New Medicines: The Present and The Future

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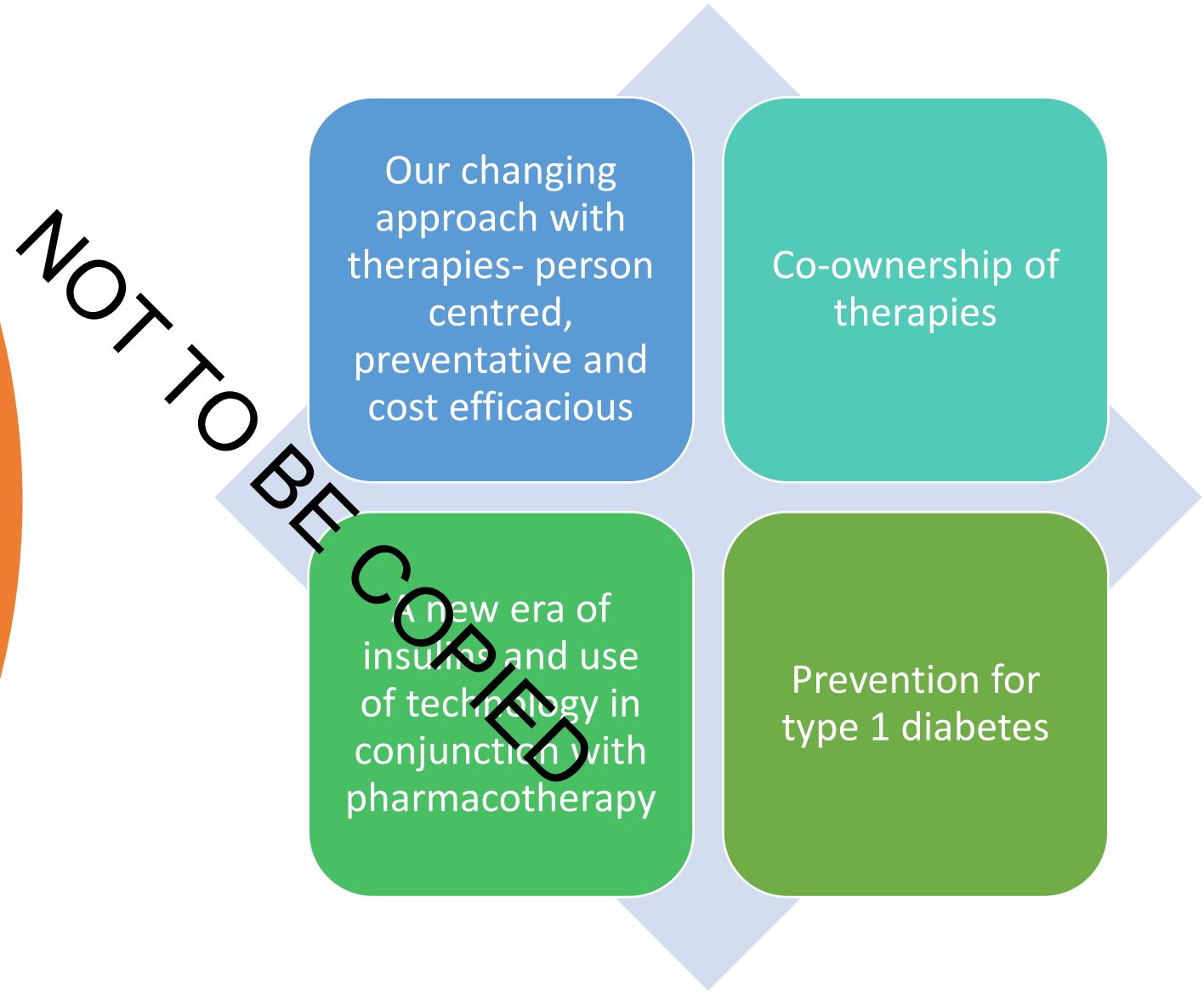
Declarations of Interest

Pharmaceutical and other medical companies for which you have attended an Advisory Board in the past 3 years	EASD attendance 2024 – sponsorship from Daiichi Sankyo ADA virtual attendance 2023 – sponsorship from Lilly EASD attendance 2023 – sponsorship from Daiichi Sankyo ADA virtual attendance 2022 – sponsorship from Lilly EASD in person attendance 2022- sponsorship from Novonordisk EASD virtual attendance 2021 – sponsorship from Novonordisk Since joining Leeds CCG and now Leeds Health and Care Partnership/West Yorkshire Health and Care partnership no personal payments have been made to myself from pharmaceutical companies for advisory boards. I am part of an advisory board for Leeds/Manchester University for the Aster AKI Study. No payment received to me personally. I am part of an advisory board for Astra Zeneca, looking at implementation of NG28. No payment received. I have participated in the public policy projects webinars. No payment received.
Pharmaceutical and other medical companies for which you have delivered or received sponsored education in the past 3 years	Since joining Leeds CCG and now Leeds Health and Care Partnership/West Yorkshire Health and Care Partnership no personal payments have been made to myself from pharmaceutical companies for education. I have done unpaid education linked to: Kings fund, i2i, CPPE, DPC, SPS, Newcastle University, PM Management, PCDS, Amgen, Lilly, Daiichi Sankyo, Sunderland University, Astra Zeneca, Leeds University, DSN Forum, RPS, PCDE, DUK, Cardiology Professional Care, PCPA, Sanofi, PITSTOP, BHS, BCS, UKKW
Roles that you hold a professional contract with (i.e. for which you earn a salary/fee)	Consultant Pharmacist for West Yorkshire and Leeds Health and Care Partnership Tutor for Warwick university MSC in Diabetes
Professional non-financial roles	Co-chair of Diabetes UK Council of Healthcare Professionals Member of the UKCPA Diabetes and Endocrinology Committee Trustee of the Primary Care Diabetes Society Member of Royal Pharmaceutical Society Chair of the Expert Reference Group for Cardio-Renal and Metabolic Medicine at Leeds Health and Care Partnership Chair for the Diabetes Steering Group at Leeds Health and Care partnership
Other relevant potential conflicts of interest	I am working with Kidney Research UK and Ashridge Business School to understand opportunities around a leadership course for CaReMe in the UK. Currently exploratory.

