

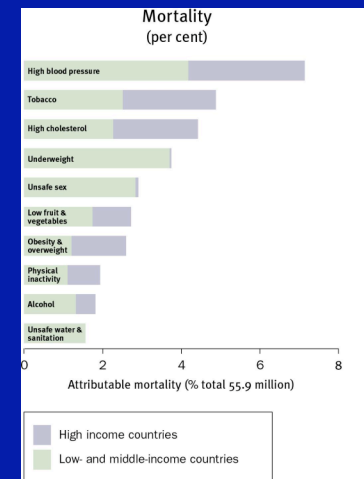
## Optimal Management in the Treatment of Global Cardiovascular Risk: Result of ASCOT 2x2

Anatoly Langer, MD

### Conflict of Interest: Global Risk

- Research grant support, consulting fees and honorarium: Pfizer, Merck Schering, Sanofi Aventis, Biovail
- Research Grant: Astra Zeneca, Merck, Novartis

## Global Burden of Disease



2002 World Health Report

## INTERHEART Study: Risk of Acute Myocardial Infarction Associated with Risk Factors in the Overall Population (52 countries)

### After Adjustment for Age, Sex, and Geographic Region

Risk factor	Sex	Control(%)	Case(%)	Odds ratio (99% CI)	PAR (99% CI)	
Current smoking	F	9.3	20.1	2.86 (2.36-3.48)	15.8% (12.9-19.3)	■
	M	33.0	53.1	3.05 (2.78-3.33)	44.0% (40.9-47.2)	
Diabetes	F	7.9	25.5	4.26 (3.51-5.18)	19.1% (16.8-21.7)	■
	M	7.4	16.2	2.67 (2.36-3.02)	10.1% (8.9-11.4)	
Hypertension	F	28.3	53.0	2.95 (2.57-3.39)	35.8% (32.1-39.6)	■
	M	19.7	34.6	2.32 (2.12-2.53)	19.5% (17.7-21.5)	
Abdominal Obesity	F	33.3	45.6	2.26 (1.90-2.68)	35.9% (28.9-43.6)	■
	M	33.3	46.5	2.24 (2.03-2.47)	32.1% (28.0-36.5)	
Psychosocial Index	F	-	-	3.49 (2.41-5.04)	40.0% (28.6-52.6)	■
	M	-	-	2.58 (2.11-3.14)	25.3% (18.2-34.0)	
ApoB/ApoA1 ratio	F	14.1	27.0	4.42 (3.43-5.70)	52.1% (44.0-60.2)	■
	M	21.9	35.5	3.76 (3.23-4.38)	53.8% (48.3-59.2)	

Odds ratio (99% CI)

Reference: INTERHEART, Yusuf et al., Lancet 2004;937-952

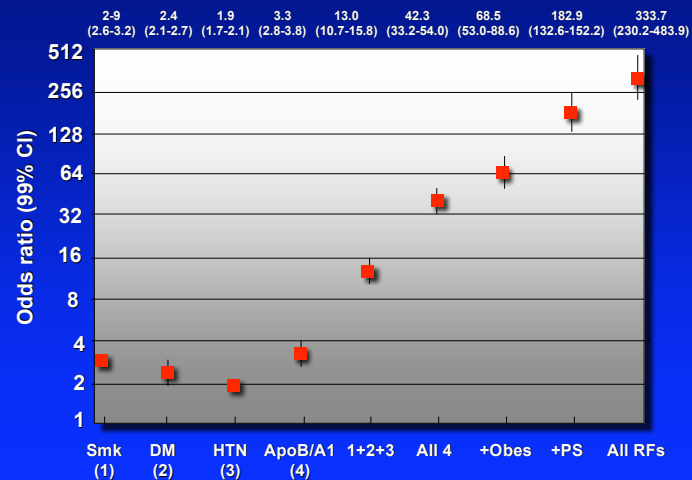
## Association of Risk of Acute Myocardial Infarction in Men and Women After Adjustment for Age, Sex, and Geographic Region

