Cardiovascular Management of a Patient with Diabetes

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Summary

- People with diabetes take a lot of medication
  - Compliance and Side Effects
- Most die from CVD
- Everyone is not created equal
  - Calculate individual CVD risk
- Primary vs Secondary Prevention

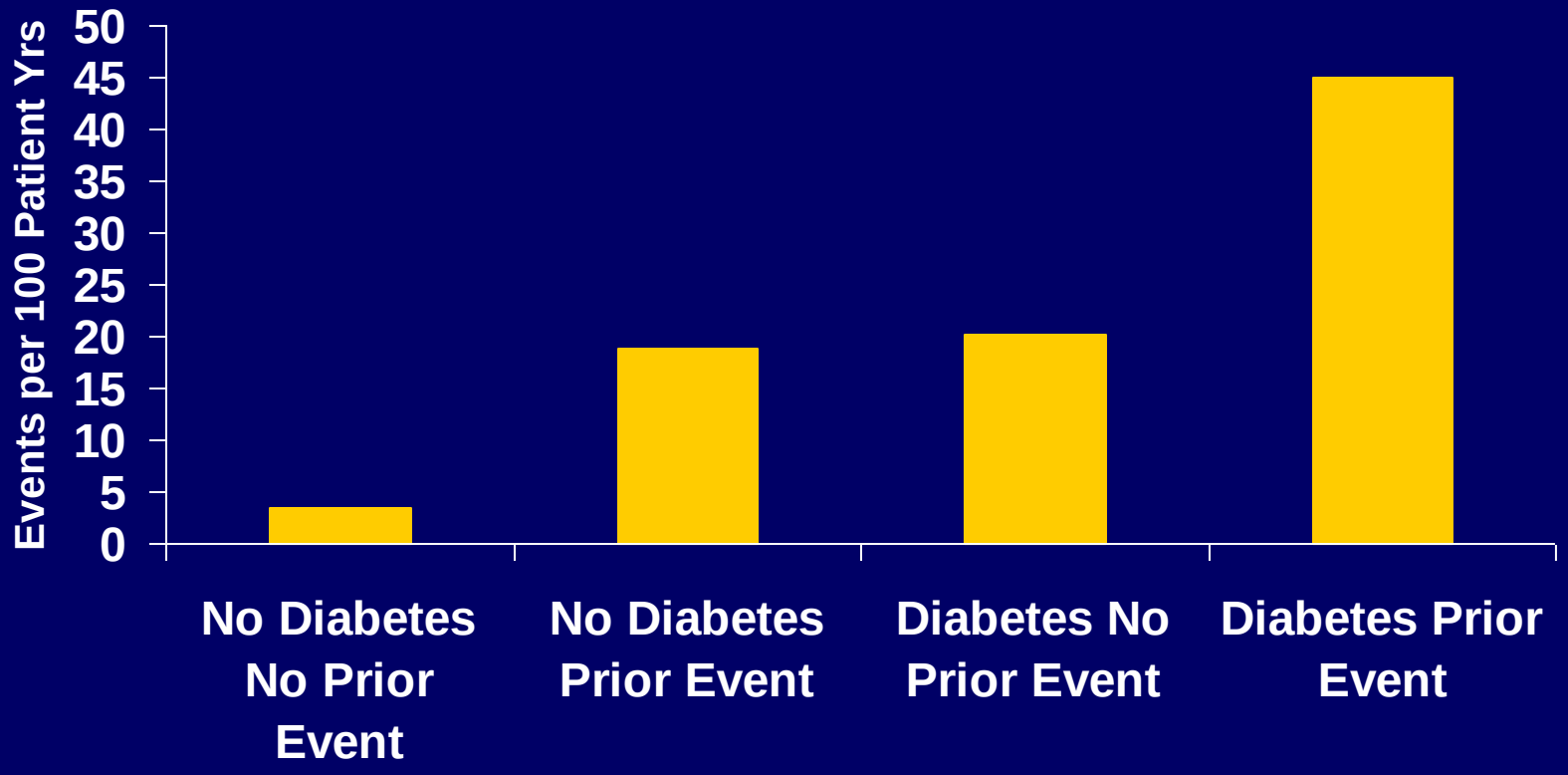
- If you decide to treat – GO HARD!

Summary

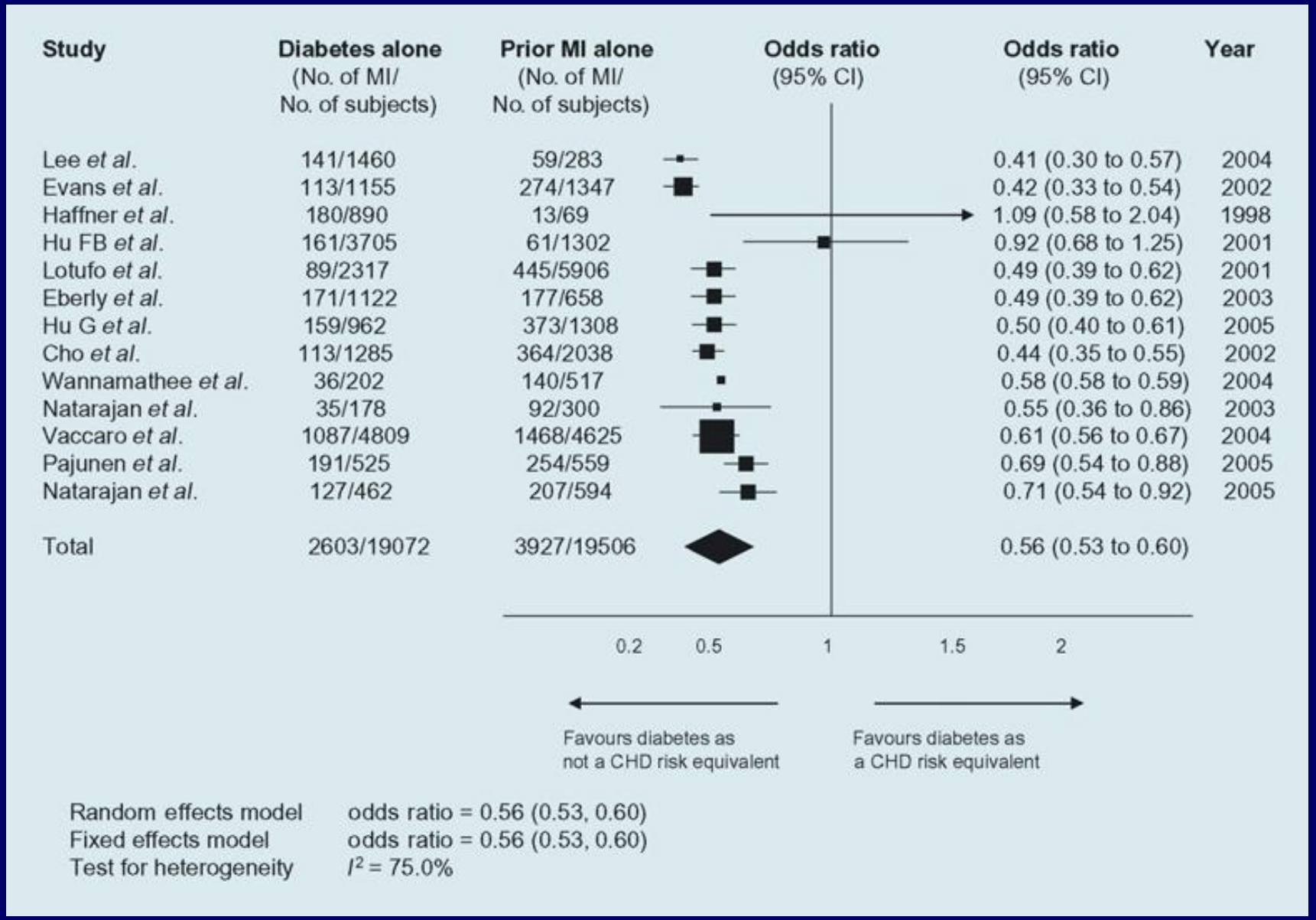
- Weight and Exercise
- Stop Smoking
- Glucose control
  - Legacy effect – Treat early
  - Avoid hypoglycaemia
- Blood Pressure
  - Aim 130/80mmHg
  - But not too low
- Lipids
  - Statin first line
  - Primary vs Secondary – consider your target
    - Maybe Fibrate if TG v high
    - Maybe Ezetimibe or Nicotinic acid
- Aspirin
  - Yes for secondary prevention
  - Probably not for primary unless high risk

MORTALITY FROM CORONARY HEART DISEASE IN SUBJECTS WITH TYPE 2 DIABETES AND IN NONDIABETIC SUBJECTS WITH AND WITHOUT PRIOR MYOCARDIAL INFARCTION

STEVEN M. HAFFNER, M.D., SEPPO LEHTO, M.D., TAPANI RÖNNEMAA, M.D., KALEVI PYÖRÄLÄ, M.D., AND MARKKU LAAKSO, M.D.



Haffner S. NEJM 1998:339;229-34



Bulugahapitiya U. Diabetic Med 2009:26;142-148

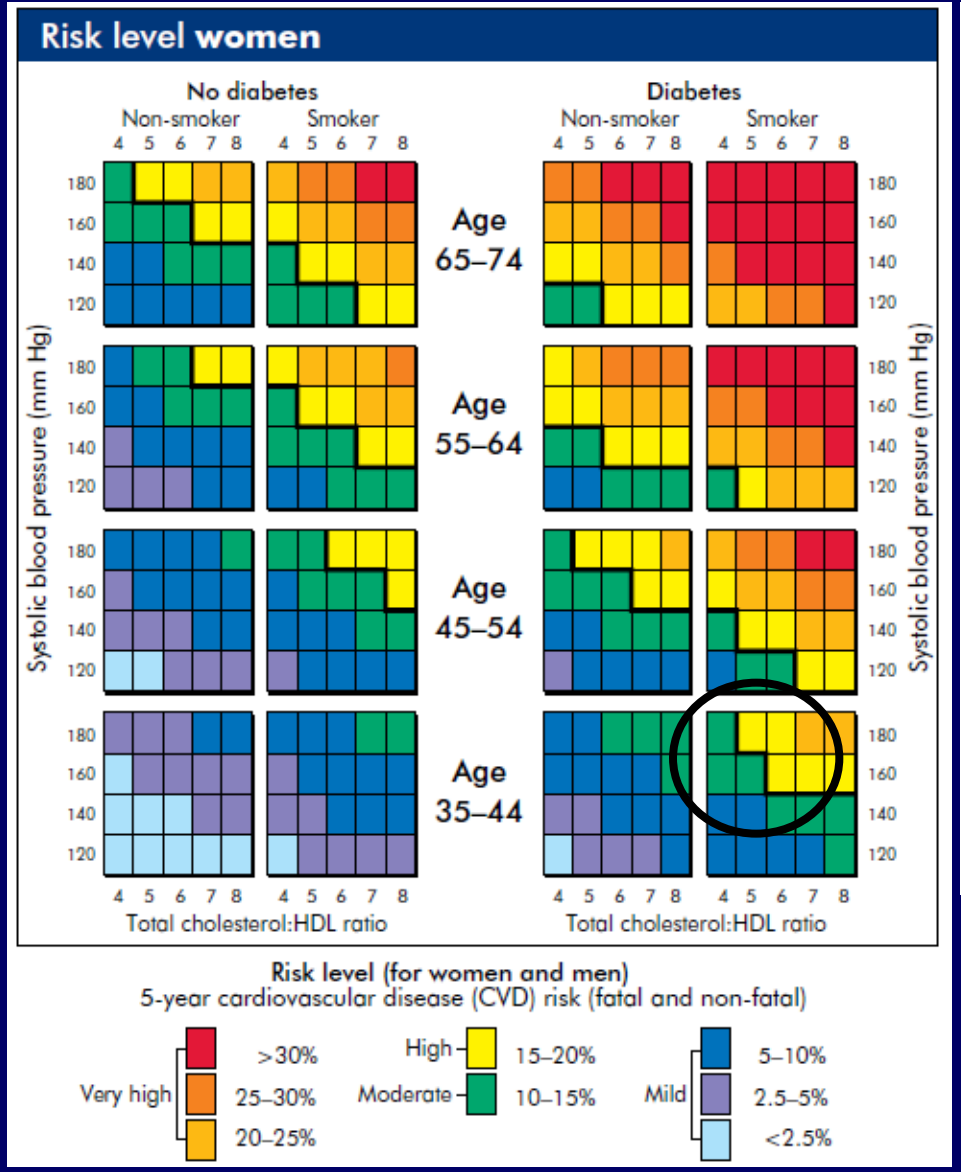
All Things Are Not Created Equal

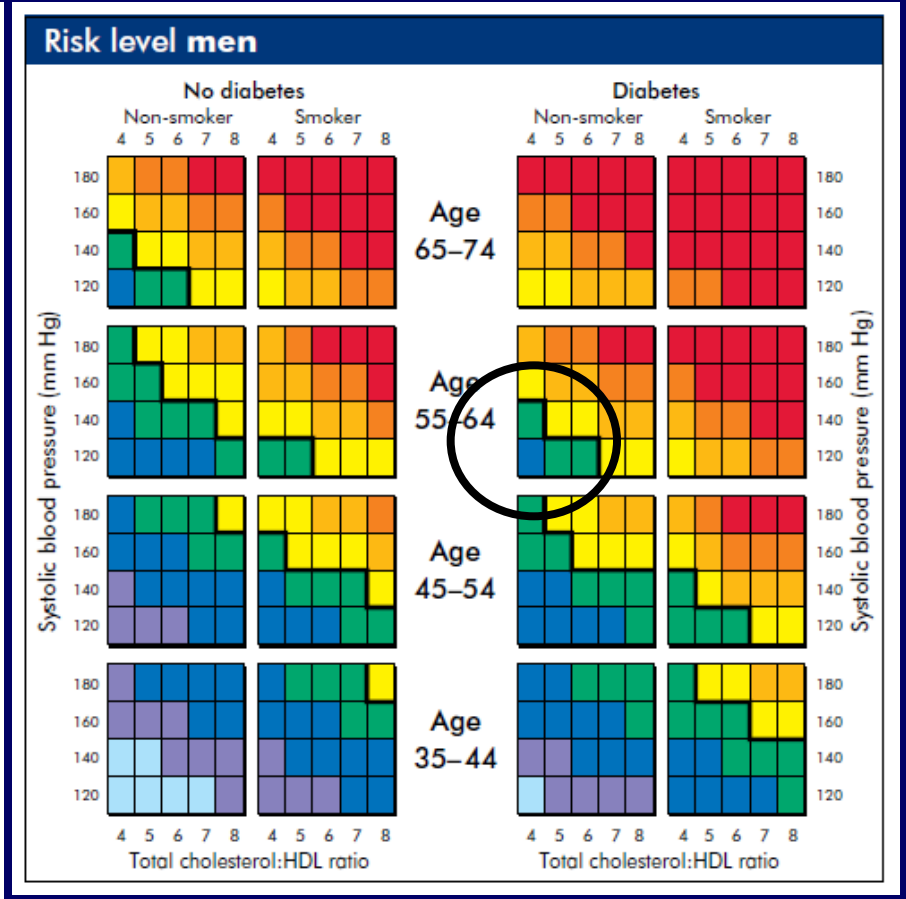

411
412
and friend Maxine enjoying
AL Duathlon Series

All Things Are Not Created Equal

- **Mrs T 39yr**
  - Type 2 diabetes 11 years
  - BMI 36 kg/m^2
  - Smoker
  - BP 148/84 mmHg
  - TC 4.9 mmol/l
  - TG 2.3 mmol/l
  - HDL 0.8 mmol/l
  - LDL 2.8 mmol/L
  - UACR 4.5

- **Mr T 63yr**
  - Type 2 diabetes 4 years
  - BMI 29 kg/m^2
  - BP 132/76 mmHg
  - TC 4.8 mmol/l
  - TG 0.9 mmol/l
  - HDL 1.4 mmol/L
  - LDL 2.8 mmol/L
  - UACR 1.8


Risk level women
No diabetes
Diabetes
Non-smoker
Smoker
Age 65–74
Age 55–64
Age 45–54
Age 35–44
Systolic blood pressure (mm Hg)
Total cholesterol:HDL ratio
Risk level (for women and men)
5-year cardiovascular disease (CVD) risk (fatal and non-fatal)
Very high
>30%
25–30%
20–25%
High
15–20%
Moderate
10–15%
Mild
5–10%
2.5–5%
<2.5%


Risk level men
No diabetes
Diabetes
Non-smoker
Smoker
Age 65–74
Age 55–64
Age 45–54
Age 35–44
Systolic blood pressure (mm Hg)
Total cholesterol:HDL ratio

Targets for CVD Risk Factors for Patients with Diabetes

Approach to setting treatment targets

- Setting treatment targets is an important component of diabetes management for all patients
- Targets given for specific parameters are based on best available evidence but should be appropriate for the individual patient

Treatment targets

Treatment targets to address risk factors:

- should be appropriate for and agreed with the individual patient
- glycaemic control target: HbA1c 50–55 mmol/mol or as individually agreed
- blood pressure target: <130/80 mm Hg. Evidence suggests a BP target <120 mm Hg may be harmful. Care should be taken to estimate likely treatment response for patients when BP approaches the target of <130 mm Hg
- lipids target: triglycerides <1.7 mmol/L; total cholesterol <4.0 mmol/L.

