

Obesity will change the cardiovascular game

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Obesity will change the cardiovascular game!



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Duality of Interest Declaration



Consulting/speaker honoraria:

Abbott Laboratories, Afimmune, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Hanmi Pharmaceuticals, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Roche Diagnostics, Sanofi

Grant: AstraZeneca, Boehringer Ingelheim, Novartis, Roche Diagnostics

Options 2^o prevention expanded

BUT where is obesity?



Patients with or at high risk for ASCVD

Despite contemporary evidence-based therapies*, residual risk of ASCVD events persists

	Residual cholesterol risk	Residual inflammatory risk	Residual thrombotic risk	Residual triglyceride risk	Residual Lp(a) risk	Residual diabetes risk
Critical biomarker	LDL-C \geq 100 mg/dL	hsCRP \geq 2 mg/L	No simple biomarker	TG \geq 150 mg/dL	Lp(a) \geq 50 mg/dL	HbA _{1c} fasting glucose
Potential intervention	Targeted LDL/Apo B reduction	Targeted inflammation reduction	Targeted antithrombotic reduction	Targeted triglyceride reduction	Targeted Lp(a) reduction	SGLT2is GLP-1RAs
Randomised trial evidence	IMPROVE-IT FOURIER SPIRE ODYSSEY	CANTOS COLCOT LoDoCo2 ZEUS	PEGASUS COMPASS THEMIS	REDUCE-IT PROMINENT	Planned	EMPA-REG CANVAS DECLARE CREDENCE LEADER SUSTAIN-6 REWIND

LDL-c main issue

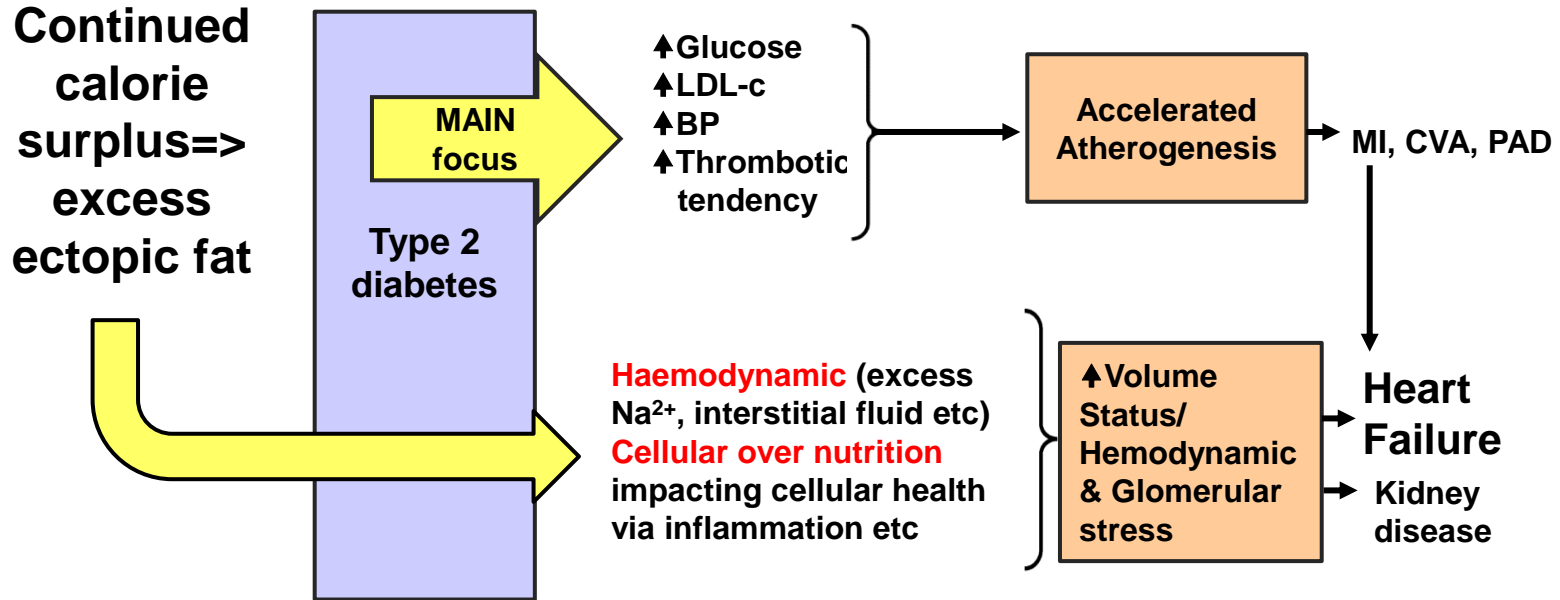
GLP-1RA /SGLT2i

Why not bothered about weight loss?

- The evidence base is poor and don't believe obesity is causal for outcomes that matter to me
- And, do not believe we can change weight much or for long enough?
- Too busy with more clever interventions?



