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The “weight” of weight loss in diabetes treatment

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A partnership between:

MONASH University | AlfredHealth

Alfred Alliance in Diabetes

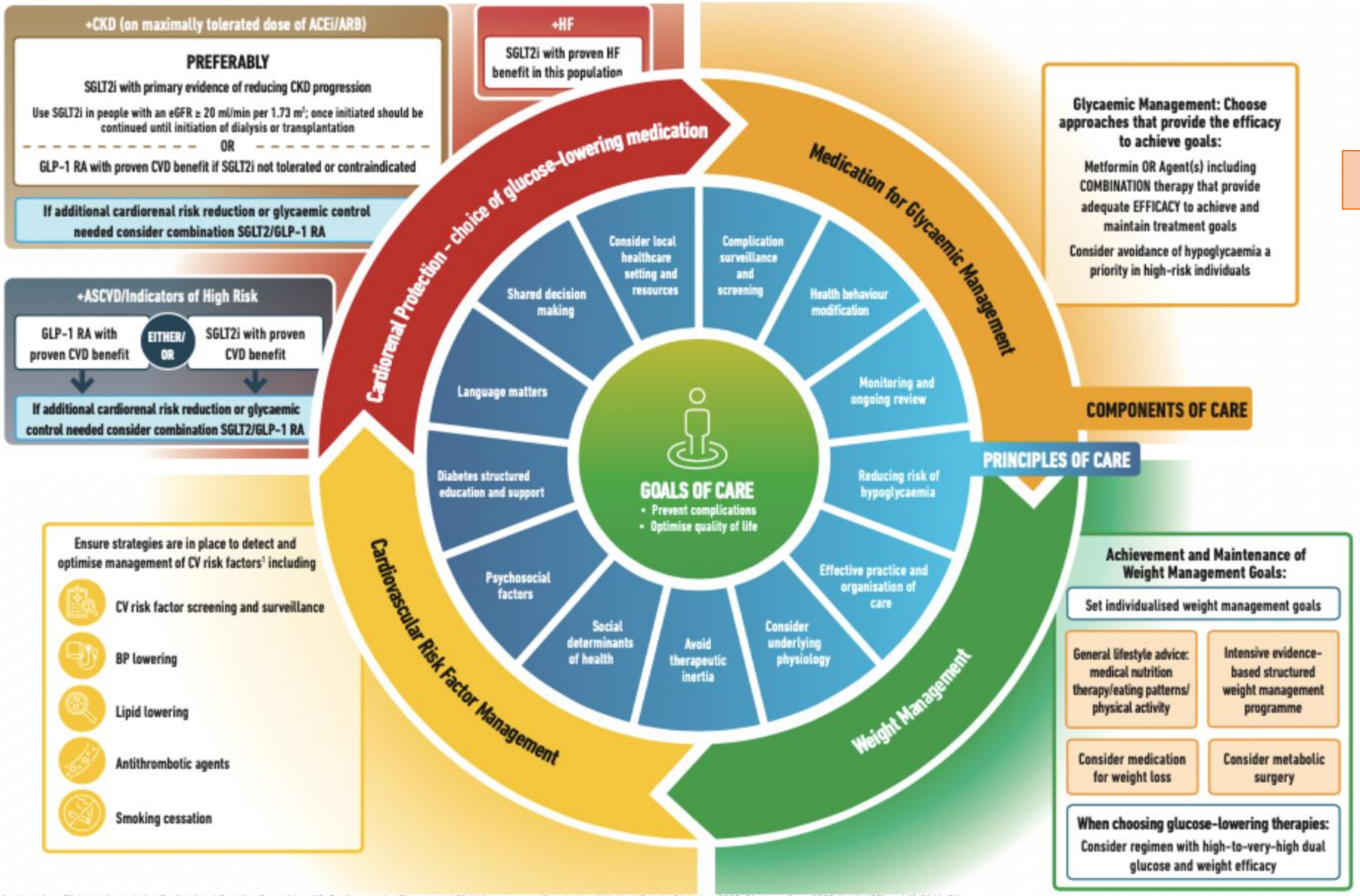
Disclosures

- Co-authorship of manuscripts with medical writer provided by Novo Nordisk, Eli Lilly

Outline

1. WHY?
2. WHEN?
3. HOW MUCH?

HOLISTIC PERSON-CENTRED APPROACH TO T2DM MANAGEMENT



1 = American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022 Jan 1;45(Suppl 1):S144–74.

ACEi, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blockers; ASCVD, Atherosclerotic Cardiovascular Disease; BP, Blood Pressure; CKD, Chronic Kidney Disease; CV, Cardiovascular; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes.

