

The Prevention of Cardiovascular Disease in People with Diabetes

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Outline

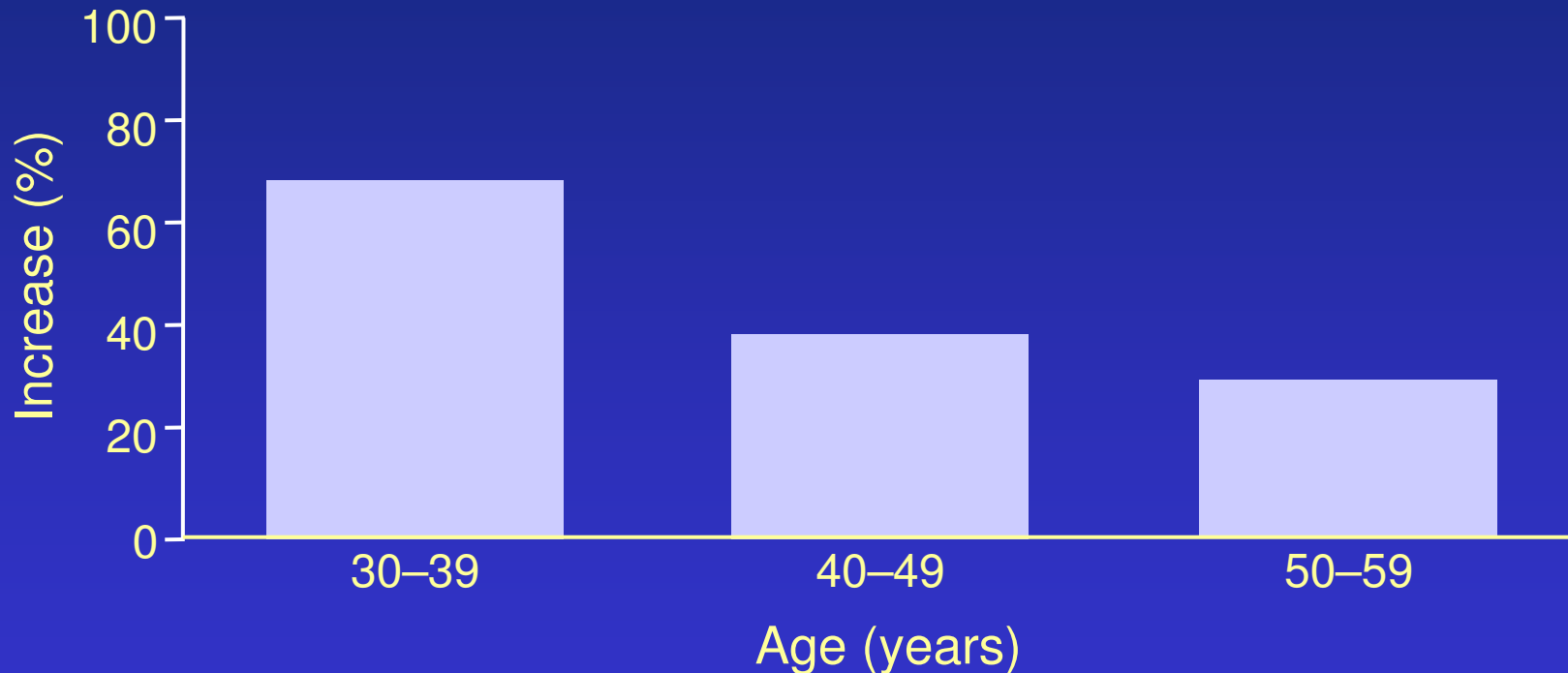
- Epidemiology
 - Diabetes incidence/prevalence
 - Impaired glucose metabolism and vascular disease
- Cardiovascular risk factors in diabetes
- Currently available treatments
 - What is known
 - What is not known

Alarming facts about diabetes

- Currently 246 million people worldwide
- Expected 380 million by 2025 (increase especially in developing countries)
- Every 10 seconds 2 people develop diabetes
- Every 10 seconds a person dies from diabetes-related causes
- On average people with diabetes will die 5-10 years before people without diabetes
- In 2007 the world is estimated to spend US \$232 billion to treat and prevent diabetes and its complications

Greatest relative increase in young

Prevalence of diagnosed diabetes increased overall by 33% from 1990 to 1998



The Behavioral Risk Factor Surveillance System, 1990 through 1998.

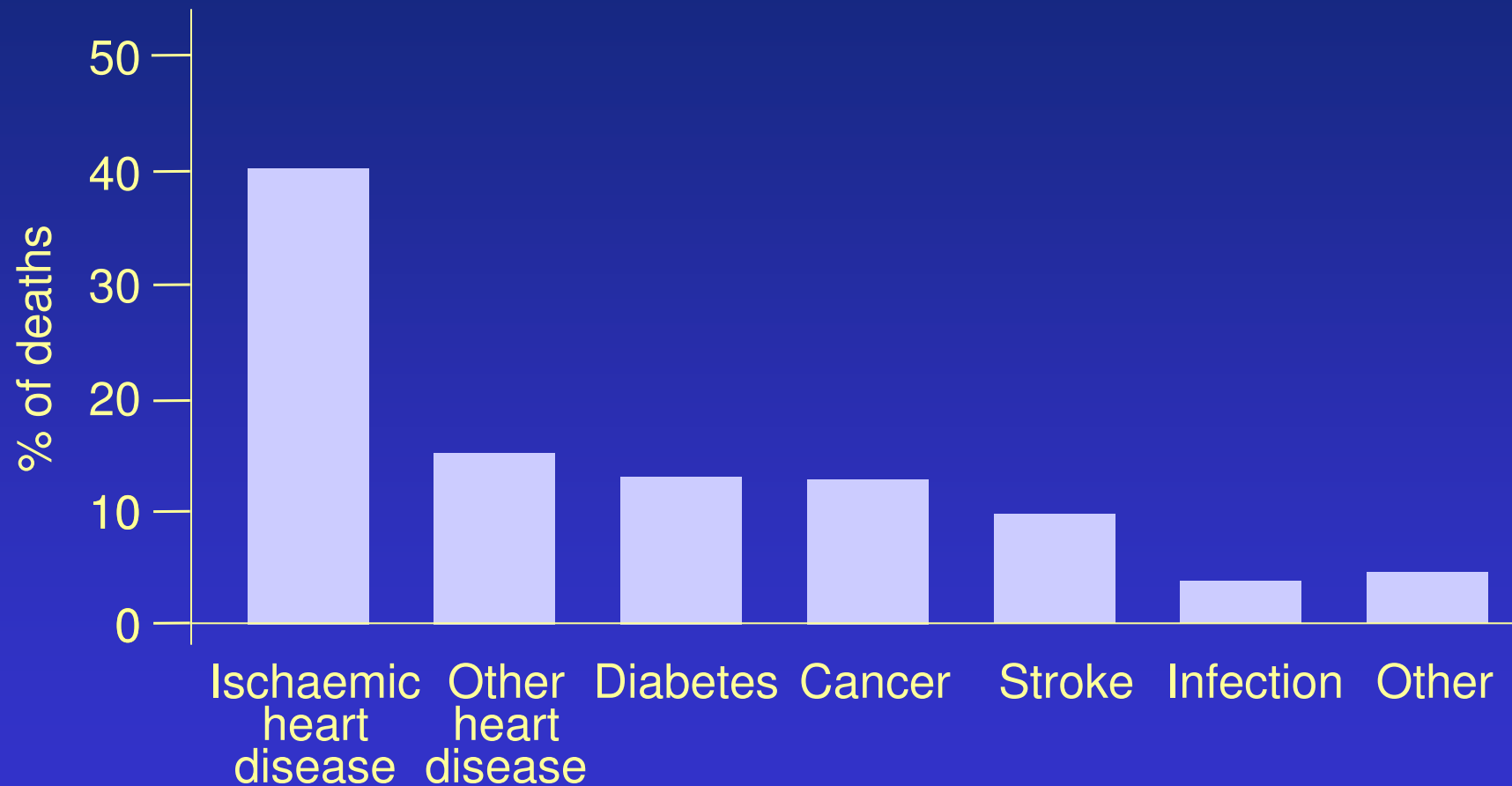
Adapted from Mokdad AH et al *Diabetes Care* 2000;23:1278-1283.

Criteria for the diagnosis of diabetes mellitus and hyperglycemia

	Fasting glucose (mmol/l)	2-hours post glucose load (mmol/l)
Diabetes Mellitus	≥ 7.0	≥ 11.1
Impaired glucose tolerance (IGT)	< 7.0	≥ 7.8 to < 11.1
Impaired fasting glucose (IFG)	≥ 6.1 to < 7.0	< 7.8

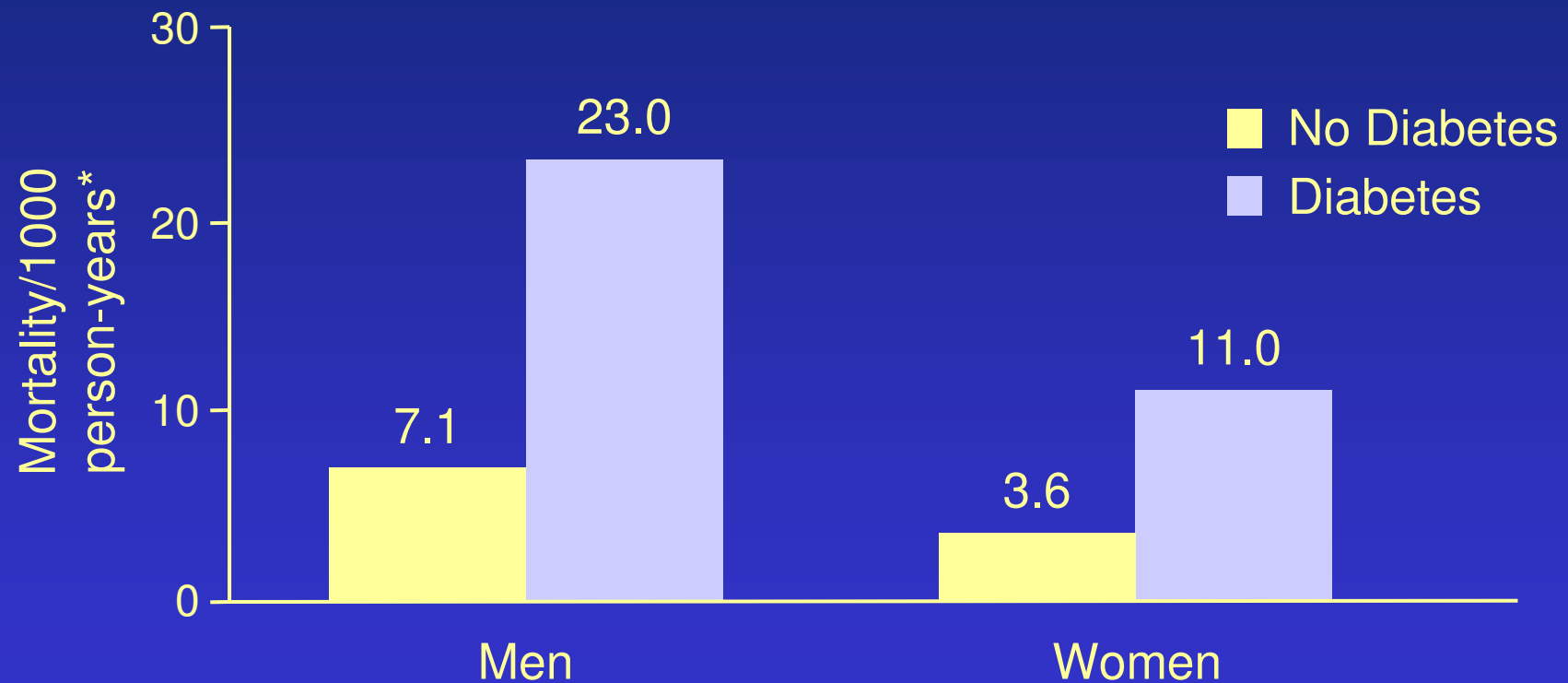
Adapted from World Health Organization *Definition, Diagnosis and Classification of Diabetes Mellitus and Its Complications*. Geneva: World Health Organization, 1999.

Mortality in people with diabetes (US)



Geiss LS et al. In: *Diabetes in America*. 2nd ed. Bethesda: National Institutes of Health, 1995:233-257.

