VENOUS THROMBOEMBOLISM AND CANCER: PREDICTION AND PREVENTION

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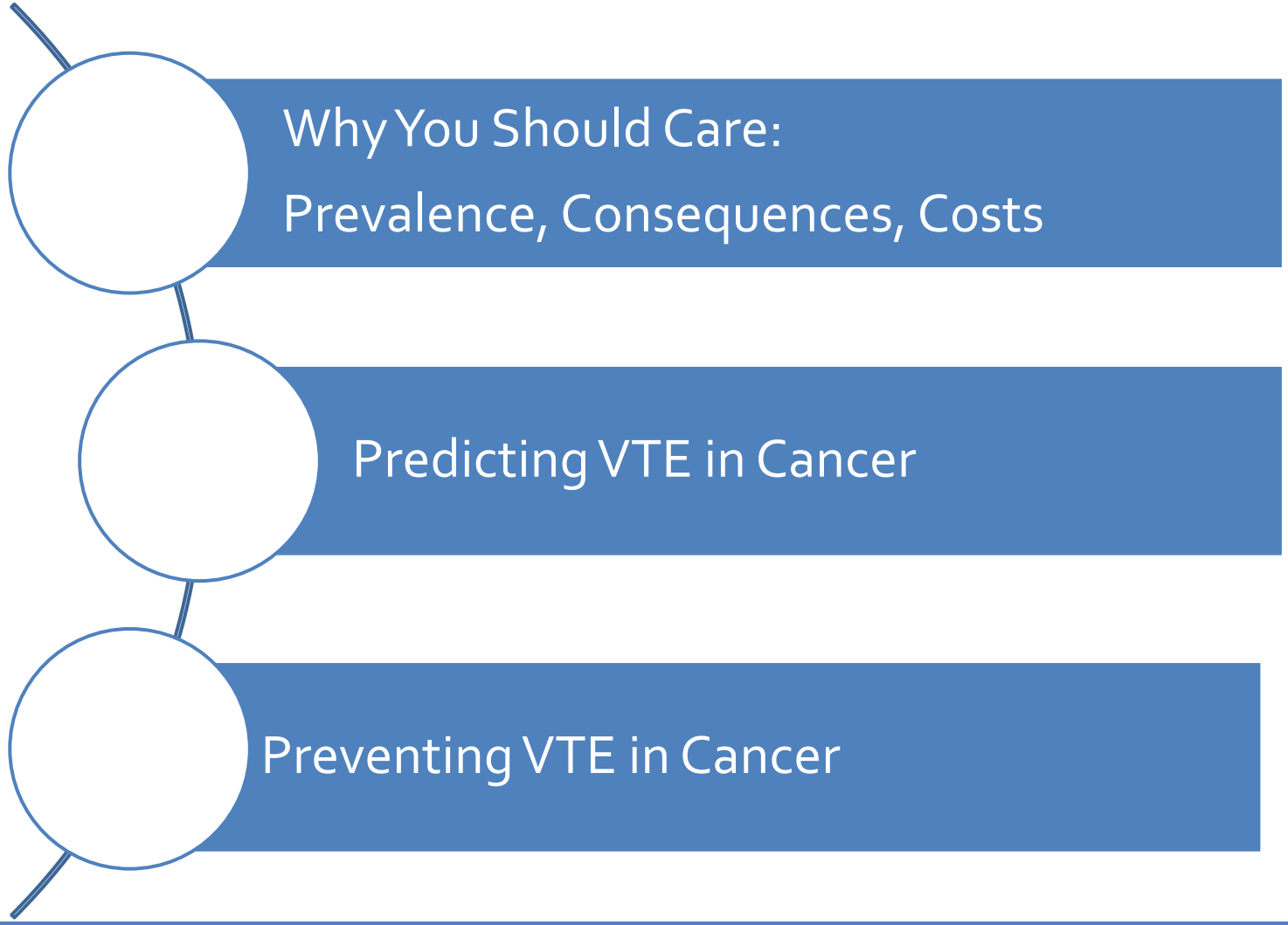
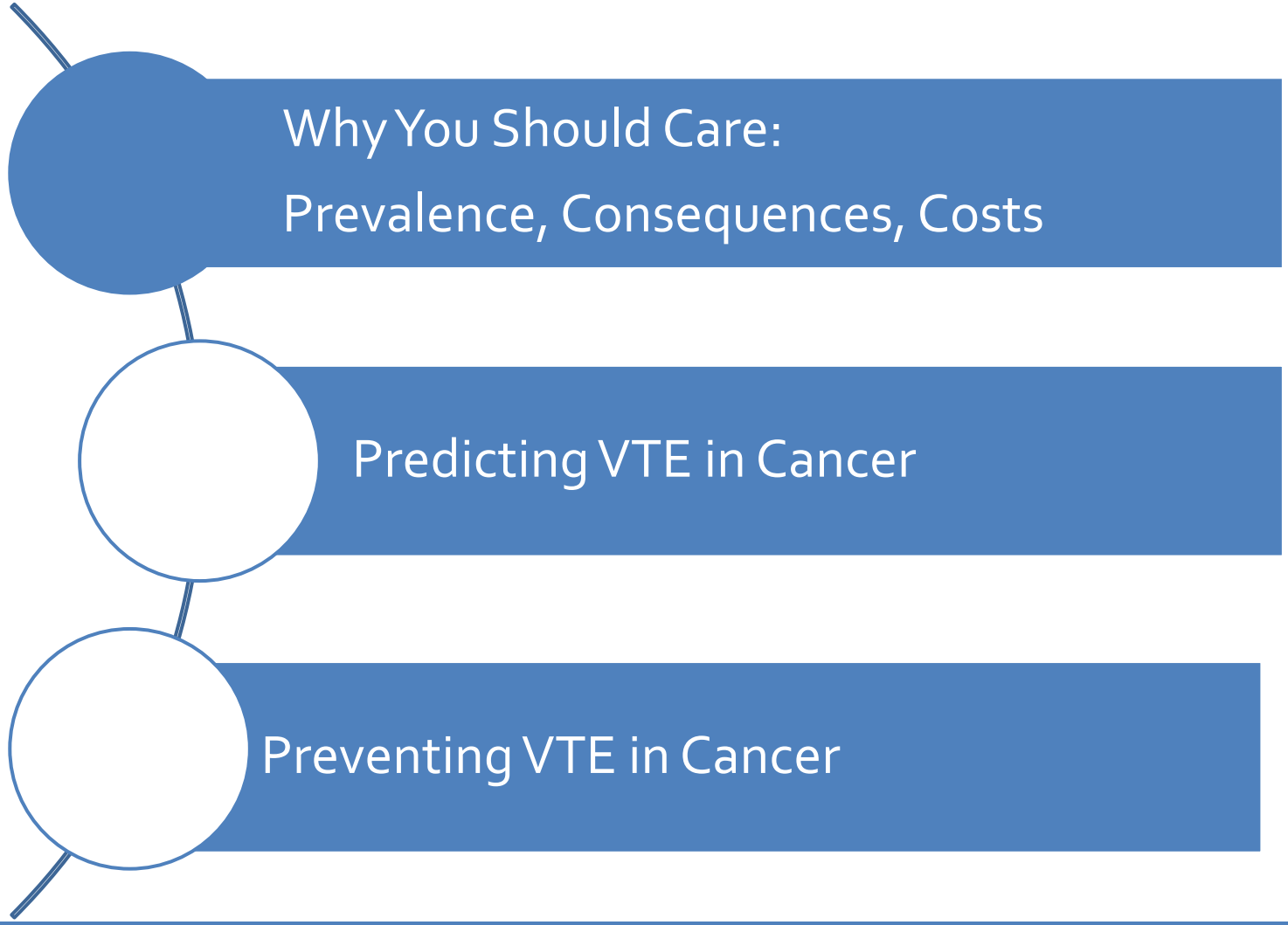
DISCLOSURES

- **Consultant for Sanofi & Leo**


Why You Should Care:
Prevalence, Consequences, Costs
Predicting VTE in Cancer
Preventing VTE in Cancer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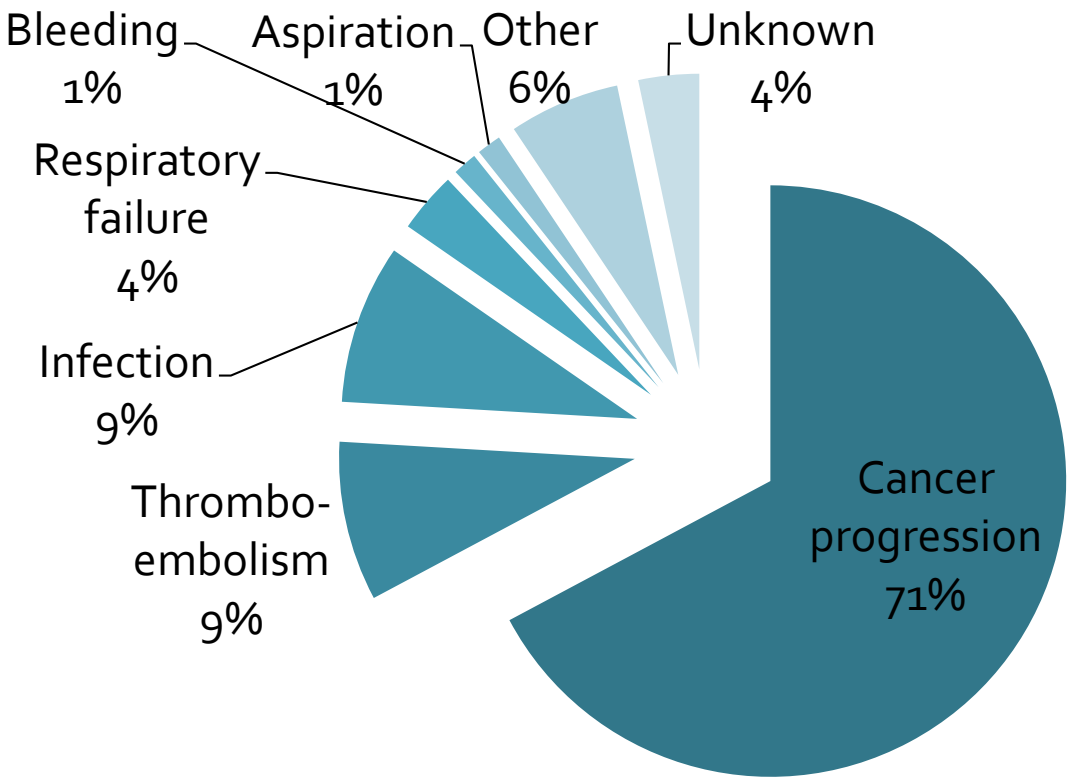
Why You Should Care: VTE AND MORTALITY

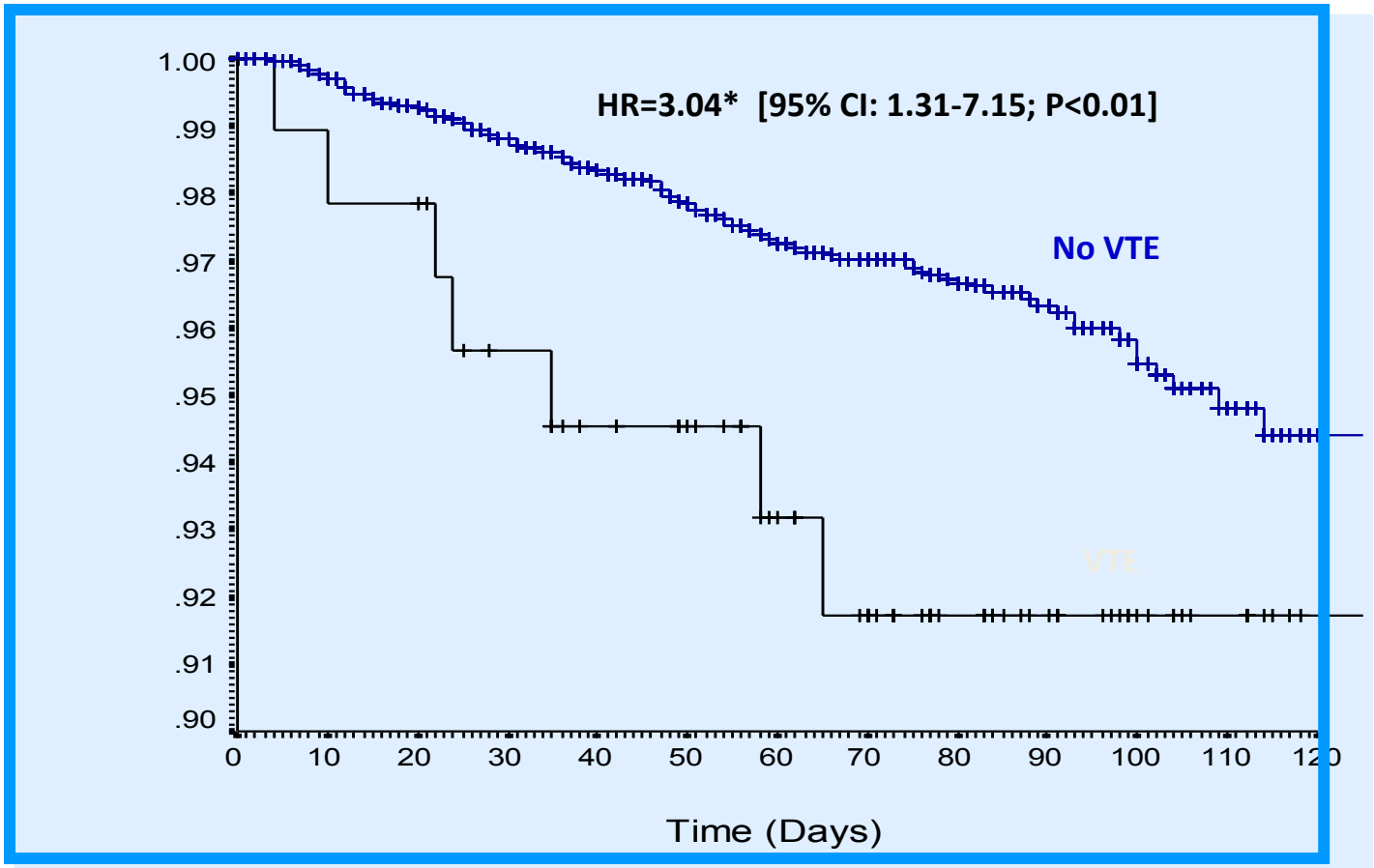


2nd leading cause of death in cancer patients

- Accounts for 9% of deaths [1]
- Associated with early mortality during chemotherapy (HR=6.98)[2]
- 47-fold increased risk of mortality from VTE[1]

