Recent advances targeting cardiovascular risk reduction

Single-Pill Therapy with Amlodipine/ Atorvastatin

SATELLITE LECTURE

Sponsored by WinMedica

Larissa, March 18, 2016

Konstantinos P. Makaritsis
Associate Professor of Medicine
University of Thessaly Medical School

Disclosures

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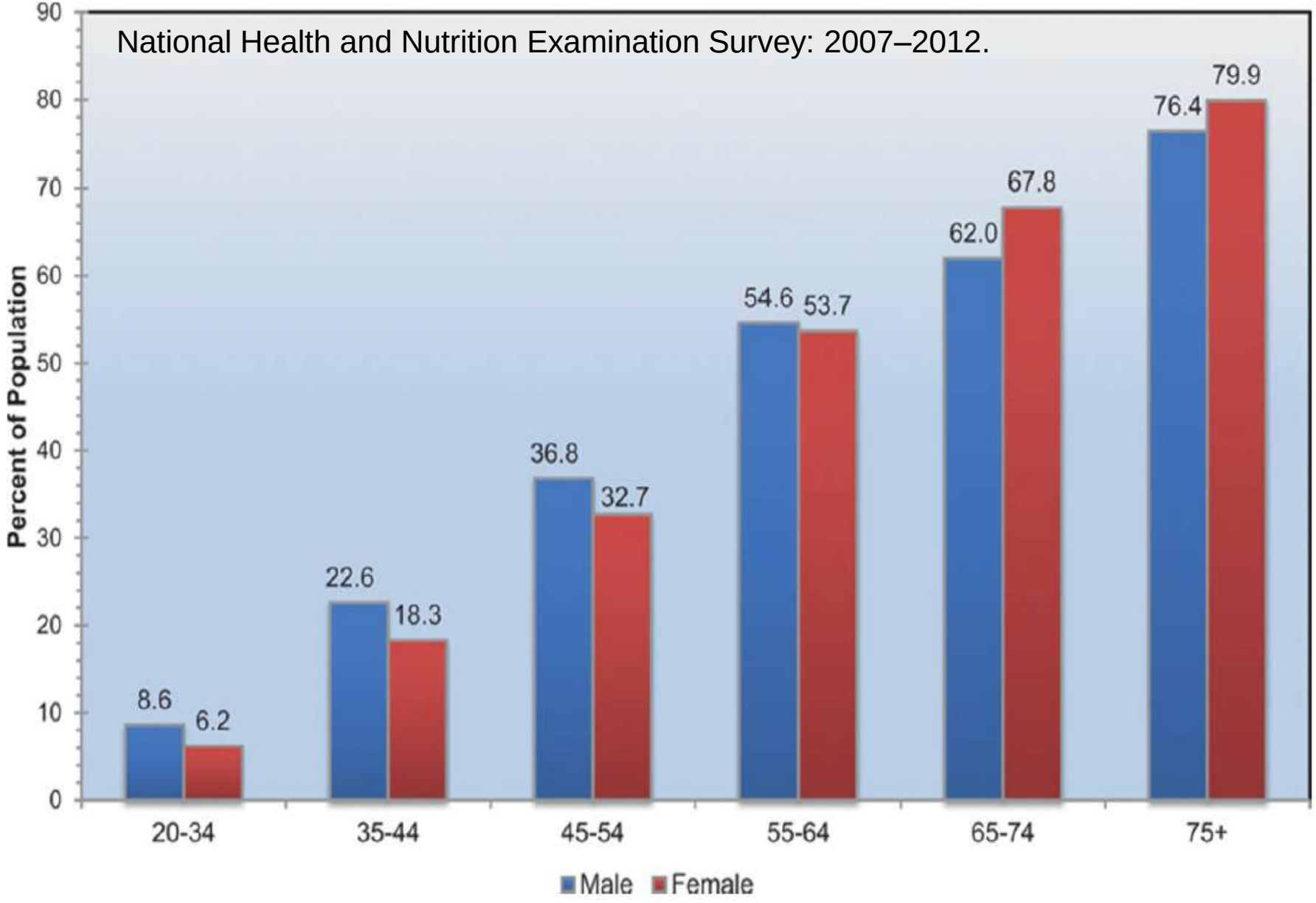
Introduction

Hypertension is the most common of the chronic diseases, affecting an estimated 1 billion adults worldwide.

The prevalence of hypertension is rising, owing in part to the increasing age of the population, the increased rates of obesity and the increased consumption of sodium in packaged and processed foods.

Kearney PM et al. *Lancet* 365, 217–223 (2005).
Fields LE et al. *Hypertension* 44, 398–404 (2004).

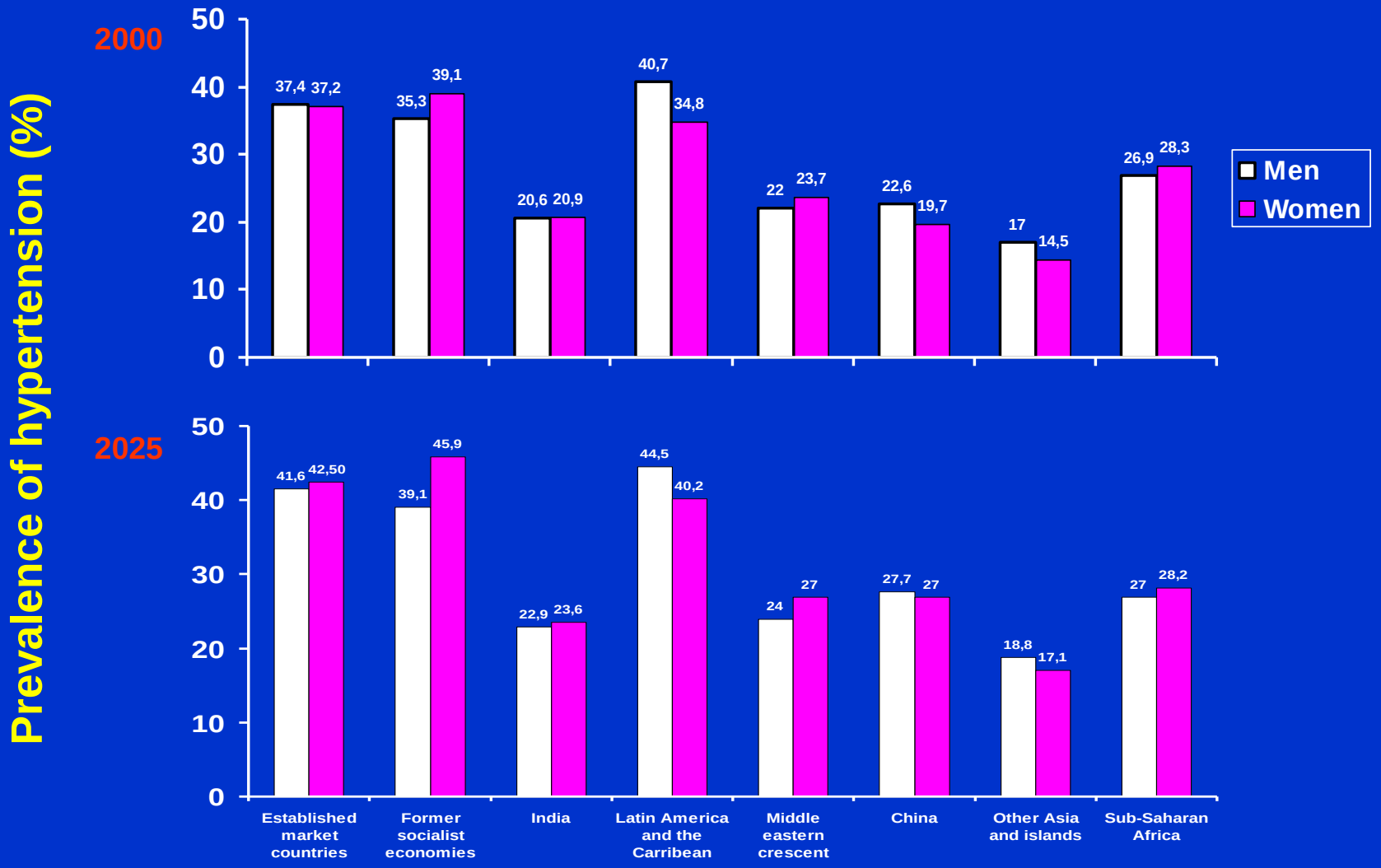
Prevalence of high blood pressure in adults ≥20 years of age by age and sex



Mozaffarian D et al. Circulation. 2015;131:e29-e322

Prevalence of hypertension is high

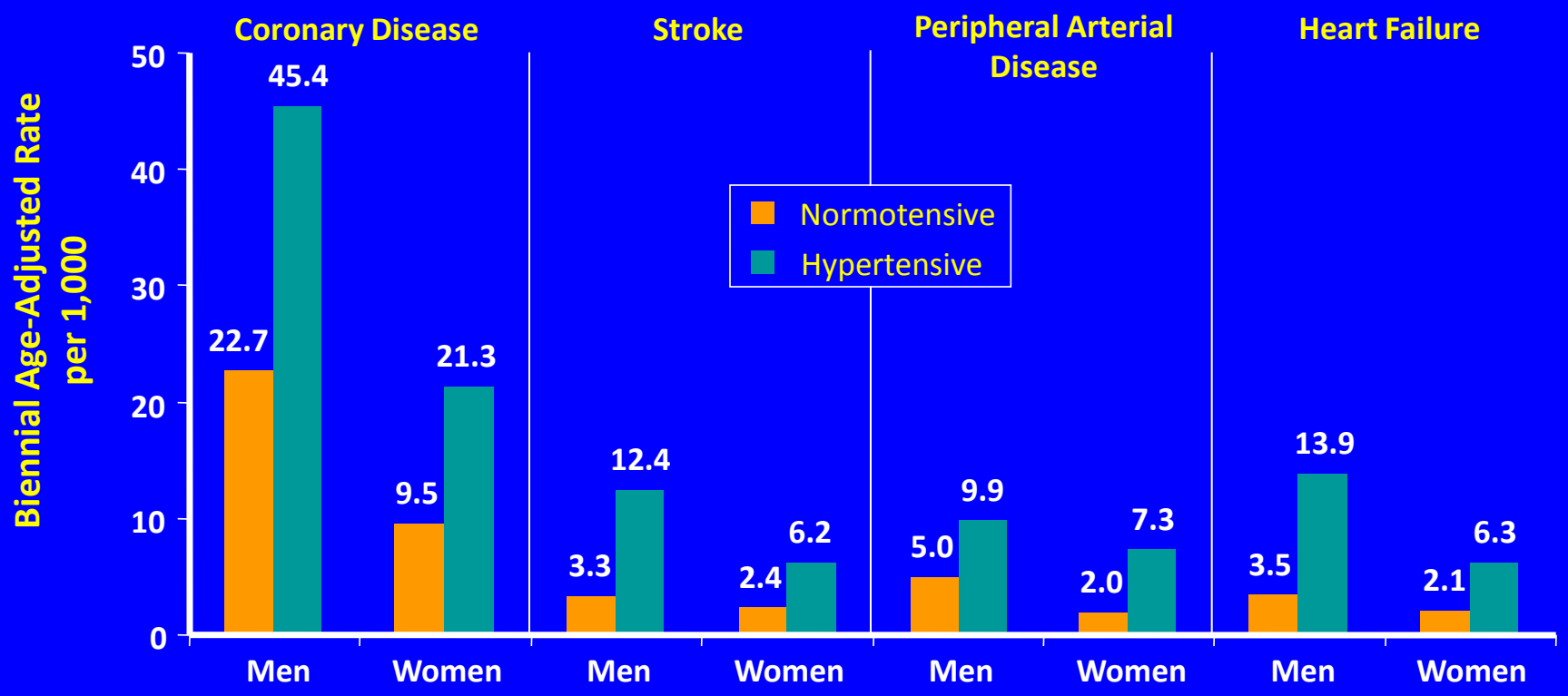
Prevalence of hypertension in people aged 20 years and older



Kearney PM et al.,Lancet. 2005;365:217-223.

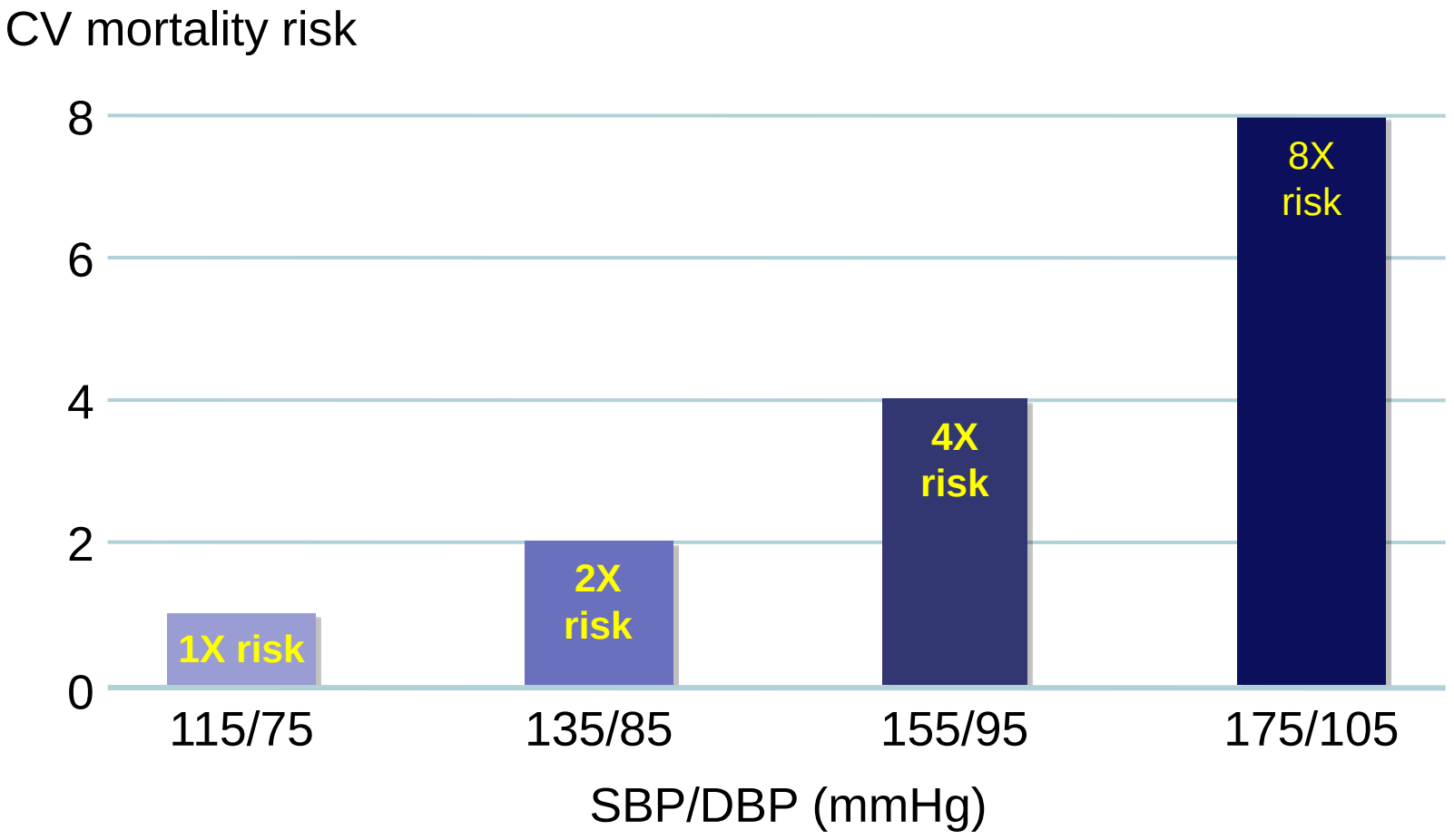
Hypertension is a leading cause for cardiovascular morbidity

36-Year Follow-up in Patients Aged 35-64 Years[1,2]



1. Kannel W.B. et al., JAMA 1996; 275: 1571-1576
2. Kannel W.B. et al., J Hum Hypertens 2000; 14: 83-90

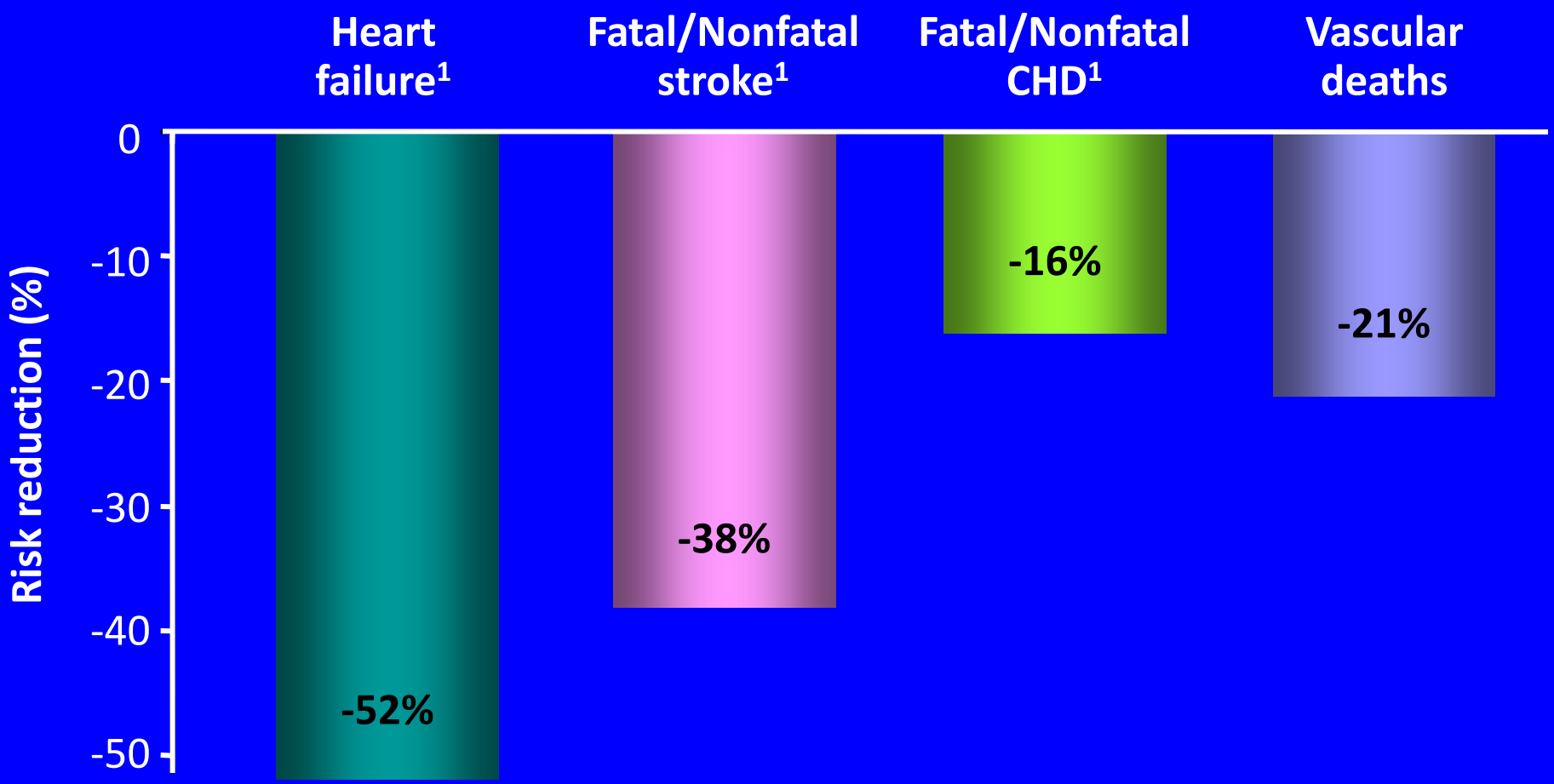
Cardiovascular (CV) Mortality Risk Doubles with Each 20/10 mmHg Increment in Systolic/Diastolic BP (SBP/DBP)*



*Individuals aged 40–69 years

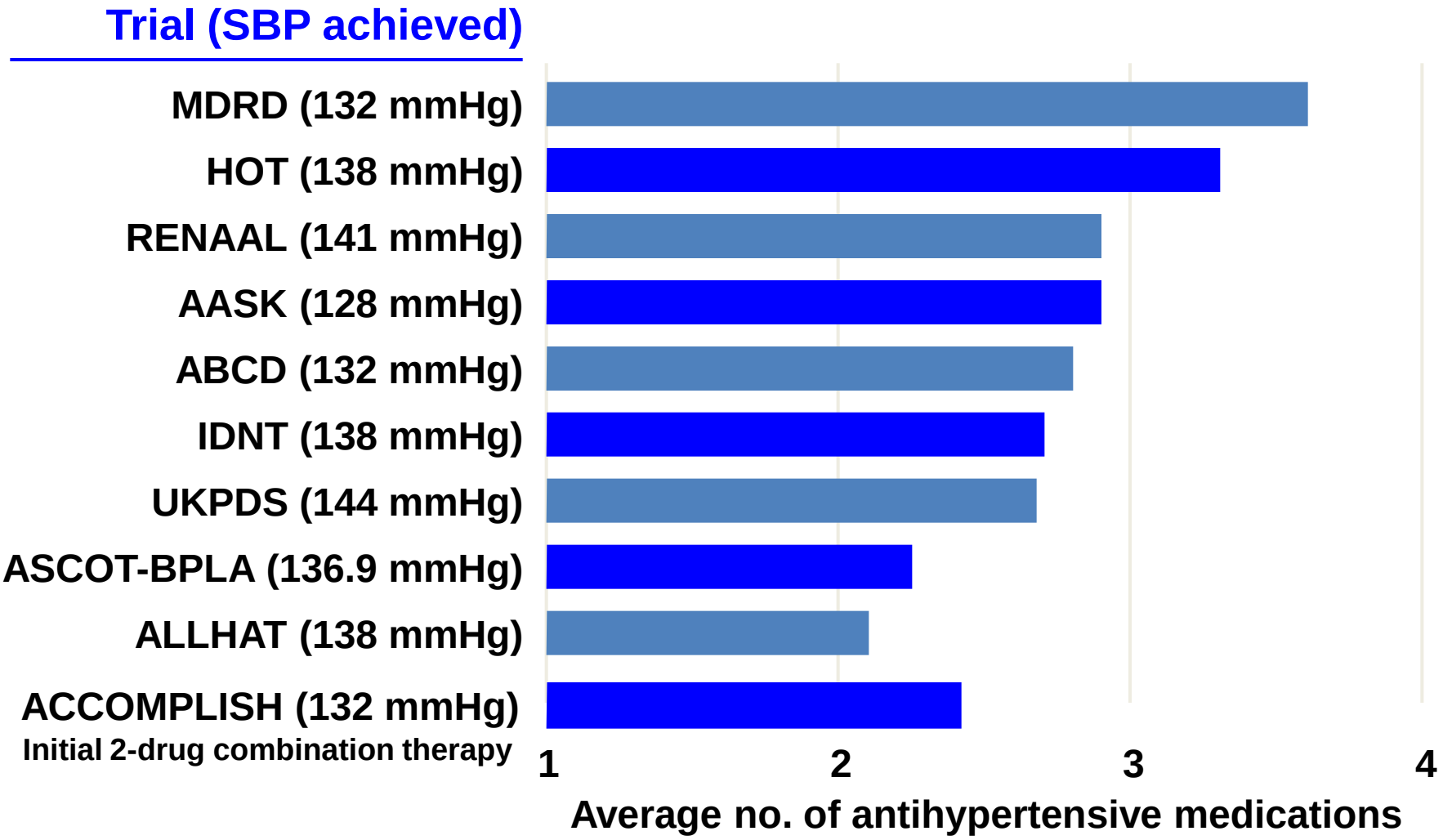
Lewington et al. Lancet 2002;360:1903–13

