Strategies to Achieve Target Blood Pressure in Asians with Resistant Hypertension

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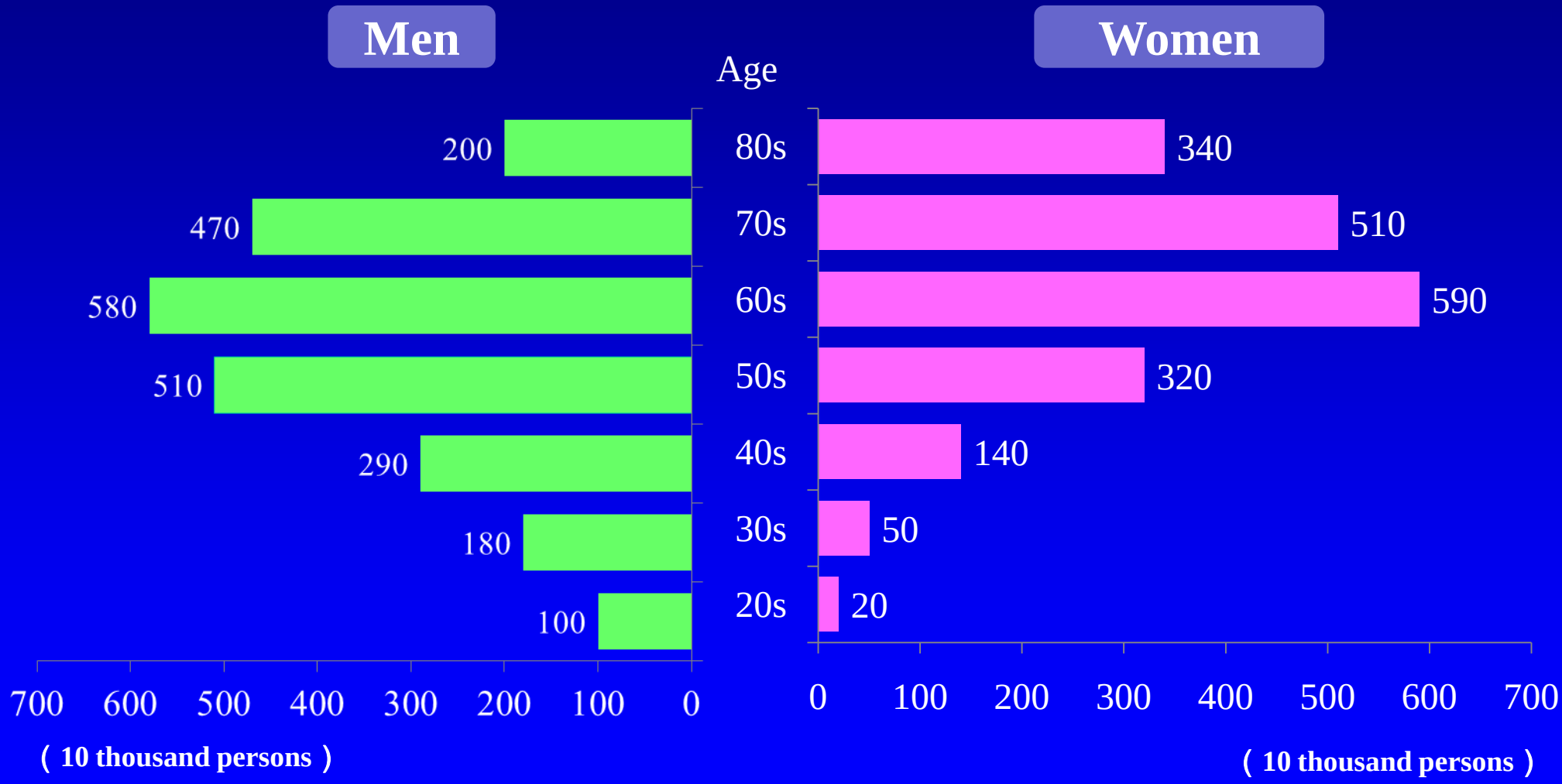
COI Disclosure （2013-2015）

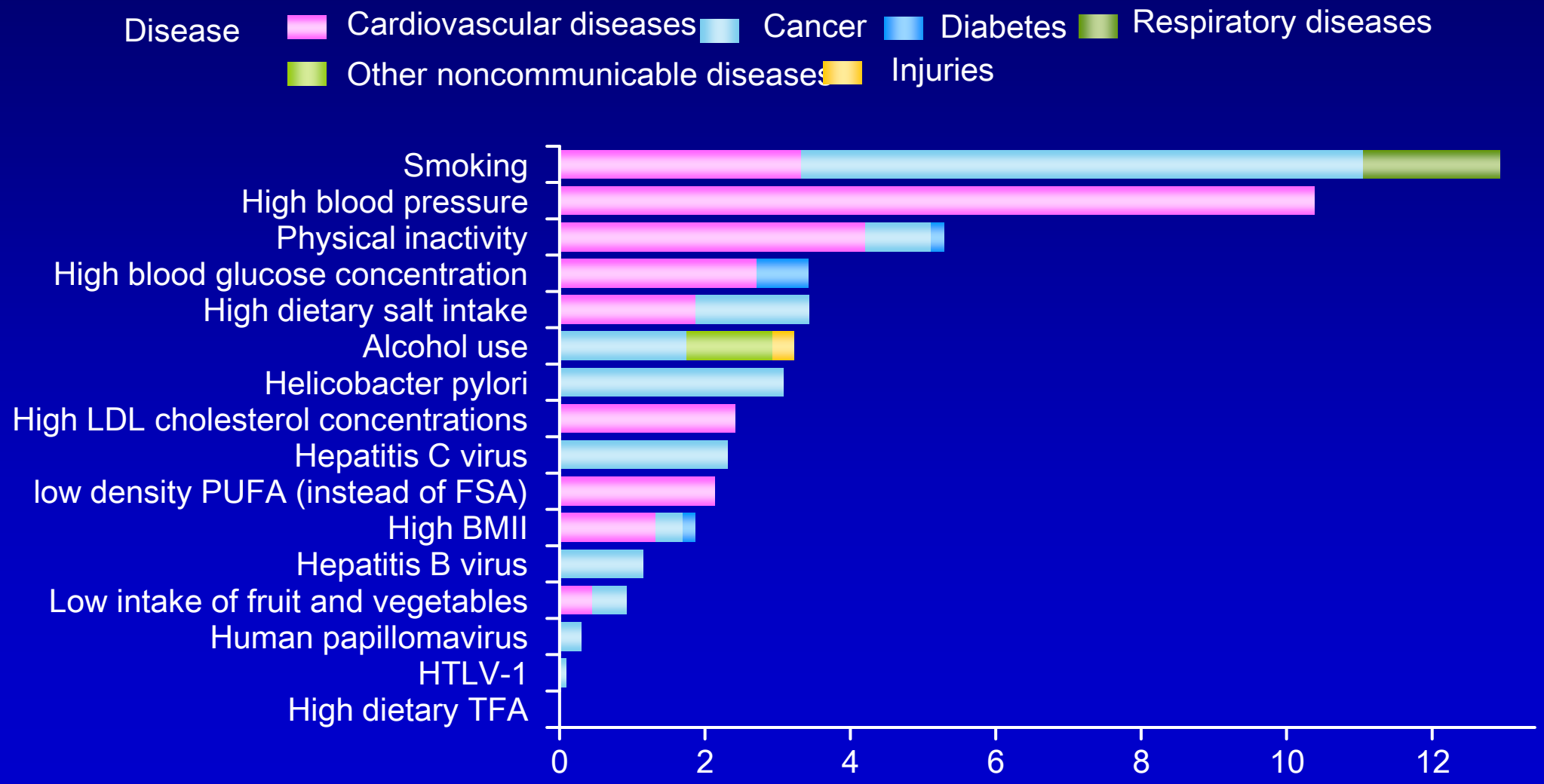
Dr. Higaki received honoraria of 1,000,000 yen or more in one year for lectures, article contributions or such activities to support promotional activities from Astellas Pharm. Inc., Boehringer-Ingelheim Japan Co., and Mochida Pharm Co. Ltd., and research grants of 2,000,000 yen or more in one year from Astellas Pharm. Inc., Beringer-Ingerheim Japan Co., Daiichi-Sankyo Inc., Sumitomo Dainippon Pharm., Mochida Pharm Co. Ltd., MSD Co., Novartis Parma Co., Teijin Pharma Co., Takeda Pharm. Co., Ltd.