1. Khorana AA et al. *J Thromb Haemost* 2007
2. Kuderer NM et al *ASCO* 2008 # 9521

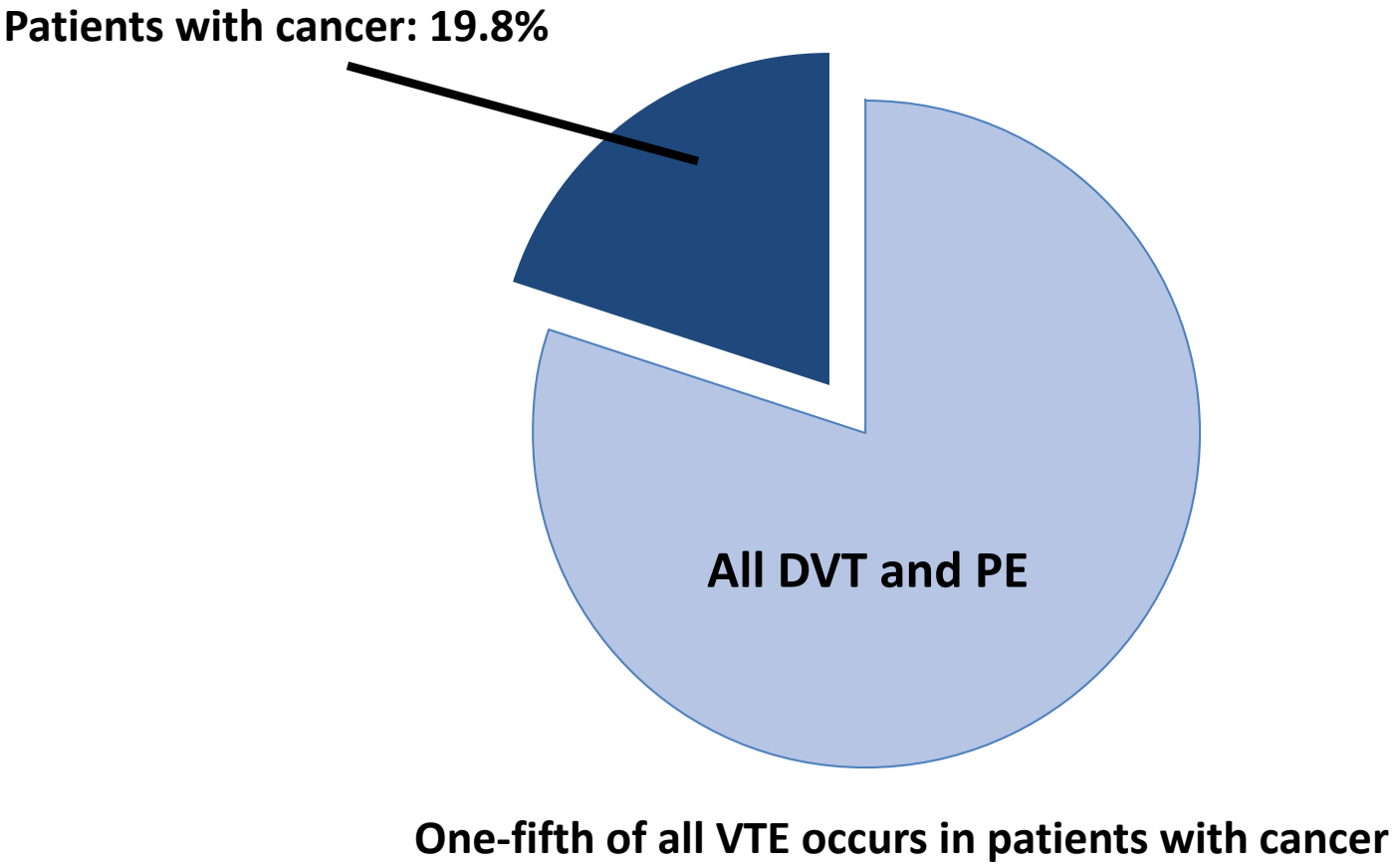
Why You Should Care: VTE and Mortality



Kuderer et al. *ASCO 2009*

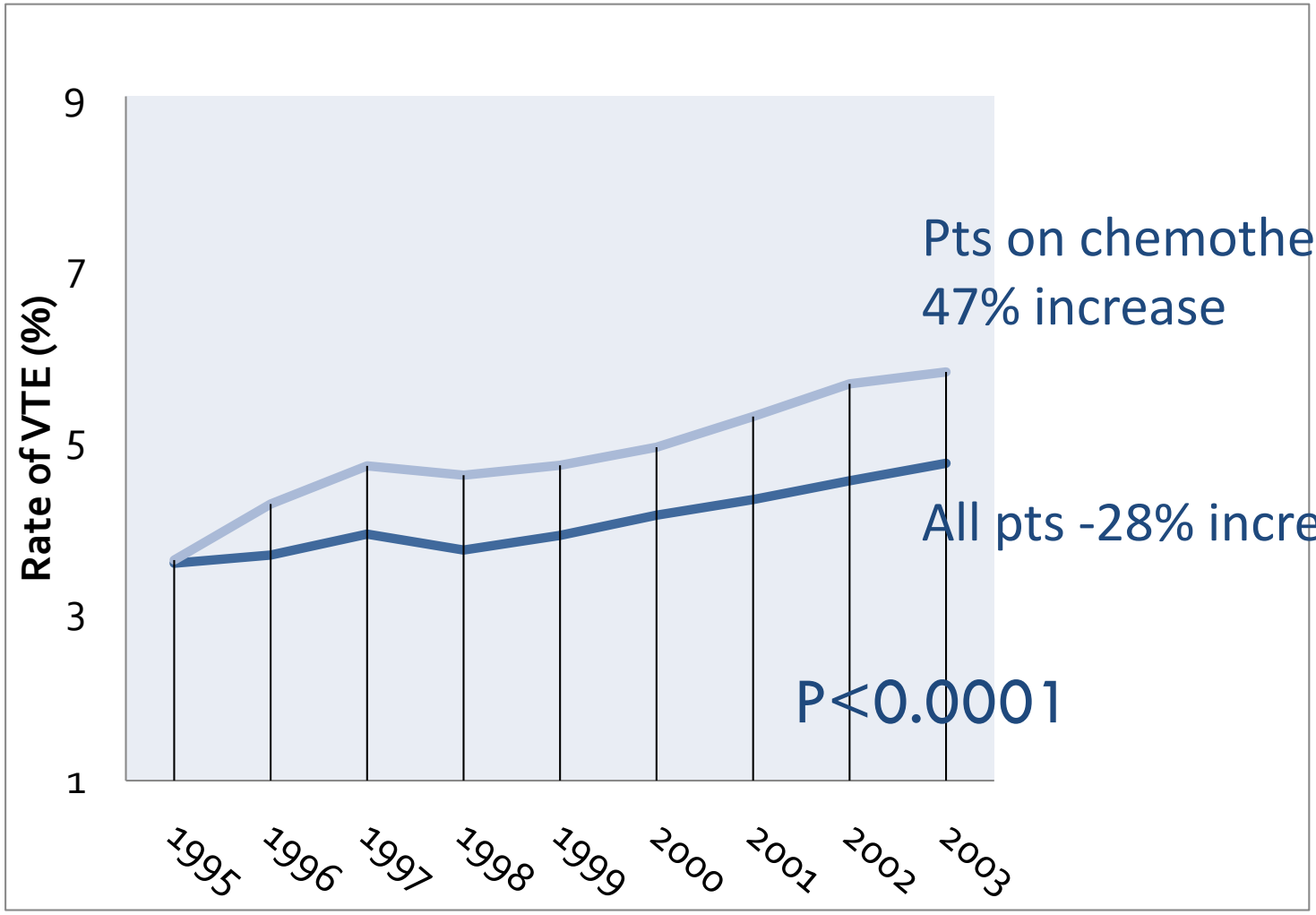
*Adjusted for major confounders: Age, gender, race, cancer type, stage, year of therapy, chemotherapy type and dose intensity, major laboratory abnormalities, PS, BMI, and comorbid conditions

Why You Should Care: VTE and Public Health Burden



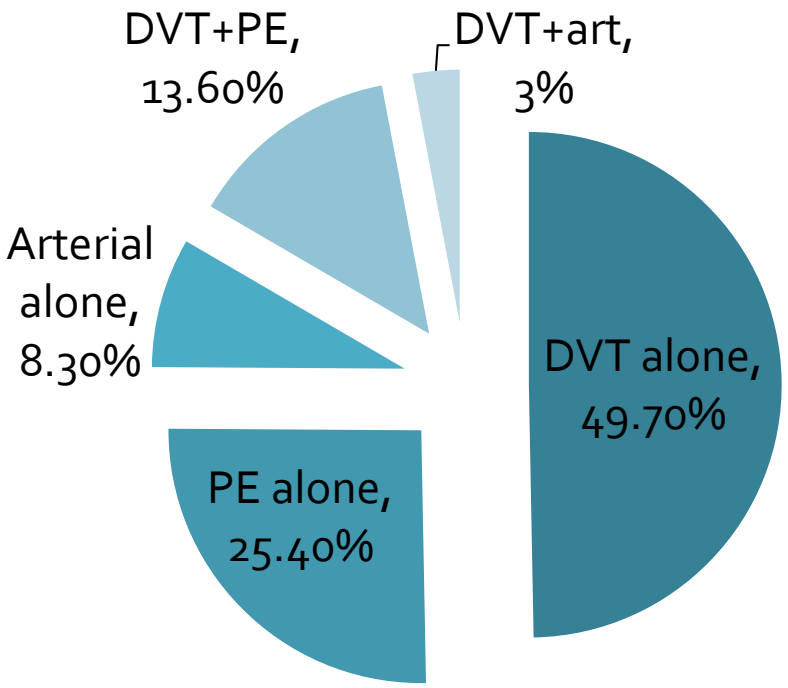
One-fifth of all VTE occurs in patients with cancer

Why You Should Care:
Increasing Frequency of VTE In Malignancy



Khorana AA et al. *Cancer* 2007

MSKCC Retrospective Analysis



- 932 patients receiving cisplatin-based chemotherapy at MSKCC in 2008
- TEE occurred in 18.1%

Moore et al, JCO 2011

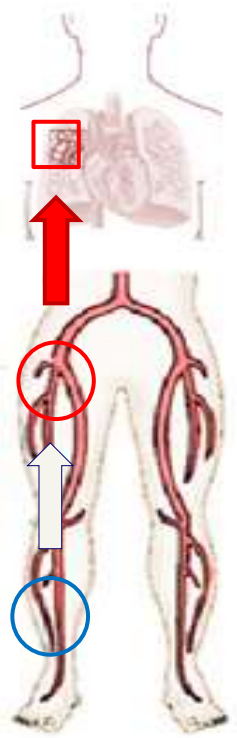
Cancer is *Omni*coagulable

Natural history following major surgery

1/3

1/3

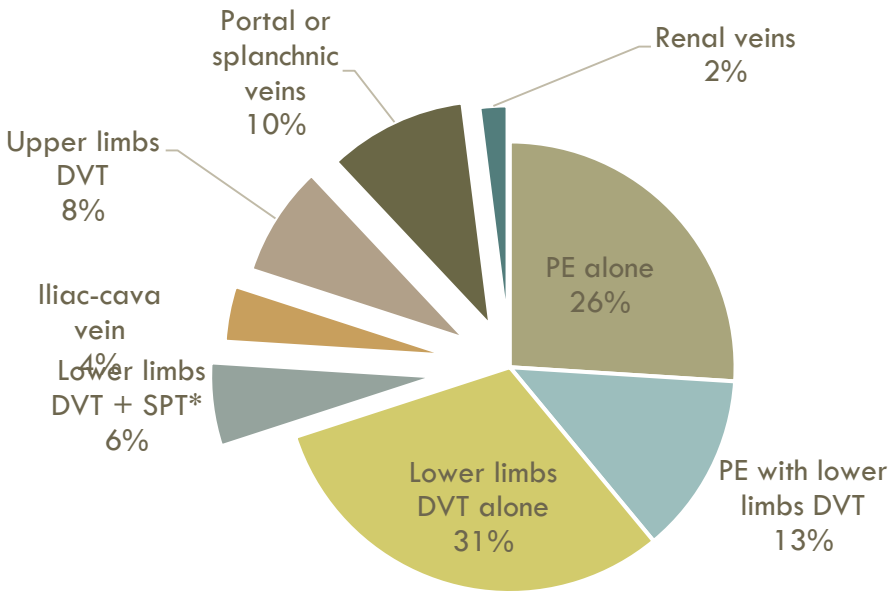
2/3



Kakkar VV et al. Lancet 1969, August 2: 230-33

VTE in cancer with chemotherapy

- Retrospective, single institution cohort study
- N = 1,921 medical records of cancer patients (solid T + chemotherapy)



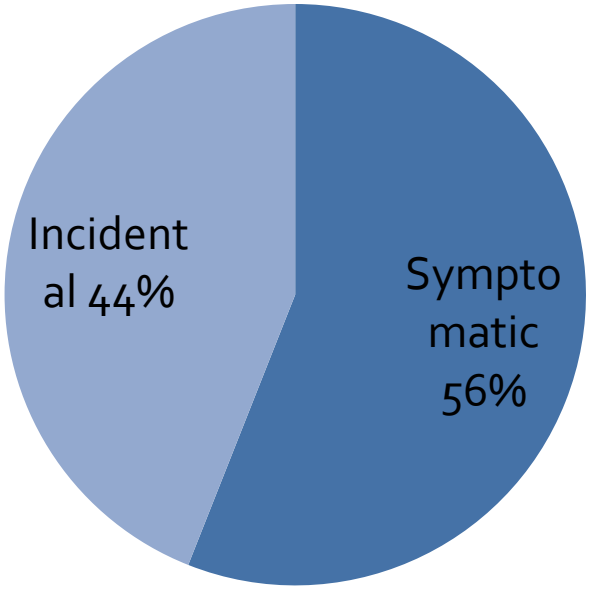
Di Nisio et al. Thromb Haemost. 2010 Nov 3;104(5):1049-54.

