



Glycaemia, diabetes, obesity: state of the (he)art



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Duality of Interest Declaration



Consulting/speaker honoraria:

Abbott Laboratories, AbbVie, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Hanmi Pharmaceuticals, Janssen, Menarini-Ricerche, Novartis, Novo Nordisk, Pfizer, Roche Diagnostics, Sanofi, ZP Therapeutics

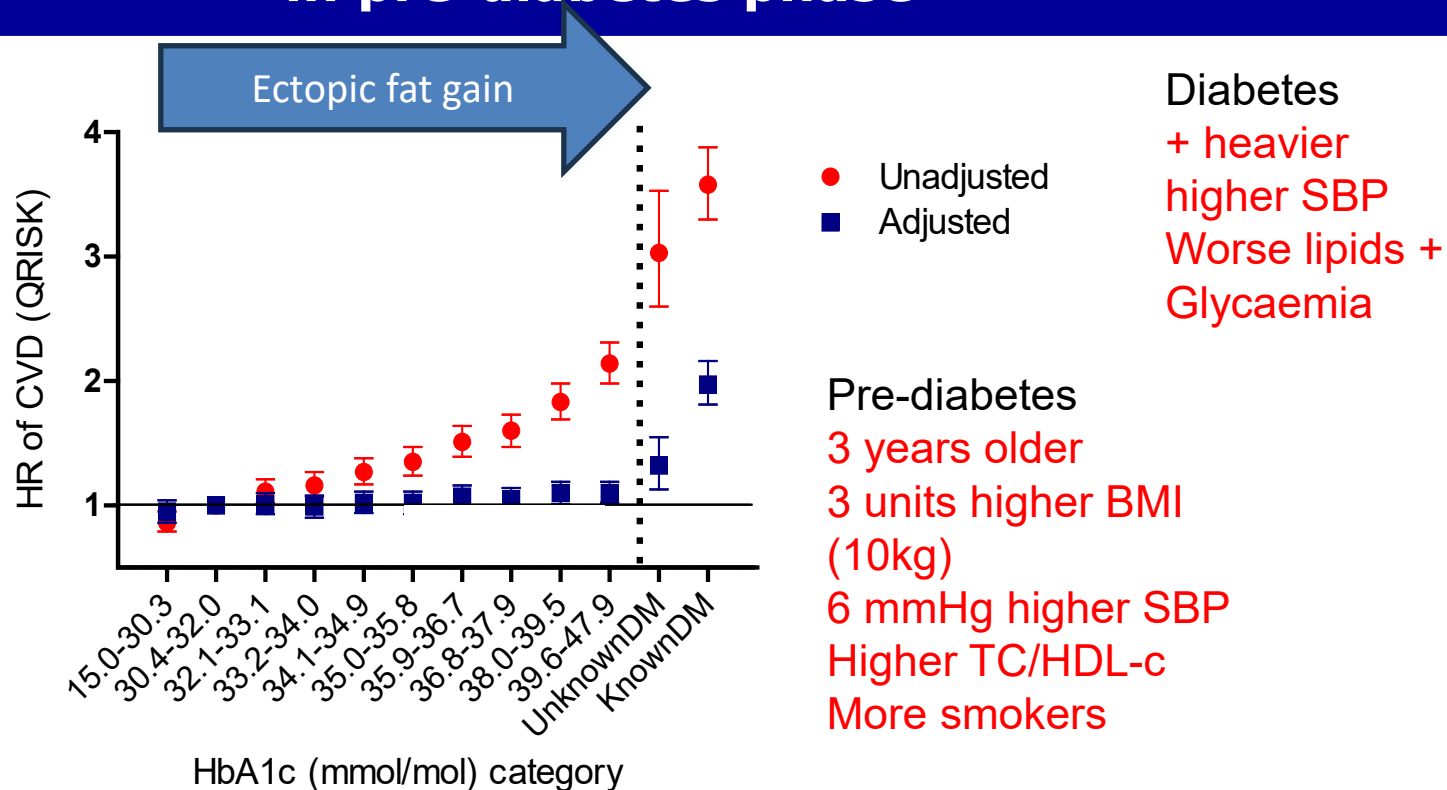
Grant: AstraZeneca, Boehringer Ingelheim, Novartis, Roche Diagnostics

Top lines: obesity much more important than realised

- Ectopic fat is upstream of T2D
- Obesity and ectopic fat critical to many T2D complications – genetics say same
- Disease patterns over time give clues
- Recent trial data also
- **If possible**, target weight change first in T2D



Diabetes risk >> doubles ASCVD but risk begins in pre-diabetes phase



Obesity- is causally upstream of

T2 Diabetes = ectopic fat!!!

Many with hypertension (salt intake?)