Antihypertensive drug therapy is effective at reducing risk of CV events



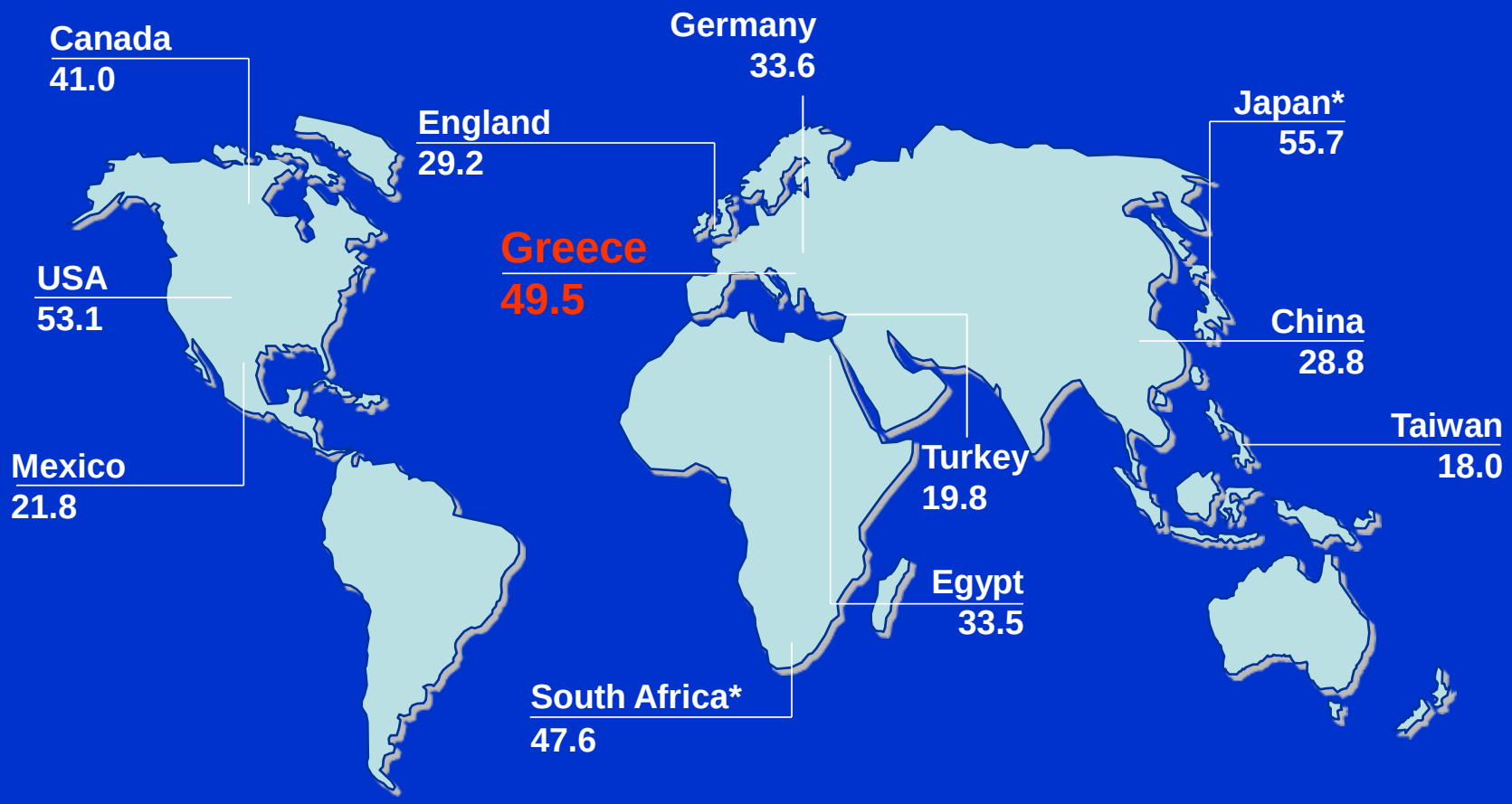
1. Moser and Herbert. *J Am Coll Cardiol.* 1996;
2. Collins R *et al*. *Lancet* 1990.

Multiple Antihypertensive Agents are Needed to Reach BP Goal



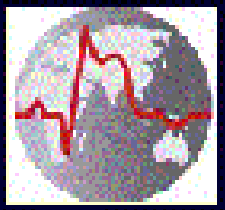
1. Bakris et al. Am J Med 2004;116(5A):30S–8; 2. Dahlöf et al. Lancet 2005;366:895–906
3. Jamerson et al. Blood Press 2007;16:80–6; 4. Jamerson et al. N Engl J Med 2008;359:2417–28

Worldwide blood pressure control rates in treated hypertensive patients are low



Kearney P.M. et al., J Hypertens 2004; 22: 11–19; * Data for men only

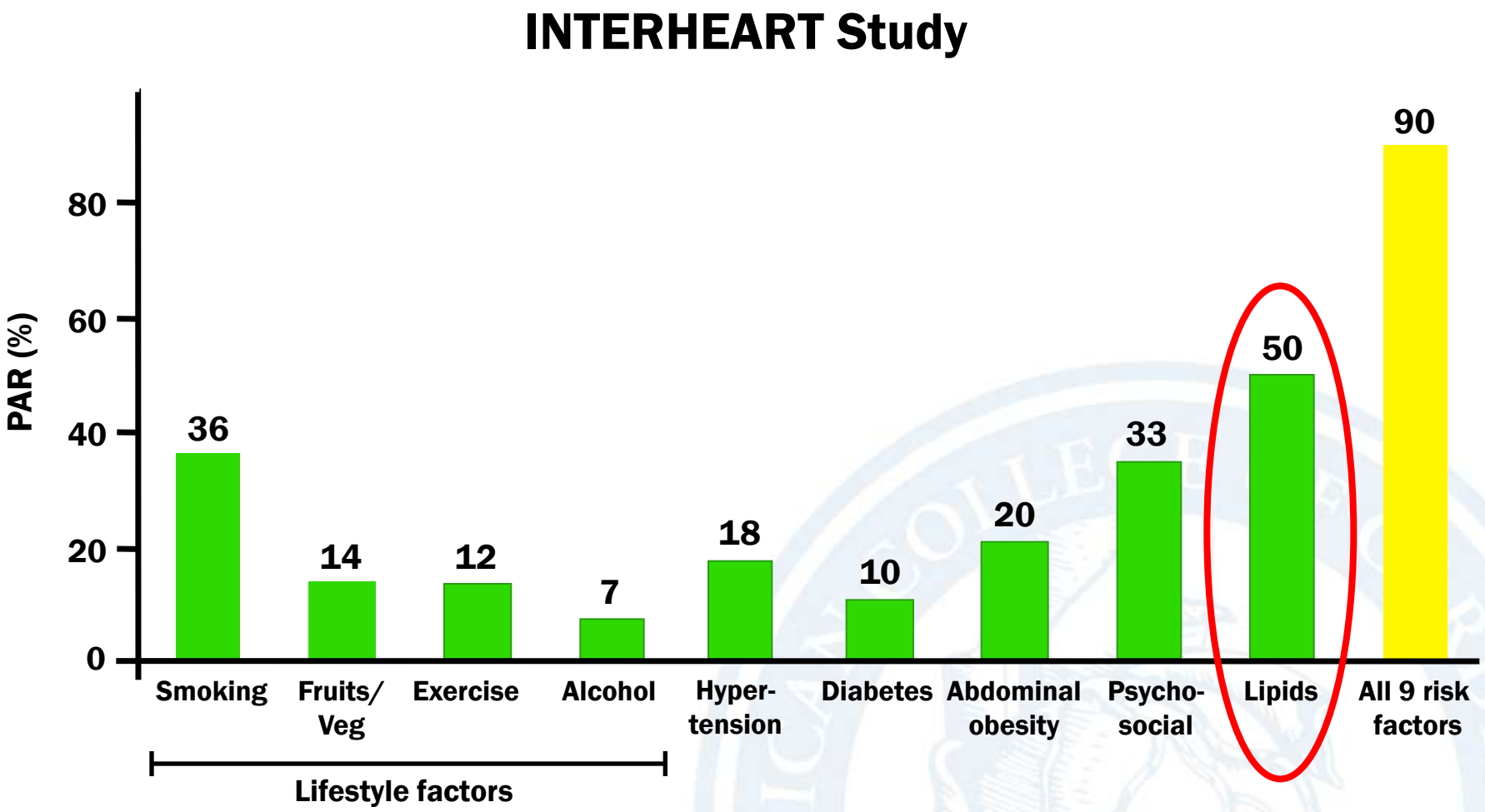
PROCAM: Ranking of Risk Factors



	R
1. Age	0.2395
2. LDL cholesterol	0.2096
3. Smoking	0.1309
4. HDL cholesterol	-0.1018
5. Systolic blood pressure	0.0955
6. Diabetes	0.0635
7. Triglycerides	0.0625
8. Family history of MI	0.0523

Assmann, Cullen, Schulte; Circulation. 105: 310-315; 2002

Attributable Risk Factors for a First Myocardial Infarction



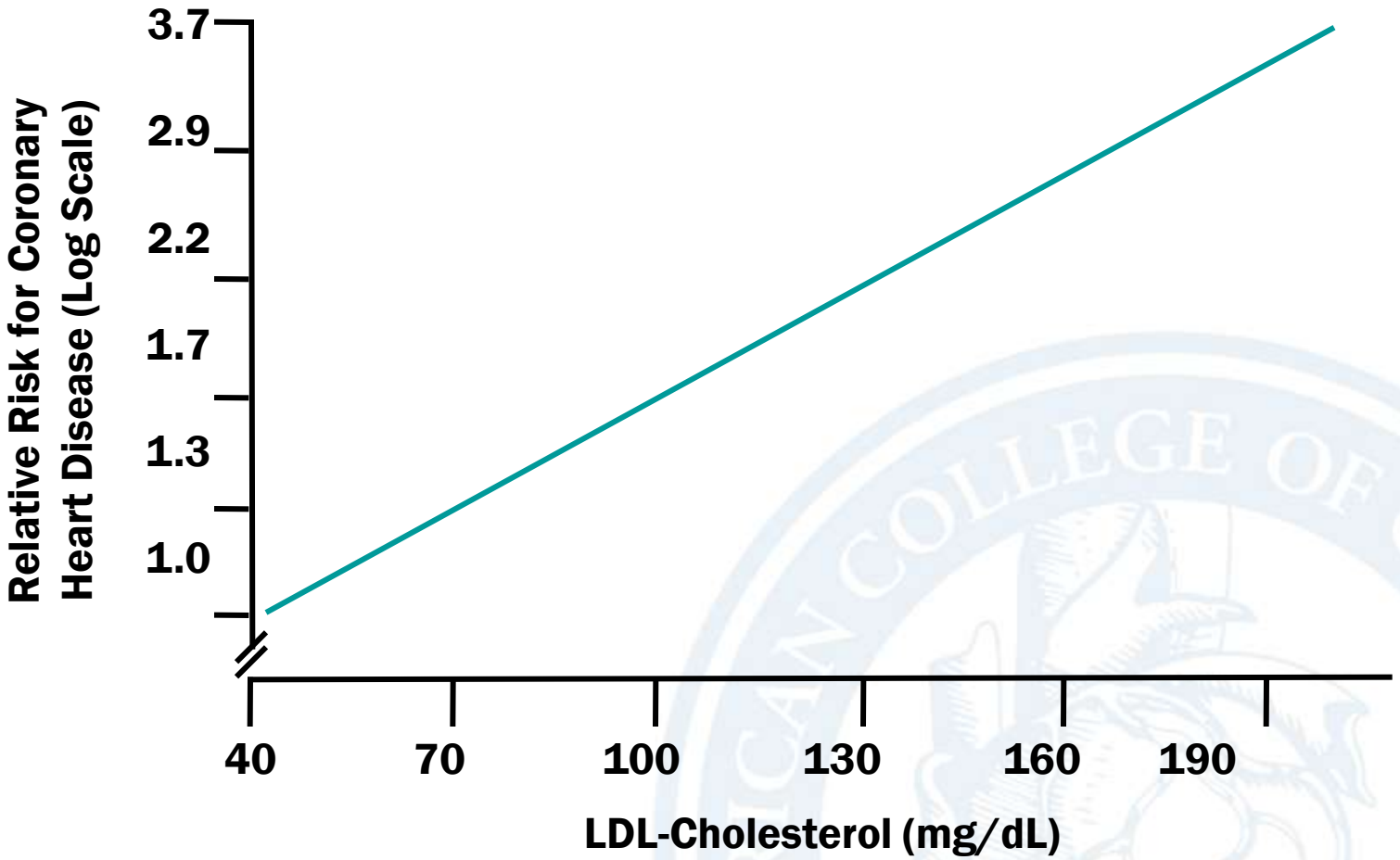
Helping Cardiovascular Professionals Learn. Advance. Heal.

n=15,152 patients and 14,820 controls in 52 countries

MI=Myocardial infarction, PAR=Population attributable risk (adjusted for all risk factors)

Yusuf S et al. Lancet. 2004;364:937-952

Coronary Heart Disease Risk According to LDL-C Level

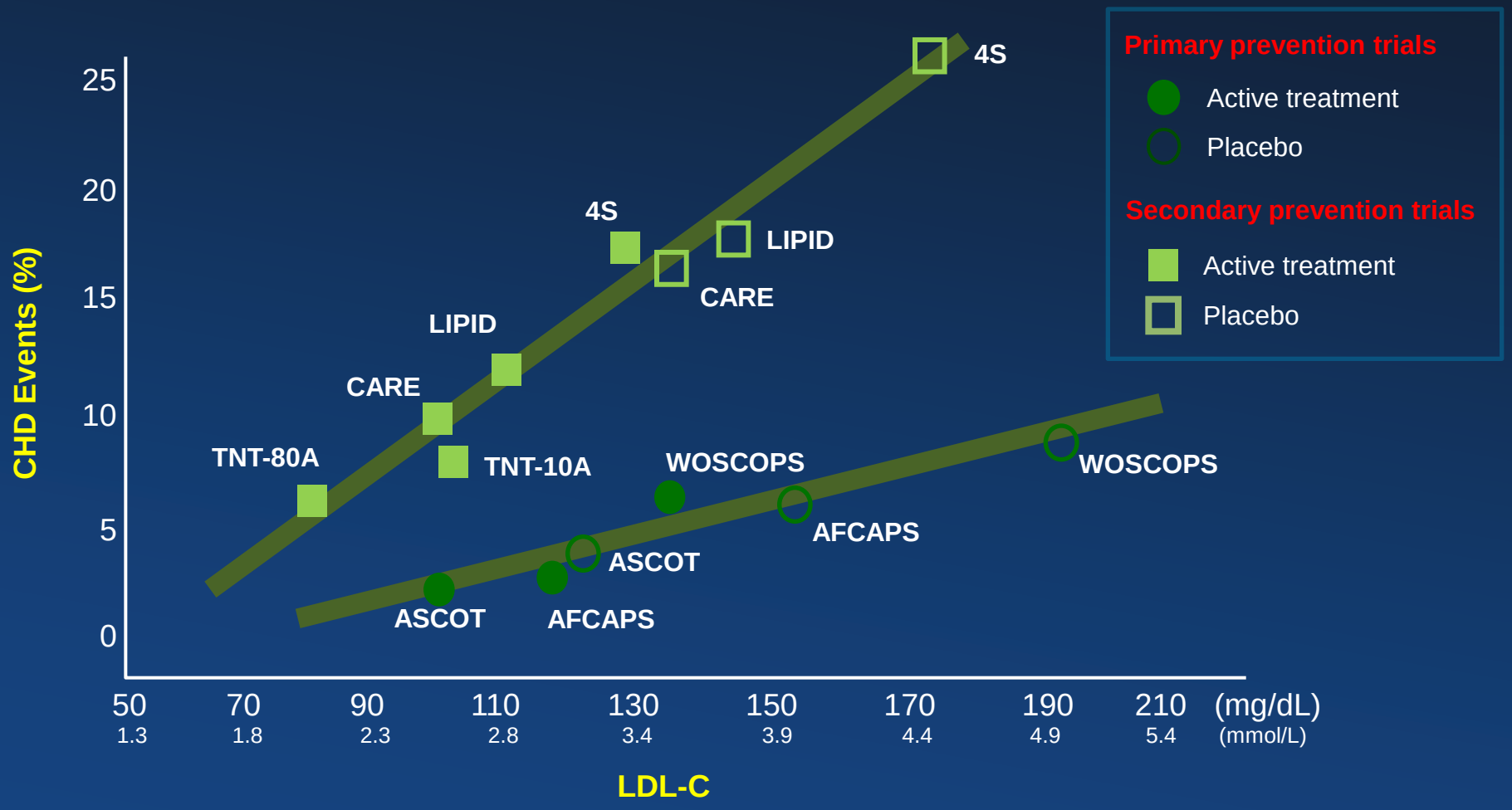


Helping Cardiovascular Professionals Learn. Advance. Heal.

CHD=Coronary heart disease, LDL-C=Low-density lipoprotein cholesterol

Grundy S et al. Circulation 2004;110:227-239

Lowering LDL-C With Statins Reduces CV Risk in Both Primary and Secondary Prevention

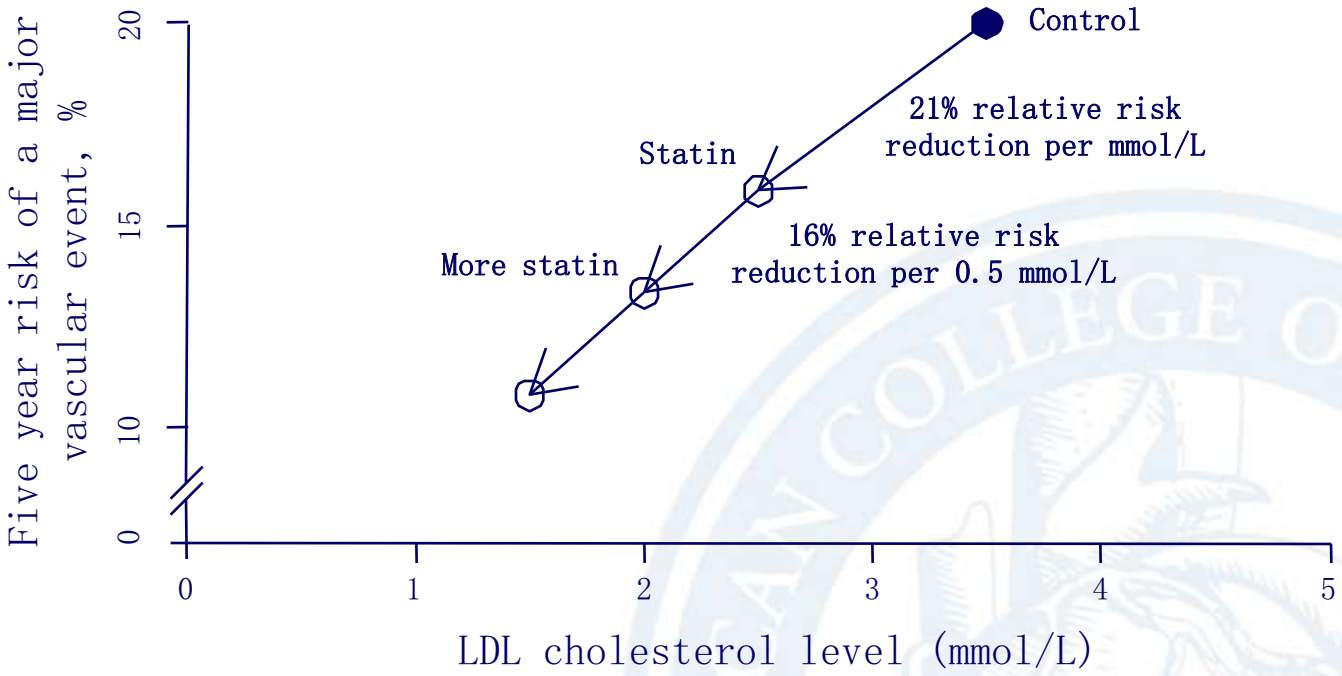


Adapted from O'Keefe et al. *J Am Coll Cardiol* 2004;43:2142-6;
LaRosa JC et al. *N Engl J Med* 2005;352:1425-35.

