# Potential synergy between lipid-lowering and blood-pressure-lowering, and Single pill benefit in patient's adherence

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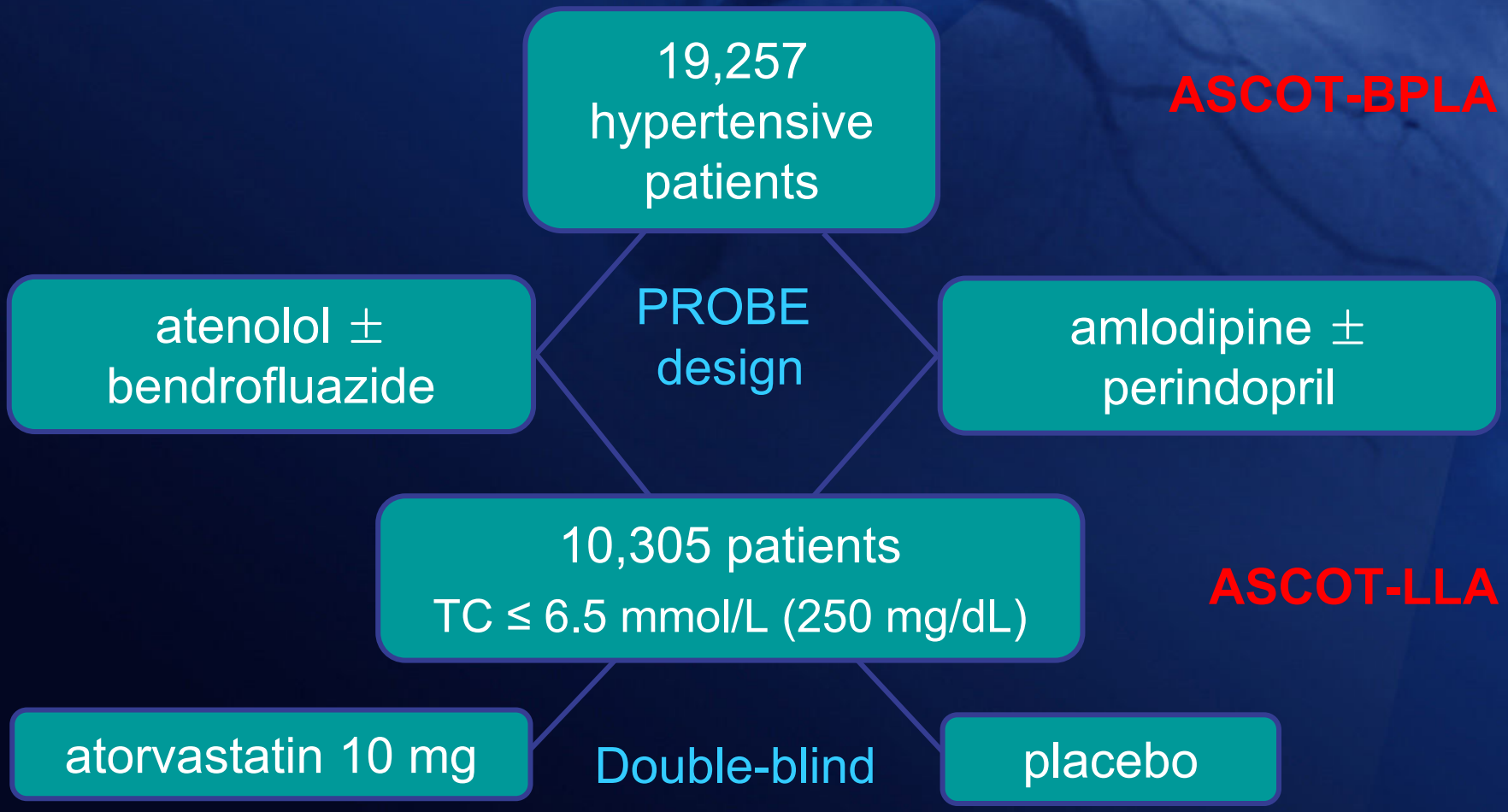
# ASCOT-BPLA and LLA

## Primary Objectives

- To compare the effect on non-fatal myocardial infarction (MI) and fatal CHD
- A standard antihypertensive regimen (β-blocker +/- diuretic) with a more contemporary regimen (CCB +/- ACE inhibitor)
- And Atorvastatin with placebo in those with total cholesterol < 6.5 mmol/L(250mg/dl)

# ASCOT Study Design

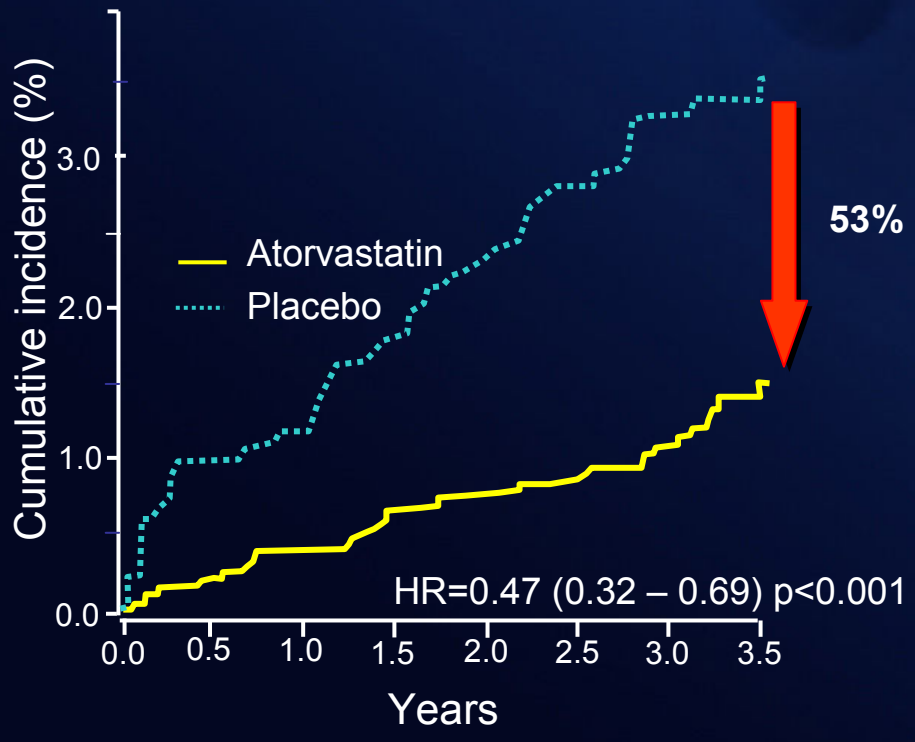


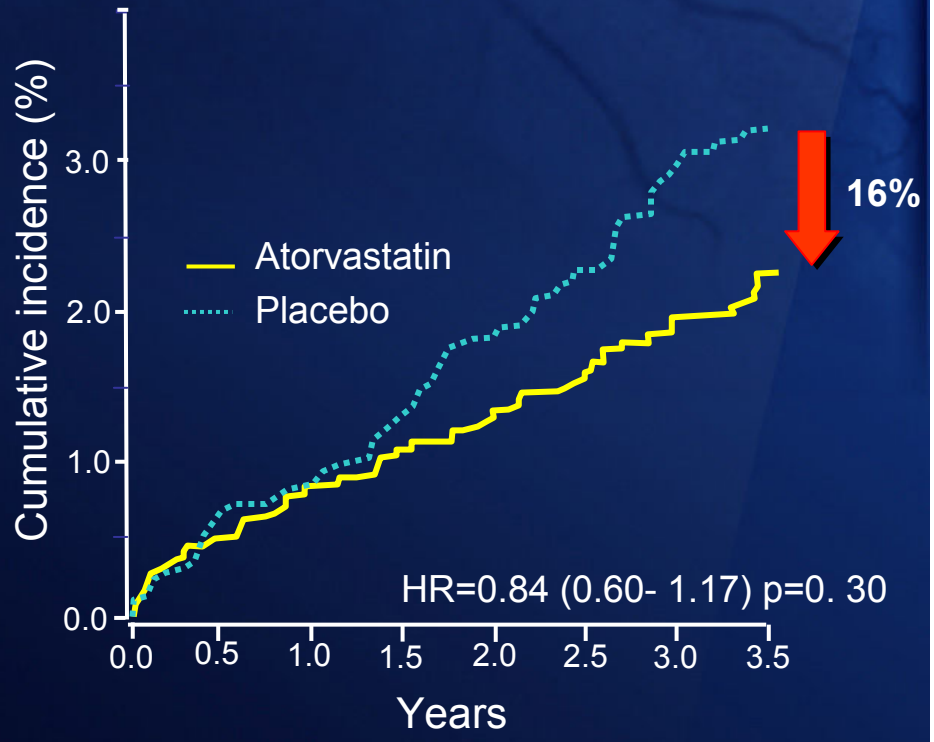

**Investigator-lead, multinational randomized controlled trial**

# ASCOT-LLA

## Fatal CHD and non-fatal MI

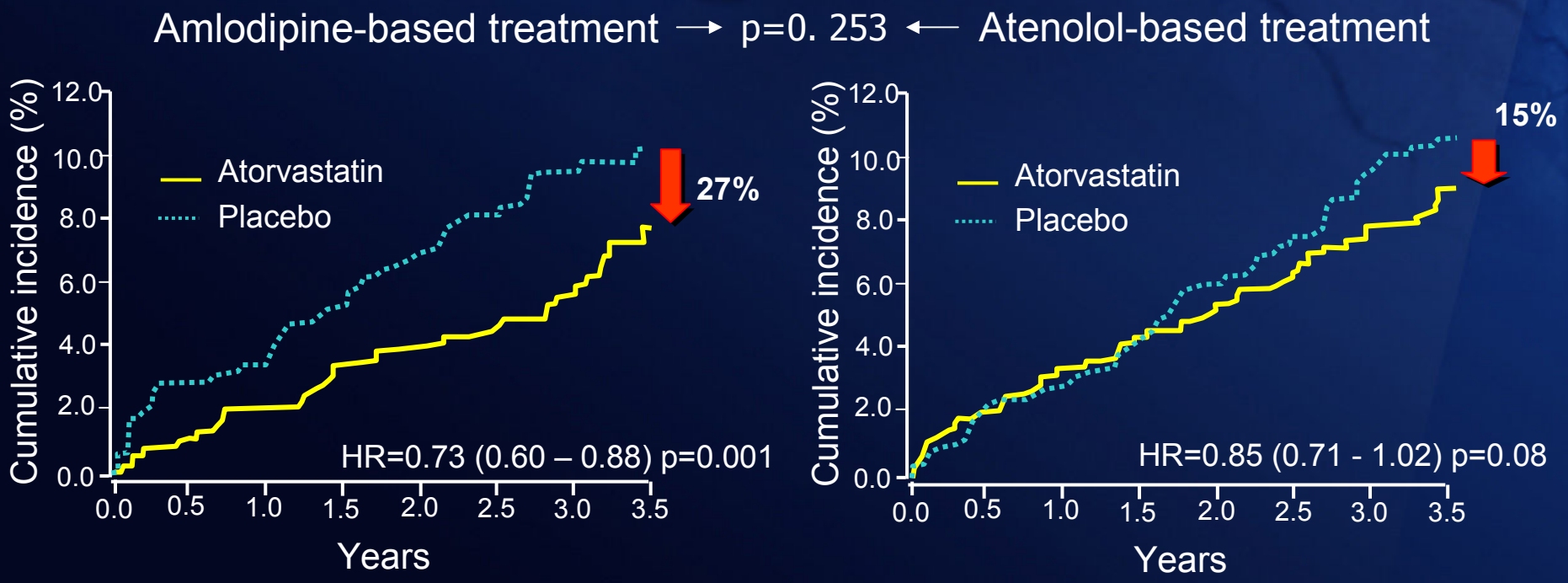
Amlodipine-based treatment → **p=0.025** ← Atenolol-based treatment



