5 Minute JournalClub

Key ASH Presentations

Issue 5, 2012

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CME Information

LEARNING OBJECTIVES

- Assess the benefit-risk profile of the novel ultra-low-molecular-weight anticoagulant semuloparin for the treatment of venous thromboembolism in patients with locally advanced or metastatic cancer.
- Evaluate the efficacy and safety data with anticoagulant therapy for patients with deep vein thrombosis and venous thromboembolism, and incorporate this information into your personal therapeutic algorithm.
- Develop an understanding of the incidence and risk factors for venous thrombosis and venous thromboembolism, and be able to counsel patients with newly diagnosed or recurrent cancer about the appropriate prophylactic treatments available.

CREDIT DESIGNATION STATEMENT

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CME Information (Continued)

FACULTY DISCLOSURES
The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

Kenneth A Bauer, MD
Professor of Medicine
Harvard Medical School
Chief, Hematology Section
VA Boston Healthcare System
Director, Thrombosis Clinical Research
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Consulting Agreements: Bristol-Myers Squibb Company, GTC Biotherapeutics Inc, Instrumentation Laboratory, Johnson & Johnson Pharmaceuticals, LFB Biotechnologies, Pfizer Inc.

Semuloparin for Thromboprophylaxis in Patients Receiving Chemotherapy for Cancer

Agnelli G et al.
N Engl J Med 2012;366(7):601-9.

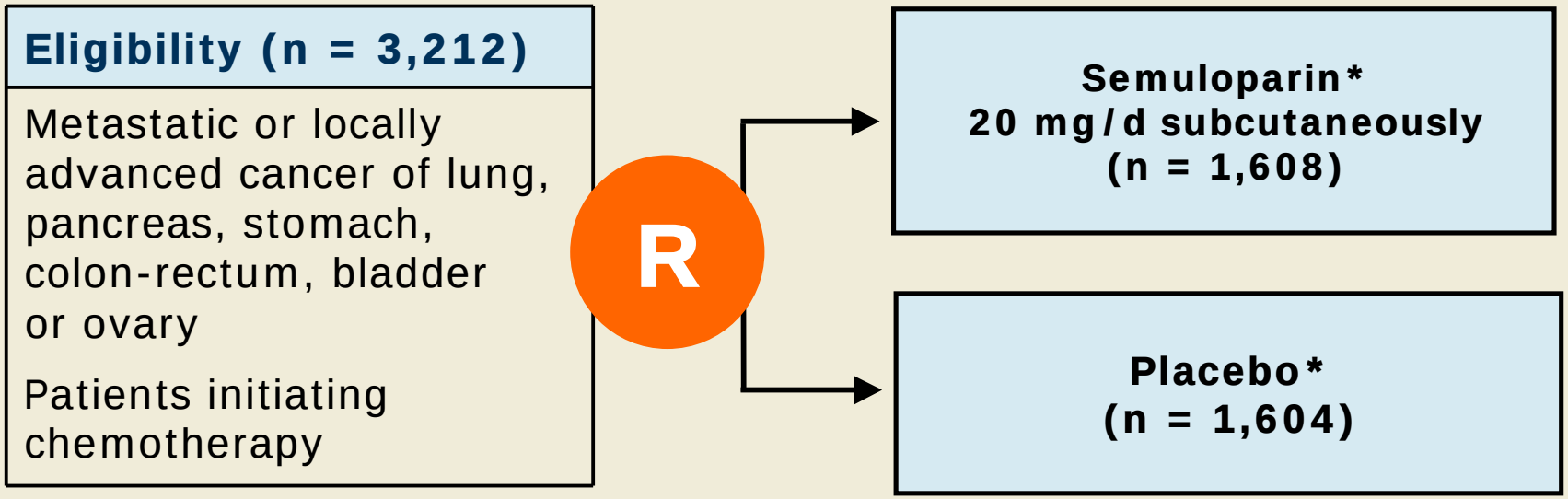
George D et al.
Proc ASH 2011;Abstract 206.

Background

- There is an increased risk of developing venous thrombo-embolism (VTE) in patients (pts) with cancer who are receiving chemotherapy due to multiple cancer- and patient-specific risk factors.
- Semuloparin is a new ultra-low molecular weight heparin (ULMWH) with high antifactor Xa and minimal antifactor IIa activity that may inhibit the development of VTE.
- **Objective:**
  - Assess semuloparin versus placebo for VTE prevention in pts with cancer who are receiving chemotherapy for a locally advanced or metastatic solid tumor.

Agnelli G et al. *N Engl J Med* 2012;366(7):601-9.

SAVE-ONCO Study Design

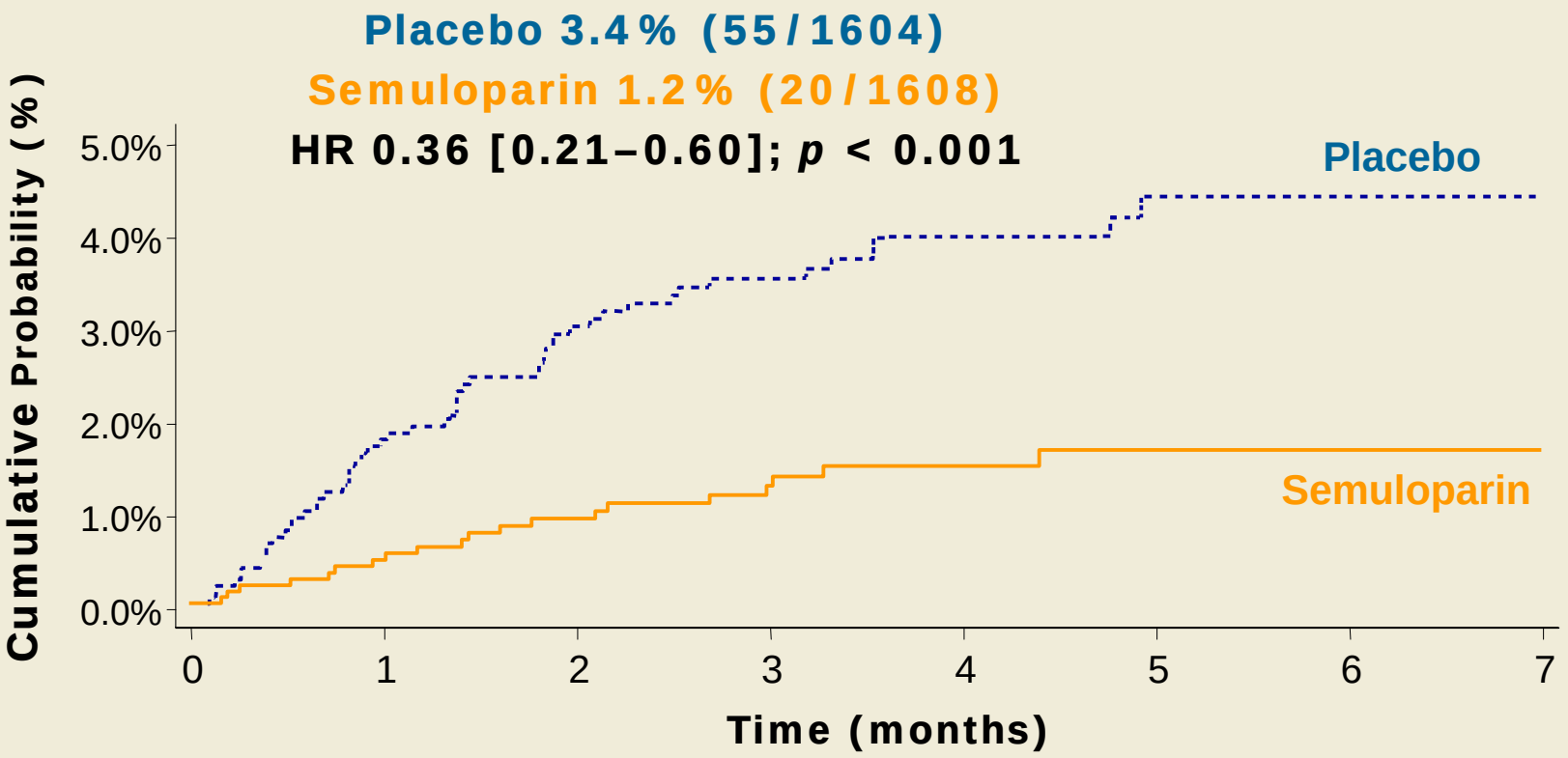


* Semuloparin and placebo were administered until change of chemotherapy.

