

27th ANNUAL EXCELLENCE IN CARDIAC CARE CONFERENCE

|  January 24, 2026 |  8:00-13:00 p.m. EST





WELCOME BACK!



Dr. Taryn Becker

Diabetes Update

Financial disclosure

Relationships with financial sponsors:

Direct financial relationships including receipt of honoraria	<ul style="list-style-type: none">• AstraZeneca• Abbott• Boehringer Ingelheim• Janssen• Lilly• Merck• Sanofi• Corcare Quality & Education Platform
Membership on advisory boards or speakers' bureaus	<ul style="list-style-type: none">• Astrazeneca• Lilly• Novo Nordisk• Sanofi
All other investments or relationships	<ul style="list-style-type: none">• None

Learning Objectives

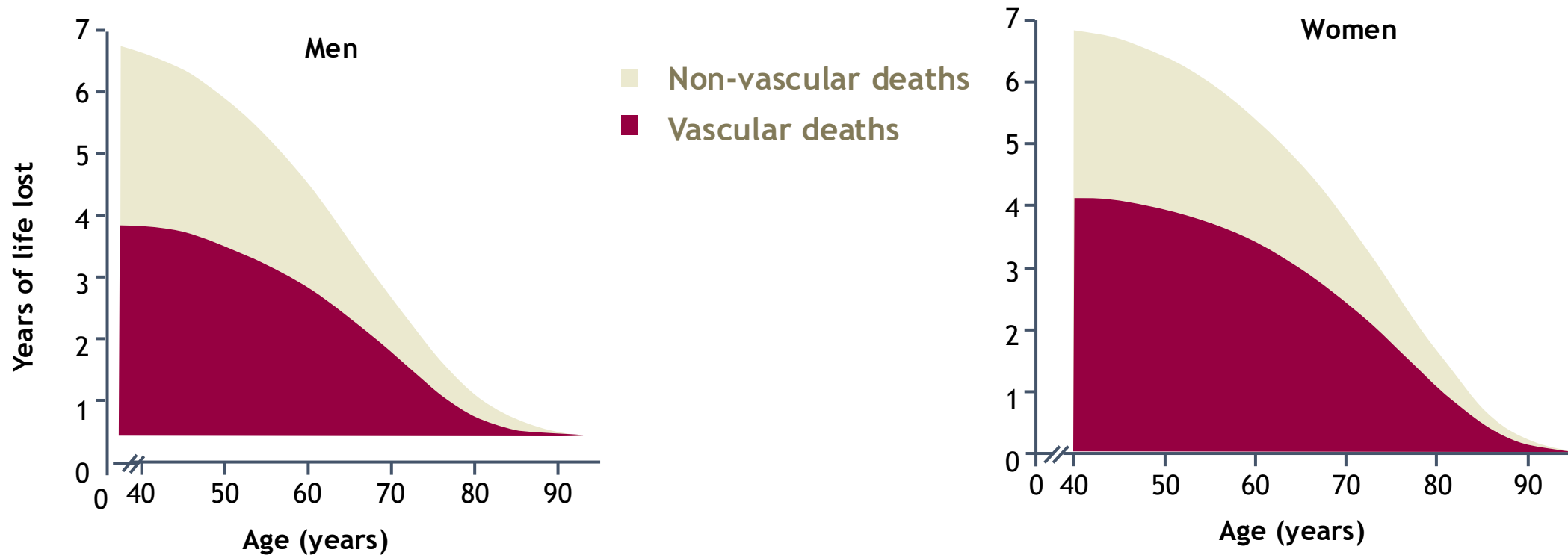
During this session, participants will analyze and interpret the:

- Value of secondary prevention in patients with diabetes
- Management strategies to optimize cardiovascular risk in patient with diabetes with ASCVD
- Current guidelines recommendations on the use of SGLT2i and GLP-1 receptor agonists (GLP1-RA) in patients with diabetes
- Clinical evidence supporting the cardiovascular and renal benefits of GLP1-RA therapies.

Type 2 DM in Primary Care

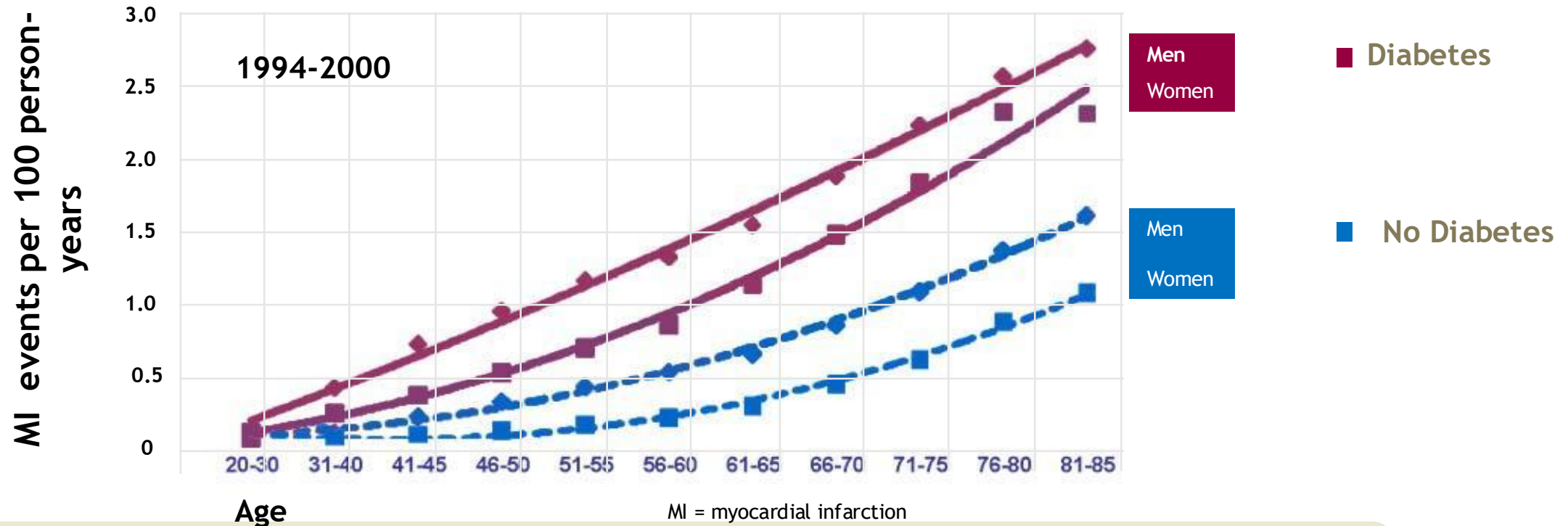
- The WHO estimates that globally, high glucose is the 3rd highest risk factors for premature mortality
- Estimated >500million cases of DM worldwide
- **The majority of DM management occurs in primary care**

Diabetes is associated with Significant loss of life years



On average, a 50-year-old individual with diabetes and no history of vascular disease will die 6 years earlier compared to someone without diabetes

Absolute risk of MI is higher in people with Diabetes

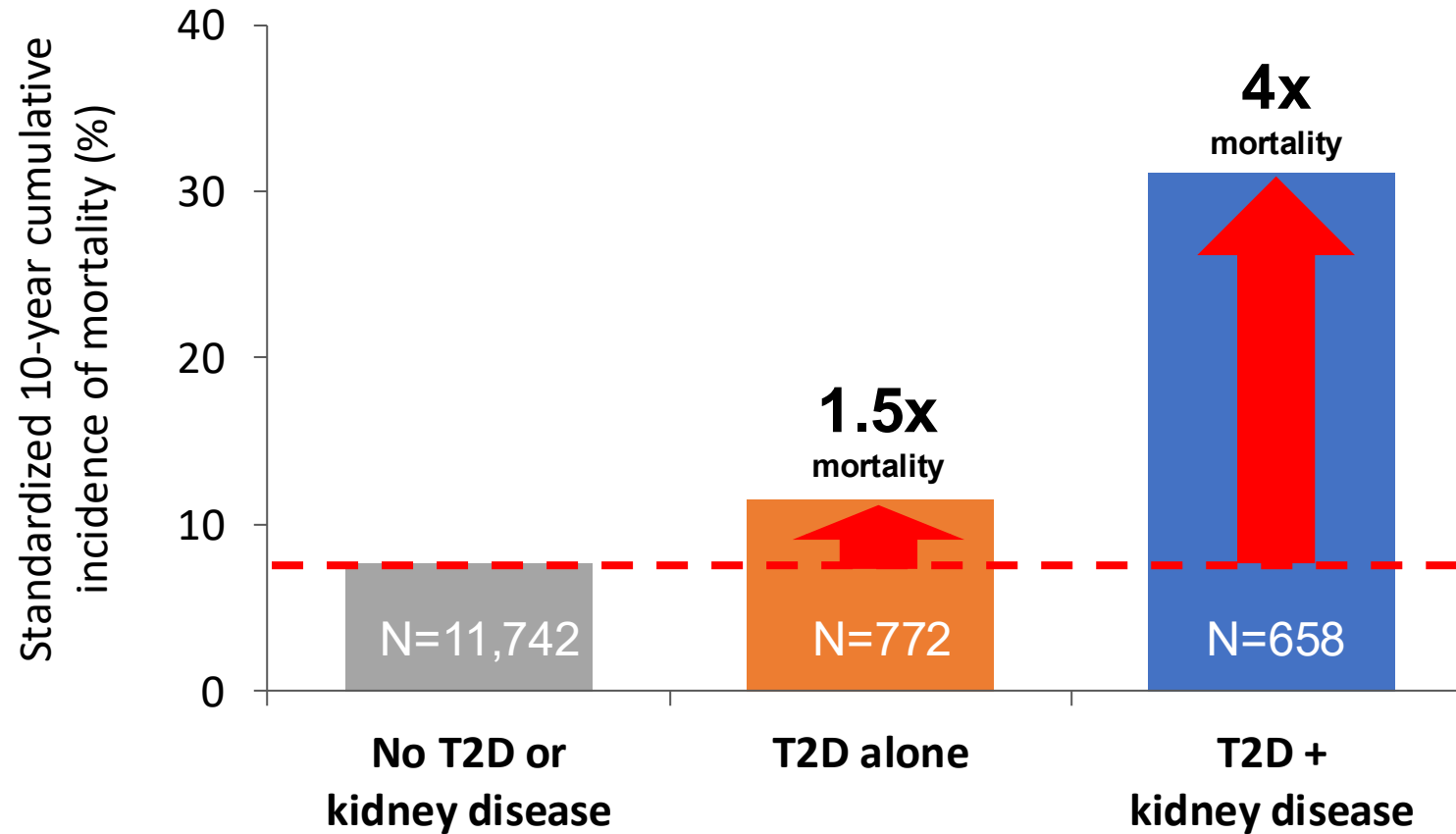


On average, men and women with diabetes have twice the rate of myocardial infarction

Type 2 DM and CVD

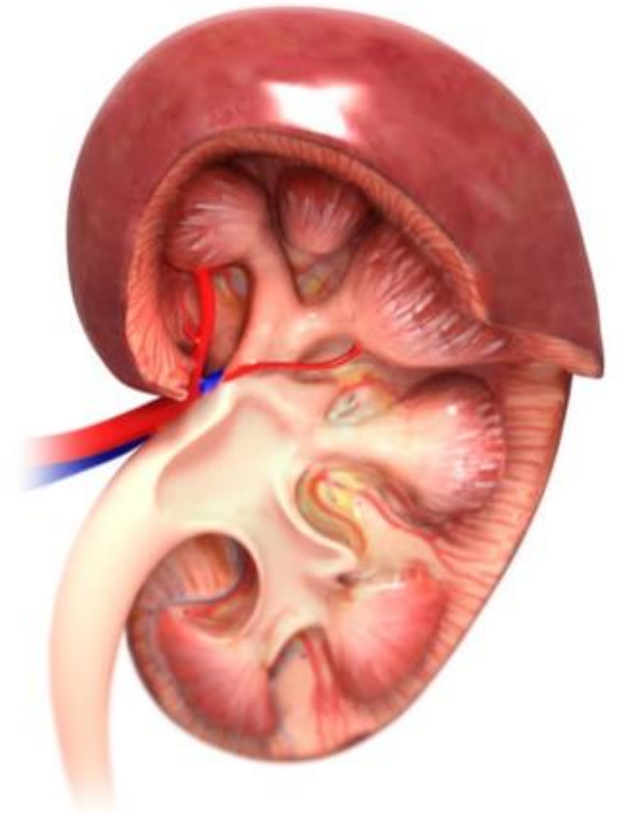
- DM significantly accelerates the development and natural history of CVD compared to individuals without DM
- CV events have the greatest capacity to cause premature death or devastating disability
- MI, stroke and amputation are all manifestations of aggressive atherosclerosis
- There is growing appreciation of heart failure as an important cause of CV morbidity and mortality

CKD is a Powerful Predictor of Mortality in T2D, Regardless of Cardiovascular Disease Status



Presence of CKD and T2D significantly increases the risk of MACE, heart failure and death

- 40-50% of people with diabetes develop CKD ¹
- Prevalence of CKD similar to CVD in type 2 diabetes
- 24.1% vs 21.6%, respectively
- *DKD shortens survival by 6-15 years³*
- Prevention of CVD and CKD is a major focus in the management of people with DM type 2, CKD or obesity
- Given their inter-relationships, these conditions are collectively referred to as cardiovascular-kidney-metabolic syndrome



Managing DM type 2 in Primary Care

- The WHO estimates that globally, high glucose is the 3rd highest risk factors for premature mortality
- CVD is the leading cause of morbidity and mortality in people with DM type 2
- Estimated >500million cases of DM worldwide
- **The majority of DM management occurs in primary care**
- Focus is not only on glycemic control but on multi-morbidity risk reduction

2024 UPDATE TO T2DM PHARMACOTHERAPY CPG



Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage:
www.canadianjournalofdiabetes.com

DIABETES
CANADA



Special Article

Pharmacologic Glycemic Management of Type 2 Diabetes in Adults—2024 Update



Diabetes Canada Clinical Practice Guidelines Expert Working Group:

Baiju R. Shah MD, FRCPC, PhD; Harpreet S. Bajaj MD, MPH, FACE;
Sonia Butalia MD, FRCPC, MSc; Kaberi Dasgupta MD, CM, MSc; Dean T. Eurich BSP, PhD;
Rahul Jain MD, CCFP, MScCH; Karen Leung MD, MSc, CCFP(COE);
Kerry Mansell BSP, PharmD, MBA; Scot Simpson BSP, PharmD, MSc

Key Messages

- Metformin should be the initial agent of choice in most people with type 2 diabetes who require pharmacotherapy to reach glycemic targets.
- Insulin should be initiated immediately, with or without metformin, in individuals with metabolic decompensation and/or severe symptomatic hyperglycemia.
- When glycated hemoglobin (A1C) is more than 1.5% above target, other antihyperglycemic agents in combination with metformin may be needed.
- Certain glucagon-like peptide-1 receptor agonists (GLP1-RAs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors should be used for cardiorenal protection in people with high cardiovascular (CV) risk, heart failure (HF), or chronic kidney disease (CKD). These medications should be initiated if these comorbidities or complications are already present at diagnosis or if they develop over the person's lifetime, even if the A1C is in target.
- Choice of additional antihyperglycemic agents, when treatment intensification is required to improve glycemia, should consider individual priorities, preferences, and comorbidities. Clinical priorities may include weight loss, avoidance of hypoglycemia, desired magnitude of glucose lowering, cost, side-effect profile, possibility of pregnancy, and comorbidities.

medications to use depends on many factors, including glucose levels, other health problems, and medication costs.

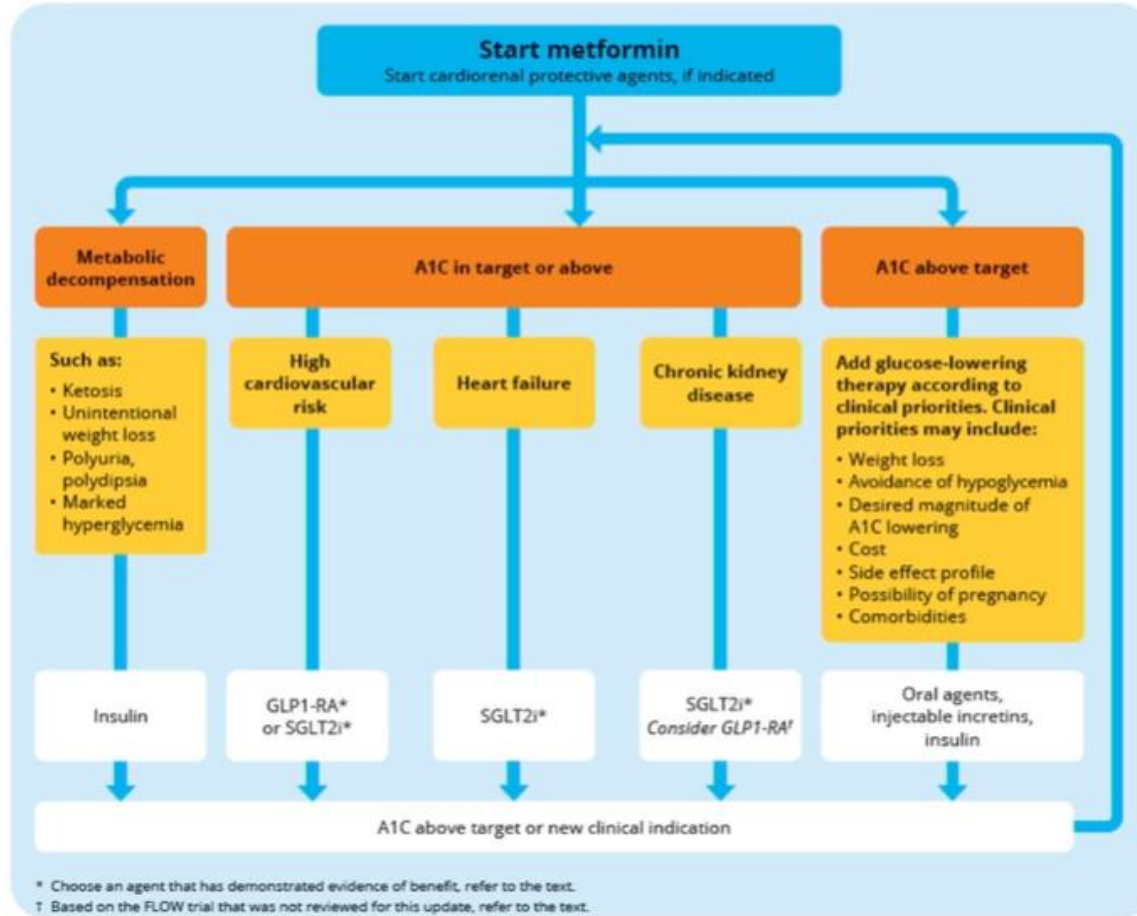
- Certain medications have specific benefits on the heart and the kidneys for people who have these problems already. Therefore, these medications should be used by anybody with these problems, even if their glucose levels are already good.
- Sometimes, people with type 2 diabetes also need insulin. Different types of insulin may be needed at different times of day. Other glucose-lowering medications are usually continued because they can reduce the amount of insulin needed.
- People with type 2 diabetes should discuss the pros and cons of different treatment plans with their health-care providers to decide together on what approach is best.

Introduction

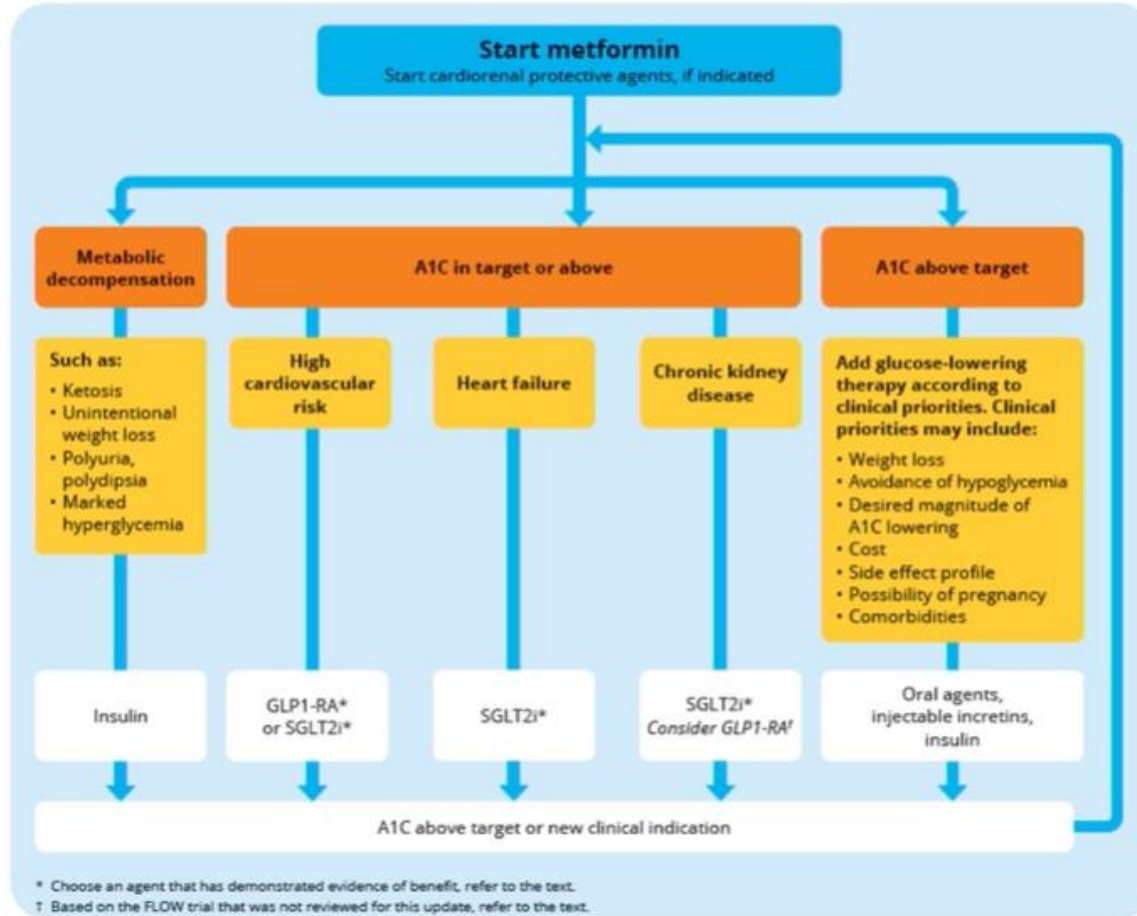
The United Kingdom Prospective Diabetes Study (UKPDS) established the importance of glycemic management to reduce the risk of long-term complications in people with type 2 diabetes [1]. More recently, clinical trials have demonstrated that certain glucose-lowering medications can reduce cardiac and renal complications of diabetes in certain populations, beyond the effects of glucose lowering alone. We conducted a thorough review of the



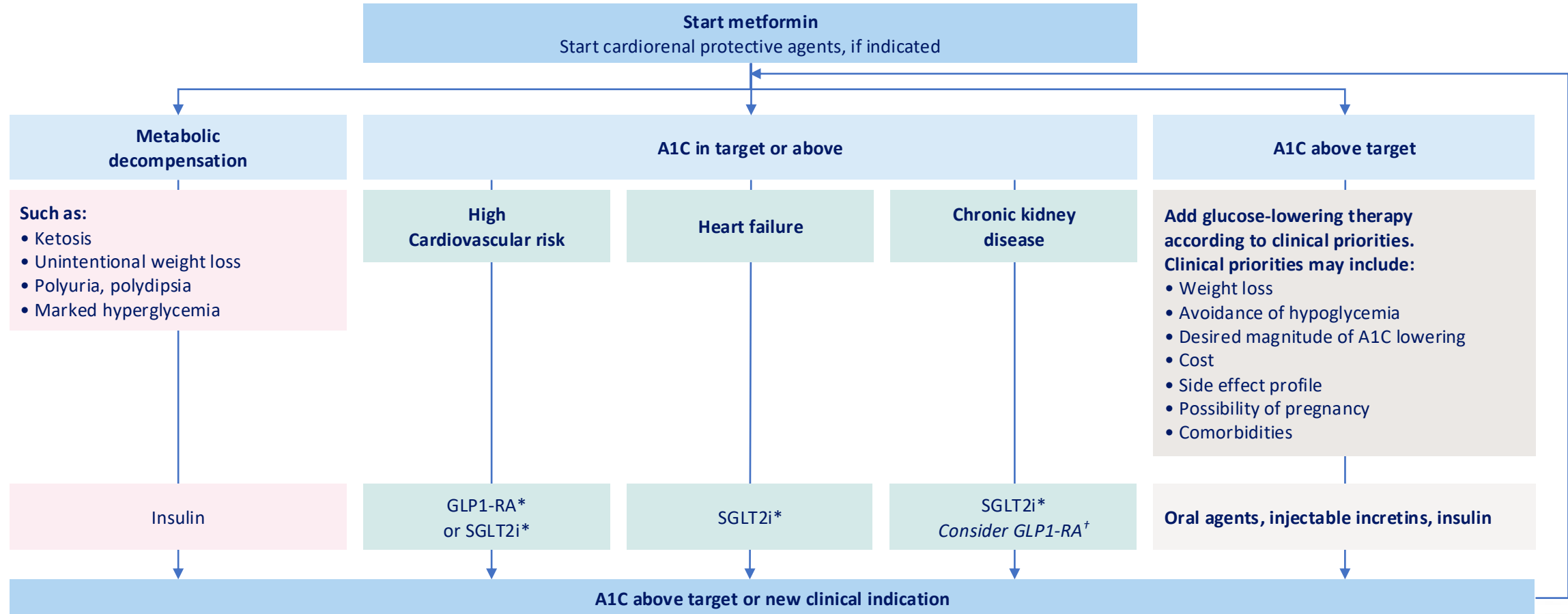
ALGORITHM FOR PHARMACOTHERAPY



ALGORITHM FOR PHARMACOTHERAPY



Pharmacotherapy for optimizing glycemia and cardiorenal risk



- Shah BR et al, Can J Diabetes 48 (2024) 415e424

- *Choose an agent that has demonstrated evidence of benefit, refer to the text in speaker note. †Based on the FLOW trial that was not reviewed for this update, refer to the text in speaker note.

- GLP1-RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter-2 inhibitor

CHANGES TO RECOMMENDATIONS

2
0
2
4

Priority should be given to medications with specific cardiorenal benefits for certain subgroups of individuals, regardless of the A1C level.

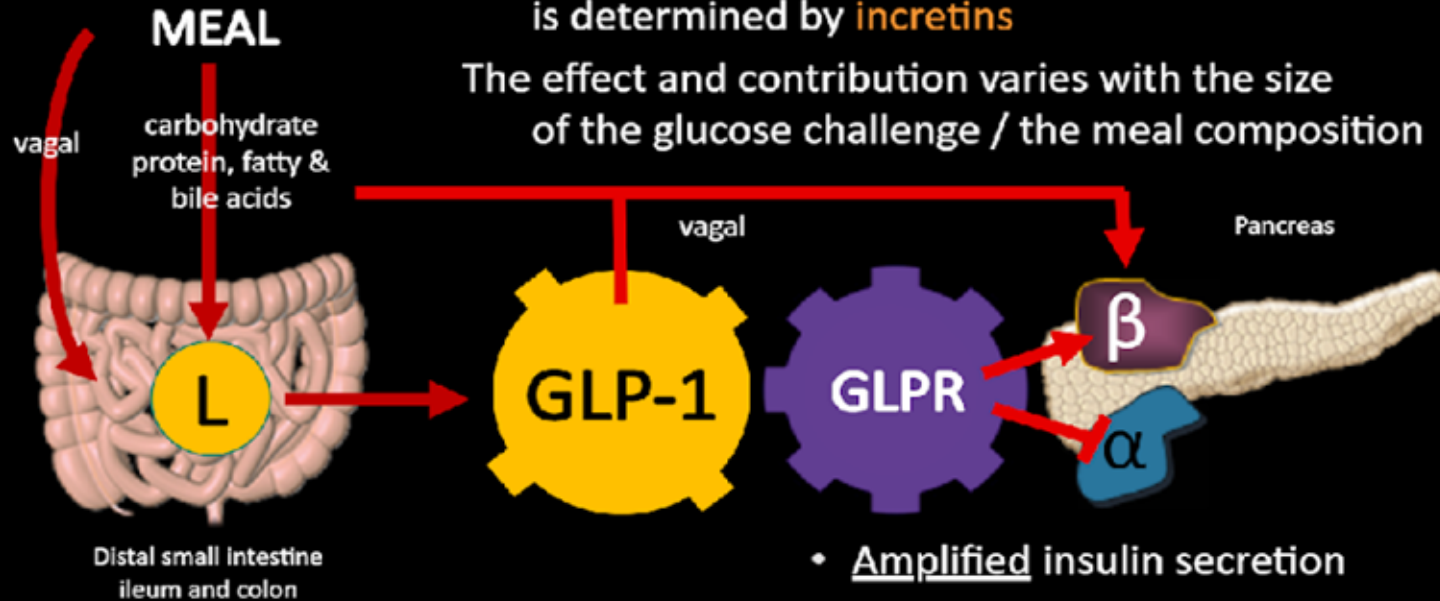
- a. A GLP1-RA and/or SGLT2 inhibitor with demonstrated evidence of benefit is recommended for individuals at high CV risk [Grade A, Level 1A for dulaglutide, liraglutide, or subcutaneous semaglutide; Grade A, Level 1A for empagliflozin; Grade B, Level 2 for canagliflozin].
- b. An SGLT2 inhibitor with demonstrated evidence of benefit is recommended for individuals with HF with reduced ejection fraction or HF with preserved ejection fraction [Grade A, Level 1A for dapagliflozin or empagliflozin].
- c. An SGLT2 inhibitor with demonstrated evidence of benefit is recommended for individuals with CKD [Grade A, Level 1A for canagliflozin, dapagliflozin, or empagliflozin].

