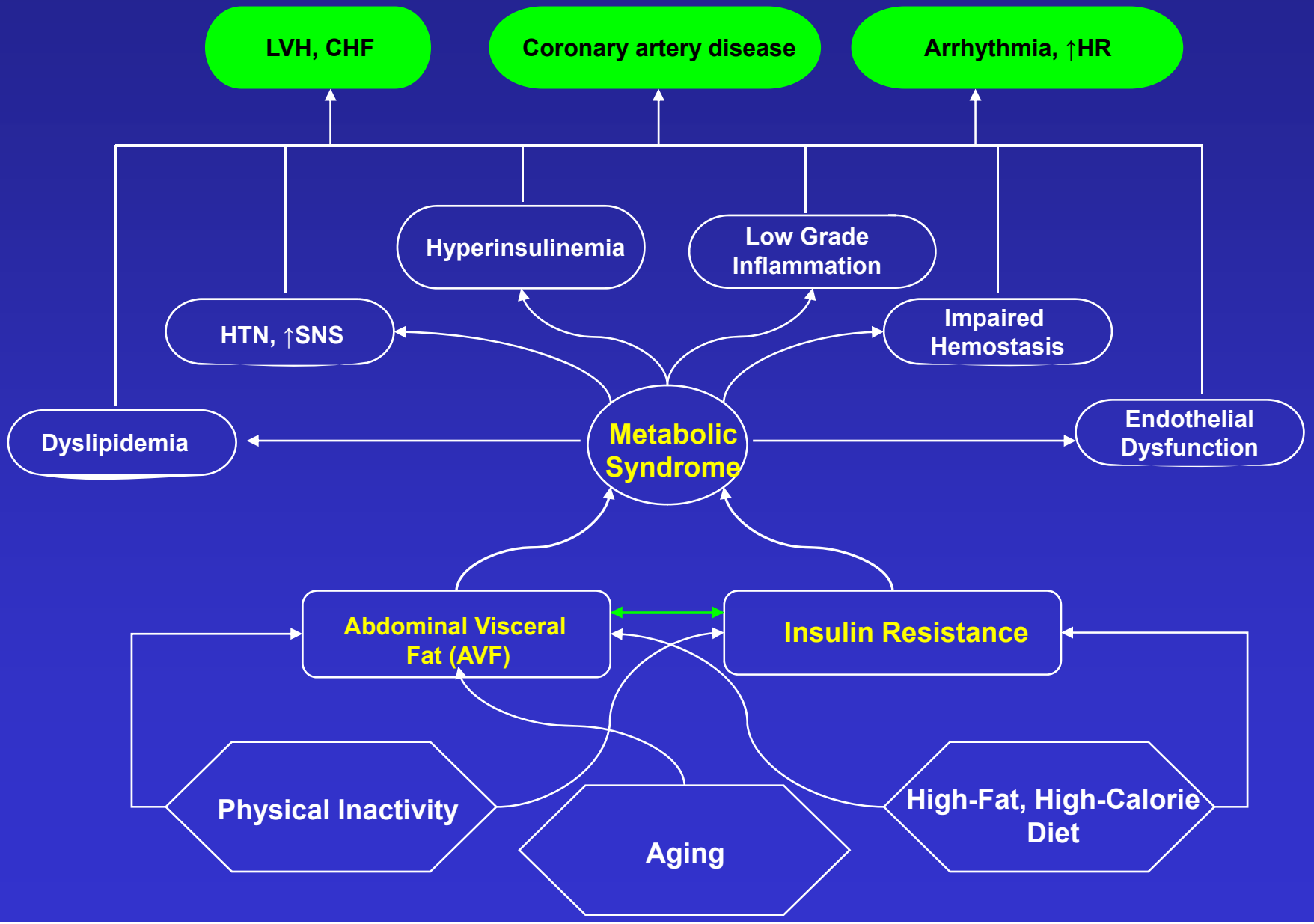
# Management of Hypertension on the Basis of Cardiometabolic Risk profile

연세대학교 심장혈관병원
심장내과
박 성 하

# Agenda

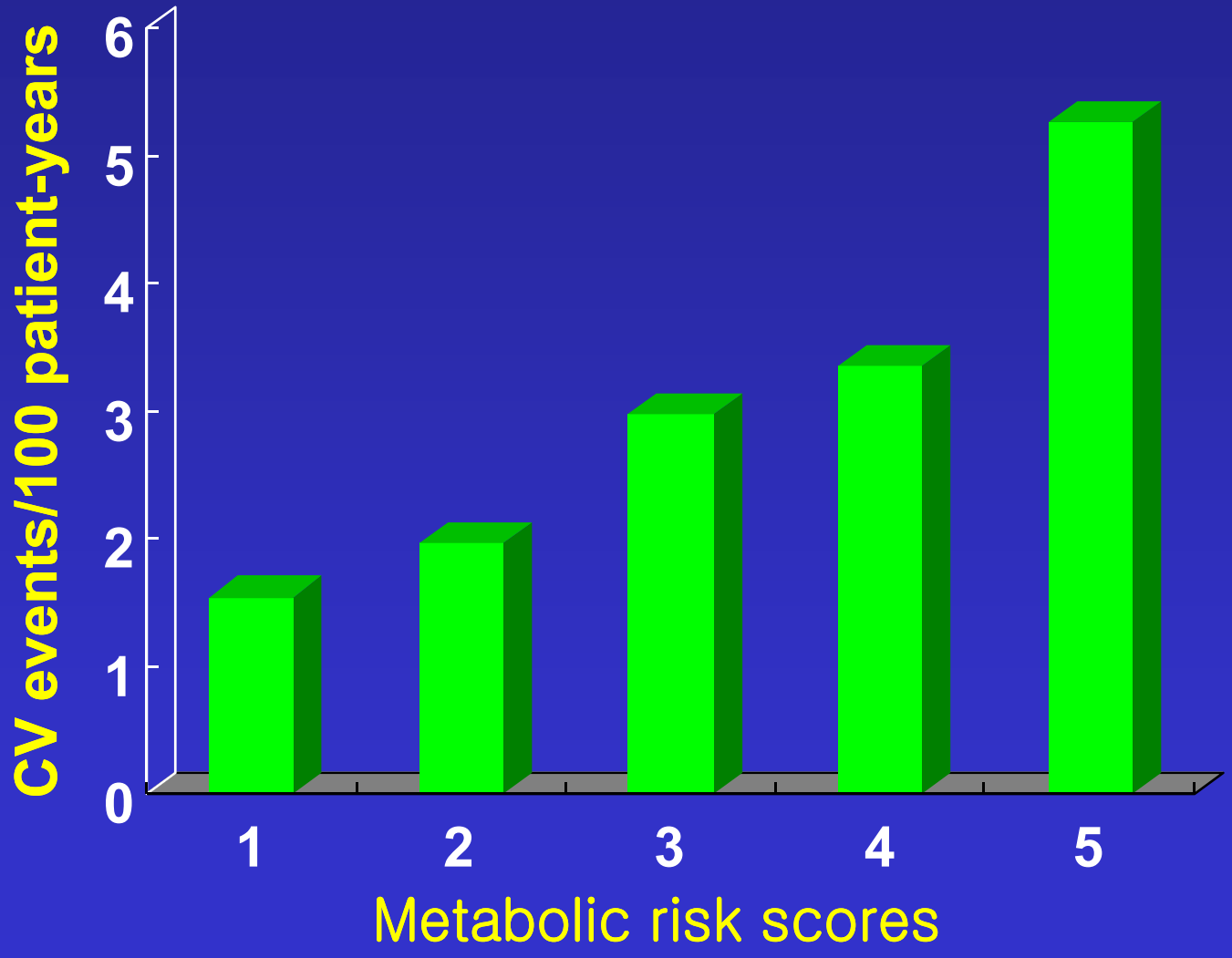
- **Cardiometabolic syndrome and Hypertension**
- Metabolic side effects of blood pressure medication: Is new onset DM during antihypertensive treatment a bad thing?
- Guideline for hypertension medication selection in cardiometabolic syndrome

# CardioMetabolic Syndrome



# Metabolic syndrome and HT

PIUMA study: prospective FU of 1742 HT for 10.5years

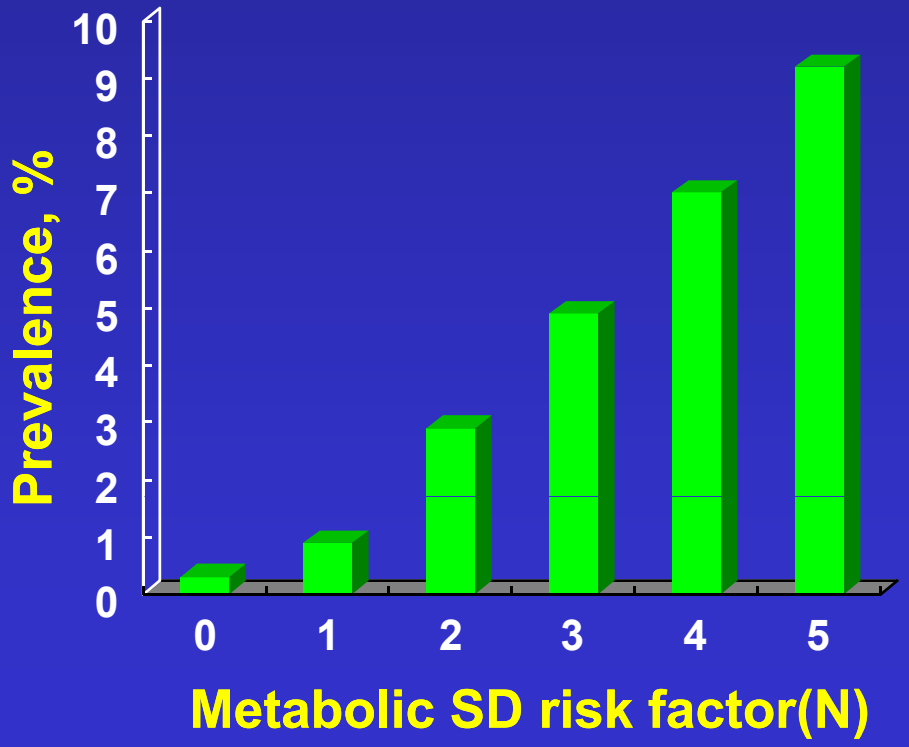



*Schillaci G et al. J Am Coll Cardiol 2004;43:1817-1822*

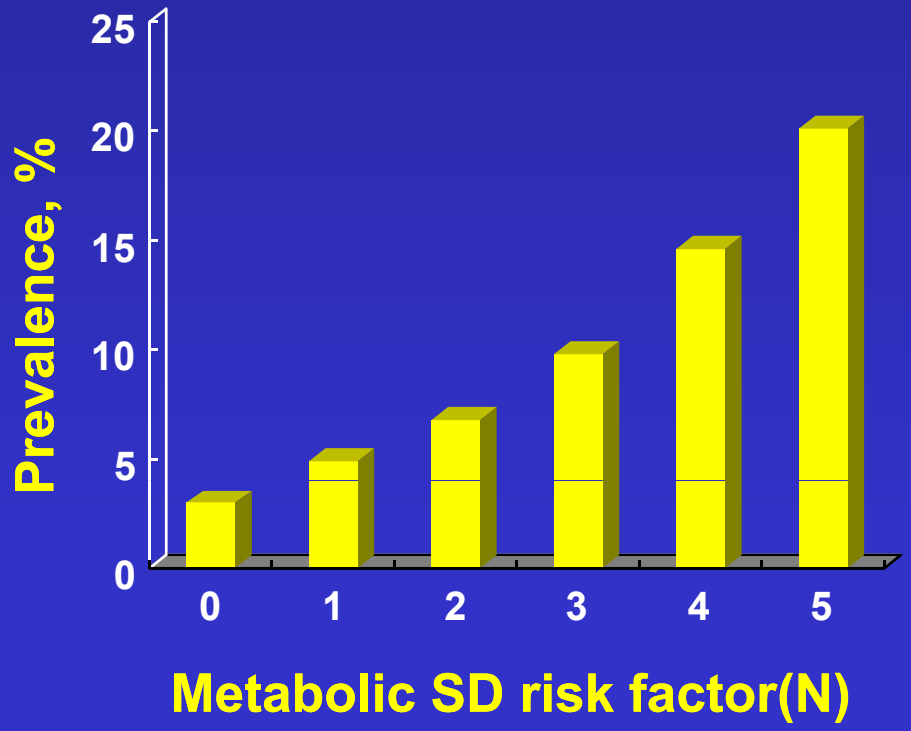
# Metabolic syndrome and chronic kidney disease