NZ Primary Care Guidelines 2012

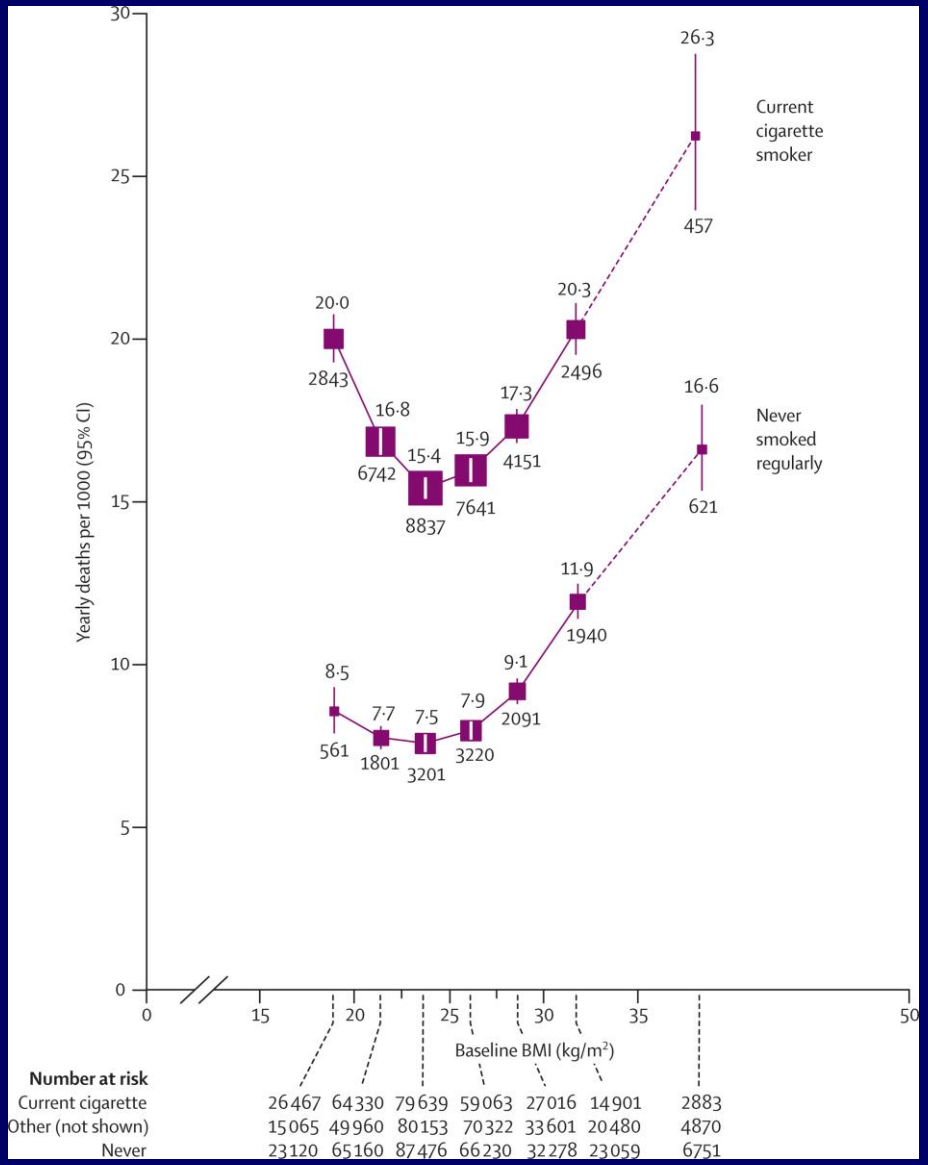
Table 8 Optimal levels (targets) for people with known cardiovascular disease, or cardiovascular risk >15% or diabetes

	Known cardiovascular disease or cardiovascular risk >15% or diabetes*
Lipids	
Total cholesterol	<4.0 mmol/L
LDL cholesterol	<2.0 mmol/L
HDL cholesterol	≥1.0 mmol/L
TC:HDL ratio	<4.0
Triglycerides	<1.7 mmol/L
Blood pressure	
BP	<130/80 mm Hg
Glycaemic control in people with diabetes	
HbA1c	50–55 mmol/mol or as individually agreed
Smoking cessation	
Smoking cessation should be strongly and repeatedly recommended at any level of CVD risk. All people who smoke should be advised to quit and offered treatment to help them stop completely. Reducing cigarette consumption is not a recommended treatment strategy	

* Content on diabetes has been updated to align with 2011 guidance on the management of people with type 2 diabetes (see Chapter 4 *Management of type 2 diabetes*).

NZ Primary Care Guidelines 2012

Smoking

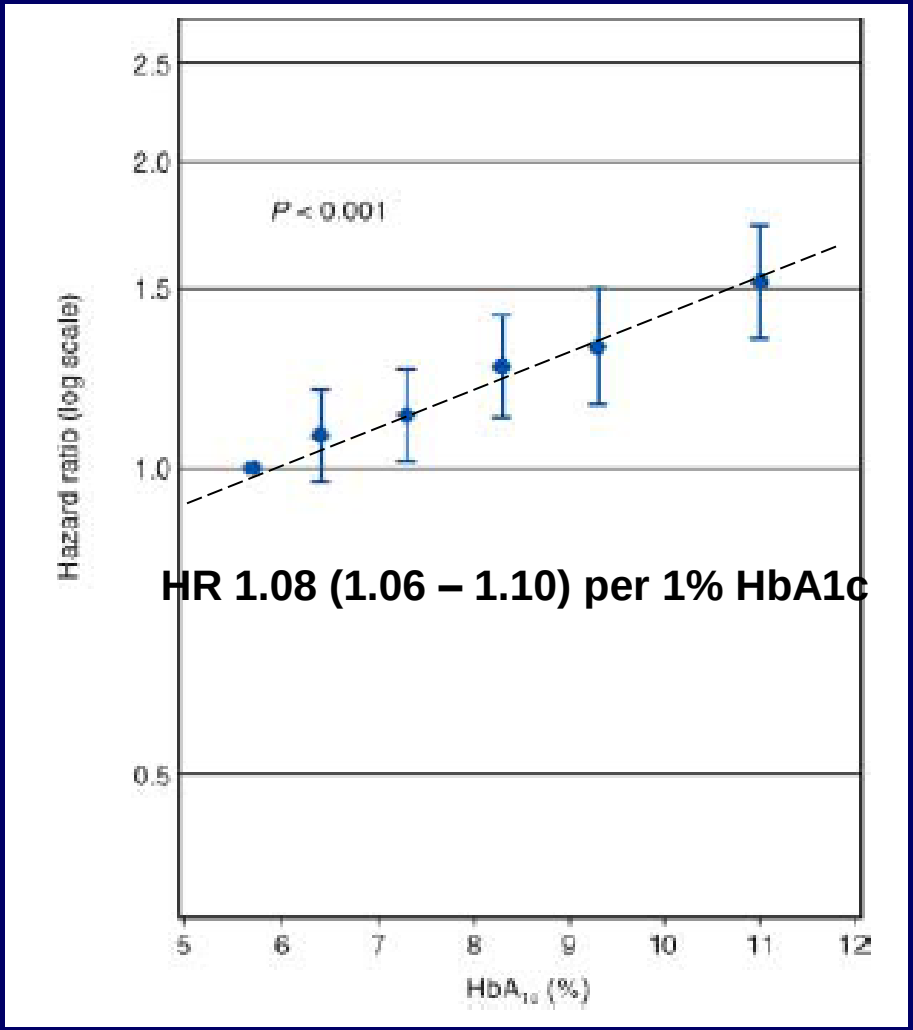


- Baseline BMI vs Mortality
- 57 Prospective studies
- 894 576 individuals
- Mean age 46 yrs

Prospective Studies Collaboration. Lancet 2009 373;1083

Glucose Control

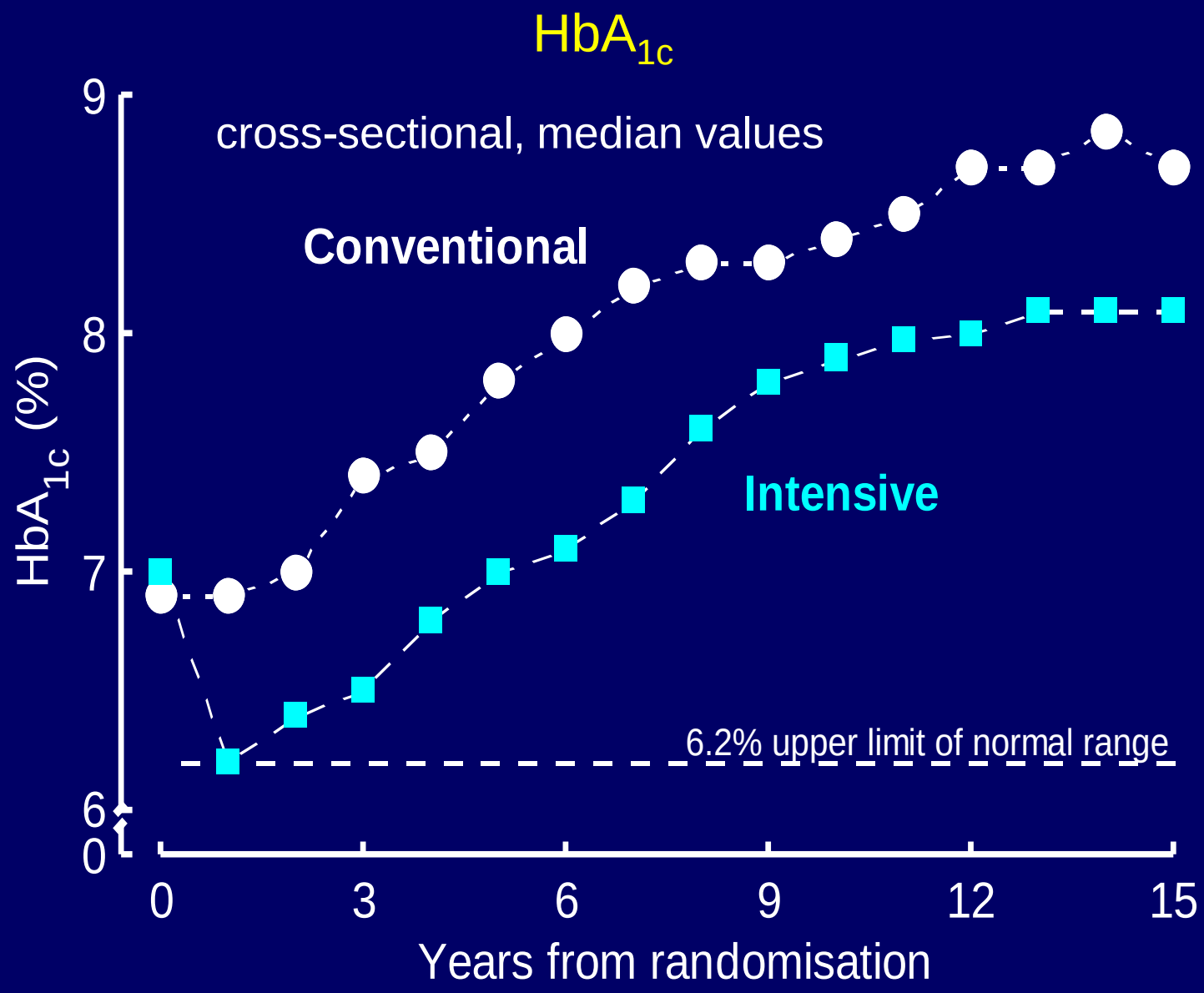
NZ Cohort Study (Get Checked) adjusted hazard ratio for CV events by HbA1c.



- n= 48 444
- n= 5667 first events
- Median follow up 2.4yrs

Elley CR. Diabetic Med 2008.

UKPDS


HbA1c
cross-sectional, median values
Conventional
Intensive
6.2% upper limit of normal range
HbA1c (%)
9
8
7
6
0
0
3
6
9
12
15
Years from randomisation

UKPDS Glucose Control Study
Summary

12% for any diabetes related endpoint (p=0.029)

16% for myocardial infarction (p=0.052)

25% for microvascular endpoints (p=0.0099)

24% for cataract extraction (p=0.046)

21% for retinopathy at twelve years (p=0.015)

33% for albuminuria at twelve years (p=0.000054)

Legacy Effect of Earlier Glucose Control

After median 8.5 years post-trial follow-up

Aggregate Endpoint		1997	2007
Any diabetes related endpoint	*RRR:*	12%	**9%**
	P:	0.029	**0.040**
Microvascular disease	*RRR:*	25%	**24%**
	P:	0.0099	**0.001**
Myocardial infarction	*RRR:*	16%	**15%**
	P:	0.052	**0.014**
All-cause mortality	*RRR:*	6%	**13%**
	P:	0.44	**0.007**

RRR = Relative Risk Reduction, P = Log Rank

Recent Trials of Glycaemic Control

- Advance, Accord
- 10 year post diagnosis, middle age
- Despite intensive HBA1c management have failed to show CVD benefit

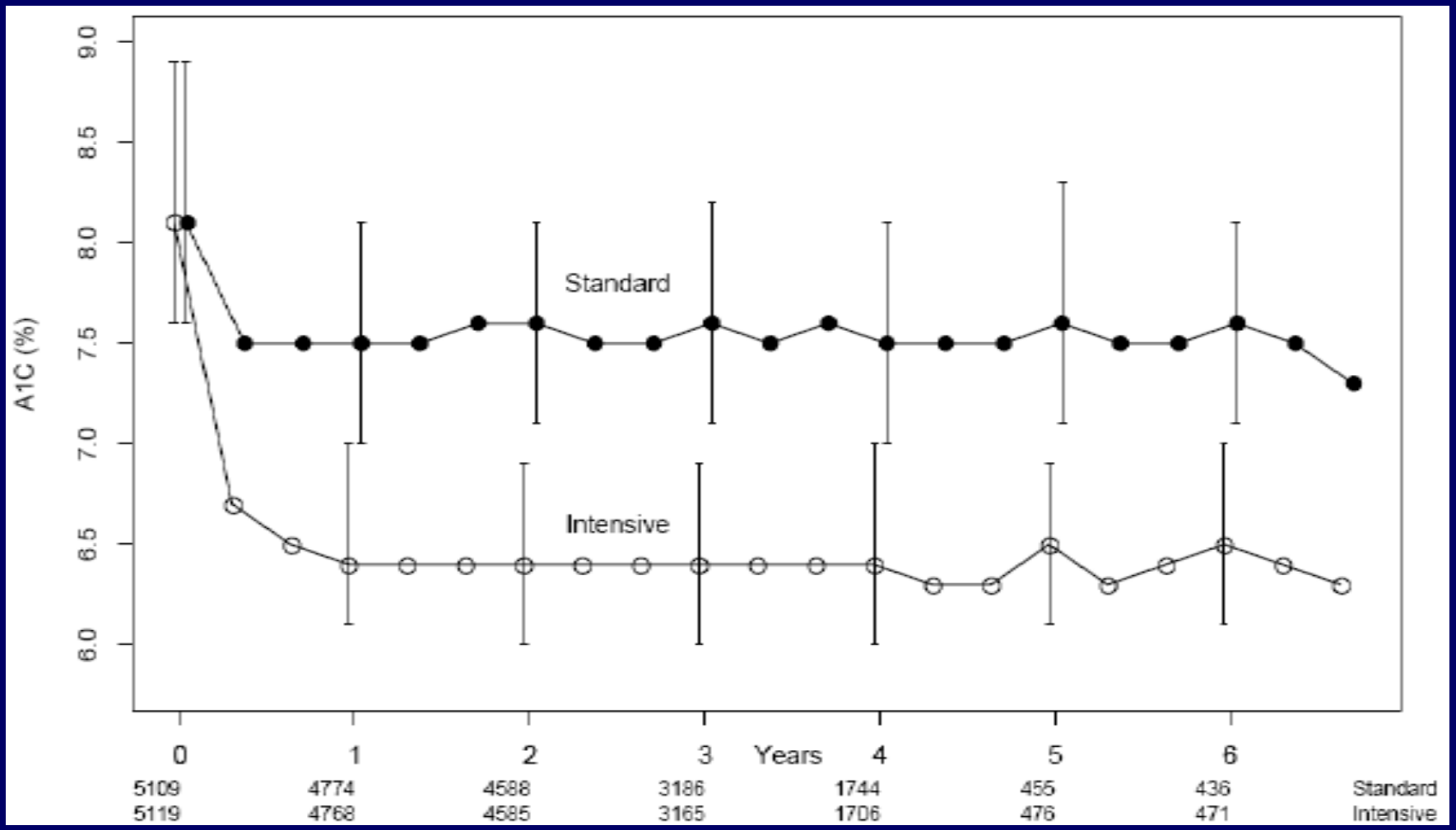
ACCORD Study

The Action to Control Cardiovascular Risk in Diabetes Study Group

- N=10,000
  - 1/3 already on insulin
  - 1/3 prevalent CVD events
  - Mean Age 62
  - Diabetes for 10 years
  - HbA1c 8.3

