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The experience from the Progetto CUORE

Cardiovascular Risk Factors. Their Use In Clinical Practice

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Health Unit 4 "Medio Friuli" and Regional Health Agency of Friuli-Venezia Giulia
Udine, Italy

Il Progetto CUORE

Aims

1. To implement a surveillance system through a national register
2. To describe risk factors through an health examination survey
3. To evaluate the risk of the first major cardiovascular event through Italian longitudinal studies

Supported by the Italian Ministry of Health and coordinated by Italian Institute of Health - 1998

S. Giampaoli, **L. Palmieri** Istituto Superiore di Sanità, Rome

G Cesana, Università Milano-Bicocca, Monza, **M. Ferrario**, Università dell'Insubria, Varese

D. Vanuzzo, **L. Pilotto** Centro Prevenzione Cardiovascolare, Udine

S. Panico, Università Federico II, Napoli

Base-Line risk factors

Questionnaire

- Gender
- Age
- Smoking habit
- History of diabetes
- History of coronary heart diseases (Rose-Q, ECG-Minnesota)
- Family history of CVD
- Anti-hypertensive medications

Exam

- Systolic and diastolic blood pressure (2 measurements)
- Total serum cholesterol, HDL-cholesterol, triglycerides, fasting blood glucose (63%)
- Body mass index

FOLLOW-UP

Events

Myocardial infarction, coronary death, sudden death, intracerebral and subaracnoid hemorragia, trombosis, stroke, rivascularization.
For each partecipant who experienced one of the previous diseases or death from baseline examination and december 2002 were collected:

hospital medical record

death certificate

medical records from GPs

Events were validated following the MONICA criteria

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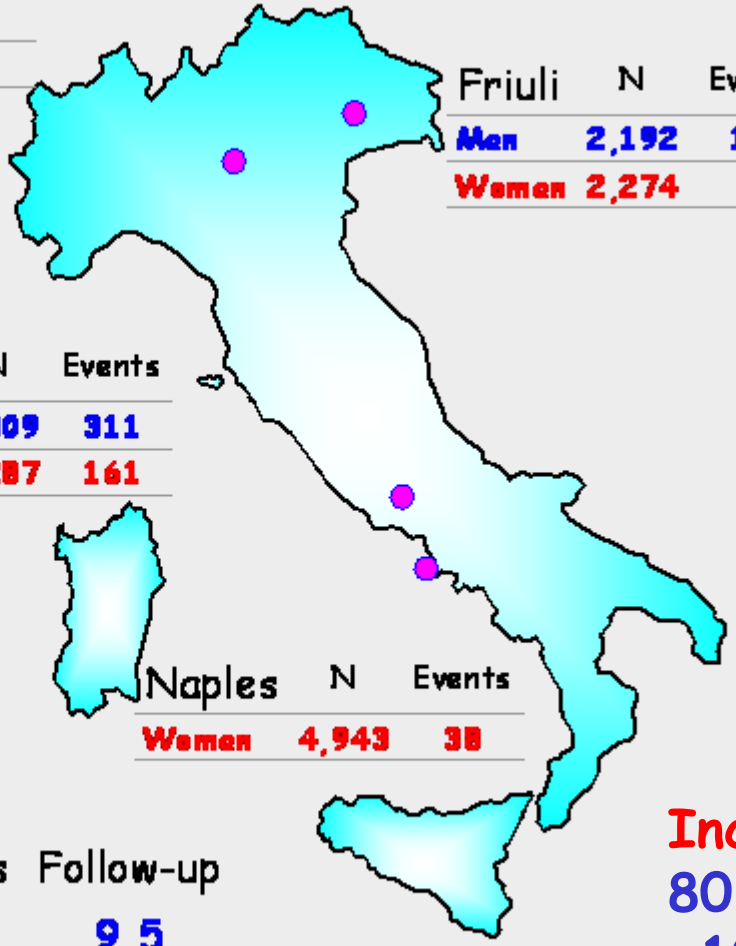
Cohort distributions, men and women 35-69 years

Brianza	N	Events
Men	2,519	172
Women	2,623	54

Friuli	N	Events
Men	2,192	160
Women	2,274	75

Latina	N	Events
Men	2,809	311
Women	3,287	161

Naples	N	Events
Women	4,943	38

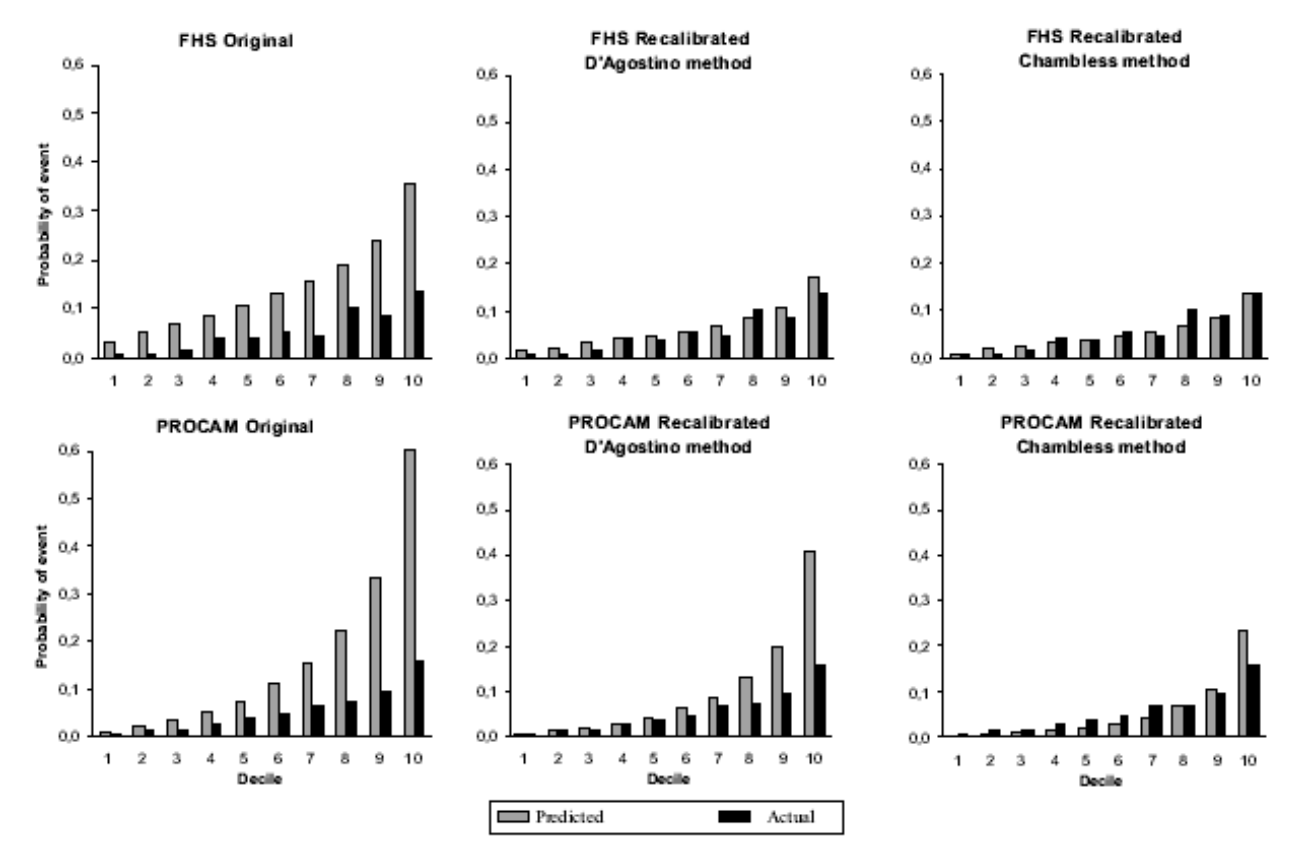


TOTAL	N	Events	Follow-up
Men	7,520	643	9.5
Women	13,127	328	8.0

Incidence:
80 (men) and 31 (women)
x10,000 person-years

Data analyses to identify risk factors and their aetiological role:

- risk factor description
- correlation analysis
- univariate analysis (hazard ratio and significativity)
- multivariate analysis (Cox model)
- model effectiveness testing (Receiver Operating Characteristic curve, Hosmer-Lemeshow test)
- choice of the best model
- validation (cross-validation, bootstrap)



Predicted and actual 10-year risk of incident major coronary events, for deciles of risk estimated by the Framingham and PROCAM equations, in the CUORE dataset

Ferrario et al., Int. J. Epidemiol 2005

The Third Joint Task Force decided to focus not only on the prevention of coronary heart disease but also on the prevention of other clinical manifestations of atherothrombotic disease including thrombotic stroke and peripheral artery disease

Baseline descriptive statistics, men and women ages 35-69 years, free of previous CVD (1)

Variables	Men		Women	
	mean	*s.d.*	mean	*s.d.*
Age (years)	50.6	*9.2*	50.3	*8.5*
Systolic Pressure (mm Hg)	138.7	*20.5*	135.9	*22.0*
Diastolic Pressure (mm Hg)	86.9	*11.1*	83.4	*11.2*
Serum Total Cholesterol (mg/dl)	225.4	*44.4*	229.0	*44.6*
Serum HDL-Cholesterol (mg/dl)	50.4	*14.0*	60.0	*15.4*
Serum Non HDL-Cholesterol (mg/dl)	174.8	*45.0*	168.9	*45.0*
(Total / HDL) Cholesterol	4.8	*1.6*	4.1	*1.3*
(Non HDL / HDL) Cholesterol	3.8	*1.6*	3.1	*1.3*
Body Mass Index (BMI) (kg/m^2)	26.7	*3.7*	27.2	*4.8*
BMI (kg/m^2) [Current Smokers]	26.3	*3.7*	26.1	*4.3*
BMI (kg/m^2) [Never/Past Smokers]	27.0	*3.6*	27.6	*5.0*
Plasma Fasting Glucose (mg/dl)	98.0	*25.0*	92.6	*22.7*
Cigs^ /Day (All)	6.9	*10.8*	3.2	*7.0*
Cigs^/Day (Current Smokers only)	17.3	*10.7*	12.5	*8.5*
Waist circumference (cm)	93.2	*9.9*	84.3	*11.2*
Hip circumference (cm)	100.2	*7.7*	102.2	*9.7*
Waist/Hip	0.9	*0.1*	0.8	*0.1*
Serum LDL-Cholesterol (mg/dl)	143.6	*37.9*	145.8	*40.3*
Triglycerides (mg/dl)	152.2	*107.6*	115.5	*67.5*

Baseline descriptive statistics, men and women ages 35-69 years, free of previous CVD (2)

Variables		Men	Women
		percent	percent
Diabetes		5.9	3.8
Hypertension Treatment		9.4	14.5
Family History of CVD		26.5	27.2
Cigarette Smoking			
Never		25.5	61.4
Past		34.5	12.7
Current		40.1	25.9
Cigarette Smoking			
Never/Past		60.0	74.1
< 10		8.5	9.8
10-19		11.5	8.5
≥ 20		20.0	7.6
Blood Pressure -- SBP/DBP			
Normal		13.8	23.1
Prehypertension		30.8	30.6
Hypertension-Stage I		29.7	21.8
Hypertension-Stage II	***or treated***	25.7	24.5

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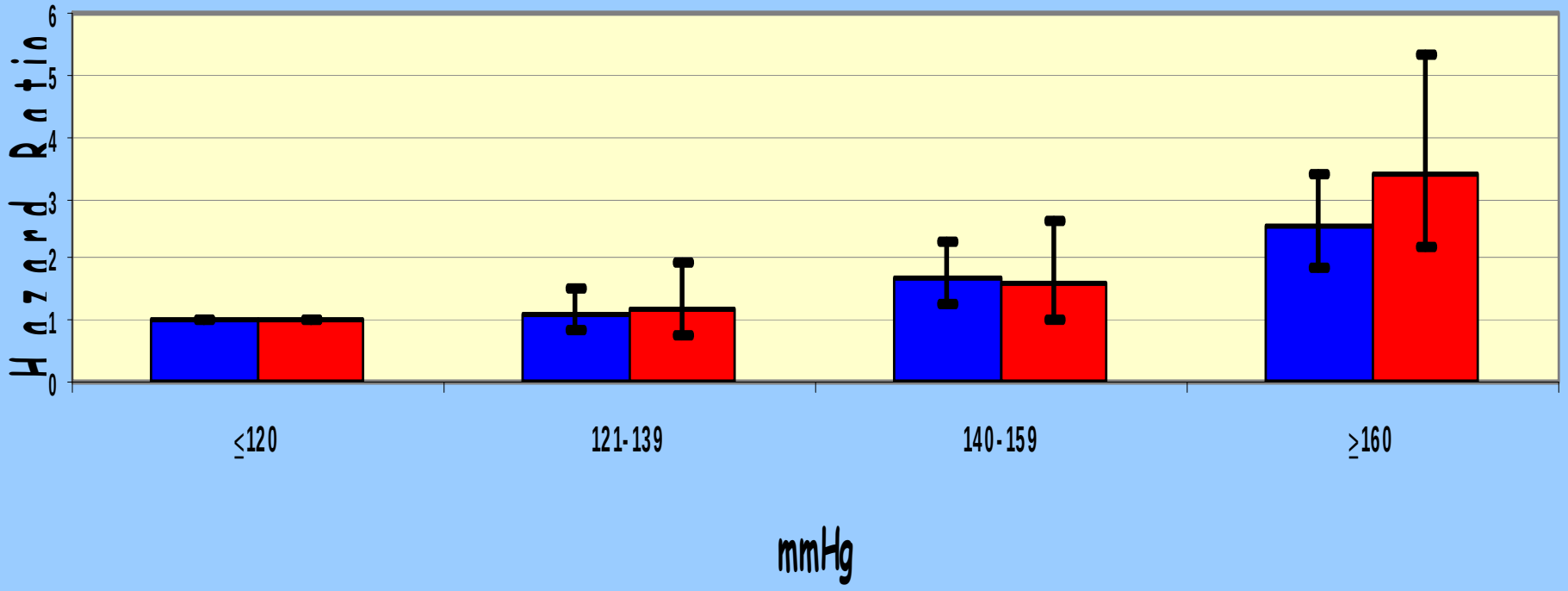
Partial correlation coefficients and *p*-value controlled by age and gender, previous CVD free;
Men & Women ages 35-69 years

Controlling for AGE & GENDER, including GLYCEMIA
N = 12493

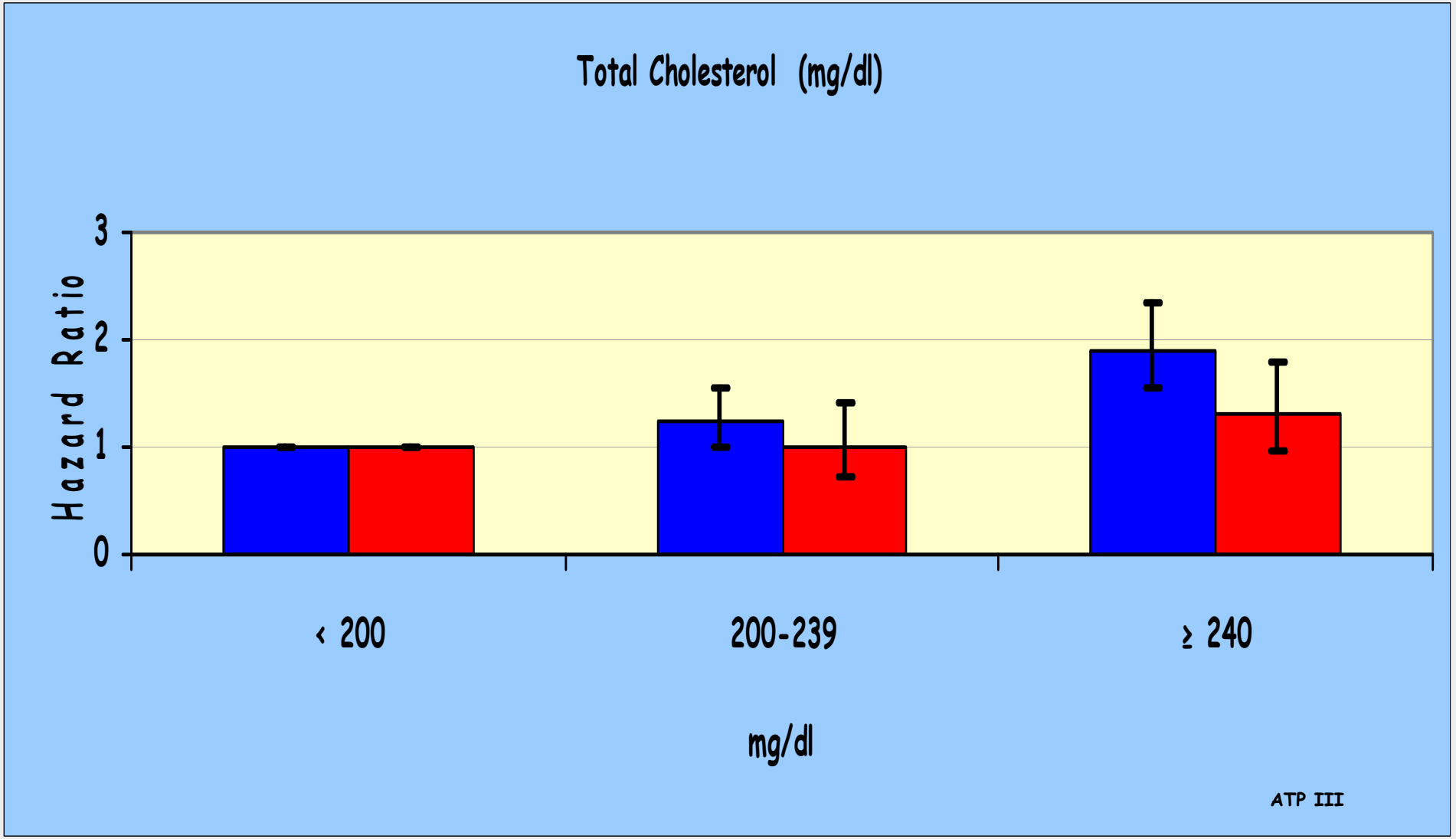
	SBP	DBP	T-CHOL	HDL	CHOL-HDL	CHOL/HDL	BMI	CIGS/DAY	GLY
SBP	1	0.6984	0.1002	-0.0392	0.1117	0.0895	0.247	-0.0537	0.1575
		P= .000	*P= .000*	*P= .000*	*P= .000*	*P= .000*	*P= .000*	*P= .000*	*P= .000*
DBP		1	0.1152	-0.0678	0.136	0.1176	0.3046	-0.0771	0.0947
			P= .000	*P= .000*	*P= .000*	*P= .000*	*P= .000*	*P= .000*	*P= .000*
T-CHOL			1	0.1246	0.9447	0.5166	0.0695	0.0571	0.0394
				P= .000	*P= .000*	*P= .000*	*P= .000*	*P= .000*	*P= .000*
HDL				1	-0.2075	-0.7047	-0.2949	-0.0819	-0.0827
					P= .000	*P= .000*	*P= .000*	*P= .000*	*P= .000*
CHOL-HDL					1	0.7421	0.166	0.0833	0.0662
						P= .000	*P= .000*	*P= .000*	*P= .000*
CHOL/HDL						1	0.268	0.1342	0.1026
							P= .000	*P= .000*	*P= .000*
BMI							1	-0.0505	0.1666
								P= .000	*P= .000*
CIGS/DAY								1	-0.0194
									P= .030
GLY									1

Men and Women 35-69 years

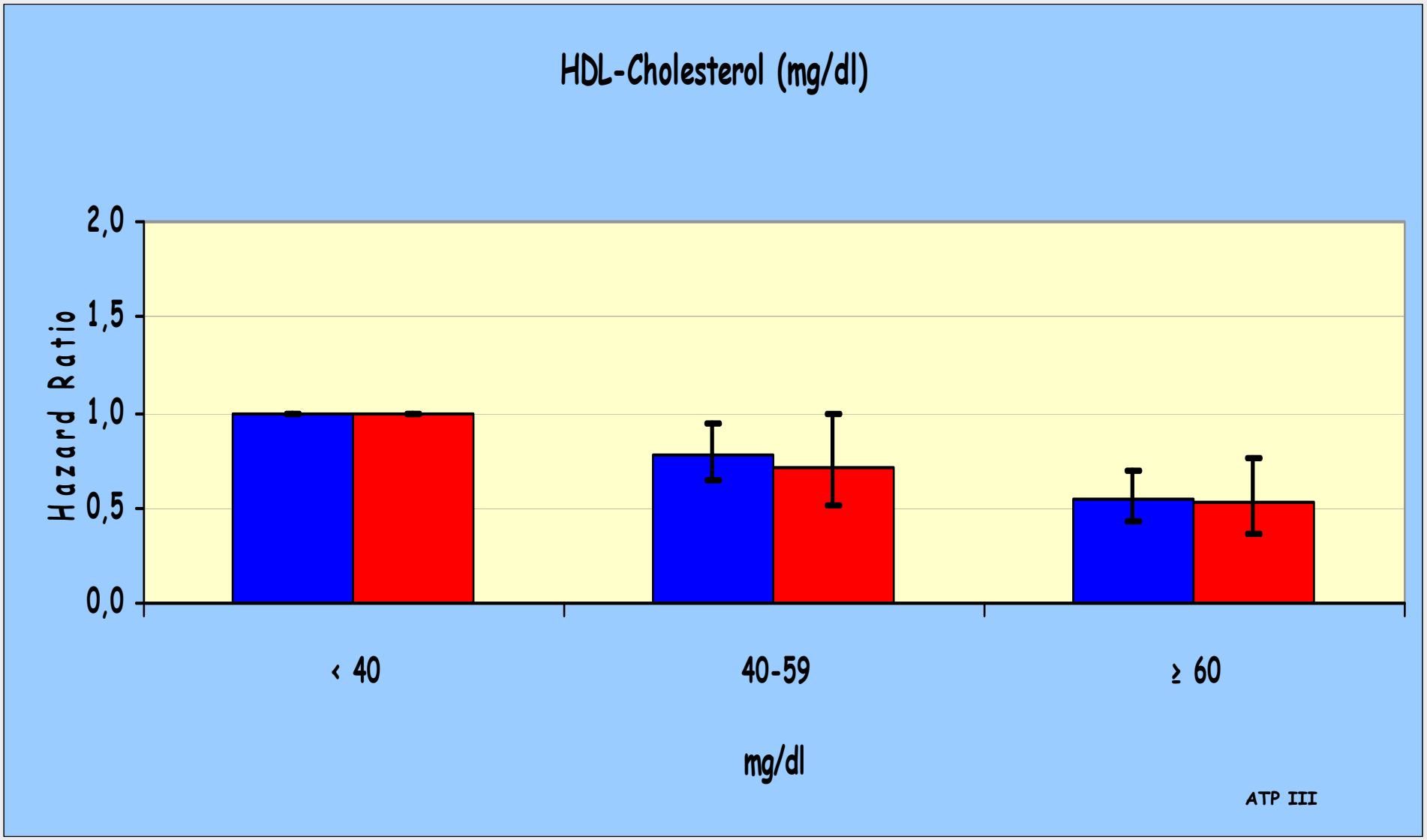


JNC 7 - 2003

Men and Women, 35-69 years



Men and Women, 35-69 years



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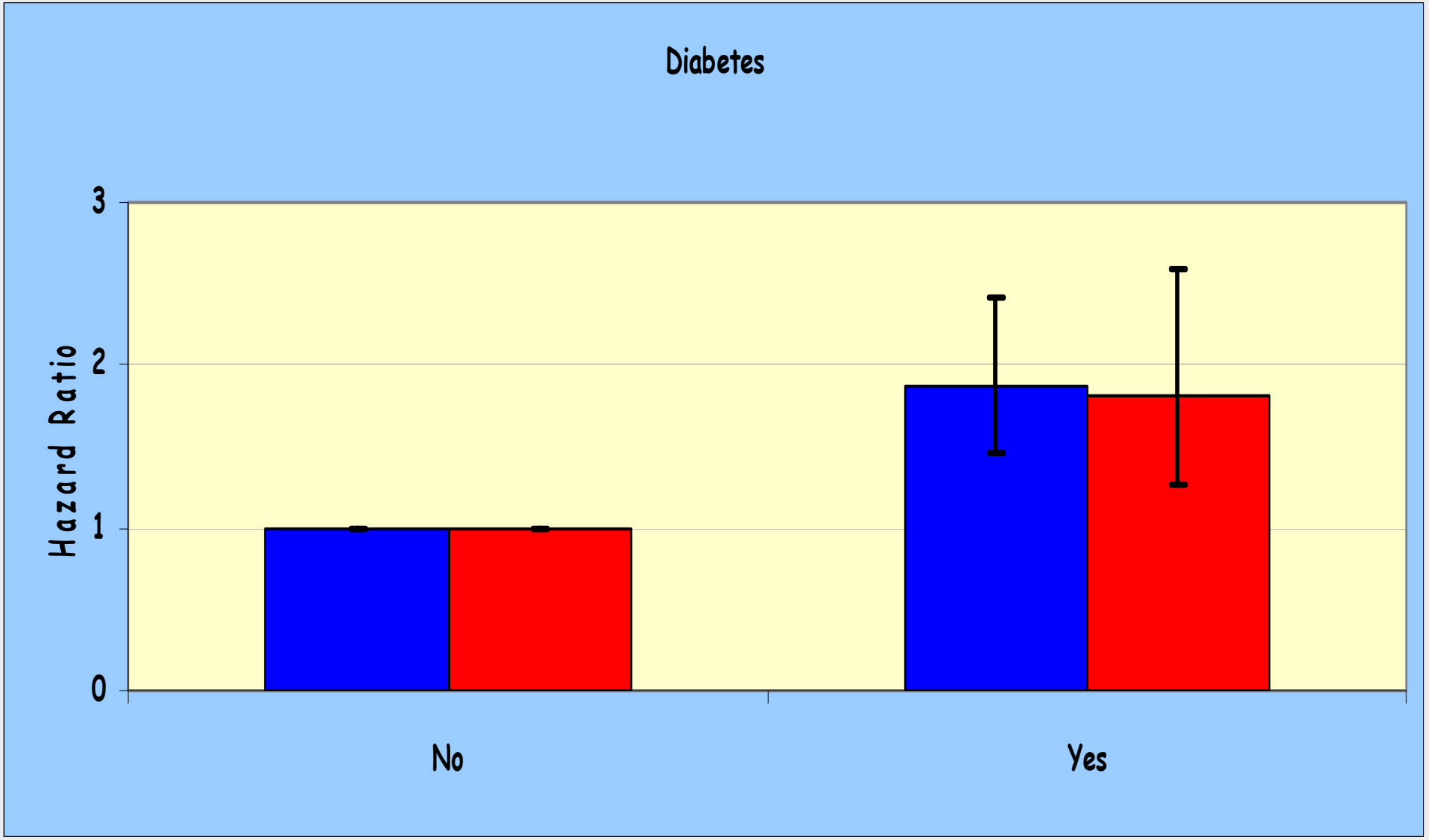
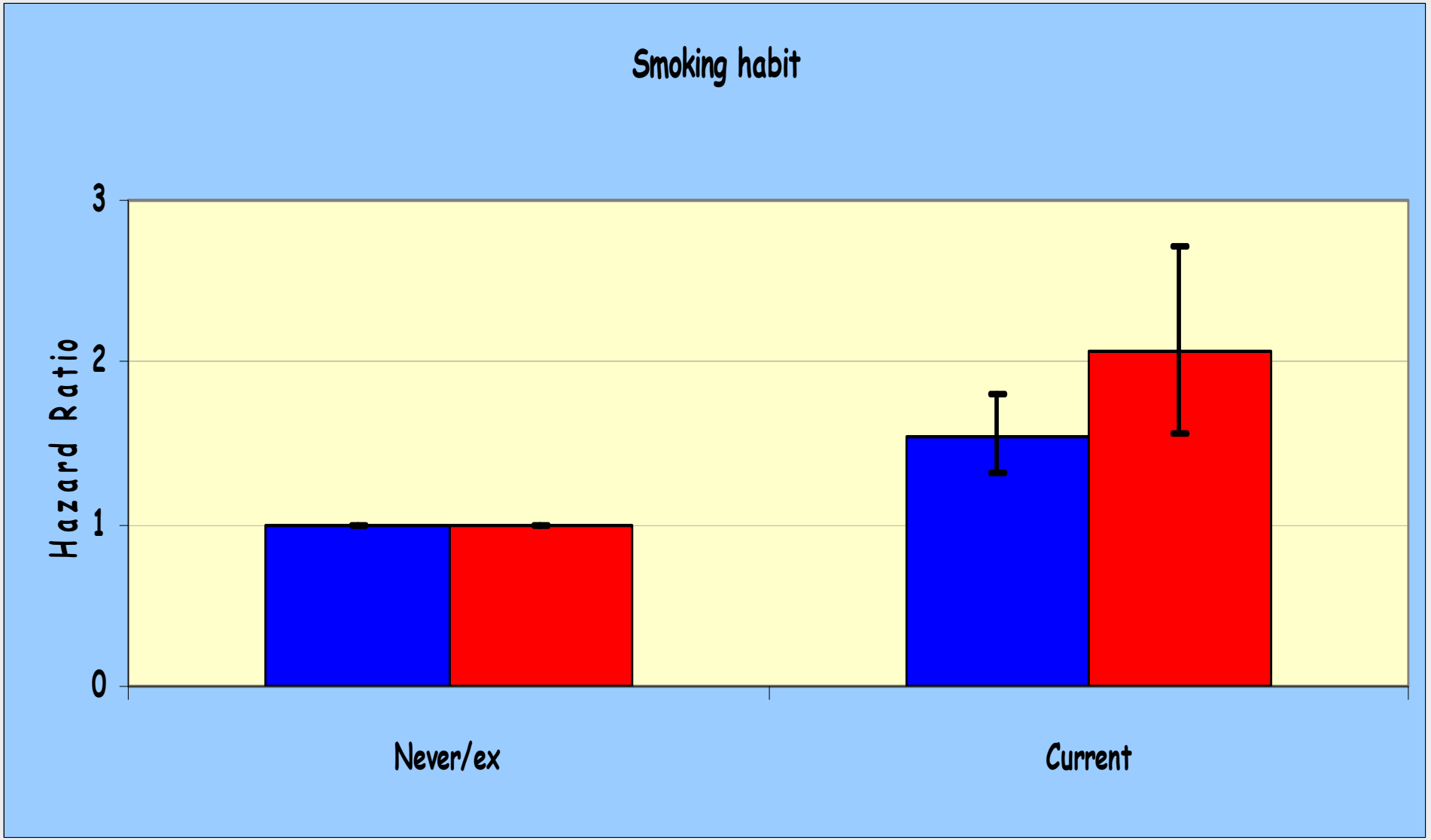
Men and Women, 35-69 years



Men and Women, 35-69 years



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'Best model' for predicting CVD even within 10 years

	10-year CVD risk MEN			10-year CVD risk WOMEN		
	β	More adverse level HR	More favourable level HR	β	More adverse level HR	More favourable level HR
AGE, years	0.076	2.01	0.50	0.079	1.95	0.51
Systolic BP, mmHg	0.013	1.31	0.76	0.016	1.41	0.71
T-CHOL mg/dl	0.006	1.31	0.76	0.003	1.14	0.88
HDL-CHOL mg/d	-0.013	1.20	0.83	-0.015	1.26	0.80
SMOKING, yes vs no	0.508	1.66	0.60	0.773	2.17	0.46
DIABETES, yes vs no	0.462	1.59	0.63	0.339	1.40	0.71
TREATMENT, yes vs no	0.490	1.63	0.61	0.590	1.80	0.55
G(μ)	6.583			6.016		
Survival at baseline, S(t)	0.953			0.989		

Study limitations

- ✓ Only one measure of the risk factors
- ✓ Cohorts enrolled in different time periods
- ✓ Old diagnostic criteria for event validation

Improvements over previous studies

- ✓ cohorts enrolled between 80s and 90s
- ✓ end-points included fatal and non fatal, coronary and cerebrovascular events and revascularizations
- ✓ women are involved
- ✓ cohorts are distributed throughout Italy (North, Centre and South)
- ✓ International standardized validation criteria

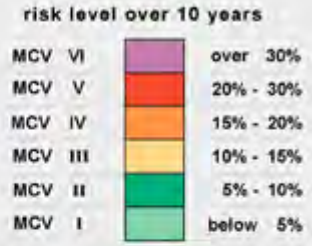
Cardiovascular risk chart

diabetic men

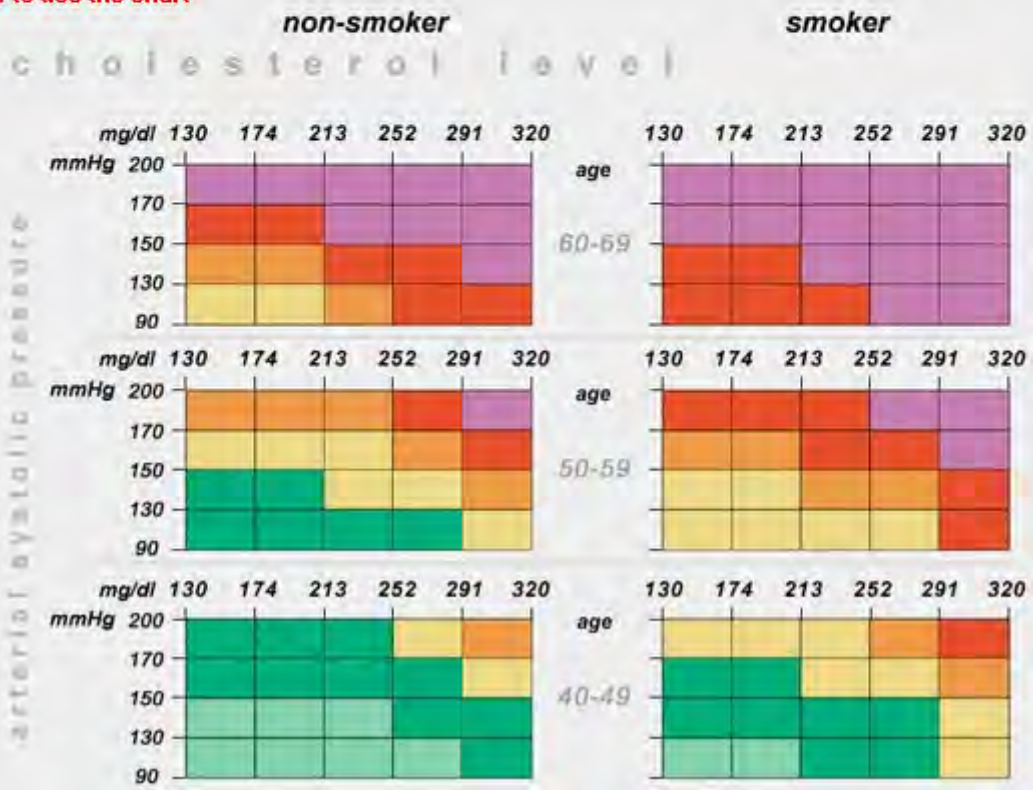
Cardiovascular risk over 10 years

How to use the chart

- Choose smoker / non smoker section.
- Select your age decade.
- Go to the level corresponding to your arterial systolic blood pressure and serum cholesterol.
- Each colour corresponds to a level of risk which is explained by the key on the side.



how to use the chart



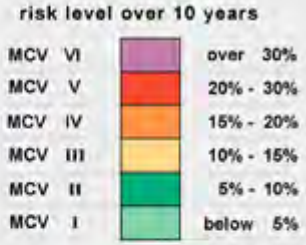
Cardiovascular risk chart

non-diabetic men

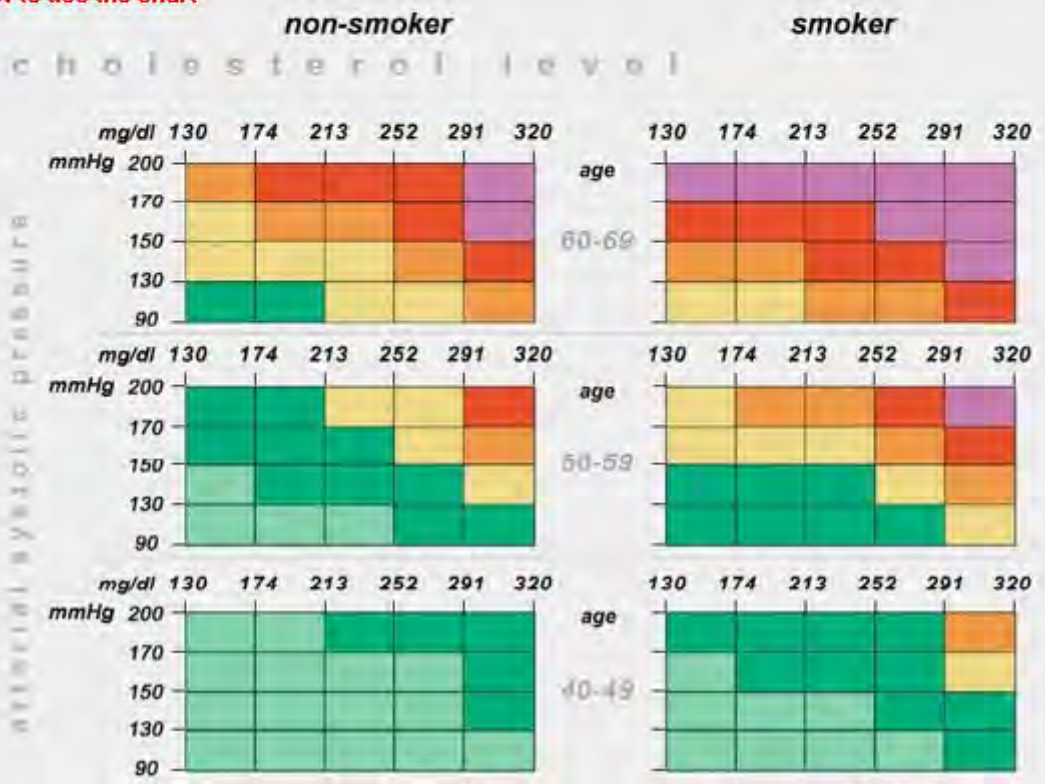
Cardiovascular risk over 10 years

How to use the chart

- Choose smoker / non smoker section.
- Select your age decade.
- Go to the level corresponding to your arterial systolic blood pressure and serum cholesterol.
- Each colour corresponds to a level of risk which is explained by the key on the side.



