

**REVIEWS:**

**Anticoagulant rodenticides  
intoxication in dogs**

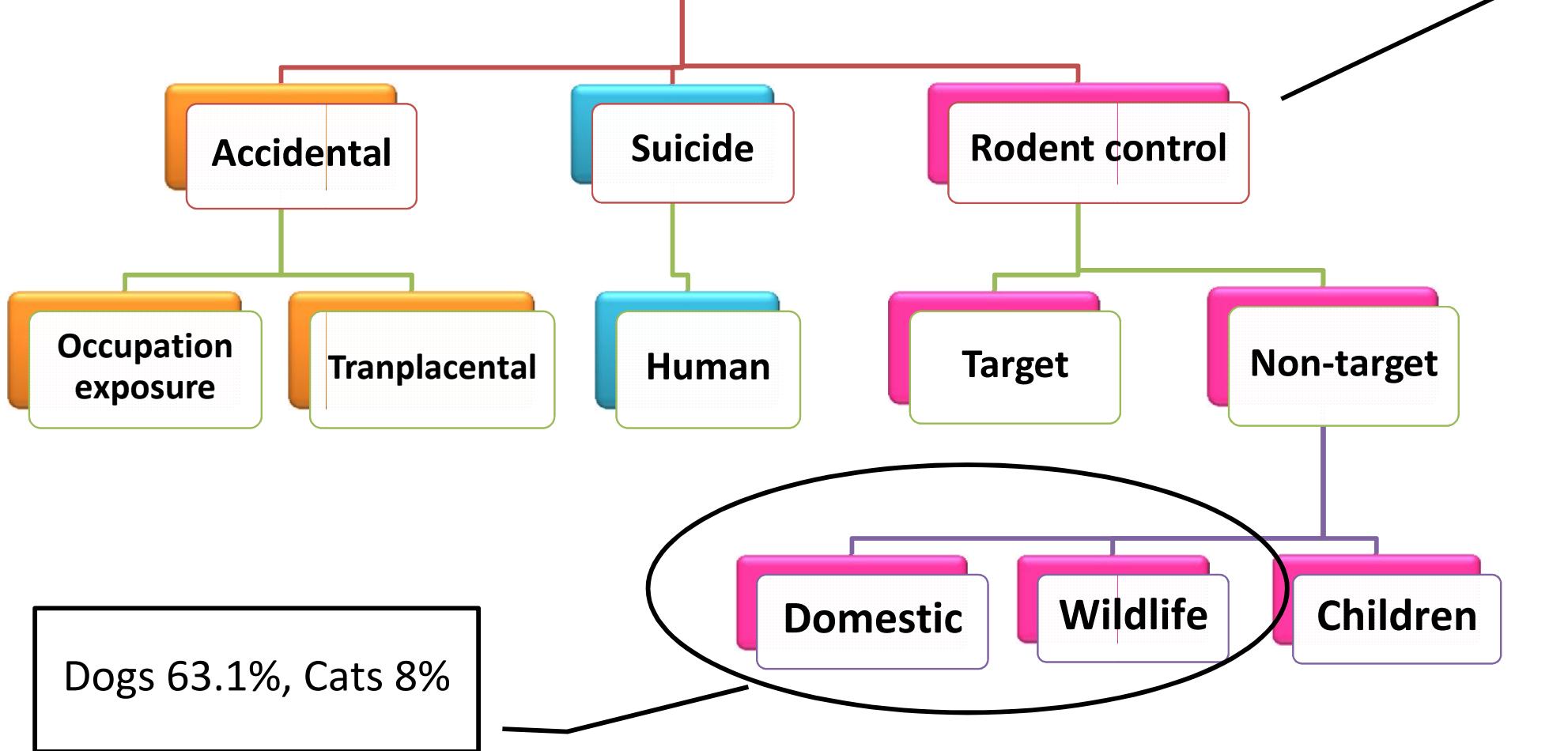
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# Introduction

- Anticoagulant rodenticides intoxication is 18.9% of pesticides intoxication  
(Wang et al., 2007)
- It has been estimated that approximately 95% of all rodenticides used are anticoagulant baits (Binev et al., 2005)
- Dogs were intoxication from anticoagulant rodenticides about 63.1% (Lorgue et al., 1986)

# Incidence of coumarin derivative rodenticides poisoning



Andre and Guillaume, 2004; Lorgue et al., 1986; Munday and Thompson, 2003; Nelson et al., 2000; Svenden et al., 2002

# Anticoagulant rodenticides

## Hydroxycoumarin rodenticides

- **First generation :**  
warfarin, coumatetralyl, coumachlor, coumafuryl
- **Second generation :**  
brodifacoum, bromadiolone, difenacoum,  
difethialone, flocoumafen