Overview

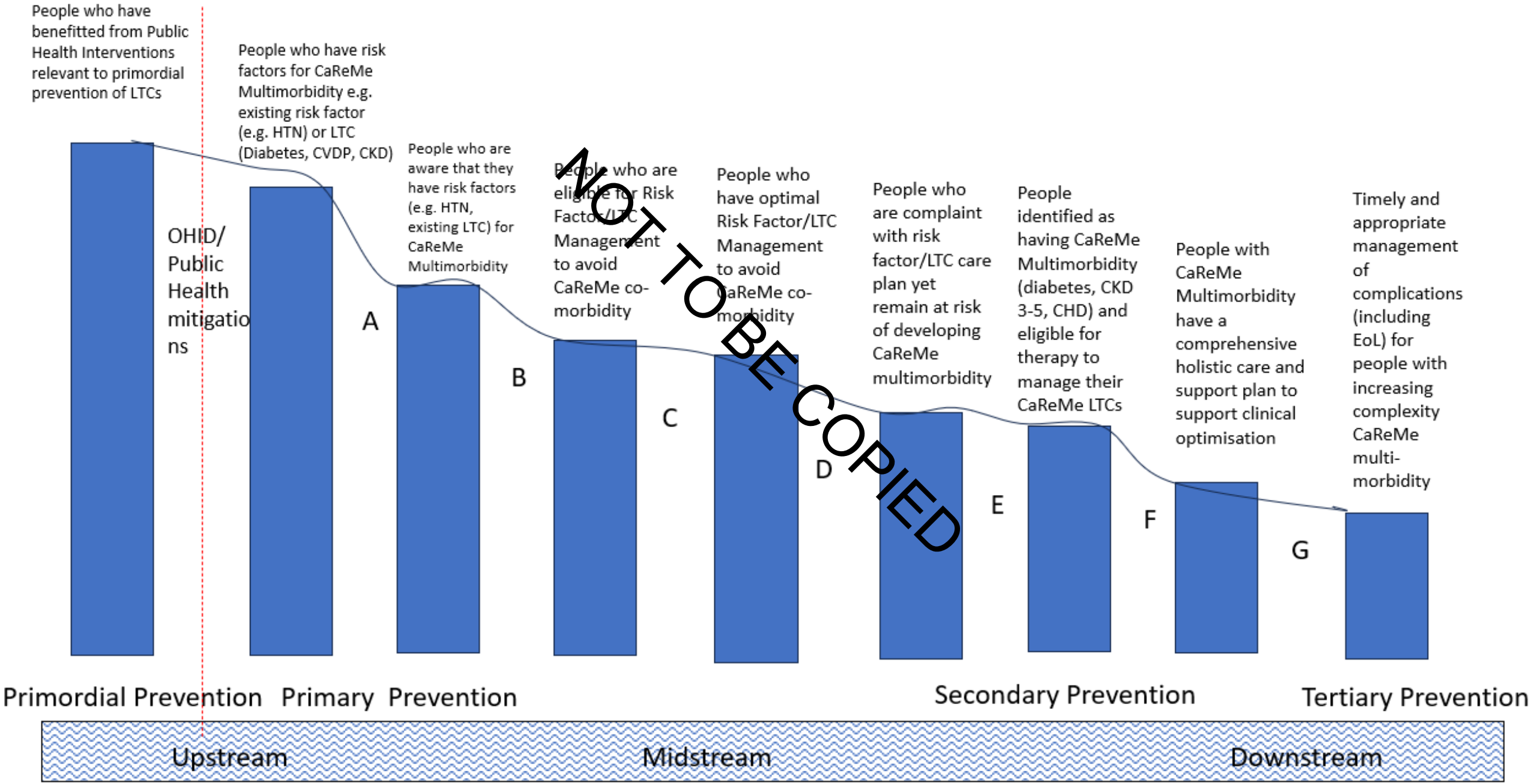


We are winning !!

From Gluco-Centric Care to Person- Centric Care

NOT TO BE COPIED

Decay Model – CaReMe Multimorbidity



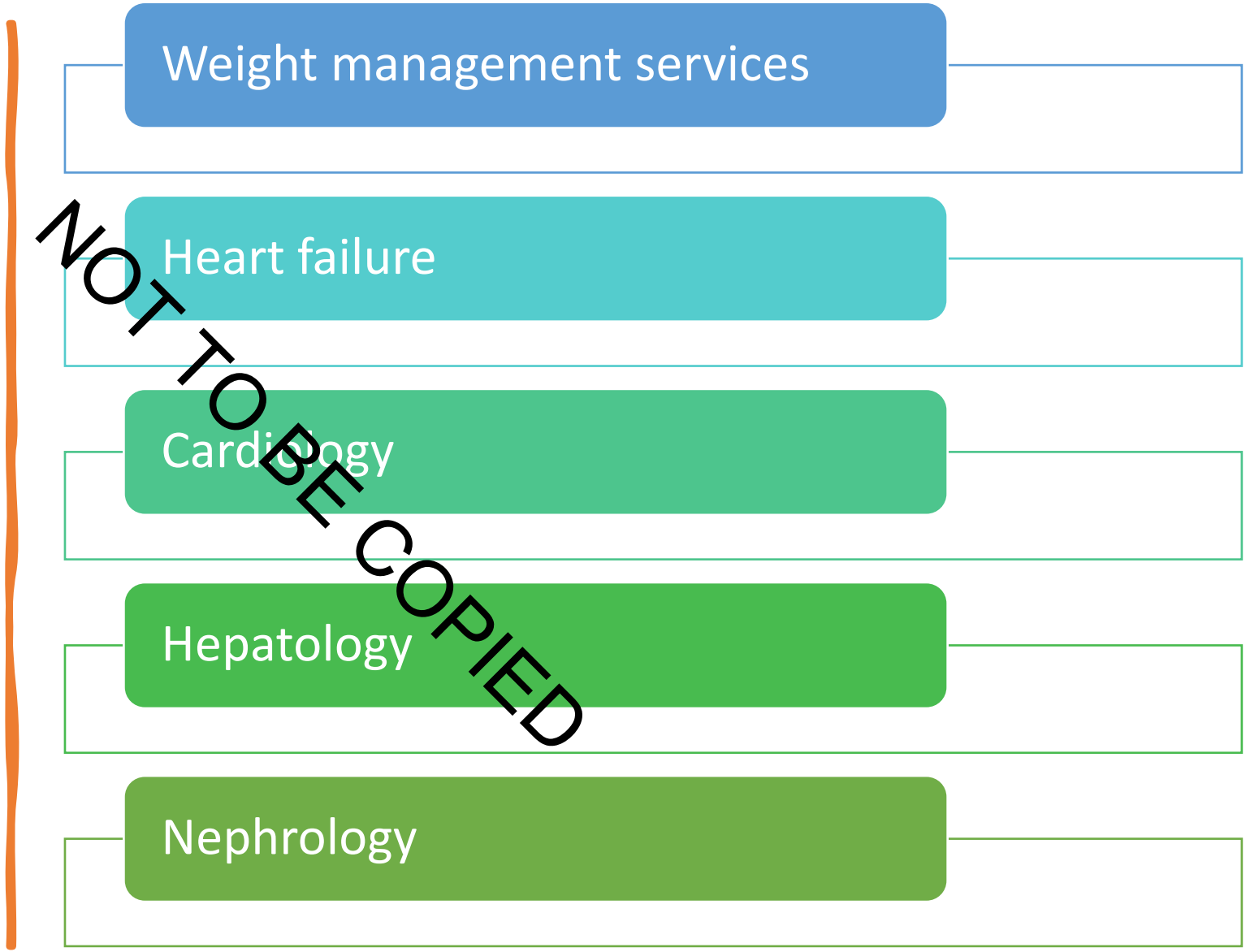
Costs of Complications

We are spending over £10.7 million pounds in the UK on diabetes direct costs and £3.3 billion is being spent on indirect costs.

Complications	Type 1	Type 2
Renal Replacement Therapy	£150,520,000	£690,425,000
MI	£11,095,000	£353,536,000
Stroke	£9,9930,000	£184,916,000
CHD	£48,700,000	£1,440,475,000
HF	£12,318,000	£313,831,000

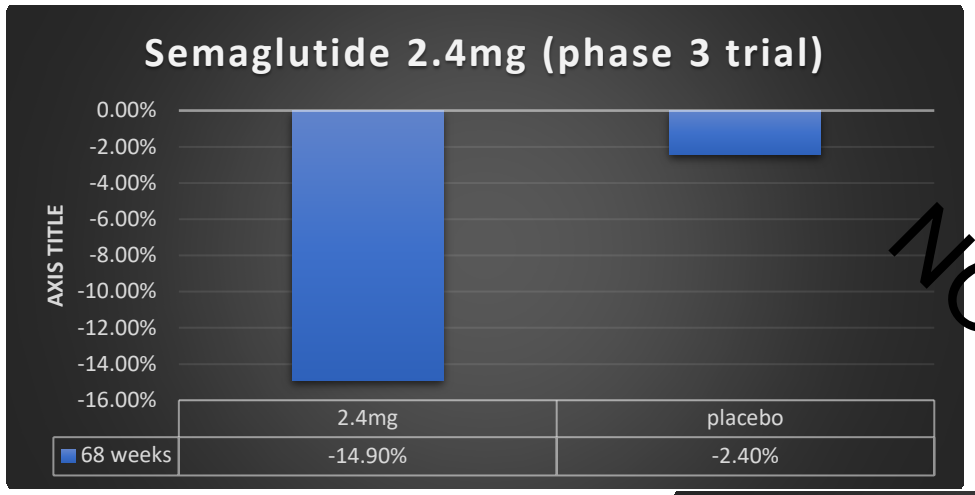
Hex N, MacDonald R,Pocock J, et al. Estimation of the direct health andindirect societal costs of diabetes in the UK using acost of illness model. Diabet Med. 2024;41:e15326.doi:10.1111/dme.15326

