Is there a role for hypolipidaemic and hypotensive therapy in preventing vascular disease in children and adolescents?

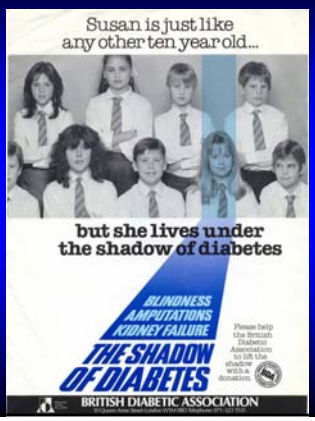
UNIVERSITY OF CAMBRIDGE

Professor David Dunger

Association of British Clinical Diabetologists
Autumn Meeting

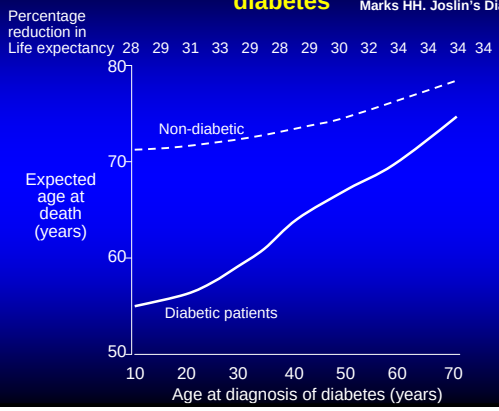
Hotel Russell, London
20th November 2009

Shadow of Diabetes



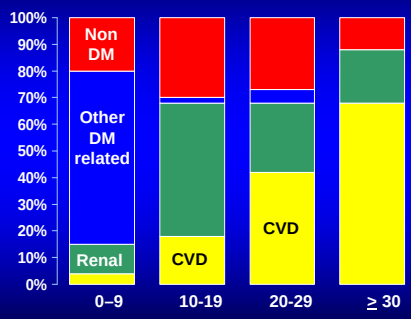
Expectation of life in patients with & without diabetes

Marks HH. Joslin's Diabetes 1971



Proportional mortality by duration of Type 1 diabetes

Pittsburgh Epidemiology of Diabetes Complications Study



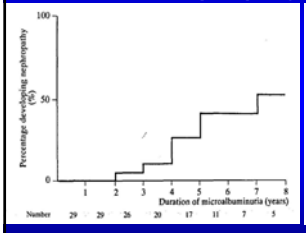
Orchard T. Diabetes Care 1994;17:326-38

Hypolipidaemic and hypotensive therapy to prevent vascular disease

- **Microalbuminuria**
- **Generalised endotheliopathy**
- **Interventions**

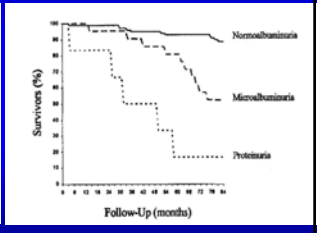
Microalbuminuria - Prediction

MA and Diabetic Nephropathy



Mathiesen 1995

MA and Survival



Arun 2003

Microalbuminuria

- Highly predictive of later development of clinical proteinuria and diabetic nephropathy
- Strong predictor of cardiovascular morbidity
- Present in 10-20% of adolescents with IDDM
- No longitudinal studies

Oxford Regional Prospective Study (ORPS)

Geographically defined population from 6 districts in Southern England

Principal aims

To examine the natural history and determinants of microalbuminuria (incipient nephropathy) in children followed from diagnosis of type 1 diabetes mellitus.