how to use the chart



Cardiovascular risk chart

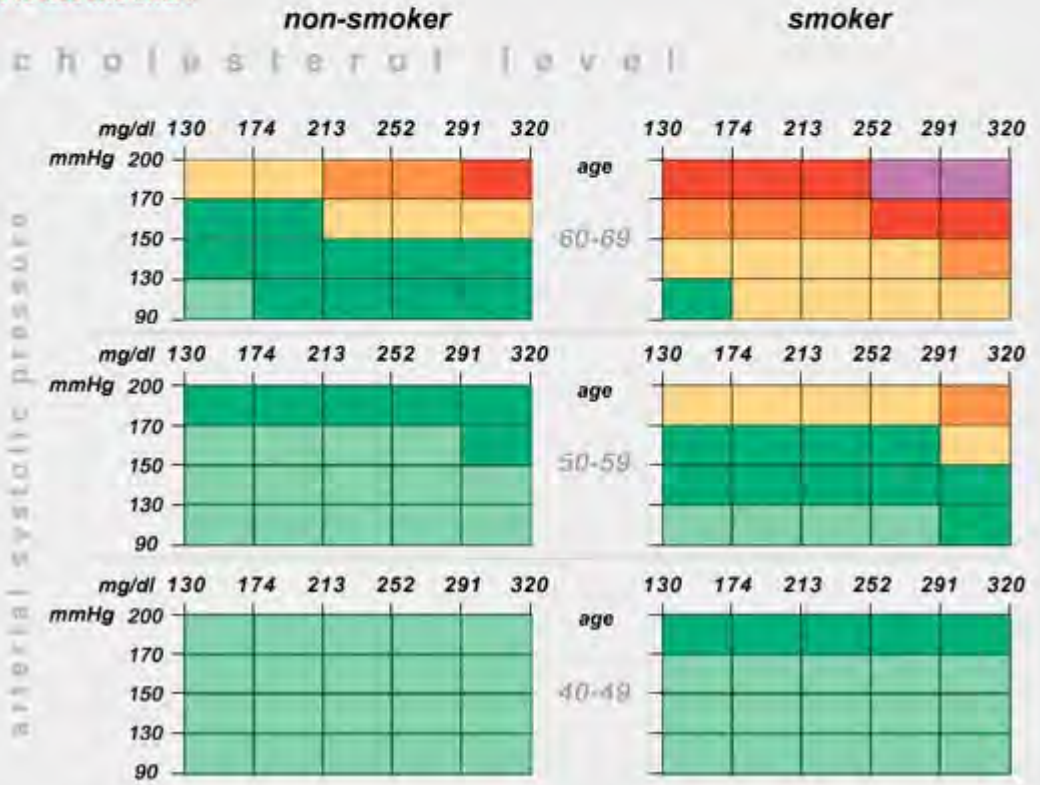
diabetic women

Cardiovascular risk over 10 years

How to use the chart

- Choose smoker / non smoker section.
- Select your age decade.
- Go to the level corresponding to your arterial systolic blood pressure and serum cholesterol.
- Each colour corresponds to a level of risk which is explained by the key on the side.

how to use the chart



Cardiovascular risk chart

non-diabetic women

Cardiovascular risk over 10 years

How to use the chart

- Choose smoker / non smoker section.
- Select your age decade.
- Go to the level corresponding to your arterial systolic blood pressure and serum cholesterol.
- Each colour corresponds to a level of risk which is explained by the key on the side.

how to use the chart

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Software 'CUORE.exe'

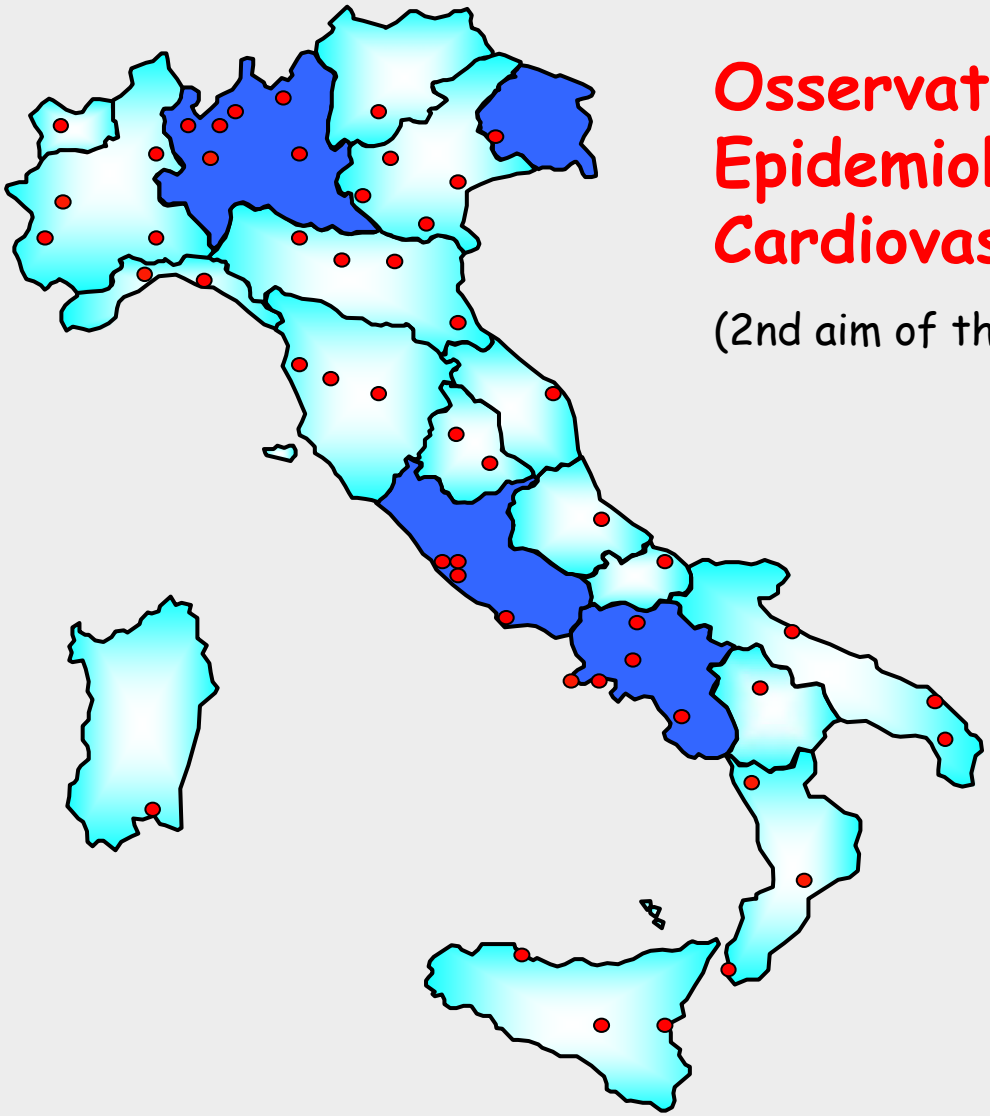
Benefits from using risk charts in clinical practice

- Simple tools
- Respect the multifactorial aetiology of cardiovascular diseases
- Provide multiple options of treatment
- Make assessment more objective and comparable over time
- Cost/benefit ratio can be calculated

…..future

Risk chart updating – Istituto Superiore di Sanità, Rome

- New cohorts whose baseline is to be found in 1990s have been enrolled,10.711 men and 14.870 women ages 35-74 years
- Vital status of all cohorts has been checked. Death certificates have been collected and coded
- Non-fatal events are being identified
- Suspet fatal events need to be validated



Osservatorio Epidemiologico Cardiovascolare

(2nd aim of the Progetto CUORE)

…..and then?

Progetto RIACE

RIschio Assoluto Cardiovascolare Epidemiologia

Agenzia Italiana del Farmaco

The RIACE project was launched by the Italian Medicines Agency following the decision that statin reimbursement in primary prevention is correlated to global absolute risk assessment

Aims

- ✓ distributing the risk charts to GPs
- ✓ training GPs to use global absolute risk as a tool for the identification of high risk individuals
- ✓ promoting rational prescription of drugs useful to the prevention of global absolute cardiovascular risk
- ✓ training GPs to counsel patients against smoking and to recommend a regular physical activity and an healthier diet and lifestyle

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La Carta del rischio cardiovascolare nella pratica clinica

www.cuore.iss.it

…..and then?

Agreement between Italian government and regions Cernobbio 2004

Active prevention plan – health priorities (national preventive plan 2005-2007):

1. Cardiovascular risk
2. Complications of diabetes
3. Oncological Screenings
4. Vaccination

…..and then?

Italian Ministry of Health

Centre of Disease Control

Progetto CUORE – 2005-2006

Aims

To implement of global absolute risk assessment

To promote and support at regional level preventive activities in order to reduce risk factors (population and individual strategies)

Conclusions

The assessment of absolute risk is currently accepted as a clinical decision aid

If absolute risk is misclassified, part of the population will be inappropriately elected for medical treatment, therefore charts and scores need to be based on local updated epidemiological data

A cloose cooperation among Ministry of Health, Italian Medicines Agency, Institute of Health, Federation of Cardiologists and Italian College of General Practitioners is the greatest step forward national disease prevention strategies

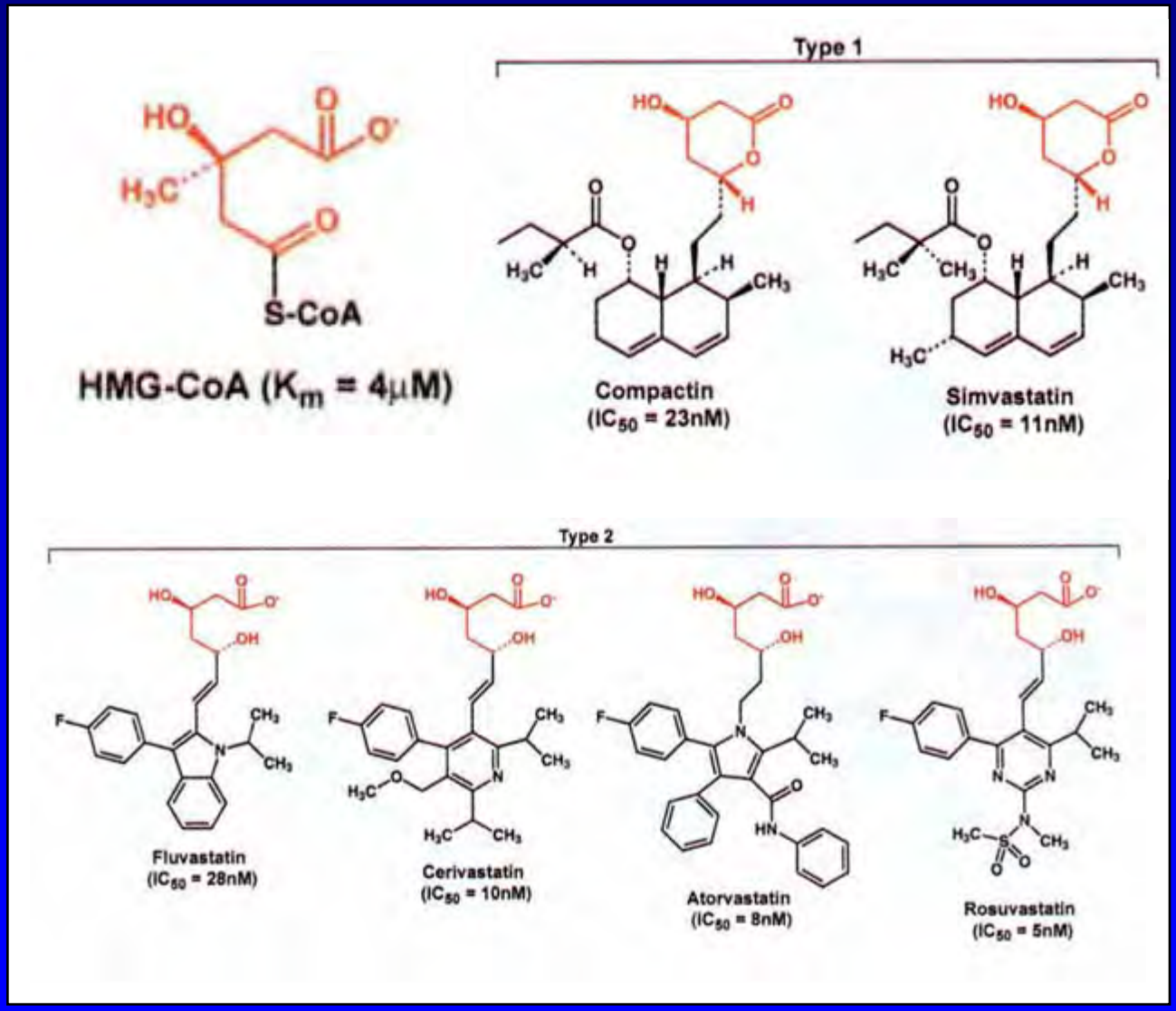
Statins: just a cholesterol lowering effect ?

Prof. P. Pauletto

Dip. di Medicina Clinica e Sperimentale
Università degli Studi di Padova

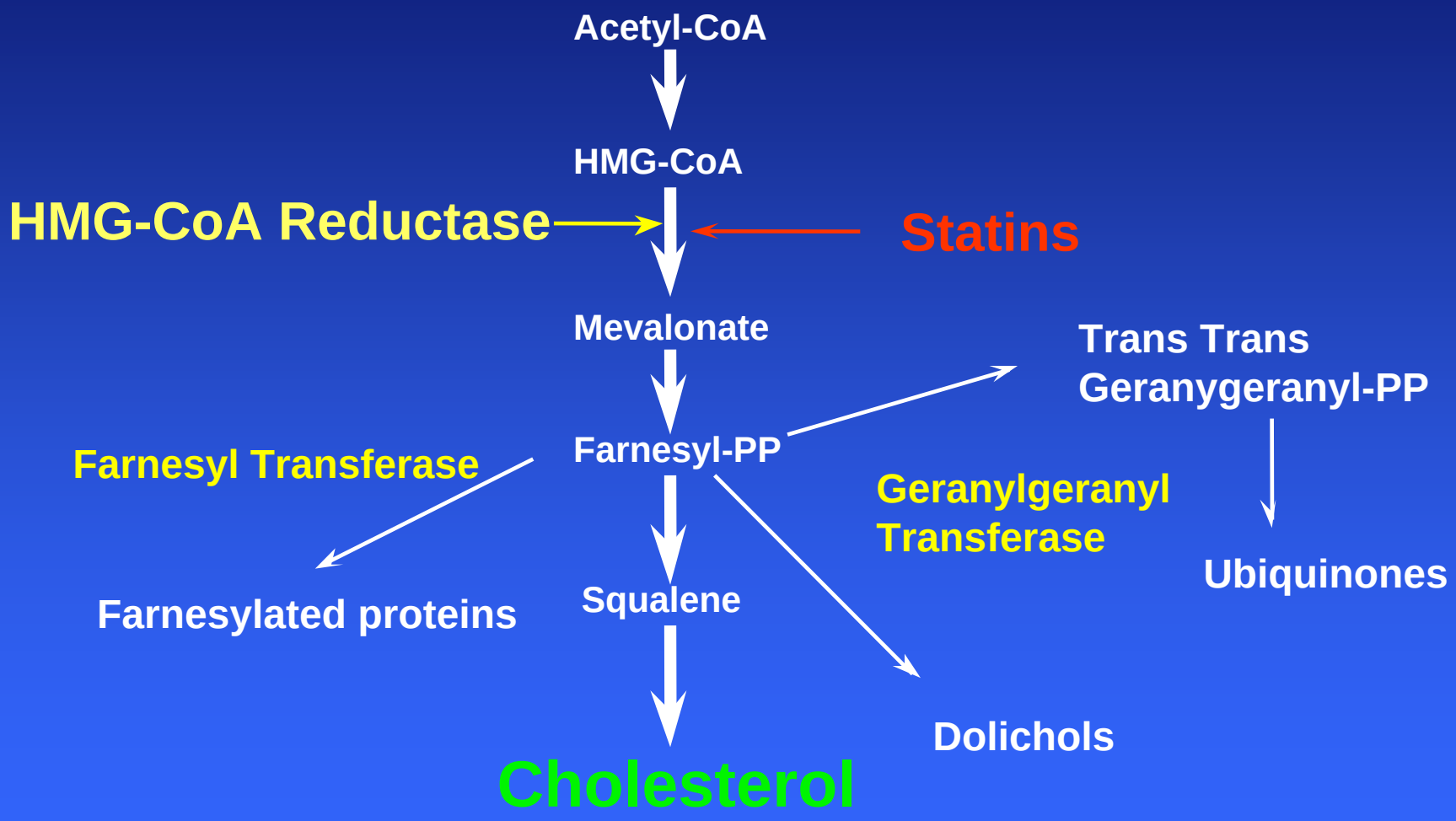
U.O. di Medicina Interna I^
U.L.S.S. n° 9, Ospedale di Treviso

Structural Formulas of HMG-CoA and of some Type 1 and Type 2 Statins



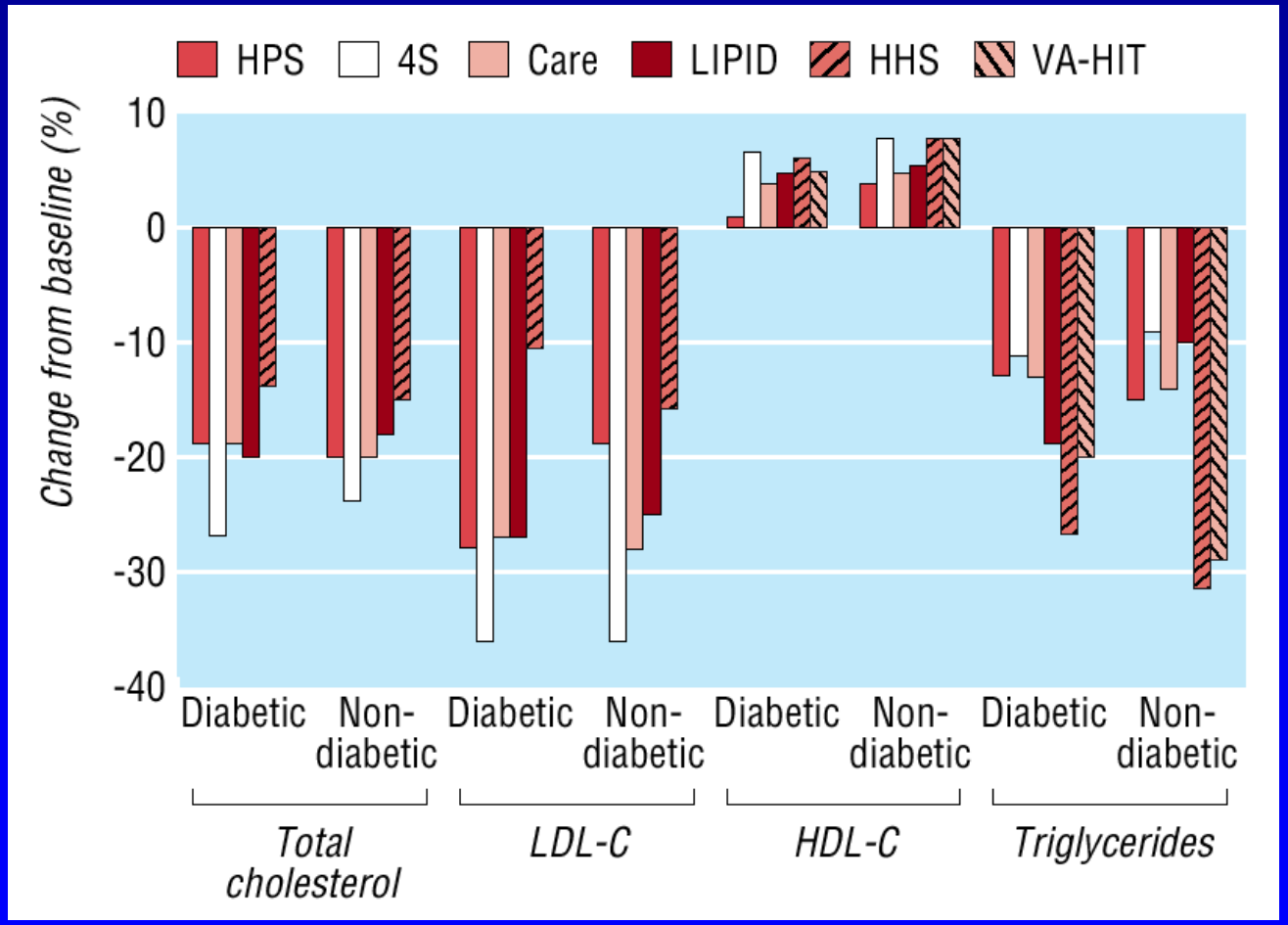
ES Istvan, J Deisenhofer *Science* 2001; 292: 1160-1164

The mevalonate pathway



Change in blood lipid concentrations

(no data for total cholesterol were available in VA-HIT)



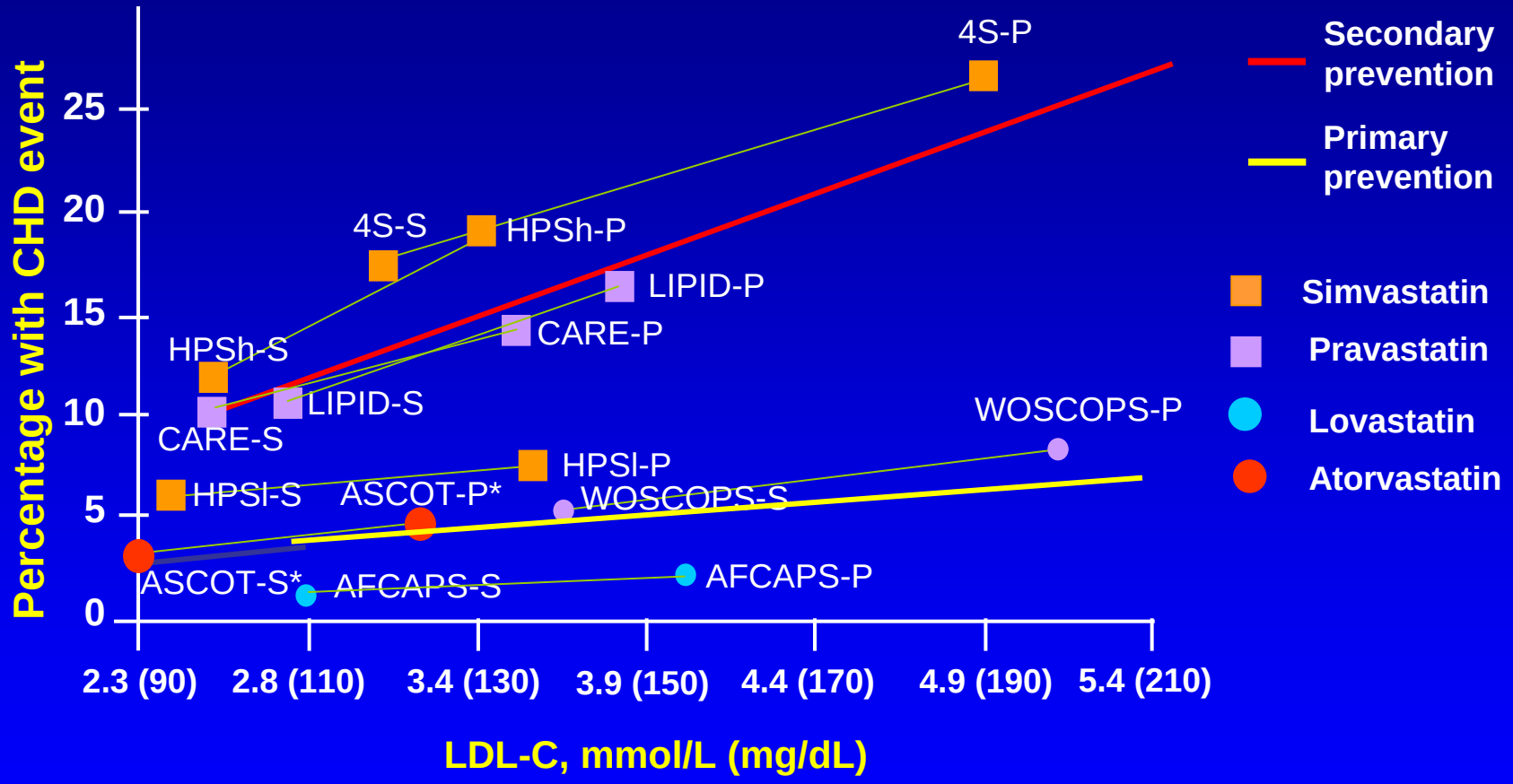
João Costa, et al. BMJ; 2006;332:1115-1124

Number needed to treat and benefit for 1000 patients

	DM patients	Non-DM patients	ALL
Primary prevention			
Major coronary event	37 (24 to 75)	47 (35 to 73)	44 (33 to 64)
Secondary prevention			
Major coronary event	15 (11 to 24)	17 (14 to 20)	16 (14 to 19)

João Costa, et al. BMJ; 2006;332:1115-1124

Landmark Statin Trials: LDL-C Levels vs Events at 5 Years Follow-up

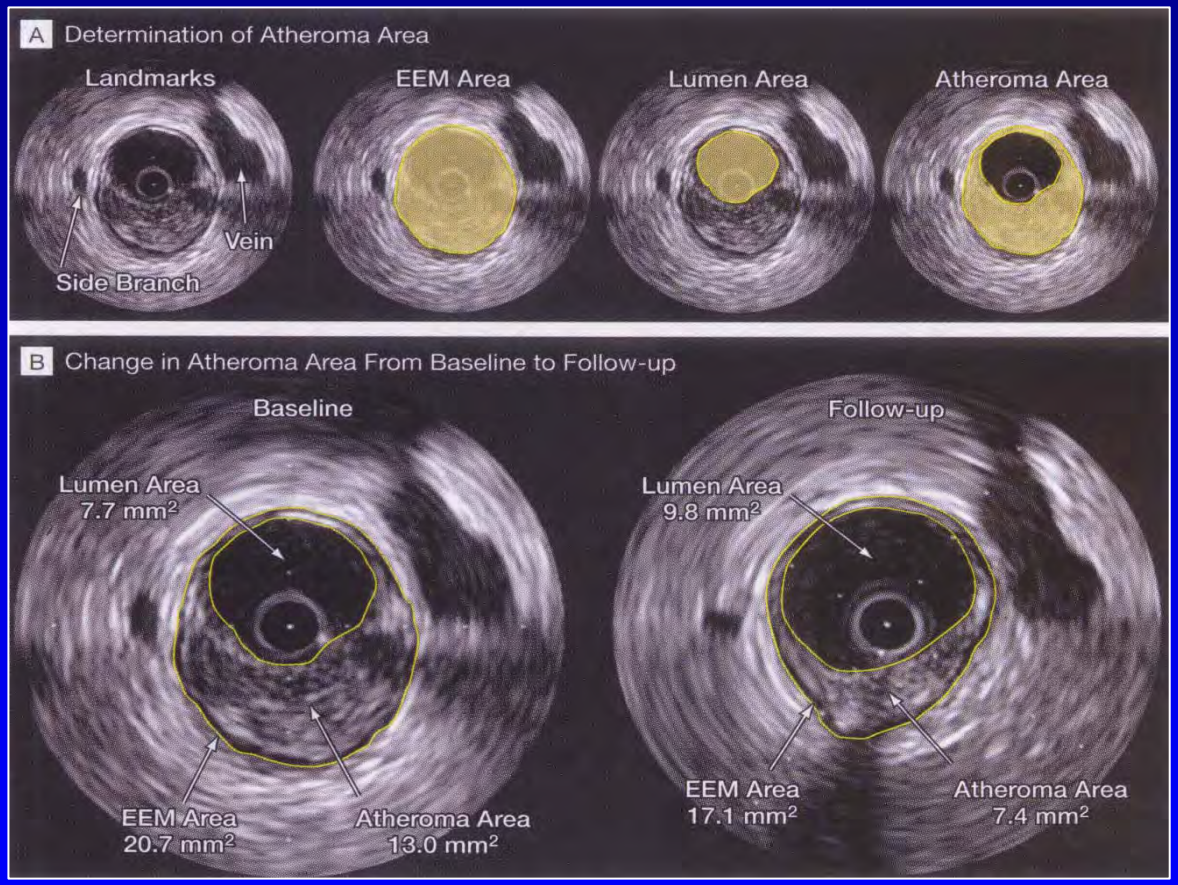


S=statin treated; P=placebo treated
* Extrapolated to 5 Years

Modified from Kastelein JJP. *Atherosclerosis.* 1999;143(suppl 1):S17-S21.

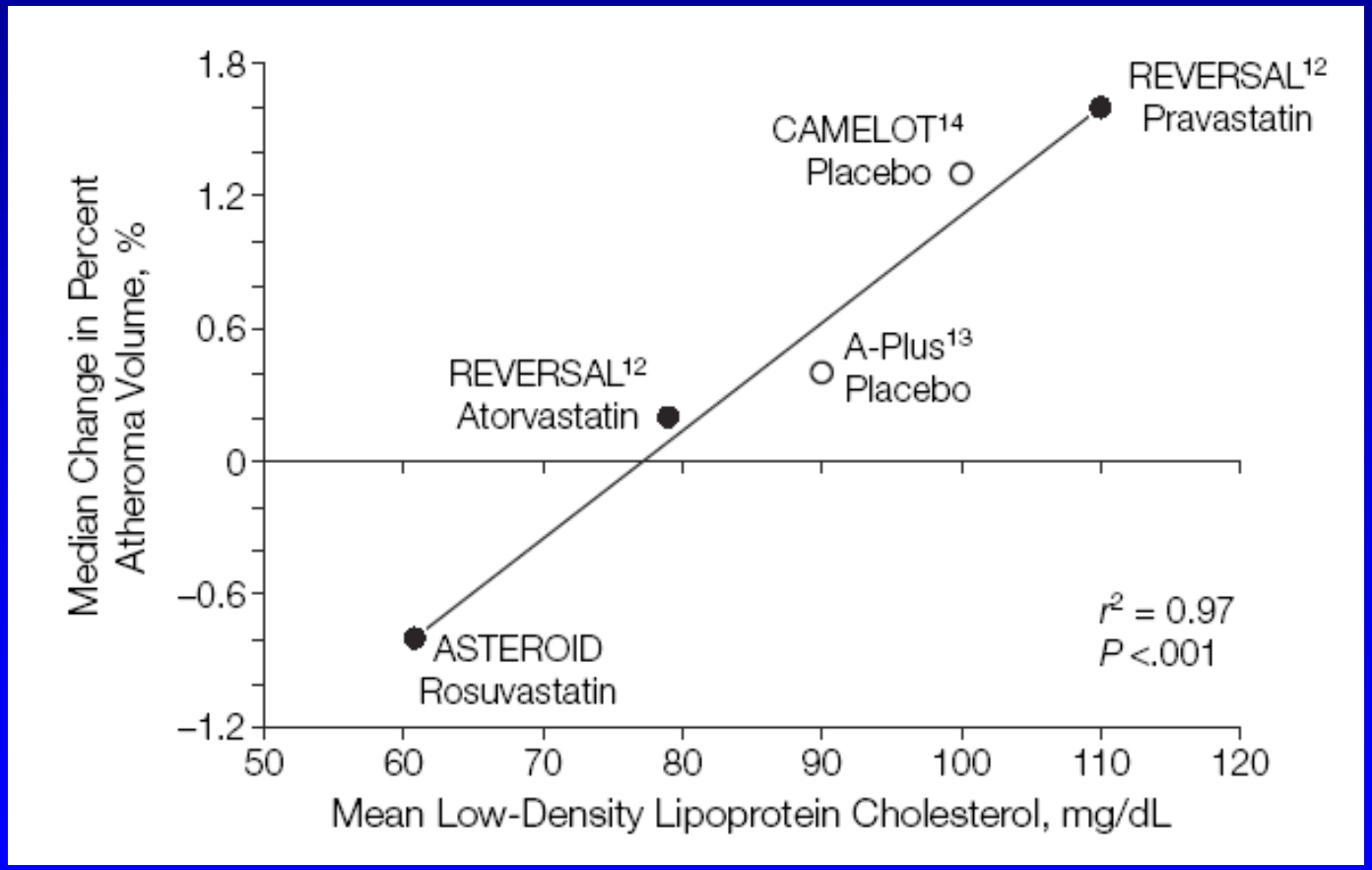
Intravascular Ultrasound Images at Baseline and Follow-up

— an example of plaque regression —



Nissen et al. JAMA 2004; 291: 1079

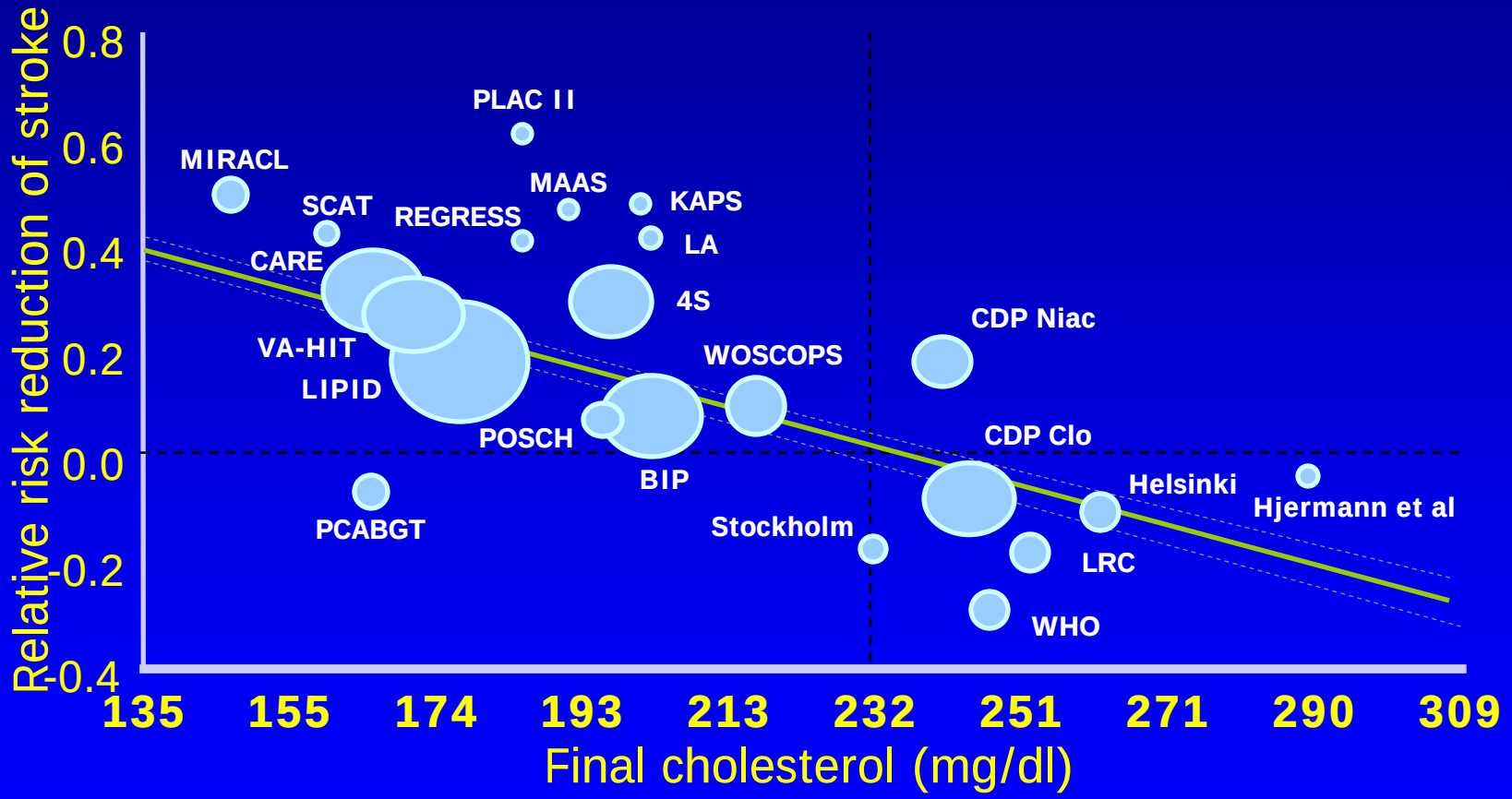
Relationship between mean LDL-C levels and median change in percent atheroma volume for several intravascular ultrasound trials



Nissen et al. JAMA 2006

“JUST A CHOLESTEROL-LOWERING EFFECT ?”

Relationship between final cholesterol level and effect of lipid-lowering therapies on stroke



"No epidemiological studies have assessed the correlation between cholesterol concentration as a continuous variable and the risk of incident strokes in a high-risk cohort selected on the basis of global CV risk approaches"

The Lancet 2004;3:271-278.

Mundy G. et al:

Stimulation of bone formation in vitro and in rodents by statins.

