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***Plenary Session 6***  
***Thromboprophylaxis in Cancer***

# **Thromboembolism in Hospitalized Cancer Patients: Update on 16 years of data from US**

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# Disclosures

- No relevant financial COI
- Co-Chair, ASCO and ASH Guidelines on Cancer and Thrombosis

# VTE in Hospitalized Patients with Cancer

- **Venous thromboembolism (VTE) is one of the most frequent causes of preventable mortality and morbidity in hospitalized patients**
- **About 25% of all cases of VTE are related to hospitalization**
- **50 - 75% of cases of VTE in hospitalized patients are on the medical service**
- **Pulmonary embolism is associated with 5% to 10% of deaths in patients in hospitals**

# ASCO VTE Guidelines (2006 – 2018): Clinical Questions

(1) Should hospitalized patients with cancer receive anti-coagulation for VTE prophylaxis?

(2) Should ambulatory patients with cancer receive anticoagulation for VTE prophylaxis during systemic chemotherapy?

(3) Should patients with cancer undergoing surgery receive periop VTE prophylaxis?

(4) What is the best method for treatment of patients with cancer with established VTE to prevent recurrence?

(5) Should patients with cancer receive anticoagulants in the absence of established VTE to improve survival?

(6) What is known about risk factors and risk prediction of VTE among patients with cancer?





# Recommendations

## *Inpatient Prophylaxis*

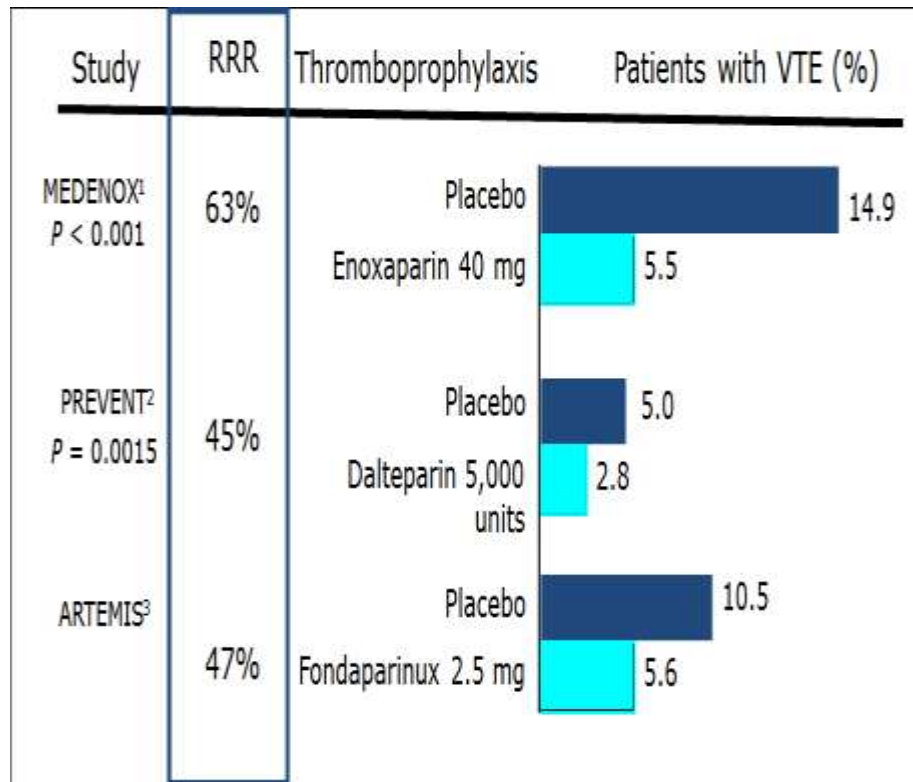
1.1 Hospitalized patients with **active malignancy and acute medical illness or reduced mobility** should receive pharmacologic thromboprophylaxis in the absence of bleeding or other contraindications

1.2 Hospitalized patients who have **active malignancy without additional risk factors** may be considered for pharmacologic thromboprophylaxis in the absence of bleeding or other contraindications.

1.3 Data are inadequate to support routine thromboprophylaxis in patients admitted for **minor procedures or short chemotherapy infusion, or in patients undergoing stem cell/ bone marrow transplantation.**

# Evidence Base

## RCTs of Hospitalized Medically Ill Patients



<sup>1</sup>Samama MM, et al. *N Engl J Med*. 1999;341:793-800.

<sup>2</sup>Leizorovicz A, et al. *Circulation*. 2004;110:874-9.

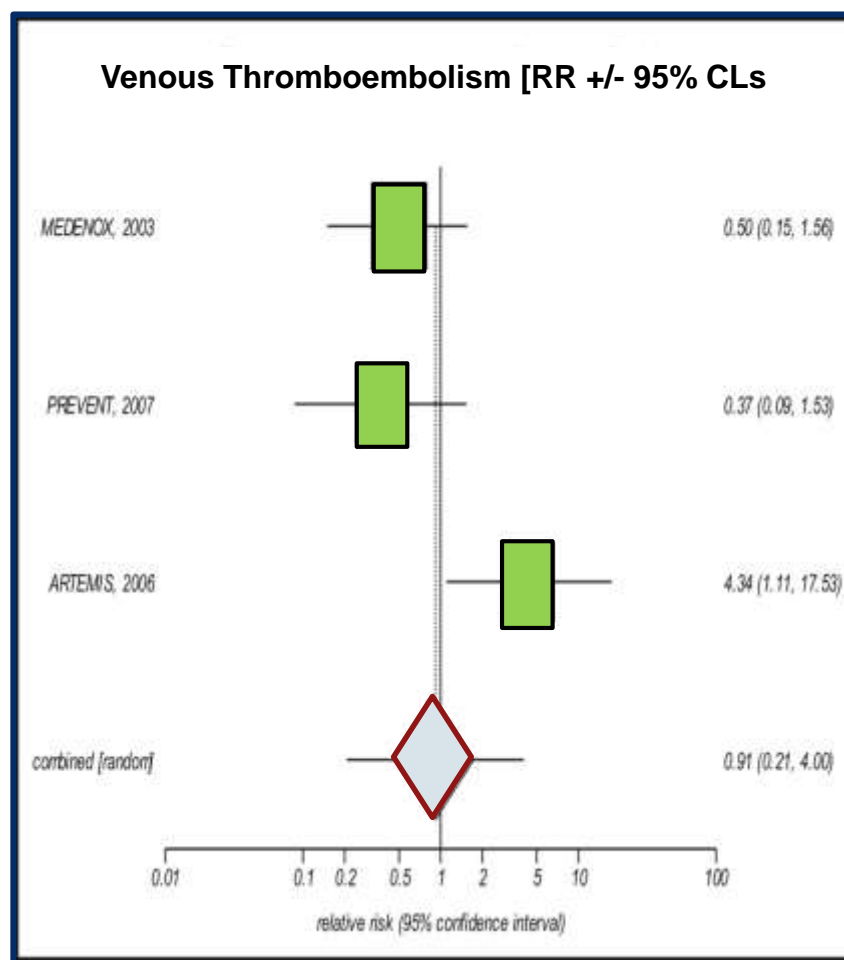
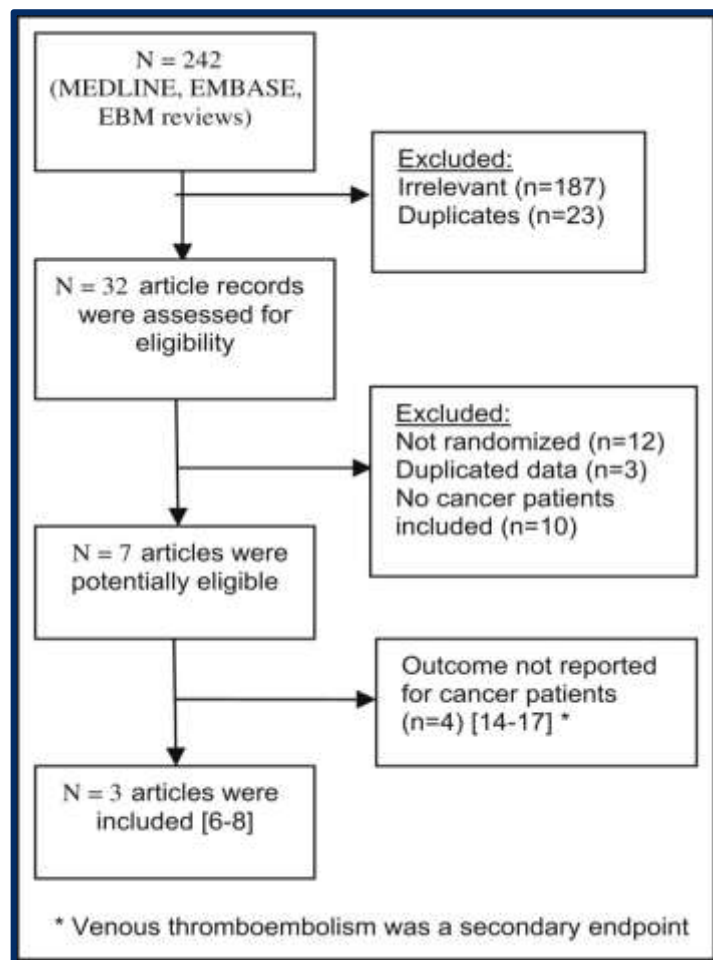
<sup>3</sup>Cohen AT, et al. *BMJ* 2006; 332: 325-329.

