

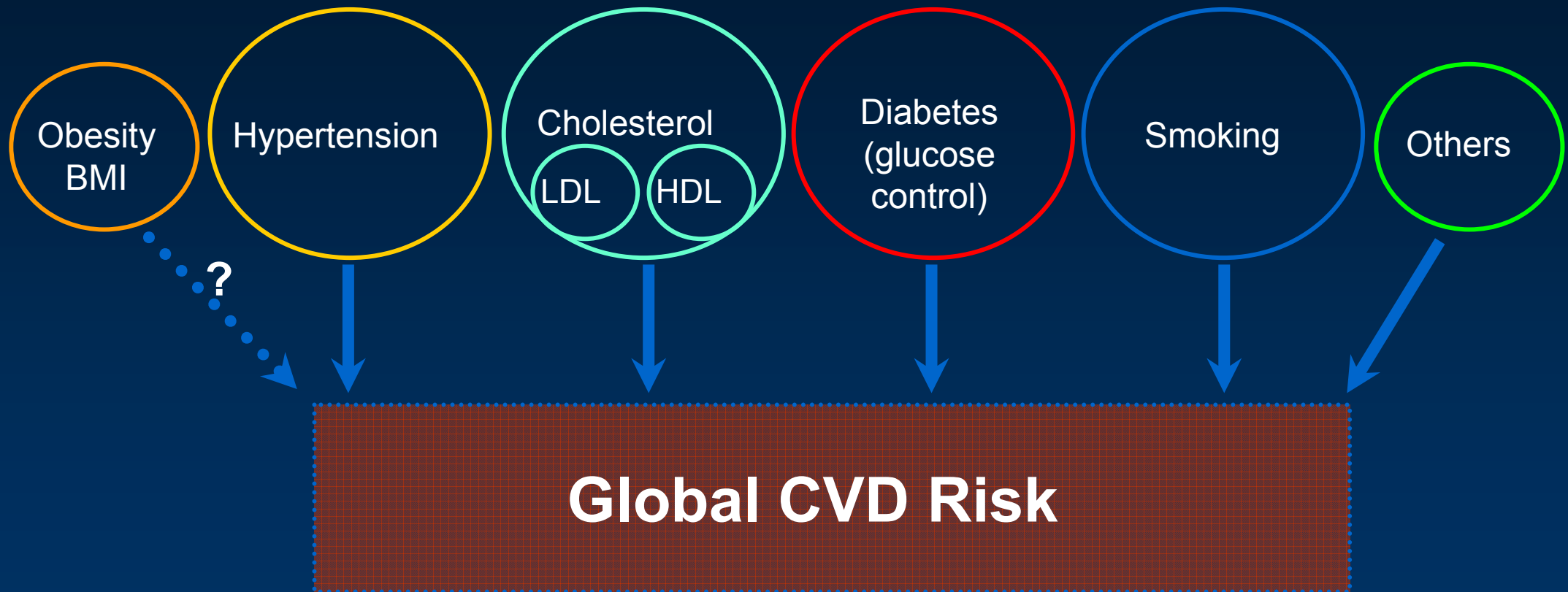


Improve the Adherence, Save the Life

Park, Chang Gyu

Korea University Guro Hospital
Cardiovascular Center
Seoul, Korea

Modifiable CVD Risk Factors



Individual risk factors by themselves are weak predictors of absolute CHD risk

ESH 2007: Stratification of CV Risk into 4 Categories

Blood Pressure (mm Hg)

Other risk factors, TOD, or disease	Normal SBP 120-129 or DBP 80-84	High normal SBP 130-139 or DBP 85-89	Grade 1 HTN SBP 140-159 or DBP 90-99	Grade 2 HTN SBP 160-179 or DBP 100-109	Grade 3 HTN 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, diabetes, TOD, or MS	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

TOD = target organ damage; HTN = hypertension; MS = metabolic syndrome.

ESH Guidelines. *Eur Heart J.* 2007. <http://eurheartj.oxfordjournals.org/cgi/content/full/ehm236v1#SEC10>.

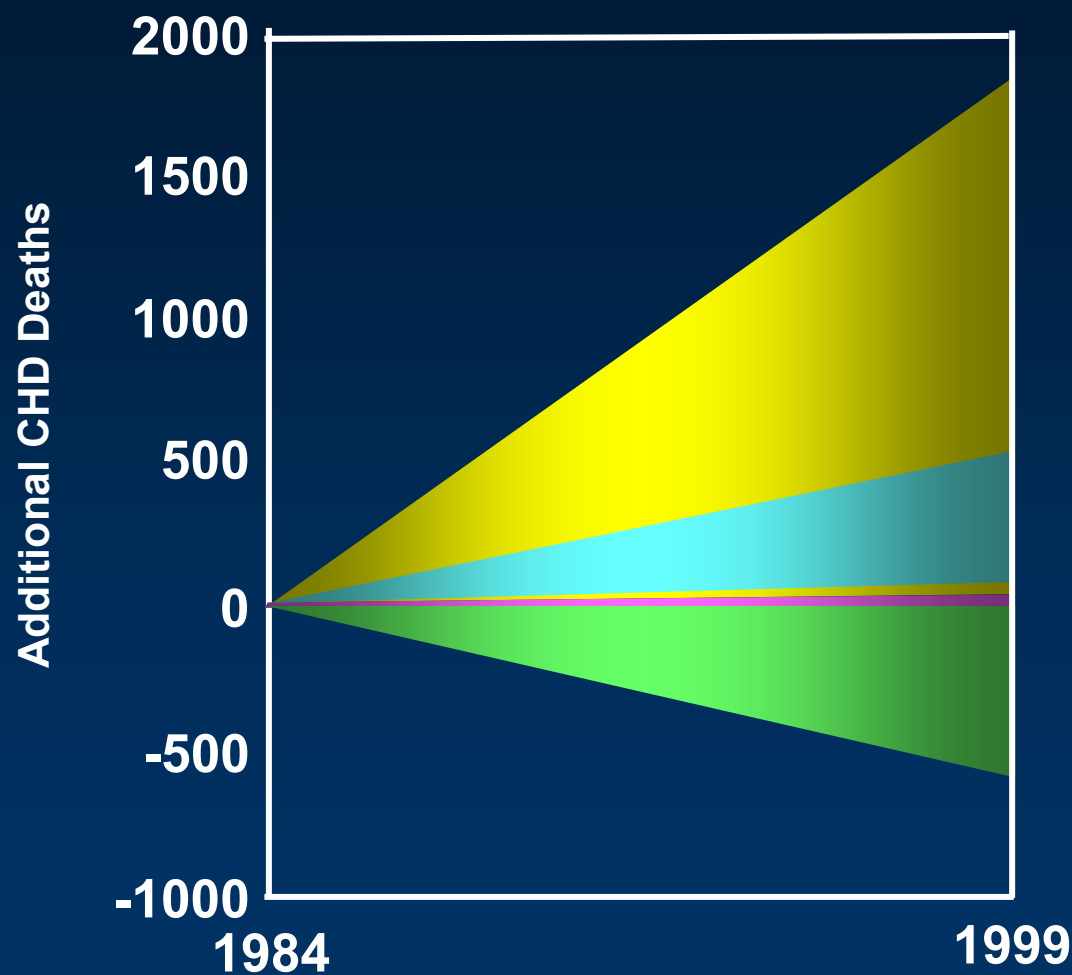
Box 21 Position statement: Treatment of associated risk factors

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 ($\geq 20\%$ 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.

Coronary Heart Disease Mortality in Beijing 1984-1999



**1822 Extra Deaths Attributable
to Risk Factor Changes**

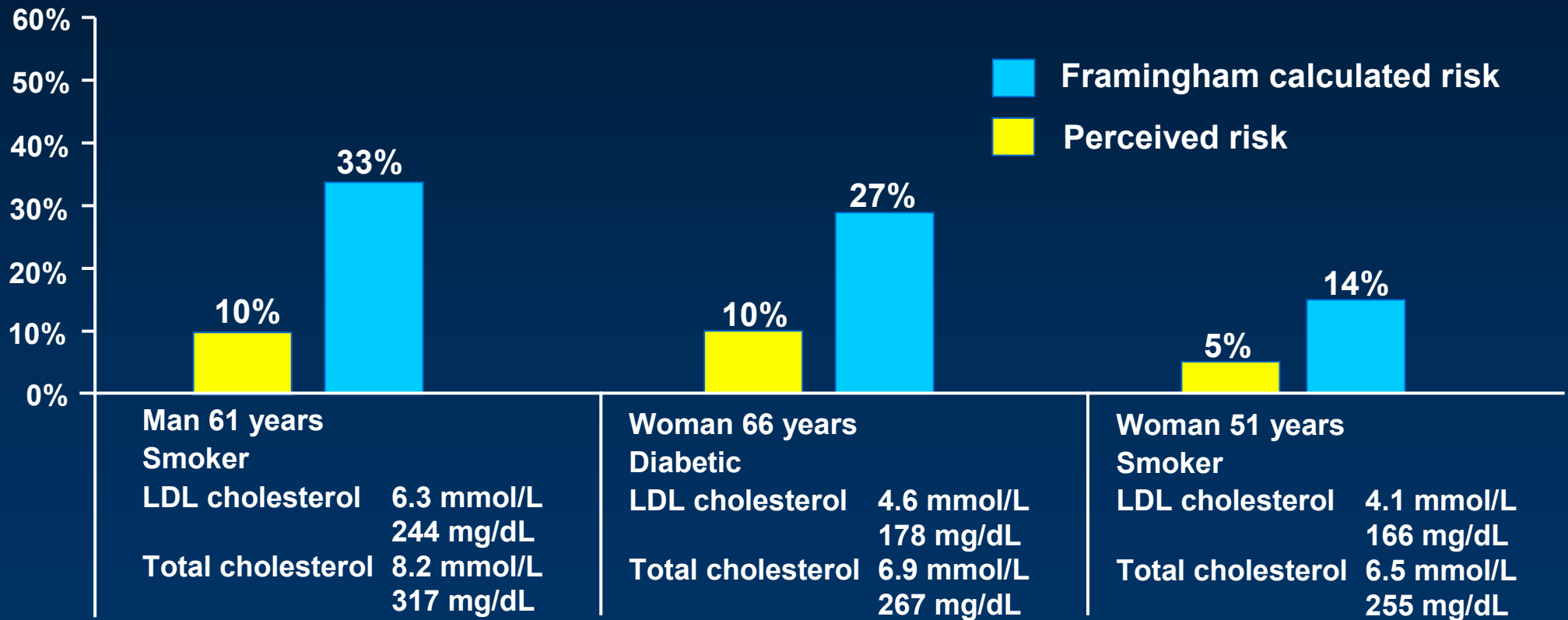
Cholesterol	77%
Diabetes	19%
BMI	4%
Smoking	1%

642 Fewer Deaths by Treatments

AMI treatments	41%
Hypertension treatment	24%
Secondary prevention	11%
Heart failure	10%
Aspirin for angina	10%
Angina: CABG & PTCA	2%

Physicians Often Underestimate Their Patients' CV Risk

Comparison of actual vs perceived 10-year risk among 80 Swedish GPs asked to estimate the risk of a number of given patient profiles



Patient SJ

73-year-old diabetic woman whose high blood pressure is not adequately controlled with an ACEI.

