The role of intensified multifactorial intervention on micro- and macrovascular complications in patients with type 2 diabetes

Peter Gæde
MD, DMSci, Specialist in Internal Medicine and Endocrinolgy
Steno Diabetes Center

An opportunity to make a difference

Peter Gæde
MD, DMSci, Specialist in Internal Medicine
Steno Diabetes Center

Risk factor profile in diabetes

- Hyperglycaemia
- Blood pressure
- Dyslipidaemia
- Urinary albumin excretion rate
- Smoking
- BMI
- Left ventricular hypertrophy
- Autonomic dysfunction
- Endothelial dysfunction
- Insulin resistance / Hyperinsulinaemia
- Familial predisposition to CVD

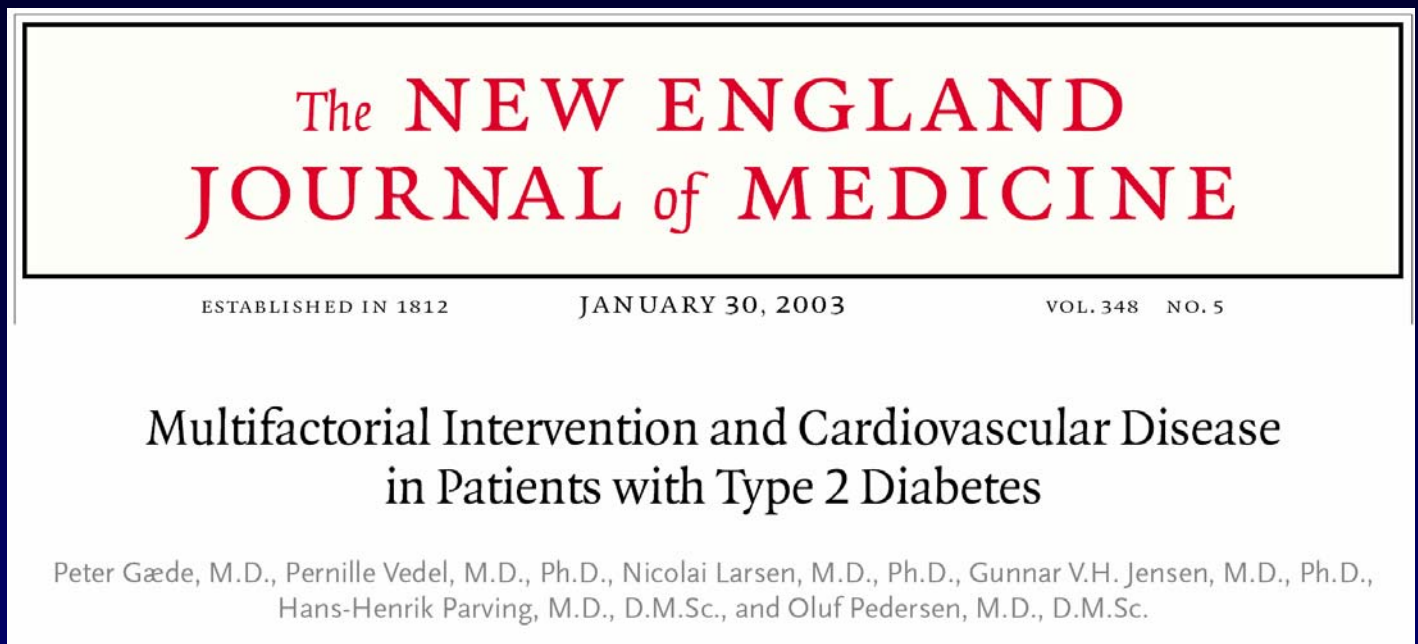
Clinical Dogma

I want evidence based diabetology

Steno-2: Major papers

Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study

Peter Gæde, Pernille Vedel, Hans-Henrik Parving, Oluf Pedersen

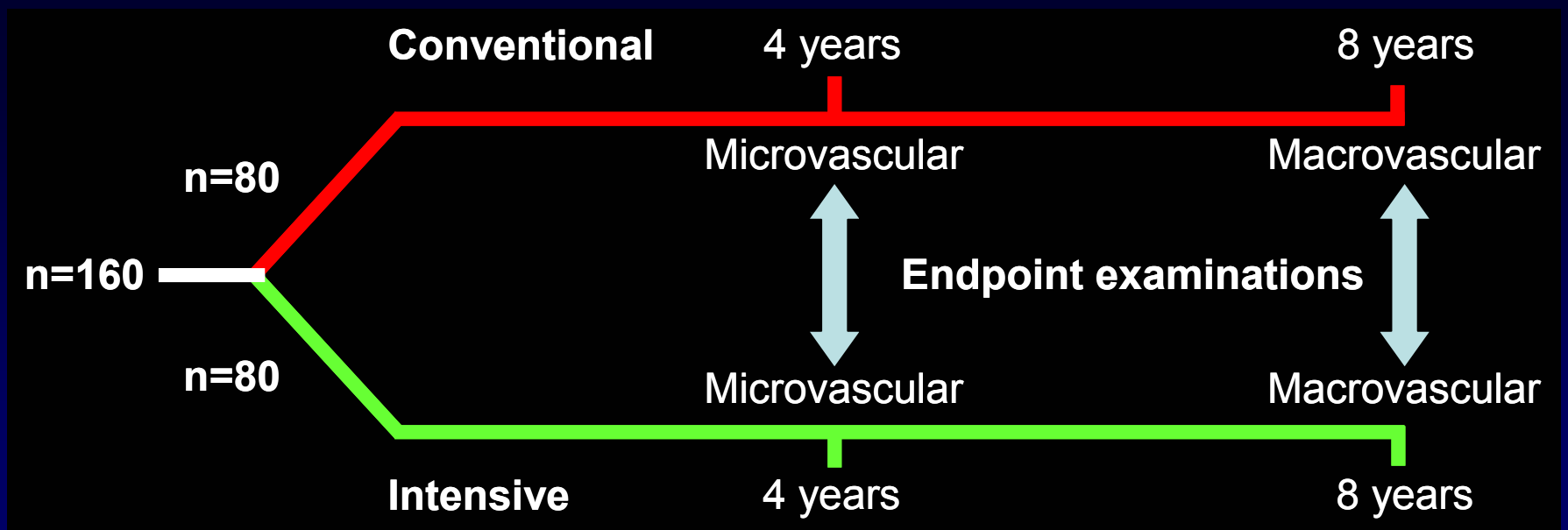


Lancet 1999; 353: 617-22

New Engl J Med 2003; 348: 383-93

Design

- An open, parallel trial comprising 160 Caucasian type 2 diabetic patients with microalbuminuria
- With consealed randomisation patients were allocated either to conventional therapy at their GP or intensive treatment at Steno Diabetes Center



Endpoints

Microvascular disease

- Progression to nephropathy
- Progression in retinopathy
- Progression in neuropathy

*Composite for cardiovascular disease**

- Cardiovascular mortality
- Non-fatal myocardial infarction
- Non-fatal stroke
- Revascularization (including CABG and PCI)
- Amputation

* Adapted from HOPE study (Can J Cardiol 1996;12:127-37)

Treatment goals

	Conventional*	Intensive
Haemoglobin A_{1c} (%)	<7.5 / <6.5	<6.5 / <6.5
Fasting s-total cholesterol (mmol/l)	<6.5 / <5.0	<5.0 / <4.5
Fasting s-triglycerides (mmol/l)	<2.2 / <2.0	<1.7 / <1.7
Systolic BP (mm Hg)	<160 / <135	<140 / <130
Diastolic BP (mm Hg)	<95 / <85	<85 / <80
ACEi irrespective of BP	No / Yes	Yes / Yes
Aspirin as primary prevention	No / No	No / Yes

* **Guidelines from the Danish Medical Association 1988 / 2000**

Drug treatment

Stepwise, target driven drug intervention

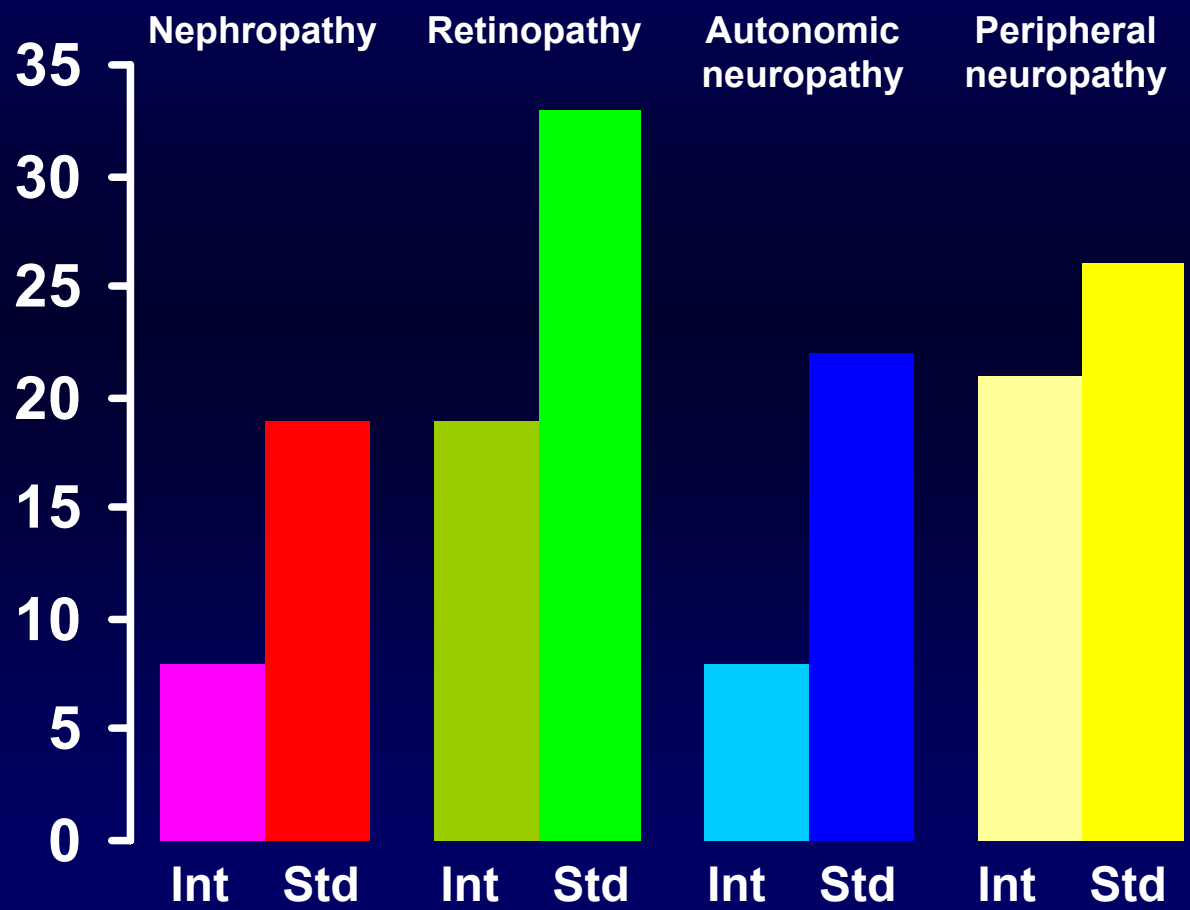
Hyperglycaemia : Sulphonylureas
Metformin
Insulin

Dyslipidaemia : Statins
Fibrates

Hypertension : ACE-inhibitors / AII receptor blockers
Diuretics
Calcium channel blockers
β-blockers

Results after 4 years

Number of patients progressing in microvascular endpoint



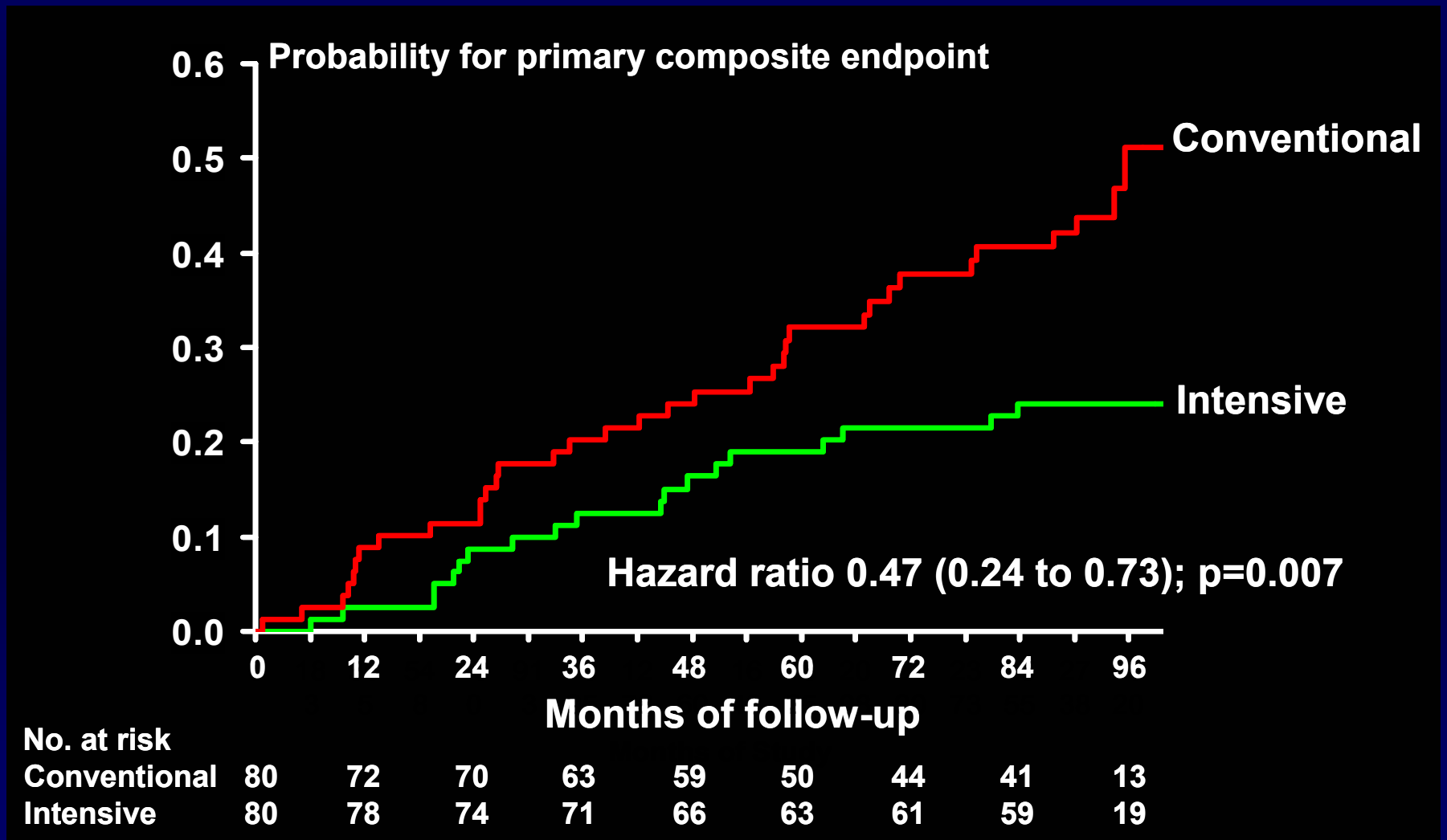
Risk factors at 8 years

	Conventional n=63	Intensive n=67
Haemoglobin A1c (%)	9.0	7.9
F-s-total-cholesterol (mg/dl)	220	159
F-s-LDL-cholesterol (mg/dl)	120	81
F-s-triglycerides (mg/dl)	120	66
Systolic BP (mm Hg)	146	132
Diastolic BP (mm Hg)	78	73
Albumin excretion rate (mg/24h)*	99	58

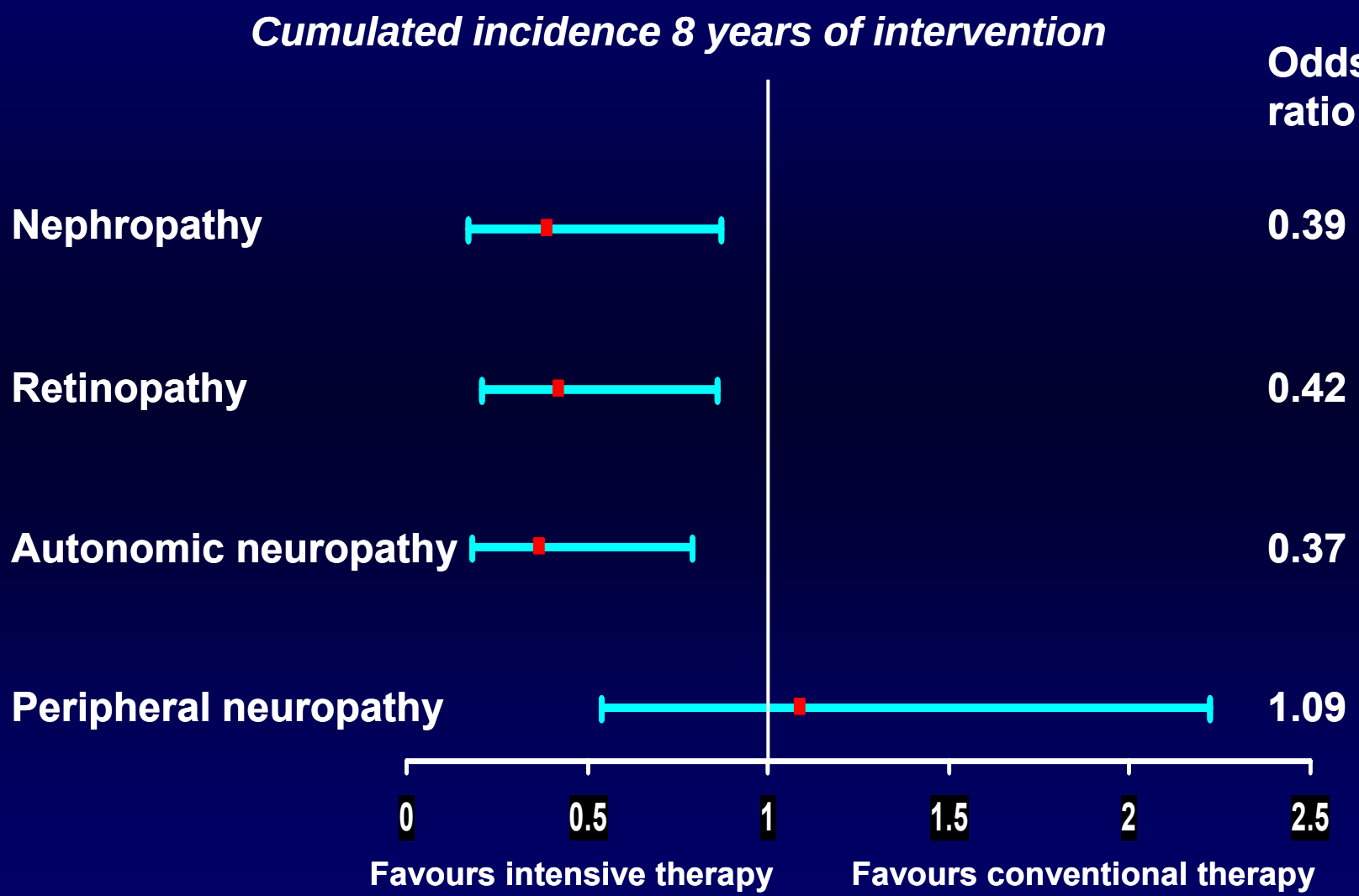
Values are mean

* median

Cardiovascular events

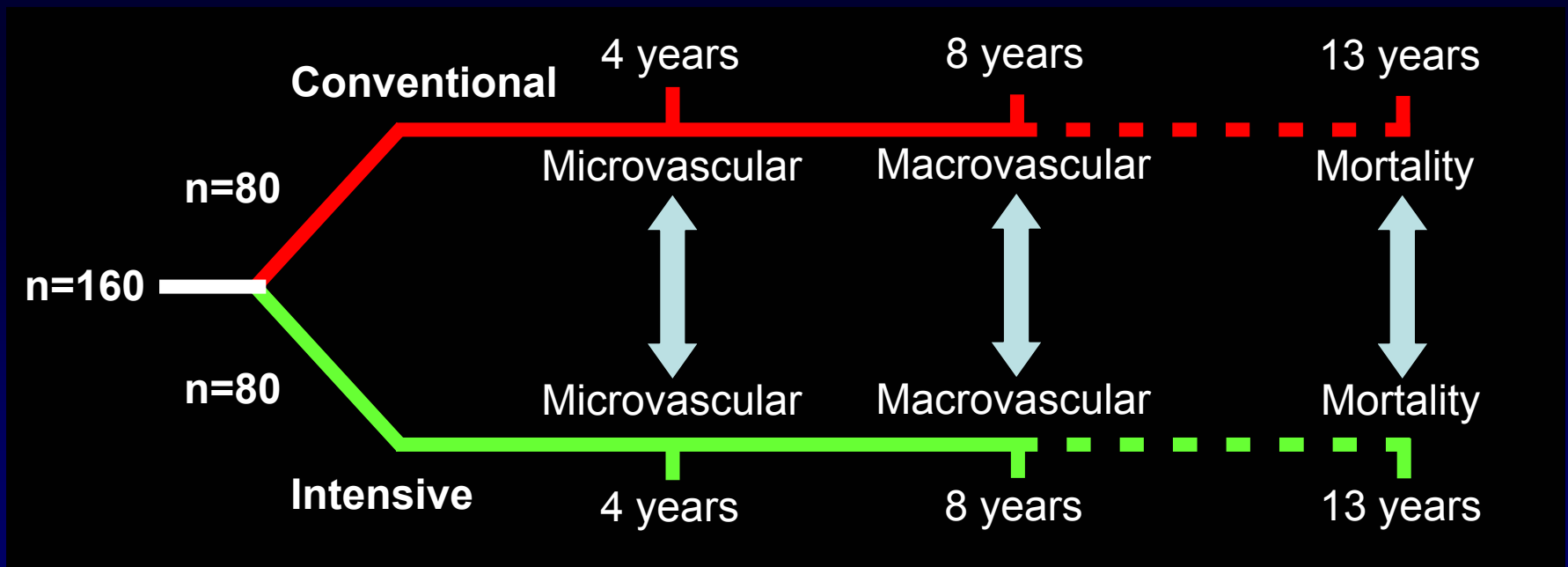


Microvascular complications



Steno-2: Design

- **Planned endpoint examinations at 4, 8 years after randomization and after 60 cases of mortality**
- **Interventional part of study ended after 8 years**