GLP-1 Receptor Agonists

Incretins in β -cell biology^{3,4}

Up to 70% of total post-prandial insulin production is determined by **incretins**

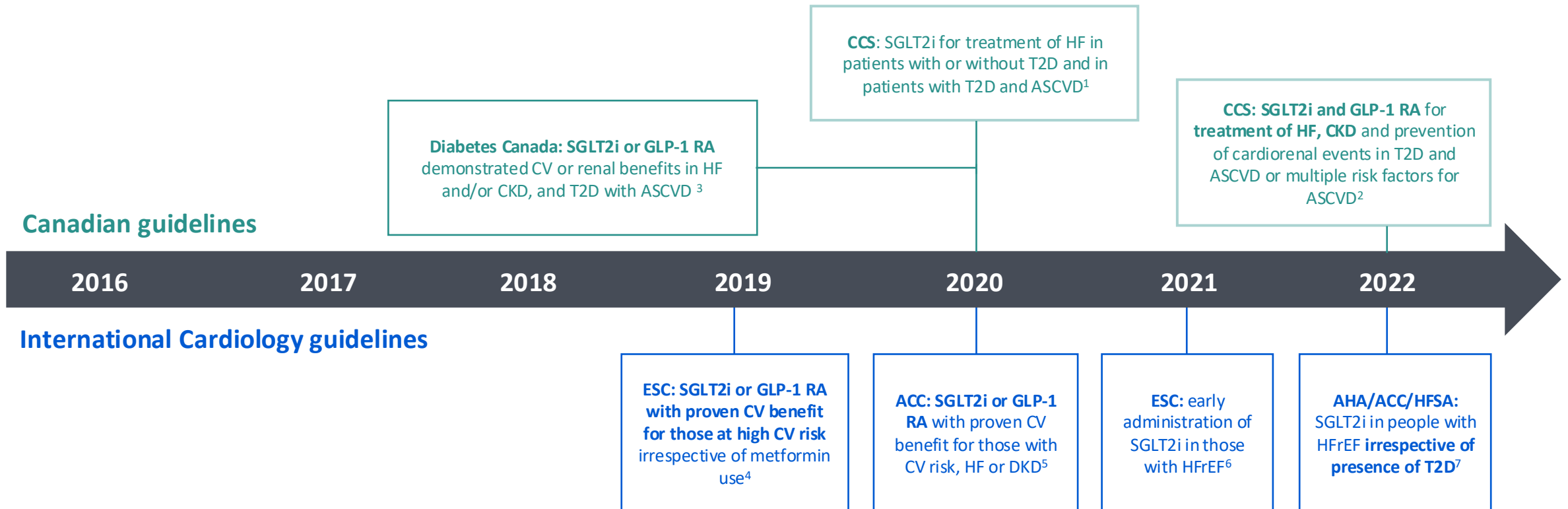
The effect and contribution varies with the size of the glucose challenge / the meal composition



- Amplified insulin secretion
- Improved glucose sensitivity
- β -cell proliferation/neogenesis
- Reduced β -cell apoptosis

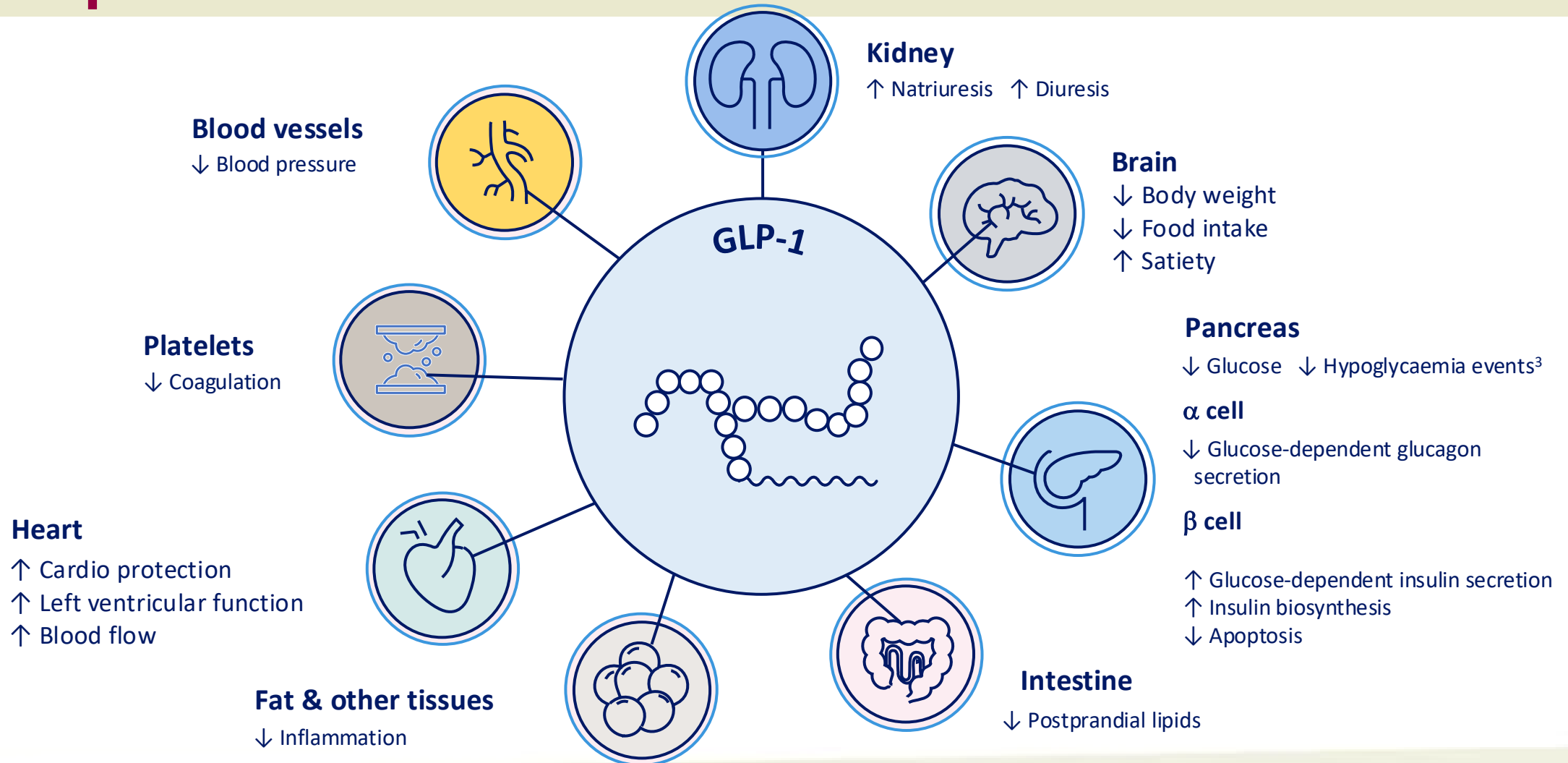
3. Campbell & Drucker. Cell Metabolism (2013); 4. Diakogiannaki, et al. Physiol. Behav. (2012).

GLP-1RAs have gradually been incorporated into major guidelines



ACC, American College of Cardiology; ADA, American Diabetes Association; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; DKD, diabetic kidney disease; ESC, European Society of Cardiology; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFSA, Heart Failure Society of America; SGLT2i, sodium-glucose cotransporter-2 inhibitor; T2D, type 2 diabetes.
 1. Diabetes Canada Clinical Practice Guidelines Expert Committee; Lipscombe L, et al. Can J Diabetes. 2020;44(7):575-591. 2. Mancini GBJ, et al. Can J Cardiol. 2022;38(8):1153-1167. 3. Ivers NM, et al. Can Fam Physician. 2019;65(1):14-24. 4. Cosentino F et al. Eur Heart J 2020;41:255-323; 5. Das SR et al. J Am Coll Cardiol 2020;76:1117-45; 6. McDonagh TA et al. Eur Heart J 2021;42:3599-726; 7. Heidenreich PA et al. Circulation 2022;145:e876-94.

Pleiotropic local and systemic actions of GLP-1¹⁻³



Phase 3 programme - STEP

Effects of semaglutide 2.4 mg OW in participants with overweight and obesity



The primary endpoint for all STEP trials is **weight loss**



STEP is the phase 3a/3b clinical development programme for subcutaneous semaglutide 2.4 mg weekly for weight management

STEP 1–4
Phase 3a

Semaglutide 2.4 mg

68 weeks + 7 week follow-up

The treatment period in all STEP trials is followed by a 7-week period off treatment to account for the long half-life of semaglutide

STEP 5
Phase 3b

Semaglutide 2.4 mg

104 weeks + 7 week follow-up

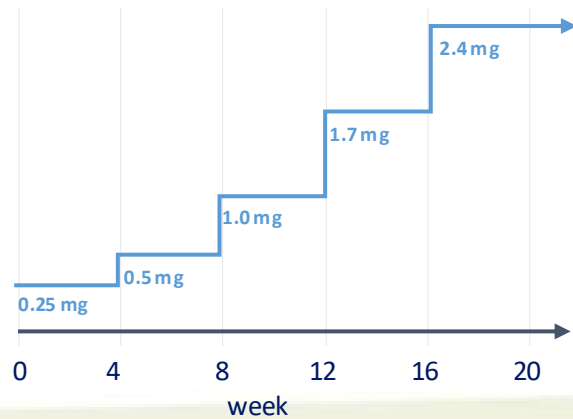
STEP 6
East Asian
Phase 3a

Semaglutide 1.7 and 2.4 mg

68 weeks + 7 week follow-up

Dose escalation

Semaglutide 2.4 mg OW treatment is initiated at 0.25 mg, followed by increments every 4 weeks to 0.5, 1.0, 1.7, and 2.4 mg OW

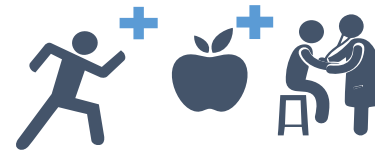


Across the STEP programme



Treatment with semaglutide 2.4 mg OW will be compared to placebo, as an adjunct to lifestyle intervention

STEP 3



In STEP 3 only, lifestyle intervention comprises IBT, an initial 8-week low-energy diet and higher target for physical activity

STEP 7 (China MRCT) Weight management in predominantly Asian population (44 weeks)

STEP 8 Head-to-head vs liraglutide 3.0 mg

STEP 9 in participants with obesity and knee osteoarthritis

STEP 10 reversal of pre-diabetes in participants with obesity and pre-diabetes

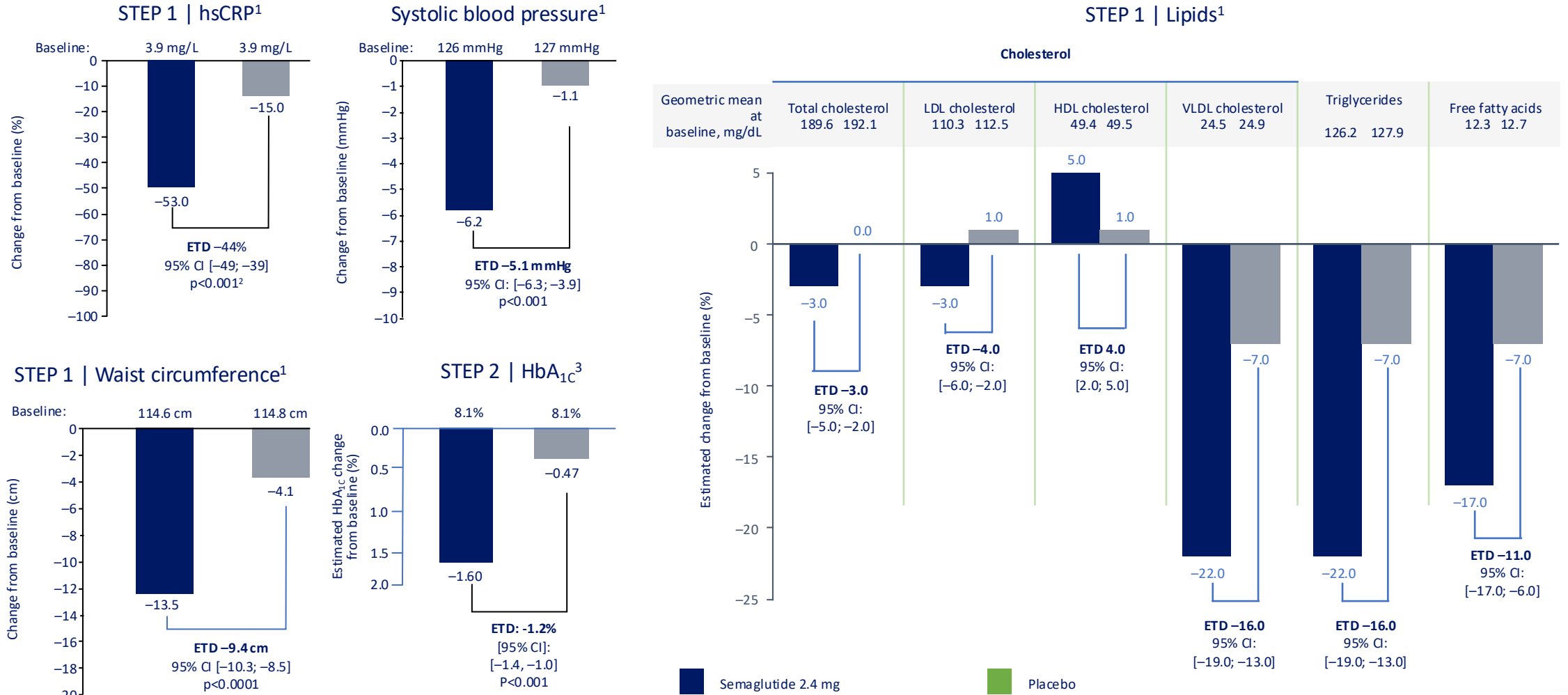
HFpEF in participants with obesity and heart failure with preserved ejection fraction

HFpEF DM in participants with obesity and type 2 diabetes

SELECT CV outcomes trial

Semaglutide has benefits on several CV risk factors

Semaglutide has benefits on several CV risk factors



CI, confidence interval; CV, cardiovascular; ETD, estimated treatment difference; ETR, estimated treatment ratio; HbA_{1c}, glycated haemoglobin; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein. Wilding et al. *N Engl J Med* 2021;384:989-1002; 2. Kosoribod M et al. Poster presented at the American College of Cardiology (ACC) conference, May 15-17 2021, virtual meeting; 3. Davies M et al. *Lancet* 2021;397:971-84.

Several studies examined role of GLP1-RA in DM type 2 and major cardiac events (MACE)

ELIXA (*Lixisenatide*)

LEADER (*Liraglutide*)

SUSTAIN-6 (*OW-Semaglutide*)

EXSCEL (*Exenatide*)

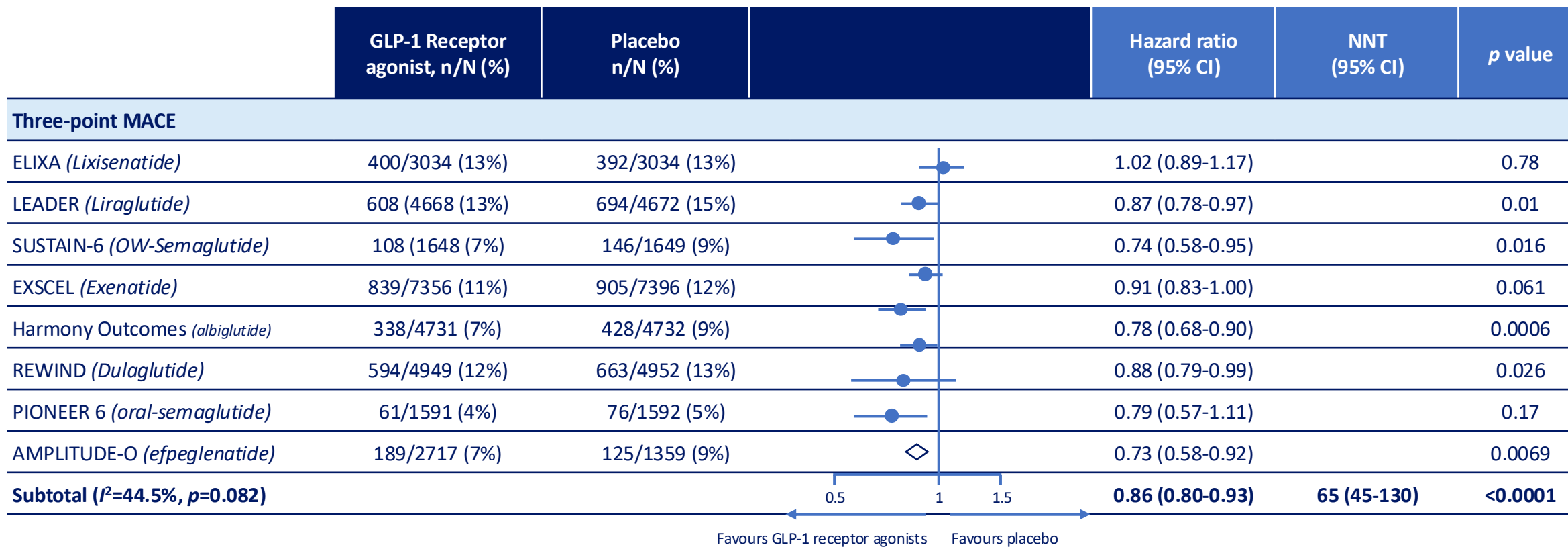
Harmony Outcomes (*albiglutide*)

REWIND (*Dulaglutide*)

PIONEER 6 (*oral-semaglutide*)

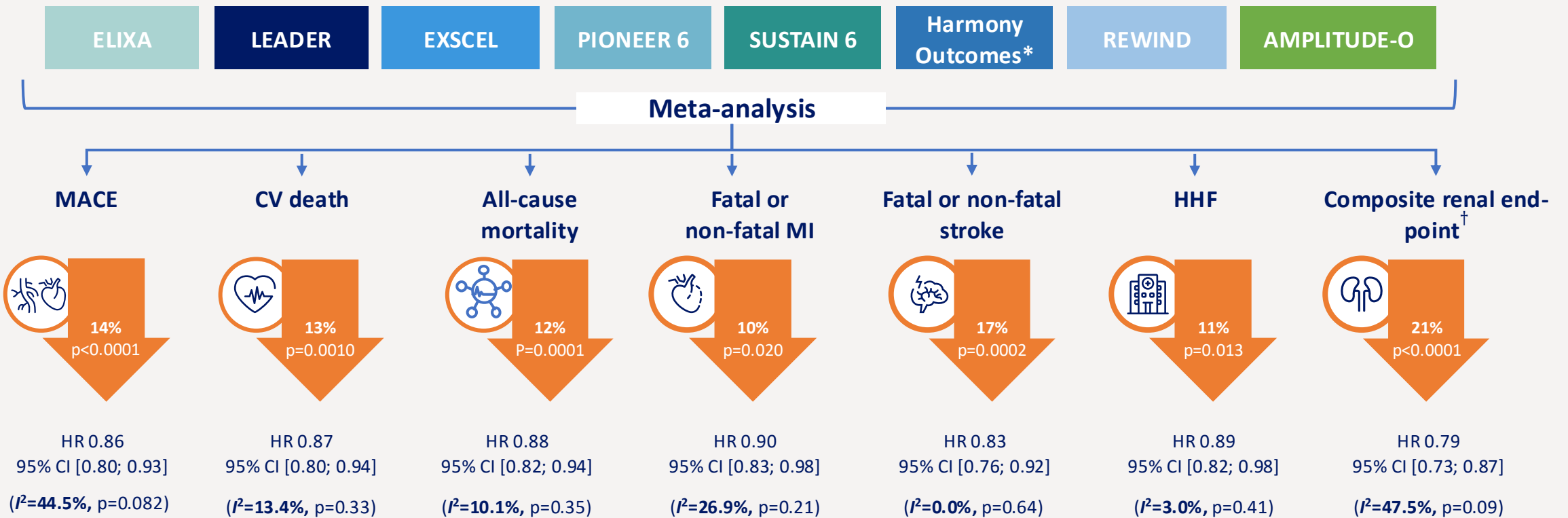
AMPLITUDE-O (*efpeglenatide*)

Previous evidence from T2D CVOTs shows GLP1-RA protect from major cardiac events (MACE)



**GLP-1 RAs reduced MACE by 14% (HR 0.86 [95% CI 0.80–0.93]; $p < 0.0001$),
 with no significant heterogeneity across GLP-1 receptor agonists**

Meta-analysis of GLP-1RA T2D CVOTs demonstrated a significant reduction in all measured CV events



*Albiglutide was withdrawn from worldwide commercial market in July 2018; †Composite renal endpoint including microalbuminuria.
 CI, confidence interval; CV, cardiovascular; CVOT, cardiovascular outcomes trial; GLP-1RA, glucagon-like peptide-1 receptor agonist; HHF, hospitalisations for heart failure; HR, hazard ratio; I^2 , heterogeneity; MACE, major adverse cardiovascular events; MI, myocardial infarction; T2D, Type 2 diabetes. Sattar N et al. Lancet Diabetes Endocrinol 2021;9:653-62.

SELECT trial

- Some GLP-1 RA's have demonstrated a reduction in MACE in pts with DM type 2 who are at high cardiovascular risk
- Hypothesis: semaglutide 2.4mg SC once weekly, in addition to standard of care, will reduce the incidence of CV events among patients with overweight or obesity and pre-existing CV disease, but no diabetes
 - Randomized, double-blind, placebo controlled
 - Event driven
 - Superiority
 - 804 clinical sites in 41 countries

SELECT trial: Key Endpoints

Primary Composite (Time to first event):

- CV death, nonfatal MI, or nonfatal stroke

Confirmatory Secondary (Time to first event and tested in hierarchical order):

- CV death
- Heart failure composite (CV death or hospitalization or urgent visit for heart failure)
- All cause death

Supportive Secondary (Time to first event):

- Expanded CV composites
- nonfatal MI, or nonfatal stroke
- Hospitalization or urgent visit for heart failure
- Coronary revascularization or unstable angina
- Nephropathy composite
- Progression to diabetes or prediabetes

SELECT: Eligibility criteria

Key inclusion criteria^{1,2}

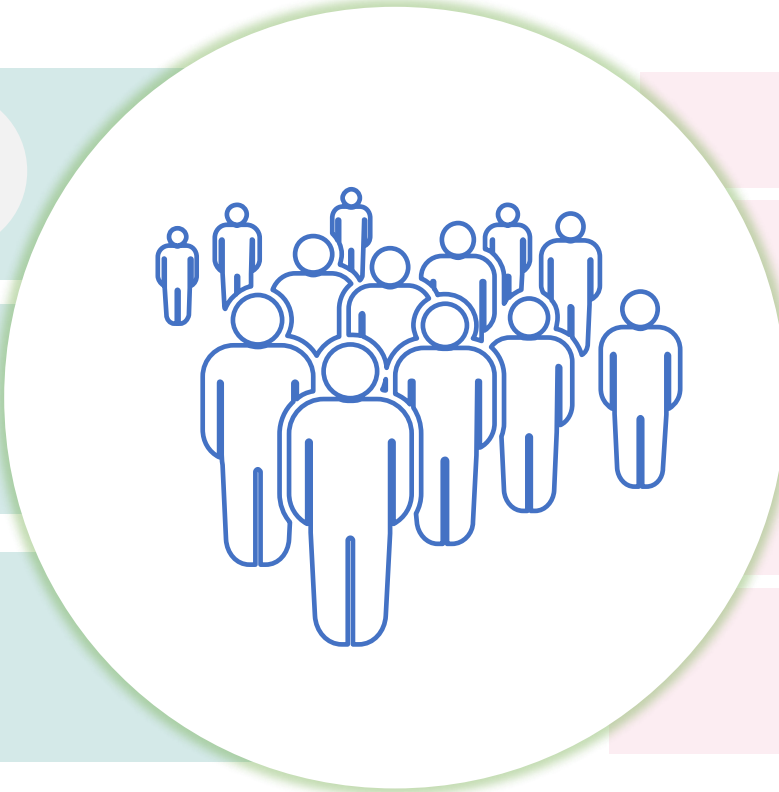
Prior MI / stroke*
Symptomatic PAD[†]



Male or female
≥45 years of age



BMI: ≥27 kg/m²



Key exclusion criteria^{1,2}

HbA_{1c} ≥6.5%



History of type 1
or type 2 diabetes[‡]



Treatment with glucose
lowering agents within the
last 90 days

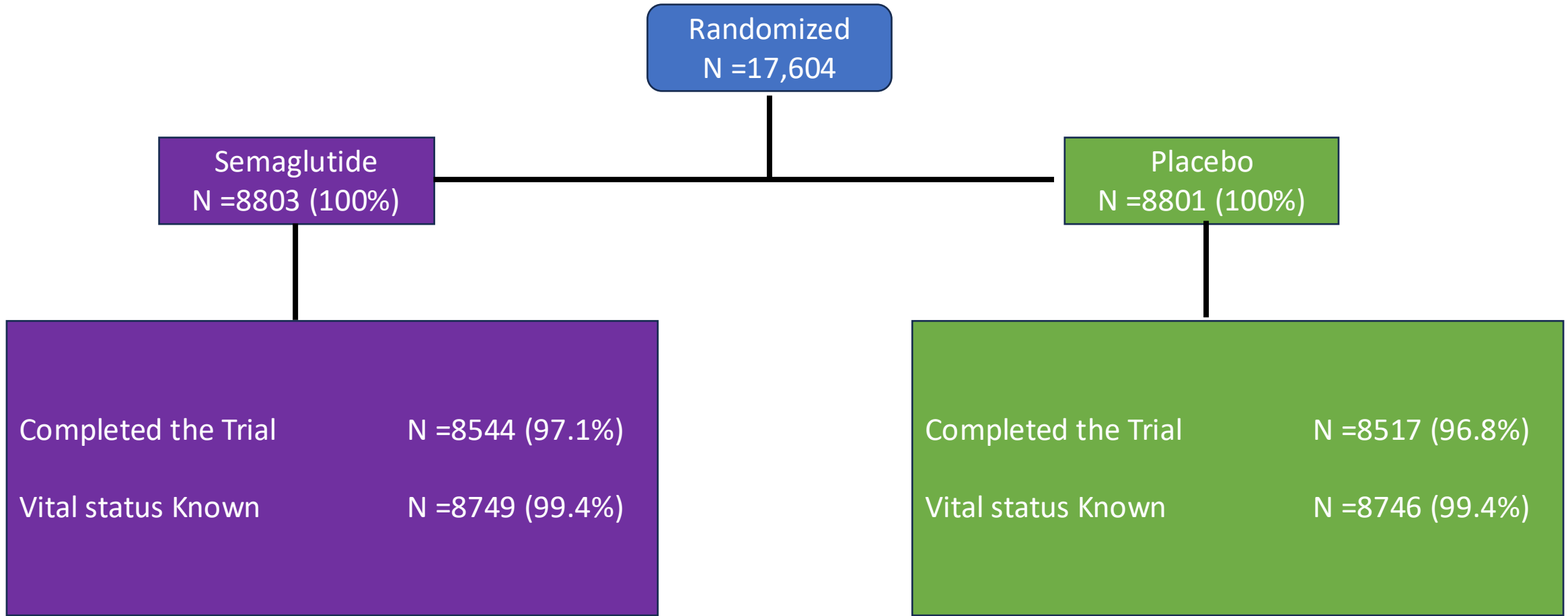


Presently classified
as being in NYHA
class IV heart failure



*>60 days prior to the day of screening. †Symptomatic PAD evidenced by intermittent claudication with ankle-brachial index less than 0.85 (at rest), or peripheral arterial revascularization procedure, or amputation due to atherosclerotic disease. ‡Gestational diabetes was allowed. BMI, body mass index; HbA_{1c}, glycated hemoglobin; MI, myocardial infarction; NYHA, New York Heart Association; PAD, peripheral artery disease; SELECT, semaglutide effects on cardiovascular outcomes in people with overweight or obesity. 1. Ryan DH et al. Am Heart J 2020;229:61-9; 2. Lingvay I et al. Obesity (Silver Spring) 2023;31:111-22.

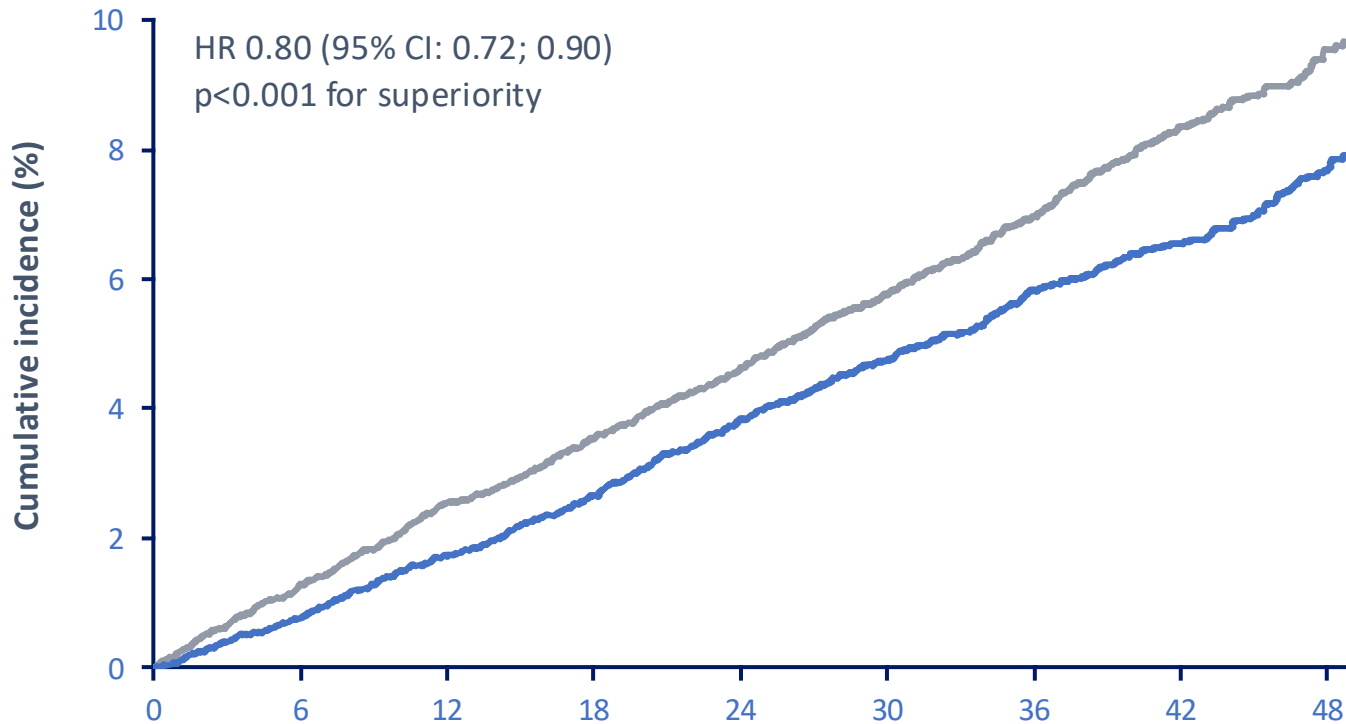
Select Trial: Flow of patients



Follow-up 39.8 ± 9.4 months

SELECT: Cumulative incidence of MACE

(Primary cardiovascular composite endpoint)



No. at risk	0	6	12	18	24	30	36	42	48
Semaglutide	8,803	8,695	8,561	8,427	8,254	7,229	5,777	4,126	1,734
Placebo	8,801	8,652	8,487	8,326	8,164	7,101	5,660	4,015	1,672

— Semaglutide 2.4 mg — Placebo

20%
reduction in
risk of MACE*

Semaglutide 2.4 mg significantly reduced the risk of MACE by 20% compared with placebo in people with obesity and established CVD, without T2D^{1,2}



All three components (death from CV causes, non-fatal MI and non-fatal stroke) contributed to MACE risk reduction

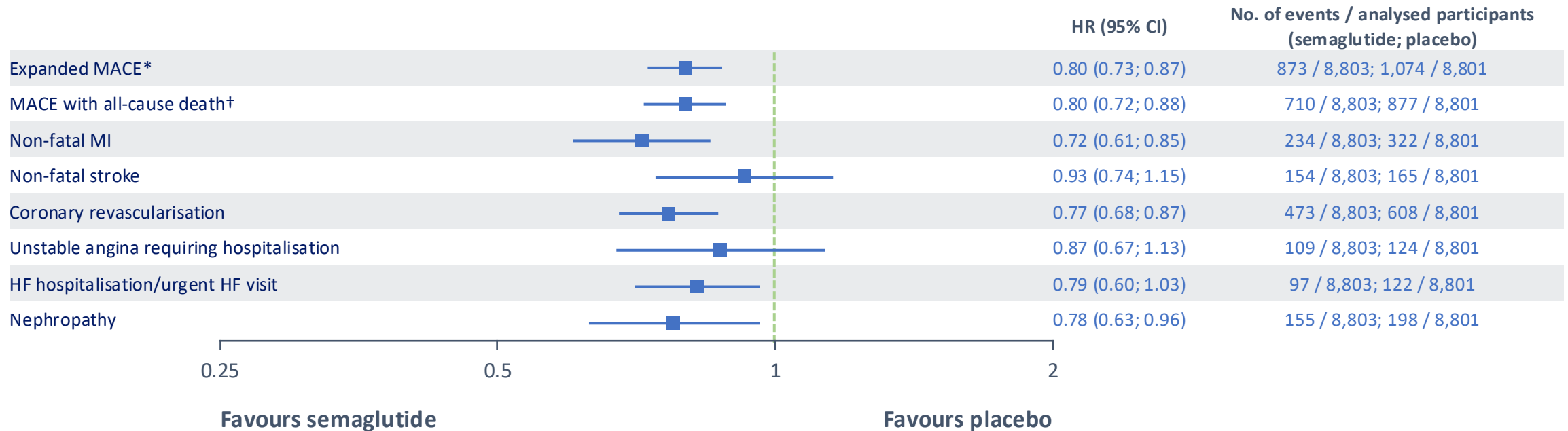


Mean follow-up time was 39.8 months

Cumulative incidence (using the Aalen-Johansen method) of the composite MACE primary endpoint. The HR was estimated using a Cox proportional hazards regression model. The proportion of participants with MACE was 6.5% with semaglutide 2.4 mg and 8.0% with placebo. MACE was defined as death from CV causes, non-fatal myocardial infarction, or non-fatal stroke. CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction. 1. Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563; 2. Novo Nordisk A/S. Company announcement, 8 August 2023. Available at: <https://www.novonordisk.com/content/nrncorp/global/en/news-and-media/news-and-ir-materials/news-details.html?id=166301>. Accessed October 2023.

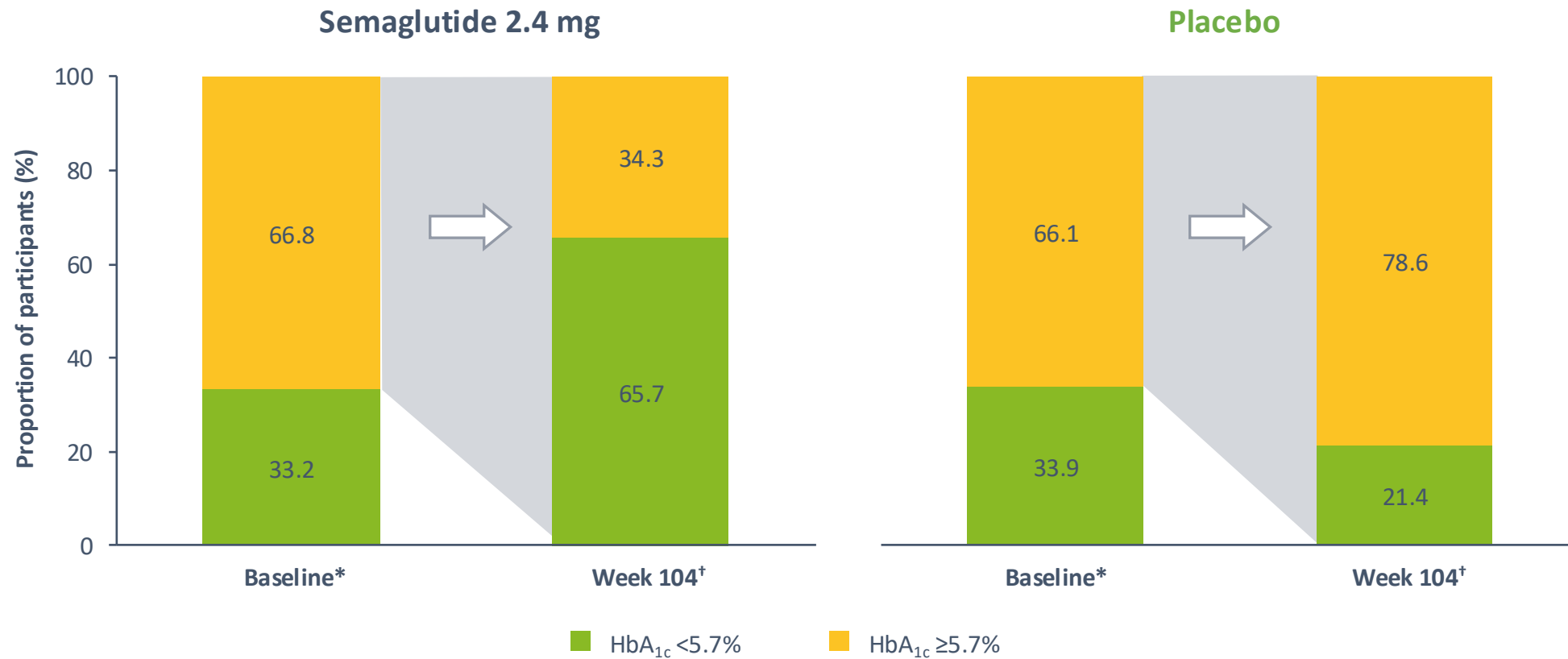
SELECT: Secondary CV endpoints

Semaglutide 2.4 mg had **consistent beneficial effects** across measured CV endpoints



HRs were estimated using a Cox proportional hazards regression model. Widths of the CIs have not been adjusted for multiplicity. *Death from CV causes, non-fatal MI, non-fatal stroke, coronary revascularisation or unstable angina requiring hospitalisation. †All-cause death, non-fatal MI or non-fatal stroke. CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction. Lincoff AM et al. N Engl J Med 2023;DOI:10.1056/NEJMoa2307563.