## 6217 persons analyzed for CKD and 6125 persons Analyzed for microalbuminuria in NHANES III

Prevalence of CKD
(GFR < 60ml/min/1.73m²)

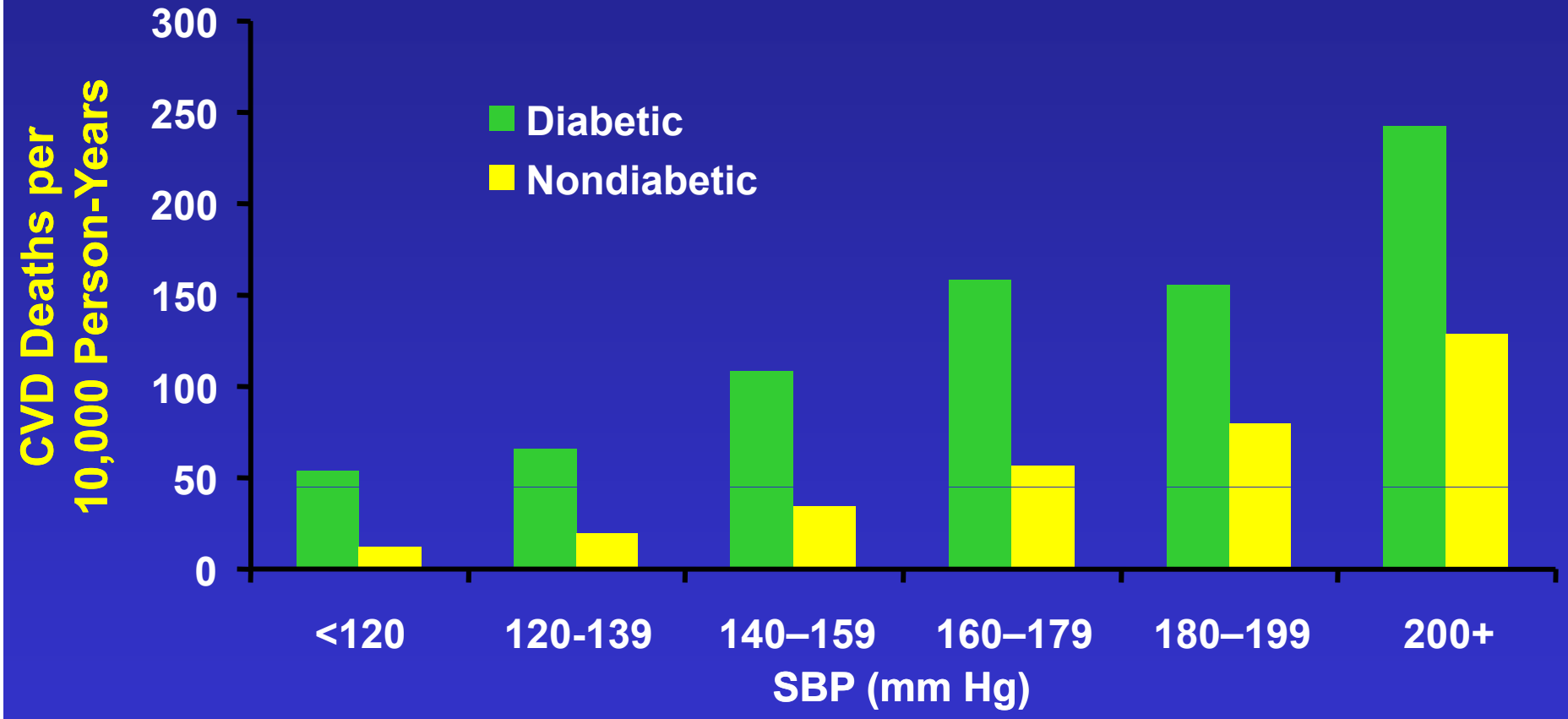



Prevalence of Microalbuminuria
(AC ratio 30–300mg/g)




*Jing C et al. Ann Intern Med 2004;140:167-174*

# Combined SBP and Diabetes Increase CVD Risk




**MRFIT Data: Diabetic Men With Elevated SBP at Greater Risk for CVD Than Those Without Diabetes**

*Stamler et al. Diabetes Care. 1993;16:434-444*

# Agenda

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- Guideline for hypertension medication selection in cardiometabolic syndrome

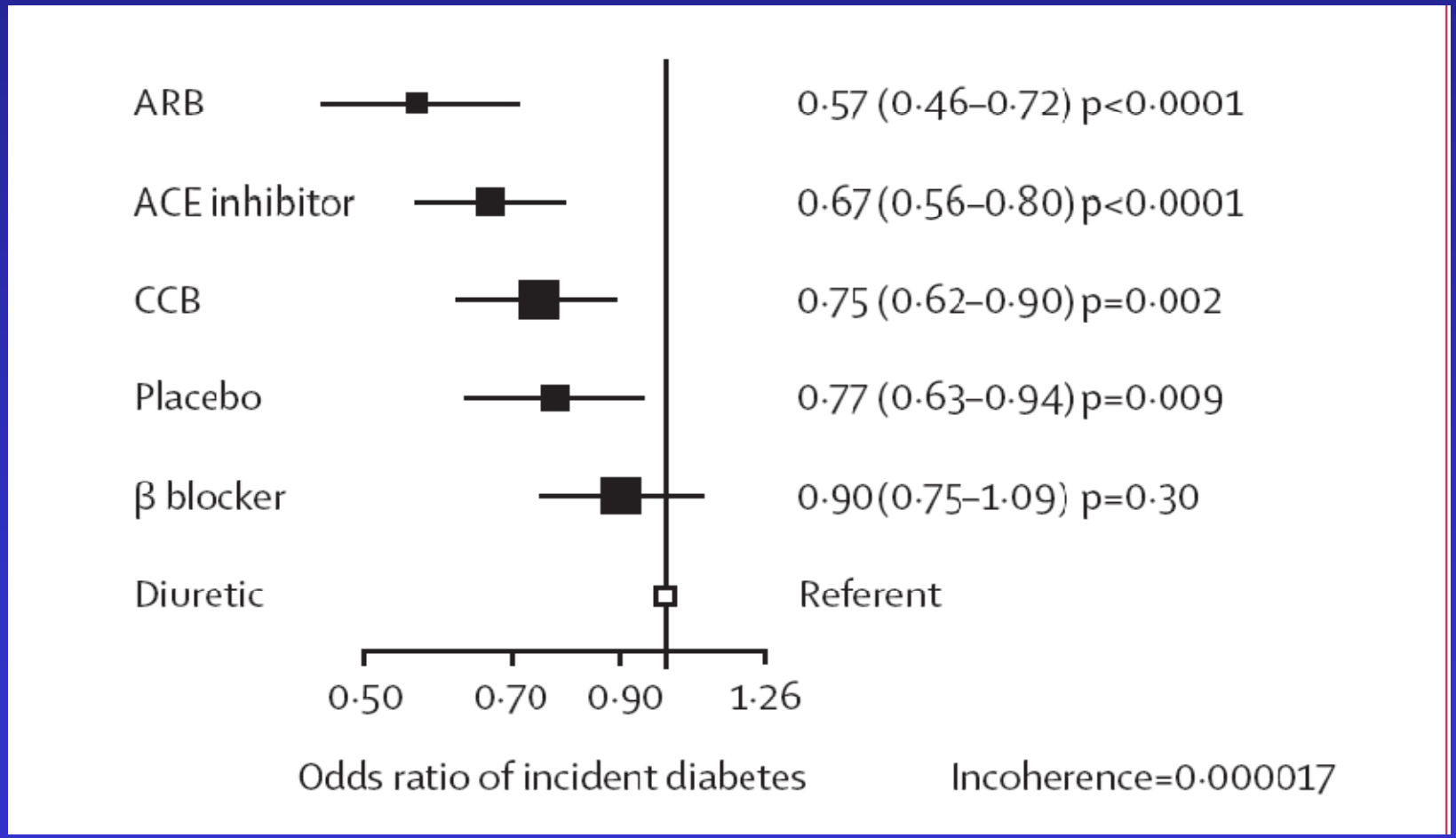
# ALLHAT
# : Biochemical Outcomes at 4 Years

| | Amlodipine vs Chlorthalidone | Lisinopril vs Chlorthalidone |
|---|---|---|
| Fasting glucose | Trend to reduction (2.6 mg/dL) in amlodipine vs chlorthalidone | Significantly reduced (4.8 mg/dL) in lisinopril vs chlorthalidone *P*=.002 |
| New-onset diabetes | 18% ↑ in chlorthalidone vs amlodipine (9.8%) (*P*=.04) | 43% ↑ in chlorthalidone vs lisinopril (*P*<.001) |
| Cholesterol | Significantly increased (1.6 mg/dL) in chlorthalidone vs amlodipine (*P*=.009) | Significantly increased (2.2 mg/dL) in chlorthalidone vs lisinopril groups (*P*<.001) |
| Potassium | Significantly decreased (.3 mEq/L) in chlorthalidone vs amlodipine (*P*<.001) | Significantly decreased (0.4 mEq/L) in chlorthalidone vs lisinopril (*P*<.001) |

*The ALLHAT Collaborative Research Group. JAMA. 2002;288:2981-2997.*

# Antihypertensive drugs and diabetes

## Meta-analysis of 143,153 participants in 22 clinical trials




*Elliott WJ, Meyer PM. Lancet 2007;369:201-207*

# Diuretics and metabolic syndrome

- Hypokalemia associated decrease in insulin secretion(K < 4.0mEq/L): **Metabolic side effects may potentially be minimized by K supplementation or drugs that elevate K**

- Decrease in glucose disposal rate

→ **Reduced blood flow to the skeletal muscle tissue via reduction in blood volume**


*Nilsson PM. J Hypertens 2007;25:1201-1204*

*Pollare T et al. N Engl J Med 1989;321:868-873*

*Mancia G et al. J Hypertens 2006;24:3-10*

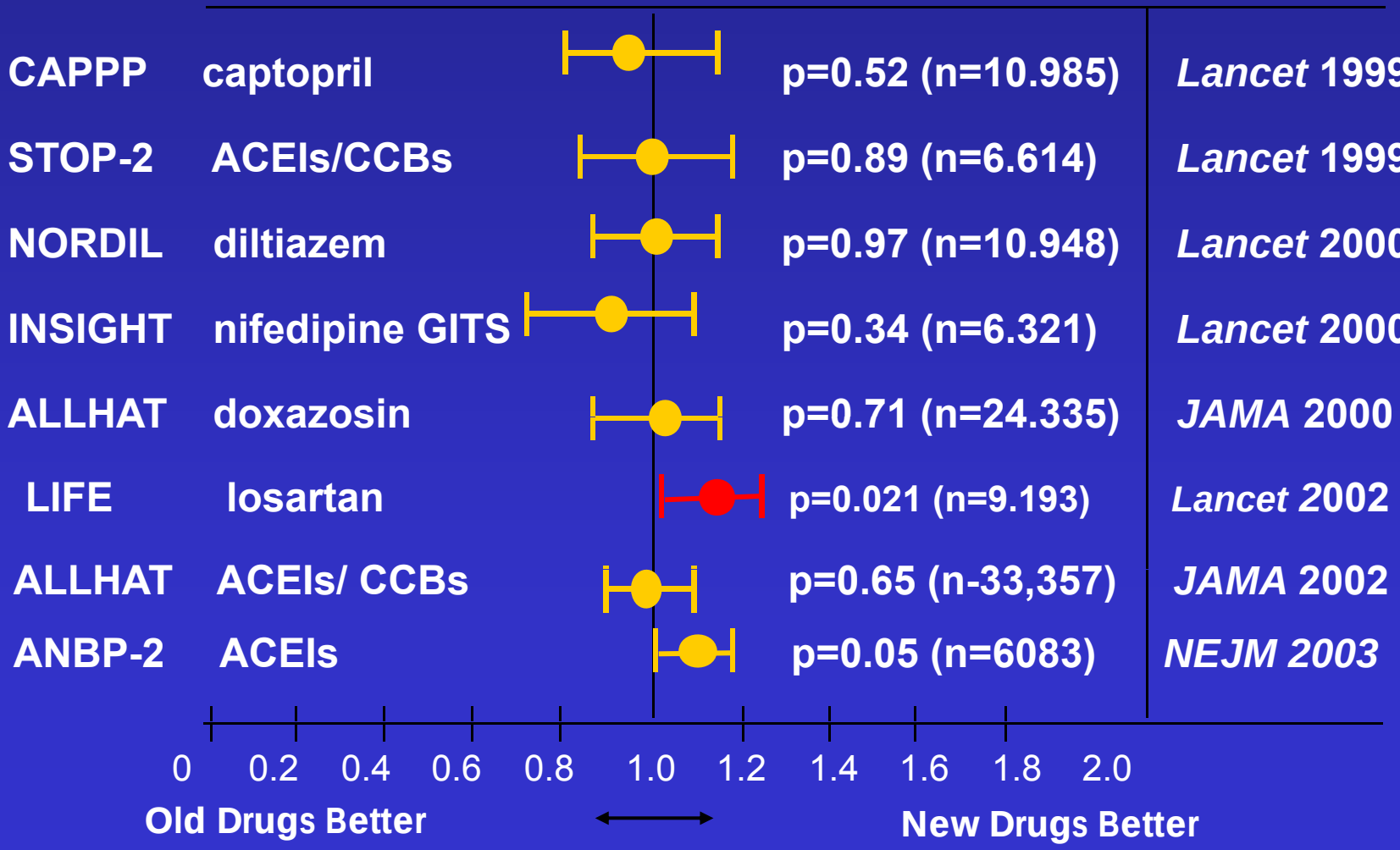
# Beta blockers and metabolic syndrome

- Inhibition of beta 2 adrenergic mediated insulin release
- Decreased in blood flow(insulin delivery) to the skeletal muscle
- Increased fat accumulation and weight gain

