Congresso Interassociativo SID - AMD Emilia Romagna
Prevenzione e cura: un ponte fra presente e futuro
12 Ottobre 2024 – Bologna (BO)
NH BOLOGNA DE LA GARE

La sindrome cardio-nefro-metabolica

Stefano Urbinati
Direttore Dipartimento della Rete Medico-Specialistica
Ospedaliera e Territoriale - Azienda USL di Bologna

Il /la dr./sa Stefano Urbinati dichiara di NON aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche

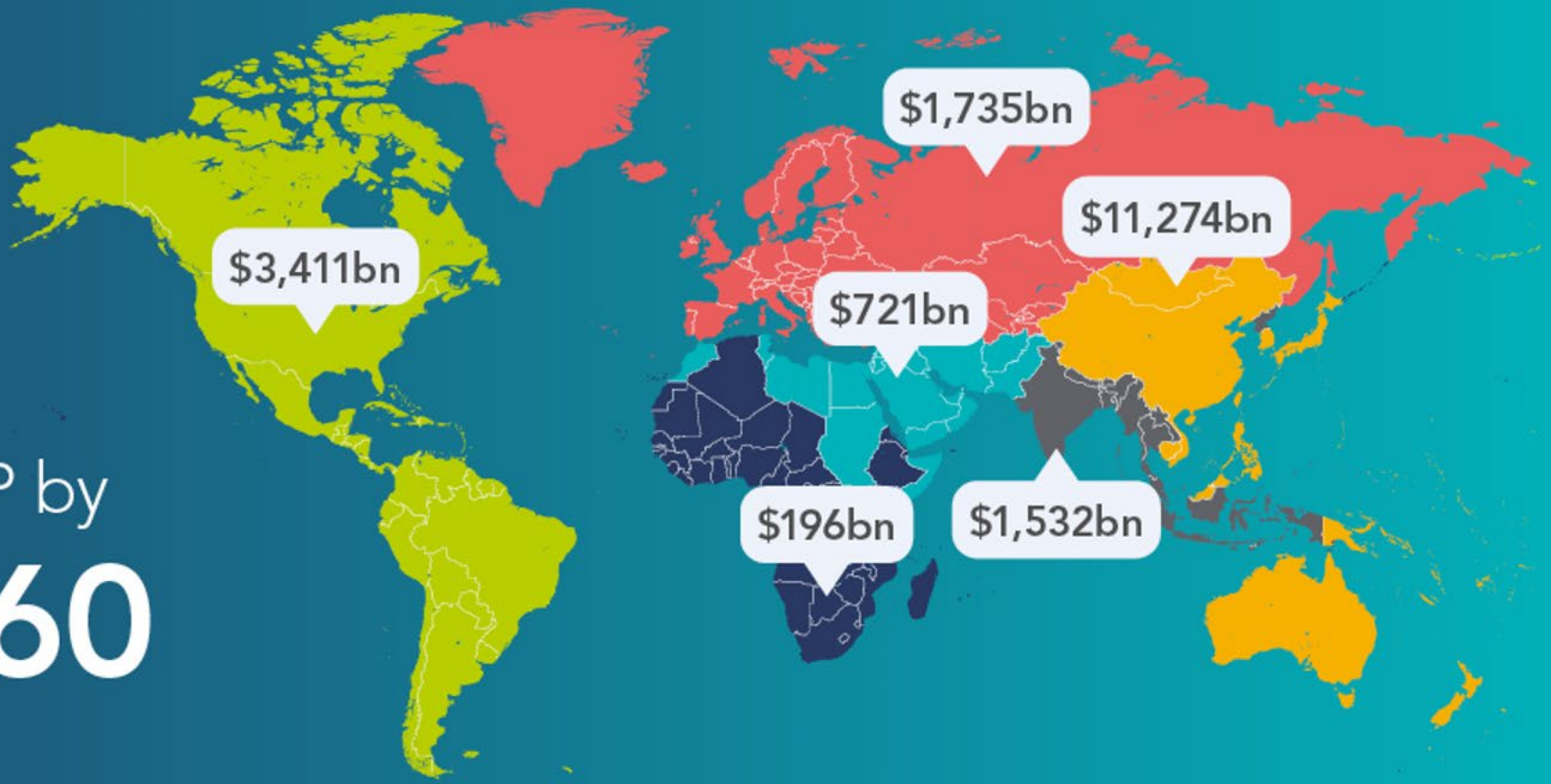
Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