- Three large, placebo-controlled, double-blind RCTs in high-risk medical patients
  - MEDENOX (enoxaparin)
  - PREVENT (dalteparin)
  - ARTEMIS (fondaparinux)
- Screening for asymptomatic DVT with venography or US
- Subgroup analysis in cancer pts\*
  - Post-hoc analysis: MEDENOX
  - Cancer patients: 12.4%
  - VTE with 40mg enoxaparin vs placebo  
RR = 0.50 (95% CI, 0.14 – 1.72; NS)

\* Alikhan R et al, *Blood Coag Fibrinolysis*, 2003 14: 341-346

# Thromboprophylaxis in Hospitalized Medical Patients

## Studies Reporting Cancer Subgroups Reported



Carrier M et al: Am J Med 2014; 127: 82-86.

# Major Clinical Practice Guidelines

## *Recommendations on VTE Prophylaxis in Hospitalized Cancer Patients*

Guideline	Inpatient prophylaxis	Specific Population	Preferred agents
ASCO	✓	AC & AMI/immobile	LMWH/Fonda
NCCN	✓	Cancer Dx or Sx	LMWH/Fonda
INTERNATIONAL	✓	Cancer & immobile	LMWH/Fonda
ESMO	✓	AMI/immobile	UFH/LMWH/ Fonda
ITALIAN	✓	Cancer/AMI/immobile	LMWH/Fonda
SEOM	✓	Cancer/AMI	LMWH
BCSH	✓	AC/Recent cancer	LMWH
ACCP	✓	AMI	LMWH/Fonda/ UFH
ASH	TBD	TBD	TBD

BCSH = British Committee for Standards in Haematology

AC = active cancer; AMI = acute medical illness



## Prevention of VTE in hospitalized cancer patients: *Guidance from SSC/ISTH*



- **Thromboprophylaxis in medical hospitalized cancer patients**
  - In patients hospitalized for an acute medical illness use pharmacologic thromboprophylaxis in the absence of bleeding/other contraindications.
  - In patients admitted for minor procedures or short term chemotherapy infusion, we suggest not using thromboprophylaxis.
- **Selection of agent and duration of thromboprophylaxis**
  - In patients hospitalized for an acute medical illness, use heparins throughout hospitalization, preferably LMWH.
  - In medical hospitalized cancer patients, we recommend not using the new oral anticoagulants for VTE thromboprophylaxis.

## Prevention of VTE in hospitalized cancer patients: *Guidance from SSC/ISTH*



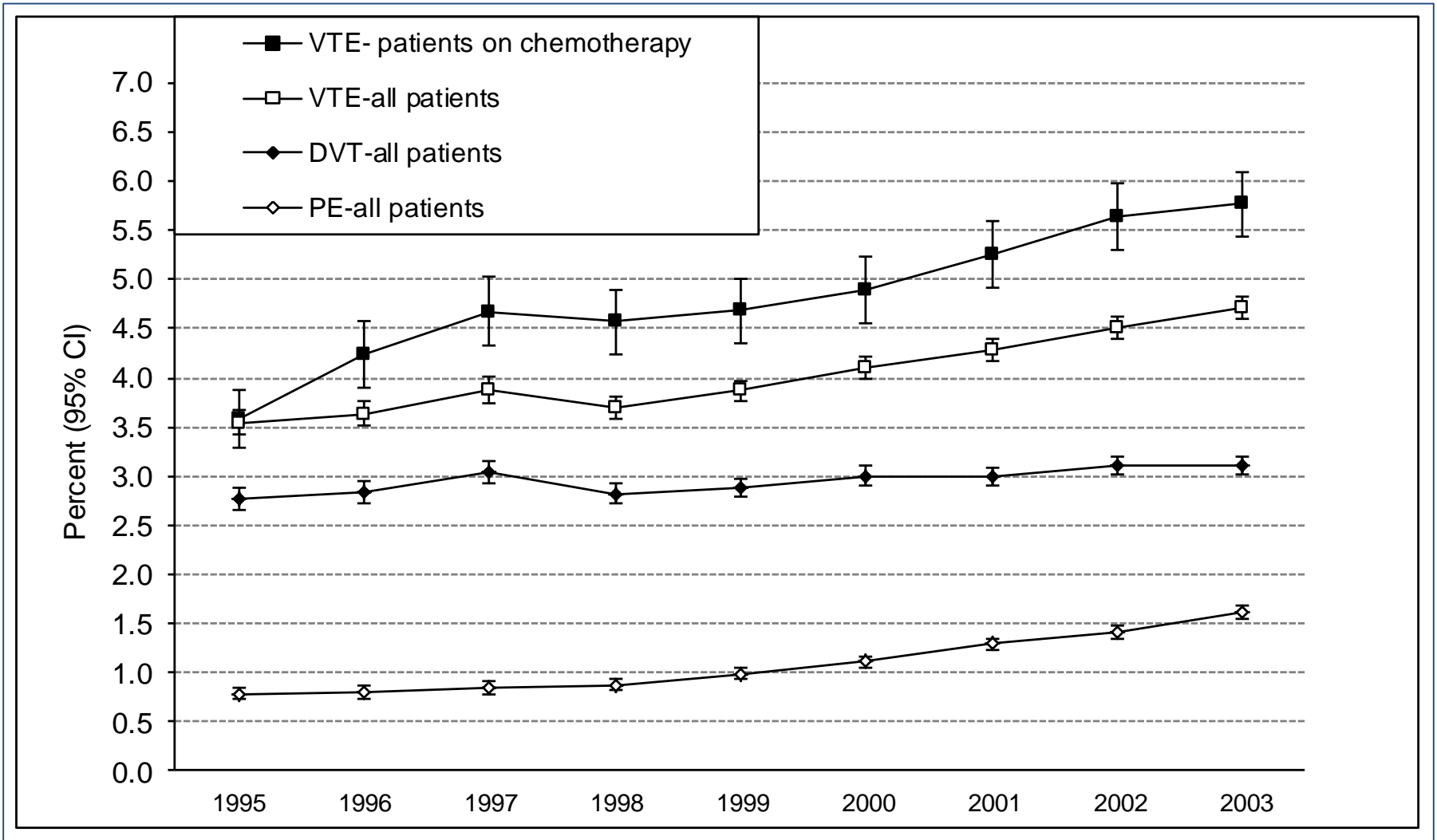
- Patients with active bleeding
  - Mechanical prophylaxis with pneumatic compression in patients with active bleeding or at high risk for bleeding.
  - Resume thromboprophylaxis once resolved
- Patients with thrombocytopenia
  - Pharmacologic thromboprophylaxis if the platelet count is  $\geq 50 \times 10^9/L$  in absence of other contraindications.
  - If the platelet count between  $25 - 50 \times 10^9/L$ , individualize.
  - No thromboprophylaxis in patients with platelet count of  $< 25 \times 10^9/L$ .
- Patients with renal insufficiency
  - Standard prophylactic doses of LMWH with a creatinine clearance rate of  $\geq 30$  mL/min, in the absence of other contraindications.
  - With a creatinine clearance below 30 mL/min, LMWH with a low bioaccumulation or UFH.