- **Primary endpoints**:
  - Efficacy: VTE (symptomatic deep vein thrombosis or nonfatal pulmonary embolism) or VTE-related deaths
  - Safety: Any clinically relevant bleeding (major or nonmajor)
- **Baseline VTE risk**: Assessed by a score specifically developed and validated in patients receiving chemotherapy for cancer (*Blood* 2008;111:4902).

Agnelli G et al. *N Engl J Med* 2012;366(7):601-9.

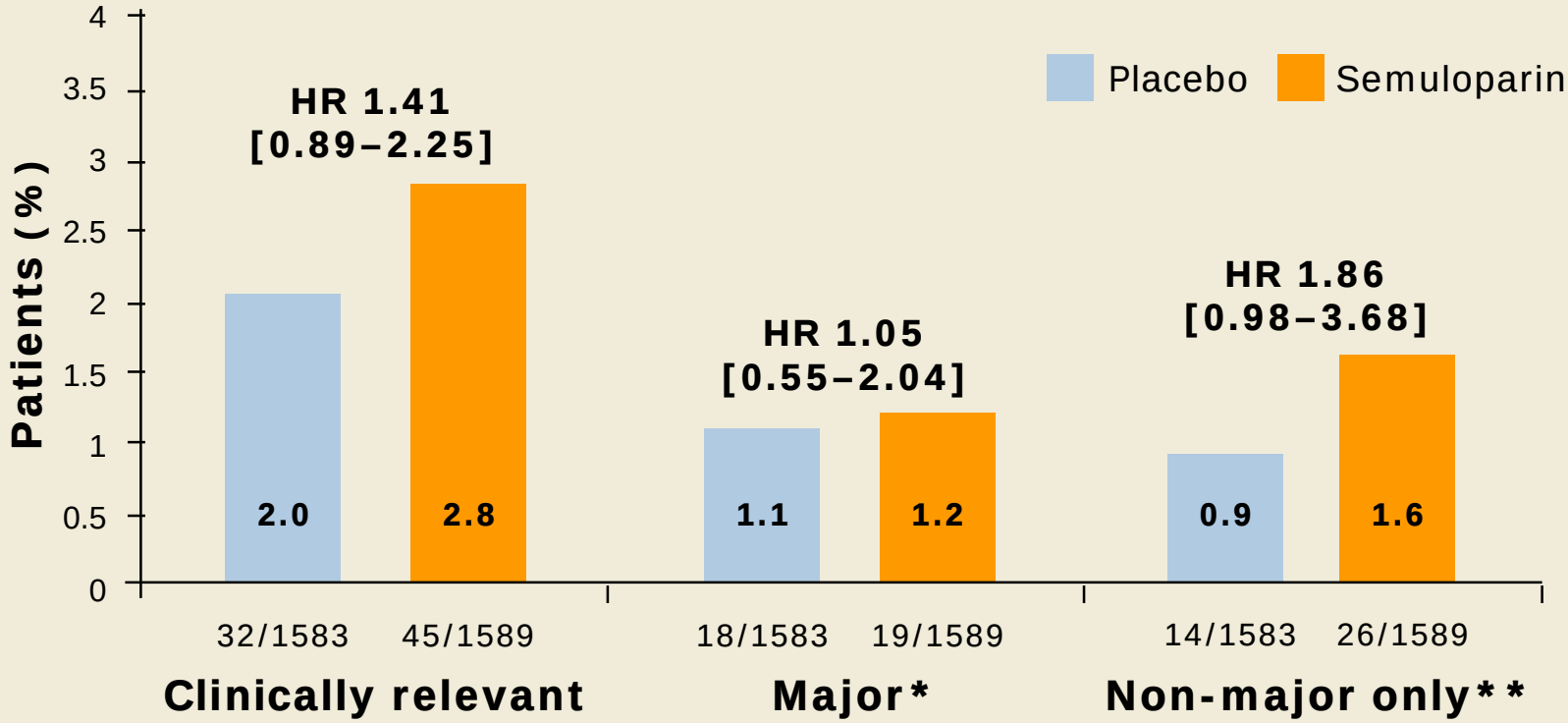
Primary Endpoint: Composite of VTE or VTE-Related Deaths



HR = hazard ratio

A 64% relative risk reduction was observed over median treatment duration of approximately 3.5 months.

Primary Endpoint: Bleeding

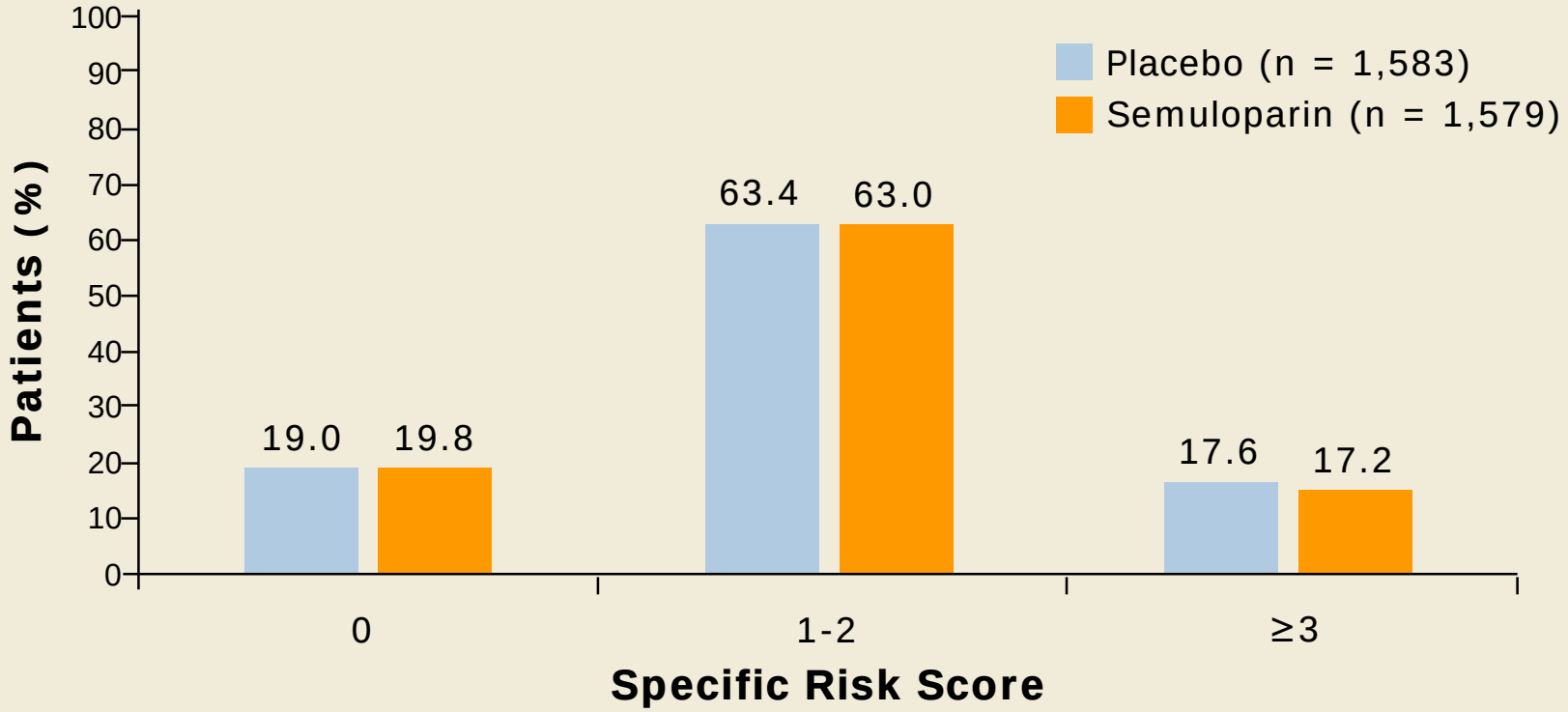


* Includes 6 pts with fatal bleedings: 4 (placebo) and 2 (semuloparin); 5 nonfatal bleedings (semuloparin)