Science 1999;286:1946

Cummings SR, Bauer DC:

Do statins prevent both cardiovascular disease *and* fracture?

JAMA, 2000:283:1947

Jick H, et al:

Statins and the risk of dementia

Lancet 2000;356:1627

A STATIN-INDUCED BLOOD PRESSURE-LOWERING EFFECT ON ISCHEMIC STROKE ?

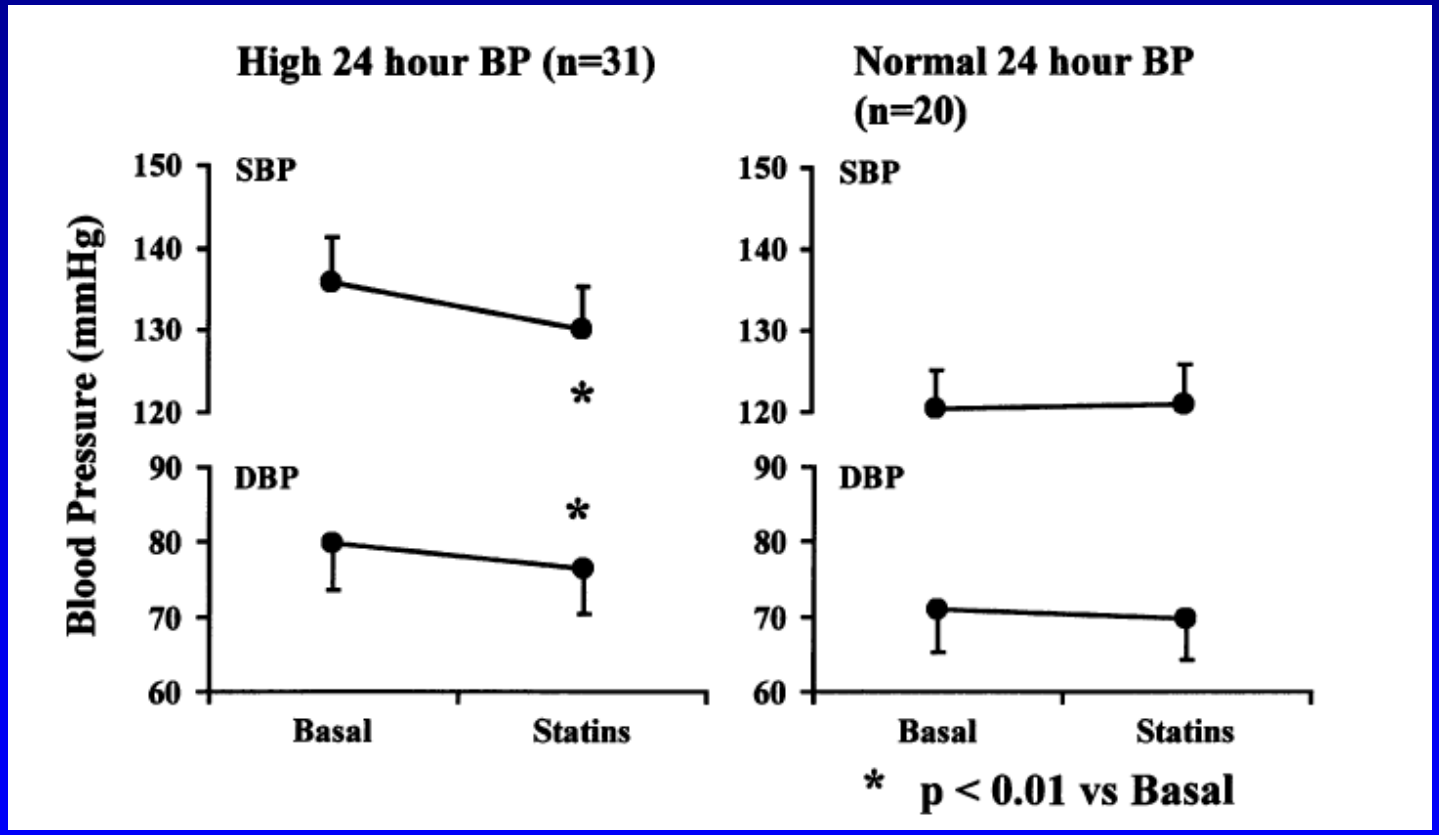
ORIGINAL ARTICLE

Lowering of Elevated Ambulatory Blood Pressure by HMG-CoA Reductase Inhibitors

Laura Terzoli, Luca Mircoli,‡§ Roberta Raco,* and Alberto U. Ferrari*†§*

Statins moderately but significantly lower blood pressure in patients with high (but not with normal) ambulatory blood pressure; the effect is confined to the daytime period and is unrelated to the extent of cholesterol lowering

Average 24-hour systolic and diastolic blood pressure values before and during statin treatment



Terzoli L et al. J Cardiovasc Pharmacol 2005

Non lipid-lowering effects of statins that may be associated with blood pressure reduction

- Restoration of endothelial dysfunction
- Increased nitric oxide synthesis
- Decreased synthesis of endothelin-1
- Decreased synthesis of aldosterone
- Decreased expression of type 1 angiotensin II receptors
- Decreased arterial stiffness
- Sympatho-inhibitory effects
- Up-regulation of NO synthesis

Use of statin in hypertensive patients: data from landmark statin trials

Primary prevention

WOSCOPS

AFCAPS/texCAPS

Secondary prevention

4S

CARE

LIPID

TNT

IDEAL

High-risk individuals

PROSPER

HPS

ASCOT-LLA

CARDS

Reasons for the absence of an antihypertensive effect associated with statin therapy in the landamark trials

- The influence of statin treatment on blood pressure was not included in the study design
- A beneficial effect on blood pressure in hypertensive patients could have been attenuated by a large numbers of normotensive partecipants, in whom no effect occurred
- Statins may have masked any beneficial effect of antihypertensive drugs

“JUST A CHOLESTEROL-LOWERING EFFECT ?”

The Effect of Early, Intensive Statin Therapy on Acute Coronary Syndrome

A Meta-analysis of Randomized Controlled Trials

Eddie Hulten, MD, MPH; Jeffrey L. Jackson, MD, MPH; Kevin Douglas, MD, MPH; Susan George, MD; Todd C. Villines, MD

Background: In addition to well-established secondary prevention benefits for atherosclerotic coronary artery disease, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are hypothesized to have short-term benefit in acute coronary syndrome (ACS), yet the data are inconsistent, with some trials underpowered to demonstrate therapeutic benefit. Our objective was to determine the effects of early, intensive statin therapy for ACS.

Data Sources: Studies found in the PubMed, MEDLINE, EMBASE, BIOSIS, SciSearch, PASCAL, and International Pharmaceutical Abstracts (IPA) databases and the Cochrane Controlled Trials Register published between January 1974 and May 2006.

Study Selection: Randomized controlled trials of statins begun within 14 days of hospitalization for ACS were included.

Data Extraction: Two investigators independently abstracted study quality, characteristics, and outcomes.

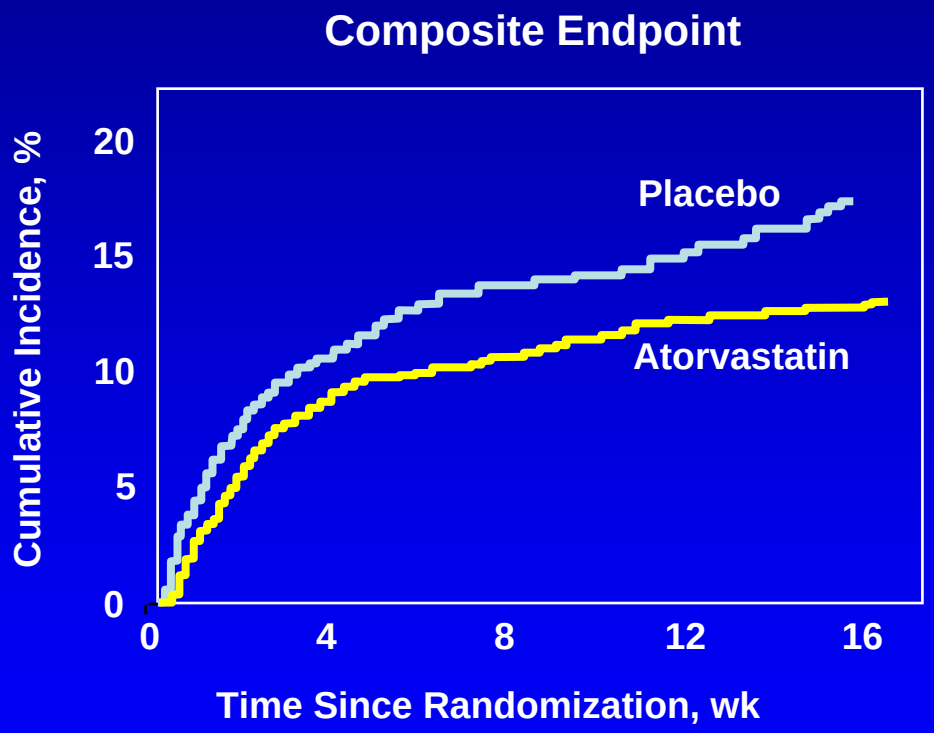
Data Synthesis: Thirteen randomized controlled trials published before May 2006 were available, involving 17 963 adults (median number of patients, 135; median follow-up, 6 months). Early, intensive statin therapy for ACS decreased the rate of death and cardiovascular events over 2 years of follow-up (hazard ratio, 0.81 [95% confidence interval, 0.77-0.87]) (Q_3=38.34; P<.001; I^2=95%). Survival curves revealed that this benefit begins to occur between 4 and 12 months, achieving statistical significance by 12 months. There was no evidence of publication bias, and sensitivity analyses did not identify a dominating study or study characteristic.

Conclusions: Early, intensive statin therapy reduces death and cardiovascular events after 4 months of treatment. The validity of this finding would be strengthened by an analysis of individual patient data.

Arch Intern Med. 2006;166:1814-1821

Results of the MIRACL Trial

— effect of atorvastatin (80mg/d) on primary endpoints —



LDL 135 vs 72

16% Risk Reduction
95% CI = 0.70 - 1.00
p = .048

Schwartz GG et al. JAMA 2001; 285:1711-18

Main effects of statin therapy other than plasma lipid regulation

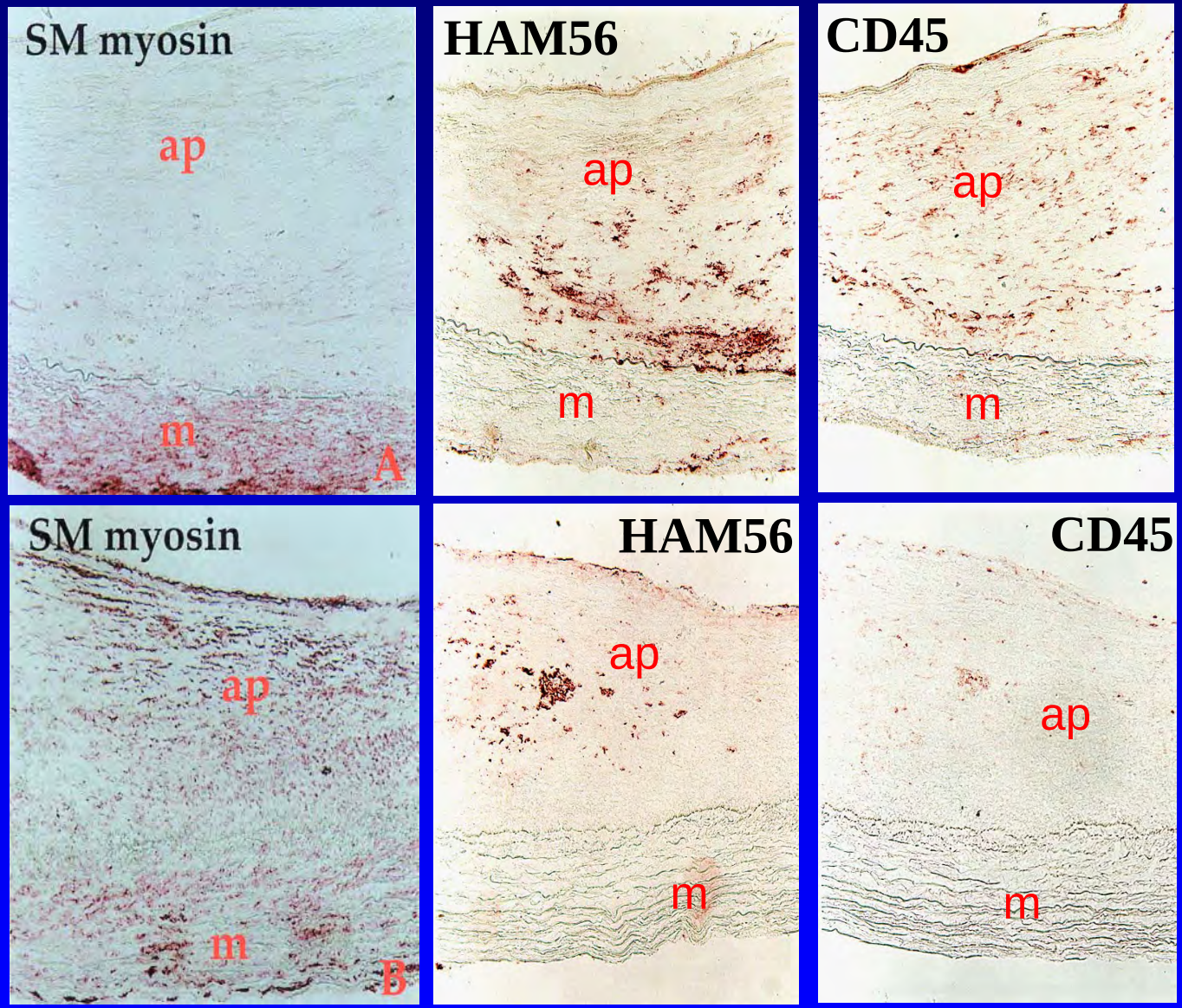
Inhibition of inflammation
Reduction in inflammatory markers
Inhibition of inflammatory cell migration
Reduction in cellular adhesion molecules

Impact on endothelial function
Increased endothelium-mediated arterial responsiveness
Increased NO bioavailability in endothelial cells
Inhibition of leukocyte and platelet adhesion

Antithrombotic effects
Reduced formation of fibrin
Inhibition of PAI-1 and increase in t-PA
Inhibition of matrix metalloproteinases

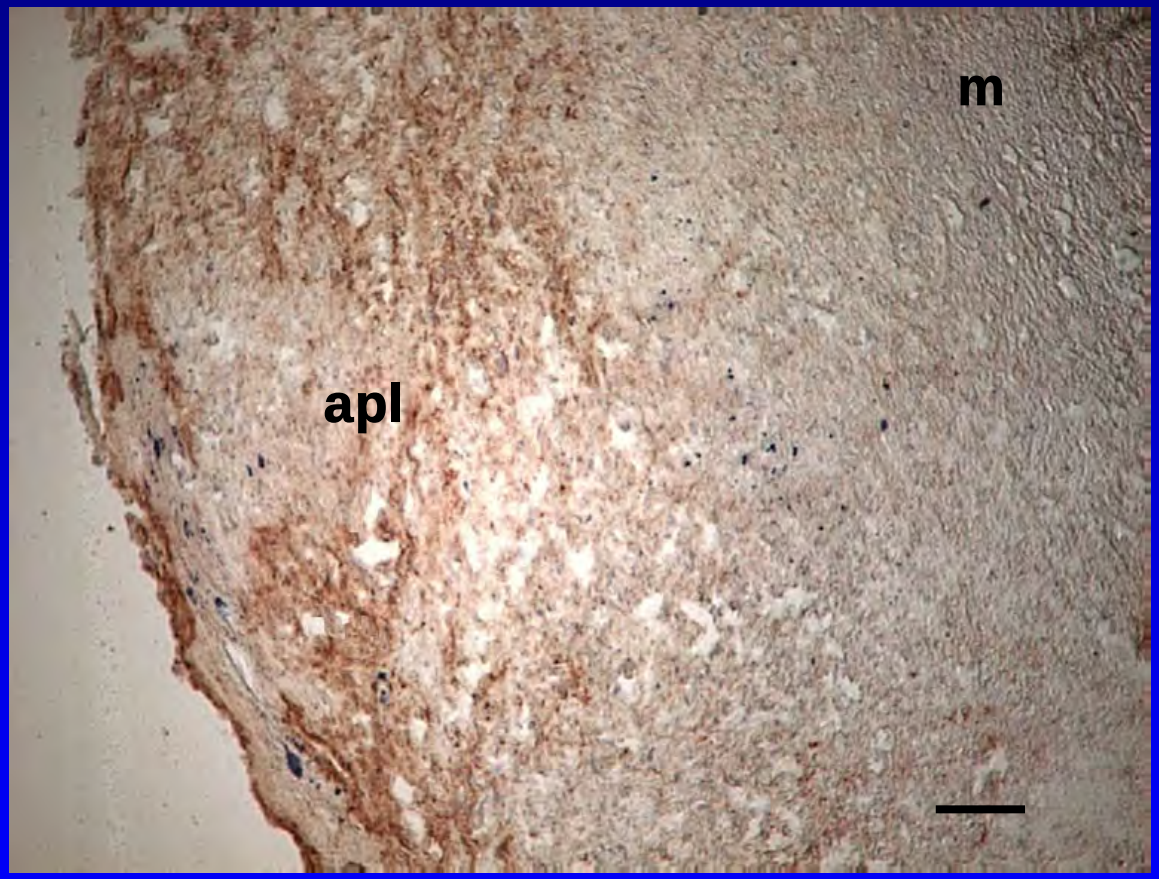
Modified from Gupta S, 2004

Features of Carotid Plaque - CARS



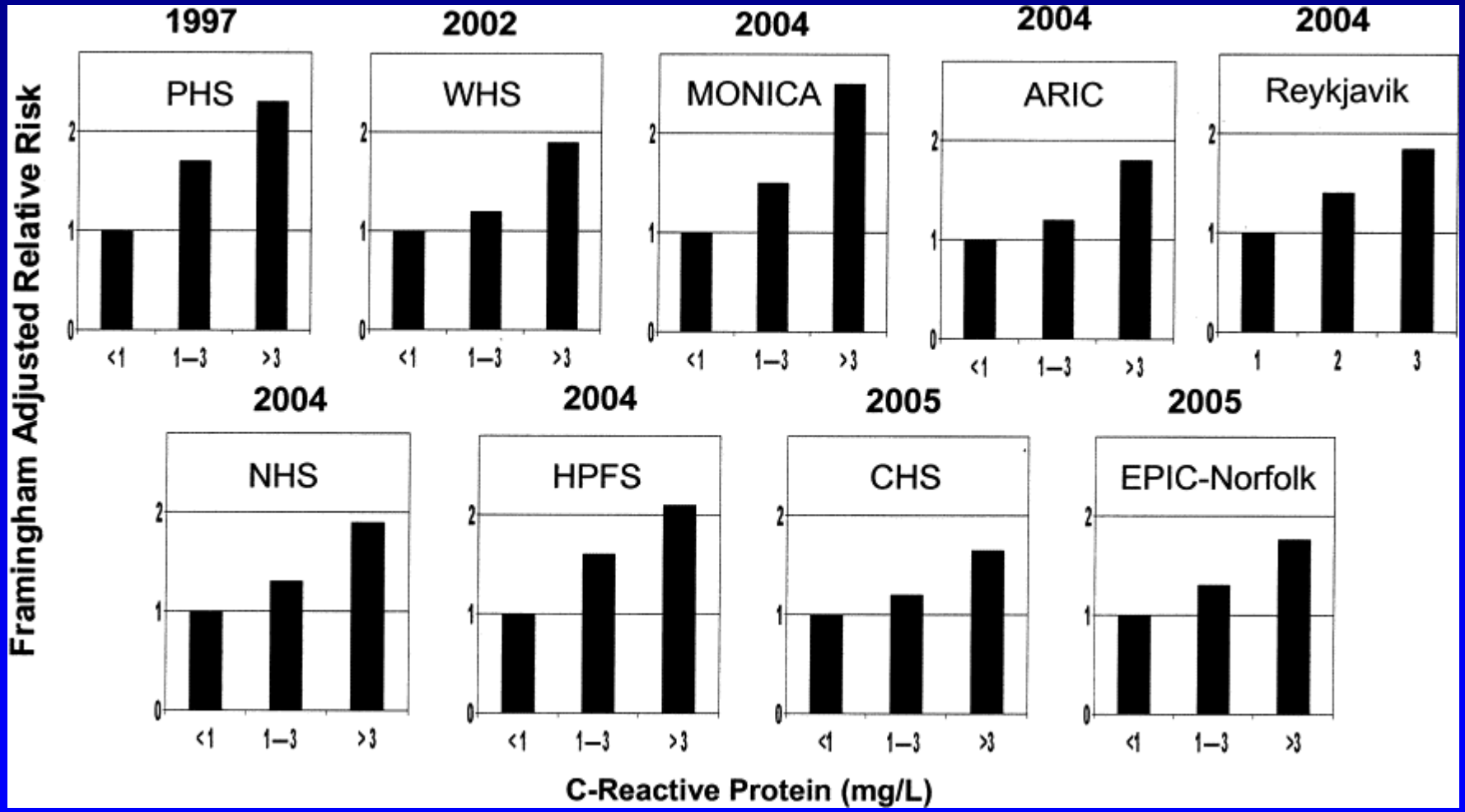
Pauletto P et al., *Circulation* 2000;102:771

Immunocytochemistry for CRP distribution within the atherosclerotic plaque



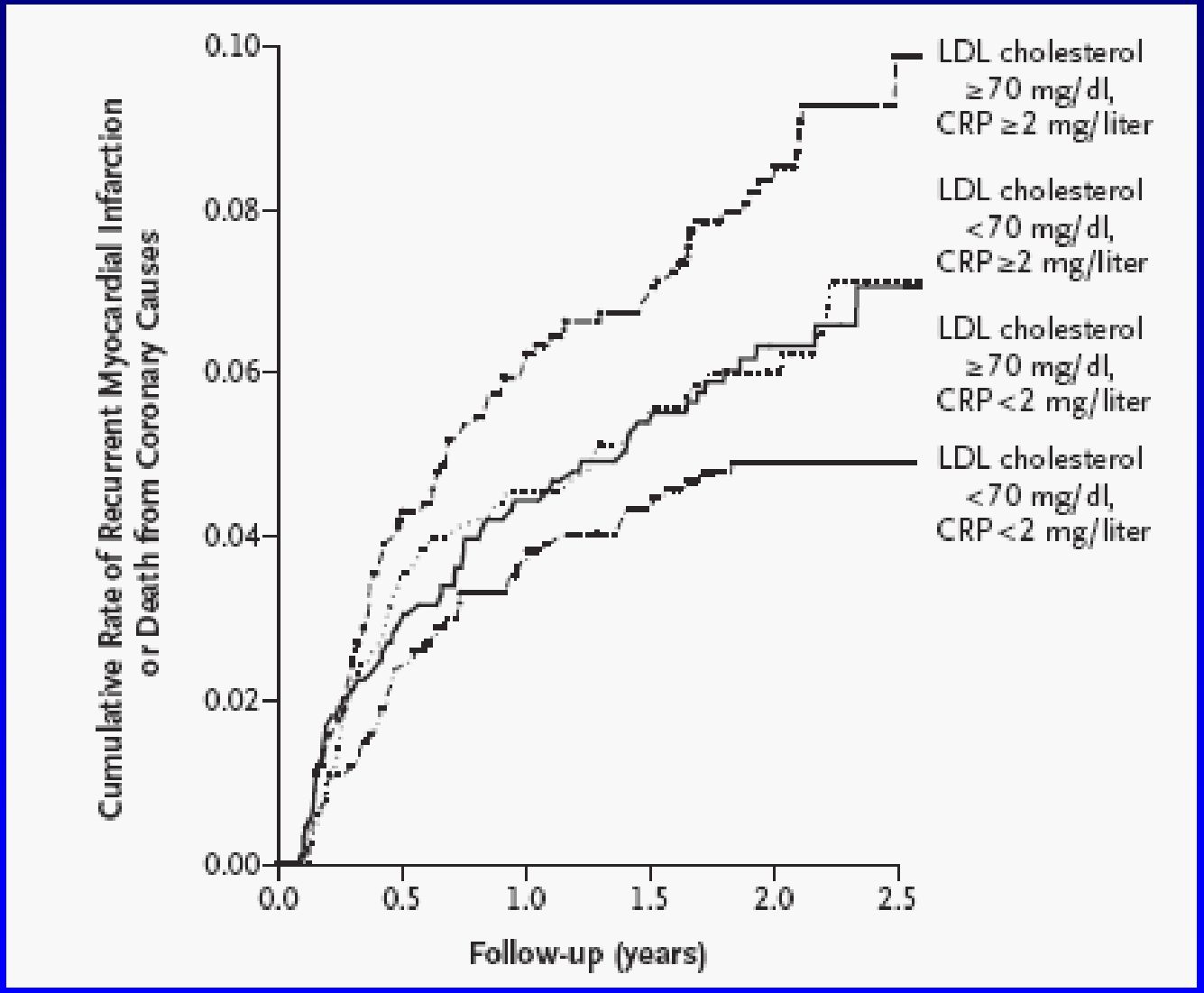
M. Rattazzi et al., 2004

CRP was an independent predictor of cardiovascular risk in 9 large prospective studies across diverse populations



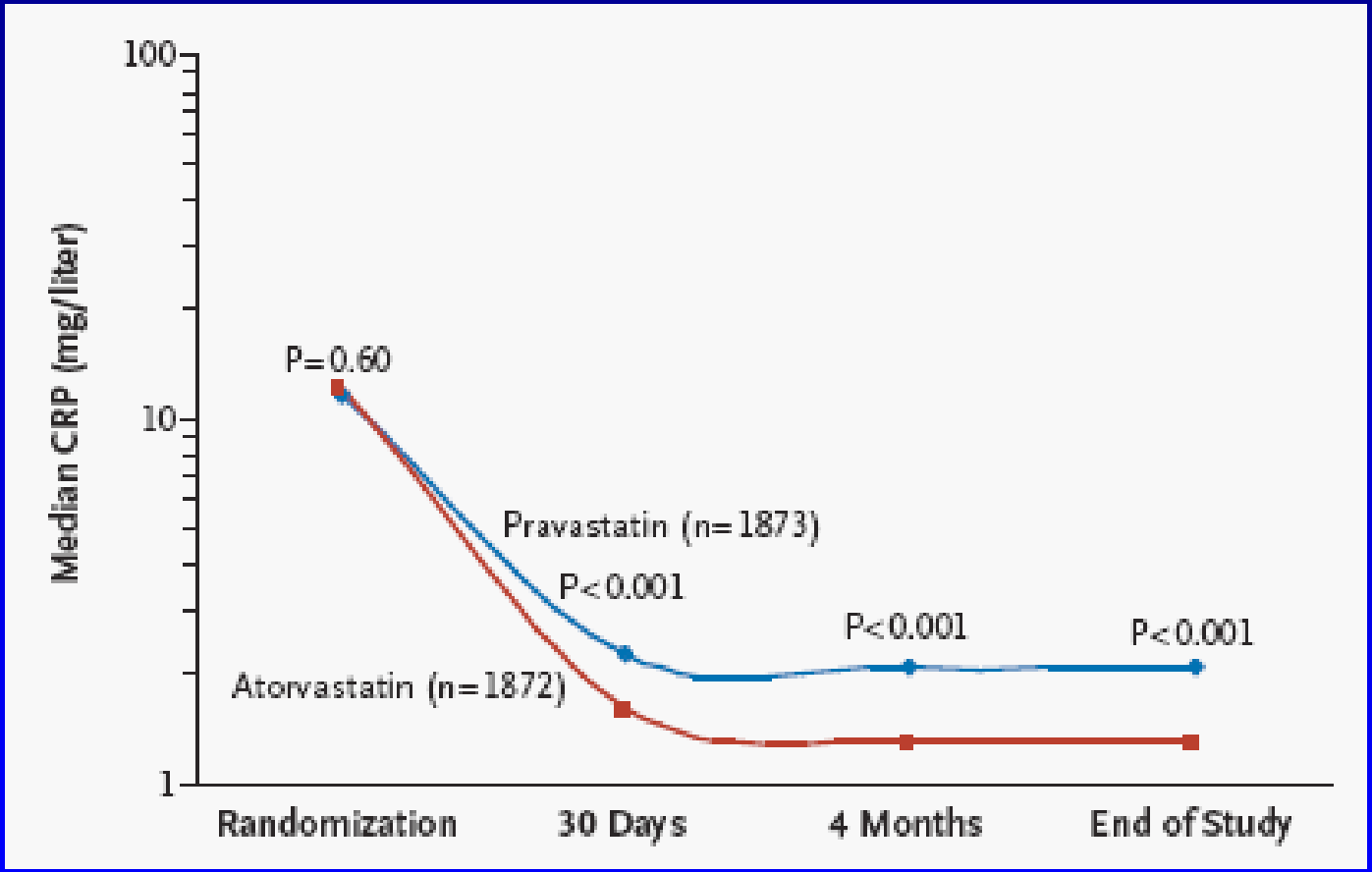
Mora et al. Am J Cardiol 2006

LDL-Chol and CRP in 3745 patients wiht ACS



PROVE IT-TIMI 22, Ridker PM et al. NEJM 2005

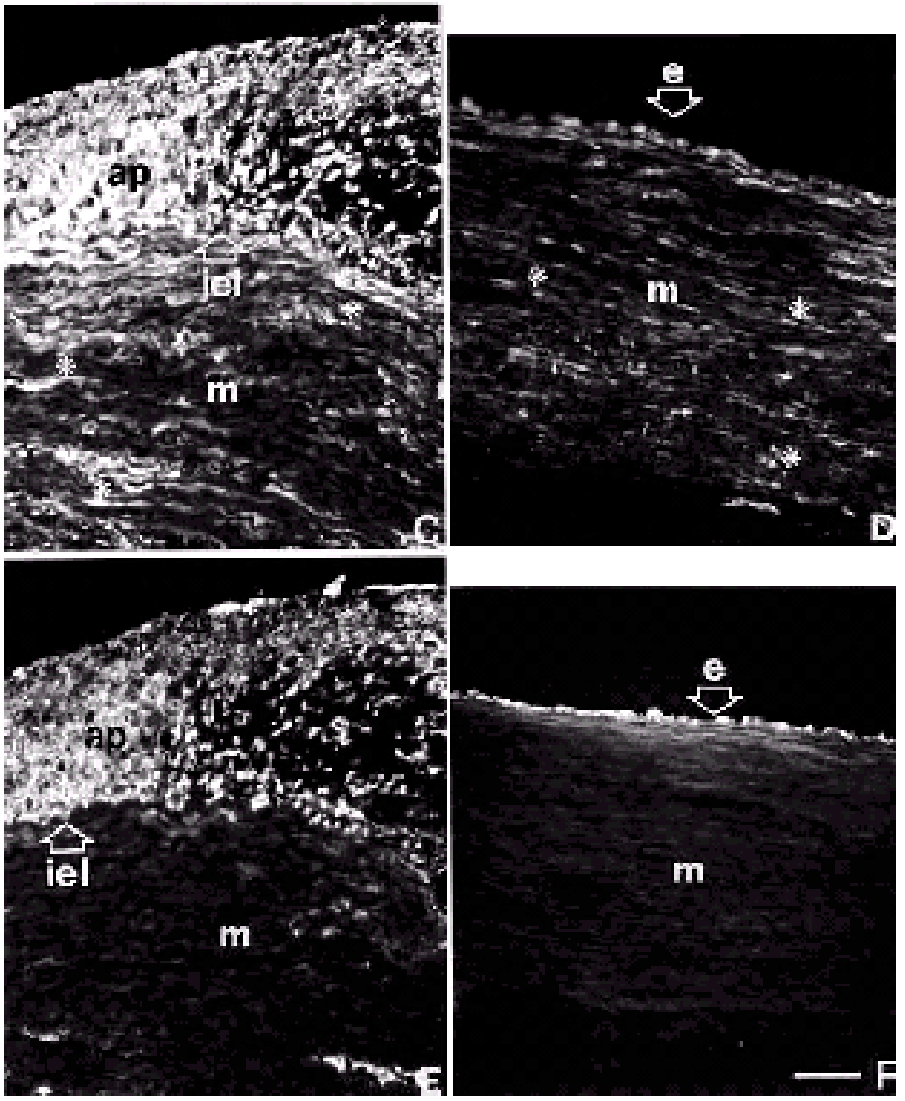
CRP in 3745 patients with ACS (PROVE IT-TIMI22)



Ridker PM et al. NEJM 2005

Low-dose Cerivastatin inhibits spontaneous atherogenesis in heterozygous Watanabe hyperlipidemic rabbits

Placebo **Cerivastatin**

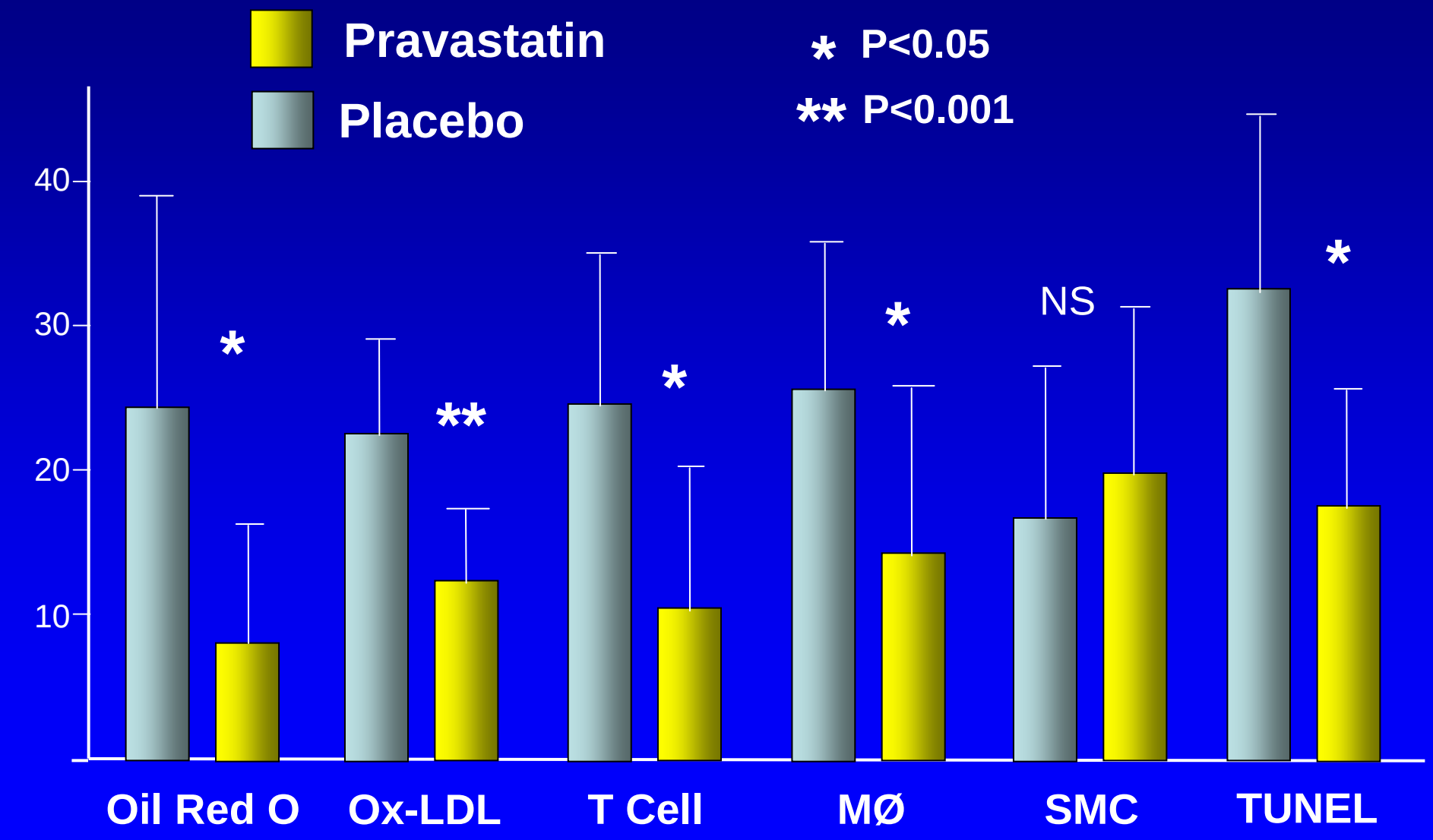


SMC

MØ

Pauletto P et al., J Vasc Res 2000;37:189-194

Percentage of lipid and cellular content of carotid endarterectomy specimens after 40 mg/d Pravastatin for 3 months



