New Role of High Dose Statin or Fixed Combination in CAD

경희대학교 동서신의학병원
심장혈관센터
김 종 진

Introduction

- **Cardiovascular disease (CVD)**
  - m/c cause of morbidity and mortality, WHO
  - 28% of all deaths
  - 49% of all mortality in Europe, over 4 million each year, overall costs 169 billion Euros
- **Coronary heart disease (CHD)**
  - The single m/c cause of mortality in Europe
  - 1.95 million deaths each year
  - Over 1 in 5 women (23%) & 1 in 5 men (21%) dying from CHD

Introduction

- **Atherothrombosis**
  - Interaction between atherosclerotic plaque and arterial thrombosis
  - Erosion or rupture of vulnerable, lipid-rich plaque triggers the formation of a platelet-rich thrombus
  - Underlies the majority of cardiovascular events
  - Comprehensive risk factor management is needed
- **Platelets**
  - Key players in all phases of atherothrombosis

Introduction

- **EUROASPIRE II Survey, 2001**
  - **Aspirin or antiplatelet drugs**
    : Use in 47% of patients on admission and
    90% at discharge following CHD
  - **High prevalence of modifiable risk factors**
    : hyperlipidemia in 70.3% of patients at discharge
    : only 43% of patients with established CHD
    receiving lipid-lowering therapy at discharge
- **INTERHEART Study, 2004**
  - elevated ratio of apoB/apoA-1 (atherogenic/atheroprotective)
    : most important risk factor of AMI in all regions

Introduction

- **Current treatment guidelines**
  - Importance of comprehensive, integrated risk factor management
  - Focusing on management of dyslipidemia and thrombosis
  - Optimal therapeutic approach in broad range of cardiovascular pathology