** Treatment discontinuation: 7 pts (placebo) and 9 pts (semuloparin); serious events: 4 pts (placebo) and 9 pts (semuloparin); recovered: 14 pts (placebo) and 24 pts (semuloparin)

With permission from George D et al. *Proc ASH* 2011;Abstract 206.

Baseline VTE Risk According to Cancer Chemotherapy-Specific Risk Score



Khorana Risk Score assigned:
+2 = high-risk cancer sites (pancreas and stomach)
+1 = high-risk cancer sites (lung, lymphoma, gynecologic, bladder, testicular cancer)
+1 = platelet count: ≥350 x 10^9/L; hemoglobin (Hb): <10 g/dL and/or use of erythropoiesis-stimulating agents; white blood cell count: >11 x 10^9/L; body mass index: ≥35 kg/m^2

With permission from George D et al. *Proc ASH* 2011;Abstract 206.

VTE or VTE-Related Death by Baseline VTE Risk Score (Abstract Only)

	Placebo	Semuloparin	HR (95% CI)
All pts	3.4%	1.2%	0.36 (0.21-0.60)
VTE risk score			
0 (n = 301, 313)	1.3%	1.0%	0.71 (0.16-3.15)
1-2 (n = 1,003, 995)	3.5%	1.3%	0.37 (0.20-0.70)
≥3 (n = 279, 271)	5.4%	1.5%	0.27 (0.09-0.82)

George D et al. *Proc ASH* 2011;Abstract 206.

Major Bleeding by VTE Risk Score or Factors

	Placebo	Semuloparin	HR	*p*-value
All pts (n = 1,583, 1,589)	1.1%	1.2%	1.05	—
Cancer chemotherapy-specific VTE risk score				
0 (n = 297, 310)	0.7%	0.6%	1.13	
1-2 (n = 988, 987)	1.1%	1.2%	1.09	0.9845
≥3 (n = 277, 264)	1.8%	1.9%	1.01	
General VTE risk factors*				
None (n = 923, 914)	0.9%	1.0%	1.11	
1 or 2 (n = 620, 643)	1.3%	1.2%	0.97	0.9391
≥3 (n = 40, 32)	5.0%	6.3%	1.16	

* Includes any risk factor, history of pulmonary embolism, use of hormonal therapy, history of deep vein thrombosis, chronic heart failure, venous insufficiency/varicose veins, chronic respiratory failure, age ≥75, obesity and central venous line at baseline

George D et al. *Proc ASH* 2011;Abstract 206.

Author Conclusions

- Semuloparin treatment at 20 mg/d produced a favorable benefit-risk profile for the prevention of VTE in patients with cancer initiating chemotherapy.
- The benefits of semuloparin were observed across different degrees of baseline VTE risk.
- The SAVE-ONCO study demonstrates that antithrombotic prophylaxis should be considered in patients with cancer initiating chemotherapy.

Agnelli G et al. *N Engl J Med* 2012;366(7):601-9.

Investigator Commentary: The SAVE-ONCO Study

VTE is a significant complication of cancer. It is a risk that is dramatically seen with some of the newer agents, especially with lenalidomide and high-dose dexamethasone in myeloma. This is a study of ULMWH versus placebo in patients with locally advanced or metastatic cancer receiving initial chemotherapy. In the metastatic or locally advanced setting, semuloparin effectively reduced the risk of VTE from 3.4% to 1.2% within an approximate 3.5-month duration as patients were only on semuloparin during the first chemotherapy regimen. It is questionable whether the risk of 3.4% with placebo is enough for the use of any form of anticoagulant. Even though the Khorana Score incorporates high platelet counts or low Hb levels, with a high risk score of 3 or higher, the incidence of VTE was only 5.4%. This raises further questions about finding better ways of determining the patients with high-risk VTE and for clinicians in identifying the patients requiring VTE prevention. This is important because the standard treatment currently does not use anticoagulants unless the patient has a history of thrombosis.

Interview with Kenneth A Bauer, MD, January 26, 2012

Higher Incidence of Venous Thromboembolism (VTE) in the Outpatient versus Inpatient Setting Among Patients with Cancer in the United States

Khorana A et al.

Proc ASH 2011;Abstract 674.

Background

- Public health efforts to reduce VTE have focused on inpatient thromboprophylaxis, which is proven to be safe and effective.
- VTE is frequent and increasing in the cancer population (*Cancer* 2007;110(10):2339).
- However, cancer care has shifted primarily to outpatient-based therapy.
- Contemporary data regarding the proportion of VTE in the outpatient versus inpatient cancer settings are lacking.
- **Current study objectives**: Determine the proportion of VTE in patients with cancer in the outpatient versus inpatient settings and determine the consequences of VTE in terms of resource utilization and costs.

Khorana A et al. *Proc ASH* 2011;Abstract 674.

