Treatment of Hypertension

‘ *Metabolic Risk Management* ’

The Metabolic Syndrome in Hypertension

An ESH Position Statement

Redon J et al. J. Hypertens 2008;26:1891

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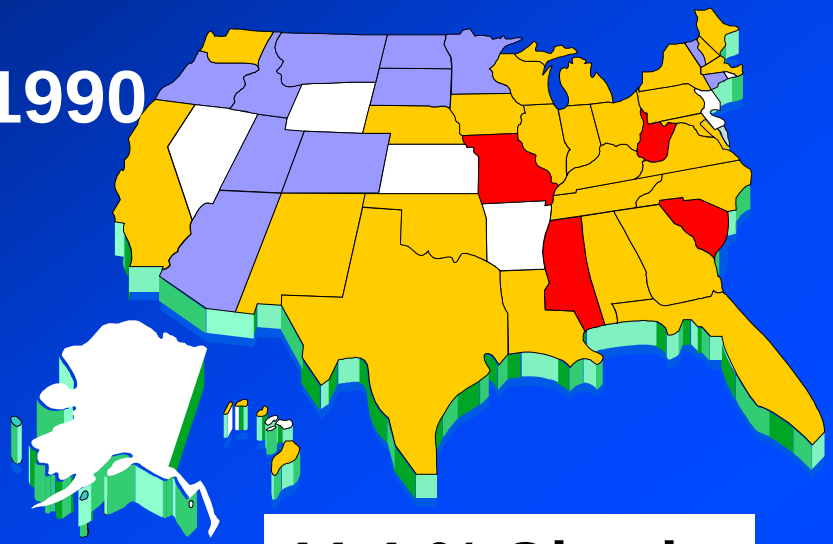
Athens, Greece

Adults With Diagnosed Diabetes*

4.9% DM Prevalence

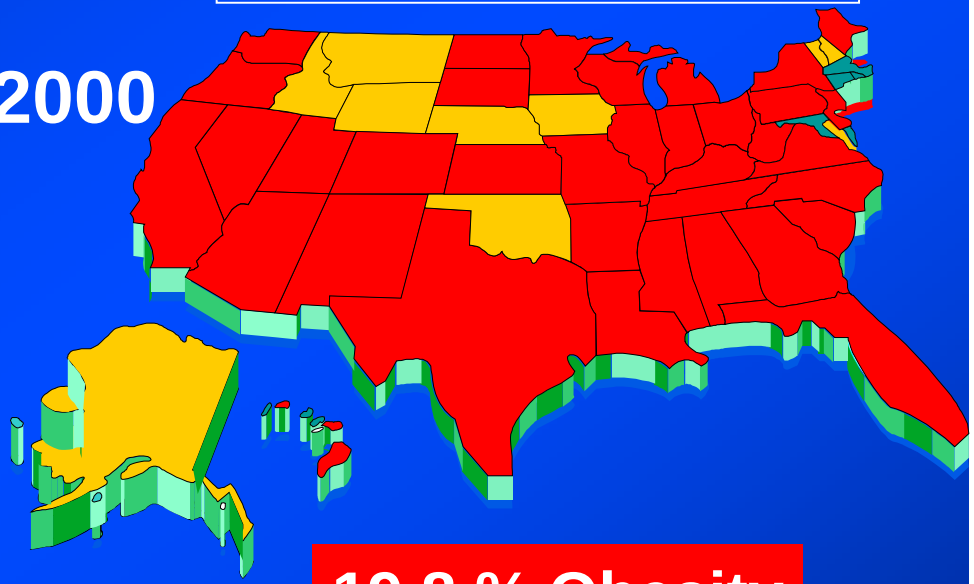
1990



11.1 % Obesity

7.3% DM Prevalence

2000



19.8 % Obesity

No data available

Less than 4 %

4 % - 6 %

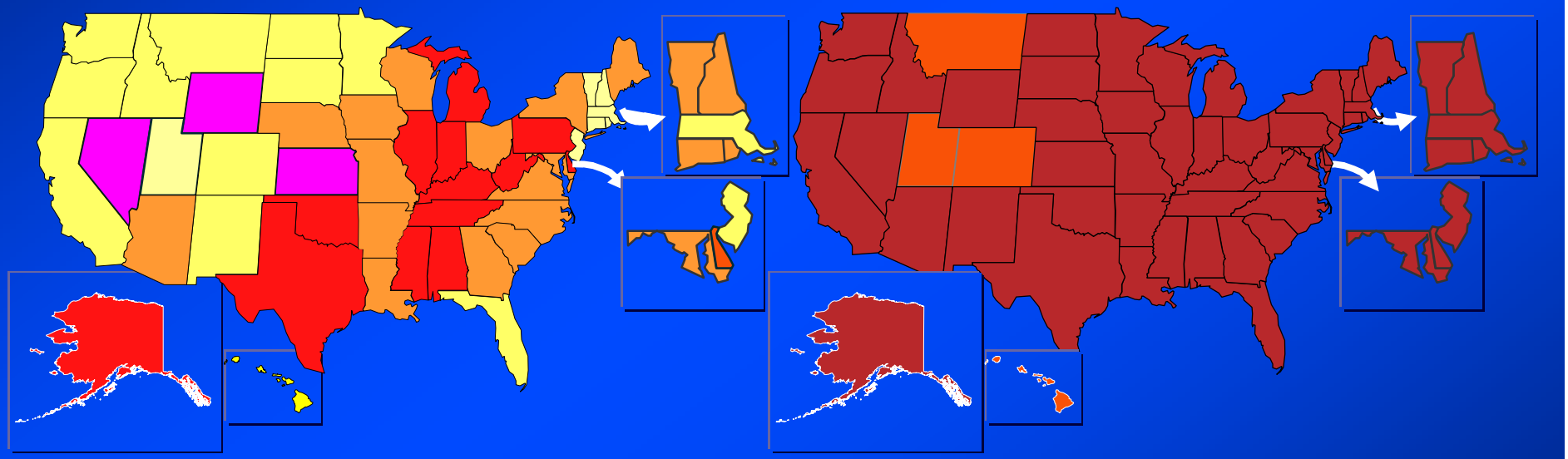
Above 6 %

*Includes women with a history of gestational diabetes.

Mokdad AH, et al. JAMA. 2001;286(10):1195-1200.

Percentage of the US Population With ≥2 Risk Factors*

Risk Factors = High BP, High Cholesterol, Diabetes,† Obesity, Smoking



Percentage of Population With ≥2 Risk Factors

<22% **22.0% to 24.9%** **25.0% to 29.9%** **≥30%** **NA**

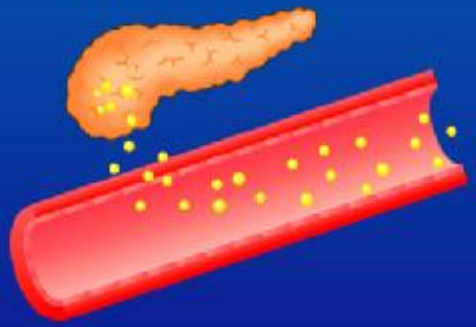
*Risk factors are self-reported. †Diabetes is a CHD risk equivalent.

Greenlund, et al. Arch Intern Med. 2004;164:181–188.
CDC. MMWR Morb Mortal Wkly Rep. 2005;54:113–117.

