# On the Haematological Risk Factors for Coronary Heart Disease

# Coronary Heart Disease

- One of the most frequently encountered multifactorial disorder.
- The most common cause of morbidity and mortality world wide*.
- Aetiological factors:
  - Genetic susceptibility--- (polygenic).
  - Environmental factors.
- Gene-environment interactions essential for CHD development.

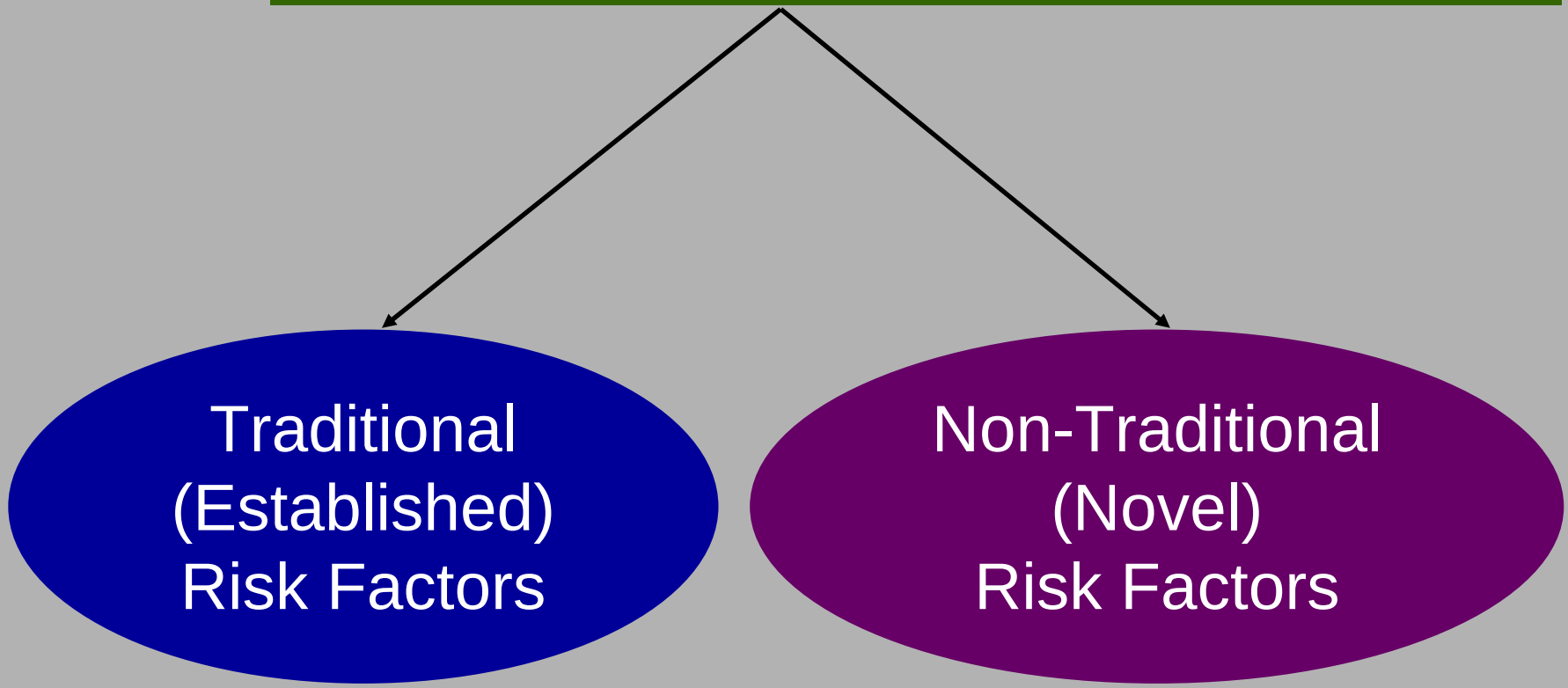
* LaRosa. Am J Cardiol 1999; 85: 545-548.

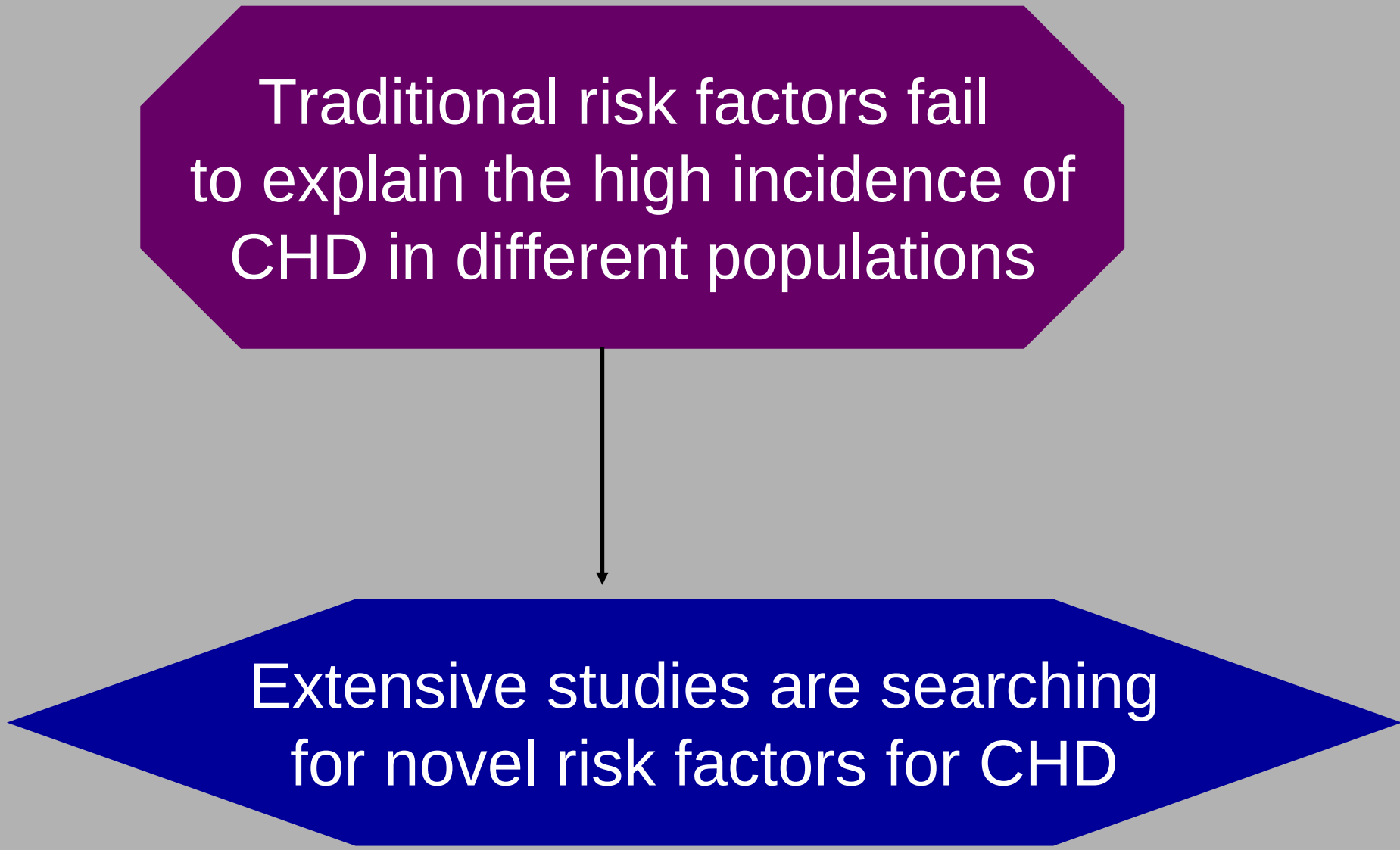
# The Framingham Study*
## (Initiated in 1948)

- Recently reached its 50 years legacy.
- Provided insight into prevalence, incidence, full clinical spectrum and predisposing factors for coronary diseases.
- Coined the term `Risk' factors and listed the "Traditional Risk Factors" for CHD development.