HMG-CoA Reductase Inhibitor Evidence: Effect of Intensive Therapy

Cholesterol Treatment Trialists' (CTT) Collaboration

Meta-analysis of 169,138 patients randomized to at least 2 years of statin therapy



There is a proportionate reduction in CV events with greater LDL-cholesterol reduction

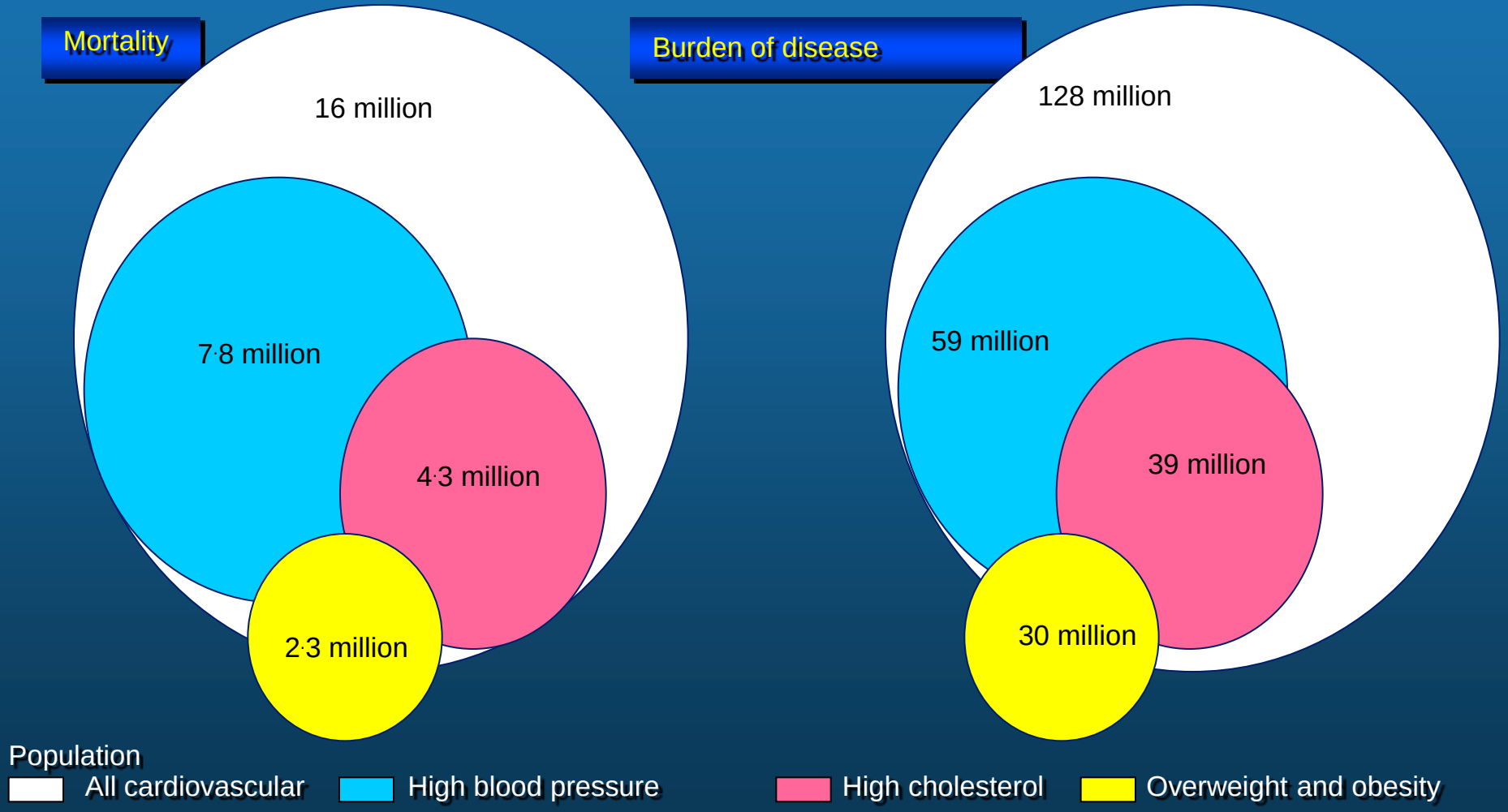
Helping Cardiovascular Professionals Learn. Advance. Heal.

CV=Cardiovascular, LDL=Low density lipoprotein

Source: Cholesterol Treatment Trialists' Collaboration. *Lancet 2010;376:1670-1681*

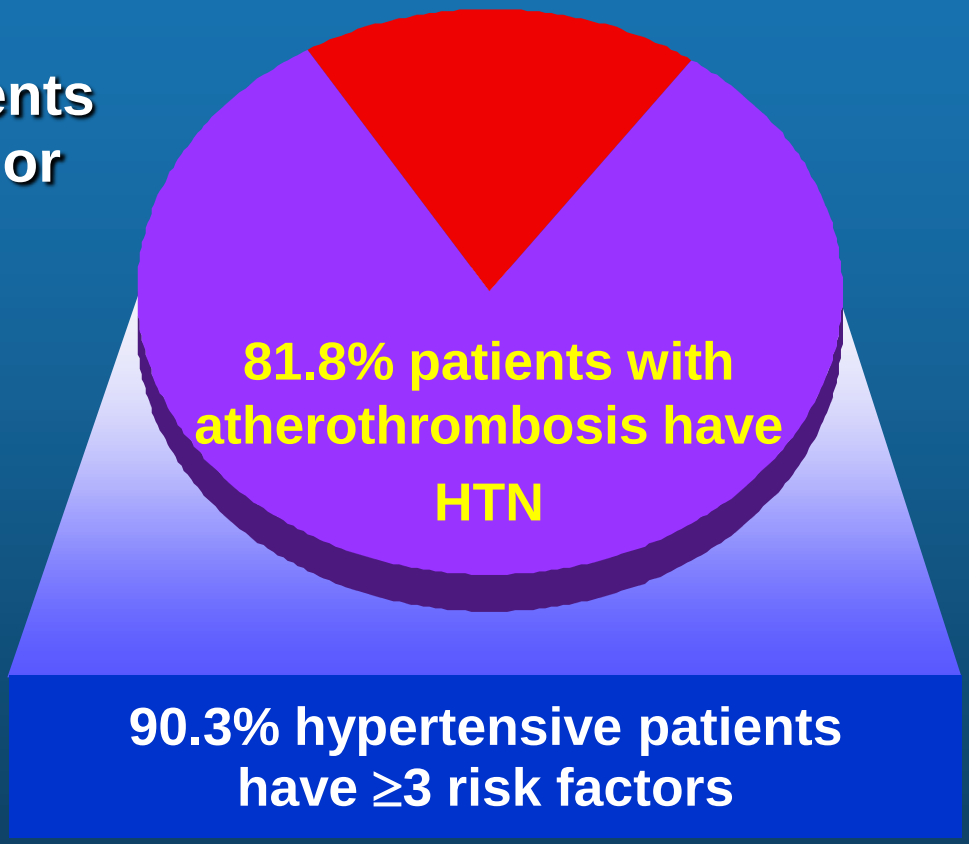
Hypertension and Dyslipidemia: The Extent of the Problem

Global mortality and burden of cardiovascular disease and major risk factors for people aged 30 years



Most Hypertensive Patients Have Additional Risk Factors: *REACH Registry*

N=67,888 patients aged 45 years or older from 44 countries

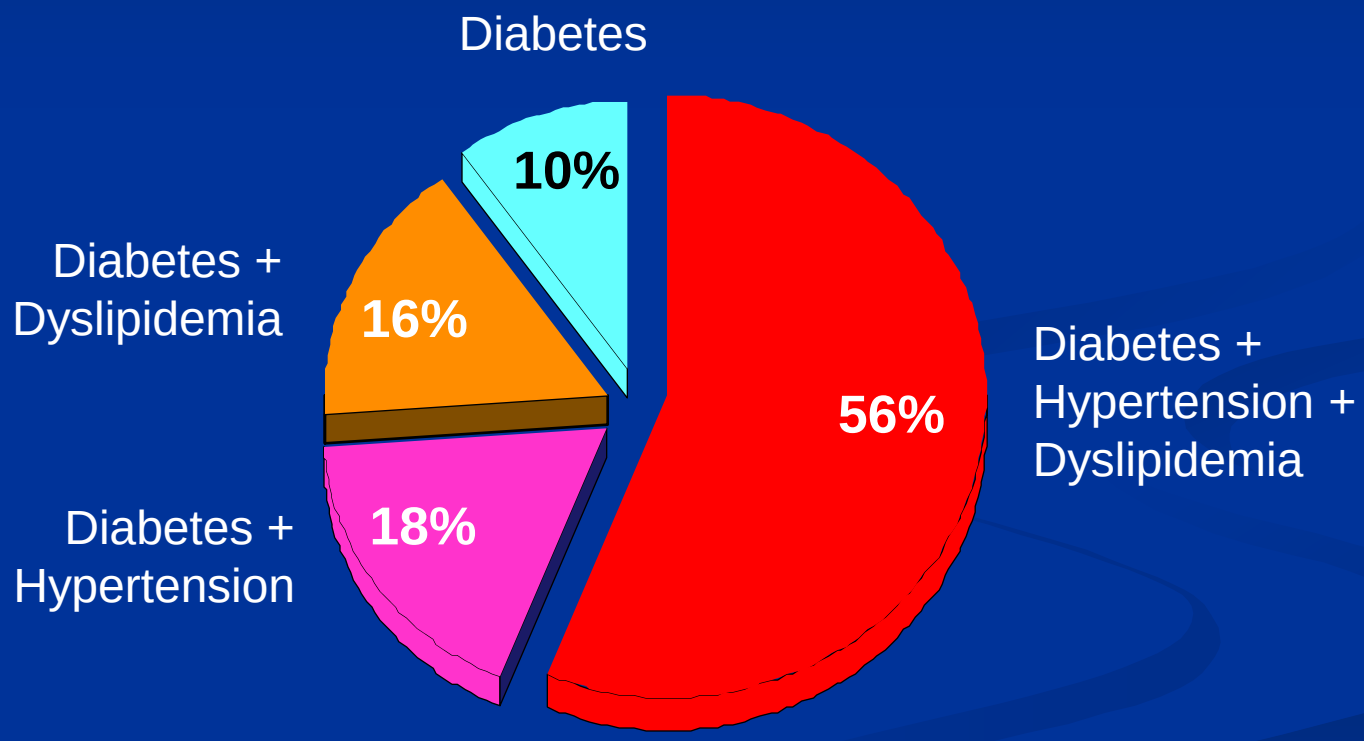


HTN=hypertension; REACH=Reduction of Atherothrombosis for Continued Health.
Risk factors include: treated diabetes mellitus, diabetic nephropathy, asymptomatic carotid stenosis ≥70%, Systolic blood pressure [SBP], ≥150 mm Hg, treated hypercholesterolaemia, current smoking, men ≥55 y, women ≥70 y.

Bhatt DL et al. *JAMA*. 2006;295:180-189.

The overlap between hypertension, diabetes, and dyslipidemia

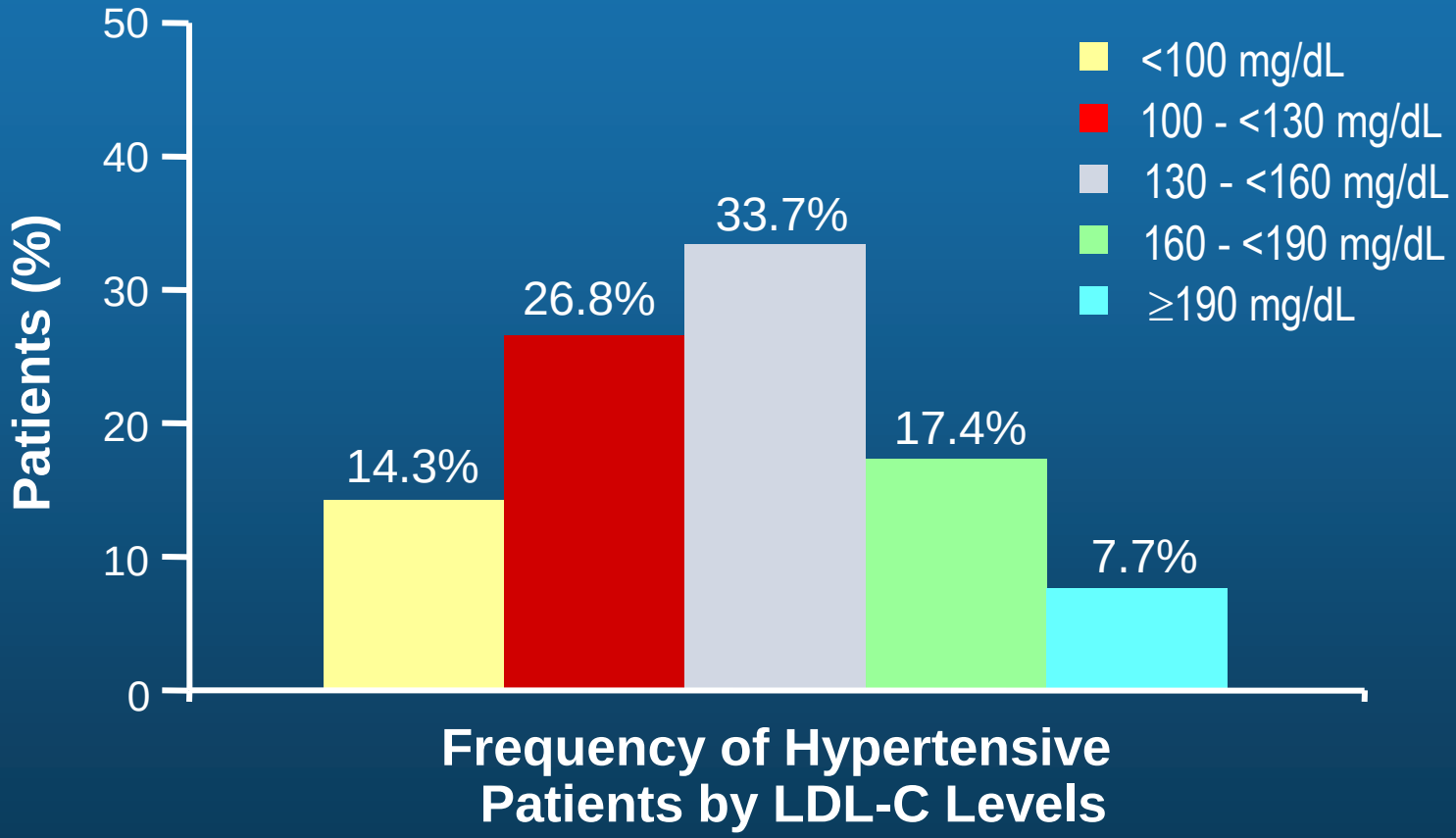
Analysis of 137,745 insurance clients
(Kaiser Permanente Medical Care Program, Northern California)



Selby JV et al. *Am J Manag Care.* 2004;10(part 2):163-70.

Majority of Hypertensive Patients Have LDL-C ≥100 mg/dL

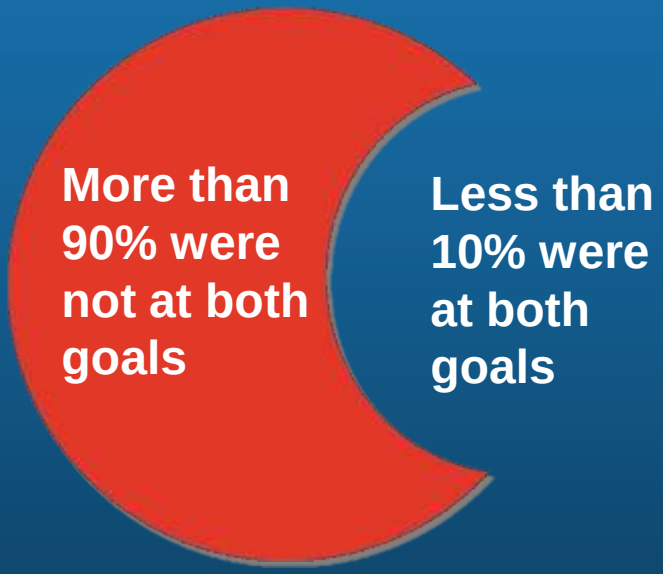
Only 14.3% of hypertensive have LDL-C <100 mg/dL



Source: NHANES III Phase 2 Morning Fasting Subset. 2000 Census Data. (Unweighted N = 7697; Weighted Sample = 200,948,641)

Most Patients Diagnosed With Hypertension and Dyslipidemia Were Not at Both Goals

In a managed care population, the vast majority of patients diagnosed with hypertension and dyslipidemia (n = 154,235) were not at both goals

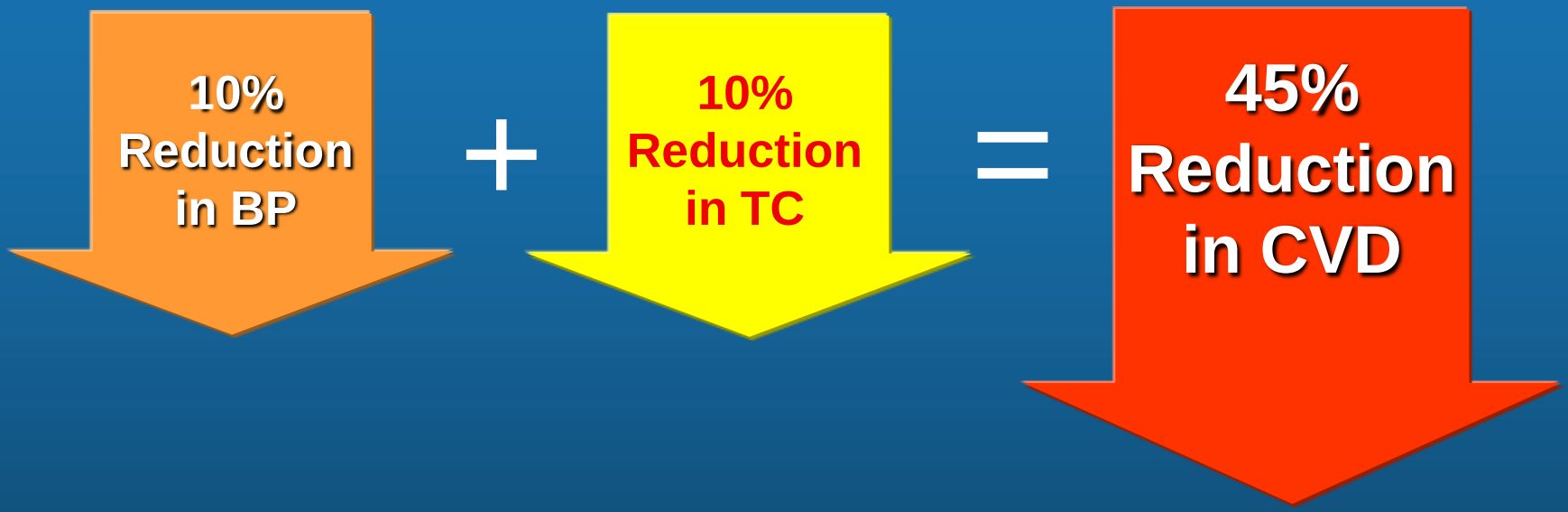


As the number of CV risk factors increased, the rate of goal attainment decreased

CV = cardiovascular.

Pettitt D et al. Poster presented at: 26th Annual Meeting of the Society of General Internal Medicine 2003; Vancouver, Canada.

Multiple CV Risk Management Results in Dramatic Reductions in CVD



"Attention should be moved from knowing one's BP and cholesterol concentrations to knowing one's absolute CV risk and its determinants."

– J. Emberson et al
- Jackson et al

Emberson J et al. *Eur Heart J.* 2004;25:484-491.

Jackson R et al. *Lancet.* 2005;365:434-441.

European Heart Journal
doi:10.1093/eurheartj/eht151

ESH AND ESC GUIDELINES

2013 ESH/ESC Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)

Journal of Hypertension. 2013;31:1281–1357.

Stratification of total CV risk in categories

Other risk factors, asymptomatic organ damage or disease	Blood pressure (mmHg)			
	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 RF		Low risk	Moderate risk	High risk
1–2 RF	Low risk	Moderate risk	Moderate to high risk	High risk
≥3 RF	Low to moderate risk	Moderate to high risk	High risk	High risk
OD, CKD stage 3 or diabetes	Moderate to high risk	High risk	High risk	High to very high risk
Symptomatic CVD, CKD stage ≥ 4 or diabetes with OD/RFs	Very high risk	Very high risk	Very high risk	Very high risk

Journal of Hypertension. 2013;31:1281–1357.