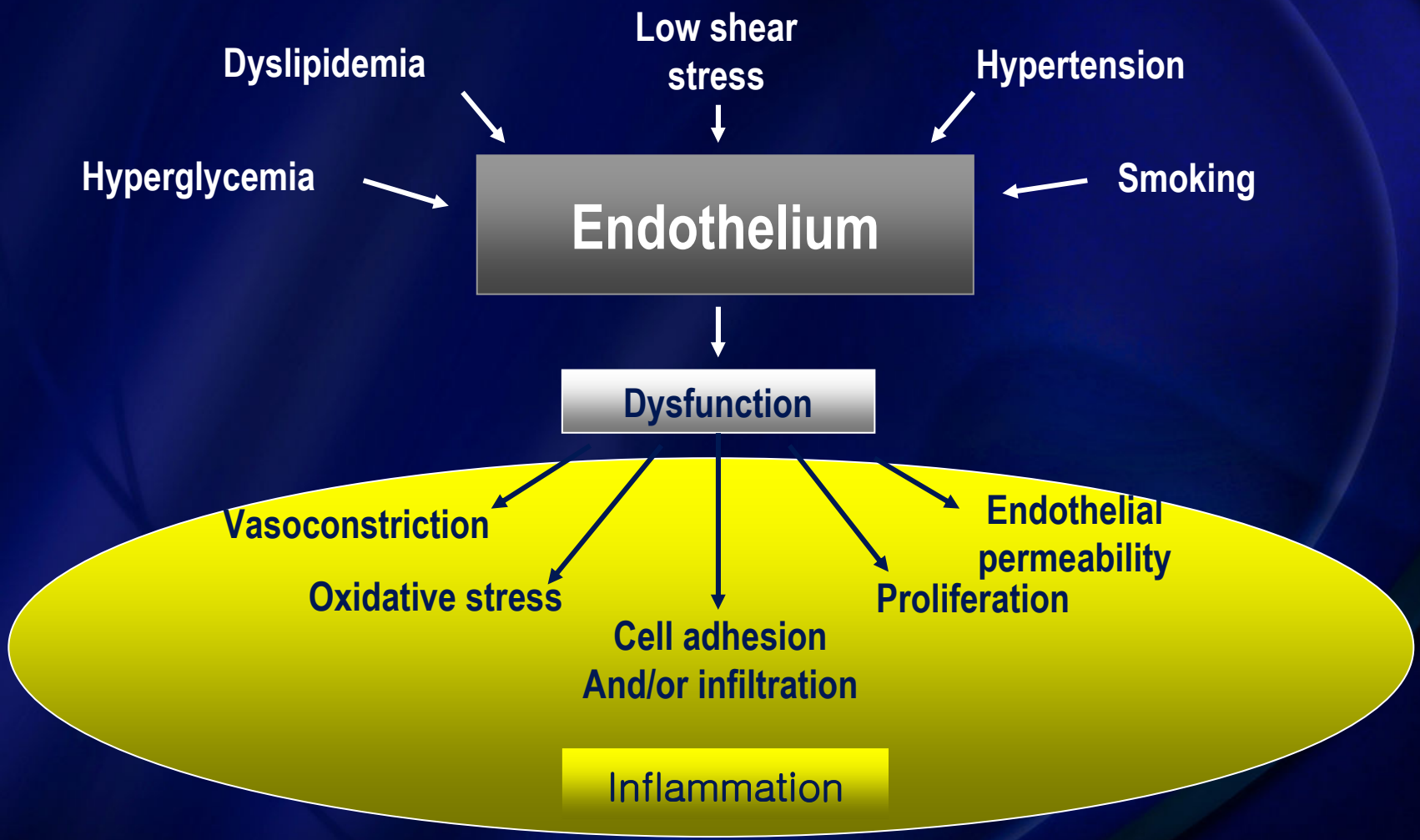
Pathophysiology of Atherothrombosis

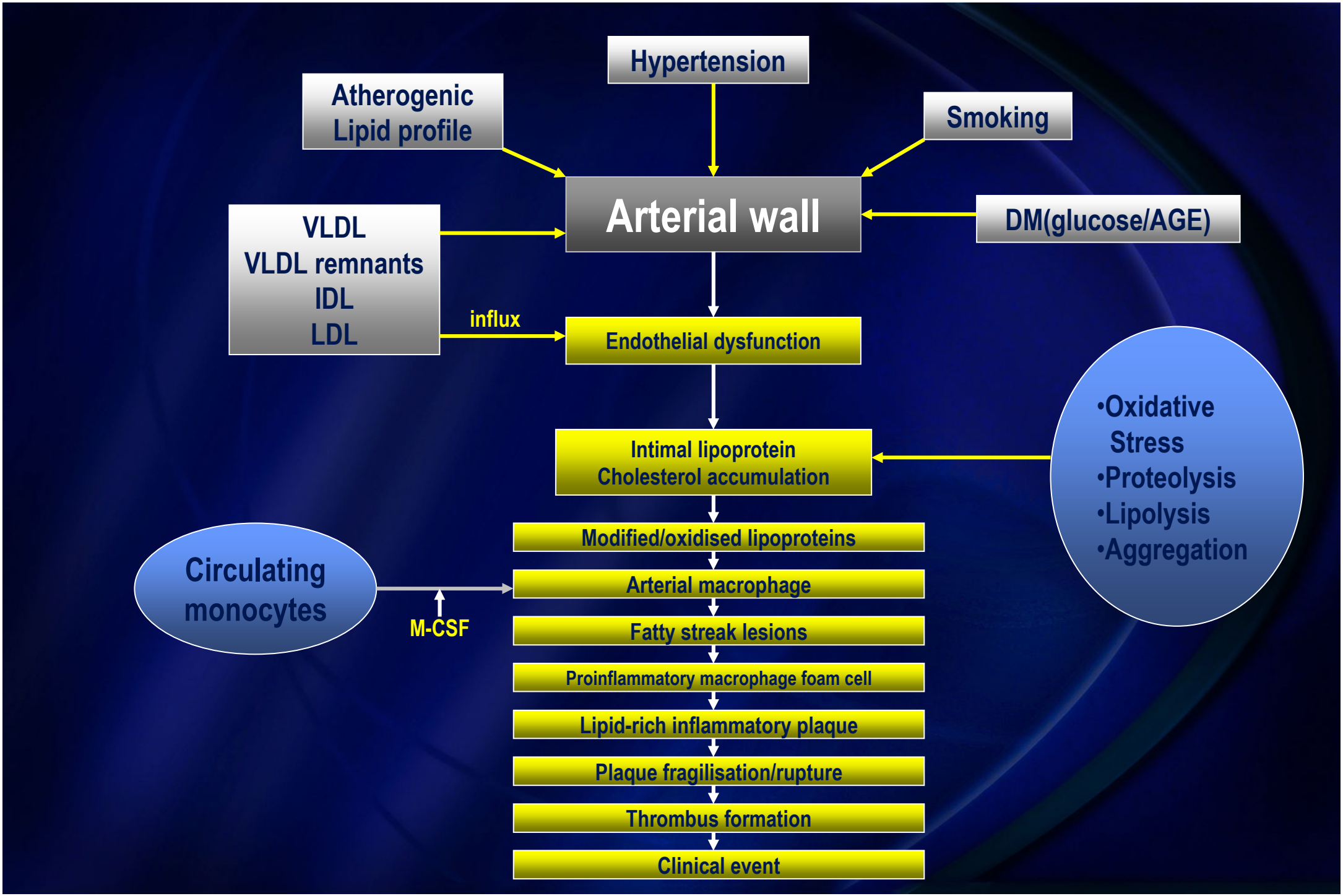
- Mainly in medium and large-sized arteries
- Accelerated by cardiovascular risk factors
  - endothelium of the arterial wall to favour plaque formation
- Atherosclerotic plaques
  - asymmetric focal thickenings of the intimal layer
  - connective tissue components, lipids & cellular debris
- Inflammatory and immune cells from blood
  - key constituents of the plaque
  - vascular endothelial & smooth muscle cells