* Kannel, J. Atheroscle. Thromb. 2000; 6: 60-66.

# Risk Factors for CHD




Traditional risk factors fail
to explain the high incidence of
CHD in different populations
Extensive studies are searching
for novel risk factors for CHD

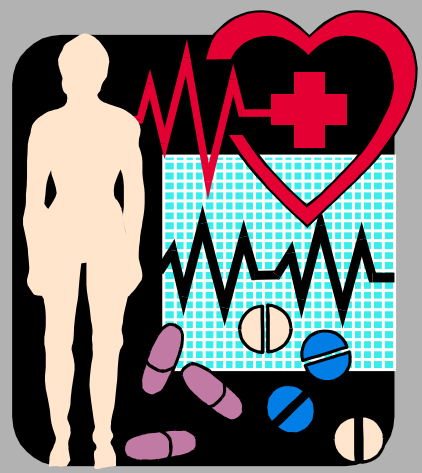
# Traditional (Established) Risk Factors for CHD

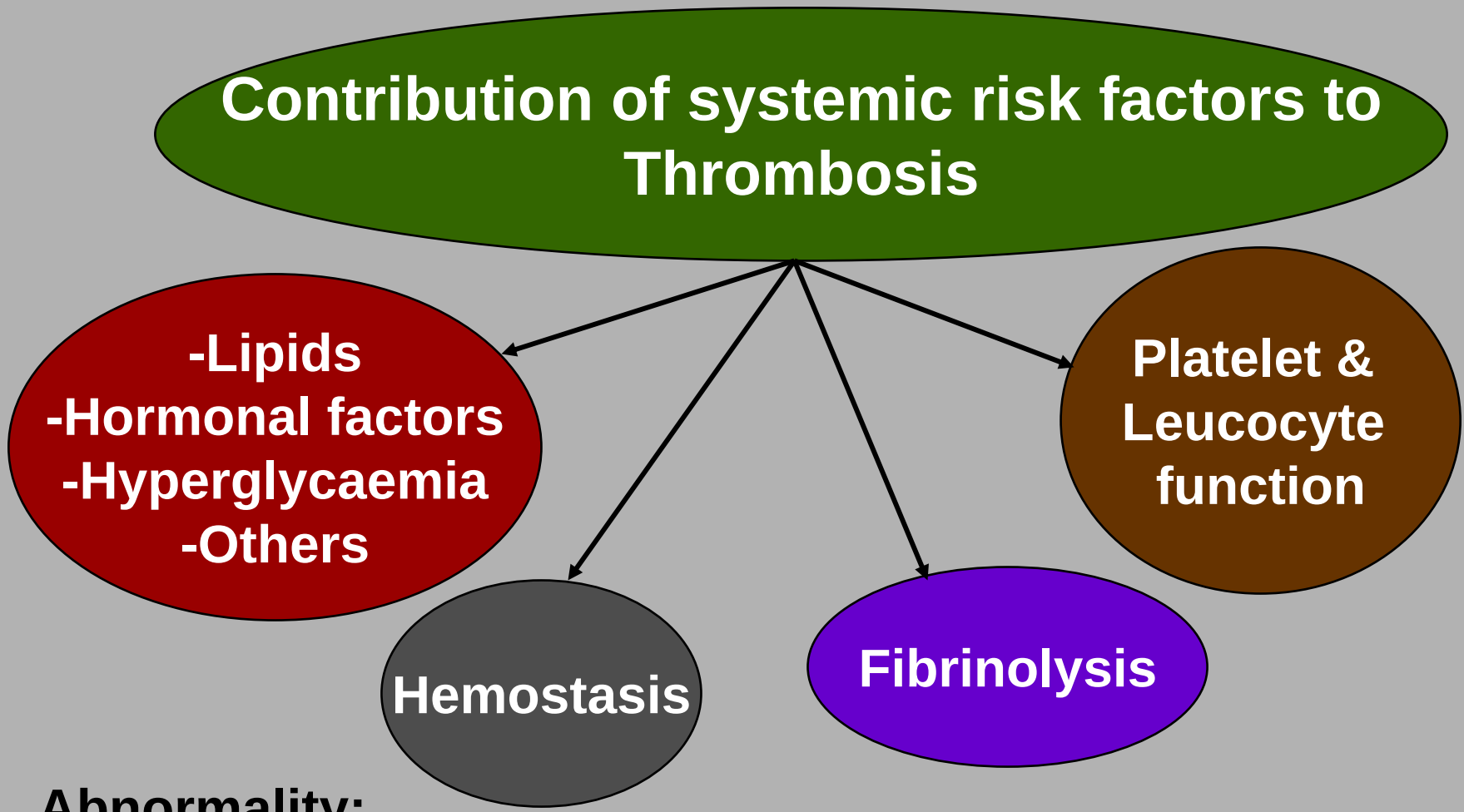
1. Age ≥ 45 years for men; > 55 years for women.
2. Family history of CVD.
3. Smoking.
4. Hypertension (BP ≥ 140/90 mmHg).
5. Hypercholesterolaemia.
6. LDL-C (≥ 160 mg/dl; ≥ 4.1 mmol/l) with < 2 risk factors.
7. LDL-C (130-159 mg/dl; 3.4-4.1 mmol/l), with ≥ 2 risk factors.
8. HDL-C (35 mg/dl; 0.9 mmol/l).
9. Obesity (BMI ≥ 30).
10. Diabetes mellitus.

# Novel (Non-Traditional) Risk Factors for CHD

* Left ventricular hypertrophy.
* Hyper homocysteinemia.
* Lipoprotein(a) excess.
* Hypertriglycerideamia.
* Oxidative stress.
* Infectious agents (e.g. *chlamydia pneumoniae, Helicobacter pylori and CMV*)
* Markers of inflammation (e.g. CRP and serum amyloid A).
* Hyperfibrinogenemia.
* Procoagulant substances (e.g. plasminogen, factor VII, plasminogen activator inhibitor, von Willebrand factor, etc).