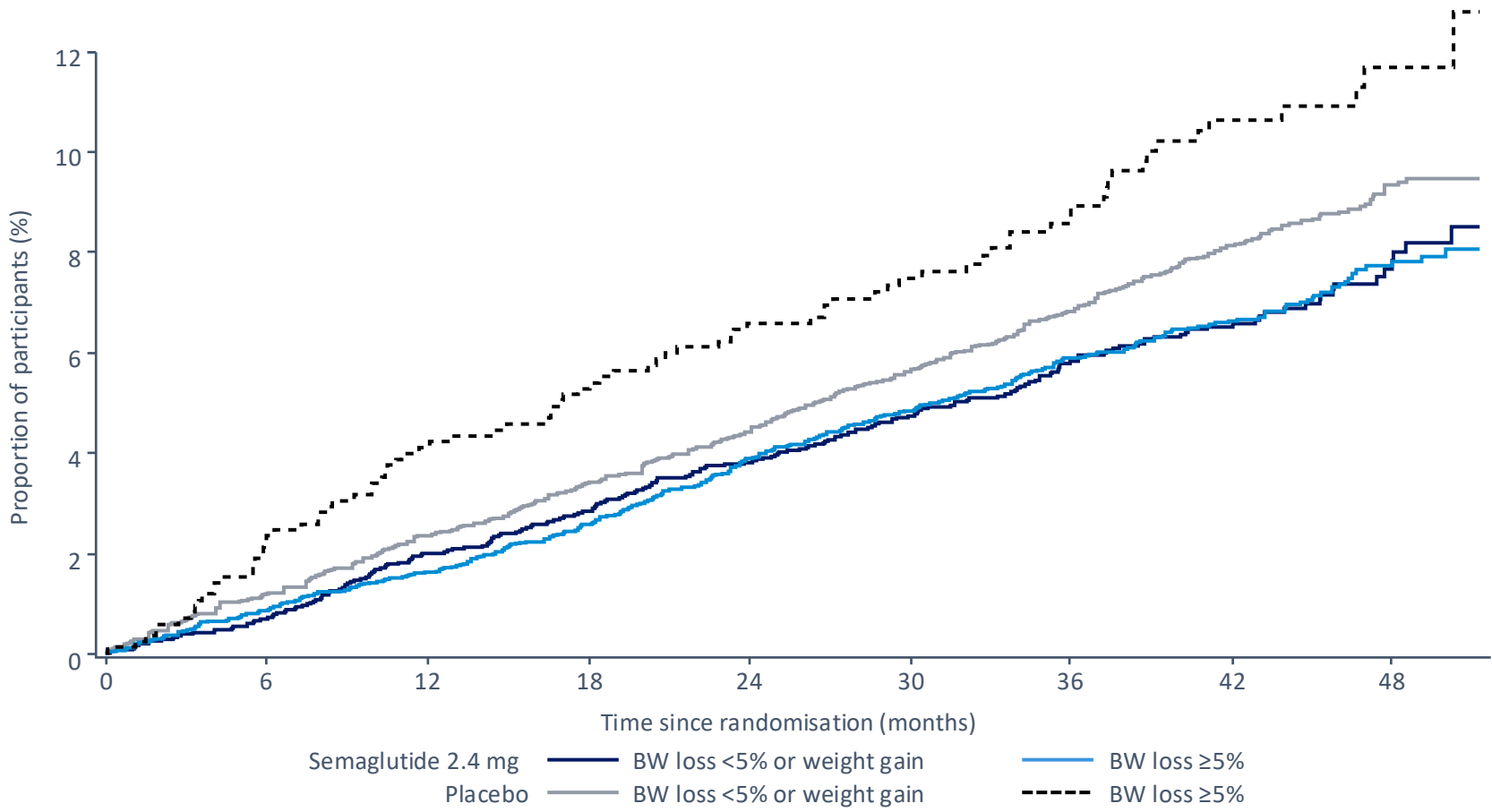
SELECT: Change in HbA_{1c}



Proportions estimated using logistic regression with treatment as factor and baseline HbA_{1c} as a covariate. *Number of participants with HbA_{1c} ≥ 5.7% at baseline was 5,877 for semaglutide and 5,819 for placebo. †Number of participants with HbA_{1c} ≥ 5.7% at baseline and evaluable data (assessment or imputation) at week 104 was 5,750 for semaglutide and 5,663 for placebo. CI, confidence interval; ETD, estimated treatment difference; HbA_{1c}, glycated haemoglobin. *Lancet* 2023; DOI: 10.1016/S0140-6736(23)00756-3.

MACE by percentage change in body weight

Baseline to week 20



Data from in-trial period.
BW, body weight; MACE, major adverse cardiovascular event.
Deanfield J, et al. Obes Facts 2024; 17 Suppl 1: 491-492.

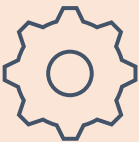
SELECT Conclusions



A consistent reduction in MACE was achieved with semaglutide 2.4 mg vs placebo regardless of the level of baseline adiposity



The magnitude of the treatment effect with semaglutide 2.4 mg on MACE was independent of the extent of weight loss (<5 and \geq 5% at week 20)



The results from this pre-specified analysis suggest alternative mechanisms of improved CV outcome with semaglutide 2.4 mg, beyond reduction in adiposity



Many people with overweight or obesity, and not just those who lose weight, may derive CV benefit from semaglutide 2.4 mg

Numbers Needed to Treat to prevent 1 MACE for GLP1-RA

2-year NNT from SUSTAIN-6 (T2D) = 45¹

3-year NNT for any GLP1-RA in T2D = 65²



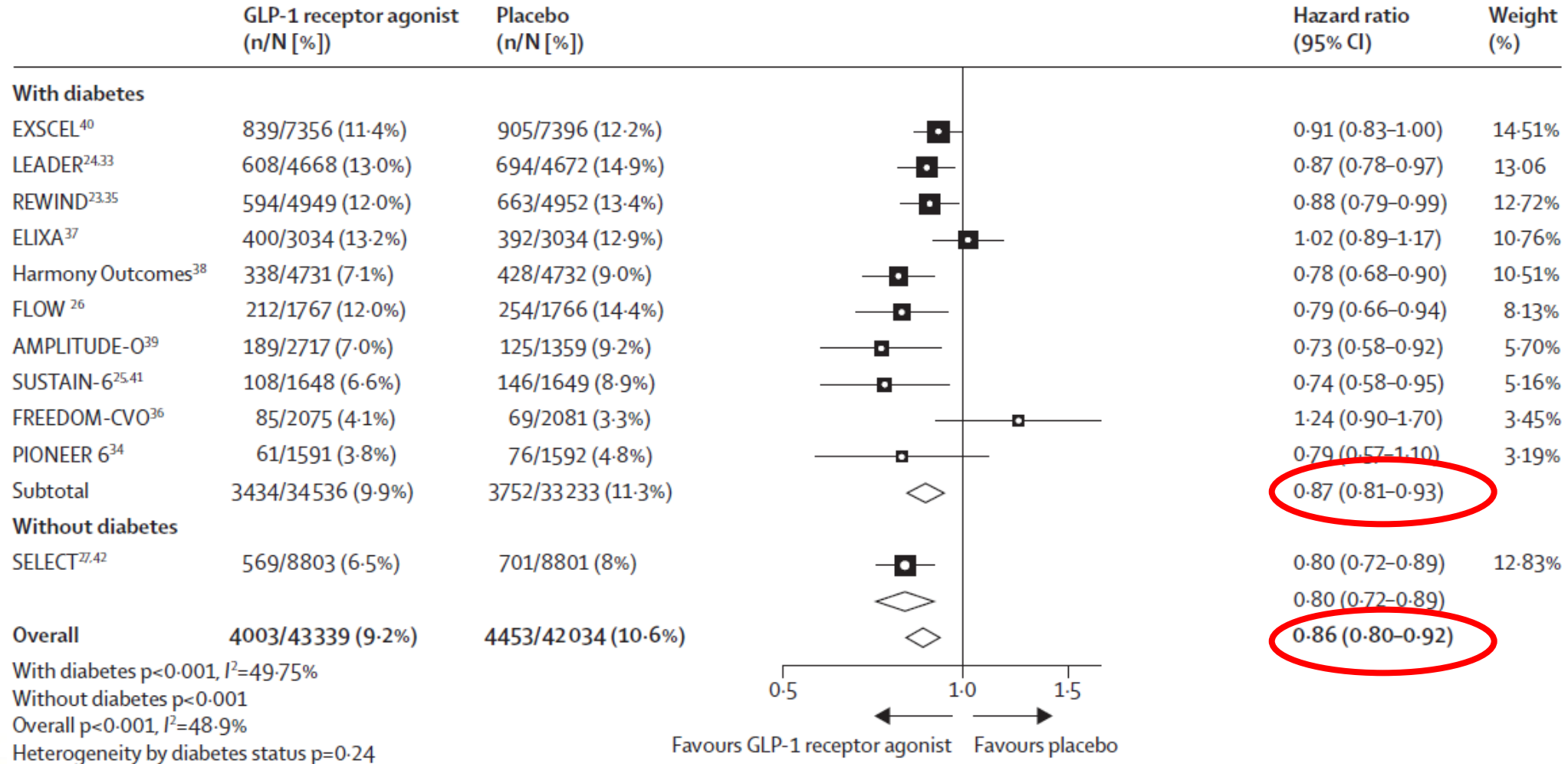
3-year NNT from FLOW (CKD) = 45⁴

5-year NNT from SUSTAIN-6 (T2D) = 18¹

5-year NNT from SELECT (obesity) = 45³

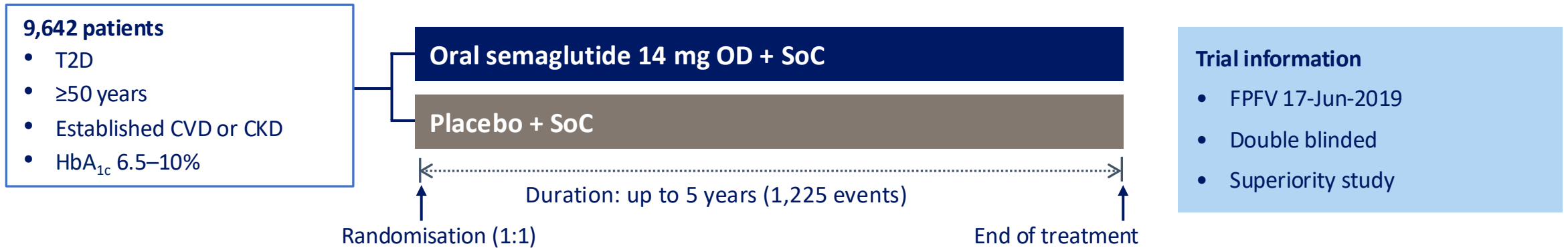
GLP-1 resulted in a significant reduction in MACE, compared to placebo

A Major adverse cardiovascular events



SOUL: trial design

Oral semaglutide cardiovascular outcomes trial in patients with T2D



Trial objective

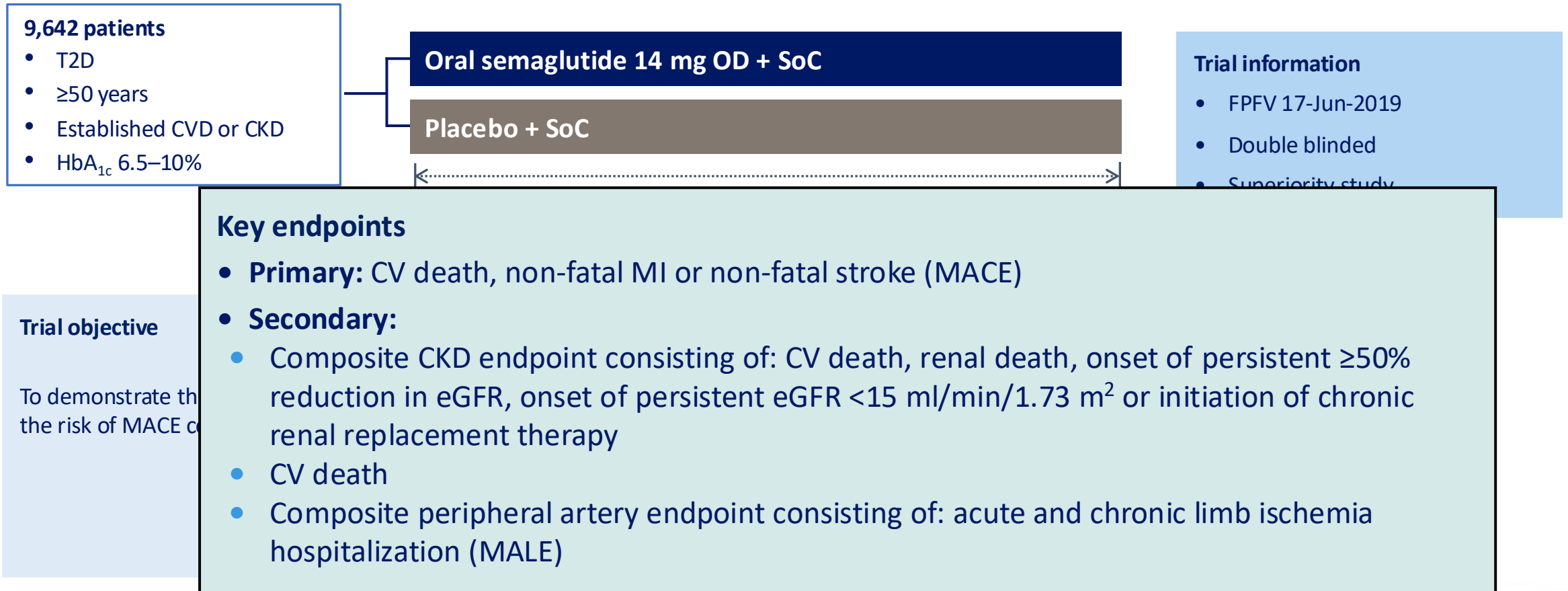
To demonstrate that oral semaglutide lowers the risk of MACE compared to placebo

Key endpoints

- **Primary:** CV death, non-fatal MI or non-fatal stroke (MACE)
- **Secondary:**
 - Composite CKD endpoint consisting of: CV death, renal death, onset of persistent ≥50% reduction in eGFR, onset of persistent eGFR <15 ml/min/1.73 m² or initiation of chronic renal replacement therapy
 - CV death
 - Composite peripheral artery endpoint consisting of: acute and chronic limb ischemia hospitalization (MALE)

SOUL: trial design

Oral semaglutide cardiovascular outcomes trial in patients with T2D



Oral semaglutide significantly decreased risk of MACE by 14% relative to placebo in people with T2D and ASCVD and/or CKD

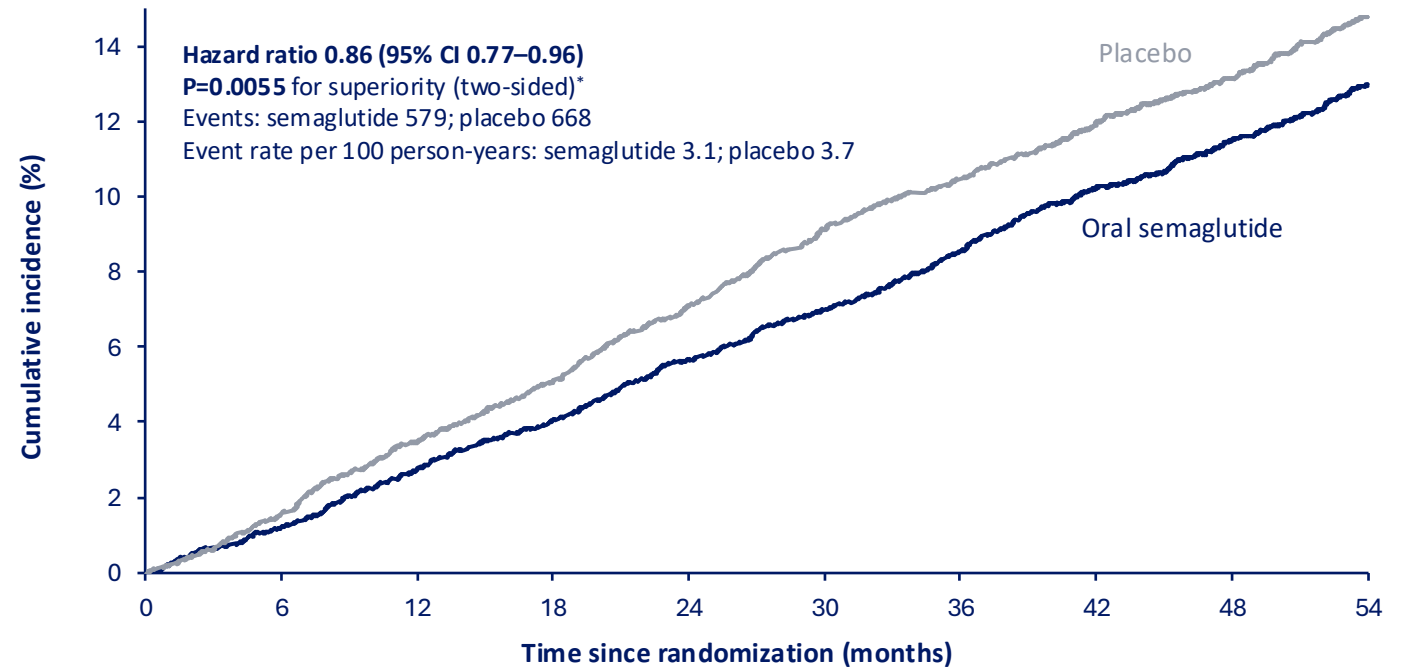
Primary cardiovascular composite outcome (3-point MACE)

Time from randomisation to first occurrence of a composite outcome consisting of:

- CV death
- Non-fatal MI
- Non-fatal stroke



Each component of the primary outcome contributed to the superior risk reduction



No. at risk

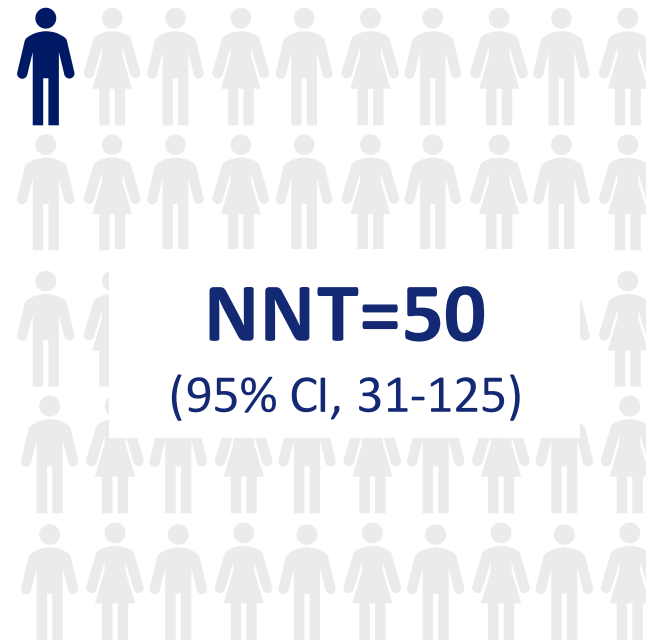
Placebo	4825	4718	4583	4455	4322	4194	4101	3727	2517	1346
Semaglutide	4825	4743	4835	4542	4438	4346	4239	3831	2555	1346

* The two-sided significance level for the primary endpoint after accounting for the interim analysis was 0.04561. ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; MACE,

Number needed to treat over 3 years

Pre-specified analysis

To prevent one
primary outcome:*



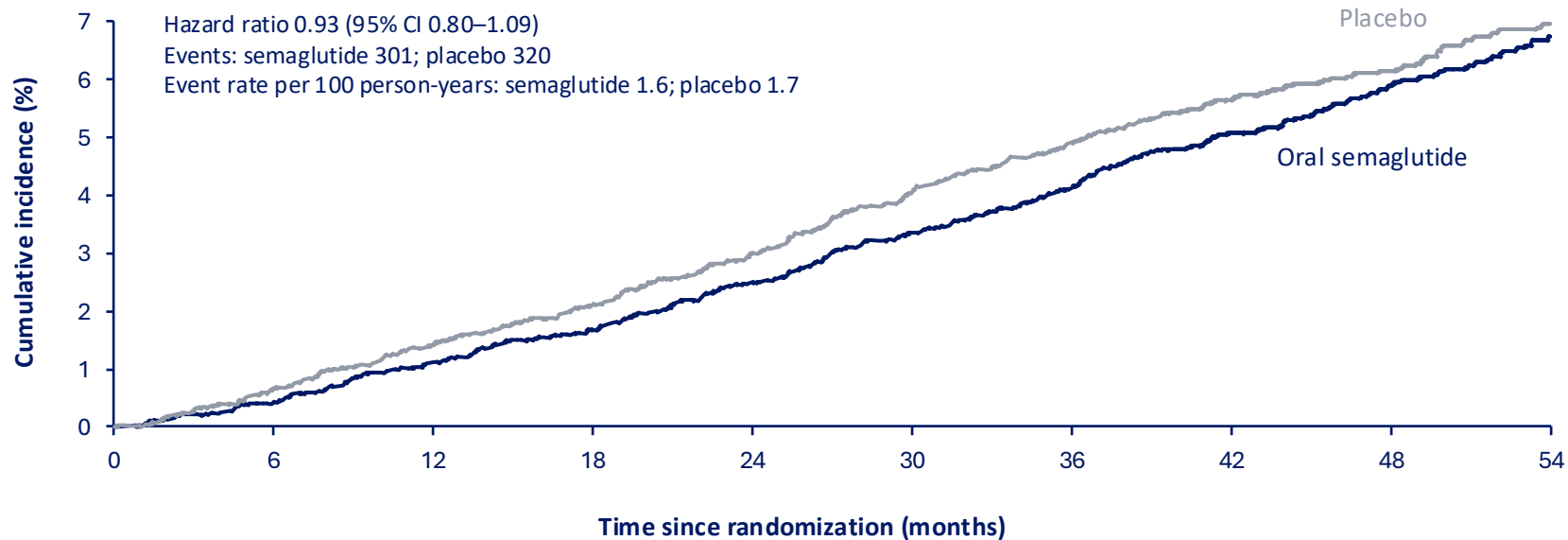
*Non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death. CI, confidence interval; NNT, number needed to treat.

McGuire DK., et al. N Engl J Med. 2025: <https://www.nejm.org/doi/full/10.1056/NEJMoa2501006>

Oral semaglutide indicated decreased risk of death from cardiovascular causes*

Component of primary outcome and a confirmatory secondary outcome

Death from cardiovascular cause



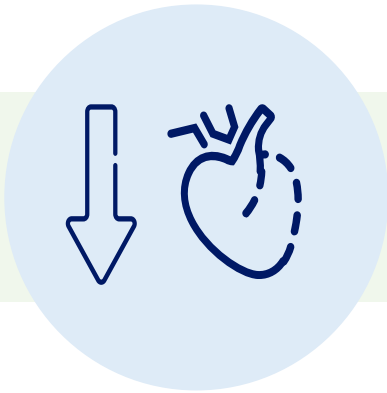
No. at risk

Placebo	4825	4760	4680	4594	4511	4427	4355	3991	2721	1460
Semaglutide	4825	4781	4712	4648	4583	4509	4436	4040	2727	1460

- The cumulative incidence of the second confirmatory secondary outcome (death from cardiovascular causes), which is also a component of the primary outcome.
 - CI, confidence interval

- * not controlled for multiplicity. McGuire DK., et al. N Engl J Med. 2025; <https://www.nejm.org/doi/full/10.1056/NEJMoa2501006>.

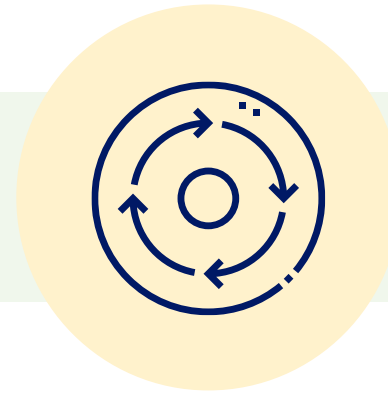
Summary of primary outcome



Oral semaglutide significantly decreased risk of **MACE by 14%** relative to placebo in people with T2D and ASCVD and/or CKD



Each component of the primary outcome **contributed** to the superior risk reduction, with non-fatal MI being the highest contributor



Results were **consistent across prespecified sensitivity analyses** of the primary outcome



Generally consistent across subgroups, including age, cardiovascular/kidney disease, eGFR, and concomitant medication



What about Tirzepatide (TZP)

Tirzepatide (TZP) - Background

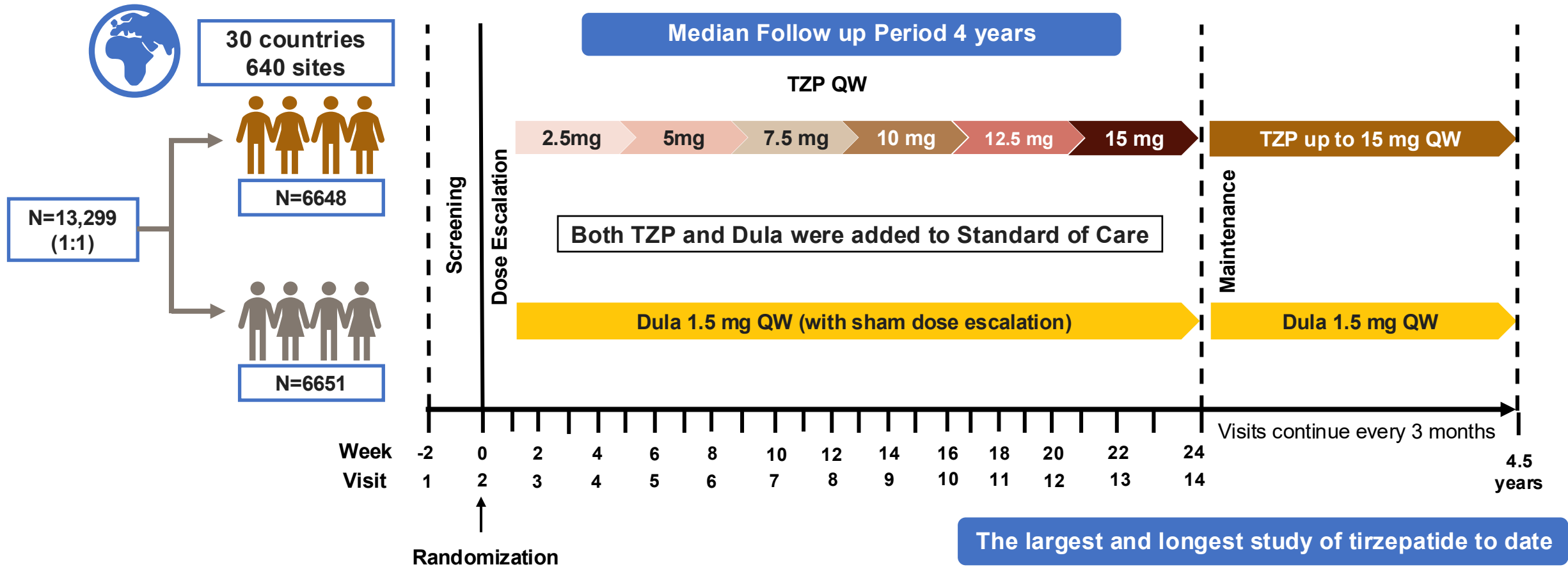
- GLP-1 RAs have demonstrated reduction in incidence of MACE in patients with high cardiovascular risk and DM Type 2, CKD, or obesity
- Based on clinical trial data, clinical guidelines have integrated the use of GLP-1 RAs into the treatment of patients at high cardiovascular risk
- Tirzepatide (TZP) is a dual agonist of the GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors
- TZP demonstrated incremental benefits for glycemic control, weight, atherogenic lipoprotein levels, blood pressure and kidney-related outcomes as compared with selective GLP-1 RAs or other glucose-lowering agents

Tirzepatide (TZP) - Background

- TZP effect on cardiovascular outcomes in randomized clinical trial has not been investigated previously
- The established role of GLP-1 RA in the management of T2D in patients with high cardiovascular risk, precluded direct comparison of TZP with a placebo control
- SURPASS-CVOT was conducted to determine the cardiovascular effects of TZP compared with the selective GLP-1 RA dulaglutide, in people with T2D and ASCVD
- As dulaglutide demonstrated reduced the incidence of MACE, compared with placebo, (REWIND trial), this study was designed to determine whether TZP was non-inferior to dulaglutide with respect to CV events, as well as whether TZP was associated with a greater CV benefit

Study Design

- Event driven, randomized, double blind, active comparator, parallel group study



Objective and Endpoints (1 of 3)



Primary Objective and Endpoint

To assess the effect of TZP in comparison with Dulaglutide on time to first occurrence of the composite MACE-3 (Cardiovascular Death, Myocardial Infarction or Stroke)

Primary analysis was conducted to demonstrate non-inferiority of TZP compared to dulaglutide for MACE-3, followed by establishing superiority of TZP compared to dulaglutide and putative placebo

Objective and Endpoints (2 of 3)



Key Secondary Endpoints

- Death from cardiovascular causes
- Myocardial Infarction
- Stroke
- Death from any cause
- Composite of death from cardiovascular causes, myocardial infarction, stroke, or coronary revascularization
- Composite of death from cardiovascular causes or hospitalization or urgent visit for heart failure
- Change from baseline to 36 months in eGFR in patients with high or very high-risk chronic kidney disease (as defined by KDIGO guideline 2024)

Objective and Endpoints (3 of 3)



Other Secondary Endpoints

- Change from baseline to 36 months in the following:
 - HbA1c
 - Body weight
 - Systolic blood pressure
- Change from baseline to 24 months in the following
 - Triglyceride level
 - Low-density lipoprotein cholesterol level (LDL-C)

Safety Endpoints



Key Safety Endpoints

- Any adverse event that emerged during treatment
- Serious Adverse events
- Adverse event leading to drug discontinuation
- Severe Hypoglycaemia
- Gastrointestinal adverse events (Nausea; Vomiting; Diarrhea)
- Severe Gastrointestinal adverse events
- Pancreatic Events (Pancreatitis; Pancreatic carcinoma)
- Gallbladder related adverse events (Cholelithiasis; Cholecystitis)
- Thyroid events (Medullary thyroid cancer; Other thyroid carcinoma)
- Serious atrial fibrillation
- Hypersensitivity reactions (Anaphylactic reaction; Hypersensitivity)
- Renal Events (Acute kidney injury; Chronic kidney disease)

Key Inclusion and Exclusion Criteria

Inclusion Criteria



Adults aged ≥ 40 years



T2D (HbA1c $\geq 7\%$ and $\leq 10.5\%$)



BMI $\geq 25\text{kg/m}^2$



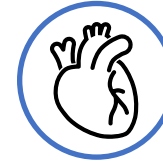
Established ASCVD, including ≥ 1 of the following

- Coronary artery disease
- Cerebrovascular disease
- Peripheral artery disease

Exclusion Criteria



HbA1c $> 10.5\%$



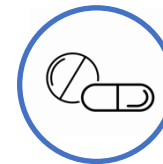
- Hospitalization for CHF within 2 months prior to screening, chronic NYHA class IV HF and planned coronary, carotid or peripheral revascularization
- CV event or intervention < 60 days prior to screening



