This House Believes That Surrogate Markers Are Of No Use In Evaluating Treatments For Diabetes

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University College London

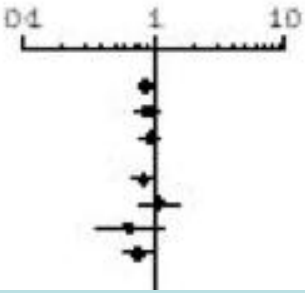
The ABCD Debate
ABCD Autumn Meeting
Royal College of Physicians, London
9th November 2012

Outline

- Diabetes management strategies frequently involve treating risk factors towards Targets set in Guidelines
- Until recently, these targets have been derived, or extrapolated, from epidemiology plus the UKPDS
- There are many assumptions inherent in assuming that changes in surrogate endpoints will confer patient benefit
- Patients are rarely presented with enough information to make informed decisions

Lessons from UKPDS

AGGREGATE ENDPOINT	Patients with clinical endpoints: Intensive (n=2729)	Patients with clinical endpoints: Conventional (n=1138)	Absolute risk: events per 1000 patient/years: Intensive	Absolute risk: events per 1000 patient/years: Conventional	Log-rank p	RR for intensive policy (CI)
Any diabetes-related endpoint	563	438	40·9	46·0	0·029	0·88 (0·79–0·99)
Diabetes-related deaths	285	129	10·4	11·5	0·34	0·90 (0·73–1·11)
All-cause mortality	469	213	17·9	18·9	0·44	0·94 (0·80–1·10)
Myocardial infarction	387	186	14·7	17·4	0·052	0·84 (0·71–1·00)
Stroke	148	55	5·6	5·0	0·52	1·11 (0·81–1·51)
Amputation or death from PVD	29	18	1·1	1·6	0·15	0·65 (0·36–1·18)
Microvascular	225	121	8·6	11·4	0·0099	0·75 (0·60–0·93)



UKPDS33

TARGETS - GUIDELINES

Reviews/Commentaries/ADA Statements

POSITION STATEMENT

Intensive Glycemic Control and the Prevention of Cardiovascular Events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials

A position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association

"Until more evidence becomes available, the general goal of <7% appears reasonable."

Global Guideline for Type 2 Diabetes

International Diabetes Federation

■ Standard care

TT1 Advise people with diabetes that maintaining a DCCT-aligned HbA_{1c} below 6.5 % should minimize their risk of developing complications.

NHS National Institute for Health and Clinical Excellence

DH Department of Health

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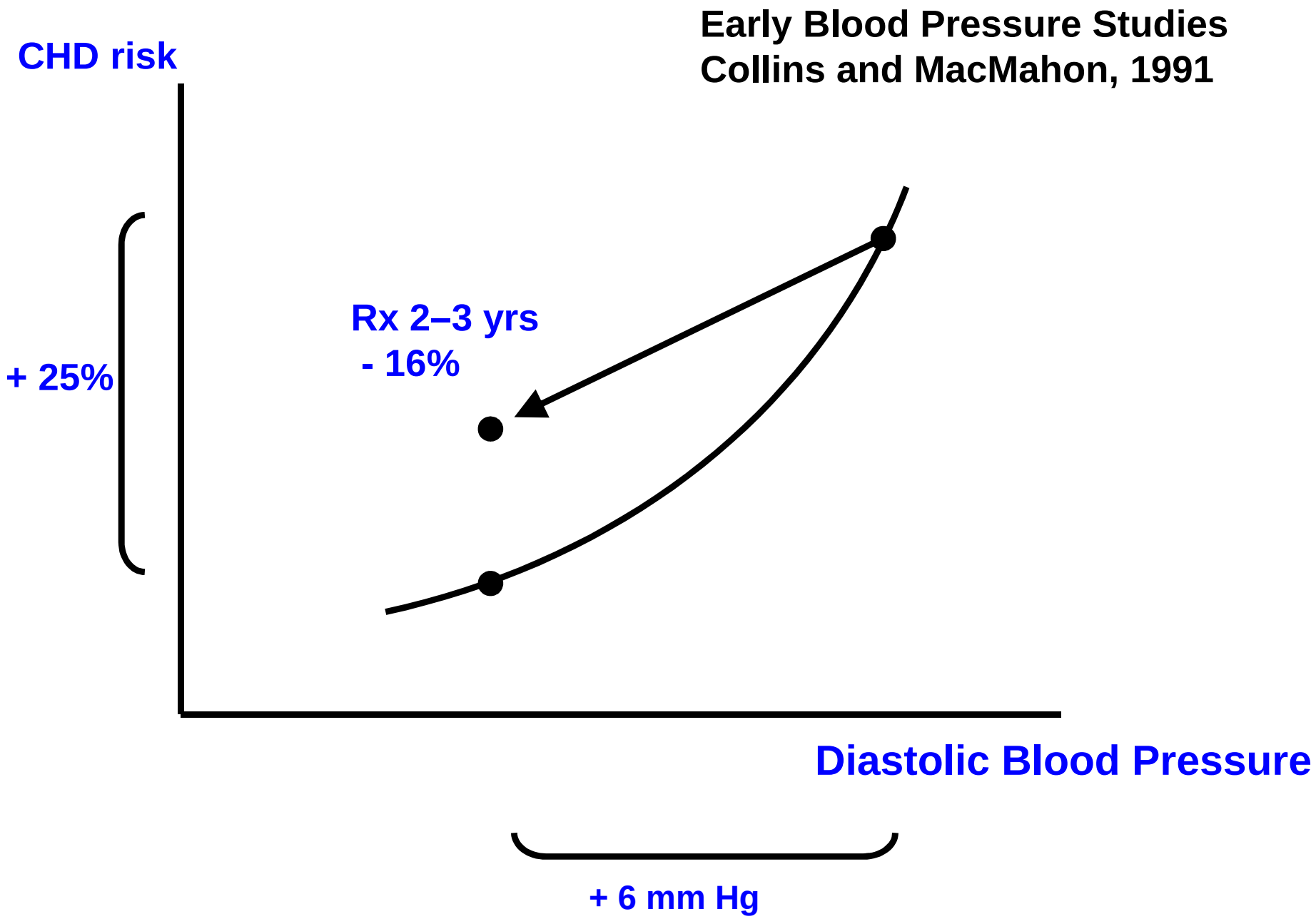
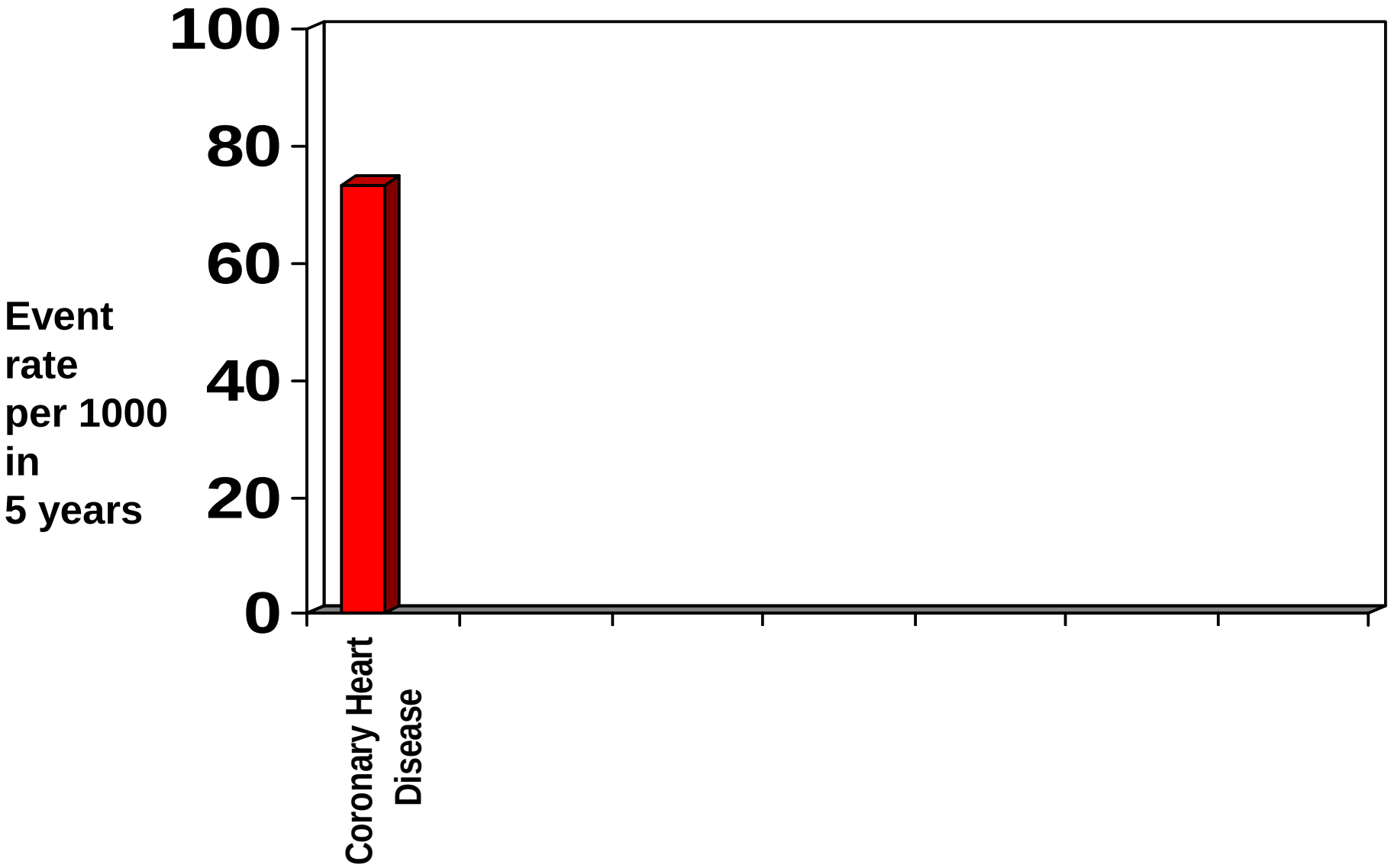
Risk Factors and Their Reduction