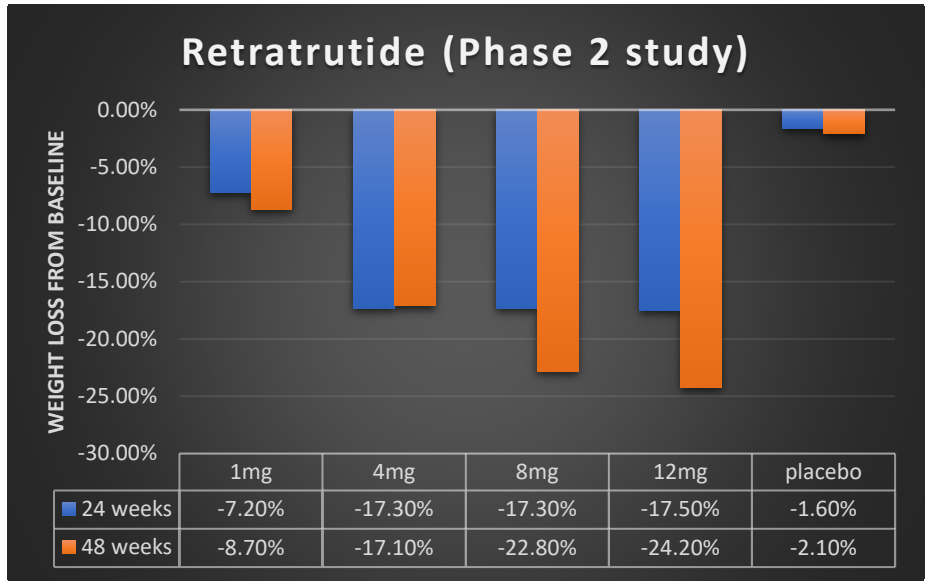
Co-Ownership of therapy

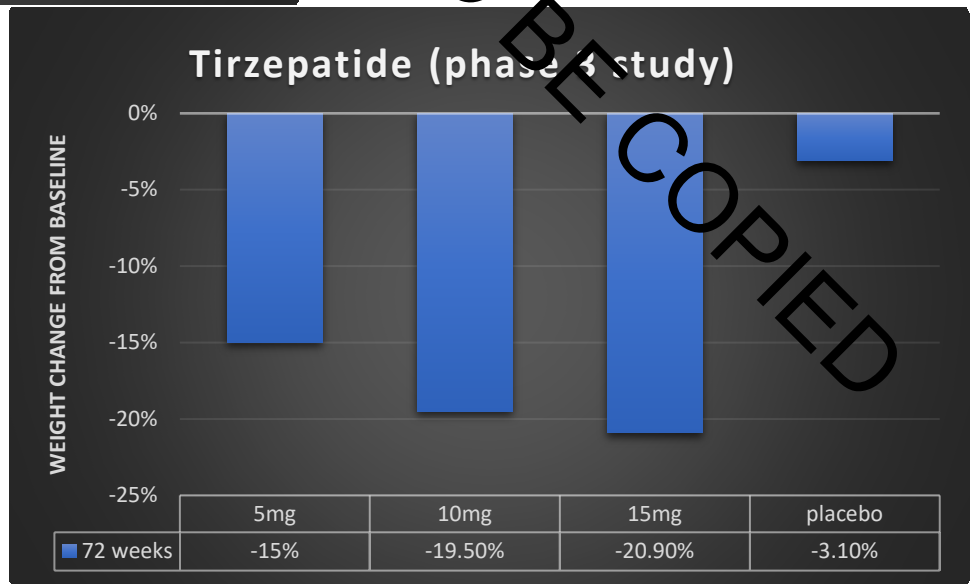



Tri incretins (GIP/GLP-1/glucagon) – Retratrutide (Phase 3 will complete 2026)
Amylin receptor agonists/GLP-1 (phase 3 studies now will complete 2027 for cagrisema) – Cagrilinitide/Semaglutide, Amycretin
GCGR/GLP-1 dual agonist – Survodutide, Cotadutide, Efinopegdutide
GLP-1/GIP receptor agonists - Tirzepatide
Setmelanotide (melanocortin 4 receptor agonist) – for severe obesity caused by genetic disorders
GLP-1 alone (higher doses) – Semaglutide 2.4mg once weekly
Obesity Management
GLP1-R/GIPR (Maridebart/Cafraglutide 'MariTide') – phase 1 studies complete, phase 2 completing 2024

Multi-Incretin Therapies







Jastreboff, Ania M., et al. "Triple–hormone-receptor agonist retatrutide for obesity—a phase 2 trial." New England Journal of Medicine 389.6 (2023): 514-526.
Wilding JP, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, McGowan BM, Rosenstock J, Tran MT, Wadden TA, Wharton S. Once-weekly semaglutide in adults with overweight or obesity. New England Journal of Medicine. 2021 Mar 18;384(11):989-1002.
Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, Kiyosue A, Zhang S, Liu B, Bunck MC, Stefanski A. Tirzepatide once weekly for the treatment of obesity. New England Journal of Medicine. 2022 Jul 21;387(3):205-16.

4 Key things in 4 months to Save Lives for Adults with CKD (ideally do in every patient with eGFR<60 or UACR ≥ 3 mg/mmol)

Month 1	Month 2		Month 3	Consider at month 4 onwards
Maximum intensity RAS/ RAAS blockade and Optimise Lipids	**Start SGLT2i (Referring to 'safe and effective use of SGLT2is' guidance)**		**Optimise Blood Pressure and Other Cardiovascular Risk Factors**	**Consider referral for Finerenone (see shared care guideline)**
Start ACE-inhibitor or ARB in the following populations: 1. Adults with hypertension and an ACR>30mg/mmol (category A3 or above) 2. Adults with diabetes and an ACR>3mg/mmol (category A2) 3. Adults without diabetes and ACR>70mg/mmol (also refer to nephrology) Titrate to maximum tolerated licensed dose (*NICE, NG203*) Ideally do this within one month (see rapid titration protocol for RAAS blockade below) Caution use Creatinine clearance (CrCl) cut-offs when titrating dose of ACE/ARB. See blood results and monitoring for further guidance. (page 4) Atorvastatin 20mg once daily should be offered as initial therapy for primary and secondary prevention and national guidelines followed for review and titration. Optimise lipid lowering therapies according to national lipid lowering guidance NHS Accelerated Access Collaborative » Summary of national guidance for lipid management (england.nhs.uk)	**Person with Type 2 Diabetes** Start Dapagliflozin 10mg once daily ensuring the person has an eGFR 25-75 mL/min/1.73m^2 recognising that glycaemic benefits will be limited at an eGFR <45ml/min/1.73m^2 **OR** Start Empagliflozin 10mg once daily ensuring the person has an eGFR 20-90ml/min/1.73m2 recognising that glycaemic benefits will be limited at an eGFR<45ml/min/1.73m^2	**Person without Type 2 Diabetes (NB not for people living with T1DM unless under specialist care)** Start Dapagliflozin 10mg once daily ensuring the person has: 1. an eGFR 25-75 mL/min/1.73m2 **and** 2. UACR of ≥22.6 mg/mmol, excluding people with polycystic kidney disease or on immunological therapy for renal disease who would not be suitable for SGLT2i therapy. **OR** Start Empagliflozin 10mg once daily ensuring the person has either: 1. An eGFR 20 ml/min/1.723m^2 to less than 45ml/min/1.73m^2 **OR** 2. An eGFR 45ml/min/1.73m^2 - 90ml/min/1.73m^2 and UACR ≥ 22.6mg/mmol.	Initiate further blood pressure agents to treat to target • UACR < 70mg/mmol: <130/80mmHg • UACR>70mg/mmol: Ideally <120/80mmHg taking into consideration frailty and co-morbidities. **Caution in the elderly/frail – consider reviewing the targets** Encourage home monitoring of Blood Pressure (NB targets are 5mmHg lower for HBPM) In those who have had a cardiovascular event, ensure offered aspirin with appropriate gastric protection (in some cases a H2 receptor antagonist may be preferred e.g., if having electrolyte abnormalities or in the instance of acute interstitial nephritis (ANI). Famotidine is the H2 receptor antagonist of choice in this situation). Aspirin may be considered for primary prevention in those at high cardiovascular risk. Initiation should be balanced with consideration of the increased bleeding risk, including thrombocytopathy with low eGFR. In those with established CAD or PAD at high risk of ischaemic events (see NICE) consider 2.5mg bd rivaroxaban alongside aspirin. Only if eGFR>15ml/min.	Only for people living with Type 2 Diabetes and who also has: - stage 3 or 4 CKD (eGFR ≥25-<60ml/min/1.73m^2) with albuminuria (UACR ≥3mg/mmol) - been optimised on standard care (RAAS blockade and SGLT2ihibitors) Finerenone can only be initiated if serum potassium ≤4.8mmol/L or if serum potassium >4.8 to 5 mmol/L then initiation can be considered with additional monitoring in the first 4 weeks based on patient characteristics and potassium levels. Initiate the lower dose of Finerenone 10mg if eGFR 25-59ml/min/1.73m2
	(NB: Agents are listed in alphabetical rather than preferential order) Follow the guidance in the document 'Safe and Effective Use of SGLT2is' *We would not advocate switching SGLT2is so in those already established (including those on Canagliflozin) we would advise they continue and those already established on empagliflozin 25mg once daily should continue unless indicated to drop dose. Specialist initiation only if history of: transplantation; on immunological therapy; polycystic kidney disease; haemodialysis.			