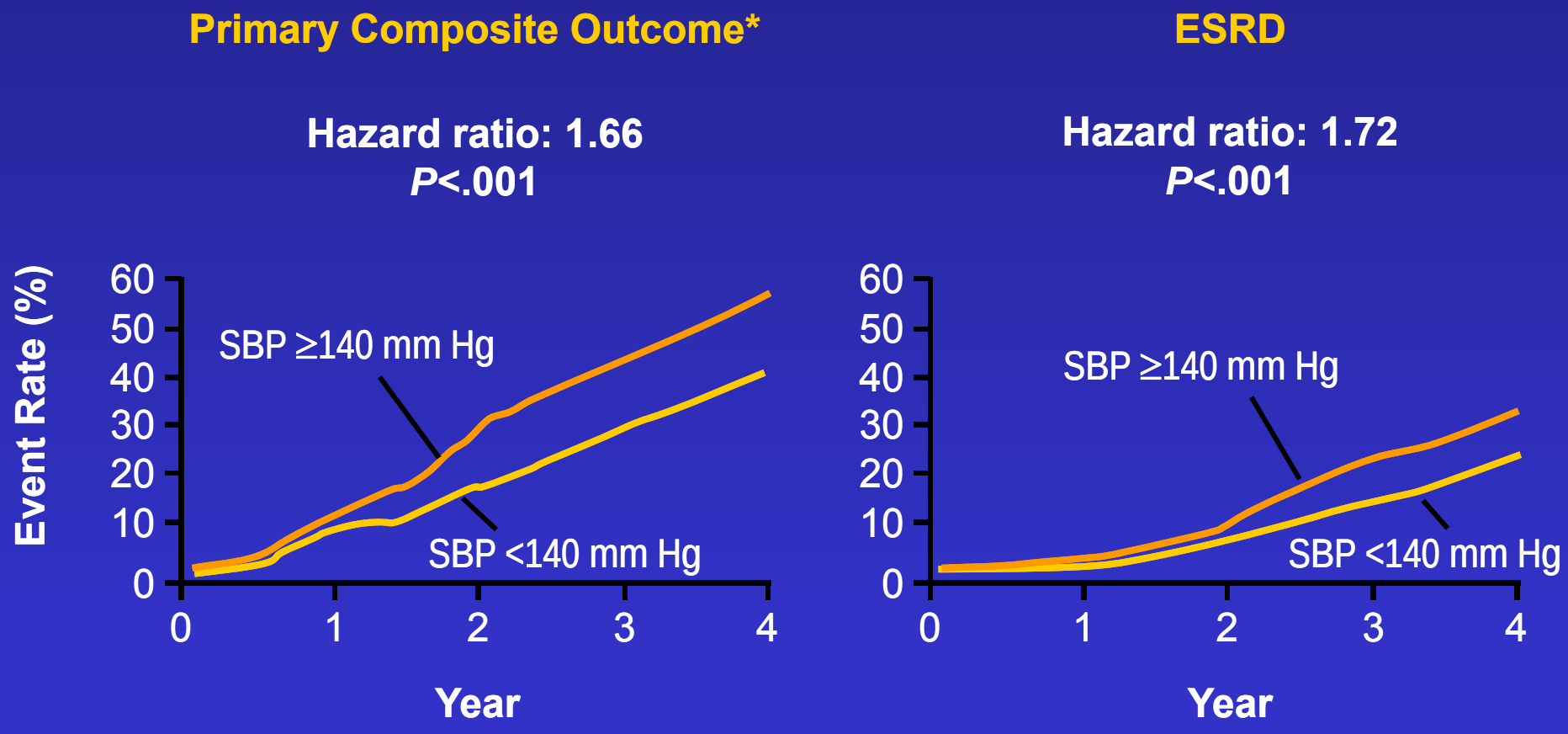
*Nilsson PM. J Hypertens 2007;25:1201-1204*

# Recent Hypertension Trials With "New" Versus "Old" Drugs

## Primary Endpoint (RR ± 95% CI)



# RENAAL: Primary Composite Outcome and ESRD for Baseline Systolic BP ≥140 vs <140 mm Hg

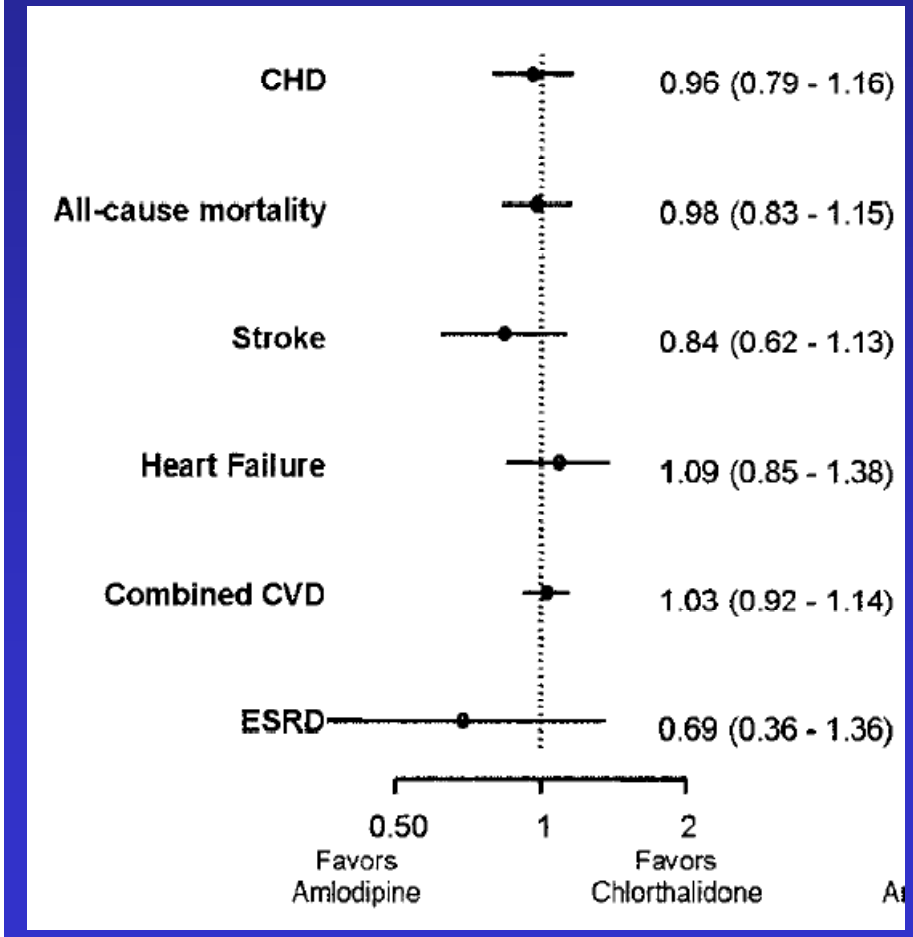



*Doubling of baseline SCr, ESRD, or death.

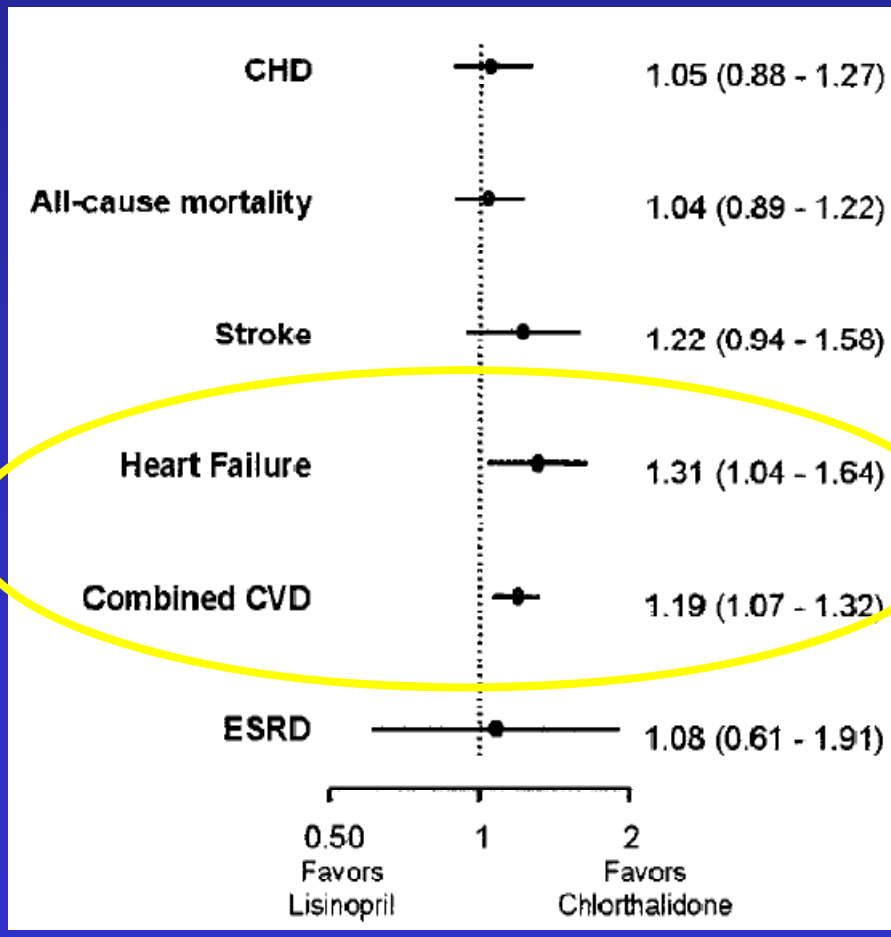
*Bakris et al. Arch Intern Med. 2003;163:1555-1565.*

