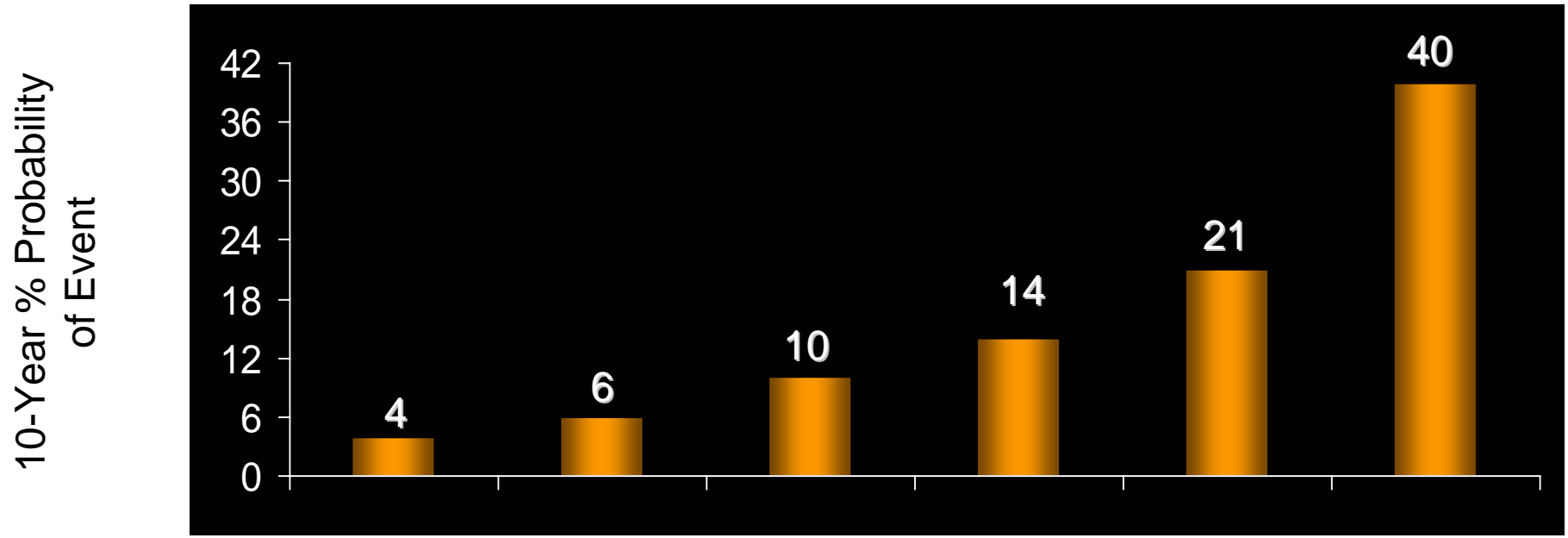


Dyslipidemia and hypertension

Effect of Multiple Risk Factors on Probability of CAD

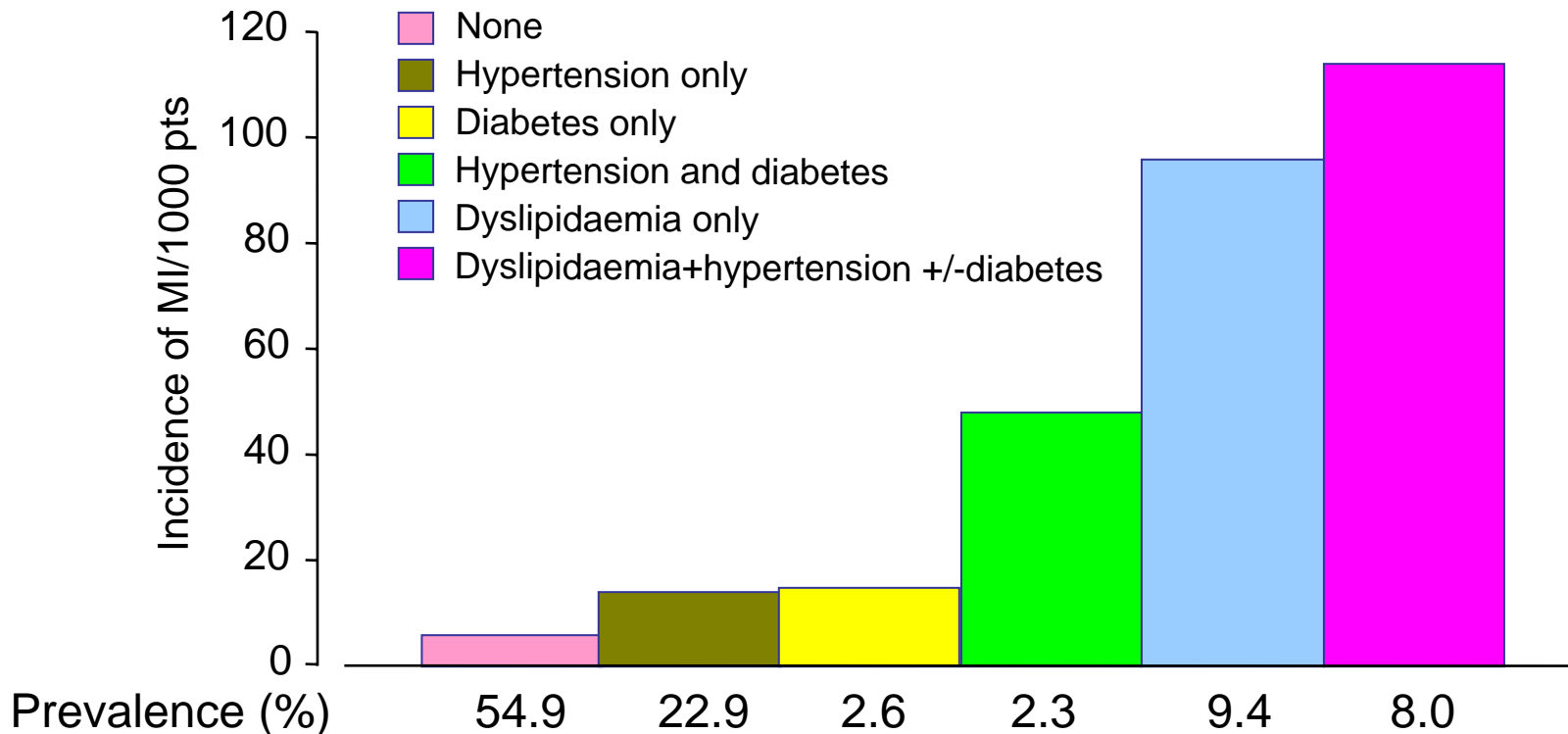
Framingham Study



SBP 150-160	+	+	+	+	+	+
Cholesterol 240-262	-	+	+	+	+	+
HDL-C 33-35	-	-	+	+	+	+
Diabetes	-	-	-	+	+	+
Cigarettes	-	-	-	-	+	+
ECG-LVH	-	-	-	-	-	+

(Kannel. Am J Hypertens. 2000;13:3S-10S)

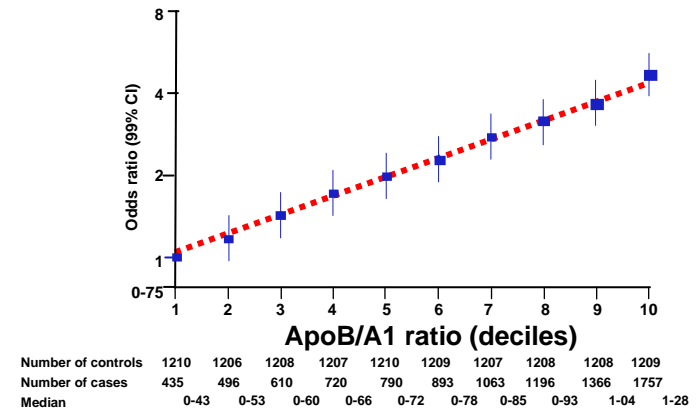
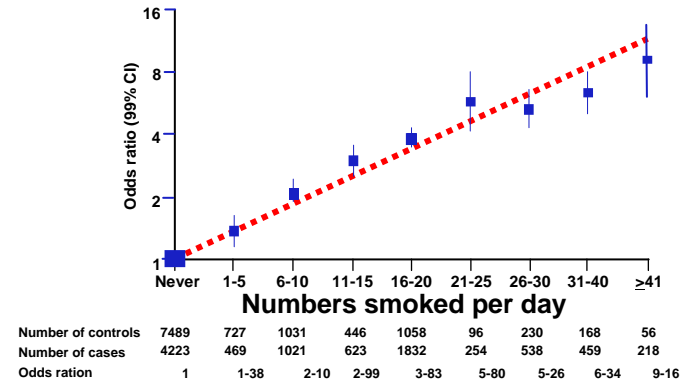
Combination of Risk Factors Increases Risk of MI: PROCAM



(Assmann G, Schulte H. Am Heart J 1988;116:1713-1724)