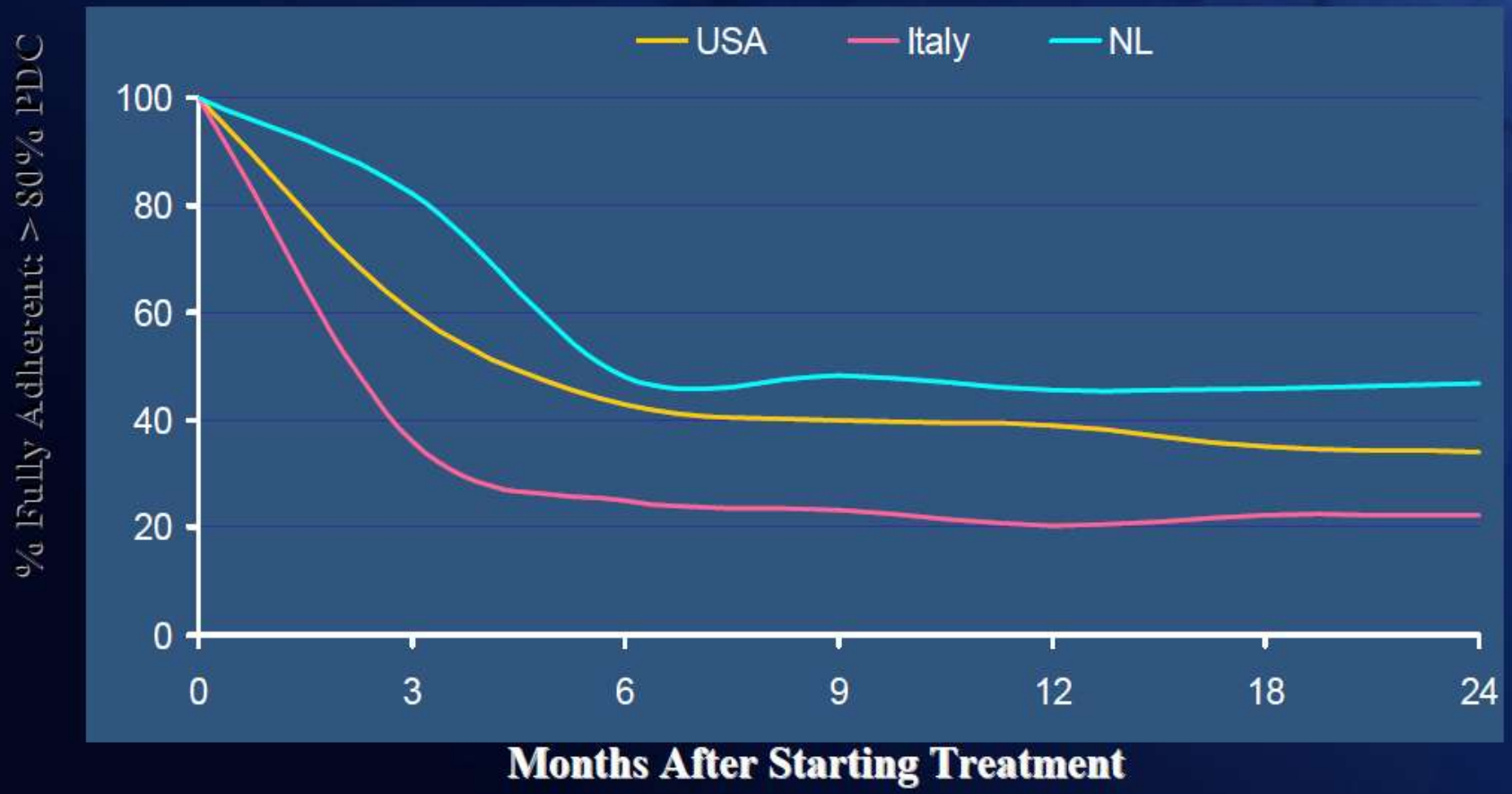
Treatment of risk factors associated with hypertension

Recommendations	Class[a]	Level[b]
It is recommended to use statin therapy in hypertensive patients at moderate to high CV risk, targeting a low-density lipoprotein cholesterol value <3.0 mmol/L (115 mg/dL).	I	A
When overt CHD is present, it is recommended to administer statin therapy to achieve low-density lipoprotein cholesterol levels <1.8 mmol/L (70 mg/dL).	I	A
Antiplatelet therapy, in particular low-dose aspirin, is recommended in hypertensive patients with previous CV events.	I	A

Journal of Hypertension. 2013;31:1281–1357.

Adherence

Adherence to Lipid Lowering Drugs



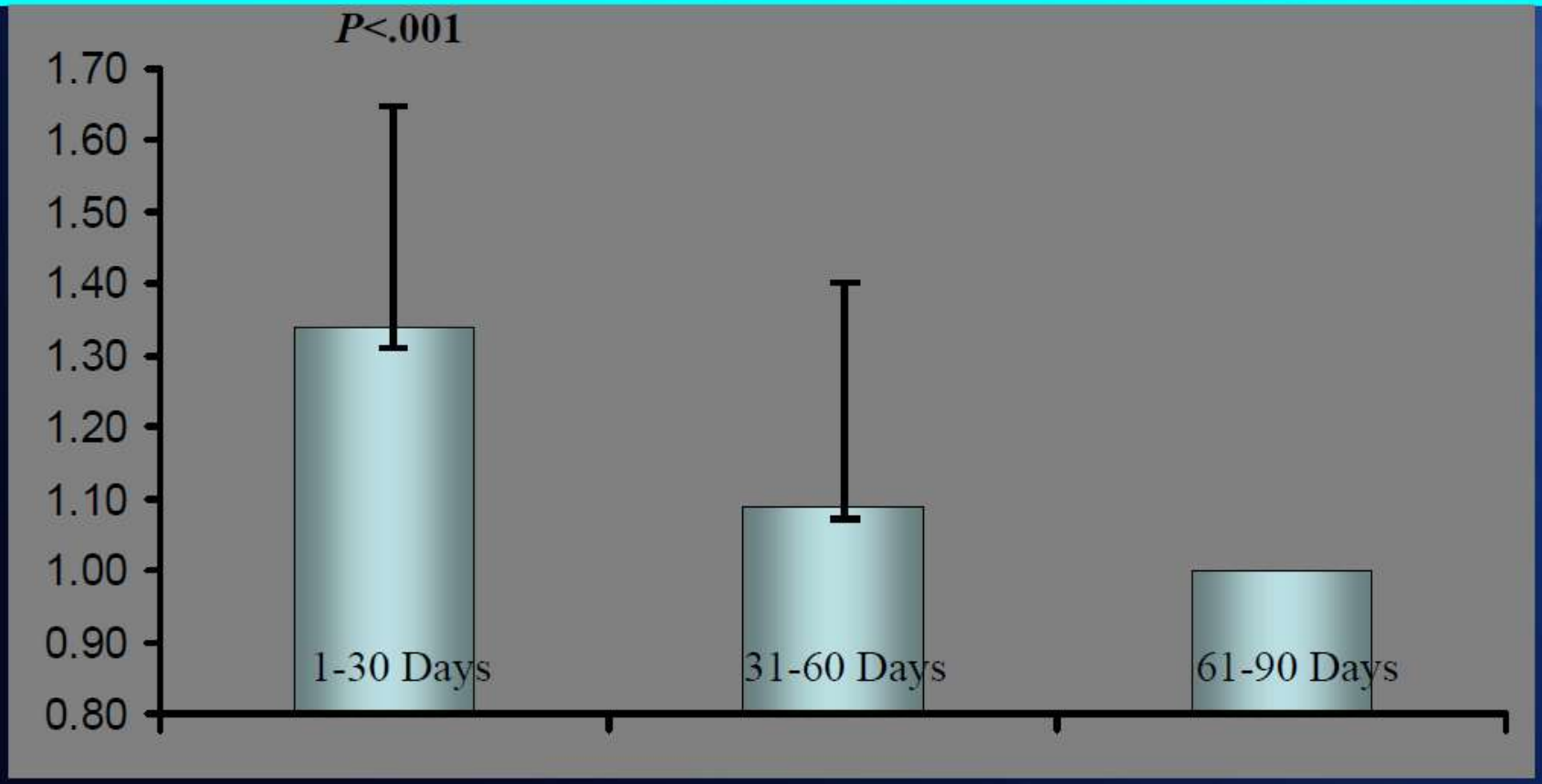
US data: Benner JS et al. *JAMA*. 2002;288:255-261. Other data from general practice databases in NL and

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.

Concurrently Starting 2 Medications Improved Adherence

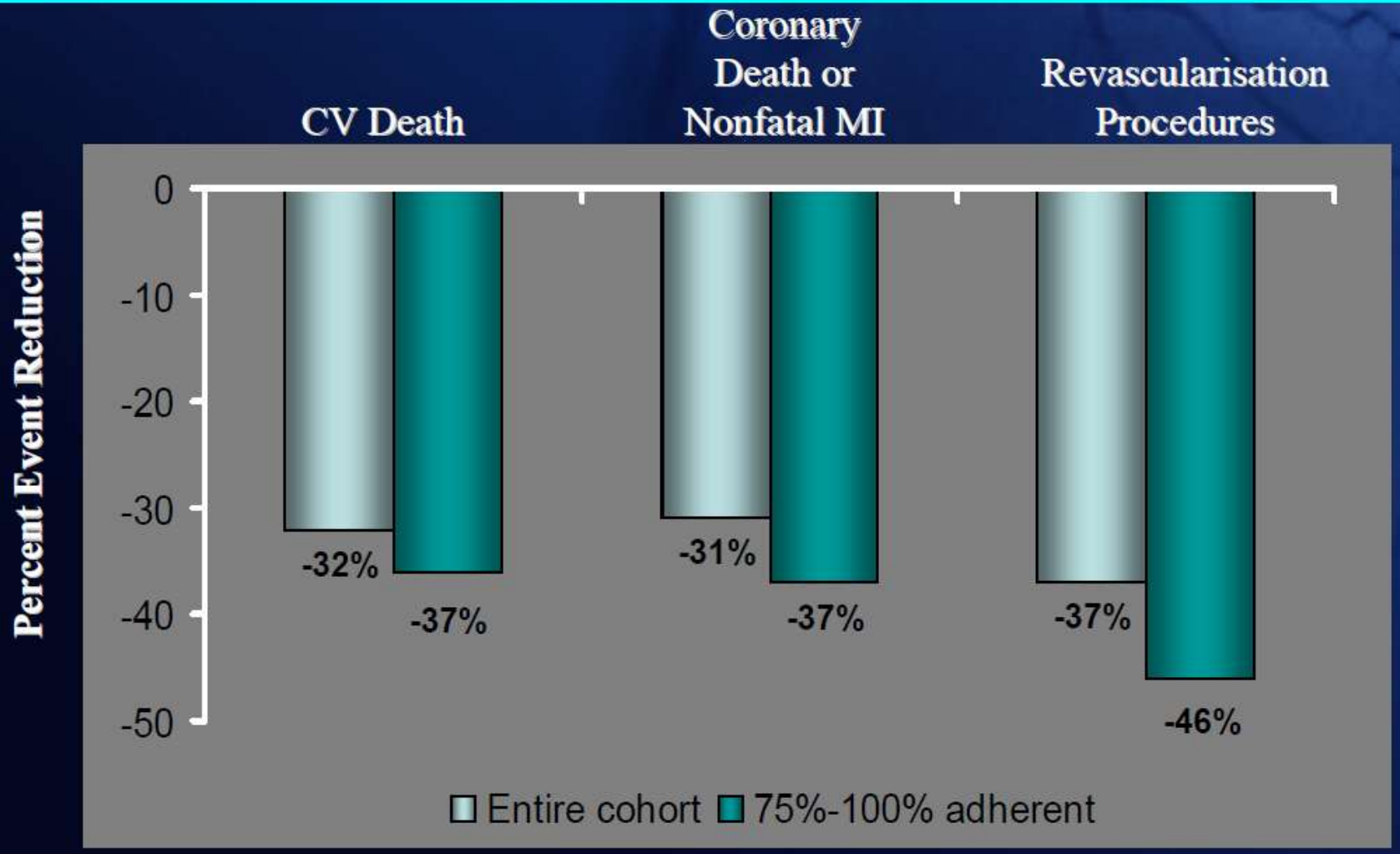


Retrospective cohort study in a large managed-care population (N=8406).

*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.

Improved Outcomes Achieved in Clinical Trials with Higher Adherence

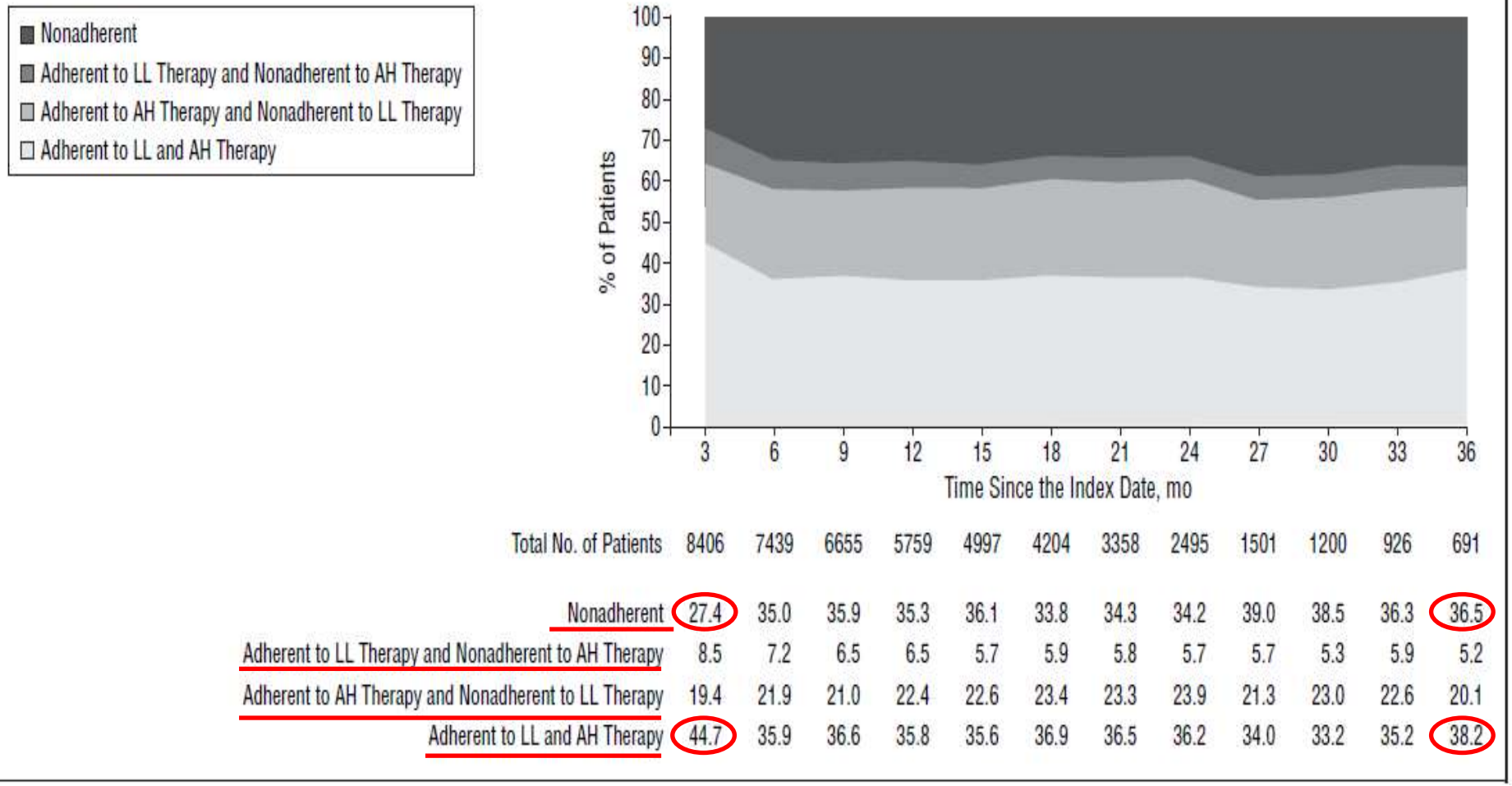


The West of Scotland Coronary Prevention Study Group. *Eur Heart J.* 1997;18:1718-1724.

Predictors of Adherence With Antihypertensive and Lipid-Lowering Therapy

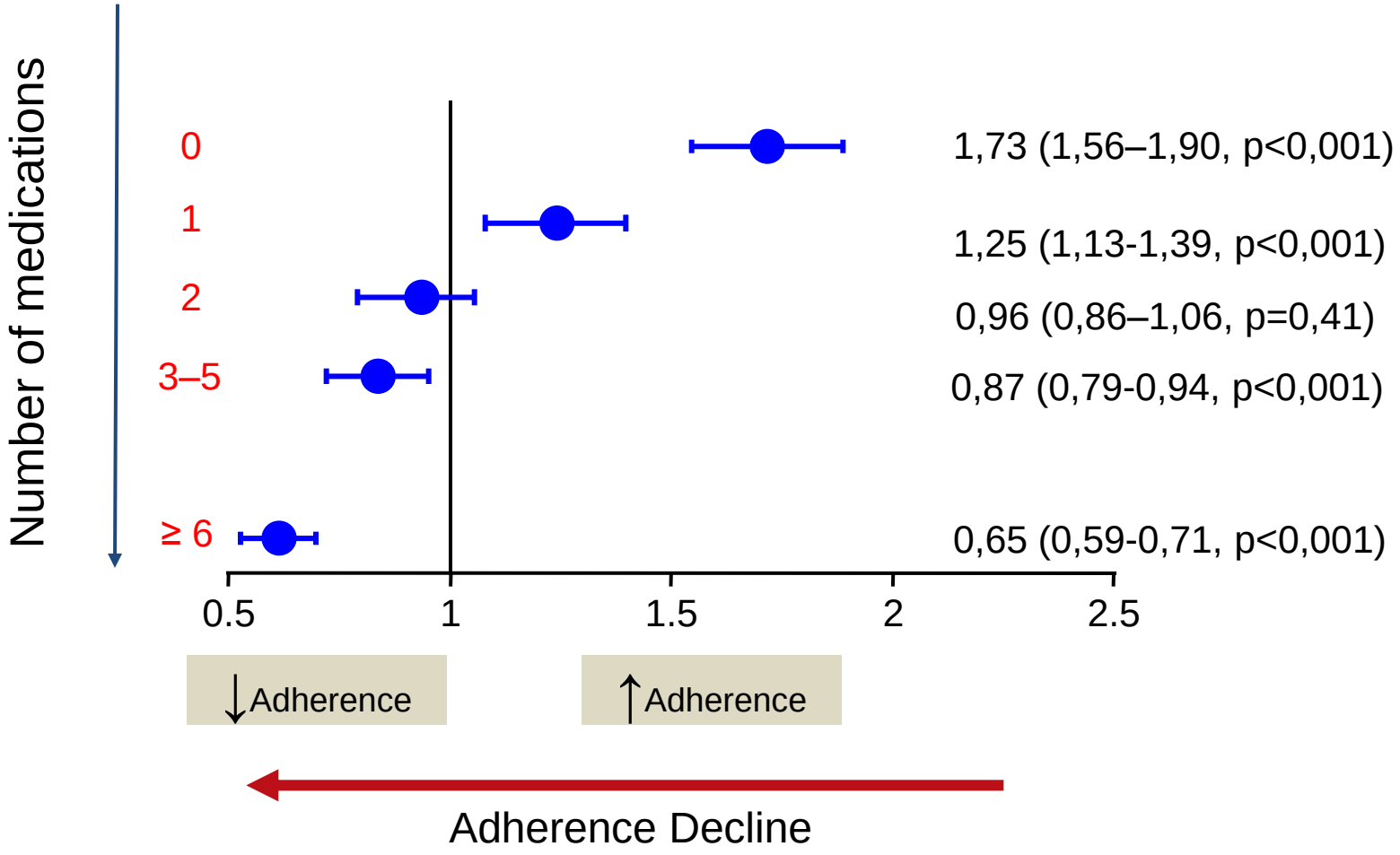
Arch Intern Med. 2005;165:1147-1152

Richard H. Chapman, PhD; Joshua S. Benner, PharmD, ScD; Allison A. Petrilla, BA; Jonothan C. Tierce, CPhil; S. Robert Collins, BS; David S. Battleman, MD; J. Sanford Schwartz, MD



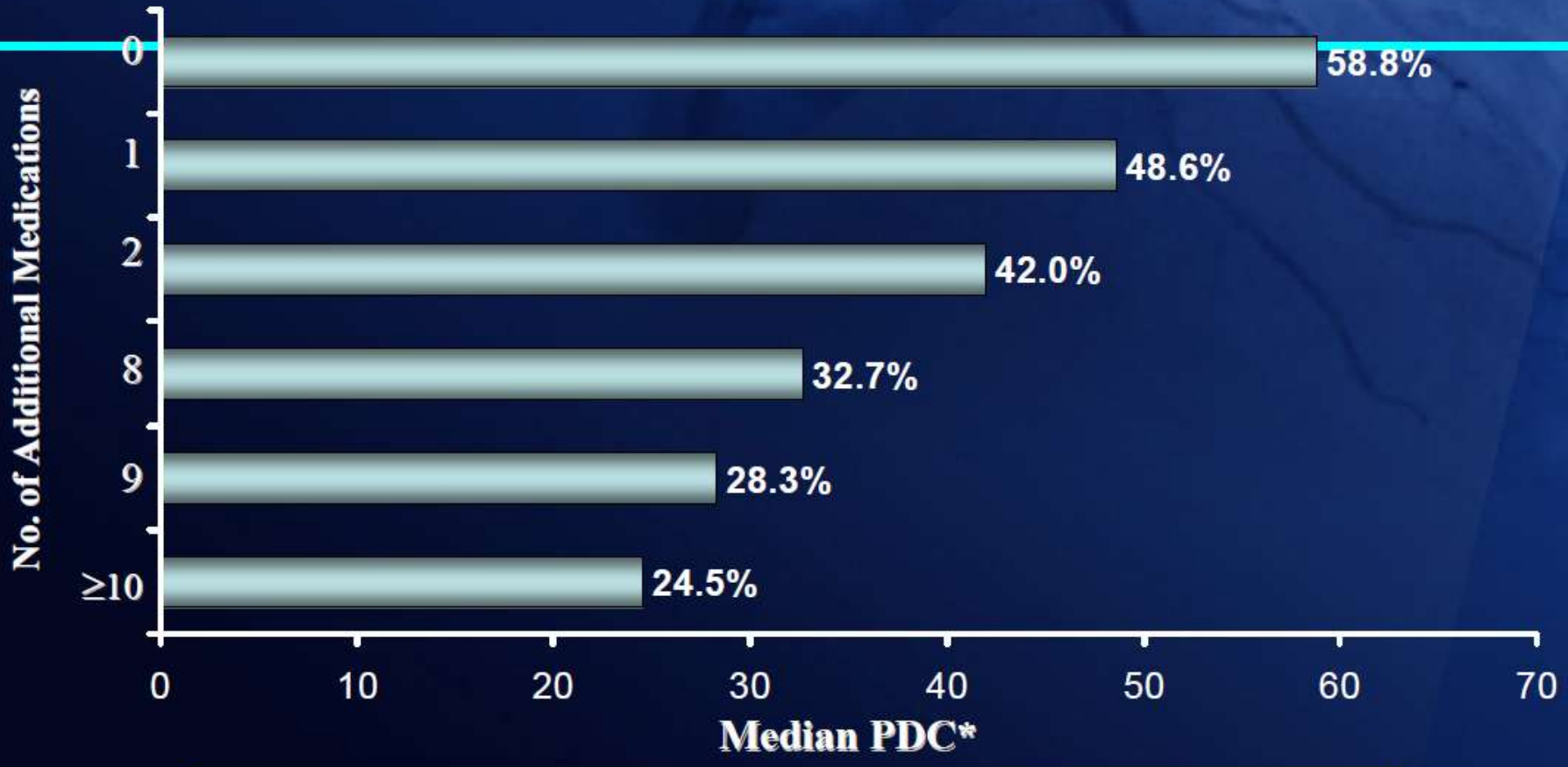
Total No. of Patients	8406	7439	6655	5759	4997	4204	3358	2495	1501	1200	926	691
Nonadherent	27.4	35.0	35.9	35.3	36.1	33.8	34.3	34.2	39.0	38.5	36.3	36.5
Adherent to LL Therapy and Nonadherent to AH Therapy	8.5	7.2	6.5	6.5	5.7	5.9	5.8	5.7	5.7	5.3	5.9	5.2
Adherent to AH Therapy and Nonadherent to LL Therapy	19.4	21.9	21.0	22.4	22.6	23.4	23.3	23.9	21.3	23.0	22.6	20.1
Adherent to LL and AH Therapy	44.7	35.9	36.6	35.8	35.6	36.9	36.5	36.2	34.0	33.2	35.2	38.2