The Metabolic Syndrome

Reduced glucose tolerance

Hyperinsulinemia



Hypertension

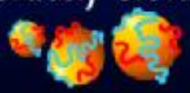
Visceral obesity

Hemostatic disorders

Lipid disorders

- Triglycerides elevated

- LDL-cholesterol normal or moderately elevated



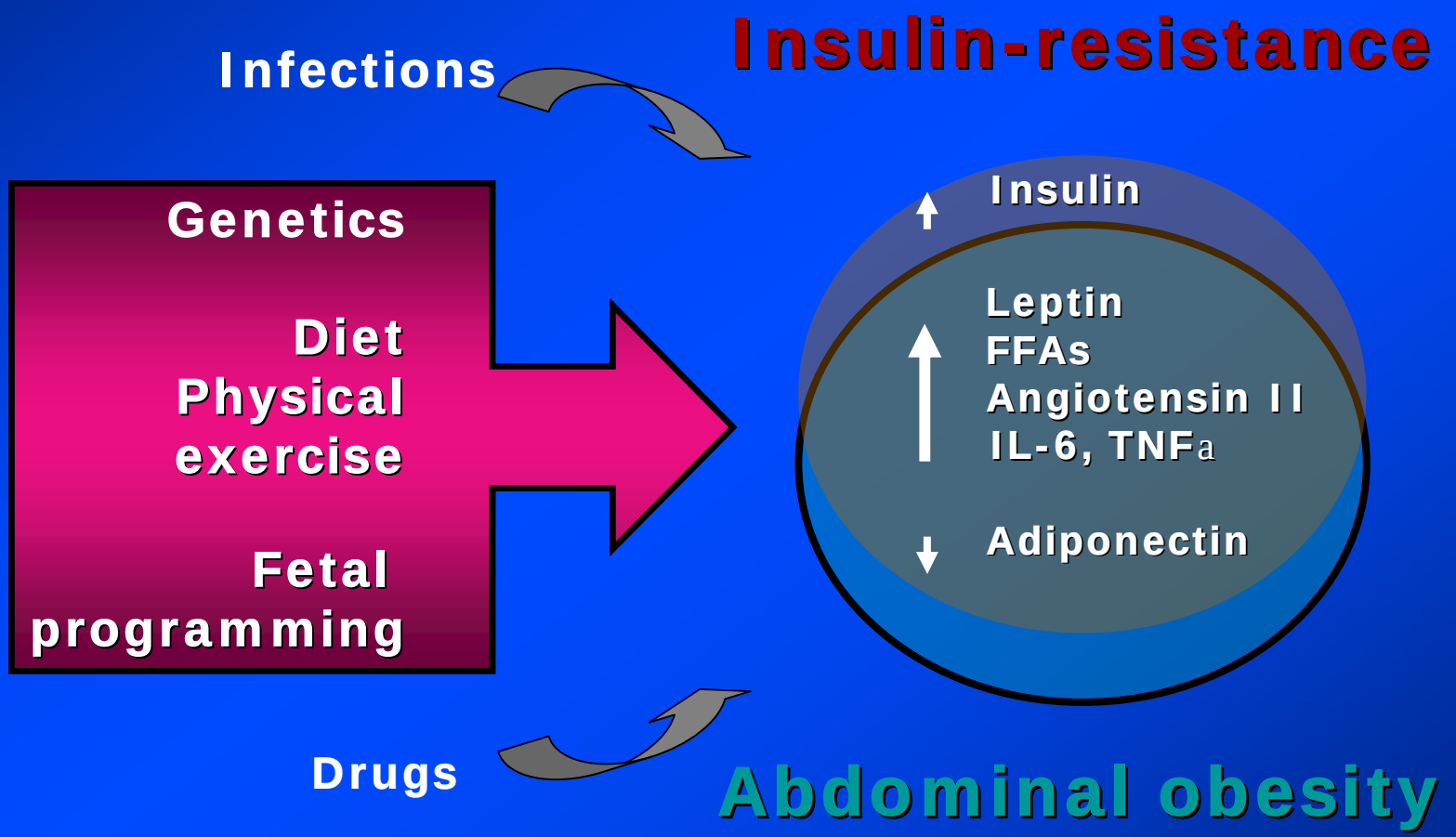
- HDL-C diminished

Definitions of Metabolic Syndrome

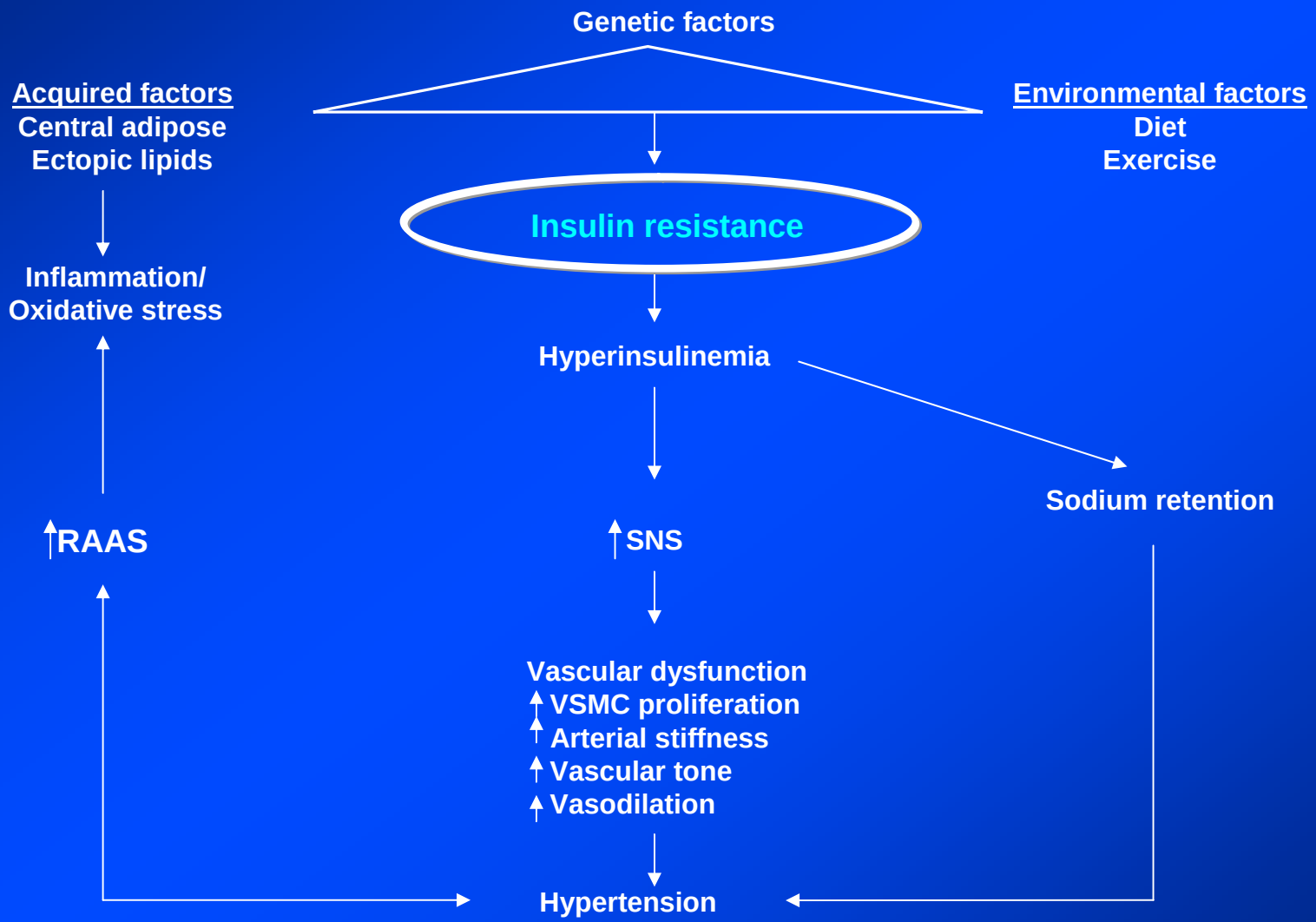
	Principal criteria	Abdominal obesity	Glucose mg/dl	HDL mg/dl	Trigl mg/dl	BP mmHg
WHO	DM, GI or IR	BMI ≥ 30 k/m^2 M ≥ 0.9 W ≥ 0.85		M≤35 W≤39	≥150	≥140/90*
EGIR	IR or FI >P75	BMI ≥ 30 k/m^2 M ≥ 102 cm W ≥ 88 cm	≥110*	40	≥180	≥140/90*
ATPIII		*M ≥ 102 cm* *W ≥ 88 cm*	*≥110**	*M≤40* *W≤50*	*≥150*	*≥135/85**
IDF	Central obesity	M ≥ 94 cm W ≥ 80 cm	≥100*	M≤40 W≤50*	≥150*	≥135/85*
AHA		M ≥ 94 cm W ≥ 80 cm	≥100*	M≤40 W≤50*	≥150*	≥135/85*

Principal + 2 criteria or 3 criteria
**or treatment for*

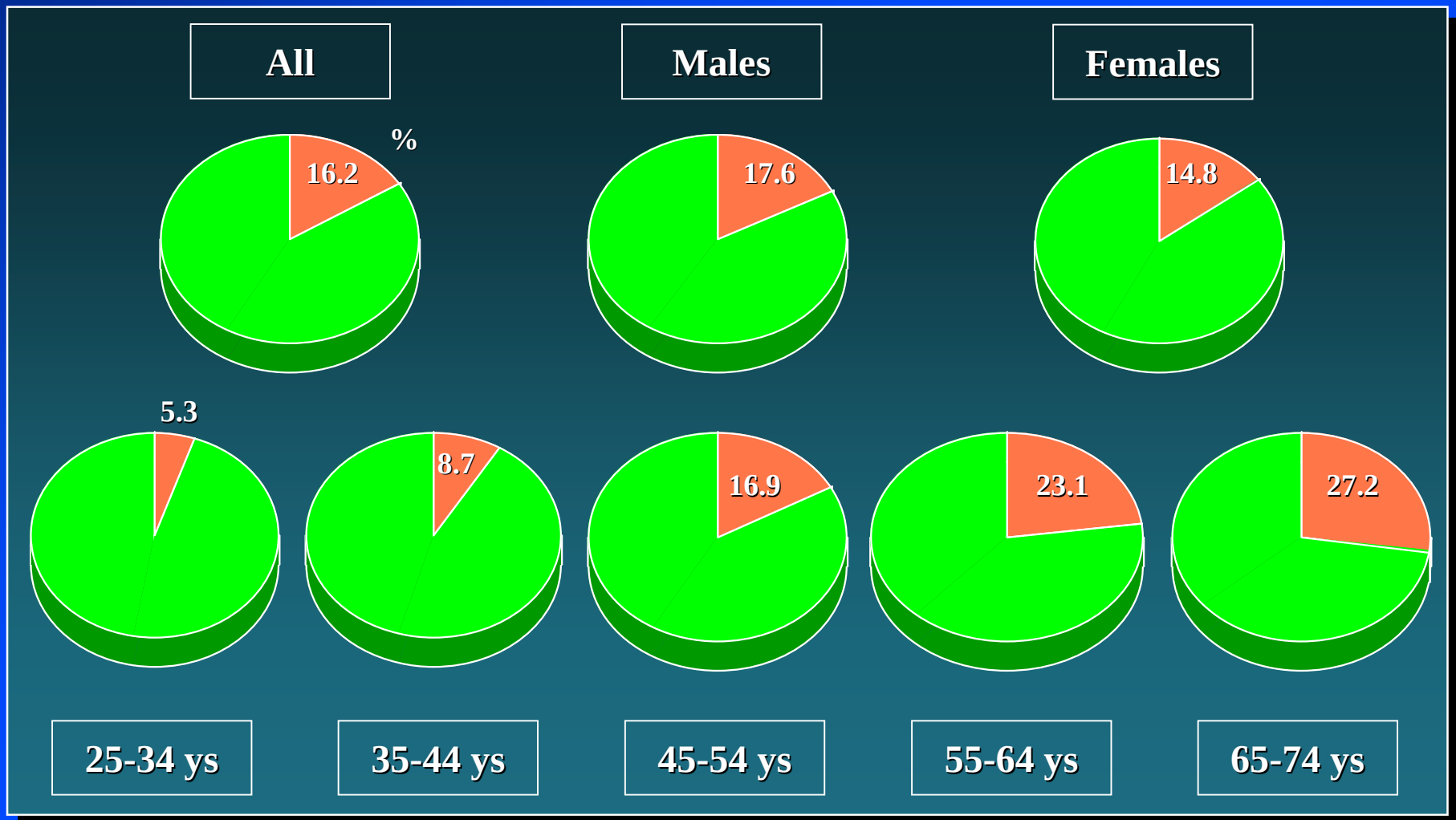
Mechanisms of the Metabolic Syndrome



Insulin Resistance and Hypertension



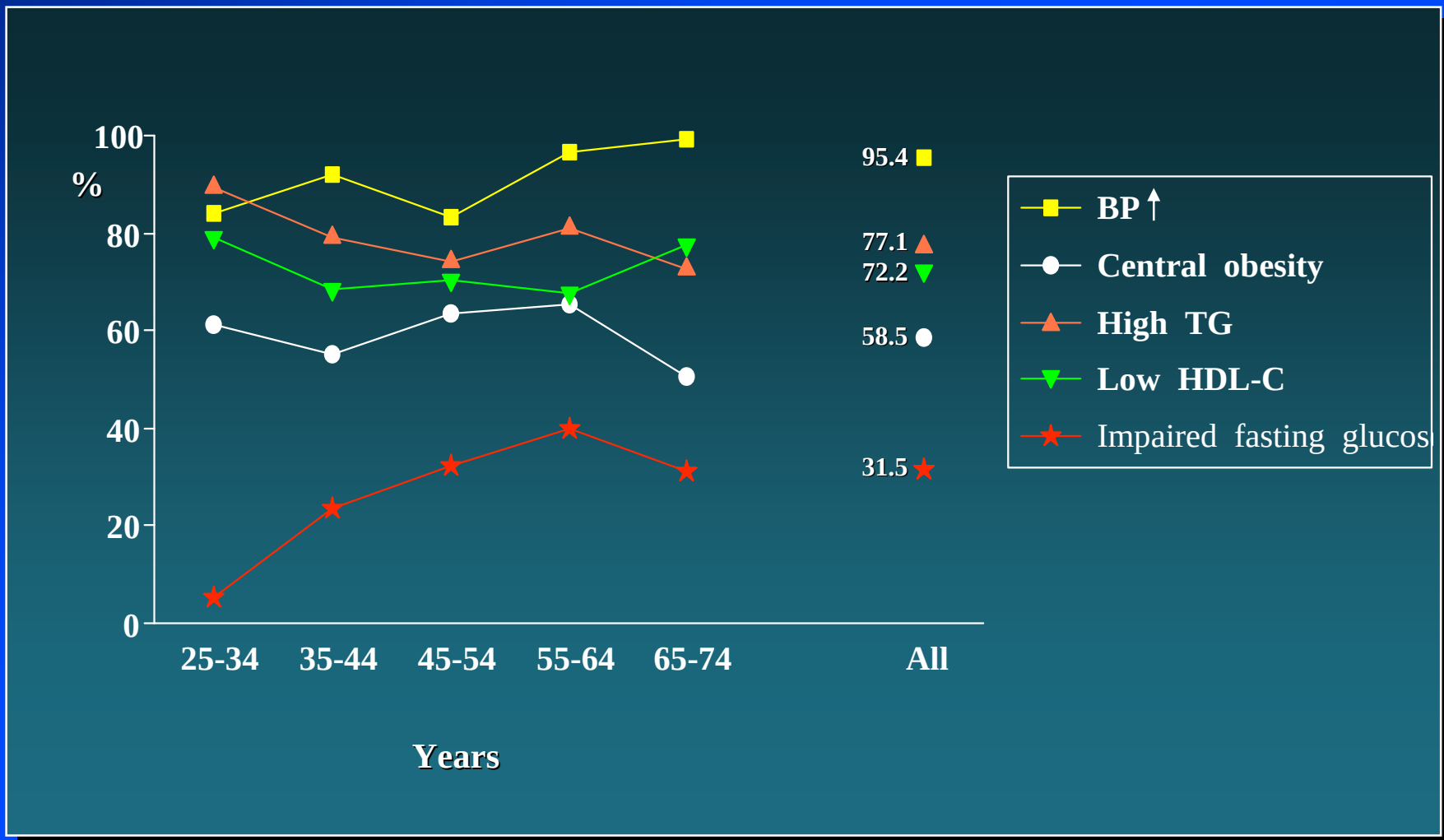
Prevalence of the Metabolic Syndrome in PAMELA