# Clinical outcome of non diabetic MS according to BP medication

## Amlodipine vs chlorthalidone



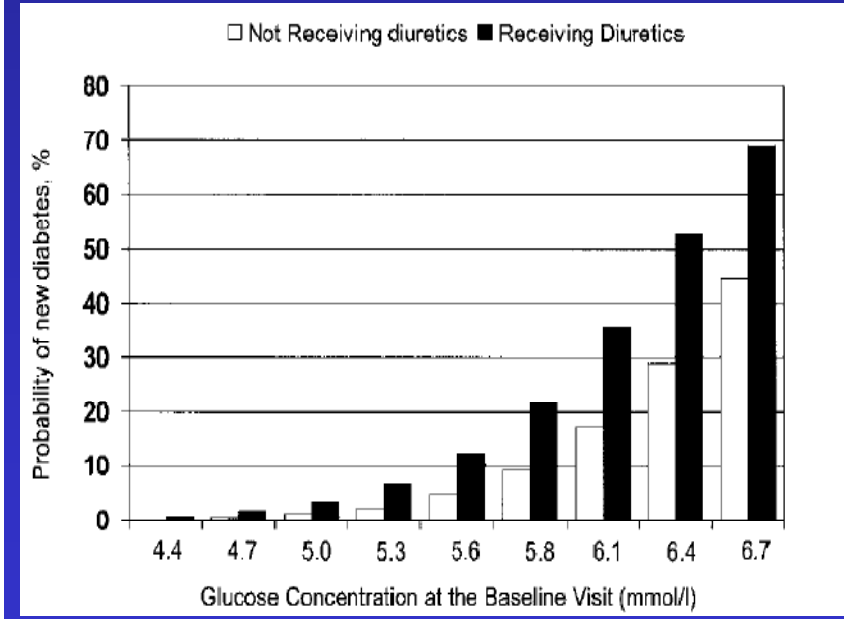

## Chlorthalidone vs Lisinopril

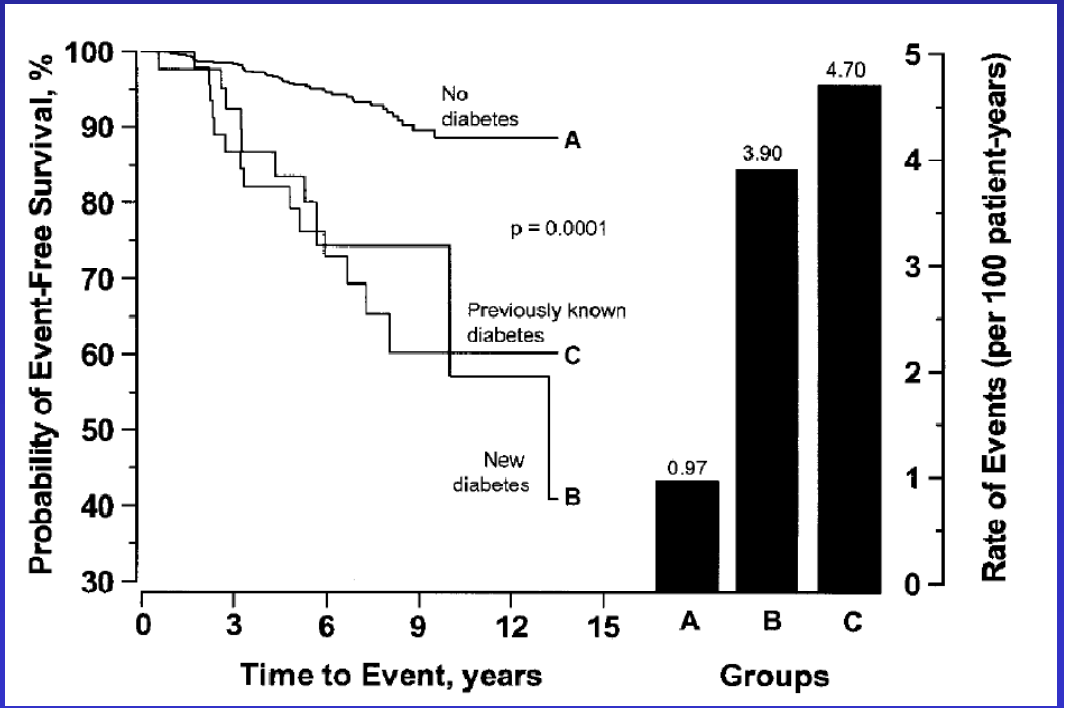



*Black HR et al. Diabetes Care 2008;31(2):353-360*

# New onset diabetes increases CV outcomes: Pro

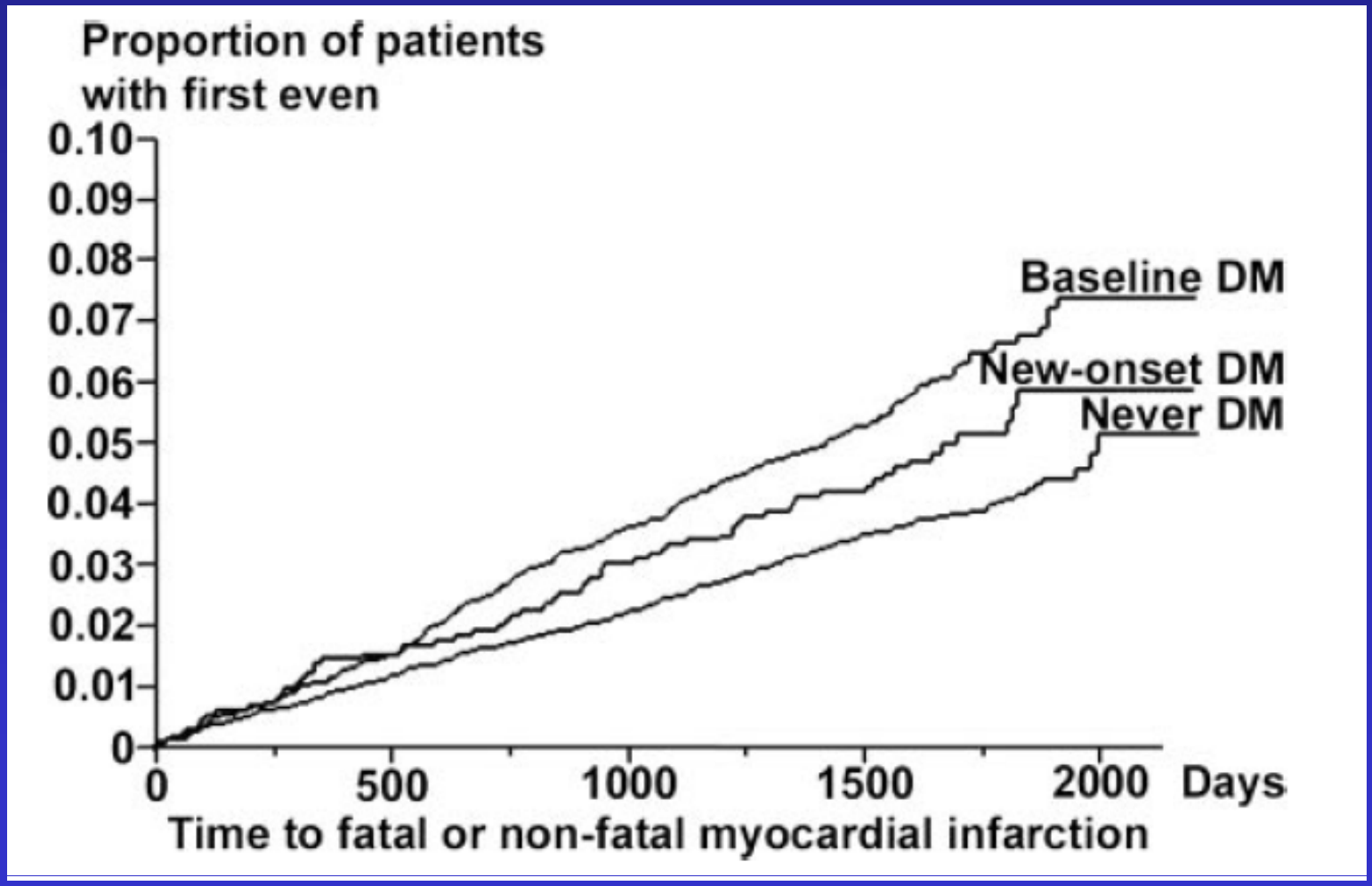
795 initially untreated HT cohort: FU median 6 years
→ 63 Cardiovascular events during followup




*Verdecchia P et al. Hypertension 2004;43:963-969*

# Prognosis of New Onset Diabetes in the VALUE trial




*Aksnes TA et al. Hypertension 2007;50:467-473*

**Diabetes in treated hypertension is common and carries a high cardiovascular risk: results from a 28-year follow-up**

Torbjörn Almgren[a], Lars Wilhelmsen[e], Ola Samuelsson[b], Anders Himmelmann[c], Annika Rosengren[d] and Ove K. Andersson[a]

**754 HT subjects aged 47-54 FU for 25-28 years: 20.4% developed DM during FU**

Hazard ratio of New onset DM for Stroke 1.67(1.10-2.56) → Mean time to development: **9.1 years**

Hazard ratio of New onset DM for AMI 1.66(1.10-2.50) → Mean time to development: **9.3 years**

*Almgren T et al. J Hypertens 2007;25:1311-1317*

# Agenda

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- Metabolic side effects of blood pressure medication: Is new onset DM during antihypertensive treatment a bad thing?
- **Guideline for hypertension medication selection in cardiometabolic syndrome**

# Point of Discussion

All the clinical trials are based upon evidence lasting 4-5 years. Based on current evidence, would you really use diuretics or beta blockers as primary agents for treatment of hypertension in metabolic syndrome for a prolonged period time?

# European guideline emphasizes global risk Assessment

| Blood pressure (mmHg) | | | | | |
|---|---|---|---|---|---|
| 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 |

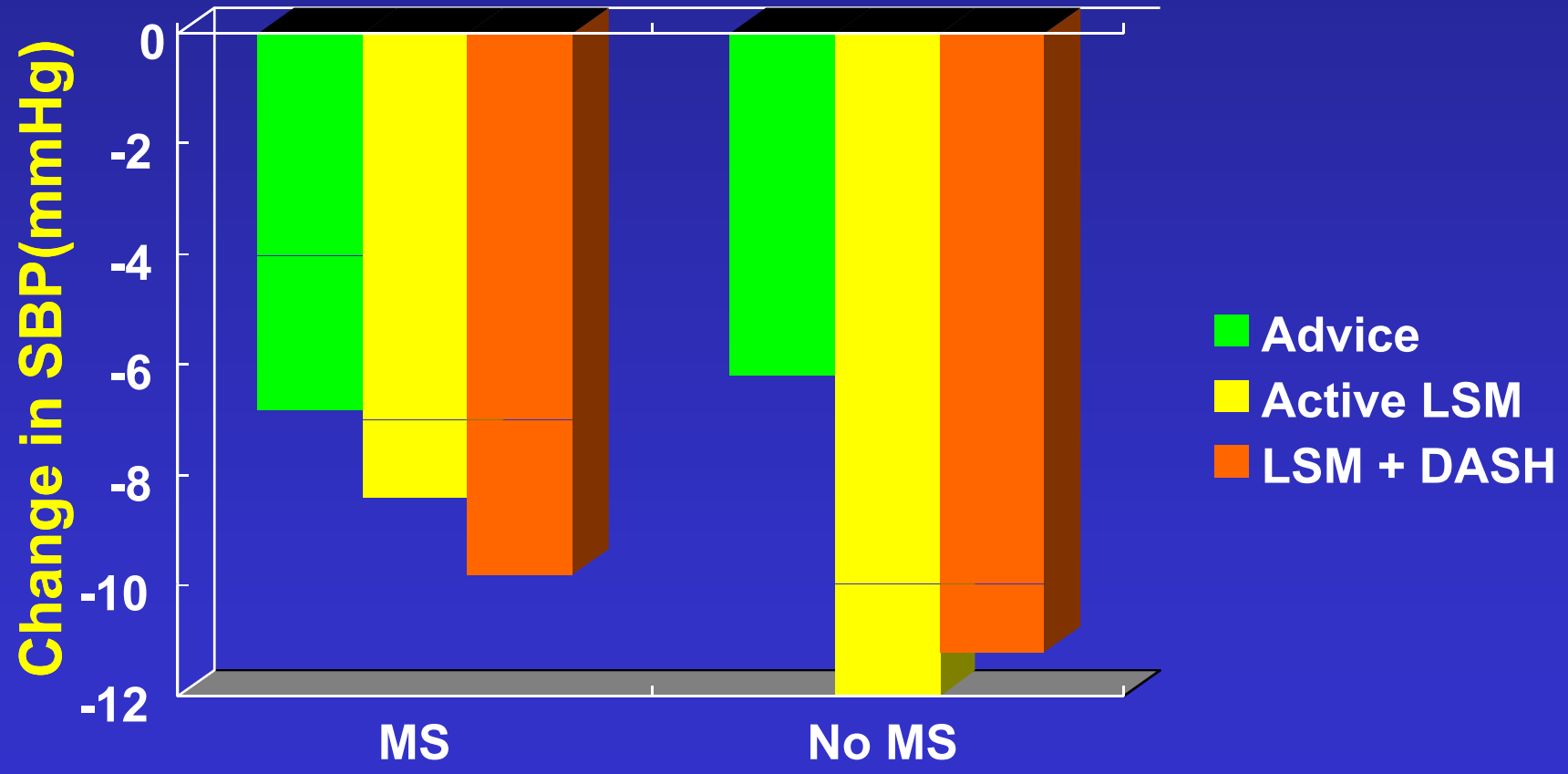
| Blood pressure (mmHg) | | | | | |
|---|---|---|---|---|---|
| Other risk factors OD or disease | Normal SBP 120–129 or DBP 80–84 | High normal SBP 130–139 or DBP 85–89 | Grade 1 HT SBP 140–159 or DBP 90–99 | Grade 2 HT SBP 160–179 or DBP 100–109 | Grade 3 HT SBP≥180 or DBP≥110 |
| No other risk factors | No BP intervention | No BP intervention | Lifestyle changes for several months then drug treatment if BP uncontrolled | Lifestyle changes for several weeks then drug treatment if BP uncontrolled | Lifestyle changes + Immediate drug treatment |
| 1–2 risk factors | Lifestyle changes | Lifestyle changes | Lifestyle changes for several weeks then drug treatment if BP uncontrolled | Lifestyle changes for several weeks then drug treatment if BP uncontrolled | Lifestyle changes + Immediate drug treatment |
| ≥3 risk factors, MS or OD | Lifestyle changes | Lifestyle changes and consider drug treatment | Lifestyle changes + Drug treatment | Lifestyle changes + Drug treatment | Lifestyle changes + Immediate drug treatment |
| Diabetes | Lifestyle changes | Lifestyle changes + Drug treatment | | | |
| Established CV or renal disease | Lifestyle changes + Immediate drug treatment | Lifestyle changes + Immediate drug treatment | Lifestyle changes + Immediate drug treatment | Lifestyle changes + Immediate drug treatment | Lifestyle changes + Immediate drug treatment |