Subjects

- Children aged <16 years at diagnosis of type 1 diabetes mellitus
- Barts-Oxford diabetes register
- Case ascertainment > 95%

Oxford Regional Prospective Study (ORPS) (n=500)

Incident cohort study (ascertainment 92%)
Recruited at diagnosis of T1DM

Annual	5 yrs	10 yrs	Single assessment	Parental assessments
ACR x 3	GFR	GFR	ABP	ABP
HbA1c	Renal size	Renal size	DNA Cell lines	DNA cell lines
Lipids	Retinal photographs	Retinal photographs		ACR x 3
BP	ECG	ECG		Lipids

JDRF/Wellcome Trust Diabetes and Inflammation Laboratory

Definitions

Early morning urines

Microalbuminuria:

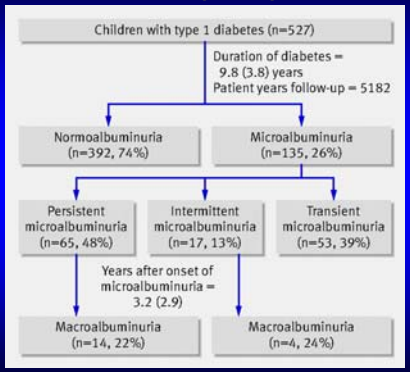
Albumin/creatinine ratio

≥ 3.5 mg/mmol in males or

≥ 4.0 mg/mmol in females

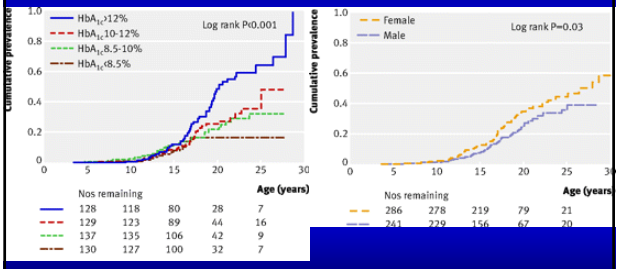
in 2/3 consecutive samples

Numbers with microalbuminuria and progression to macroalbuminuria up to September 2005



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

Kaplan-Meier survival curves showing cumulative prevalence of developing microalbuminuria

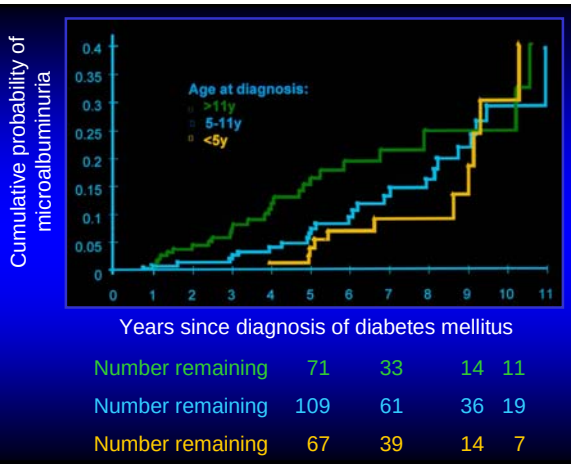


Amin, R. et al. BMJ 2008;336:697-701

Comparison Childhood Adult Incipient Cohort Studies

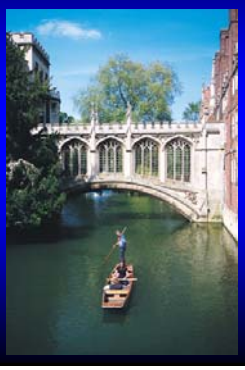
	ORPS	STENO
n	479	286
Patient yrs F/U	5182	4706
Median age at diagnosis (yrs)	9.5	18.0
Duration Follow up (yrs)	10.3 (0.9-19.2)	18.0 (1.0-21.5)
Cumulative Incidence MA	50.7% after 17 yr	34% after 18yr
Macroalbuminuria (%)	13.6	14.6
Age at Macroalbuminuria (yrs)	19.1	41
Duration at Macro	11.5	11.2

