

VTE PREVENTION FOR MEDICAL PATIENTS

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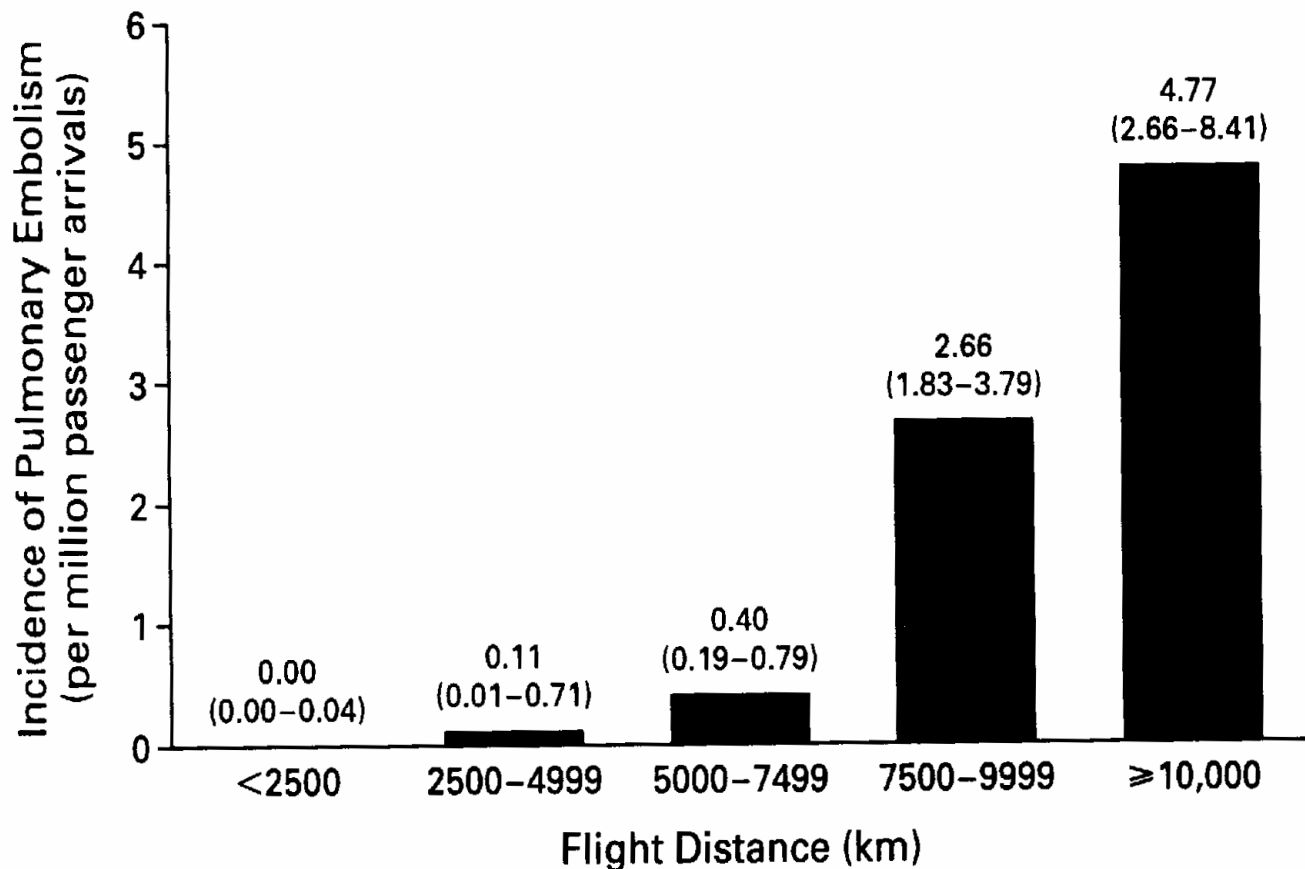
OBJECTIVES

1. Risk factors
2. Primary Prevention
3. Secondary Prevention

RISK FACTORS FOR PE

- Long-haul air travel
- Obesity
- Cigarettes
- Hypertension
- Increasing age
- Cancer
- HRT

PE DURING AIR TRAVEL: FLIGHT DISTANCE INCREASES RISK



(Lapostolle F, et al: NEJM 345: 779-783)

RISK FACTORS FOR PE

Nurses' Health Study

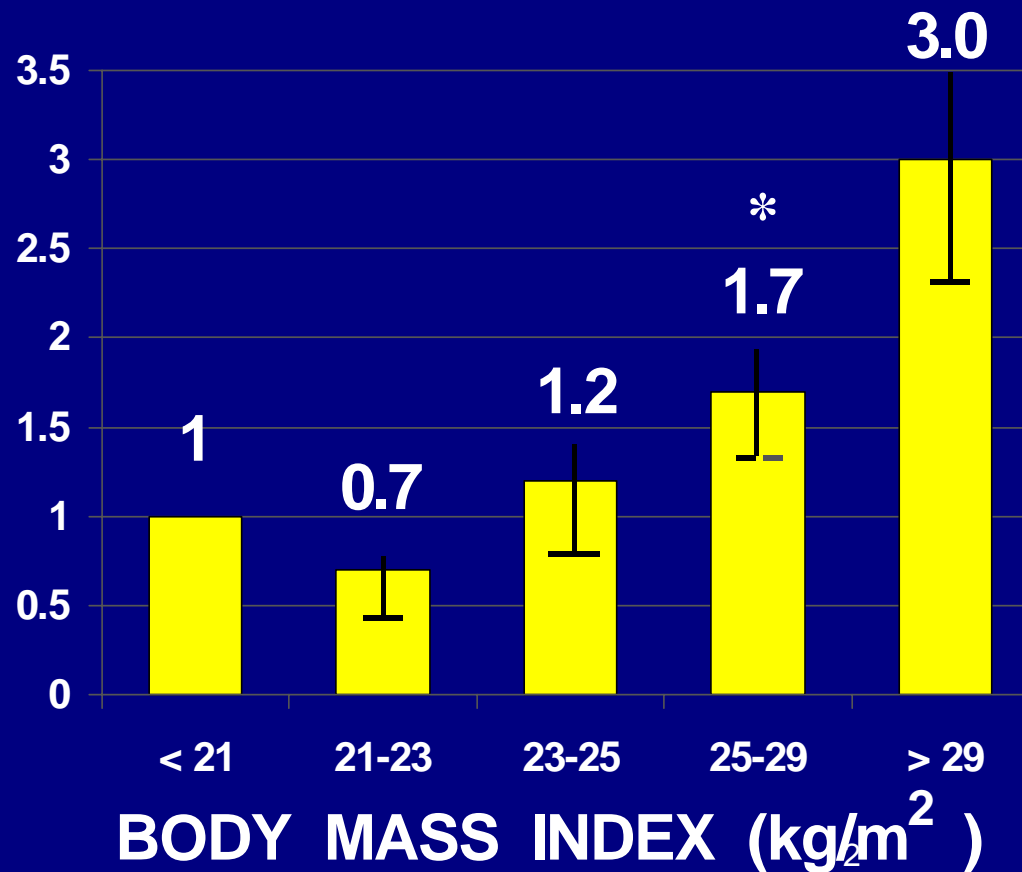
(JAMA 1997; 277: 642)

- **Obesity** (RR = 3.0 with BMI > 29)
- **Cigarette smoking**
(RR = 2.1 with > 35 cigs/d)
- **Hypertension** (RR = 1.5)

