BRIGHAM AND
WOMEN'S HOSPITAL

# Critical Unmet Need in VTE Prevention: A Pervasive and Persistent Crisis

Gregory Piazza, MD, MS
Cardiovascular Division
November 27, 2017

HARVARD MEDICAL
SCHOOL
*TEACHING AFFILIATE*

There WILL NOT be off-label and/or investigational discussion in this presentation.

# Conflict of Interest Statement

- Grant/Research Support
  - Bristol-Myers Squibb
  - Daiichi Sankyo
  - Janssen

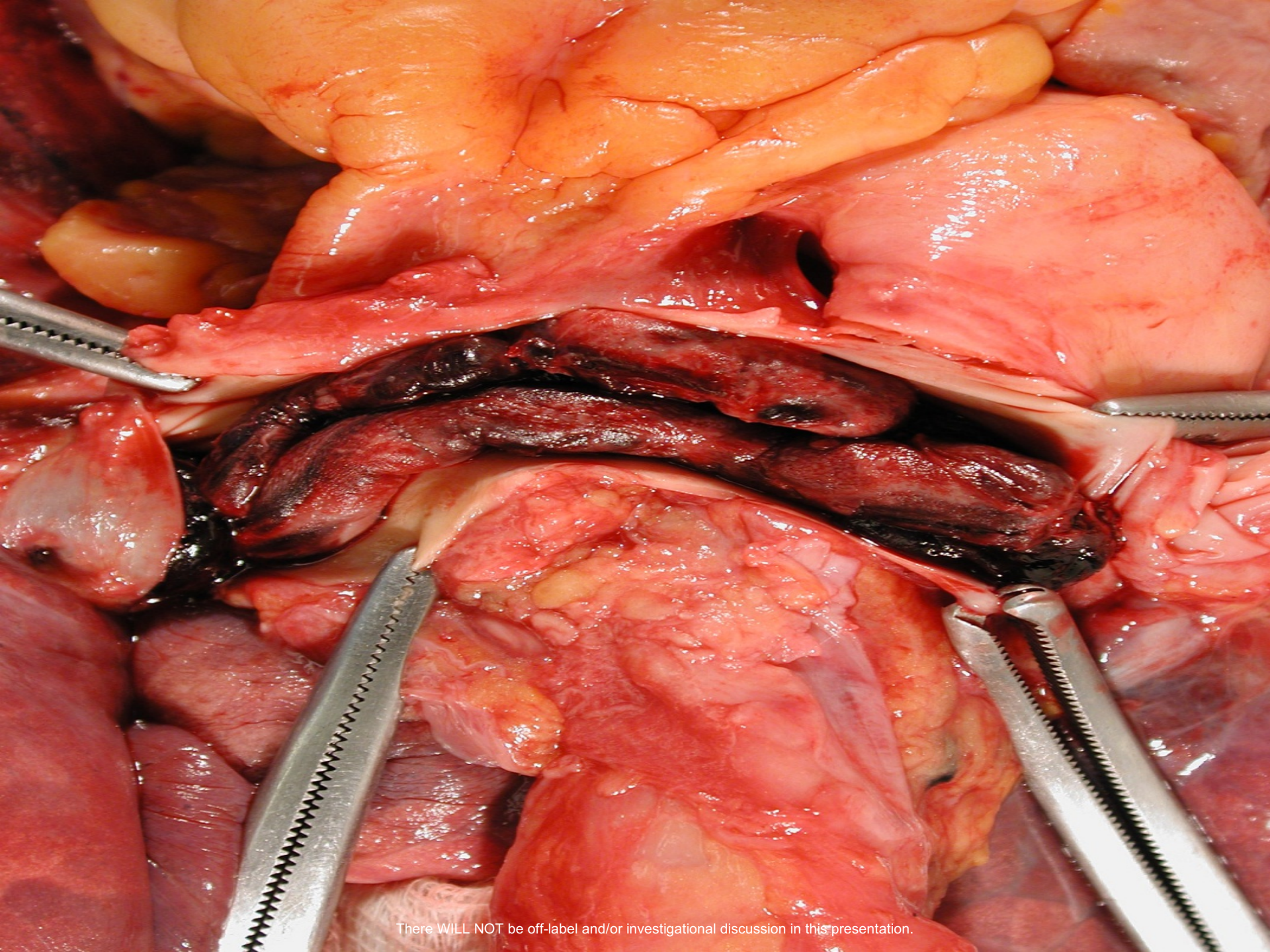
- Scientific Housing Panel
  - Portola Pharmaceuticals
  - eXITHERA

There WILL NOT be off-label and/or investigational discussion in this presentation.

# Learning Objectives

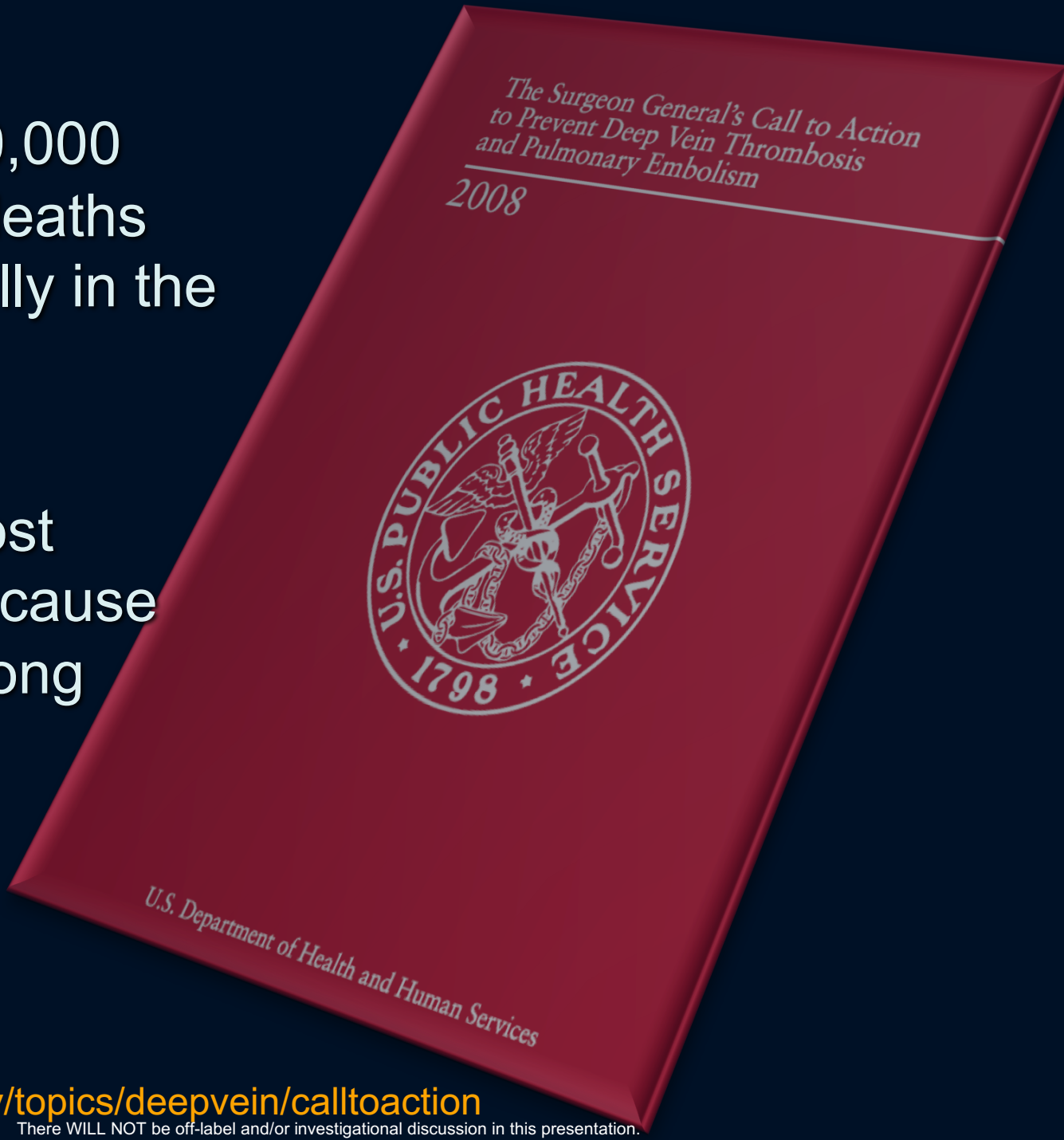
- Describe that the rate of VTE is on the rise in the US.
- Recall which patients with high risk medical conditions are at a higher risk for VTE.
- Describe the link between venous thrombosis and atherothrombosis.
- Identify those patients at risk for VTE and use appropriate prophylaxis strategy.

There WILL NOT be off-label and/or investigational discussion in this presentation.



There WILL NOT be off-label and/or investigational discussion in this presentation.

