

# Post-Operative Beta-blockers & Anticoagulation

Jeffrey P Schaefer, MD

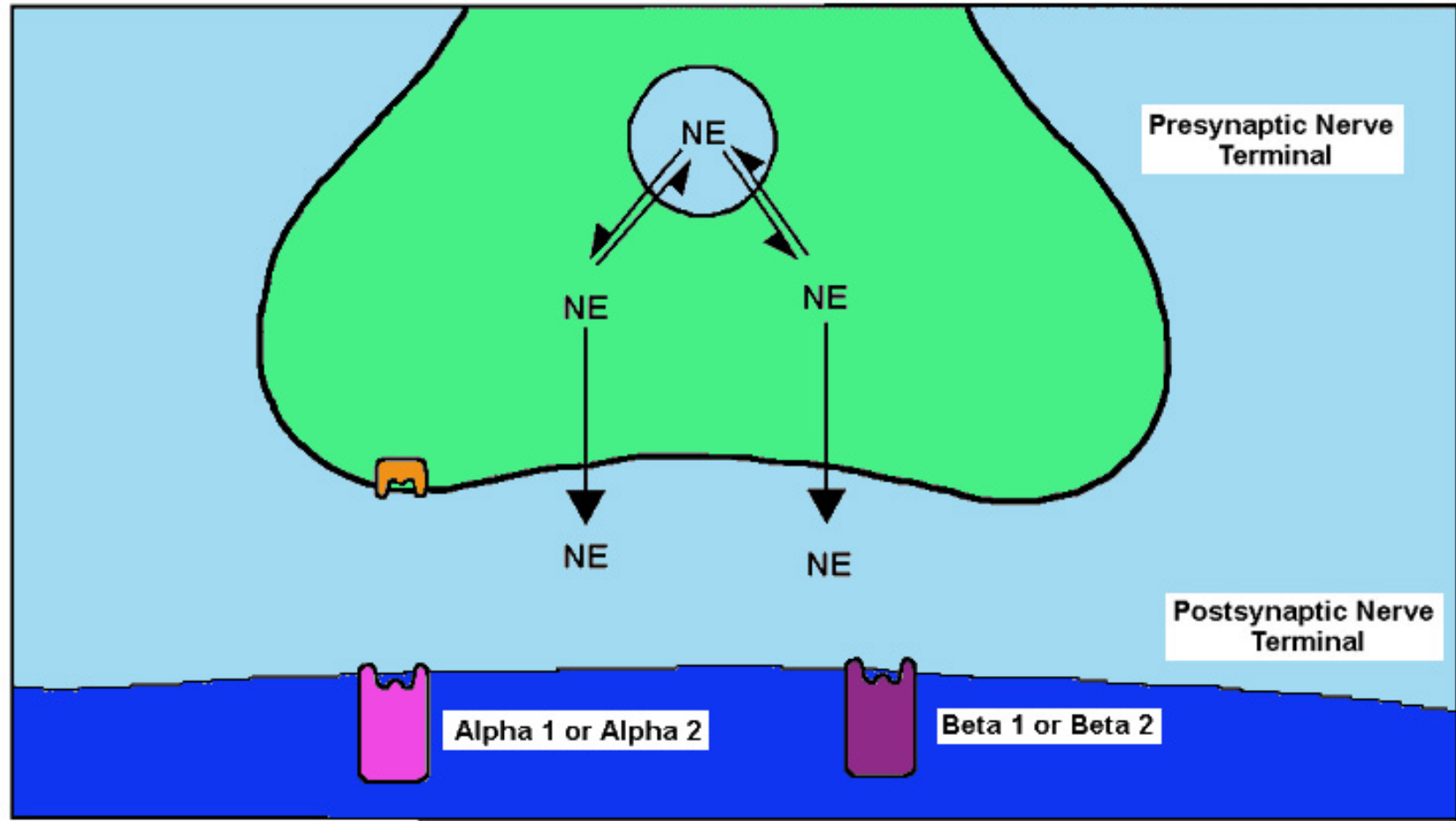
April 17, 2004

# Objectives

- Peri-operative use of Beta-blockers
  - What do they do?
  - Why are they prescribed?
  - When should they be stopped?
- Peri-operative anti-coagulation
  - What are the options?
  - Typical indications?
  - VTED prophylaxis and therapy

# Beta-blockers...

- Beta-adrenergic receptor antagonists
- Let's talk receptors...



# Beta-1 receptors

- **Beta-1 receptors**
  - Adrenaline (epinephrine),
  - Nor-adrenaline (nor-epinephrine),
  - Dopamine, Dobutamine, Phenylephrine,
  - Cocaine
- **Activation of Beta-1**
  - Increase heart rate
  - Increase contractility

# Beta-blockers

- 'gets in the way' of catecholamines.
- reduces heart rate
- reduce contractility

# Adverse effects

- asthma (worsen)
- peripheral arterial disease
- sexual dysfunction
- vivid dreams
- depression
- fatigue

# Beta-blocker types

- Non-selective for beta-1 and beta-2
  - Propranolol (used for migraines / tremor)
- Selective for beta-1 (cardioselective)
  - Atenolol (Tenormin)
  - Metoprolol (Lopressor)
  - Bisoprolol (Monacor)
- ISA (partial blocker)
  - Acebutolol (Sectral)
- Alpha and Beta
  - Labetolol (Trandate)

# Typical Indications

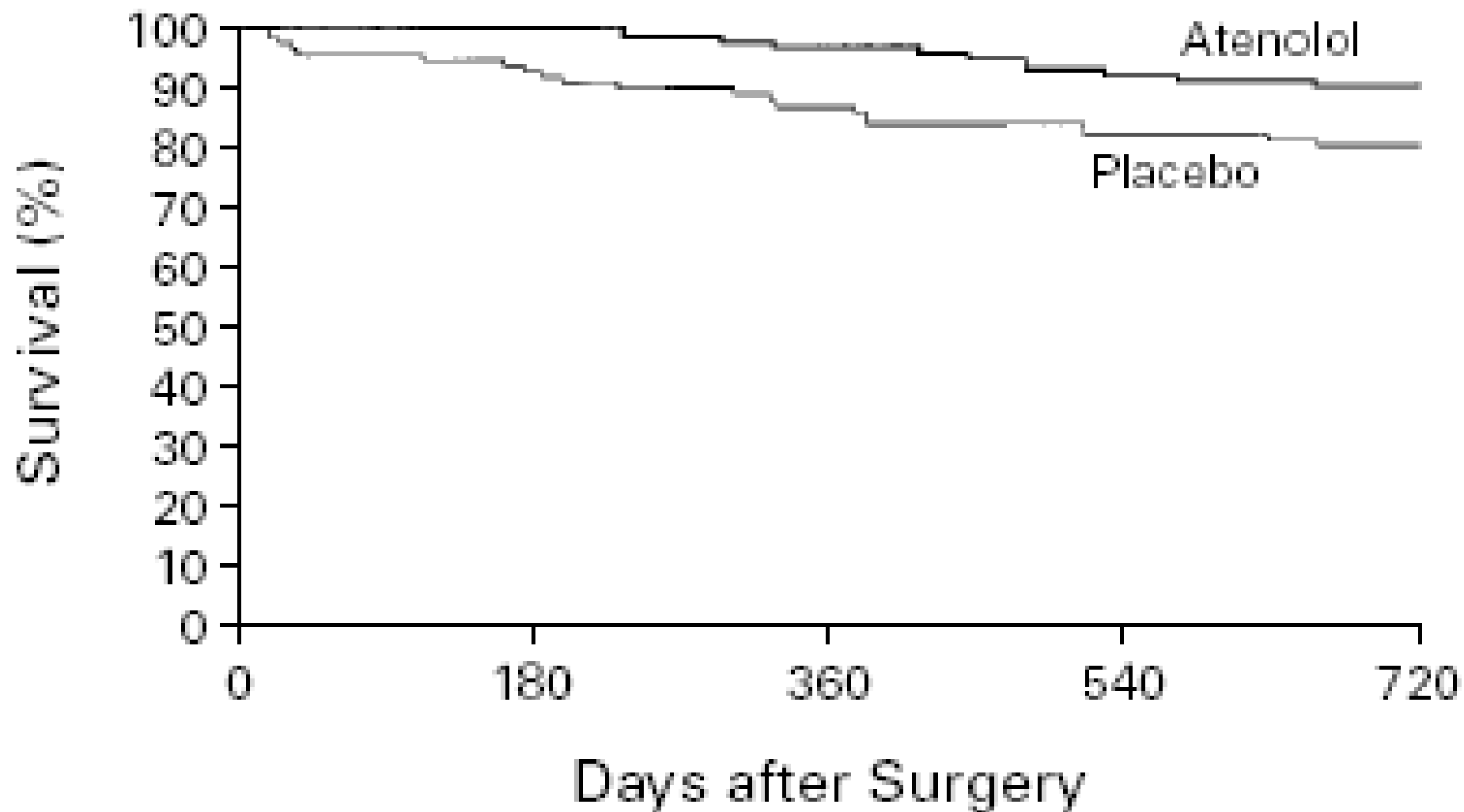
- Angina
- Acute Myocardial Infarction
- Hypertension
- Dysrhythmia (atrial fibrillation)
- Heart Failure \*\*
  
