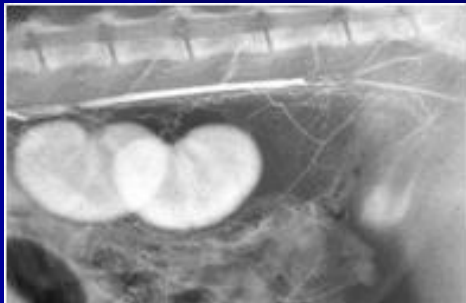




# Cardiogenic Thromboembolic Disease

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# Introduction

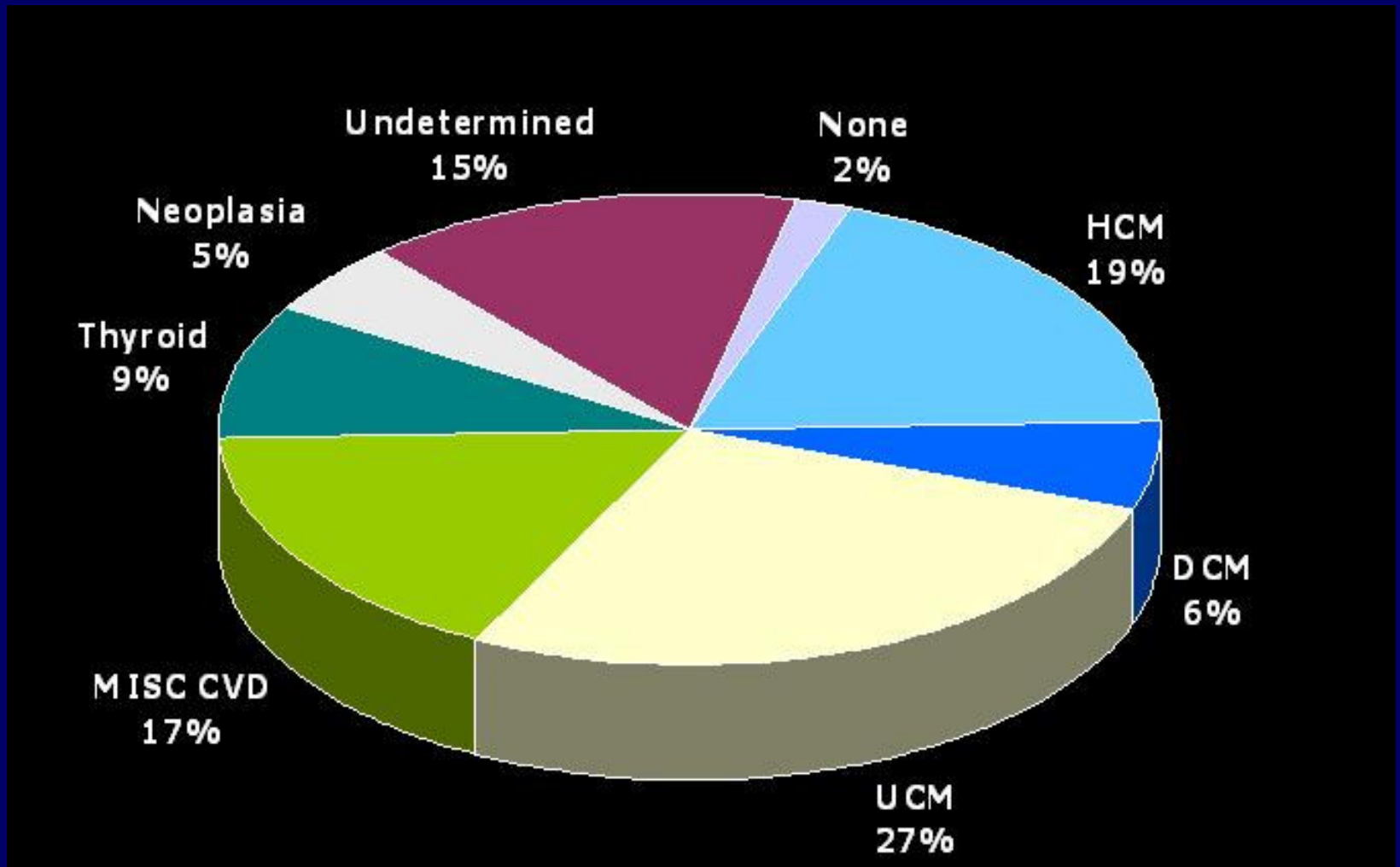
- Feline ATE clinical syndrome associated with
  - Thrombus-Formation of clot in heart or vascular lumen
  - Embolism- Clot or clot fragment lodges in a distal vessel
- Usually associated with poor prognosis
  - SHOULD IT BE?

# Introduction

- Also Known As:
  - Arterial Thromboembolism (ATE)
  - Systemic Arterial Thromboembolism (SATE)
  - Feline Arterial Thromboembolism (FATE)
  - **Cardiogenic Embolism (CE)**