BMI: 29 kg/m²

BP: 158/99 mm Hg

Lipid profile:

TC 5.4 mmol/L (211 mg/dL)

LDL-C 3.6 mmol/L (139 mg/dL)

HDL-C 1.0 mmol/L (39 mg/dL)

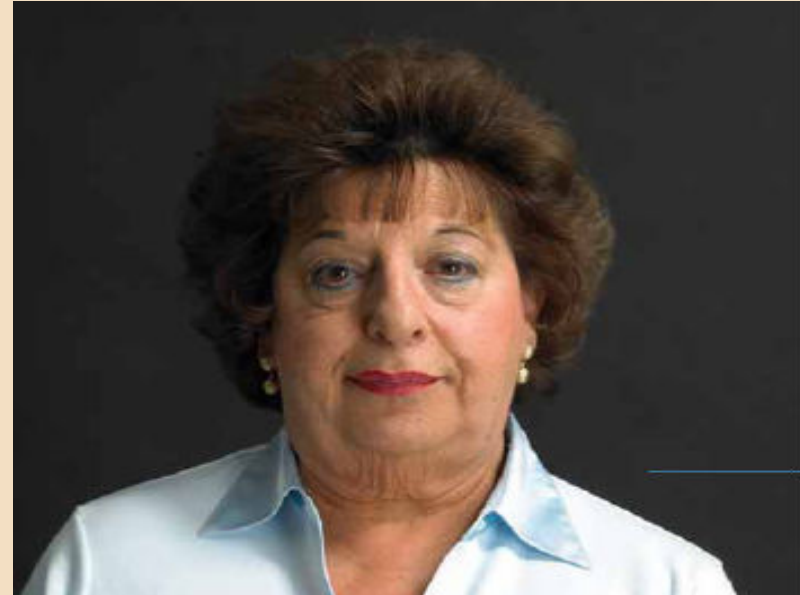
TGs 1.8 mmol/L (165 mg/dL)

TC:HDL ratio 5.4

Current medications:

Metformin

ACEI at maximum dose



Total CVD Risk = 41.2%

Started on

Amlodipine besylate 5 mg and

Atorvastatin calcium 10 mg

Patient SJ – Six Months Later

73-year-old diabetic woman, treated for hypertension. Has lost 3 kg with diet and exercise. Reports that she occasionally forgets to take her pills.

BP: 142/90 mm Hg

Lipid profile:

TC 5.0 mmol/L (196 mg/dL)

LDL-C 3.2 mmol/L (125 mg/dL)

HDL-C 1.1 mmol/L (43 mg/dL)

TGs 1.6 mmol/L (140 mg/dL)

TC:HDL ratio 4.5

Current medications:

Metformin

ACEI

Amlodipine besylate 5 mg

Atorvastatin calcium 10 mg



What Are Possible Causes of This Patient's Failure to Reach Targets?

1. Nonresponder to statins
2. Amlodipine besylate dose too low
3. Poor adherence to medication
4. All of the above

What Are Possible Causes of This Patient's Nonadherence?

1. Overall pill burden
2. Timing of antihypertensive and lipid-lowering therapy initiation
3. Dose frequency
4. All of the above

Reasons for poor BP control

- Clinical inertia or lack of aggressive Tx by physicians.
- Resistant hypertension
 - due to **poor patients adherence** (13%)

Hidden Risk Factor—Nonadherence

80% can be achieved by forced medication titration and close monitoring.

ALLHAT, HOT, CONVINCe extra

Nonadherence

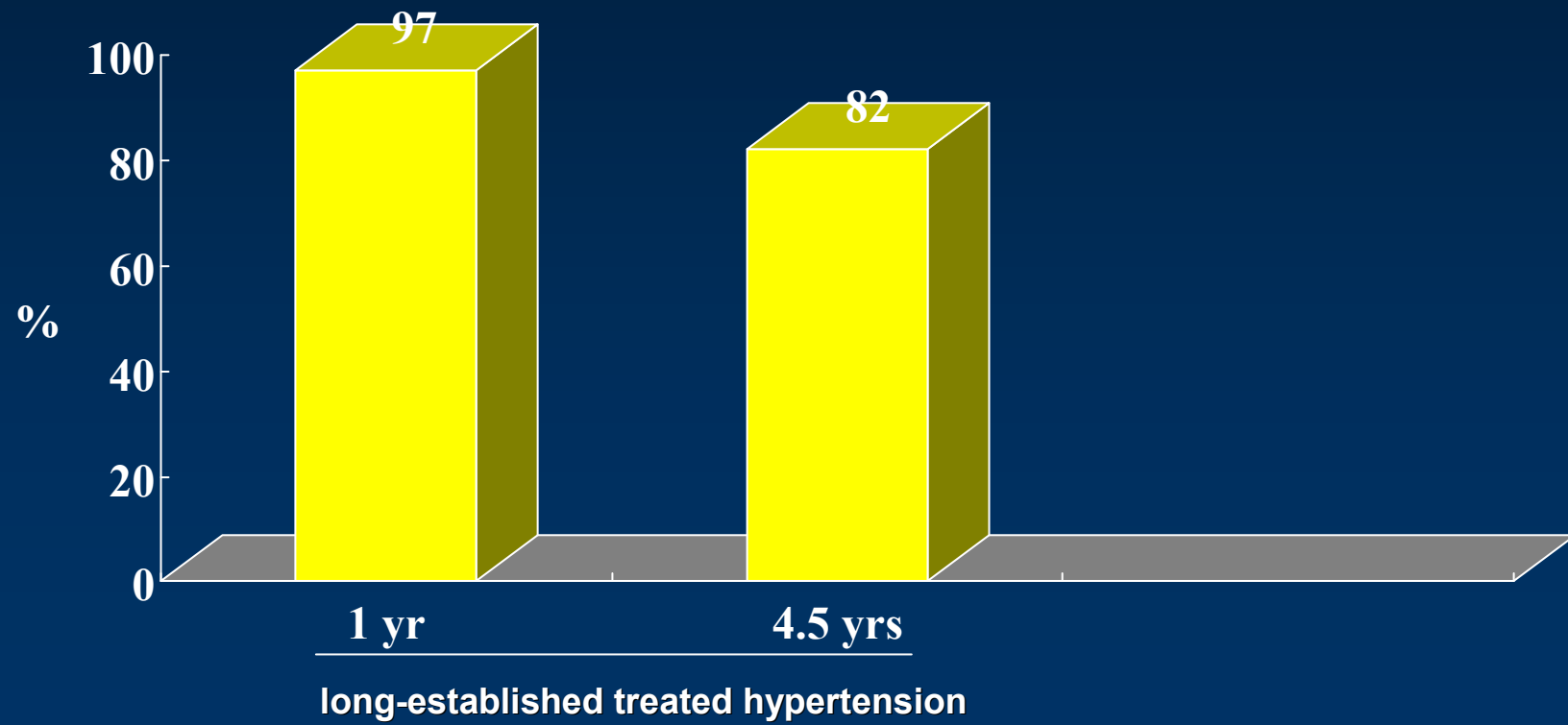
- Defined as taking medications as prescribed 75% of the time or less

Association of medication nonadherence with CHD death, MI, and stroke in 1007 participants with stable CHD and 3.9 years follow-up data

Variable	Adjusted HR*	P
CHD death	3.8	0.01
MI	1.5	0.33
Stroke	4.4	0.01
Any of the above	2.3	0.006