Modified from M.Crisby, 2001

The Multicentre Atorvastatin Plaque Stabilisation (MAPS) Study

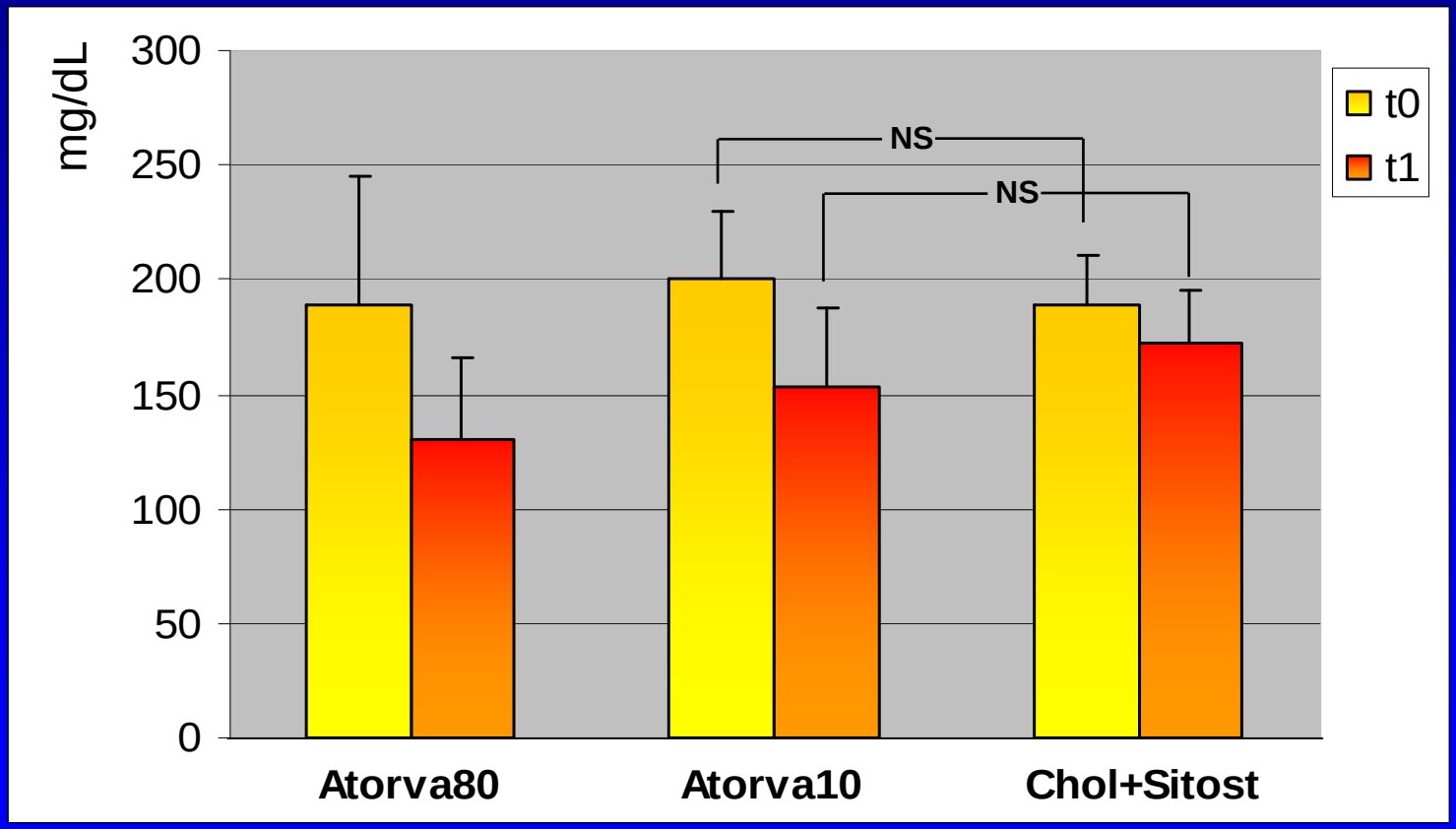
Proposed Rationale and Study Design

Paolo Pauletto,[1] *Claudio Ferri,*[2] *Massimo Volpe,*[3] *Enrico Agabiti-Rosei,*[4] *Maria Lorenza Muiesan,*[4] *Massimo Puato,*[5] *Elisabetta Faggin,*[5] *Marcello Rattazzi,*[5] *Mario Plebani,*[6] *Alberto Zambon,*[7] *Giovambattista Desideri,*[2] *Luca De Siati,*[3] *Sante Pierdomenico,*[8] *Massimo Salvetti,*[4] *Francesco Cipollone*[8] and *Andrea Mezzetti*[8]

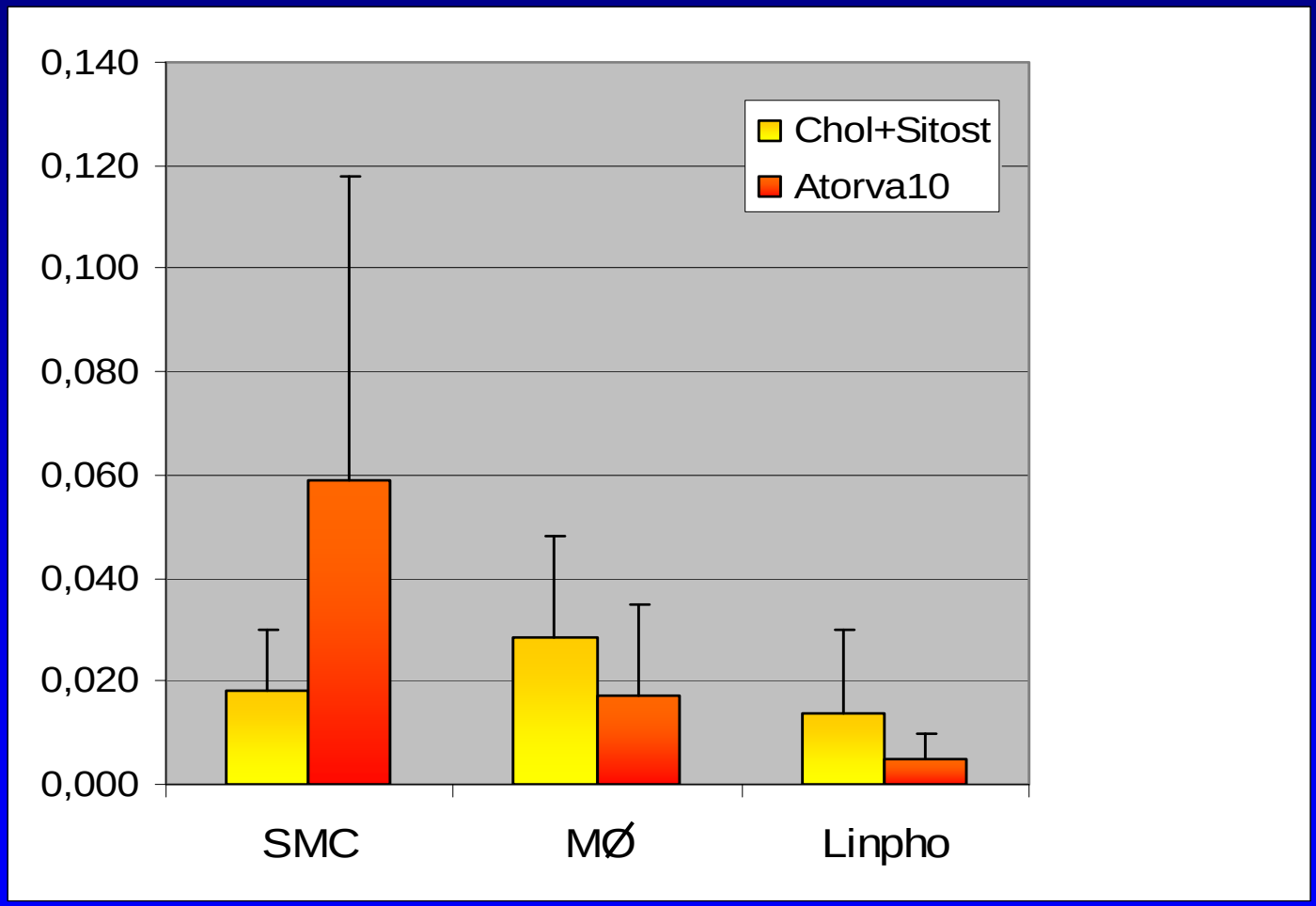
STUDY DESIGN AND RESEARCH PROJECTS

High Blood Press Cardiovasc Prev 2003; 10 (1): 11-18
1120-9879/03/0001-0011/$30.00/0

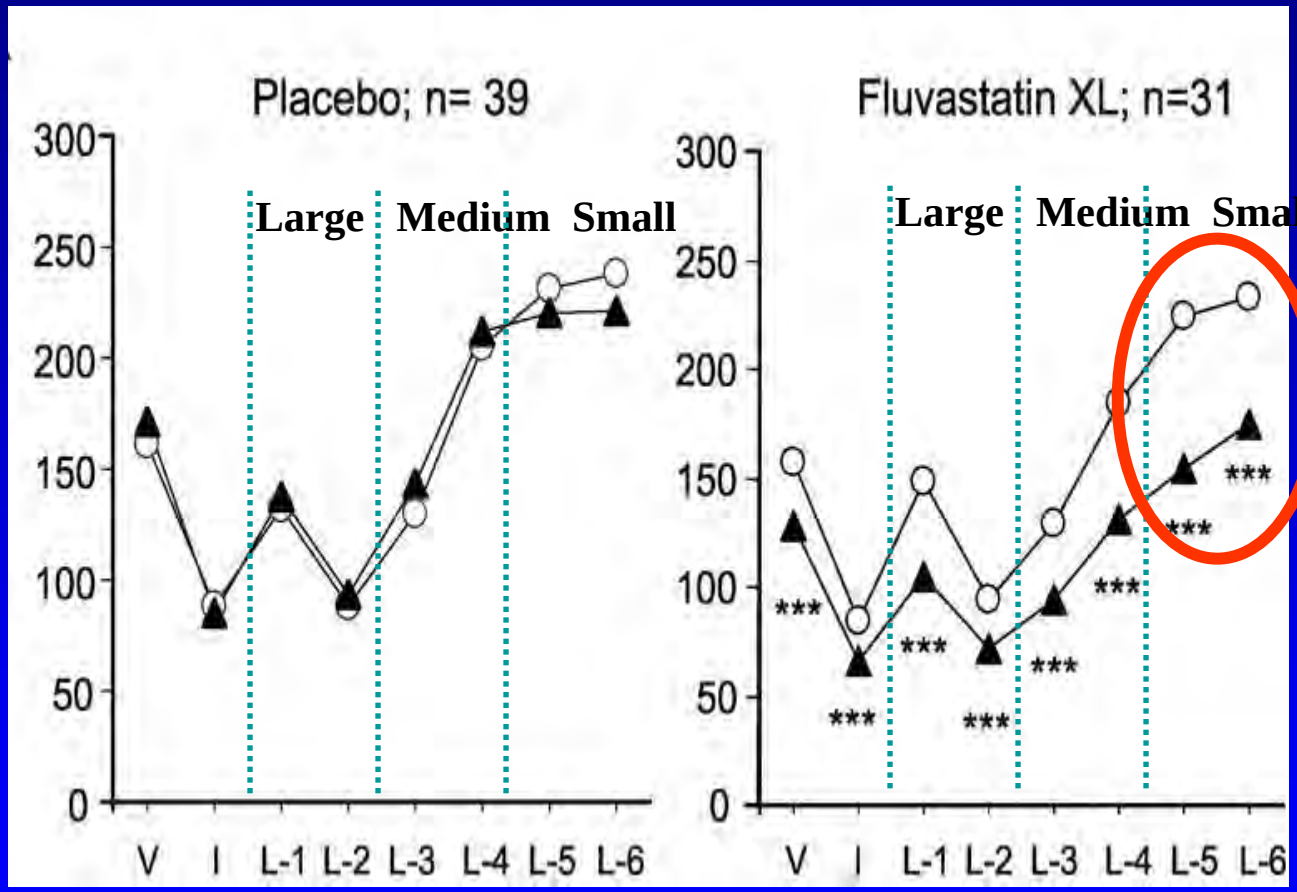
Plasma LDL-Chol levels before and after a 3-month lipid lowering therapy



Effect of a 3-month lipid lowering therapy on cell composition of carotid plaque



LDL (pro-inflammatory) subfractions in patients after a 8-week treatment with Fluvastatin



Winkler K. Et al, J Clin Endocrinol Metab 87:5485-5490,2002

“JUST A CHOLESTEROL-LOWERING EFFECT ?”

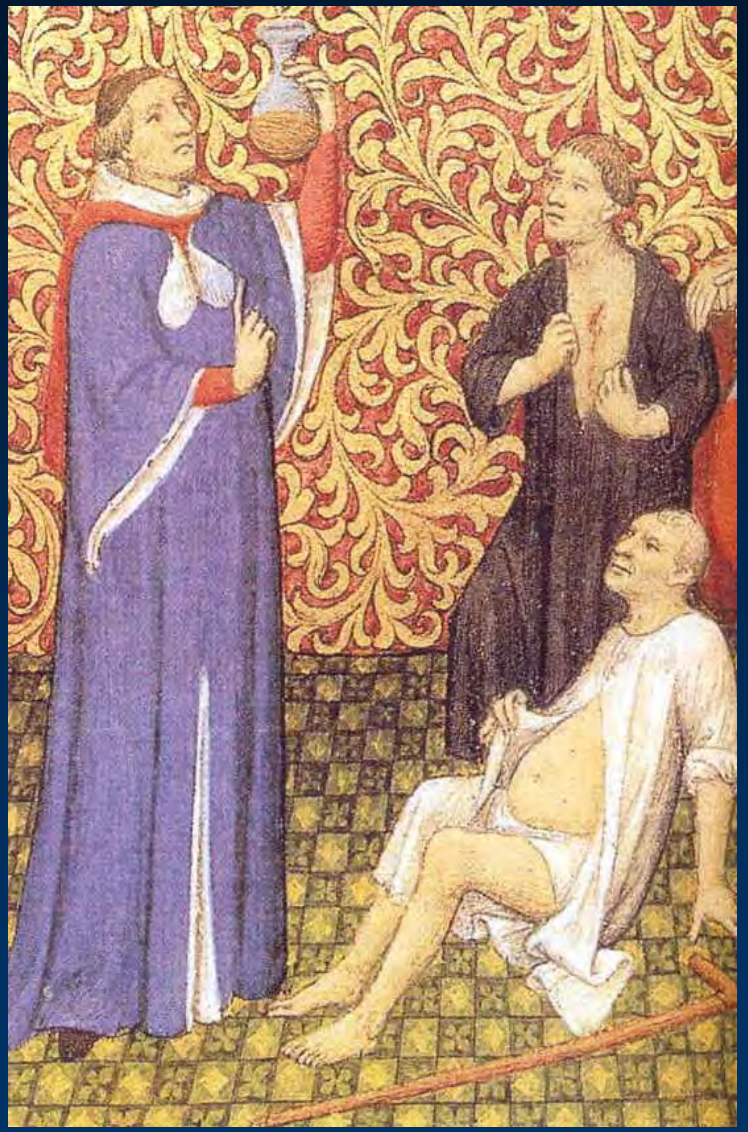
Conclusion

- LONG-TERM BENEFIT: STRONG EVIDENCE
- SHORT-TERM BENEFIT: ADDITIONAL EFFECT EXPECTED TO COME FROM ANTIINFLAMMATORY PROPERTIES OF STATINS

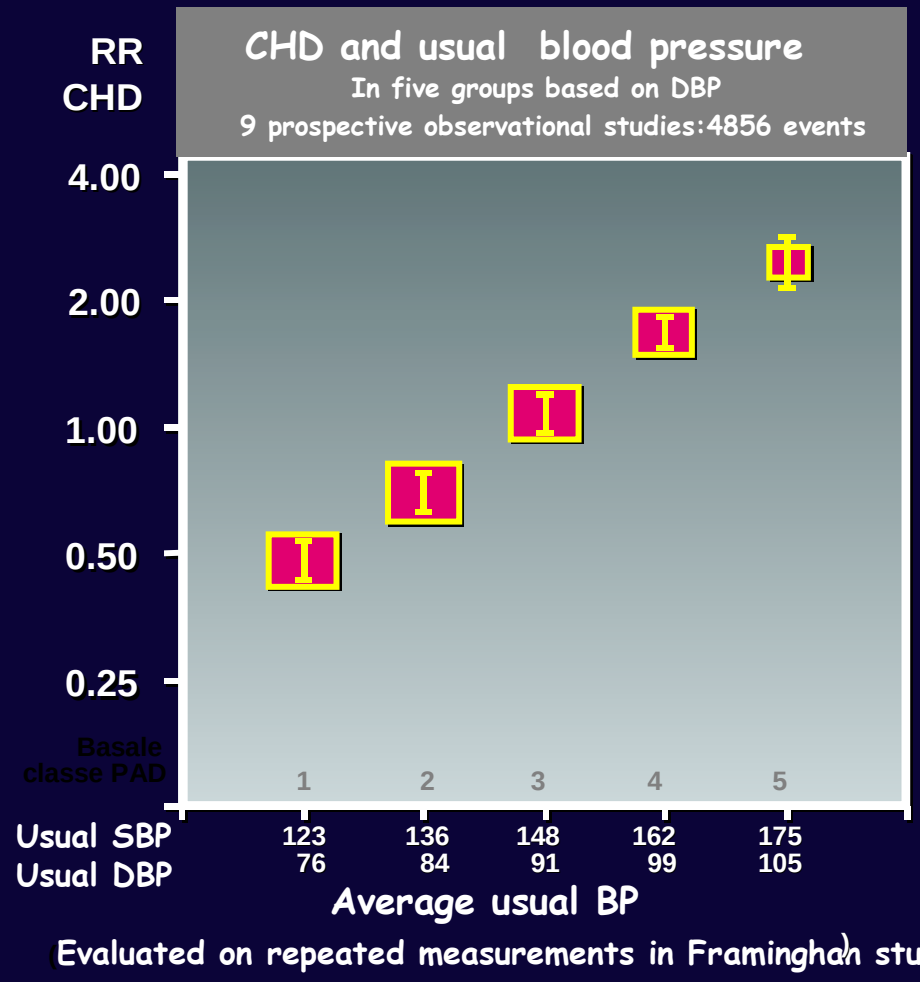
Antihypertensive Drugs : Just a Blood Pressure Lowering Effect ?

Giampietro Beltramello
Unit of Internal Medicine
Bassano del Grappa

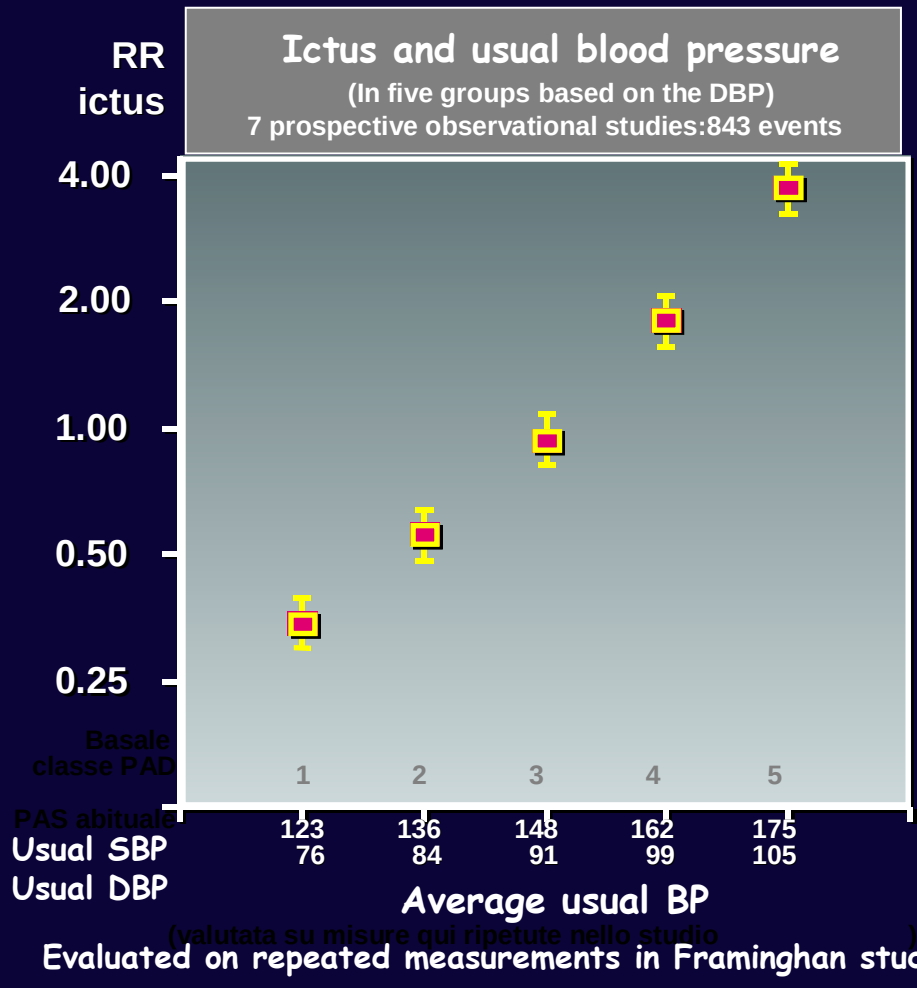
Verona,Friday,October 27,2006



Blood Pressure and cardiovascular events



Evaluated on repeated measurements in Framinghan study

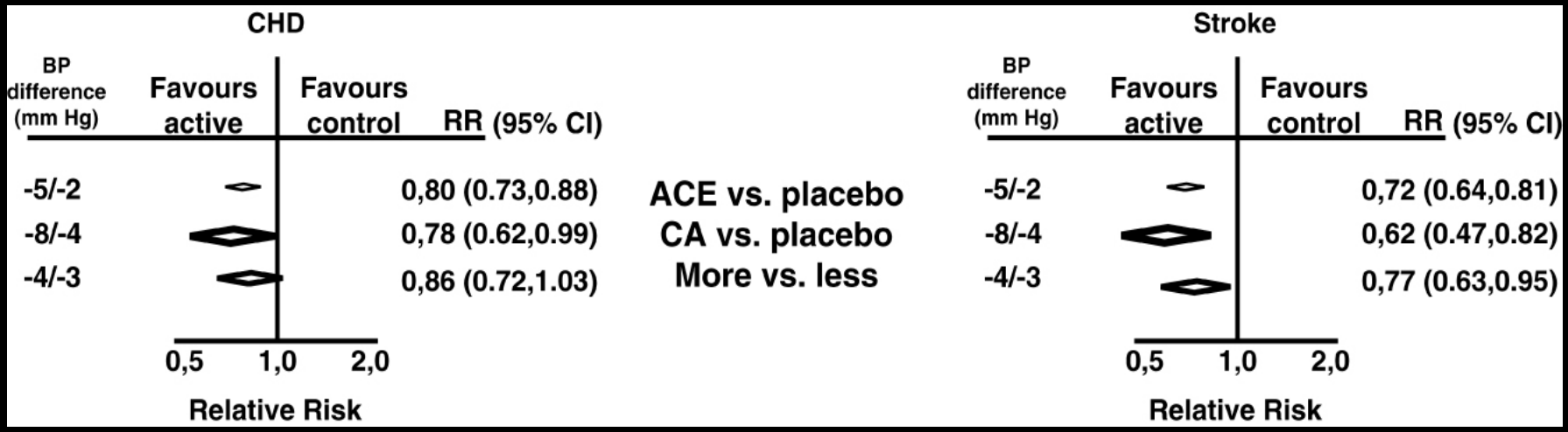


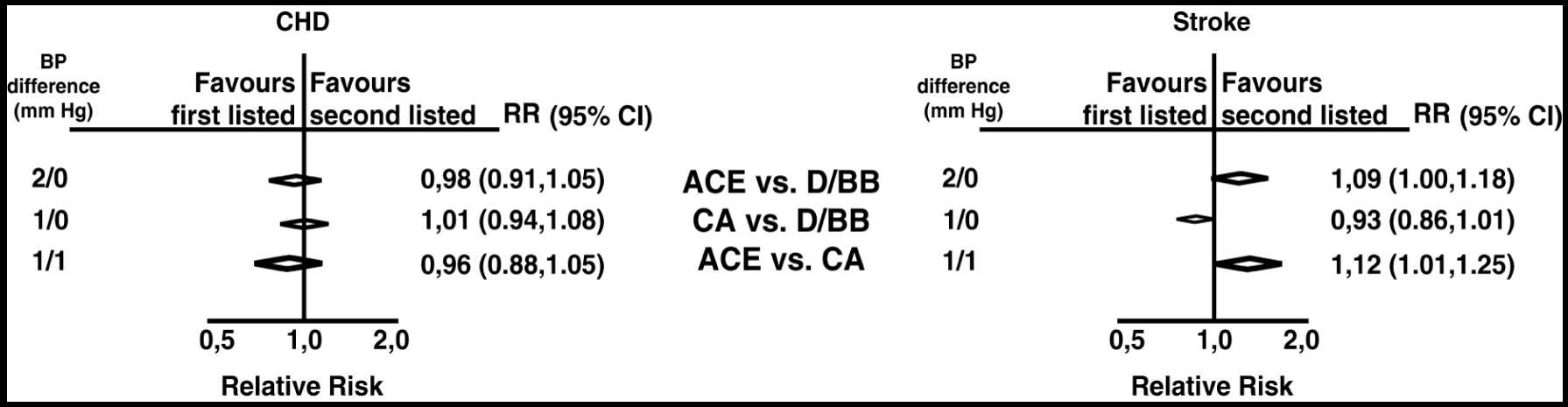
(valutata su misure qui ripetute nello studio)

Evaluated on repeated measurements in Framinghan study

Collins and McMahon, British Medical Bullettin 1994

CHD and Stroke events in studies comparing ACEs and Calcium antagonists with placebo and more and less intensive blood pressure lowering regimens





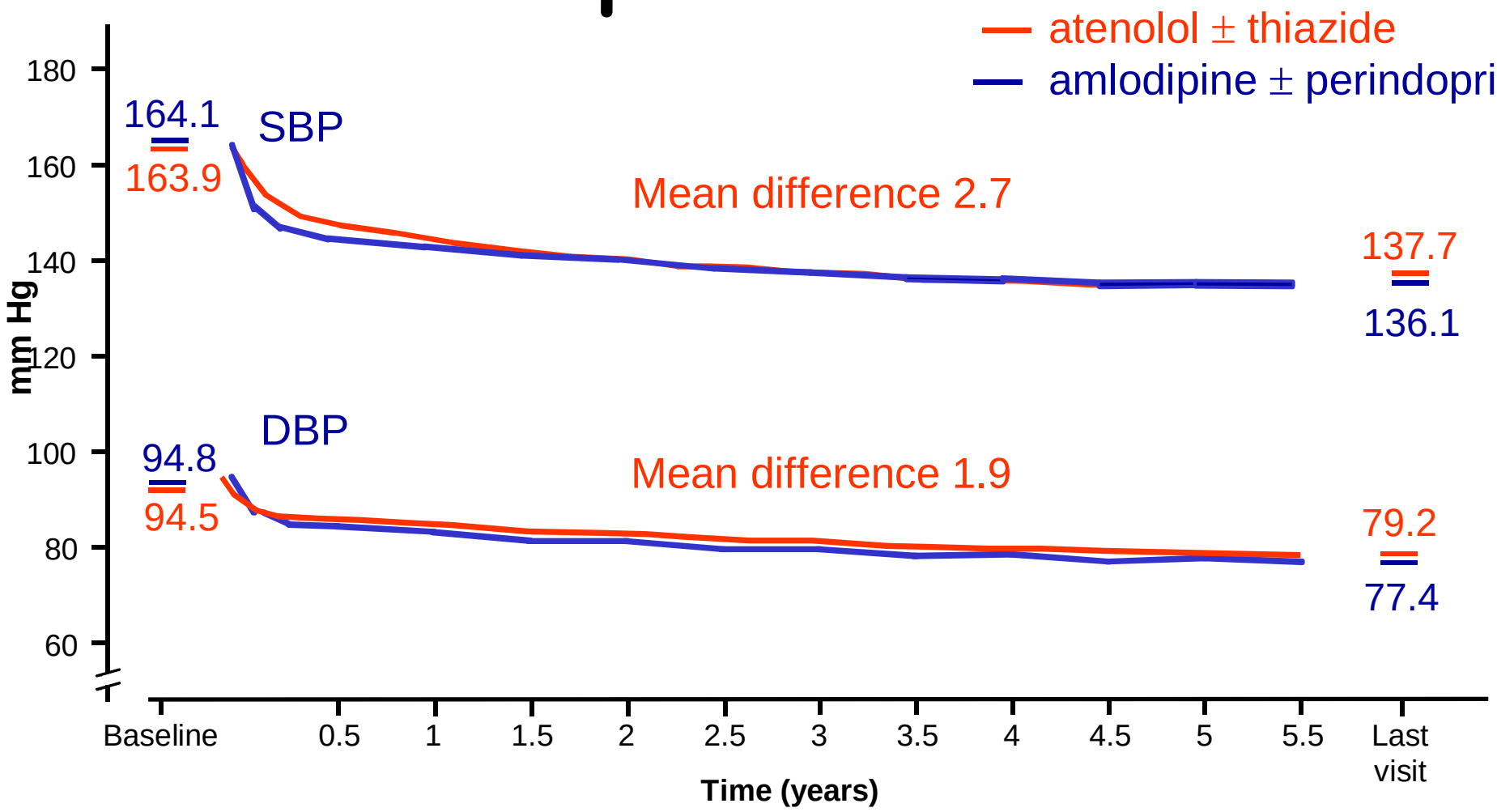
(Peter Server, Circulation.2006;113:2754-2774)

- In some clinical trials the reduction in recurrent Cardiovascular events is too large to be attribuited to lower Blood Pressure which often was absent or very modest (1-2 mmHg)

- This observation is relevant to the debate about how much of the benefit of blood pressure-lowering drugs in clinical trials can be attribuited to blood pressure lowering per se or to alternative mechanisms "beyond Blood pressure".

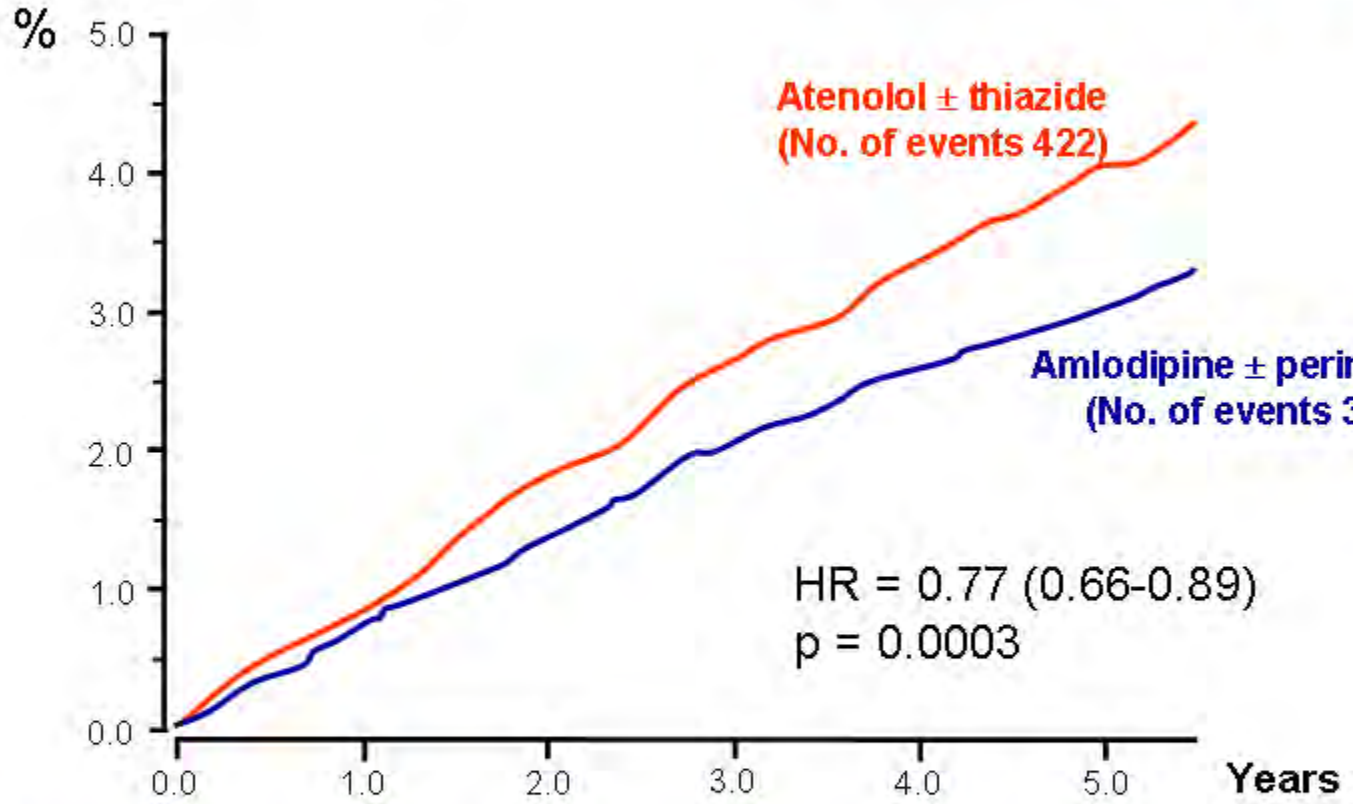
Systolic and diastolic blood pressure

Anglo-Scandinavian ascot Cardiac Outcomes Trial



Fatal and non-fatal stroke

Anglo-Scandinavian ascot Cardiac Outcomes Trial



Number at risk						
Amlodipine ± perindopril	9639	9483	9331	9156	8972	7863
Atenolol ± thiazide	9618	9461	9274	9059	8843	7720

Differential Impact of Blood Pressure–Lowering Drugs on Central Aortic Pressure and Clinical Outcomes

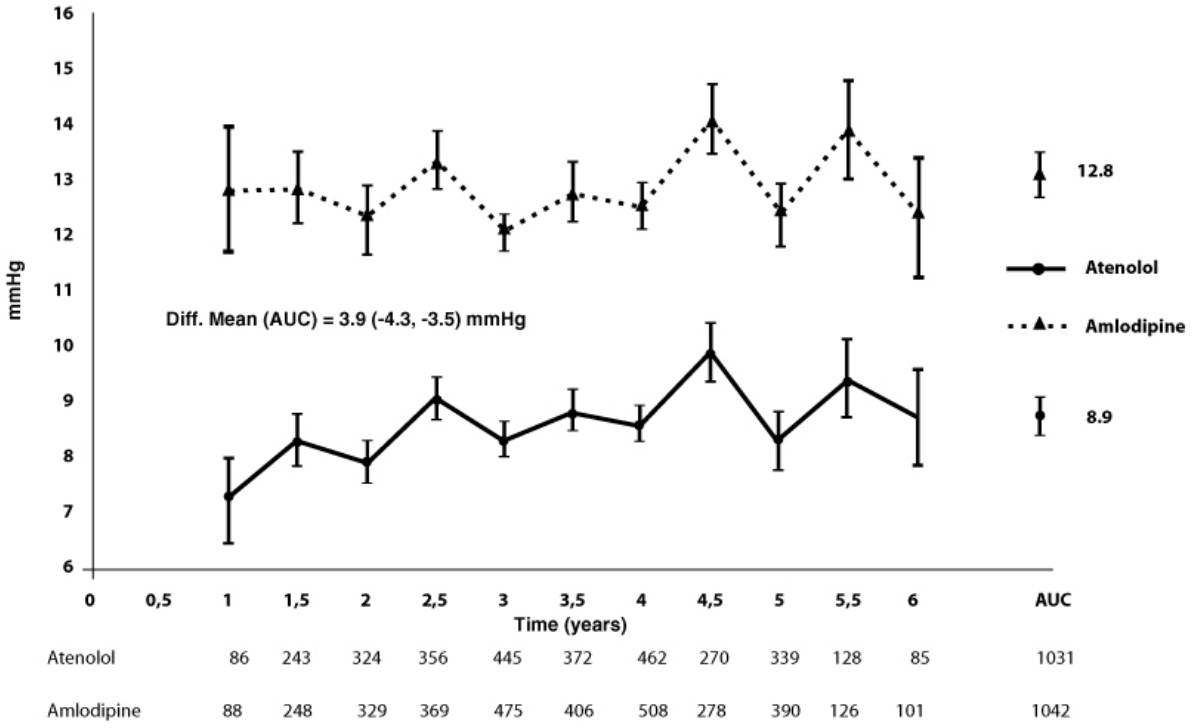
Principal Results of the Conduit Artery Function Evaluation (CAFE) Study

The CAFE Investigators, for the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) Investigators

CAFE Steering Committee and Writing Committee: Bryan Williams, MD, FRCP; Peter S. Lacy, PhD; Simon M. Thom, MD, FRCP; Kennedy Cruickshank, MD; Alice Stanton, MB, PhD, FRCPI; David Collier, MBBS, PhD; Alun D. Hughes, MBBS, PhD; H. Thurston, MD, FRCP

Study Advisor: Michael O'Rourke, MD, FRACP

PULSE PRESSURE DIFFERENCE
(brachial –derived central Aortic;mean 95% CI) with time



(Circulation. 2006;113:1213-1225)

The New England
Journal of Medicine

VOLUME 342 JANUARY 20, 2000 NUMBER 3

EFFECTS OF AN ANGIOTENSIN-CONVERTING–ENZYME INHIBITOR, RAMIPRIL, ON CARDIOVASCULAR EVENTS IN HIGH-RISK PATIENTS

THE HEART OUTCOMES PREVENTION EVALUATION STUDY INVESTIGATORS*

- ✓The mean blood pressure at entry was 139/79 mmHg in ramipril group and placebo group.
- ✓At the end of the study the blood pressure was,136/76 and 139/77 mmHg respectively. No significative difference between two groups.

