Primary Outcome Results of DiRECT
the Diabetes REmission Clinical Trial

Mike Lean, Roy Taylor, and the DiRECT Team

Finding a practical management solution for T2DM, in primary care
Disclosures

• Departmental research funds, support for conference attendance and fees for Advisory Boards from Novo Nordisk, Orexigen, Janssen, and Cambridge Weight Plan. Medical consultancy fees from Counterweight Ltd.
Life-expectancy is still reduced by T2DM despite guidelines & drugs to lower glucose/HbA1c, LDL & BP

Estimated future years of life lost due to diabetes by sex, age and cause

- Vascular deaths
- Cancer deaths
- Non-cancer non-vascular deaths
- Unknown causes

European Risk Factor Consortium, NEJM 2011
Weight gain/obesity is the main driver of T2DM


Adjusted RR

(BMI <22 = referent)

BMI (kg/m²)

0 10 20 30 40 50 60 70 80 90 100

<22 22-22.9 23-23.9 24-24.9 25-26.9 27-28.9 29-30.9 31-32.9 33-34.9 >35

Median BMI 30-31 at diagnosis
Major weight loss brings multiple clinical benefits

4 y after laparoscopic adjustable gastric banding

T2DM 'resolved' in 78%
Meta-analysis, N=4070,

Frigg et al. Obes Surg, 2004
15 kg weight loss achieve most T2DM remissions

2-year RCT, gastric band vs usual diet advice

Remissions of T2DM in Look AHEAD

Remission was not the primary outcome
- Main focus on fitness
- Highly complex specialist trial

Remission more frequent/ longer:
- >6.5% weight loss at 1 year
- <2y history of diabetes
- Lower baseline HbA1c
- Not taking antihypertensives

Gregg et al JAMA 2012
DiRECT: Aim and Design

Aim: To assess whether intensive weight management, within routine primary care, would achieve remission of T2DM

Design: Open-label, cluster-randomised, clinical trial
Randomised by GP practices: stratified for sex and practice size

- Intervention:
  - Weight management programme: Target ≥15kg weight loss
  - Withdraw all anti-diabetes and antihypertensive medications
  - Plus best practice care, by guidelines

- Control: best practice care, by guidelines
DiRECT: Aim and Design

**Aim**: To assess whether intensive weight management, within routine primary care, would achieve remission of T2DM

**Design**: Open-label, cluster-randomised, clinical trial
Randomised by GP practices: stratified for sex and practice size

- **Intervention**:
  - Weight management programme: Target ≥15kg weight loss
  - Withdraw all anti-diabetes and antihypertensive medications
  - Plus best practice care, by guidelines

- **Control**: best practice care, by guidelines
DiRECT: outcomes, assumptions & statistical power

• Co-primary outcomes
  – Numbers maintaining ≥15kg weight loss at 12 months
  – Numbers with remission of diabetes (HbA1c <48mmol/mol, off anti-diabetes medications for at least 2 months)

• Power analysis:
  – Clinically significant remission rate = 22% (vs. 5%)
  – Anticipated loss to follow up = 25%
  – Intra-class correlation coefficient = 0.05

• Number required for 80% power = 280
  – Assume 70% with ≥15kg loss (Dixon), 30% will lose ≥15kg (Lean et al)
Counterweight-Plus feasibility pilot (n = 91, BMI 47)
(820kcal Total Diet Replacement, Food Reintroduction and Maintenance)

Lean et al., Br J General Practice (2013)
Counterweight-Plus feasibility pilot (n = 91, BMI 47)
(820kcal Total Diet Replacement, Food Reintroduction and Maintenance)

Maintaining weight loss ≥15kg at 12 months:
• 33% of all 91 patients
• 44% of patients with a known 12-month weight
• 57% of those who lost >15kg on LELD

Highly cost-effective:
• 4 times more lose >15kg as with bariatric surgery

Lean et al, Br J General Practice (2013)
**Total Diet Replacement** - Counterweight Pro800