cardiorenal protection

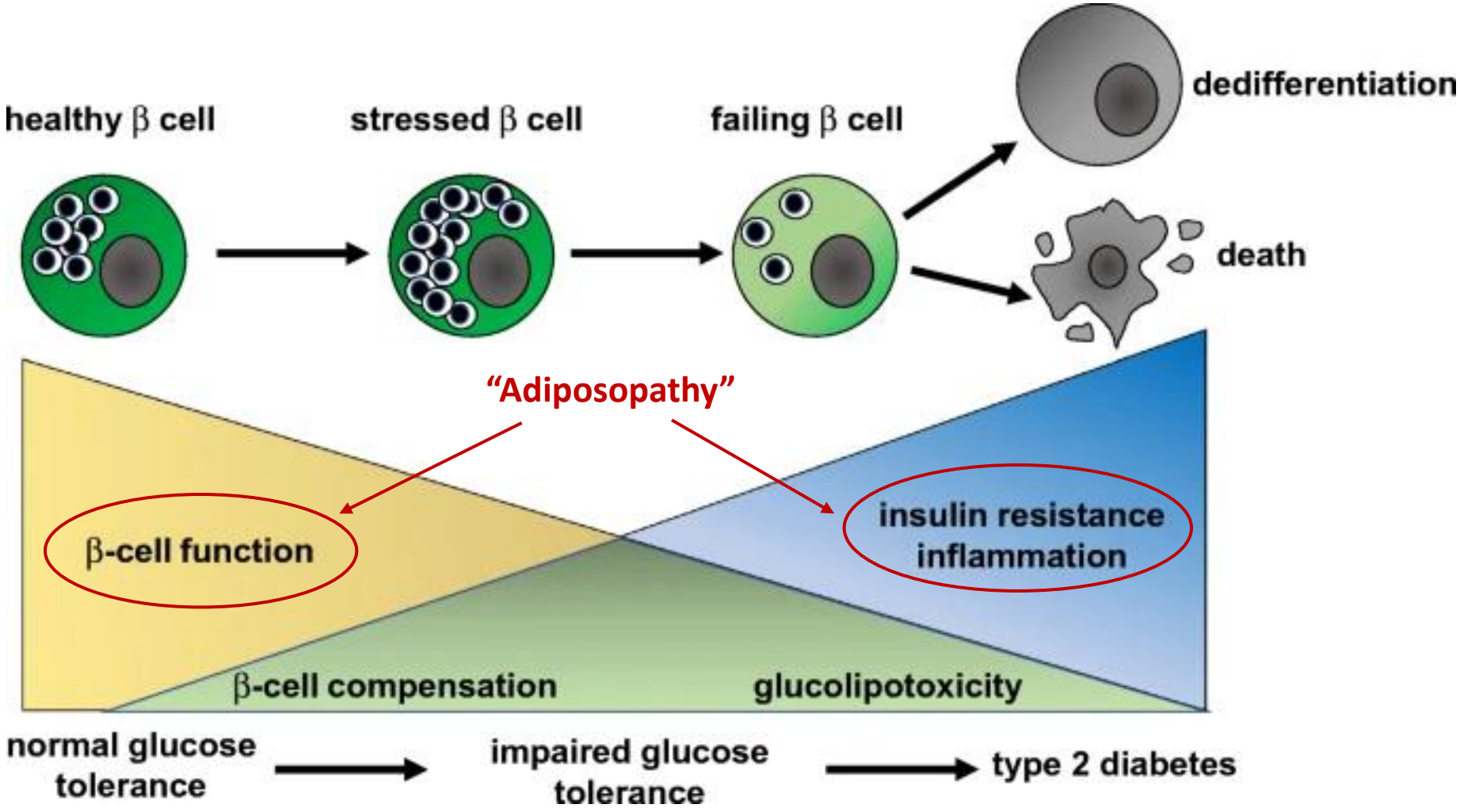
glycaemia

CV risk factors

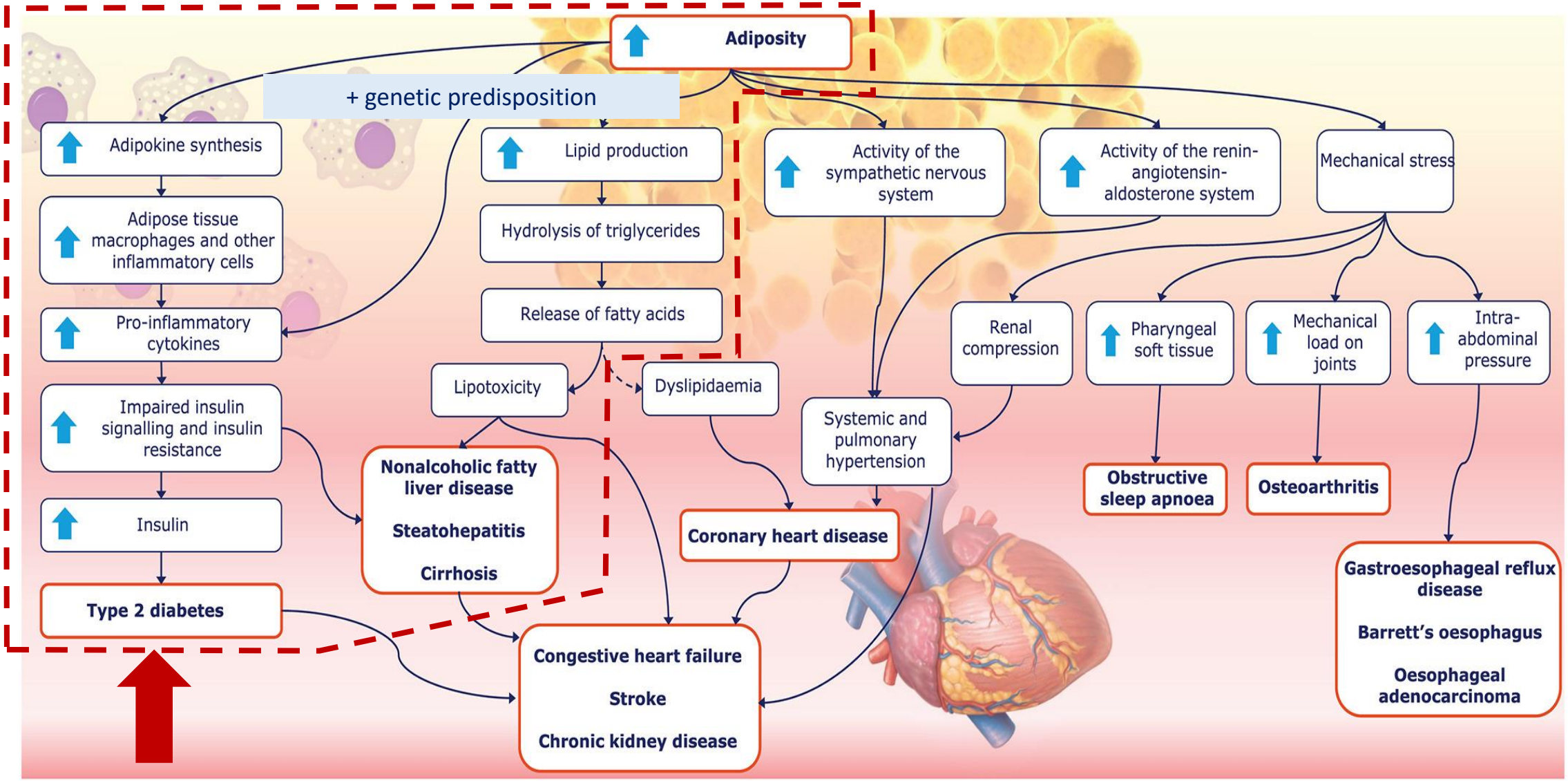
*

weight

Davies *Diab Care* 2022



Christensen *Curr Diab Reports* 2019



Wilding *Obes Rev* 2020 reproduced from Heymsfield *NEJM* 2017

Weight loss has dose-dependent and tissue-dependent effects

Effects of progressive weight loss on metabolic function and adipose tissue biology in humans with obesity