Estimated Number of Hypertensives in Japan



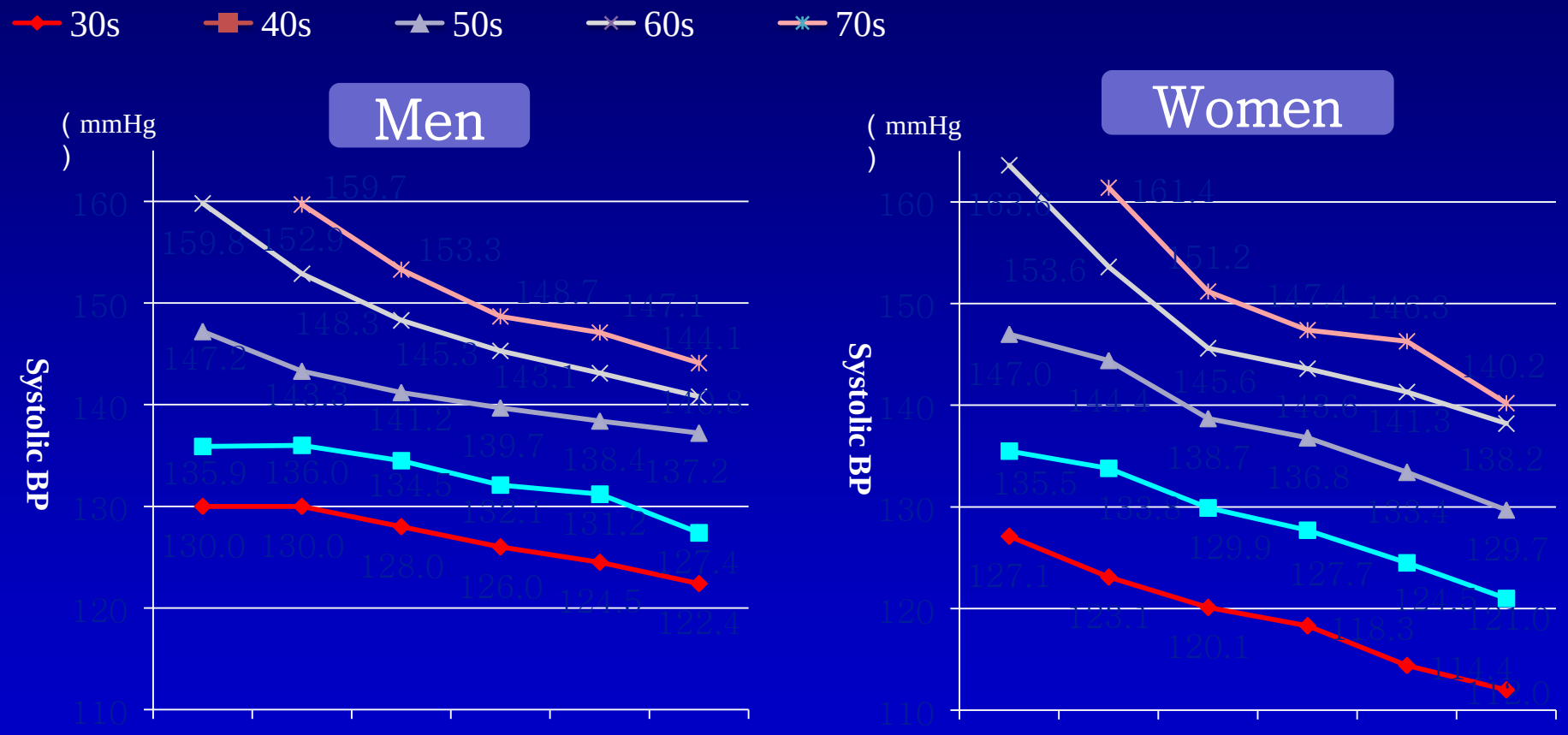
（Estimated from NIPPON DATA2010 and 2010 National census of Japan）

The Number of Deaths from Noncommunicable diseases and injuries that were attributable to risk factors in Japan in 2007 (Total men and women)



Ikeda N, et al.: Lancet 2011; 378: 1094-11

The 50-year Trend in the Blood Pressure (mmHg) by Sex and AGE Group (1961-2010)

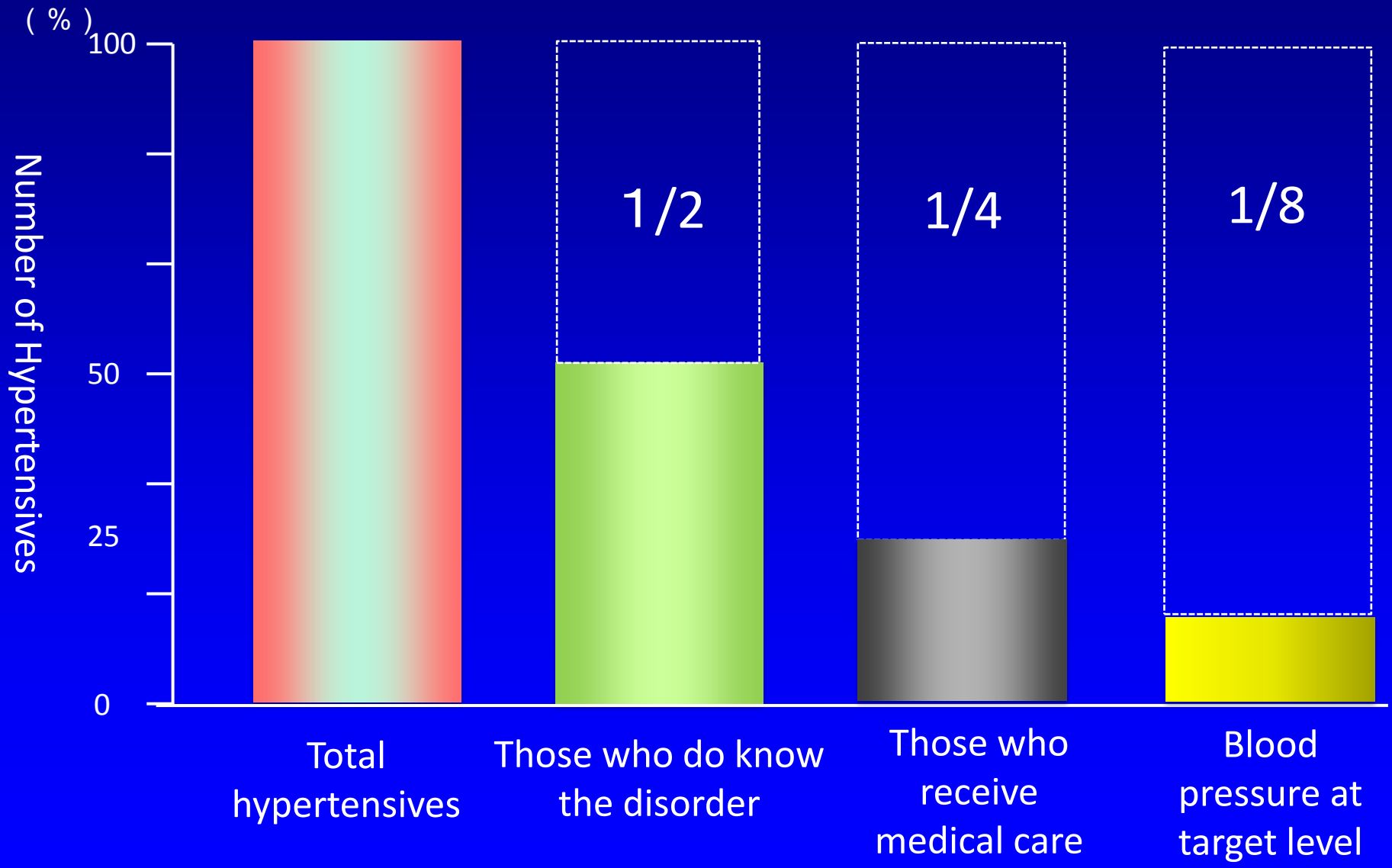


(First order adult basic research, second order adult basic research, third order adult basic research – NIPPON DATA80, fourth order adult basic research – NIPPON DATA90, fifth order adult basic research – NIPPON DATA2010)

TARGET BLOOD PRESSURE
JSH2014

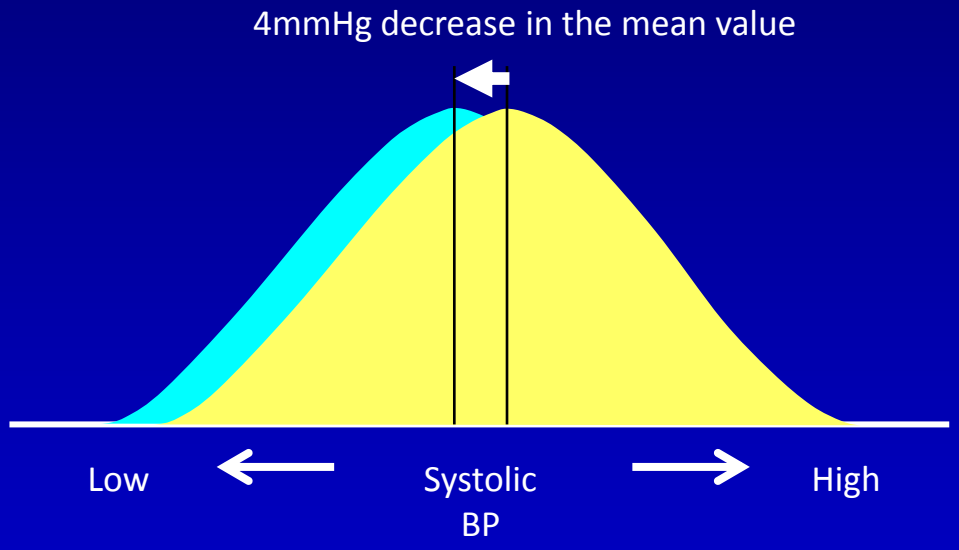
	Clinic blood pressure	*Home blood pressure*
Young, middle-aged and early-phase elderly patients	<140/90 mm Hg	<135/85 mm Hg
Late-phase elderly patients	<150/90 mm Hg (<140/90 mm Hg if toleranted)	<145/85 mm Hg (<135/85 mm Hg if toleranted)
Diabetic patients	<130/80 mm Hg	<125/75 mm Hg
Patients with CKD (with proteinuria)	<130/80 mm Hg	<125/75 mm Hg (criterion)
Patients with cerebrovascular diseases Patients with coronary artery disease	<140/90 mm Hg	<135/85 mm Hg (criterion)