# Disorders of 127 Cats with FATE

Smith et al. JVIM 2003;17:73-83



# Prevalence/Demographics

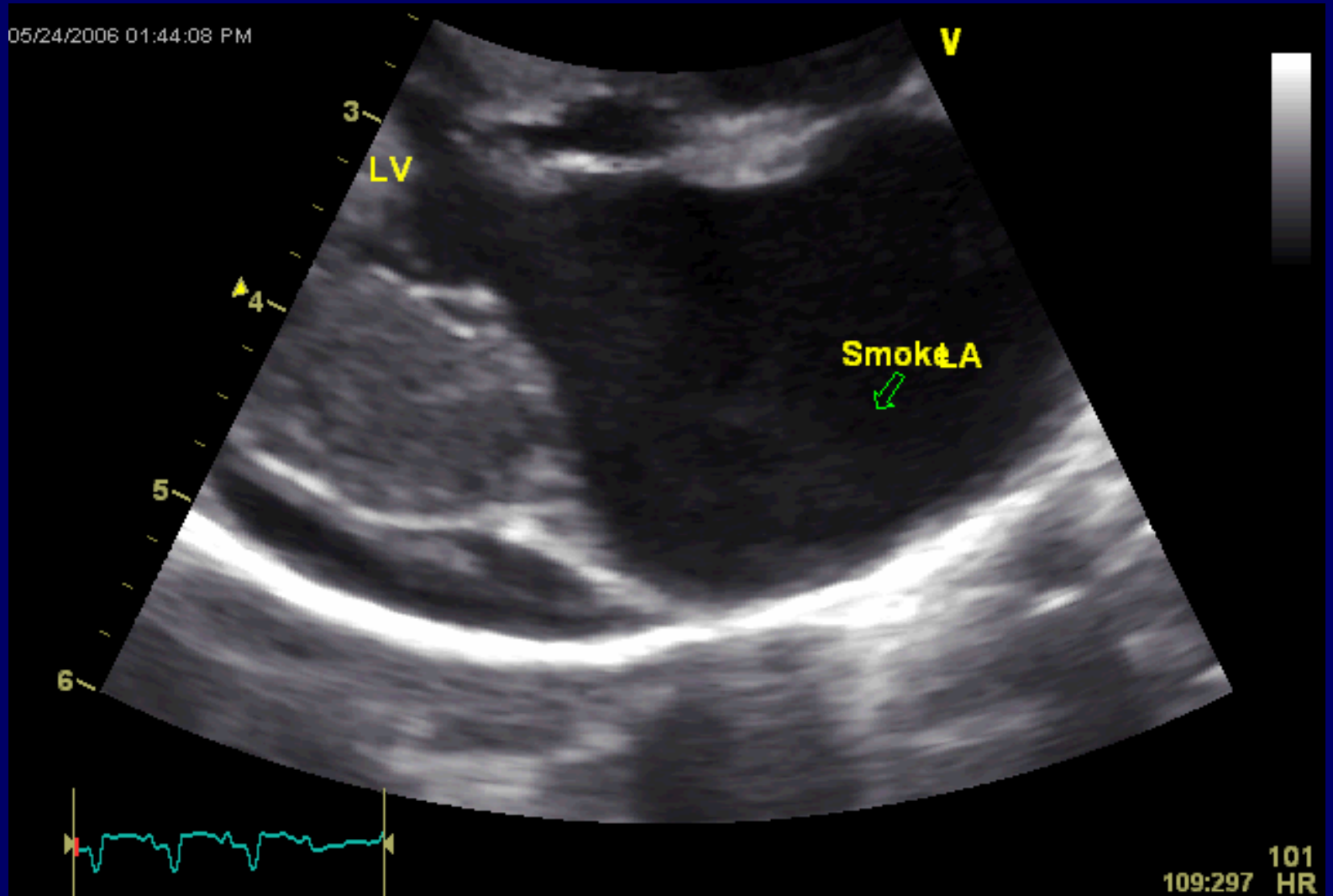
- Overall occurrence of 0.1% to 0.5% of all cats presenting to NAVTH
- Mean frequency in feline myocardial disease ~6-8%
- Males overrepresented ~67%
  - 65 % neutered male
  - Parallels occurrence of heart disease in males cats – 65%
- Middle aged cats ~ 7.7 years
- Most common
  - Domestic Breeds -80%-90%
  - Overrepresented Purebreds
    - Abyssinians, Birman, Ragdoll, Maine Coon, Siamese, Persian, and Tonkinese

# **Pathophysiology**

# Thrombus Formation

- Virchow's Triad
  - Blood Stasis
  - Endothelial Injury
  - Hypercoagulable State

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# Thrombus Formation

- Virchow's Triad
  - Blood Stasis
  - Endothelial Injury
  - Hypercoagulable State

# Endothelial Injury

- Left atrial dilatation
  - Stretching of the endothelial surface
  - Subendothelial collagen exposure
  - Allows platelet adhesion



# Thrombus Formation

- Virchow's Triad
  - Blood Stasis
  - Endothelial Injury
  - Hypercoagulable State

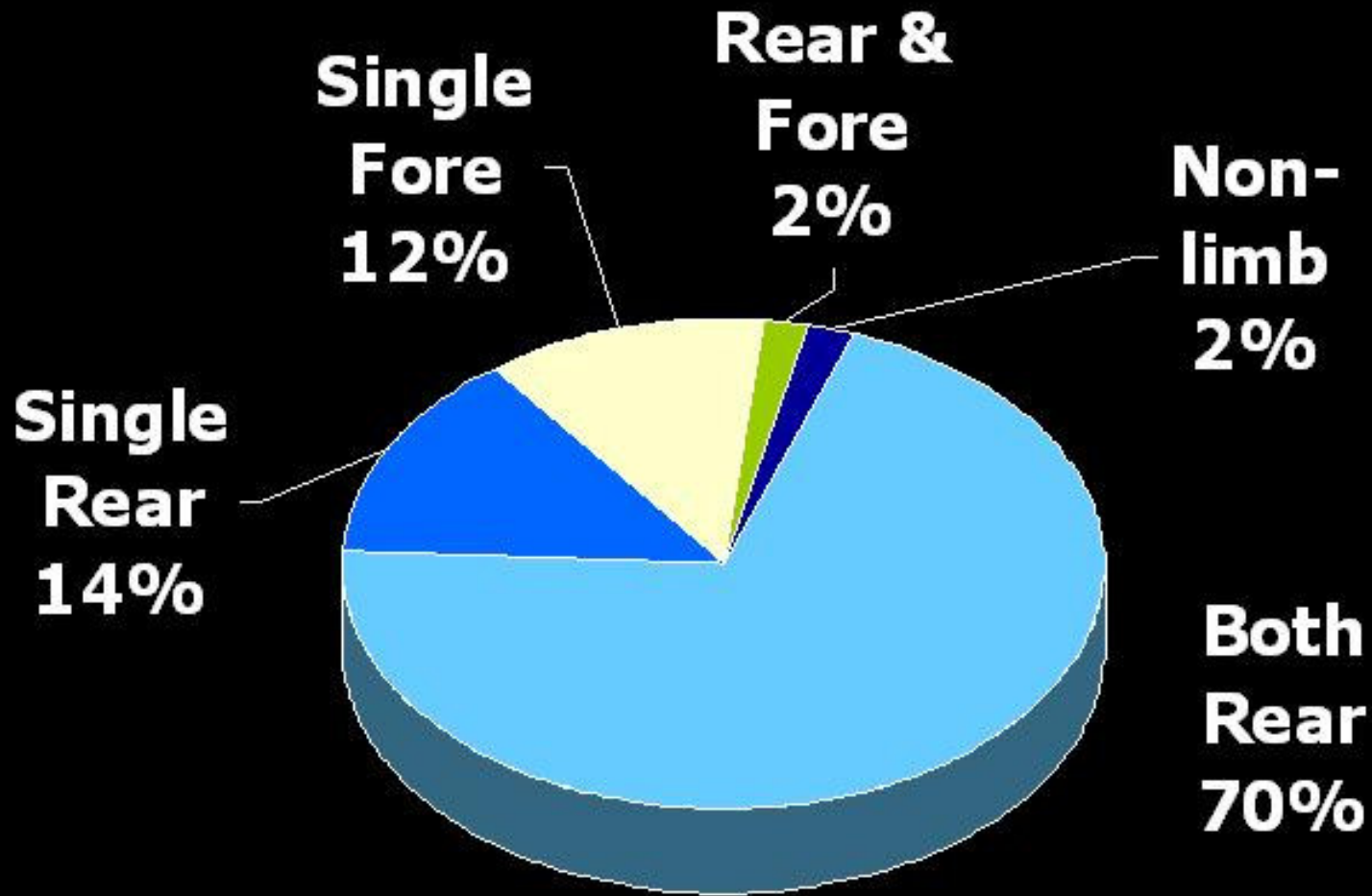
# Hypercoagulable State

- Cats with cardiac disease
  - Altered platelet aggregation
    - Helsenki et al. JVIM-1987
      - Increased platelet aggregation to ADP
    - Welles et al. AJVR-1994
      - Increased platelet aggregation to collagen
      - Decreased to ADP
  - ? Nitric Oxide-Research ?