Dyslipidaemia = trigs = ectopic fat



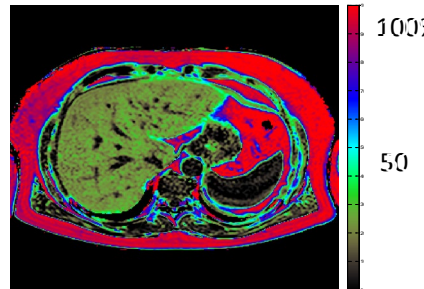
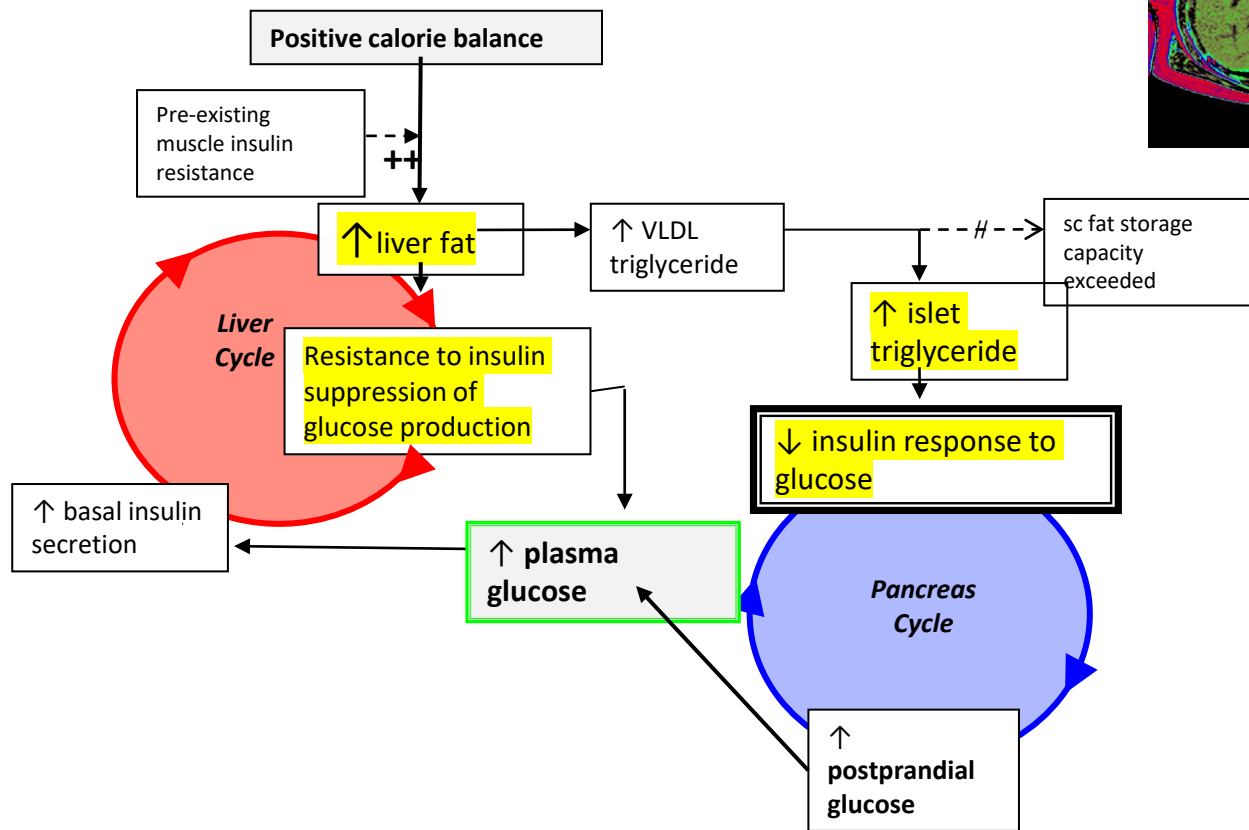
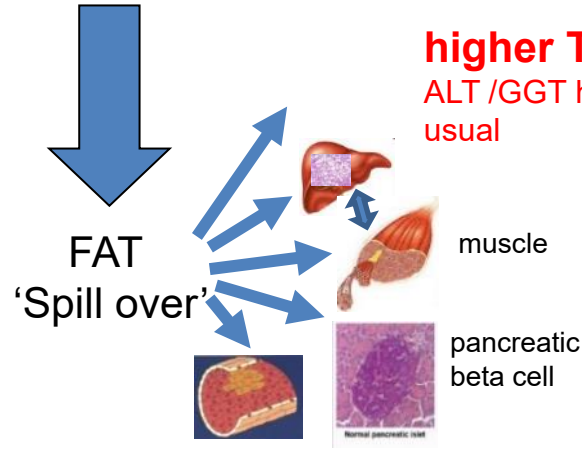
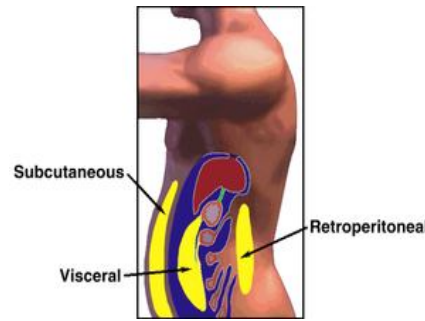


Fig 1

WEIGHT GAIN
Upstream (speed of
central fat accumulation,
dependent on age, sex
ethnicity)



higher TG / Low HDL-c
ALT /GGT higher than
usual

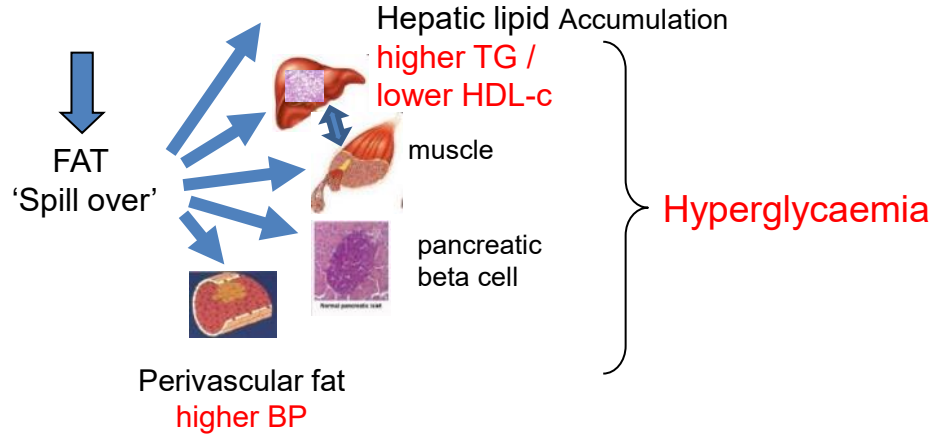
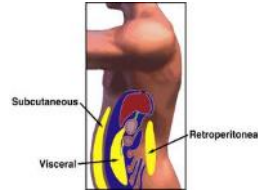
Hyperglycaemia (beta cell
failure) **HbA1c rises over time**
(broadly linear correlation to
BMI at given age)

Perivascular fat $\Rightarrow$ vasocrine signalling

Higher BP

Enhanced by higher salt intake linked to
higher calorie intake

Subcutaneous storage capacity **depends on**
age,
genes,
gender
FHx,
ethnicity)



Sattar and Gill
 (2014) BMC
 Medicine

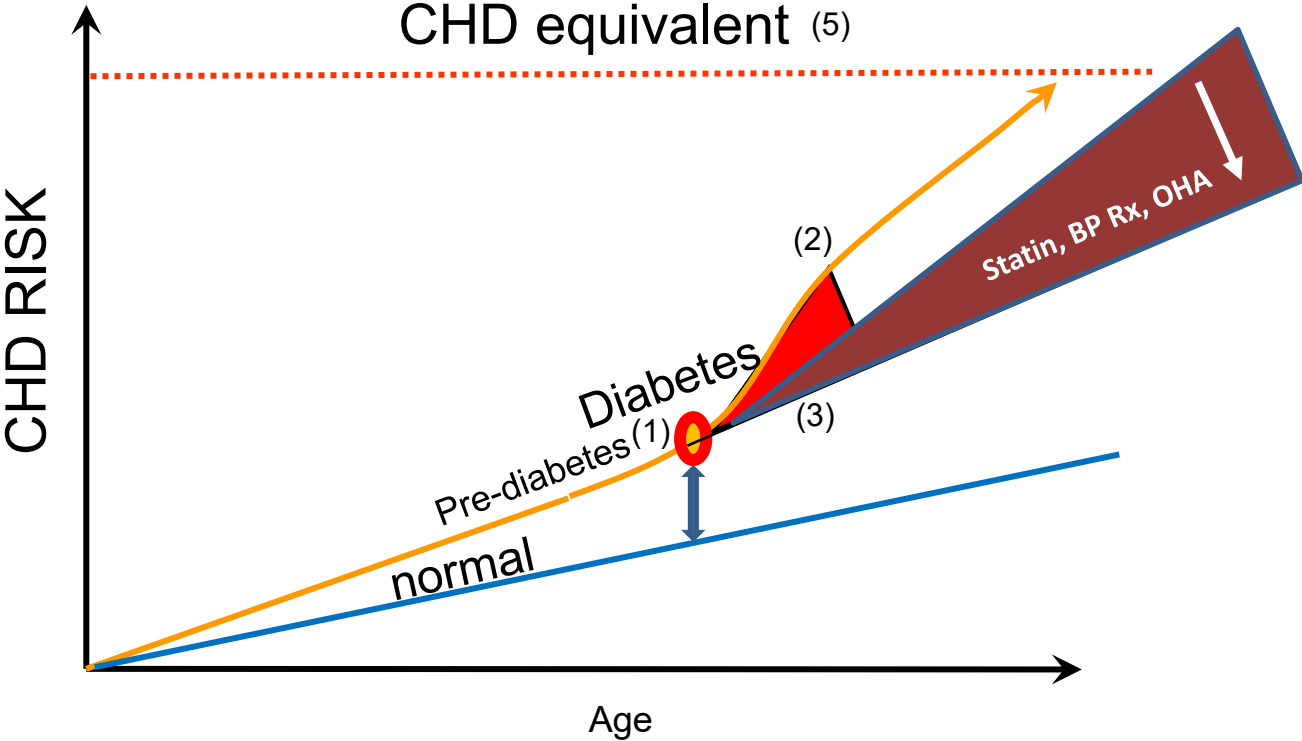
Giovanni – Giovanni –
 42 y/o 46 y/o
 FHx T2DM

