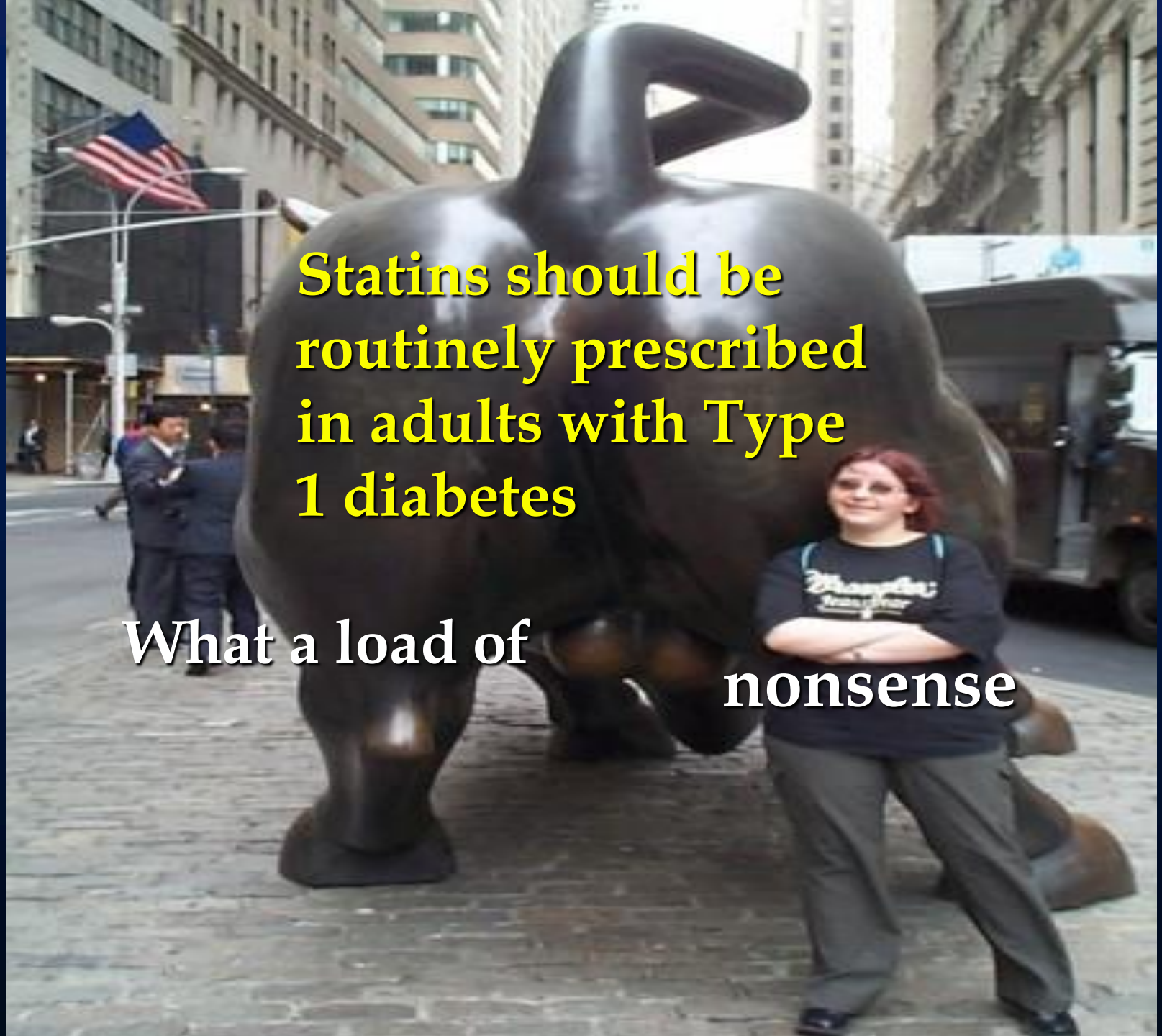
ABCD debate 06042006

John McKnight


Statins should be routinely prescribed in adults with Type 1 diabetes
What a load of
nonsense

Reflections

- Prescribing
  - Media
  - Politics/finance
  - Medical literature
  - Guidelines committees
  - Pharmaceutical industry

Conflict of interest

- Pfizer
  - CARDS investigator
  - ADA with Pfizer
  - Few talks for them (local)
  - Advisory Board

THE SCOTSMAN
Tue 14 Mar 2006

Heart surgery: May be needed less frequently if further trials confirm original findings. Picture: Julie Bull

Doctors discover drug to reverse heart disease

LYNDSAY MOSS
HEALTH CORRESPONDENT

- 'Holy grail' drug breaks up fat that leads to heart attacks and strokes
- Four out of five patients successfully treated; no serious side effects
- Around 2m British people affected by narrowed arteries caused by fat

Key quote "For the first time, we have shown that it is possible to turn the clock back in the arteries of people with heart disease" - *Dr Neal Uren, Edinburgh Royal Infirmary*

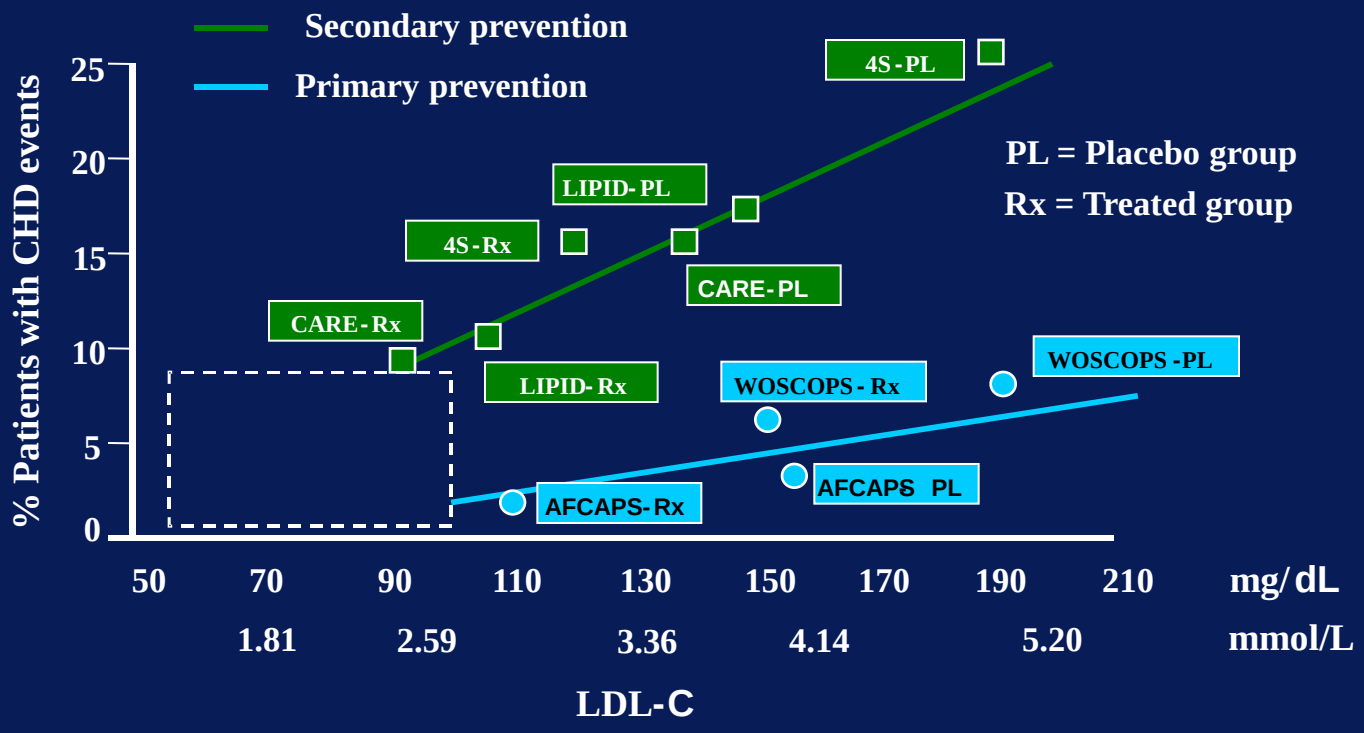
Politics

- New GP contract
- Insulin pump therapy

Literature

- Publication bias
- Enthusiasm of authors
- Different interpretation
- Extrapolation of results to different populations
- Information overload

