Glucose Lowering Agents, Insulins and Cardiovascular Risk Reduction in People with Diabetes

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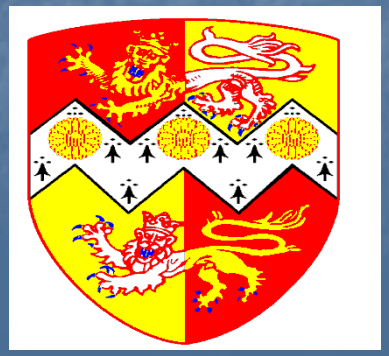
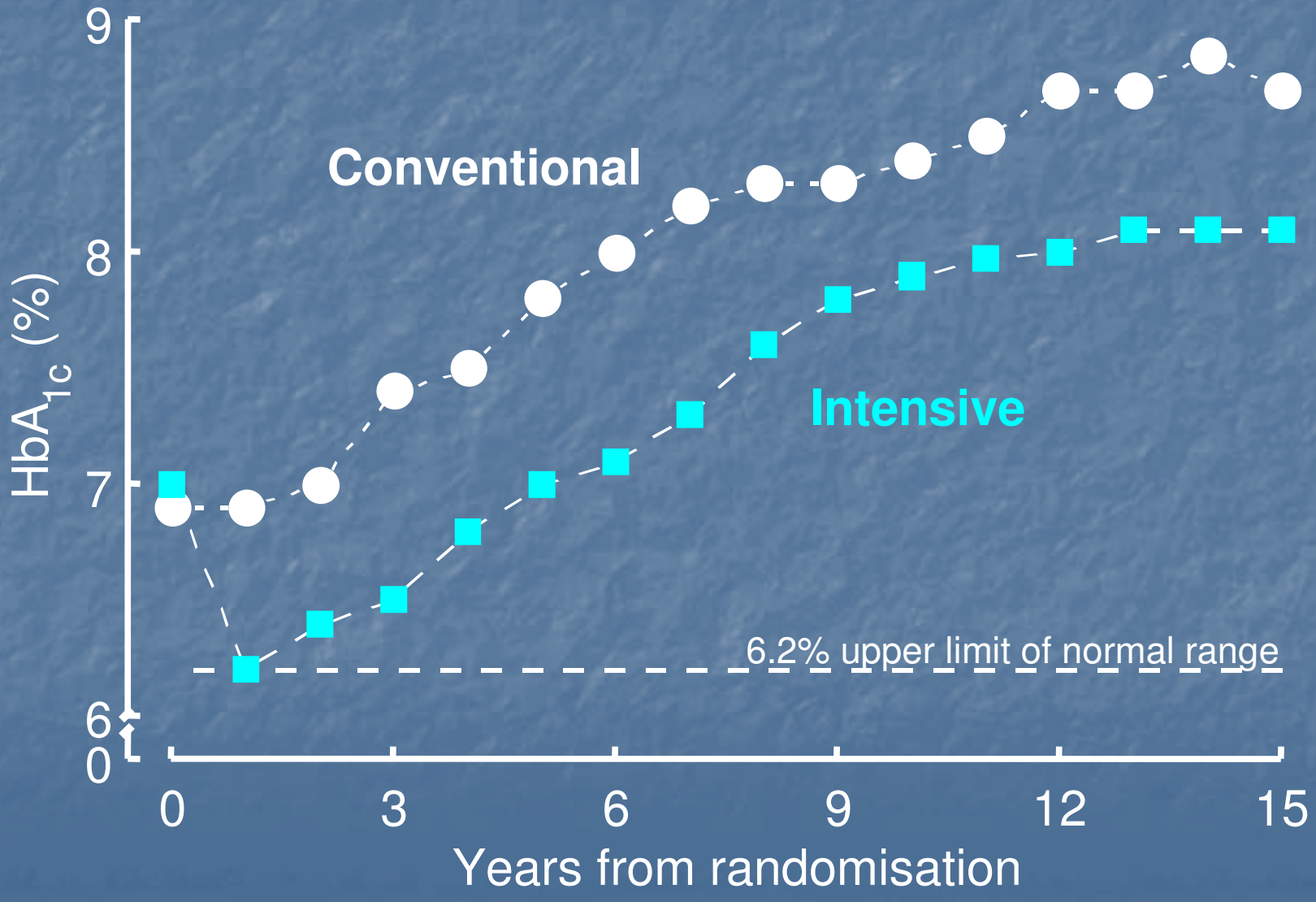
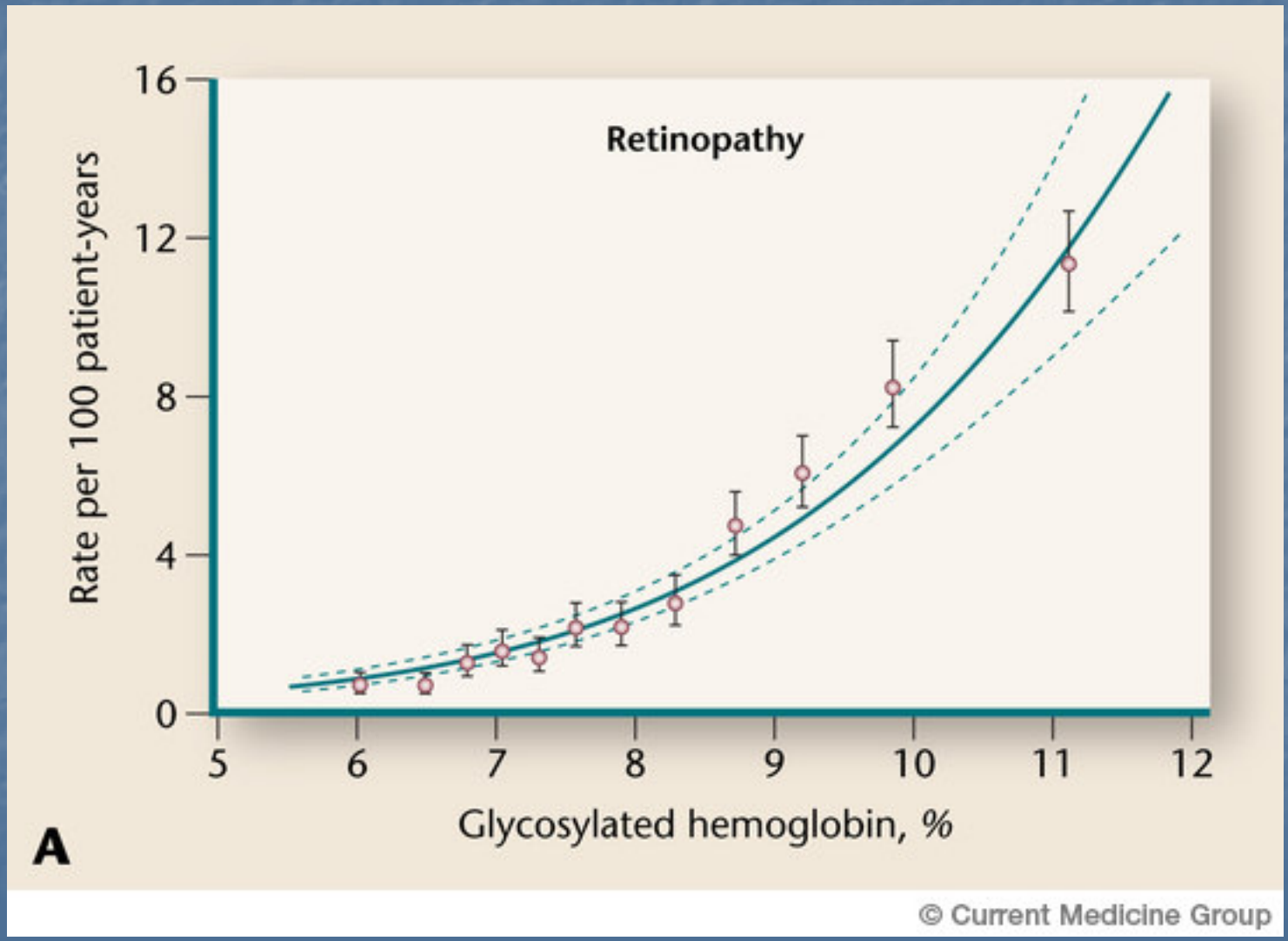


