

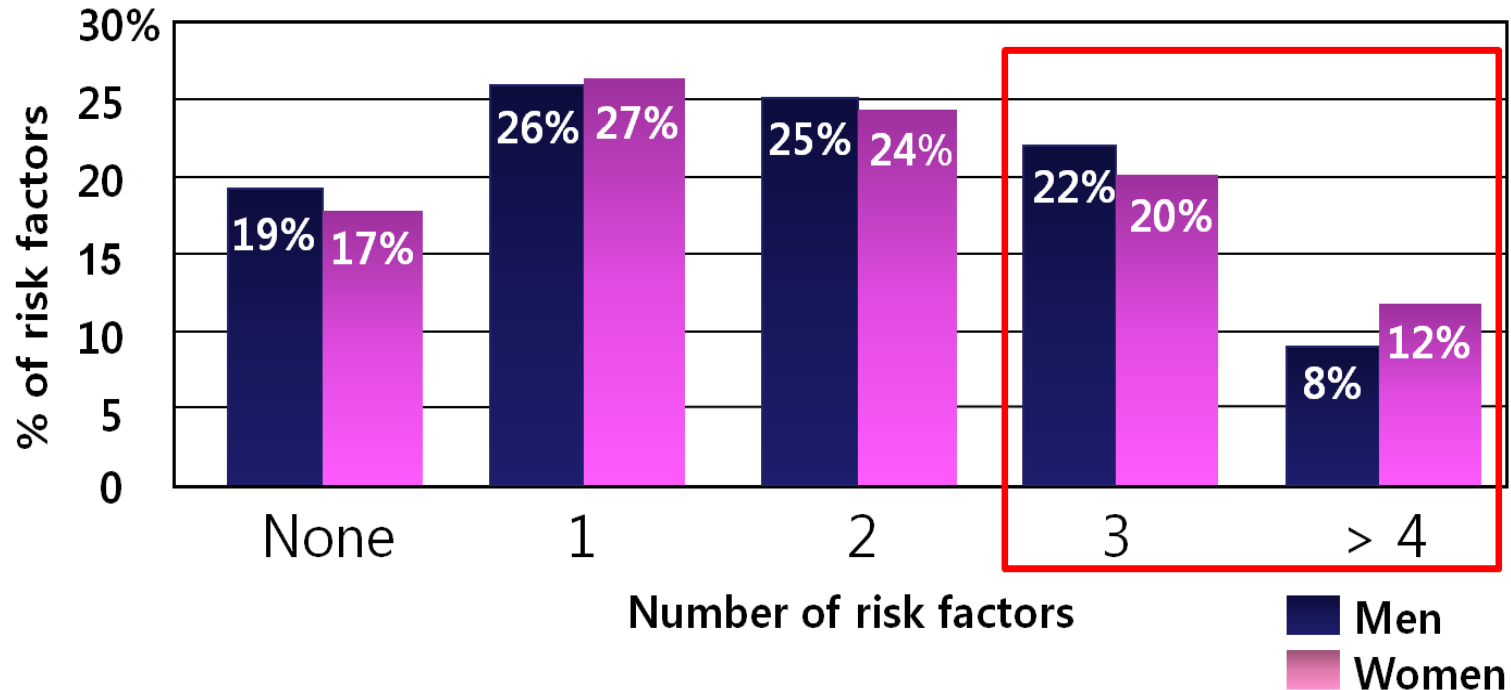
Metabolic Syndrome & Atrial fibrillation

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Content

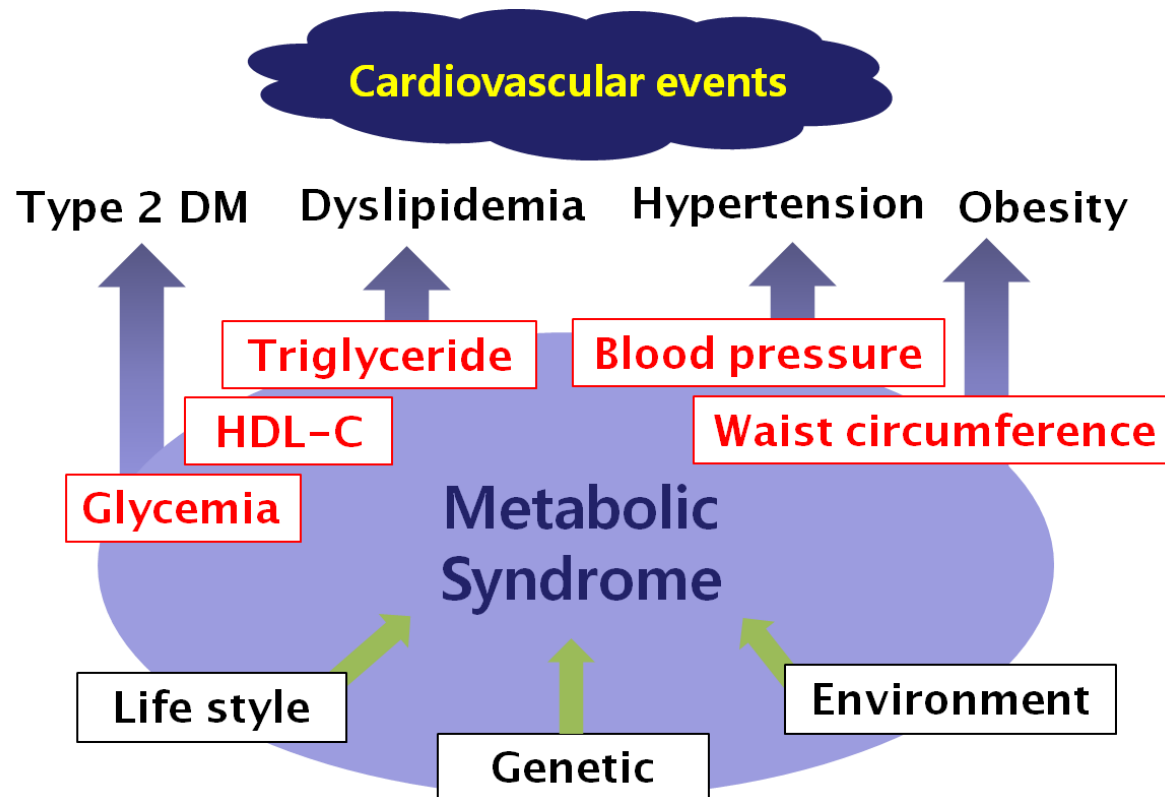
- Metabolic syndrome in hypertension
- Impact of metabolic syndrome on target organ damage
- Possible relationship between metabolic syndrome and atrial fibrillation
- Summary and conclusion