- Tremor
- Migraine

# Role in Pre-op Care

- Mangano et al. Dec, 1996 NEJM
- Prospective randomized trial of
  - Adults about to have non-vascular surgery
  - Known CAD or at risk for CAD
    - Previous MI, angina, positive stress test
    - Diabetes mellitus, hypertension

# Intervention

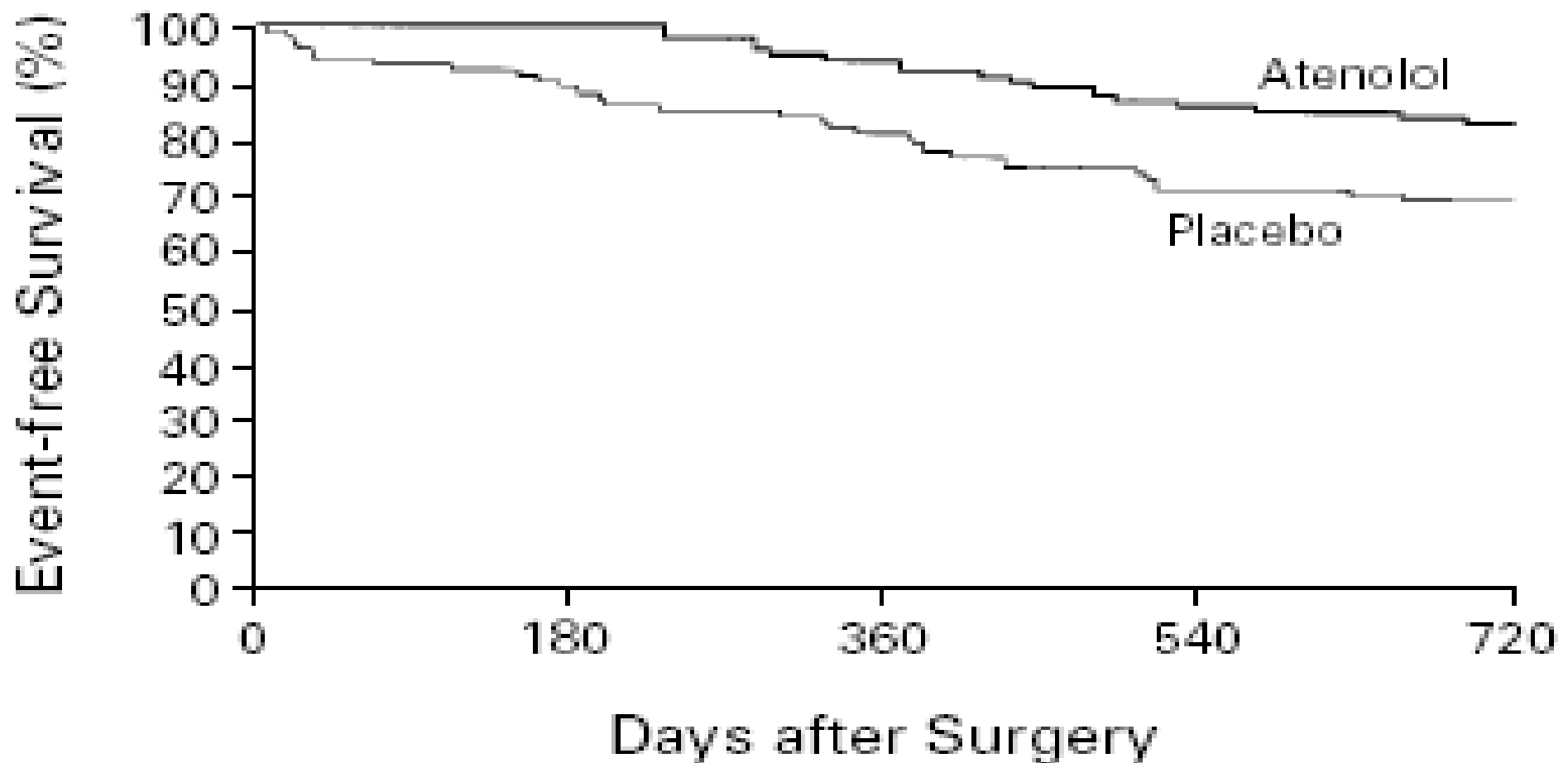
- AM of surgery
  - If HR > 55 and SBP > 100 →
  - Atenolol 5 mg IV and repeat x 1 if needed
- Post-op
  - If HR > 55 and SBP > 100 →
  - Atenolol 5 mg IV and repeat if needed OR
  - Atenolol 50 mg or 100 mg once daily
  - (target was HR 55 – 65)
- TREATMENT UNTIL D/C or MAX 7 days



**Figure 1.** Overall Survival in the Two Years after Noncardiac Surgery among 192 Patients in the Atenolol and Placebo Groups Who Survived to Hospital Discharge.

# Survival

	Atenolol	Placebo
6 months	100%	92%
1 year	97%	86%
2 year	90%	79%



**Figure 2.** Event-free Survival in the Two Years after Noncardiac Surgery among 192 Patients in the Atenolol and Placebo Groups Who Survived to Hospital Discharge.

The outcome measure combined the following events: myocardial infarction, unstable angina, the need for coronary-artery bypass surgery, and congestive heart failure. The rate of event-

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# Event Free (MI, Unstable Angina, Revascularization)