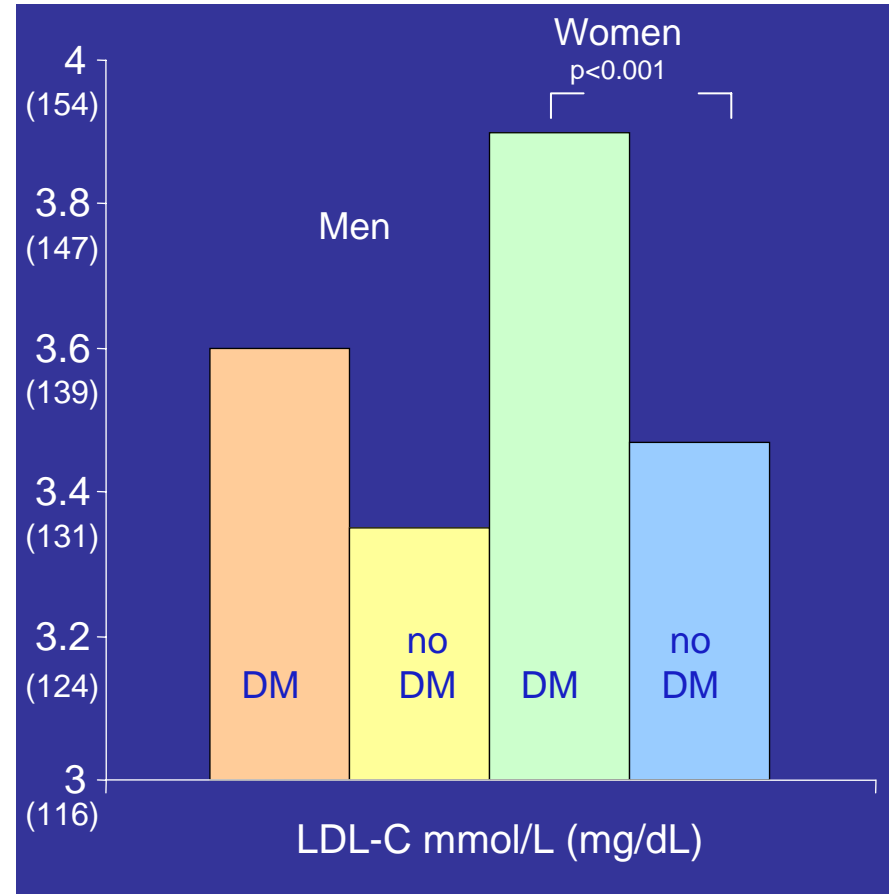
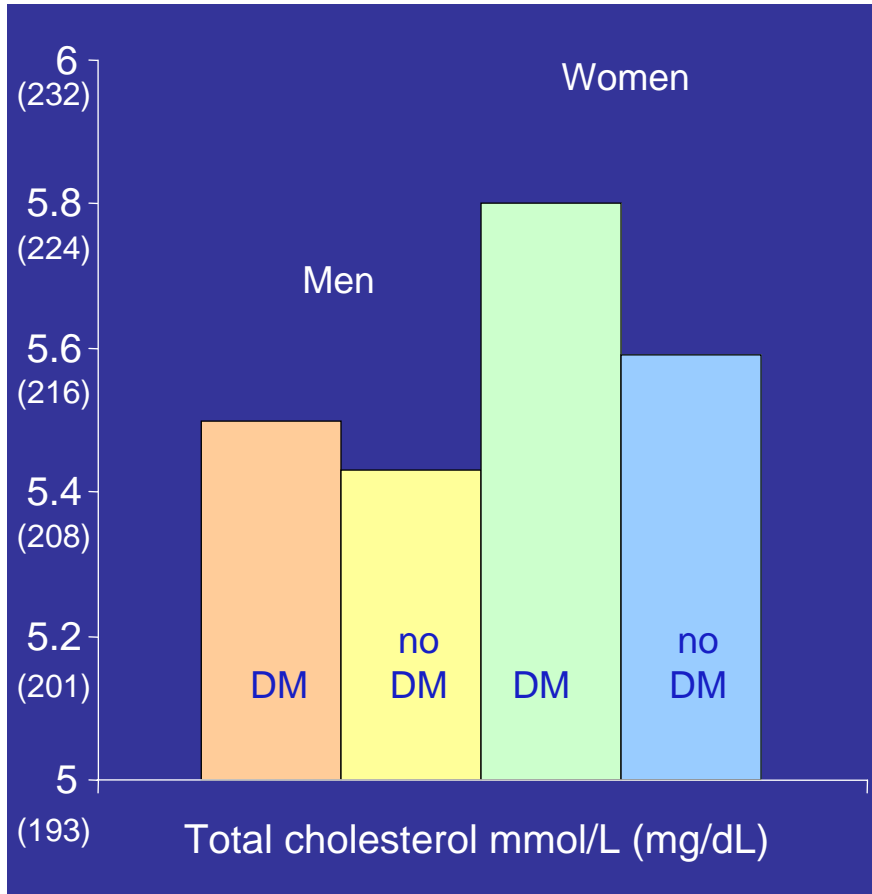
INTERHEART Study: Effect of Potentially Modifiable Risk Factors Associated with Myocardial Infarction in 52 Countries

Risk factor	PAR
Smoking	36%
Diabetes	12%
Hypertension	23%
Abdominal obesity	34%
Psychosocial	29%
Veg/fruit daily	13%
Exercise	26%
Alcohol intake	14%
ApoB/ApoA-1 ratio (5vs1)	54%
All above combined	90%



(Yusuf et al, on behalf of the INTERHEART Study Investigators Lancet, 2004;364 Pages 937-952)

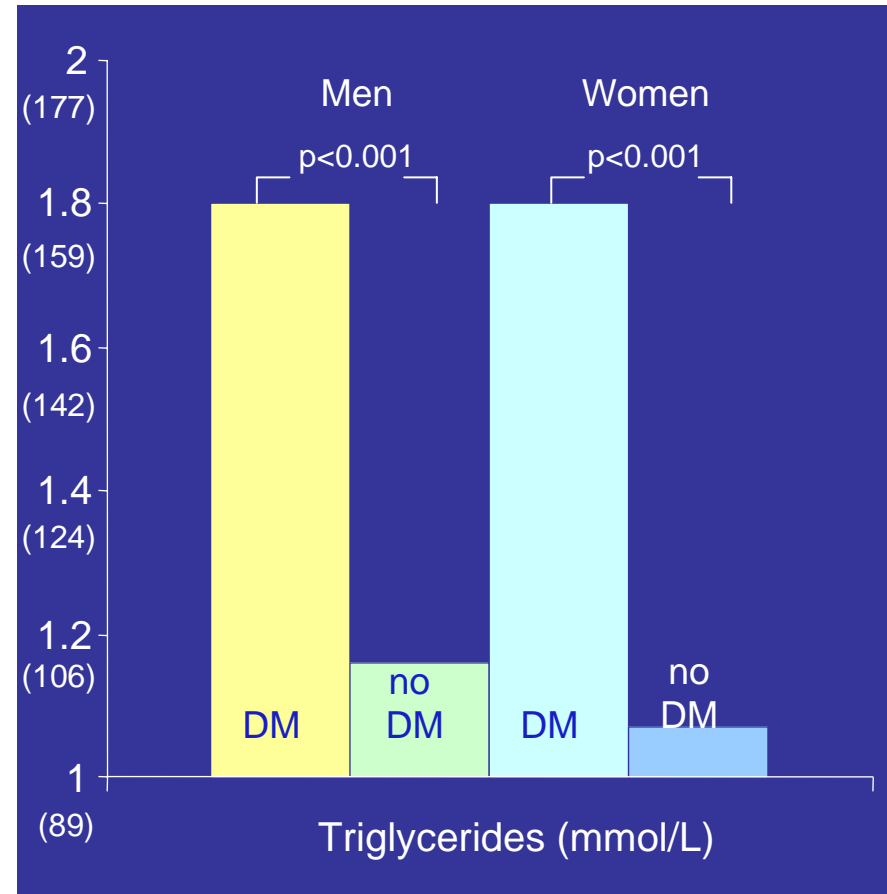
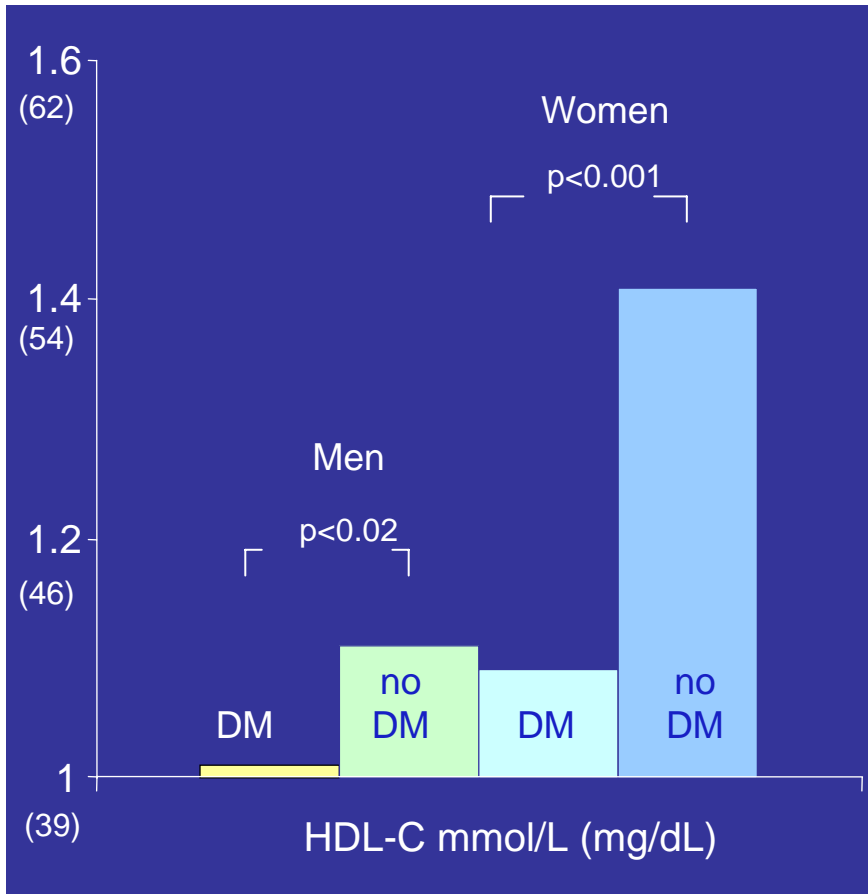
Typical Lipid Profile in Patients with Diabetes Compared with No Diabetes (1): UKPDS



DM diabetes mellitus

(UKPDS Diabetes Care 1997;20:1683-1687)

Typical Lipid Profile in Patients with Diabetes Compared with No Diabetes (2): UKPDS



DM diabetes mellitus

(UKPDS Diabetes Care 1997;20:1683-1687)

Targets for lipid profile

Lipid profile (mmol/L) (mg/dL)	Total cholesterol	<4.5 (175)	
	LDL cholesterol	≤1.8 (70)	
	HDL cholesterol		
		Men	>1.0 (40)
		Women	>1.2 (>46)
	Triglycerides*	<1.7 (<150)	
	Total/HDL cholesterol*	<3	

Dyslipidemia

Recommendation	Class	Level
Elevated LDL and low HDL cholesterol are important risk factors in people with diabetes.	I	A
Statins are first-line agents for lowering LDL cholesterol in diabetic patients.	I	A
In diabetic patients with CVD, statin therapy should be initiated regardless of baseline LDL cholesterol, with a treatment target of <1.8–2.0 mmol/L (<70–77 mg/dL).	I	B
Statin therapy should be considered in adult patients with type 2 diabetes, without CVD, if total cholesterol >3.5 mmol/L (>135 mg/dL), with a treatment targeting an LDL cholesterol reduction of 30–40%.	IIb	B

Dyslipidemia

Given the high lifetime risk of CVD, it is suggested that all type 1 patients over the age of 40 years should be considered for statin therapy.