Patient adherence and medication number



Chapman et al. Arch Intern Med 2005;165:1147–52

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



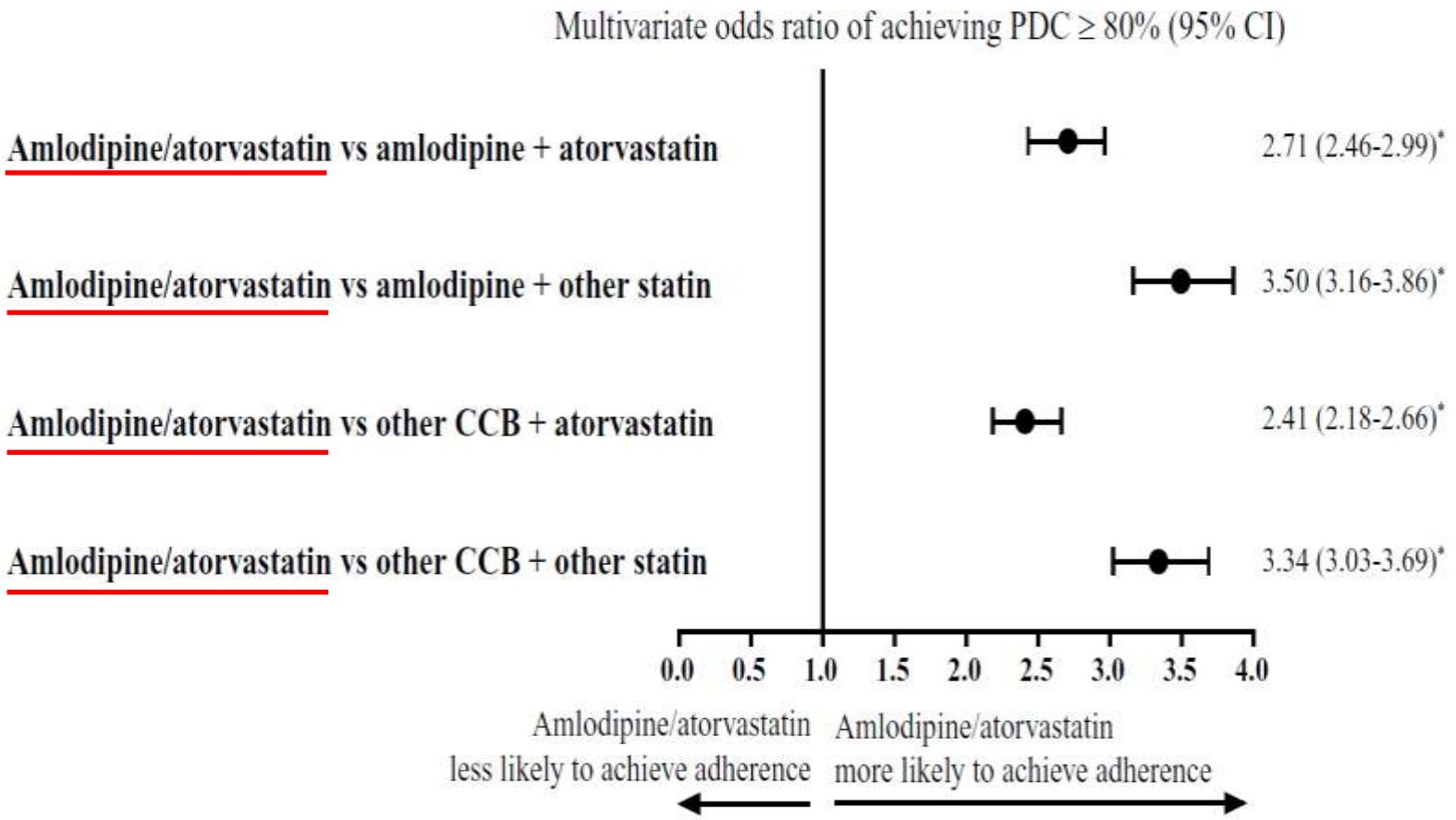
Incremental pill burden had greatest effect on adherence in patients taking the fewest medications

*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.

Adherence with single-pill amlodipine/atorvastatin vs a two-pill regimen

Adherence with single- vs two-pill regimen



Vasc Health Risk Manag. 2008; 4(3): 673–681.

Chapman *et al. BMC Cardiovascular Disorders* 2010, **10**:29
http://www.biomedcentral.com/1471-2261/10/29

BMC Cardiovascular Disorders

RESEARCH ARTICLE Open Access

Association between adherence to calcium-channel blocker and statin medications and likelihood of cardiovascular events among US managed care enrollees

Richard H Chapman*[1], Jason Yeaw[1] and Craig S Roberts[2]

17,910 CCB/statin patients
Retrospective study

SPAA patients (1-pill) were more likely to be adherent (OR = 4.7, $p < 0.001$) than CCB/statin patients.

Being adherent to either regimen was associated with significantly lower risk of CV event (HR = 0.77, p = 0.003).

Being adherent to SPAA was associated with significantly lower risk of CV event vs. CCB/statin patients (HR = 0.68, p = 0.02).

Conclusions: Patients receiving SPAA rather than a 2-pill CCB/statin regimen are more likely to be adherent. Adherence to CCB and statin medications is associated with lower risk of CV events in primary prevention patients.

Chapman et al. BMC Cardiovascular Disorders 2010, 10:29
http://www.biomedcentral.com/1471-2261/10/29

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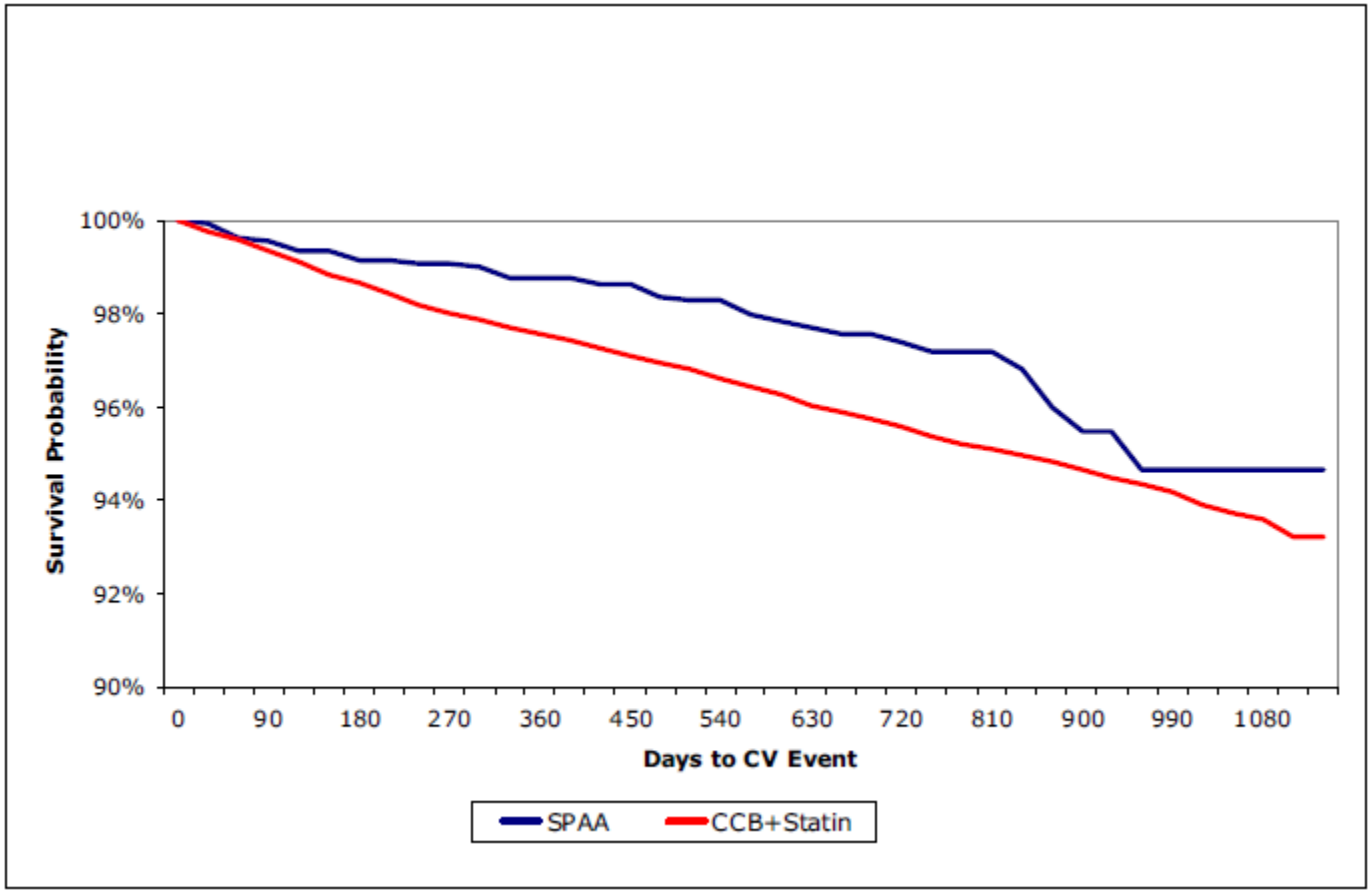


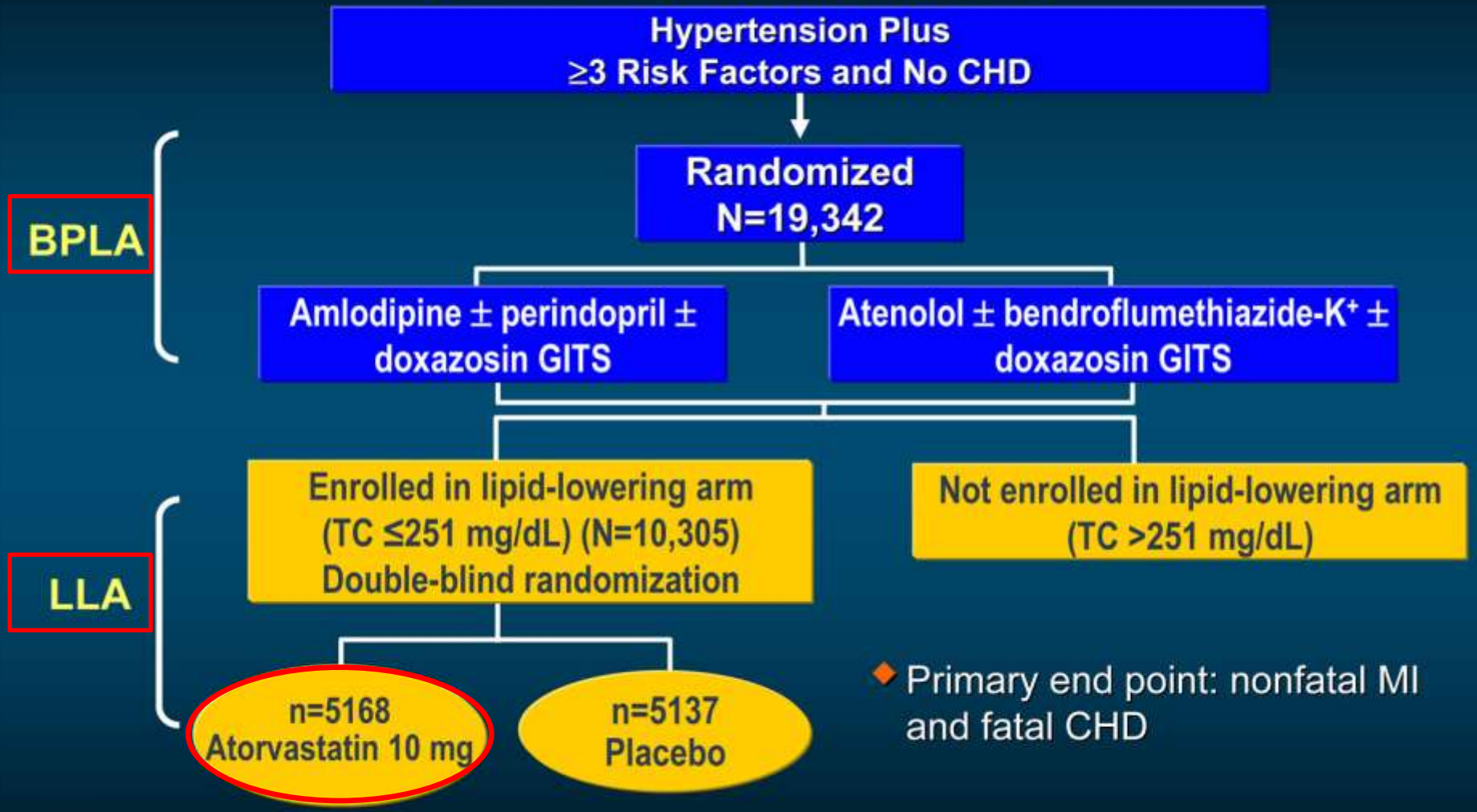
Assist Your Patient to Adhere

- 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 Canadian Hypertension Education Program Recommendations

Clinical Studies

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT): Study Design

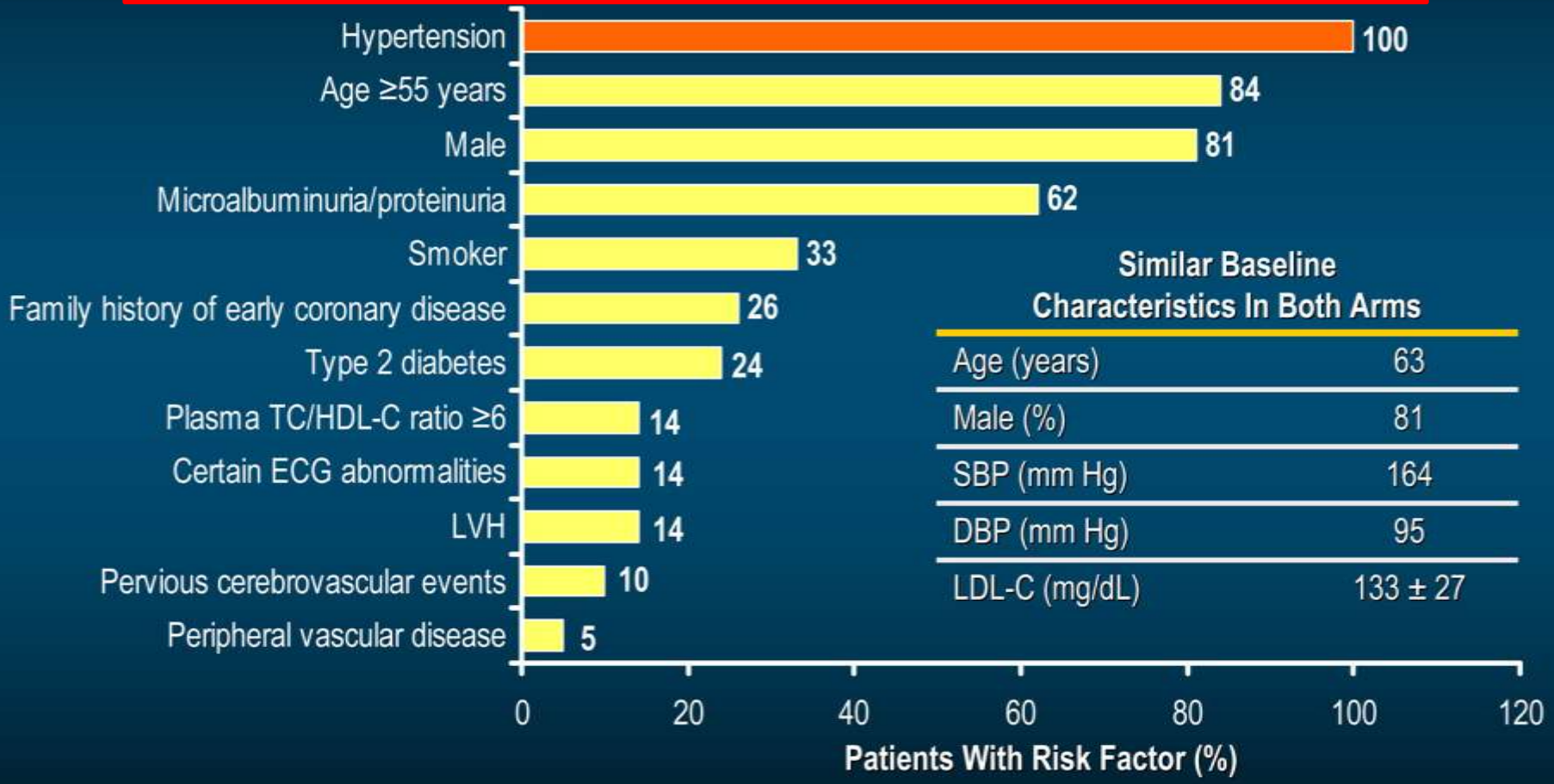


GITS=gastrointestinal transport system.

Adapted from Sever PS et al, for the ASCOT Investigators. *J Hypertens*. 2001;19:1139-1147 and Sever PS et al, for the ASCOT Investigators. *Lancet*. 2003;361:1149-1158.

ASCOT-LLA: Patient Population Risk Factor Profile

All Patients Had Hypertension Plus ≥3 Risk Factors and No CHD



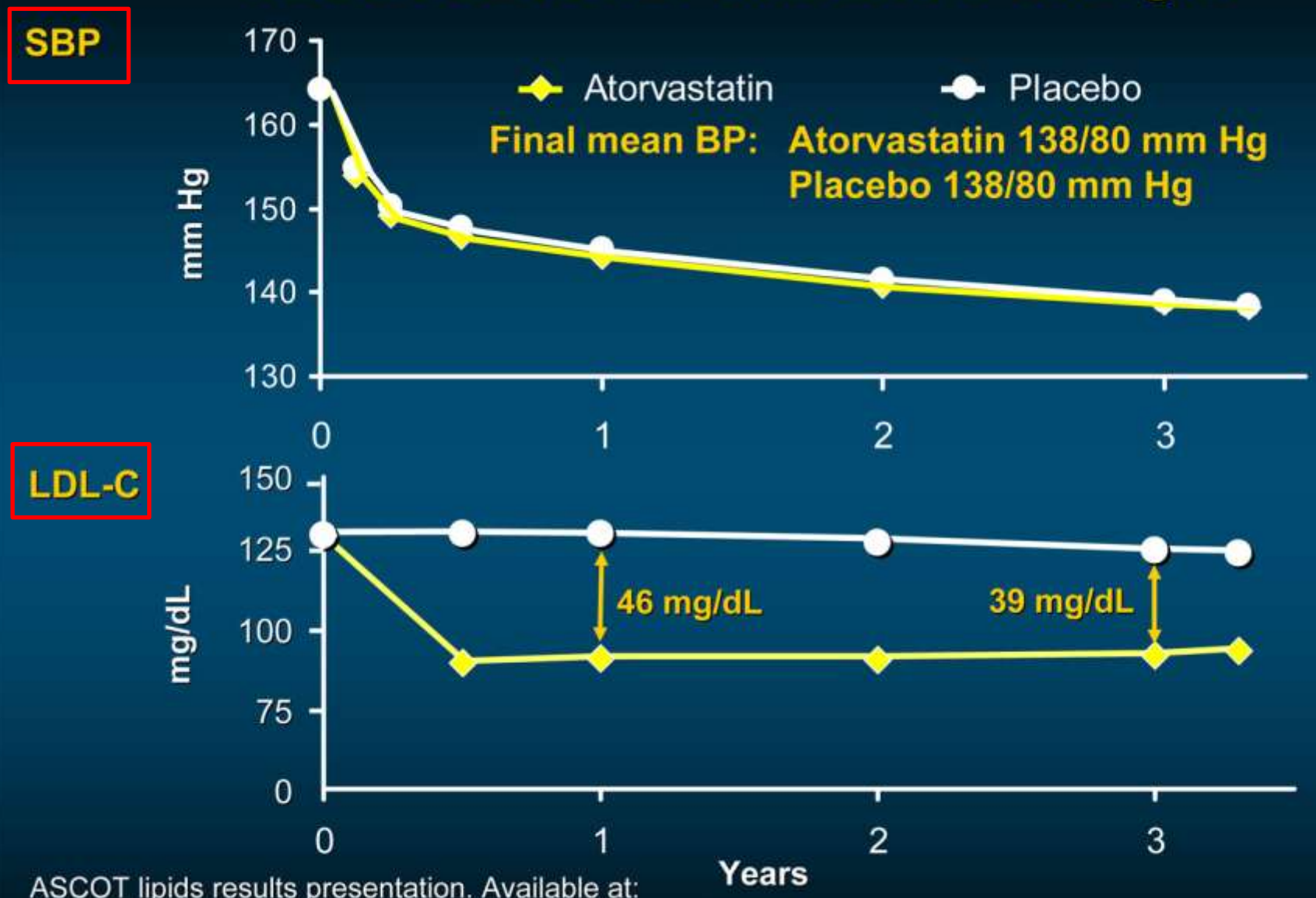
Similar Baseline Characteristics In Both Arms

Age (years)	63
Male (%)	81
SBP (mm Hg)	164
DBP (mm Hg)	95
LDL-C (mg/dL)	133 ± 27

TC/HDL=plasma total cholesterol/high-density lipoprotein ratio; LVH=left ventricular hypertrophy.