Risk factor	Sex	Control(%)	Case(%)	Odds ratio (99% CI)	PAR (99% CI)	
Fruits/Veg	F	50.3	39.4	0.58 (0.48-0.71)	17.8% (12.9-24.1)	■
	M	39.6	34.7	0.74 (0.66-0.83)	10.3% (6.9-15.2)	
Exercise	F	16.5	9.3	0.48 (0.39-0.59)	37.3% (26.1-50.0)	■
	M	20.3	15.8	0.77 (0.69-0.85)	22.9% (16.9-30.2)	
Alcohol	F	11.2	6.3	0.41 (0.32-0.53)	46.9% (34.3-60.0)	■
	M	29.1	29.6	0.88 (0.81-0.96)	10.5% (6.1-17.5)	

0.25 0.5 1

Reference: INTERHEART, Yusuf et al., Lancet 2004;937-952

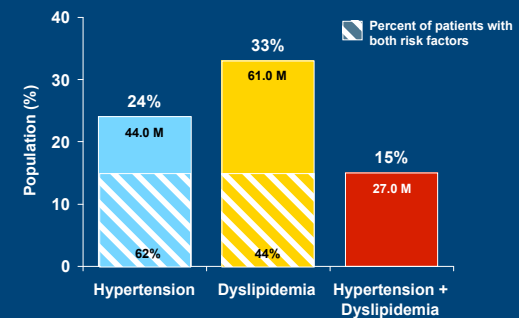
### Risk of Acute Myocardial Infarction Associated with Exposure to Multiple Risk Factors : Case-Control Study in 52 Countries



Reference: INTERHEART, Yusuf et al., Lancet 2004:937-952

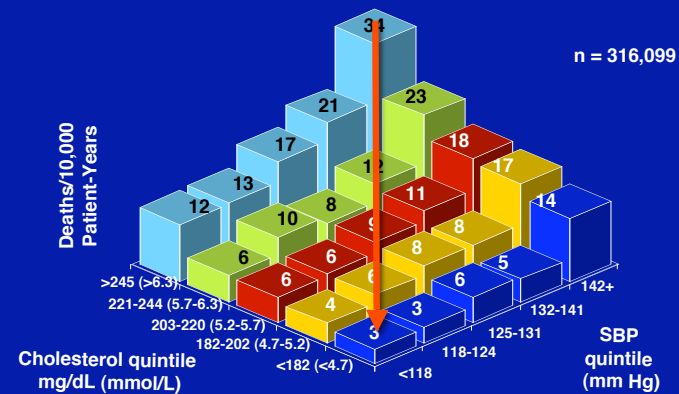
### Concurrent Hypertension and Dyslipidemia is Prevalent in the United States

- 15% of total adult population have concurrent hypertension and dyslipidemia



US Dept of Health and Human Services (DHHS), National Center for Health Statistics. Unpublished data from the Third National Health and Nutrition Examination Survey (NHANES III) Phase 2: 1991-1994; CDC, 1994.

### Combined Effects of SBP and Cholesterol on CHD Mortality

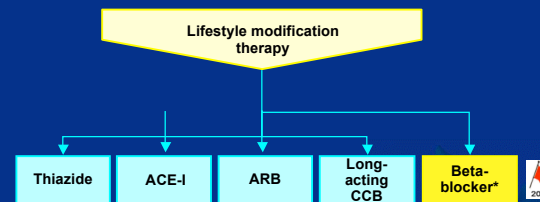


Neaton JD, et al, for the Multiple Risk Factor Intervention Trial Research Group. Arch Intern Med. 1992;152:56-64.