Effects of Lipid Lowering Therapy on CHD Events in Statin Trials



Adapted from Kastelein JJP. Atheroscler 1999;143 (Suppl 1):S17 S21.

Problems with interpretation

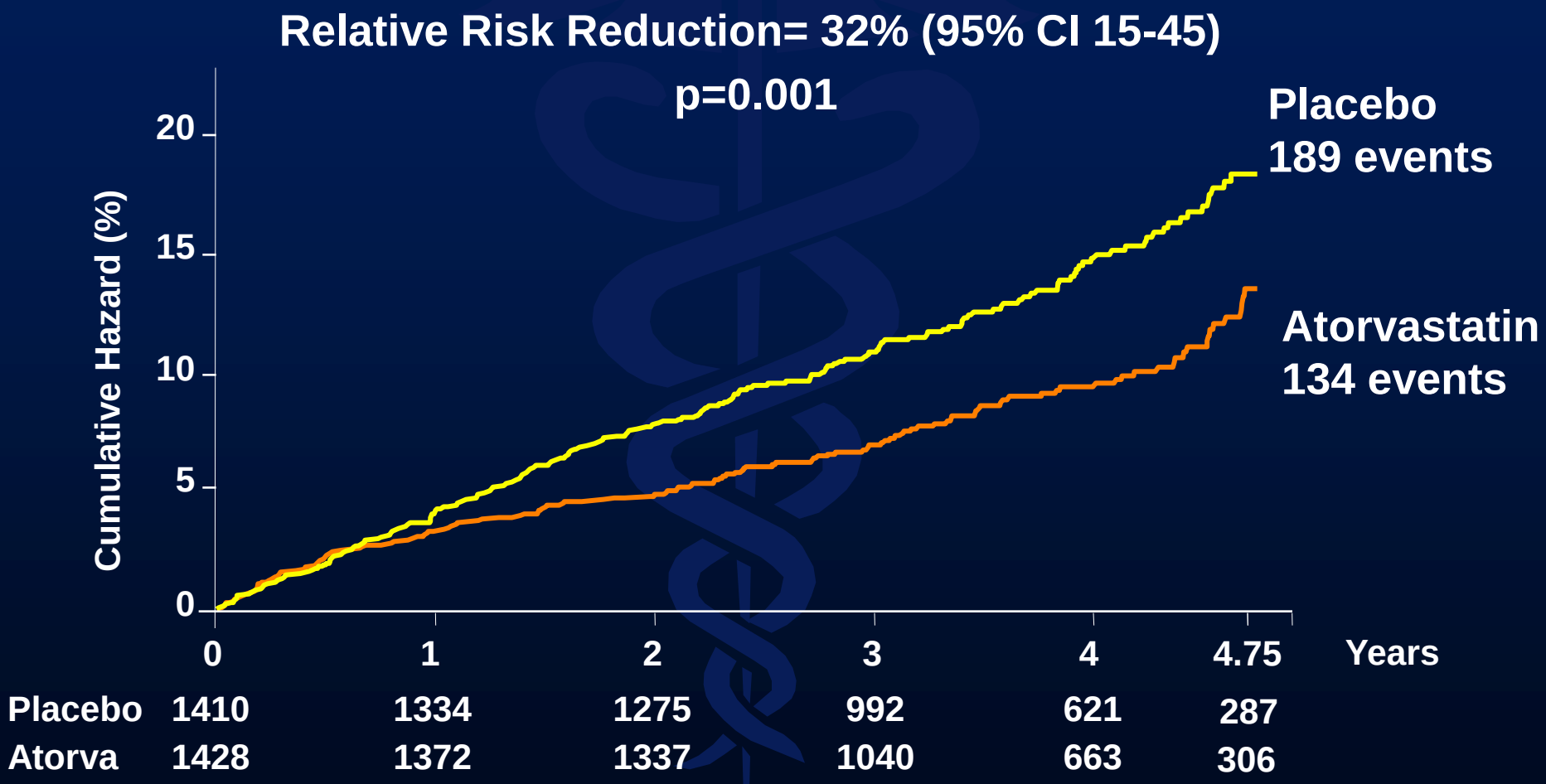
- Events count vs individuals with an event
- Major vs minor events
  - Angina, NSTEMI vs coronary death/severe stroke
- Few truly primary prevention studies