History of acute or chronic pancreatitis



eGFR < 15 mL/minute/1.73m² or on chronic dialysis



GLP-1 RA or pramlintide treatment within 3 months prior to screening

Baseline Characteristics

SURPASS-CVOT

Baseline Characteristics^{1,2}



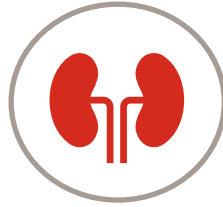
Mean Age 64.1 ± 8.8 years
29% were women



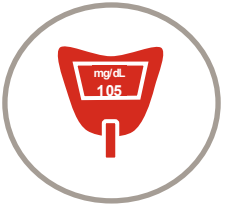
Tobacco use 14.9%



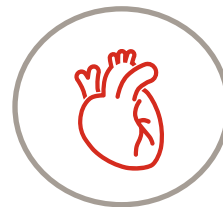
Mean Weight 92.5 ± 18.8 kg
Mean BMI 32.6 ± 5.5 kg/m²



- eGFR (CKD-EPI) 78.9 ± 23.8 mL/min/1.73m²
- Percentage of patients with high or very high-risk CKD 22.7%
- UACR 2.49 mg/mmol
- Microalbuminuria 32%
- Macroalbuminuria 11.5%



Mean diabetes duration 14.7 ± 8.8 years
HbA1c $8.4 \pm 0.9\%$



SBP 135.3 ± 15.7 mmHg
DBP 78.0 ± 9.7 mmHg



Participants Distribution
North America 14.7%
South America 28.8%
Europe 46.2%
Asia-Pacific 10.2%



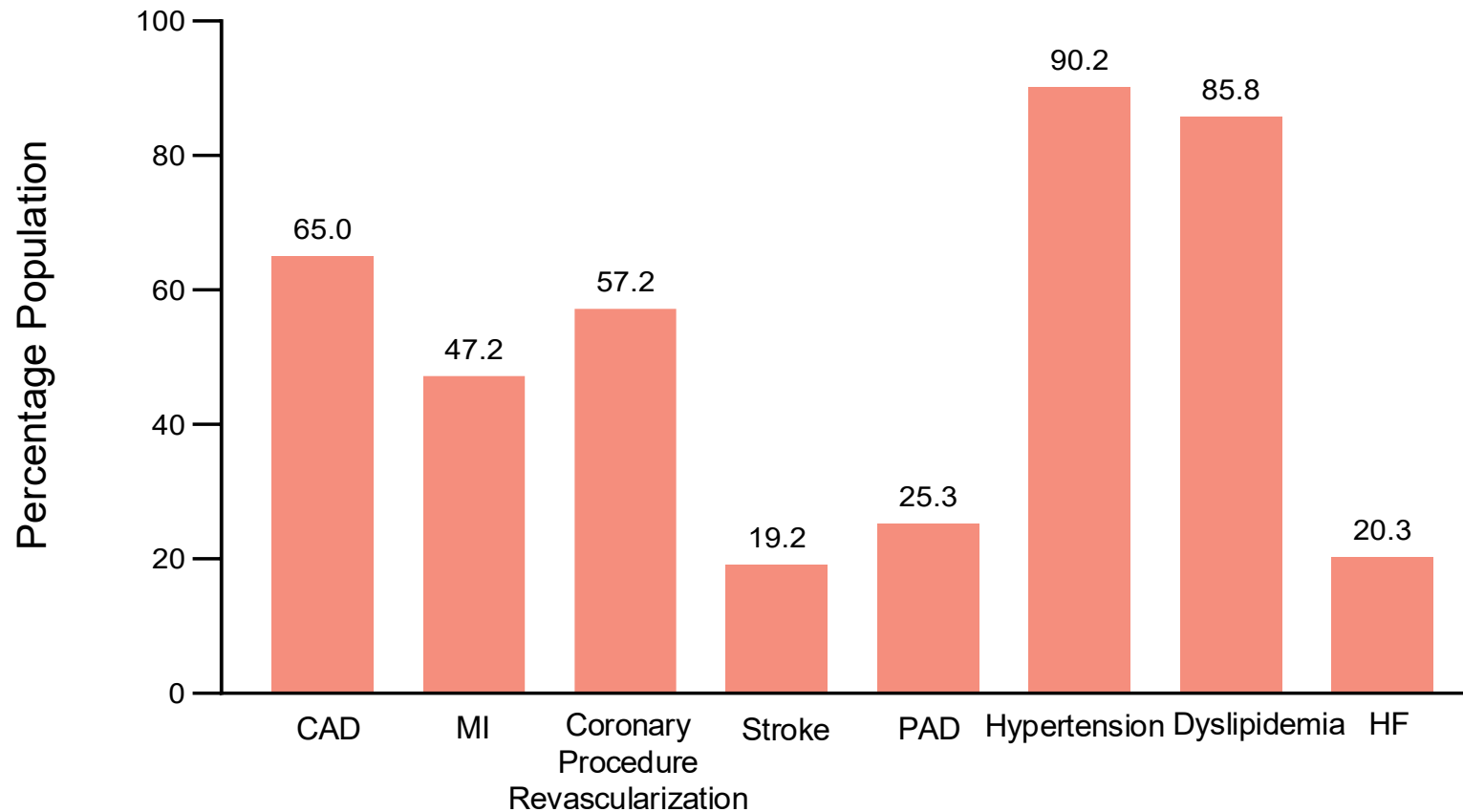
LDL cholesterol 2.08 mmol/L

Note: Data are mean \pm SD, n (%), or median (interquartile range). Percentage is based on number of participants with nonmissing measurement at baseline.

BMI=Body Mass Index; CKD-EPI=Chronic Kidney Disease-Epidemiology; DBP=Diastolic Blood Pressure; eGFR=Estimated Glomerular Filtration Rate; HbA1c=Glycated Hemoglobin; LDL=Low Density Lipoprotein; SBP=Systolic Blood Pressure; UACR=Urinary Albumin Creatinine Ratio

1. Nicholls SJ, et al. *Am Heart J.* 2024;267:1-112. Nicholls S.J. et al. *N Engl J Med.* 2025;393:2409-2420

Selected Baseline Characteristics: ASCVD and Medical History^{1,2}

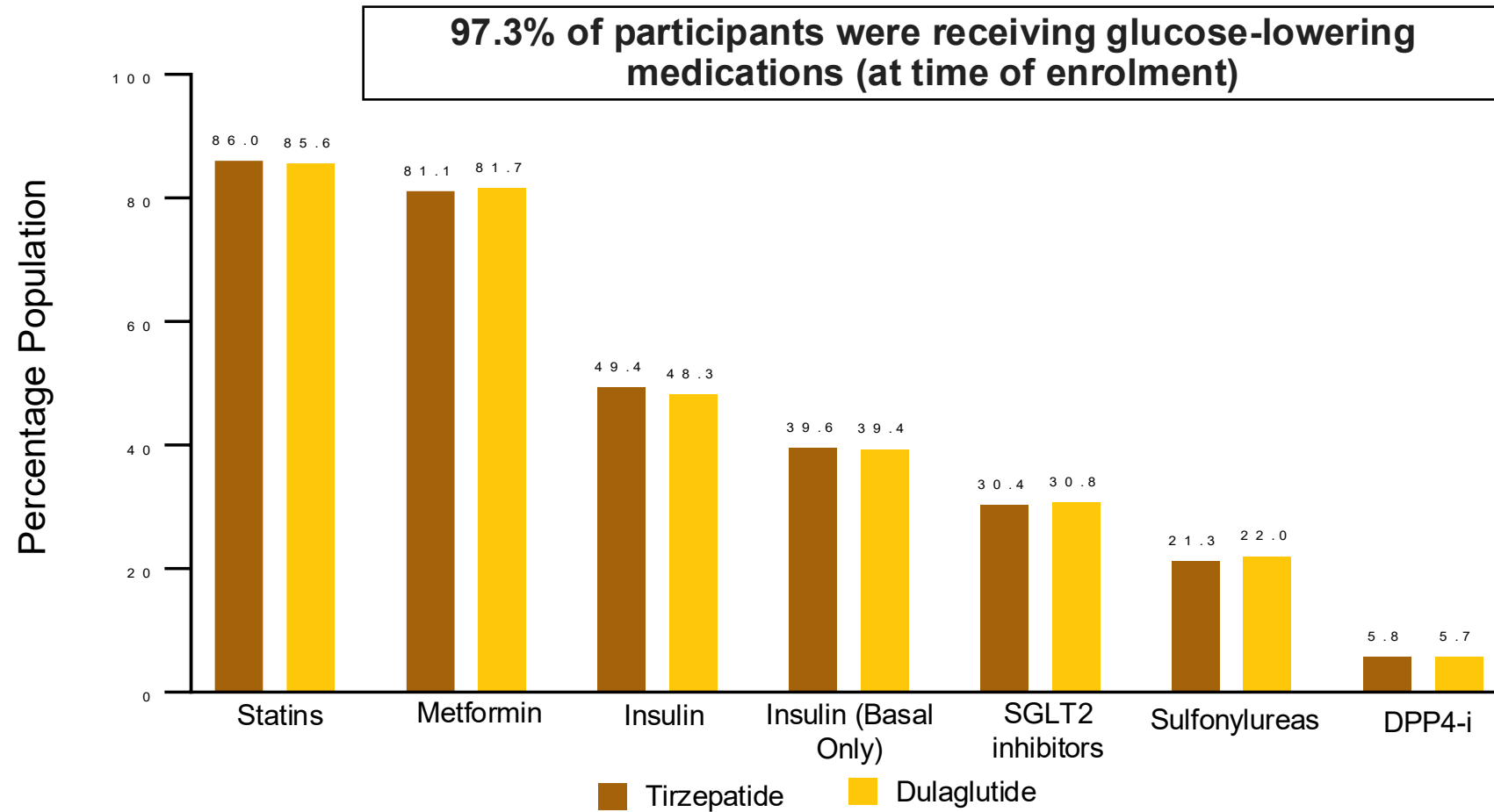


Note: Data are n (%). Percentage is based on number of participants with non-missing measurement at baseline.

ASCVD=Atherosclerotic Cardiovascular Disease; CAD=Coronary Artery Disease; MI=Myocardial Infarction; PAD=Peripheral Artery Disease; HF=Heart Failure.

1. Nicholls SJ, et al. *Am Heart J.* 2024;267:1-11 2. Nicholls S.J. et al. *N Engl J Med.* 2025;393:2409-2420

Baseline Glucose-lowering Medication Use



- Note: Data are n (%). Percentage is based on number of participants with non-missing measurement at baseline.

- CVOT=Cardiovascular Outcomes Trial; DPP4i=Dipeptidyl Peptidase-4 Inhibitor; SGLT2i=Sodium Glucose Cotransporter 2 Inhibitor; TZD=Thiazolidinediones.

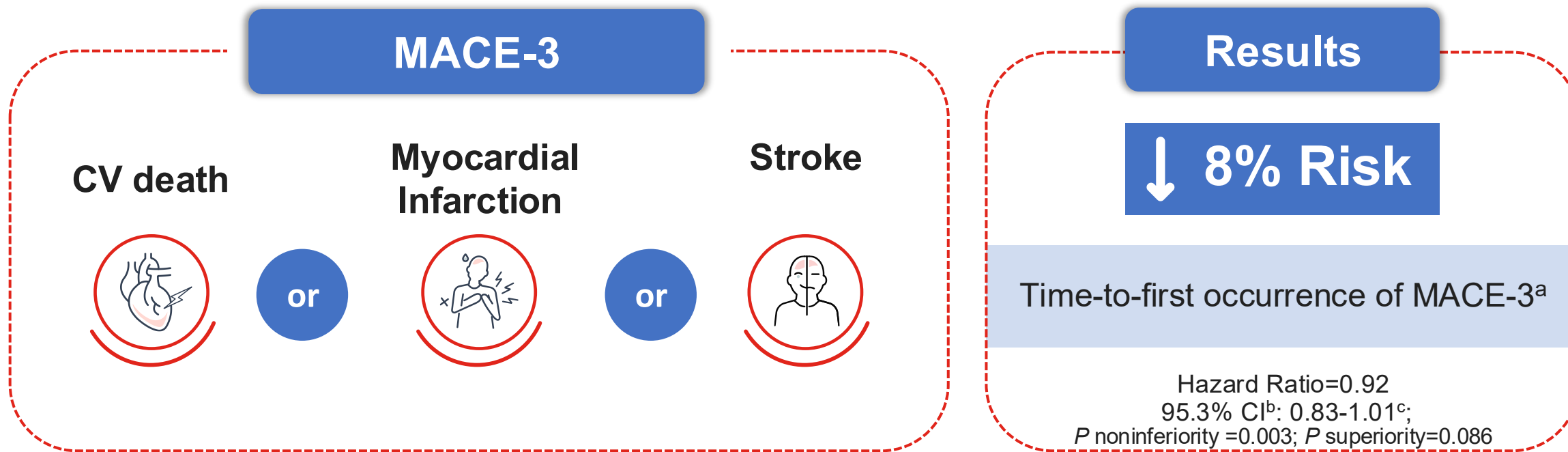
- Nichols S.J., et al. *N Engl J Med.* 2025;393:2409-2420

Efficacy Endpoints

SURPASS-CVOT

Tirzepatide Demonstrated Non-Inferior Rate of MACE-3 vs Dulaglutide

- Primary Outcome

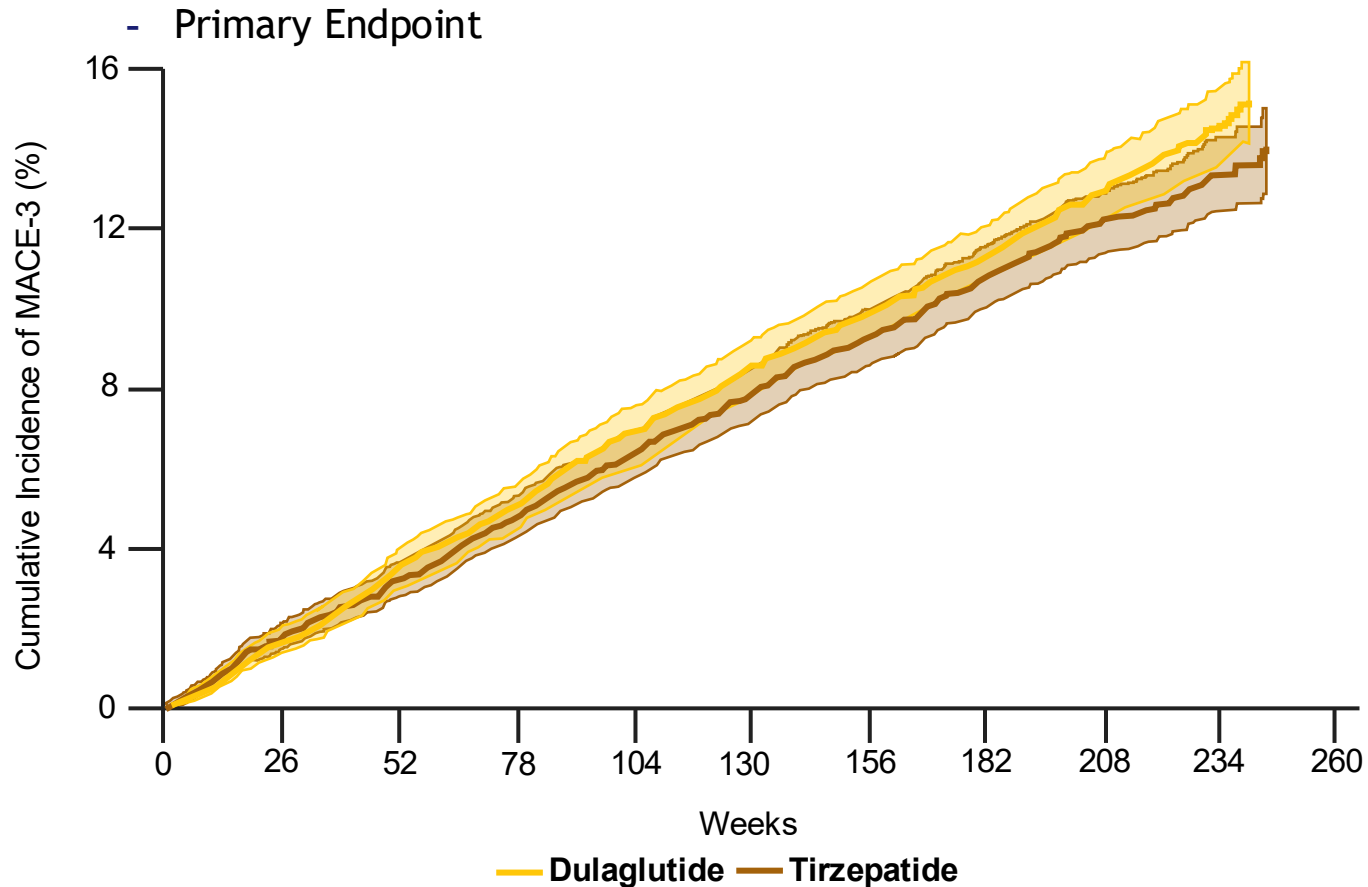


Tirzepatide demonstrated consistent results across all three components of the MACE-3 composite endpoint

^aTime-to-first event analysis using Cox proportional hazard model. ^b95.3% CI reported due to type 1 error rate adjusted for efficacy interim analysis. ^cBoundary for non-inferiority statistical significance <1.05.

CI=Confidence Interval; CV=Cardiovascular; CVOT=Cardiovascular Outcomes Trial; MACE-3=3-Point Major Adverse Cardiovascular Event;

Time to First Occurrence of MACE-3



↓ 8% Risk

Hazard Ratio=0.92
95.3 % CI: 0.83-1.01;
P noninferiority =0.003; *P* superiority=0.086

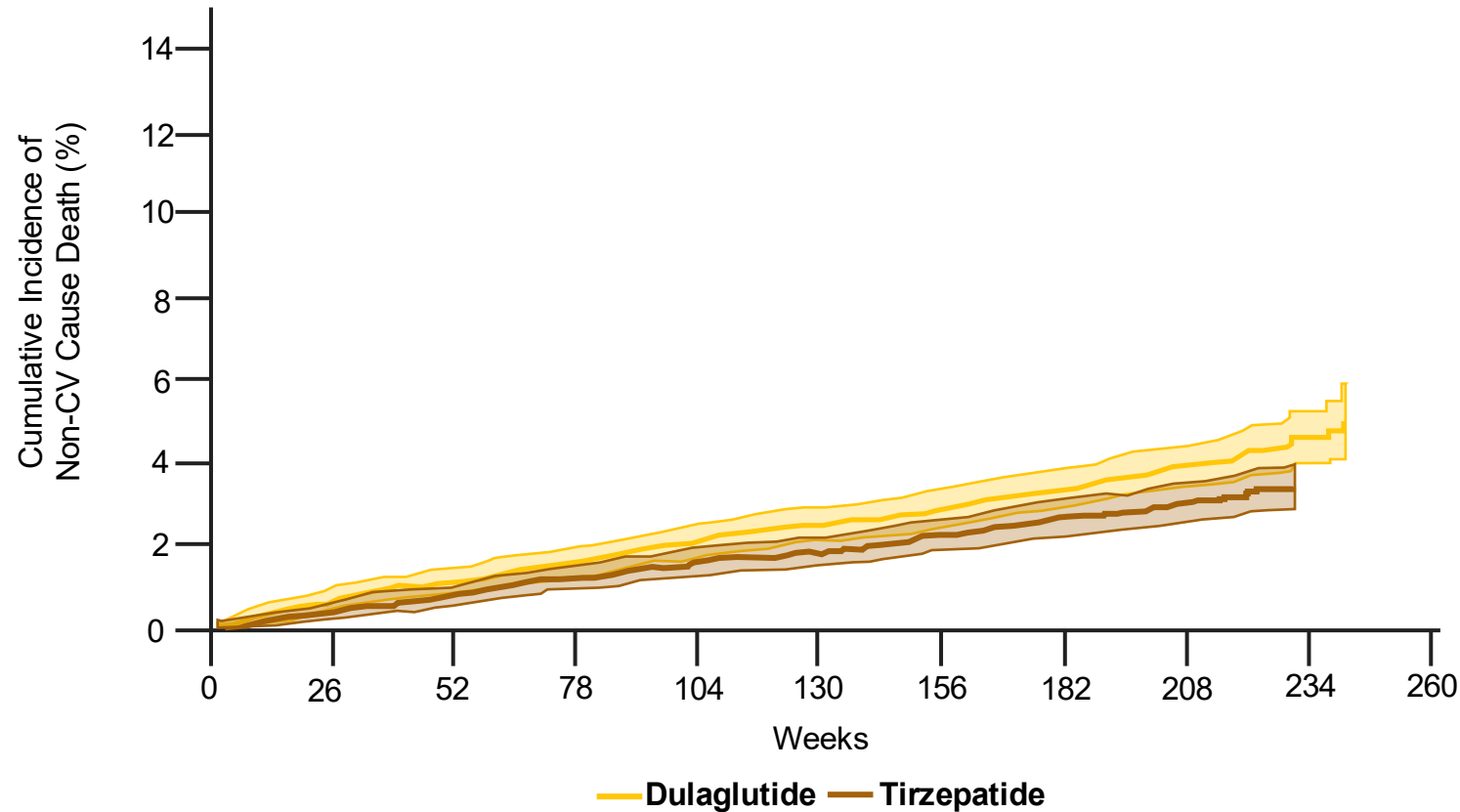
No. of Events
Dula: 862 (13.1%)
TZP:801 (12.2%)

- p for non-inferiority <0.003; p for superiority 0.086. Data are for the modified intention to treat population from randomization to the end of follow-up. Time to event end points were analysed using a Cox proportional hazards model with treatment as a factor and stratified by SGLT2 inhibitor use at baseline. Cumulative incidences were estimated using the Kaplan-Meier method. The P values are calculated with the use of Wald tests. The widths of the confidence intervals were not adjusted for multiplicity and should not be used in place of hypothesis testing.

- CI=Confidence Interval; Dula=Dulaglutide; MACE-3=3-point Major Adverse Cardiovascular Events; TZP=Tirzepatide

- Nicholls S.J. et al. *N Engl J Med.* 2025;393:2409-2420

Time to Non-cardiovascular Cause Death

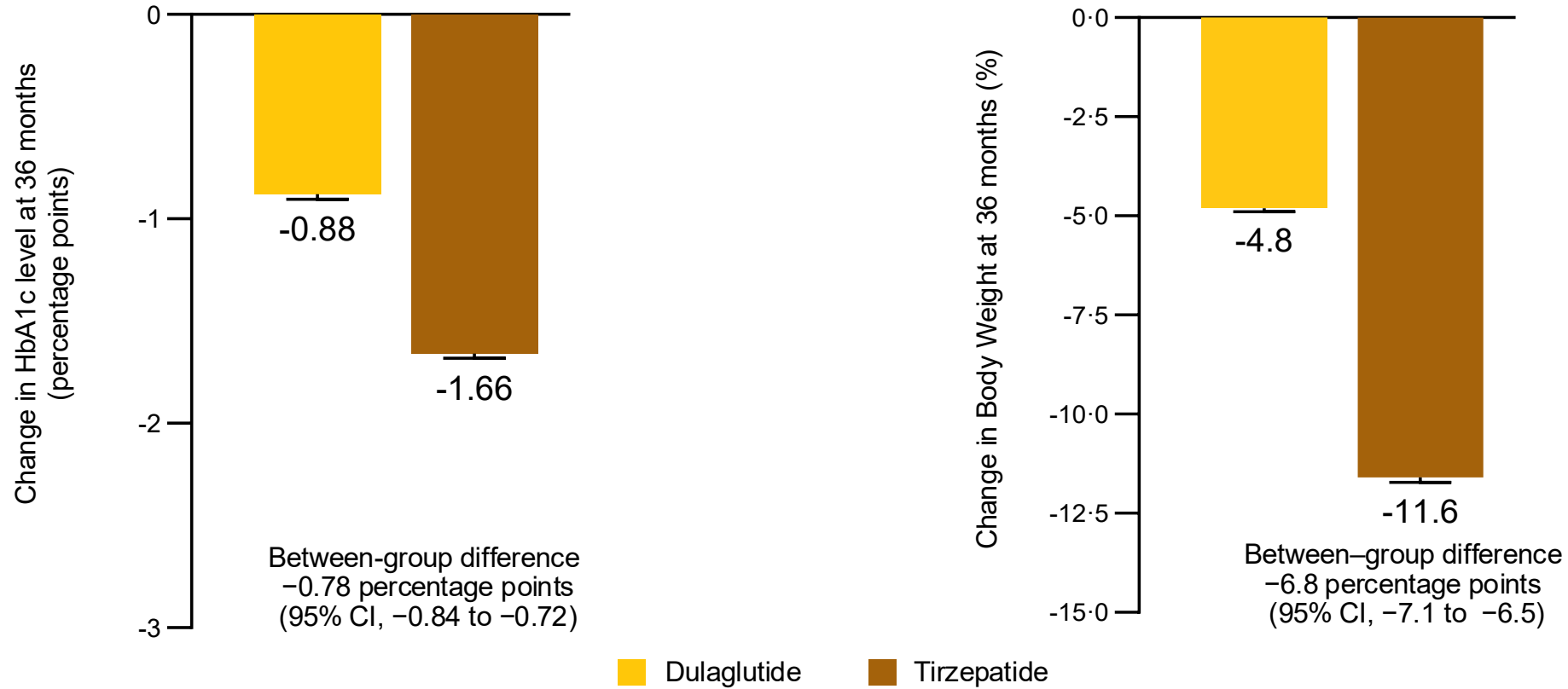


Hazard Ratio=0.75
95% CI: 0.63-0.91

No. of events:
Dula: 261 (4.0%)
TZP: 199 (3.0%)

Effect on Metabolic Risk Factors: HbA1c and Body Weight

- Additional Secondary Endpoints



- Data are LSM ± SE. Changes from baseline to the landmark timepoint were analysed using an analysis of covariance model with treatment, SGLT2 inhibitor use at baseline and country as fixed factors and baseline value as a covariate, with multiple imputation of missing values. Analysis not controlled for multiplicity adjusted type 1 error.

- HbA1c=Glycated Hemoglobin; LSM=Least Square Mean; SE=Standard Error; SGLT2i=Sodium Glucose Co-Transporter-2 Inhibitor

- Nicholls S.J., et al. *N Engl J Med.* 2025;393:2409-2420

Summary of Primary and Secondary Endpoints

Characteristic	Dulaglutide (N=6579)	Tirzepatide (N=6586)	Hazard Ratio (95% CI)	Difference (95% CI)
Primary Endpoint				
Death from cardiovascular causes, MI or stroke	862 (13.1)	801 (12.2)	0.92 (0.83-1.01) ^a	–
Key Secondary Endpoints				
Myocardial infarction	357 (5.4)	311 (4.7)	0.86 (0.74-1.00)	–
Stroke	249 (3.8)	229 (3.5)	0.91 (0.76-1.09)	–
Death from CV causes	408 (6.2)	367 (5.6)	0.89 (0.77-1.02)	–
Death from Cardiovascular causes, MI, stroke, or coronary revascularization	1217 (18.5)	1089 (16.5)	0.88 (0.81-0.96)	–
Death from CV causes or hospitalization or urgent visit for heart failure	557 (8.5)	512 (7.8)	0.91 (0.81-1.03)	–
Death from any cause	669 (10.2)	566 (8.6)	0.84 (0.75-0.94)	–
Change in eGFR (mL/min/1.73 m ²) from baseline to 36 months in patients with high or very-high risk chronic kidney disease ^b	–8.90 ± 0.39	–5.72 ± 0.44	–	3.17 (2.09-4.26)

^aThe confidence level for the primary end point was adjusted for the interim efficacy analysis; shown is the 95.3% confidence interval, which corresponds to the nominal two-sided significance level of 0.047. P = 0.003 for noninferiority; P = 0.09 for superiority. ^bData are shown for 1520 patients in the tirzepatide group and 1403 patients in the dulaglutide group with high-risk or very-high-risk chronic kidney disease. Plus-minus values are mean ± SE. Data from randomization to the end of follow-up are shown for the modified intention-to-treat population. End points assessed in a time-to-event analysis were analyzed with a Cox proportional-hazards model with treatment as a factor and with stratification according to use of sodium-glucose cotransporter 2 (SGLT2) inhibitors at baseline. The widths of the confidence intervals were not adjusted for multiplicity and should not be used in place of hypothesis testing.

Summary of Change in Metabolic Risk Factors

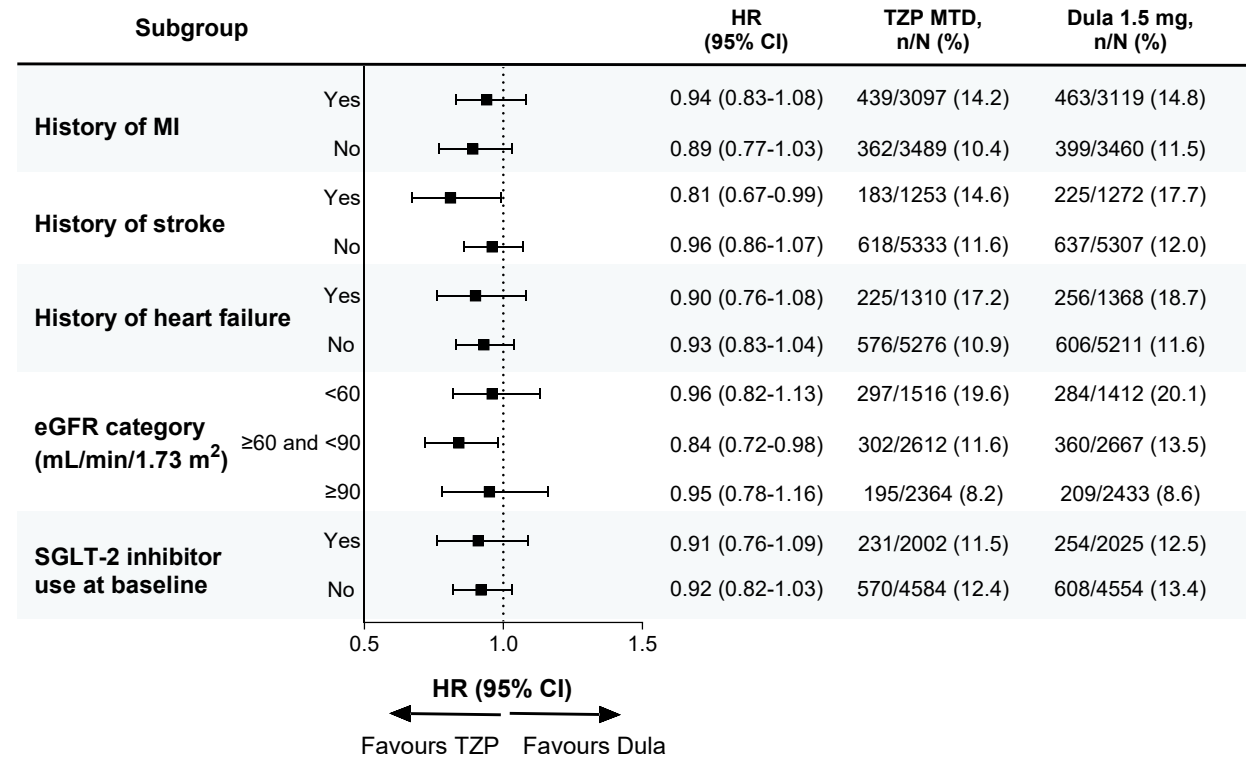
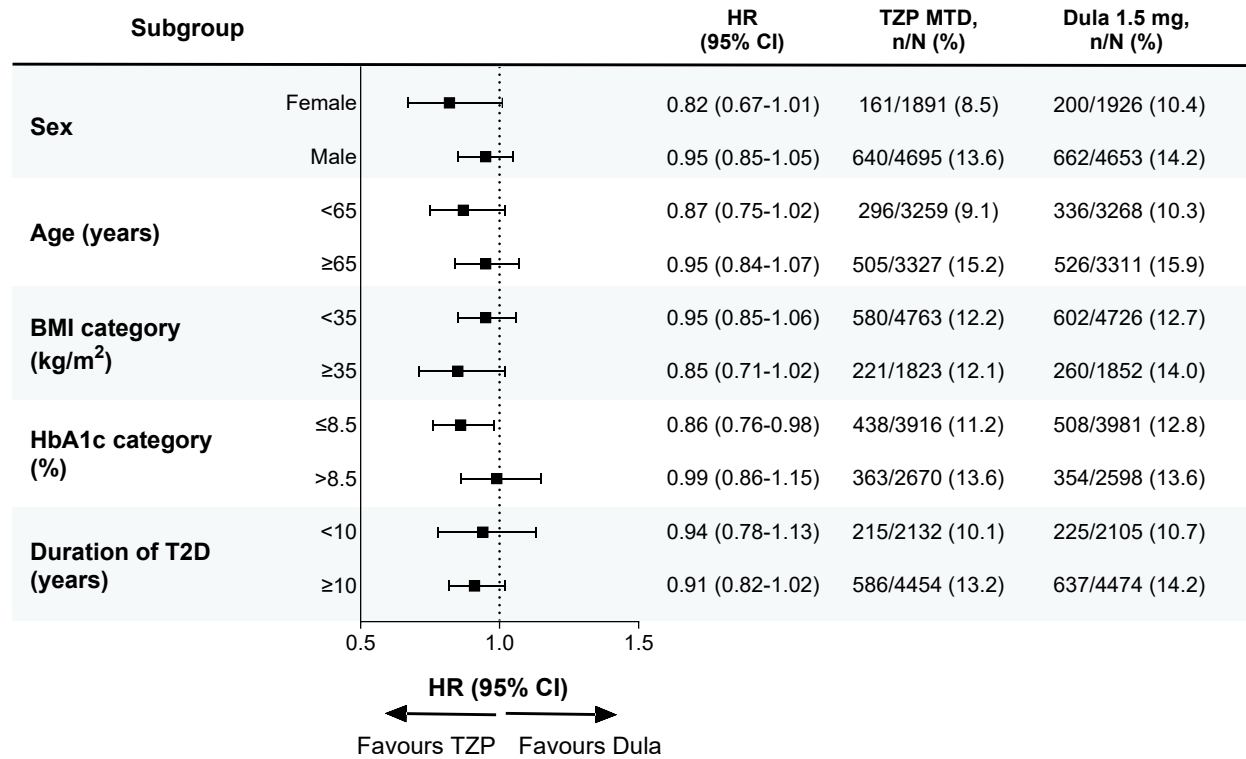
Characteristic		Dulaglutide (N=6578)	Tirzepatide (N=6586)	Hazard Ratio (95% CI)	Difference (95% CI)
HbA1c	Baseline (%) (95% CI)	8.38 (8.36 to 8.40)	8.40 (8.38 to 8.43)	-	NA
	Change at 36 months – percentage points (95% CI)	-0.88 (-0.92 to -0.83)	-1.66 (-1.70 to -1.62)	-	-0.78 (-0.84 to -0.72)
Body Weight	Baseline (kg) (95% CI)	92.5 (92.1 to 93.0)	92.6 (92.2 to 93.1)	-	NA
	Change at 36 months (%) (95% CI)	-4.8 (-5.0 to -4.6)	-11.6 (-11.8 to -11.4)	-	-6.8 (-7.1 to -6.5)
Triglycerides	Baseline (mmol/L) (95% CI)	1.87 (1.84 to 1.89)	1.88 (1.85 to 1.90)	-	NA
	Change at 24 months (%)	-10.2 (-11.2 to -9.1)	-24.2 (-25.1 to -23.3)	-	-15.6 (-16.9 to -14.3)
Systolic BP	Baseline (mmHg) (95% CI)	135.3 (134.9 to 135.6)	134.8 (134.0 to 135.2)	-	NA
	Change at 36 months (mmHg) (95% CI)	-4.1 (-4.6 to -3.7)	-6.2 (-6.6 to -5.8)	-	-2.1 (-2.6 to -1.5)
LDL Cholesterol	Baseline (mmol/L) (95% CI)	1.86 (1.84 to 1.89)	1.87 (1.84 to 1.89)	-	NA
	Change at 24 months (%) (95% CI)	-2.9 (-4.0 to -1.8)	-1.6 (-2.7 to -0.5)	-	1.3 (-0.2 to 2.8)

- Data are mean estimates ± SE. The continuous end points assessing changes from randomization to the landmark timepoint were analysed using an analysis of covariance model with treatment, SGLT2 inhibitor use at baseline and country as fixed factors and baseline value as a covariate, with multiple imputation of missing values. ; Analyses not controlled for multiplicity-adjusted type 1 error rate

- BP=Blood Pressure; CI=Confidence Interval; HbA1c=Glycated Hemoglobin

- Nicholls S.J., et al. *N Engl J Med.* 2025;393:2409-2420

Subgroup Analysis of the Primary Endpoint



Safety Endpoints

SURPASS-CVOT

Treatment Emergent Adverse Events

	Dulaglutide (N=6647)	Tirzepatide (N=6647)
Any adverse event that emerged during treatment, n (%)	5894 (88.7)	5956 (89.6)
Serious adverse event, n (%) ^a	2121 (31.9)	2117 (31.8)
Adverse event leading to drug discontinuation, n (%)	672 (10.1)	878 (13.2)

^aExcluding CV endpoints confirmed by clinical endpoint committee. The two-sided p-values, calculated from Fisher's Exact tests, were not adjusted for multiple comparison and therefore not intended for statistical inference.

