

# Venous Thromboembolism Prophylaxis in Surgical Patients

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# Conflict of Interest

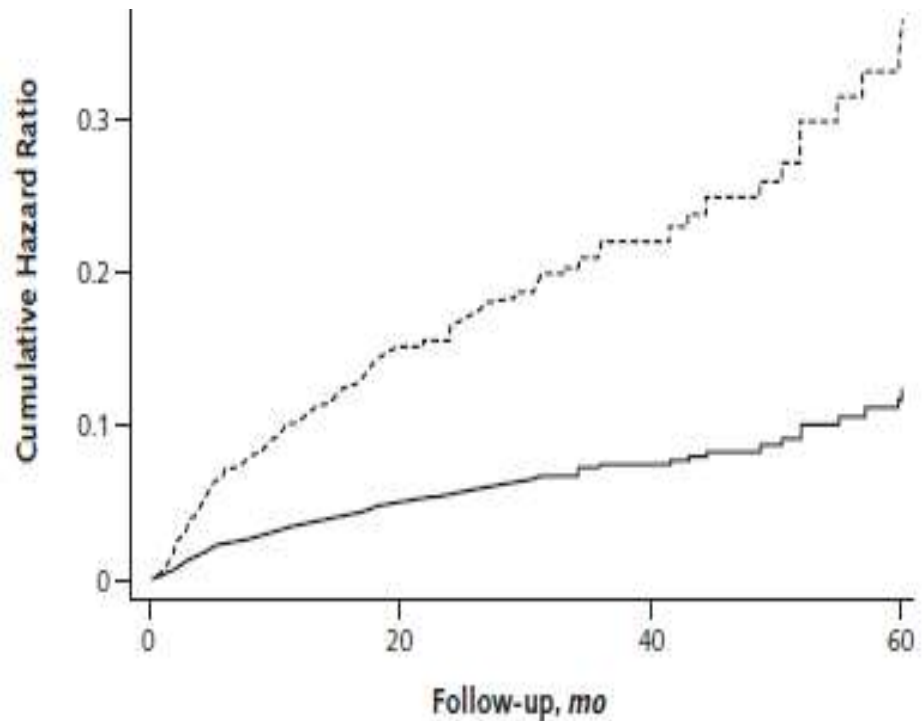
- Boehringer-Ingelheim expert panel 2011: dabigatran for AF

# Objectives

- Identify VTE risk factors
- Describe risk assessment instruments
- Describe clinical trial data for VTE prophylaxis
- Describe VTE prophylaxis guidelines for surgical patients

# VTE Epidemiology and Outcome

- 247,000 PE admissions (2006); 10-18% mortality<sup>1</sup>
- Recurrent DVT or PE<sup>2</sup>
  - 5% at 3 months
  - 18% at 2 years
  - 30% at 8 years



1 Tsai J, *et al.* *Arch Intern Med* 2012; Apr 2 [Epub ahead of print]

2 Prandoni P, *Pathophysiol Haemost Thromb.* 2002;32:72

Douketis J. *Ann Intern Med* 2010;153:523-31

# Post Thrombotic Syndrome

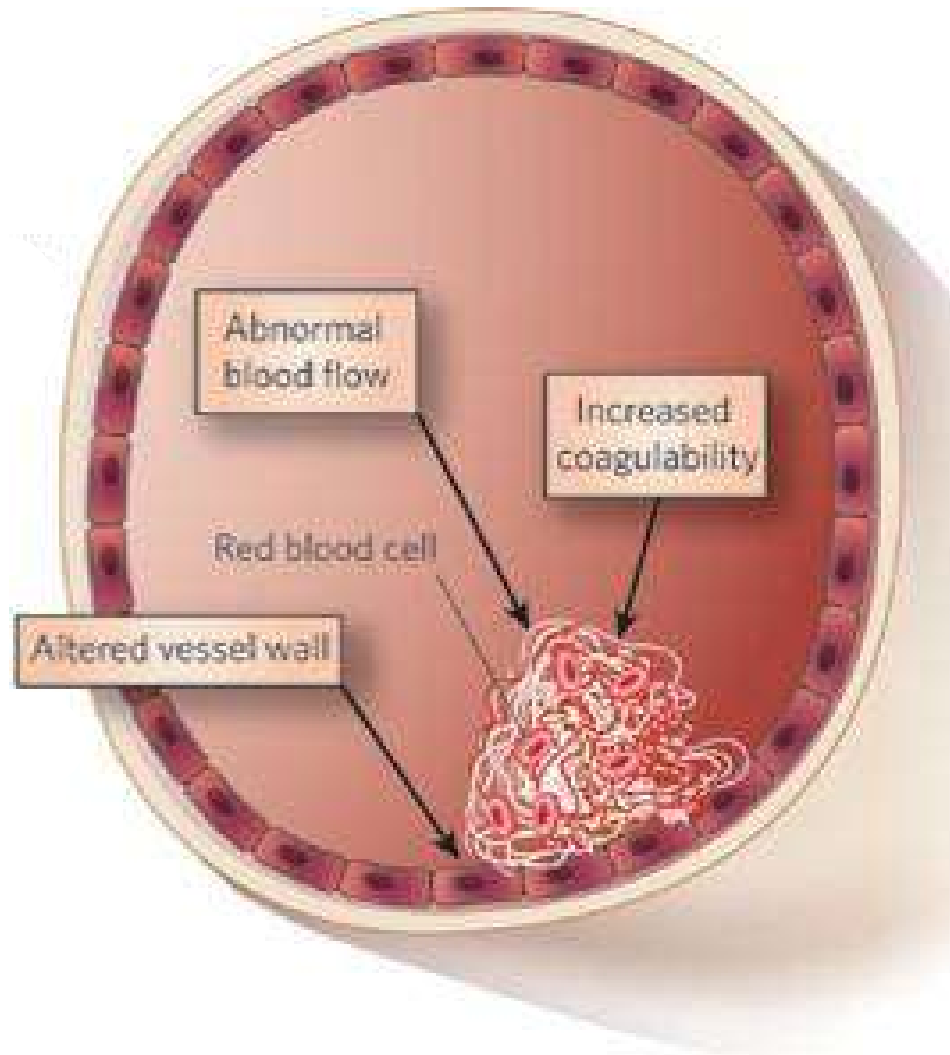
- Incidence
  - 23% at 2 years
  - 29% at 8 years
- Symptoms
  - chronic edema
  - Brawny skin discoloration
  - pain on standing
  - pruritis
  - varicosities



# Hospital Acquired Conditions (HACs)

- CMS Hospital Acquired Conditions (HACs) (2008)  
*If a patient experiences a DVT or PE perioperatively with THR/TKR, a portion of hospital payment will be withheld*
- Partnership for Patients (CMMI)
- Value-based purchasing (inpatient care)
- JCAHO