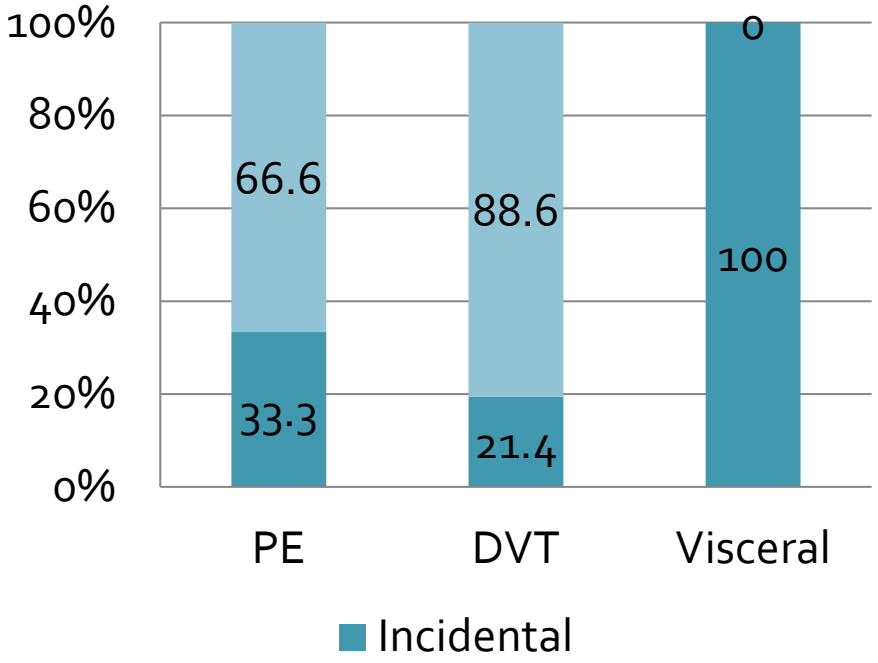
Incidental VTE

- VTE detected on imaging studies conducted for other indications, typically staging[1]
  - PE or DVT
  - Visceral vein thrombosis
- Term "asymptomatic" VTE discouraged; patients often have unrecognized symptoms[2]
- Prevalence varies
  - 1.5-3.4% per scan in outpatient staging
  - 4-9% in hospitalized cancer patients

[1]Khorana AA, et al. *JTH* 2012; [2]O'Connell CL, et al. *J Clin Oncol*. 2006;24:4928-4932

Proportion of Incidental VTE



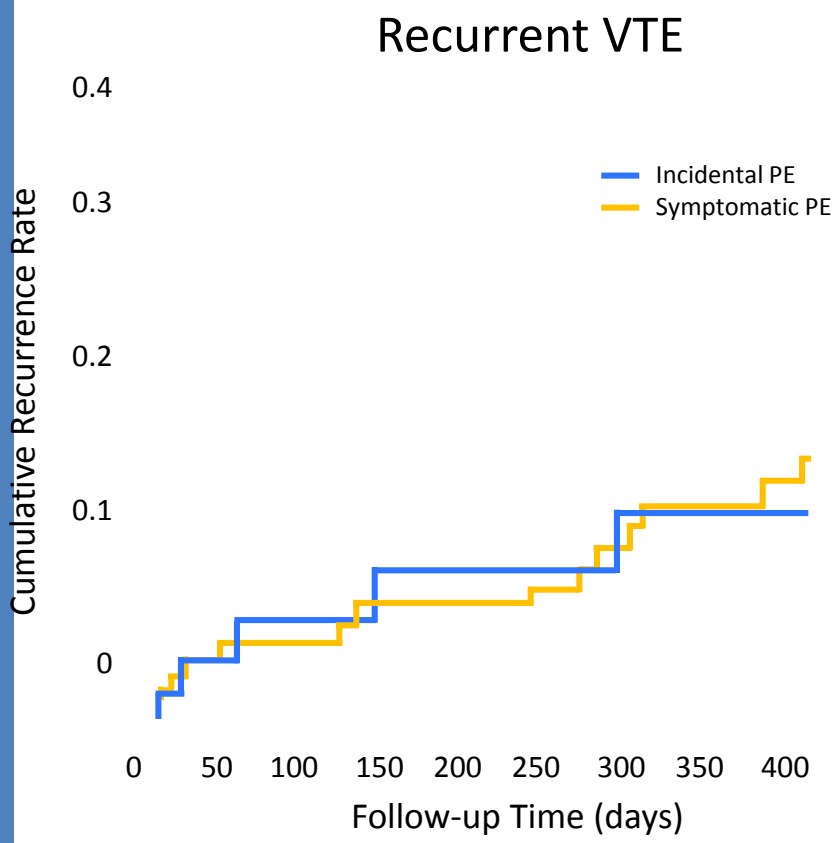


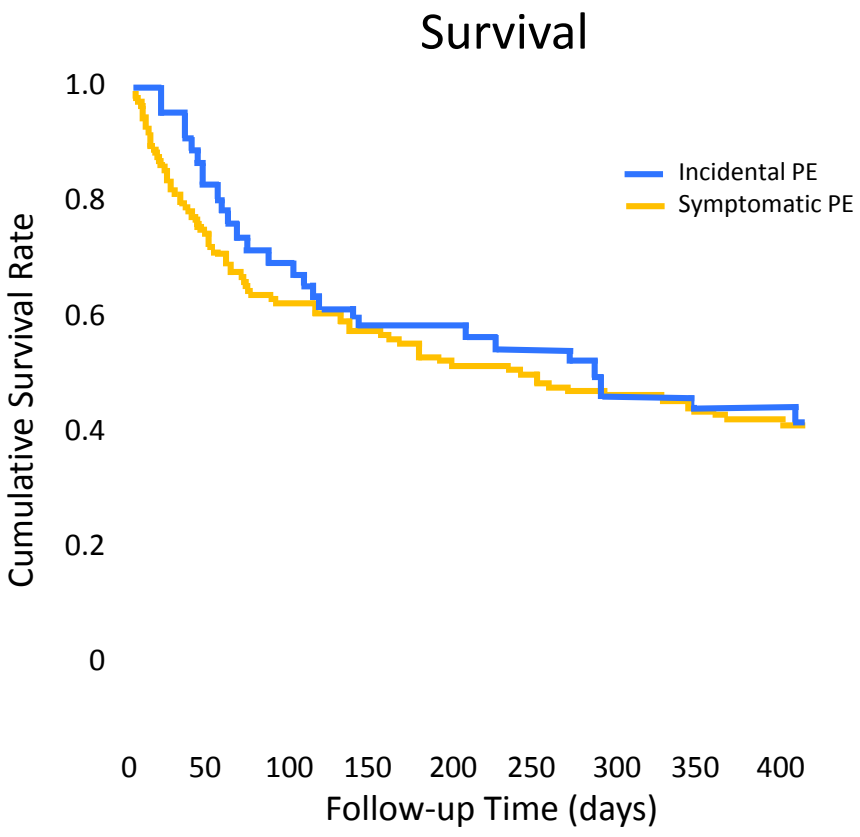
N=932 patients receiving cisplatin-based chemotherapy at MSKCC[1]

N=1,151 scans of 135 pancreatic cancer patients at UR[2]

1. Moore et al, *J Clin Oncol* 2011
2. Menapace et al, *Throm Haem* 2011

Incidental vs Symptomatic PE in Cancer

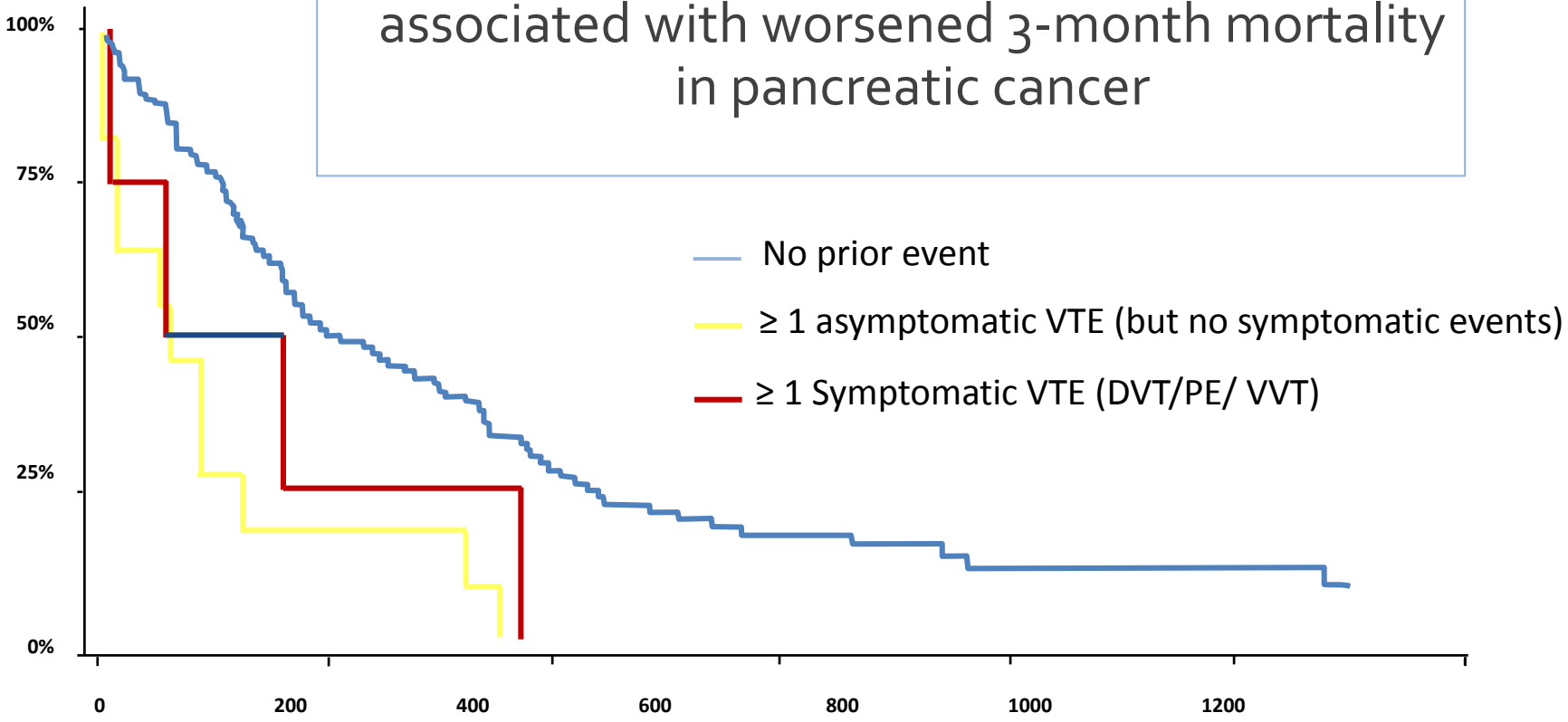




P=0.77 Den Exter PL, et al. *J Clin Oncol* 2011 *P*=0.70

Incidental VTE in Pancreas Cancer

Incidental and symptomatic VTE are both associated with worsened 3-month mortality in pancreatic cancer