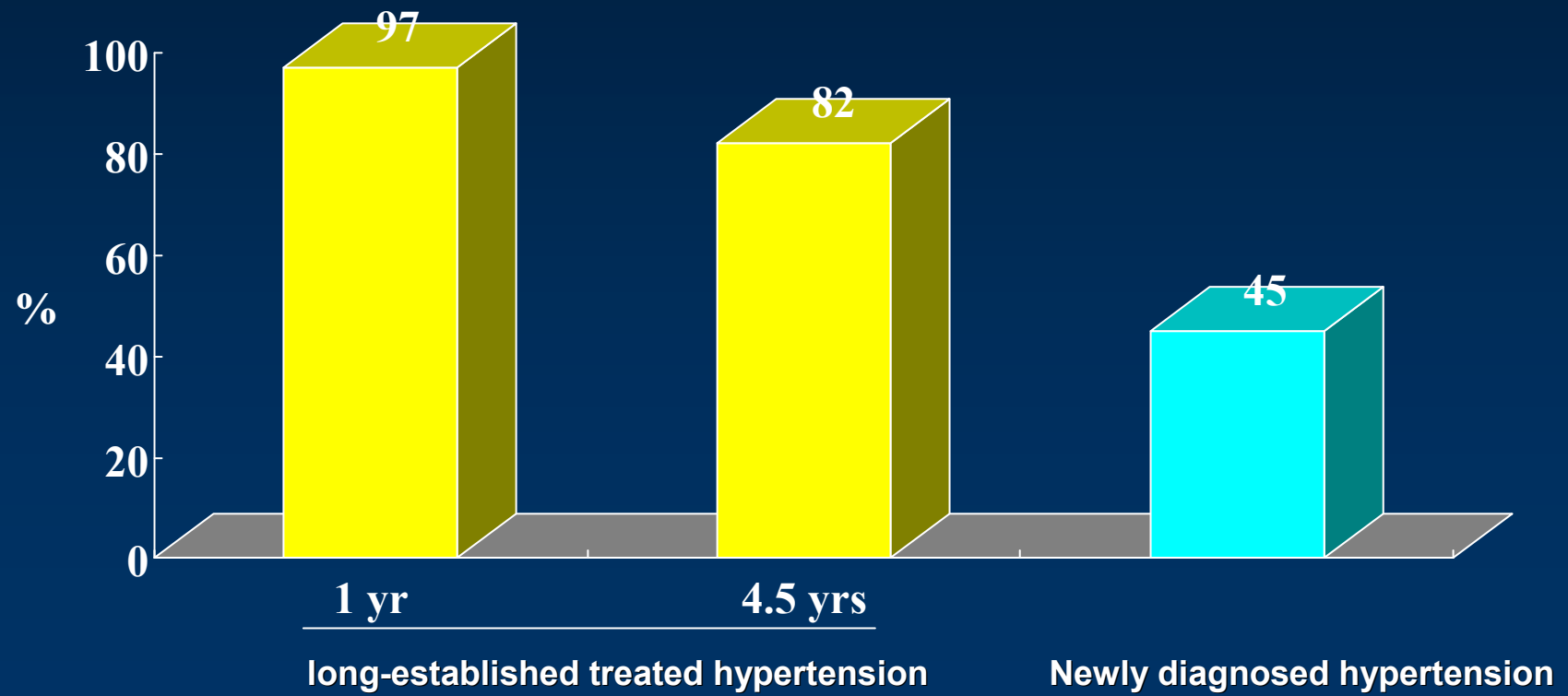
Adherence

Medication Persistent Rates



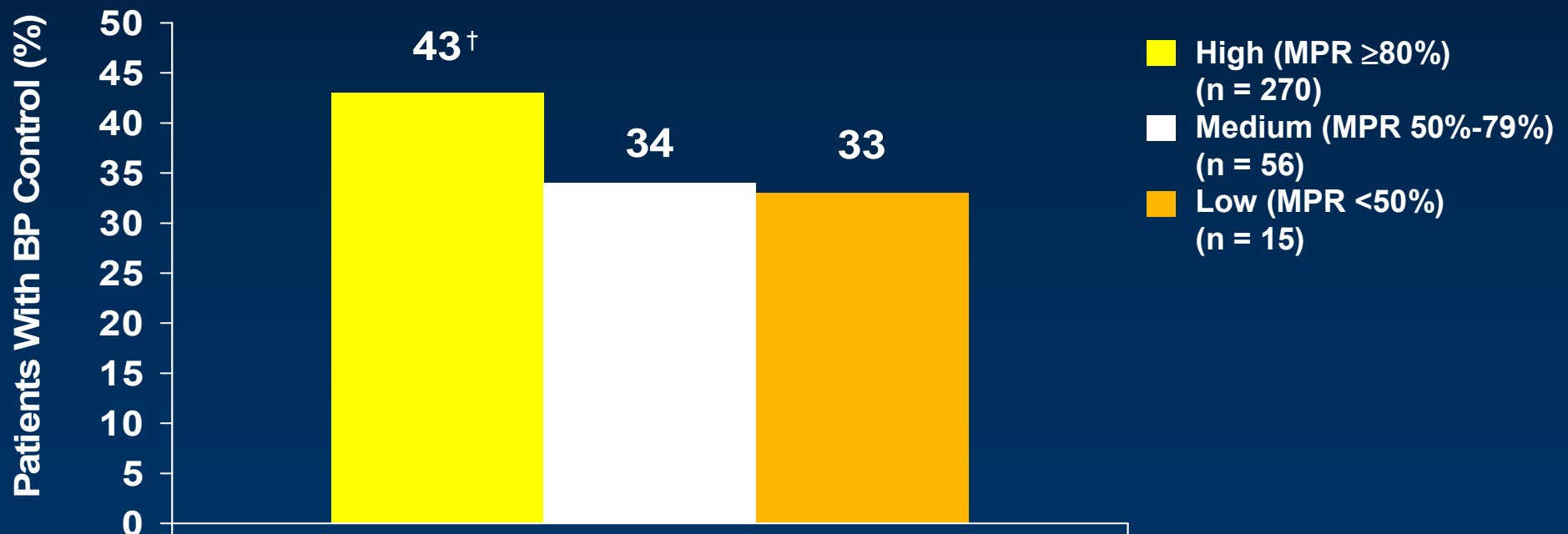
Adherence

Medication Persistent Rates



Low Adherence to Antihypertensive Medication Is Associated With Poor BP Control

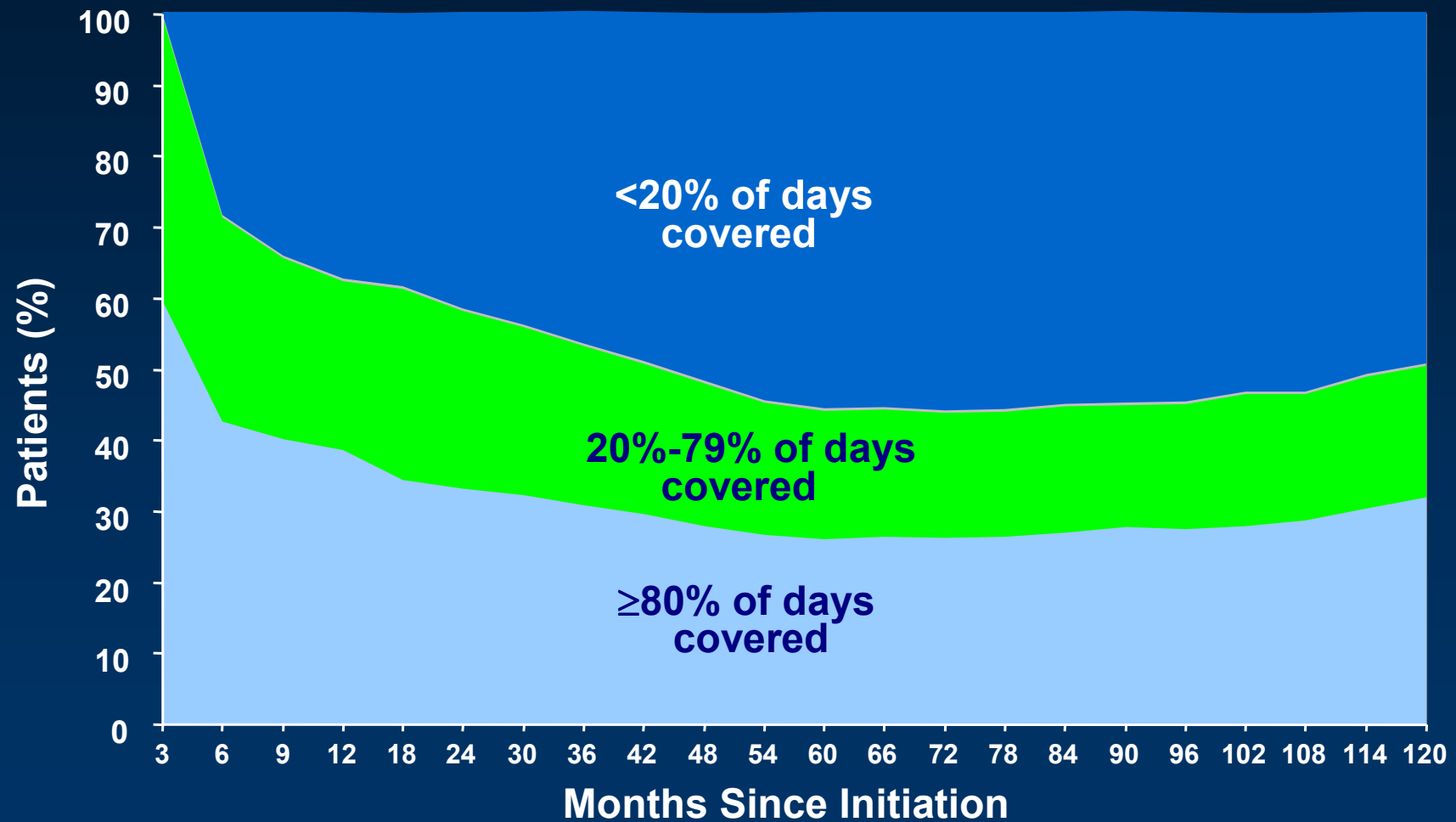
- Highly adherent patients had 45% greater odds of achieving blood pressure (BP) control than patients with medium or low adherence in regression analysis*



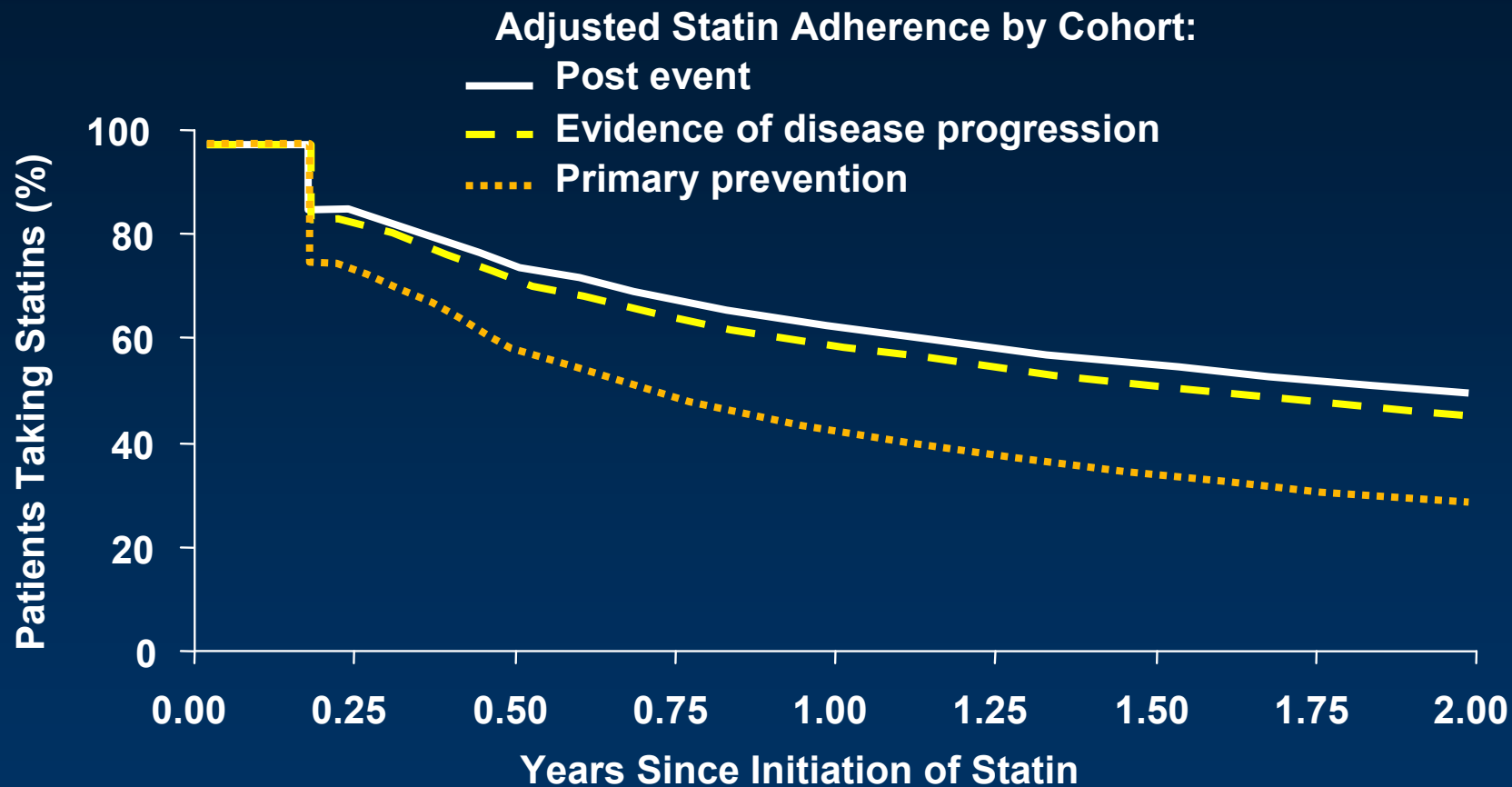
*When controlled for age, gender, and comorbidities (OR = 1.45; $P = .026$ in regression analysis).

[†] $P = .06$ prior to adjustment.

Adherence With Statins Drops Over Time in Elderly Patients



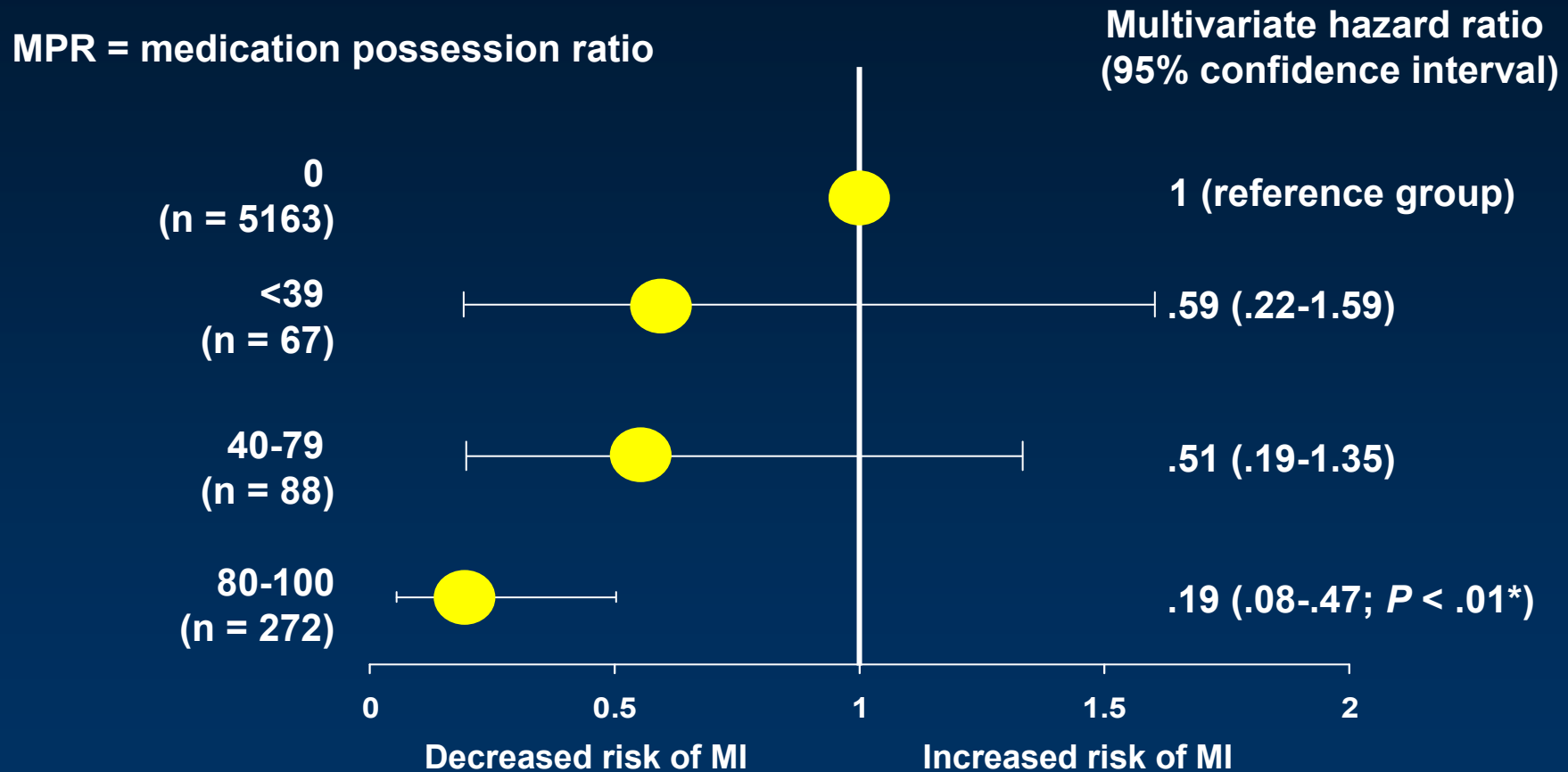
Adherence to Statin Therapy Is Lowest in Primary Prevention



Cohort study using linked, blinded, population-based administration data sources from Ontario, Canada. Subjects (N = 143,505) were outpatients ≥ 66 years with a new statin prescription. Adherence: statin dispensation at least every 120 days.

Jackevicius CA et al. *JAMA*. 2002;288:462-467.