Strategy of (ultra) intensive glycaemic control aiming for HbA1c 6 (achieved 6.3)

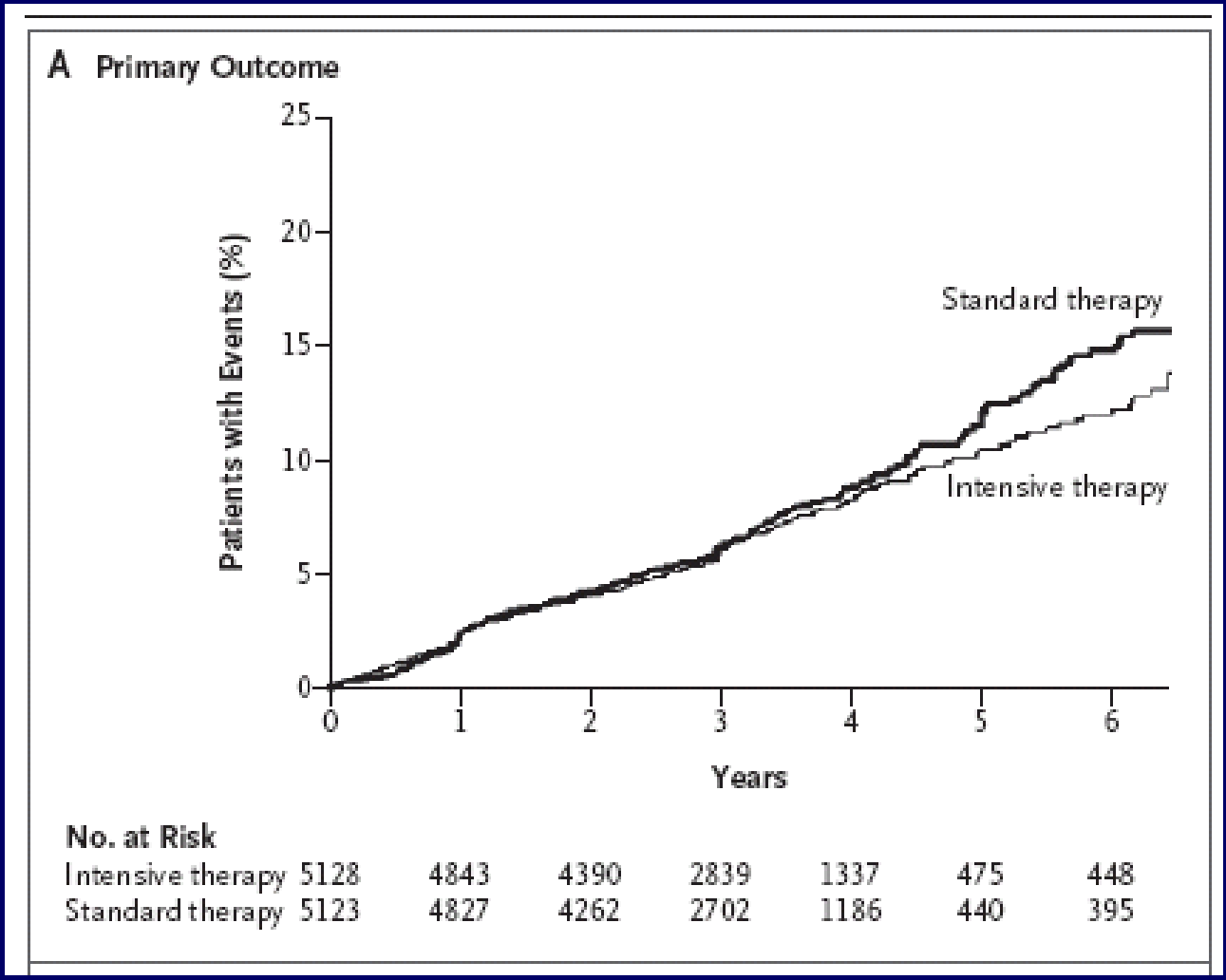
ACCORD Study



The mean difference during the trial was 1.1%

Accord June 2008

Primary Outcome: First occurrence of nonfatal MI, stroke or death from Cardiovascular cause



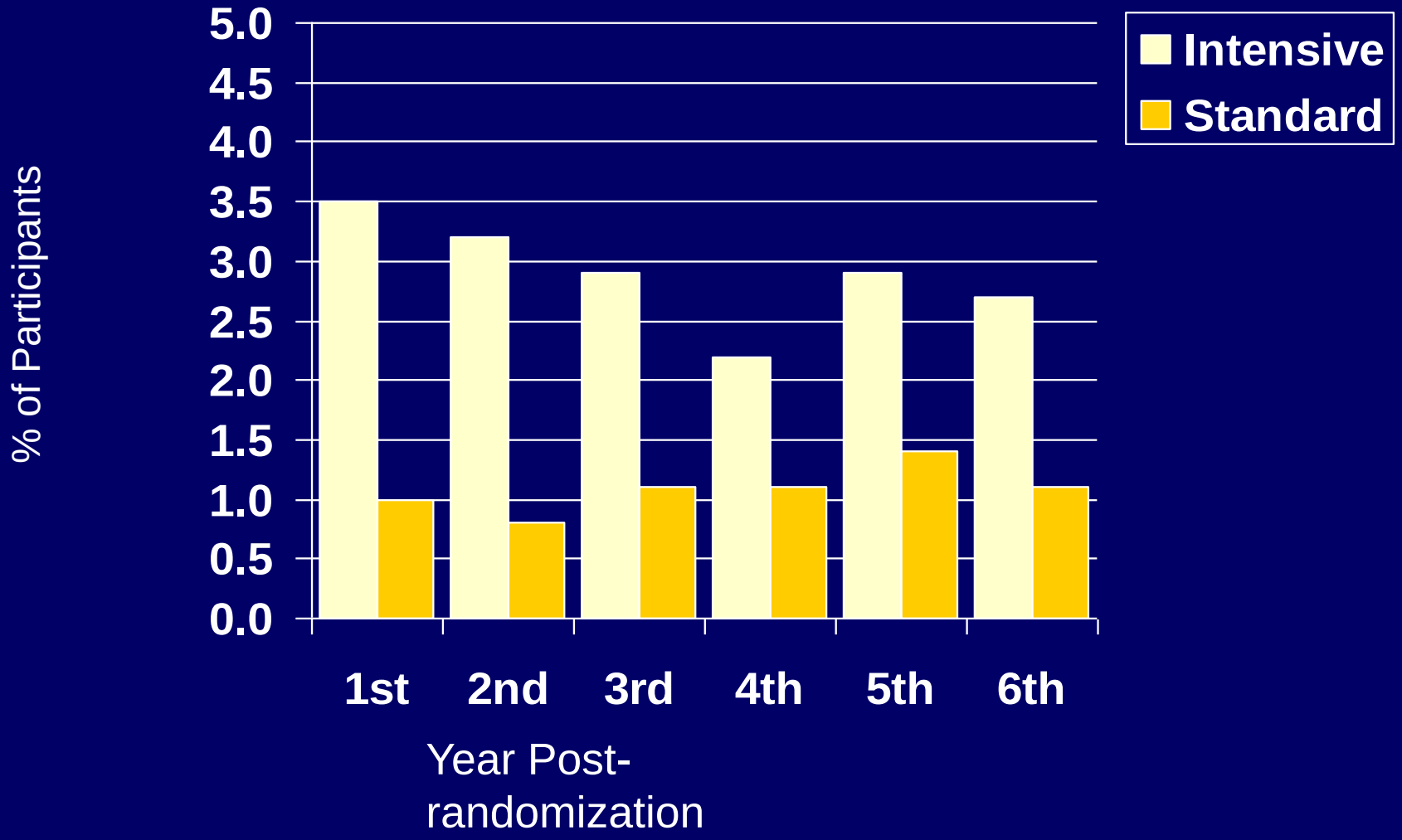
352 vs 371 events

HR 0.9 (0.78-1.04, p=0.16)

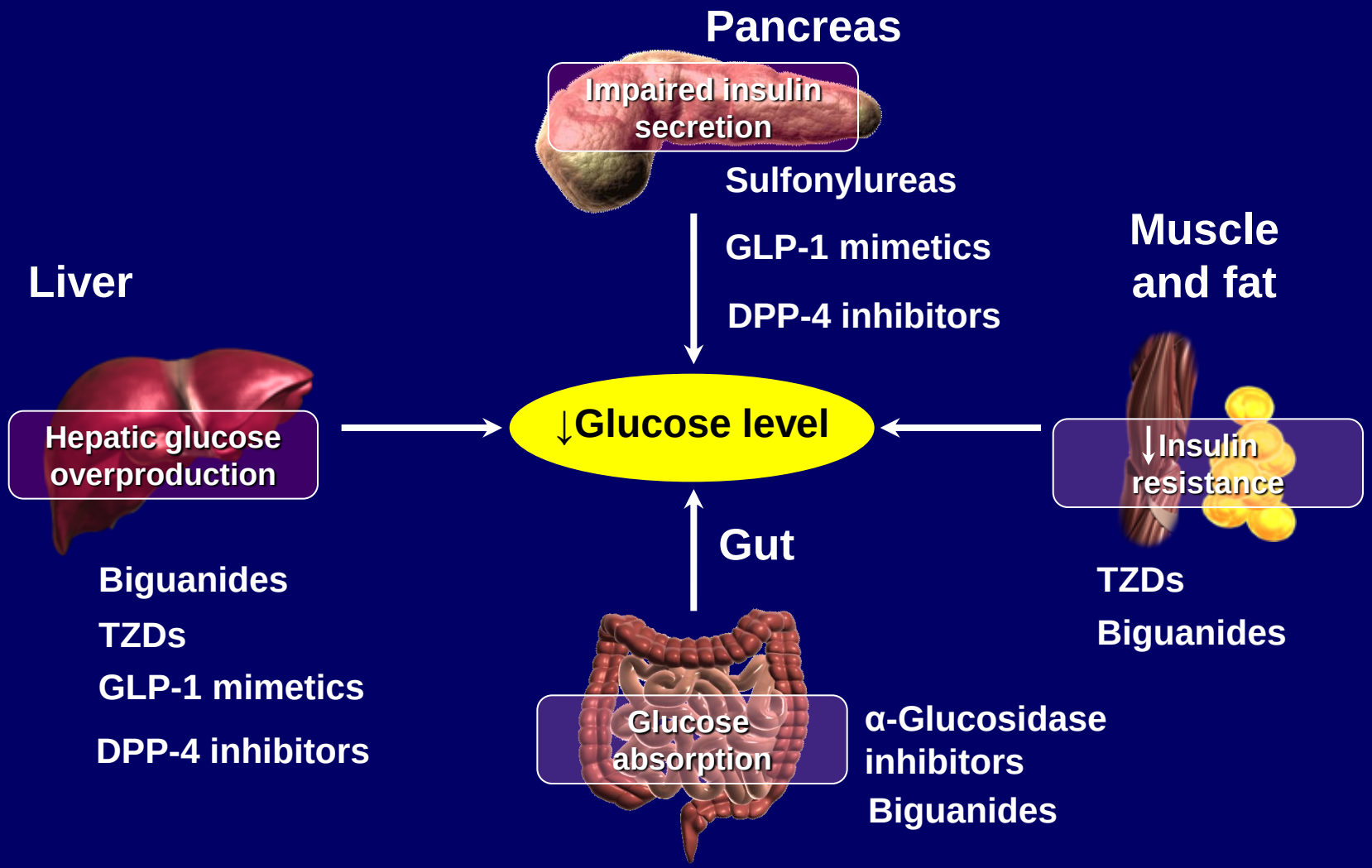
Accord Study
Primary and Secondary Outcomes

	Intensive N (%)	Standard N (%)	HR (95% CI)	P
Primary	352 (6.86)	371 (7.23)	0.90 (0.78-1.04)	0.16
Secondary				
Mortality	257 (5.01)	203 (3.96)	1.22 (1.01-1.46)	0.04
Nonfatal MI	186 (3.63)	235 (4.59)	0.76 (0.62-0.92)	0.004
Nonfatal Stroke	67 (1.31)	61 (1.19)	1.06 (0.75-1.50)	0.74
CVD Death	135 (2.63)	94 (1.83)	1.35 (1.04-1.76)	0.02
CHF	152 (2.96)	124 (2.42)	1.18 (0.93-1.49)	0.17

Incidence of Hypoglycaemia (first event) per Year



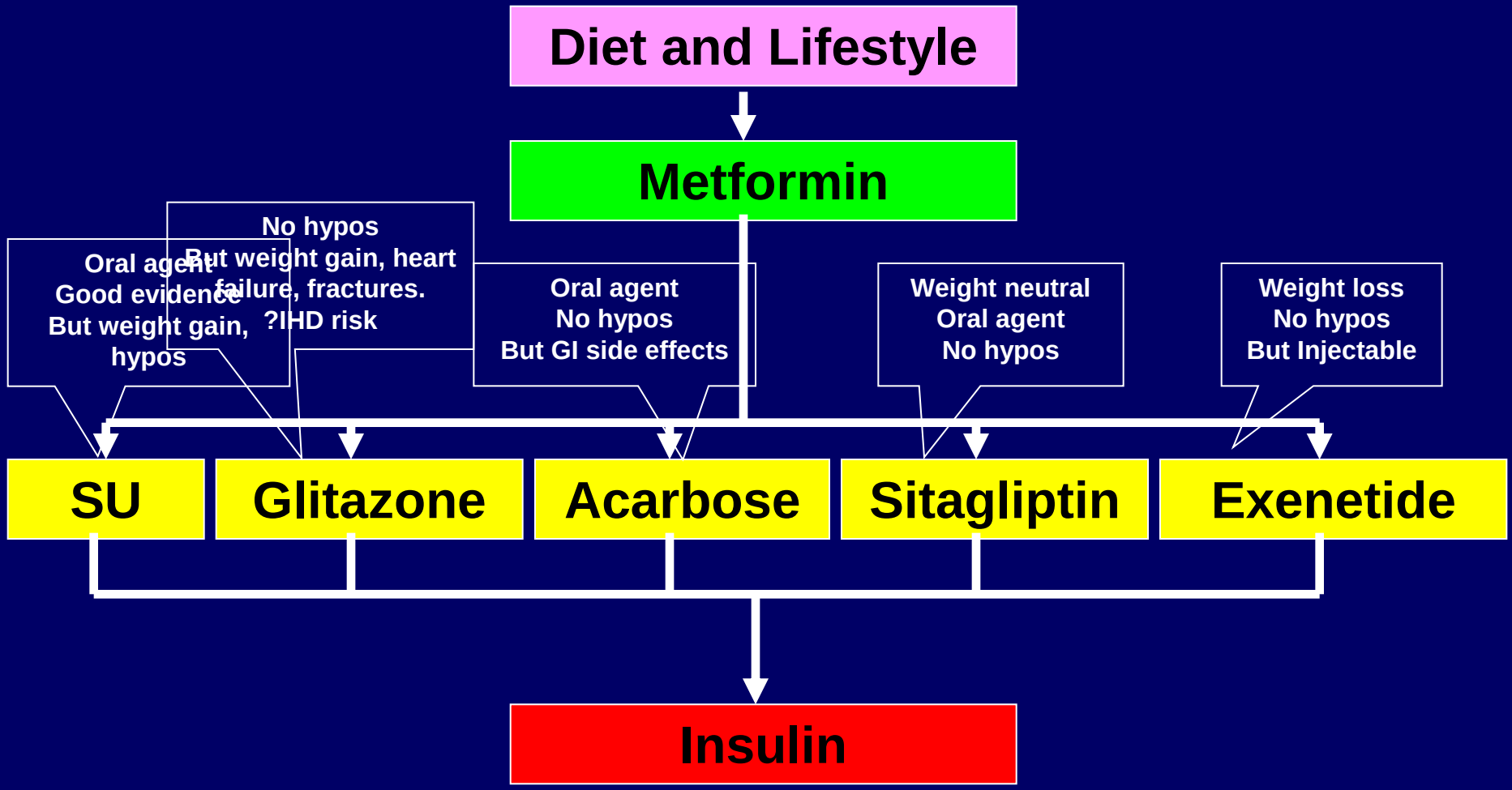
Major Targeted Sites of Oral Drug Classes



DPP-4=dipeptidyl peptidase 4; TZDs=thiazolidinediones.