9965 M

Mancia et al., Hypertension 2006; 49: 40-47

Prevalence of Various Components of MS + in Subjects from PAMELA



9966 M

Mancia et al., Hypertension 2006; 49: 40-47

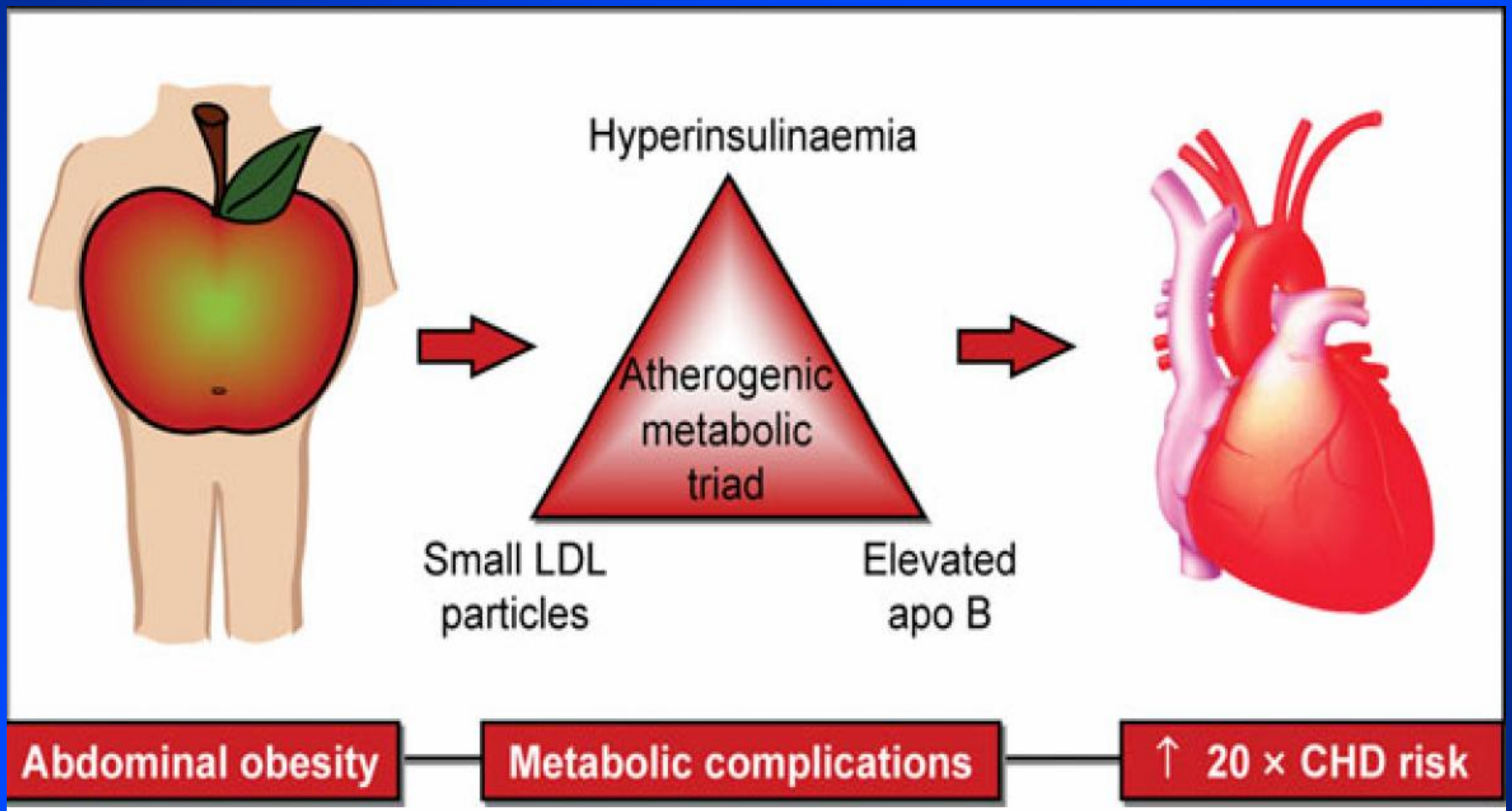
Impact of Lifestyle Habits on the Prevalence of the MS among Greek Adults from the ATTICA Study

Distribution of the components of the MS in the population study by sex

	Males	Females
Waist circumference (>102 or 88 cm)	359 (31.8)	343 (29.7)
TG levels >150 mg/dL	320 (28.4)	146 (12.7) *
HDL < 40 mg/dL	424 (37.6)	432 (37.4)
Blood pressure >130/85 mm Hg	494 (43.7)	403 (34.9) *
Fasting blood glucose `>110 mg/dL	160 (14.2)	89 (7.7) *

Panagiotakos D. et al. Am Heart J 2004

From individual RF and the metabolic syndrome to global cardiometabolic risk

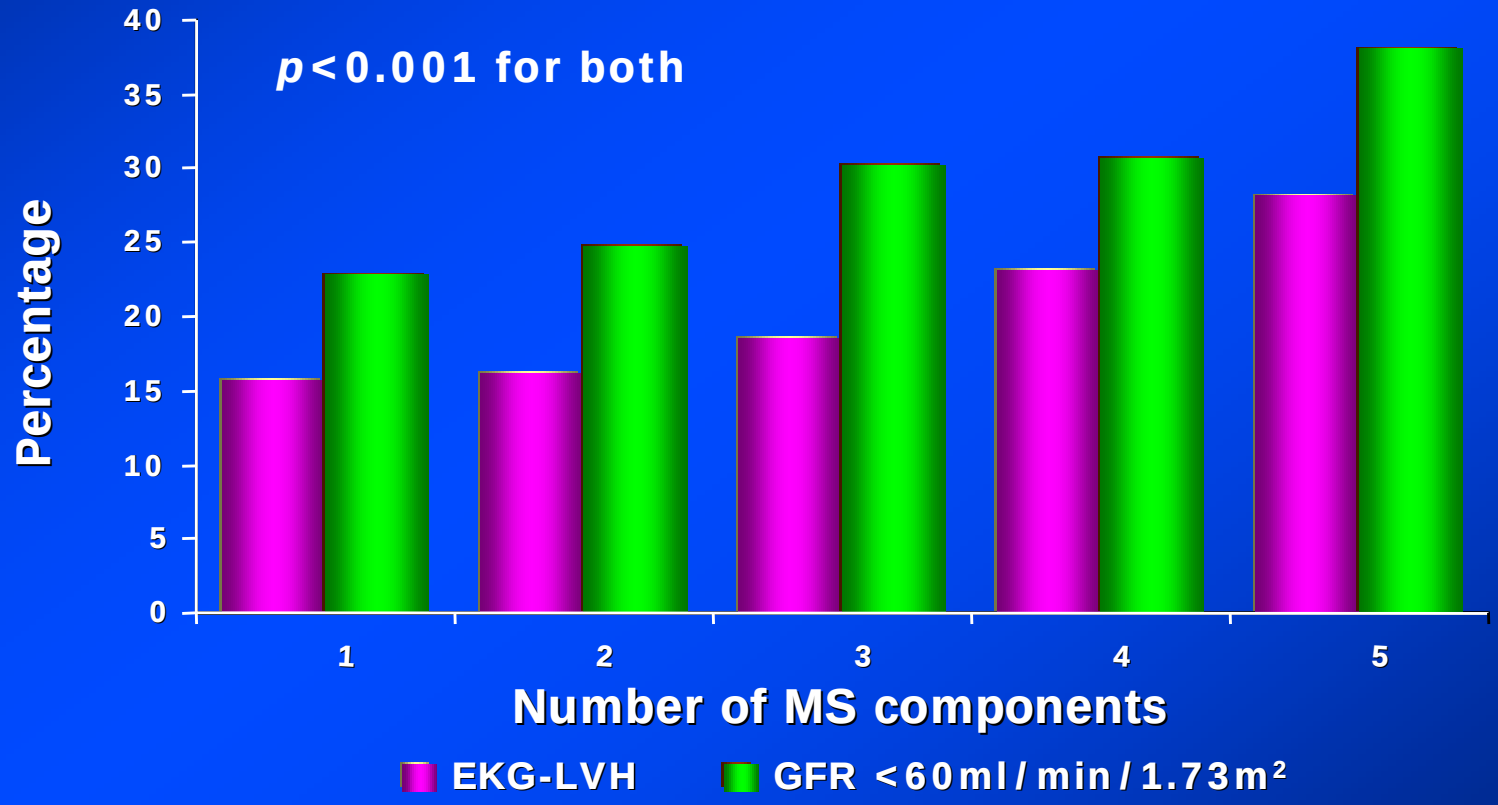


Despres JP et al. Eur Heart J 2008

Number of Metabolic Syndrome components and organ damage

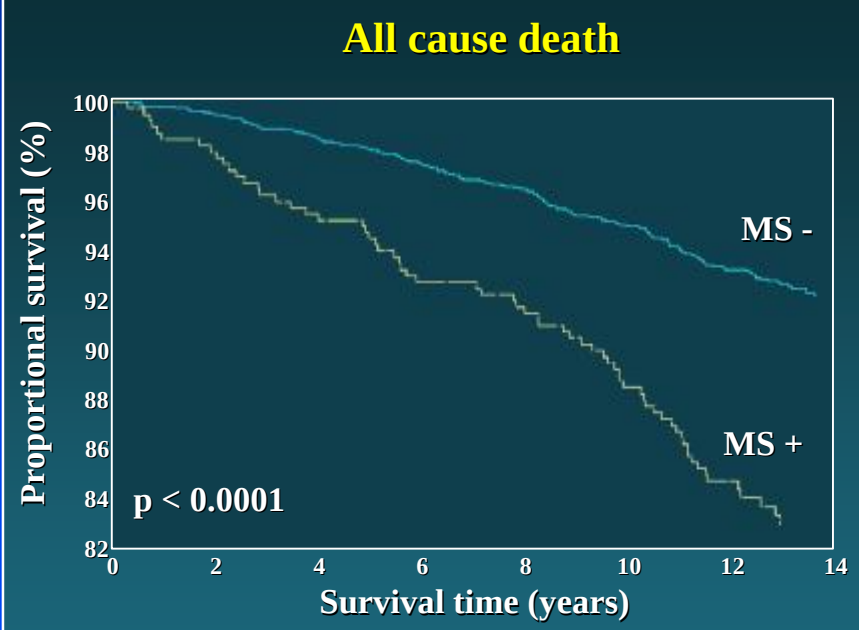
8331 hypertensives, >54 yrs, from Primary Care