Patients with organ damage, established CVD, DM
**Metabolic syndrome or** ≥ 3 other risk factors
need immediate treatment

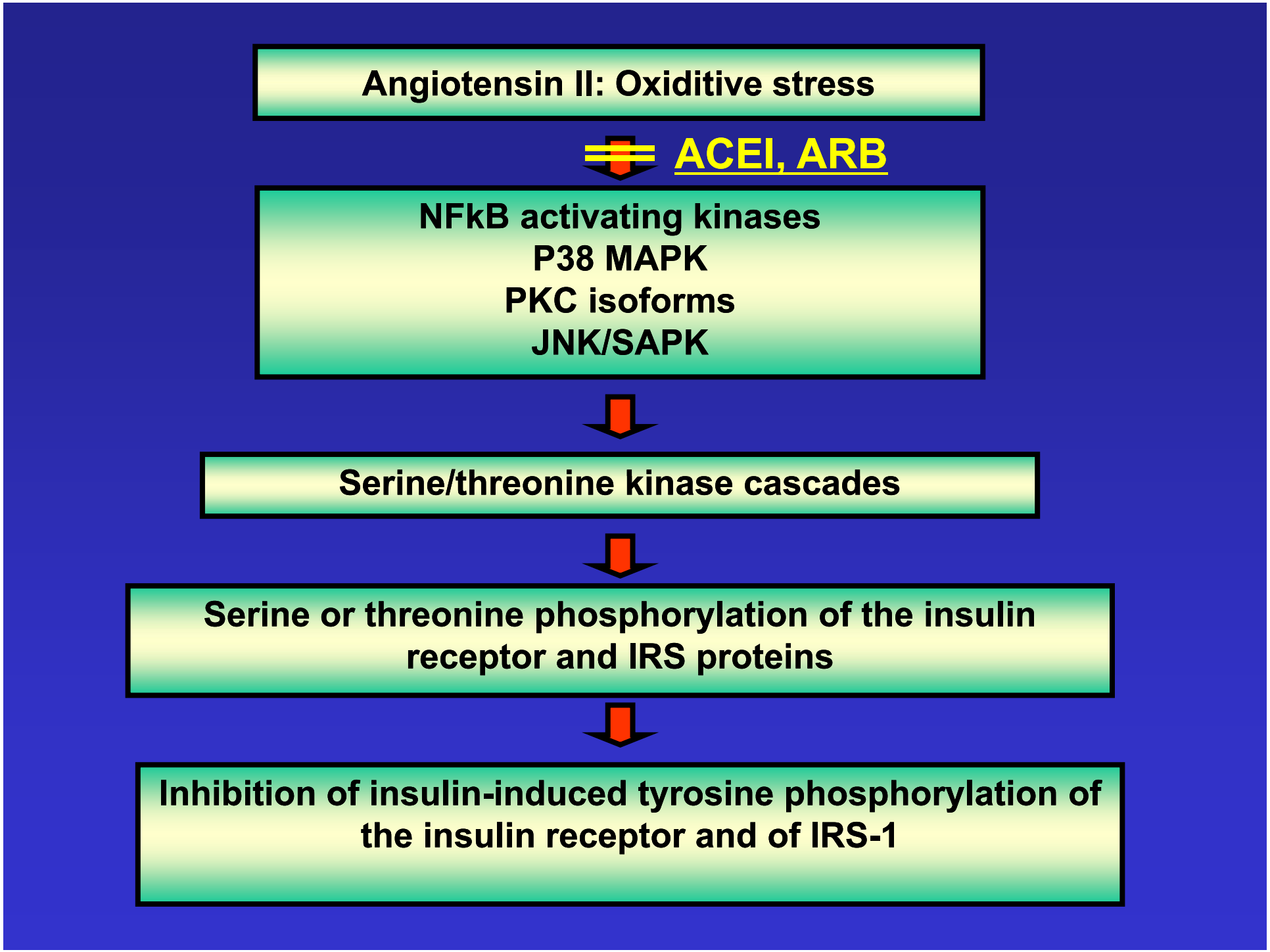
*2007 ESC/ESH guideline. 2007;25:1105-1187*

# Effects of PREMIER Lifestyle Modifications on Participants With and Without the Metabolic Syndrome

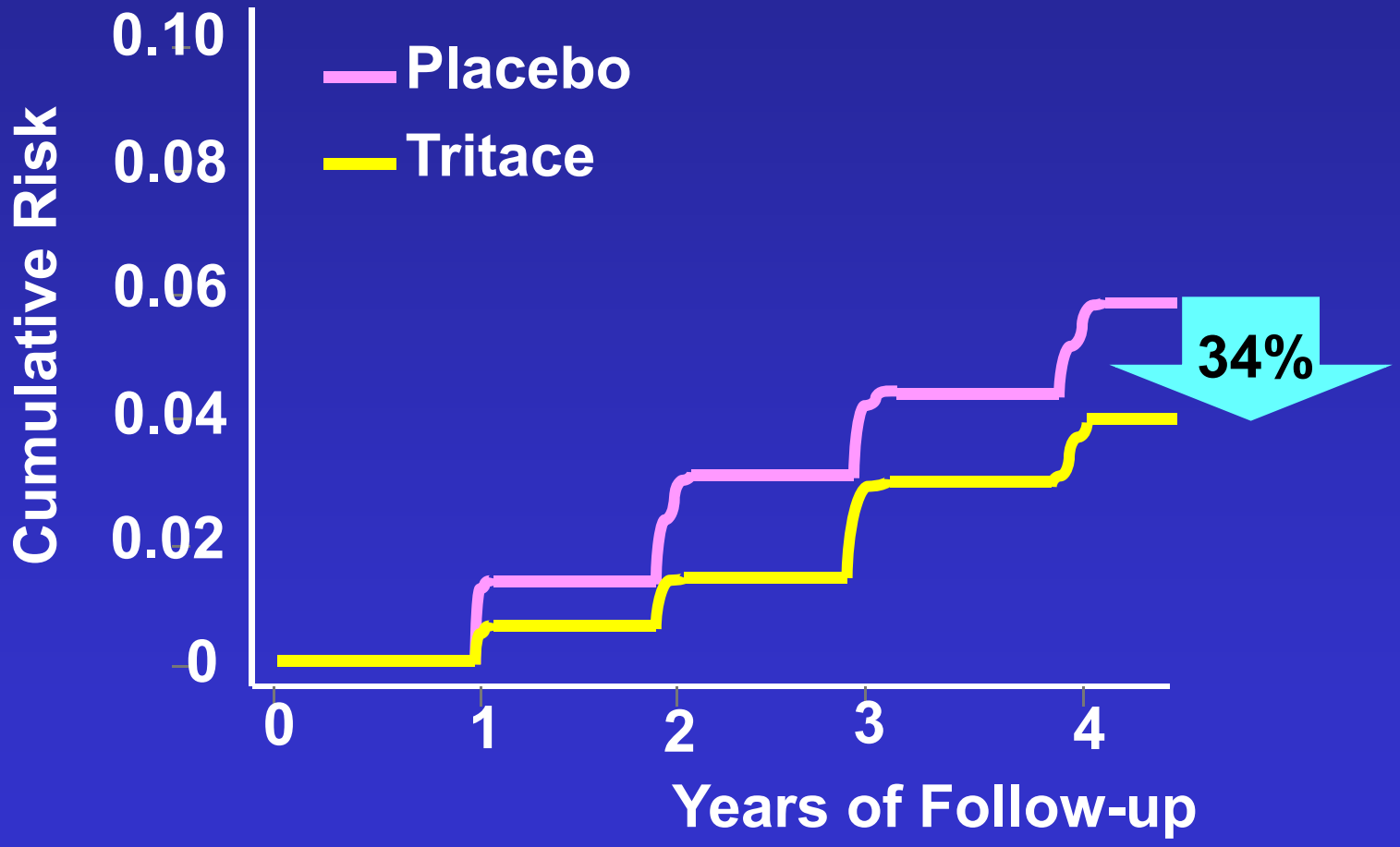
Lillian F. Lien, Ann J. Brown, Jamy D. Ard, Catherine Loria, Thomas P. Erlinger, Adrianne C. Feldstein, Pao-Hwa Lin, Catherine M. Champagne, Abby C. King, Heather L. McGuire, Victor J. Stevens, Phillip J. Brantley, David W. Harsha, Mary Ann McBurnie, Lawrence J. Appel, Laura P. Svetkey




*Lien LF et al. Hypertension 2007;50:609-616*

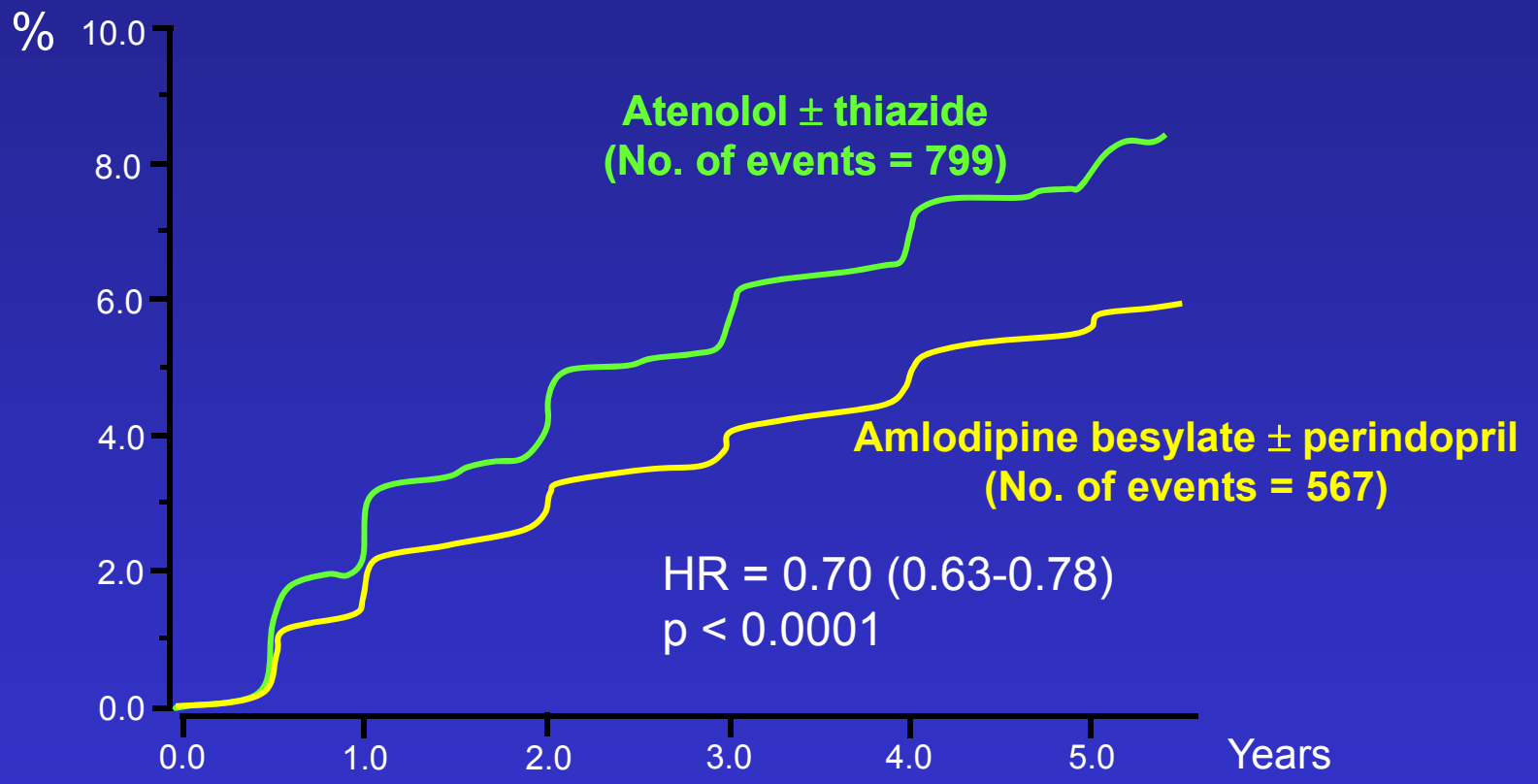

Angiotensin II: Oxiditive stress
ACEI, ARB
NFkB activating kinases
P38 MAPK
PKC isoforms
JNK/SAPK
Serine/threonine kinase cascades
Serine or threonine phosphorylation of the insulin receptor and IRS proteins
Inhibition of insulin-induced tyrosine phosphorylation of the insulin receptor and of IRS-1

