

The VTE Epidemic

Summary of Care Issues

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4:20-4:40

Disclosure

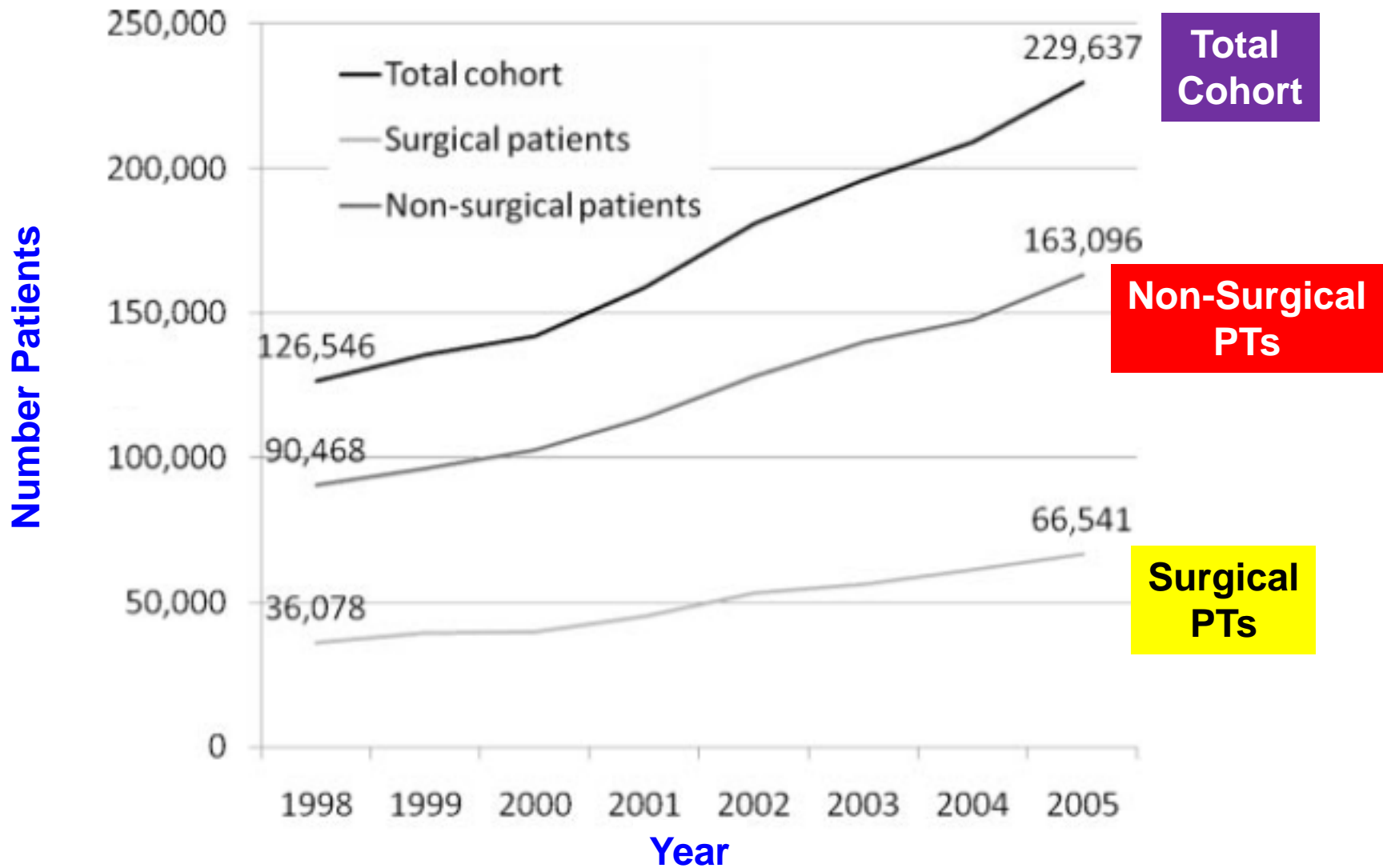
Financial Relationships

Geno J. Merli, MD, MACP, FHM, FSVM

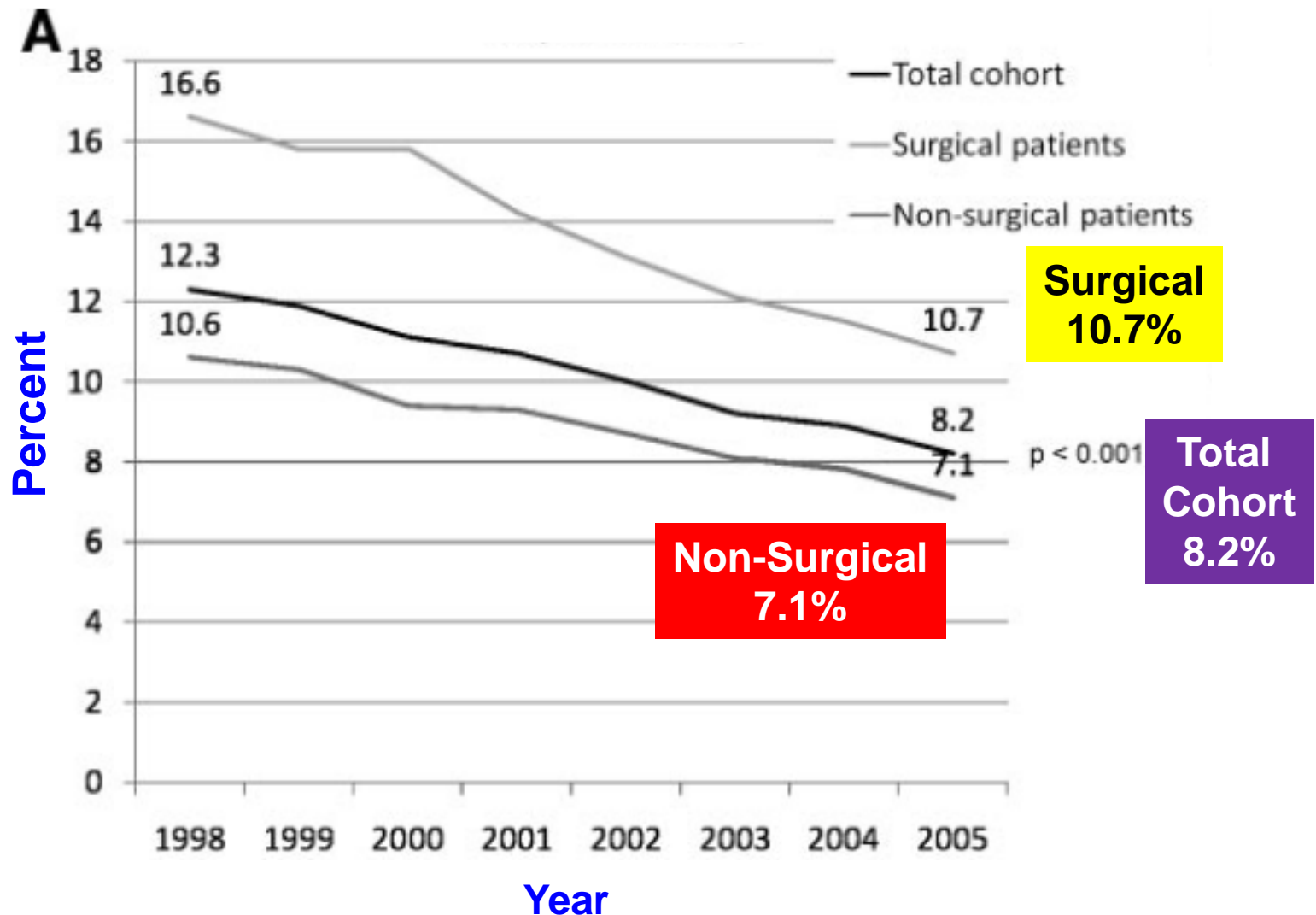
- **Janssen: Research MARINER Study (completed 2017)**
- **Bristol-Meyer Squibb: ADIOS Study (completed 2018)**
- **Portola: APEX Study (completed 2017)**
- **LoweRisk LLC, Co-Chief Development Officer**