Adapted from Sever PS et al for the ASCOT Investigators. *Lancet.* 2003;361:1149-1158. ASCOT Lipids Results Presentation.

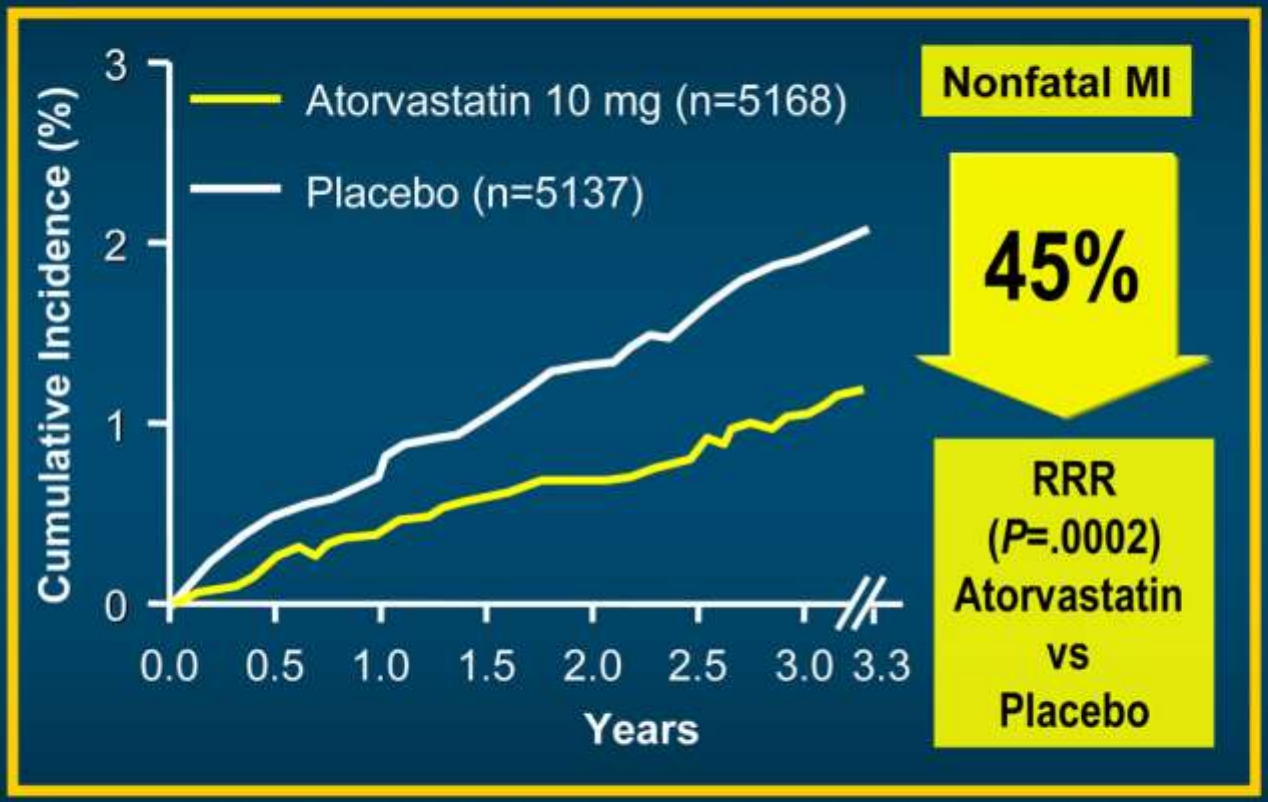
ASCOT-LLA: SBP and LDL-C Changes



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



*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.

ASCOT Provides an Alternative Approach to Treating Hypertensive Patients With Additional Risk Factors and Without CHD

- ASCOT-LLA demonstrated that in **treated** hypertensive patients with additional risk factors, adding atorvastatin delivered risk reduction of nonfatal MI (*P*=.0002) and stroke* (*P*=.033)
- ASCOT-BPLA demonstrated that the BP values were lower throughout the trial in those allocated the amlodipine-based regimen (*P*<.0001)

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

Dahlöf B et al, for the ASCOT Investigators. *Lancet*. 2005;366:895-906. Sever PS et al, for the ASCOT Investigators. *Lancet*. 2003;361:1149-1158. Data on file. Pfizer Inc, New York, NY.

CARDS Design: A Study in a Diabetic Patient Population

Patient population

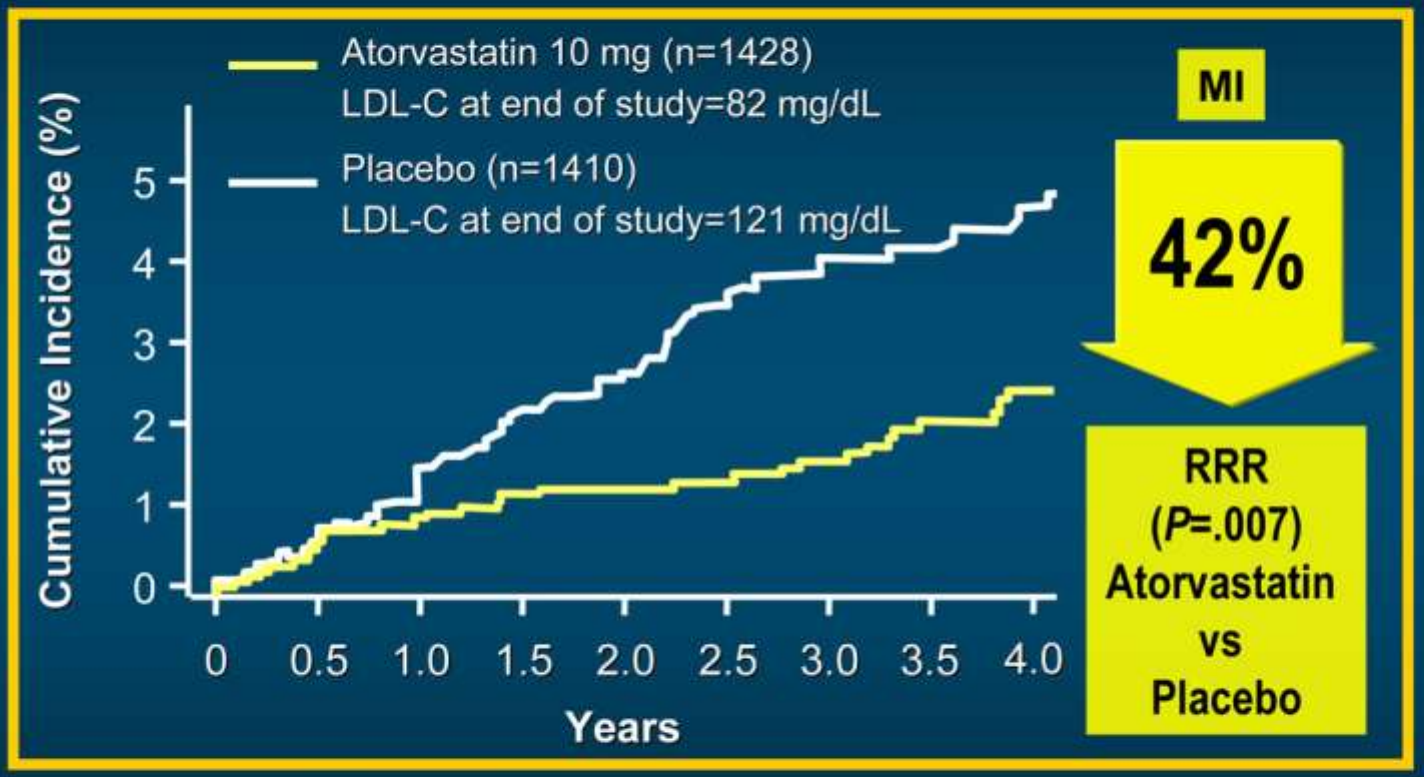
- Men and women
- Aged 40 to 75 years
- Type 2 diabetes
- At least 1 other CHD risk factor
  - 84% of patients had hypertension (67% on antihypertensive therapy)
- No prior CVD
- LDL-C ≤160 mg/dL and TG ≤600 mg/dL

Primary end point

- Time to major CV event: acute CHD event (MI including silent infarction, unstable angina, acute CHD death, resuscitated cardiac arrest), coronary revascularization procedures, or stroke.

Colhoun HM et al. *Diabet Med*. 2002;19:201-211; Colhoun HM et al. *Lancet*. 2004;364:685-696.

CARDS Trial Stopped Early Because Atorvastatin was Associated With Significant CV Event Reduction in Patients With Type 2 Diabetes



MI

42%

RRR (*P*=.007) Atorvastatin vs Placebo

Stroke

48%

RRR (*P*=.016) Atorvastatin vs Placebo

***Median duration of follow-up=3.9 years.**

Trial was stopped nearly 2 years early because of significant reductions in CV events.

Primary end point=composite of acute CHD events (MI including silent MI, unstable angina, acute CHD death, resuscitated cardiac arrest), coronary revascularization, or stroke.

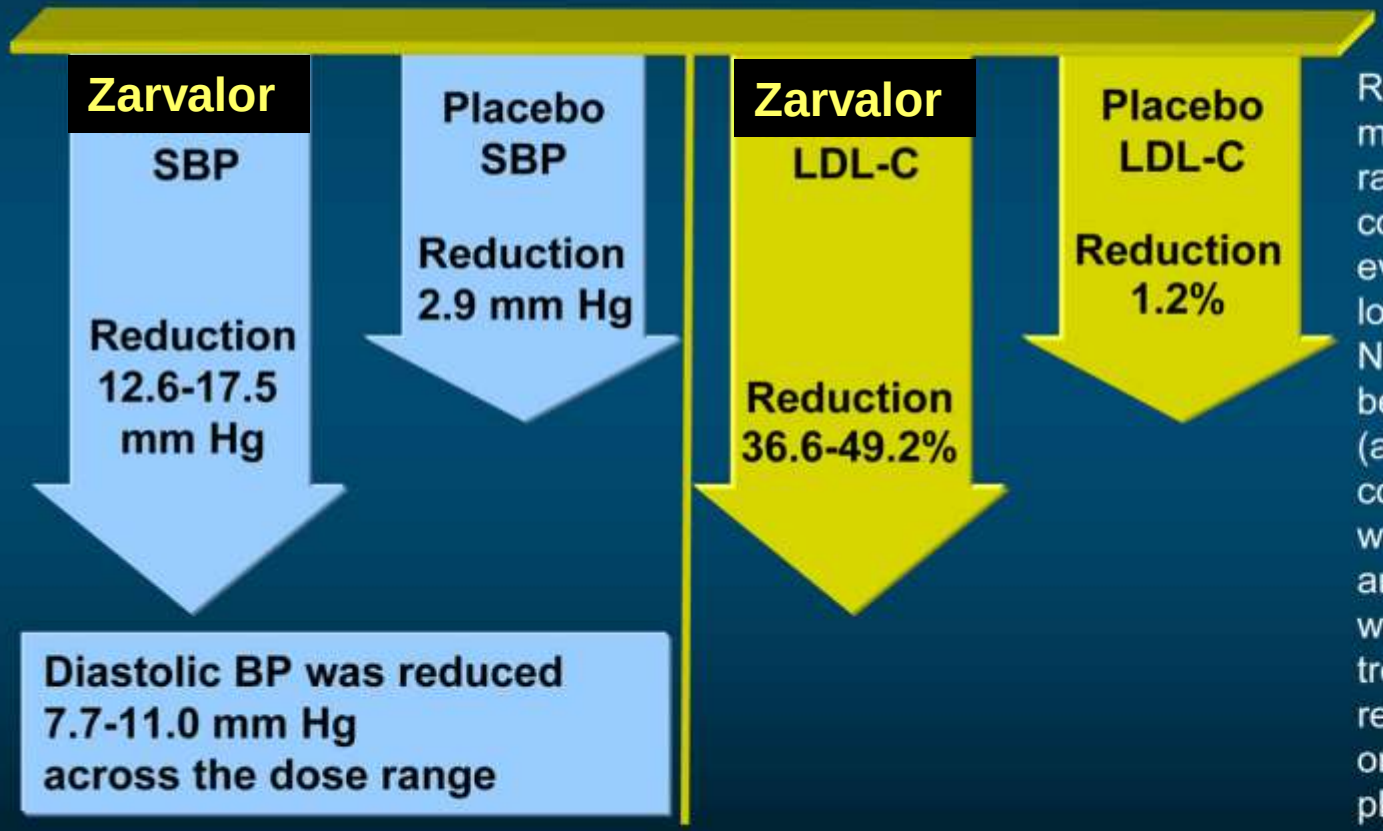
Colhoun HM et al. *Diabet Med*. 2002;19:201-211; Colhoun HM et al. *Lancet*. 2004;364:685-696; Data on file.

CARDS Demonstrated The Benefit Of Atorvastatin In Patients With Diabetes, Near-Normal LDL-C Levels, and Additional Risk Factors

- CARDS demonstrated that in patients with type 2 diabetes and at least 1 additional risk factor and without CHD, atorvastatin delivered significant risk reduction of MI (*P*=.007) and stroke (*P*=.016)

Zarvalor (amlodipine besylate/ atorvastatin calcium): Reductions in SBP and LDL-C Across the Dose Range*: Respond Study

(5 mg/10 mg to 10 mg/80 mg)



Diastolic BP was reduced 7.7-11.0 mm Hg across the dose range

*When used with diet and exercise.

Respond (N=1660) was a multicenter, double-blind, randomized, placebo-controlled study designed to evaluate the BP- and lipid-lowering efficacy and safety of Norvasc® (amlodipine besylate) and Lipitor® (atorvastatin calcium) coadministered in patients with comorbid hypertension and dyslipidemia. Patients were randomized to receive treatment for 8 weeks and received both Norvasc 5 mg or 10 mg qd or matching placebo, and Lipitor 10, 20, 40 or 80 mg qd or matching placebo

Zarvalor (amlodipine besylate/ atorvastatin calcium) Treatment-Emergent AEs*: Respond Study

Body System	Placebo (%) (n=111)	Norvasc (amlodipine besylate) Only (%) (n=221)	Zarator (atorvastatin calcium) Only (%) (n=443)	Zarvalor (amlodipine besylate + atorvastatin calcium) (%) (n=885)
Cardiovascular	8 (7.2)	16 (7.2)	26 (5.9)	67 (7.6)
Gastrointestinal	10 (9.0)	16 (7.2)	39 (8.8)	77 (8.7)
Peripheral edema	3 (2.7)	27 (12.2)	5 (1.1)	88 (9.9)
Musculoskeletal	7 (6.3)	12 (5.4)	25 (5.6)	35 (4.0)
Myalgia	2 (1.8)	3 (1.4)	8 (1.8)	14 (1.6)
Nervous system	9 (8.1)	12 (5.4)	25 (5.6)	47 (5.3)
Respiratory	9 (8.1)	12 (5.4)	28 (6.3)	69 (7.8)
Skin and appendages	4 (3.6)	4 (1.8)	6 (1.4)	32 (3.6)

*Incidences of treatment-emergent AEs that occurred in ≥1% of combination-treated subjects.

Original Paper

Single-Pill Therapy in the Treatment of Concomitant Hypertension and Dyslipidemia (The Amlodipine/Atorvastatin Gemini Study)

Roy Blank, MD;[1] James LaSalle, DO;[2] Russell Reeves, MD;[3] Jaman Maroni, MD;[4]
Lisa Tarasenko, PharmD, MBA;[4] Franklin Sun, MS, MPhil[4]

J Clin Hypertens. 2005;7:264–273

GEMINI: Study Design

14-week, open-label period

Patient population

- 1220 patients with concomitant hypertension and dyslipidemia (treated or untreated)
- BP not at goal
- LDL-C either at goal with medication or not at goal, with or without medication

Zarvalor

(amlodipine besylate/ atorvastatin calcium)

- Added to an antihypertensive regimen
- Substituted for existing treatment with either parent compound
- Used as initial drug therapy with diet and exercise

Primary efficacy assessment: attainment of both systolic BP and LDL-C goals at week 14

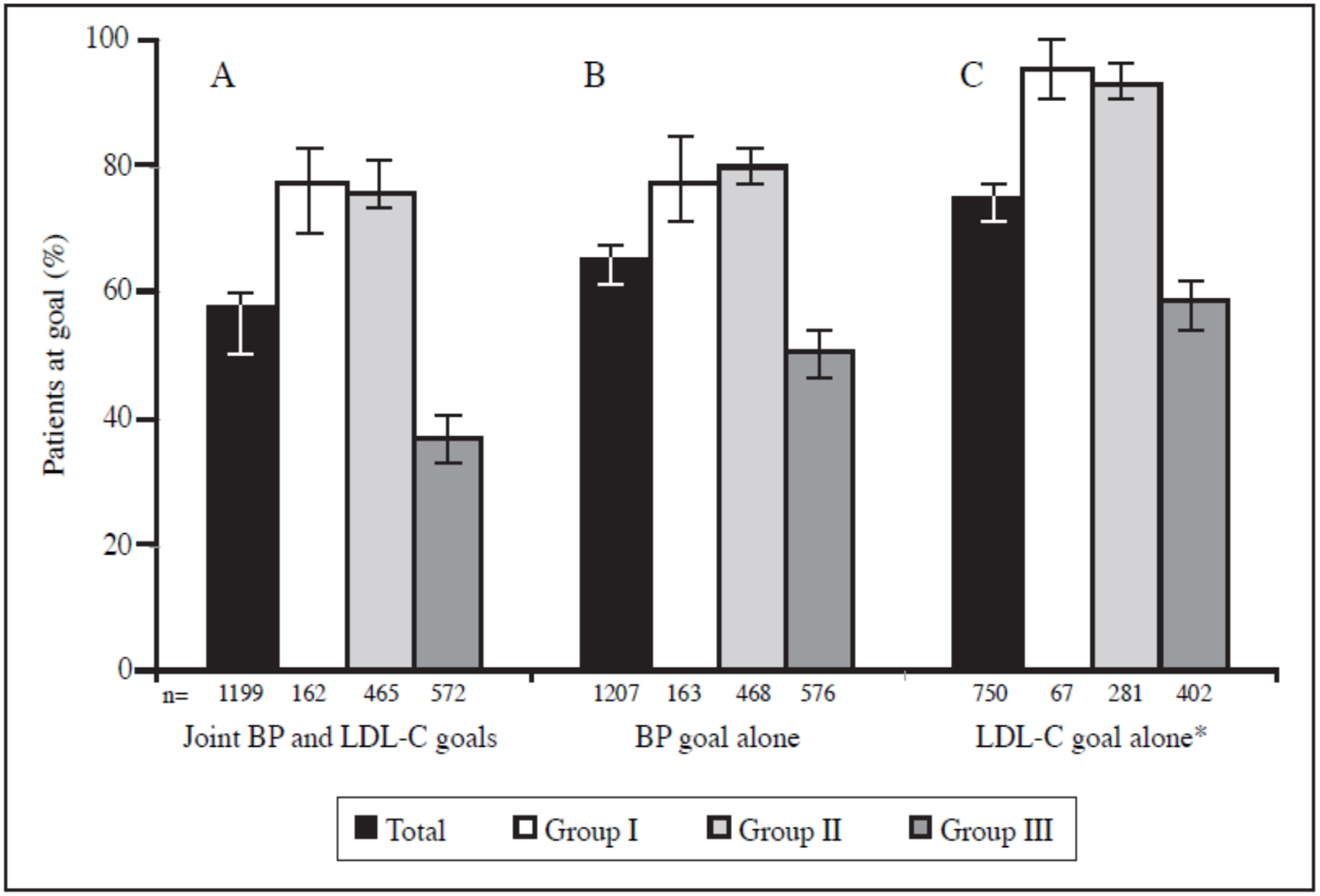
Blank et al. *J Clin Hypertens*. 2005;7:264-273.

Criteria for Assignment to CV Risk Categories & Recommended BP & LDL-C Target Levels for Each Risk Group

	CV Risk Group		
	Group I	Group II	Group III
Group assignment			
CV risk factors for CHD	Hypertension and dyslipidemia with no additional CV risk factors	Hypertension and dyslipidemia with one or more additional CV risk factors,* excluding CHD and diabetes mellitus	Hypertension and dyslipidemia with CHD or CHD risk equivalent (diabetes mellitus or other atherosclerotic disease)
Entry criteria			
BP (mm Hg)	SBP 140–179 and/or DBP 90–109	SBP 140–179 and/or DBP 90–109	SBP 130–159 and/or DBP 85–99
LDL-C (drug-naïve**) (mg/dL)	160–250	130–250	100–250
LDL-C (treated†) (mg/dL)	≤170	≤170	≤170
Treatment goals			
JNC VI[4] BP goal (mm Hg)	<140/90	<140/90	<130/85
NCEP ATP III[6] LDL-C goal (mg/dL)	<160	<130	<100

J Clin Hypertens. 2005;7:264–273

Goal attainment at end point overall and within each of the three cardiovascular risk groups



J Clin Hypertens. 2005;7:264–273

GEMINI: Clinical Utility

- **Zarvalor** (amlodipine besylate/atorvastatin calcium) was used in a
  - Broad range of patients: hypertension plus additional risk factors, dyslipidemia, diabetes, CHD
  - Variety of treatment situations
    - Substituted for existing treatment with amlodipine besylate or atorvastatin calcium (n=455, 37%)
    - Added to existing antihypertensive drug treatment (n=679, 56%)
    - Initiated in patients not receiving BP- or lipid-lowering drug treatment, along with diet and exercise (n=153, 13%)

Blank R et al. *J Clin Hypertens*. 2005;7:264-273.