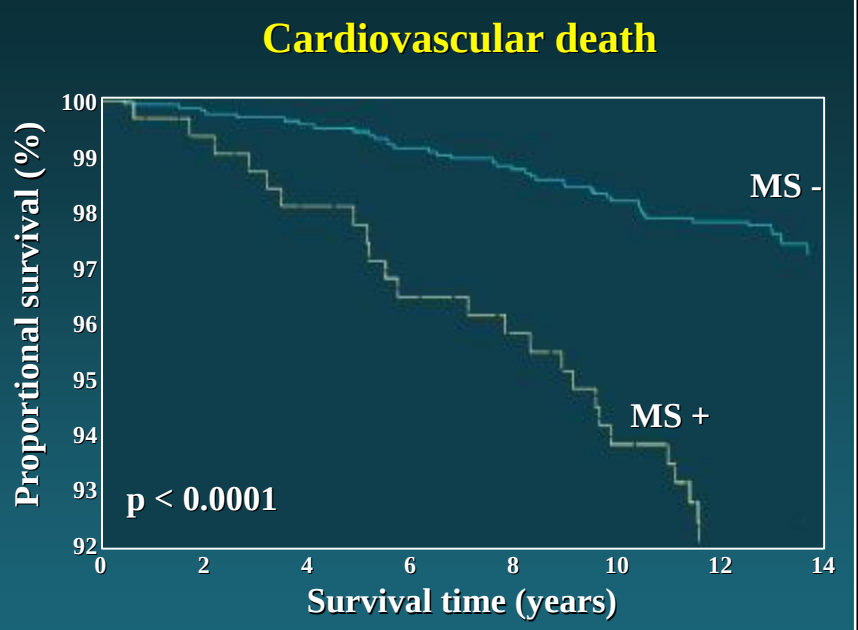
ATPIII criteria



Navarro, Redon et al. Blood Pressure 2007

Kaplan-Meier Survival Curves for CV Death and All Cause Death in Subjects Without and With Metabolic Syndrome





11064 M

Mancia et al., Hypertension 2007; 49: 40-47

ESH/ESC Guidelines
Stratification of CV Risk in Four Categories

Other Risk Factors, OD or Disease	Normal SBP 120-129 or DBP 80-84	High Normal SBP 130-139 or DBP 85-89	Grade 1 HT SBP 140-159 or DBP 90-99	Grade 2 HT SBP 160-179 or DBP 100-109	Grade 3 HT SBP ≥ 180 or DBP ≥ 110
No other risk factors	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
1-2 risk factors	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
3 or more Risk Factors, MS, OD or Diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
Established CV or renal disease	Very high added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk

<10%	10-15%	15-20%	20-30%	>30%
	< 4%	4-5%	5-8%	>8%

Cardiovascular event rate in 10 years

Risk for cardiovascular death in 10 years (SCORE)

ESH/ESC Guidelines and Search for Subclinical Organ Damage (OD)

2007 GLs

Routine

- - SCr (> 1.4-1.5 mg/dl)
- ¯ eCrCl / GFR
- MA / Proteinuria
- EKG †

Recommended

- LVH (Echo)
- Concentric LVH
- LA enlargement
- CA thickening / plaques
- Ankle/Brachial ratio
- Arterial stiffening (PWV)*

→

- Search for multiorgan D
- OD (MA / EKG / echo) to be assessed also during treatment

* Depending on availability / also shown by high SBP / low DBP

† LVH / MI-ischemia / Arrhythmias

What Do You Want Your Levels To Be?

- Blood pressure
- LDL cholesterol
- Haemoglobin A1c

Goals of hypertension treatment in the Metabolic Syndrome

- Threshold to define: 130/85 mmHg
- BP ≥140/90 mmHg (≥130/80 mmHg if diabetes) requires antihypertensive treatment
- Goal: <130/80 mmHg

Lipid Targets Continue to Evolve: Treatment Goals and New Therapeutic Options

Risk Level	NCEP ATP III LDL-C Goal (mg/dL)	NCEP ATP III Update LDL-C Goal (mg/dL)
Very high risk*: CHD† or CHD risk equivalents‡		<70 (Therapeutic option)
High risk: CHD† or CHD risk equivalents‡, 10-year risk>20%	*<100*	*<100*
Moderately high risk: 2+ risk factors, 10-year risk 10% to 20%		<130 (Therapeutic option: <100)
Moderate risk: 2+ risk factors, 10-year risk <10%	<130 (Optimal level: <100)	<130
Lower risk: 0-1 risk factor	<160 (Optimal level: <100)	<160

- NCEP ATP III Update: In moderate- or high-risk patients, lipid-lowering therapy should result in at least a 30% to 40% reduction in LDL-C
- Identify major risk factors (exclusive of LDL-C) that may modify lipid goals

*For example, patients with established CVD plus multiple major risk factors (especially diabetes) have an optional goal of <70 mg/dL; †CHD includes history of MI, stable or unstable angina, coronary artery procedures, or evidence of clinically significant myocardial ischemia; ‡CHD risk equivalent includes diabetes, noncoronary forms of atherosclerotic disease, and 2+ risk factors with 10-year risk of CHD >20%.

Grundy SM et al, for the Coordinating Committee of the National Cholesterol Education Program. Circulation. 2004;110:227-239.

TARGETS IN HYPERTENSION AND DIABETES MELLITUS

- **Aggressive EARLY attainment of known risk factors for CV/renal risk (BP <130, *glucose-HbA1c<7%,* lipids-<70?) reduce risk.**
- **Once established nephropathy (eGFR <60 ml/min)-BP <140 is appropriate to reduce risk-pending ACCORD)-Proteinuria>300 mg/day BP should be <130**

2007 ESH/ESC Guidelines
Lifestyle Changes in MS

Modest ¯ of caloric intake

- ¯ Saturated fat < 7%
- ¯ Transfatty acids
- ¯ Cholesterol <200 mg
- ¯ Simple carbohydrates 50%
- - Fruit / vegetables
- - Whole grain

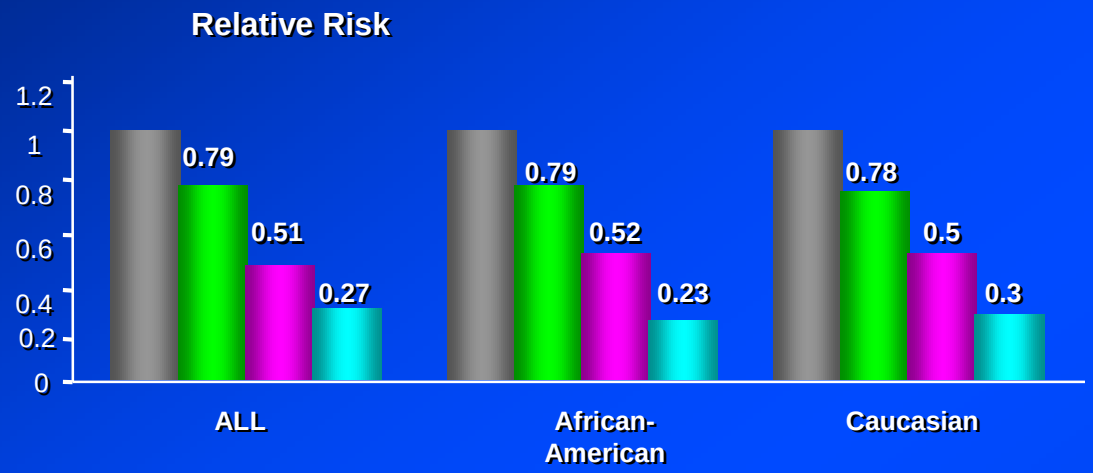
- - Physical exercise
- 30 min daily of moderate exercise

At least 7-10% ¯ BW in 6-12 months

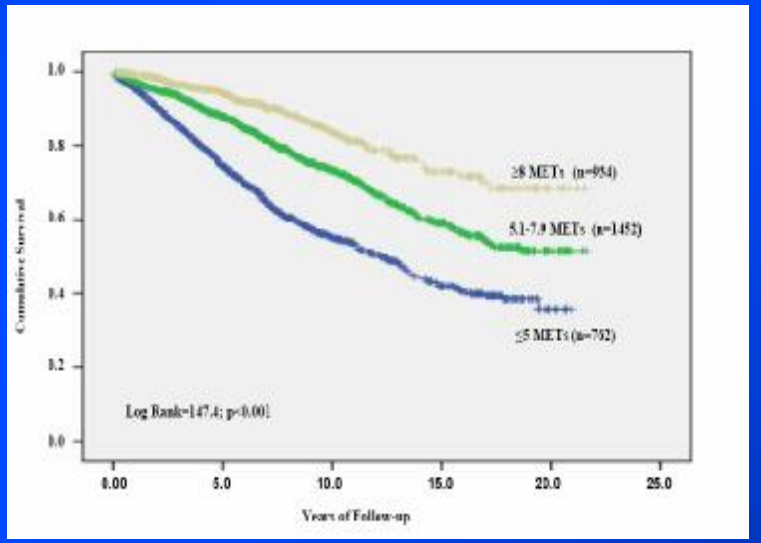
Marked reduction (~60%) of NOD
Marked reduction (~40-50%) of MS prevalence

Exercise Capacity and Mortality in Black and White Men, in Diabetics, Prehypertensives, and High Risk

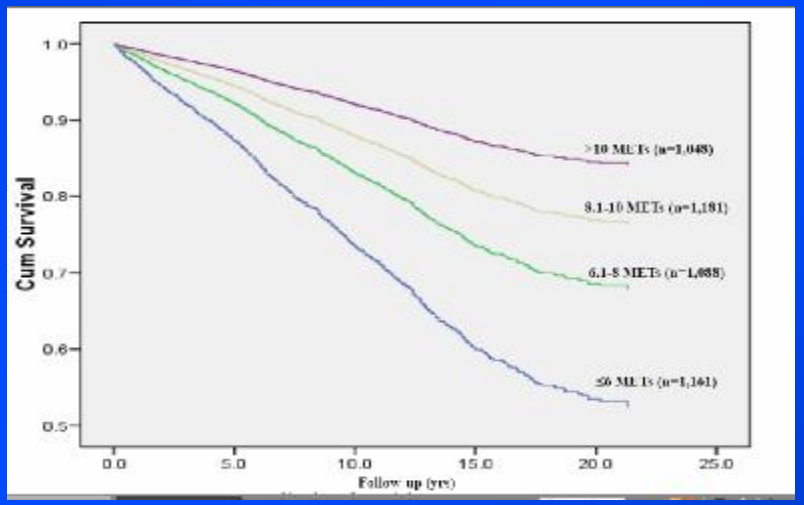
RR of all cause mortality in individuals with no CVD



