# Macrovascular Risk Factors in Childhood Diabetes

## Are we doing enough?

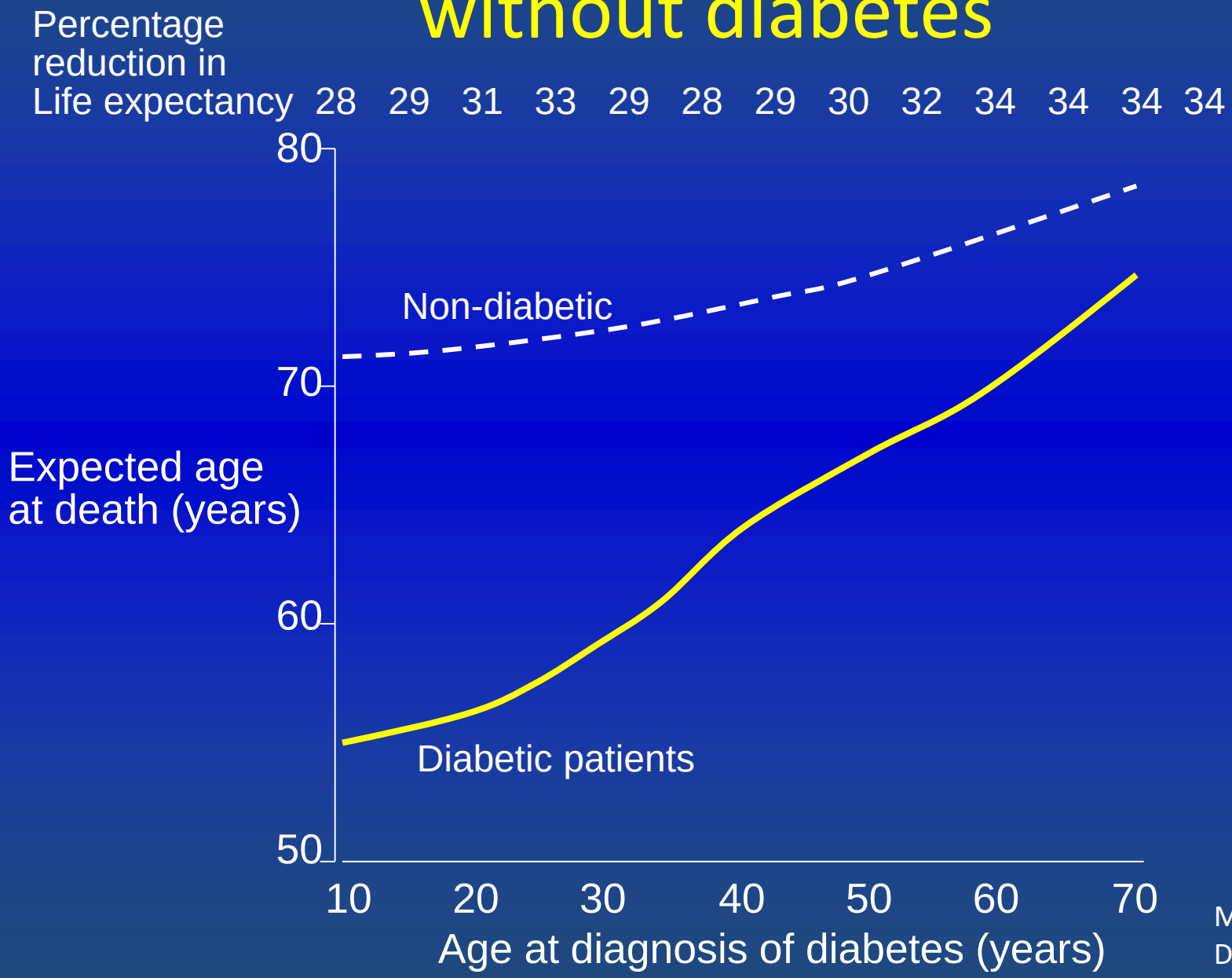
Professor David Dunger

Department of Paediatrics

UNIVERSITY OF CAMBRIDGE

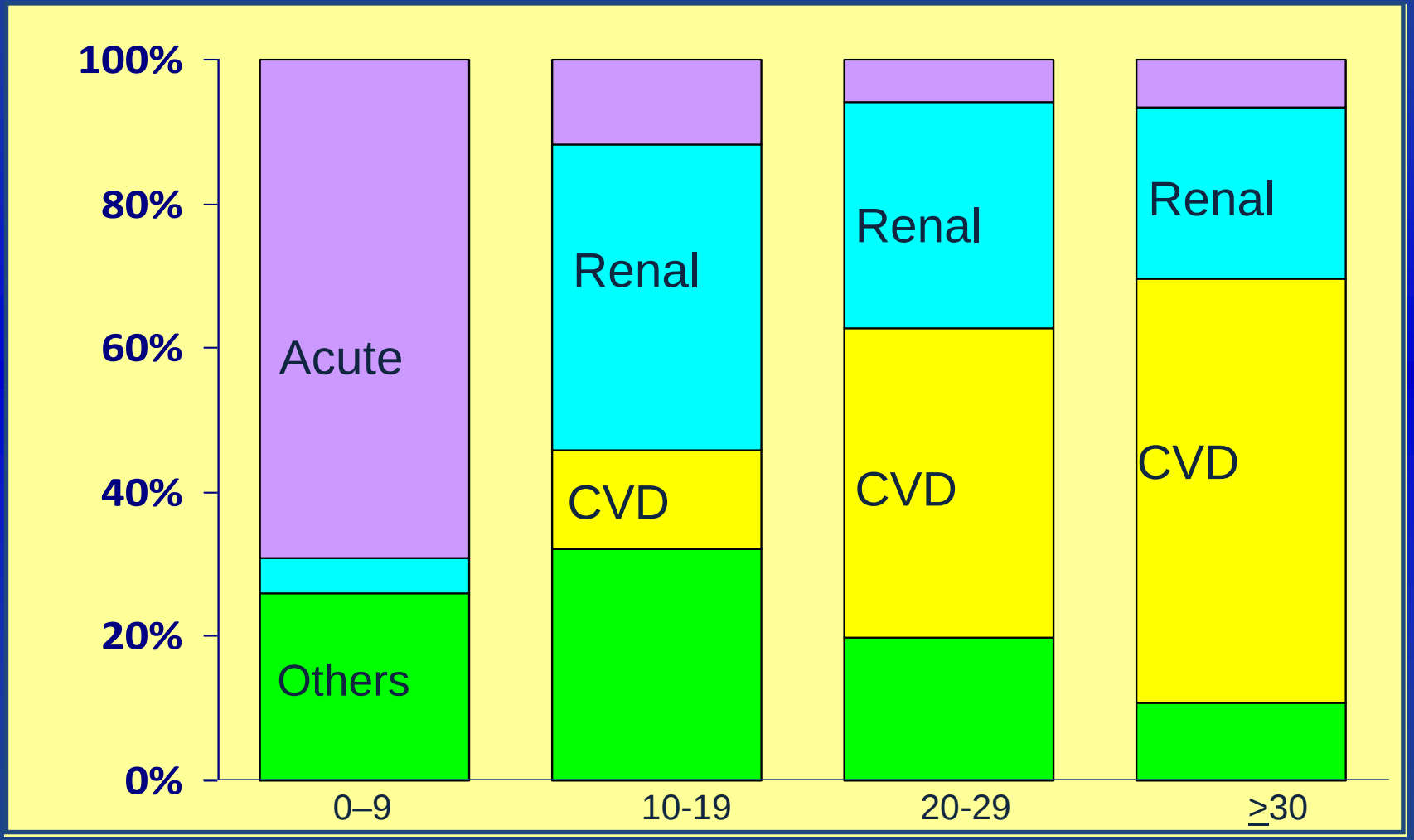
# Shadow of Diabetes

# Expectation of life in patients with & without diabetes




Marks HH. Joslin's Diabetes 1971

# Cause of mortality in relation T1D duration




Orchard TJ et al., Diabetes 2010

# Macrovascular risk factors in childhood diabetes

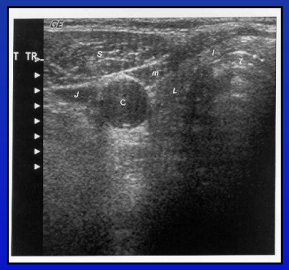
- Early markers of CVD
- Possible interventions
- The way forwards

# Direct measure of CVD risk

- Carotid and Aortic IMT
- Pulse wave velocity
- FMD
- Aortic calcification

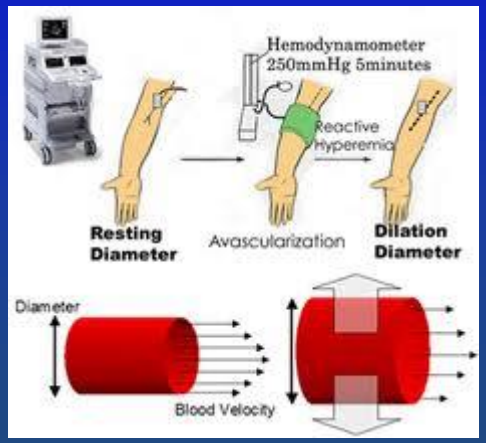
# Vascular assessment

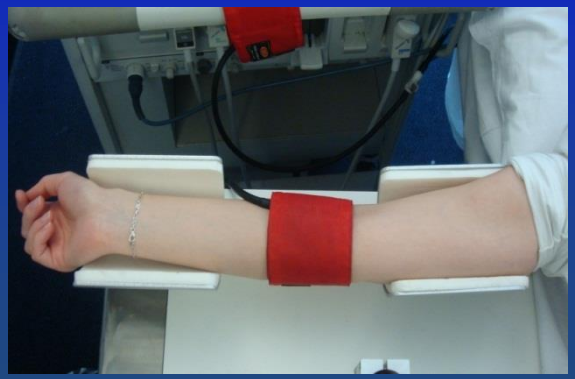
## Carotid Intima-Media Thickness

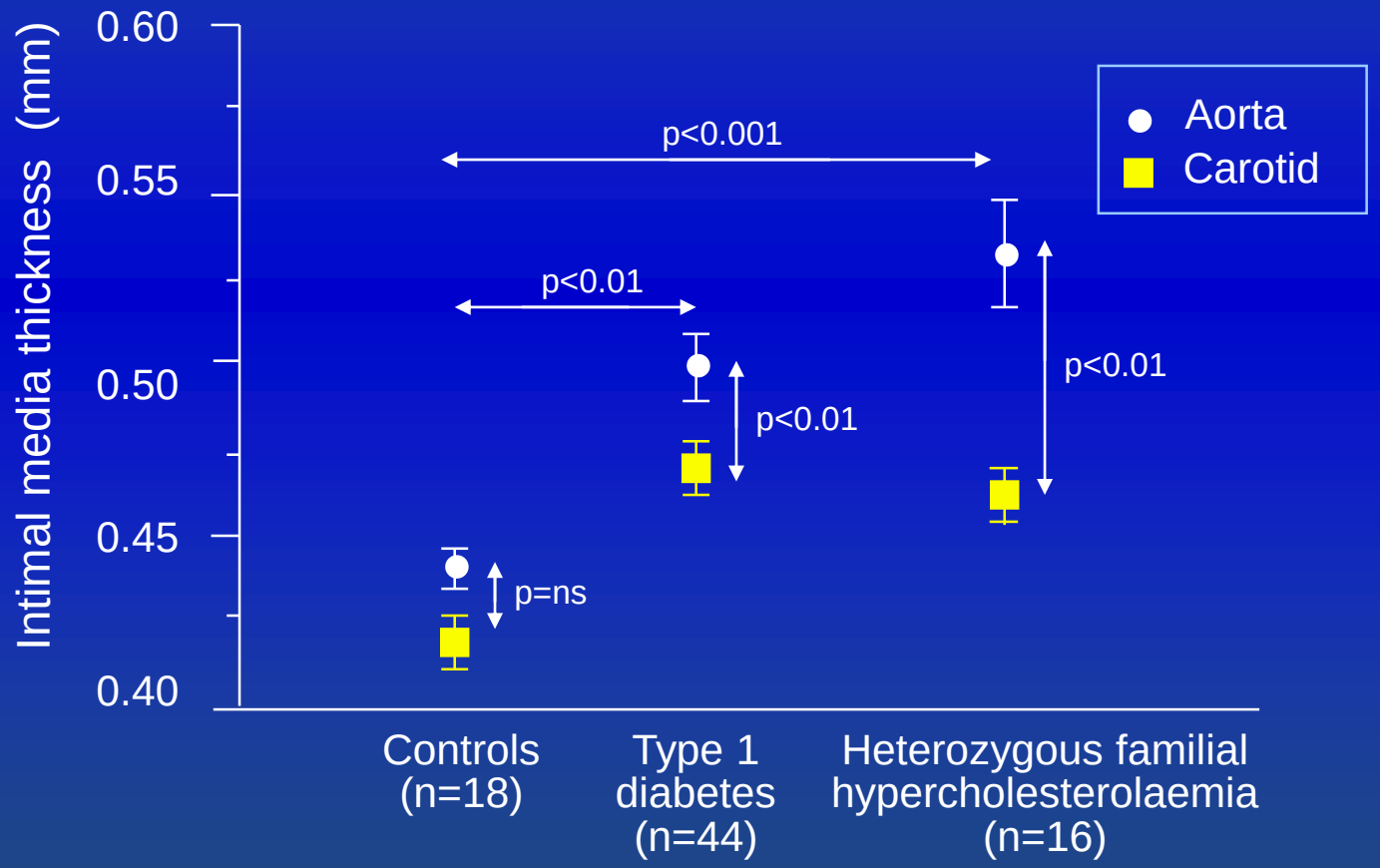
## Pulse wave velocity (PWV)

## Flow Mediated Dilatation (FMD)
## Endothelial Pulse Amplitude Tonometry (EndoPAT)



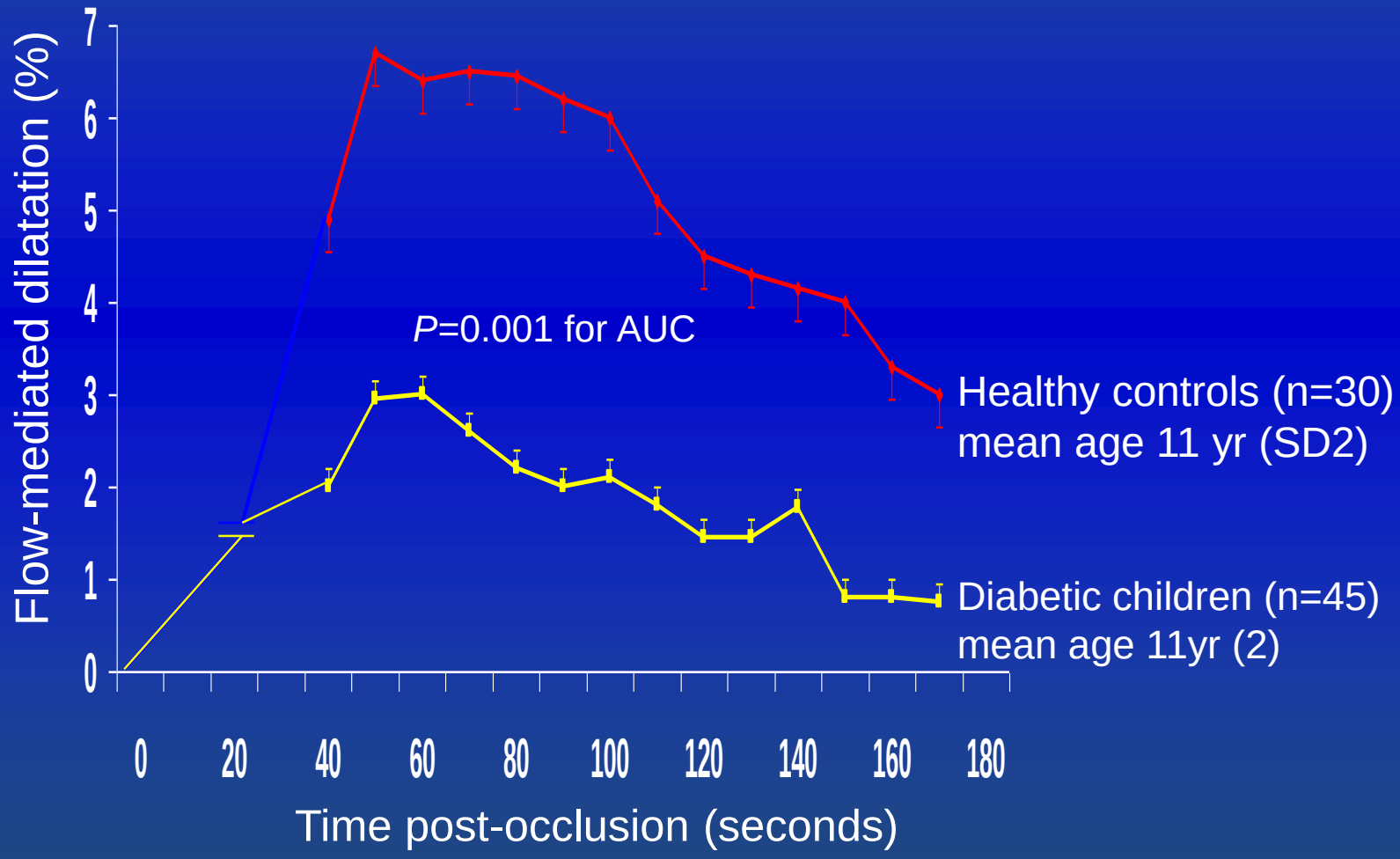



# Increased aortic and carotid intimal-media thickness in children with type 1 diabetes & in those with heterozygous familial hypercholesterolaemia compared with controls (mean age 11 years)