Venous Thromboembolism

Treated for Pulmonary Embolism

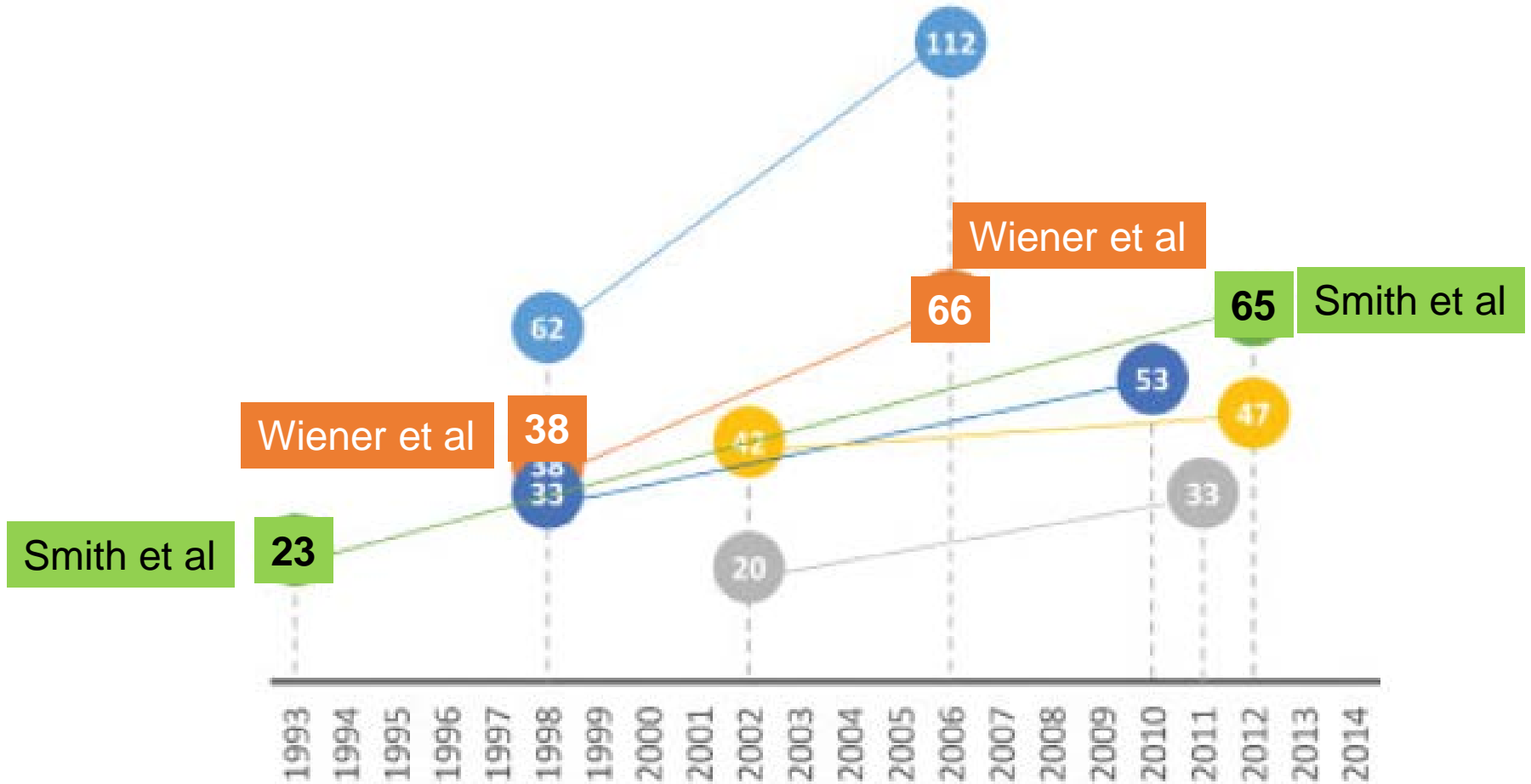


Pulmonary Embolism In-Hospital Mortality



Annual PE Incidence Rate

PE Diagnosis / 100,000 people



● Wiener et al. (US)

● Wiener et al. (US)

● de Miguel-Diez et al. (Spain)