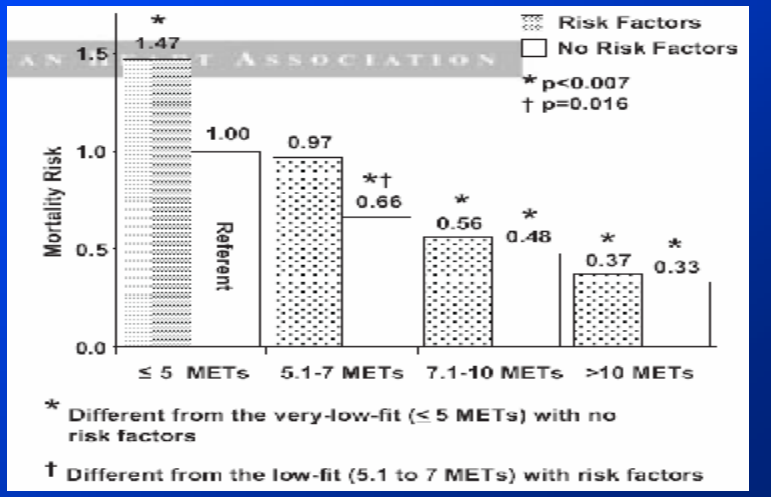
Kokkinos P, Pittaras A, Manolis AJ et al. Circulation 2008



Kokkinos P, Pittaras A, Manolis AJ et al. Diabetes Care 2009

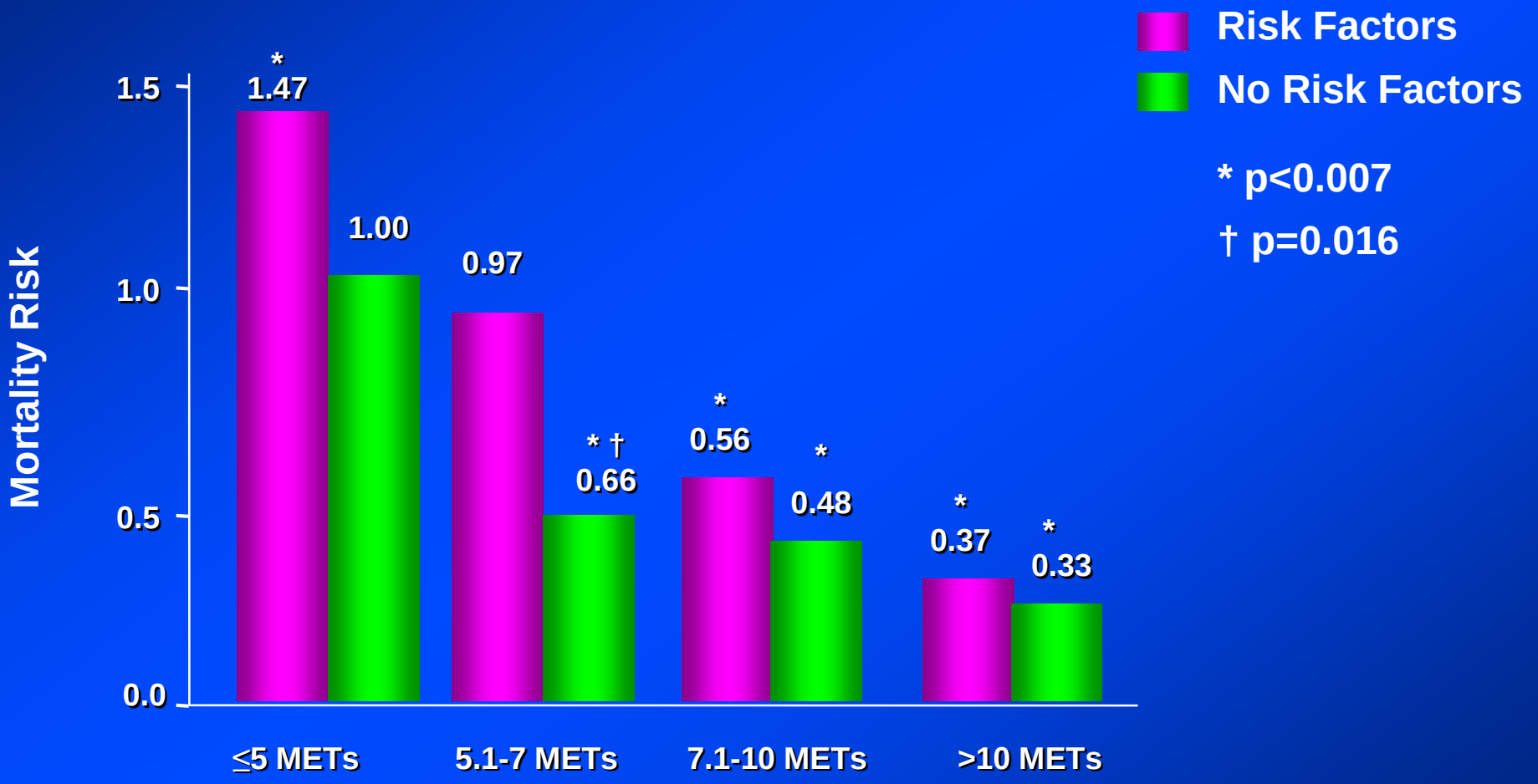


Kokkinos P, Pittaras A, Manolis AJ et al. Am J Hypertens. 2009



Kokkinos P, Pittaras A, Manolis AJ et al. Hypertension2009

Exercise capacity and Mortality in Hypertensive Men With and Without Cardiovascular Risk Factors



* Different from the very-low-fit (≤ 5 Mets) with no risk factors

† Different from the low-fit (5.1 to 7 METs) with risk factors

Kokkinos P, A. Pittaras, Manolis AJ et al. Hypertension 2009;53

2007 ESH/ESC Hypertension Guidelines
First Choice Drug Treatment

- Diuretics
- ACE-inhibitors
- Calcium antagonists
- Angiotensin receptor antagonists
- Beta-blockers

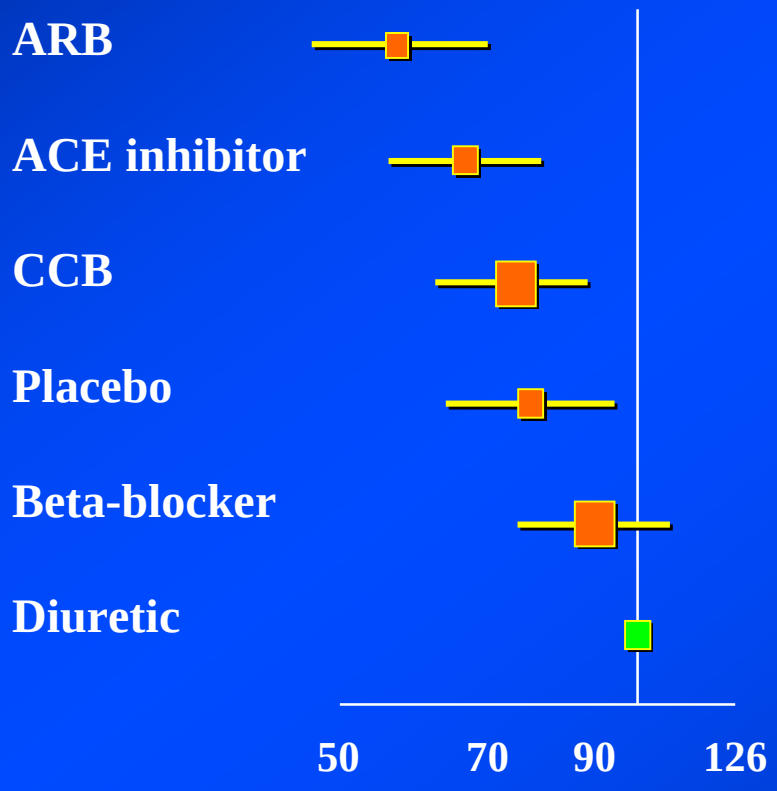
Ideal Antihypertensive in the Patient With Metabolic Syndrome

- Does not worsen — Insulin resistance
- Does not cause
  - Hyperglycemia
  - New-onset diabetes
  - Dyslipidemia
- Protects kidney and heart

What are the effects of antihypertensive drugs on insulin sensitivity?

Drugs	Insulin sensitivity	
Diuretics	↓	(except celiprolol, carvedilol, nebivolol)
Β-blockers	↓	(Diltiazem ↓ or ~)
CCB's	↑	
ACE-I	↑	
ARB's	↑	

Results of a Meta-analysis for Incident Diabetes - Twenty-two Clinical Trials of 143,153 Hypertensive Patients



