Adolescent renal and cardiovascular disease protection in type 1 diabetes – AdDIT Study

Professor David Dunger
Department of Paediatrics

Keystone, Colorado, July 2013
Practical Ways to Achieve Targets in Diabetes Care
Financial Disclosures

Research Grant (*Pfizer – unrestricted research grant*)
Learning Objectives of Presentation

• Potential risk for CVD and nephropathy associated with albumin excretion in adolescents with type 1 diabetes.

• Current evidence for the use of ACE inhibitors and statins in young people with type 1 diabetes.

• Design of current adolescent renoprotective study in young people with type 1 diabetes.

• Projected evidence base for the use of ACE inhibitors and statins in young people with type 1 diabetes.
Susan is just like any other ten year old...

but she lives under the shadow of diabetes

BLINDNESS | AMPUTATIONS | KIDNEY FAILURE

Please help the British Diabetic Association to lift the shadow with a donation

BRITISH DIABETIC ASSOCIATION
10 Queen Anne Street London W1M 6BD Telephone: 071-833 1931

Shadow of Diabetes
Expectation of life in patients with & without diabetes

Percentage reduction in Life expectancy: 28, 29, 31, 33, 29, 28, 30, 34, 34, 34, 34, 34

Expected age at death (years):

Marks HH. Joslin’s Diabetes 1971
Cause of mortality in relation to Type 1 diabetes (T1D) duration

- **0–9 years**: Acute
- **10–19 years**: Renal
- **20–29 years**: CVD
- **≥30 years**: Renal

**Others**

Orchard TJ et al., Diabetes 2010
Diabetic Nephropathy

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

Groop P-H et al., Diabetes 2009
• Microalbuminuria

• Prediction and Prevention

• AdDIT Intervention
Oxford Regional Prospective study (ORPS) : Natural history of microalbuminuria from diagnosis in childhood

Early morning urines x 3 annually

MA : Albumin/creatinine ratio

≥ 3.5 mg/mmol in males or
≥ 4.0 mg/mmol in females

in 2/3 consecutive samples
Kaplan-Meier survival curves showing cumulative prevalence of developing microalbuminuria

Amin R et al. BMJ 2008
Cumulative probability of microalbuminuria

Years since diagnosis of diabetes mellitus

<table>
<thead>
<tr>
<th>Age at diagnosis:</th>
<th>&gt;11y</th>
<th>5-11y</th>
<th>&lt;5y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number remaining</td>
<td>71</td>
<td>33</td>
<td>14</td>
</tr>
<tr>
<td>Number remaining</td>
<td>109</td>
<td>61</td>
<td>36</td>
</tr>
<tr>
<td>Number remaining</td>
<td>67</td>
<td>39</td>
<td>14</td>
</tr>
</tbody>
</table>
Numbers with microalbuminuria and progression to macroalbuminuria up to September 2005

Children with type 1 diabetes (n=527)

Duration of diabetes = 9.8 (3.8) years
Patient years follow-up = 5182

Normoalbuminuria (n=392, 74%)

Microalbuminuria (n=135, 26%)

Persistent microalbuminuria (n=65, 48%)

Intermittent microalbuminuria (n=17, 13%)

Transient microalbuminuria (n=53, 39%)

Years after onset of microalbuminuria = 3.2 (2.9)

Macroalbuminuria (n=14, 22%)

Macroalbuminuria (n=4, 24%)

Amin R et al. BMJ 2008
## Comparison of Childhood Adult Incipient Cohort Studies

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

BMJ 2004; 328; 1105
MA is a marker of a generalised endotheliopathy

- HbA1c
- Microalbuminuria
- Renal size
- Renal function

- Blood pressure
- Blood lipids
- Joint contractures

- Carotid artery intima medial thickness
- Brachial artery flow mediated dilatation

- Renal function
Renal Size

Pre puberty  137.6 ± 32.1 mls  p < 0.001
Post puberty  227.7 ± 57.2 mls
MA  247 ± 63.2 mls  p 0.04
No MA  192.9 ± 63.0 mls

Correlation renal size and ACR  r=0.3  p 0.02
Symmetric dimethylarginine (SDMA) vs Age

Marcovecchio ML et al., Arch Dis Child 2010
Lipids vs age: MA+ vs MA-

Marcovecchio ML et al., Diabetes Care 2009
MA is a marker of a generalised endotheliopathy

Links with family history

- Hypertension
- Hyperlipidaemia
- Insulin resistance
- Type 2 diabetes
- Microalbuminuria

? Genetic or environmental
• Microalbuminuria

• Prediction and prevention

• AdDIT Intervention
DCCT: Adolescents

HbA$_{1c}$

Year of Study

Conventional (N): (103)
Intensive (N): (89)
(80) (73) (51) (51) (39) (44)

DCCT Research Group, Journal of Pediatrics, 1994
### Comparison of efficacy and safety of intensive treatment between adolescents and adults