Association of Cardiovascular risk factors among hypertensive patients

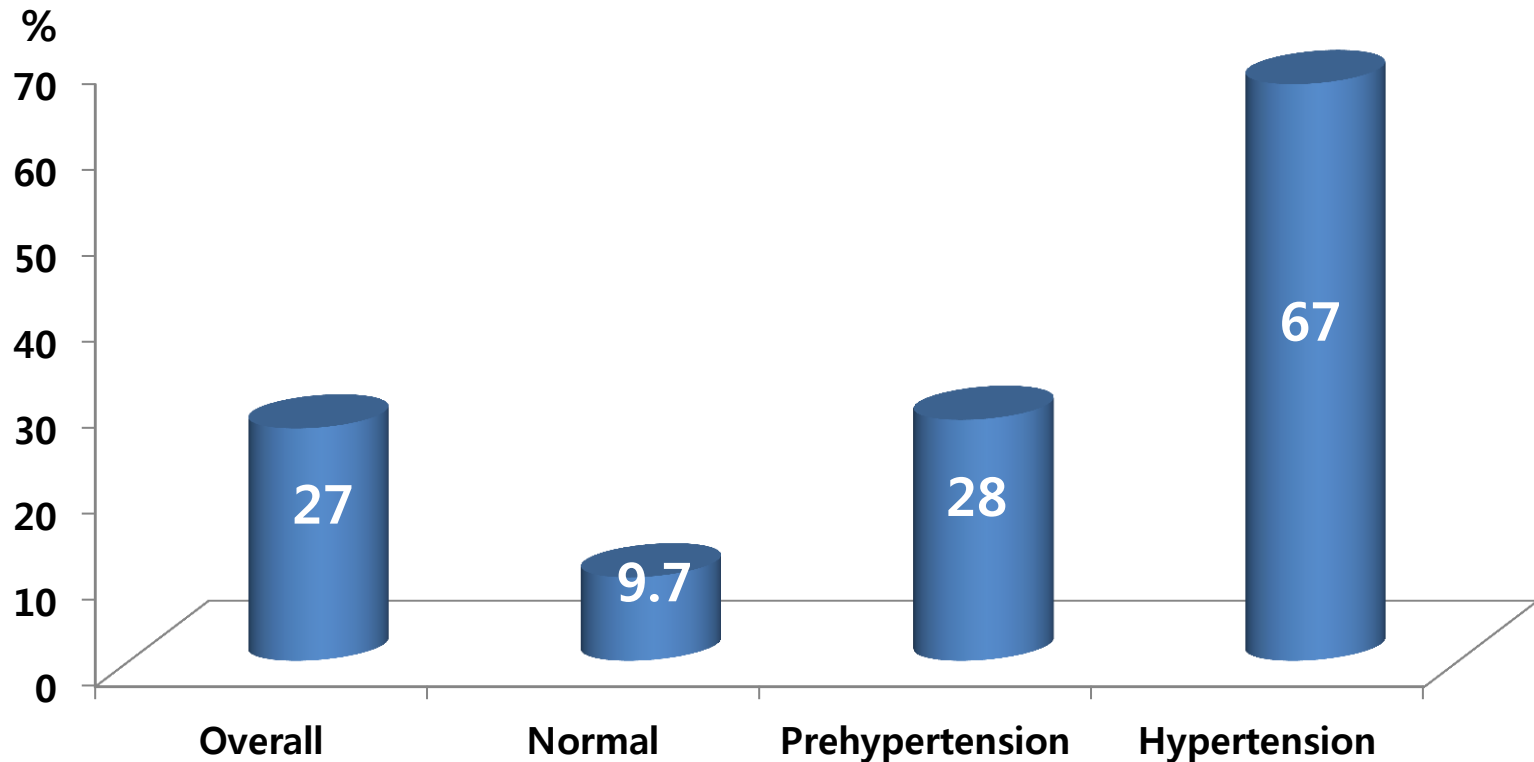


Framingham Heart Study, Kannel WB *Am J Hypertens.* 2000

Metabolic syndrome (MetS) as a cluster of cardiovascular risk factors

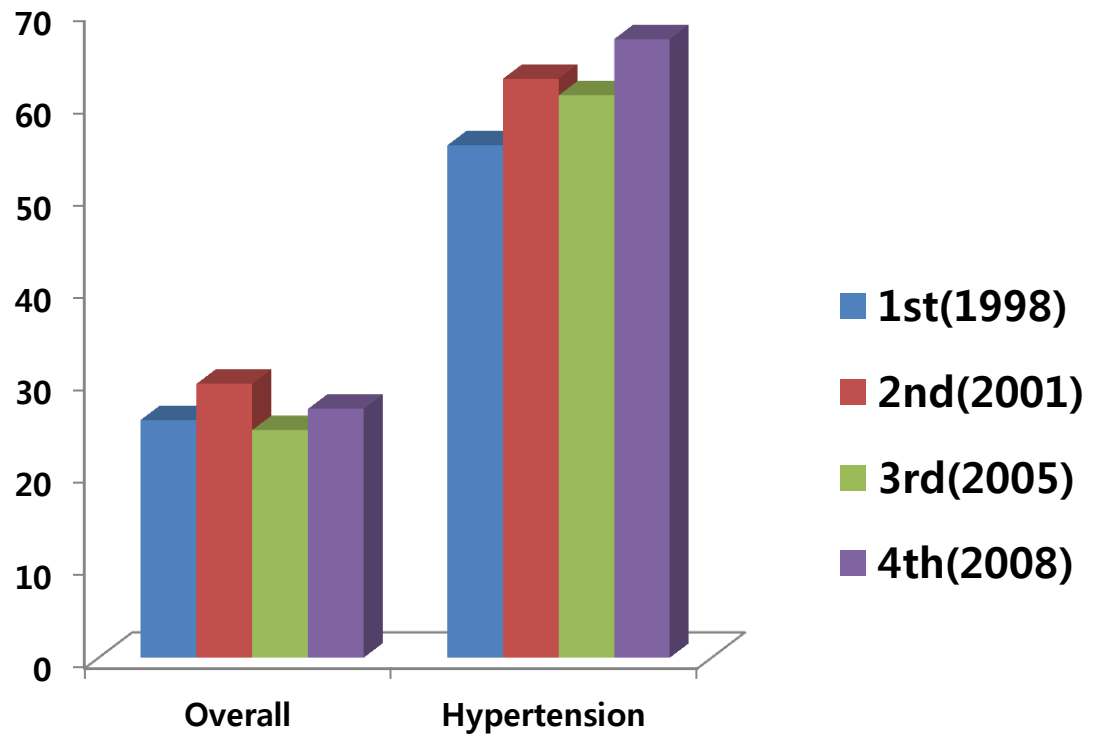


MetS prevalence among HT population is more than twice that of general population



4th KNHANES data

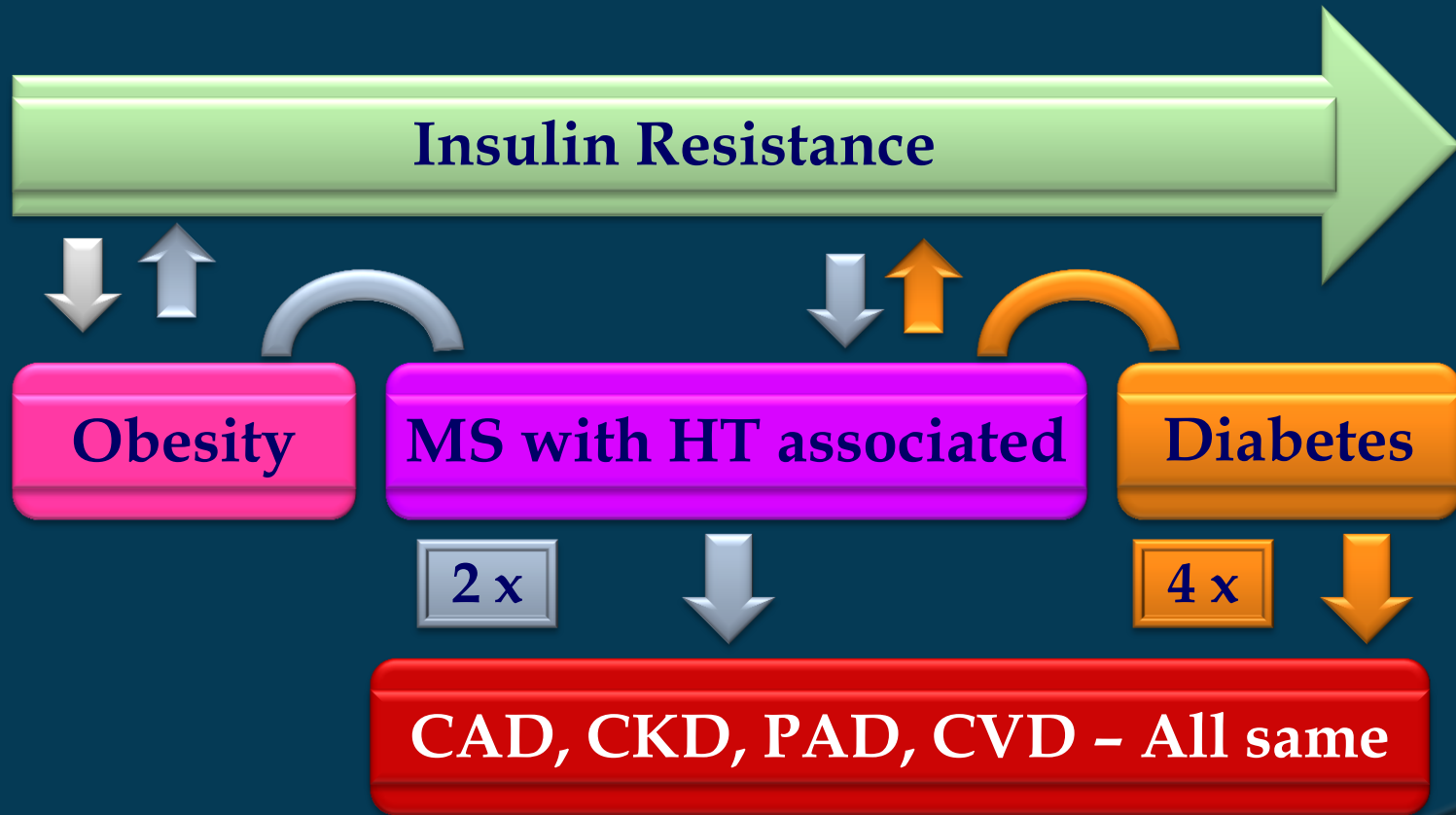
High prevalence of MetS among HT population is sustained through 1st to 4th KNHANES.