Higher BMI over years



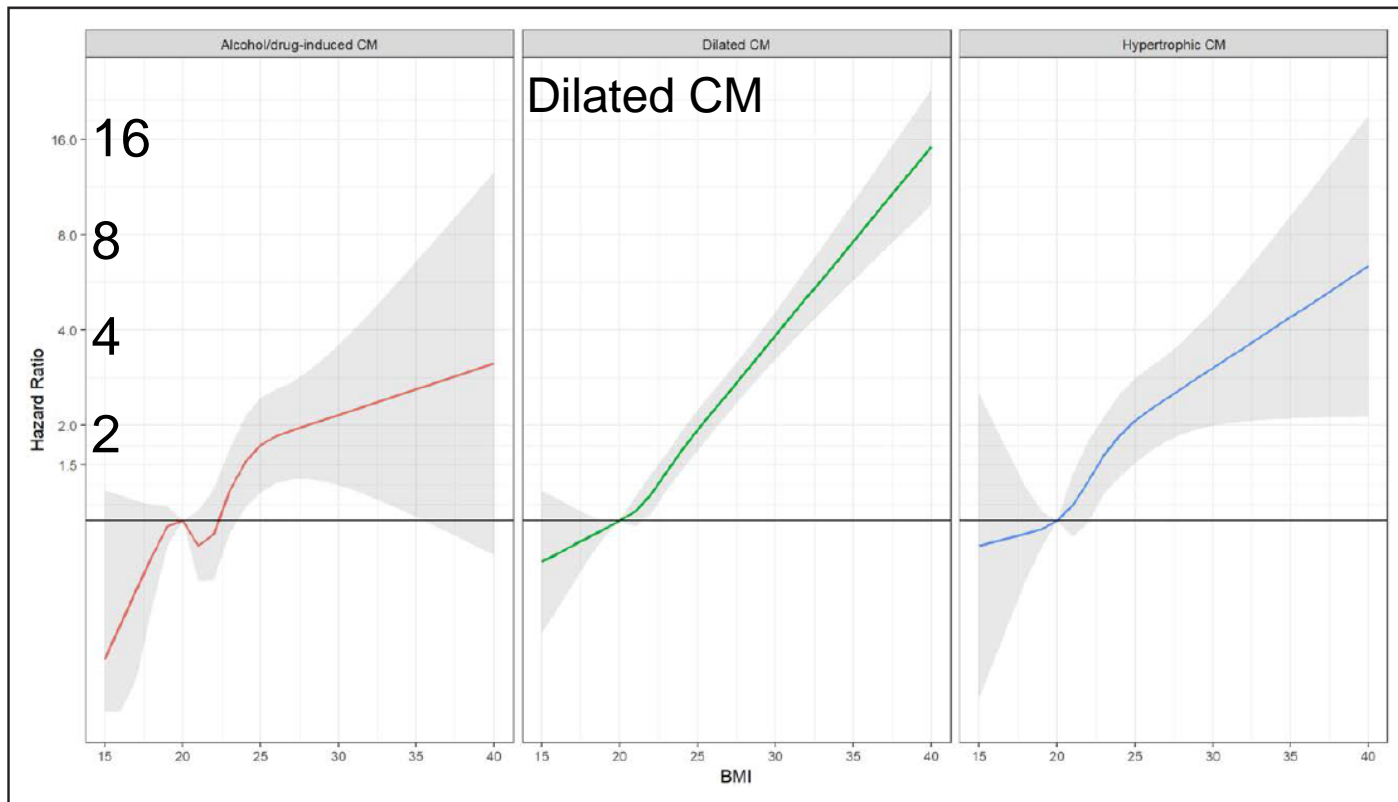
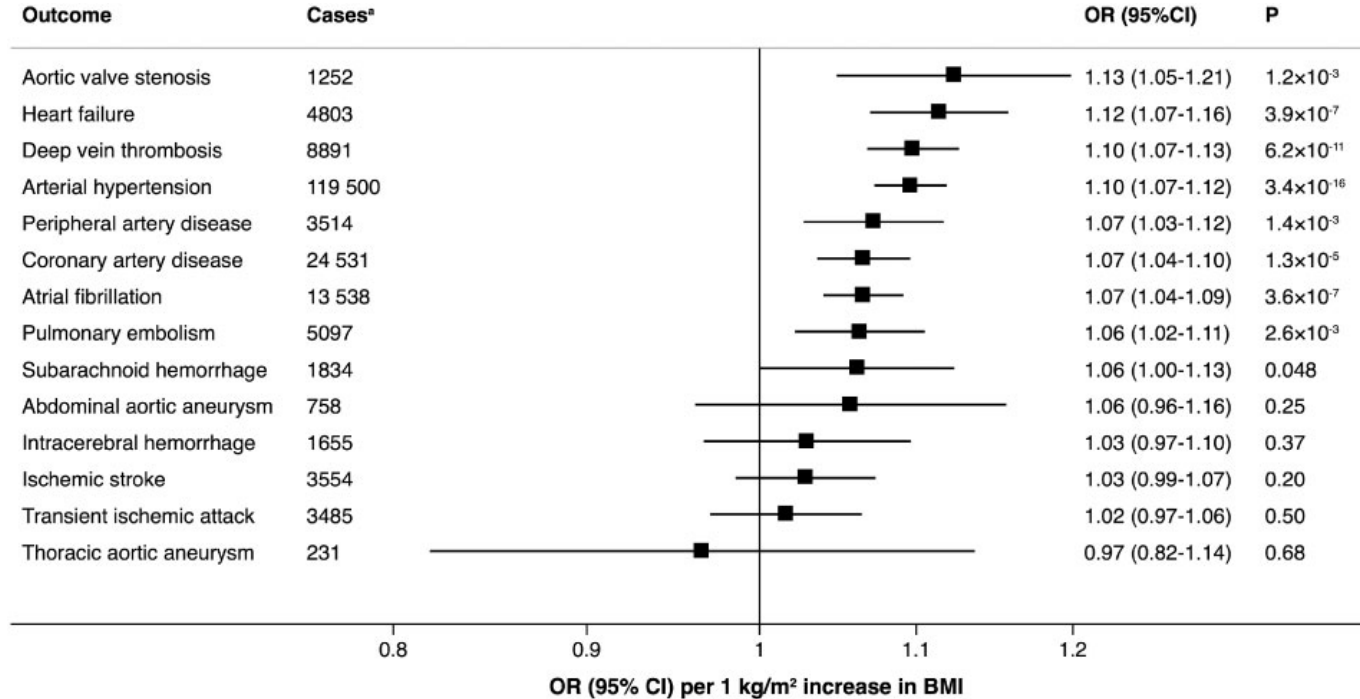


Figure. Association between body mass index (BMI) at conscription and risk for cardiomyopathy (CM).

The model was adjusted for age, conscription year (as a spline with knots at 5%, 35%, 65%, and 95%, ie, 1971, 1982, 1992, and 2004), test center, and baseline comorbidities (diabetes mellitus, hypertension, congenital heart disease), systolic blood pressure, diastolic blood pressure, cardiorespiratory fitness, muscle strength, parental education, and alcohol or substance use disorder ($n=773\ 679$). BMI was restricted to BMI between 15 and 40 kg/m² and modeled as a restricted cubic spline with knots at 5%, 35%, 65%, and 95% (ie, 18.0, 20.5, 22.4, and 27.5 kg/m²), with BMI of 20 kg/m² as reference. The unadjusted model is presented in Figure II in the online-only Data Supplement.

Genetically higher BMI and CVD outcomes

Larsson et al (2019) EHJ

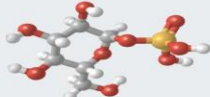


Large scale intentional weight loss

Rapid
Days/weeks



↓ Liver fat



↓ Glucose

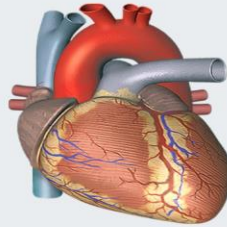


↓ Triglyceride



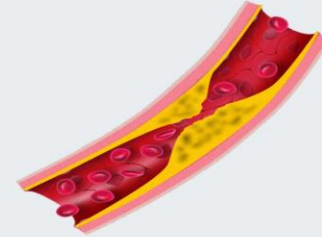
↓ BP

Intermediate
Likely few months
(More data needed)