Steno-2: Major papers

The NEW ENGLAND JOURNAL of MEDICINE
N ENGL J MED 358;6 WWW.NEJM.ORG FEBRUARY 7, 2008

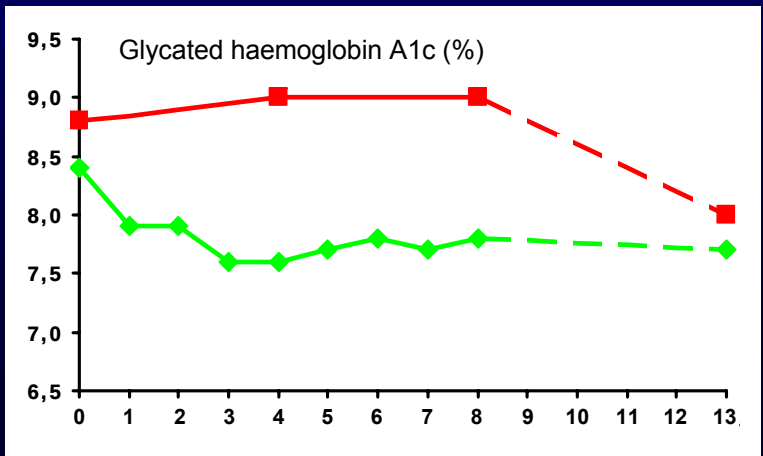
ORIGINAL ARTICLE

Effect of a Multifactorial Intervention on Mortality in Type 2 Diabetes

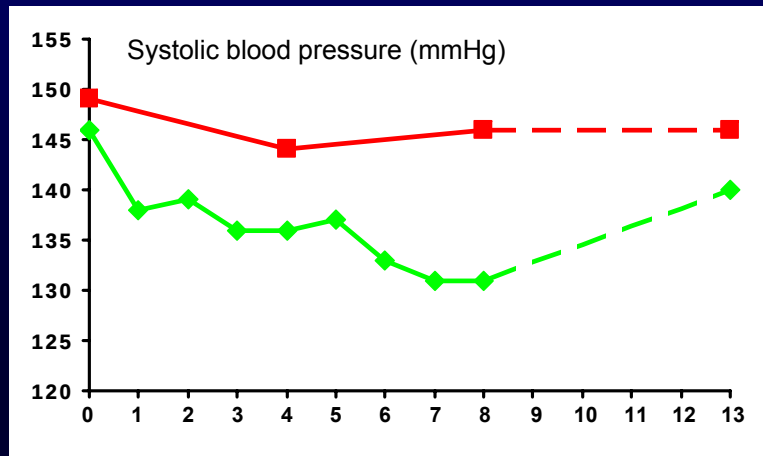
Peter Gæde, M.D., D.M.Sc., Henrik Lund-Andersen, M.D., D.M.Sc., Hans-Henrik Parving, M.D., D.M.Sc., and Oluf Pedersen, M.D., D.M.Sc.

New Engl J Med 2008; 358: 580-91

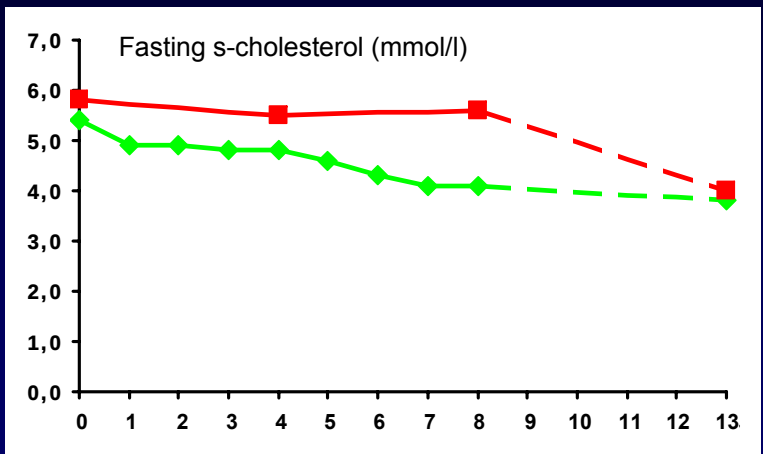
Risk markers during follow-up



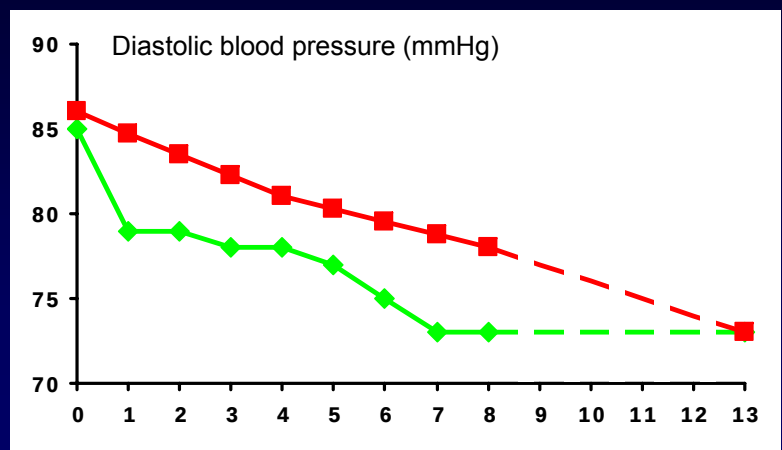
Years of follow-up



Years of follow-up



Years of follow-up



Years of follow-up

Risk markers at end of Steno-2 Post Trial at 13 years

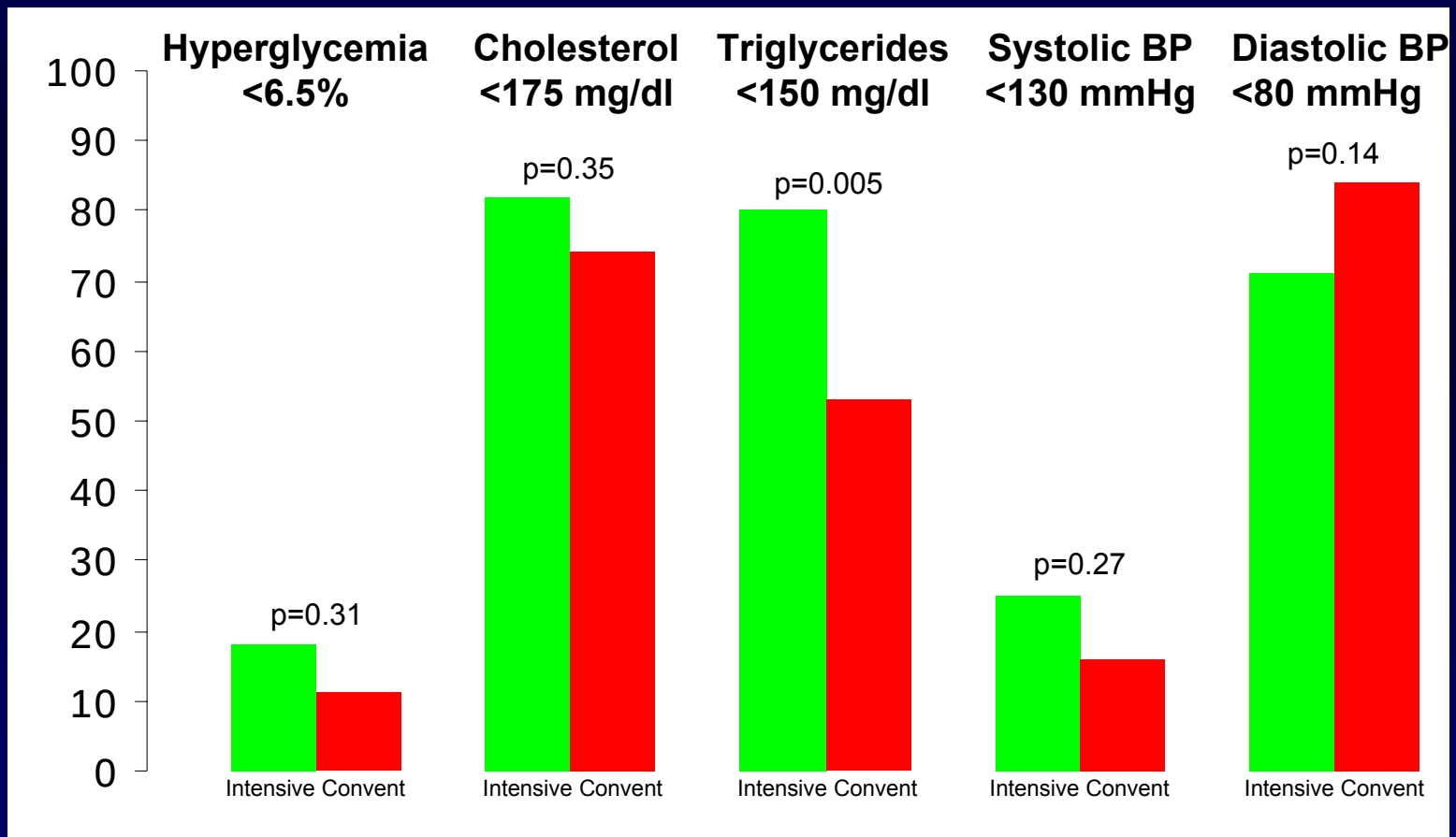
	Intensive N=55	Standard N=38
HbA_{1c} (%)	7.7	8.0
Cholesterol (mmol/l)	3.8	4.0
LDL-cholesterol (mmol/l)	1.8	2.0
HDL-cholesterol (mmol/l)	1.32	1.22
Triglycerides (mmol/l)	1.12	1.67
Systolic BP (mmHg)	140	146
Diastolic BT (mmHg)	74	73
Albumin excretion rate (mg/24h)*	69	75

*median

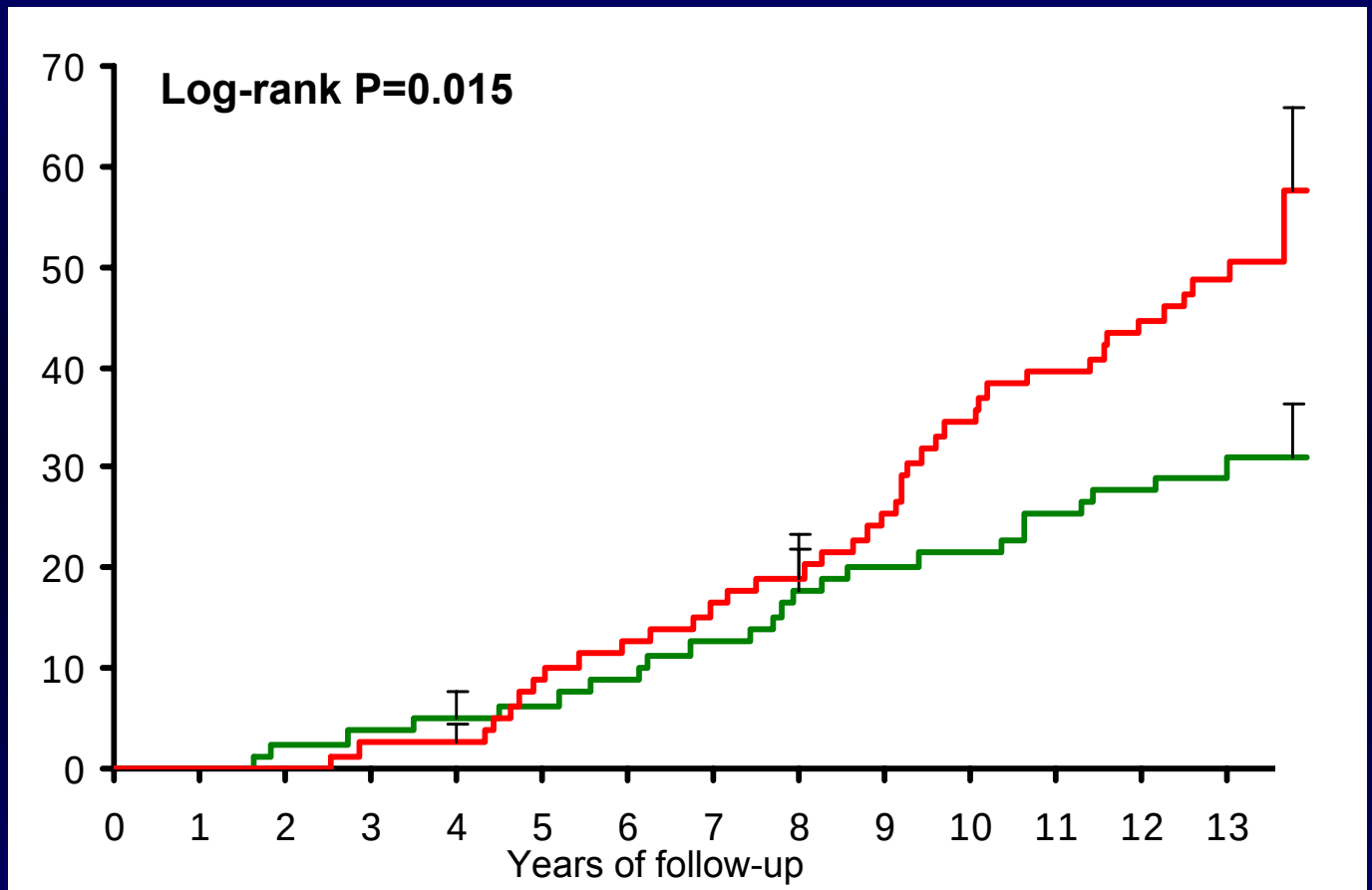
Steno-2 Post Trial

Patients on target

Percentage of patients obtaining treatment goal for intensive regimen at 13 years



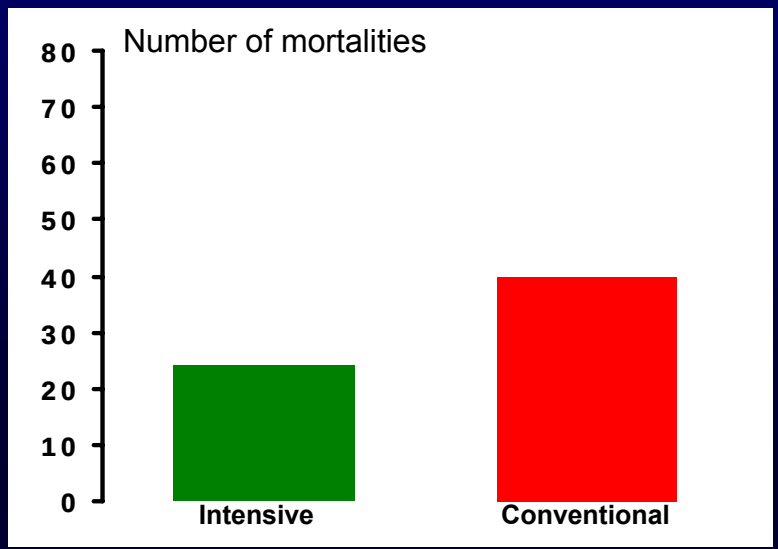
Steno-2 Post Trial: Mortality



Numbers at risk

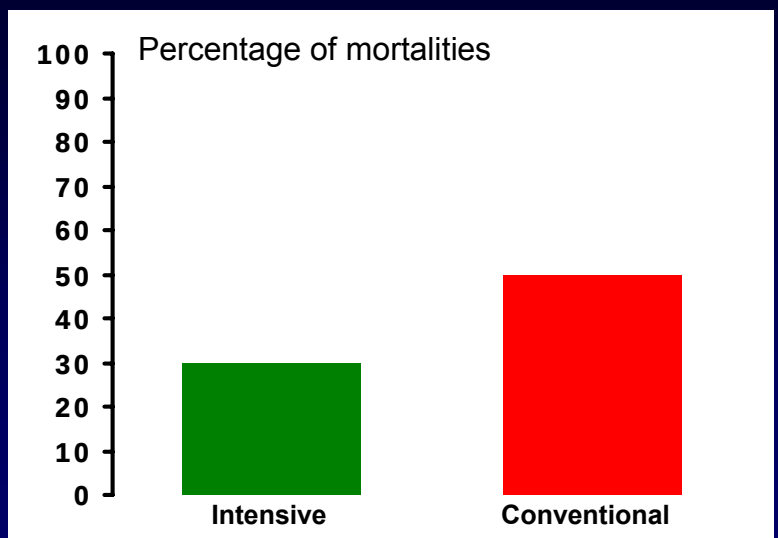
Conventional	80	80	77	69	63	51	43	30
Intensive	80	78	75	72	65	62	57	39

Steno-2 Post Trial: Mortality



24 patients died in the intensive group compared to 40 patients in the conventional group