	Atenolol	Placebo
6 months	100%	88%
1 year	92%	78%
2 year	83%	68%

TABLE 4. DAILY DOSE AND SIDE EFFECTS OF ATENOLOL.\*

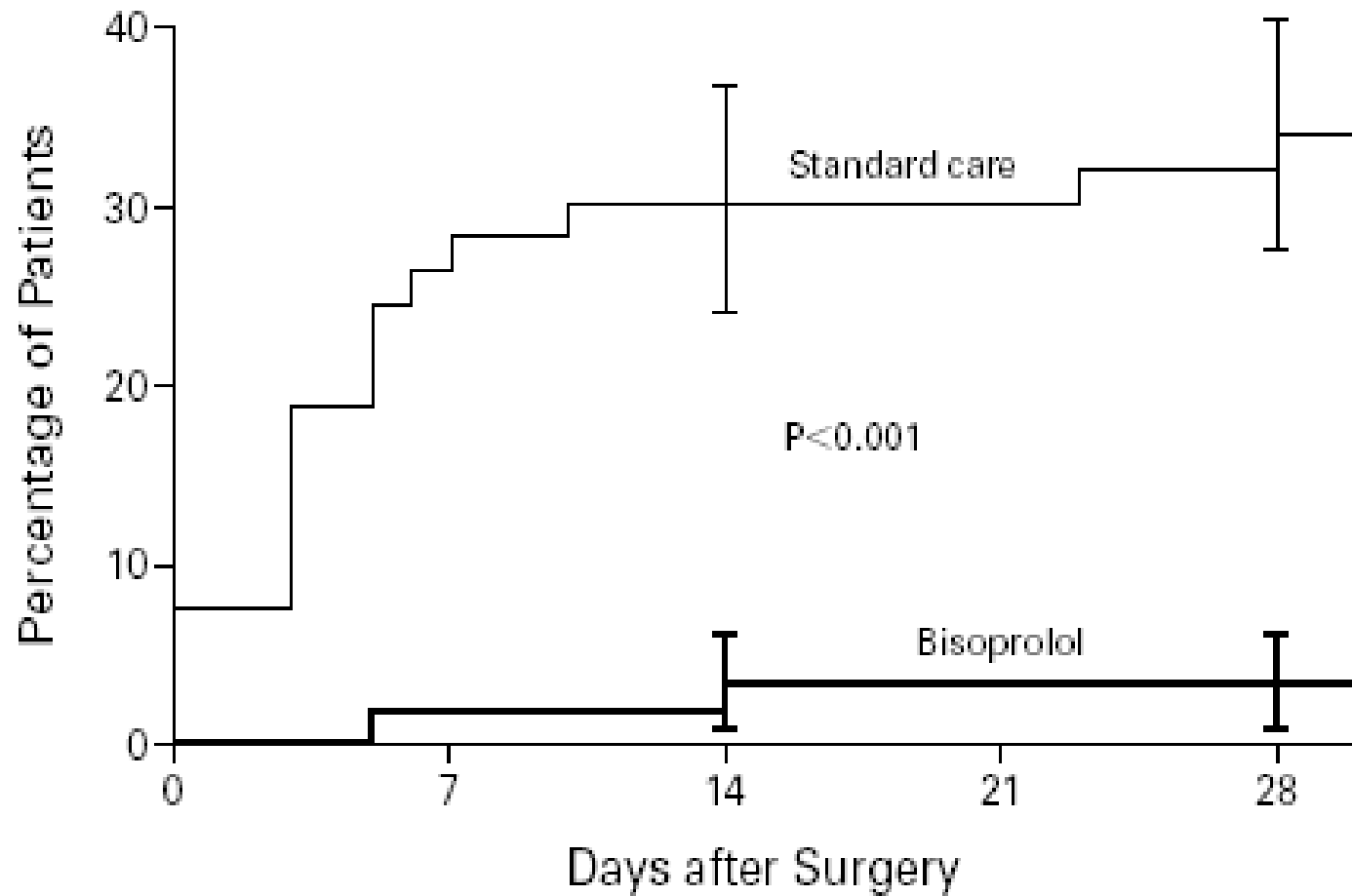
VARIABLE	DAY OF SURGERY				DAYS 1-7†	
	BEFORE SURGERY		AFTER SURGERY		<i>Atenolol</i>	<i>Placebo</i>
	<i>Atenolol</i>	<i>Placebo</i>	<i>Atenolol</i>	<i>Placebo</i>		
	percentage of patients					
Dosage‡						
Full dose	69	79	74	88	63	82
Half dose	19	10	10	6	30	18
Not treated	11	12	15	7	6	1
Side effects						
Hypotension						
Systolic BP <90 mm Hg	0	0	0	0	14	12
>20% decrease in systolic BP	4	0	2	0	—	—
Treated	0	0	0	0	0	0
Bradycardia§						
Heart rate <40 bpm	0	0	0	0	6	5
>20% decrease in heart rate	9	0	4	0	—	—
Treated	0	0	0	0	0	0
Bradycardia and hypotension						
Systolic BP <90 mm Hg and	0	0	0	0	0	0
heart rate <40 bpm						
>20% decrease in heart rate	2	0	1	0	—	—
and systolic BP						
Treated	0	0	0	0	0	0
Congestive heart failure	0	0	0	0	2	5
Bronchospasm¶	3	0	0	0	0	0

# Conclusion

- Atenolol protects against CV events and death among high risk patients undergoing surgery.
- Problem: Why would effect last so long?

# Bisoprolol in Vascular Surgery

- 112 patients undergoing vascular surgery (aneurysm) with Positive Stress Echos
- Bisoprolol versus Placebo
- 30 day cardiac mortality
  - Bisoprolol 3.4%
  - Placebo 34.0%



No. AT RISK

Standard care	53	38	37	37	35
Bisoprolol	59	58	57	57	57

**Figure 1.** Kaplan–Meier Estimates of the Cumulative Percentages of Patients Who Died of Cardiac Causes or Had a Nonfatal Myocardial Infarction during the Perioperative Period.

I bars indicate standard errors. The difference between groups was significant ( $P < 0.001$  by the log-rank test).

# Conclusion

- Beta-blocker confers benefits for vascular surgery patients.

# When to stop Beta-blocker?

- According to Magano study...
  - HR < 55 / minute
  - SBP < 100
- Might be prudent to be more cautious
  - HR < 65 / minute
  - SBP < 110
  - Avoid Stopping in patients who usually are on a beta-blocker, or hold other hypotensives
- 7 days or discharge

# Post-operative Anticoagulation

# Common Anticoagulants

- Anti-platelet agents
  - aspirin (ASA)
  - clopidogrel bisulfate (Plavix)
  - dipyridamole + ASA (Aggrenox)
- Indication
  - stroke and myocardial infarction prevention
- Traditional NSAIDs and COXIBS
  - little, reversible or no antiplatelet activity

# Antiplatelet Agents

- Immediate Onset of Action
- ASA
  - irreversible platelet dysfunction
  - 10 days for platelet pool to be replaced
- Gastric and duodenal ulcer risk

# Common Anticoagulants

- Heparins
  - unfractionated heparin (IV, sq)
  - low molecular weight heparin
    - dalteparin (Fragmin)
    - tinzaparin (Innohep)
    - enoxaparin (Lovenox)
- Indications
  - prevention / treatment DVT / PE
  - prevention of cardioembolism

# Heparins

- work immediately
- given parenterally (sq or IV route)
- oral version being studied
- safe in pregnancy
- adverse effects
  - Heparin Induced Thrombocytopenia
  - Heparin Induced Thrombosis
  - osteoporosis

# Heparins

- **Prevention of DVT / PE**
  - Dalteparin (Fragmin) 2,500 - 5,000 U sq od
  - Unfractionated Heparin 5,000 U sq bid
- **Treatment of DVT / PE**
  - Tinzaparin (Innohep) 175 anti-Xa U/kg sq
  - IV unfractionated infusion per protocol
- **Prevention of Cardioembolism**
  - Tinzaparin (Innohep) 175 anti-Xa U/kg sq
  - IV unfractionated infusion per protocol

# Unfractionated vs LMW heparins

- Equal efficacy and risk
  - DVT / PE therapy
- Unequal pharmacokinetics
  - IV quicker to 'shut-off'
  - SQ likely to be within therapeutic window

# Common Anticoagulants

- Vitamin K antagonists
  - warfarin
  - other coumarins (Europe)
- Indications
  - prevention of cardioembolism
    - atrial fibrillation, mechanical valves, MI, CHF
  - prevention / treatment of PE / DVT

# Warfarin

- Creates defective clotting factors
- Must wait until normal factors are cleared
- Adverse Effects
  - hemorrhage
  - rarely nausea
  - rarely skin necrosis (among protein C / S def)

# Combinations

- Indicated (ASA + Warfarin)
  - mechanical heart valves
  - some patients with ischemic heart disease