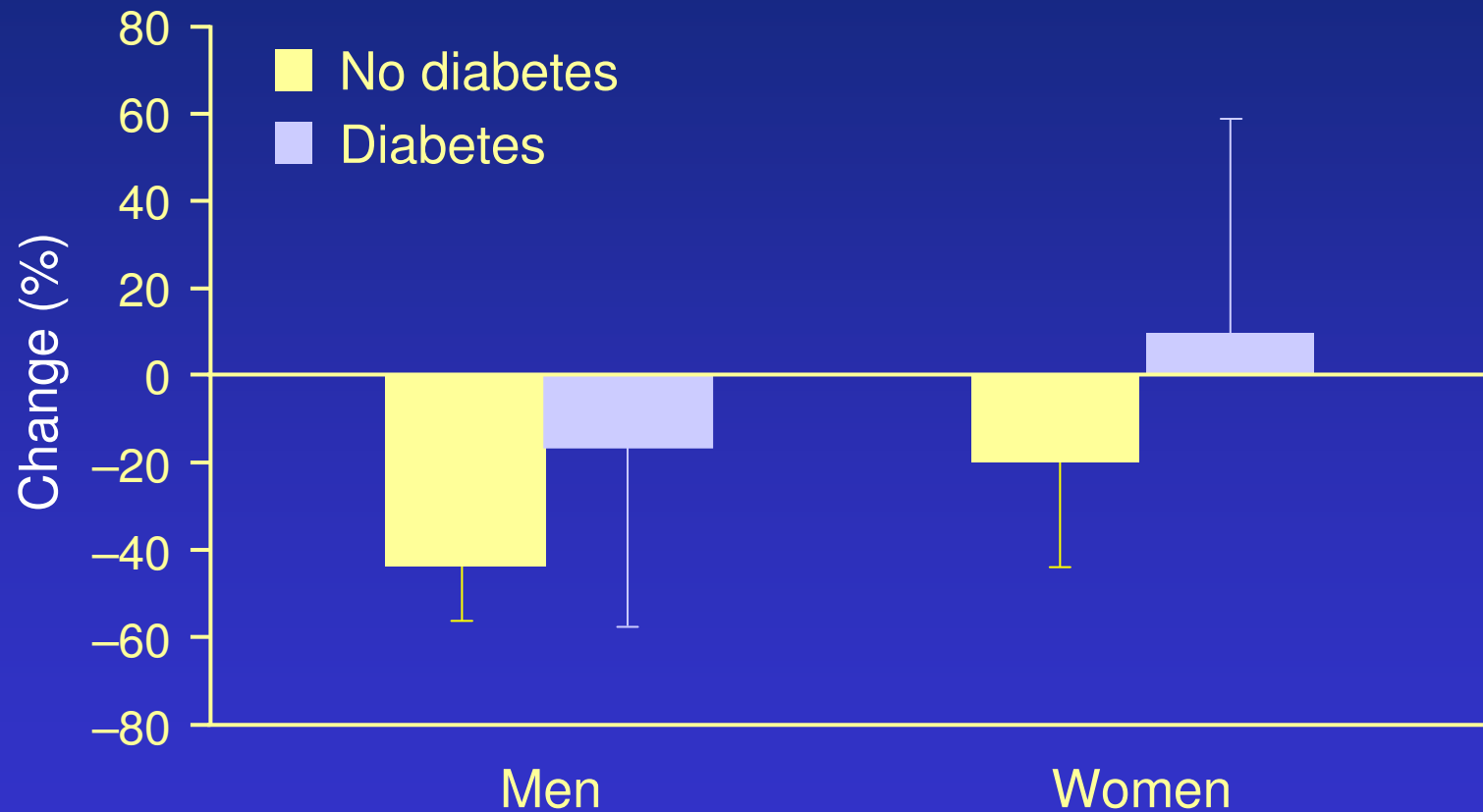
Mortality due to ischemic heart disease in men and women with or without diabetes (US)



*Age-adjusted; National Health and Nutrition Examination Survey (NHANES I), 1971 through 1993

Adapted from Gu K et al *Diabetes Care* 1998;21:1138–1145.

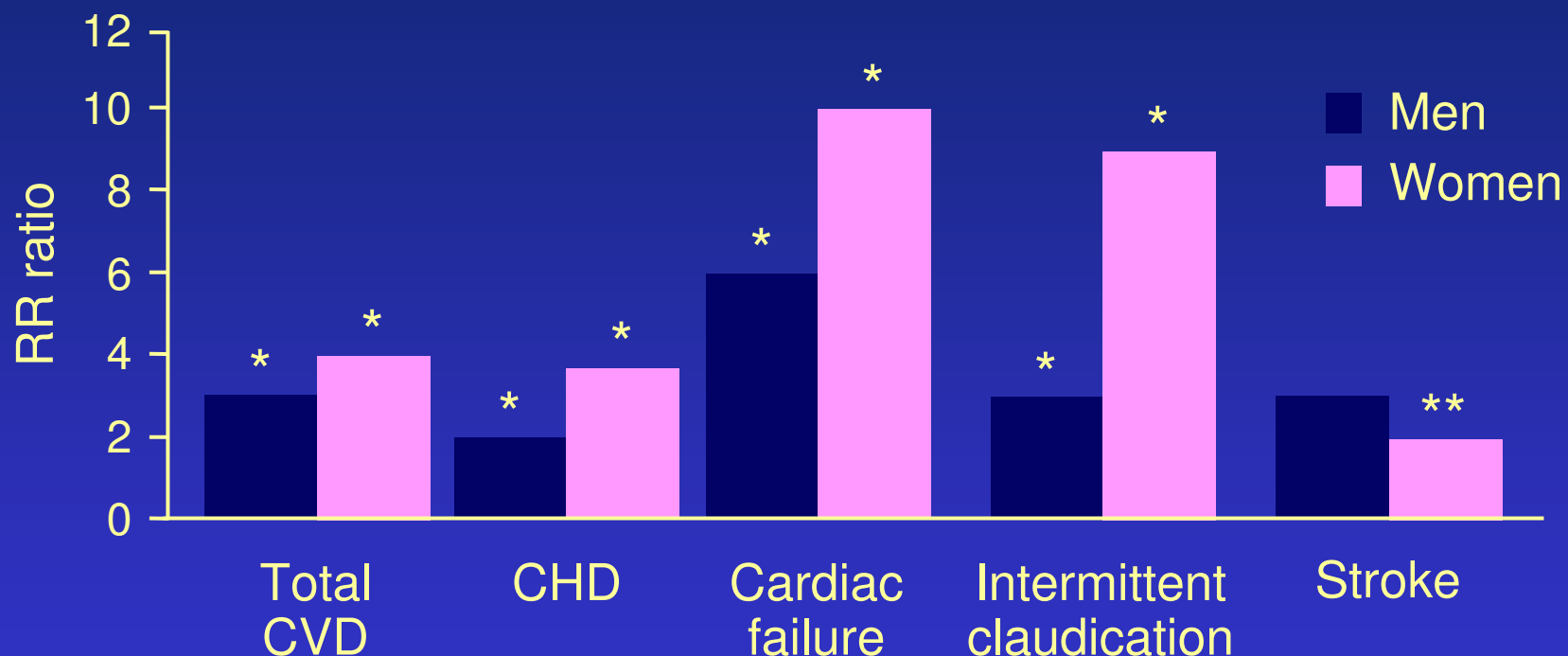
Change in IHD mortality between two cohorts* of patients with and without diabetes



*1971–1975 and 1982–1984

Adapted from Gu K et al *JAMA* 1999;281:1291–1297.

Framingham Study 30-year follow-up: CVD events in patients (ages 35–64) with diabetes



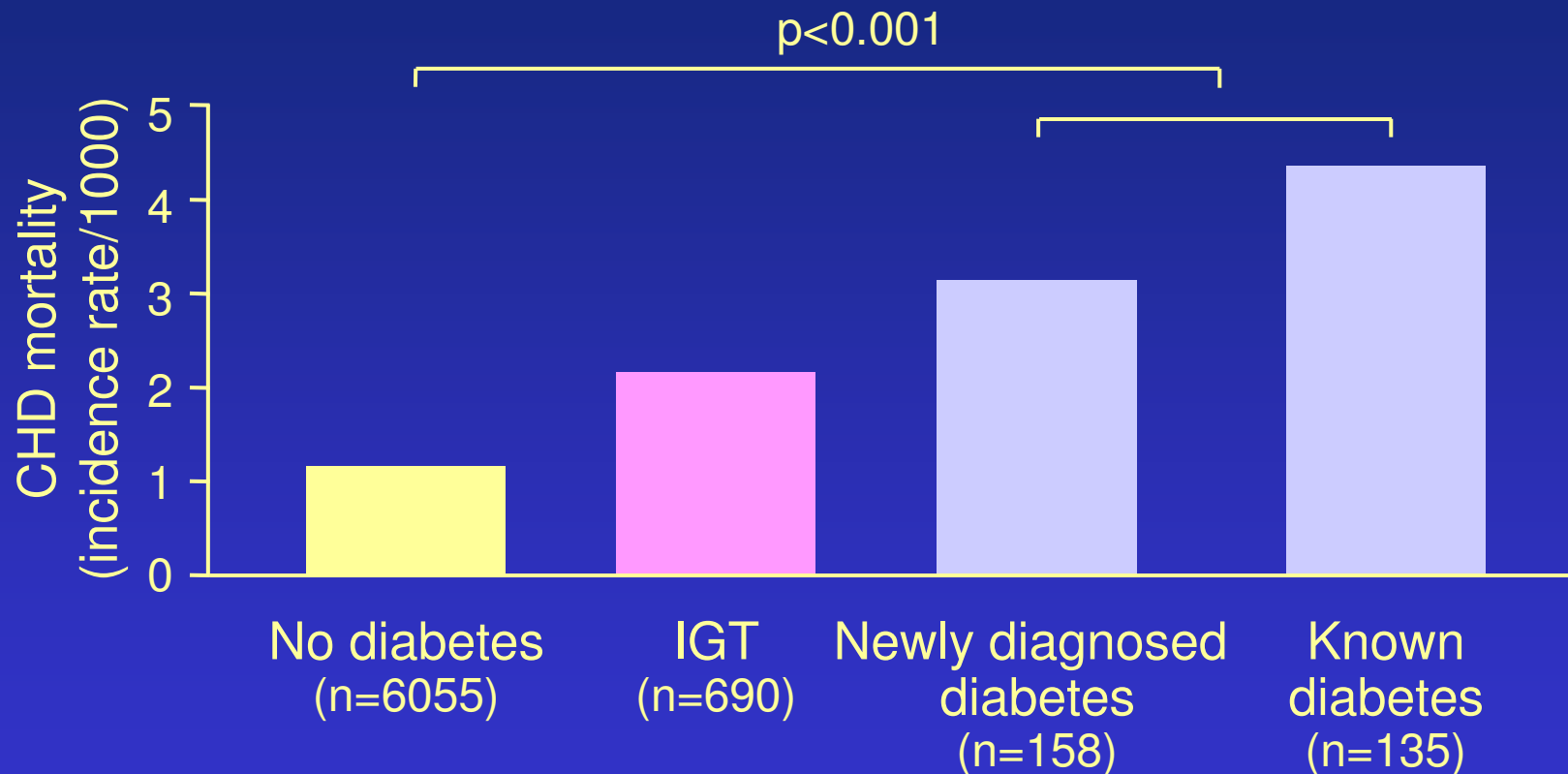
*0.001<p<0.01 for diabetics vs. nondiabetics, **p<0.05 for diabetics vs. nondiabetics

CHD = coronary heart disease; RR = relative risk

Adapted from Wilson PWF, Kannel WB. In *Hyperglycemia, Diabetes and Vascular Disease*. Oxford: Oxford University Press. 1992:21–29.