82kg 88kg
 LDL-c 3.0 LDL-c 2.9
 Trig 2.1 Trig 3.1
 HDLc 1.1 HDLc 1.0

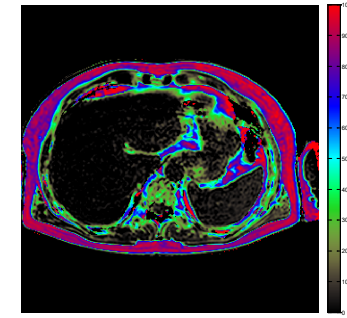
ALT 36 ALT 44
 HbA1c 44 HbA1c 49
 SBP 134 SBP 141

Less
 active

Fig 2

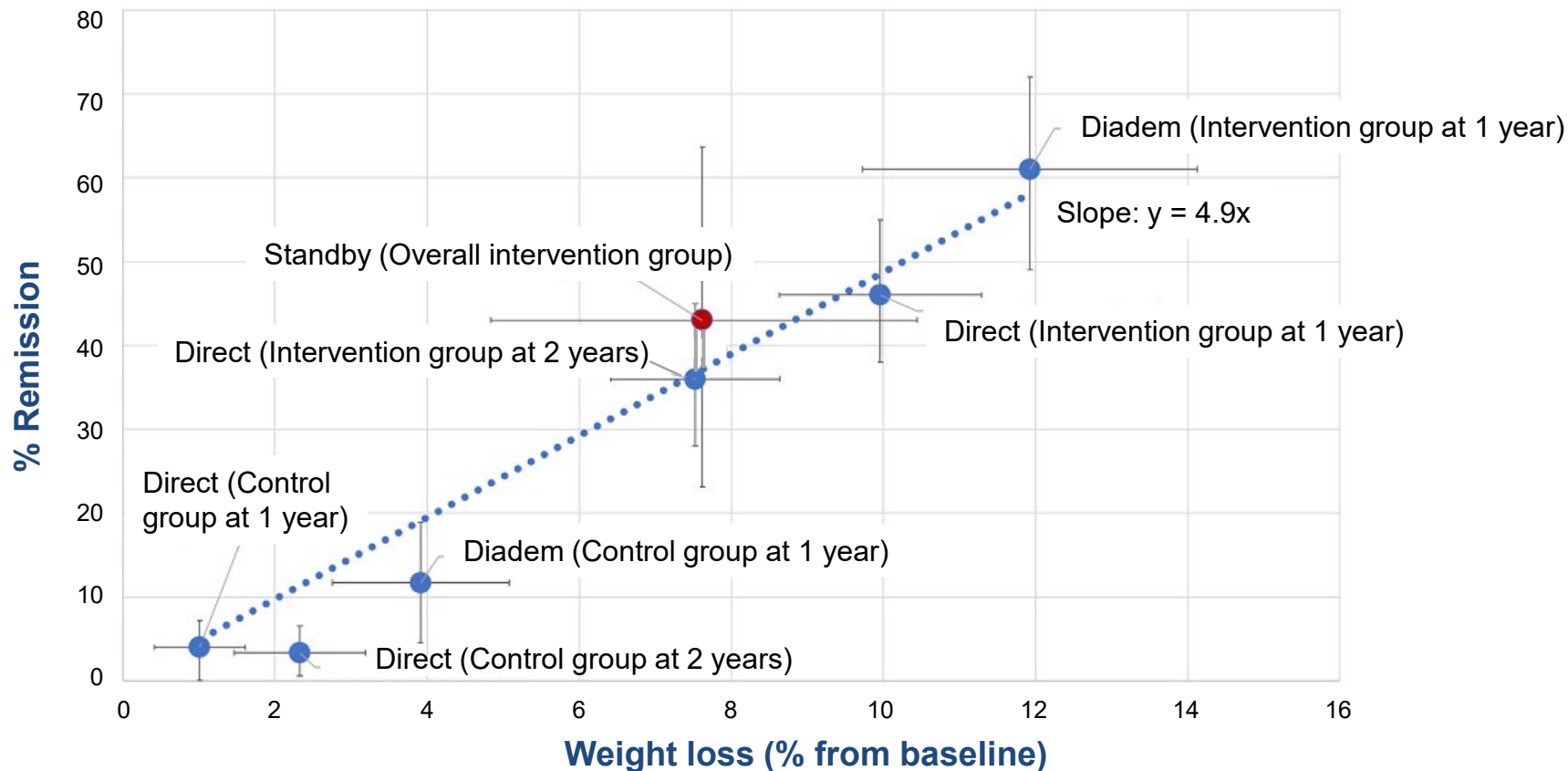


Weight loss?