CARDS Eligibility Criteria

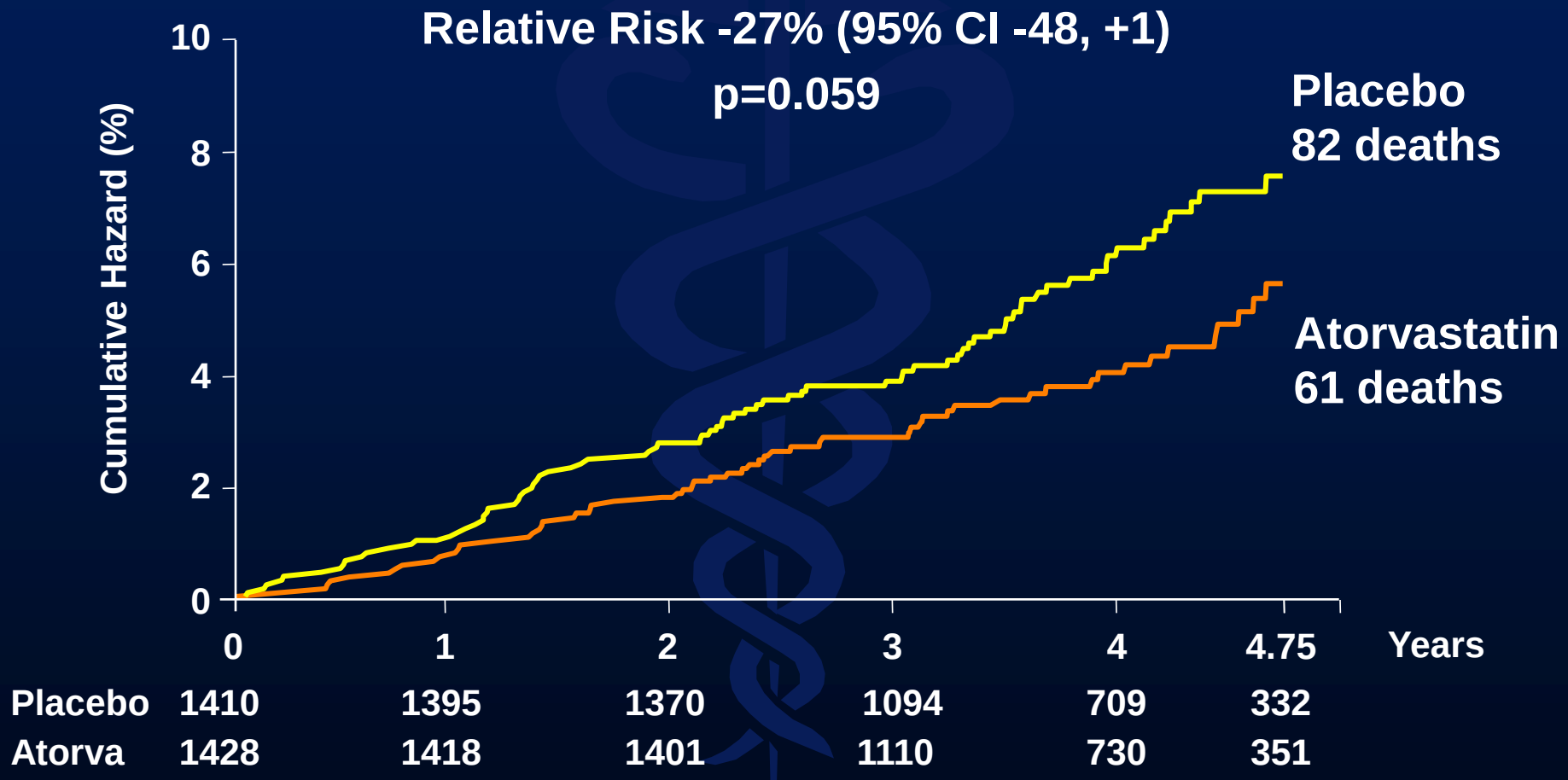
- **Type 2 diabetes, 40-75 years of age**
- Cholesterol not very elevated
- **But high vascular risk:**
  - **Hypertension defined as receiving antihypertensive treatment or SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg**
  - **Retinopathy**
  - **Microalbuminuria or macroalbuminuria**
  - **Current smoking**

Colhoun HM et al. Diabetic Med. 2002;19:201-211.

Cumulative Hazard for Any CVD Endpoint



Cumulative Hazard for All Cause Mortality



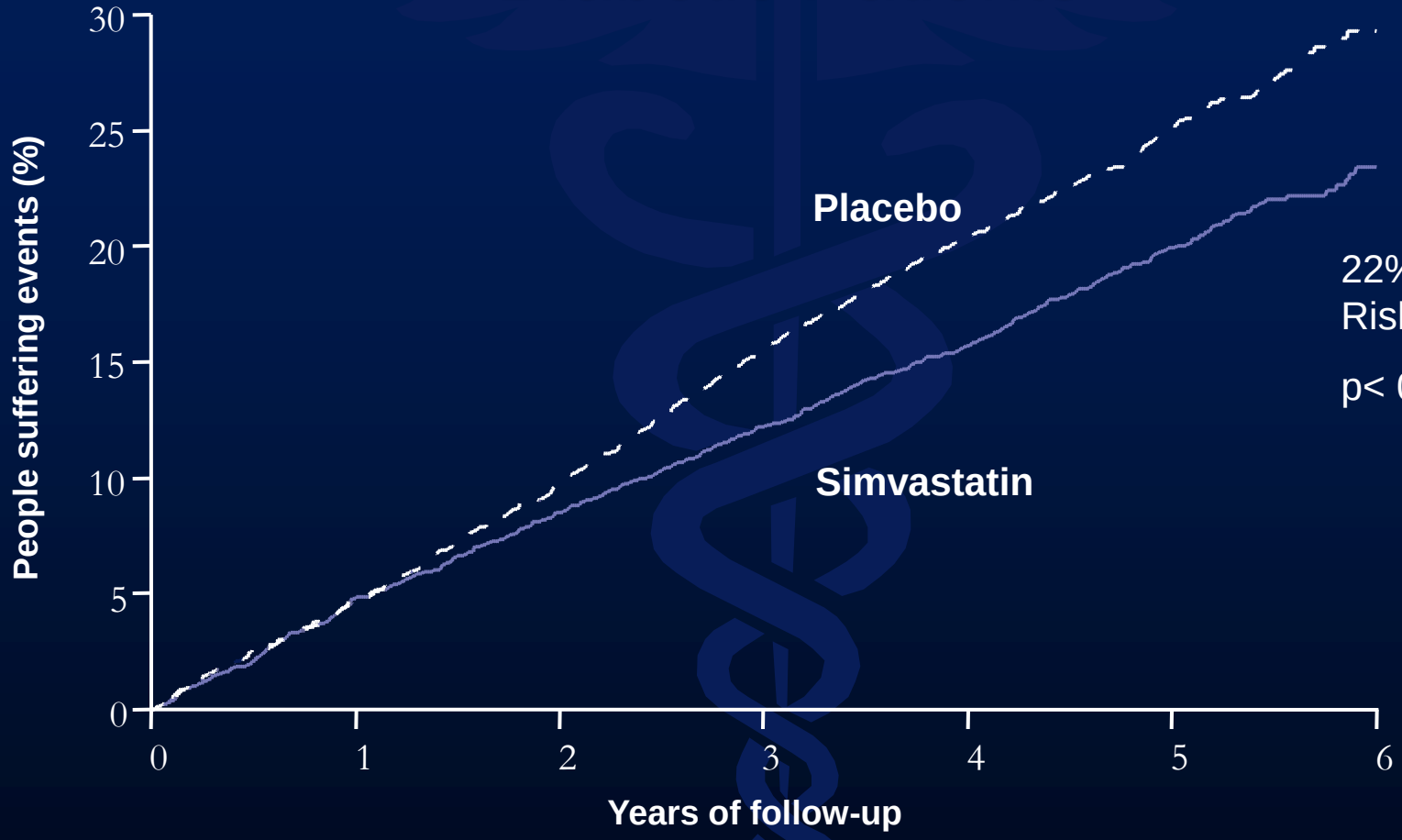
Cause of Death By Treatment Arm

	Placebo	Atorvastatin
Total deaths	**82**	**61**
Coronary	25	21
Other cardiac	3	1
Cerebrovascular	7	1
Other cardiovascular	2	2
Total cardiovascular deaths	37 (2.6%)	25 (1.8%)
Diabetes related death	1	2
Cancer death	30	20
Suicide,accident or violent death	3	4
Other death	11	10
Total non-cardiovascular deaths	45 (3.2%)	36 (2.5%)

Baseline characteristics of HPS with diabetes

- 5963 patients
- Men 70 %
- Smokers 13 %
- Vascular disease present 51 %

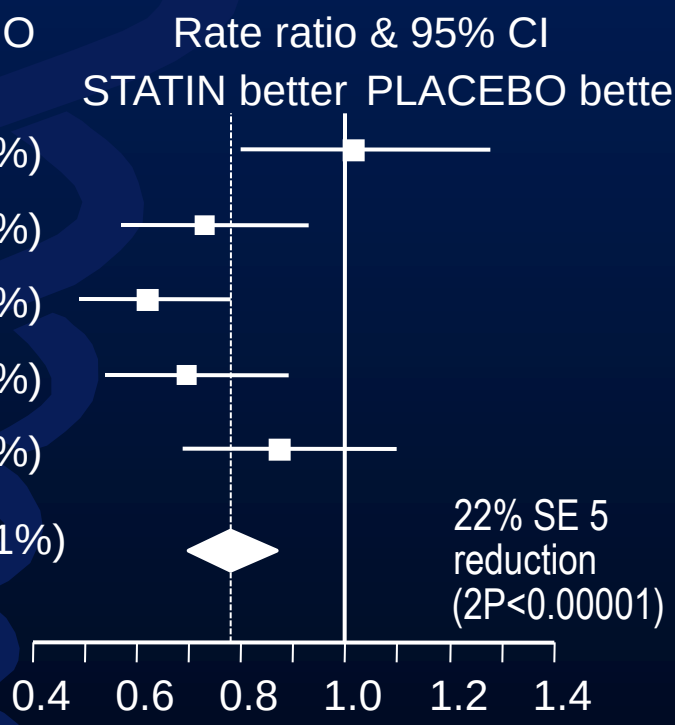
HPS - Major Vascular Events by Year in Diabetic Patients



HPS, *Lancet* 2003; 361:2005-16.

