



STANDING STONE
DEVELOPERS OF DISEASE MANAGEMENT SOLUTIONS



are pleased to present

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Update in Anticoagulation Management

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Patient Case #1

- 67 y/o male is admitted to the hospital for a total hip replacement discharged on enoxaparin 40mg SC daily for 4 weeks for VTE prophylaxis
- Patient presents a prescription for enoxaparin 40mg to the outpatient pharmacy on Friday afternoon
- RPH informs patient that they don't have enough enoxaparin 40mg syringes in stock to fill entire prescription. The RPh gives the patient a 4 day supply and instructs patient to return to the pharmacy on Monday to pick up remainder of prescription
- On Monday the RPh receives a supply of enoxaparin and fills prescription

Patient Case #1

- One week later, the patient has not returned to pick up prescription
- Pharmacist contacts patient, learns patient suffered a fatal pulmonary embolism 3 days earlier



Patient Case #2

- 57 y/o woman presents prescription for warfarin 1mg tabs
- Pharmacy technician fills prescription for warfarin 10mg tabs
- Pharmacist checks prescription and dispenses medication
- Patient suffers massive ICH
- Florida jury awarded damages of \$25.8 million

ABC News - 20/20

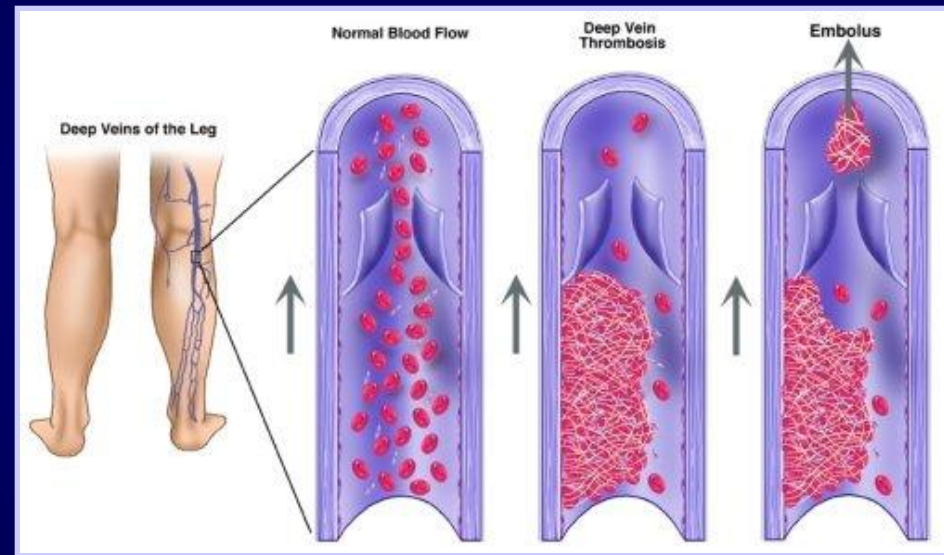
- Last March, a team of 20/20 producers conducted an undercover 4 month investigation
- In three major U.S. cities, 100 big-chain drugstores were tested for pharmacy errors using first-time prescriptions
- Producers were instructed to select a large bottle of aspirin and take it to the counter at the same time they picked up a prescription for the blood thinner warfarin
- **Results**
 - In just over 30% of cases (8 out of 25), pharmacists identified the potentially dangerous combination of drugs and warned patients
 - The other 70% were never told about the deadly drug interaction between aspirin and warfarin
 - Counseling was only offered in 27 of 100 cases
 - In 73% of cases, no counseling was given without prompting by producers

Objectives

- State the pathology and epidemiology associated with Venous Thromboembolism (VTE);
- Review the evidence on new and current options for VTE treatment and prophylaxis
- Identify strategies to increase use of VTE prophylaxis

WHAT IS VENOUS THROMBOEMBOLISM (VTE)?

- Deep vein thrombosis (DVT): Formation of a blood clot within a deep vein (e.g., popliteal vein)
 - Signs may include swelling, pain and redness of the affected area
- Pulmonary embolism (PE): Blockage of the pulmonary artery or one of its branches when a deep vein clot migrates to the lungs
 - Severe cases can lead to collapse, circulatory instability, and sudden death



Surgeon General's Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism September 15, 2008

- Failure to provide appropriate screening and preventive treatment (thromboprophylaxis) to hospitalized, at-risk patients is now classified as a medical error
- Provision of preventive treatment is one of the most important things that can be done to improve patient safety
- “Must disseminate information widely” to “address gap” between evidence and implementation

The Surgeon General's Call to Action
to Prevent Deep Vein Thrombosis
and Pulmonary Embolism