# Significant Reduction of New Diagnosis of Diabetes




*S. Yusuf et al. JAMA 286:1882-1885, 2001*

# New-onset diabetes mellitus




| Number at risk | | | | | | |
|---|---|---|---|---|---|---|
| Amlodipine besylate ± perindopril | 9639 | 9383 | 9165 | 8966 | 8726 | 7618 |
| Atenolol ± thiazide | 9618 | 9295 | 9014 | 8735 | 8455 | 7319 |

*ASCOT Investigators. Lancet. 2005;366:907-913*

# Avoiding Cardiovascular Events in COMbination Therapy in Patients LIving with Systolic Hypertension(ACCOMPLISH)

- Prospective, multinational, multicenter, double-blind, randomized, parallel-group, active-controlled trial
- **N=11,463 subjects**
- US= 8110 subjects, 407 sites
- Event-driven
- Estimated total duration of study: 5 years
- BP target: <140/<90 mm Hg
  - A more aggressive target is encouraged in specific populations (i.e., <130/80 mm Hg for patients with diabetes or renal disease), at the discretion of the investigator

*Jamerson KA et al. ACC 2008 Late breaking Clinical Trial*

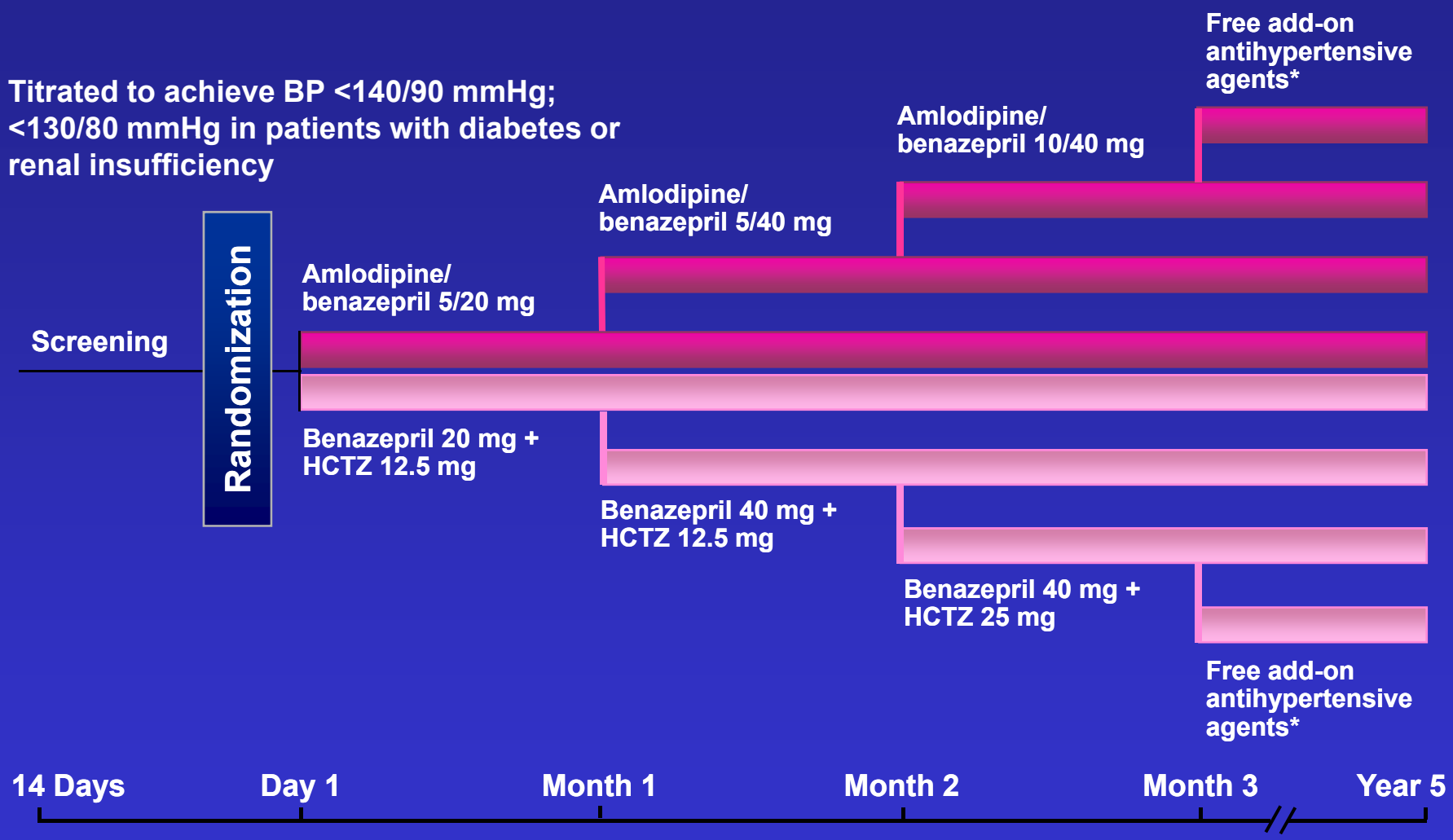
# Inclusion Criteria

- Men and women ≥55 years of age
- SBP ≥160 mm Hg and DBP ≤115 mm H g for previously untreated subjects
- SBP ≤210 mm Hg and DBP ≤115 mm H g for subjects already on antihypertensi ve treatment
- At least one (2 if 55-59) cardiovascular disease factor or evidence of target organ diseases*

*Documented history of diabetes, CHD (myocardial infarction, coronary revascularization, or unstable angina), stroke, peripheral arterial disease, LVH, proteinuria, chronic renal insufficiency (serum creatinine ≥1.6 (men) or ≥1.8 mg/dL (women).

***Jamerson KA et al. ACC 2008 Late breaking Clinical Trial***

# ACCOMPLISH: Design




*Beta blockers; alpha blockers; clonidine; loop diuretics.

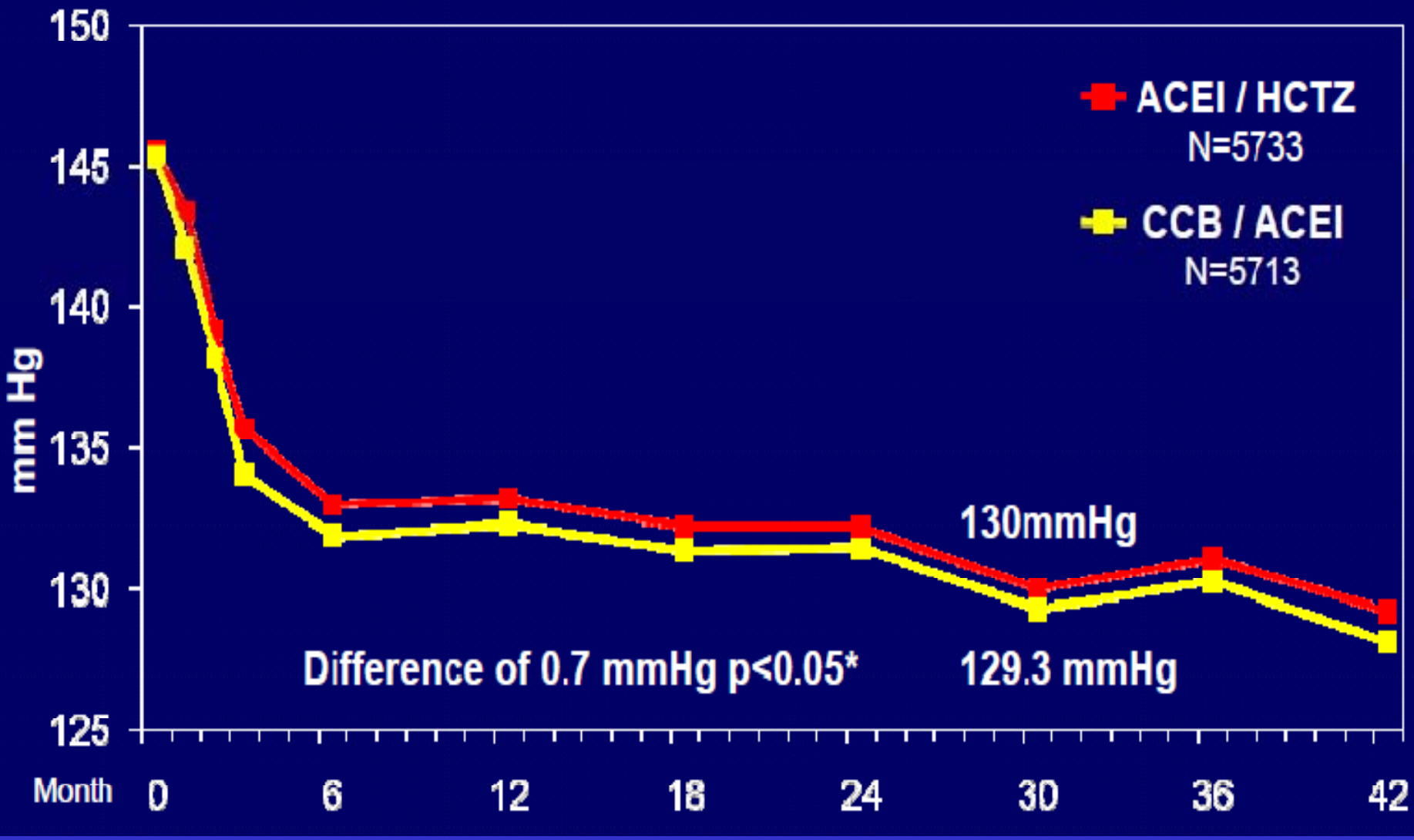
*Jamerson KA et al. ACC 2008 Late breaking Clinical Trial*

# Baseline characteristics of randomized patients

| | | | |
|---|---|---|---|
| **Number of Patients (n)** | Total 11,454 | U.S.A 8,110 (70.7%) | Nordics 3,353 (29.3%) |
| **Age** | Mean (68.4 ±6.9 yrs) | ≥70 years old 4,664 (40.9%) | <70 years old 6,740 (59.1%) |
| **Gender** | Male 6,929 (60.7%) | Female 4,479 (39.3%) | |
| **Weight (kg)** | 88.6 ± 19.1 kg's | | |
| **BMI (kg/m$^2$) (Mean 31.0 ± 6.3)** | **<25 - 1,574 (13.9%)** | **25 ->30 - 4,105 (36.1%)** | **>30 - 5,680 (50.0%)** |
| **Previous Hx of HT <3 months 258 (2.3%)** | Previous Hx of HT 3-<12 months 258 (2.3%) | Previous Hx of HT 1–5 years 3,234 (29%) | Previous Hx of HT >5 years 7,046 (63.1%) |