Lower Adherence to Statin Therapy Is Linked to Increased Risk of MI Recurrence



*Compared with reference group, patients not taking statins.

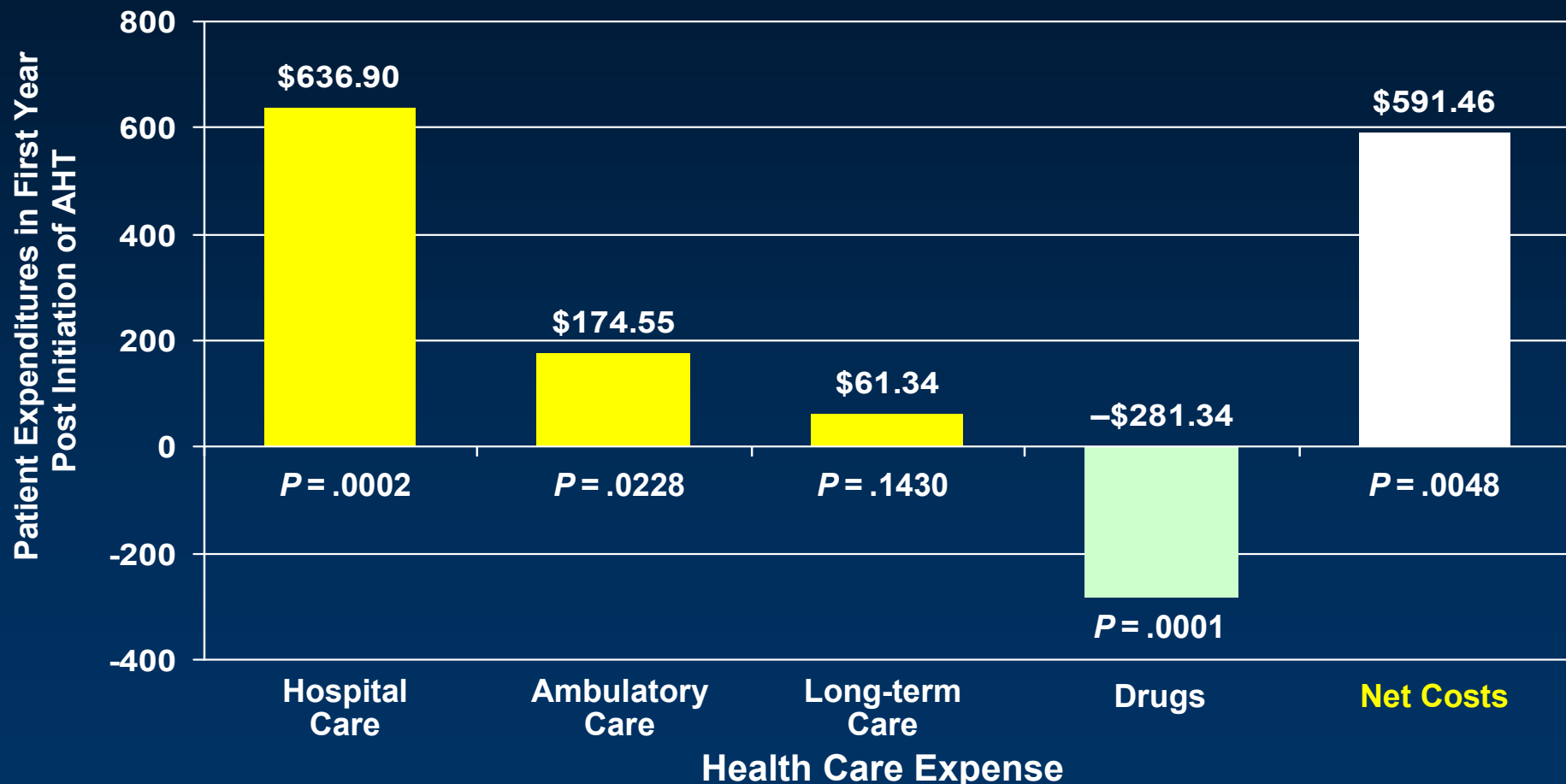
Cohort study using a record linkage database in Tayside, Scotland (N = 5590). 2.4 years average follow-up post initial MI.

MI = myocardial infarction. MPR was the basis for adherence measurement.

Wei L et al. *Heart*. 2002;88:229-233.

Nonadherence to AHT Was Associated With Increased Total Health Care Costs

Estimated effect of interrupting or terminating AHT by type of service



Retrospective study of Medi-Cal paid claims data. N = 6419 patients with ≥ 1 AHT Rx. 1994 US dollars. Continuous therapy: filling each antihypertensive prescription within 30 days + 15-day grace period over the course of a year from date of initial dispensation.

McCombs JS et al. *Med Care*. 1994;32:214-226.

Patient Barriers to Adherence

- **Insufficient knowledge**
- **Negative beliefs about hypertension or its Tx**
- **Poor self-efficacy or lack of control**
- **Younger age, male gender, minority race**
- **Cognitive impairment**
- **Active depression**
- **Alcohol or substance abuse, Smokers**
- **Low socioeconomic status**
- **Complicated or costly medication regimen**
- **Rapid lowering of BP or excess initial medication dose**

Adherence Facilitators

- **Female gender**
- **Higher education, higher socioeconomic status**
- **Married**
- **Multiple chronic conditions, especially a prior CVE**
- **Higher level of BP**
- **Strong patient-provider relationship**
- **Patients who are involved with their Tx decision**
- **Patient knows BP goal**
- **Self-monitoring of BP**
- **Clinic and refill reminders, pill boxes, adherence aids**

Predictors of Adherence

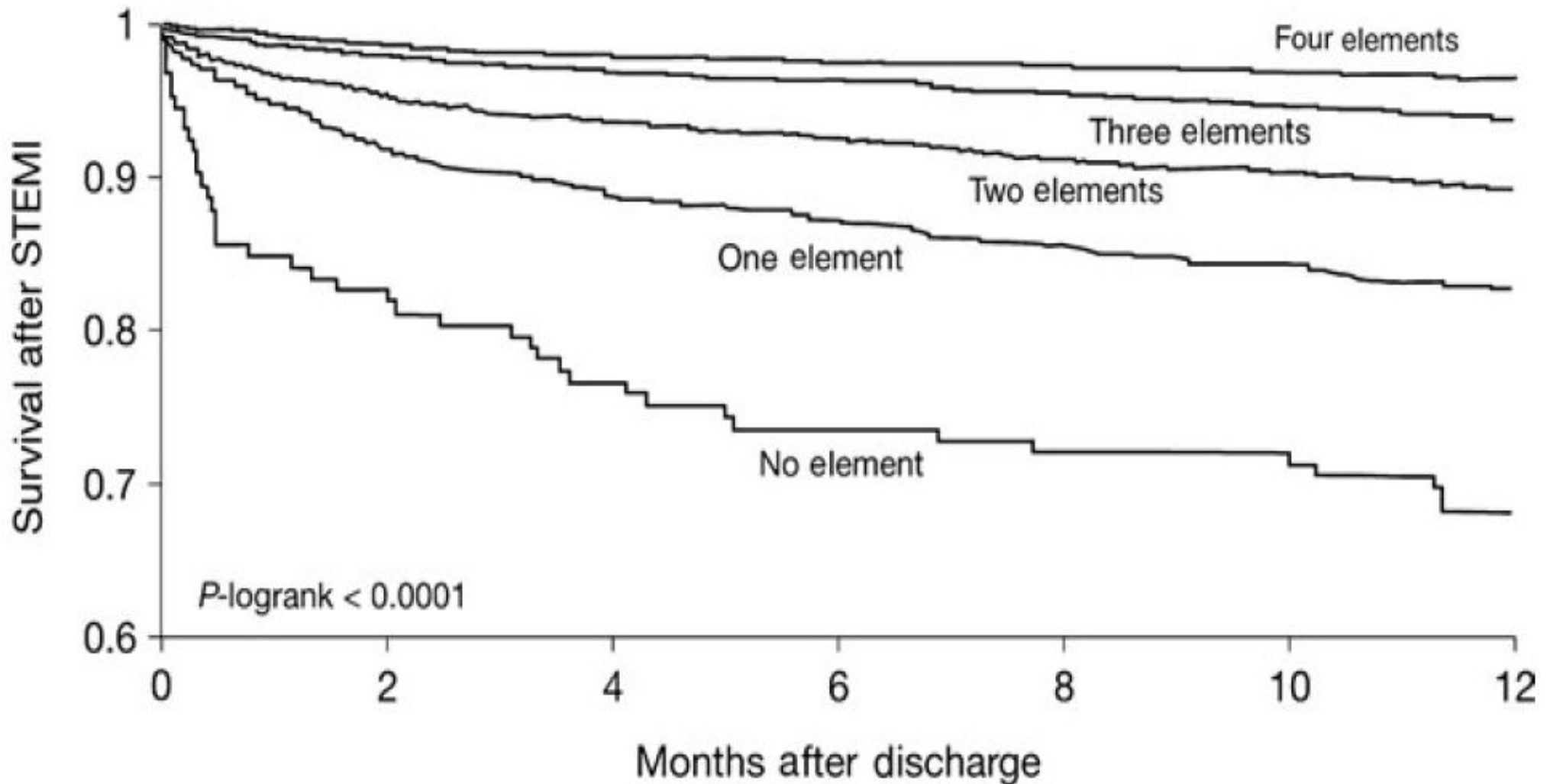
CV medication regimen

- *Overall pill burden*
- *Timing of AHT and LLT initiation*
- *Dose frequency*
- *Single-pill vs 2-pill therapy*

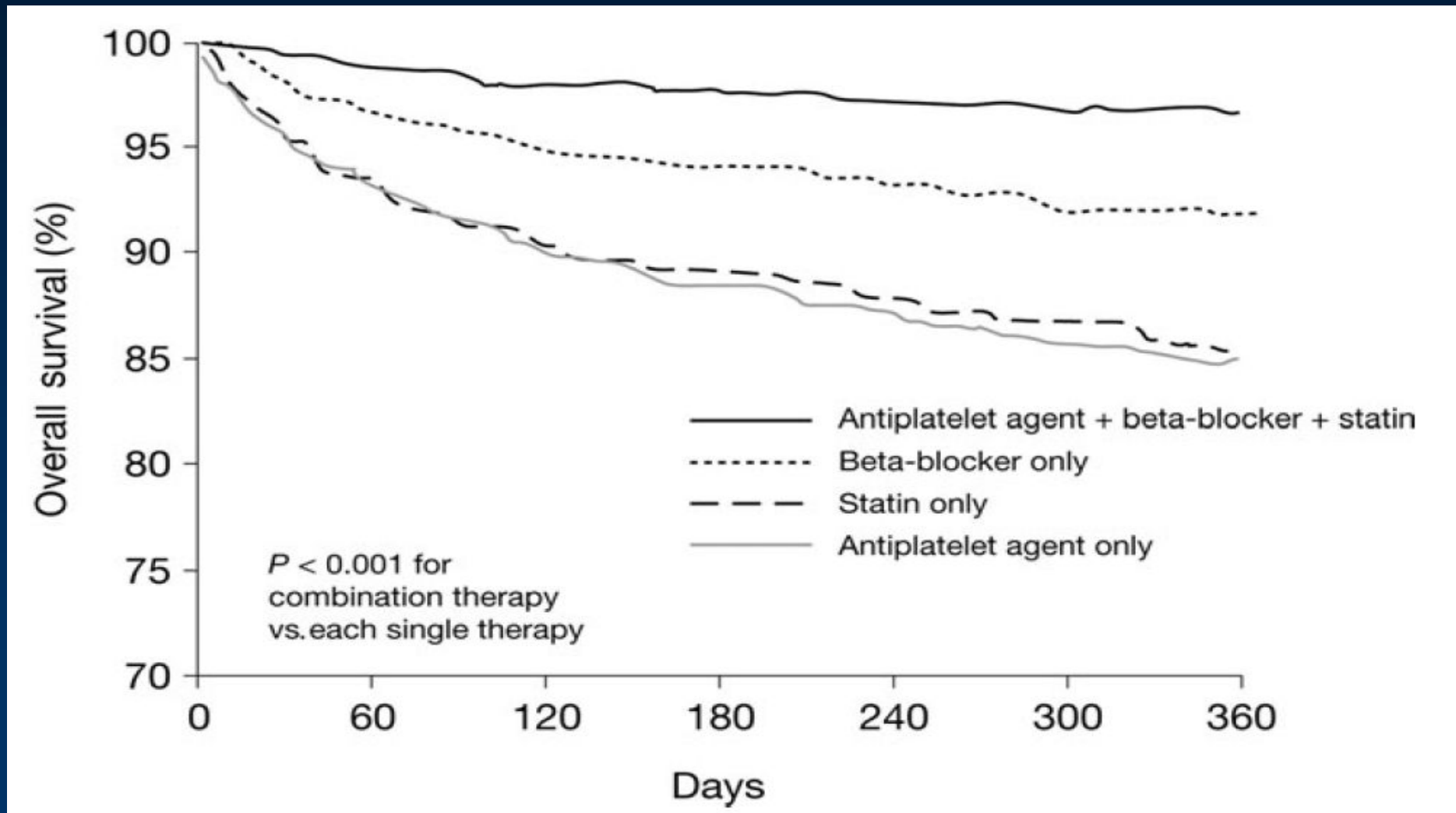
**Pill Burden
Too many?
What can we do?**