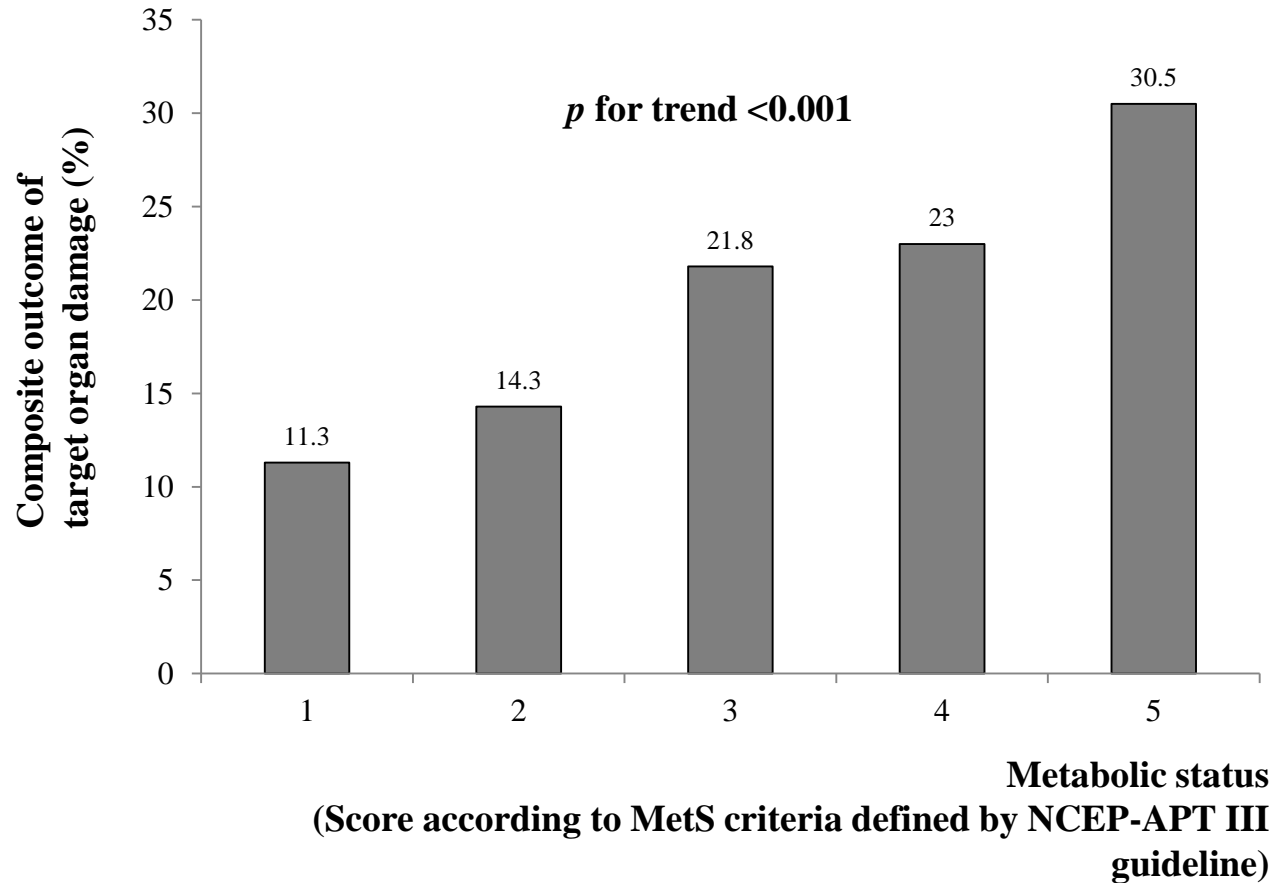
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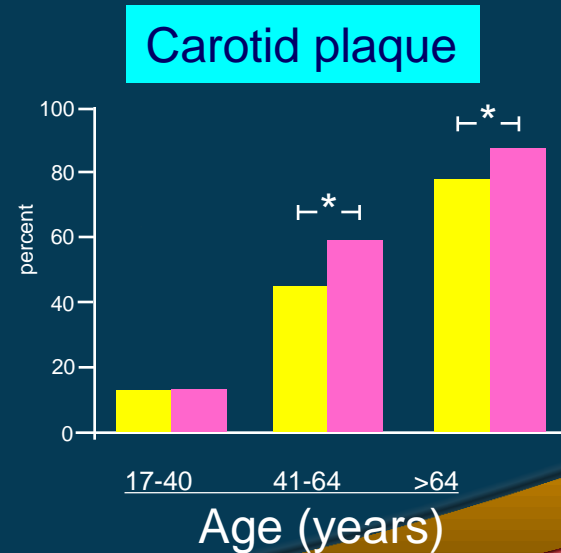
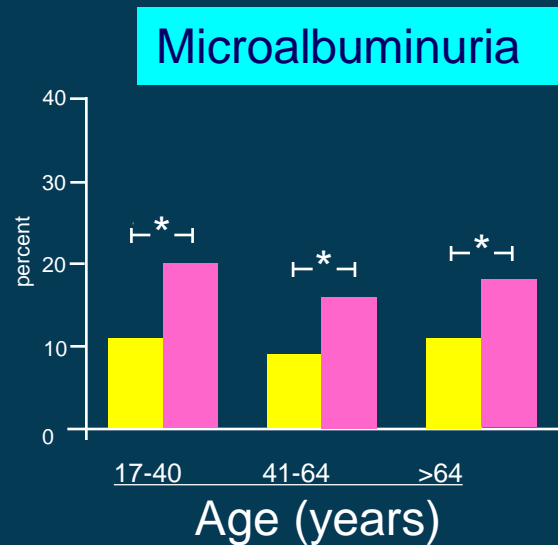
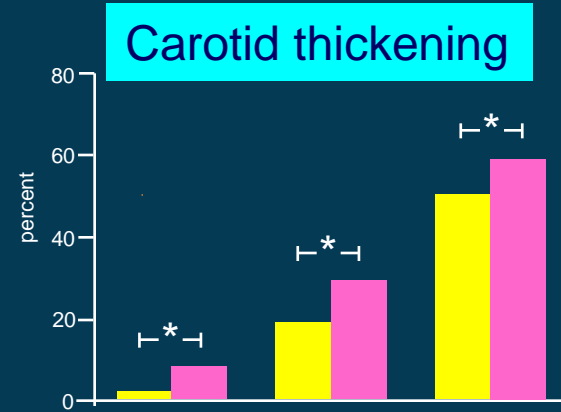
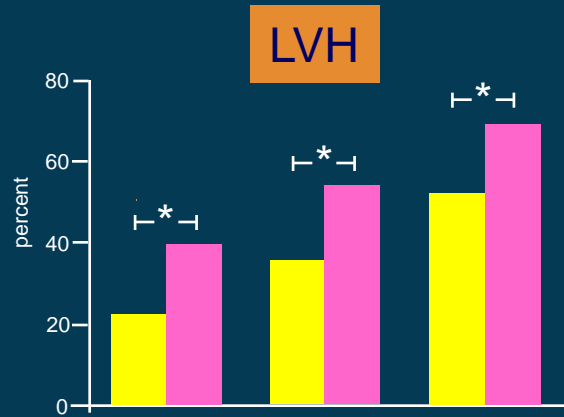
The Compound Jeopardy !!



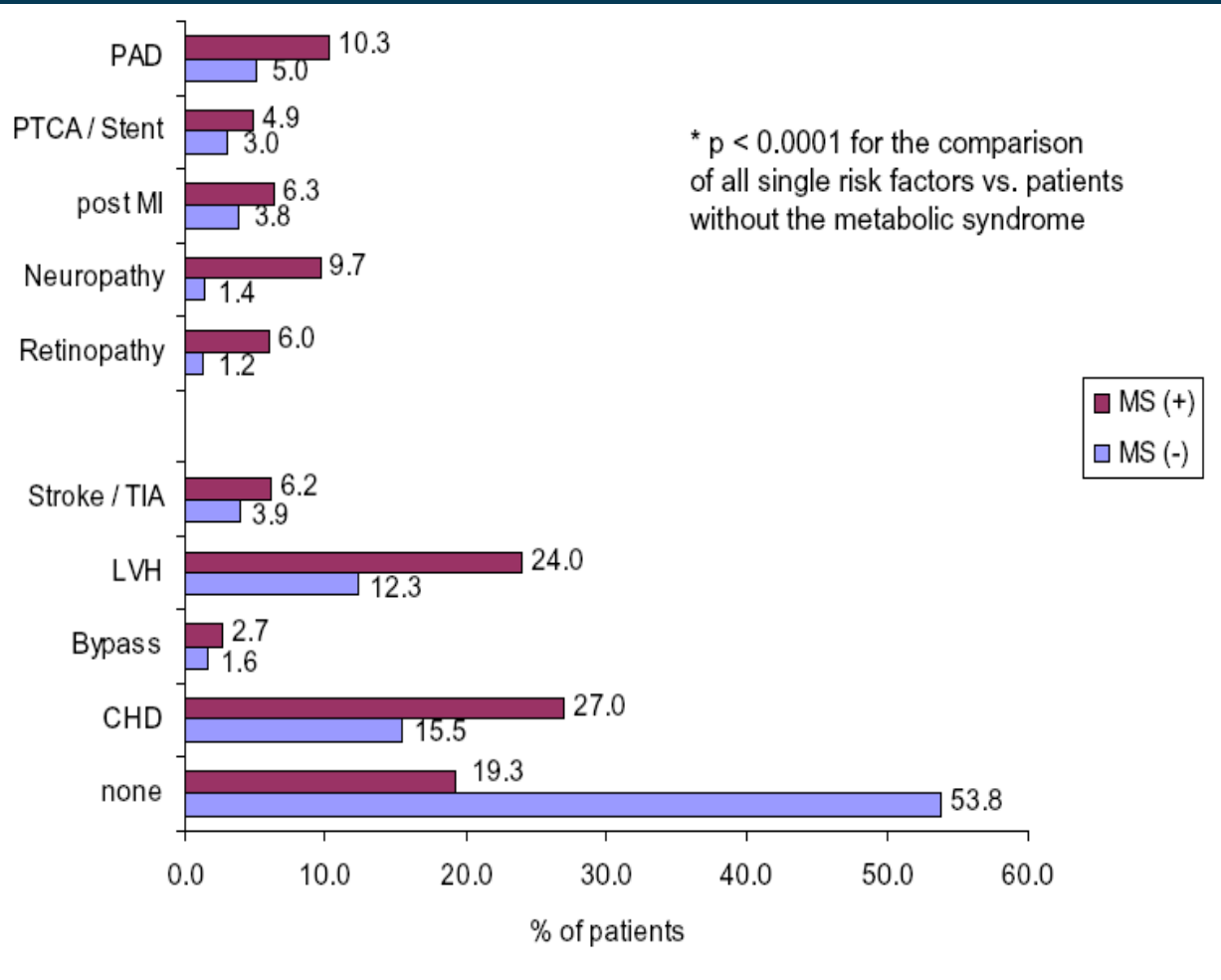
Prevalence of TOD in hypertensive patients according to MetS component