Pathophysiology

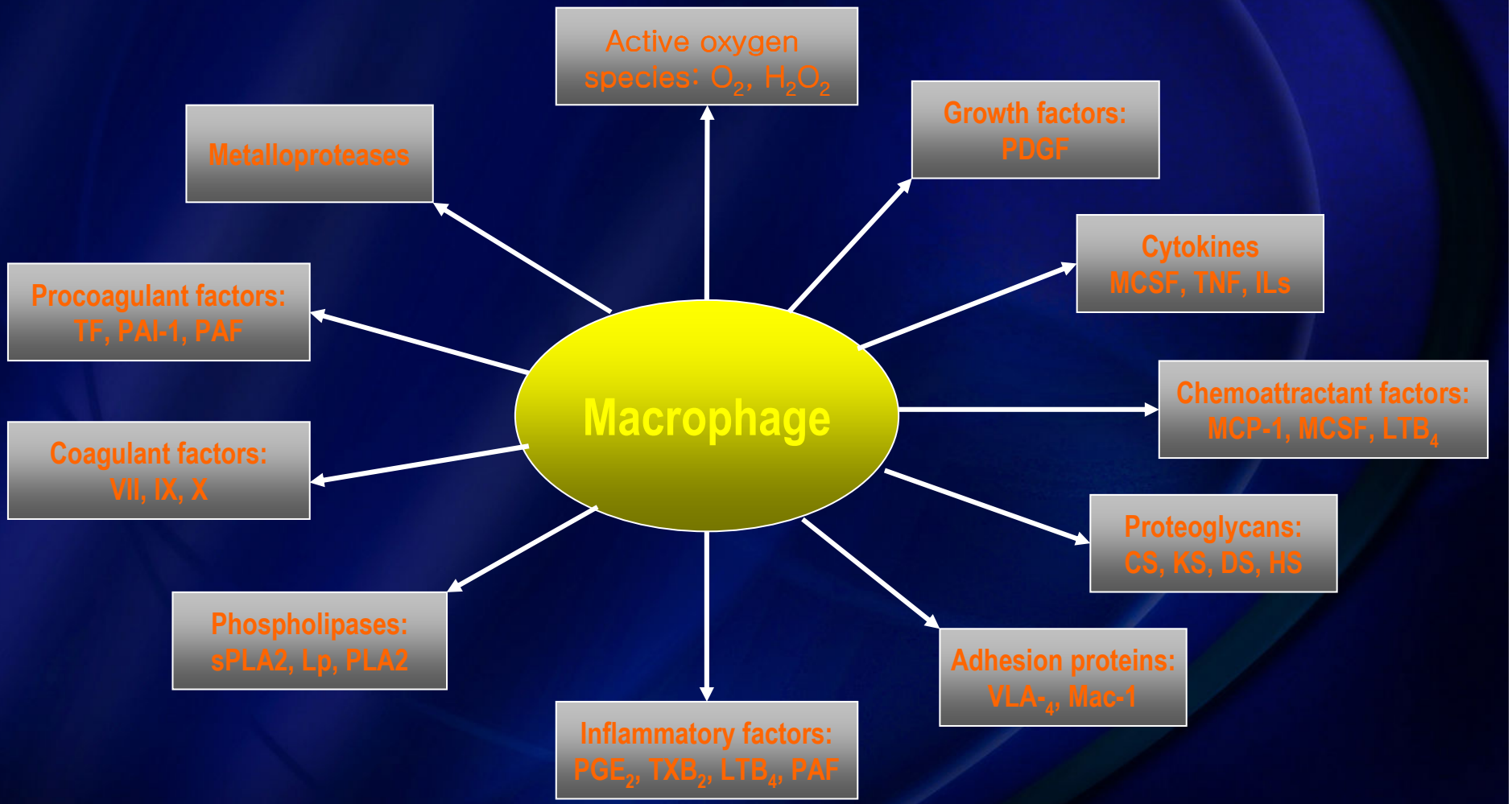
- Endothelial dysfunction
- Lipoprotein cholesterol retention in the arterial intima
- Formation of pro-inflammatory oxidised LDL
- Role of the monocyte-macrophage
- Immuno-inflammatory dimension of atherosclerosis
- Apoptotic dimension
- Plaque rupture & thrombus formation