### V. Treatment of Adults with Systolic/Diastolic Hypertension without Other Compelling Indications

TARGET <140/90 mmHg

INITIAL TREATMENT AND MONOTHERAPY

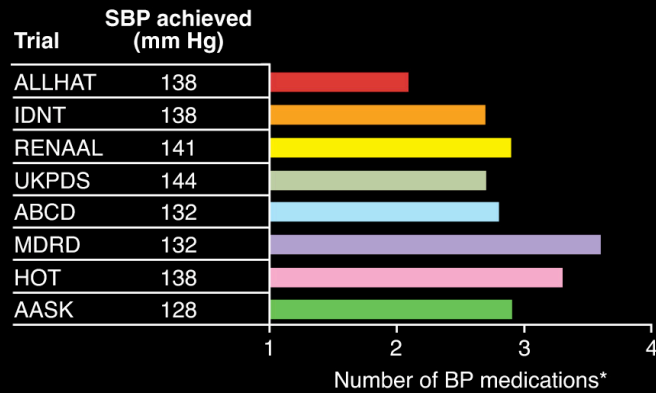


\* BBs are not indicated as first line therapy for age 60 and above

2006 Canadian Hypertension Education Program Recommendations

## Number of antihypertensive agents needed to achieve systolic BP control

VBWG

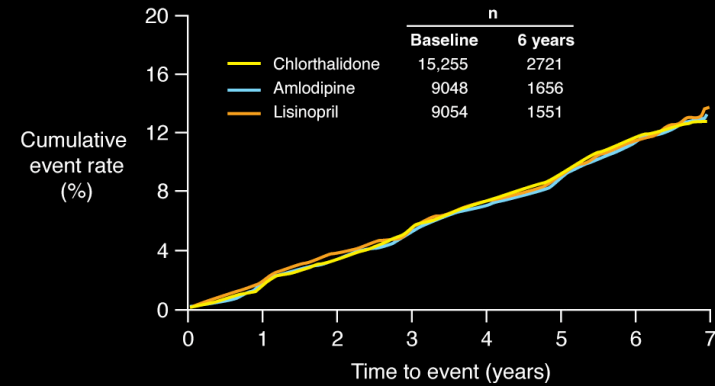


\*Average per patient

Updated from Bakris GL et al. *Am J Kidney Dis.* 2000;36:646-61.

## ALLHAT: Primary outcome—Fatal CHD or nonfatal MI

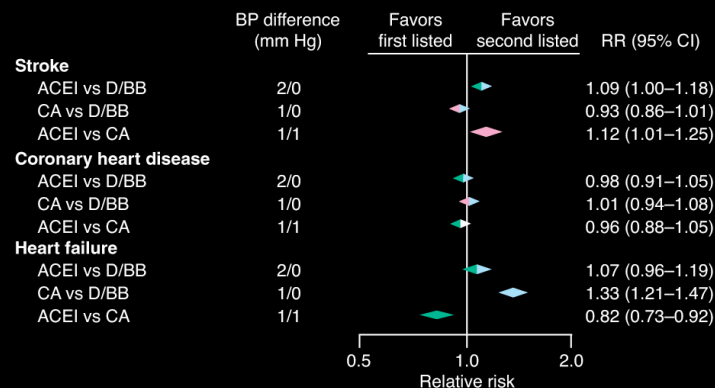
VBWG



ALLHAT Collaborative Research Group. *JAMA.* 2002;288:2981-97.

## BPLTTC: Comparison of different active treatments

VBWG

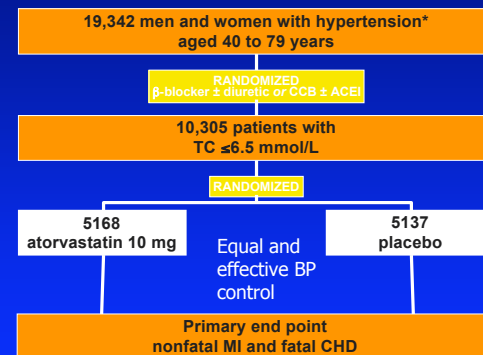


BPLTTC = Blood Pressure Lowering Treatment Treats Collaboration

BPLTTC. *Lancet.* 2003;362:1527-35.