## Indandione rodenticides

- chlorophacinone, diphacinone, pindone, valone

# First generation

Warfarin



Coumatetralyl



# Second generation

Bromadiolone



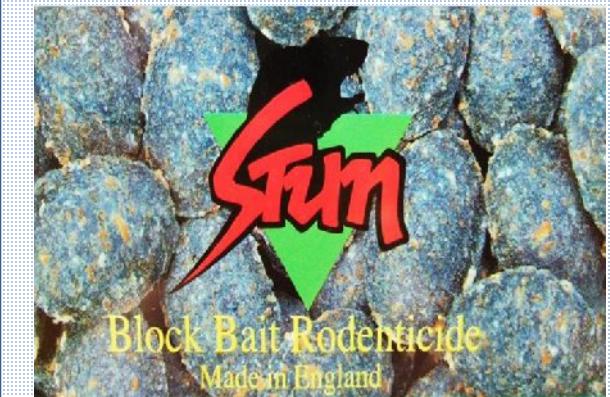
Difenacoum



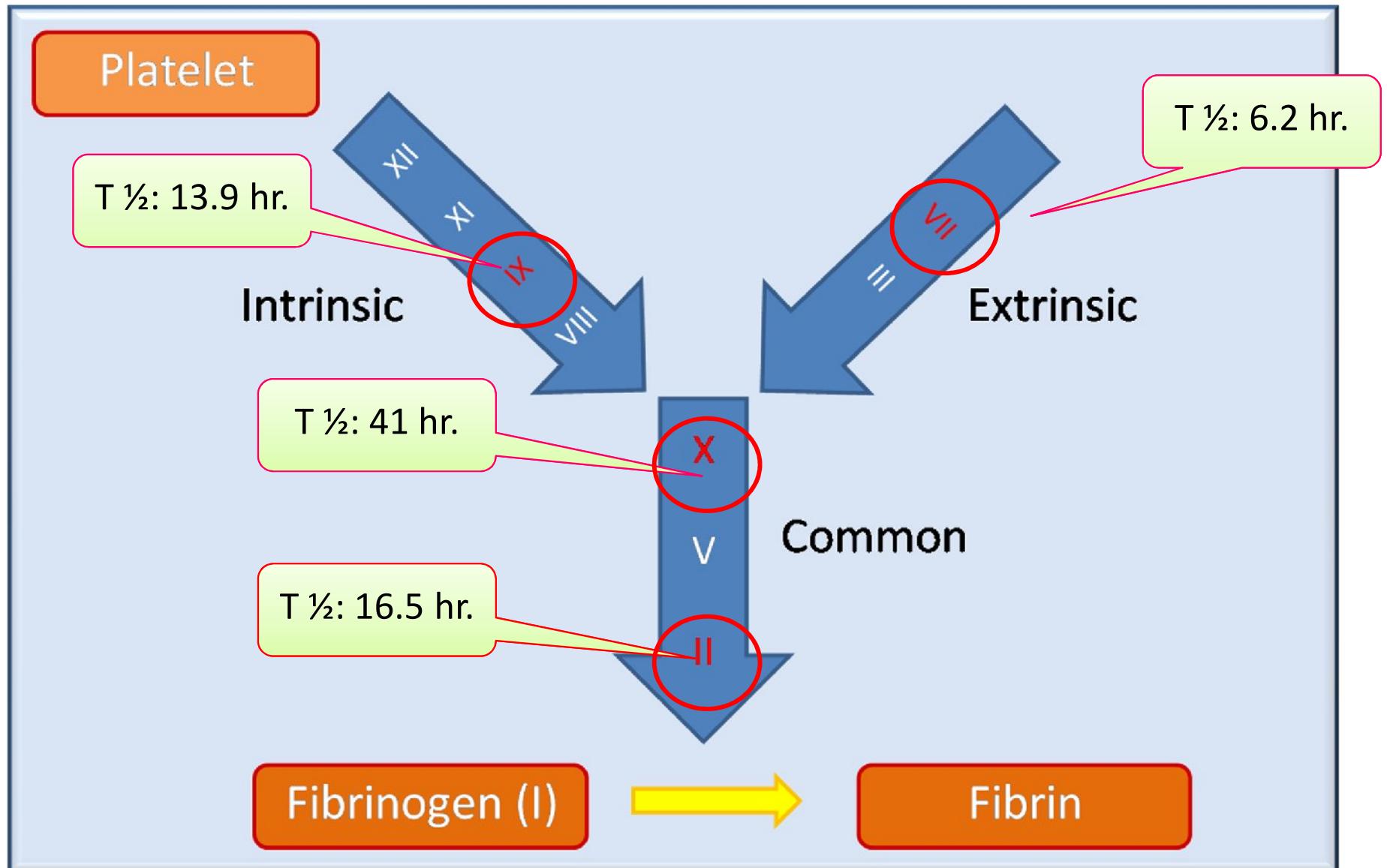
Difethialone



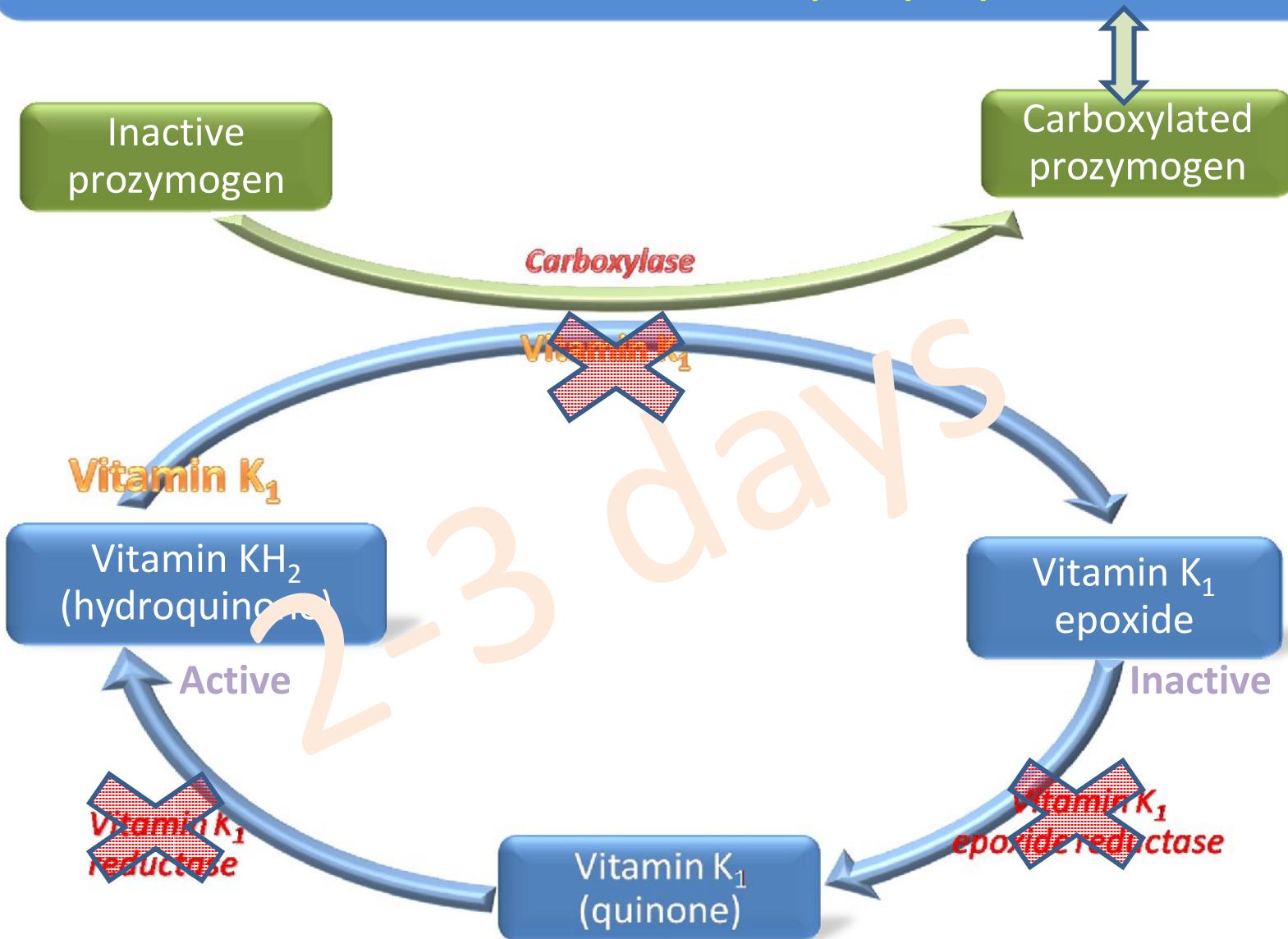