# Anticoagulation in Surgery

- Patient had previous indication for A/C
  - prevention of arterial thrombosis
    - atrial fibrillation, heart valve, MI
    - prevent atheroembolic strokes
  - treatment of venothrombotic disease
- Patient developed a new indication for A/C
- Patient simply needs VTED prevention

# VTED

- Venothromboembolic disease
  - Surgery is a risk factor for VTED
  - Risk varies with procedure type and patient
  - common reason for A/C among surgical pts

# Virchow's Triad

stasis



DVT

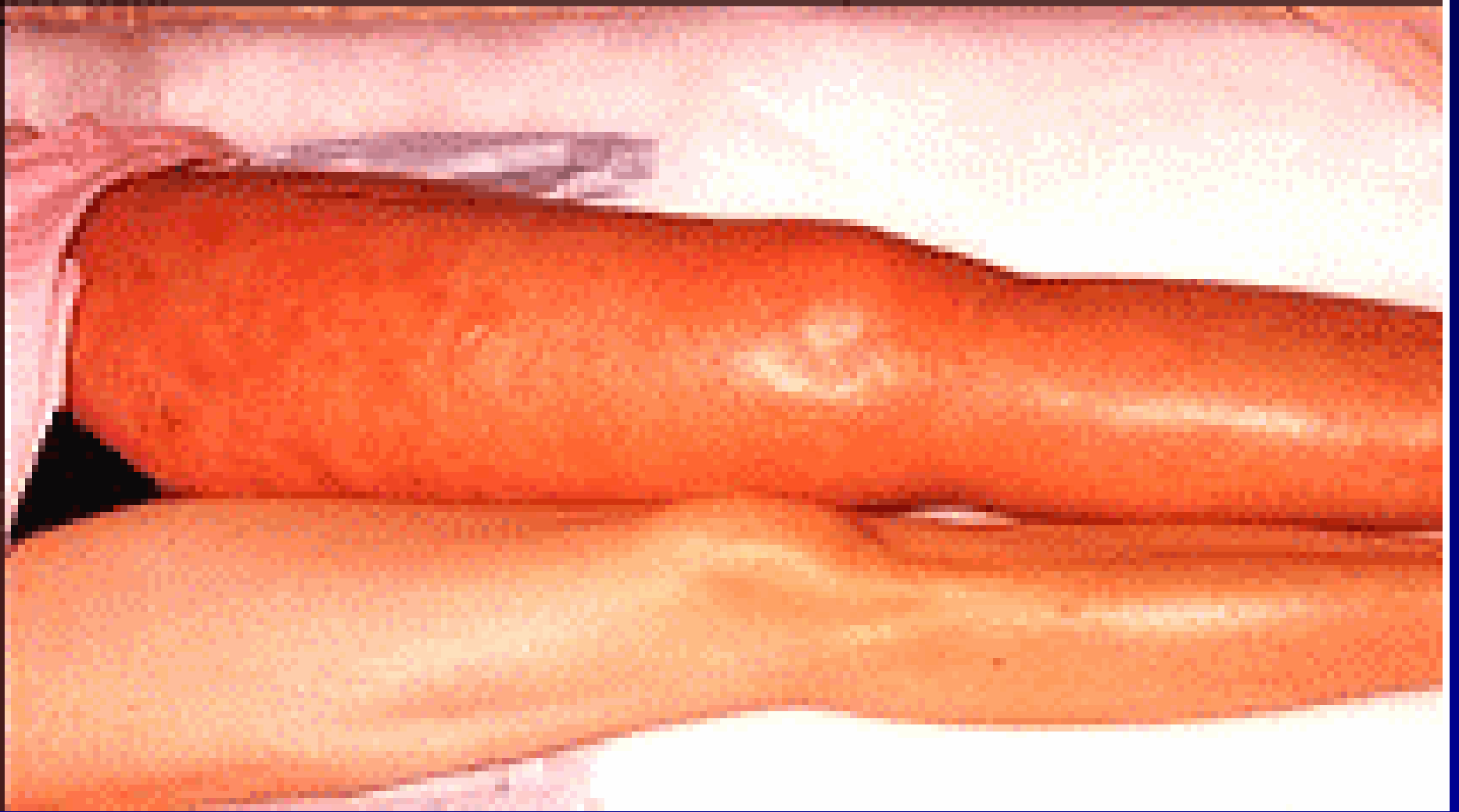
hypercoagulability

damaged veins

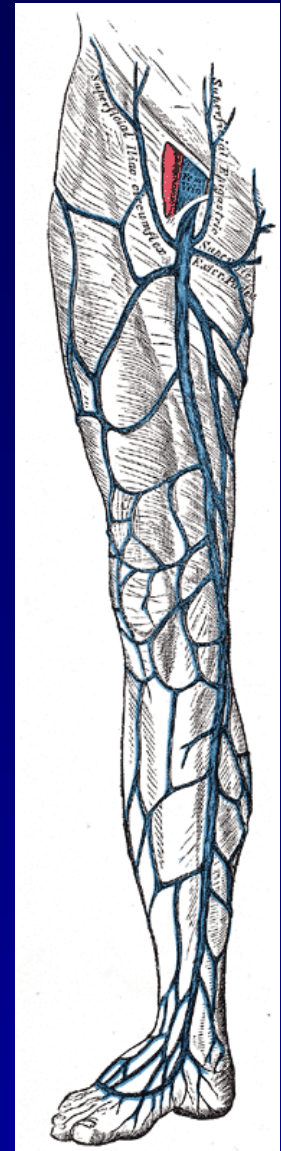
# Deep Vein Thrombosis (DVT)

- behavior of above knee DVT's
  - associated with chronic venous stasis
  - associated with pulmonary embolism