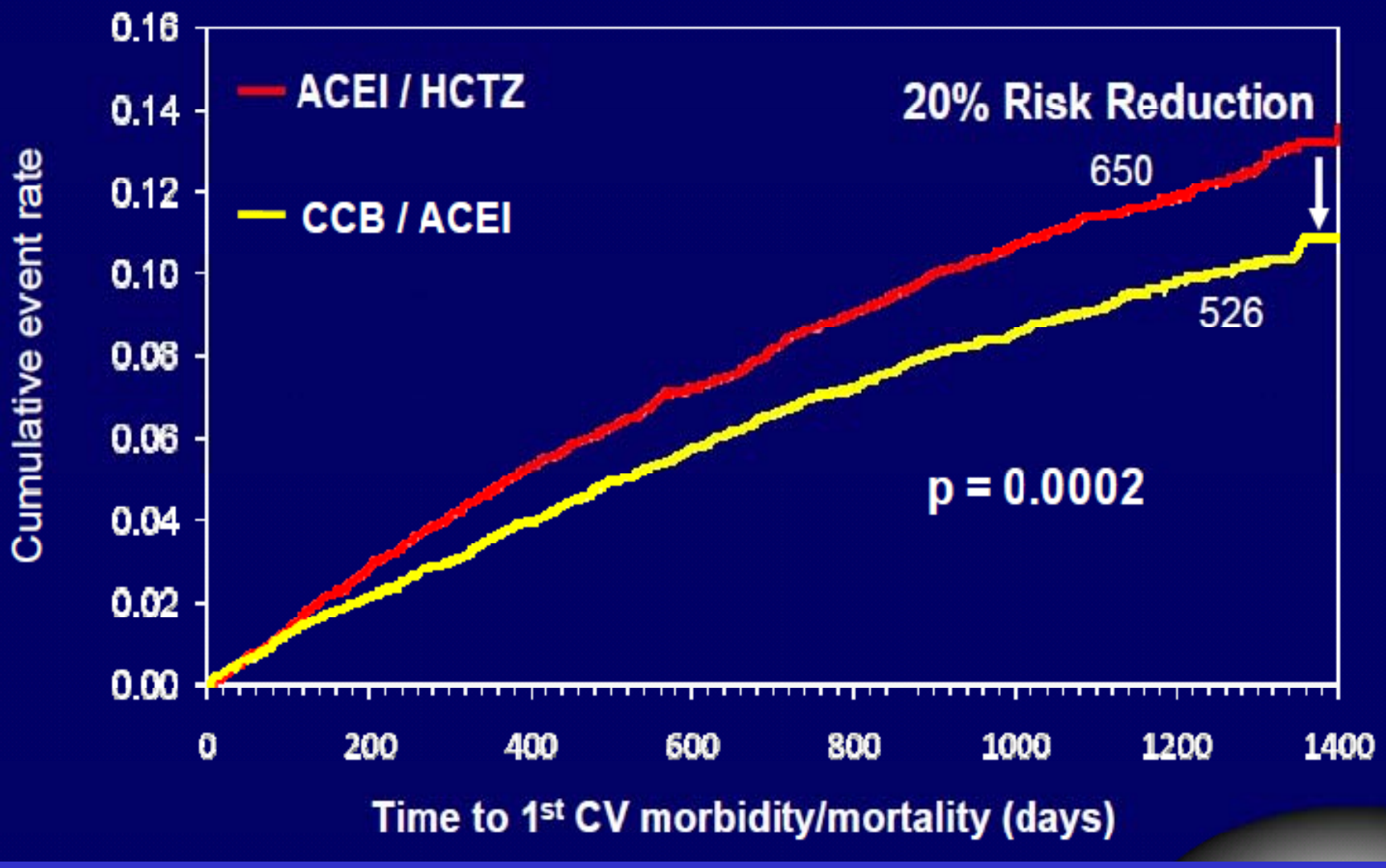
**History of DM in 60%, 86.1% obese or overweight**

# Systolic Blood Pressure Over time




*Jamerson KA et al. ACC 2008 Late breaking Clinical Trial*

# Kaplan Meier for primary analysis




*Jamerson KA et al. ACC 2008 Late breaking Clinical Trial*

# ACCOMPLISH summary

- Single tablet combination therapy was initated in 11,462 high risk hypertensive subjects
- After **mean FU of 39 months**,

- The combination of ACEI/CCB was superior to ACEI/diuretics
- CV morbidity/mortality was reduced by 20%(p=0.0002)
- Hard CV endpoints(CV death, stroke, and MI) was reduced by 20%(p=0.007)

*Jamerson KA et al. ACC 2008 Late breaking Clinical Trial*

# Metabolic syndrome

(K sparing)

DIURETIC*

(Thiazide)

β-blocker*

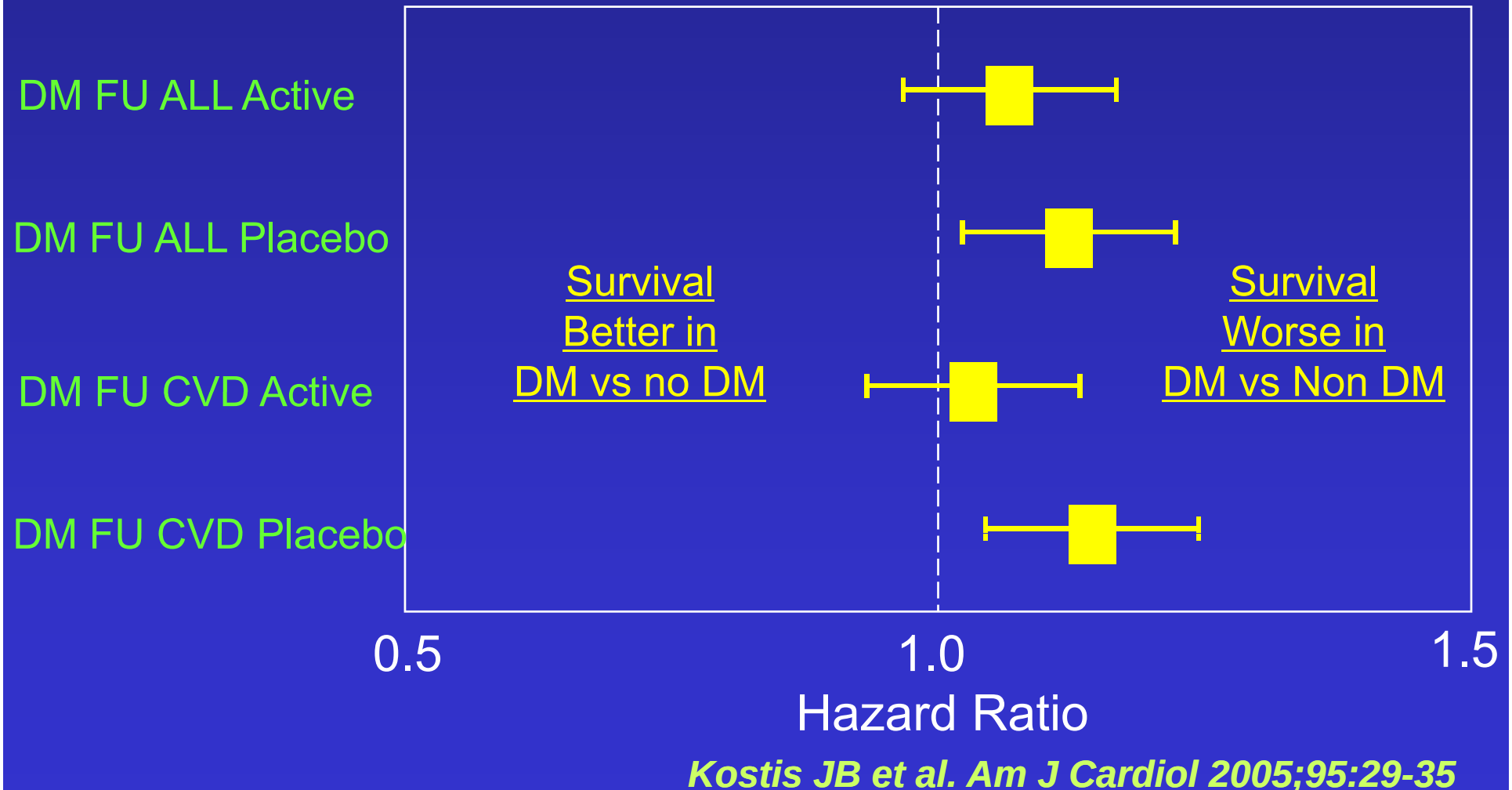
Long Acting CCB*

ACE inhibitor or ARB

** Avoid diuretics and beta blockers if possible as first line agents in metabolic syndrome*

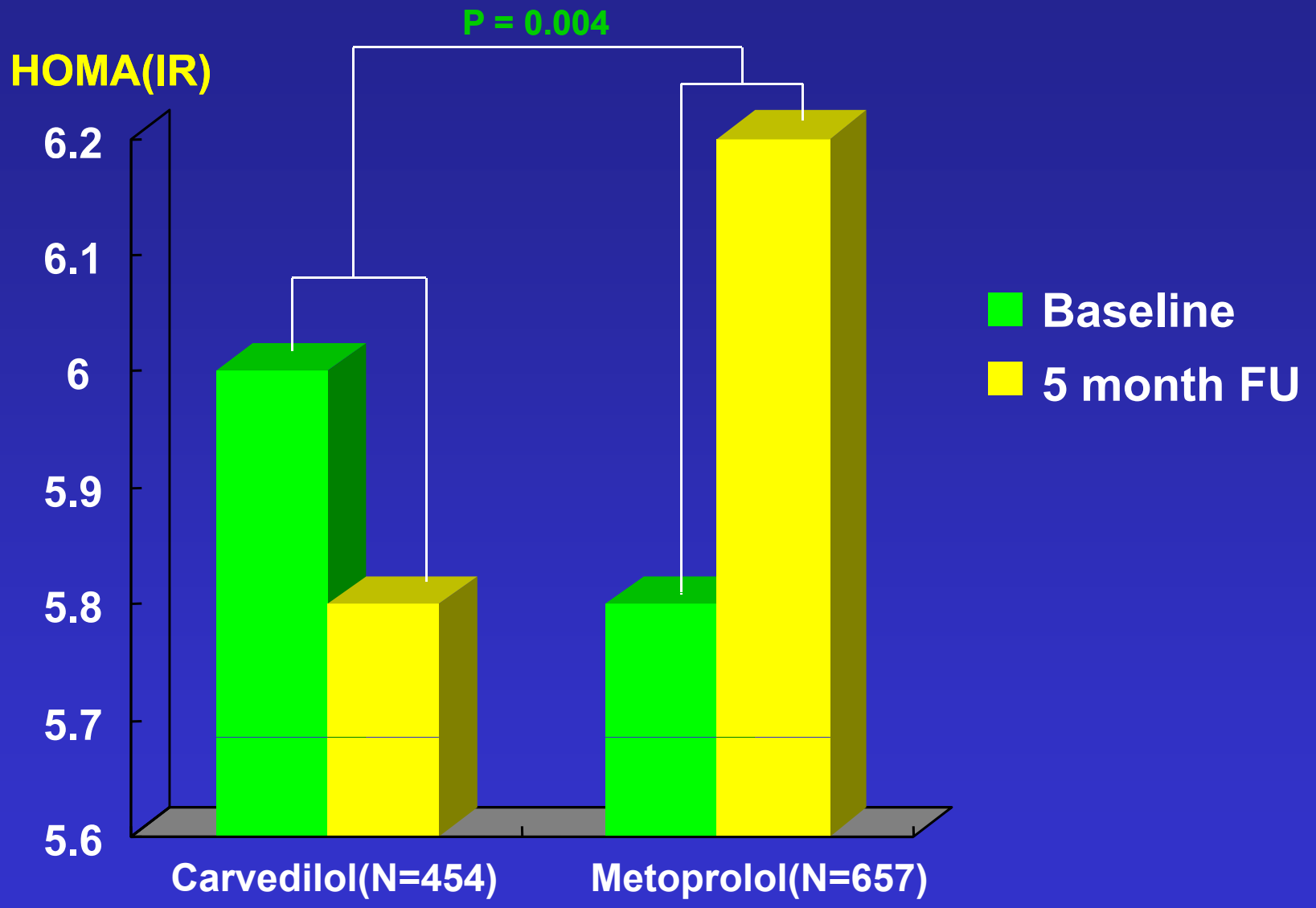
*2007 ESC/ESH guideline. 2007;25:1105-1187*