2008

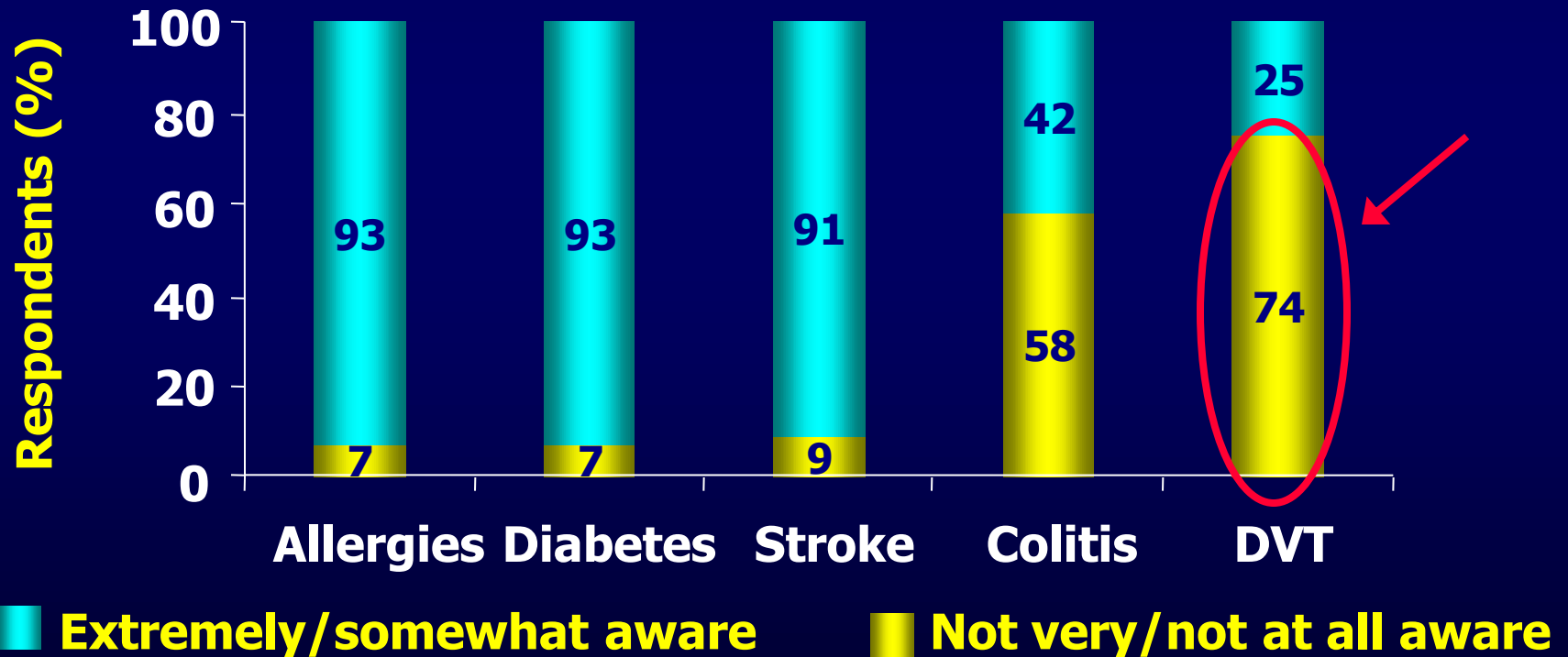


The Surgeon General's Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism: <http://www.surgeongeneral.gov/topics/deepvein/calltoaction/call-to-action-on-dvt-2008.pdf>. Accessed: May 7, 2009.