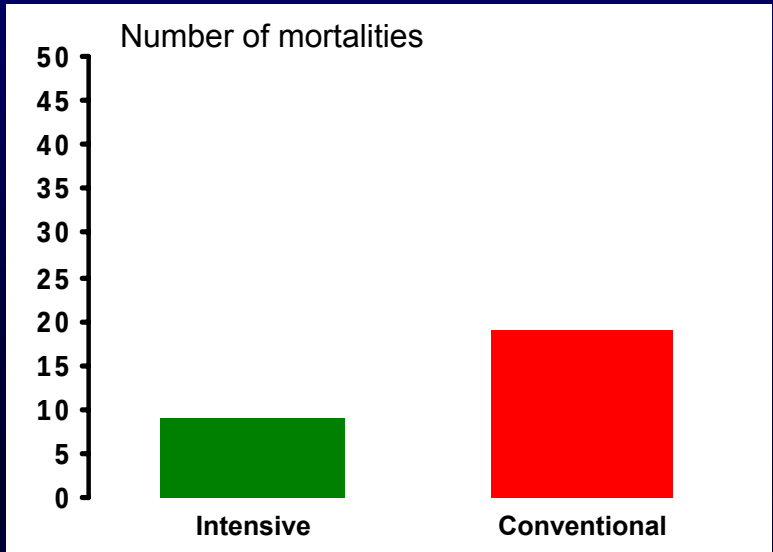
HR = 0.54 (0.32-0.89), P=0.016



30% of patients died in the intensive group compared to 50% of patients in the conventional group

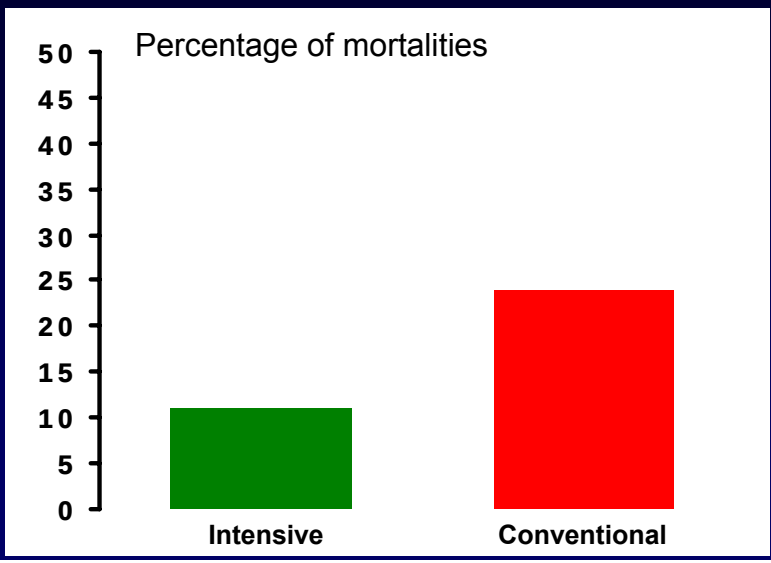
Absolute risk reduction = 20%

Steno-2 Post Trial: CVD Mortality



9 patients died of CVD in the intensive group compared to 19 patients in the conventional group

HR = 0.43 (0.19-0.94), P=0.036

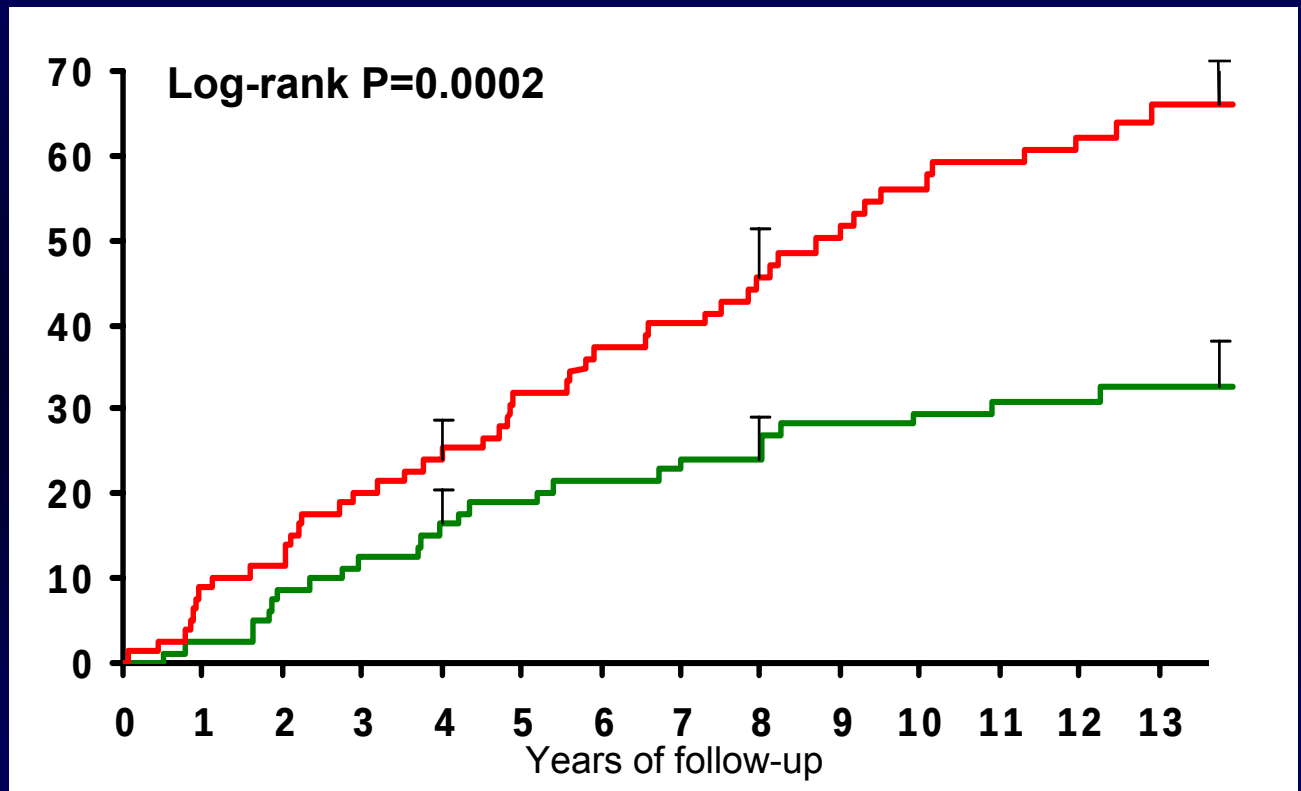


11% of patients died in the intensive group compared to 24% of patients in the conventional group

Absolute risk reduction = 13%

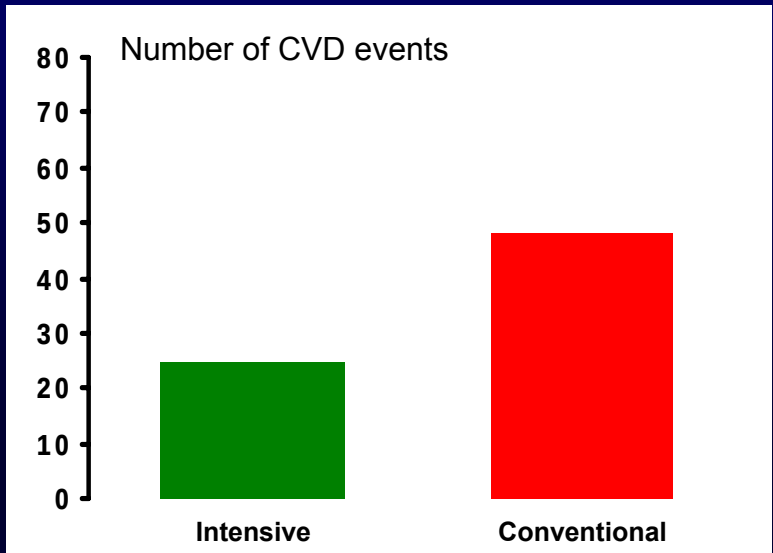
Steno-2 Post Trial: Any CVD events

Cumulative incidence of patients with a major CVD event during follow-up



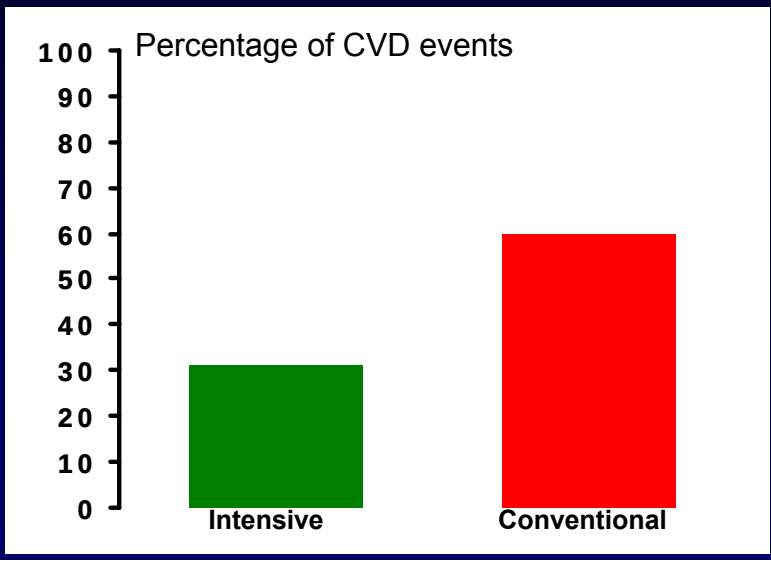
Numbers at risk								
Conventional	80	70	60	46	38	29	25	14
Intensive	80	72	65	61	56	50	47	31

Steno-2 Post Trial: Any CVD events



25 patients had a CVD event in the intensive group compared to 48 patients in the conventional group

HR = 0.41 (0.25-0.67), P=0.0003

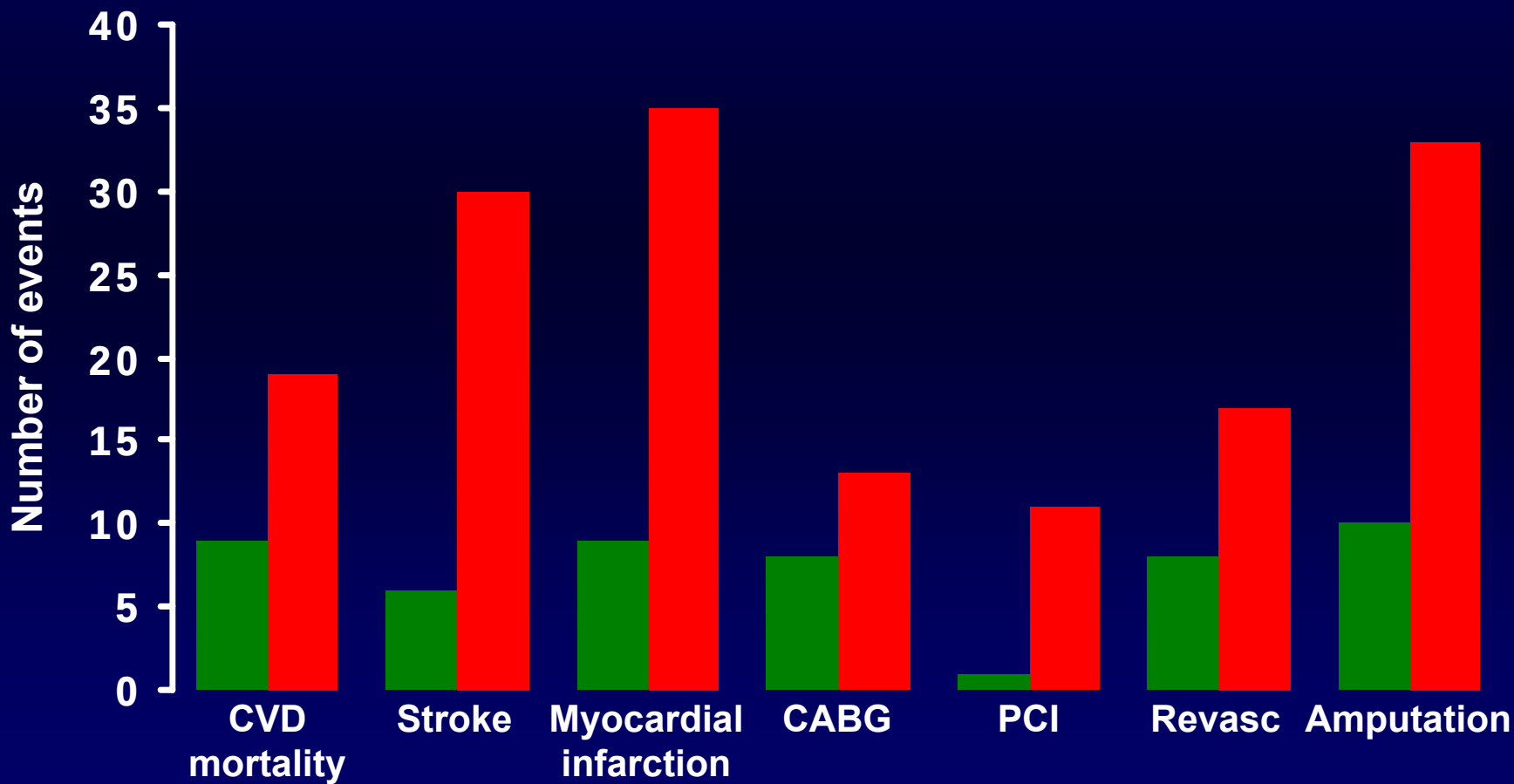


31% of patients had a CVD event in the intensive group compared to 60% of patients in the conventional group

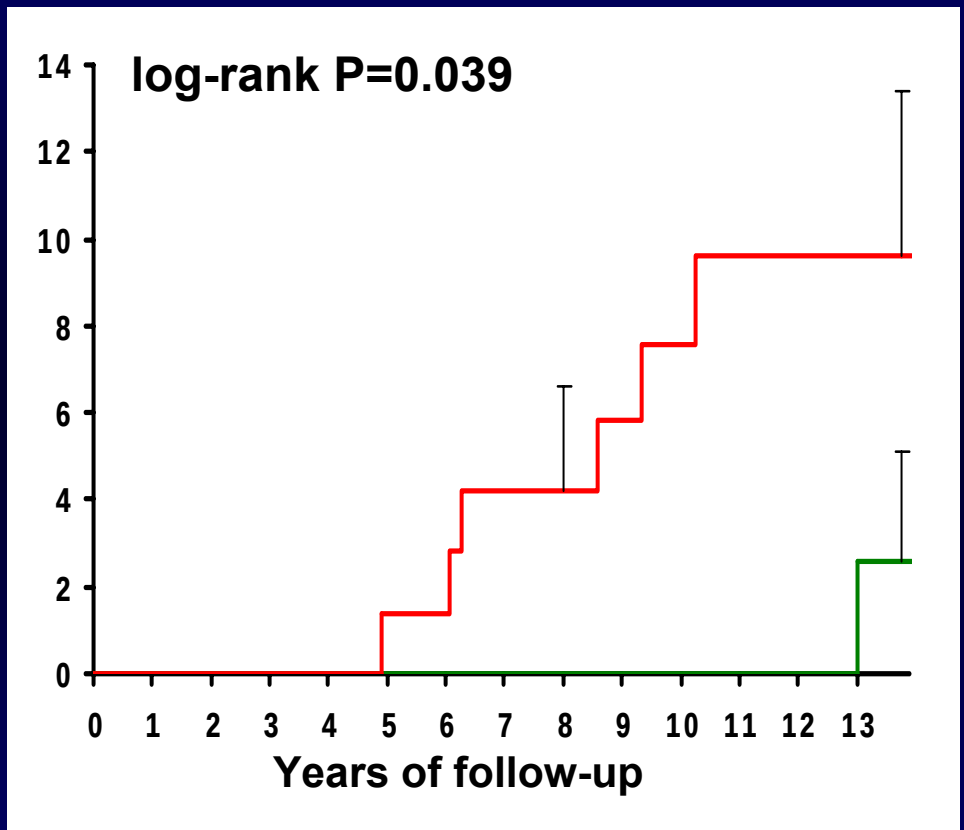
Absolute risk reduction = 29%

Steno-2 Post Trial: Any CVD events

51 major CVD events in 25 patients (31%) occurred in the intensive group compared to 158 events in 48 patients (60%) in the conventional group



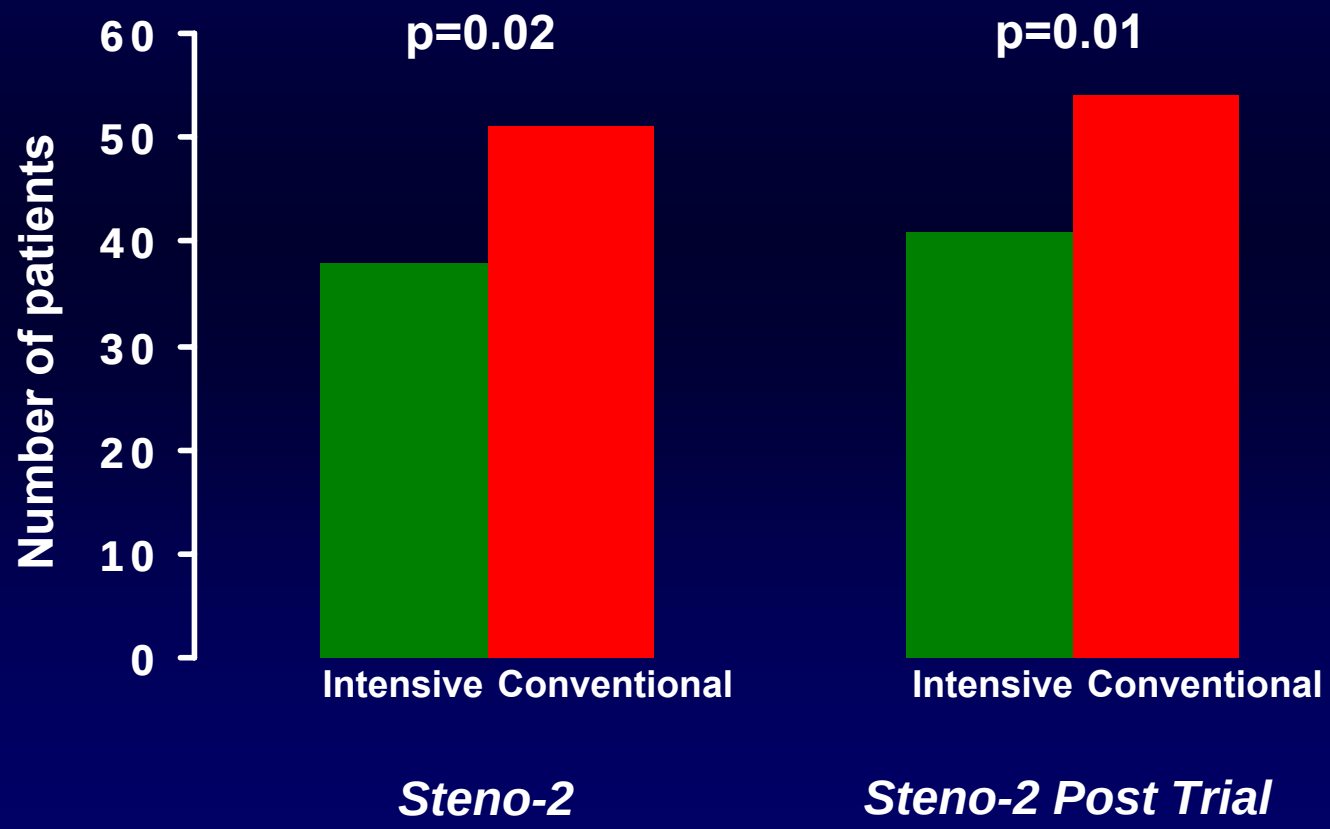
End-stage renal failure requiring dialysis