Jarvisalo MJ et al. *Circulation* 2001;104:2943-47

# Endothelial dysfunction: brachial artery flow-mediated dilatation




Jarvisalo MJ et al. Circulation 2004;109:1750-55

# Surrogate markers of CVD risk

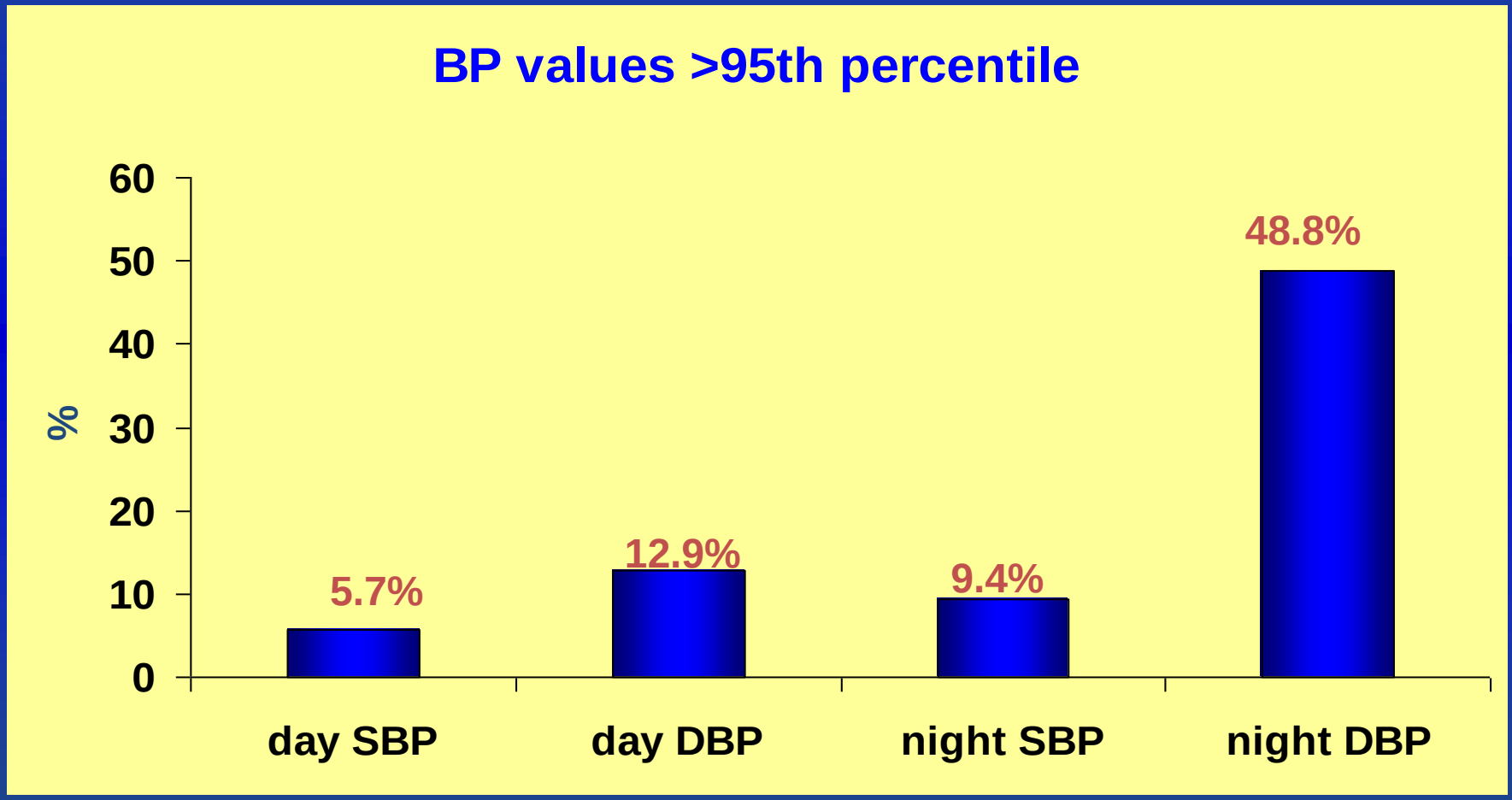
- Traditional risk factors
  - Age, sex, lipids, SBP, cholesterol
  - Classical scores (Framingham, NICE)
- Microalbuminuria

# LIPIDS and BLOOD PRESSURE IN ADOLESCENTS WITH TYPE 1 DIABETES

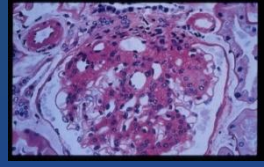
| Orchard TJ et al, Diabetes Care 2001 | | | NFS data (11-18 years) | |
|---|---|---|---|---|
| | | | | |
| | **Mortality** | **CAD** | **n (912)** | **%** |
| **LDL-C** | | | | |
| 100-129 mg/dl (2.6-3.35 mmol/l) | **5.3*** | **1.8 °** | 405 | **44.9** |
| 130-159 mg/dl (3.36-4.13 mmol/l) | 5.6* | 2.3* | 64 | **7.1** |
| >=160 mg/dl (4.14 mmol/l) | 12.1* | 3.0* | 18 | **2.0** |
| **HDL-C** | | | | |
| 45-54 mg/dl (1.6-1.39 mmol/l) | 0.7 | 0.4* | 198 | **21.7** |
| >=55 mg/dl (1.4 mmol/l) | 0.5° | 0.4* | 623 | **68.3** |
| **Triglycerides** | | | | |
| 100-149 mg/dl (1.13-1.68 mmol/l) | 2.0 | 2.5° | 232 | **25.5** |
| 150-199 mg/dl (1.69-2.25 mmol/l) | 4.3* | 3.3* | 87 | **9.5** |
| >=200 mg/dl (2.26 mmol/l) | 7.1° | 4.0* | 111 | **12.2** |
| | | | | |
| **Systolic blood pressure** | | | N (318) | **%** |
| 110-119 mmHg | 2.1 | **1.8°** | 118 | **37.1** |
| 120-129 mmHg | 3.0* | **2.5*** | 87 | **27.4** |
| >=130 mmHg | 7.2* | **5.6*** | 31 | **9.7** |
| **Diastolic blood pressure** | | | | |
| 80-84 mmHg | 2.4* | **1.4** | 39 | **12.3** |
| 85-89 mmHg | 1.6 | **2.0** | 20 | **6.3** |
| >=90 mmHg | 4.0* | **4.2*** | 5 | **1.6** |

°p<0.05;
*p< 0.01

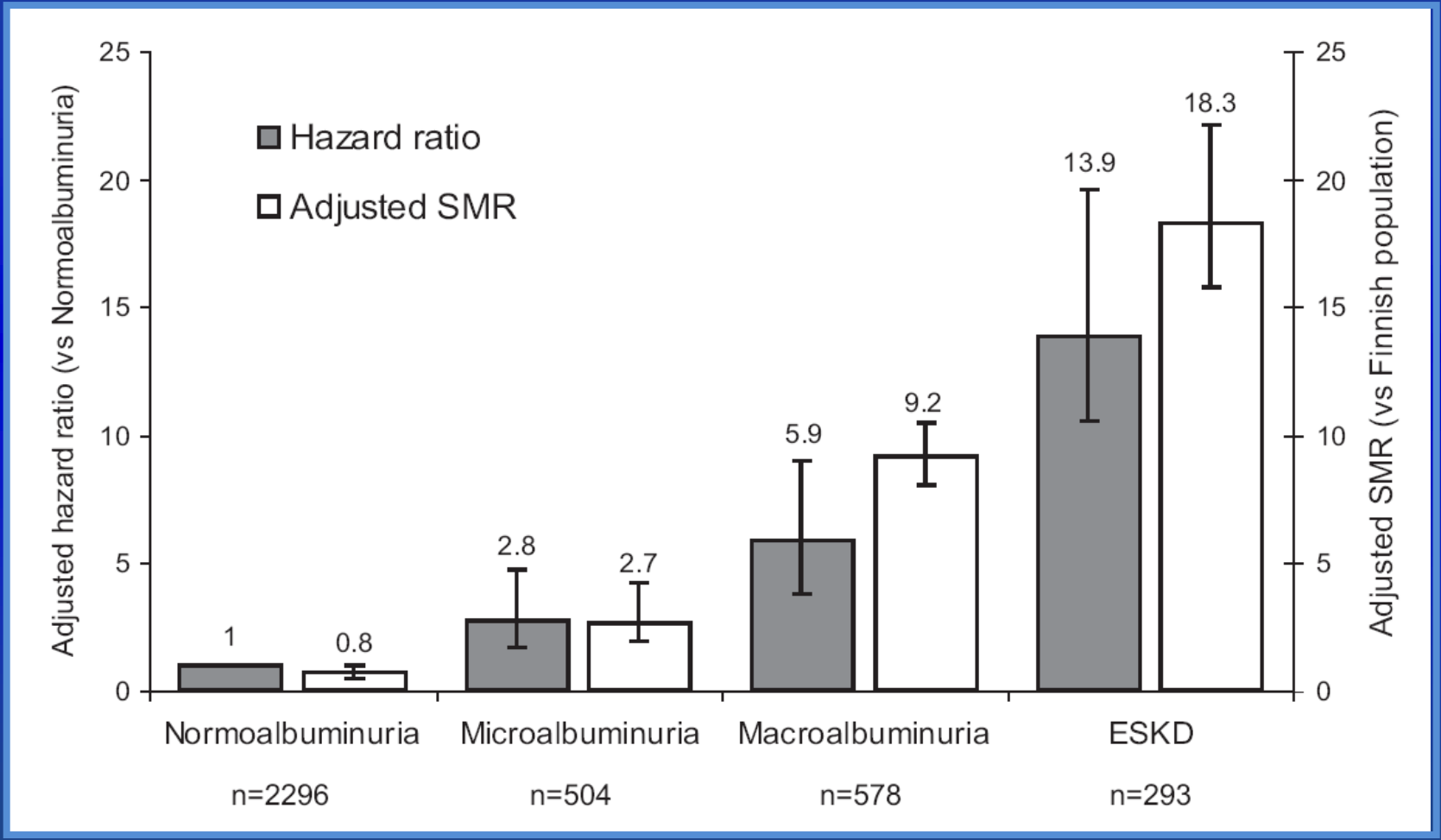
# ABPM in 509 adolescents from the NFS cohort: pathological BP values



# Diabetic Nephropathy and CVD

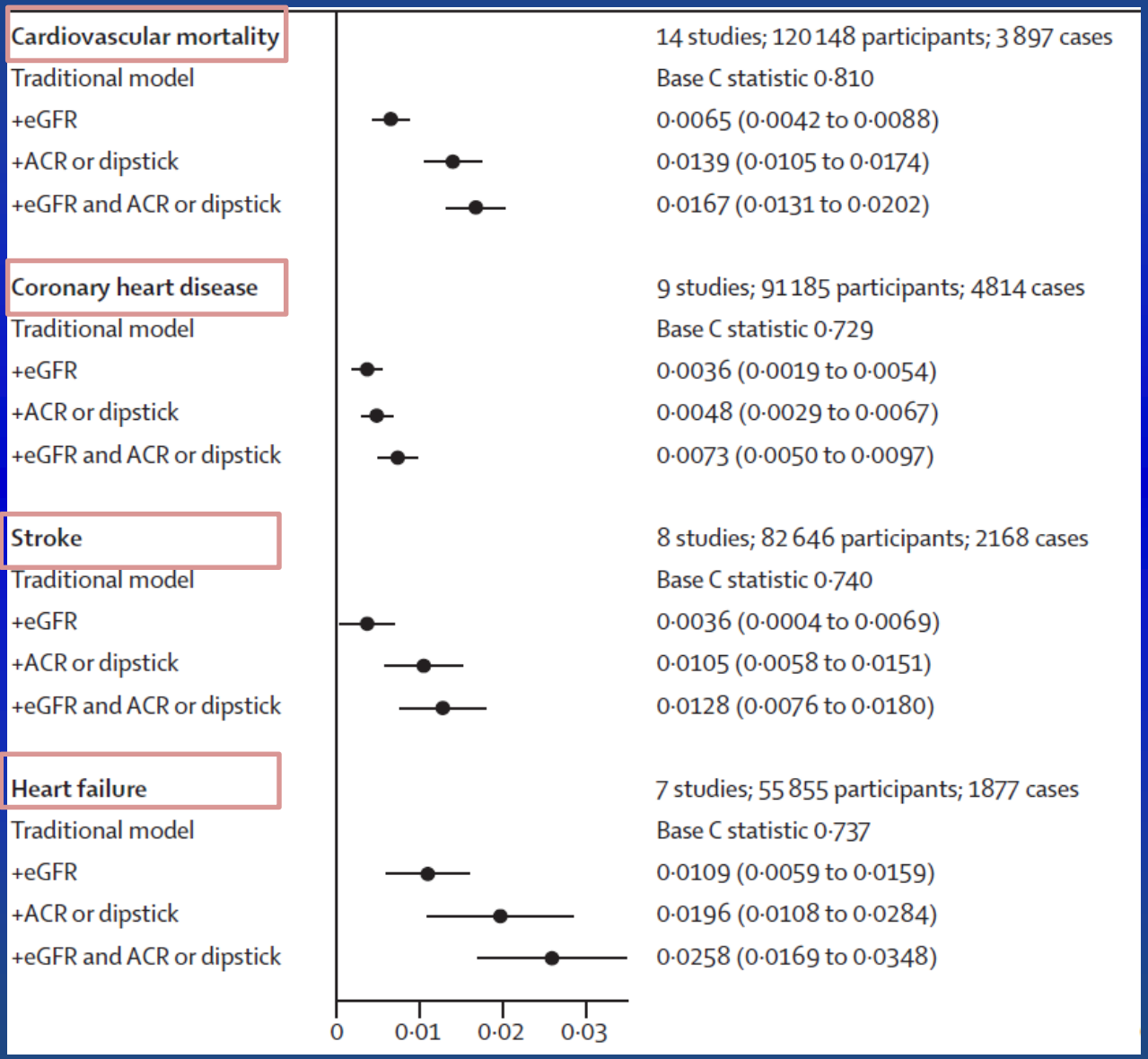


- **Leading cause of end stage renal failure**
- **Major determinant of cardiovascular morbidity and mortality**