RISK OF PE: Body Mass Index

Nurses' Health Study
(JAMA 1997; 277: 642) *

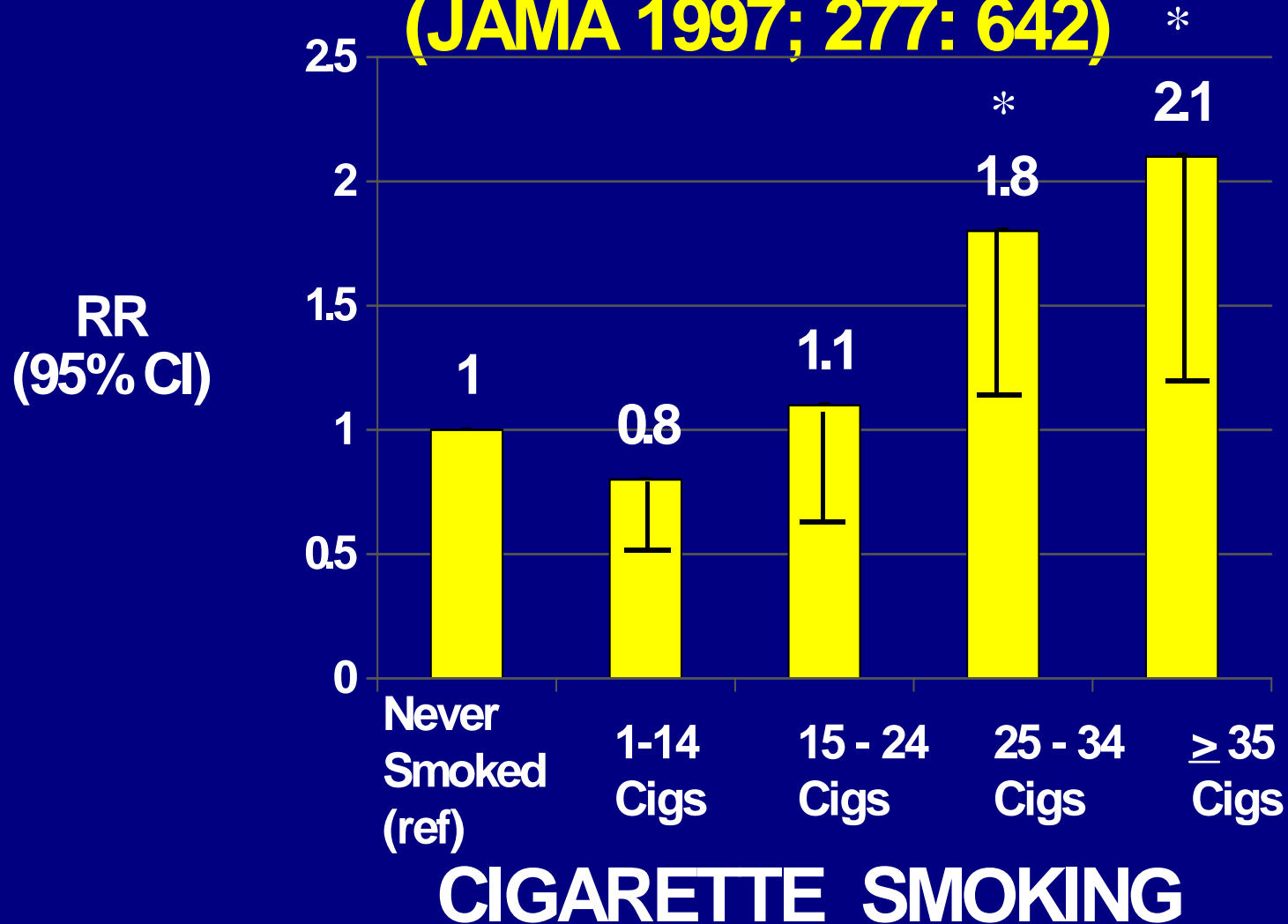
RR
(95% CI)



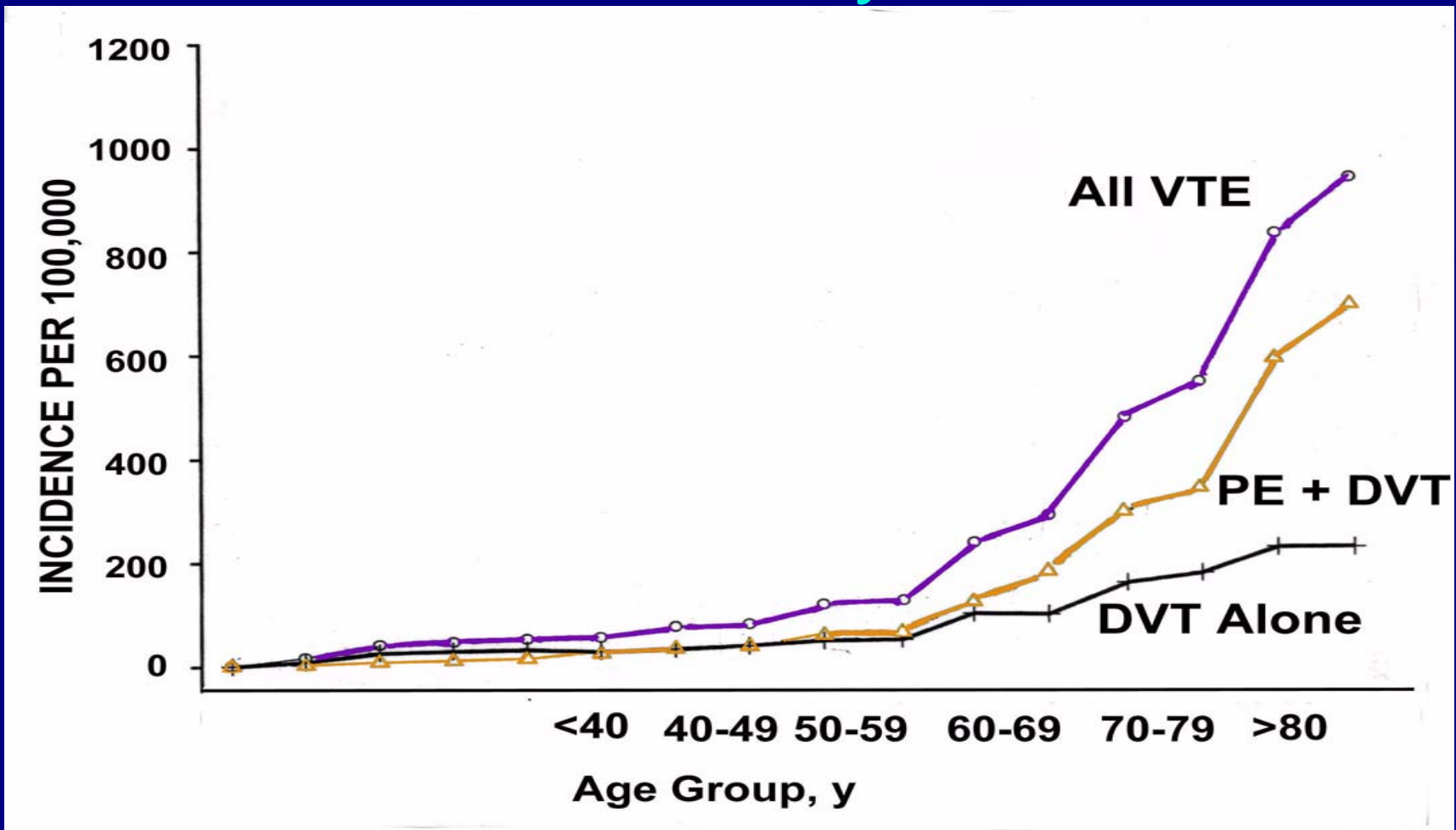
PE AND CIGARETTE SMOKING

Nurses' Health Study

(JAMA 1997; 277: 642)



AGE AND VTE Olmsted County, MN



(Arch Intern Med 1998; 158: 585)