Original Paper • CME

Efficacy and Safety of Coadministered Amlodipine and Atorvastatin in Patients With Hypertension and Dyslipidemia: Results of the AVALON Trial

Franz H. Messerli, MD;[1] George L. Bakris, MD;[2] R. David Ferrera, MD;[3] Mark C. Houston, MD, MS;[4] Robert J. Petrella, MD, PhD;[5] John M. Flack, MD, MPH;[6] William Sun, PhD;[7] EunMee Lee, PharmD;[7] Joel M. Neutel, MD;[8] on behalf of the AVALON Investigators*

The AVALON study was a randomized, multicenter trial to assess the efficacy and safety of co-administered amlodipine and atorvastatin in patients with hypertension and dyslipidemia.

Phase 1 was an 8-week, double-blind, placebo-controlled period whereby patients received amlodipine 5 mg, atorvastatin 10 mg, amlodipine 5 mg and atorvastatin 10 mg, or placebo.

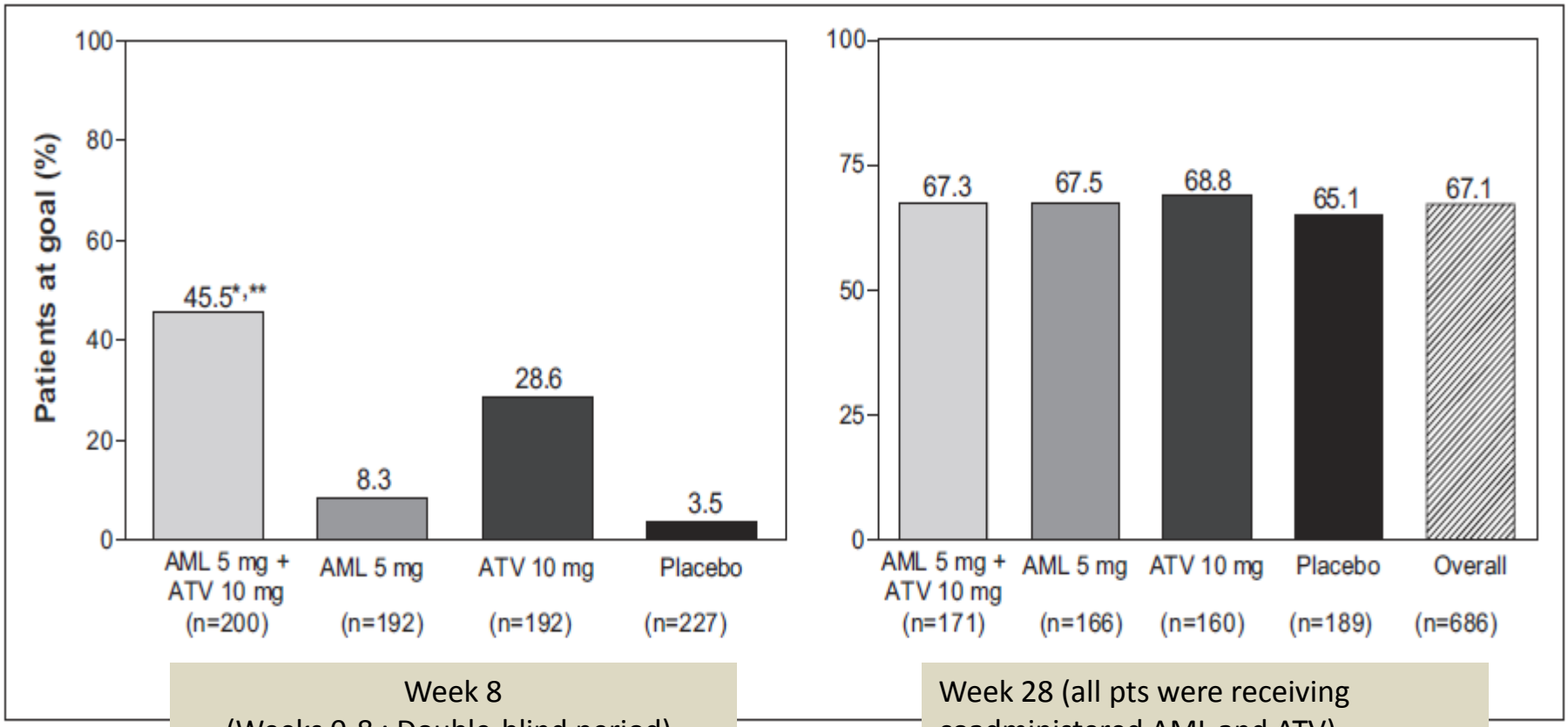
J Clin Hypertens. 2006;8:571–581.

Original Paper • CME

Efficacy and Safety of Coadministered Amlodipine and Atorvastatin in Patients With Hypertension and Dyslipidemia: Results of the AVALON Trial

Franz H. Messerli, MD;[1] George L. Bakris, MD;[2] R. David Ferrera, MD;[3] Mark C. Houston, MD, MS;[4] Robert J. Petrella, MD, PhD;[5] John M. Flack, MD, MPH;[6] William Sun, PhD;[7] EunMee Lee, PharmD;[7] Joel M. Neutel, MD;[8] on behalf of the AVALON Investigators*

Percentage of patients that reached target levels for both blood pressure and low-density lipoprotein cholesterol



Week 8
(Weeks 0-8 : Double-blind period).

Week 28 (all pts were receiving coadministered AML and ATV).

J Clin Hypertens. 2006;8:571–581.

Wolters Kluwer Health | Lippincott Williams & Wilkins

EUROPEAN SOCIETY OF CARDIOLOGY®

Original Scientific Paper

International open-label studies to assess the efficacy and safety of single-pill amlodipine/atorvastatin in attaining blood pressure and lipid targets recommended by country-specific guidelines: the JEWEL programme

Frederick D. Richard Hobbs[a], Gianfranco Gensini[c], Giovanni B. John Mancini[f], Athanasios J. Manolis[d,e], Beverly Bauer[g], Jacques Genest[h], Ross D. Feldman[i], Peter Harvey[b], Trond G. Jenssen[j,k] and Pedro Marques da Silva[l] for the JEWEL Study Group

European Journal of Cardiovascular Prevention and Rehabilitation 2009, 16:472–480

JEWEL: Objectives

- Evaluate the utility of single-pill amlodipine/atorvastatin in European and Canadian real-world primary care settings

- Assess the efficacy of amlodipine/atorvastatin to achieve national lipid and hypertension goals as set out in clinical guidelines

European Journal of Cardiovascular Prevention and Rehabilitation 2009, 16:472–480

JEWEL Design

- 16-week multicentre, open-label, titration-to-goal study in patients with hypertension and dyslipideamia
  - JEWEL I: UK and Canada
  - JEWEL II: 11 EU countries (Italy, Ireland, Belgium, Spain, Greece, Switzerland, Austria, Portugal, Finland, Hungary, Slovenia)
- Eight dosage strengths of single-pill amlodipine/atorvastatin therapy (5/10, 10/10, 5/20, 10/20, 5/40, 10/40, 5/80, 10/80 mg/mg) were titrated to reduce BP and LDL-C to country-specific target levels

European Journal of Cardiovascular Prevention and Rehabilitation 2009, 16:472–480

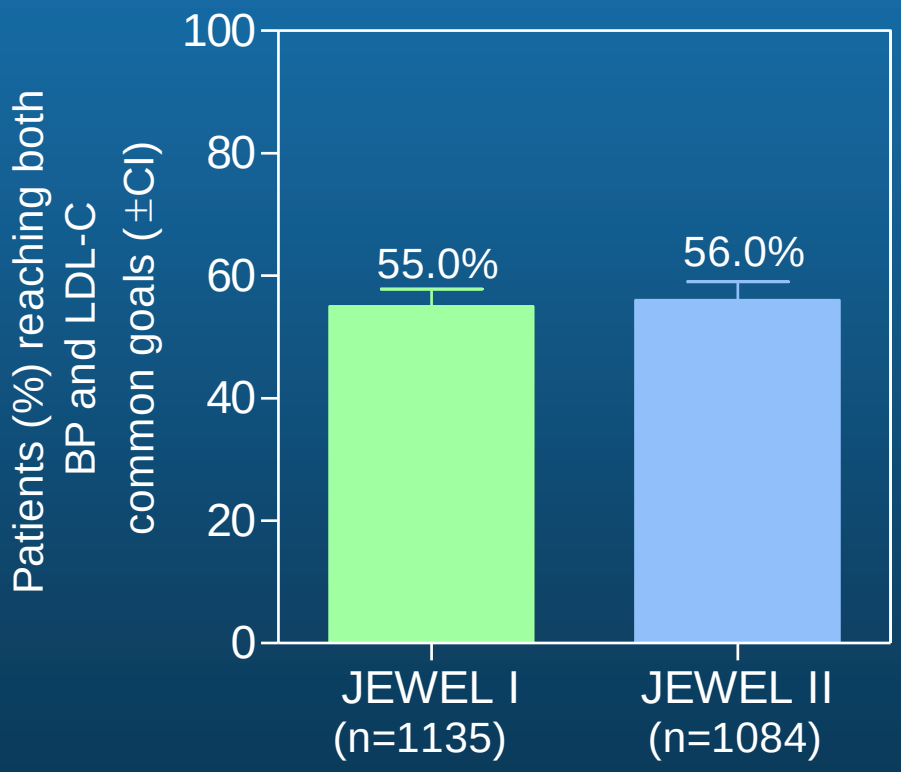
Study Population

- **Inclusion criteria:**
  - Male or female aged 18–80 years
  - Diagnosis of concurrent hypertension (uncontrolled) and dyslipideamia (controlled or uncontrolled)
  - Untreated, or if treated on stable medication
  - BP above target, LDL-C must be above target or (if on treatment), at or above target

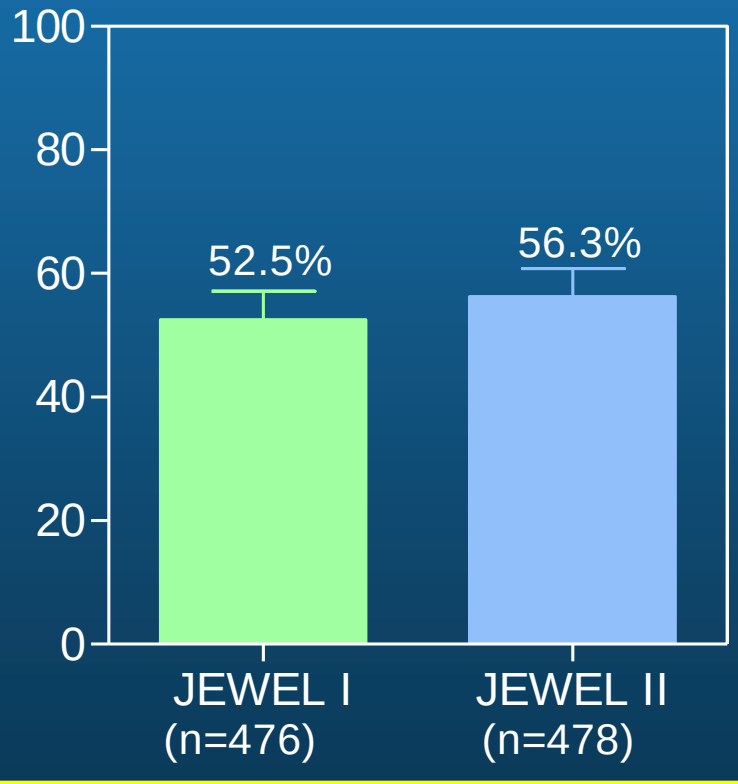
- **Exclusion criteria:**
  - Adequately controlled BP at baseline
  - Currently receiving treatment with:
    - Amlodipine and atorvastatin
    - Atorvastatin 80 mg but with a LDL-C ≥2.6 mmol/L (100 mg/dL)
  - Treated with amlodipine 10 mg or another CCB at maximum dose

Patients Achieving Common BP and LDL-C Goals

Amlodipine/atorvastatin All doses



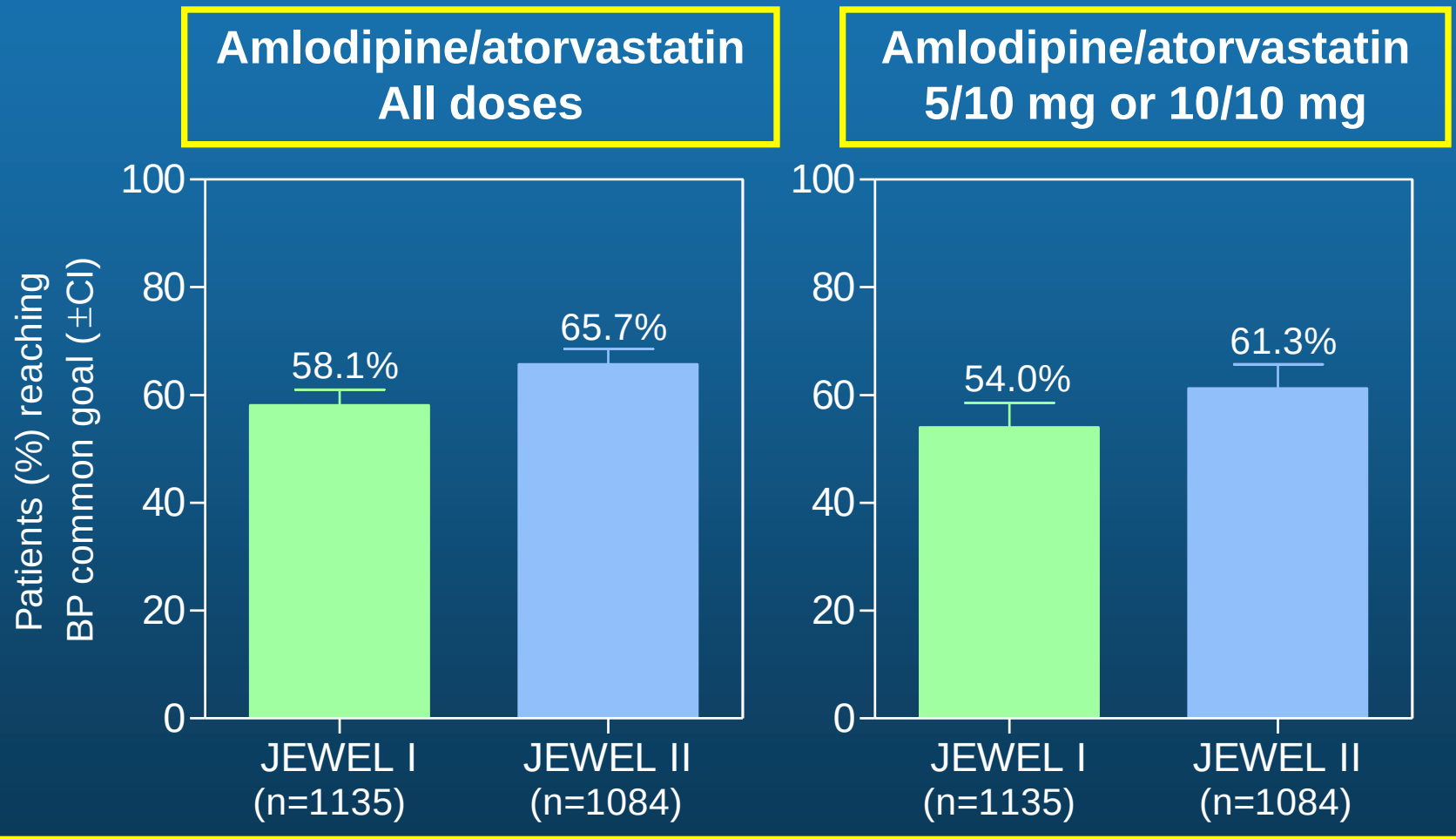
Amlodipine/atorvastatin 5/10 mg or 10/10 mg



Common goals defined as: LDL-C <3.0 mmol/L (116.0 mg/mL)

SBP <140 and DBP <90 mm Hg; Patients with diabetes: SBP <130 and DBP <80 mm Hg

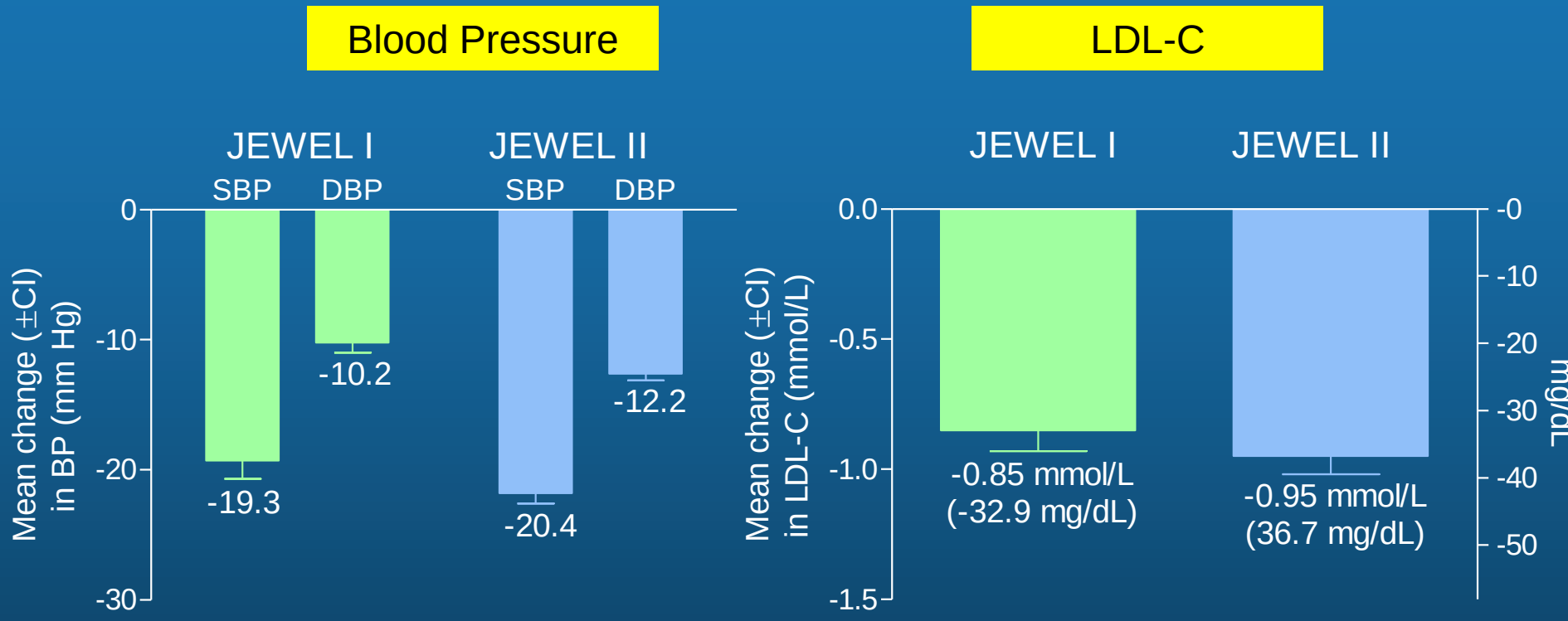
Patients Achieving Common BP Goal only



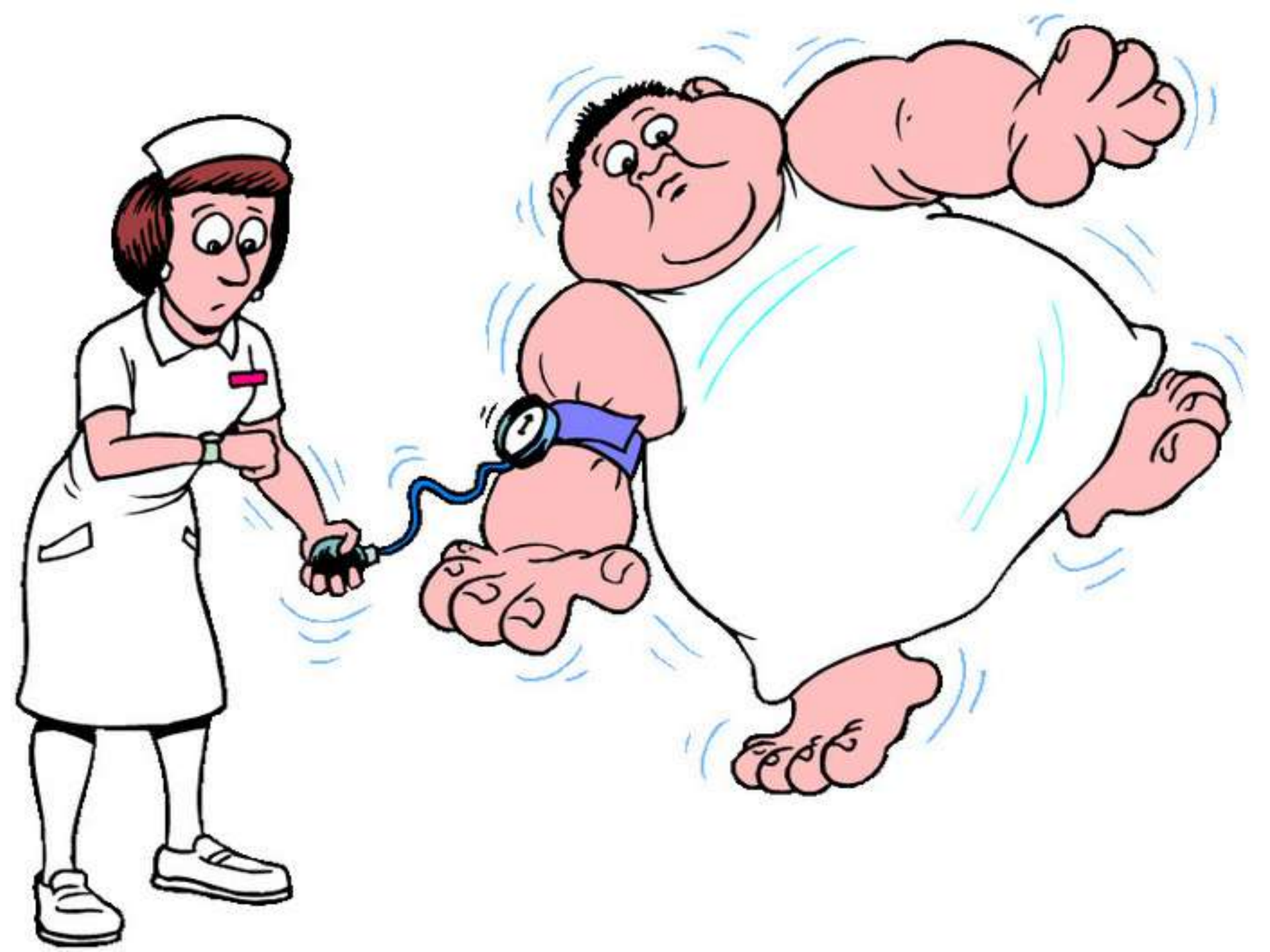
Common BP goal defined as: SBP <140 and DBP <90 mm Hg;

Patients with diabetes: SBP <130 and DBP <80 mm Hg

Mean Change in Blood Pressure and LDL-C



Amlodipine/atorvastatin 5/10 mg or 10/10 mg



Atorvastatin and Amlodipine: A *Synergistic* Effect?