HOPE STUDY

Myocardial Infarction, Stroke, Death

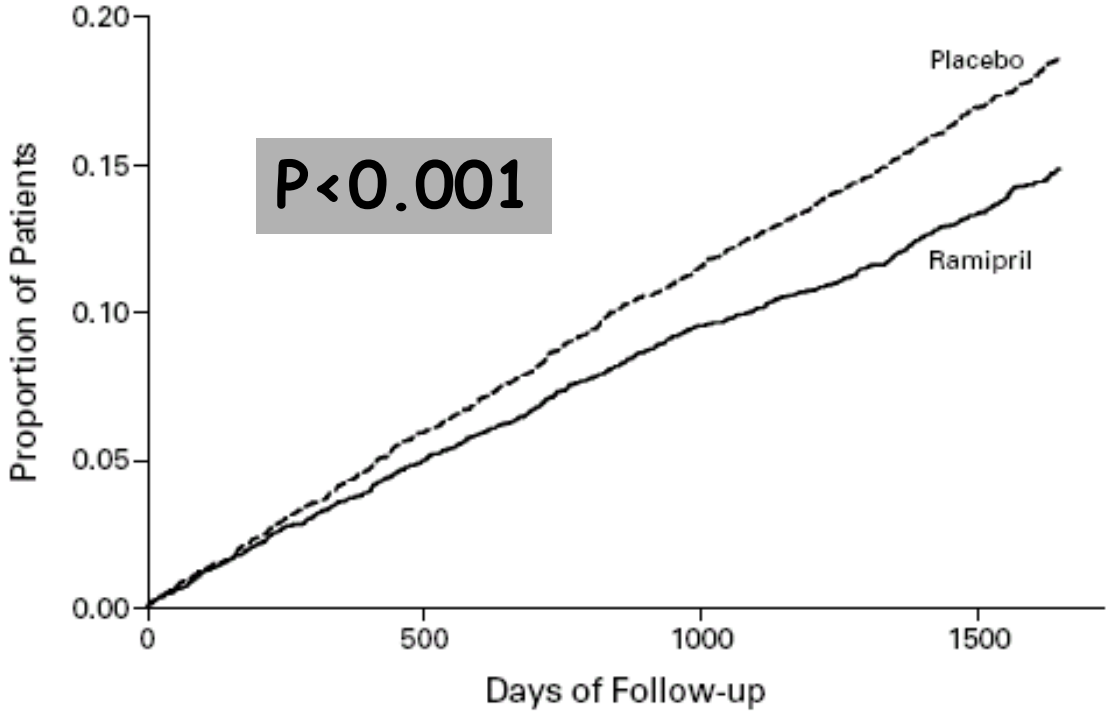


Figure 1. Kaplan–Meier Estimates of the Composite Outcome of Myocardial Infarction, Stroke, or Death from Cardiovascular Causes in the Ramipril Group and the Placebo Group.

(N. England J Med ; HOPE ; January,2000)

The New England
Journal of Medicine

VOLUME 342 JANUARY 20, 2000 NUMBER 3

EFFECTS OF AN ANGIOTENSIN-CONVERTING–ENZYME INHIBITOR, RAMIPRIL, ON CARDIOVASCULAR EVENTS IN HIGH-RISK PATIENTS

THE HEART OUTCOMES PREVENTION EVALUATION STUDY INVESTIGATORS*

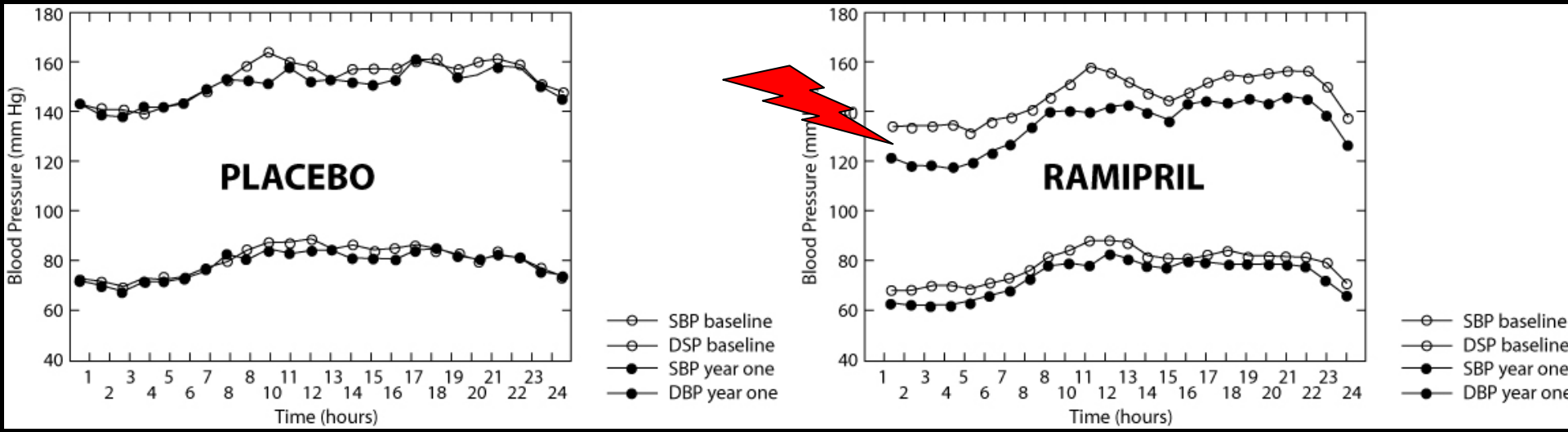
- ✓The mean blood pressure at entry was 139/79 mmHg in ramipril group and placebo group.
- ✓At the end of the study the blood pressure was,136/76 and 139/77 mmHg respectively. No significative difference between two groups.

HOPE Trial gave rise the hypotesis that angiotensin converting enzyme inhybitors (ACEs) might reduce cardiovascular complic. beyond blood pressure control.

Comparative Effects of Ramipril on Ambulatory and Office Blood Pressures

A HOPE Substudy

Per Svensson, Ulf de Faire, Peter Sleight, Salim Yusuf, Jan Östergren



"In conclusion : ABP showhed greater falls,especially at night, than did OBP during treatment with ramipril given once daily at bedtime."

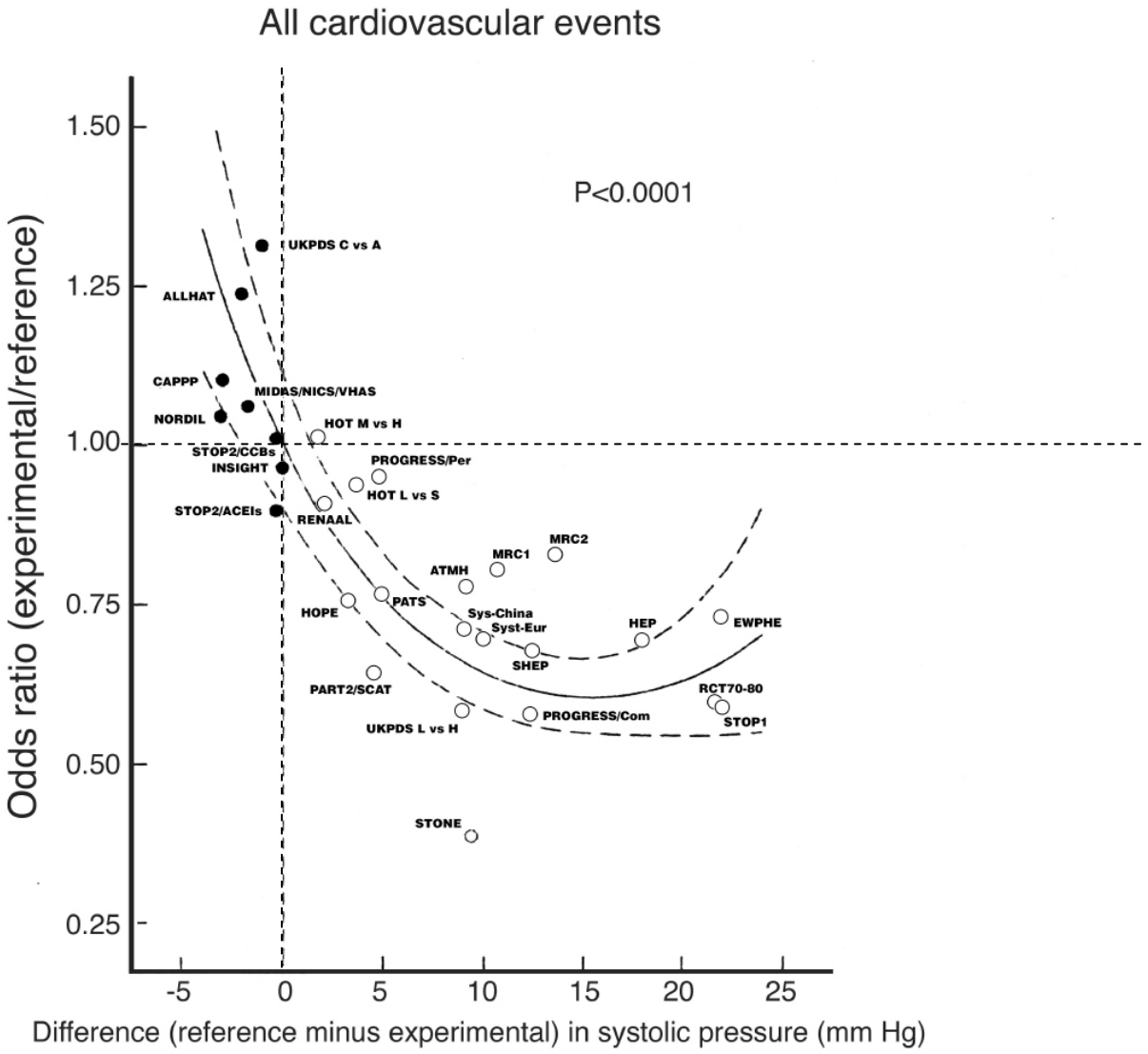
(P. Svensson. Hypertension.2001;38:e28-e32)

Outcome beyond blood pressure control?

European Heart Journal (2003) 24, 504–514

Jan A. Staessen[a*], Ji-Guang Wang[a], Willem H. Birkenhäger[b]

ELSEVIER



(European Heart Journal.2003;24:504-514)

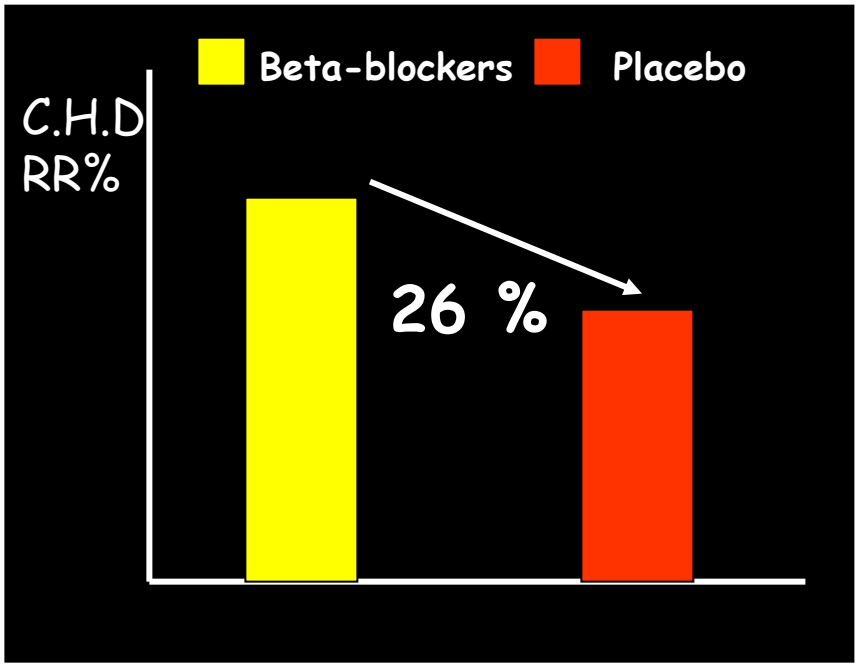
Whether certain classes of antihypertensive drugs confer benefits beyond those associated with lowering blood pressure, remains a very controversial issue.

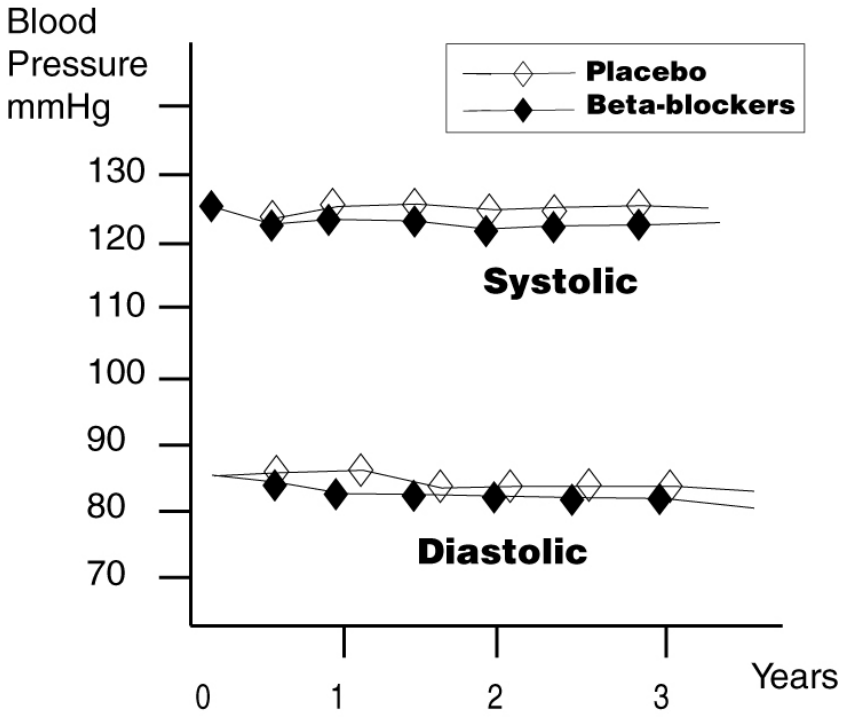
More recently,meta-analyses of Beta-blockers based trials in hypertension have suggested that this class of agents confers less reduction in cardovascular risk than other classes of antihypertensive drugs.

(Lindholm LH ; Lancet 2005; 366:1545-1553)

But.....

When Beta-Blockers have been assessed in long term trials after myocardial infarction the reduction in in recurrent C.H.D. events was of 26 %, too large to be attribuited to the little degree of blood pressure reduction (1-2 mmHg in some individual trials).





These observations highlight the hypotesis that some drug-induced benefits on C.V. events to be dependent on the Patient subgroup and beyond the capacity to lowering blood pressure.

Effect of Carvedilol on the Morbidity of Patients With Severe Chronic Heart Failure

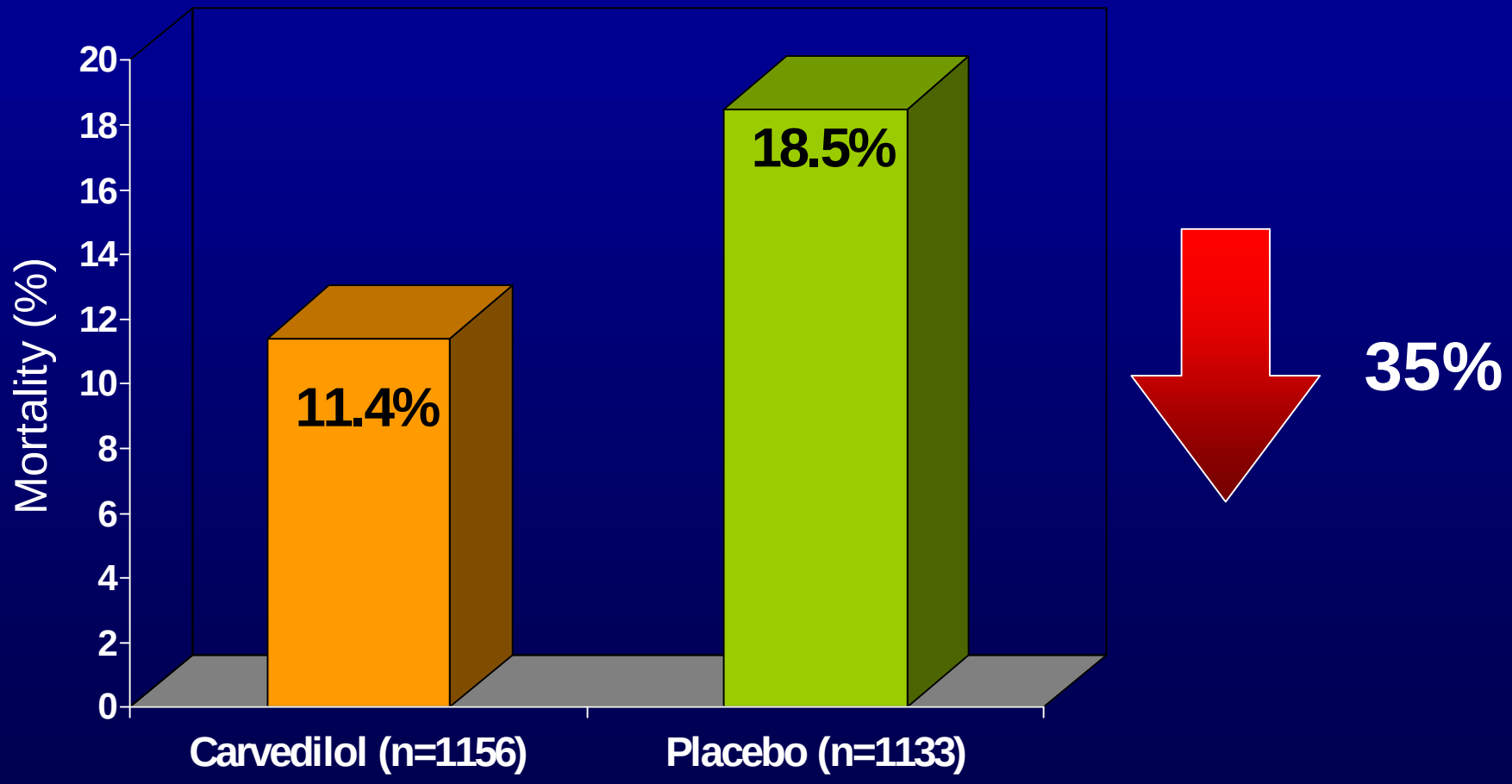
Results of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study

	Placebo (N=398)	Carvedilol (N=696)	
Systolic blood pressure (mmHg)	115±17	116±17	ns
Diastolic blood pressure (mmHg)	73±11	72±10	ns

Neither group had significant changes in systolic or diastolic Blood Pressure pre and post-treatment

(Circulation. 2002; 106:2194-2199)

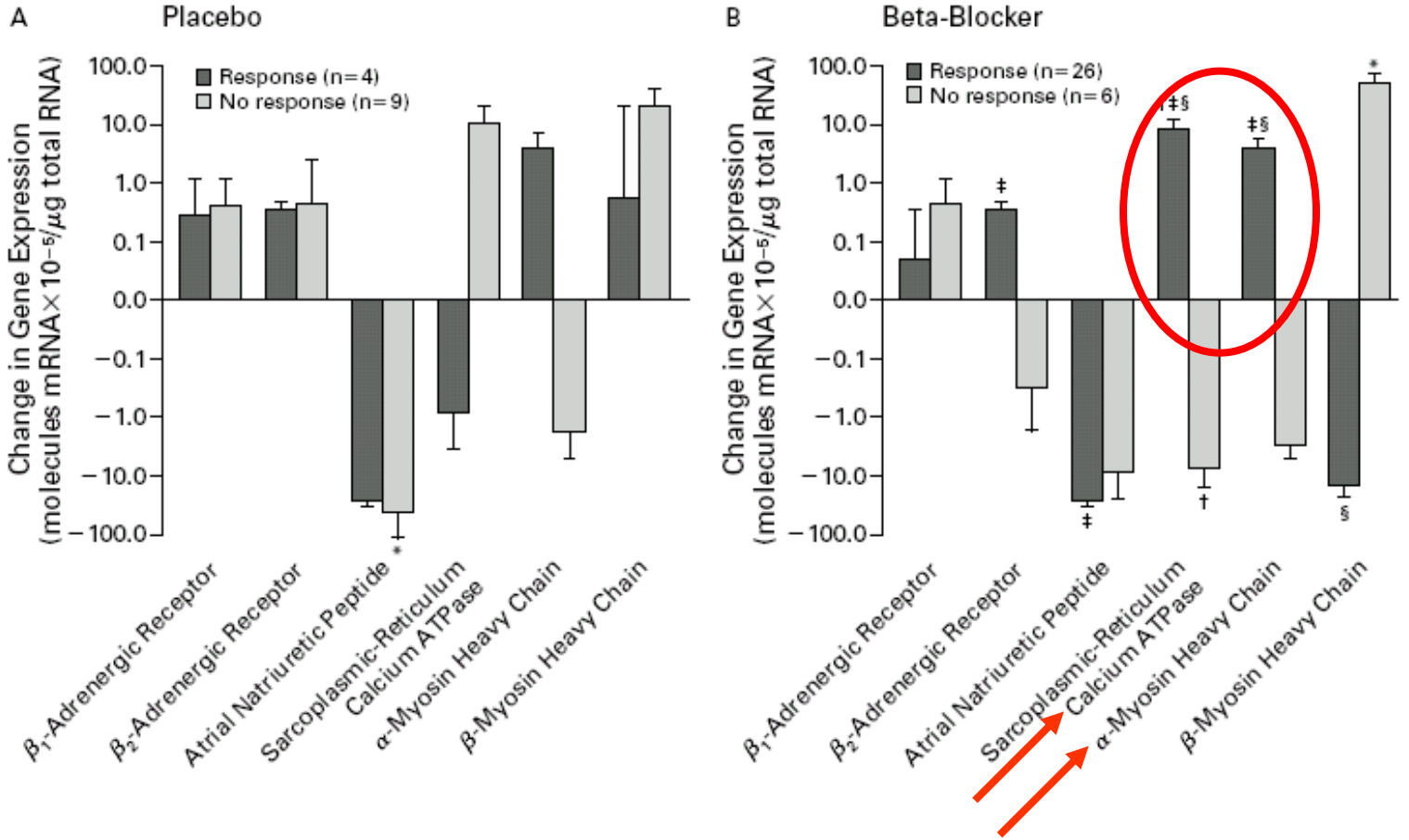
COPERNICUS: Effect on Mortality



22nd Congress of European Society of Cardiology, August 2000

MYOCARDIAL GENE EXPRESSION IN DILATED CARDIOMYOPATHY TREATED WITH BETA-BLOCKING AGENTS

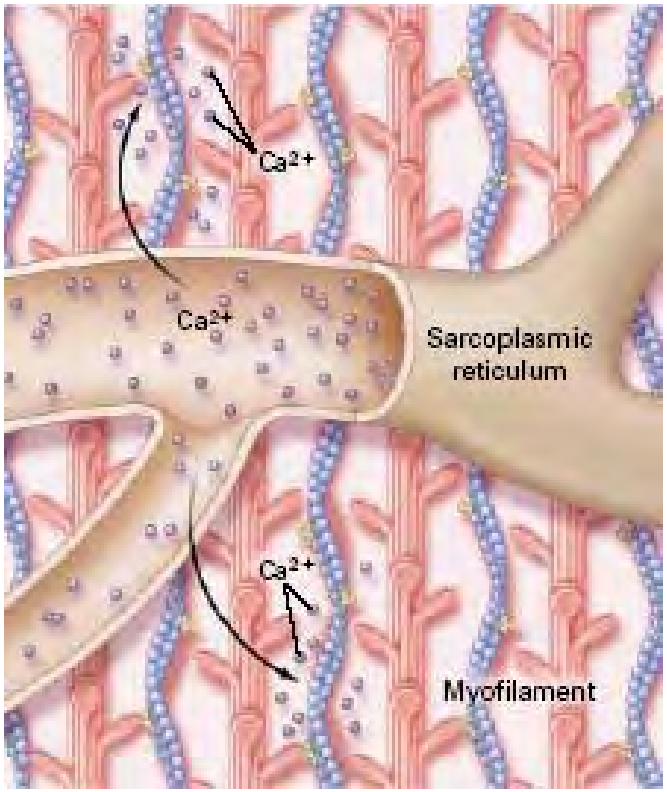
BRIAN D. LOWES, M.D., EDWARD M. GILBERT, M.D., WILLIAM T. ABRAHAM, M.D., WAYNE A. MINOBE, B.S., PATTI LARRABEE, B.S., DEBRA FERGUSON, M.S., EUGENE E. WOLFEL, M.D., JOANN LINDENFELD, M.D., TATIANA TSVETKOVA, M.D., ALASTAIR D. ROBERTSON, PH.D., ROBERT A. QUAIFE, M.D., AND MICHAEL R. BRISTOW, M.D., PH.D.



(N. Engl. J. Med. 2002;346:1357-65.)

This Week in the Journal

May 2, 2002

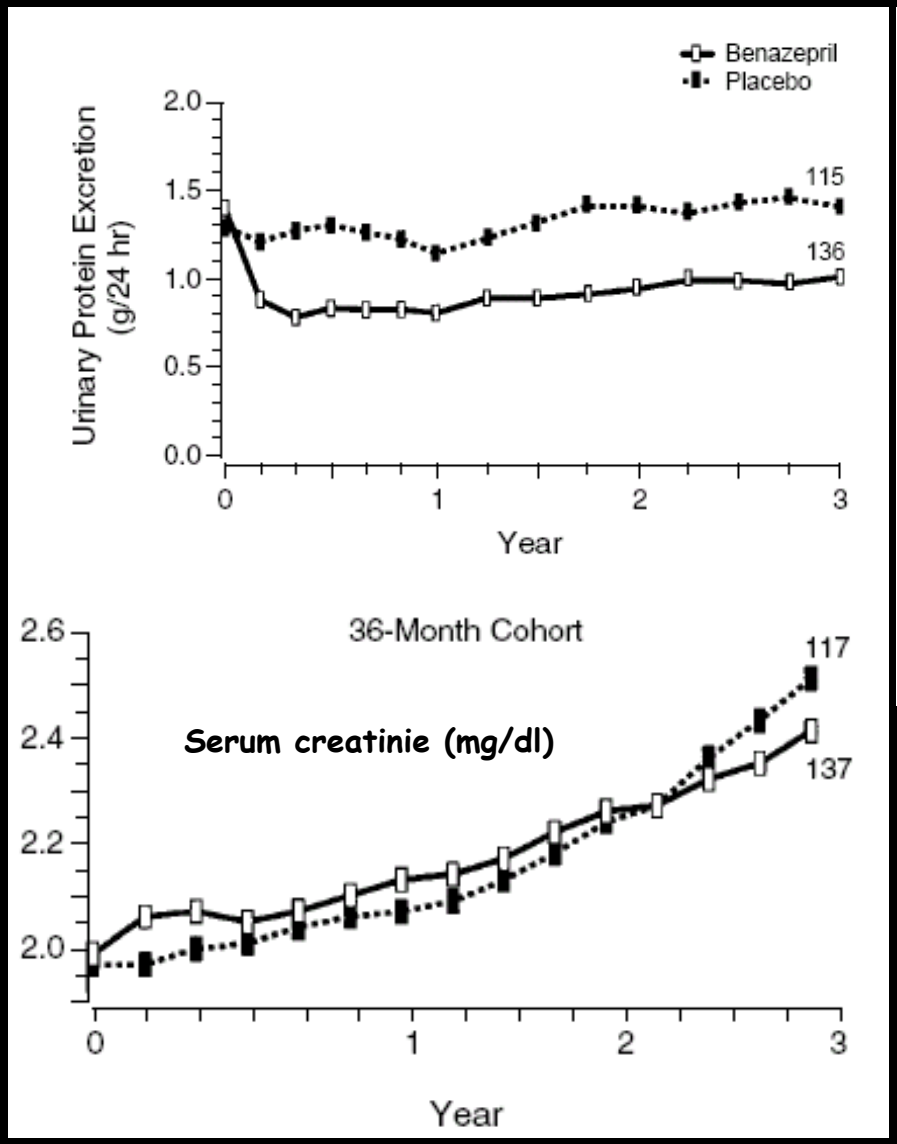


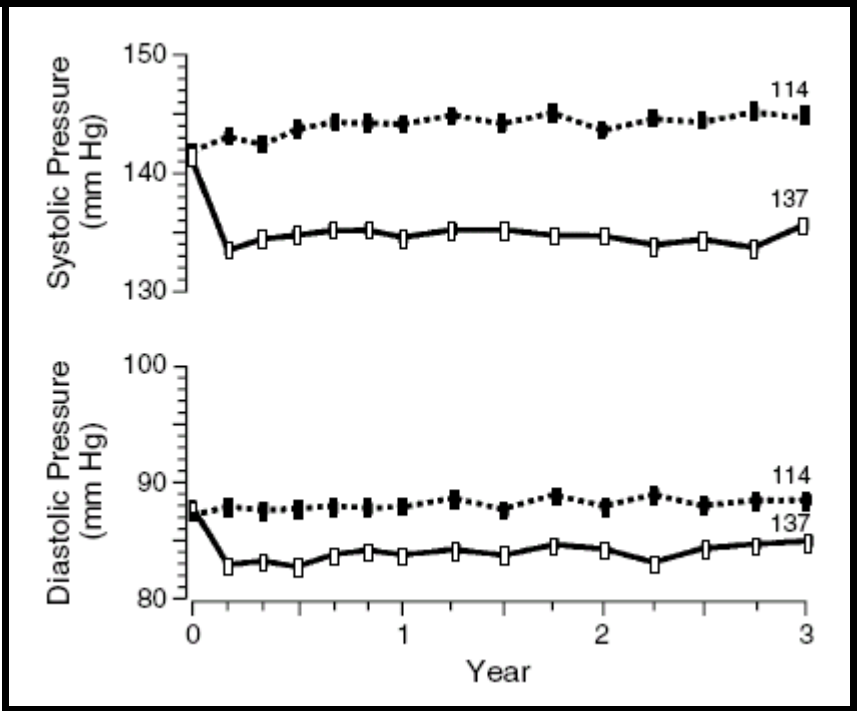
The therapy with beta-blockers, is accompanied by changes in the expression of key myocardial genes (encoding alfa-miosin heavy chain and calcium ATP-ase in the sarcoplasmic reticulum) that are involved in the regulation of the cardiac contractility.

(N. Engl. J. Med. 2002;346:1357-65.)

EFFECT OF THE ANGIOTENSIN-CONVERTING–ENZYME INHIBITOR BENAZEPRIL ON THE PROGRESSION OF CHRONIC RENAL INSUFFICIENCY

GIUSEPPE MASCHIO, M.D., DANIELE ALBERTI, M.D., GÉRARD JANIN, M.D., FRANCESCO LOCATELLI, M.D., JOHANNES F.E. MANN, M.D., MARIO MOTOLESE, M.D., CLAUDIO PONTICELLI, M.D., EBERHARD RITZ, M.D., PIETRO ZUCCHELLI, M.D., AND THE ANGIOTENSIN-CONVERTING–ENZYME INHIBITION IN PROGRESSIVE RENAL INSUFFICIENCY STUDY GROUP*





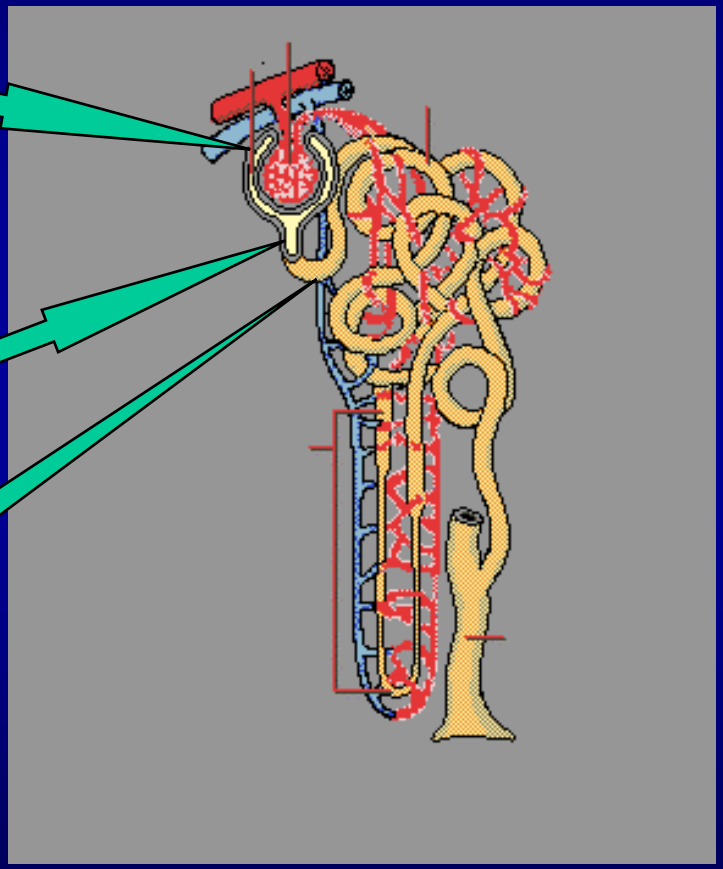
(N Engl J Med 1996;334:939-45)

Trophic effects of angiotensin II in the kidney

Muscle cells hypertrophy of vascular bed

Mesangial cells hypertrophy matrix increase, endotelial cells hyperplasia

Tubular cells hypertrophy



and…. increase intraglomerular capillary pressure

The NEW ENGLAND JOURNAL of MEDICINE

Volume 345 September 20, 2001 Number 12

- "Renoprotective Effect of the Angiotensin-Receptor Antagonist Irbesartan in Patients with Nephropaty Due to Type 2 Diabetes"
  E. J. Lewis and Others

- "Effects of Losartan on Renal and cardiovascular Outcomes in Patients With Type 2 Diabetes and Nephropaty"
  B. M. Brenner and Others

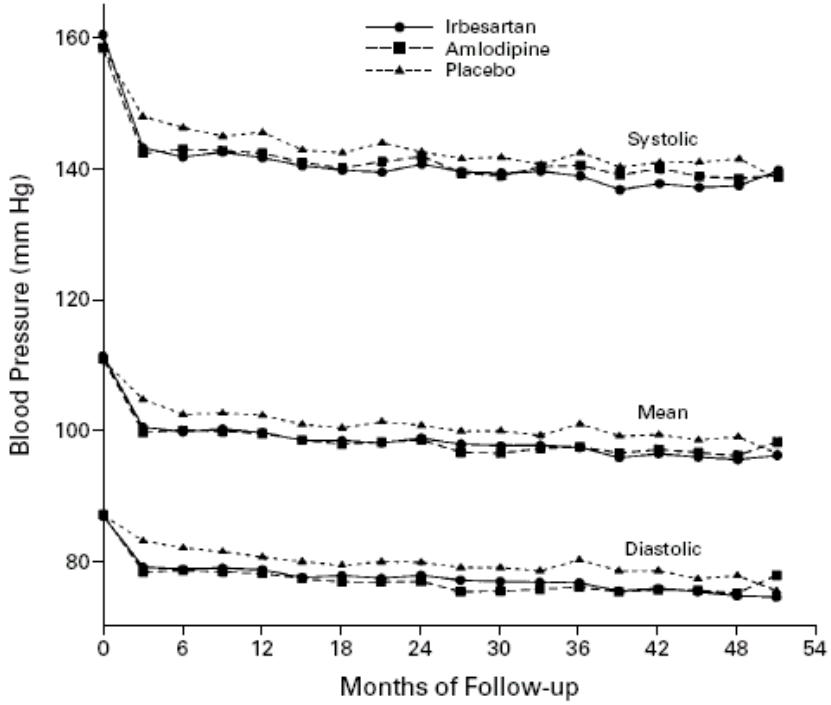
- "The effect of Irbesartan on the Developement of Diabetic Nephropaty in Patients with Type 2 Diabetes"
  H. H. Parving and Others

The New England
Journal of Medicine

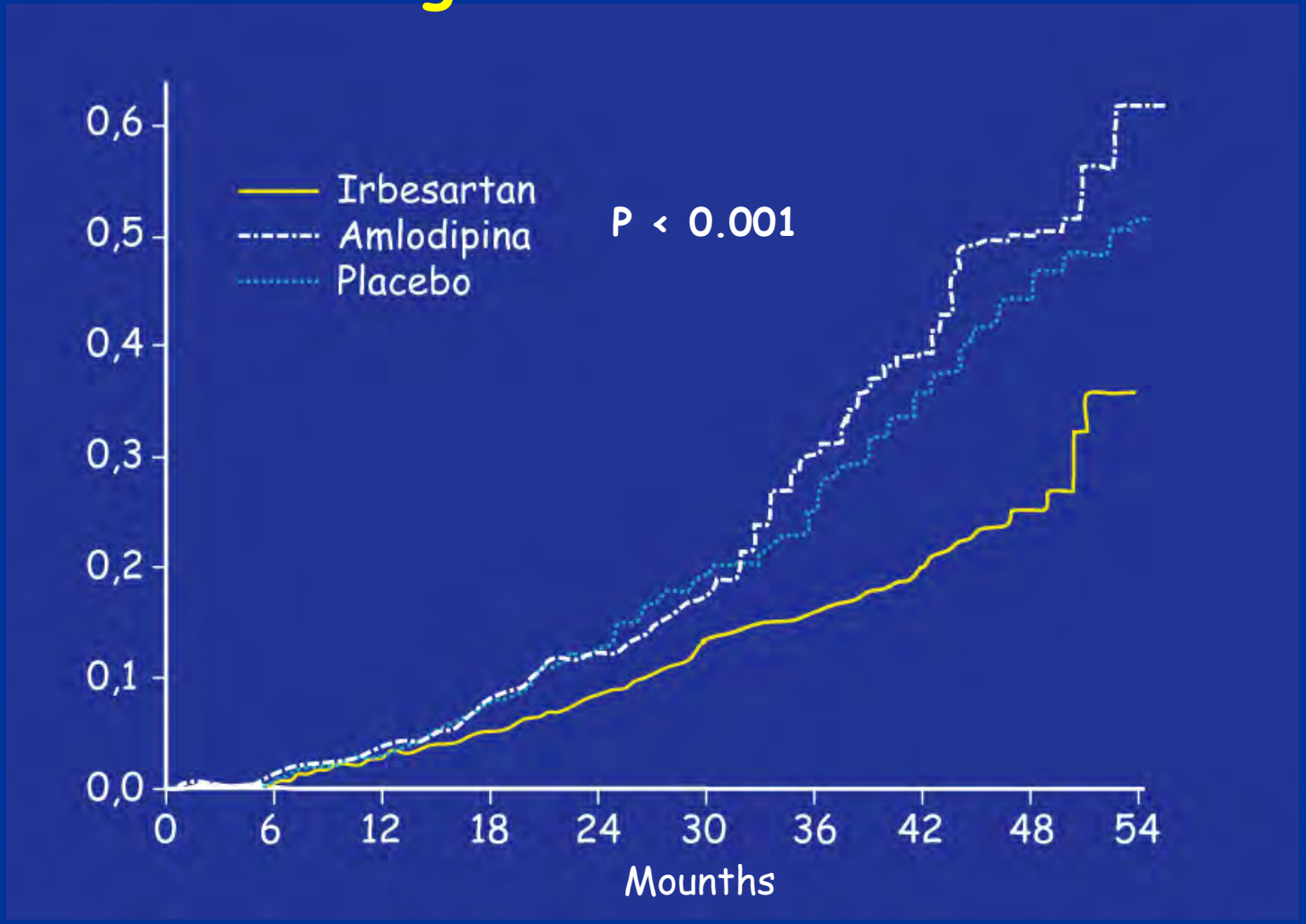
VOLUME 345 SEPTEMBER 20, 2001 NUMBER 12

RENOPROTECTIVE EFFECT OF THE ANGIOTENSIN-RECEPTOR ANTAGONIST IRBESARTAN IN PATIENTS WITH NEPHROPATHY DUE TO TYPE 2 DIABETES