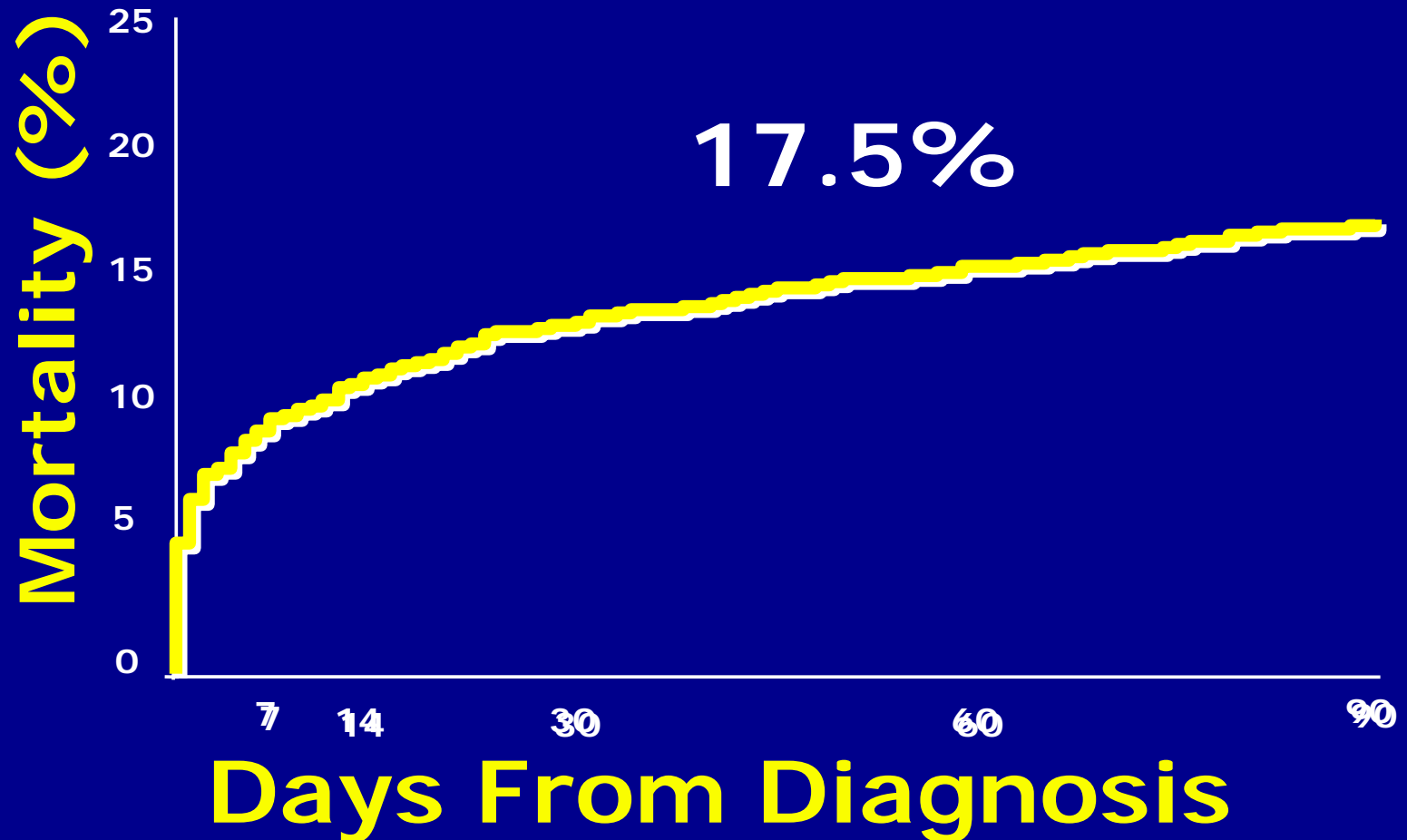
PRIMARY

PREVENTION

VTE PROPHYLAXIS

1. Failure to prophylax hospitalized medical patients can be lethal.
2. Omitting prophylaxis is a much greater problem in medical than surgical patients.
3. When prophylaxed, medical patients often receive inadequate prophylaxis.

ICOPER Cumulative Mortality After Diagnosis



***Lancet.* 1999;353:1386-1389.**

DVT REGISTRY (n=5,541) :
TOP 5 MEDICAL COMORBIDITIES

1. Hypertension
 2. Immobility
 3. Cancer
 4. Obesity (BMI > 30)
 5. Cigarette Smoking
- (Am J Cardiol 2004; 93: 259-262)**

DVT REGISTRY (n=5451)

More than twice as many hospitalized medical patients failed to receive prophylaxis as surgical patients.

(Am J Cardiol 2004; 93: 259-262)

HOSPITALIZED MEDICAL PATIENTS

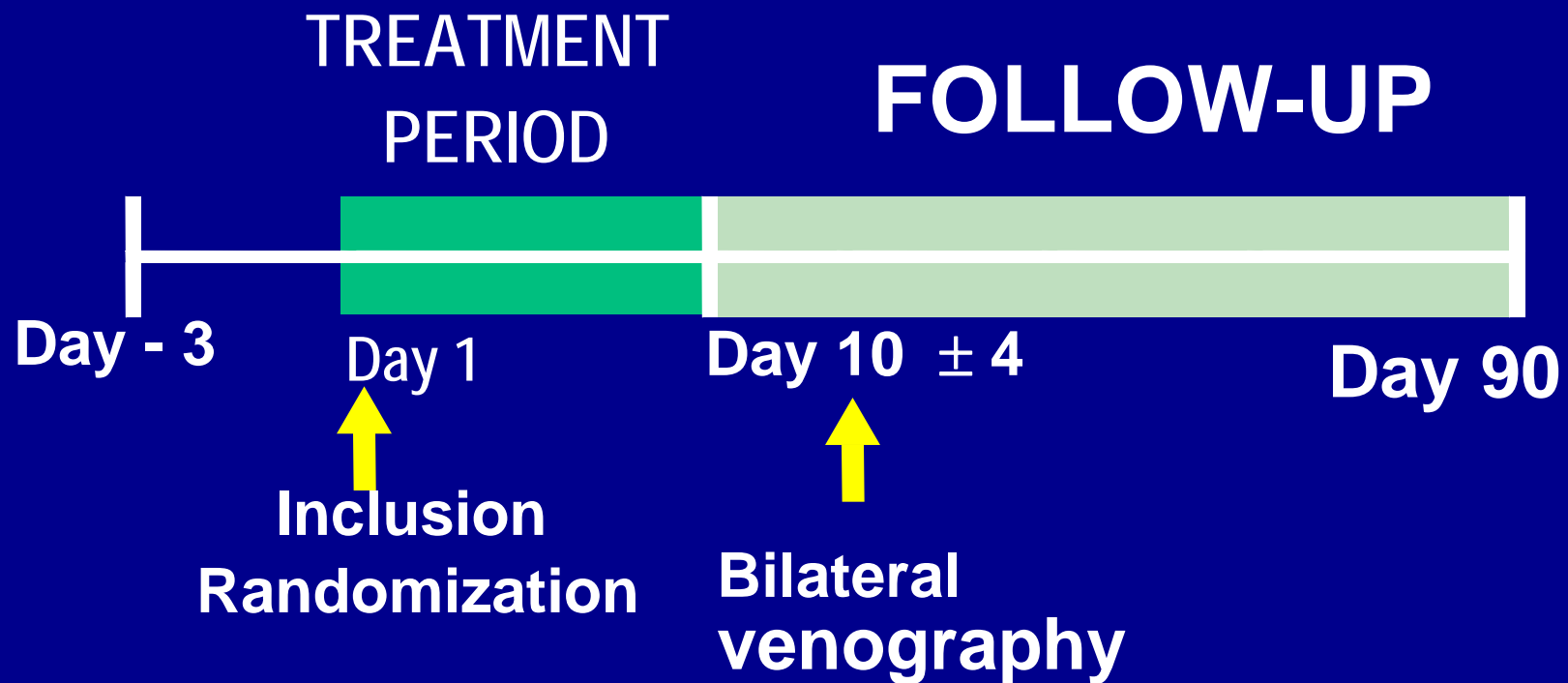
- **MEDENOX** (enoxaparin 40 mg)
 - (NEJM 1999; 341: 793)
- **PREVENT** (dalteparin 5,000 U)
 - (Circulation 2004; 110: 874)
- **ARTEMIS** (fondaparinux 2.5 mg)
 - (ISTH Abstract 2003)

MEDENOX DESIGN

- A placebo-controlled trial to prevent VTE in acutely ill hospitalized medical patients
- Enoxaparin 20 mg or 40 mg SC QD vs placebo for 6-14 days
- 1102 hospitalized patients

(Samama MM, et al. *N Engl J Med*. 1999;341:793-800)

MEDENOX DESIGN

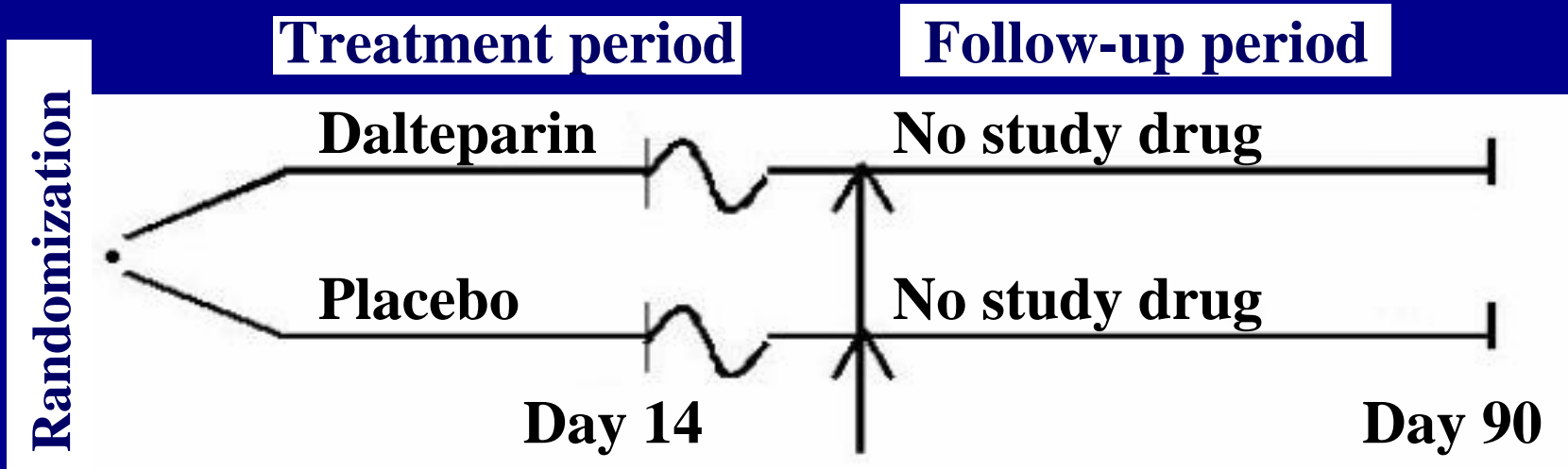


MEDENOX RESULTS

- Incidence of VTE by day 14
 - Placebo 14.9% (43/288)
 - Enoxaparin 40 mg 5.5% (16/291), ($P < 0.001$)
- Major bleeding (No significant difference)
 - Placebo 1.1%
 - Enoxaparin 40 mg 1.7%