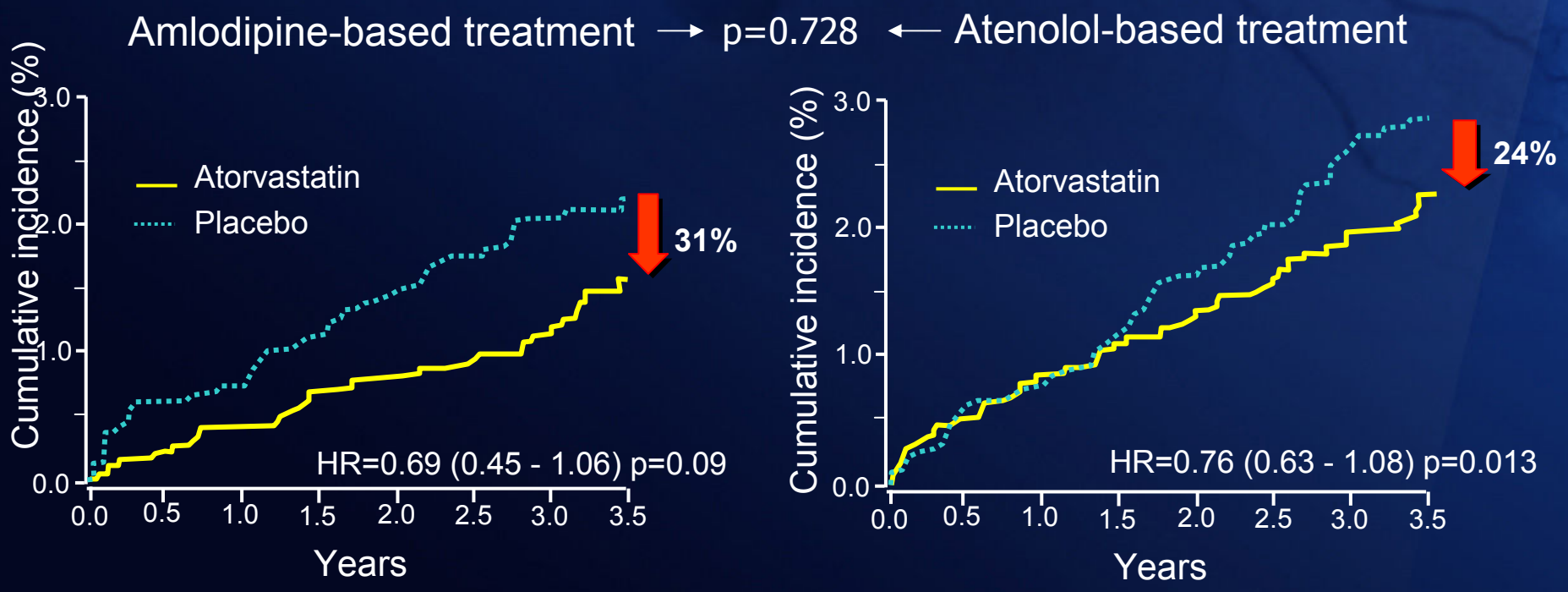
# ASCOT-LLA

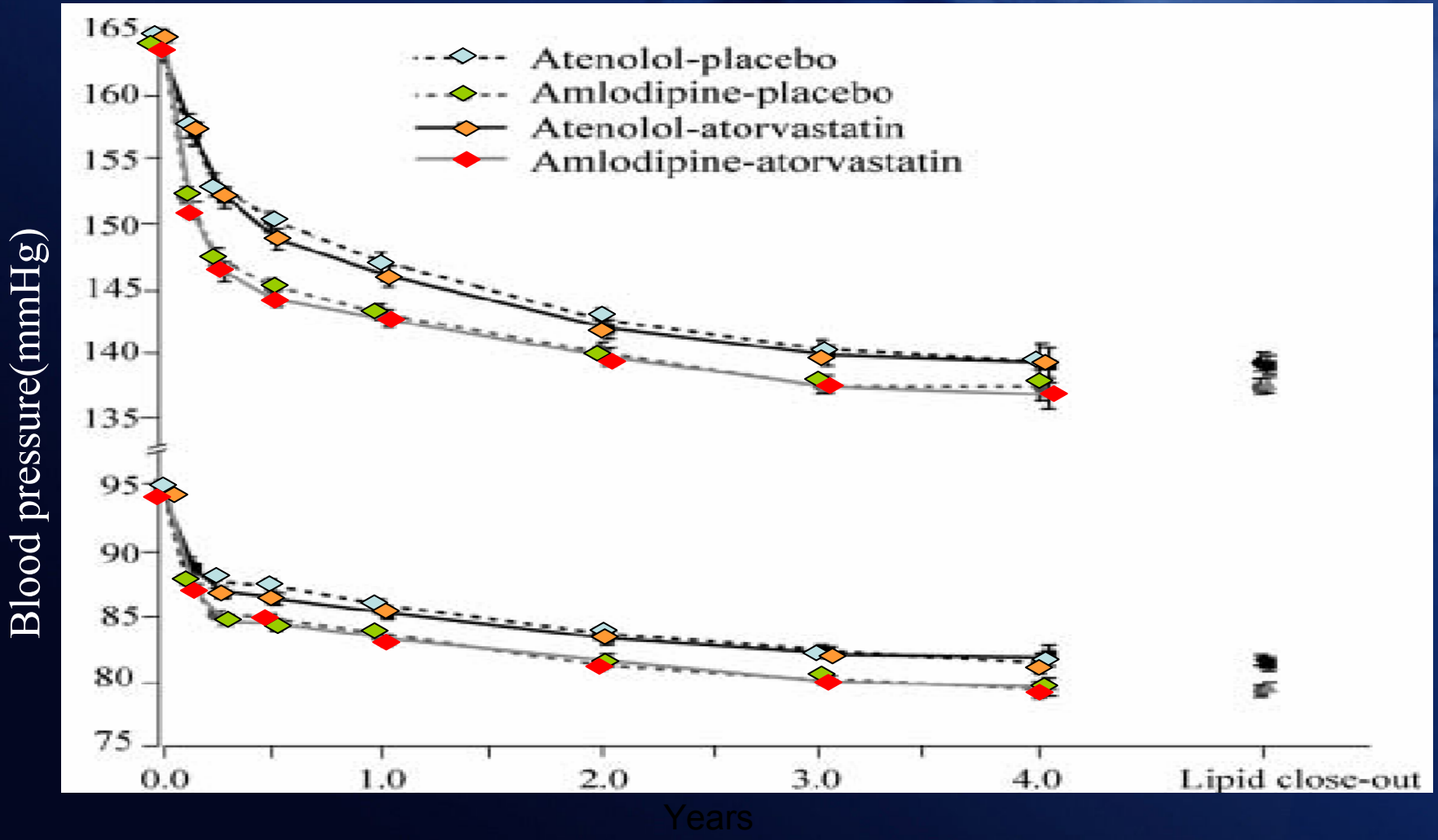
## Total CV Events & Procedures



# ASCOT-LLA

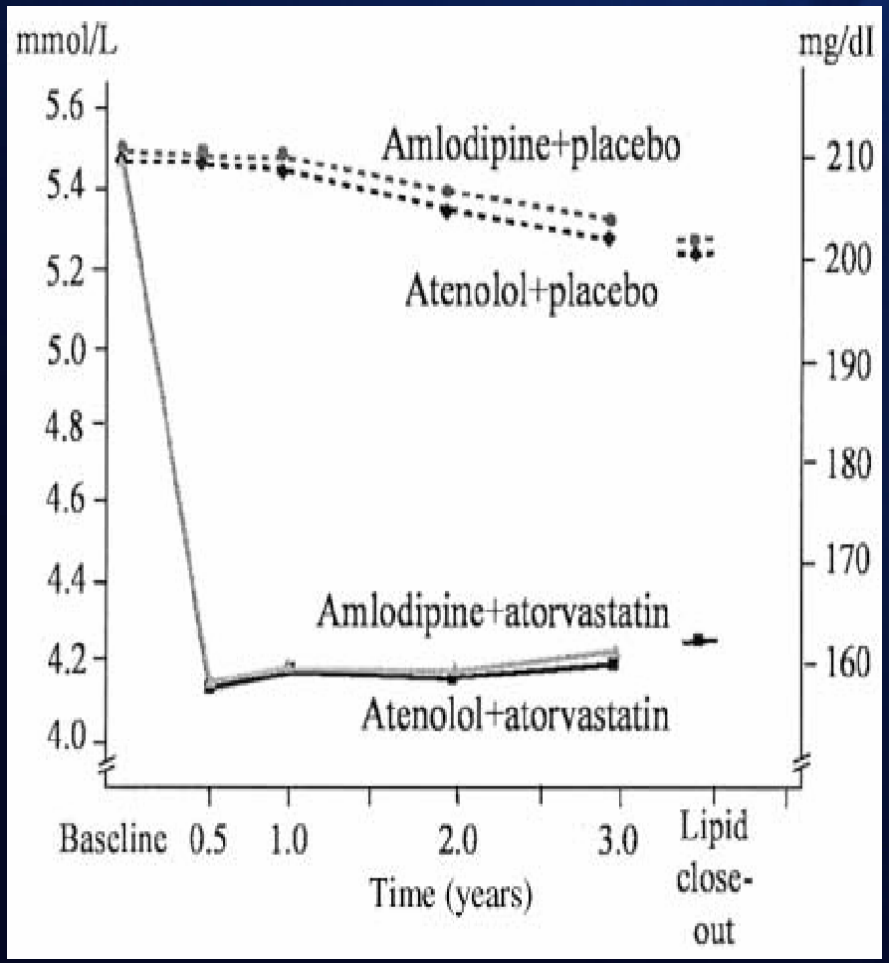
## Fatal and non-fatal stroke



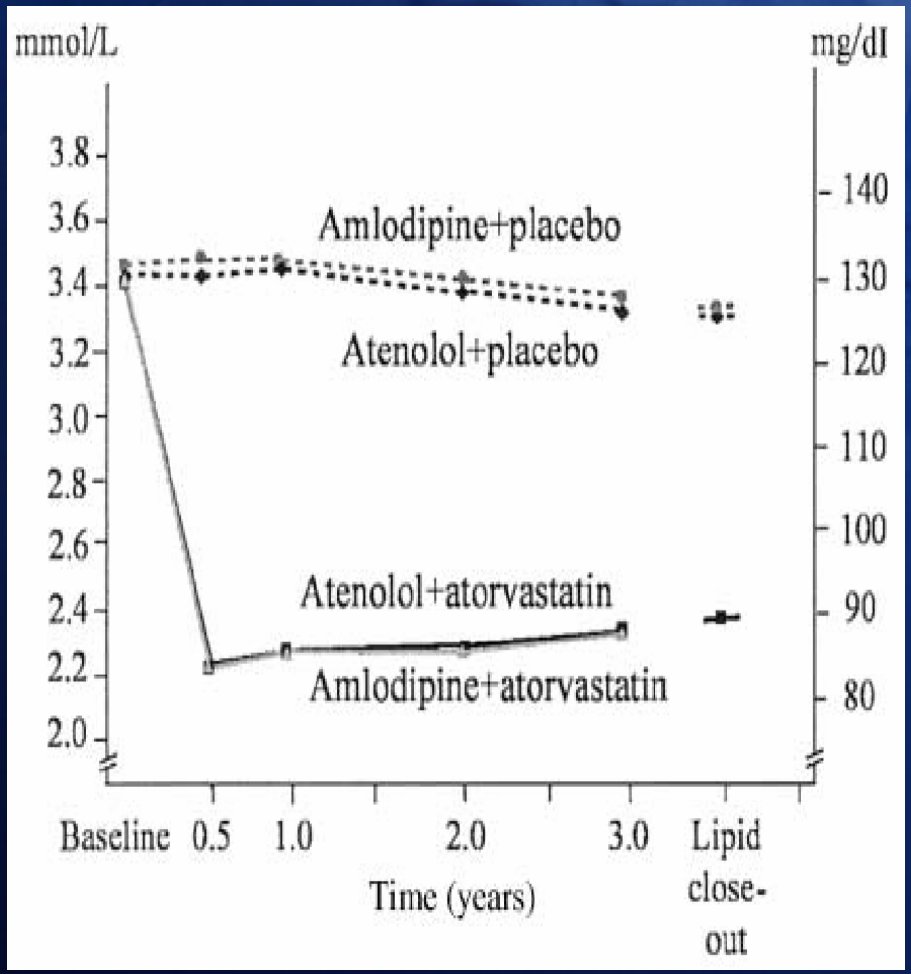



**BP fell by 2.9/2.0 mmHg more on amlodipine-based than atenolol-based treatment, but these differences were very similar among those allocated either atorvastatin or placebo**

## Total Cholesterol

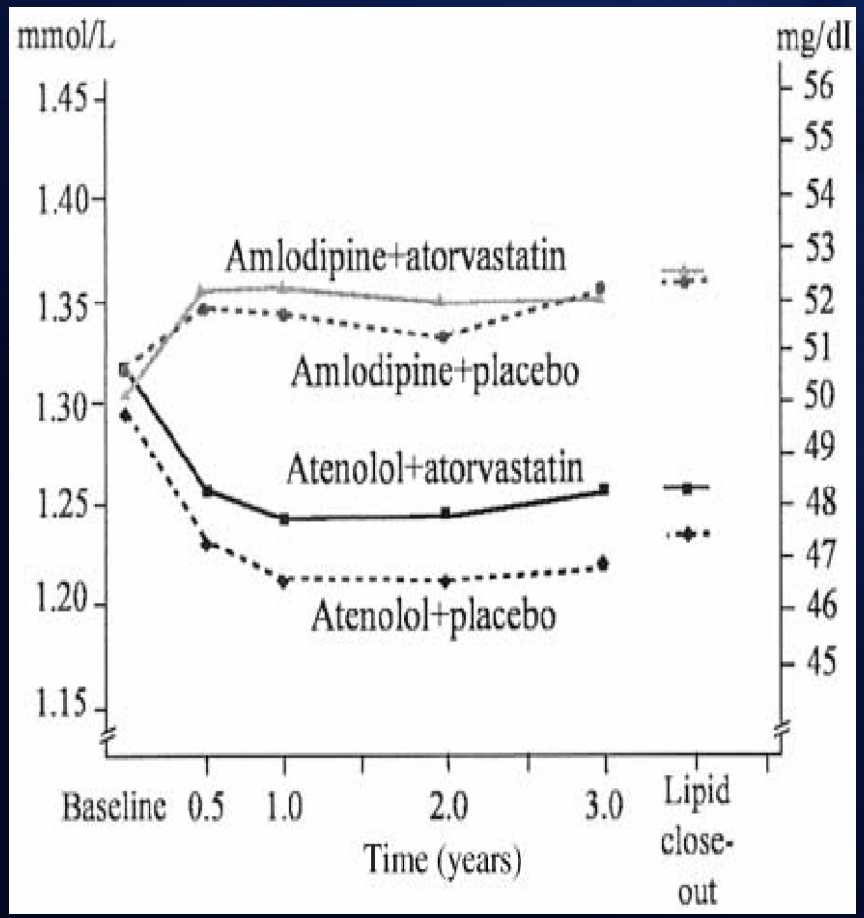



## LDL Cholesterol

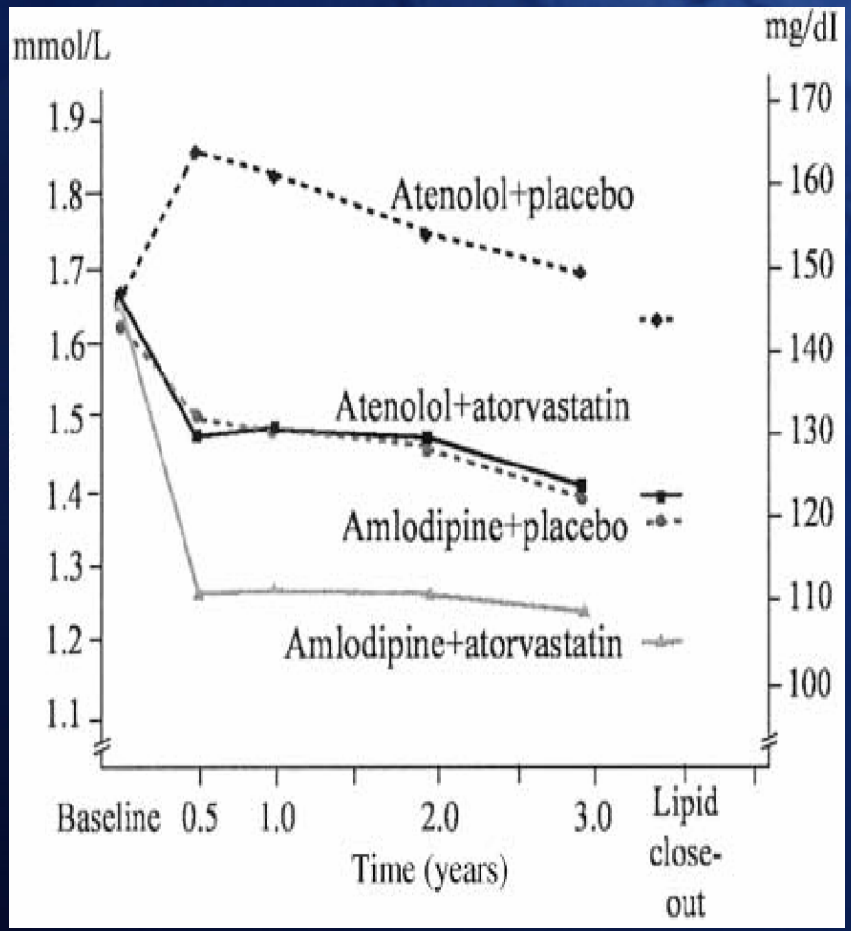



**No apparent differences between the amlodipine-based and atenolol-based regimens in the extent to which total and LDL cholesterol**