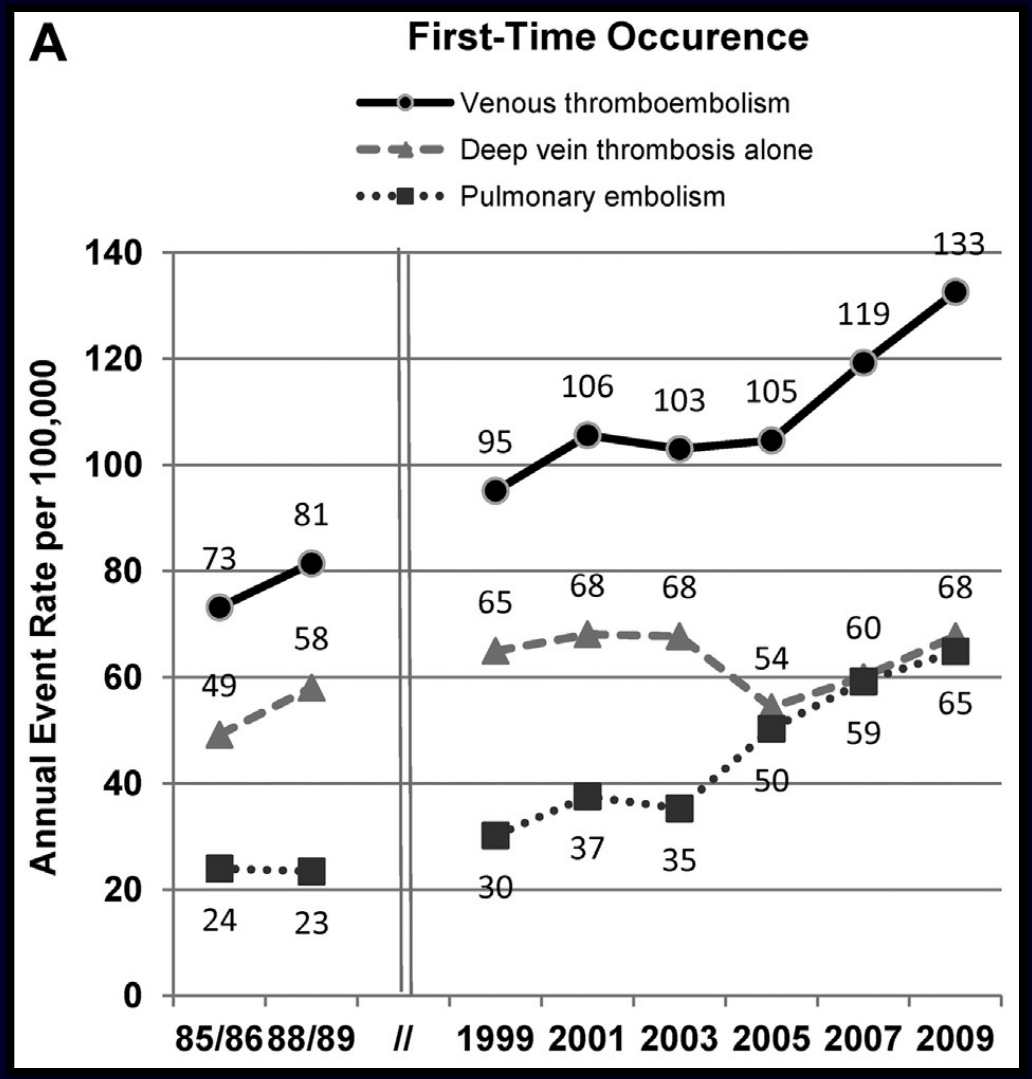
- 100,000-180,000 PE-related deaths occur annually in the U.S. alone.
- PE is the most preventable cause of death among hospitalized patients.




www.surgeongeneral.gov/topics/deepvein/calltoaction

There WILL NOT be off-label and/or investigational discussion in this presentation.

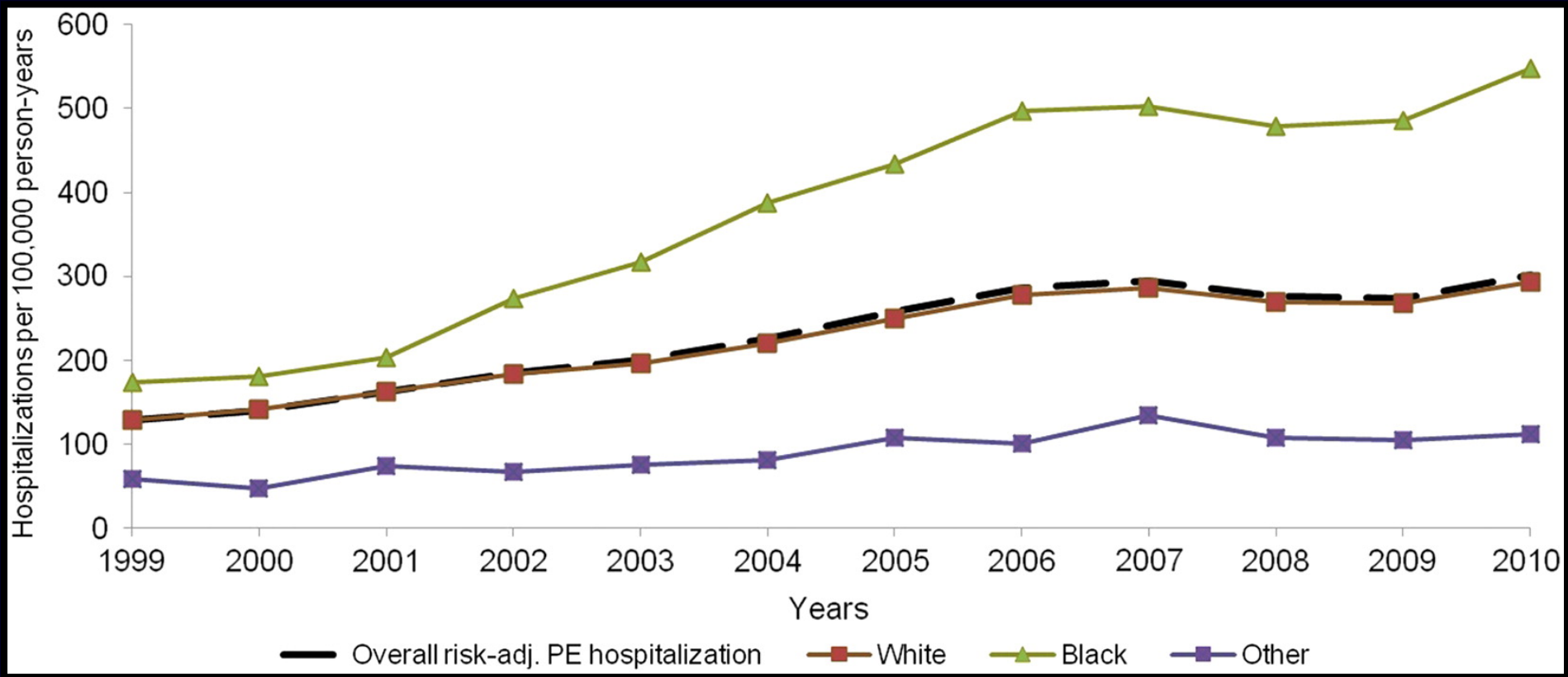
# VTE Incidence




Huang W, et al. Am J Med 2014;127:829

There WILL NOT be off-label and/or investigational discussion in this presentation.

# PE Hospitalization Rate is Increasing: Medicare Cohort




Minges KE, et al. Am J Cardiol 2015; 116:1436

There WILL NOT be off-label and/or investigational discussion in this presentation.

# High-Risk Medical Conditions

**Table 3: Estimates of venous thromboembolic events in acutely ill hospitalised medical patients with current thromboprophylaxis rates.** CI, confidence interval; DVT, deep venous thrombosis; PE, pulmonary embolism.

| Diagnosis | Prophylaxis rate (%) | Symptomatic DVT events (95% CI) | Symptomatic PE events (95% CI) | VTE-related deaths (95% CI) | Total VTE events |
|---|---|---|---|---|---|
| Heart failure | 40.1 | 19,135 (11,091–31,426) | 5,112 (2,137–12,628) | 6,457 (2,950–15,870) | 30,704 |
| Respiratory failure | 31.0 | 15,830 (9,170–27,659) | 4,229 (1,784–10,300) | 5,341 (2,048–12,814) | 25,400 |
| Pneumonia | 31.0 | 14,731 (6,565–22,775) | 3,935 (1,329–7,775) | 4,970 (1,548–9,751) | 23,636 |
| Cancer | 27.6 | 17,726 (6,273–22,070) | 4,735 (1,171–7,050) | 5,981 (1,423–8,828) | 28,442 |
| Stroke | 49.2 | 21,327 (10,674–30,108) | 5,697 (2,013–11,824) | 7,196 (2,474–14,699) | 34,220 |
| Acute myocardial infarction | 43.0 | 9,844 (4,719–17,369) | 2,630 (908–5,498) | 3,322 (1,152–7,241) | 15,796 |
| Non-surgical trauma | 20.3 | 6,550 (2,424–8,742) | 1,750 (502–2,807) | 2,210 (590–3,684) | 10,510 |
| Arthropathy / spondylopathy | 15.3 | 10,196 (3,118–11,041) | 2,724 (609–3,665) | 3,440 (781–4,640) | 16,360 |
| Sepsis | 15.3 | 5,919 (2,275–8,718) | 1,581 (499–2,807) | 1,998 (627–3,701) | 9,498 |
| Paralysis / coma | 15.3 | 977 (414–1,464) | 261 (81–464) | 330 (100–621) | 1,568 |
| **TOTAL** | **28.8** | **122,235 (57,014–181,372** | **32,654 (11,033–64,818)** | **41,245 (13,693–81,849)** | **196,134** |

There WILL NOT be off-label and/or investigational discussion in this presentation.