Health and Human Services

Awareness of DVT as a Medical Condition

N = 1003 US public survey respondents

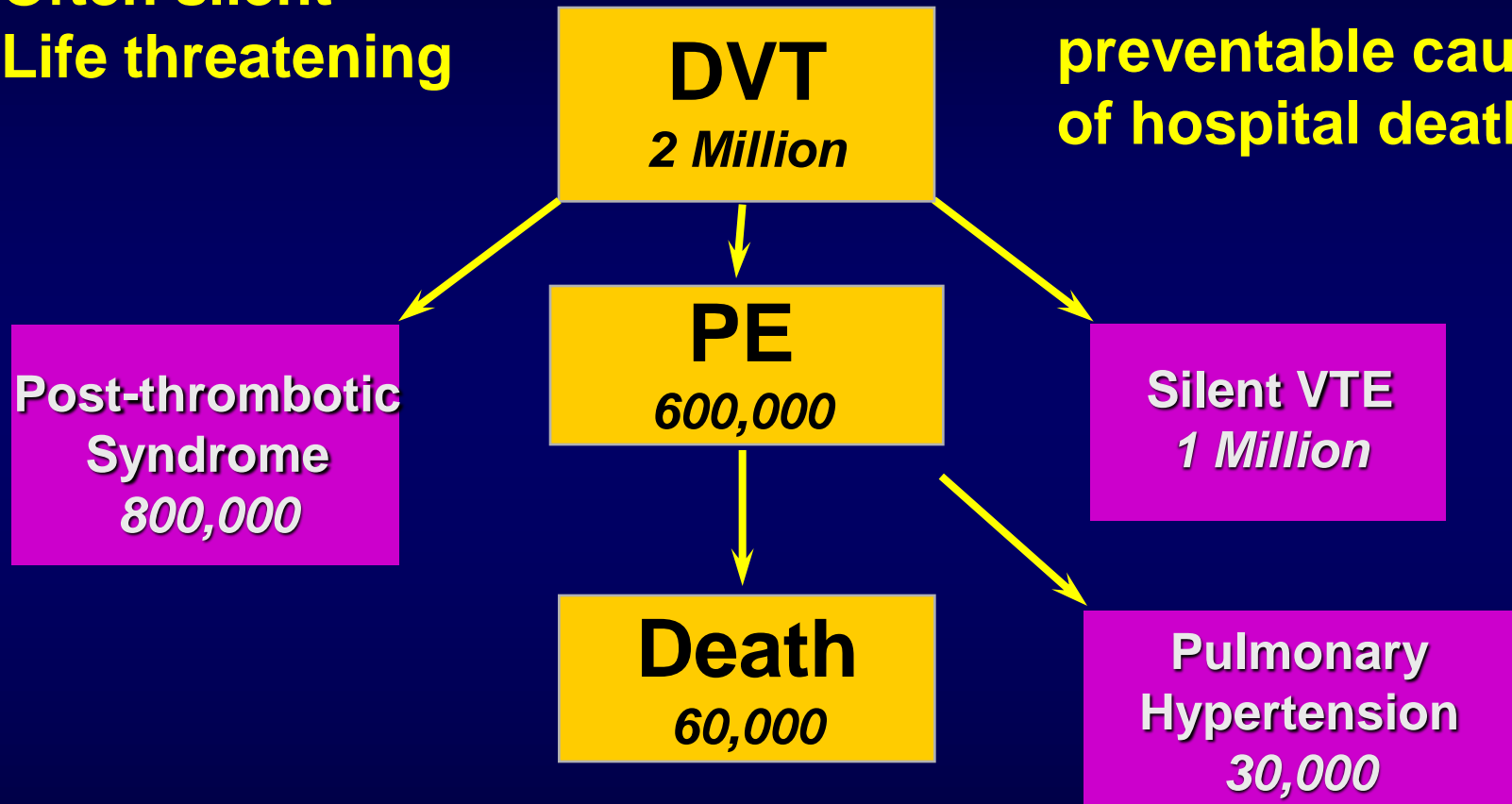


American Public Health Association Deep-Vein Thrombosis Omnibus Survey, 2002

Scope of Venous Thromboembolism

Often silent
Life threatening

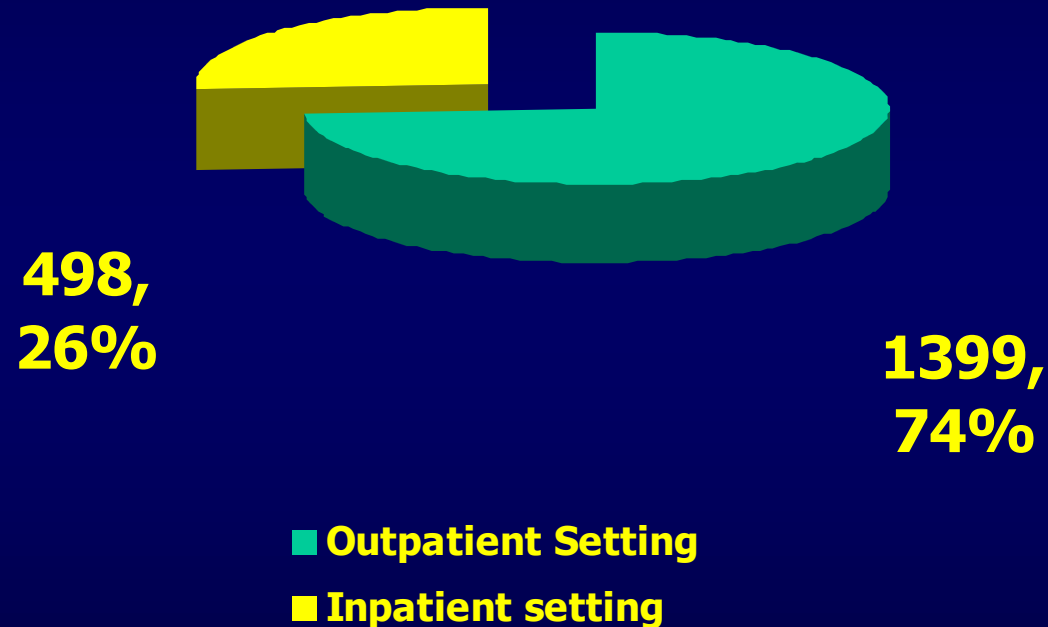
Most common
preventable cause
of hospital death



Estimated VTE Costs: \$1.5 billion per year

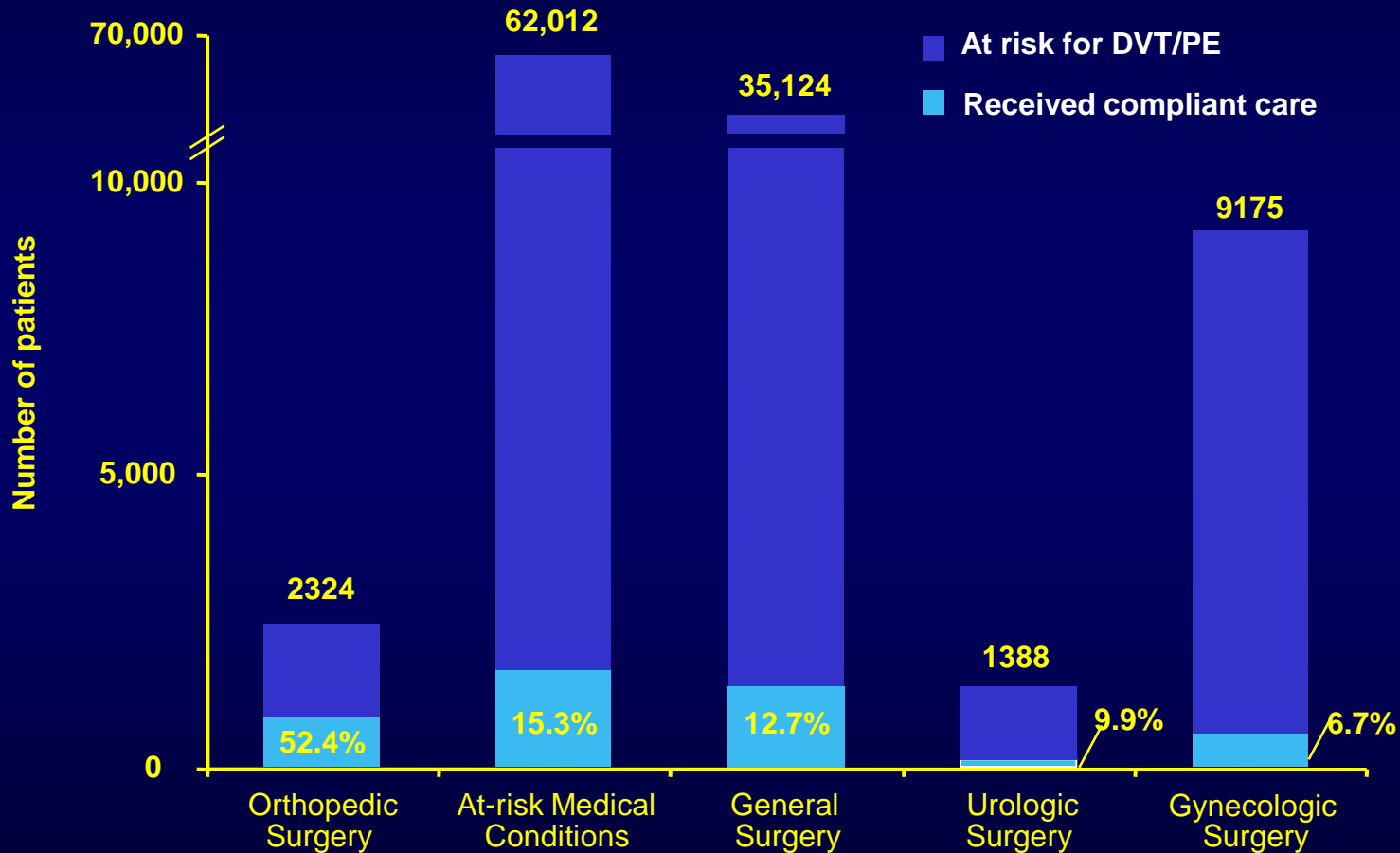
Venous Thromboembolism in the Outpatient Setting

- Worcester, MA USA
- n=7,222 medical records via ICD-9 codes
- 1,897 VTE episodes
 - 1,348 DVT
 - 385 PE
 - 264 DVT and PE
- 74% presented from the outpatient setting with signs and symptoms of VTE



Compliance With ACCP DVT/PE Prophylaxis Guidelines Is Poor

Compliance With VTE Prophylaxis Guidelines in Hospitals by Patient Group



Note: Data collected January 2001 to March 2005; 123,340 hospital admissions. Compliance assessment was based on the 6th American College of Chest Physicians (ACCP) guidelines.