SIMVASTATIN: MAJOR VASCULAR EVENT by YEAR in DIABETIC PATIENTS

Year of follow-up	SIMVASTATIN (2978)	PLACEBO (2985)
1	143 (4.8%)	141 (4.7%)
2	110 (3.9%)	150 (5.3%)
3	109 (4.0%)	172 (6.5%)
4	101 (3.9%)	138 (5.6%)
5+	138 (5.7%)	147 (6.4%)
ALL FOLLOW-UP	601 (20.2%)	748 (25.1%)



Conclusions

- HPS
  - Statin therapy should be now be considered routinely for all diabetic patients **at sufficiently high risk of major vascular events……**

Conclusions

- HPS
  - Statin therapy should be now be considered routinely for all diabetic patients at sufficiently high risk of major vascular events…….
- CARDS
  - The debate about whether all people with this disorder warrant statin treatment should now focus on whether any patients are at sufficiently low risk for this treatment to be withheld

Negative aspects

- Harm
  - Side effects
  - Labelling
- Financial cost
- Wrong emphasis
- Compliance

Guidelines, targets and consensus statements

Guidelines/ targets

- ‘Value is almost always a round number made up by international jet-setting, moralistic time-expired self appointed gurus producing glossy consensus statements.
- The higher the moral ground the lower the value’

David Matthews RCPE

Targets

- We're always told we must have a target, or otherwise no-one will know what we are aiming at.
- Fine – you tell me a number and I'll better it by telling you in a serious voice that you are far too conservative, and if you were as good a doctor as I am you'd certainly be aiming lower than that.

SIGN Guidelines

Methodological Principles

- Development is carried out by multidisciplinary, nationally representative groups
- A systematic review is conducted to identify and critically appraise the evidence
- Recommendations are explicitly linked to the supporting evidence

GOBSAT methodology

- Advantages
  - Cheap, quick, fits the hierarchical nature of the medical profession
- Disadvantages
  - Unreliable, could be open to bias, outdated

Risk reduction of 25 %

- Sufficient risk
- CVD risk charts
  - Predict risk of non-fatal MI or stroke, coronary or stroke death or new onset of angina
- Treat those at 20 % risk

Benefit depends on absolute risk

- 100 patients at 20 % risk over 10 years
- 80 don't have an event
- 20 have an event

- Treat 100 patients at 20 % risk over 10 years
- 80 don't have an event
- Of 20 who would have an event
  - **15 still do**
  - **5 events prevented**

NNT 20

‘Benefit’ or NNT depend on absolute risk

25 % risk reduction

- Risk 1 % in 10 years
- NNT 400 to prevent one event

- Risk 40 % in 10 year
- NNT 10

The question is:

Which (if any) patients with type 1 diabetes are at sufficient risk to require intervention?

20 % 10 yr risk

JBS 2 (Diabetes)

- All patients above 40 yr
- 18 to 39 with
  - **Retinopathy**
  - **Nephropathy or microalbuminuria**
  - **HbA1c >9 %**
  - **Treated HT**
  - **Total chol >6 mmol/l**
  - **Metabolic syndrome**
  - **FH of premature CVD in 1st degree relative**

That's more than half of my patients aged 20 to 40!

Diabetes UK Cohort

- 22,848 patients - England and Scotland
- Date of entry 1972 – 1993
- Flagged at NHSCR – Death
  Emigration
  Cancer
- Follow-up to June 2004

  Deaths = 1944

Laing SP et al, Diabetologia 2003
Stroke 2003

Mortality rates and SMRs for all-cause deaths

All ages 1-84	No. deaths	Rate Type 1	Rate Gen pop	SMR
Males	1163	469	160	2.9*
Females	781	357	86	4.1*

