Management of cardiovascular diseases

Acute coronary syndromes

Klas Malmberg

Cardiovascular treatment in patients with diabetes

Limitation with available information

- Retrospective data
- Subgroup analysis
- Diabetes not well defined
- Poorly described glucose lowering treatment

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Evidence based treatments

- Thrombolysis
- Aspirin
- ß-blockade
- ACE-I
- Lipid lowering
- Metabolic intervention
- Invasive interventions

Prof Klas Malmberg, MD, PhD, FESC

Evidence based treatments

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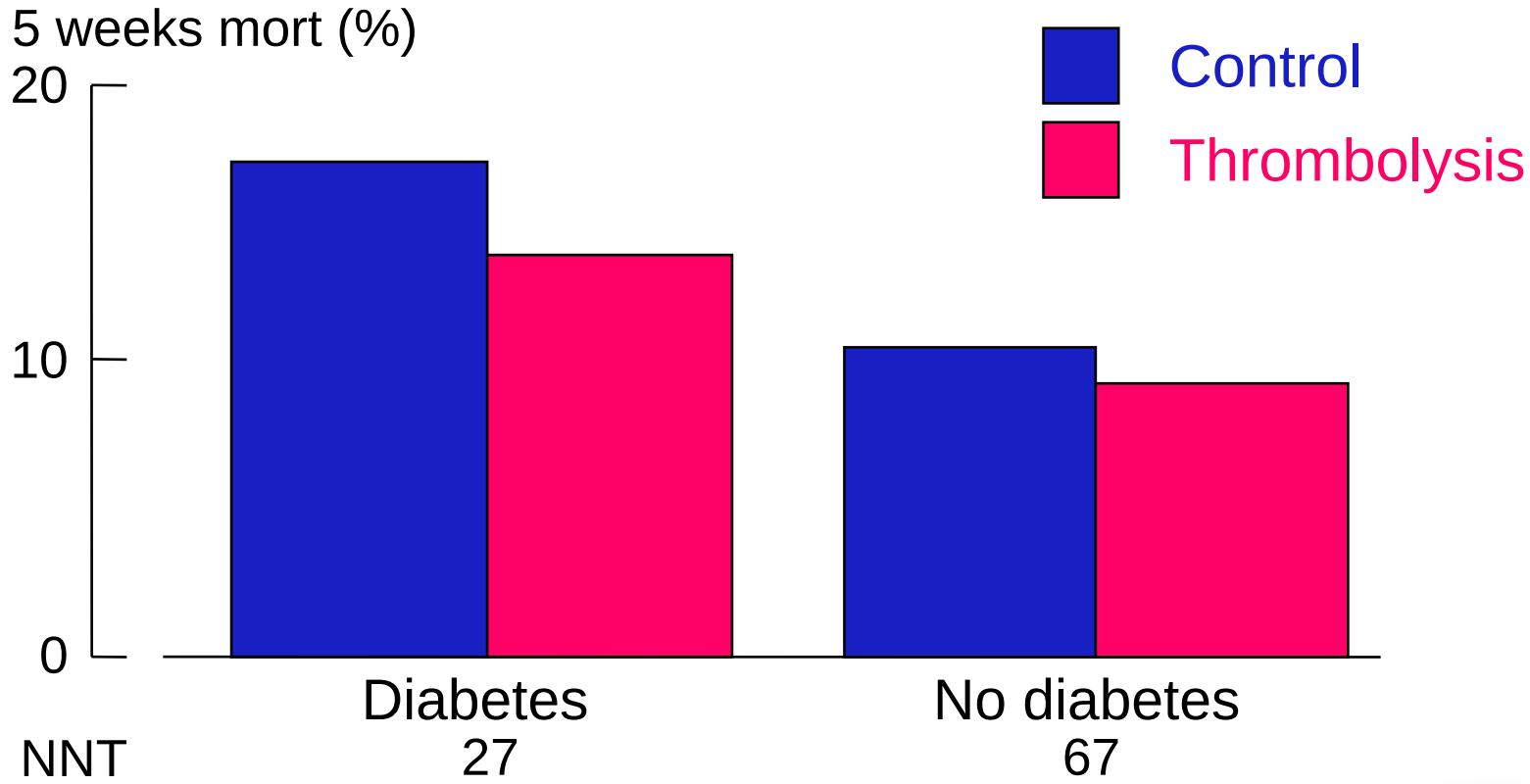
Thrombolysis in the diabetic MI patient

From fibrinolytic therapy trialists

n = 43 343 Diabetes ~ 4 300 (10%)



(FTT Collaboration Group Lancet 1994;31)

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Thrombolysis in the diabetic patient

GUSTO I

n = 40 000 Diabetes ~ 6 000 (15%)

Bleeding	Diabetics	Non-diabetics
Extraocular	1	10
Intraocular	0	1

(Mahaffey et al JACC 1997;30:1606)

ESC/EASD Pocket Guidelines
Diabetes, prediabetes and cardiovascular disease
Management of cardiovascular risk
Coronary artery disease

Recommendation	Class	Level
Early risk stratification should be part of the evaluation of the diabetic patient after ACS.	IIa	C
Treatment targets, as listed in Table 1, should be outlined and applied in each diabetic patient following an ACS.	IIa	C
Patients with acute MI and diabetes should be considered for thrombolytic therapy on the same grounds as their non-diabetic counterparts.	IIa	A
Whenever possible, patients with diabetes and ACS should be offered early angiography and mechanical revascularization.	IIa	B
Beta-blockers reduce morbidity and mortality in patients with diabetes and ACS.	IIa	B
Aspirin should be given for the same indications and in similar dosages to diabetic and non-diabetic patients.	IIa	B
Adenosine diphosphate (ADP) receptor dependent platelet aggregation inhibitor (clopidogrel) may be considered in diabetic patients with ACS in addition to aspirin.	IIa	C
The addition of an ACE-inhibitor to other therapies reduces the risk for cardiovascular events in patients with diabetes and established CVD.	I	A
Diabetic patients with acute MI benefit from tight glucometabolic control. This may be accomplished by different treatment strategies.	IIa	B

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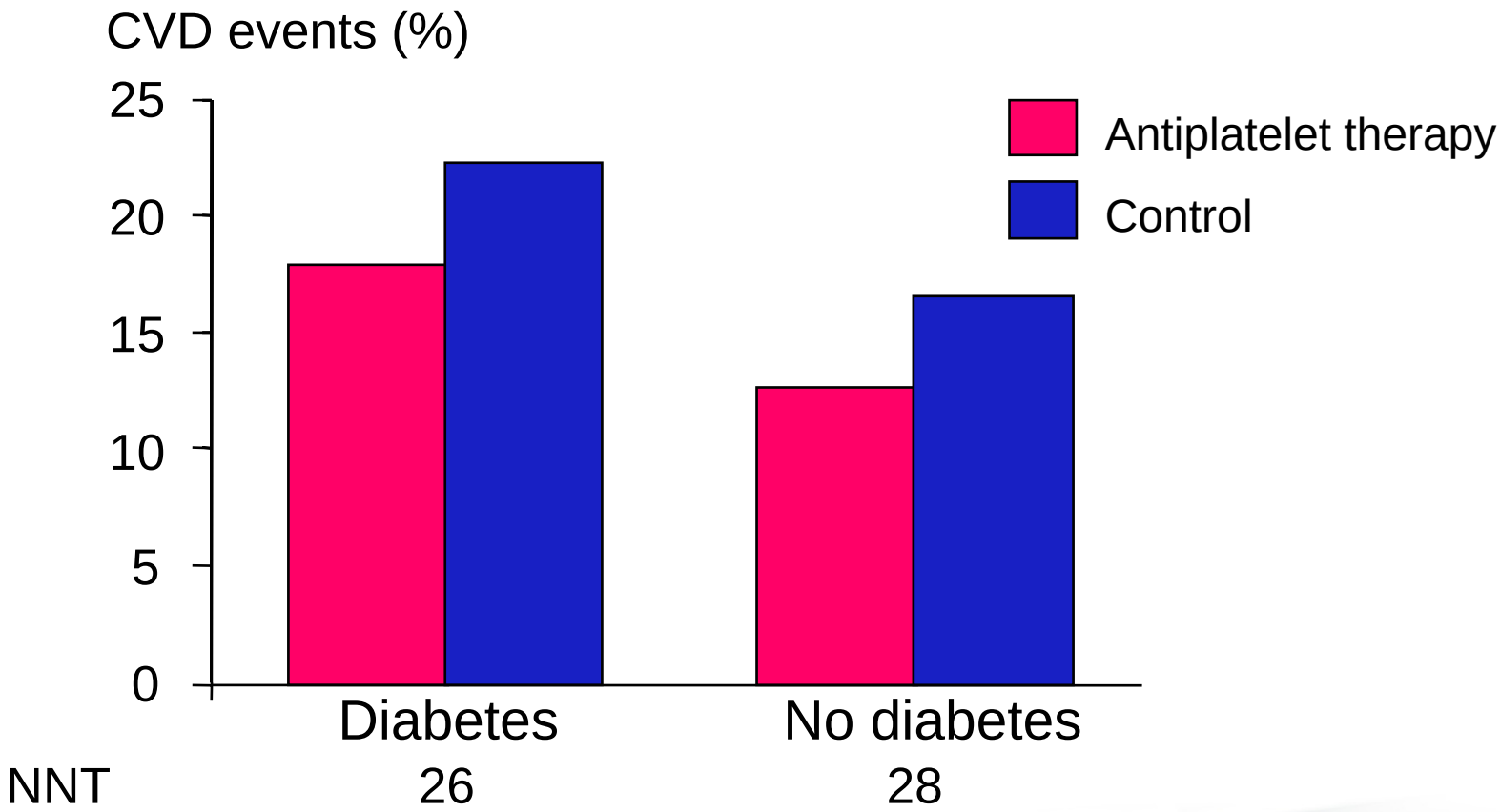
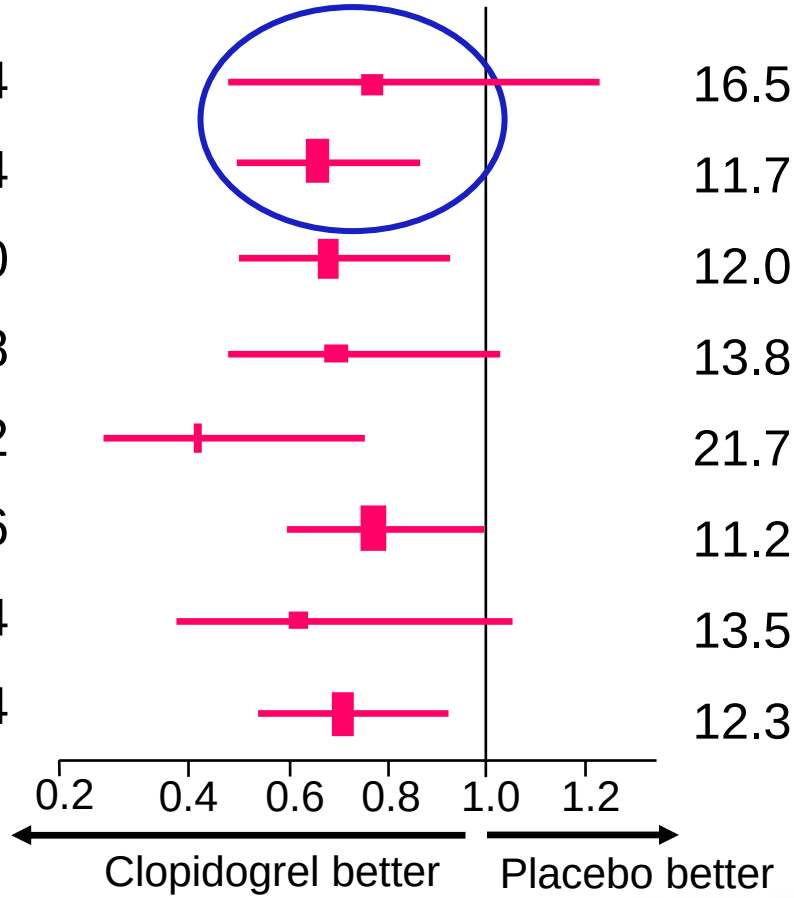
Effect of anti platelet agents on CVD events in high risk patients: Meta analysis