IGT increases risk of CHD mortality

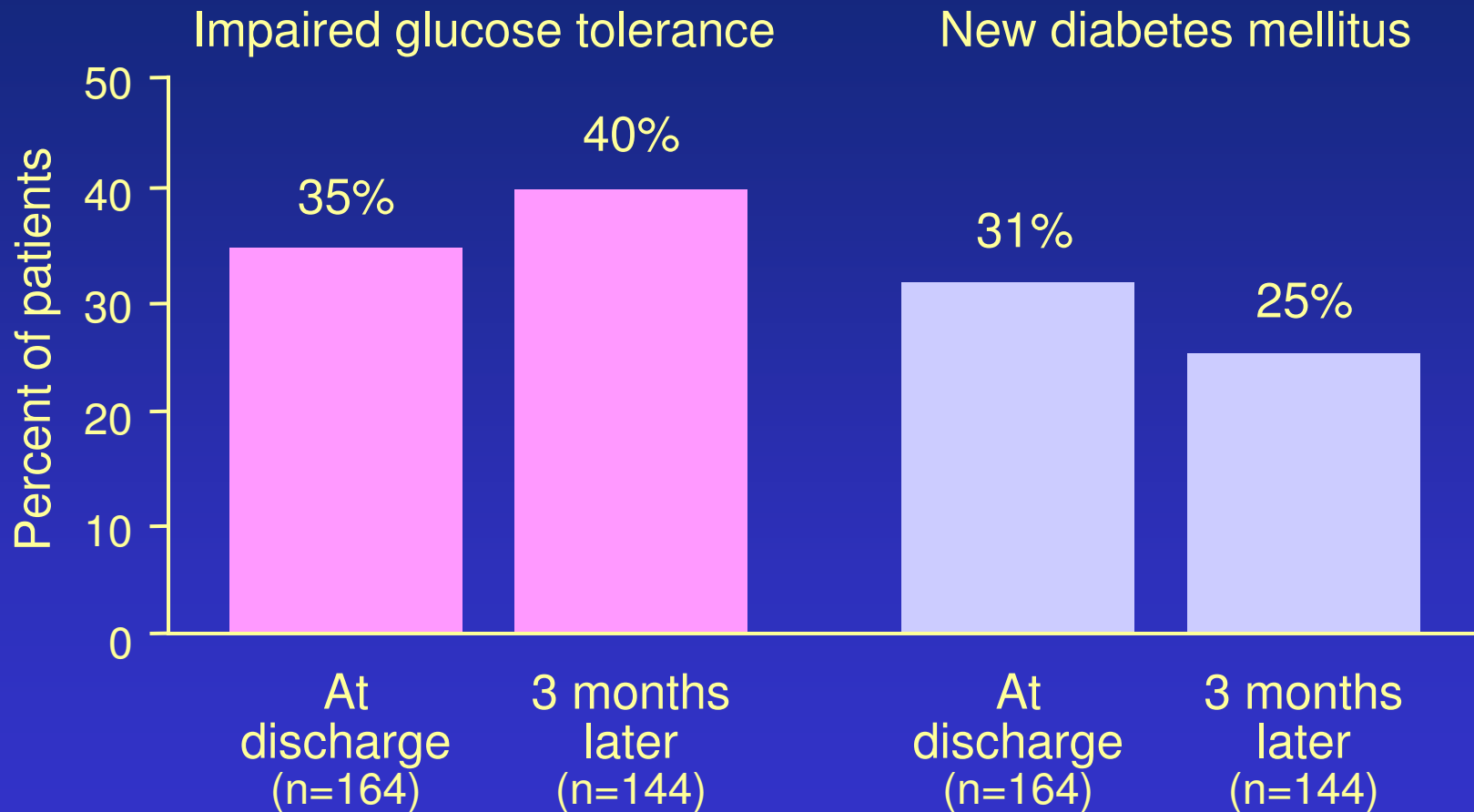
Paris Prospective Study 11-year follow-up



IGT = impaired glucose tolerance; CHD = coronary heart disease

Adapted from Eschwege E et al *Horm Metab Res* 1985;15(suppl):41–46.

Results of OGTT in patients with acute MI and previously unknown diabetes mellitus



Adapted from Norhammar A et al *Lancet* 2002;359:2140–2144.

Diabetes mellitus (impaired glucose metabolism) and CVD: summary

- The incidence of diabetes is rising
- CVD morbidity and mortality are increased in diabetes

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???

Established cardiovascular risk factors in diabetic patients relative to nondiabetics

Risk Factor	Type 1	Type 2
Dyslipidemia		
Hypertriglyceridemia	++	++
Decreased HDL	+/-	++
Small, dense LDL	+	++
Increased apo B	+	++
Hypertension	+	++
Hyperinsulinemia/insulin resistance	+	++
Central obesity	-	++
Family history of atherosclerosis	-	+
Cigarette smoking	-	-

+ = moderately increased compared with nondiabetic population

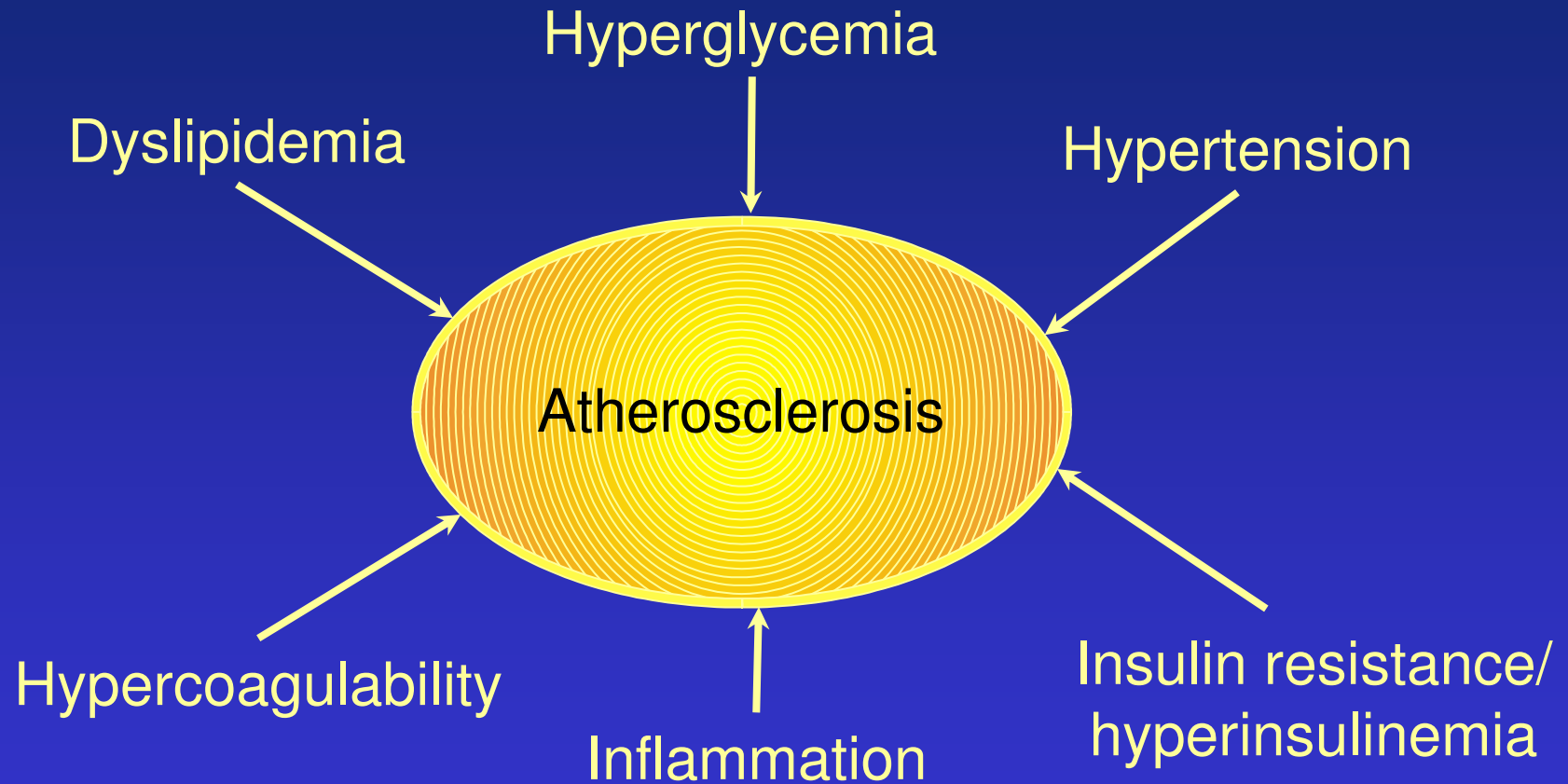
++ = markedly increased compared with nondiabetic population

- = not different compared with nondiabetic population

Emerging risk factors/biomarkers for CVD

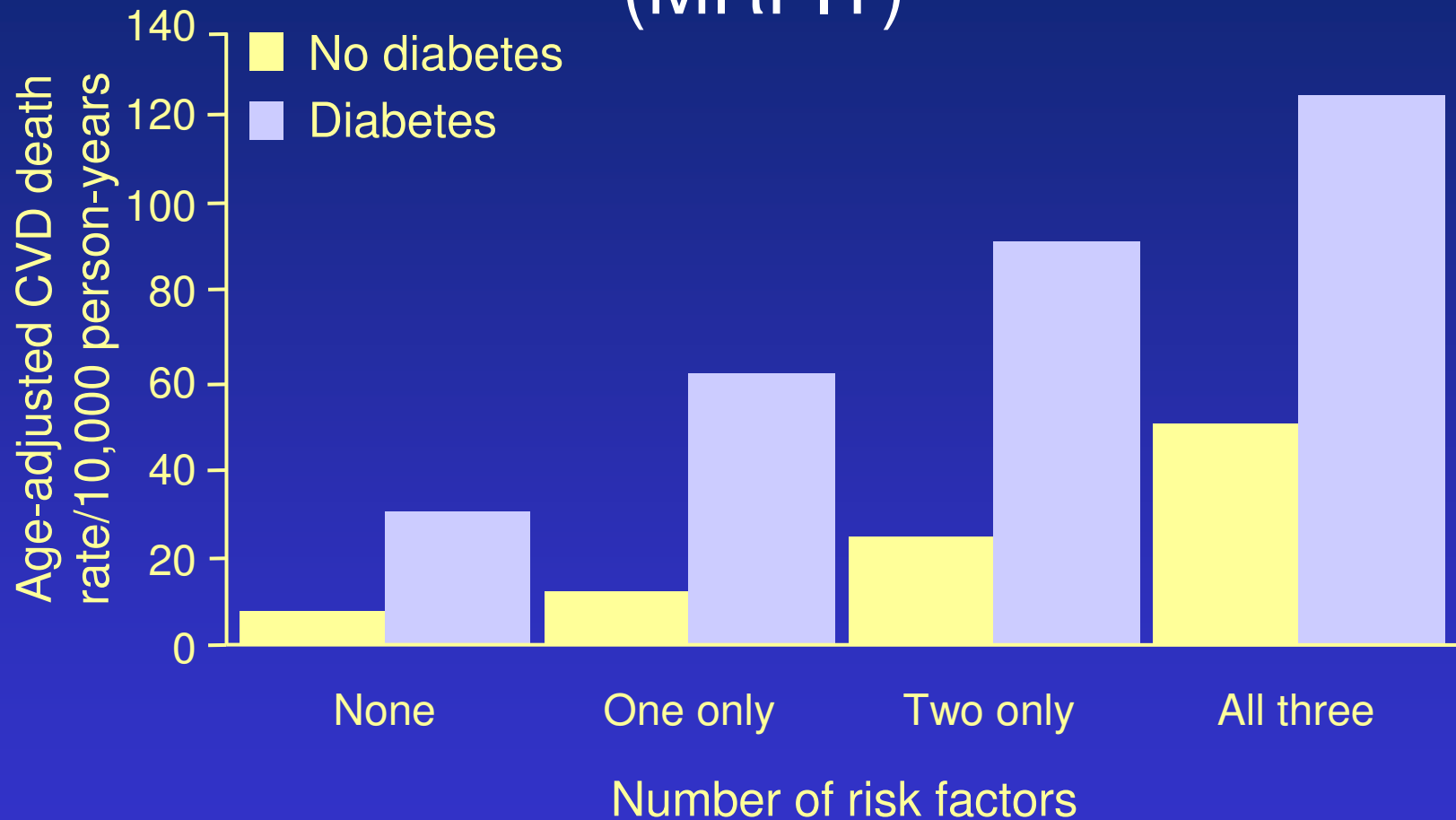
- Lipoprotein heterogeneity
- Inflammatory markers (e.g., C-reactive protein)
- Prothrombotic/hemostatic factors
- Homocysteine
- Lipoprotein (a)

Potential mechanisms for atherosclerosis in the metabolic syndrome/diabetes



Adapted from Chait A, Bierman EL. In *Joslin's Diabetes Mellitus*. 13th ed. Philadelphia: Lea & Febiger, 1994:648–664.

Influence of multiple risk factors* on CVD death rates in diabetic and nondiabetic men (MRFIT)



*Serum cholesterol >200 mg/dl, smoking, systolic blood pressure >120 mmHg

MRFIT = Multiple Risk Factor Intervention Trial

Adapted from Stamler J et al *Diabetes Care* 1993;16:434-444.

