DiRECT
Diabetes Remission Clinical Trial

Finding a practical management solution for T2DM, in primary care

Primary Outcome Results of DiRECT

the Diabetes REmission Clinical Trial

Mike Lean, Roy Taylor, and the DiRECT Team

IDF Abu Dhabi, December 5th 2017, 16.30-16.55

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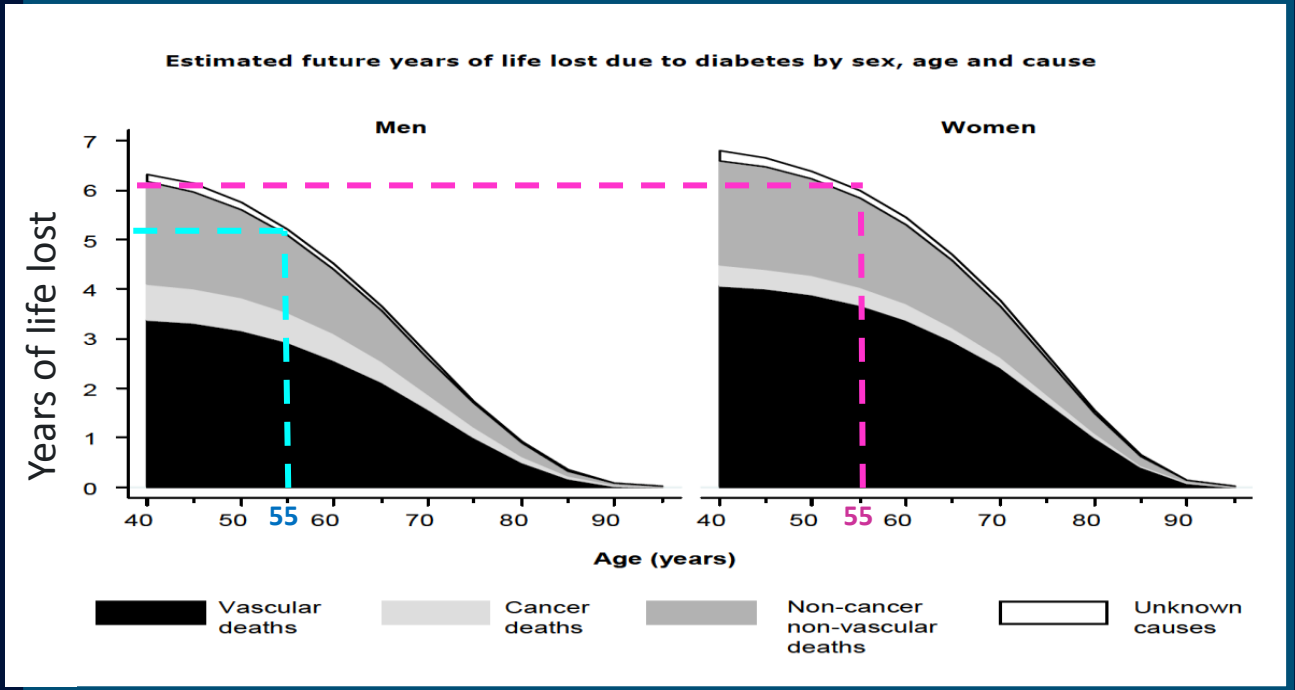
Disclosures

- 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

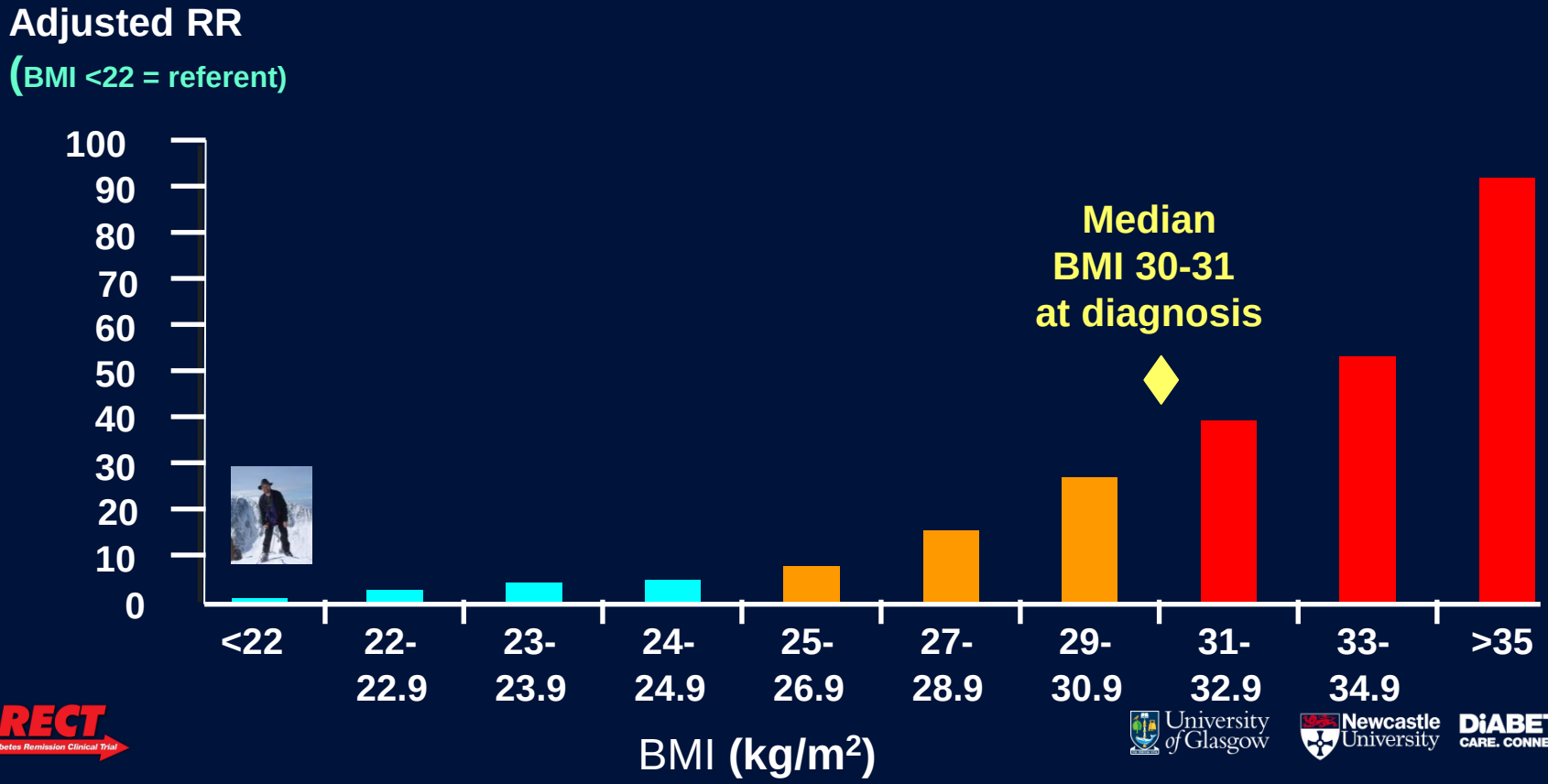
despite guidelines & drugs to lower glucose/HbA1c, LDL & BP