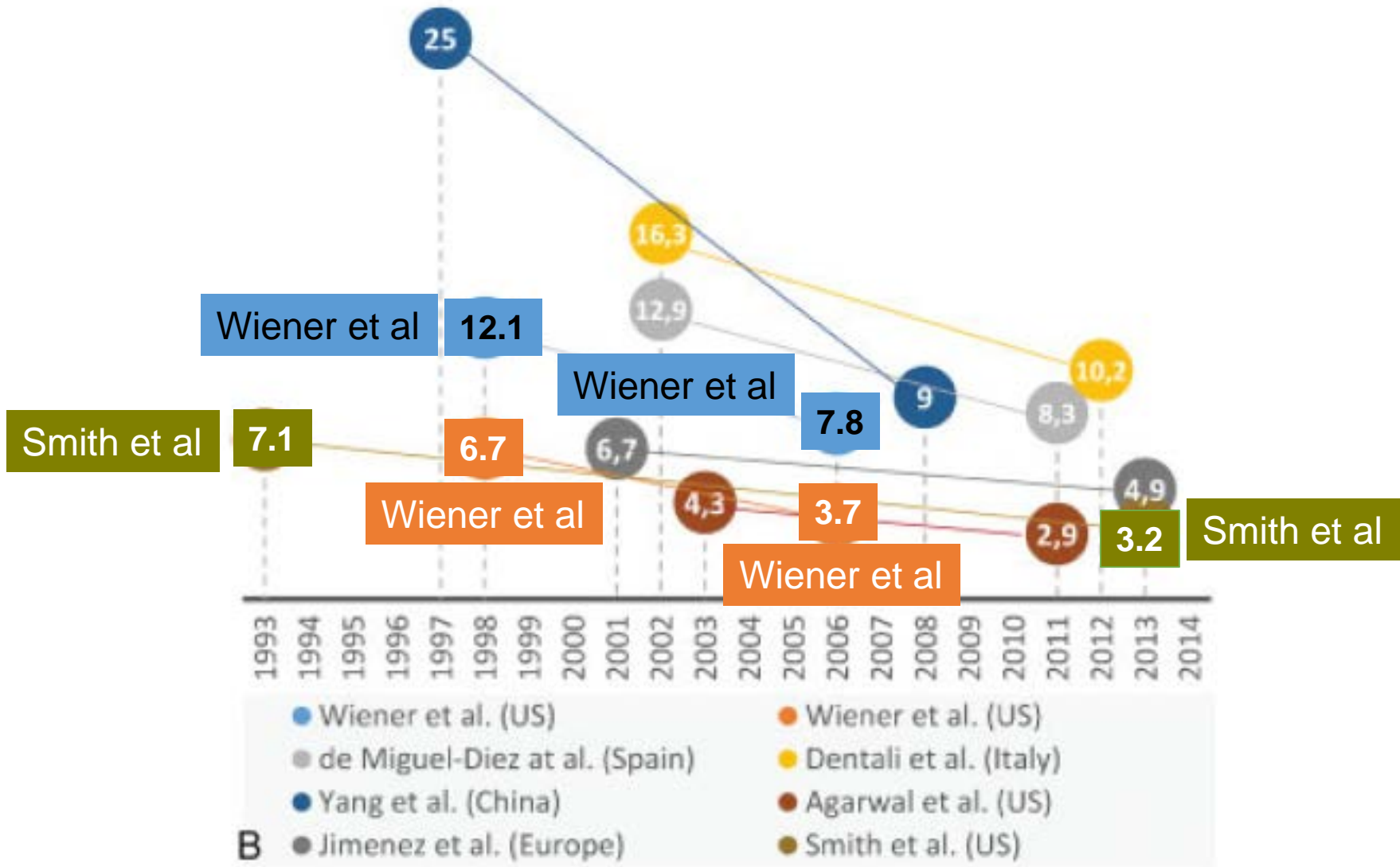
● Dentali et al. (Italy)

A ● Shiraev et al. (Australia)

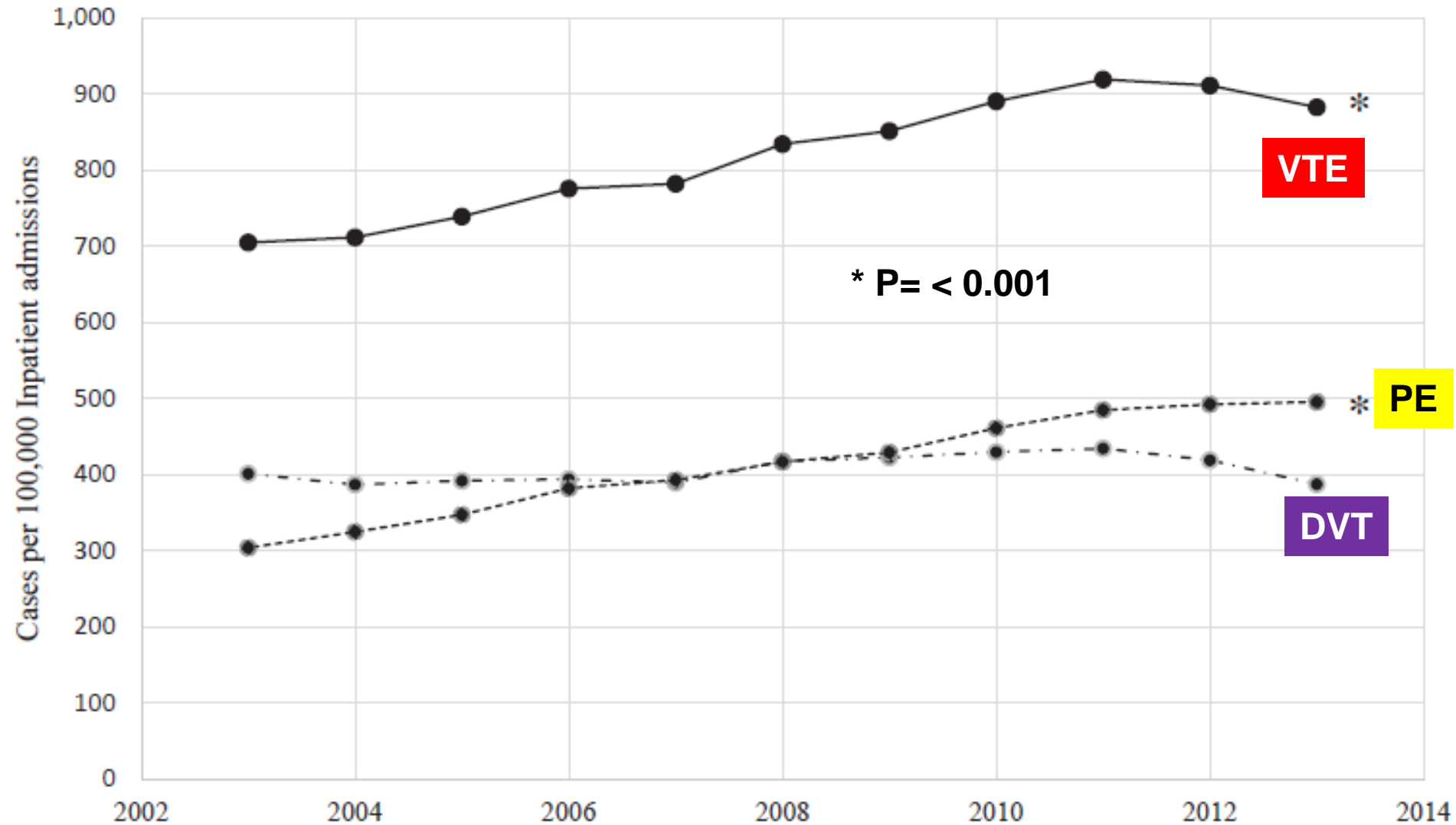
● Smith et al. (US)