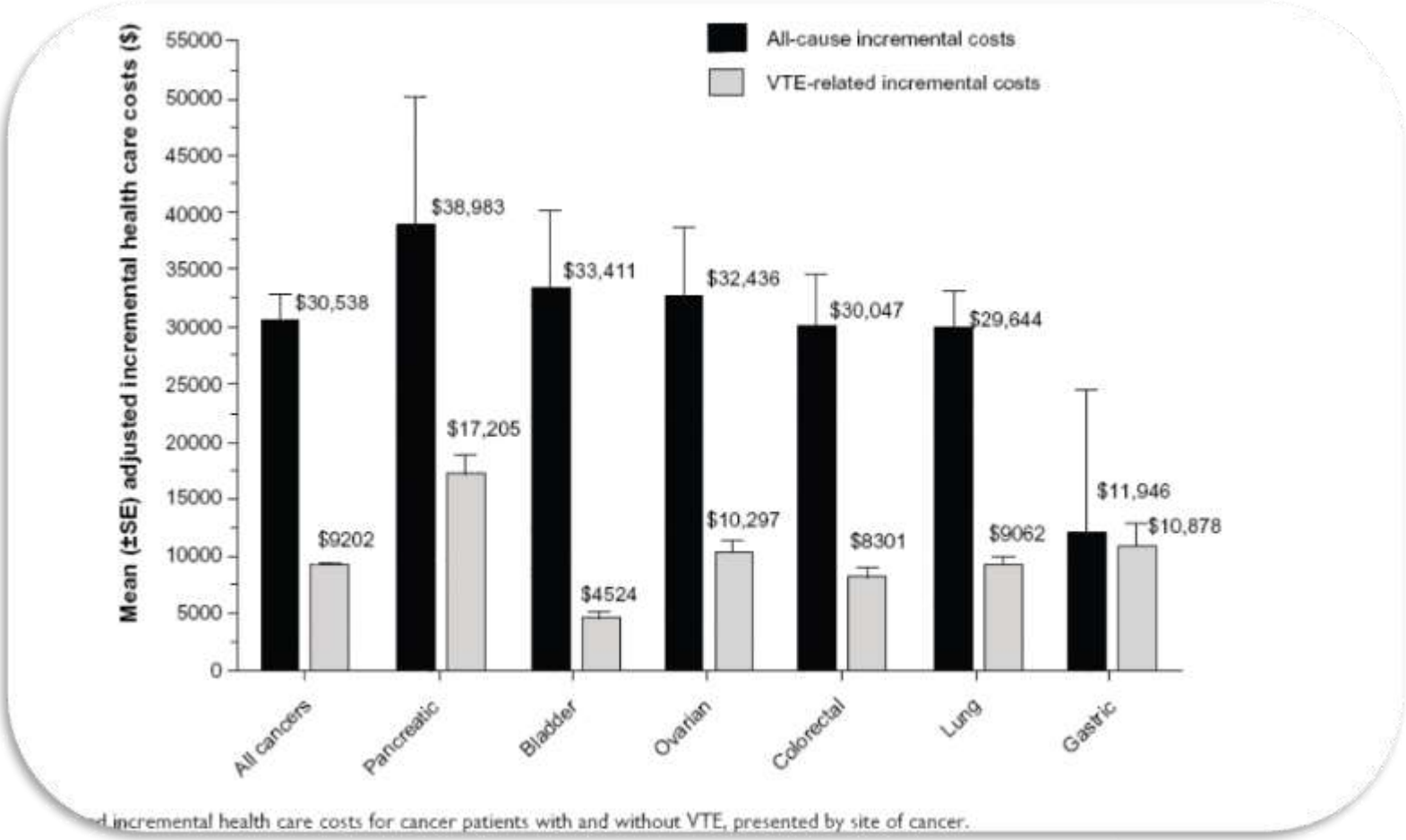
Menapace et al *Throm Haem* 2011

Why You Should Care: Costs

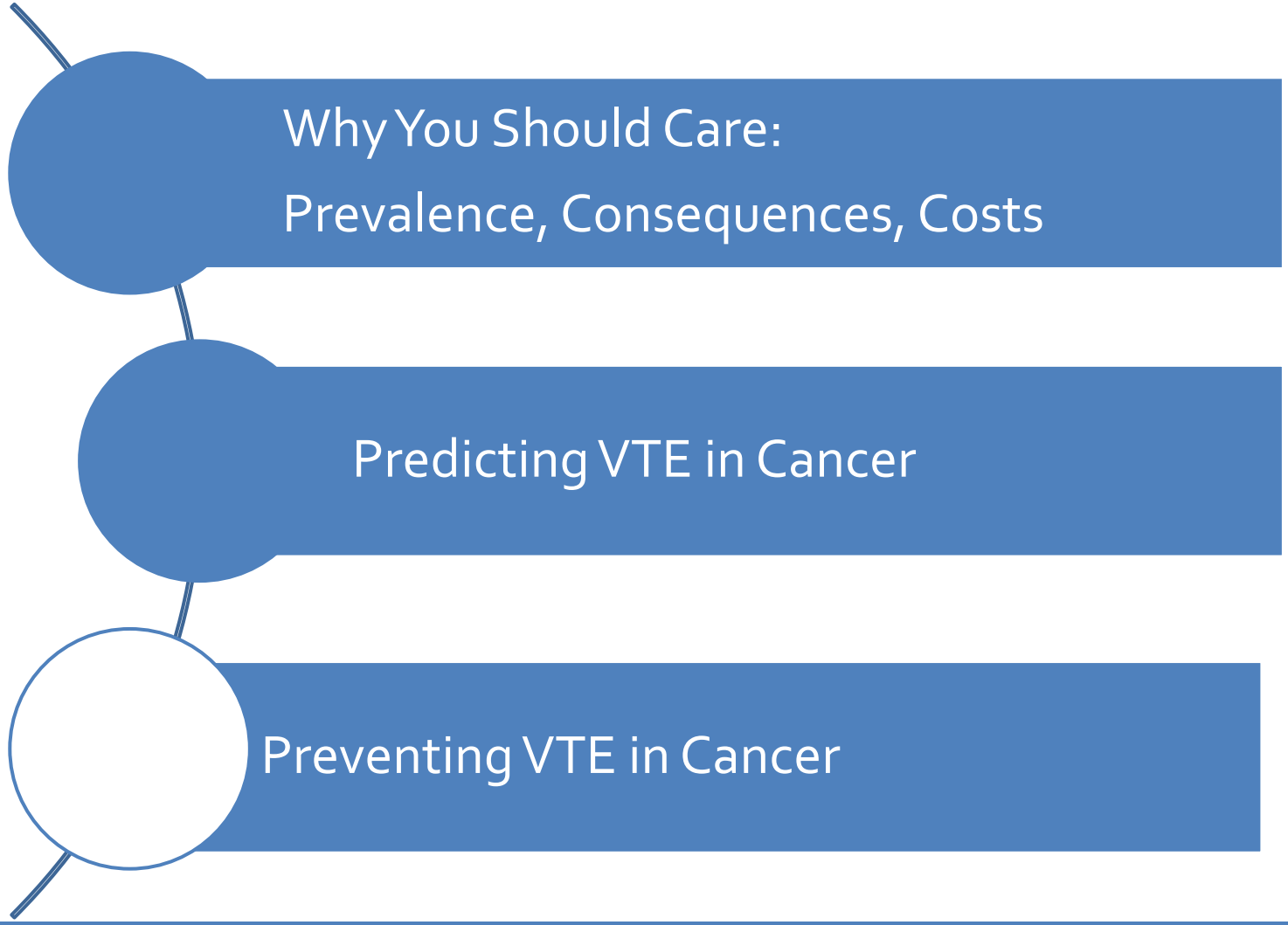
- Cancer patients with VTE had 3 times
  - increase in all-cause hospitalizations (mean 1.38 versus 0.55 per patient)
  - days in hospital (10.19 versus 3.37) (all P < 0.0001).
- Cancer patients with VTE incurred
  - higher overall all-cause inpatient costs (mean $21,299 versus $7459 per patient),
  - outpatient costs ($53,660 versus $34,232 per patient), and
  - total health care costs ($74,959 versus $ 41,691 per patient) (all P < 0.0001).
- **MeanVTE-related costs : $9247 / patient / year**
- **Adjusted mean incremental all-cause costs of VTE : $30,538 /patient**

Khorana et al, *Clin Econ Outcomes Res*; 2013

Why You Should Care: Costs



Khorana et al, *Clin Econ Outcomes Res*; 2013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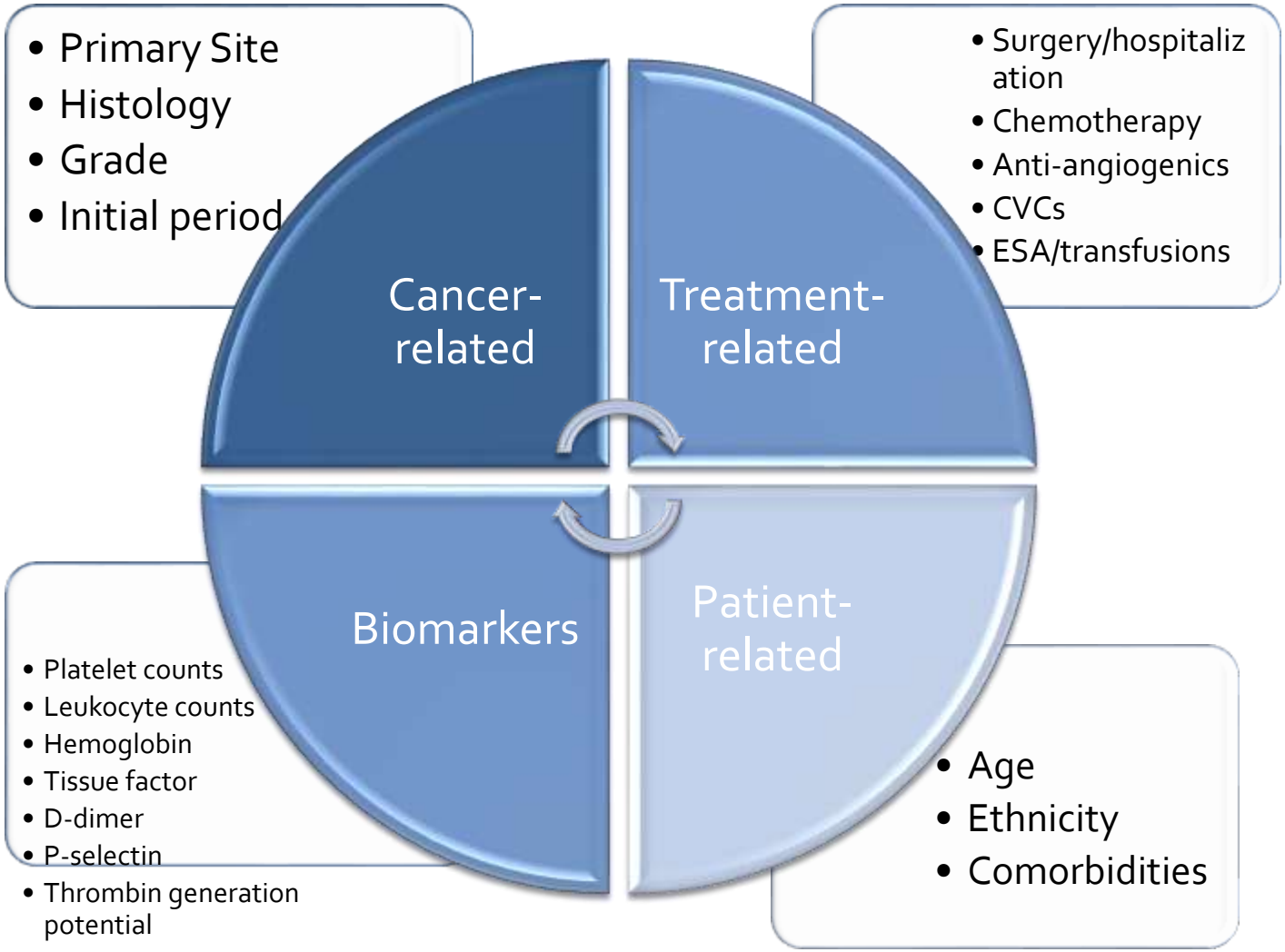
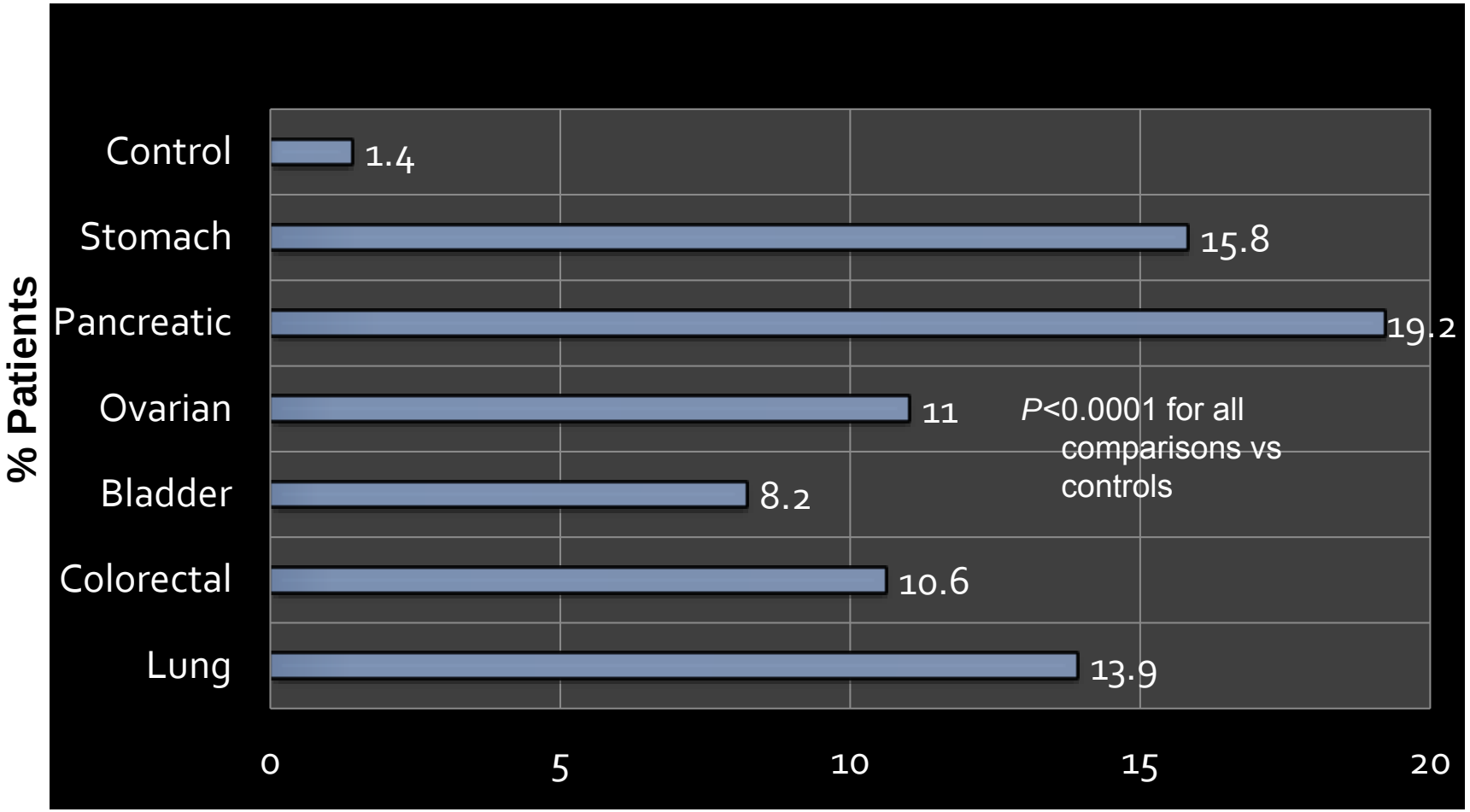
Risk Factors

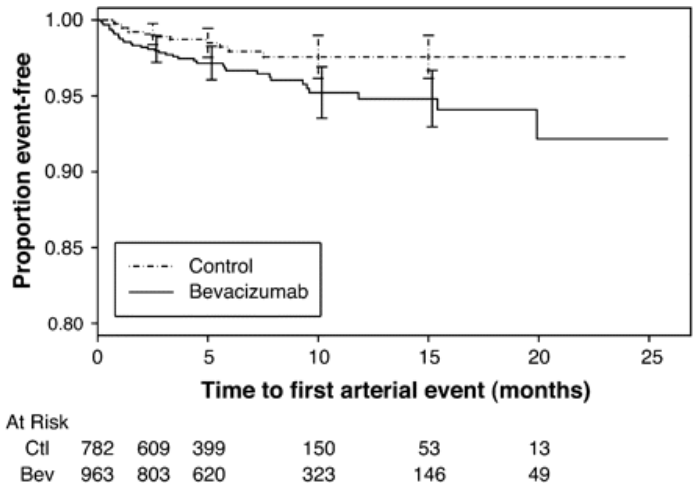


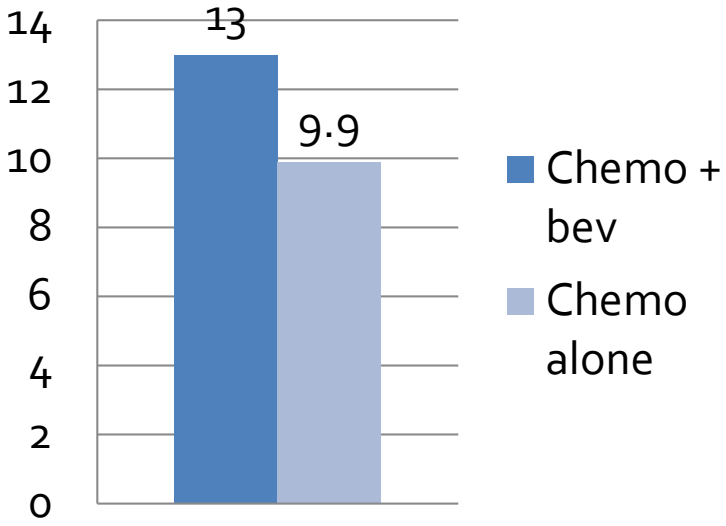
Risk of VTE by Primary Site



Khorana AA et al, *Cancer* 2012

Risk with Bevacizumab





- 2-fold increased risk of arterial events[1]
- Possible increased risk of VTE [RR=1.29 (95% CI, 1.03-1.63)][2]
- Not significant if adjusted for exposure time [RR 1.10 (95% CI, 0.89-1.36)][3]
- Not seen in a newer pooled analysis (OR 1.14; 95% CI, 0.96 to 1.35; P = .13)[4]

[1]Scappaticci et al *JNCI* 2007;99(16):1232-9; [2] Nalluri SR, et al. *JAMA*. 2008;300:2277-2285; [3]Chu & Wu *JAMA*. 2009;301(14):1434-1436; [4]Hurwitz et al *JCO* 29(13):1757-6

Risk with Other Anti-Angiogenic Agents

- Sunitinib and sorafenib are associated with risk of arterial events [RR 3.03 (95% CI, 1.25 to 7.37; P=.015)][1]
- VEGFR-TKIs (pazopanib, sunitinib, sorafenib and vandetanib) are not associated with VTE(RR=0.912, 95%CI: 0.617-1.348, p = 0.643)[2]
- Risk of VTE with thalidomide- and lenalidomide-based regimens is well-known[3]

1.Choueiri et al *JCO* 2010; 28:2280-2285

2. Qi, et al. *Int J Ca.* 2013; 132(12):2967-7

3. Carrier et al J *Thromb Haemost*. 20119(4):653-63

Risk with Other Targeted Therapies

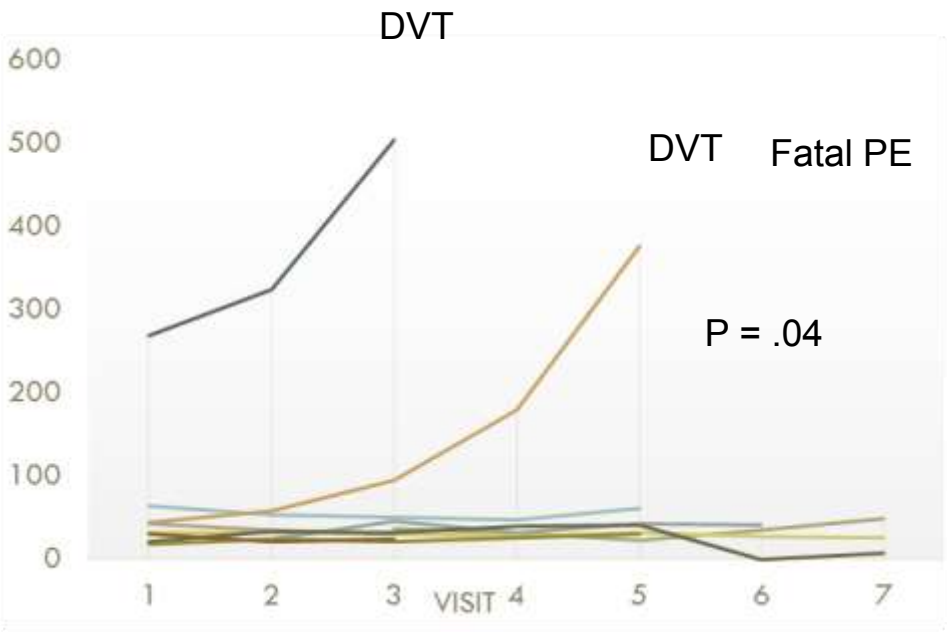
- Anti-EGFR agents are associated with risk of VTE
  - RR 1.32 (95% CI 1.07–1.63; *P* = 0.01)
  - Risk primarily with antibodies (RR 1.34; P = 0.01) rather than oral TKIs (RR 1.16; P = 0.65)