Yu H-T et al. *Am J Health-Syst Pharm.* 2007;64:69-76.

Clinical Inertia

- Clinical inertia is failure of health care provider to initiate or intensify treatment
 - Overrating of substandard care for fear of increasing adverse drug events
 - Lack of knowledge, tools, training and systems support
- Leading cause of preventable adverse events, disability, death and excess costs

Clinical Inertia

- Mechanisms to reduce clinical inertia have been identified
- Quality improvement efforts should focus on altering provider behavior
 - use of information system interventions
 - educational reminders
 - feedback to providers relative to compliance with guidelines

Background

- At Brigham and Women's Hospital, we have initiated a series of trials aimed at increasing prophylaxis by:
 - changing MD behavior and
 - improving implementation of prophylaxis via a high-reliability process

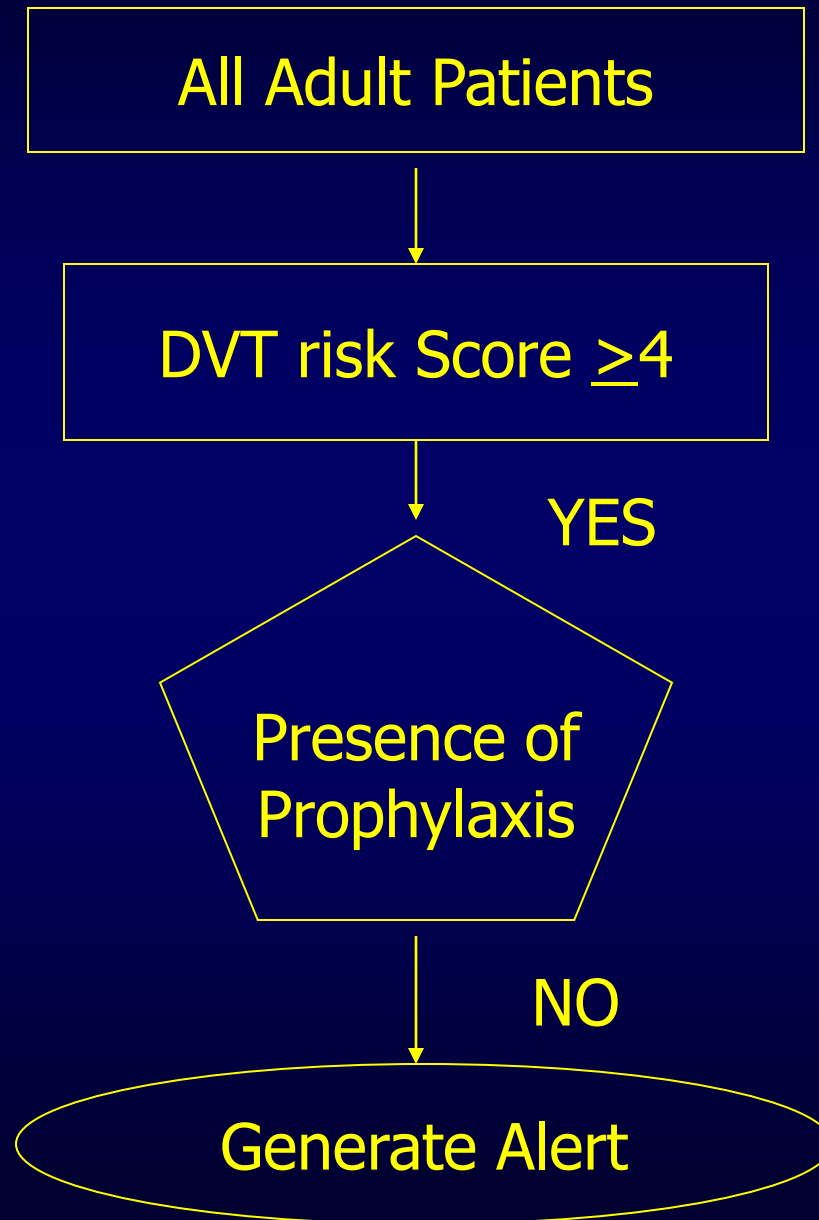
First Generation Electronic Alerts

- BWH utilizes BICS (Brigham Integrated Computing System) for all order entry functions
 - Admitting records, demographic information, lab results, medication orders, etc.
- VTE group utilized computer system to screen all patients admitted to the hospital for High Risk VTE Status

First Generation Alert: Development

- Aim: to increase rate of prophylaxis in patients at risk for DVT and PE
- Alert the responsible physician of high risk patient (via e alert) and offer opportunity to order appropriate prophylaxis

Study Schema



DEFINITION OF “HIGH RISK”

VTE risk score ≥ 4 points:

- Cancer 3 (ICD codes)
- Prior VTE 3 (ICD codes)
- Hypercoagulability 3 (Leiden, ACCLA)
- Major surgery 2 (> 60 minutes)
- Bed rest 1 (“bed rest” order)
- Advanced age 1 (> 70 years)
- Obesity 1 (BMI > 29 kg/m²)
- HRT/OC 1 (order entry)

RANDOMIZATION

**VTE risk score ≥ 4
No prophylaxis
N = 2506**

```
graph TD; A["VTE risk score ≥ 4  
No prophylaxis  
N = 2506"] --> B["INTERVENTION  
Single alert  
n = 1255"]; A --> C["CONTROL  
No alert  
n = 1251"];
```

INTERVENTION
Single alert
n = 1255

CONTROL
No alert
n = 1251

Physician Notification of Alerts

Alerts

You are None, M.D. ↓

There are new alerts on these patients. Mark one and
<Enter> to deal with it now, or <Esc> to skip them all.