0.57 (0.46-0.72) p < 0.0001

0.67 (0.56-0.80) p < 0.0001

0.75 (0.62-0.90) p = 0.002

0.77 (0.63-0.94) p = 0.009

0.90 (0.75-1.09) p = 0.30

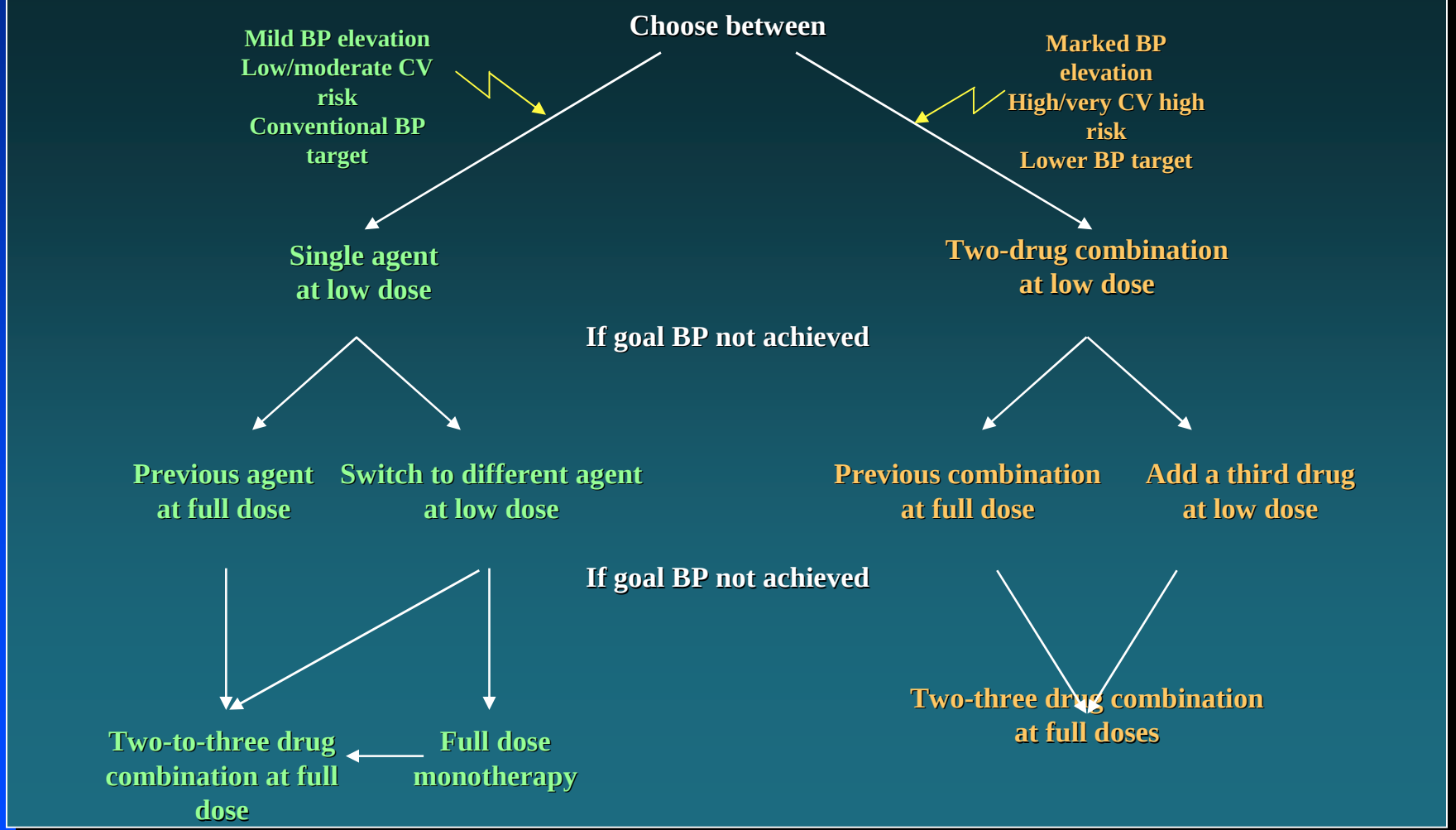
Referent

Incoherence = 0.000017

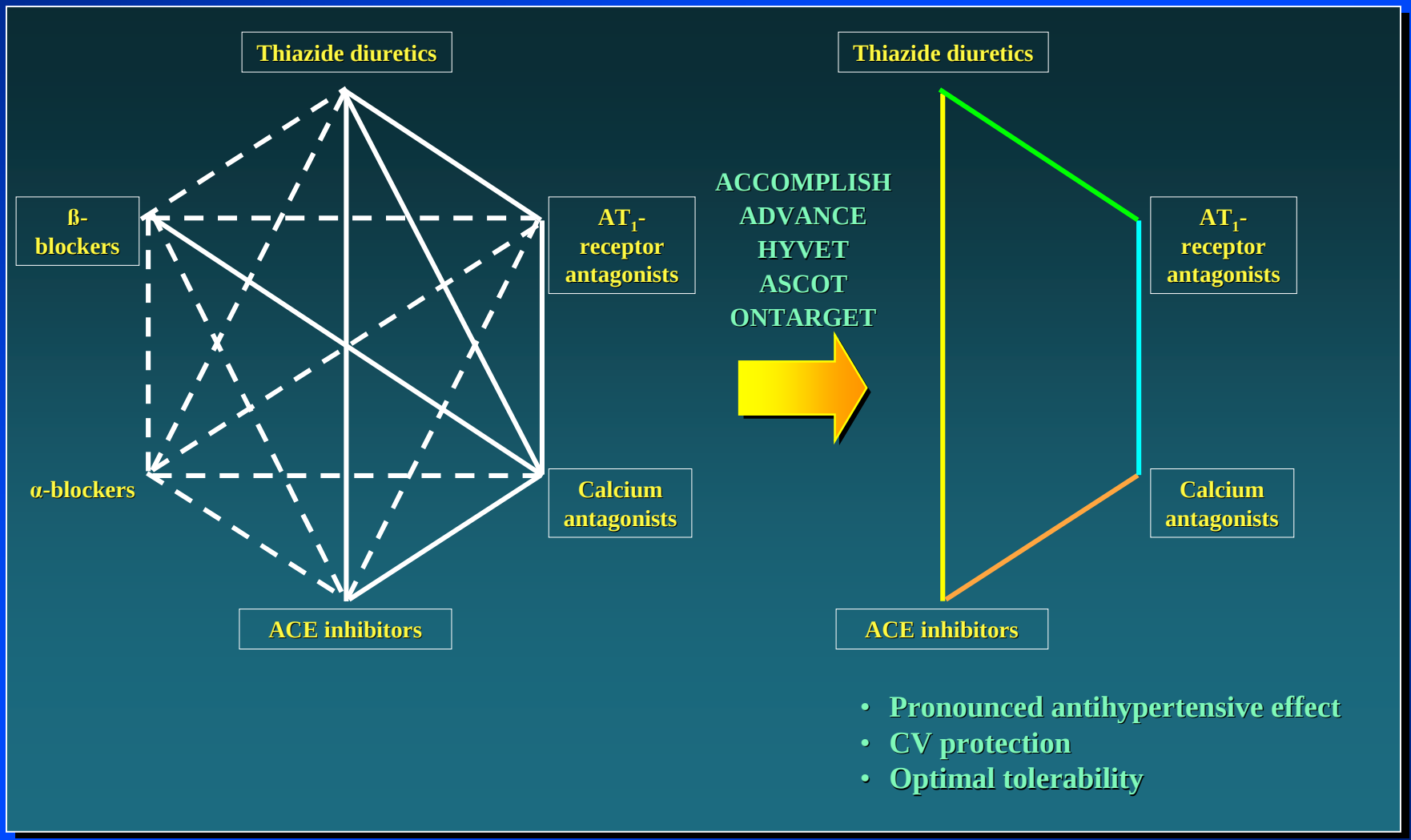
Elliott WJ, Lancet 2007; 369: 201

2007 ESH/ESC Guidelines

Monotherapy versus Combination Therapy Strategies



2007 ESH/ESC Guidelines
Combinations between Some Classes of Antihypertensive Drugs



- Pronounced antihypertensive effect
- CV protection
- Optimal tolerability

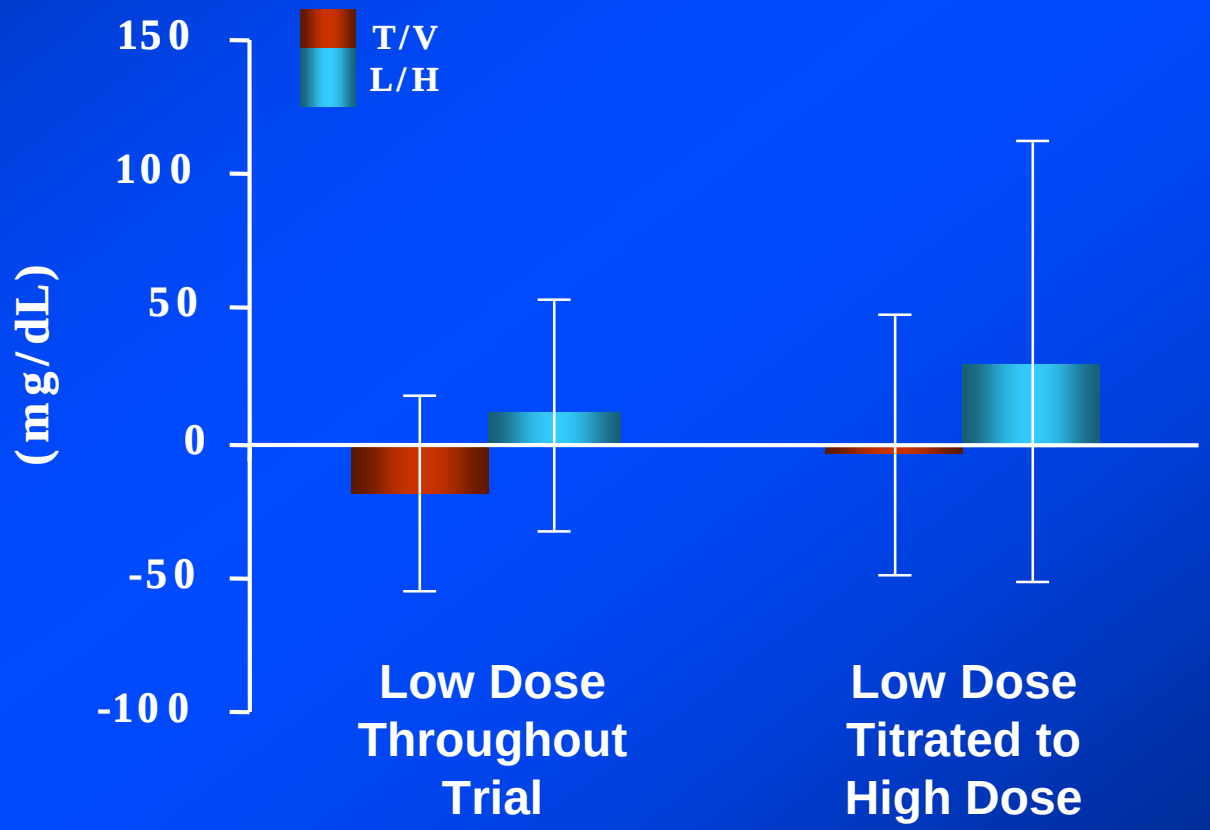
2007 ESH/ESC Guidelines
Choice of Antihypertensive Drugs

“ BB, especially in combination with a diuretic, should not be used in patients with metabolic syndrome or at high risk of diabetes.”

STARLET Trial: Low Versus High Diuretic Dose

- Post hoc evaluation of dose titration is clinically relevant, although confounded by requirement for dose titration to achieve better BP control

2-hour OGTT change in blood glucose from Baseline to Study End (mean ± SD)



Bakris GL et.al. Diabetes Care 2006;29:2592-2597

ADVANCE

Summary

Routine treatment of type 2 diabetic patients with perindopril-indapamide resulted in:

- 14% reduction in total mortality
- 18% reduction in cardiovascular death
- 9% reduction in major vascular events
- 14% reduction in total coronary events
- 21% reduction in total renal events

Benefits appeared to be similar in all major subgroups. Treatment was very well tolerated, with few side effects and adherence similar to that with placebo.