# Thrombus Formation

- LA dilation
  - Subendothelial collagen exposure
- Platelet response
  - Adhesion
  - Activation
    - Release of vasoactive substances
    - Platelet Aggregation
- Coagulation cascade initiated
- Maturation
  - Lamellated and superficial portions break off

# Clinical Presentation



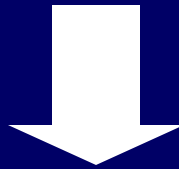
Smith et al. ATE in 127 cats

# Clinical Signs (ACUTE)

- Renal Infarcts → Kidney Pain/Failure
- Mesenteric Infarct → Abdominal Pain/Vomiting
- CNS → Neurologic signs/seizures/death
- Limb (S) → Classically 4 P's
  - Paralysis, Pain, Pulseless, and Polar
  - Firm musculature, cyanotic or pale nail beds

# Ischemic Neuromyopathy

Activated Platelets within the thromboembolism



Release vasoactive substances

Serotonin

Thromboxane A<sub>2</sub>

Collateral Vasoconstriction



# Other Presenting Signs

- Vomiting – 10% - 21%
- Tachypnea/dyspnea – 41% - 90%
- Cardiac auscultatory changes- 55% - 69%
  - Murmurs – 23% - 35%
  - Gallops – 14% - 26%
  - Both – 5% - 10%
- Hypothermia – 35% - 76%
- Concurrent CHF – 43% - 65%

# Biochemical Changes

- Hyperglycemia
- Increased AST/CK
- Azotemia
- Hypercholesterolemia
- Hypocalcemia
- Hyperkalemia
- Coagulation Disturbances

# MANAGEMENT

- Pain Management
- Improve Arterial Flow
  - Aorta
  - Collateral Circulation
- Prevention
- CHF Therapy
- Supportive Care

# Pain Management

## ■ Pain Exhibited

- Vocalization
- Self-mutilation
- Stoic
- Anorexia
- Increased heart rates

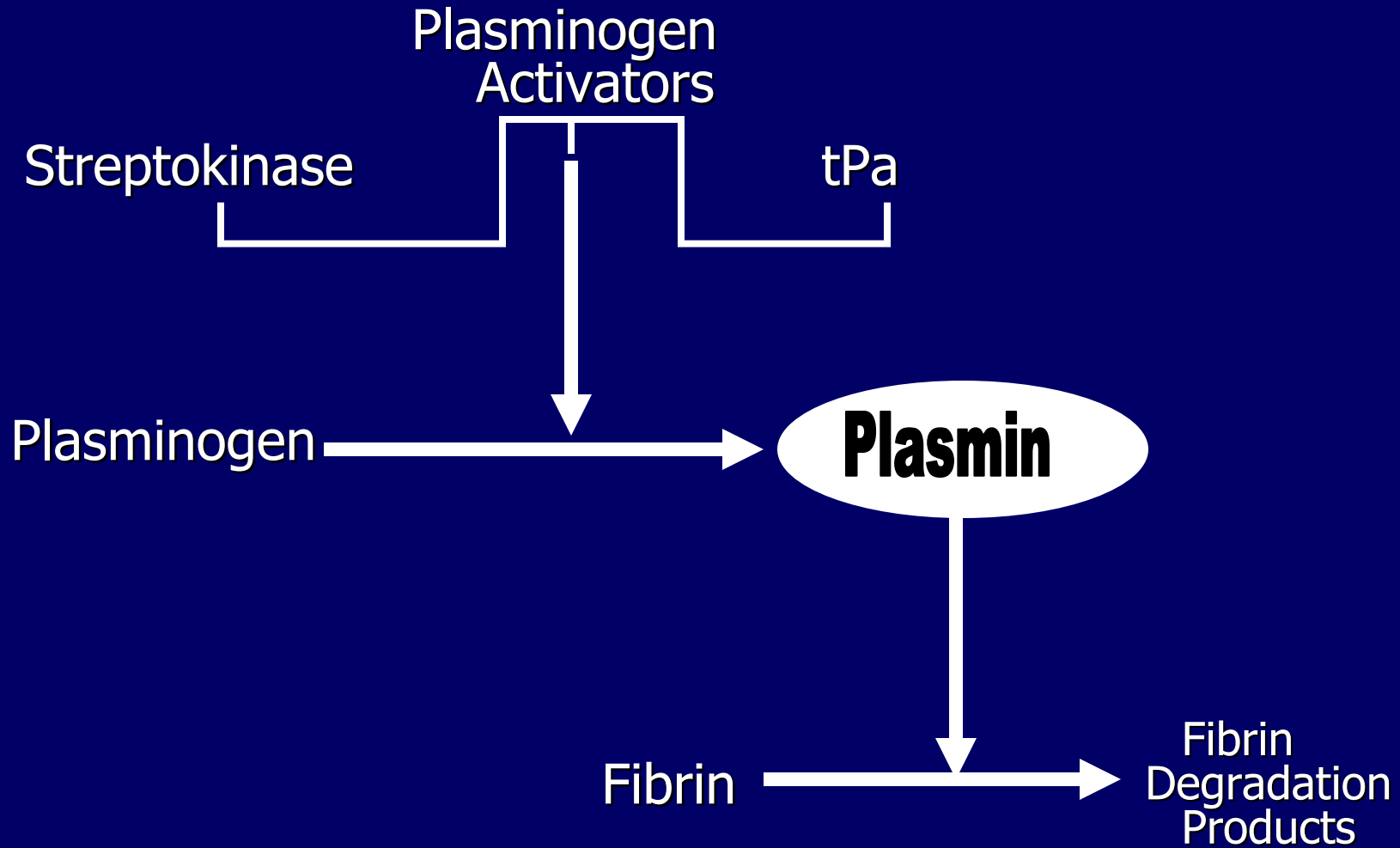
## ■ Treatment Options

- Butorphanol
  - 0.2-0.4mg/kg q 1-4 hrs
- Hydromorphone
  - 0.08-0.3mg/kg q2-6 hrs
- Oxymorphone
  - 0.05-0.1mg/kg q 1-3 hrs
- Buprenorphine
  - 0.005-0.01mg/kg q6-12hrs
- Acepromazine
  - Remember - SEDATIVE