Lifestyle advice – diet, exercise, weight management, smoking cessation

FINEARTS-HF

Trial Population

- HFmrEF or HFpEF (EF ≥40%)
- >40 years old
- Elevated pro-BNP
- Evidence of structural heart disease

Intervention

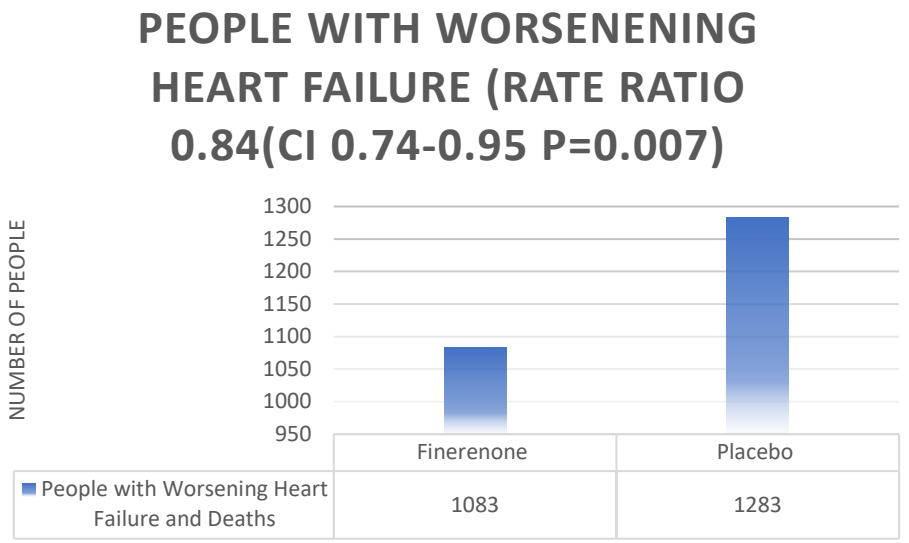
- 1:1 finerenone (either 20mg or 40mg depending on baseline eGFR) or placebo

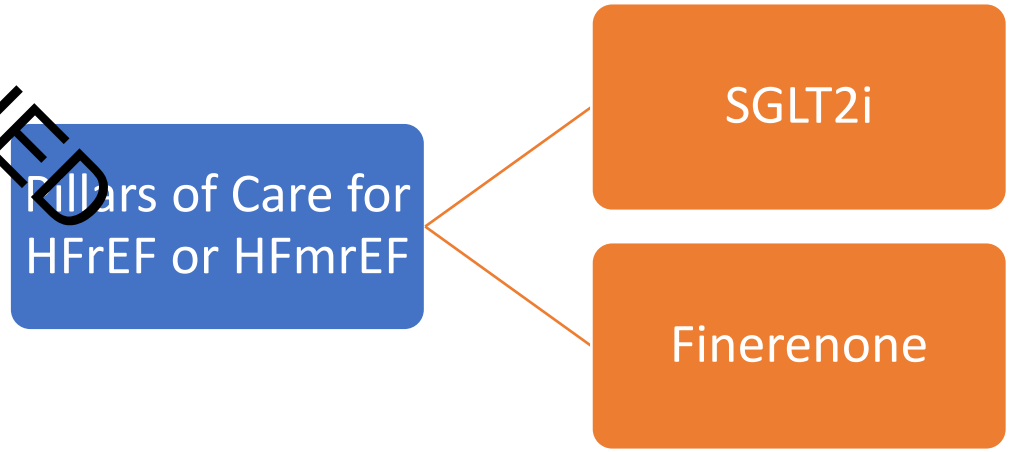
Primary Endpoint

composite of total (first and repeat) worsening HF events and cardiovascular death

Secondary Endpoints

all-cause mortality and a composite kidney outcome (sustained 50% or greater decline in eGFR, sustained decline in eGFR to less than 15 ml/min/1.73 m2 or initiation of chronic dialysis or kidney transplantation





Solomon SD, McMurray JJ, Vaduganathan M, Claggett B, Jhund PS, Desai AS, Henderson AD, Lam CS, Pitt B, Senni M, Shah SJ. Finerenone in heart failure with mildly reduced or preserved ejection fraction. New England Journal of Medicine. 2024 Sep 1.

GLP1-RAs Reduce CV Risk in People Living with Diabetes

	Lixisenatide (ELIXA)[1]	Exenatide QW (EXSCEL)[2]	Liraglutide (LEADER)[3]	S/C Semaglutide (SUSTAIN 6)[4]	Dulaglutide (REWIND)[5]	Oral Semagutide (PIONEER)[6]
MACE	↑ 2%	↓9%	↓13%	↓26%	↓12%	↓21%
Non-fatal MI	↑2%	↓9%	↓12%	↓26%	↓4%	↑18%
Non-Fatal Stroke	↑12%	↓15%	↓11%	↓29%	↓24%	↓26%
CV Death	↓2%	↓12%	↓22%	↓2%	↓9%	↓51%
All-cause death	↓6%	↓14%	↓15%	↑5%	↓10%	↓49%
HF Hospitalisation	↓4%	↓6%	↓13%	↓11%	↓7%	↓14%

1. Pfeffer MA, Claggett B, Diaz R et al. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome N Engl J Med 2015; 373:2247-2257
2. Holman RR, Bethel MA, Mentz RJ et al. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes N Engl J Med 2017; 377:1228-1239
3. Marso SP, Bain SC, Consoli A et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes N Engl J Med 2016; 375:1834-1844
4. Marso P, Daniels GH et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes N Engl J Med 2016; 354:311-22
5. Gerstein et al.2019. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet.394:121-130
6. Husain M et al. 2019. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. NEJM. 381:841-851

SELECT Trial – Semaglutide and Cardiovascular Outcomes in People without Diabetes

