Venous Thromboembolism Update: 2016

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Disclosures

Sanofi Poland - Visiting Professor
Janssen R&D - Steering Committee
Pfizer - Bleeding Advisory Board
BMS - Advisory Board
CHEST Enterprises - Lecturer

Venous thromboembolism (VTE) is a leading cause of death worldwide. In the western world, someone develops a VTE every 16 seconds.

VTE Incidence

Incidence:[1]

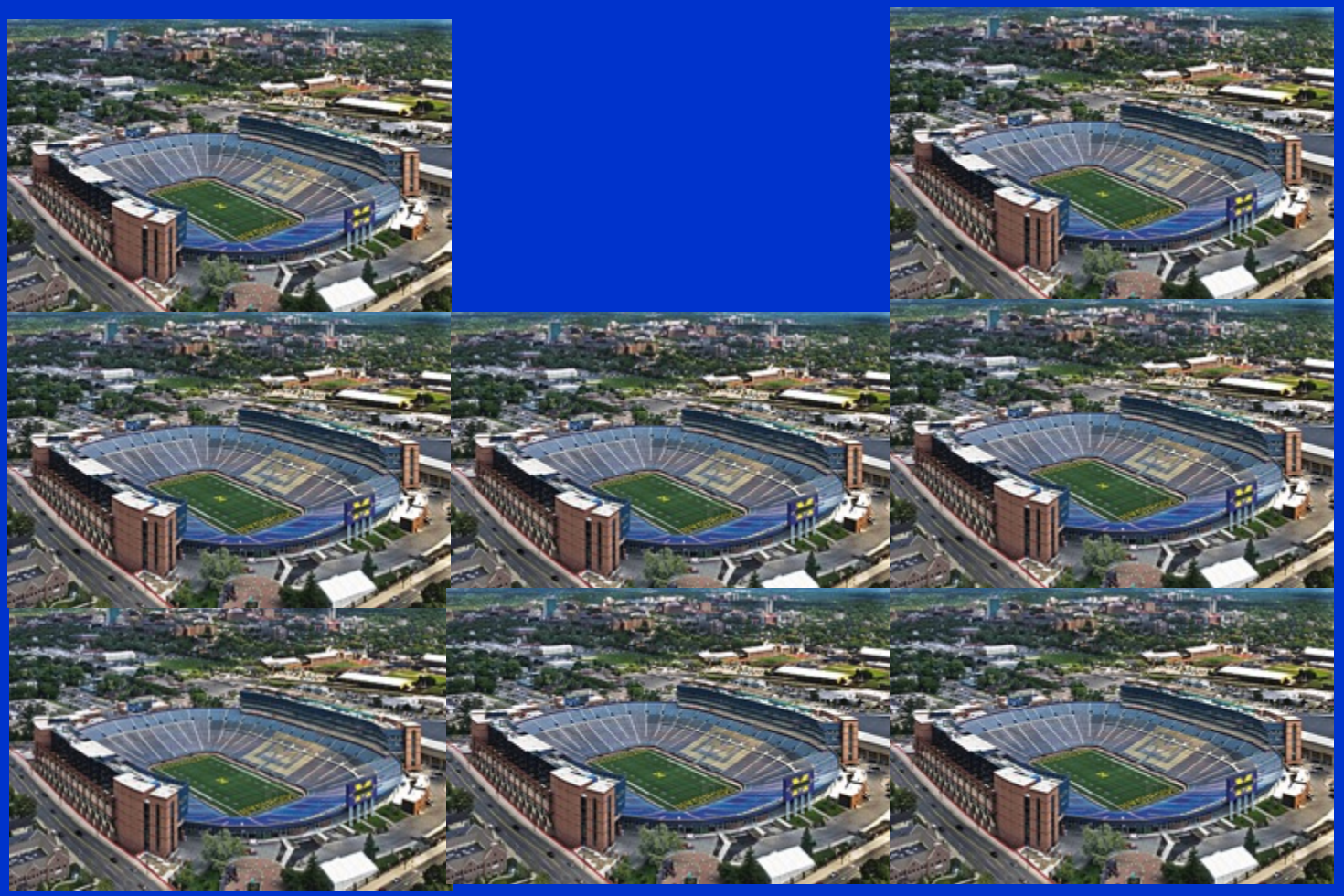
- 900,000 PEs and DVTs in the U.S. in 2002
- Estimated 296,000 PE deaths
  - 7% treated unsuccessfully, 34% sudden and fatal and 59% undetected

Annual number at risk for VTE: U.S. hospitals:[2]

- 7.7 million medical service inpatients
- 4.3 million surgical service inpatients
- Based upon ACCP guidelines for VTE prophylaxis
- 2/3 of VTE cases and deaths are hospital-acquired[1]

1. Heit J, et al. *Blood*. 2005;106:Abstract 910.
2. Anderson FA Jr, et al. *Am J Hematol*. 2007;82:777-782.

Venous Thromboembolism estimated to occur in 900,000 U.S. patients/year



University Of Michigan stadium
113,000 Capacity

Fatal Pulmonary Emboli estimated to occur in 296,000 patients/year

University Of Michigan stadium
113,000 Capacity

The Many Faces of Venous Thromboembolism

- Fatal pulmonary emboli.
  - 1-5% incidence in patients with >4 risk factors
  - 16.7% mortality at three months
  - 34% of those with Pulmonary emboli present as sudden death

- Chronic pulmonary hypertension
  - 4% of patients suffering PE

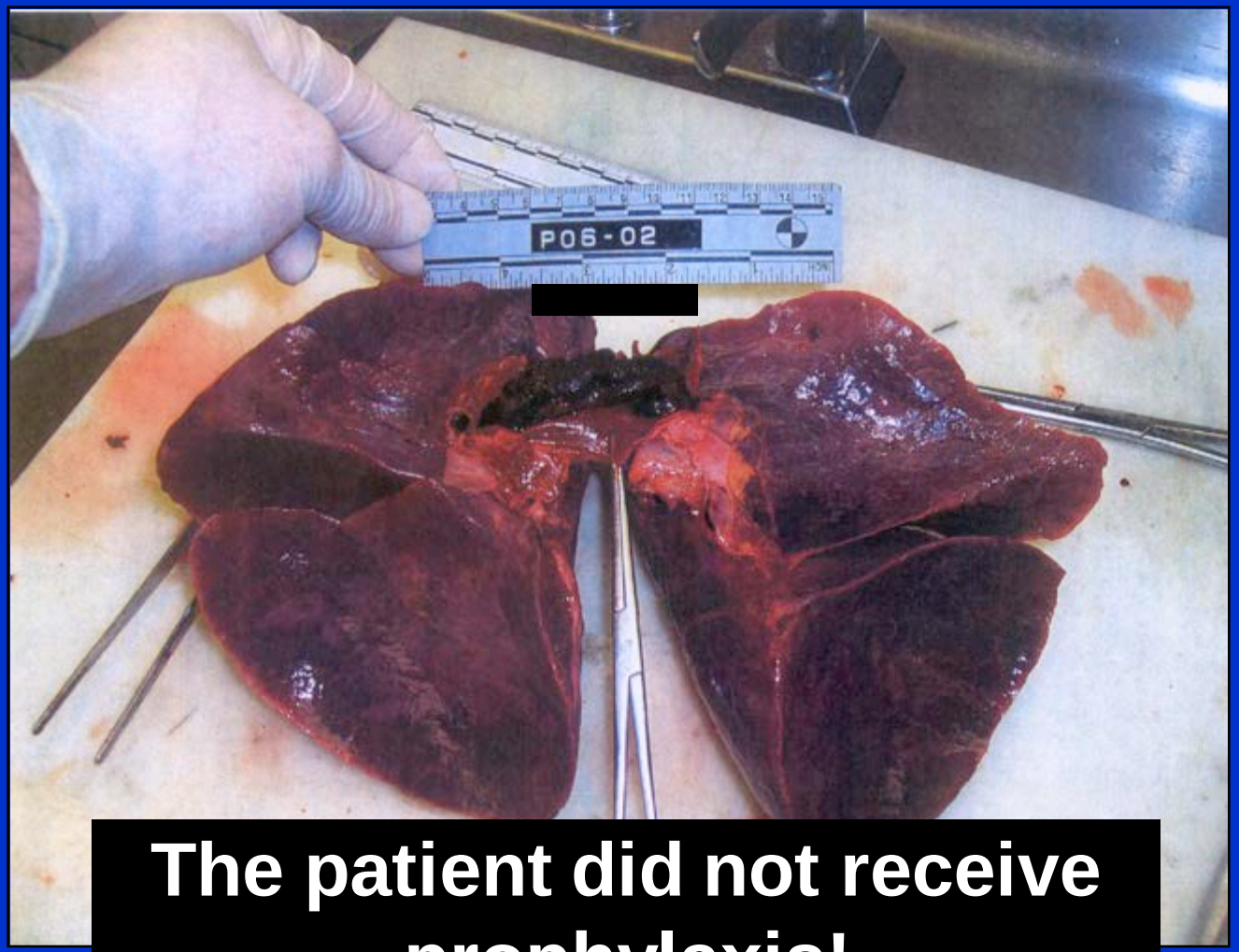
- Clinical venous thromboembolism.
  - Morbidity, drugs, tests, hose, changes in life style
  - Phlegmasia Cerula & alba Dolens
  - Venous Gangrene with limb loss

The Many Faces of Venous Thromboembolism

- Silent venous thromboembolism.
  - Risk of subsequent event double that of control population
- Embolic stroke (20-30% PFO rate).
  - 50% disabled; 20% die; 30% recover
- **The Post Thrombotic Syndrome and Venous Insufficiency-induced Lymphedema**
  - 25-40% incidence following DVT and 7% severe
  - May not be evident for 2-5 -10 YEARS.