- Nutritionally complete (vitamins & minerals)
- 830 kcal: 61%E carbohydrate, 13% fat, 26% protein
- >2.25 litres fluid per day
- Fibre supplement

- **Maintain PA** ~30mins/ day

- **STOP** all anti-diabetes medications
- **STOP** all antihypertensive medications

---

Lean et al, Br J General Practice (2013),
Leslie et al, BMC Family Practice (2016)
DiRECT Intervention: Counterweight-Plus Protocol

**Stepped Food Reintroduction**
- Add a ~400kcal meal every 2-3 weeks
- Step-counters: gradually increase PA

**Weight Loss Maintenance**
- Food-based diet
- 50%E carbohydrate, 35% fat, 15% protein
- Encourage up to 15,000 steps/day

**Relapse Management**
(regain >2kg, relapse of diabetes)
- Tool-kit approach: offer orlistat, meal replacement, brief TDR and FR

---

Lean et al, Br J General Practice (2013),
Leslie et al, BMC Family Practice (2016)
DiRECT Intervention: Counterweight-Plus Protocol

Patients attended their own primary care practice centres

Programme delivered and supervised by
• Practice nurse or local dietitian (after ~8 hours training)
  On-job mentoring & fidelity checks

Individual appointments:
Planned 2 x 1 hour, then 25-30 minutes
• TDR: 2-weekly
• Food Reintroduction: 2-weekly
• Maintenance: 4-weekly

Lean et al, Br J General Practice (2013)
Leslie et al, BMC Family Practice (2016)
DiRECT: inclusion & exclusion criteria

Inclusion

• Men and women
• Age 20–65 years
• BMI 27–45kg/m²
• T2DM diagnosed within 6 years
• HbA1c ≥ 48 mmol/mol
  (≥ 43 mmol/mol on anti-diabetes drugs)
• Signed informed consent

Exclusion

• Insulin treatment, anti-obesity drugs
• Learning difficulties
• Pregnancy or considering pregnancy,
• Weight loss >5kg within 6m, eGFR <30 mls/min,
  severe or unstable heart failure, known cancer,
  myocardial infarction within 6m
• Eating disorder/ purging , severe depression,
  antipsychotic drugs, substance abuse

Leslie et al, BMC Family Practice (2016)
DiRECT Recruitment (2014-2016)

- Practices invited 523
- Practices agreed 55
- Practices recruited 49
- Eligible patients identified by SPCRN 1510
  - Letter and one reminder
- Agreed to participate 423 (28% both arms)
- Patients recruited 306
Results: participant retention

306 individuals consented and enrolled

157 individuals assigned to the intervention group
  86 in Scotland
  71 in Tyneside

149 individuals assigned to the control group
  125 in Scotland
  124 in Tyneside

7 randomised in error (already in remission at baseline)†

150 commenced intervention

1 withdrew consent for data use

32 withdrew from intervention

149 included in ITT analysis

149 included in ITT analysis
Results: participant retention

306 individuals consented and enrolled

157 individuals assigned to the intervention group
  86 in Scotland
  71 in Tyneside

149 individuals assigned to the control group
  125 in Scotland
  124 in Tyneside

- 7 randomised in error (already in remission at baseline)
- 1 withdrew consent for data use
- 32 withdrew from intervention

149 included in ITT analysis
149 included in ITT analysis

Drop-outs: 12 month outcome data collected within a 3 month window from routine GP clinic records
Demographics: Invited vs analysed participants