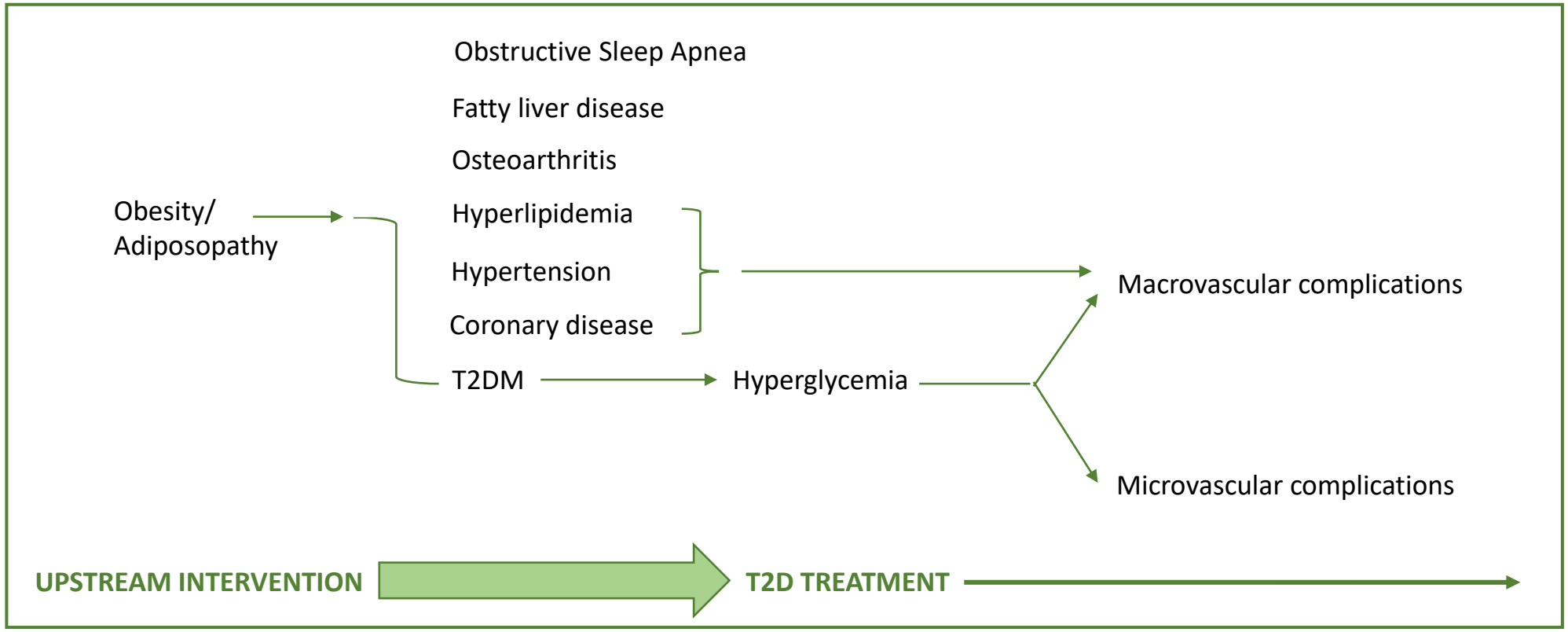
	5% Weight loss	11% Weight Loss	16% Weight Loss
Intrahepatic triglyceride content	✓	✓✓	✓✓✓
Intra-abdominal adipose tissue volume	✓	✓✓	✓✓✓
Adipose tissue insulin sensitivity	✓	✓	✓
Liver insulin sensitivity	✓	✓	✓
Muscle insulin sensitivity	✓	✓✓	✓✓✓
Beta cell function	✓	✓✓	✓✓✓
Adipose tissue biology*		✓	✓✓
Inflammatory markers			✓

*Upregulation of genes involved in cholesterol flux, downregulation of genes involved in lipid synthesis, ECM remodeling and oxidative stress. ECM, extracellular matrix

Slide courtesy of Prof Donna Ryan

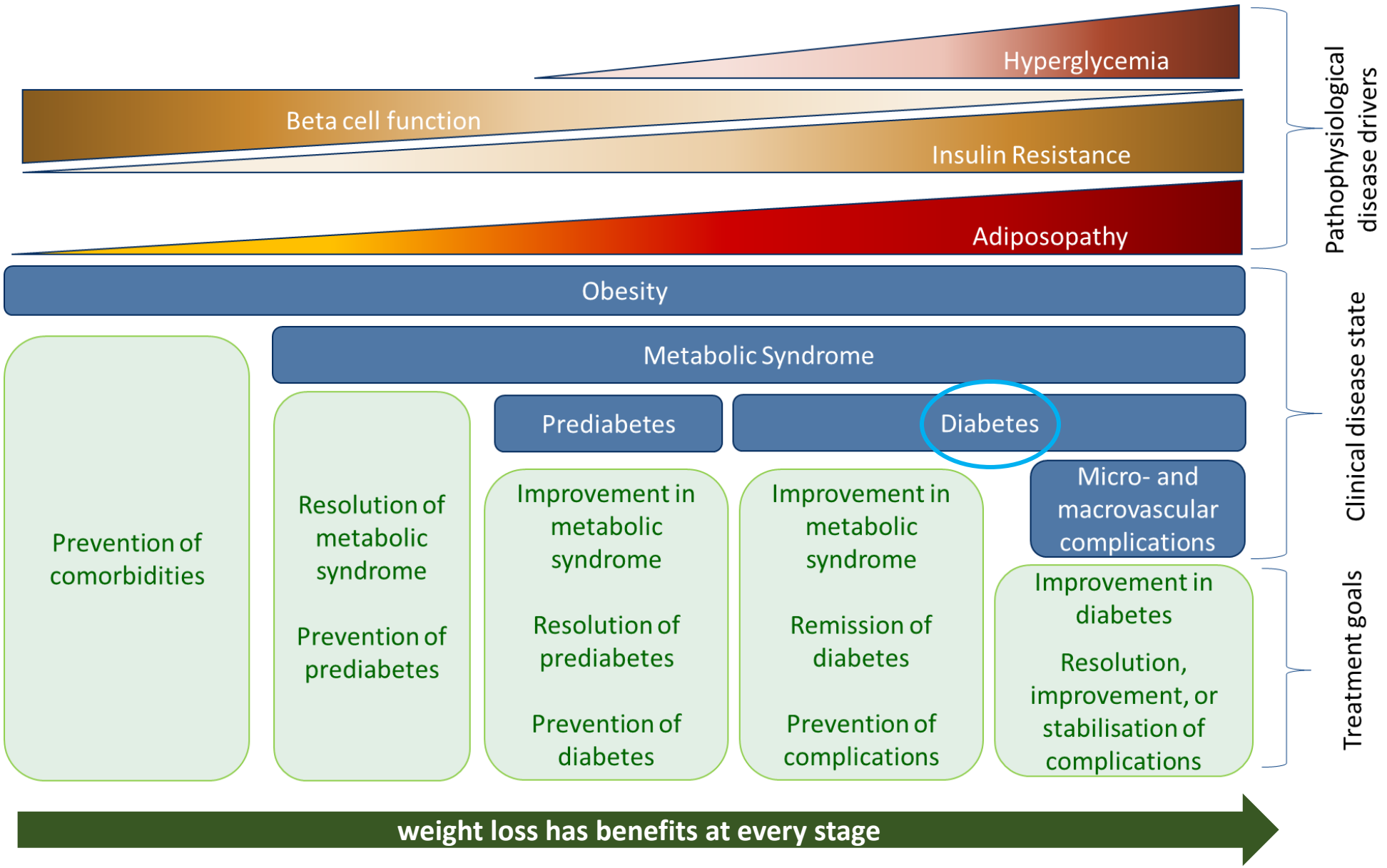
Magkos *Cell Metabolism* 2016

Weight loss has ‘upstream’ benefits in T2D



Lingvay, Sumithran et al *Lancet* 2022

When?