UKPDS HbA_{1c} Median Values

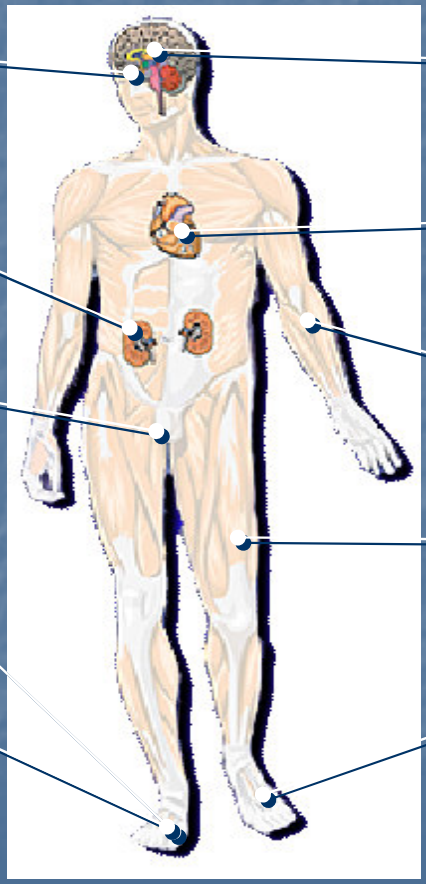


Retinopathy and Glycaemic Control



DCCT Research Group NEJM 1993;329(14):977-986

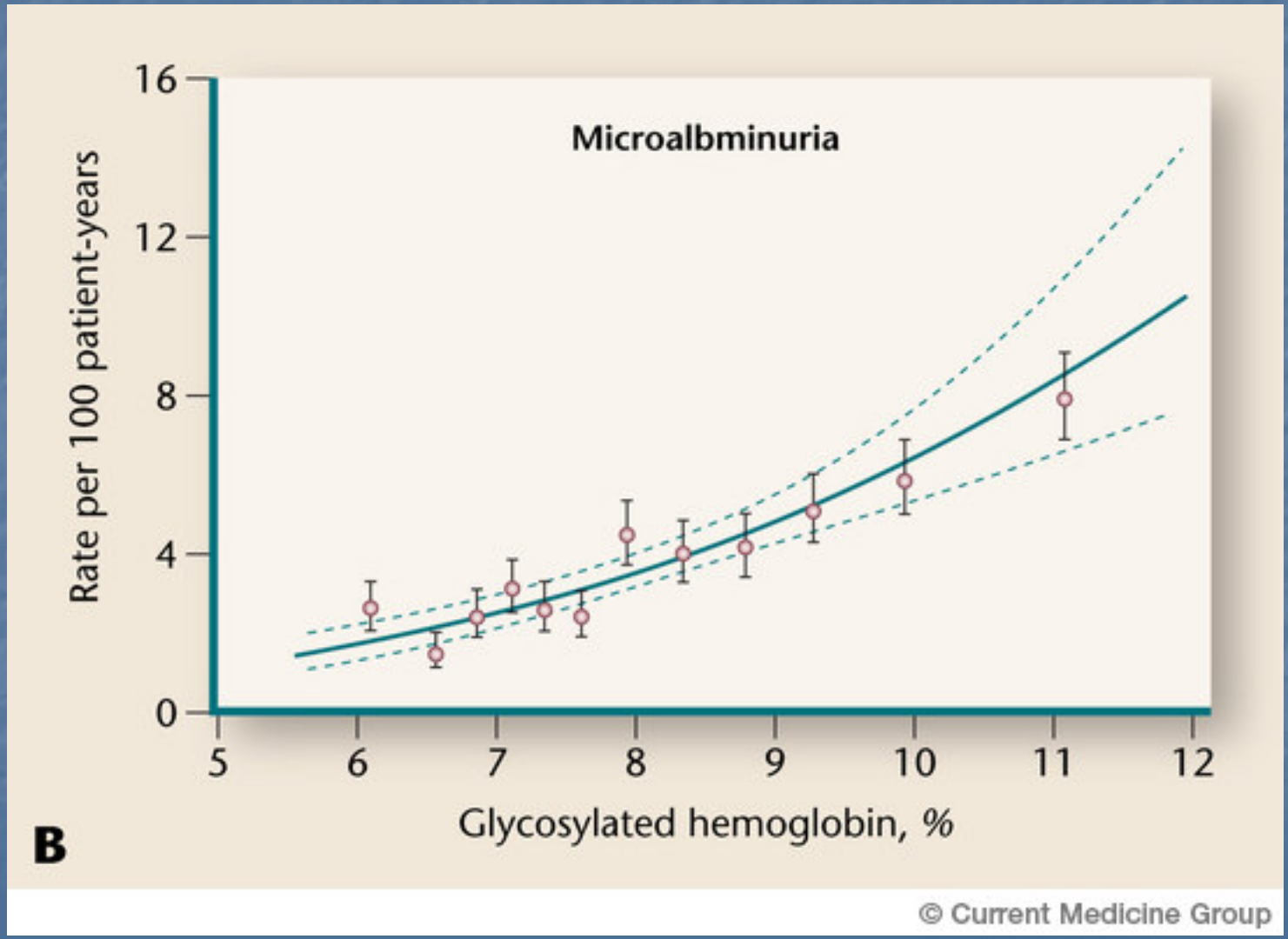
Vascular Complications Of Type 2 Diabetes At The Time Of Diagnosis



Retinopathy[1]	21%	7%	Cerebrovascular disease[3]
Nephropathy[2]	18%	18%	Abnormal ECG[1]
Erectile dysfunction[1]	20%	35%	Hypertension[1]
Ischaemic skin changes (foot)[1]	6%	4.5%	Intermittent claudication[3]
Abnormal vibration threshold (foot)[1]	7%	13%	Absent foot pulses[1]

1. UKPDS Group. *Diabetes Res* 1990; **13**: 1–11. 2. The Hypertension in Diabetes Study Group. *J Hypertension* 1993; **11**: 30–17. 3. Wingard DL *et al. Diabetes Care* 1993; **16**: 1022–5.

Nephropathy and Glycaemic Control



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Lessons from UKPDS: Better Control Means Fewer Complications

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EVERY 9 mmol/mol (1%) reduction in HbA_{1c}

REDUCED RISK*

UKPDS 35. BMJ 2000;321:405–12

*p<0.0001

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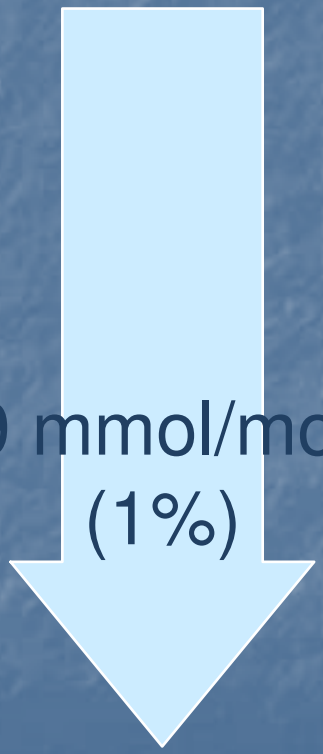

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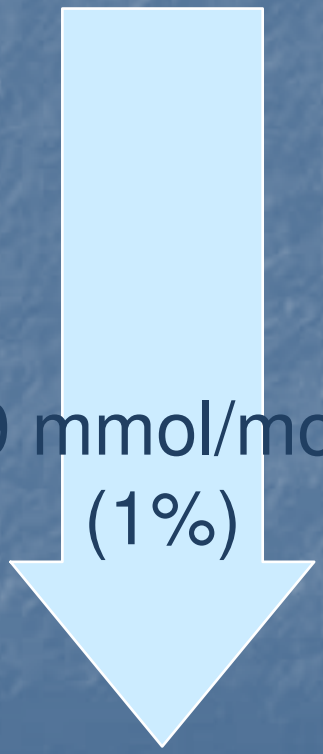

Deaths from diabetes

REDUCED RISK*

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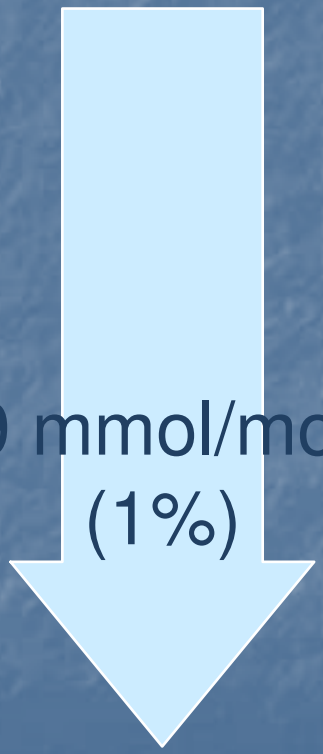
Lessons from UKPDS: Better Control Means Fewer Complications

EVERY 9 mmol/mol (1%) reduction in HbA_{1c}



REDUCED RISK*

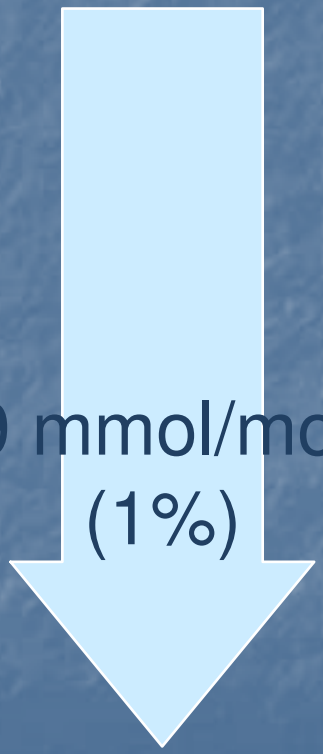
Deaths from diabetes	–21%
Heart attacks	–14%

UKPDS 35. BMJ 2000;321:405–12

*p<0.0001

Lessons from UKPDS: Better Control Means Fewer Complications

EVERY 9 mmol/mol (1%) reduction in HbA_{1c}

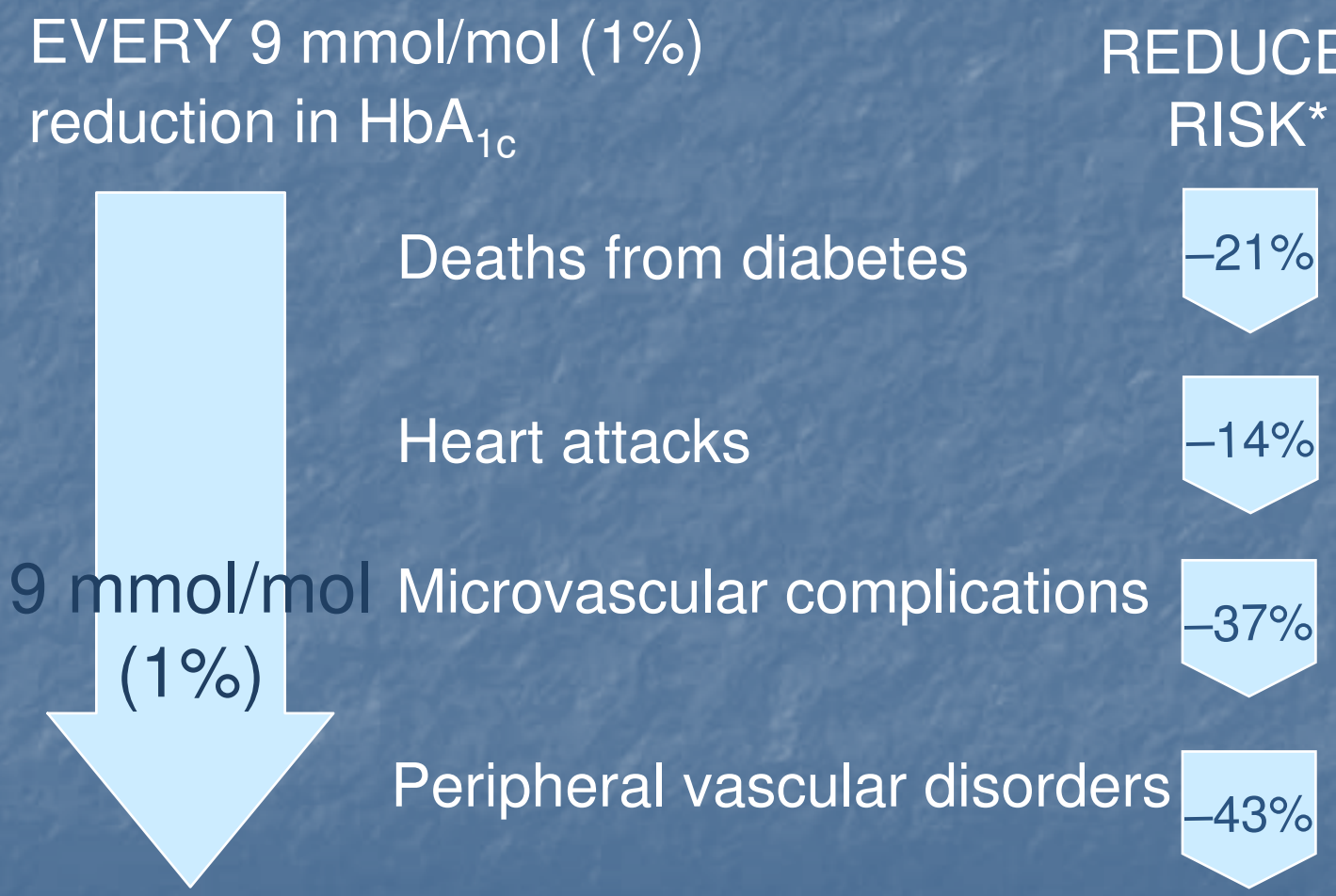


	REDUCED RISK*
Deaths from diabetes	–21%
Heart attacks	–14%
Microvascular complications	–37%