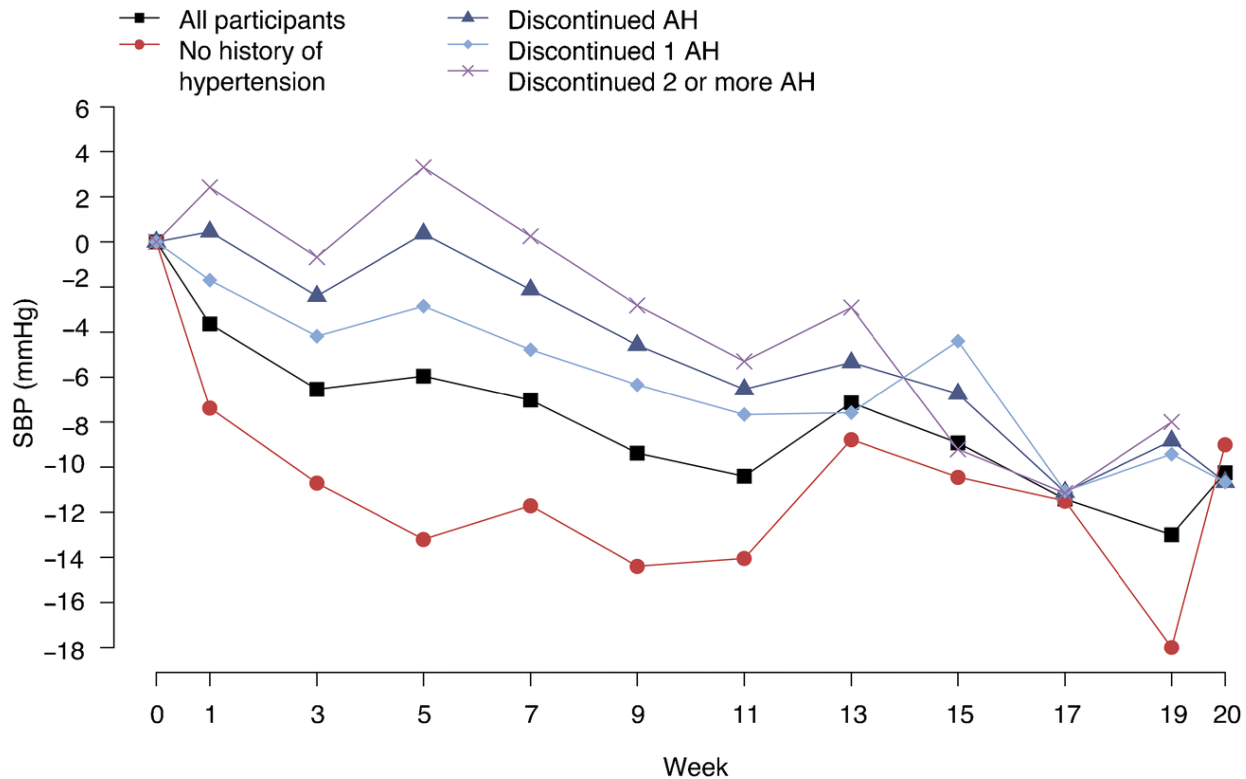


Favourable cardiac
remodelling

Longer
Likely years



↓ Atherosclerotic
cardiovascular disease



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

Leslie et al (2021) Diabetologia

↑ blood triglyceride
(LDL-C not necessarily high and could be at target)



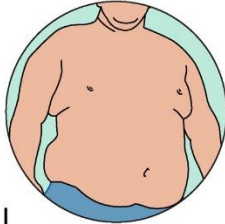
①

Exclude secondary causes
(e.g. excess alcohol, nephrotic
syndrome, hypothyroidism)



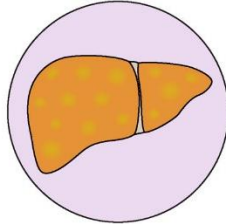
②

Check for signs of
excess adiposity?
(overweight or obese)



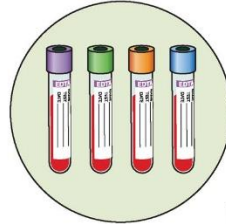
③

Check for excess liver fat
intermediates (e.g. *high-normal*
ALT (±GGT) levels OR
liver ultrasound /MRI)

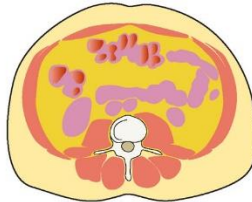


④

Check for dysglycemia?
↑HbA1c or fasting glucose?
Ask about family history of
type 2 diabetes