BMJ 2004; 328; 1105

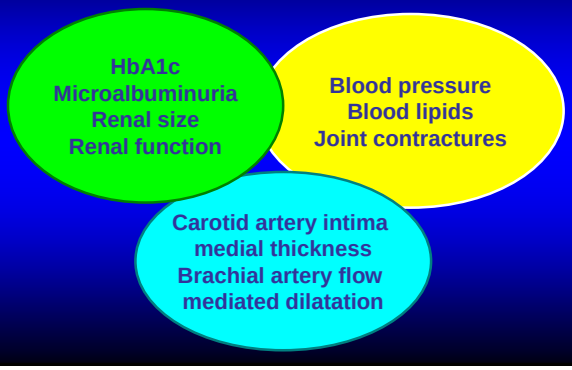


Hypolipidaemic and hypotensive therapy to prevent vascular disease

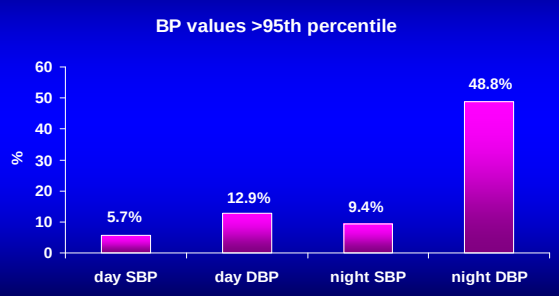
- Microalbuminuria
- Generalised endotheliopathy
- Interventions



MA is a marker of a generalised endotheliopathy



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



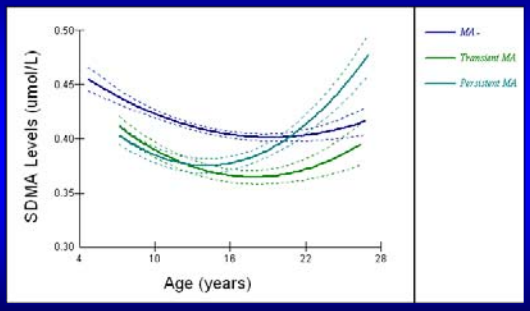
Cox proportional hazards for development of microalbuminuria

Time variable is years of follow-up after the ABPM assessment

Variable	Exp(B)	95% CI	p value
Day DBP (mmHg)	1.11	1.03–1.19	0.005
HbA1c (%)	1.44	1.08–1.92	0.014
ACR (mg/mmol)	2.99	1.82–4.90	<0.001

Marcovecchio et al 2009; Diabetologia 52: 1173 - 1181

Symmetric dimethylarginine (SDMA) vs Age



Contribution of covariates to risk of developing MA

Duration of diabetes = variable, puberty = time-dependent covariate

	Significance	Exp(B) (95% CI)
HbA1c %	0.002	1.3 (1.1-1.5)
GFR	0.001	1.02 (1.01-1.03)

Covariates not contributing to model: puberty, sex, age of diagnosis of diabetes, baseline ACR, and BP

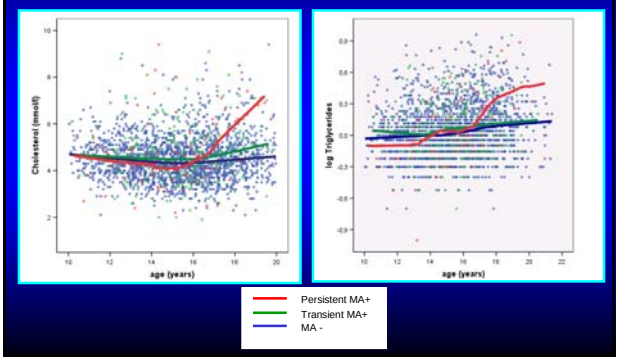
Amin R *et al* Kidney International 2005;68:1740-1749

Lipids: MA- vs MA+

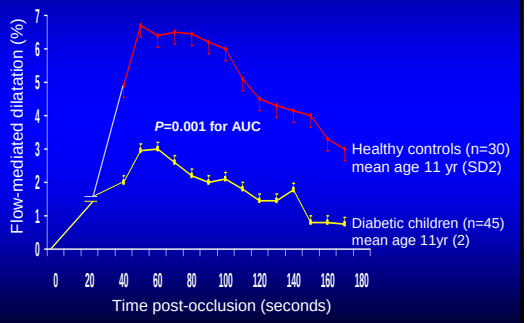
	MA-	MA+	p
N	780	115	
Gender (%F)	334 (43%)	70 (61%)	<0.001
Age at diagnosis (yrs)	8.9 ± 3.8	9.2 ± 3.6	ns
Age at first assessment (yrs)	15.3 ± 2.2	15.4 ± 1.8	ns
Duration at 1st assessment (yrs)	6.4 ± 3.8	6.2 ± 3.2	ns
HbA1c (%)	9.3 ± 1.6	9.9 ± 1.8	0.001
Total cholesterol (mmol/l)*	4.5 ± 0.8	4.7 ± 1.2	0.04*
HDL-cholesterol (mmol/l)*	1.6 ± 0.3	1.6 ± 0.3	ns
LDL-cholesterol (mmol/l)*	2.4 ± 0.7	2.5 ± 0.9	ns
Triglycerides (mmol/l)	1.4 ± 0.8	1.5 ± 1.1	ns
NonHDL-cholesterol (mmol/l)*	2.9 ± 0.8	3.2 ± 1.2	0.03*