Buse JB et al. In: *Williams Textbook of Endocrinology*. 10th ed. Philadelphia: WB Saunders; 2003:1427–1483; DeFronzo RA. *Ann Intern Med*. 1999;131:281–303; Inzucchi SE. *JAMA* 2002;287:360-372; Porte D et al. *Clin Invest Med*. 1995;18:247–254.

Type 2 Diabetes Algorithm



Blood Pressure

UKPDS

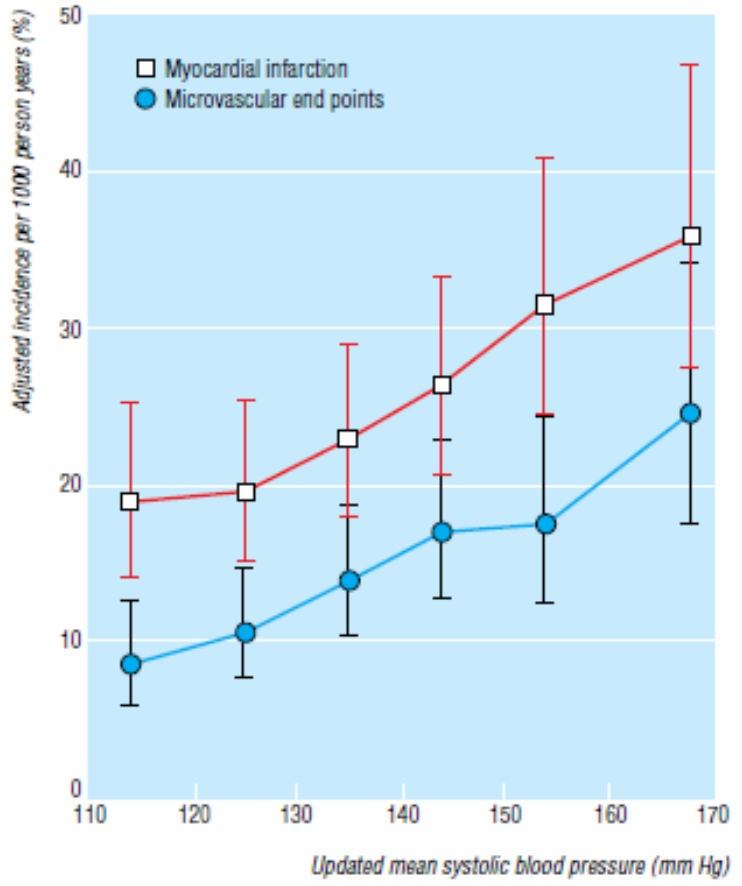
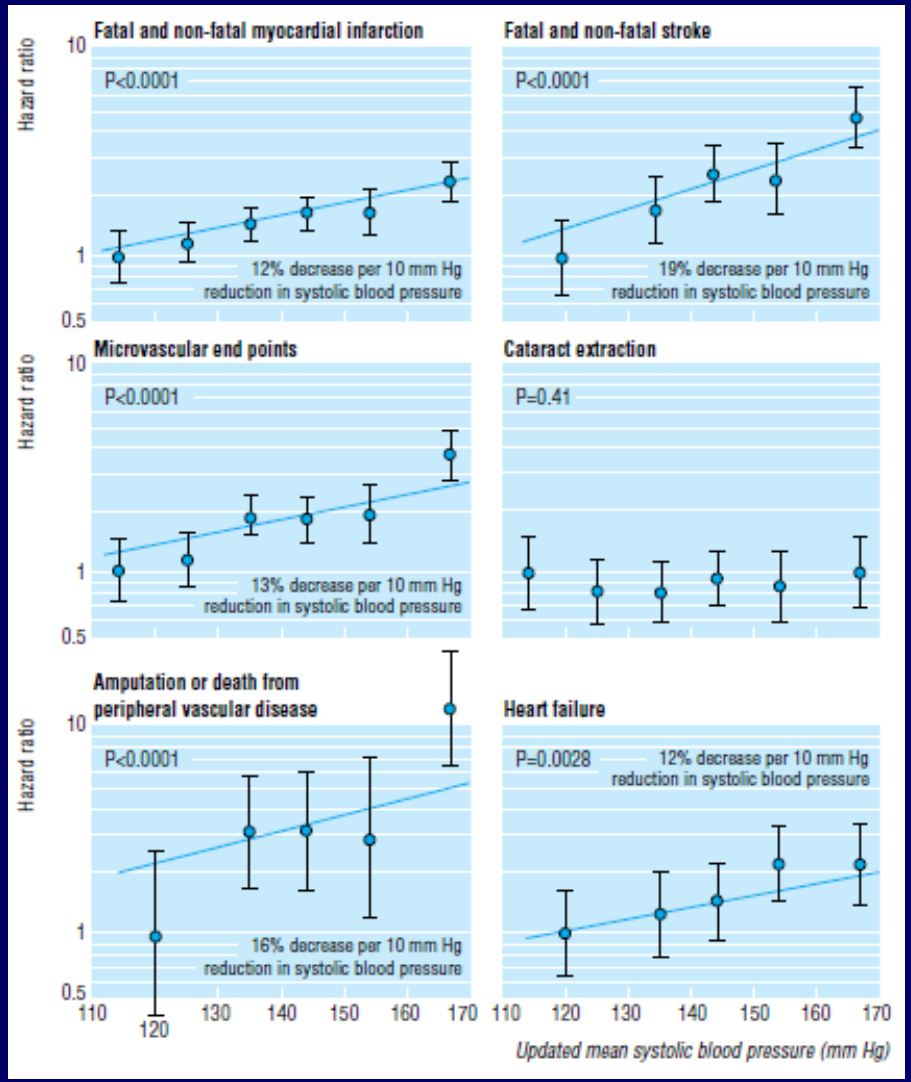
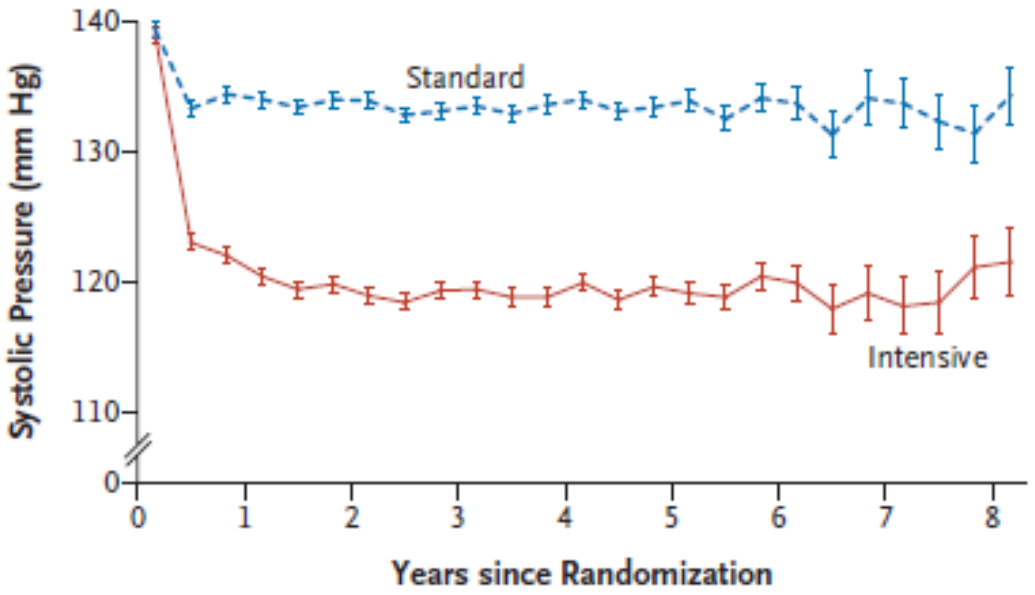


Fig 2 Incidence rates (95% confidence interval) of myocardial infarction and microvascular end points by category of updated mean systolic blood pressure, adjusted for age, sex, and ethnic group expressed for white men aged 50-54 years at diagnosis and mean duration of diabetes of 10 years



ACCORD BP trial



Mean No. of Medications Prescribed								
Intensive	3.2	3.4	3.4	3.5	3.5	3.5	3.4	3.4
Standard	1.9	2.1	2.1	2.2	2.2	2.3	2.3	2.3
No. of Patients								
Intensive	2174	2071	1973	1792	1150	445	156	156
Standard	2208	2136	2077	1860	1241	504	203	201

Figure 1. Mean Systolic Blood-Pressure Levels at Each Study Visit.

I bars indicate 95% confidence intervals.

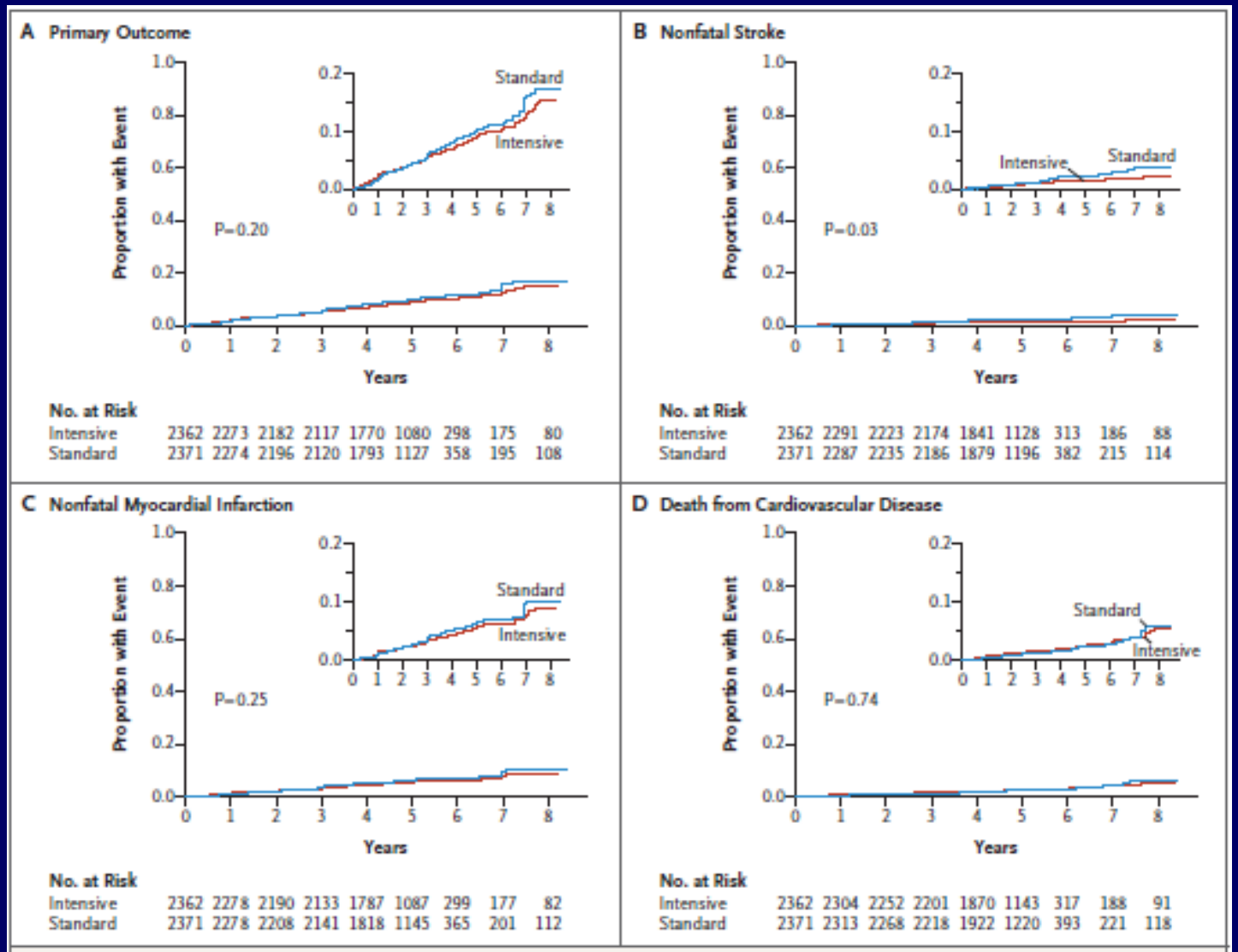


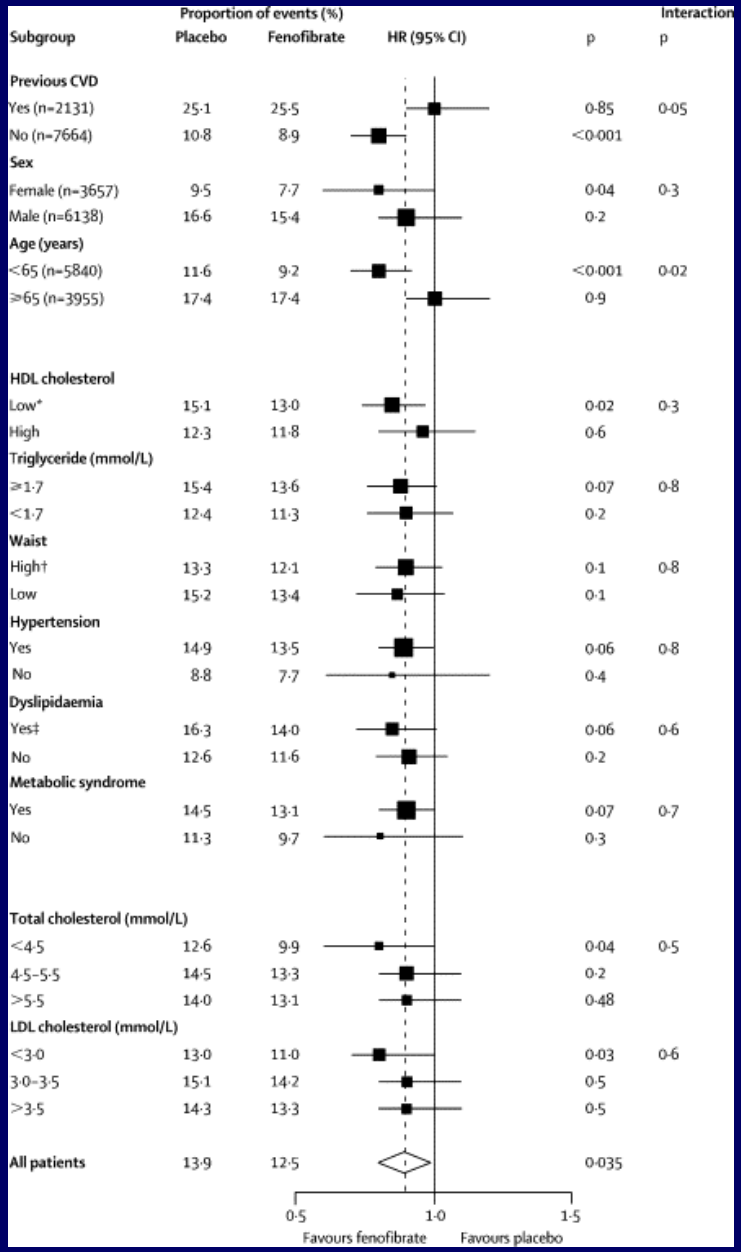
Figure 2. Kaplan–Meier Analyses of Selected Outcomes.