(Samama MM, et al. *N Engl J Med.* 1999;341:793-800)

PREVENT Design



Day 21
**Primary end point/
Bilateral compression ultrasound**

Treatment groups:

- Dalteparin 5000 IU subcutaneously (SC) once daily (12 to 14 days' treatment)
- Placebo SC once daily (12 to 14 days' treatment)

Primary Efficacy End Point

Dalteparin N=1518	Placebo N=1473	Risk Ratio
42 2.77%	73 4.96%	0.55

95% CI

0.38 to 0.80

P=0.0015*

IMPLICATIONS OF MEDENOX AND PREVENT

LMWH has been shown in 2 large randomized placebo-controlled trials to reduce DVT rates in patients hospitalized with medical illness, without increased bleeding.

Clear benefits of thromboprophylaxis over placebo

Study	RRR	Thromboprophylaxis	Patients with VTE (%)
MEDENOX ¹	63%	Placebo	14.9*
		Enoxaparin	5.5
PREVENT ²	49%	Placebo	5.0*
		Dalteparin	2.8
ARTEMIS ³	47%	Placebo	10.5 [†]
		Fondaparinux	5.6

$p < 0.001$
 $p = 0.0015$
 $p = 0.029$

¹Samama MM, et al. *N Engl J Med.* 1999;341:793

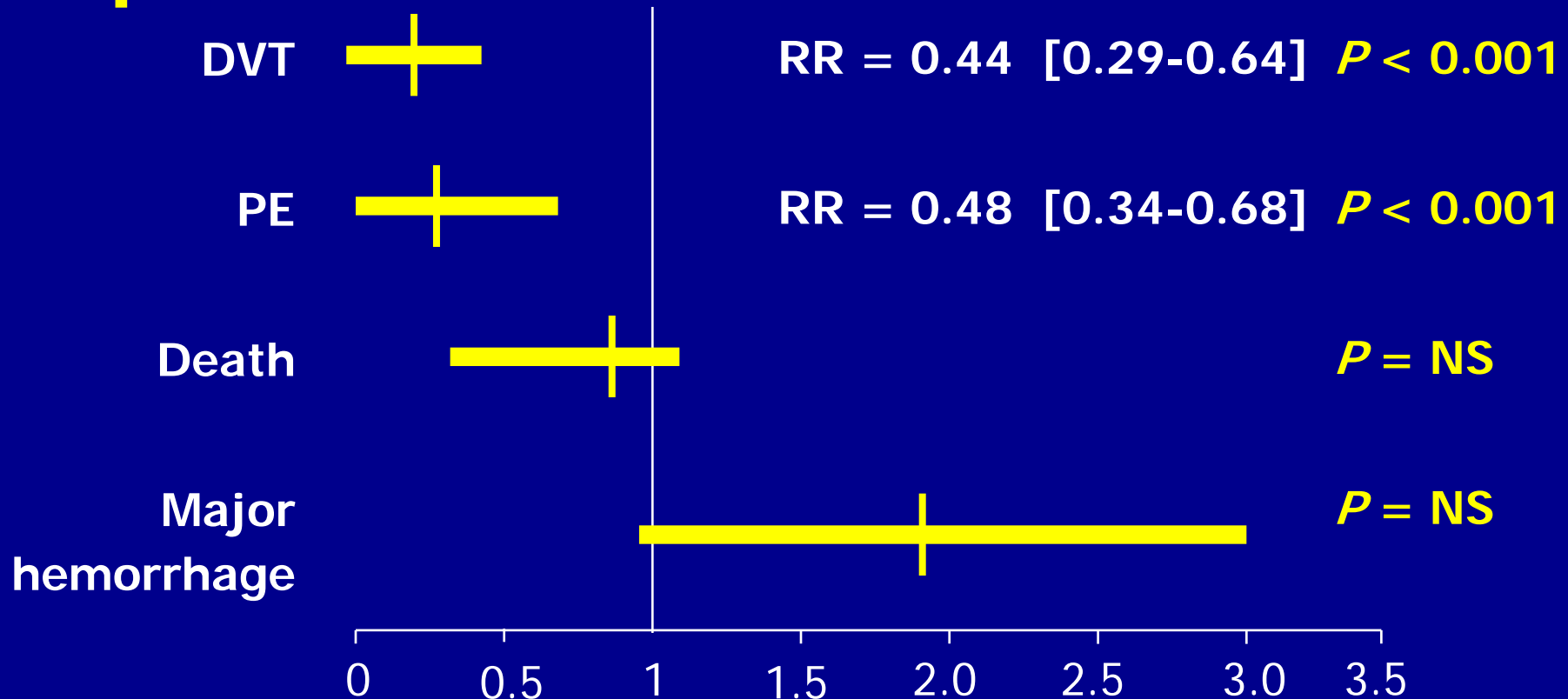
²Leizorovicz A, et al. *Circulation.* 2004;110:874

³Cohen AT. *J Thromb Haemost.* 2003;1 (Suppl 1):P2046.

Prophylaxis in medical patients: heparins (UFH/ LMWH) vs control

Heparins better


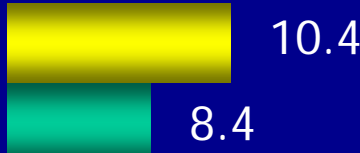
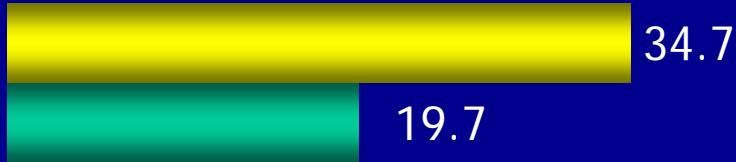
Control better



RR
Meta-analysis of 7 trials (N = 15,095)

(Mismetti P, et al. *Thromb Haemost*2000;83:14)

LMWH vs UFH

Trial	RRR	Prophylaxis	Patients with VTE (%)
PRIME¹ <i>P</i> < 0.001 for equivalence	86%	UFH 5000 IU tid Enoxaparin 40 mg	 1.4 0.2
THE-PRINCE² <i>P</i> = 0.015 for equivalence	19%	UFH 5000 IU tid Enoxaparin 40 mg	 10.4 8.4
Hillbom, et al³ <i>P</i> = 0.044	43%	UFH 5000 IU tid Enoxaparin 40 mg	 34.7 19.7

¹Lechler E, et al. *Haemostasis*. 1996;26 Suppl 2:49-56.