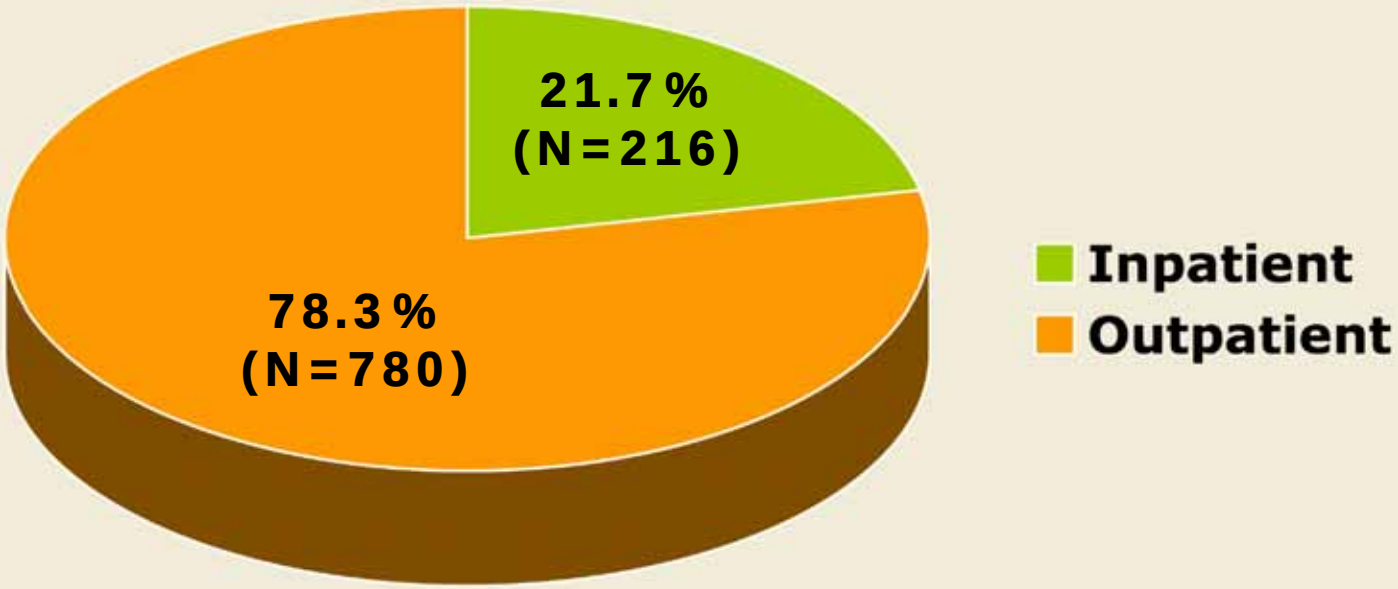
Methods

- Observational, retrospective cohort analysis of data extracted from the Premier Perspective™ Database* linked with claims data.
- ICD-9-CM codes were used to identify VTE events, including deep vein thrombosis (DVT) or pulmonary embolism (PE).
- Patients with ≥1 inpatient or outpatient claims containing a cancer diagnosis between 2006 and 2008 were included.
- Baseline characteristics of patients were assessed during a 6-month preindex period.
- Demographics, clinical characteristics and cost were assessed.
- Multivariate analyses were conducted to adjust for differences in patient characteristics before and after the index event.

* A deidentified United States hospital clinical and economic database

Khorana A et al. *Proc ASH* 2011;Abstract 674.

VTE in Cancer
Outpatient versus Inpatient



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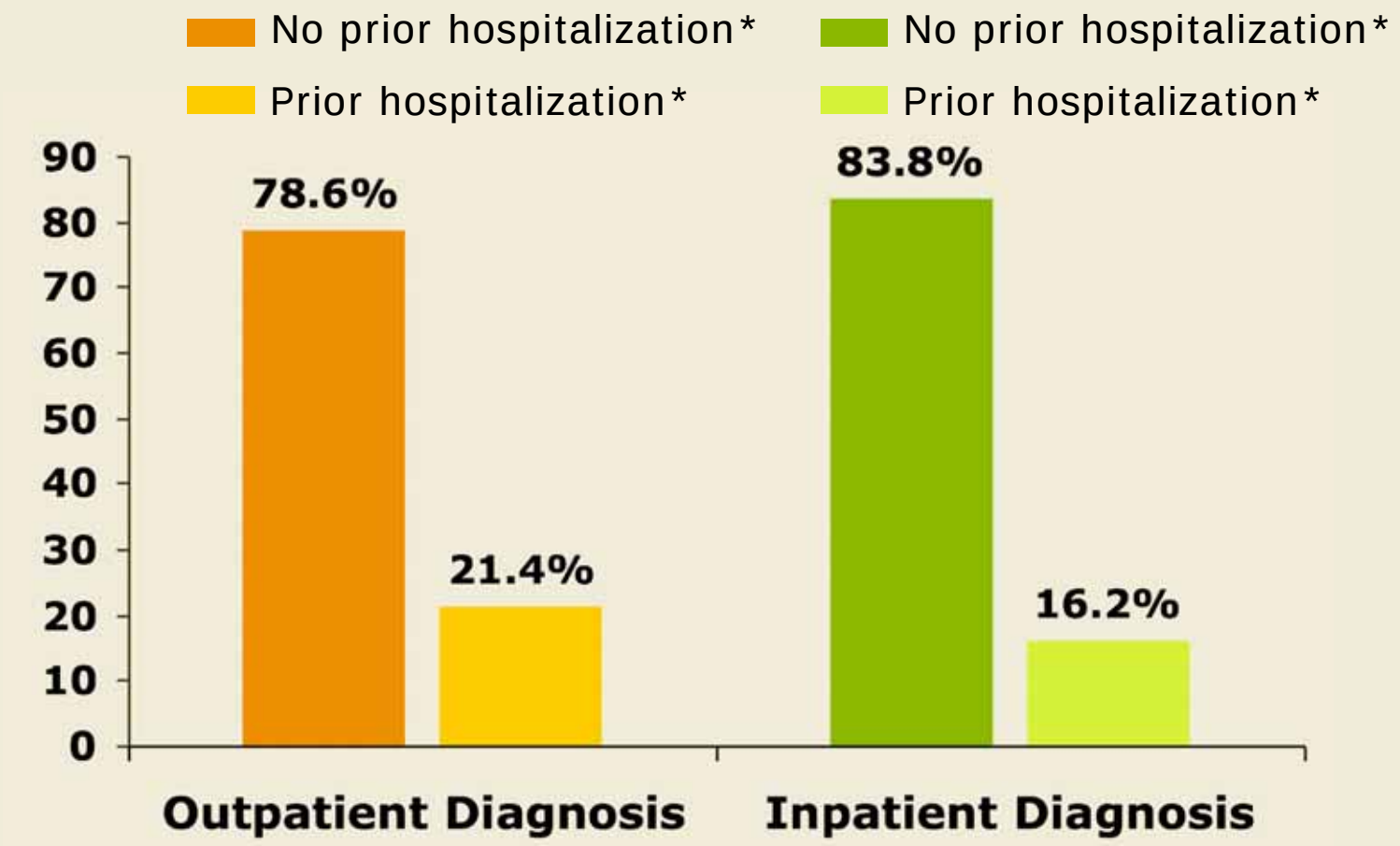
All-Cause Hospitalization Within 30 Days of VTE