# Haematological Genetic Risk Factors for CHD



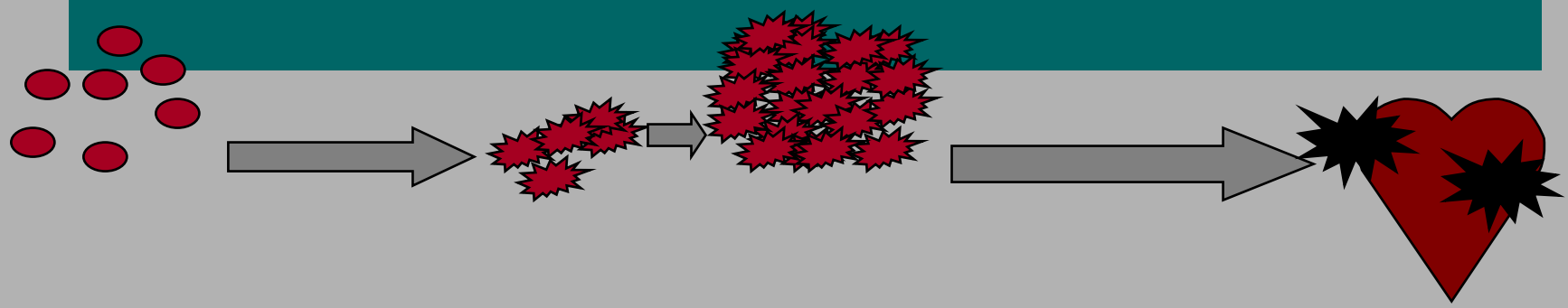



**Abnormality:**

***Increased Thrombogenicity (Hypercoagulable state)***

***Local Thrombotic Occulsions*** - - - - - - → ***CHD***

# Defects in Hemostatis → CHD



# Hemostasis

# Hemostasis

A property of the blood circulation system that maintains the blood in a fluid state within the vessel walls in combination with an ability to prevent excessive blood loss when injured

Due to balanced interaction between:

- Blood vessel walls
- Circulating platelets
- The plasma coagulation factors
- The fibrinolytic factors

Any defect in these may lead to thrombus formation

# Thrombophilia

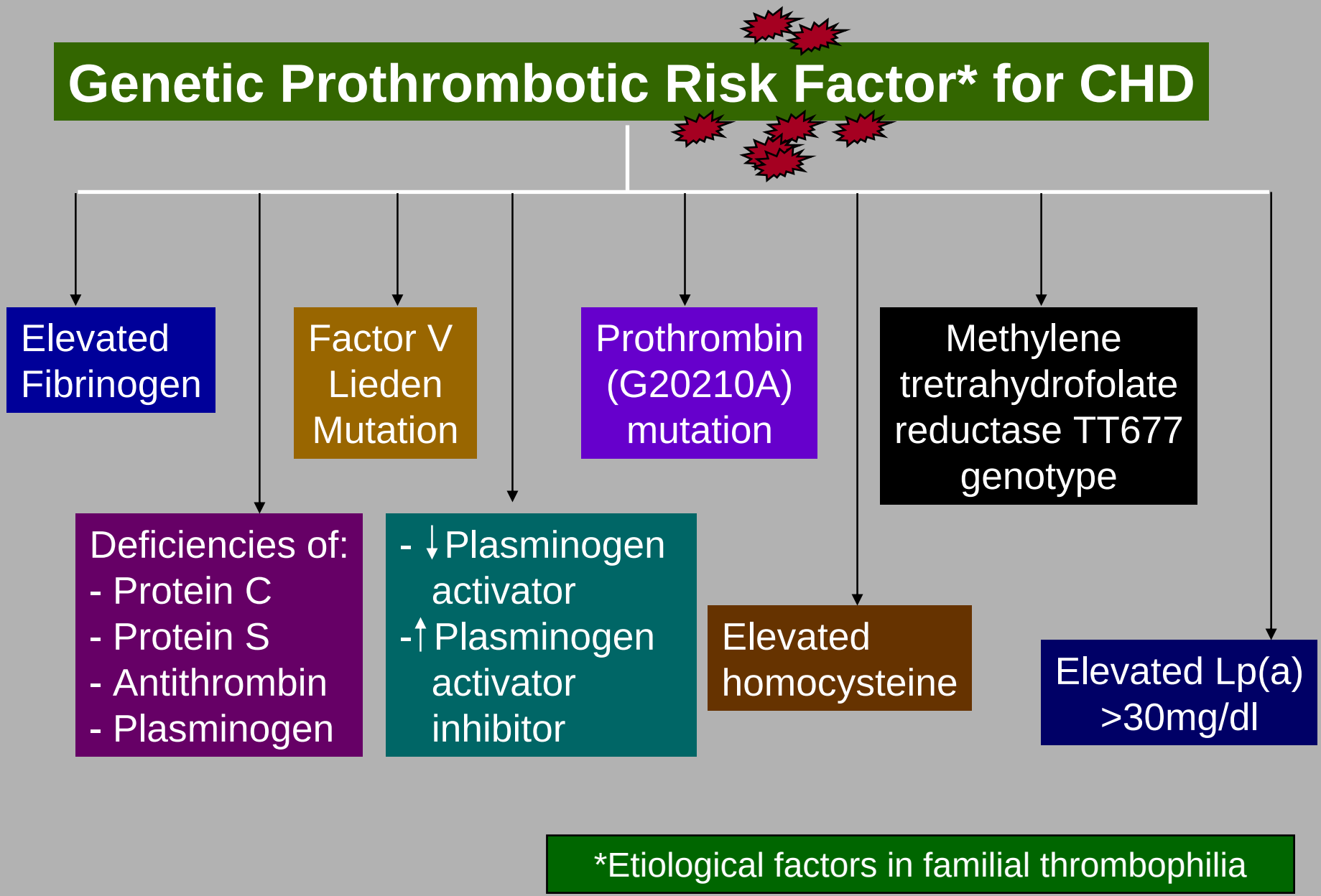
* An increased tendency to thrombosis.
* Due to:
  - An ongoing stimulus to thrombosis.
  - Defect of natural anticoagulant or fibrinolytic mechanism that predisposes to thrombus

# Inherited Molecular defects in thrombophilia

* ATIII deficiency.
* Protein C deficiency.
* Protein S deficiency.
* Dysfibrinogenemia.
* Activated protein C resistance.
* Plasminogen deficiency.
* ↓Plasminogen activator activity.
* ↑ Increased PA inhibitor.