<table>
<thead>
<tr>
<th></th>
<th>Invited population</th>
<th>DiRECT participants</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>1155a</td>
<td>298</td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>699 (61.3)</td>
<td>176 (59.1)</td>
</tr>
<tr>
<td>Female</td>
<td>442 (38.7)</td>
<td>122 (40.9)</td>
</tr>
<tr>
<td><strong>Year of birth</strong></td>
<td>1961 (8)</td>
<td>1961 (8)</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>33.5 (6.9)</td>
<td>34.6 (4.4)</td>
</tr>
<tr>
<td><strong>Duration of type 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diabetes (years)</td>
<td>3.5 (3.2)</td>
<td>3.0 (1.7)</td>
</tr>
<tr>
<td><strong>Index of Multiple</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deprivation quintile, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 – Most deprived</td>
<td>257 (22.8)</td>
<td>63 (21.4)</td>
</tr>
<tr>
<td>Q2</td>
<td>185 (16.4)</td>
<td>52 (17.6)</td>
</tr>
<tr>
<td>Q3</td>
<td>226 (20.0)</td>
<td>64 (21.7)</td>
</tr>
<tr>
<td>Q4</td>
<td>238 (21.1)</td>
<td>67 (22.7)</td>
</tr>
<tr>
<td>Q5 – Least deprived</td>
<td>222 (19.7)</td>
<td>49 (16.6)</td>
</tr>
</tbody>
</table>

Data are mean (SD) unless otherwise stated
## Baseline data: analysed participants (100%)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>298</td>
</tr>
<tr>
<td>Men / women</td>
<td>59% / 41%</td>
</tr>
<tr>
<td>Age (years)</td>
<td>54 (SD 7)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
</tr>
<tr>
<td>men</td>
<td>106 (SD 16)</td>
</tr>
<tr>
<td>women</td>
<td>91 (SD 13)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>35 (SD 4)</td>
</tr>
<tr>
<td>Duration of T2DM (y)</td>
<td>3.1 (SD 1.7)</td>
</tr>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>59 (SD 14) (7.6%)</td>
</tr>
<tr>
<td>Diet alone</td>
<td>24%</td>
</tr>
<tr>
<td>I drug</td>
<td>48%</td>
</tr>
<tr>
<td>2+ drugs</td>
<td>28%</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>135/85</td>
</tr>
<tr>
<td>Smoking (current)</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>38%</td>
</tr>
<tr>
<td>Never</td>
<td>50%</td>
</tr>
</tbody>
</table>

Intervention and Control groups well balanced for all criteria.
Baseline medical backgrounds of ITT population

- Diabetic Retinopathy: 35 (12%)
- Hypertension (BP>130/80): 169 (57%)
  - 1 antihypertensive drug: 69 (23%)
  - 2+ antihypertensive drugs: 94 (32%)
- Antidepressant drugs: 68 (23%)
- Total prescribed drugs:
  - none: 6 (2%)
  - 1-2: 47 (16%)
  - 3-5: 116 (39%)
  - 6-9: 89 (30%)
  - 10+: 40 (13%)
Results: weight changes over 12 months

Figure 2: Change in weight of participants who remained in the trial and those who dropped out during each phase of the intervention. Error bars represent 95% CIs.
ITT Primary Outcome Results

1\textsuperscript{st} Co-Primary Outcome: $\geq 15$ kg weight loss

2\textsuperscript{nd} Co-Primary Outcome: Remission of diabetes
<table>
<thead>
<tr>
<th>Co-Primary Outcome</th>
<th>Intervention</th>
<th>Control</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>≥15 kg weight loss</td>
<td>36/149 (24%)</td>
<td>0/149</td>
</tr>
<tr>
<td>2nd</td>
<td>Remission of diabetes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ITT Primary Outcome Results

1st Co-Primary Outcome:  ≥15 kg weight loss

<table>
<thead>
<tr>
<th>Intervention</th>
<th>36/149 (24%)</th>
<th>p &lt;0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0/149</td>
<td></td>
</tr>
</tbody>
</table>

2nd Co-Primary Outcome: Remission of diabetes*

<table>
<thead>
<tr>
<th>Intervention</th>
<th>68/149 (46%)</th>
<th>p &lt;0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>6/149 (4%)</td>
<td></td>
</tr>
</tbody>
</table>

* HbA1c <48 mmol/mol, off all anti-diabetes medication for at least 2 months
Remissions by 12m weight loss: entire study population