Endothelial Dysfunction




Hypertension
Atherogenic
Lipid profile
Smoking
Arterial wall
VLDL
VLDL remnants
IDL
LDL
DM(glucose/AGE)
influx
Endothelial dysfunction
•Oxidative
Stress
•Proteolysis
•Lipolysis
•Aggregation
Intimal lipoprotein
Cholesterol accumulation
Modified/oxidised lipoproteins
Circulating
monocytes
M-CSF
Arterial macrophage
Fatty streak lesions
Proinflammatory macrophage foam cell
Lipid-rich inflammatory plaque
Plaque fragilisation/rupture
Thrombus formation
Clinical event

Role of the monocyte-macrophage



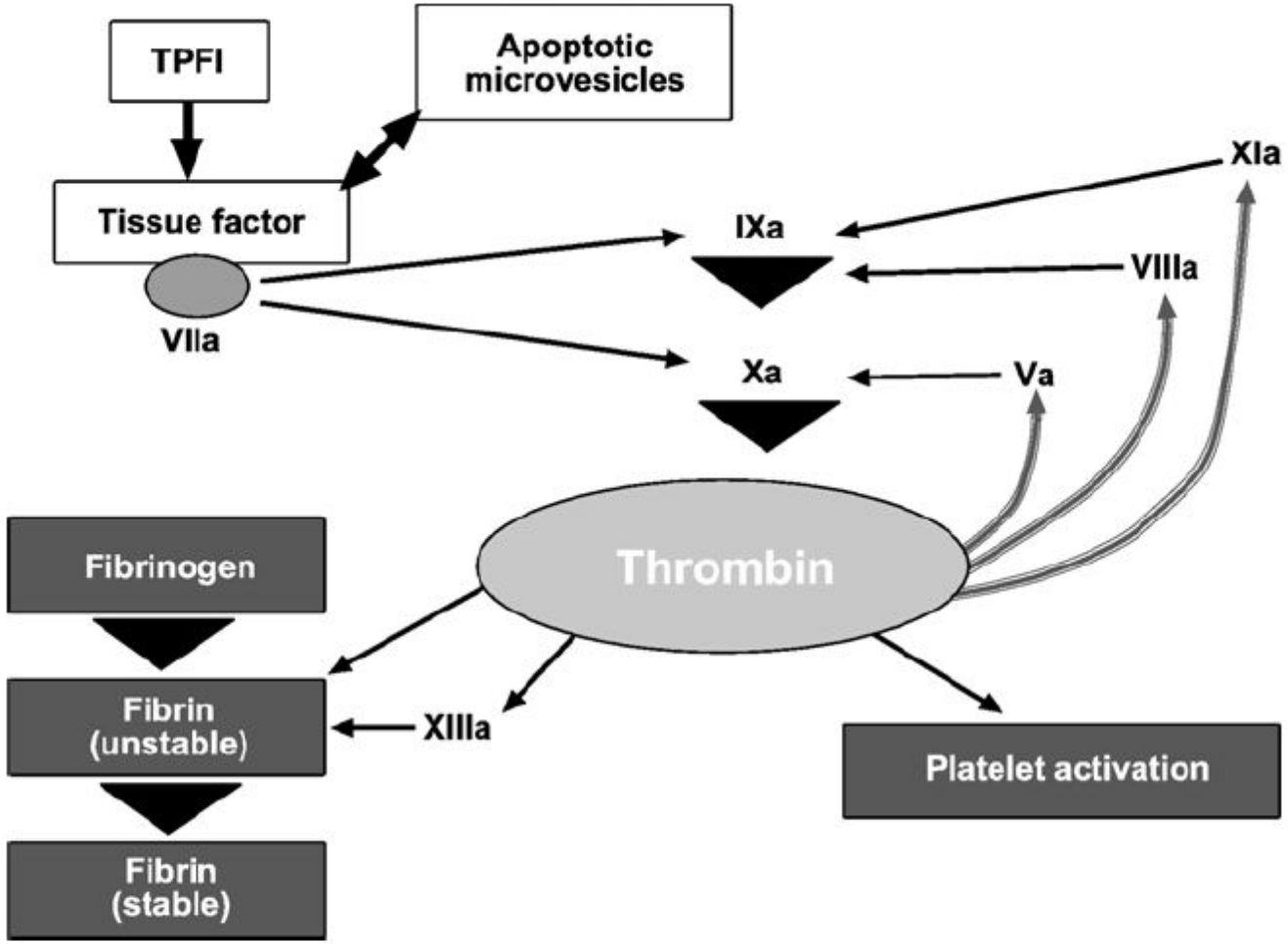


Fig. 5. Tissue factor (TF) plays a key role in activation of the coagulation cascade.

Statins

- **Cholesterol-lowering effect**
  - Up-regulation of LDL receptor activity
    : Hepatic uptake ↑ of atherogenic apoB-containing lipoproteins (VLDL, VLDL remnants, IDL & LDL)
  - Partial inhibition of hepatic VLDL synthesis
  - Small increase in levels of antiatherogenic HDL

Statins

- **Intensive statin therapy**
  - ► Atheroma plaque volume ↓
  - ► Plaque stabilization
  - ► Modification of plaque morphology
  - ► Attenuation of inflammation

Statins

- **PLAC I (Pravastatin Limitation of Atherosclerosis in the Coronary Arteries)**
  - Pravastatin 40 mg/day
  - Significant attenuation of progression
    : reduction in minimal vessel diameter
    0.05– 0.03 mm/yr with pravastatin
    : 60% reduction in the risk of MI
  - benefit of treatment evident after 1 year

Pitt, B., Mancini, G. B. J., Ellis, S. G., Rosman, H. S., Park, J. S., & McGovern, M. E. (1995). Pravastatin limitation of atherosclerosis in the coronary arteries (PLAC I): reduction in atherosclerosis progression and clinical events. J Am Coll Cardiol 26, 1133 ─1139.

Statins

- **PLAC II (Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries)**
  - Pravastatin (20–40 mg/day)
  - 12% reduction in progression of mean-maximum IMT
    : from 0.068 to 0.059 mm/yr
  - 35% reduction in IMT progression in CCA
    : from 0.046 to 0.029 mm/yr
  - Significant reduction in any fatal & nonfatal MI

Crouse, J. R., Byington, R. P., Bond, M. G., Espeland, M. A., Craven, T. E., Sprinkler, J. W., et al. (1995). Pravastatin, lipids, and atherosclerosis in the carotid arteries (PLAC II). Am J Cardiol 75, 455 ─459.

Statins

- **REVERSAL and ASTEROID Studies**
  - Statin treatment for 18–24 months
  - Significant reduction in total coronary atheroma volume
  - 6.8% median reduction in ASTEROID

Nissen, S. E. (2005). Halting the progression of atherosclerosis with intensive lipid lowering: results from the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial. Am J Cardiol 118(12A), 22S –27S.
Nissen, S. E., Nicholls, S. J., Sipahi, I., Libby, P., Raichlen, J. S., Ballantyne, C. M., et al. (2006). Effect of very high-intensity statin therapy on regression of coronary atherosclerosis. The ASTEROID trial. JAMA 295, 1556 –1565.