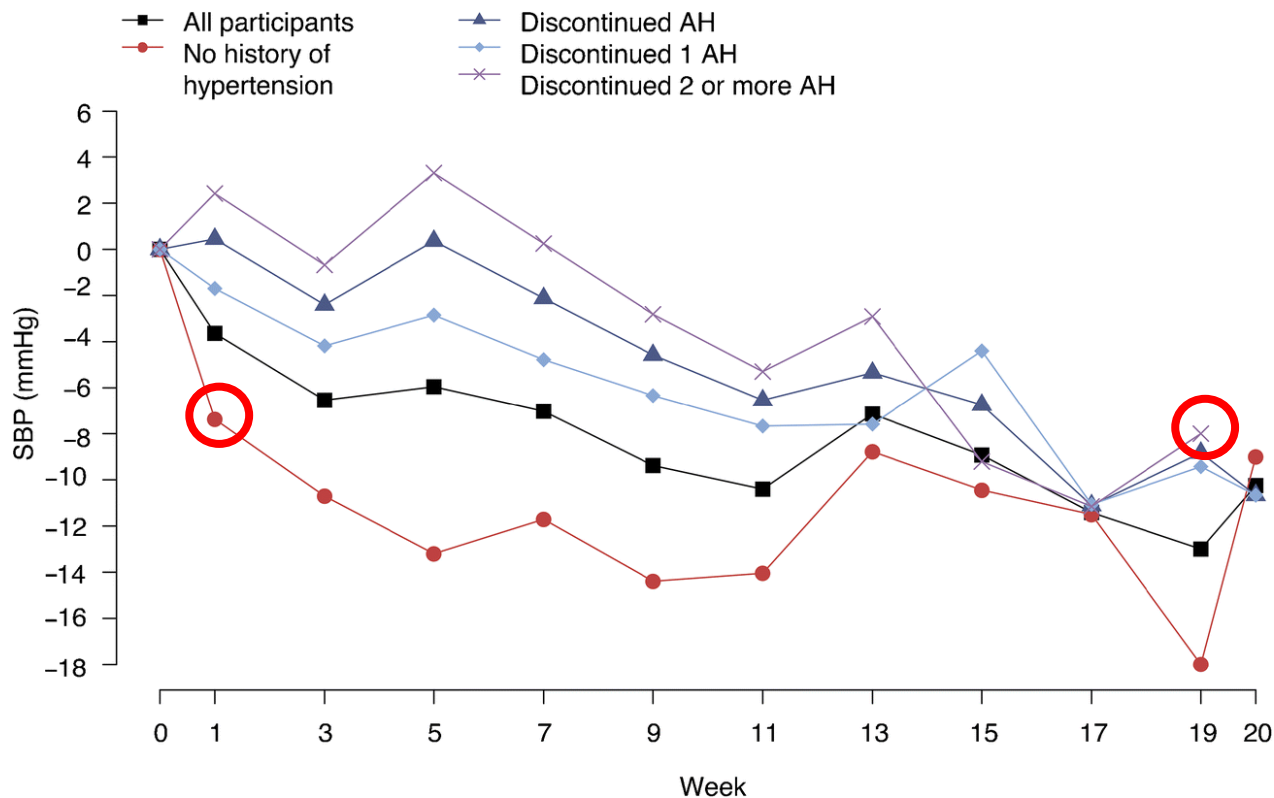


#1

Weight loss reverses diabetes in randomised trials (~5% remission per 1% wt loss **EARLY T2D short to medium term**)



SBP & weight change

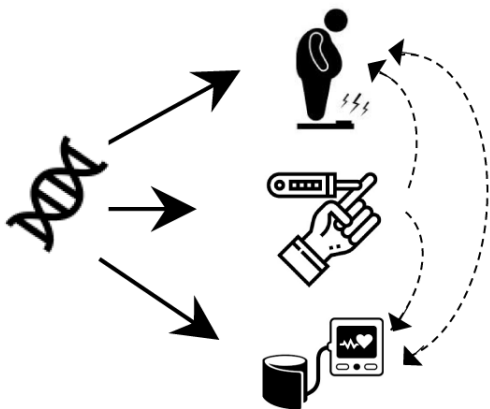


SBP down 8-10mmHg after low cal diet in T2DM with ~12kg weight loss
Including in those who stop AH meds!!! Natriuresis early on?

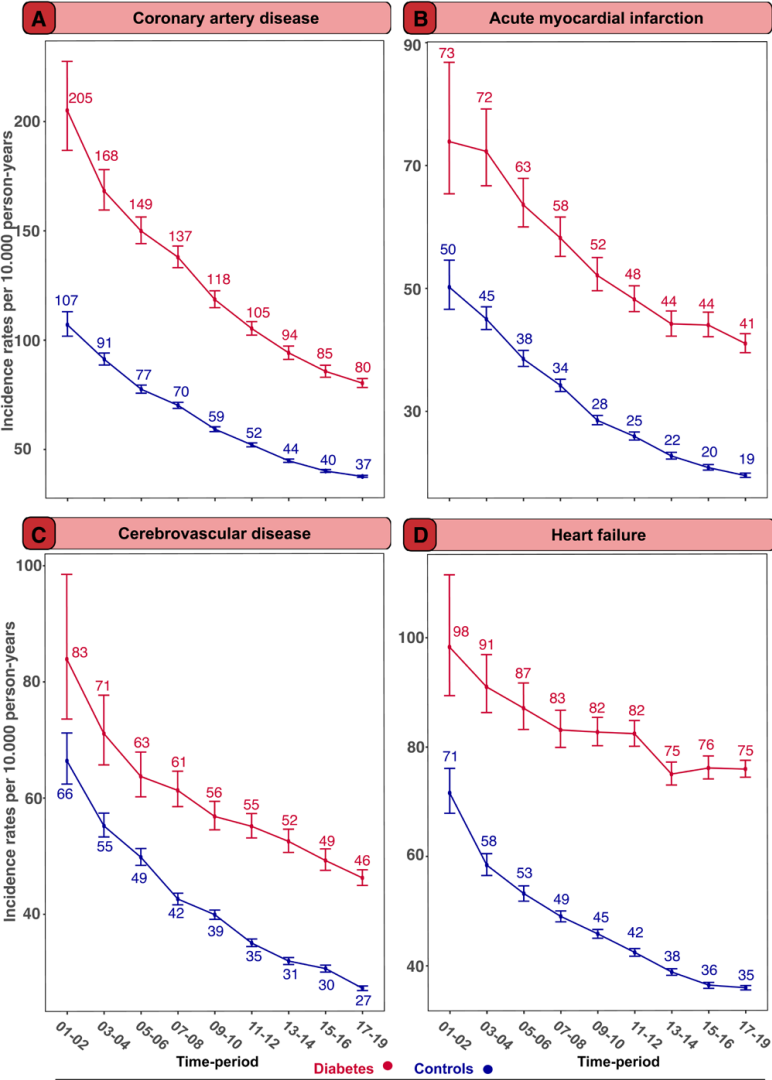
Leslie et al (2021) Diabetologia

↑ Evidence of causal independent effect

↑ Evidence of causal total effect



	Ischemic stroke	Intracerebral hemorrhage	subarachnoid hemorrhage	Cerebral aneurysm	Ischemic heart diseases	Heart failure	Atrial fibrillation	Myocardial infarction	Pulmonary embolism	Aortic aneurysm	Retinal vascular occlusion	Chronic kidney disease	Peripheral artery disease	Peripheral atherosclerosis
Independent effect	↑	X	X	X	↑	↑	↑	↑	↑	↑	X	↑	↑	↑
Total effect	↑	↑	↑	X	↑	↑	X	↑	X	X	X	↑	↑	↑
Medication effect	↑	↑	↑	↑	↑	↑	↑	X	X	↑	↑	↑	↑	↑