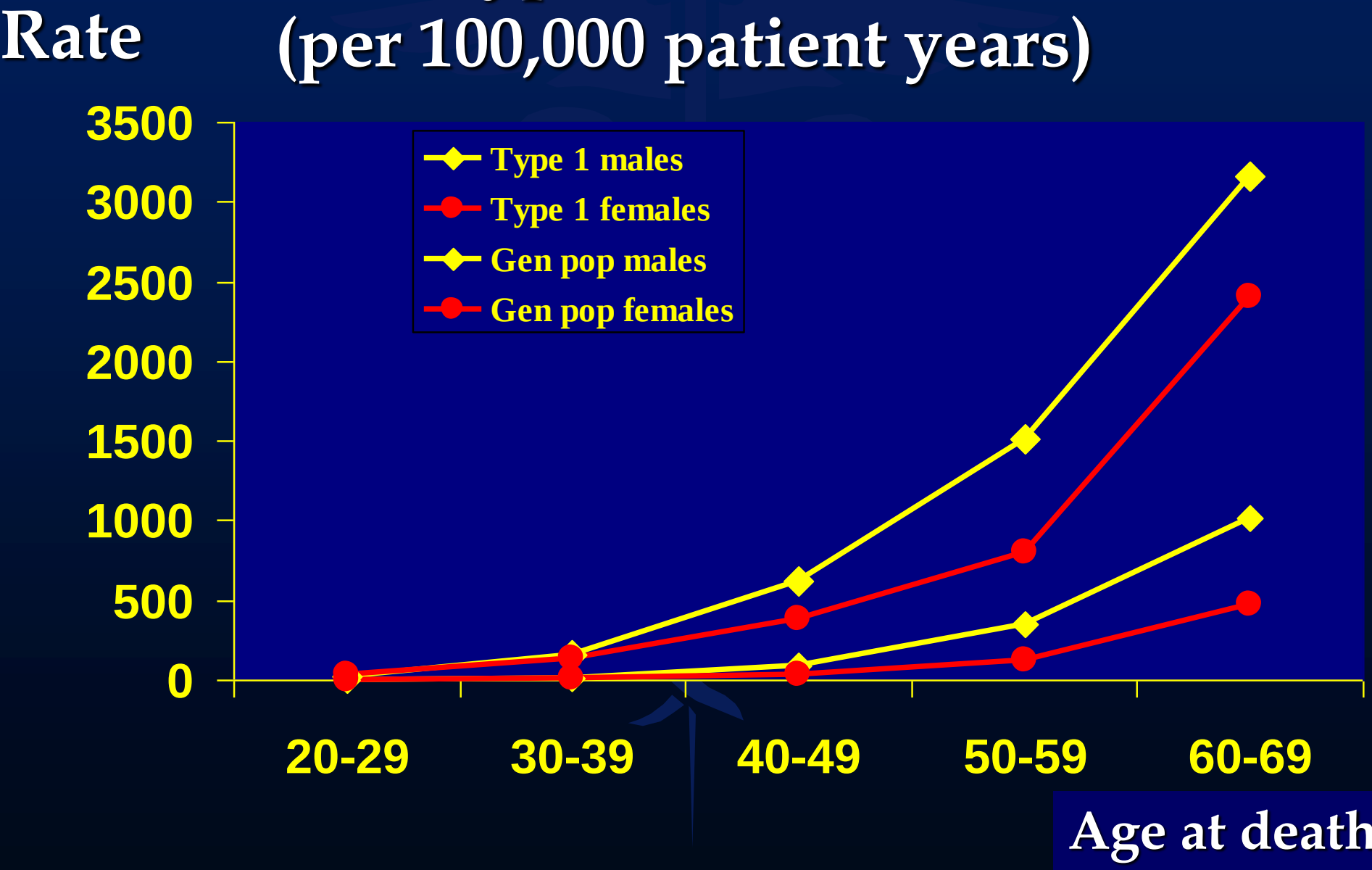
Rate per 100,000 person years

Cardiovascular mortality Type I diabetes

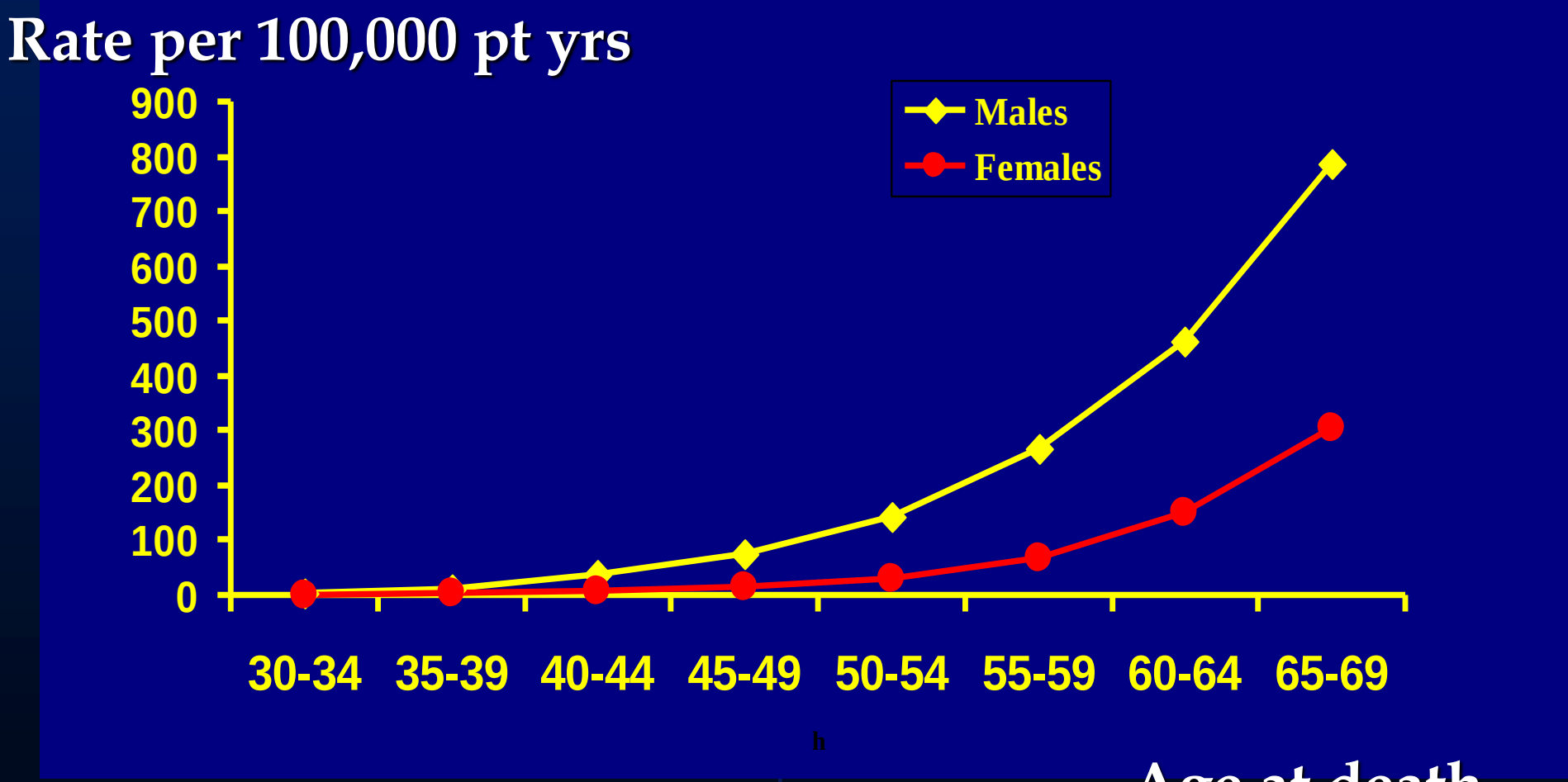
- Males n=438
  - **IHD** **n=312 (71%)**
  - Other heart n=45
  - **Cerebrovascular** **n=60 (14%)**
  - Other n=21

- Females n=295
  - **IHD** **n=193 (65%)**
  - Other heart n=29
  - **Cerebrovascular** **n=60 (18%)**
  - Other n=19