Statins

- **Reduction in hs-CRP**
  - A key marker of inflammation
  - Cholesterol and Recurrent Events (CARE) Trial
    : Pravastatin
    : progressive reduction of CRP levels
    37.8% ↓ during the 5-year follow-up period
    : anti-inflammatory effect is progressive and sustained over a long period

Statins

- **Change in plaque composition and reduction in inflammation in carotid artery**

  - Pravastatin 40mg for 3 months
  - reduction in lipid content, oxidised LDL, macrophages and T cell
  - increases collagen and tissue inhibitor of metalloproteinases

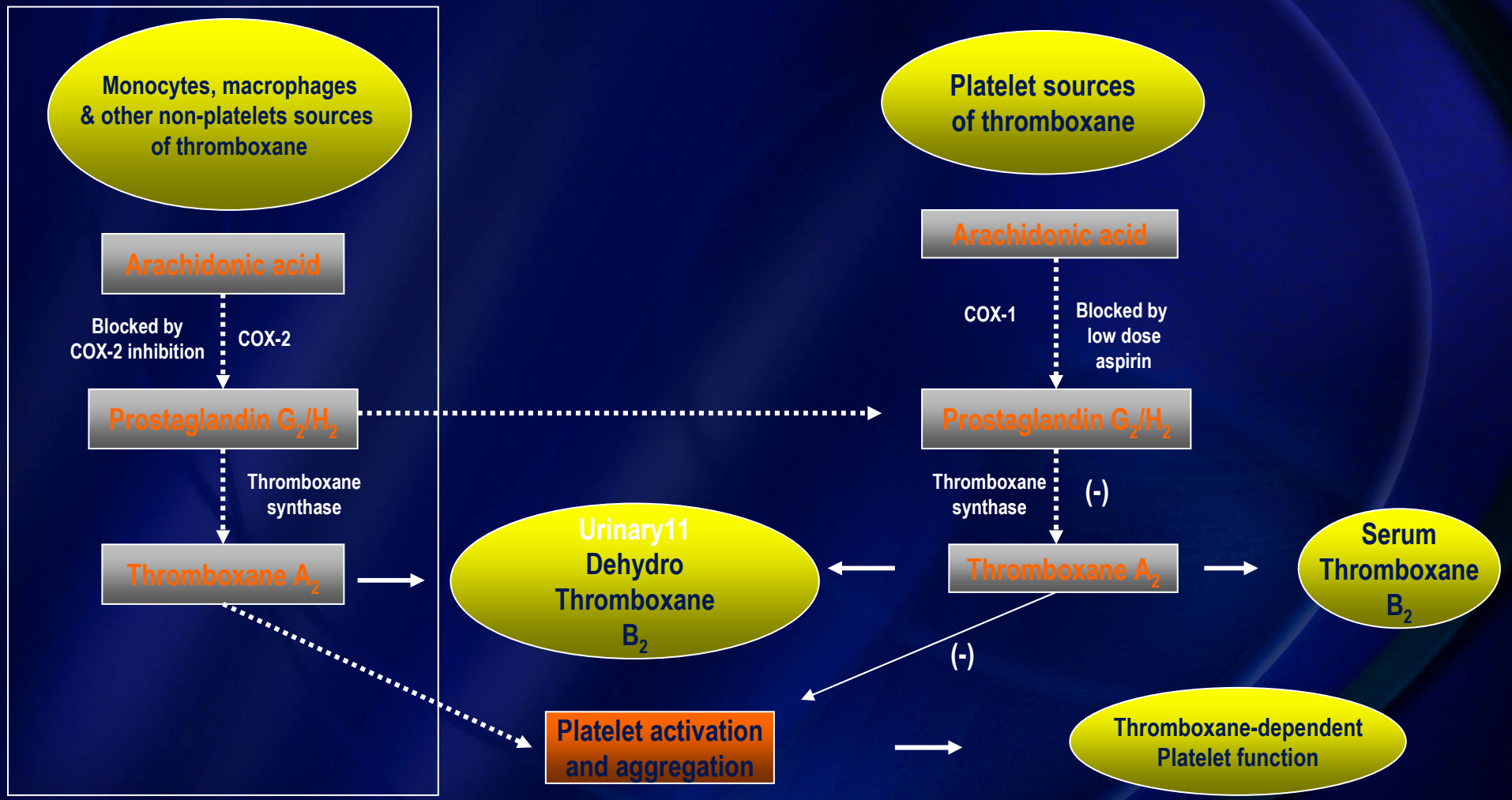
Statins

- **Residence time ↓ of LDL in plasma**
  - ► Substrate available for generation of oxLDL ↓
  - ► Inflammatory stimulus ↓
- **Direct effect in attenuating the inflammatory response**
  : early onset of anti-inflammatory effects
  (Atorvastatin 80mg) in recent data (after 1 month)
- **Reduce platelet aggregation**
  : by reduction of TXA2 production and platelet membrane
  : same pathway with Aspirin
  : precedes plaque stabilization, as early as 3 months