Lingvay, Sumithran et al *Lancet* 2022

Pre-diabetes: PREVENTION

VOLUME 346 FEBRUARY 7, 2002 NUMBER 6

REDUCTION IN THE INCIDENCE OF TYPE 2 DIABETES WITH LIFESTYLE INTERVENTION OR METFORMIN

DIABETES PREVENTION PROGRAM RESEARCH GROUP*

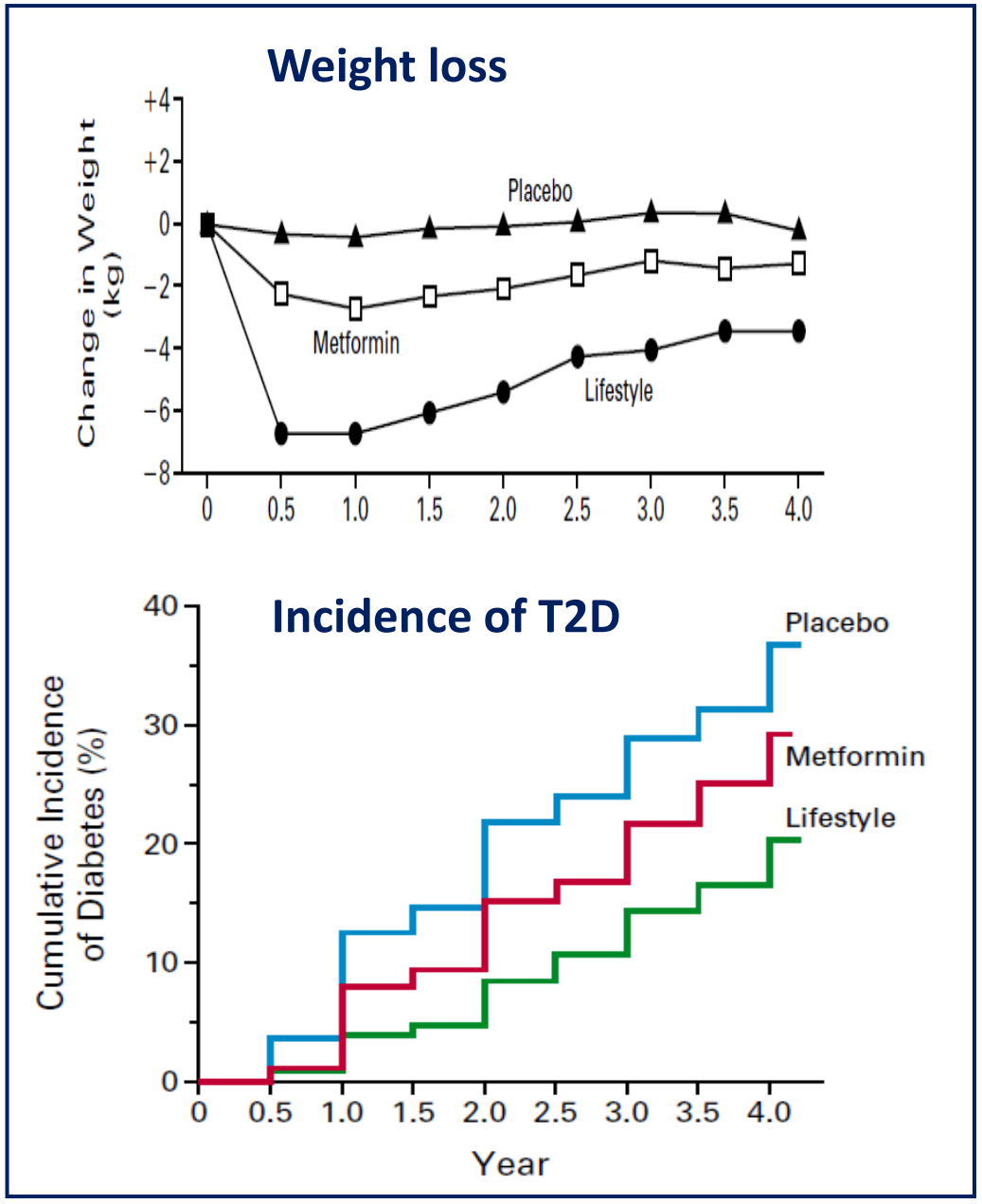
Multicentre RCT; n=3234

Aim: to assess whether a lifestyle intervention or metformin could prevent or delay onset of T2D

Inclusion: age >25y + BMI >24 kg/m^2 AND
impaired fasting glucose and impaired glucose tolerance

Intervention: intensive lifestyle intervention with goals of
≥ 7% weight loss and
≥ 150 minutes of physical activity per week
vs standard lifestyle + placebo or
metformin 850 mg twice daily