EDMUND J. LEWIS, M.D., LAWRENCE G. HUNSICKER, M.D., WILLIAM R. CLARKE, PH.D., TOMAS BERL, M.D., MARC A. POHL, M.D., JULIA B. LEWIS, M.D., EBERHARD RITZ, M.D., ROBERT C. ATKINS, M.D., RICHARD ROHDE, B.S., AND ITAMAR RAZ, M.D., FOR THE COLLABORATIVE STUDY GROUP*



Reduction in doubling of baseline serum creatinine

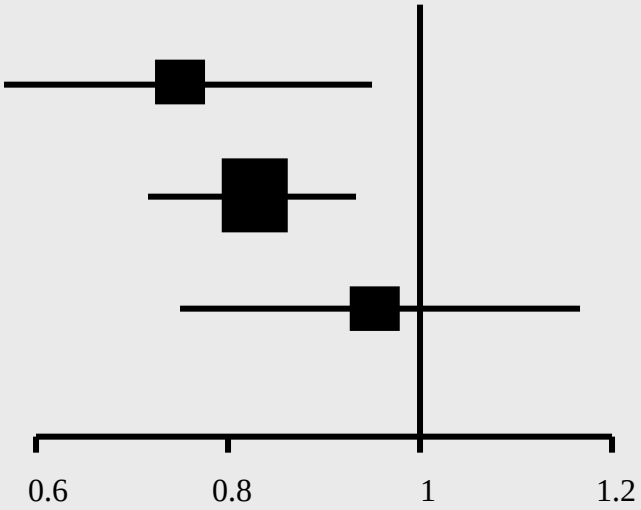


(N England J Med 2001;345:851-60)

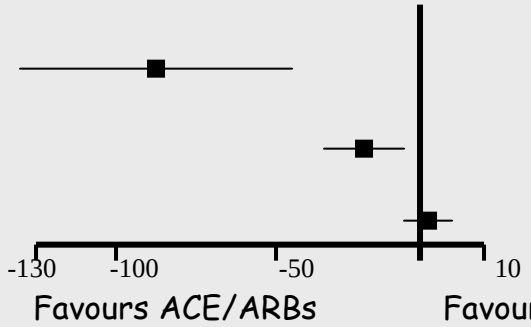
Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis

Juan P Casas, Weiliang Chua, Stavros Loukogeorgakis, Patrick Vallance, Liam Smeeth, Aroon D Hingorani, Raymond J MacAllister

Degree of change of Systolic B P Mean difference (95% IC)	ACE-I/ARBs (n/N)	Others active Interventions (n/N)	RR of ESRD ACE-I/ARBs vs Others Interv.	RR (95% CI)
-6.9 mmHg (-9.1 to 4.8)	117/1346	155/1291		0.74 (0.59 to 0.92)
-1.6 mmHg (-2.8 to 0.4)	273/6344	356/6327		0-77 (0.67 to 0.89)
1.5 mmHg (0.1 to 2.9)	206/11049	397/27043		0.90 (0.72 to 1.12)

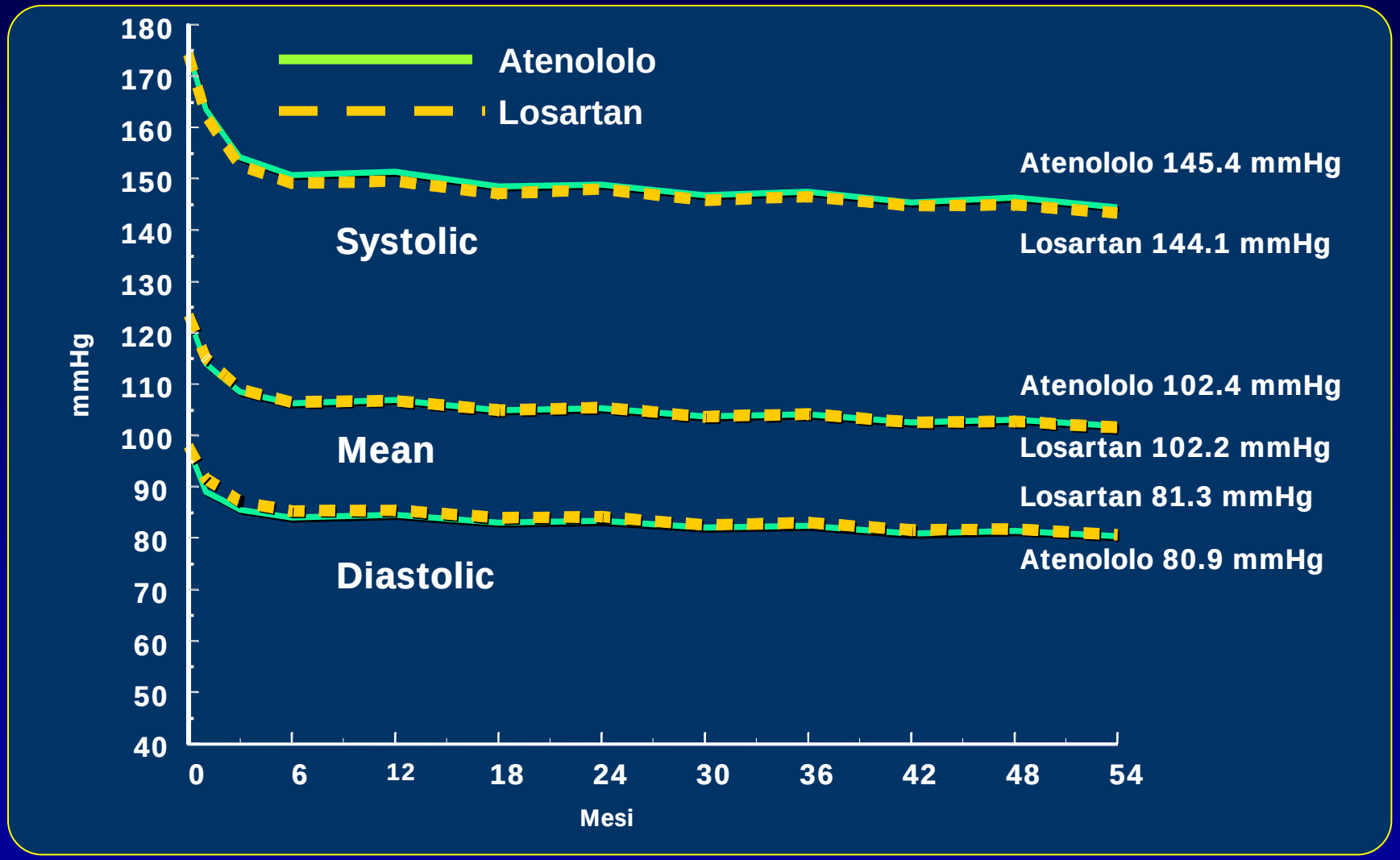


	Number of studies (Number of Patients)	Diff. of change of Albuminuria	mean difference of change
-7.6 mmHg	23 (1668)		-83.12 (-126 to -39)
-1.2 mmHg	15 (1734)		-32.73 (- 51 to –13)
3.41 mmHg	17 (2321)		-1.81 (-2.4 to 6.9)



(Lancet 2005;366:2026-33)

LIFE: no difference on blood pressure



Dahlöf B et al Lancet 2002; 359: 995-1003

Stroke reduction on isolated systolic hypertension

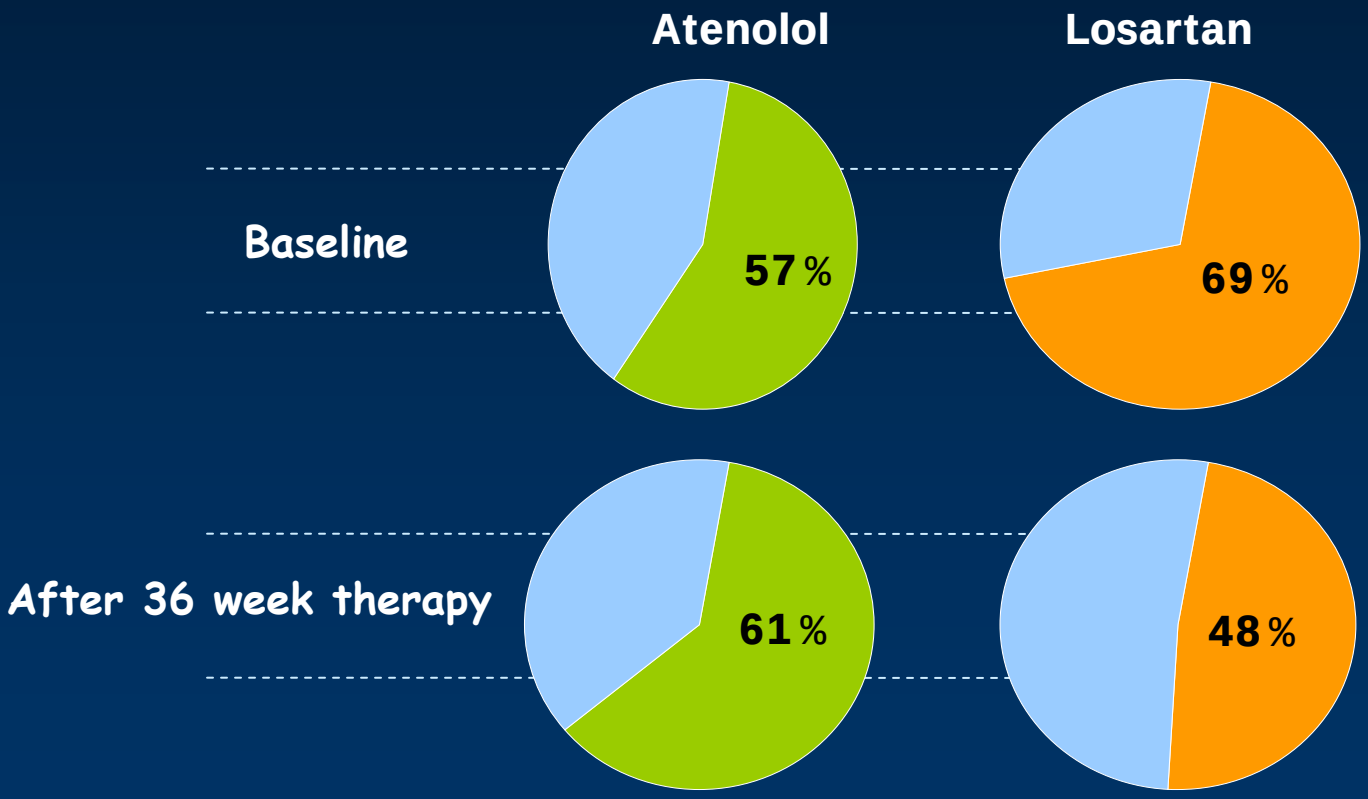
Kjeldsen SE et al. JAMA. 2002; 288:1491-1498.

Different Effects of Antihypertensive Therapies Based on Losartan or Atenolol on Ultrasound and Biochemical Markers of Myocardial Fibrosis

Results of a Randomized Trial

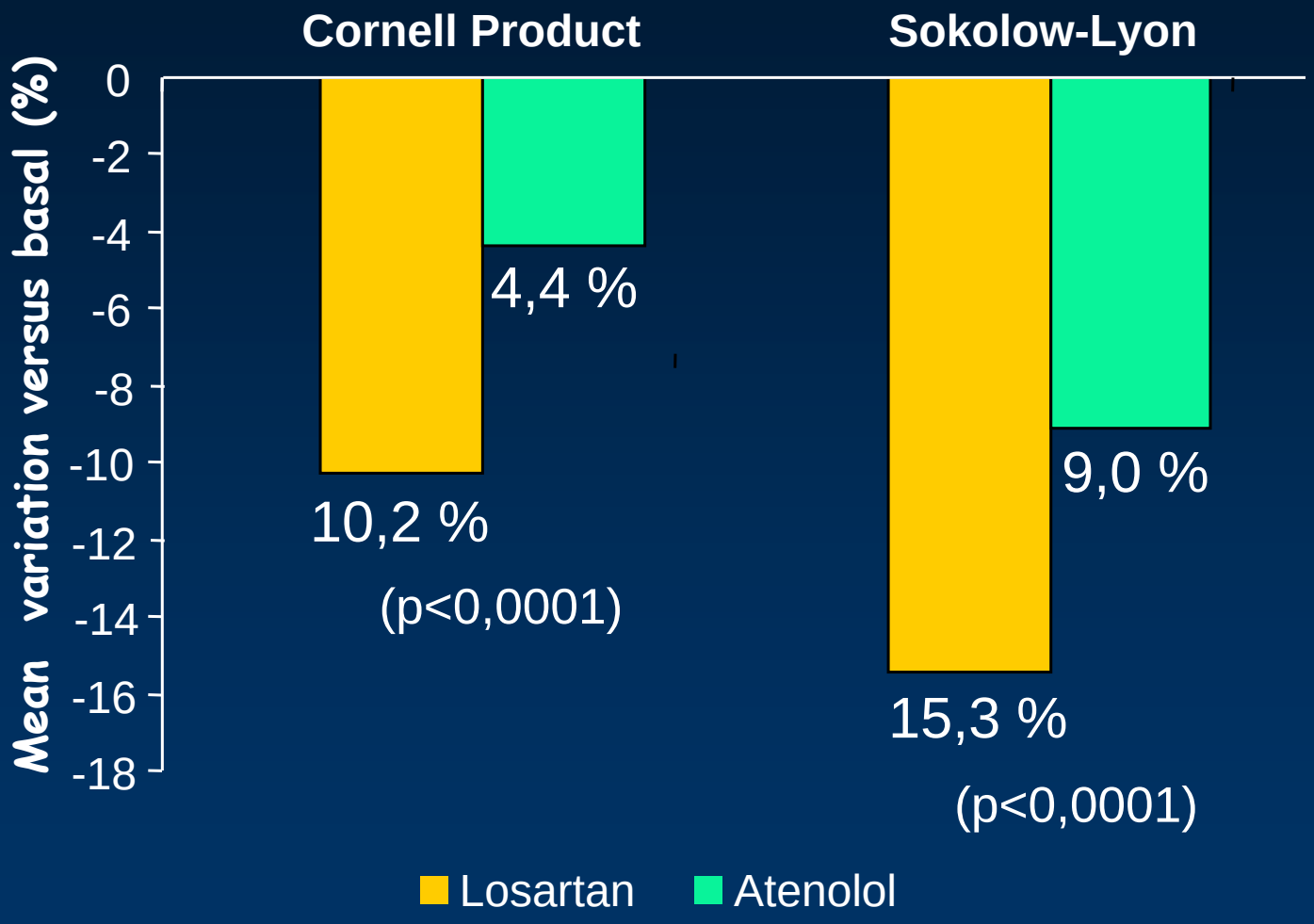
Michele M. Ciulla, MD, PhD; Roberta Paliotti, MD, PhD; Arturo Esposito, MD; Javier Diez, MD; Begoña López, BSc; Björn Dahlöf, MD; M. Gary Nicholls, MD; Ronald D. Smith, MD; Leen Gilles, PhD; Fabio Magrini, MD; Alberto Zanchetti, MD

Prevalence of excessive fibrosis in atenolol and losartan-trated patients

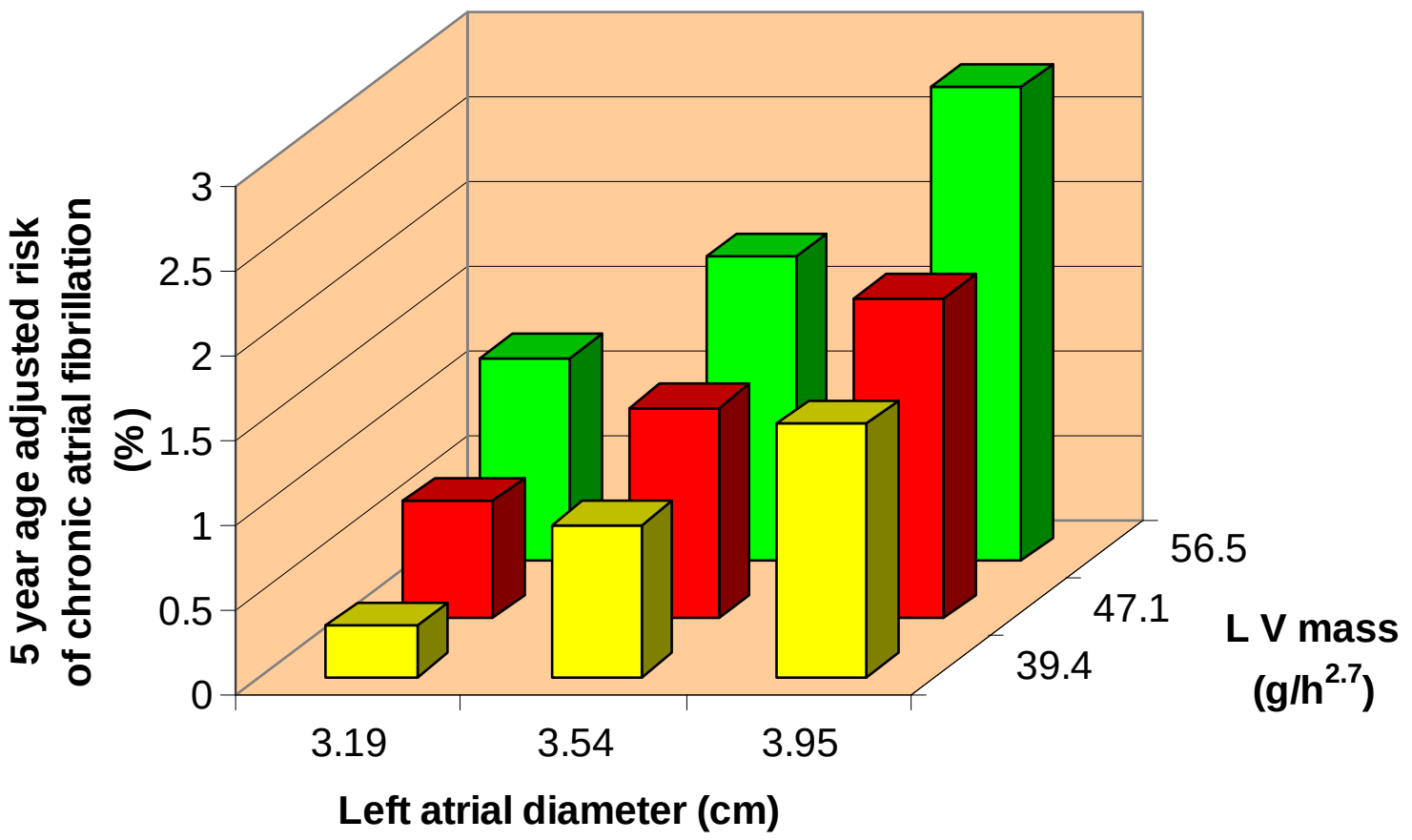


(Circulation.2004;110:552-557)

LIFE STUDY

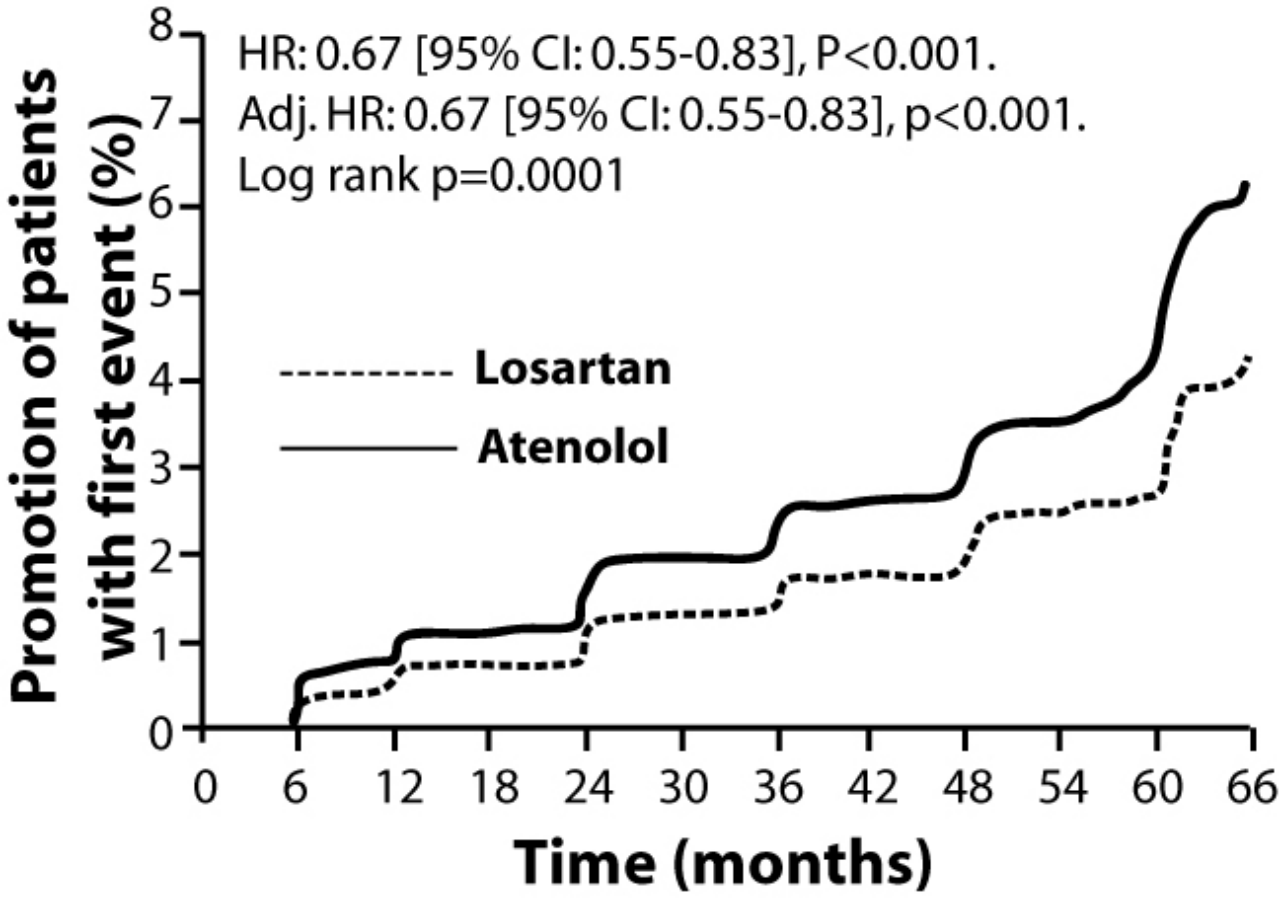


Dahlöf B et al *Lancet* 2002;359:995-1003.



(Verdecchia et al. Hypertension. 2003;41:218-223)

LIFE STUDY :New-onset E.C.G. verified atrial fibrillation



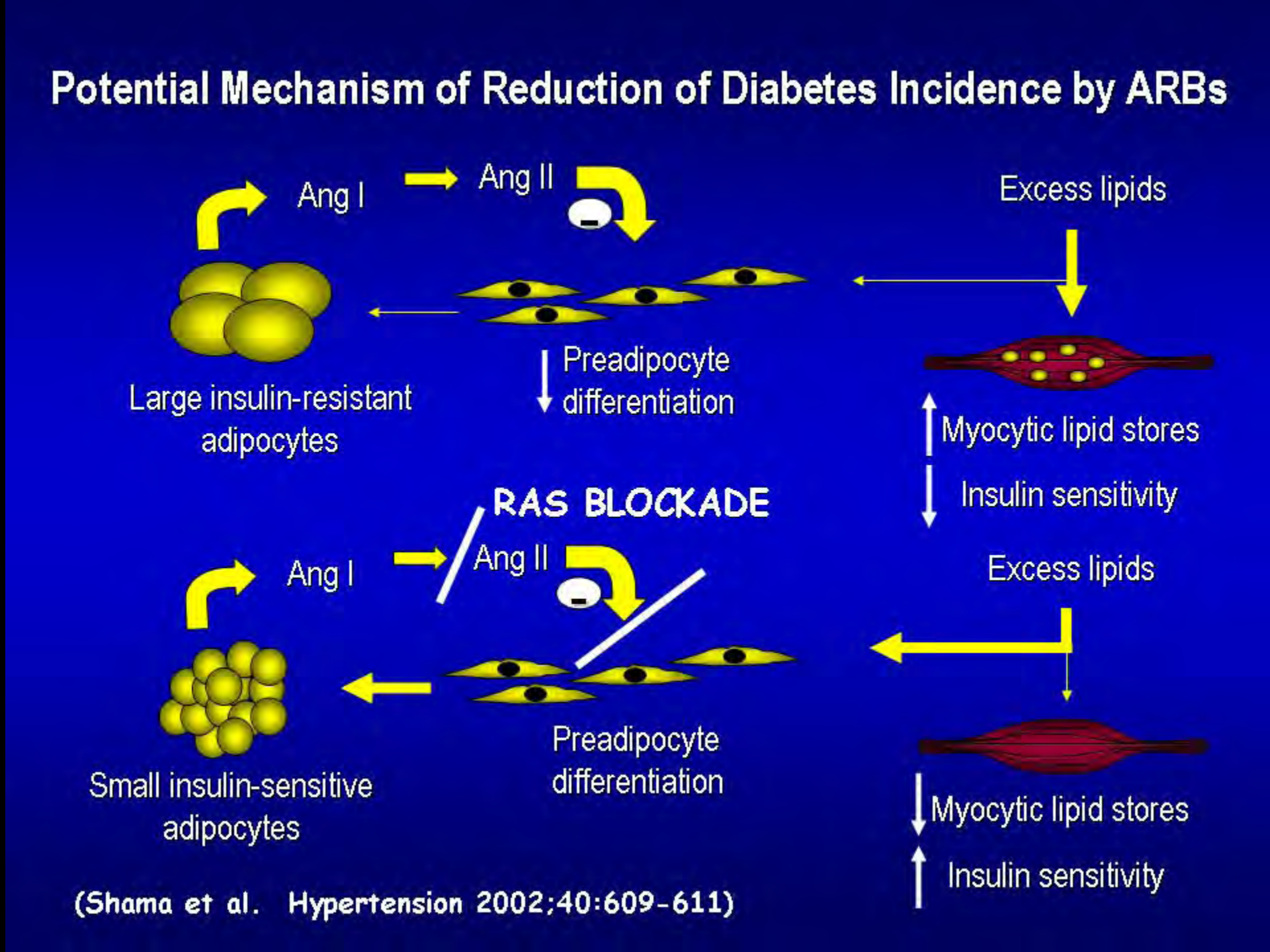
(J.Am. Coll. Cardiol. 2005;45:712-19)

Properties of ACE-Inhibitors

- Inhibition of the Renin-Angiotensin system with ACE inhibitors:
  - Lowers BP
  - Reduces mortality, MI & strokes in people with :
    - Heart failure
    - Previous CV events without heart failure
    - Diabetes plus other CV risk factors

The HOPE trial suggested that the ACE-I ramipril may also reduce diabetes mellitus

Potential Mechanism of Reduction of Diabetes Incidence by ARBs

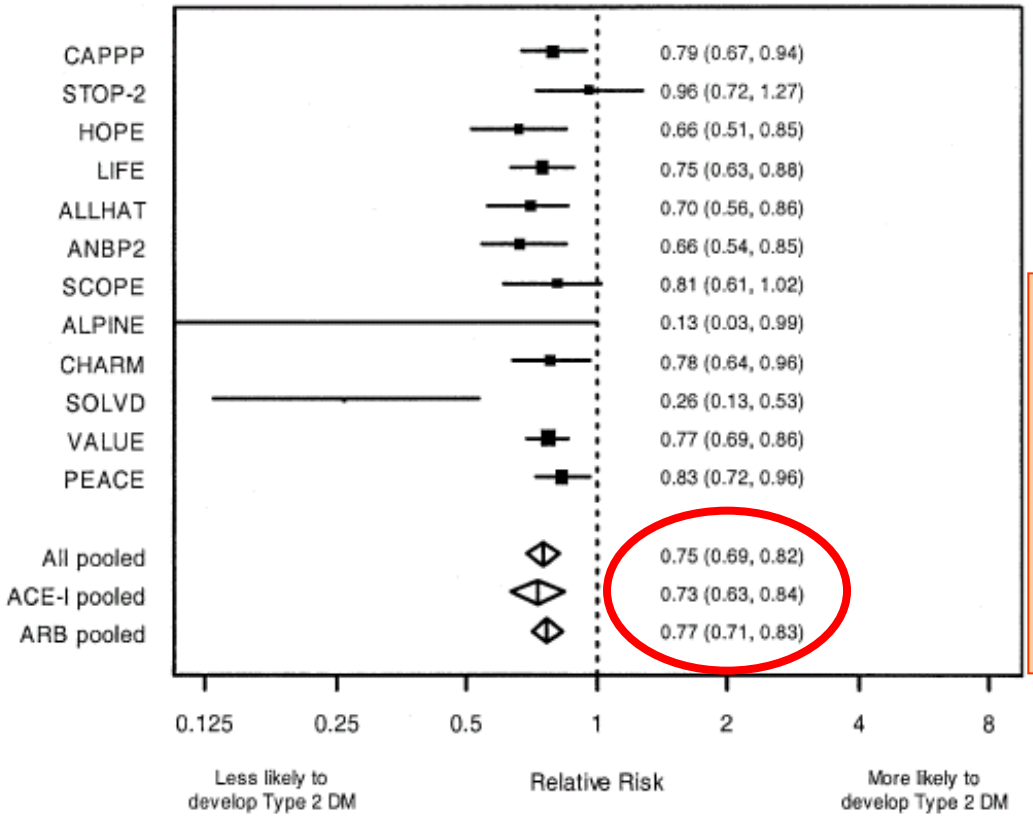


(Shama et al. Hypertension 2002;40:609-611)

Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Blockers for Prevention of Type 2 Diabetes

A Meta-Analysis of Randomized Clinical Trials

Hussam Abuissa, MD, Philip G. Jones, MS, Steven P. Marso, MD, James H. O'Keefe, Jr, MD
Kansas City, Missouri



None of these trials were designed with a reduction in the incidence of Diabetes as the primary end – point,and glucose tolerance was not assessed routinely

(J Am Coll Cardiol 2005;46:821-6)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Ramipril on the Incidence of Diabetes

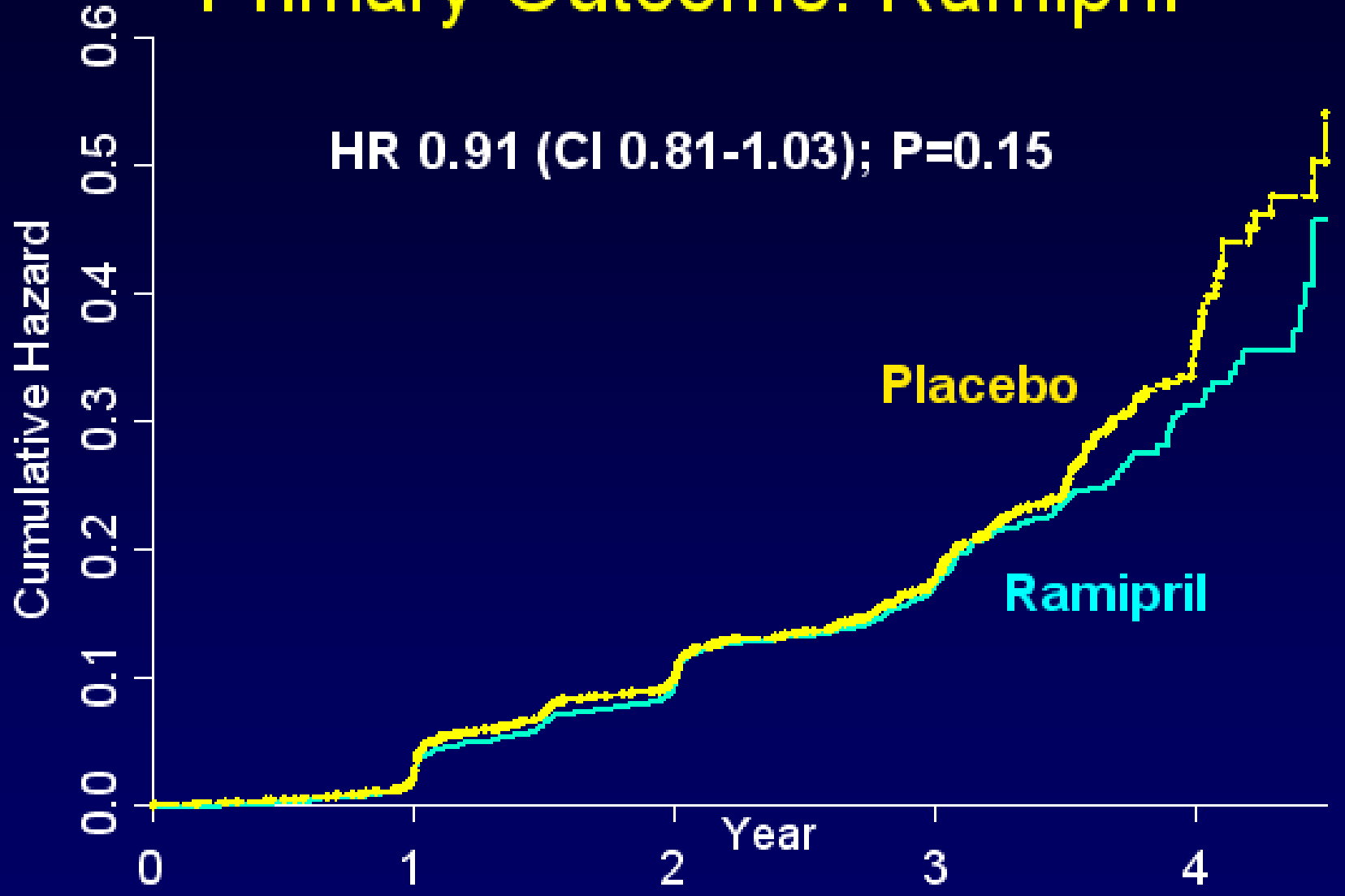
The DREAM Trial Investigators*

- Double blind randomized trial
- 5269 partecipants without CV disease but with IFG or IGT
- Randomly assigned to receive ramipril 15 mg or placebo
- Followed for a median of 3 years

Primary endpoint:development of diabetes or death
Secondary endpoint:regression to normoglycemia

(N Engl J Med 2006;355:1551-62)

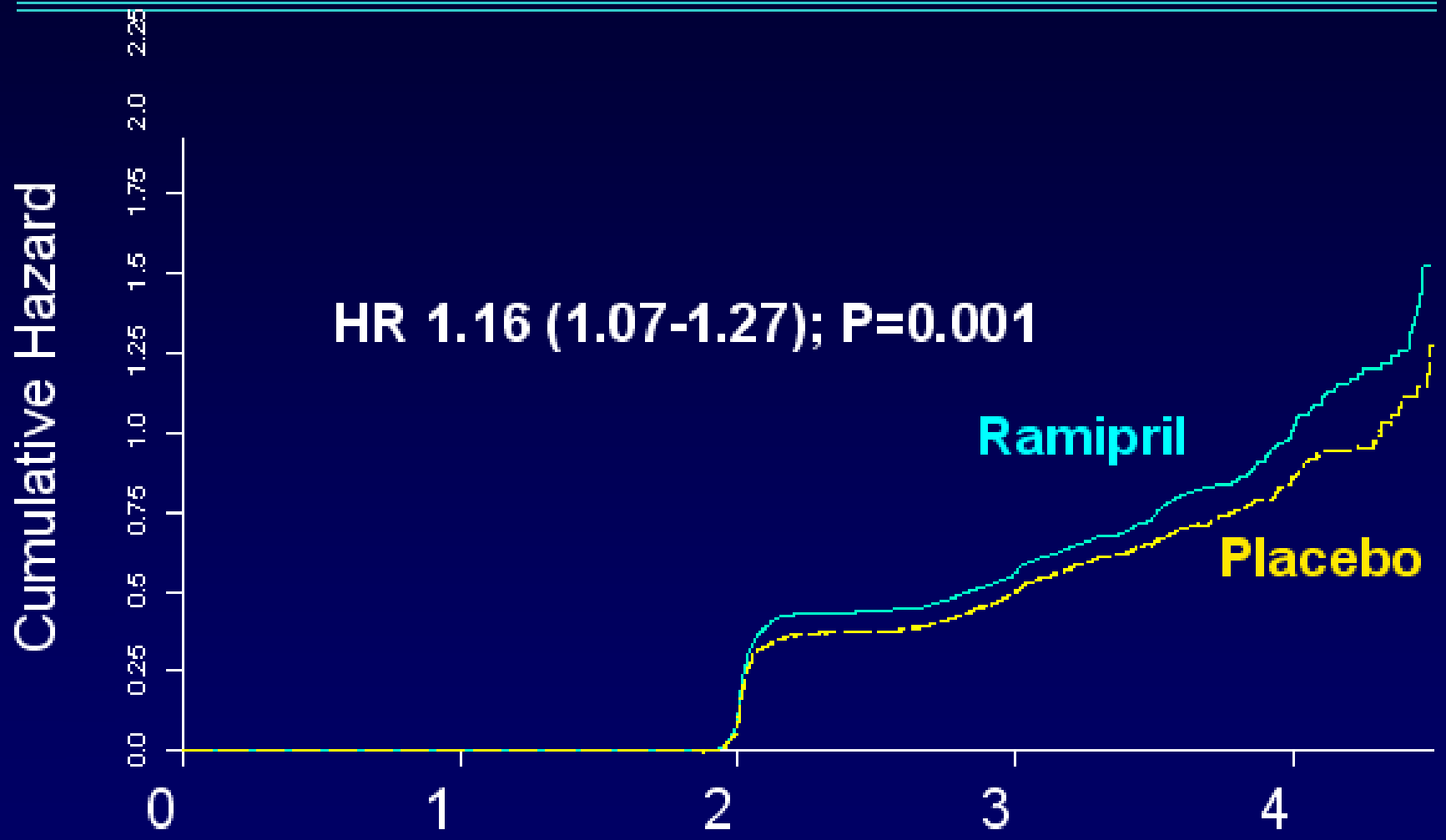
Primary Outcome: Ramipril



Placebo	2646	2510	2277	1240	200
Ramipril	2623	2498	2287	1218	194

DREAM

Regression: Ramipril



Ramipril	2623	2487	2060	791	127
Placebo	2646	2494	2090	876	145

TAKE HOME MESSAGE

- The main benefits of antihypertensive therapy are due to lowering of blood pressure "per se" largely independently of the drugs used to lower blood pressure
- The benefits of hypotensive drugs on cardiovasc. events are dependent on the patient subgroup
- There is a close relationship between BP reduction and renoprotection, in particular in patients with more proteinuria

TAKE HOME MESSAGE

- The ACEs and ARBs inhibitors have a modest nephroprotective effect
- The ACEs and ARBs in high risk patients provide evidence of greater cardiovascular risk reduction than expected on the basis of B.P. reduction
- These results suggest that at least some of the benefits are independent on blood pressure reduction

It is not beyond the blood pressure

It is the blood pressure !