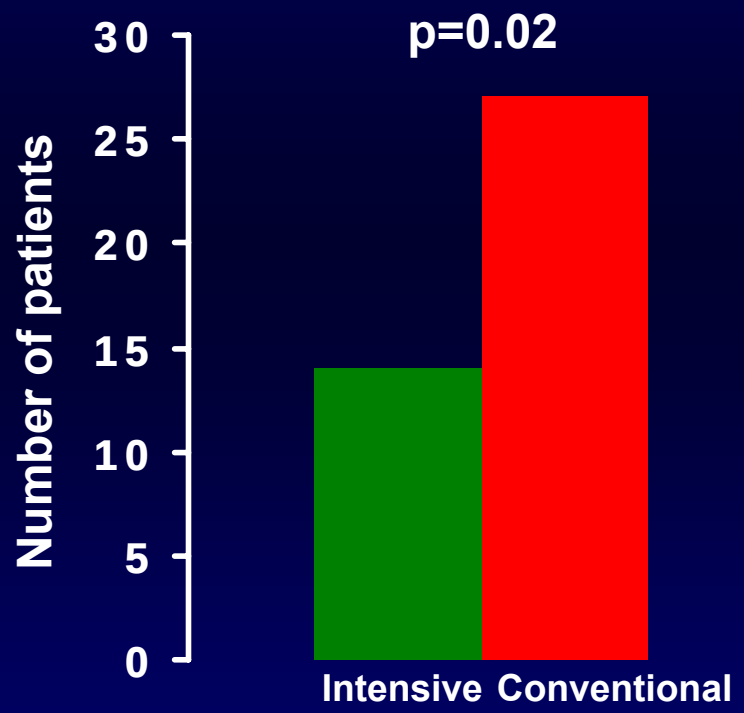
6 patients in the original conventionally treated group versus 1 patient in the intensively treated group progressed to end-stage renal disease requiring dialysis treatment

Progression in diabetic retinopathy

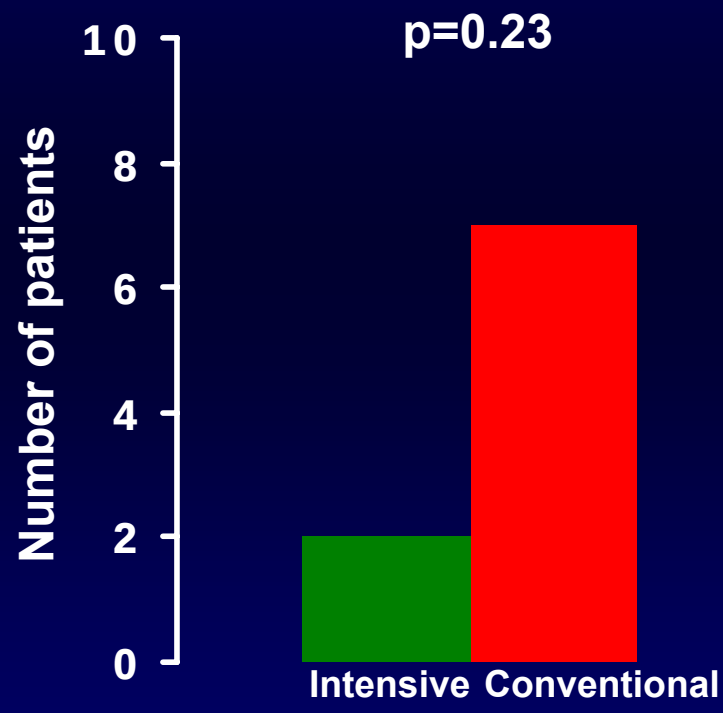
Worsening of at least one level in the EURODIAB grading scale



Laser treatment and blindness at 13 years



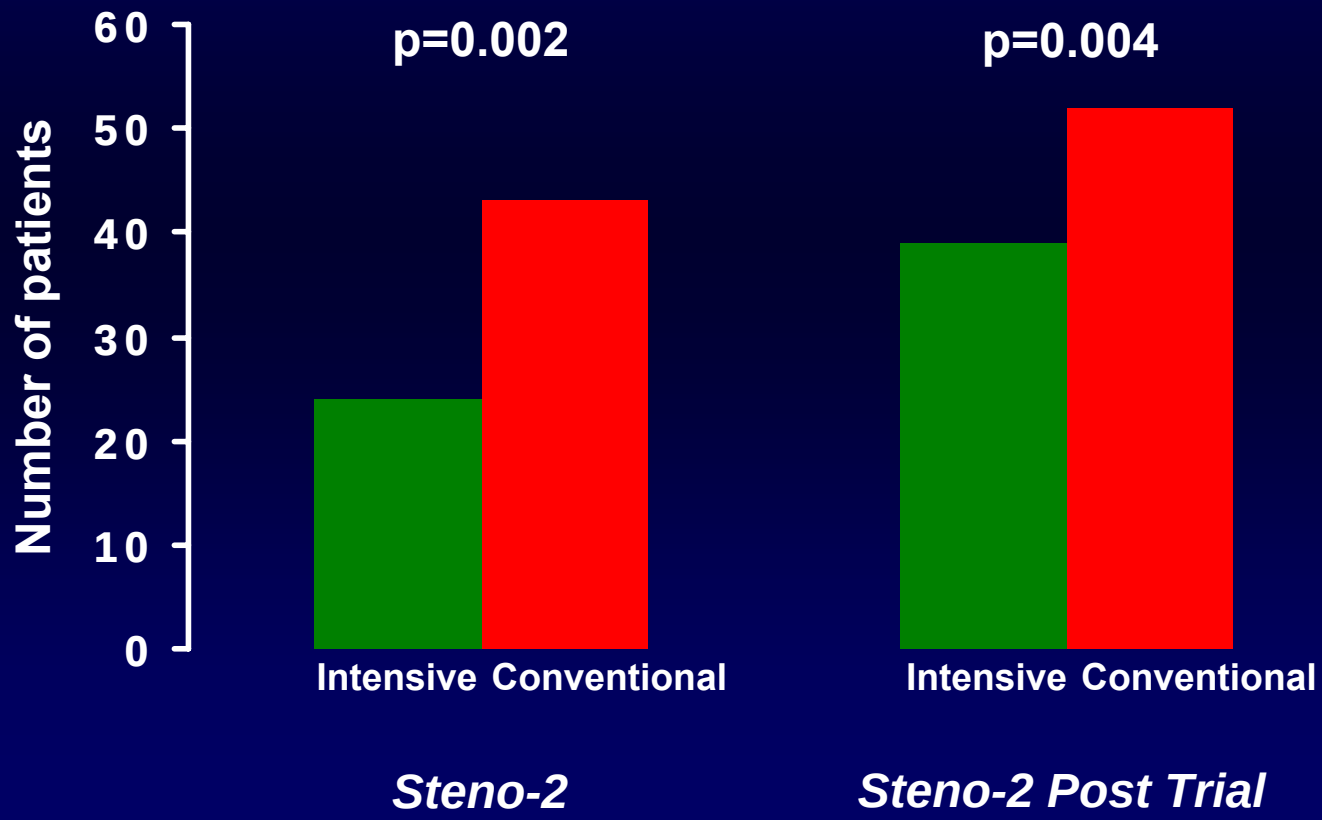
Laser treatment



Blindness in any eye

Progression in autonomic neuropathy

Worsening in orthostatic hypotension or beat-to-beat variation in ECG



Steno-2: Number needed to treat

Number of microalbuminuric patients with type 2 diabetes needed to treat for 13 years to prevent one …..

Death	*5 patients*
Cardiovascular death	*8 patients*
Major cardiovascular event	*3 patients*
Progression to nephropathy	*5 patients*
Dialysis	*16 patients*
Laser treatment	*7 patients*

Steno-2: Major clinical results

- A 50 % relative risk reduction in all-cause mortality or CVD mortality after 13 years of follow-up corresponding to an absolute risk reduction of 20% and 13%, respectively
- A 50 % relative risk reduction in major cardiovascular events after 8 years of intervention maintained throughout the rest of follow-up
- A 50 % relative risk reduction in microvascular disease after 4 years of intervention maintained throughout the rest of follow-up

Intensive blood glucose and blood pressure lowering in diabetic patients: the ADVANCE Study

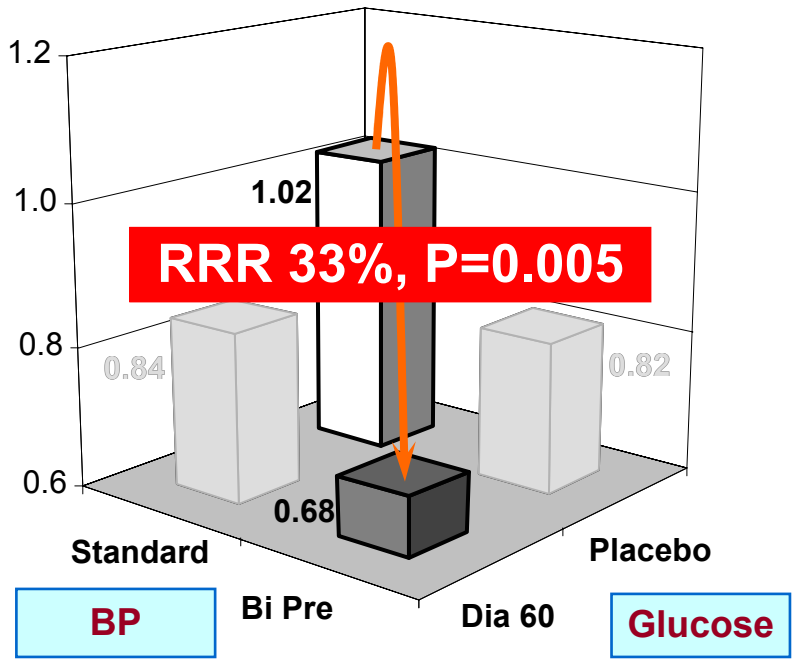
ADVANCE Collaborative Group

Factorial design

Intensive glucose control using Gliclazide MR + Routine BP lowering therapy Perindopril-Indapamide	Standard glucose control + Routine BP lowering therapy Perindopril-Indapamide
Intensive glucose control using Gliclazide MR + Placebo	Standard glucose control + Placebo

New or worsening nephropathy

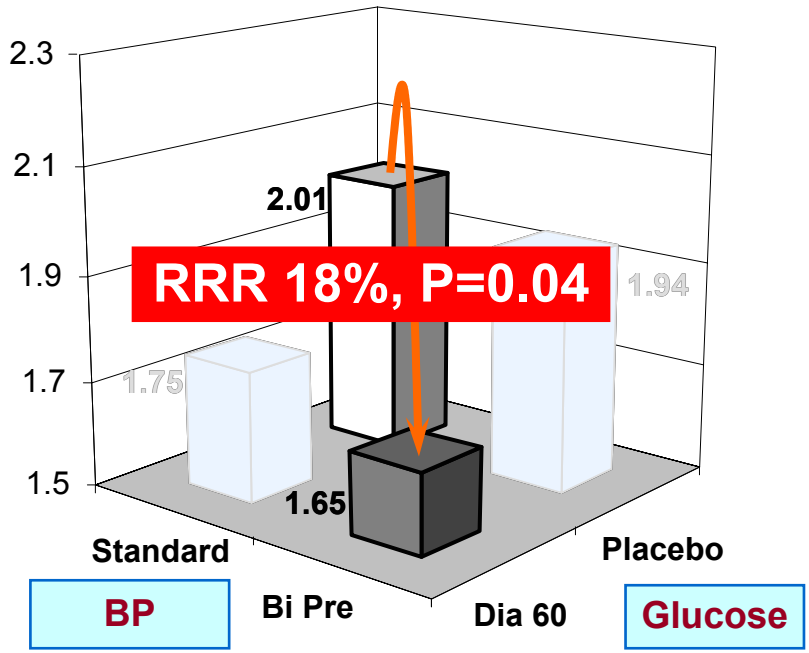
Annual event rate %



P for interaction=0.93

All cause mortality

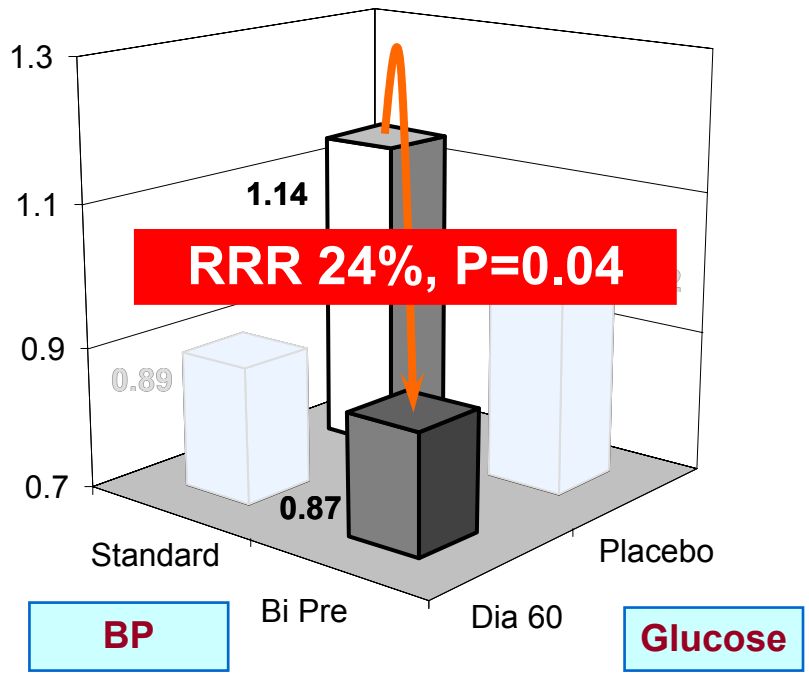
Annual event rate %



P for interaction=0.90

Cardiovascular death

Annual event rate %



P for interaction=0.62

Clinical Question

Which risk factor intervention is the most important in reducing cardiovascular complications?

Impact of single risk factor interventions to reduce CVD in patients with type 2 diabetes

	Relative risk reduction	Yearly event rate in Steno-2 standard group
None	. . . . .	7.0%
Cholesterol (0.6 mmol/l)	25%	5.3%
BP (10/5 mm Hg)	27%	3.9%
$HbA1_c$ (0.9%)	13%	3.4%
Aspirin	9%	3.1%

Cumulative relative risk reduction of about 57%

Huang et al. Am J Med 2001;111:633-642, Turner R.C. BMJ 1998;316:823-828, He et al. JAMA 1999;282:2027-2034, Antitrombotic Trialits BMJ 2002;324:71-86

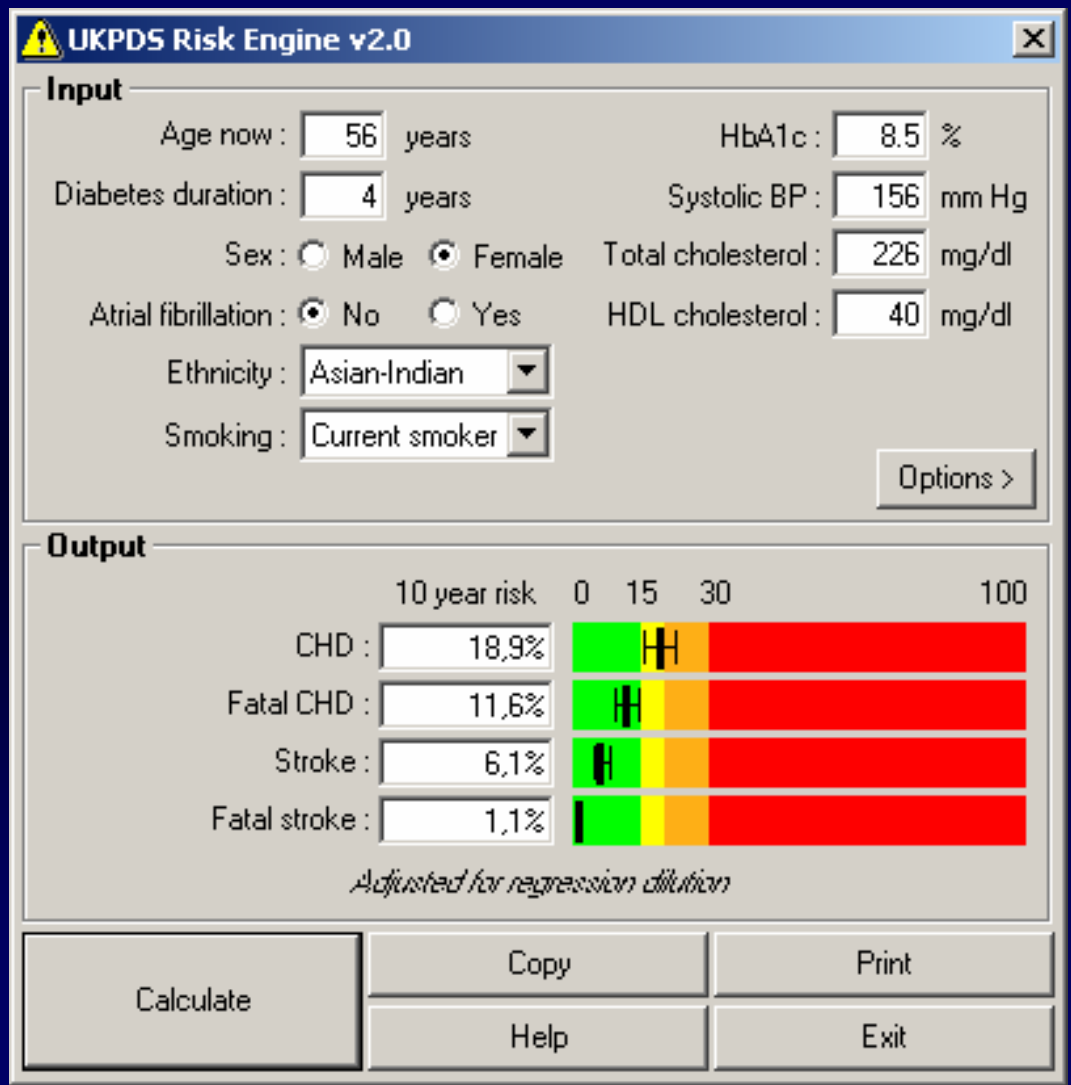
Prioritizing Treatment
Use of risk calculators

UKPDS Risk Engine v Framingham

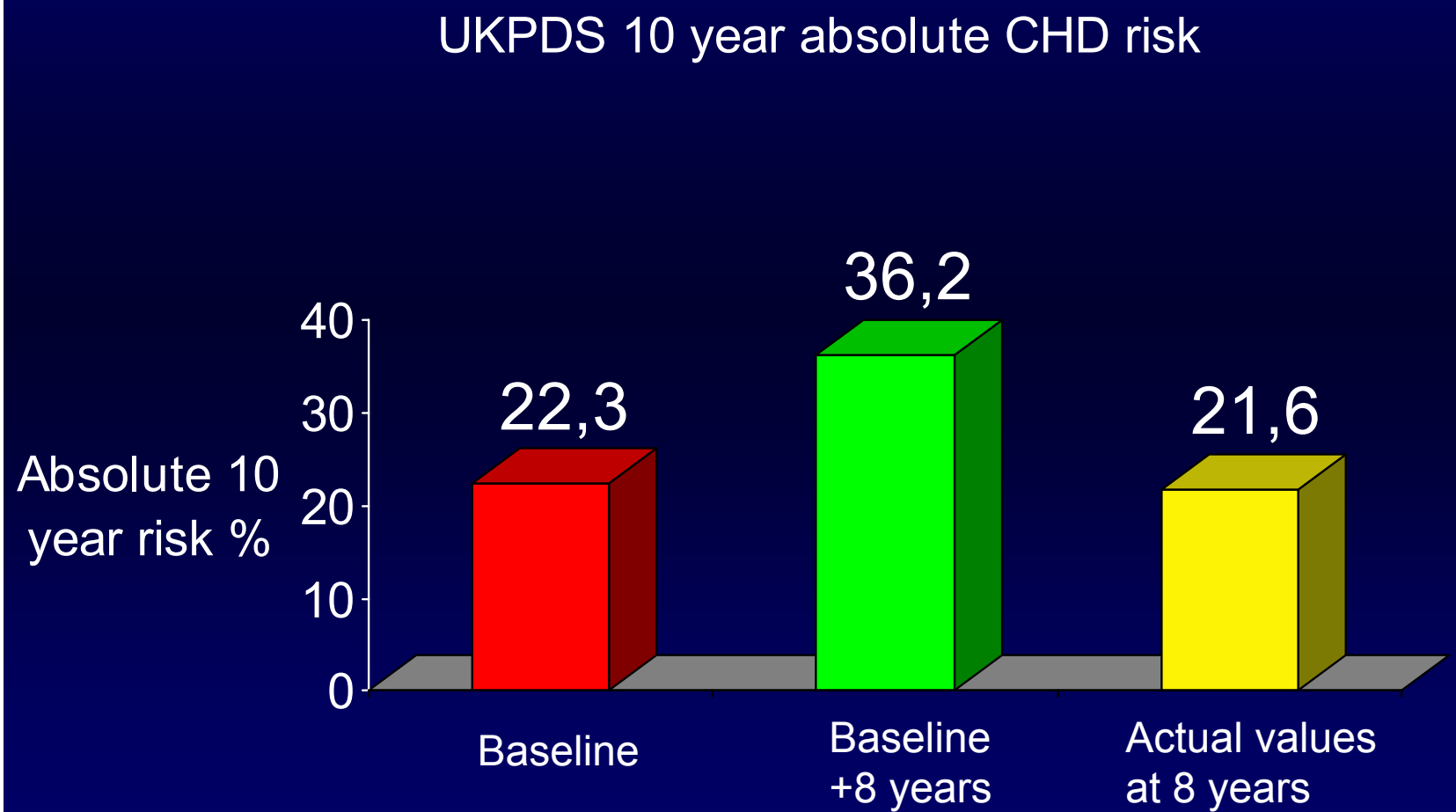
UKPDS
- **Current age**
- **Sex**
- **Smoking status**
- **Systolic blood pressure**
- **Total cholesterol**
- **HDL cholesterol**
- **Atrial fibrillation**
- ***Duration of diabetes***
- ***HbA1c***
- **Ethnic group**