Pulmonary Embolism

- The patient presented to ER with non-productive cough, mild wheezing, dyspnea and moderate back pain for five days
- The patient developed a massive PE and died three days after admission to intensive care unit



The patient did not receive prophylaxis!

Photo courtesy of Victor F. Tapson, MD: Duke University Hospital

Venous Gangrene

Patient developed acute DVT with major venous obstruction limiting arterial inflow

Thrombosis extended above the inguinal ligament obstructing the venous circulation of the leg producing venous gangrene

Thrombus Lodged in a Patent Foramen Ovale

Clot in a PFO as seen in surgery

Paradoxical embolism
Patent foramen ovale

Picture taken from Color Atlas of the CV System, Thomas et al.

Post-Thrombotic Syndrome

- A common event
- Caused by both symptomatic and asymptomatic deep venous thrombosis (DVT)
- Characterized by leg aching, pain, swelling in the early stages
- Late manifestations include skin changes, a variety of skin rashes and, sometimes, eczema
- Brawny edema, bronze discoloration, varicose and spider veins can be seen
- Venous ulceration is the end result, along with venous insufficiency-induced lymphedema

Venous Insufficiency-Induced Lymphedema

Post Thrombotic Syndrome

Thirty-eight year-old male suffered a leg fracture and developed a major DVT while in a cast. This is his leg 10 years later. The ulcer first appeared 2 years previously and failed to respond to treatment due in part to the poor compliance of the patient once the ulcer appeared.

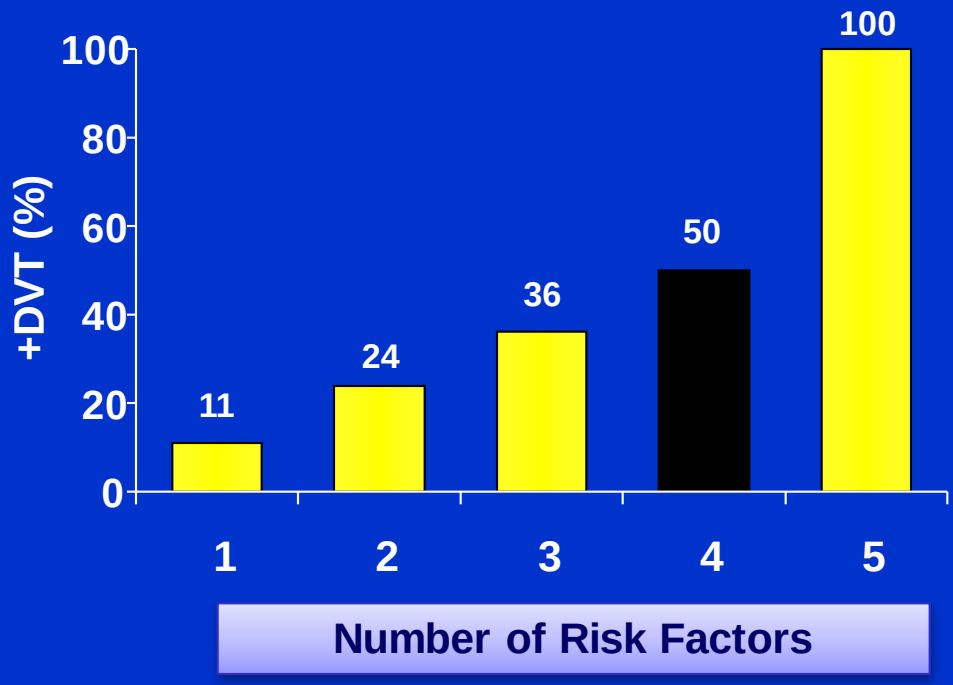
Risk Assessment as a Guide to Thrombosis Prophylaxis

VTE Risk Factors

1231 Patients Treated for VTE

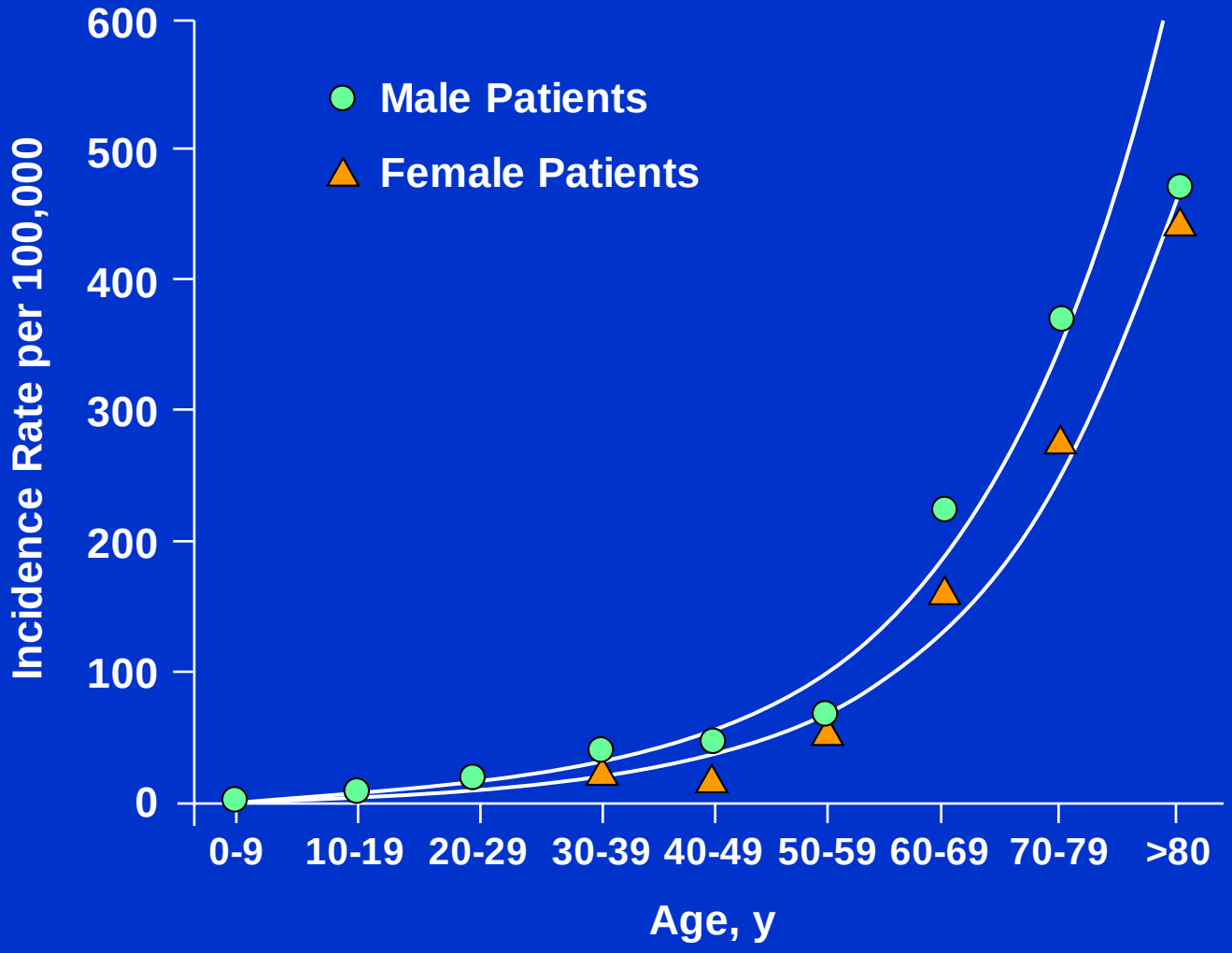
Risk Factors	Patients %
Age > 40 yrs	88.5
Obesity	37.8
History of VTE	26.0
Cancer	22.3
Immobility	12.0
Major surgery	11.2
CHF	8.2
Varicose veins	5.8
Stroke	1.8
1 or more risks	96.3
2 or more risks	76.0
3 or more risks	39.0

Evidence of VTE, %



Anderson FA, et al. *Circulation.* 2003;107(Suppl 1):I9-I16.