CV=Cardiovascular

Nichols S.J. et al. *N Engl J Med.* 2025;393:2409-2420

Prespecified Adverse Events of Special Interests (1 of 2)

	Dulaglutide (N=6647)	Tirzepatide (N=6647)
Severe hypoglycemia, n (%)	48 (0.7)	49 (0.7)
Gastrointestinal adverse events ^a , n (%)	2387 (35.9)	2827 (42.5)
Severe ^b gastrointestinal adverse events, n (%)	118 (1.8)	171 (2.6)
Nausea, n (%)	1486 (22.4)	1667 (25.1)
Severe nausea, n (%)	51 (0.8)	76 (1.1)
Vomiting, n (%)	642 (9.7)	772 (11.6)
Severe vomiting, n (%)	37 (0.6)	60 (0.9)
Diarrhea, n (%)	1267 (19.1)	1651 (24.8)
Severe diarrhea, n (%)	53 (0.8)	79 (1.2)
Major pancreatic events		
Pancreatitis ^c , n (%)	39 (0.6)	41 (0.6)
Pancreatic carcinoma ^d , n (%)	17 (0.3)	17 (0.3)
Major gallbladder adverse events		
Cholelithiasis, n (%)	134 (2.0)	158 (2.4)
Cholecystitis ^e , n (%)	84 (1.3)	91 (1.4)

^aGastrointestinal events is a cluster of terms that included nausea, vomiting and diarrhea. ^bSeverity for adverse events were determined by the investigators. ^cPancreatitis was adjudicated by a clinical endpoint committee. ^dPancreatic carcinoma is a cluster of terms that included: pancreatic carcinoma; pancreatic carcinoma metastatic; pancreatic carcinoma stage IV; pancreatic carcinoma recurrent; pancreatic neuroendocrine tumour; adenocarcinoma pancreas; pancreatic neoplasm. ^eCholecystitis is a cluster of terms that included cholecystitis acute, cholecystitis chronic, cholecystitis and acute cholecystitis. The two-sided p-values, calculated from Fisher's Exact tests, were not adjusted for multiple comparison and therefore not intended for statistical inference.

Prespecified Adverse Events of Special Interests (2 of 2)

	Dulaglutide (N=6647)	Tirzepatide (N=6647)
Thyroid events		
Medullary thyroid cancer, n (%)	0 (0)	2 (<0.1)
Other thyroid carcinoma, n (%)	2 (<0.1)	9 (0.1)
Serious atrial fibrillation, n (%)	58 (0.9)	59 (0.9)
Hypersensitivity reactions^a		
Anaphylactic reaction, n (%)	15 (0.2)	12 (0.2)
Hypersensitivity, n (%)	330 (5.0)	377 (5.7)
Renal events		
Acute kidney injury, n (%)	178 (2.7)	226 (3.4)
Chronic kidney disease, n (%)	170 (2.6)	147 (2.2)

^aHypersensitivity was determined using the Standard MedDRA Query anaphylactic reaction and hypersensitivity. The two-sided p-values, calculated from Fisher's Exact tests, were not adjusted for multiple comparison and therefore not intended for statistical inference.

Summary: SURPASS-CVOT



Primary Outcome

In patients with T2D & ASCVD, treatment with TZP was noninferior to treatment with dulaglutide with respect to the primary composite endpoint MACE-3, at a median follow-up of 4 years, with consistent effects among subgroups stratified according to cardiovascular and diabetes-related clinical characteristics



Safety Profile

No major differences in lipid parameters, metabolic risk factors, or serious adverse events between groups; however, gastrointestinal events were more frequently reported by patients assigned to tirzepatide treatment



Prespecified secondary analyses (exploratory)

- Possible lower incidence of death from any cause and of death from noncardiovascular causes with tirzepatide treatment compared with dulaglutide treatment
- Slower decline in eGFR with tirzepatide compared with dulaglutide (-5.72 vs. -8.90 mL/min/1.73m²) in patients with high-risk or very high -risk CKD.

The noninferior effect of TZP compared with dulaglutide on the primary cardiovascular outcome provides additional evidence that targeting the incretin axis by multiple approaches has a favorable effect on cardiovascular risk in patients with T2D.

Conclusion: : SURPASS-CVOT

In patients with T2D and ASCVD, Tirzepatide was non-inferior to dulaglutide with respect to death from cardiovascular causes, myocardial infarction or stroke confirming cardiovascular benefits



Diabetes Care Volume 49, Supplement 1, January 2026



Summary of Revisions: Standards of Care in Diabetes—2026

*American Diabetes Association
Professional Practice Committee for
Diabetes**

Diabetes Care 2026;49(Suppl. 1):S6–S12 | <https://doi.org/10.2337/dc26-SREV>

Recommendations for CVD risk management in diabetes

- GLP1-RA with demonstrated CV benefits is recommended in people with T2D /CKD to reduce risk of CV events
- GLP1-RA with HF-prevention is recommend for people with T2D and asymptomatic heart failure with high risk, or established CVD
- GIP/GLP-1 RA are recommended for reduction of HF in people with DM, obesity and symptomatic HF

SUMMARY

- DM type 2 is associated with significant cardiovascular and renal morbidity and mortality
- Guideline-directed therapy focuses beyond glycemic control, to cardio-renal risk reduction
- There is a growing body of evidence demonstrating with high certainty the use of GLP1-RAs in reducing important CV and renal outcomes
- GLP1-RAs should be considered as heart-protective and kidney-protective treatment to reducing morbidity in people with DM2, CKD, and overweight and obesity
- GLP/GIP –RA should be considered as an alternative for people with T2D



Dr. Joseph Ricci

Cardiac Care Amyloid: Detection starts in community practice

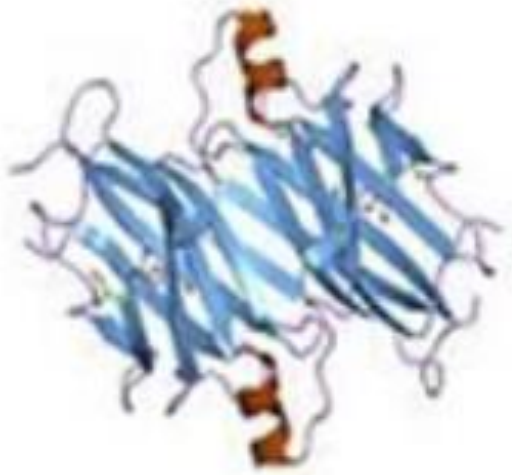
Learning Objectives

Under Diagnosed
You Can Change That!

During this session, participants will analyze and interpret:

- What is “Amyloid Protein”
- How “Amyloid” impacts your patients Health
- ‘Red Flags’ that signal ATTR amyloid
- Diagnosis of Amyloid is Easy, Low Cost and Rapid

What is Cardiac Amyloid?



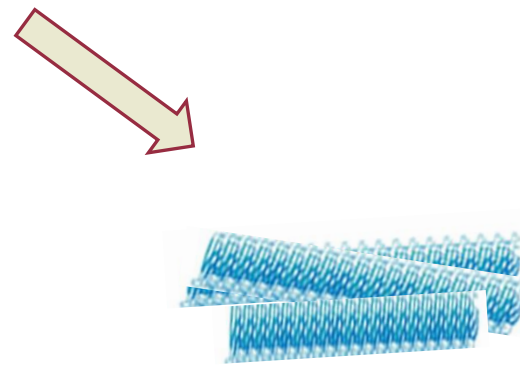
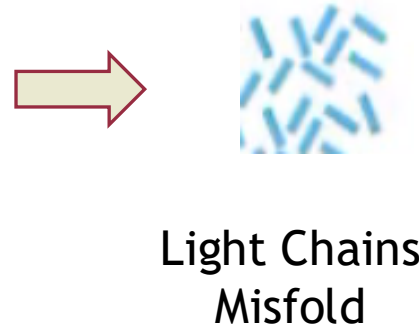
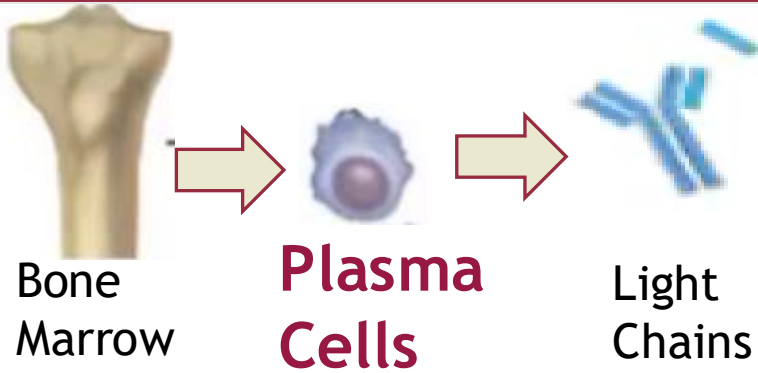
An Abnormal Protein
Circulates in the
blood

Clumps
Into fibrils

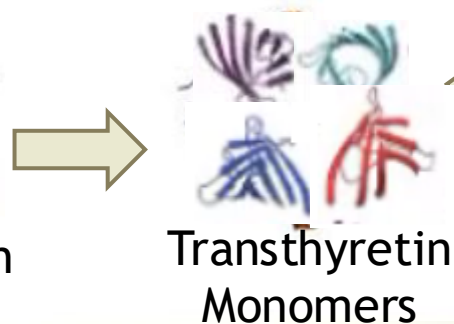
Deposits in
Connective
Tissue

2 Sources of Cardiac Amyloid Fibrils

AL Amyloidosis



ATTR Amyloidosis

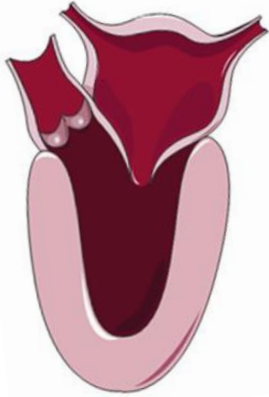


End Organ Deposition

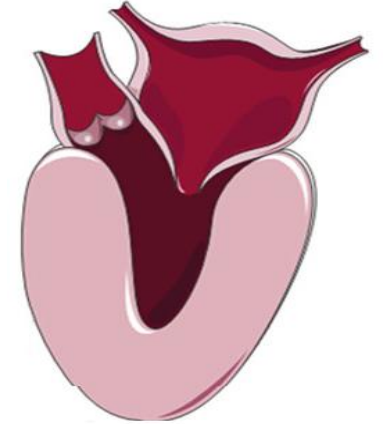
How Amyloid Causes Disease

Fibrils Infiltrate Connective Tissues

Normal
Heart



Amyloid
Cardiomyopathy



Amyloid fibrils
Expand intercellular spaces

Amyloid is Detected Where Fibrils Accumulate

Hiding in Plain Sight.....

Waving

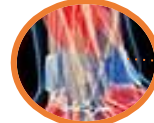


Nerves and Surrounding Tissues

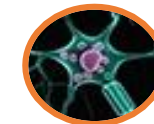
LUMBAR SPINAL STENOSIS^{4,5}



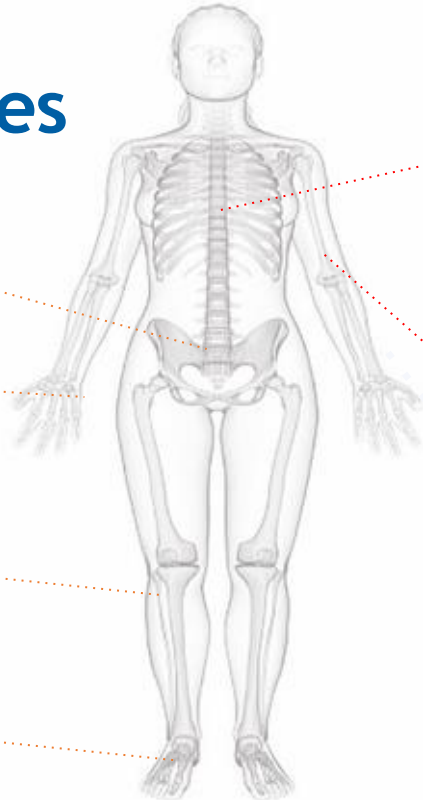
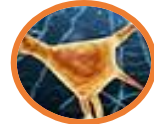
BILATERAL CARPEL TUNNEL



SENSORIMOTOR NEUROPATHY



AUTONOMIC NEUROPATHY^{1,3}



The Heart

Hypertrophy
Heart failure



Tendons

Tendon rupture



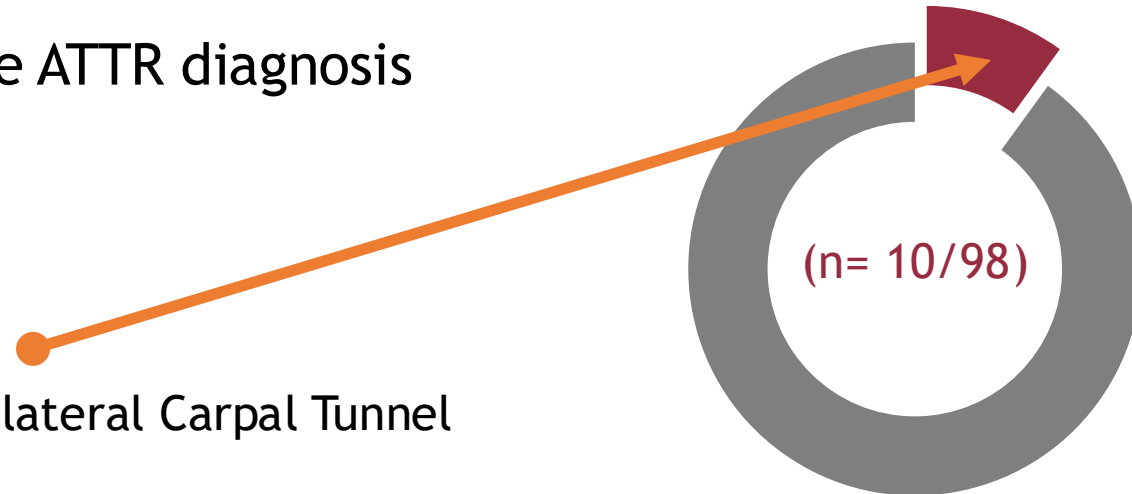


Neurologic 'Red Flags' for Amyloid

Amyloid Fibrils in Connective Tissue Causes Nerve Entrapment Syndromes

Carpal Tunnel Syndrome

- Up to **10 years** before ATTR diagnosis
- Typically bilateral
- **10%** Biopsy positive if bilateral Carpal Tunnel



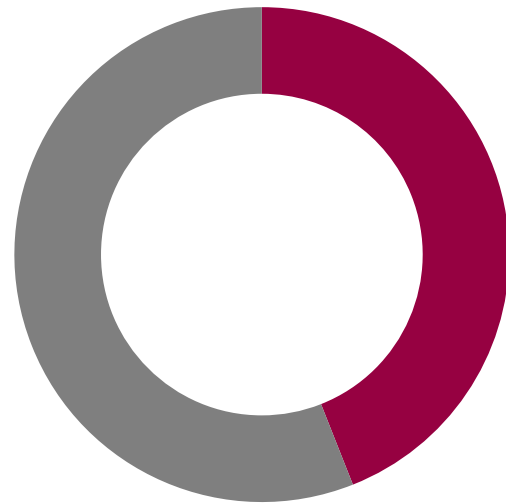
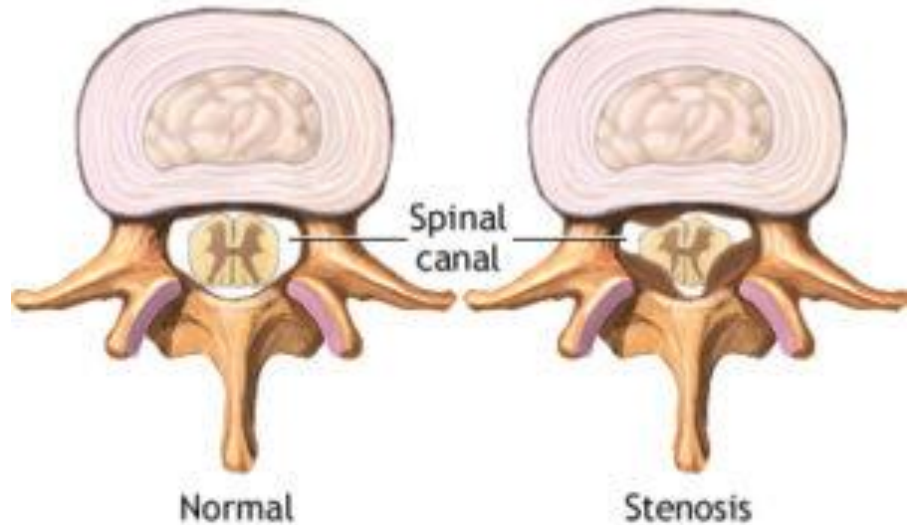


Neurologic 'Red Flags' for Amyloid

Amyloid Fibrils in Connective Tissue Causes Nerve Entrapment Syndromes

Lumbar Spinal Stenosis

Narrowing of Spinal Canal by Amyloid Accumulation



33-44%

■ ATTR detected
■ No ATTR

United Kingdom (Westermarck 2014, n = 15)

Kumamoto University Hospital, Japan (Sueyoshi 2011, n = 36)

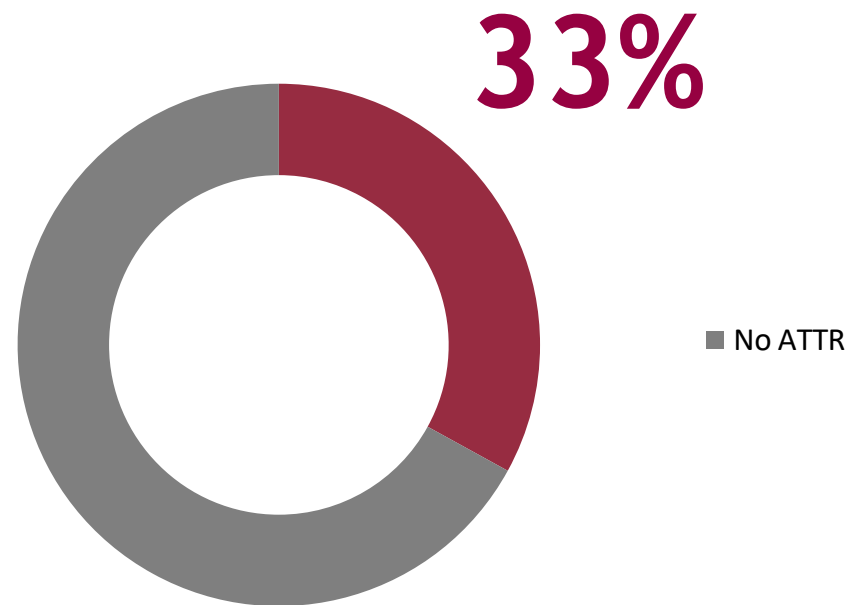


Orthopedic 'Red Flags' for Amyloid

Amyloid Fibrils in Connective Tissue Weaken Tendos

Spontaneous Biceps Tendon Rupture

- 33% of amyloid patient's vs 2.5% in General population
- 40% asymptomatic



NIH (2024)
2014, n = 111)

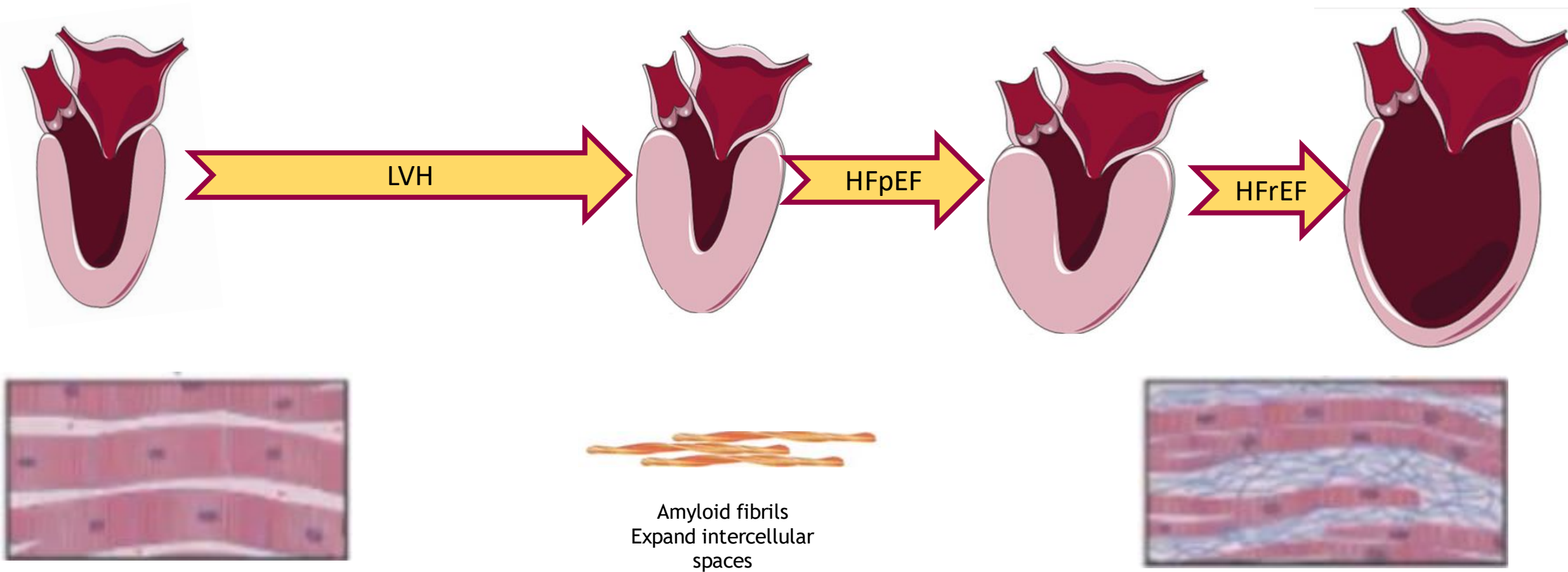


'Popeye' Sign



Amyloid Heart Disease

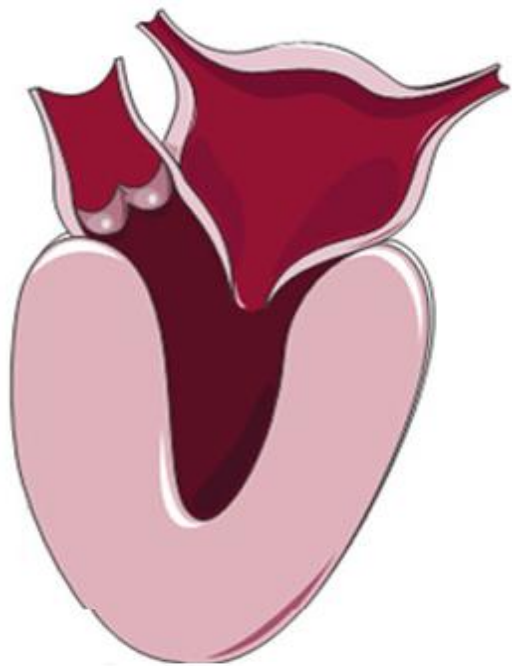
Years in the Making: First LVH then HFpEF





Cardiac 'Red Flags'

Amyloid Masquerading as Common Things



Unexplained Hypertrophy

Idiopathic LV hypertrophy 5-6%

Heart Failure with Preserved EF

HF preserved EF 20-30%
HF Reduced EF 2-5%

Common but Non-Specific

Atrial Fibrillation 69%
Asymptomatic LVH 25%
Atrial dilation 60%



RED FLAGS Are the ‘Gateway’ to Diagnosis and Improved Outcomes

Screen for Amyloid If you See Any Red Flag

Heart Failure

Spinal Stenosis

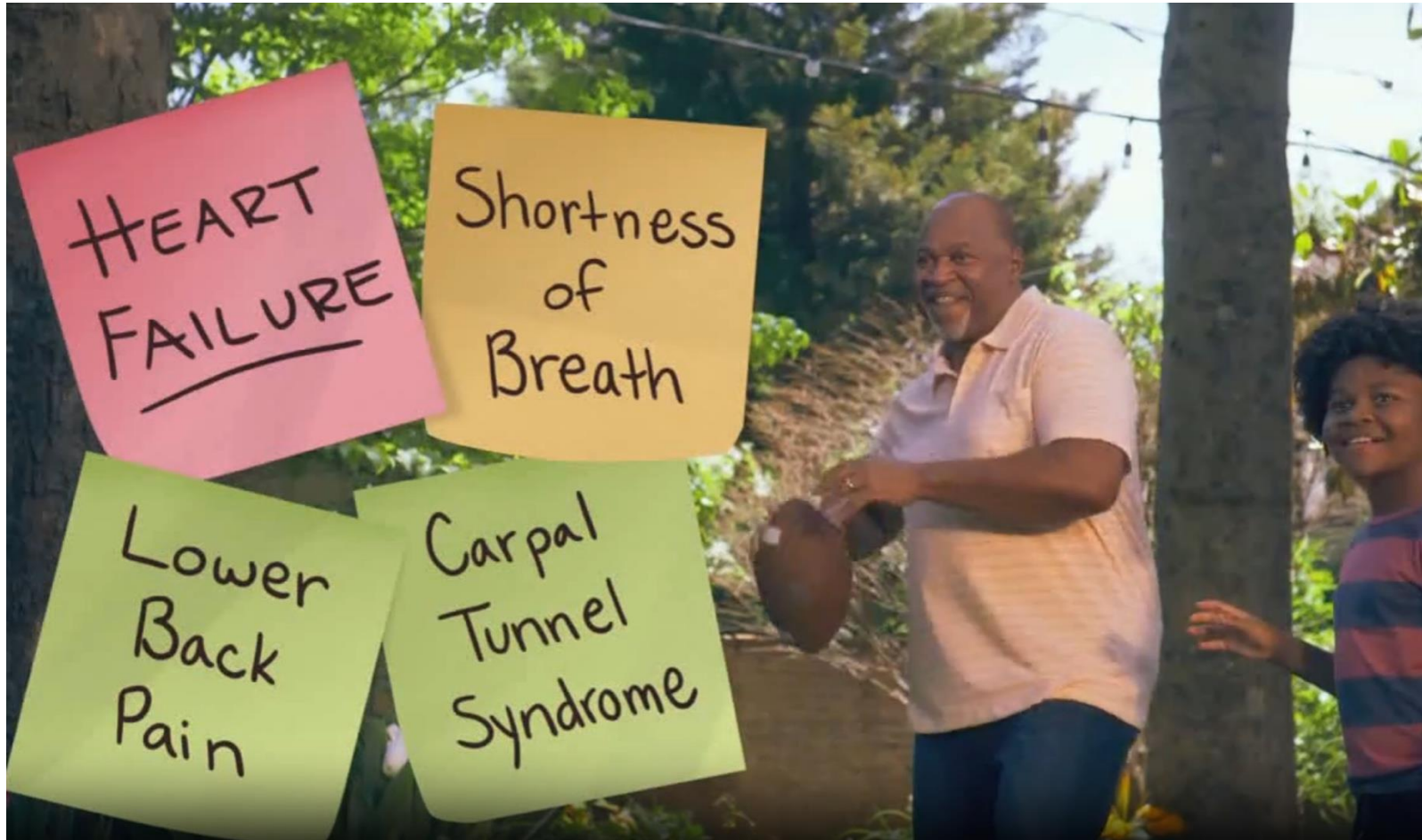
Biceps Tendon Rupture

Unexplained LVH

Bilateral Carpal Tunnel

Sensory Motor Polyneuropathy

Patients are Aware of the ‘Red Flags’”



Commercial on Golf Channel, CCN, CBC 2024

Diagnosis Used to Be Difficult

....And Took a L-O-N-G time.