European Risk Factor Consortium, NEJM 2011

Weight gain/ obesity is the main driver of T2DM

Colditz GA et al. Ann Int Med, 1995



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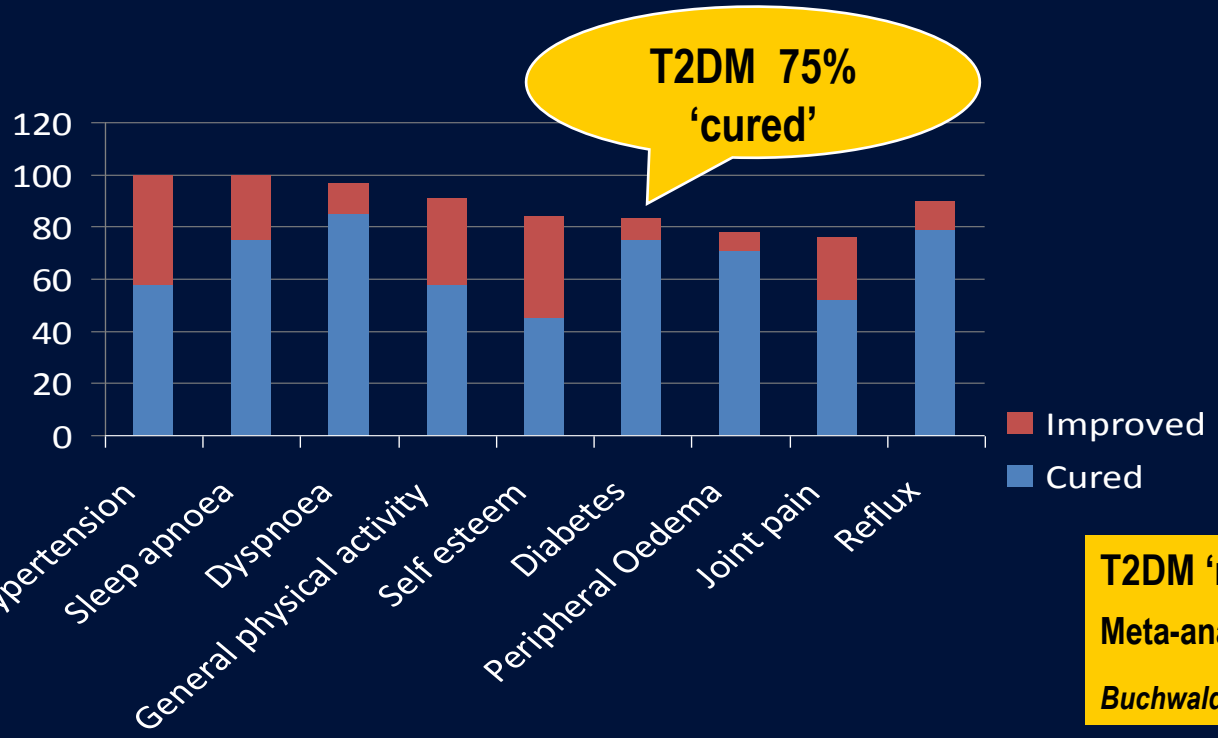
Major weight loss brings multiple clinical benefits