Primary outcome: diagnosis of T2D



Short duration T2D: REMISSION

Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial

Lancet 2018; 391: 541–51

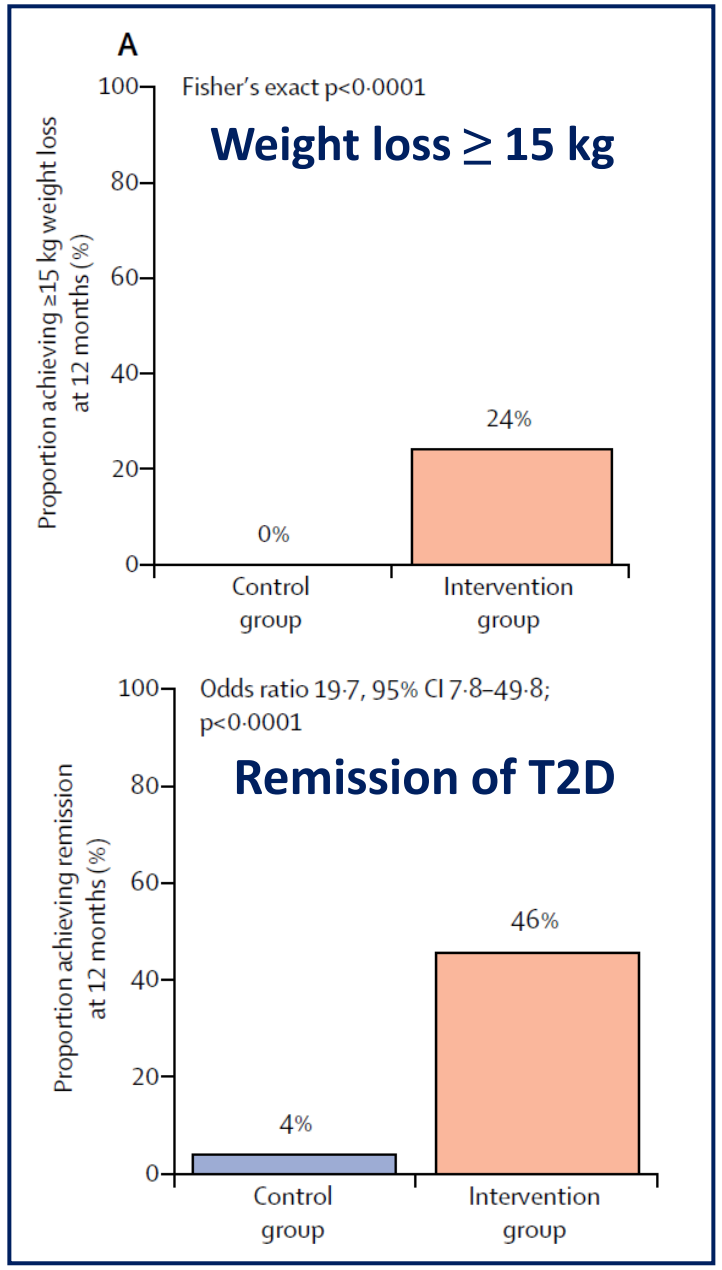
Michael E J Lean, Wilma S Leslie, Alison C Barnes, Naomi Brosnahan, George Thom, Louise McCombie, Carl Peters, Sviatlana Zhyzhneuskaya, Ahmad Al-Mrabeh, Kieren G Hollingsworth, Angela M Rodrigues, Lucia Rehackova, Ashley J Adamson, Falko F Sniehotta, John C Mathers, Hazel M Ross, Yvonne McIlvenna, Renae Stefanetti, Michael Trenell, Paul Welsh, Sharon Kean, Ian Ford, Alex McConnachie, Naveed Sattar, Roy Taylor**

Aim: to assess whether intensive weight management within primary care would achieve remission of T2D

Inclusion: 20-65yo + BMI 27-45 kg/m^2 + T2D <6y duration + no insulin

Intervention: withdrawal of T2D and HT meds +
total diet replacement (825–853 kcal/day for 3–5 months) +
stepped food reintroduction (2–8 weeks) +
structured support (up to 52 weeks)
vs standard care as per guidelines

Co-primary outcomes:
weight loss of 15 kg or more +
remission of diabetes from baseline to 12 months
(HbA1c <6.5% [48 mmol/mol] after ≥2 months off medications)



Longstanding T2D: IMPROVEMENT

Metabolic surgery versus conventional medical therapy in patients with type 2 diabetes: 10-year follow-up of an open-label, single-centre, randomised controlled trial

Geltrude Mingrone, Simona Panunzi, Andrea De Gaetano, Caterina Guidone, Amerigo Iaconelli, Esmeralda Capristo, Ghassan Chamseddine, Stefan R Bornstein, Francesco Rubino

***Lancet* 2021; 397: 293–304**

Aim: to compare metabolic surgery with medical therapy for the treatment of type 2 diabetes in people with obesity

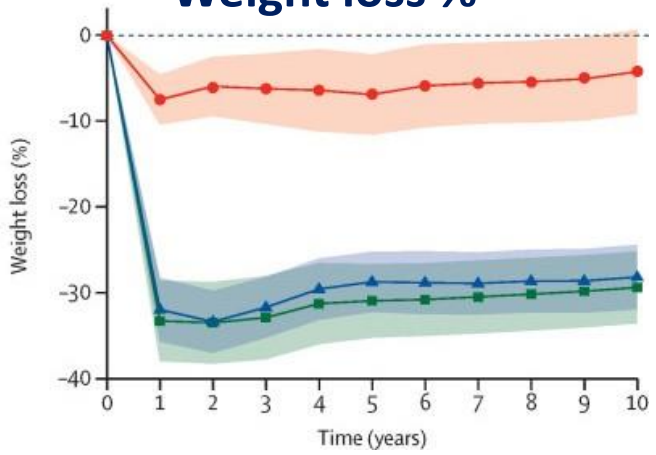
Inclusion: 30-60yo + BMI >35 kg/m^2 + T2D >5y + HbA1c >7.0%

Intervention: lifestyle modification and target-driven adjustment of T2D medications vs RYGB or BPD

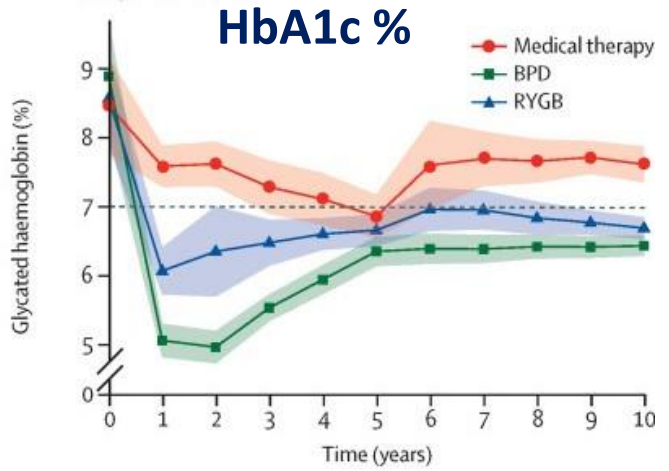
Primary outcome: T2D remission at 2 years (fasting glucose <100 mg/dL [5.6 mmol/L] and HbA1c <6.5% for >1y without medication)

10-year durability (n=58 of original 60 participants)