Framingham
- **Current age**
- **Sex**
- **Smoking status**
- **Systolic blood pressure**
- **Total cholesterol**
- **HDL cholesterol**
- **Left ventricular hypertrophy**
- **Diabetes status (yes/no)**

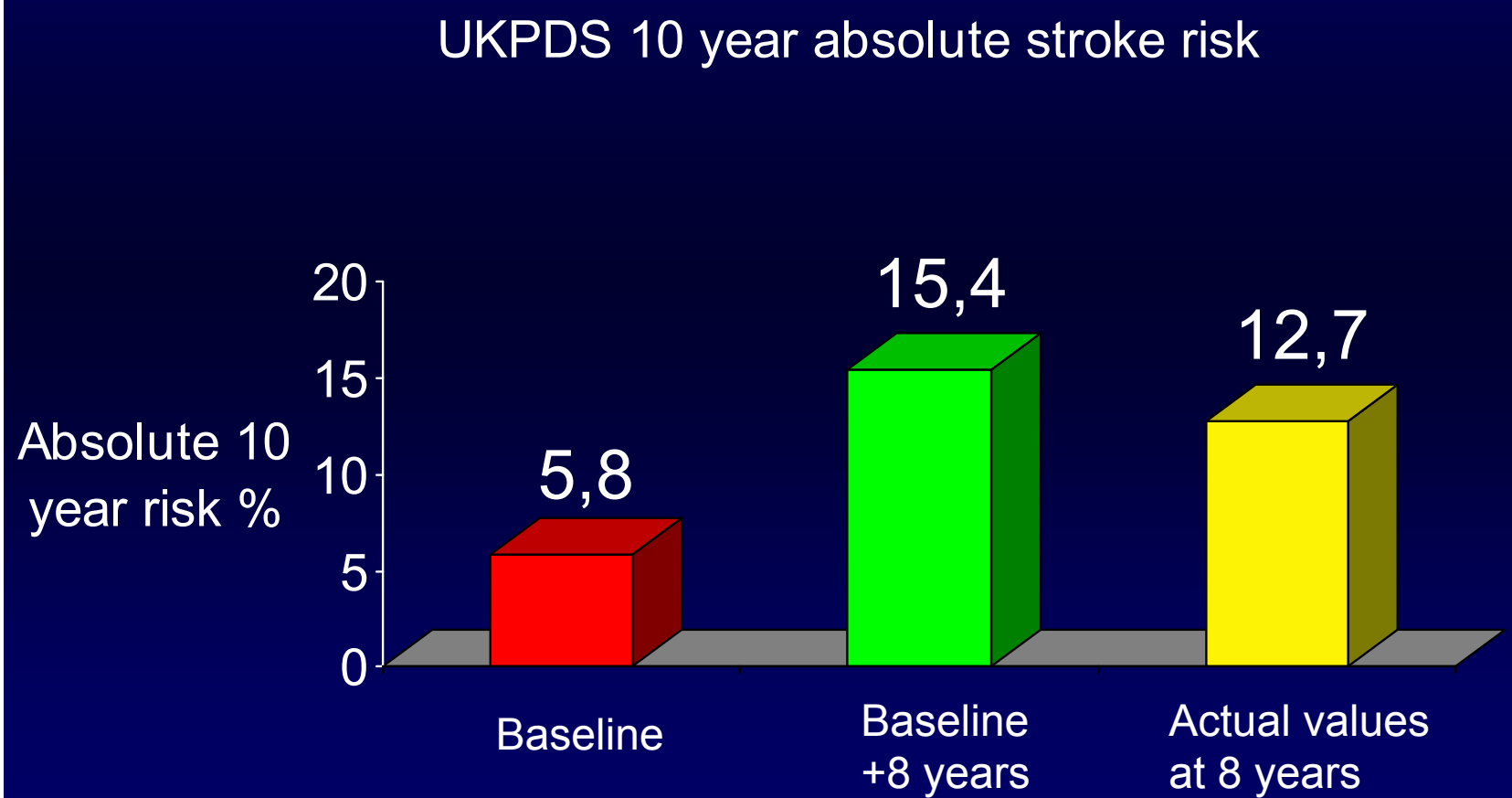
UKPDS Risk Engine



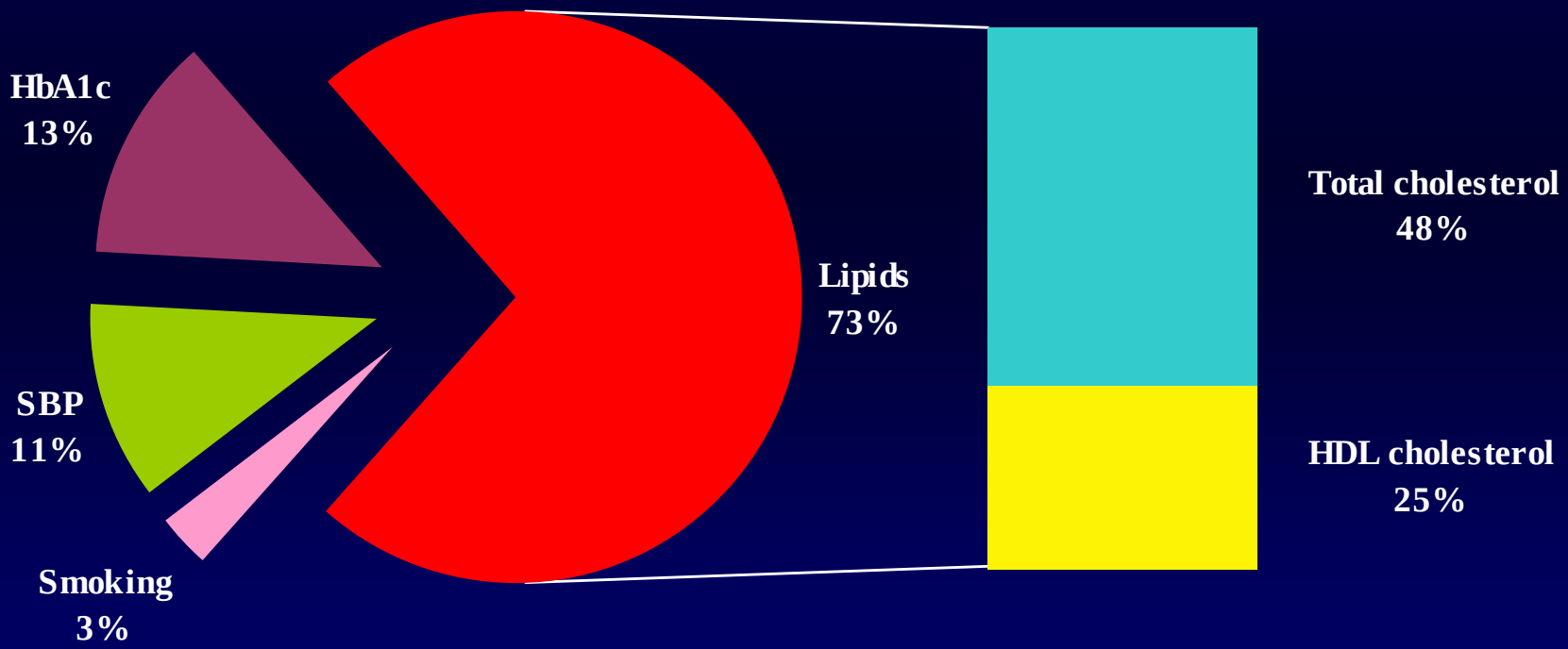
Heart Disease Risk Score for Steno-2 intensive treatment arm



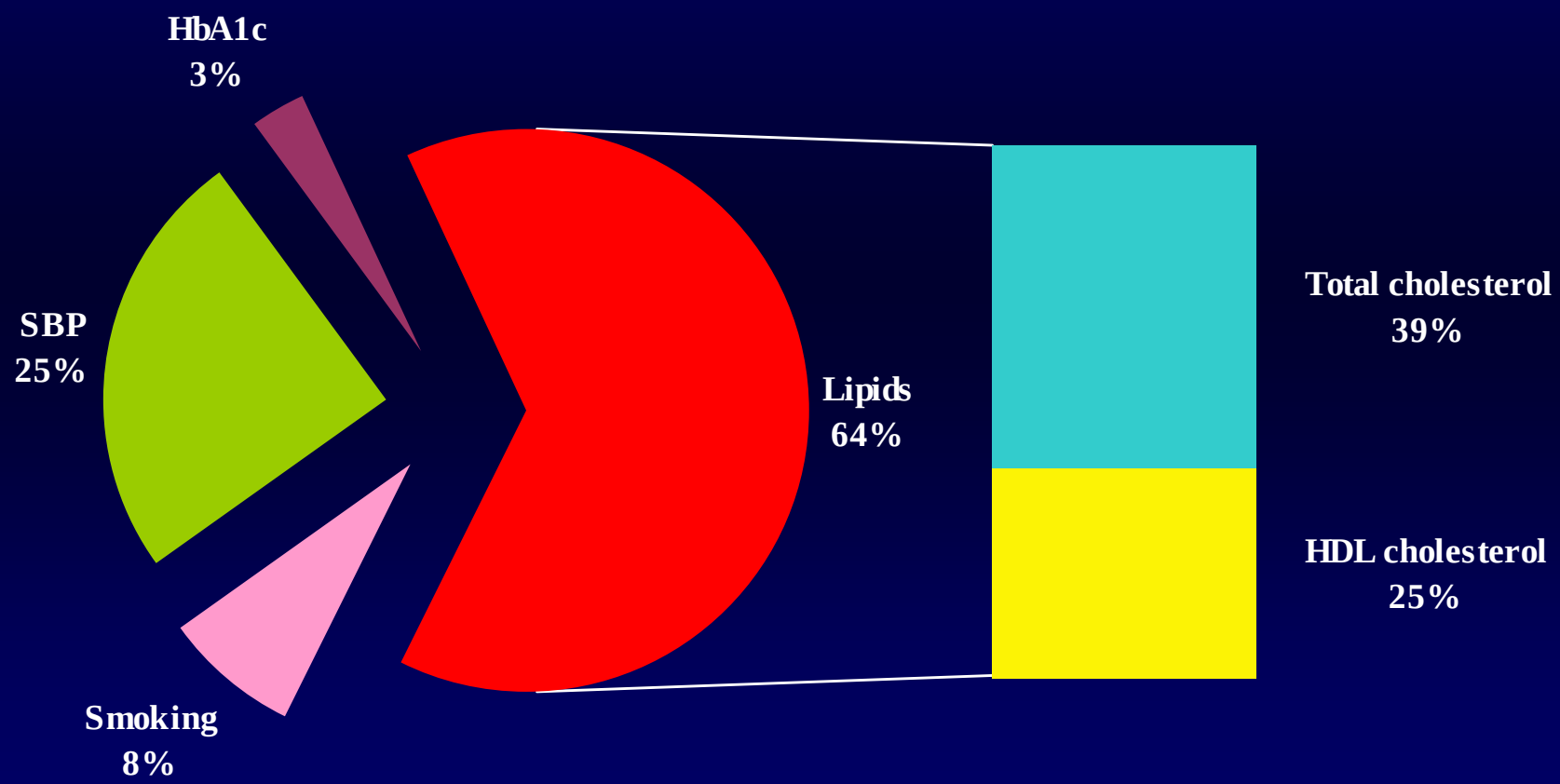
Stroke Risk Score for Steno-2 intensive treatment arm



Actual contribution of each risk factor in improving the UKPDS *CHD risk score* for Steno-2 intensive treatment arm



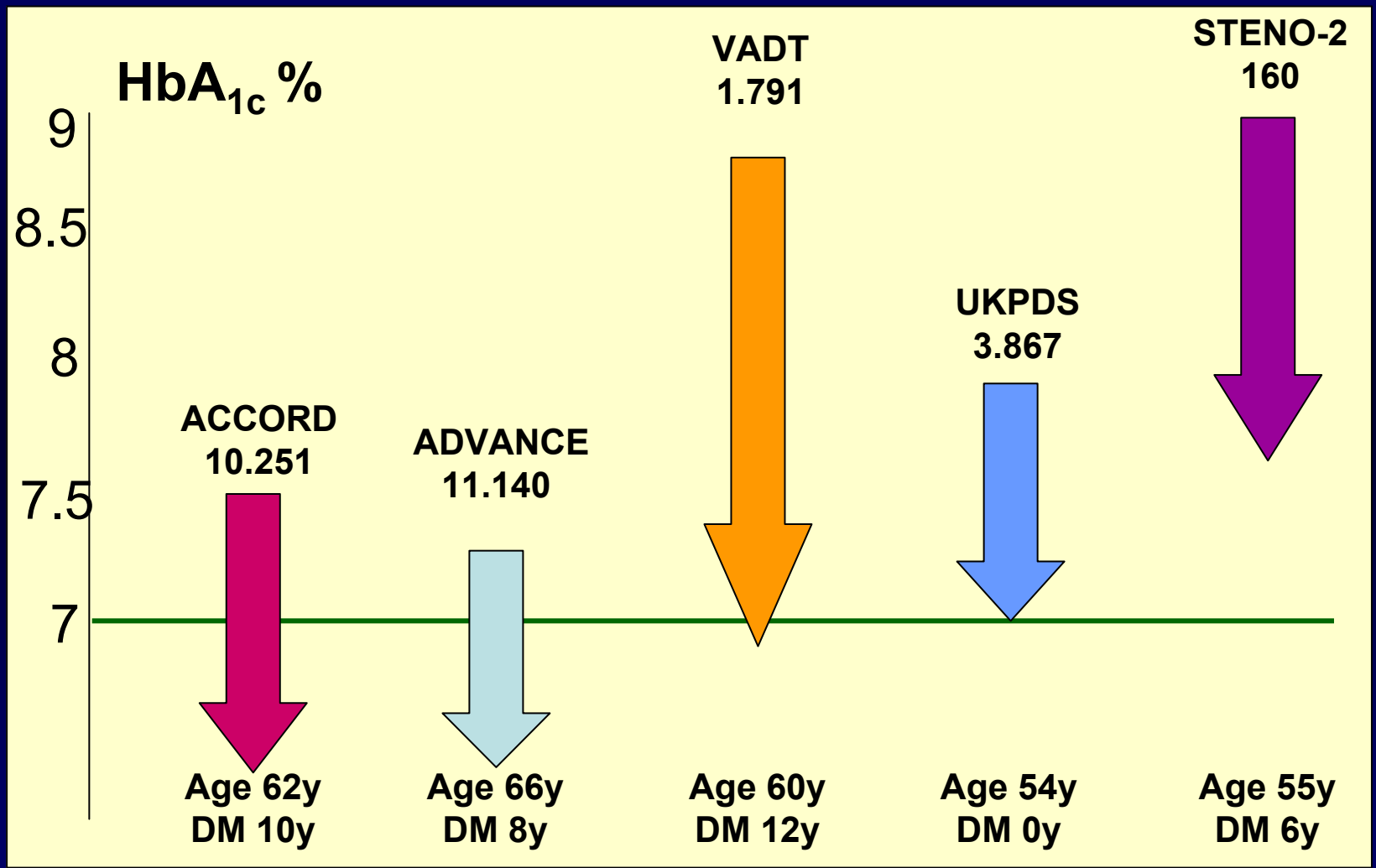
Actual contribution of each risk factor in improving the UKPDS *stroke risk score* for Steno-2 intensive treatment arm



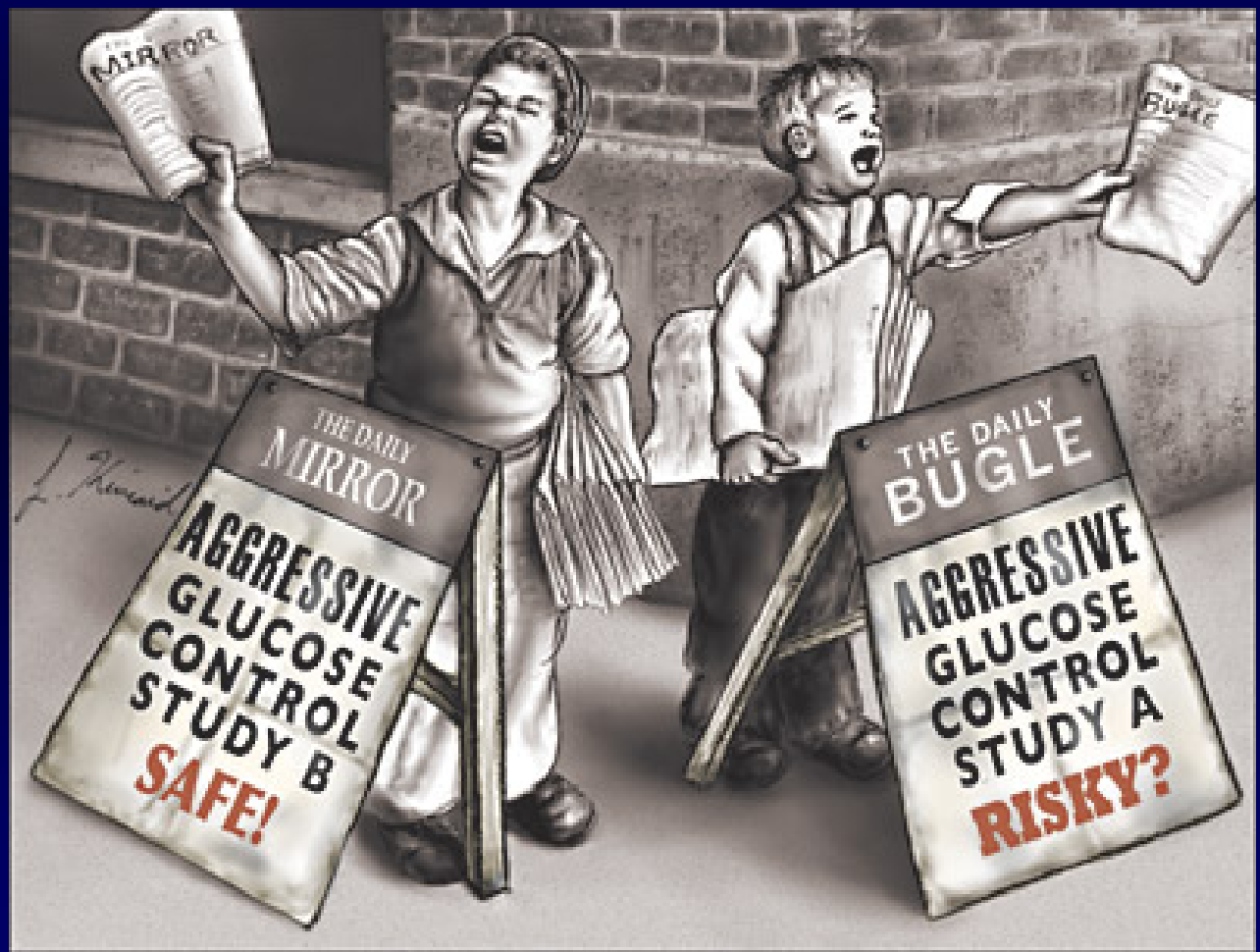
Clinical Question

Hyperglycemia is a strong risk marker for CVD in both epidemiological and interventional studies. How low should you go?