4 y after laparoscopic adjustable gastric banding



T2DM 'resolved' in 78%

Meta-analysis, N=4070,

Buchwald et al Am J Med, 2009

Frigg et al. Obes Surg, 2004

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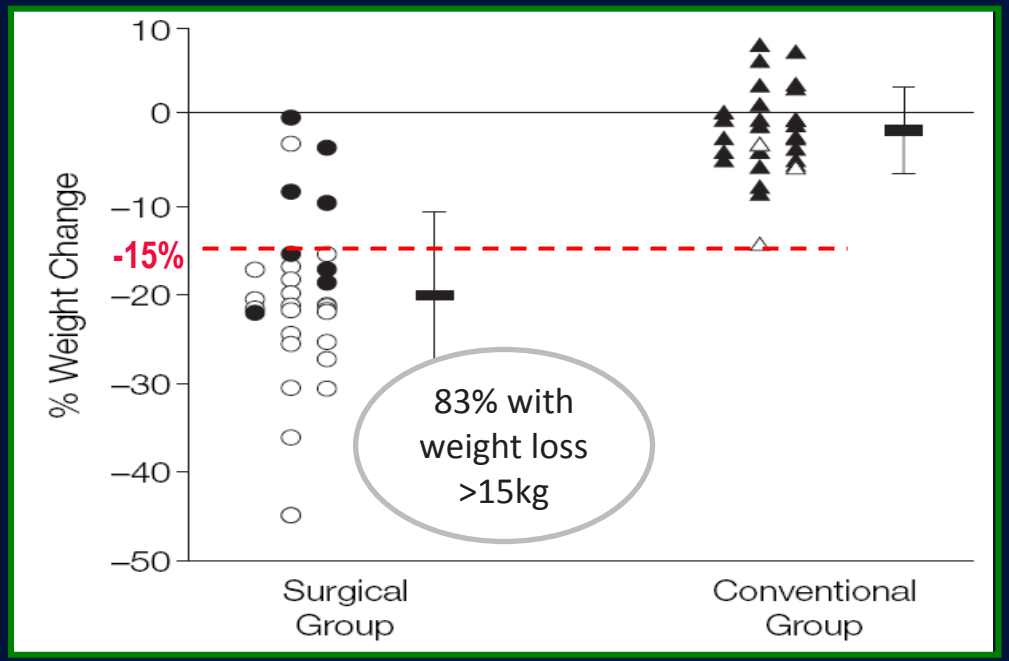
15 kg weight loss achieve most T2DM remissions

2-year RCT, gastric band vs usual diet advice



Conventional group
- △ Achieved remission of type 2 diabetes 13%
- ▲ Did not achieve remission of type 2 diabetes

Surgical group
- ○ Achieved remission of type 2 diabetes 73%
- ● Did not achieve remission of type 2 diabetes

Dixon et al (2008) JAMA

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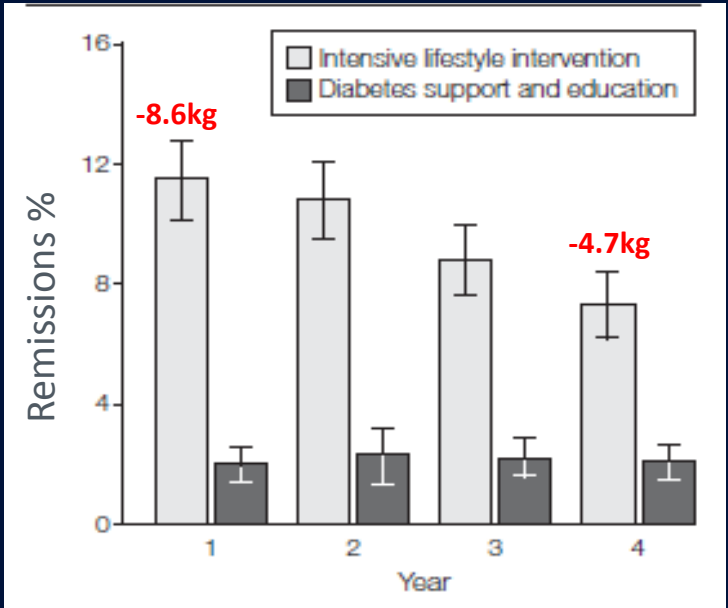
Remissions of T2DM in Look AHEAD



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

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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

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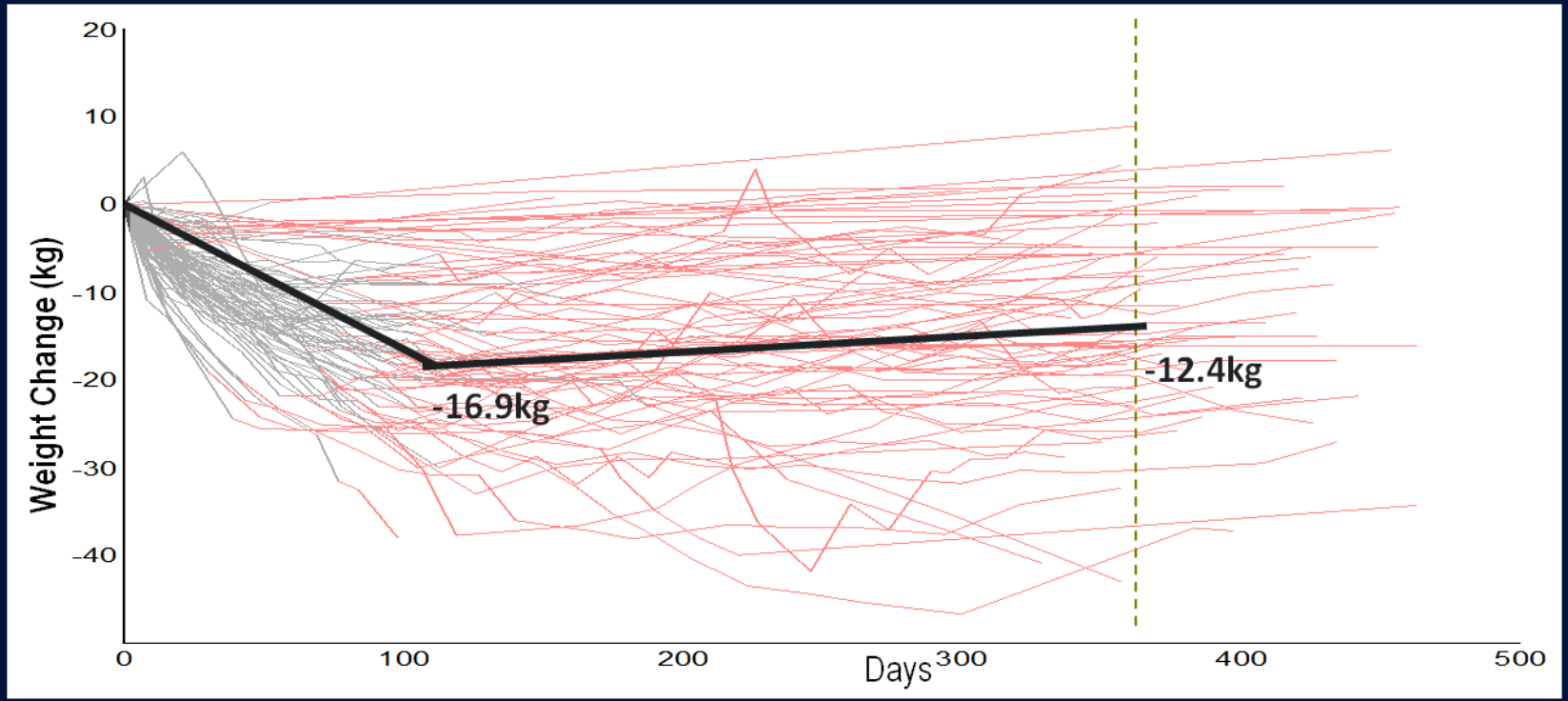
DiRECT: outcomes, assumptions & statistical power