In patients 18–39 years (either type 1 or type 2), statin therapy should be considered when other risk factors are present, e.g. nephropathy, poor glycaemic control, retinopathy, hypertension, hypercholesterolaemia, features of the metabolic syndrome, or family history of premature vascular disease.

In diabetic patients with hypertriglyceridaemia > 2 mmol/L (177 mg/dL) remaining after having reached the LDL cholesterol target with statins, statin therapy should be increased to reduce the secondary target of non-HDL cholesterol. In some cases, combination therapy with the addition of ezetimibe, nicotinic acid, or fibrates may be considered.

IIb

C

IIb

B

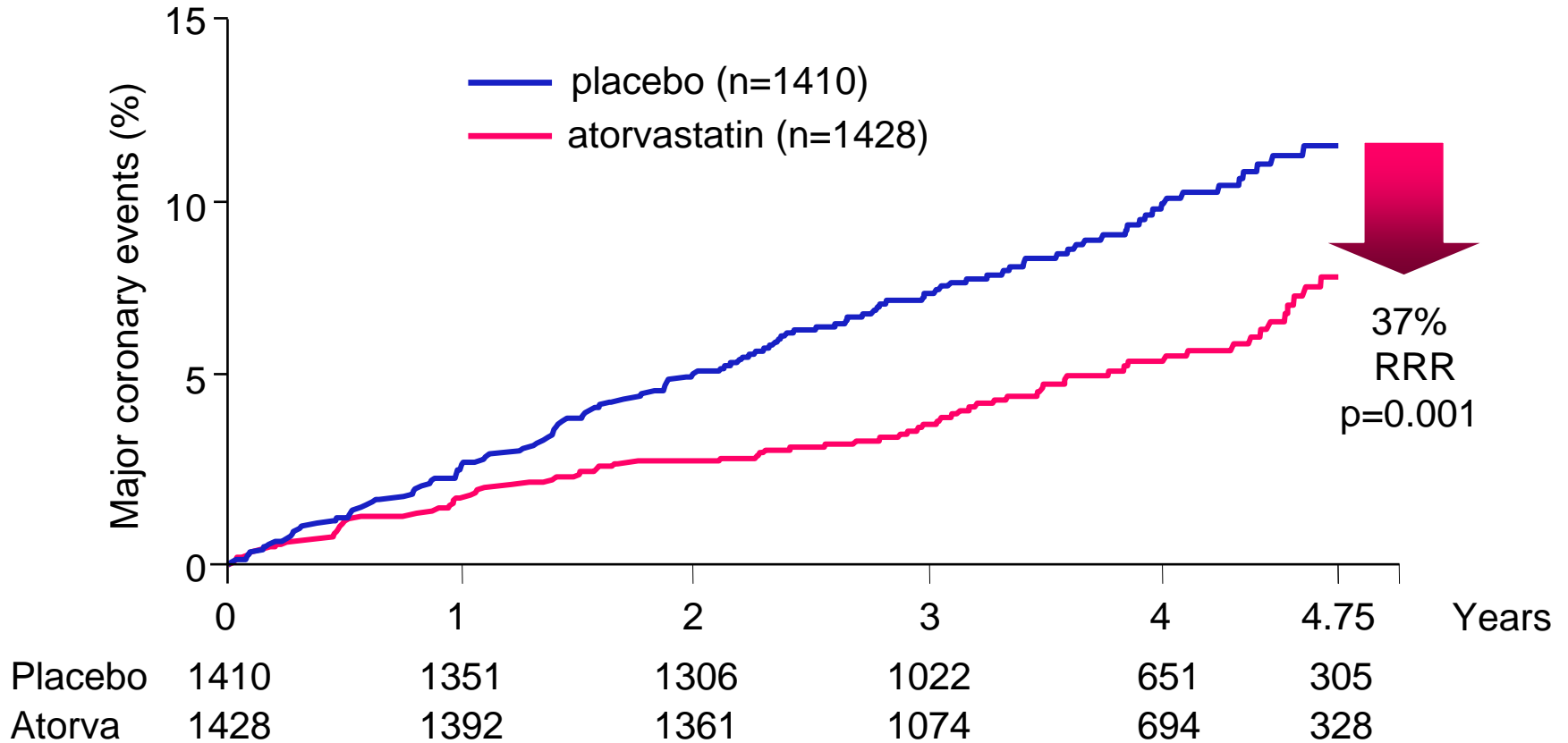
Subgroups of patients with DM in the major secondary prevention trials with statins and the proportionate risk reduction in patients with and without diabetes

Variables			Proportion of events (%)		Relative risk reduction (%)	
Trial	Type of event	Treatment	Diabetes present		type of patients	
			No	Yes	All	Diabetes
4S Diabetes <i>n</i> = 202	CHD death or non-fatal MI	Simvastatin	19	23	32	55
		Placebo	27	45		
4S Reanalysis Diabetes <i>n</i> = 483	CHD death or non-fatal MI	Simvastatin	19	24	32	42
		Placebo	26	38		
HPS Diabetes <i>n</i> = 3050	Major coronary event, stroke, or revascularization	Simvastatin	20	31	24	18
		Placebo	25	36		
CARE Diabetes <i>n</i> = 586	CHD death or non-fatal MI	Pravastatin	12	19	23	25
		Placebo	15	23		
LIPID Diabetes <i>n</i> = 782	CHD death, non-fatal MI, revascularization	Pravastatin	19	29	24	19
		Placebo	25	37		
LIPS Diabetes <i>n</i> = 202	CHD death, non-fatal MI, revascularization	Fluvastatin	21	22	22	47
		Placebo	25	38		
GREACE Diabetes <i>n</i> = 313	CHD death, non-fatal MI, UAP, CHF, revascularization, stroke	Atorvastatin	12	13	51	58
		Standard care	25	30		

CHD Prevention Trials with Statins in Patients with Diabetes - Subgroup Analyses

	Statin	Diabetes pts (n)	CHD % Risk Reduction	
			Overall	Diabetes
<i>Primary prevention</i>				
AFCAPS/TexCAPS ¹	Lovastatin	155	37	43 (ns)
ASCOT-LLA ²	Atorvastatin	2532	36	16 (ns)
HPS ³	Simvastatin	2912	27	33 (p=0.0003)
<i>Secondary prevention</i>				
CARE ⁴	Pravastatin	586	23	25 (p=0.05)
4S ⁵	Simvastatin	202	32	55 (p=0.002)
4S extended ⁶	Simvastatin	483	32	42 (p=0.001)
LIPID ⁷	Pravastatin	1077	24	19 (ns)
HPS ³	Simvastatin	1981	27	18 (p=0.002)
TNT ⁸	Atorvastatin	1500	22	25 (p=0.026)
<i>Primary/Secondary</i>				
ALLHAT-LLT ⁹	Pravastatin	3638	9	11 (ns)