Petrelli et al *Ann Onc* 2012 Jul;23(7):1672-9

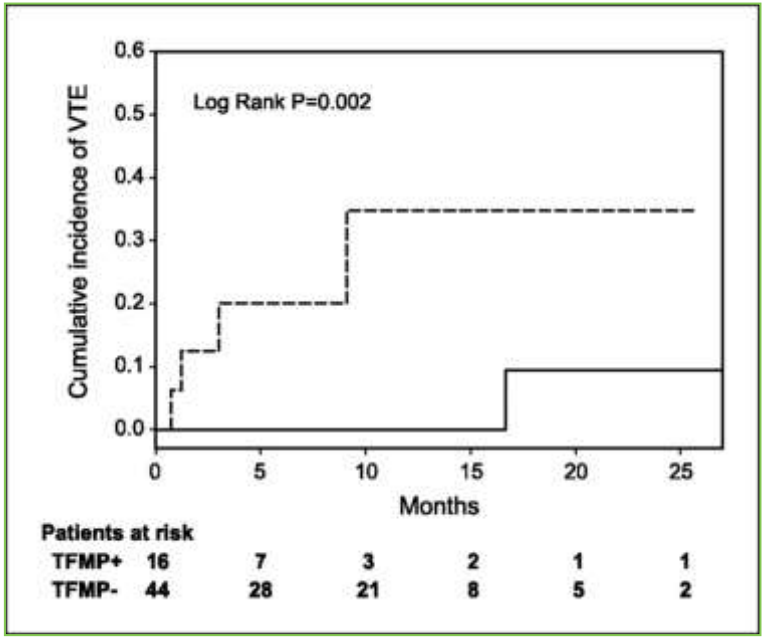
Biomarkers

- Leukocyte count
- Platelet count
- Hemoglobin
- Tissue factor
- D-dimer
- Factor VIII

TF and VTE

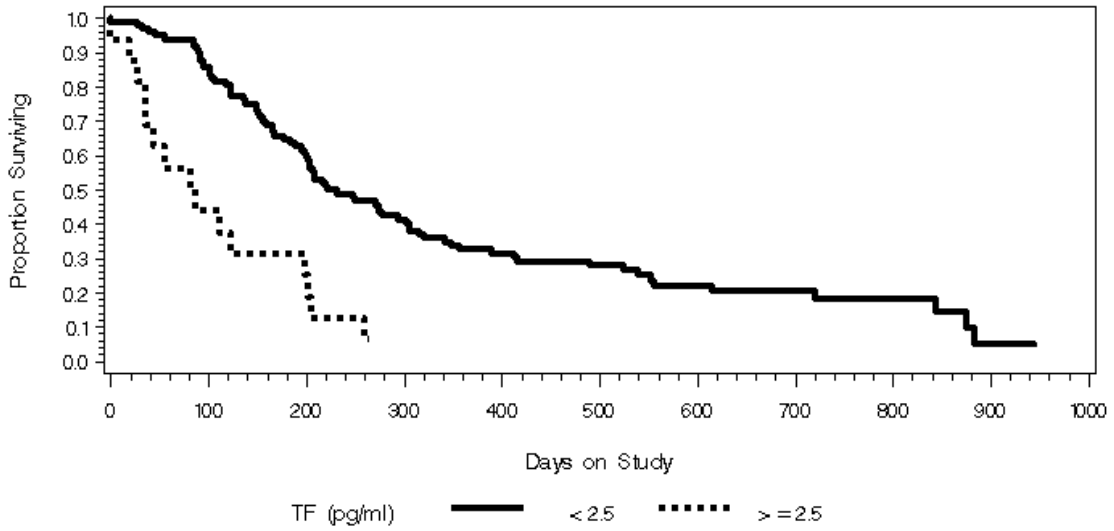


Systemic TF by ELISA[1]



Systemic TF-MPs by flow cytometry[2]

TF In Pancreatic & biliary Cancers



Median Survival in 117 pts with TF MP-PCA >2.5 and </=2.5pg/ml.

- Elevated TF was significantly associated with TE in a logistic regression analysis, (OR = 1.22, p = 0.04)
- Elevated TF was also associated with overall survival (HR = 1.05, p = 0.01)
- Median survival was **98.5 days** vs. **231 days** for high vs low TF (p< 0.0001)
- Correlated with D-dimer and leukocyte count

TF and VTE: Not So Fast

Journal of Thrombosis and Haemostasis, 10: 1363–1370 DOI: 10.1111/j.1538-7836.2012.04754.x

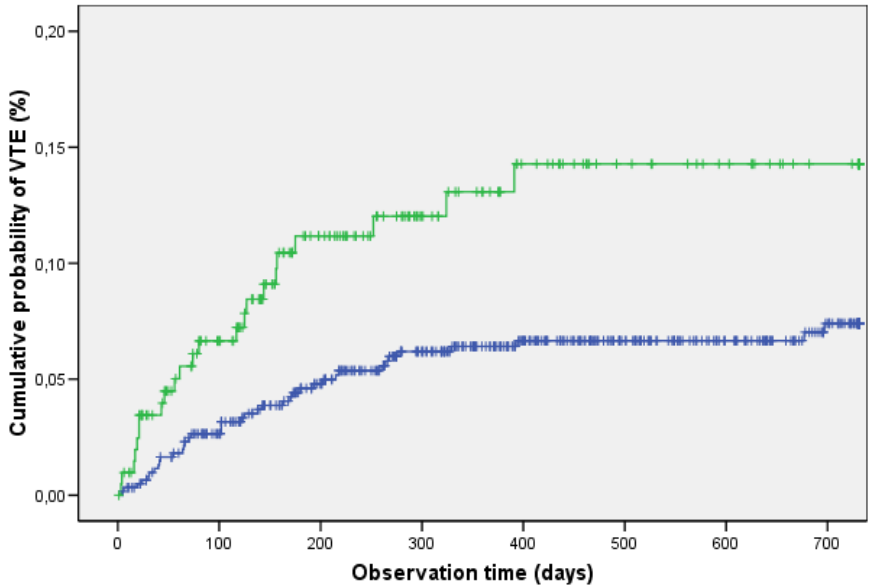
ORIGINAL ARTICLE

Microparticle-associated tissue factor activity, venous thromboembolism and mortality in pancreatic, gastric, colorectal and brain cancer patients

J. THALER,*†[1] C. AY,*†[1] N. MACKMAN,‡ R. M. BERTINA,§ A. KAIDER,¶ C. MAROSI,**† N. S. KEY,‡ D. A. BARCEL,‡ W. SCHEITHAUER,**† G. KORNEK,**† C. ZIELINSKI**† and I. PABINGER*†

- N= 348
- MP-TF activity was *not* associated with future VTE
- MP-TF activity was associated with mortality in pancreatic cancer
- MP-TF activity correlated with D-dimer in pancreatic cancer

D-dimer and VTE



Elevated D-dimer (>75th percentile, 1.44µg/mL); **HR 2.2** (95% CI: 1.3 - 3.6), p=0.003

- No consensus on cut-off levels
- Widely available
- Potential to discriminate intermediate-risk patients
- Poor person's TF?

Risk Assessment
ASCO 2013 Guideline Update

"Individual risk factors, including biomarkers or cancer site, do not reliably identify cancer patients at high risk for VTE"

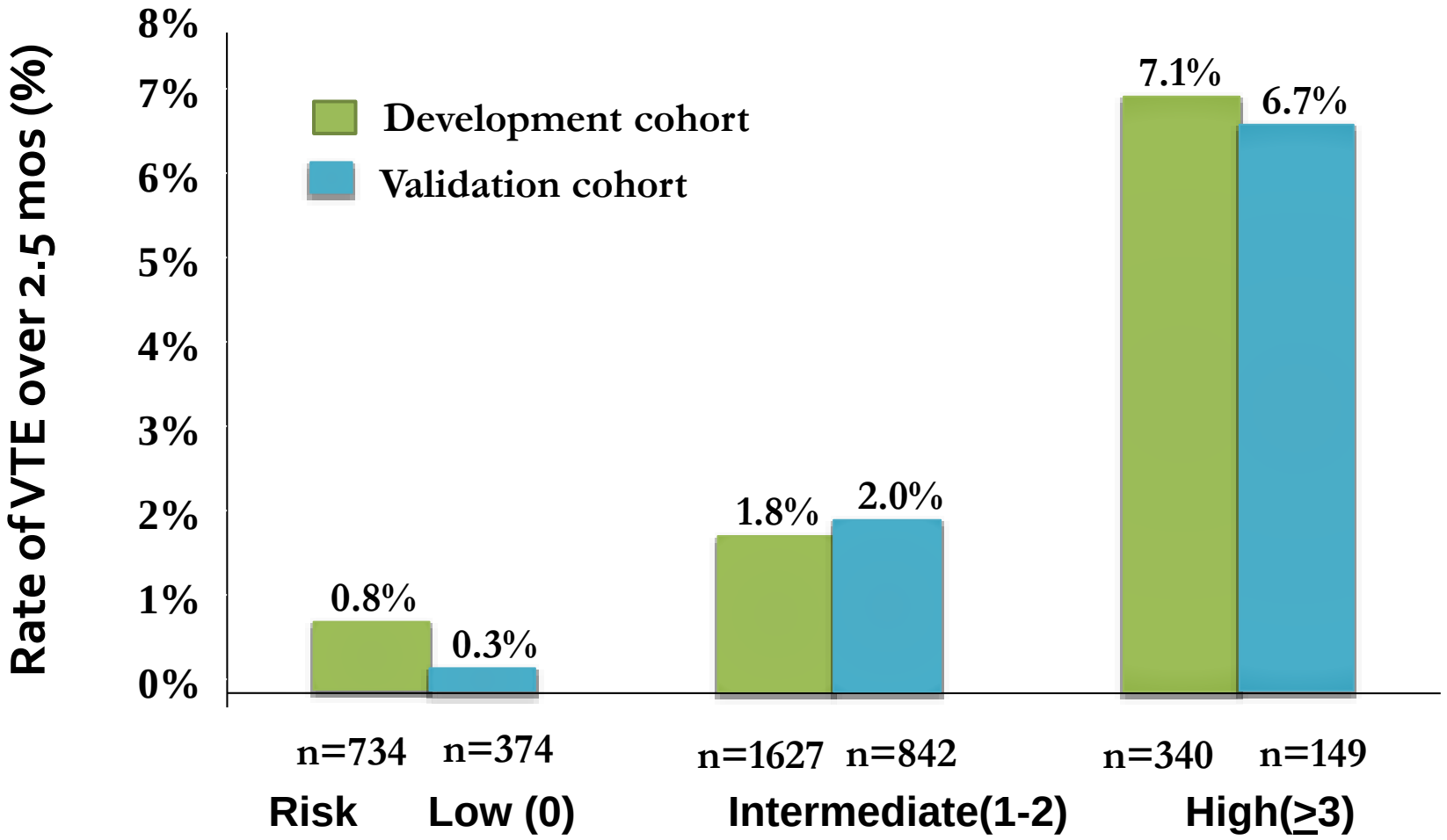
Lyman GH, et al. *J Clin Onc* 2013

Risk Score

Patient Characteristic	Score
Site of Cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, GU excluding prostate)	1
Platelet count $\geq$ 350,000/mm^3	1
Hb < 10g/dL or use of ESA	1
Leukocyte count > 11,000/mm^3	1
BMI $\geq$ 35 kg/m^2	1

Khorana AA et al. *Blood* 2008

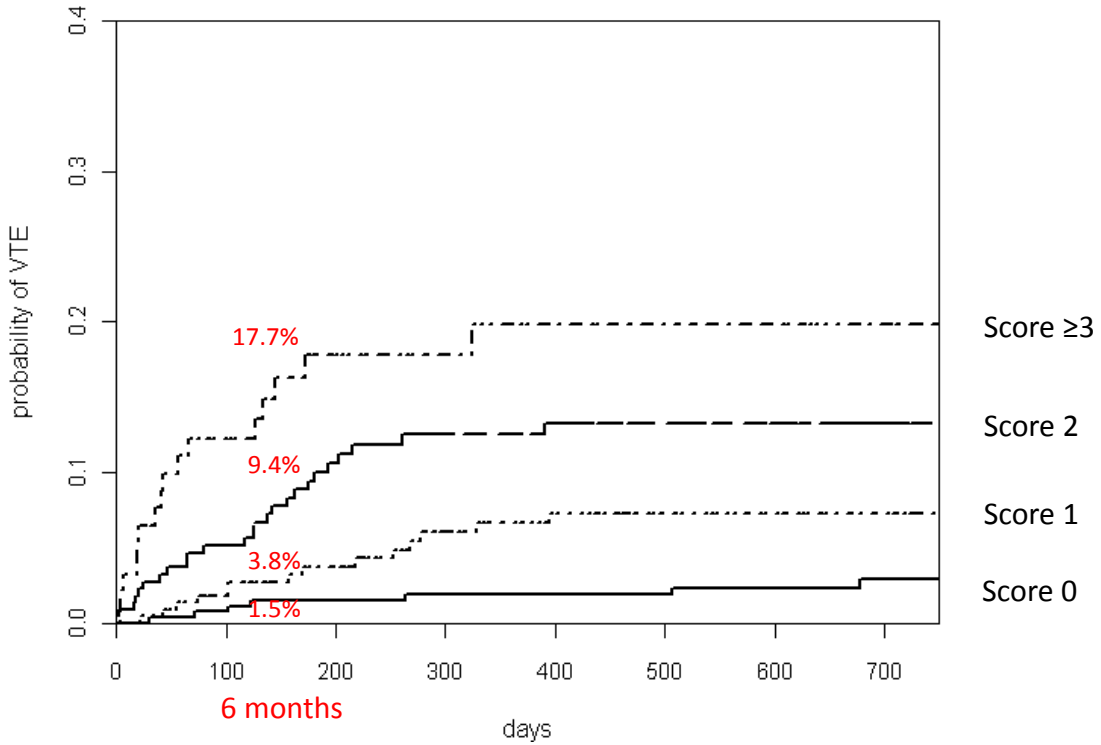
Risk Model Validation



Khorana AA et al. *Blood* 2008

Vienna CATS validation

- Full data available in 839 patients
- Median observation time/follow-up: 643 days



	Number of	
	Patients	Events
	n	n (%)
Score ≥3	96	16 (17%)
Score 2	231	25 (11%)
Score 1	233	14 (6%)
Score 0	279	7 (3%)

Ay et al *Blood* 2011

External Validation of Risk Score

Table 5. Multivariate Analysis of Baseline and Treatment Variables

Variable	Odds Ratio	95% CI	Adjusted *P*
Sex			.15
Male	1		
Female	1.31	0.91 to 1.88	
Age (per 10-year increase)	1.19	1.02 to 1.39	.03
Race/ethnicity			.51
White	1		
Asian	0.87	0.41 to 1.85	
African American	1.43	0.74 to 2.76	
KPS (per 10-unit increase)	0.92	0.86 to 0.98	.02
Central venous catheter/pacemaker	1.61	1.10 to 2.36	.01
Stage			.57
Early	1		
Locally advanced	0.84	0.41 to 1.72	
Metastatic	1.03	0.50 to 2.13	
Khorana risk group			.04
Low	1		
Intermediate	1.33	0.81 to 2.16	
High	2.06	1.16 to 3.65	

Abbreviation: KPS, Karnofsky performance status.