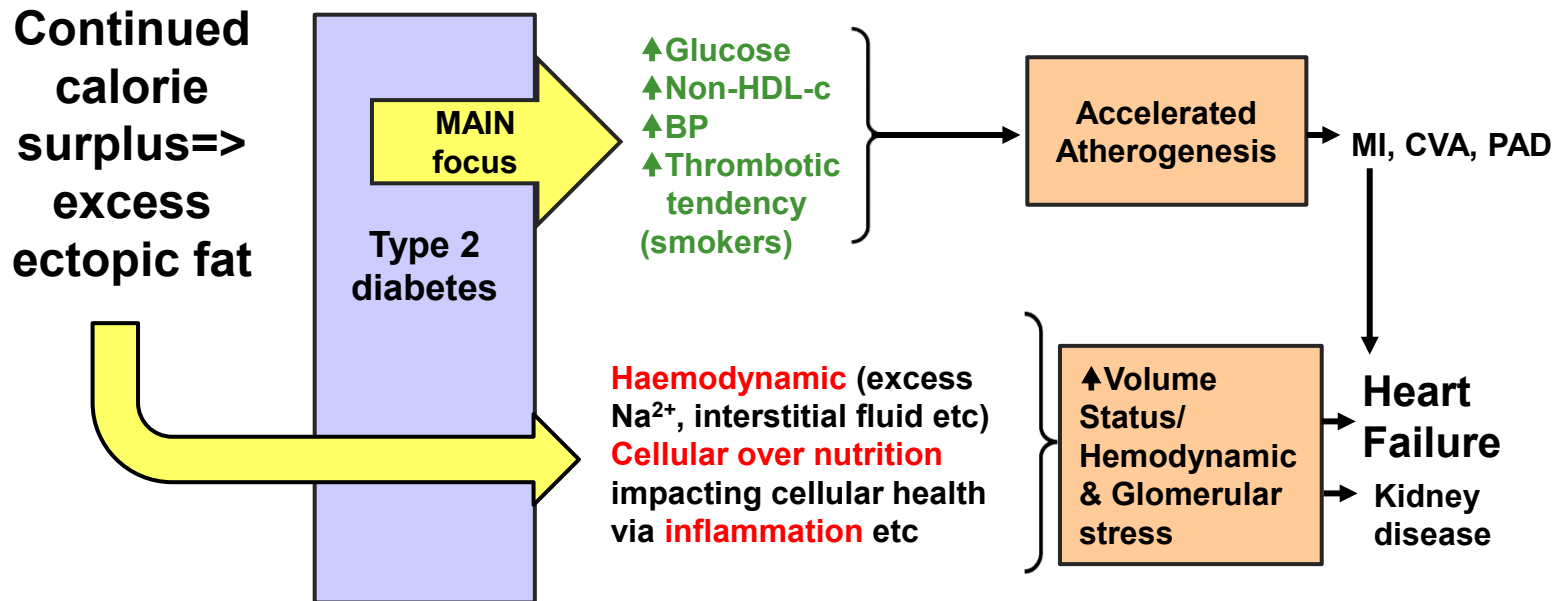
**Evidence from
Sweden – last 2
decades**

**Red T2D
Blue controls**

**HF not come down
as much**

Sattar, Rawshani et al (2023) Circulation

Higher BMI over years

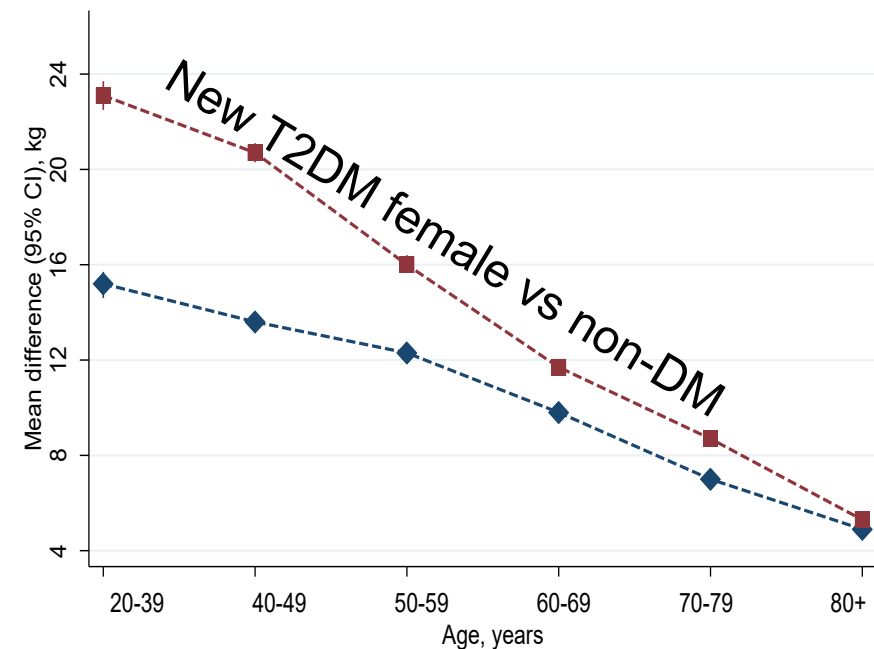


Glycaemia important BUT obesity more so

- Problem is we defined DM on glucose levels
- Weight up to get T2D in first place
- Years of excess and rising adiposity / ectopic fat stressing vessels and organs
- We've neglected as tools limited



Weight

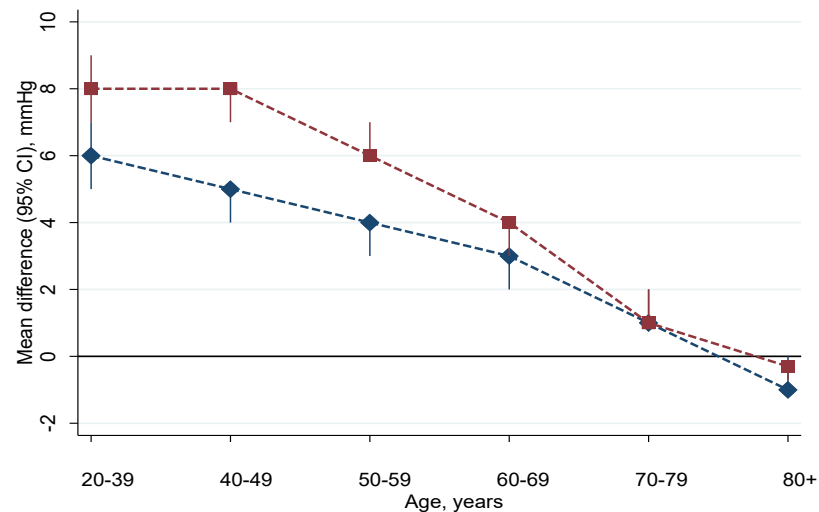


---■--- Women

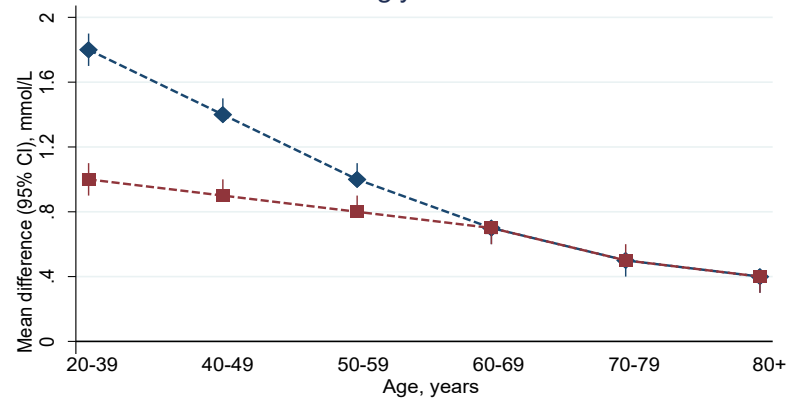
---◆--- Men



sBP



Triglycerides



- Trial data – what do they tell us
- Lowering glucose alone – very modest benefit on outcomes – no CV benefits from DPP4i, insulin, debate over metformin continues