## HDL Cholesterol




## Triglyceride




——— **Amlodipine**

------- **Atenolol**

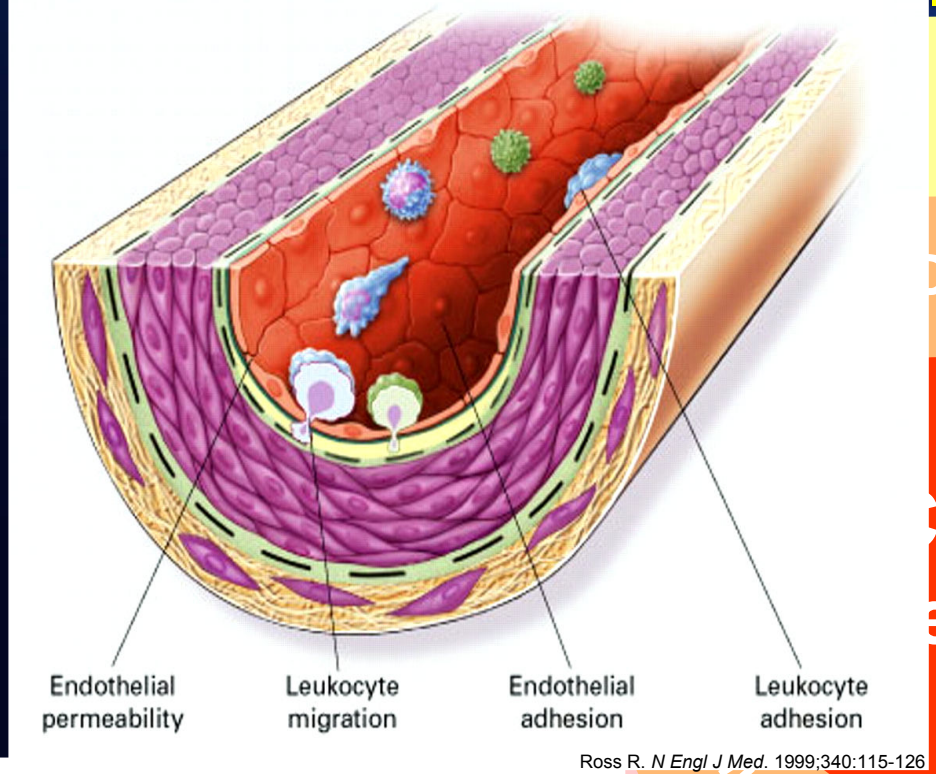
# Summary

- Benefits of atorvastatin on coronary end points greater in those allocated amlodipine compared with atenolol-based treatment.
- No significant interaction was evident for two other endpoints (total CV events and procedures and fatal and non-fatal stroke).
- Whilst these observations could be a chance finding, there is a plausible biological explanation for a synergistic effect of atorvastatin and amlodipine-based treatment on acute coronary events

# Atorvastatin and Amlodipine: A *Synergistic* Effect?

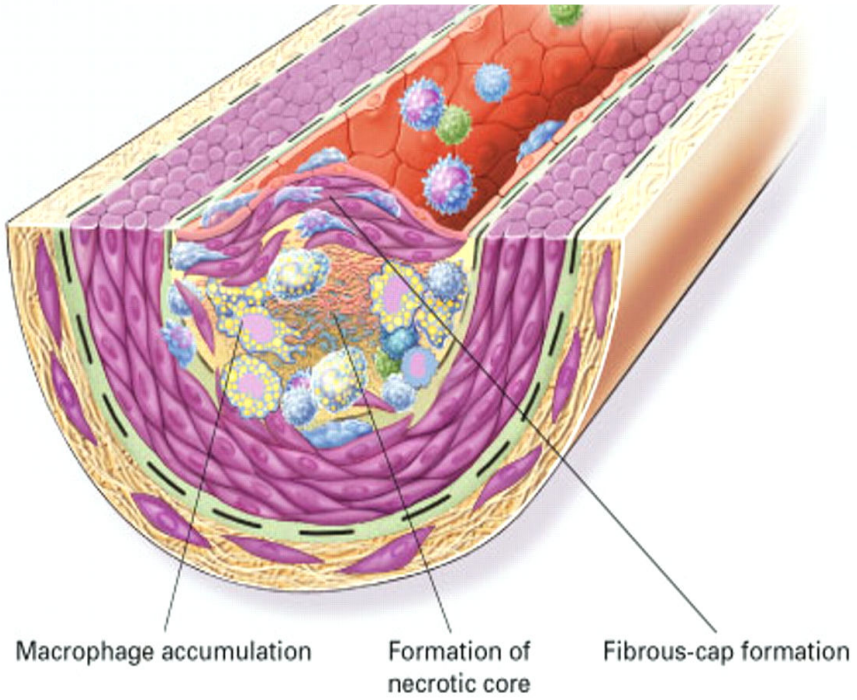
1 + 1 = 3

# Integrated Perspective on CV Risk Factors and Vascular Disease




Ross R. *N Engl J Med*. 1999;340:115-126

**Endothelial Dysfunction**




**Oxidative Stress & Inflammation**

Dyslipider

Diabete

RP Mason

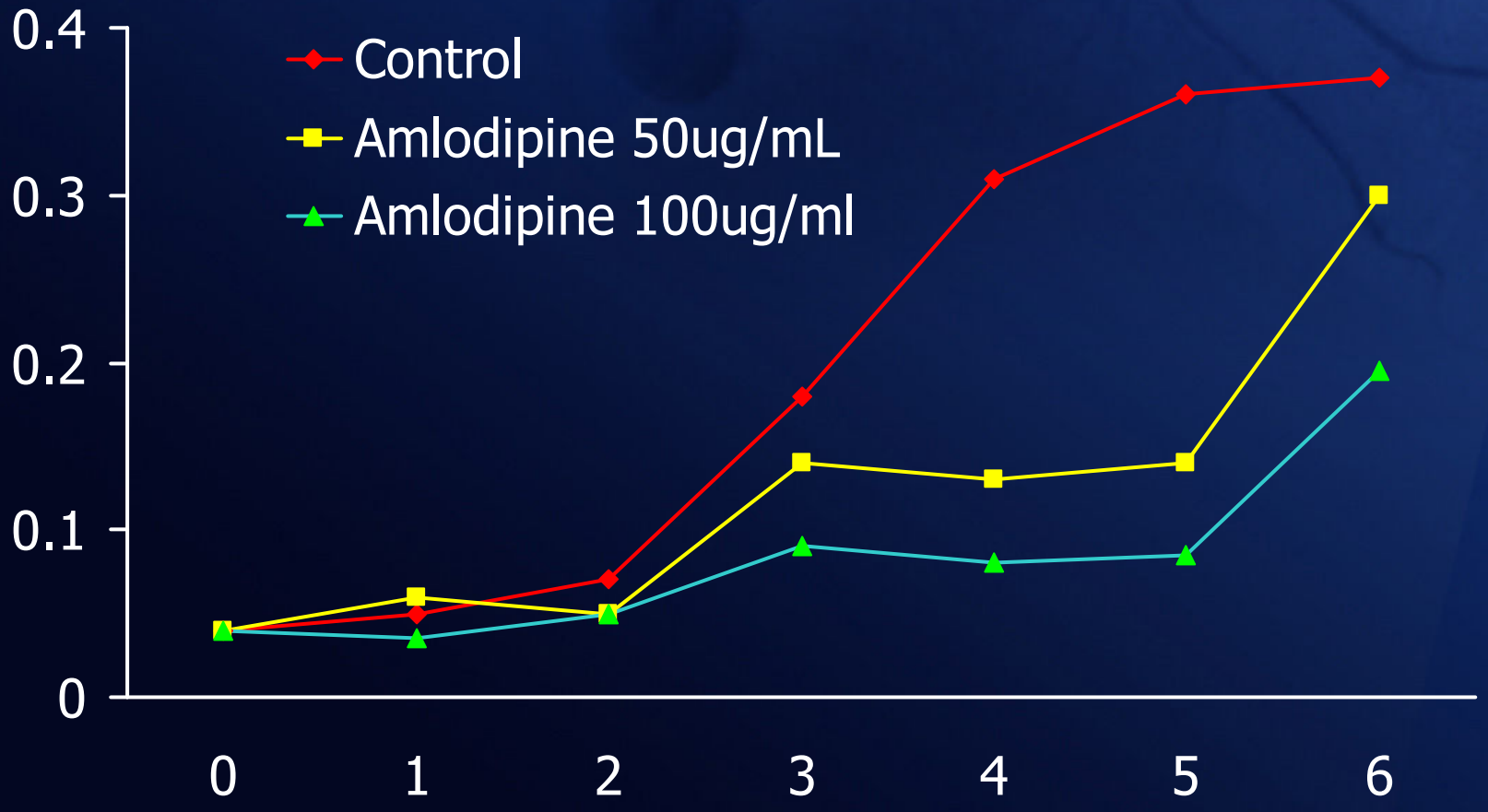
**Hypertension**

**Hyperlipidemia**

***Oxidative Stress***

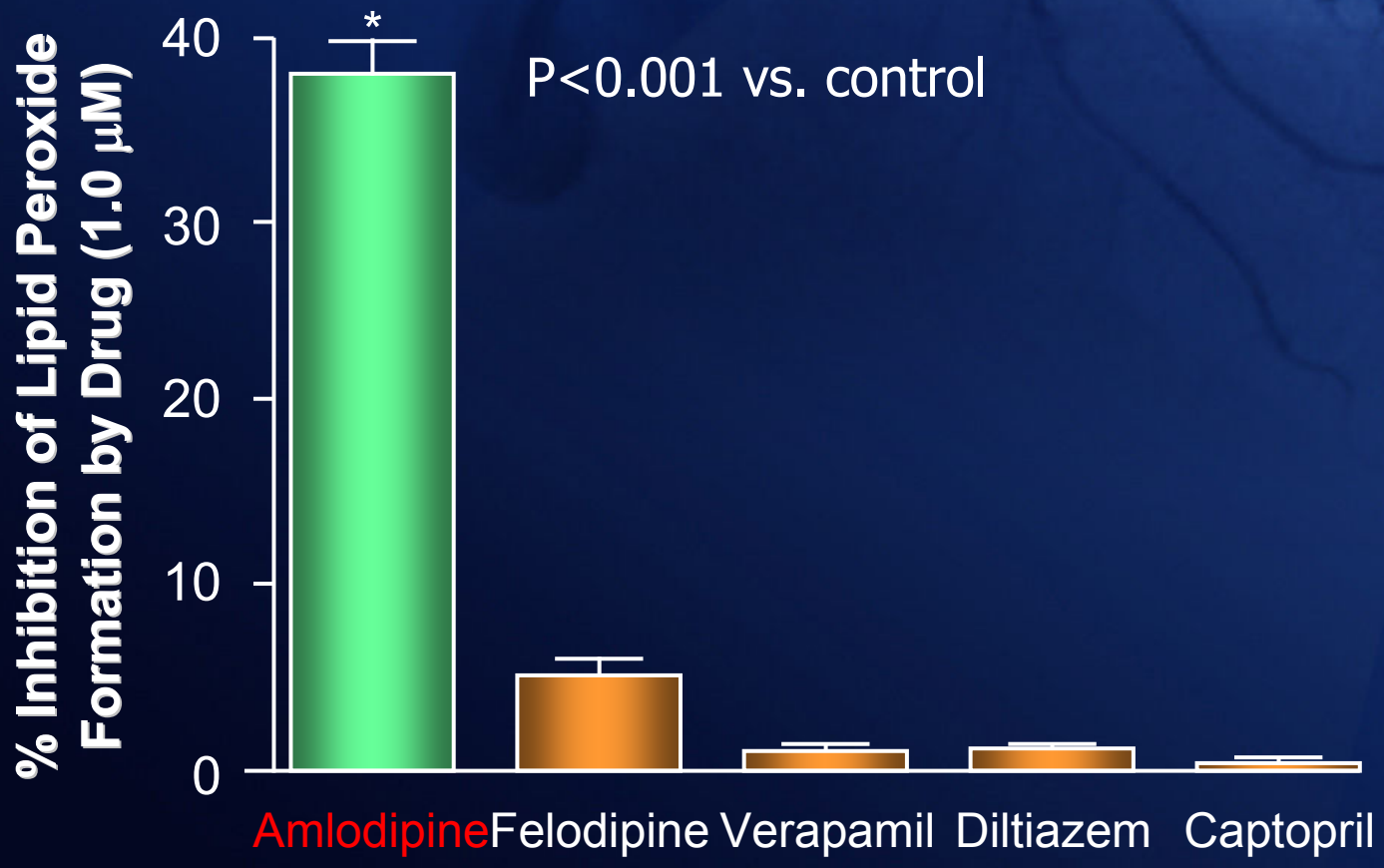
***Endothelial Dysfunction***

# Effect of Amlodipine on Oxidizability of LDL by rabbit leukocyte




Chen L et al. J Am Coll Cardiol 1997;30:569-75

# Amlodipine Inhibits Membrane Lipid Peroxidation as compared to Other CCBs

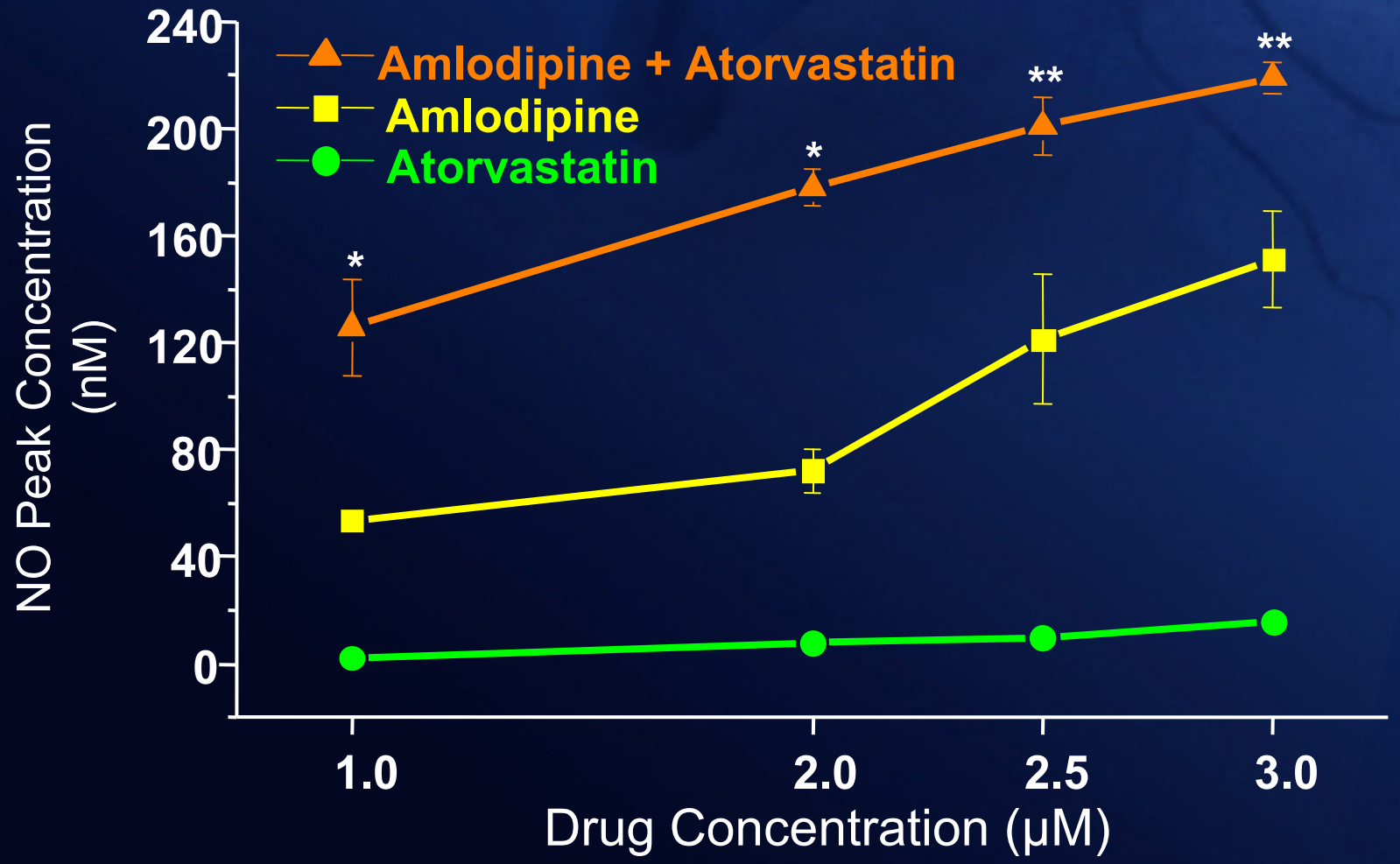



Mean ± SD.