## ASCOT—Study Design

2 × 2 factorial trial design



\*Patients studied also had ≥3 of the following additional CV risk factors: left ventricular hypertrophy (LVH), other specified abnormalities on electrocardiography (ECG), type 2 diabetes, peripheral arterial disease, previous stroke or transient ischemic attack, male gender, age 55 years or older, microalbuminuria or proteinuria, smoking, plasma TC to HDL-C ratio ≥6, or premature family history of CHD.

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

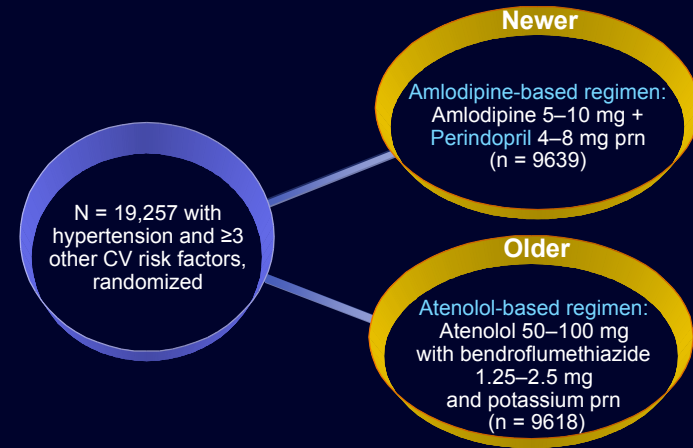
## Evidence in 1° Prevention ASCOT: Patient Population Lipid Lowering Arm (LLA)

### Eligibility criteria

- SBP  $\geq$ 160 mm Hg and/or DBP  $\geq$ 100 mm Hg (untreated) or SBP  $\geq$ 140 mm Hg and/or BP  $\geq$ 90 mm Hg (treated)
- TC  $\leq$ 6.5 mmol/L (250 mg/dL) and TGs  $\leq$ 4.5 mmol/L (400 mg/dL)
- 40-79 years of age
- 3+ CVD risk factors:
  - Male
  - >55 years of age
  - LVH or ECG abnormality
  - Type 2 DM
  - PAD or CVD (CVA or TIA) or family Hx of premature CHD
  - Microalbuminuria/proteinuria
  - Smoking
  - TC/HDL >6
- No history of CHD

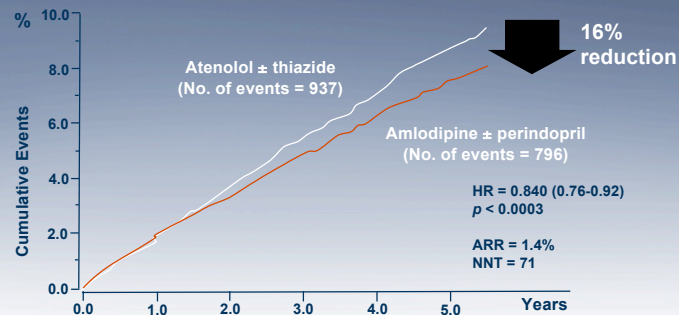
Sever et al, for the ASCOT Investigators. *Lancet*. 2003;361:1149-58

## ASCOT-BPLA: Methods



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

## ASCOT-BPLA: CV Death + MI + Stroke

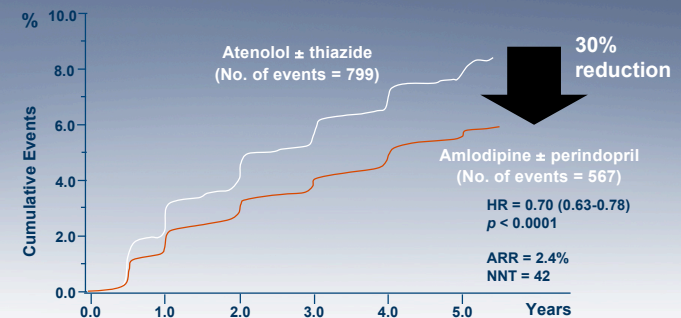


### Number at risk

	0.0	1.0	2.0	3.0	4.0	5.0	Years
Amlodipine $\pm$ perindopril	9,639	9,415	9,228	9,007	8,778	7,655	
Atenolol $\pm$ thiazide	9,618	9,400	9,152	8,891	8,629	7,500	

Dahlöf B, Sever PS, Poulter NR, et al. *Lancet*. 2005;366:895-906.