Piazza G, et al. Thromb Haemost 2009;102:505

# The Link Between Two Growing Epidemics

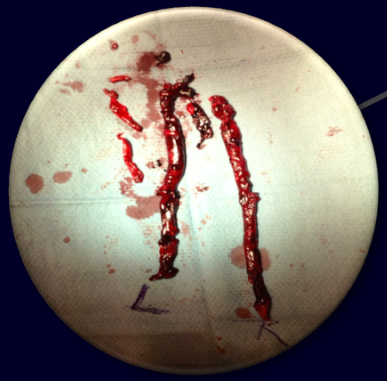
**Shared Pro-Inflammatory Risk Factors:**

- Obesity
- Tobacco use
- Diabetes
- Stress
- Diet
- Chronic inflammatory disorders

**Shared Pathophysiology:**

- Hypercoagulability
- Endothelial Injury
- Inflammation

## Venous Thrombosis

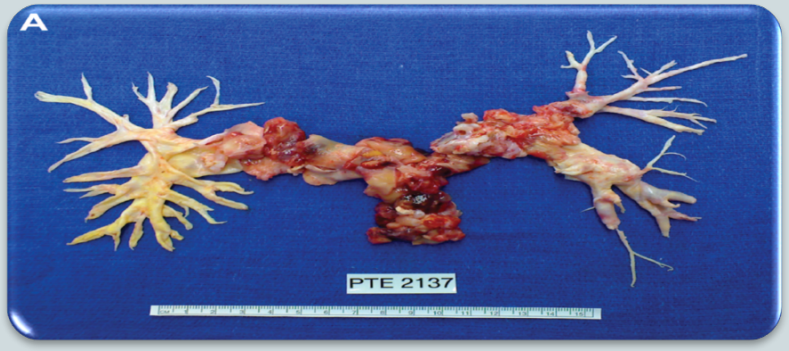


## Atherothrombosis

Piazza G and Ridker PM. Clin Chem 2015;61:313

There WILL NOT be off-label and/or investigational discussion in this presentation.

# We Can't Afford to Risk the Complications of VTE



**Chronic Thromboembolic Pulmonary Hypertension**

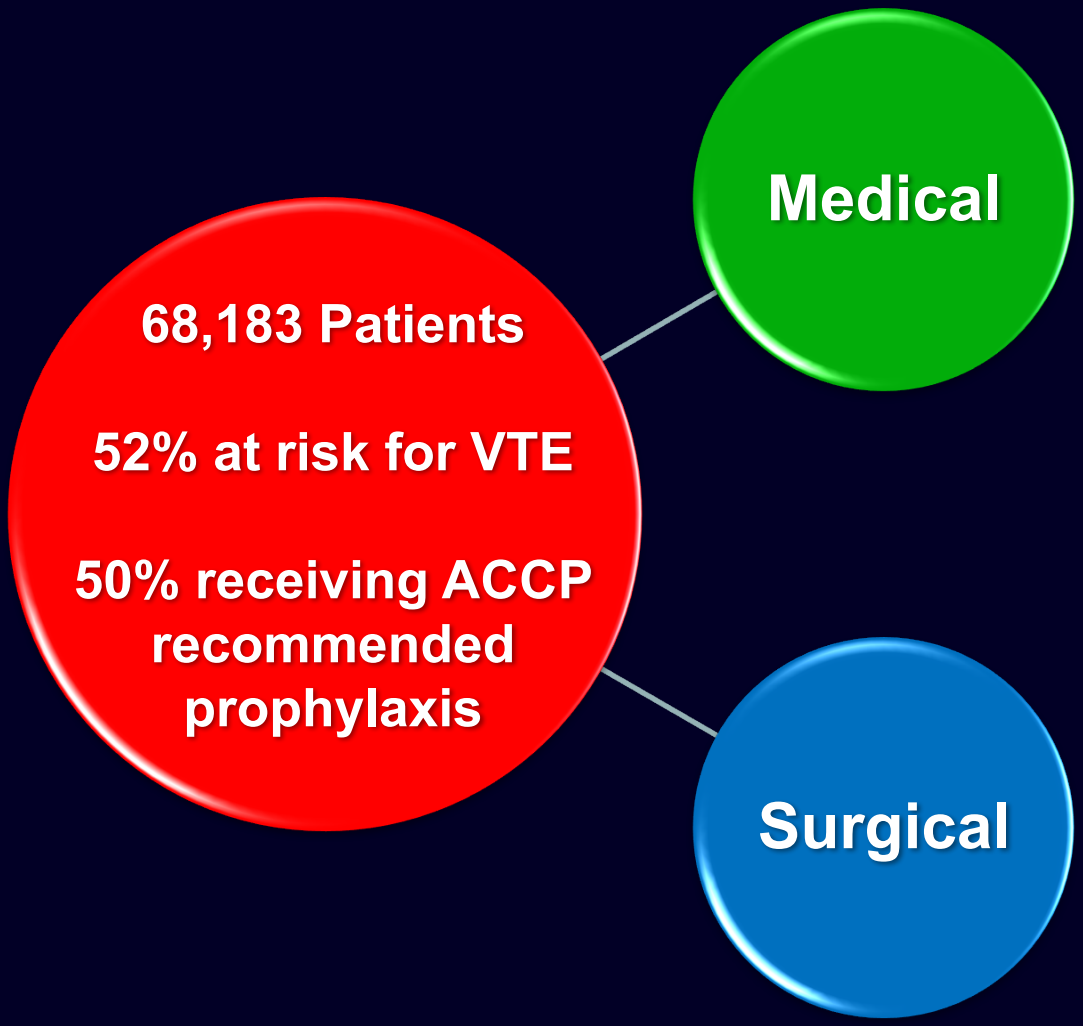
(~4% of PE patients)

**Post-Thrombotic Syndrome**

(25-50% of treated DVT patients)

There WILL NOT be off-label and/or investigational discussion in this presentation.

# Crisis in VTE Prophylaxis: ENDORSE




- 42% at risk
- 40% given prophylaxis

- 64% at risk
- 59% given prophylaxis

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

There WILL NOT be off-label and/or investigational discussion in this presentation.

# Crisis on the Homefront: Thromboprophylaxis at U.S. Centers

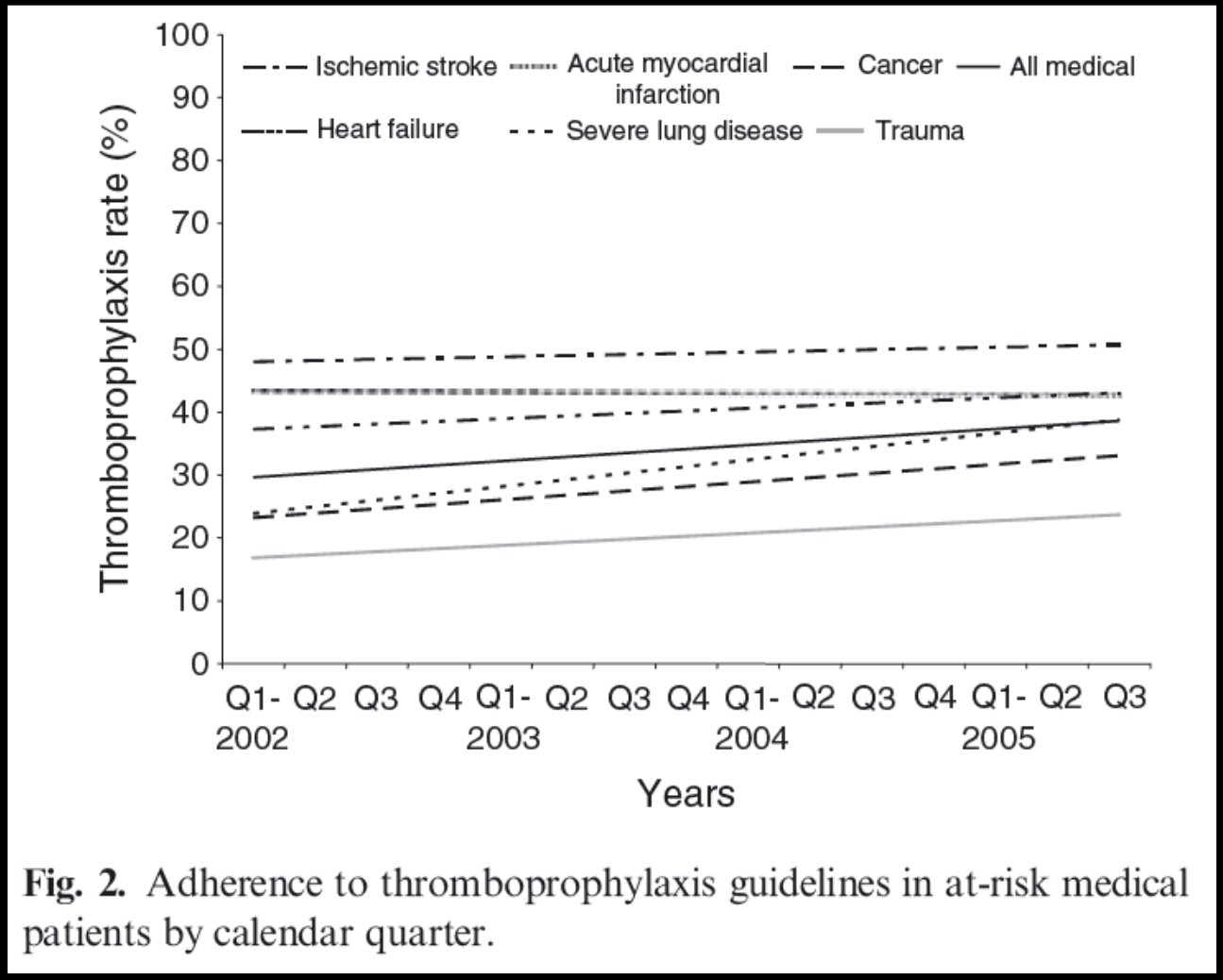



**Fig. 2.** Adherence to thromboprophylaxis guidelines in at-risk medical patients by calendar quarter.

There WILL NOT be off-label and/or investigational discussion in this presentation.