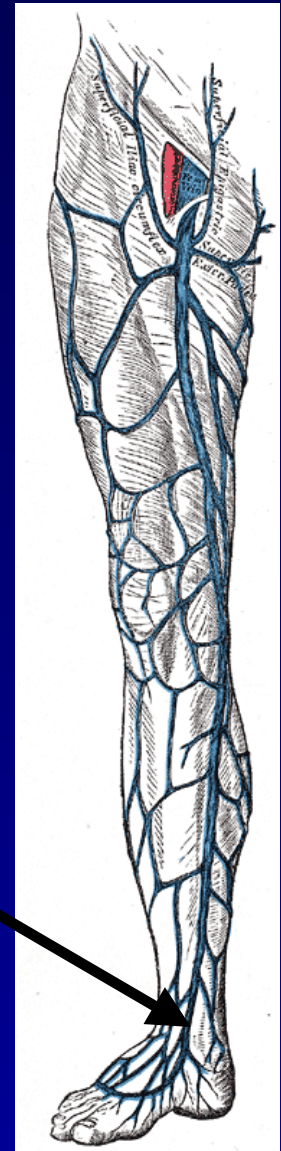
# DVT



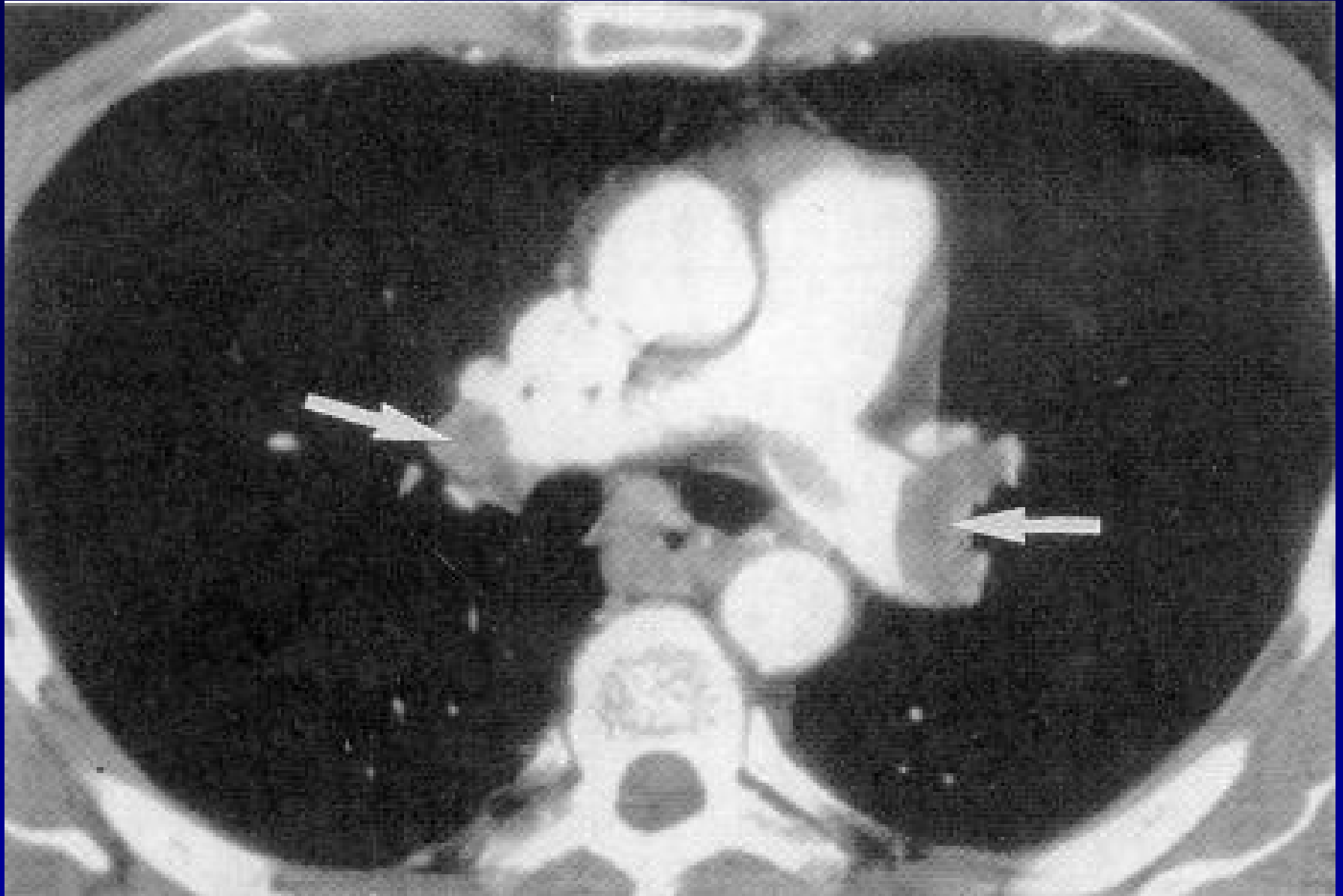
# Chronic Venous Stasis - ankle



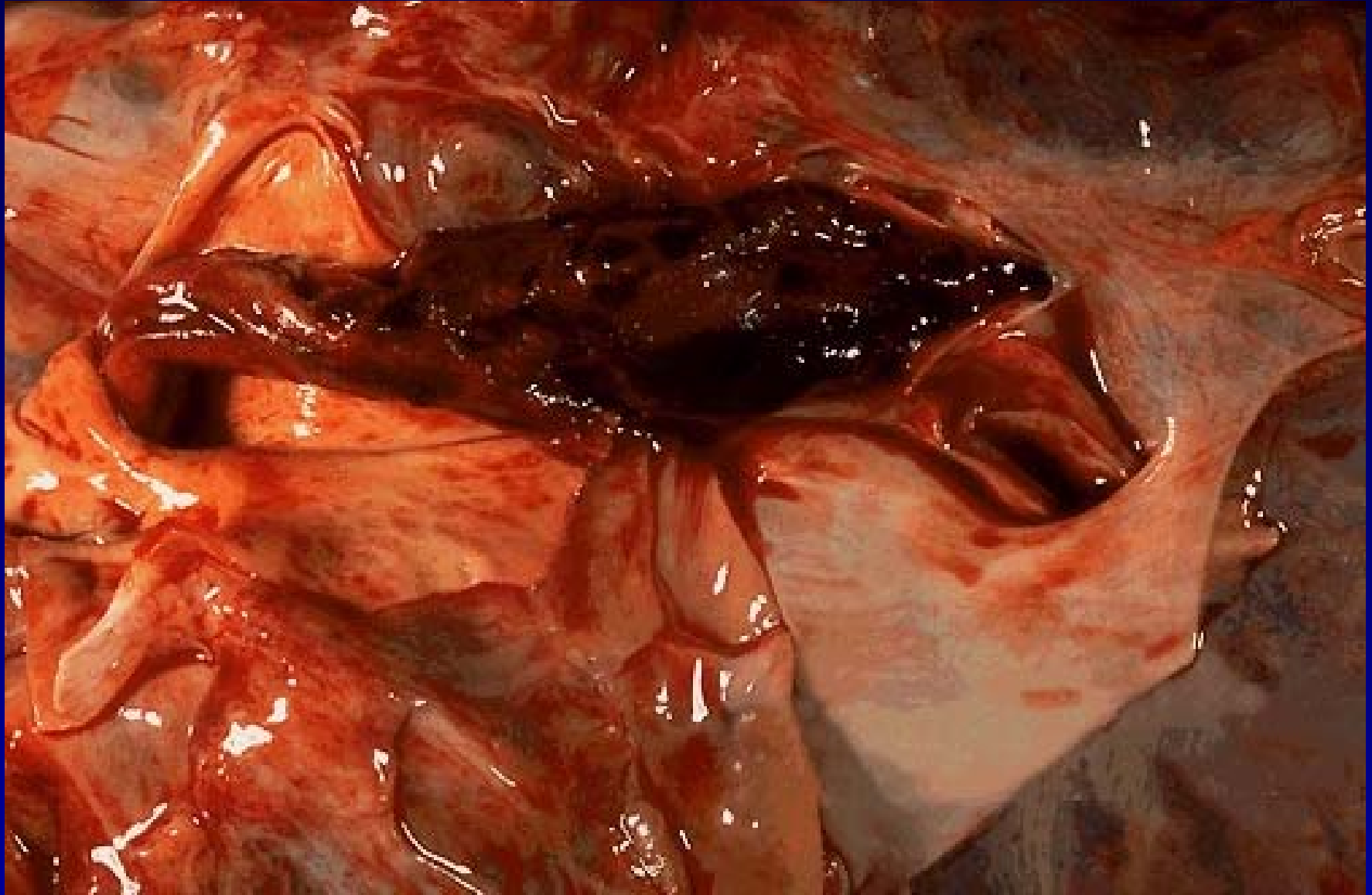
# Chronic Venous Stasis - ankle



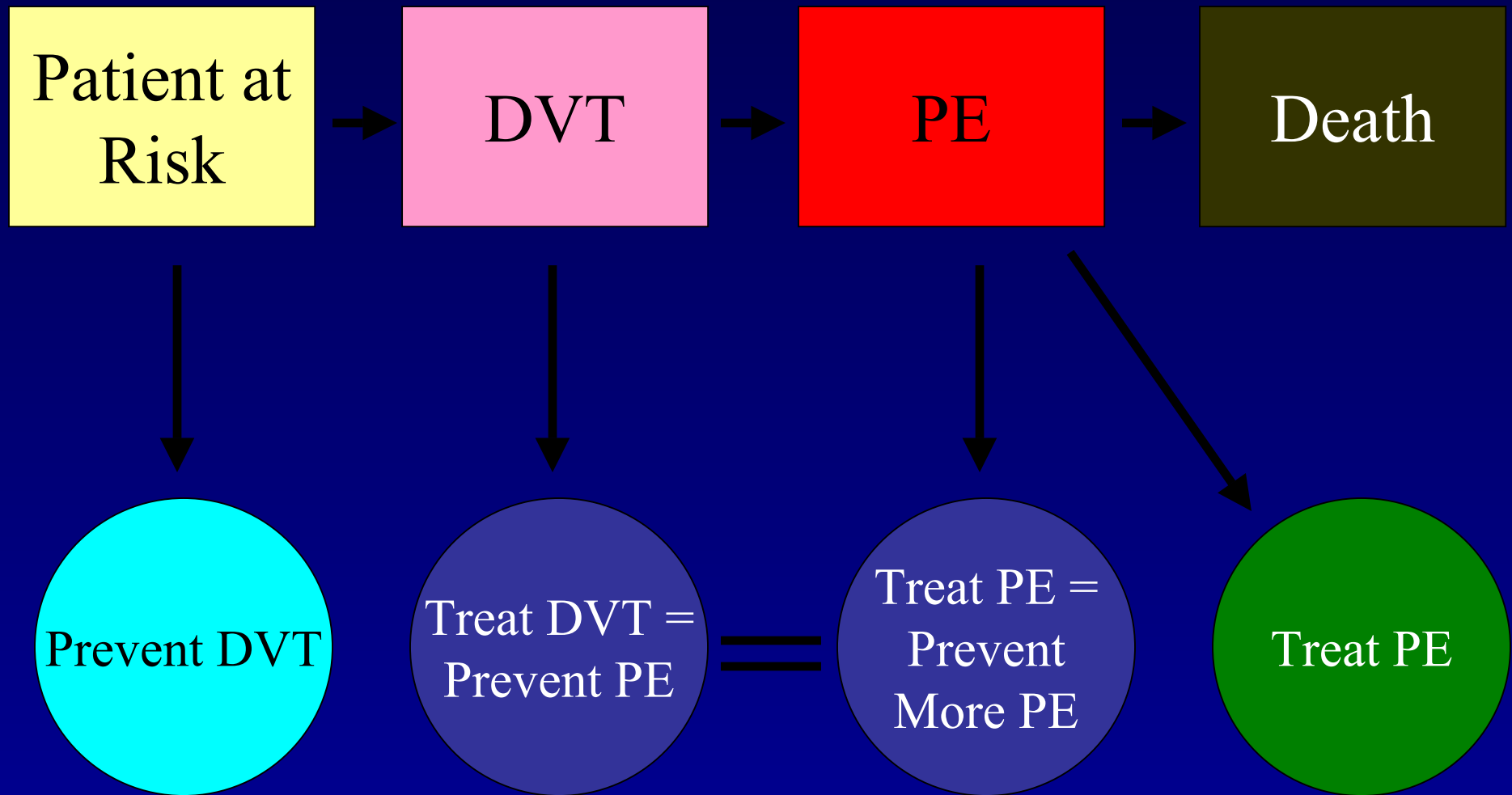
# PE - diagnosis (spiral CT scan)



# Pulmonary Thromboembolism



# Overview of Prevention / Treatment



# Overview of Prevention / Treatment

Patient at  
Risk



Prevent DVT

# Risk Without Prophylaxis (%)

	calf dvt	prox dvt	clin PE	fatal PE
Low	2	0.4	0.2	0.002
Mod	10-20	2-4	1-2	0.1-0.4
High	20-40	4-8	2-4	0.4-1.0
V High	40-80	10-20	4-10	0.2-5.0

# Risk Without Prophylaxis (%)

minor surgery: < 40 yr and no risk factors\*

Mod	10-20	2-4	1-2	0.1-0.4
High	20-40	4-8	2-4	0.4-1.0
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# Risk Without Prophylaxis (%)

minor surgery: < 40 yr and no risk factors\*

minor surgery: 40 - 60 yr or with risk factors

High	20-40	4-8	2-4	0.4-1.0
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V High	40-80	10-20	4-10	0.2-5.0
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# Risk Without Prophylaxis (%)

minor surgery: < 40 yr and no risk factors\*

minor surgery: 40 - 60 yr or with risk factors

minor surgery >60 yr or major surgery > 40 yr or with risk

V High 40-80

10-20

4-10

0.2-5.0

# Risk Without Prophylaxis (%)

minor surgery: < 40 yr and no risk factors\*

minor surgery: 40 - 60 yr or with risk factors

minor surgery >60 yr or major surgery > 40 yr or with risk

major surgery > 40 yr with prior VTE, cancer  