Flocoumafen



# Coagulation pathway

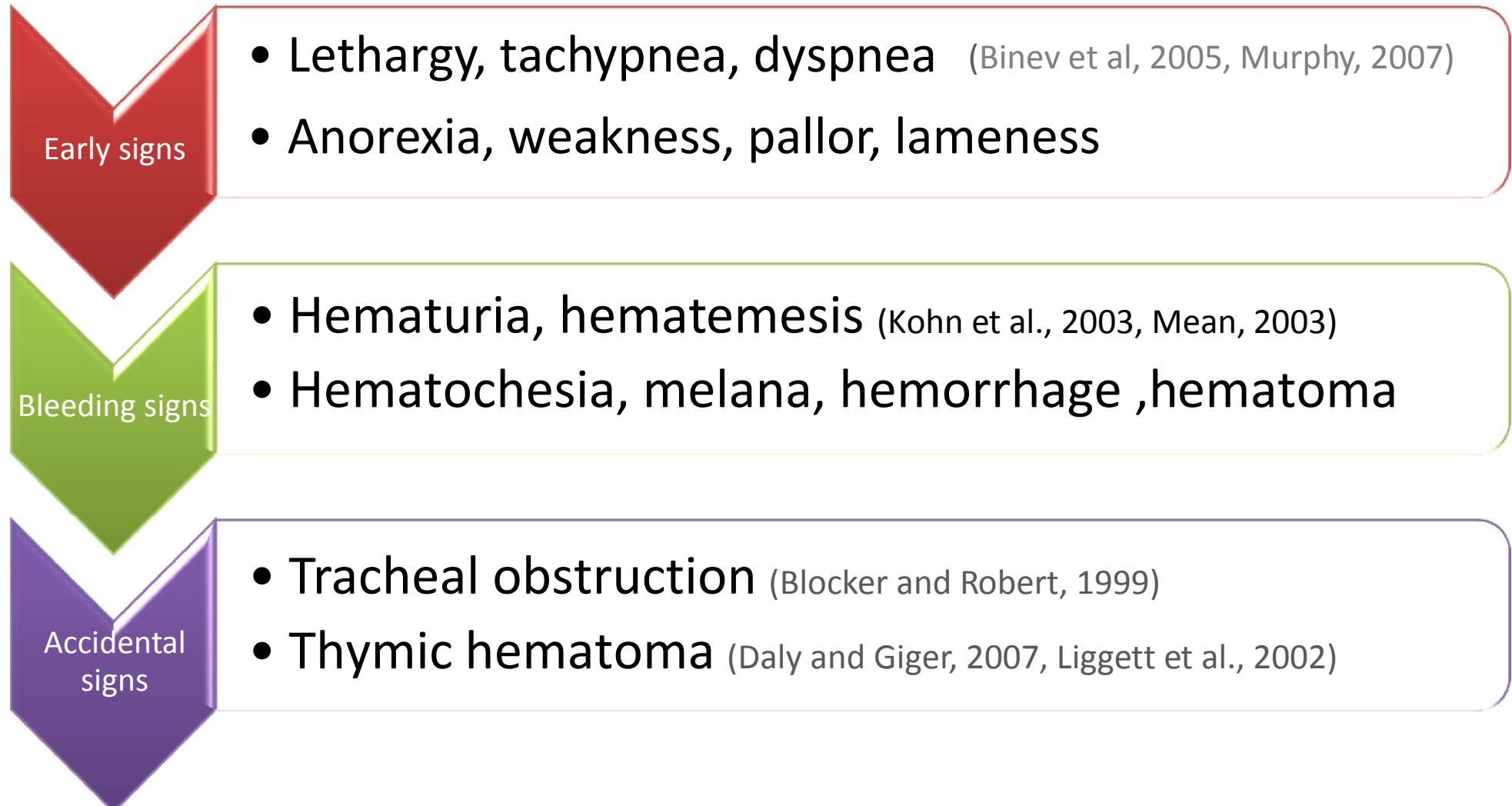


# Vitamin K<sub>1</sub>-dependent clotting factors: Factor II, VII, IX, X



(Harrell et al, 2003)

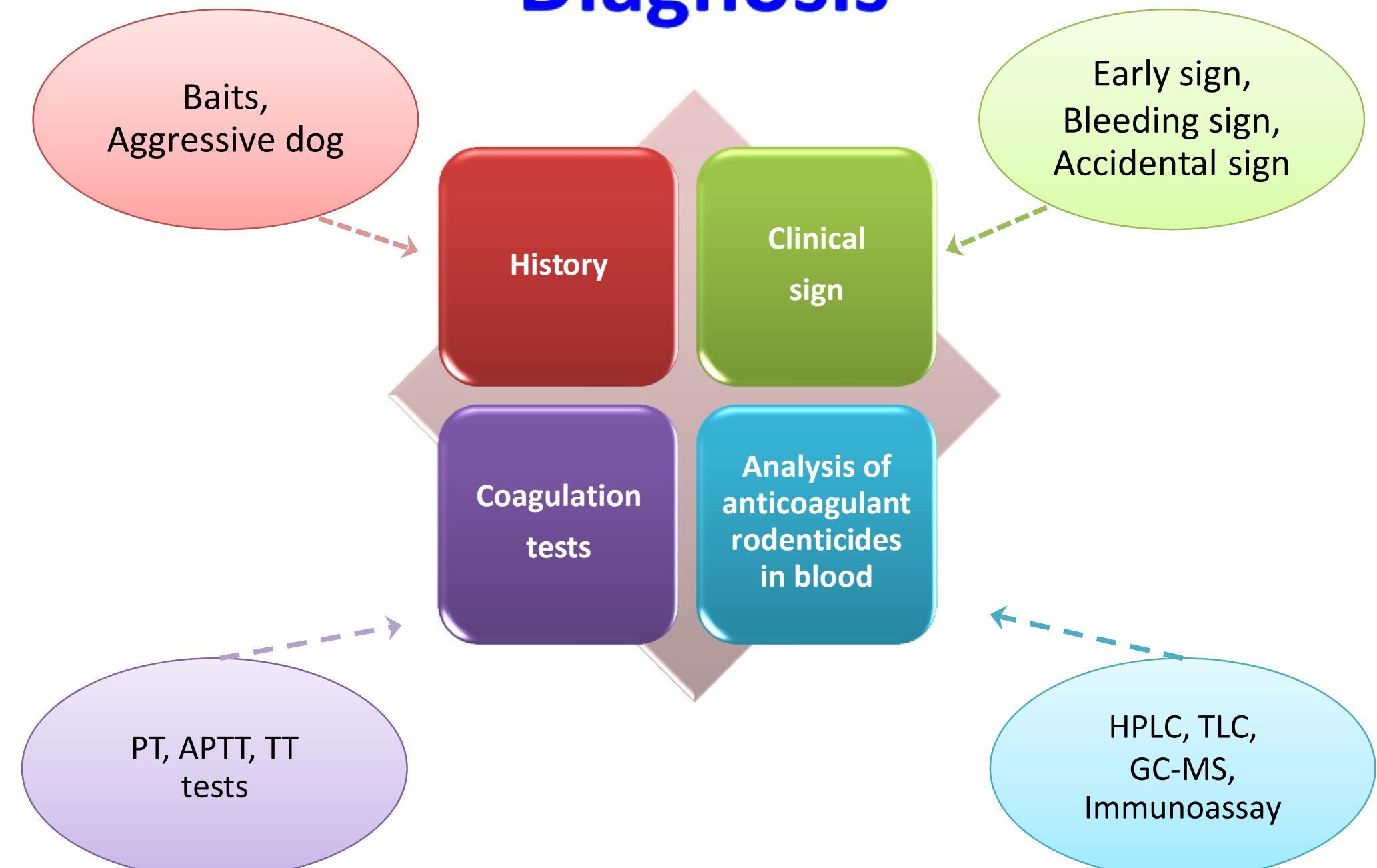
# Clinical signs

- 
- Lethargy, tachypnea, dyspnea (Binev et al, 2005, Murphy, 2007)
  - Anorexia, weakness, pallor, lameness
- 
- Hematuria, hematemesis (Kohn et al., 2003, Mean, 2003)
  - Hematochesia, melana, hemorrhage ,hematoma
- 
- Tracheal obstruction (Blocker and Robert, 1999)
  - Thymic hematoma (Daly and Giger, 2007, Liggett et al., 2002)