Incidence of VTE Increases With Age



Reprinted with permission from Anderson FA Jr, et al. *Arch Intern Med*. 1991;151:933-938.

Risk Factors Associated With Venous Thromboembolism (VTE): Basic Assumptions

1. The more risk factors present, the greater the likelihood of developing a VTE
2. Strength of each risk factor – for example

Abdominal operations

- Benign disease (20% VTE incidence)
  - » [Caprini score = 2]
- Malignant disease (36% VTE incidence)
  - » [Caprini score= 4]

Caprini Thrombosis Risk Scoring

- Assign a point value to each risk factor according to the relative risk of VTE, based on the literature and validation studies
  - Total the points to obtain a score
  - Compare the scores to 30- and 60-day incidence of clinically relevant VTE
  - Balance the risks and benefits of anticoagulation according to the relative probability of bleeding vs. thrombosis
  - Account for ALL risk factors that could affect the outcome of a procedure or illness

Caprini JA, Arcelus JI, Hasty JH, et al. Clinical assessment of venous thromboembolic risk in surgical patients. Seminars in Thrombosis & Hemostasis 1991;17 Suppl 3:304-12.

The patient should fill out the intake risk assessment form

The person performing the history and physical should complete the Caprini Risk Assessment

The Risk Assessment should be recalculated if additional events occur during hospitalization

The Assessment should be updated at hospital discharge

VTE Risk Factor Assessment

Each Risk Factor Represents 1 Point

- ❑ Age 40-59 years
- ❑ Minor surgery planned
- ❑ History of prior major surgery
- ❑ Varicose veins
- ❑ History of inflammatory bowel disease
- ❑ Swollen legs (current)
- ❑ Obesity (BMI >30)
- ❑ Acute myocardial infarction (< I month)
- ❑ 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
- ❑ Leg plaster cast or brace
- ❑ Central venous access
- ❑ Other risk factor _____
- ❑ Blood transfusion (<1 month)

Each Risk Factor Represents 2 Points

- ❑ Age 60-74 years
- ❑ Major surgery (> 60 minutes)*
- ❑ Arthroscopic surgery (> 60 minutes)*
- ❑ Laparoscopic surgery (> 60 minutes)*
- ❑ Previous malignancy
- ❑ Morbid obesity (BMI >40)

Each Risk Factor Represents 3 Points

- ❑ Age 75 years or more
- ❑ Major surgery lasting 2-3 hours*
- ❑ BMI > 50 (venous stasis syndrome)
- ❑ History of SVT, DVT/PE
- ❑ **Family history of DVT/PE**
- ❑ Present cancer or chemotherapy
- ❑ Positive Factor V Leiden
- ❑ Positive Prothrombin 20210A
- ❑ Elevated serum homocysteine
- ❑ Positive Lupus anticoagulant
- ❑ Elevated anticardiolipin antibodies
- ❑ Heparin-induced thrombocytopenia (HIT)
- ❑ Other thrombophilia

  Type_____

*Select only one from the surgery category

V. Bahl, V, etal: Ann Surg 2010;251:344-350

VTE Risk Factor Assessment

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- Heparin-induced thrombocytopenia (HIT)
- Other thrombophilia
  Type_____

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

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)
- Major surgery lasting over 3 hours*

Total Risk Factor Score ☐

V. Bahl, V, etal: Ann Surg 2010;251:344-350

Prophylaxis Safety Considerations: Check box if answer is 'YES'

Anticoagulants: Factors Associated with Increased Bleeding
❑ Is patient experiencing any active bleeding?
❑ Does patient have (or has had history of) heparin-induced thrombocytopenia?
❑ Is patient's platelet count <100,000/mm^3?
❑ Is patient taking oral anticoagulants, platelet inhibitors (e.g., NSAIDS, Clopidogrel, Salicylates)?
❑ Is patient's creatinine clearance abnormal? If yes, please indicate value _____
If any of the above boxes are checked, the patient may not be a candidate for anticoagulant therapy and you should consider alternative prophylactic measures such as IPC or FP.
Intermittent Pneumatic Compression (IPC)
❑ Does patient have severe peripheral arterial disease?
❑ Does patient have congestive heart failure?
❑ Does patient have an acute superficial/deep vein thrombosis?
If any of the above boxes are checked, then patient may not be a candidate for intermittent compression therapy and you should consider alternative prophylactic measures. (IVC filter?)

Based on: V. Bahl, H. Hu, P. K. Henke, T. W. Wakefield, D. A. Campbell J, Caprini JA. Ann Surg 2009:DOI: 10.1097/SLA.0b013e3181b7fca6; Zakai NA, Wright J, Cushman M. J Thromb Haem 2004;2:2156-61; Seruya M, Venturi ML, Iorio ML. J Plastic & Reconstructive Surgery 2008;122:1701-8; Hatef D, Kenkel J, Nguyen M. Plastic & Reconstructive Surgery 2008;122:269-79; McLafferty RB, Lohr JM, Caprini JA, et al. J Vasc Surg 2007;45:142-8; McLafferty RB, Passman MA, Caprini JA, et al. J Vasc Surg 2008;48: 394-9; Nicolaides AN et al: INT Angiol 2006; 25:101-161.; Arcelus JI, Caprini JA, Traverso CI. Semin Thromb Hemost 1991;17(4):322-5.; Borow M, Goldson HJ. Am J Surg 1981;141(2):245-51.; Caprini JA, Arcelus I, Traverso CI, et al. Semin Thromb Hemost 1991;17(suppl 3):304-12.; Caprini JA, Arcelus JI et al: Scope 2001; 8: 228-240.; Caprini JA, Arcelus JI, Reyna JJ. *Seminars in Hematology*, April 2001;38(2)Suppl 5:12-19.; Caprini, JA. Dis Mon 2005;51:70-78.; Oger E: Thromb Haem, 2000; 657-660.; Turpie AG, Bauer KA, Eriksson BI, et al. Arch Intern Med 2002; 162(16):1833-40.; Ringley et al: American Surgeon 2002; 68(3): 286-9.; Morris et al. Arch Surg 2002. 137(11):1269-73.; Sugarman HJ et al, Ann Surg: 2001:234 (1) 41-46, , Nguyen, NT, Hinojosa, MW, Fayad, C, et al. Ann Surg 2007;246(6):1021-1027