THE ECONOMIC IMPACT OF OVERWEIGHT & OBESITY IN 2020 AND 2060

Overweight and obesity prevalence is set to cost the global economy

3.3% of GDP by

2060



WORLD OBESITY

RTI INTERNATION

Obesity contributes to up to half of new diabetes cases annually in the United States

Journal of the American Heart Association Report

The New York Times

Diabetes Often Leads to Heart and Kidney Disease, Too

The three illnesses are closely linked — and increasingly common. Here's what to know about the shared risk factors for these conditions.

May 20, 2024

Circulation

AHA PRESIDENTIAL ADVISORY

Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association

Chiadi E. Ndumele, MD, PhD, FAHA, Chair; Janani Rangaswami, MD, FAHA, Vice Chair; Sheryl L. Chow, PharmD, FAHA, Vice Chair; Ian J. Neeland, MD, FAHA; Katherine R. Tuttle, MD; Sadiya S. Khan, MD, MSc, FAHA; Josef Coresh, MD, PhD; Roy O. Mathew, MD; Carissa M. Baker-Smith, MD, MPH, FAHA; Mercedes R. Carnethon, PhD, FAHA; Jean-Pierre Despres, PhD, FAHA; Jennifer E. Ho, MD, FAHA; Joshua J. Joseph, MD, MPH, FAHA; Walter N. Kernan, MD; Amit Khera, MD, MSc, FAHA; Mikhail N. Kosiborod, MD; Carolyn L. Lekavich, PhD; Eldrin F. Lewis, MD, MPH, FAHA; Kevin B. Lo, MD; Bige Ozkan, MD, ScM; Latha P. Palaniappan, MD, MS, FAHA; Sonali S. Patel, MD, PhD; Michael J. Pencina, PhD; Tiffany M. Powell-Wiley, MD, MPH, FAHA; Laurence S. Sperling, MD, FAHA; Salim S. Virani, MD, PhD, FAHA; Jackson T. Wright, MD, PhD; Radhika Rajgopal Singh, PhD, FAHA; Mitchell S.V. Elkind, MD, MS, FAHA; on behalf of the American Heart Association