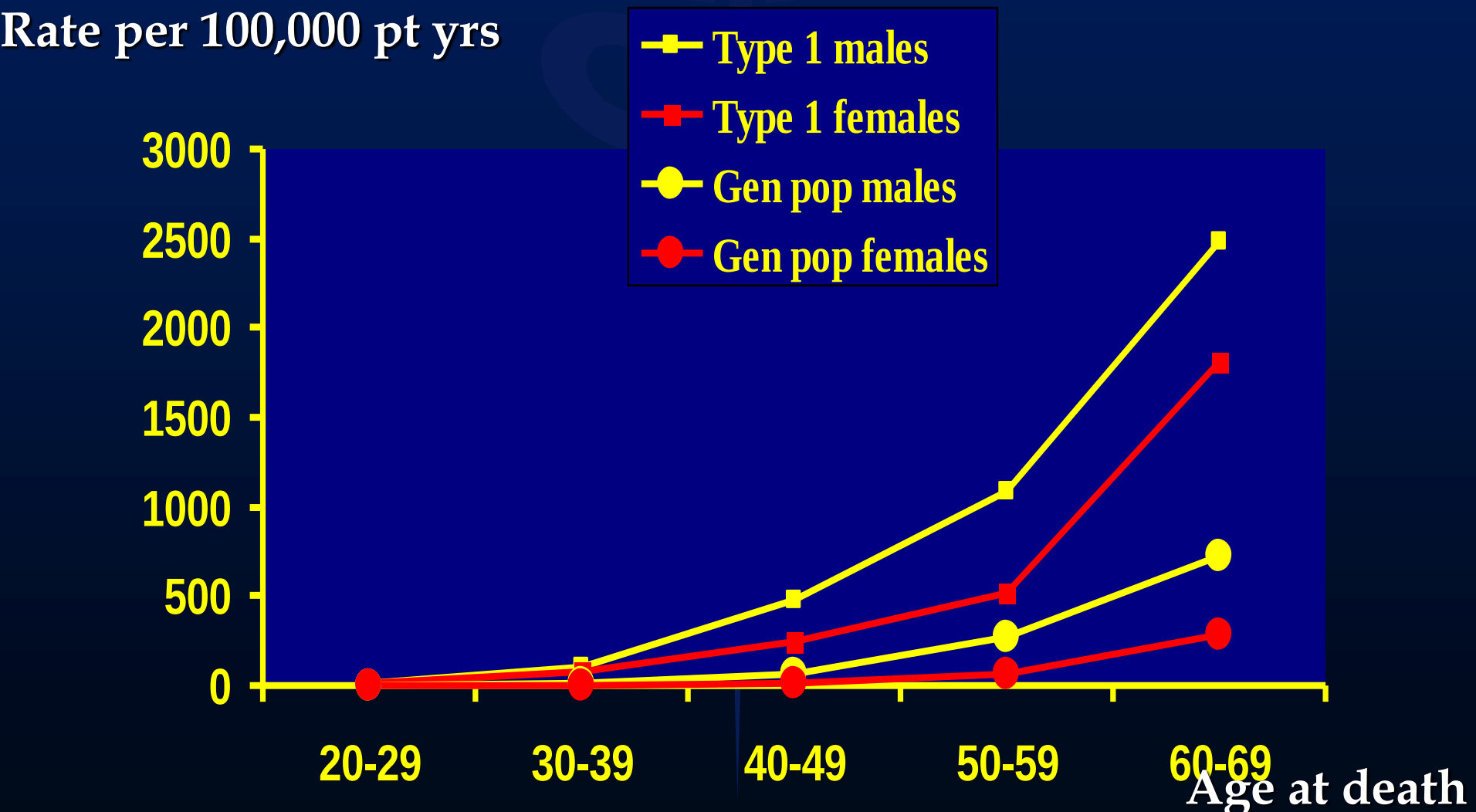
CVD mortality in patients with Type 1 diabetes (per 100,000 patient years)



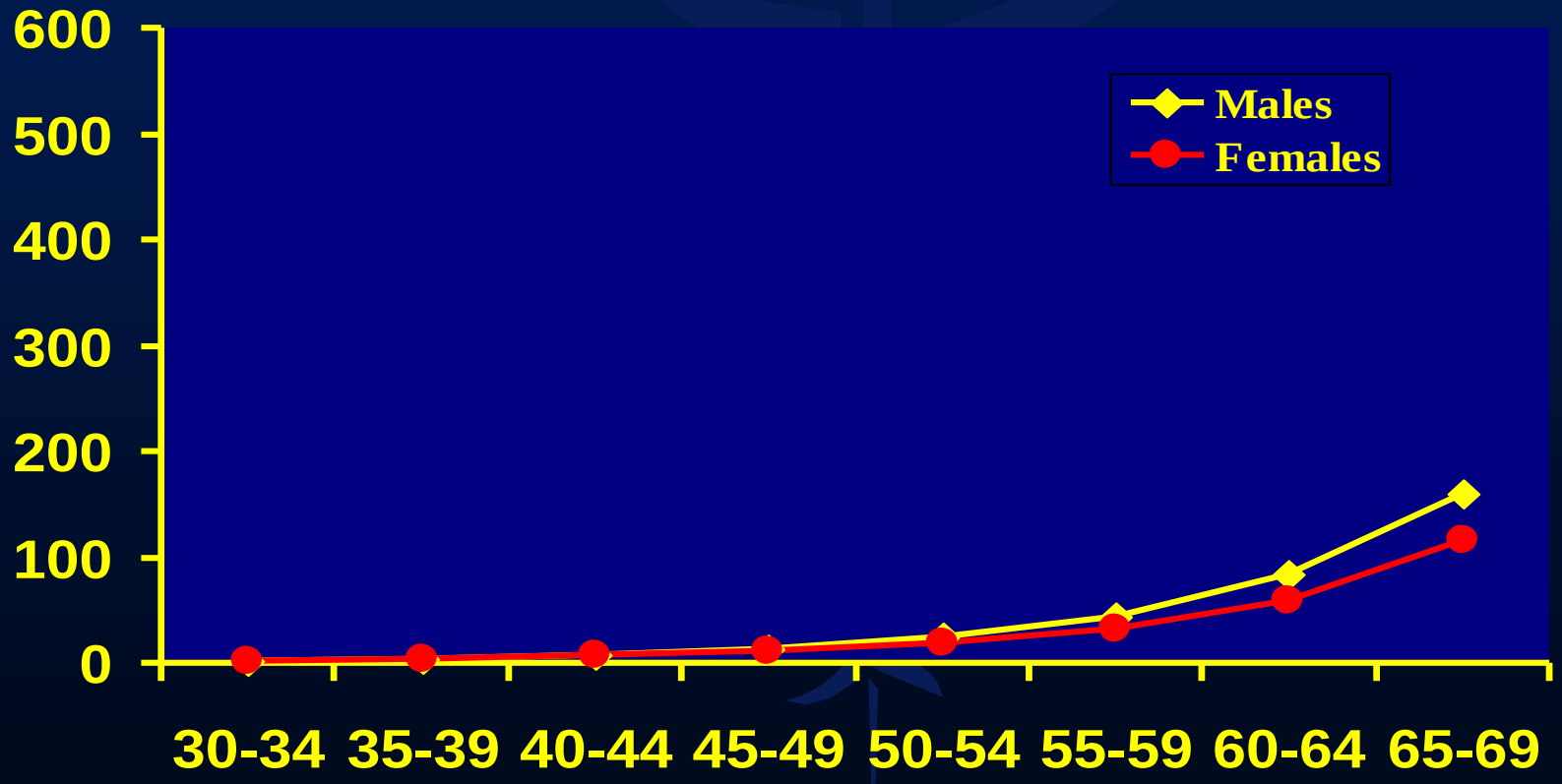
General Population UK – IHD mortality 30-69 years