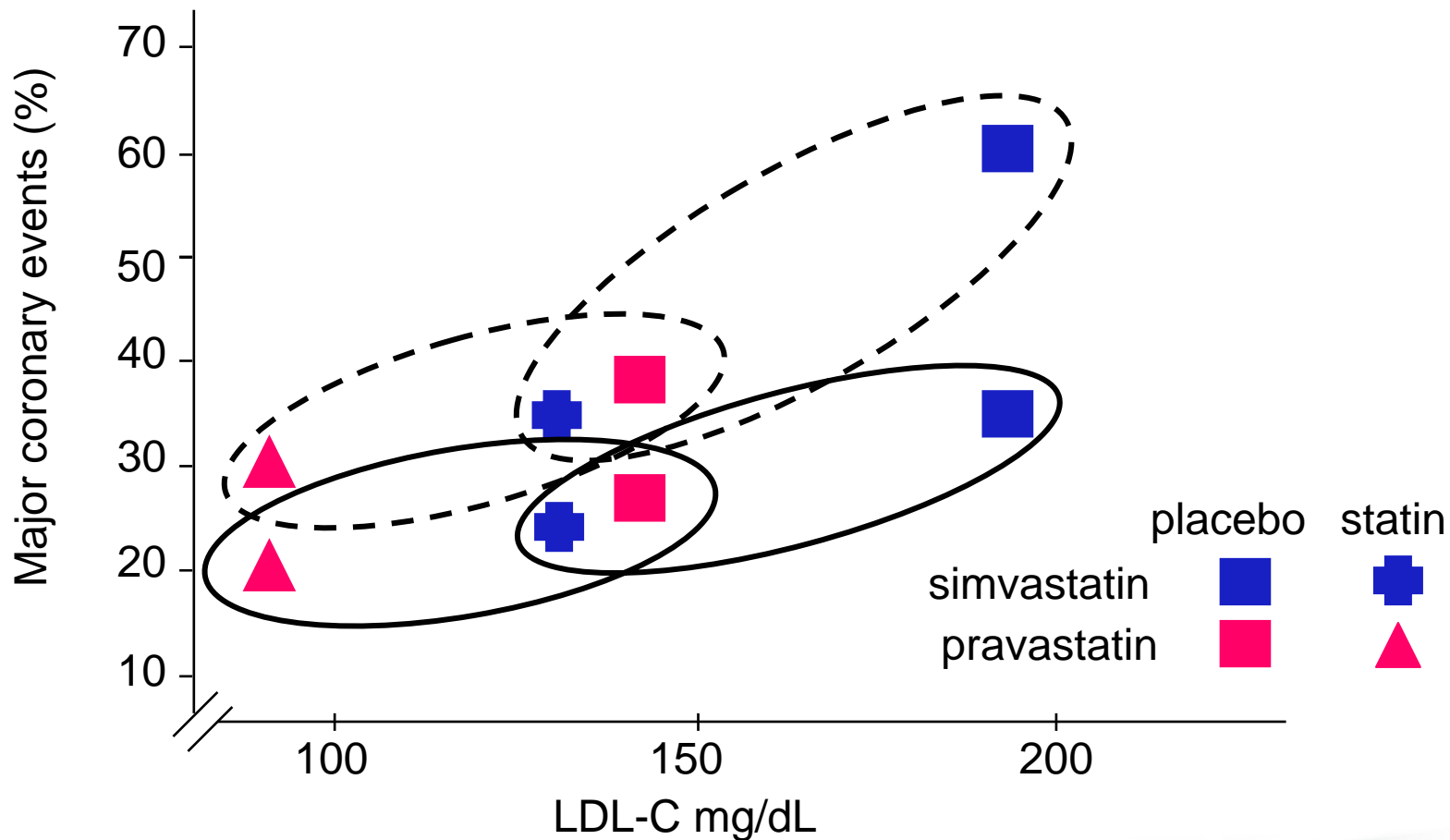
Primary Prevention Treatment with Statins Reduce Major Coronary Events in Patients with Diabetes: CARDS



RRR relative risk reduction

(Colhoun HM et al. Lancet 2004;364:685–696)

Efficacy of Statins in Patients with (---) vs without (○) Diabetes: 4S/CARE



(Kreisberg RA et al. Am J Cardiol 1998;82:67U-73U)

Fibrates

Reduces CVD Risk in Diabetes

Study	Fibrate	Diabetes pts (n)	Clinical Outcomes
Helsinki Heart Study ^{1*}	Gemfibrozil	135	68% risk reduction in MI or sudden cardiac death (<i>ns</i>)
SENDCAP ^{2*}	Bezafibrate	164	70% reduction in definite CHD events ($p=0.01$)
VA-HIT ^{3*}	Gemfibrozil	769	32% risk reduction for composite endpoint ($p=0.004$)
DAIS ⁴	Fenofibrate	418	23% reduction in combined cardiac endpoints (<i>ns</i>)

* Post hoc subgroup analysis

(1. Koskinen et al. Diabetes Care 1992;15:820–825. 2. Elkeles et al. Diabetes Care 1998;21(4):641–648. 3. Rubins et al. Arch Int Med 2002;162:2597–2604. 4. DAIS Investigators. Lancet 2001;357:905–910)

Blood pressure

Recommended treatment targets for patients with diabetes and coronary artery disease

	Variable	Treatment target
Blood pressure	Systolic/diastolic (mm Hg)	<130/80
	In case of renal impairment or proteinuria >1 g/24 h	<125/75

Blood pressure 1

Recommendation	Class	Level
In patients with diabetes and hypertension, the recommended target for blood pressure control is <130/80 mm Hg.	I	B
The cardiovascular risk in patients with diabetes and hypertension is substantially enhanced. The risk can be effectively reduced by blood pressure-lowering treatment.	I	A
The diabetic patient usually requires a combination of several anti-hypertensive drugs for satisfactory blood pressure control.	I	A

Blood pressure 2

The diabetic patient should be prescribed a renin-angiotensin-system inhibitor as part of the blood pressure-lowering treatment.

I

A

Screening for microalbuminuria and adequate blood pressure-lowering therapy including the use of ACE-inhibitors and angiotensin receptor II blockers improves micro-and macrovascular morbidity in type 1 and type 2 diabetes.

I

A

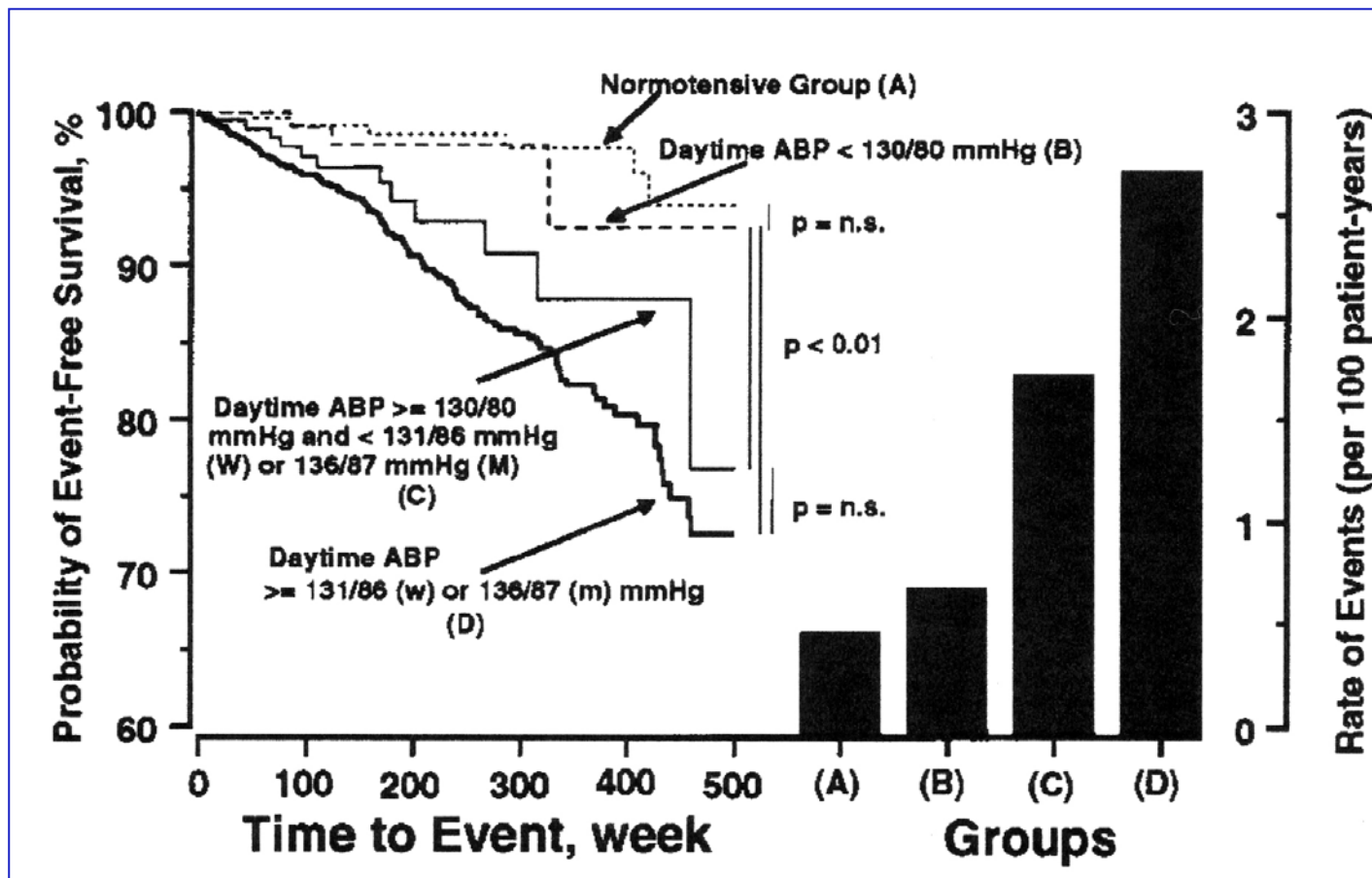
Risk assessment according to hypertension and other risk factors

Table 2 Stratification of risk to quantify prognosis

Other risk factors and disease history	Blood pressure (mmHg)				
	Normal SBP 120–129 or DBP 80–84	High normal SBP 130–139 or DBP 85–89	Grade 1 SBP 140–159 or DBP 90–99	Grade 2 SBP 160–179 or DBP 100–109	Grade 3 SBP \geq 180 or DBP \geq 110
No other risk factors	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
1–2 risk factors	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
3 or more risk factors or TOD or diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
ACC	High added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk

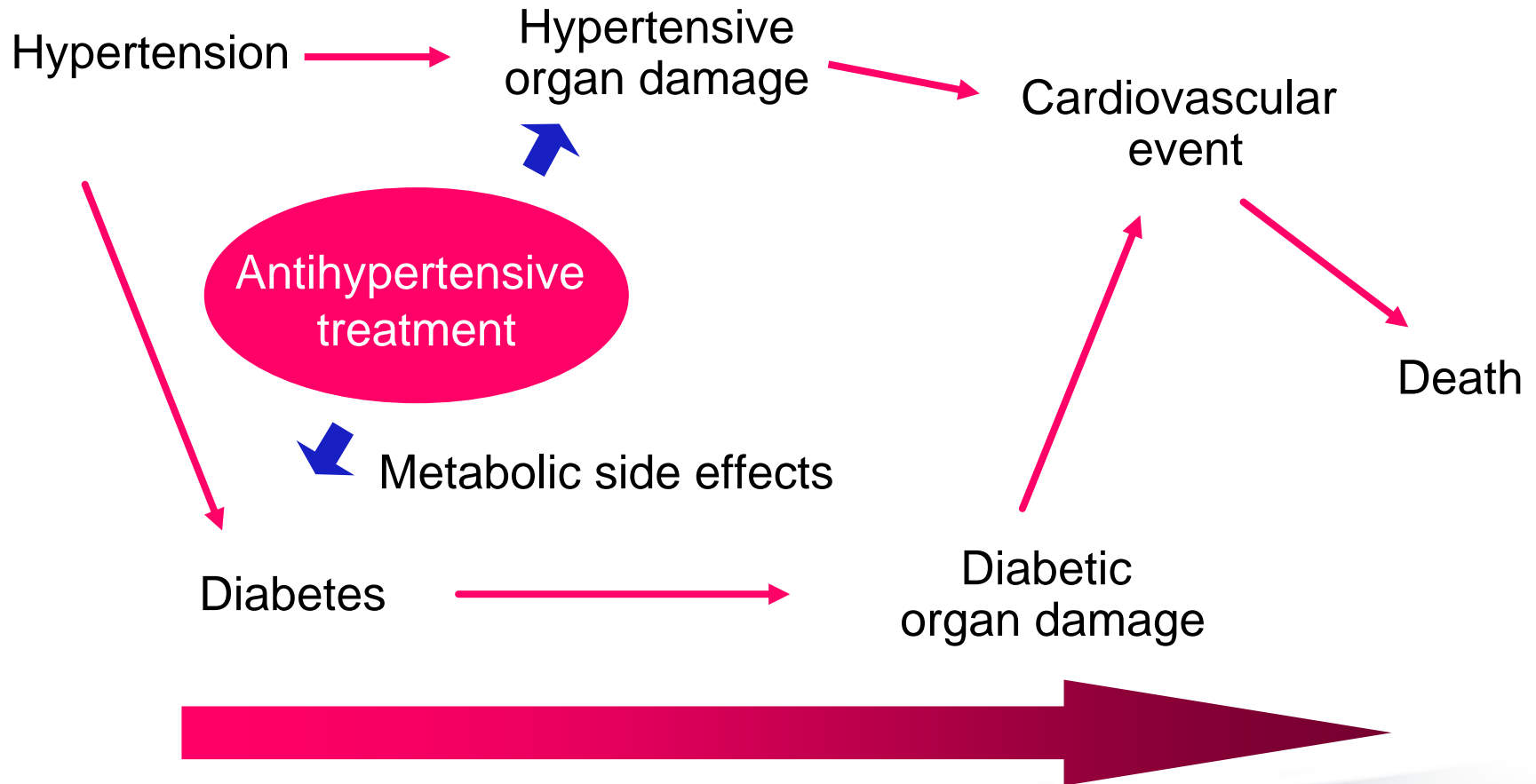
ACC, associated clinical conditions; TOD, target organ damage; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Rate of major CV morbid events in a normotensive group (A), 2 groups with WCH defined with a restrictive (B) or liberal (C) criterion, and a group with ambulatory hypertension (D)



(From Verdecchia Hypertension 2000)

Antihypertensive therapy and long-term prognosis



Antihypertensive drugs and glucose homeostasis

Negative

Positive

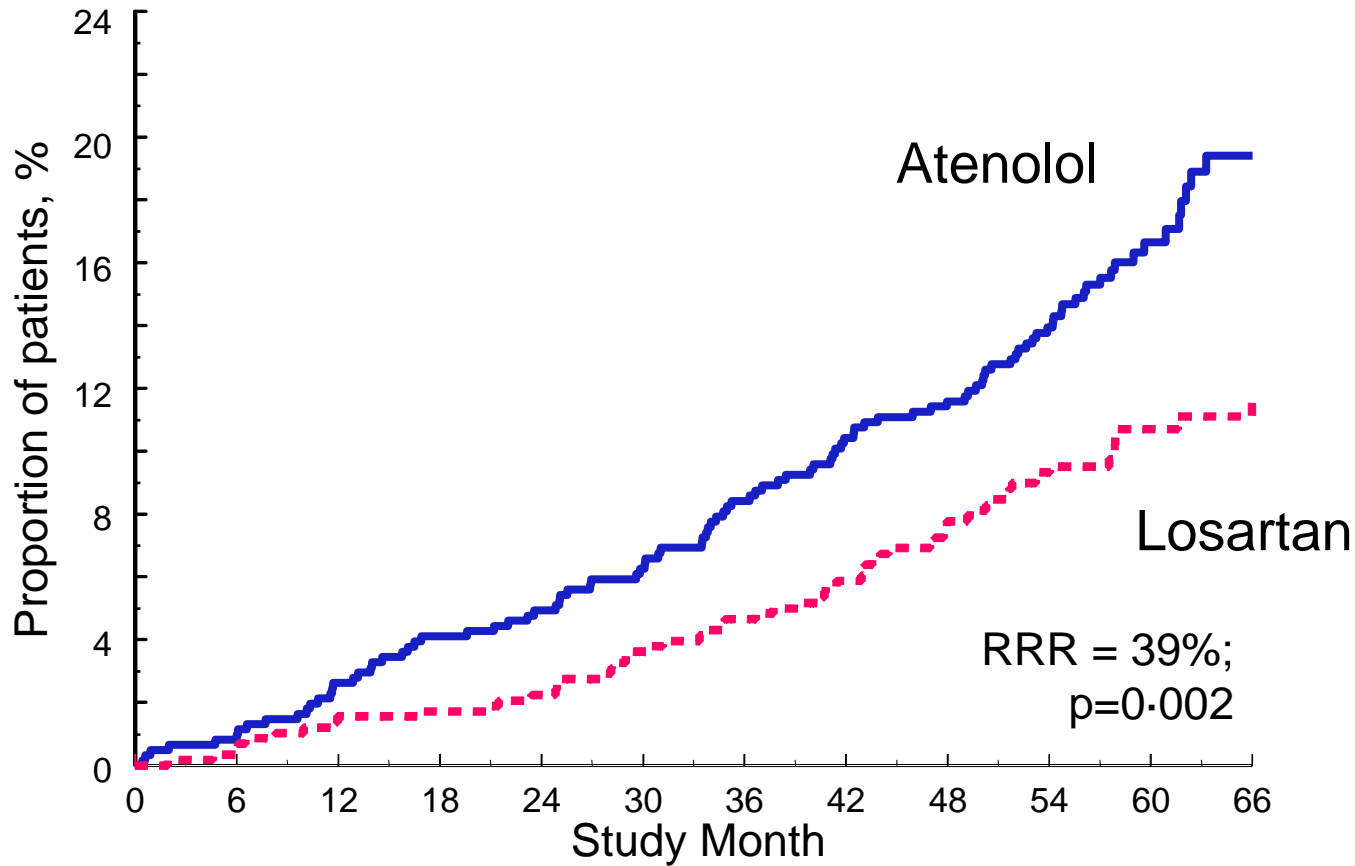
Diuretics

CCB
Alpha-blockers

ACE-I
ARB

Beta-blockers

LIFE: Total Mortality – Diabetes Subgroup

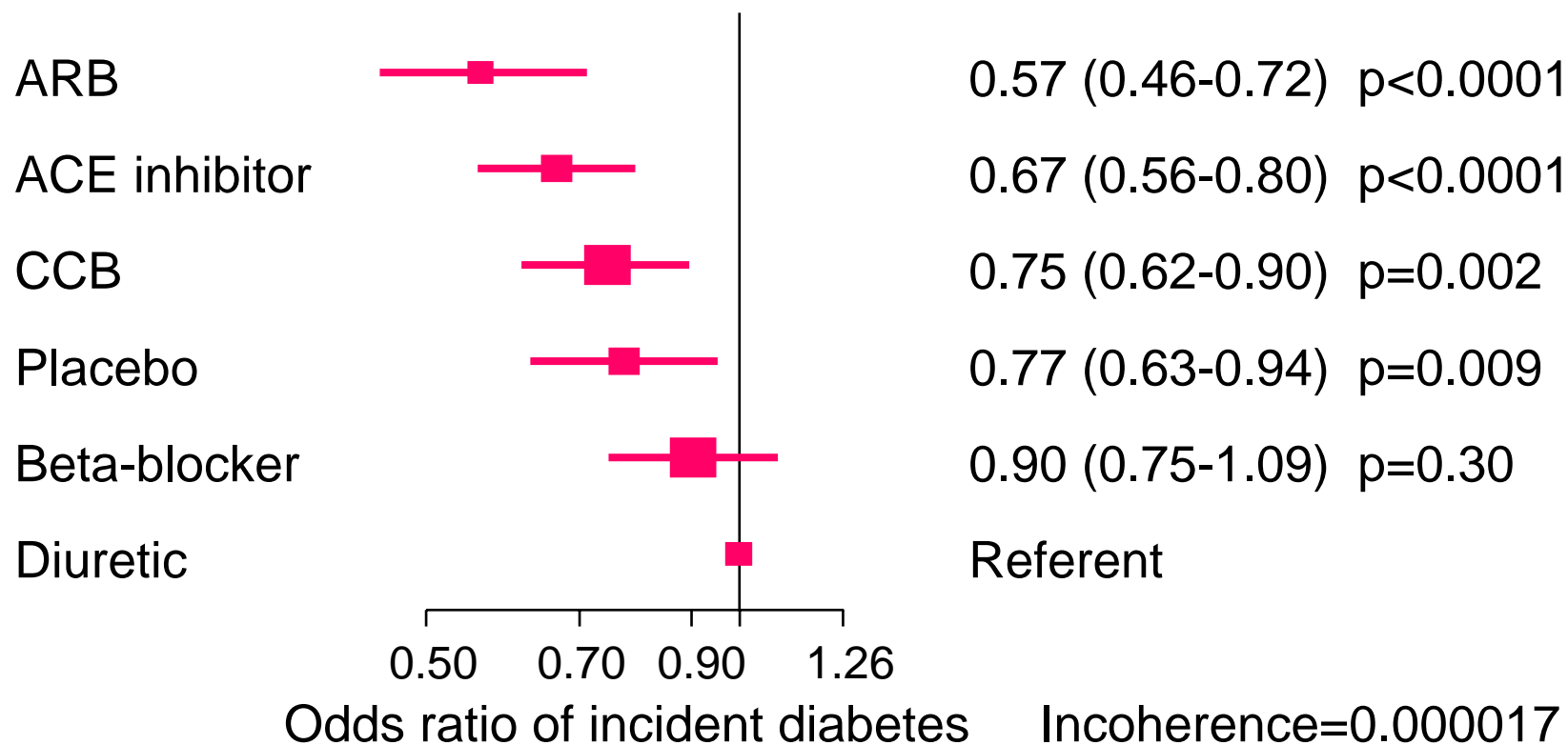


(L H Lindholm et al. Lancet 2002;359:1004-1010)