Shown are the proportions of patients with events for the primary composite outcome (Panel A) and for the individual components of the primary outcome (Panels B, C, and D). The insets show close-up versions of the graphs in each panel.

Lipids

Dyslipidaemia in Diabetes

- Typical dyslipidaemia in type 2 diabetes
  - Elevated Triglycerides
  - Suppressed HDL cholesterol
  - Total and LDL cholesterol more variable
- So TREAT THE TG AND HDL



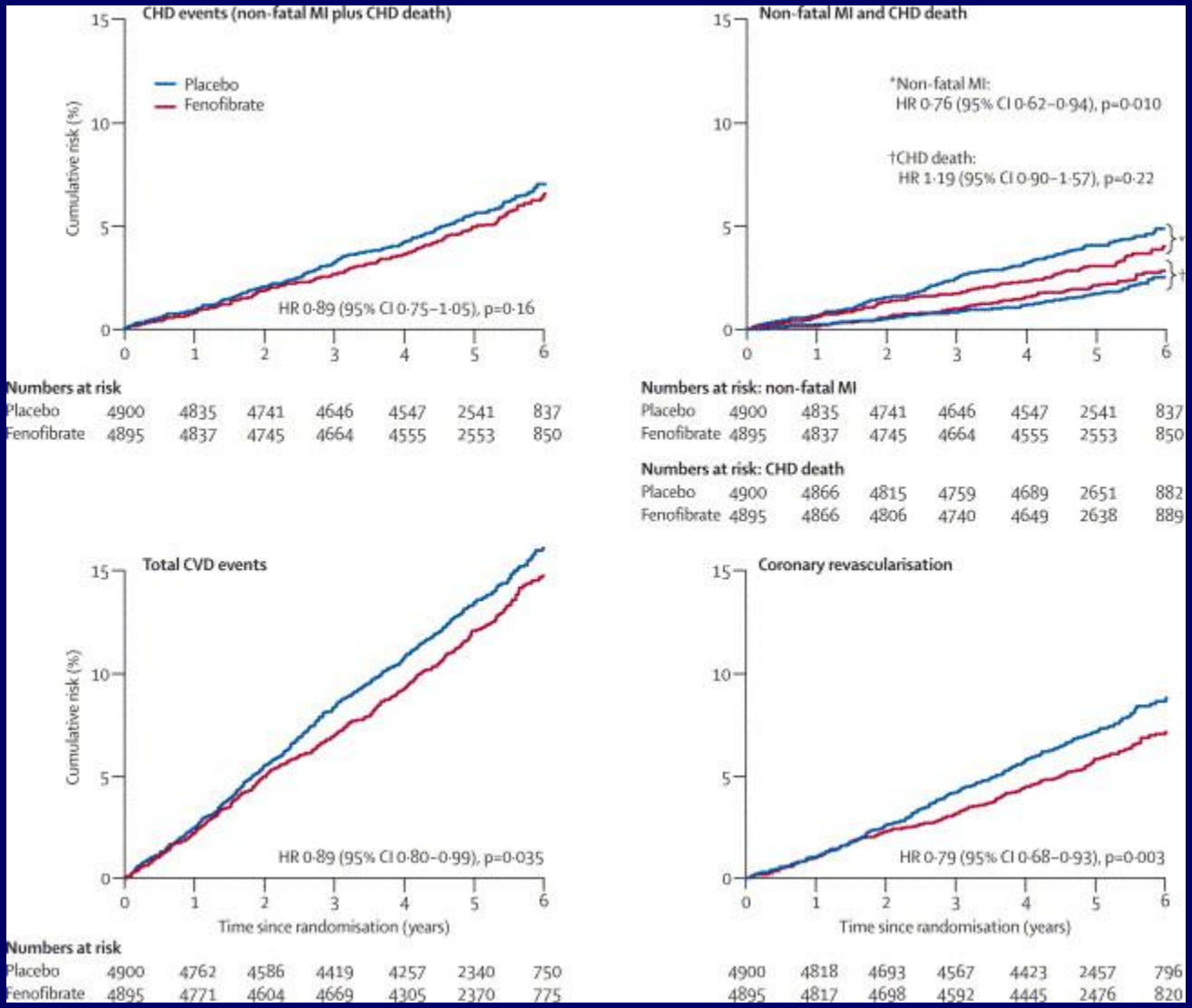
Total CV events. Death, MI, Stroke, Revascularisation

FIELD Study

- Fenofibrate vs Placebo
- N=9795 age 50-75yrs
  - 2131 pre CVD
  - 7664 no CVD
- Not on a statin
  - (17% placebo and 8% fibrate group started)
- Primary Outcome Death or nonfatal MI
  - RR 0.89 (0.75-1.05)

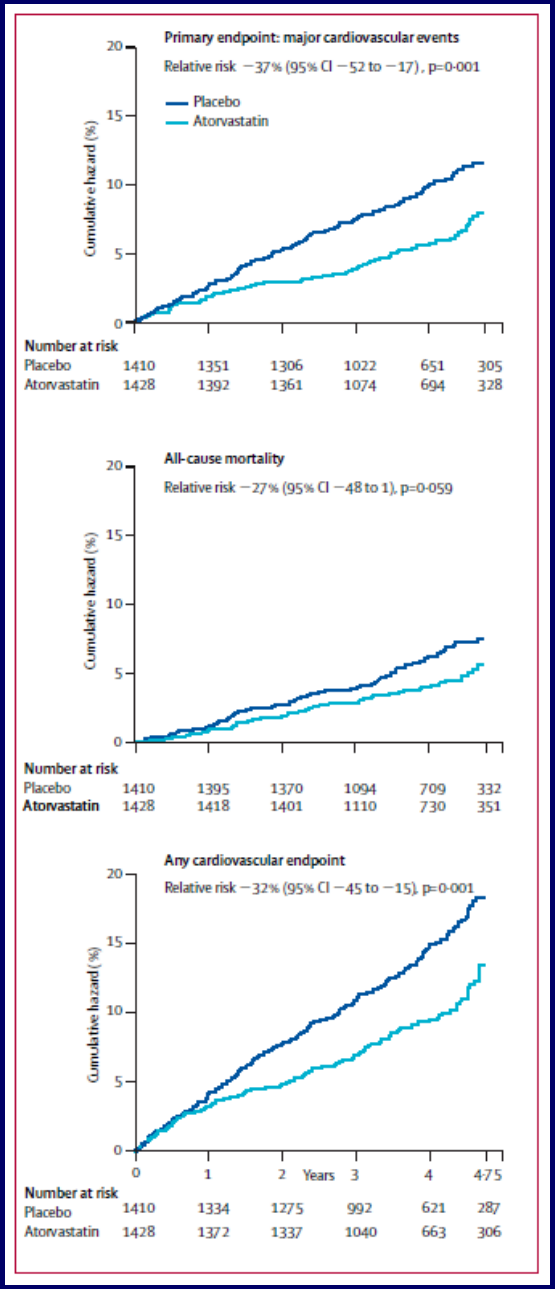
Lancet 2005: 366;1849-61

FIELD Study


CHD events (non-fatal MI plus CHD death)
Placebo
Fenofibrate
Cumulative risk (%)
HR 0·89 (95% CI 0·75–1·05), p=0·16
Numbers at risk
Placebo 4900 4835 4741 4646 4547 2541 837
Fenofibrate 4895 4837 4745 4664 4555 2553 850
Non-fatal MI and CHD death
*Non-fatal MI:
HR 0·76 (95% CI 0·62–0·94), p=0·010
†CHD death:
HR 1·19 (95% CI 0·90–1·57), p=0·22
Numbers at risk: non-fatal MI
Placebo 4900 4835 4741 4646 4547 2541 837
Fenofibrate 4895 4837 4745 4664 4555 2553 850
Numbers at risk: CHD death
Placebo 4900 4866 4815 4759 4689 2651 882
Fenofibrate 4895 4866 4806 4740 4649 2638 889
Total CVD events
Cumulative risk (%)
HR 0·89 (95% CI 0·80–0·99), p=0·035
Time since randomisation (years)
Numbers at risk
Placebo 4900 4762 4586 4419 4257 2340 750
Fenofibrate 4895 4771 4604 4669 4305 2370 775
Coronary revascularisation
HR 0·79 (95% CI 0·68–0·93), p=0·003
Time since randomisation (years)
4900 4818 4693 4567 4423 2457 796
4895 4817 4698 4592 4445 2476 820

Statins in Diabetes

- Secondary Prevention
  - Yes – Go for it!
    - Let the cardiologist zealots drive your LDL down!
- Primary Prevention
  - Yes – Maybe
    - Listen to your heart (and your Endocrinologist)



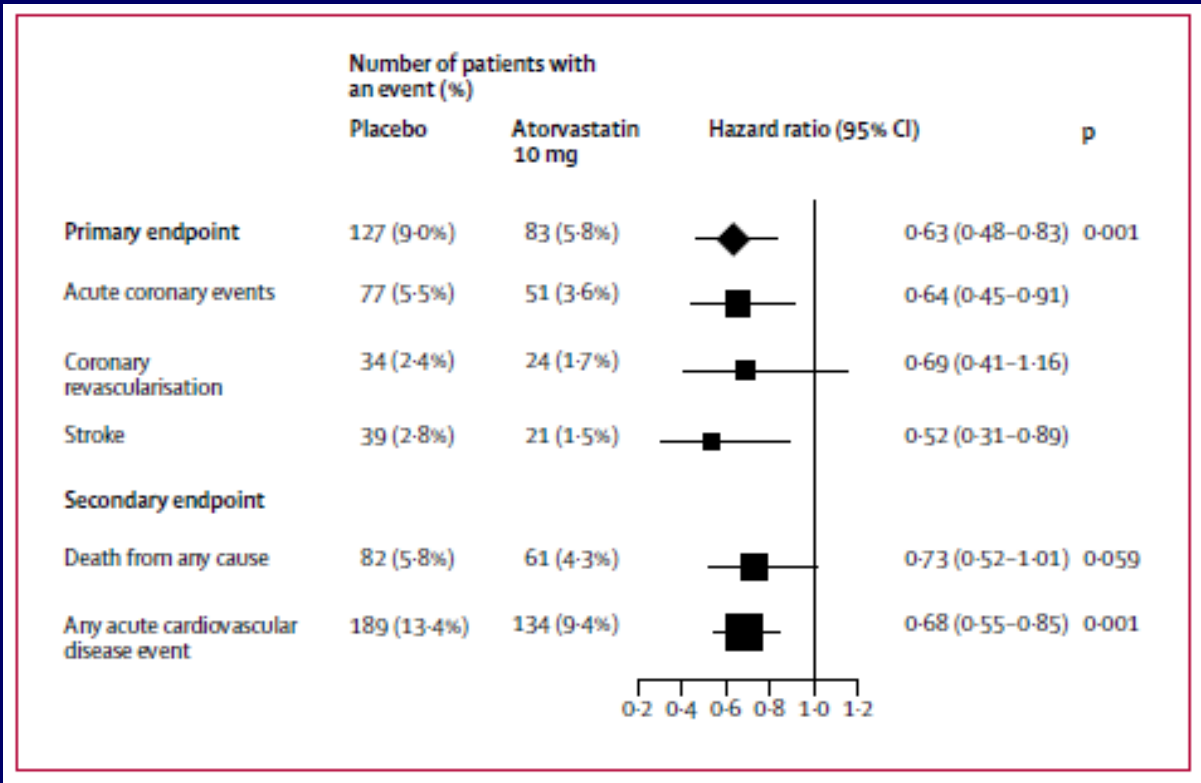
CARDS Study

- Primary prevention study
  - But ! Retinopathy, albuminuria, smoking or hypertension
- 2838 patients 40-75yrs with diabetes
- Atorvastatin vs Placebo

- LDL<4.14
- TG<6.78

Colhoun H. Lancet 2004: 364;685

CARDS study



Colhoun H. Lancet 2004: 364;685

Statins in Diabetes

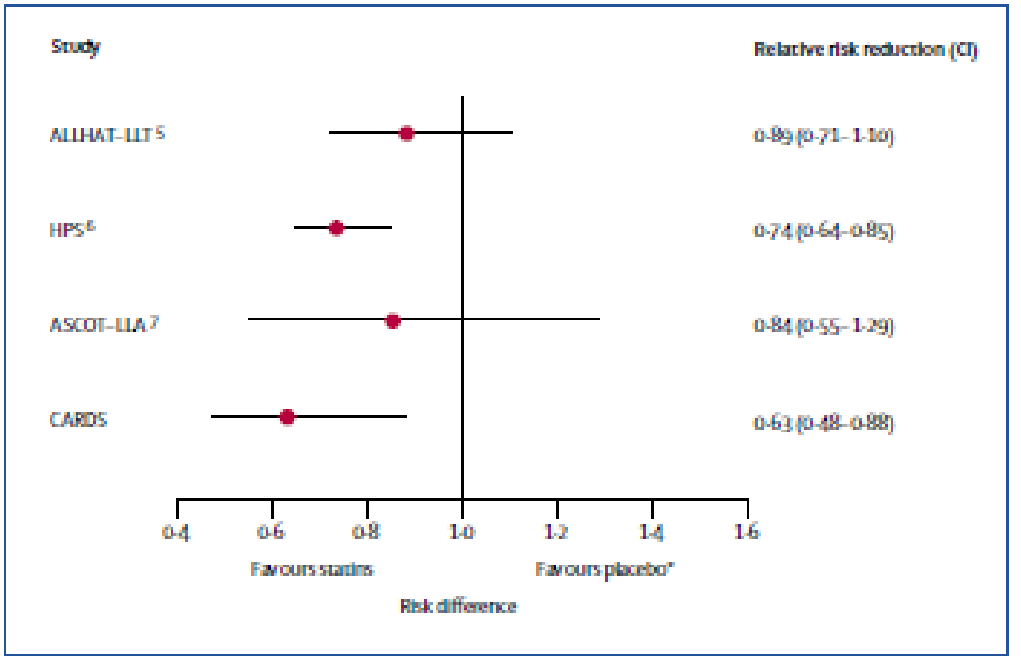


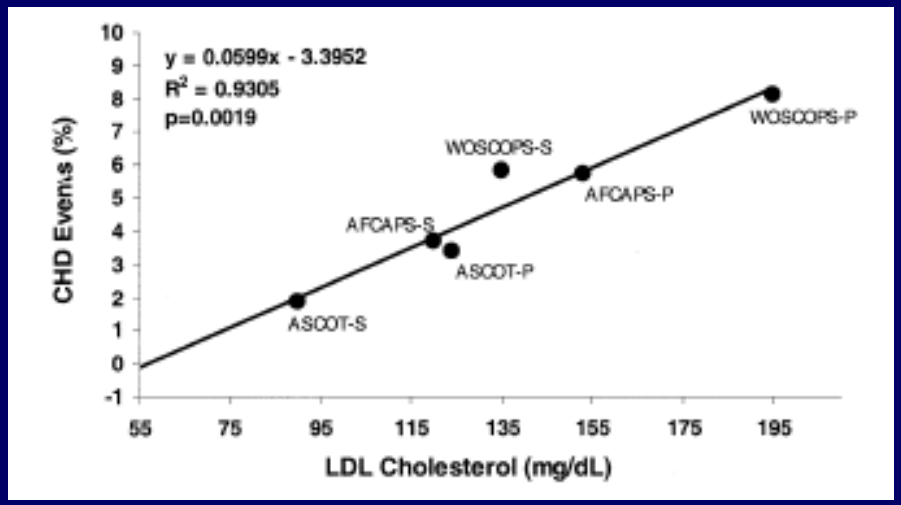
Figure: Relative risk reduction by statin therapy for primary prevention of coronary heart disease in patients with diabetes in the four major trials

- Primary prevention studies

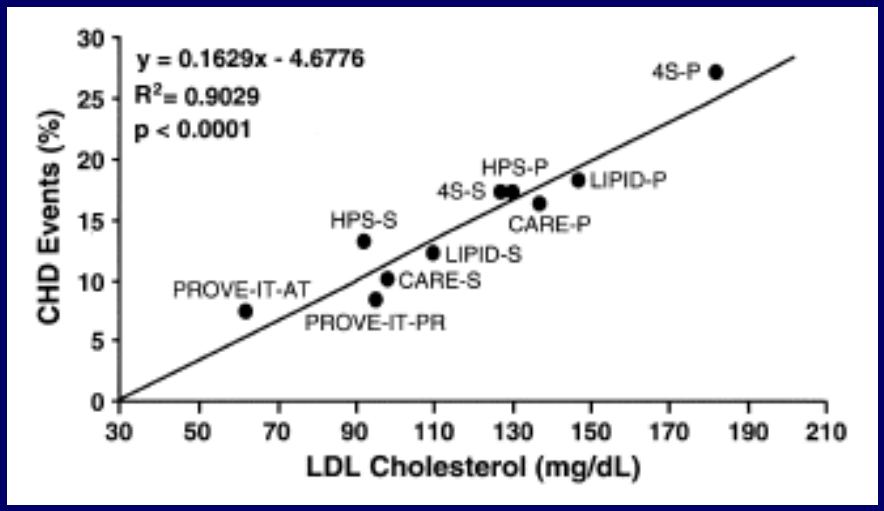
Large Subgroups with Diabetes

  - ALLHAT
    - Pravastatin
    - NS reduction in death or MI
  - HPS
    - Simvastatin
    - Sig reduction both 1˚ and 2˚
  - ASCOT
    - Atorvastatin
    - NS

LDL
How Low Do You Go?