Revised November 5, 2009

V. Bahl, H. Hu, P. K. Henke, T. W. Wakefield, D. A. Campbell J, Caprini JA. Annals of Surgery In press 2009.

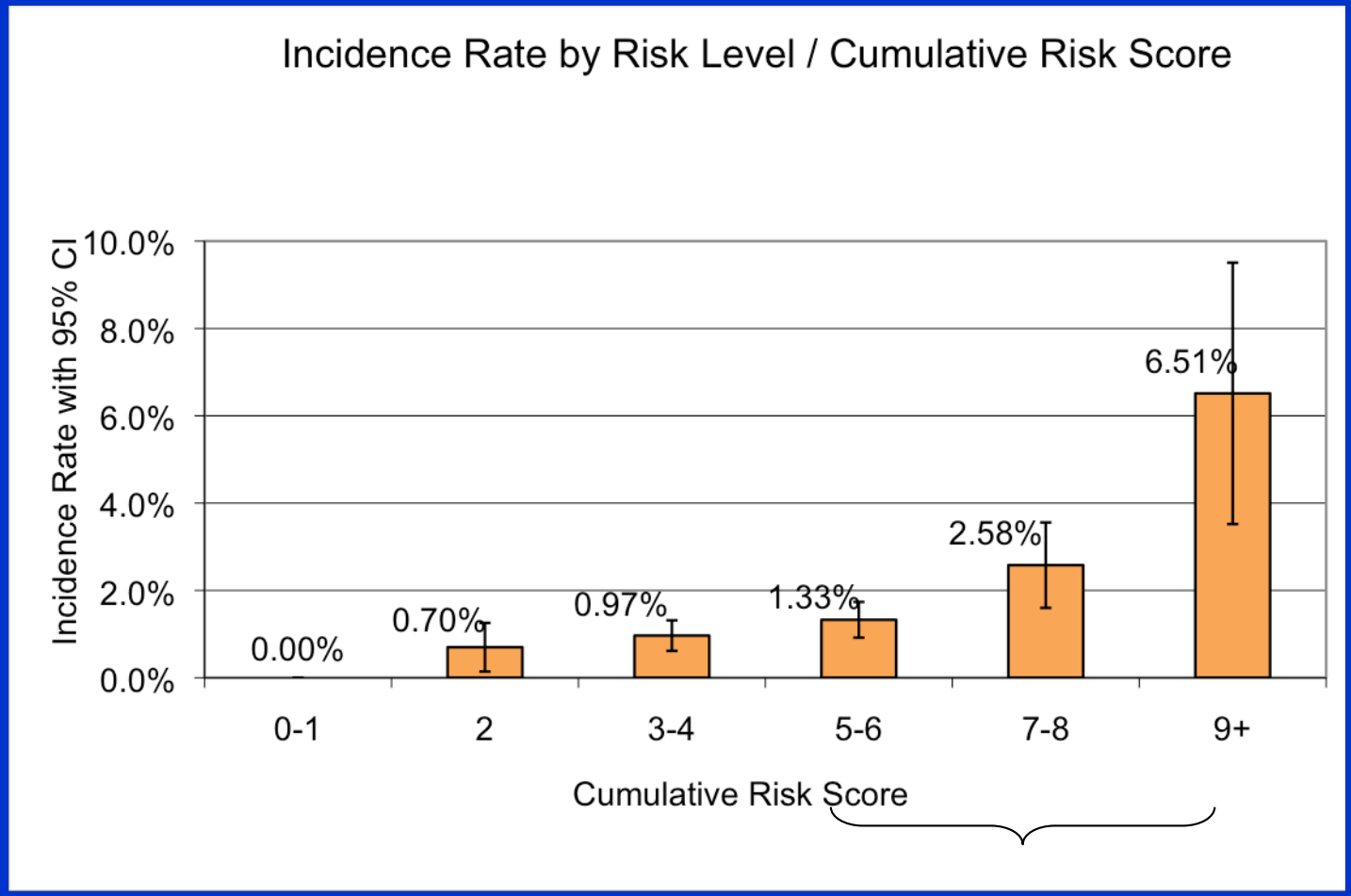
CHEST Guidelines 2012

Risk	Caprini Score	*VTE incidence	Prophylaxis
Very low	0	0.5%	Early ambulation
Low	1-2	1.5%	IPC
Moderate	3-4	3.0%	LMWH, UFH,IPC
High	5+	6.0%	LMWH, UFH + IPC or GS

Estimated baseline risk in the absence of pharmacologic or mechanical prophylaxis

Gould, MK et al; CHEST 2012;141(2) (Suppl):e327S-e227S

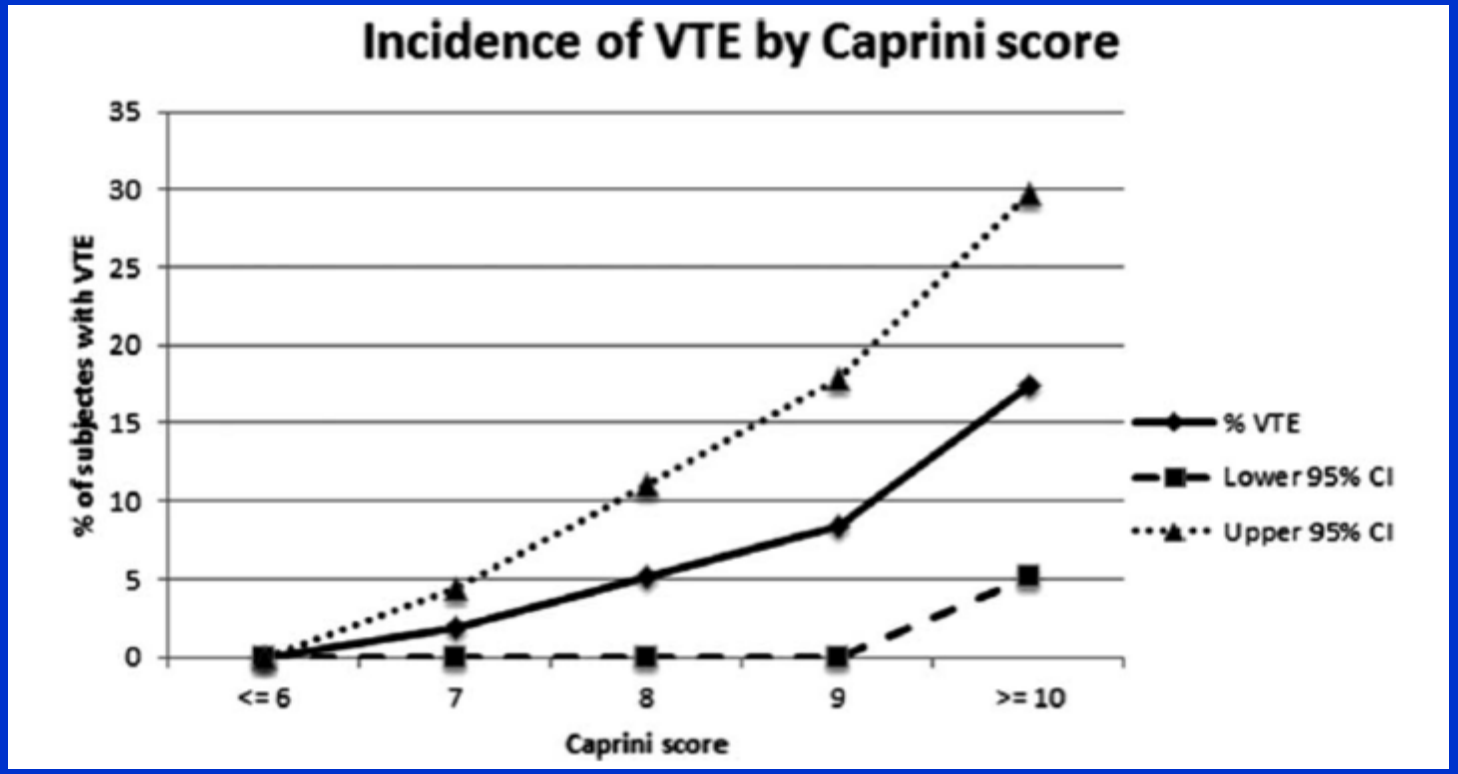
A Validation Study of a Retrospective Venous Thromboembolism Risk Scoring Method



Clinically evident-imaging proven VTE rates at 30 days

**V. Bahl, H. Hu, P. K. Henke, T. W. Wakefield, D. A. Campbell, J, Caprini JA. Ann Surg: 2010; 251: 344-5*

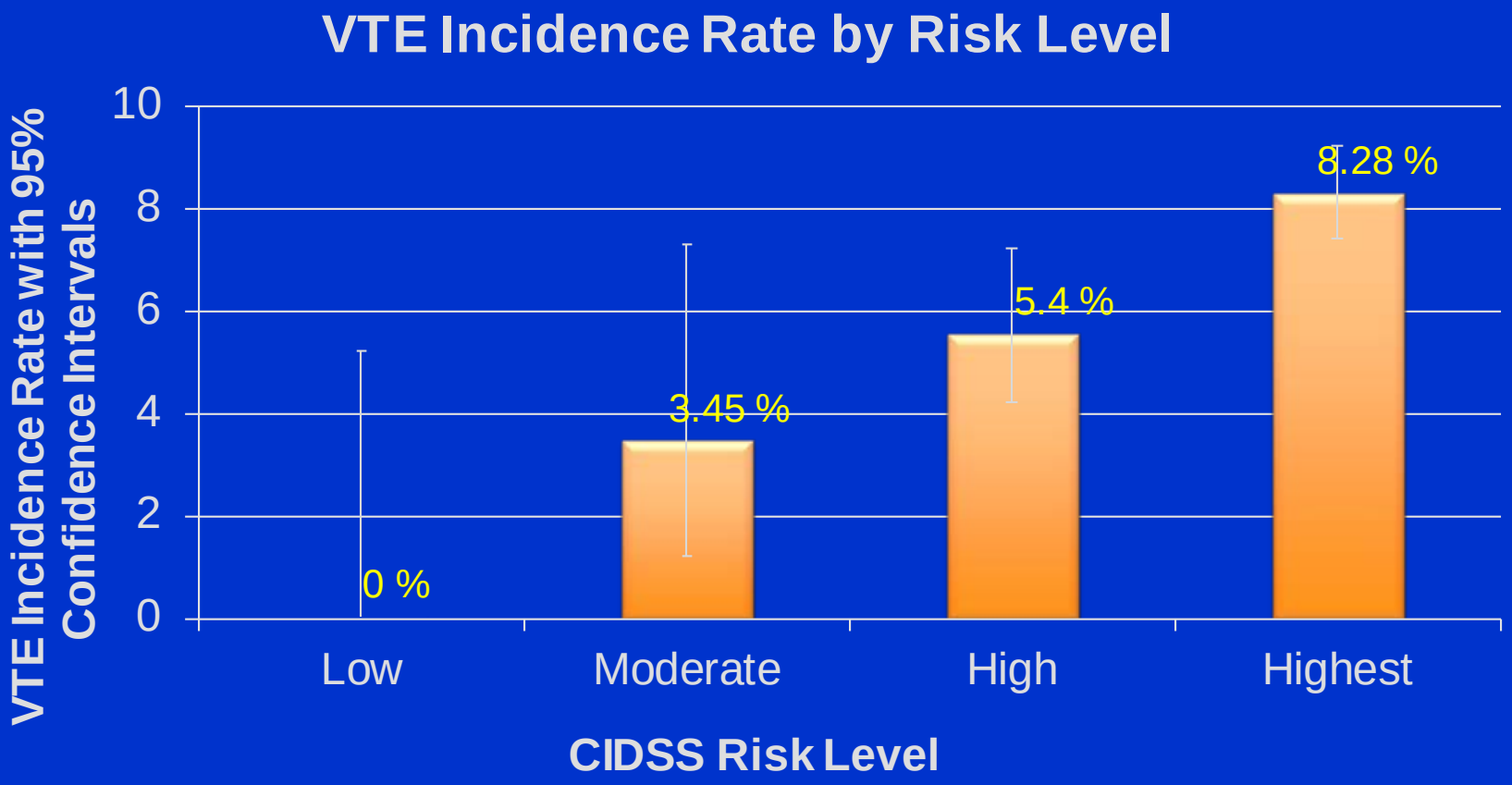
Venous Thromboembolism in Otolaryngology Surgical Inpatients Receiving Chemoprophylaxis