Groop P-H et al., Diabetes 2009

# Improved prediction of Cardiovascular outcomes in the general population and high risk cohorts (diabetes, hypertension), with addition of kidney measures (ACR and eGFR)



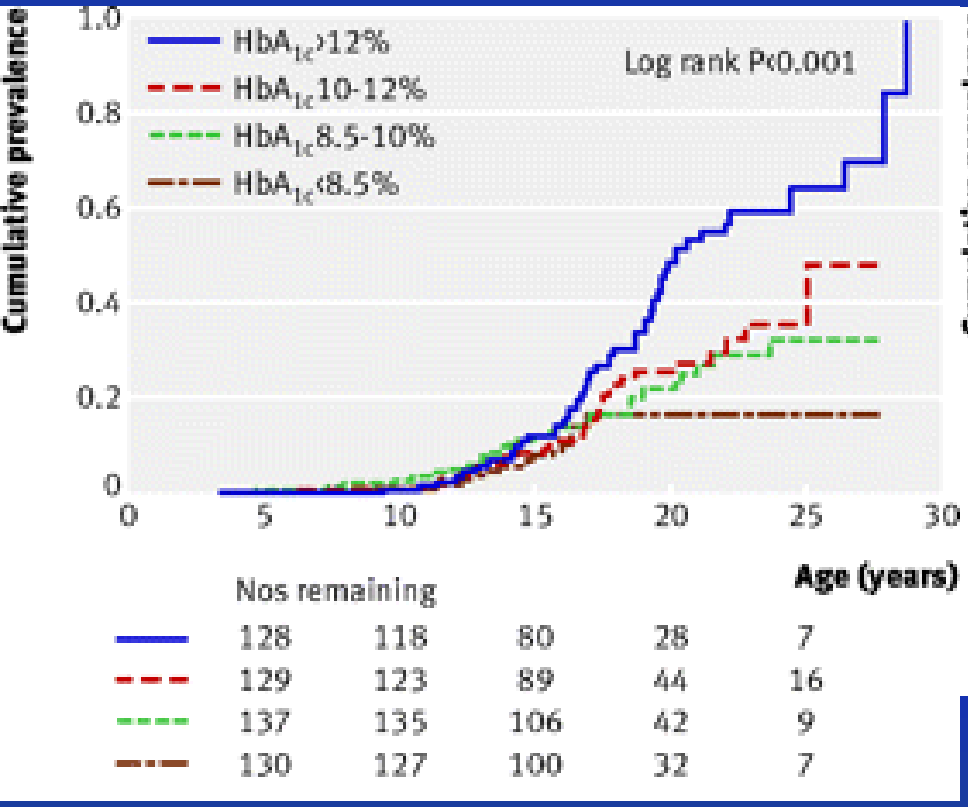

*Matsushita K et al., Lancet Diabetes Endocrinol* 2015

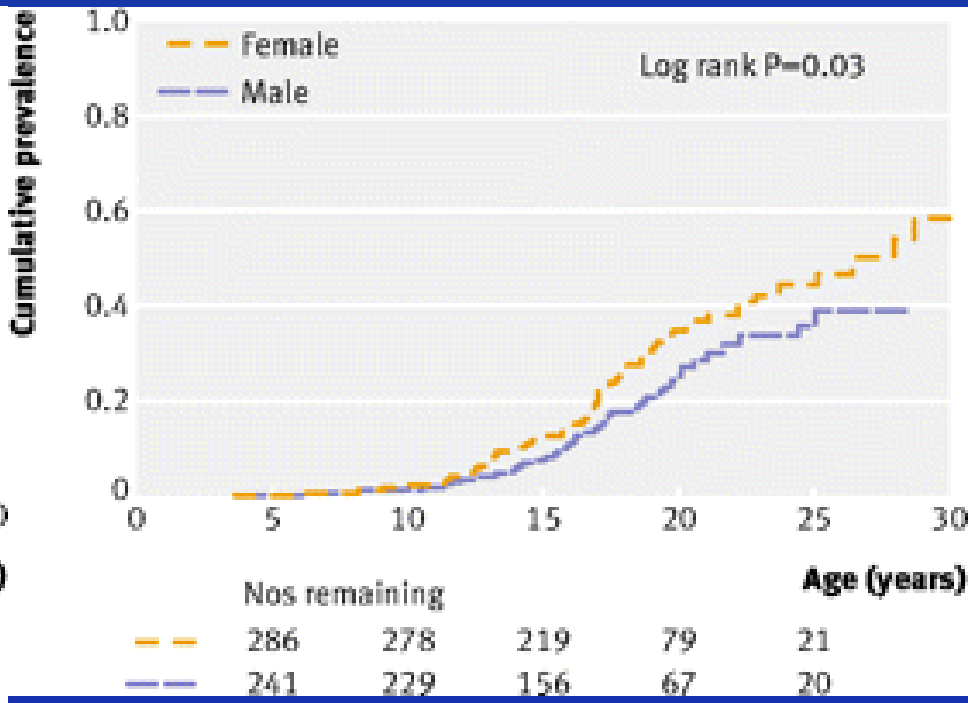
# Oxford Regional Prospective Study (ORPS)

**Geographically defined population.**
**527 subjects recruited at diagnosis age <16 yrs.**

**Followed median**
**10 (3-8) yrs**
**Natural history**
**MA**

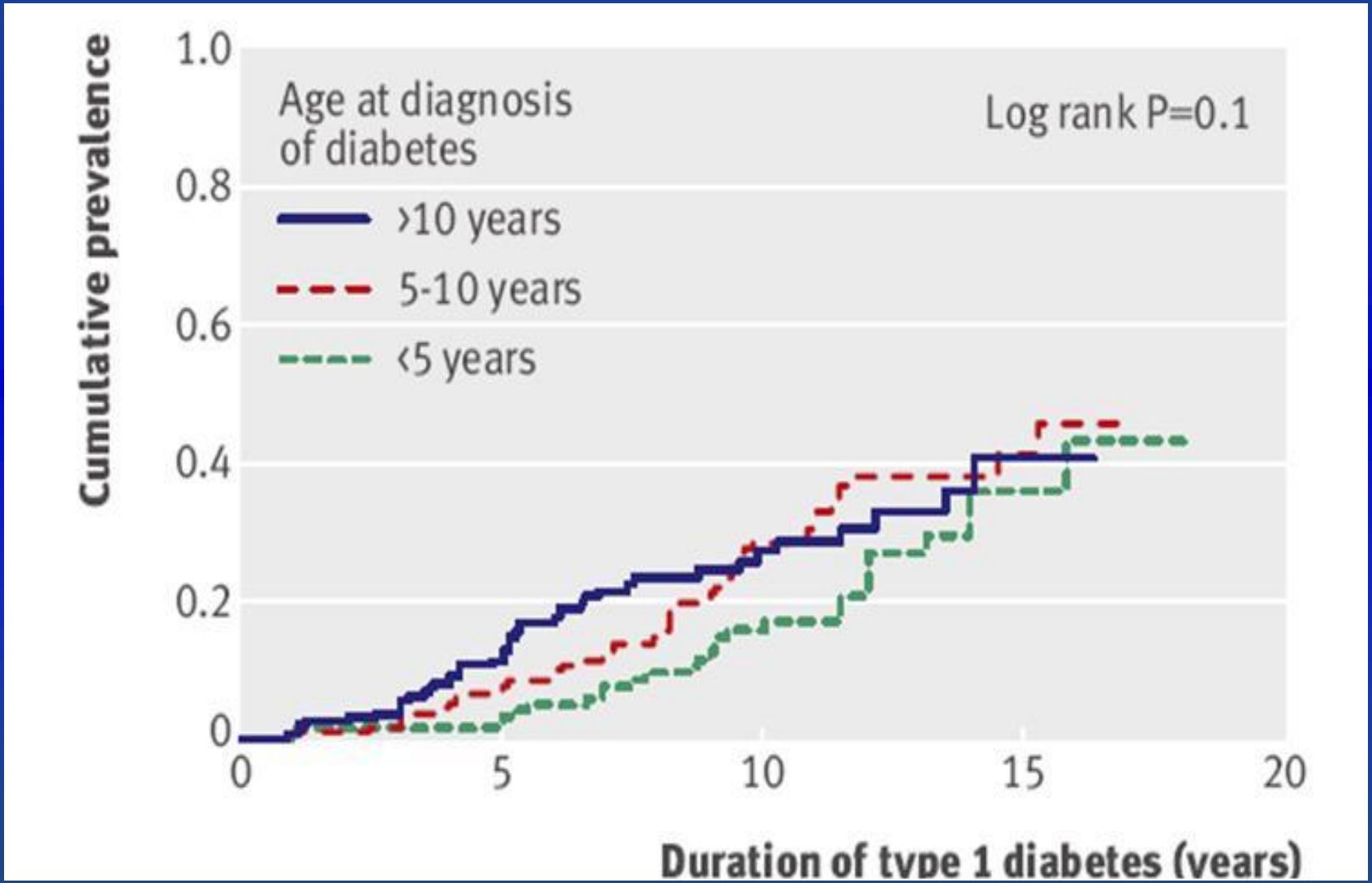
# Kaplan-Meier survival curves showing cumulative prevalence of developing microalbuminuria