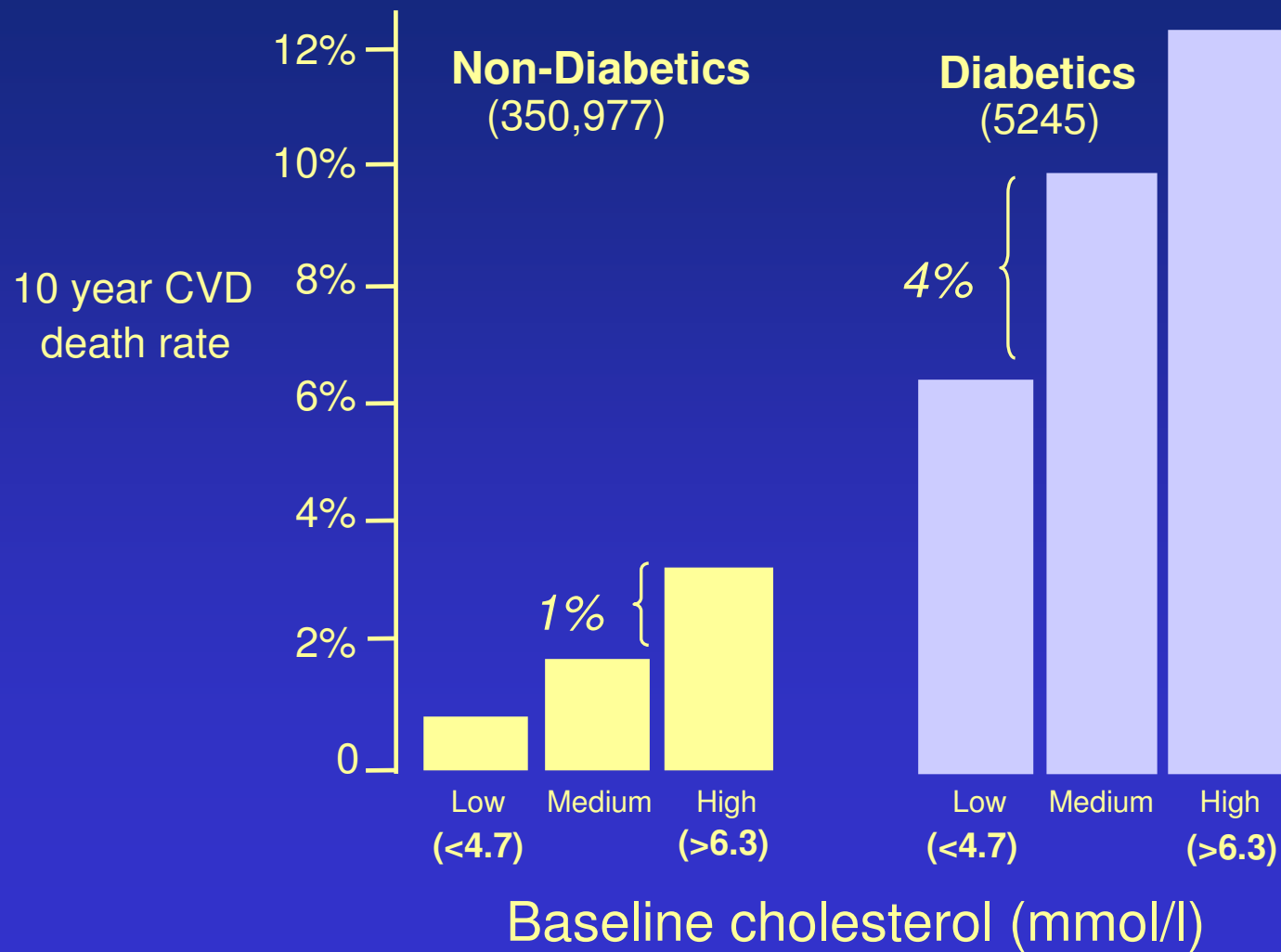
Potential targets for therapy

- Lifestyle factors (smoking, diet, exercise)
- Lipid-lowering treatment
- Blood pressure-lowering treatment
- Glucose-lowering treatment
- Antiplatelet treatment

Targeting individual risk factors:

Lipid-lowering treatment

CVD mortality rates in MRFIT



Eligibility: MRC/BHF Heart Protection Study

- Increased risk of CHD death due to prior disease:
 - Myocardial infarction or other coronary heart disease;
 - Occlusive disease of non-coronary arteries; or
 - Diabetes mellitus or treated hypertension
- Age 40-80 years
- Total cholesterol >3.5 mmol/l
- Statin or vitamins not considered clearly indicated or contraindicated by patient's own doctors

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hps

Prior disease at baseline

Prior disease	Number	Percentage
Any MI	8510	41%
Other CHD	4876	24%
No CHD*	7150	35%
Cerebrovascular	1820	
Peripheral vascular	2701	
Diabetes	3982	
ALL PATIENTS	20,536	100%

* Overlap between categories within “No CHD” group

Numbers with diabetes at baseline

Disease history	Type 1 (615)	Type 2 (5348)	All diabetes (5963)
Prior MI	5%	20%	1125
Other CHD	5%	15%	853
Other vascular	20%	18%	1072
No vascular	70%	46%	2913

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Factorial treatment comparisons

Simvastatin
(40 mg daily)

vs

Placebo
tablets

Vitamins
(600 mg E, 250 mg C
& 20 mg beta-carotene)

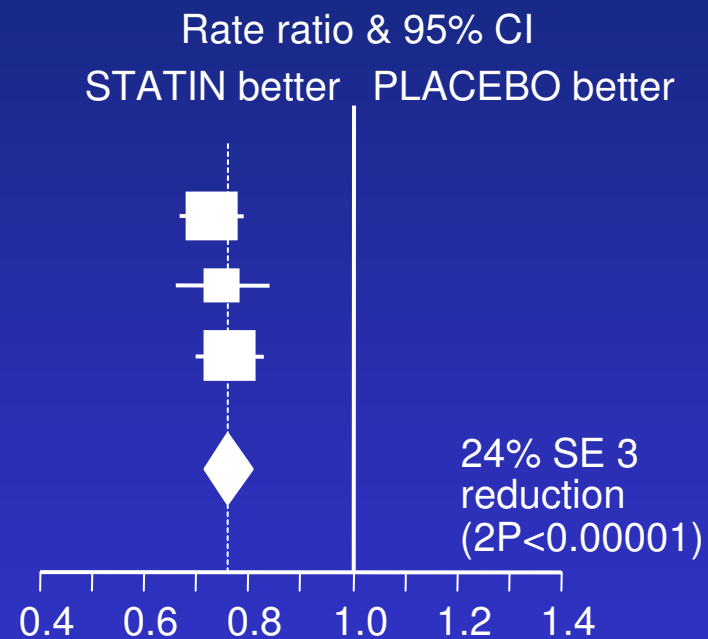
vs

Placebo
capsules

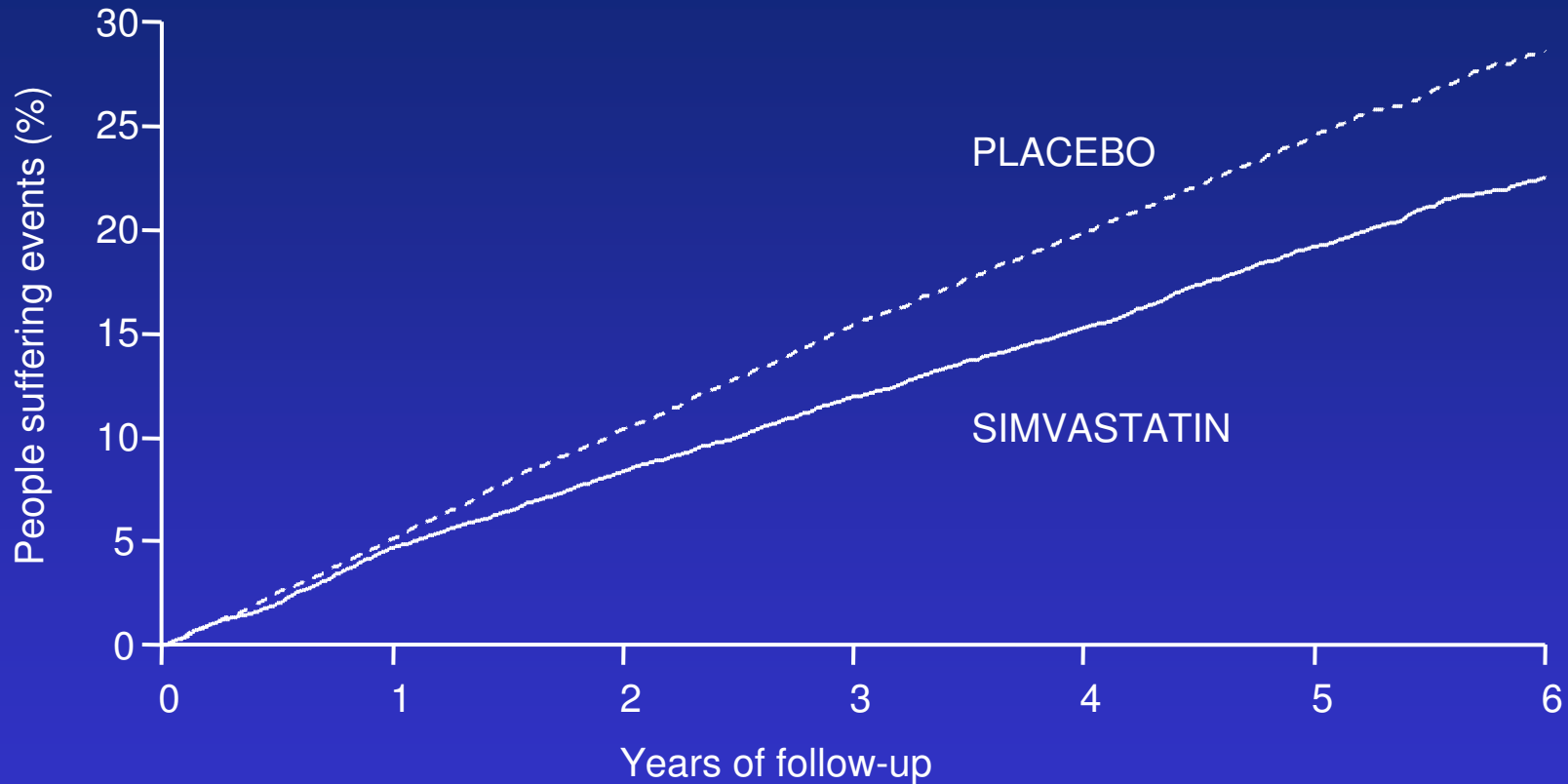
5 years average duration of follow-up

Simvastatin: major vascular events

Vascular event	SIMVASTATIN (10269)	PLACEBO (10267)
Major coronary	898	1212
Any stroke	444	585
Revascularisation	939	1205
ANY OF ABOVE	2033 (19.8%)	2585 (25.2%)



Simvastatin: major vascular events by year

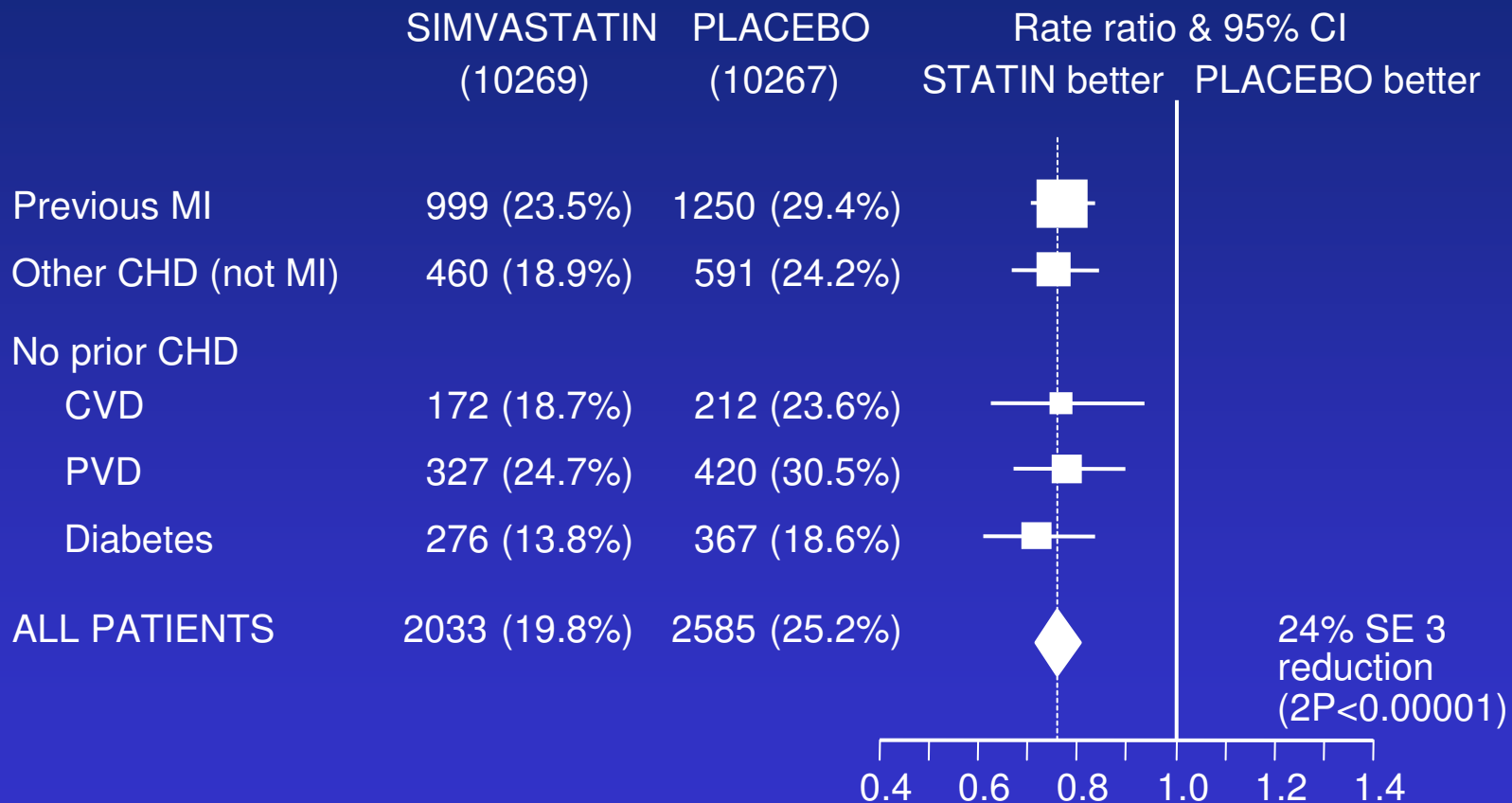


Benefit/1000 (SE): 5(3) 20(4) 35(5) 46(5) 54(7) 60(18)