09:11 AM 10/28	Rxtest, M	DVT HIGH RISK
09:11 AM 10/28	Rxtest, J	DVT HIGH RISK

<F1> Info. <Esc> Cancel.

OK

Cancel

View PtLookup

Patient: XXXXXXXX,XXXXX 76M 00000000 Adm: 03/02/2005 Room: 8B-312
Time: 03:03 AM Mar 3, 2005 Alert #1881848 8B phone: x7725
Alert: Patient is at high risk for deep vein thrombosis, according to BWH
guidelines.
Reason: Total DVT risk assessment score is 6.
Patient does not have any active Anti-Embolism orders.
Patient is currently NOT on a drug from ANTICOAGULANTS drug family.

Relevant medications and lab results: <alert Details>

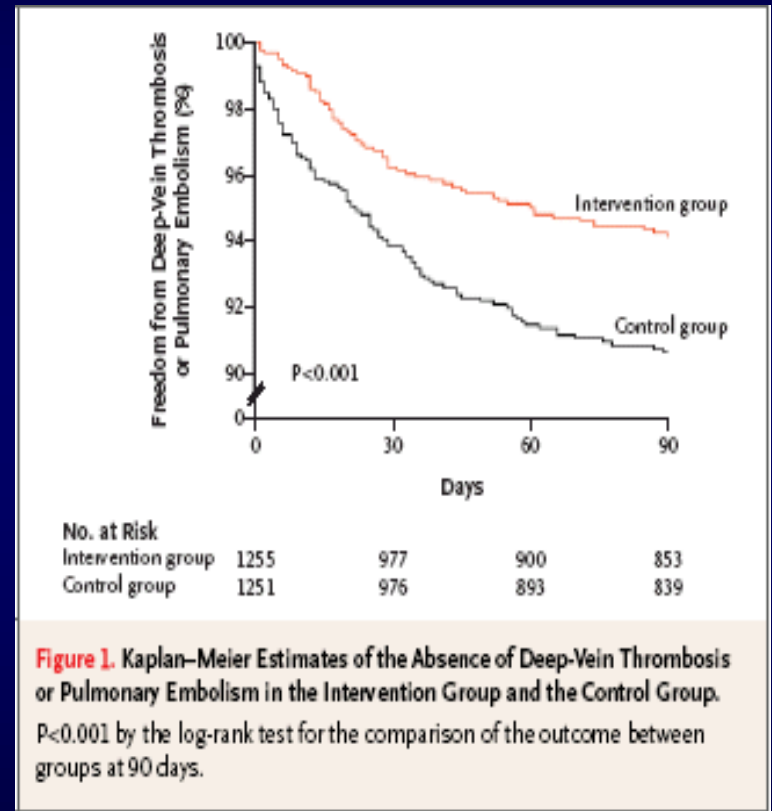
Act- [IA Order set: DVT Prophylaxis
ions: [IB Quick Ref: Prevention
[IC Exit to order entry

Covering M.D.: Bp#
<dOne>

<Not my patient> <page M.D.>
<coMments> < Logic >

First Generation Computerized Alerts for VTE prevention

- Utilization of computer generated alerts to house staff reduced the incidence of VTE by 41%
- VTE prophylaxis was prescribed in 33.5% of patients in the intervention group
- Following study conclusion randomization was turned off and all patients at high risk were included



Second Generation: Electronic Computer Generated Alerts

BWH VTE Alerts: The Future

- Goals:
 - Engage the house officer with an interactive alert to increase acceptance and gain feedback
 - Update the DVT prophylaxis template to meet current practice guidelines
 - Provide real-time knowledge link
 - Determine clinical rational for omission of prophylaxis

Interactive Techniques

- Provide objective data to the house officer that this alert positively impacts patient outcome
- Create opportunity to capture rationale for declining alert
 - Hypothesized that many physicians fear a risk of bleeding with anticoagulation
- Provide a final opportunity to order mechanical prophylaxis
- Alert attending physician if alert is not acknowledged after 24 hours

DVT Alert Screen

Time: 03:24 AM Dec 4, 2002 Alert #1014346 14B phone: x7905

Alert: Patient is at high risk for deep vein thrombosis, according to BWH guidelines.

Reason: Total DVT risk assessment score is 4.
Patient does not have any active Anti-Embolism orders.
Patient is currently NOT on a drug from ANTICOAGULANTS drug family.

Relevant medications and lab results: [<alert Details>](#)

Study at BWH published in NEJM 2005;352:969-977 demonstrated a 41% decrease in incidence of VTE using computer generated alerts to House Staff physicians

Act- [JA Order set: DVT PROPHYLAXIS TEMPLATE.
ions:[IB Partners Handbook: VTE Guidebook 4th edition
[IC Exit to order entry

Covering M.D.: Bp#
<dOne>

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<Not my patient> <coMments> < Logic >



QA

Rule Logic – Alert Details

Time: 03:22 AM Nov 2, 2004 Alert #1740559 7A phone: x7695

Details for alert #1740559

Rule: Patient is at high risk for deep vein thrombosis, according to BWH guidelines.

The following risk factors were found to be positive (score applied):

Patient is overweight: BMI >29 kg/m² (1)

has history of deep vein thrombosis or pulmonary embolism (3).

-and-

Patient does not have any active Anti-Embolism orders.

-and-

Patient is currently NOT on a drug from ANTICOAGULANTS drug family.

Option A

Time: 03:24 AM Dec 4, 2002 Alert #1014346 14B phone: x7905
Alert: Patient is at high risk for deep vein thrombosis, according to BWH guidelines.

Reason: Total DVT risk assessment score is 4.
Patient does not have any active Anti-Embolism orders.
Patient is currently NOT on a drug from ANTICOAGULANTS drug family.

Relevant medications and lab results: [<alert Details>](#)

Study at BWH published in NEJM 2005;352:969-977 demonstrated a 41% decrease in incidence of VTE using computer generated alerts to House Staff physicians

Act- [1A Order set: DVT PROPHYLAXIS TEMPLATE.
ions:[1B Partners Handbook: VTE Guidebook 4th edition
[1C Exit to order entry



Covering M.D.: Bp#
[<dOne>](#)

[<Not my patient>](#)

[<pAge M.D.>](#)
[<coMments>](#)

[< Logic >](#)



QA

OETEST,CLOVIS 32F 11489945

Adm: 11/01/91 Room: 17A-444

DVT Prophylaxis Order Set Page 1

Consider combined pharmacological and mechanical prophylaxis in high-risk patients.