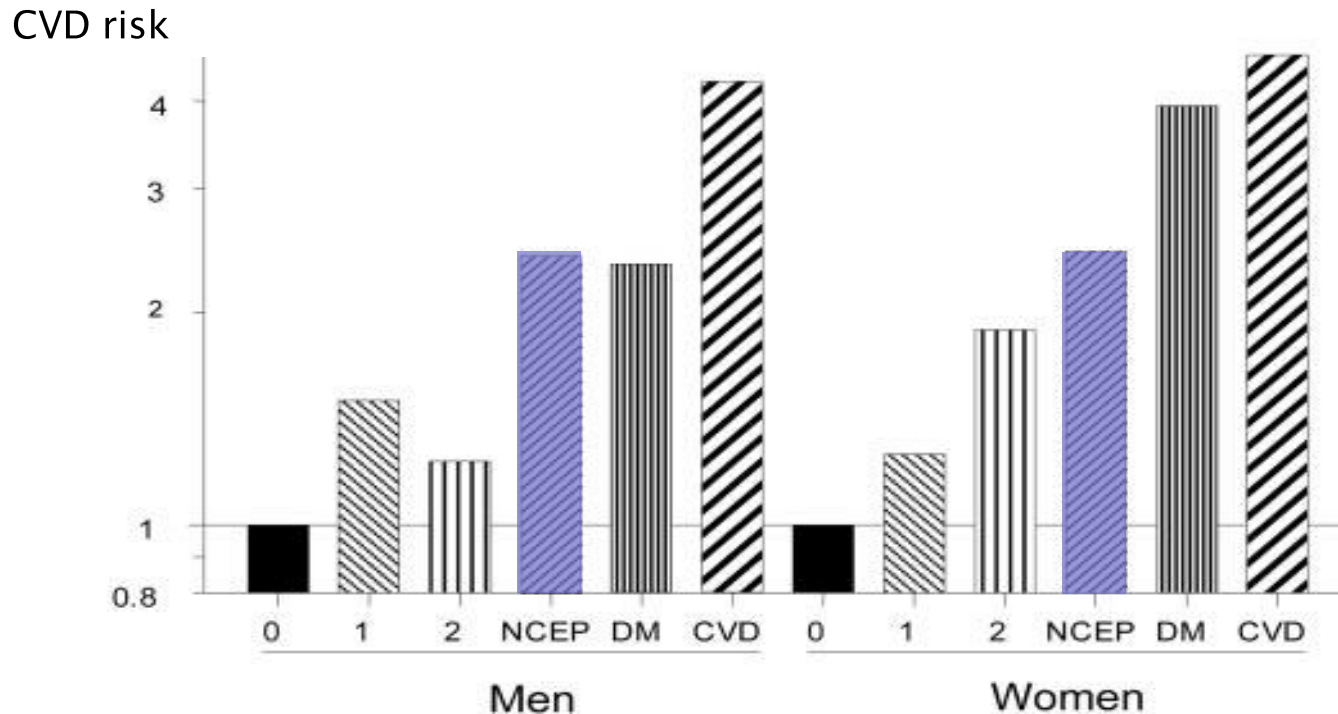
Increased prevalence of subclinical organ damage with metabolic syndrome in HT population



Comorbidity with or without metabolic syndrome



Increased CV risk associated with MetS



The cardiovascular morbidity and mortality of MetS patients markedly higher than those of individuals without the syndrome.

Dekker et al. *Circulation*. 2005

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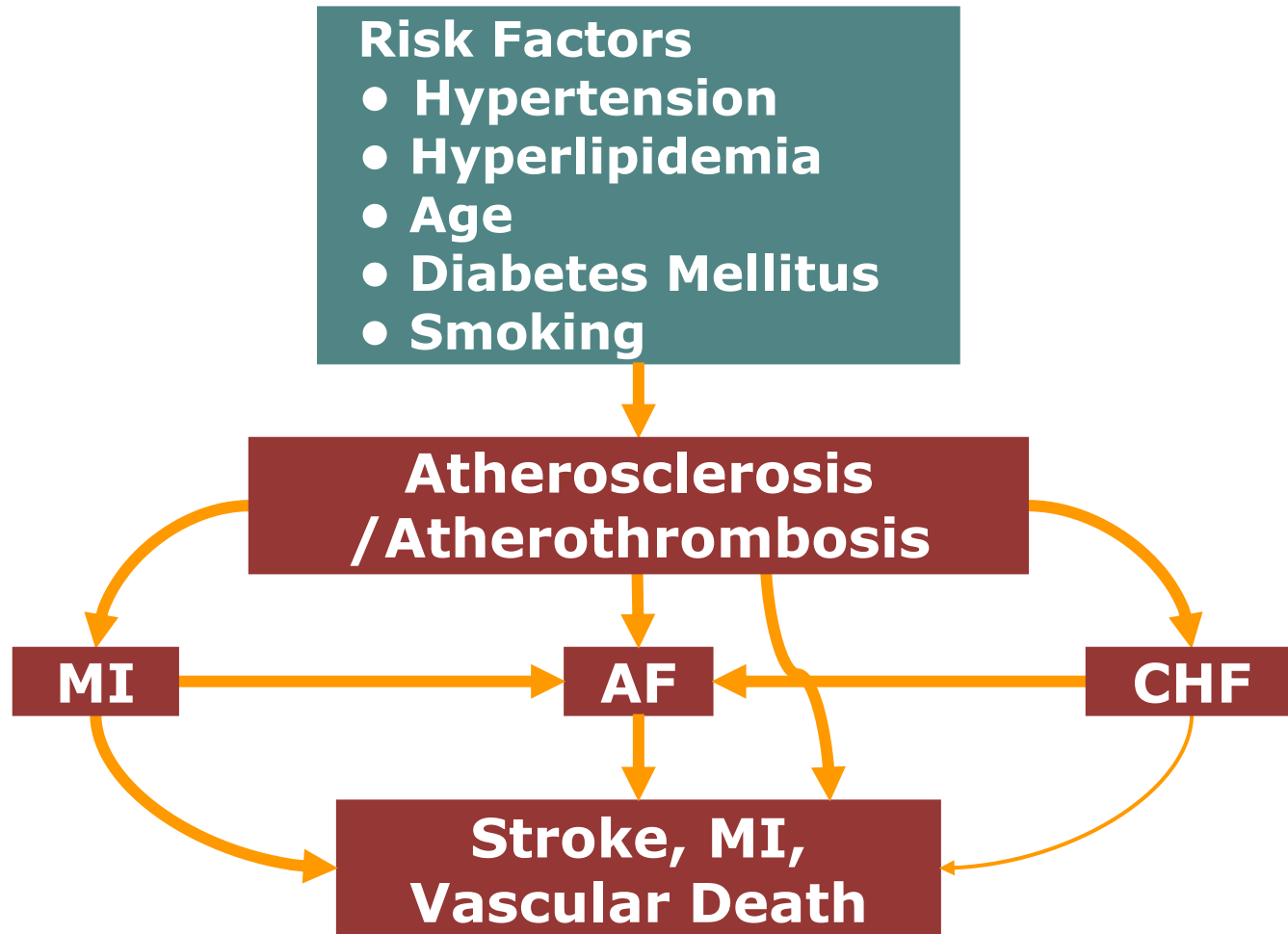
Impact of metabolic syndrome on atrial fibrillation occurrence

Tanner et al ⁴⁰	23 650 African American and white US adults > 45 years of age	MS is associated with an increased prevalence of AF. Each MS component except serum triglycerides was significantly associated with AF.
Chamberlain et al ⁴¹	15 094 adults age 45–64 years from general population	MS and most of its components (except triglycerides level) were associated with a higher risk of AF in both blacks and whites.
Watanabe et al ⁵⁰	28 449 Japanese patients ≥ 20 years of age without baseline AF	MS was associated with higher AF occurrence.
Liu et al ⁵⁸	972 hypertensive patients without left ventricular hypertrophy	MS, hypertension duration, age, and left atrial diameter correlated with AF occurrence.

The vast majority of epidemiological and observational studies conducted in general population have shown that subjects with MS have a greater likelihood of Af than their non-MS counterparts

vyssoulis et al ⁷³	15,075 consecutive nondiabetic patients with essential hypertension	MS is directly and independently related to the AF prevalence in nondiabetic patients with essential hypertension.
Hu et al ⁷⁴	3775 hypertensive patients age 55–80 years	MS does not increase the risk for AF in elderly hypertensive patients. Aging, heart failure, and LV hypertrophy played more important roles.
Tang et al ⁷⁵	654 consecutive AF patients who underwent pulmonary vein ablation	MS is an independent predictor of AF recurrence.
Chang et al ⁷⁶	282 patients with AF who underwent catheter ablation	MS is associated with larger left atrial size and the risk for AF recurrence after the ablation of AF.
Mohanty et al ⁷⁷	1496 consecutive patients with AF undergoing first catheter ablation	MS, independently of its components, predicted higher recurrence after ablation in patients with nonparoxysmal AF.
Cai et al ⁷⁸	186 patients with paroxysmal and nonparoxysmal AF	Overweight/obesity and MS, independently of diabetes and hypertension, were predictors of late recurrence of AF.