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Simvastatin: major vascular events by prior disease

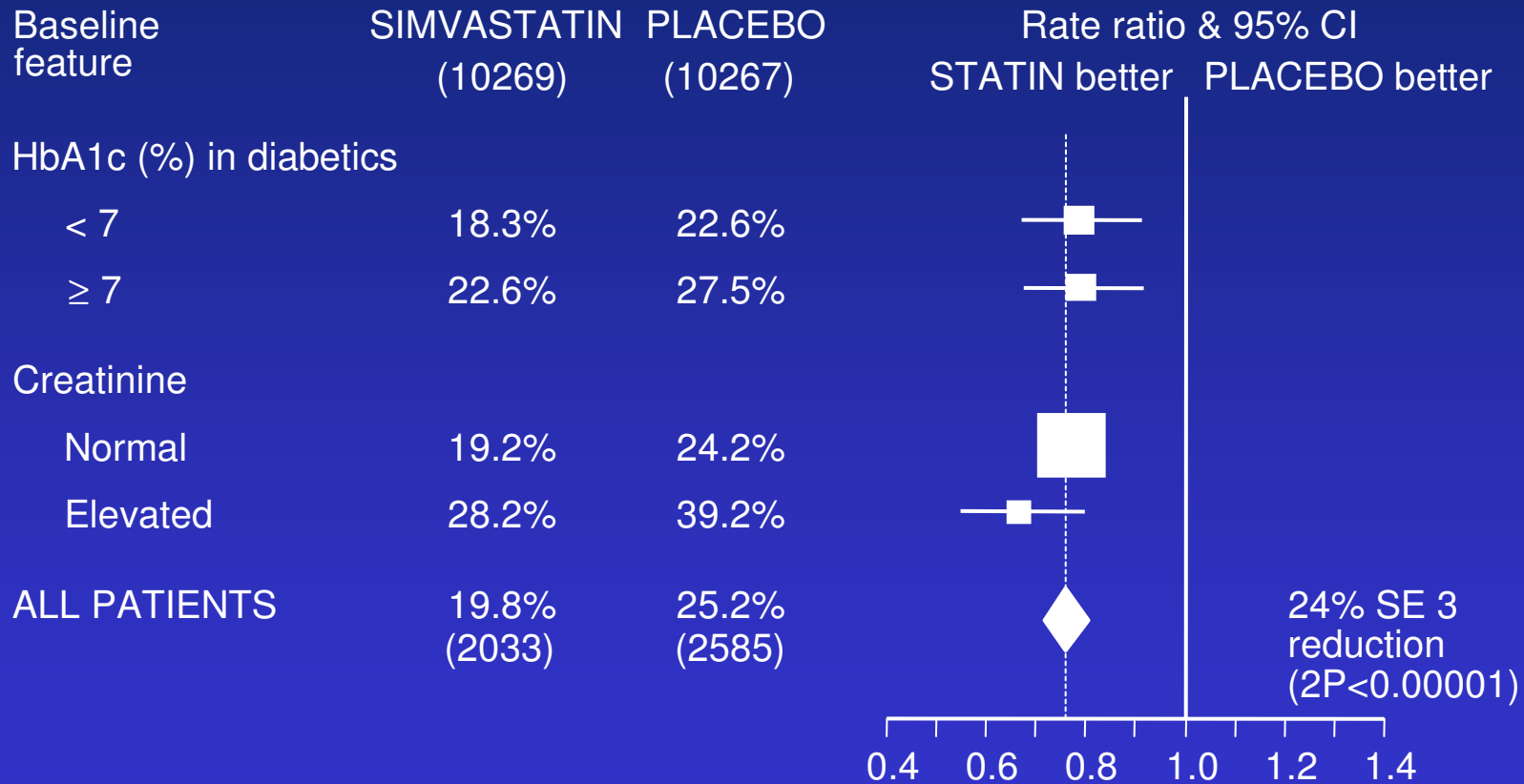


Simvastatin: major vascular events in people with diabetes (without vascular disease)

SIMVASTATIN (1455)	PLACEBO (1457)	Rate ratio (& 95% CI)
135 (9.3%)	196 (13.5%)	0.67 (0.54-0.83)

P < 0.0001

Simvastatin: major vascular events by HbA1c & creatinine

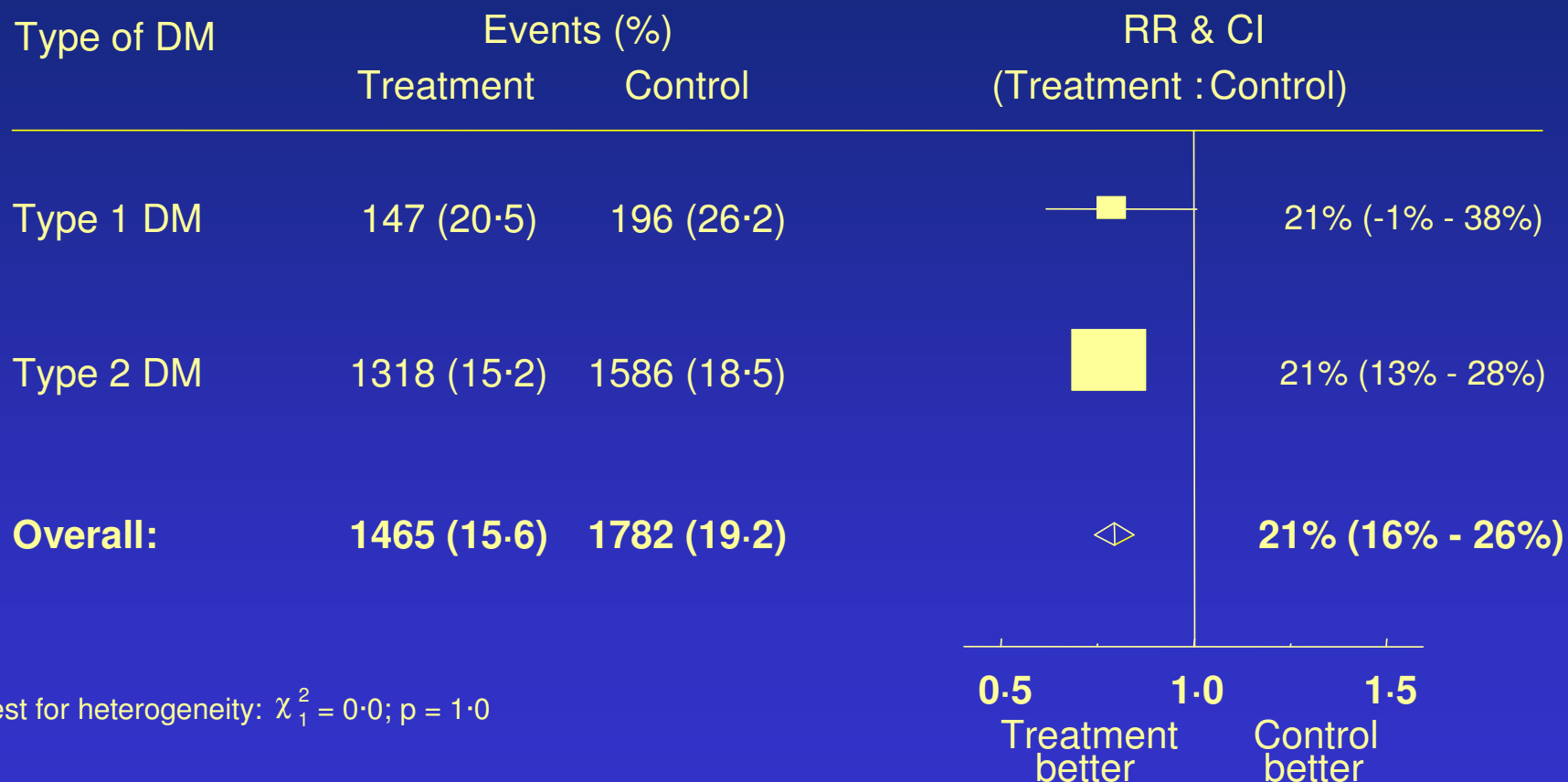


Simvastatin: major vascular events by diabetes type and LDL/HDL ratio

Baseline feature	SIMVASTATIN (10269)	PLACEBO (10267)
Type 1 DM	13.7%	17.5%
Type 2 DM	20.9%	25.9%
No Diabetes	19.6%	25.2%
LDL/HDL ratio		
<3.5 Diabetes	15.5%	19.8%
<3.5 No diabetes	18.8%	22.3%
ALL PATIENTS	19.8% (2033)	25.2% (2585)



CTT: Effects on major vascular events per 1 mmol/L LDL cholesterol reduction by type of diabetes



Fibrates: FIELD study

- 9795 patients with diabetes +/- CVD
- 200mg fenofibrate vs placebo
- Primary outcome CHD events:
 - non-significant 11% reduction
- Secondary outcome total CVD events
 - 11% reduction $p=0.035$

FIELD: conclusions

- Observed effects of fenofibrate attenuated by differential statin use
- Use of fenofibrate should now be considered in the context of well-established statin therapy
 - its main use is likely to be in combination
 - fenofibrate was well tolerated alone and in combination with statins.

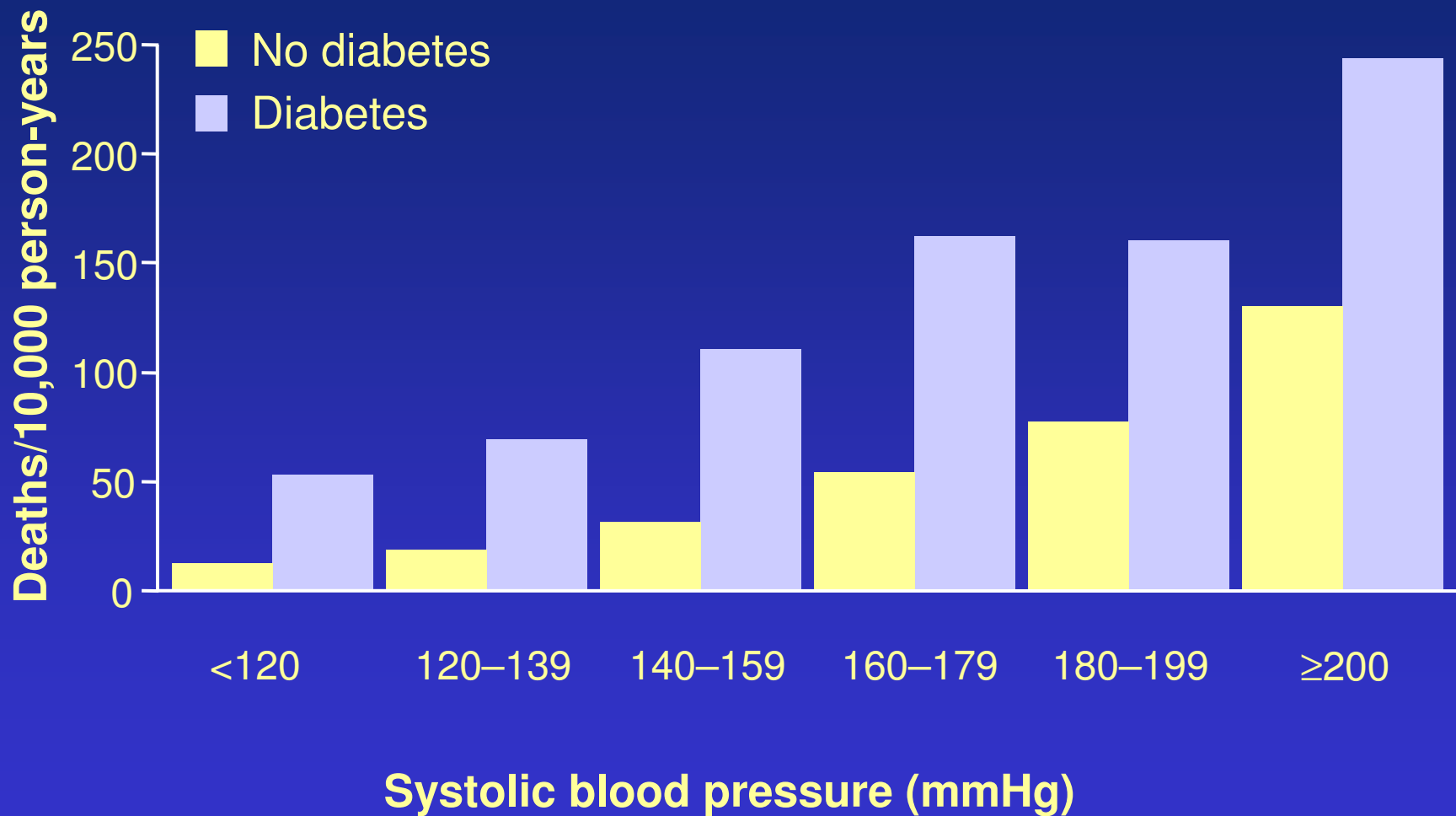
Recommendations for lipid lowering in people with diabetes

- Statin therapy for all those aged 40 years or more with either type 1 or type 2 diabetes
- LDL target ?
- Younger patients with additional risk factors ?
- Add fibrate if triglycerides remain elevated ?
- Add niacin if low HDL ?