PE: Case Fatality Rate

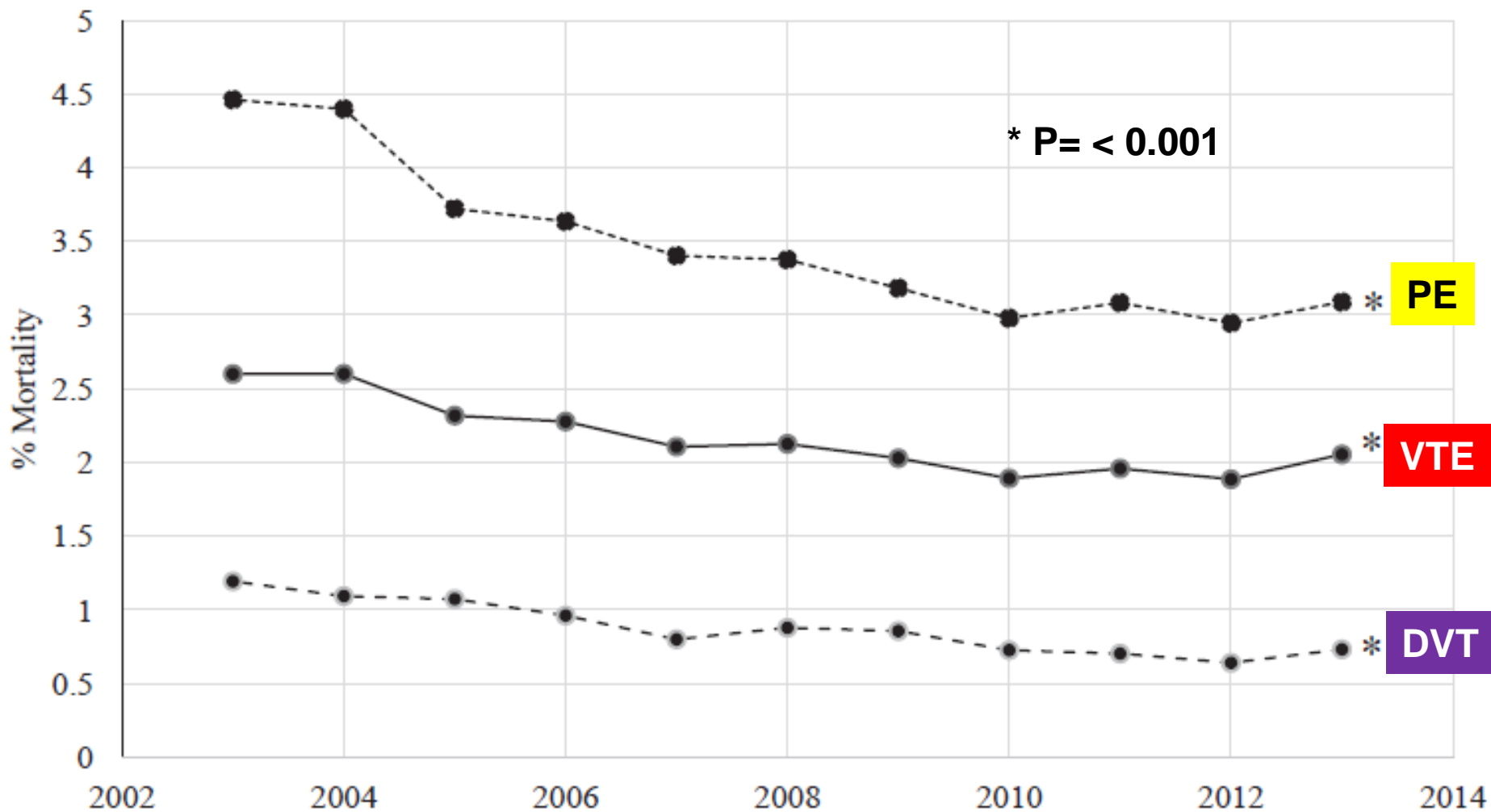
In-Hospital Deaths/100 PE Diagnoses



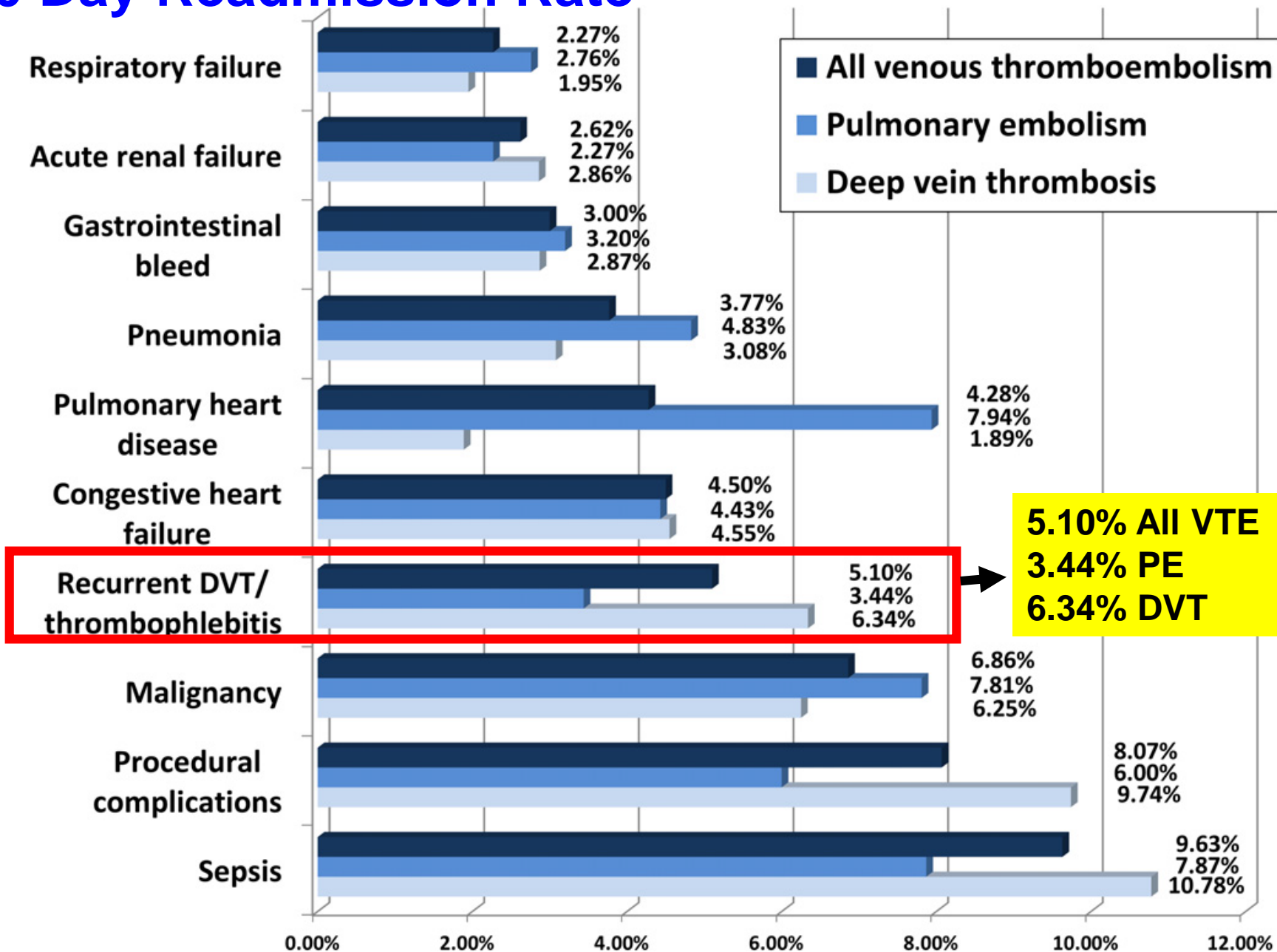
Hospitalization Trends: Venous Thromboembolism