UKPDS 35. BMJ 2000;321:405–12

*p<0.0001

Lessons from UKPDS: Better Control Means Fewer Complications



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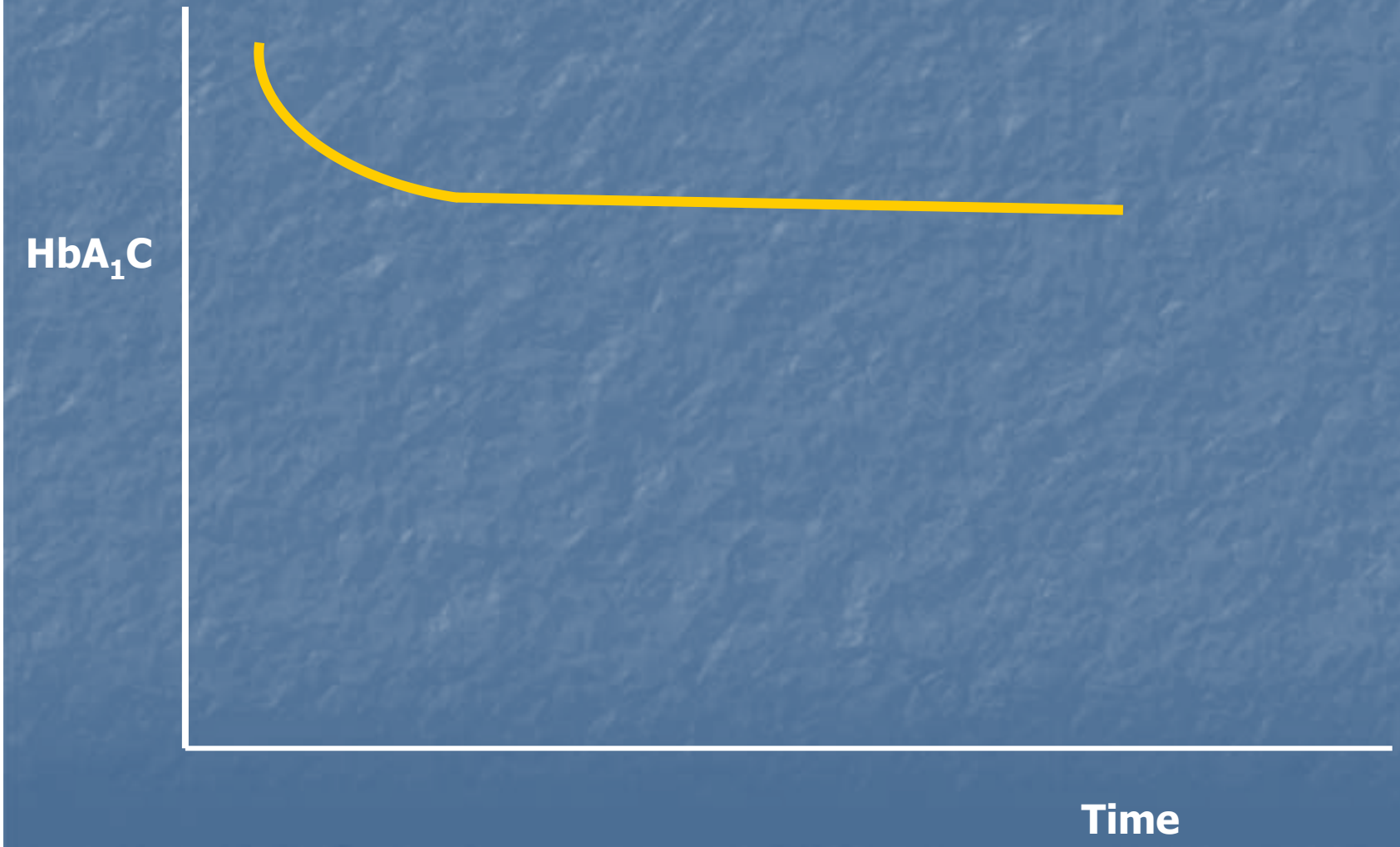
Hypoglycaemic Agents

- α glucosidase inhibitors
- Metaglinides
- Metformin
- Sulphonylureas
- Thiazolidindiones
- GLP – 1 analogues
- DPP IV inhibitors

Their Effects Are Additive



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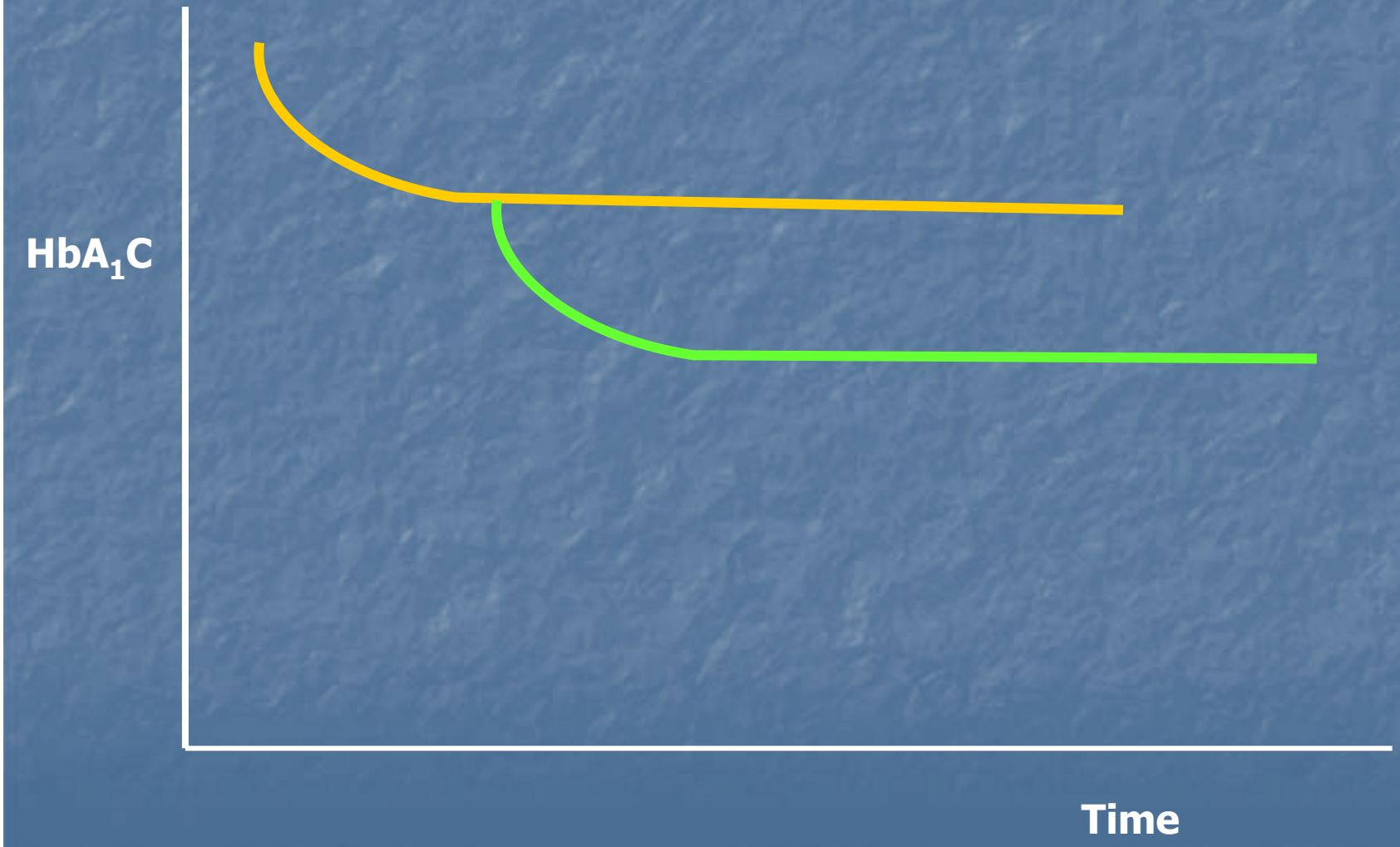

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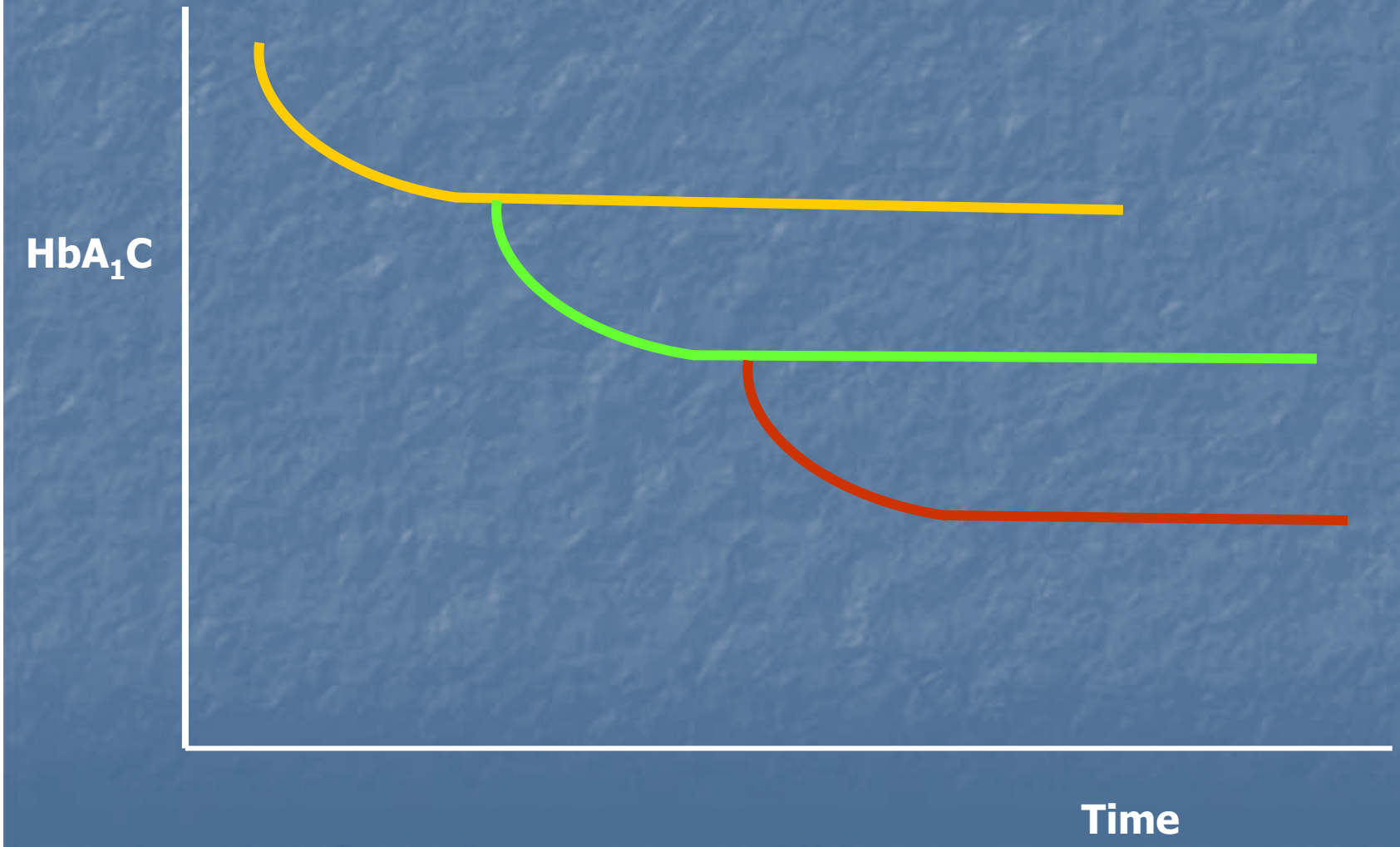