# Improve Arterial Flow

- Aortic removal by embolectomy
  - Rheolytic thrombectomy
  - Often contraindicated
  - Reperfusion injury
- Dissolution by thrombolytic drugs
  - Streptokinase
  - Tissue plasminogen activator (tPa)
  - Complications frequent in cats
    - Complete infarction
    - Delayed presentation
- Benefit to risk ratio

# Thrombolytics



# Streptokinase

- Non-specific plasmin activator
  - Binds circulating and bound plasminogen
- Creates systemic proteolytic state
  - Predispose to bleeding
    - Loss of coagulation factors and increased FDP's
- Dosed
  - 90,000 IU IV over 1 hr
  - 45,000 IU/hr up to 8 hrs
- Available as 750,000 IU (~ \$300)

# Streptokinase

- Moore et al. 2000

- **Clinical Thrombolysis**

- 50 % return femoral pulses
- 30% return of motor function

- **Single limb cats**

- 100 % FP return
- 80 % MF return

- **Complications**

- Hyperkalemia ~40%
- Coagulation abnormalities ~65%
- Bleeding ~ 24%
  - Transfusion ~27%

- **Survival Rate ~ 33%**

- 39% Died in hospital
  - Complications
- 28% were euthanized
  - Prognosis



# Tissue Plasminogen Activator (tPa)

- High fibrin affinity
  - Generally thrombus specific effects
- Bleeding complications less likely
- Protocol
  - 0.25 – 1 mg/kg/hr IV to total 1-10 mg/kg
- Supplied in 50mg and 100mg bottles
  - \$1500 and \$3000 respectively
  - Cathflo™ (Activase®) - 2mg vials - \$100
    - Cost effective low end dosing

# Tissue Plasminogen Activator (tPa)

- Pion et al
  - Showed 50% survival
  - Deaths all related to reperfusion injury
  - Surviving Cats
    - 100 % Bilaterally affected
    - 100% perfused within 36 hrs
    - 100% Motor function within 48hrs
  - SMALL STUDY

# Improve Arterial Flow

## ■ Collateral Blood Flow

= Antiplatelet Drugs

- Reducing vasoactive substances released
  - Not shown to be effective at dilating collaterals
  - Aspirin
    - Reduces thromboxane  $A_2$  from activated platelets
    - High dose needed (150 mg/kg)
  - Clopidogrel (Plavix<sup>®</sup>)
    - Reduces serotonin from activated platelets in cats
    - Reduces thromboxane  $A_2$  in other species
    - ??? 75mg loading dose ???

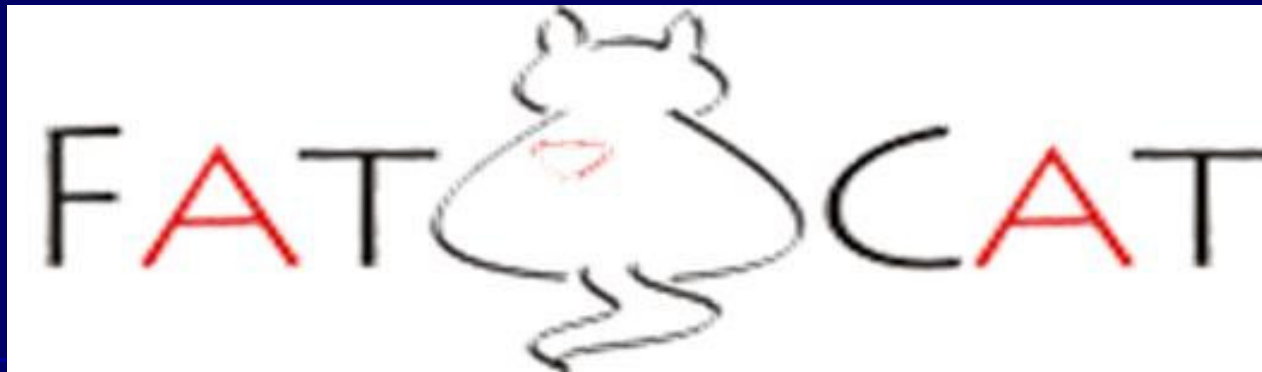
# Prevention

## ■ Primary

- Ideal given incidence and survival rates
- Recommended
  - LA diameter > 1.7cm
  - LA/Ao ratio >2.0
  - Smoke noted
- No scientific support

## ■ Secondary

- Preventing subsequent CE events
- Recurrence rates w/o 40%
- Recurrence rates with 17%-25%
- Retrospective studies
- No scientific support
  - YET!!!