The Rule of Halves in Hypertensives



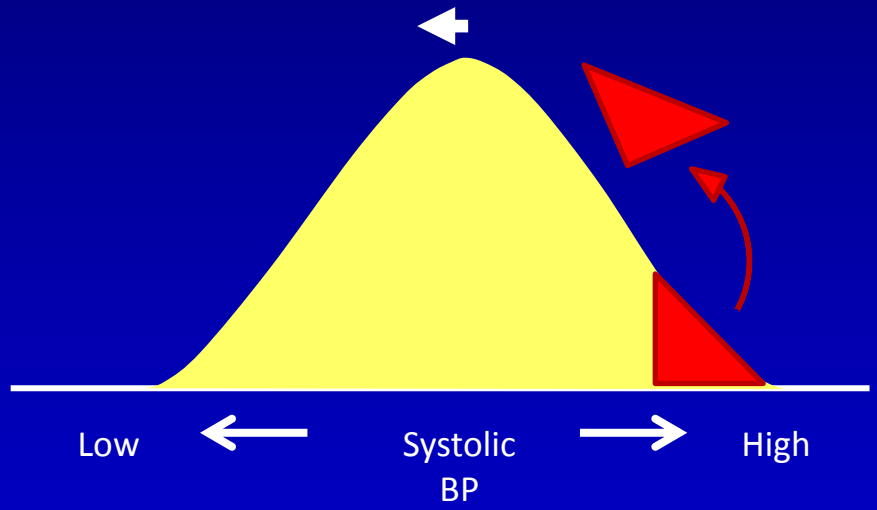
Public Health Measures against Hypertension

Population strategy



Nutrition/diet
Physical activity/exercise
Alcohol drinking
10% increase in the proportion taking antihypertensive drugs

High-risk strategy



Resistant hypertension
poorly controlled hypertension

* 3-30% of all hypertensives who receive three different antihypertensive drugs

Why Lower Blood Pressure to Achieve Target Blood Pressure ?

「High Salt Intake」

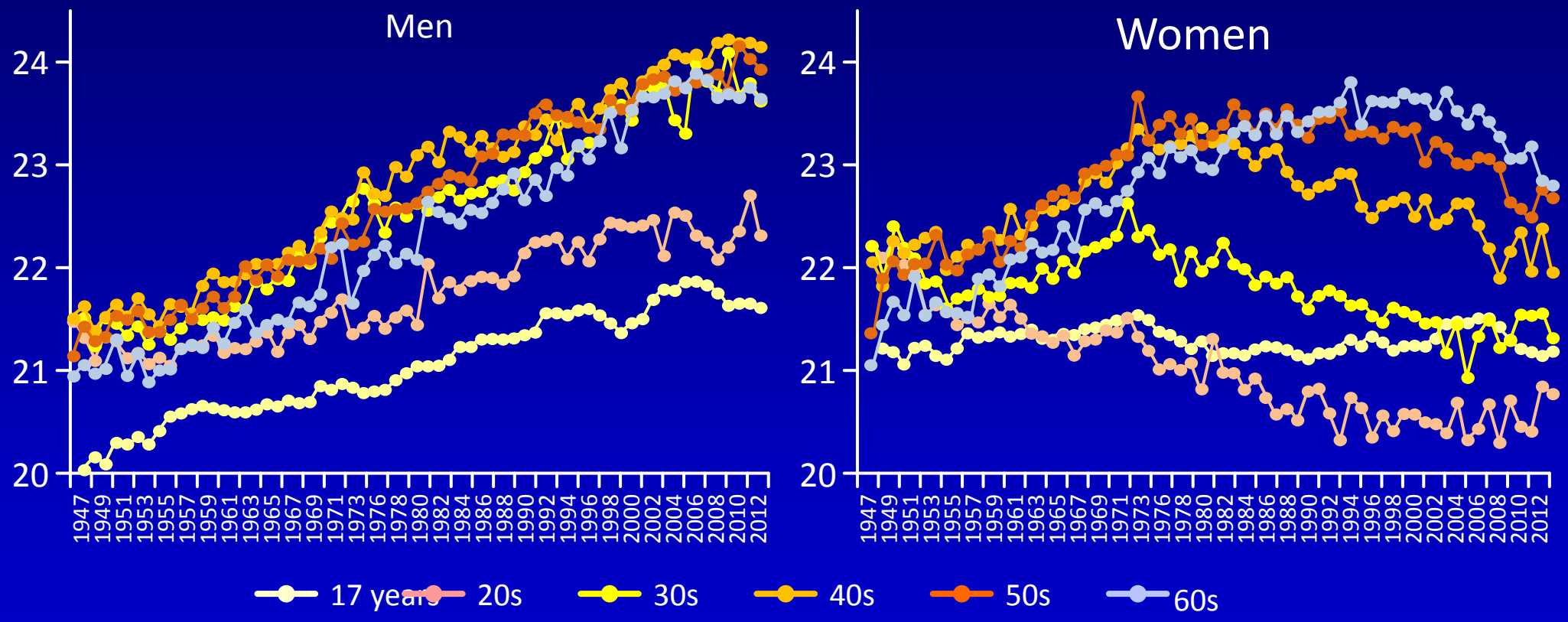
「Obesity」

Cardiometabolic Disease

Change of BMI in Japanese

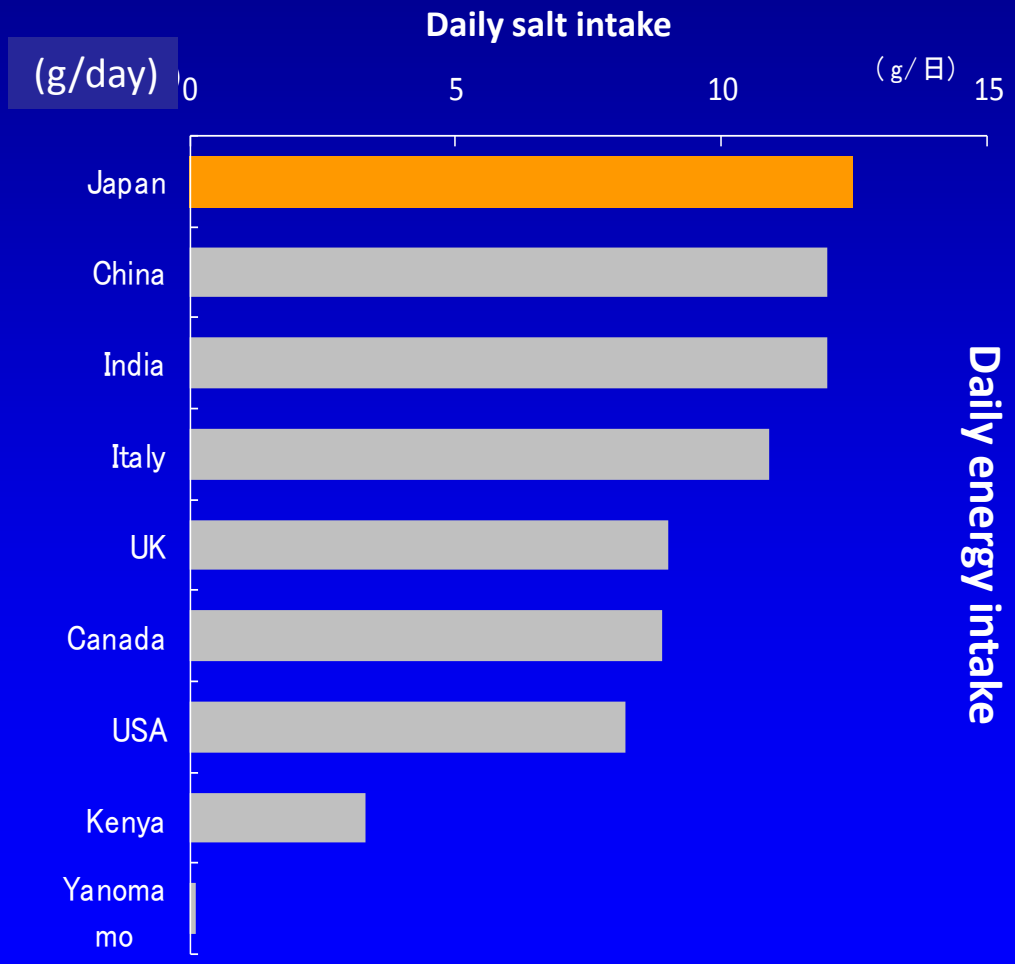
Change in BMI in Japan (1947 – 2012)