Oral Hypoglycaemic Agents

- α glucosidase inhibitors
- Metaglinides
- Metformin
- Sulphonylureas
- Thiazolidindiones
- GLP – 1 analogues
- DPP IV inhibitors

Acarbose

- Has no overall effect on hyperinsulinaemia or insulin sensitivity
- Best for individuals with normal fasting glucose but high postprandial glucose levels – this is often too late!
- Maximum HbA_1C reduction of 6 mmol/mol (0.75%)
- Can be used in combination with insulin, metformin or SU's

Acarbose

- GI side effects abound therefore dose gradually built up
- Contraindicated in inflammatory bowel disease, cirrhosis, severe renal impairment, history of abdominal surgery

Hypoglycaemic Agents

- α glucosidase inhibitors
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Metaglinides

- Repaglinide and Nateglinide
  - First introduced in 1998
  - Work by binding to the sulphonylurea receptor and 'squeezing' the β cell to release insulin
  - Short acting
  - Taken only with meals
  - Maximum HbA_1C reduction of 9 mmol/mol (1.0%)

Hypoglycaemic Agents

- α glucosidase inhibitors
- Metaglinides
- Metformin
- Sulphonylureas
- Thiazolidindiones
- GLP – 1 analogues
- DPP IV inhibitors

Metformin

- Used since medieval times in some form or other
- Should be the first line oral hypoglycaemic agent for almost all individuals with type 2 diabetes
- BMI is no longer an issue

Ungar G, Freedman L, Shapira S. Pharmacological studies of a new oral hypoglycaemic drug. Proceedings of the Society for Experimental Biology and Medicine. 1957;95:190-192

Metformin

- Works by decreasing hepatic gluconeogenesis, decreasing gut glucose uptake and increasing peripheral insulin sensitivity
- Relies on adequate β cell function
- Weight neutral
- Can be used in combination with other oral agents or insulin

Metformin

- GI disturbance is common so dose titrated
- If GI disturbance continues, use modified release version
- Maximum HbA_1C reduction is 14 mmol/mol (1.5%)

Metformin

- Hypoglycaemia is NOT usually a side effect of treatment
- Avoid in conditions predisposing to renal insufficiency – creatinine of $\geq$ 150 µmol/L or eGFR < 30ml/Kg/min
- Lactic acidosis is a theoretical risk

Hypoglycaemic Agents

- α glucosidase inhibitors
- Metaglinides
- Metformin
- Sulphonylureas
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- GLP – 1 analogues
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Sulphonylureas

- Have been around since the 1950's
- Act by binding to the SU receptor causing an influx of Ca^{2+} and an exocytosis of insulin containing vesicles
- Rely on adequate β cell function
- Excellent for rapid symptom relief

Sulphonylureas

- Use is mainly limited to individuals with a BMI < 25 Kg/m^2 or in whom metformin is contraindicated
- Can be used in combination with most other oral hypoglycaemic agents
- Their long half life makes hypoglycaemia more likely, especially in the elderly

Sulphonylureas

- Maximum HbA_1C reduction is 9 mmol/mol (1.5%)
- Weight is common
- Need to be avoided in hepatic and renal failure

Hypoglycaemic Agents

- α glucosidase inhibitors
- Metaglinides
- Metformin
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- DPP IV inhibitors

Thiazolidinediones

- Rosiglitazone and Pioglitazone
- Work by increasing peripheral insulin sensitivity at a nuclear level on peroxisome proliferator-activated receptor γ (PPAR γ)
- "First do no harm"

Thiazolidinediones

- Maximum HbA_1C reduction is 14 mmol/mol (1.5%)
- But this takes 4 to 6 months to achieve maximal benefit so give it time!

Thiazolidinediones

- Lots of potential side effects emerging
  - Macular oedema
  - Increased fracture risk
  - Fluid retention and heart failure
  - Possibility of increased CV death rates with rosiglitazone
- Avoid if possible – use pioglitazone if you must

Hypoglycaemic Agents

- α glucosidase inhibitors
- Metaglinides
- Metformin
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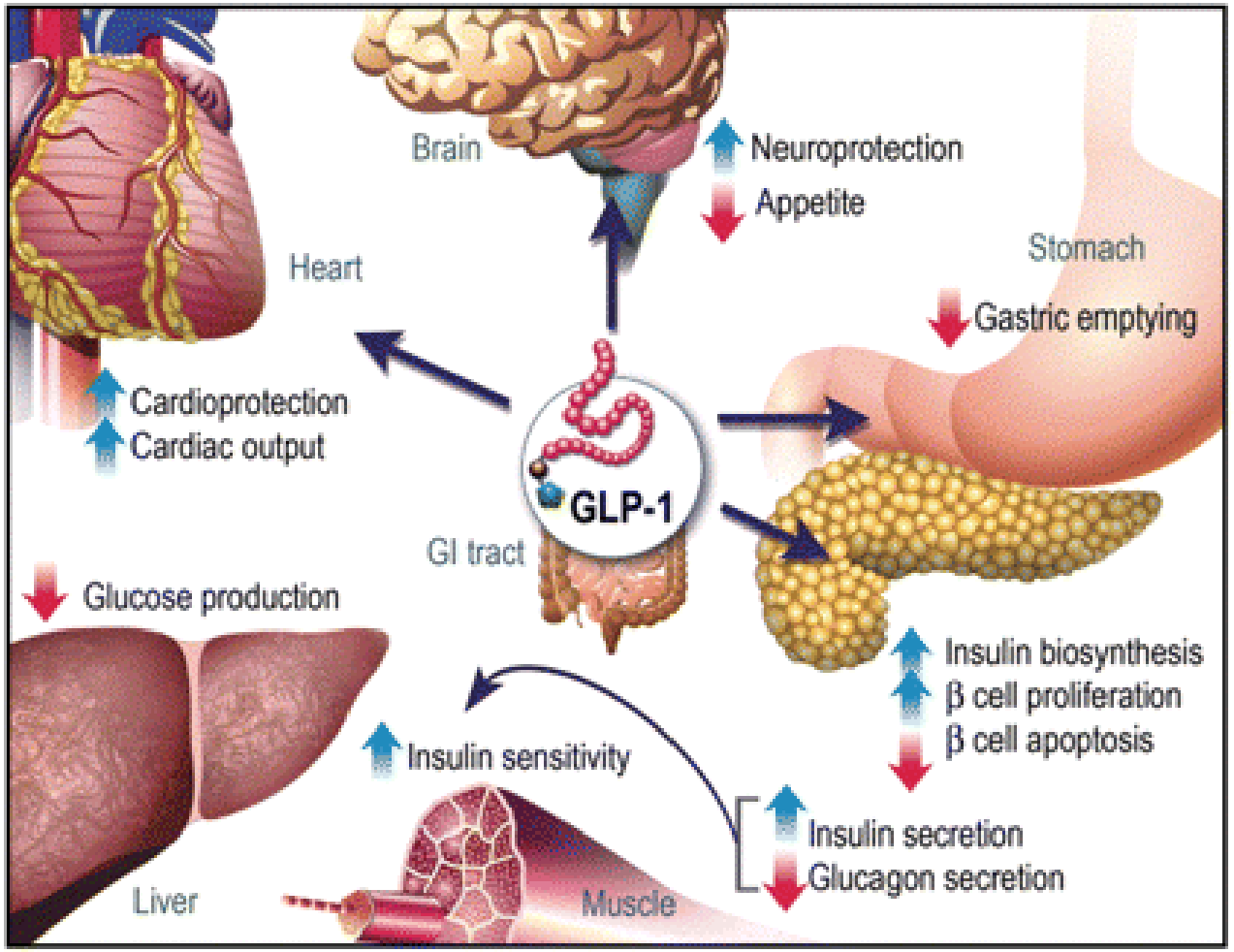
GLP-1 Analogues

- Exentatide and Liragultide

What Does GLP-1 Do?



Abu-Hamdah et al JCEM 2009;94(6):1843-1852

Do They Work?

- HbA_1C reduction of about 10 mmol/mol (1.1%)
- Extensive weight loss
- ? β cell preservation
- Expensive
- Extensive experience in the UK – most of which is positive

DPP-IV Antagonists

- Sitagliptin, Vildagliptin and Saxagliptin

Do They Work?