# Pathophysiology of VTE



- Tissue factor release initiates the coagulation cascade
- Localized clots comprised of red cells and fibrin

# VTE Risk Factors

## Stasis

- Advanced age
- Immobility (bed rest > 4 d)
- CHF, severe COPD
- Stroke, paralysis, casting
- Spinal cord Injury
- Increased viscosity
- Obesity
- Varicose veins

## Endothelial Damage

- Surgery, esp. orthopedic
- Prior DVT, PE

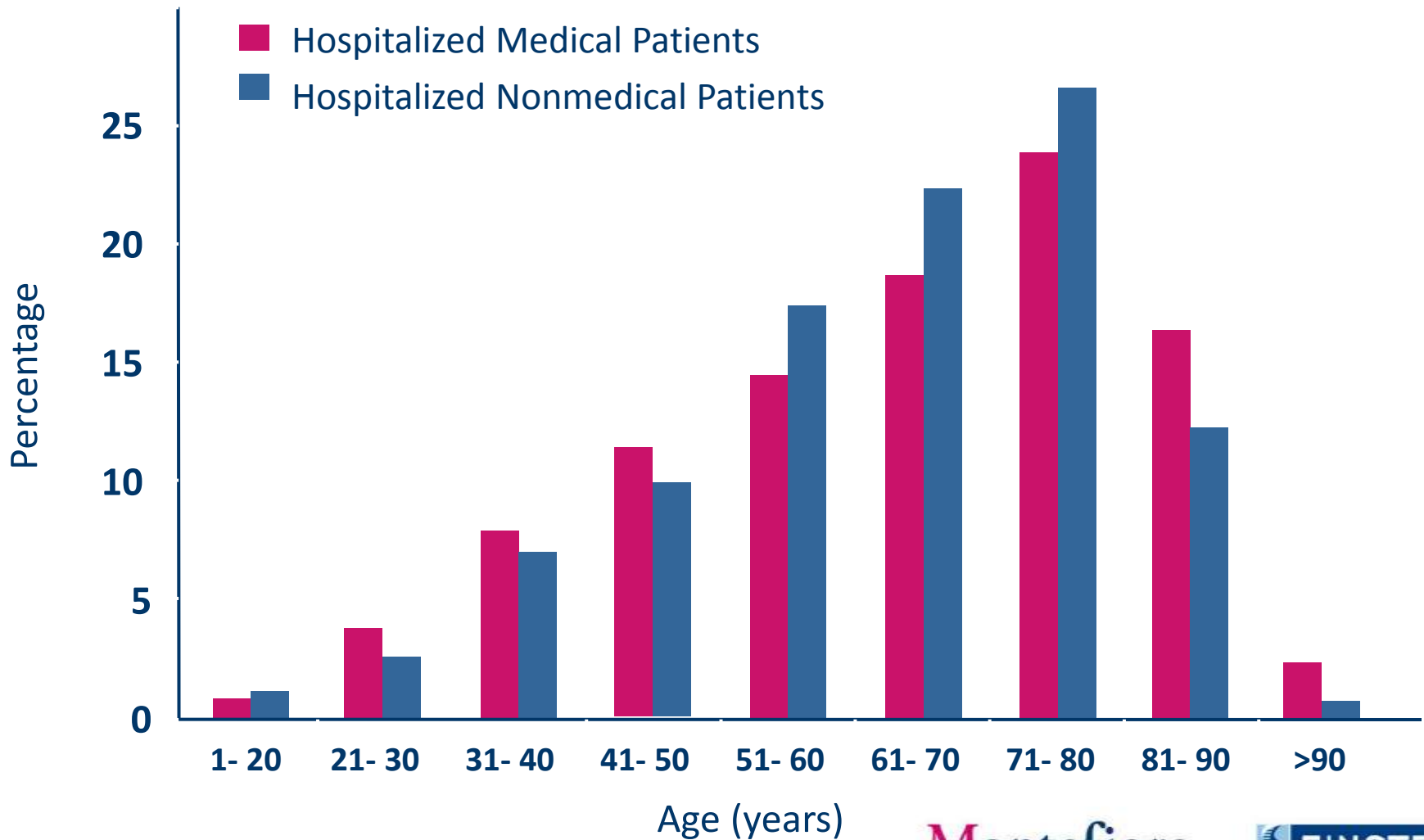
## Hypercoagulability

- Advanced age
- Active cancer
- High estrogen states
- Thrombophilia
- Inflammatory states
- Surgery
- Increased blood viscosity

- Trauma
- Central lines, devices



# Age of DVT Patients



Piazza G, et al. *Chest*. 2007;132:554-561.

# Independent Risk Factors for First VTE

	AR*	95% CI
Hospitalization or nursing home	58.8	53.4 - 64.2
Hospitalization with surgery		20.3 - 27.3
Hospitalization without surgery	21.5	17.3 - 25.6
Nursing home	13.3	9.9 - 16.8
Active malignant neoplasm	18.0	13.4 - 22.6
Trauma	12.0	9.0 - 14.9
Congestive heart failure	9.5	3.3 - 15.8
Prior central venous catheter, pacemaker	9.1	5.7 - 12.6
Neurological disease w/extremity paresis	6.9	3.5 - 10.2
Prior superficial vein thrombosis	5.4	3.0 - 7.7

Heit JA, et al. *Arch Intern Med.* 2002;162:1245-1248.

\*adjusted population attributable risk (age, sex, yr)

# VTE Risk Factors

## Patient-related

- Age
- Obesity
- Cancer and Rx
- Prior VTE
- Bedrest
- Thrombophilia
- Hormonal Rx
- other