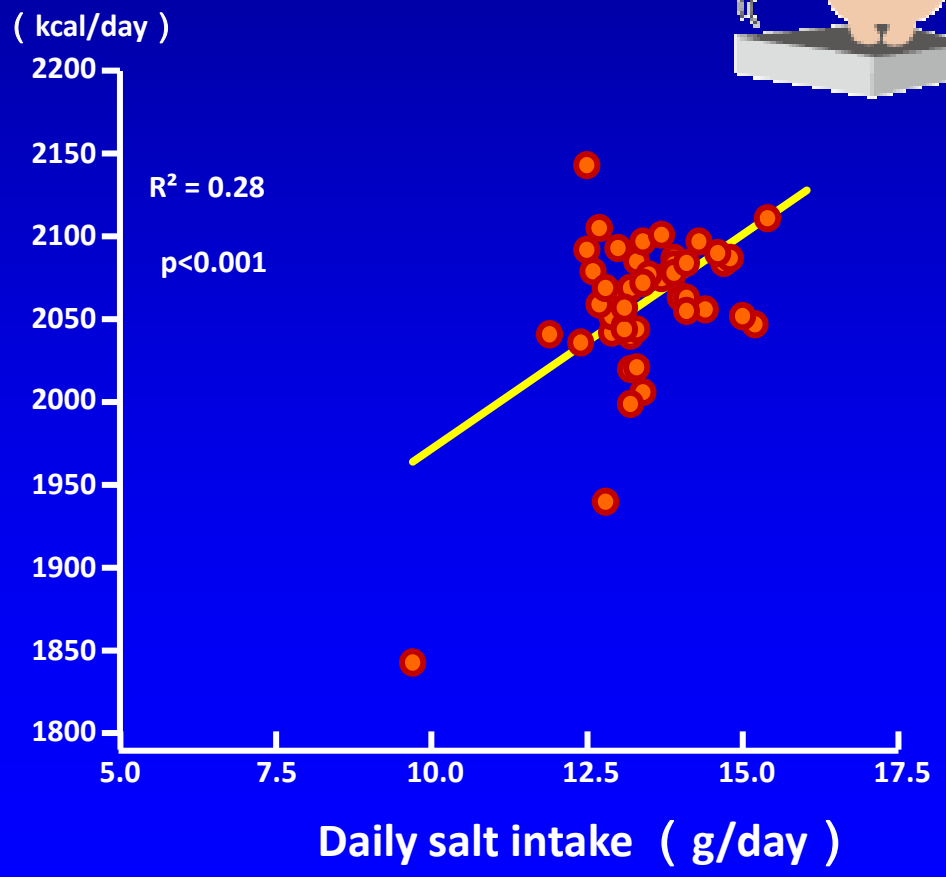
BMI： Body mass index



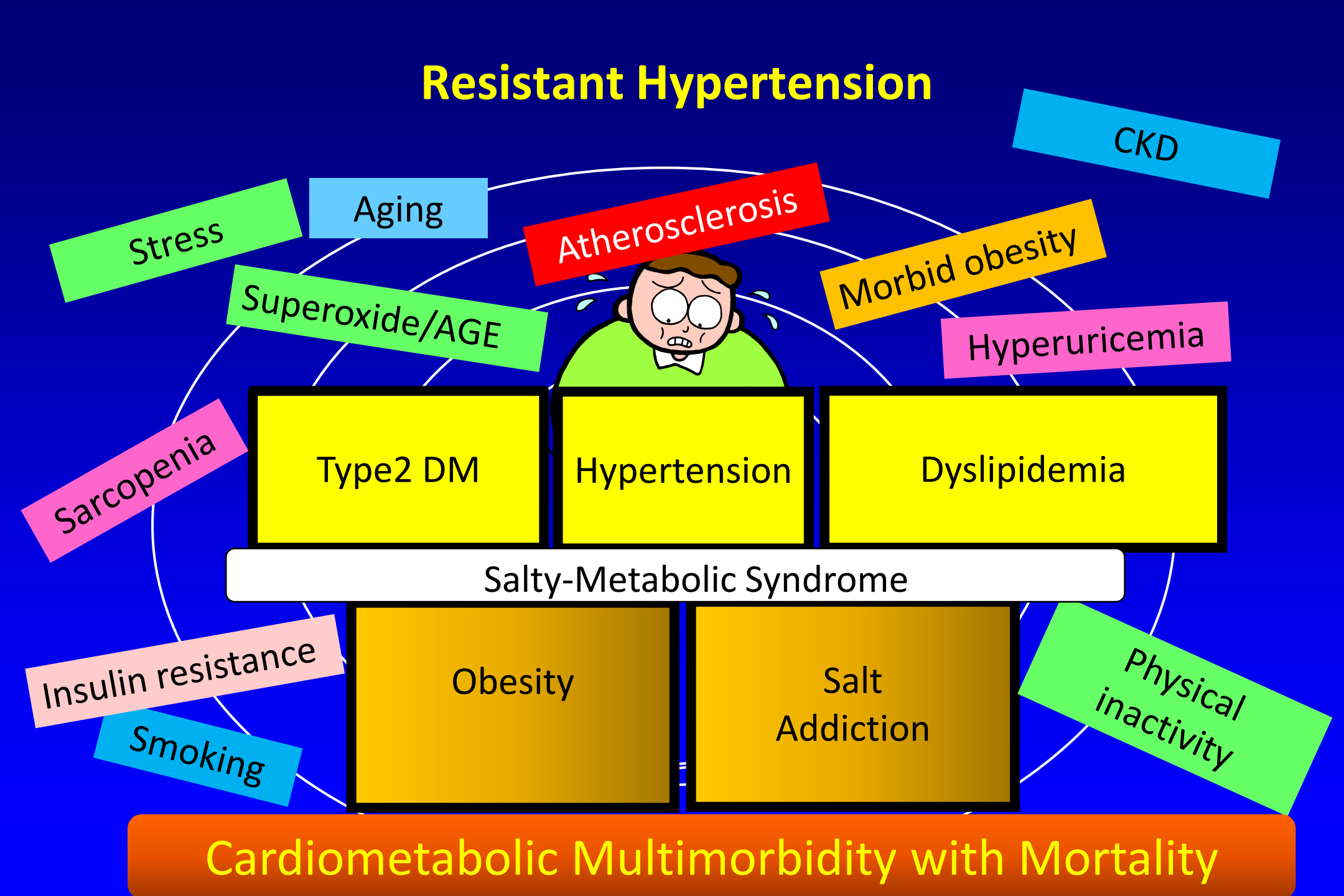
National Health and Nutrition Survey (Ministry of Health, Labour, Welfare, 1974 Survey)
School health statistics (Ministry of Education, Culture, Sports, Science, and Technology, 17 years) Social data catalogues (http://www2.ttcn.ne.jp/honkawa/)