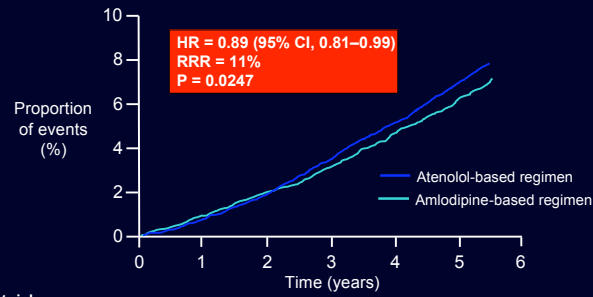
## ASCOT-BPLA: New-onset Diabetes Mellitus



### Number at risk

	0.0	1.0	2.0	3.0	4.0	5.0	Years
Amlodipine $\pm$ perindopril	9,639	9,383	9,165	8,966	8,726	7,618	
Atenolol $\pm$ thiazide	9,618	9,295	9,014	8,735	8,455	7,319	

## ASCOT-BPLA: Reduction in all-cause mortality



**Number at risk**

Time (years)	0	1	2	3	4	5	6
Amlodipine-based regimen (738 events)	9639	9544	9441	9322	9167	8078	
Atenolol-based regimen (820 events)	9618	9532	9415	9261	9085	7975	

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

## ASCOT-BPLA: Other Endpoints

	Amlodipine-based* (n = 9639)	Atenolol-based † (n = 9618)		P
<b>Secondary endpoints</b>				
Nonfatal MI (excluding silent) + fatal CHD	7.4	8.5	Amlodipine-based better	<0.05
Total coronary endpoint	14.6	16.8		<0.01
Total CV events and procedures	27.4	32.8		<0.0001
All-cause mortality	13.9	15.5		<0.05
CV mortality	4.9	6.5		0.001
Fatal/nonfatal stroke	6.2	8.1		<0.001
Fatal/nonfatal HF	2.5	3.0		NS
<b>Tertiary endpoints</b>				
Development of diabetes	11.0	15.9		<0.0001
Development of renal impairment	7.7	9.1		<0.05

\*Amlodipine 5-10 mg ± perindopril 4-8 mg prn

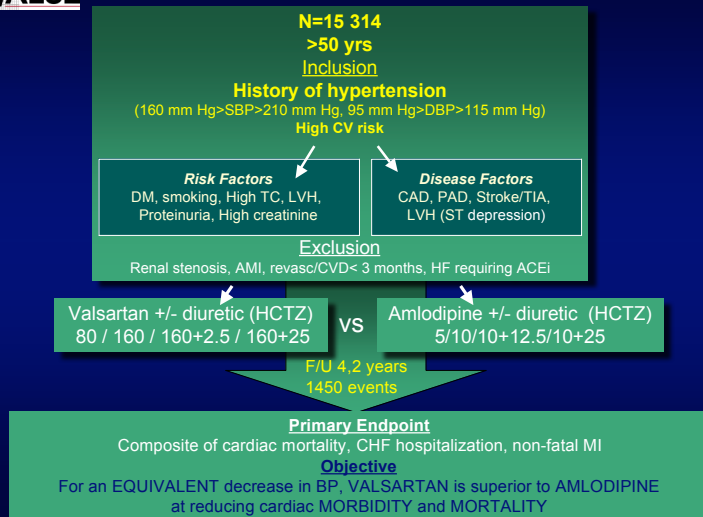
†Atenolol 50-100 mg ± bendroflumethiazide 1.25-2.5 mg/potassium prn