If Yes (to 2, 3, ±4), consider high triglyceride to be ectopic fat



Suggest weight loss ± ↑ activity

typically, 1.5 to 18
mmol/l

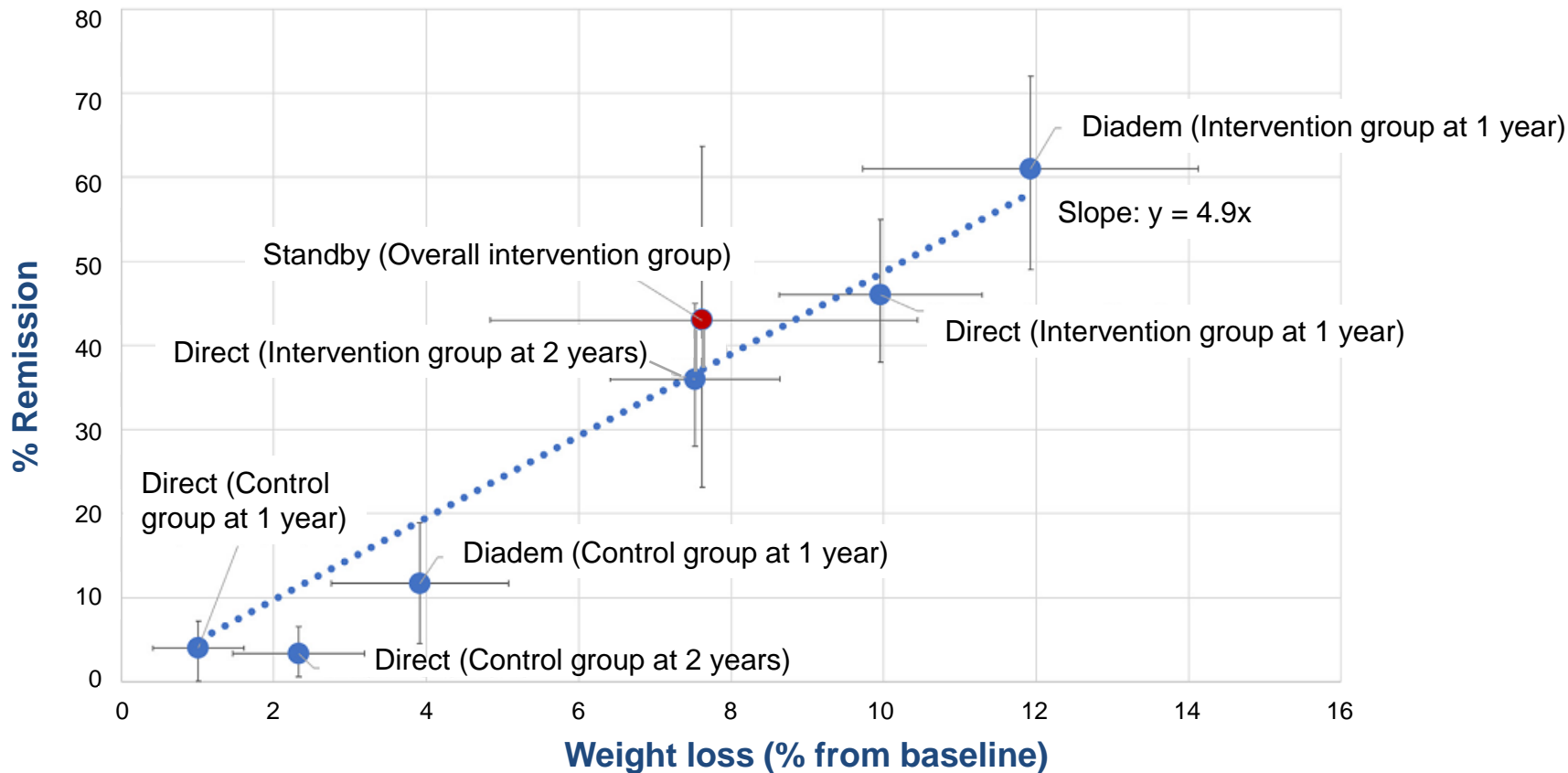
19kg weight gain

Lost once pandemic
abated

Trib back to 2mmol/l
ALT 81 to 22

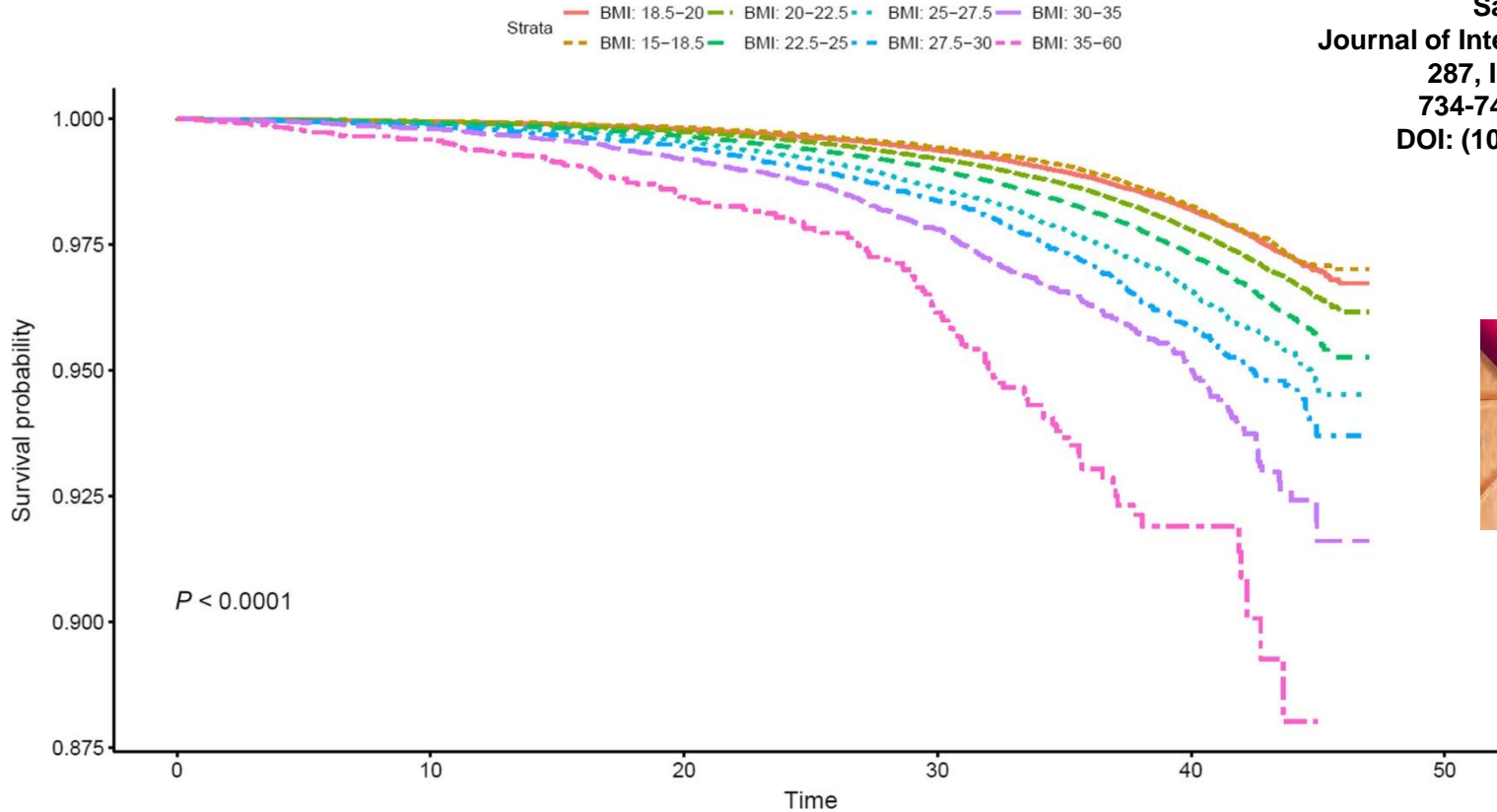
If diagnosis correct, triglyceride, ALT, GGT, HbA1c levels will often improve in parallel with weight loss providing motivation to sustain weight improvements and lower cardiovascular and diabetes risks

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

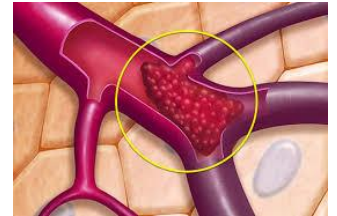


Obesity in adolescent men ↑ risk of VTE in adult life

Kaplan–Meier plot for Venous thromboembolism by BMI



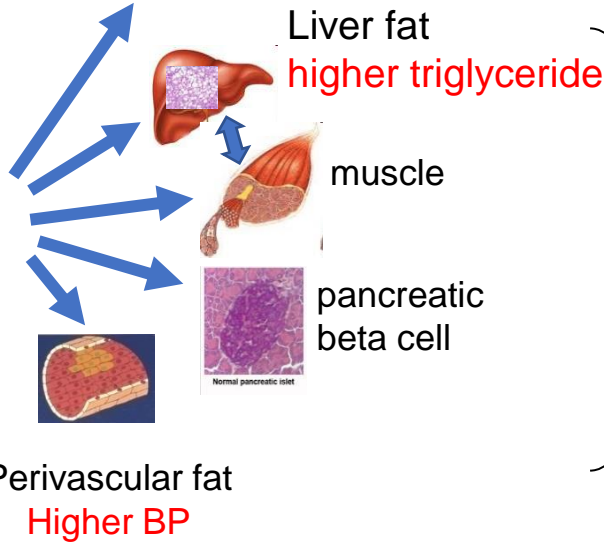
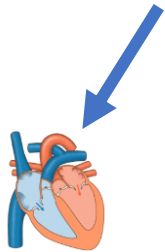
Sandblad et al
Journal of Internal Medicine, Volume:
287, Issue: 6, Pages:
734-745 27 April 2020,
DOI: (10.1111/joim.13044)