Correlationship between Salt Intake and Energy Intake

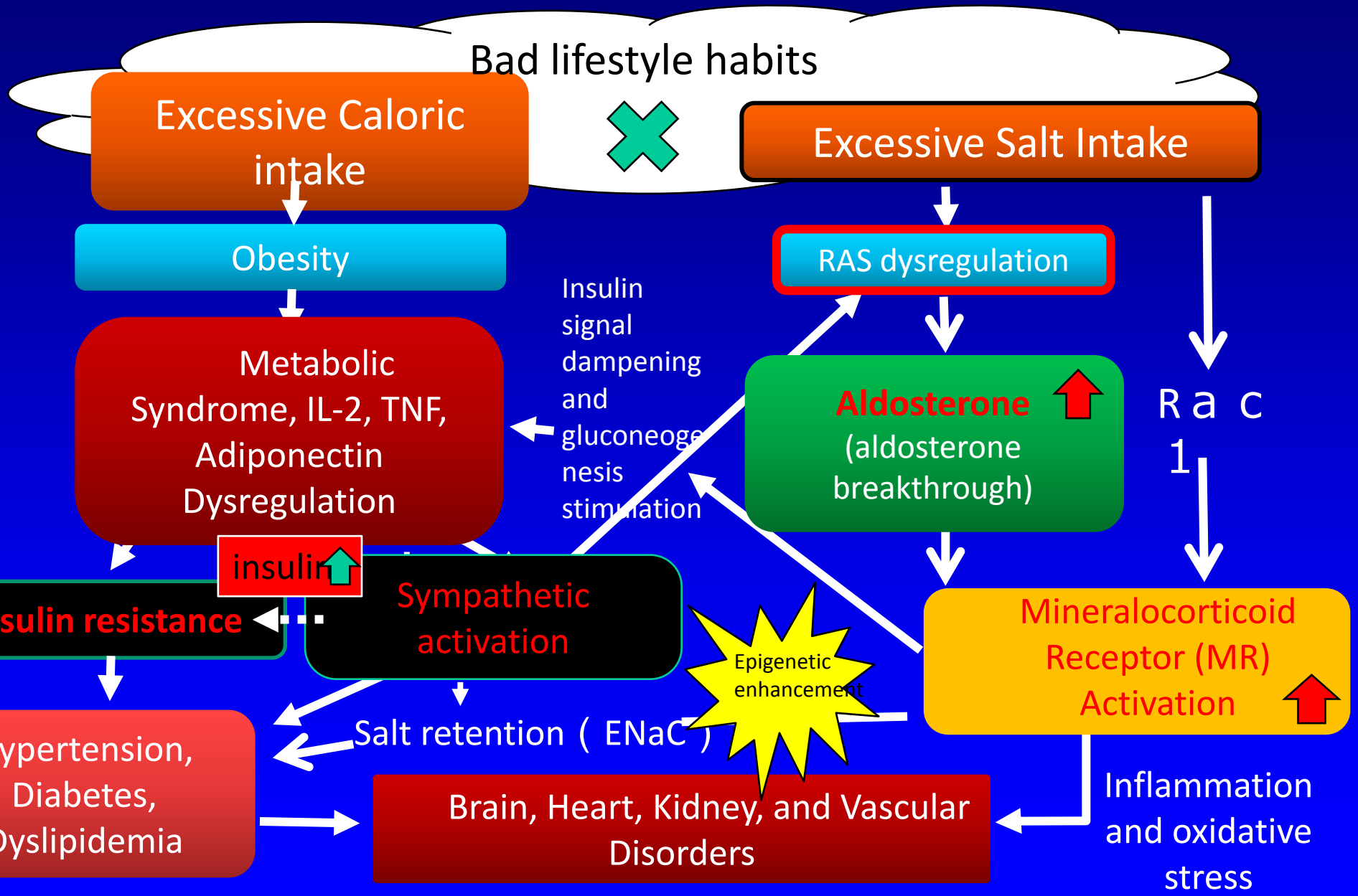




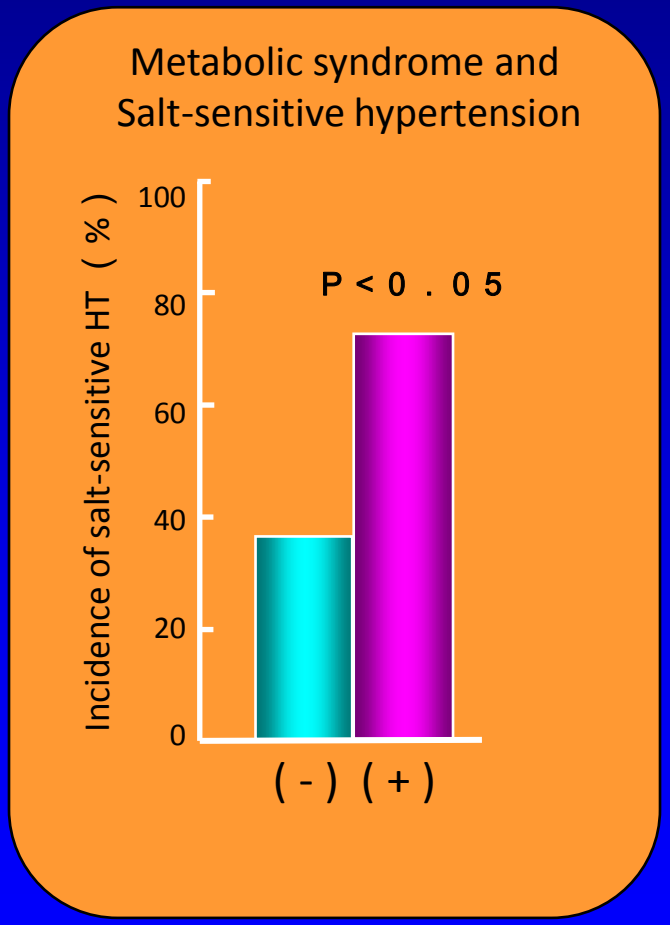
Edited from National survey supervised by Syoukei Kim


Resistant Hypertension
CKD
Stress
Aging
Atherosclerosis
Morbid obesity
Superoxide/AGE
Hyperuricemia
Sarcopenia
Type2 DM
Hypertension
Dyslipidemia
Salty-Metabolic Syndrome
Insulin resistance
Obesity
Salt Addiction
Physical inactivity
Smoking
Cardiometabolic Multimorbidity with Mortality

Salty Metabolic Syndrome out of Control



Character of Japanese Hypertensives
Possibly North-eastern Asians ?

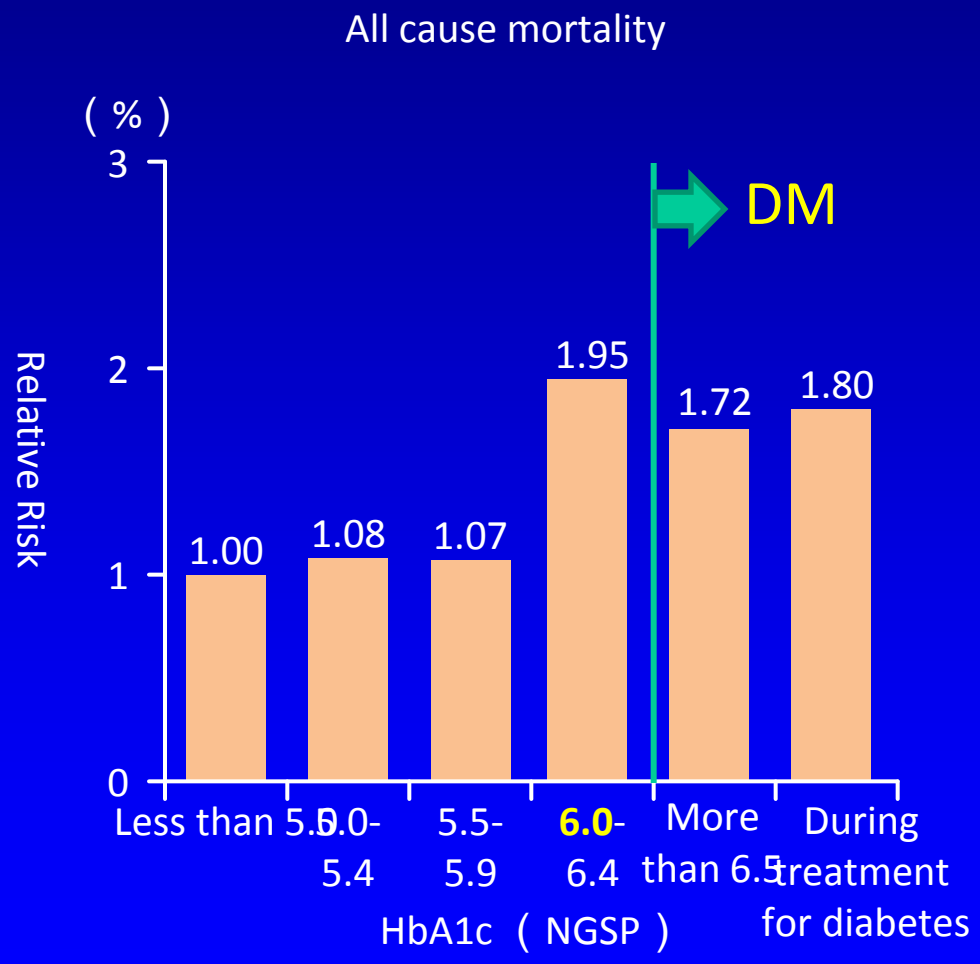


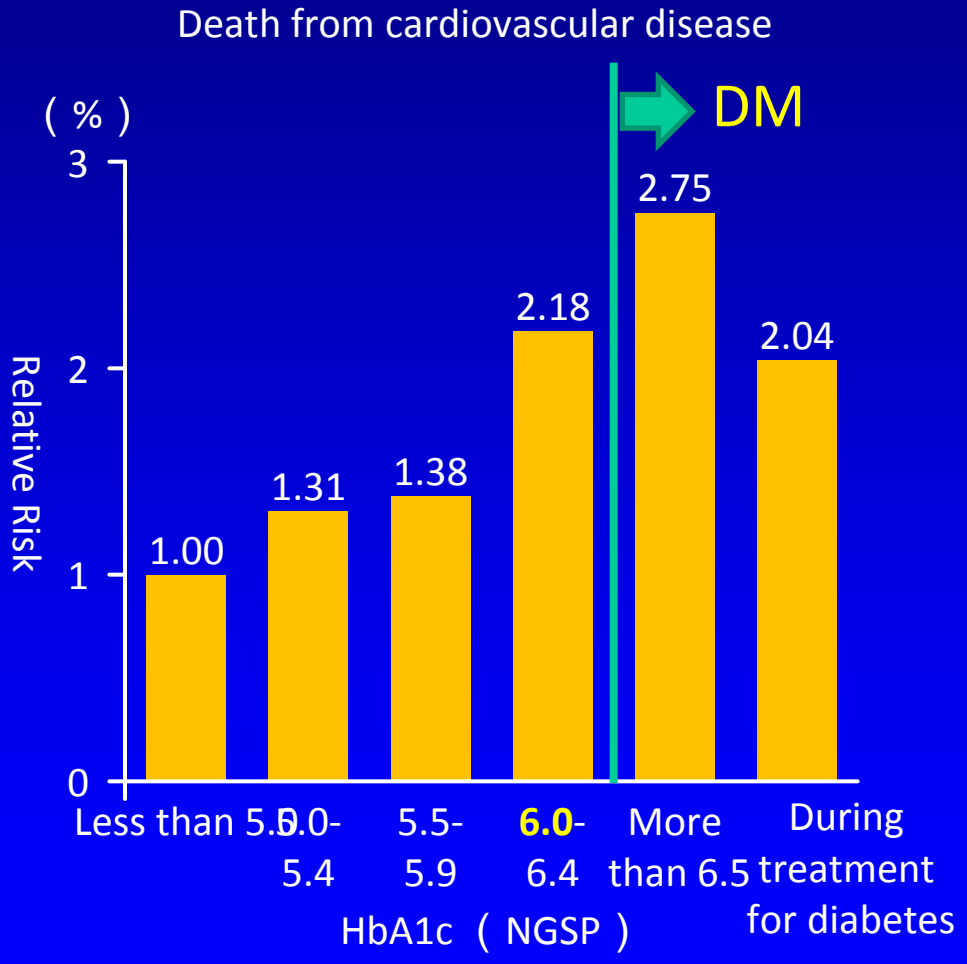
Uzu T, et al, J Hypertension 2006

1. **Stroke - more common than coronary artery disease**
2. **High salt intake with high salt sensitivity (ethnically specific & epigenetic enhancement)**
3. **Epidemic obesity and metabolic syndrome**
4. **Strong insulin-resistance**