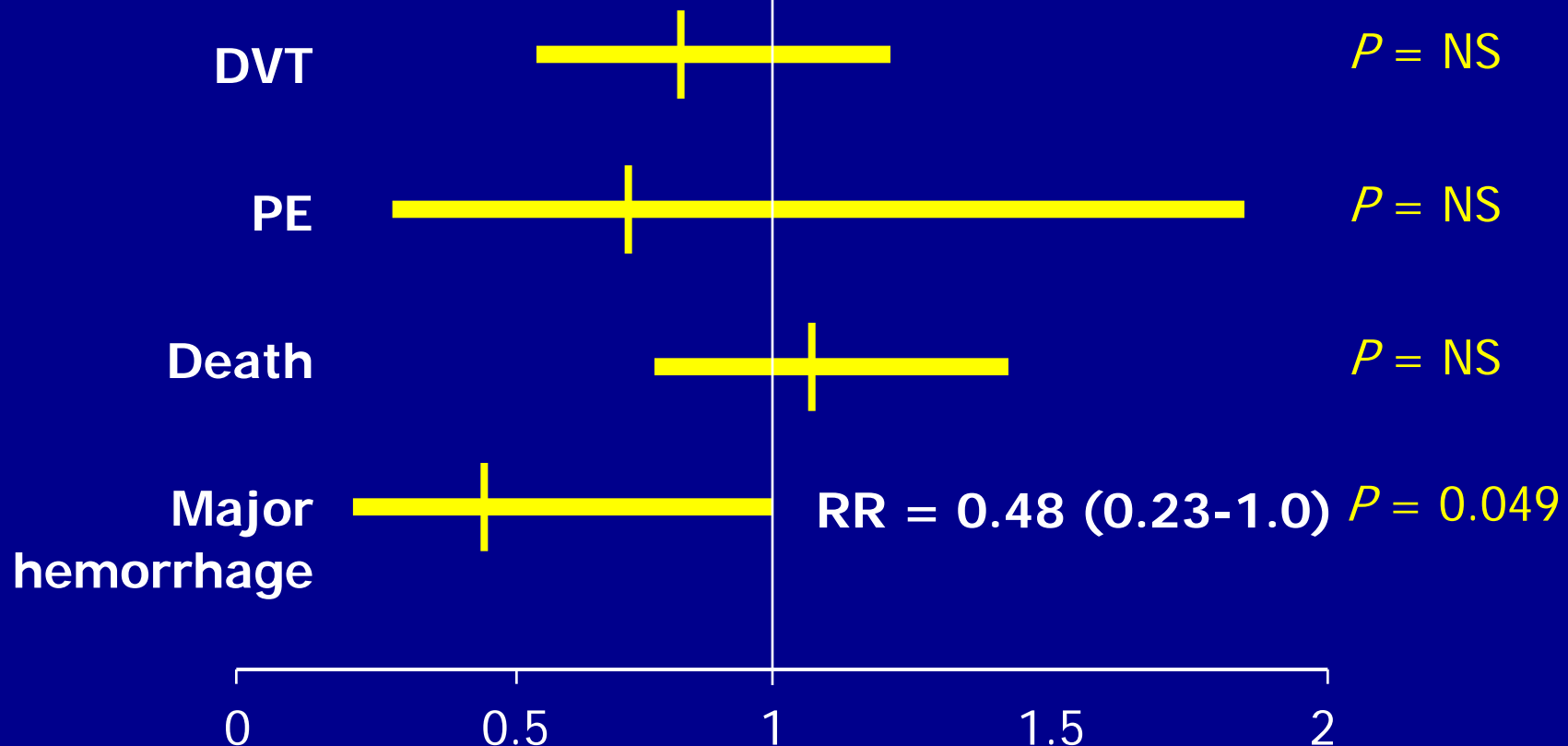
²Kleber FX, et al. *Am Heart J*. 2003;145:614-21.

³Hillbom M, et al. *Acta Neurol Scand*. 2002;106:84-92.

Thromboprophylaxis in medical patients: LMWH vs UFH

LMWH better

UFH better

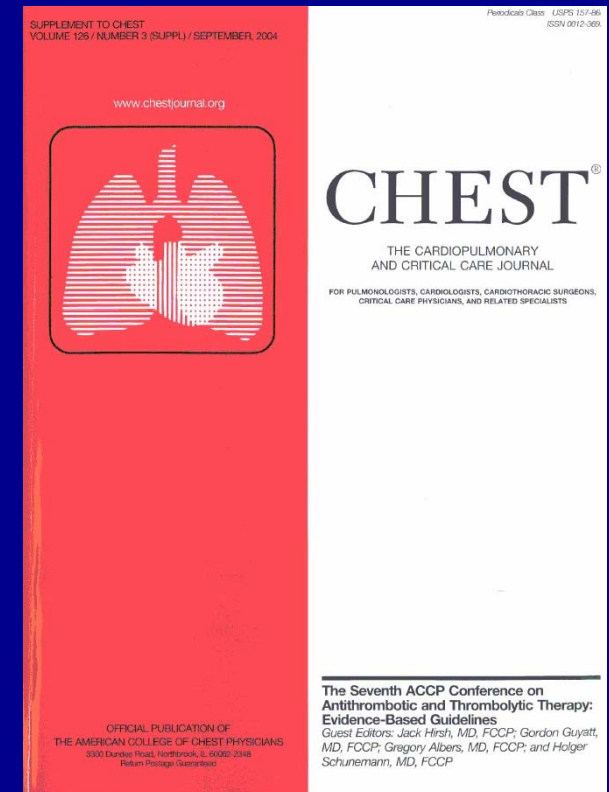


Meta-analysis (N = 4469)

Mismetti P, et al. *Thromb Haemost.* 2000;83:14.

ACCP Recommendations

- ACCP grade 1A options for thromboprophylaxis in general medical patients with clinical risk factors for VTE (including cancer, bed rest, heart failure, and severe lung disease)
 - LMWH
 - Low-dose UFH



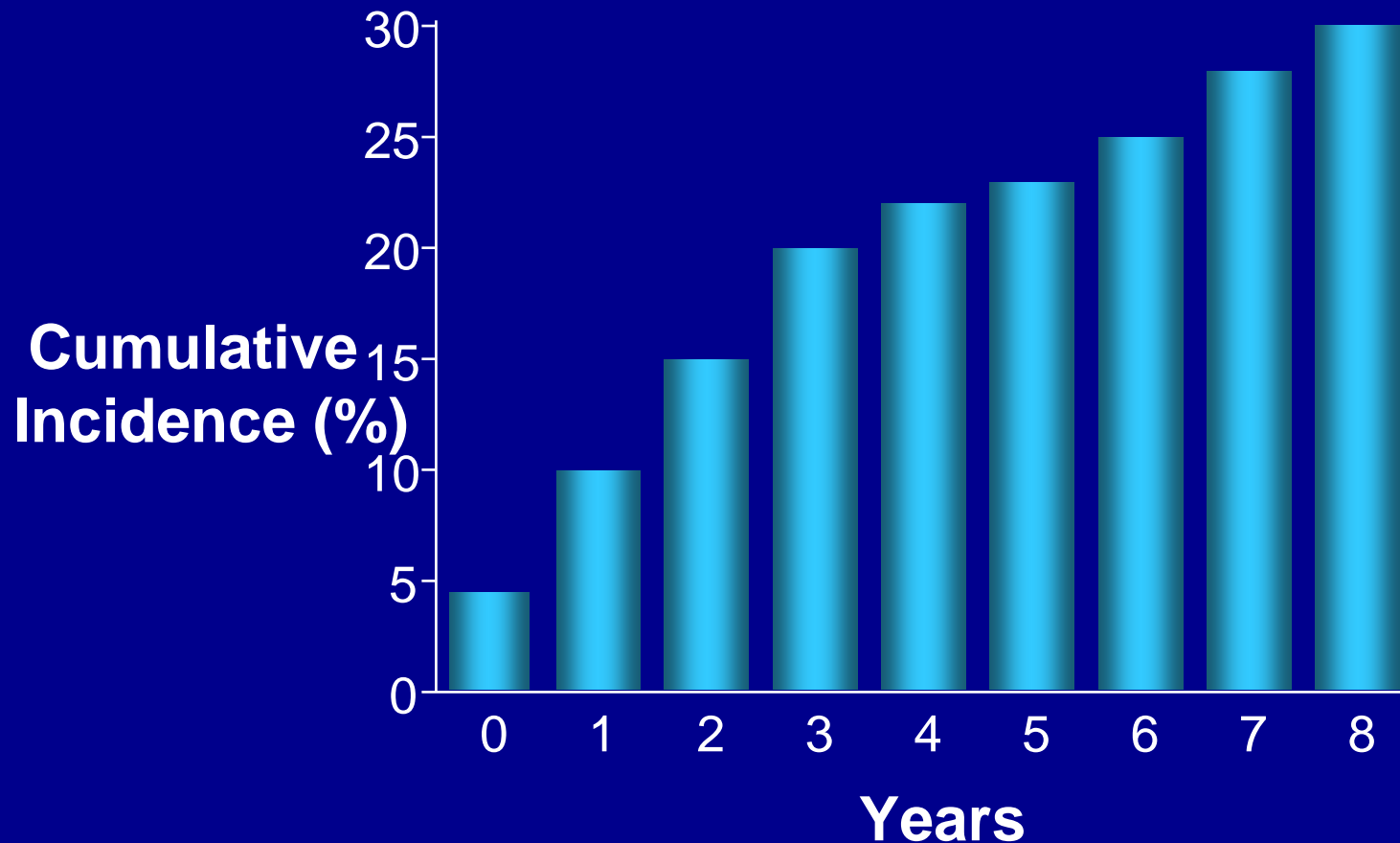
Adapted from Geerts WH. *Chest* 2004; 126: 338S