- 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)

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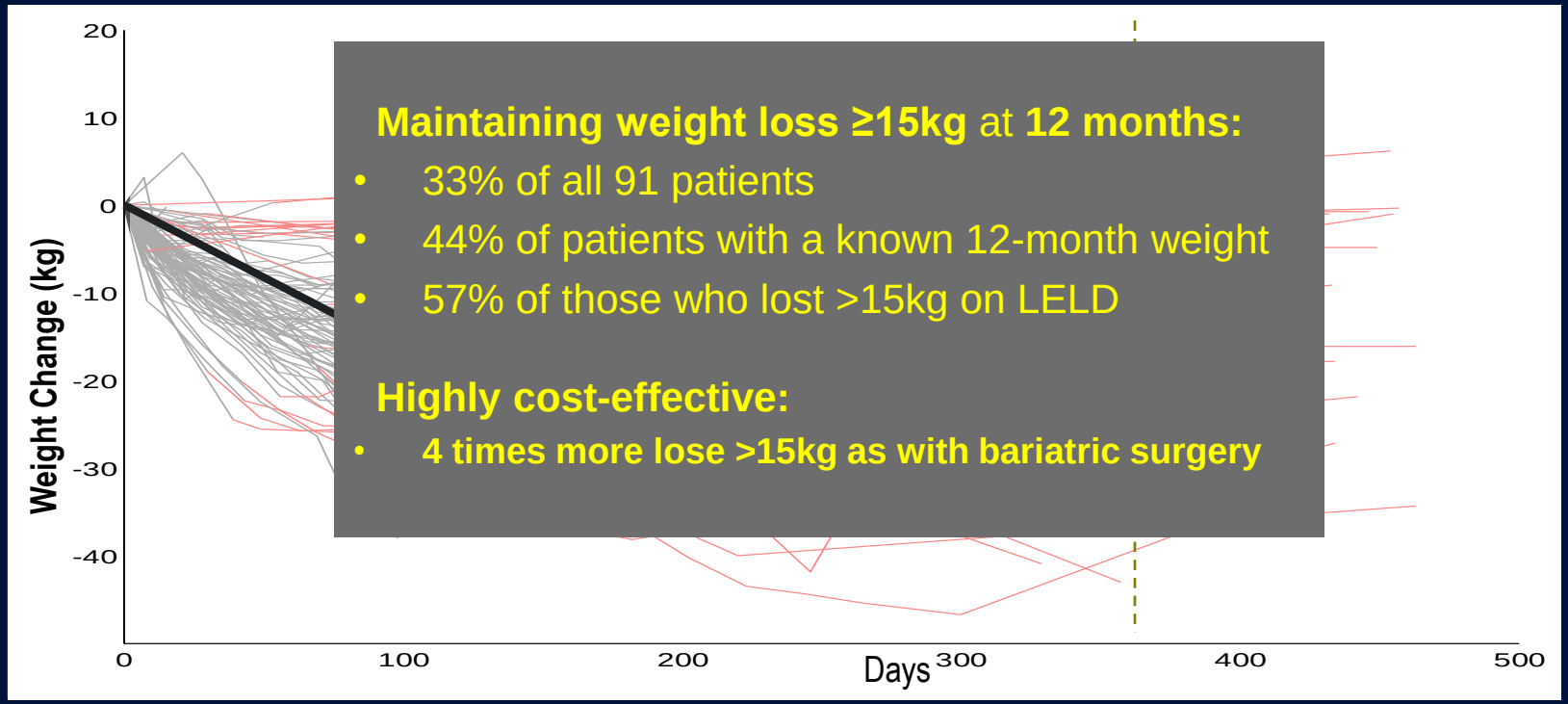

Maintaining weight loss ≥15kg at **12 months:**

- 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)

DiRECT Intervention: Counterweight-Plus Protocol

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

Screening

↓

Total Diet Replacement

Lean et al, Br J General Practice (2013),

Leslie et al, BMC Family Practice (2016)

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DiRECT Intervention: Counterweight-Plus Protocol

Stepped Food Reintroduction

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

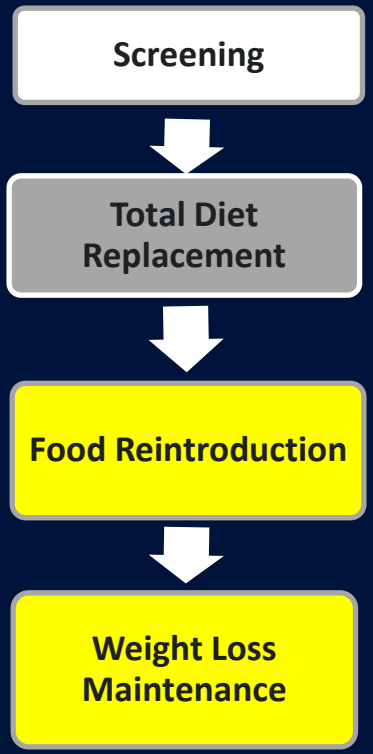
Weight Loss Maintenance

- 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)