(Antiplatelets Trialists Collaboration BMJ1994;305:81-106)

CV death or MI from randomization to end

	2N	Relative Risk	Plac	Clopid
Diabetes	504		16.5	12.9
No Diabetes	2154		11.7	7.9
PCI in 1st Hosp.	1730		12.0	8.3
PCI After 1st Hosp.	928		13.8	9.8
H/O CABG	332		21.7	9.6
No H/O CABG	2326		11.2	8.7
PCI ≤ 72 h Rand	544		13.5	8.5
PCI > 72 h Rand	2114		12.3	8.9



(Mehta SR et al. Lancet 2001:358:527-33)

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- Invasive interventions

Prof Klas Malmberg, MD, PhD, FESC

Betablockade in patient with diabetes and CHD

- Deteriorates glucose control
- Masks hypoglaemic symptoms
- Prolongs hypoglycaemia

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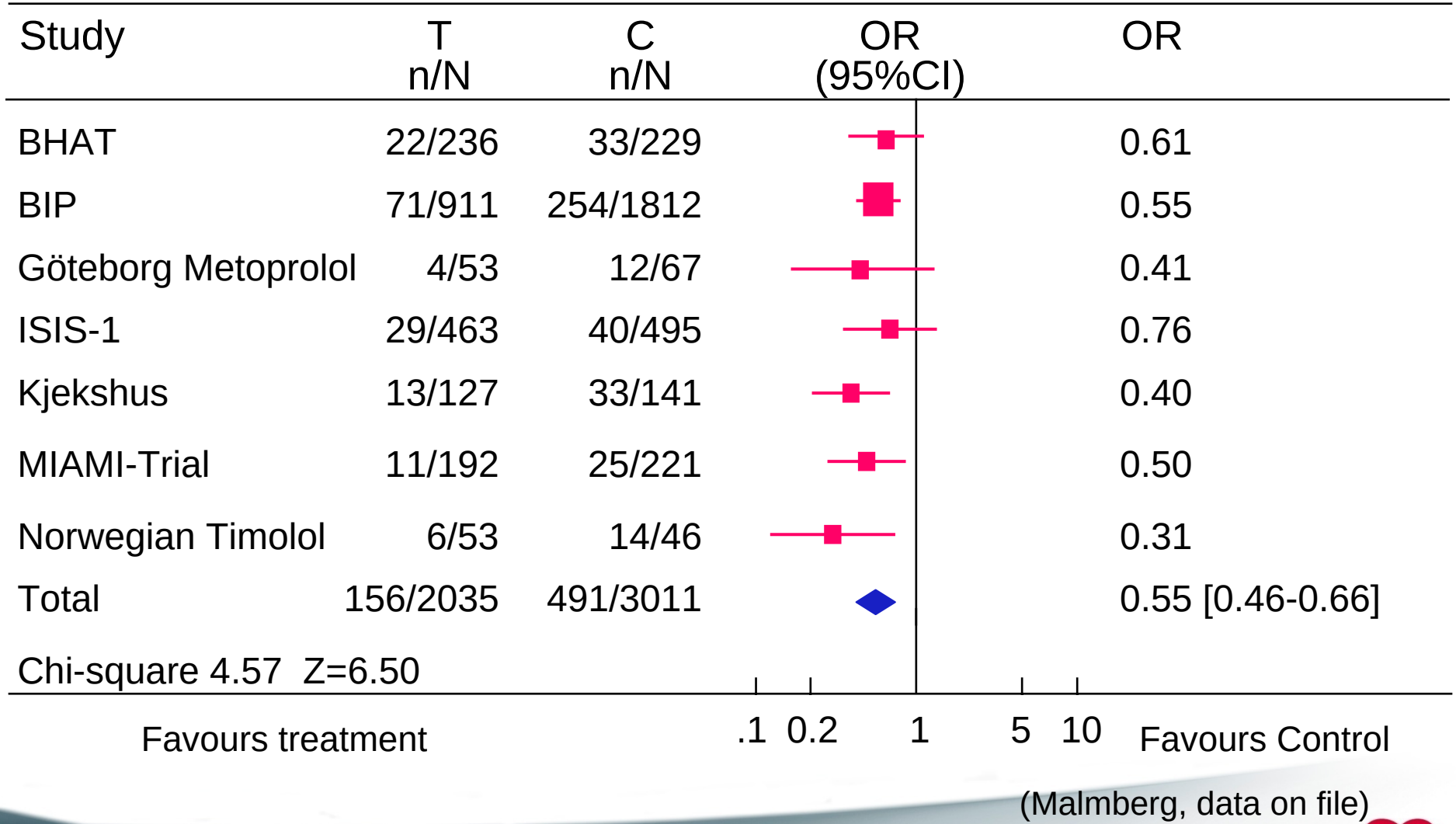
Diabetic patients - All studies



(Malmberg, data on file)

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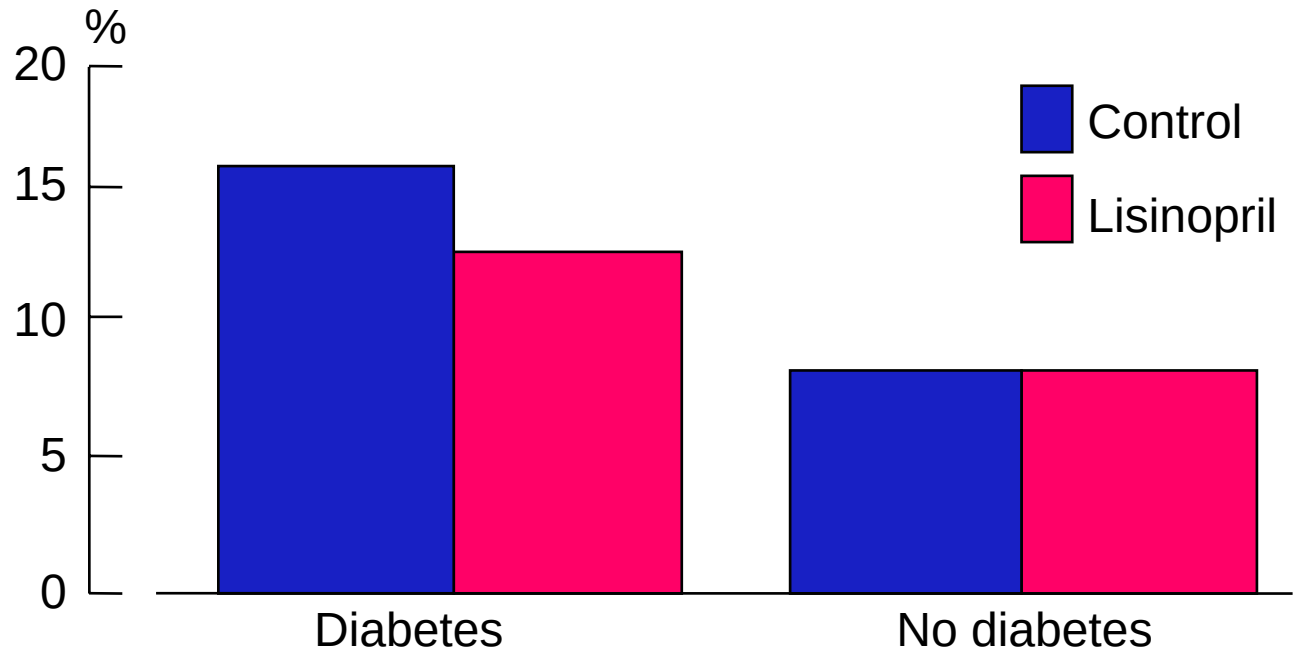
ACE-Inhibitors in diabetic patients with acute myocardial Infarction