MECHANICAL PROPHYLAXIS

Select one or more.

- A Anti-embolism - TED stockings KNEE HIGH
- B Anti-embolism - TED stockings THIGH HIGH
- C Anti-Embolism - Pneumatic Compression - CALF ONLY
- D Anti-Embolism - Pneumatic Compression - CALF and THIGH

PHARMACOLOGICAL PROPHYLAXIS

Select only one.

- E ENOXAPARIN 40 MG SC QD
- F ENOXAPARIN 30 MG SC QD for patients with renal impairment
- G HEPARIN 5,000 UNITS SC TID
- H HEPARIN 5,000 UNITS SC BID
- I FONDAPARINUX 2.5 MG SC QD
- J FONDAPARINUX 2.5 MG SC QOD For patients with renal impairment

OK

Cancel

Option B

Time: 03:24 AM Dec 4, 2002 Alert #1014346 14B phone: x7905

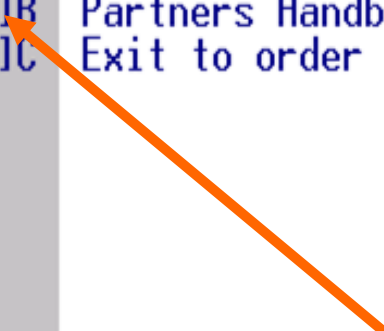
Alert: Patient is at high risk for deep vein thrombosis, according to BWH guidelines.

Reason: Total DVT risk assessment score is 4.
Patient does not have any active Anti-Embolism orders.
Patient is currently NOT on a drug from ANTICOAGULANTS drug family.

Relevant medications and lab results: [<alert Details>](#)

Study at BWH published in NEJM 2005;352:969-977 demonstrated a 41% decrease in incidence of VTE using computer generated alerts to House Staff physicians

Act- []A Order set: DVT PROPHYLAXIS TEMPLATE.
ions:[]B Partners Handbook: VTE Guidebook 4th edition
[]C Exit to order entry



Covering M.D.: Bp#

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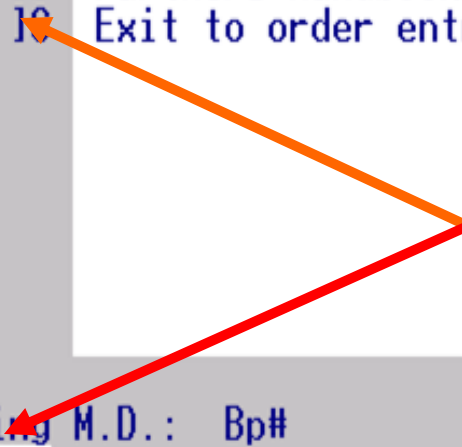


Option C or "Done"

Time: 03:24 AM Dec 4, 2002 Alert #1014346 14B phone: x7905
Alert: Patient is at high risk for deep vein thrombosis, according to BWH guidelines.
Reason: Total DVT risk assessment score is 4.
Patient does not have any active Anti-Embolism orders.
Patient is currently NOT on a drug from ANTICOAGULANTS drug family.
Relevant medications and lab results: [<alert Details>](#)
Study at BWH published in NEJM 2005;352:969-977 demonstrated a 41% decrease in incidence of VTE using computer generated alerts to House Staff physicians

Act- [JA Order set: DVT PROPHYLAXIS TEMPLATE.
ions:[JB Partners Handbook: VTE Guidebook 4th edition
[JC Exit to order entry

Covering M.D.: Bp# [<Done>](#) [<Not my patient>](#) [<Page M.D.>](#) [<Comments>](#) [<Logic >](#)



View PtLookup

Reason for Declining VTE Prophylaxis

Study at BWH published in NEJM 2005;352:969-977
demonstrated a 41% decrease in incidence of VTE using
computer generated alerts to the House Staff physicians

Provide Reason for Declining VTE Prophylaxis

- Patient already receiving anticoagulants
- Risk of bleed outweighs benefit of anticoagulant therapy
- Patient is "Comfort Measures Only"
- Scheduled procedure
- Other

Other reason (minimum of 15 characters)

|

|

Done



Mechanical DVT Prophylaxis Page 1

There is not an increased risk of bleed with mechanical prophylaxis such as graduated compression stockings or intermittent pneumatic compression devices. Consider ordering one or more of the following mechanical prophylaxis orders.

Select one or more:

- A > [X] Anti-embolism - TED stockings KNEE HIGH
- B [] Anti-embolism - TED stockings THIGH HIGH
- C [] Anti-embolism - Pneumatic boots CALF ONLY
- D [] Anti-embolism - Pneumatic boots CALF AND THIGH

Edit

OK

Cancel

[DEV]

Escalation and Timing of Alerts

- Alerts should be set up to generate each day at 8:30 AM
- If an alert was not acknowledged after 24 hours the attending physician on record should be text paged.

Date	Time	Recipient	Message
10/28/2005	02:37:11PM	Goldhaber, Samuel Zachary, MD	8888-19327139 MRN: 19327139 LOC: 17A-301 High risk VTE patient without prophylaxis orders.
10/28/2005	02:36:08PM	Goldhaber, Samuel Zachary, MD	8888-19327147 MRN: 19327147 LOC: 17A-311 High risk VTE patient without prophylaxis orders.

3-Screen Alert Results

Prophylactic measure	One-screen alert (n=425)	Three-screen alert* (n=455)	P-value
Any prophylaxis, n (%)	216 (50.8)	266 (58.4)	0.02
Mechanical, n (%)	121 (18.0)	176 (26.2)	0.001
Graduated compression stockings	73 (10.9)	116 (17.3)	0.003
Pneumatic compression boots	48 (7.2)	60 (8.9)	0.39
Pharmacological, n (%)	95 (14.2)	90 (13.4)	0.35
Unfractionated heparin	49 (7.3)	43 (6.4)	0.31
Warfarin	3 (0.4)	6 (0.9)	0.18
Enoxaparin	38 (5.7)	41 (6.1)	0.97

*No patients in this group were prescribed prophylaxis after their physicians received the first of the three screens.