hypercoagulable state, hip/knee surg, spinal cord,  
major trauma

# General Surgery

	<u>DVT</u>	<u>all PE</u>	<u>Fatal PE</u>
no prophylaxis	25%	1.6%	0.9%

	<u>DVT</u>	<u>No. Patients</u>
ASA	20%	372
elastic stocking	14%	196
heparin 5000 bid	8%	10,339
LMWH	6%	9,364
IPC / SCD	3%	132

# Gynecological Surgery

<u>Studied</u>	<u>DVT%</u>	<u>No. Patients</u>
no prophylaxis	16	945
warfarin	13	372
IPC / SCD	9	253
heparin 5000 bid	7	1,092
elastic stocking	0	104

# THR, TKR, Hip#, No Prophylaxis

	<u>Prox DVT%</u>	<u>PE%</u>	<u>Fatal</u>
<u>PE%</u>			
THR	23-36	0.7-30	0.1-0.4
TKR	9-20	9-20	0.2-0.7
Hip#	17-36	4-24	3.6-12.9

# Total Hip Replacement Surgery

	<u>P-DVT%</u>	<u>No Pts Studied</u>
no prophylaxis	26	626
elastic stocking	26	290
ASA	11	473
heparin 5000 bid	19	1,092
warfarin	5	1,828
IPC/SCD	14	423
LMWH	6	6,216

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Hip# 48% without --> LMWH, warfarin, LDUH 25%

# Total Hip Replacement Surgery

- Extended Prophylaxis Post Discharge
  - 5 studies show significant benefit for reducing risk of proximal DVT (about 66% risk reduction)

# Recommendations: Gen Surg

- Low Risk
  - minor procedure, < 40 yr, no RF
  - aggressive mobilization
- Moderate Risk
  - minor procedure with RF
  - minor procedure, 40-60yr, no RF
  - major surgery <40
  - LDUH, LMWH, ES, or IPC

# Recommendations: Gen Surg

- Higher Risk
  - minor procedure > 60 or with RF
  - LDUH, LMWH, IPC
- Highest Risk
  - ES, IPC/SCD
  - PLUS
  - LDUH, LMWH