Odds Ratio (per kg weight loss): 1.32
(95% CI: 1.23, 1.41)
p<0.0001

Percentage achieving remission at 12 months:
- None: 0%
- 0-5 kg: 6.7%
- 5-10 kg: 33.9%
- 10-15 kg: 57.1%
- ≥15 kg: 86.1%
Remissions by 12m weight loss: entire study population

Weight loss at 12 months:
- None: 0%
- 0-5 kg: 6.7%
- 5-10 kg: 33.9%
- 10-15 kg: 57.1%
- ≥15 kg: 86.1%

Odds Ratio (per kg weight loss): 1.32
(95% CI: 1.23, 1.41)
p<0.0001

≥10 kg loss: 73% are in remission
### ITT secondary outcomes: mean changes at 12m

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>-10</td>
<td>-1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>-10</td>
<td>+1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>-0.9</td>
<td>+0.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% on anti-diabetes meds</td>
<td>22%</td>
<td>82%</td>
<td>0.0032</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>-1.3</td>
<td>-1.7</td>
<td>ns</td>
</tr>
<tr>
<td>% on antihypertensive meds</td>
<td>32%</td>
<td>61%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum Triglycerides (mmol/l)</td>
<td>-0.3</td>
<td>+0.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Quality of Life (EQ5)</td>
<td>+7.2</td>
<td>-2.9</td>
<td>0.0012</td>
</tr>
</tbody>
</table>
Adverse Events: 0-12 months

Serious Adverse Events

• Control Group 2 in 2 participants
• Intervention Group 9 in 7 participants
• Possibly intervention-related 2 in 1 participant
  (biliary colic and abdo pain)

• No withdrawals as a result of SAEs
N(%) reporting symptoms (AEs) pre-specified as of interest, and sought, during Total Diet Replacement phase

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Total (n=139)</th>
<th>Mild (n=139)</th>
<th>Moderate (n=139)</th>
<th>Severe (n=139)</th>
<th>Total (n=124)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>65 (46-8)</td>
<td>30 (21-6)</td>
<td>24 (17-3)</td>
<td>11 (7-9)</td>
<td>18 (14-5)</td>
</tr>
<tr>
<td>Sensitivity to cold</td>
<td>57 (41-0)</td>
<td>37 (26-6)</td>
<td>12 (8-6)</td>
<td>8 (5-8)</td>
<td>30 (24-2)</td>
</tr>
<tr>
<td>Headache</td>
<td>53 (38-1)</td>
<td>31 (22-3)</td>
<td>13 (9-4)</td>
<td>9 (6-5)</td>
<td>15 (12-1)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>49 (35-3)</td>
<td>40 (28-8)</td>
<td>7 (5-0)</td>
<td>2 (1-4)</td>
<td>11 (8-9)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>45 (32-4)</td>
<td>24 (17-3)</td>
<td>11 (7-9)</td>
<td>10 (7-2)</td>
<td>18 (14-5)</td>
</tr>
<tr>
<td>Mood change</td>
<td>35 (25-2)</td>
<td>16 (11-5)</td>
<td>12 (8-6)</td>
<td>7 (5-0)</td>
<td>10 (8-1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>25 (18-0)</td>
<td>15 (10-8)</td>
<td>4 (2-9)</td>
<td>6 (4-3)</td>
<td>3 (2-4)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>23 (16-5)</td>
<td>11 (7-9)</td>
<td>10 (7-2)</td>
<td>2 (1-4)</td>
<td>5 (4-0)</td>
</tr>
<tr>
<td>Indigestion</td>
<td>20 (14-4)</td>
<td>15 (10-8)</td>
<td>3 (2-2)</td>
<td>2 (1-4)</td>
<td>4 (3-2)</td>
</tr>
<tr>
<td>Hair Loss</td>
<td>19 (13-7)</td>
<td>10 (7-2)</td>
<td>7 (5-0)</td>
<td>2 (1-4)</td>
<td>13 (10-5)</td>
</tr>
</tbody>
</table>