Targeting individual risk factors:

Blood pressure-lowering treatment

Cardiovascular Mortality Rates*



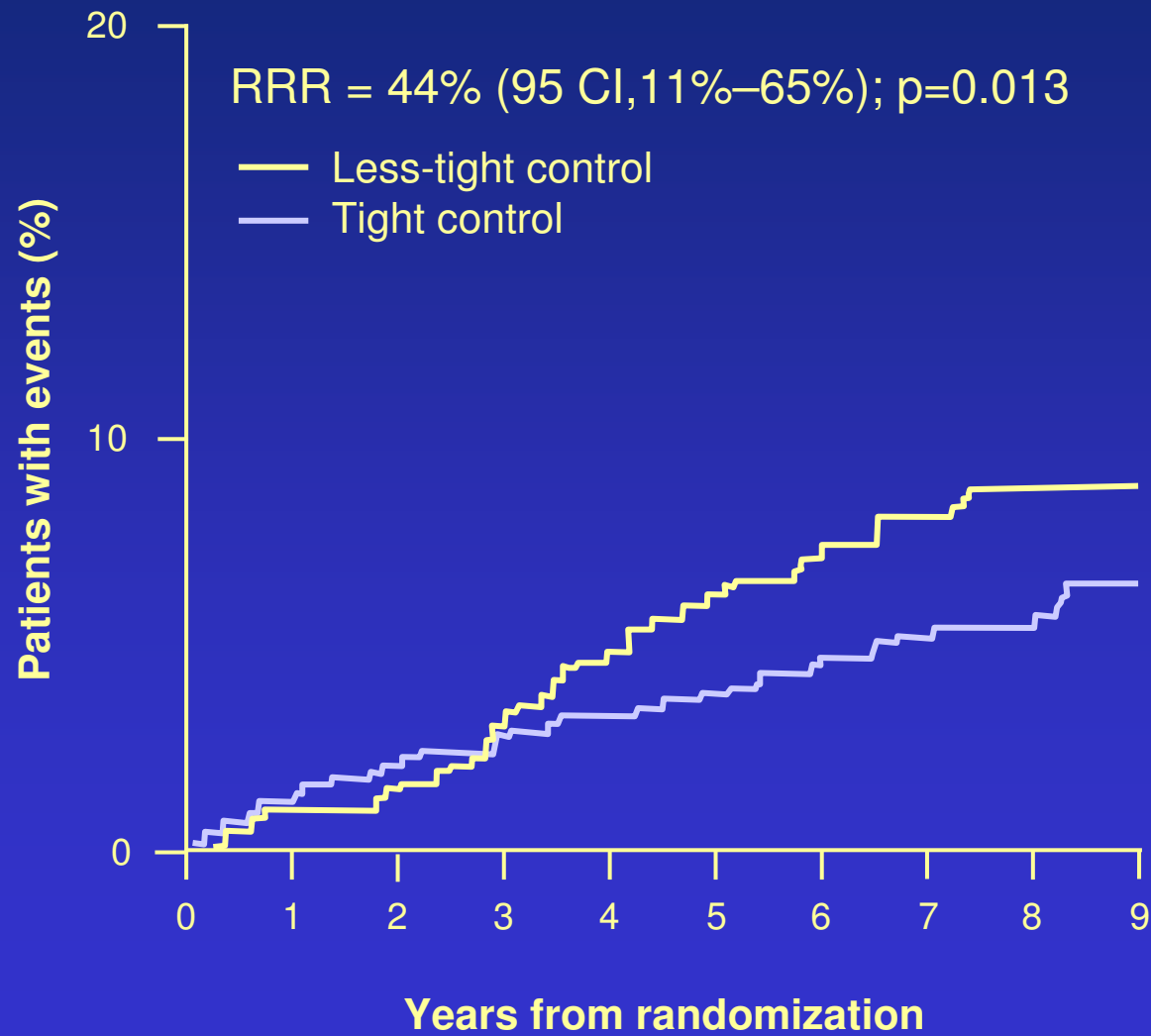
*Age-adjusted

Adapted from Stamler J et al *JAMA* 1993;16:434–444.

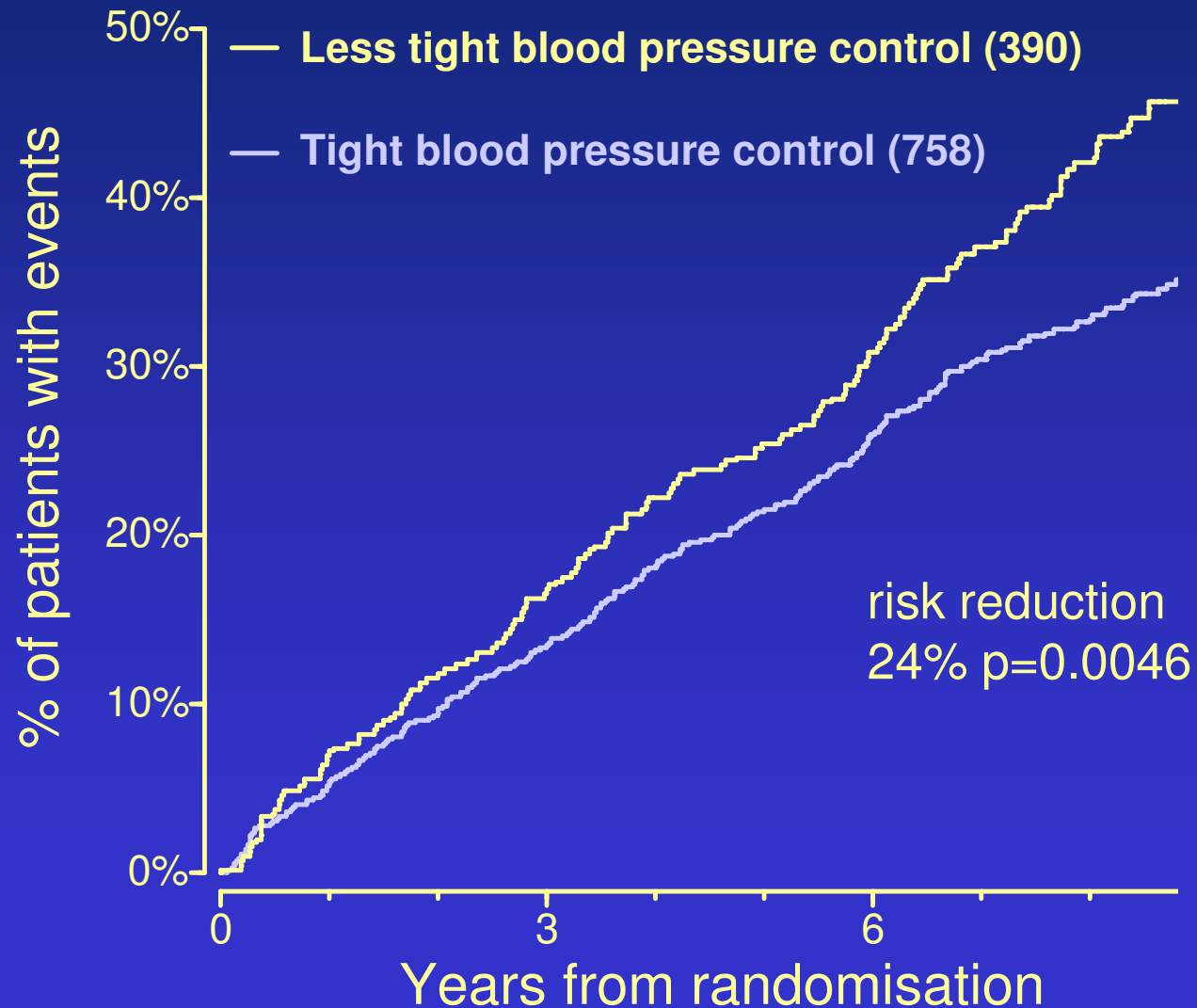
UKPDS: Tight blood pressure control in type 2 diabetes

- Population
 - 1148 patients, mean age 56; mean blood pressure at entry, 160/94 mmHg
- Treatment
 - Tight control (captopril/atenolol) vs less tight control (aim <150/85 mmHg vs aim <180/105 mmHg)
 - Mean blood pressure during follow-up 144/82 vs 154/87 mmHg
- RRR
 - 24% diabetes-related endpoints, $p=0.0046$
 - 32% diabetes-related deaths, $p=0.019$
 - 37% microvascular endpoints, $p=0.0092$

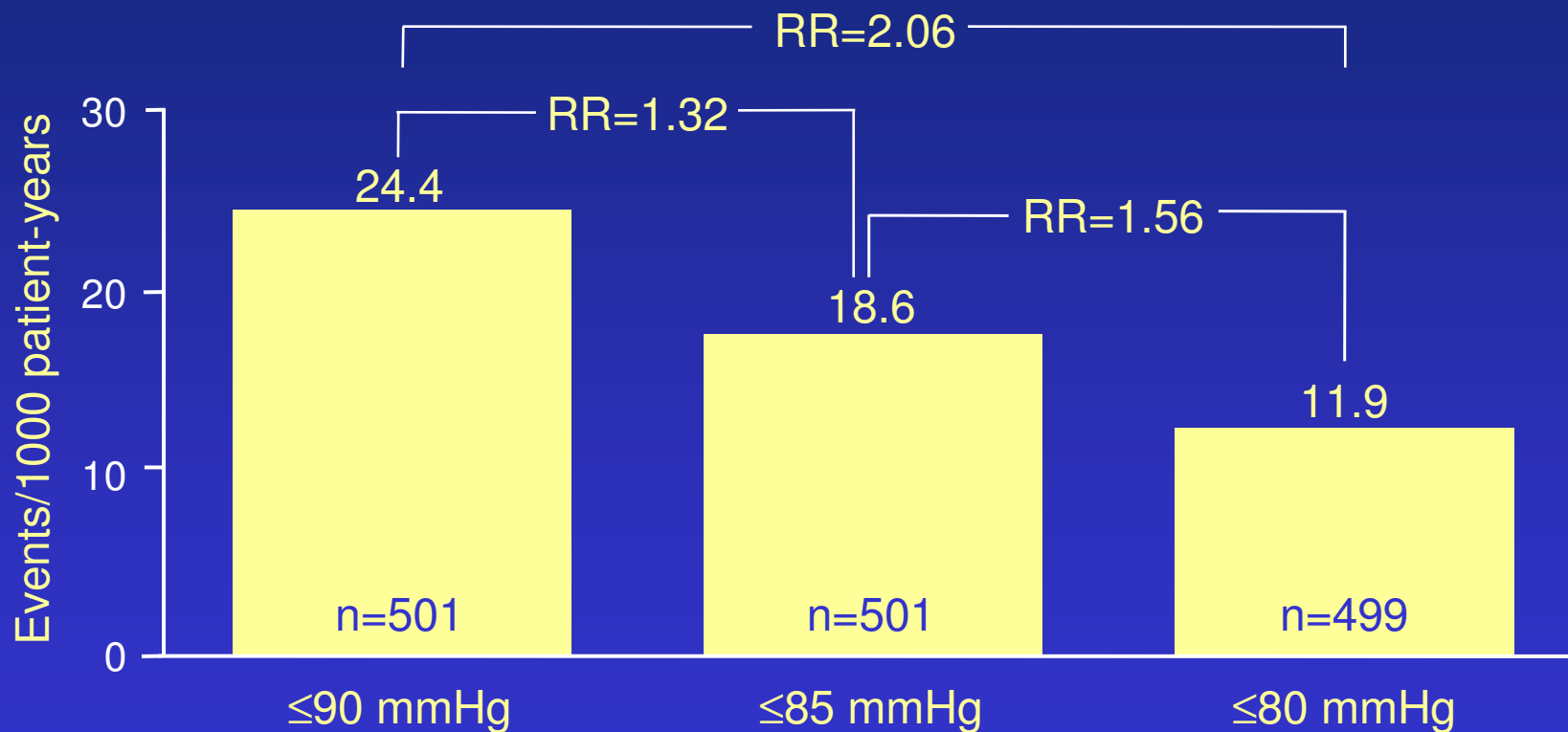
UKPDS: stroke



UKPDS: any diabetes-related endpoint



HOT trial: major cardiovascular events in patients with diabetes mellitus, by target blood pressure



HOT = Hypertension Optimal Treatment; RR = relative risk
Adapted from Hansson L et al *Lancet* 1998;351:1755–1762.