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

DCCT Research Group, Journal of Pediatrics, 1994
EDIC

C

Hazard Reduction with Intensive Therapy: 32% (-12%, 58%), P=0.1339

D

Hazard Reduction with Intensive Therapy: 56% (46%, 64%), P<.0001

White et al. Diabetes 2011
Early prevention of MA associated risk of DN and CVD during adolescence

Statins
ACE Inhibitors
### HbA1c (%)

<table>
<thead>
<tr>
<th></th>
<th>Pre MA</th>
<th>Post MA</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA -</td>
<td>10.5 (1.6)</td>
<td>9.5 (1.5)</td>
</tr>
<tr>
<td>Transient MA</td>
<td>10.1 (1.7)</td>
<td>10.1 (1.7)</td>
</tr>
<tr>
<td>Persistent MA</td>
<td>11.7 (2.8)</td>
<td>11.4 (1.9)</td>
</tr>
</tbody>
</table>
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

Survival Probability

Time to first microalbuminuria (years)

Number of subjects at risk
Lower: 155
Middle: 155
Upper: 160

Lower: 63
Middle: 29
Upper: 8

* adjusted for age, gender & duration of diabetes

Dunger DB et al. Diabet Med 2007
• Microalbuminuria

• Prediction and prevention

• AdDIT Intervention
Adolescent Diabetes Intervention Trial AdDIT

• Adolescence is a time of high risk
• Early prevention of MA associated risk of DN and CVD
• Statins and ACEI
• In higher risk subjects based on tertiles of ACR
AdDIT Screening

- Age 10-16 yrs
- x2 sets of 3 EMUs for ACR
- Assessment age, duration, age, sex adjusted log ACR
- Allocation of tertiles of risk based on ORPS algorithms
# ACR tertiles

<table>
<thead>
<tr>
<th></th>
<th>Total assigned</th>
<th>Lower</th>
<th>Middle</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>3353</td>
<td>959 (28.6%)</td>
<td>1112 (33.2%)</td>
<td>1282 (38.2%)</td>
</tr>
<tr>
<td>UK</td>
<td>765</td>
<td>191 (25.0%)</td>
<td>278 (36.3%)</td>
<td>296 (38.7%)</td>
</tr>
<tr>
<td>Australia</td>
<td>1588</td>
<td>464 (29.2%)</td>
<td>524 (33.0%)</td>
<td>600 (37.8%)</td>
</tr>
<tr>
<td>Canada</td>
<td>1000</td>
<td>304 (30.4%)</td>
<td>310 (31.0%)</td>
<td>386 (38.6%)</td>
</tr>
</tbody>
</table>
**Prevalence of microalbuminuria at screening**

ACR values (geometric mean of three consecutive measurements):

- >3.5 mg/mmol in boys and >4 mg/mmol in girls

<table>
<thead>
<tr>
<th></th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Both visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases with MA</td>
<td>78</td>
<td>86</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>(2.3%)</td>
<td>(2.6 %)</td>
<td>(0.7%)</td>
</tr>
<tr>
<td>% within upper tertile</td>
<td>6.1%</td>
<td>6.7%</td>
<td>1.7%</td>
</tr>
</tbody>
</table>
### HbA1c distribution across tertiles of ACR

<table>
<thead>
<tr>
<th></th>
<th>LOWER</th>
<th>MIDDLE</th>
<th>UPPER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>8.2±1.2</td>
<td>8.3±1.3</td>
<td>8.4±1.5</td>
</tr>
<tr>
<td>Median [IQR]</td>
<td>8.1 [7.4-9.0]</td>
<td>8.2 [7.5-8.9]</td>
<td>8.2 [7.5-9.1]</td>
</tr>
<tr>
<td>HbA1c ≥7.5%</td>
<td>73.2%</td>
<td>76.3%</td>
<td>75.4%</td>
</tr>
</tbody>
</table>

**HbA1c ≥7.5%: 75%**
AdDIT Intervention and Observational studies

- Highest tertile
- Trial group: n=463
- RCT statins and ACEI

- Low and middle tertiles
- Observational group: n=400
- No intervention
Aim
To determine in a double blind placebo controlled 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

<table>
<thead>
<tr>
<th>Statin arm</th>
<th>ACE inhibitor arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>Atorvastatin</td>
</tr>
<tr>
<td>Quinapril</td>
<td>Placebo</td>
</tr>
<tr>
<td>n = 125</td>
<td>n = 125</td>
</tr>
<tr>
<td>n = 250 active Atorvastatin 10 mg daily</td>
<td>n = 250 active Quinapril 5-10 mg daily</td>
</tr>
<tr>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Quinapril</td>
<td>Placebo</td>
</tr>
<tr>
<td>n = 125</td>
<td>n = 125</td>
</tr>
<tr>
<td>n = 250 placebo Quinapril</td>
<td>n = 250 placebo</td>
</tr>
</tbody>
</table>

Total: \[ n = 500 \]