Calories surfeit + salt (increased intake or reduced energy expenditure)

Excess total and ectopic weight

FAT 'Spill over'



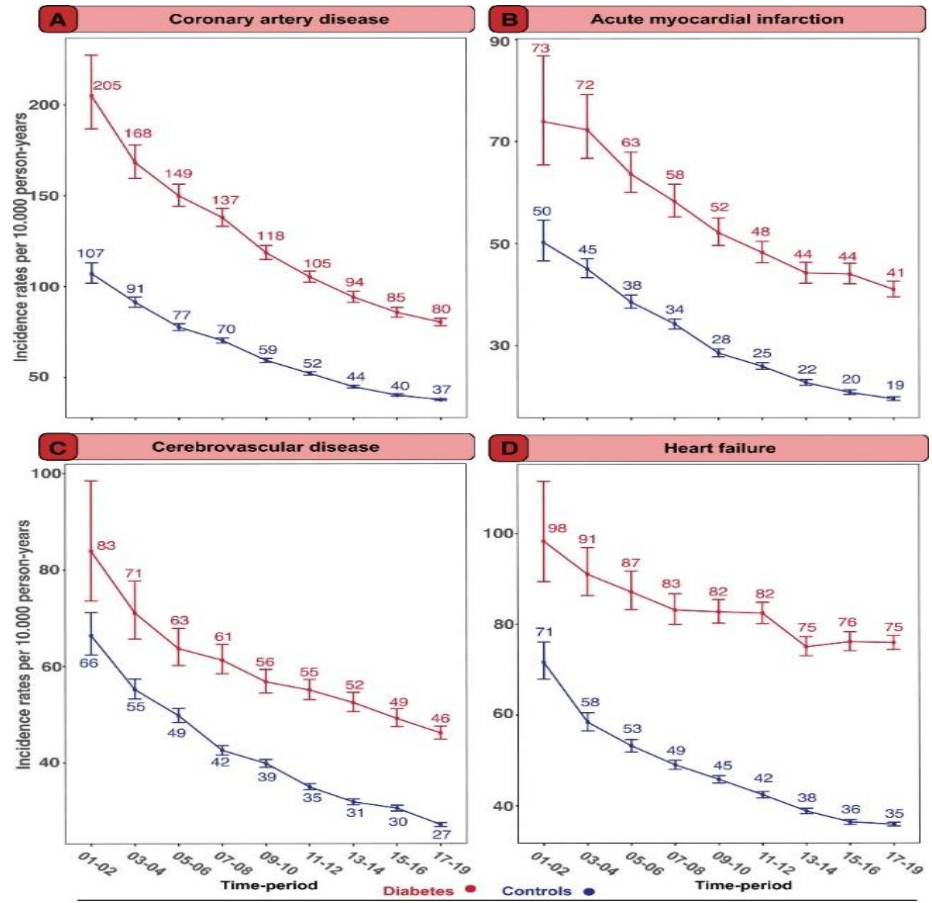
But other CV risk factors
LDLc, smoking

Greater Insulin resistance

Hyperglycaemia

(beta cell failure)

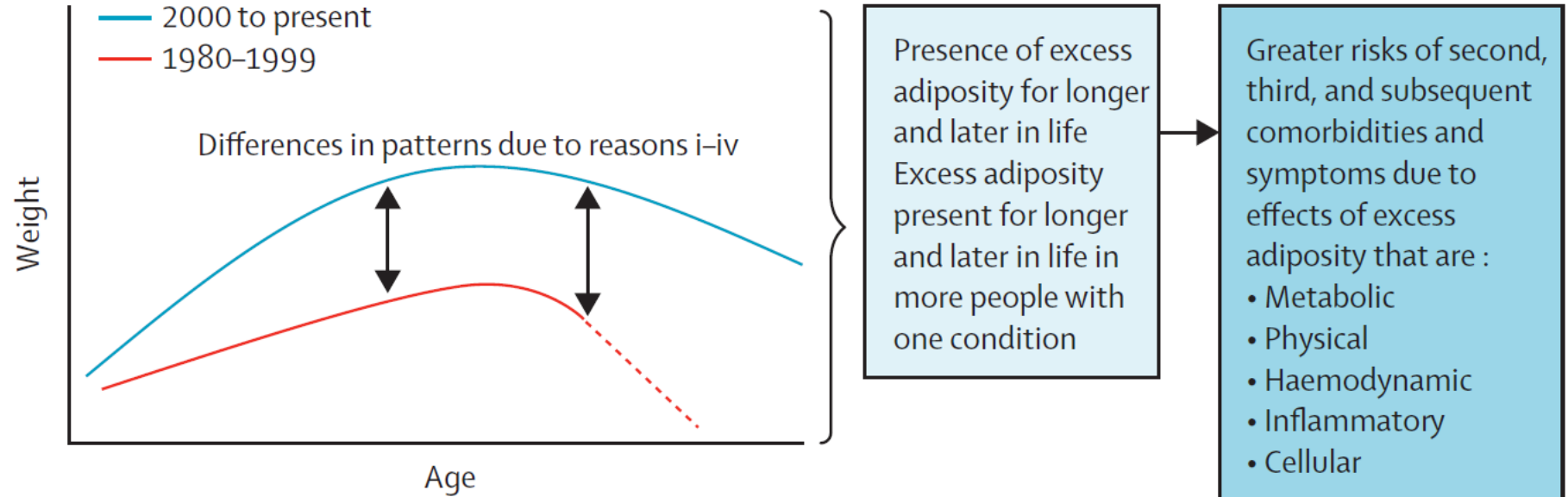
Change in CV risks in diabetes and general population in Sweden over the last two decades



Treating chronic diseases without tackling excess adiposity promotes multimorbidity