Weight loss %



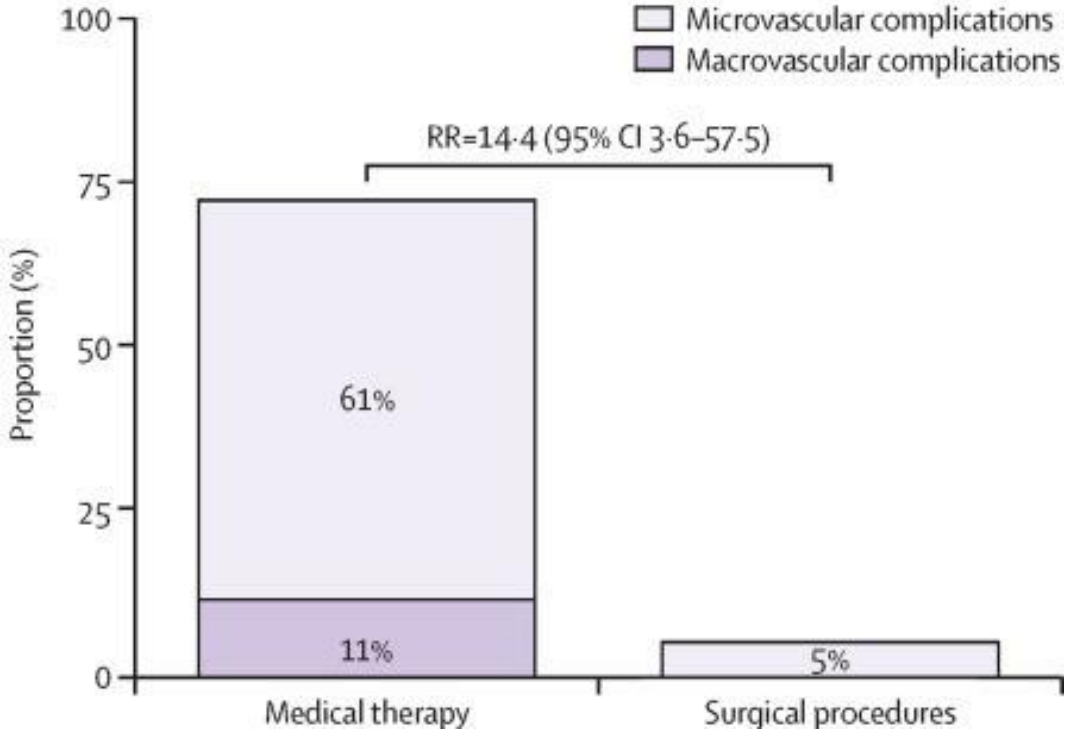
HbA1c %



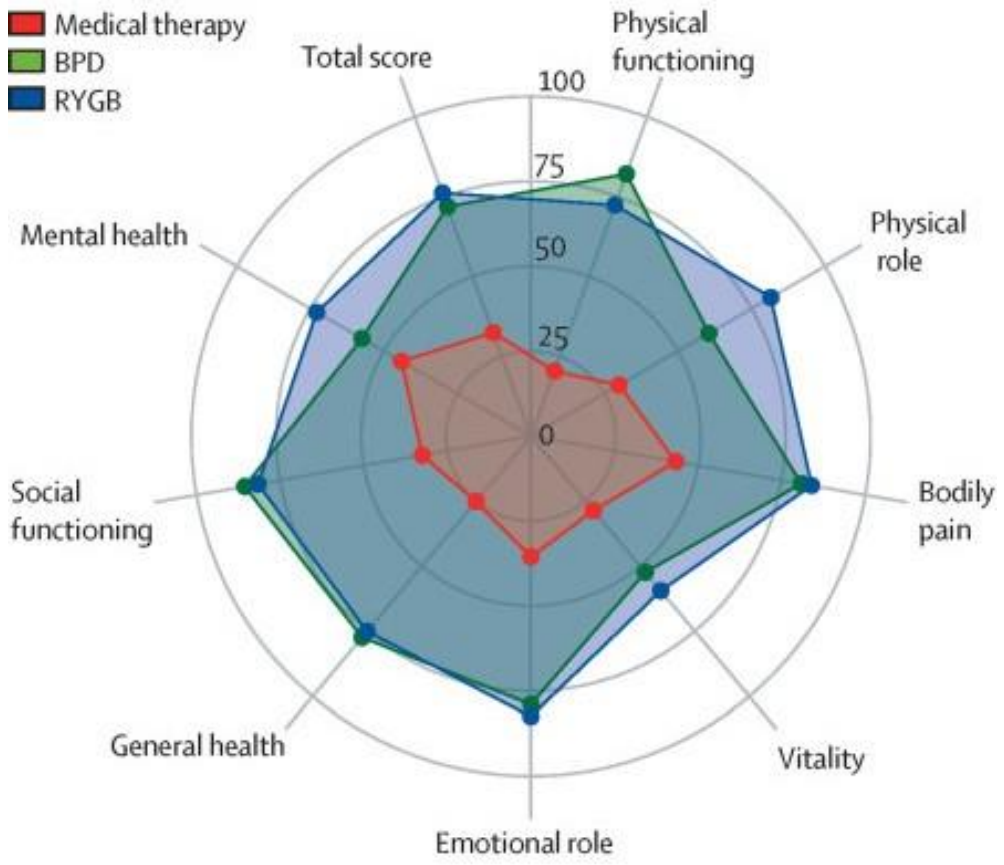
Remission at 10 years: 37% with surgery

Longstanding T2D: PREVENTION OF COMPLICATIONS

Diabetes complications (10y)

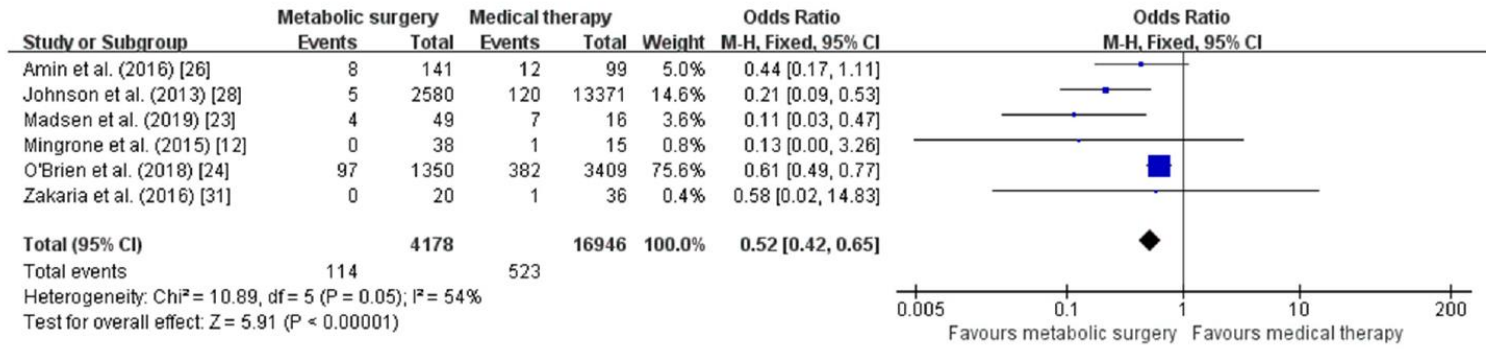


Quality of life (10y)