* Within 30 days prior to VTE

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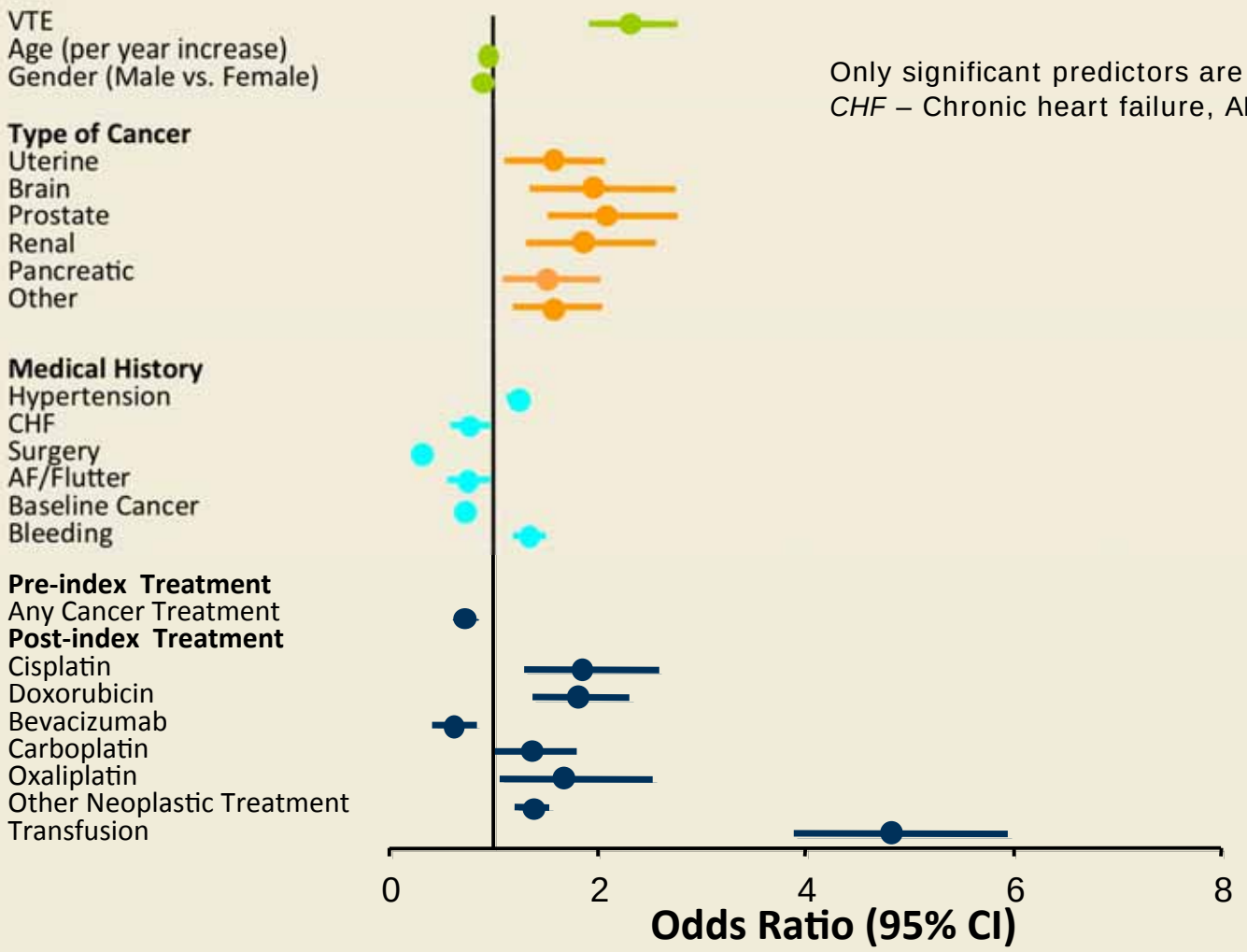
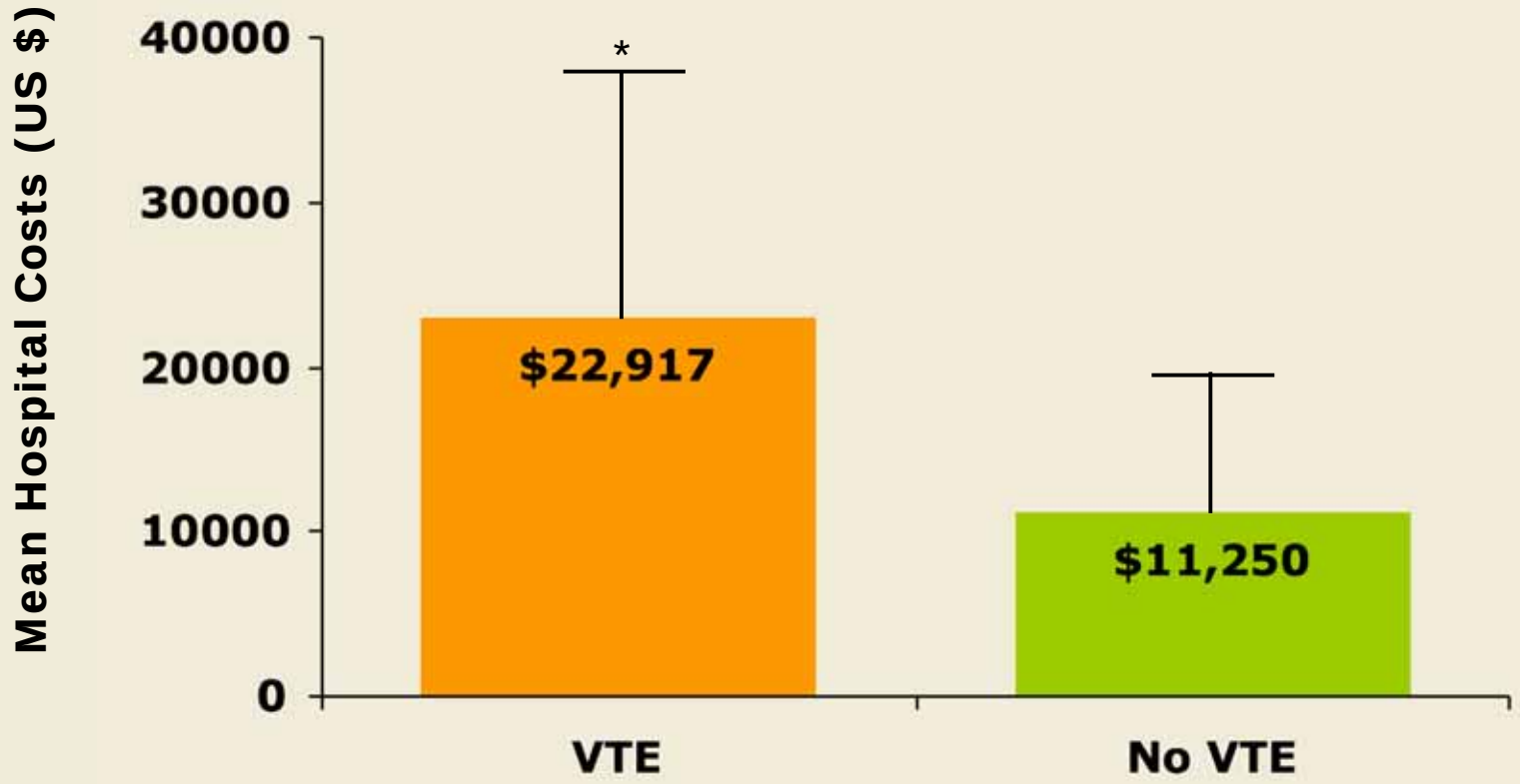
Predictors of All-Cause Hospitalization



Only significant predictors are shown ($p<0.05$).
CHF – Chronic heart failure, AF – Atrial fibrillation

With permission from Khorana A et al. *Proc ASH* 2011;Abstract 674.

Economic Burden of VTE in Cancer



VTE is an independent predictor of higher hospital costs†

* $p < 0.0001$

† Multivariate model adjusting for patient and treatment characteristics. Values shown are mean ± standard deviation.

With permission from Khorana A et al. *Proc ASH* 2011;Abstract 674.

Author Conclusions

- Over three quarters of all VTE in cancer occurs in the outpatient setting.
- One fifth of outpatients with VTE were recently hospitalized.
- Cancer-associated VTE is associated with hospitalization and increased costs.
- As all data were extracted from an insurance claims database, the study cohort represents a commercially insured population and findings may not be applicable to other populations.
- Public health efforts to reduce the burden of VTE in cancer will need to focus on outpatient (and postdischarge) thromboprophylaxis in patients at high risk.

Khorana A et al. *Proc ASH* 2011;Abstract 674.

Investigator Commentary: Higher Incidence of VTE in Patients with Cancer in the Outpatient versus Inpatient Settings in the United States

This was a large database study that evaluated the risk of developing VTE for patients with cancer in the outpatient versus the inpatient setting.

The whole area of medical prophylaxis is quite controversial. Some previous studies showed no mortality benefit with heparin in a hospital setting. In this study, about 78% of the patients developed VTE out of the hospital. So it is important to identify the outpatients who are at high risk for VTE. About 21% of the outpatients who developed VTE had been hospitalized in the previous month. So the question is whether using prophylaxis for an extended period after patients leave the hospital can prevent VTE. We know that patients have a major risk of VTE for 90 days after hospitalization.

Interview with Kenneth A Bauer, MD, January 26, 2012

Development and Testing of a Risk Assessment Model for Venous Thrombosis in Medical Inpatients: The Medical Inpatients and Thrombosis (MITH) Study Score

Zakai N et al.

Proc ASH 2011;Abstract 173.

Background

- For hospitalized patients, venous thrombosis (VT) risk assessment and provision of VT prophylaxis are mandated by various governmental organizations such as:
  - The Joint Commission, United States
  - The National Institute for Health and Clinical Excellence, United Kingdom
- No validated VT risk assessment models (RAMs) are available for use with medical inpatients.
- **Current study objective:**
  - Develop a validated RAM that assesses the risk of developing VT in medical inpatients.