"The incidence of VTE increases with Caprini risk assessment model score, and a score of >8 predicts a high risk (>13%) of VTE in postoperative otolaryngology inpatients, despite chemoprophylaxis"

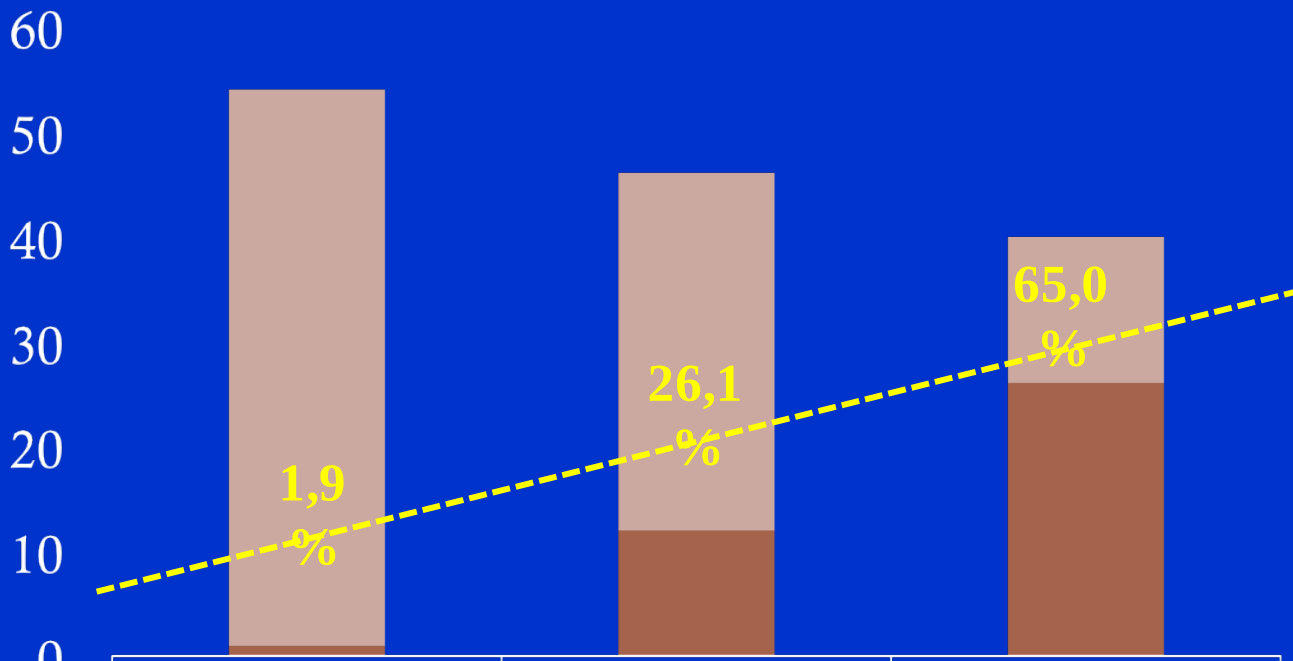
Yarlagadda,, BB: Head Neck 36: 1087–1093, 2014

Venous Thromboembolism Risk Assessment Scoring in the Critically Ill: A Validation Study



4,856 patients U. of Michigan ICU (submitted for publication, 2012)

The Correlation between Caprini Score and DVT Rate



P<0,0001 for trend, chi-squared test

	5-8	9-11	12-15
non-DVT	53	34	14
DVT	1	12	26

All patients had from five to 15 Caprini scores and were divided in three tertiles 5-8 (n=54), 9-11 (n=46) and 12-15 (n=40)

Validation of a Venous Thromboembolism Risk Assessment Model in Gynecologic Oncology

This study included 1,123 gynecologic oncology patients

- The overall incidence of VTE was 3.3%, including 17 DVTs and 20 pulmonary emboli.
- 92% of patients had a score of five or more.

The Caprini RAM accurately predicted all 37 VTEs, all of which scored in the "Highest Risk" category

The percentage of patients that received double prophylaxis increased with time from 12% in 2004 to 63% in 2010. Importantly, 25 of the 37 VTEs (68%) did not receive double prophylaxis.

Of importance, all patients with VTE were within the highest group, and there was a statistically significant difference in the raw Caprini score (8.82 vs. 6.39; $p < 0.001$).

W. Stroud et al. / Gynecologic Oncology 134 (2014) 160–163

The best U.S. application so far uses the Caprini Score to reduce the incidence of postoperative venous thromboembolism

NEW ENGLAND SURGICAL SOCIETY ARTICLES

Reducing Postoperative Venous Thromboembolism Complications with a Standardized Risk-Stratified Prophylaxis Protocol and Mobilization Program

Michael R Cassidy, MD, Pamela Rosenkranz, RN, BSN, MEd, David McAneny, MD, FACS

While the Caprini scoring system has been well validated in terms of its predictive value for VTE, to our knowledge, this is the first study to demonstrate a reduction of VTE events based upon its standardized and required use, in conjunction with a formal mobilization program.

Cassidy MR et al. J Am Coll Surg 2014;218:1095-1104

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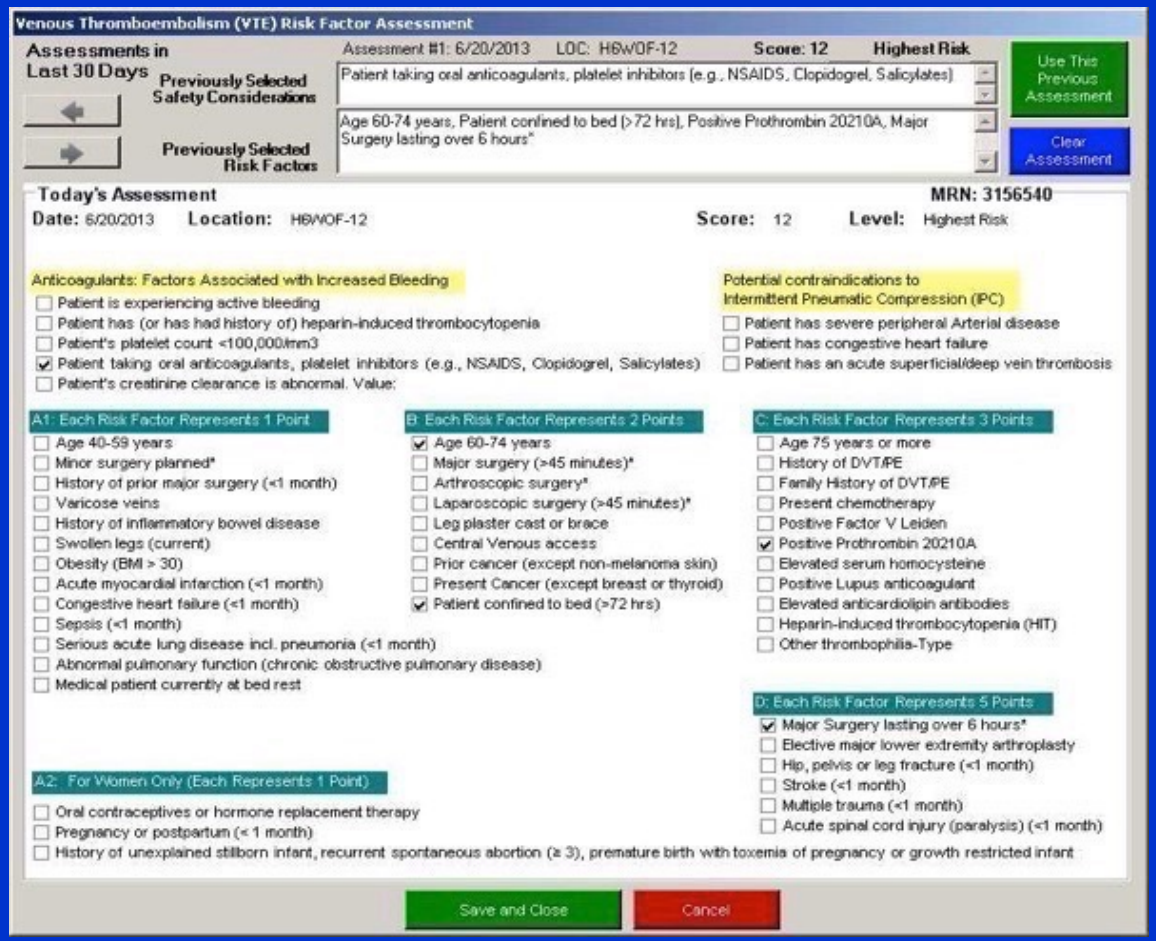
Mandatory Electronic Risk Assessment System and Prophylaxis