Result of network meta-analysis of 22 clinical trials

Different drug classes compared with diuretics

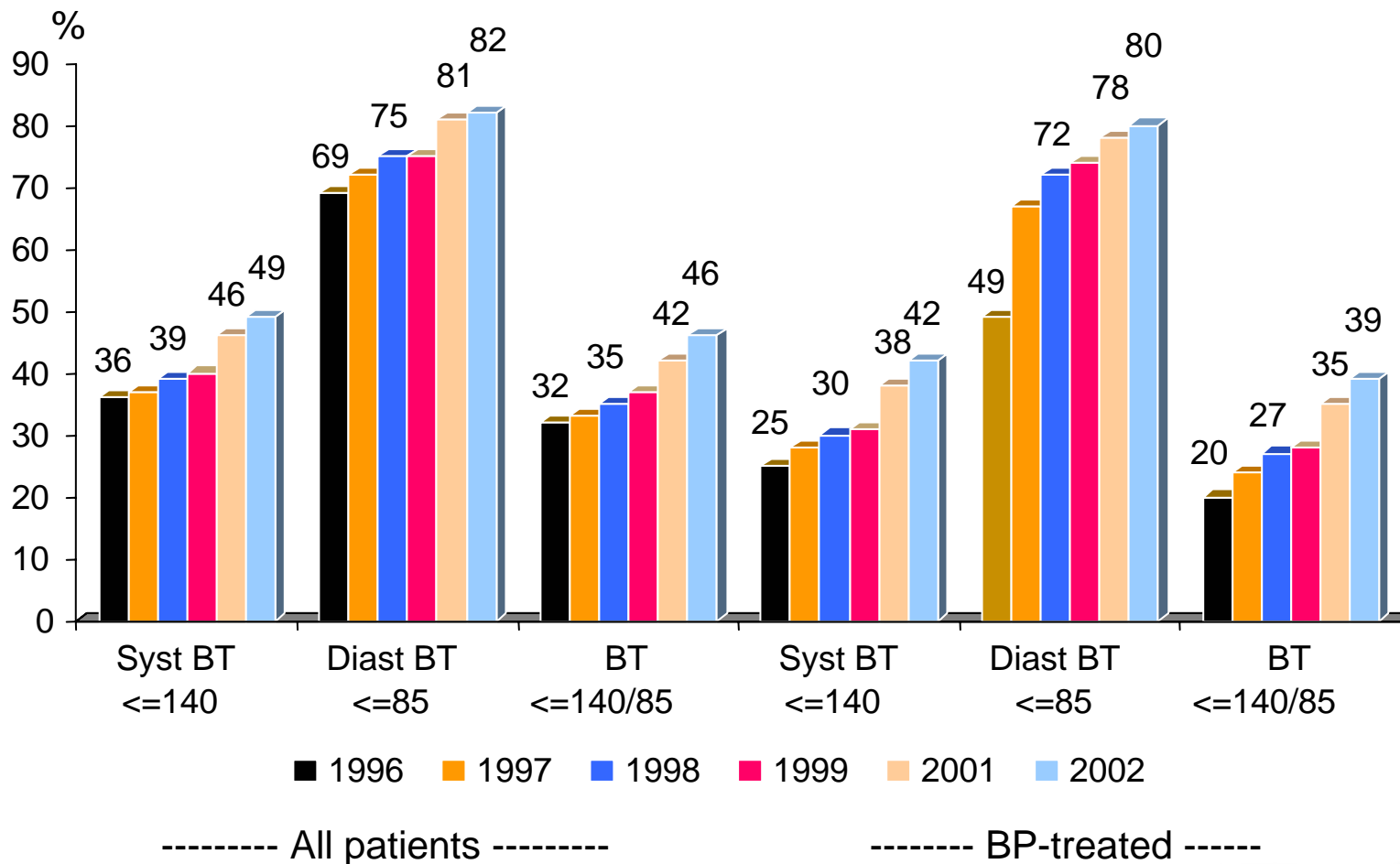
Incident diabetes



(Lancet 2007;369:2001-7)

Blood pressure - At goal

Diabetic patients in primary care 1996-2002

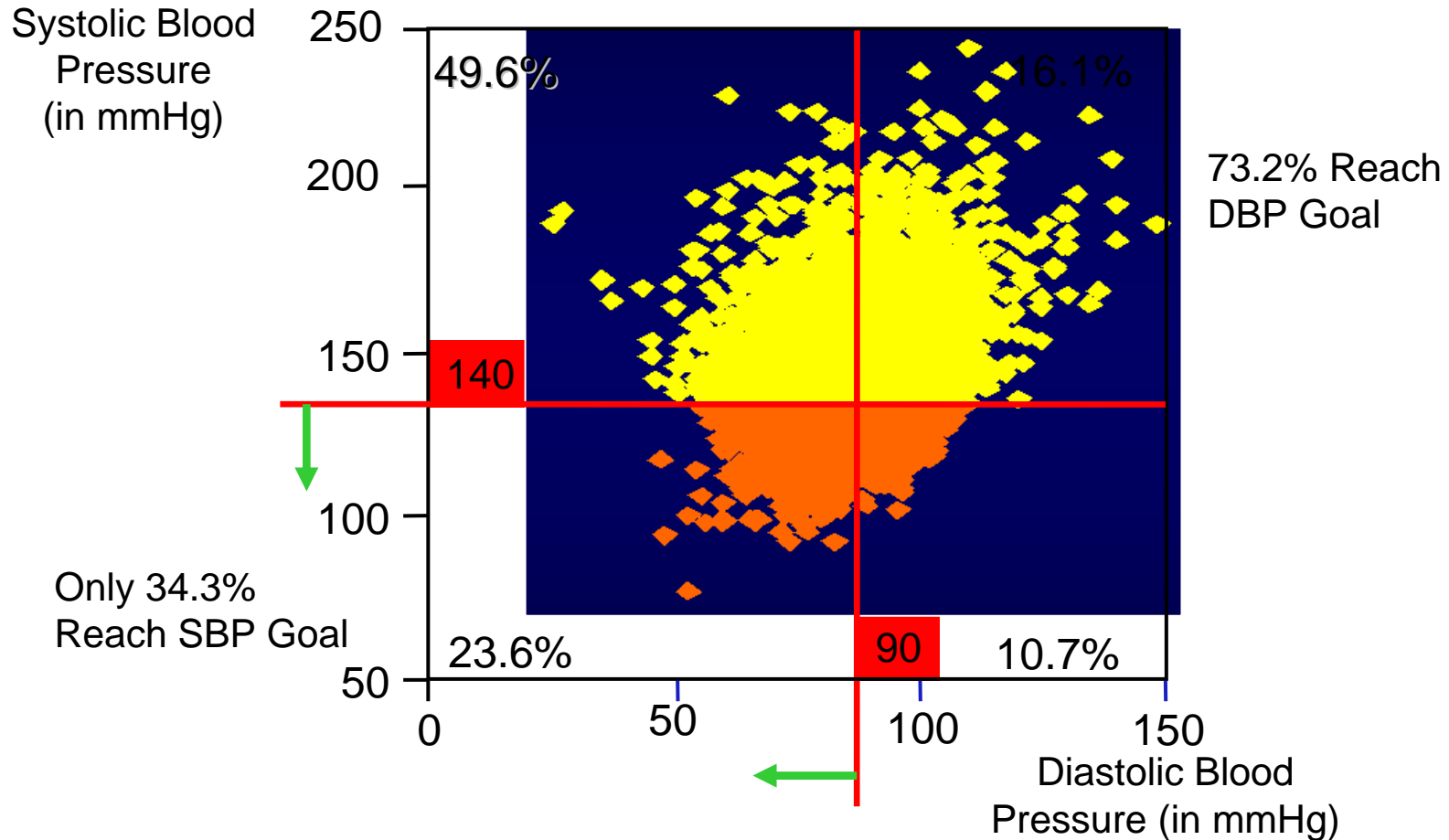


If systolic blood pressure is 20 mm Hg or diastolic 10 mm Hg lower the risk for cv-death is 50% lower: MRFIT

Cause of death	Age group (yrs)	Lower risk, %
Stroke	40–49	70
	50–59	67
	60–69	65
Ischemic heart disease	40–49	58
	50–59	56
	60–69	54
Other cv death	40–49	65
	50–59	58
	60–69	56