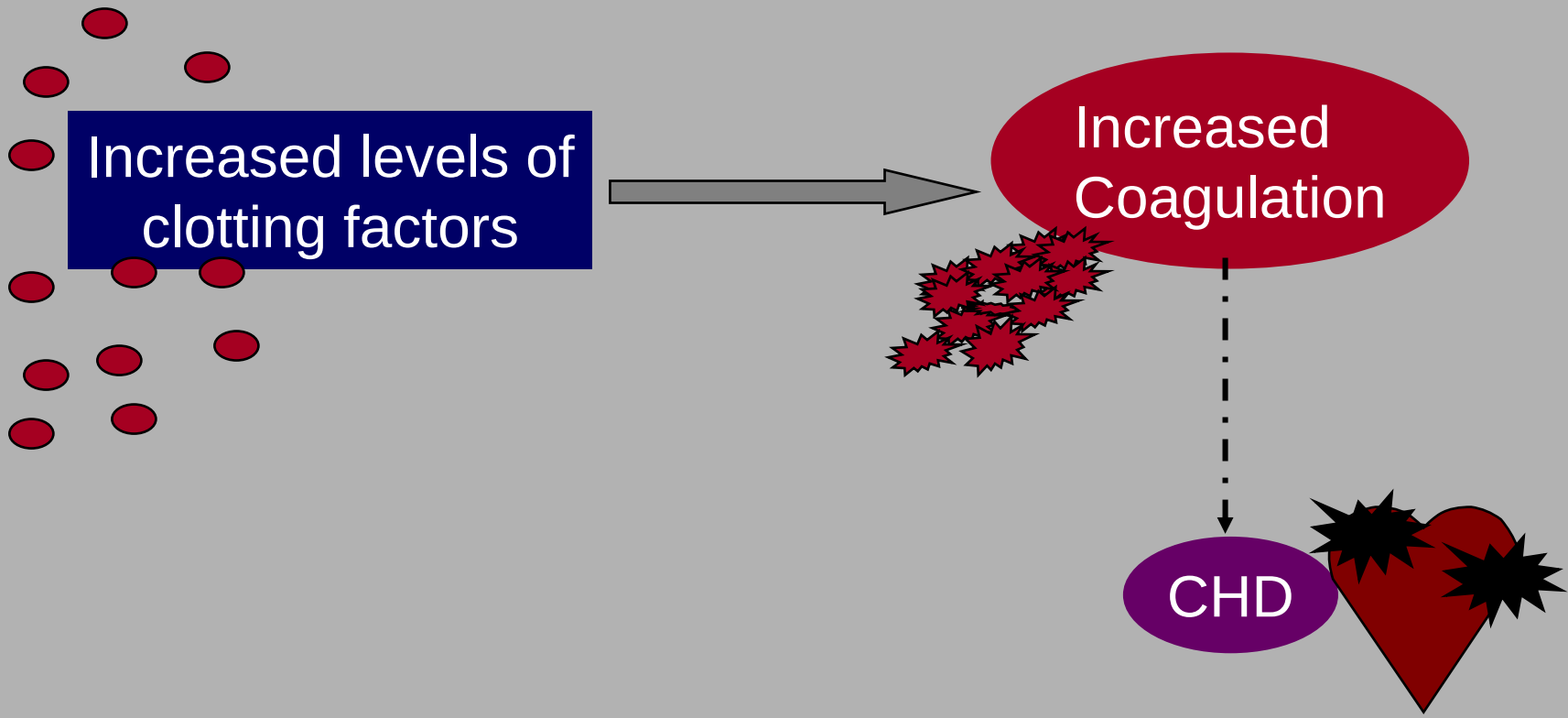
Approx.20-60% of patients with thrombophilia have APC resistance & the other defects are present in appprox. 10%.

# Genetic Prothrombotic Risk Factor* for CHD

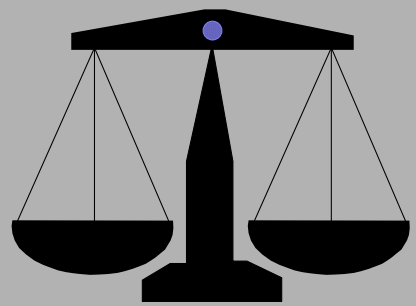



*Etiological factors in familial thrombophilia

# Clotting Factors and CHD



# Clotting Factors & their Defects



# Fibrinogen

- Major protein in blood plasma (200-400 mg/dl)
- Important clotting factor

Synthesised in the liver

<u>During clotting:</u>

thrombin

Fibrinogen → Fibrin

↓

Clot ← (Polymer)

Affects:

- Blood
  - Coagulation
  - rheology
- Platelet aggregation
- Vascular walls
- Acute-phase reactant

# Fibrinogen in CHD

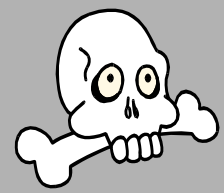
- Elevated fibrinogen increases risk of:
  - CHD
  - Stroke
  - MI
  - Peripheral arterial disease

Involved in:

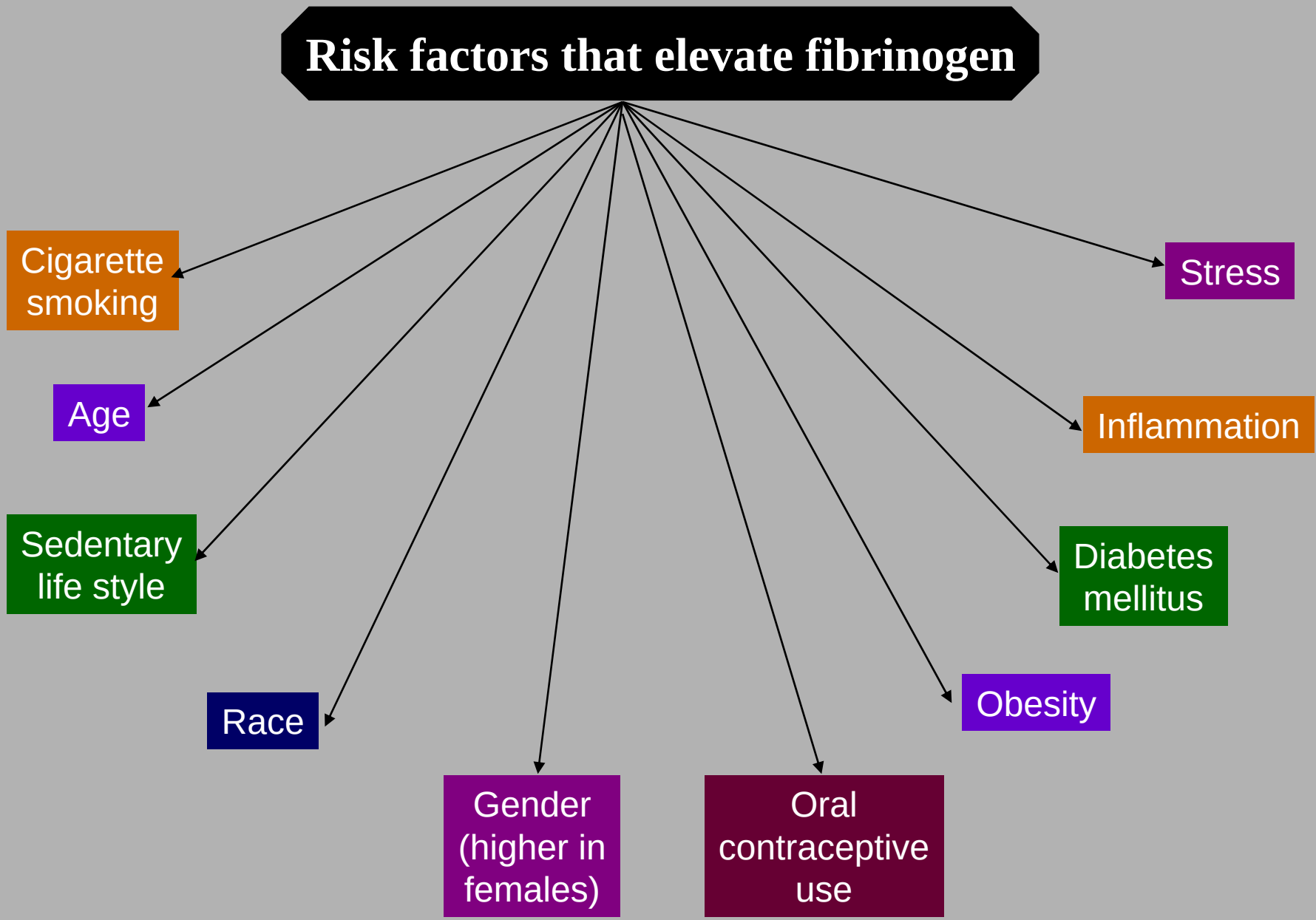
- Pathogenesis of arterial disease
- Strong independent predictor of death*
- Pathogenesis of atherosclerosis**