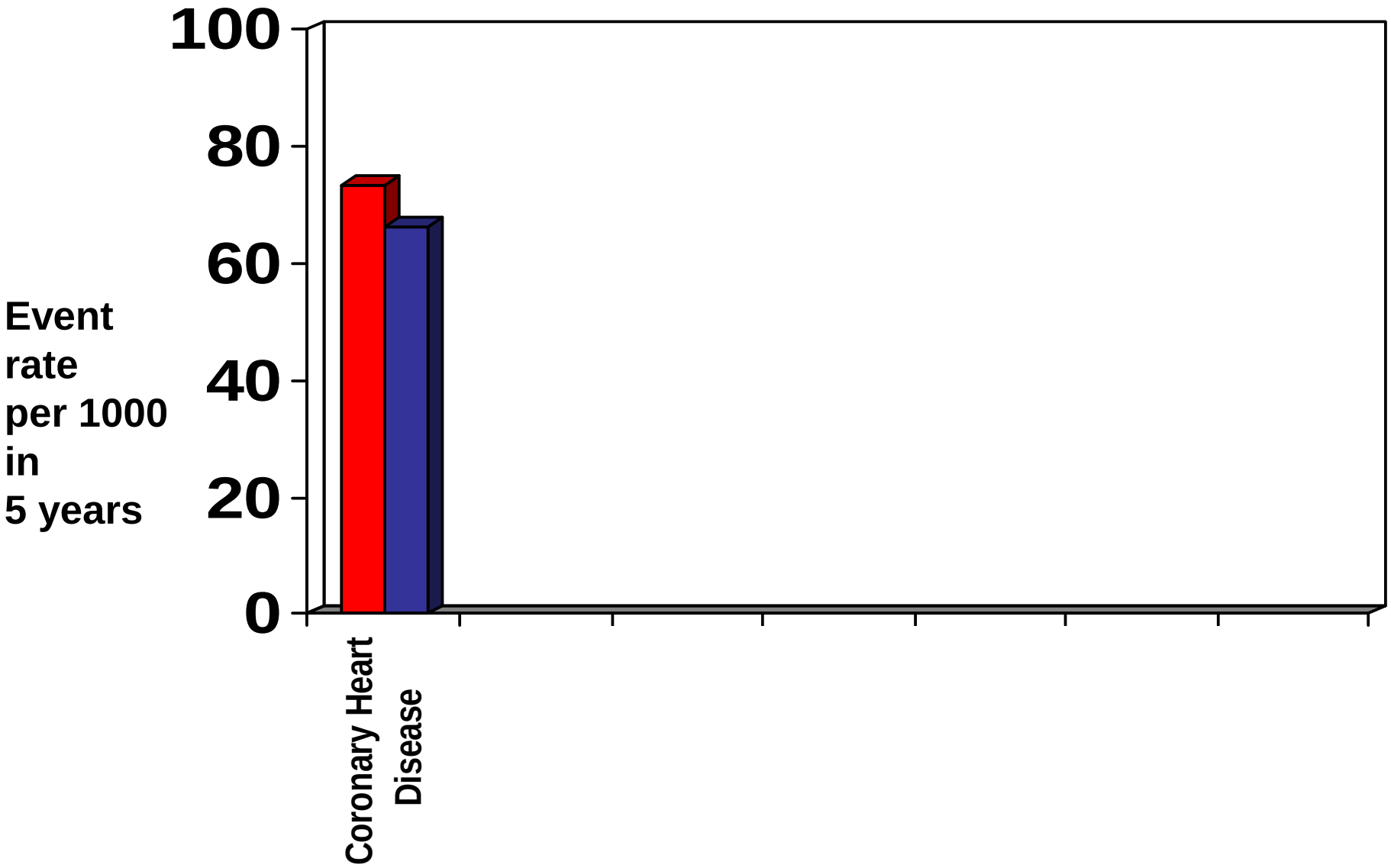


Risk Factors and Their Reduction

	CHD	Stroke (all)
Cholesterol (1mmol/l)		
Epidemiological	**+30%**	**+10%**
Intervention	**- 23%**	**- 17%**
Blood Pressure (10/6mmHg)		
Epidemiological	**+25%**	**+36%**
Intervention	**- 22%**	**- 41%**
Glucose (HbA1c 0.9%)		
Epidemiological	**+12%**	**+15%**