- Check box format
- Score automatically calculated
- Mandatory for every patient
- Score must be calculated before completing preop and postop orders
- e-Reminder at discharge



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Caprini Score	Risk Category	Recommended Prophylaxis	Recommended Duration of Chemoprophylaxis
0	Lowest	Early frequent ambulation only, OR *At discretion of surgery team*: Compression boots OR Low dose heparin OR Low molecular weight heparin	During hospitalization
1-2	Low	Compression boots OR Low dose heparin OR Low molecular weight heparin (*Choose one item*)	During hospitalization
3-4	Moderate	Compression boots AND Low dose heparin OR Low molecular weight heparin (*Choose one medication*)	During hospitalization
5-8	High	Compression boots AND Low dose heparin OR Low molecular weight heparin (*Choose one medication*)	7 – 10 days total
≥9	Highest	Compression boots AND Low dose heparin OR Low molecular weight heparin (*Choose one medication*)	30 days total

VTE Prophylaxis Compliance

Risk Category	Compliance with Recommended Prophylaxis	Contraindication	Surgeon Discretion
Low - Moderate	**100%**	0%	0%
High	**89%**	1%	10%
Highest	**77%**	23%	0%

No patient received inappropriate or inadequate prophylaxis without electronic documentation. We cannot confirm compliance at home.

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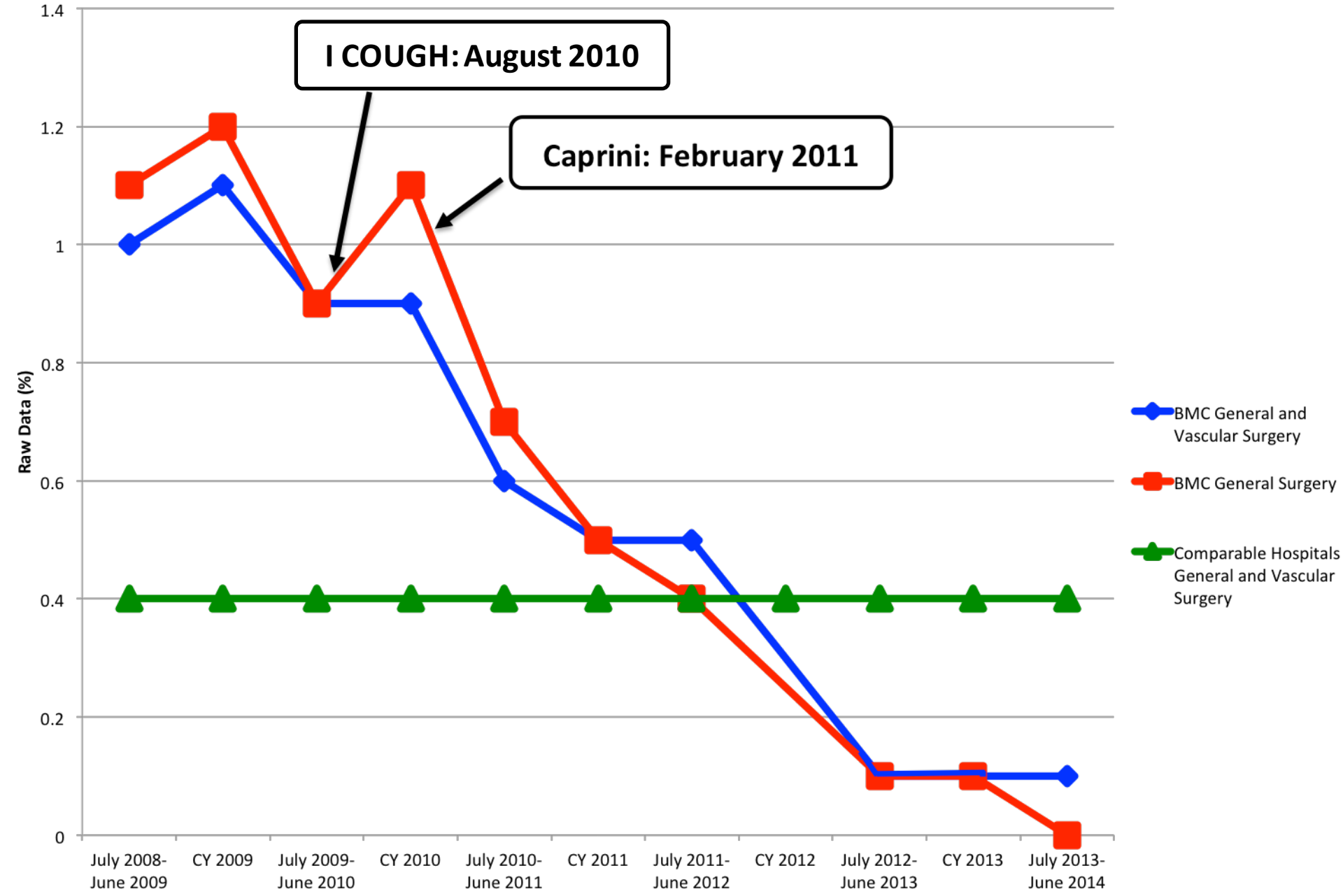
BMC General Surgery Pulmonary Embolism



The 2005 Caprini Score Predicts Both Baseline VTE Risk and Effectiveness of Chemoprophylaxis: a Meta-Analysis of 13,605 Surgical Patients

1. The 2005 Caprini score predicts post-operative VTE events in surgical patients who do not receive chemoprophylaxis
2. The 2005 Caprini score identifies patients who will and will not benefit from chemoprophylaxis in the peri-operative period
3. There is no association between 2005 Caprini score and risk for peri-operative bleeding when chemoprophylaxis is provided

Christopher Pannucci, MD, Lukasz Swistun, MD, John MacDOnald, MA, Ben Brooke, MD, PhD, Peter Henke, MD. Presented at the 28th annual meeting of the American Venous Forum, Orlando, FL; February 26, 2015

Process Measure
vs.
Outcome Measure

Current VTE Metrics

- **Process Measure**:
  - SCIP-VTE-2: VTE prophylaxis administration
  - ***Problem****: Only measures the 24 hours before and after surgery* ***FLAWED MEASURE***
- **Outcome Measure:**
  - PSI 12: Risk-adjusted VTE rate after surgery
  - ***Problem****: Surveillance bias significantly affects VTE outcome measurement* and thus comparison between hospitals is impossible
  - *Venous duplex scanning documents the VTE incidence postoperatively*
  - *The incidence of VTE associated with the process measure is revealed*
  - *If it is high, one can assume the process measure is flawed*

Association between Surgical Care Improvement Program VTE Measures And Postoperative Events

- Study evaluated SCIP-VTE adherence for 30,531 operations from 2006 to 2009 linked with VA Surgical Quality Improvement Program data
- It was noted that 89.9% of the patients adhered to the SCIP-VTE measure and ***1.4%*** suffered a VTE event
- The incidence of VTE events in those not complying with the SCIP-VTE mandate was ***1.3%***
- The authors concluded that there was no association between SCIP-VTE adherence and the incidence of postoperative VTE

Altom LK, Deierhoi RJ, Grams J et al; Am J Surg: (2012) 204, 591-597

Process Measures vs. Outcome Measures

Process measures should remain central in efforts to measure and improve care

(THE CURRENT PROCESS MEASURE IS FLAWED)