<u>> 350 mg/dl</u>
Independent risk factor for infarction of brain and heart

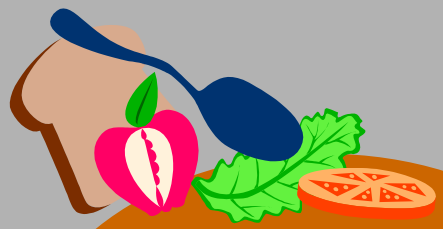
Increase of 1 mg/dl Fibrinogen → correlates with nearly 2-fold increase in probability of death within 6 years



*Banerjee et al, 1992 **Lassila et al, 1993

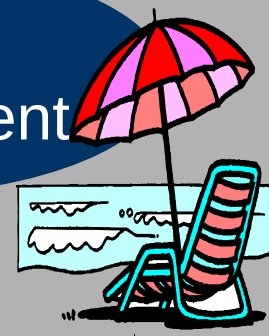

Risk factors that elevate fibrinogen
Cigarette smoking
Age
Sedentary life style
Race
Gender (higher in females)
Oral contraceptive use
Obesity
Diabetes mellitus
Inflammation
Stress

# Factors effective in reducing fibrinogen



Diets rich in Omega-3 and Omega-6 fatty acids

Stress management



Exercise

Weight reduction

Smoking cessation

# Coagulation factors II, V, VII, X and CHD*

| Elevation of | Independent Risk for CHD |
|---|---|
| Factor II | Not significant |
| Factor V | Significant ($p < 0.0001$) |
| Factor VII | Significant ($p < 0.0001$) |
| Factor X | Significant ($p = 0.005$) |

*In several studies.

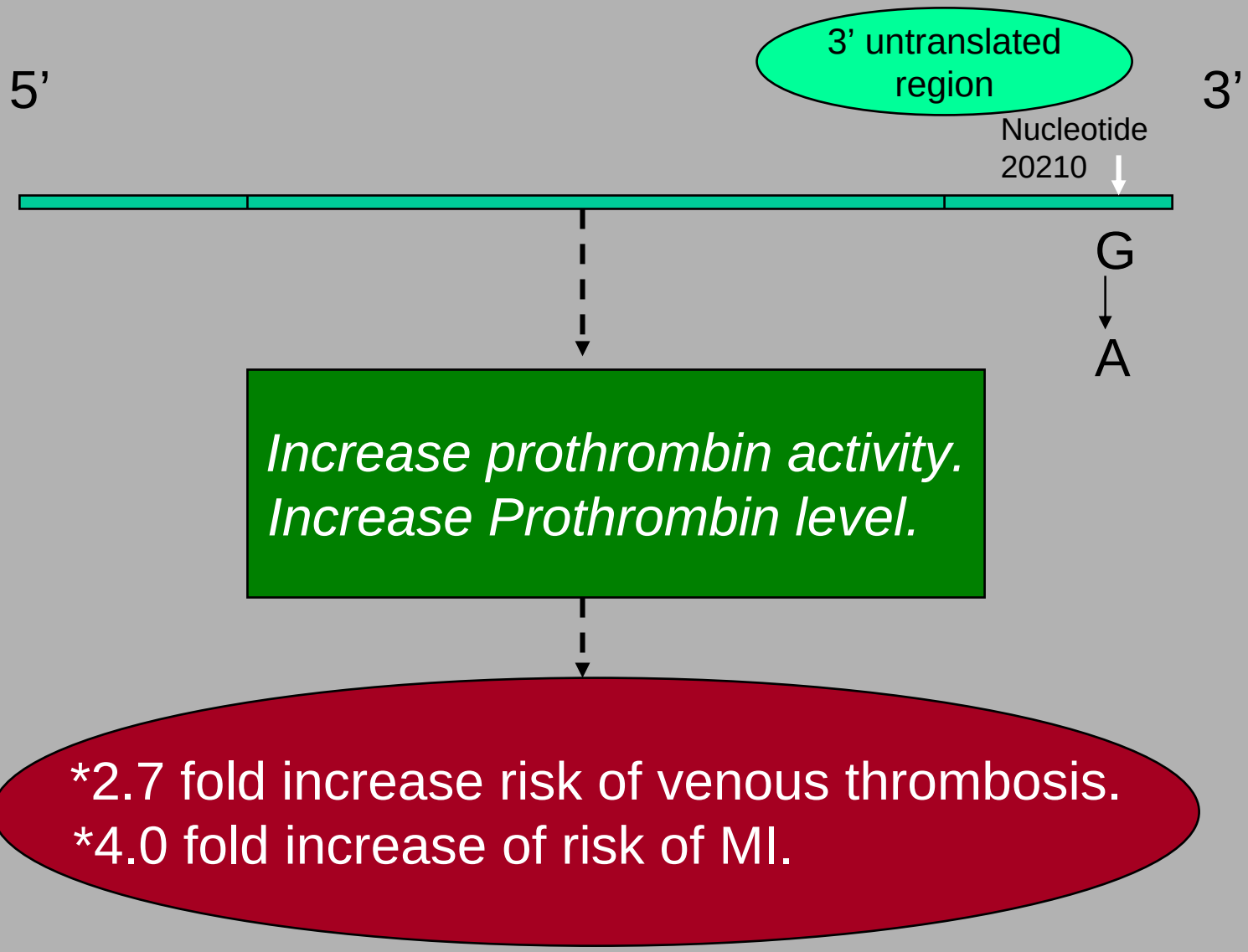
# Clotting activity of coagulation factors II, V, VII and X in MI patients and controls