(William J. Elliot Circulation; 2006)

6th AME National Meeting
Italian Association of Clinical Endocrinilogists

3th Joint Meeting with AACE
American Association of Clinical Endocrinilogists

Controversies in the Management of Cardiovascular Risk Factors

Intima-media Thickness: Just an Epidemiological Information or an Every Day Practice Tool ?

Francesco Logoluso
Medicina Interna, Endocrinologia e Malattie Metaboliche
Direttore Prof. Francesco Giorgino
Dipartimento dell'Emergenza e dei Trapianti di Organi
Università degli Studi di Bari

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doi:10.1016/S0735-1097(03)00363-2

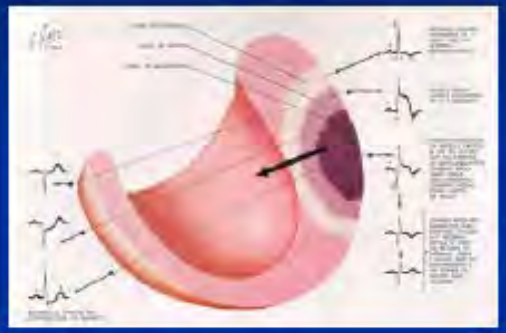
34TH BETHESDA CONFERENCE

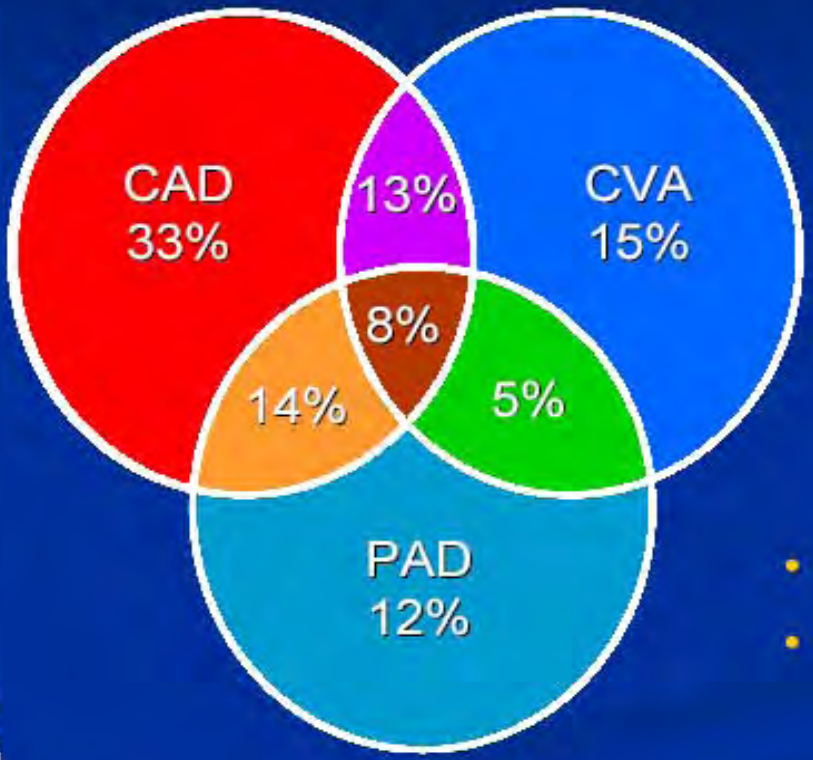
Executive Summary—Can Atherosclerosis Imaging Techniques Improve the Detection of Patients at Risk for Ischemic Heart Disease?

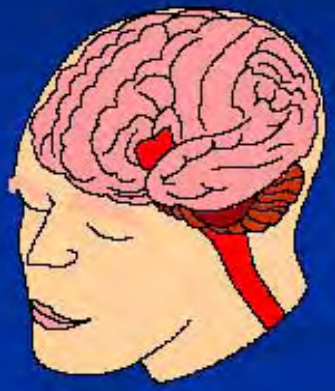
Allen J. Taylor, MD, FACC, *Conference Co-Chair*, C. Noel Bairey Merz, MD, FACC, *Conference Co-Chair*, James E. Udelson, MD, FACC, *Conference Co-Chair*

The purpose of Bethesda Conference 34 (BC 34) was to review the current status and *controversies* within the integration of atherosclerosis imaging into clinical cardiovascular medicine.

Atherosclerosis: A Systemic Disease







- 1886 patients
- Age ≥62 yrs

Aronow & Ahn. *Am J Cardiol.* 1994;74:64-65.

Vascular Echography

- **Ultrasound measurement of Carotid artery IMT is a reliable method to identify early Atherosclerotic lesions particularly in early stages when, for the outward vascular remodeling the plaque develops without compromising the lumen.**

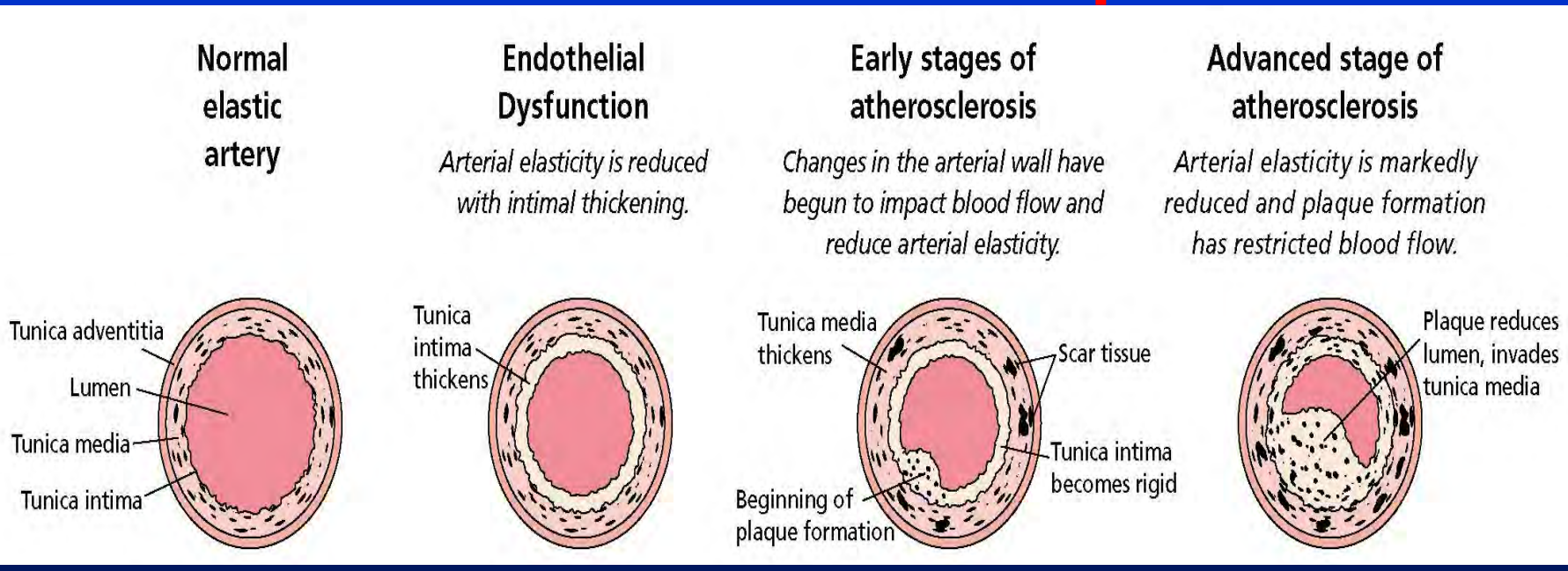
The Pathogenesis of Cardiovascular Disease:
Different stages of atherosclerotic plaque development

- IMT
(Carotid Artery)

- IVUS
(Peripheral and Coronary Artery)

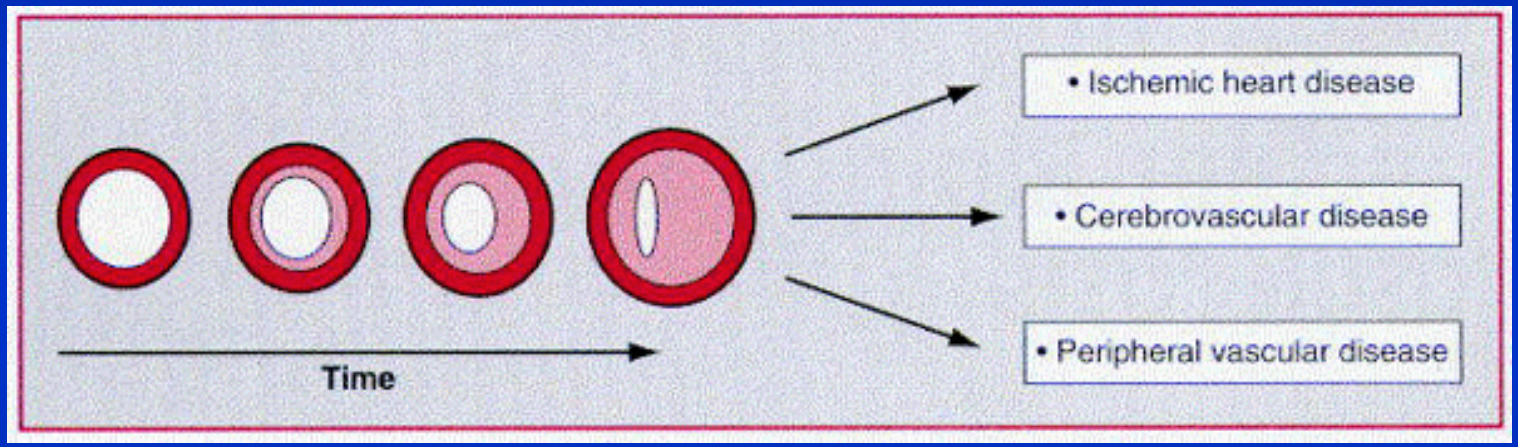
→ IMT Evaluation

→ Intimal media-thickness



Challenge

not only to “detect” atherosclerosis



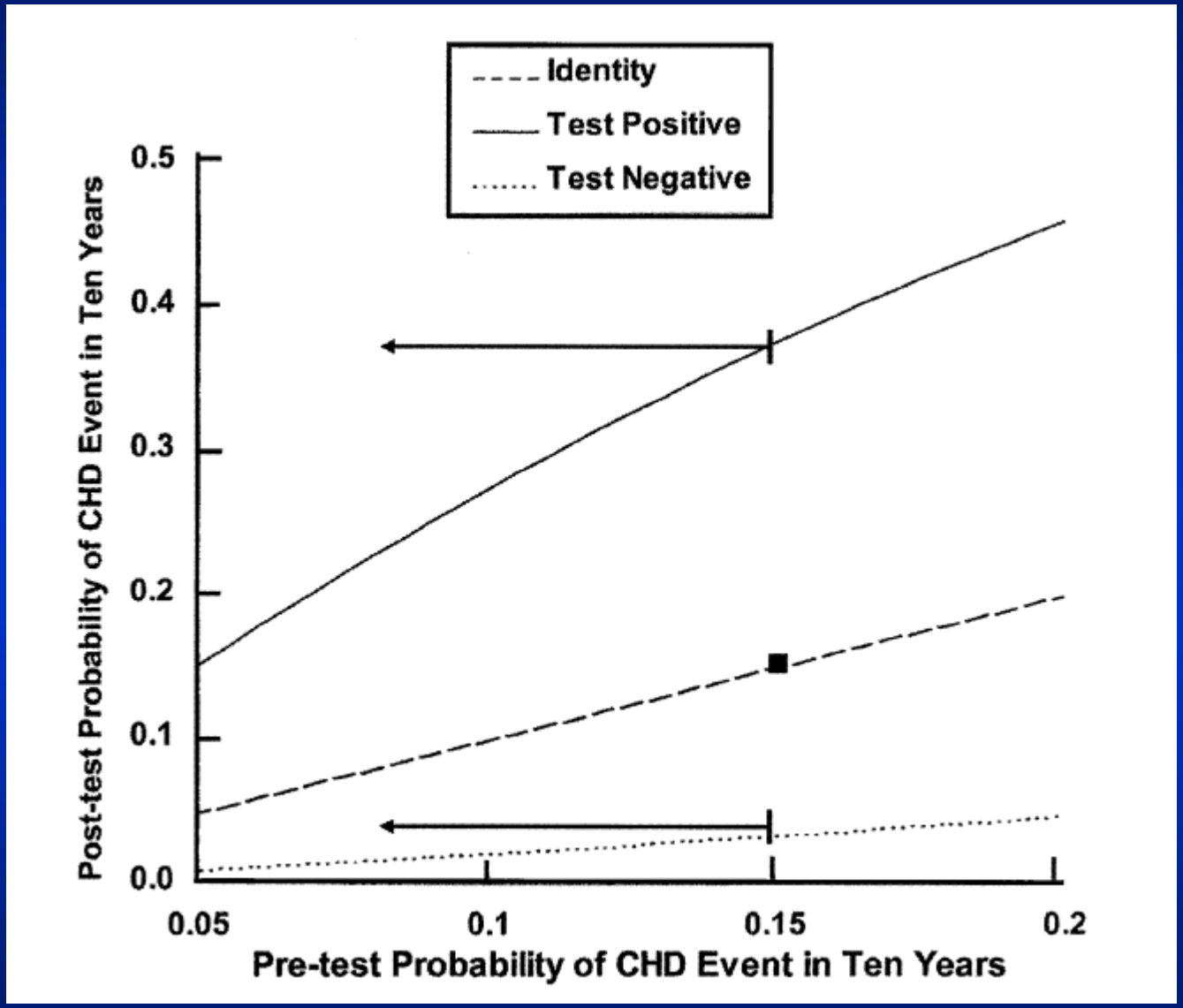
but also to “predict” which individuals will progress to develop events

In Search of the Vulnerable Patient

~500,000 First Heart Attacks Every Year

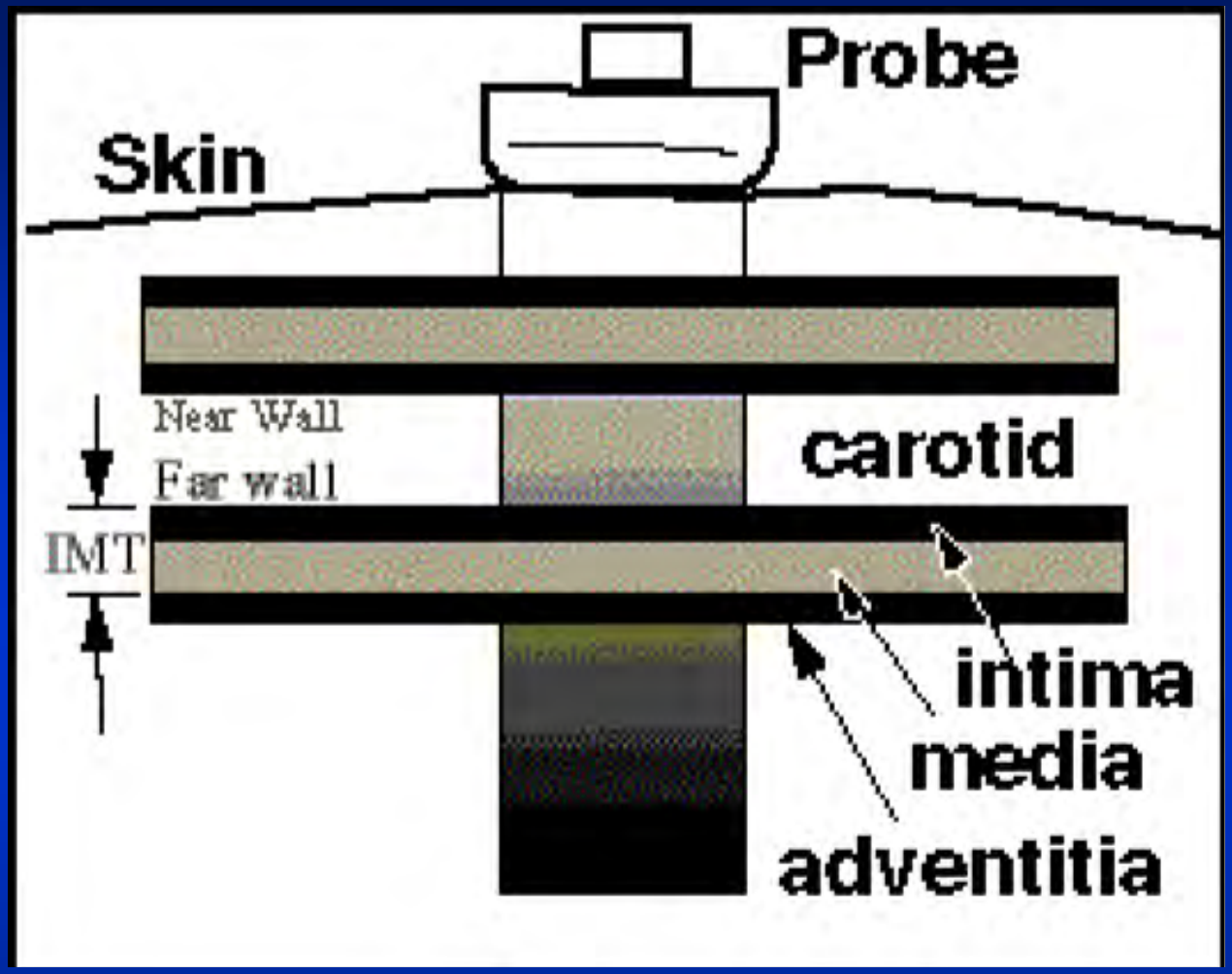
Total Population Subject to Screening for Atherosclerosis

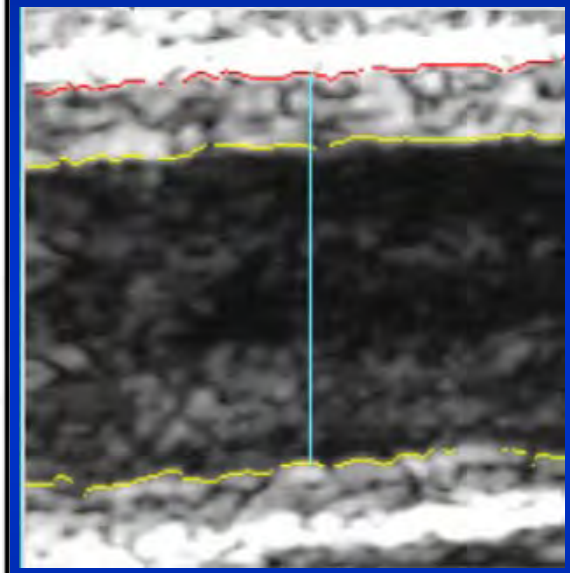
- ~50,000,000 Americans
- At-Risk & Asymptomatic
- Men age 45-75 years
- Women age 55-75 years


Identity
Test Positive
Test Negative
Post-test Probability of CHD Event in Ten Years
0.0
0.1
0.2
0.3
0.4
0.5
0.05
0.1
0.15
0.2
Pre-test Probability of CHD Event in Ten Years

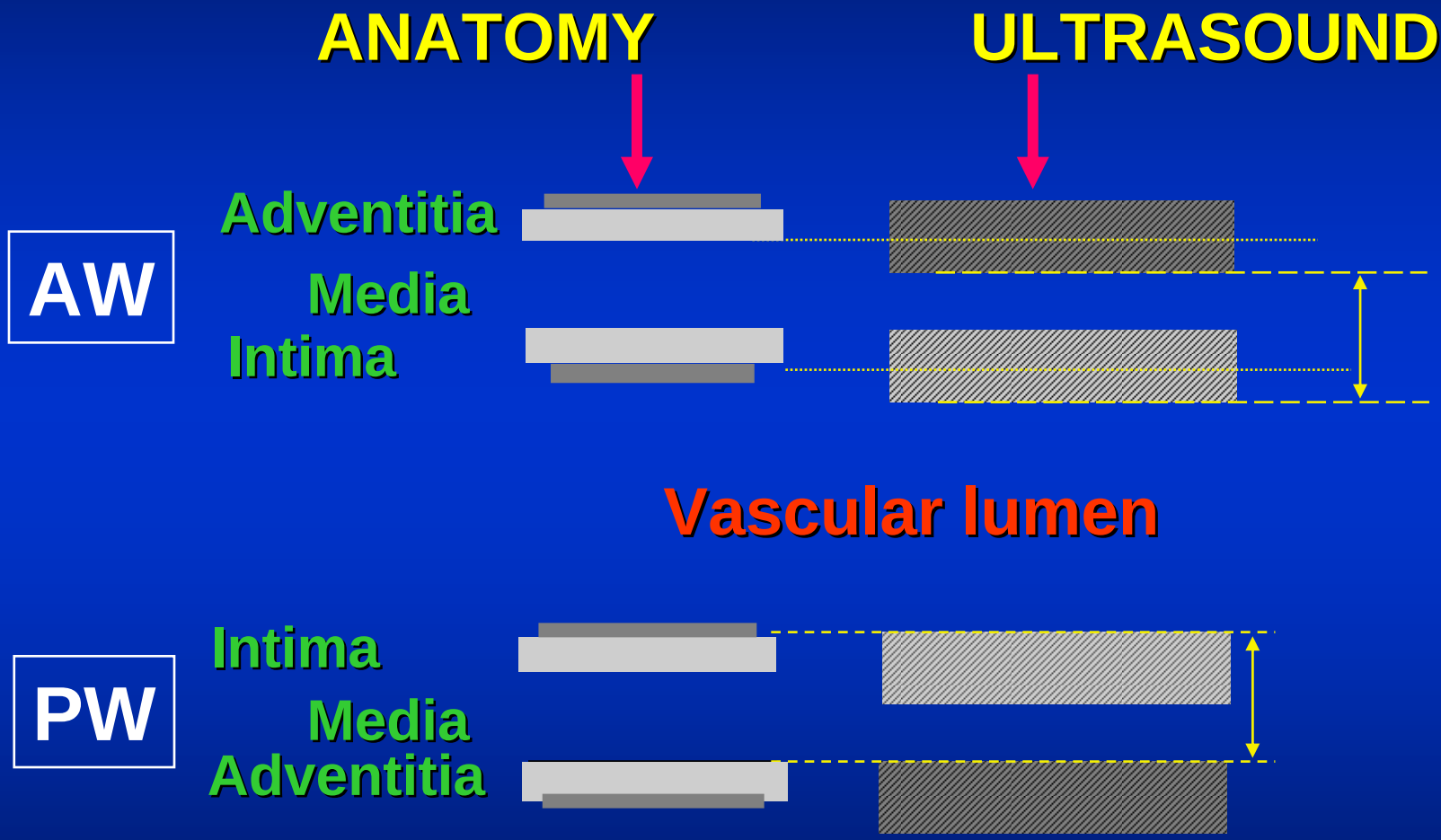
INTIMA-MEDIA THICKNESS
DEFINITION

- Thickness of intima-media complex of carotid wall.
- IMT is defined as the distance between the lumen-intima interface and the media-adventitia interface.


Probe
Skin
Near Wall
Far wall
IMT
carotid
intima
media
adventitia



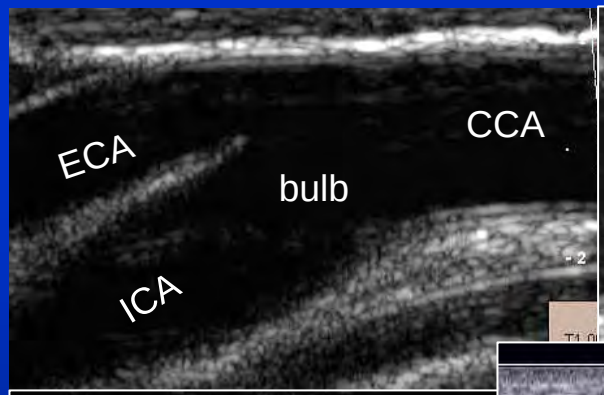
VALUATION IMT

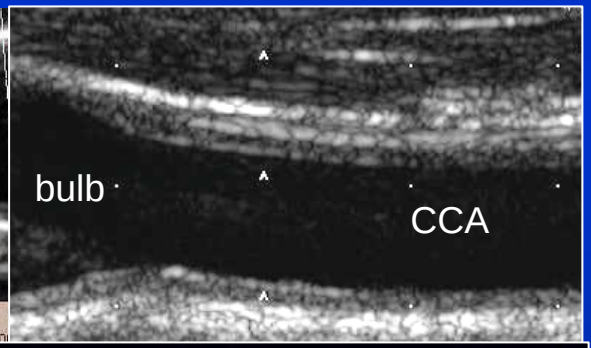


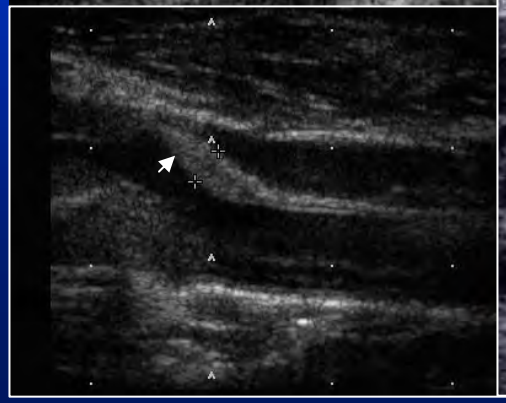
Normal and Abnormal Carotid IMT

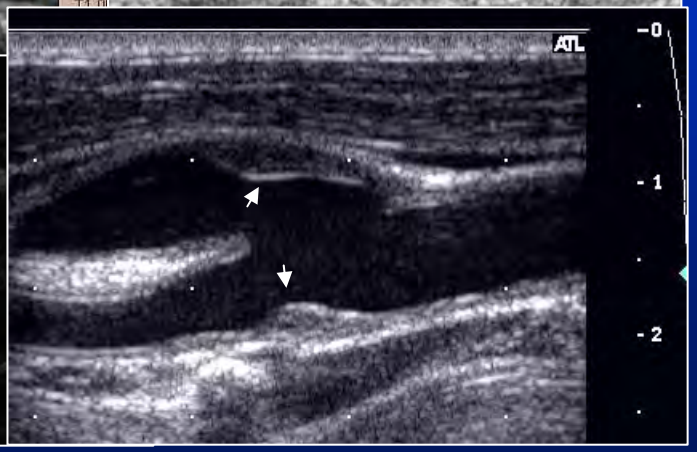
Near wall

Far wall









CLINICAL APPLICATIONS OF IMT

- Correlation with the Risk Factors for Atherosclerosis
- Surrogate Marker of CAD and Atherosclerosis in other Vascular Regions
- Indicator of Cardiovascular Risk
- Evaluation of the Effect of Drug Therapy

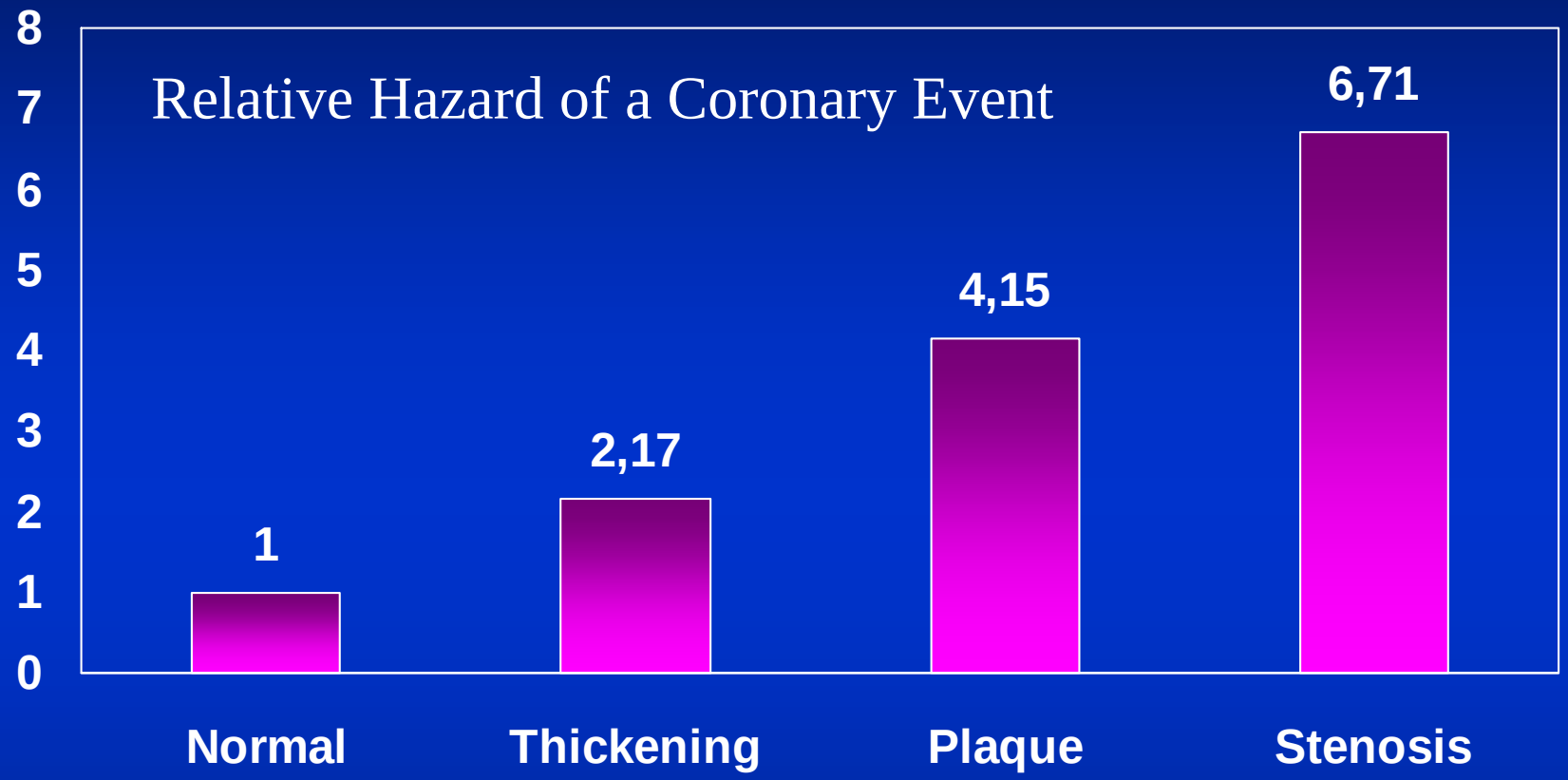
OBSERVATIONAL STUDIES
IMT: RELATION TO CLINICAL EVENTS

Increase in IMT	Site of measure	Study (country)	Subject (sex, age)	Follow-up duration (years)	Outcome	Risk ratio (95% confidence interval)
At or above 1 mm	CCA	KIHD [94] (Finland)	M, 40–60	3	AMI	2.2 (0.07–6.7)
At or above 1 mm	Mean maximum 6 sites	ARIC [95,96] (USA)	M, 45–64	4–7	CHD	1.9 (1.3–2.7)*
			W, 45–64	4–7	CHD	5.1 (3.1–8.4)*
			M, 45–64	6–9	Stroke	3.6 (1.5–9.2)*
			W, 45–64	6–9	Stroke	5.5 (3.5–20.7)*
At or above 1.18 mm	CCA	CHS [97] (USA)	M-W, ⩾ 64	6	AMI and stroke	2.9 (2–4)†
Per 0.16 mm	CCA	Rotterdam [98] (Holland)	M-W, ⩾ 55	3	AMI	1.4 (1.2–1.8)†
			M-W, ⩾ 55	3	Stroke	1.4 (1.3–1.8)†

KIHD, Kuopio Ischaemic Heart Disease; ARIC, Atherosclerosis Risk In Communities; CHS, Cardiovascular Health Study; CCA, common carotid artery; AMI, acute myocardial infarction; CHD, coronary heart disease. *Adjusted for age and race; †adjusted for age and sex.