Intervention studies in Type-2 Diabetes



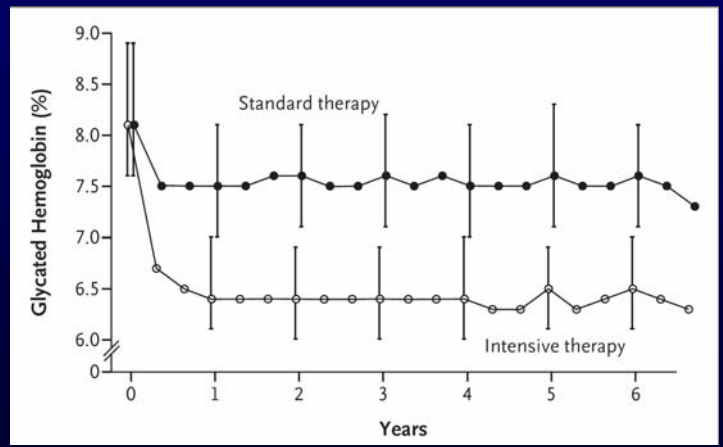
ADVANCE and ACCORD Studies 2008

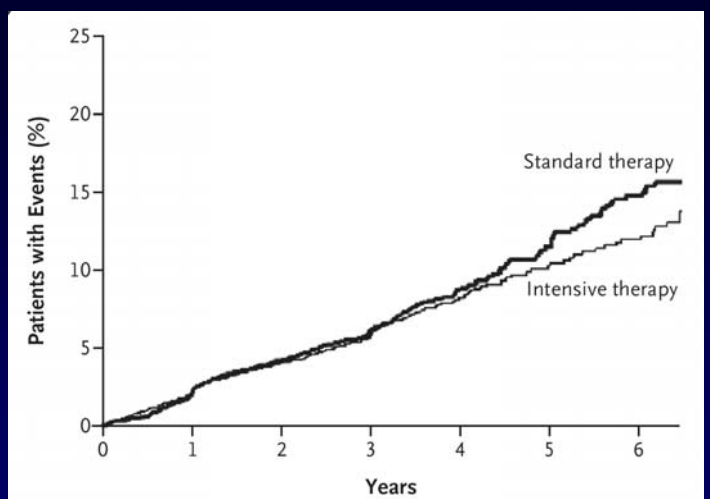


Is tight glucose control harmful?

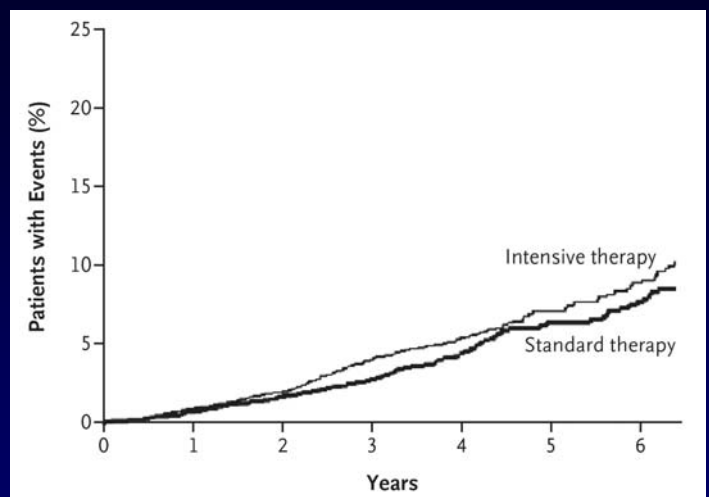
ACCORD

10,251 middle-aged or older type 2 diabetic patients with either evidence of or increased risk for cardiovascular disease





HR 0.90 (0.78 to 1.04); p = 0.16



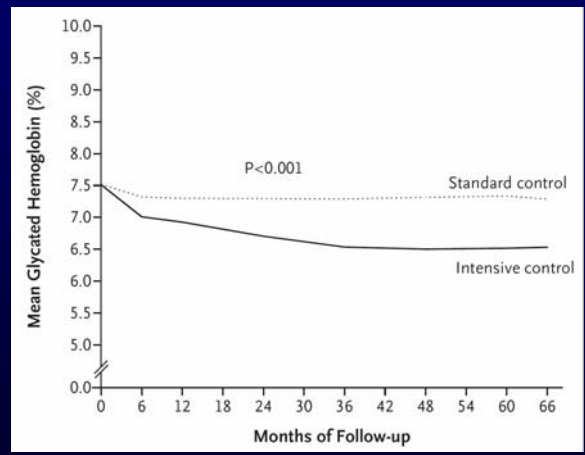
HR 1.22 (1.01 to 1.46); p = 0.04

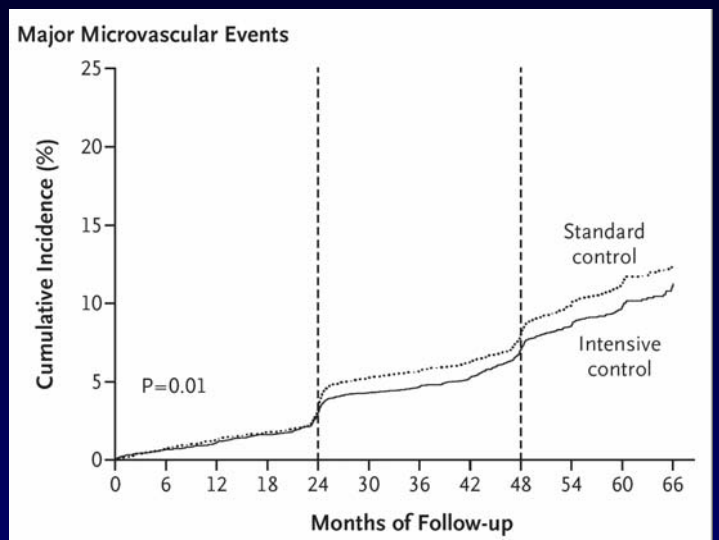
N Engl J Med. 2008;358:2545-2559

Is tight glucose control harmful?

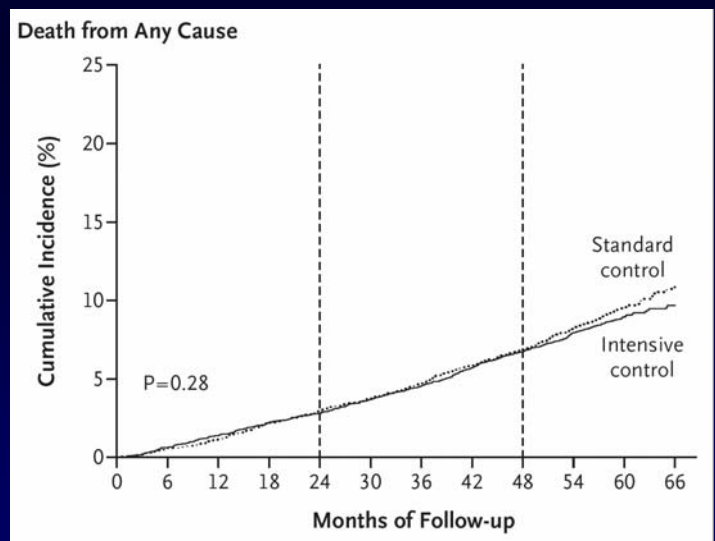
ADVANCE

11,140 patients with type 2 diabetes with a history of major macro- or microvascular disease or at least one other risk factor for cardiovascular disease





HR 0.86 (0.77 to 0.97), p=0.01



HR 0.93 (0.83 to 1.06), p=0.28

N Engl J Med 2008;358:2560-72

UK Prospective Diabetes Study

20-year Interventional Trial from 1977 to 1997

- 5,102 patients with newly-diagnosed type 2 diabetes recruited between 1977 and 1991
- Median follow-up 10.0 years, range 6 to 20 years
- Results presented at the 1998 EASD Barcelona meeting

10-year Post-Trial Monitoring from 1997 to 2007

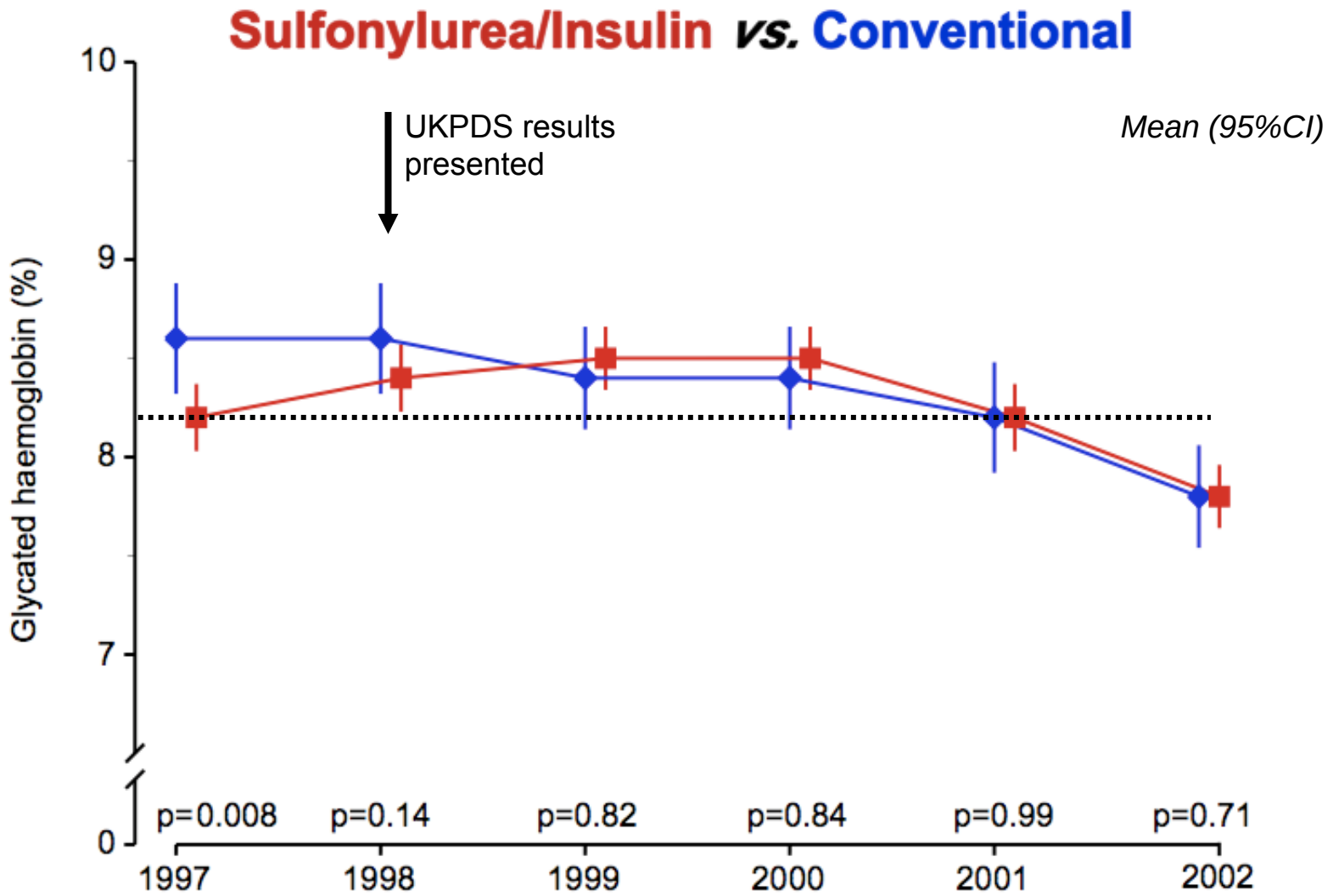
- Annual follow-up of the survivor cohort
- Clinic-based for first five years
- Questionnaire-based for last five years