Mortality Hospitalization *Venous Thromboembolism*



30 Day Readmission Rate



VTE Special Groups

Incidence VTE

Acute Medically ill Patients

- Independently associated with 8-fold increase VTE risk
- 10-30% Acute Medically ill patients develop VTE
- 70-80% of Fatal PE occur in acute medically ill (non-surgical patients)
- ACCP Guidelines recommend use of in-hospital VTE prophylaxis for up to ten days in acute medically ill hospitalized patients

Heit, et al. *Arch Int Med.* 2000;160

Cohen, et al. *Thromb Haemost.* 2005;94

Goldhaber, et al. *Chest.* 2000;118

Leizorwicz, et al. *J Thrombosis Hemostasis.* 2003

Kahn SR et al. *Chest.* 2012;141.

VTE Burden

Extends Beyond Hospitalization

- More than **150,000** of the **20,000,000** acute medically ill patients each year survive their medical condition but die of VTE
- Rate symptomatic VTE **doubles** during the 21 days post-discharge *even after 10 days of VTE prophylaxis (ADOPT)*
- Fatal VTE increases **5-fold** between day 10 and day 35 post-discharge *even after 10 days of VTE prophylaxis (MAGELLAN)*
- Hospital **lengths of stay are decreasing** in the US, pushing more of the burden on thromboprophylaxis into the post-acute care setting

Spyropoulos AC, et al. *Chest*. 2011;10:1378;10:194

Goldhaber, et al. *N Engl J Med*. 2011;365:2167

Cohen, et al. *J Thromb Thrombolysis*. 2011;4:407

Inpatient VTE Prophylaxis Trials

Medically Ill Patients

(Average duration 7 – 14 days)

Study	RRR	Thromboprophylaxis	Patients with VTE (%)
MEDENOX n = 1102	63% p<0.001	Placebo Enoxaparin 40mg qd	 14.9* 5.5
PREVENT n = 3706	49% p=0.0015	Placebo Dalteparin 5000 IU qd	 5.0* 2.8
ARTEMIS n = 849	47% p=0.029	Placebo Fondaparinux 2.5mg qd	 10.5† 5.6

* VTE at day 14; † VTE at day 15.

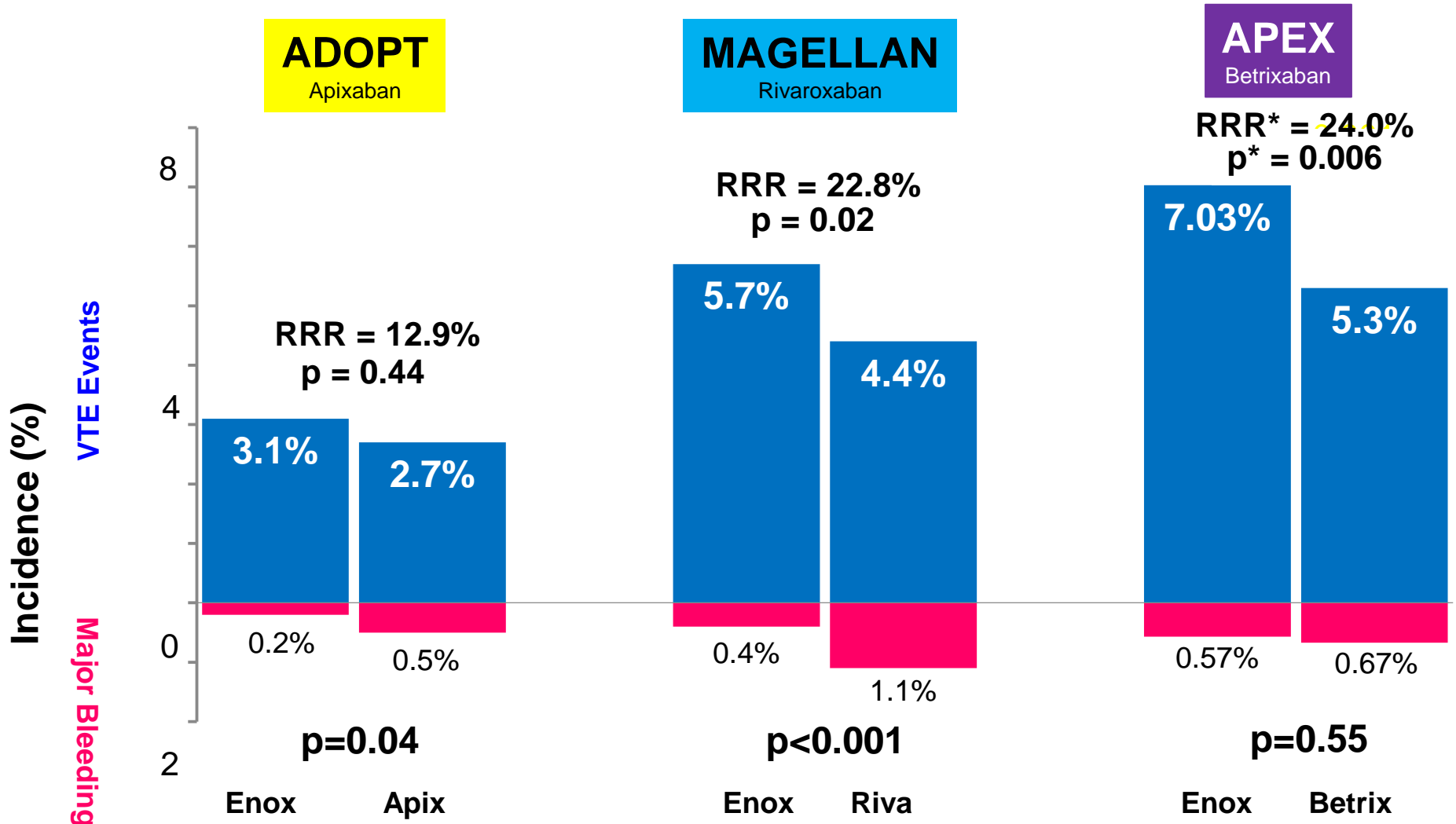
Samama MM, et al. *N Engl J Med.* 1999;341:793

Leizorovicz A, et al. *Circulation.* 2004;110:874

Cohen AT, et al. *BMJ.*2006;332:325

Comparison Medically ill

Extended Thromboprophylaxis



Goldhaber S, et al. N Engl J Med 2011; 365: 2167
 Cohen A, et al. NEJM 2013;368:513
 Cohen et al. N Engl J Med. 2016; 375:534