The Association between Abnormal Glucose Metabolism (HbA1c) and Death

NIPPON DATA90



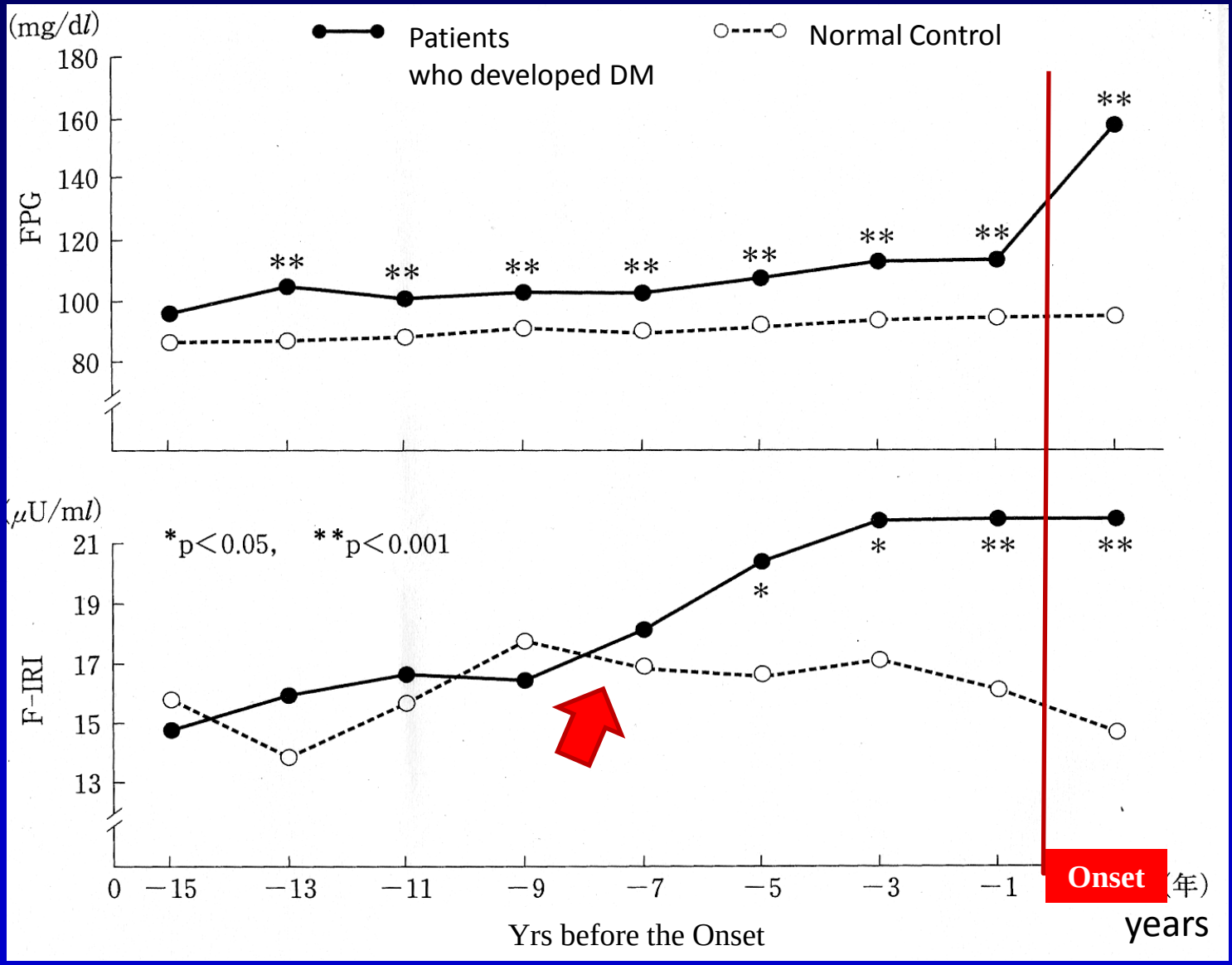


Sakurai M, et al. *Diabetes Care*. 2013; 36: 3759-3765 より作図.

Hyperinsulinemia Precedes Type 2 Diabetes

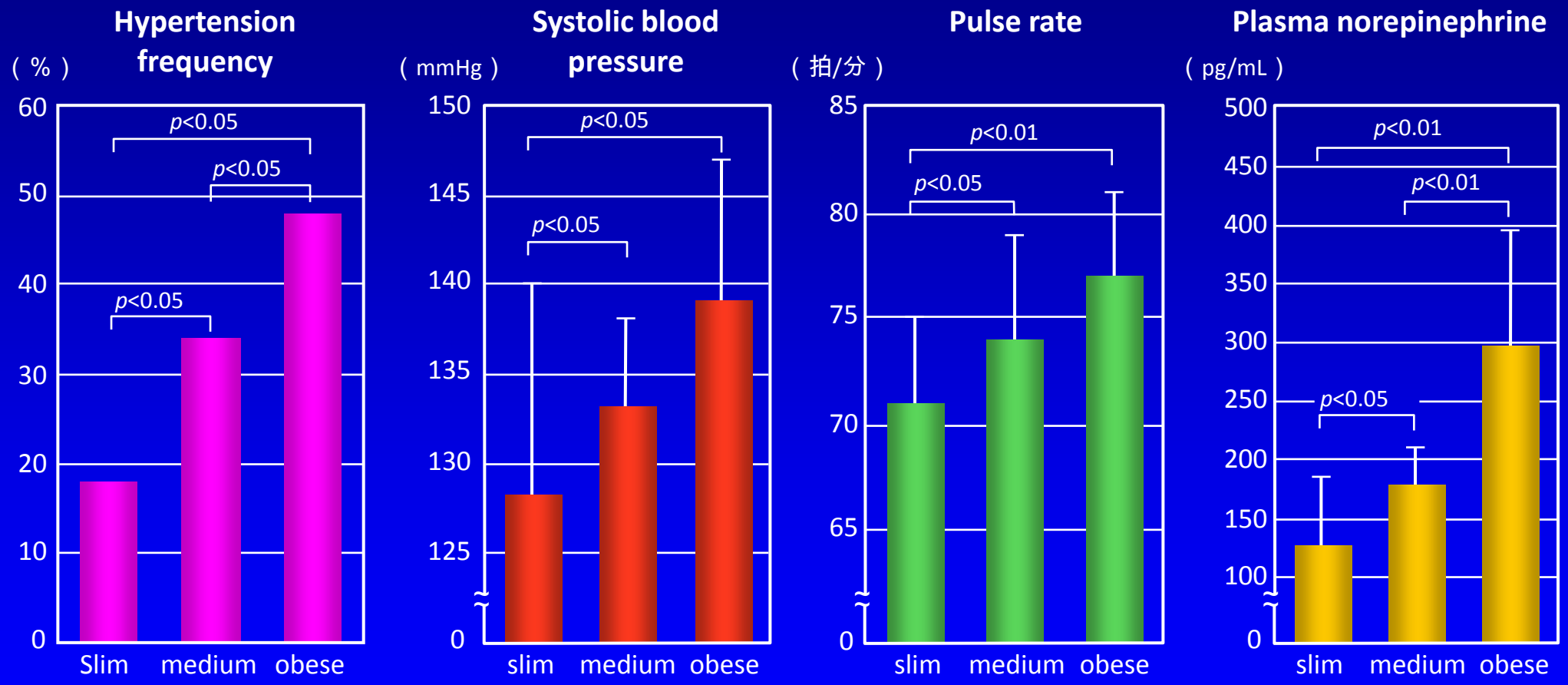
FBS

Fasting insulin level



Chikako Ito, Diabetes Primary Prevention, Diagnosis, and Treatment, 2001

Frequency of Hypertension, Systolic Blood Pressure Pulse Rate, and Plasma Norepinephrine Concentration stratified by BMI group