Atrial fibrillation as a risk factor for vascular event



Wolf PA et al. Arch Intern Med 1987; 147: 1561-1564.

Leckey R et al. Can J Cardiol 2000; 16: 481-485.

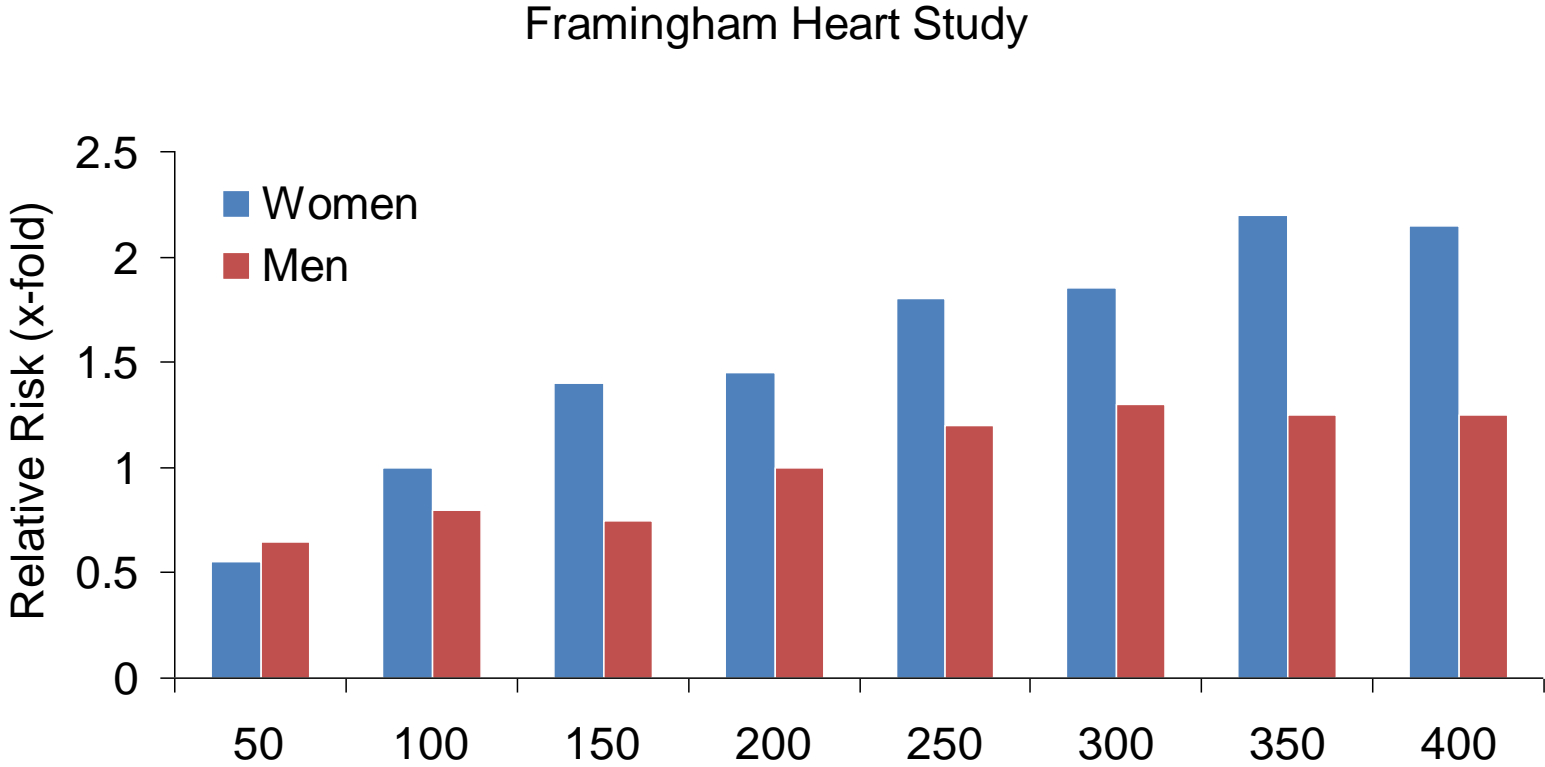
Important epidemiologic study with MetS population

- Atherosclerosis Risk in Communities (ARIC) study
 - 15-year follow-up involved 15,094 subjects
 - Higher cumulative probabilities of incident Af with greater numbers of MS components
 - Cumulative risk of 5.1% among those with 0 components vs 20.4% among those with all 5 criteria
- Contributing hazard of each component
 - elevated BP associated with the highest relative risk of AF occurrence (hazard ratio [HR]: 1.95)
 - abdominal obesity had lower relative risk (HR: 1.40)
 - ↓ HDL and ↑ fasting glucose levels related with similar risks (HR: 1.20 and 1.16, respectively)

Important epidemiologic study with Af population

- Reasons for Geographic and Racial Differences in Stroke (REGARDS) study
 - 23,650 African American and white US adults >45 yo
 - increased BP, ↓ HDL-C, and ↑ fasting glucose level had a similar relative risk for AF development (OR: 1.21, 1.17, 1.17, respectively)
 - Abdominal obesity associated with lower risk (OR: 1.14)
 - Hypertriglyceridemia was not an independent predictor
- MS as independent predictor of Af recurrence after catheter ablation
 - In study by Mohanty et al included 1496 consecutive patients with Af who underwent their first ablation, MetS but not its individual components associated with Af recurrence (JACC. 2012)
 - Obesity and MetS, independent of diabetes and hypertension, associated with late Af recurrence after ablation (Int J Cardiol. 2013)

Impact of triglyceride levels on relative risk of CAD



Castelli WP. *Can J Cardiol.* 1988

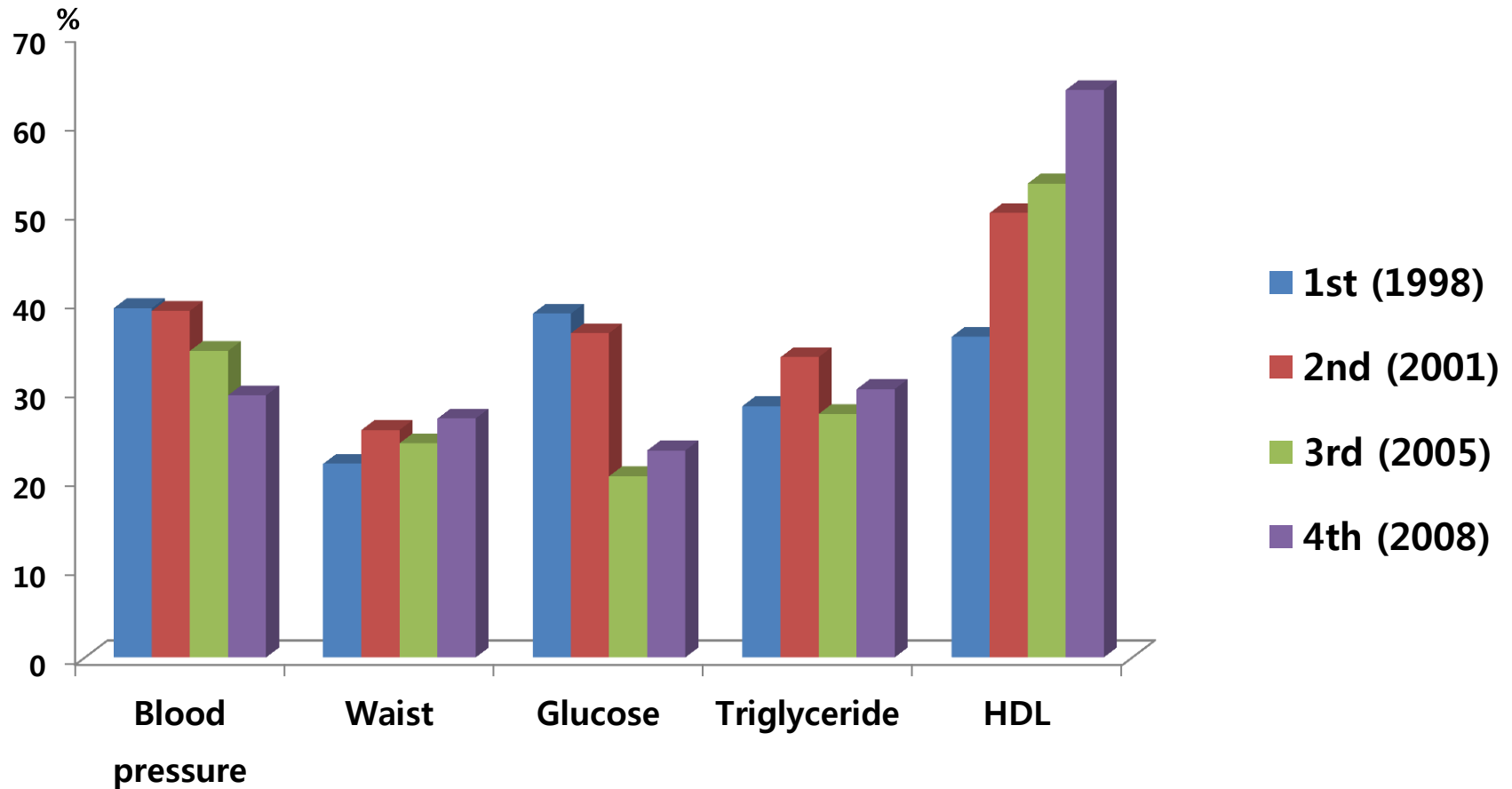
Pathophysiology of atrial fibrillation

- Atrium
 - Atrial fibrosis and ischemia
 - Atrial stretch and enlargement
- Left ventricle
 - Left ventricular hypertrophy
 - Diastolic dysfunction affecting stretch receptors in pulmonary veins & left atrium
- Inflammation
- Sympathetic activation
 - Autonomic Nervous System activity
 - Expression of angiotensin-converting enzyme