Postoperative VTE Surgery

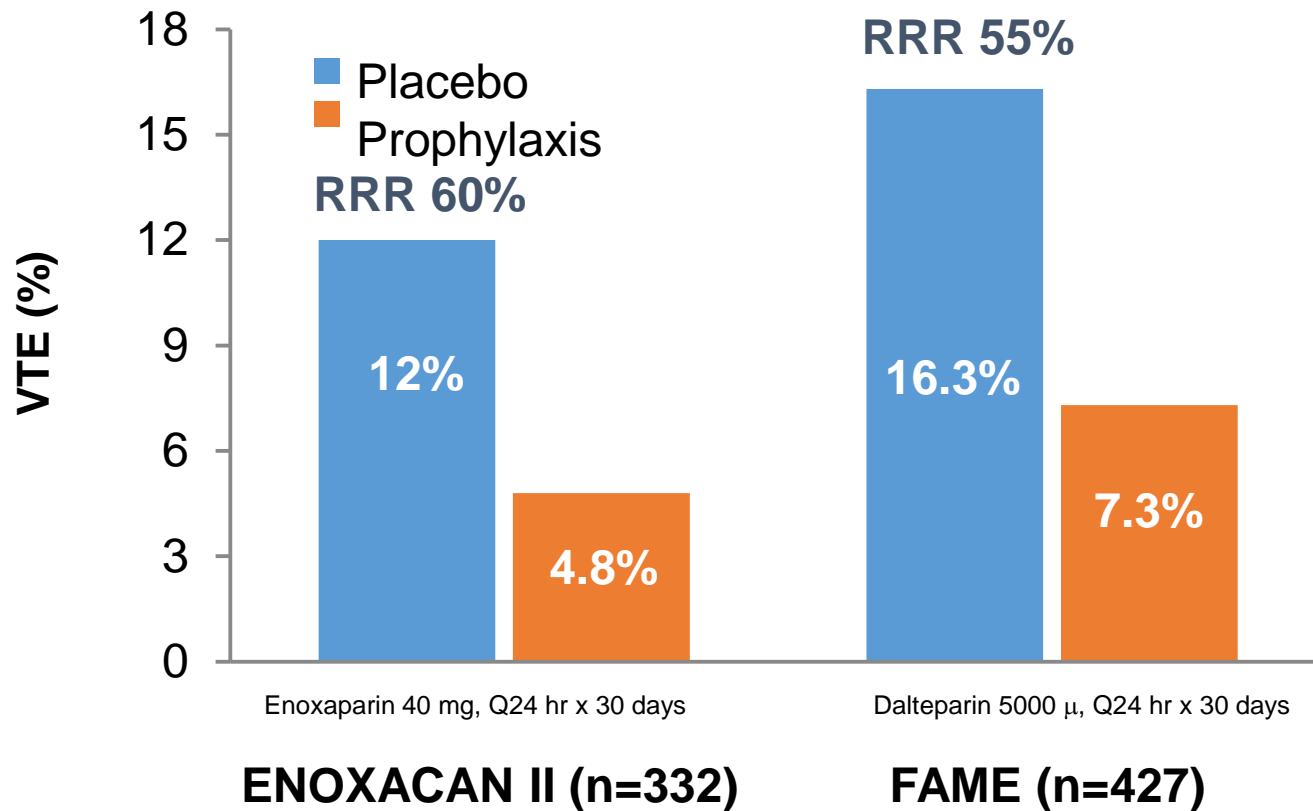
VTE Prophylaxis

Patients With Cancer

- Practice surveys and registries report low rates of thromboprophylaxis in patients with cancer
 - FRONTLINE: 52% of surgical oncologists and 5% of medical oncologists routinely use VTE prophylaxis
 - Use of VTE prophylaxis is low even among patients with high-risk tumors
 - ENDORSE: 37% of patients with active cancer received prophylaxis
 - IMPROVE: 45% of patients with current cancer received prophylaxis