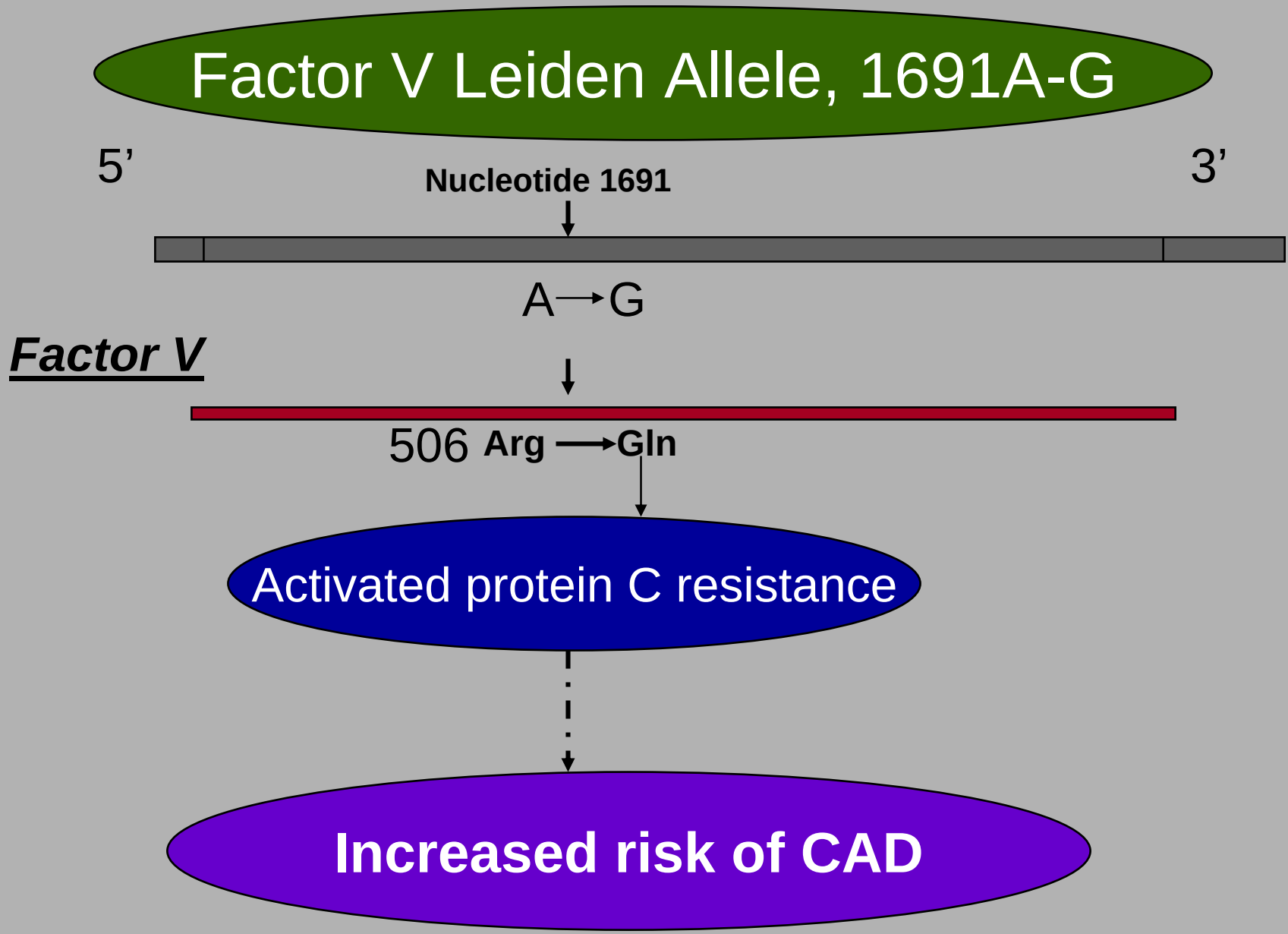
| Factor | Synonym | Patients | Control | p |
|---|---|---|---|---|
| F II(%) | Prothrombin | 96 | 95 | 0.979 |
| F V(%) | Proaccerleriin | 111 | 103 | <0.0001* |
| F VII(%) | Prothrombin conversion accelerator | 118 | 100 | <0.0001* |
| F X | Stuart-Prower factor | 108 | 99 | 0.005* |

# Relative Risk of MI in patients with elevated coagulation factors

| Elevated Factor | RR | 95% CI |
|---|---|---|
| F II | 1.0 | 0.4 - 1.7 |
| F V | 3.3 | 1.8 - 6.6 |
| F VII | 5.2 | 2.4 - 11.2 |
| F X | 2.2 | 1.03 - 4.52 |
| Fibrinogen | 5.4 | 2.5 - 11.9 |

# Prothrombin 20210 G → A allele

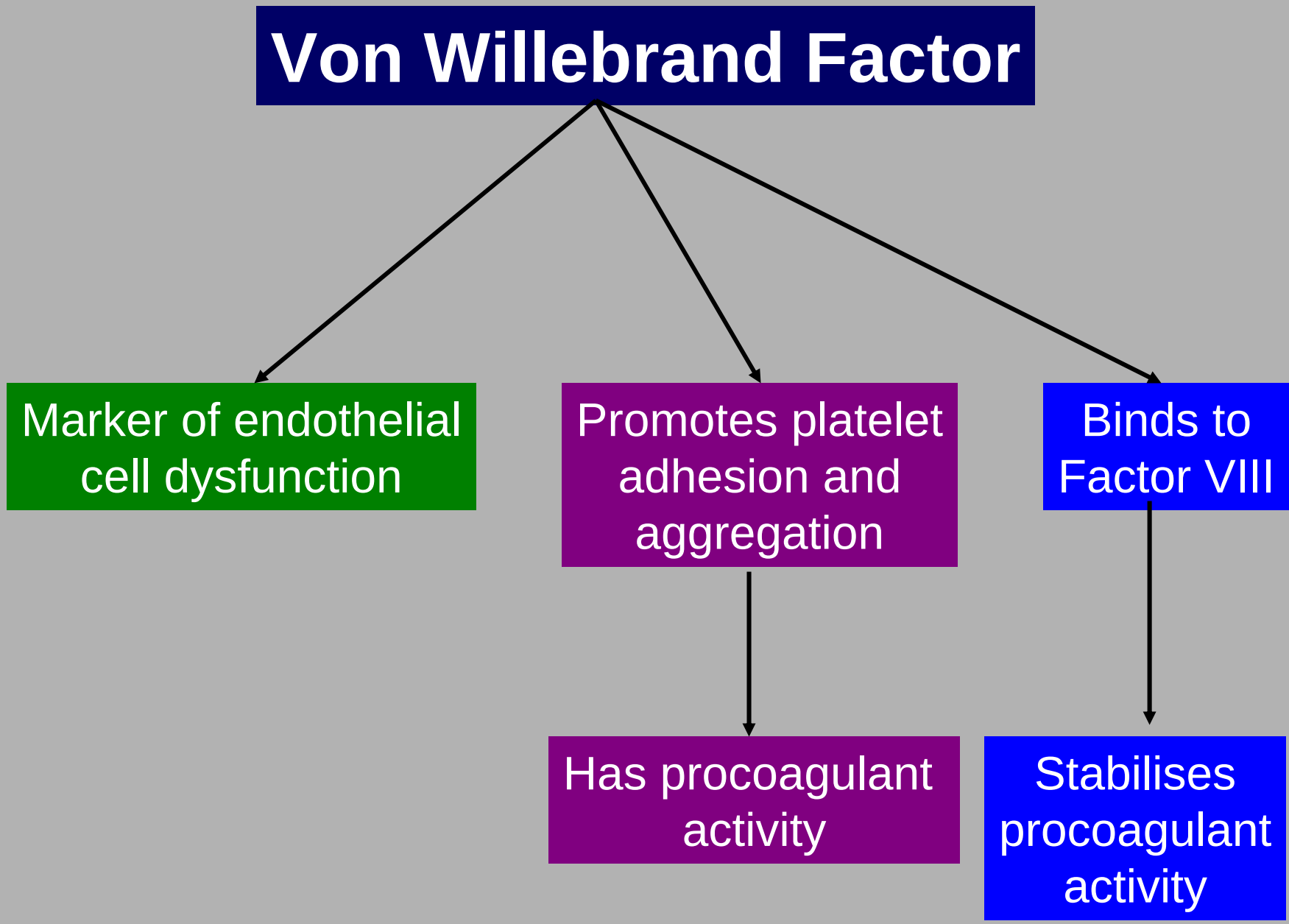



Factor V Leiden Allele, 1691A-G
5’
3’
Nucleotide 1691
A→G
Factor V
506 Arg→Gln
Activated protein C resistance
Increased risk of CAD

# Activated Protein C Resistance

- Autosomal Dominant Disorder.

- Results from several genetic defects:
  eg.* Mutant factor V Leiden resists proteolysis.