*$P$<.001 vs control.

Mason et al. *J Mol Cell Cardiol*. 1999;31:275-281.

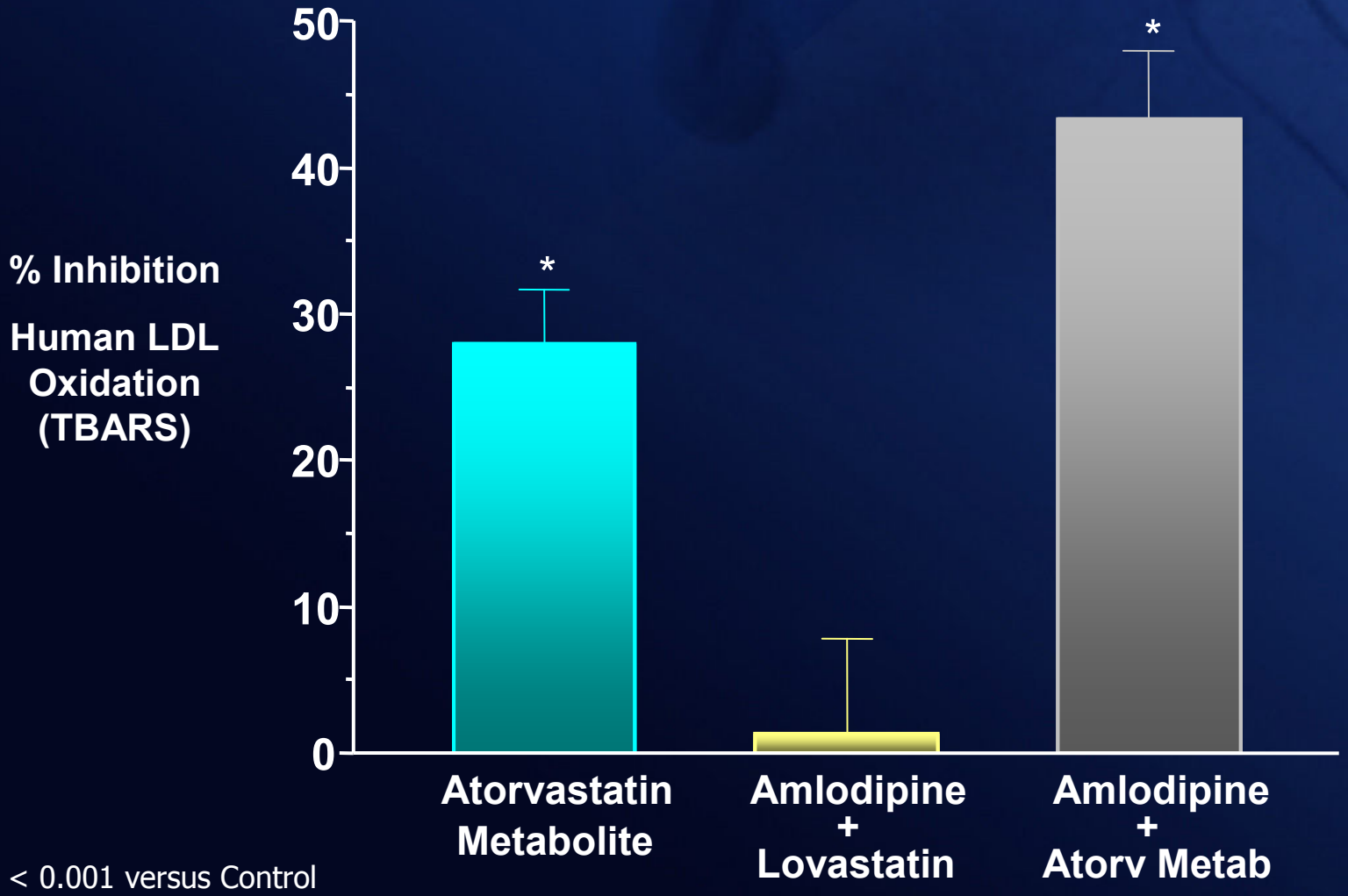
# Synergistic Effect of Amlodipine and Atorvastatin on NO Release from Human Endothelial Cells




*$p < 0.01$, **$p < 0.05$ vs. individual drug treatments

Mason RP et al. European Society of Cardiology (2003)

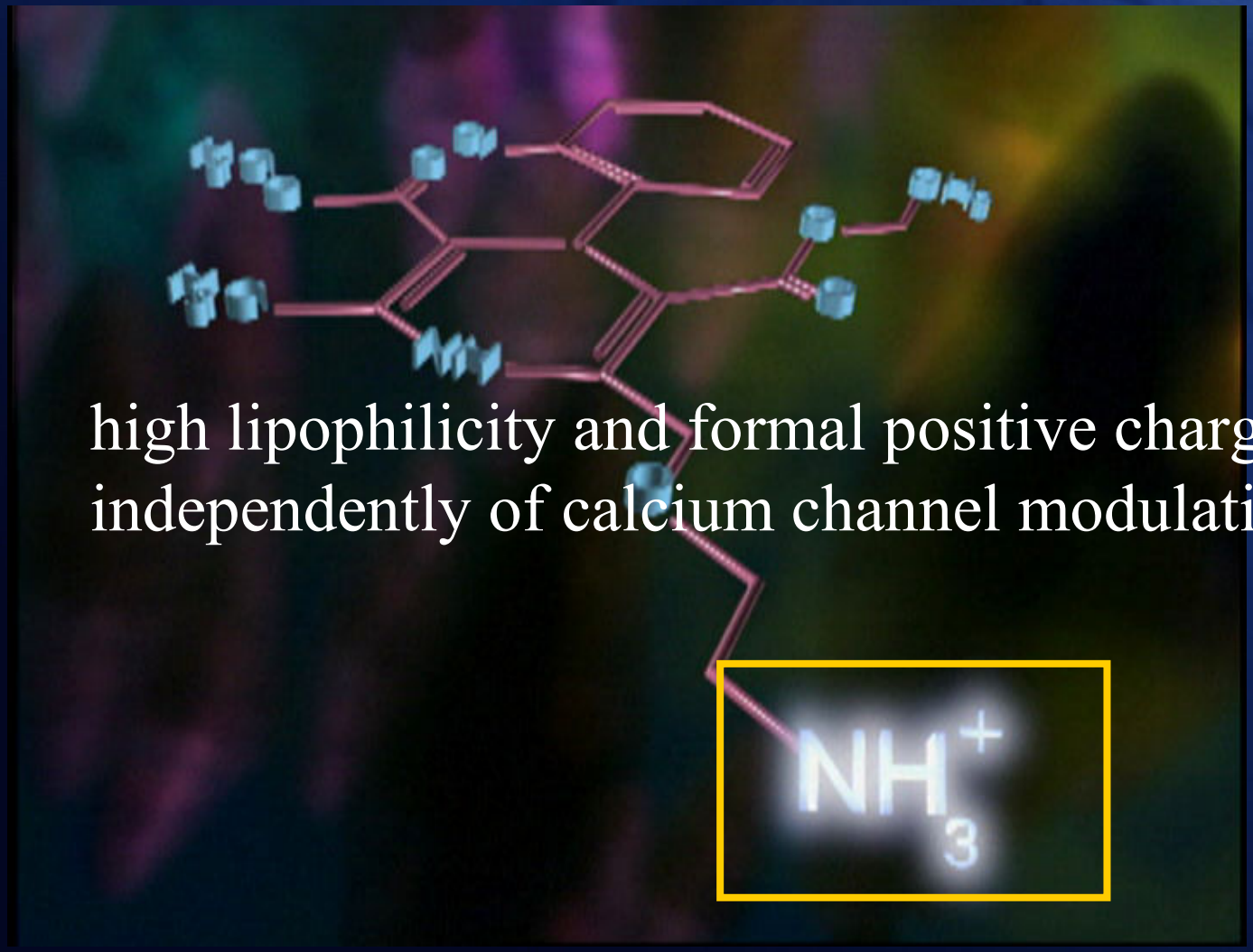
# Effects of Amlodipine and Atorvastatin Active Metabolite vs Lovastatin on Human LDL Oxidation



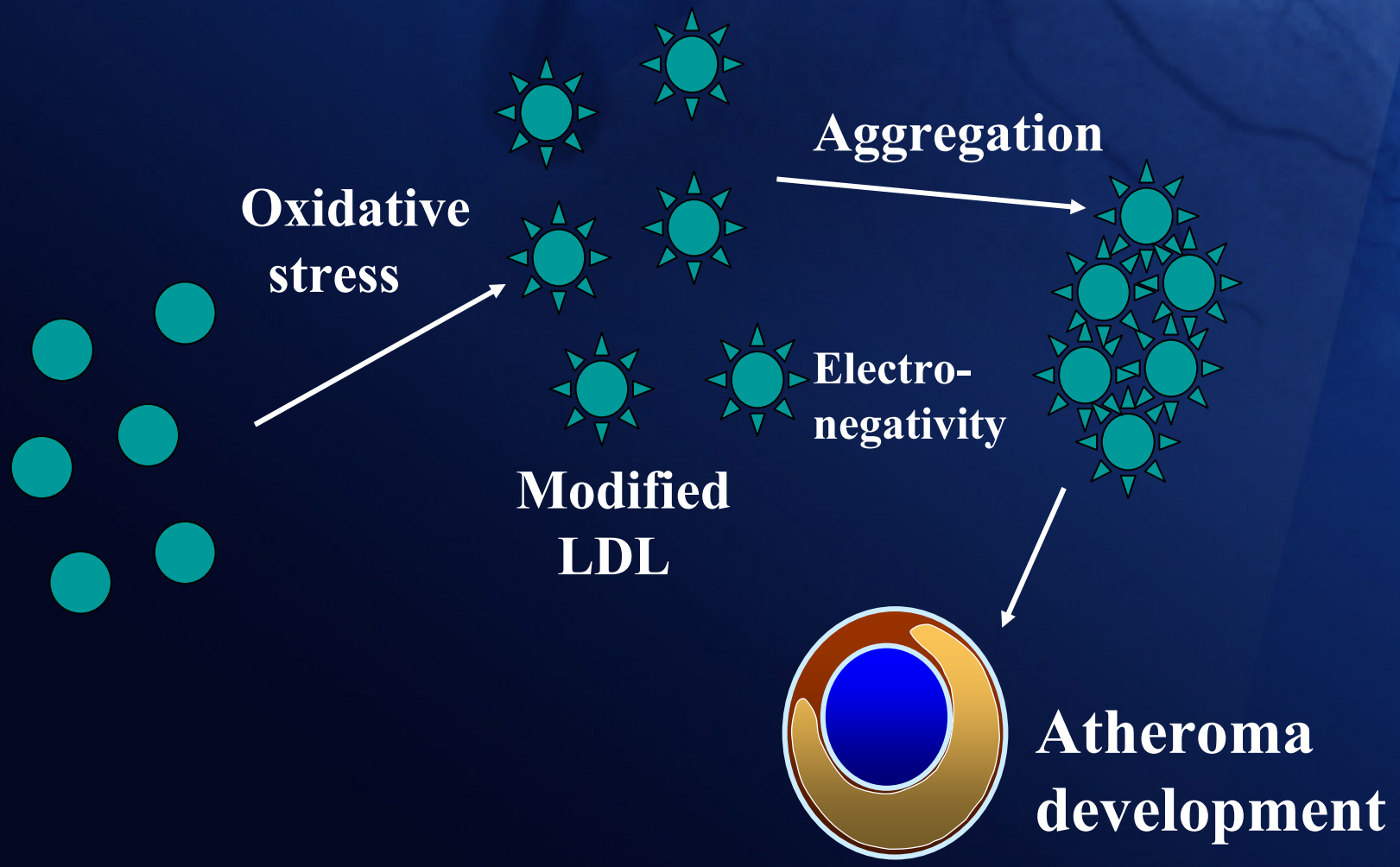

*p < 0.001 versus Control

Reproduced from Mason et al. Am J Cardiol. 2005;96(suppl):11F, with permission.