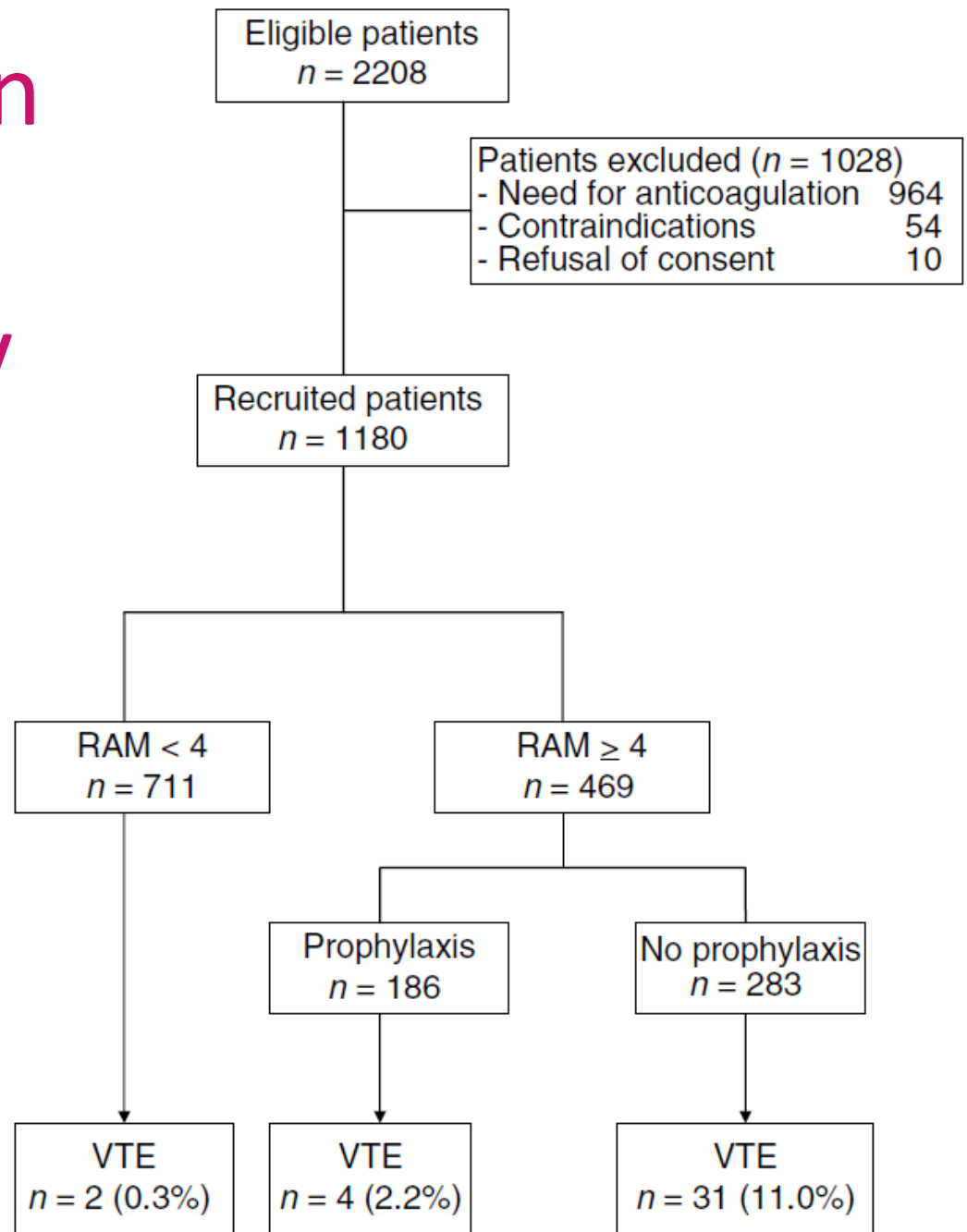
## Treatment-related

- Type of surgery
- Duration of surgery
- Type of anesthesia/analgesia

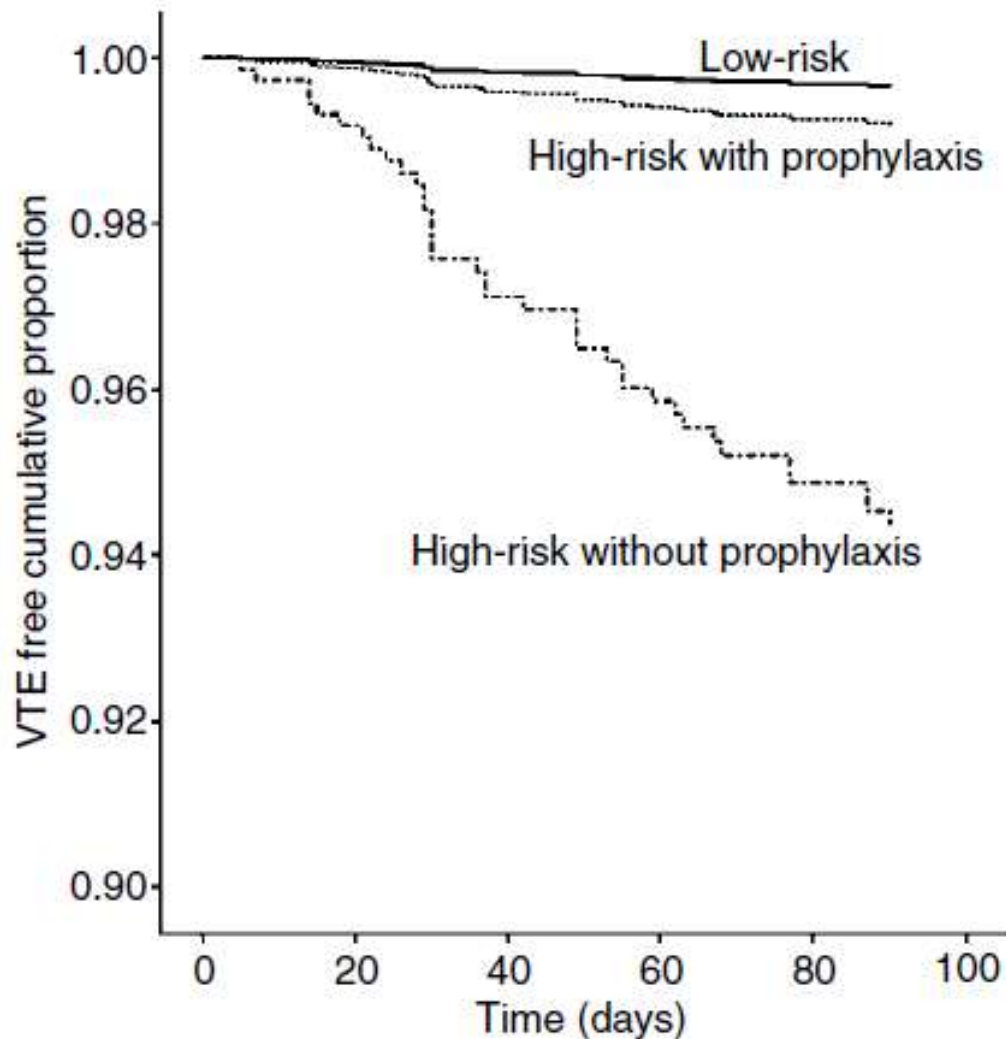
# Padua Prediction Score High Risk Score $\geq 4$