# Intoxicated dogs from warfarin



# Diagnosis

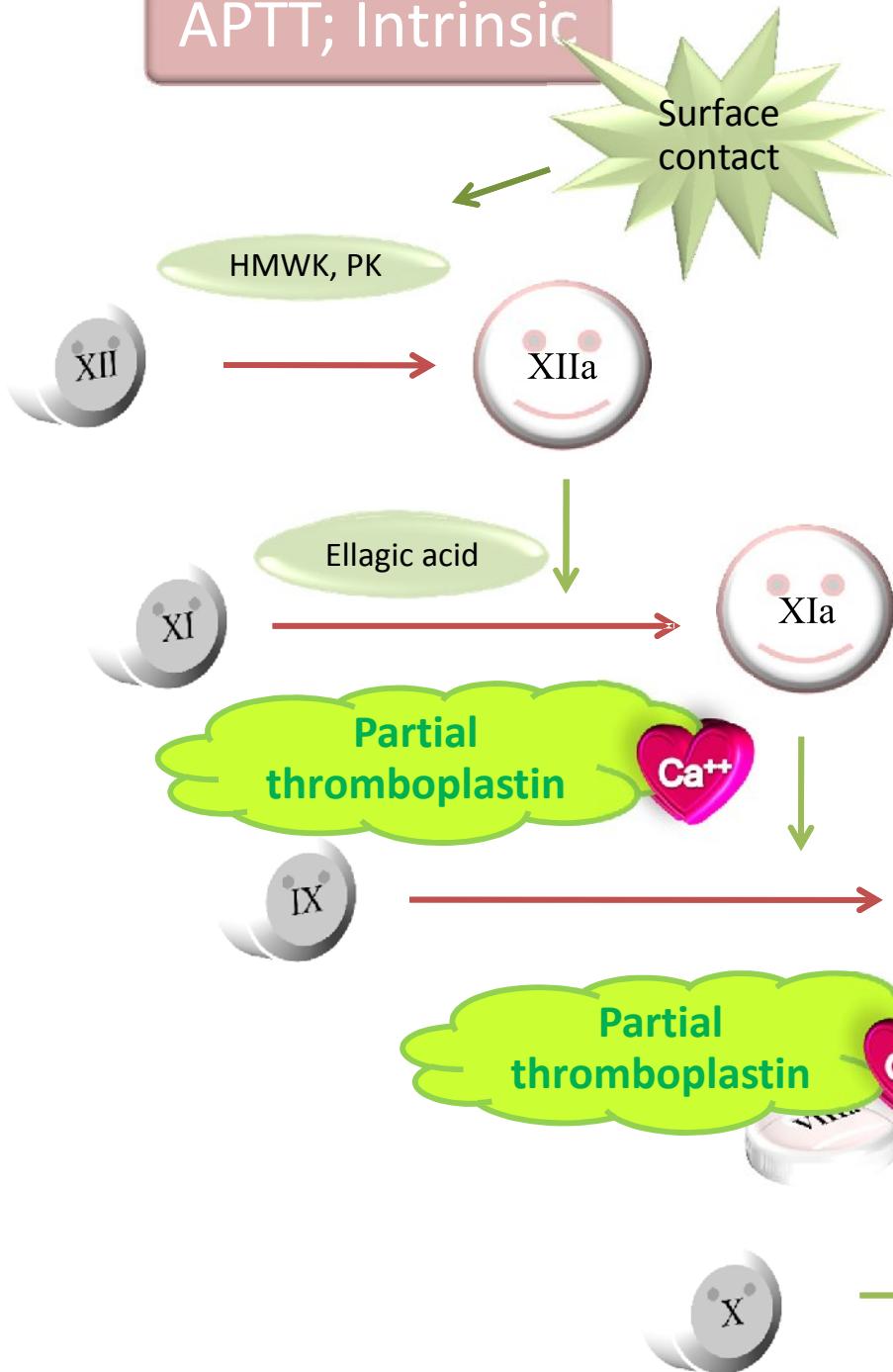


(Binev et al., 2005, Daly and Giger, 2007, Murphy, 2007, Nelson, 2006, Rozanski et al., 1999, Sheafor and Couto, 1999)