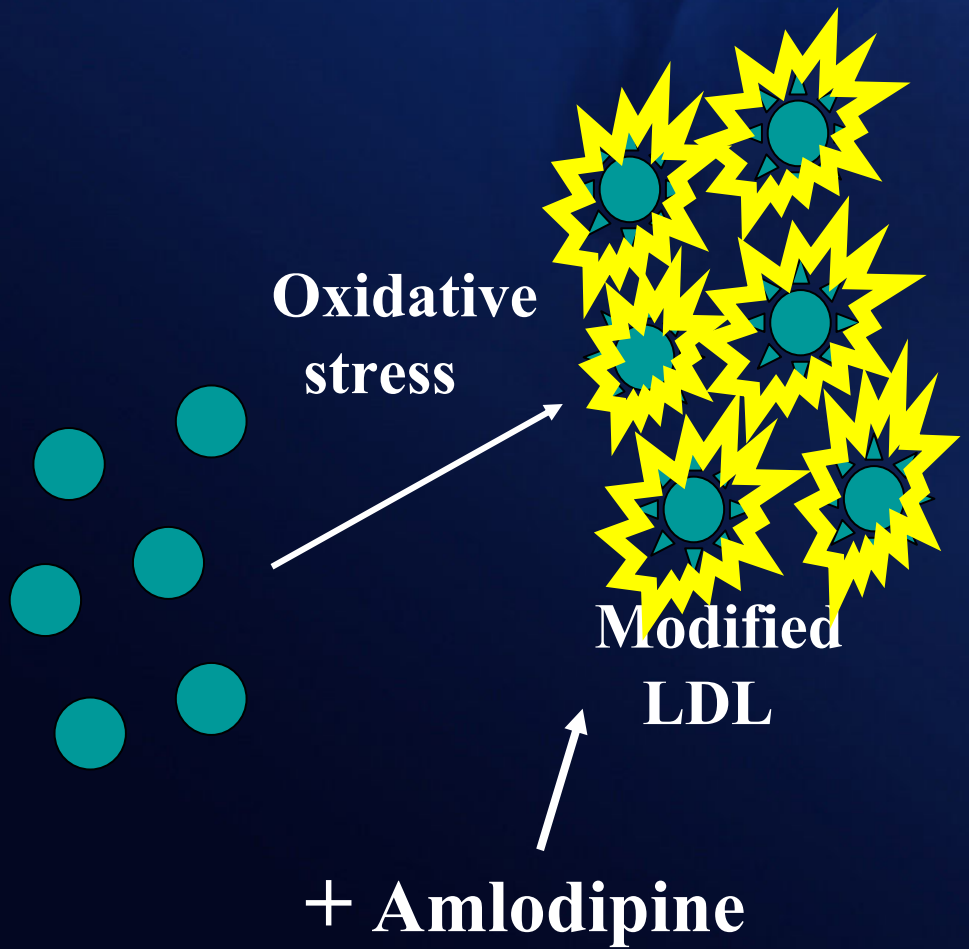
# Amlodipine Charged Molecule



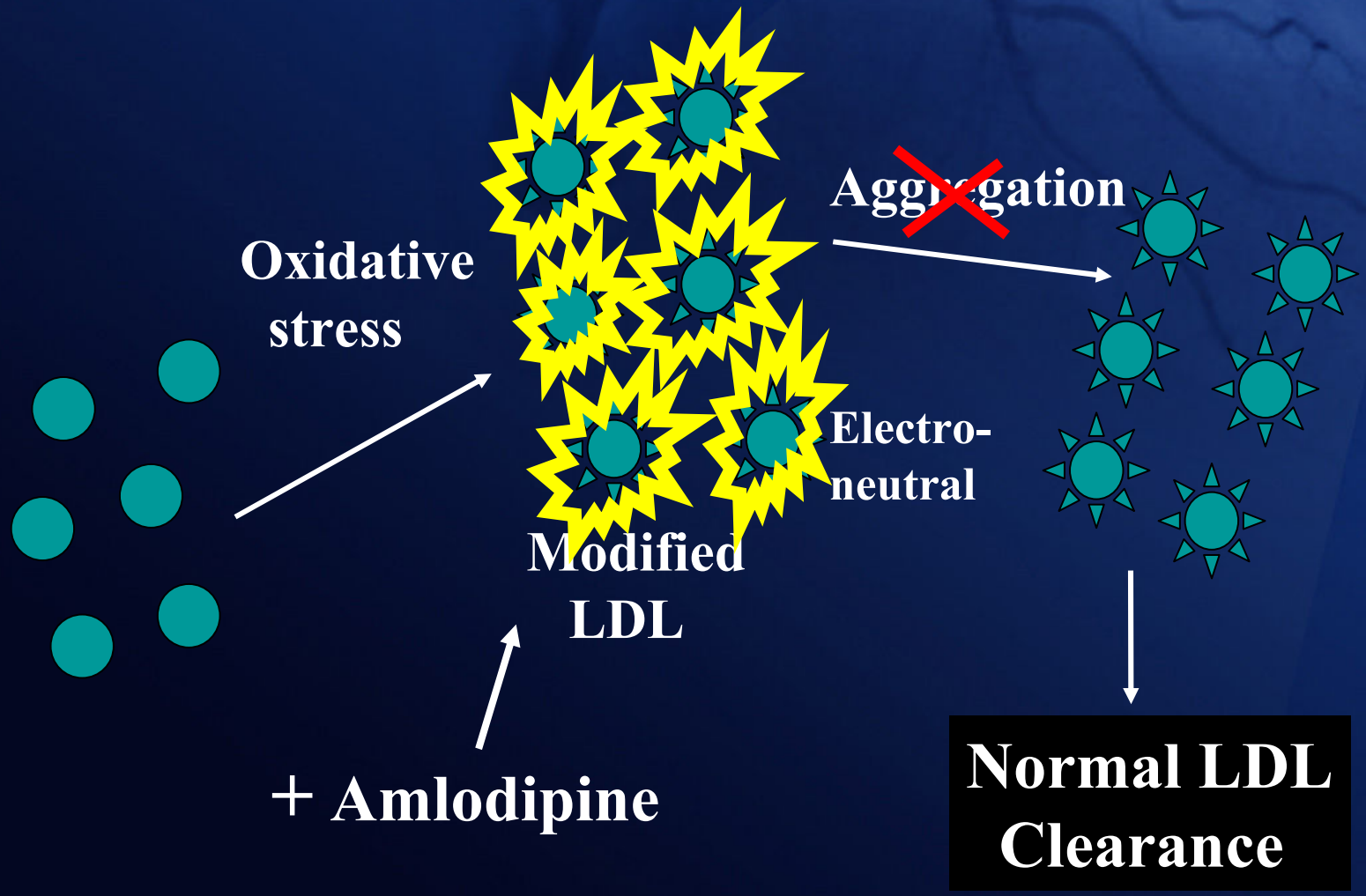
# Modification of LDL leads to endothelial dysfunction and atheroma development