Extended VTE Prophylaxis

High-Risk Abdominal Surgery

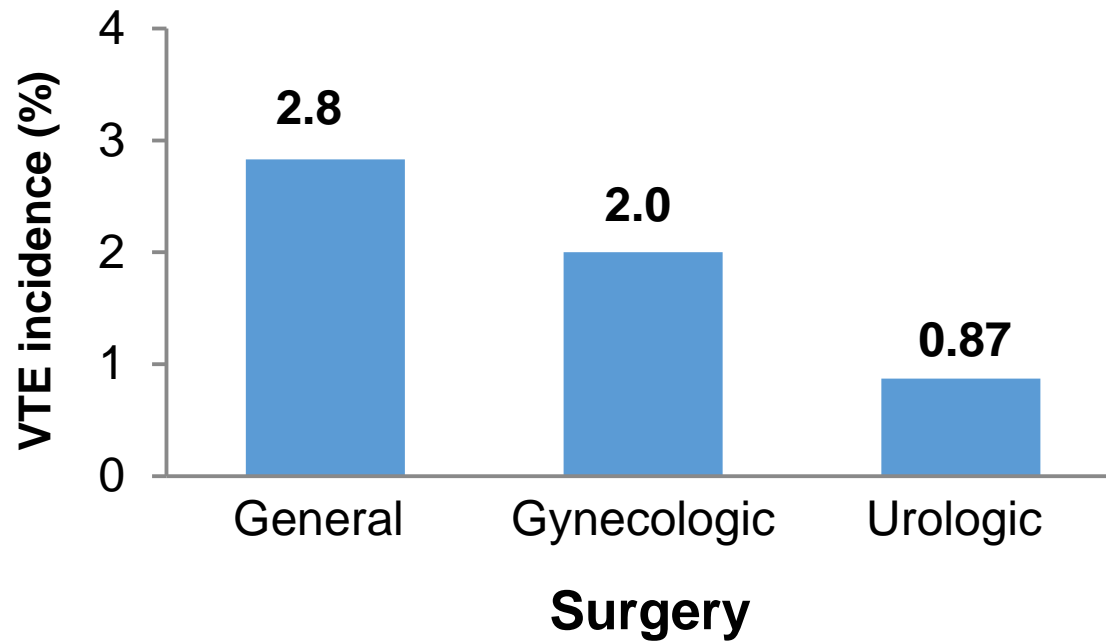


Bergqvist D et al: NEJM 346:975, 2002

Rasmussen MS et al: J Thromb Haemost 4:2384, 2006

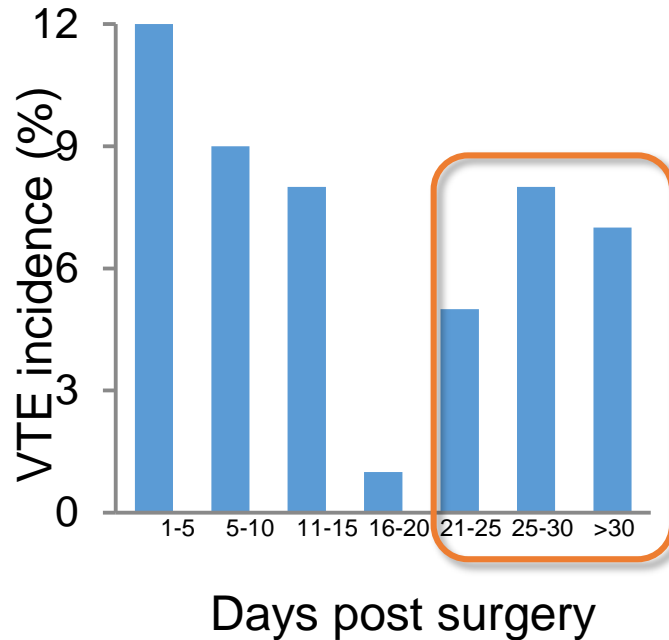
@RISTOS Project

Clinical Outcomes After Cancer Surgery



Surgical Cancer Patients @ *Ristos Study*

40% occur after
discharge



@RISTOS

Prospective Cohort

n=2,373

Symptomatic VTE
2.1%

Overall mortality
1.7%

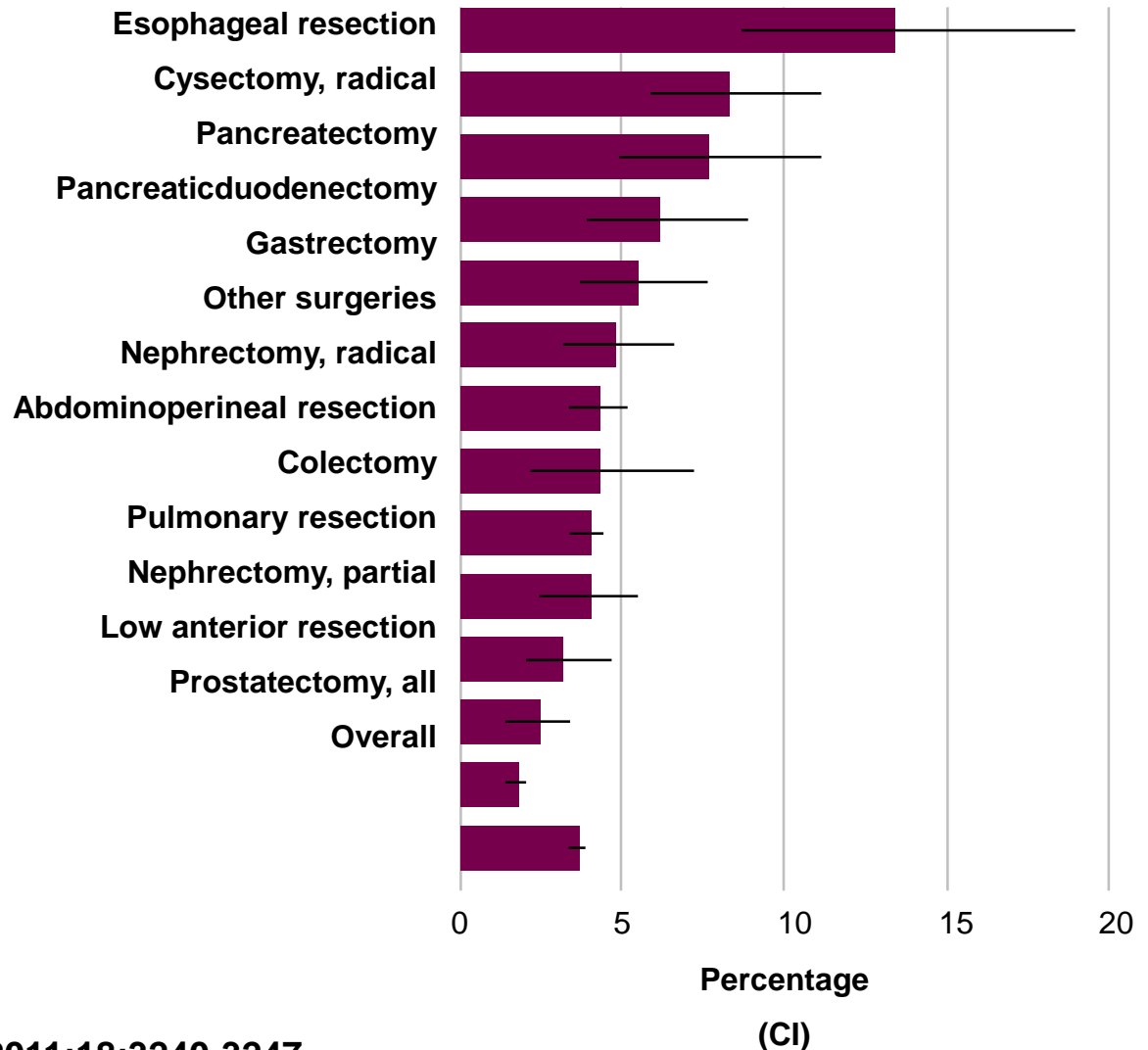


46%
Fatal PE

Postsurgical VTE Rate

Cancer Surgery

- Data from large national administrative claims database representing ~22 million lives
- Overall 30-day postsurgical VTE rate: 3.5%
 - Of patients with VTE diagnosis by day 30, 73% had diagnosis by postsurgical day 14



ACCP and ASCO Guidelines

Extended VTE Prophylaxis

ACCP Guidelines

- High-risk patient undergoing abdominal or pelvic surgery for cancer who are not high risk for major bleeding [1B]
 - Extended prophylaxis 4 weeks with LMWH
 - Dalteparin 5,000 U, Q24h
 - Enoxaparin 40 mg, Q24h

ASCO Guidelines

- Pharmacologic VTE Px for 7 to 10 days
- Extended VTE Px for 4 weeks
 - Dalteparin 5000 U, Q24h
 - Enoxaparin 40 mg, Q24h
- Risk Factors
 - Restricted mobility
 - Obesity
 - Hx VTE

International Clinical Guidelines

VTE Prophylaxis Surgery: Cancer Patient

- **LMWH once per day or low-dose UFH Q8hrs recommended to prevent postoperative VTE in patients with cancer and continued for at least 7–10 days (1A)**
- **Extended prophylaxis (4 weeks) with LMWH after major laparotomy (grade 1B) and laparoscopic (2C) surgeries in patients in patients with a high VTE risk and low bleeding risk.**
- **Mechanical methods are not recommended as monotherapy, except when pharmacological methods are contraindicated (2B).**
- **Inferior vena cava filters are not recommended for routine prophylaxis (1A).**

Cancer Population

Epidemiology

Cancer-Associated Thrombosis

- ~20%–30% of all first VTEs are cancer related¹
- Cancer patients have a RR of VTE 4–7-fold higher than normal controls^{2,3}
 - MEGA population-based case-control study²
 - Overall: OR: 6.7 (95% CI: 5.2, 8.6)
 - Hematologic malignancy: OR: 28 (95% CI: 4.0, 199.7)
 - Olmstead County population-based study³
 - Overall: OR: 4.1 (95% CI: 1.9, 8.5)
- Incidence of VTE in cancer patients in the US may exceed 8%^{1,4}
 - Absolute VTE risk varies depending on tumor type⁴⁻⁶

1. Timp JF, et al. *Blood*. 2013;122(10):1712-1723;
2. Blom JW, et al. *JAMA*. 2005;293(6):715-722;
3. Heit JA, et al. *Arch Intern Med*. 2000;160(6):809-815;
4. Lyman GH, et al. *Thromb Res*. 2018;164(Suppl 1):S112-S118;
5. Chew HK, et al. *Arch Intern Med*. 2006;166(4):458-464;
6. Khorana AA, et al. *Cancer*. 2007;110:2339-2346.