Ndumele C et al. AHA Advisory. Circulation 2023, november 14

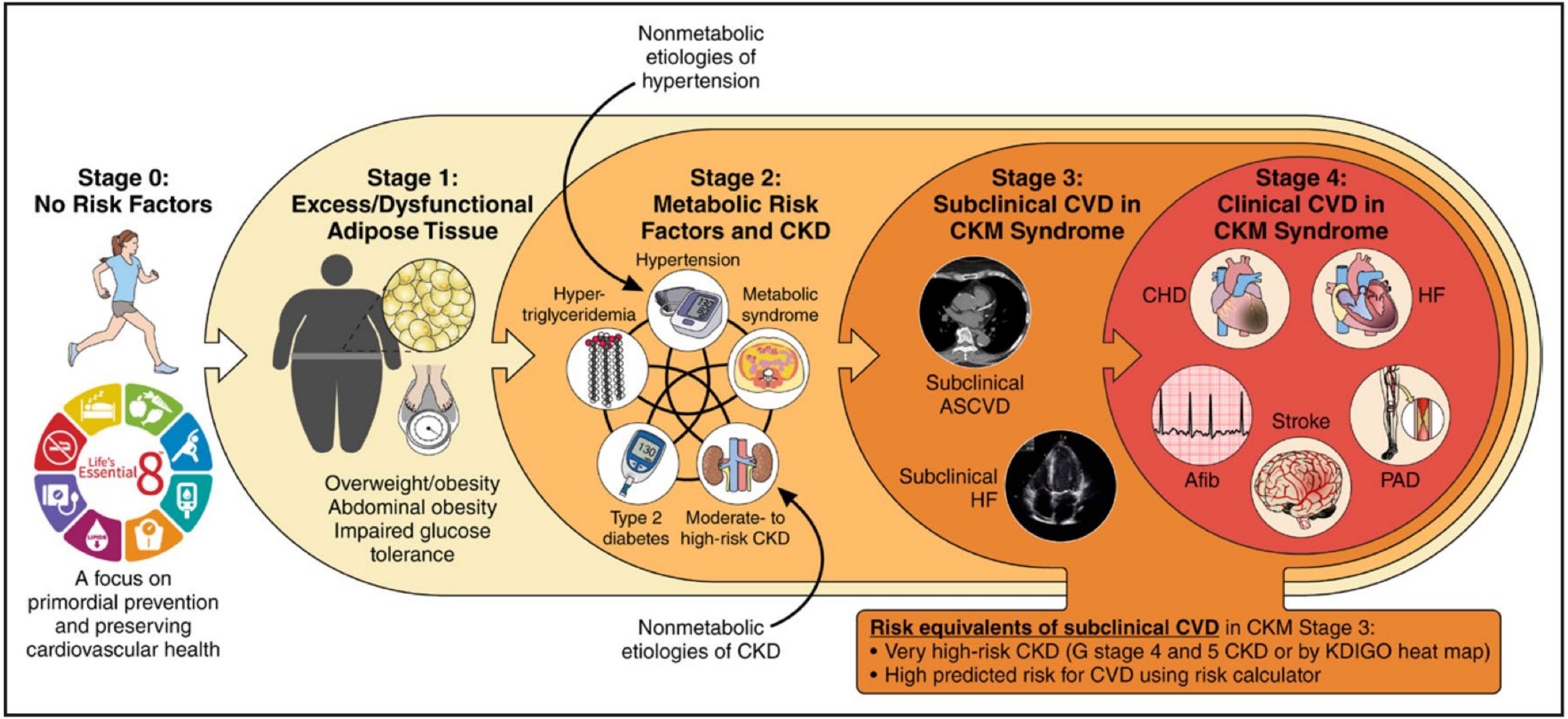
Table 1. Definitions of CKM Syndrome Stages

CKM syndrome stages	Definition
Stage 0: No CKM risk factors	Individuals with normal BMI and waist circumference, normoglycemia, normotension, a normal lipid profile, and no evidence of CKD or subclinical or clinical CVD
Stage 1: Excess or dysfunctional adiposity	Individuals with overweight/obesity, abdominal obesity, or dysfunctional adipose tissue, without the presence of other metabolic risk factors or CKD BMI ≥25 kg/m^2 (or ≥23 kg/m^2 if Asian ancestry), Waist circumference ≥88/102 cm in women/men (or if Asian ancestry ≥80/90 cm in women/men), or Fasting blood glucose ≥100–124 mg/dL or HbA1c between 5.7% and 6.4%*
Stage 2: Metabolic risk factors and CKD	Individuals with metabolic risk factors (hypertriglyceridemia [≥135 mg/dL], hypertension, MetS,† diabetes), or CKD

Ndumele C et al. AHA Advisory. Circulation 2023, november 14

Stage 3: Subclinical CVD in CKM	Subclinical ASCVD or subclinical HF among individuals with excess/dysfunctional adiposity, other metabolic risk factors, or CKD Subclinical ASCVD to be principally diagnosed by coronary artery calcification (subclinical atherosclerosis by coronary catheterization/CT angiography also meets criteria) Subclinical HF diagnosed by elevated cardiac biomarkers (NT-proBNP ≥125 pg/mL, hs-troponin T ≥14 ng/L for women and ≥22 ng/L for men, hs-troponin I ≥10 ng/L for women and ≥12 ng/L for men) or by echocardiographic parameters, with a combination of the 2 indicating highest HF risk. Risk equivalents of subclinical CVD Very high-risk CKD (stage G4 or G5 CKD or very high risk per KDIGO classification) High predicted 10-y CVD risk
Stage 4: Clinical CVD in CKM	Clinical CVD (coronary heart disease, HF, stroke, peripheral artery disease, atrial fibrillation) among individuals with excess/dysfunctional adiposity, other CKM risk factors, or CKD Stage 4a: no kidney failure Stage 4b: kidney failure present