- Typically low index of suspicion
- More than 5 physicians before diagnosis
- Time to diagnosis typically 4 - 6+ years



Poll Question

The Screening for ATTR Amyloidosis is best made by:

1. Cardiac Magnetic Resonance imaging
2. Cardiac and liver CT scan
3. Echocardiography
4. Nuclear Tc99 cardiac Scan
5. Salivary Gland Biopsy
6. Cardiac biopsy (EMB)
7. Measuring circulating amyloid protein in blood

Canadian Cardiovascular Society Guidelines

ATTR Cardiac Tc99 Scan

+

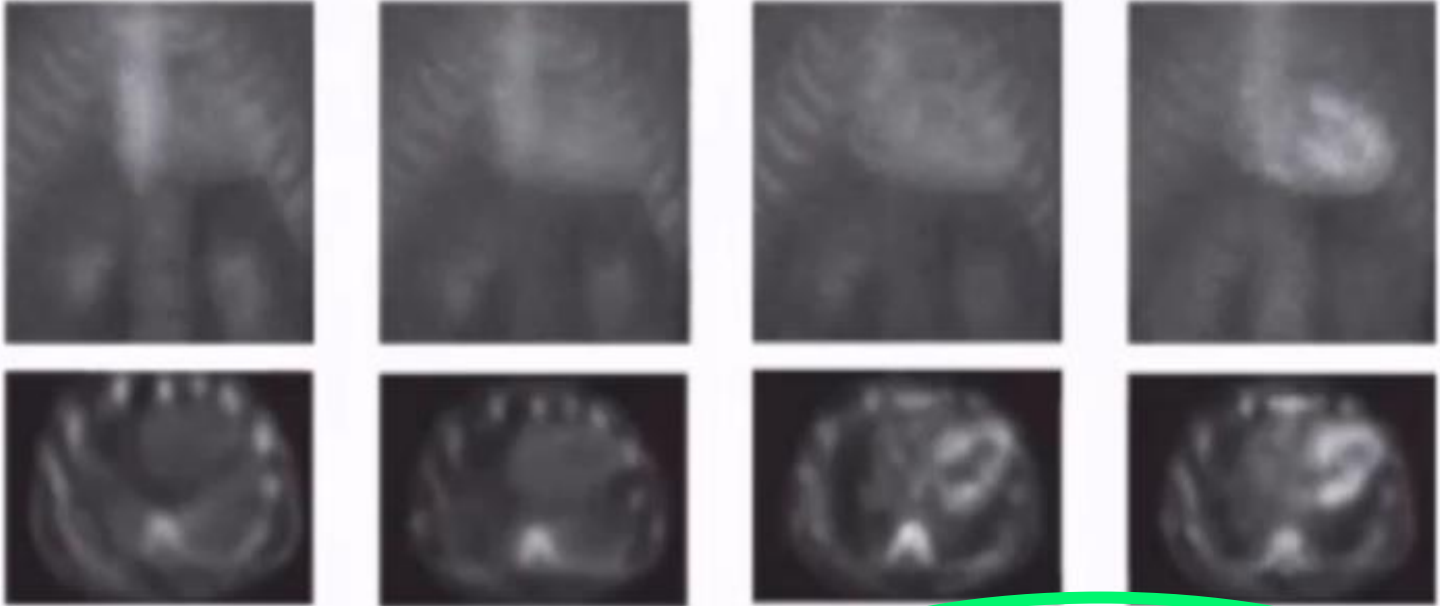
Rule out Light Chain Diseases
(Urine Immunofixation & Light Chain Assay)

Cardiac ATTR Scan for Diagnosis of Amyloid

Extremely Sensitive and Specific

Sensitivity: 95+%

Specificity: 90%



Grade 2+ tracer uptake without monoclonal protein

- Specificity 99.9%
- Positive predictive value 99.9%

Grade 0	Grade 1	Grade 2	Grade 3
No uptake and normal bone uptake	Uptake less than rib uptake	Uptake equal to rib uptake	Uptake greater than rib uptake with mild/absent rib uptake

Reference: Urbain et al. CANM Cardiac Amyloid PYP Imaging Guidelines https://canm-acmn.ca/resources/Documents/Guidelines%20CA_CANM_EN.pdf accessed on Feb 22, 2022

Cardiac ATTR Scan for Diagnosis

Rapid, Inexpensive, Available & Safe

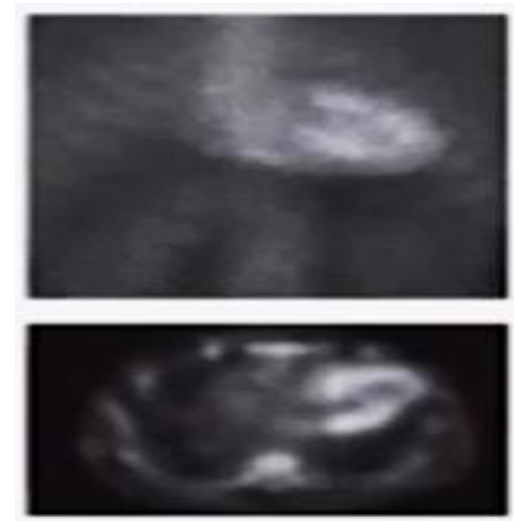
A Gamma Detector Is Used to Image Uptake of a Technetium⁹⁹ in the Heart



Radiotracer



Camera



SPECT Scan¹

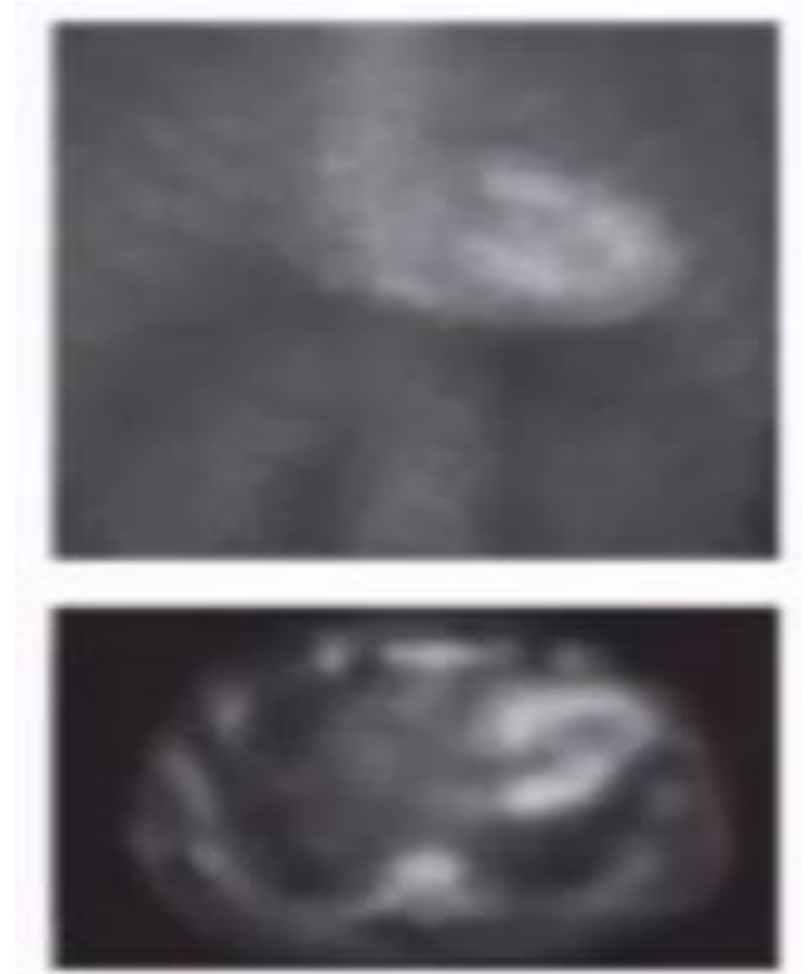
Cardiac TC99 ATTR Scan is Low Risk

No contraindications for:

- Renal failure
- Atrial fibrillation
- Devices
- Obesity

Single Rest image only at 3 hours

Low radiation at 15mCi 3.2 mSV



Echocardiography

A necessary test but NOT a sensitive or Specific Screening test

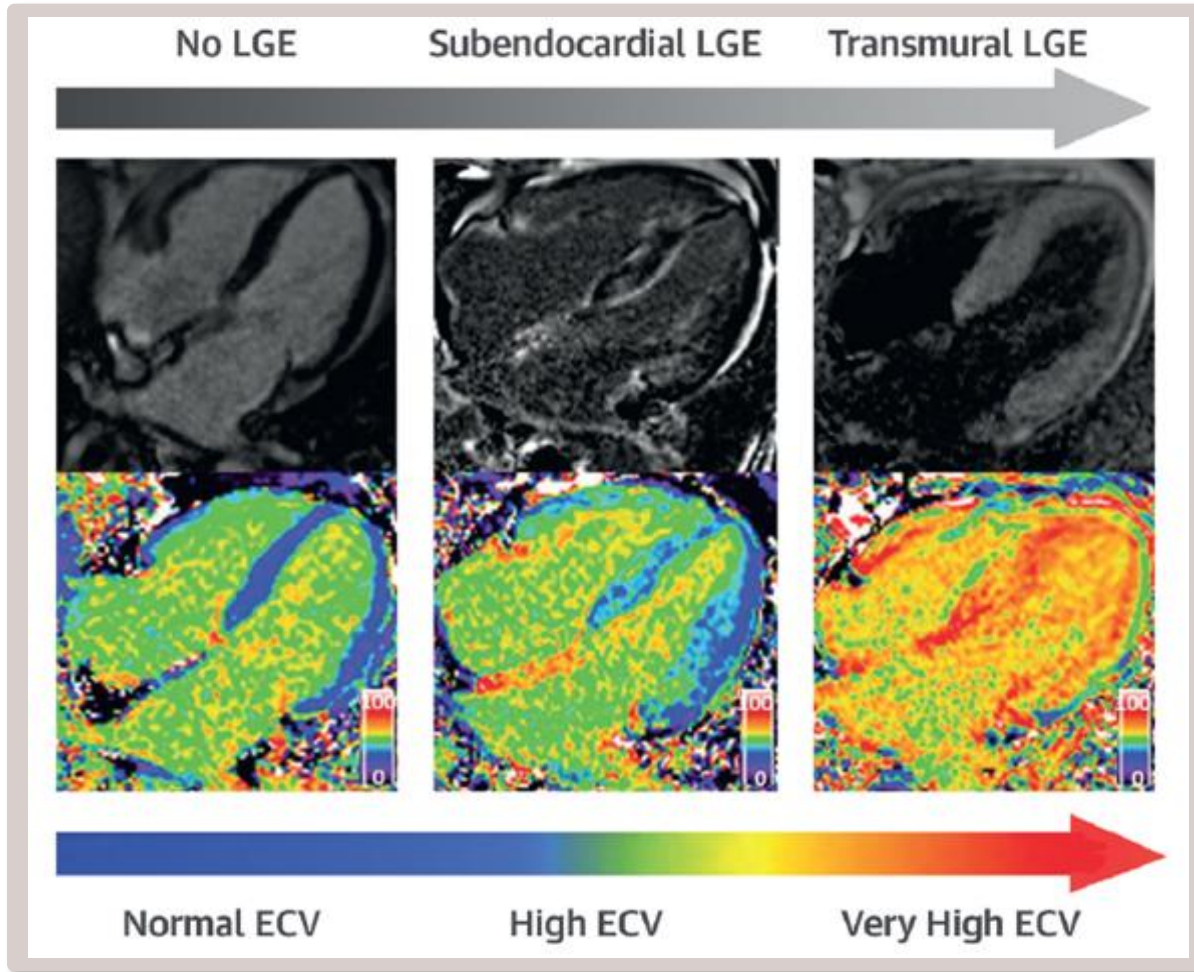


• Biventricular wall thickening (>12 mm)

• Left atrial enlargement

MRI

Not recommended for screening (cost, availability, wait-time)
Valuable for confirmation



- Extracellular volume expansion
- Diffuse late gadolinium enhancement

Poll Question



64 Male, Black, Caribbean Descent

Mild but Progressive SOB > 6 months

Hypertension under good control 115/60

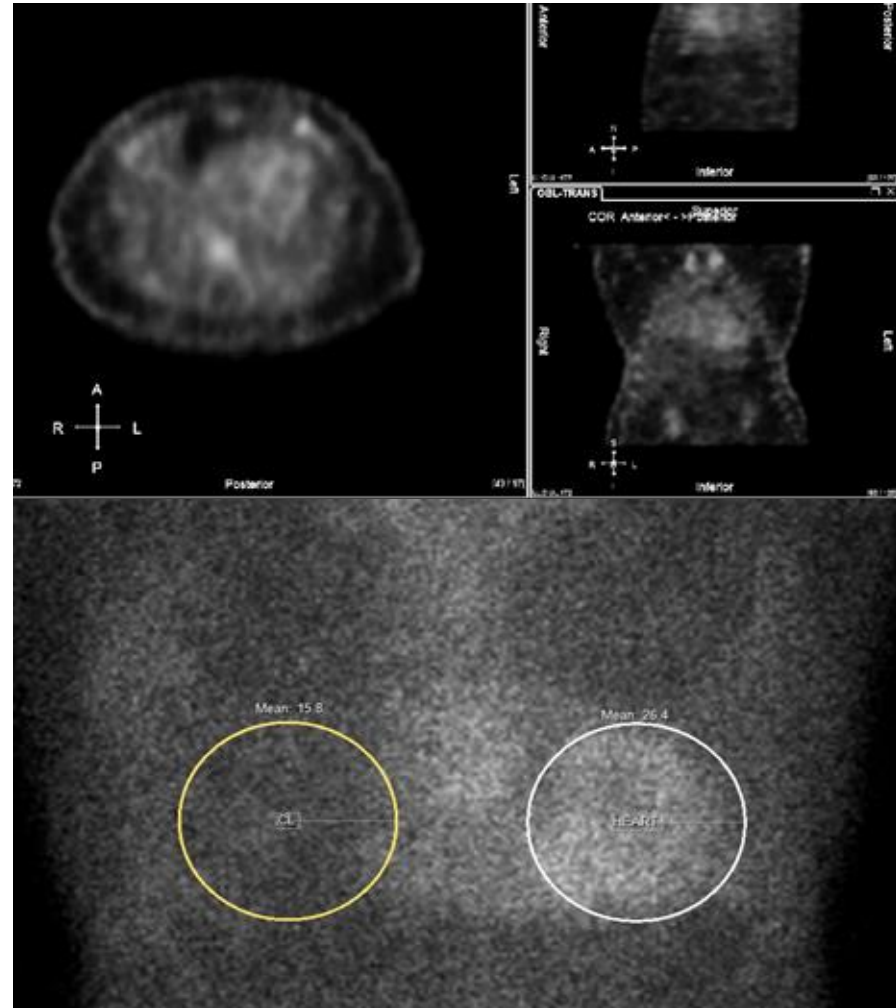
Echo: LVEF 50% with septum 1.3 cm

Medication Lasix 40 mg po od
 Spironolactone
 Valsartan 80 mg po od

What would you do first?

1. MRI
2. Cardiac Tc⁹⁹ Scan
3. Immunoelectrophoresis & Lt chain assay
4. Genetic testing for hATTR
5. Referral for cardiac consultation
6. Nothing, reassess BP diary in 3 months

Evaluation of Dyspnea with ? LVH



Investigations:

PYP Scan Visual grade 3, strongly suggestive of ATTR amyloid
Serum/Urine IEP, IF, LC: Negative
Genetic testing: negative

Cardiac investigation

EMB biopsies 6/6 strongly positive for ATTR amyloid

Therapy

EAP approval for tafamidis

The Impact of Using Amyloid Scans

Amyloid is More Common than We Knew!

The prevalence of ATTR in a higher risk population is approximately **1/500**



Canadian Guidelines Simplified Screening with Tc⁹⁹ Identifies a high prevalence in populations with red flags

The Impact of Using Amyloid Scans

Dramatic Reduction in Time To Diagnosis! < 10 weeks

A Real World Evaluation 239 practices in Europe and North America

Average time to diagnosis	6-9 weeks
Primary physician made diagnosis	35%

AVERAGE TIME TO DIAGNOSIS



NUMBER OF MD BEFORE DIAGNOSIS



Tc99 ATTR scan + IEP is now Routine

Tc99 Amyloid Scan Widely Available

The Corcare Experience

> 900 PYP reported scans

26 diagnostic ATTR cardiac scan

14 on therapy for ATTR (7), hATTR(1)

Canadian Cardiovascular Society Guidelines

Society Position Statement

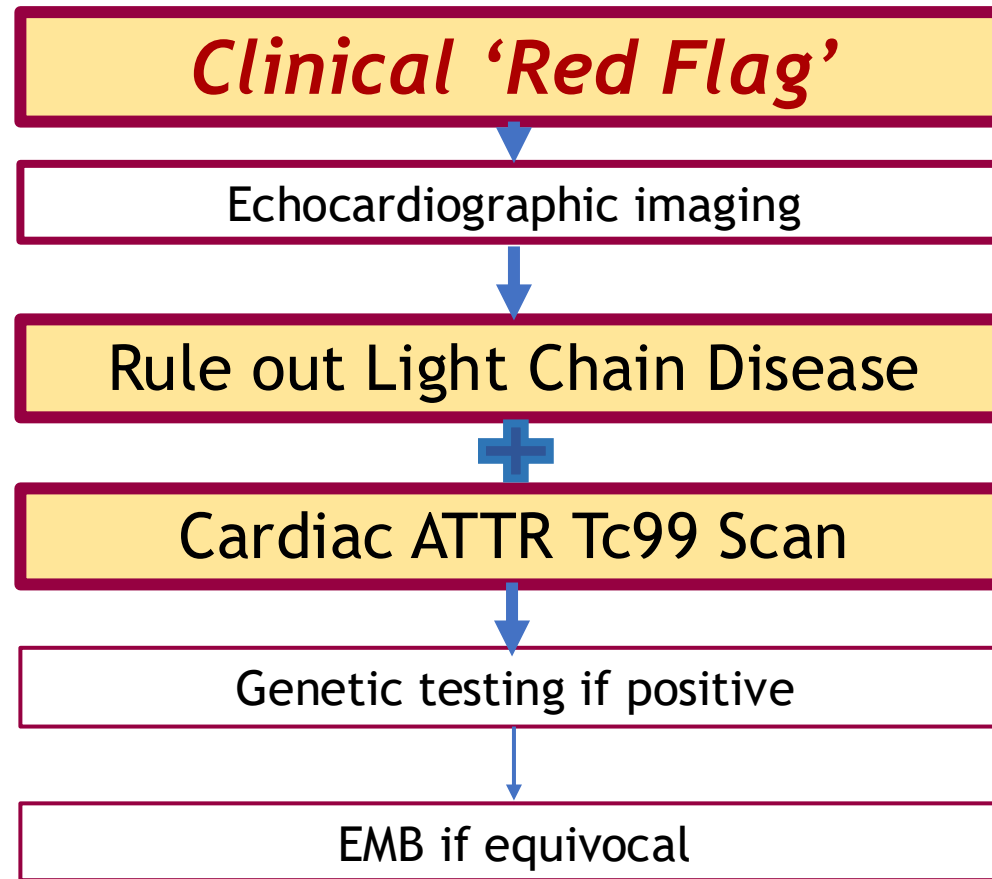
Canadian Cardiovascular Society/Canadian Heart Failure Society Joint Position Statement on the Evaluation and Management of Patients With Cardiac Amyloidosis

Primary Panel: Nowell M. Fine, MD, SM (Co-chair),^a Margot K. Davis, MD, SM (Co-chair),^b Kim Anderson, MD,^c Diego H. Delgado, MD,^d Genevieve Giraldeau, MD,^c Abhijat Kitchlu, MD,^d Rami Massie, MD,^f Jane Narayan, NP,^b Elizabeth Swiggum, MD,^g Christopher P. Venner, MD,^h

Secondary Panel: Anique Ducharme, MD, MSc,^c Natalie J. Galant, PhD,^d Christopher Hahn, MD,^a Jonathan G. Howlett, MD,^a Lisa Mielniczuk, MD,ⁱ Marie-Claude Parent, MD,^c Donna Reece, MD,^d Virginie Royal, MD,^j Mustafa Toma, MD,^b Sean A. Virani, MD,^b and Shelley Zieroth, MD^k

Canadian Cardiovascular Society Guidelines

'Simple' Diagnostic Algorithm: Suspect -> Detect



Tc99 Amyloid Scan Widely Available In the Eastern GTA

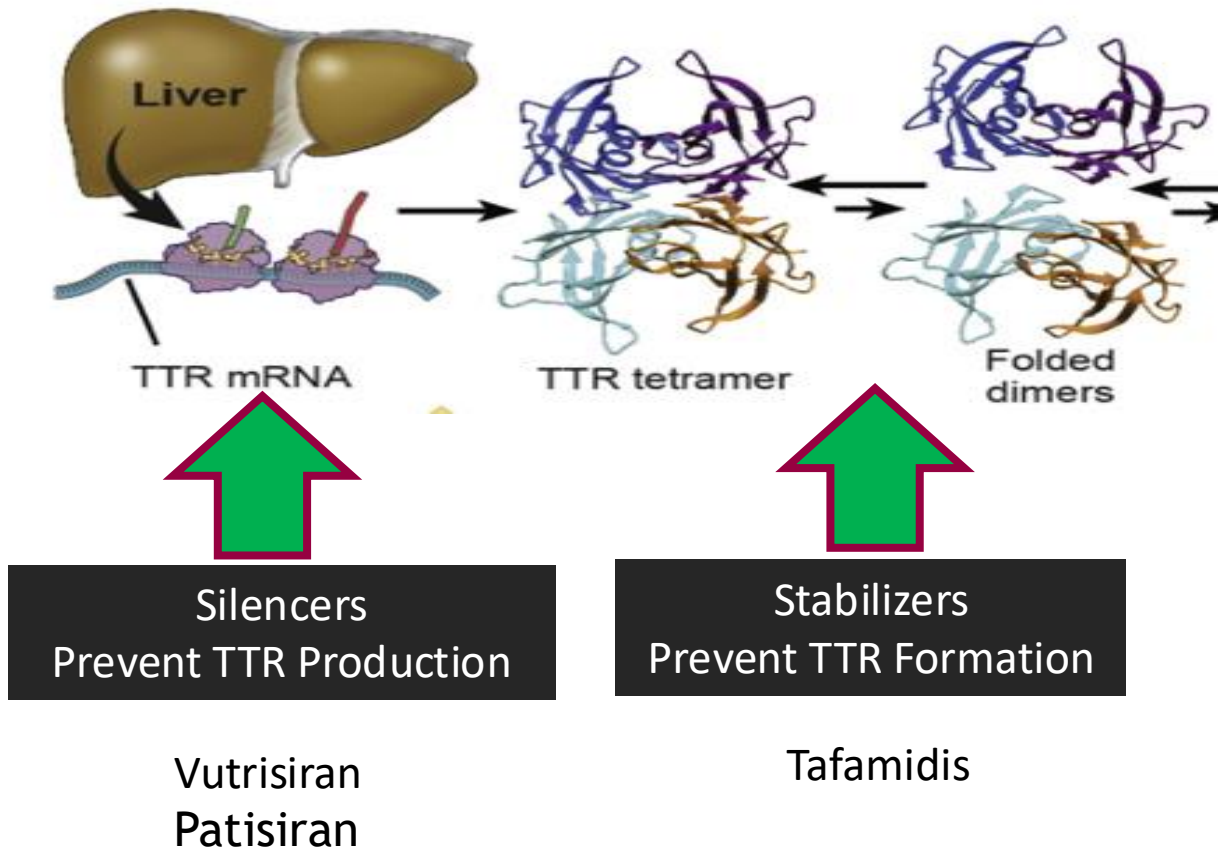
Corcare 325 Milner Avenue, Scarborough

SHN: Birchmount Site, Scarborough

UHN: College Street, Toronto

SMH: Shuter Street, Toronto

Canadian Cardiovascular Society Treatment Guidelines



Strong recommendation

- Tafamidis

Strong recommendation

- Vutrisiran
- Patisiran

Prognosis Without Therapy Poor

Median survival:

Wild Type	3.5 years
Hereditary > Wild Type	2.5 years

By Presentation

Polyneuropathy	8-10 years
Heart Failure	2.5-3.5 years

Non Predictors:

LVH
Diastology
LVMass
Atrial fibrillation

Recommended Therapies

Multiple New Therapies on the Way

Light Chain Amyloidosis:

Oncology

ATTR Cardiac Amyloidosis (ATTRwt or ATTRv)

Tafamidis

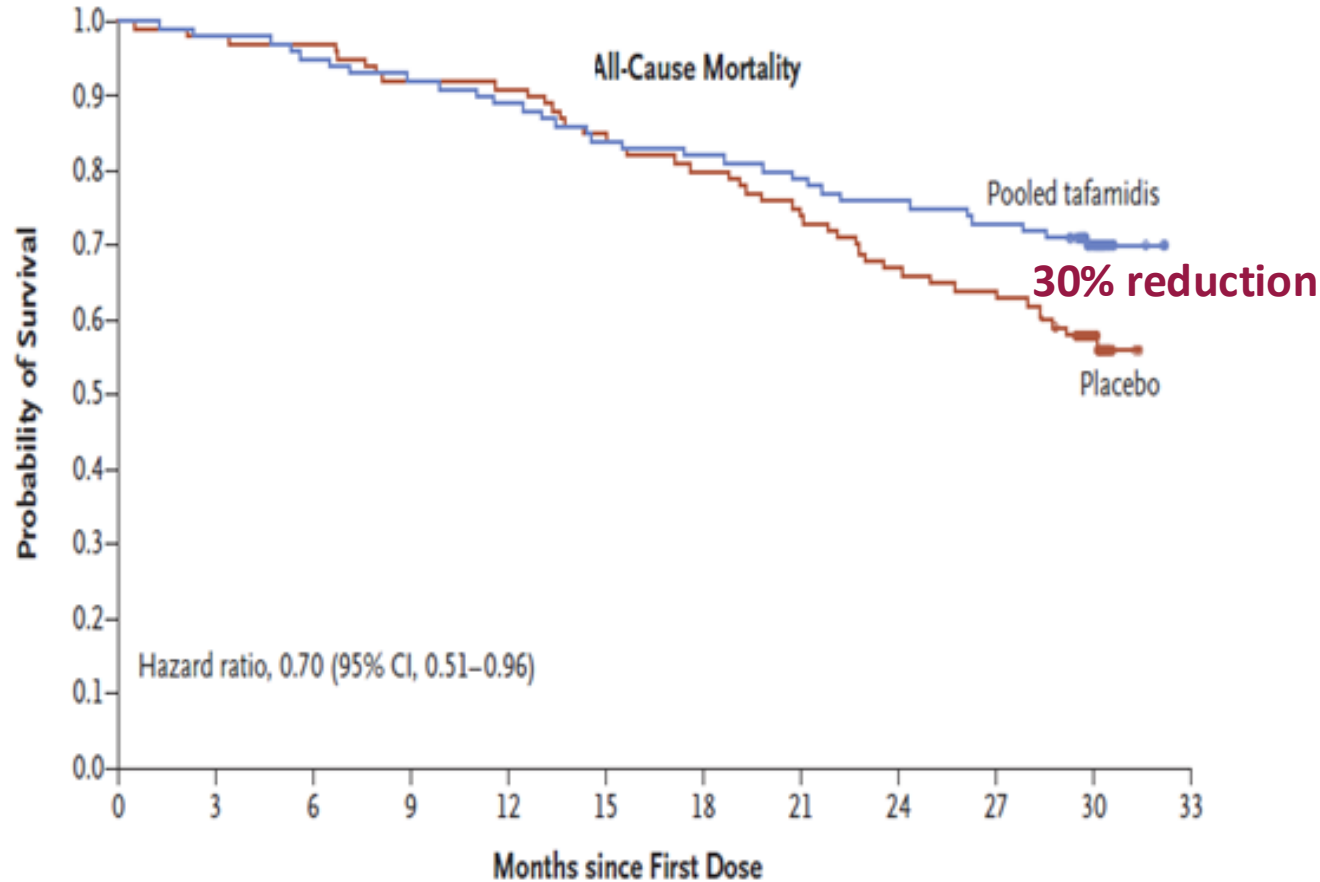
ATTR polyneuropathy:

Vutrisiran

Patisiran

ATTR ACT Trial Tafamidis

28% Reduction in the Composite of All-Cause Mortality and Recurrent CV Events



Survival benefit evident after 18 months

30% reduction All cause mortality

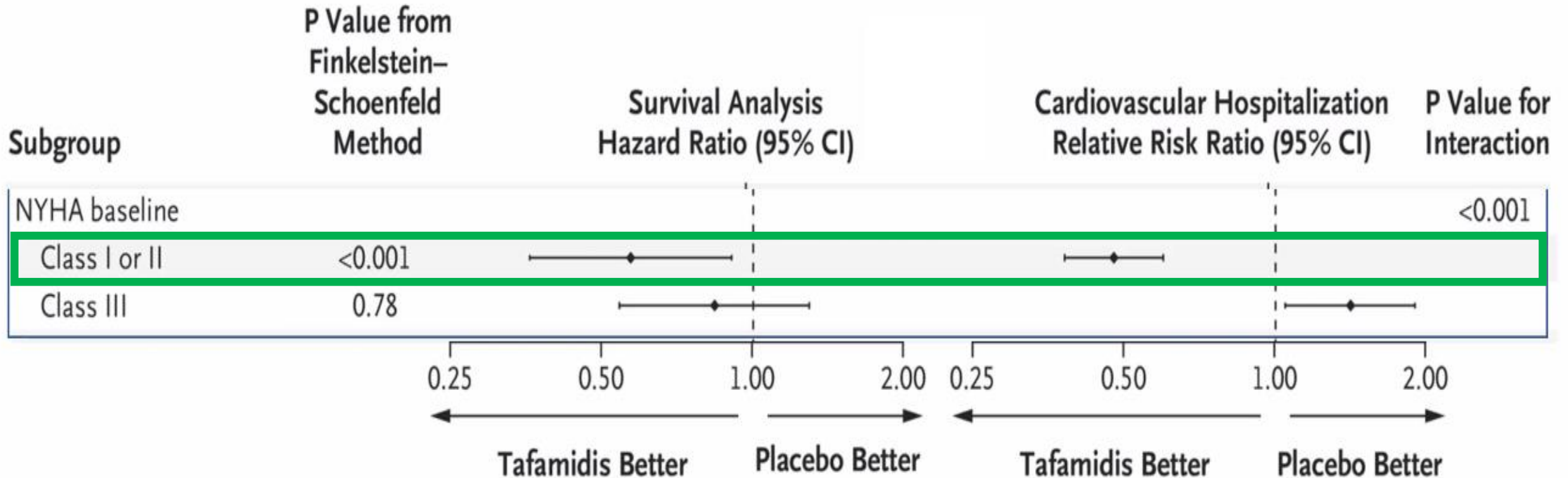
30% reduction Cardiovascular Hospitalization

Improved quality of life

Improved functional capacity

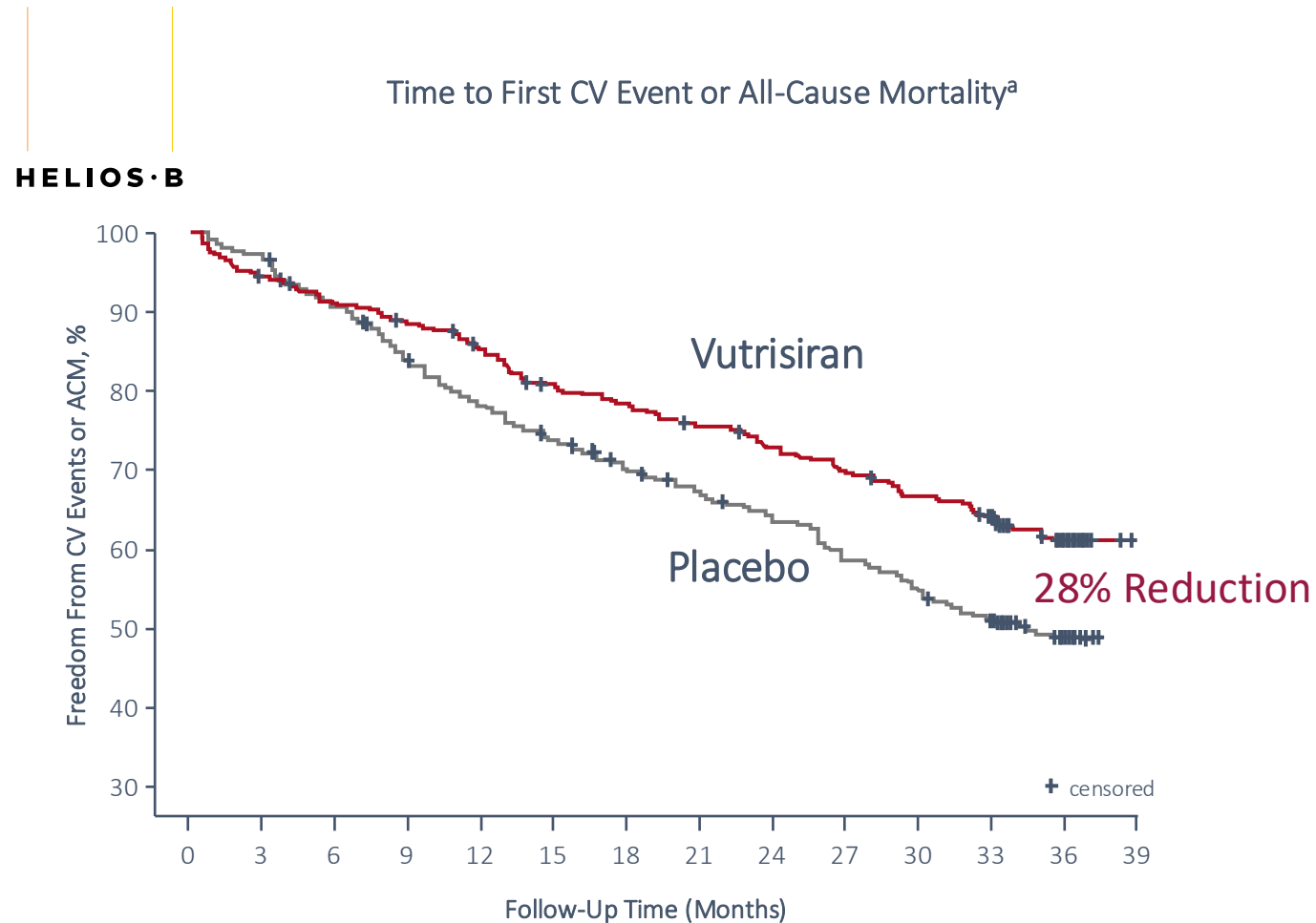
ATTR ACT Trial

Early Treatment Matters.....Late Treatment is INEFFECTIVE



Silencers: Helios B Vutrisiran

28% Reduction in the Composite of All-Cause Mortality and Recurrent CV Events

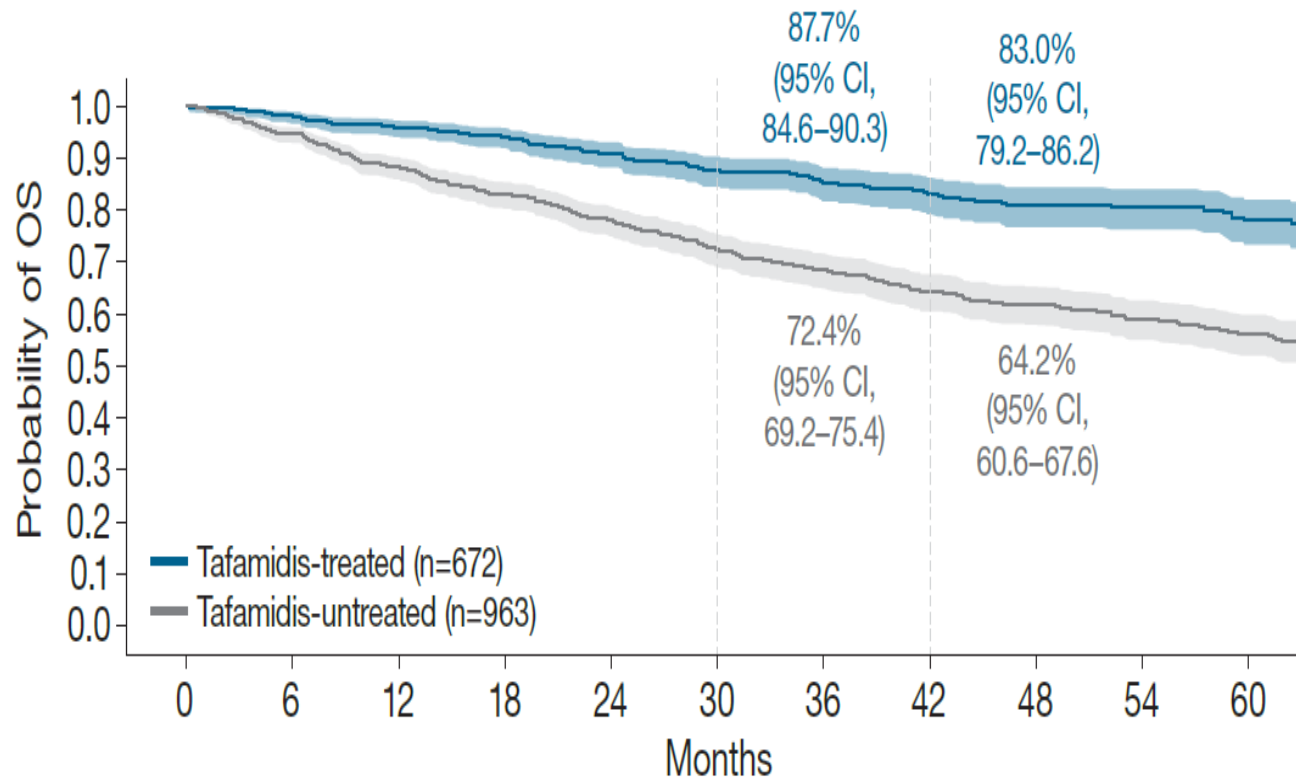


28% reduction in primary endpoint

40% on concomitant tafamidis

Real World Long Term Data

Transthyretin Amyloidosis Outcomes Survey Mayo Clinic



- Results consistent for Wild Type and Variant ATTR
- Safety matched published profiles