Baseline Features	Score
Active Cancer	3
Prior VTE	3
Reduced mobility ( $\geq 3$ days)	3
Thrombophilia (antithrombin, protein C or S, factor V Leiden, G20210A prothrombin mutation, antiphospholipid syndrome)	3
Trauma or surgery $\leq 1$ month	2
Age $\geq 70$	1
Heart or Respiratory Failure	1
Acute MI or Ischemic CVA	1
Acute infection and/or rheumatologic disorder	1
Obesity (BMI $\geq 30$ )	1
Hormonal Rx	1

# Padua Prediction Score Validation Study



# Padua Prediction Score Validation

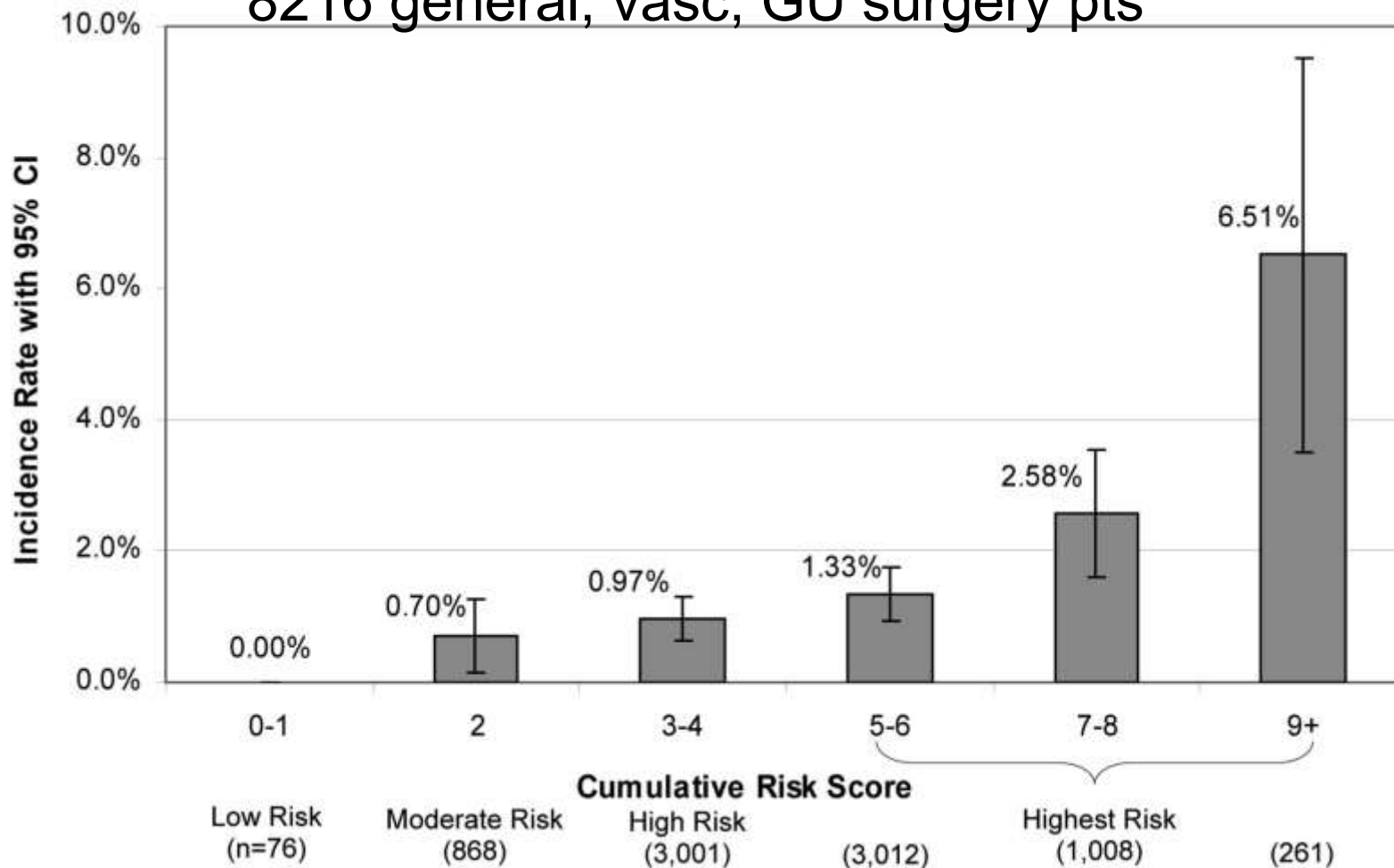


# Caprini Risk Assessment Model

1 point each	2 Points each	3 Points each	5 Points each
Age 41-60	Age 61-74	Age $\geq$ 75	Stroke (< 1 mo)
Minor surgery	Arthro. Surgery	Hx VTE	Elect. arthroplasty
BMI > 25 Kg/m <sup>2</sup>	Major open surgery (> 45 min)	Family Hx VTE	Hip, pelvis or leg fracture
Swollen legs	Laparoscopic Surgery (>45 min)	Factor V Leiden	Acute spinal cord injury (<1 mo)
Varicose veins	Malignancy	Prothrombin 20210	
Hormone Rx	Bedrest (>72h)	Anticardiolipin Ab	
Sepsis (< 1 mo)	Immobil. plaster cast	$\uparrow$ homocysteine	
Lung Dz (< 1mo, Pn)	Central Venous cath.	HIT	
Abn PFT		Other cong or acquired thrombophilia	
Acute MI			
CHF (< 1 mo)			
IBD Hx			
Med pt bedrest			
		<b>TOTAL SCORE:</b>	

# Caprini Risk Score Validation Study

Incidence Rate by Risk Level / Cumulative Risk Score  
8216 general, vasc, GU surgery pts





# Risk Score & Prophylaxis (Gen, GU, GYN)

Score	Risk Level	DVT Incidence	ACCP Prophylaxis Recommendation
0	Low	2%	Early ambulation
1 - 2	Moderate	10 - 20%	Mechanical, pref. IPC
3 - 4	Higher, low bleed risk	20 - 40%	LDUH or LMWH or mechanical (IPC)
3 - 4	Higher, high bleed risk	20 - 40%	Mechanical (IPC)
≥ 5	Highest	40 - 80%	IPC + (LDUH or LMWH)
≥ 5	Highest; cancer surgery	40 - 80%	IPC + LMWH; Continue LMWH for 4 weeks