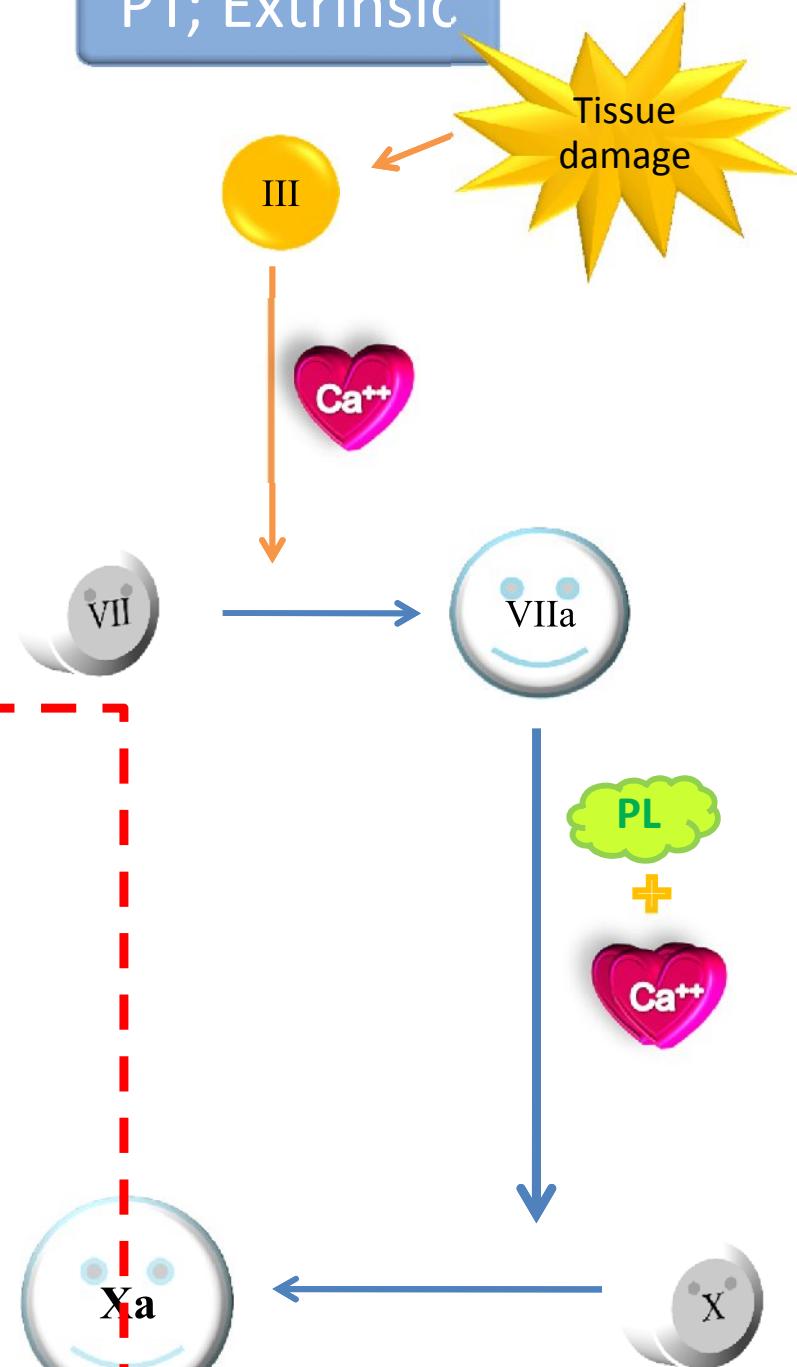
# Expected results of coagulation tests in various coagulopathies

Diseases \ Tests	APTT	OSPT	PIVKA	TT	FDPs	Fragmented RBC
Diseases						
Anticoagulant rodenticides	Prolonged	Prolonged	Prolonged	Normal	Negative	Negative
Disseminated Intravascular Coagulopathy	Prolonged	Prolonged	Prolonged	Prolonged	Positive	Schistocyte
Thrombocytopathy	Normal	Normal	Normal	-	-	-
References	Woody, 1992  Sheafor and Couto, 1999,  Sodikoff, 2001,  Daly and Giger, 2007	Woody, 1992  Sheafor and Couto, 1999,  Sodikoff, 2001,  Daly and Giger, 2007	Woody, 1992  Rozanski et al. 1999  Sheafor and Couto, 1999,  Daly and Giger, 2007	Woody, 1992  Daly and Giger, 2007,	Woody, 1992  Sheafor and Couto, 1999,  Daly and Giger, 2007	Sodikoff, 2001  Sheafor and Couto, 1999,

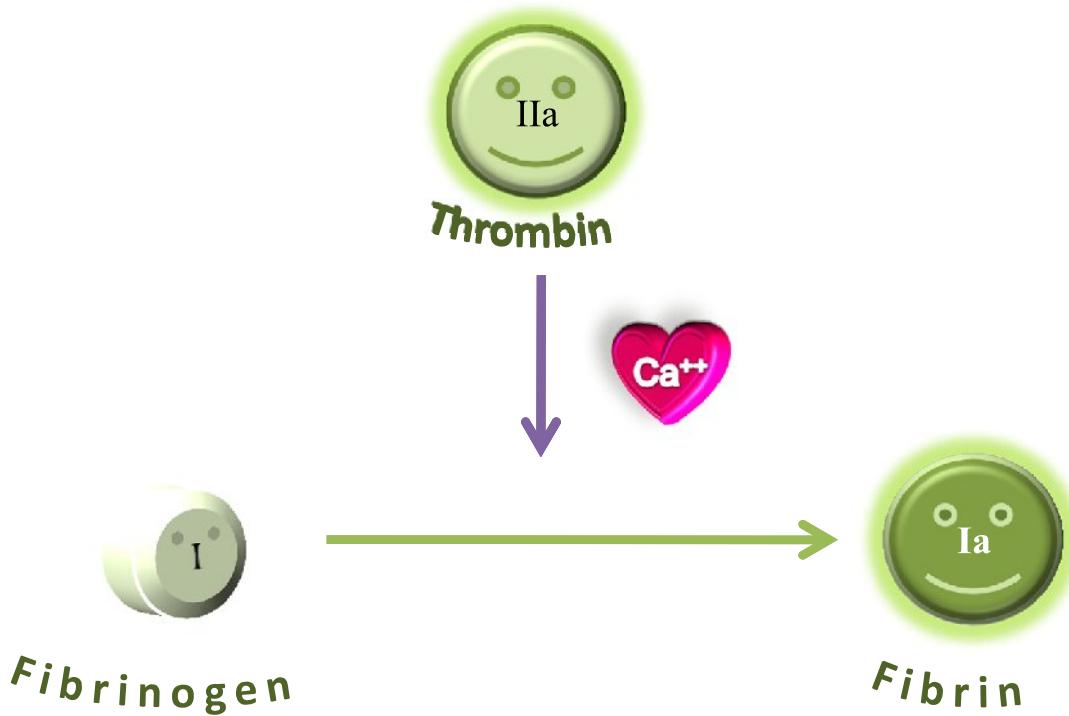
## APTT; Intrinsic



## PT; Extrinsic



## Fibrinogen : Thrombin Time (TT)



# Analysis of anticoagulant rodenticides in blood

- Thin layer chromatography (TLC)
- Immunoassay ← 

Low specific  
(Vandenbroucke et al., 2008)
- Gas chromatography-Mass spectrometry (GC-MS)
- High performance liquid chromatography (HPLC) with UV or Fluorescence detection