# Long term effect of diuretic therapy in subjects with DM at FU: SHEP extended FU



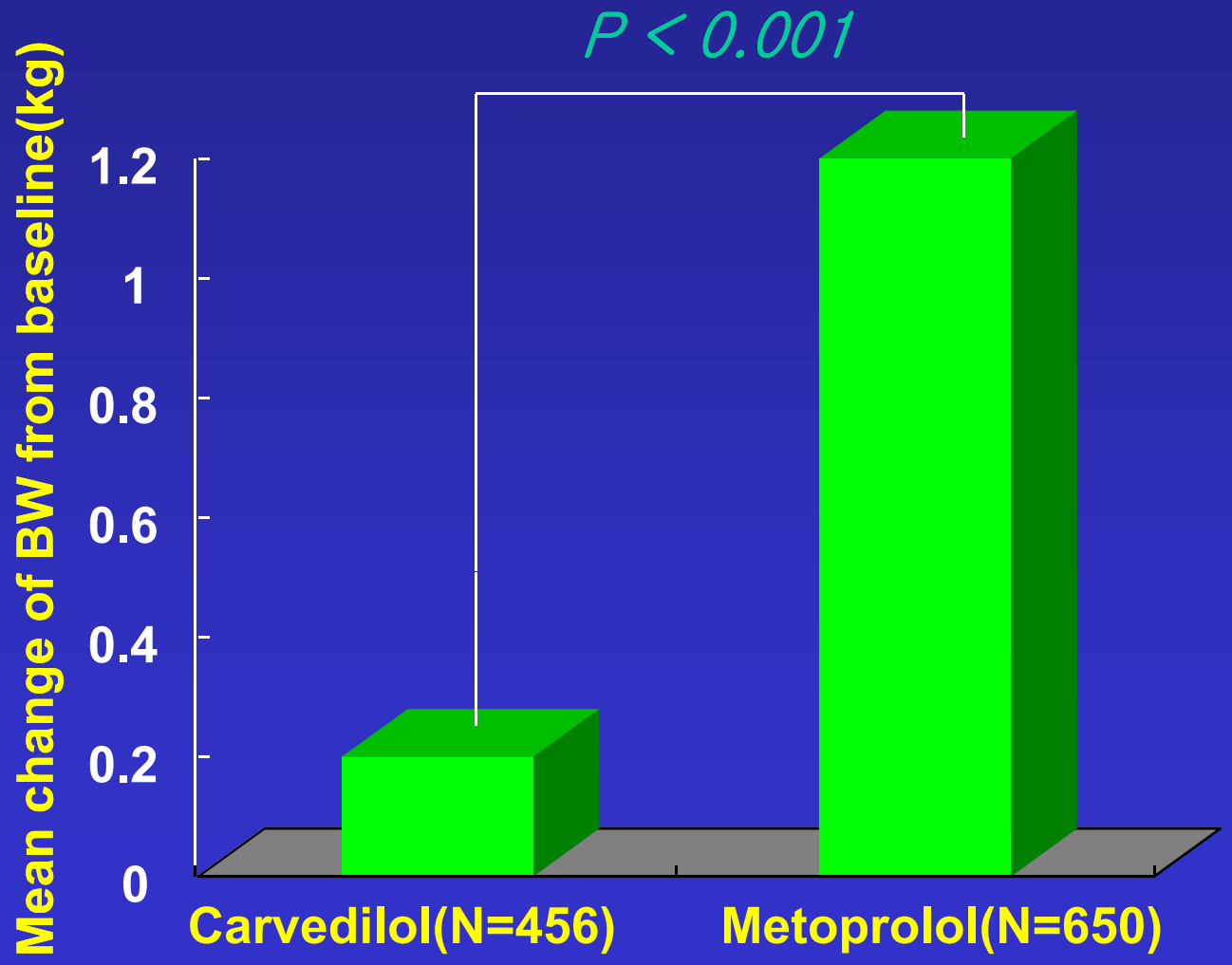

*Kostis JB et al. Am J Cardiol 2005;95:29-35*

# Gemini Study




*Bakris GL. JAMA 2004;292:2227-2236*

# Differential effect of beta blockers on weight gain:GEMINI




*Messerli FH. Am J Med 2007;120:610-615*

# Recommendation for diuretics and beta blockers in metabolic syndrome

- Diuretics and beta blockers are **still important drugs for target blood pressure achievement**

- Do not use diuretics or beta blockers(unless compelling indication) as primary agents in metabolic syndrome and DM

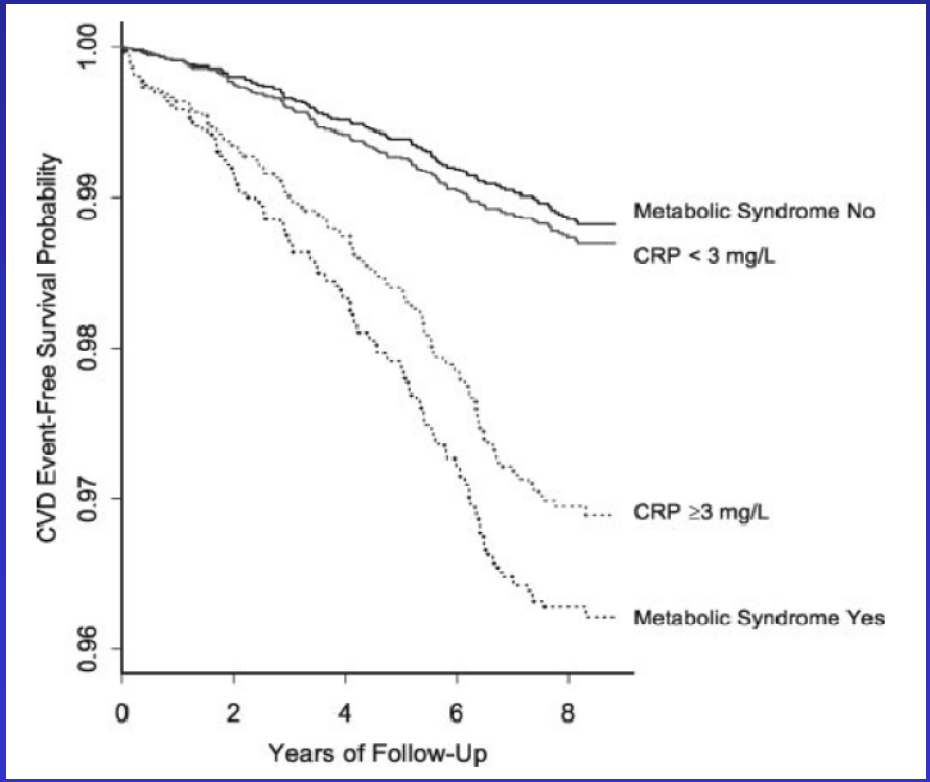
- Use diuretics and beta blockers **to achieve target BP goal** if not controlled by other 1st line drugs.(ACEI, ARB, CCB) Consideration for 3rd generation beta blockers

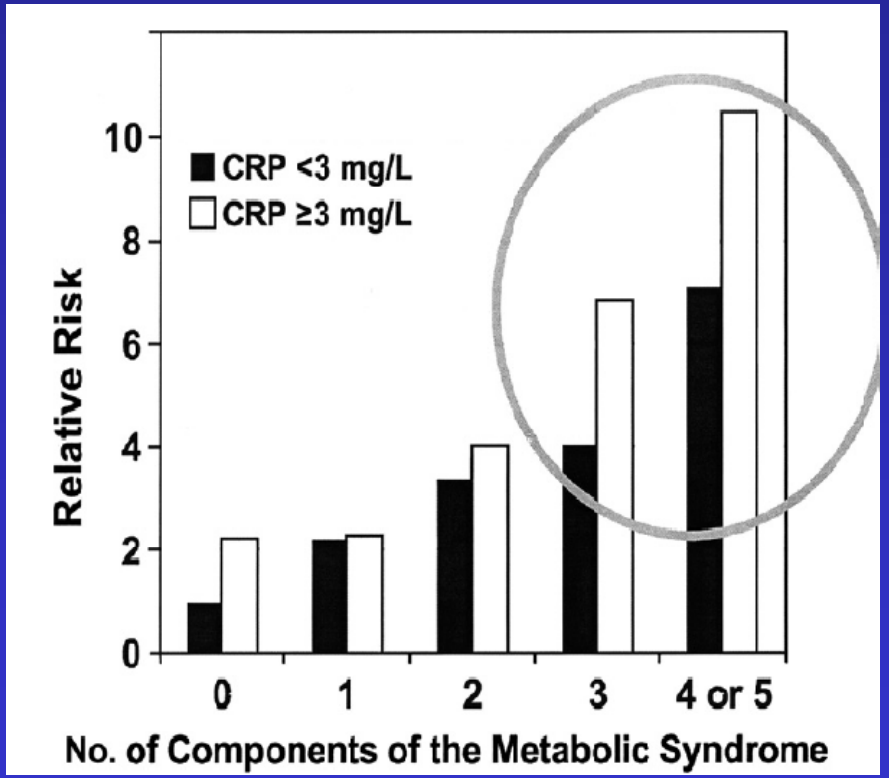
# Yonsei Cardiovascular Hospital

# Yonsei University College of Medicine

# Metabolic syndrome and risk of cardiovascular events

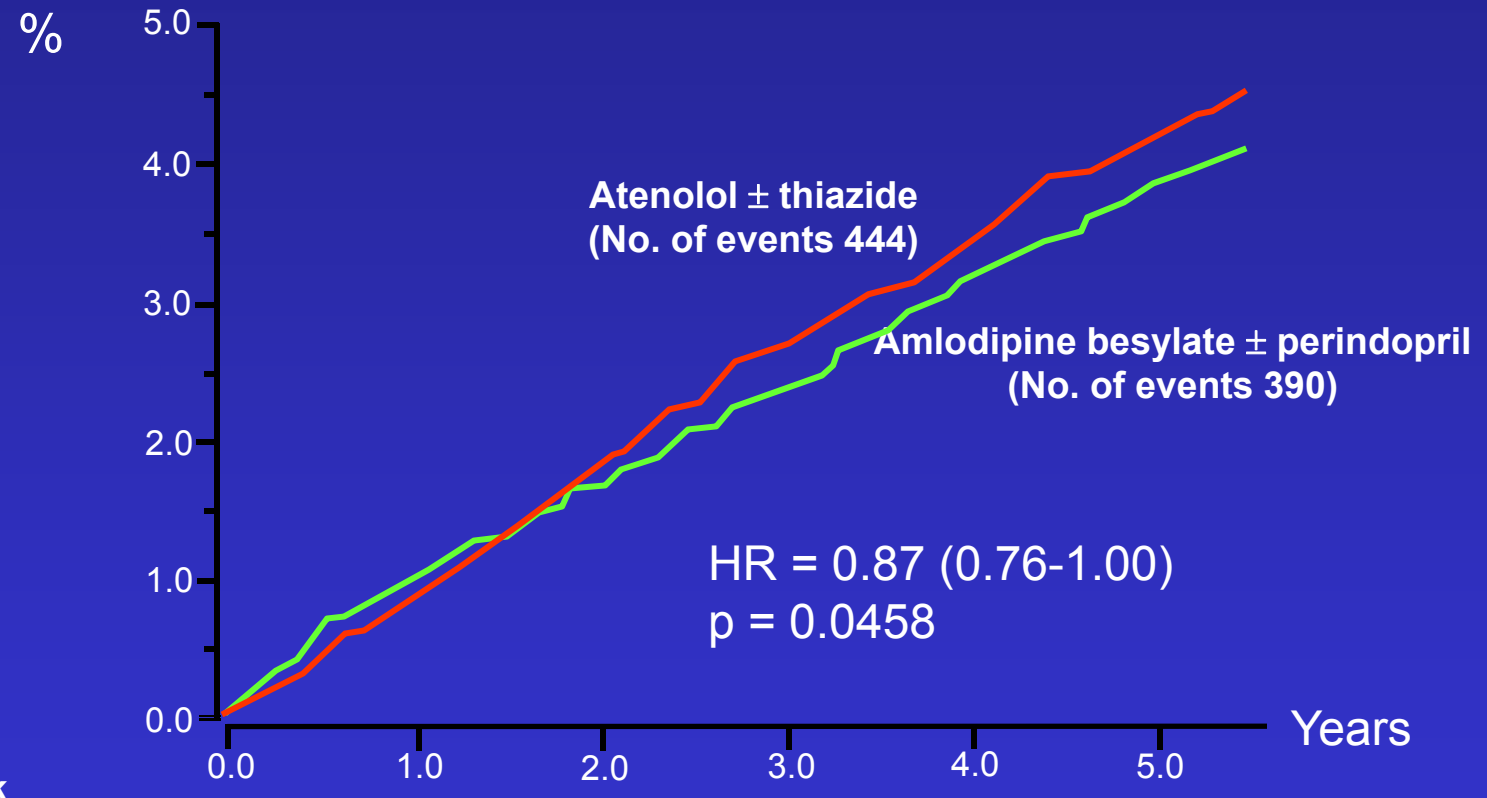
***N = 14719 healthy women FU for 8 years***




*Ridker PM et al. Circulation 2003;107:391-397*

# Endpoints: Non-fatal MI (excl silent) + fatal CHD




| Number at risk | 0.0 | 1.0 | 2.0 | 3.0 | 4.0 | 5.0 |
|---|---|---|---|---|---|---|
| Amlodipine besylate ± perindopril | 9639 | 9485 | 9354 | 9193 | 8998 | 7895 |
| Atenolol ± thiazide | 9618 | 9475 | 9302 | 9099 | 8881 | 7768 |

*Dahlöf B et al. Lancet 2005;366:895-906*