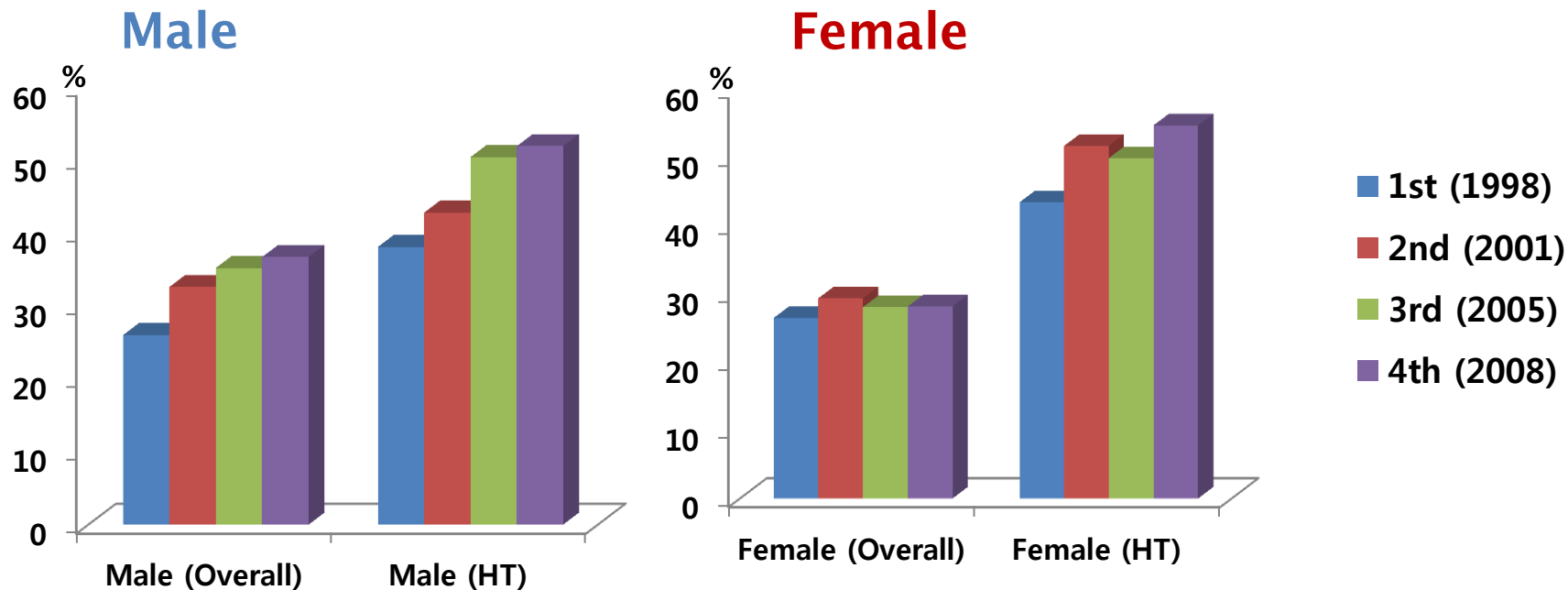
Suggested cardiac structural change in MetS

- Increased left ventricular mass
- Higher prevalence of left ventricular
diastolic dysfunction
- Dilated left atrium

Distribution of metabolic risk component



Prevalence of Obesity

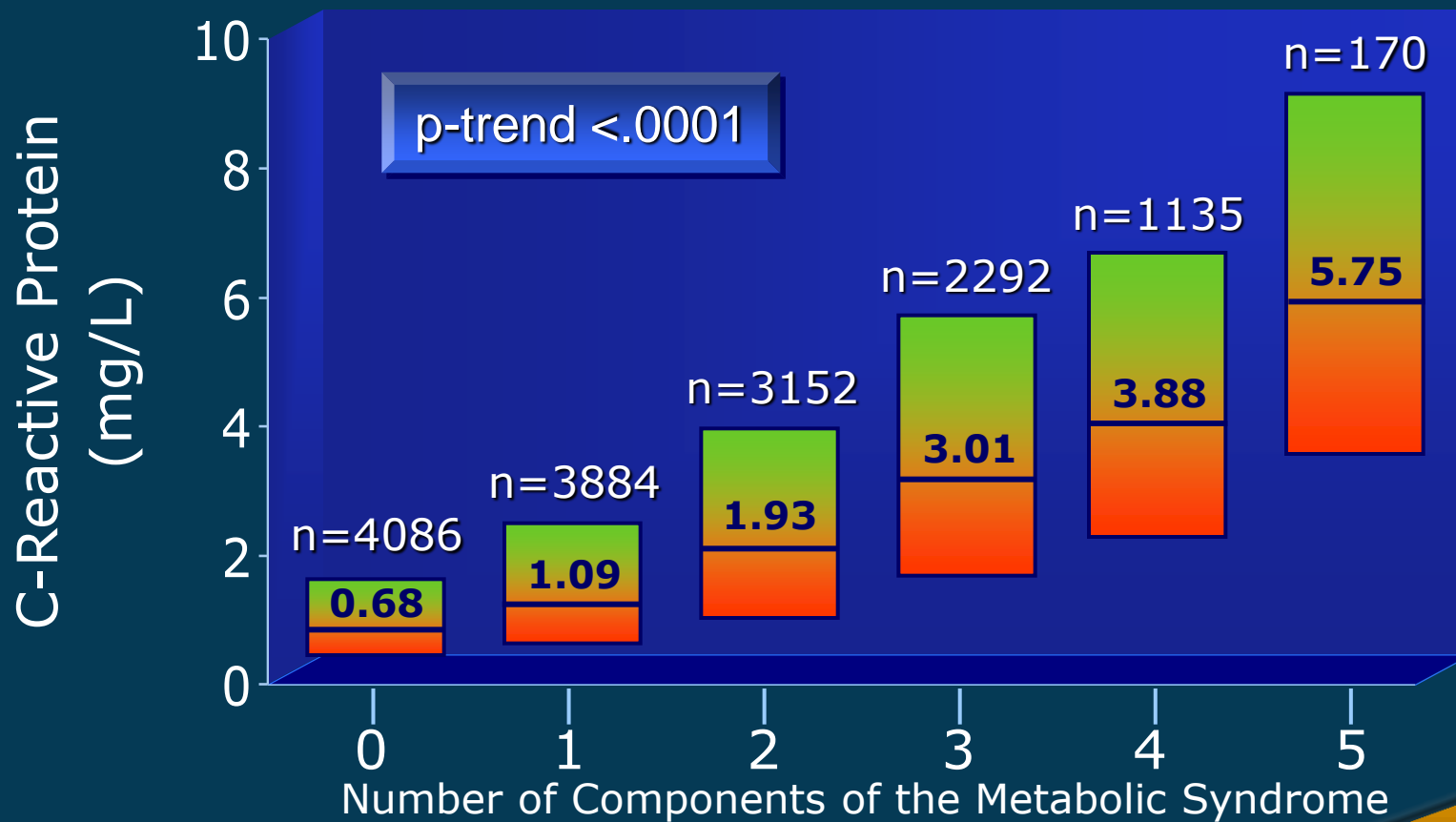


Prevalence of obesity is higher in HT group.

Obesity and atrial fibrillation

- each 1-unit increase in BMI associated with 7% greater risk of permanent Af, and 4% greater risk of intermittent Af
 - Significant relationship btw waist circumference and AF in both genders (REGARDS, ARIC study)
- Significant difference in left atrial dilation in obese men compared to overweight men ($p < .001$).
 - LA enlargement due to \uparrow plasma volume, \uparrow preload, and LVEDP
 - BMI is one of the most important markers of atrial size and volume
- Even after LA size adjustment, BMI still remained significantly associated with Af progression to permanent.
 - Shortened effective refractory period in LA and pulmonary veins
- Neurohormonal activation especially in obesity with MetS
 - \uparrow circulating RAAS reported in MS patients with visceral obesity
- Inflammation, oxidative stress, and myocardial fibrosis