High specific,  
sensitivity, cost  
(Vandenbroucke et al., 2008)

**HPLC:** High sensitivity, stability, specific  
(Marek et al., 2007, Osman et al., 2005)

**Sensitivity:** Fluorescence > UV detection  
(Rangel and Friedrich, 1997, Vandenbroucke et al., 2008)

# Treatment

## 1. Detoxification

- Induce emesis : within 2-4 hr
- Gastric lavage: within 2-4 hr
- Activated charcoal: grind + saline cathartic

## 2. Supportive

- Prothrombin complex concentrate ( $F_{II,VII,IX,X}$ ): 50 units/kg
- Blood transfusion, thoracocentesis

## 3. Specific

- Vitamin K1

**“ Prognosis is generally good ”**



# Treatment: Antidote

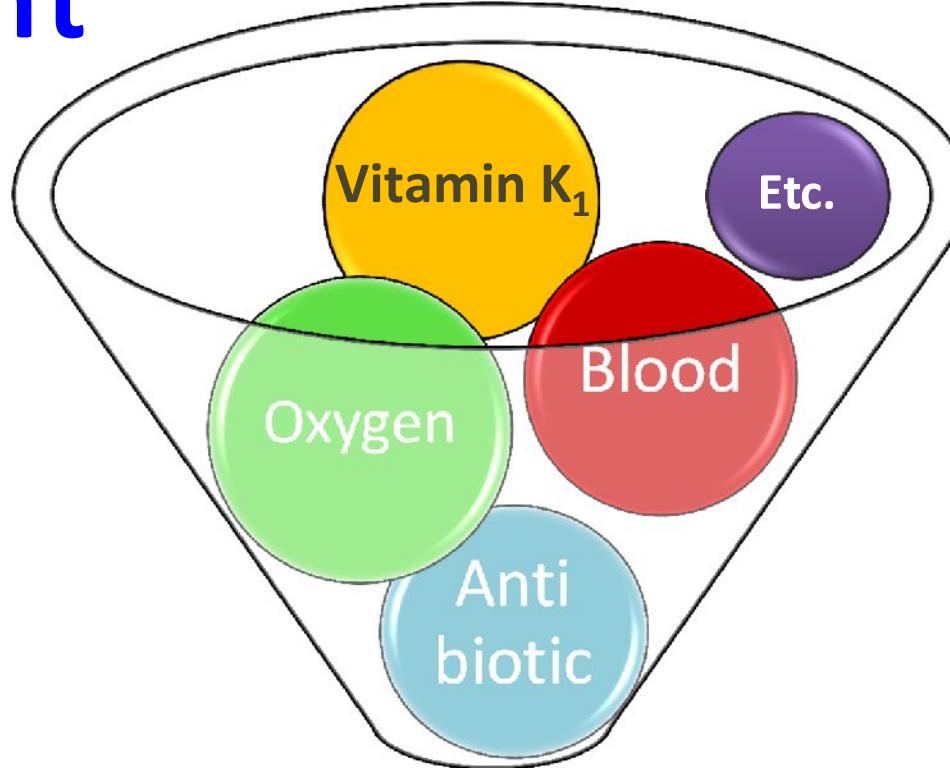
- Vitmain K1  
(Phytoneadione/Phytomenadione/Phylloquinone)
- 2-5mg/kg, bid-sid
- SC,IM, PO (**not IV**)
- 7-14, 21-30 day (up to coagulation tests)
- Confirm by normal APTT and PT

Anaphylaxis !!!



Vitamin K2, K3 ???

# Treatment



How long are treated?

# **Complete blood count and Blood chemistry**

# Coagulation test and coumarin derivative rodenticides analysis

NO.	History to poisoning	Confirm by HPLC	Concentration (ng/mL)			Tx.vit K1 before blood collection	Coagulation tests								
							PT (normal 7-11 sec)			APTT (normal 9-16 sec)			TT (normal 6.5-10.5 sec)		
			1 <sup>st</sup>	7 <sup>th</sup>	14 <sup>th</sup>		1 <sup>st</sup>	7 <sup>th</sup>	14 <sup>th</sup>	1 <sup>st</sup>	7 <sup>th</sup>	14 <sup>th</sup>	1 <sup>st</sup>	7 <sup>th</sup>	14 <sup>th</sup>
Day															
1	uk	-	nd	d	d	✓	9	-	-	48	-	-	19.5	-	-
2	uk	-	nd	d	d	✓	>60	-	-	>60	-	-	>60	-	-
3	uk	-	nd	d	d	✗	>60	-	-	>60	-	-	>60	-	-
4	uk	-	nd	d	d	✗	25	-	-	17	-	-	8	-	-
5	uk	-	nd	d	d	✓	7	-	-	33	-	-	19.5	-	-
6	uk	-	nd	nd	nd	✓	8.5	7	9	22.5	13	12	8	10	9
7	uk	-	nd	nd	nd	✓	8.5	12	9	15.5	15	14.5	8	11	8.5
8	uk	coumatetralyl	36.544	-	-	✓	11	-	-	18	-	-	8	-	-
9	bromadiolone	-	nd	nd	-	✗	9	7.5	-	13.5	12	-	6	10	-
10	flocoumafen	-	nd	-	-	✓	11	-	-	16.5	-	-	14	-	-
11	warfarin	warfarin	28.437	nd	nd	✓	9	14	8.5	18	27	15	16	11.2	9
12	warfarin	warfarin	131.50	-	-	✗	8	-	-	27	-	-	16	-	-
13	warfarin	warfarin	95.93	nd	-	✓	7	8.5	-	12	12	-	8	10	-
14	warfarin	warfarin	166.70	nd	-	✗	6	7.5	-	14.5	15	-	5	10	-