Thromboembolism and Cancer

- VTE is the second leading cause of death in patients with known malignancy
- Death rate from cancer is 4-fold higher if patient has concurrent VTE
- Incidence rate of VTE varies by cancer type

Incidence rate (95% CI) of first VTE per 100 person-years by Cancer Type

Age	Bladder	Breast	Colon	Lung	Prostate	Uterus	Haem.	Brain	Ovary	Pancreas	Stomach
≥18	2.7 (2.4–3.0)	3.2 (2.9–3.4)	6.7 (6.3–7.2)	10.1 (9.5–10.8)	4.4 (4.0–4.7)	7.0 (5.9–8.3)	4.5 (4.1–4.8)	12.1 (10.3–14.0)	11.9 (10.6–13.2)	14.6 (12.9–16.5)	10.8 (9.5–12.3)

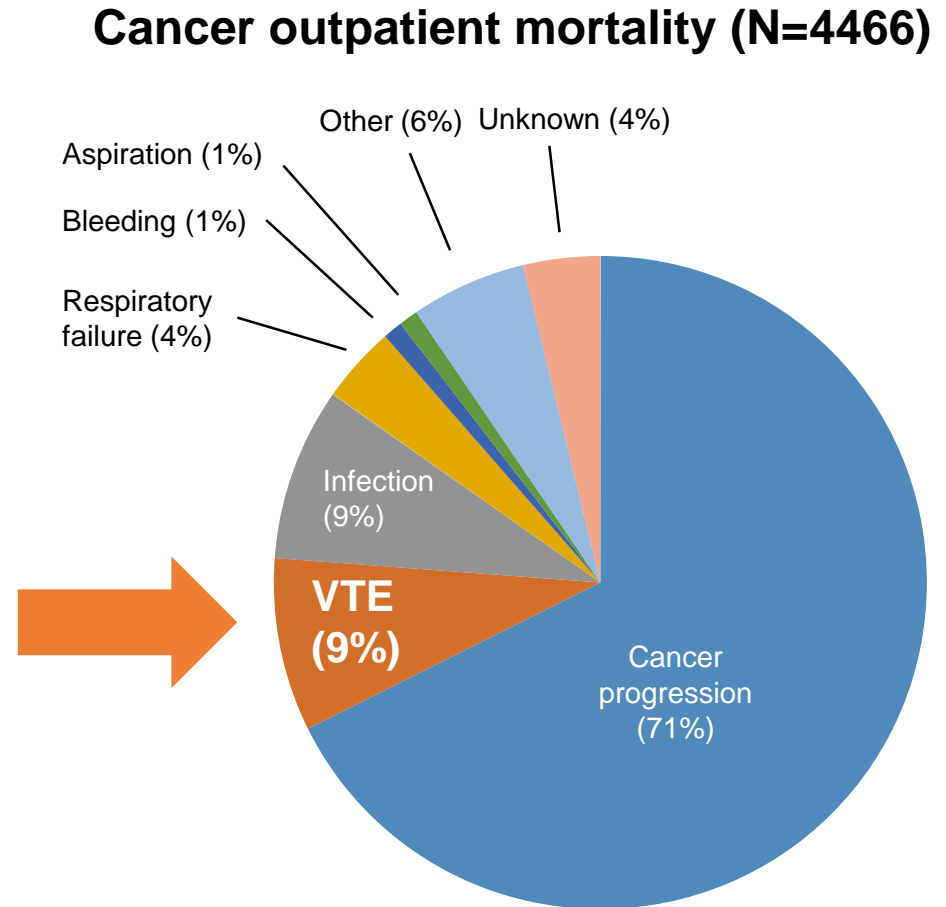
- Twice the risk for post-op VTE in patients with cancer
- Increasing incidence due to
 - Improved cancer treatment outcomes
 - More thrombogenic regimens
 - Aging population

Khorana AA, et al. *J Thromb Haemost.* 2007;5(3):632
 Timp JF, et al. *Blood.* 2013;122(10):1712
 Cohen AT et al, *Thromb Haemost* 2017;117:57
 White RH, et al. *Thromb Haemost.* 2003;90(3):446
 Gangireddy C, et al. *J Vasc Surg.* 2007;45(2):335
 Streiff MB. *Clin Adv Hematol Oncol.* 2013;11:349.

VTE Cause of Death

Cancer Mortality

- Thromboembolism is the **second leading** cause of death in patients with cancer
- Annual death rate for VTE: 448 per 100,000 cancer outpatients
 - **47-fold increase** over the general population



VTE Epidemic: Why More Cases?

- **Consider the Risk Factors for VTE:**
 - **Increasing age**
 - Population aging; fastest US demographic is > 75
 - **Cancer/Cancer Surgery**
 - More common, and improved survival after diagnosis
 - Thrombogenic Chemo Regimens
 - **Heart failure**
 - Better medical and device therapy prolongs life
 - **Other chronic illnesses with longer lifespan**
 - **Obesity**
 - Incidence higher

Cushman M, *Semin Hematol* 2007;44:62-9
Stein PD, *Arch Intern Med* 2004;154:2260-5.
Lee AYY, *Circulation* 2003;107:I-17-I-21.
Deitelzweig SB, *Am J Hematol* 2011;86:217-20.

VTE Epidemic

- **Better Diagnostic Imaging**
- **ED and Hospital Protocols for VTE Diagnosis**
- **PERT Teams**
- **Interventional Modalities for Reduction Clot Burden**
- **National Awareness**

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Mortality Following Acute PE

Source	Year	N	Follow-Up	Mortality Rate, %			
				Massive PE	Submassive PE	Massive PE Given Lytic	Submassive PE Given Lytic
MAPPET	1997	719	30	NA	9.6	NA	4.7
ICOPER	1999	2284	90	52.4	14.7	46.3	21
RIETE	2007	6264	90	9.3	3.0	1.3	7.7
EMPEROR ¹⁴⁰	2008	1840	In-hospital	14.6	3.0	0	9.5
HCUP-2007 NIS ¹⁴¹	2007	32,263	In-hospital		3.6		NA

Circulation 2011;123:1788-830