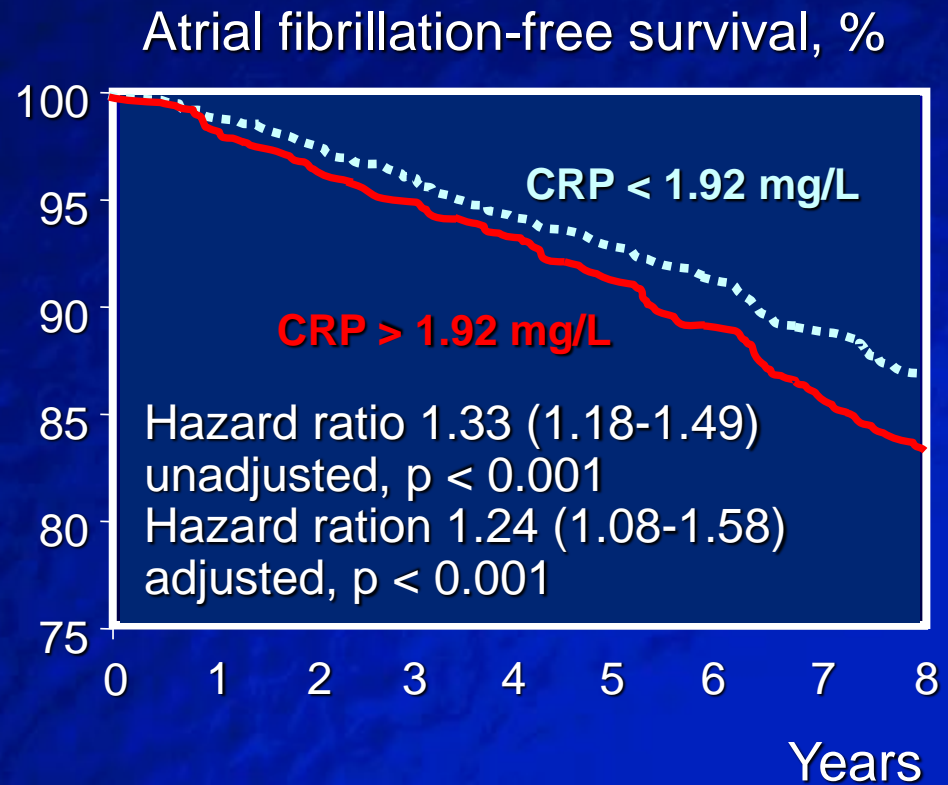
Distribution of CRP levels by number of metabolic syndrome components : WHS



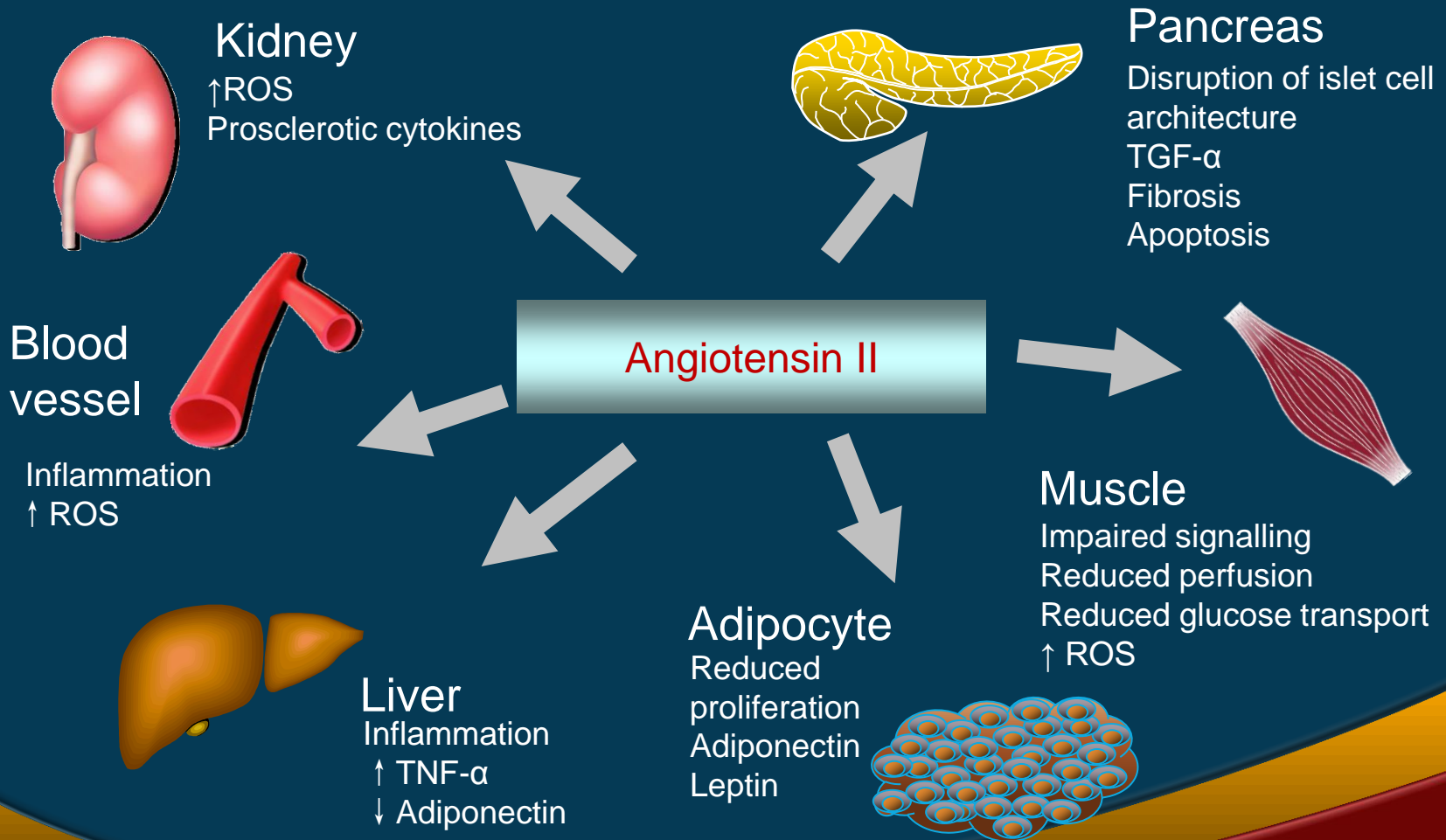
Box plots denote median and 25th and 75th percentile CRP values

Inflammation and AF: Cardiovascular Health Study

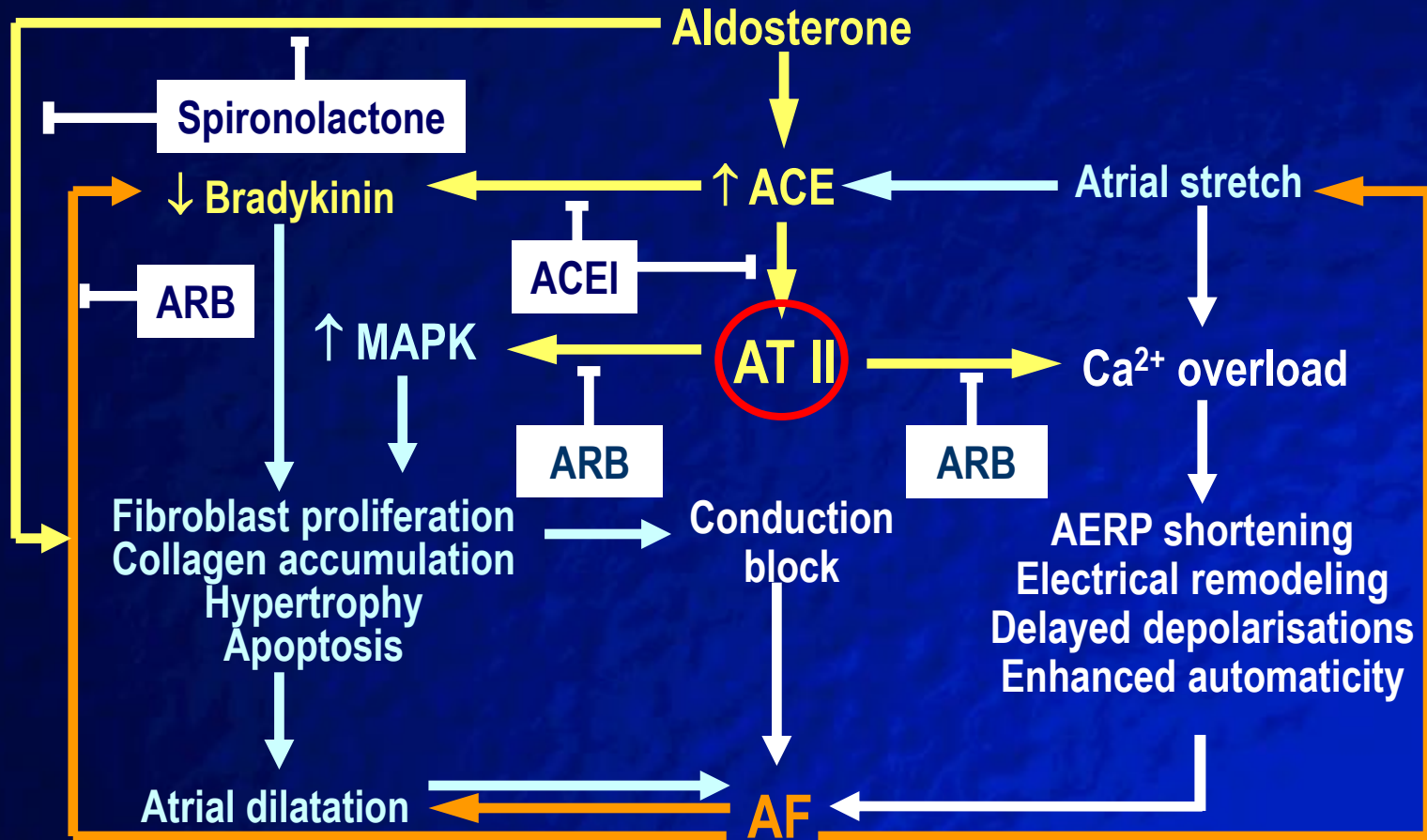
- 5806 subjects ≥ 65 years
- 897 developed AF
- 7.8 years of follow-up
- Median CRP
- 2.41 mg/L (1.29-5.02) in AF
- 1.89 mg/L (0.95-3.37) in non-AF