Amin A, et al. J Thromb Haemost 2007;5:1610

ACP Clinical Practice®
American College of Physicians
GUIDELINES

## Summary of the American College of Physicians Guideline on Venous Thromboembolism Prophylaxis in Hospitalized Patients

| | |
|---|---|
| **Disease or condition** | VTE |
| **Target audience** | Internists, family physicians, other clinicians |
| **Target patient population** | Adults with VTE |
| **Interventions** | Low-dose heparin products<br>Mechanical devices |
| **Outcomes** | Total mortality<br>PE<br>All bleeding<br>Major bleeding |
| **Recommendations** | *Recommendation 1: ACP recommends assessment of the risk for thromboembolism and bleeding in medical (including stroke) patients prior to initiation of prophylaxis of venous thromboembolism (Grade: strong recommendation, moderate-quality evidence).*<br>*Recommendation 2: ACP recommends pharmacologic prophylaxis with heparin or a related drug for venous thromboembolism in medical (including stroke) patients unless the assessed risk for bleeding outweighs the likely benefits (Grade: strong recommendation, moderate-quality evidence).*<br>*Recommendation 3: ACP recommends against the use of mechanical prophylaxis with graduated compression stockings for prevention of venous thromboembolism (Grade: strong recommendation, moderate-quality evidence).*<br>*Policy Implication*<br>*ACP does not support the application of performance measures in medical (including stroke) patients that promotes universal venous thromboembolism prophylaxis regardless of risk.* |
| **Clinical considerations** | • This guideline refers to hospitalized medical patients and patients with acute stroke at risk for VTE.<br>• Treatment benefits for VTE are primarily related to reduction in mortality, symptomatic DVT, and PE events.<br>• Assessment of risk for thromboembolism and bleeding is important before initiation of prophylaxis for VTE.<br>• Clinicians who initiate VTE prophylaxis should select heparin (or related) drugs rather than mechanical prophylaxis. |

# VTE Risk Assessment

Complete Assessment at ADMISSION, POST-OP, AND TRANSFER

**DVT/ PE RISK LEVEL & PROPHYLAXIS ORDERS**

| | |
|---|---|
| ☐ **Low** Risk<br>Observation patients, expected LOS <48 hrs: Minor/ Ambulatory surgery **or** Age< 50 and NO other risk factors , or Already on therapeutic anticoagulation | ☐ Early ambulation, education<br>☐ Education |
| ☐ **Moderate** Risk<br>**Most medical /surgical patients**<br>CHF,pneumonia, active inflammation, advanced age, dehydration, varicose veins, less than fully and independently ambulatory, many other factors. All patients not in the Low or Highest Risk Categories (see reverse for more risk factors) | **CHOOSE ONE** PHARMACOLOGIC option<br>☐ Enoxaparin 40 mg SC q 24 hrs<br>☐ Enoxaparin 30 mg SC q 24 hrs (renal insufficiency dosing)<br>☐ Heparin 5000 units SC q 8 hrs<br>☐ Heparin 5000 units SC every 12hrs (if weight <50kg or age> 75)<br>**Also (OPTIONAL)**<br>☐ Sequential compression device |
| ☐ **Highest** Risk<br>Elective hip or knee arthroplasty<br>Acute spinal cord injury with paresis<br>Multiple major trauma<br>Abdominal or pelvic surgery for cancer | **CHOOSE ONE** PHARMACOLOGIC option<br>☐ Enoxaparin 40 mg SC q day<br>☐ Enoxaparin 30 mg SC q 24 hrs (for renal insufficiency)<br>☐ Heparin 5000 units SC q 8 hrs (End stage renal disease only)<br>☐ Enoxaparin 30 mg SC q 12 hrs (knee replacement)<br>☐ Fondaparinux 2.5 mg SC q day<br>**AND**<br>■ Sequential compression device |

**OR**

**The risk of adverse effects of pharmacologic prophylaxis outweighs the risk of DVT / PE**

**Contraindication to pharmacologic prophylaxis (see reverse):** _____

☐ Mechanical prophylaxis with sequential compression device OR

☐ Contraindicated (peripheral vascular disease or wounds)

Maynard GA, Stein J. J Thromb Thrombolysis 2010;29:159

There WILL NOT be off-label and/or investigational discussion in this presentation.

# VTE Risk Assessment

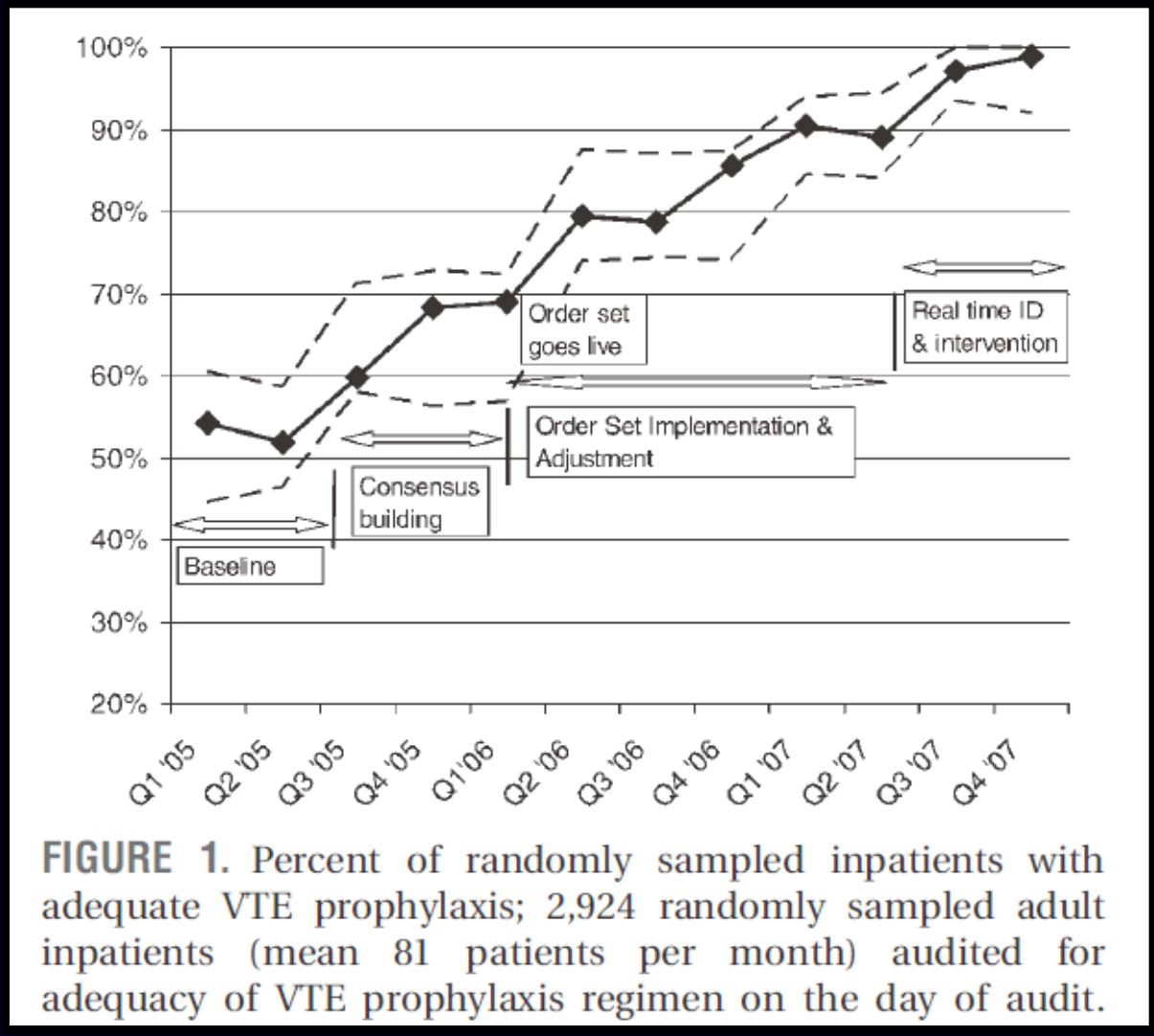



**FIGURE 1.** Percent of randomly sampled inpatients with adequate VTE prophylaxis; 2,924 randomly sampled adult inpatients (mean 81 patients per month) audited for adequacy of VTE prophylaxis regimen on the day of audit.

Maynard GA, Stein J. J Thromb Thrombolysis 2010;29:159

There WILL NOT be off-label and/or investigational discussion in this presentation.

# VTE Prophylaxis Options

## Mechanical

- Graduated compression stockings
- Intermittent pneumatic compression
- Inferior vena cava (IVC) filter

## Pharmacological

- Unfractionated heparin
- Low-molecular weight heparin (enoxaparin, dalteparin)
- Fondaparinux

## Combination

- Pharmacological plus mechanical

There WILL NOT be off-label and/or investigational discussion in this presentation.