- HbA_1C reduction of about 10 mmol/mol (1.1%)
- Oral
- ? β cell preservation
- Weight neutral
- Expensive

In Summary - Hypoglycaemic Agents

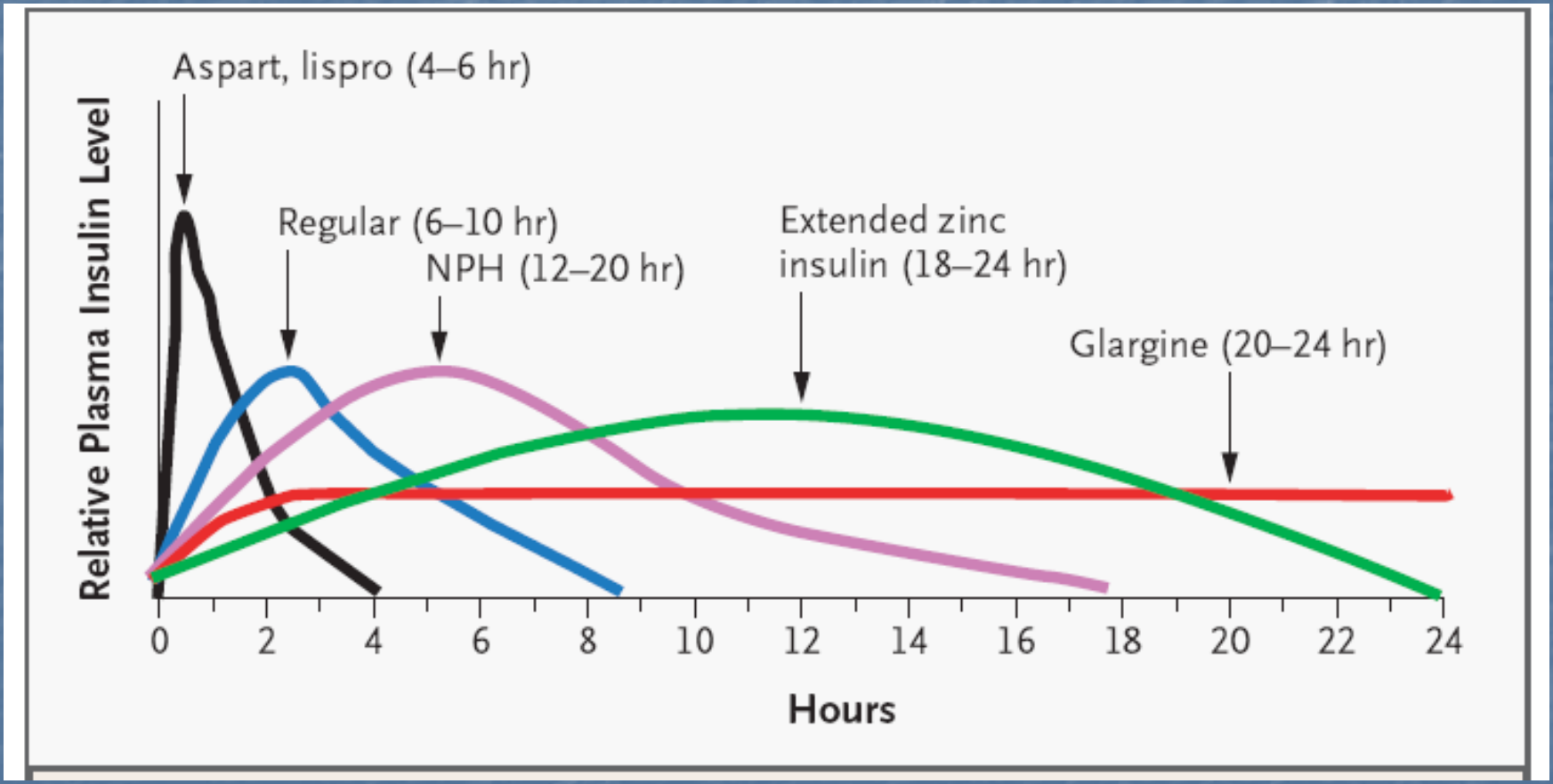
- α glucosidase inhibitors
- Metaglinides
- Metformin
- Sulphonylureas
- Thiazolidindiones
- GLP – 1 analogues
- DPP IV inhibitors

Insulins

Types of Insulin

- There are over 60 different types of insulin or insulin preparation listed in the BNF
- The important things to remember are
  - What is the duration of action of the insulin
  - Who is it for and what is their life style like?
  - What device can they use with ease?

Insulin Durations



Hirsch NEJM 2005;352 (2):174-183

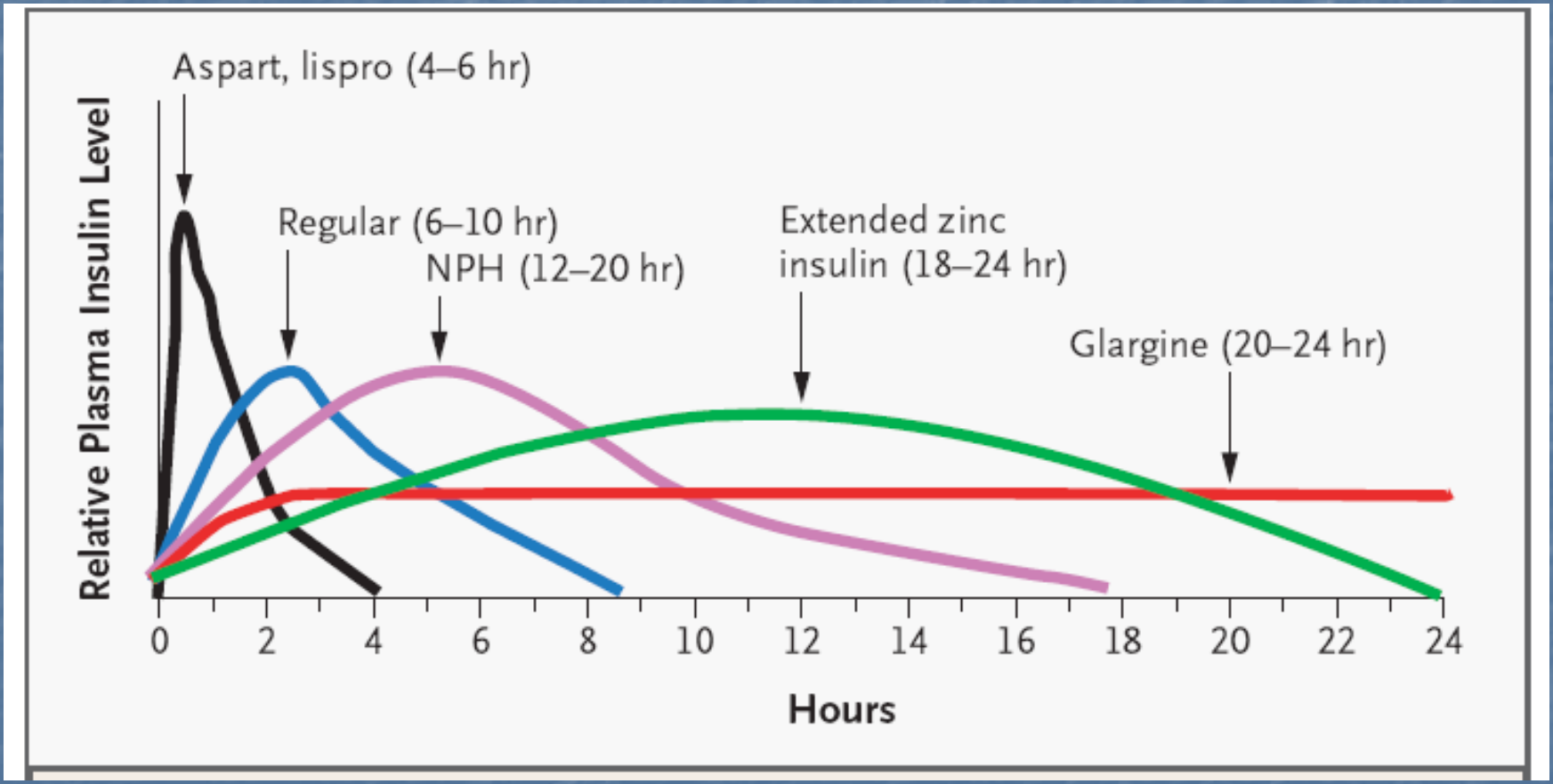
Types of Insulin

- Apart from duration of action, they can be divided into three types, depending on their origin
  - Animal
  - Human
  - Analogue

Animal Insulin

- Bovine and porcine neutral (soluble), isophane (NPH), ultra slow acting, or mixtures
- Very few people on this insulin now
- Almost no-one is started on these de novo

Insulin Durations



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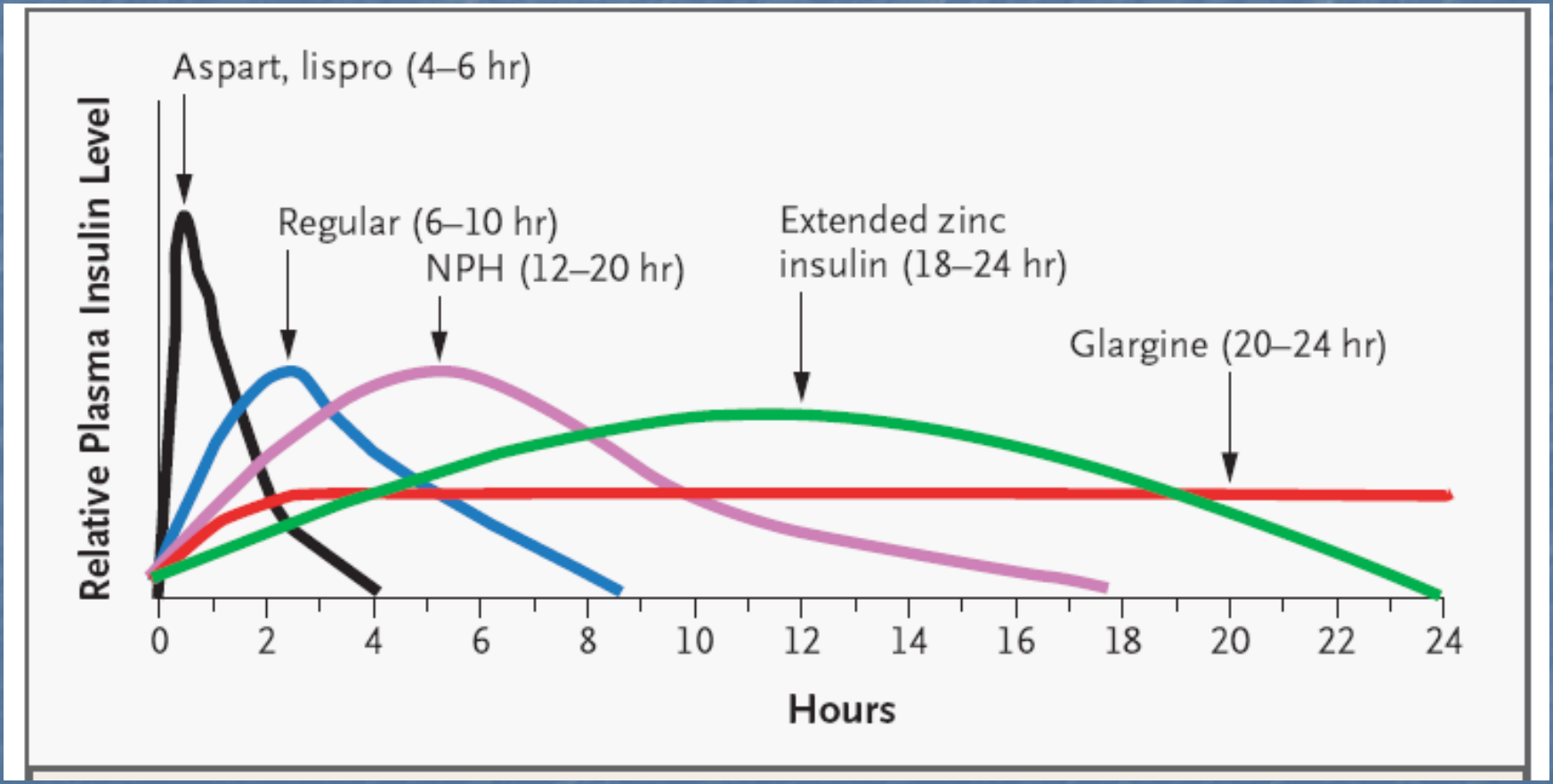
Human Insulin