GISSI 3

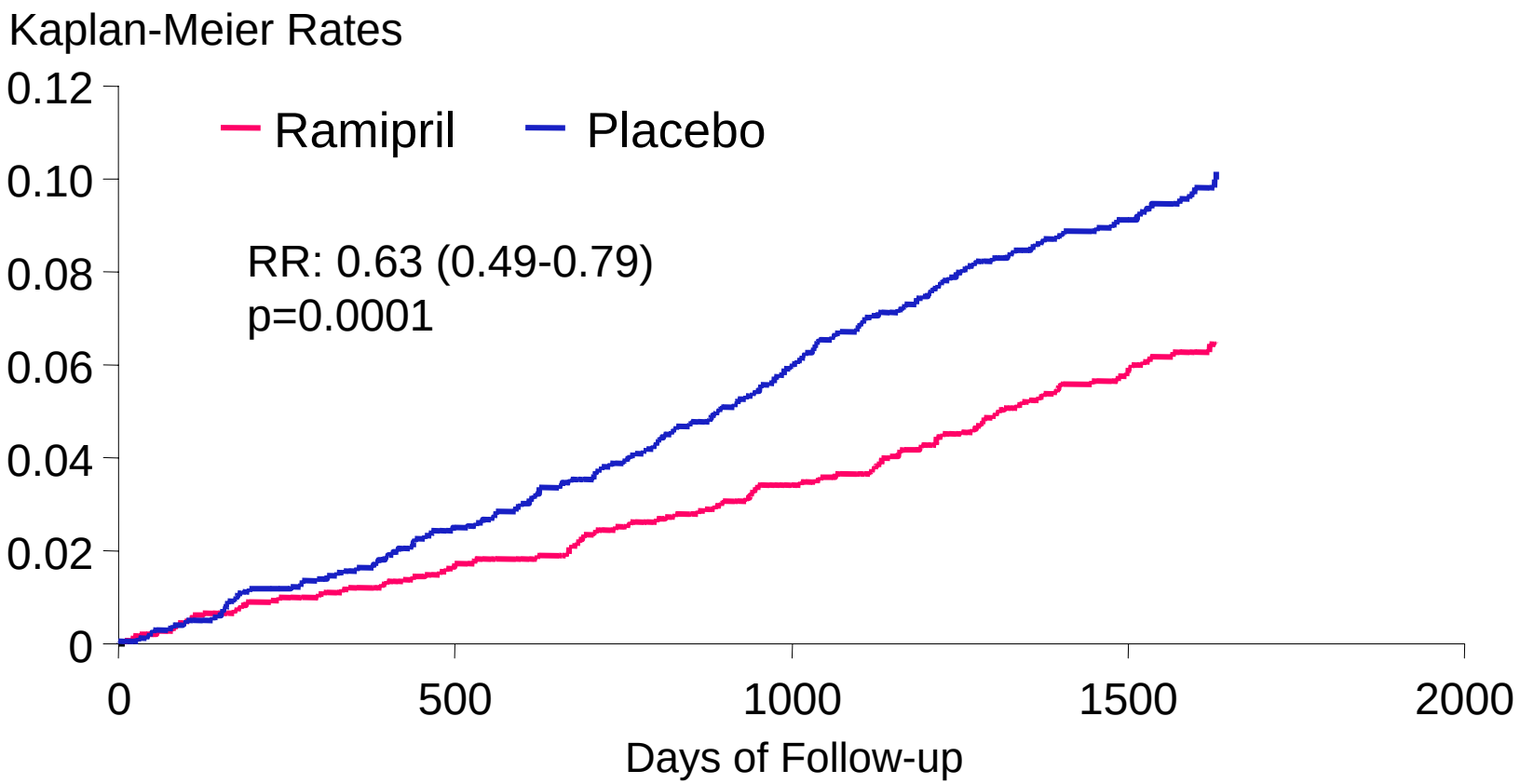
n = 18 000 Diabetes ~ 2 700 (15%)

Six months mortality



(Zuanetti et al Circulation 1997;96:4239)

CV Death - Ramipril vs Placebo - DM



(HOPE Study investigators Lancet 2000;355:253)

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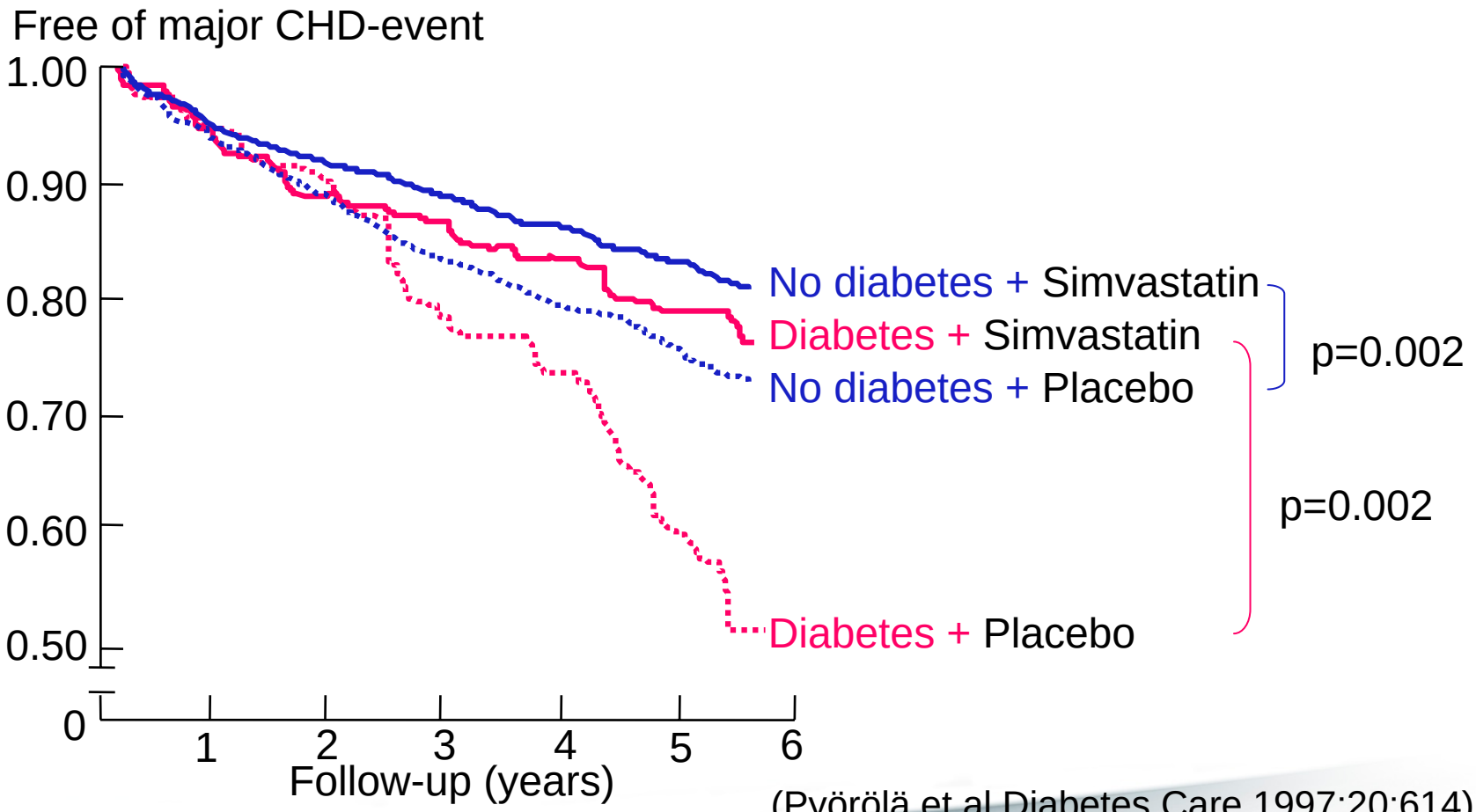
Cholesterol lowering in the diabetic patient

4S

n = 4 444 Diabetes 202 (5%)



(Pyörölä et al Diabetes Care 1997;20:614)

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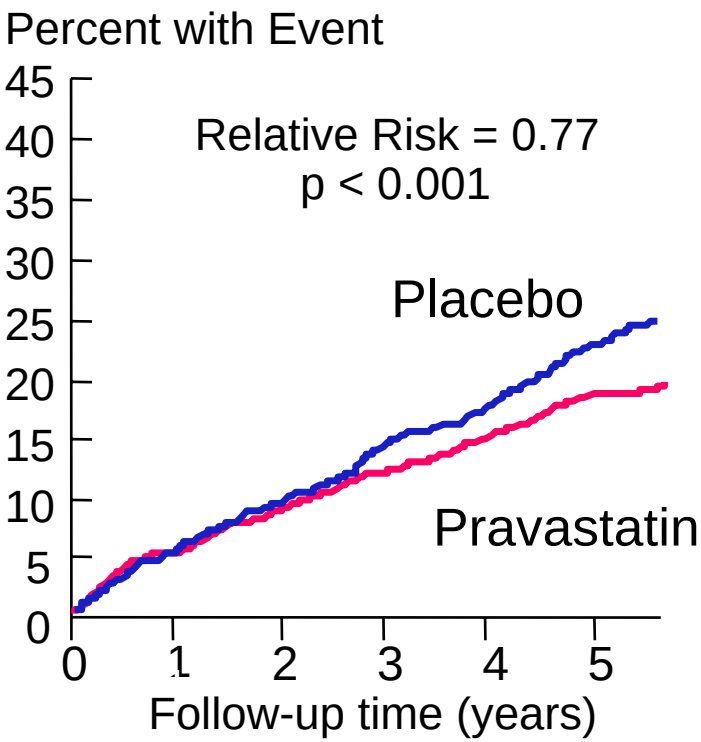
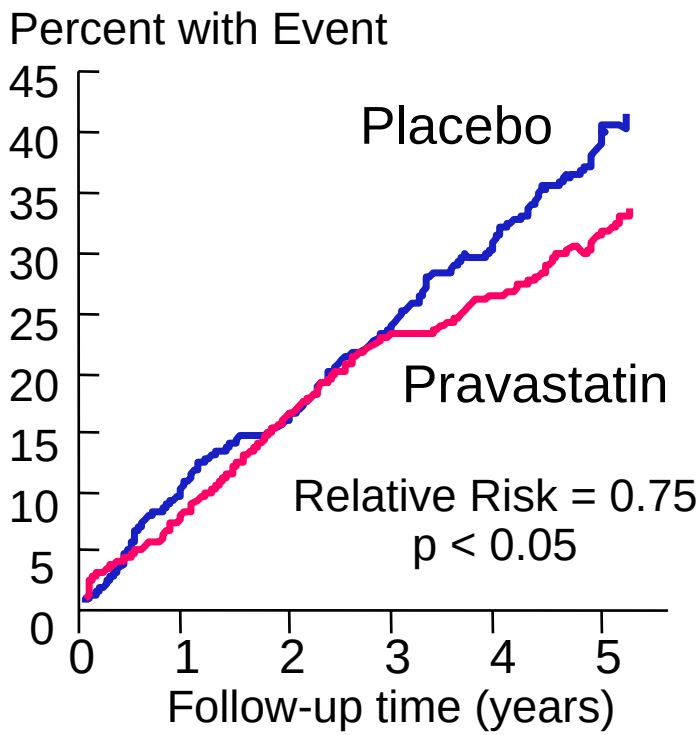
Lipid lowering in diabetes
CARE

Non-Diabetic by History



Diabetic by History



(Goldberg R et al, Circulation 1998;98:2513-2519)