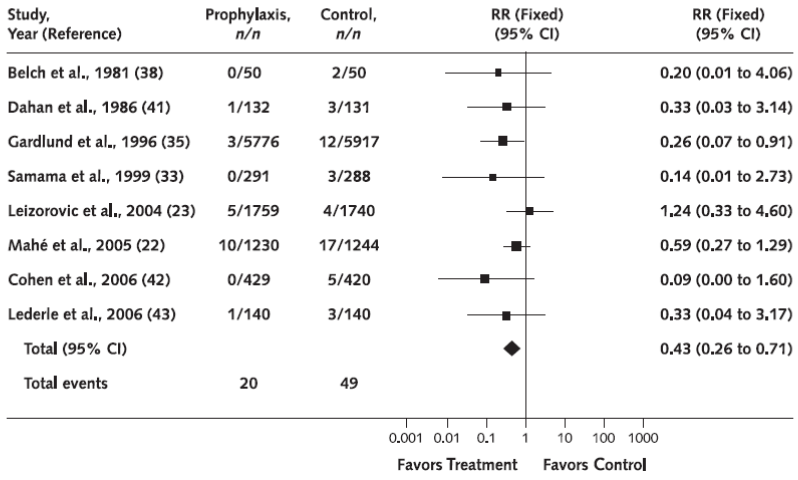
ACP Clinical Practice®
American College of Physicians
GUIDELINES

## Summary of the American College of Physicians Guideline on Venous Thromboembolism Prophylaxis in Hospitalized Patients

| | |
|---|---|
| **Disease or condition** | VTE |
| **Target audience** | Internists, family physicians, other clinicians |
| **Target patient population** | Adults with VTE |
| **Interventions** | Low-dose heparin products<br>Mechanical devices |
| **Outcomes** | Total mortality<br>PE<br>All bleeding<br>Major bleeding |
| **Recommendations** | *Recommendation 1: ACP recommends assessment of the risk for thromboembolism and bleeding in medical (including stroke) patients prior to initiation of prophylaxis of venous thromboembolism (Grade: strong recommendation, moderate-quality evidence).*<br>*Recommendation 2: ACP recommends pharmacologic prophylaxis with heparin or a related drug for venous thromboembolism in medical (including stroke) patients unless the assessed risk for bleeding outweighs the likely benefits (Grade: strong recommendation, moderate-quality evidence).*<br>*Recommendation 3: ACP recommends against the use of mechanical prophylaxis with graduated compression stockings for prevention of venous thromboembolism (Grade: strong recommendation, moderate-quality evidence).*<br>*Policy Implication*<br>*ACP does not support the application of performance measures in medical (including stroke) patients that promotes universal venous thromboembolism prophylaxis regardless of risk.* |
| **Clinical considerations** | • This guideline refers to hospitalized medical patients and patients with acute stroke at risk for VTE.<br>• Treatment benefits for VTE are primarily related to reduction in mortality, symptomatic DVT, and PE events.<br>• Assessment of risk for thromboembolism and bleeding is important before initiation of prophylaxis for VTE.<br>• Clinicians who initiate VTE prophylaxis should select heparin (or related) drugs rather than mechanical prophylaxis. |

# Trials of VTE Prophylaxis: Hospitalized Medical Patients

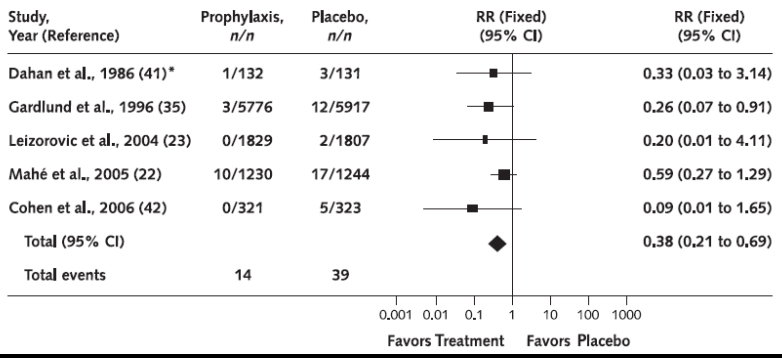
*Figure 2.* Any pulmonary embolism during anticoagulant prophylaxis.



| Study, Year (Reference) | Prophylaxis, *n/n* | Control, *n/n* | RR (Fixed) (95% CI) | RR (Fixed) (95% CI) |
|---|---|---|---|---|
| Belch et al., 1981 (38) | 0/50 | 2/50 | | 0.20 (0.01 to 4.06) |
| Dahan et al., 1986 (41) | 1/132 | 3/131 | | 0.33 (0.03 to 3.14) |
| Gardlund et al., 1996 (35) | 3/5776 | 12/5917 | | 0.26 (0.07 to 0.91) |
| Samama et al., 1999 (33) | 0/291 | 3/288 | | 0.14 (0.01 to 2.73) |
| Leizorovic et al., 2004 (23) | 5/1759 | 4/1740 | | 1.24 (0.33 to 4.60) |
| Mahé et al., 2005 (22) | 10/1230 | 17/1244 | | 0.59 (0.27 to 1.29) |
| Cohen et al., 2006 (42) | 0/429 | 5/420 | | 0.09 (0.00 to 1.60) |
| Lederle et al., 2006 (43) | 1/140 | 3/140 | | 0.33 (0.04 to 3.17) |
| Total (95% CI) | | | | 0.43 (0.26 to 0.71) |
| Total events | 20 | 49 | | |



*Figure 3.* Fatal pulmonary embolism during anticoagulant prophylaxis.



| Study, Year (Reference) | Prophylaxis, *n/n* | Placebo, *n/n* | RR (Fixed) (95% CI) | RR (Fixed) (95% CI) |
|---|---|---|---|---|
| Dahan et al., 1986 (41)* | 1/132 | 3/131 | | 0.33 (0.03 to 3.14) |
| Gardlund et al., 1996 (35) | 3/5776 | 12/5917 | | 0.26 (0.07 to 0.91) |
| Leizorovic et al., 2004 (23) | 0/1829 | 2/1807 | | 0.20 (0.01 to 4.11) |
| Mahé et al., 2005 (22) | 10/1230 | 17/1244 | | 0.59 (0.27 to 1.29) |
| Cohen et al., 2006 (42) | 0/321 | 5/323 | | 0.09 (0.01 to 1.65) |
| Total (95% CI) | | | | 0.38 (0.21 to 0.69) |
| Total events | 14 | 39 | | |

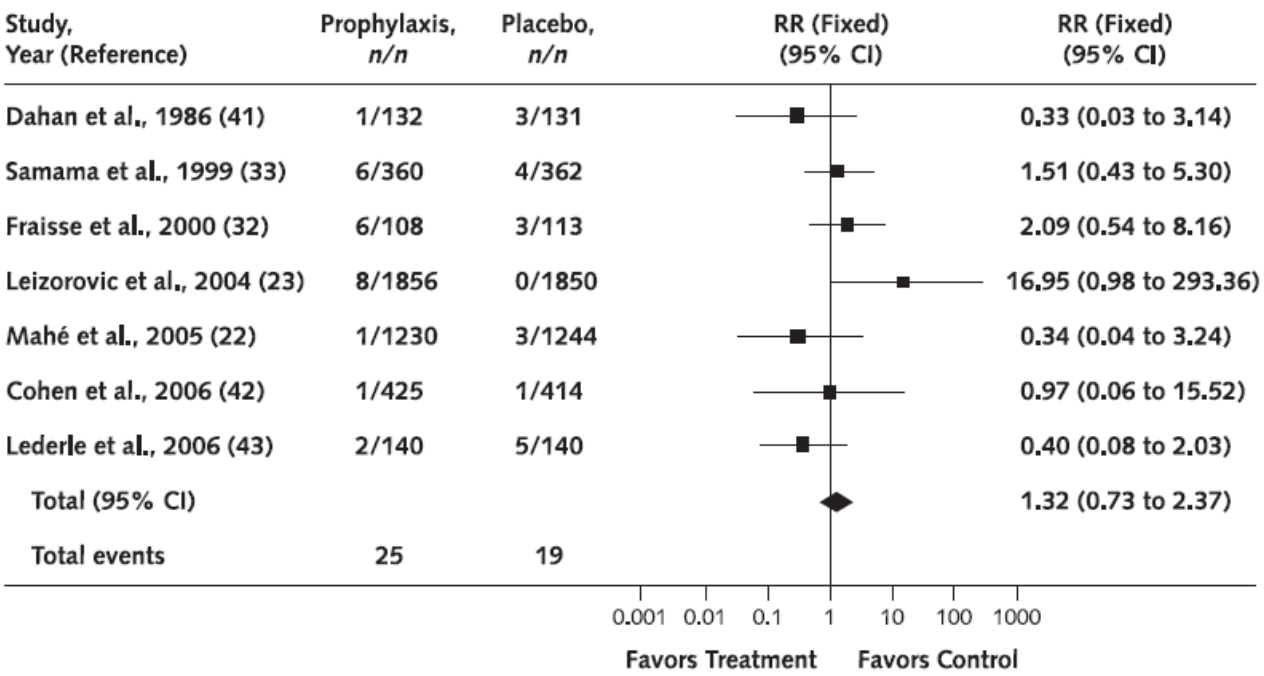


Dentali F, et al. Ann Intern Med 2007 Feb 20;146:278

There WILL NOT be off-label and/or investigational discussion in this presentation.