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DiRECT Intervention: Counterweight-Plus Protocol

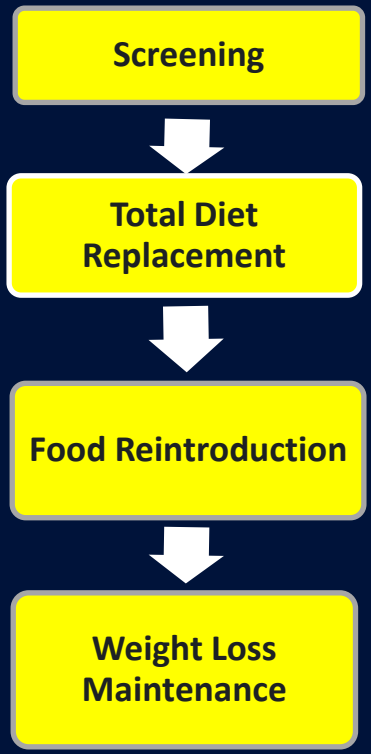
Patients attended their own primary care practice centres

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)

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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)

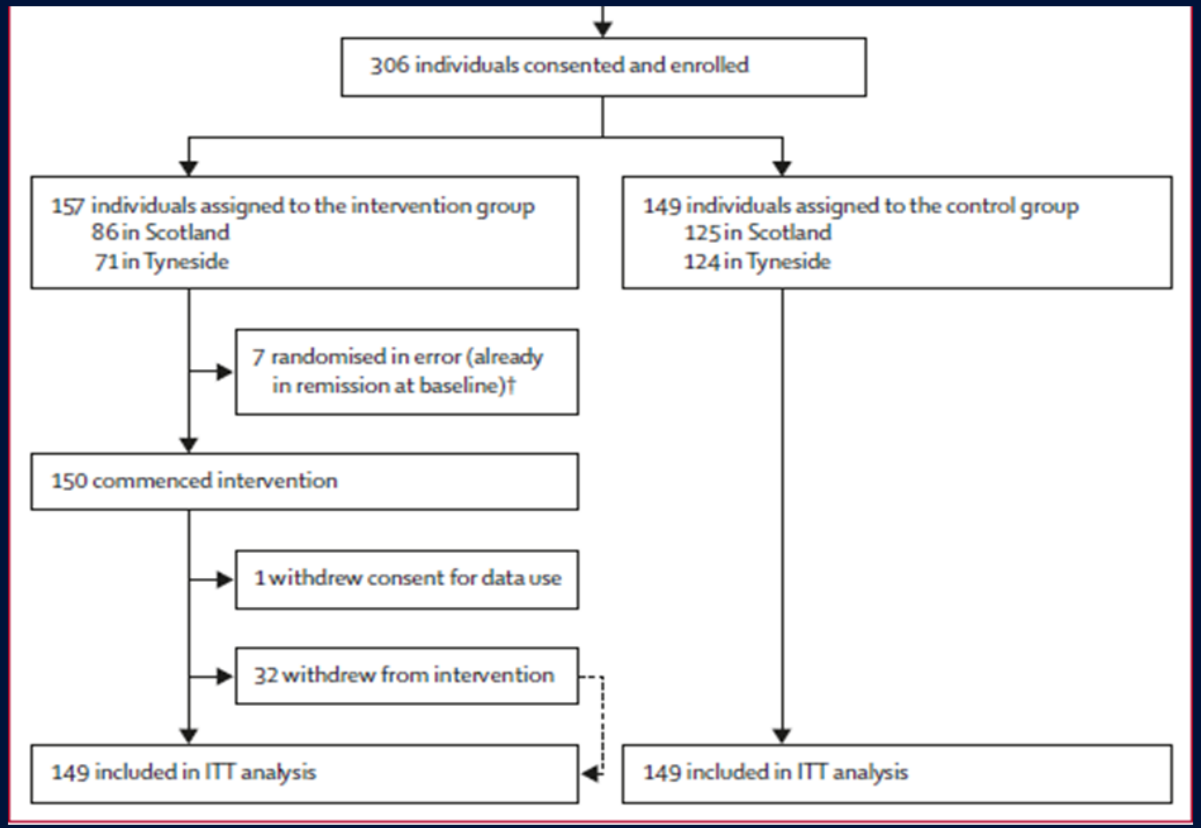
- Practices invited 523
- Practices agreed 55
- Practices recruited 49

- Eligible patients identified by SPCRN 1510
  - Letter and one reminder
- Agreed to participate 423 (28% both arms)