Primary Prevention Trials



Secondary Prevention Trials

Add on to Statins

- Fibrates
  - Maybe if TG high
- Ezetimibe
  - Maybe if LDL still high
    - Lowers LDL well in combination
    - No outcome data
- Nicotinic Acid
  - Maybe if LDL high and HDL low
    - No outcome data

IMPROVE-IT Study

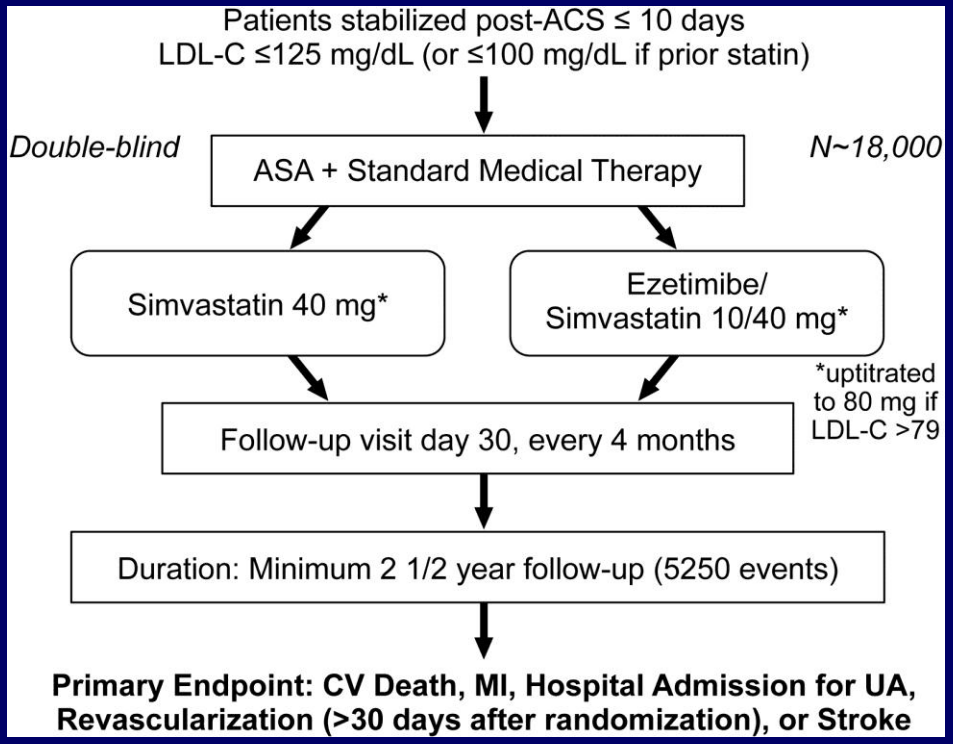


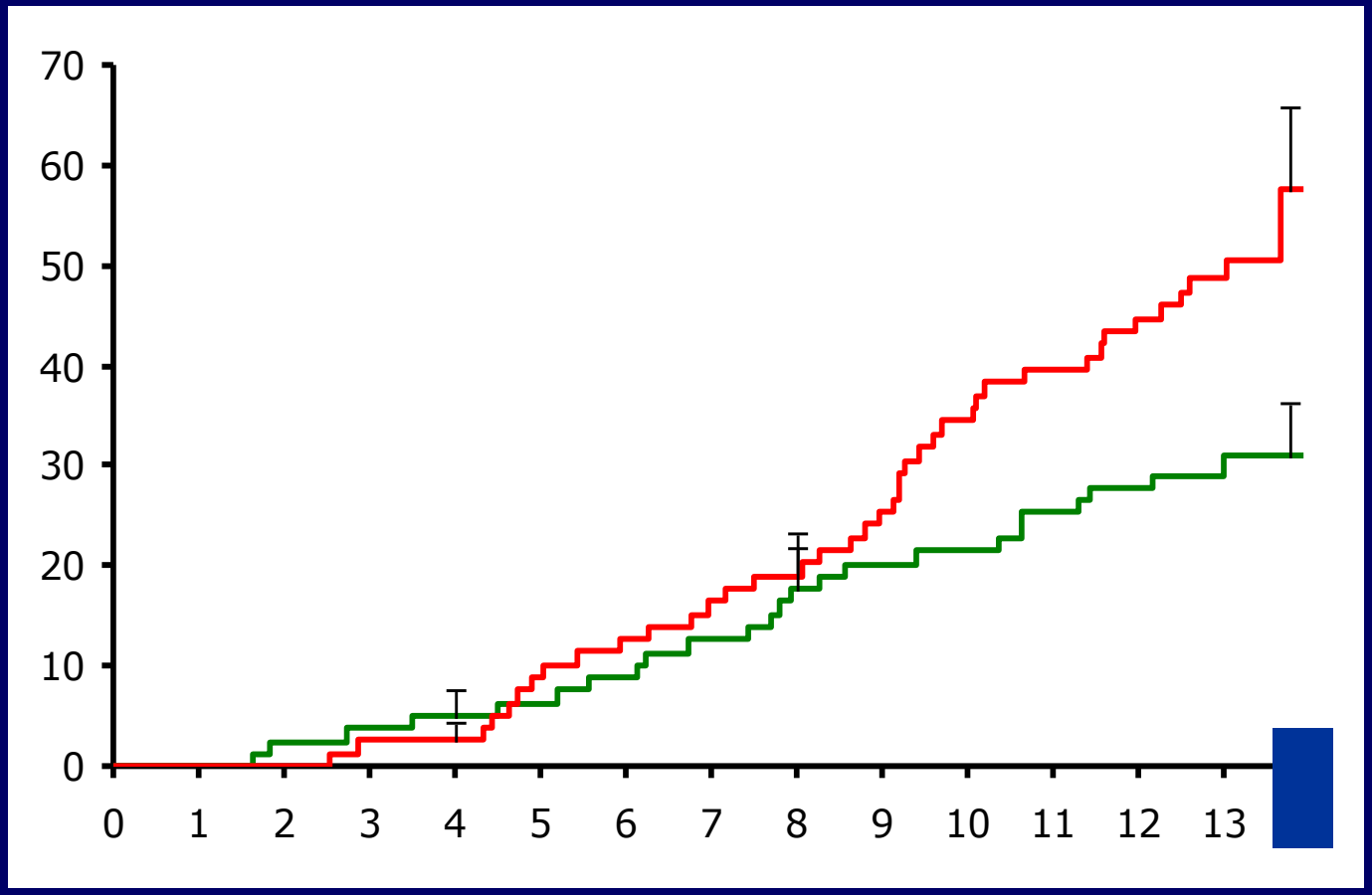
Table I. Baseline characteristics of the first 10,000 patients enrolled

Age (median [interquartile range]) in years	62 (55, 70)
Male (%)	77
Diabetes (%)	22
Prior MI (%)	17
Acute event	
STEMI (%)	47
NSTEMI (%)	37
UA (%)	16
Preenrollment coronary angiography	91
Preenrollment PCI after ACS event	76
Baseline LDL-C (median [interquartile range]) (mg/dL)	97 (81, 112)
No prior lipid-lowering therapy	104 (89, 116)
Prior lipid-lowering therapy	80 (68, 90)

The Whole Package

"Control my diet, control my life style, control my carbs... What are you, some kind of freak?"

Steno-2 Post Trial: Mortality of any cause



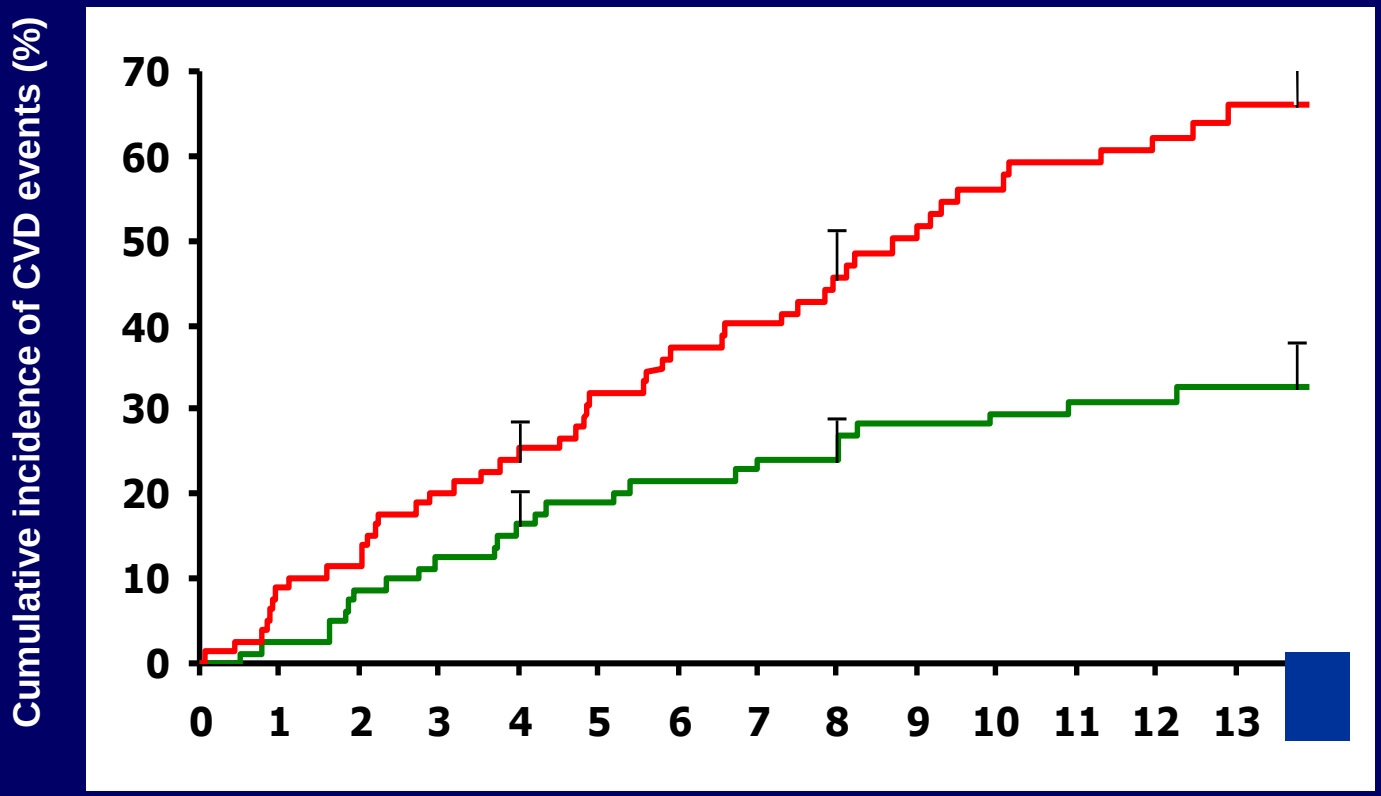
Numbers at risk

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

Gaede et al. NEJM 2008

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

Gaede et al. NEJM 2008

Steno 2

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

(from Gaede et al 2008 Steno 2, 13 year study)

Spot the Difference

Summary

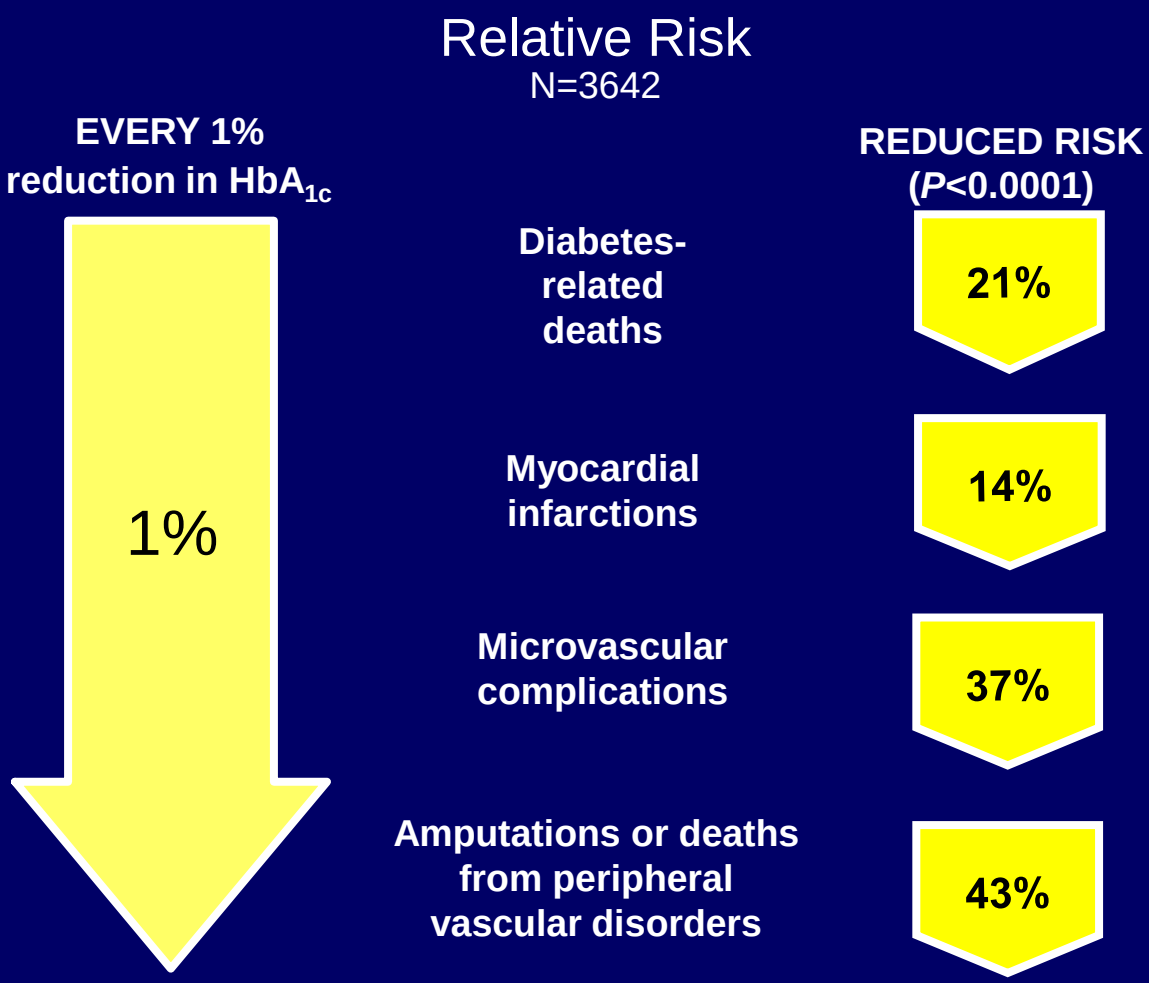
- People with diabetes take a lot of medication
  - Compliance and Side Effects
- Most die from CVD
- Everyone is not created equal
  - Calculate individual CVD risk
- Primary vs Secondary Prevention

- If you decide to treat – GO HARD!

Summary

- Weight and Exercise
- Stop Smoking
- Glucose control
  - Legacy effect – Treat early
  - Avoid hypoglycaemia
- Blood Pressure
  - Aim 130/80mmHg
  - But not too low
- Lipids
  - Statin first line
  - Primary vs Secondary – consider your target
    - Maybe Fibrate if TG v high
    - Maybe Ezetimibe or Nicotinic acid
- Aspirin
  - Yes for secondary prevention
  - Probably not for primary unless high risk

UKPDS: Improving HbA_{1c} Control Reduced Diabetes-Related Complications



UKPDF=United Kingdom Prospective Diabetes Study.
Data adjusted for age, sex, and ethnic group, expressed for white men aged 50–54 years at diagnosis and with mean duration of diabetes of 10 years.
Stratton IM et al. UKPDS 35. *BMJ* 2000;321:405–412.