Von Willebrand Factor
Marker of endothelial cell dysfunction
Promotes platelet adhesion and aggregation
Binds to Factor VIII
Has procoagulant activity
Stabilises procoagulant activity

# Homocysteine

Intermediate derived from methionine:

Met → Homocys

↓

$CH_3$

Normal fasting plasma level: 5-15 mmol/l

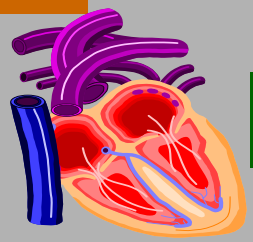
Homocystinuria:

- Rare, AR disorder
- deficiency of cystationine β-synthase.
- Elevated homocyst in blood and urine.

***- Atherosclerosis***
***- Thrombotic vascular disease***
***- MR***
***- Skeletal defect***

# Hyperhomocysteinemia associated with*:

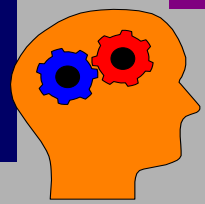
CAD



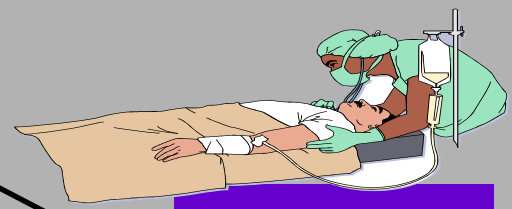
MI

Peripheral vascular disease

Cerebro-vascular disease



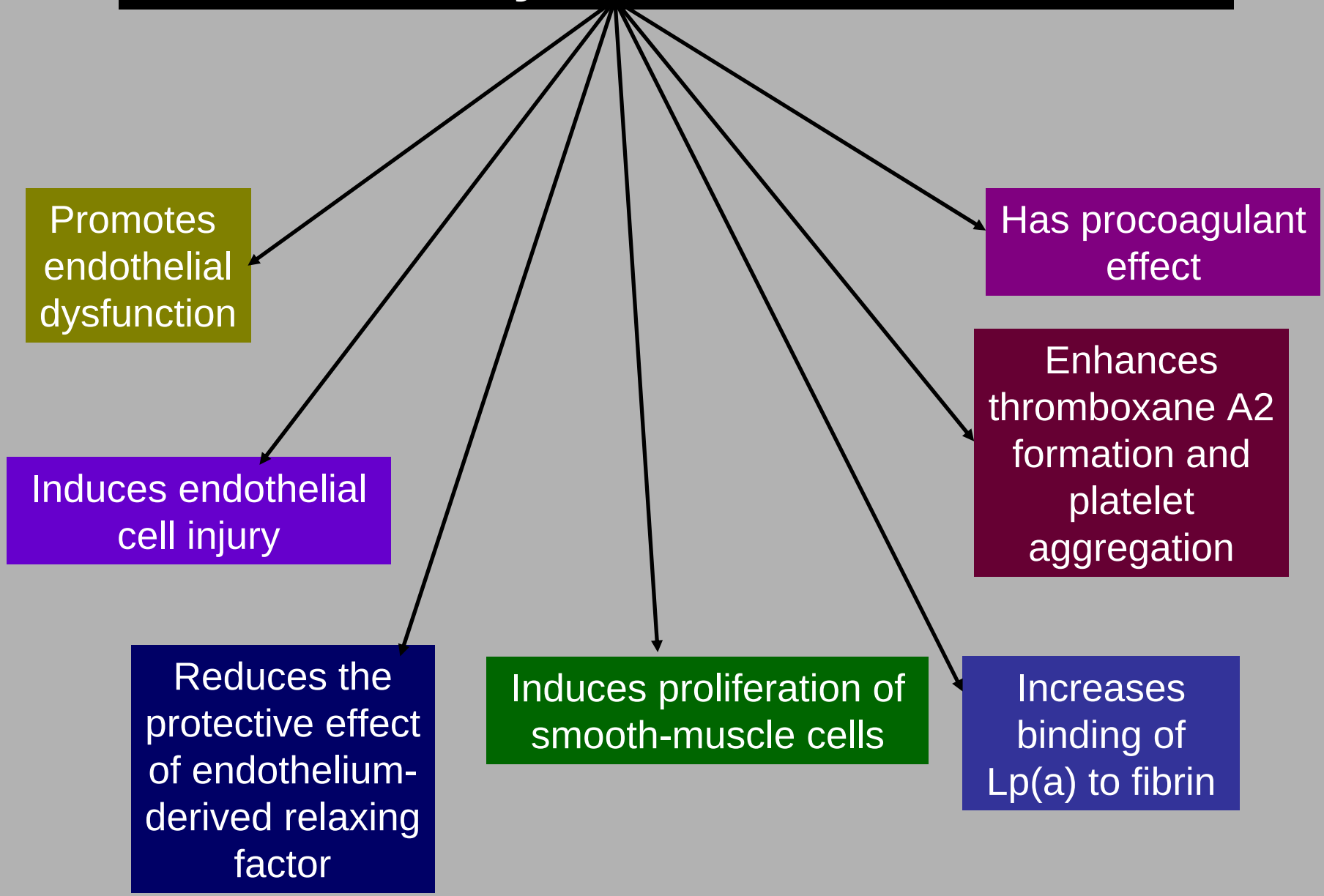
Stroke



Death from CAD

*Harjai. Ann Intern Med 1999; 131: 376-386.

# Role of homocysteine in vascular disease



# Homocysteine (conti.)

- Increase of fasting homocysteine by 5 mmol/l increases the incidence of coronary disease by 1.6-1.8 fold*.
- However, some prospective studies failed to show relation between homocysteine level and coronary heart disease**.
- Why the controversal results???

  ???? Genetic variability.

* Boushey et al. JAMA 1995; 274: 1049-57.
**Folson et al. Circulation 1998; 98: 204-210.