Table 4. Venous thromboembolism according to age, time from first tumor diagnosis, Khorana score and the use of antiangiogenic agents: multivariate analysis

Covariates	Chi-square	*P*-value	HR (95% CI)
Age	2.3749	0.1233	1.019 (0.995–1.044)
Time from first tumor diagnosis (years)	2.1908	0.1388	0.921 (0.825–1.027)
Khorana score			
High (≥3)	15.9257	<0.0001	7.876 (2.858–21.704)
Intermediate (1–2)	6.6582	0.0099	2.747 (1.275–5.919)
Low (0)	—	—	1*
Antiangiogenic with cytotoxic			
Yes	1.6730	0.1959	1.617 (0.781–3.352)
No	—	—	1*

*Reference class.

[1]Moore et al, *J Clin Oncol* 2011
[2]Mandala et al, *Ann Onc* 2012

Evaluation of Risk Score

N=10, 694

Study	Type, duration	N	Low-risk (score = 0)	Intermediate-risk (score = 1-2)	High-risk (score ≥3)
Khorana et al, 2008	Development cohort, 2.5 months	2701	0.8%	1.8%	7.1%
Khorana et al, 2008	Validation cohort, 2.5 months	1365	0.3%	2%	6.7%
Kearney et al, 2009	Retrospective, 2 years	112	5%	15.9%	41.4%
Price et al, 2010	Retrospective, pancreatic, NA	108	- *	14%	27%
Ay et al, 2010	Prospective, 643 days	819	1.5%	9.6% (score= 2) 3.8% (score=1)	17.7%
Khorana et al, 2010	Prospective**, 3 months	30	- ***	-	27%
Moore et al, 2011	Retrospective, cisplatin-based chemo only	932	13%	17.1%	28.2%
Mandala et al, 2012	Retrospective, phase I patients only, 2 months	1415	1.5%	4.8%	12.9%

NA=not available; *=pancreatic cancer patients assigned a score of 2 based on site of cancer and therefore no patients in the low-risk category; **included 4-weekly screening ultrasonography; ***enrolled only high-risk patients

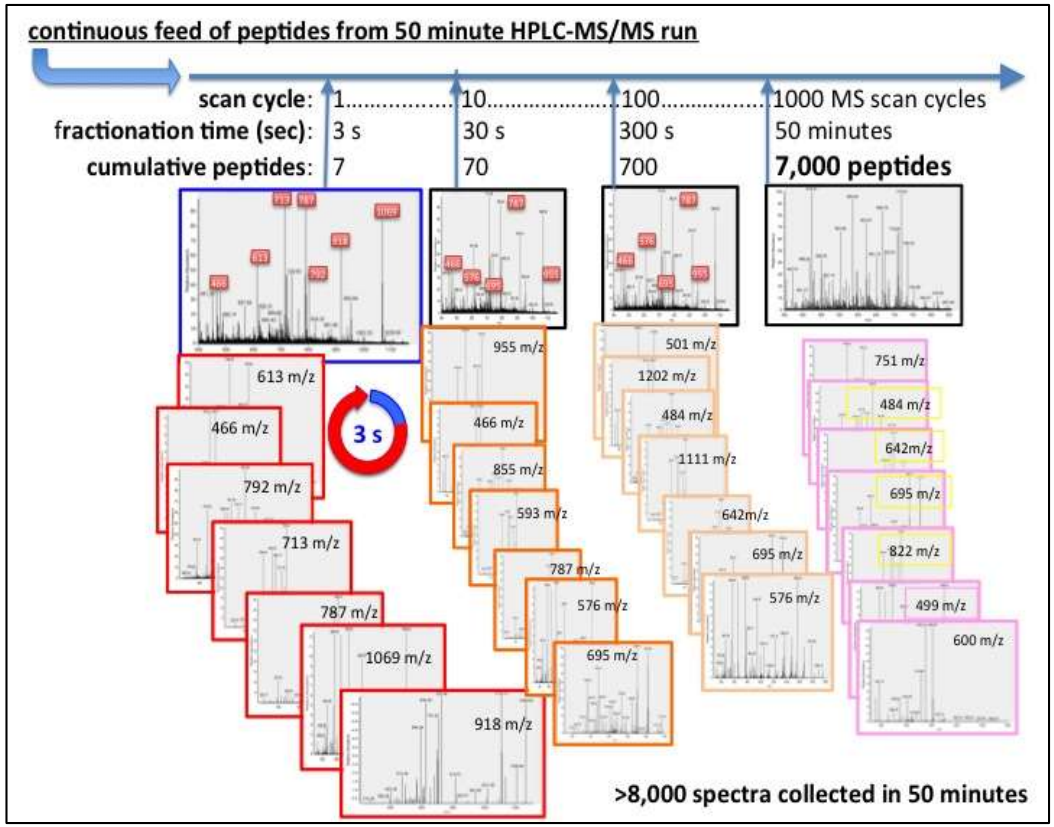
Risk Assessment: The Present
ASCO 2013 New Recommendation

Q6. VTE Risk Assessment

6.1 Based on consensus, the Panel recommends that cancer patients should be assessed for VTE risk at the time of chemotherapy initiation and periodically thereafter. Individual risk factors, including biomarkers or cancer site, do not reliably identify cancer patients at high risk of VTE. In the outpatient setting, risk assessment can be conducted based on a validated risk assessment tool.

Lyman GH, et al. *J Clin Onc* 2013

Risk Assessment: The Future
High coverage LC-MS/MS



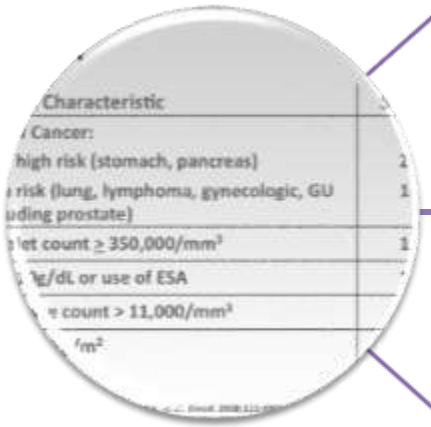
- >50637 spectra
- 2145 unique peptides
- 149 proteins
- 116 protein groups
- Differential expression
  - 9 proteins p <0.05
  - 23 proteins p<0.10

Match criteria: 3 peptide minimum and 95% probability of match

Connolly et al, ISTH 2013

Applying Risk Assessment

Risk Score

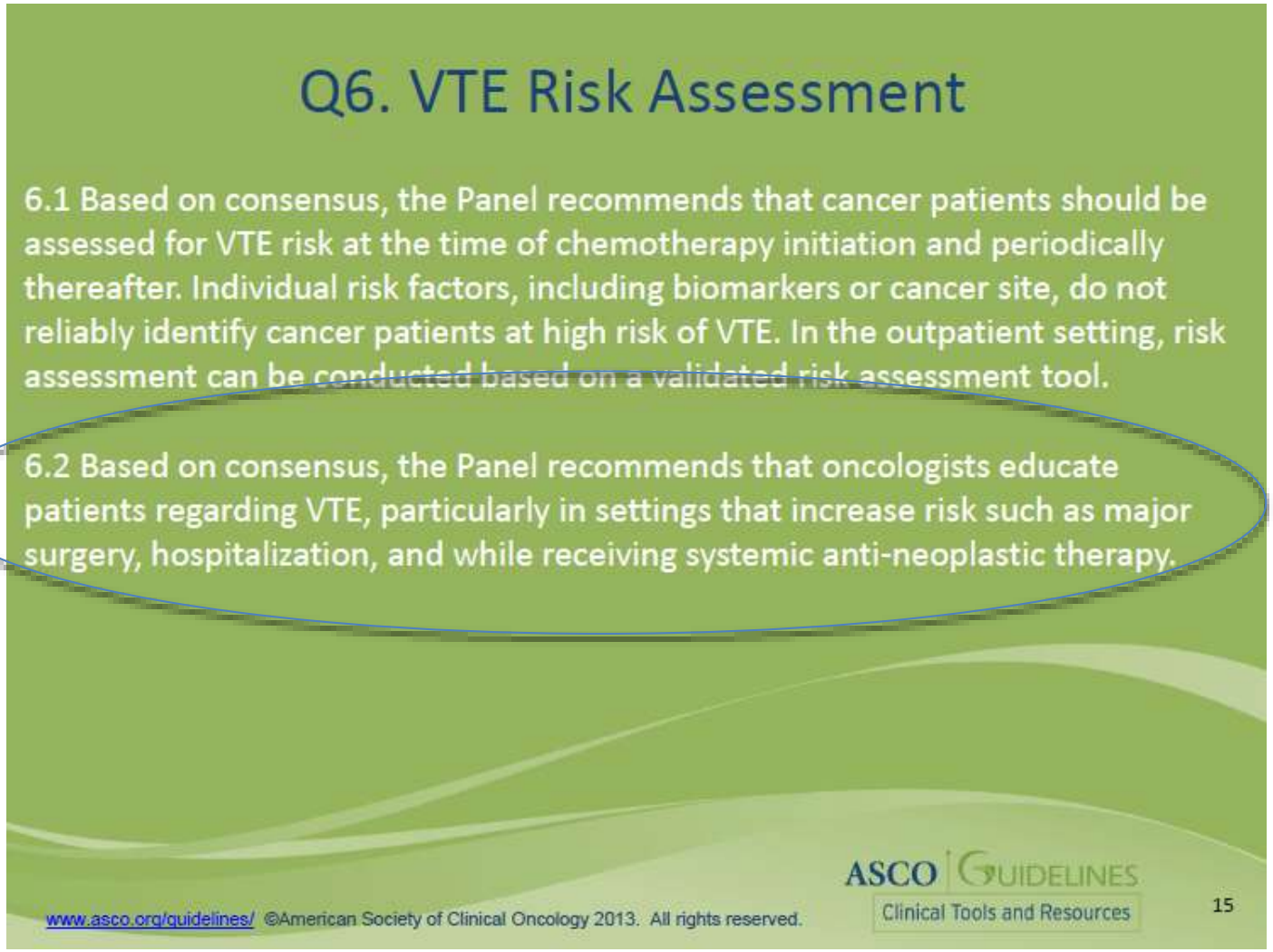


Patient Awareness and Education

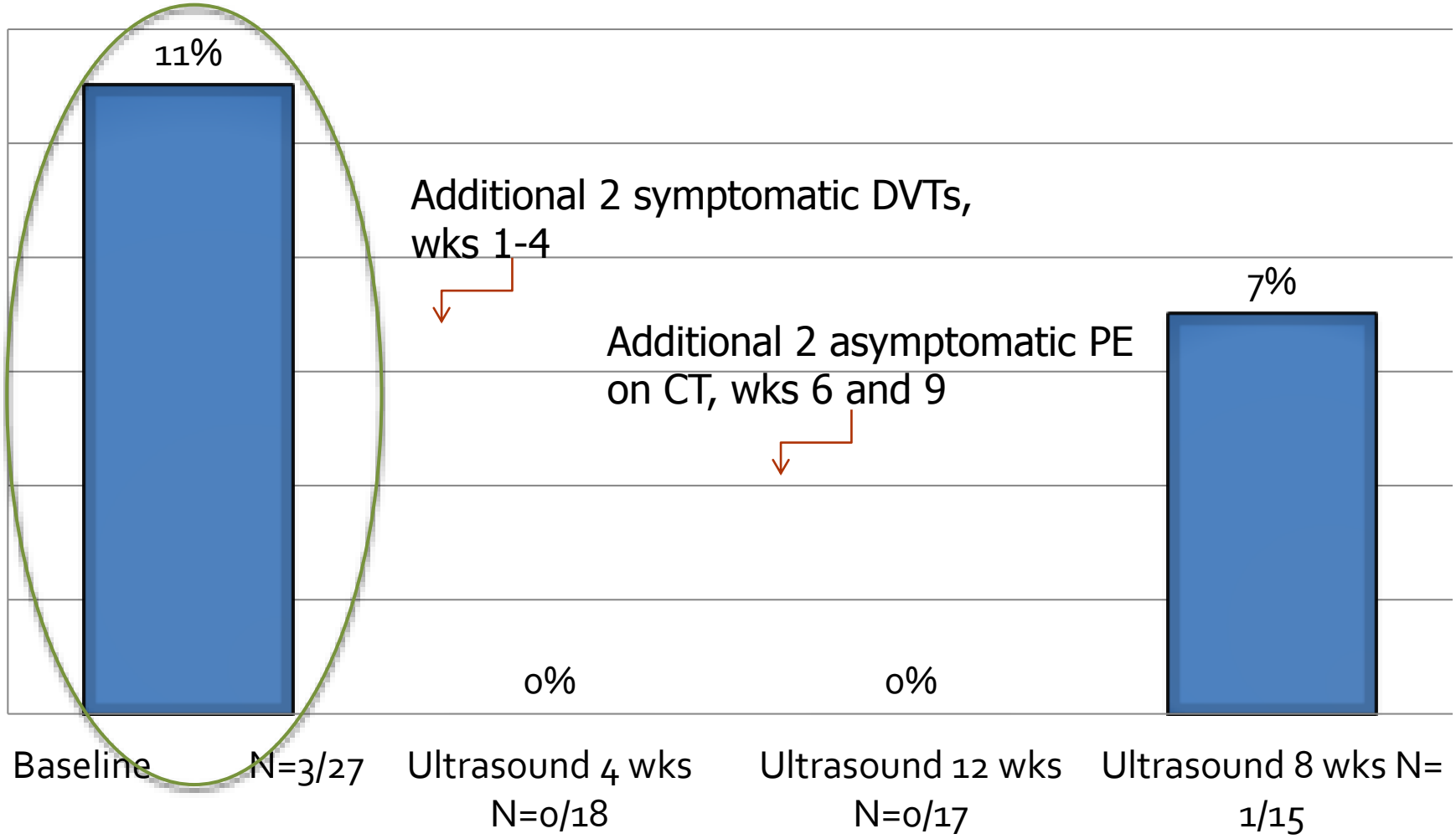
Screening?