3-Screen Alert Results

End point	One-screen alert (n=425)	Three-screen alert (n=455)	P-value
Symptomatic DVT or PE at 90 days, n (%)	12 (2.8)	10 (2.2)	0.55
PE at 90 days	4 (0.9)	5 (1.1)	0.25
Major haemorrhage at 30 days, n (%)	8 (1.8)	6 (1.3)	0.51
Minor haemorrhage at 30 days, n (%)	18 (4.2)	23 (5.1)	0.56
Rehospitalisation during the follow-up period, n (%)	148 (34.8)	154 (33.8)	0.76

Rational for Thromboprophylaxis

What is the data?

- Hundreds of randomized trials
- Thromboprophylaxis reduces:
 - DVT
 - PE, fatal PE
 - All-cause mortality
 - Costs
- Thromboprophylaxis ranks as the number 1 patient safety strategy in hospitalized patients
- More than 25 published evidence-based guidelines since 1986 show clear evidence of benefit and safety

VTE: Prophylaxis vs. Treatment

- Prophylaxis
 - Mechanical methods
 - Pharmacologic (anticoagulant) methods
- Treatment
 - LMWH
 - Anti-Xa inhibitors
 - IV unfractionated heparin
 - Bridge to warfarin

Prophylaxis - Good house-keeping

- Frequent leg movement, calf “pumping”
- Early, frequent ambulation

These methods are **used**,
but **alone** are **insufficient**
for most patients.

Mechanical Prophylaxis

- Graduated compression stockings
- Intermittent pneumatic compression devices
- Foot pumps
- Portable devices (continuous enhanced circulation therapy)
- Often not used properly due to low compliance in hospital setting

Pharmacologic Prophylaxis

- Reduces symptomatic and asymptomatic VTE by 50-65%
- Serious bleeding is rare complication (based on currently available meta-analysis and clinical trial data)
 - Warfarin (oral vitamin K antagonist)
 - Low molecular weight heparin (LMWH)
 - Enoxaparin
 - Dalteparin
 - Fondaparinux
 - Heparin
 - New oral factor Xa and direct thrombin inhibitors*

Geerts WH, et al. *Chest*. 2008;133:381S-453S.

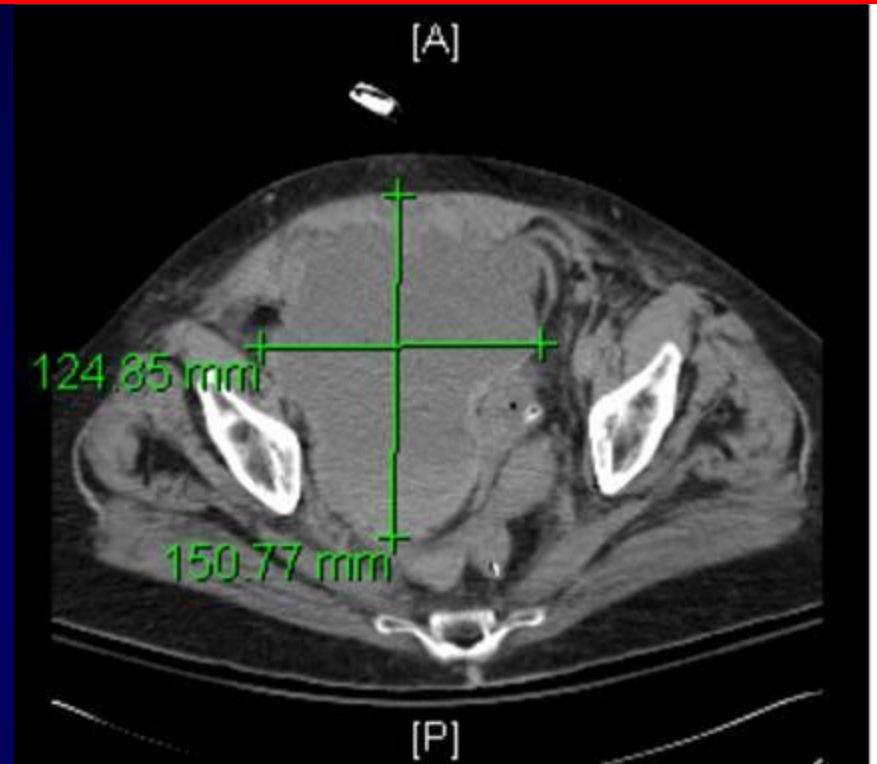
* Not yet approved in the US

Key Clinical Pearls

- Warfarin
 - Oral, reversible
 - Delayed onset, daily monitoring required, drug/diet interactions, complex to manage safely
- LMWH
 - Enoxparin and dalteparin
 - Rapid onset, no monitoring
 - Subcutaneous injection, onset within 1-2 hours, more difficult to reverse, rare heparin-induced thrombocytopenia

Patient Case

- 77 yo, 63.6 kg female with complaints of abdominal pain & brown-colored emesis
- Five days PTA, suffered DVT in her lower left leg
- Prescribed enoxaparin (80 mg twice daily) & warfarin (INR 2.0-3.0)
- CT showed massive retroperitoneal bleed
- Transfused with 2 units of whole blood & 2 L normal saline
- To reverse anticoagulation, she was treated with IV vitamin K 10 mg, protamine 25 mg, & 6 units of fresh frozen plasma



- 4 units of PRBC administered, after which she was transferred to the MICU
- Remained sedated & continued to receive blood product support
- Expired on hospital day 23

Key Clinical Pearls

- Fondaparinux
 - Advantages
 - Rapid onset, no monitoring required, HIT very rare
 - Disadvantages
 - Rapid onset, difficult to reverse
 - no neuraxial analgesia option
 - accumulates in renal insufficiency
- Heparin
 - Renal dysfunction is not prohibitive
 - Injection only
 - HIT