# Effect of Amlodipine against modification of LDL

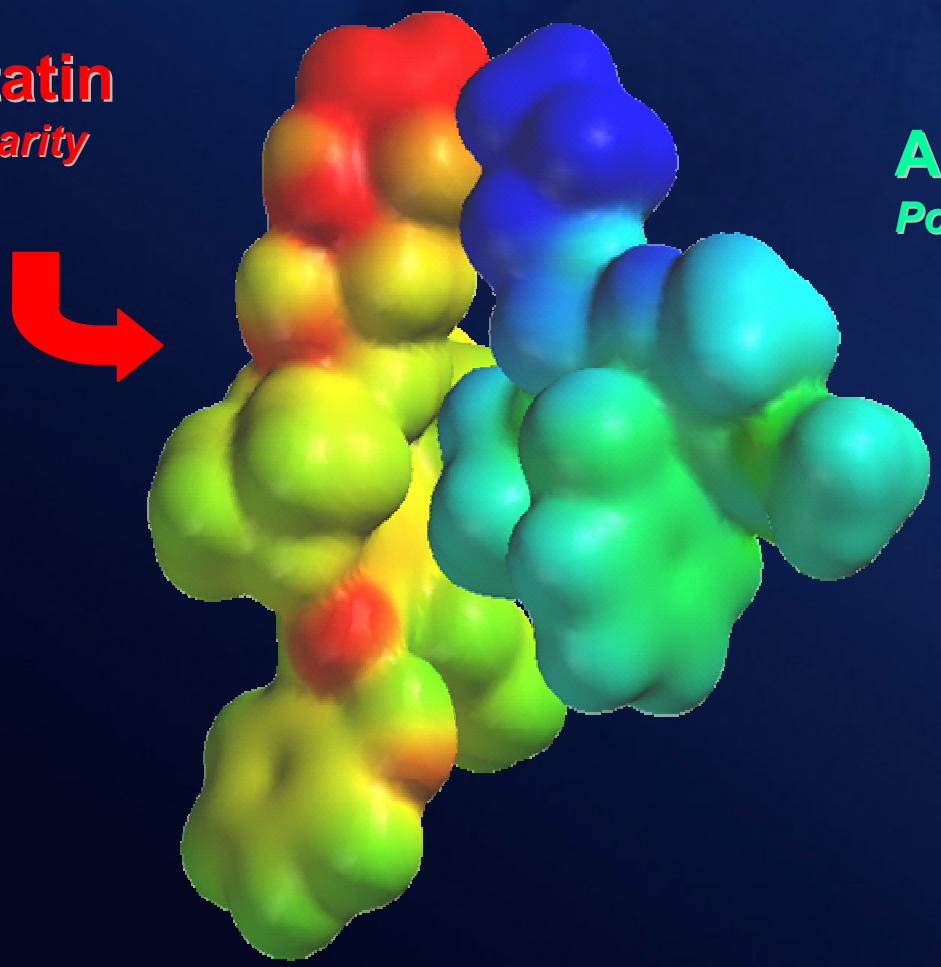


# Effect of Amlodipine against modification of LDL



# Scientific Rationale for Synergy with Amlodipine and Atorvastatin: "Opposites Attract"

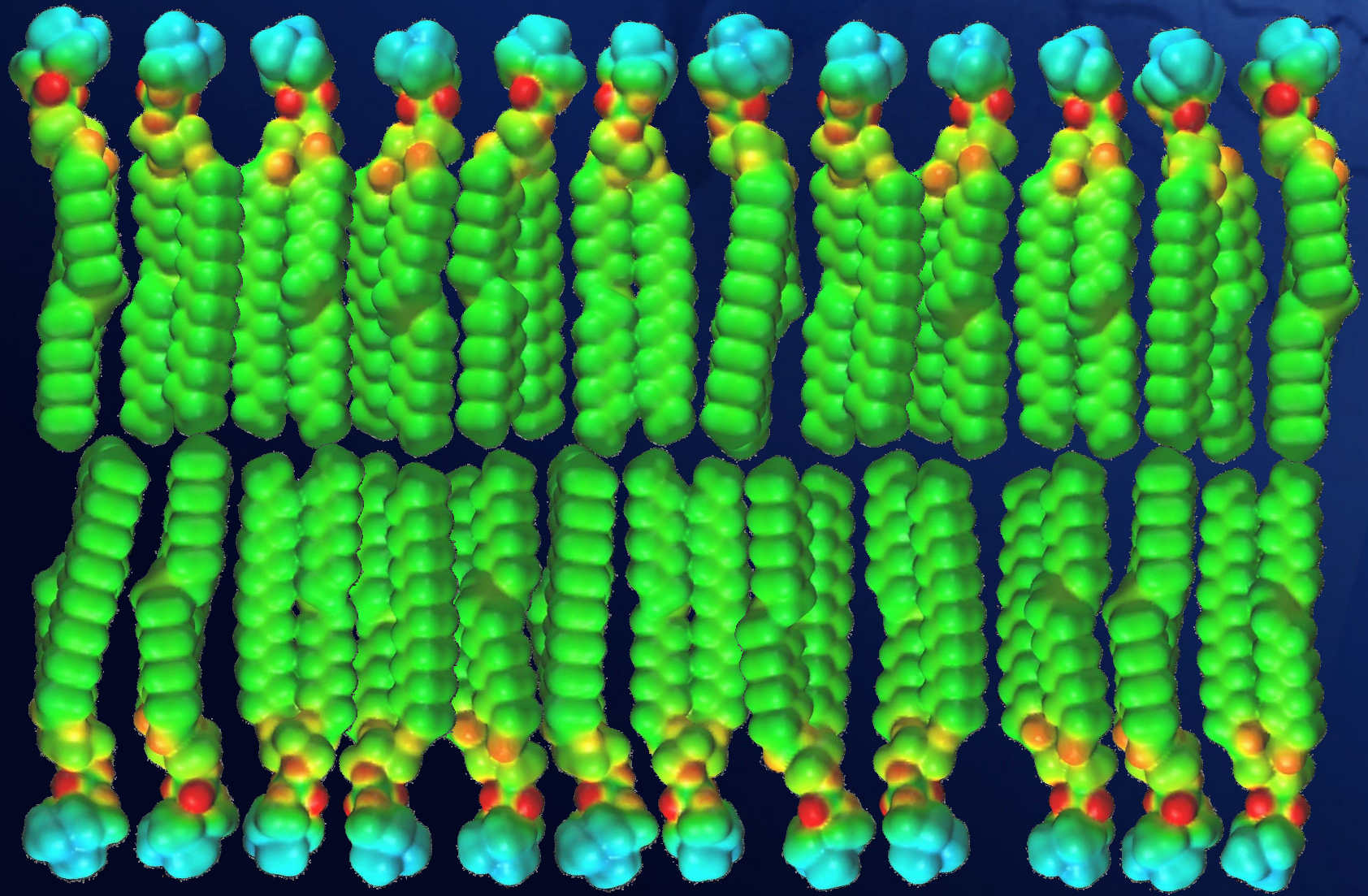
**Atorvastatin**
*Negative Polarity*



**Amlodipine**
*Positive Charge*

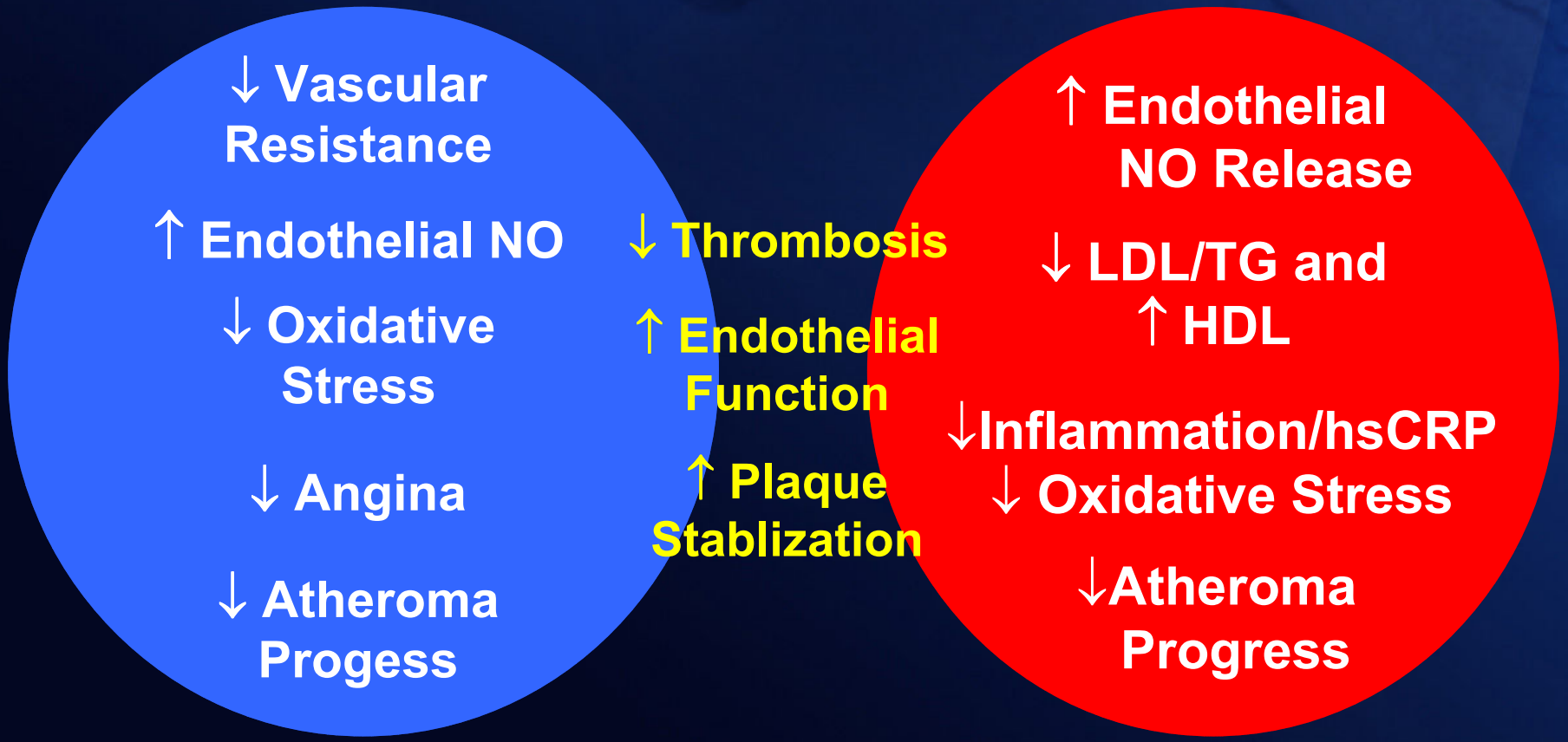
RP Mason and R Kay

# Cell Membrane Bilayer



RP Mason and R Kay

# Atheroprotection with Amolodipine-besylate /Atorvastatin: Risk Factor Management and Beyond

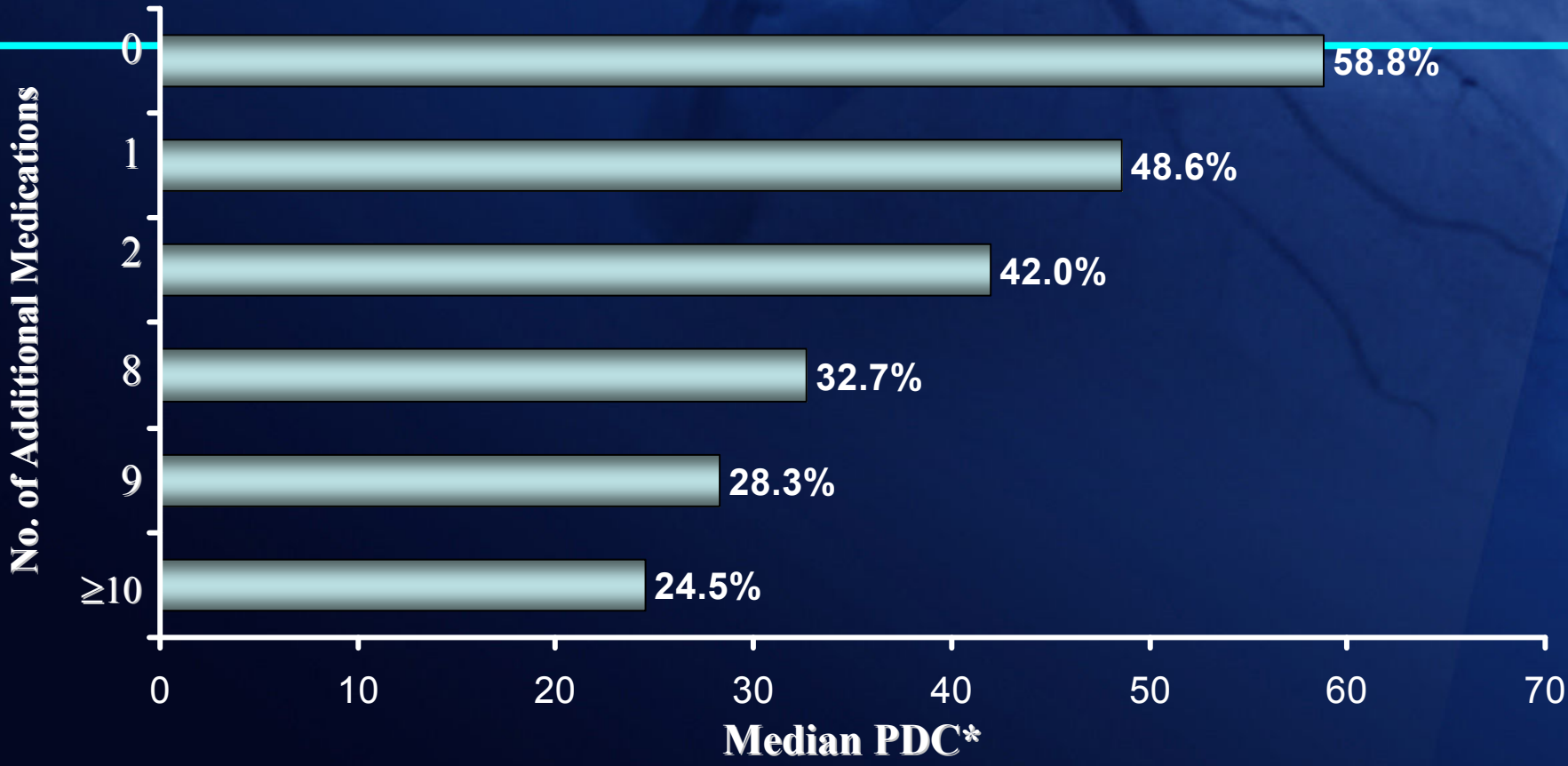



Mason RP et al. *ATVB.* 23:2155;2003

Mason RP et al. *Circulation* 109:II34-II41;2004

A Single pill to improve adherence of patients with high blood pressure and dyslipidemia

# Adherence to Concomitant Antihypertensive & Lipid-Lowering Therapy Decreases as Number of Medications Increases

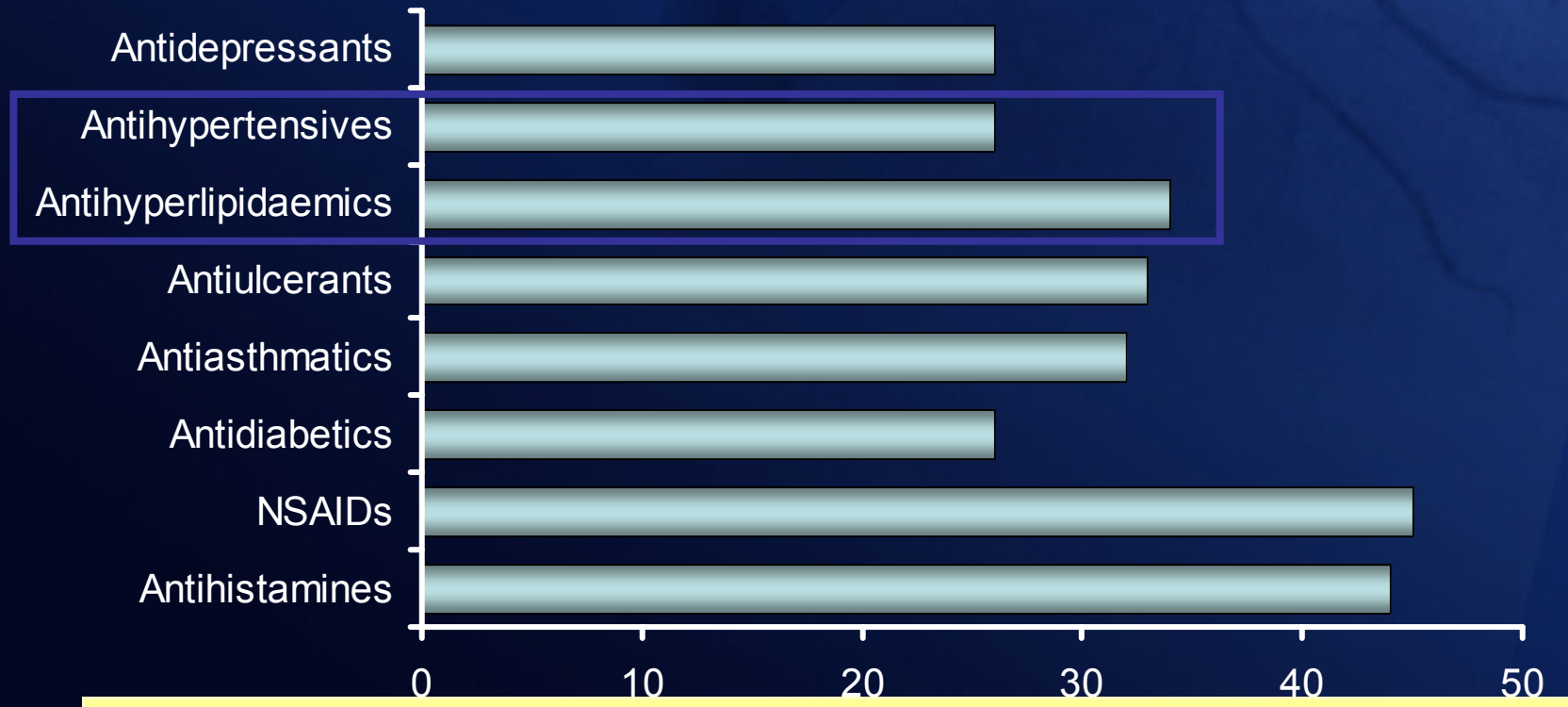



**Incremental pill burden had greatest effect on adherence in patients taking the fewest medications**

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

Benner JS et al. ACC 2006. Abstract.

# Increases in Out-of-Pocket Costs Are Associated with Decreased Adherence Rates




**Doubling copayments is associated with significant reductions in medication use**

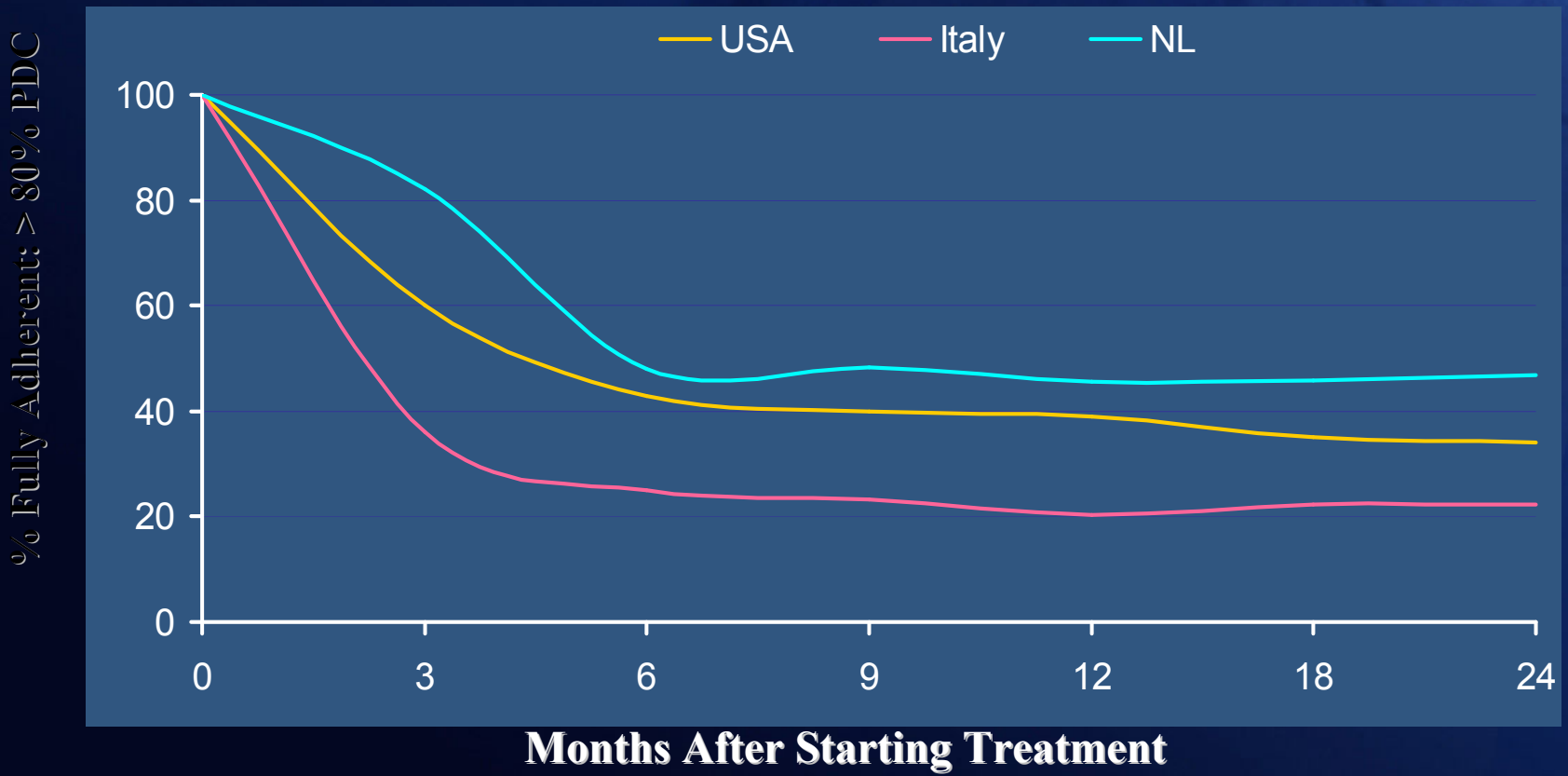
NSAIDs
Retrospe
2000. N
997-

Goldman DP et al. *JAMA*. 2004;291:2344-2350.

Please see prescribing information at the end of this slide presentation.

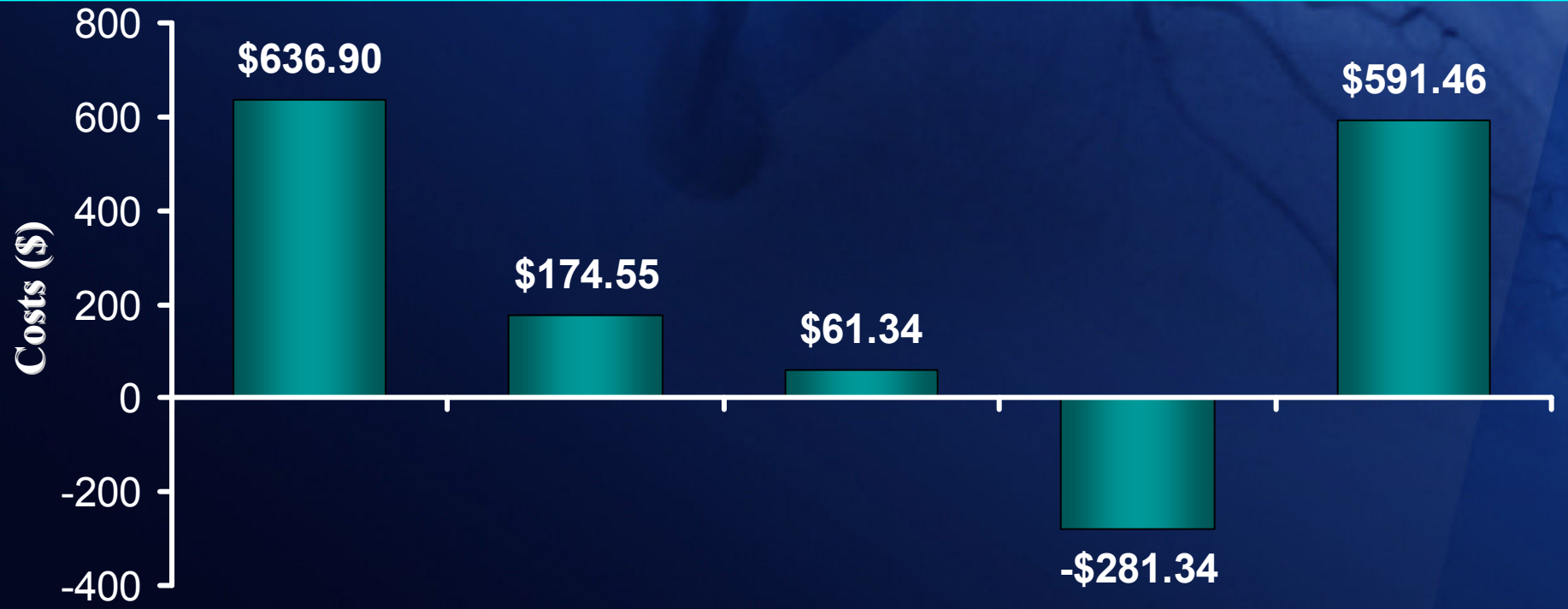
# Persistence and Adherence with Lipid Lowering Drugs

# Adherence to Lipid Lowering Drugs




US data: Benner JS et al. *JAMA*. 2002;288:255-261. Other data from general practice databases in NL and Italy data on file Pfizer Inc, NY, USA.