Median overall follow-up 17.0 years, range 16 to 30 years

UKPDS 80. N Eng J Med 2008; ***359****:*

ukpds~ptm

Post-Trial Changes in HbA_{1c}

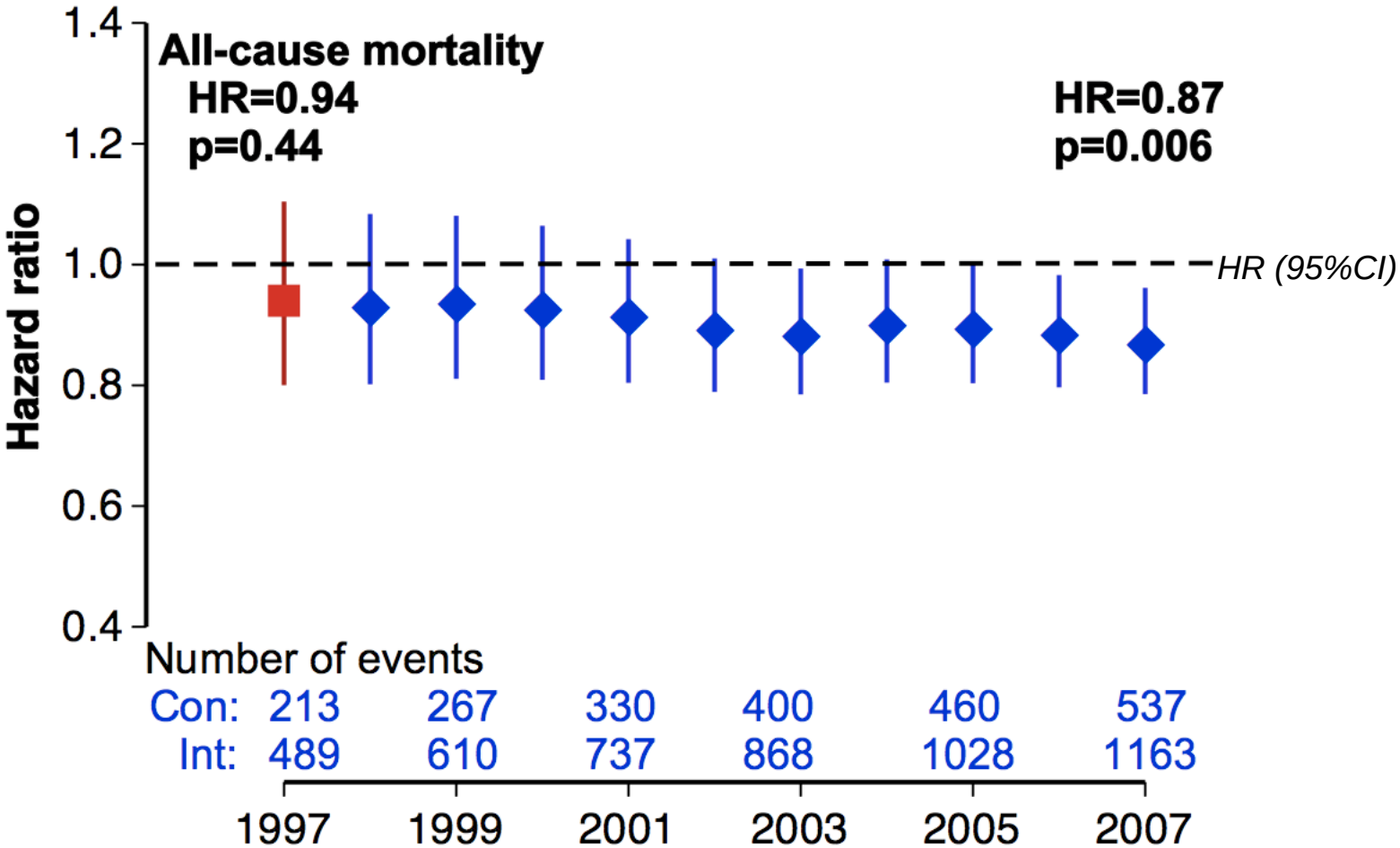


UKPDS 80. N Eng J Med 2008; ***359****:*

ukpds-ptm

All-cause Mortality Hazard Ratio

Intensive (SU/Ins) *vs.* Conventional glucose control

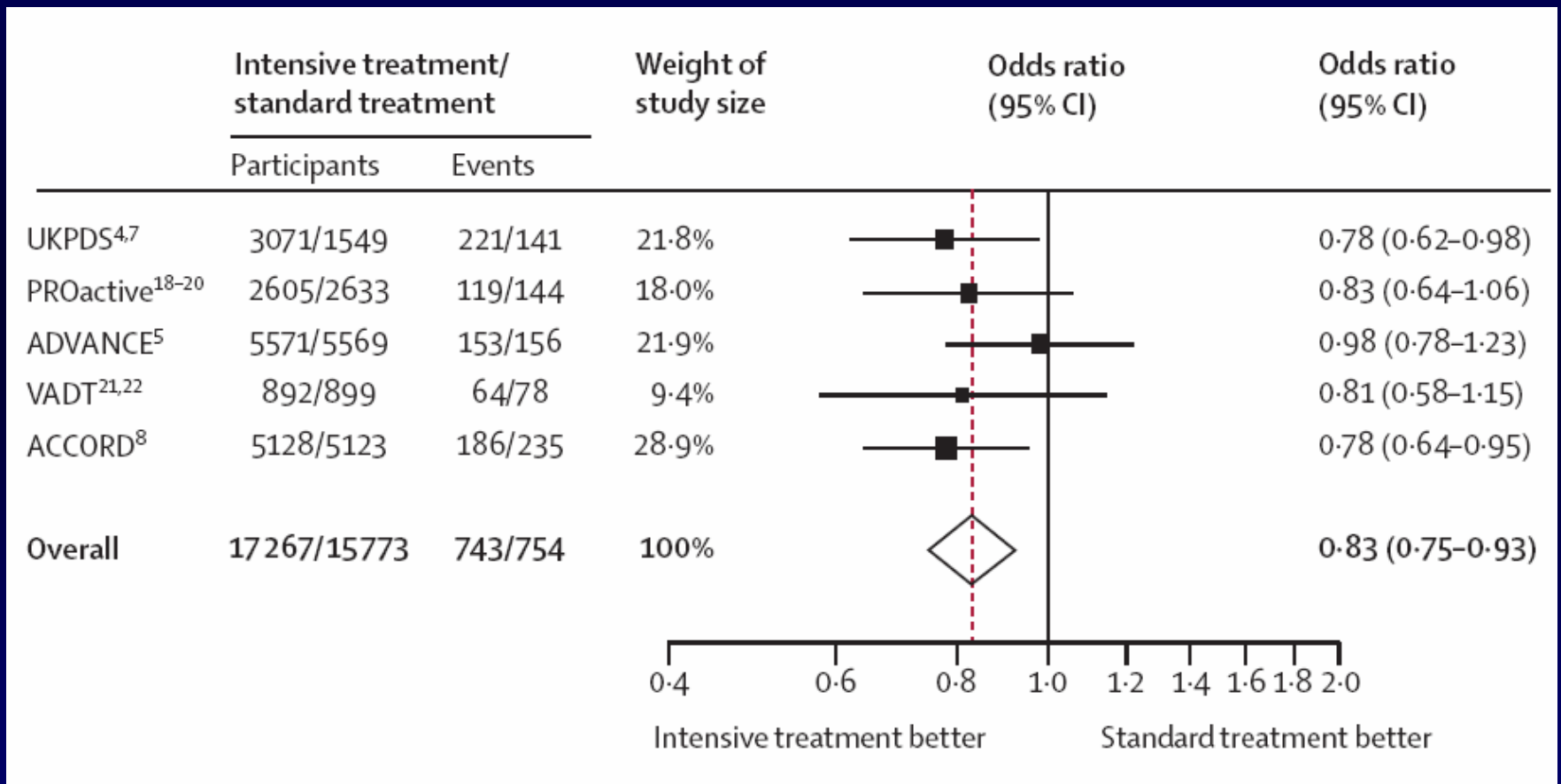


UKPDS 80. N Eng J Med 2008; ***359****:*

ukpds-ptm

Glucose control and CVD: meta-analysis

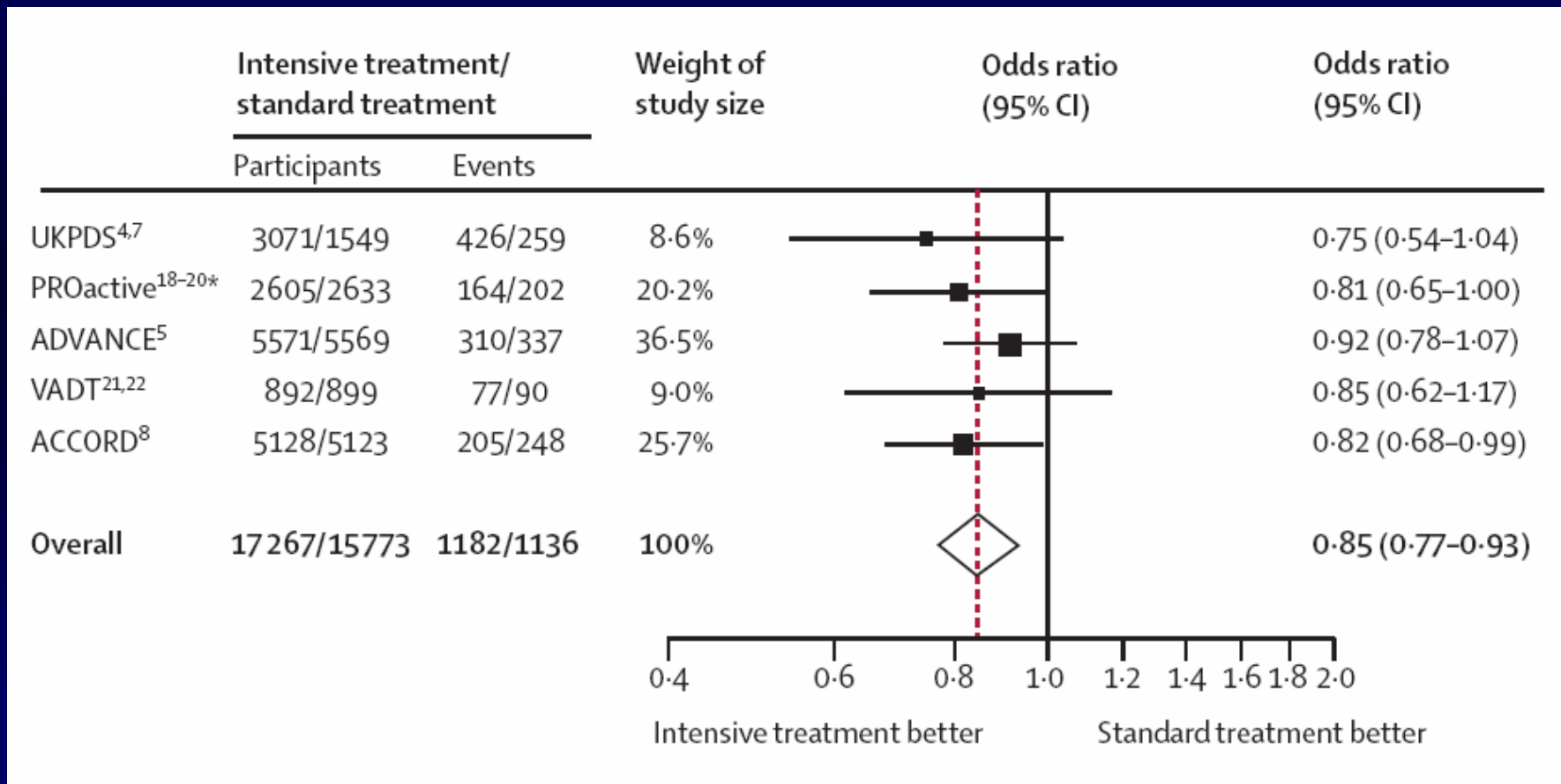
Probability of events of non-fatal myocardial infarction with intensive glucose-lowering versus standard treatment



Ray et al. Lancet 2009; 373: 1765–72

Glucose control and CVD: meta-analysis

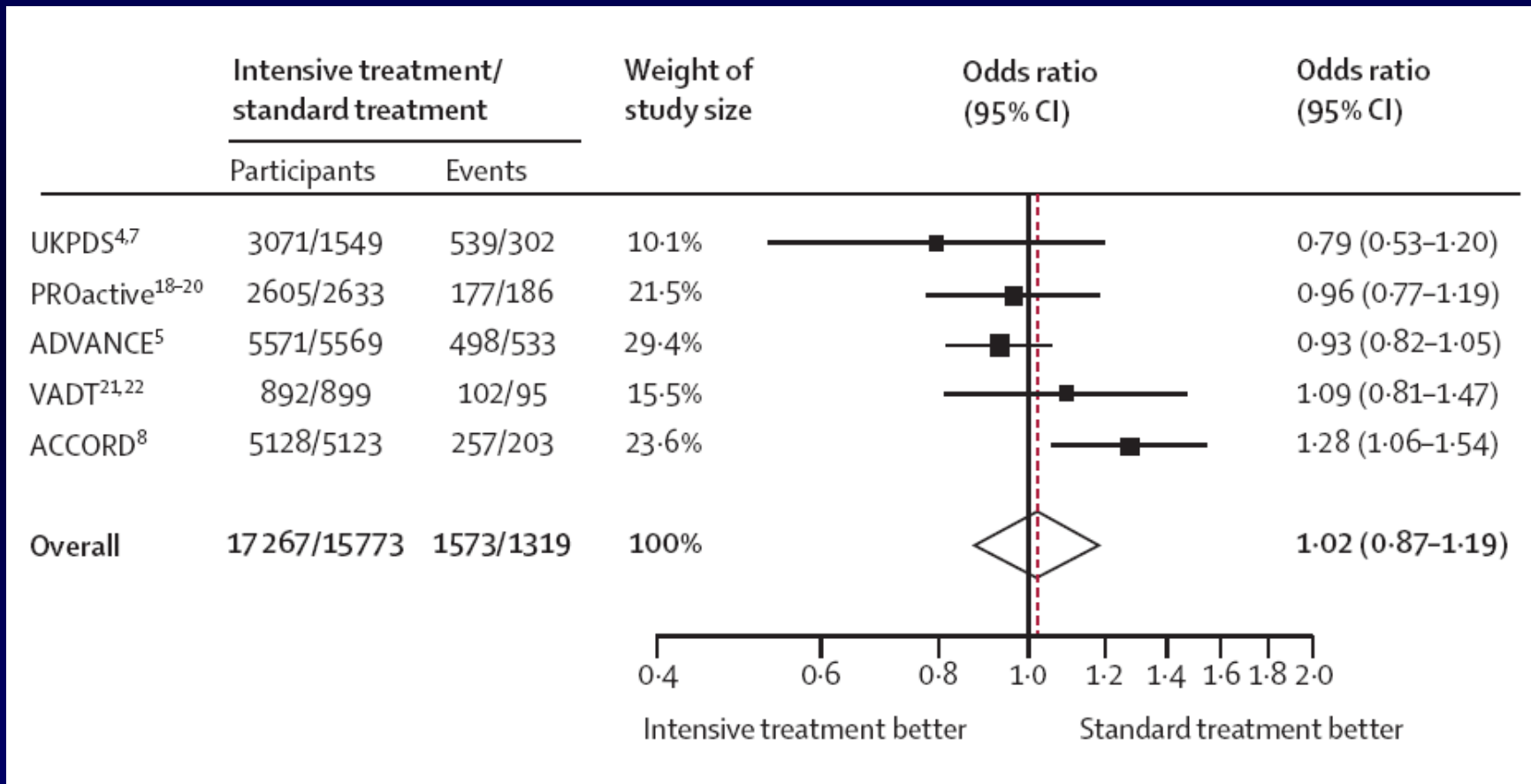
Probability of events of *coronary heart disease* with intensive glucose-lowering versus standard treatment



Ray et al. Lancet 2009; 373: 1765–72

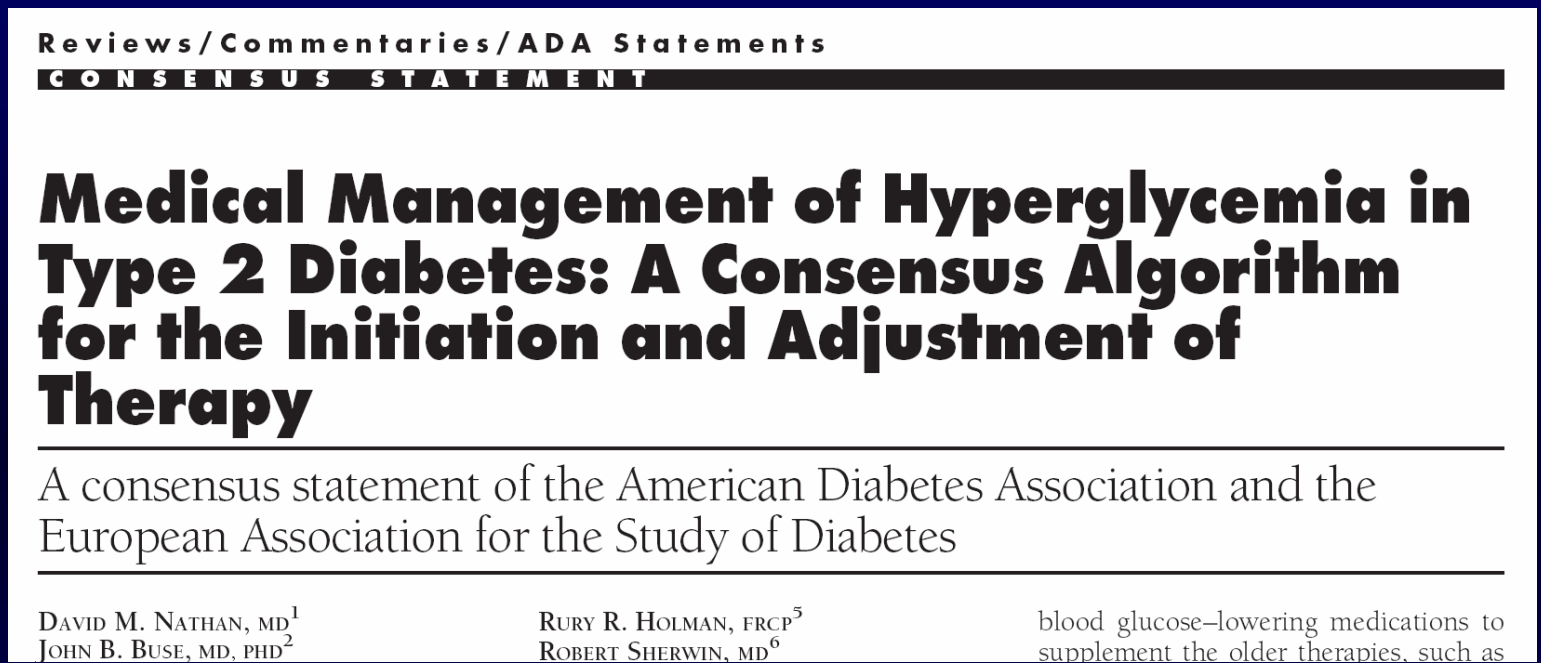
Glucose control and CVD: meta-analysis

Probability of events of *all-cause mortality* with intensive glucose-lowering versus standard treatment



Ray et al. Lancet 2009; 373: 1765–72

Is tight glucose control harmful?



Reviews/Commentaries/ADA Statements

CONSENSUS STATEMENT

Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy

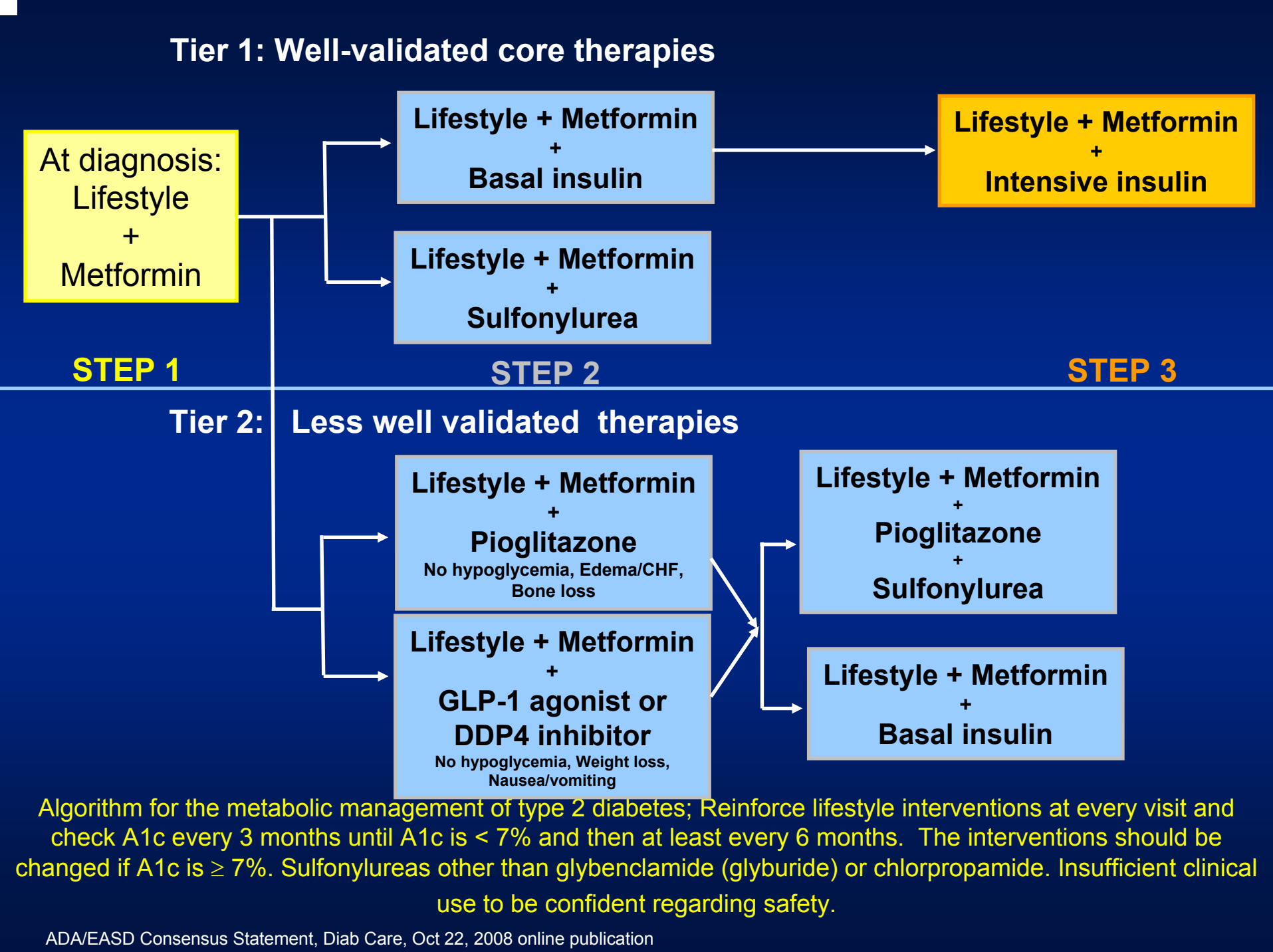
A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes

DAVID M. NATHAN, MD[1]
JOHN B. BUSE, MD, PHD[2]
RURY R. HOLMAN, FRCP[5]
ROBERT SHERWIN, MD[6]

blood glucose–lowering medications to supplement the older therapies, such as

”Our consensus is that an A1C level of ≥7% should serve as a call to action to initiate or change therapy with the goal of achieving an A1C level of <7%.”

Diabetes Care 2009;32:1-11



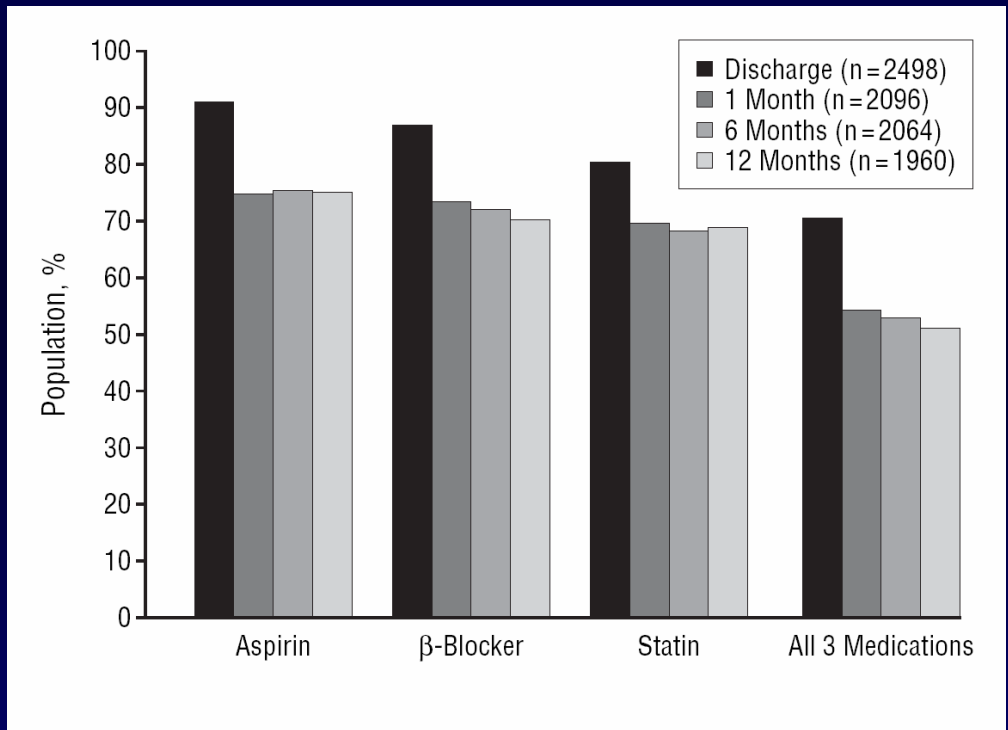
Algorithm for the metabolic management of type 2 diabetes; Reinforce lifestyle interventions at every visit and check A1c every 3 months until A1c is < 7% and then at least every 6 months. The interventions should be changed if A1c is ≥ 7%. Sulfonylureas other than glybenclamide (glyburide) or chlorpropamide. Insufficient clinical use to be confident regarding safety.