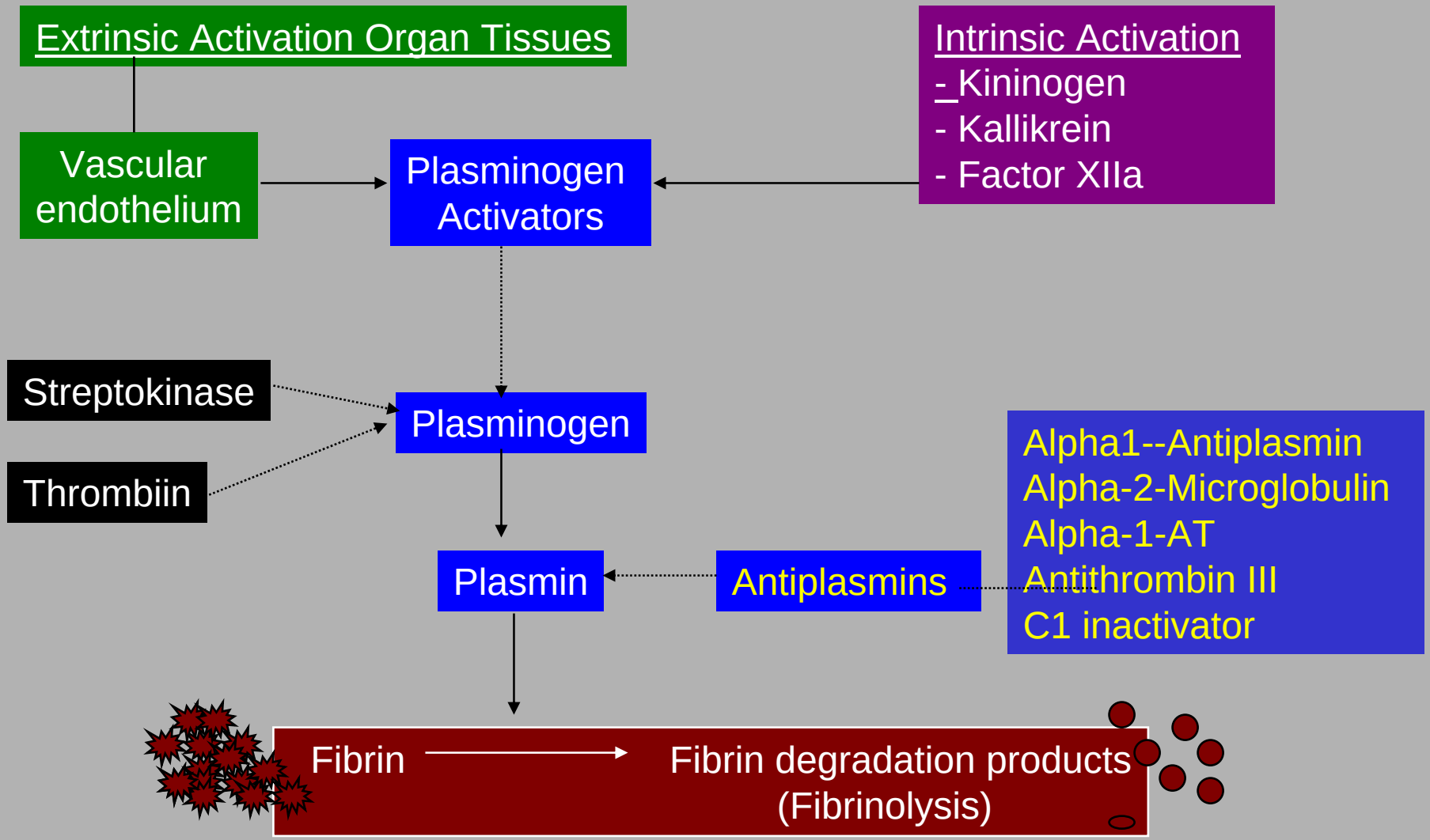
# Factors reducing homocysteine in hyperhomocysteinemia

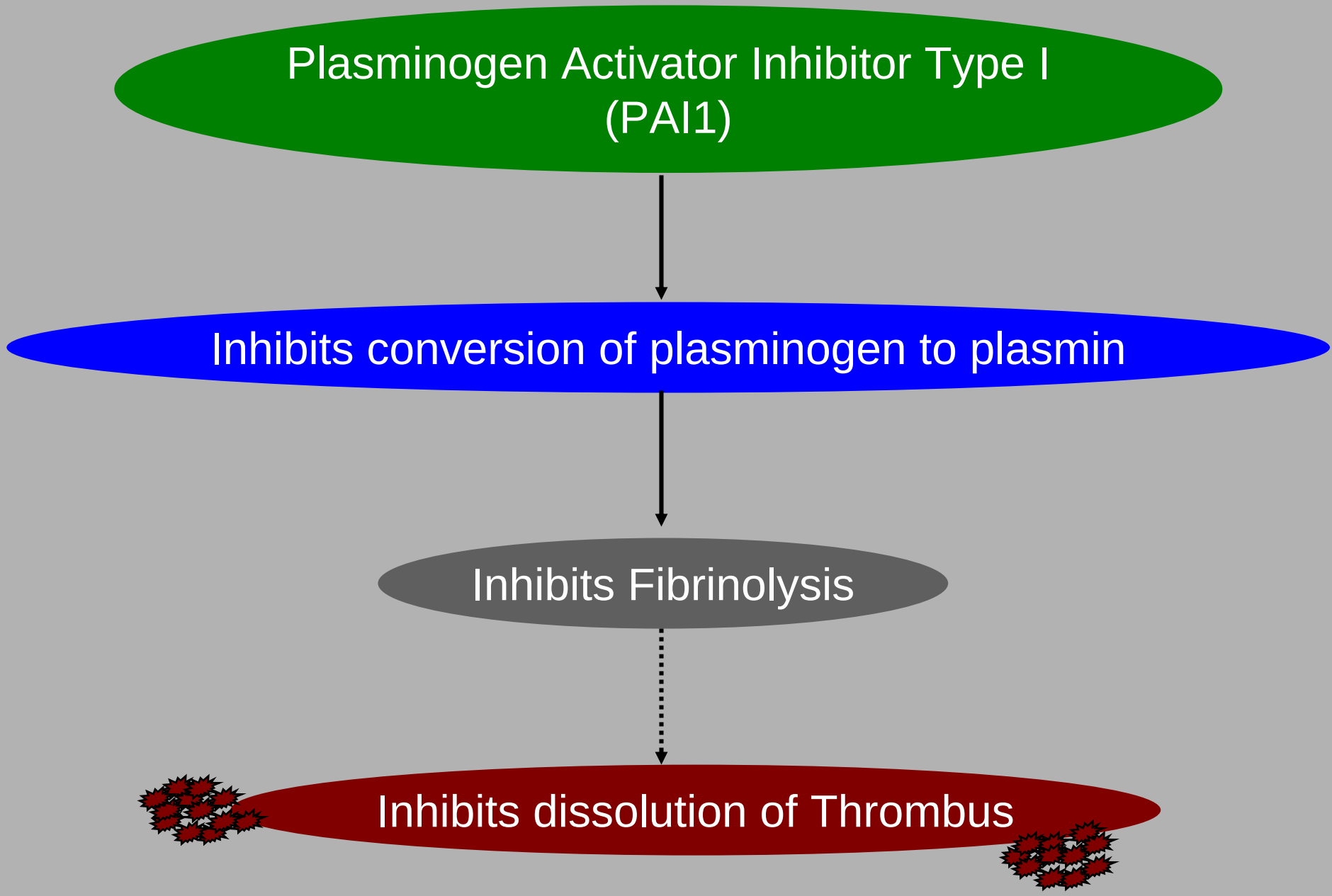
Supplementation with:
- Folate
- Vit. B12
- Vit. B6

Use of oral estrogen in men and postmenopausal women
→ 11-14% reduction in homocysteine level

# Fibrinolysis

# The Fibrinolytic Pathway




Plasminogen Activator Inhibitor Type I
(PAI1)
Inhibits conversion of plasminogen to plasmin
Inhibits Fibrinolysis
Inhibits dissolution of Thrombus

# Steps towards Control& Prevention of CHD

# The Healthy Heart Program

- Increase anti-oxidants in diet( e.g vit.C vit.E, beta-carotenes, flavonoids etc)
- Increase folate, vit.B6, vit.B12 in diet.
- Reduce obesity & excess calorie intake.
- Decrease sugar & other carbohydrates in diet.
- Increase exercise.
- Decrease smoking.
- Maintain Blood glucose level.
- Decrease salt.
- Increase sea food and fish oil in diet.
- Decrease stress in life.

THANK YOU FOR LISTENING