Management Goals for Diabetes

NZ Guidelines Group: Dec 2002

- Glycaemic control
  - HbA1c 6.5 - 7.5%
- Blood Pressure
  - <130/80 (125/75)
- Lipids
  - TC<4.0mmol/L (LDL<2.0, HDL>1.0)
  - TG<1.7mmol/L

MORTALITY FROM CORONARY HEART DISEASE IN SUBJECTS WITH TYPE 2 DIABETES AND IN NONDIABETIC SUBJECTS WITH AND WITHOUT PRIOR MYOCARDIAL INFARCTION

STEVEN M. HAFFNER, M.D., SEPPO LEHTO, M.D., TAPANI RÖNNEMAA, M.D., KALEVI PYÖRÄLÄ, M.D., AND MARKKU LAAKSO, M.D.

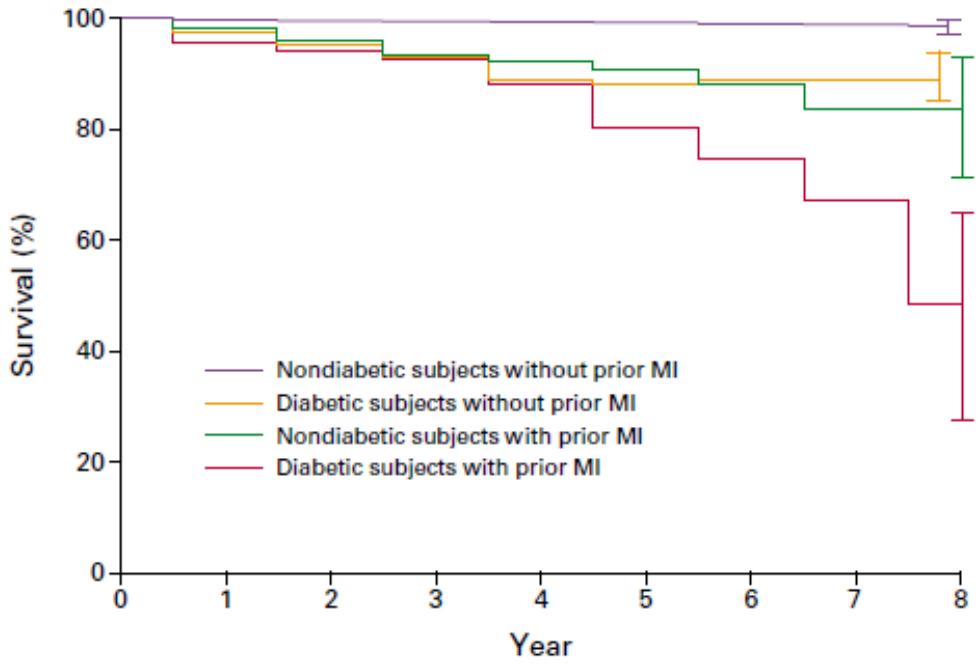
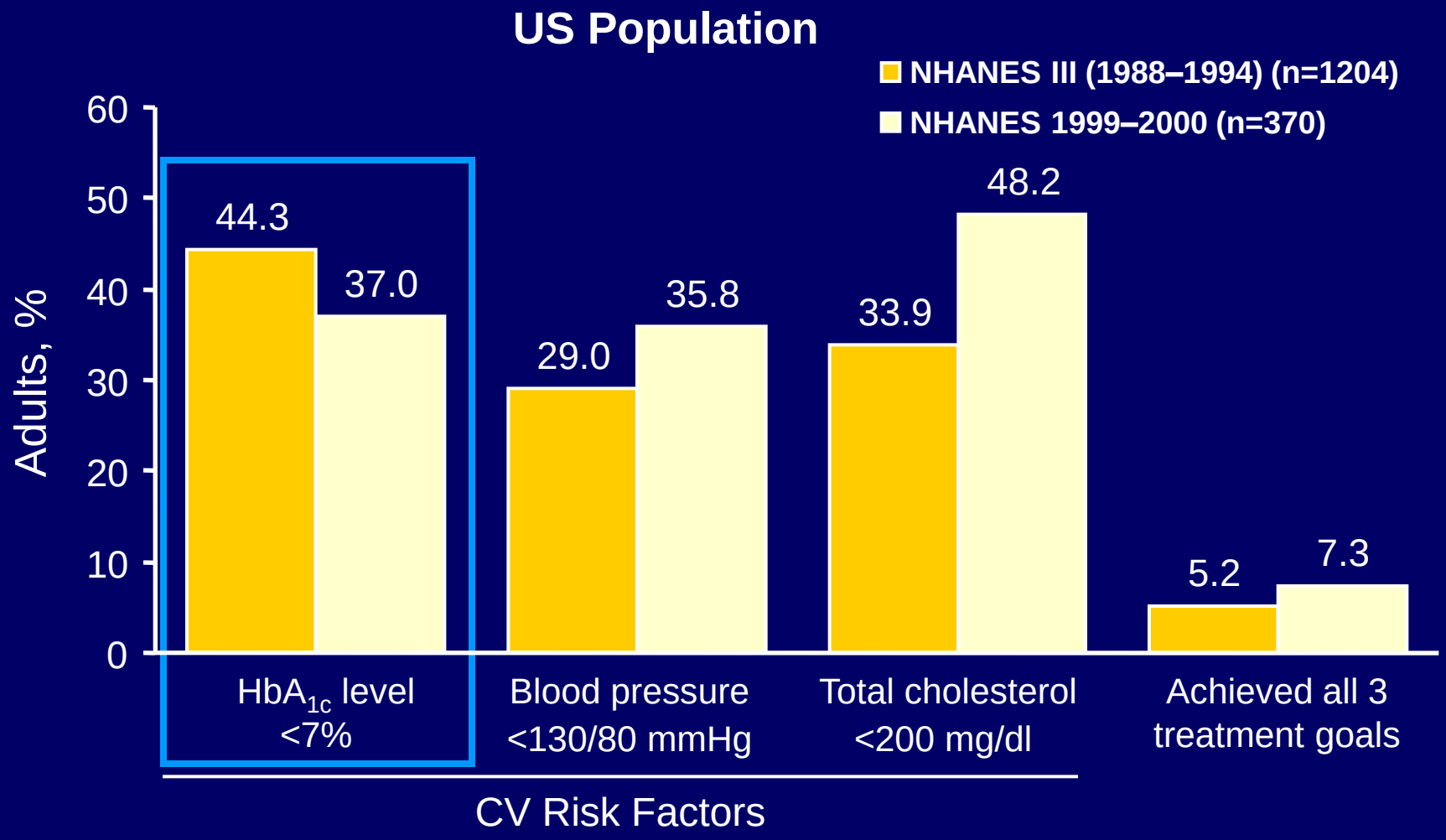


Figure 1. Kaplan–Meier Estimates of the Probability of Death from Coronary Heart Disease in 1059 Subjects with Type 2 Diabetes and 1378 Nondiabetic Subjects with and without Prior Myocardial Infarction. MI denotes myocardial infarction. I bars indicate 95 percent confidence intervals.

Less than 50% of Adults With Type 2 Diabetes Have Achieved HbA_{1c} Goals



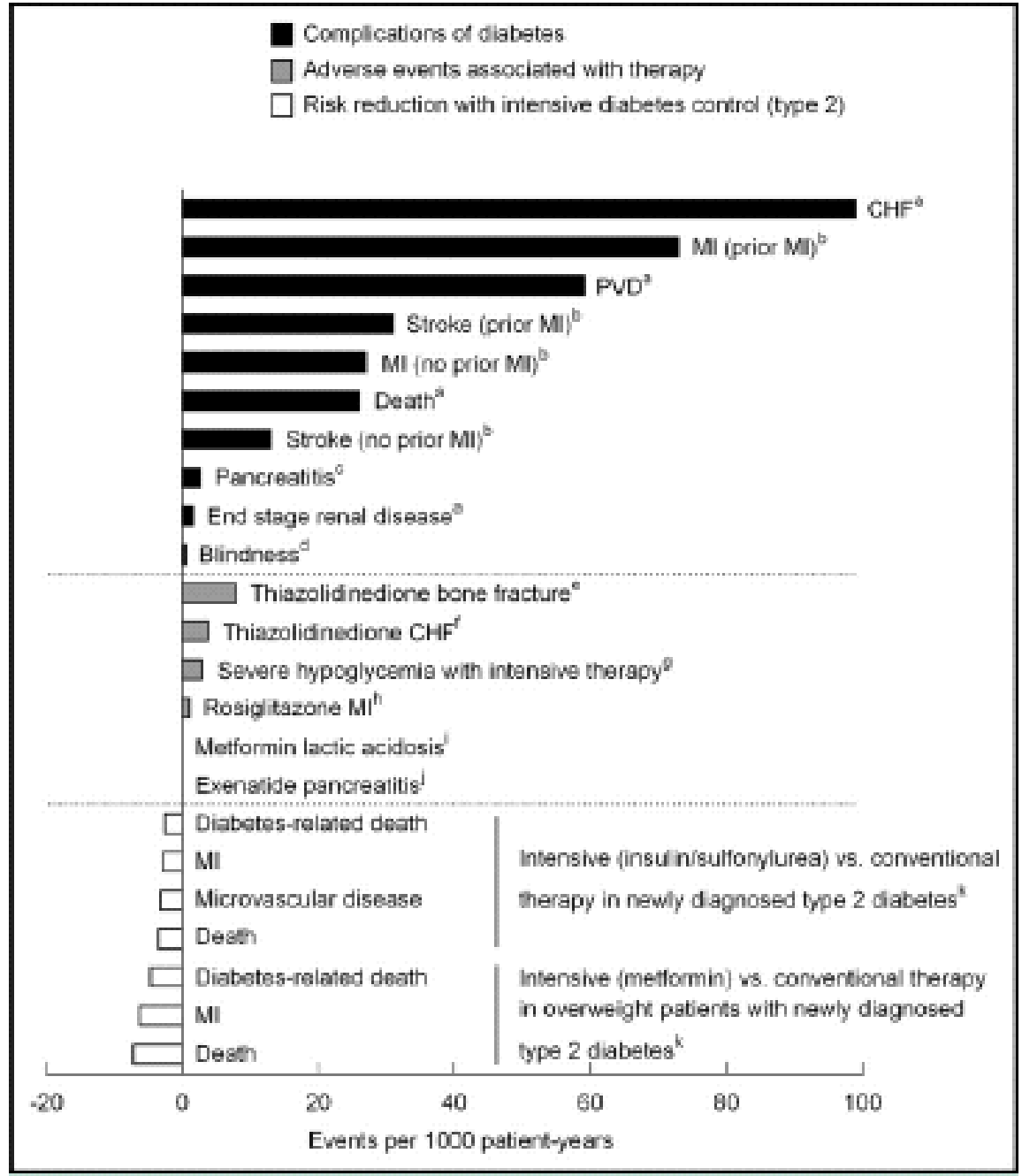
NHANES=National Health and Nutrition Examination Survey of a US population.
Adapted from Saydah SH et al. *JAMA.* 2004;291:335–342.

Antihyperglycemic Agents in Type 2 Diabetes

Class	A1C Reduction	Severe Hypo-glycemia	Weight Change	CVD Risk Factor Improvement	Dosing (times/day)	Diabetes Comorbidity Contraindications
Metformin	1.5	No	Neutral	Minimal	1-2	Kidney, liver
NPH, Glargine, Detemir	1.5 - 2.5	Yes	Gain	TG	1-2, Injected	None
R, Lispro, Aspart, Glulisine	1.5 - 2.5	Yes	Gain	TG	1-4, Injected	None
Glipizide ER, Glimepiride	1.5	Yes	Gain	None	1	None
Pioglitazone	0.5 - 1.4	No	Gain	Lipids, BP	1	CHF, liver
Repaglinide	1 - 1.5	Yes	Gain	None	3	None
Nateglinide	0.5 - 0.8	Rare	Gain	None	3	None
Acarbose, Miglitol	0.5 - 0.8	No	Neutral	Minimal	3	None
Pramlintide	0.5 – 0.9	No	Loss	w/ weight loss	3, Injected	None
Exenatide	0.5 - 1.0	No	Loss	w/ weight loss	2, Injected	Kidney
Sitagliptin, saxagliptin	0.6 - 0.8	No	Neutral	Minimal	1	None
Colesevelam	~0.5	No	Neutral	LDL	1-2	Severe TG's

Adapted from Skyler JS, et al. *Diabetes Care.* 2009;32:193-203. ADA. *Diabetes Care.* 2010;33:S11-S61. WelChol PI 12/2008. Cycloset PI, 10/2010. Victoza PI. 1/2010.

Risks vs Benefits of Glucose Lowering therapy



Bergenstal R et al. Am J Med 2010;123:374

From: **Effect of Lower Targets for Blood Pressure and LDL Cholesterol on Atherosclerosis in Diabetes: Title and subTitle BreakThe SANDS Randomized Trial**