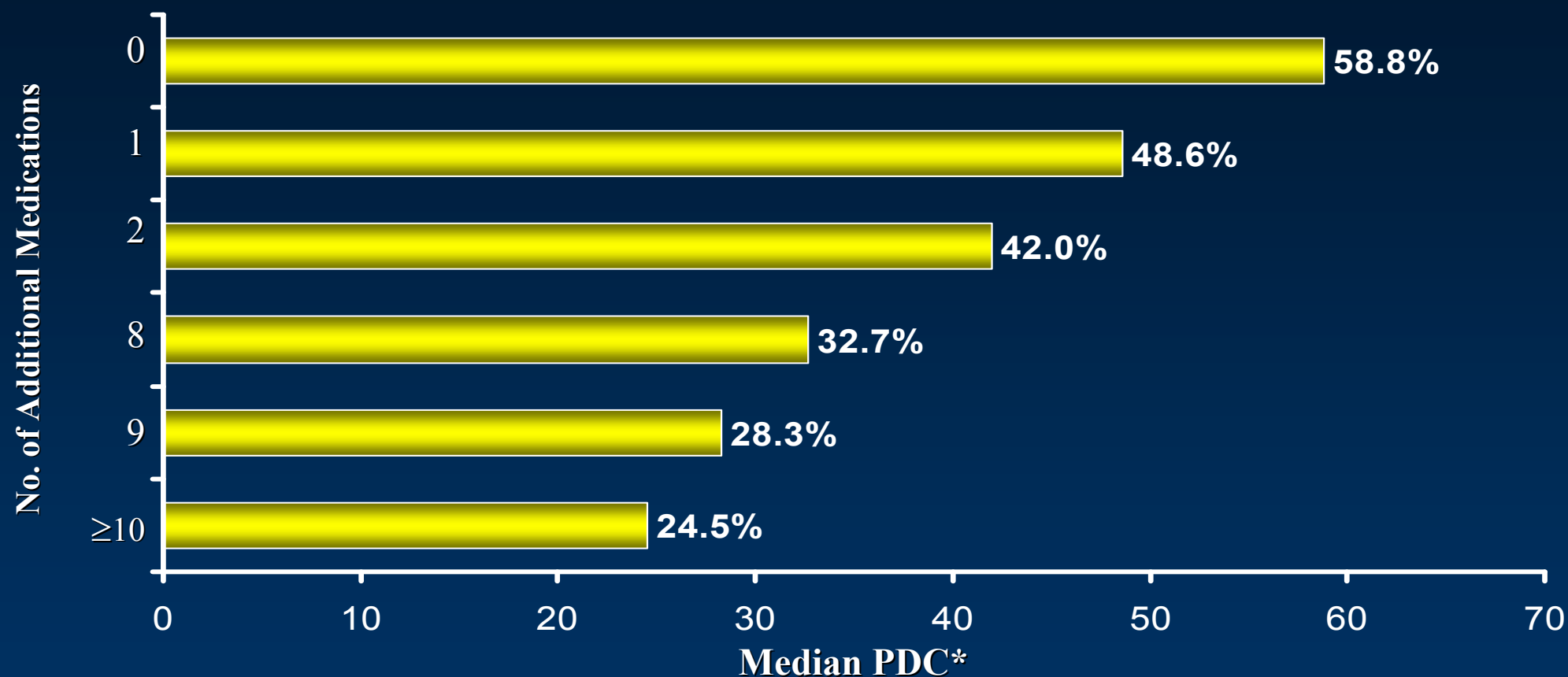
Post-MI survival according to number of medications (aspirin, beta-blocker, ACEI, statin)



Comparison with single target treated and triple-combination therapy in patients with acute MI



Adherence to Concomitant Antihypertensive Decreases as Number of Medications Increases



Incremental pill burden had greatest effect on adherence in patients taking the fewest medications

*Calculated for first year of concomitant therapy with antihypertensive and lipid-lowering drugs. Patients adherent if PDC \geq 80% for both classes. PDC=proportion of days covered by antihypertensive and lipid-lowering drugs.

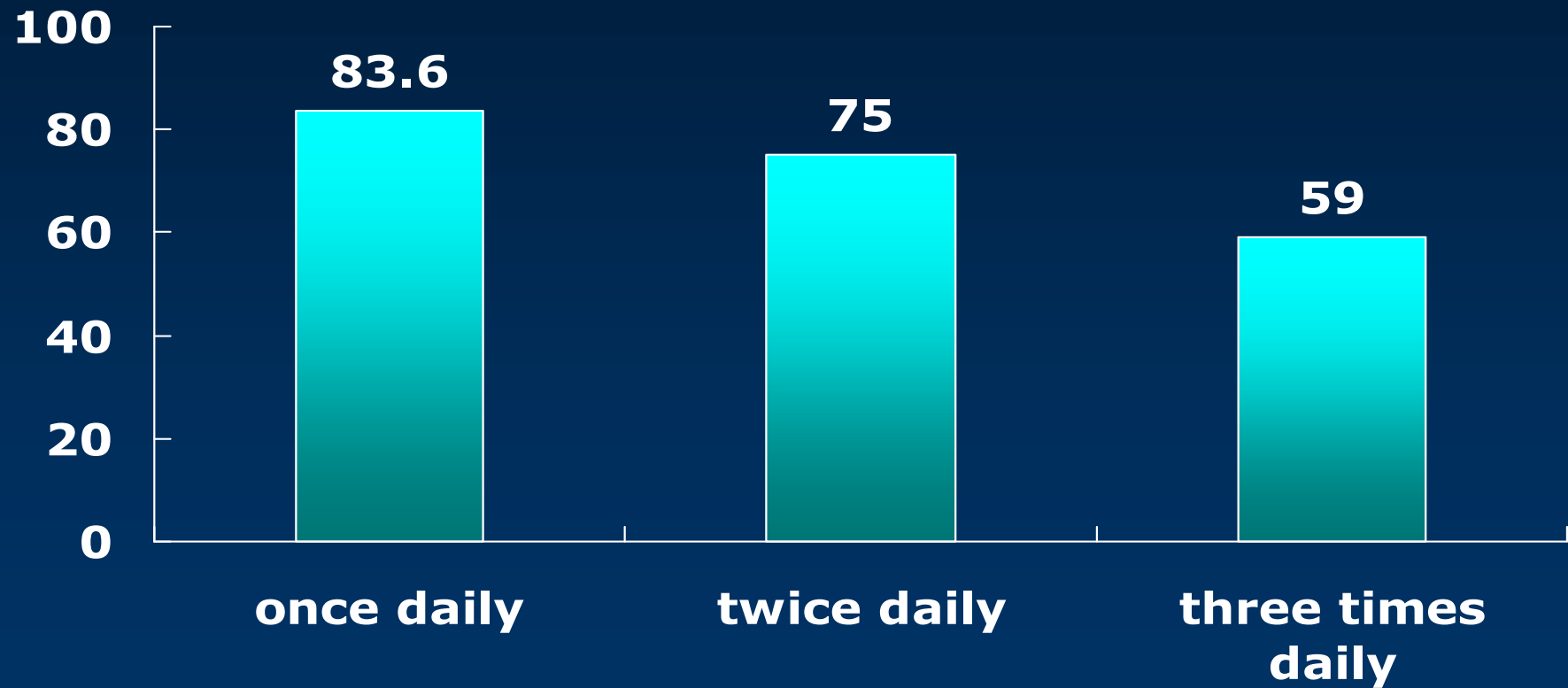
Benner JS et al. ACC 2006. Abstract.

How are we improve adherence?

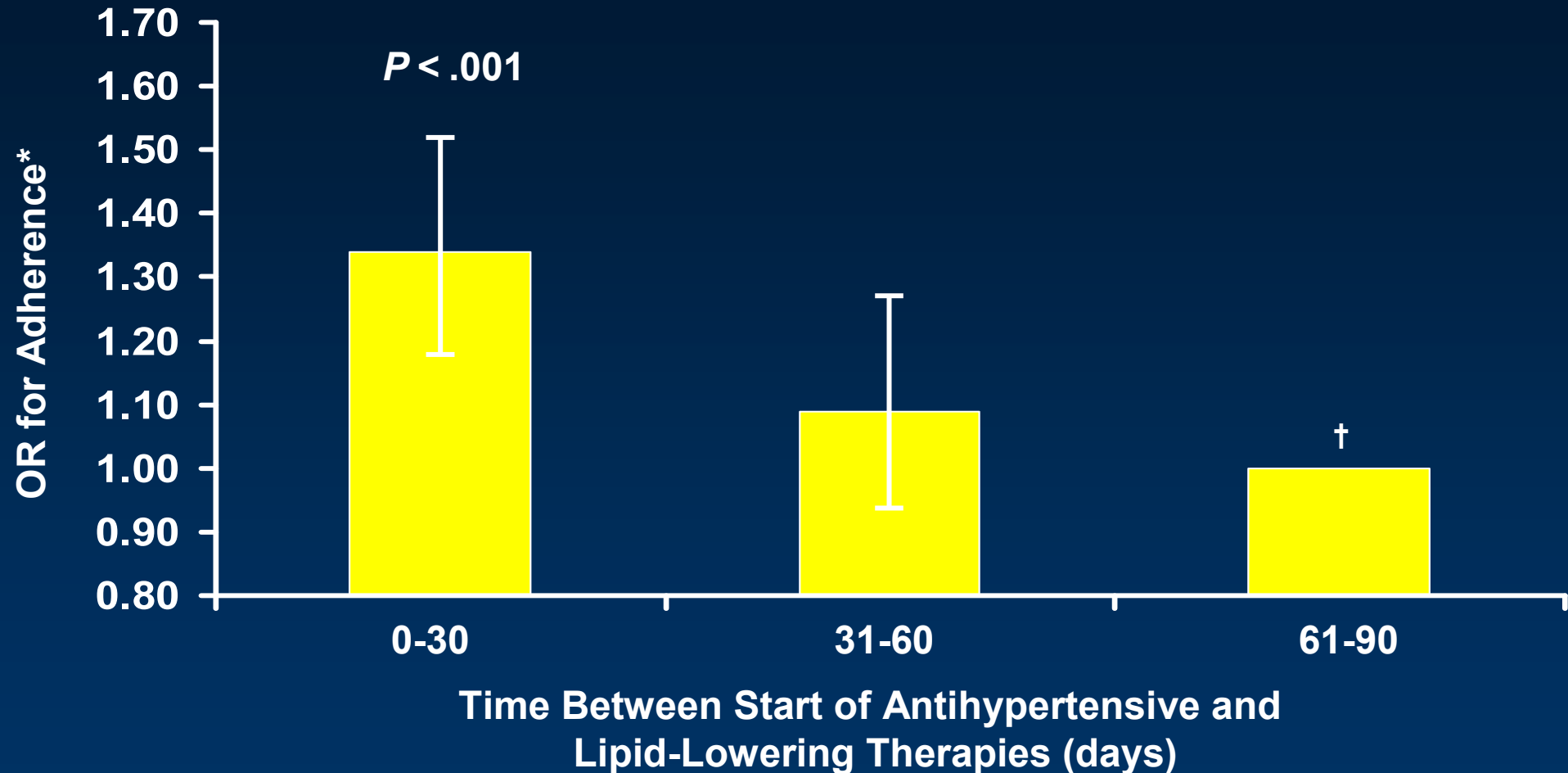
Physician acceptability

- Physicians like to have the flexibility to titrate individual agents
- They, as a result, are often hostile to the concept of fixed-dose combination pills.