Zakai N et al. *Proc ASH* 2011;Abstract 173.

Study Method

- Between 01/2002 and 06/2009, all cases of VT-complicating medical admissions were:
  - Identified by ICD-9 codes
  - Confirmed by review of medical records at a 500-bed teaching hospital
- Controls without VT (n = 601) were matched to each case (n = 299) in a 2:1 ratio by admission service and admission year.
- VT required positive imaging or autopsy.
- Medical history, comorbidities and the use of VT prophylaxis in cases and controls were assessed by chart review.

Zakai N et al. *Proc ASH* 2011;Abstract 173.

Study Method (Continued)

- Weighted logistic regression was used to calculate the odds ratio (OR) for VT.
  - The Taylor series method for 95% CI was used to assess mechanical and pharmacologic VT prophylaxis use.
- A point value was assigned to each risk factor.
- A RAM was developed by clinical judgment and sequentially adding risk factors into a multivariate model.
- The 95% CI for the C statistic was used to validate the RAM model.

Zakai N et al. *Proc ASH* 2011;Abstract 173.

VT Risk Assessment Model* (Abstract Only)

Risk factor	PIC	OR (95% CI)	Points
History of congestive heart failure	5.4%	8.6 (4.1-22.6)	5
History of rheumatologic or ID	1.0%	7.7 (3.3-18.1)	4
Fracture in the past 3 months	1.9%	3.8 (1.6-9.0)	3
History of VT	6.2%	2.7 (1.5-5.0)	2
History of cancer in the past 12 months	17.6%	1.6 (1.1-2.4)	1
Heart rate ≥ 100 on admission (OD)	17.0%	2.5 (1.7-3.7)	2
Oxygen saturation < 90%/intubated OD	16.3%	1.9 (1.2-2.9)	1
White cell count ≥ 11 OD	29.8%	1.9 (1.2-2.9)	1
Platelet count ≥ 350 OD	10.0%	1.9 (1.1-3.1)	1

PIC = prevalence in controls; ID = inflammatory disease

* A point value was assigned to each risk factor based on statistical principles.

- The C statistic for the model was 0.73 (95% CI: 0.70–0.76).

Zakai N et al. *Proc ASH* 2011;Abstract 173.

RAM Outcomes (Abstract Only)

Rate of VT per 1,000 admissions	95% CI
4.6	3.9-5.4
Probability of VT without VT prophylaxis per 1,000 admissions (score <2)*	**95% CI**
1.5	1.0-2.3
Probability of VT without VT prophylaxis per 1,000 admissions (score ≥2)*	**95% CI**
8.8	4.1-18.8
C statistic to validate the developed RAM model	**95% CI**
0.71	0.68-0.74

* Represents sum of point values for VT risk factors present. Using a cutoff of ≥2 points as high risk, 79% of cases and 39% of controls were classified as high risk.

Zakai N et al. *Proc ASH* 2011;Abstract 173.

Author Conclusions

- The internally validated RAM assesses the risk of VT complicating medical admission.
- The score is simple, relies only on information easily known at the time of admission and could be incorporated into an electronic medical record.
- The score allows clinicians to assess VT risk at admission for medical inpatients and to weigh the risks and benefits of pharmacologic VT prophylaxis.
- The RAM will enable further studies to determine optimal VT prevention strategies for medical inpatients.

Zakai N et al. *Proc ASH* 2011;Abstract 173.

Investigator Commentary: Development and Testing of a Risk Assessment Model for VT in Medical Inpatients

The issues associated with assessing medical patients for the risk of developing VT has controversies brewing about universal prophylaxis for these patients. Identifying patients who have a high risk of developing VT with certitude in addition to determining the patient in need of VT-preventive therapy have been problematic. This study addresses these issues by attempting to develop a risk score for patients potentially at risk for developing VT.

A real knowledge gap exists among many patients in the general population about the problem of venous thromboembolism. The Surgeon General issued a call to action a few years ago to reduce the number of cases of deep vein thrombosis and pulmonary embolism. Once the population becomes more aware of the problems associated with VT, it may be easier to discuss these issues with individual patients.

Interview with Kenneth A Bauer, MD, January 26, 2012

Long-Term Outcome After Additional Catheter-Directed Thrombolysis versus Standard Treatment for Acute Iliofemoral Deep Vein Thrombosis (The CaVenT Study): A Randomised Controlled Trial

Enden T et al.

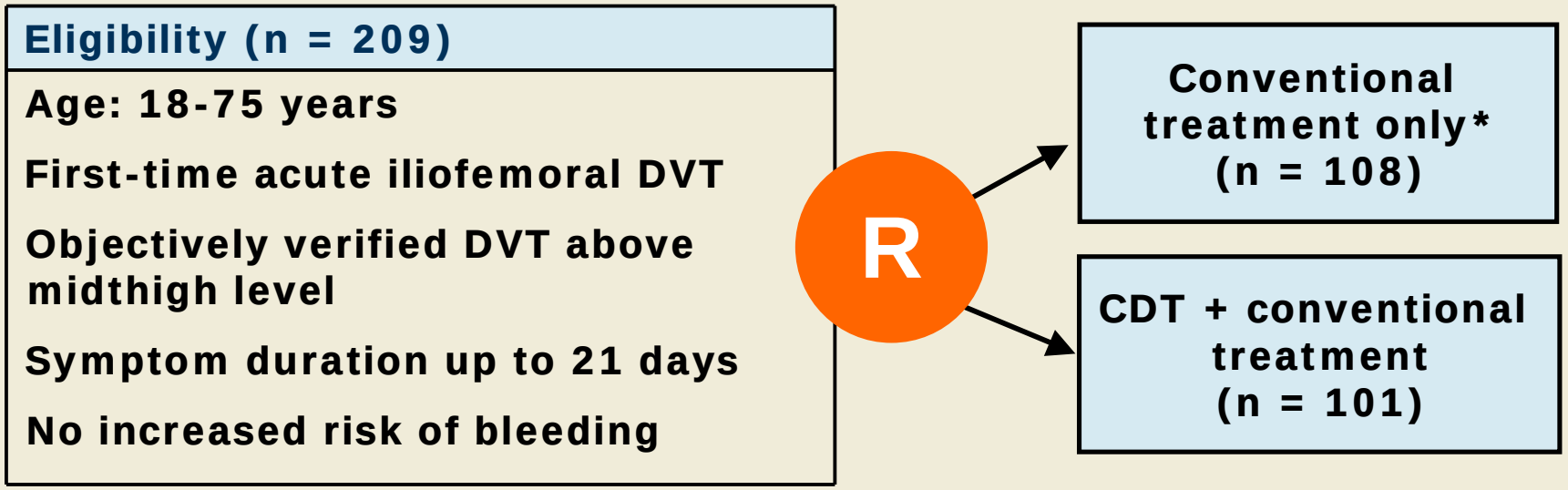
Lancet 2012;379(9810):31-8.
Proc ASH 2011;Abstract LBA-1.

Background

- Conventional anticoagulant treatment of acute deep vein thrombosis (DVT) effectively prevents thrombus extension and recurrence.
- However, such treatment of DVT does not dissolve the clot leading to the development of post-thrombotic syndrome (PTS) in many patients.
- Catheter-directed thrombolysis (CDT) is a novel and promising modality whereby multiple side holes enable delivery of reduced doses of the thrombolytic agent into the clot.
- **Objective:**
  - Examine whether additional therapy with CDT with alteplase for acute iliofemoral vein thrombosis (VT) improves long-term outcomes by reducing the risk of PTS.