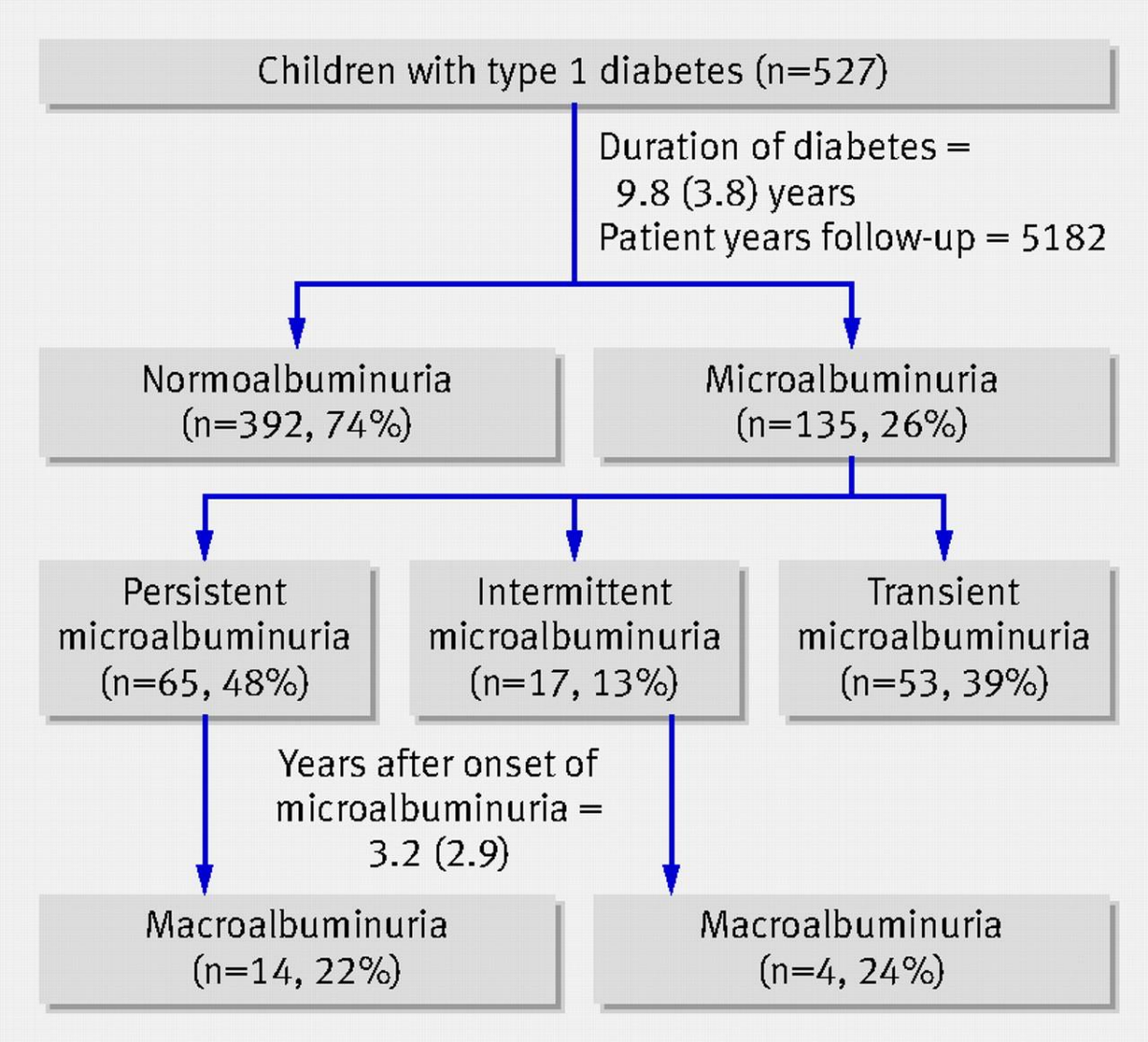

Amin, R. et al. *BMJ* 2008;336:697-701

# Cumulative prevalence of MA in relation to age at diagnosis



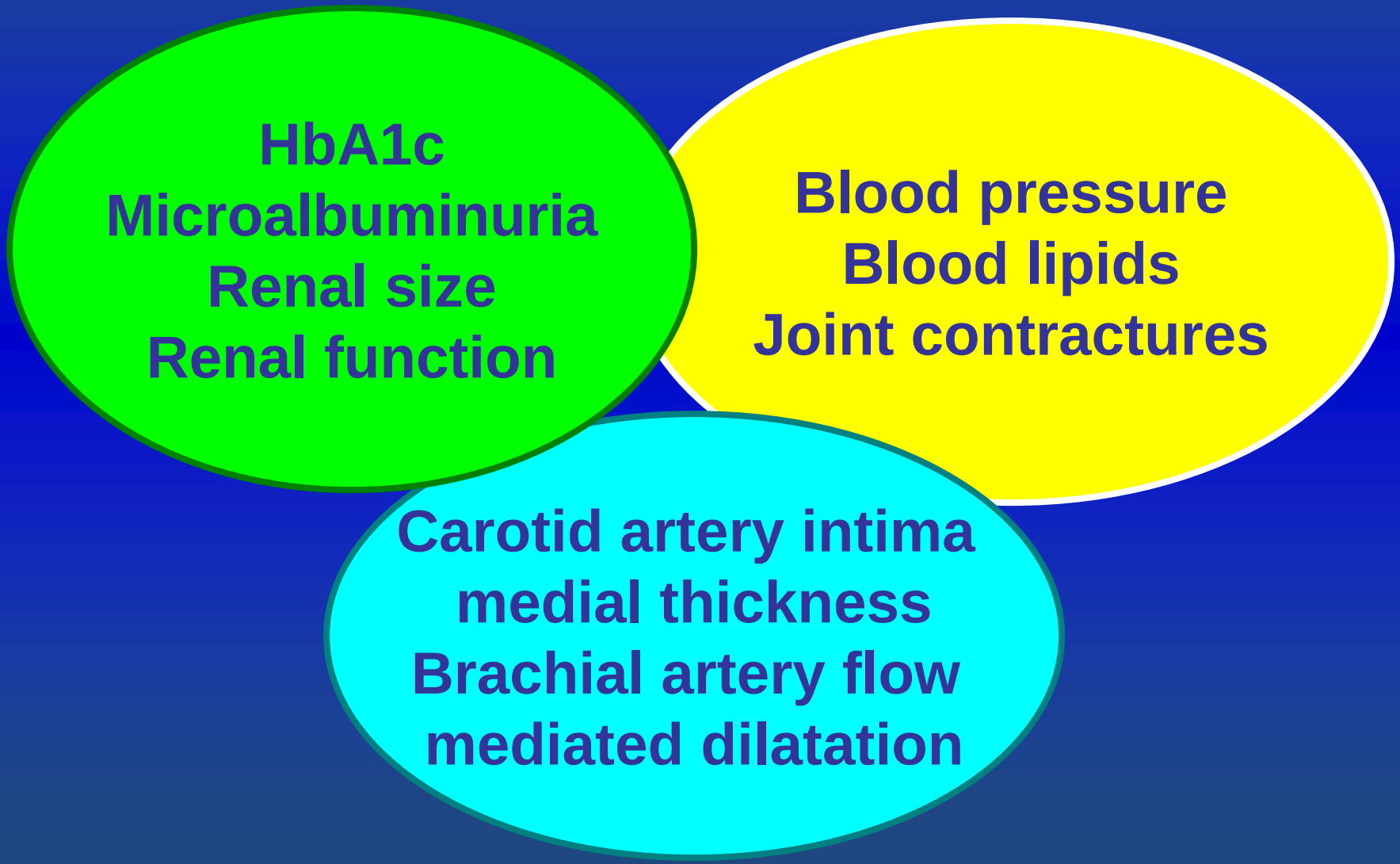

Amin R et al., *BMJ* 2008

# Numbers with microalbuminuria and progression to macroalbuminuria up to September 2005



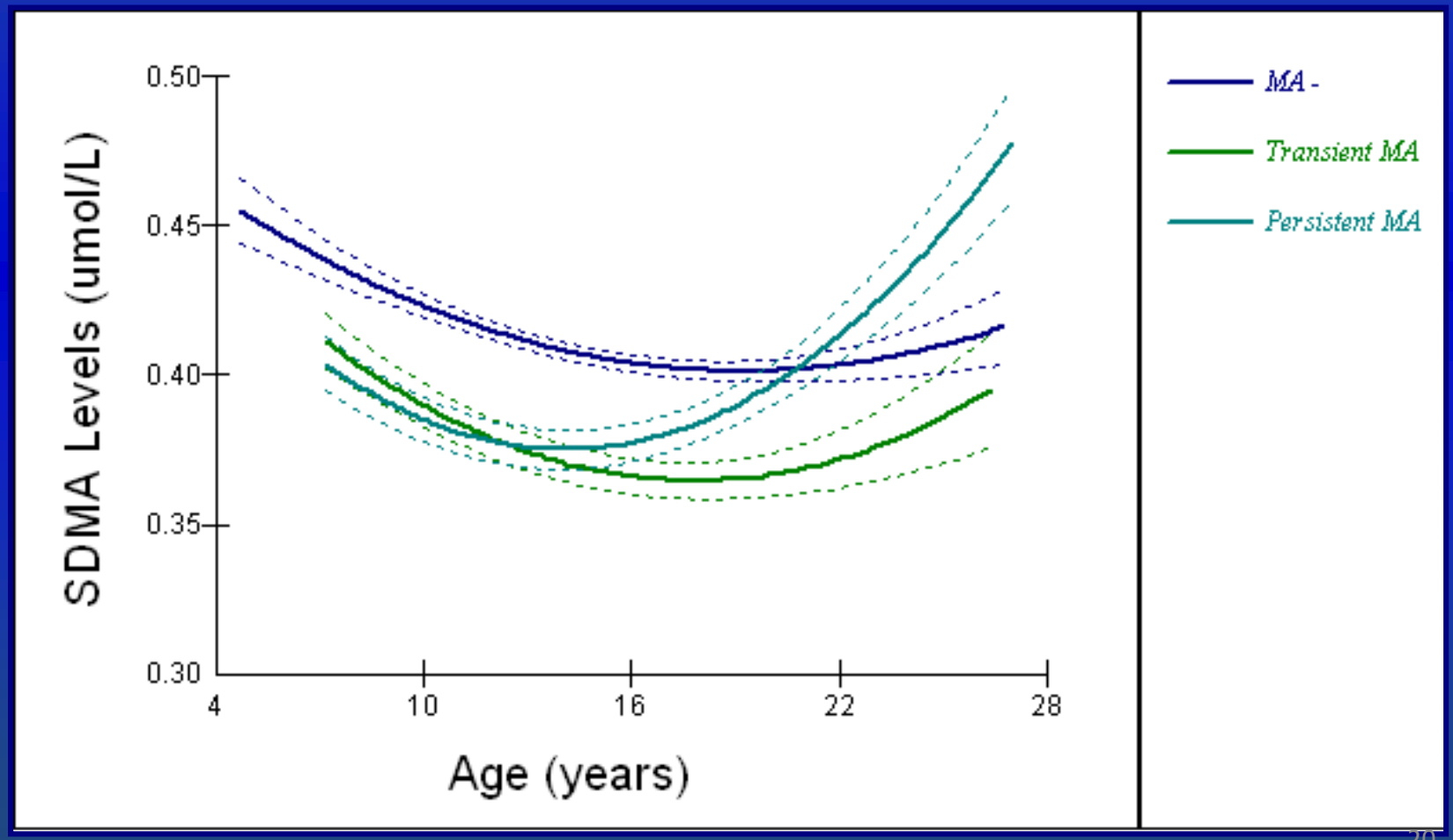

Amin, R. et al. *BMJ* 2008;336:697-701

# MA is a marker of a generalised endotheliopathy

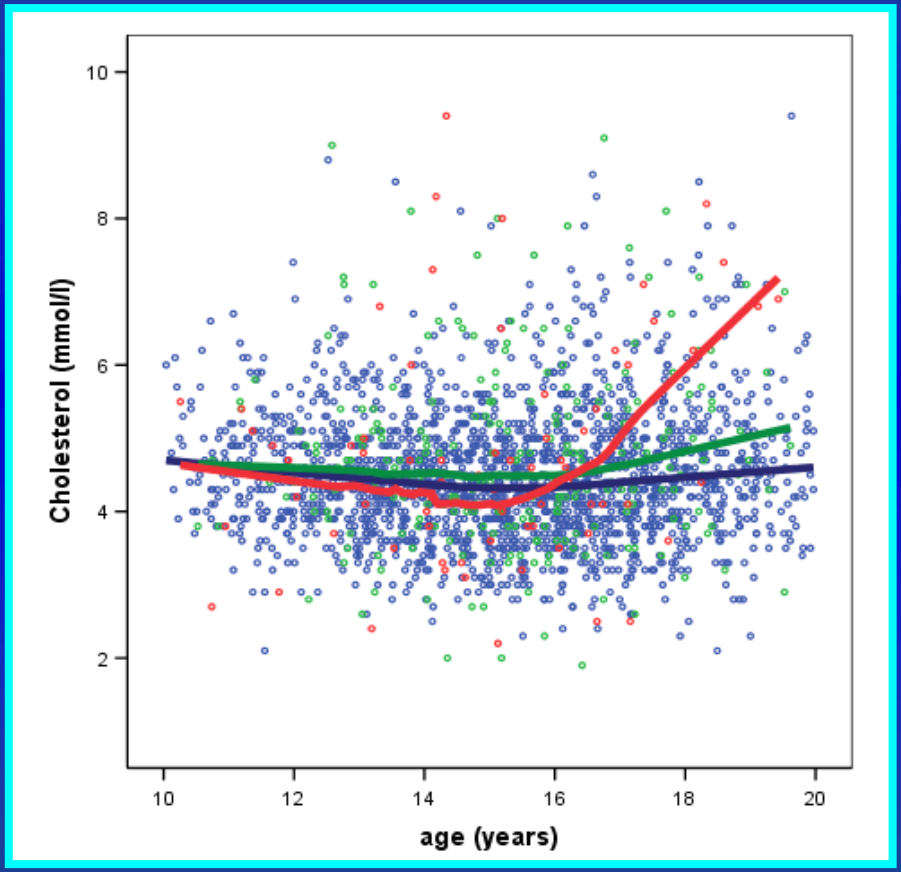


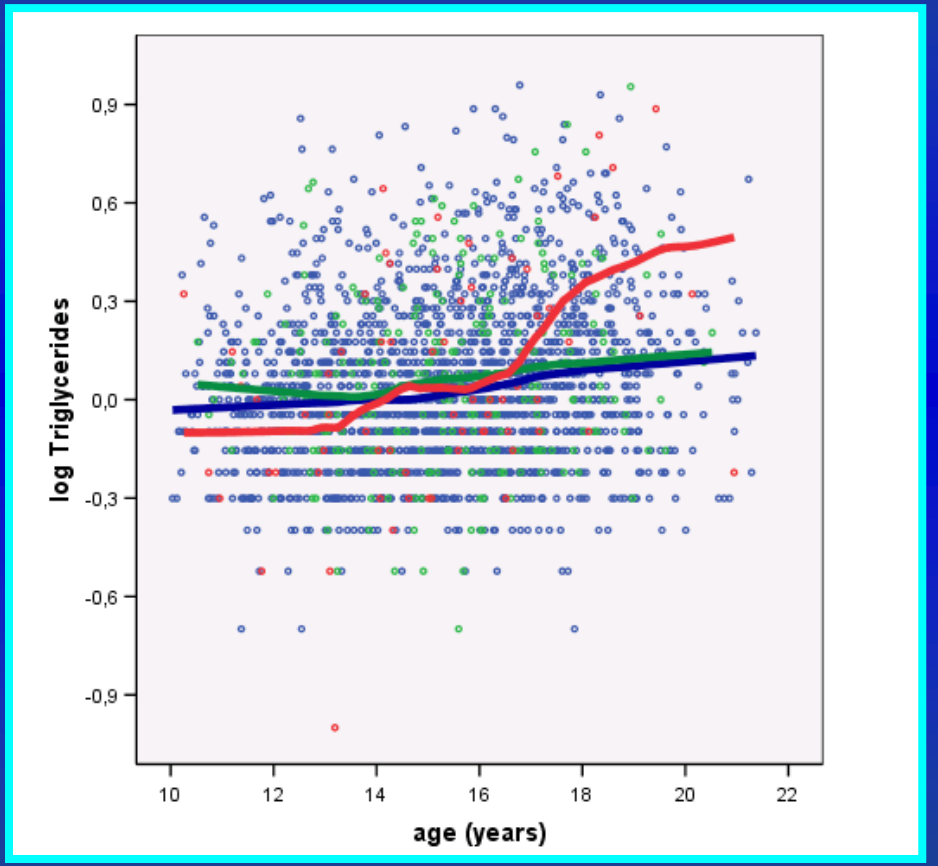
# Symmetric dimethylarginine (SDMA) vs Age

## Endogenous marker of GFR



# Lipids vs age: MA+ vs MA-




Persistent MA+

Transient MA+

MA -

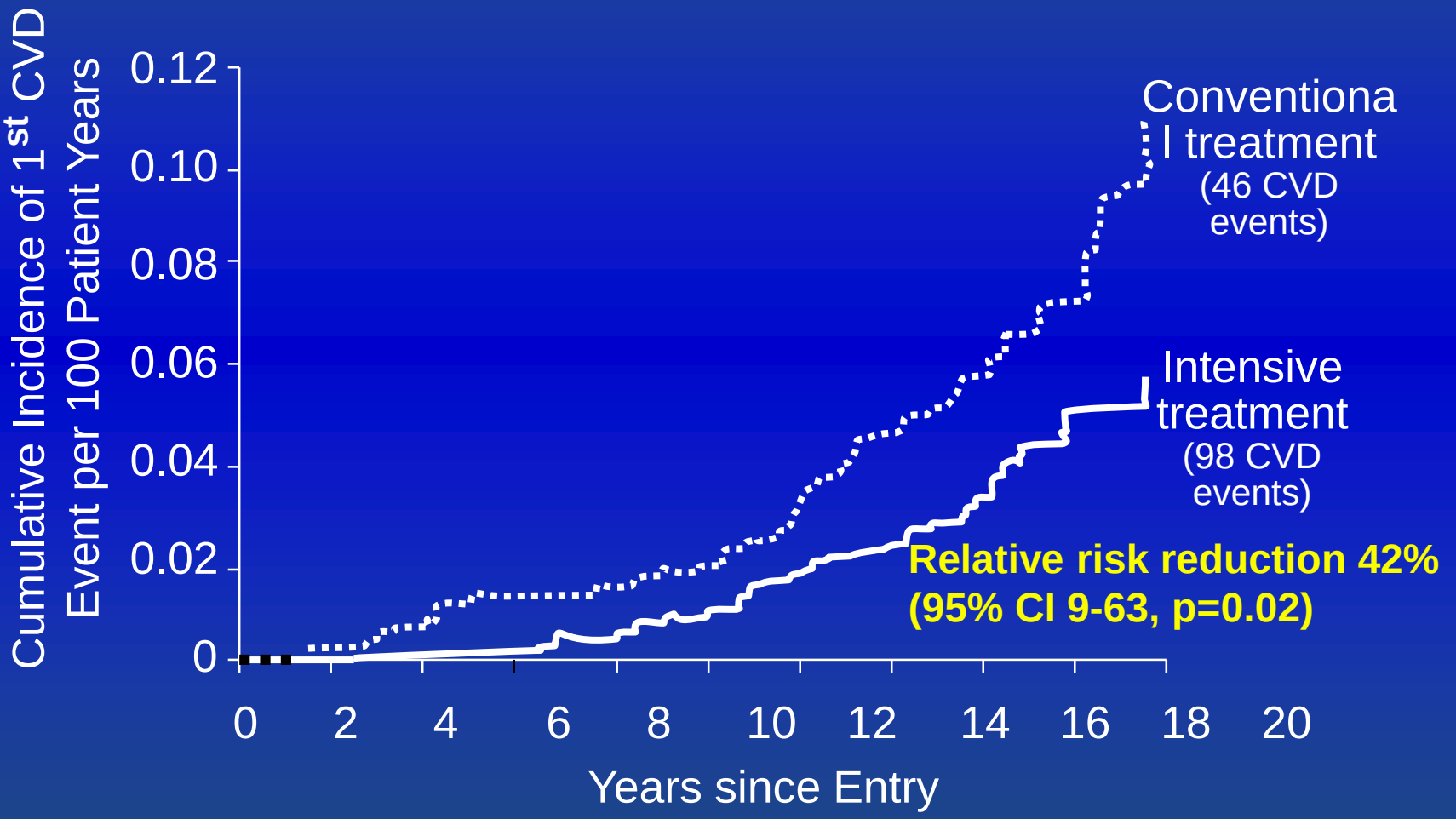
- Early markers of CVD
- Possible interventions
- The way forwards

# Comparison of efficacy and safety of intensive treatment between adolescents and adults

| | Adolescents | Adults | p |
|---|---|---|---|
| **Mean HbA1c (%)** | | | |
| Intensive | 8.06 ± 0.13 | 7.12 ± 0.03 | <0.001 |
| Conventional | 9.76 ± 0.12 | 9.02 ± 0.05 | <0.001 |
| **Decreased Risk (%)** | | | |
| Retinopathy | 61 | 63 | 0.802 |
| Microalbuminuria | 35 | 45 | 0.886 |
| **All severe hypoglycaemia** | | | |
| Rate / 100 PYR | 85.7 | 56.9 | 0.004 |
| **Coma / seizure** | | | |
| Rate / 100 PYR | 26.7 | 14.4 | 0.001 |