Compliance according to Frequencies



Later Start of Combined Medication Reduces Adherence

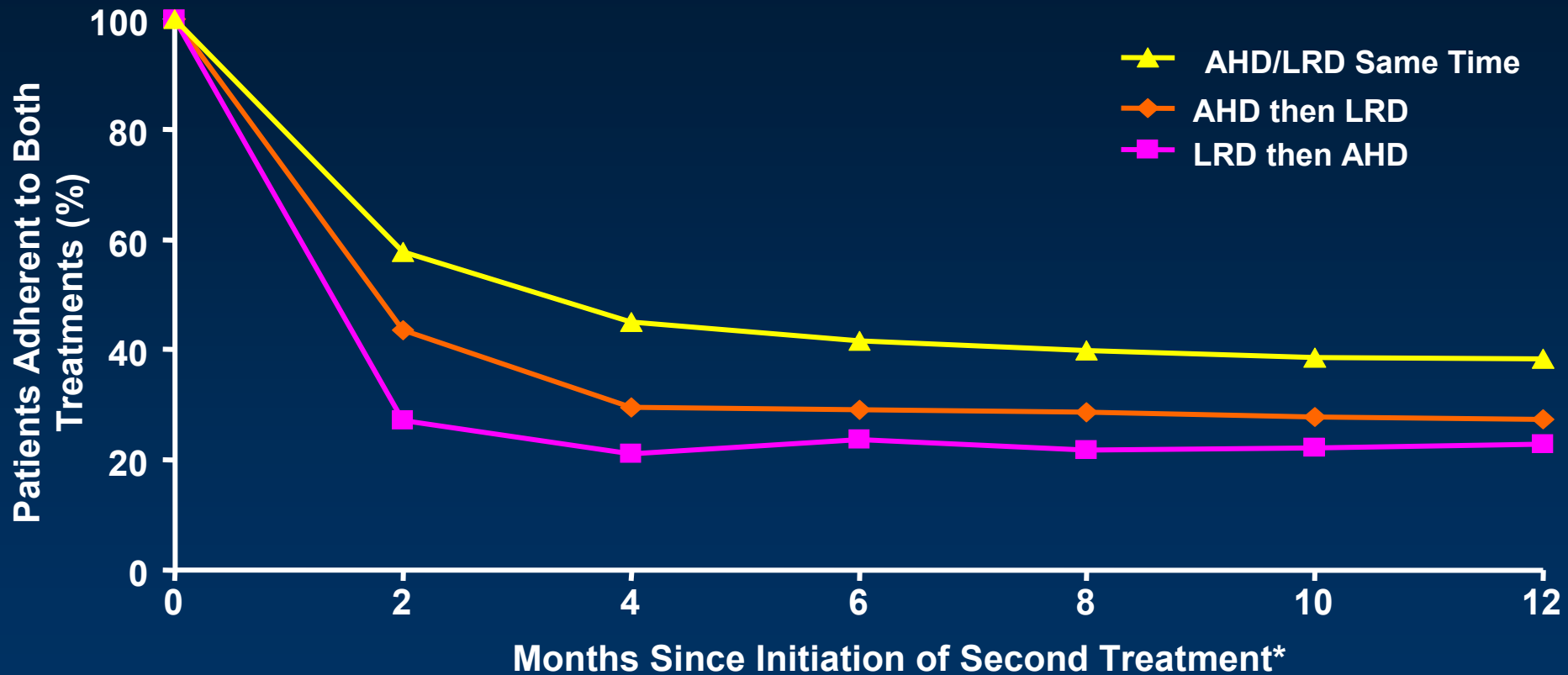


Retrospective cohort study in a large managed care population (N = 8406).

*Relative odds of being adherent with both antihypertensive and lipid-lowering therapy at any point in time; †Reference group.

Chapman RH et al. *Arch Intern Med.* 2005;165:1147-1152.

Concomitant Treatment With Antihypertensives and Statins: Start Both at the Same Time!



- Patients starting AHD and LRD at the same time were more adherent to both therapies over the year than patients who started 1 treatment and then the other

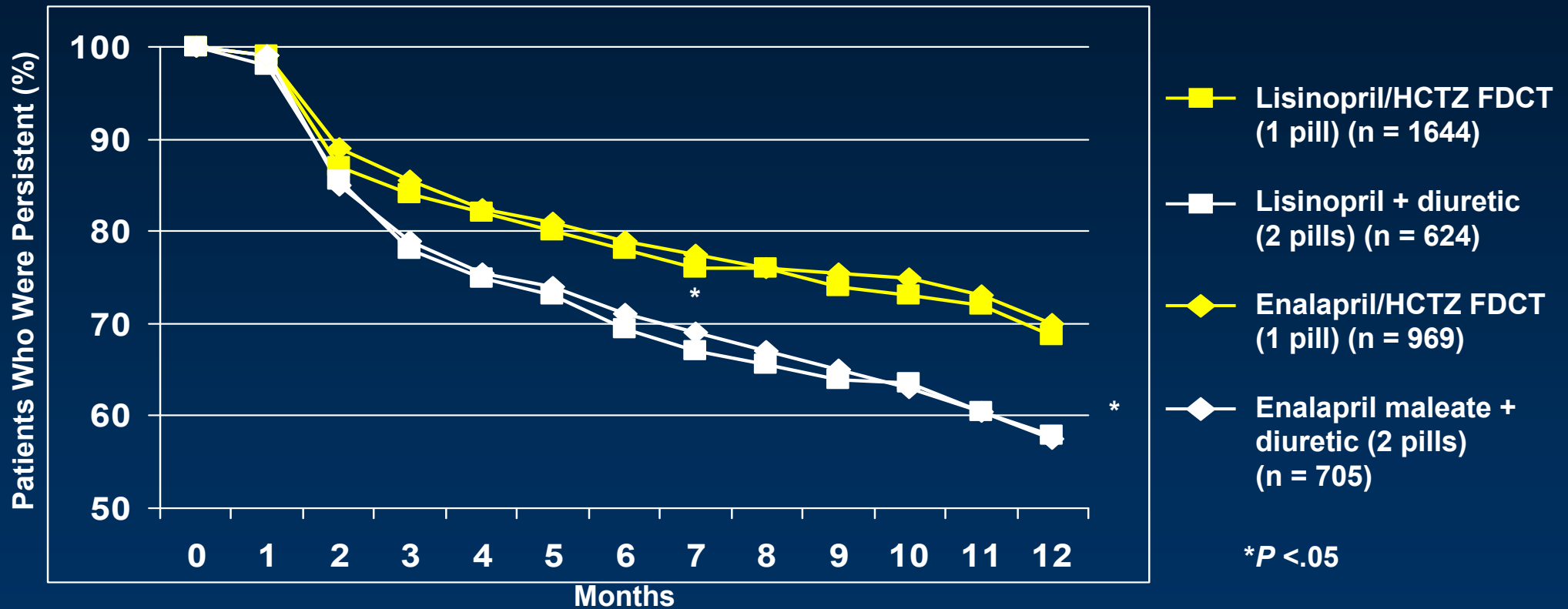
AHD = antihypertensive drug; LRD = lipid-regulating therapy.

*Mean of 116 days between Drug 1 and Drug 2 initiation. "Same time" defined as within 30 days.

Schwartz JS et al. Presented at: 52nd Annual Scientific Session of the ACC; March 30-April 2, 2003; Chicago, IL.

One Pill Medication Regimen Improves Persistence

Persistence to equivalent therapies: 1 pill vs 2 pills



* $P < .05$ at months 6 and 12 for lisinopril/HCTZ FDCT vs lisinopril + diuretic and for enalapril/HCTZ FDCT vs enalapril maleate + diuretic.

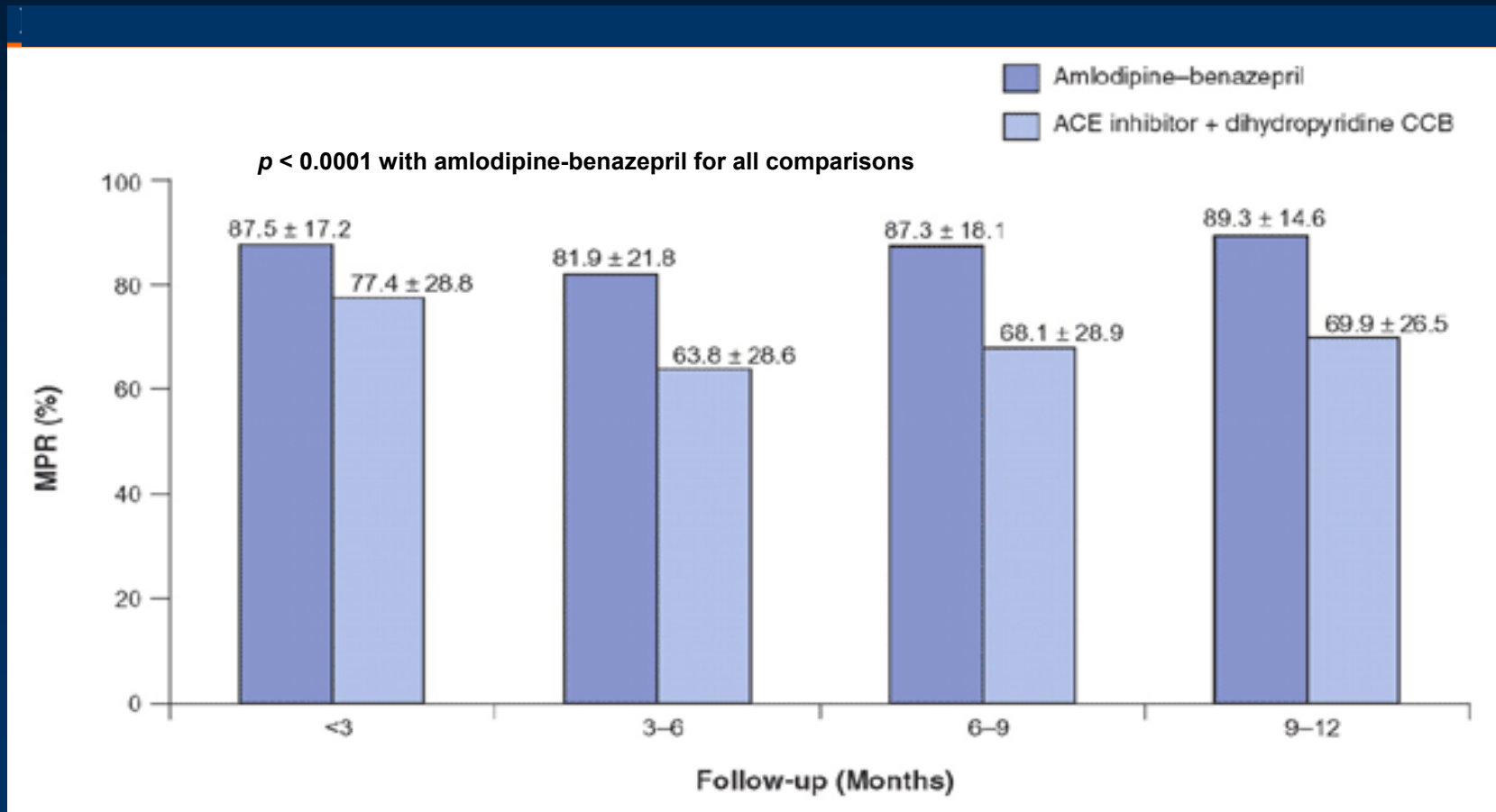
Retrospective analysis of database records of a national commercial PBM. N = 3942 patients new to AHT, ACE inhibitor plus diuretic via 2- or 1-pill dosing. Persistence: minimum Rx renewal within 3x days supplied.

Not persistent: failure to obtain any 3 scheduled refills.

ACE = angiotensin-converting enzyme; HCTZ = hydrochlorothiazide; FDCT = fixed-dose combination therapy.

Dezii CM. *Manag Care*. 2000;9(suppl):S6-S10.