Enden T et al. *Lancet* 2012;379(9810):31-8.

CaVenT Trial: Study Design



* Initial low molecular weight heparin (LMWH) and warfarin followed by warfarin alone with target intensity international normalized ratio (INR) of 2.0-3.0

- Randomization was stratified for involvement of the pelvic veins.
- **Primary outcomes:**
  - Frequency of PTS at 24 months, assessed by the Villalta score
  - Iliofemoral patency after 6 months

Enden T et al. *Lancet* 2012;379(9810):31-8.

Villalta Scoring Scale

Five patient-related venous symptoms	Six clinician-rated signs
Pain	Pretibial edema
Cramps	Skin induration
Heaviness	Hyperpigmentation
Paraesthesia	Pain during calf compression
Pruritus	Venous ectasia
	Redness

Scoring — Each sign or symptom is rated as:

0 = None
1 = Mild
2 = Moderate
3 = Severe

Summed-up ratings = total score:

- <5 = no PTS
- 5-14 = mild/moderate PTS
- ≥15/venous ulcer = severe PTS

Enden T et al. *Lancet* 2012;379(9810):31-8.

Outcomes: Additional CDT versus Standard Therapy

Outcome	Additional CDT (n = 90)		Standard therapy only (n = 99)		*p*-value
	n	% (95% CI)	n	% (95% CI)	
PTS after 6 mo	27	30.3 (21.8-40.5)	32	32.2 (23.9-42.1)	0.77
PTS after 24 mo	37	**41.1** (31.5-51.4)	55	**55.6** (45.7-65.0)	0.047
Iliofemoral patency after 6 mo*	58	**65.9** (55.5-75.0)	45	**47.4** (37.6-57.3)	0.012

* Five patients had inconclusive patency assessments, and 1 was lost to follow-up. At completion of 24 months of follow-up, 189 patients were available for analysis.

- PTS is defined as a Villalta score ≥5.
- *p*-values stated are from an unadjusted Chi-square test.
- Absolute risk reduction of long-term endpoint PTS at 24 months of follow-up in CDT versus standard therapy: 14.4% (95% CI 4-502).

Enden T et al. *Lancet* 2012;379(9810):31-8.

PTS After 24 Months in Patients with Iliofemoral Patency or Insufficient Recanalization After 6 Months

Outcome	Regained iliofemoral patency (n = 103)		Insufficient recanalization (n = 80)		*p*-value
	n	% (95% CI)	n	% (95% CI)	
PTS after 24 mo	38	**36.9** (28.2-46.5)	49	**61.3** (50.3-71.2)	0.001

- Absolute gain in short-term endpoint iliofemoral patency after 6 months in CDT versus standard therapy group: 18.5% (95% CI 4.2–31.8).
- Absolute risk reduction in the frequency of PTS after 24 months in patency versus insufficient recanalization: 24.4% (95% CI 9.8–37.6).

Enden T et al. *Lancet* 2012;379(9810):31-8.

Adverse Events (AEs)

AEs	Additional CDT (n = 101)	Standard treatment (n = 108)
Bleeding complications	20	0
Major bleeding complications	3	0
Clinically relevant bleeding complications	5	0
Deaths	0	NR
Pulmonary embolisms	0	NR
Cerebral hemorrhages	0	NR
Nonbleeding complications	4	NR
Recurrent VTE at 24 mo	10	18

NR = not reported

During follow-up, 28 patients had recurrent VTE and 11 had cancer; no significant difference between treatment groups ($p > 0.05$).

Enden T et al. *Lancet* 2012;379(9810):31-8.

Author Conclusions

- Additional CDT improved the clinically relevant long-term outcome after iliofemoral DVT by decreasing PTS compared to conventional therapy.
- No significant difference was observed in PTS between additional CDT and conventional therapy after 6 months of follow-up ($p = 0.77$).
- The effect of CDT on severe PTS remains unclear for the following reason:
  - Despite the high frequency of PTS overall, severe PTS occurred in only 1 patient (data not shown).
- The CaVenT study demonstrates that additional CDT should be considered as treatment for patients with a high proximal DVT and low risk of bleeding.

Enden T et al. *Lancet* 2012;379(9810):31-8.

Investigator Commentary: Long-Term Outcome After Additional Catheter-Directed Thrombolysis versus Standard Treatment for Acute Iliofemoral Deep Vein Thrombosis — CaVenT Study

For many years, one area of interest in the treatment of massive DVT has been the use of aggressive therapies, be it thrombolysis, modern-day catheter-directed thrombolysis or even mechanical types of thrombectomies conducted by interventional radiologists. However, the problem has always been the lack of clear evidence that the outcomes, in terms of post-thrombotic or postphlebitic syndrome, were better. This is the first of several methodologically well-conducted randomized trials asking if CDT or even other interventions are better than anticoagulation therapy alone. The finding of a 14% significant reduction in postphlebitic syndrome, as measured by the Villalta score at 2 years, is important. Though the *p*-value of 0.047 was just under 0.05, this is the first relatively methodologically sound trial to clearly show a benefit for aggressive therapies, at least thrombolysis, in postclot syndrome. Therefore, for a symptomatic patient with a bad leg and with no active cancer who has low risk factors for bleeding, additional CDT should be seriously considered because the morbidity of postclot syndrome is great.

Interview with Kenneth A Bauer, MD, January 26, 2012

A Randomized Trial of Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism

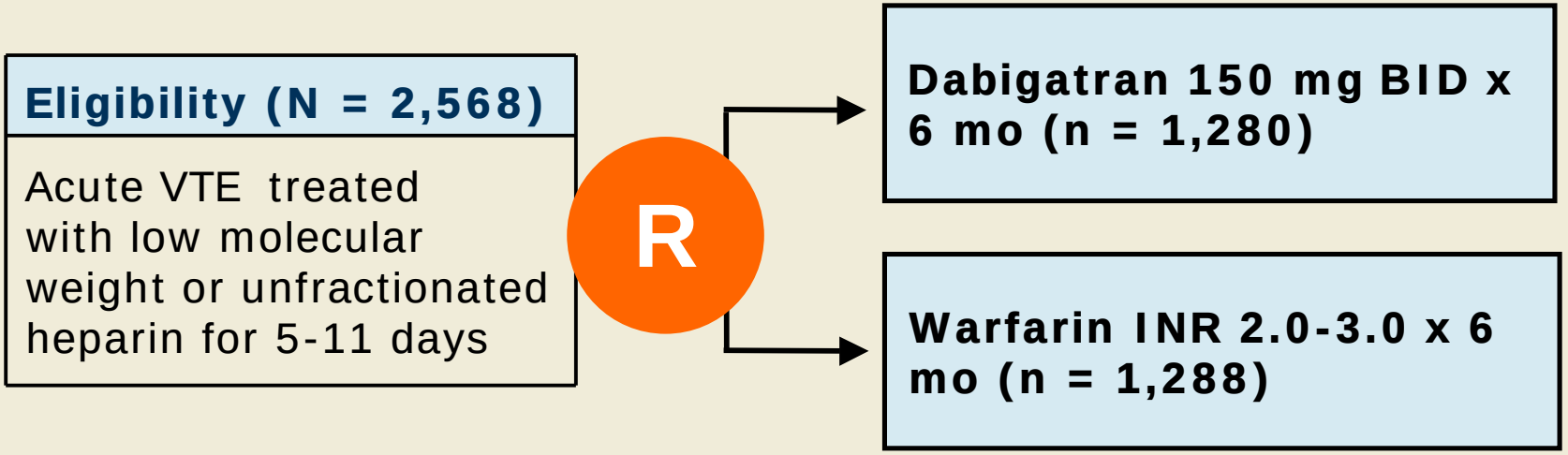
Schulman S et al.
Proc ASH 2011;Abstract 205.