- It is known that protecting the patient for the period of time that they are "at risk" lowers the VTE rate
- Making sure that patients receive appropriate anticoagulation ***during their entire hospitalization*** is a CRITICAL factor in reducing the VTE incidence ***(IMPORTANT ISQIC INITIATIVE)***

Bilimoria, JAMA 2013, 2015

Anticoagulants need to be given for the entire period of time that the patients are at risk for VTE

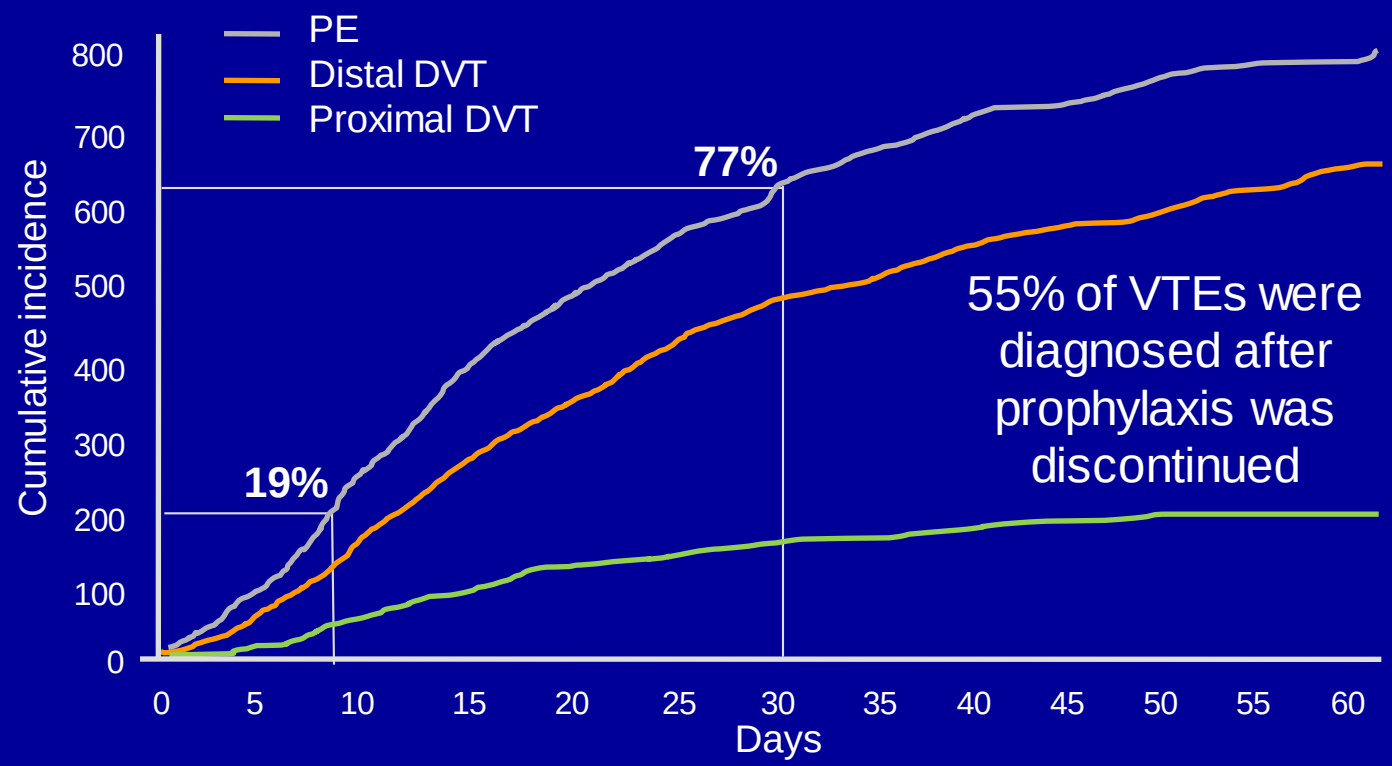
That should include the ENTIRE hospitalization at the very least

The SCIP Measure was envisioned as a first step and did not imply that one dose of anticoagulation was sufficient to prevent VTE during the entire hospitalization

THIS POINT WAS NEVER MADE CLEAR BY THE AUTHORITIES

Thrombosis Prophylaxis Following Hospital Discharge

Time Course and Clinical Presentation of Postoperative VTE in RIETE



	24 hours	48 hours	7 days	15 days	30 days	60 days
Clinically overt PE	22 (2.8%)	41 (5.2%)	149 (19%)	376 (48%)	608 (77%)	787
Distal DVT	2 (1.1%)	5 (2.78%)	34 (19%)	98 (54%)	145 (80%)	182
Proximal DVT	9 (1.4%)	21 (3.3%)	91 (14%)	248 (39%)	432 (68%)	633

Arcelus JI, et al. Thromb Haemost. 2008;99:546-51.

Validated Risk Assessment Studies: Very High-Risk Patients

Population	Caprini Score	VTE incidence
General & Vascular Surgery	>8	6.3%*
Plastic Surgery	>8	11.3%**
Otolaryngology	>8	18.3%*
ICU Population	>8	8.28%*

Clinically-Relevant Venous Thromboembolism Rate * 30 Days **60 Days

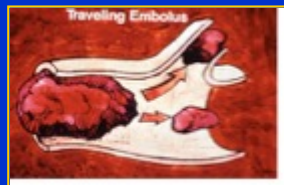
Extended Prophylaxis Suggested

V. Bahl, et al: Ann Surg: 2010; 251: 344-5
Pannucci,C. et al: J Am Coll Surg 2011;212:105–112
Shuman, AG et al. Otolaryngology -- Head and Neck Surgery 2012 146: 719
4,856 patients U. of Michigan ICU (submitted for publication, 2012)

Risk Assessment for Bleeding

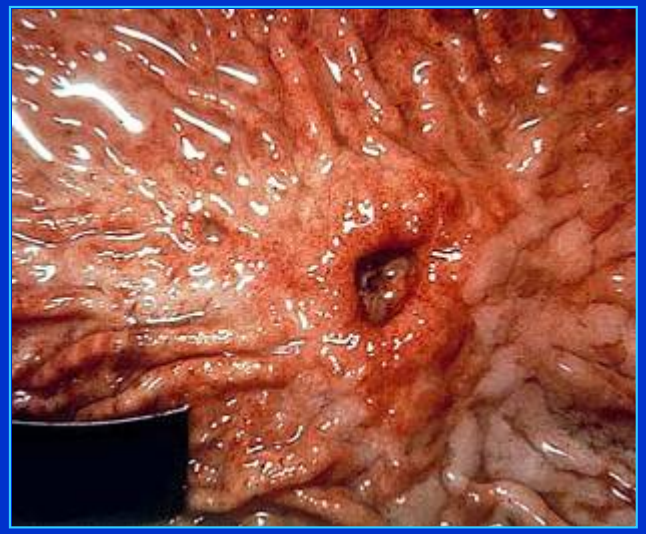
Hemostasis is a *balance* between multiple pro-coagulant and anti-coagulant components

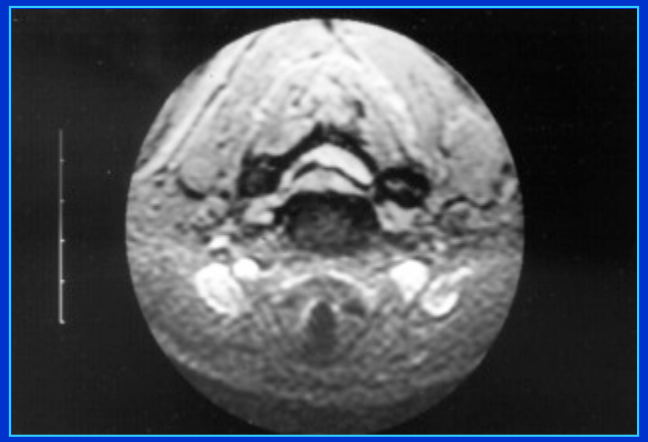
Thrombosis (Clotting)



Hemorrhage (Bleeding)