- Patients recruited 306

Taylor et al Diabetologia 2017

Results: participant retention



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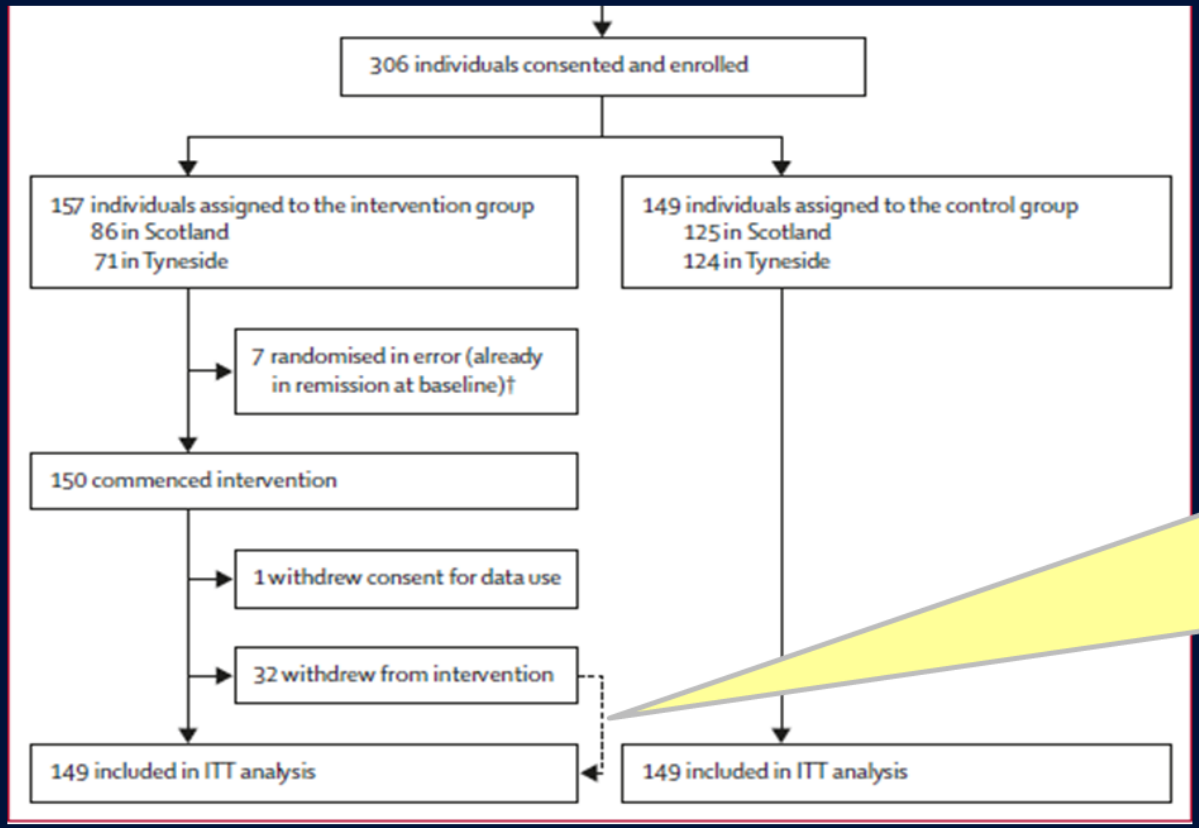

Drop-outs:
12 month outcome data collected within a 3 month window from routine GP clinic records

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Demographics: Invited vs analysed participants

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

Data are mean (SD) unless otherwise stated

Baseline data: analysed participants

(100%)

Total number	298
Men / women	59% / 41%
Age (years)	54 (SD 7)
Weight (kg)	men 106 (SD 16) women 91 (SD 13)
BMI (kg/m^2)	35 (SD 4)

Duration of T2DM (y)	3.1 (SD 1.7)
HbA1c (mmol/mol)	59 (SD14) (7.6%)
Diet alone	24%
I drug	48%
2+ drugs	28%
Blood Pressure	135/85
Smoking (current)	12%
Former	38%
Never	50%

Intervention and Control groups well balanced for all criteria

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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%)

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Results: weight changes over 12 months

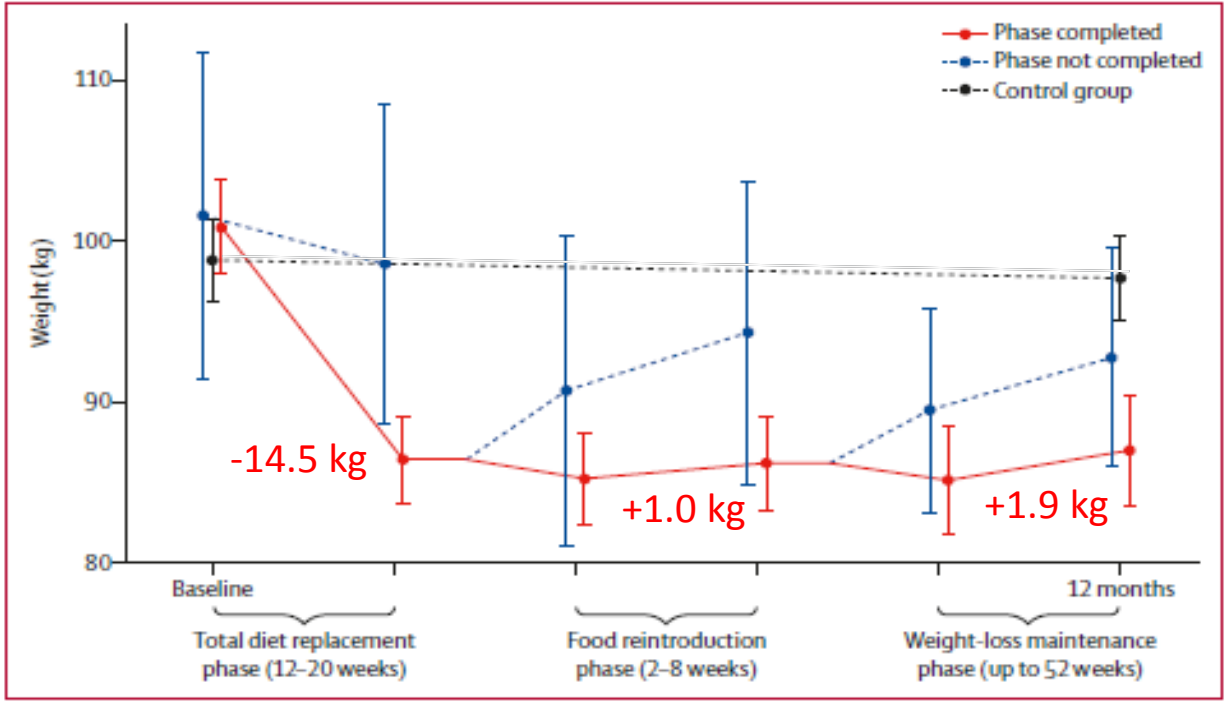

Figure 2: **Change in weight of participants who remained in the trial and those who dropped out during each phase of the intervention**

Error bars represent 95% CIs.

