Clinical outcomes at 24 months

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On behalf of the DiRECT team
Overview: DiRECT Study Design

Cluster randomisation (by GP Practice n=49)

Tyneside & Scotland

Control
(n = 26 practices)
Usual diabetes care
(Best Practice Guidelines)

Intervention
(n = 23 practices)
+ Structured weight management programme ‘Counterweight Plus®’

Main Inclusion Criteria
- Age (years) 20-65
- BMI (kg/m²) 27-45
- T2DM duration (years) ≤ 6

Main Exclusion Criteria
- Not on insulin

28% agreed to participate

Leslie WS et al BMC Family Practice 2016; 17:20
DiRECT population is representative of type 2 diabetes

Recruited population (n=298)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>59</td>
</tr>
<tr>
<td>Most deprived SMS Quintile (%)</td>
<td>21</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>34.6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>54.4</td>
</tr>
<tr>
<td>Duration T2DM (years)</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Baseline Intervention Control

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline</th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>% on diabetes medications</td>
<td></td>
<td>75</td>
<td>77</td>
</tr>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>60.4</td>
<td>58.2</td>
<td></td>
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</tbody>
</table>

Structured Programme in Primary Care Setting

Practice nurse/dietitian programme delivery

- Withdraw Anti-diabetic and anti-hypertensive medications
- Total Diet Replacement ~ 3 months
- Food Reintroduction ~ 2 months
- Weight Loss Maintenance to 24 months

During year 2, average number of ‘monthly’ appointments was 7.7

Leslie WS et al BMC Family Practice 2016; 17:20
24 month analysis

Data analysed by intention to treat

- 16 withdrew from intervention during year 2
- 86% attended 24 month review (n=256)
- Data from GP records for non-attenders at 24m review (n=16)
- 91% had data available
- No data available: assumed primary outcomes not met (n=26)
- Therefore analysis includes all 149 participants per group
Co-Primary Outcomes

Weight loss $\geq$ 15kg

Remission T2DM
HbA1c < 48mmol/mol on no diabetes medications

Lean ME et al *The Lancet* 2018; 391: 54151
Remissions at 24 months

- Control: 6/149 (4%)
- Intervention: 53/149 (36%)

P < 0.0001 at 12 and 24 months.

Lean ME et al. Lancet Digital Health End 2019

DiRECT Diabetes Remission Control Tool
Change in Diabetes Medications & HbA1c
(Post-hoc analyses)

Numbers on diabetes meds

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>24m</th>
<th>Baseline</th>
<th>24m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent</td>
<td>75</td>
<td>40</td>
<td>77</td>
<td>84</td>
</tr>
<tr>
<td>(111/149)</td>
<td>(51/129)</td>
<td>(115/149)</td>
<td>(120/143)</td>
<td></td>
</tr>
</tbody>
</table>

HbA1c
(baseline – 24m)

<table>
<thead>
<tr>
<th>Δ (mmol/mol)</th>
<th>-6</th>
<th>+0.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>(p = 0.0063)</td>
<td>(p = NS)</td>
<td></td>
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</tbody>
</table>
HbA1c by remission group

Intervention group: post-hoc analyses:

- n= 60: No remission at any time
- n= 16: Remission at 12m but not 24m
- n= 5: Remission at both 12 & 24m
- n= 48: Remission achieved during year 2
Who achieves durable remission? (entire study population)

- Remission at 24 months was more likely with
  - Greater weight loss from baseline (aOR 1.2 per kg loss)
  - Greater weight loss from 12-24m (aOR 1.11 per kg loss)

- Remission did not vary with baseline BMI or duration of diabetes

- Remission was slightly more likely with
  - Older age (aOR 1.08 per year)
  - Male sex (aOR 0.44 female v male)

Lean ME et al Lancet Db&End 2019
1. 36% of intervention participants had sustained remission at 24 months.