- Shot acting insulins given alone or as pre-mixed combinations
- Examples include
  - Humulin S
  - Insuman rapid
  - Actrapid
  - Humulin M3
  - Insuman comb 15 / 25 / 50

Insulin Durations



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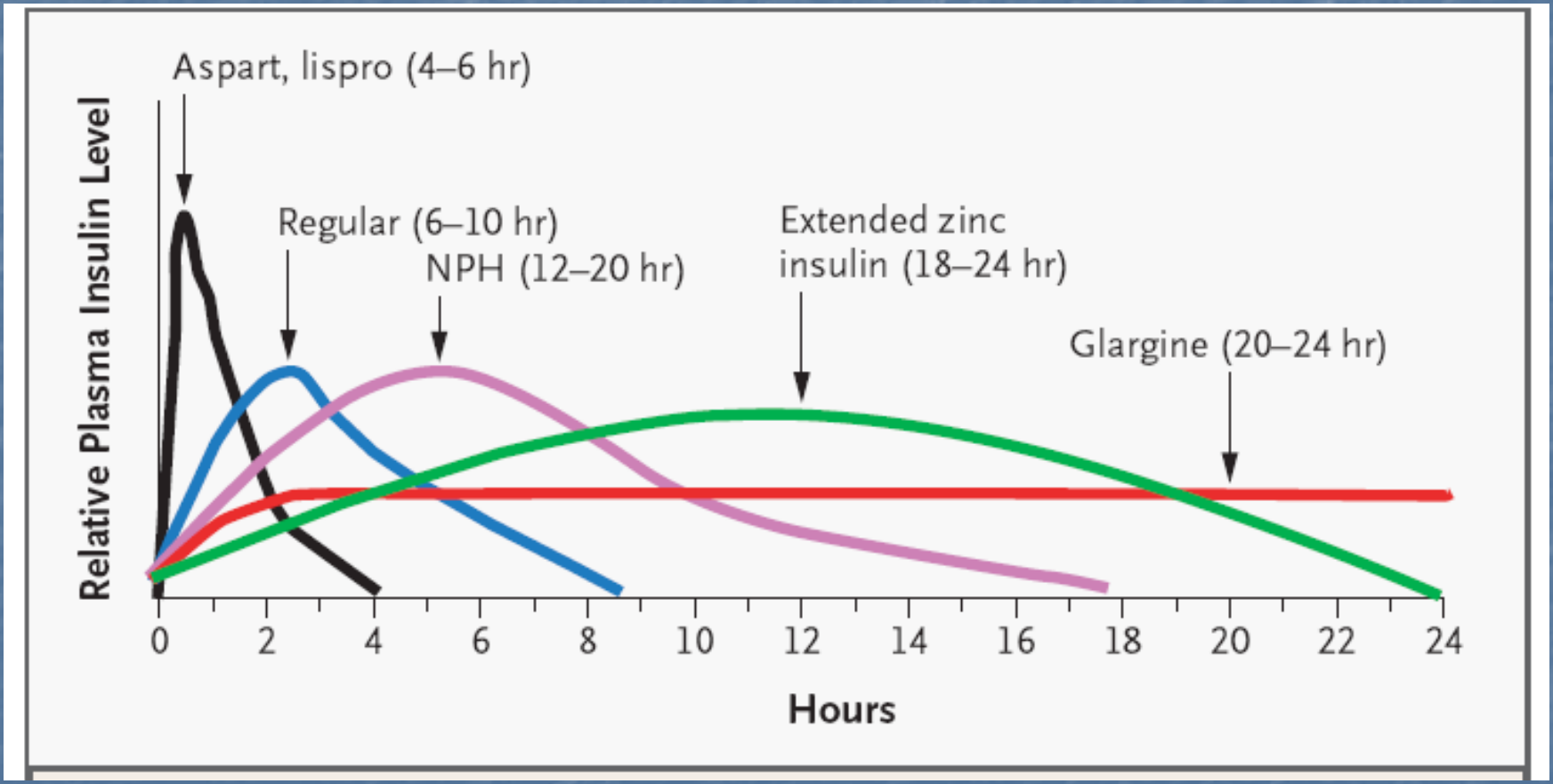
Analogue Insulin

- Ultra short acting insulin – usually a dose given with each meal
  - Aspart (Novorapid)
  - Glulisine (Apidra)
  - Lispro (Humalog)
- Long acting – used as a basal insulin once or twice daily
  - Detemir (Levemir)
  - Glargine (Lantus)

Analogue Mixtures

- Novomix 30
- Humalog Mix 25 / Mix 50
- Often for people with more ‘fixed’, routine lives

Insulin Durations



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Cardiovascular Risk Reduction

Things That Make the Most Difference

Smoking	OR 2.87
Raised ApoB/ApoA1 ratio	OR 3.25
History of hypertension	OR 1.91
Diabetes	OR 2.37
Abdominal obesity	OR 1.12
Psychosocial factors	OR 2.67
Daily fruit and veg intake	OR 0.7
Regular alcohol consumption	OR 0.9
Regular physical activity	OR 0.86

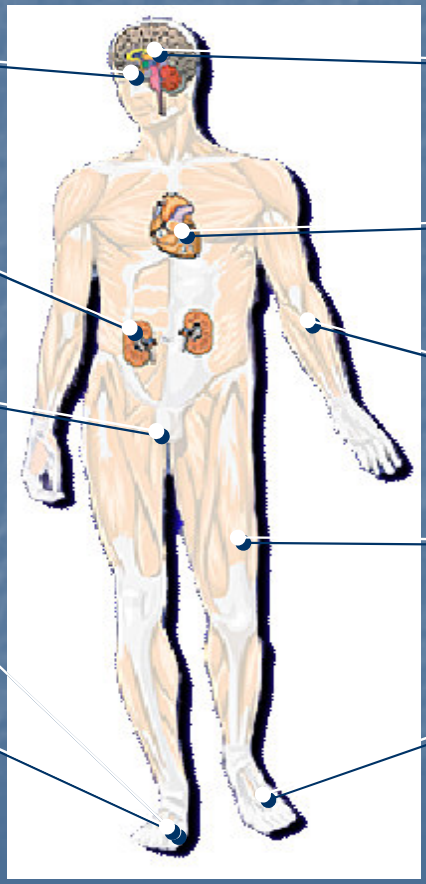
Yusuf et al Lancet 2004 364:937-952

The INTERHEART Study

- Together, these 9 factors account for over 90% of the population attributable risk in men, and 94% of the PAR in women
- The inference is that intervening in these factors will potentially make the most difference to outcomes

Yusuf et al Lancet 2004 364:937-952

Vascular Complications Of Type 2 Diabetes At The Time Of Diagnosis



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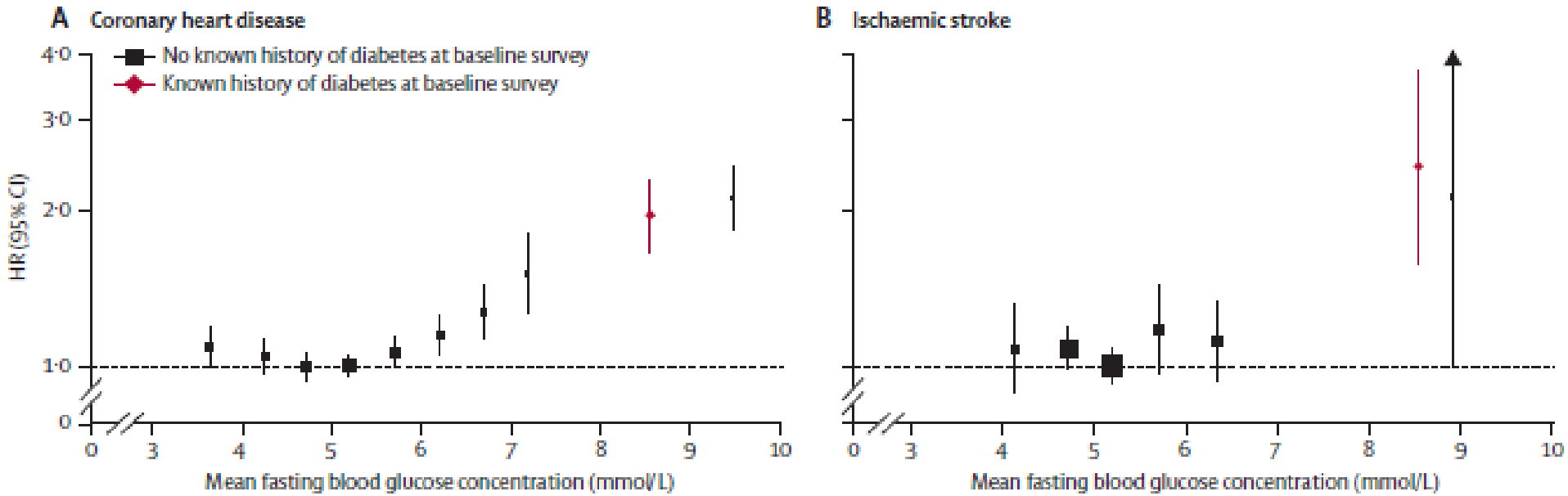
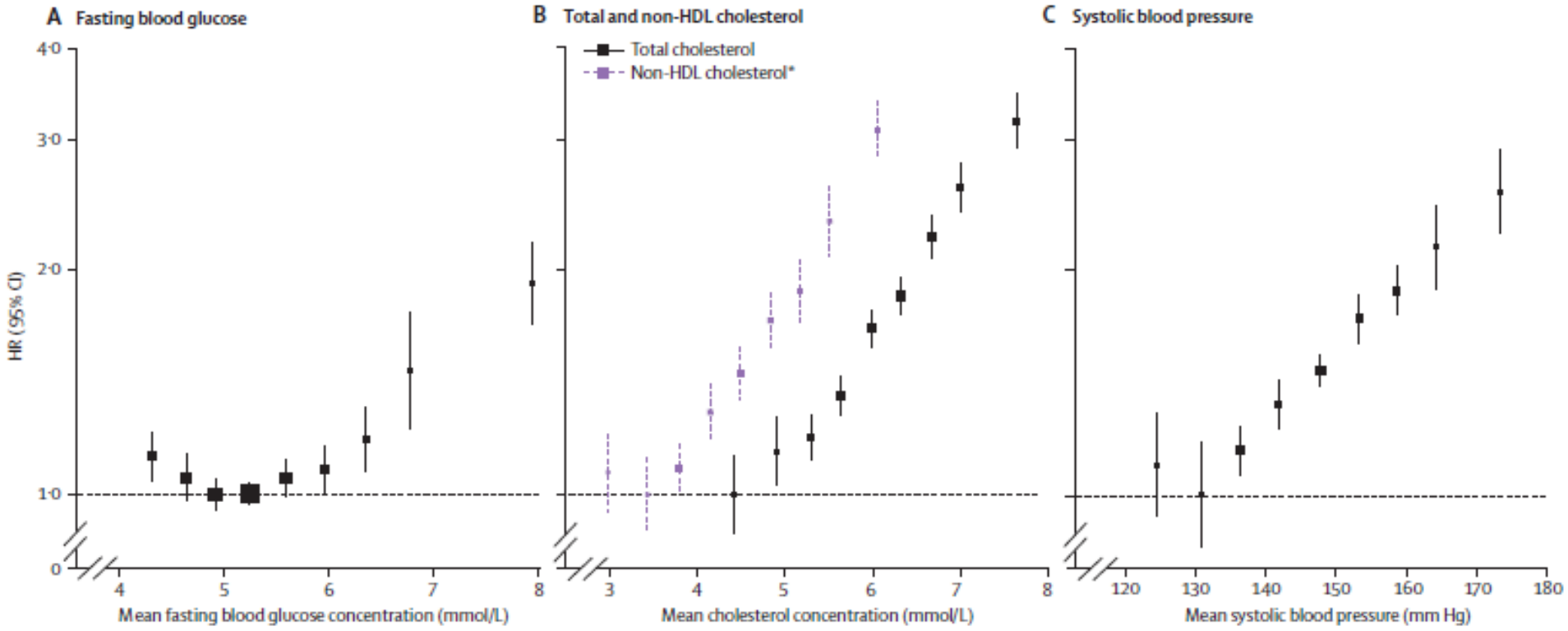
Data from 700,000 People