# DVT Prophylaxis

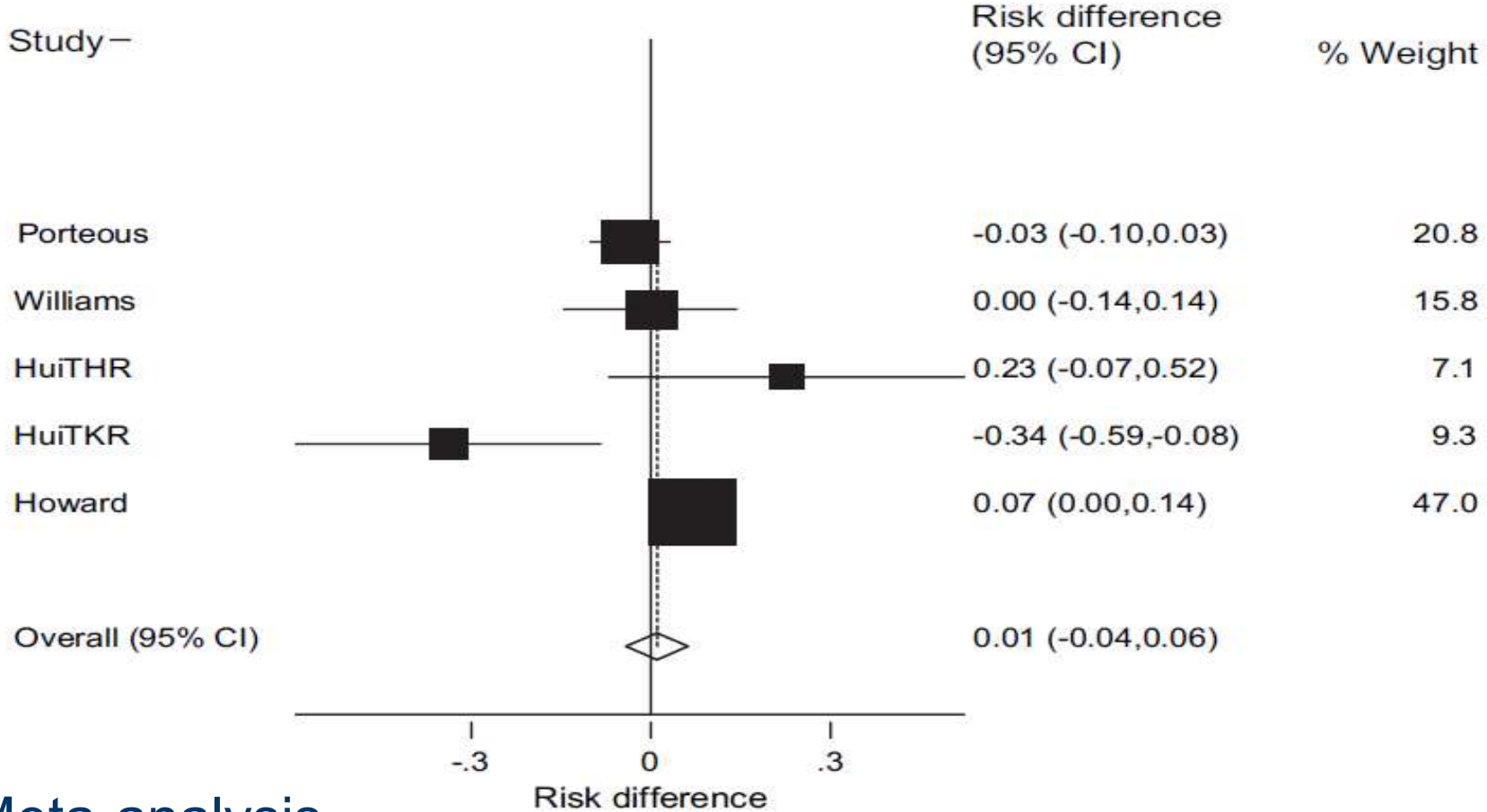
## Non-pharmacologic

- compression stockings (CGS)
- leg elevation
- early mobilization
- intermittent pneumatic compression (IPC)
- Foot pumps

## Anticoagulant

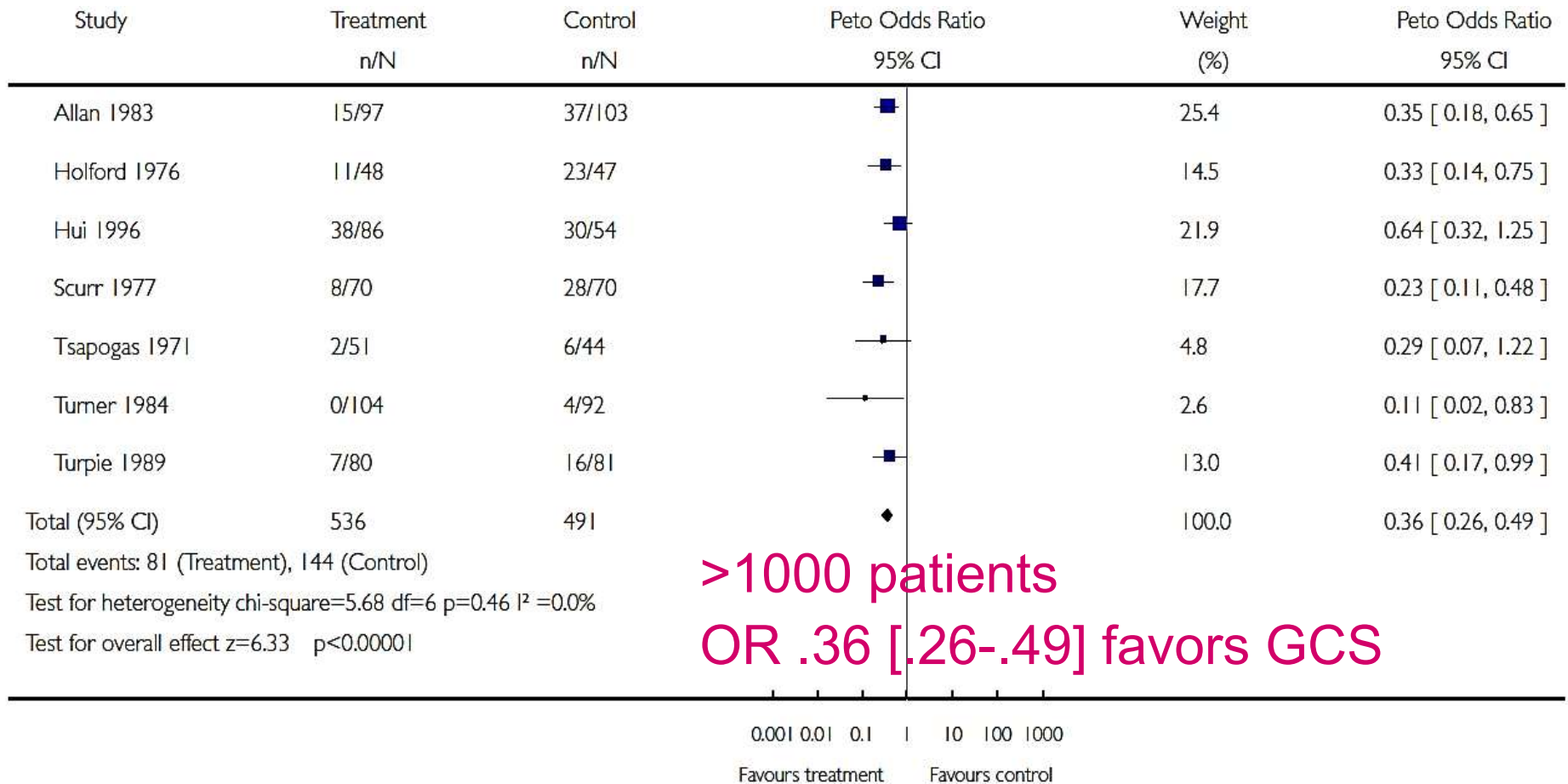
- Heparins
  - SC UF Heparin
  - LMWH
  - fondaparinux
- Warfarin
- Factor Xa inhibitors, rivaroxaban (apixaban)
- Direct Thrombin inhibitors: dabigatran
- Aspirin (antiplatelet)