SECONDARY

PREVENTION

Recurrent Venous Thrombosis is Common Following a First Episode of Symptomatic DVT

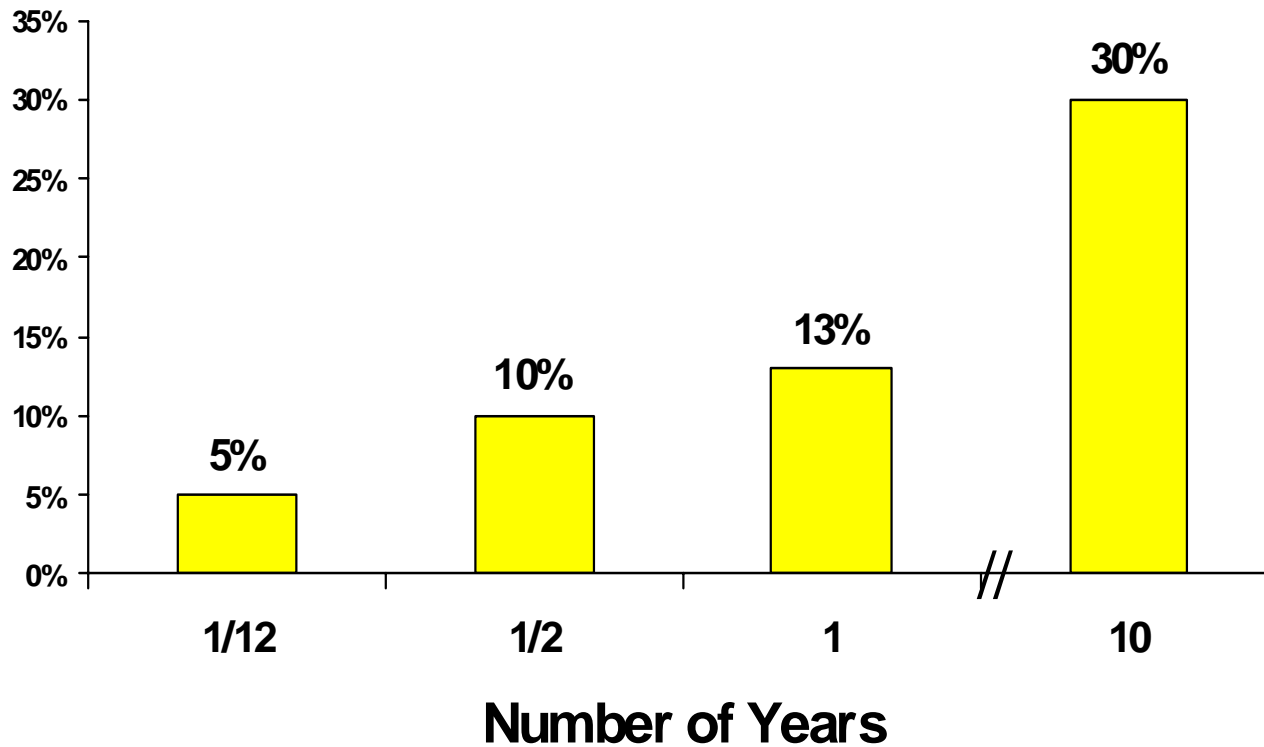
355 patients: 1st episode of DVT followed for 8 years



(Prandoni et al, *Ann Intern Med* 1996;125:1-7)

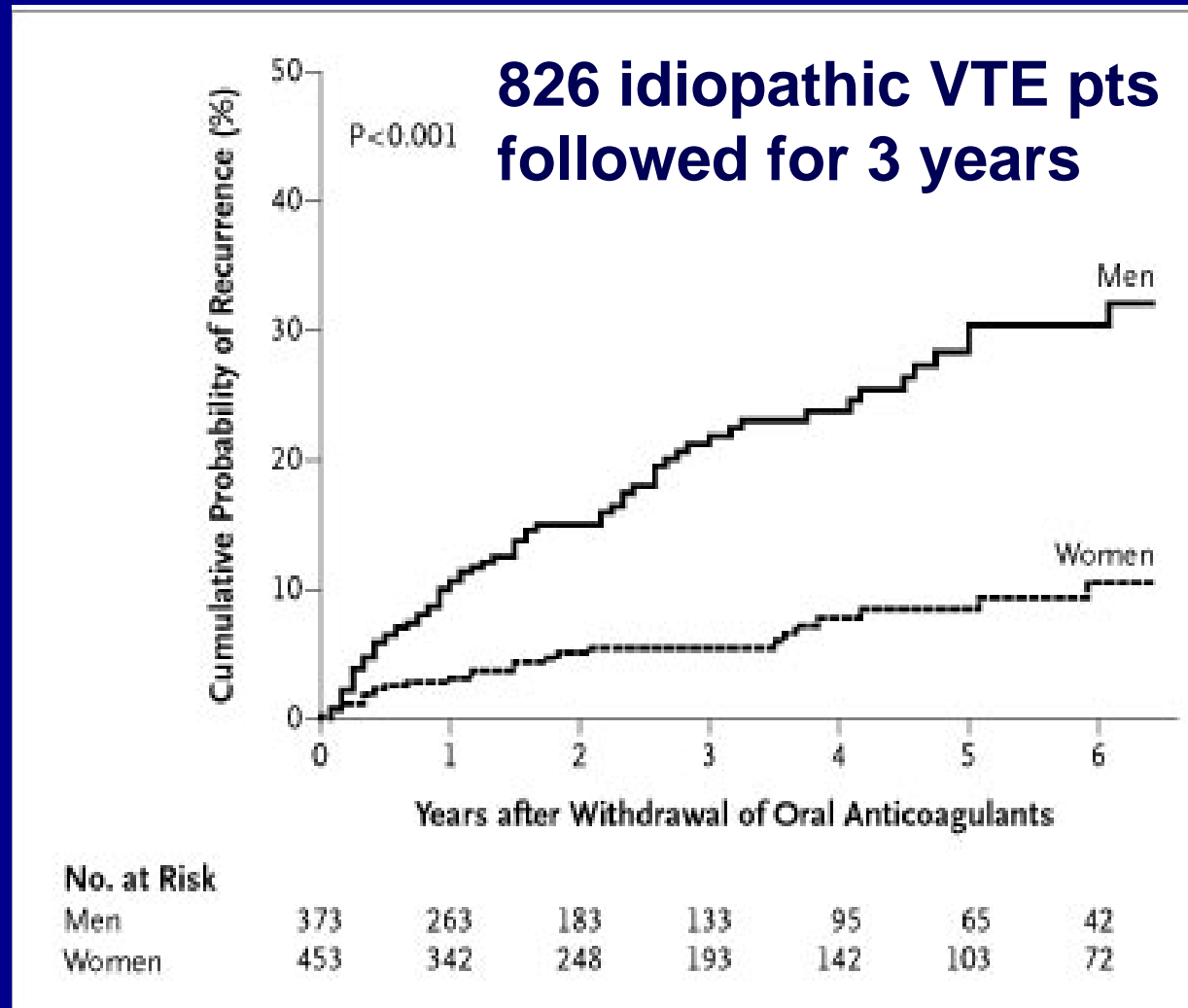
RATE OF RECURRENT VTE

Olmsted County



(Arch Intern Med 2000; 160: 761-768)

RECURRENT VTE: GENDER



(Kyrle et al. NEJM 2004; 350: 2558-63)

RECURRENCE AFTER IDIOPATHIC VTE: 2003

TRIAL
PREVENT

TAKE-HOME POINT

Low intensity A/C (INR 1.5-2.0) reduces recurrence rate by 2/3.

ELATE

Standard A/C (INR 2.0-3.0) is more effective but as safe as low intensity A/C.

THRIVE-3

Ximelagatran effective, safe.