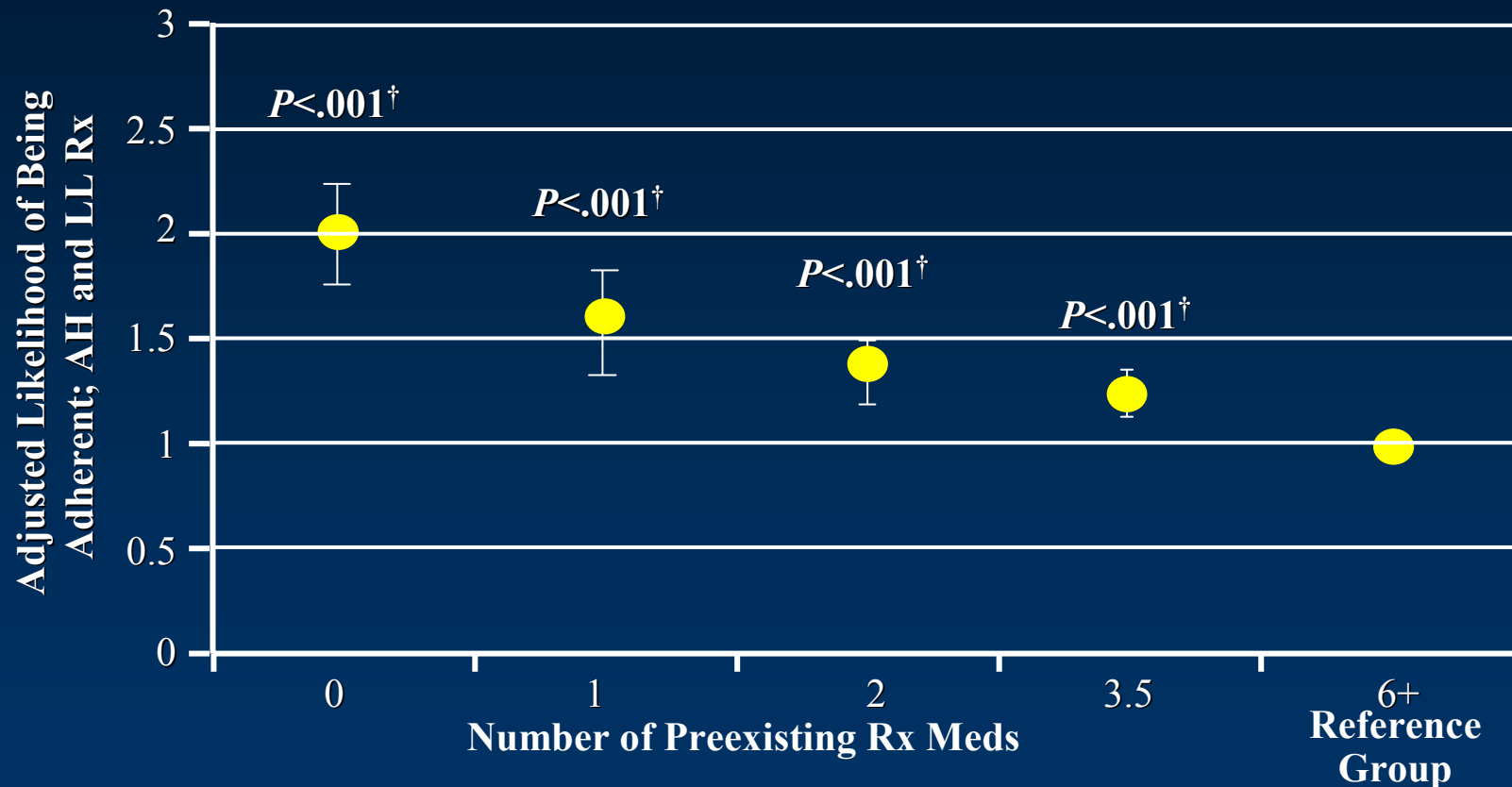
Adherence Patterns Among Patients Treated With Fixed-dose Combination versus Separate Antihypertensive Agents



MPR; medication possession ratio

Source: Am J Health-Syst Pharm © 2007 American Society of Health-System Pharmacists

Lower Pill Burden is Associated with Better Adherence to Antihypertensive



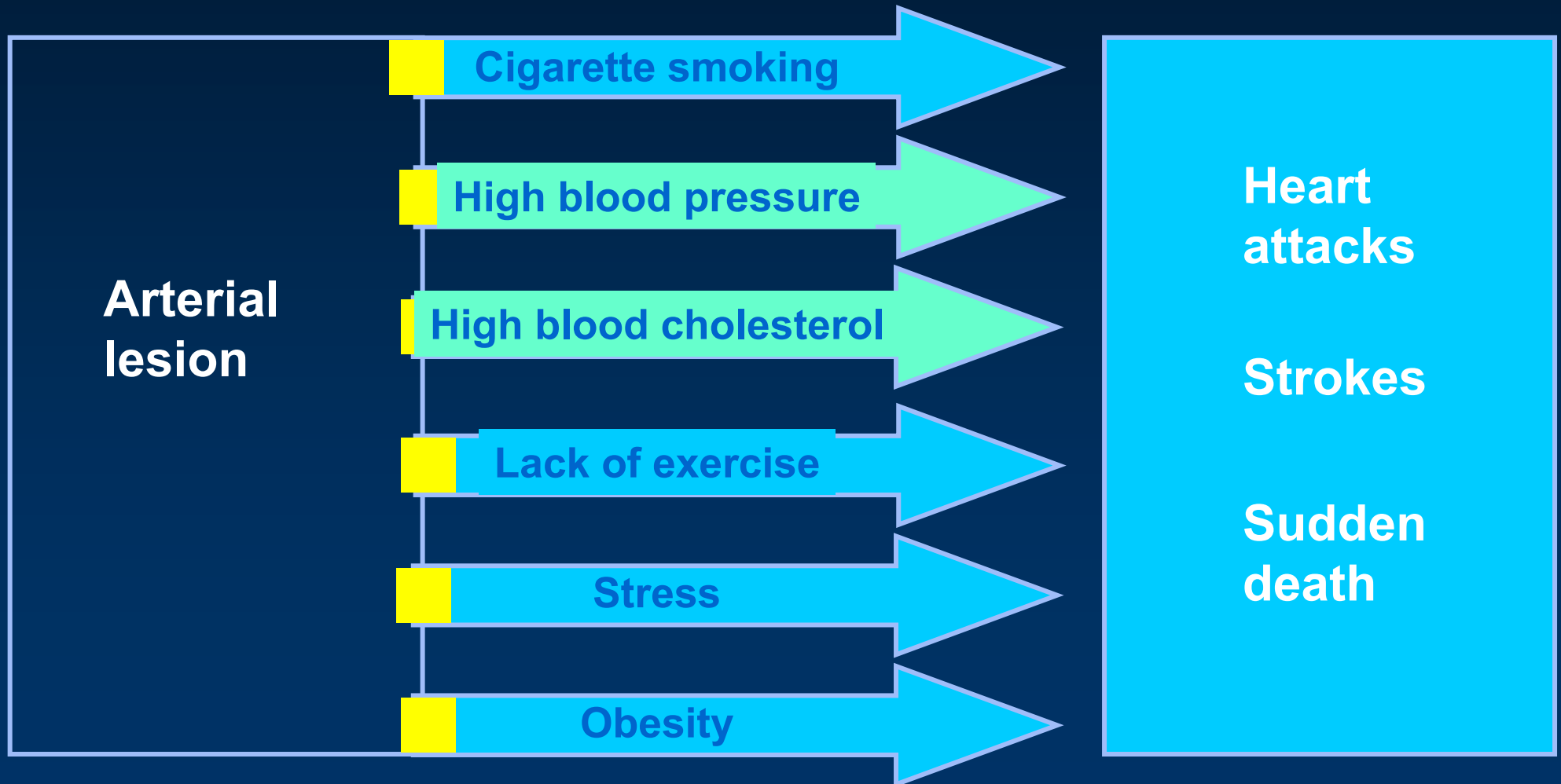
*Preexisting is defined as the number of prescription medications a patient was taking in the year prior to initiating AH and LL medications. †Comparisons were statistically significant vs a patient taking 6+ preexisting Rx medications.

Rx=prescription; meds=medications; AH=antihypertensive therapy; LL=lipid-lowering therapy.

Chapman RH et al. *Arch Intern Med.* 2005;165:1147-1152.