Background

- Dabigatran is a novel oral direct thrombin inhibitor that has been shown to have similar efficacy and safety to enoxaparin for the prevention of venous thromboembolism (VTE).
- Dabigatran offers the advantage of a fixed dose without the need for blood monitoring, versus the regular monitoring and dose adjustment needed with warfarin.
- The RE-COVER I study showed that dabigatran is as effective and as safe as warfarin in patients with acute VTE and it may be an alternative therapy to warfarin for these patients (*N Engl J Med* 2009;361:2342).
- **Current Study Objective:**
  - To confirm the results of RE-COVER I and conduct a more rigorous subgroup analysis.

Schulman S et al. *Proc ASH* 2011;Abstract 205.

Study Design



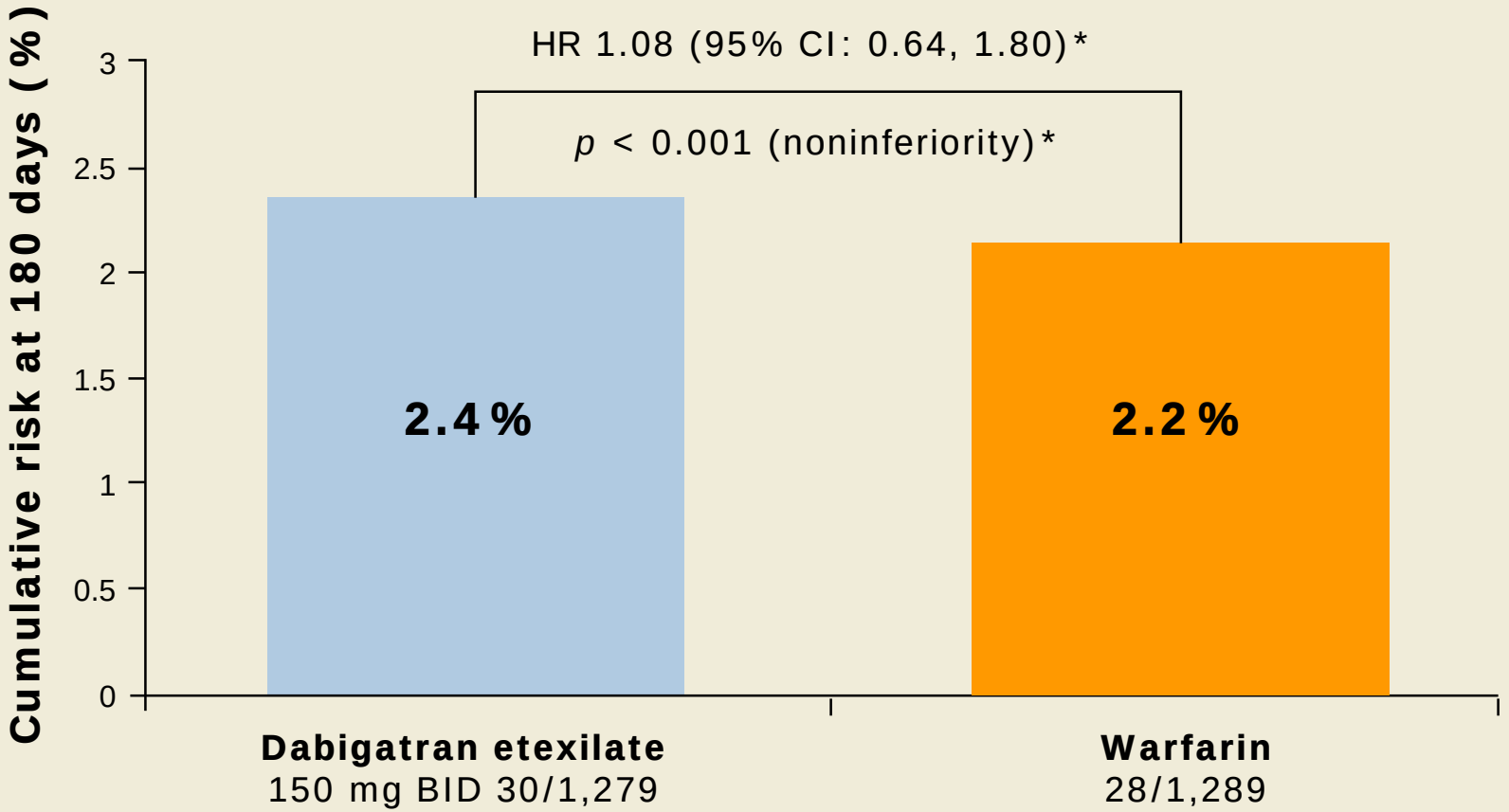
Primary outcomes: Recurrent, symptomatic, objectively confirmed VTE, deaths related to VTE during 6 months

Secondary outcomes: Bleeding events, acute coronary syndrome, elevated liver function tests, adverse events

Noninferiority was defined by 2 margins: 2.75 in hazard ratio (HR) until end of post-treatment period and 3.6% in risk difference at day 180. If noninferiority was met, hierarchical testing for superiority was conducted.

Schulman S et al. *Proc ASH* 2011;Abstract 205.

Recurrent Symptomatic VTE and VTE-Related Deaths



* HR and *p*-value at 180 days.

Schulman S et al. *Proc ASH* 2011;Abstract 205.

Adverse Events — Bleeding

Adverse event	Dabigatran (n = 1,280)	Warfarin (n = 1,288)	HR*	*p*-value
Major bleeding	1.2%	1.8%	0.69	0.26[a]
Any bleeding	16.4%	23.3%	0.67	p < 0.001[b]

* Hazard ratio (treatment period + 6 days)
[a]*p* = 0.19 (superiority) at 180 days; [b]*p* < 0.001 (superiority) at 180 days

There were 25 deaths in each study arm during treatment.

Schulman S et al. *Proc ASH* 2011;Abstract 205.

Adverse Events During Treatment

Adverse event	Dabigatran (n = 1,280)	Warfarin (n = 1,288)
Any adverse event	66.6%	71.1%
Severe adverse event	9.3%	8.9%
Serious adverse event	12.2%	11.9%
Investigator-defined drug-related adverse event	15.2%	21.9%
Adverse event leading to discontinuation of study drug	7.8%	7.8%

Schulman S et al. *Proc ASH* 2011;Abstract 205.

Author Conclusions

- Dabigatran was noninferior to well-controlled warfarin for the acute treatment of symptomatic VTE following initial parenteral anticoagulant treatment.
- No significant differences between treatments were observed for any of the primary or secondary efficacy endpoints.
- A lower rate of major bleeding events and a statistically significant lower rate of bleeding events were recorded with dabigatran than with warfarin.
- The frequency of myocardial infarction was low, but numerically more adjudicated and confirmed acute coronary syndrome events were recorded in patients receiving dabigatran compared to warfarin (data not shown).

Schulman S et al. *Proc ASH* 2011;Abstract 205.

Investigator Commentary: Dabigatran versus Warfarin in the Treatment of Acute VTE (RE-COVER II)

RE-COVER II showed that dabigatran was as effective as warfarin in preventing VTE recurrence. The risk of bleeding is comparable to warfarin with a slightly lower risk of nonmajor bleeding with dabigatran.

A signal that's emerging not so much with this trial but with some of the other studies is a slightly higher rate of myocardial infarction. The signal is small, so other than in coronary-prone patients there is no disincentive to use dabigatran.

This is one of the trials in the new oral anticoagulant era, in which we have several new oral, selectively targeted anticoagulants that either target thrombin, which dabigatran does, or target factor Xa, which agents like rivaroxaban do. The challenge will be whether to use the new agents as opposed to the existing ones and if so which ones to use.

Interview with Kenneth A Bauer, MD, January 26, 2012