Mingrone *Lancet* 2021

Longstanding T2D: PREVENTION OF COMPLICATIONS



Study or Subgroup	Metabolic surgery Events	Total	Medical therapy Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Amin et al. (2016) [26]	8	141	12	99	5.0%	0.44 [0.17, 1.11]
Johnson et al. (2013) [28]	5	2580	120	13371	14.6%	0.21 [0.09, 0.53]
Madsen et al. (2019) [23]	4	49	7	16	3.6%	0.11 [0.03, 0.47]
Mingrone et al. (2015) [12]	0	38	1	15	0.8%	0.13 [0.00, 3.26]
O'Brien et al. (2018) [24]	97	1350	382	3409	75.6%	0.61 [0.49, 0.77]
Zakaria et al. (2016) [31]	0	20	1	36	0.4%	0.58 [0.02, 14.83]
Total (95% CI)		**4178**		**16946**	**100.0%**	**0.52 [0.42, 0.65]**
Total events	114		523			

Heterogeneity: Chi² = 10.89, df = 5 (P = 0.05); I² = 54%
Test for overall effect: Z = 5.91 (P < 0.00001)

Odds Ratio M-H, Fixed, 95% CI
0.005 0.1 1 10 200
Favours metabolic surgery Favours medical therapy

Study or Subgroup	Metabolic surgery Events	Total	Medical therapy Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Iaconelli et al. (2011) [30]	2	22	14	28	4.6%	0.10 [0.02, 0.51]
Johnson et al. (2013) [28]	0	2580	77	13371	10.4%	0.03 [0.00, 0.54]
Mingrone et al. (2015) [12]	1	38	1	15	0.6%	0.38 [0.02, 6.47]
Miras et al. (2015) [27]	5	43	5	14	2.8%	0.24 [0.06, 1.00]
O'Brien et al. (2018) [24]	68	1380	350	3495	77.8%	0.47 [0.36, 0.61]
Schauer et al. (2017) [32]	6	92	7	37	3.9%	0.30 [0.09, 0.96]
Total (95% CI)		**4155**		**16960**	**100.0%**	**0.39 [0.30, 0.50]**
Total events	82		454			

Heterogeneity: Chi² = 8.02, df = 5 (P = 0.16); I² = 38%
Test for overall effect: Z = 7.33 (P < 0.00001)

Odds Ratio M-H, Fixed, 95% CI
0.002 0.1 1 10 500
Favours metabolic surgery Favours medical therapy

Study or Subgroup	Metabolic surgery Events	Total	Medical therapy Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Ikramuddin et al. (2015) [33]	2	57	2	57	0.5%	1.00 [0.14, 7.35]
Johnson et al. (2013) [28]	1	2580	94	13371	7.4%	0.05 [0.01, 0.39]
Mingrone et al. (2015) [12]	0	38	2	15	0.9%	0.07 [0.00, 1.56]
O'Brien et al. (2018) [24]	97	1353	642	2998	90.0%	0.28 [0.23, 0.35]
Schauer et al. (2017) [32]	6	99	4	43	1.3%	0.63 [0.17, 2.35]
Total (95% CI)		**4127**		**16484**	**100.0%**	**0.27 [0.22, 0.34]**
Total events	106		744			

Heterogeneity: Chi² = 6.58, df = 4 (P = 0.16); I² = 39%
Test for overall effect: Z = 11.76 (P < 0.00001)

Odds Ratio M-H, Fixed, 95% CI
0.005 0.1 1 10 200
Favours metabolic surgery Favours medical therapy

Bariatric/metabolic surgery is associated with lower odds of:

retinopathy: OR 0.52
95% CI 0.42–0.65; P<0.001

nephropathy: OR 0.39
95% CI 0.30–0.50; P<0.001

neuropathy: OR 0.27
95% CI 0.22–0.34; P<0.001

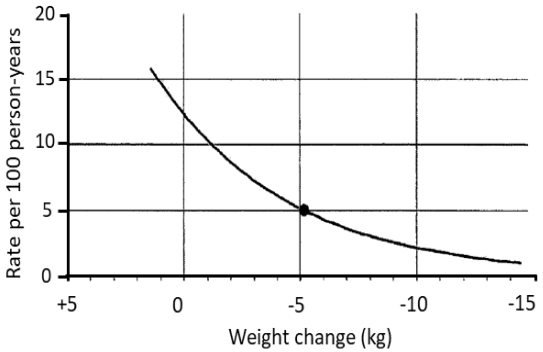
Meta-analysis, 3 RCTs, 9 cohort studies, follow-up 1-15 years

Chen *SOARD* 2021

How much?

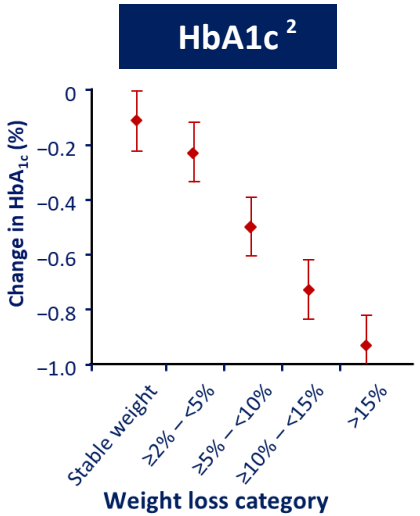
Glycaemic outcomes

Prevention[1]



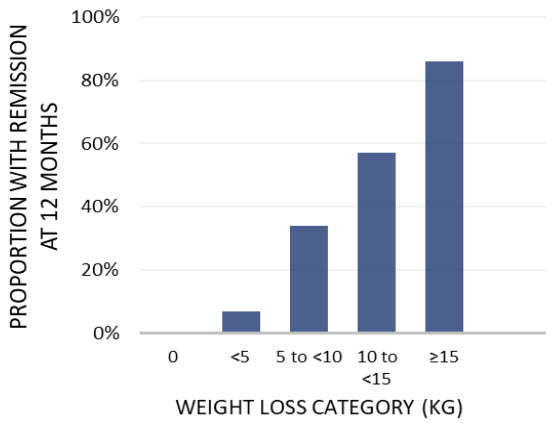
Each 1kg ↓ weight = 16% ↓ risk of T2D

Improvement

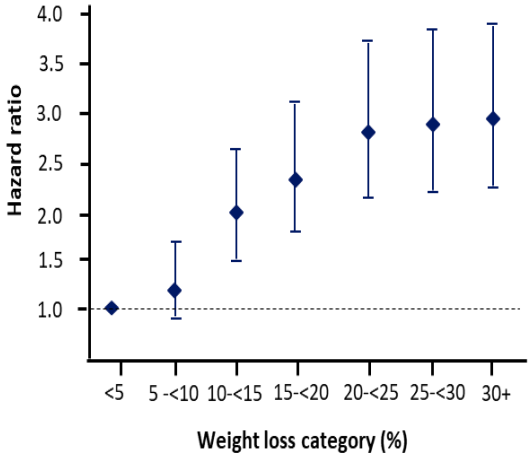


Remission

Lifestyle intervention[3]



Bariatric surgery[4]