Unadjusted risk reduction

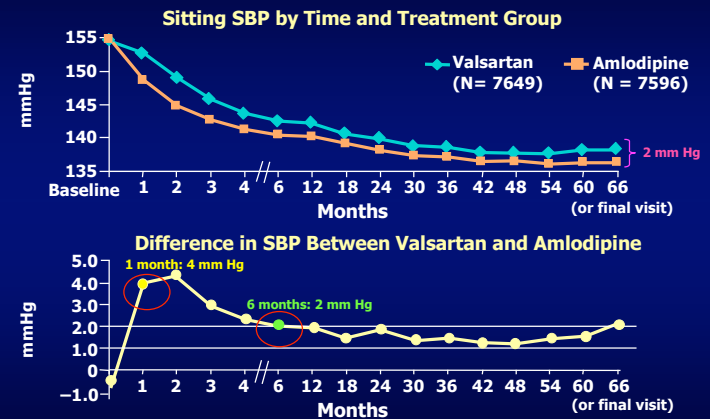
Dahlöf B et al; ASCOT Investigators. *Lancet*. 2005;366:895-906.

VALUE

## Objective and Study Design

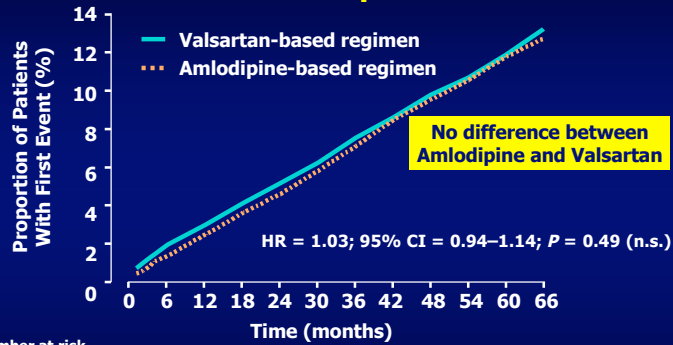


## VALUE: Systolic Blood Pressure in Study



Julius S et al. *Lancet*. June 2004;363.

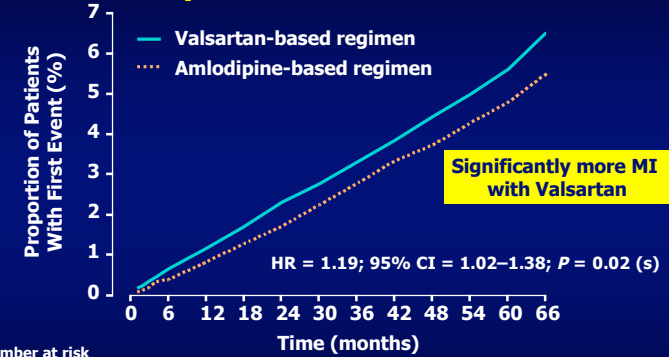
### VALUE: Primary Composite Cardiac Endpoint



Number at risk	
Valsartan	7649 7459 7407 7250 7085 6906 6732 6536 6349 5911 3765 1474
Amlodipine	7596 7469 7424 7267 7117 6955 6772 6576 6391 5959 3725 1474

Julius S et al. *Lancet*. June 2004;363.

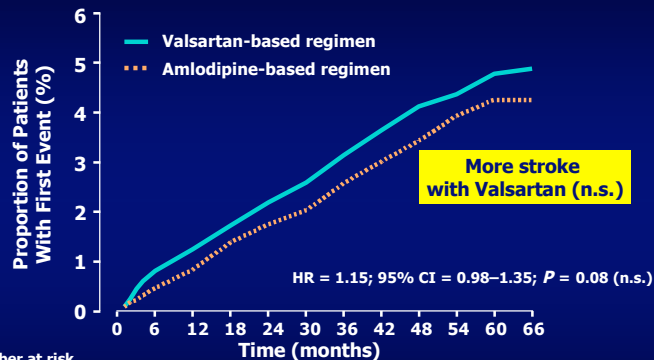
### VALUE: Fatal and Non-Fatal Myocardial Infarction



Number at risk	
Valsartan	7649 7499 7458 7319 7177 7016 6853 6680 6504 6078 3864 1520
Amlodipine	7596 7497 7458 7332 7205 7065 6905 6727 6562 6141 3840 1532

Julius S et al. *Lancet*. June 2004;363.