Statins

- **Abrupt cessation of chronic statin therapy**
  - ► rapid increase in CRP & IL-6 (rebound inflammatory response)
  - ► incidence ↑ of cardiovascular events

Aspirin


Monocytes, macrophages & other non-platelets sources of thromboxane
Arachidonic acid
Blocked by COX-2 inhibition
COX-2
Prostaglandin G_2/H_2
Thromboxane synthase
Thromboxane A_2
Platelet sources of thromboxane
Arachidonic acid
COX-1
Blocked by low dose aspirin
Prostaglandin G_2/H_2
Thromboxane synthase
(-)
Thromboxane A_2
Urinary11 Dehydro Thromboxane B_2
Serum Thromboxane B_2
(-)
Platelet activation and aggregation
Thromboxane-dependent Platelet function

Aspirin

- **Aspirin resistance**
  : Inability of Aspirin to reduce platelet production of thromboxane A2
  ► platelet activation & aggregation ↑
  ► cardiovascular events risk ↑

Aspirin

- **Statin**
  - Platelet aggregation ↓
    : via thromboxane A2 production ↓ &
    cholesterol content of platelet membranes ↓
  - Thrombogenic potential ↓
    : via effect on tissue factor
- **Combination statin plus aspirin**
  - Atherothrombotic risk ↓ in established CVD
  - Effective potentially with Aspirin resistance


Statin
Aspirin
↓Plaque cholesterol
↓Inflammation
↓Platelet activation aggregation
Statin
Aspirin
↓CV events

Combination Statin plus Aspirin

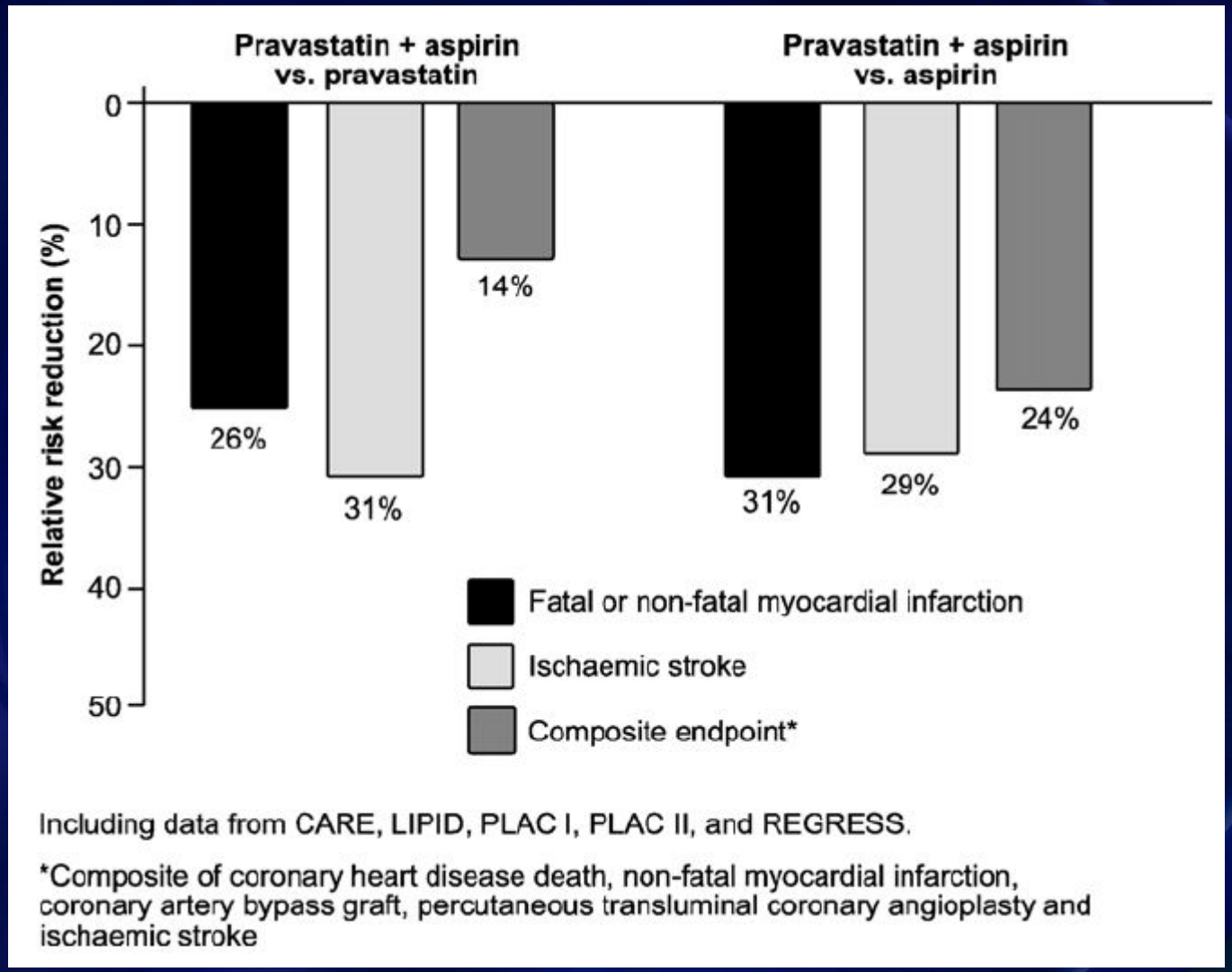
- **Pravastatin**
  - Suitable choice for combination
  - Apparent after at least 1 year on treatment
- **Aspirin**
  - Immediate antiplatelet effect
  - Clinical benefits within months of initiation of Tx