- Feline Aortic Thromboembolism  
Clopidogrel vs Aspirin Trial

<http://www.vin.com/FATCAT>

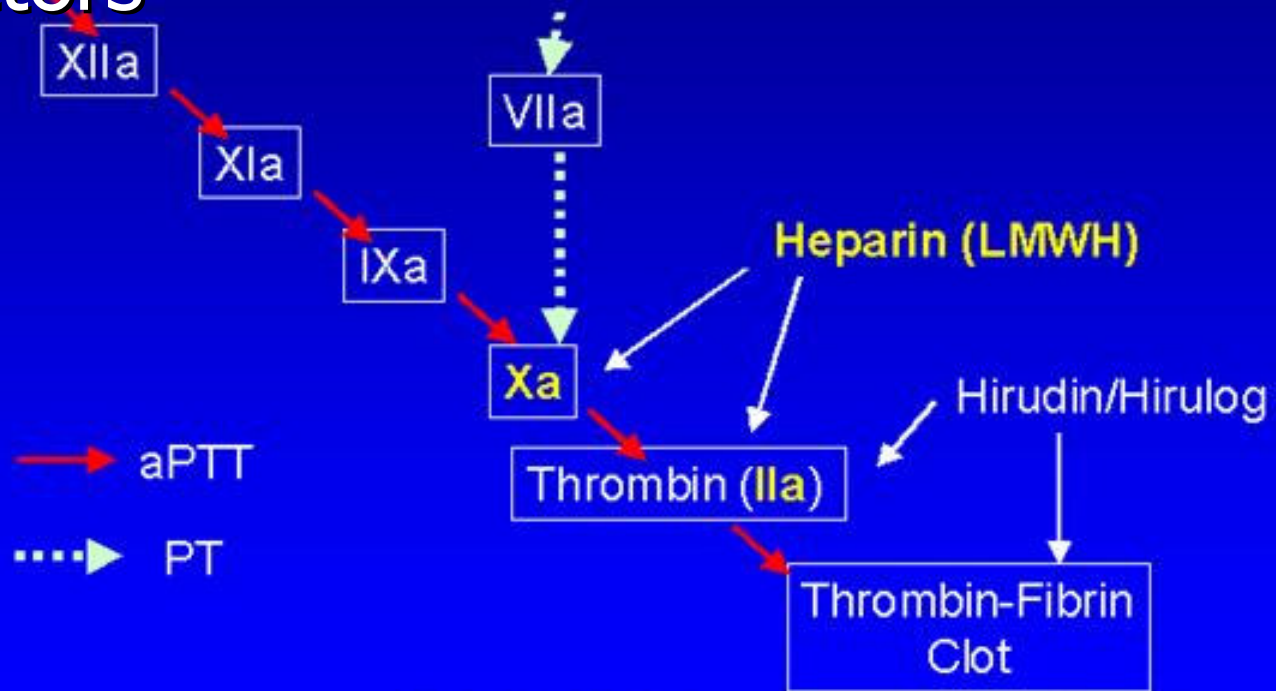
# Prevention: Anticoagulants

- **Prevent the formation of active coagulation factors**
- **Minor antiplatelet effects**
- **Drugs**
  - **Wafarin**
  - **Heparin**
  - **Low molecular weight heparin**

# Wafarin (W)

## Coagulation Cascade

- Inhibits vitamin K dependent factors



# Wafarin

- Inhibits vitamin K dependent factors
- Hypercoagulable state
  - Anticoagulant proteins
- High inter- & intra-individual response
  - Enterohepatic recirculation after oral administration
- Initial Dosing
  - 0.06-0.09 mg/kg qd PO (0.25mg – 0.5mg/cat)
  - Smallest pill 1 mg
    - Compounding recommended
- Concurrent heparin therapy for 1<sup>st</sup> 2-5 days
- Goal
  - Prolong PT 1.3-1.6X baseline
  - INR=PT/control PT 2-3 times
    - Give Vitamin K if >5 times



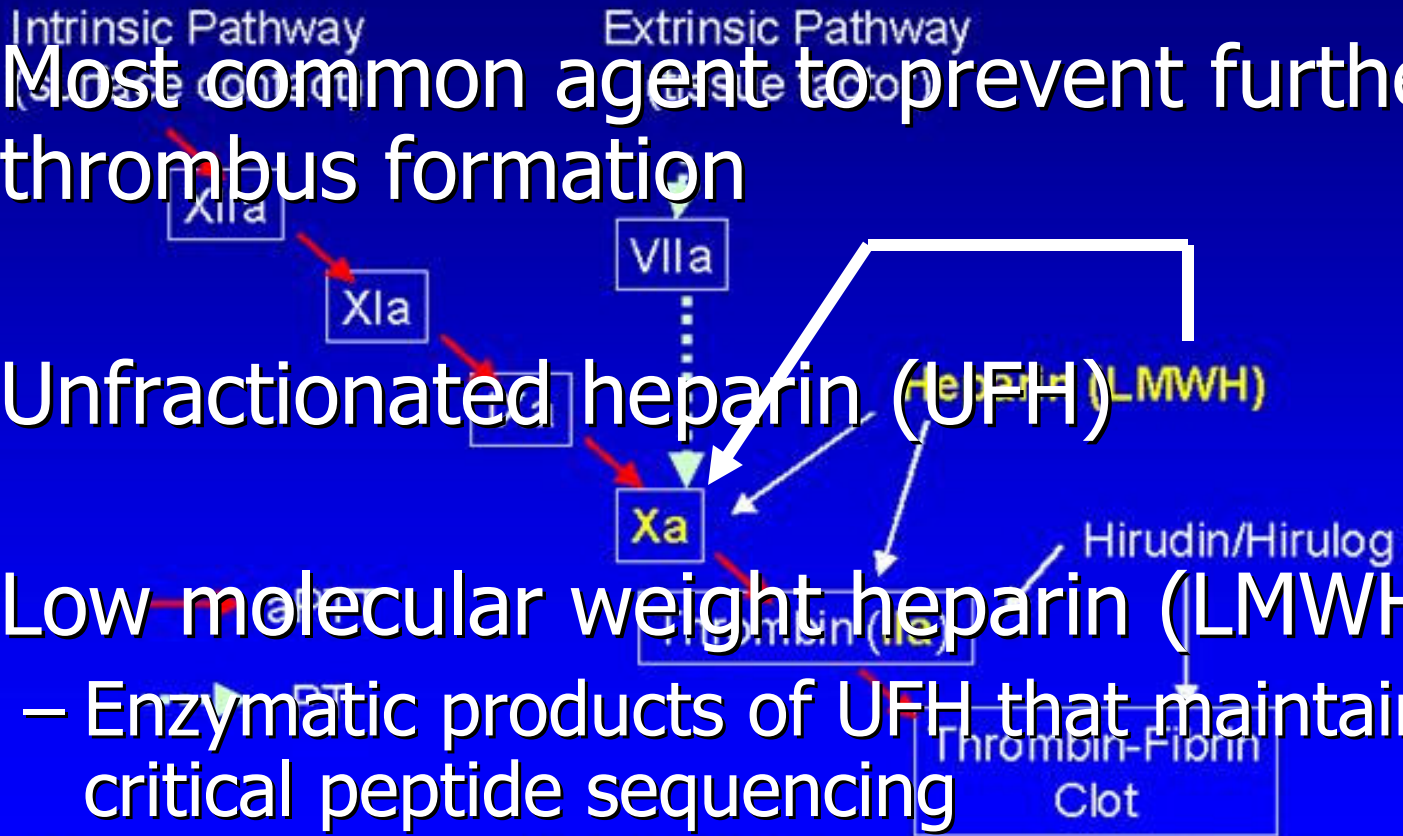
# Wafarin

- **Monitoring**
  - Daily for 1<sup>st</sup> 5-7 days
  - Twice weekly for 2-3 weeks
  - Once weekly for 2 months
  - Once every 6-8 months
  - Adjust total weekly dose as needed
- **Bleeding ~13%-20%**
  - Fatally ~13%
- **CE recurrence ~34%-53%**
- **Cats should become indoor cats**

# Heparin Therapy

## Coagulation Cascade

- Most common agent to prevent further thrombus formation
- Unfractionated heparin (UFH)
- Low molecular weight heparin (LMWH)
  - Enzymatic products of UFH that maintain critical peptide sequencing



# Unfractionated Heparin

- **Large molecule with highly variable protein binding**
- **Adequate dose range**
  - **Highly variable**
  - **Bleeding complications**
  - **Regimen**
    - **250-375 IU/kg IV initially**
    - **150 – 250 IU/kg SQ q 6-8 hrs**
- **Target to increase aPTT 1.5-2.0 X baseline**
- **Antiplatelet activity in humans**
  - **Inhibits von Willebrand Factor (?cats?)**
- **No scientific support**