DCCT Research Group, Journal of Pediatrics, 1994

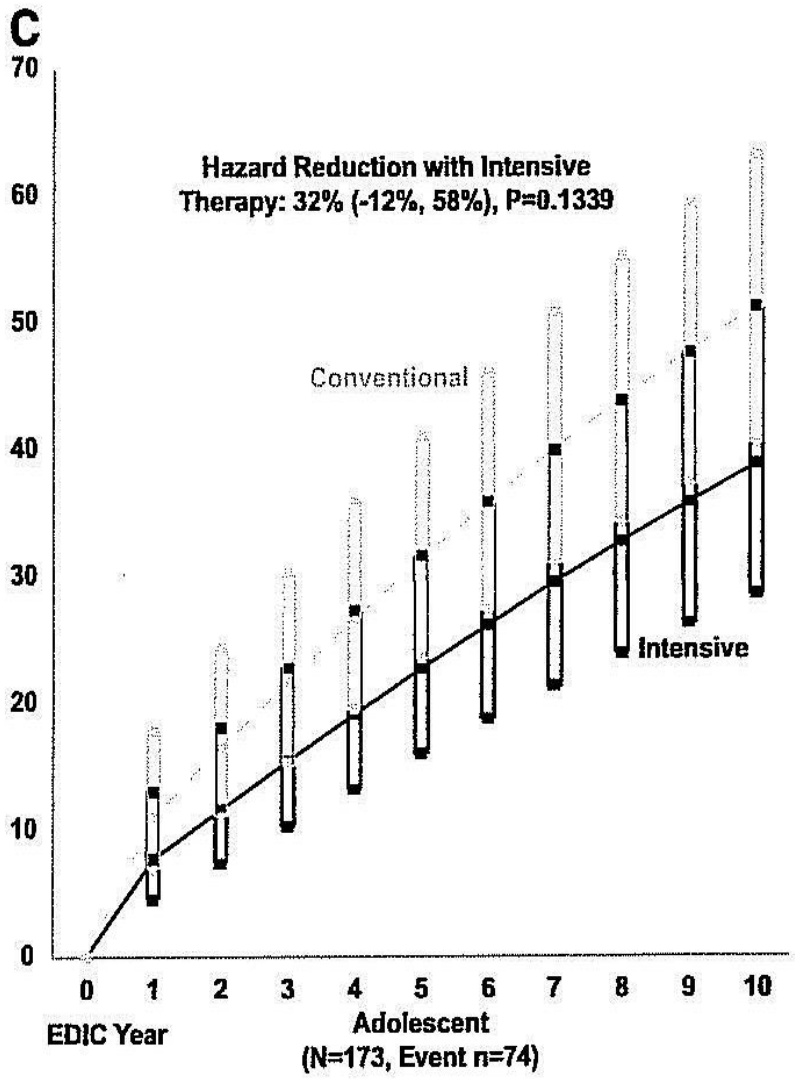
# Intensive Diabetes Treatment and Incidence of Cardiovascular Disease in Patients with Type 1 Diabetes during DCCT/EDIC mean follow-up of 17 years

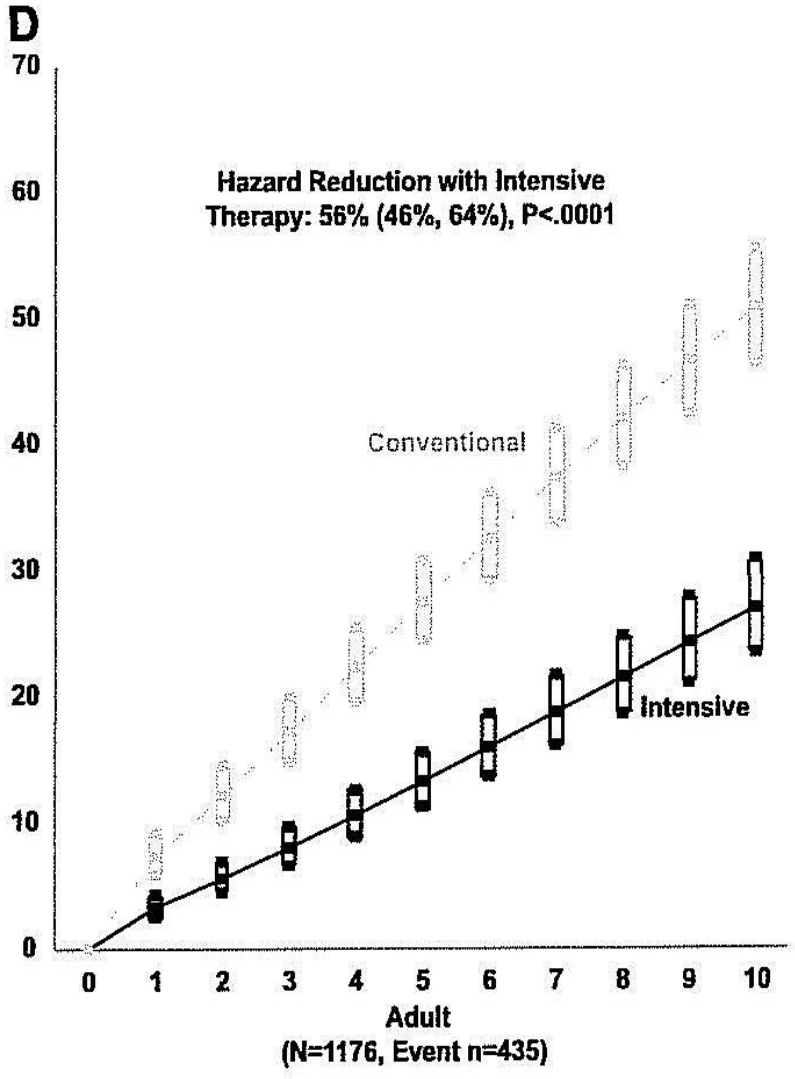



Microalbuminuria: HR for CVD = 2.93 (95% CI 1.85-4.65)

DCCT/EDIC Study Research Group. NEJM 2005;353:2643-53

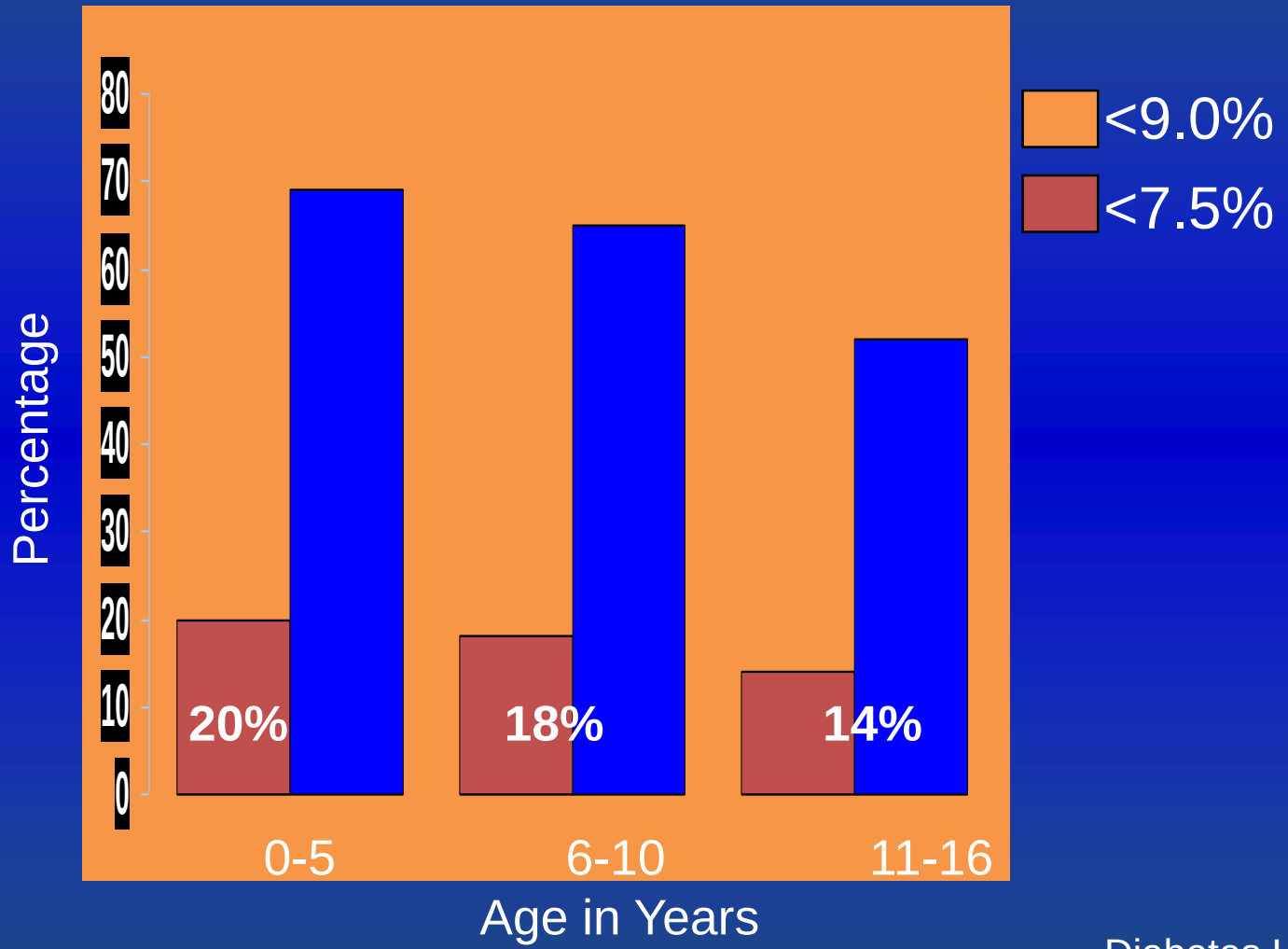
# EDIC STUDY




White et al Diabetes:2011;59:May

# HbA1c target attainment by age group in UK National Paediatric Diabetes Audit in (n=11,696)

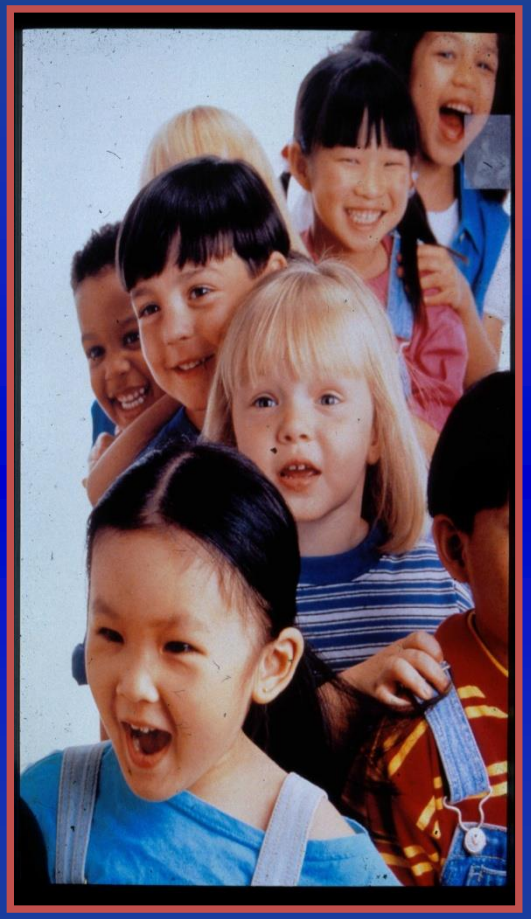



Diabetes UK

# The Concept


- Achieving targets for optimal glycaemic control during adolescence is challenging
- Targeted intervention in at risk subjects with statins/ACE inhibitors may provide Cardio Renal protection and reduce long term CVD and renal morbidity/mortality

# Adolescent Diabetes Intervention Trial *AdDIT*



## Aim

To determine In a double blind placebo controlled parallel group trial whether intervention with ACE inhibitors, Statins or a combination of both drugs in high risk subjects will:

- Reduce albumin excretion and prevent decline in renal function
- Reduce CVD risk
- Well tolerated
- Cost effective