The George Institute for International Health

Lancet 2nd September 2007

ESH/ISH Guidelines: Treatment of Associated Risk Factors

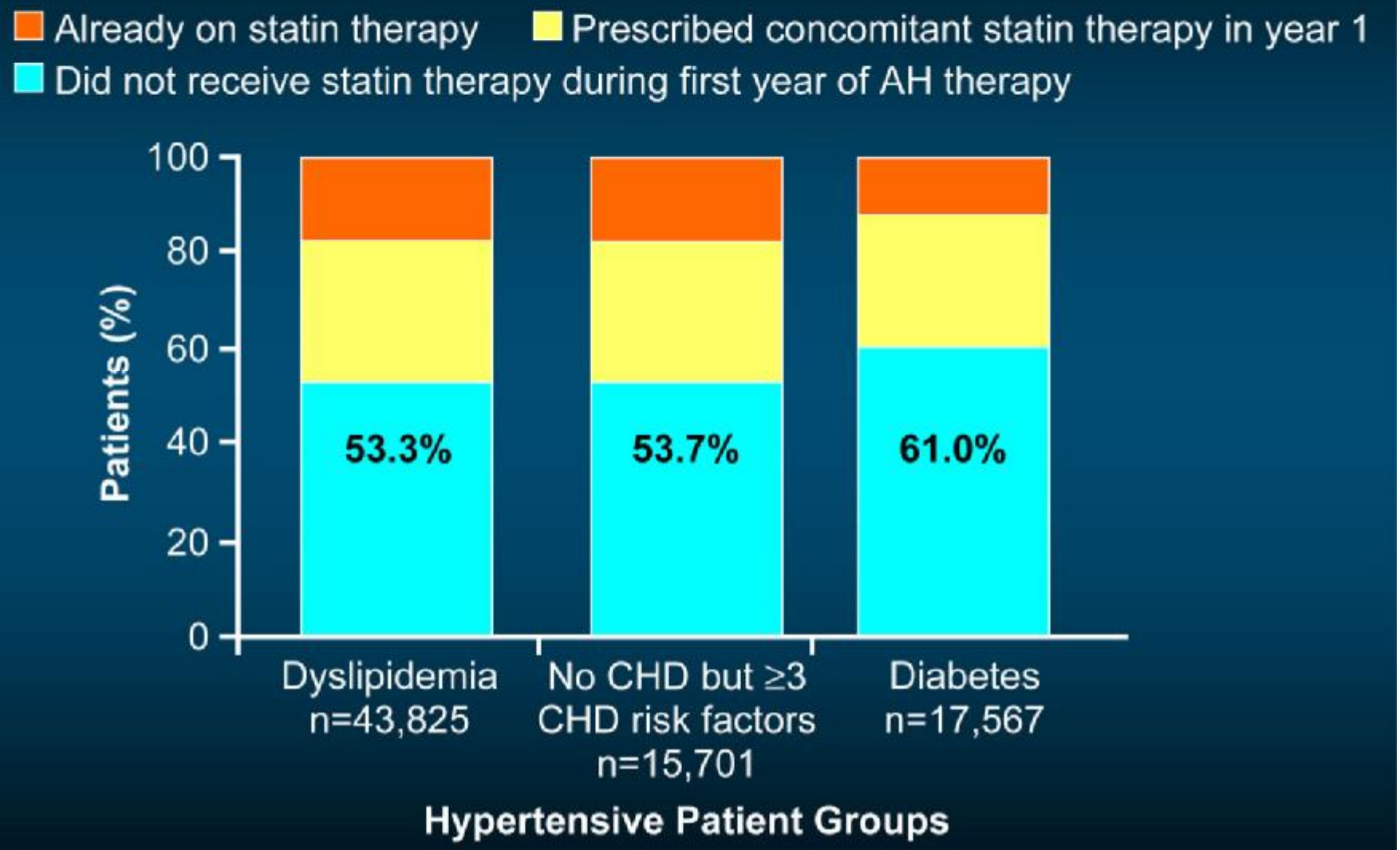
Lipid Lowering Agents

- All hypertensive patients with established cardiovascular disease or with type 2 diabetes should be considered for statin therapy aiming at serum total and LDL cholesterol levels of, respectively, <4.5 mmol/L (175 mg/dL) and <2.5 mmol/L (100 mg/dL) and lower, if possible.
- Hypertensive patients without overt cardiovascular disease but with high cardiovascular risk (≥20% risk of events in 10 years) should also be considered for statin treatment even if their baseline total and LDL serum cholesterol levels are not elevated.

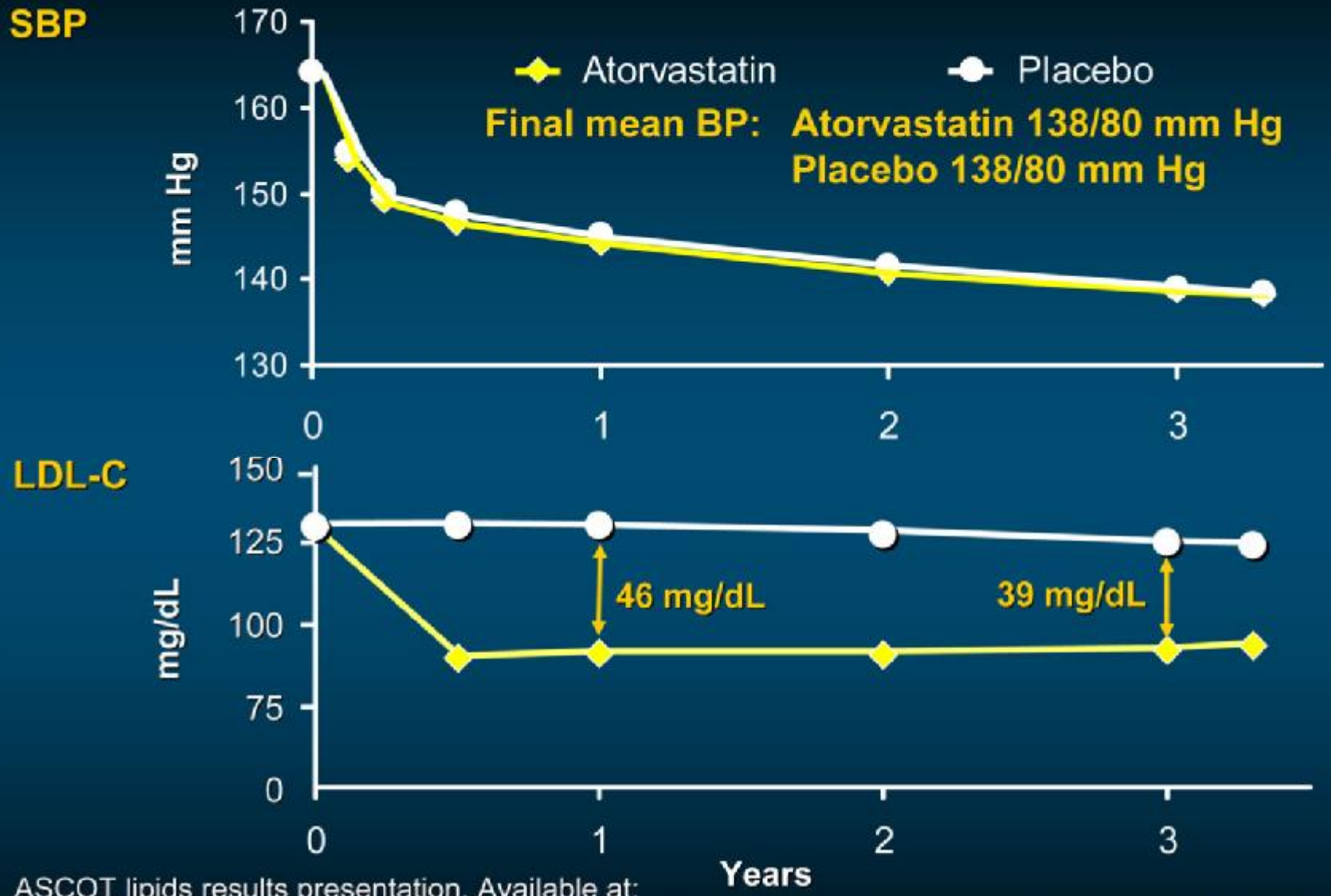
HYPERTENSION AND DYSLIPIDEMIA

- If TGs remain elevated (200-499 mg/dL) after the LDL-C target is achieved, then the patient should be treated with TG lowering drugs (e.g. fibrate or niacin)
- If TG exeed 500 mg/dL, the patient should be treated with TG lowering drugs and a very low fat diet (< 15% of total daily calories) in order to reduce the risk of CV events and pancreatitis
- When serum TG do not normalize additional intervention with orlistat or high dose fish oil can be considered

Many Patients Newly Treated for Hypertension Do Not Receive Concomitant Statin Therapy Within 1 Year



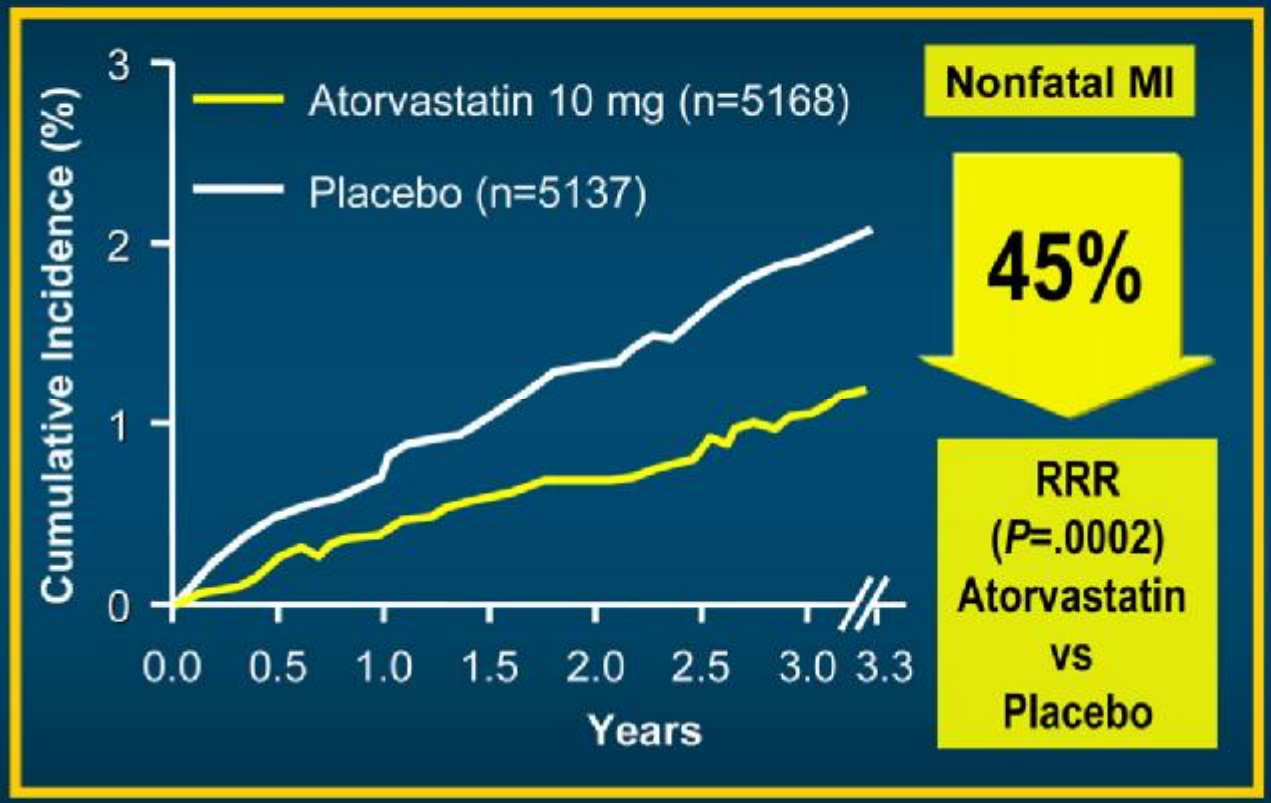
ASCOT-LLA: SBP and LDL-C Changes



ASCOT lipids results presentation. Available at: http://www.ascotstudy.org/healthcare_professionals/slides_and_resources.htm. Accessed April 24, 2006.

ASCOT-LLA: Reductions in Nonfatal MI and Stroke

100% Were Treated Hypertensive Patients With Additional Risk Factors and Without CHD



Nonfatal MI

45%

RRR (*P*=.0002) Atorvastatin vs Placebo

Stroke*

26%

RRR (*P*=.033) Atorvastatin vs Placebo

*Although the reduction of fatal and nonfatal stroke did not reach a predefined significance level (*P*=.01), a favorable trend was observed.