*not significant after adjusting for HbA1c and gender

Lipids vs age: MA+ vs MA-

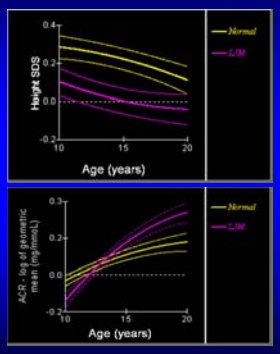


Endothelial dysfunction: brachial artery flow-mediated dilatation



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

Pubertal growth and MA



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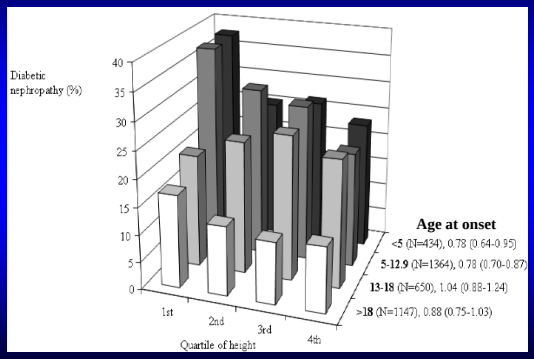
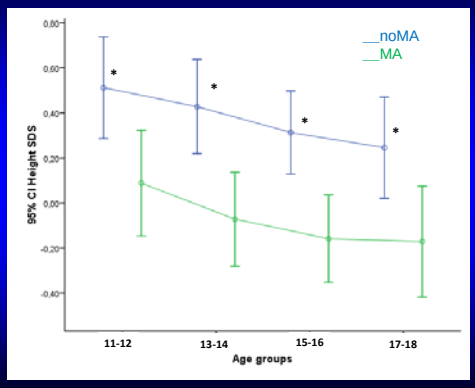
Amin R *et al* Arch Disease in Childhood 2005

Interaction of height, age at diagnosis and risk for Diabetic Nephropathy



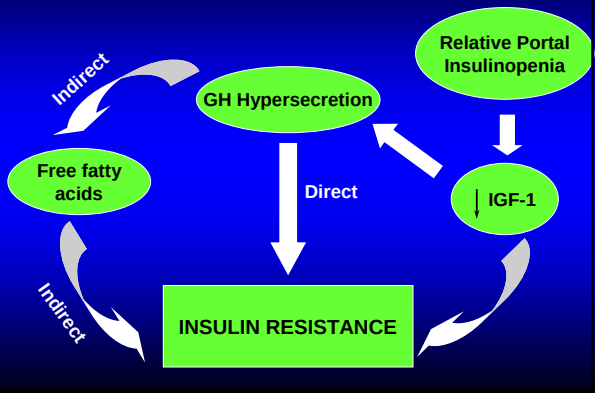
Wadén et al; Diabetes 2009; 58: 1914-20

ORPS: height SDS: MA- vs MA+ patients

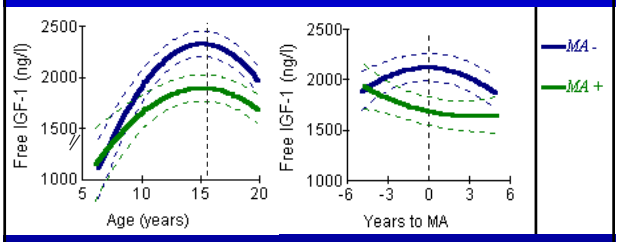


* p<0.05

The GH/ IGF-1 axis in Type 1 DM



Free IGF-1 levels in females : cases (MA+, n=34) and controls (MA-)