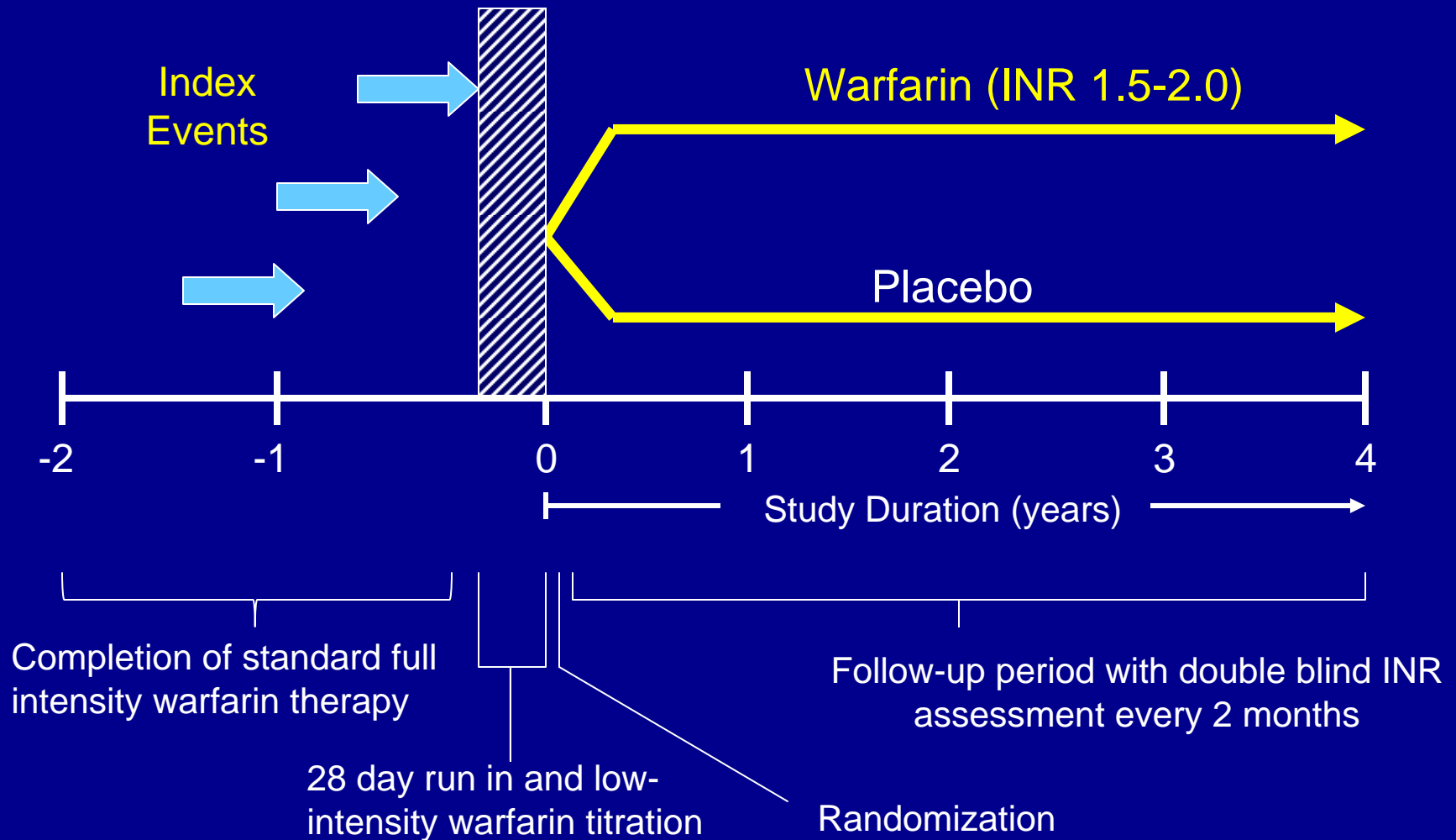
PREVENT TRIAL

NIH-Sponsored Randomized Trial of the Optimal Duration, Intensity of Anticoagulation in Patients with idiopathic VTE

- Recruited at 52 centers in USA, Canada, Geneva
- 508 patients randomized, including 119 at BWH
- Double-blind; Coumadin vs. placebo, target INR= 1.5–2.0

(NEJM April 10, 2003)

PREVENT: Study Design



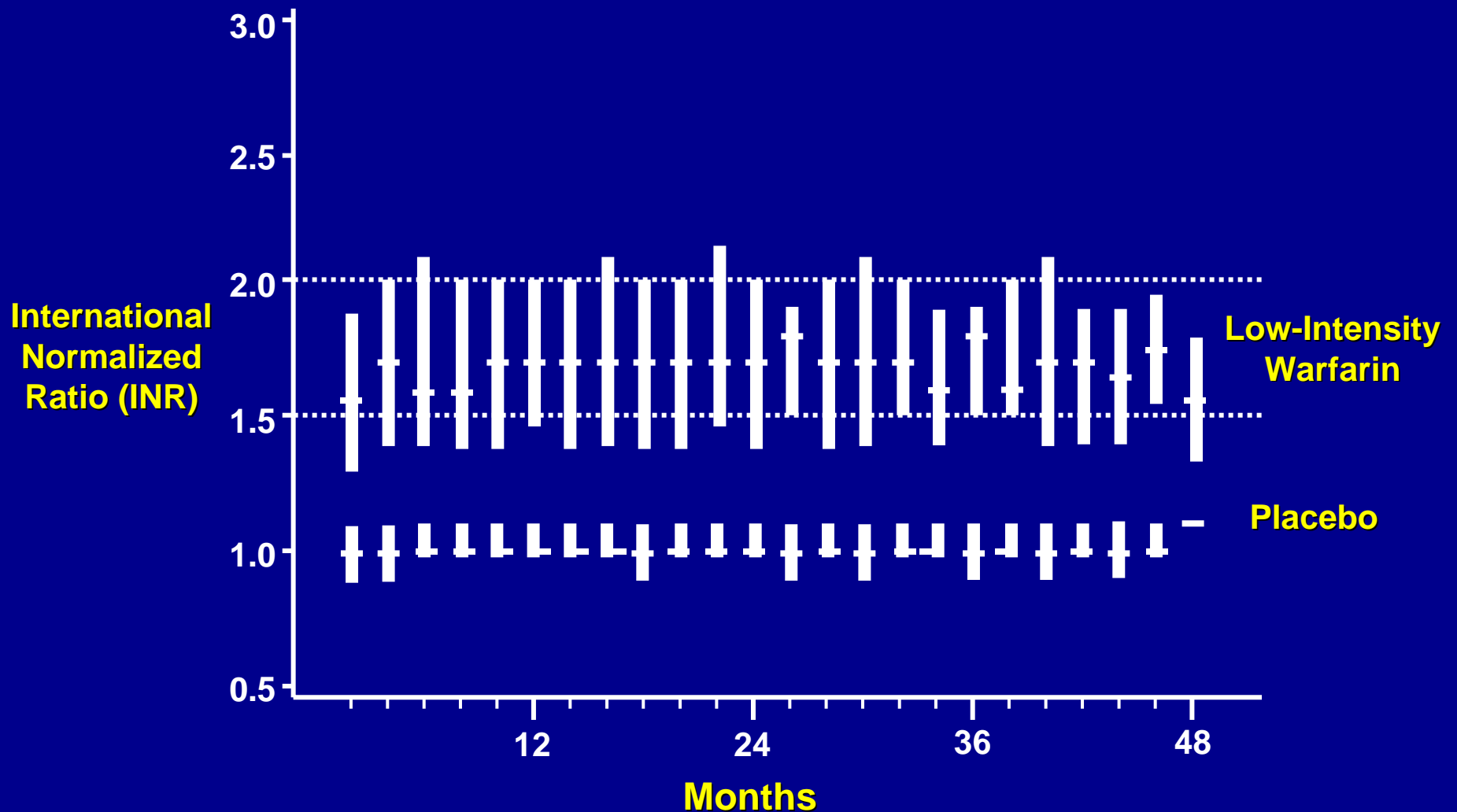


PREVENT: Double-Blind Low-Intensity Warfarin Monitoring Every Two Months

Blinded INR	Dose Adjustment	Repeat INR
< 1.3	↑ by 2mg/day	1 week
≥ 1.3 and < 1.5	↑ by 1mg/day	8 weeks
≥ 1.5 and ≤ 2.0	Maintain current dose	8 weeks
> 2.0 and ≤ 3.0	↓ by 1mg/day	8 weeks
> 3.0 and ≤ 4.0	↓ by 2mg/day	1 week
> 4.0	Stop study drug 3 days	3 days*

* If repeat INR > 4.0, then discontinue therapy
* If repeat INR < 4.0, then ↓ dose by 2mg/day and repeat INR in 1 week

PREVENT: Distribution of INR Levels During Follow-Up, According to Treatment Group



N Engl J Med 2003 (April 10, 2003)