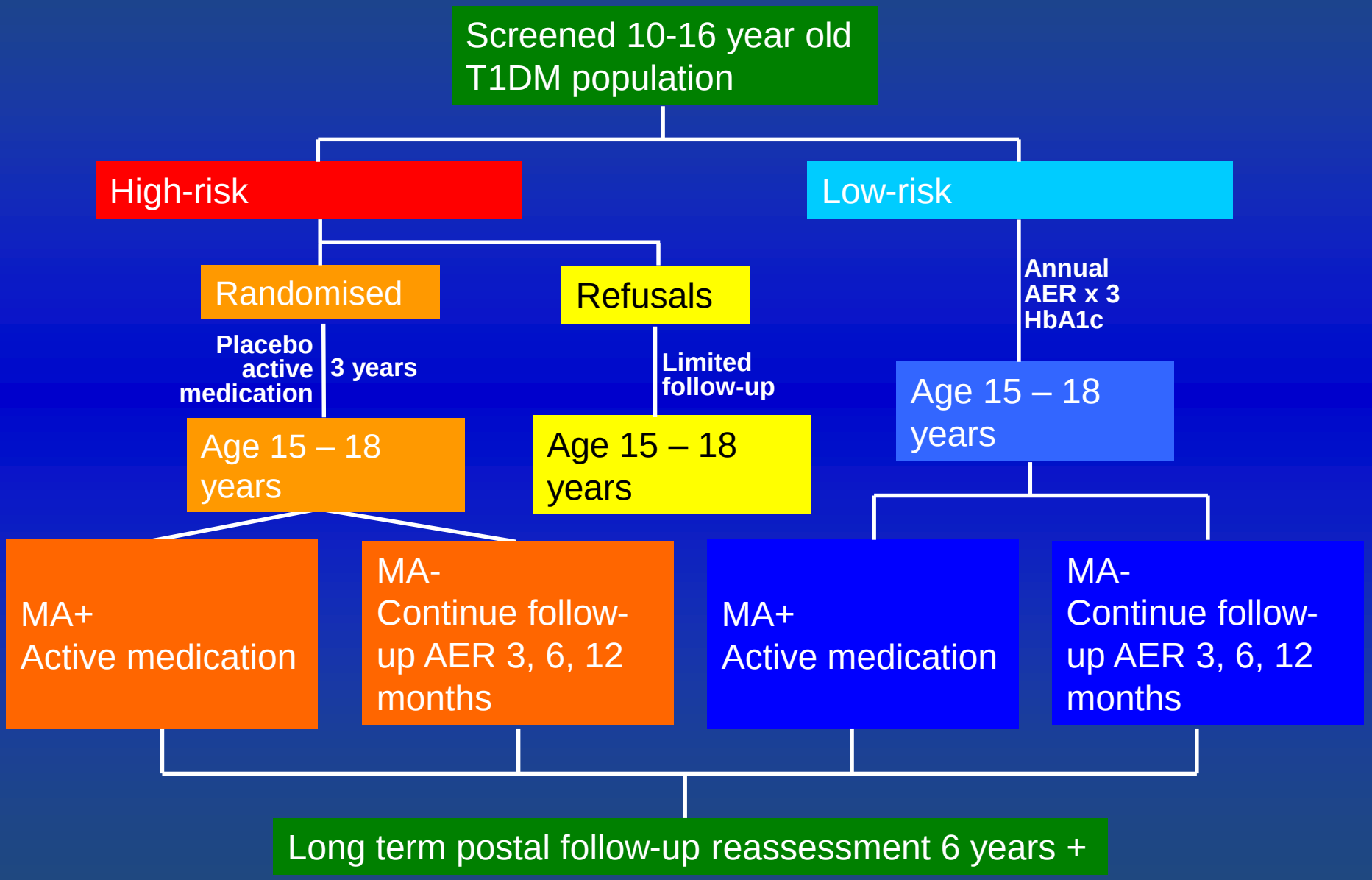
British Heart Foundation

JDRF Juvenile Diabetes Research Foundation

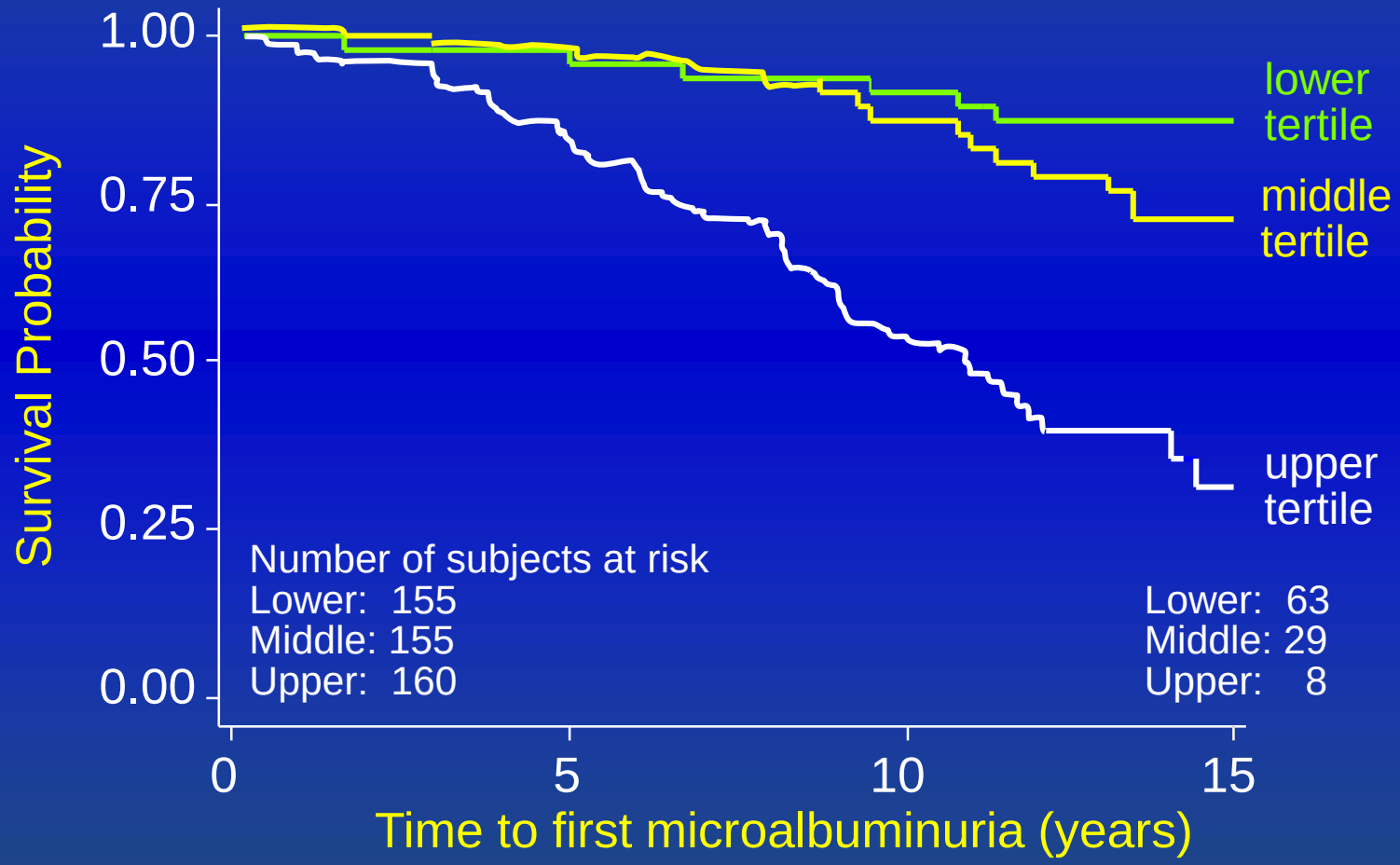
Diabetes UK

Pfizer

# AdDIT Study Design



# Kaplan-Meier survival risk of developing microalbuminuria in ORPS subjects aged ≥16 years based on tertiles of albumin excretion phenotype* defined using assessments aged 11-16




* adjusted for age, gender & duration of diabetes



Dunger DB et al. Diabet Med 2007

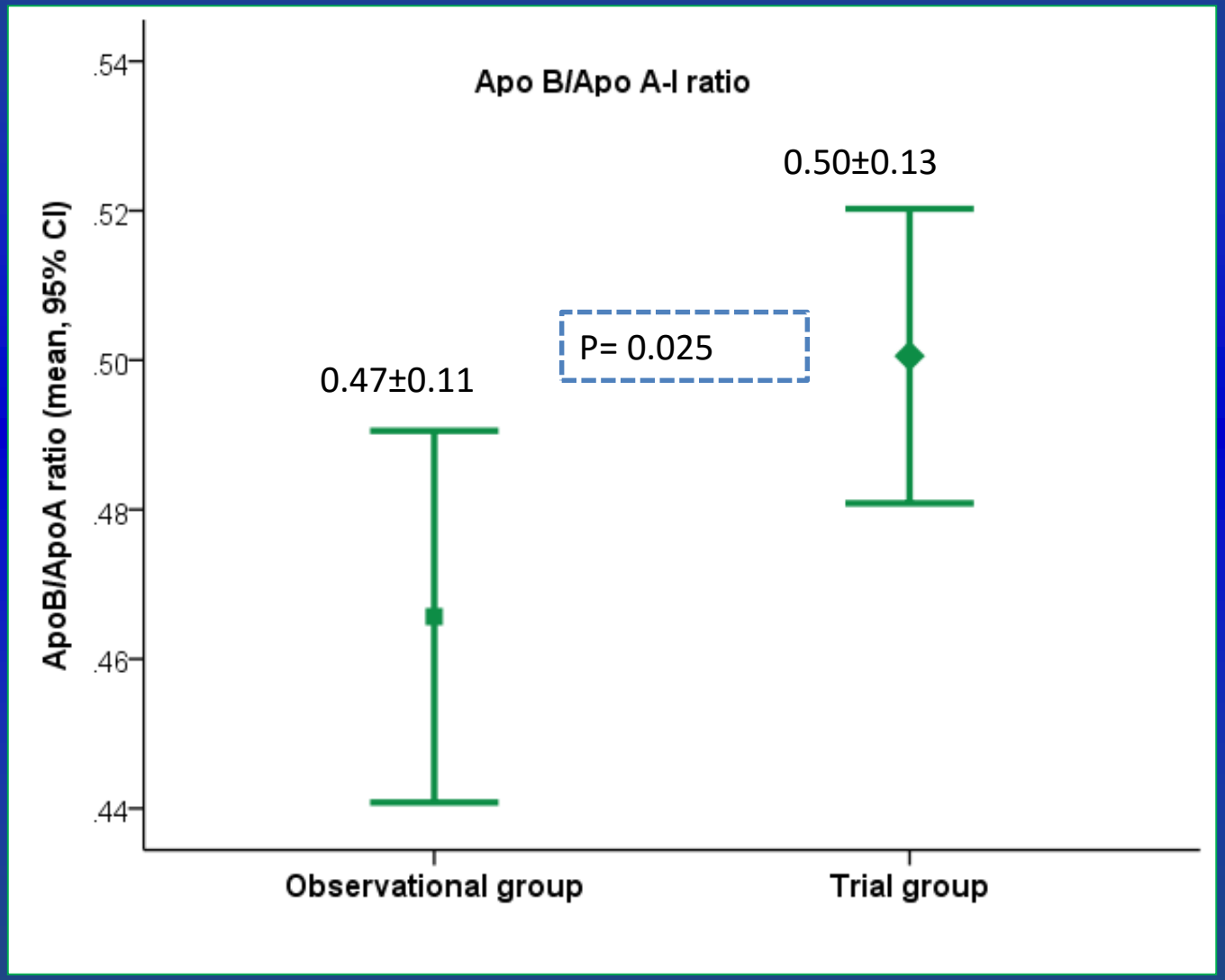
**Prof. Neil Dalton and the WellChild Laboratory (St Thomas' Hospital, London) have processed 11,165 sets of urines since 1986 - 223 litres!**

# AdDIT Screening results by ACR tertiles

| | Total assigned ACR tertiles | Lower ACR tertile | Middle ACR tertile | Upper ACR tertile |
|---|---|---|---|---|
| N | 3353 | 959 (28.6%) | 1112 (33.2%) | 1282 (38.2%) |
| Sex (Male/female,%) | 54.6/45.4 | 48.0/52.0 | 60.3/39.7 | 54.6/45.4 |
| ACR visit 1 (mmol/mg) | 0.75 [0.57-1.10] | 0.52 [0.41-0.62] | 0.70 [0.59-0.87] | 1.22 [0.92-1.77] |
| ACR visit 2 (mmol/mg) | 0.75 [0.57-1.11] | 0.52 [0.43-0.62] | 0.71 [0.59-0.85] | 1.24 [0.91-1.82] |
| HbA1c(%) | 8.3±1.4 | 8.2±1.2 | 8.3±1.3 | 8.4±1.5 |

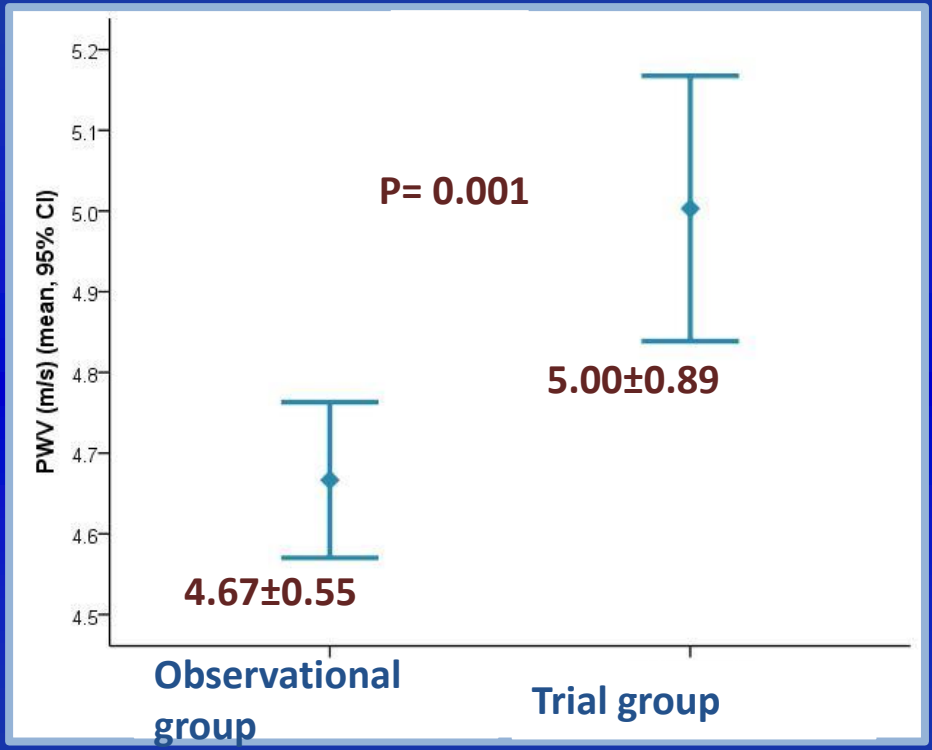
| | Visit 1 | Visit 2 | Both visits |
|---|---|---|---|
| Cases with MA | 78 (2.3%) | 86 (2.6 %) | 22 **(0.7%)** |
| % within upper tertile | 6.1% | 6.7% | **1.7%** |