# Real World Data on VTE in Hospitalized Cancer Patients

- Retrospective cohort study of discharges using the *University HealthSystem Consortium*
- Adult cancer patients hospitalized between 1995 and 2002 at 115 US academic centers
- 8% experienced thrombosis
  - 5.4% venous and 1.5% arterial in 1<sup>st</sup> hospitalization
- Major predictors
  - Age over 65
  - Site (lung, GI, gynecologic, brain)
  - Comorbidities (infection, pulmonary and renal disease, obesity)

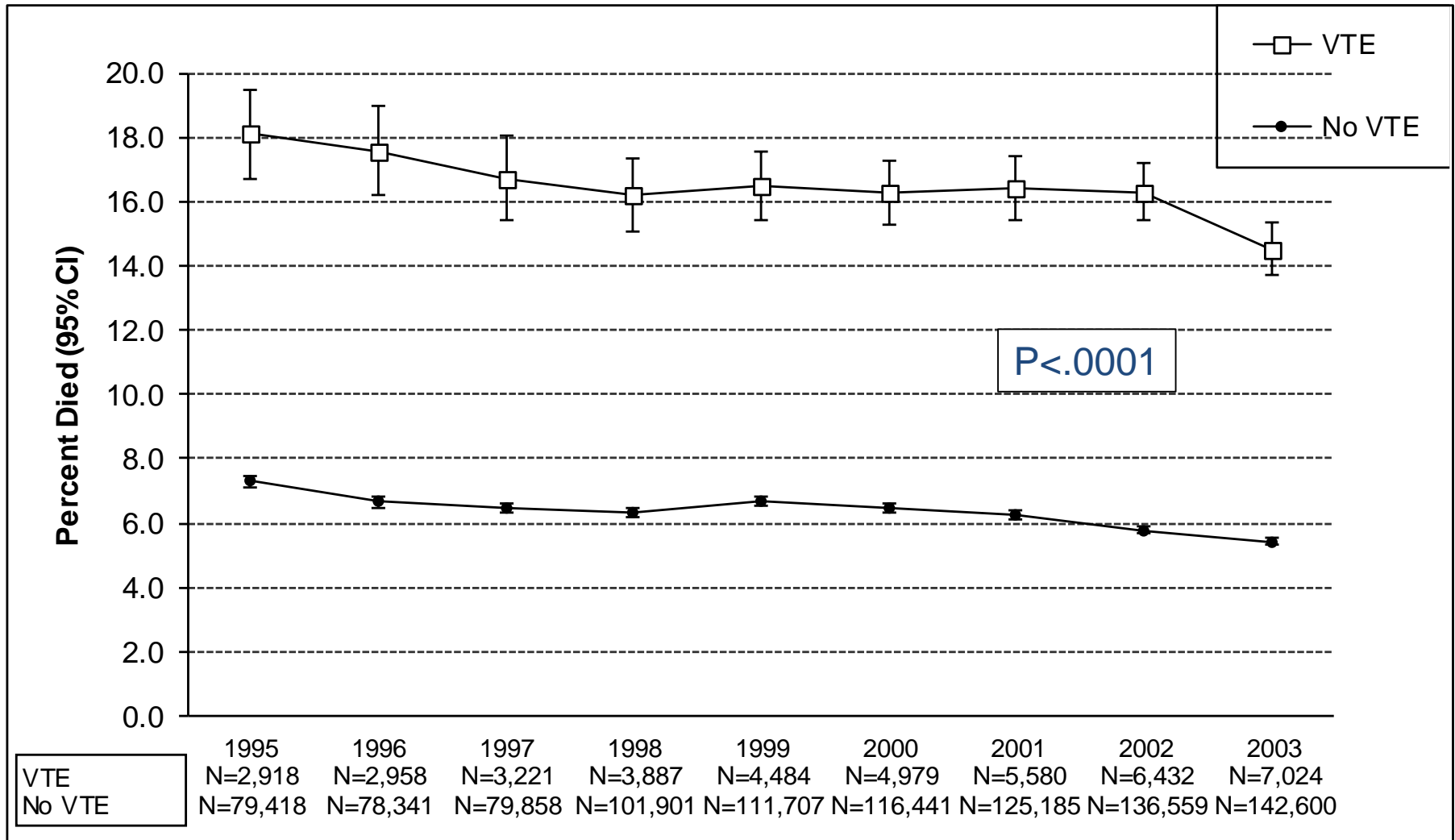
N = 1,015,598

## VTE in ALL hospitalized cancer patients



N = 1,015,598

# VTE and inpatient mortality in all hospitalized cancer patients



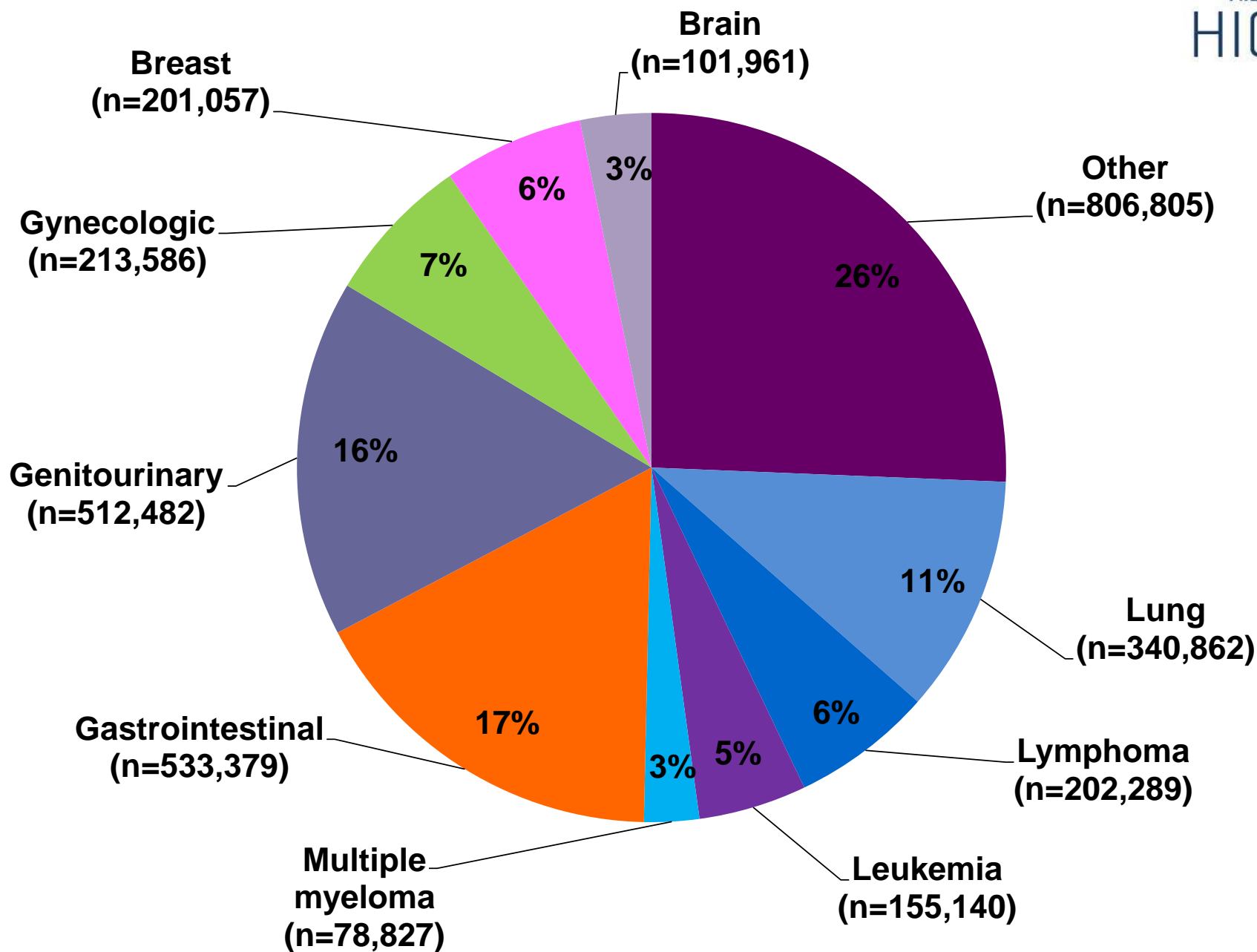


# VTE in Hospitalized Cancer Patients

*An Update 1995 - 2012*

- Retrospective cohort study of cancer patient hospitalizations between 1995-2012
- Nearly 6 million hospitalizations of 3,146,388 individual patients with cancers from more than 200 institutions.
- For patients with multiple hospitalizations, a single admission was selected at random