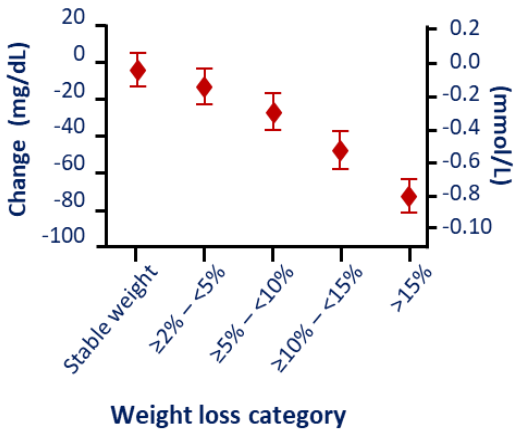


Figures for Look AHEAD 1y data[2] courtesy of Prof Donna Ryan

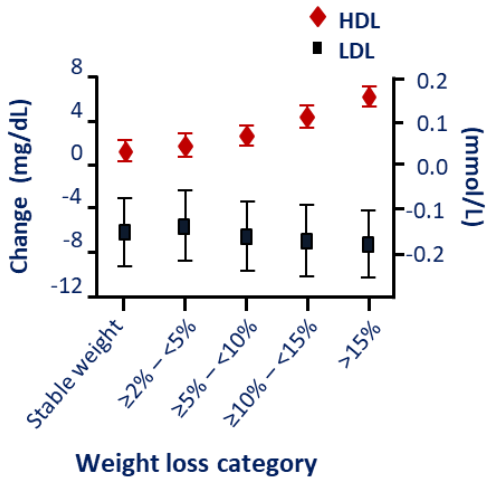
1. Hamman 2006; 2. Wing 2011; 3. Lean 2018; 4. Barthold 2021

Benefits beyond glycaemia

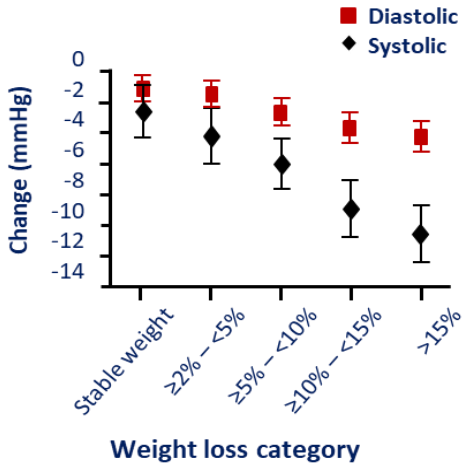
Triglycerides [1]



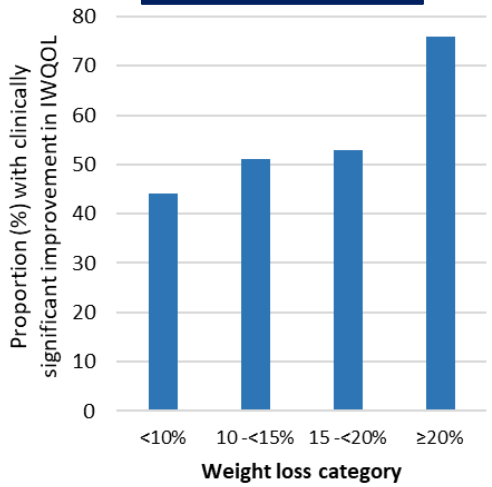
HDL and LDL [1]

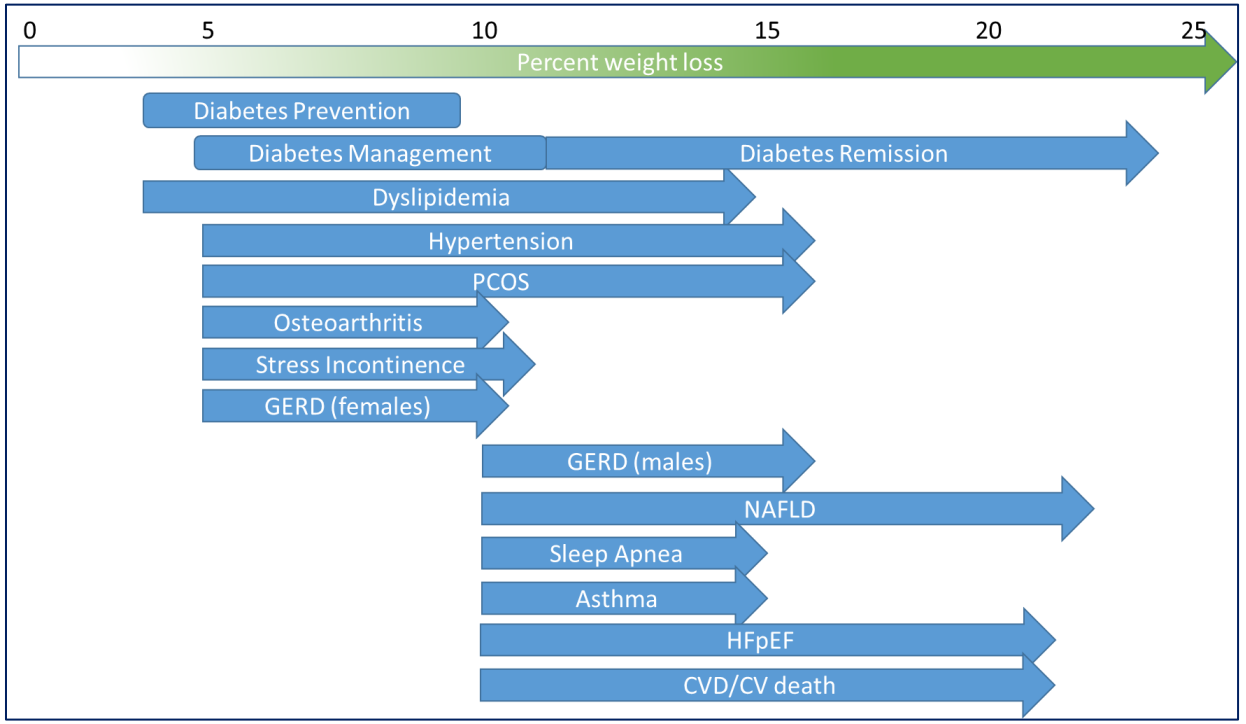


Blood pressure [1]



Quality of life [2]





Figures for Look AHEAD 1y data[1] courtesy of Prof Donna Ryan

1. Wing 2011; 2. Kolotkin 2001; 3. Lingvay 2022

Summary

- obesity/adiposopathy causes both insulin resistance and beta cell dysfunction
- weight loss
  - is beneficial regardless of stage of T2D
  - is beneficial even at <5%
  - >10% weight loss is disease-modifying and has wide-ranging impact
  - has upstream benefits on health and quality of life