# AdDIT Screening ApoB/ApoA-I ratio

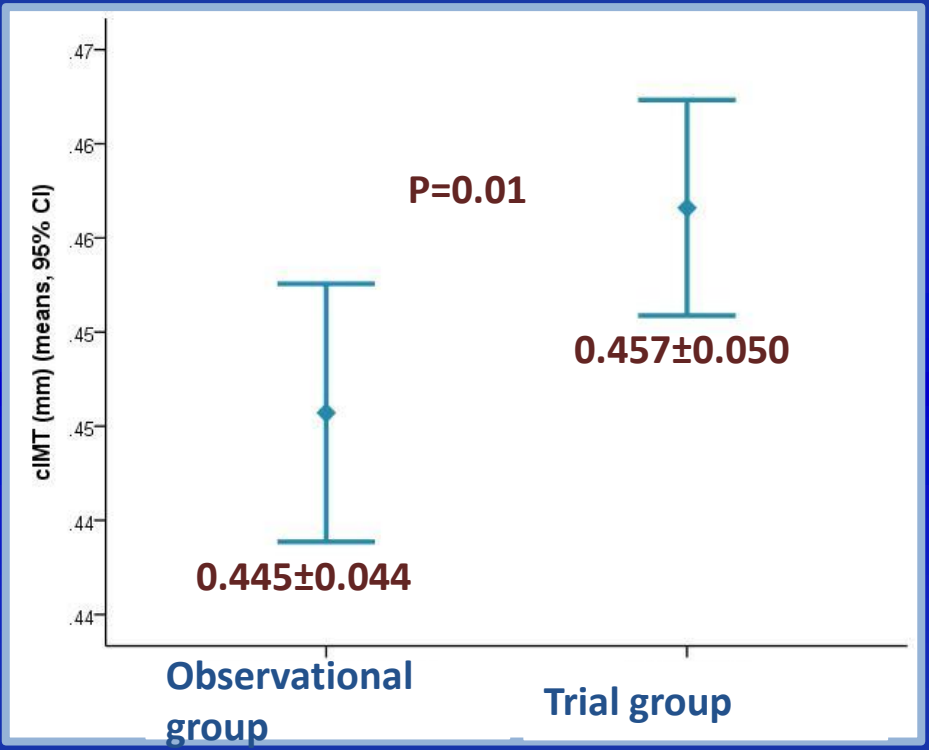



AdDIT: preliminary baseline data

# Pulse Wave Velocity

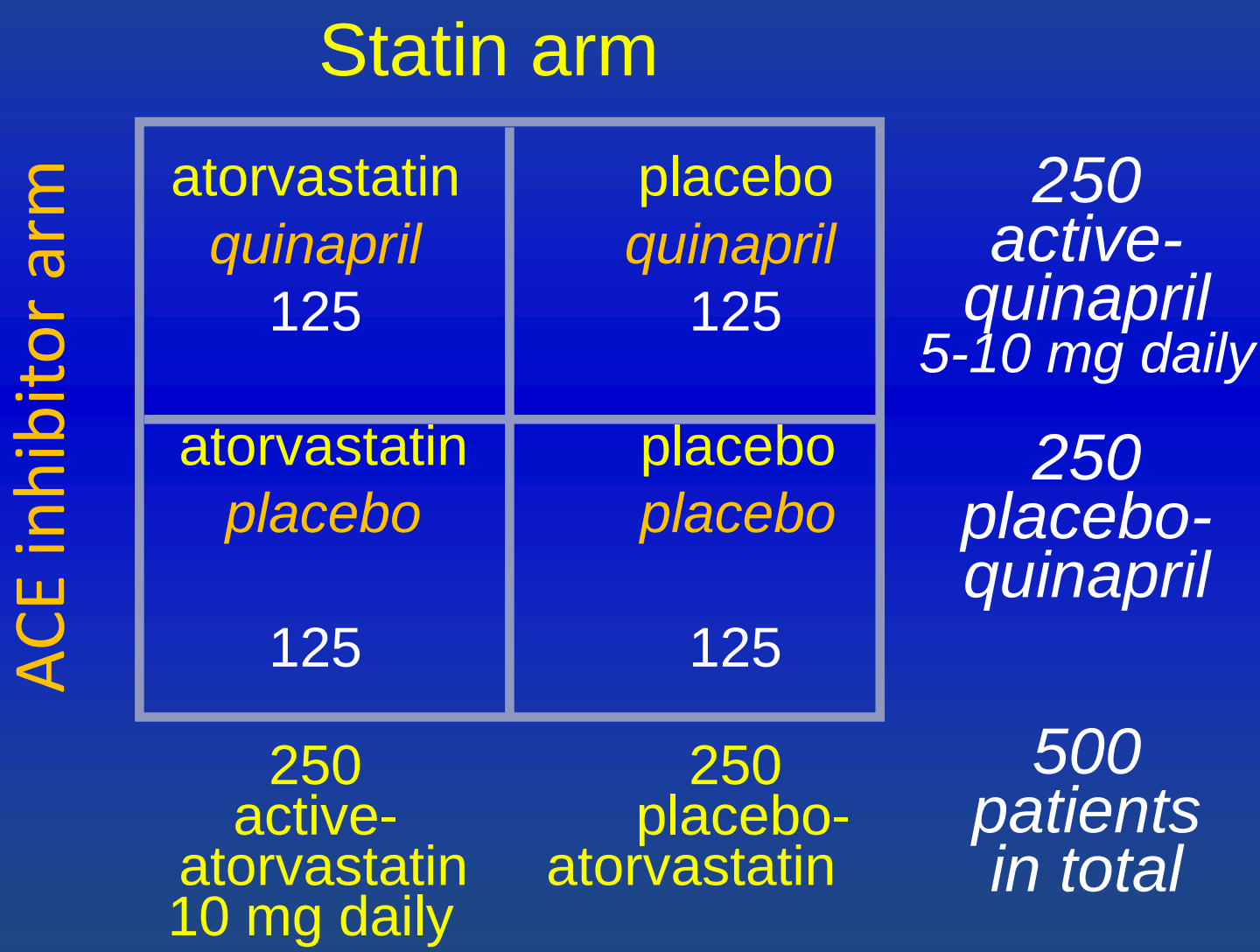



# Aortic IMT

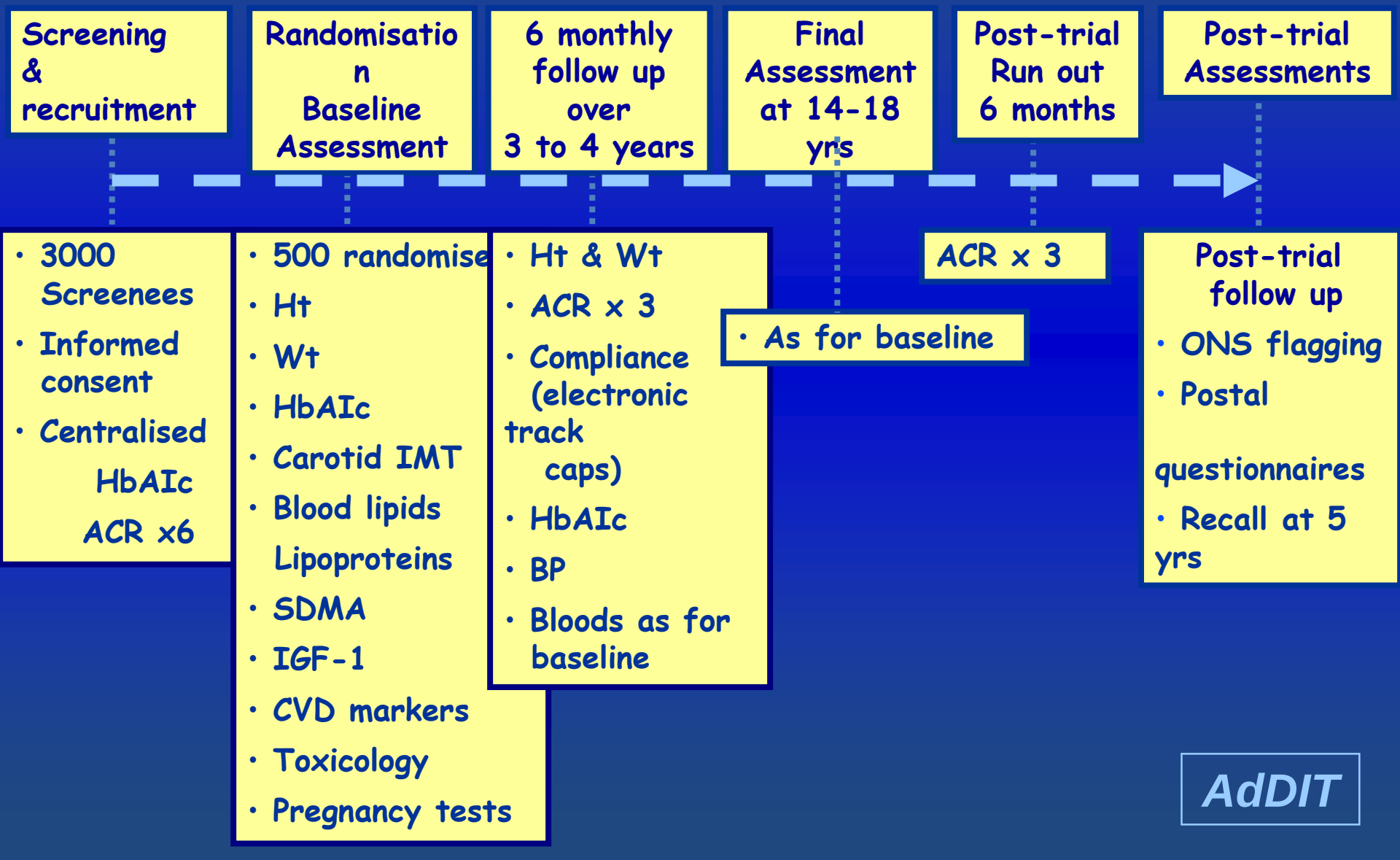



AdDIT: preliminary baseline data

# 2 x 2 "Factorial" Randomisation



# Trial Flow Diagram




AdDIT

# Adherence (whole study)

Totals for track caps in use

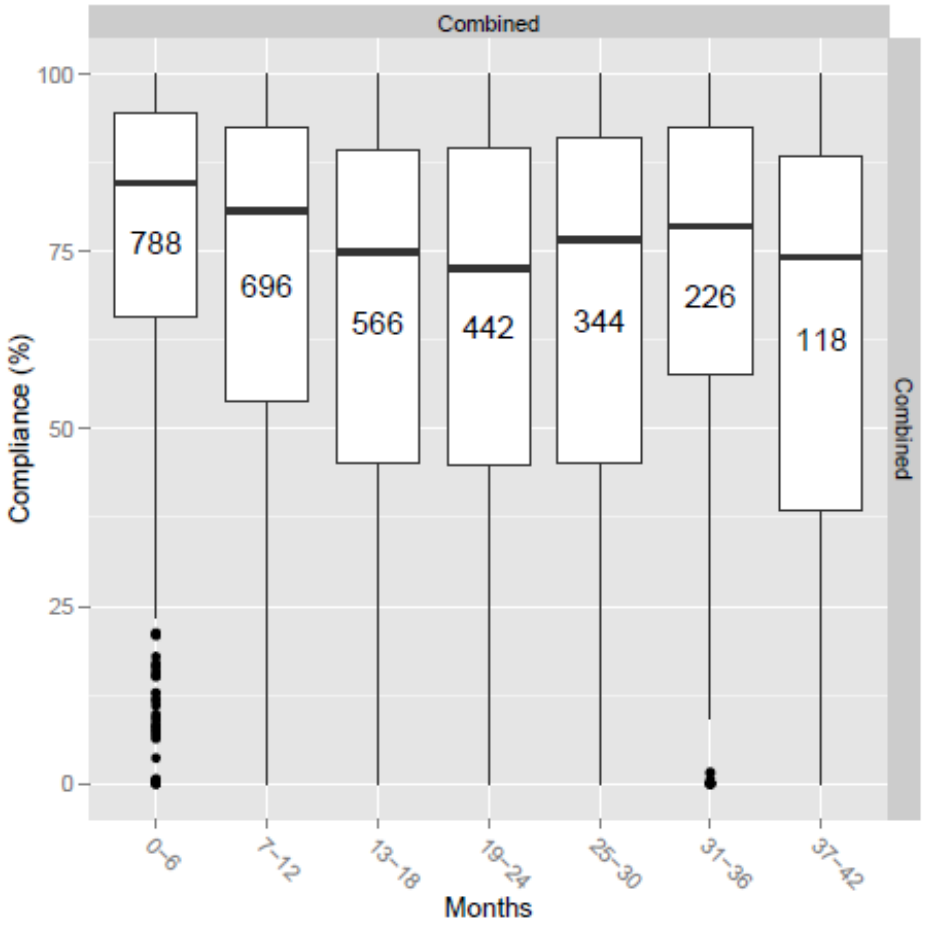
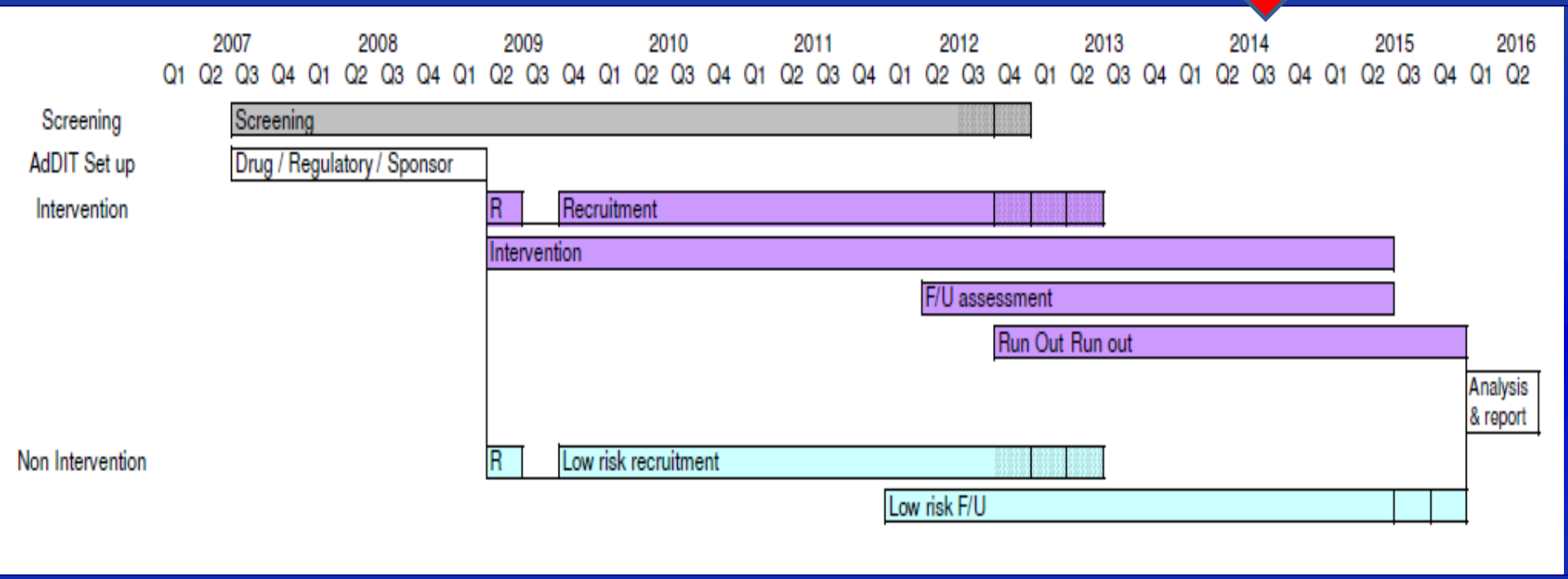



Figure 2: Compliance Overall (the sample size is printed in each box at the mean value). Compliance is assessed by return of medication and electronic tagged drug dispensers.

# Timeline




***Minimum intervention of 2 years (drugs expire August 2015)***

# Trial Endpoints

## Primary endpoints

- The area under the curve over time of log standardised albumin creatinine ratio per year standardised for gender, age and duration of disease

## Secondary endpoints

*Changes from baseline in:*

- Carotid intima-media thickness
- Blood pressure, lipids & lipoproteins, & other CVD risk markers
- GFR assessed by plasma symmetric dimethylarginine (SDMA)
- Quality of life, compliance & cost-effectiveness

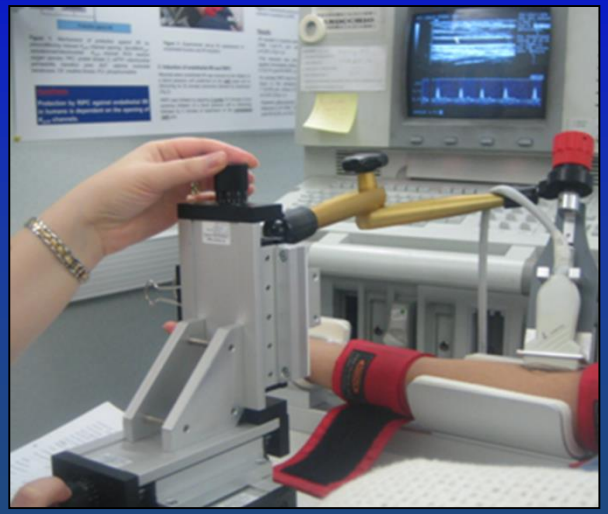
***AdDIT***

# Tracking of Risk - Diabetic nephropathy and cardiovascular disease in young people with T1D

AdDIT
Supported by Juvenile Diabetes Research Foundation, Diabetes UK, British Heart Foundation & Pfizer

– Carotid IntimaMedia Thickness Scan (cIMT)

Pulse Wave Velocity (PWV) –



– Flow Mediated Dilatation (FMD)

- Early markers of CVD
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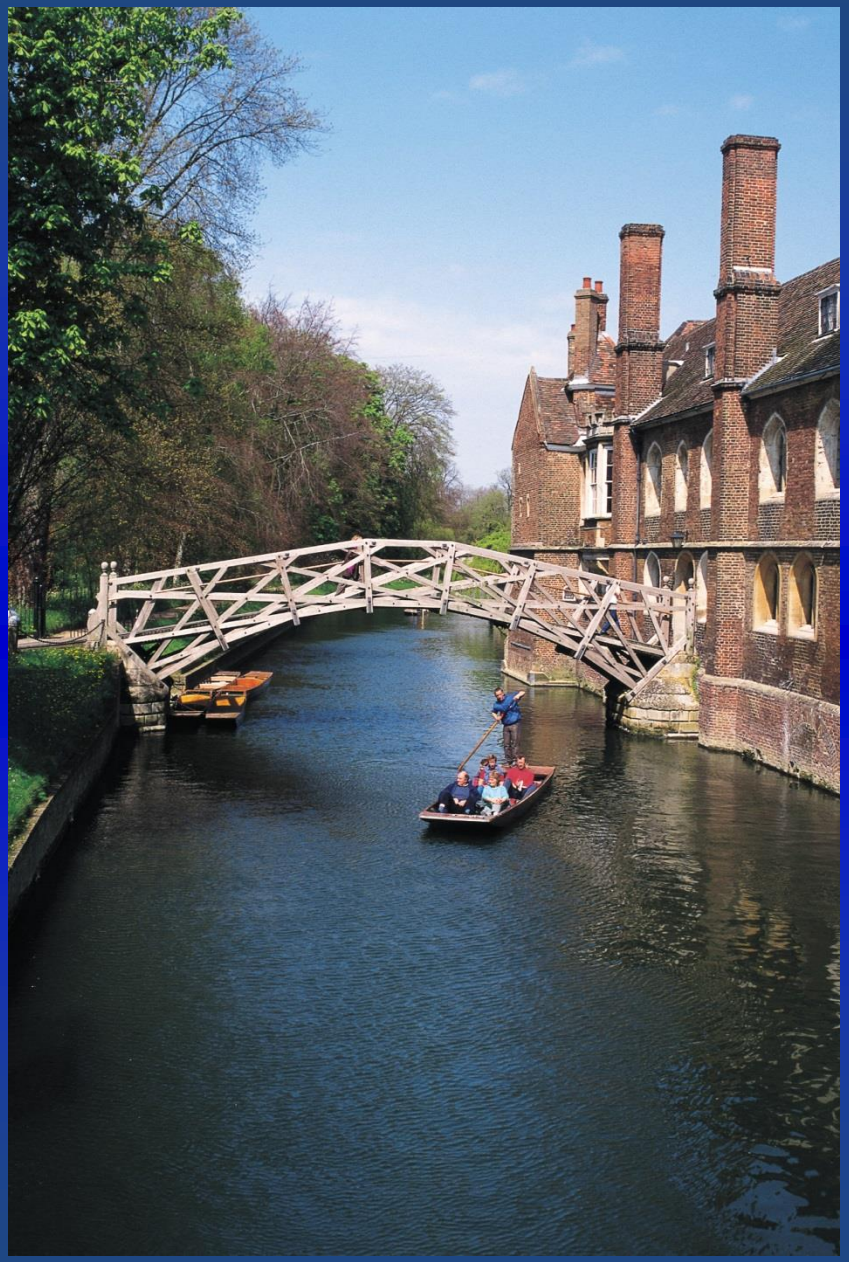

# The Future

## Decisions

Role of statins/ACE Inhibitors

Managing BP and lipids

Taking ACR screening seriously

British Heart Foundation

JDRF Juvenile Diabetes Research Foundation

Diabetes UK

# Acknowledgements


- John Todd
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- Julian Shield
- Michael Thompson
- Gerry Rayman
- Tim Barrett
- Liz Crowne
- Steve Rose
- Steve Bain
- Loredana Marcovecchio

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- Charles Fox
- Nick Mann
- Raymond Brown
- Fran Ackland

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- Neil Dalton

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- Loredana Marcovecchio

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- Dot Harris
- Zahra Madgwick
- Angie Watts
- Di Wingate
- Karen Whitehead

All the field workers and consultants!