- There were no major differences in demographic characteristics, geographic region or cancer type over time
- Number of reported comorbidities increased over time among hospitalized patients with cancer including a doubling of patients with 3+ comorbidities

Lyman GH et al. Thromb Res 2018



# VTE in Hospitalized Cancer Patients

*An Update 1995 - 2012*

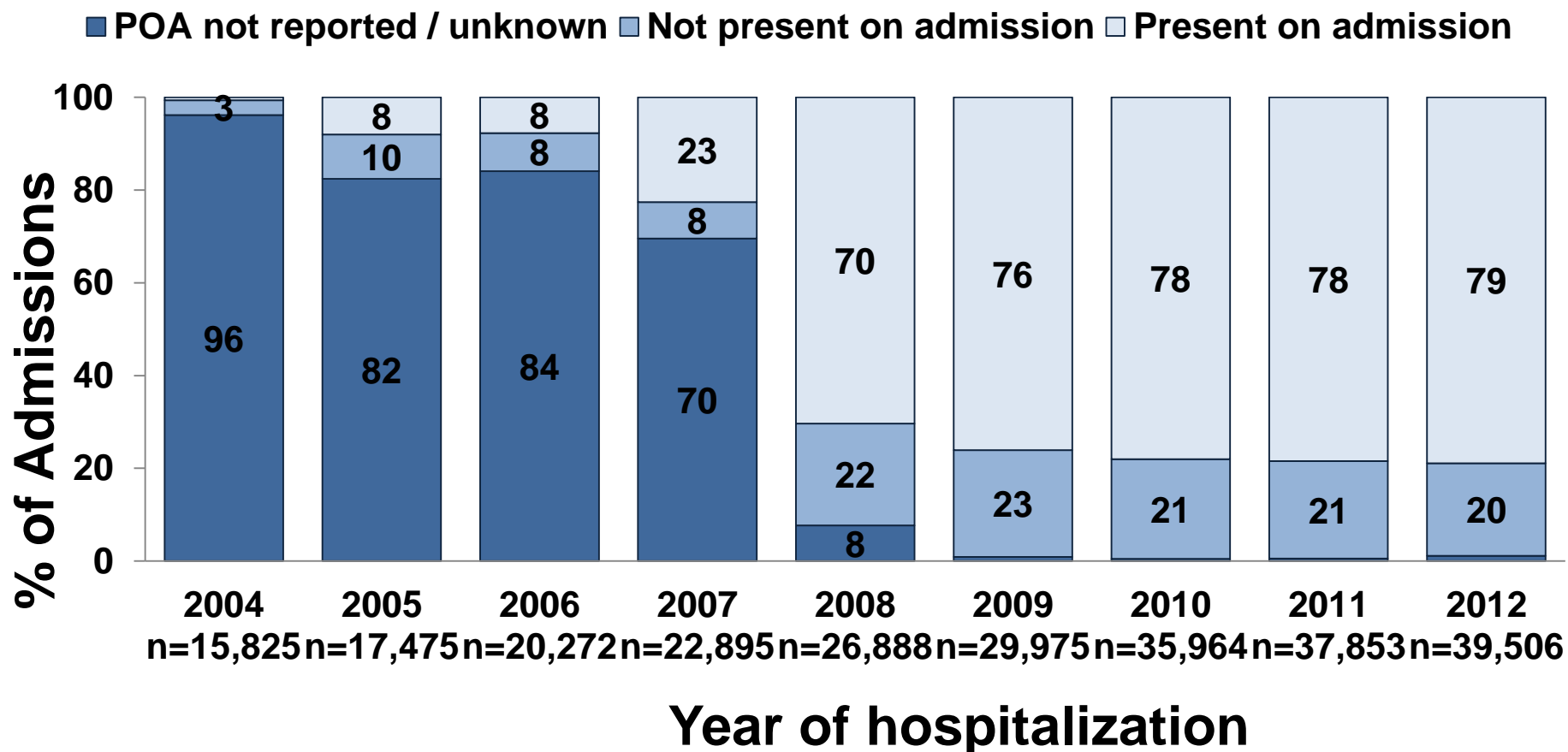
- VTE was reported in 8.4% of patients when all admissions
- When a randomly selected hospitalization is considered for each patient, VTE was diagnosed in 5.3% (1.8% with PE).
- Annual rate of VTE increased from 3.5% in 1995 to over 6.5% in 2012 with PE nearly tripling from 0.8% to 2.3%.
- Annual rate of VTE increased from 3.6% in 1995 to 8.3% in 2012 in patients receiving chemotherapy
- Highest rates of VTE observed with pancreatic (10.2%), gastric (7.1%), ovarian (7.1%), lung (6.8%), and esophageal cancers (6.3%).
- The occurrence of VTE increased within the number of comorbidities (0: 2.3%; 4+: >11%).