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ITT Primary Outcome Results

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

2nd Co-Primary Outcome: Remission of diabetes

ITT Primary Outcome Results

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

Intervention	36/149	(24%)	p <0.0001
Control	0/149		

2nd Co-Primary Outcome: Remission of diabetes

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ITT Primary Outcome Results

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

Intervention	36/149	(24%)	p <0.0001
Control	0/149		

2nd Co-Primary Outcome: Remission of diabetes*

Intervention	68/149	(46%)	p <0.0001
Control	6/149	(4%)	

* HbA1c <48 mmol/mol,
off all anti-diabetes medication for at least 2 months

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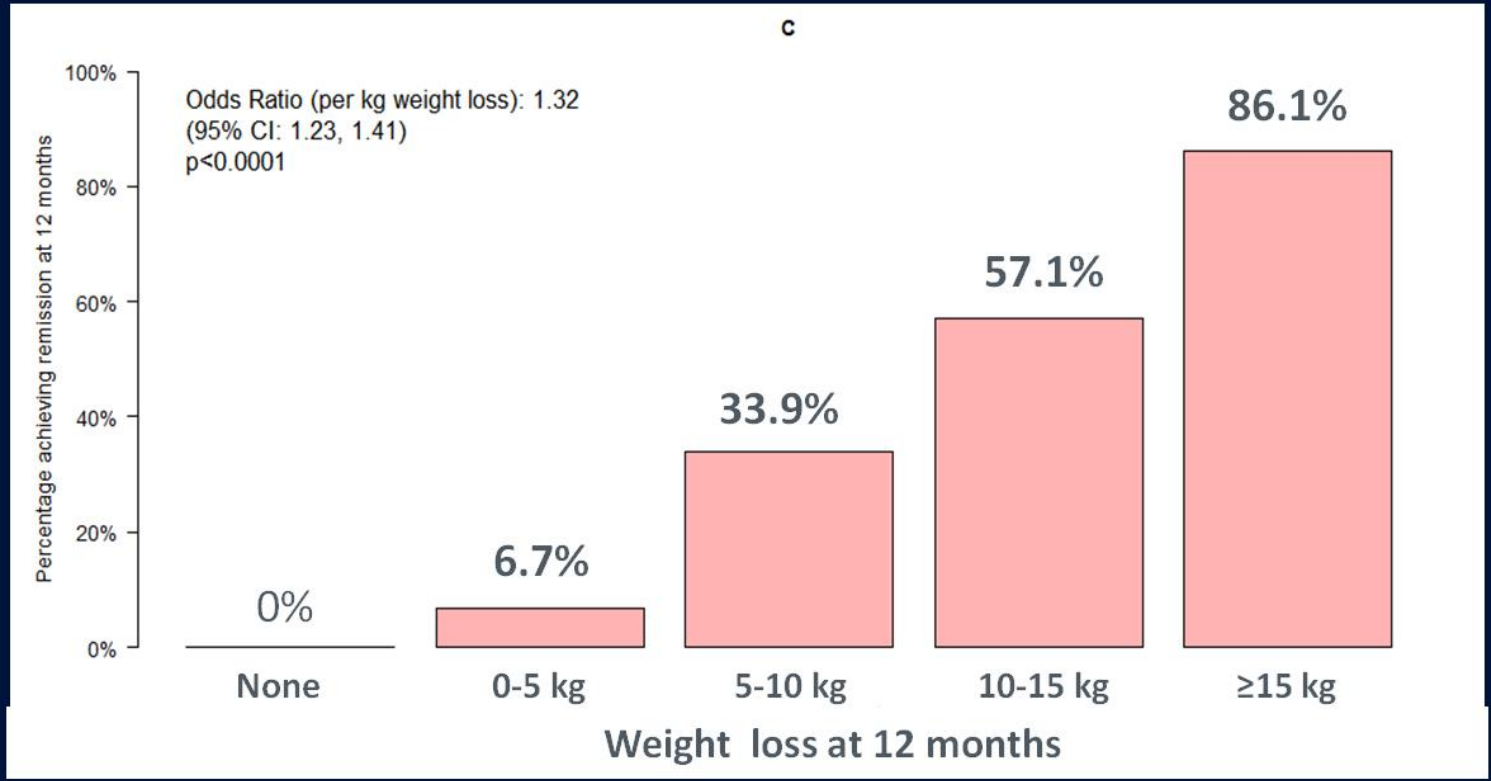
Remissions by 12m weight loss: entire study population