# Graded Compression Stockings for VTE Prophylaxis in Surgical Patients



## Meta-analysis

# GCS for VTE Prevention in Hospitalized Patients: Cochrane Meta-analysis



# CLOTS: VTE Prophylaxis for Stroke Patients: Thigh high stockings vs. Placebo

## Methods:

- 2518 immobile stroke patients ( $\leq 1$  wk)
- Randomized for stockings or placebo during stay
- Evaluations: USG 7–10 d; 25–30 days
- Outcome: proximal DVT, symptomatic or not

## Results:

- Proximal DVT
  - GPS 10.0% (126 pts)
  - Placebo 10.5% (133 pts)
  - P=.05, 95% CI -1.9-2.9
- Skin Break
  - GPS 5% (64)
  - Placebo 1% (16)
  - OR=4.18, 95% CI 2.4-7.27

# CLOTS 2: Knee High vs. Thigh High Stockings in Stroke Patients

## Methods:

- 3114 immobile stroke patients
- Randomized for stocking height during hospital
- Evaluations: USG 7–10 days; 25-30 days
- Outcome: proximal DVT, symptomatic or not

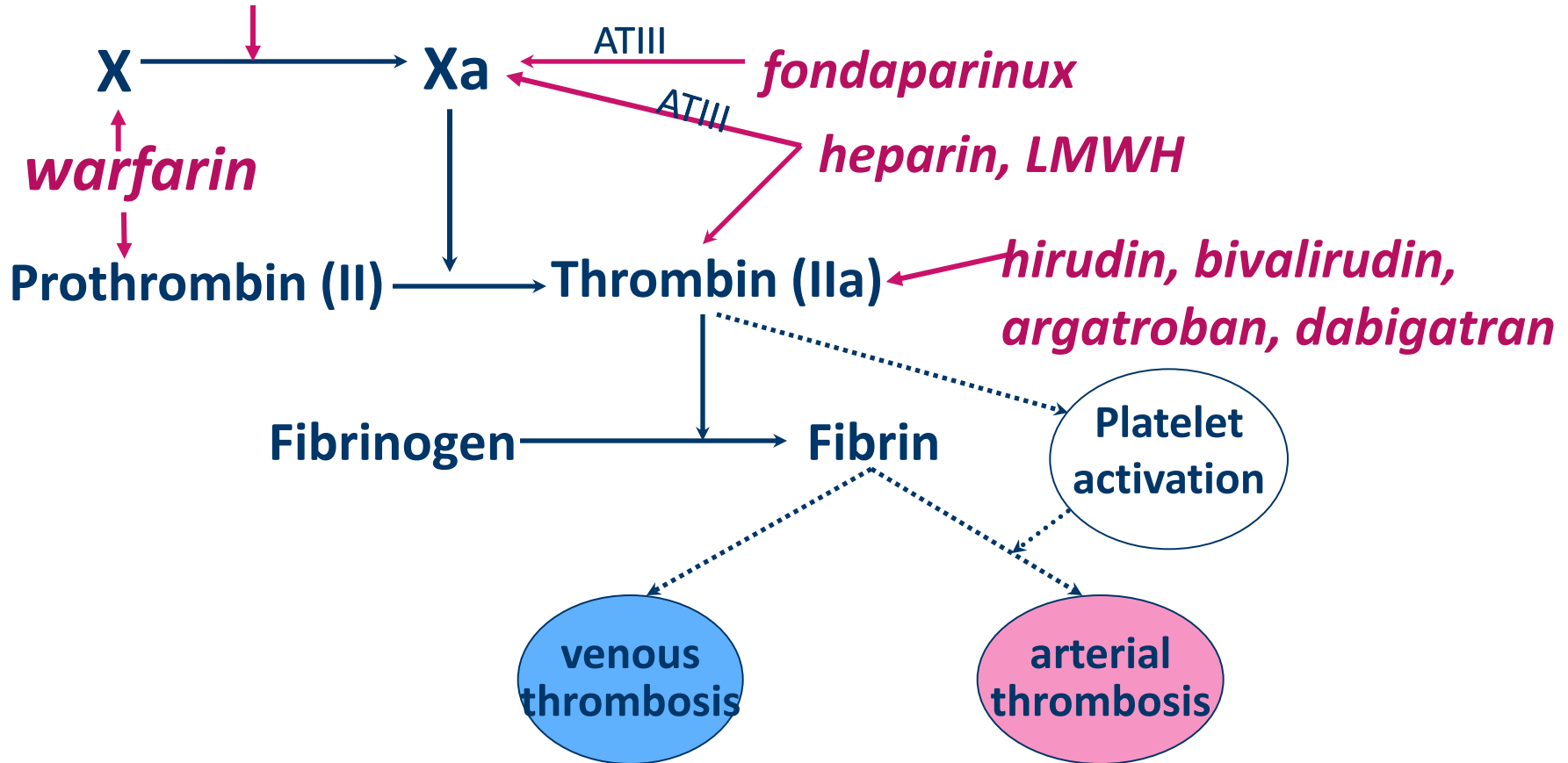
## Results:

- Proximal DVT
  - Thigh high 6.3% (98 pts)
  - Knee high 8.8% (138 pts)

P=.008; OR 31%
- Skin Breaks (3.9% v. 2.9%)
- No difference in survival, calf DVT, PE, adherence

# Anticoagulant Actions

*apixaban, rivaroxaban,  
edoxaban, betrixaban*



# Indirect Anticoagulants

	warfarin	UF Heparin	LMWH	fondaparinux
Target	Factor II, VII, IX, X	Ila, Xa via ATII	Ila, Xa via ATII	Xa
Bioavail.	30%	90%	100%	
Half life	~ 40 hrs	1 hour	4 hours	17 hours
Metab	Liver/ many interactions			
Renal excr	no	No	Yes	yes
Reversal	Yes	Complete	Partial	no