# Low Molecular Weight Heparin

- **Highly efficacious in human studies**
- **More reliable bioavailability & plasma  $T_{1/2}$** 
  - Dalteparin (Fragmin<sup>®</sup>)– 100 IU/kg SQ q 24-12 hrs
  - Enoxaparin (Lovenox<sup>®</sup>) 1.0-1.5mg/kg SQ q24-12 hrs
- **Little to no effects on thrombin**
- **Anti-Xa activity can be monitored ? ? ?**
- **Considered twice daily drugs in humans**
  - Current feline studies suggest 2-3 X/ days
  - Potentially different pharmacokinetics in CE cats

# Low Molecular Weight Heparin

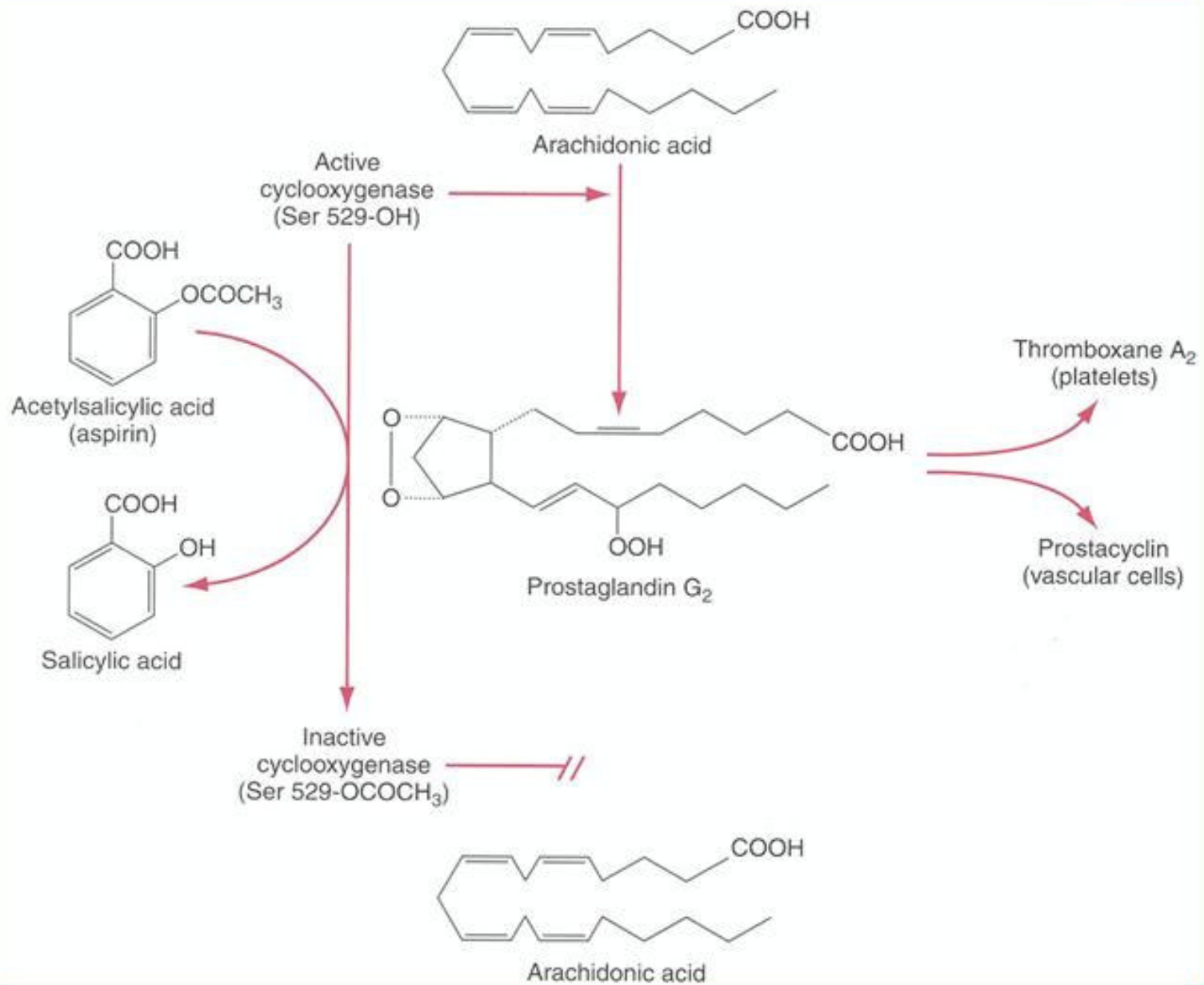
- DeFrancesco et al. 2003
  - Warfarin group survival only 69 days vs. 255 in LMWH group
  - CE recurrence rate 43% compared with warfarin 34% (retrospectively)
- Pharmacokinetics in normal and CE cats?
- Cost Prohibitive
  - Dalteparin ~ \$60-\$80/month (multi-dose vial)
  - Enoxaparin ~ \$ 160/month
- Clinically
  - 22 cats on Dalteparin 100 IU/kg SQ daily
  - 8 cats on combination therapy with antiplatelet drugs
  - No side effects and 6 recurrence (2 on combination)
  - 8 death due to progression of heart disease (3 related to recurrence)

# Antiplatelet Therapy

- Inhibit platelet
  - Adhesion, aggregation, or release reactions
  - Exhibit vasomodulating effects
- Aspirin
- Thienopyridines
  - Ticlopidine (Ticlid<sup>®</sup>)
  - Clopidogrel (Plavix<sup>®</sup>)

# Aspirin

- **Greene et al. 1985**
  - Inhibit platelet response to arachidonic acid
- **Behrend et al. 1996**
  - No inhibitory response on ADP induced platelets
- **Standard dosing 25mg/kg PO q 72-48 hrs**
  - ~81 mg/cat
  - GI side effects reported ~22%
  - CE Recurrence rates 17%-33%
    - Small study 75%
  - Median survival times 117-180 days