Note: d = death, uk = unknown, nd = non detectable, - = un test

Case study

# Discussion

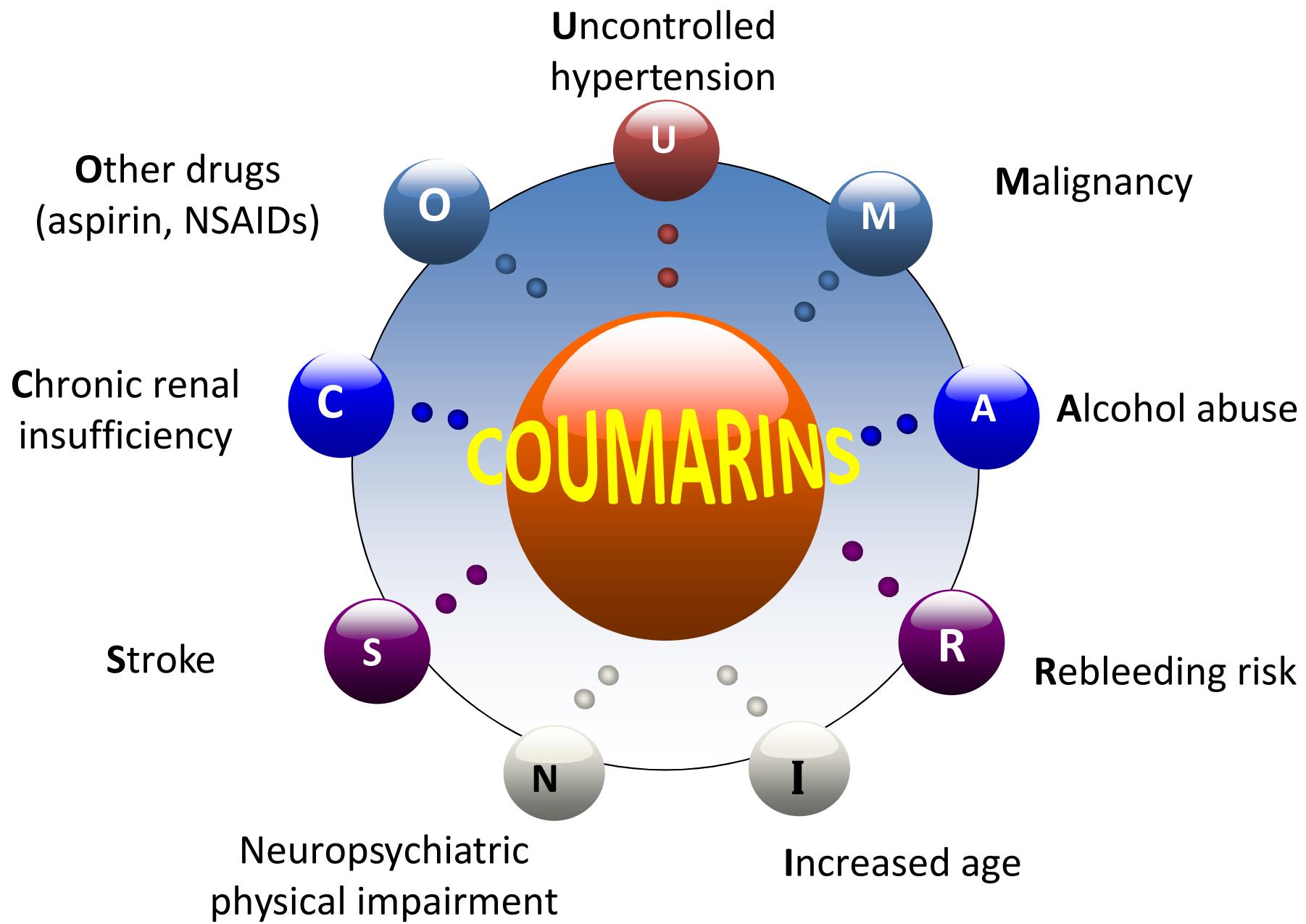
- Anticoagulant rodenticides concentration in plasma are not correlated with coagulation times
  - Time of sample taken (Mallinckrot and Meyer, 2009)
  - Type and amount intake (Mallinckrot and Meyer, 2009)
  - Individual health status & coagulation times

Hepatic dysfunctions :

- synthesis of coagulation factors. (D'Andrea et al., 2008)
- decreased metabolism of the drug. (Jacobs, 2008)

Before blood collection: tx. Vitamin K1

# Risk factors of bleeding



(Gage and Eby, 2003, Jacobs, 2008, Olson et al, 2008)

**THANK YOU  
FOR  
YOUR ATTENTION**