Trial Population

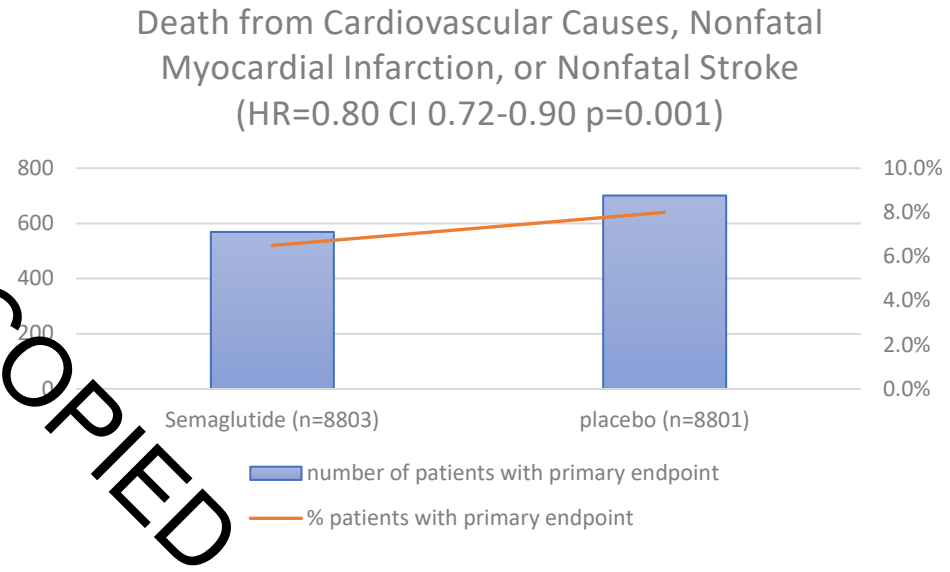
- Non diabetes
- Pre-existing cardiovascular disease (stroke, MI, PVD or combo)
- Overweight and obese (BMI≥27kg/m^2)
- 45 years of age or older

Intervention

1:1 Semaglutide 2.4mg vs. placebo

Primary Endpoint

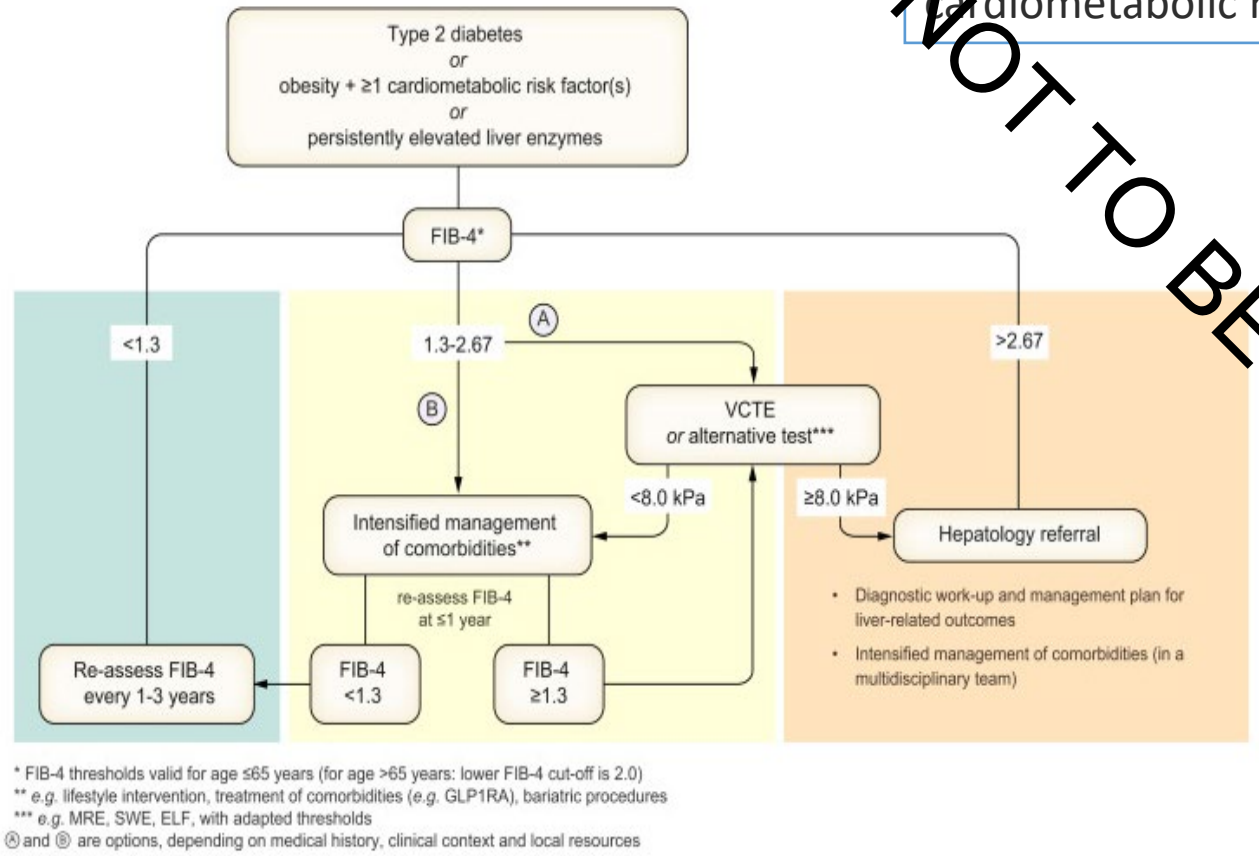
composite of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke in a time-to-event analysis

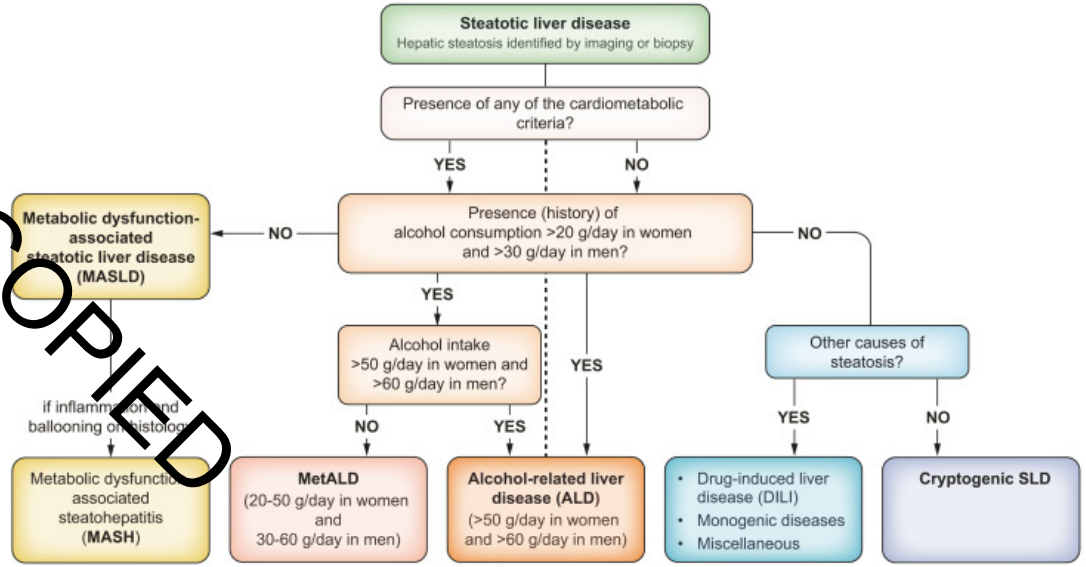


Lincoff, A.M., Brown-Frandsen, K., Colhoun, H.M., Deanfield, J., Emerson, S.S., Esbjerg, S., Hardt-Lindberg, S., Hovingh, G.K., Kahn, S.E., Kushner, R.F. and Lingvay, I., 2023. Semaglutide and cardiovascular outcomes in obesity without diabetes. *New England Journal of Medicine*, *389*(24), pp.2221-2232.

MAFLD – Metabolic Associated Fatty Liver Disease

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously termed non-alcoholic fatty liver disease (NAFLD), is defined as steatotic liver disease (SLD) in the presence of one or more cardiometabolic risk factor(s) and the absence of harmful alcohol intake.





EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD)Tacke, Frank et al. Journal of Hepatology, Volume 81, Issue 3, 492 - 542

SYNERGY -NASH

Trial Population

- biopsy-confirmed MASH and stage F2 or F3 (moderate or severe) fibrosis
- With or without Diabetes
- Age 18-80 years old
- BMI 27-50

Intervention

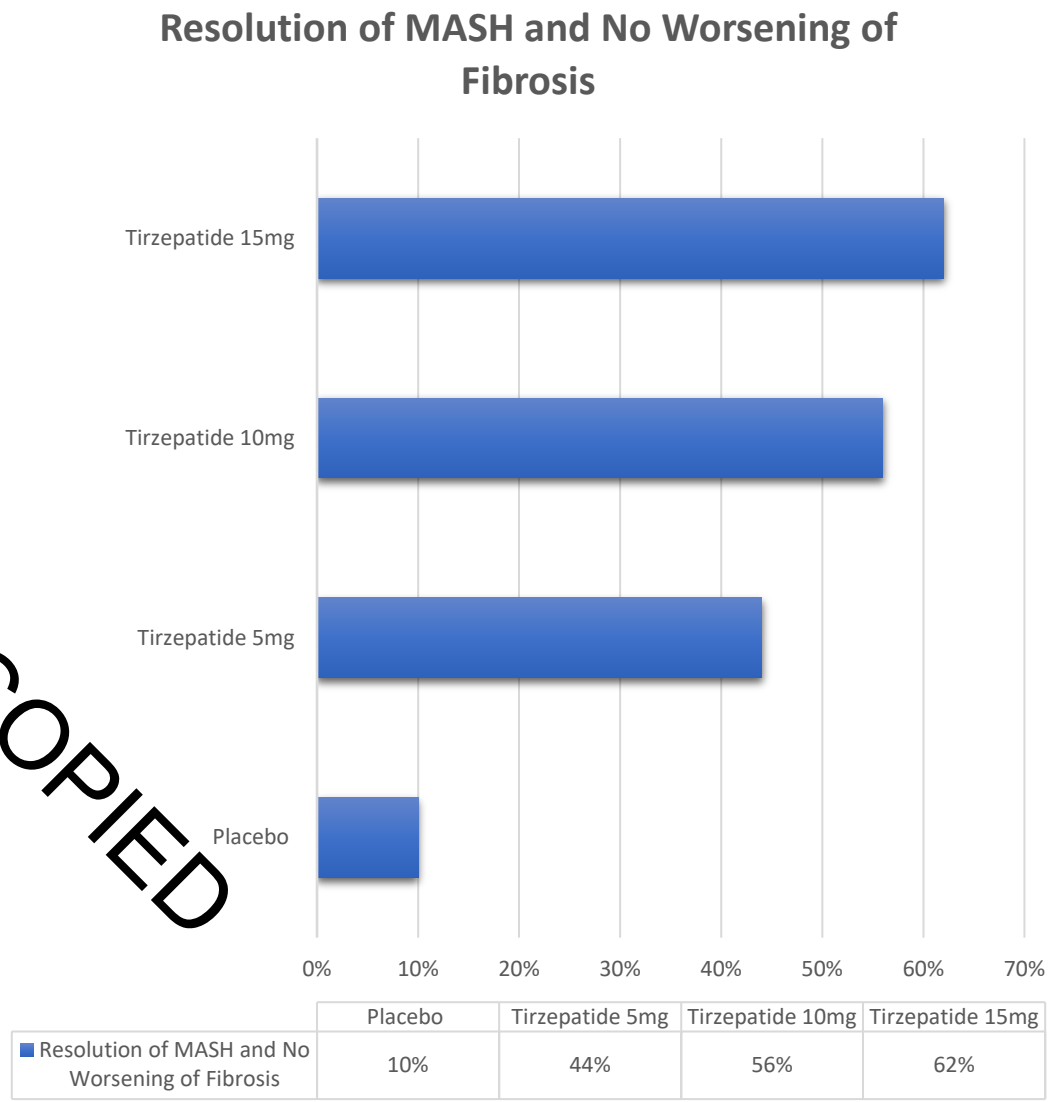
Tirzepatide 5mg, Tirzepatide 10mg, Tirzepatide 15mg vs. placebo

Primary Endpoint

primary end point was resolution of MASH without worsening of fibrosis at 52 weeks

Secondary Endpoint

improvement (decrease) of at least one fibrosis stage without worsening of MASH



	Placebo	Tirzepatide 5mg	Tirzepatide 10mg	Tirzepatide 15mg
Resolution of MASH and No Worsening of Fibrosis	10%	44%	56%	62%

Loomba R, Hartman ML, Lawitz EJ, Vuppalanchi R, Boursier J, Bugianesi E, Yoneda M, Behling C, Cummings OW, Tang Y, Brouwers B. Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with Liver Fibrosis. New England Journal of Medicine. 2024 Jun 8.

FLOW – Semaglutide 1mg ow + T2D and CKD standard of care

Trial Population
Adults
Type 2 Diabetes
HbA1c ≤ 10% (≤86mmol/mol)
eGFR ≥50 - ≤75ml/min/1.73m2 and UACR >300- <5000mg/g OR eGFR ≥25 - <50ml/min/1.73m2 and UACR >100-<5000mg/g
RA Blockade

Primary Endpoint	Secondary Endpoints
Time to first occurrence of major kidney outcomes consisting of: • Kidney failure: onset of persistent eGFR<15ml/min/1.73m2 or initiation of chronic kidney replacement therapy (dialysis or transplant) • at least a 50% reduction in the eGFR from baseline • Kidney death • CV death	Annual rate of change in eGFR (total eGFR slope) Time to first occurrence of a composite MACE outcome consisting of CV death, non-fatal MI or non-fatal stroke Time to occurrence of all-cause death

eGFR (ml/min/1.73m²)	UACR <30mg/g	UACR≥30-<300mg/g	≥300mg/g
≥90	1(<0.1)	7(0.2)	23(0.6)
≥60-<90	24(0.7)	173(4.9)	491(13.9)
≥45-<60	37(1.0)	324(9.2)	694(19.6)
≥30-<45	40(1.1)	414(11.7)	905(25.6)
≥15-<30	7(0.2)	87(2.5)	306(8.6)

93% of patients in the trial were high risk

Perkovic, V., Tuttle, K. R., Rossing, P et al. (2024). Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. *New England Journal of Medicine*, *391*(2), 109-121.