Amin R et al Diabetes Care 2005;28:1843

Low IGF-1 and GH Hypersecretion

Muscle	Ovary	Kidney
Insulin resistance	Androgen production	Paracrine IGF-I

- Microalbuminuria
- Hypertension
- Cardiovascular disease
- T2D

Size at birth

Adult stature

Heritability of Nephropathy and CVD risk

Links with family history

- Hypertension
- Hyperlipidaemia
- Insulin resistance
- Type 2 diabetes
- Microalbuminuria
- Metabolic syndrome
- ? Genetic or environmental
- Impaired glucose tolerance
- Type 2 diabetes

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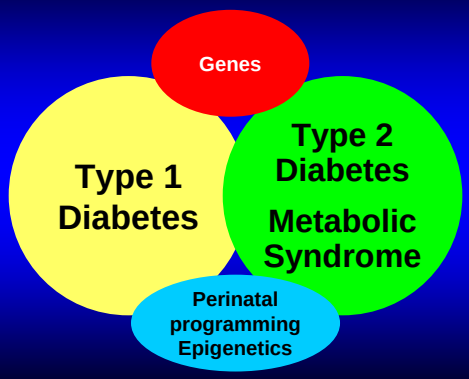


GoKinD

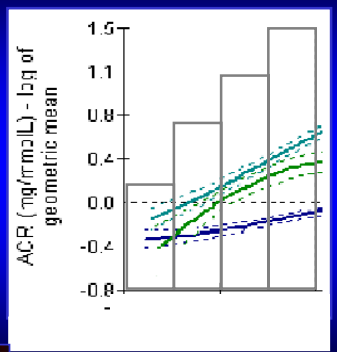
GoKinD
Genetics of Kidneys in Diabetes Study

JDRF Juvenile Diabetes Research Foundation

Diabetes UK

- MA trait
- End stage Renal failure = 1000
- Long-term survivors = 1000
- Whole genome association studies

MA Quantitative Trait



Log10(ACR) at assessment ~ sex + age at diagnosis of diabetes + log10(HbA1c) at assessment + duration of diabetes at assessment + date of assessment

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Hypolipidaemic and hypotensive therapy to prevent vascular disease

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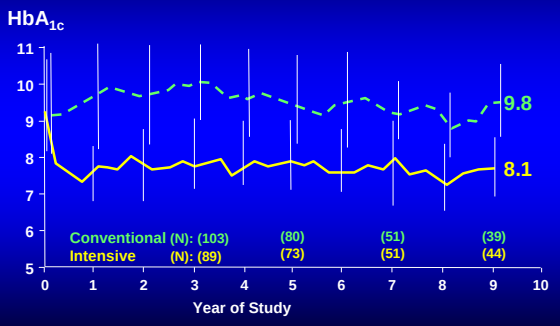
DCCT: Adolescents



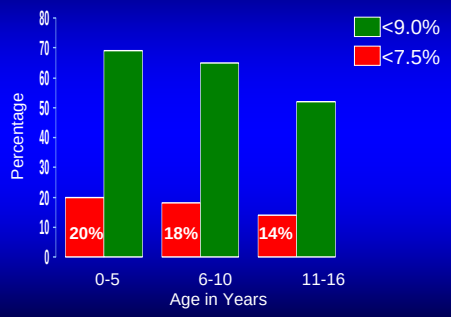
J Ped 1994;125:177-88

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

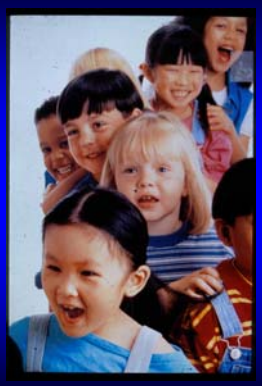
	Adolescents	Adults	p
Mean HbA1c (%)			
Intensive	8.06 ± 0.13	7.12 ± 0.03	<0.001
Conventional	9.76 ± 0.12	9.02 ± 0.05	<0.001
Decreased Risk (%)			
Retinopathy	61	63	0.802
Microalbuminuria	35	45	0.886
All severe hypoglycaemia			
Rate / 100 PYR	85.7	56.9	0.004
Coma / seizure			
Rate / 100 PYR	26.7	14.4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