Lipid lowering in diabetes

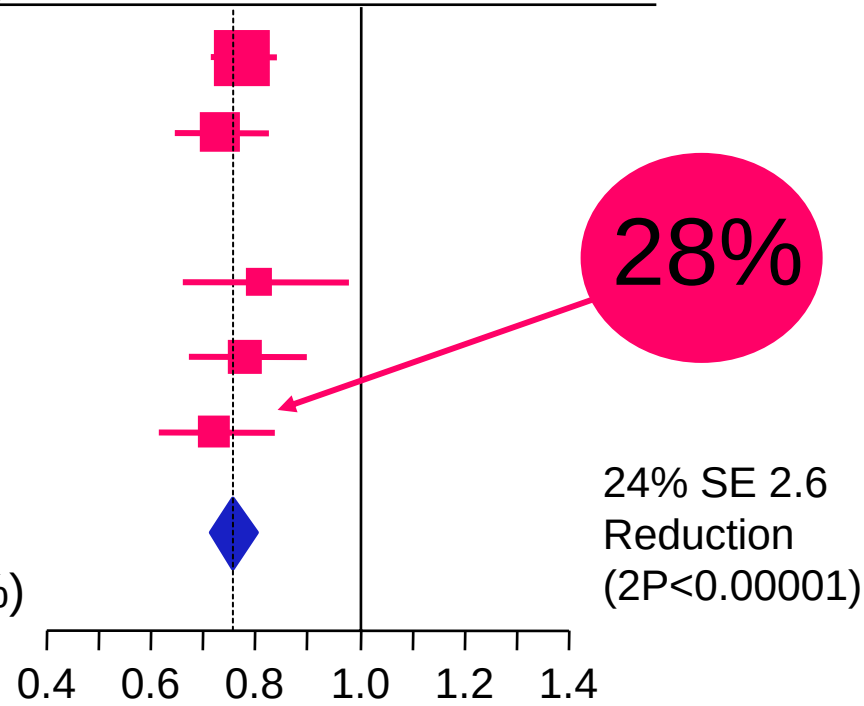
LIPIDS

	RR (%)	95%CI
Non diabetics	25	(15-33)
Diabetics	19	(-10-41)

(N Engl J Med 1998;339:1349-1357)

Vascular events by prior disease

Baseline feature	Statin (10269)	Placebo (10267)
Previous MI	1007	1255
Other CHD (not MI)	452	597
No prior CHD		
CVD	182	215
PVD	332	427
Diabetes	279	369
ALL PATIENTS	2042 (19.9%)	2606 (25.4%)



(HPS Collaborative group. Lancet 2003; 361: 2005–16)

ESC/EASD Pocket Guidelines
Diabetes, prediabetes and cardiovascular disease

Recommended treatment targets for patients with diabetes and CAD

	Variable	Treatment target
Blood pressure	Systolic/diastolic (mm Hg)	< 130/80
	In case of renal impairment or proteinuria > 1 g/24 h	< 125/75
Glycaemic control	HbA_{1c} (%)*	≤ 6.5
	Glucose (venous plasma; mmol/L) mg/dL	
	Fasting	< 6.0 (108)
	Post-prandial (peak)	
	Type 1 diabetes	7.5-9.0 (135-160)
	Type 2 diabetes	< 7.5 (135)
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

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ESC/EASD Pocket Guidelines
Diabetes, prediabetes and cardiovascular disease

Dyslipidemia

Recommendation	Class	Level
Elevated LDL and low HDL cholesterol are important risk factors for CVD 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
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.	IIb	C
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	B

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Effect of treatment

- Glucose reduction
- Cardiac metabolic support

  - The GIK story

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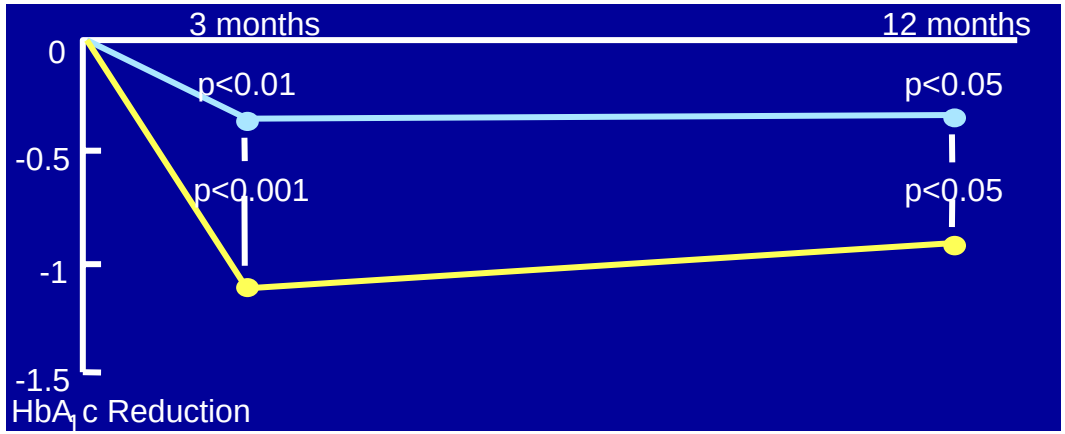
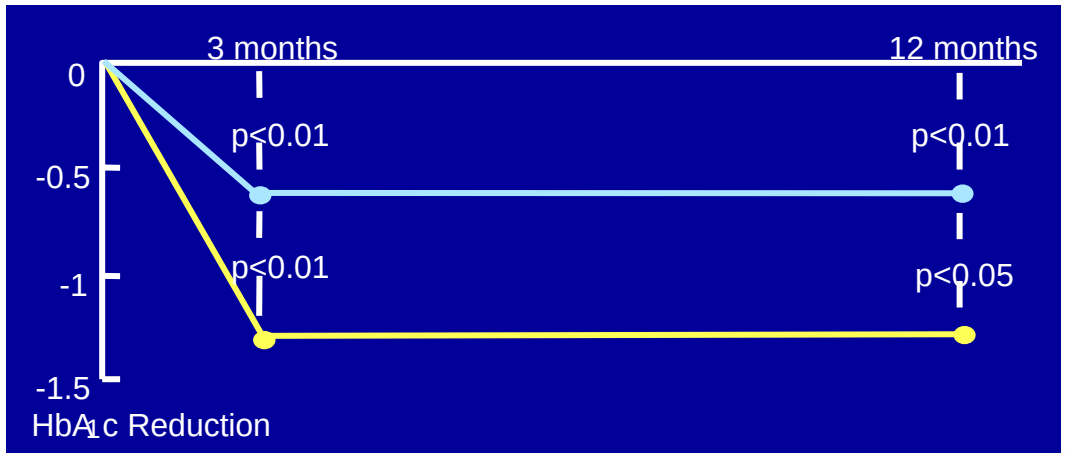
DIGAMI 1 – Metabolic control

HbA1c
All patients

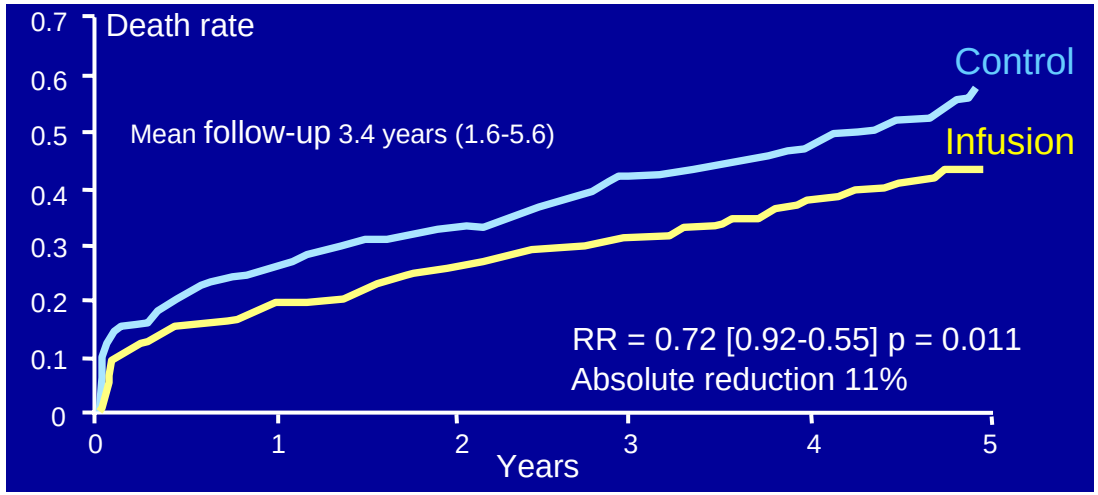


Stratum 1

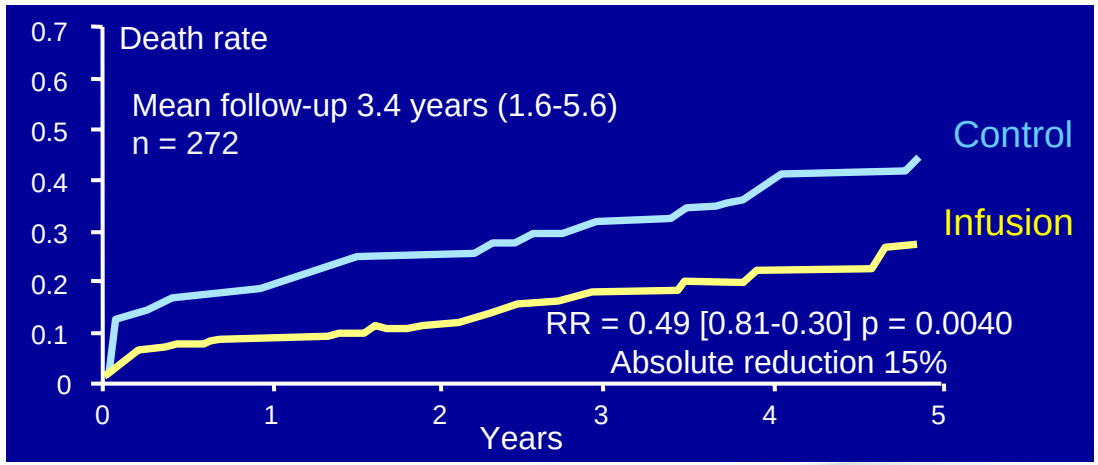


DIGAMI 1 – Mortality

All patients



Stratum 1

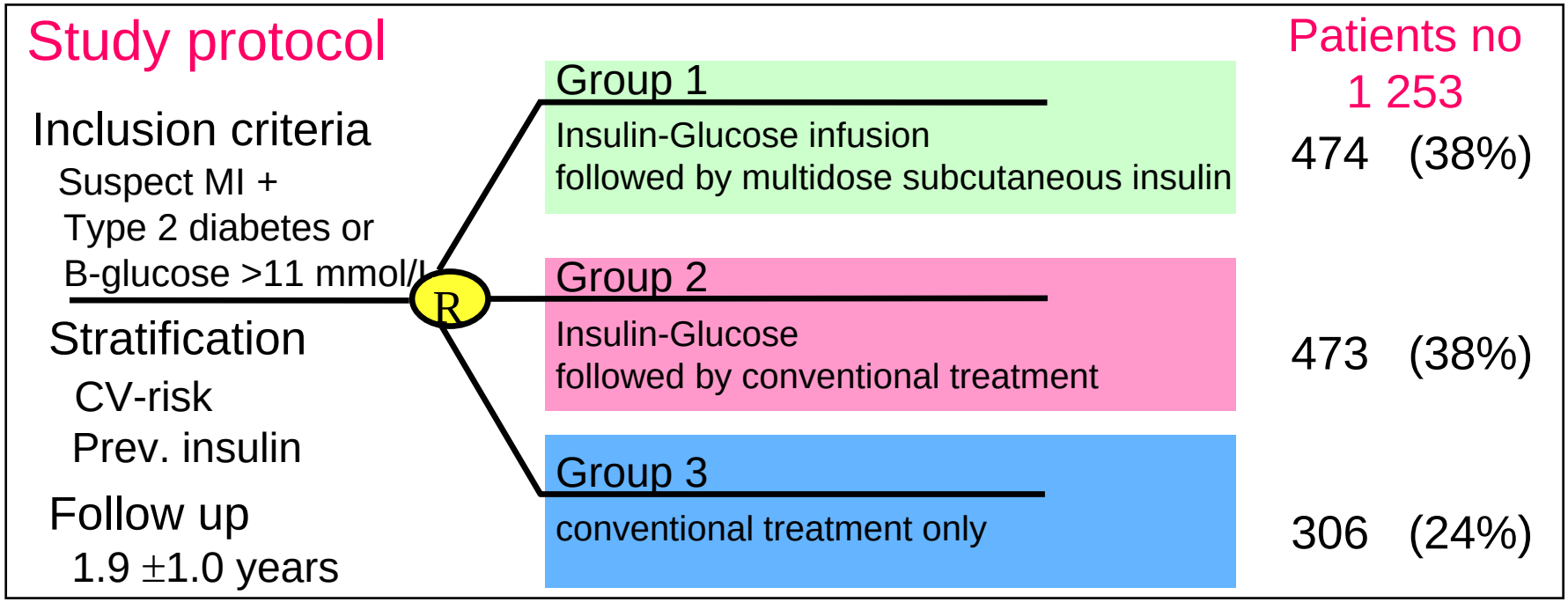


(Malmberg for DIGAMI study group Brit Med J 1997, 314:1512)