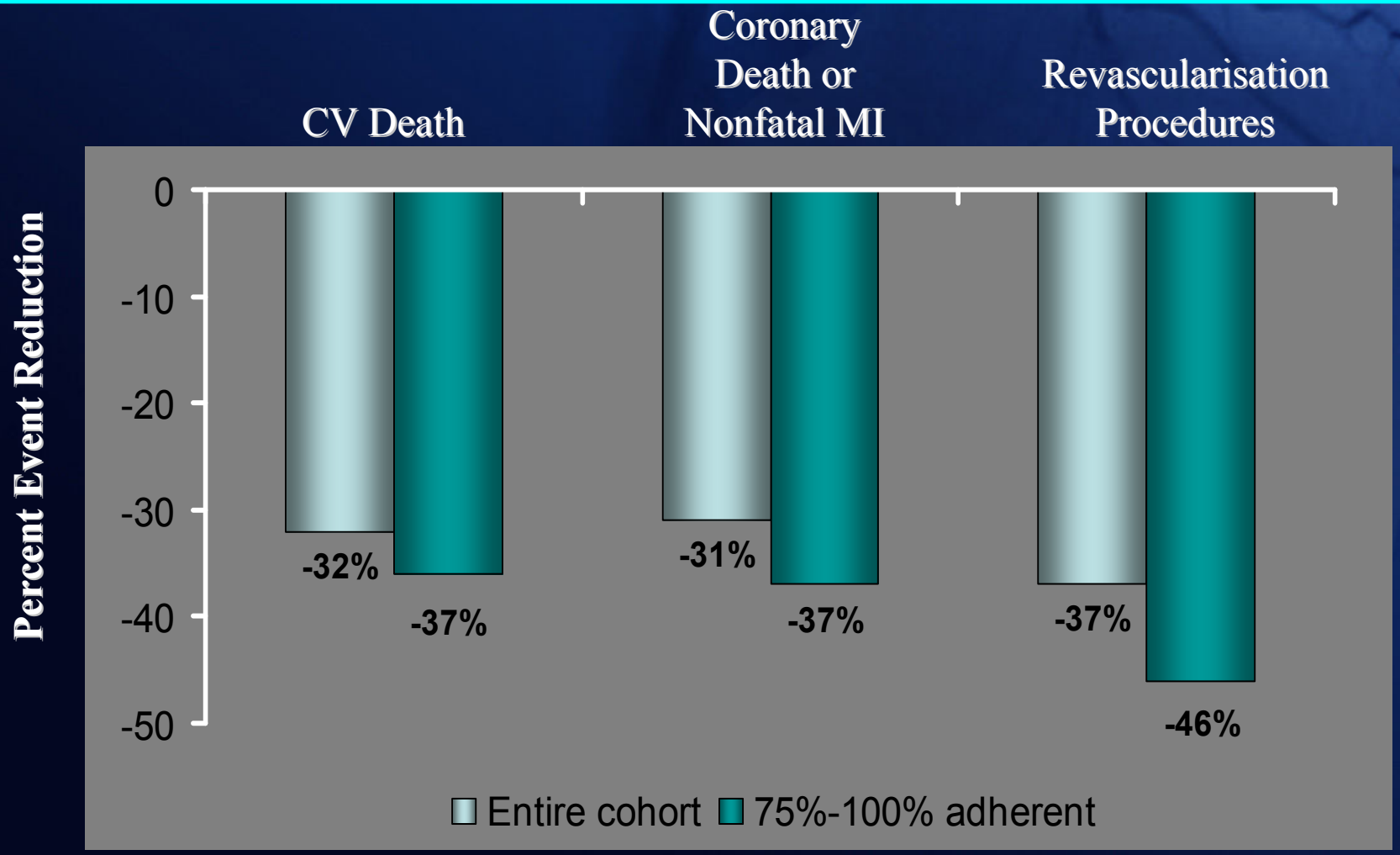
# Nonadherence was Associated with Increased Total Health Care Costs




| | Hospital care | Ambulatory care | Long-term care | Drugs | Total costs |
|---|---|---|---|---|---|
| *P* value | .0002 | .0228 | .1430 | .0001 | .0048 |

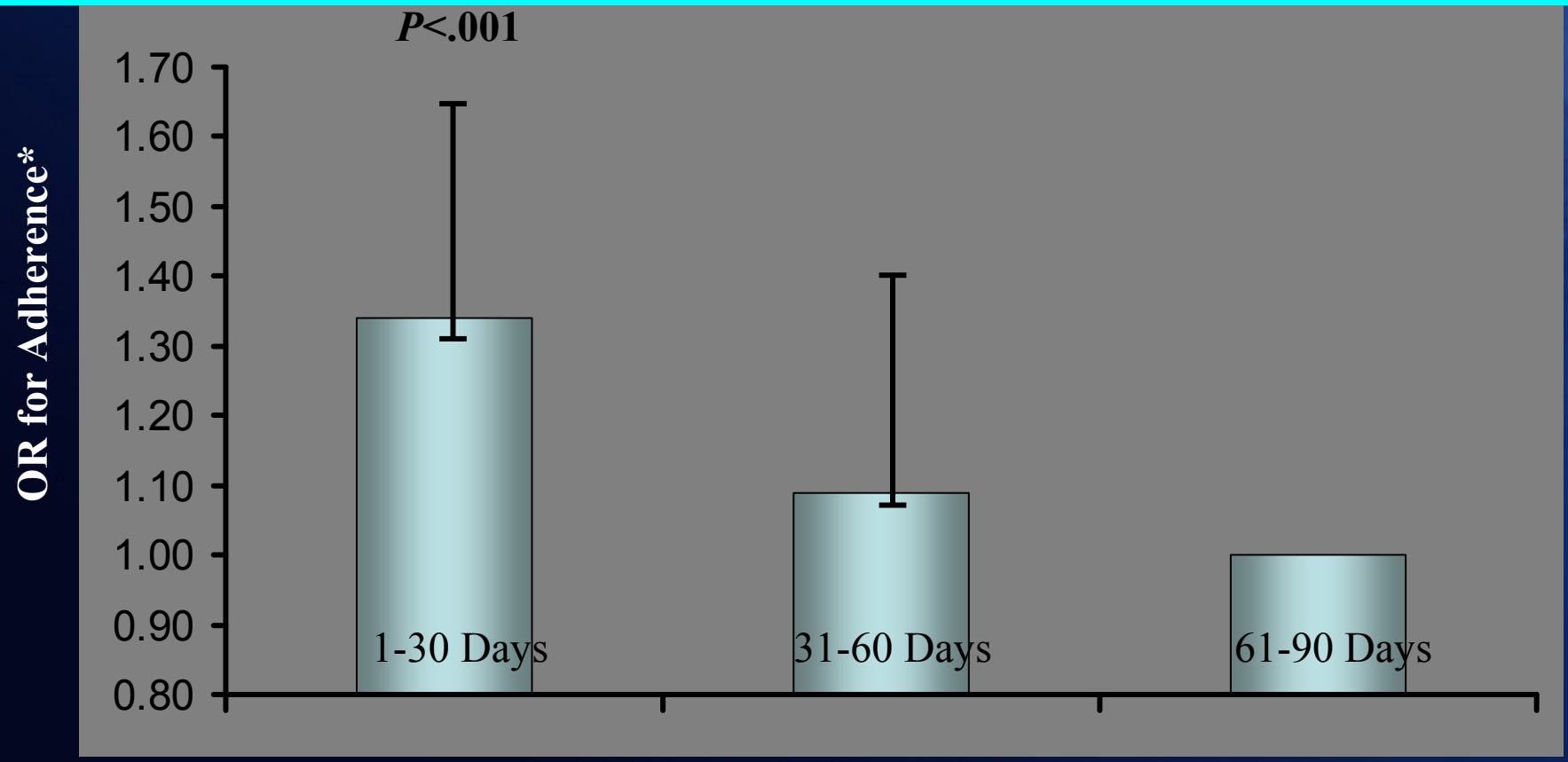
McCombs JS et al. *Med Care*. 1994;32:214-226.

# Improved Outcomes Achieved in Clinical Trials with Higher Adherence




The West of Scotland Coronary Prevention Study Group. *Eur Heart J*. 1997;18:1718-1724.

# Concurrently Starting 2 Medications Improved Adherence



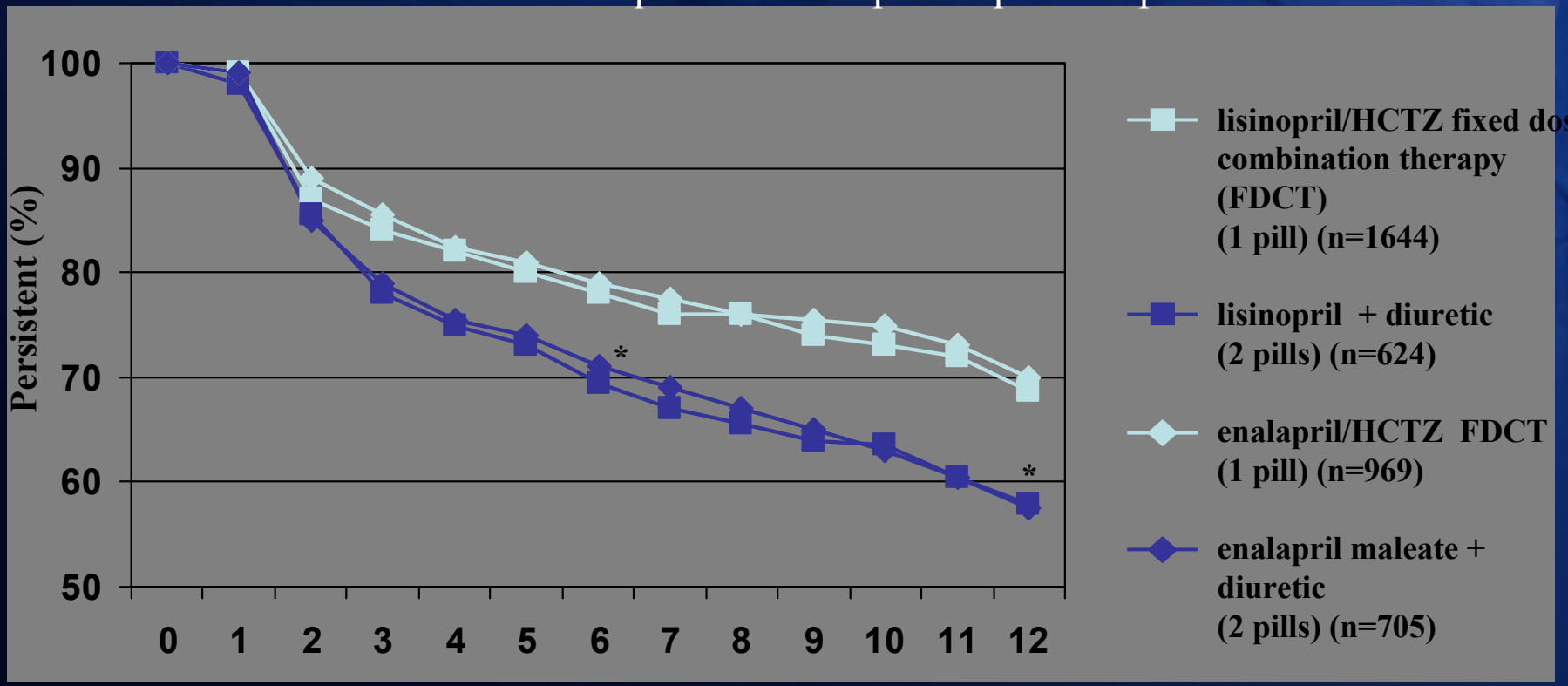

Retrospective cohort study in a large managed-care population (N=8406).

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

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

# Single-pill Regimens Are Associated With Better Persistence

Persistence to equivalent therapies: 1 pill vs 2 pills




*$P<.05$

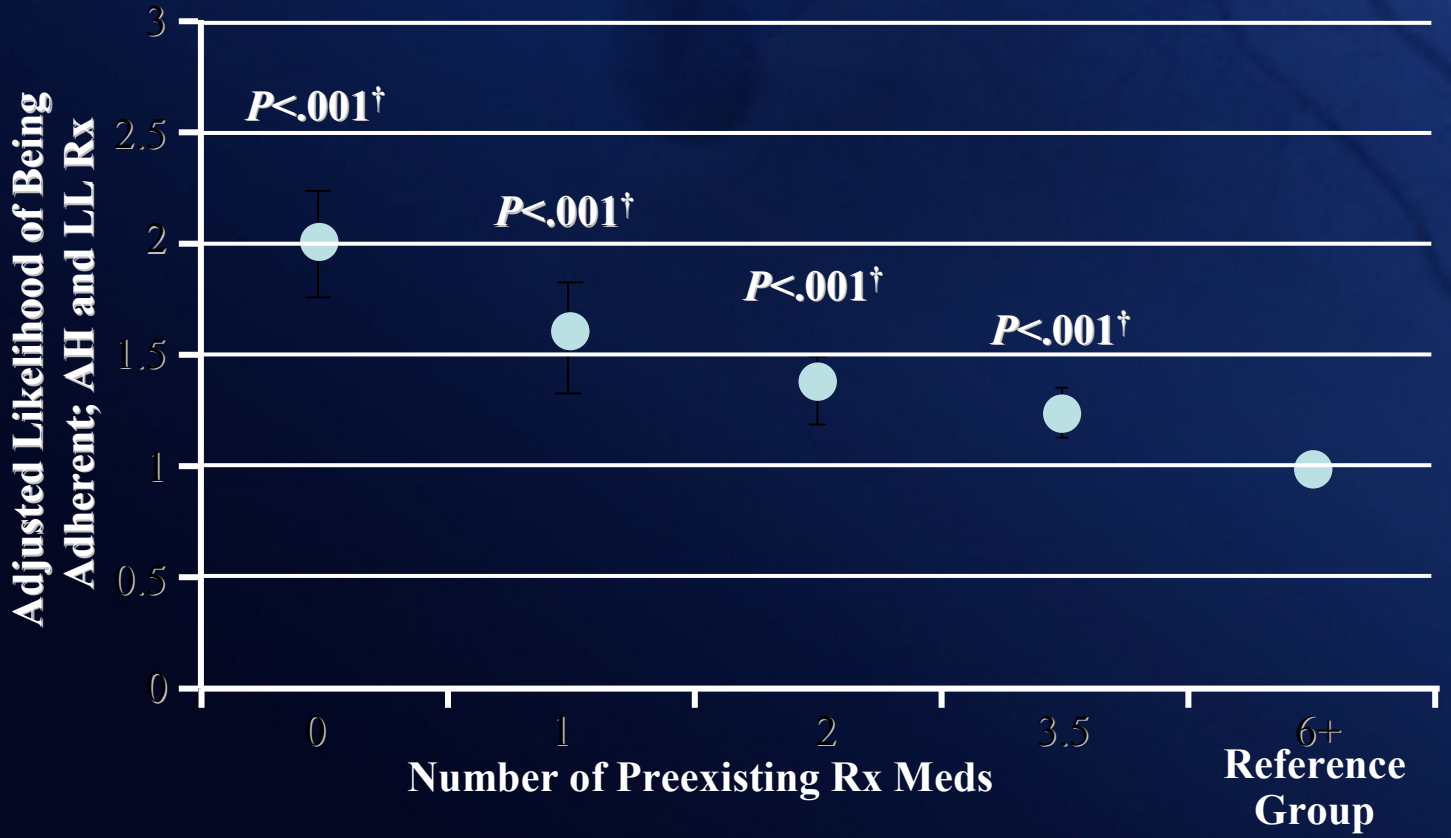
Retrospective analysis of database records of a national commercial PBM. N=7179 patients new to ATH therapy, ACE inhibitor plus diuretic via 2- or 1-pill dosing. Persistence: minimum Rx renewal within 3 times of days supplied. Not persistent: failure to obtain any 3 scheduled refills.