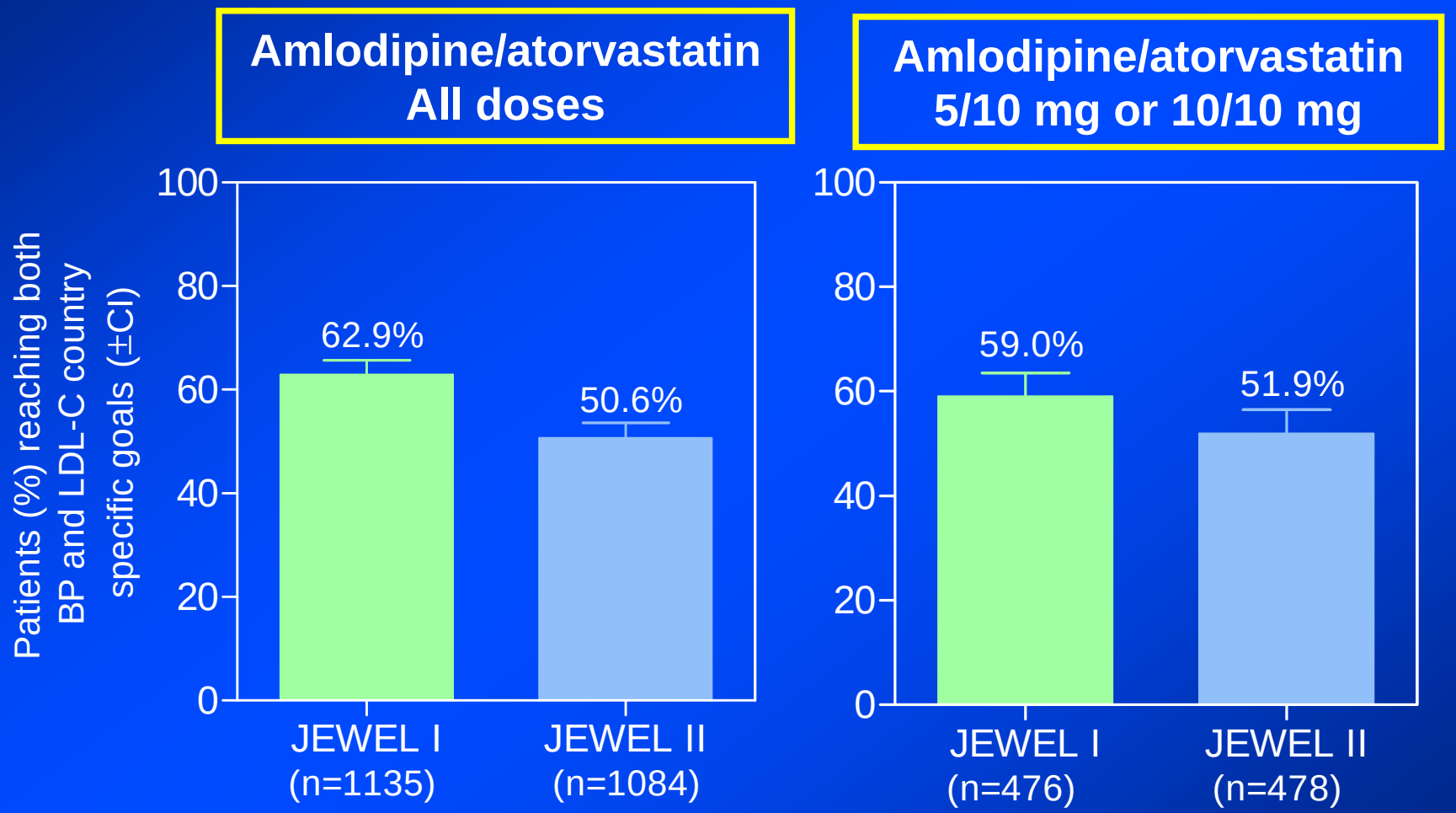
RRR=relative risk reduction.

Data on file. Pfizer Inc, New York, NY.

Sever PS et al, for the ASCOT Investigators. *Lancet*. 2003;361:1149-1158.

Please consult speaker for full prescribing information.

JEWEL I, JEWEL II Trial:
Patients Achieving Country-specific BP and LDL-C goals



Hobbs R, Manolis A. et al. Eur J cardiovasc Prev Rehab 2009

Blood-pressure reductions in the statin arms vs placebo

Statin treatment	Reduction in SBP (mm Hg)	P	Reduction in DBP (mm Hg)	P
Statins	2.2	0.02	2.4	<0.001
Pravastatin	1.5	0.20	2.3	0.002
Simvastatin	2.9	0.009	3.0	<0.001

Excluding those with high blood pressure or taking hypertensive medication at baseline

Statins	2.6	0.006	2.5	<0.001
Pravastatin	2.2	0.048	2.3	0.006
Simvastatin	3.0	0.005	2.7	0.002

HYPERTENSION AND OBESITY

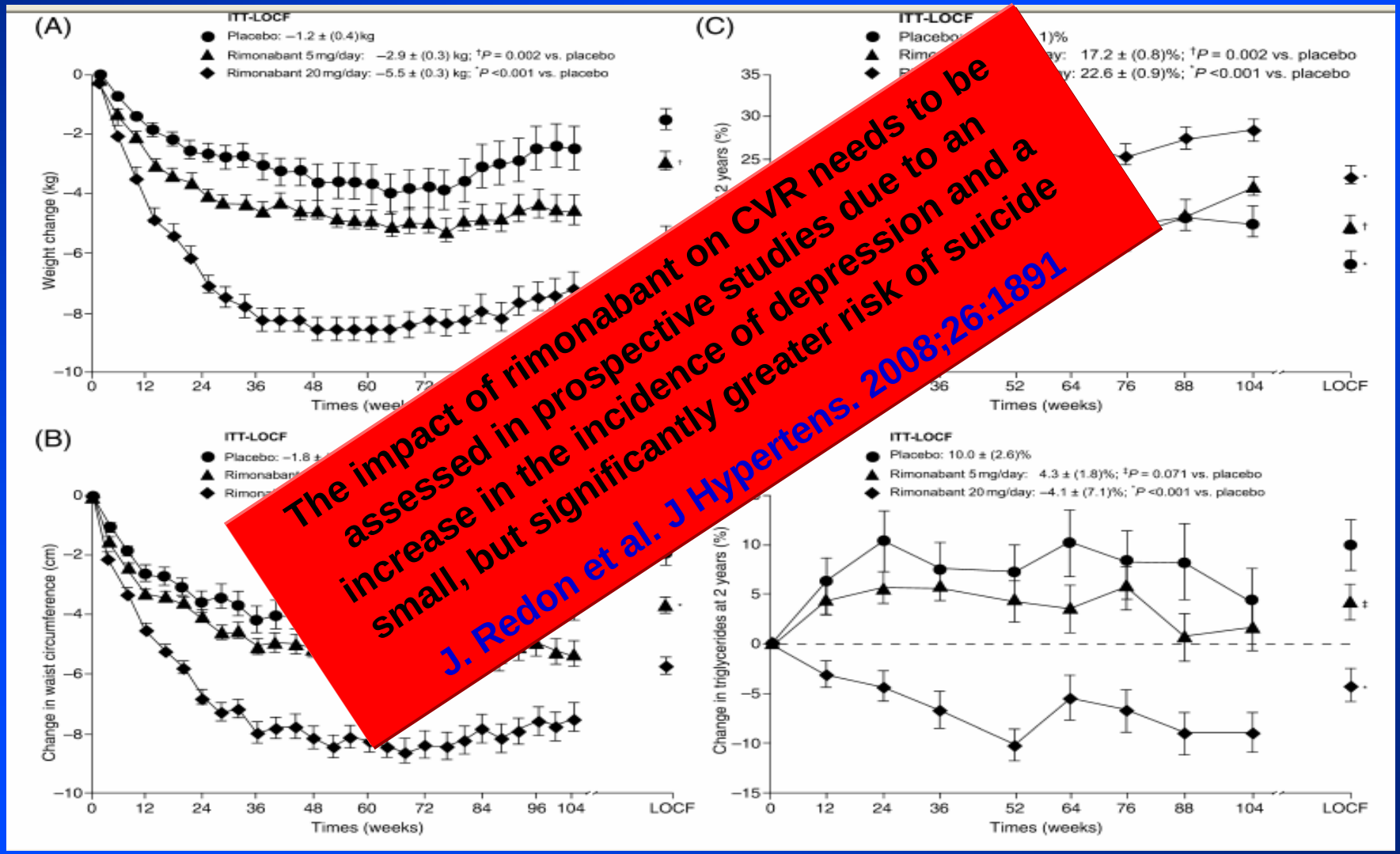
Target : reduction of body weight 10-15%

- Ø Psychosocial evaluation
- Ø Behavior modification
- Ø Dietary changes
- Ø Physical activity

Drugs : After 6mos of diet etc if BMI > 25 kg/m^2 pharmacotherapy can be used

1. Sirbutamine (4.5-6.8 kg/2yrs)
   Contraindicated in CHD, severe HTN
2. Orlistat (same as sirbutamine)
3. Rimonabant

Long Term Effect of Blockade With Rimonabant on Cardiometabolic RF: Two Year Results From RIO-Europe



The impact of rimonabant on CVR needs to be assessed in prospective studies due to an increase in the incidence of depression and a small, but significantly greater risk of suicide

J. Redon et al. J Hypertens. 2008;26:1891

Van Gaal LF et al. Eur Heart J 2008;

Summary of the Benefits, Adverse Effects and Potential Concerns of Diabetic Drugs

	Long-term data	Other benefits	HbA_{1c} decrease	Hypoglycaemia risk	Body Weight change	Other Potential concerns
SUs	Proven efficacy/safety	Low cost	0.8-2.0%	YES	Gain	CV events?
Biguanides (metformin)	Proven efficacy/safety	Low cost	1.0-1.5%	NO	None or possible loss	Lactic acidosis(very rare)
Alpha-glucosidase Inhibitors	Limited data	CV benefits?	0.5-0.8%	NO	NO	Unknown
Glinides	Limited data	Rapid acting	0.8-1.5%	LOW	Gain	Unknown
TZDs	Improve β-cell function	Lipid profile (pioglitazone)	0.8-1.0%	NO	Gain	Oedema, heart failure, fracture
GLP-1 agonists	Unknown	Improved β-cell mass?	0.6-1.0%	NO	Loss	Risk of pancreatitis
Amylin analogues	Unknown	-	~0.6%	NO	Loss	Unknown
DPP-IV inhibitors	Unknown	Improved β-cell mass?	0.05-0.9%	NO	Neutral	Unknown

HbA_{1c}, glycated haemoglobin; GI, gastrointestinal;SUs, sulphonylureas; cardiovascular; TZDs, thiazolidinediones; GLP-1, glucagon-like peptide-1; DPP-IV, dipeptidyl peptidase-IV

Management Recommendations for Hypertension and the Metabolic Syndrome

- **Threshold:** 130/85 mmHg
- **Goal:** <130/80 mmHg
- **Recommended:**
  - Non-pharmacological treatment
  - First choice: ACEi or ARB
  - Second choice: CCB or vasodilating b-blockers
- **Observations:**
  - Thiazide-like diuretics should be avoided in monotherapy or in high dose
  - b-blockers should be avoided if not compelling indications exists
  - Combination of b-blockers of thiazide diuretics should be avoided

Redon et al. J Hypertens 2009

Thank You

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