Journal of Hypertension 2002, 20:159±169

Carotid IMT and Incident Cardiovascular Disease (KIHD Study)



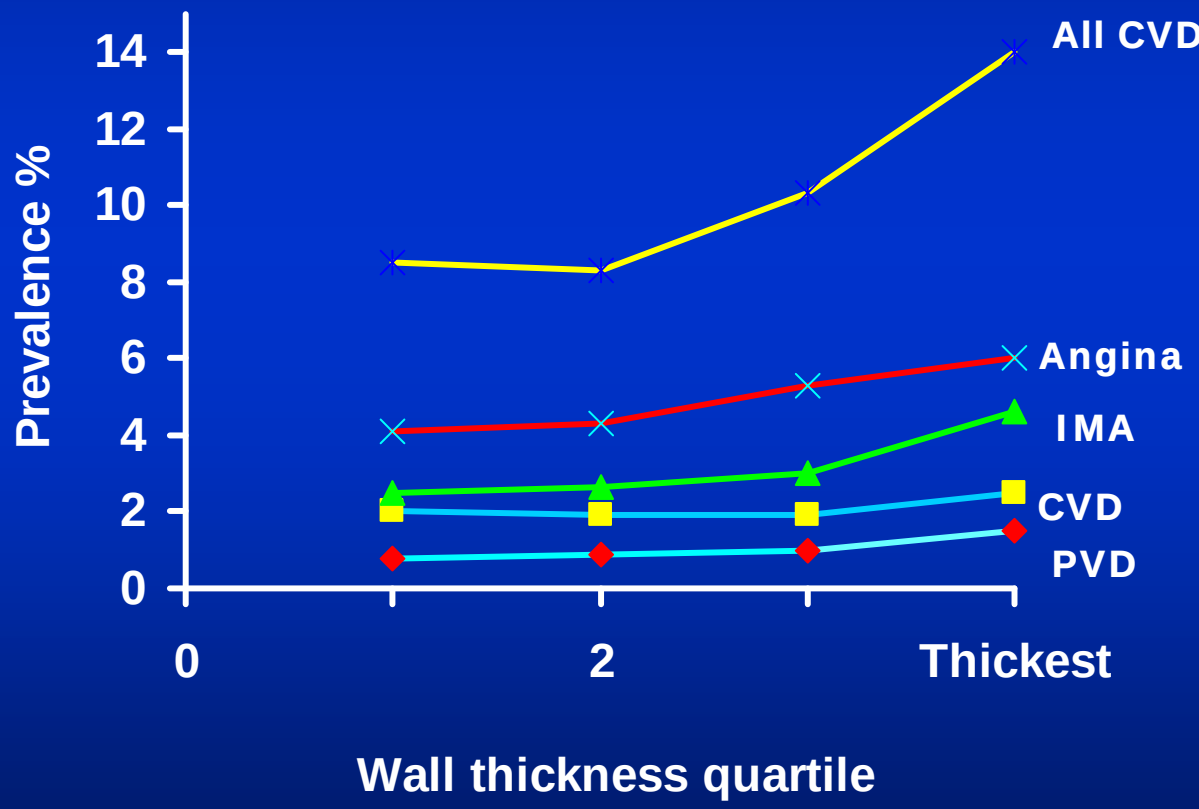
	Normal	Thickening	Plaque	Stenosis
Events	5	6	11	2
Men at risk	608	257	386	37

Arteriosclerosis and Thrombosis *Vol 11, No 5 September/October 1991*

Atherosclerosis Risk in Communities (ARIC) Study (12,800 subjects, 45-64 years of age at baseline)

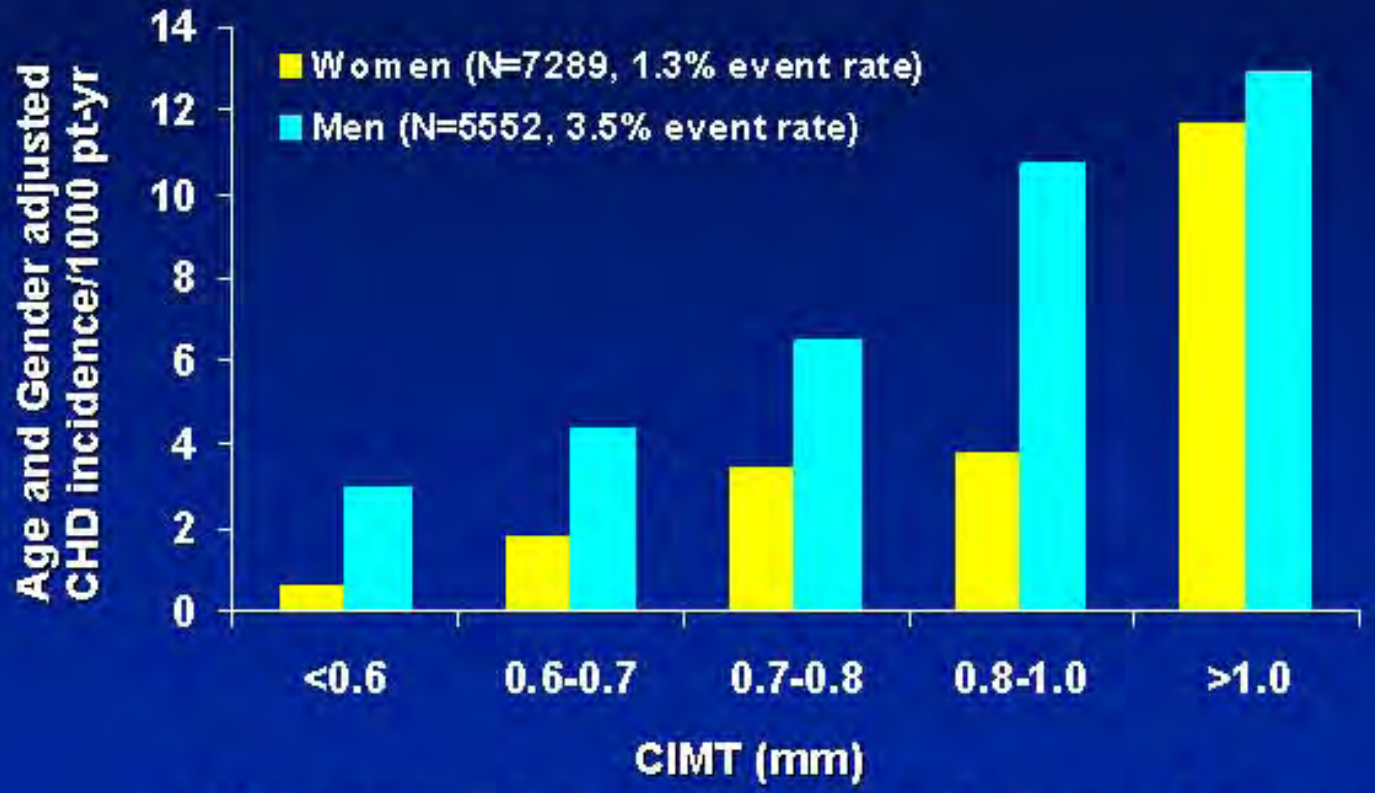
Clinical Events within 5.2 Years of Follow-Up for ***IMT***

ARIC Study (1995)



GL Burke-Stroke 1995

CIMT Predicts Future CHD Events
ARIC Study

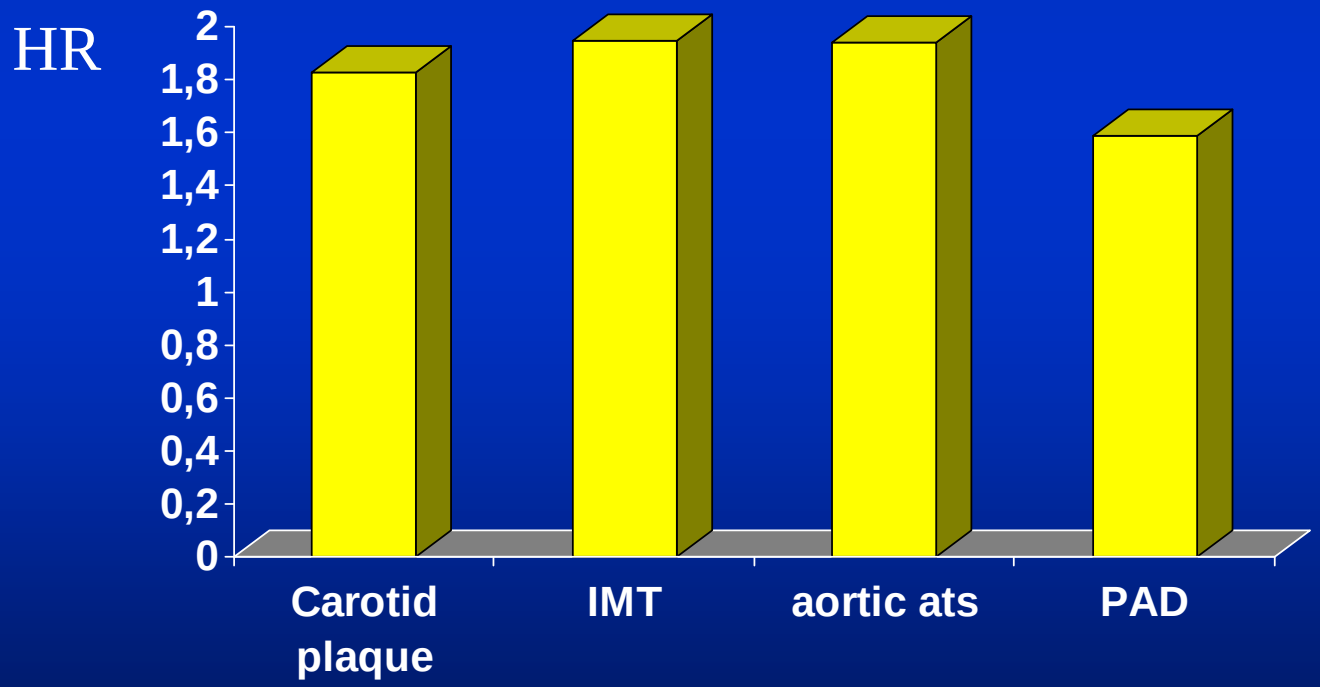


- CHD = MI/cardiac death; mean follow-up = 5.2 years

Chambless LE, et al. Am J Epidemiol 1997;146:483

Predictive Value of Noninvasive Measures of Atherosclerosis for Incident Myocardial Infarction The Rotterdam Study

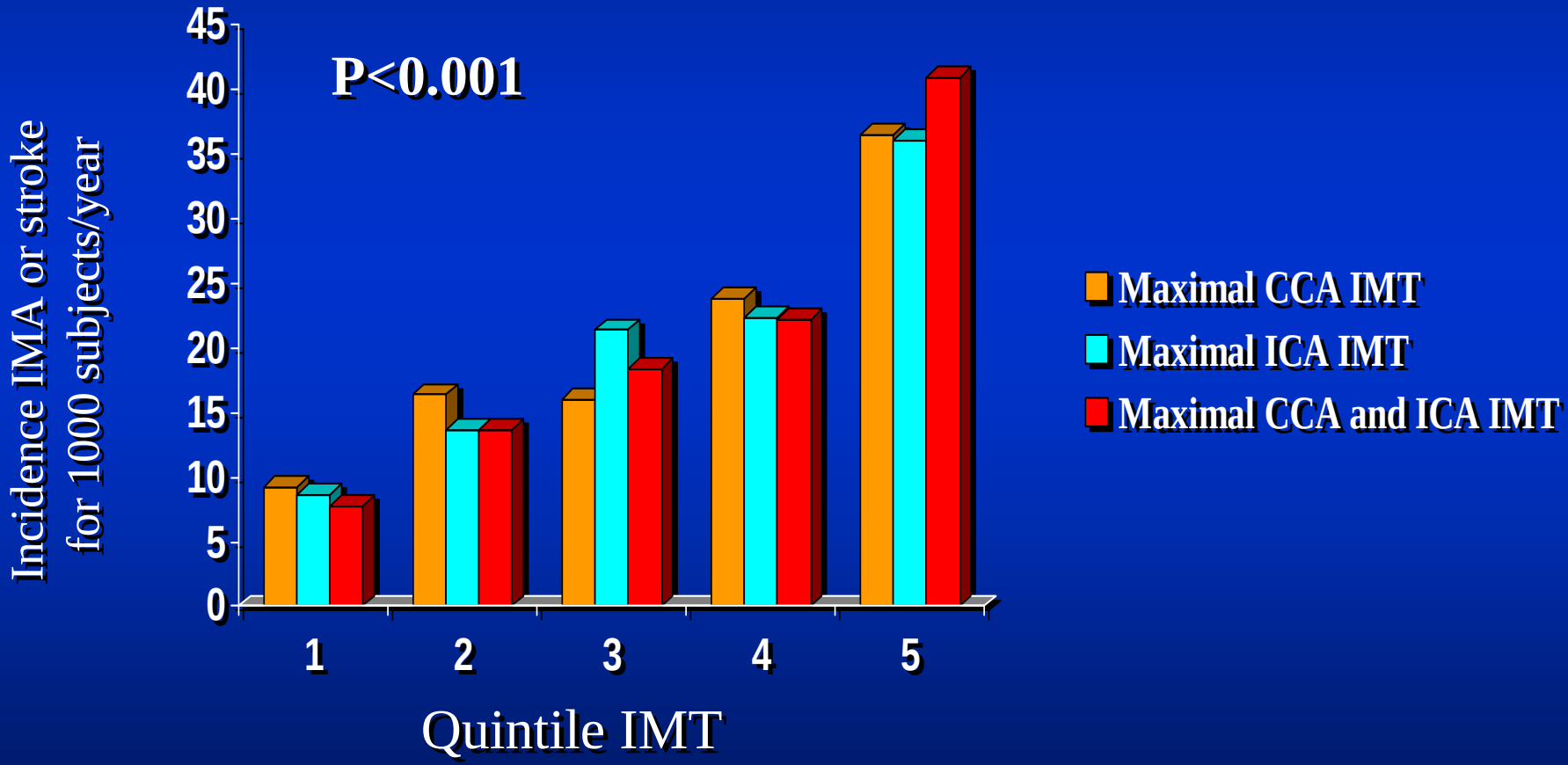
In the present study, 6389 subjects were included; 258 cases of incident MI occurred before January 1, 2000. All 4 measures of atherosclerosis were good predictors of MI independently of traditional cardiovascular risk factors.



Noninvasive measures of extracoronary atherosclerosis are strong predictors of MI.

PREDICTIVE OF IMT IN THE ELDERLY CHS STUDY

CAROTID ARTERY INTIMA AND MEDIA THICKNESS AS A RISK FACTOR FOR MYOCARDIAL INFARCTION AND STROKE IN OLDER ADULTS

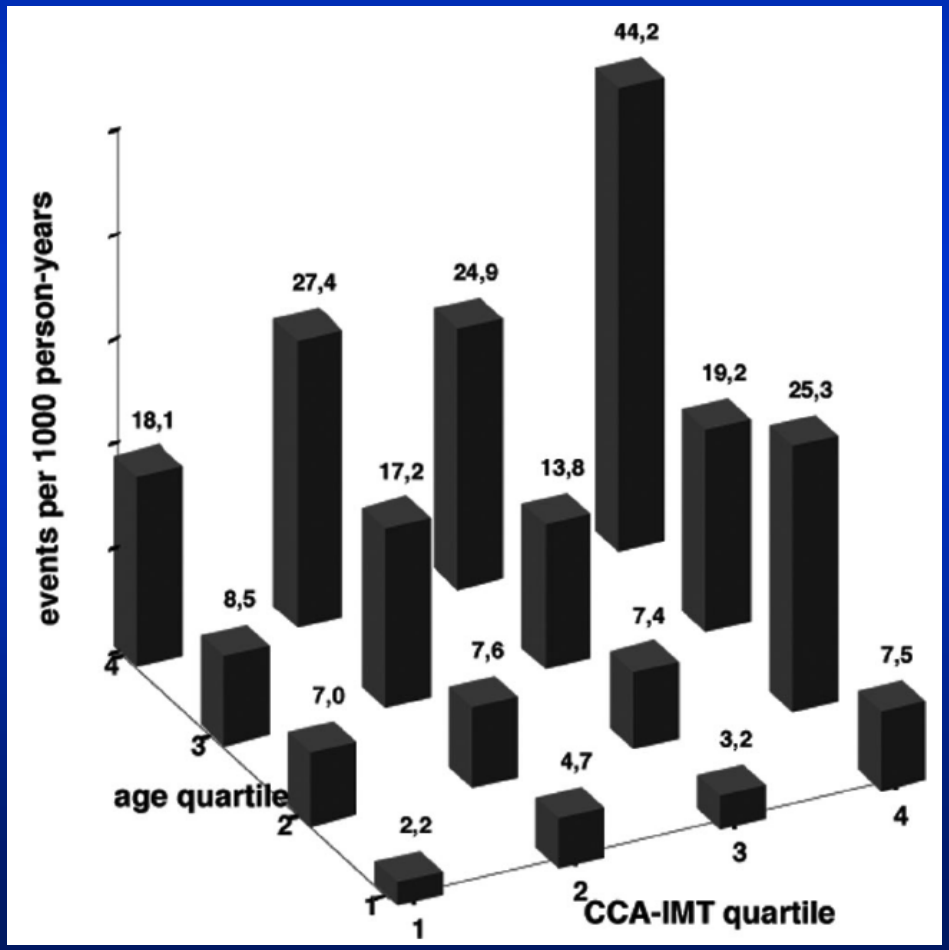


DH O'Leary, N Eng J Med 1999

Carotid Intima-Media Thickening Indicates a Higher Vascular Risk Across a Wide Age Range

Prospective Data From the Carotid Atherosclerosis Progression Study (CAPS)

Matthias W. Lorenz, MD; Stefan von Kegler, MD; Helmuth Steinmetz, MD; Hugh S. Markus, FRCP; Matthias Sitzer, MD



Event rates for the combined end point (MI, stroke or death) by age and IMT quartiles

Stroke, 2006;37:87-92

CLINICAL TRIALS ON IMT

Effect of lipid-lowering drugs on carotid intima±media thickness (IMT) in randomized double-blind trials

Treatment	Study	Outcome	Patients	Follow-up (years)	IMT progression rate (mm/year)		
					Drug	Control	*P*
Colestipol/niacin versus placebo	CLAS [110]	Mean CCA	Coronary	4	−0.012 ± 0.003	0.012 ± 0.003	< 0.001
Pravastatin versus placebo	PLAC II [102]	Mean maximum 12 sites	Coronary	3	0.059 ± 0.008	0.068 ± 0.008	NS
	REGRESS [103]	Mean CA-FE	Coronary	2	0.00 ± 0.20	0.05 ± 0.20	0.008
	KAPS [100]	Mean maximum 12 sites	Asymptomatic	3	0.017 ± 0.004	0.031 ± 0.003	0.005
	LIPID [112]	Mean CCA	Coronary	4	−0.003 ± 0.002	0.012 ± 0.002	< 0.001
	CAIUS [101]	Mean maximum 12 sites	Asymptomatic	3	−0.004 ± 0.003	0.009 ± 0.003	< 0.001
Lovastatin versus placebo	ACAPS [104]	Mean maximum 12 sites	Asymptomatic	3	−0.009 ± 0.003	0.006 ± 0.003	0.001
	MARS [111]	Mean CCA	Coronary	4	−0.028 ± 0.003	0.015 ± 0.005	< 0.001
Atorvastatin versus simvastatin	ASAP [105]	Mean maximum 12 sites	Familial Hypercholesterolemic	2	−0.015*	0.018*	< 0.001

Data are mean ± SE. CCA, Common carotid artery; CA, carotid; FE, femoral; NS, non significant. *Estimated from change in IMT after 2 years.

Journal of Hypertension 2002, 20:159-169

CLINICAL TRIALS ON IMT

Effect of calcium antagonism and angiotensin-converting enzyme inhibition on carotid intima±media thickness (IMT) in randomized double-blind trials

Treatment	Study	Outcome	Patients	Follow-up	IMT progression rate (mm/year)		
					Drug	Control	*P*
Isradipine versus hydrochlorothiazide	MIDAS [106]	Mean maximum 12 sites	Hypertensive	3	0.04 ± 0.002	0.05 ± 0.002	NS
Verapamil versus chlortalidone	VHAS [107]	Mean maximum 6 sites	Hypertensive	4	0.015 ± 0.005	0.016 ± 0.005	NS
Lacidipine versus atenolol	ELSA [22]	Mean maximum 4 sites	Hypertensive	4	-	-	
Nifedipine versus hydrochlorothiezide/amiloride	INSIGHT [113] IMT	Mean CCA	Hypertensive	4	-0.007 ± 0.002	0.0077 ± 0.002	0.002
Amlodipine versus placebo	PREVENT [108]	Mean maximum 12 sites	Coronary	3	-0.012 ± 0.012	0.033 ± 0.012	0.007
Ramipril versus placebo	SECURE [109]	Mean maximum 12 sites	High risk	4.5	0.014 ± 0.002	0.022 ± 0.003	0.03

Journal of Hypertension 2002, 20:159±169

Screening for Atherosclerosis

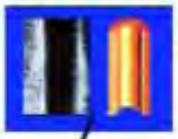
Risk Factors vs Disease

Numerous Risk Factors

- High LDL
- Low HDL
- High BP
- Diabetes
- Smoking
- CRP
- Metabolic Syn
- Lp(a)
- Homocysteine
- Dense LDL
- Lp-PLA2
- ApoB/ApoA
- Family History
- Sedentary Life
- Obesity
- Stress
- ...
- ?

Over 200 risk factors have been reported.

Examples of Arterial Structure Tests



Carotid IMT and Plaque Measured by Ultrasound

Aortic and Carotid Plaque Detected by MRI

Coronary Calcium Score Measured by CT

Ankle Brachial Index

Brachial Vasoreactivity Measured by Ultrasound

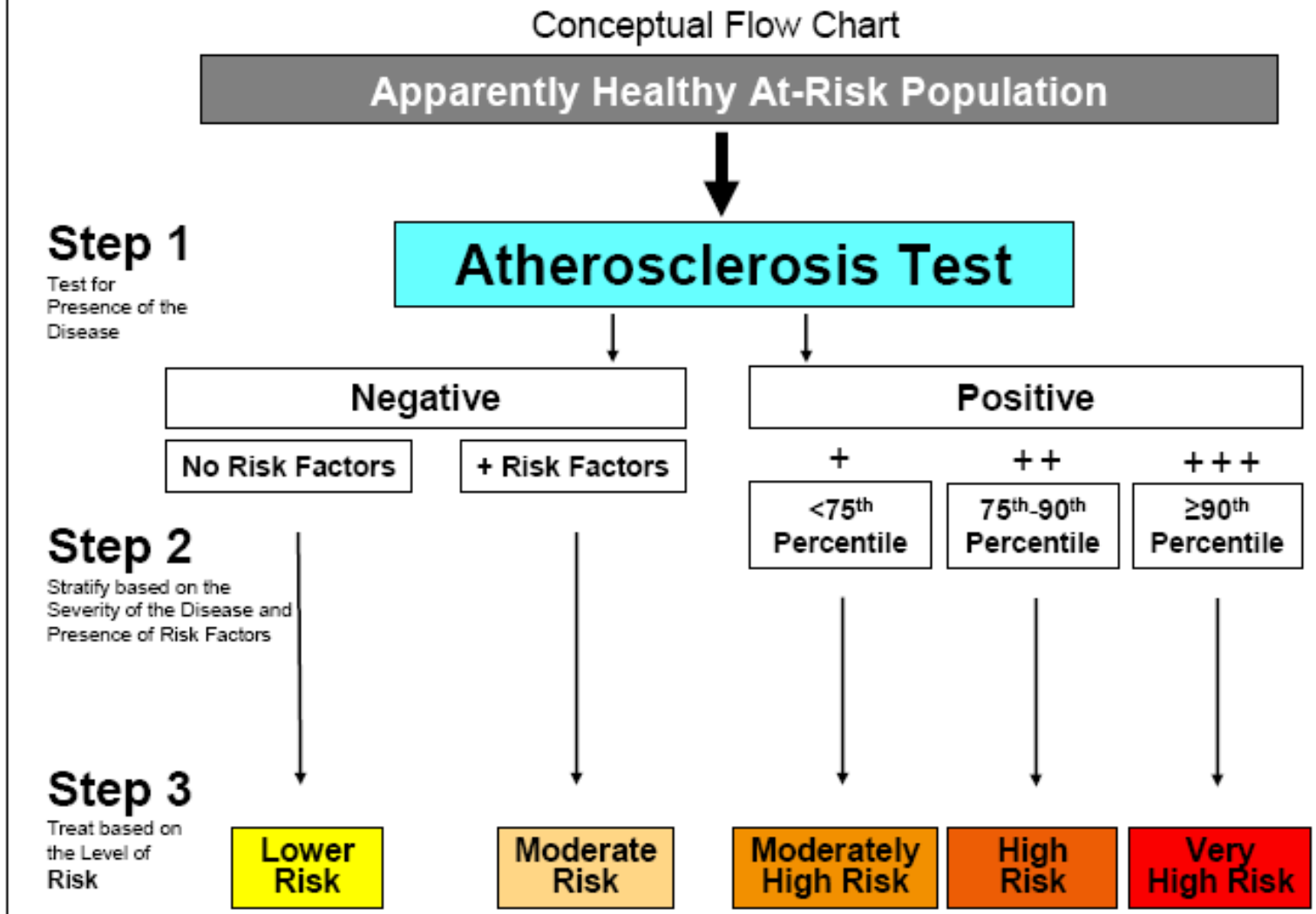
Vascular Compliance Measured by Radial Tonometry

Examples of Arterial Function Tests

Microvascular Reactivity Measured by Fingertip Tonometry

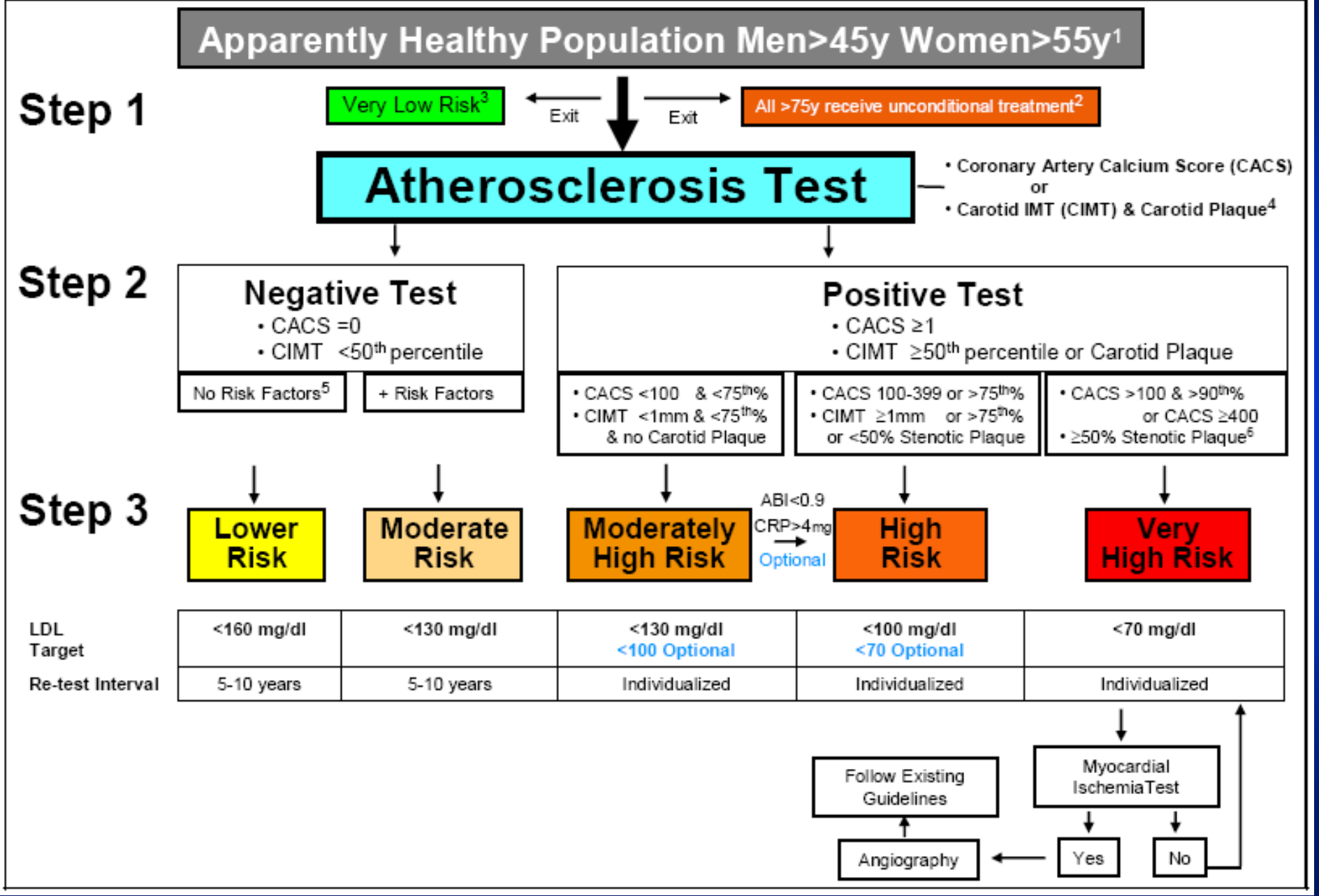
The 1st S.H.A.P.E. Guideline

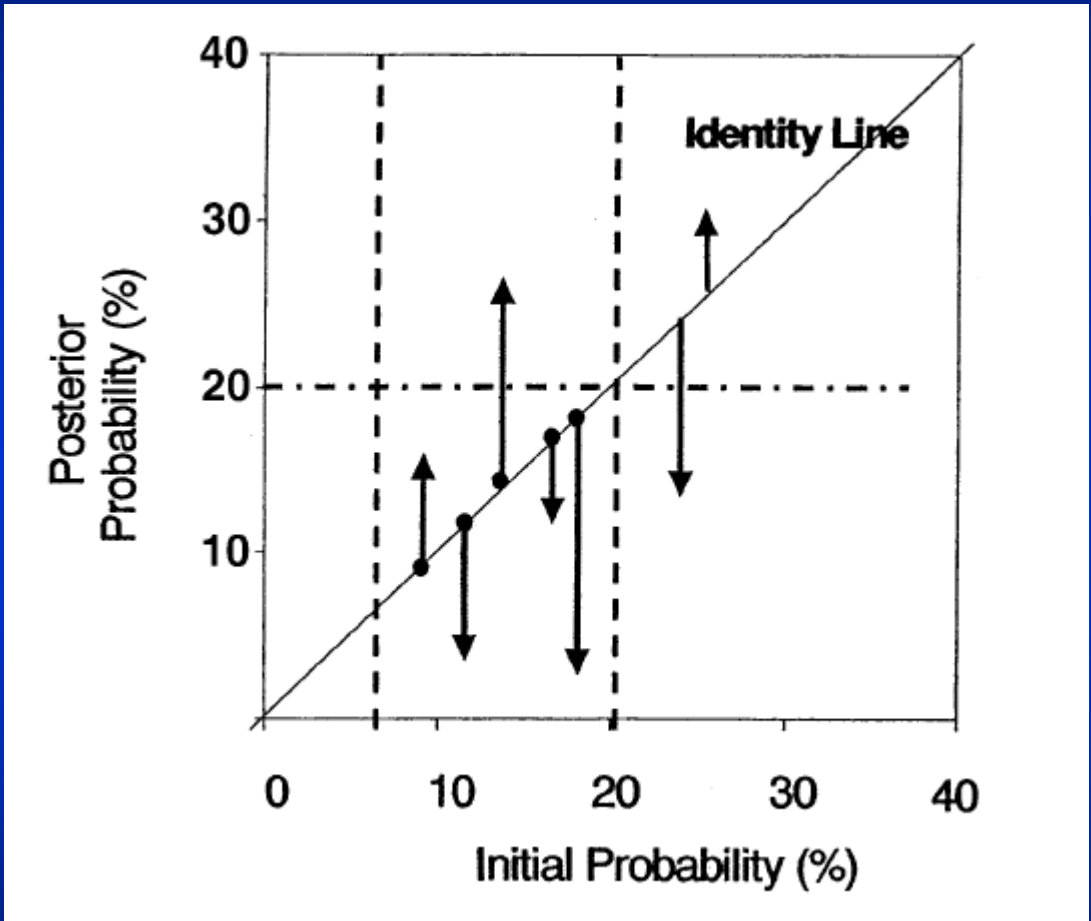
Towards the National Screening for Heart Attack Prevention and Education (**SHAPE**) Program



The 1st S.H.A.P.E. Guideline

Towards the National Screening for Heart Attack Prevention and Education (SHAPE) Program




40
30
20
10
Identity Line
Posterior Probability (%)
0
10
20
30
40
Initial Probability (%)

Screening for atherosclerosis in “real world” settings

It is important to note that the vast majority of data that documents the importance of subclinical disease markers to predict CVD outcome has been collected in highly controlled research settings (28,29). Thus, excellent quality control measures, very detailed protocols, and highly trained personnel were involved in all phases of the imaging and reading components. Translating the results of clinical studies to real-world settings will require similar attention to quality control and accuracy. *Without such controls, the potential exists for misclassification of subclinical disease, resulting in errors in the cardiovascular risk assessment.*

Screening for atherosclerosis in “real world” settings

Although carotid IMT has clearly been shown to be associated with risk of cardiovascular events and stroke in large-scale population-based studies, guidelines do not exist to recommend specific follow-up above certain age- and gender-based cut points for IMT, nor how these recommendations may be modified according to an individual’s cardiovascular risk factor profile. In addition, the reproducibility of the measurement may be in question unless done at a highly skilled facility.

AHA Prevention Conference V – "Beyond Secondary Prevention: Identifying the High-Risk Patient for Primary Prevention"

"Carotid artery B-mode ultrasound imaging is a safe, noninvasive, and relatively inexpensive means of assessing subclinical atherosclerosis. The technique is a valid and reliable means of measuring IMT, an operational measure of atherosclerosis. The severity of carotid IMT is an independent predictor of transient cerebral ischemia, stroke, and coronary events such as MI. Writing Group III concluded that ***in asymptomatic persons >45 years old, carefully performed carotid ultrasound examination with IMT measurement can add incremental information*** to traditional risk factor assessment. ***In experienced laboratories, this test can now be considered for further clarification of CHD risk assessment at the request of a physician."***

Greenland P, et al. Writing Group III. *Circulation* 2000; Jan 4;101(1):E16-22.

Role of Noninvasive Testing in the Clinical Evaluation of Women With Suspected Coronary Artery Disease

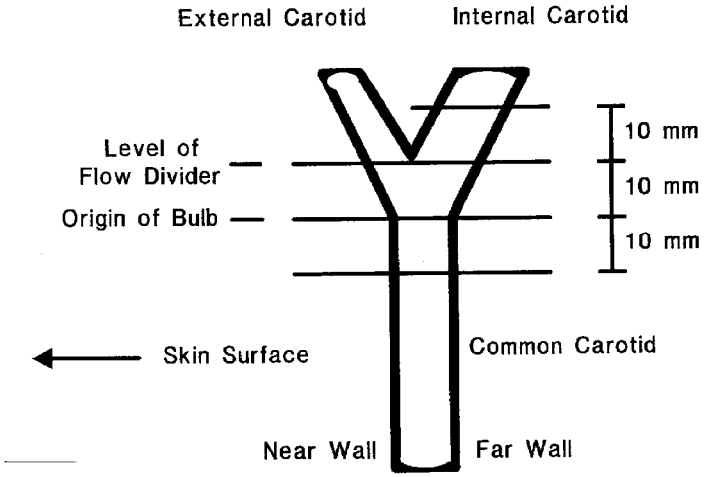
Consensus Statement From the Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association

Jennifer H. Mieres, MD, Chair; Leslee J. Shaw, PhD; Andrew Arai, MD; Matthew J. Budoff, MD; Scott D. Flamm, MD; W. Gregory Hundley, MD; Thomas H. Marwick, MD, PhD; Lori Mosca, MD, PhD; Ayan R. Patel, MD; Miguel A. Quinones, MD; Rita F. Redberg, MD, MSc; Kathryn A. Taubert, PhD; Allen J. Taylor, MD; Gregory S. Thomas, MD, MPH; Nanette K. Wenger, MD

"Similar to other techniques for the noninvasive measurement of atherosclerosis burden for CAD risk stratification in asymptomatic women, the clinical use of carotid IMT has not been shown to result in improved outcomes."

Circulation 2005;11:682-696

INTIMA-MEDIA THICKNESS METHODS OF MEASUREMENT



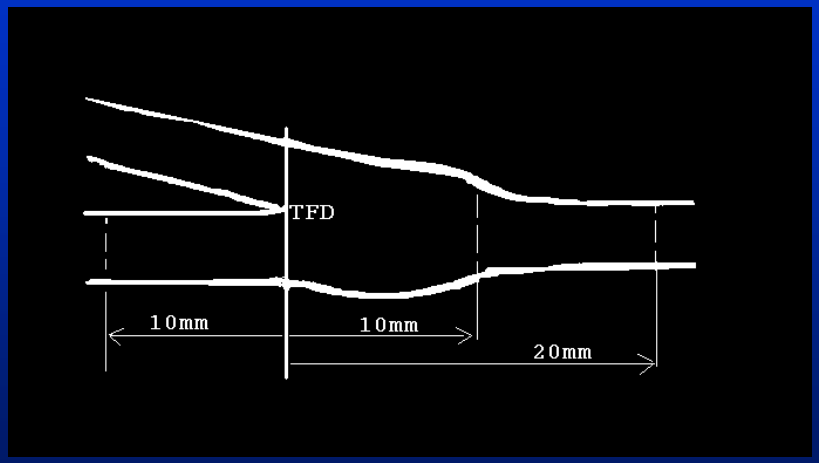


Image acquisition	Segment: CCA, bulb, ICA, right/left Wall: far, near
Type of measure	Mean and maximum value of IMT Mean of measures over 1 cm (>100)
Methods of analysis	Manual cursor placement Automated computerized edge-detection

CCA, Common carotid artery; ICA: internal carotid artery.

INTIMA-MEDIA THICKNESS METHODS OF MEASUREMENT

STUDY	IMAGE ACQUISITION		METHODS OF IMT MEASUREMENT	
	segment	Wall	Type of measure	Method of analysis
CLAS 1993	CCA	FAR	Mean of maximal IMT measurements	Automated
ARIC 1993	CCA-bulb CIA	FAR	Mean of IMT measurements 6 sites	Manual
ACAPS 1994	CCA-bulb CIA	FAR	Mean of maximal IMT measurements	Manual
CHS 1999	CCA-CIA Bulb	FAR NEAR	Mean of maximal IMT measurements	Manual
Balbarini 2000	CCA	FAR	Mean and maximal value. 6 IMT measurements	Manual
Rotterdam 2003	CCA-bulb CIA	FAR NEAR	Mean of maximal CCA IMT	Manual
Mesa 2006	CCA	FAR NEAR	Mean of maximal CCA IMT	Manual

Special Article

Cerebrovascular Diseases

Cerebrovasc Dis 2004;18:346–349
DOI: 10.1159/000081812

Published online: November 2, 2004

Mannheim Intima-Media Thickness Consensus

on Behalf of the Advisory Board of the 3rd Watching the Risk Symposium 2004, 13th European Stroke Conference, Mannheim, Germany, May 14, 2004

P.-J. Touboul M.G. Hennerici S. Meairs H. Adams P. Amarenco
M. Desvarieux S. Ebrahim M. Fatar R. Hernandez Hernandez S. Kownator
P. Prati T. Rundek A. Taylor N. Bornstein L. Csiba E. Vicaut K.S. Woo
F. Zannad

- **Common carotid artery**
- **Far wall measurements**
- **Minimum 7MHz probes**
- **Minimum 10 mm length of IMT from well-visualized segment**

CONCLUSIONS

US non invasive measure of IMT is:

- A simple technique
- A marker of early stages of atherosclerosis (preintrusive stage)
- A surrogate peripheral arterial marker of CAD
- A strong indicator of cardiovascular risk
- A reliable method to evaluate the efficacy of drug therapy
- The strenght of the arguments is better supported if the IMT measurements are standardize by a Consensus