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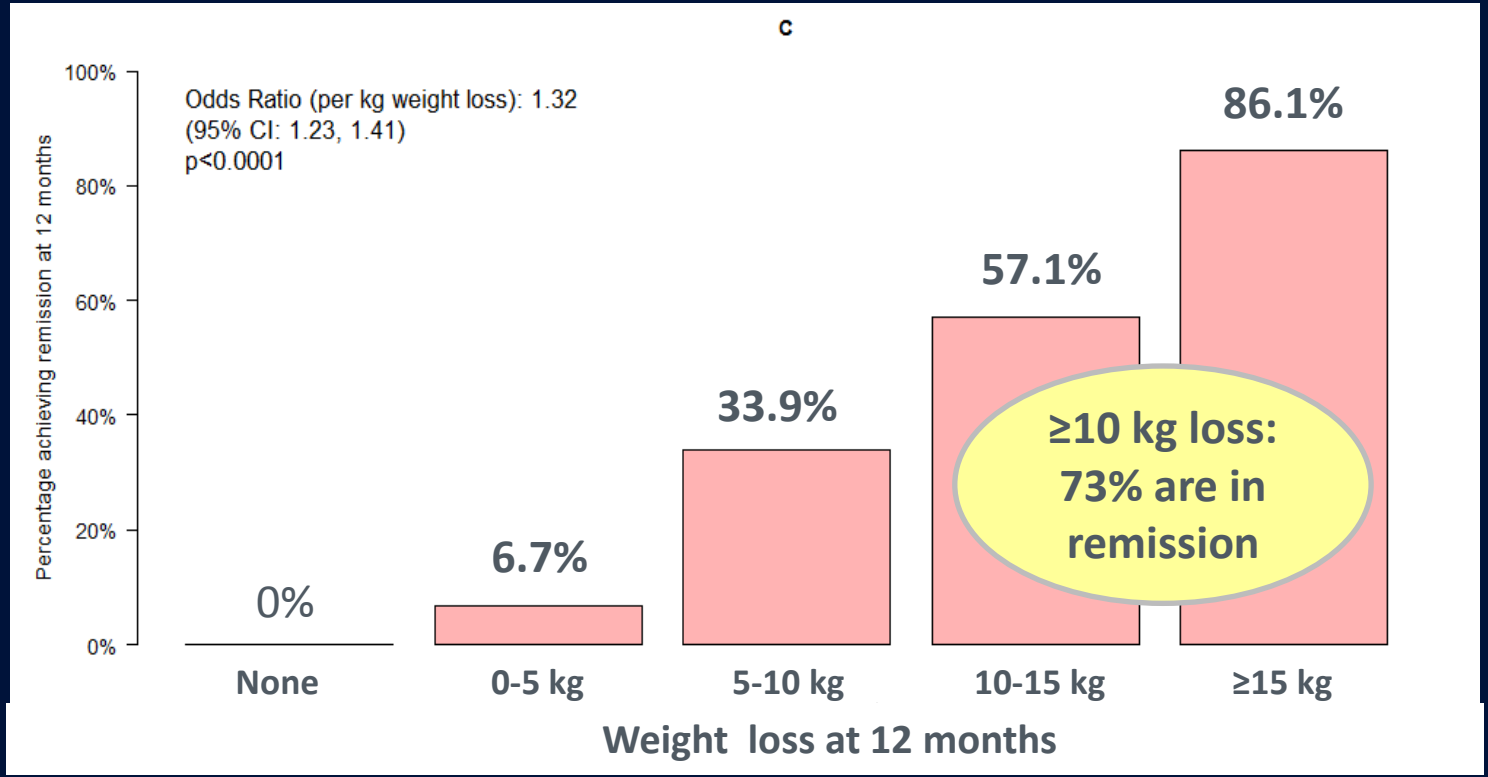

ITT secondary outcomes: mean changes at 12m

	Intervention	Control	P
Weight (kg)	-10	-1	<0.0001
HbA1c (mmol/mol)	-10	+1	<0.0001
HbA1c (%)	-0.9	+0.1	<0.0001
% on anti-diabetes meds	22%	82%	0.0032
Systolic BP (mm Hg)	-1.3	-1.7	ns
% on antihypertensive meds	32%	61%	<0.0001
Serum Triglycerides (mmol/l)	-0.3	+0.1	<0.0001
Quality of Life (EQ5)	+7.2	-2.9	0.0012

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

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N(%) reporting symptoms (AEs) pre-specified as of interest, and sought, during Total Diet Replacement

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

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^{o} care weight management welcomed by patients, & staff

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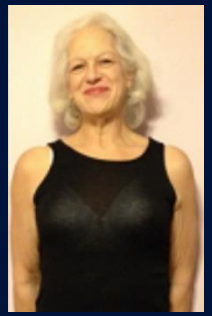


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	Criteria for remission of diabetes	Confirmation
Buse et al (20090 ADA Consensus Group	'Partial Remission' (= no longer diabetic) Both HbA1c < 6.5% (<48mmol/mol) & FBG 5.6-6.9 mmol/l, off anti-diabetes medications (time not specified).	Maintained for 1 year
	'Complete Remission' (= no longer pre-diabetic) Both HbA1c < 6% (<42mmol/mol) & FBG <5.6 mmol/l, off anti-diabetes medications (time not specified).	Maintained for 1 year
Buchwald et al (bariatric surgery)	HbA1c < 6% (42mmol/mol) OR FBG <5.6 mmol/l off diabetic medications (time not specified).	None
Lean et al BMJ2017 proposal for coding in routine practice	Previous diagnosis of type 2 diabetes by WHO criteria. • off anti-diabetes medications for at least 2 months. • HbA1c <6.5% (<48mmol/mol), OR FBG <7mmol/l AND 2-h glucose <11mmol/l.	• Two non-diabetic tests, at least 2 months apart. • Then reviewed annually

McCombie et al BMJ 2017

Medical benefits of diabetes remission	Value of appropriate coding for patients, epidemiology and healthcare planning
1. Removes need for life-long multiple daily drug treatments indicated under clinical guidelines 2. Other CVD risk factors, BP and lipids improve or normalise, reducing need for specific drugs 3. Multisystem improvements in health and QoL with sustained weight loss 4. Likely reduction in microvascular complications – possible arrest	1. Removes personal & social stigmata: diseased, 'diabetic' 2. Provides a target and reward for the sustained hard work to achieve and maintain substantial weight loss 3. Avoids high costs, of healthcare insurance, life assurance, mortgages, travel insurance etc. 4. Removes some occupational restrictions. 5. Identifies a valuable indicator of success in healthcare, through national disease register monitoring 6. Allows better analysis of long-term morbidity and mortality risks. 7. Improves resource requirement forecasting

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