Prophylaxis?

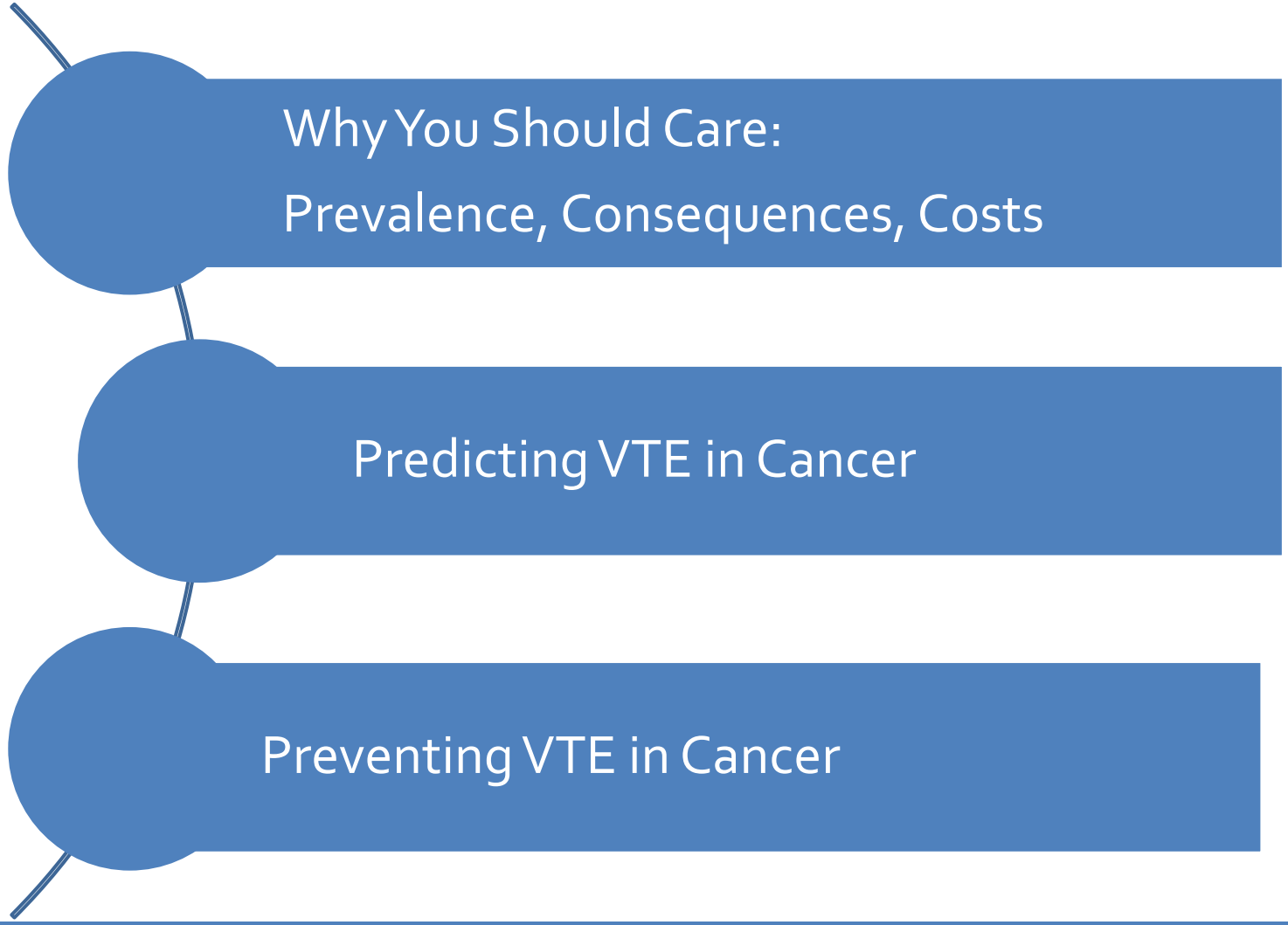
Risk Assessment



Applying Risk Assessment
Screening



Khorana AA et al. *ASH* 2010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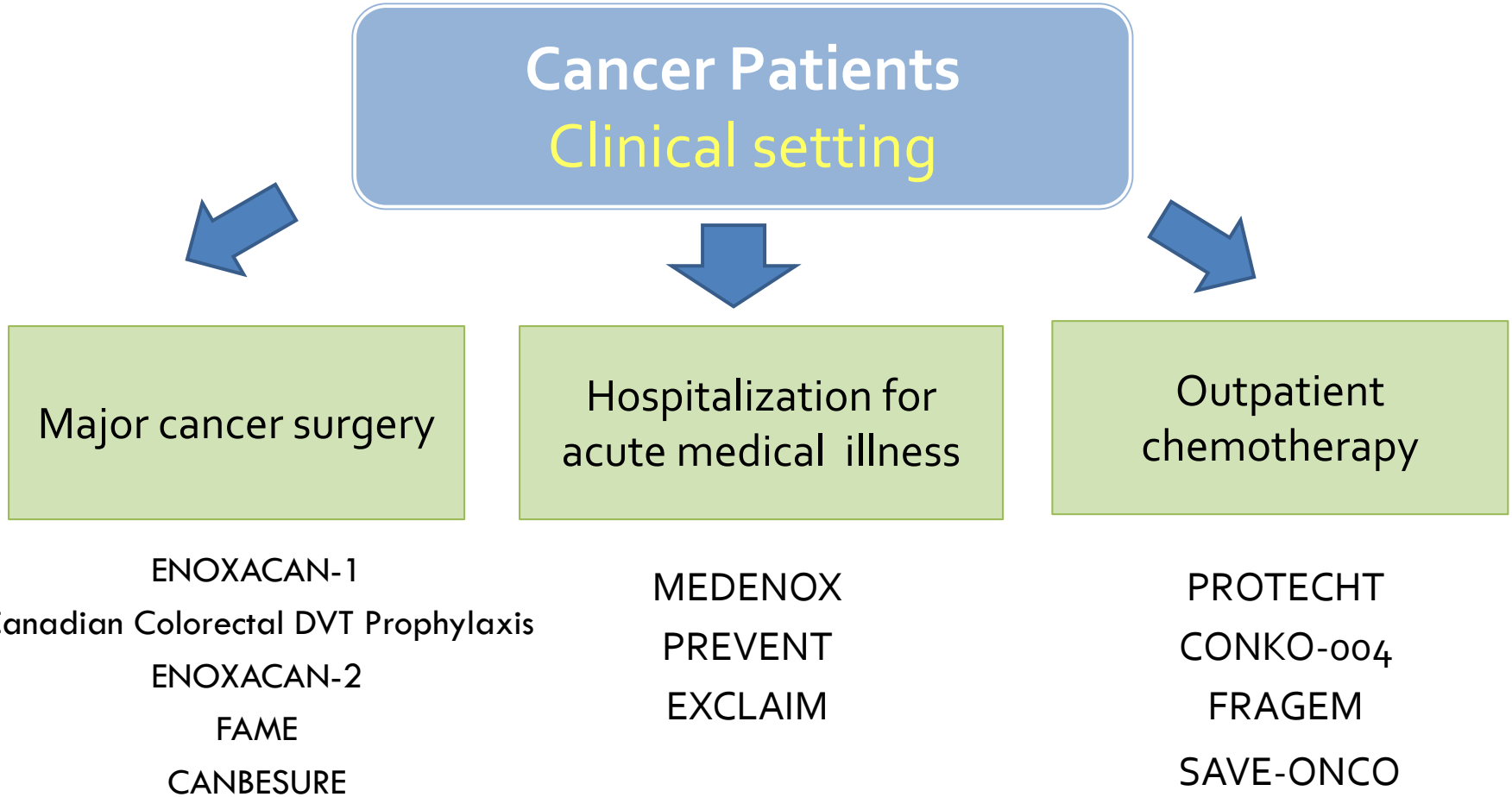


Despite Evidence, Prophylaxis Is Underused

ENDORSE[1]

	Medical	Surgical
No. of patients	37,356	30,827
At risk for VTE	42%	64%
Received prophylaxis (ACCP)	40%	59%

IMPROVE[2]

	United States	Other Countries
No. of patients	3,410	11,746
VTE prophylaxis	1852 (54%)	5788 (49%)
LMWH	476 (14%)	4657 (40%)
UFH	717 (21%)	1014 (9%)

1. Cohen AT et al. *Lancet*. 2008;371:387-394.
2. Tapson VF et al. *Chest.* 2007;132:936-945.

Prophylaxis is underutilized in cancer patients

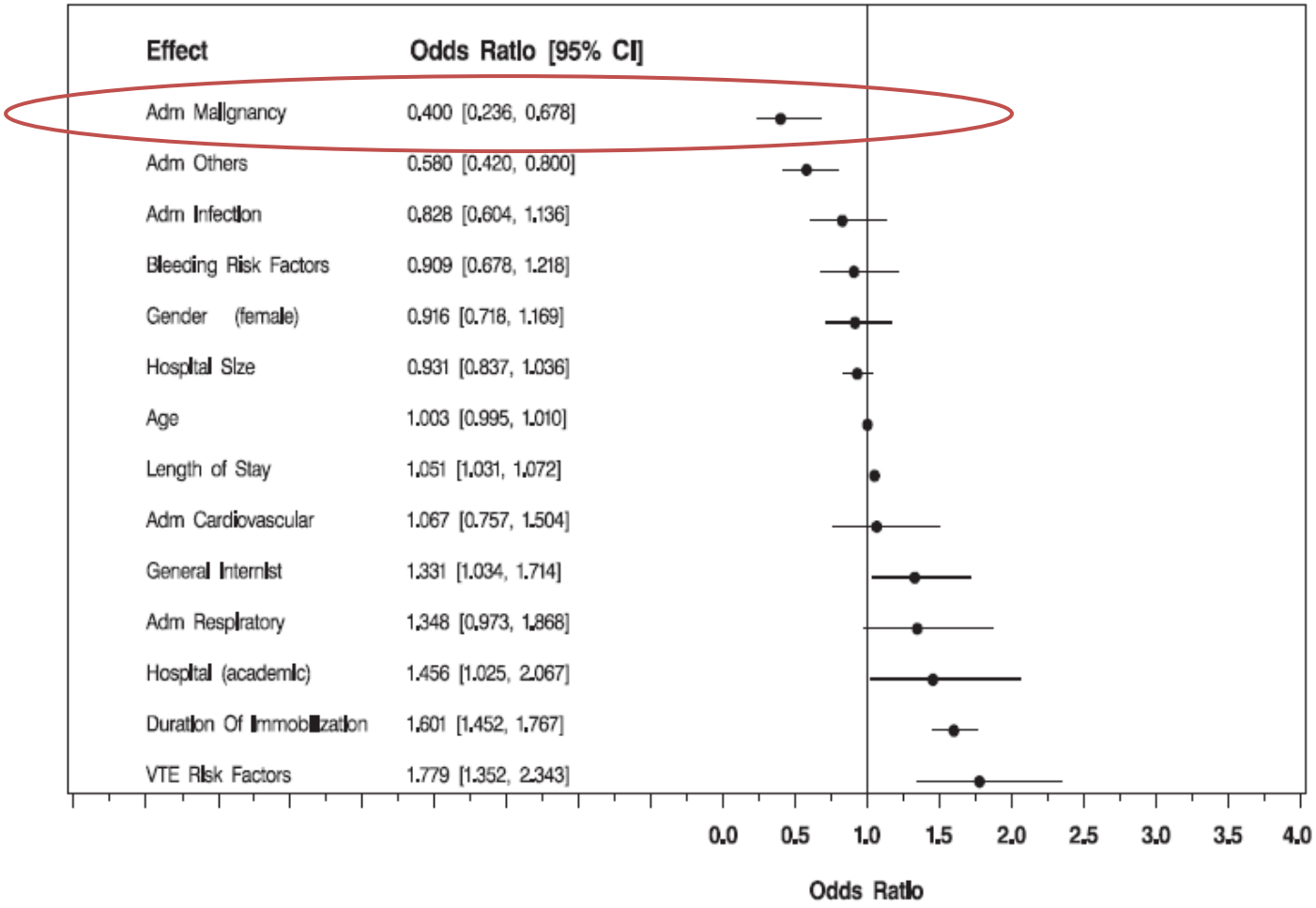
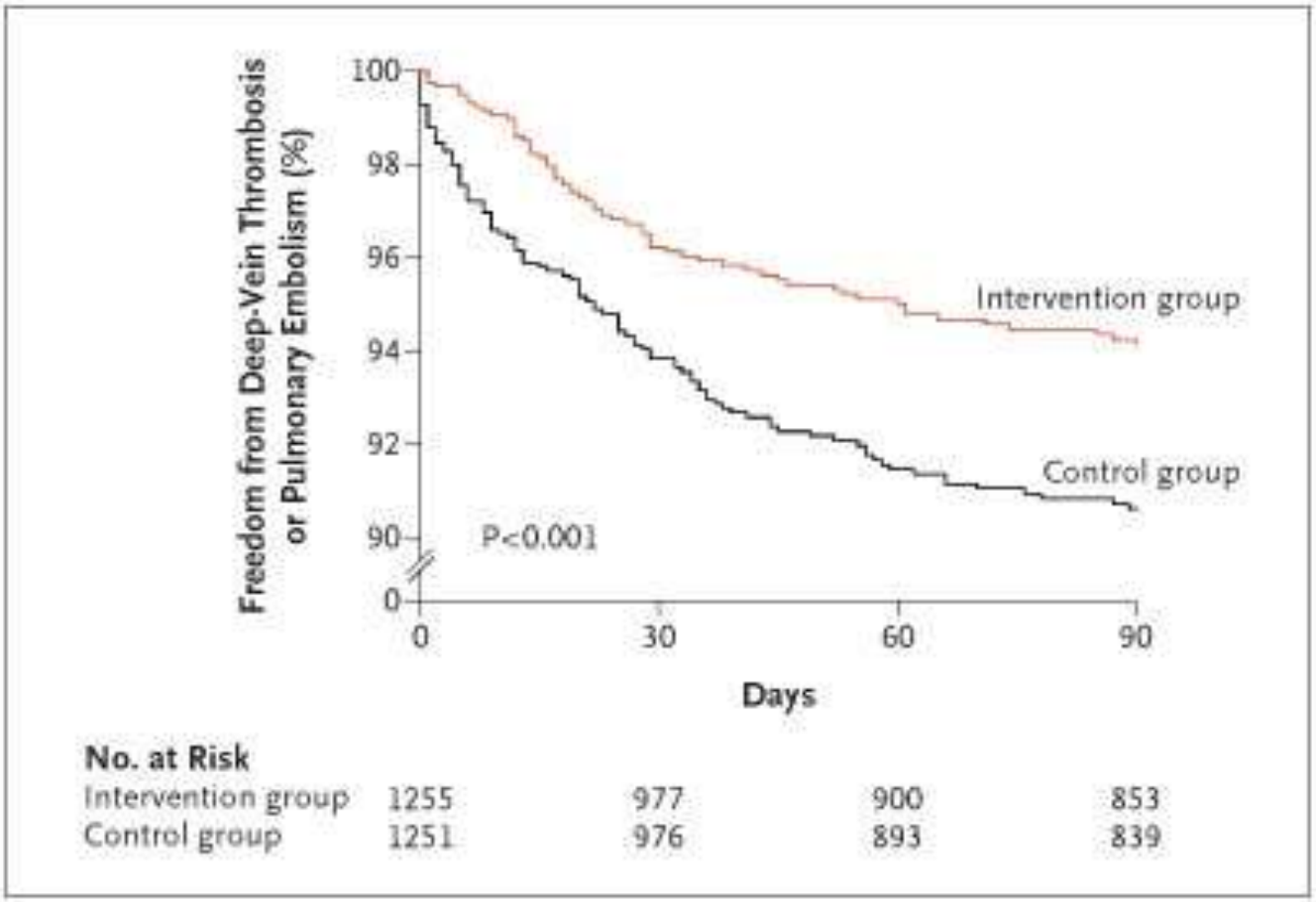


Figure 3 Results of logistic regression: predictors of use of any prophylaxis in study population.