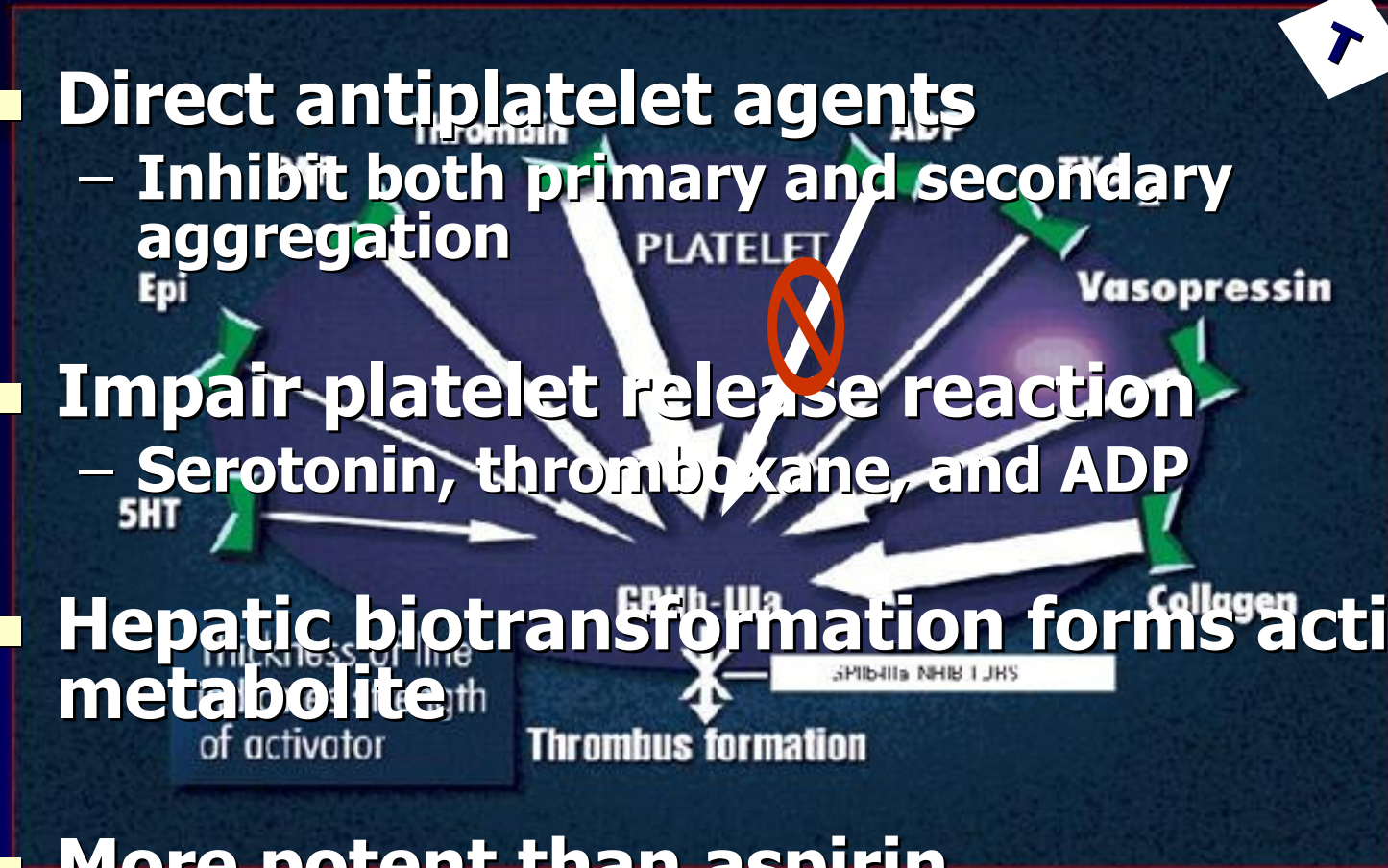
# Low Dose Aspirin

- **Theory:**
  - High dose inhibits endothelial cyclooxygenase
  - Reduce prostacyclin production
- **Smith et al. 2003**
  - 5 mg/cat q 72 hrs
  - No significant difference
    - Recurrence or median survival time
  - Decreased GI side effects

# Thienopyridines

## Platelet Activation Agonists

- **Direct antiplatelet agents**
  - Inhibit both primary and secondary aggregation
- **Impair platelet release reaction**
  - Serotonin, thromboxane, and ADP
- **Hepatic biotransformation forms active metabolite**
- **More potent than aspirin**



# Thienopyridines

## ■ Clopidogrel (Plavix®)

- Dosed at 18.75mg, 37.5mg, & 75mg PO qD
- Achieved 95% inhibitory response to ADP
- 92% inhibition to serotonin release
- Maximal effects occurred at 3 days resolved 7 days after discontinuing
- Minimum side effects noted
  - Rare GI upset, 1 cat gum bleeding
- Cost approximately \$30-45%/month/cat

# Outcomes

## ■ Survival Rates

- Conservative: 35%-39%
- Thrombolytic: 33%-50%
- Single limb: 68%-93%
- Bilateral: 15%-36%

## ■ Death rates

- Natural death rates: 28%-40%
- Euthanasia: 25%-35%

# Outcomes

## ■ Poor Prognostic Indicators

- CHF
- 4-6 weeks most regain motor function
- Thrombus in LA
- May take months to become normal
- = Limb necrosis ~5%
- = Hypothermia
- = Limb contracture ~2%
- = Bradycardia
- Amputation or wound management
- Recurrent CE