Primary analysis: comparison of statin irrespective of ACEI & vice versa
Secondary analysis: comparison of individual cells
**Trial Flow Diagram**

- **Screening & recruitment**
  - Informed consent
  - Centralised
  - ACR x 6

- **Randomisation**
  - 463 randomised
  - Ht
  - Wt
  - HbA1c
  - Carotid IMT
  - Blood lipids
  - Lipoproteins
  - SDMA
  - IGF-1
  - CVD markers
  - Toxicology
  - Pregnancy tests

- **Baseline Assessment**
  - Ht & Wt
  - ACR x 3
  - Compliance (electronic track caps)
  - HbA1c
  - BP
  - Bloods as for baseline

- **6 monthly follow up over 3 to 4 years**

- **Final Assessment at 14-18 yrs**
  - ACR x 3
  - As for baseline

- **Post-trial Run out 6 months**

- **Post-trial Assessments**
  - ONS flagging
  - Postal questionnaires
  - Recall at 5 years

- **Post-trial follow up**
  - 6 months
AdDIT Study Design

Screened 10-16 year old T1DM population

High-risk

Randomised
Placebo active medication 3 years
Age 15 – 18 years

MA+
Active medication
Continue follow-up AER 3, 6, 12 months

Low-risk

Refusals
Limited follow-up

Age 15 – 18 years

MA+
Active medication
Continue follow-up AER 3, 6, 12 months

Limited follow-up

Age 15 – 18 years

MA-
Active medication

Annual AER x 3 HbA1c

Long term postal follow-up reassessment 6 years +
Baseline data: Renal markers

- eGFR
  - P < 0.001

- Cystatin C
  - P = 0.03
# Lipid profiles

<table>
<thead>
<tr>
<th></th>
<th>Trial N= 304</th>
<th>Observational N= 254</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total cholesterol (mmol/l)</strong></td>
<td>4.50±0.86</td>
<td>4.37±0.80</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>HDL-C (mmol/l)</strong></td>
<td>1.54±0.36</td>
<td>1.56±0.37</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>LDL-C (mmol/l)</strong></td>
<td>2.38±0.65</td>
<td>2.31±0.65</td>
<td>0.21</td>
</tr>
<tr>
<td><strong>Triglycerides (mmol/l)</strong></td>
<td>0.85 [0.62-1.23]</td>
<td>0.81 [0.62-1.19]</td>
<td>0.21</td>
</tr>
<tr>
<td><strong>Non-HDL-C (mmol/l)</strong></td>
<td>2.95±0.83</td>
<td>2.81±0.78</td>
<td>0.014</td>
</tr>
<tr>
<td><strong>Apo A-I (g/l)</strong></td>
<td>1.51±0.23</td>
<td>1.53±0.24</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Apo B (g/l)</strong></td>
<td>0.74±0.20</td>
<td>0.71±0.16</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>Apo B/Apo A-I ratio</strong></td>
<td>0.50±0.14</td>
<td>0.47±0.11</td>
<td>0.025</td>
</tr>
</tbody>
</table>

*p adjusted for age and sex
ApoB/ApoA-I ratio

AdDIT: preliminary baseline data
Pulse Wave Velocity (PWV)

P=0.02
AdDIT Screening Summary

- Adolescents with log adjusted ACR in the highest tertile despite very similar glycaemic control to those in the other tertiles have renal and cardiovascular abnormalities including:
  - Glomerular Hyperfiltration
  - Increased non-HDL-cholesterol
  - Increased ApoB/ApoA-I ratio
  - Increased arterial stiffness (PWV)
The Future

Will statins/ACE Inhibitors Make a difference To risk for MA and long term outcomes such as DN and CVD Will they be tolerated Will we be able to identify other Genetic and biochemical markers of risk and drug response which will inform future management
Acknowledgement:

**UK Central Coordination**
- Neil Dalton Central laboratory St Thomas Hospital, London
- John Deanfield Cardiovascular laboratory Hospital for Sick Children, Gt Ormond Street London

**Canada**
- Denis Daneman The Hospital for Sick Children, Toronto

**AUSTRALIA**
- Tim Jones Telethon Institute for Child health Research, Perth

- Steering Committee Chairperson Sally Marshall
- Data Monitoring and Ethics Committee Colin Baigent Oxford

- ALL of the AdDIT sites (22) investigators, nurses, labs, patients, parents and countless other supporters
Acknowledgement: Funders

Diabetes UK

Juvenile Diabetes Research Foundation

British Heart Foundation

Pfizer
AdDIT

- Compliance
- Adherence

Track Cap Vs Return Trends over time

![Graph showing pill count adherence vs MEMS openings adherence]
Decline over time

- Adherence (%) vs Months into the trial
- Lines represent different age groups:
  - <12
  - 12-13
  - 13-14
  - 14-15
  - 15-16
  - 16+

The graph shows a decline in adherence over time for all age groups, with the <12 group starting higher but showing a steeper decline than the other groups.