Combination Statin plus Aspirin

- **Meta-analysis of 5 recent major clinical studies performed in secondary prevention of all-cause mortality in pts with CHD**
  - CARE, LIPID, PLAC I, PLAC II, REGRESS
  - BASI (Beta-blocker, ACE-inhibitor, Statin, Aspirin)
  - 1 of the combination of 2 drugs associated with the greatest reduction in mortality

    : statin/aspirin combination

Hippisley-Cox, J., & Coupland, C. (2005). Effect of combinations of drugs on all cause mortality in patients with ischaemic heart disease: nested casecontrol analysis. BMJ 330, 1059–1068.



Including data from CARE, LIPID, PLAC I, PLAC II, and REGRESS.

*Composite of coronary heart disease death, non-fatal myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty and ischaemic stroke

Combination Statin plus Aspirin

- **Statin and aspirin**
  - additive effect in reducing cardiovascular events
- **Aggressive statin use in the absence of aspirin**
  - substantially reduced cardiovascular events
- **Aspirin use in the absence of statin**
  - reduced clinical events in comparison to patients not treated with either drug

Athyros VG, et al. Effect of statins and aspirin alone and in combination on clinical outcome in dyslipidaemic patients with coronary heart disease. A subgroup analysis of the GREACE study Platelets, March 2005; 16(2): 65–71

Combination Statin plus Aspirin

- **Aspirin compared with no treatment**
  - less costly & more effective for preventing CHD events in middle-aged men whose 10-year risk for CHD is 7.5% or higher
- **Addition of a statin to Aspirin therapy**
  - more cost-effective when the patient's 10-year CHD risk before treatment is higher than 10%

Pignone M, et al. Aspirin, Statins, or Both Drugs for the Primary Prevention of Coronary Heart Disease Events in Men: A Cost–Utility Analysis
Ann Intern Med. 2006;144:326-336.

Combination Statin plus Aspirin

- **Cost effectiveness**
  - cost of treating 1 MI: 8,000 Euros
  - cost of treating 1 stroke: 31,000 Euros
  - cost of statin and aspirin therapy for 1 month: less than 50 Euros

Summary

- **Aspirin** is well established in thromboprophylaxis of CHD
- **Statins** are recommended (evidence class I) in secondary prevention management of CHD patients
- **Combination** would be a logical choice for reducing cardiovascular risk in patients with established CHD

Conclusion

Combination of Pravastatin and Aspirin may potentially represent an important, cost-efficient means of preventing recurrent atherothrombotic events in patient with CVD

Thank you for your attention!