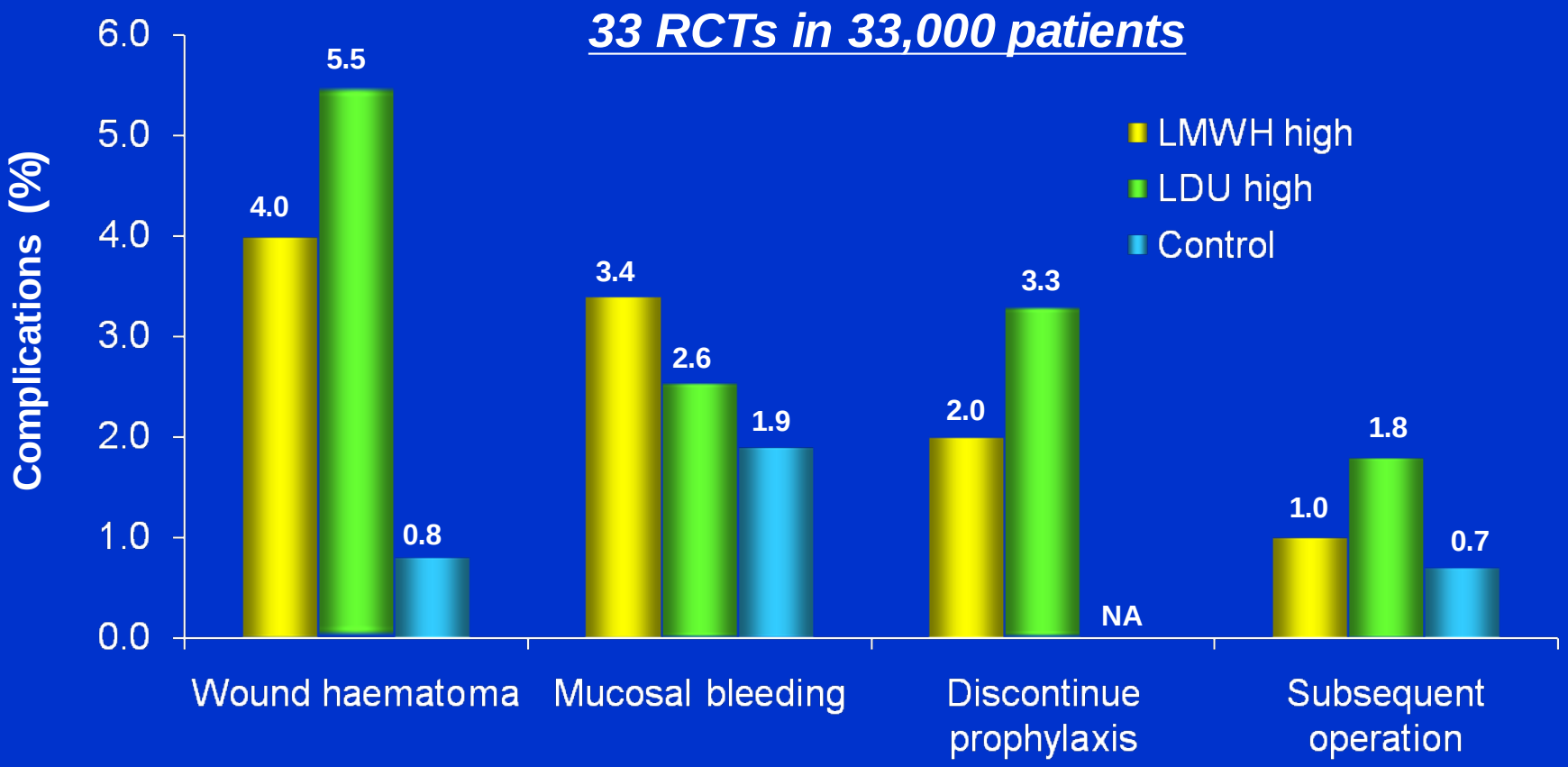
Bleeding Events





Rate of Bleeding Complications after Pharmacological DVT Prophylaxis

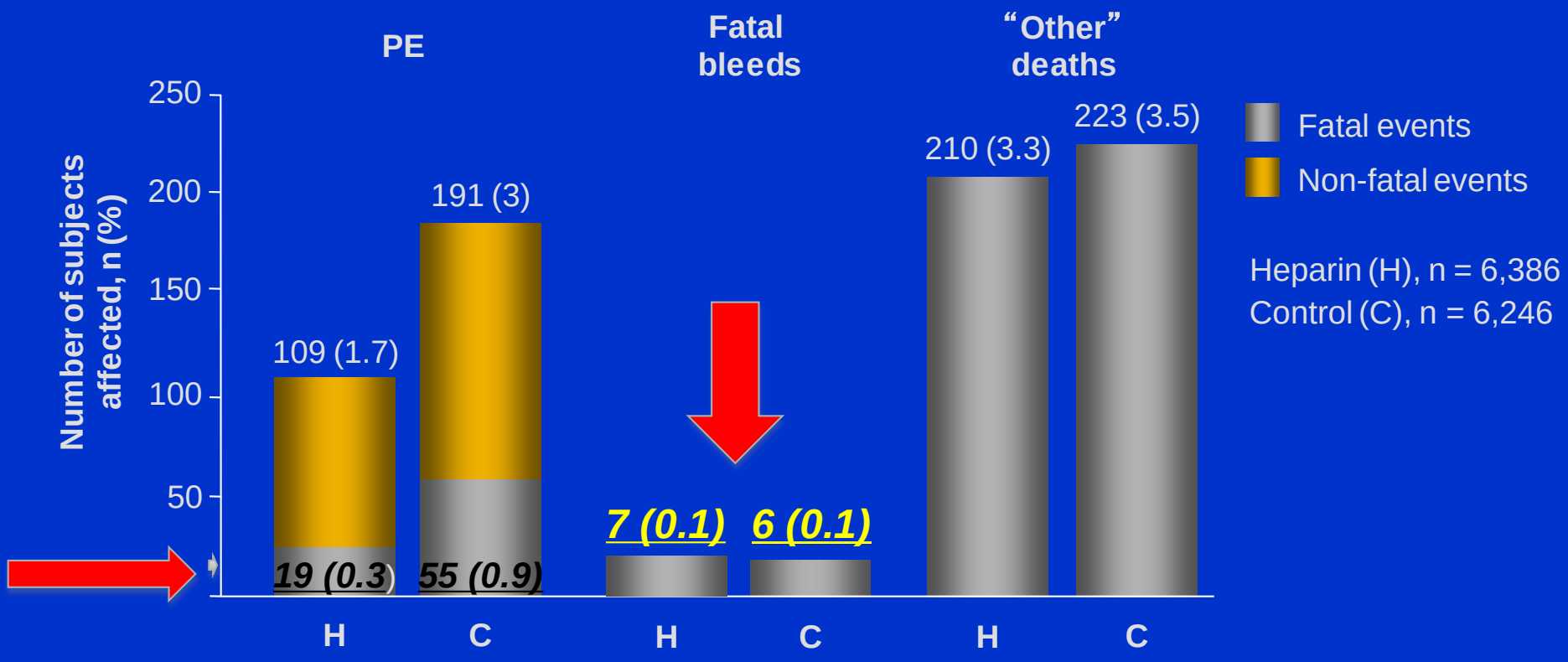
*Bleeding incidence not trivial



Leonardi MJ, et al. Arch Surg. 2006;141:790-9.

Death From PE but not Death From Bleeding

Evenly randomized trials of perioperative s.c. heparin in general, orthopaedic and urological surgery



Collins R, et al. N Engl J Med. 1988;318:1162-73.

Fatal Pulmonary Embolism in Surgical Patients

Randomized double-blind comparison of LMWH with UFH, involving 23,078 surgical patients

Outcome	LMWH (N = 11,542) N (%)	UFH (N = 11,536) N (%)	p
PE (at autopsy)	22 (0.191)	22 (0.191)	
Fatal	17 (0.147)	18 (0.156)	0.87
Non-fatal	5 (0.043)	4 (0.035)	1

Anticoagulant prophylaxis reduces the risk of death to 0.15%

No deaths from anticoagulant bleeding occurred in this large series

Haas S, et al. Thromb Haemost. 2005;94:814-9.

The New Oral Anticoagulants

To Do

- Greater physician education regarding the nuances of each compound
- To bridge or not to bridge; when?
- Appropriate testing for clinical scenarios as outlined by ISTH and suggested by the FDA using specific assays
- Proper use of antidotes under development; how to prevent rebound thrombosis is a **must!**
- How to maintain patient compliance; quarterly visits?
- Understand when ***not*** to prescribe one of these drugs

Conclusions

- There are many faces of VTE
- VTE is associated with 300,00 deaths yearly in the U.S.
- Postoperative anticoagulant prophylaxis saves lives from fatal PE while fatal bleeding events are rare
- The Boston program of Caprini Score-driven mandated prophylaxis is a method to reduce the VTE incidence at 30 days to an absolute minimum

Conclusions

- The new anticoagulants are a great step forward in the prophylaxis and treatment of VTE
- Widespread use of these amazing new drugs await:
  - Further clinical experience and results with the newly approved antidotes
  - Availability of appropriate tests to monitor these drugs in special situations
  - Establishing clinics for periodic monitoring of the patients, at least quarterly, to evaluate compliance and adjust care according to changing medical issues

Yellowstone Park

Questions