Special Considerations

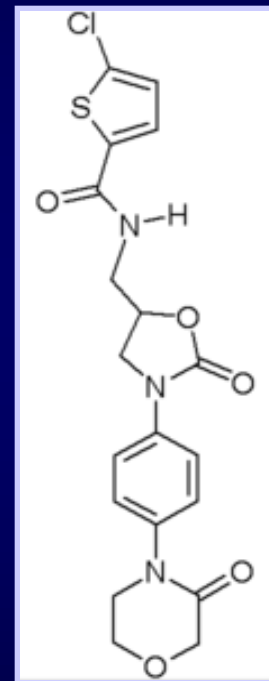
- Type of prophylaxis
 - Pharmacologic is more efficacious than mechanical
 - Mechanical should be used in patients with contraindications to anticoagulant prophylaxis
 - Mechanical methods must be used continuously to be effective
- Renal insufficiency (CrCl <30 mL/min)
 - LMWH should be used with caution
 - Enoxaparin 30 mg sc once daily (reduced dose)
 - Fondaparinux should be avoided
- Morbid obesity (weight >100 kg)
 - Consider enoxaparin 40 mg sc every 12 hours (or more depending on weight)

Ideal Anticoagulant

- Oral route
- Easy population based pharmacokinetics – one dose for most patients
- Inexpensive
- Predictable efficacy
- Low bleeding risk
- Reversible
- Rapid onset of action
- No need for therapeutic monitoring

Oral Direct Factor Xa Inhibitor: Rivaroxaban

- Direct, competitive Factor Xa inhibitor
- Inhibits free and fibrin-bound Factor Xa
- Rapid onset within 2-4 hours
- High bioavailability: > 80%
- No dosage adjustment for gender, age, extreme body weight
- Clearance: Renal (66%), hepatic/fecal (28%)
- Half-life: 7-11 hours
- Approved in Canada, Europe



Perzborn E, et al. *J Thromb Haemost.* 2005;3(3):514-21.

Kubitza D, et al. *J Clin Pharmacol.* 2007;47(2):218-26.

Gulseth MP, et al. *Am J Health Syst Pharm.* 2008;65(16):1520-9.

Rivaroxaban Phase III orthopedic Trials “RECORD” Trials

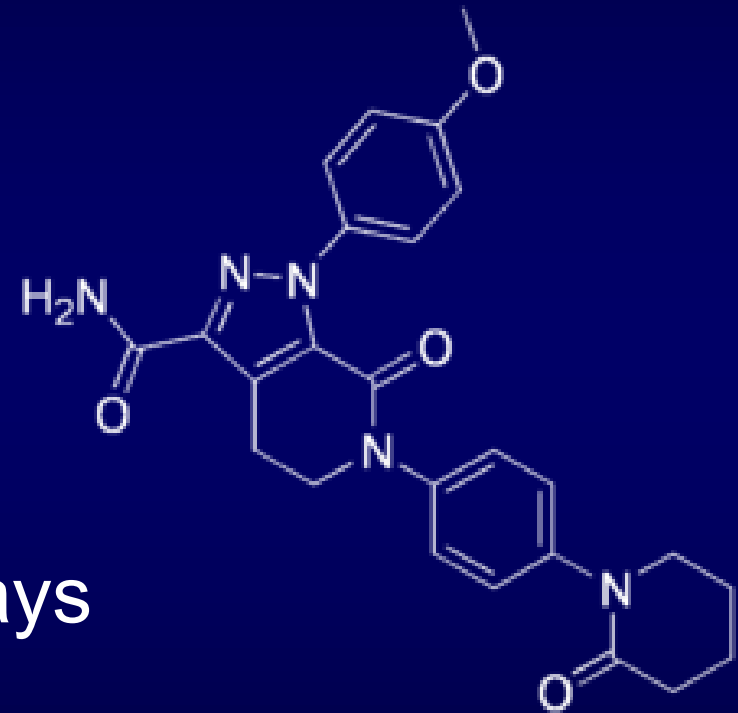
Outcome	Enoxaparin N=6,200	Rivaroxaban N=6,183	<i>P-value</i>
Symptomatic VTE + death	101 (1.6%)	50 (0.8%)	<0.001
Death	25 (0.4%)	13 (0.2%)	0.055
Major bleeding	17 (0.3%)	27 (0.4%)	0.135
Any bleeding	415 (6.7%)	452 (7.3%)	0.207
Death + MI + stroke + symptomatic VTE + major bleeding	139 (2.2%)	96 (1.6%)	0.004

MI = myocardial infarction

Turpie A, et al. *Blood*. 2008;112:36A.

Oral Direct Factor Xa Inhibitor: Apixaban

- Direct, reversible Factor Xa inhibitor
- Rapid onset; peak within 3 hours
- Bioavailability of 51-85%
- Multiple elimination pathways
 - 25% renal
 - 75% biliary



Dabigatran Phase III orthopedic Trials

	Enoxaparin	Dabigatran 150 mg	Dabigatran 220 mg
No.	1,409	1,400	1,383
Total VTE + mortality	20.3%	24.7%	21.3%
Major VTE	3.3%	3.8%	3.0%

Contraindications to Pharmacologic prophylaxis

- Active bleeding
- High risk of bleeding
- Therapeutic anticoagulation
- Severe uncontrolled hypertension
- Platelet count $<50,000/\mu\text{L}$

New Oral Anticoagulants: Strengths

- Oral administration
 - No antithrombotic laboratory monitoring
 - Few drug interactions
 - Rapid onset
 - Won't cause HIT
 - Potential major impact on clinical practice: greater proportion of patients get prophylaxis
- Greater patient convenience

New Oral Anticoagulants: Limitations

- Limited indications
- Uncertain patient restrictions – renal, age, body mass index, epidural
- No specific reversibility agents
- New, short track record
- Reimbursement and cost uncertainty

Summary

- VTE is frequent and associated with significant morbidity and mortality
- Guidelines exist to drive evidence based practice but adherence to guidelines is poor
- Nurses and pharmacists are key players in ensuring safe and efficacious use of anticoagulants

Questions and Answers

Address for CE Forms:

Standing Stone Inc.

49 Richmondville Avenue

Westport, CT 06880

ATTN: Barbara Chopin



STANDING STONE

DEVELOPERS OF DISEASE MANAGEMENT SOLUTIONS

Upcoming webinars

September – Establishing a Patient as a
Self-Tester

October -- Point of Care Vs Lab Testing