Lyman GH et al. Thromb Res 2018

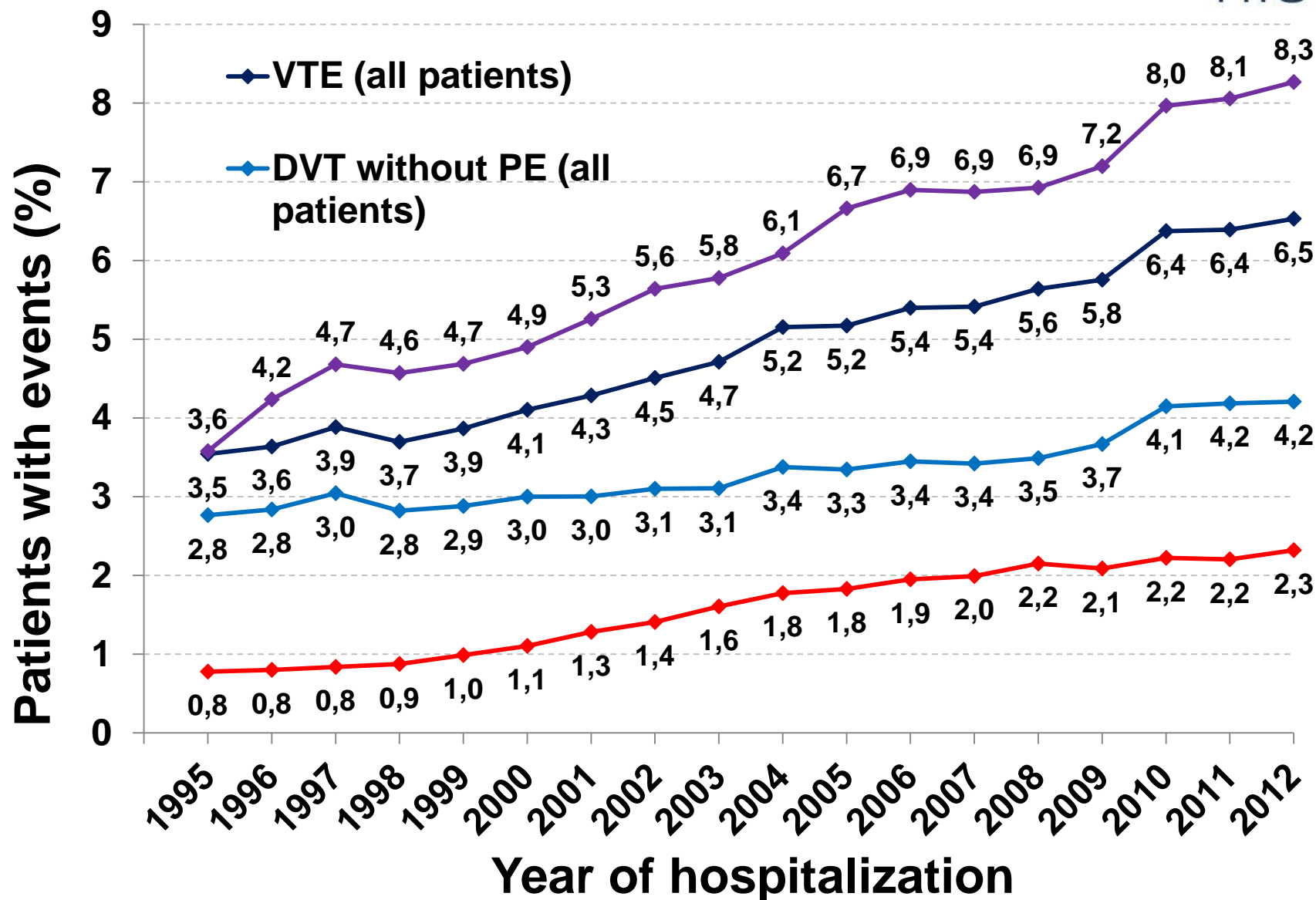
# Admissions with VTE

ICD-9-CM DVT 451-453.99 or ICD-9-CM PE 415.1-415.19  
(246,653 hospitalizations in 198,173 patients)