Yudkin et al 2010


100
80
60
40
20
0
Event rate per 1000 in 5 years
Coronary Heart Disease


100
80
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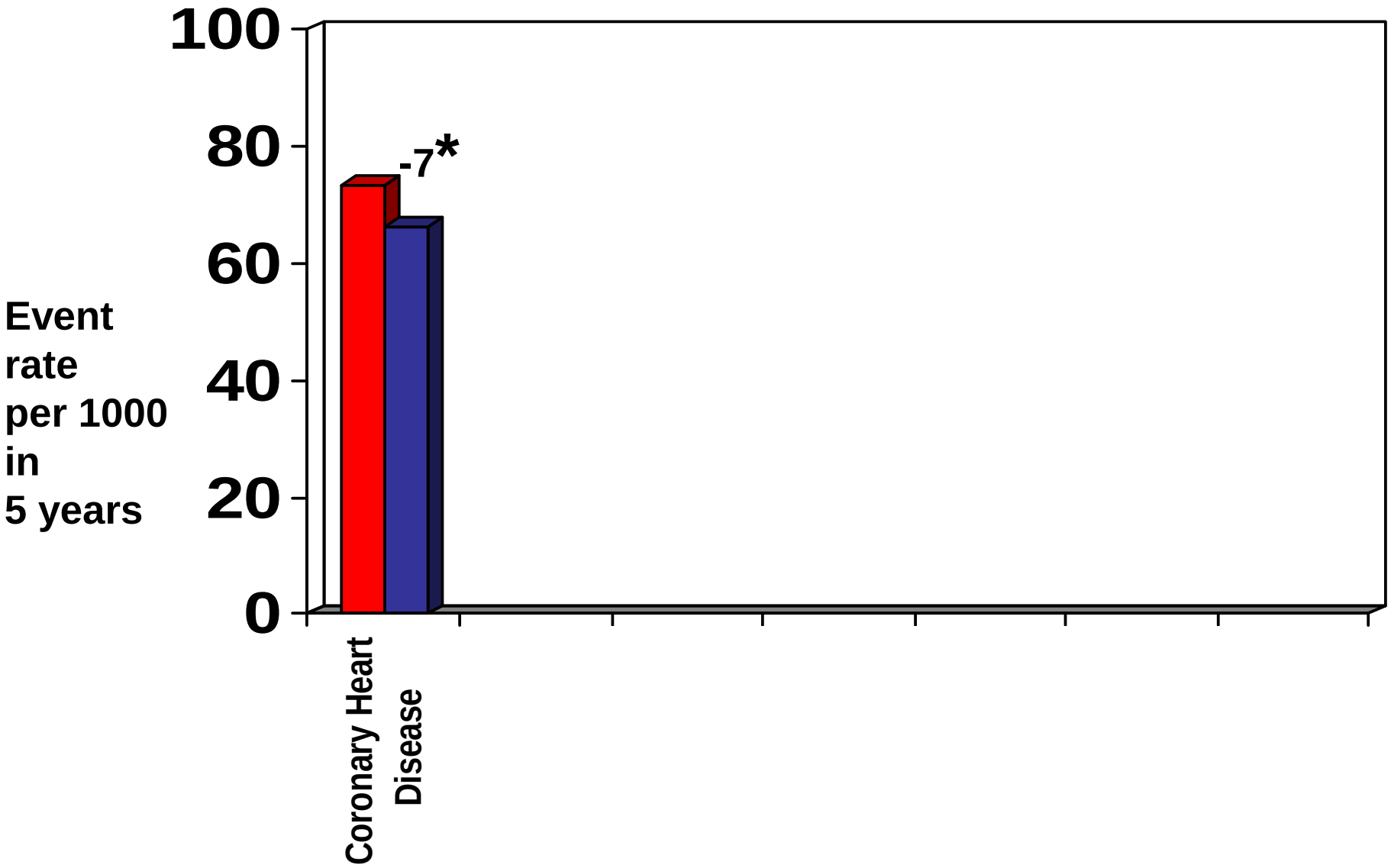
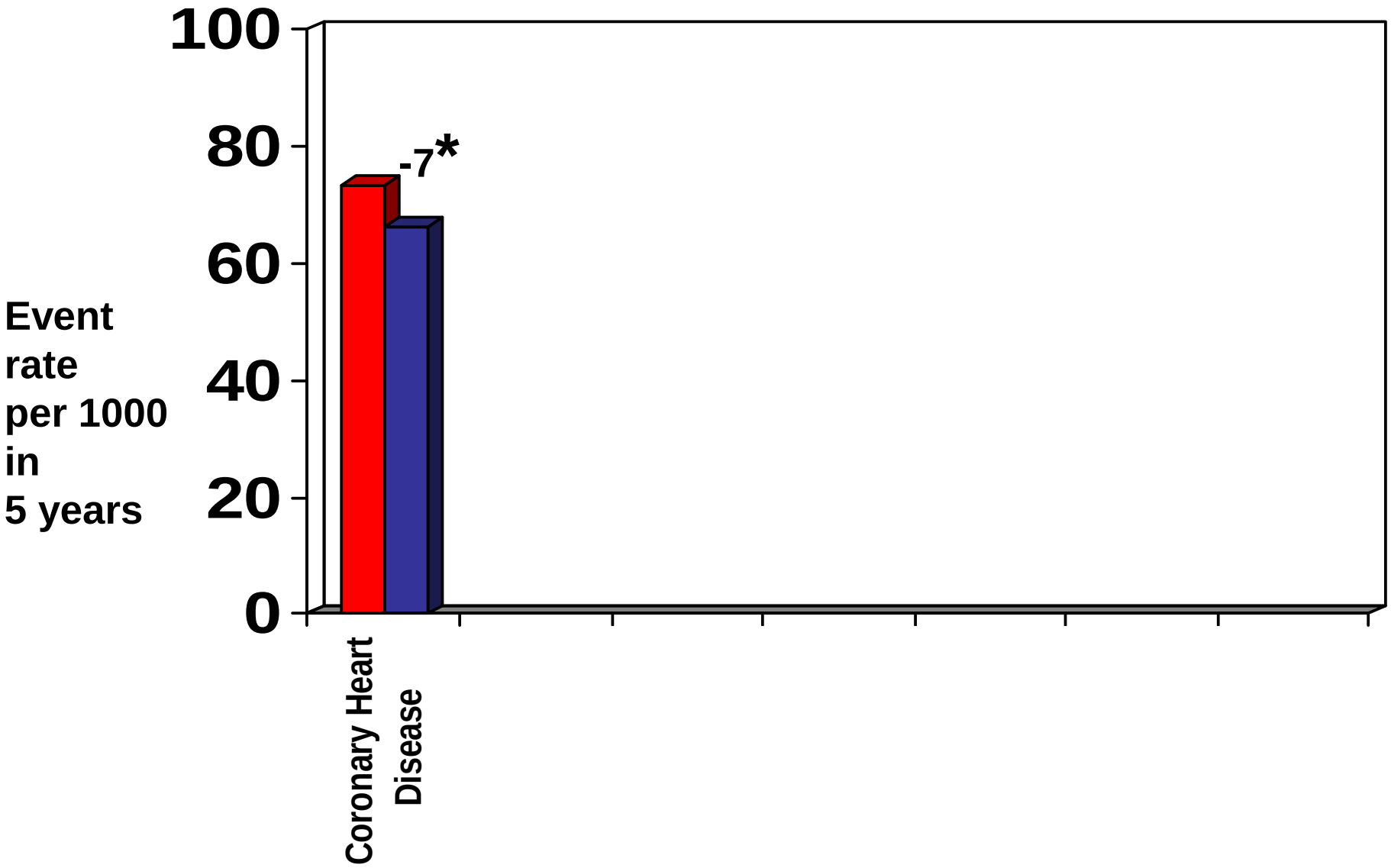
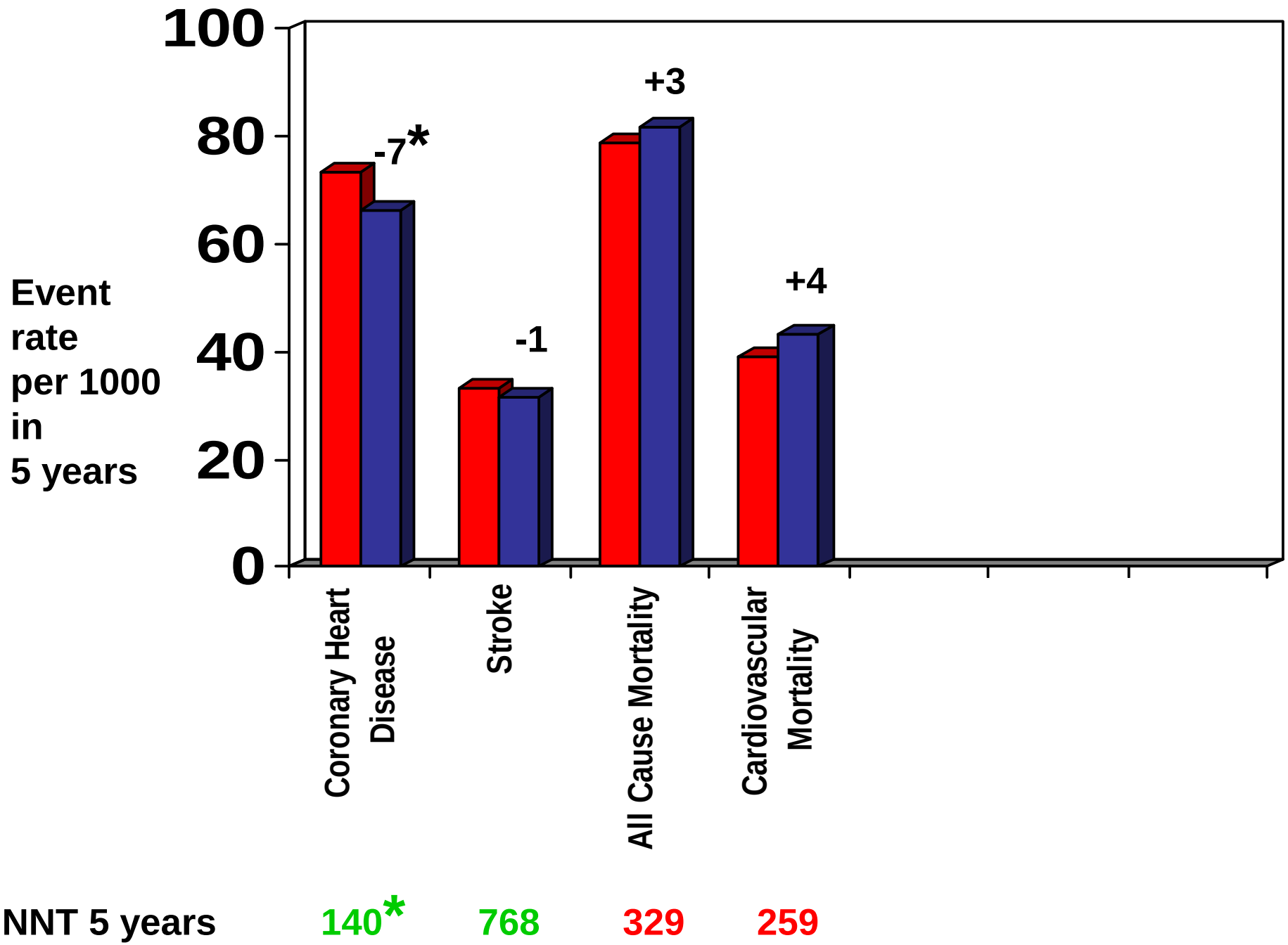