### VALUE: Fatal and Non-fatal Stroke



Number at risk	
Valsartan	7649 7494 7448 7312 7170 7022 6877 6692 6515 6093 3859 1516
Amlodipine	7596 7499 7455 7334 7195 7055 6918 6744 6587 6163 3846 1532

Julius S et al. *Lancet*. June 2004;363.

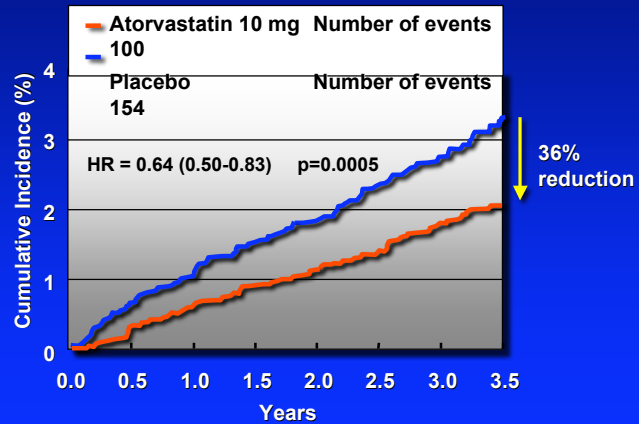
## Vascular Protection for Hypertensive Patients: Statins *CHEP recommendations 2004*

Statins are recommended in hypertensive patients with 3 or more CV risk factors in patients older than 40\* or with established atherosclerotic disease regardless of age.

\* **Risk Factors, 3 or more of:**

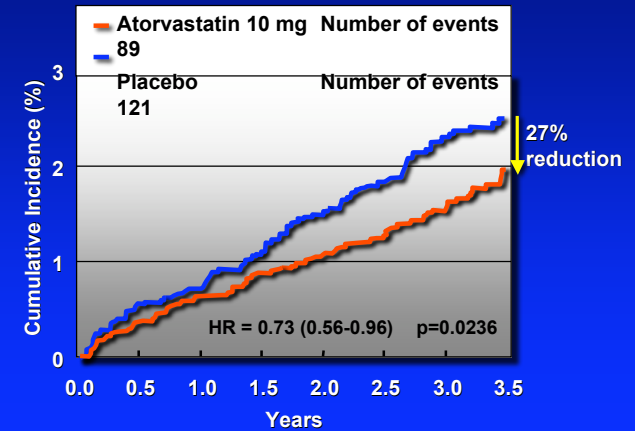
- Male gender
- 55 y or older
- Smoking
- Type 2 Diabetes
- Total-C/HDL-C ratio of 6 or higher
- Premature Family History of CV disease
- Previous Stroke or TIA
- LVH
- ECG abnormalities
- Microalbuminuria or Proteinuria
- Peripheral Vascular Disease

## Primary End Point: Nonfatal MI and Fatal CHD



Sever et al, for the ASCOT Investigators. Lancet. 2003;361:1149-58

## Secondary End Point: Fatal and Nonfatal Stroke



Sever et al, for the ASCOT Investigators. Lancet. 2003;361:1149-58

## Summary

- *Global risk assessment*
  - Risk ↑ as number of risk factors ↑
- *Comprehensive management*
  - Targets are lower in patients at higher risk
  - Higher risk requires multiple interventions
- *Combination therapy: Believe it or not – 5 to 10 drugs*
  - HT: 3 drugs – ACEI + diuretic + CCB (amlodipine)
  - Cholesterol – statin ± absorption inhibitor
  - Diabetes – metformin + other (TZDs or incretin hormones)
  - Smoking cessation
  - Aspirin ± clopidogrel