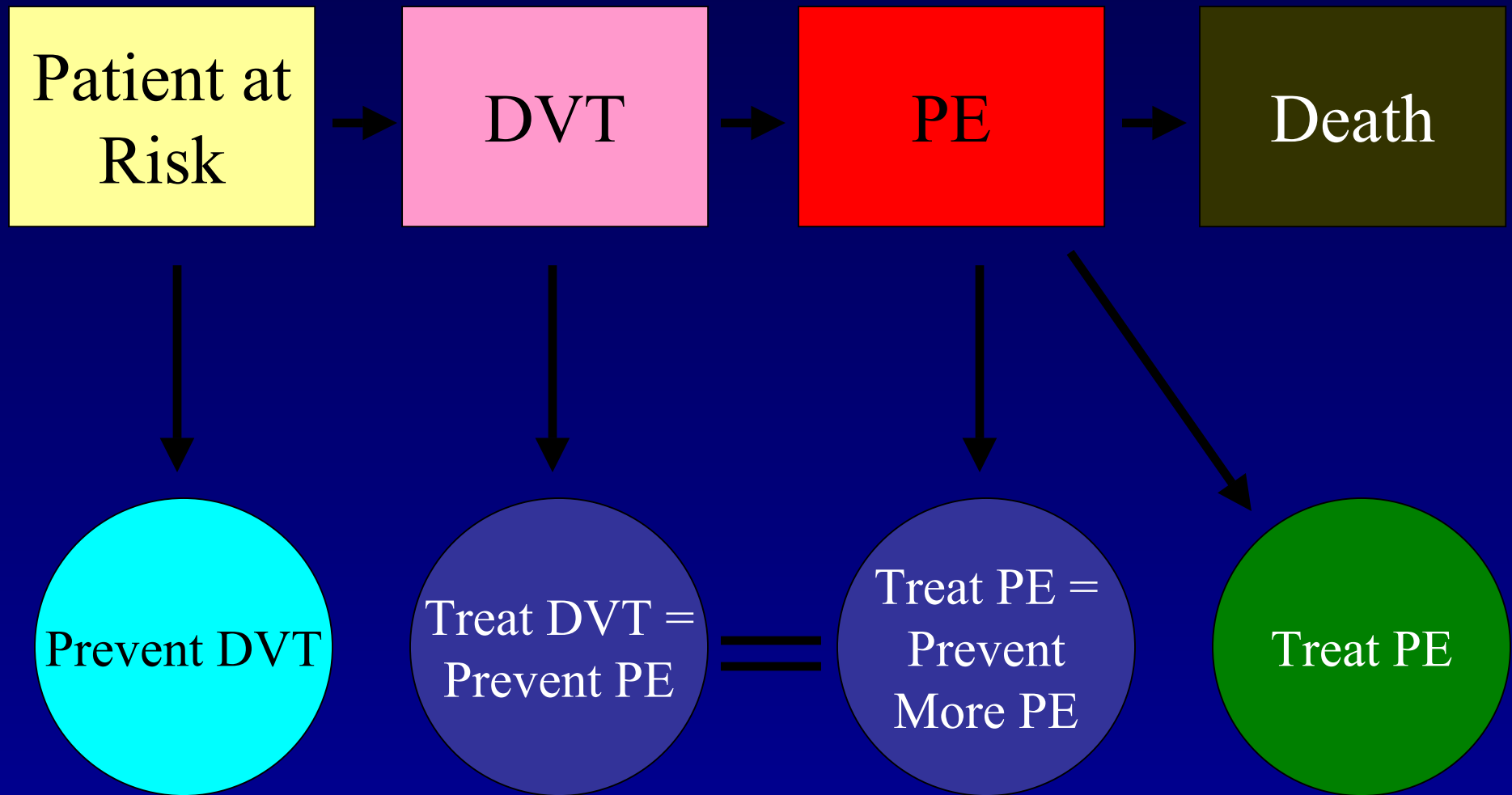
# Gyn/Uro Surg

- Low Risk (minor gyn, closed uro)
  - mobilize
- Moderate Risk (major / benign)
  - LDUH or LMWH or IPC/SCD
- High Risk (major / malignant)
  - LDUH tid or LDUH
  - PLUS
  - IPC/SCD or ES

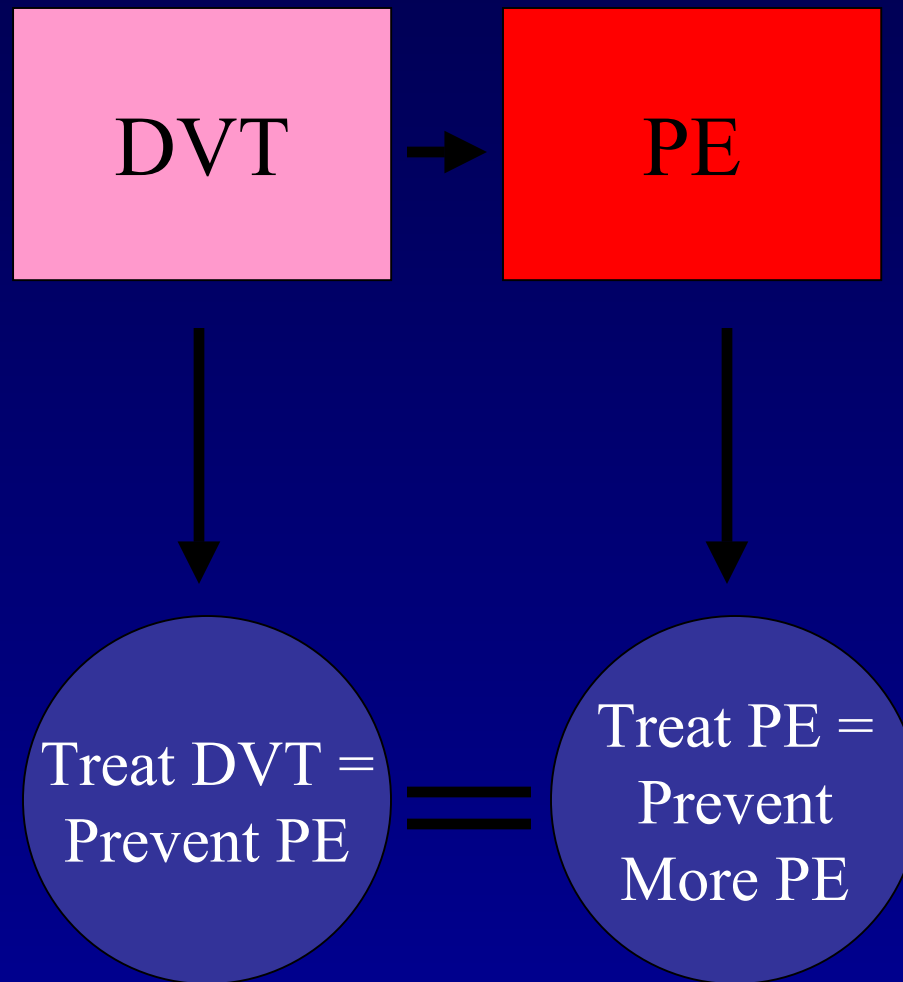
# Recommendations: THR, TKR, Hip#

- LMWH started
  - 12 hr pre-op or (epidural hematoma risk)
  - 12-24 hr post-op or
  - 4-6 hr post-op at 1/2 dose or
- Warfarin started
  - immediately pre-op
  - post-op
- Extended (post-discharge) is acceptable

# Overview of Prevention / Treatment



# Overview of Prevention / Treatment



# Treatment of Proximal DVT/PE

- “Best Guesses”
  - Untreated DVT 20% risk of PE
  - Mortality of PE about 25%

# 1 Year Mortality

- 1 year mortality
  - PE 1.5%
  - DVT 0.4%

# Treatment of DVT/PE

- Baseline CBC, PTT, and INR and start:

Low Molecular Weight Heparin

or

Adjusted Dose Unfractionated Heparin IV

or

Adjusted Dose Unfractionated Heparin SQ

# Treatment of DVT/PE

- Duration of heparin:
  - minimum 5 days
  - INR > 2.0 for two days
  - BOTH CONDITIONS APPLY

# Treatment of DVT/PE

- Warfarin (if not pregnant)
  - start concurrently with heparin
  - target INR 2.0 - 3.0
- Duration of warfarin
  - time reversible risk factors: > 3 months
  - first idiopathic DVT/PE: > 6 months
  - recurrent DVT/PE: > 12 months
  - continuing risk factor > 12 months
    - cancer, anticardiolipin,
    - AT deficiency

# Risk of Recurrent PE

- Multiple studies show:
  - appropriate heparin followed by warfarin
  - recurrent PE in about 5%