Flow: Outcomes

20 people

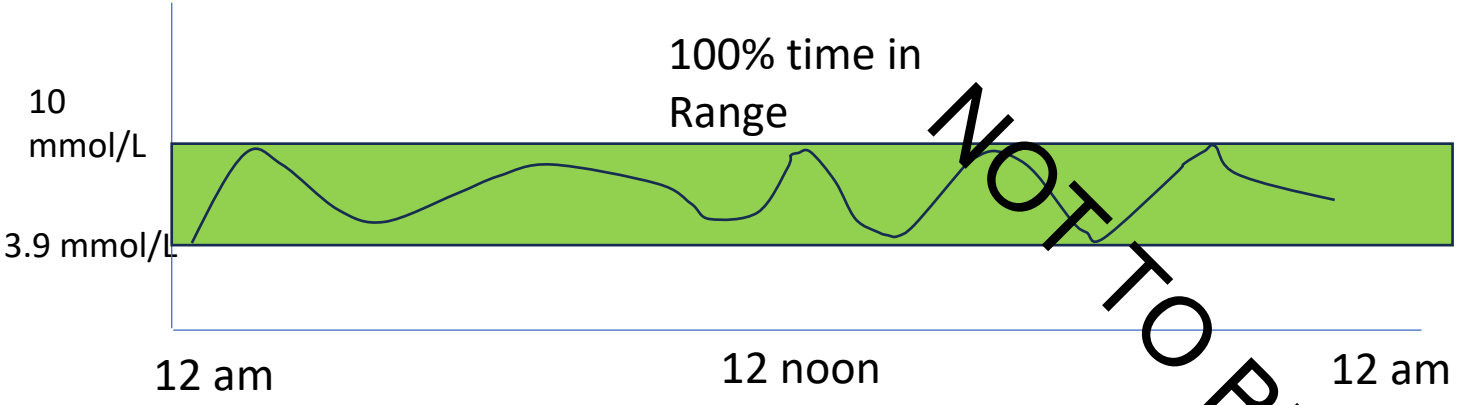
3 years

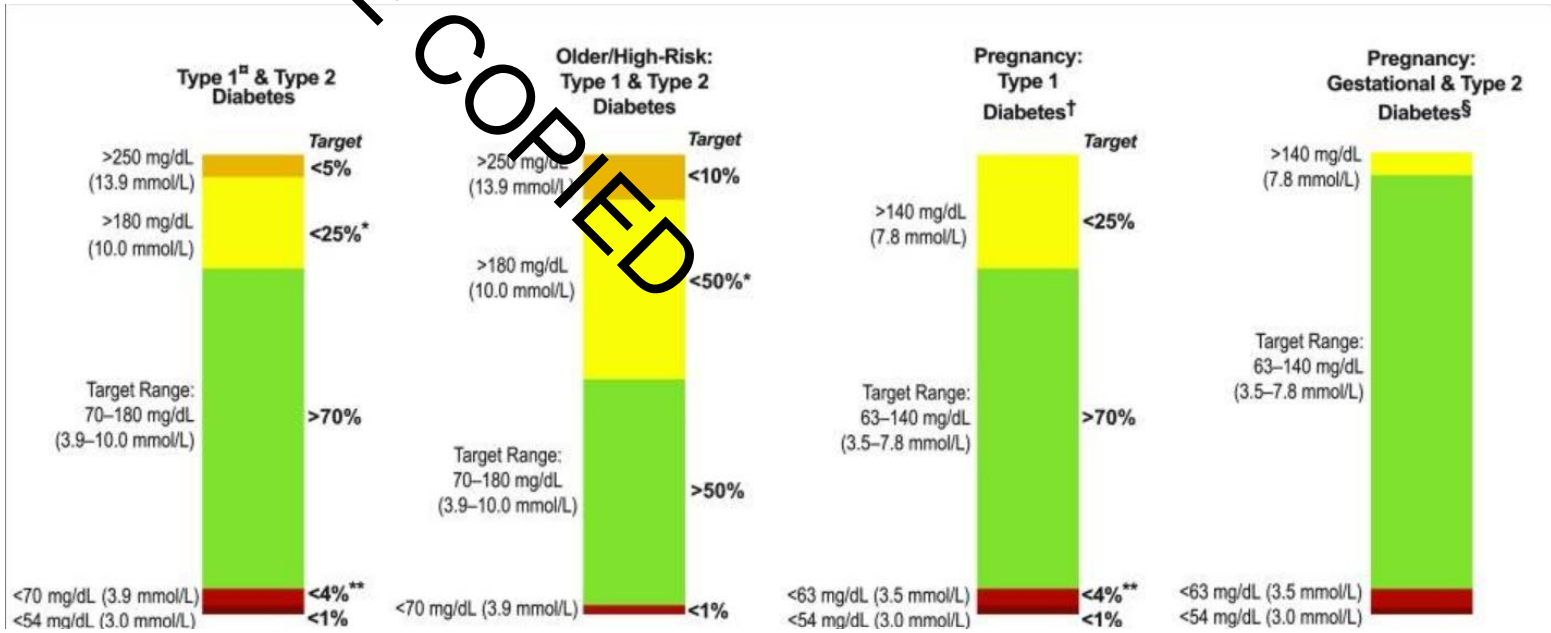
To prevent 1 composite kidney outcome (driven by CV death and reduction in number of people having a 50% reduction in the eGFR from baseline)

Problems
Non-steroidal MRAs and SGLT2is were not licenced specifically for CKD at the time of the trial (when those who were on SGLT2is were looked at alone, less convincing benefit for Semgalutide)
Certain ethnicities at higher risk were under represented in the trial (black and indigenous)
May not be translatable results to lower risk populations

Perkovic, V., Tuttle, K. R., Rossing, P et al. (2024). Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. *New England Journal of Medicine*, *391*(2), 109-121.

Thinking About how medications effect our Time In Range





Battelino T, Danne T, Bergenstal RM et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Diabetes Care. 2019 Aug;42(8):1593-1603. doi: 10.2337/dci19-0028. Epub 2019 Jun 8. PMID: 31177185; PMCID: PMC6973648.

Type 2 Diabetes and Continuous Glucose Monitoring

Continuous Glucose Monitoring Type 2 Diabetes

Improved glycaemic control (mean difference (MD) in HbA_{1c} of −3.43 mmol/mol (−0.31%; 95% CI −4.75, −2.11, p<0.00001, I^2=15%; moderate certainty)

Increased time in range. TIR (+6.36%; 95% CI +2.48, +10.24, p=0.001, I^2=9%)

Decrease in TBR (−0.66%; 95% CI −1.21, −0.12, p=0.02, I^2=45%)

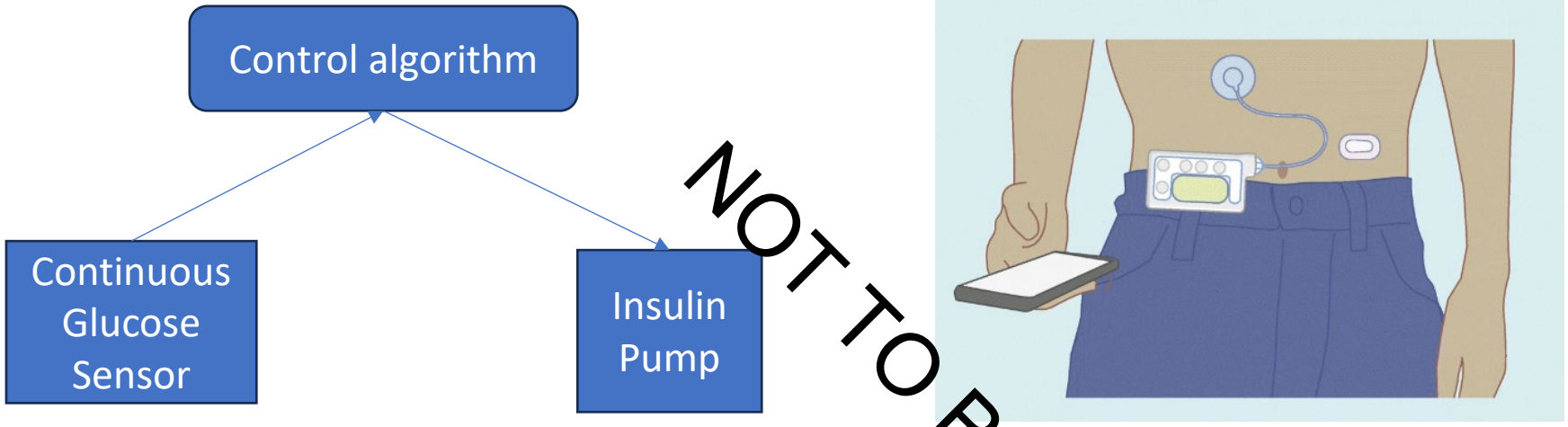
Decrease in TAR (−5.86%; 95% CI −10.88, −0.84, p=0.02, I^2=37%)

Decrease glycaemic variability (−1.47%; 95% CI −2.94, −0.01, p=0.05, I^2=0%)

Lack of outcomes data on severe hypoglycaemia, microvascular and macrovascular complications

Jancev M, Vissers TACM, Visseren FLJ, van Bon AC, Serné EH, DeVries JH, de Valk HW, van Sloten TT. Continuous glucose monitoring in adults with type 2 diabetes: a systematic review and meta-analysis. Diabetologia. 2024 May;67(5):798-810. doi: 10.1007/s00125-024-06107-6. Epub 2024 Feb 16. PMID: 38363342; PMCID: PMC10954850.