SGLT2i & GLP-1RA in T2DM

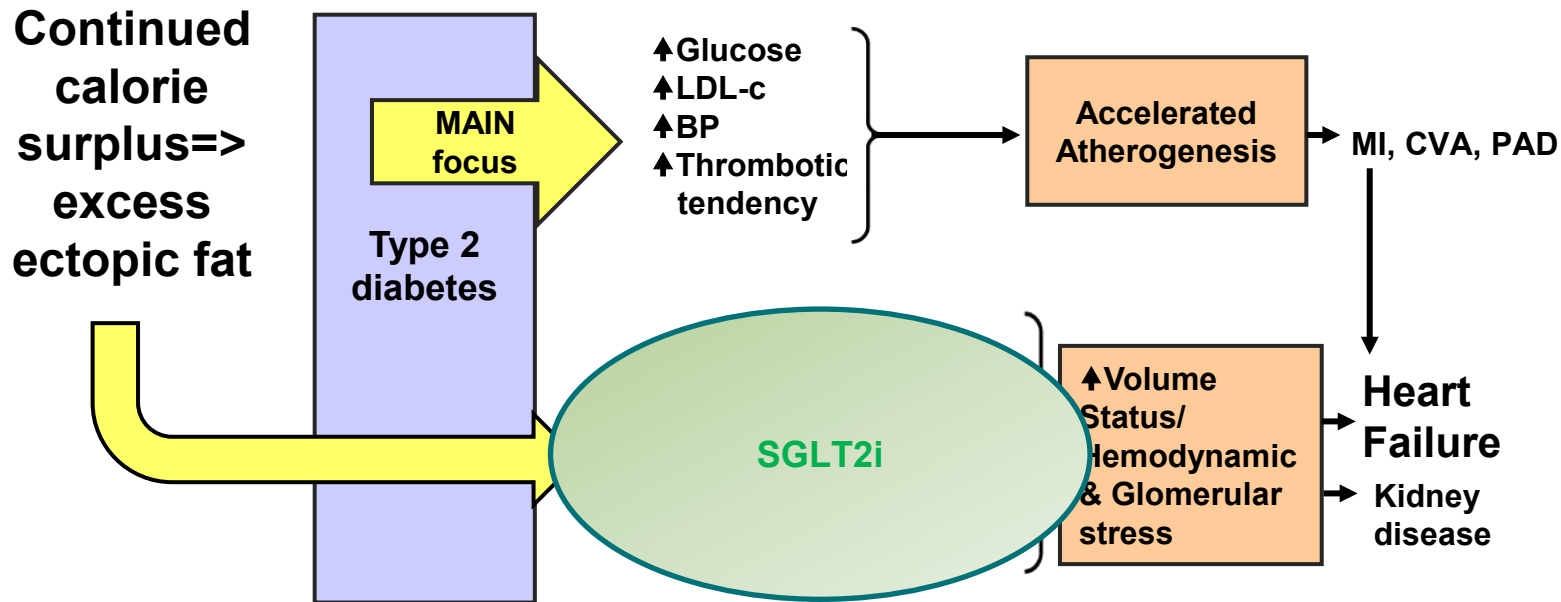
	SGLT2i	GLP-1RA - ELIXA
MACE	↓10%	↓15%
CV Death	↓15%	↓15%
MI	↓9%	↓12%
Stroke	↓4% NS	↓19%
HFH	↓32%	↓12%
CKD	↓38%	↓22% (TBC)

McGuire et al (2021) JAMA-C

Sattar et al (2021) Lancet DE

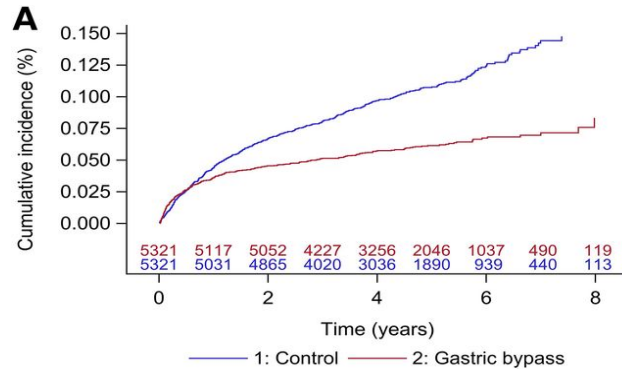
Higher BMI over years

TZP lowers SBP by 8 mmHg
10kg weight loss 50% DM remission

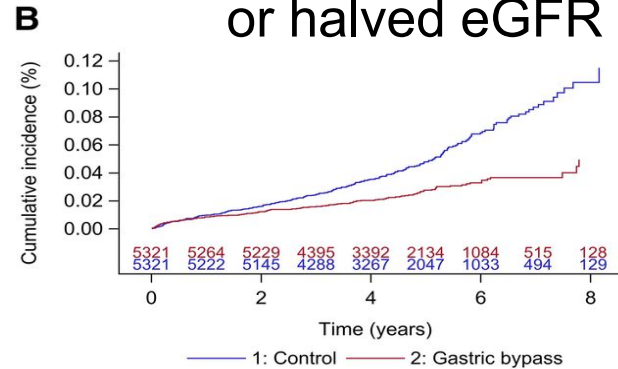


2b. Intentional weight loss bariatric surgery: not randomised – but give optimism?