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



Solution

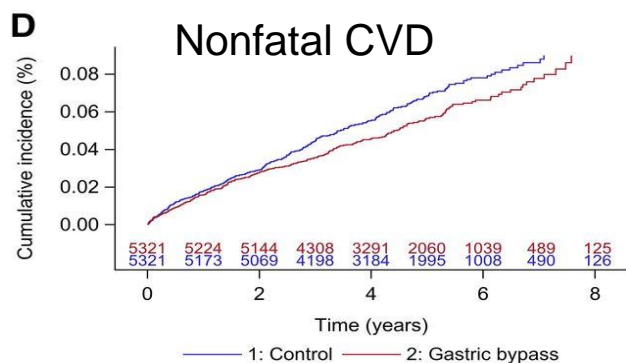
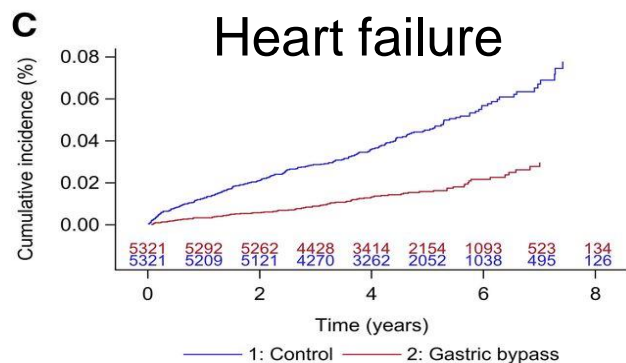
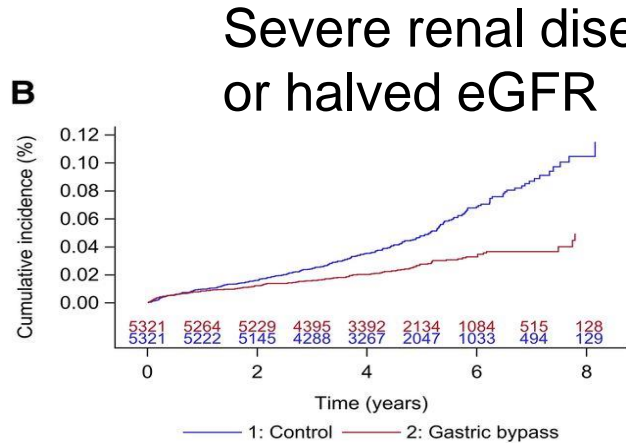
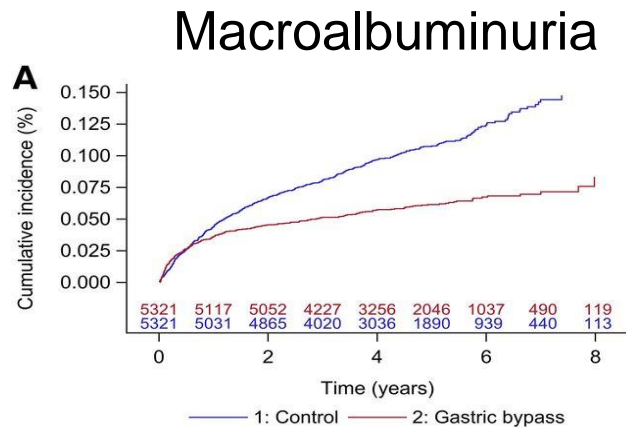
Target weight management much earlier in many chronic conditions and upscale preventive policies

Evidence for weight loss and CV outcomes?

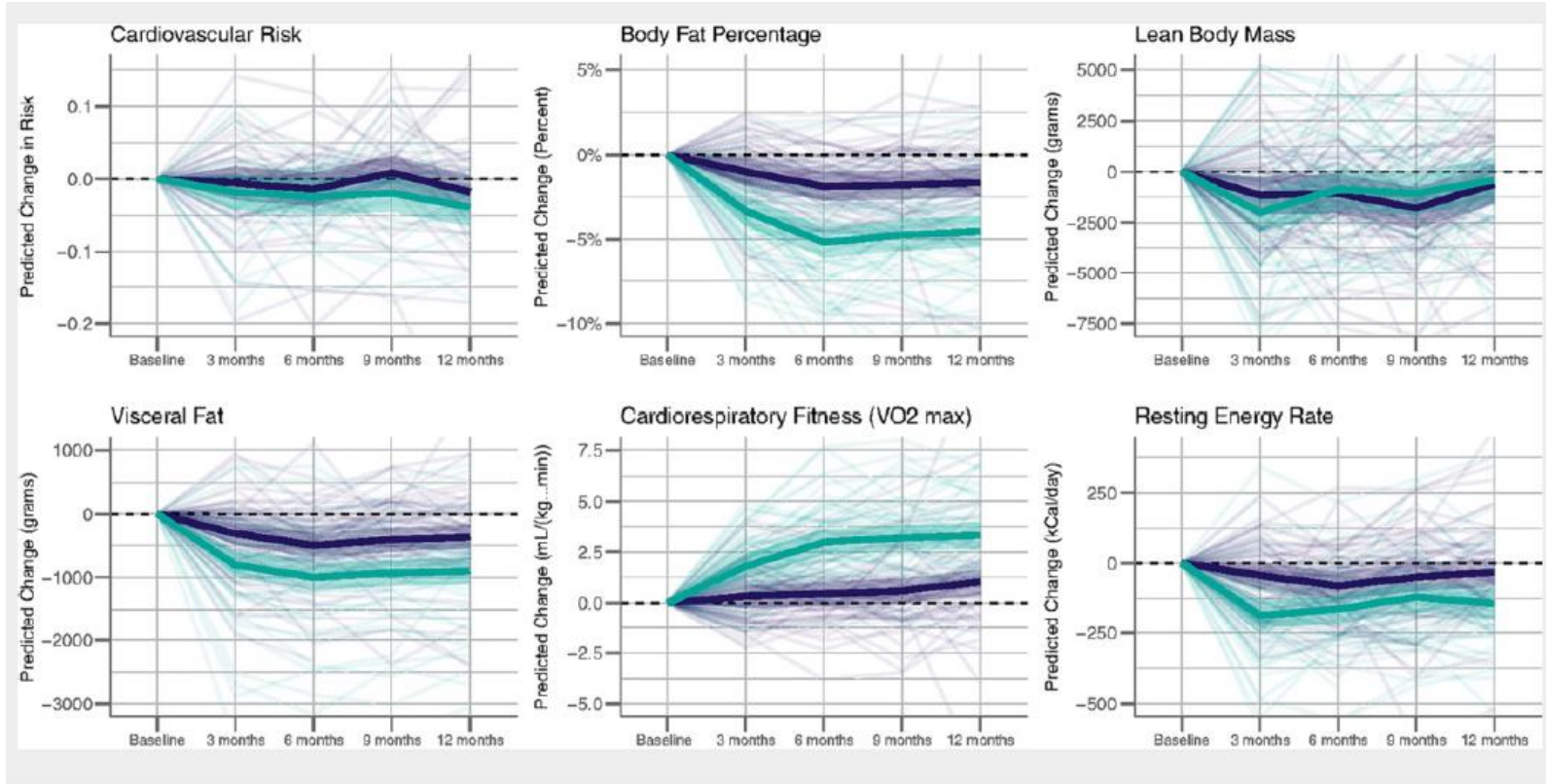
1. Risk factors: BP, DM, trigs, **YES**
2. Surrogate evidence – observational, surgery, biomarkers, other types? **Yes**
3. **Trial outcomes?**