Tools to Help You in Your Practice

CQEP Website for Community Care Providers

1

Accredited Educational Modules

2

Patient Care Resources

- Attr Tc99 Imaging Locator
- Ontario Genetic testing forms
- Local ATTR amyloid management service

CEQP Online Education Resources¹

**Why ATTR
Amyloidosis
Matters**

**Understanding
Cardiac
Amyloidosis**

**Recognizing
Red Flags**

**Hereditary ATTR
Amyloidosis**

Diagnosis

**ATTR
Scan Locator**

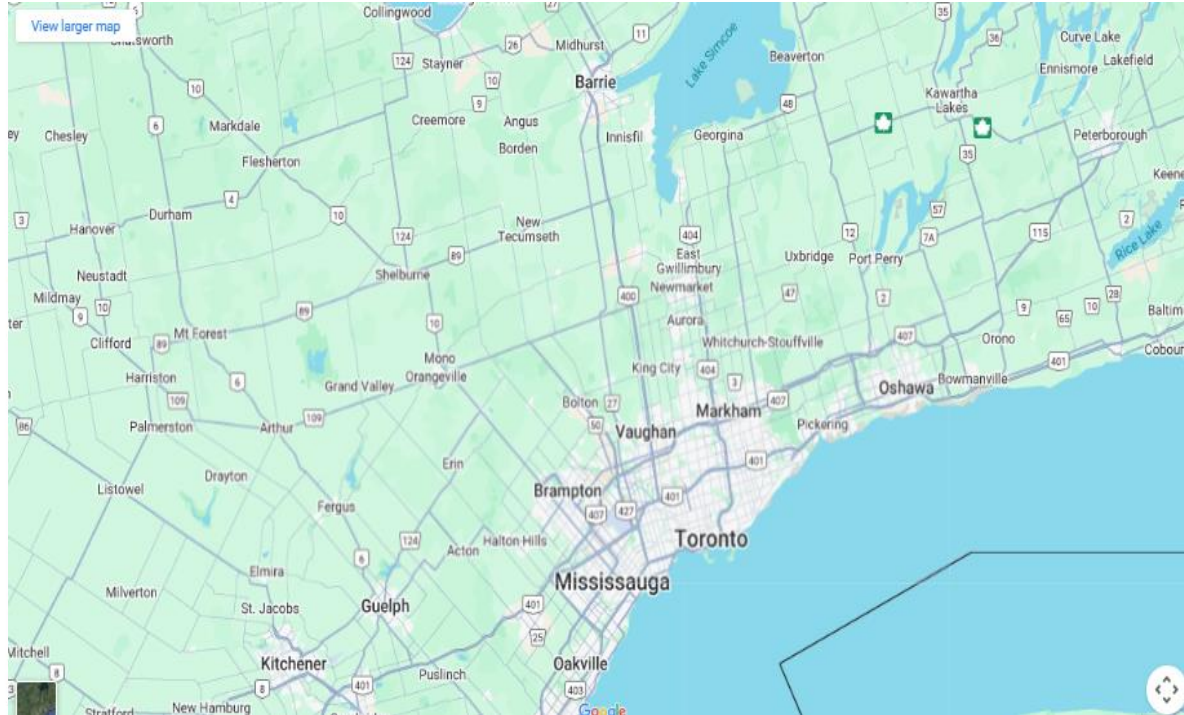
Therapies

Ontario ATTR Testing Site Locator

Search by address, city, or postal code

 Use my location

Search Filters 



Select Radius for Search

10 km

50 km

15 km

50+ km

Specialty Management Services



Corcare Amyloid Management Service

Leads: Dr Paul Galiwango, Dr Ash Mukherjee, Dr Joe Ricci



SHN Amyloid Clinic

Lead Dr Natalie Ho



North York General Hospital Amyloid Clinic

Lead: Dr Kareem Morant



Key Messages:

Look for Red Flags & Screen All!

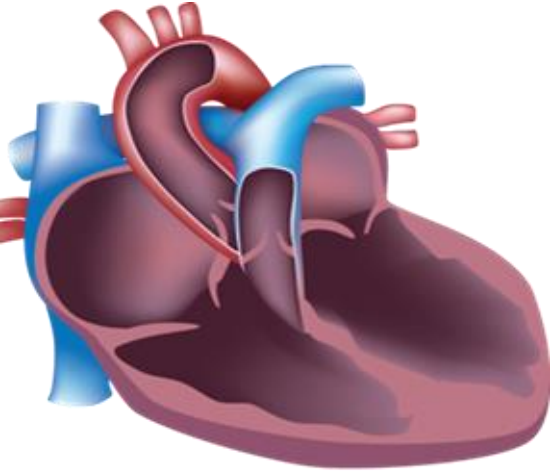
1. Amyloid is common in patients with 'Red Flags'.
2. Primary care physicians screening "Red flag" are critical for early diagnosis.
3. Cardiac TC99 Scanning is sensitive, safe, available and low cost
4. Patient awareness is rising
5. Multiple, effective therapies



Heart Failure with Non-Reduced Ejection fraction: 2025 CCS guidelines

Learning Objectives

During this session, participants will analyze and interpret the:



- New Definitions : HFrEF and the New HF without rEF
- Foundational therapies for Patients for HF
- Management is a Partnership... No Silos Please
- practical approaches to delivering care

Heart Failure is a Large Problem



Prevalence CANADA

- 787,000 HF patients in Canada > 40 old
- 111,900 New diagnosis of HF each year



Prevalence Our Community 1M (3% Canada)

- >23,000 HF patients in Scarborough/Durham
- > 3,000 New diagnosis of HF each year

Large Demand = No Silos

Requires Teamwork & Scalable Solutions

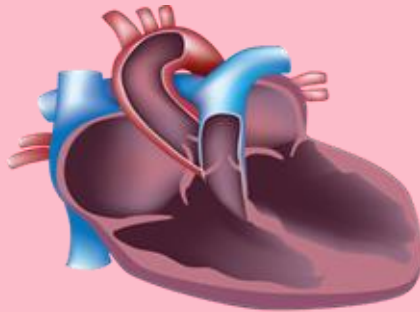
- >23,000 Chronic HF patients in Scarborough/Durham
- > 3,000 New diagnosis of HF each year

The Canadian Heart Failure Terms

Goodbye to MEF and PEF!

HF-rEF

reduced ejection fraction
EF \leq 40%



Significant Systolic dysfunction

Enlarged

HF- nrEF

nonreduced ejection fraction
EF $>$ 40%



Systolic Function: Near Normal or Normal

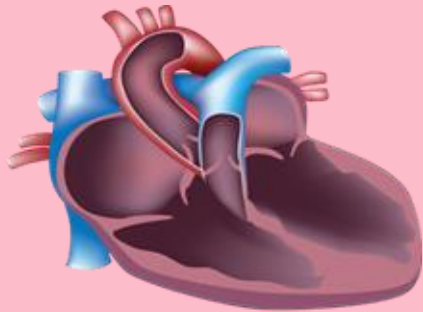
normal to normal Size

The Canadian Heart Failure Terms

Recognition of a rEF to non rEF Gradient

HF-rEF

reduced ejection fraction
EF \leq 40%



Significant Systolic dysfunction

Enlarged

HF nrEF

nonreduced ejection fraction
EF $>$ 40%



Systolic Function: Near Normal or Normal

normal to normal Size

4 Facts About HFrEF vs HFnrEF

- HFrEF and HFnrEF are equally common
- HFrEF and HFnrEF cannot be distinguished by HF symptoms
- Amyloidosis is an underdiagnosed cause of HFrEF (5%) and HFnrEF (30%)
- HFrEF Foundational therapies are effective and disease altering, but less so for HFnrEF

Diagnosis of Heart Failure

Assess symptoms breathlessness, fatigue, angina, palpitations or syncope

Assess signs HR, BP, murmurs, fluid overload,

ECG ECG

Laboratory nt-pro BNP

Chest X-ray Pulmonary congestion

Echocardiography HFrEF vs HFnrEF, wall motion, valve, LV function; valves

HFrEF and HFpEF are Different Conditions

HFrEF

reduced ejection fraction
EF \leq 40 %

Ischemic Heart Disease:

50%

Non Ischemic Heart Disease

50%

Idiopathic/DM/BP/Obesity
Amyloidosis

90%
10%



HFpEF

Heart failure with preserved
ejection fraction EF > 40%

Ischemic Heart Disease

0%

Non Ischemic Heart Disease

100%

Idiopathic/DM/BP/Obesity
Amyloidosis

70%
30%



Diagnosis of the Cause of Heart Failure

Echocardiogram	Ejection Fraction Wall motion Hypertrophy Valve Disease
CAD	Myocardial Perfusion Scan
Amyloid	Cardiac aTTR Tc99 amyloid scan
Laboratory	Immunoelectrophoretic, Light Chains Thyroid Function, Ferritin
Genetics *	hATTR Cardiomyopathy, Hypertrophic Cardiomyopathy
Cardiac Consultation	CCS guideline recommended

* Now covered in the Province of Ontario

My Patient has Reduced Ejection Fraction . What do I do first?

- I. Review goals with patient, start foundational medications and provide follow-up
- II. Review goals with patient, Initiate foundational therapies and refer to a cardiologist for concurrent care
- III. Refer to a cardiologist to initiate care and jointly follow patient
- IV. Refer to cardiologist to assume care
- V. Refer to a heart failure clinic

7 Facts About Heart Failure Therapy

- Heart Failure is a chronic condition
- Foundation therapy improves quality of care and survival
- Ejection fraction improves and can normalize with optimal therapy
- Effective therapy requires doses tested in trials
- Time under treatment matters: Early Better
- Best outcomes occur when the primary care and physicians collaborate
- Stopping therapy not recommended when stable as up to 44% 'Rebound' (even if Ejection Fraction Normalizes!!)

The “Pillars of Care”

CCS Heart Failure Guidelines # 27

We recommend using specific drugs at target doses proven beneficial in clinical trials as optimal medical therapy.

If these doses cannot be achieved, the maximally tolerated dose is acceptable

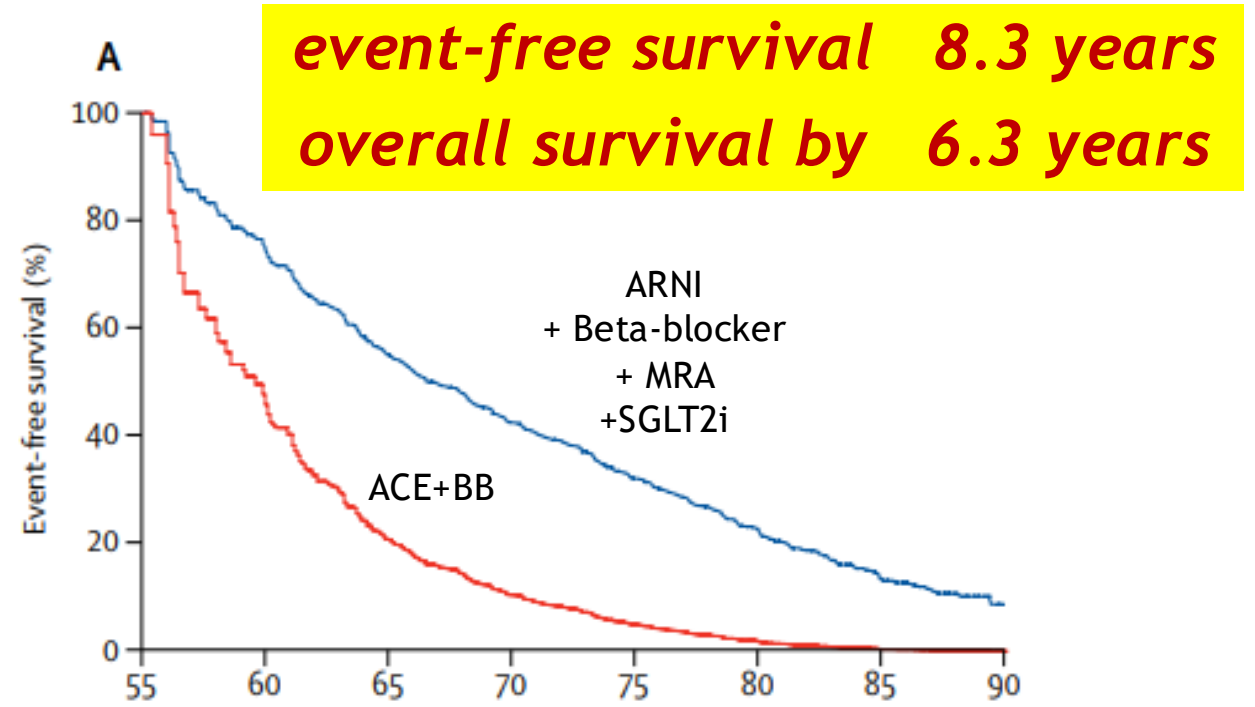
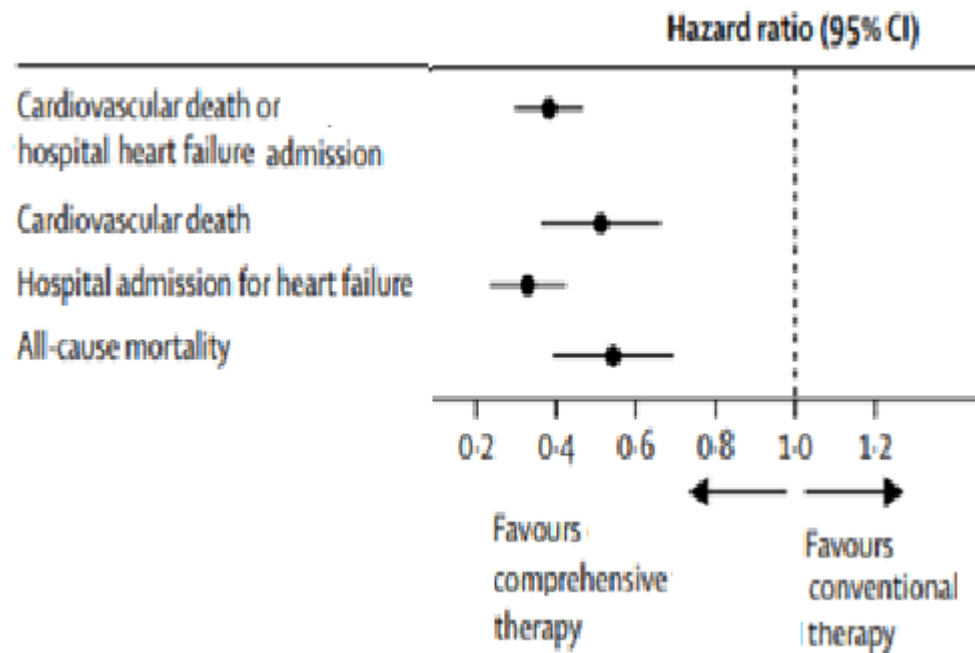
Strong recommendation: High Quality Evidence

THESE ARE STANDARDS
OF CARE

NOT

GUIDELINES

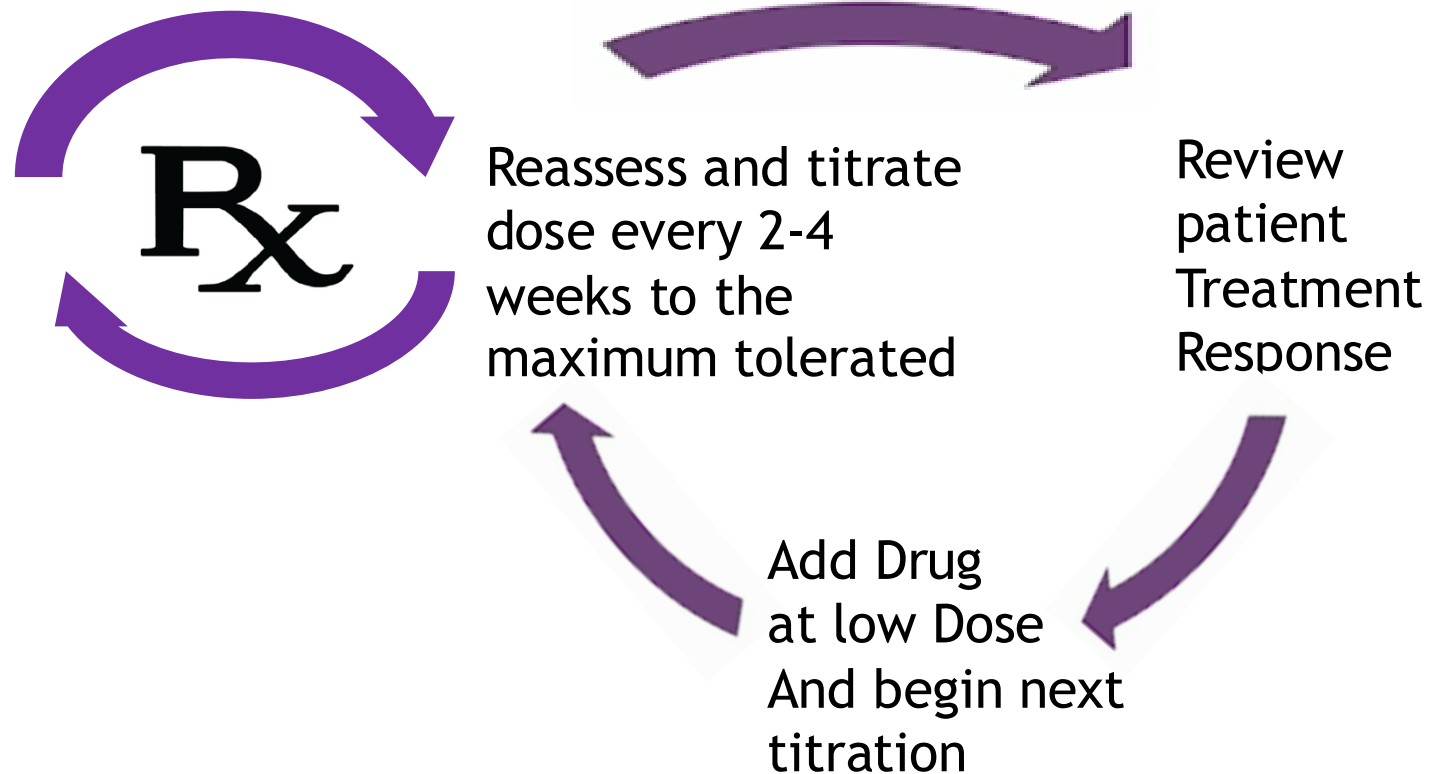
Multiple Pillars = Best Outcome



How Best to Get My Patient on GDMT??



Abandon the *'Old School'* Approach





New Canadian Guidelines Give Thumbs up for 'Clustered Care'

- ✓ **Begin with combinations**
- ✓ **Easy steps first**
- ✓ **Start Low**
- ✓ **Go up as tolerated**

Day 1 "The Easy Starts"

Patient Discussion and Contract

Heart BP, Weight HR diary

Start Easy pillars

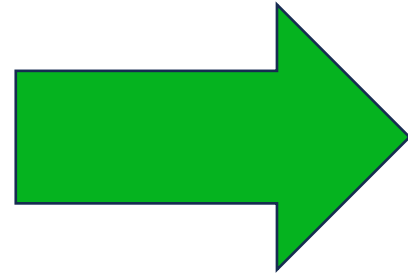
Spirolactone
SGLT2i
Lasix for edema

Engage Your Community Team

Team Nurse
Cardiac rehabilitation
Cardiologist
Pharmacy script

Clustered Care Benefits

- ✓ **Early initiation**
- ✓ **Faster completion**
- ✓ **Better tolerance**
- ✓ **Better compliance**
- ✓ **Fewer Visits**



- ✓ **Earlier Outcome Improvement**
 - ✓ **Functional class**
 - ✓ **Reduced Hospitalization**
 - ✓ **Mortality reduction**
 - ✓ **Ejection fraction**

The 'Easy' Pillars

MRA

Mineralocorticoid Receptor Antagonist

Goal: Spironolactone 25-50 mg (Alternative Eplerenone 50 mg if gynecomastia occurs)

Practical tips:

Value not dependent on diuresis

Caution with CKD or elevated K⁺

Lytes, BUN, Cr at next visit 2-4 weeks

Target Therapy:

Dapaflagozin 10 mg

Empaflagozin 10 mg

Practical tips:

Approved for low EGFR > 20

No advantage for high dose in HF

Expect initial fall in EGFR up to 20%

GLP1 agonist not a problem

The Easy Steps

Avoid Harm



High Salt Diet/Processed foods



Non-dihydropyridine CCBs : Verapamil, Diltiazem



- negative inotropic effect

NSAIDs and COX-2 inhibitors :



- sodium and water retention, worsening renal function and worsening HF

ARB + ACE-I together



- renal dysfunction and hyperkalemia

The Easy Steps Connect To Community Partners

1. Cardiologist for lifelong collaboration
2. Cardiac Rehabilitation Services
3. Pharmacists for medication support
4. Team nurse support if available (more Later)

The Easy Steps

Cardiac Rehabilitation



17 SITES

SCARBOROUGH

Scarborough Health Network (SHN) Centenary hospital
2867 Ellesmere Road

Toronto Pan-Am Sports Centre
875 Morningside Avenue

Stephen Leacock Community
Recreation Centre
2500 Birchmount Road

PICKERING

Pickering Soccer Centre
1975 Clements Road

AJAX

Ajax Community Centre
1975 Clements Road

Complete Performance Centre
72 Orchard Road

WHITBY

Abilities Centre
55 Gordon Street

OSHAWA

Oshawa Civic Complex
99 Thomson Road South

Delpark Homes Centre
1661 Harmony Road North

BOWMANVILLE

Bowmanville Indoor
Soccer Complex
2375 Baseline Road West

COBOURG

Cobourg Community Centre
750 Drury Street

LINDSAY

Ross Memorial hospital
10 Angelina Street North

PORT PERRY

Scugog Community
Recreation Centre
1655 Reach Street

BOBCAYGEON

Kawartha Lakes
Retirement Residence
60 West Street

PETERBOROUGH

Peterborough Sport &
Wellness Centre
775 Breakley Drive

HASTINGS

Hastings Field House
97 Elgin Street

EVERY HF PATIENT SHOULD BE REFERRED

24 sessions over 6 months

- Education
- Exercise training and supervision
- Heart failure oversight
- Medication support

Cluster Therapy: Step 2 'The Long Game'



Start Clustered Beta Blockade and ARNI

Sactubtril Valsartan 24/26 bid staggered
Carvedilol 24/26 bid staggered

The Long Game

Beta Blockade

Goal: Carvedilol 25 mg po bid
Bisoprolol 10 mg po od

Practical tips: Stagger with ACE/ARB/ARNI (qid schedule) to avoid hypotension
Heart rate goal 50-70 bpm

The Long Game

Sacubitril-Valsartan

Goal: Sacubitril-Valsartan 97/103 bid

ACE/ARB IF ARNI NOT TOLERATED

Practical tips: Stop ACE x 2 days

Start low Sacubitril-Valsartan 24/26 mg bid

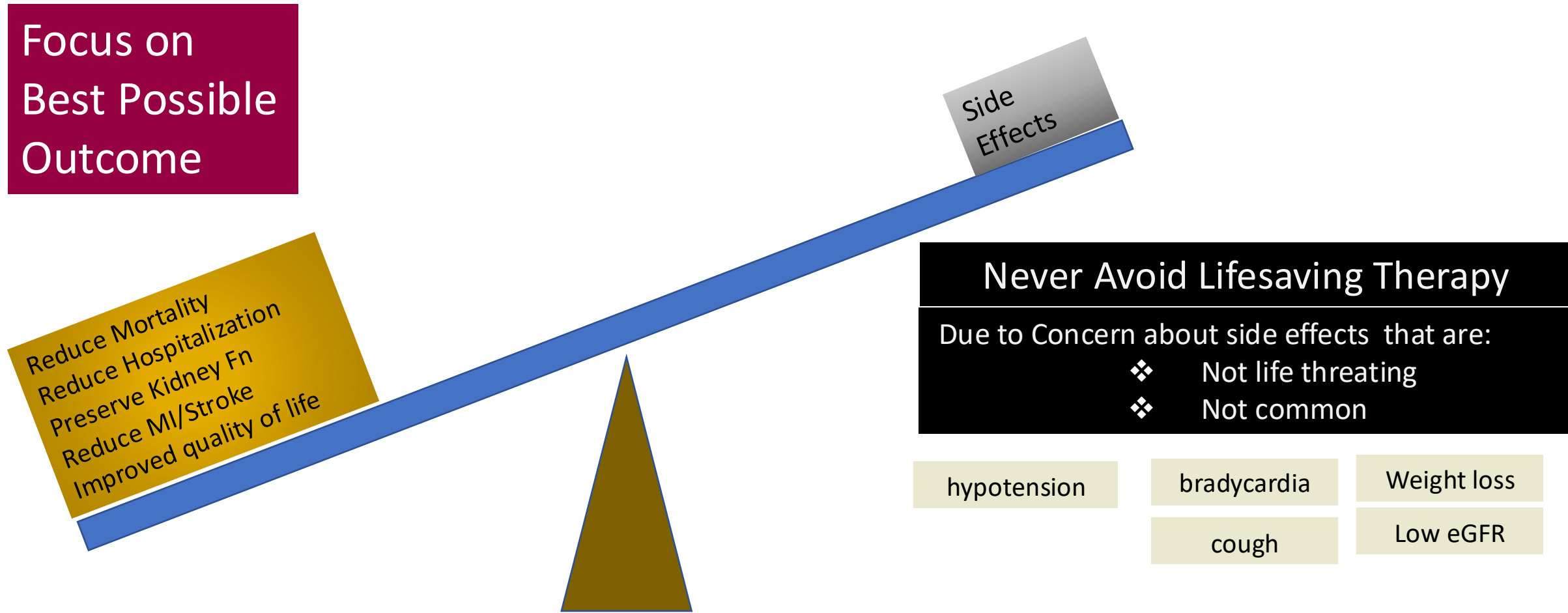
Titrate slowly every 3-4 weeks to max tolerated

May see up to 30% fall in eGFR

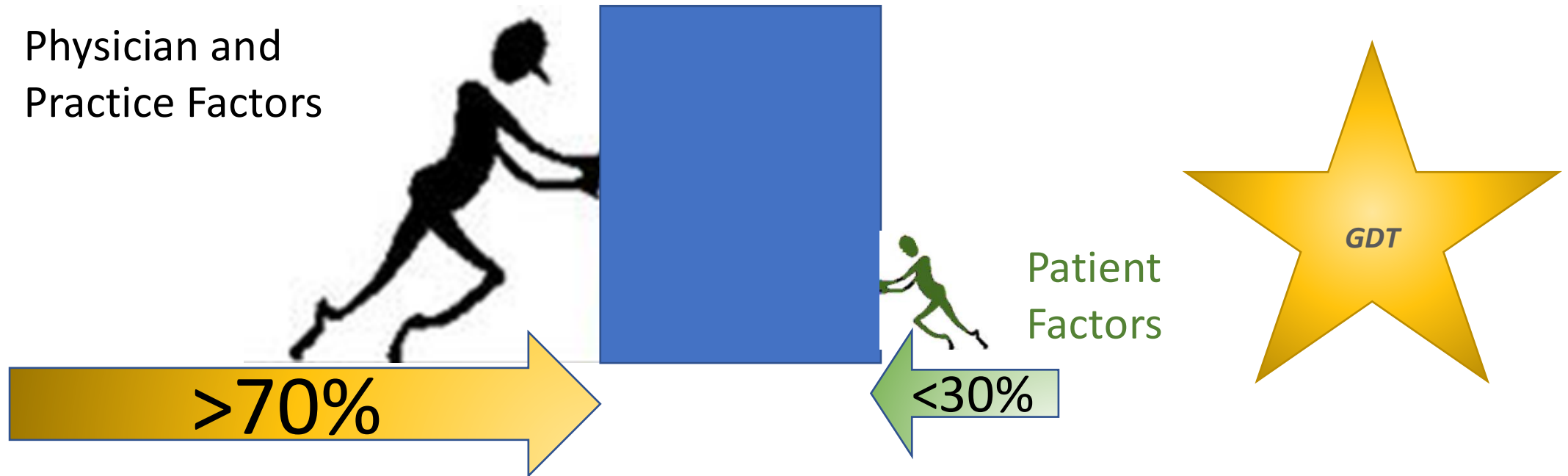
Fall back to ACE/ARB if not tolerated due to Low BP

(If low BP an issue, always look to ↓ or d/c furosemide if possible)

'Soft risks' DO NOT JUSTIFY holding GDMT



No Inertia: You in the Leadership Role!



Physicians **NOT** Patients are Main Drivers of Outcome for Patients

Beyond the Foundations- Specialty Tools



How often should HF patients be seen?

- Acute change in symptoms **24-48 hours**
- After a HF ER visit or hospitalization **1-2 weeks**
- After an initiation or change in medications **2-4 weeks**
- Stable on optimized therapy **3-6 months**

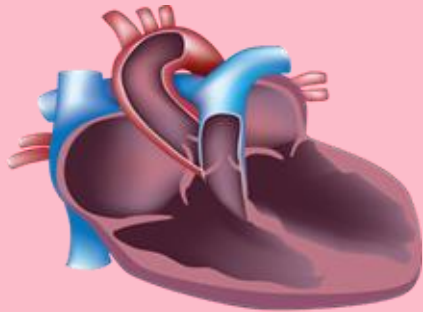
**My Patient has HFnrEF.
Which of the Following are of NOT of Value?**

- a) Beta blockers
- b) Spironolactone
- c) SGLT2 inhibitors
- d) Cardiac ATTR amyloid Scan
- e) All are of value for some patients
- f) None are of any value

Recognition of a rEF → nrEF Gradient

HF-rEF

reduced ejection fraction
 $EF \leq 40\%$



Significant Systolic dysfunction

Enlarged

HF nrEF

Moderate to Normal ejection fraction
 $EF > 40\%$



Systolic Function: Near Normal or Normal

normal to normal Size

Whats New in 2025 Guideline Heart Failure without Reduced EF?