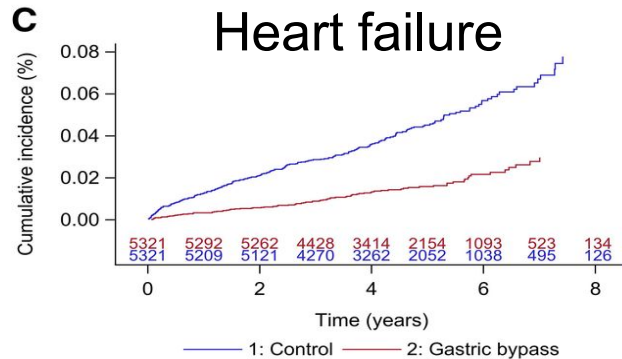
Macroalbuminuria



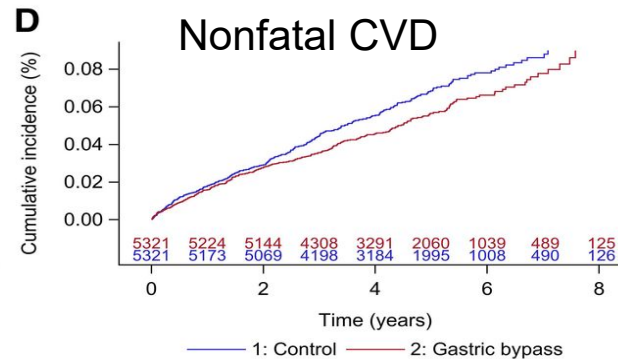
Severe renal disease or halved eGFR



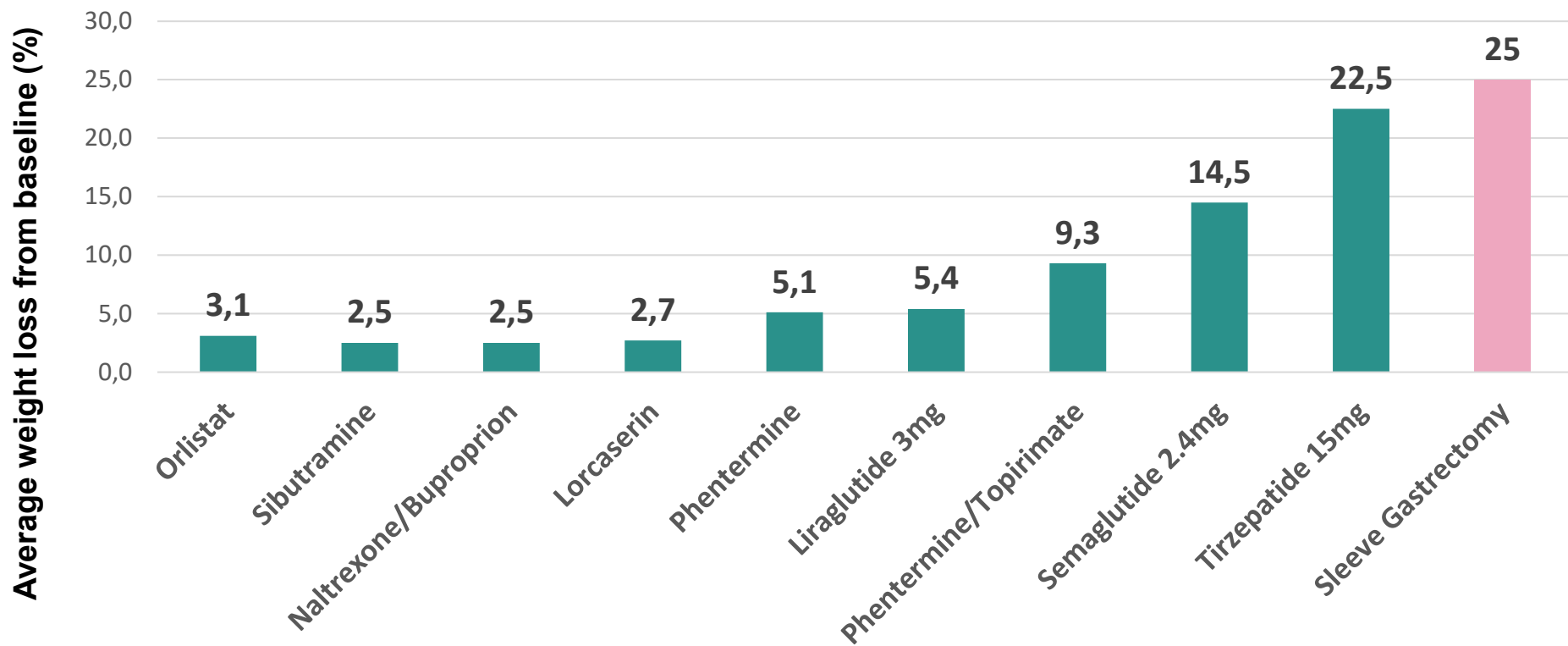
Heart failure



Nonfatal CVD



Average Weight Loss Achieved with Obesity Pharmacotherapies and Sleeve Gastrectomy



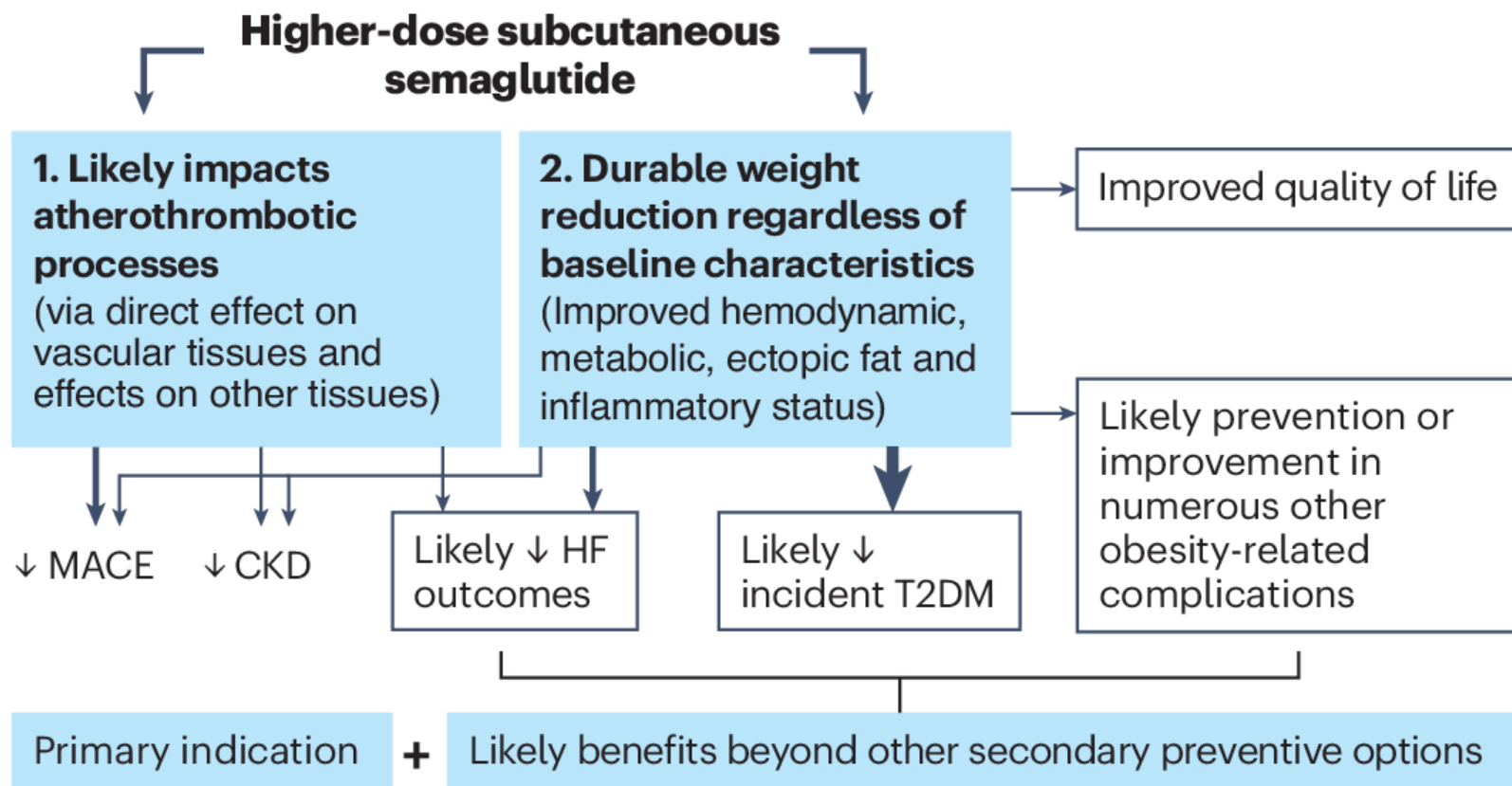
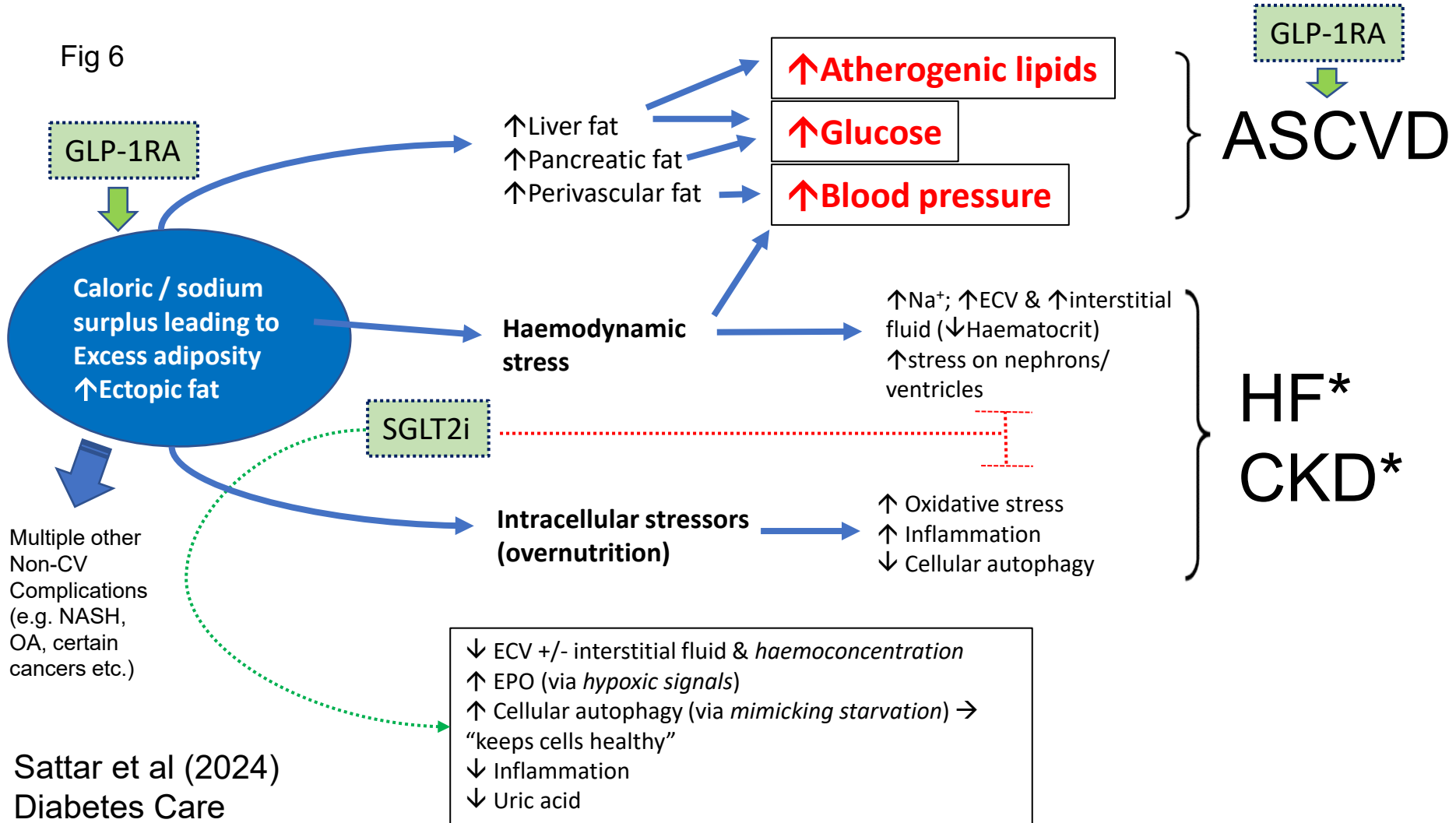