DIGAMI 2

Study outline and objectives

- Confirm DIGAMI 1
- Infusion or long-term insulin important?



(Malmberg et al Europ Heart J 2005;26:650)

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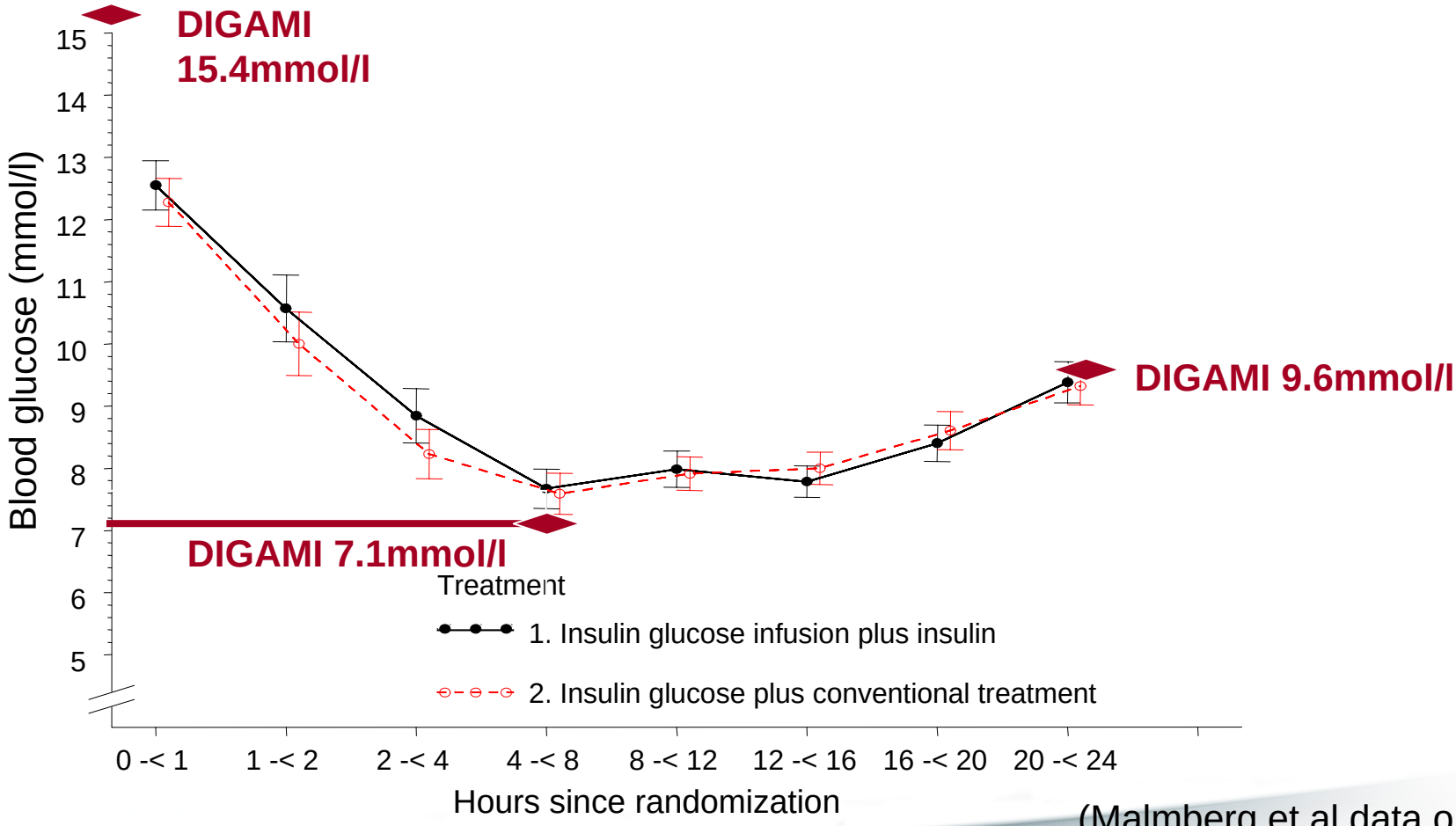
DIGAMI 2

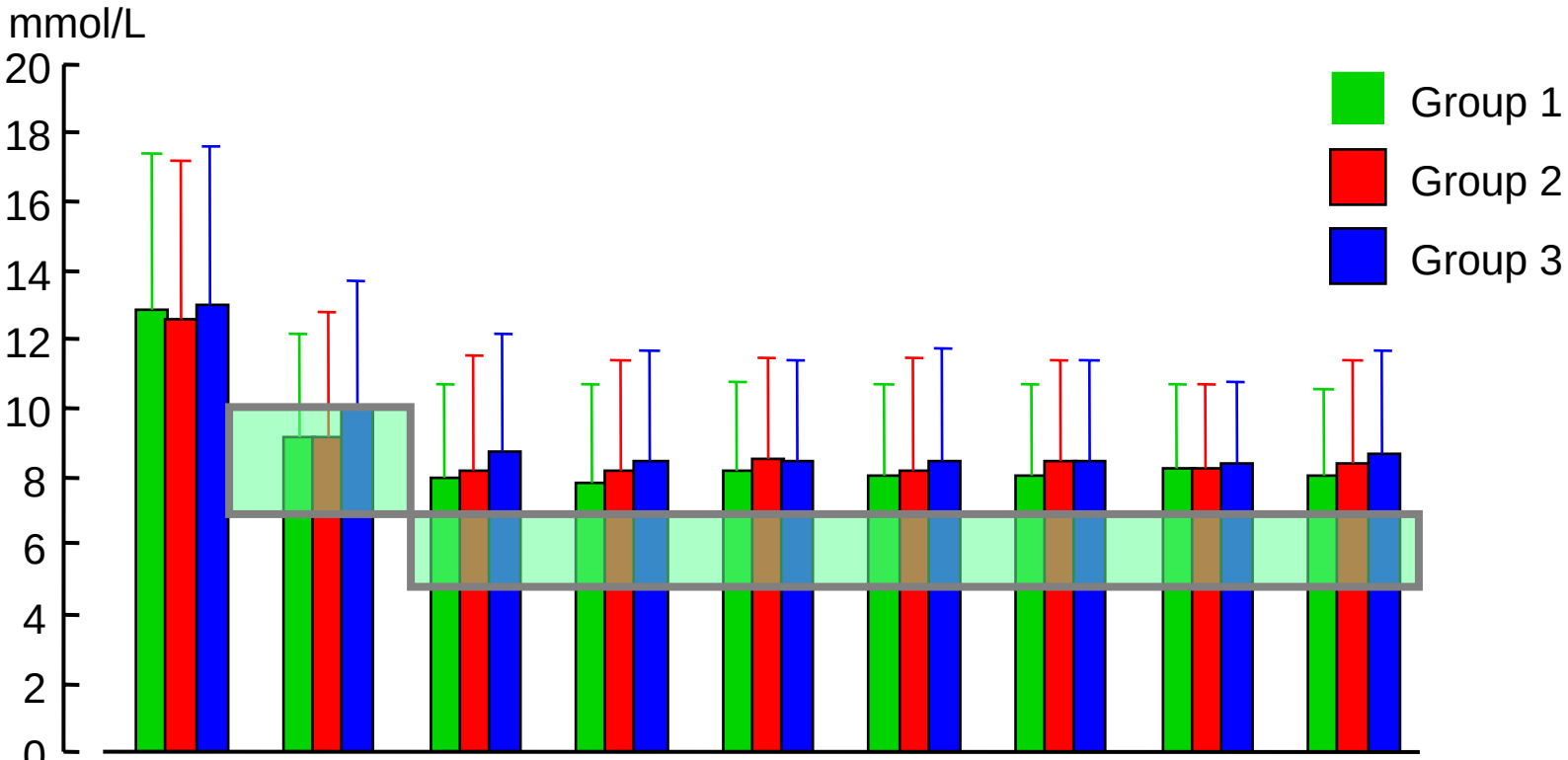
Blood glucose first 24 hours



(Malmberg et al data on file)

DIGAMI 2

Blood glucose levels by visit and treatment group



No		Baseline	24 h	3	6	12	18	24	30	36 months
	Group 1	469	454	329	313	295	228	197	144	114
	Group 2	469	452	331	320	304	219	195	151	108
	Group 3	304	282	214	199	184	154	125	98	77

(Malmberg et al European Heart J 2005;26:650-661)