Event rate per 1000 in 5 years
100
80
60
40
20
0
-7*
Coronary Heart Disease



NNT 5 years **140***



NNT 5 years	140*	768	329	259

Risk Factors and Their Reduction

	CHD	Stroke (all)
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Intervention	**- 23%**	**- 17%**
Blood Pressure (10/6mmHg)		
Epidemiological	**+25%**	**+36%**
Intervention	**- 22%**	**- 41%**
Glucose (HbA1c 0.9%)		
Epidemiological	**+12%**	**+15%**
Intervention	**-10%**	**-4.0%**

Yudkin et al 2010

Numbers Needed to Treat

Glucose (HbA1c 0.9%)

NNT for 5 years to prevent 1 CVD event **119**

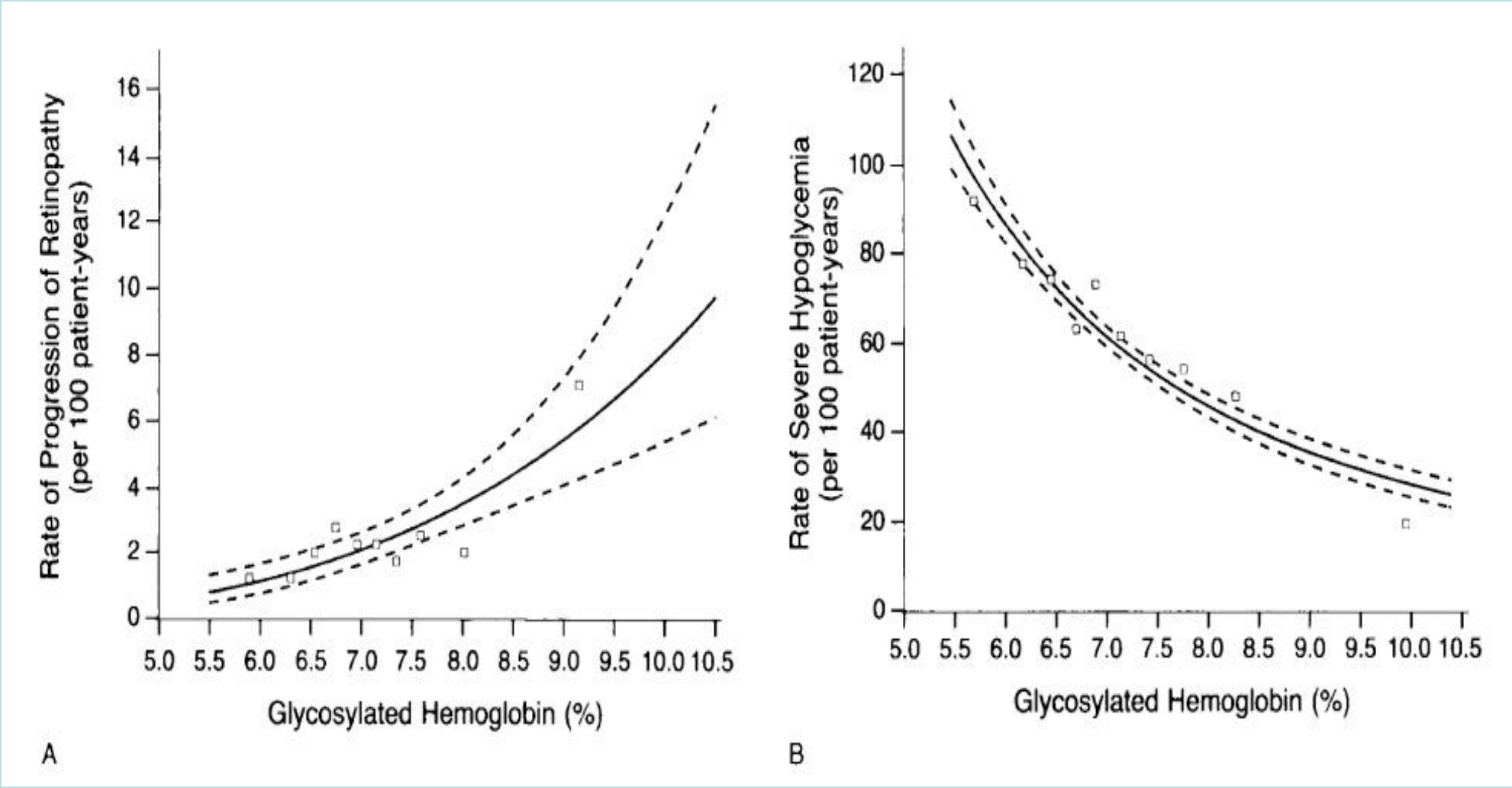
Cholesterol lowering trials (1mmol/l)

NNT for 5 years to prevent 1 CVD event **44**

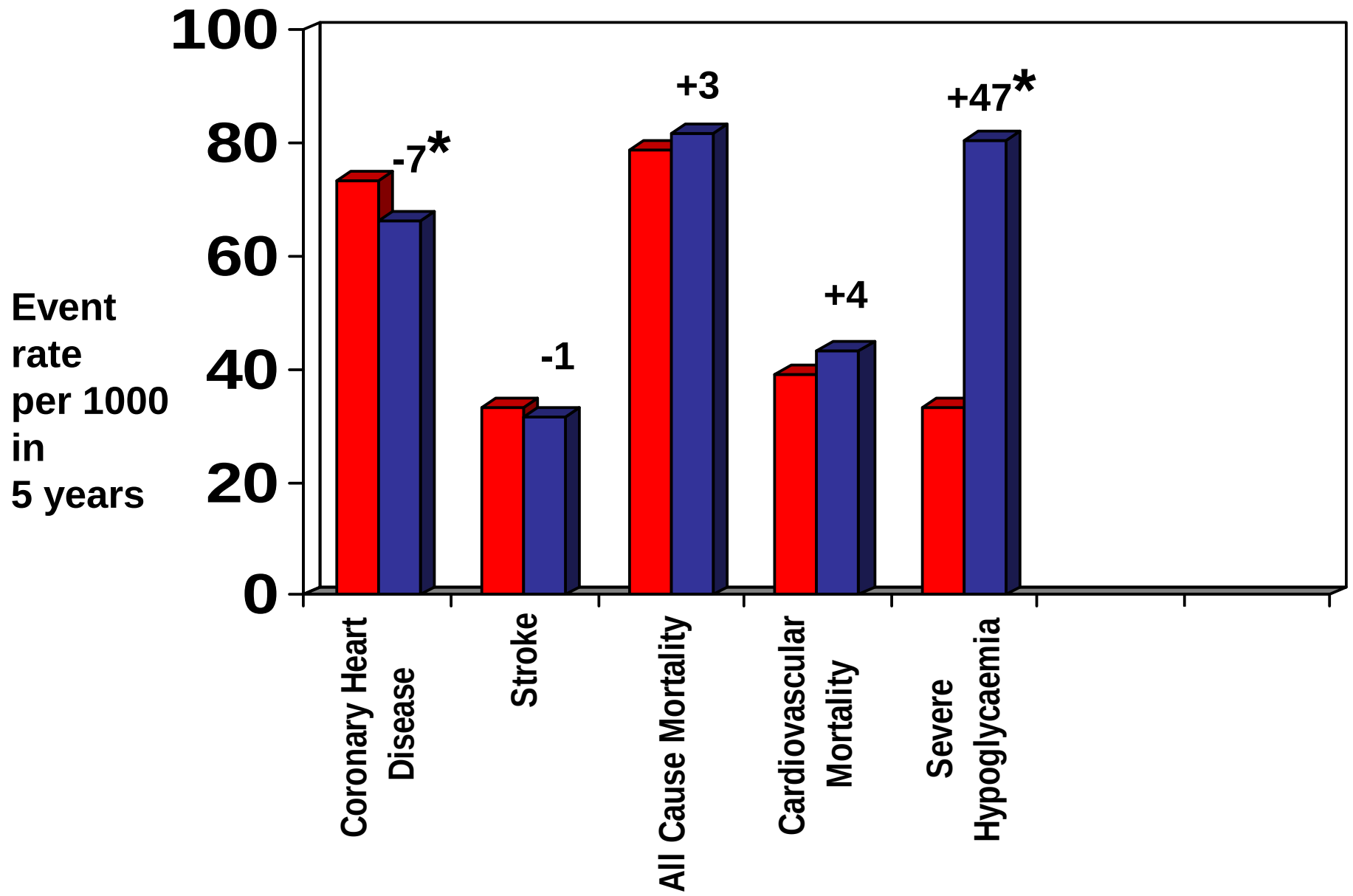
Blood Pressure lowering trials (10/6mmHg)

NNT for 5 years to prevent 1 CVD event **34**

Risk-Benefit Ratio



DCCT, NEJM 1993



NNT 5 years	140*	768	329	259	21*

Risk-Benefit Ratio

- **So for every 119 people put on intensive glucose control and monitoring for 5 years, one will benefit**
- **The event prevented will be a non-fatal myocardial infarct**
- **During this time 6 people will need external assistance, or hospital admission, for a severe hypoglycaemic event**

Lessons from UKPDS

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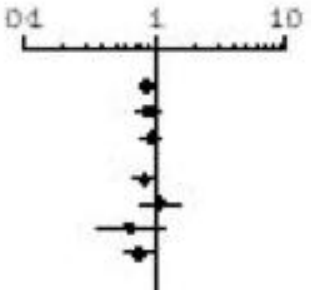