# Trials of VTE Prophylaxis: Hospitalized Medical Patients

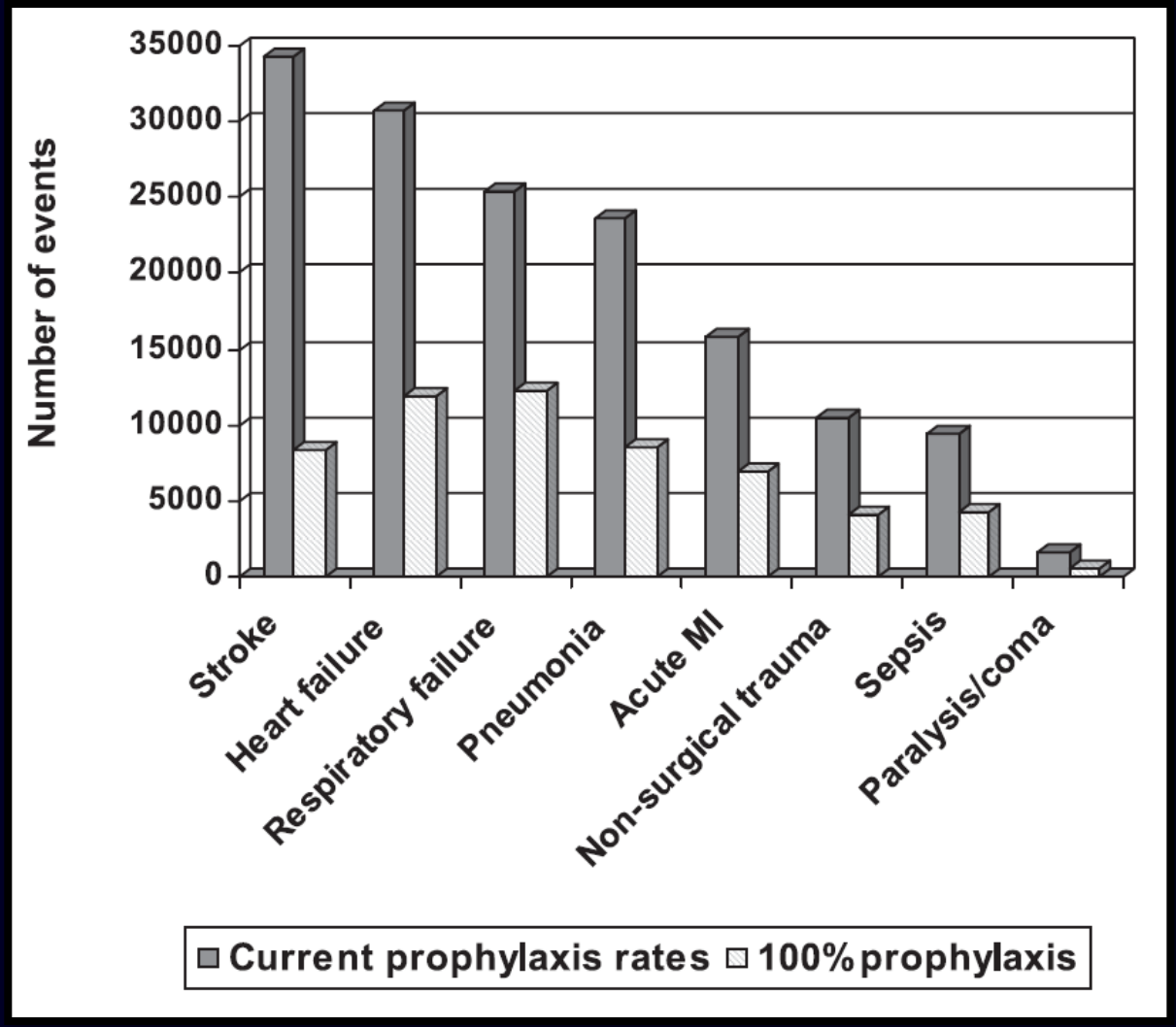
*Figure 6.* Major bleeding during anticoagulant prophylaxis.




There WILL NOT be off-label and/or investigational discussion in this presentation.

Dentali F, et al. Ann Intern Med 2007;146:278

# Preventing In-Hospital VTE: Lessons from the 2003 HCUP Database




Piazza G, et al. Thromb Haemost 2009;102:505

There WILL NOT be off-label and/or investigational discussion in this presentation.

# Electronic Alert Trial: Results

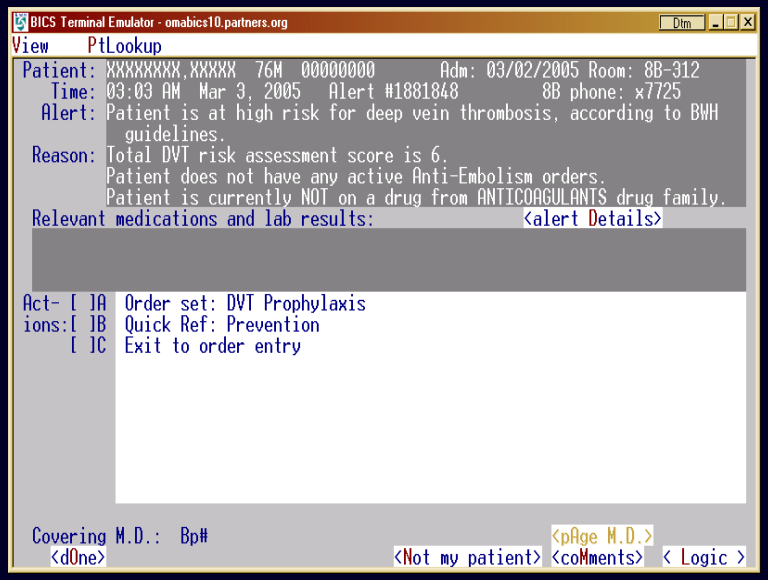



**Table 2. Prophylactic Measures against Venous Thromboembolism.**

| Measure | Intervention Group (N=1255) | Control Group (N=1251) | P Value |
|---|---|---|---|
| | *no. of patients (%)* | | |
| Mechanical | 125 (10.0) | 19 (1.5) | <0.001 |
| Compression stockings | 52 (4.1) | 7 (0.6) | <0.001 |
| Pneumatic boots | 73 (5.8) | 12 (1.0) | <0.001 |
| Pharmacologic | 296 (23.6) | 163 (13.0) | <0.001 |
| Unfractionated heparin | 213 (17.0) | 81 (6.5) | <0.001 |
| Warfarin | 28 (2.2) | 41 (3.3) | 0.11 |
| Enoxaparin | 55 (4.4) | 41 (3.3) | 0.18 |