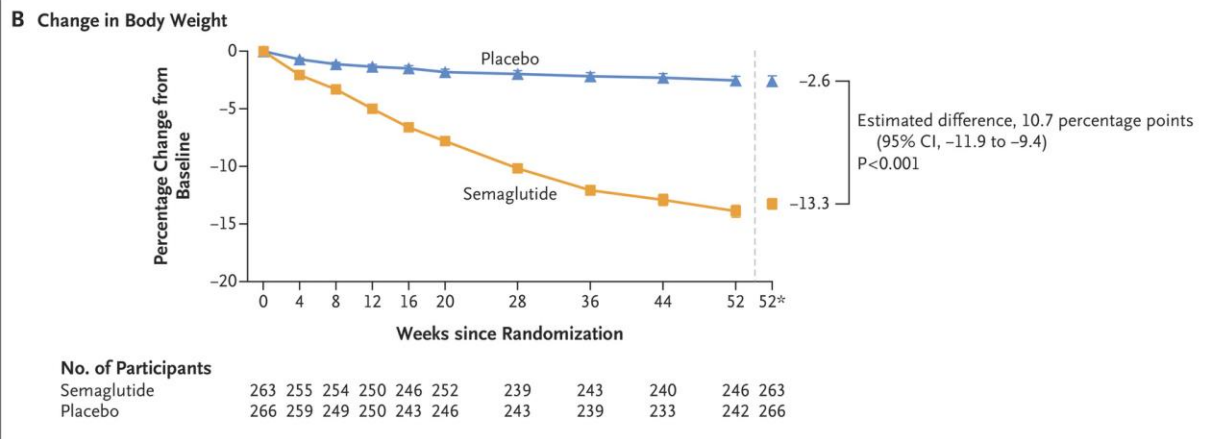
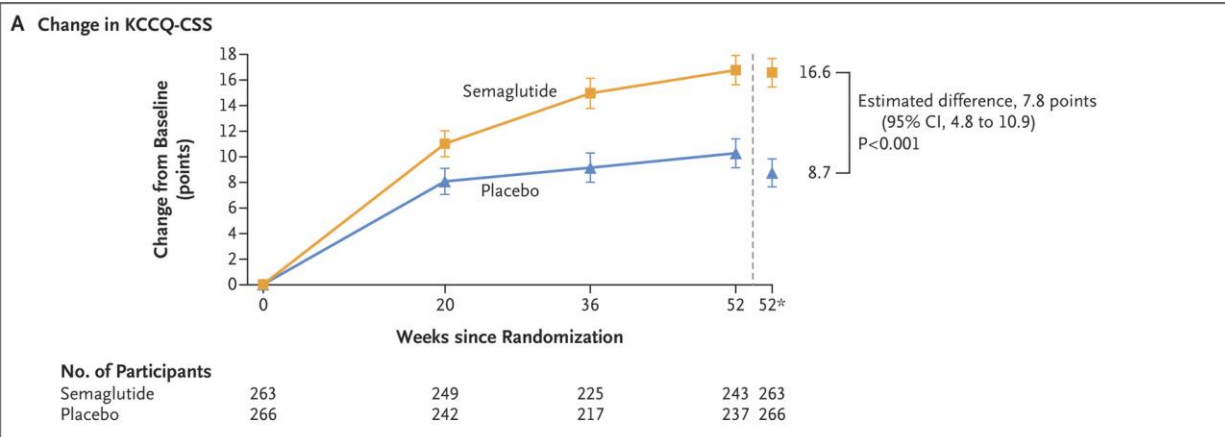
2b. Intentional weight loss bariatric surgery: not randomised – but give optimism?



Proteomic marker changes with 10% weight loss suggest rapid improvement in CR Fitness and 20% lower CV outcomes



STEP HFpEF



- 10.7 % weight loss – 7.8 KCCQ improvements

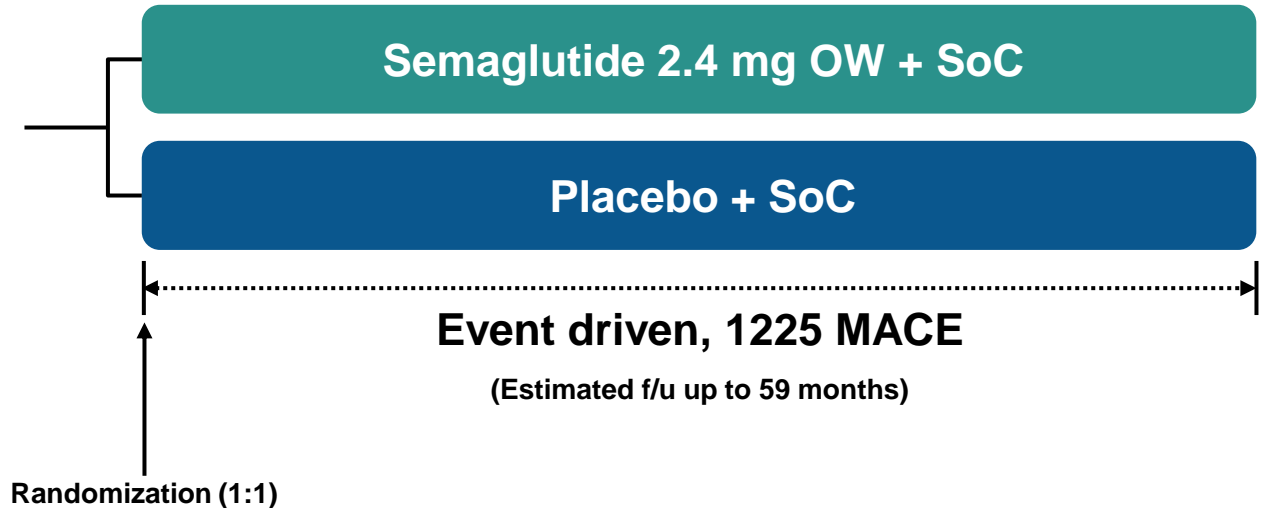
- REDUCTION in NT-proBNP
- 6 min walk test improved

- How much weight loss vs direct effects of Semaglutide?