UKPDS33

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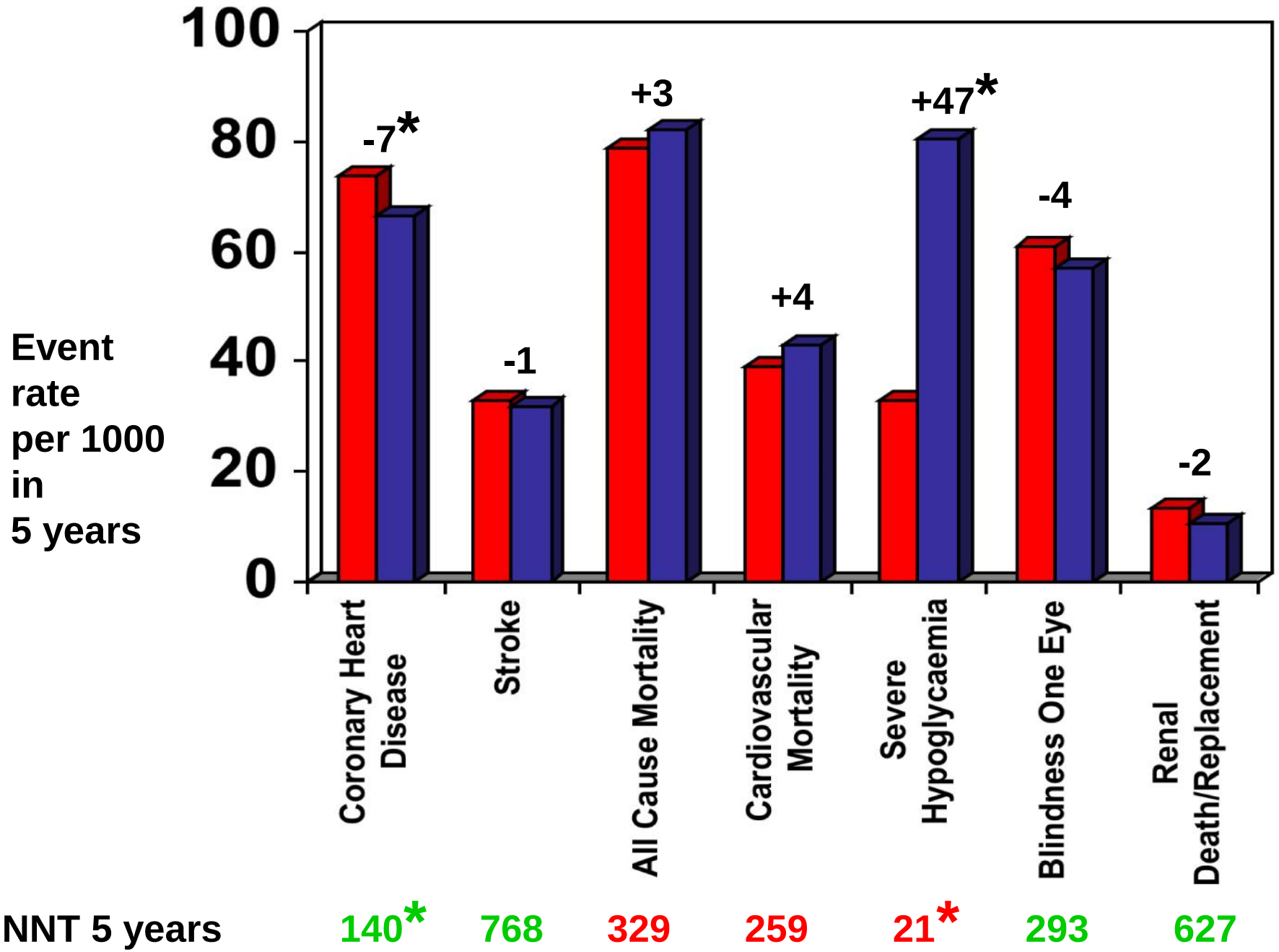
Microvascular	225	121	8·6	11·4	0·0099	0·75 (0·60–0·93)
Retinal photocoagulation	207	117	7·9	11·0	0·0031	0·71 (0·53–0·96)
Vitreous haemorrhage	19	10	0·7	0·9	0·51	0·77 (0·28–2·11)
Blind in one eye	78	38	2·9	3·5	0·39	0·84 (0·51–1·40)
Cataract extraction	149	80	5·6	7·4	0·046	0·76 (0·53–1·08)

UKPDS33


Event rate per 1000 in 5 years
100
80
60
40
20
0
-7*
-1
+3
+4
+47*
-4
-2
Coronary Heart Disease
Stroke
All Cause Mortality
Cardiovascular Mortality
Severe Hypoglycaemia
Blindness One Eye
Renal Death/Replacement
NNT 5 years
140*
768
329
259
21*
293
627

SURROGATES AS DISEASE PROGRESSION MARKERS?

Role of Intensive Glucose Control in Development of Renal End Points in Type 2 Diabetes Mellitus

Systematic Review and Meta-analysis

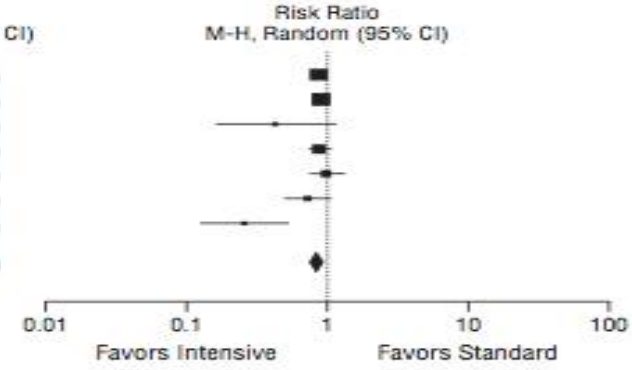
Steven G. Coca, DO, MS; Faramarz Ismail-Beigi, MD, PhD; Nowreen Haq, MD, MPH; Harlan M. Krumholz, MD, SM; Chirag R. Parikh, MD, PhD

Arch Intern Med. 2012;172(10):761-769

A Microalbuminuria

Study or Subgroup	Intensive Therapy Events	Intensive Therapy Total	Standard Therapy Events	Standard Therapy Total	Weight, %	Risk Ratio M-H, Random (95% CI)
ACCORD[8,14]	720	3250	828	3273	27.3	0.88 (0.80-0.96)
ADVANCE[12]	1318	5571	1434	5569	29.3	0.92 (0.86-0.98)
Kumamoto[4,15]	5	52	11	50	1.3	0.44 (0.16-1.17)
UKPDS 33[16]	368	2277	172	938	19.6	0.88 (0.75-1.04)
UKPDS 34[17]	79	342	95	411	12.2	1.00 (0.77-1.30)
VADT[11]	43	442	61	463	7.6	0.74 (0.51-1.07)
VA Feasibility Trial[5]	7	42	30	46	2.5	0.26 (0.13-0.52)
Total (95% CI)		**11976**		**10750**	**100.0**	**0.86 (0.76-0.96)**
Total events	**2540**		**2631**			