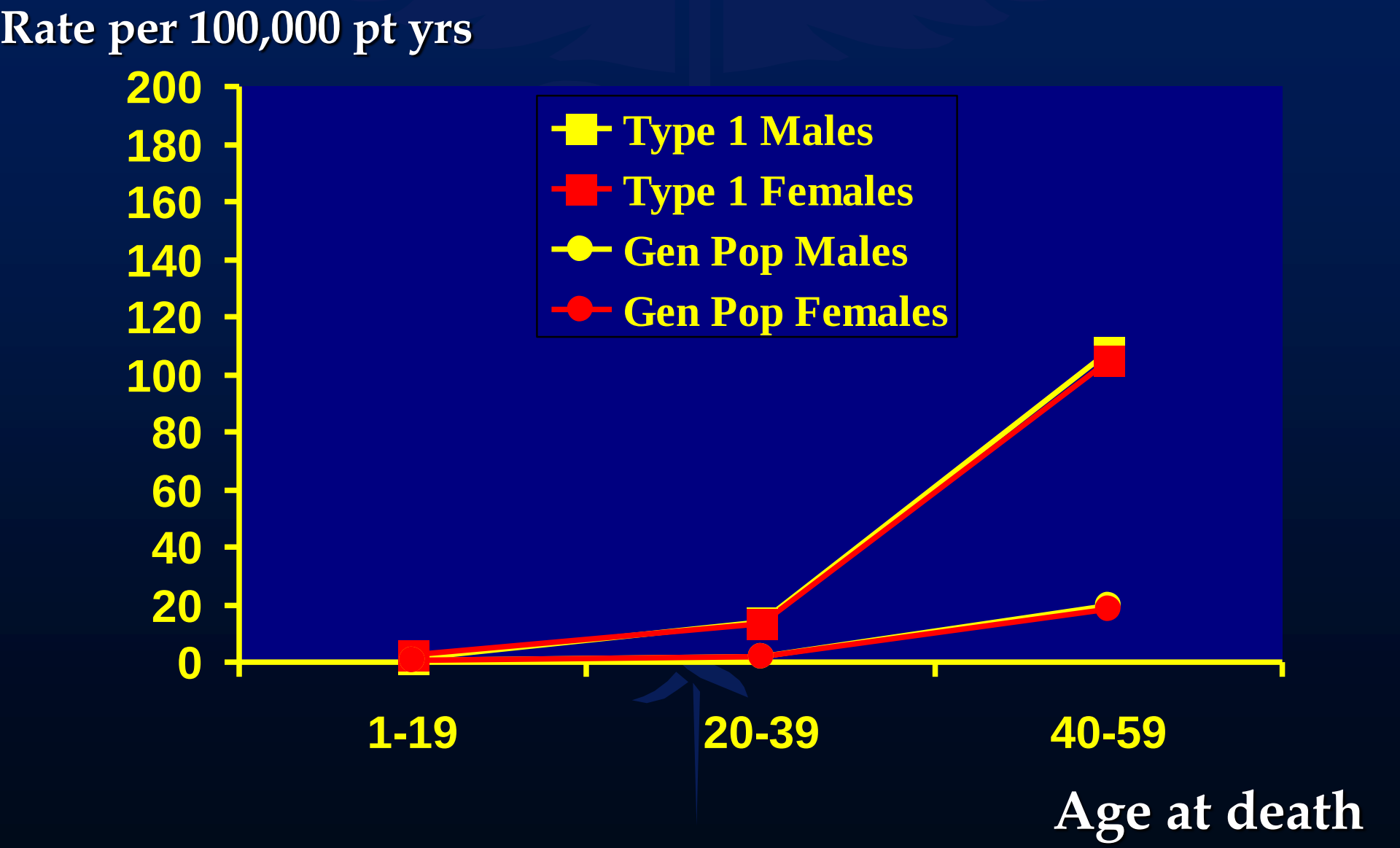
IHD mortality in patients with Type 1 diabetes, 20-69 years



General Population UK – Cerebrovascular mortality 30-69 years (per 100,000 pt years)



Cerebrovascular mortality <60 years



Ischaemic heart disease mortality by age

Age		Rate Type 1	Rate Gen pop	SMR
20-29		12		
30-39	M	98	8	12.1*
	F	83	2	42.1*
40-49	M	478	64	7.5*
	F	240	14	17.4*
50-59	M	1080	265	4.1*
	F	519	70	7.5*
60-69	M	2483	729	3.4*
	F	1815	287	6.3*

Summary…. (Death)

Age range	Stroke/IHD mortality rate (100,000 pt yr)	10 Yr risk (%)	NNT for 10 yrs to prevent one death
20 -29	26	0.26	1538
30-39	104	1.04	385
40-49	462	4.62	87
50-59	2340	23.4	17

Laing SP et al. Diabetologia 2003

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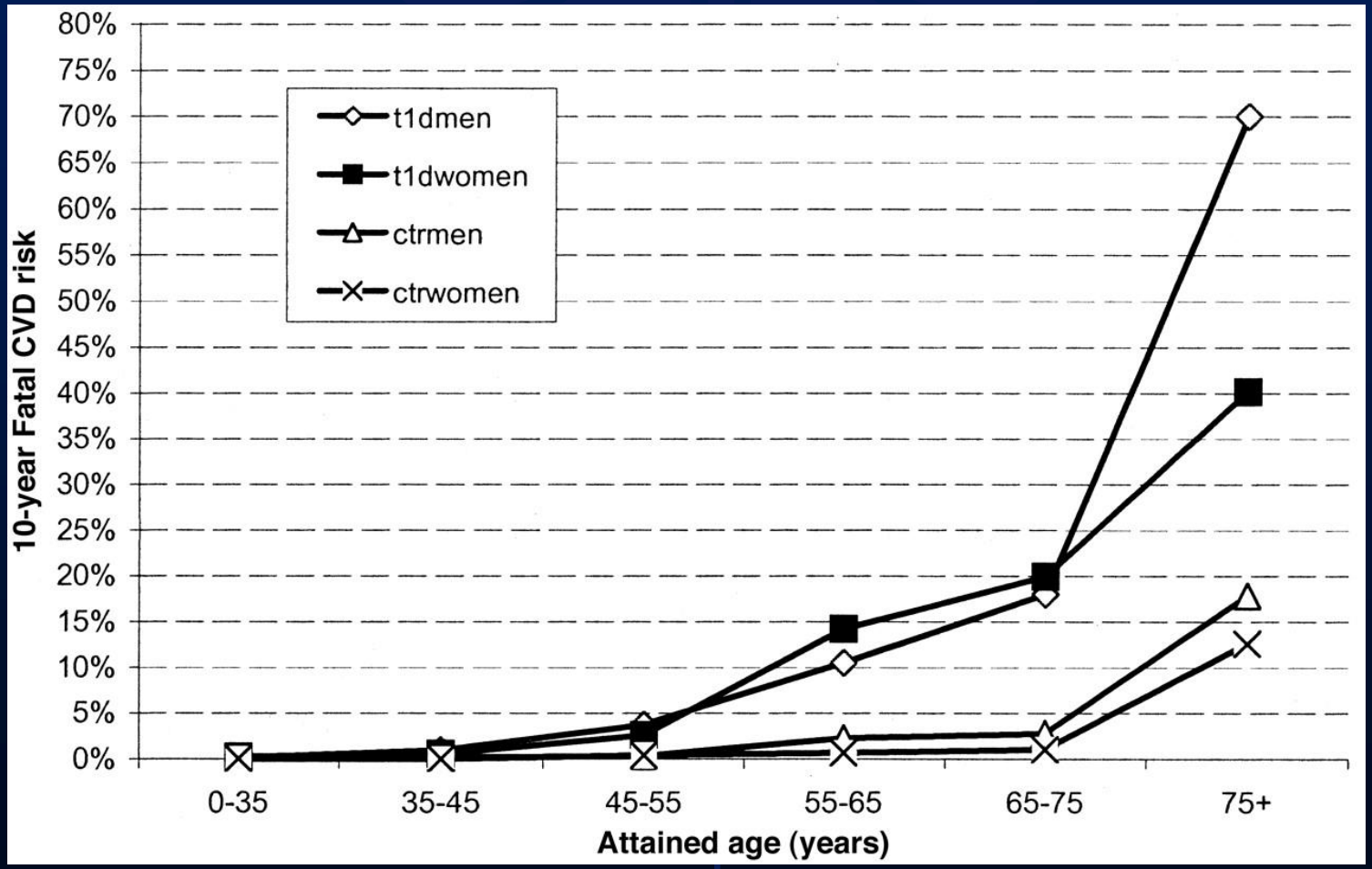
Laing SP et al, Diabetologia 2003

Figure 1— Estimated 10-year fatal CVD risk by current (or attained) age in type 1 diabetic (t1d) men and women compared with nondiabetic comparison group (ctr).