# New Oral Anticoagulants

	Dabigatran	Rivaroxaban	Apixaban
Target	Thrombin (II) inhibitor	Direct Factor Xa active site inhibitor, free and bound Factor Xa	Direct reversible Factor Xa inhibitor
Bioavail.	6.5% ; prodrug req. hydrolysis	86%	51-85%
Peak plasma concent.	0.5– 2 hrs	2 – 4 hrs	3 hrs
Half life	12-17 hrs (bid dosing)	7-11 hrs (qd to bid)	8-15hrs
Metabolism	Hepatic gluc.	CYP3A4	CYP3A4
Renal Clear.	80%	65%	25%

# New Oral Anticoagulants

	Dabigatran	Rivaroxaban	Apixaban
Dosing VTE Px	(once daily)	Once daily for ortho Px	(Twice daily)
Interactions	Potent inhibitors or inducers of P-gp, (Verapamil, amiodarone, macrolides), anticoagulants, NSAIDS, platelet aggregation inhibitors	CYP3A4, Pgp inhibitors, Verapamil, macrolides, protease inhibitors, azole antifungals, etc	CYP3A4 inhibitors
Antidote	None	None	None
Coagulation Monitoring	No	No	No

# Rivaroxaban VTE Prophylaxis in TKR

	<b>Rivaroxaban</b> 10 mg daily 6-8 hrs postop (n=1595)	<b>Enoxaparin</b> 40 mg sc 12 hrs preop; 8 hrs postop (n=1558)	10-14d Px, then bilateral venogram
All VTE + death @13-17 days	79/824 (9.6%)	166/878 (18.9%)	ARR 9.2%, CI [5.9-12.4] p<.001
Major VTE	9/908 (1.0%)	24/925 (2.6%)	ARR 1.6%, CI [0.4-2.8] p=.01
Major bleed	0.6%	0.5%	
Drug-related ADEs (GI)	12%	13%	

# Rivaroxaban VTE Prophylaxis in THR

	Rivaroxaban 10 mg daily 6-8 hrs postop (n=1595)	Enoxaparin 40 mg sc 12 hrs preop; 8 hrs postop (n=1558)	35 d Px, then bilateral venogram
All VTE + death @ 36 days	18 (1.1%)	58 (3.7%)	ARR 2.6% (1.5-3.7) p<.001
Major VTE	4/1686 (0.2%)	33/1678 (2%)	ARR 1.7% (1.0-2.5) p<.001
Major bleed	6/2209 (0.3%)	2/2224 (.1%)	P = 0.18

# VTE Prophylaxis in THR: ADVANCE-3

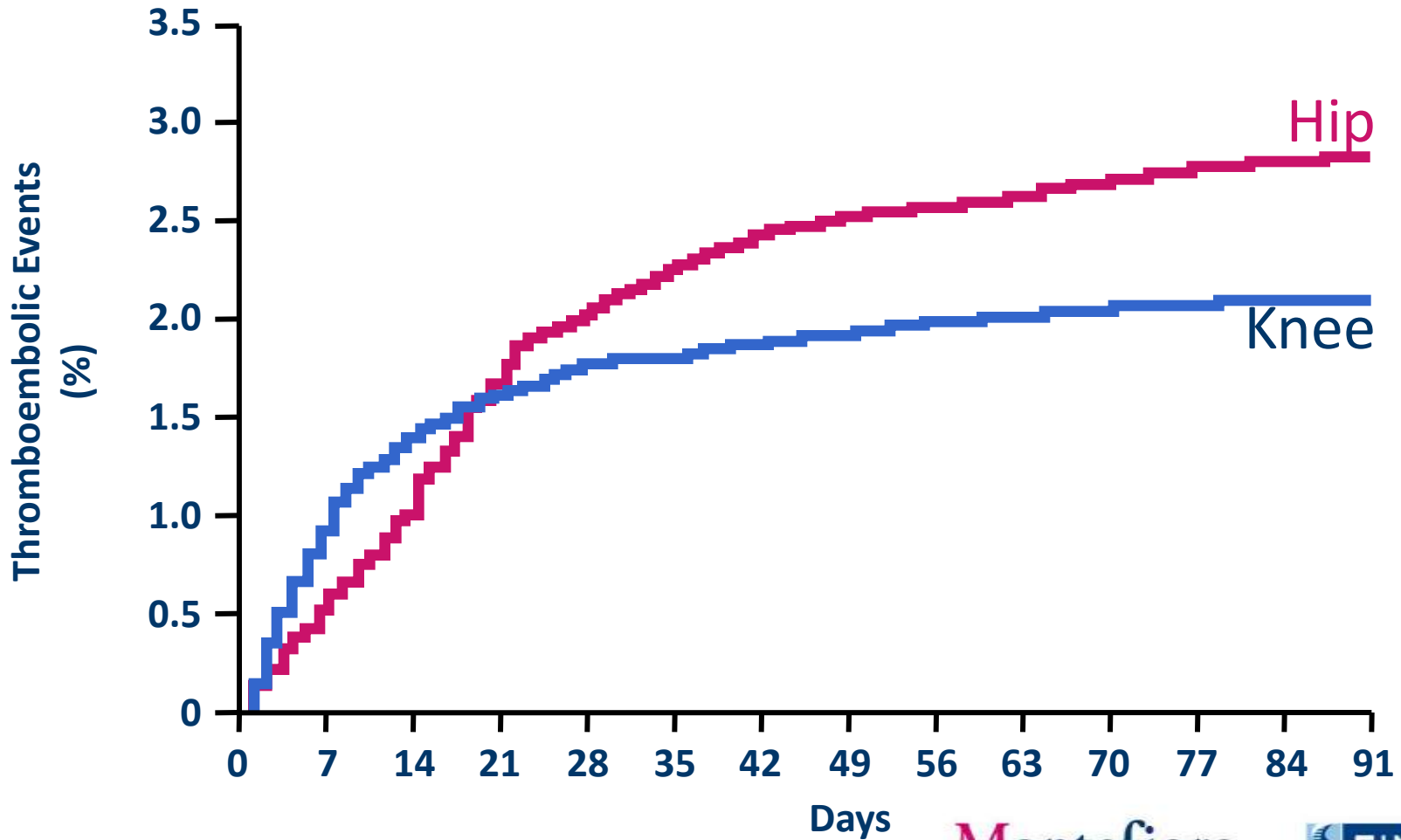
	Apixaban* (n=1949)	Enoxaparin** (n=1917)	P Value
All VTE + death	1.4% (n=27)	3.9% (n=74)	<0.001
Major VTE	0.5% (n=10)	1.1% (n=25)	0.01
Major bleed	0.8% (n=22)	0.7% (n=18)	0.54
Clinically relevant nonmajor bleed	4.8% (n=129)	5.0% (n=134)	0.72