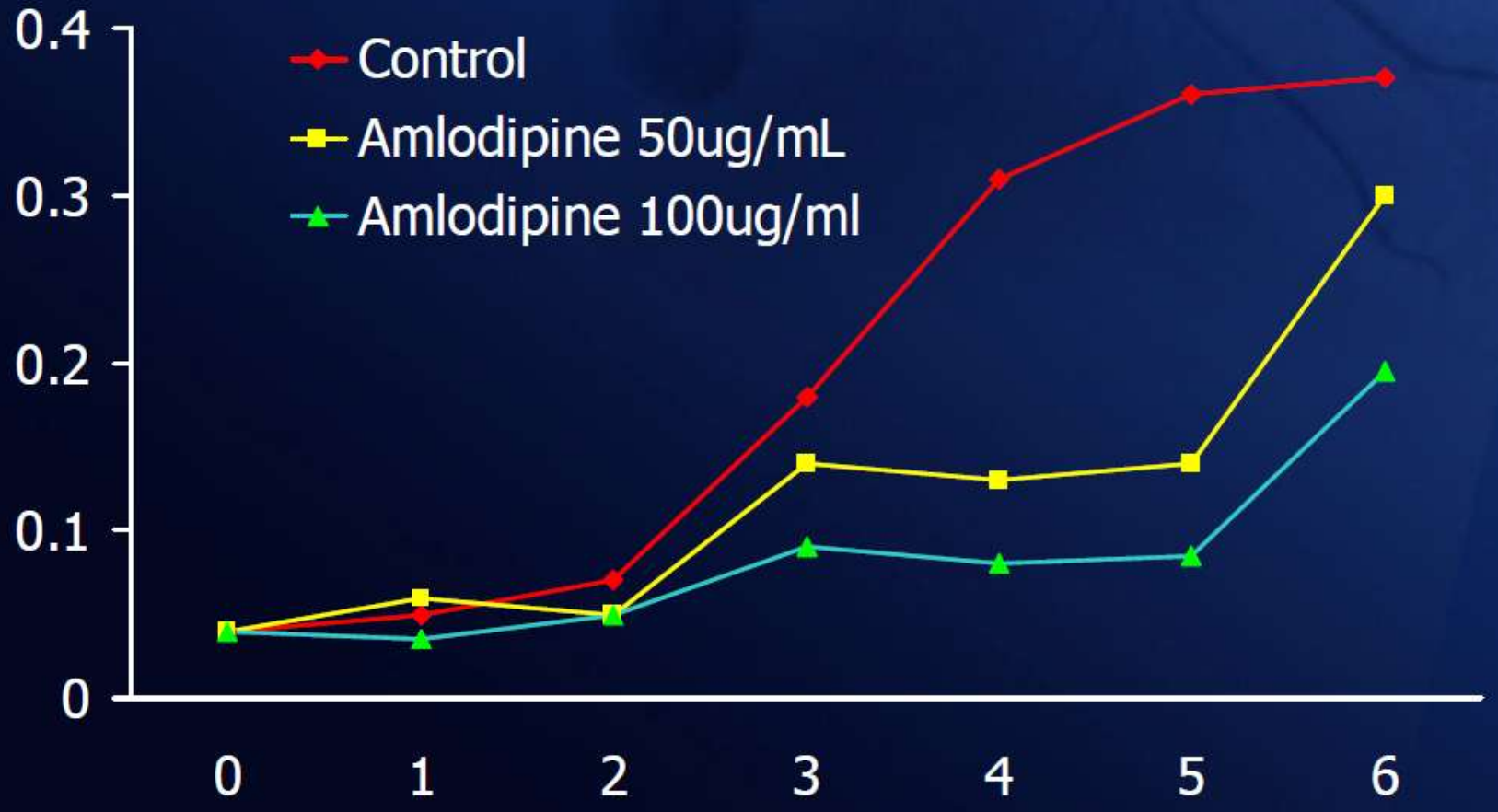
Hypertension

Hyperlipidemia

Oxidative Stress

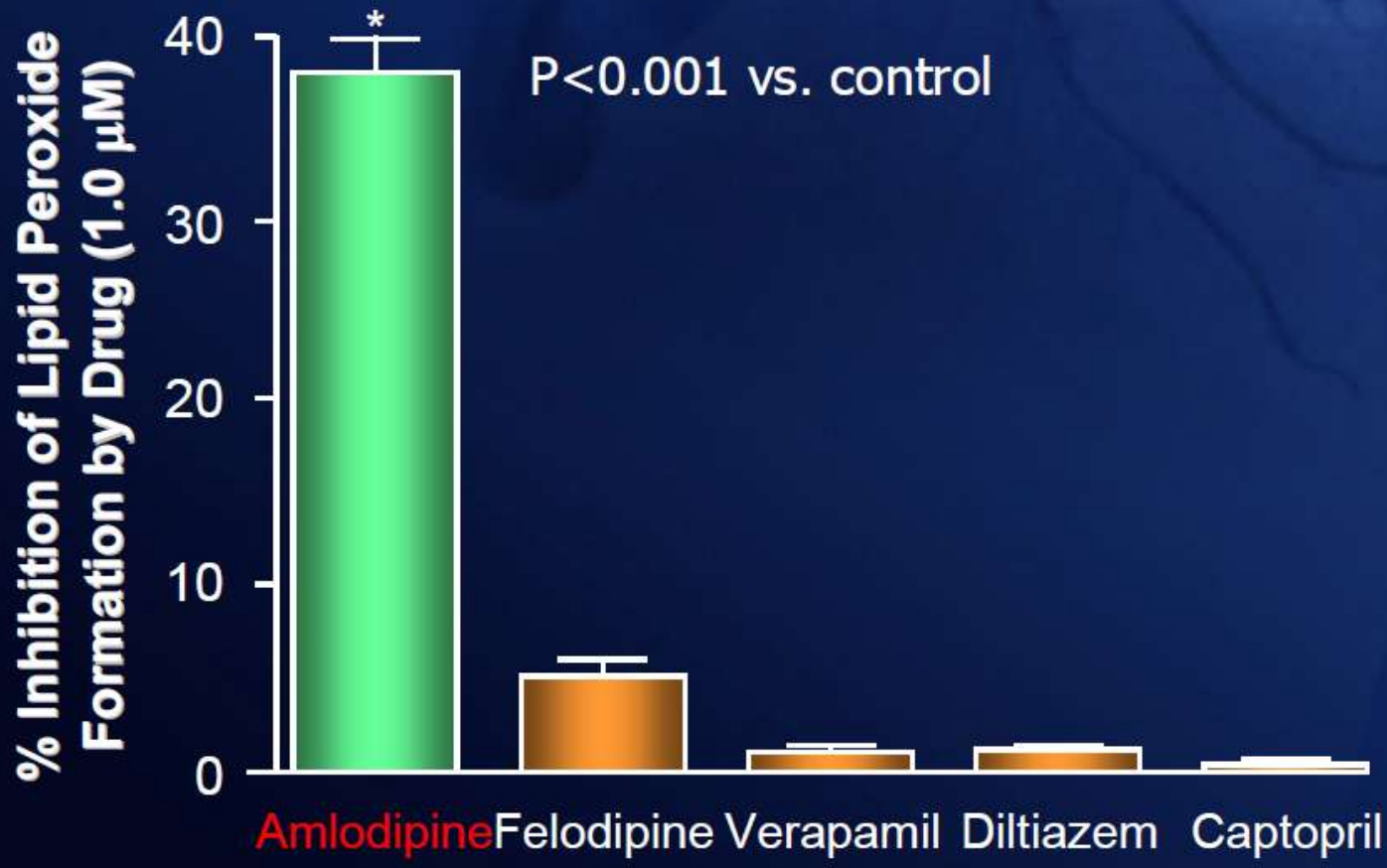
Endothelial Dysfunction

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

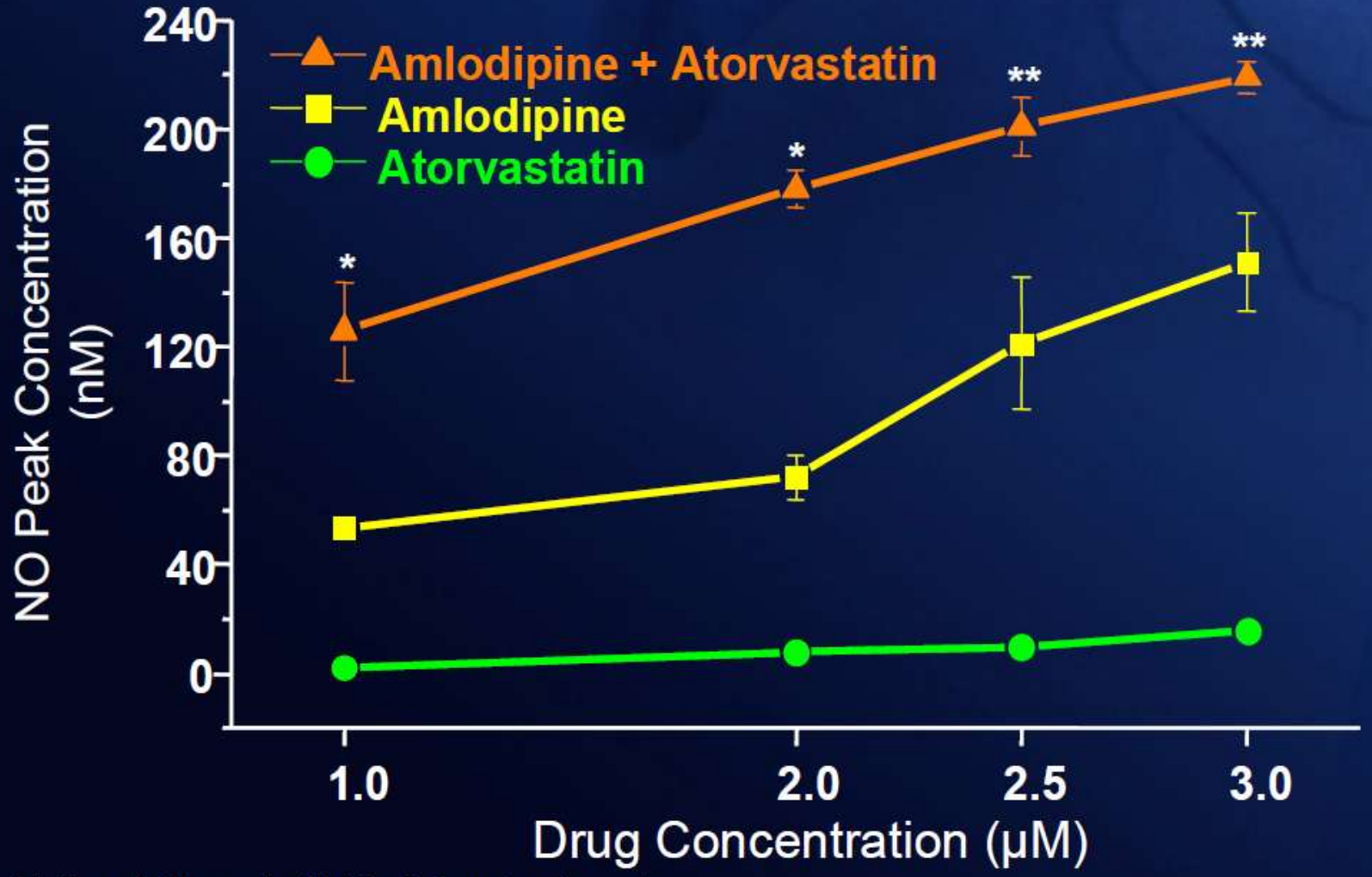


Mean ± SD.

*P<.001 vs control.

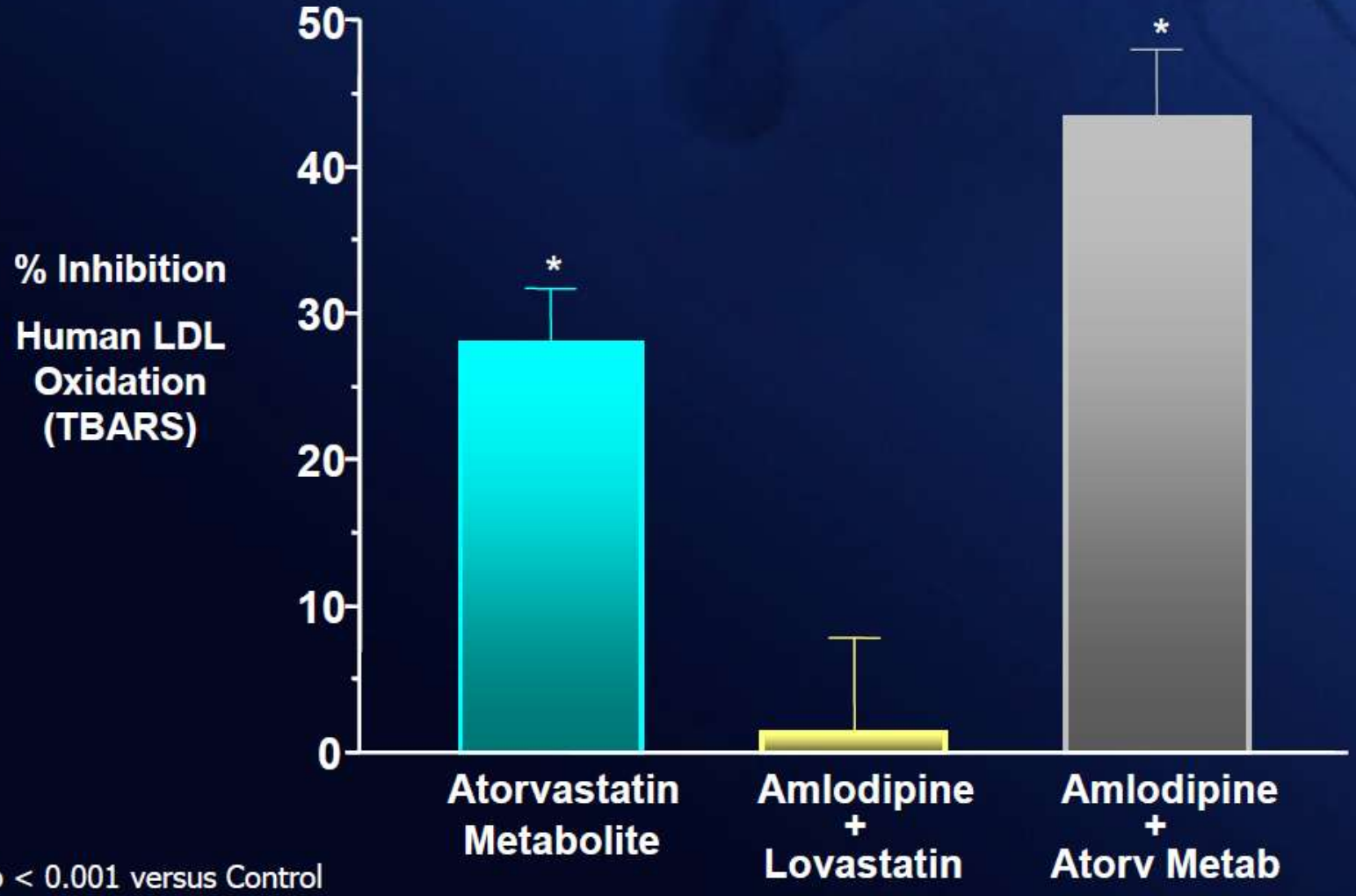
Mason et al. *J Mol Cell Cardiol*. 1999;31:275-281.

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



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

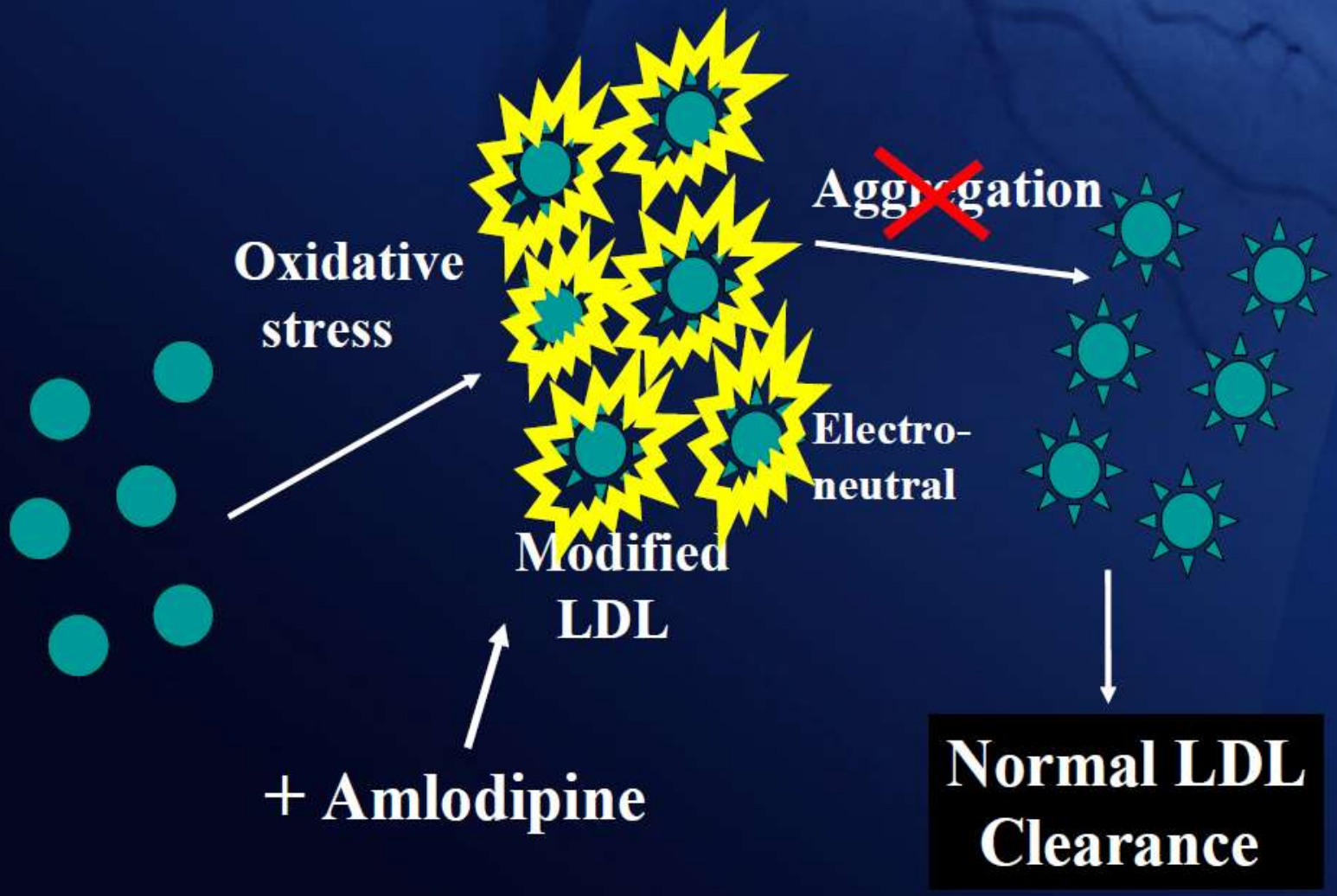
Effects of Amlodipine and Atorvastatin Active Metabolite vs Lovastatin on Human LDL Oxidation



*p < 0.001 versus Control

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

Effect of Amlodipine against modification of LDL



Summary

- There are about 65 million hypertensive patients, and over 75% have LDL-C greater than optimal levels
- The majority of hypertensive patients with dyslipidemia do not receive statin therapy within 1 year of initiating antihypertensive therapy
- Hypertensive patients need aggressive BP management and often need multiple antihypertensive medications to manage BP
- Hypertensive patients with additional risk factors, including dyslipidemia, and without CHD would benefit from CADUET in a single pill that delivers:
  - The significant BP reductions of Norvasc® (amlodipine besylate)
  - The impressive LDL-C* and MI and stroke risk reductions of Lipitor® (atorvastatin calcium)

*When used with diet and exercise.

Chobanian AV et al. *Hypertension*. 2003;42:1206-1252; Fields LE et al. *Hypertension*. 2004;44:398-404;

Single-Pill Amlodipine/Atorvastatin (Zarvalor)

- A single-pill combination therapy targeting **hypertension** and **dyslipidemia** is useful in:
  - Co-treatment of these 2 CV risk factors by treating a patient's overall risk of cardiovascular disease
  - Lower prescription costs
  - Reduce a patient's pill burden and improve patient adherence
- The efficacy and safety of this combination has been demonstrated in a clinical practice setting, in several studies.
  - Furthermore, patients taking the single pill amlodpine/atorvastatin are more likely to be adherent with both therapies.

Treatment of risk factors associated with hypertension

Recommendations	Class[a]	Level[b]
It is recommended to use statin therapy in hypertensive patients at moderate to high CV risk, targeting a low-density lipoprotein cholesterol value <3.0 mmol/L (115 mg/dL).	I	A
When overt CHD is present, it is recommended to administer statin therapy to achieve low-density lipoprotein cholesterol levels <1.8 mmol/L (70 mg/dL).	I	A
Antiplatelet therapy, in particular low-dose aspirin, is recommended in hypertensive patients with previous CV events.	I	A

Journal of Hypertension. 2013;31:1281–1357.

Zarvalor®

Amlodipine / Atorvastatin

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3rd Century B.C.