# Acknowledgement


- AdDIT Investigators:

- John Deanfield GOSH
- Neil Dalton Guys
- A. Neil Oxford
- Tim Jones Perth
- Denis Daneman Toronto

# Comparison Childhood Adult Incident Cohort Studies

| | ORPS | STENO |
|---|---|---|
| n | 479 | 286 |
| Patient yrs F/U | 5182 | 4706 |
| Median age at diagnosis (yrs) | 9.5 | 18.0 |
| Duration Follow up (yrs) | 10.3 (0.9-19.2) | 18.0 (1.0-21.5) |
| Cumulative Incidence MA | 50.7% after 17 yr | 34% after 18yr |
| Macroabuminuria (%) | 13.6 | 14.6 |
| Age at Macroabuminuria (yrs) | 19.1 | 41 |
| Duration at Macro | 11.5 | 11.2 |

BMJ 2004; 328; 1105

# Screening of screening results by ACR tertiles

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| HbA1c(%) | 8.3±1.4 | 8.2±1.2 | 8.3±1.3 | 8.4±1.5 |

| | Visit 1 | Visit 2 | Both visits |
|---|---|---|---|
| Cases with MA | 78 (2.3%) | 86 (2.6 %) | 22 **(0.7%)** |
| % within upper tertile | 6.1% | 6.7% | **1.7%** |

# AdDIT Screening
# Lipid profiles

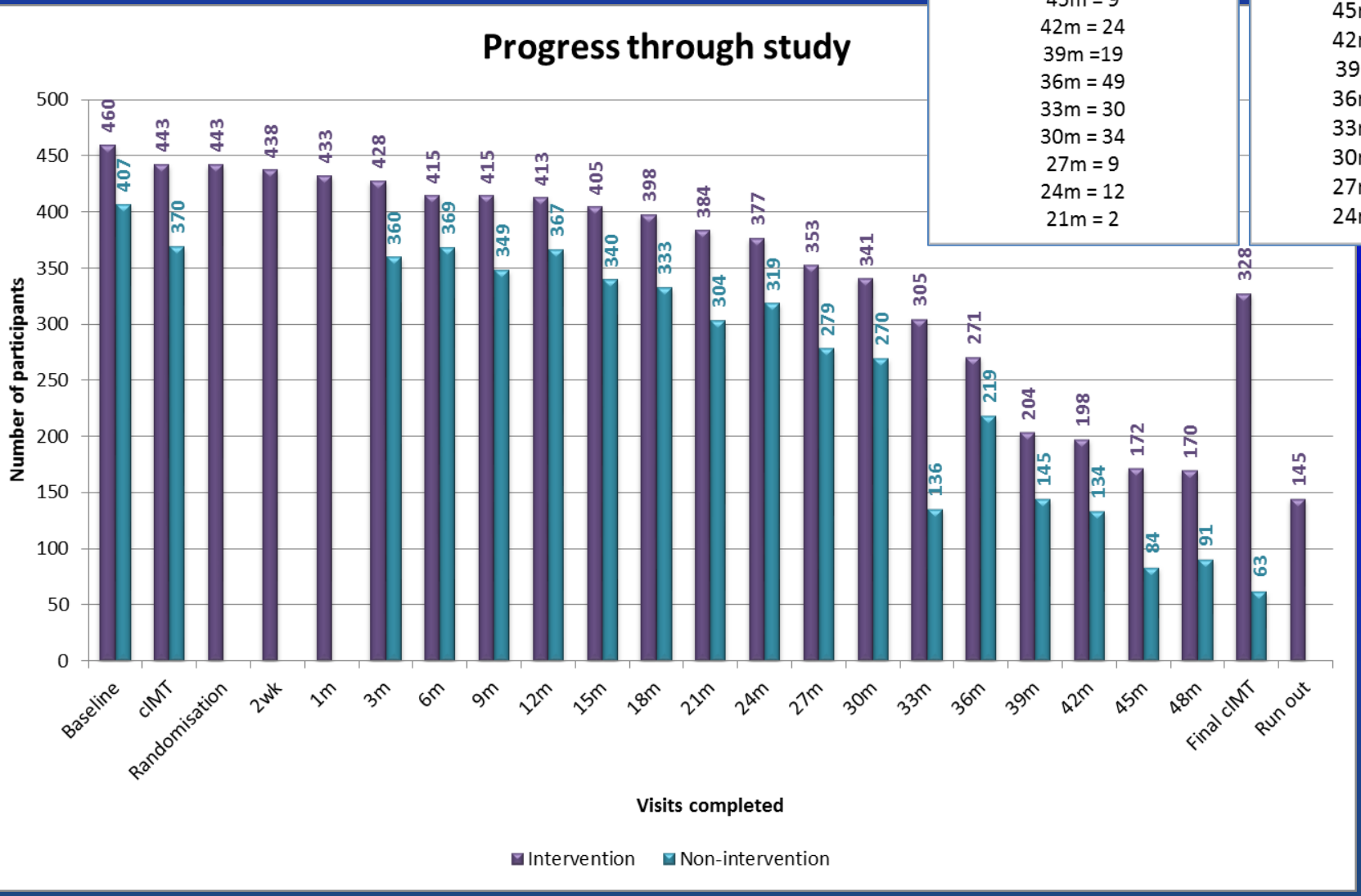
| | Trial N= 304 | Observational N= 254 | P* |
|---|---|---|---|
| **Total cholesterol (mmol/l)** | 4.50±0.86 | 4.37±0.80 | 0.09 |
| **HDL-C (mmol/l)** | 1.54±0.36 | 1.56±0.37 | 0.09 |
| **LDL-C (mmol/l)** | 2.38±0.65 | 2.31±0.65 | 0.21 |
| **Triglycerides (mmol/l)** | 0.85 [0.62-1.23] | 0.81 [0.62-1.19] | 0.21 |
| **Non-HDL-C (mmol/l)** | 2.95±0.83 | 2.81±0.78 | 0.014 |
| **Apo A-I (g/l)** | 1.51±0.23 | 1.53±0.24 | 0.06 |
| **Apo B (g/l)** | 0.74±0.20 | 0.71±0.16 | 0.20 |

*p adjusted for age and sex

# Progress through the Study (1)

358 participants completed final visit (intervention ended)
48m = 170
45m = 9
42m = 24
39m =19
36m = 49
33m = 30
30m = 34
27m = 9
24m = 12
21m = 2

112 participants completed final visit (non-intervention)
48m = 91
45m = 6
42m = 3
39m =1
36m = 6
33m = 2
30m = 1
27m = 1
24m = 1

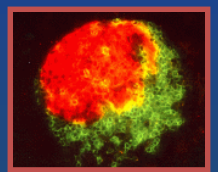


# ORPS Lipid Study

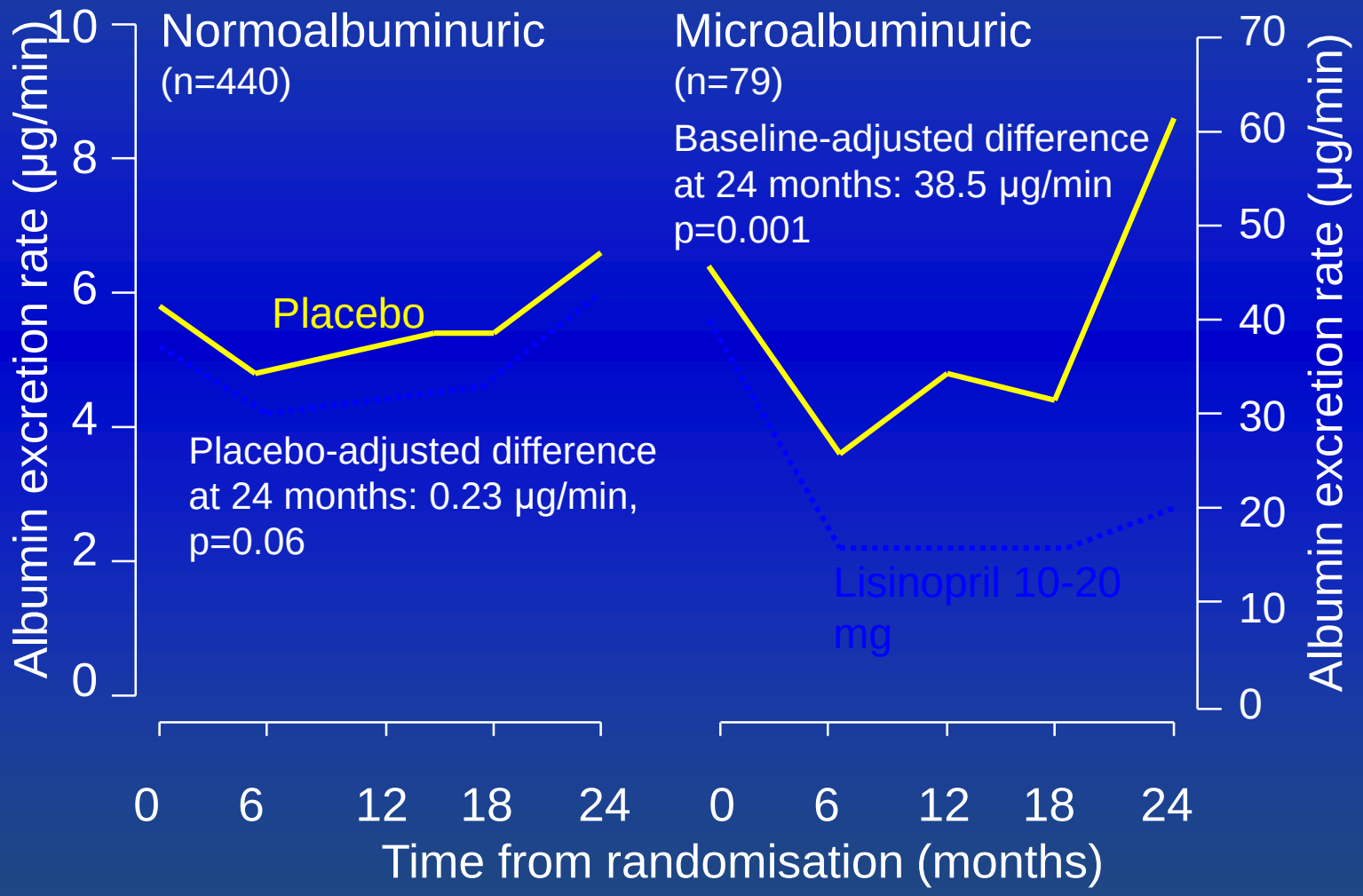
## Stepwise multiple regression model. Variables initially included: HbA1c, child's age, sex, mother's, father's and mean parental total cholesterol

| Df = 75 | | | P-value | | |
|---|---|---|---|---|---|
| **Dependent Variable** | **Covariates** | **Standardised regression coefficient** | **Covariates** | **Model** | **Variance explained** |
| **Childs total cholesterol** | **Mean parental total cholesterol** | **0.44** | **<0.001** | | |
| | | | | **0.001** | **16%** |
| | **HbA1c** | **0.23** | **0.04** | | |

Abraha et al. Diabetic Medicine 1999; 16: 1-7

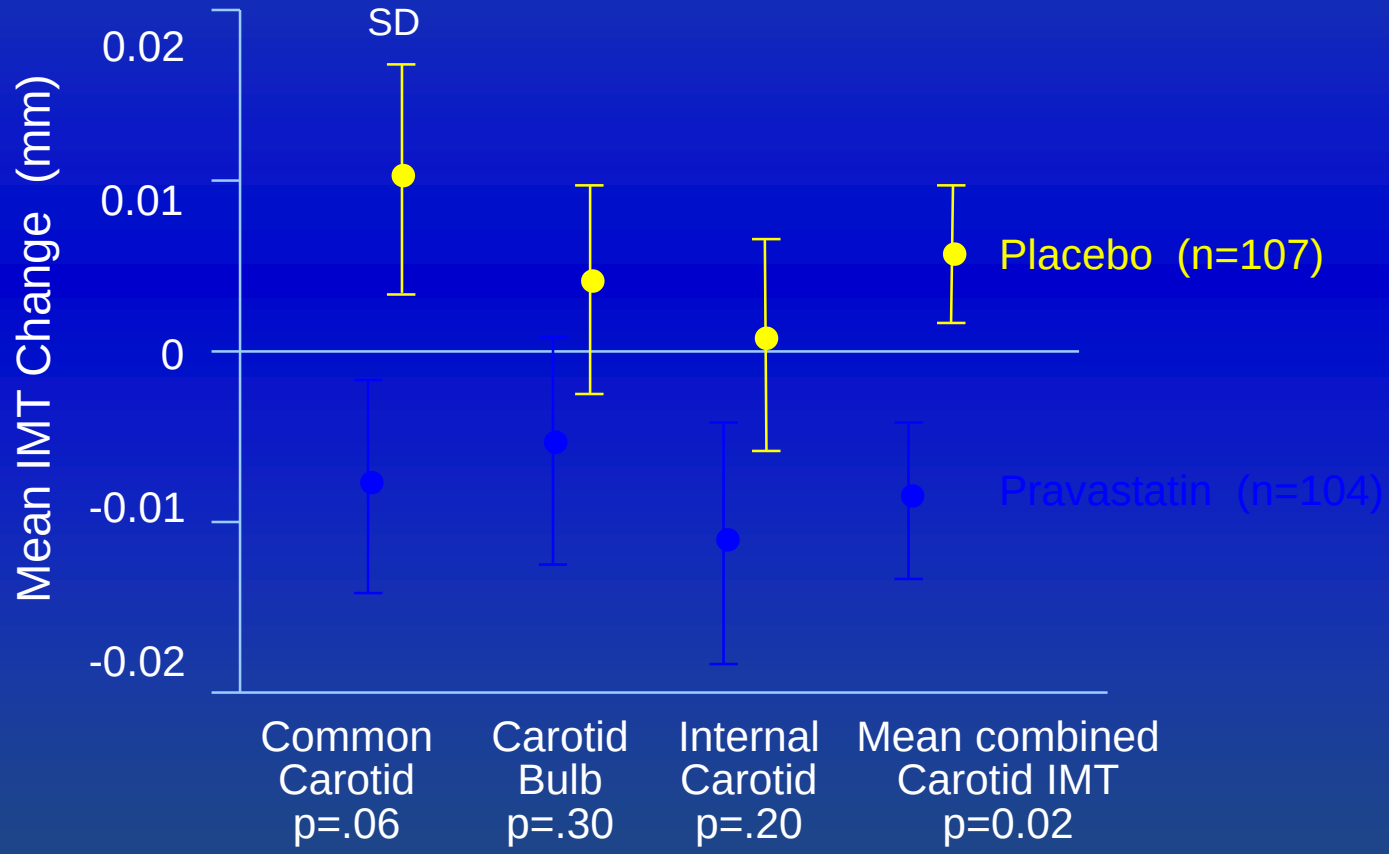


# EUCLID controlled trial of lisinopril in normotensive normoalbuminuria & microalbuminuric adults with Type 1 diabetes




Chaturvedi N et al for EUCLID Study Group. Lancet 1997;349:1787-92

# Change in carotid IMT over 2 years in 211 children aged 8-18 years with heterozygous familial hypercholesterolaemia (active treatment pravastatin 20-40 mg)




Wiegman A et al. *JAMA*2004;292:331-7