Insulin resistance associated with RAS activation

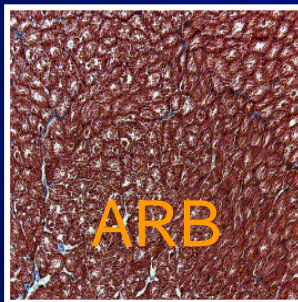
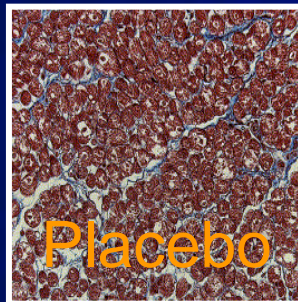


Angiotensin II in pathophysiology of Af

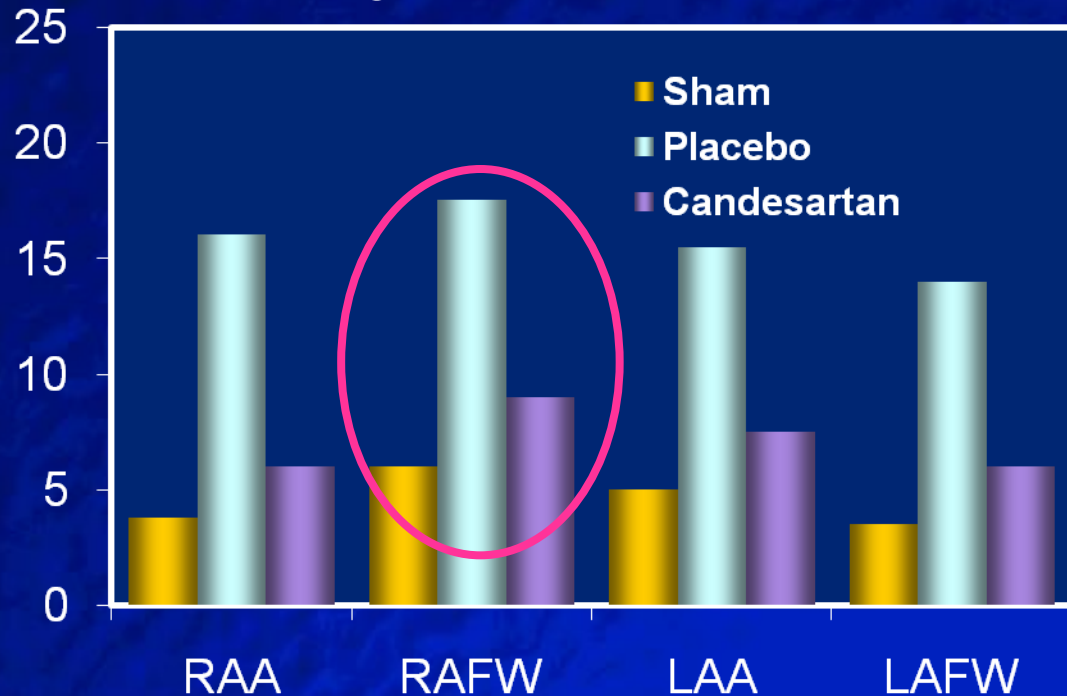


Candesartan and atrial fibrosis

RA pacing
at 400 bpm
for five
weeks
RA free wall
(masson
trichrome
stain)



Percentage of fibrosis



Pathophysiology of atrial fibrillation in metabolic syndrome

Risk factors

Metabolic syndrome
Obesity, Hypertension

Morphology

Atrial dilation

Genetic causes
Inflammation

LA enlargement



Left ventricular hypertrophy

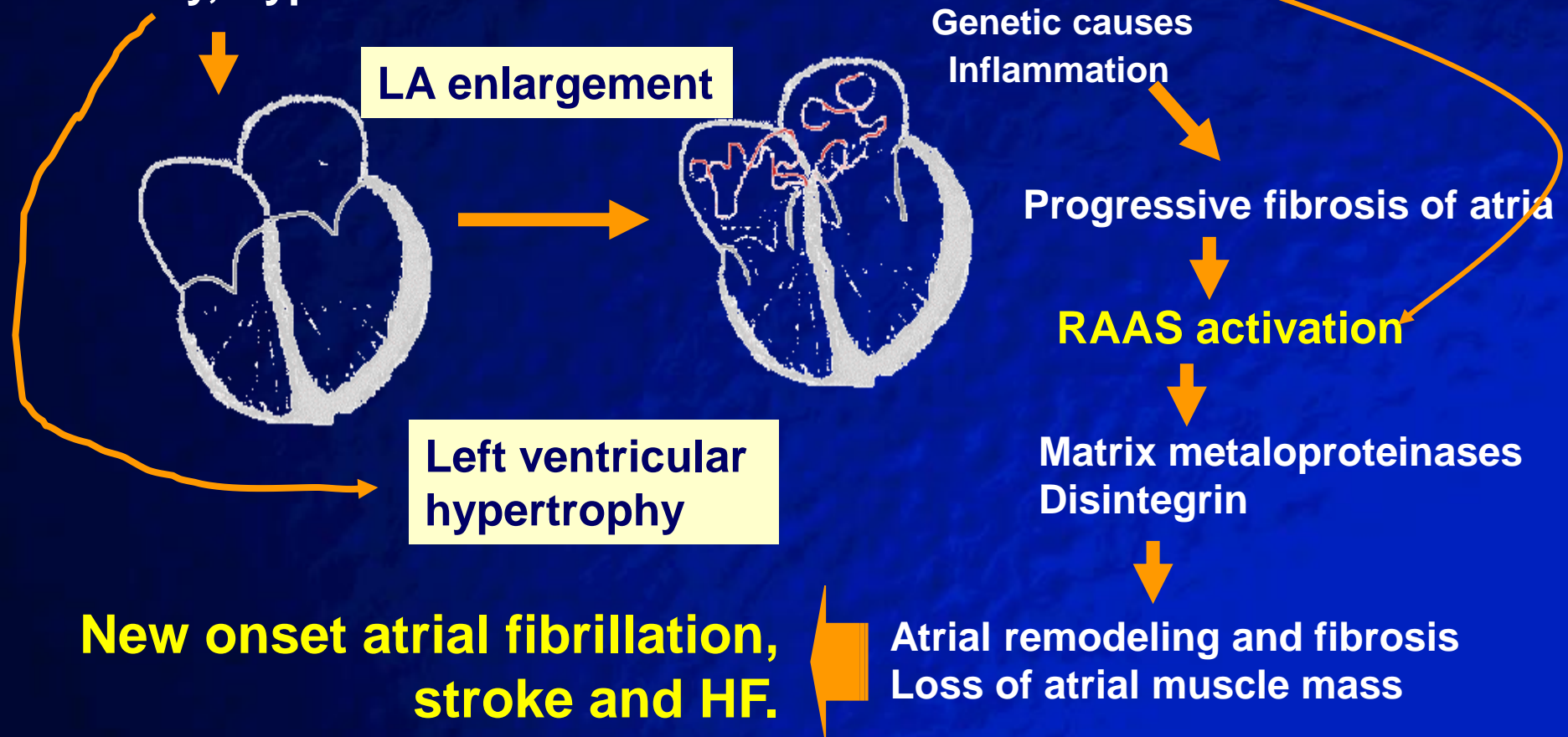
Progressive fibrosis of atria

RAAS activation

Matrix metalloproteinases
Disintegrin

**New onset atrial fibrillation,
stroke and HF.**

Atrial remodeling and fibrosis
Loss of atrial muscle mass



Therapeutic strategies for patients with MetS and Af

- **Statins potentially reduced Af risk**
 - lipid-lowering + antioxidant, anti-ischemic, anti-inflammatory, & antiarrhythmic effect.
- **RAS inhibitor in case of hypertension**
 - Promising in Af prevention but failed to prove in RCT
 - Failure of ACTIVE-I (Irbesartan) and Candesartan trials
- **Polyunsaturated fatty acids (n-3 PUFAs)**
 - Initially considered promising with myocyte membrane stabilizing effect and anti-inflammation.
 - Meta-analysis revealed disappointing results in Af prevention.
- **Lifestyle modification**
 - Obesity guideline recommends 5-10% of body weight reduction
 - Physical fitness improvement
- **Anticoagulant therapy based on CHA2DS2-VASc score**

Summary and conclusion

- All of the components of metabolic syndrome (MetS) could influence the development of atrial fibrillation (Af).
- Epidemiological studies suggested higher cumulative probabilities of incident Af with MetS components, with 4 fold increase of cumulative risk from 5% with no component to > 20% among those with all 5 criteria.
- Oxidative stress, inflammation and renin-angiotensin system activation have been involved in the pathogenesis of both MetS and Af.
- MetS combined with Af are associated with increased cardiovascular morbidity and mortality.
- Physical activity, weight loss, dietary changes, and appropriate pharmacologic interventions, especially renin-angiotensin system inhibition, will be effective in both disorders.

Thank you for your attention.