HCTZ = hydroclorothiazide.

Dezii CM. *Manag Care*. 2000.

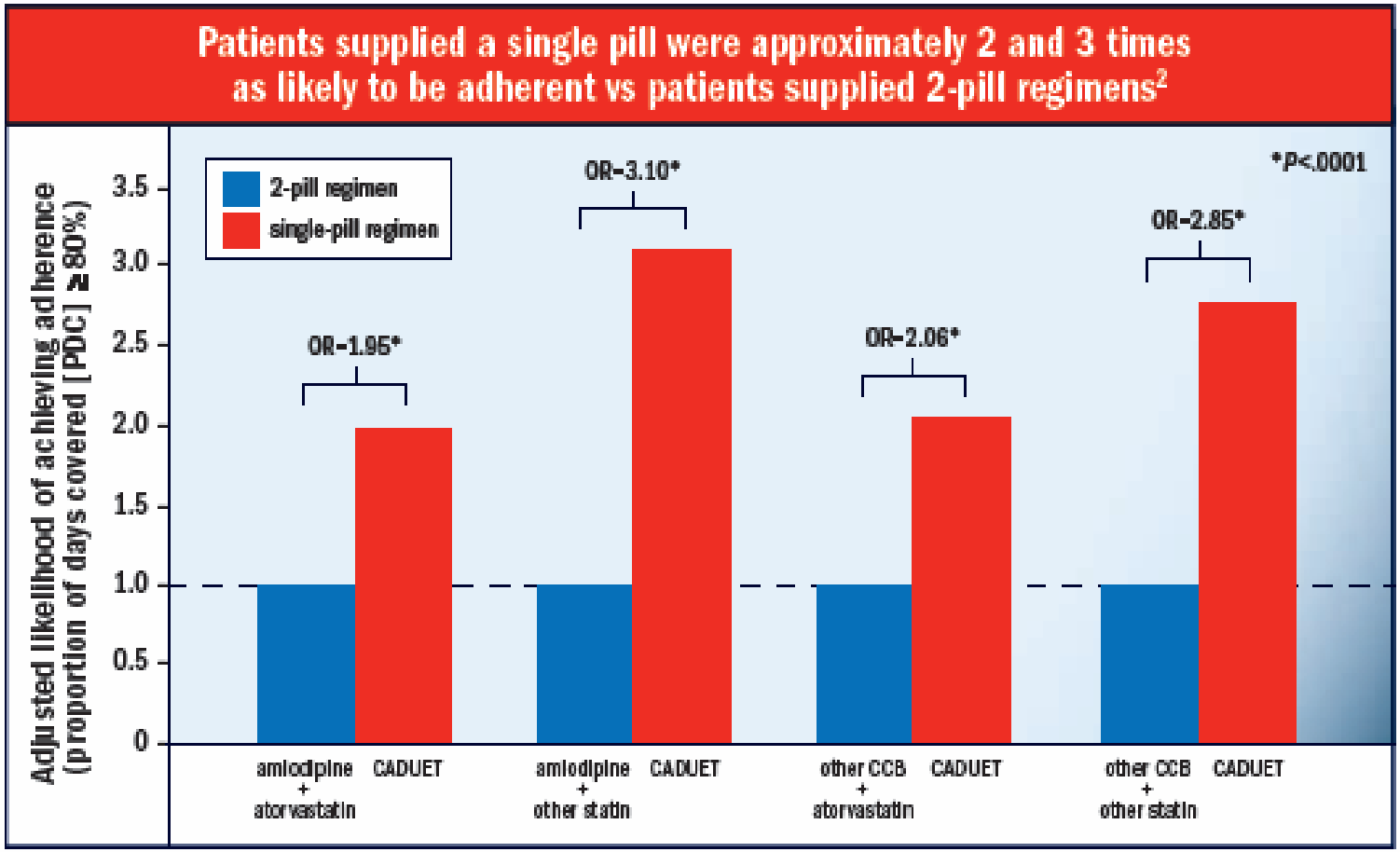
# Lower Pill Burden is Associated with Better Adherence to Antihypertensive and Lipid-Lowering Therapy

- As the number of preexisting* Rx meds increased, the likelihood of adequately refilling AH and LL meds decreased




*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.

# Patients supplied Caduet were approximately 2 and 3 times as likely to be adherent vs. patients supplied 2-pill regiments




Nichol MB et al. *Journal of Clinical Hypertension*, 2006;8(6):456.
Presented at American Society of Hypertension 2006; New York, NY

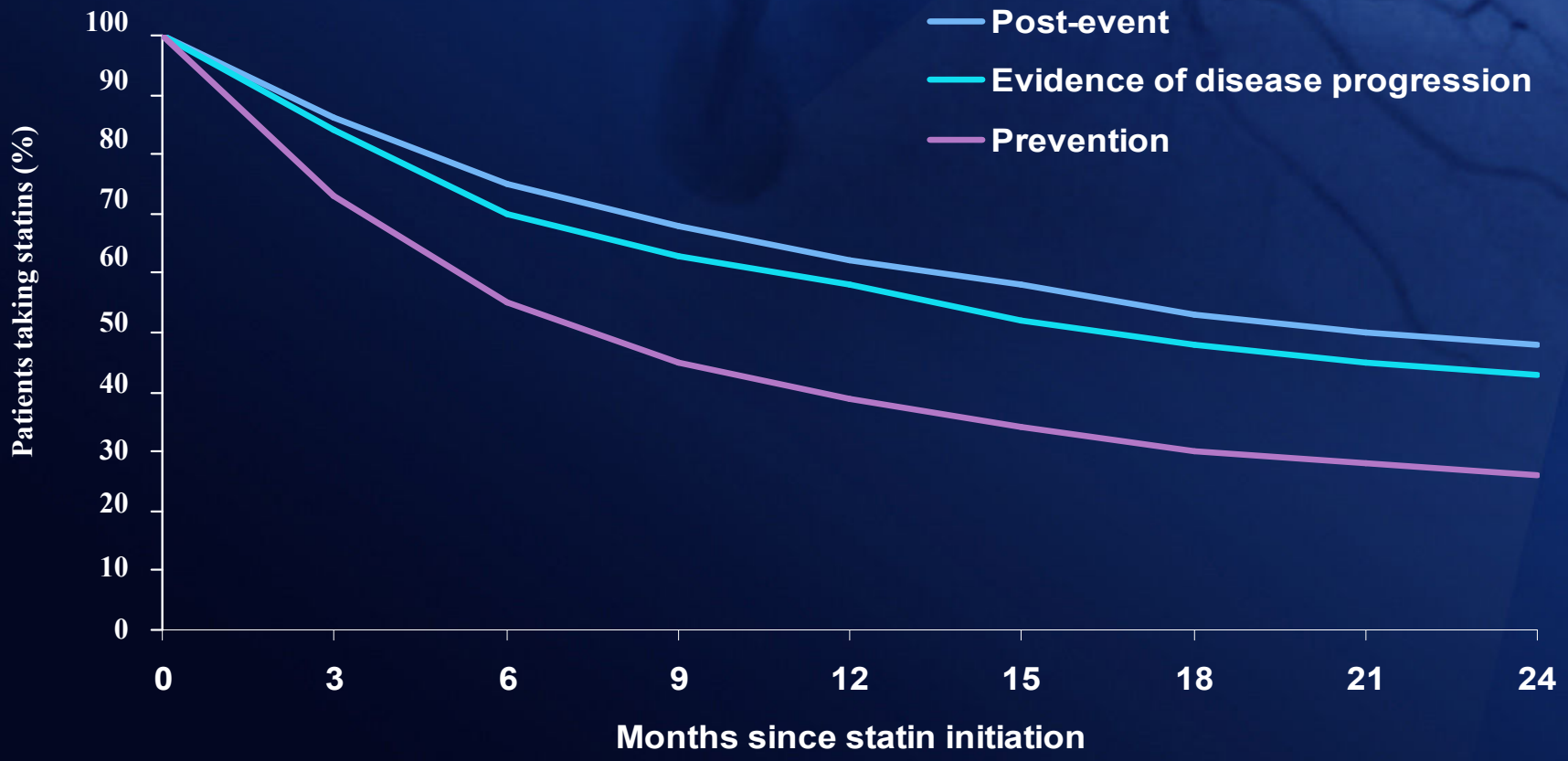
# Is Poor Adherence the Final CV Risk Factor?

- **Increasing pill burden decreases adherence**
- **In clinical trials, worse outcomes were attained when adherence was lower**
- **Patients need to adhere to their medications in order to effectively treat their CV risk factors**
  - **Improved adherence when starting 2 medications concurrently**
  - **Combination therapy reduces pill burden**
  - **Reduced pill burden improves adherence**

➢ **Nonadherence to medication increases CV risk**

# Strategies for Improving Adherence

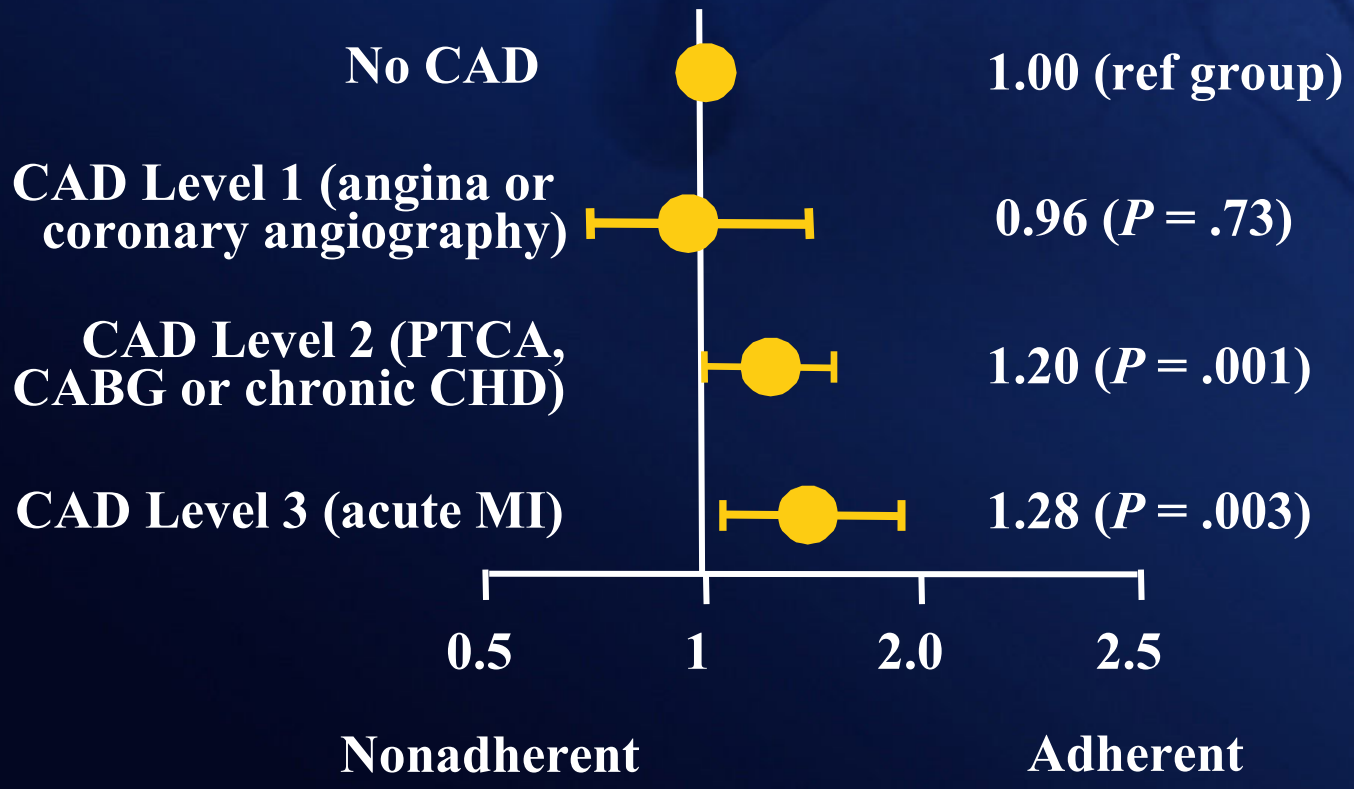
# Adherence Lowest When Therapy Was Preventive: Perception of Risk Key Factor




Cohort study using linked population-based administration data from Ontario, Canada (N=143,505).

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

# Increased CVD Risk Status Associated With Improved Adherence




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

# Cardiovascular Regimen Characteristics Affect Adherence

- Complexity/pill burden
  - Single AH pill versus two AH pills
- Dose frequency
- Side effects
- Lifestyle fit/ therapy initiation
- Copayments

# Assist Your Patient to Adhere

- **Teach patients to take their pills on a regular schedule associated with a routine daily activity e.g. brushing teeth.**
- **Simplify medication regimens using long-acting once-daily dosing**
- **Utilize fixed-dose combination pills**
- **Utilize unit-of-use packaging e.g. blister packaging**

2006 **C**anadian **H**ypertension **E**ducation **P**rogram Recommendations

# Prescribing Practices Can Positively Influence Adherence

- Providers should consider prescribing:
  - Regimens with the lowest appropriate pill burden
  - Drugs with reduced dose frequencies
  - Drugs with favorable side effect profiles
  - Drugs with a lower cost

Aronow HD et al. *Arch Intern Med.* 2003;163:2576-2582; Avorn J et al. *JAMA.* 1998;279:1458-1462; Bloom BS. *Clin Ther.* 1998;20:671-681; Dezii CM. *Manag Care.* 2000;9(suppl):S2-S6; Monane M et al. *Am J Hypertens.* 1997;10:697-704; Newell SA et al. *Prev Med.* 1999;29:535-548.