35 d Px, followed 60+ days after last dose; then bilateral venogram

\*Apixaban 2.5 mg po bid; 12-24 h postop

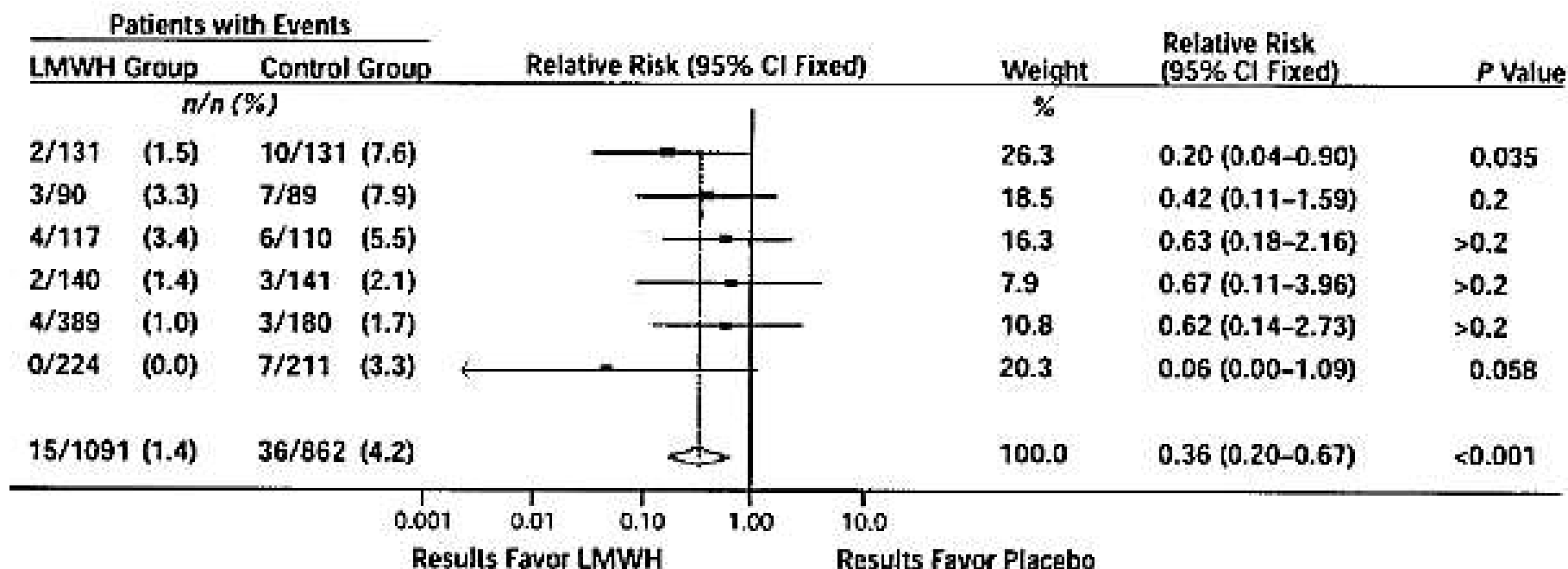
\*\*Enoxaparin 40 mg sc 12 h preop, then postop

# Symptomatic VTE after THR and TKR



# Extended Prophylaxis after THR

RR for Symptomatic VTE during out-of-hospital period



# AAOS: VTE Prophylaxis in Orthopedics

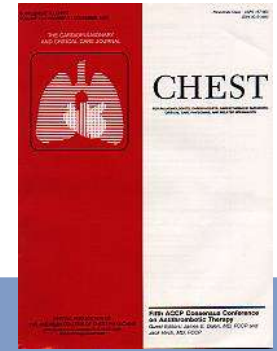
- VTE not considered a critical outcome
- VTE Px decisions individualized based upon perceived thrombotic and bleeding risks
- No specific anticoagulants recommended

[http://www.aaos.org/Research/guidelines/VTE/VTE\\_full\\_guideline.pdf](http://www.aaos.org/Research/guidelines/VTE/VTE_full_guideline.pdf)

Accessed



# ACCP: VTE Prophylaxis in Orthopedic Patients



VTE Risk	Group	Prophylaxis	Duration
Low <10%	Arthroscopic spine	Early ambulation	
High 40-80%	THR, TKR	<u>LMWH</u> ; fondaparinux; LDUH, warfarin (INR 2-3); apixaban, dabigatran, rivaroxaban, aspirin (all Grade 1B); IPCD (Grade 1C)	10 – 14 d; to 35 d + IPC in hospital
High 40-80%	Hip Fracture Surgery	<u>LMWH</u> , fondaparinux, LDUH, Warfarin (INR 2-3); aspirin (all Grade 1B) , or an IPCD (Grade1C)	≥ 10 – 14 d; to 35 d + IPC in hospital

# ACCP Guidelines for General and Abdominal-pelvic Surgical Patients

VTE Risk	Prophylaxis
Low (~1.5%) Caprini 1-2	Mechanical - IPC
Mod (~3.0%) Caprini 3-4	<u>LMWH</u> , LDUH (grade B); IPC (Grade 2C) esp. for bleeding risk
High (~6.0%) Caprini $\geq 5$	<u>LMWH</u> , LDUH (Gr 1B) Plus Mechanical ES or IPC (Gr 2C)
High ; Cancer	Extended Px (4 wks) LMWH
High risk, high bleeding risk	Mechanical prophylaxis

# Bleeding after VTE Prophylaxis in General Surgery

Meta-analysis: 52 RCTs of VTE prophylaxis in 33,813 pts

	<u>Prophylaxis</u>	<u>Control</u>
Injection site bruising	6.9%	2.8%
Wound hematoma	5.7%	0.8%
Drain site bleeding	2.0%	0.6%
Hematuria	1.6%	0
GI bleeding	0.2%	1.9%
Retroperitoneal bleeding	< 0.1%	0
Discontinuation	2%	0
Surgical intervention	0.7%	0.7%

# Summary

- VTE risk factors are identifiable, and risk stratification scales are available for surgical patients
- VTE prophylaxis is generally recommended for surgical and particularly orthopedic patients
- Mechanical and/or anticoagulant therapy may be selected
- Extended prophylaxis:
  - General surgery, high risk patients (28 days)
  - Cancer surgery (28 days)
  - Orthopedic surgery (Hip fx, THR, TKR) (35 days)