## Diagnosis Present on Admission (POA)



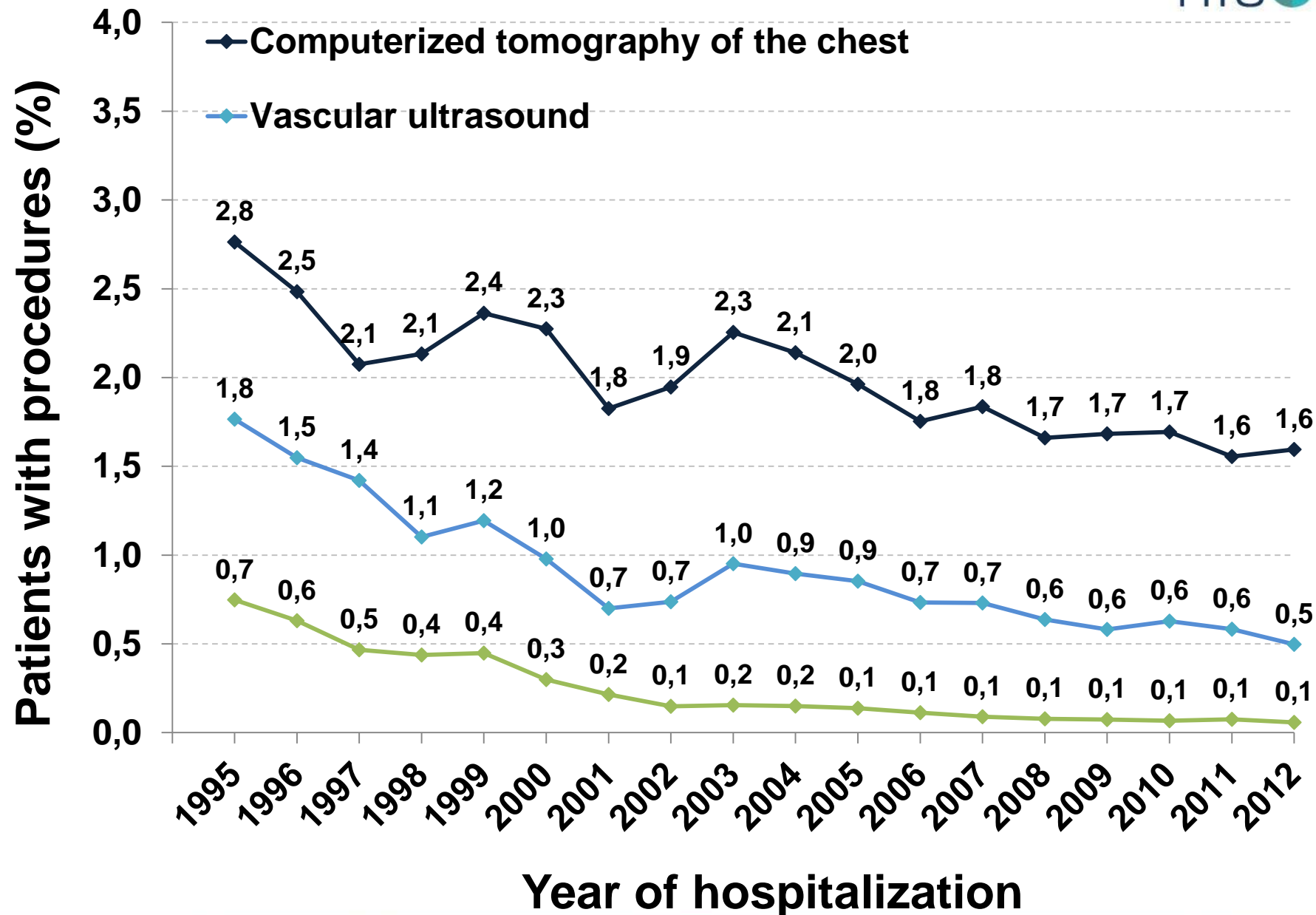
# Trends in Thromboembolism



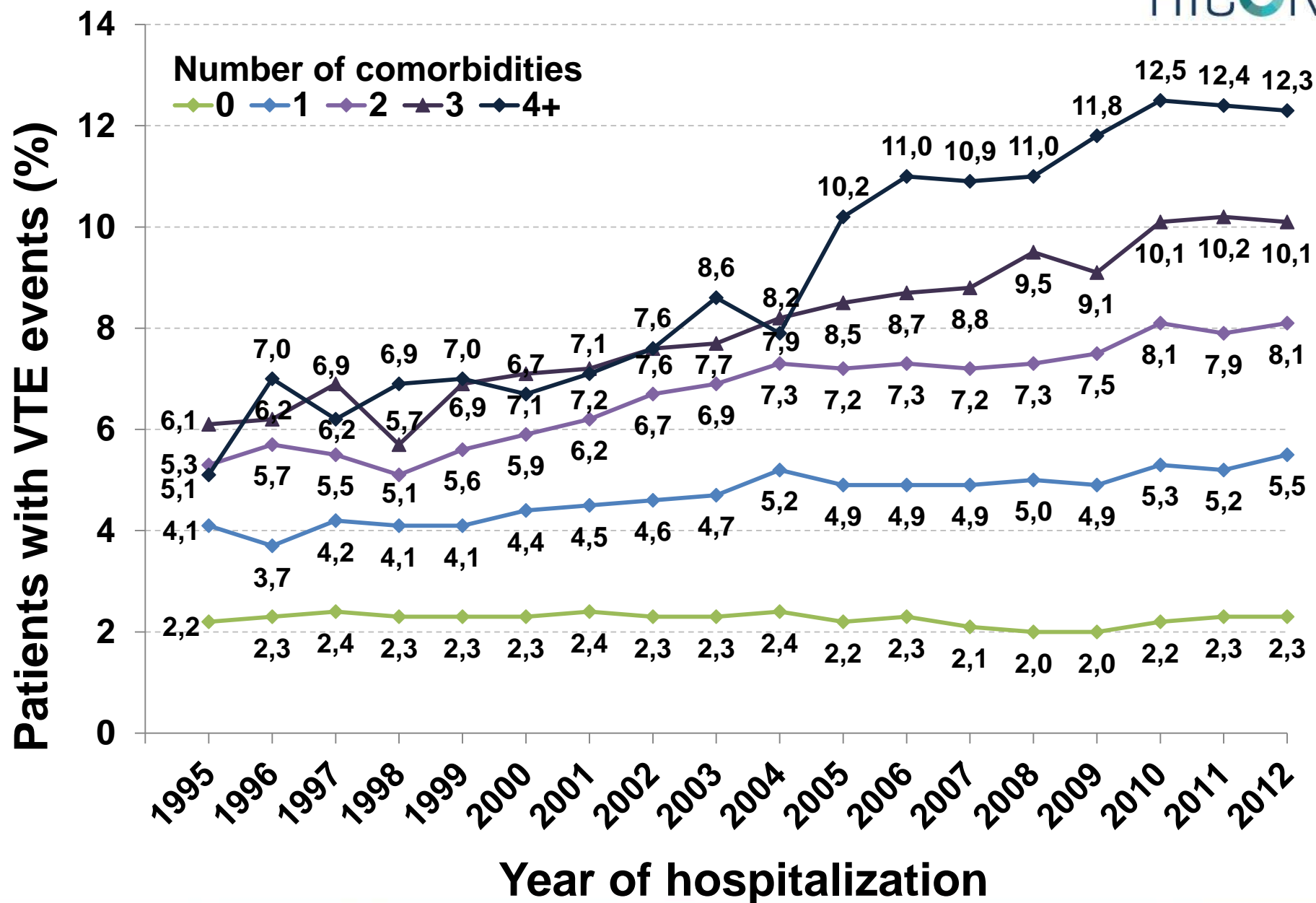
VTE=venous thromboembolism; DVT=deep vein thrombosis; PE=pulmonary embolism