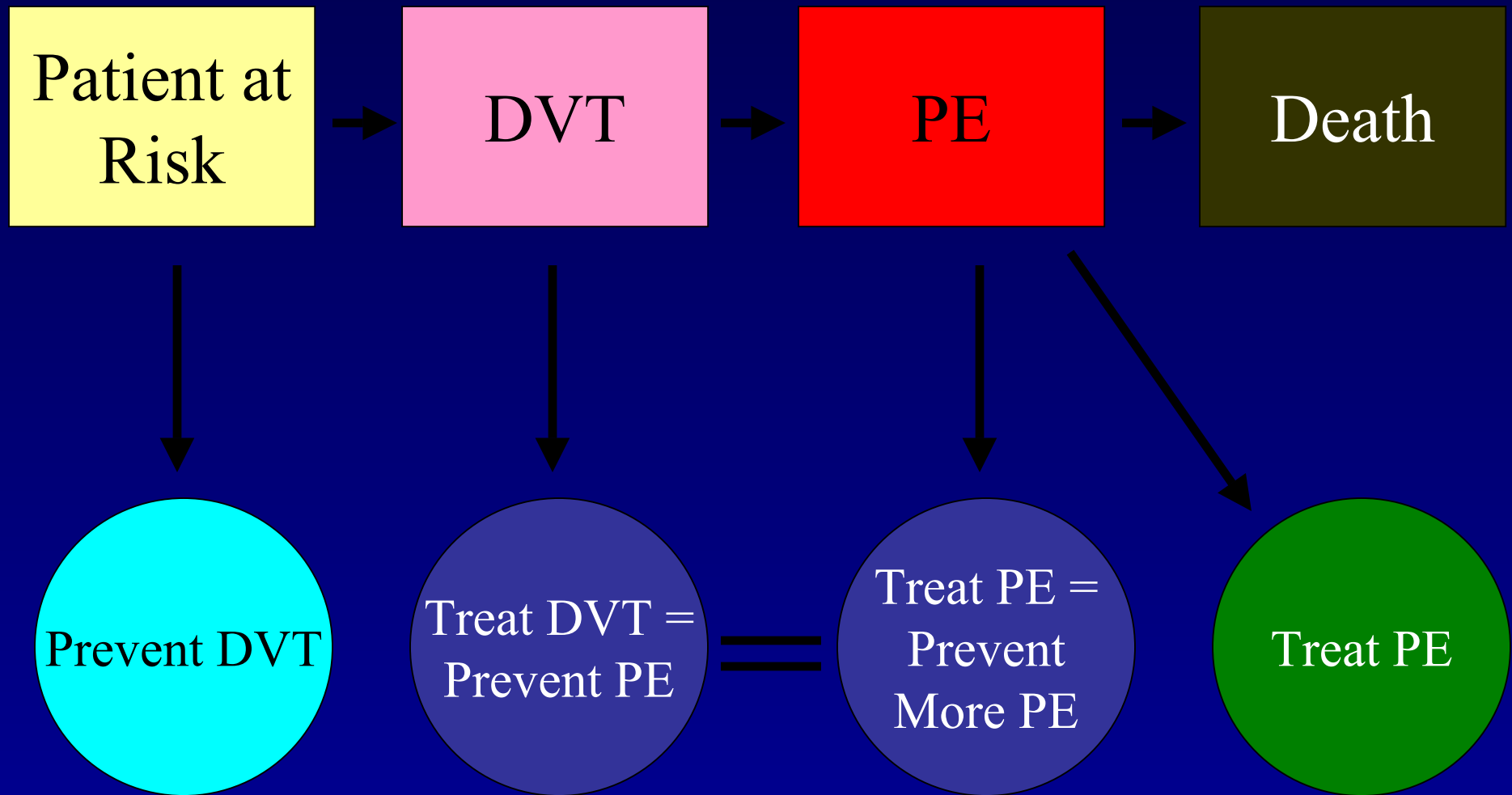
# Calf DVT

- anticoagulate for 6 - 12 weeks

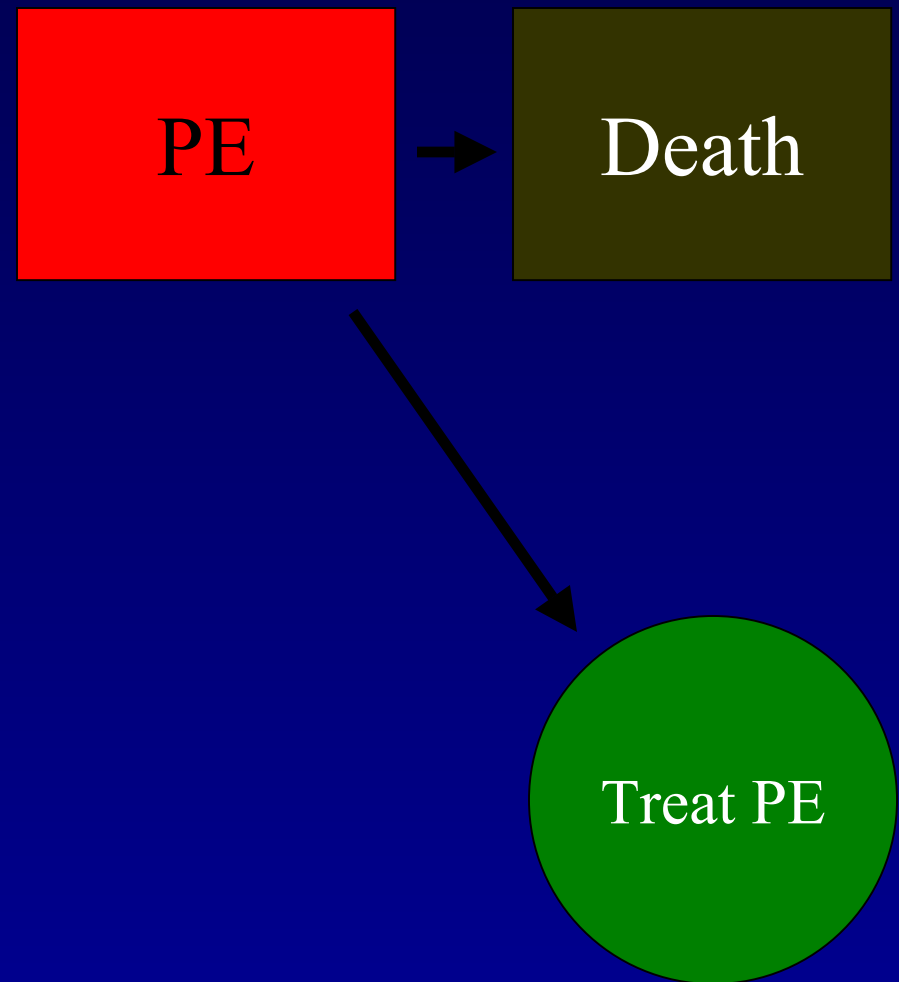
or

- serial Doppler's for 10 - 14 days

# Overview of Prevention / Treatment



# Overview of Prevention / Treatment



# Massive PE

- Thrombolytic Therapy
  - highly individualized
  - ICU admission
  - reserved for shock or profound hypoxia

# Long Term Risk of Bleeding?

- Major Bleeding in atrial fibrillation
  - INR 2.0-3.0 major bleeding = 1.3% / year
  - control group = 1.0% / year

# Longer Term Risk of Bleeding?

- Major Bleeding in DVT / PE > 7 studies
  - INR 2.0-3.0 major bleeding = 0 / 3 mo
  - Dalteparin 5000 units bid = 0 / 3 mo
  
  - warfarin INR 2.7 = 12.8% / 3 mo
  - enoxaparin 4000 u sq od = 3% / 3 mo
  
  - no fatal bleeding over 3 months

# Short Term Risk of Bleeding?

- Heparin Phase in DVT / PE (>10 trials)
- IV Heparin
  - frequency of major bleed ranges 0 - 7%
  - frequency of fatal bleed ranges 0 - 2%
- LMWH
  - frequency of major bleed ranges 0 - 3%
  - frequency of fatal bleed ranges 0 - 0.8%

# Summary

- Unless patient had prior indication most AC is for VTED
- Heparin / Warfarin

Your questions?