DCCT Research Group, Journal of Pediatrics, 1994

HbA1c target attainment by age group in UK National Paediatric Diabetes Audit in 2002 (n=11,696)



Diabetes UK 2004



Early prevention of MA associated risk of DN and CVD

Statins
ACEI

Adolescent Diabetes Intervention Trial AdDIT

Aim

To determine in a 2x2 factorial 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**

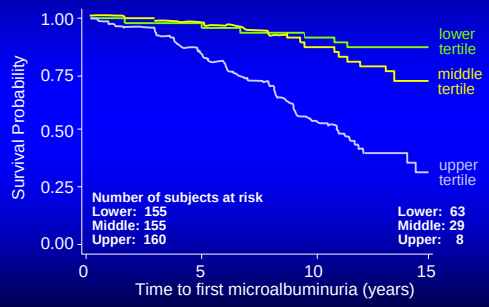
2 x 2 "Factorial" Randomisation

Statin arm

ACE inhibitor arm		
Atorvastatin Quinapril n 125	Placebo Quinapril n 125	n = 250 active Quinapril 5-10 mg daily
Atorvastatin Placebo n 125	Placebo Placebo n 125	n = 250 placebo Quinapril
n = 250 active Atorvastatin 10 mg daily	n = 250 placebo Atorvastatin	*Total n = 500*

Primary analysis: comparison of statin irrespective of ACEI & vice versa
Secondary analysis: comparison of individual cells

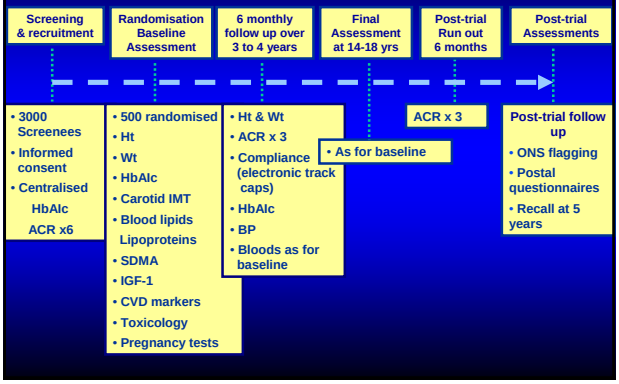
Kaplan-Meier survival risk of developing microalbuminuria in ORPS subjects aged ≥16 years based on tertiles of albumin excretion phenotype* defined using assessments aged 11-16



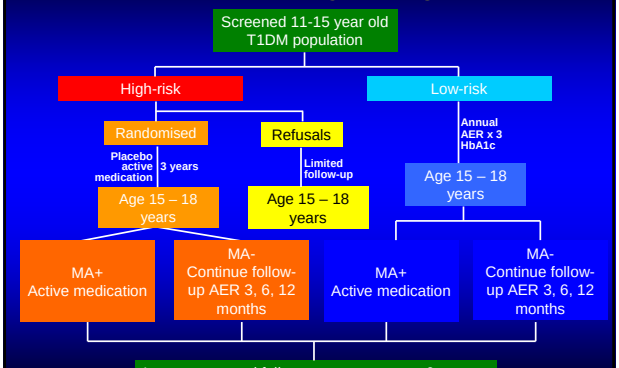
* adjusted for age, gender & duration of diabetes

Dunger DB et al. Diabet Med 2007;24:131-6

Trial Flow Diagram



AdDIT Study Design



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The Future

- **Biomarkers: Genomics Proteomics Metabolomics**
- **Glycated and oxidised modifications of Albumin and Haemoglobin**
- **Phamacogenomics**
- **Collaborations**

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Diabetes UK

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