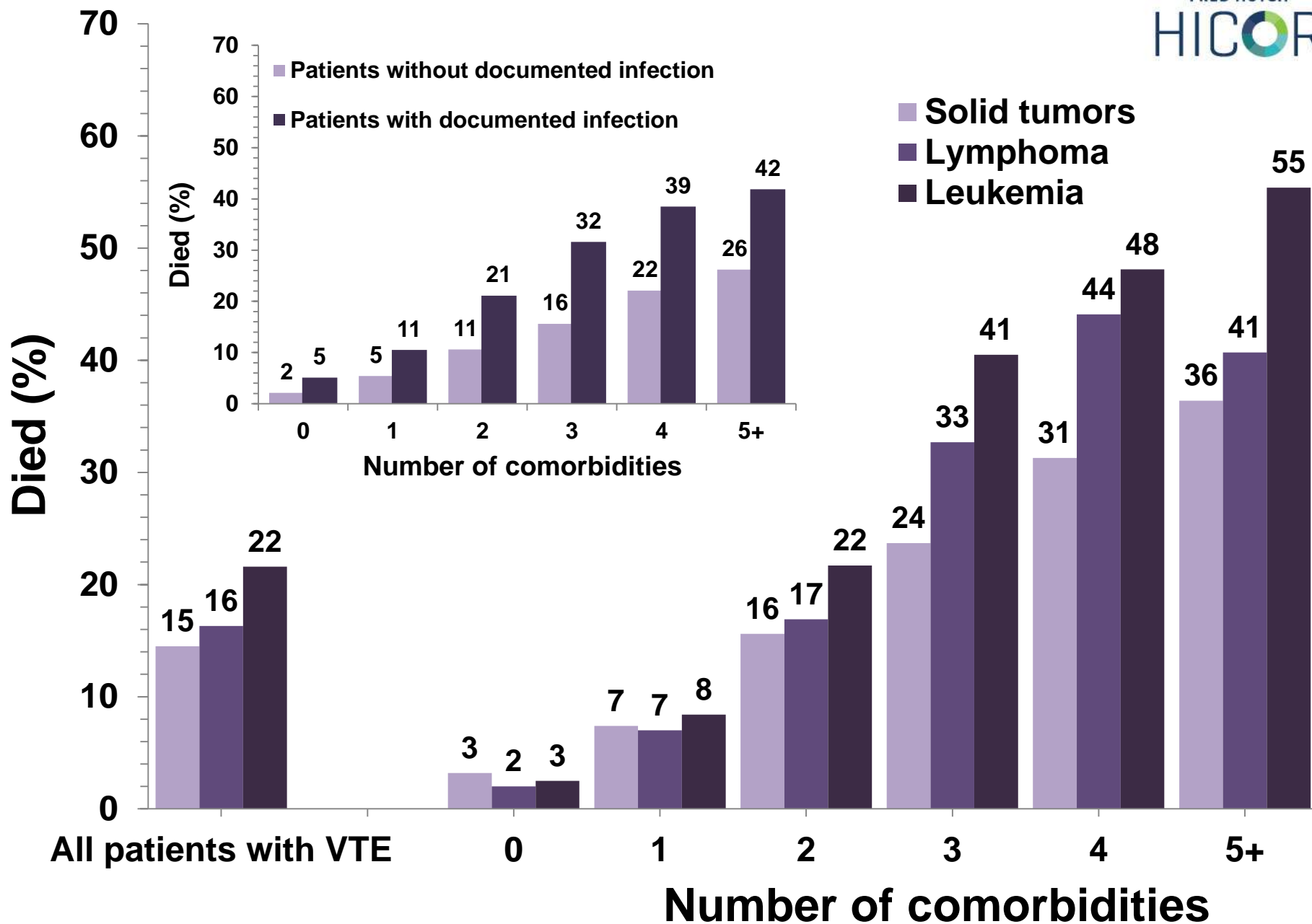


# Trends in Imaging Related to PE or DVT

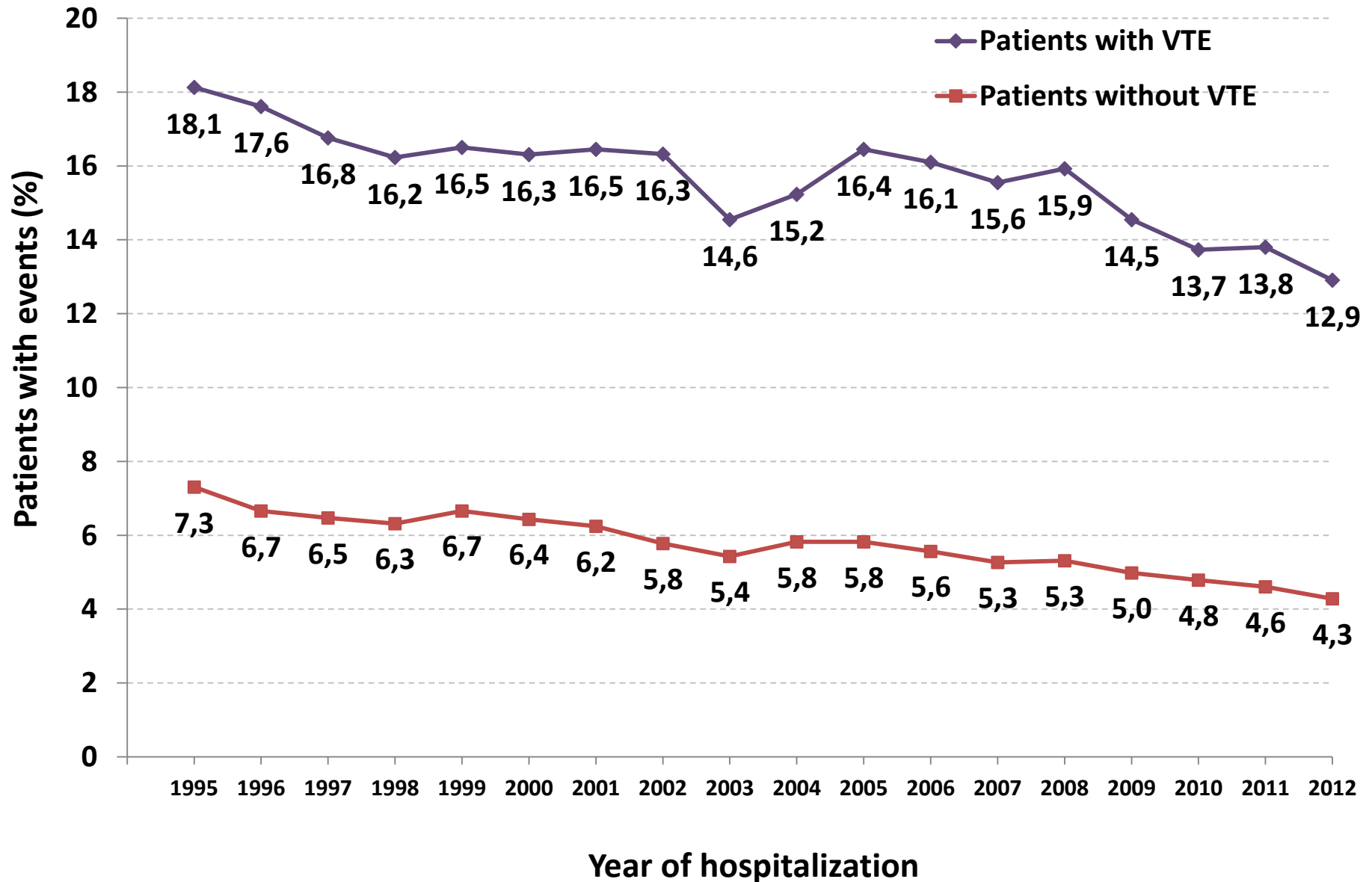


# VTE and Number of Comorbidities





# Trends in Inpatient Mortality



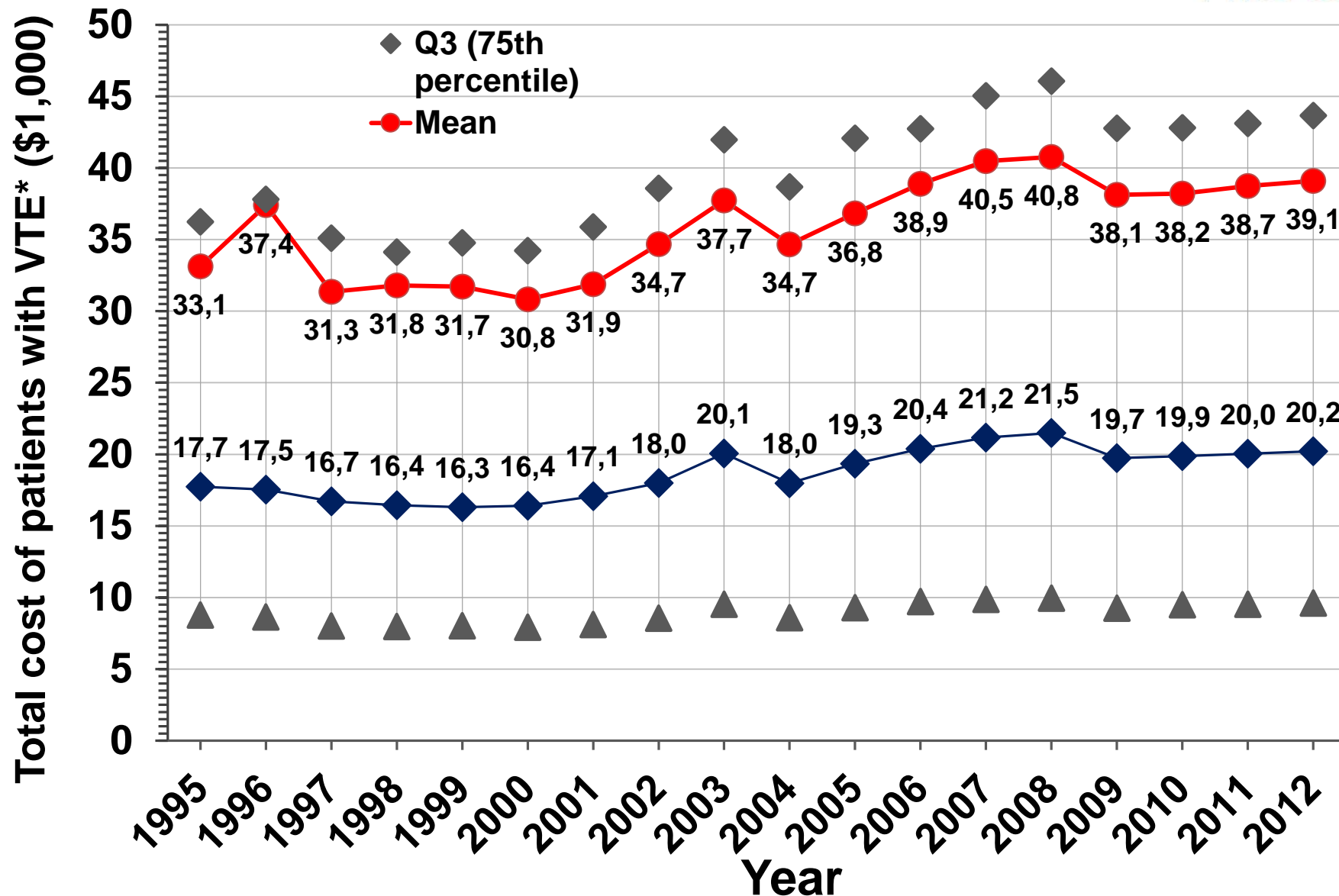
# VTE in Hospitalized Cancer Patients

## *An Update 1995 - 2012*

- In-hospital mortality reported in 5.5% of cancer patients without VTE and in 15.0% of those with VTE (PE: 19.4%).
- Mortality in patients with VTE greater with multiple comorbidities or infection
- LOS and mortality decreased with as well as without VTE.
- Inflation adjusted costs per hospitalization for patients with and without VTE were \$37,352 and \$19,994, respectively.
- Adjusted daily cost of hospitalization for patients with cancer and VTE increased from \$2,256(1995) to \$3,297(2012)
- Approximately half of total cost related to treatment of the 20% of patients with hospital stay of  $\geq 10$  days.