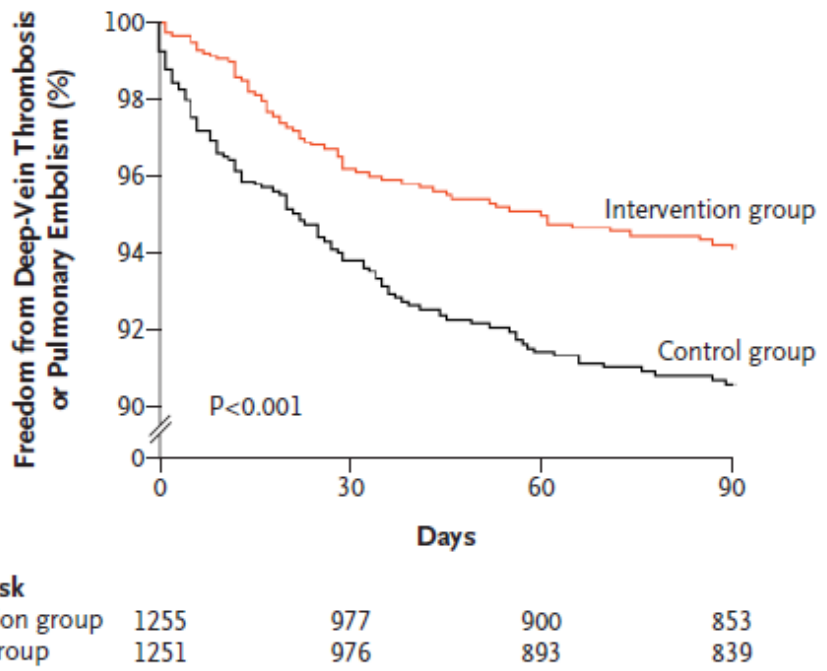


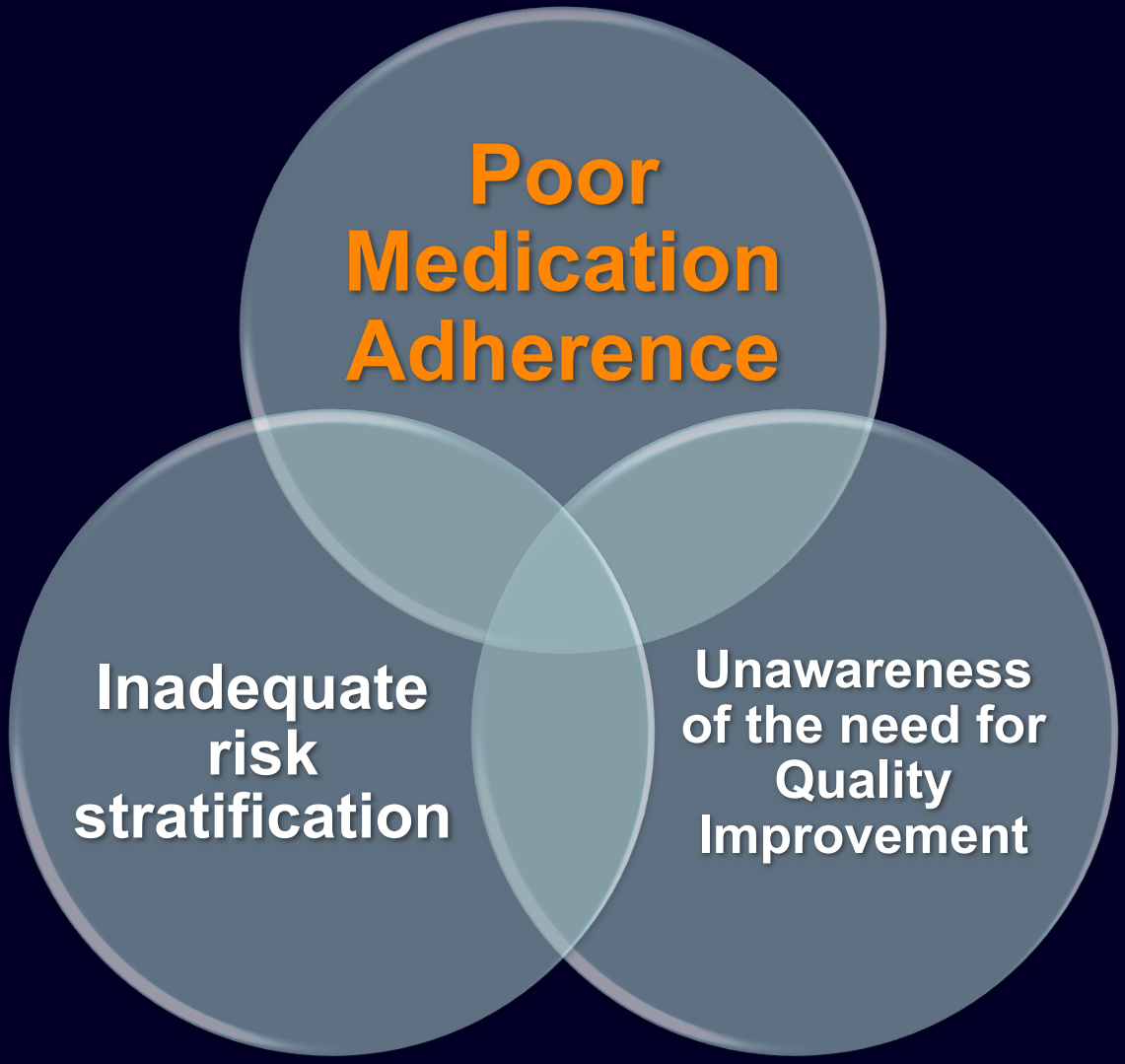

**Figure 1. Kaplan–Meier Estimates of the Absence of Deep-Vein Thrombosis or Pulmonary Embolism in the Intervention Group and the Control Group.**

P<0.001 by the log-rank test for the comparison of the outcome between groups at 90 days.

Kucher N, et al. N Engl J Med 2005;352:969

There WILL NOT be off-label and/or investigational discussion in this presentation.

# Barriers to Quality Improvement in VTE Prevention




There WILL NOT be off-label and/or investigational discussion in this presentation.

# Adherence to VTE Prophylaxis: Lessons from the Continuum of Care Study

**Table 4** Patient Outcomes and Compliance

| Outcomes/Adherence | LMWH 125 Patients | UFH Twice Daily 28 Patients | UFH 3 Times Daily 97 Patients | *P* Value |
|---|---|---|---|---|
| Number of scheduled doses | 648 | 204 | 1195 | |
| Number of doses administered | 615 | 177 | 1049 | |
| Number of doses omitted | 33 | 27 | 146 | |
| Adherence | 94.9% | 86.8% | 87.8% | <.001† |
| Number of patients that received 100% of doses | 97 (77.6%) | 15 (53.6%) | 44 (45.4%) | <.001† |
| Interval between successive administered doses* (hours) | | | | |
| Mean ± SD | 24.4 ± 5.1 | 12.7 ± 2.1 | 8.7 ± 1.0 | <.001‡ |
| Median | 23.91 | 12.14 | 8.25 | — |
| Range (min, max) | (11.75, 72.10) | (7.99, 18.32) | (7.01, 11.99) | — |
| Interval between scheduled dose and administered dose* (hours) | | | | |
| Mean ± SD | 0.64 ± 0.26 | 0.53 ± 0.22 | 0.64 ± 0.22 | .037‡ |
| Median | 0.59 | 0.49 | 0.59 | — |
| Range (min, max) | (0.20, 1.62) | (0.20, 1.13) | (0.29, 1.57) | — |

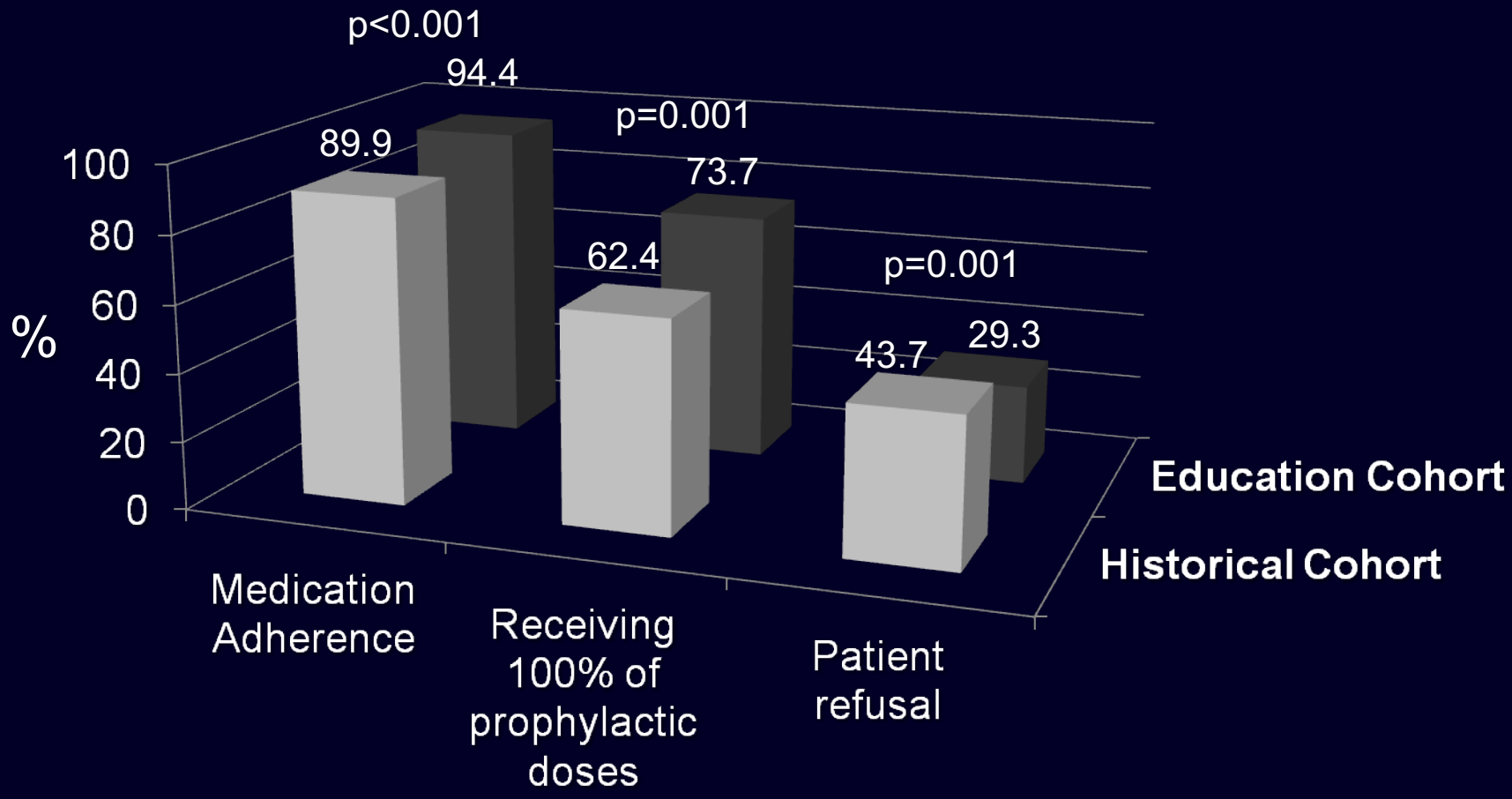
**Table 5** Reasons for Late or Omitted Doses

| Reasons for Omitted or Late Doses | LMWH 33 Doses Not Given n (%) | UFH Twice Daily 27 Doses Not Given n (%) | UFH 3 Times Daily 146 Doses Not Given n (%) | *P* Value* |
|---|---|---|---|---|
| Refused | 13 (39.4) | 16 (59.3) | 61 (41.8) | .210 |
| Other | 6 (18.2) | 6 (22.2) | 39 (26.7) | .560 |
| Held per physician | 9 (27.3) | 2 (7.4) | 24 (16.4) | .119 |
| Off floor | 5 (15.2) | 3 (11.1) | 17 (11.6) | .843 |
| Patient unable | 9 (0.0) | 0 (0.0) | 2 (1.4) | .660 |
| Med not available | 0 (0.0) | 0 (0.0) | 2 (1.4) | .660 |
| Order discontinued | 0 (0.0) | 0 (0.0) | 1 (0.7) | .813 |

There WILL NOT be off-label and/or investigational discussion in this presentation.