Fig 6



Proven benefits of treatments associated with intentional weight loss with LCDs or AOMs

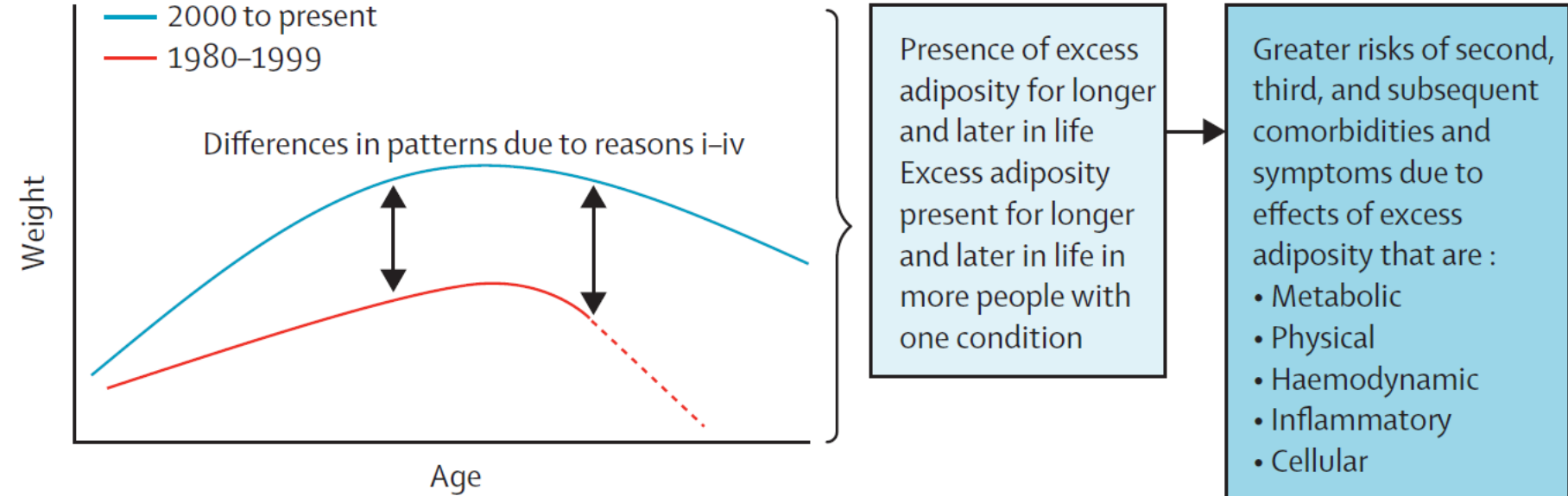
- ↑QOL, CR fitness **Yes**
- T2DM remission **Yes**
- BP reduction **Yes (up to 7/4 mmHg)**
- Improvement lipids **Yes (trigs, ↑HDL-c, ↓ non-HDLc)**
- Slow CKD **Yes (FLOW stopped early)**
- Prevent MI /CVA? **Yes (but extent weight impacts uncertain – SELECT)**
- HF benefits? **Yes (weight benefit clearer – STEPHfPEF trials)**
- Other CV conditions **AF; HFrEF; many others**
- **Cardiologists taking note**

Treating chronic diseases without tackling excess adiposity promotes multimorbidity



Naveed Sattar, John J V McMurray, Iain B McInnes, Vanita R Aroda, Mike EJ Lean

ESP. true for T2DM



Solution

Target weight management much earlier in many chronic conditions and upscale preventive policies

Conclusions



Ectopic fat upstream of diabetes and accelerates many complications



ASCVD risks down with statins, BP, but many other risks remain higher



GLP-1RA & SGLT2i: disease modifying in part by correcting pathways that link obesity to end-organ disease



Future T2D care to prioritise weight loss but tools currently expensive and more trial data awaited – must not forget lifestyle and prevention