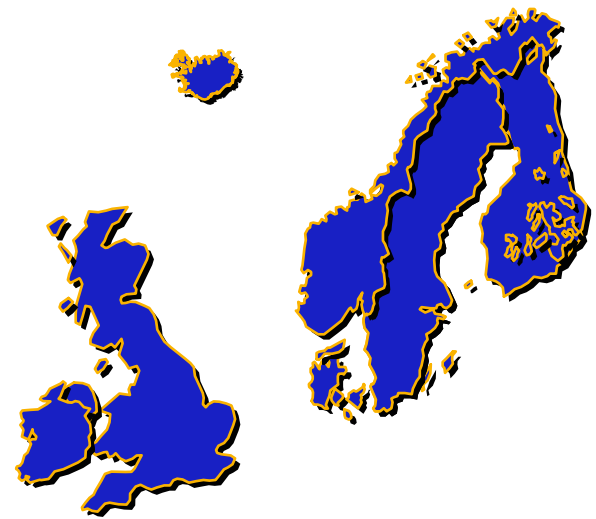
(Neaton et al, Ann Epidemiol 1993;3:493-9)

NHANES III: Lack of Systolic BP Control is Main Cause of Inadequate Blood Pressure Control



(Burt et al. Hypertension 1995;26:60. Whyte et al. J Clin Hypertens. 2001;3:211-216)

Anglo-Scandinavian
ascot
Cardiac Outcomes Trial

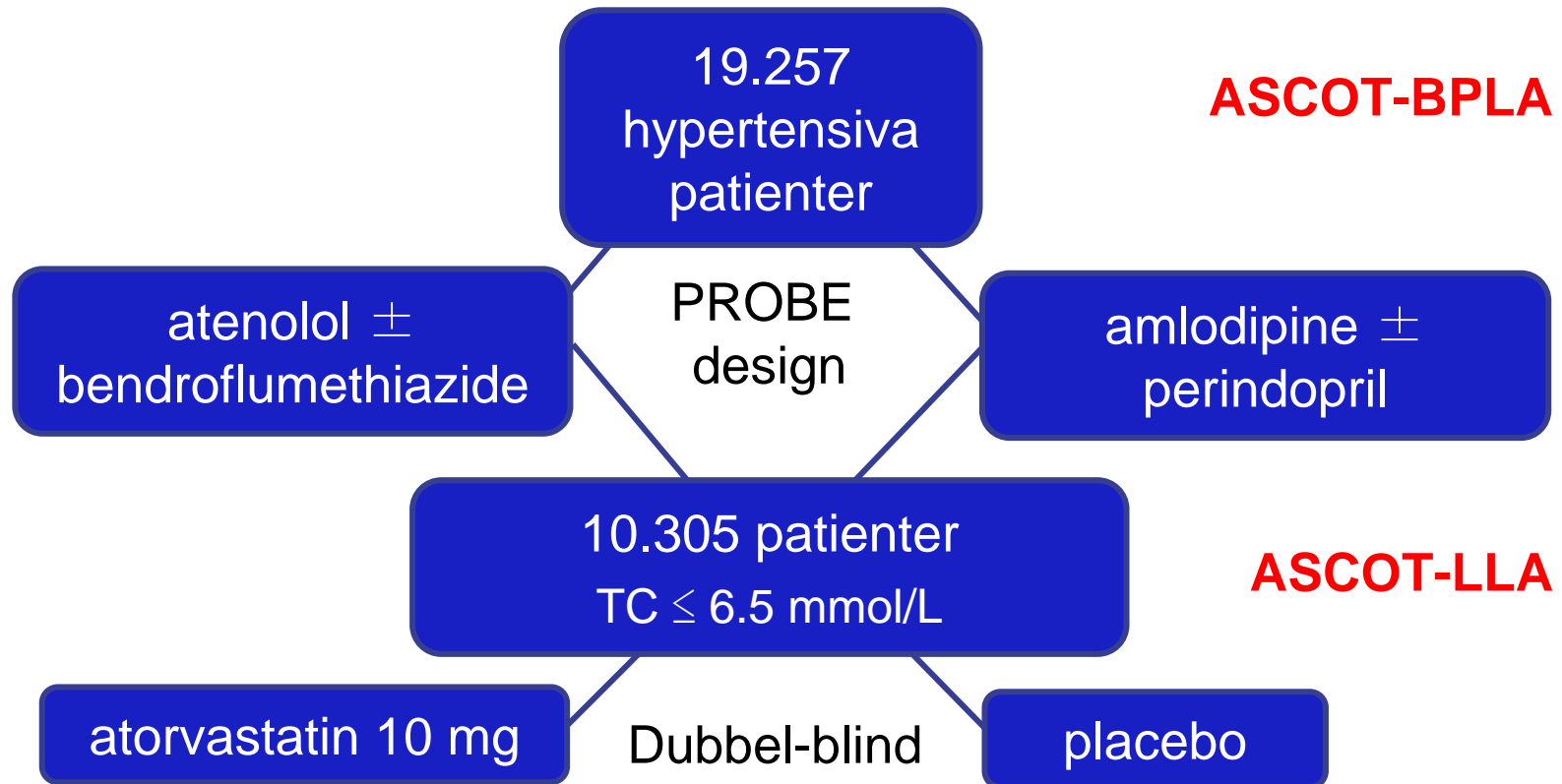


A randomised controlled trial of the prevention of
CHD and other vascular events by BP and
cholesterol lowering in a factorial study design

B.Dahlof (Co-chair), P.Sever (Co-chair), N. Poulter (Secretary)
H. Wedel (Statistician), G. Beevers, M. Caulfield, R. Collins
S. Kjeldsen, A. Kristinsson, J. Mehlsen, G. McInnes, M. Nieminen
E. O'Brien, J. Östergren, on behalf of the ASCOT Investigators

(Lancet, Sept 9, 2005)