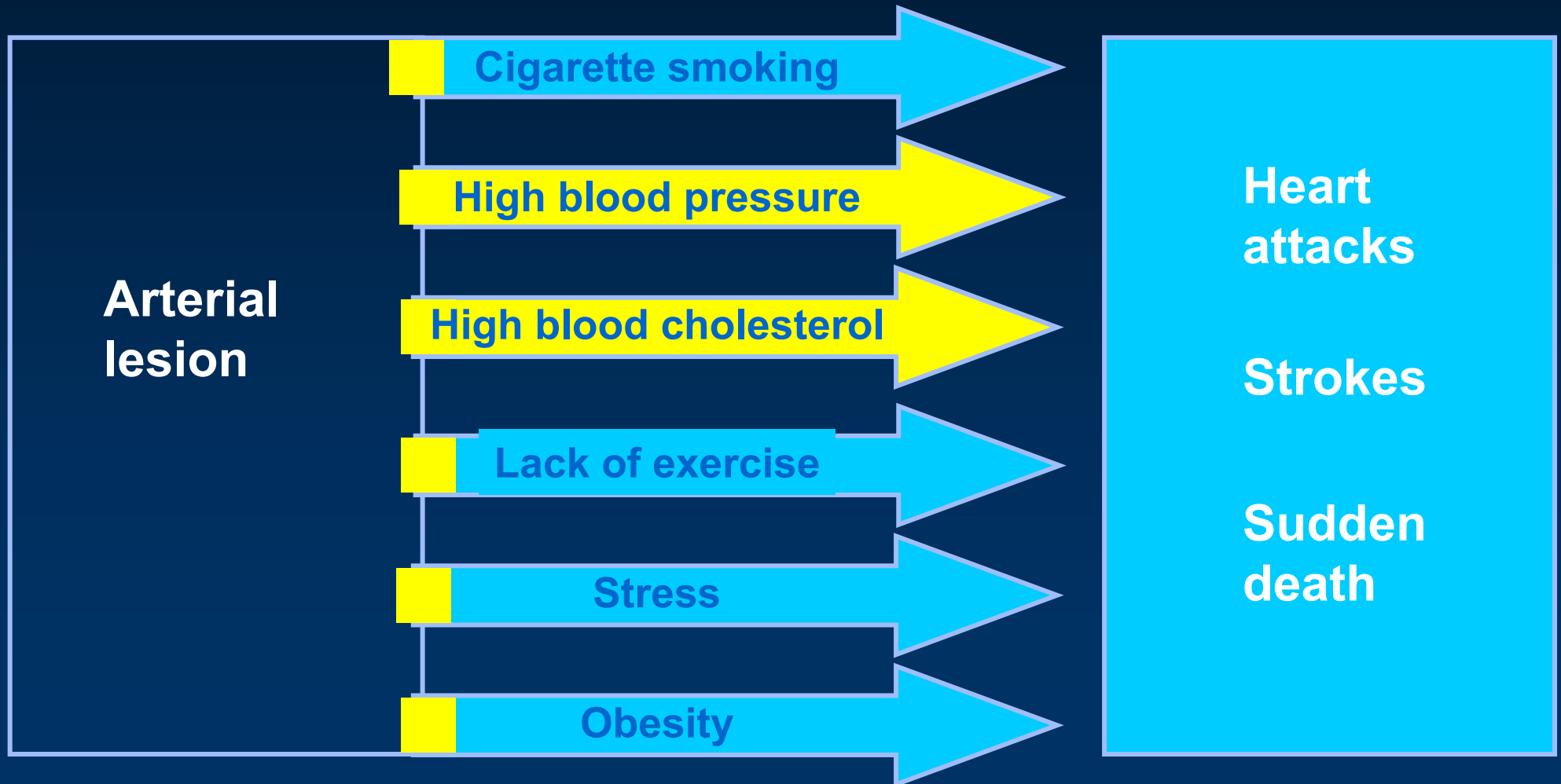
Heart and Blood Disease Risk Factors

Accelerating factors

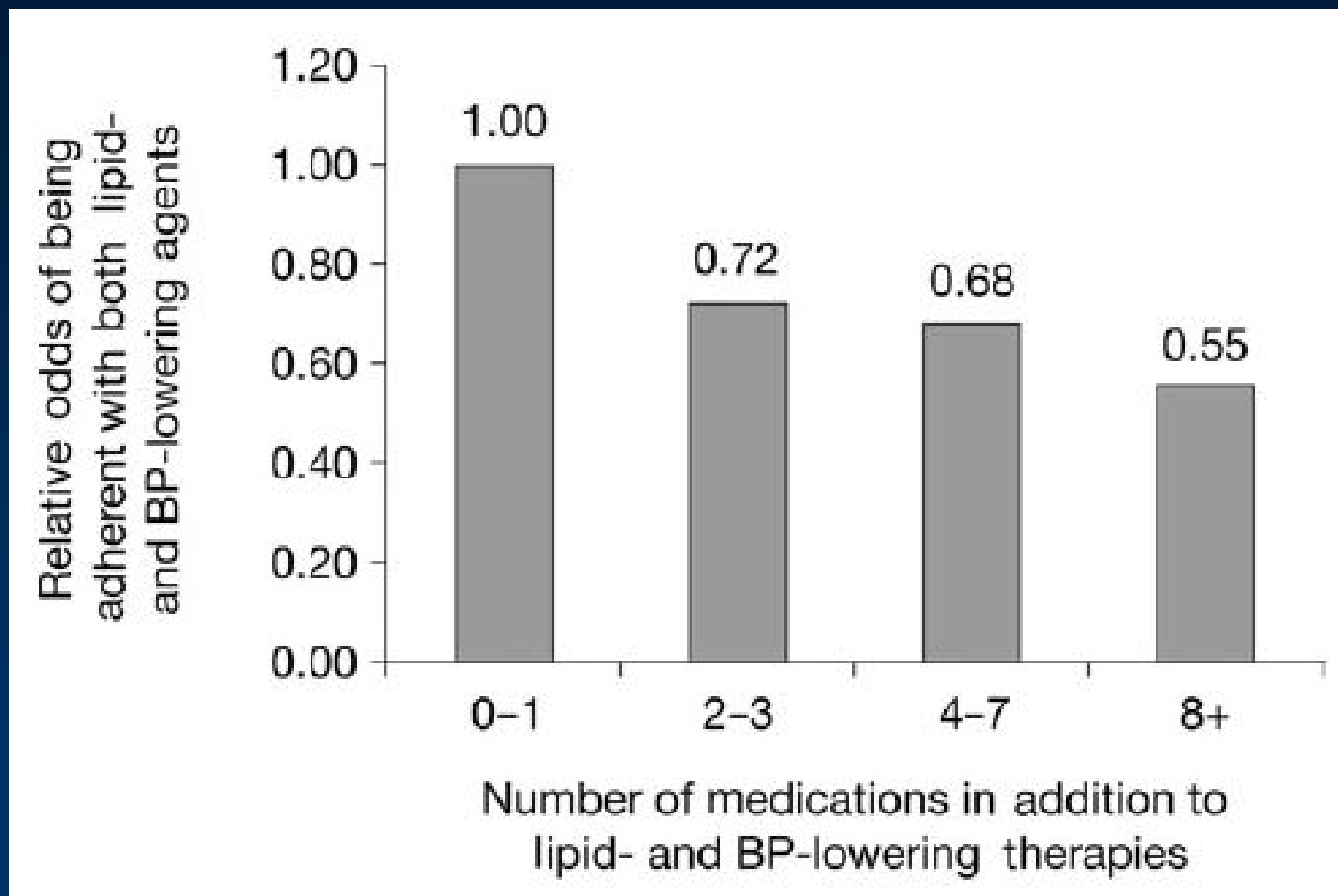


Heart and Blood Disease Risk Factors

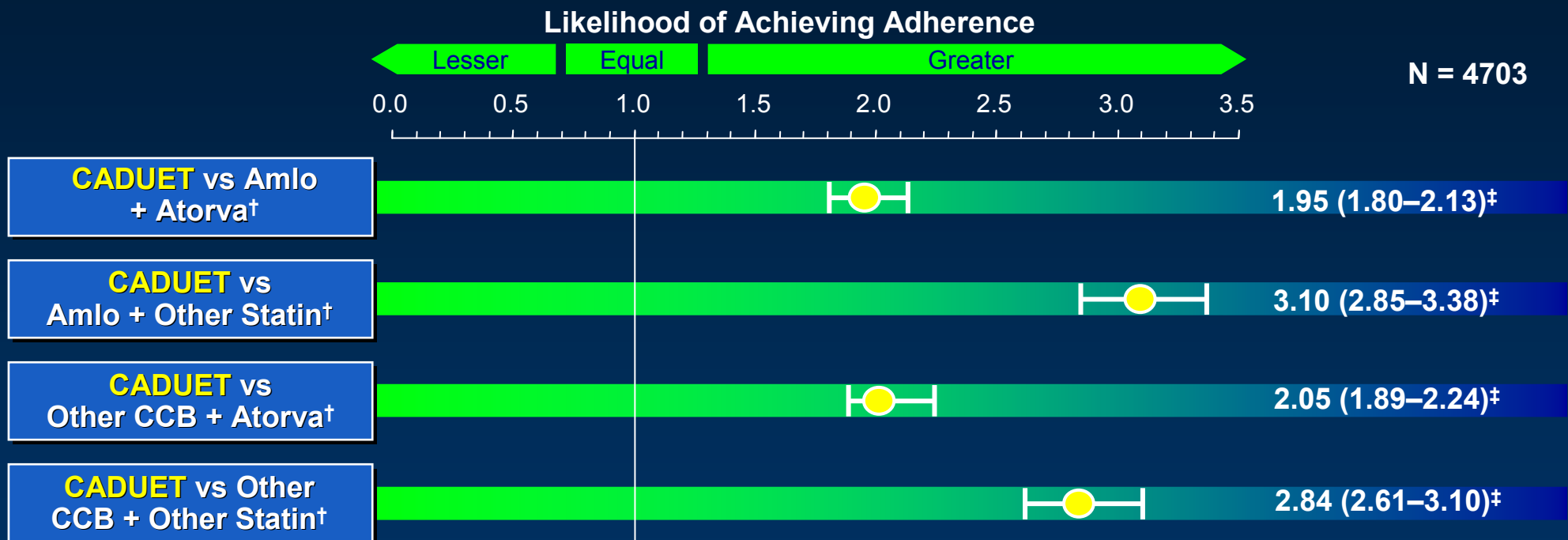
Accelerating factors



Adherence to lipid- and BP-lowering therapy decreases as the number of additional medications increases.



**CARPE-P Study: CADUET® Patients Were 2 and 3 Times
More Likely to Achieve Adherence Than Patients on
2-Pill Regimens at 6 Months**
Adjusted Odds Ratios of Achieving PDC ≥80% (95% CI)*



*Logistic regression model analysis adjusting for covariates including age, gender, business type, formulary type, baseline AHT, CVD medications, DM medications, antidepressants, number of drugs, co-payments, and maintenance medication refill %. PDC=Proportion of Days Covered

†Patients were already on either a CCB or a statin prior to adding the second drug.

‡P < .0001.

Amlo = amlodipine besylate; atorva = atorvastatin calcium; CCB = calcium channel blocker.

Nichol MB et al. *J Clin Hypertens*. 2006;8:456. Abstract P-526A.

The CV polypill

- A single daily pill combining half-doses (to minimize toxicity) of a beta-blocker, thiazide diuretic, and an ACEI, together with a statin, folic acid, and aspirin reduce the incidence of CVD by over 80%.

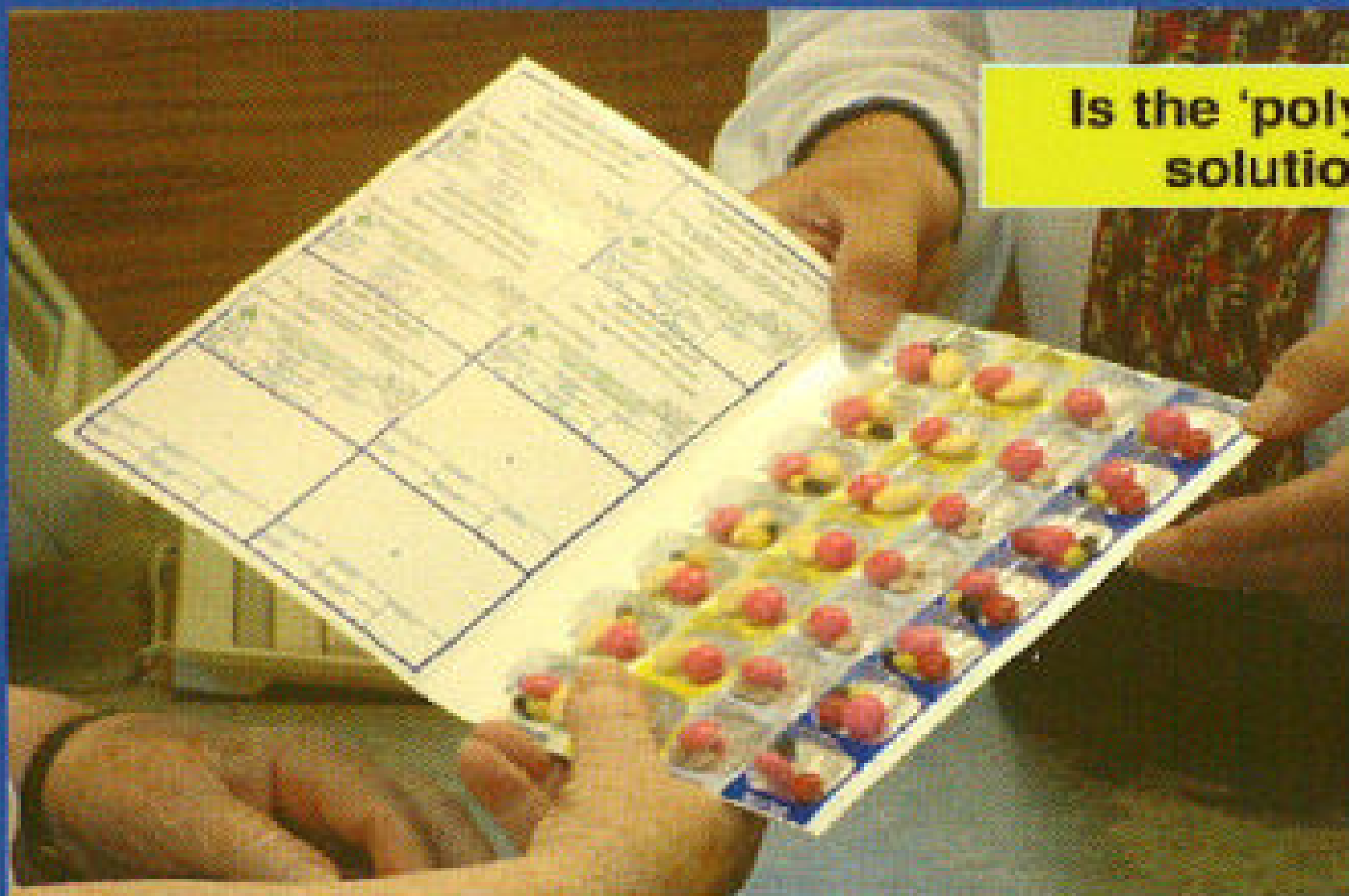
환자관리

- Monitoring of adherence and persistence
- Patient 'ownership of the disease'
 - Lifestyle adaptation
 - Home BP monitoring
- With age, more -→ more pills
- Simple treatment is key for compliance
(combination therapy could help)

Multiple-action, fixed combination medication

- Easier patient compliance
- Easier for elderly to understand dosing
- Costs are lower with generics
- Ensures that all the evidence-based medicines are given, bypassing the likelihood missing one or more components

Pack으로 투약을 단순화하여 아침에
하루 한번 투약하는 것이 좋다



Is the 'polypill' a
solution?

Summary

- **Nonadherence increases the risk of CV events, hospitalisations, and health care costs**
- **Increasing pill burden decreases adherence**
- **Start all preventive drugs at the same time**
- **Consider combination drugs to treat multiple risk factors in order to improve adherence and outcomes**

Clinical Perspective

- The use of multiple-target, fixed combination products, such as atorvastatin/amlodipine concomitantly reduce multiple risk factors without increasing the pill burden or the risk of adverse effects, has the potential to improve CV risk factor management, thereby reducing the incidence of CVD.

A vibrant, close-up photograph of a field of tall, green grass. The blades are long and thin, with some showing signs of being cut or broken. The lighting is bright, creating a rich green color with some highlights and shadows. In the center, a narrow path or clearing is visible, leading the eye towards the background. The overall texture is dense and natural.

**Thank you
for your
attention !**