PATIENT CHARACTERISTICS

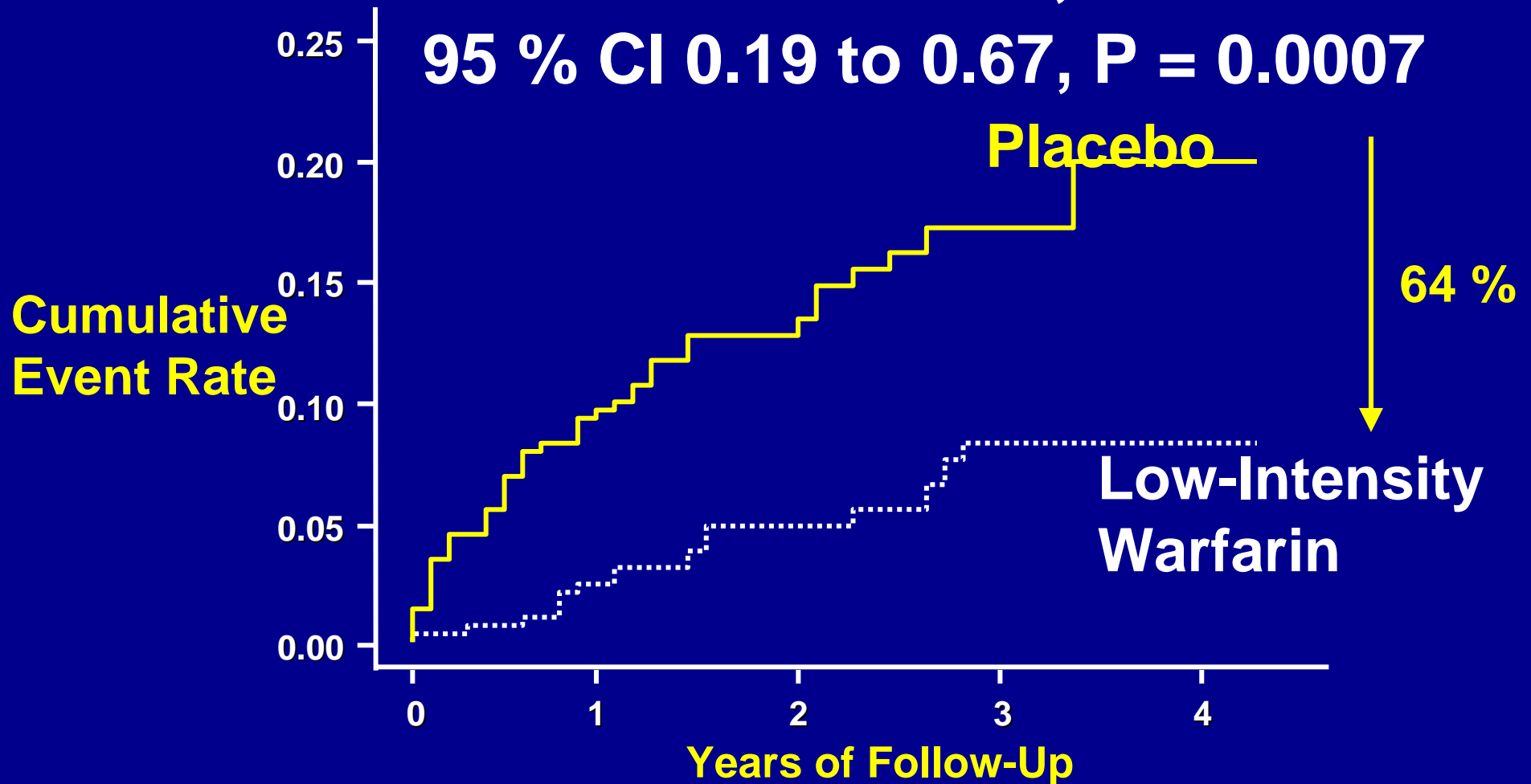
	<u>Placebo (N=253)</u>	<u>Warfarin (N=255)</u>
Age (years)	53	53
BMI (kg/m ²)	30	30
FH VTE	32%	32%
Leiden	27%	22%
Prothrombin mutation	4.7%	4.8%
Prior warfarin (months)	6.3	6.7

ADVERSE EVENTS

	Placebo	Warfarin	HR	P
Recurrent VTE	37	14	0.36	0.0007
Major bleeding	2	5	2.52	0.25
Minor bleeding	34	60	1.91	0.002
Deaths	8	4	0.51	0.26
Cancer	9	4	0.45	0.18
Composite	41	22	0.49	0.006

PREVENT Primary Endpoint: Recurrent VTE

Hazard Ratio = 0.36,
95 % CI 0.19 to 0.67, P = 0.0007



N Engl J Med 2003 (April 10, 2003)

PREVENT: Recurrent VTE by Subgroups

Number of Prior VTE

2 or more

1

Factor V Leiden or Prothrombin Mutation

Present

Absent

Gender

Men

Women

Age, years

30-44

45-64

65-89

Time after randomization

≤ 1 year

> 1 year

Hazard Ratio (95%CI)

0.43 (0.20, 0.90)

0.25 (0.08, 0.74)

0.25 (0.07, 0.87)

0.42 (0.20, 0.86)

0.47 (0.23, 0.96)

0.20 (0.06, 0.67)

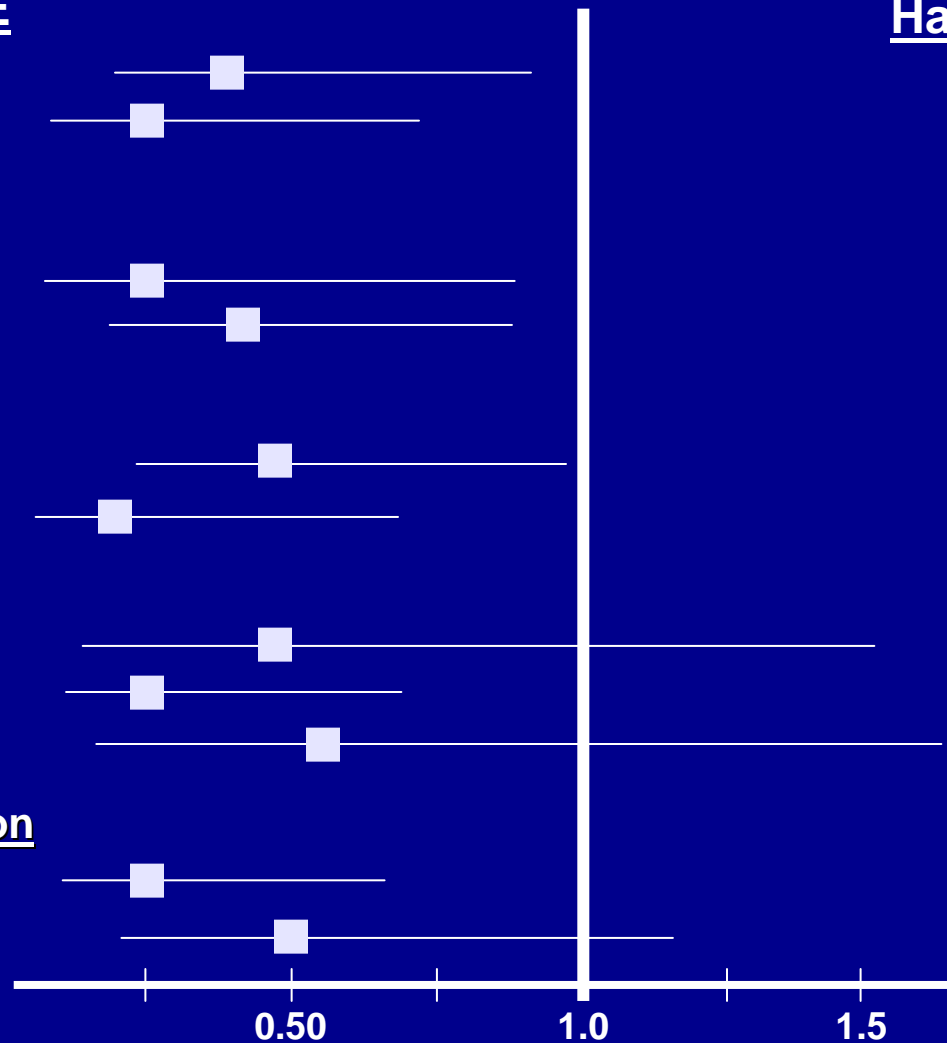
0.45 (0.14, 1.51)

0.24 (0.09, 0.65)

0.57 (0.19, 1.64)

0.27 (0.11, 0.66)

0.49 (0.21, 1.16)



Favors low-intensity warfarin

Favors placebo

N Engl J Med 2003 (April 10, 2003)

PREVENT: Conclusions

- Long-term, low-intensity warfarin is a highly effective and safe method to prevent recurrent DVT and PE.
- Long-term use of low-intensity warfarin can be considered a new standard of care to manage VTE after cessation of full-dose warfarin.

N Engl J Med 2003 (April 10, 2003)

SUMMARY

- Primary prevention is underutilized, especially in medically ill patients.
- In the absence of a provoked DVT/PE, the risk of recurrence is surprisingly high. In this setting, long-term prophylaxis against recurrent events should be considered.