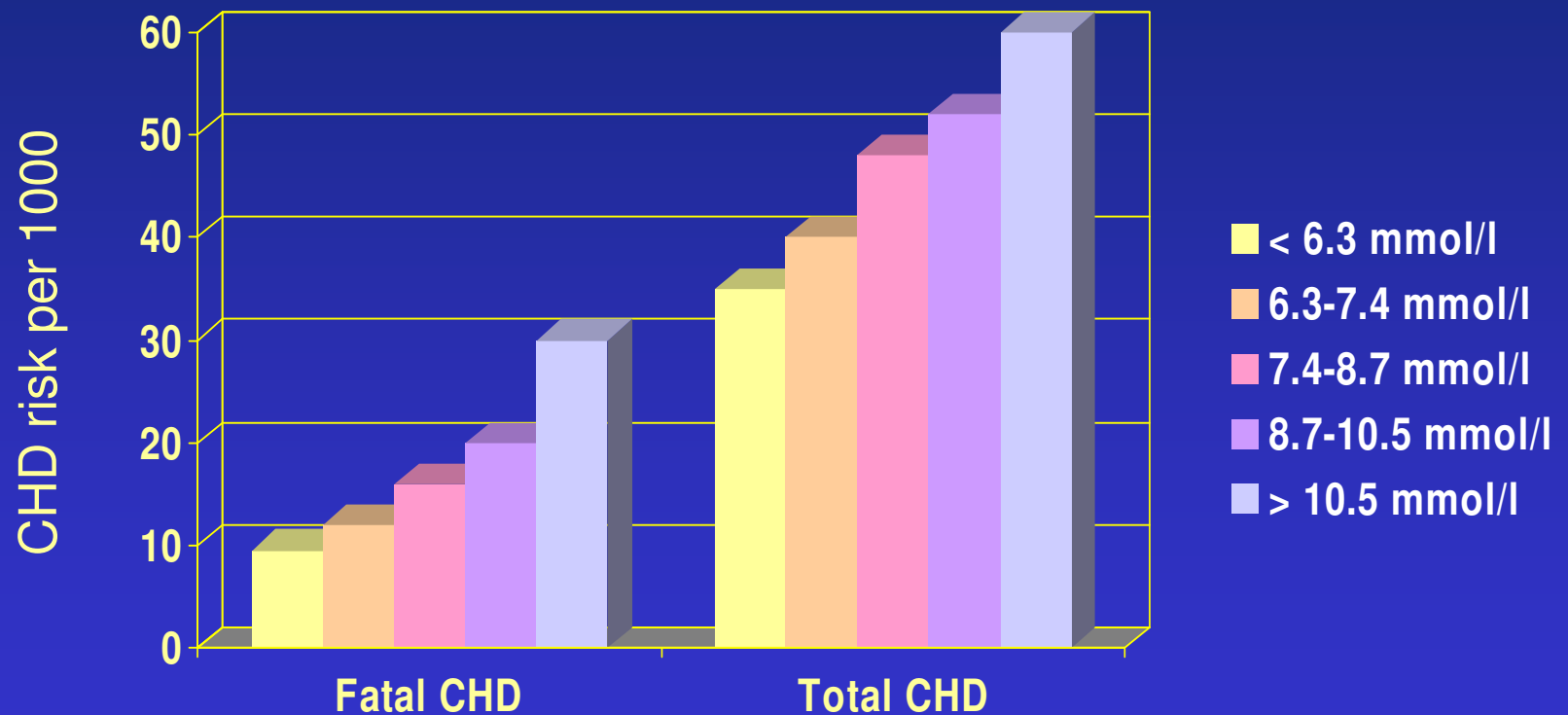
Recommendations for blood pressure lowering in people with diabetes

- Aim as low as possible (< 130/80)
- Multiple therapies often necessary
 - ACE (ARB)
 - Ca channel blocker
 - Thiazide diuretic
 - Alpha-blocker
 - B-blocker
- ACE/ARB additional reno-protective advantages

Targeting individual risk factors:

Glucose-lowering treatment

Cardiovascular disease and its relationship with postprandial plasma glucose in 8006 men: *The Honolulu Heart Study*



Adapted from: Donahue, R.P. et al. *Diabetes* 36: 689-692, 1987

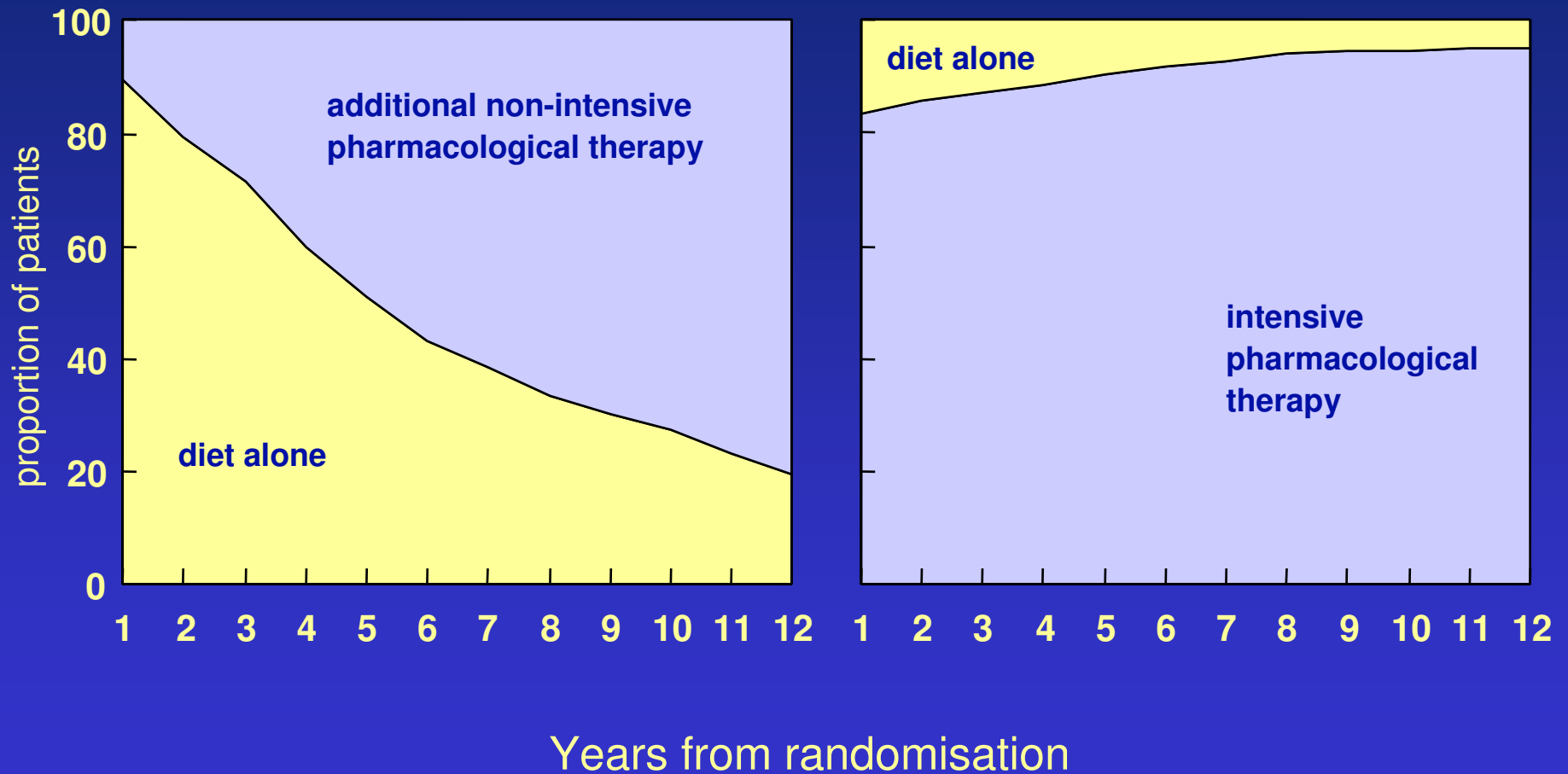
UKPDS: design

- Objective
 - To determine whether intensified blood-glucose control, with either sulfonylurea or insulin, reduces the risk of macrovascular or microvascular complications in type 2 diabetes
- Patients
 - 3867 newly diagnosed, asymptomatic after 3 months of diet; FG 6.1–15 mmol/L
 - Intensive treatment: aim FG < 6 mmol/l
 - Conventional treatment: aim FG < 15 mmol/l

UKPDS: actual therapy

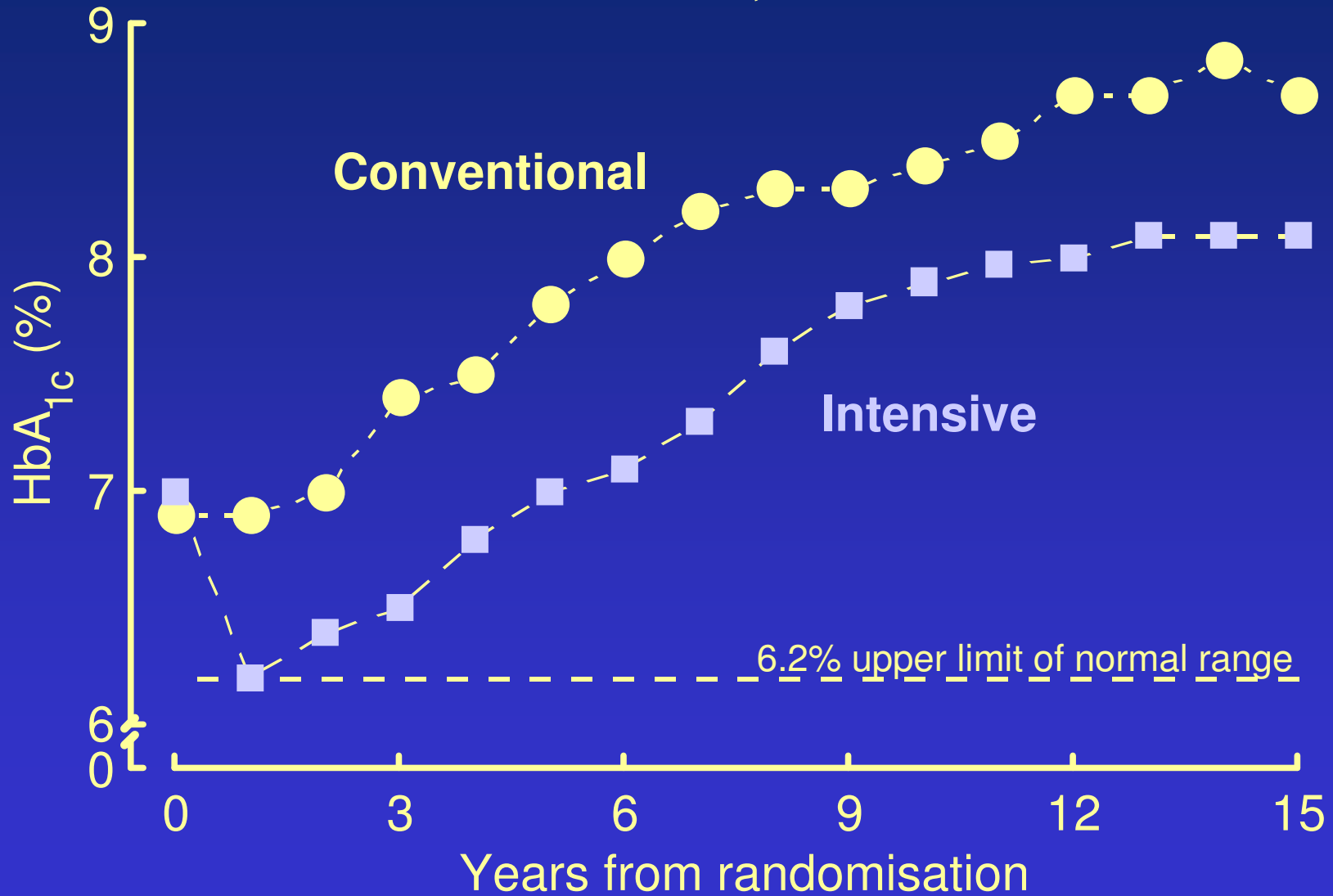
Conventional Policy
accept < 15 mmol/L

Intensive Policy
aim for < 6 mmol/L



UKPDS: HbA_{1c}

cross-sectional, median values



UKPDS: endpoints by glucose treatment

	Intensive rate/1000 patient-years	Conventional rate/1000 patient-years	p Value	RRR (%)
Any diabetes-related*	40.9	46.0	0.029	12
MI	14.7	17.4	0.052	16
Stroke	5.6	5.0	0.52	—
Peripheral vascular disease**	1.1	1.6	0.15	—
Microvascular	8.6	11.4	0.0099	25

*Combined microvascular and macrovascular events

**Amputation or death from peripheral vascular disease

Adapted from UK Prospective Diabetes Study (UKPDS) Group *Lancet* 1998;352:837-853.