## ■ Survival times

- Azotemia
- Median 51-345 days
- Hyperkalemia

# Recommendations

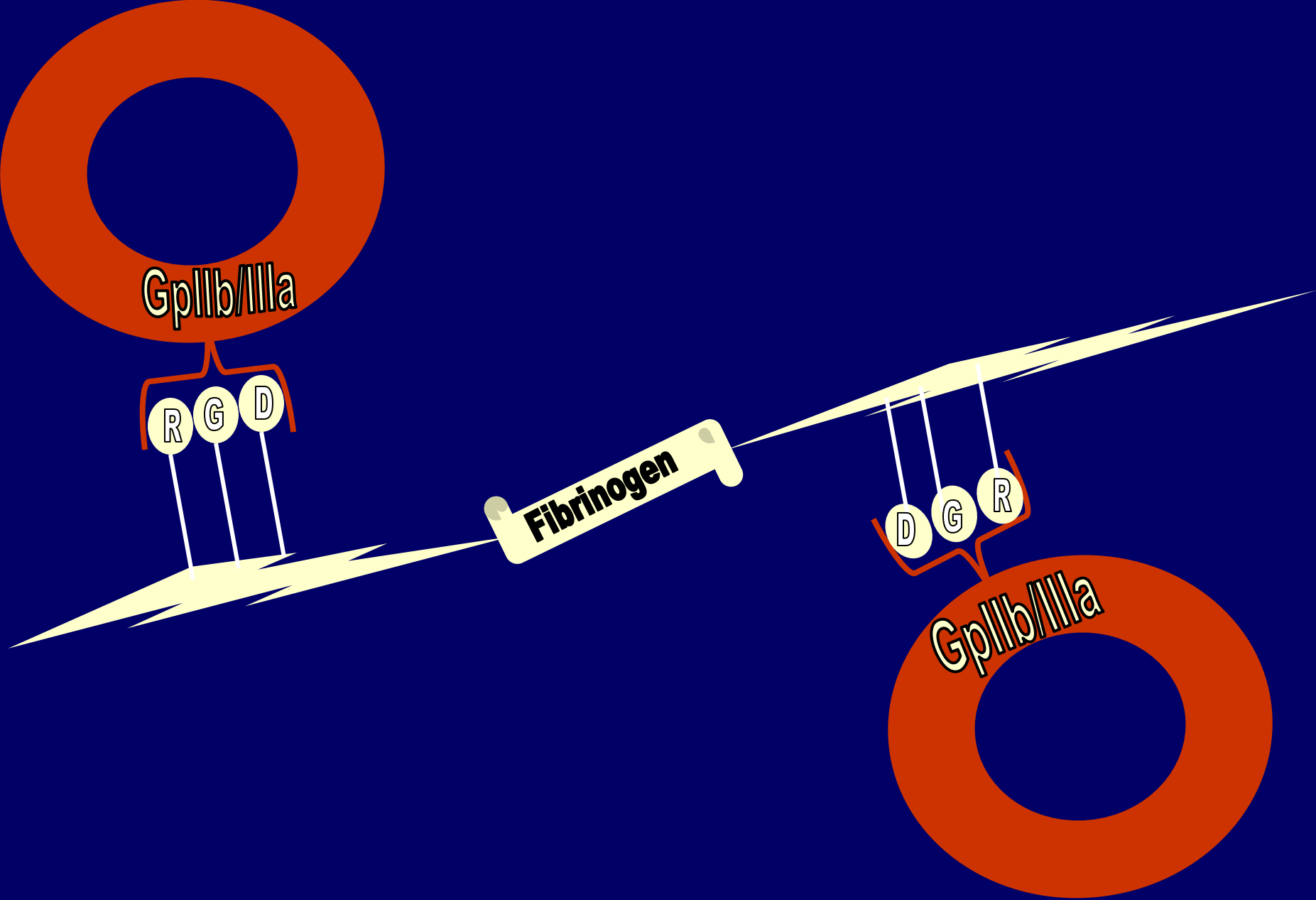
- **Diagnostic Work-up**
  - **Chemistry**
  - **Coagulation Profile**
  - **Urinalysis**
  - **Thoracic Radiographs**
  - **Echocardiogram**

# Recommendations

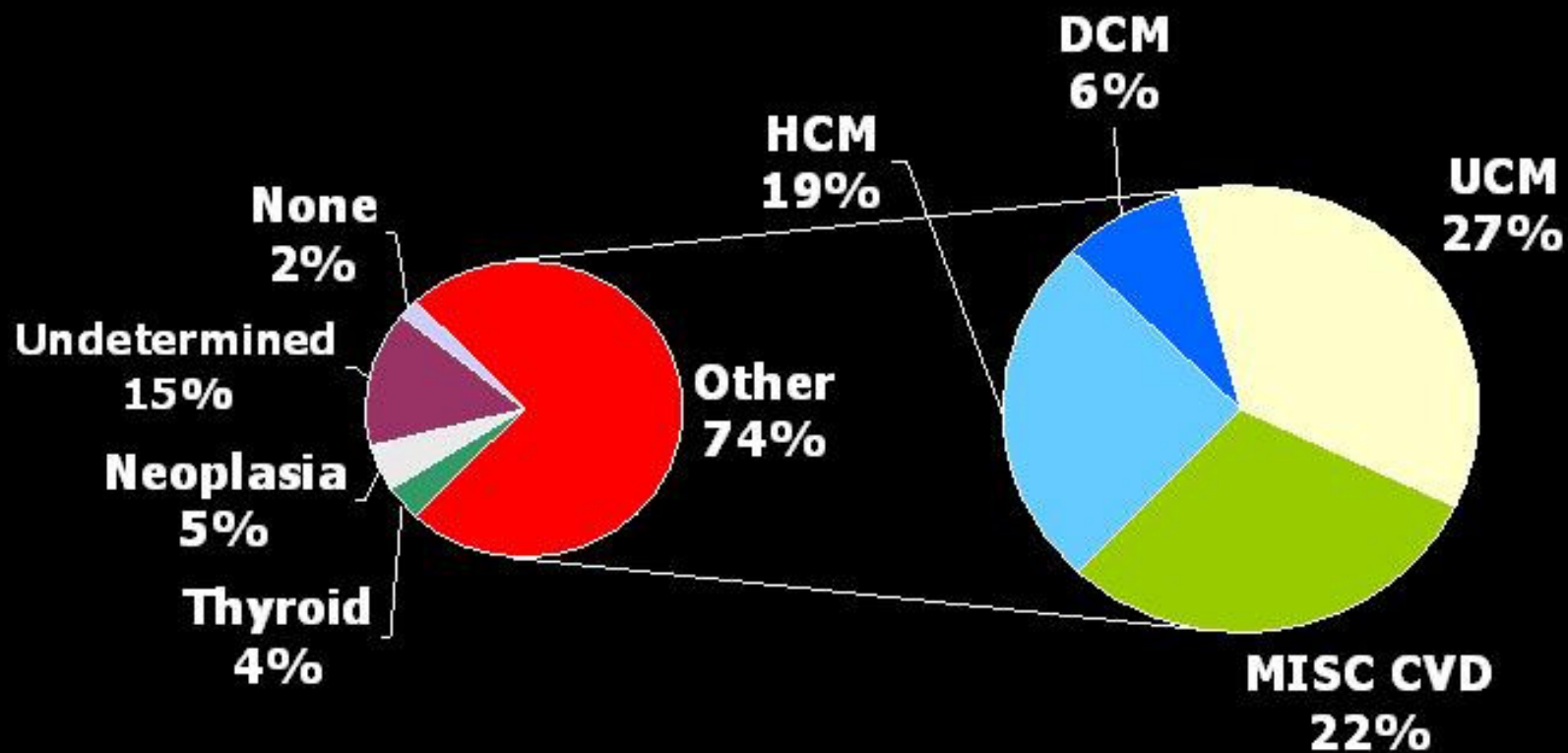
- **No scientific support**
- **Single preventative therapy**
  - **LA systolic diameter**
  - **Smoke**
  - **Thrombus present**
- **Combination therapy**
  - **Anticoagulants and antiplatelet may be synergistic**
- **CE event**
  - **Plavix loading dose**
  - **Bilateral – Thrombolytic therapy < 6-8 hrs**
  - **Single limb**
    - **Anticoagulants**
    - **Antiplatelet**
- **Significant RESEARCH NEEDED!!!**

QUESTIONS





# ATE with Cardiovascular Disease



# Blood Stasis

- Impaired Left Ventricular Filling Pressure
  - Elevates left atrial pressure
  - Left atrial dilatation
  - Blood Stasis
    - Spontaneous Contrast on Echocardiogram
      - “SMOKE”

# UFH Vs. LMWH