Hard to properly quantify BUT weight loss likely key

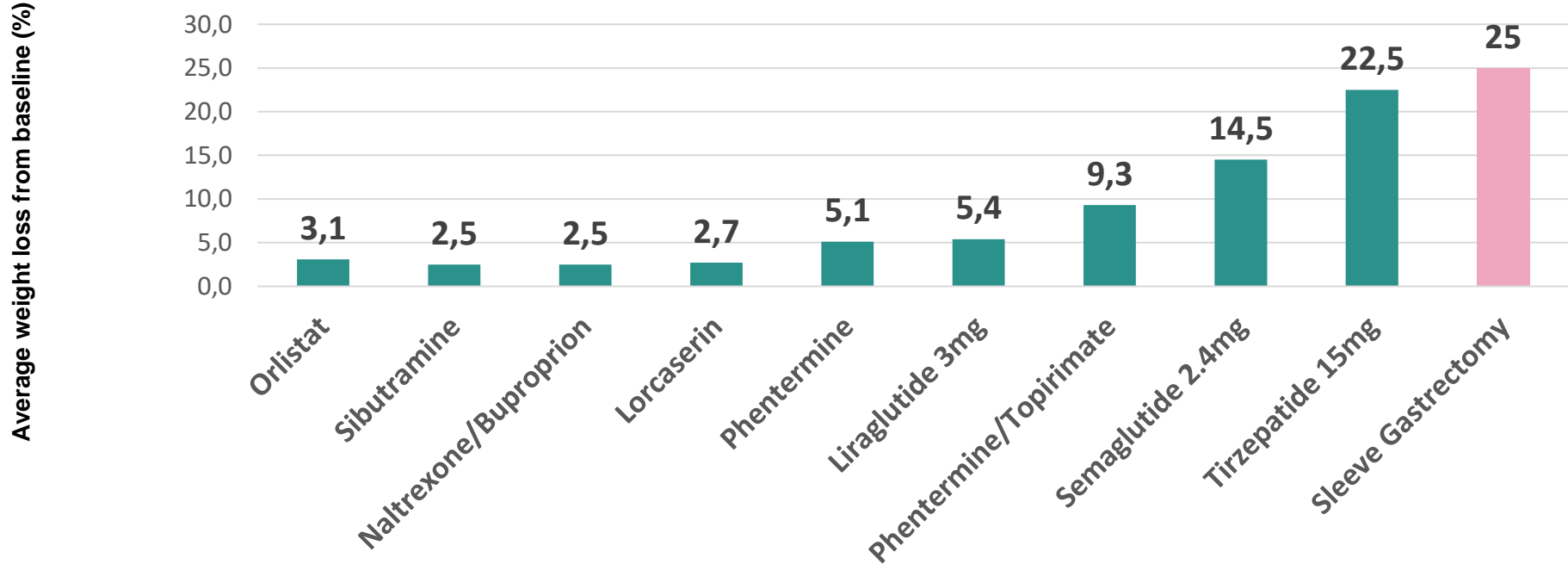
SELECT trial

- N=17,500
- Age ≥ 45 years
 - BMI ≥ 27 kg/m²
 - HbA1c $< 6.5\%$
 - Prior MI, stroke or PAD



1° outcome: CV death/MI/stroke – 20% lower
Not positive in hierarchal outcomes BUT nominal
Lower all cause mortality, HF & weight loss 8.5kg & improved QOL
and less SAE than with placebo

Average Weight Loss Achieved with Obesity Pharmacotherapies and Sleeve Gastrectomy



SURMOUNT MMO; SYNCHRONISE, others

Weight loss drugs become competitive in 2^o prevention



Patients with or at high risk for ASCVD

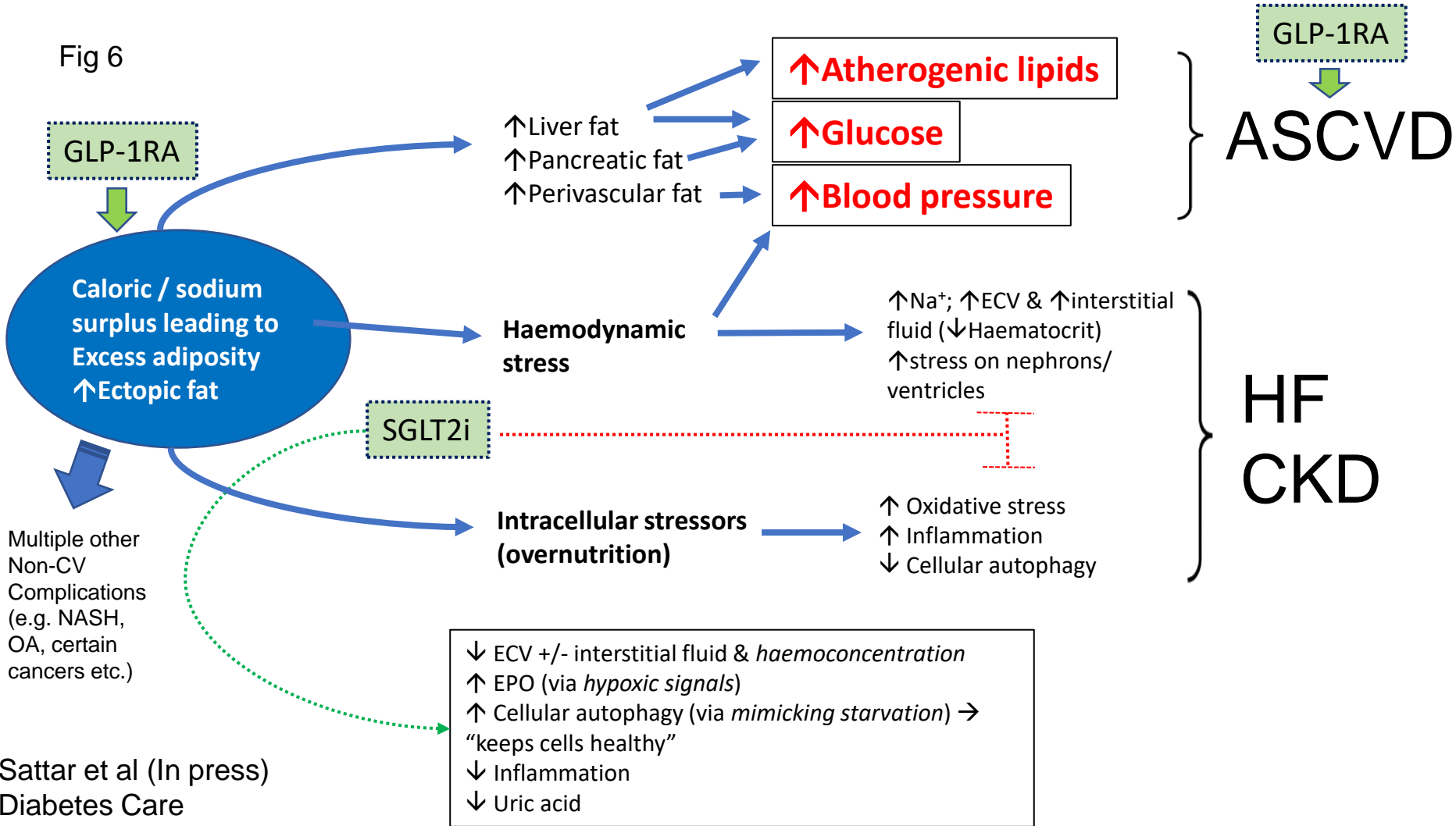
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LDL-c main issue

GLP-1RA /SGLT2i

Fig 6



Sattar et al (In press)
Diabetes Care

So what might patients want?

- Improvements in downstream biomarkers e.g. LDLc – but don't feel different?
- Or weight loss from agents that lower MACE risks
- Less multimorbidity, better QOL? Yes
- HEALTH COSTS: Reduced?
- But train cardiologists to prescribe GLP-1RA? Access to drugs, compete with other areas of medicine?



Final summary & thank you!

- Excess adiposity important risk factor for ASCVD (but takes time) and HF (somewhat missed)
 - ♦ *Previously underestimated*
- Need to treat xs weight more and PREVENT obesity
- Multiple benefits likely in 2^o prevention
- Delight to collaborate with Dutch colleagues