Type 1 Diabetes and Hybrid Closed Loop Systems



Top Tips for Primary Care
Person still needs some pen insulin for back up just in case pump/HCL system failure
Person still needs CBG monitoring just in case CGM failure
You should be able to reduce the quantities of both however do this collaboratively with the person living with diabetes

Evolution of Insulin – Once Weekly Insulin

Clinical Benefits	Pharmacotherapeutic Benefits
Convenience of once weekly dosing	Lower clearance and longer half life
Easier to overcome clinical inertia	Smoother/flatter blood insulin levels and efficacy
Improved treatment adherence	Lower within day and between day variability
Good glycaemic outcomes	Comparable blood glucose lowering effect

Shetty S, Suvarna R. Efficacy and safety of once-weekly insulin icodec in type 2 diabetes: A meta-analysis of ONWARDS phase 3 randomized controlled trials. Diabetes Obes Metab. 2024 Mar;26(3):1069-1081. doi: 10.1111/dom.15408. Epub 2024 Jan 8. PMID: 38192022.

Insulin Icodec

- Higher HbA1c reduction for Icodec when compared to Degludec and comparable effects with U100 glargine
- No significant difference in fasting plasma glucose seen
- Higher incidence of type 1 hypoglycaemia
- No difference for type 2 or 3 hypoglycaemia or combined 2/3 hypoglycaemia outcomes

Shetty S, Suvarna R. Efficacy and safety of once-weekly insulin icodec in type 2 diabetes: A meta-analysis of ONWARDS phase 3 randomized controlled trials. Diabetes Obes Metab. 2024 Mar;26(3):1069-1081. doi: 10.1111/dom.15408. Epub 2024 Jan 8. PMID: 38192022.

Insulin Efsitora Alfa

- Once weekly insulin
- Phase 3 study looking at Insulin Efitora Alfa vs. Degludec in insulin naiive patients on GLP-1 and not on GLP-1 therapy

The mean HbA1c decreased from 8.21% at baseline to 6.97% at week 52 with efsitora (least-squares mean change, −1.26 percentage points) and from 8.24% to 7.05% with degludec (least-squares mean change, −1.17 percentage points) (estimated treatment difference, −0.09 percentage points; 95% confidence interval [CI], −0.22 to 0.04), findings that showed noninferiority

Efsitora was noninferior to degludec with respect to the change in HbA1c in participants using and not using GLP-1 receptor agonists.

% time that the glucose level was within the target range was 64.3% with efsitora and 61.2% with degludec (estimated treatment difference, 3.1 percentage points; 95% CI, 0.1 to 6.1)

The rate of combined clinically significant or severe hypoglycemia was 0.58 events per participant-year of exposure with efsitora and 0.45 events per participant-year of exposure with degludec (estimated rate ratio, 1.30; 95% CI, 0.94 to 1.78). No severe hypoglycaemia was reported however with efsitora.

Wysham C, Bajaj HS, Del Prato S, Franco DR, Kiyosue A, Dahl D, Zhou C, Carr MC, Case M, Firmino Gonçalves L. Insulin Efsitora versus Degludec in Type 2 Diabetes without Previous Insulin Treatment. New England Journal of Medicine. 2024 Sep 10.

Screening for Type 1

What does the ELSA Study involve?

In the ELSA Study, we are screening children for type 1 diabetes. The study has 5 steps:

- Step 1 – Finger prick blood test to screen for antibodies (20,000 children)
- Step 2 – Venous blood test to test for antibodies (for children who screened positive at stage 1)
- Step 3 – Venous blood tests for staging of type 1 diabetes (for children who tested positive at stage 2)
- Step 4 – Education session (for parents of children at-risk)
- Step 5 - Interviews with parents/guardians to provide feedback on the screening programme

The ELSA Study

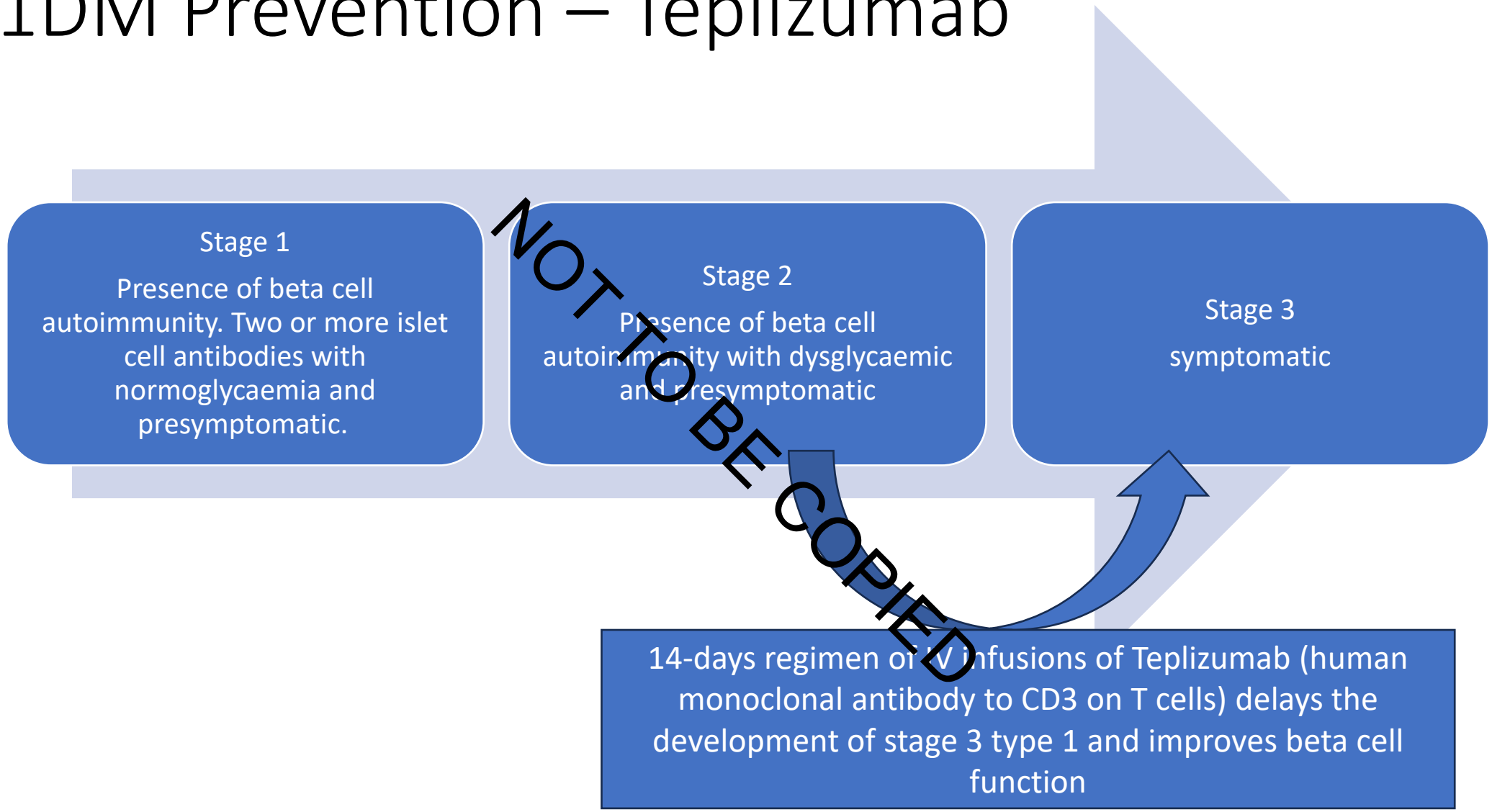
The ELSA Study is screening children for type 1 diabetes.

Children aged 3-13 years can have a simple finger stick blood test to find out their risk of developing type 1 diabetes in the future.

Currently open to families living in England, Scotland, Wales and Northern Ireland.

https://www.elsadiabetes.nhs.uk/about

T1DM Prevention – Teplizumab



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Thank you - Questions