Study design

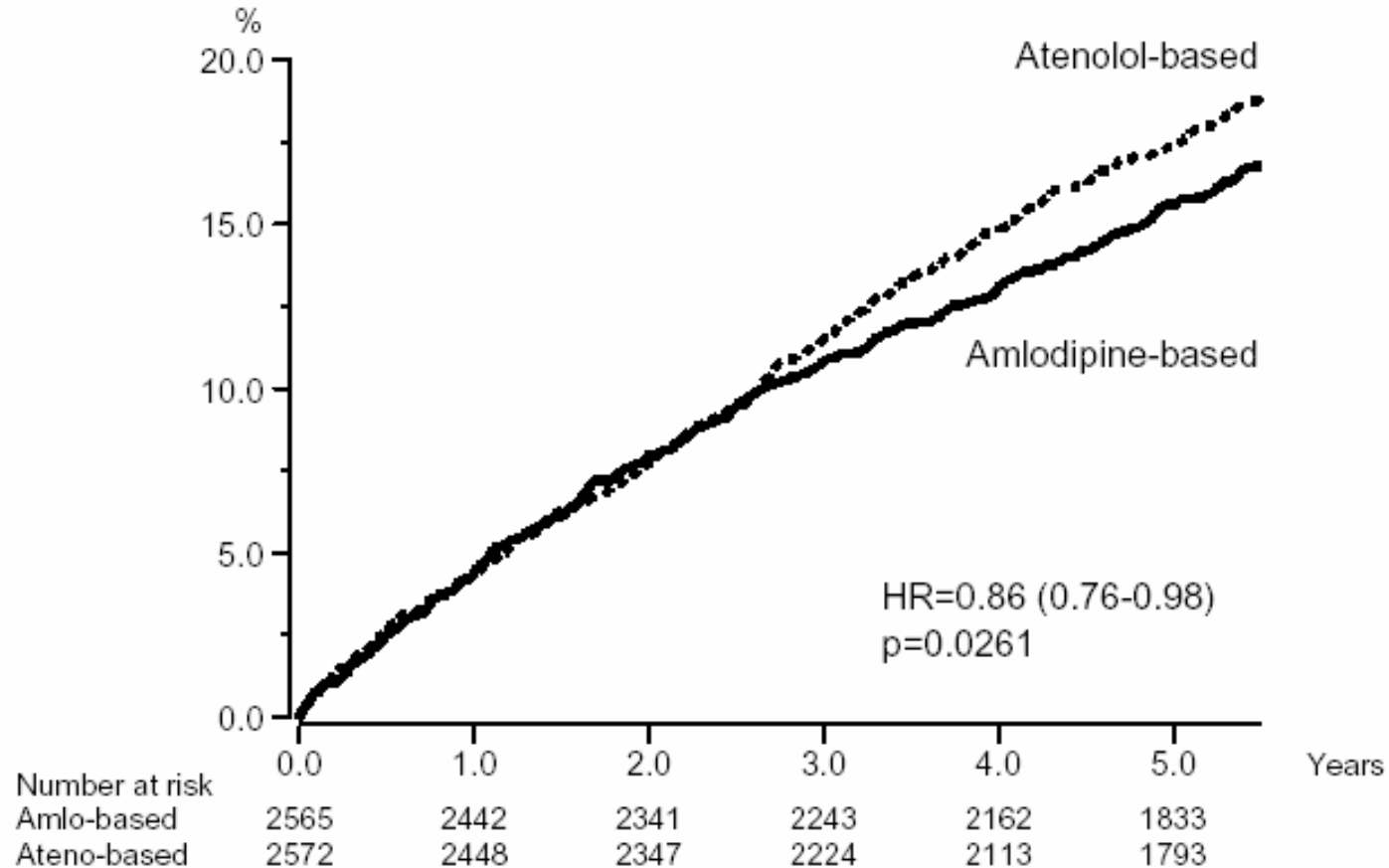


Investigator-led, multinational
randomised controlled trial

ASCOT

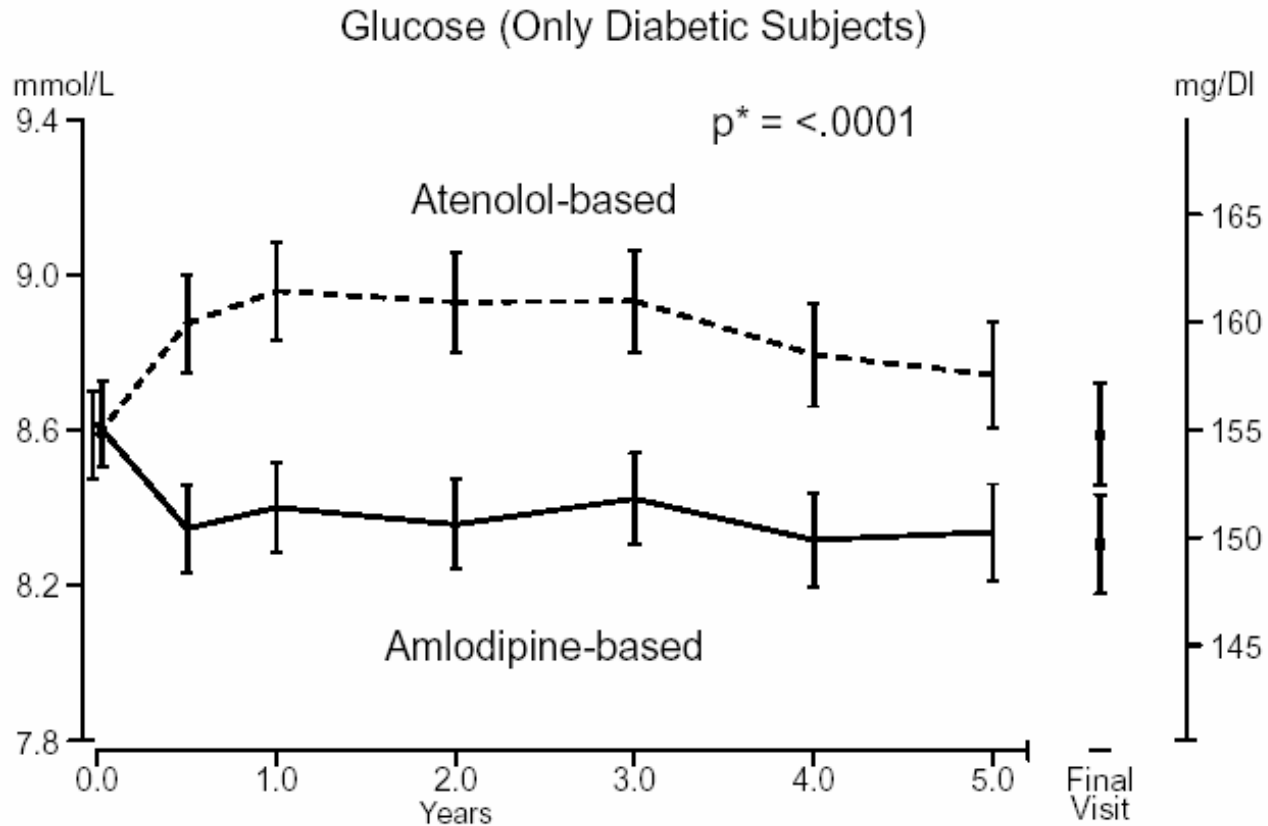
Total CV events and procedures: diabetic subpopulation

proportion of patients



ASCOT

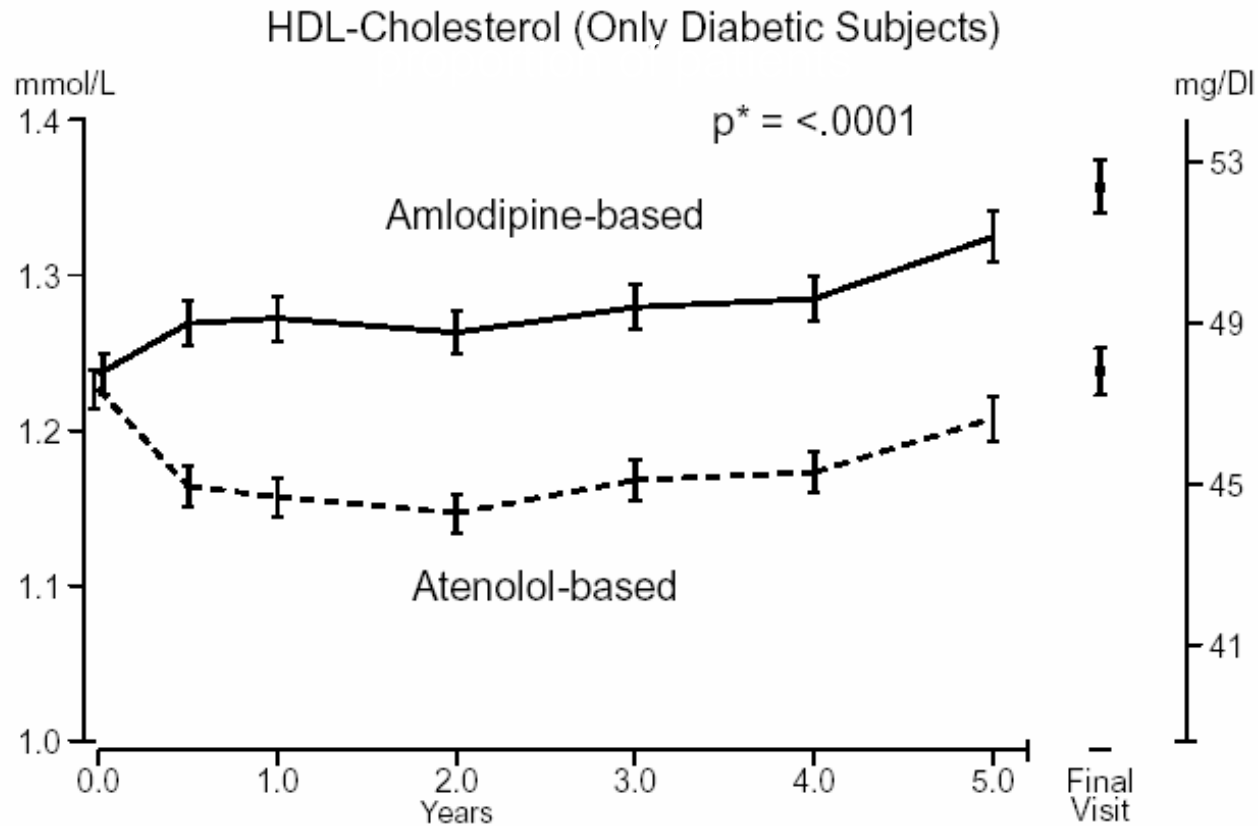
Plasma glucose in the two treatment arms



* T-test performed on Accumulated Mean AUC

ASCOT

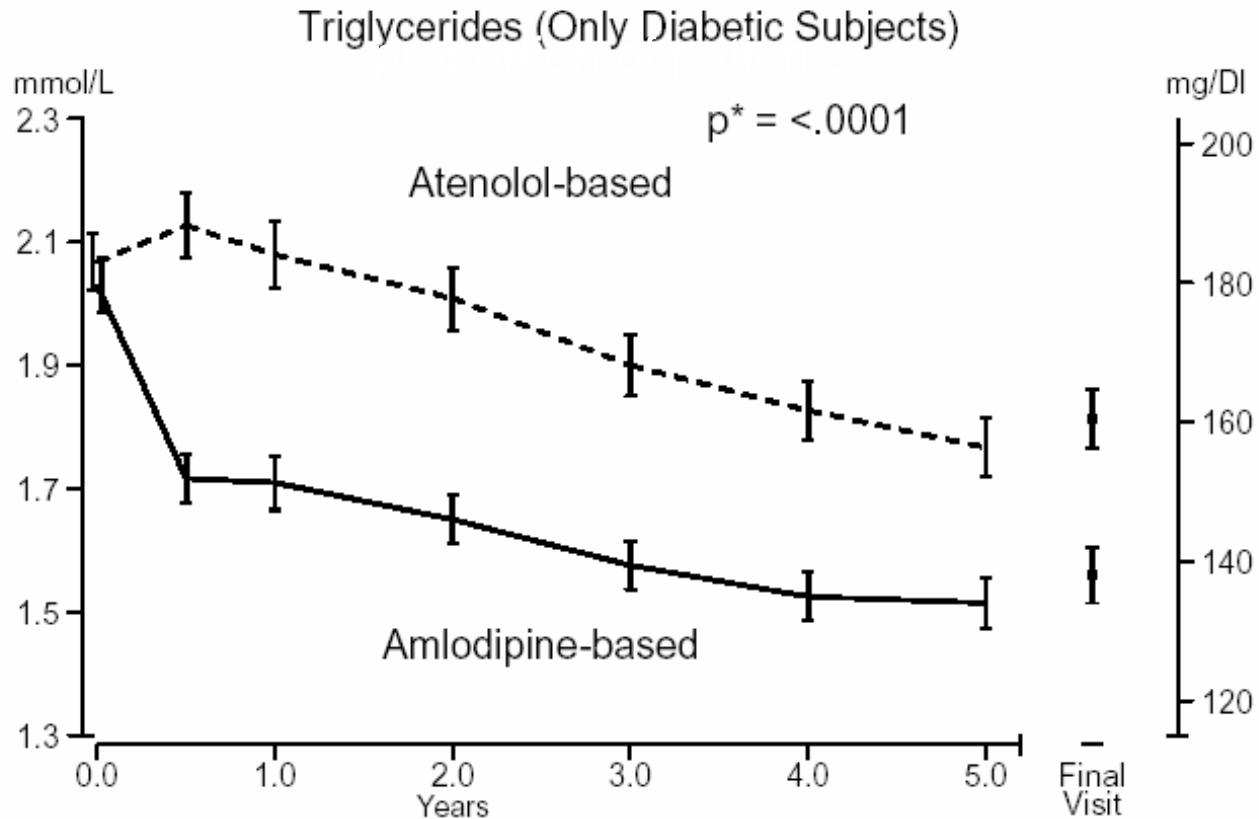
HDL-cholesterol in the two treatment arms



* T-test performed on Accumulated Mean AUC

ASCOT

Triglycerides in the two treatment arms



* T-test performed on Accumulated Mean AUC