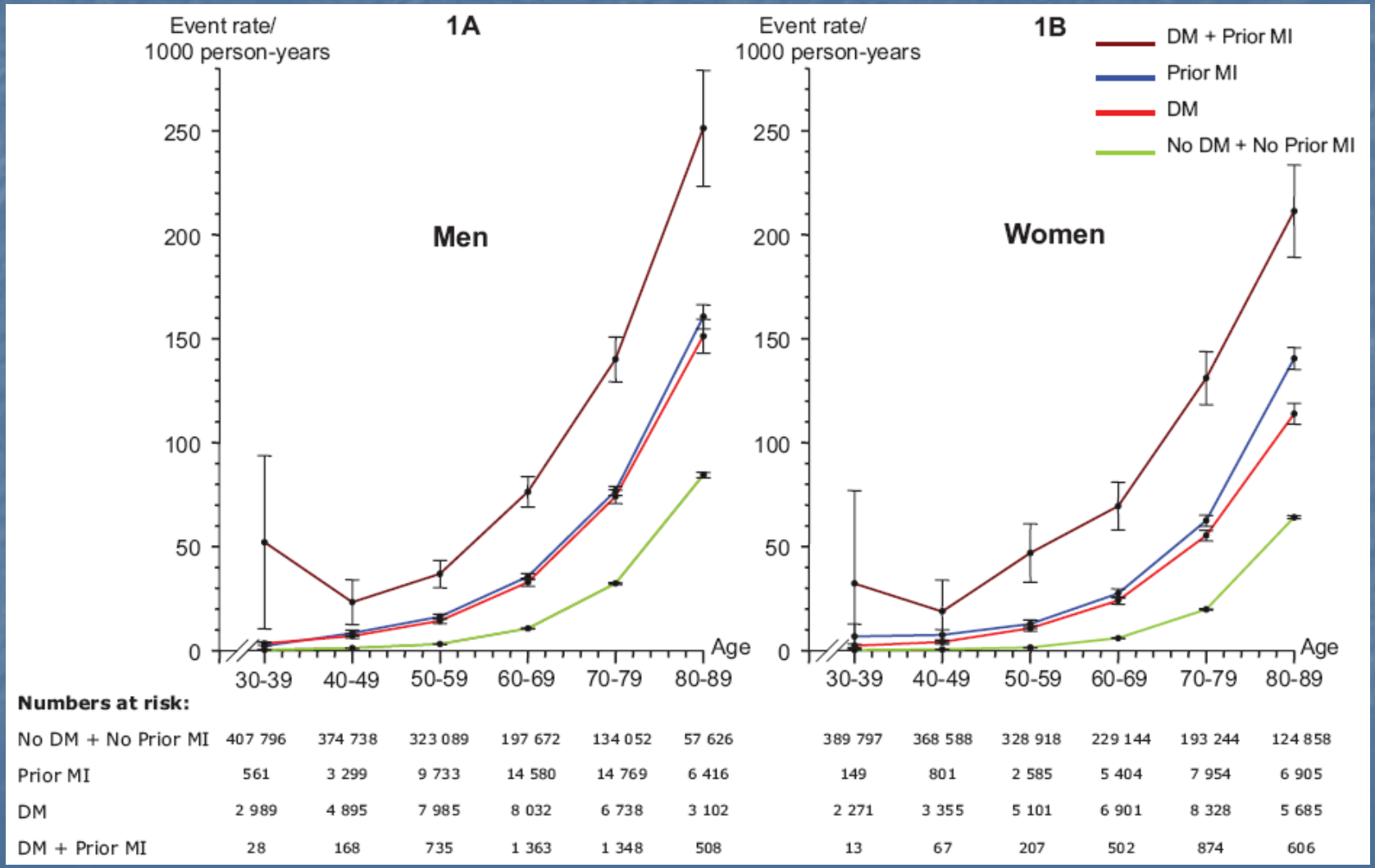
Emerging Risk Factors Collaboration Lancet 2010;375(9733):2215-2222

Risk of Developing CHD



Emerging Risk Factors Collaboration Lancet 2010;375(9733):2215-2222

Data From 3.3M Danes

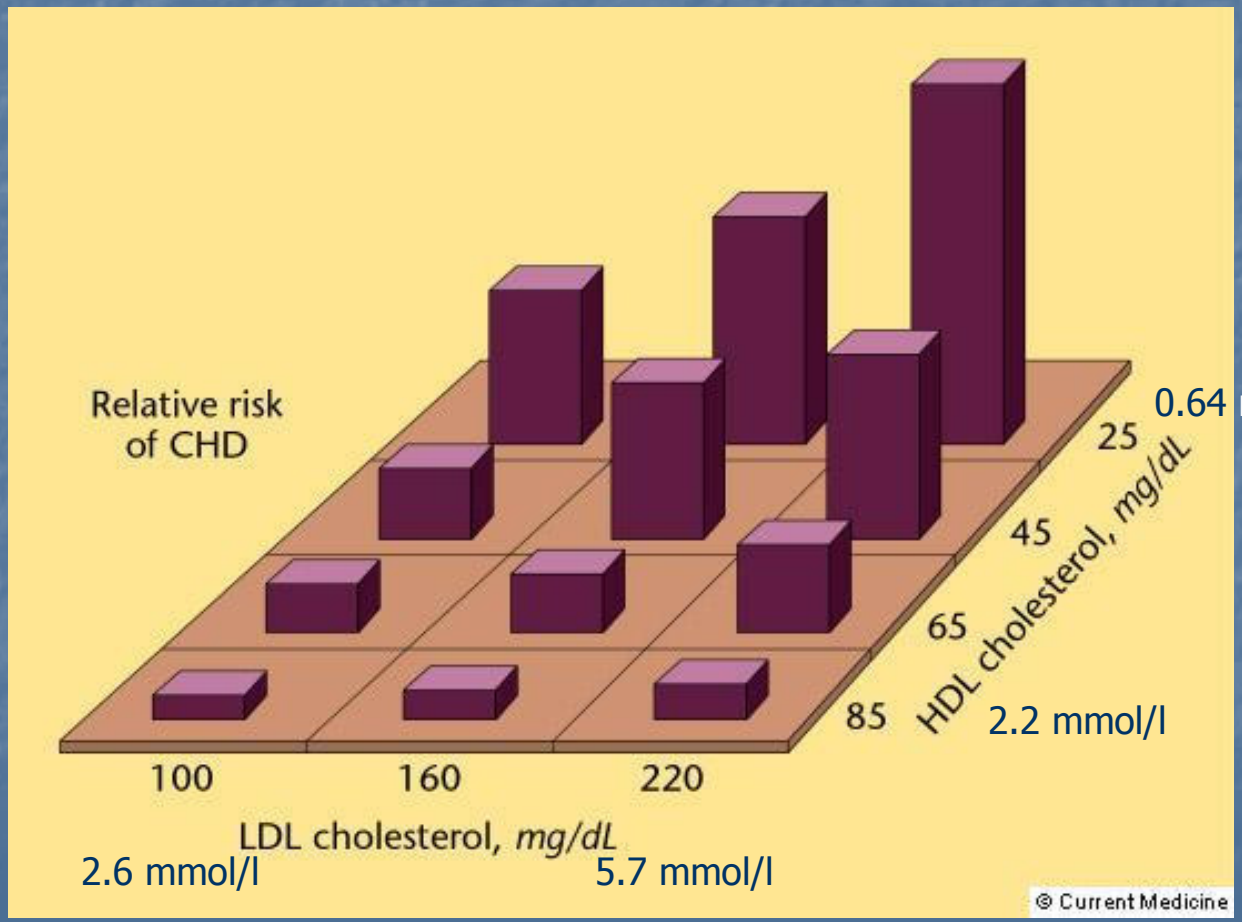


Numbers at risk:

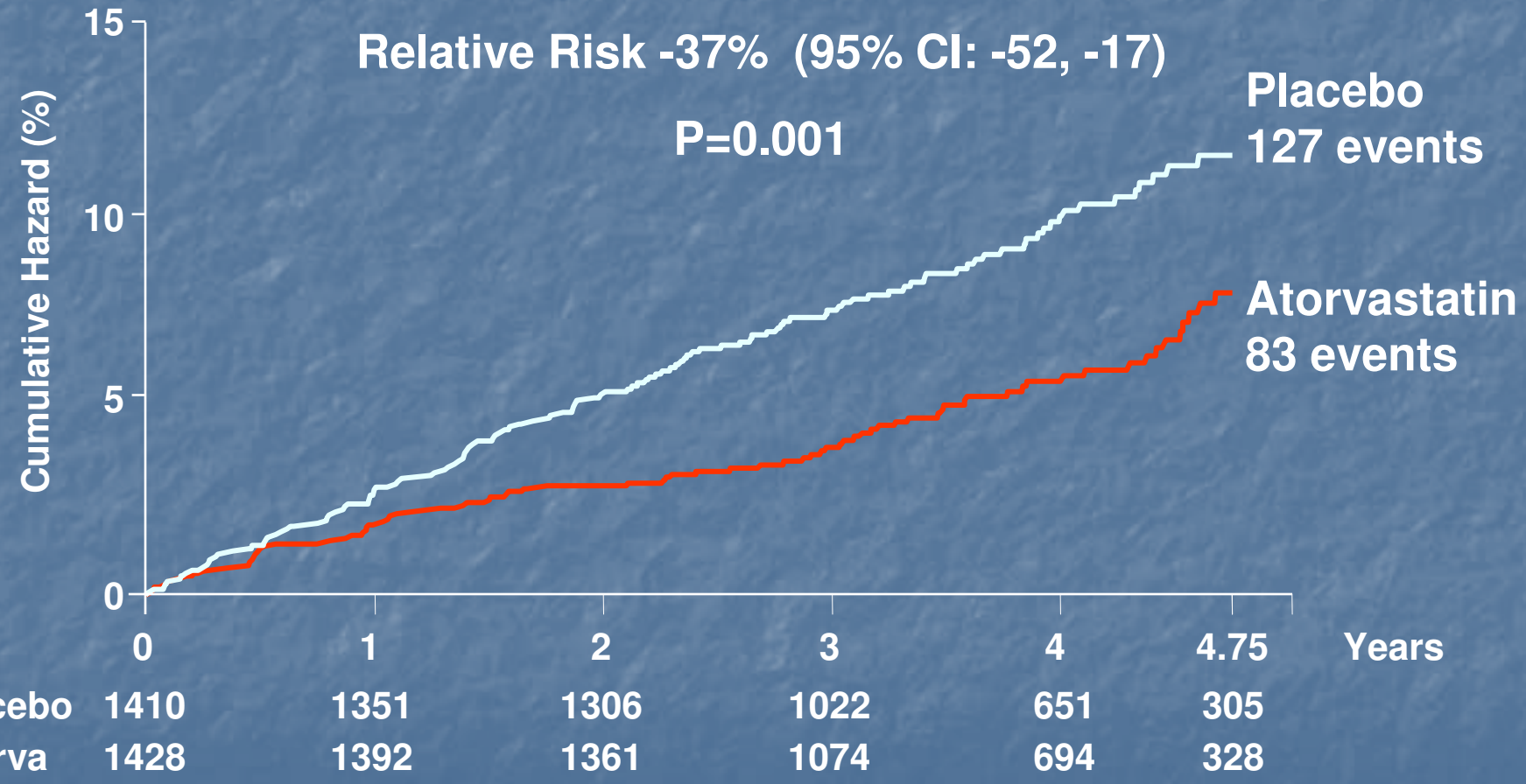
No DM + No Prior MI	407 796	374 738	323 089	197 672	134 052	57 626	389 797	368 588	328 918	229 144	193 244	124 858
Prior MI	561	3 299	9 733	14 580	14 769	6 416	149	801	2 585	5 404	7 954	6 905
DM	2 989	4 895	7 985	8 032	6 738	3 102	2 271	3 355	5 101	6 901	8 328	5 685
DM + Prior MI	28	168	735	1 363	1 348	508	13	67	207	502	874	606

Schramm TK et al Circulation 2008;117:1945-1954

The Framingham Heart Study: Risk of Coronary Heart Disease

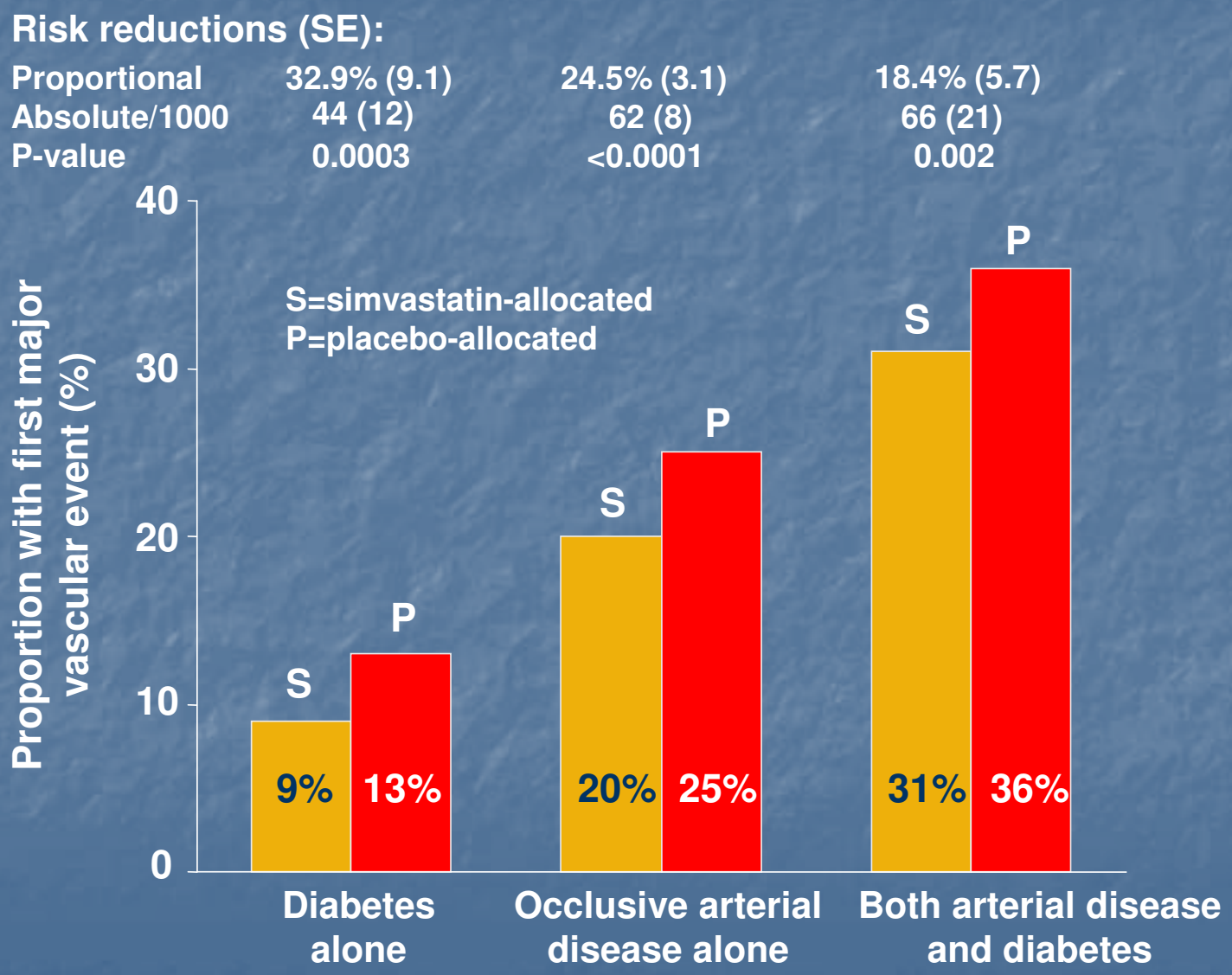


CARDS - Cumulative Hazard for Primary Endpoint



Placebo	1410	1351	1306	1022	651	305
Atorva	1428	1392	1361	1074	694	328

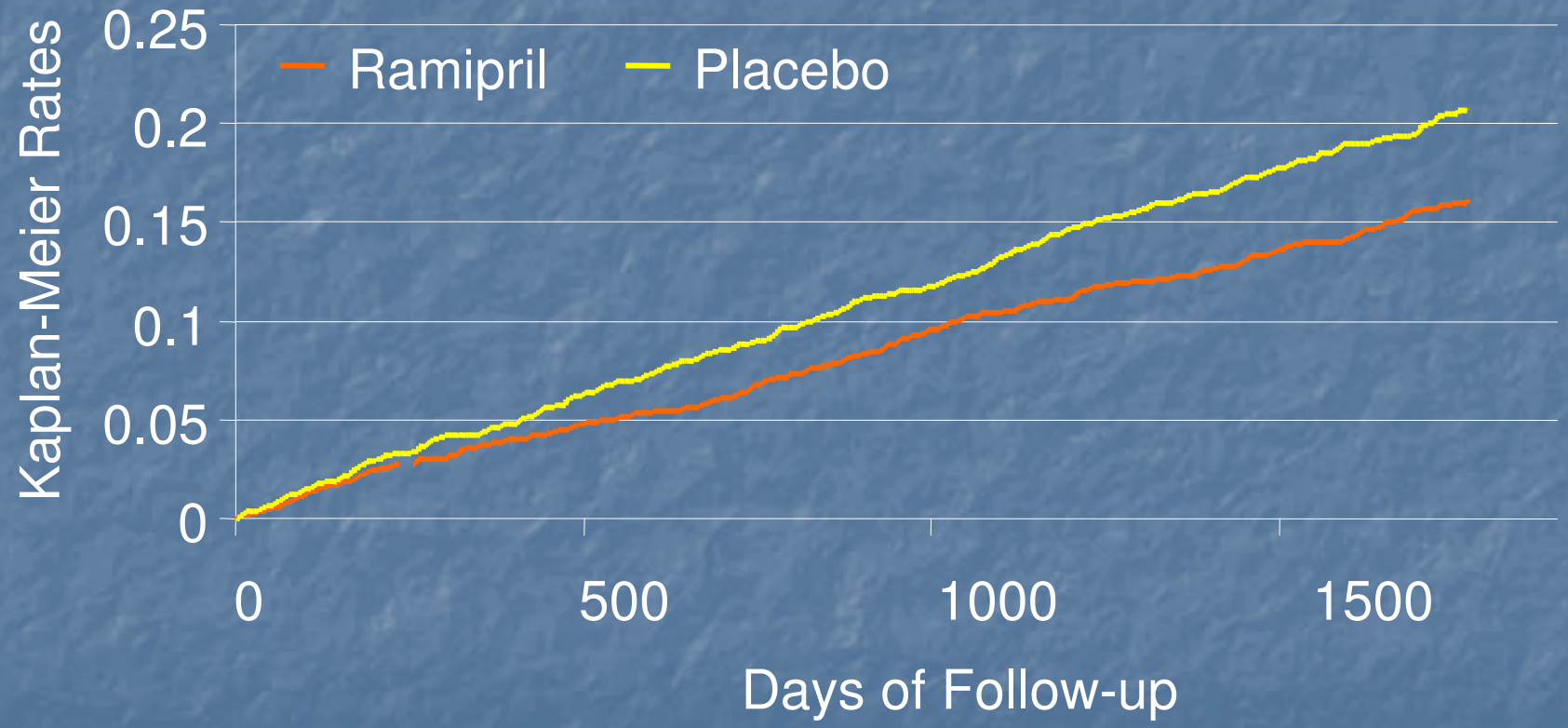
Heart Protection Study - Diabetes



Aspirin

- This is a difficult issue for primary prevention
- Aspirin is still recommended for primary prevention in most national and international guidelines
- There are several studies showing that aspirin is not beneficial in primary prevention in people with diabetes
- Watch this space – ASCEND trial

ACE Inhibition: The Hope Trial - Survival Curves On Combined Primary Outcome - DM



RRR = 25% (12 - 36) p=0.0004

Yusuf S et al NEJM 2000;342:145-153

In Summary

- In people who are increased risk
  - Overweight
  - Aged over 40
  - Hypertensive
  - Smokers
  - Family history of IHD
  - People with previous CV events
  - Evidence of end organ damage
- Statins and ACE inhibition should be used early

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