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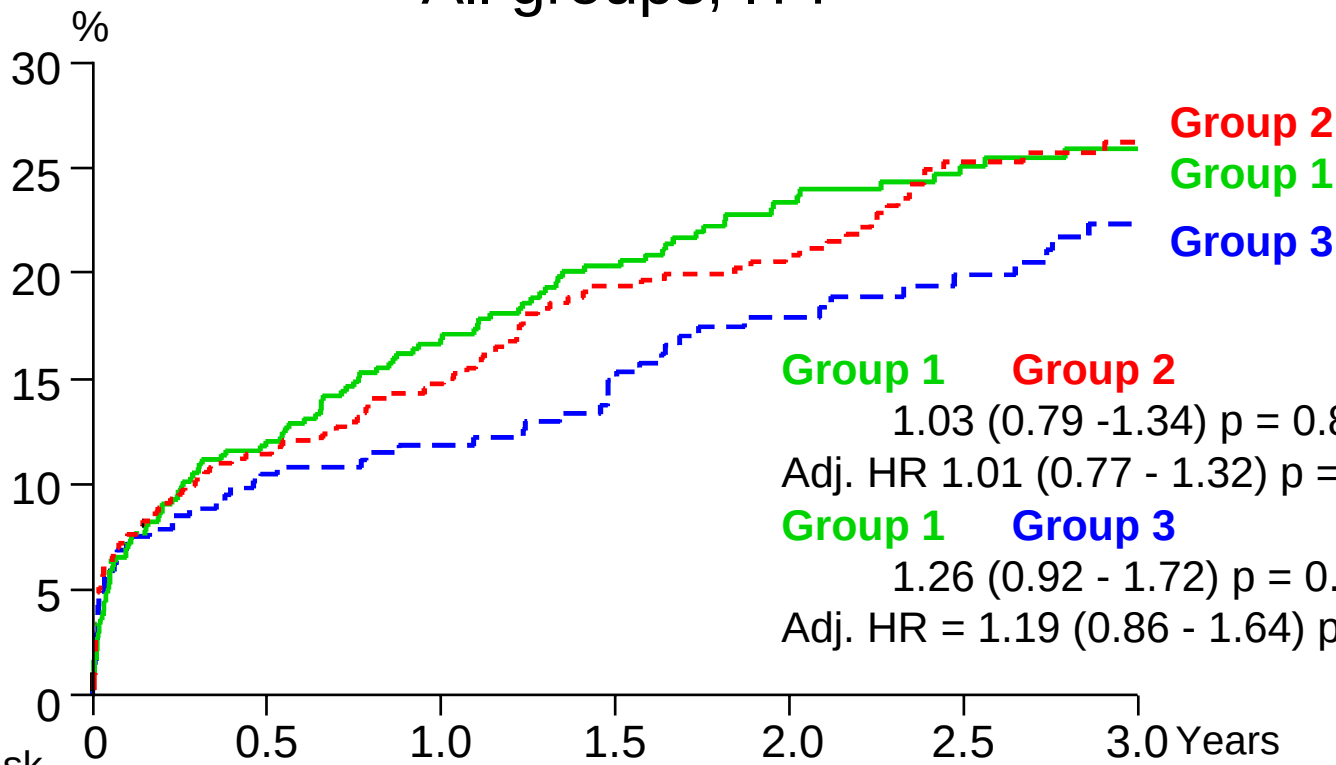
DIGAMI 2

Primary endpoints: death

All groups, ITT



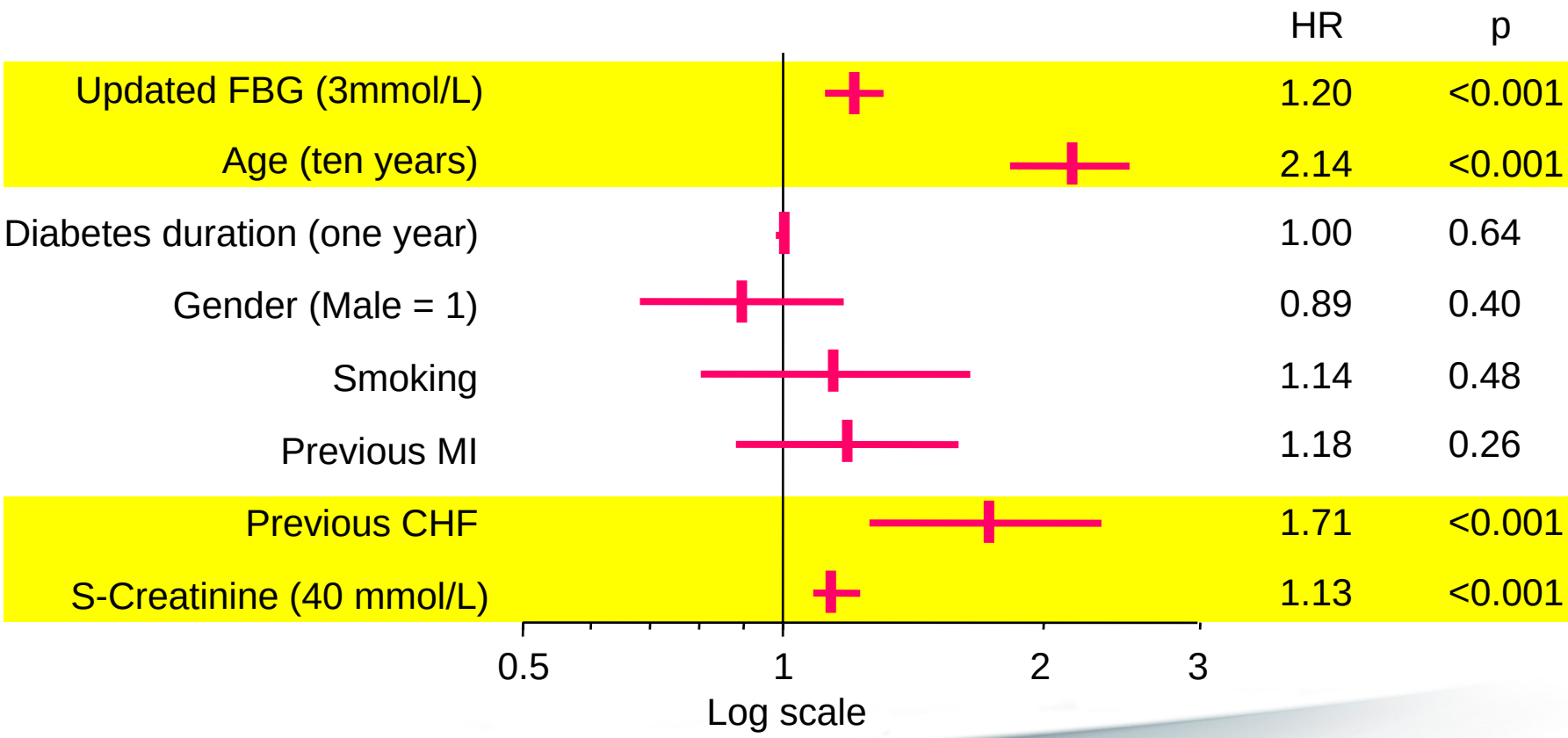
Number at risk

Group 1	474	415	357	309	252	196	113
Group 2	473	416	358	297	256	196	100
Group 3	306	272	250	211	177	150	98

(Malmberg et al European Heart J 2005;26:650-661)

DIGAMI 2

Independent baseline predictors for death including updated fasting glucose values



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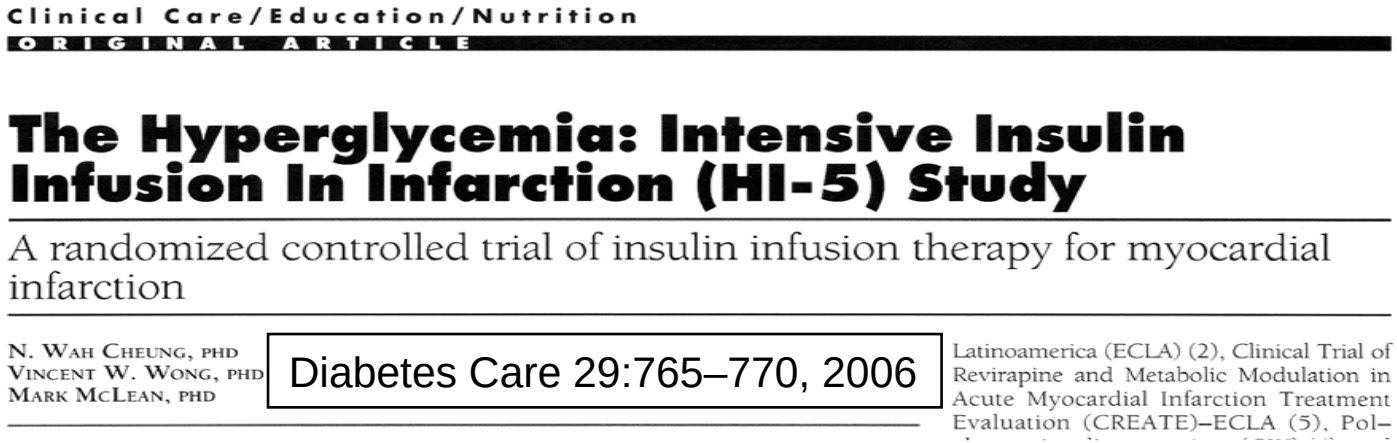

Clinical Care/Education/Nutrition

ORIGINAL ARTICLE

The Hyperglycemia: Intensive Insulin Infusion In Infarction (HI-5) Study

A randomized controlled trial of insulin infusion therapy for myocardial infarction

N. WAH CHEUNG, PHD
VINCENT W. WONG, PHD
MARK MCLEAN, PHD

Diabetes Care 29:765–770, 2006

Latinoamerica (ECLA) (2), Clinical Trial of Revirapine and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation (CREATE)–ECLA (5), Pol–

- Acute study, 24 h with DIGAMI inclusion criteria
- Target glucose level <10 mmol/l
- Power calculation: Estimated 1-year mortality 25%, 850 pat.
- Patients inclusion prematurely stopped n = 240, 6-mo mortality ≅ 7%
- As in the DIGAMI 2 no difference in glucose control
- As in the DIGAMI 2 no difference in mortality

Clinical Care/Education/Nutrition
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Diabetes Care 29:765–770, 2006

Latinoamerica (ECLA) (2), Clinical Trial of Revirapine and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation (CREATE)–ECLA (5), Pol–

However: Glucose levels during 24 h predicted mortality

	24-h mean blood glucose level ≤8 mmol/l	24-h mean blood glucose level ≥8.1 mmol/l	Signifi-cance	Adjusted odds ratio (95% CI)*	*P*
Inpatient mortality	0%	7%	0.05	7.2 (0.9–58.9)	0.07
3-month mortality	2%	9%	0.05	4.7 (1.0–22.4)	0.05
6-month mortality	2%	11%	0.02	5.6 (1.2–26.1)	0.03

*Adjusted for age, sex, and cardiac intervention (PTCA or thrombolysis).