Data reported as N(%)
DiRECT: Generalisability

• Conducted in a real-life primary care setting
• High proportion of more deprived participants
• No extra clinic staff for DIRECT, but needs staff training and support
• Needs redistribution of funding: economic analyses under way

• DiRECT results at 12m: 2 and 3-year data being collected
• Limited to UK population: Need trials in Asian & other high-risk groups

• Qualitative interview analyses under way (staff and participants)
DiRECT: Conclusions

- T2DM is a complication of weight gain and excess body fat, and it is not necessarily a permanent condition
- Almost half with early T2DM can achieve remission (73% if ≥10kg loss)
- Structured 1° care weight management welcomed by patients, & staff
DiRECT: Conclusions

• T2DM is a complication of weight gain and excess body fat, and it is not necessarily a permanent condition

• Almost half with early T2DM can achieve remission (73% if ≥10kg loss)

• Structured 1° care weight management welcomed by patients, & staff
<table>
<thead>
<tr>
<th>Criteria for remission of diabetes</th>
<th>Confirmation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Buse et al (20090 ADA Consensus Group)</strong></td>
<td>Maintained for 1 year</td>
</tr>
<tr>
<td>‘Partial Remission’ (= no longer diabetic)</td>
<td></td>
</tr>
<tr>
<td>Both HbA1c &lt; 6.5% (&lt;48mmol/mol) &amp; FBG 5.6-6.9 mmol/l, off anti-diabetes medications (time not specified).</td>
<td></td>
</tr>
<tr>
<td>‘Complete Remission’ (= no longer pre-diabetic)</td>
<td>Maintained for 1 year</td>
</tr>
<tr>
<td>Both HbA1c &lt; 6% (&lt;42mmol/mol) &amp; FBG &lt;5.6 mmol/l, off anti-diabetes medications (time not specified).</td>
<td></td>
</tr>
<tr>
<td>HbA1c &lt; 6% (42mmol/mol) <strong>OR</strong> FBG &lt;5.6 mmol/l, off diabetic medications (time not specified).</td>
<td>None</td>
</tr>
<tr>
<td>Lean et al BMJ 2017 proposal for coding in routine practice</td>
<td></td>
</tr>
<tr>
<td>Previous diagnosis of type 2 diabetes by WHO criteria.</td>
<td></td>
</tr>
<tr>
<td>• off anti-diabetes medications for at least 2 months.</td>
<td></td>
</tr>
<tr>
<td>• HbA1c &lt;6.5% (&lt;48mmol/mol), <strong>OR</strong> FBG &lt;7mmol/l AND 2-h glucose &lt;11mmol/l.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

McCombie et al BMJ 2017
<table>
<thead>
<tr>
<th>Medical benefits of diabetes remission</th>
<th>Value of appropriate coding for patients, epidemiology and healthcare planning</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Removes need for life-long multiple daily drug treatments indicated under clinical guidelines</td>
<td>1. Removes personal &amp; social stigmata: diseased, ‘diabetic’</td>
</tr>
<tr>
<td>2. Other CVD risk factors, BP and lipids improve or normalise, reducing need for specific drugs</td>
<td>2. Provides a target and reward for the sustained hard work to achieve and maintain substantial weight loss</td>
</tr>
<tr>
<td>3. Multisystem improvements in health and QoL with sustained weight loss</td>
<td>3. Avoids high costs, of healthcare insurance, life assurance, mortgages, travel insurance etc.</td>
</tr>
<tr>
<td></td>
<td>5. Identifies a valuable indicator of success in healthcare, through national disease register monitoring</td>
</tr>
<tr>
<td></td>
<td>6. Allows better analysis of long-term morbidity and mortality risks.</td>
</tr>
<tr>
<td></td>
<td>7. Improves resource requirement forecasting</td>
</tr>
</tbody>
</table>

McCombie et al BMJ 2017