Ndumele C et al. AHA Advisory. Circulation 2023, november 14

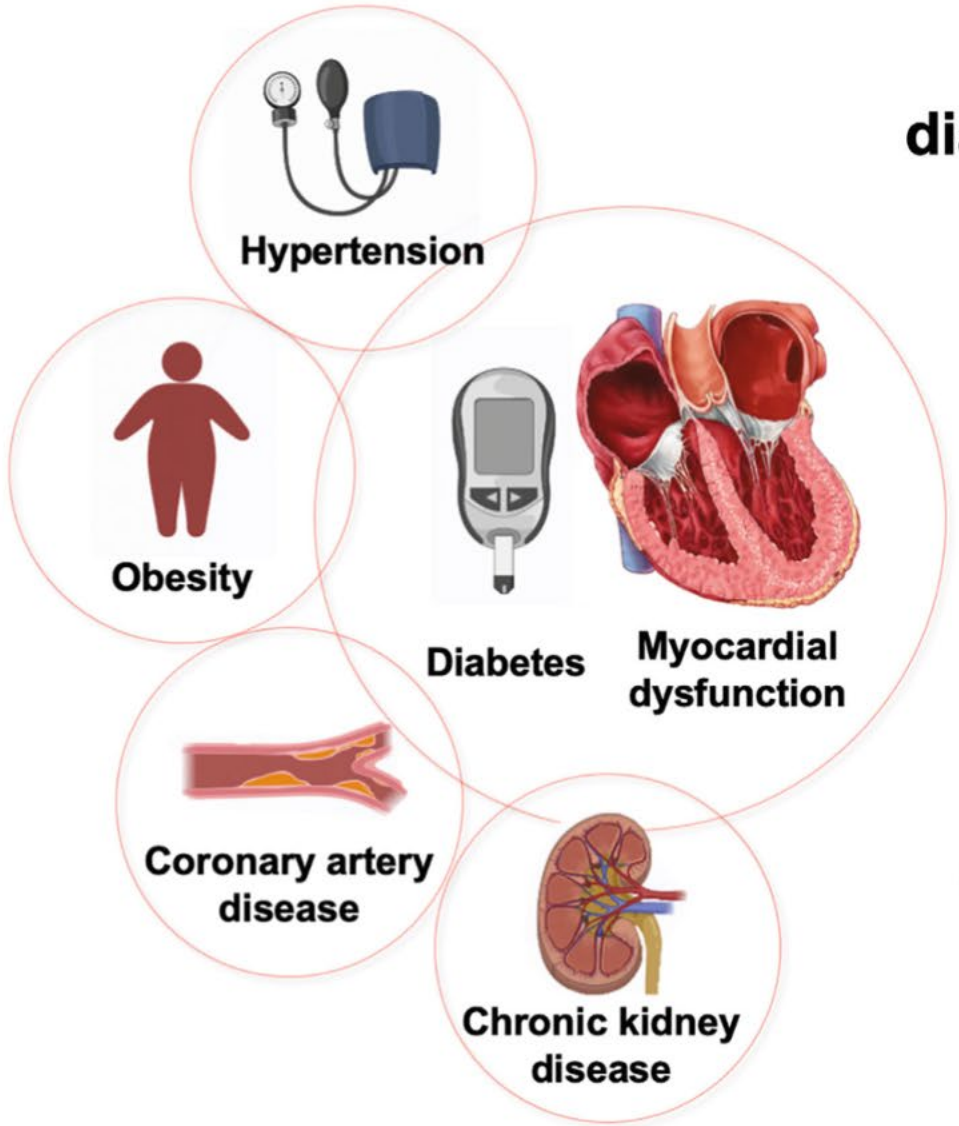


Ndumele C et al. AHA Advisory. Circulation 2023, november 14

Key issues

1. Early life prevention
2. Risk factor screening
3. Interdisciplinary care models
4. Lifestyle modification support
5. Emerging therapies
6. Systematic assessment of social determinants