Effect of treatment

- Glucose reduction
- Cardiac metabolic support

  - The GIK story

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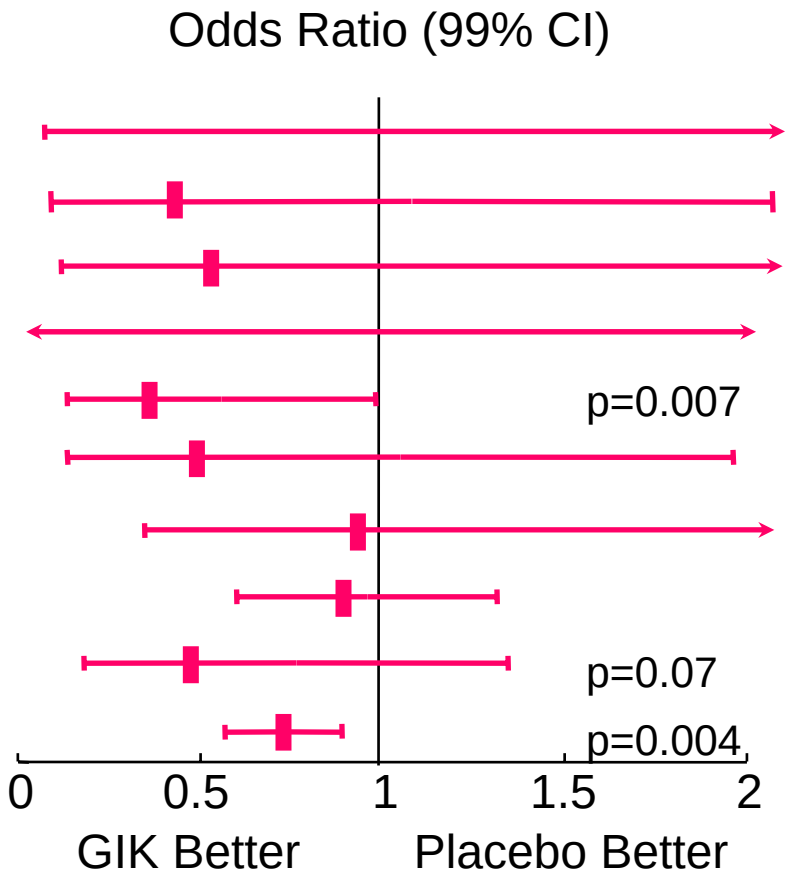
Glucose-insulin-potassium in myocardial infarction

Metaanalysis of hospital mortality in placebo controlled studies

Year	Study	No	Mortality (%) GIK	Control
1977	Heng	27	8.3	0
1978	Stanley	110	7.3	16.4
1979	Rogers	134	6.5	12.3
1987	Satler	17	0	0
1965	Mittra	170	11.6	28.2
1967	Pilcher	102	13.9	29.3
1968	Pentecost	200	15.0	16.0
1968	MRC	968	21.4	23.6
1971	Hjermann	204	10.6	20.0
All Patients		1932	16.1	21.0

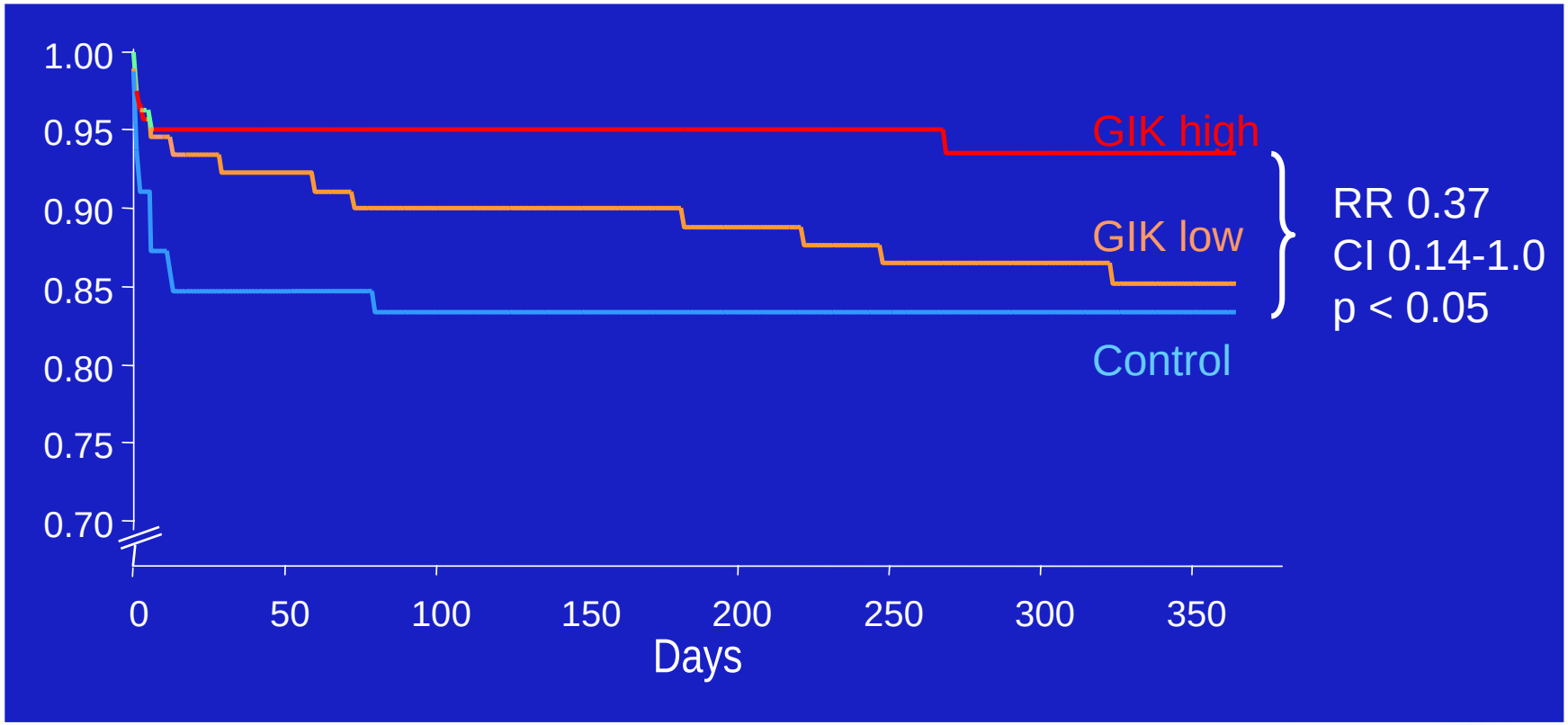
Odds Ratio (95% CI) 0.72 (0.57 - 0.90)
One life saved for 20 treated



(Fath-Ordoubadi et al Circulation 1997; 96:1152)

Glucose-insulin-potassium in myocardial infarction
The ECLA pilot trial

Mortality in reperfused patients (n=262)



(Diaz et al Circulation 1998;98: 2227)

Glucose-insulin-potassium in myocardial infarction
The CREATE-ECLA study

Myocardial infarction

STEMI

n = 20 201

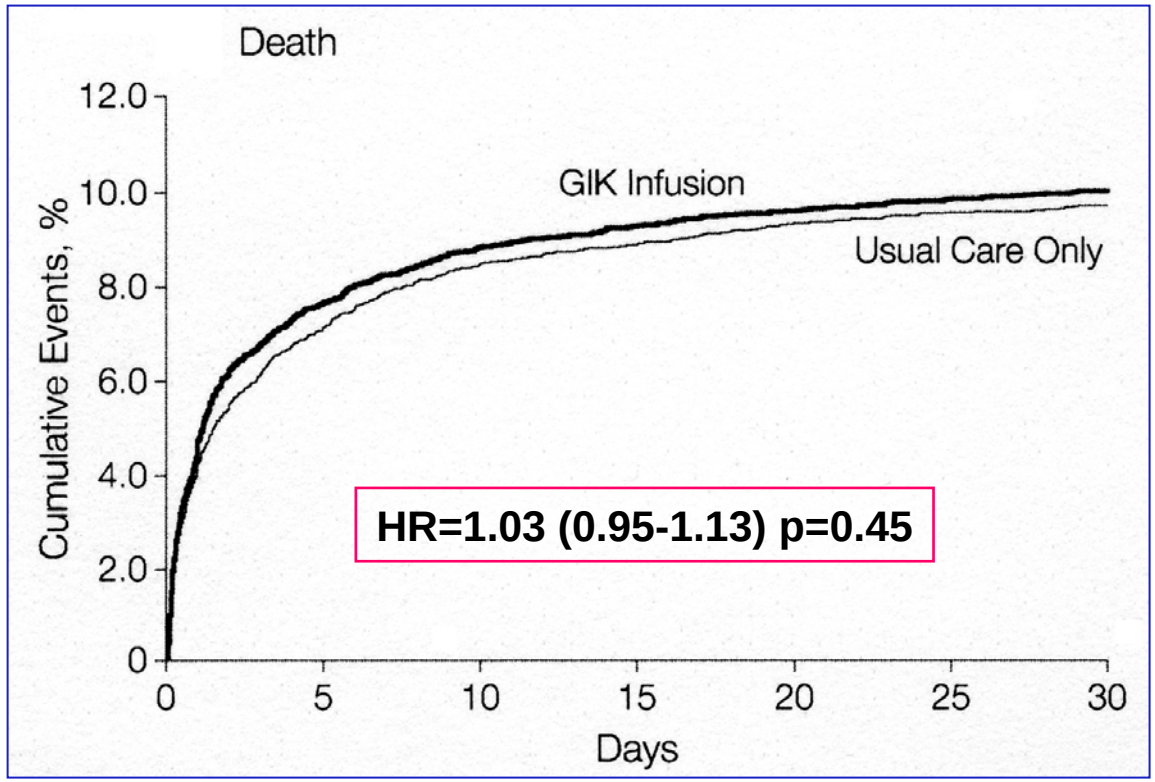
Infusion 24 hours

25 % glucose

Insulin 50 IU/L

80 mEq/L potassium

Rate 1.5 ml/kg/h



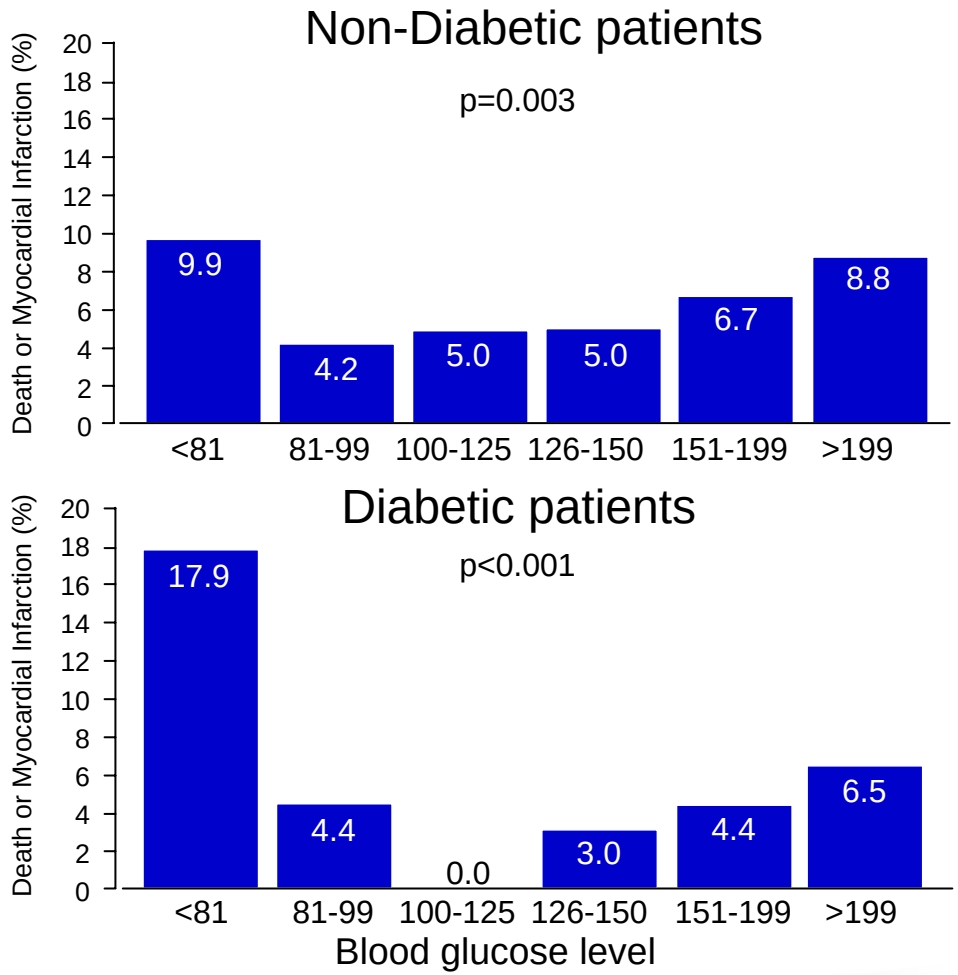
(CREATE-ECLA investigators JAMA 2005;293:437)

What about hypoglycemia?