Fanikos J, et al. Am J Med 2010;123:536

# Impact of Patient Education on VTE Prevention




There WILL NOT be off-label and/or investigational discussion in this presentation.

Piazza G, et al. Am J Med 2012;125:258

# VTE Risk after Discharge

- Although much of the emphasis placed on prevention has focused on in-hospital prophylaxis, three-quarters of patients develop venous thromboembolism (VTE) as outpatients.

- Of these patients, a substantial proportion have undergone hospitalization (37%) or surgery (23%) in the 3 months preceding the diagnosis of VTE.

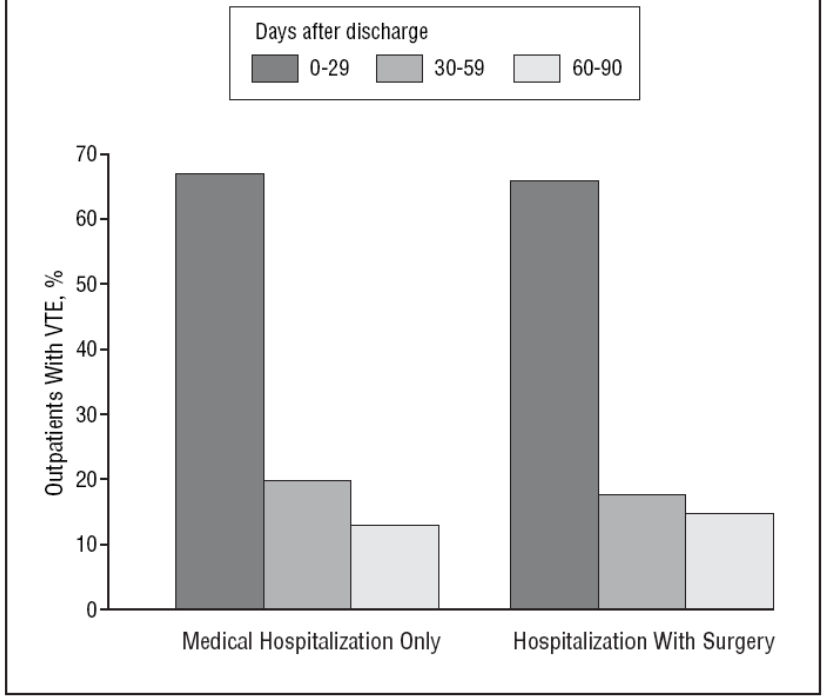
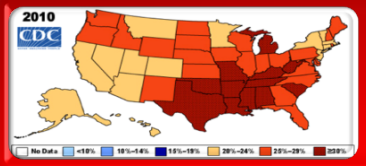



**Figure.** Timing of diagnosis of venous thromboembolism (VTE) relative to the preceding hospital discharge among individuals who developed VTE as an outpatient.

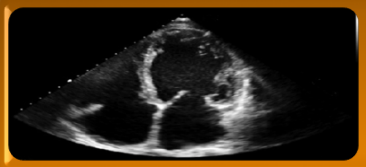
Arch Intern Med 2007;167:1471

There WILL NOT be off-label and/or investigational discussion in this presentation.

# VTE Risk Factors Do Not "Miraculously Go Away" When Patients are Discharged

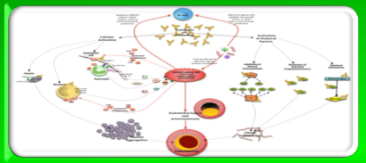



## Obesity



## Comorbid medical disease

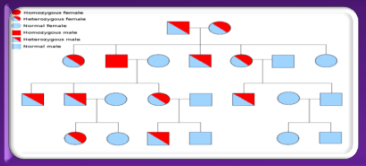
- COPD/HF
- Inflammatory disorders (IBD, RA, lupus)
- Atherosclerotic cardiovascular disease



## Thrombophilia

- Acquired (antiphospholipid antibodies)
- Inherited (anticoagulant protein deficiencies)

## Smoking



## Family history

There WILL NOT be off-label and/or investigational discussion in this presentation.

# Extended Duration Prophylaxis in Medical Patients: Net Clinical Benefit?

| Study | Study type | Study conclusion | Net clinical benefit |
|---|---|---|---|
| EXCLAIM (Hull, et al.) | RCT | VTE↓ Major bleeding↑ | No |
| MAGELLAN (Cohen, et al.) | RCT | VTE↓ Major bleeding↑ | No |
| ADOPT (Goldhaber, et al.) | RCT | VTE↔ Major bleeding↑ | No |
| DISCHARGE ALERT (Piazza, et al.) | RCT | VTE↔ Major bleeding↔ | No |
| CONTINUUM (Fanikos, et al.) | Case-Control | VTE↔ Major bleeding↑ | No |

Piazza G, et al. Am J Med 2013;126:435

There WILL NOT be off-label and/or investigational discussion in this presentation.

# Acute Medically-Ill VTE Prevention with Extended Duration Betrixaban: APEX

- **Study Population:** immobilized medical patients with heart failure, respiratory failure, infection, or stroke (**HIGH RISK**).

- **Study Design:** Double-blind randomized controlled trial: oral betrixaban 80 mg daily for 35 days vs. enoxaparin 40 mg daily for 6-10 days.

- **Primary Endpoint**: VTE plus VTE-related death

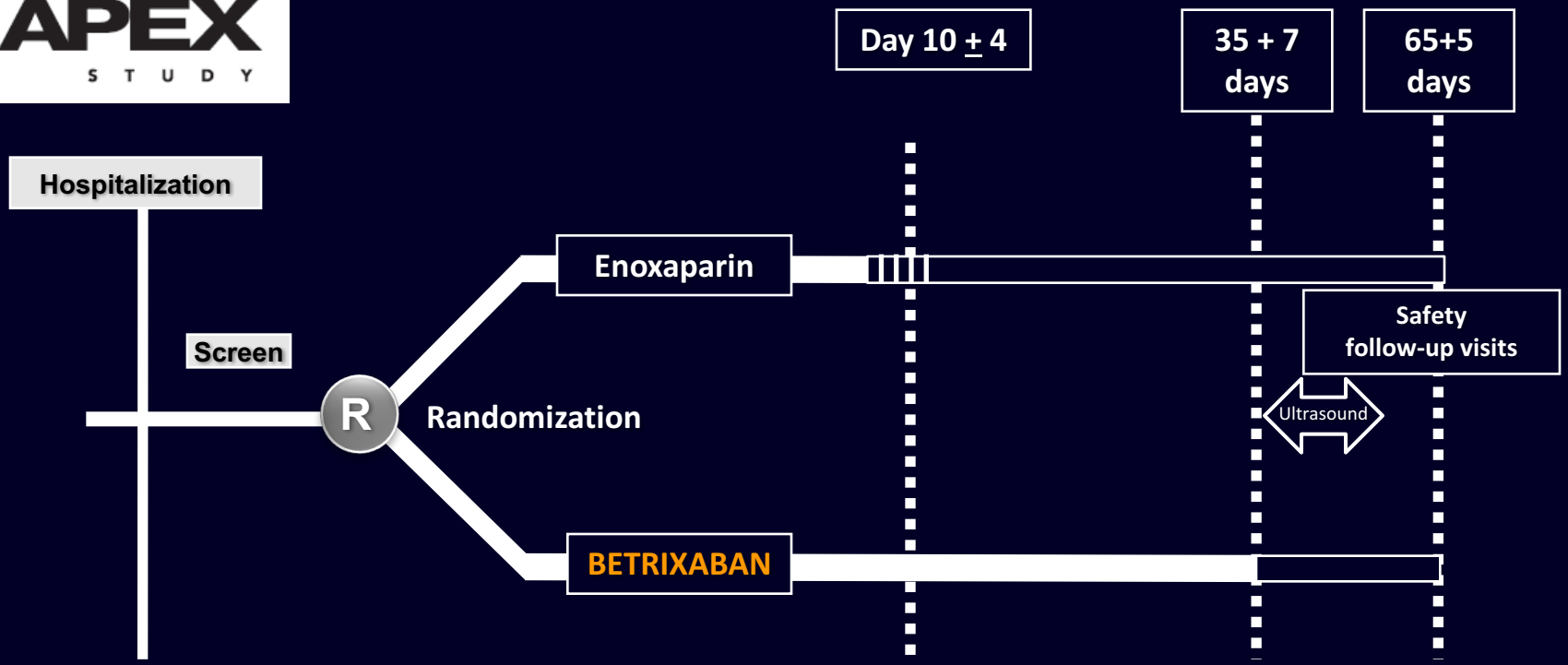
Cohen AT, et al. Am Heart J 2014;167:335

There WILL NOT be off-label and/or investigational discussion in this presentation.

# Acute Medically-Ill VTE Prevention with Extended Duration Betrixaban: APEX

APEX STUDY

N = 6,850




***No ultrasound is required at hospital discharge
Only 1 Ultrasound is required at 35 day follow up

There WILL NOT be off-label and/or investigational discussion in this presentation.

Cohen AT, et al. Am Heart J 2014;167:335

# Take Home Points

- VTE is a common and preventable complication of medical illness.
- While safe and effective, pharmacological prophylaxis for VTE prevention in medical patients is underutilized.
- Although the risk of VTE extends past hospital discharge, initial trials of extended duration prophylaxis did not show a net clinical benefit.

There WILL NOT be off-label and/or investigational discussion in this presentation.