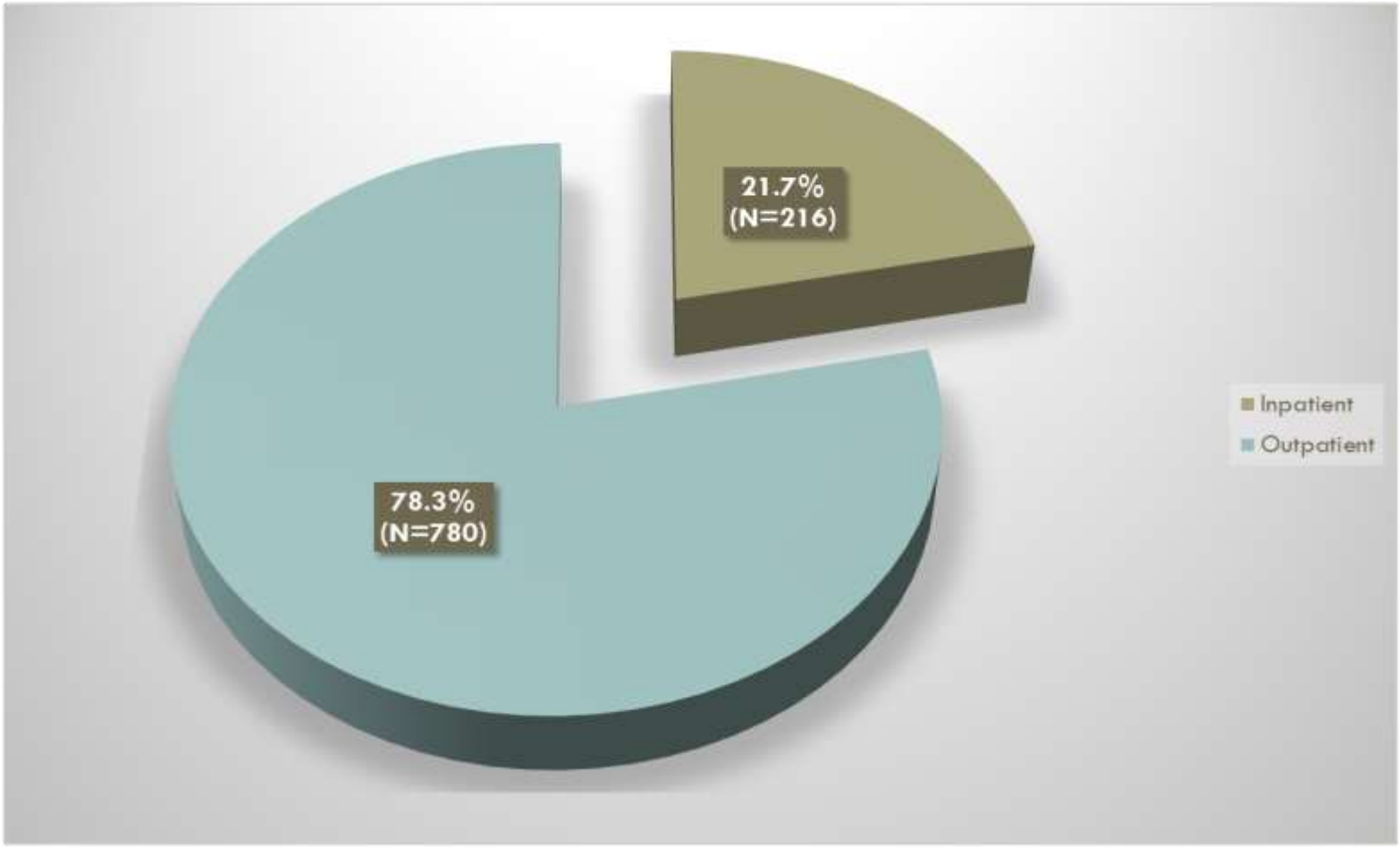
Kahn SR et al Throm Res 2007

Order Entry Alerts Improve Compliance and Reduce VTE



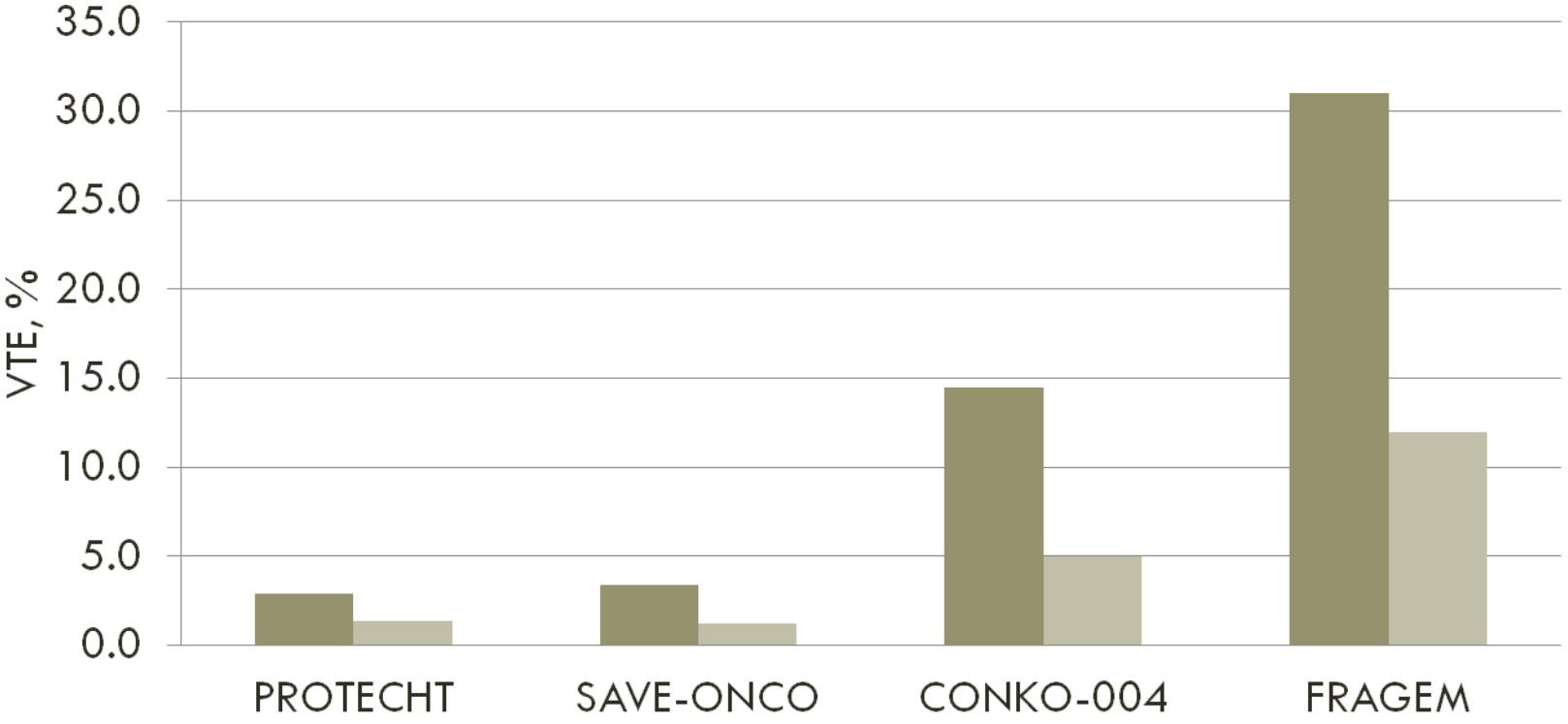
Kucher N et al. N Engl J Med 2005;352:969-977.

Prevention:
CAT is an outpatient illness



Khorana et al *ASH* 2011

Rates of VTE in Recent Prophylaxis Studies



Agnelli et al *Lancet Onc* 2009
Riess et al I*STH* 2009
Maraveyas et al *ESMO* 2009
Agnelli et al NEJM 2012

How To Approach Outpatient Prophylaxis?

"Specific" studies

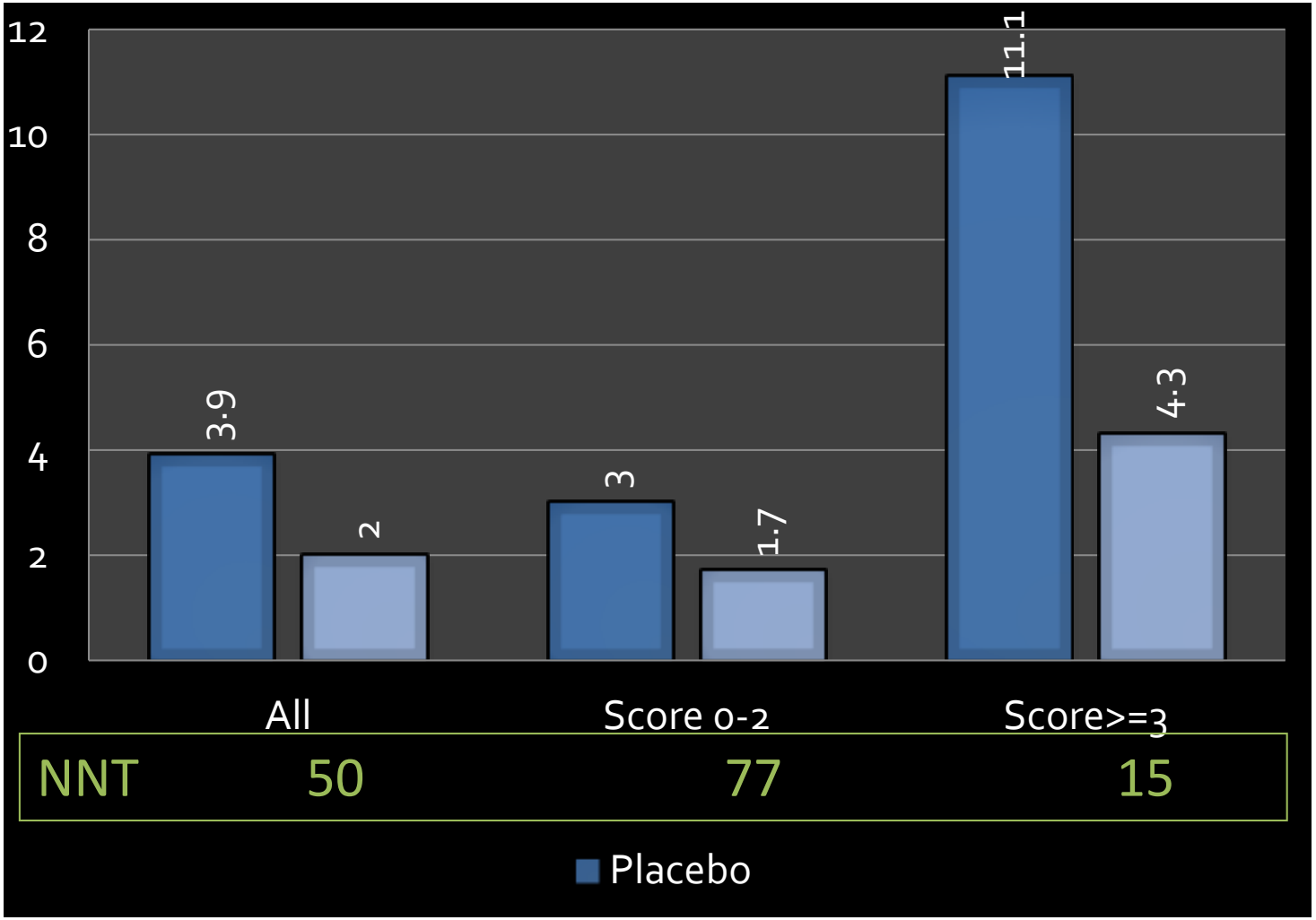
- CONKO, FRAGEM, Myeloma
- Very high event rates
- Homogenous populations (pancreas, myeloma)
- But: smaller effect on public health burden

"General" studies

- PROTECHT, SAVE-ONCO
- Lower event rates
- Heterogenous populations (multiple sites, stages, chemo)
- But: potential greater effect on public health burden

Risk Assessment: The Future-Prophylaxis

PROTECHT by Risk Score



Verso et al, *Int Emerg Med* 2012

Guideline recommendations

Patients	ASCO[1]	NCCN[2]	ESMO[3]
All cancer outpatients	Routine prophylaxis not recommended	Routine prophylaxis not recommended	Routine prophylaxis not recommended
Myeloma patients, receiving imid-based regimens	Aspirin or LMWH for low-risk and LMWH for high-risk patients is recommended	Aspirin for low-risk and LMWH or warfarin for high-risk patients is recommended	Consider LMWH, aspirin or adjusted-dose warfarin (INR ~ 1.5)
"High-risk" outpatients	Consider LMWH prophylaxis on a case-by-case basis in highly select outpatients with solid tumors on chemotherapy.	"Consider patient conversation about risks and benefits of prophylaxis in Khorana score ≥ 3 population"	Consider in high-risk ambulatory cancer patients. Predictive model may be used to identify patients clinically at high risk for VTE

1. Lyman GH, et al. J Clin Oncol. 2013
2. NCCN guidelines, 2013
3. Mandala M, et al. Ann Oncol. 2011;21:274-6.

Conclusions

The problem is bigger than we imagined

- "Unacceptably high" burden
- Incidental VTE is an emerging major clinical problem
- Association with cancer outcomes, including mortality

We have made progress

- Electronic alerts increase compliance and reduce clots
- Validation of the Risk Score by multiple groups represents a new era in collaboration and testing of predictive models
- Candidate biomarkers are being vetted in large-scale studies
- Multiple RCTs have addressed prevention of CAT in the outpatient setting

Conclusions

Outpatient prophylaxis is safe, feasible and effective

- Multiple RCTs have shown benefit, but with low event rates

Risk-adapted approaches to prophylaxis

- Identifying high-risk patients reduces NNT and optimizes risk-benefit ratio
- Slouching toward a consensus: targeted prophylaxis

The Future of CAT

Precision medicine

- "Big data" and pan-omics can be harnessed to precisely estimate the risk of primary and recurrent VTE
- Prevention and treatment can be individualized to patients based on risk of VTE and risk of bleeding