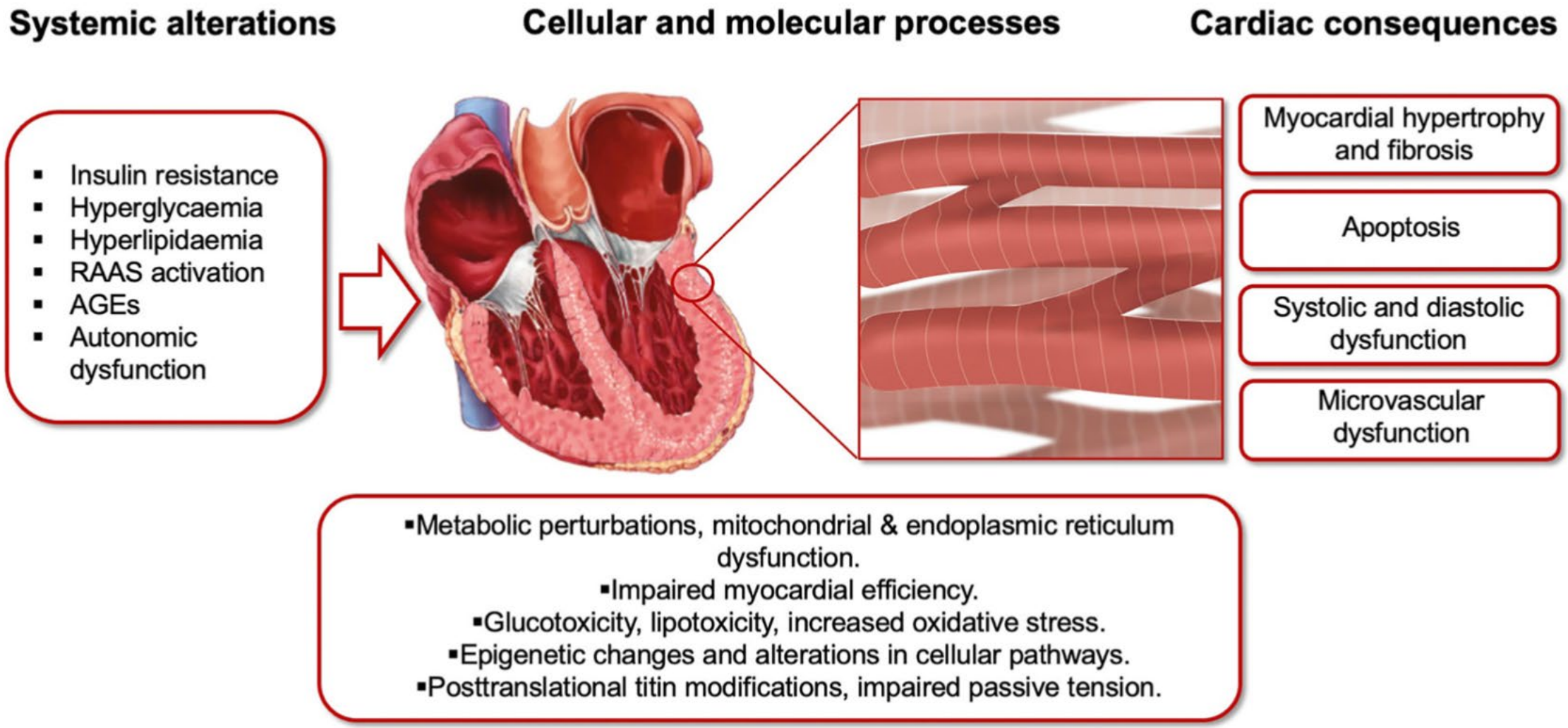
Ndumele C et al. AHA Advisory. Circulation 2023, november 14