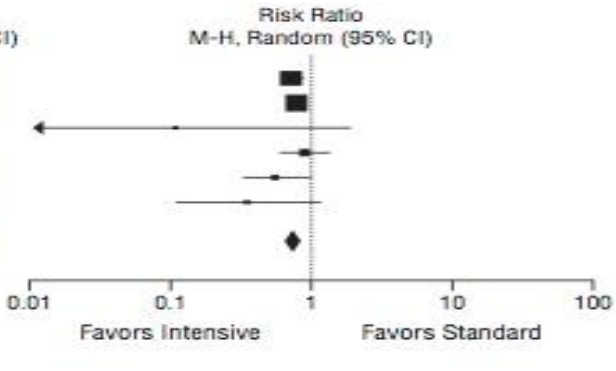
Heterogeneity: $\tau^2 = 0.01$; $\chi^2_6 = 16.71$; $P = .01$; $I^2 = 64\%$
Test for overall effect: $z = 2.60$; $P = .009$



B Macroalbuminuria

Study or Subgroup	Intensive Therapy Events	Intensive Therapy Total	Standard Therapy Events	Standard Therapy Total	Weight, %	Risk Ratio M-H, Random (95% CI)
ACCORD[8,14]	195	4397	272	4424	39.3	0.72 (0.60-0.86)
ADVANCE[12]	230	5571	292	5569	42.5	0.79 (0.67-0.93)
Kumamoto[4,15]	0	52	4	50	0.2	0.11 (0.01-1.94)
UKPDS 33[16]	72	2277	33	938	10.4	0.90 (0.60-1.35)
VADT[11]	20	693	36	703	6.2	0.56 (0.33-0.96)
VA Feasibility Trial[5]	3	24	10	28	1.4	0.35 (0.11-1.13)
Total (95% CI)		**13014**		**11712**	**100.0**	**0.74 (0.65-0.85)**
Total events	**520**		**647**			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2_5 = 5.73$; $P = .33$; $I^2 = 13\%$
Test for overall effect: $z = 4.24$; $P = .001$



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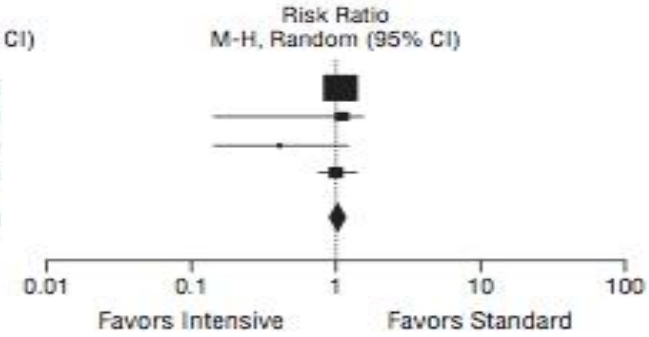
Doubling of the Serum Creatinine Level

Study or Subgroup	Intensive Therapy Events	Intensive Therapy Total	Standard Therapy Events	Standard Therapy Total	Weight, %	Risk Ratio M-H, Random (95% CI)
ACCORD[8,14]	392	5041	357	5035	62.5	1.10 (0.96-1.26)
ADVANCE[12]	67	5571	61	5569	15.6	1.10 (0.78-1.55)
UKPDS 33[16]	7	2150	7	895	1.9	0.42 (0.15-1.18)
VADT[11]	78	882	78	884	20.0	1.00 (0.74-1.35)
Total (95% CI)		**13644**		**12383**	**100.0**	**1.06 (0.92-1.22)**
Total events	**544**		**503**			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2_3 = 3.46$; $P = .33$; $I^2 = 13\%$

Test for overall effect: $z = 0.76$; $P = .44$



SURROGATES AS DISEASE PROGRESSION MARKERS?

	Microalbuminuria	ESRD	3-line↓	Vision loss
ACCORD	-21%	-5%	-16%	-5%

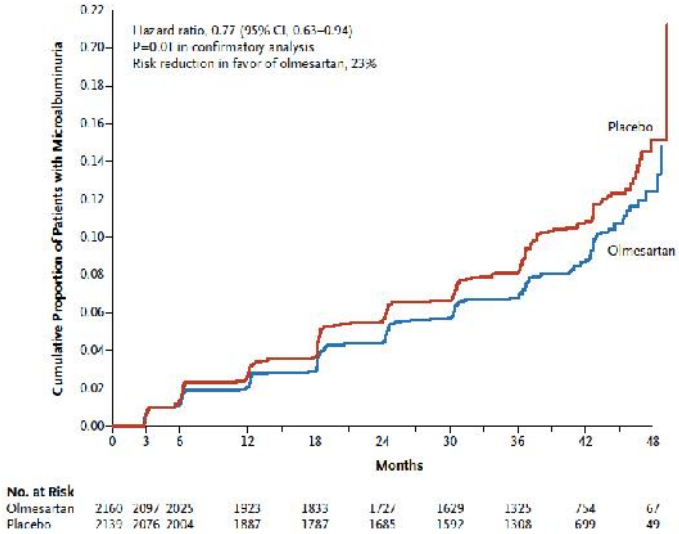
	ETDRS 3 step↓	Vision loss
ACCORD EYE		
Glycaemia	-33%	-12%
Fibrate	-40%	-5%

SURROGATES AND ‘DISEASE PREVENTION’

ROADMAP

4447 patients type 2 diabetes

Olmesartan vs placebo 3.2y



‘Microalbuminuria incidence’ reduced from 9.8% to 8.2%

Incident microalbuminuria	**-16/1000**
Excess mortality	**+5.4/1000**

Haller et al NEJM 2011

SURROGATES AND 'DISEASE PREVENTION'

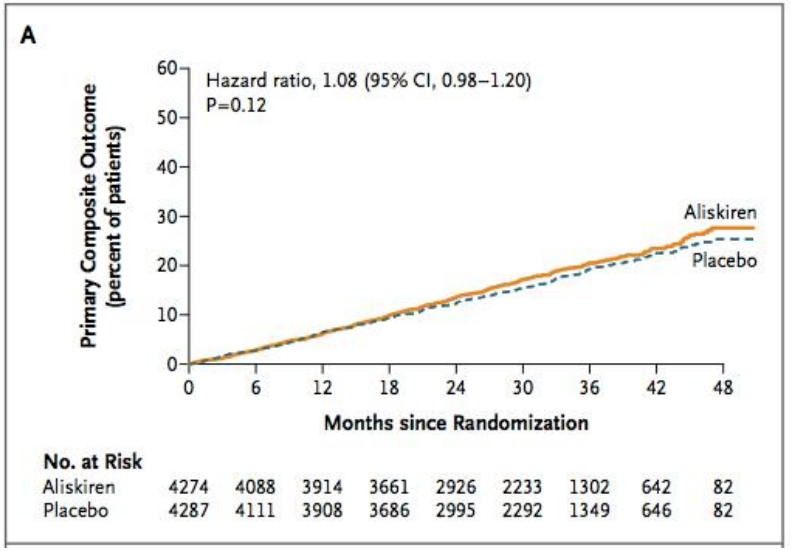
ALTITUDE Trial

8561 patients type 2 DM + CVD/CKD

Aliskiren vs placebo 2.7y

Lower blood pressure, ACR with aliskiren

Study stopped prematurely after interim analysis showed excess adverse events with aliskiren