- ✓ Valuable in all
 - ✓ Salt reduced diet
 - ✓ Weight reduction
 - ✓ Exercise and Cardiovascular Rehabilitation
 - ✓ Diuretics to manage edema and congestion
- ✓ HF without rEF in with borderline EF reduction 40-50% range
 - ✓ SGLT2 inhibitors
 - ✓ Spironolactone
 - ✓ (Sacubatril-Valsartan)

To Do Better We Need To Pull Together



- ✓ A System of care
- ✓ Collaborative Care including Patients & Providers
- ✓ Shared tools and goals
- ✓ Outcome Driven
(Quality & length of life)

The Standard of Community Care



Primary Care + Specialist Collaboration

*BETA
BLOCKER*

ARNI

MCA

SGLT2I

IVRABADINE

REHAB

*STATIN**

*DIGOXIN**

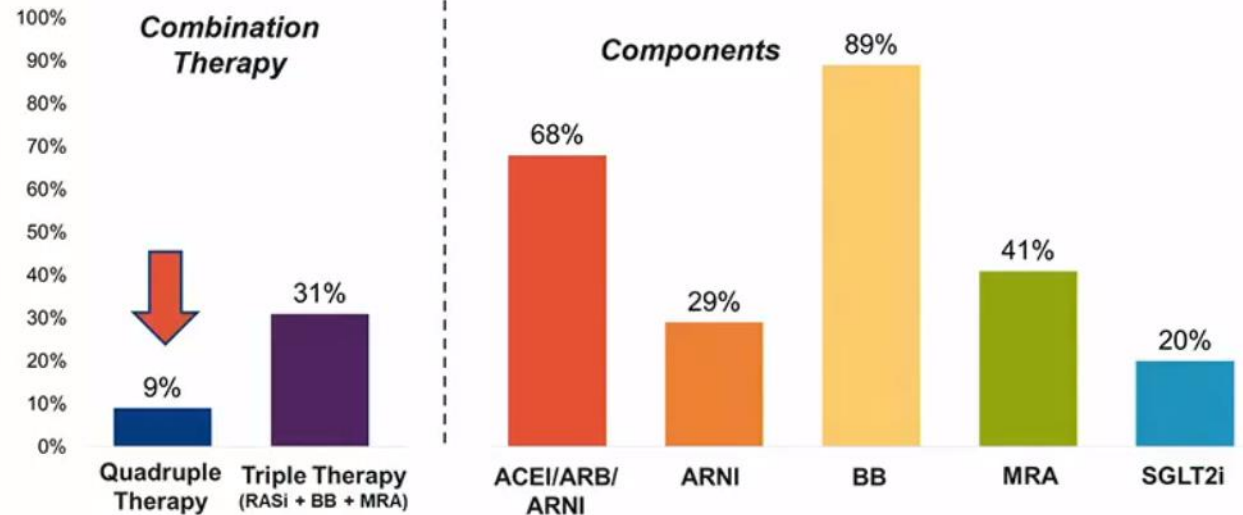
THESE ARE STANDARDS
OF CARE

***They ARE NOT
GUIDELINES***

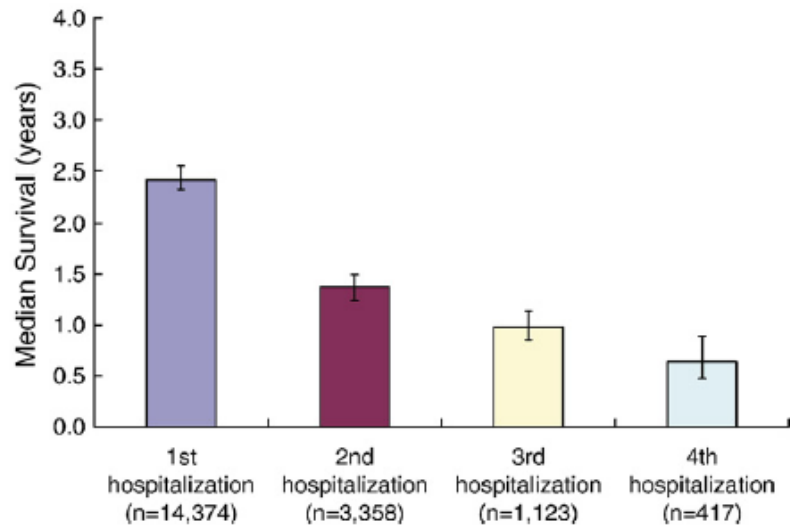
To date: We Have Not Met The Challenge

Failure to Respond Adequately to HF as a Chronic Disease

GDMT for HFrEF in the US (2021-2022)*

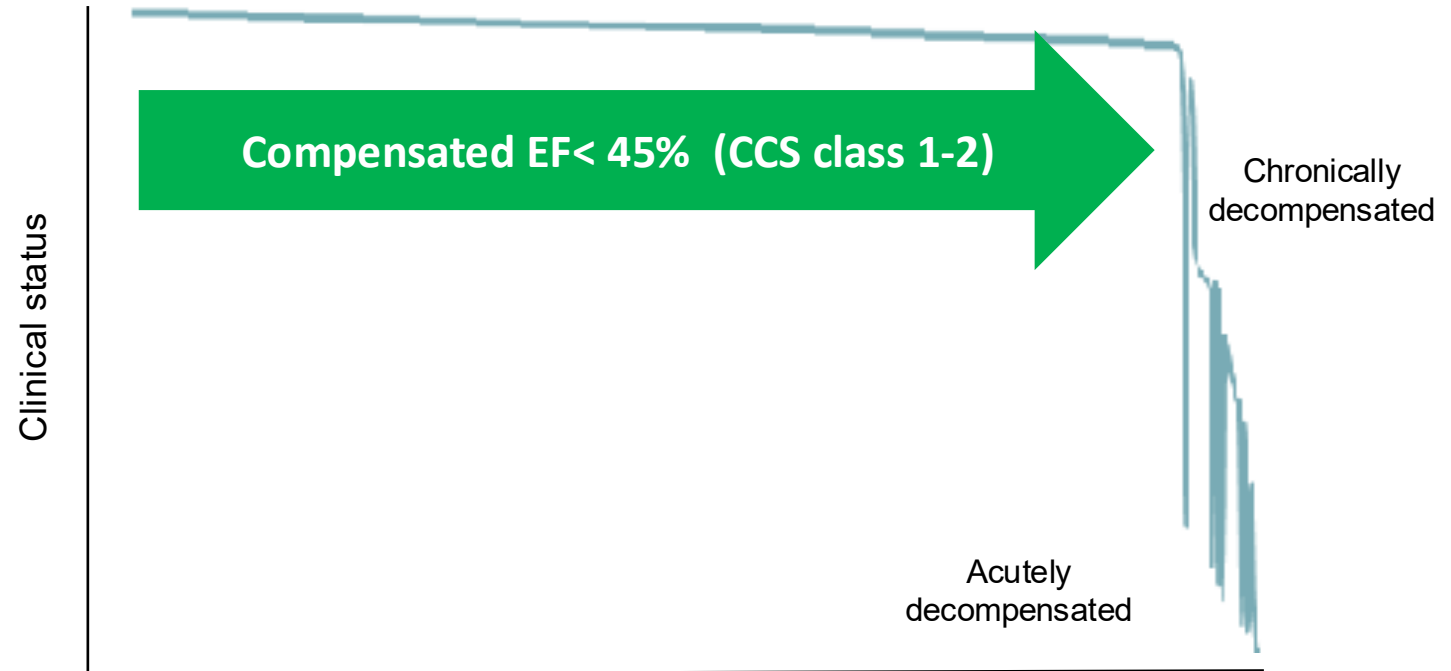


✓ Reframe Reduced Ejection Fraction as a Chronic Condition requiring Early and lifelong preventative care



Median survival (50% mortality) and 95% confidence limits in patients with HF after each HF hospitalization.

Am Heart J. 2007;154(2):260-266



“We cannot define a trajectory for individual heart failure patients”

Robert McKelvie

Systems are People Working Together with shared tools and goals.

- ✓ Reframe Heart Failure as requiring lifelong care
- ✓ Shared GDMT accountability by Patients AND Providers
- ✓ Collaboration by all providers
- ✓ Institutional accountability for tertiary support

Systems are People Working Together
with shared tools and goals.



Patients and Health Care Professionals Working Together

Family

Patient

*Primary
Care*

*Cardiology
Specialist*

*Cardiac
Rehab*

*Hospital
Care*

Our Region has the Resources To Treat HFrEF Well!

The Right Team

✓ Health Care Providers

- ✓ Primary Care network >1000 physicians
- ✓ > 50 well trained specialists
- ✓ Allied health professionals

✓ Facilities

- ✓ 11 Hospitals
- ✓ Regional Cardiac Care systems
- ✓ Regional Cardiac Rehabilitation

High Impact Playbook

✓ Effective Therapies

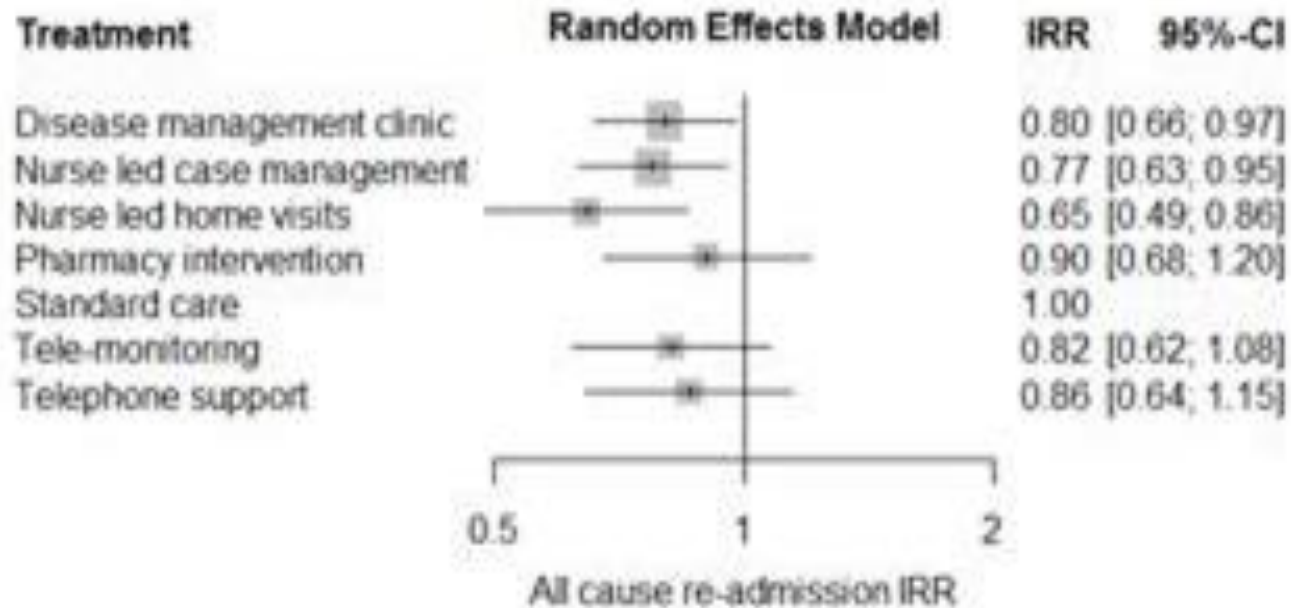
- ✓ Multiple effective GDT

✓ Effective Delivery Approaches

- ✓ Early Therapy
- ✓ Clustered therapy
- ✓ Protocol Guided GDMT
- ✓ Early post discharge reassessment

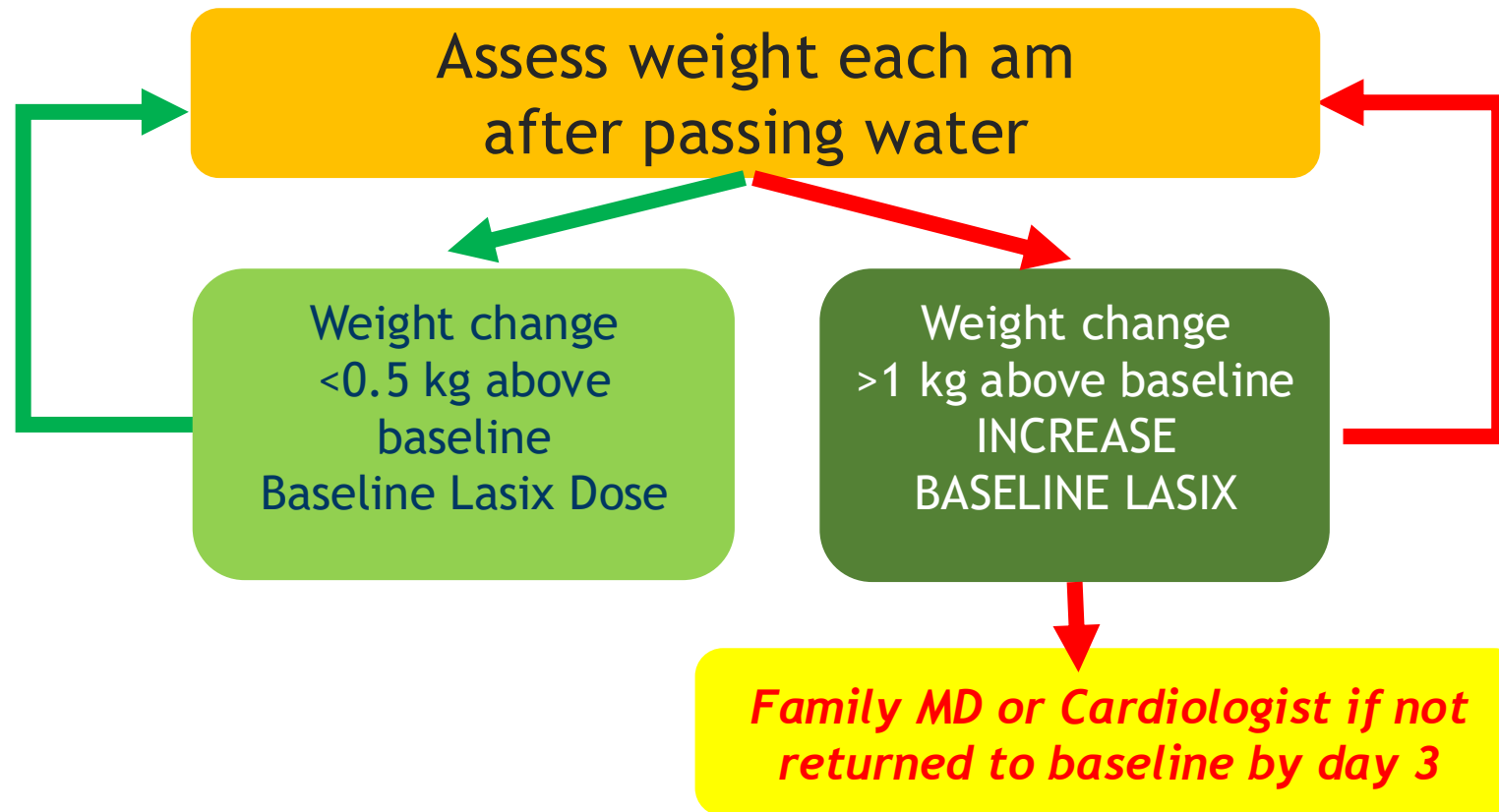
Evidence For Collaboration is DEEP

Collaborative Care Enhances Outcomes



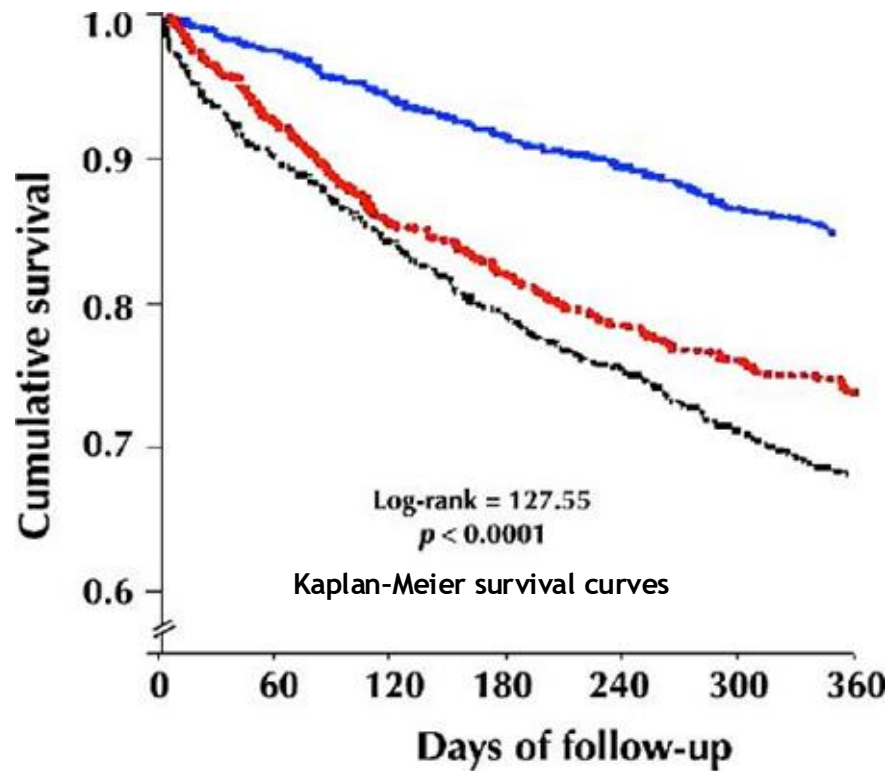
The Patient Contract

PROVIDE PRACTICAL ADVICE TO PREVENT HARD LANDINGS



Collaborative is More Effective In Our Canadian System

- ✓ Primary care engagement with Cardiology and Health Care Resources



Blue = *combined care* (both specialist and family physician),

Red = *care by family physician only*,

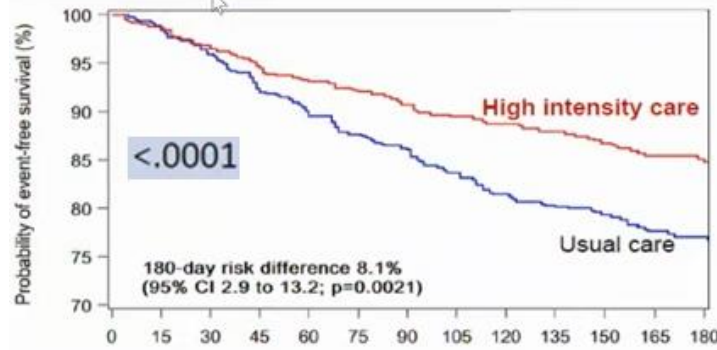
Black = *no follow-up care*

We Have the Evidence!

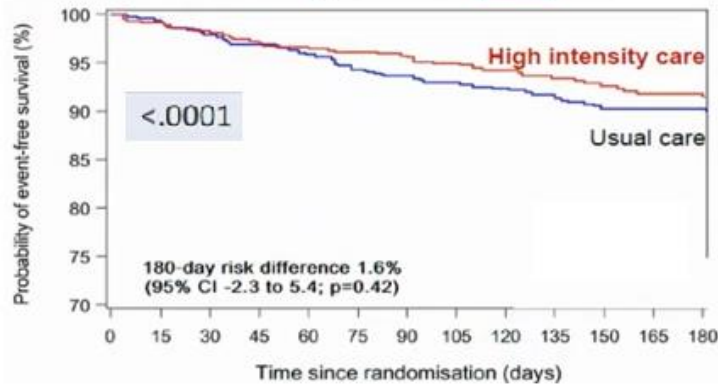


Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure : a multinational, open-label, randomized, trial

180-Day Readmission for HF or All-Cause Death



180-Day All-Cause Death



1078 Patients 89 hospitals 14 countries.

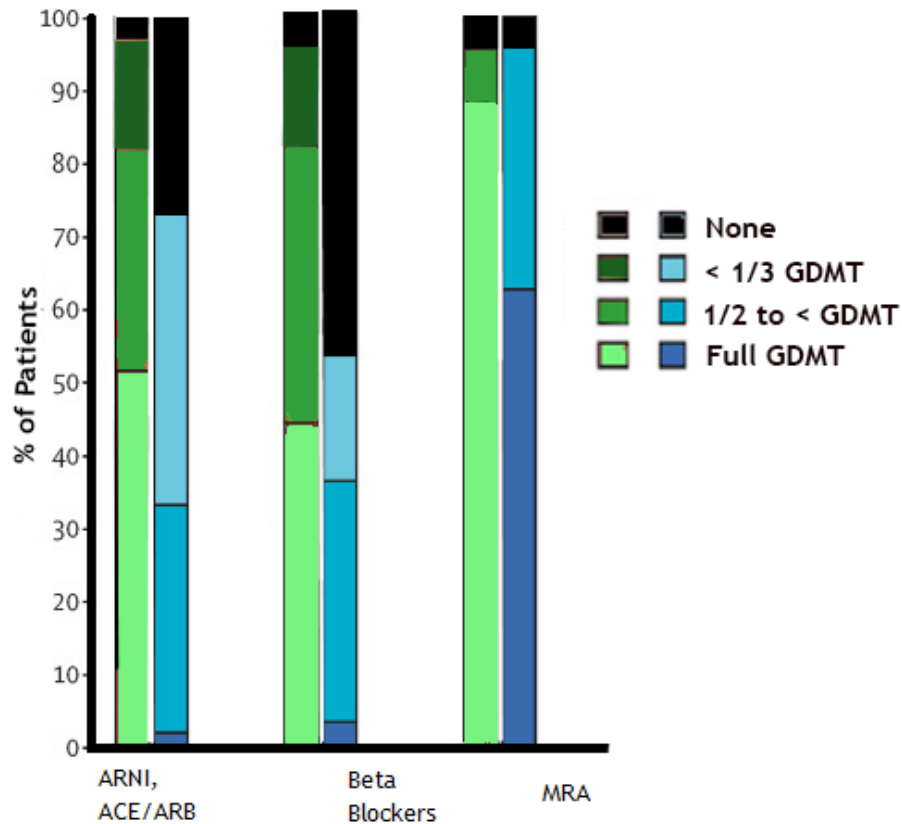
Randomly Assigned after Admission to either

- usual practice
- Protocol mandated rapid up titration of GDMT

Heart Failure: We Have Evidence for What Works



Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure : a multinational, open-label, randomized, trial



High Impact Despite Limitations

- ✓ 50% at Full Protocol Guided GDMT
- ✓ ARNI Not Mandated
- ✓ Beta Blockade difference main Driver

Strong Proof Of Concept for Value of Protocol Driven GDT

We Have the Same Evidence!

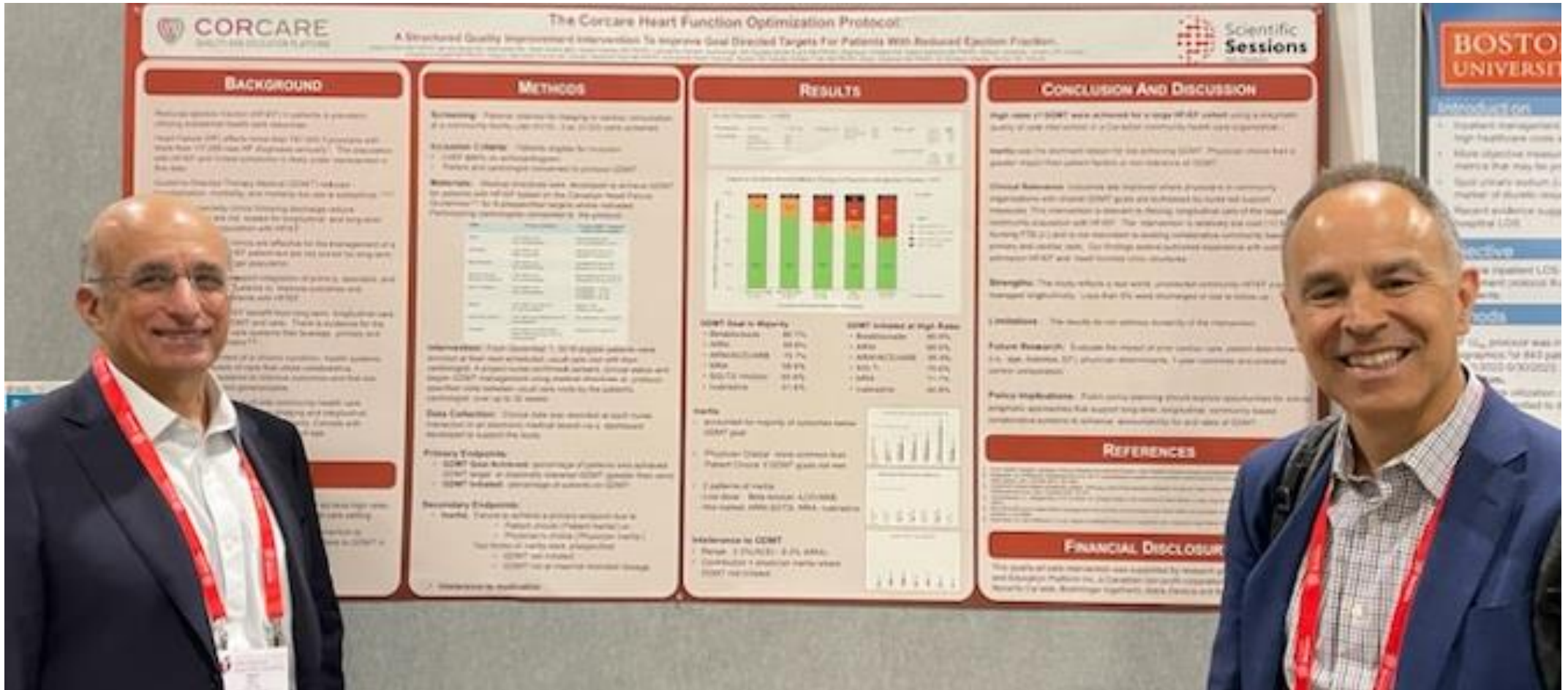
The Corcare Heart Function Optimization Protocol: A Structured Quality Improvement Intervention To Improve Goal Directed Targets For Patients With Reduced Ejection Fraction.

Joseph A Ricci MD FRCPC, Beverly Bozek RN, Maria Aprile RN , Siyam Ibrahim BSc, Saleem Kassam MD FRCPC, Luke Aprile, Corcare, Scarborough, ON, Canada; Neville Suskin MD FRCPC, Stephanie J Frisbee PhD, Robert McKelvie MD FRCPC, Western University, London, ON, Canada; Jonathan G Howlett MD FRCPC, Calgary, Libin Heart Institute AB, Canada; Stephanie Poon MD FRCPC, Sunnybrook Health Sciences, Toronto, ON, Canada; Andrew T Yan, MD FRCPC, Shaun Goodman MD FRCPC, St. Michael's Hospital, Toronto, ON, Canada .



The Corcare Optimization Protocol

5 year longitudinal Intervention in 983 Patient with EF ≤ 40%



American Heart Association Scientific Sessions Abstract: Su2145

Sunday, November 19, 2023, Philadelphia



GDMT Protocol Guided Longitudinal Care

All Patients between January 2015, and March 31, 2023

- LVEF \leq 40% on echocardiogram and
- Consent

Project RN support at protocol-specified visits between usual care visits up to 32 weeks

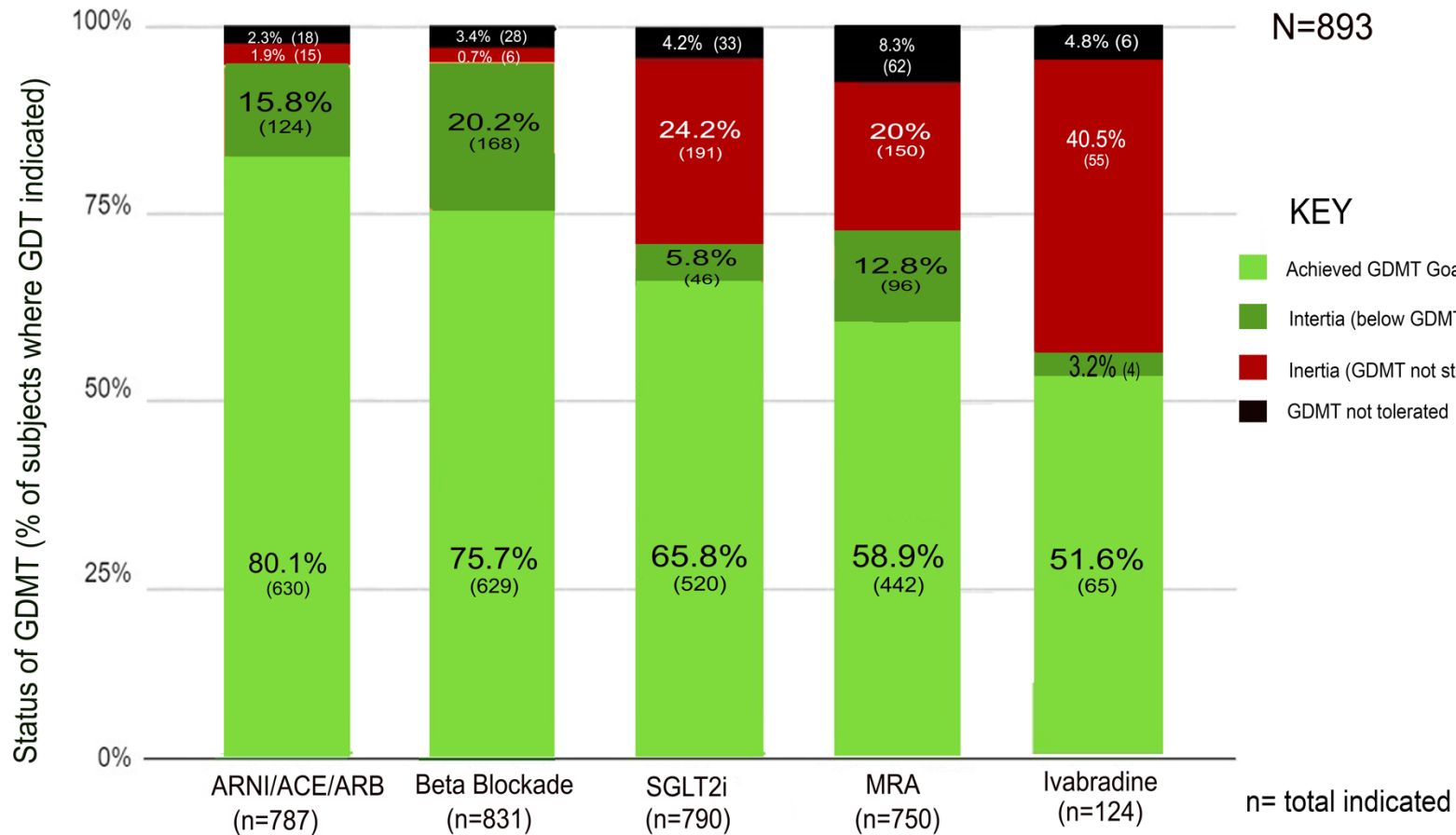
Primary Endpoints: (Intention to Treat)

- ✓ **GDMT achieved (% at target, Initiated)**
- ✓ **Failure to achieve primary endpoint**
 - **Clinical Inertia**
 - patient choice ('Patient Inertia')
 - physician's choice ('Physician Inertia')
 - **Intolerance to medication**

GDMT	GDMT Goal
ARNI	97 mg sacubitril with 103 mg Valsartan po bid
ACEi/ARB (if not on ARNI)	Perindopril 8 mg po od Ramipril 10 mg po od
Beta-blockade	Carvedilol 25 mg po bid Bisoprolol 10 mg po od
MRA	Spironolactone 25 mg po od Eplerenone 25 mg po od od
SGLT2 inhibition	Empafligozin 10 mg Dapafligozin 10 mg Canafliigozin 100 mg
Digoxin if Afib	Digoxin: NA
LDL < 1.8 if ASCVD	LDL threshold < 1.8 mg liter
Ivradabine	Ivabradine 7.5 mg po bid

95% on ACE/ARNI and Beta Blockade

75% on SGLT2i and MRI



Longitudinal Care Universal

Longitudinal care 97.2%
Lost to fup 2.8%

GDMT initiation at High Rates

Betablockade 95.9 %
ACE/ARB/ARNI 95.9 %
SGLT2i 70.6 %
MRA 71.7%
Ivabradine 54.8 %

GDMT At Target in Majority

ARNI/ACE/ARB 80.1 %
Betablockade 75.7 %
MRA 58.9 %
SGLT2i inhibitor 65.8 %
Ivabradine 51.6 %

Summary

- ✓ Heart failure remains an important public health issue
- ✓ Reduced Ejection fraction and HF should be treated early and lifelong
- ✓ Guideline Directed therapies improve outcomes for our patients
- ✓ Guideline Updates (HFrEF and HF without rEF) expand our treatment options
- ✓ Best outcomes require community care and teamwork



PANEL DISCUSSION | Q&A

SUPPORT AVAILABLE 24/7



**Have a patient question?
Reach out to our
Corcare Cardiologist directly**

416-COR-CARE



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**THANK YOU FOR
JOINING US!**