U-shaped relation blood glucose and adverse outcome in STEMI patients

Data derived from
- TIMI-10A/B
- LIMIT-AMI
- OPUS-TIMI-16

n = 4 224



(Pinto et al J Am Coll Card 2005;46:179)

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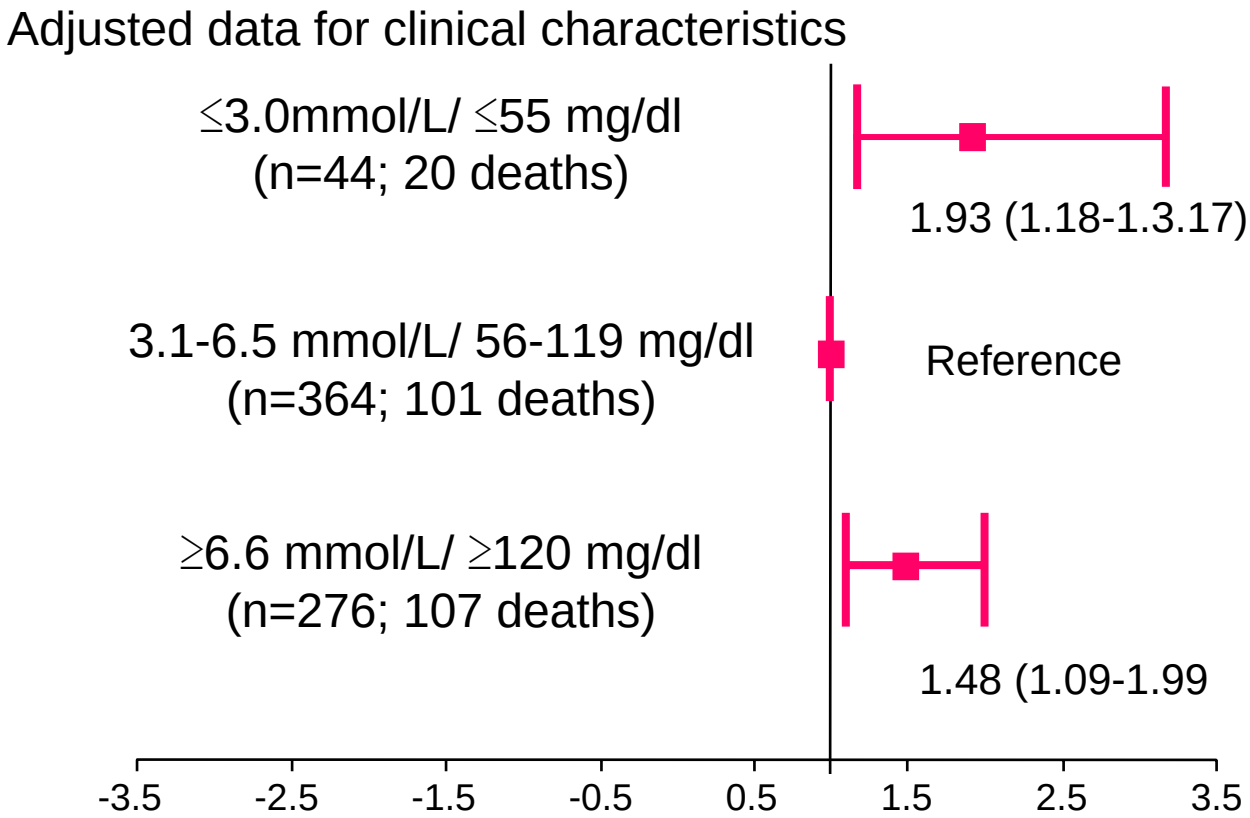
Hyper- and hypoglycaemia and 2 year mortality risk in diabetic patients with acute coronary events

Lowest blood glucose recorded during hospitalisation



(Svensson et al Europ Heart J 2005; 26:1255)

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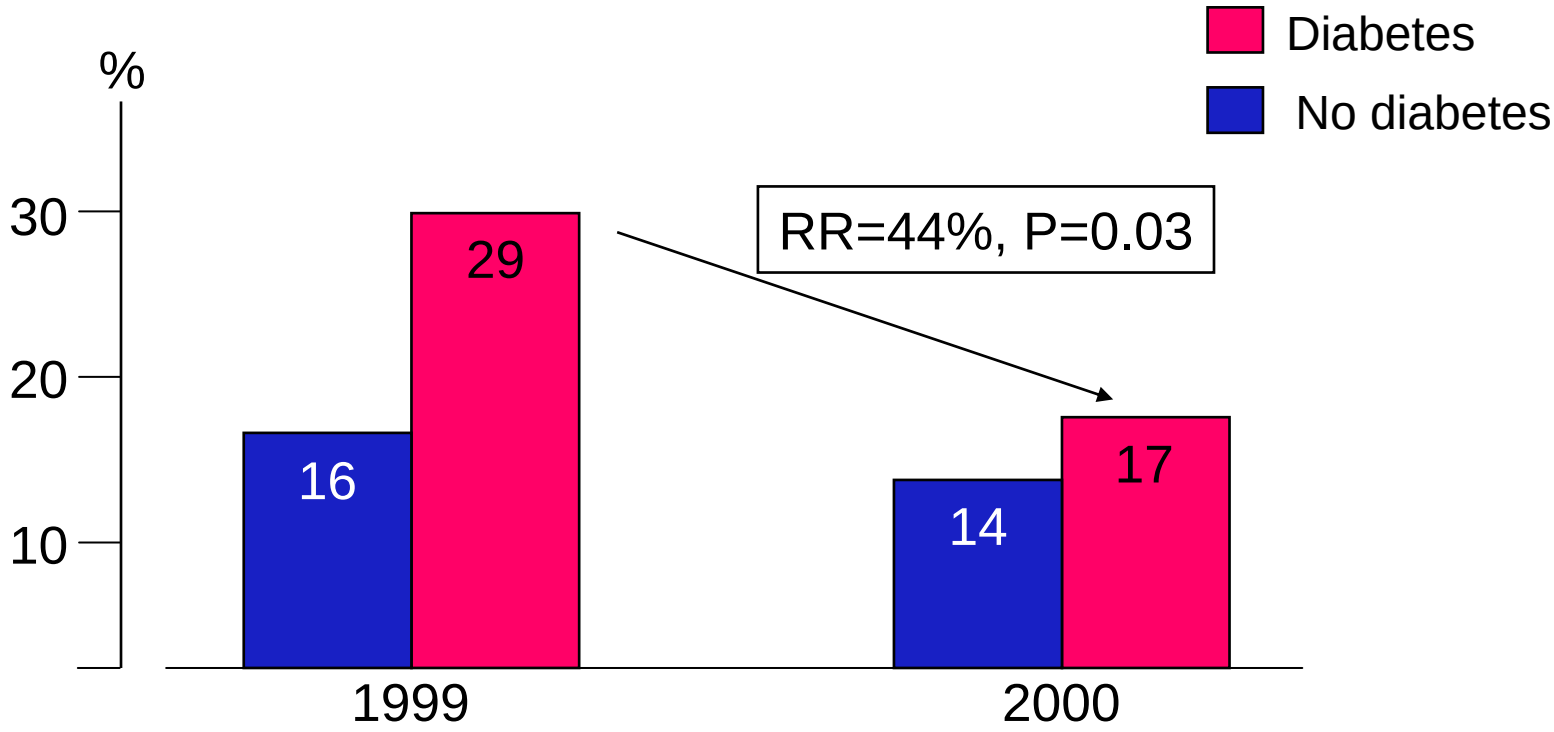
Implementation of modern treatment

The Munich registry

In-hospital mortality



Schnell et al. Diabetes Care. 2004;27:455)

Management of cardiovascular diseases : ACS

What available evidence suggest

- EBM-treatment is very effective and safe
  - Drugs and mechanical interventions

New tools or regimens needed!

- Hyperglycaemia is an important independent risk factor for future events following acute myocardial infarction
- Diabetic patients should have an intensive glucose control after an AMI. Normalisation!?
- Agents used for long-term glucose control may play an important role for future morbidity and mortality

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ESC/EASD Pocket Guidelines
Diabetes, prediabetes and cardiovascular disease
Management of cardiovascular risk
Coronary artery disease

Recommendation	Class	Level
Early risk stratification should be part of the evaluation of the diabetic patient after ACS.	IIa	C
Treatment targets, as listed in Table 1, should be outlined and applied in each diabetic patient following an ACS.	IIa	C
Patients with acute MI and diabetes should be considered for thrombolytic therapy on the same grounds as their non-diabetic counterparts.	IIa	A
Whenever possible, patients with diabetes and ACS should be offered early angiography and mechanical revascularization.	IIa	B
Beta-blockers reduce morbidity and mortality in patients with diabetes and ACS.	IIa	B
Aspirin should be given for the same indications and in similar dosages to diabetic and non-diabetic patients.	IIa	B
Adenosine diphosphate (ADP) receptor dependent platelet aggregation inhibitor (clopidogrel) may be considered in diabetic patients with ACS in addition to aspirin.	IIa	C
The addition of an ACE-inhibitor to other therapies reduces the risk for cardiovascular events in patients with diabetes and established CVD.	I	A
Diabetic patients with acute MI benefit from tight glucometabolic control. This may be accomplished by different treatment strategies.	IIa	B

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