2. HbA1c was significantly reduced in the intervention group, with 50% reduction in use of diabetes medications.

3. Durable remission of short duration T2DM is attainable in a Primary Care setting.
Weight Loss Maintenance

• Principles integrated from day-1 of TDR
• Monthly appointments with practice nurse or dietitian
  - Review BP, BG, weight
  - Review of weight and remission expectations
  - Behavioural strategies to limit weight regain
• Access to DiRECT RA support

DiRECT Intervention used Counterweight-Plus

Lean et al, Br J General Practice (2013), Leslie et al, BMC Family Practice (2016)
Greater weight loss 0-24months in intervention group

Lean et al, Lancet (2017)
Lean et al, Lancet Diabetes and Endocrinology (2019)
ITT 24-Month Primary Outcome Results

Co-Primary Outcome: \( \geq 15 \text{ kg weight loss} \)

<table>
<thead>
<tr>
<th>Group</th>
<th>Count</th>
<th>Percentage</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>17/149</td>
<td>11%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Control</td>
<td>3/149</td>
<td>2%</td>
<td></td>
</tr>
</tbody>
</table>

Lean et al, Lancet Diabetes and Endocrinology (2019)
Remissions by 24-month weight loss: entire study population

Lean et al, Lancet Diabetes and Endocrinology (2019)

- <5kg: 5% (<8/154>)
- 5-10kg: 29% (21/73)
- 10-15kg: 60% (15/25)
- ≥15kg: 70% (14/20)

≥10kg loss is associated with 64% remission rate over 24 months.
Weight management is critical for T2D remission

Lean et al, Lancet Diabetes and Endocrinology (2019)
Relapse Management
(regain >2kg/T2D relapse)

Tool-kit approach:
• Review causes of weight regain
• Review of behavioural strategies
• Brief Total Diet Replacement and/or Food Reintroduction
• Offer of orlistat

DiRECT Intervention: ‘Rescue Plans’

Lean et al, Br J General Practice (2013), Leslie et al, BMC Family Practice (2016)
‘Rescue Plans’ helped maintain weight and T2D remission

Lean et al, Lancet Diabetes and Endocrinology (2019)
Summary at 24-Months

- One third with early T2D achieve remission, -64% if ≥10kg loss
- Achieving and maintaining weight loss are critical for success
- Weight loss at 24-months remains greater than most lifestyle interventions, despite modest regain
Secondary outcomes at 24 months (ITT)

- Blood pressure
- Serum lipids
- Adverse events
- Quality of life
DiRECT: BP falls, with fewer drugs
DiRECT: Lipids improve

![Graph showing changes in triglycerides and total-cholesterol/HDL-cholesterol ratio](chart)
DiRECT: Fewer serious adverse events 12-24m

CV & cancer events (post-hoc analysis):

**Intervention**
- 1 Non-fatal MI, 1 coronary artery disease

**Control**
- 1 Sudden death, 2 CVA, 1 aortic aneurysm rupture, 1 toe amputation
- 5 cancers: 2 colon, 1 bladder, 1 renal, 1 prostate
DiRECT: Quality of life improves 😊

Scale: 0 – 100
Worst imaginable to Best imaginable
Summary:
Intervention group secondary outcomes

• Blood pressure: ↓ Systolic BP, ↓ medications
• Serum lipids: ↓ Triglycerides
• Quality of life ↑ 😊
• Adverse events ↓ SAEs in 12-24 months
DiRECT: 24 month conclusions

1. T2D is not necessarily a lifelong condition, & is reversible by weight loss
   - 36% in remission at 24 months
   - 70% in remission with >15kg loss

2. Maintaining weight loss is challenging
   - ≥10 kg weight loss achieved by 1/4 of intervention group
   - Ongoing support & relapse management limits weight regain

3. Fewer SAEs supports weight loss reducing complications of T2D

4. Early remission should be a primary management target for T2D
Thank you

• GP practices and patients
• Academic & clinical colleagues
• Ethical and R&D committees
• Cambridge Weight Plan
• Diabetes UK, and funding donors

http://www.directclinicaltrial.org.uk/
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