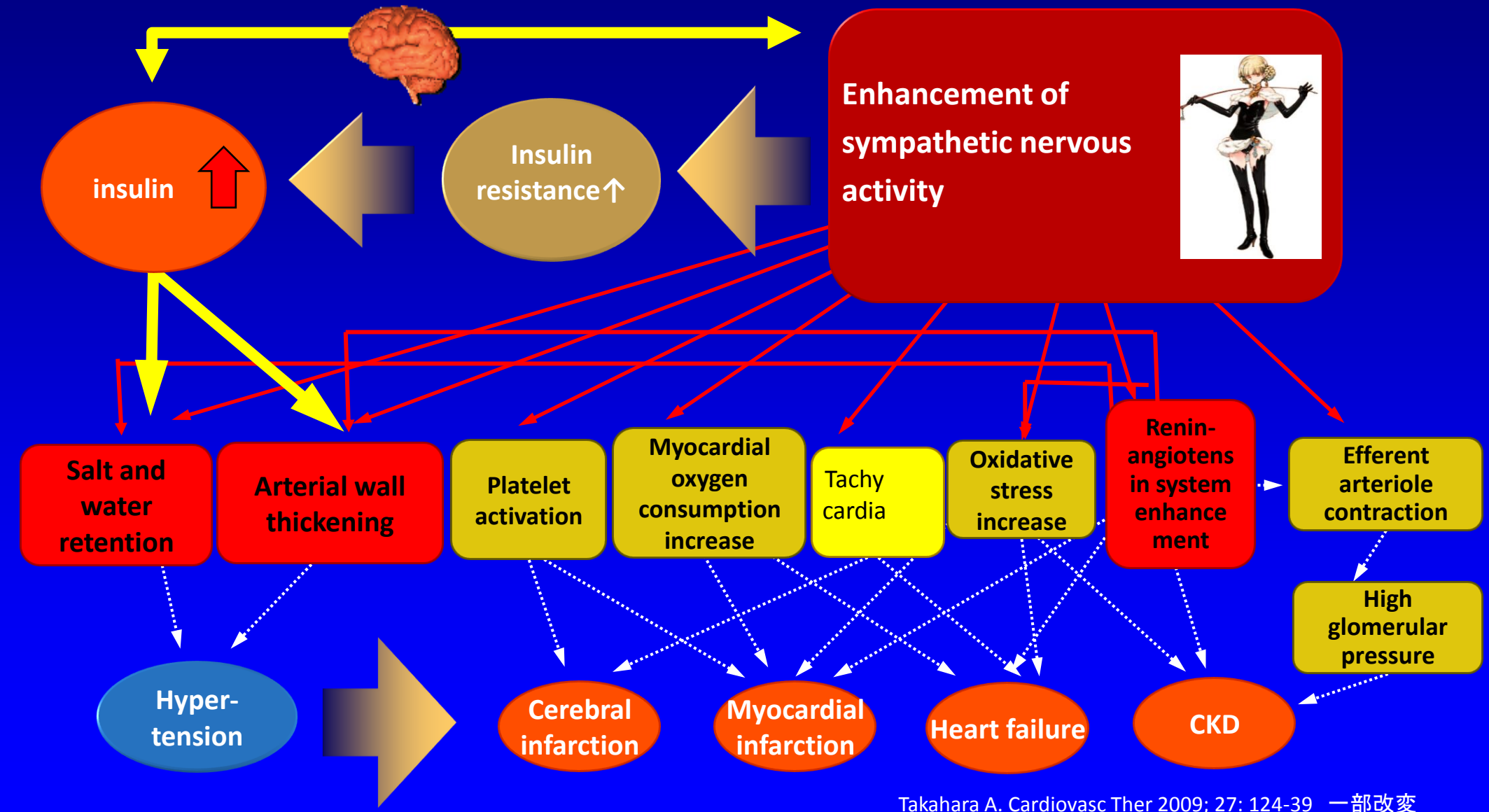


「slim group」（n=101）：BMI 20.1±1.7（kg/m²）［16.5≦＜22.2］
「medium group」（n=725）：BMI 22.5±0.2（kg/m²）［22.2 - 27.9］
「obese group」（n= 86）：BMI 30.0±1.8（kg/m²）［27.9＜≦33.6］

Mean±SD Dunnett's test

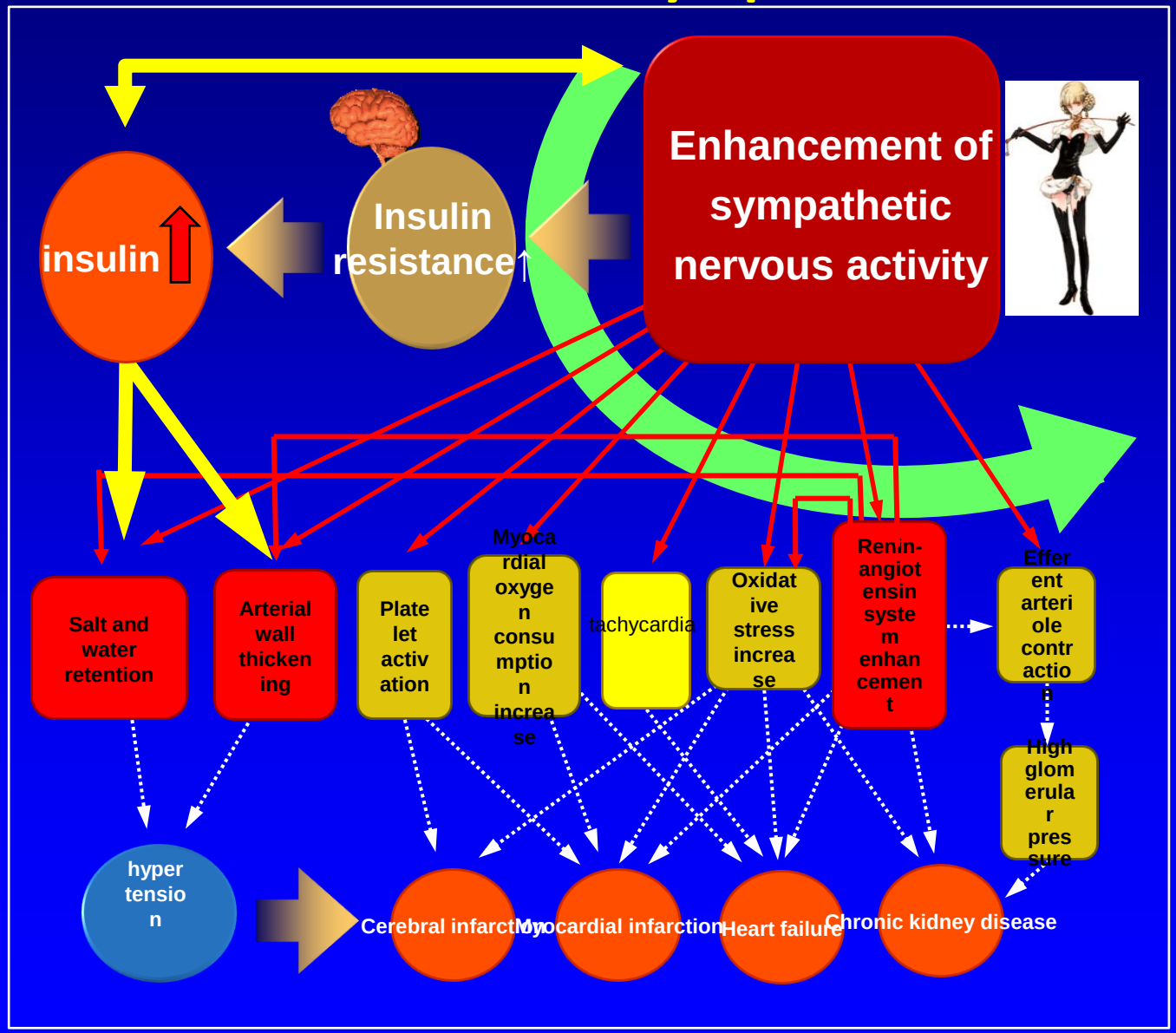
Masuo K, et al. Hypertens Res 2000; 23: 303-10 より作図

Impact on Complications of Hypertension of Enhanced Sympathetic Activity



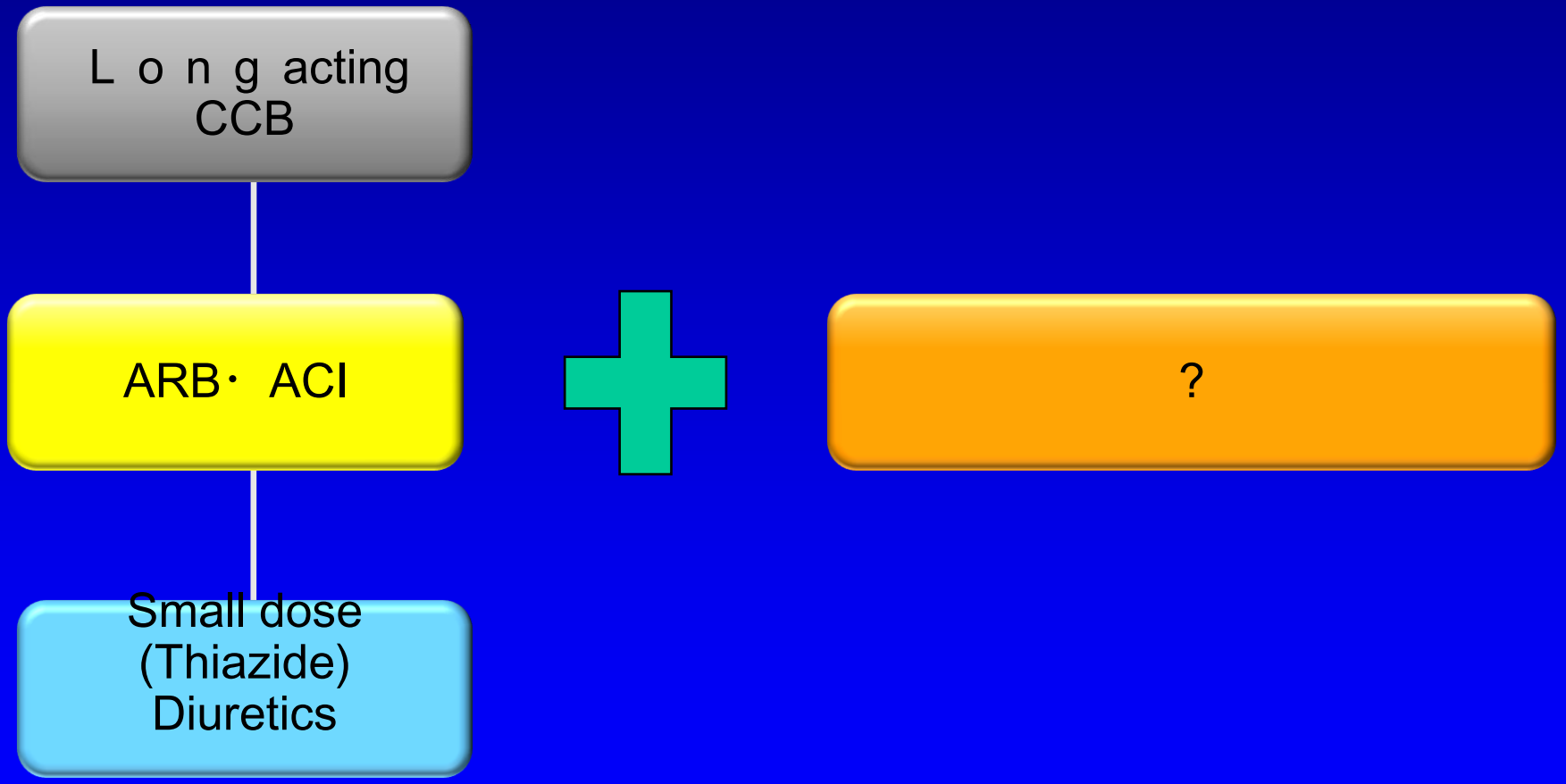
Takahara A. Cardiovasc Ther 2009; 27: 124-39 一部改変