JAMA. 2008;299(14):1678-1689. doi:10.1001/jama.299.14.1678

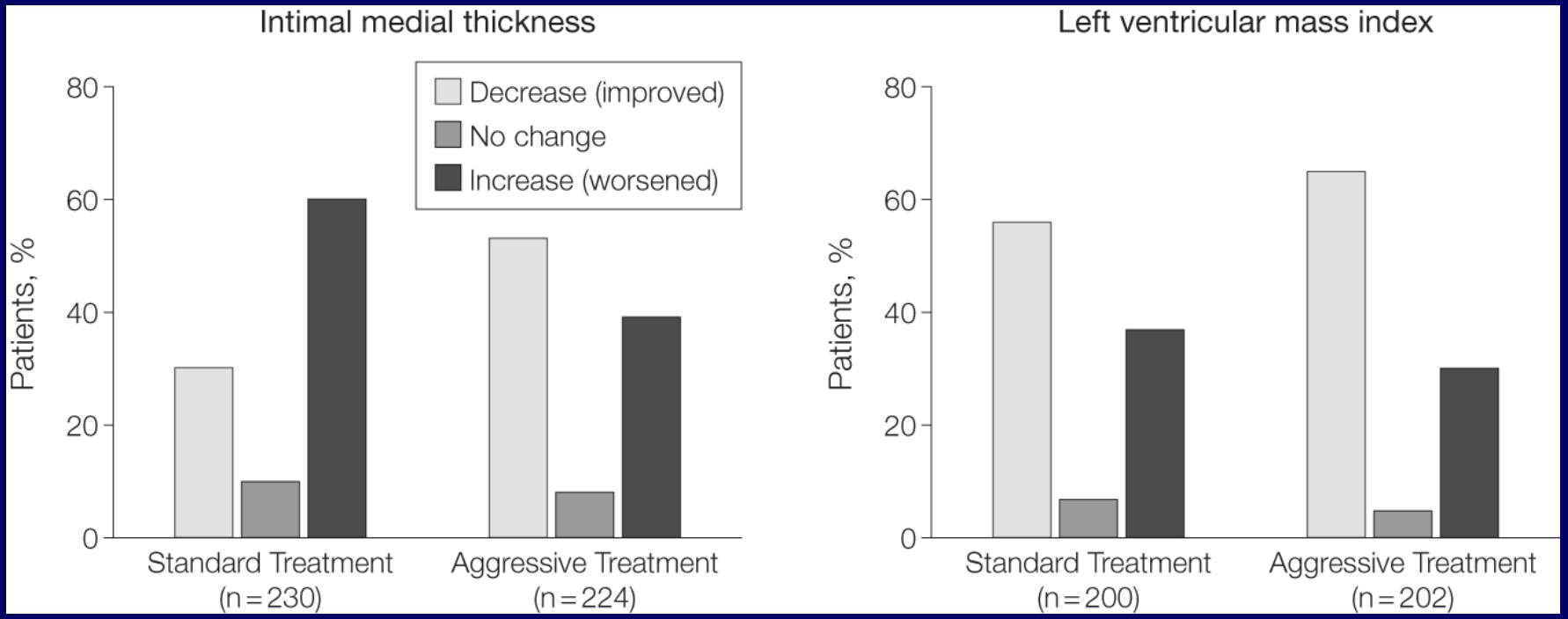
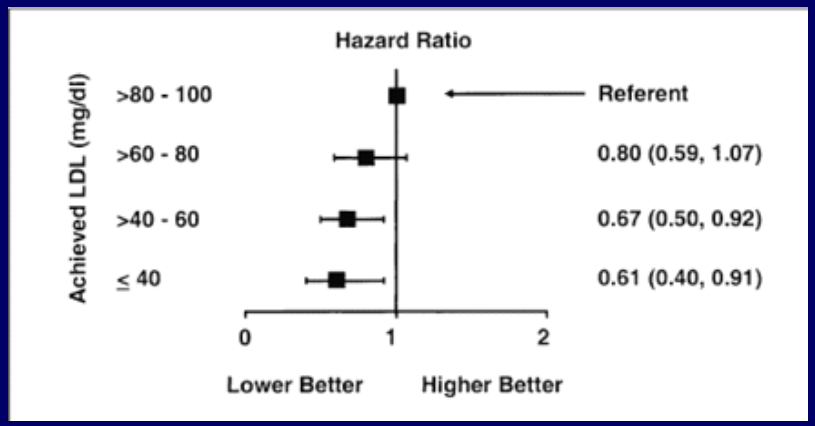
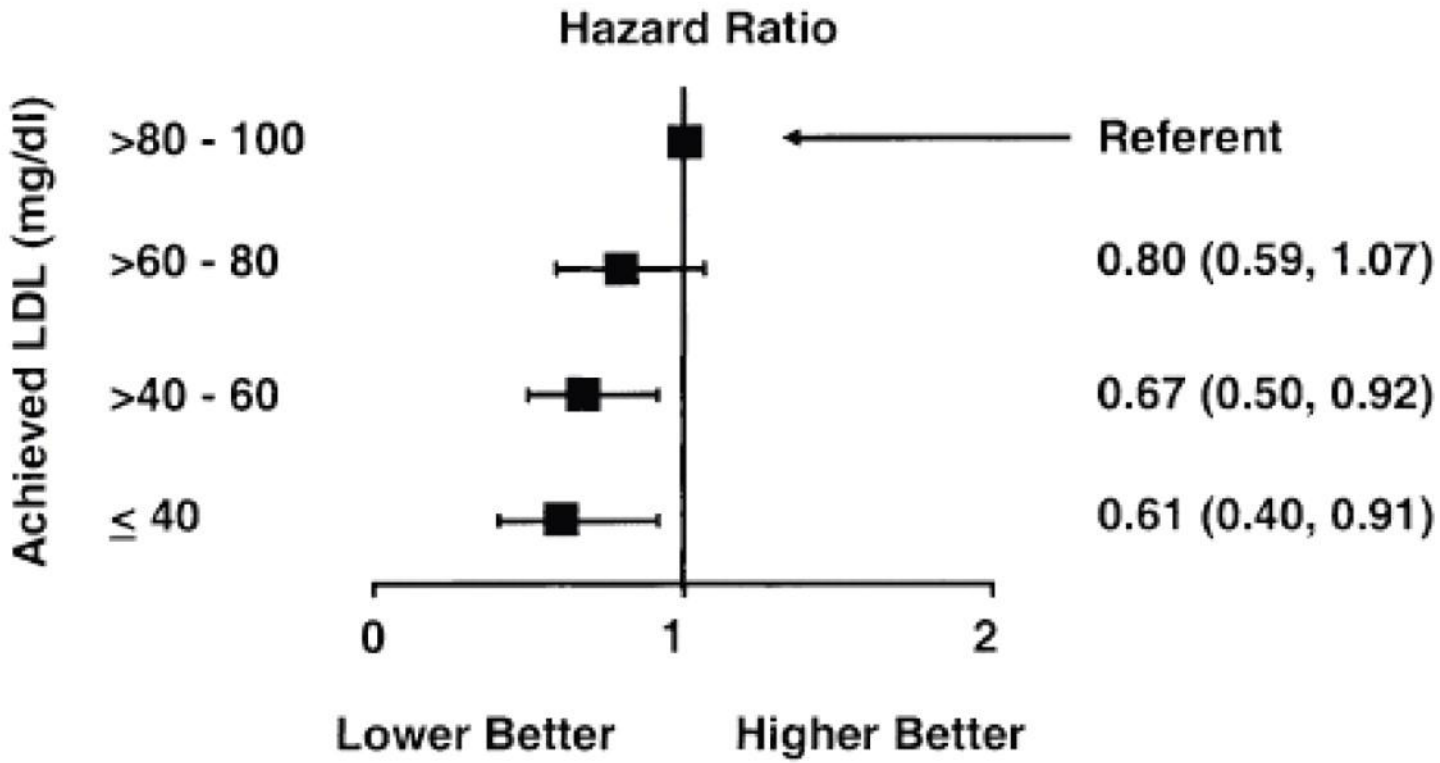


Figure Legend:

For intimal medial thickness, n = 454; P value < .001. For left ventricular mass index, n = 402; P value = .17. The “no change” category was defined as ± 0.01 mm for intimal medial thickness or ± 0.05 gm/m$^{2.7}$ for left ventricular mass index. P is for trend by each treatment group for intimal medial thickness and left ventricular mass index.


Hazard Ratio
Achieved LDL (mg/dl)
>80 - 100
>60 - 80
>40 - 60
≤ 40
Referent
0.80 (0.59, 1.07)
0.67 (0.50, 0.92)
0.61 (0.40, 0.91)
0
1
2
Lower Better
Higher Better

Hazard ratios for the primary end point by subgroup of achieved LDL cholesterol (adjusted for age, sex, baseline calculated LDL cholesterol, diabetes, and prior MI) in the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 trial.



Nesto R W Clin Diabetes 2008;26:8-13

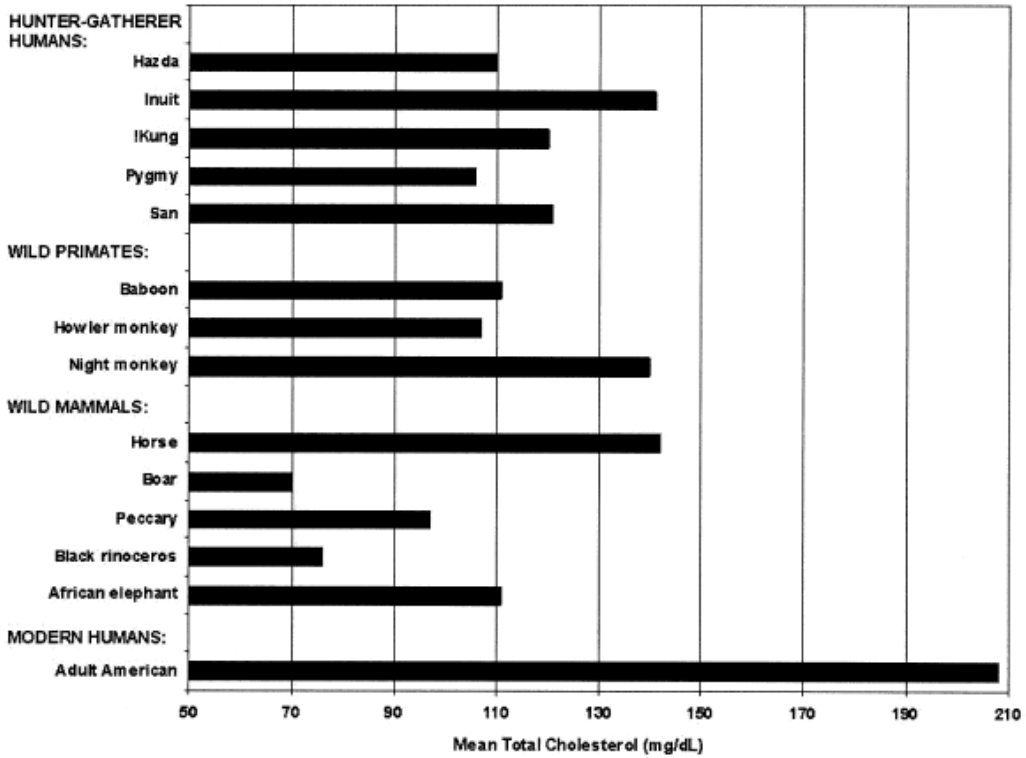
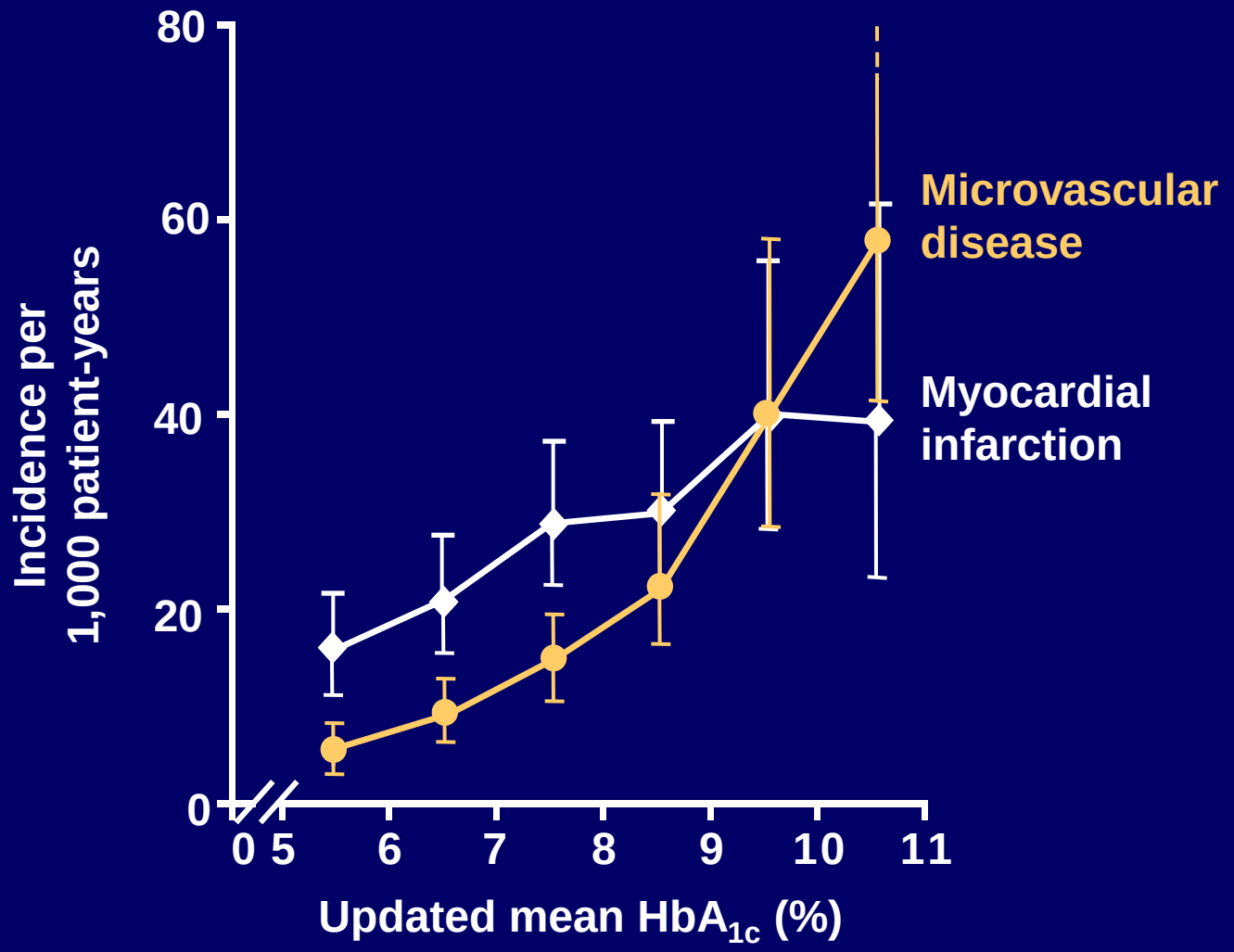


Figure 1. Total cholesterol levels for hunter-gatherers, wild primates, and wild mammals, generally range from about 70 to 140 mg/dl (corresponding to low-density lipoprotein levels of about 35 to 70 mg/dl [24,25]). The mean cholesterol levels of modern Westernized humans are almost twice these normal values (13).

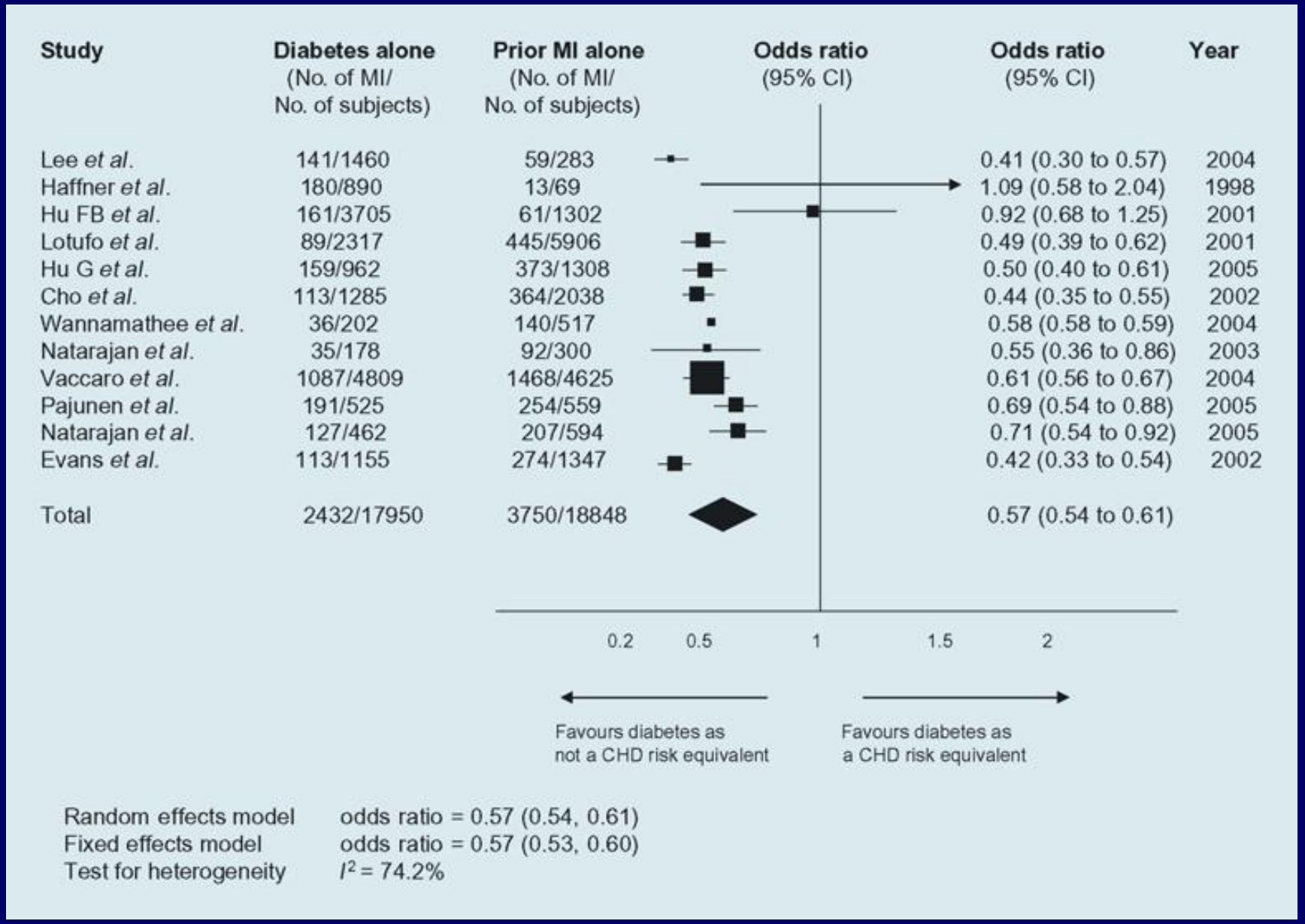
Incidence rates of MI and microvascular endpoints by mean HbA_{1c}: UKPDS



Error bars = 95% CI

Study population: white, Asian Indian, and Afro-Caribbean UKPDS patients (n = 4,585)
Adjusted for age, sex, and ethnic group

Adapted from Stratton IM, *et al. Br Med J* 2000; 321:405–412.



Bulugahapitiya U. Diabetic Med 2009:26;142-148

Success Comes From Using the Most Appropriate Tools