Soedamah-Muthu et al, Diabetes Care 2006; 29 (4): 798

Vascular risk, not death

- Myocardial infarction, acute coronary heart disease death, revascularisation or stroke
- New angina

Soedamah-Muthu et al; Diabetes Care 2006; 29: 798

- 7,479 Pts with Type 1 diabetes
- 1992 –1999
- Incident major CVD events
  - **Myocardial infarction, acute coronary heart disease death, revascularisation or stroke**

Absolute risk for major CVD in Type 1 diabetes (% 10 year risk)

Age band	Males	Females
≤ 35	0.8	0.5
35 -45	4.8	3.5
45 - 55	10.6	10.2
55 - 65	39.4	22.8
65 - 75	35.2	38.7
> 75	122	87.3

Diabetes Care 2006; 29: 798

'Numbers needed to treat' to prevent one major CV event

Age band	Males Risk	**Males NNT**	Females Risk	**Females NNT**
≤ 35	0.8	**500**	0.5	**800**
35 -45	4.8	**83**	3.5	**114**
45 - 55	10.6	**38**	10.2	**39**
55 - 65	39.4	**10**	22.8	**18**
65 - 75	35.2	**11**	38.7	**10**
> 75	122	**3?**	87.3	**5?**

Can we predict sub-groups at higher risk?

- Nephropathy
  - Overt more than microalbuminuria
- Retinopathy – confounded by nephropathy
- HbA1c
- Metabolic syndrome
- Hypertension
- Smoking
- Family history

Predicting Risk in Type 1 Diabetes

- RCPE diabetes register
  - Six clinics in Scotland
- Patients with type 1 diabetes
- Excluded those with pre-existing macrovascular disease
- Six to nine years follow up

RCPE diabetes register

- n =2136
- 55 % male
- Aged
  - < 35 1476
  - 35 to 45 433
  - 45 + 227

Outcome SMR link

Stroke	19
TIA	7
Angina	49
MI	38
Intermittent claudication	24
PVD surgery	36
Cardiac surgery	10
Any macrovascular disease	110
Died due to macrovascular disease	30

Significant associations

- Age
- Blood pressure
- Albuminuria
- HbA1c
- Cholesterol
- Smoking status

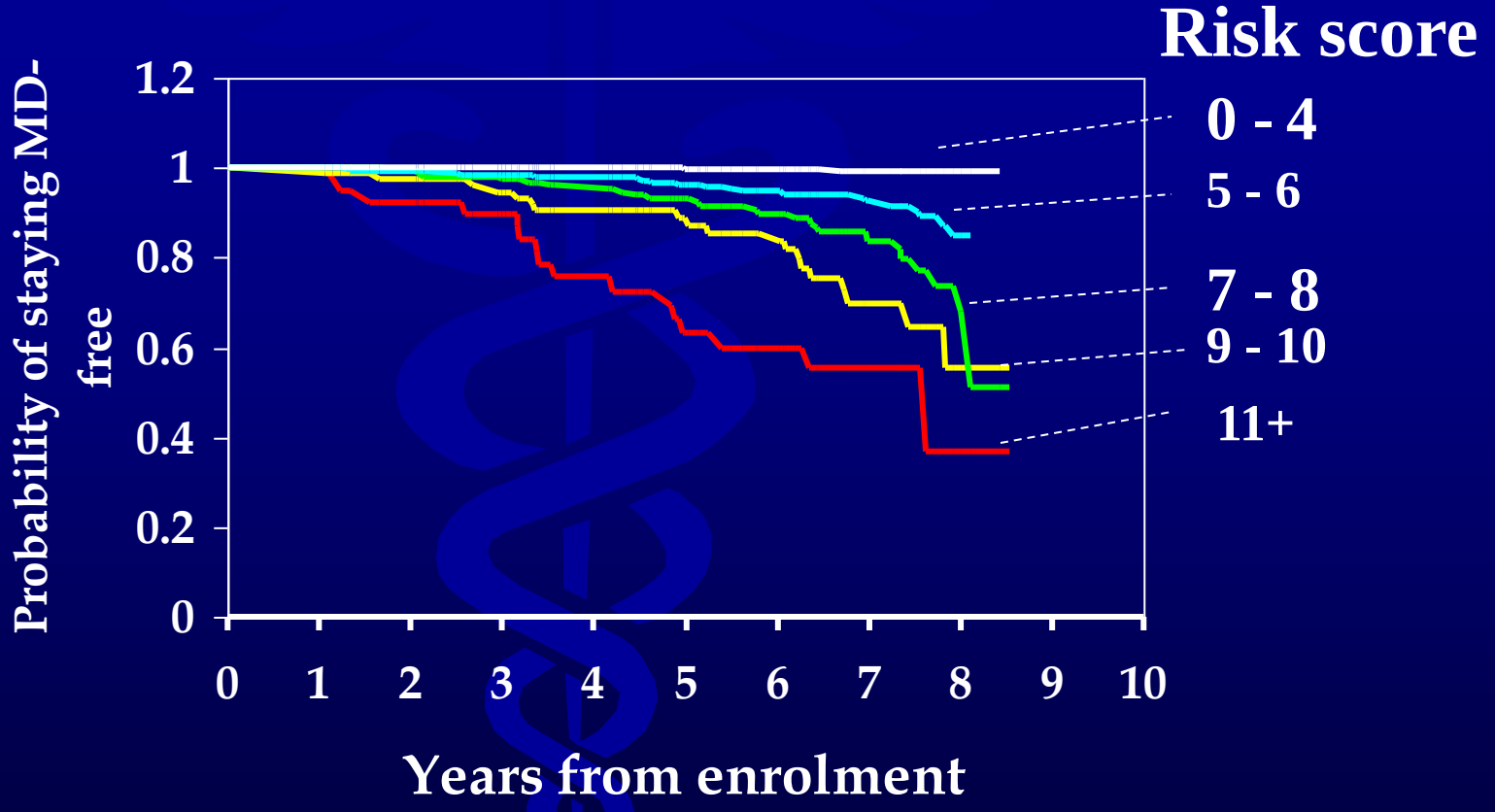
All P < 0.001

Categorisation of variables for proportional hazards regression analysis

and their derived risk scores

- Age
  - < 30……..0
  - 30 – 40 2
  - 40 – 50……..4
  - 50 – 60 6
  - > 60 8
- BP
  - <140/90 0
  - >140/90 2
- Albuminuria 4
- HbAic quartile
  - 0
  - 0
  - 1
  - 2
- Cholesterol
  - 5 – 6 2
  - > 6 3
- Smoking 2

Kaplan-Meier event free survival for different levels of summed macrovascular risk scores



Predicting risk

- Age 30 0
- BP >140/90 2
- Albuminuric 4
- HbA1c 3rd quart 1
- Smoking 2
- Cholesterol >5 2

Score > 7 treat

Conclusions

- There is now sufficient information to estimate vascular risk in adults with Type 1 diabetes
- We should use this information to aid our decision making with patients

Conclusions

- Young adults with type 1 diabetes are at low risk and are likely to attain little benefit from routine use of statins
- There may be a few that would derive benefit
- There is a potential to cost money and cause harm

Statins should

NOT

be routinely prescribed in adults with Type 1 diabetes