 2011;9:714-777

Madnala M, et al. *Annals Oncology* 2011;22 (Supplement 6): vi85-vi92

Gould, MK, et al. *9th Chest.* 2012;141(2_suppl):e227S-e277S



7 Steps to Improve VTE Prophylaxis Success

1. Hospital commitment, committee, leader
2. Written hospital policy on prophylaxis
3. Keep it simple and standard (who gets prophylaxis and what)
4. Use order sets/computer order entry +/-decision support
5. Make a prophylaxis decision mandatory
6. Involve everyone – MD, RN, pharmacist, patients
7. Audit and improve



Cochrane
Library

Cochrane Database of Systematic Reviews

Interventions for implementation of thromboprophylaxis in hospitalized patients at risk for venous thromboembolism (Review)

Kahn SR, Morrison DR, Diendéré G, Piché A, Filion KB, Klil-Drori AJ, Douketis JD, Emed J, Roussin A, Tagalakis V, Morris M, Geerts W

Our Cochrane review

- Systematic review of the effects of system-wide interventions designed to increase implementation of thromboprophylaxis and decrease incidence of VTE in hospitalized adult medical and surgical patients at risk for VTE (13 RCTs; N = 35,997 participants)
- Main findings:
 - Alerts (computer, or human) and multifaceted interventions were associated with an increase in the proportion of participants who received prophylaxis
 - Multifaceted interventions with an alert component were more effective than multifaceted interventions that did not include an alert

Gaps in knowledge

- Chronically immobilized nursing home or rehab patients
- Post C section thromboprophylaxis
- Are compression stocking effective to prevent VTE in medical patients?
- Value of extended thromboprophylaxis after hospitalization for medical illness

Merci!