Treatments that Prevent Cardiovascular Death and do not Increase Sympathetic Nervous Activity



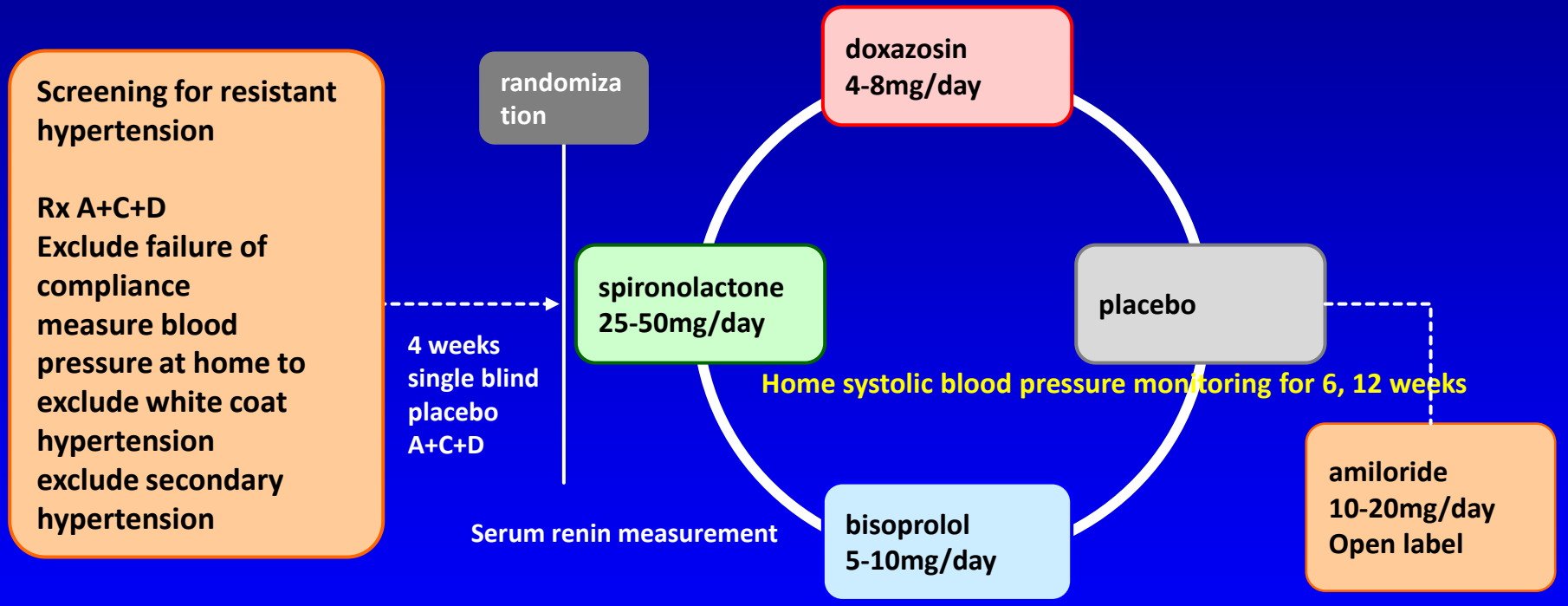
- Beta-blocker with vasodilating action
  i.e., Carvedilol
- Dual cannel CCB
  i.e., cilnidipine
- RA inhibitor
  i.e., ARB, ACI
- SGLT2 inhibitor
  i.e., Empagliflogin

Triple Therapy + 1 More Drug



PATHWAY-2 Study Design

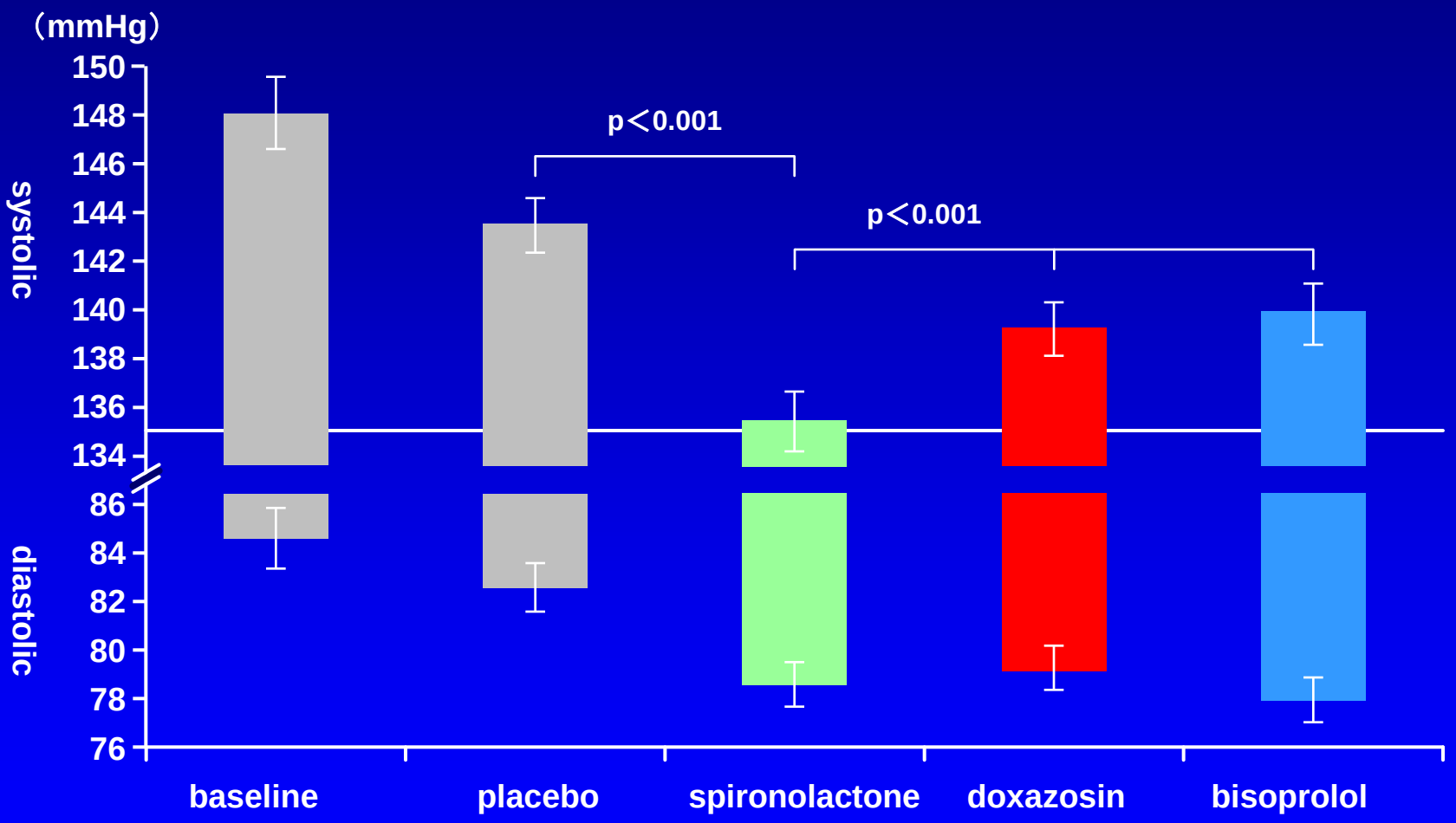
Double blind, randomized, placebo controlled, crossover study



- 1 cycle for 12 weeks
- gradual increase from low dose to high dose
- no washout between cycles

Williams B, et al., Lancet. 2015; 386:2059

Primary Endpoint: Blood Pressure



Williams B, et al., Lancet. 2015; 386:2059

Conclusion

1. Features of high blood pressure in modern Japanese (and perhaps Northeast Asians), including excessive salt intake and obesity, are complex, and also include metabolic disorder.

2. In optimizing antihypertensive therapy, in addition to setting strict targets for reduction (and Dr. Rakugi will discuss this issue afterwards), correction of metabolic abnormalities, such as insulin resistance, must also be kept in mind.

3. For resistant hypertension, in addition to the triple therapy of various antihypertensive drugs, it is important to consider the potential of a hidden increase in aldosterone and to attempt to include an aldosterone antagonist among the treatment protocol.