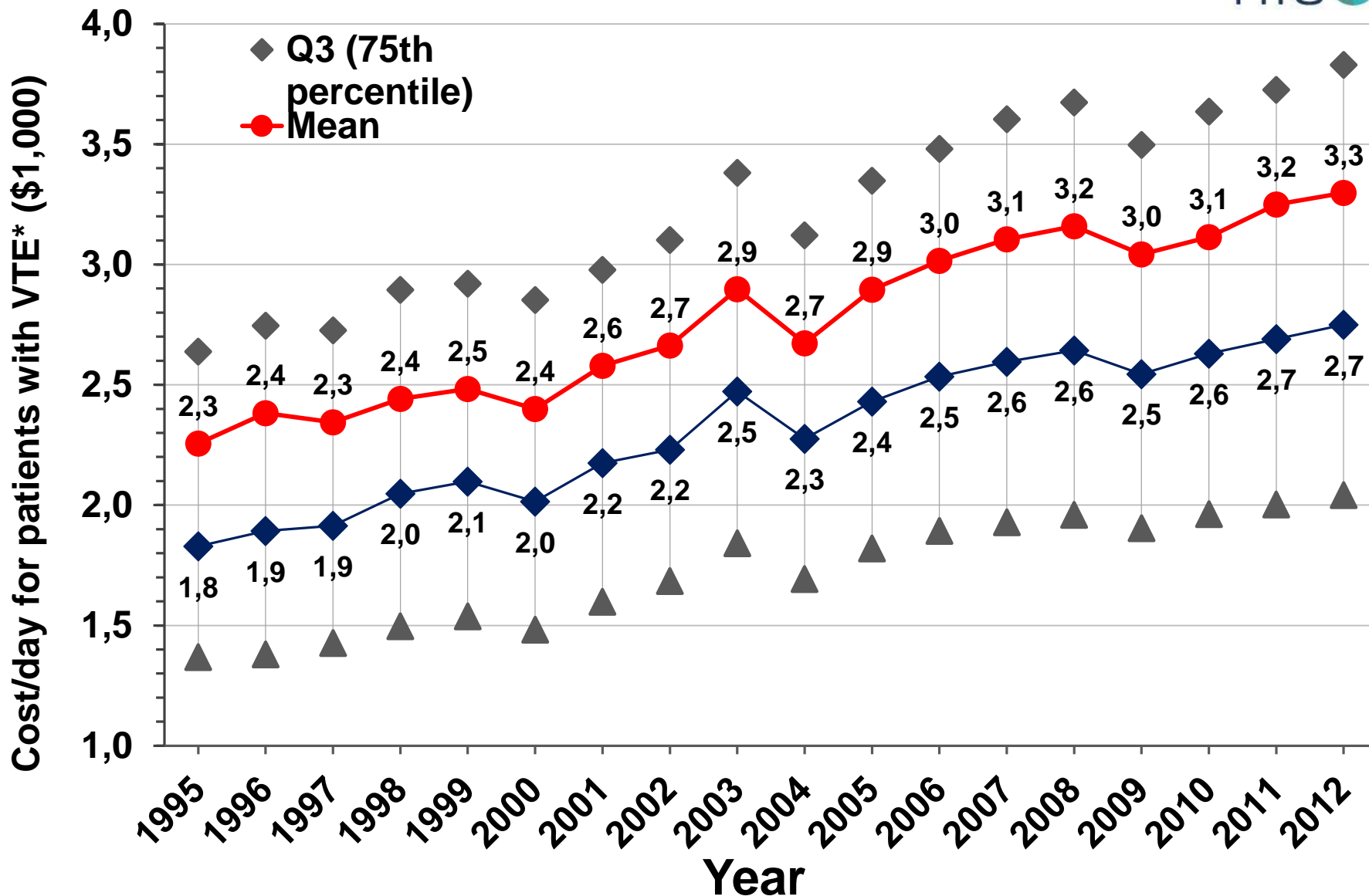


# Total Cost of Hospitalization



\*Cost is adjusted for inflation and presented in 2015 US dollars

# Cost/Day of Hospitalization



\*Cost is adjusted for inflation and presented in 2015 US dollars

# Unresolved Issues

- **No dedicated RCTs in cancer inpatients**
- **Limited real world data in routine clinical practice**
- **Better definition of contraindications (bleeding risk)**
  - eg, Special populations (brain tumors, heme malignancies)
- **Limited data on VTE risk assessment**
  - Prophylaxis frequent but non-targeted (Zwicker JCO 2014)
  - Further validation of cancer-specific risk assessment tools (Khorana Am J Hematol 2017)
- **Uncertainty on dosing and duration of prophylaxis**
- **No clear mortality benefit from thromboprophylaxis**
- **Limited data on PROs/QOL and comparative costs**
- **Role of DOACs currently**

# VTE in Hospitalized Patients with Cancer

## Summary

- **Treatment of symptomatic disease is important..... but insufficient**
  - Asymptomatic VTE is common
  - Death from PE is often rapid
- **Prophylaxis of high-risk hospitalized cancer patients without contraindication important based on:**
  - Clinical practice guideline recommendations
  - Further validation of risk models for VTE and bleeding events in hospitalized patients with cancer
  - Economic models of thromboprophylaxis in patients with cancer need to consider the rising costs of VTE-associated hospitalization

## Study Group and External Collaborators

- **Research Team**
  - Eva Culakova, PhD
  - Marek Poniewierski, MD, MS
  - Nicole Kuderer, MD
- **External Collaborators**
  - Alok Khorana, MD – Cleveland Clinic
  - Charles Francis, MD – U Rochester



*Thank You*



Admissions with VTE			Length of stay		Cost of hospitalization (adjusted for inflations)				
			Days			Total cost (2015 US dollars)		Cost/day (2015 US dollars)	
		N	Mean	Median	N	Mean	Median	Mean	Median
<b>All cancer types</b>	<b>All admissions</b>	<b>170,186</b>	<b>11.5</b>	<b>7</b>	<b>160,008</b>	<b>\$35,510</b>	<b>\$17,828</b>	<b>\$3,062</b>	<b>\$2,580</b>
	POA not reported/unknown	3,164	13.4	8	2,593	\$35,986	\$19,232	\$2,827	\$2,340
	Dx not present on admission	36,360	21.9	16	34,530	\$73,936	\$46,880	\$3,422	\$2,973
	Dx present on admission	130,662	8.6	6	122,885	\$24,702	\$13,796	\$2,966	\$2,483
<b>Solid tumors</b>	<b>All admissions</b>	<b>134,104</b>	<b>10.3</b>	<b>7</b>	<b>125,651</b>	<b>\$30,482</b>	<b>\$16,429</b>	<b>\$3,021</b>	<b>\$2,515</b>
	POA not reported/unknown	2,533	11.9	8	2,052	\$30,155	\$17,719	\$2,834	\$2,308
	Dx not present on admission	26,398	19.6	14	24,988	\$64,165	\$41,244	\$3,397	\$2,909
	Dx present on admission	105,173	8	5	98,611	\$21,953	\$13,041	\$2,930	\$2,430
<b>Lymphoma</b>	<b>All admissions</b>	<b>15,180</b>	<b>13.2</b>	<b>7</b>	<b>14,401</b>	<b>\$43,108</b>	<b>\$20,739</b>	<b>\$3,149</b>	<b>\$2,792</b>
	POA not reported/unknown	280	17.7	12	234	\$47,785	\$28,626	\$2,759	\$2,430
	Dx not present on admission	3,328	24.5	19	3,176	\$85,567	\$56,510	\$3,430	\$3,118
	Dx present on admission	11,572	9.9	6	10,991	\$30,739	\$16,048	\$3,076	\$2,710
<b>Leukemia</b>	<b>All admissions</b>	<b>12,824</b>	<b>20.4</b>	<b>13</b>	<b>12,263</b>	<b>\$72,013</b>	<b>\$38,291</b>	<b>\$3,328</b>	<b>\$2,929</b>
	POA not reported/unknown	192	24.7	16	173	\$83,736	\$41,395	\$2,884	\$2,549
	Dx not present on admission	4,612	32	28	4,432	\$117,544	\$86,884	\$3,559	\$3,190
	Dx present on admission	8,020	13.6	8	7,658	\$45,397	\$20,966	\$3,204	\$2,799
<b>Other</b>	<b>All admissions</b>	<b>8,078</b>	<b>14.3</b>	<b>9</b>	<b>7,693</b>	<b>\$45,218</b>	<b>\$24,380</b>	<b>\$3,139</b>	<b>\$2,726</b>
	POA not reported/unknown	159	16.3	10	134	\$43,027	\$20,638	\$2,753	\$2,297
	Dx not present on admission	2,022	24.2	19	1,934	\$81,141	\$56,804	\$3,423	\$3,043
	Dx present on admission	5,897	10.8	7	5,625	\$32,919	\$17,391	\$3,050	\$2,632