ADA/EASD Consensus Statement, Diab Care, Oct 22, 2008 online publication

Impact of medication discontinuation on mortality

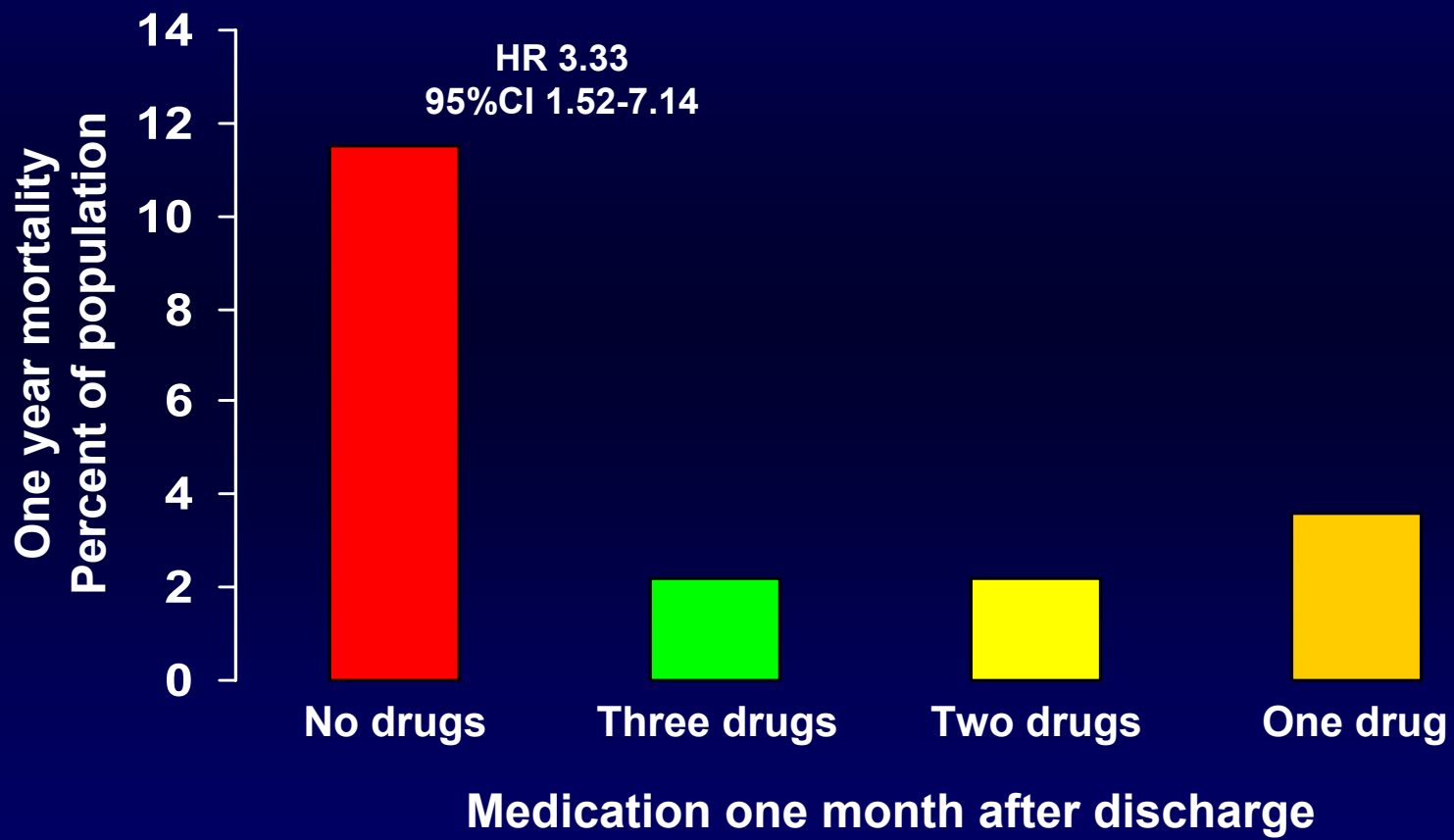
1521 patients discharged with Aspirin, β-blocker and Statin following hospitalization for myocardial infarction followed for 12 months

184 patients stopped all three medications within the first month



Ho et al. Arch Intern Med 2006;166:1842-47

Impact of medication discontinuation on mortality



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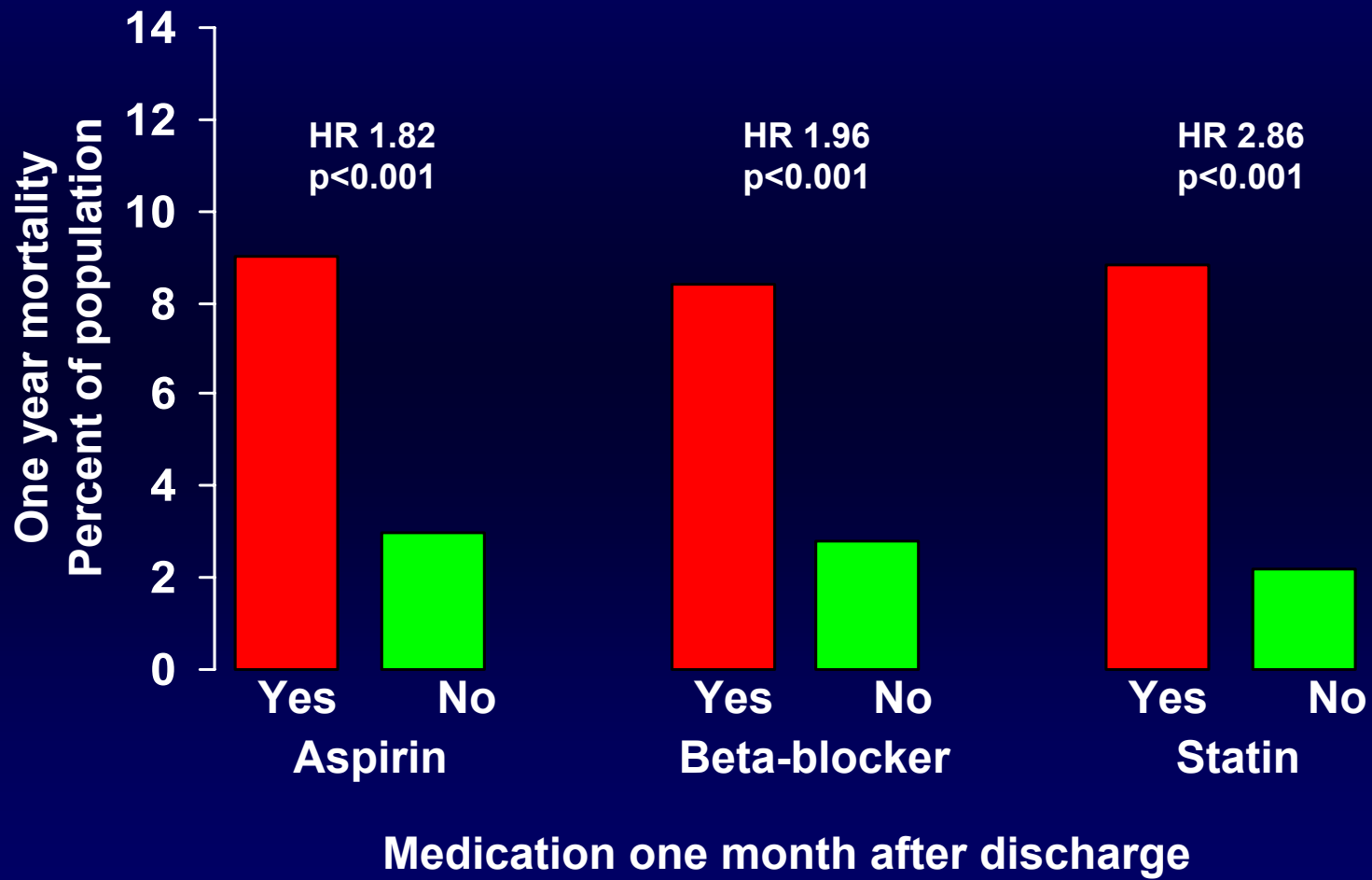
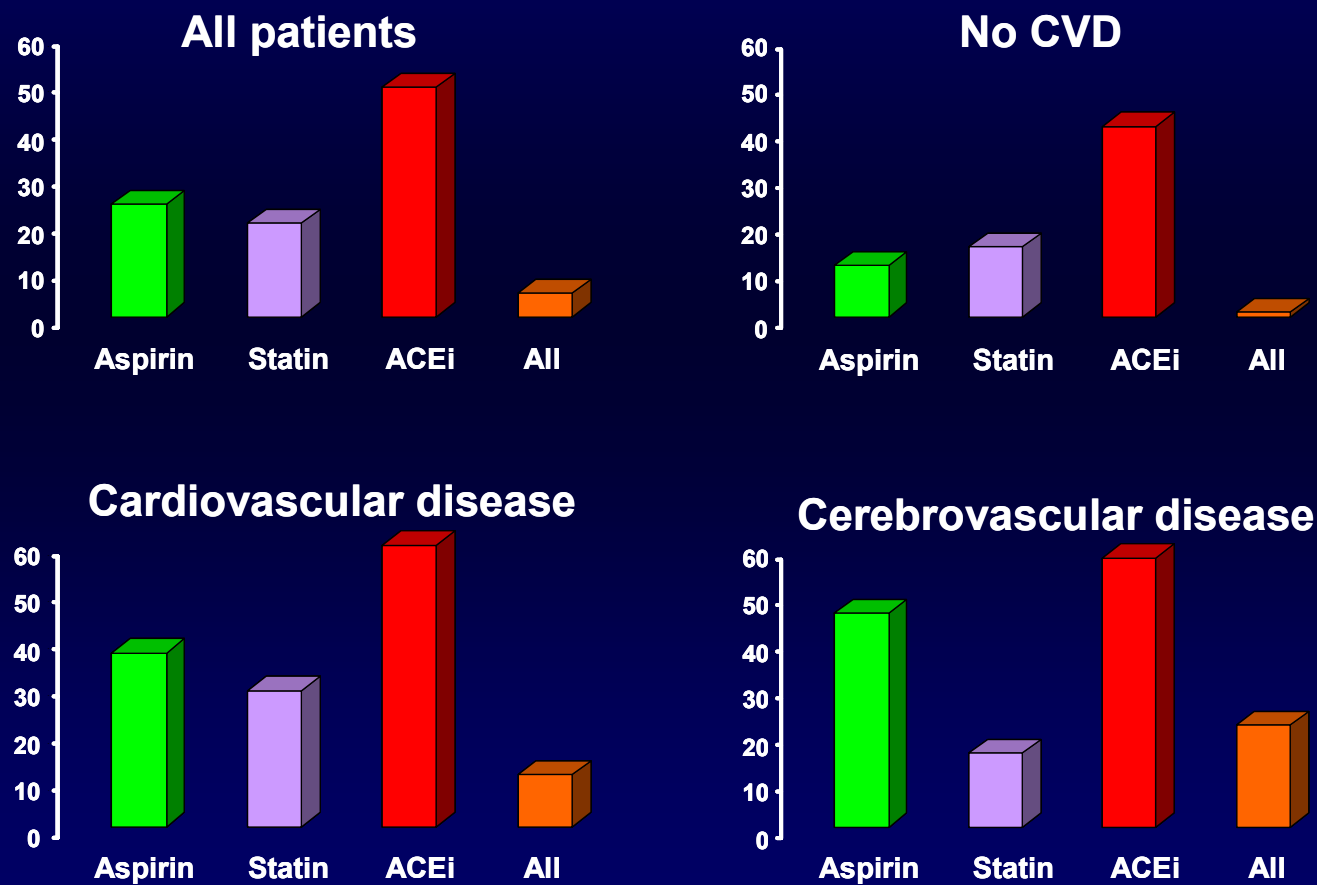
Impact of medication discontinuation on mortality



Ho et al. Arch Intern Med 2006;166:1842-47

Drug therapy underused in DM

Cohort of 12106 patients with type 2 diabetes



CMAJ 2004;171:1189

Cost-Effectiveness of Intensified Versus Conventional Multifactorial Intervention in Type 2 Diabetes

Results and projections from the Steno-2 study

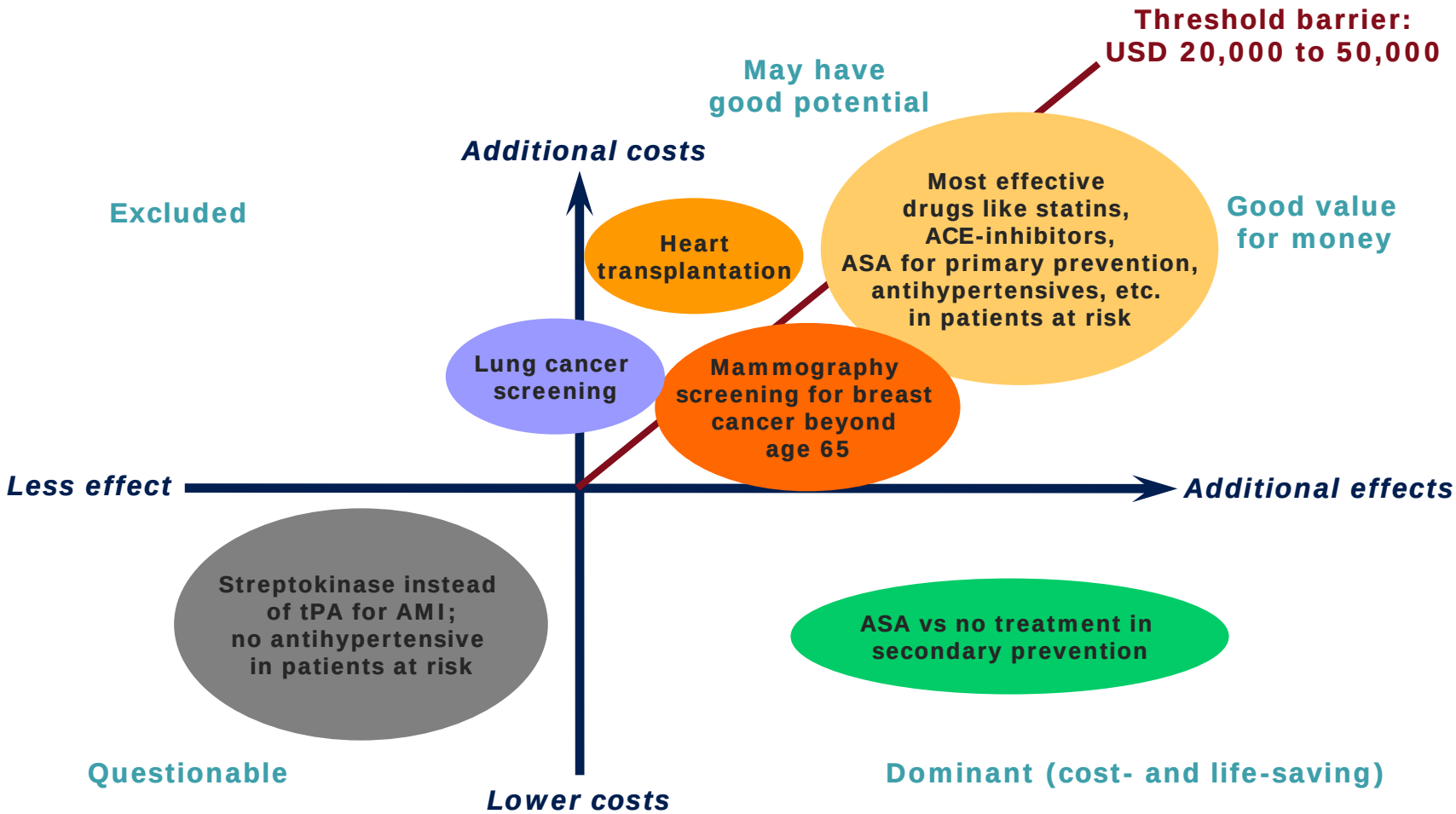
AIM

To assess the cost-effectiveness of intensive versus conventional therapy as applied in the Steno-2 study from the perspective of a Danish reimbursement authority

Gæde et al. Diabetes Care 2008; 31:1510–5

Discussion and Conclusions (1)

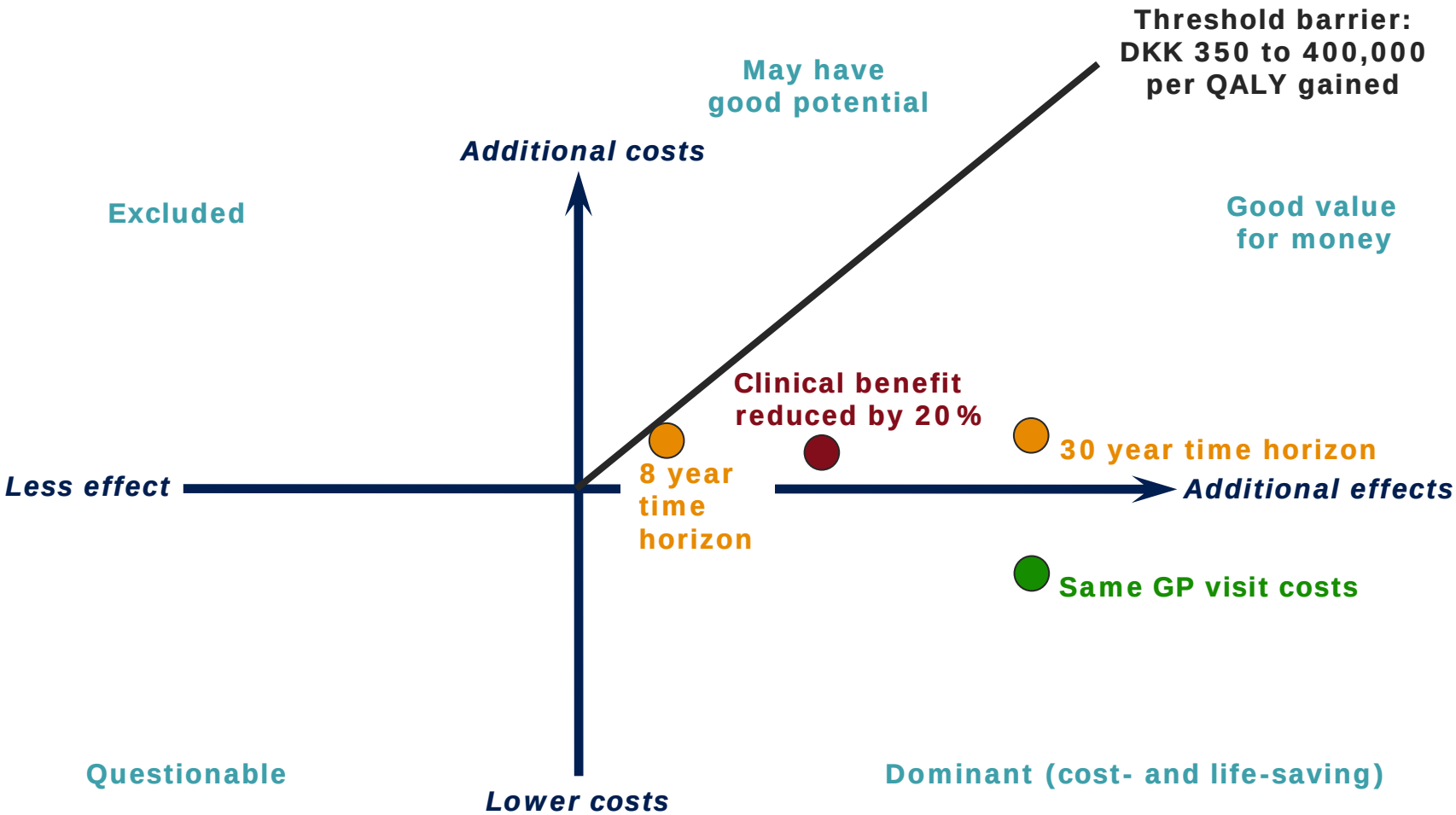
Putting the findings into perspective



Gæde et al. Diabetes Care 2008; 31:1510–5

Discussion and Conclusions (2)

Putting the findings into perspective



Gæde et al. Diabetes Care 2008; 31:1510–5

Conclusion

- Intensified multifactorial treatment in type 2 diabetes prevents both micro- and cardiovascular disease as well as mortality
- Early intervention is more beneficial than late
- The most important treatment modalities for CVD may be treatment of dyslipidemia and hypertension
- Optimal treatment of hyperglycemia still represents a major challenge regarding treatment goals and use of specific drugs

Conclusion

- Drug use in type 2 diabetes is insufficient and not according to guidelines because of physician inertia
- Continuous motivation of both patients and health care providers is
- Multiple risk factor intervention in type 2 diabetes is cost-effective