Parving et al NEJM 2012

SURROGATES AND 'DISEASE PREVENTION'

ALTITUDE Trial

8561 patients type 2 DM + CVD/CKD

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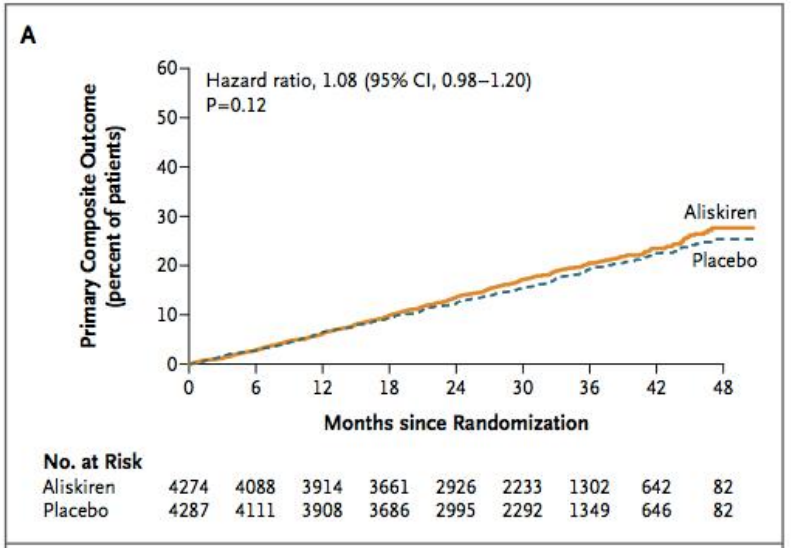


Lower blood pressure, ACR with aliskiren

Study stopped prematurely after interim analysis showed excess adverse events with aliskiren

"..underscores the need to go beyond surrogate biomarkers and obtain risk–benefit data from clinical end-point trials."

Parving et al NEJM 2012

SURROGATE ENDPOINTS

Exodus 32

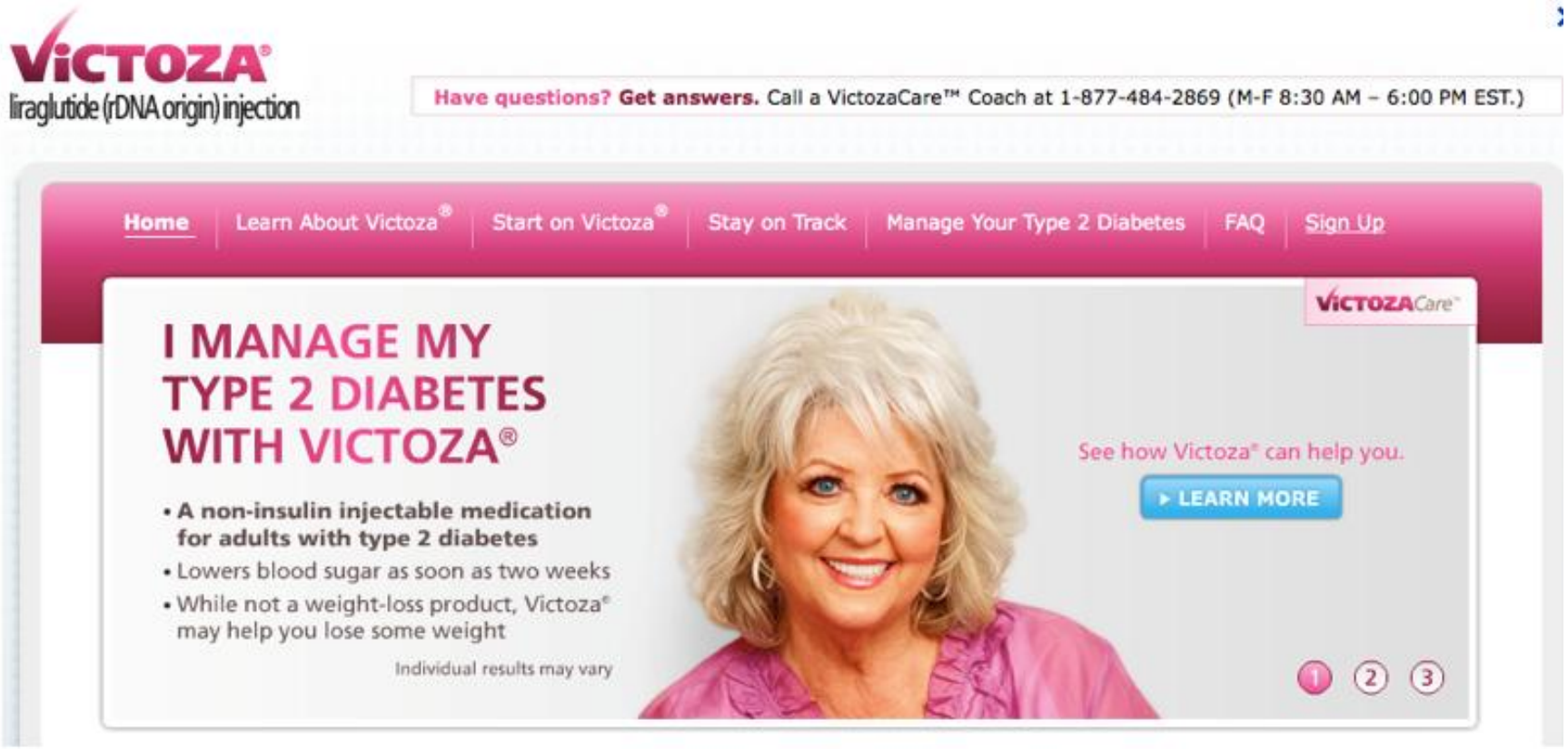
With thanks to Paul Katula

SURROGATE ENDPOINTS

Exodus 32

With thanks to Paul Katula

BYETTA AND VICTOZA



BYETTA AND VICTOZA

The new rosiglitazones?

Conclusions

- Assumptions around diabetes guideline targets are not usually based on clinically important endpoints
- Emphasis on these targets in guidelines and in reimbursements may encourage unsafe prescribing
- Surrogate endpoints may not accurately reflect hard endpoints
- Patients are rarely presented with enough information to make informed decisions
- Licensing of diabetes treatments need to be evaluated on the basis of hard endpoints

Informed Choice

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65 year old woman, HbA1c 8.0% on maximal oral Rx

Informed Choice

---

65 year old woman, HbA1c 8.0% on maximal oral Rx

“Insulin will reduce your risk of blindness and kidney failure by 25%, and may help prevent heart attacks”

Informed Choice

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65 year old woman, HbA1c 8.0% on maximal oral Rx

“Insulin will reduce your risk of blindness and kidney failure by 25%, and may help prevent heart attacks”

OR

“Your lifetime risk of blindness is 2 in 1000, and of kidney failure 5 in 1000.

We don’t know with certainty whether insulin would reduce this.

Your 5 year risk of a heart attack is around 74 in 1000 which insulin would lower to 67 in 1000, but not fatality.

Your risk of serious hypoglycaemia would be increased with insulin by 47 per 1000 in 5 years.”