Recommendations for glucose lowering in people with diabetes

- Ideal is normoglycaemia, but difficult to avoid hypoglycaemia with intensive treatment.
- HbA1c < 6.5%, FPG 4.0-6.0 mmol/l
- Metformin in overweight type 2 patients (evidence of cardiovascular benefit in UKPDS compared with insulin or sulphonylurea)

Targeting individual risk factors:

Antiplatelet treatment

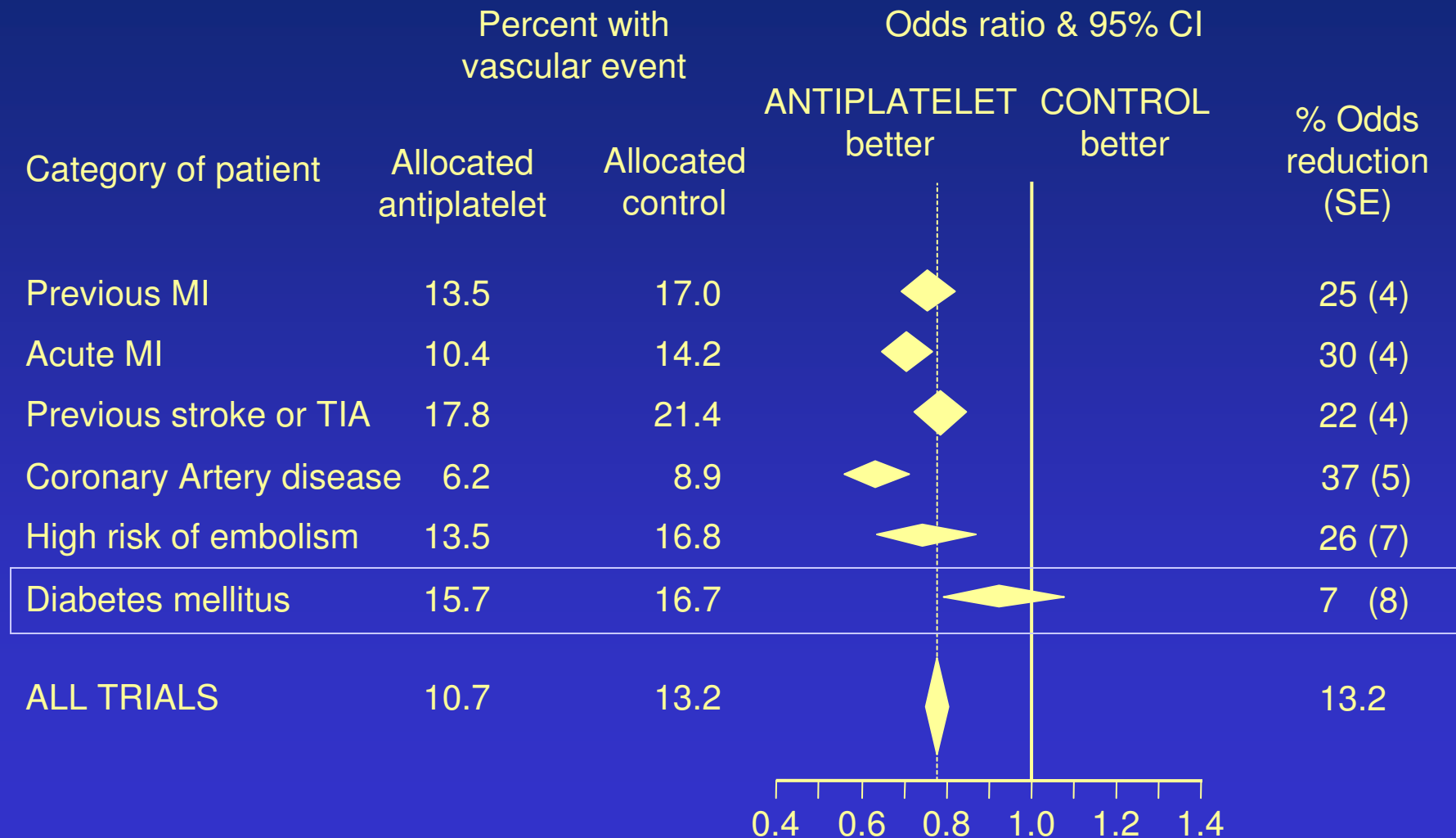
JBS-2 Guidelines: Dec 2005

“Aspirin 75 mg daily is recommended for all people with type 2 diabetes who are > 50 years of age, and selectively in younger people with one of the following criteria:

- who have had the disease for more than 10 years;
- who are already receiving treatment for hypertension;
- who have evidence of target organ damage in the form of retinopathy or nephropathy, and whose blood pressure is controlled to at least 150/90 mm Hg, and preferably to the optimal target of 130/80 mm Hg.”

Antithrombotic Trialists' Collaboration, 2002

Effects of antiplatelet therapy on vascular events



Current evidence for use of aspirin for primary prevention of CVD in diabetes

- 9 trials, 4961 diabetics
- Most data from one trial of 3711 pts
- Non-significant increase in risk of stroke: 17% (99%CI = -21% to +74%)

Risks of bleeding with aspirin

- Intracranial bleeds are increased by about 30%, and extracranial bleeds by about 50%
- Proportional increases similar in all patient groups

Events Avoided or Caused per 1000 Individuals Treated with Aspirin for 5 Years

10 year risk of CHD event	Avoided		Caused	
	CHD event	Ischaemic stroke	Haemorrhagic stroke	Major bleed
<10%	5	0	1	5
10-20%	15	0	1	5
Secondary	25-50	25-50	1	5

Is aspirin being used for primary prevention in diabetes?

- Lack of definitive evidence that the benefits outweigh the risks
- Hence lack of consistency in guidelines
- Difficulty estimating cardiovascular risk in diabetes

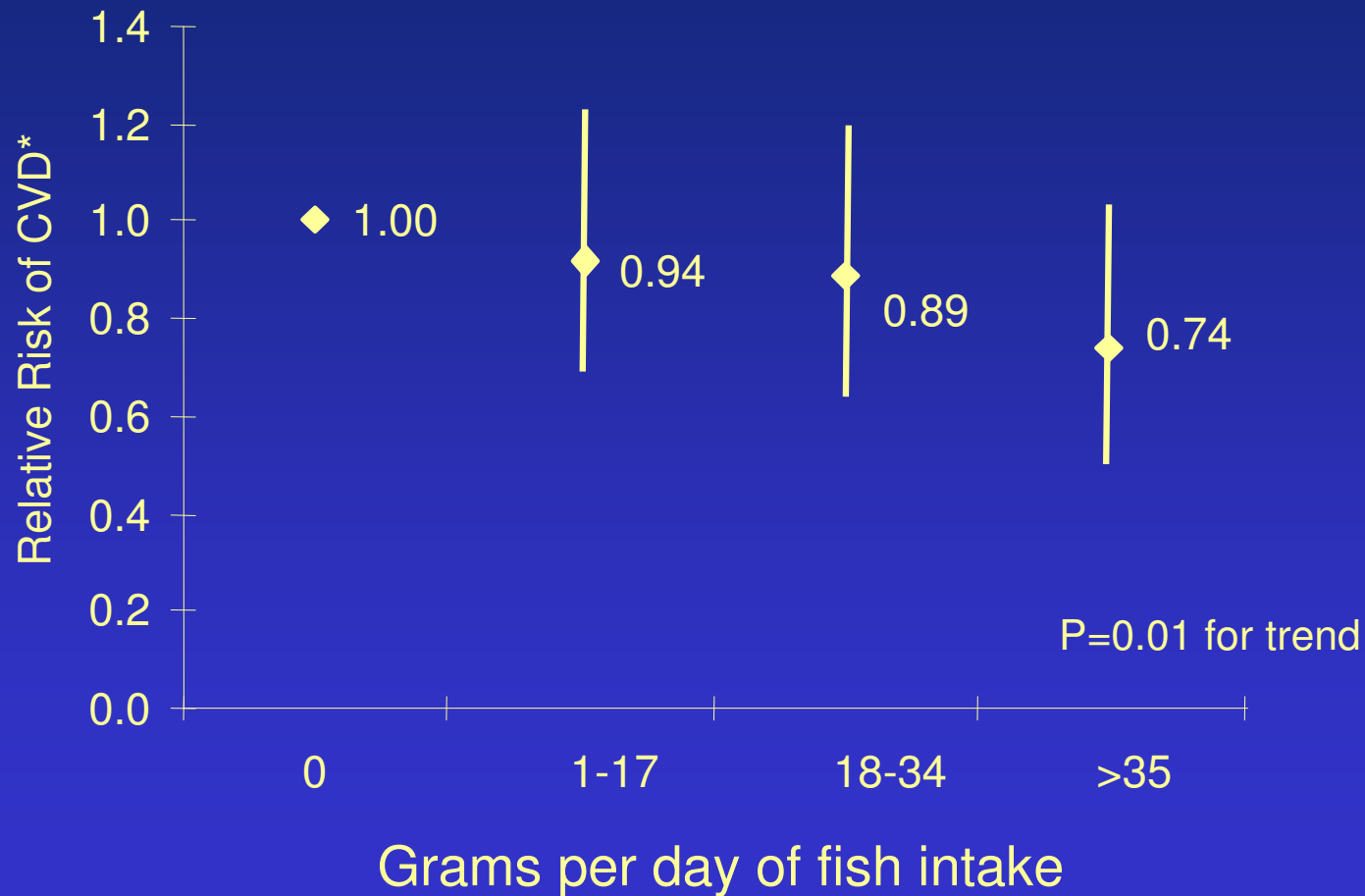
ASCEND

A Study of Cardiovascular Events in Diabetes

2x2 factorial design trial of aspirin vs placebo and omega-3 FA vs placebo

	Aspirin tablets	Placebo tablets	
Omega-3 Fatty acids (FA) capsules	2500 Aspirin + Omega-3 FA	2500 Omega-3 FA	Subtotal 1: 5000 Omega-3 FA
Placebo capsules	2500 Aspirin	2500 Neither	Subtotal 2: 5000 Placebo
	Subtotal A: 5000 Aspirin	Subtotal B: 5000 Placebo	

Risk of a major cardiovascular event by fish intake: 30 y follow-up of Chicago Western Electric Study (n=47,153 person yrs FU)



*Multivariate proportional hazards model

GISSI - Prevenzione: effect on coronary events

Omega-3 FA PLACEBO Risk ratio & 95% CI

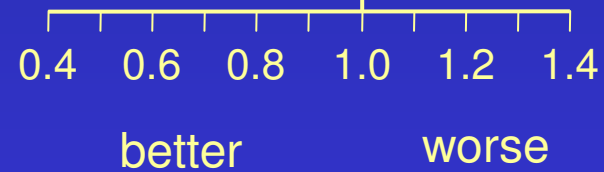
GISSI-P

424/5666

485/5668



0.87 (0.76-0.99)



ASCEND: Eligibility

- Diabetes mellitus (type 1 or 2)
- No clinical evidence of cardiovascular disease
- Aged at least 40 years (no upper limit)
- Men or women
- No contraindications to aspirin or omega-3 fatty acids
- Not currently taking aspirin (willing to stop if not clinically indicated and GP agrees)

Primary Endpoint

- Cardiovascular events
 - non-fatal myocardial infarction
 - non-fatal stroke
 - cardiovascular death
 - [excluding definite haemorrhagic stroke]
- Estimated event rate of 2% per annum

Study Status

- BHF funding: Special Project Grant awarded (£1.1M)
- Study run predominantly by mail
- Recruitment started March 2005
 - Hospital trust-held diabetes registers
 - General practice-held registers
- 1900 participants randomised to date

Recruitment from GP-held registers

- Electronic search run on practice database to identify potentially eligible people
- “Invitation packs” provided by coordinating centre but sent from local practice with covering letter of invitation in GP’s name
- 24 hr Freefone availability for questions about informed consent and participation
- E-mail ascend@ctsu.ox.ac.uk if practice interested in collaborating
- <http://www.ctsu.ox.ac.uk/ascend>

Unresolved issues for cardiovascular risk reduction in diabetes

- More intensive LDL lowering (SEARCH/CTT)
- Statin vs. fibrate
- Statin/fibrate vs. statin (ACCORD)
- PPAR-gamma agonists
- Folate/B12 (SEARCH)

The prevention of cardiovascular disease in diabetes: the individual

- Lifestyle modification (smoking, diet, exercise)
- Lower cholesterol (Statin treatment)
- Lower blood pressure (ACEI, diuretics, Beta-blockers, CCB, ARB)
- Control blood glucose (oral agents esp metformin, or insulin)
- Compliance with multiple therapies

The prevention of cardiovascular disease in diabetes: the population

- Population strategies to reduce weight, improve diet, increase exercise etc
- Ensure diabetes is diagnosed
- Cardiovascular disease prevention and treatment services