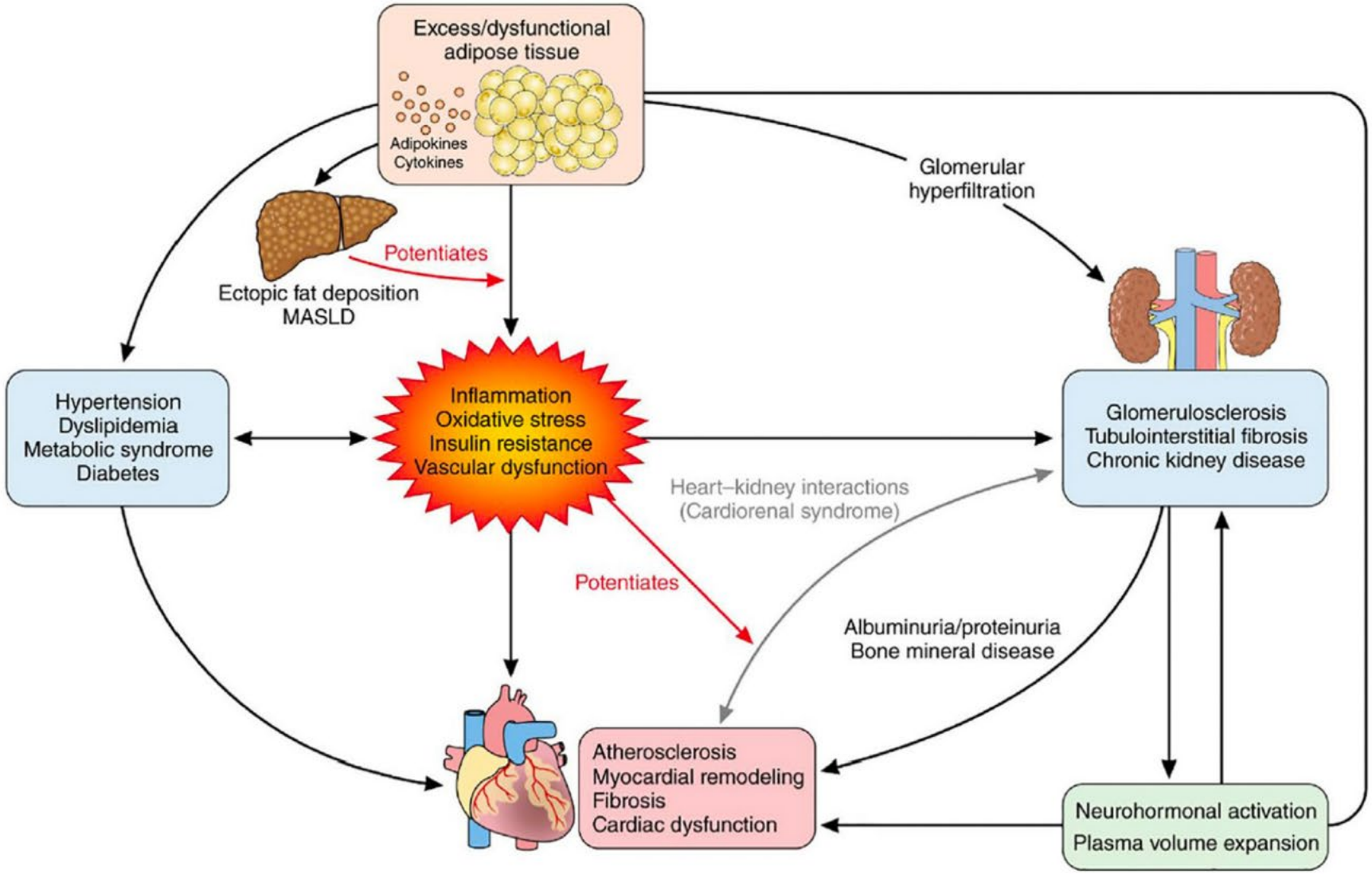
New proposed definition of diabetic myocardial disorder by the HFA of the ESC and the ESC WG on Myocardial & Pericardial Diseases

Diabetic myocardial disorder is defined as systolic and/or diastolic myocardial dysfunction in the presence of diabetes. Diabetes is rarely exclusively responsible for myocardial dysfunction, but usually acts in association with obesity, arterial hypertension, chronic kidney disease and/or coronary artery disease, causing additive myocardial impairment.

Seferovic P et al. Eur J Heart Fail 2024; 26: 1893-1903



Seferovic P et al. Eur J Heart Fail 2024; 26: 1893-1903



Massy ZA, Drueke TB. Kidney Intern Rep 2024, september

THE PRESENT AND FUTURE

JACC REVIEW TOPIC OF THE WEEK

Cardiovascular Outcomes in Patients With Diabetes and Kidney Disease

JACC Review Topic of the Week

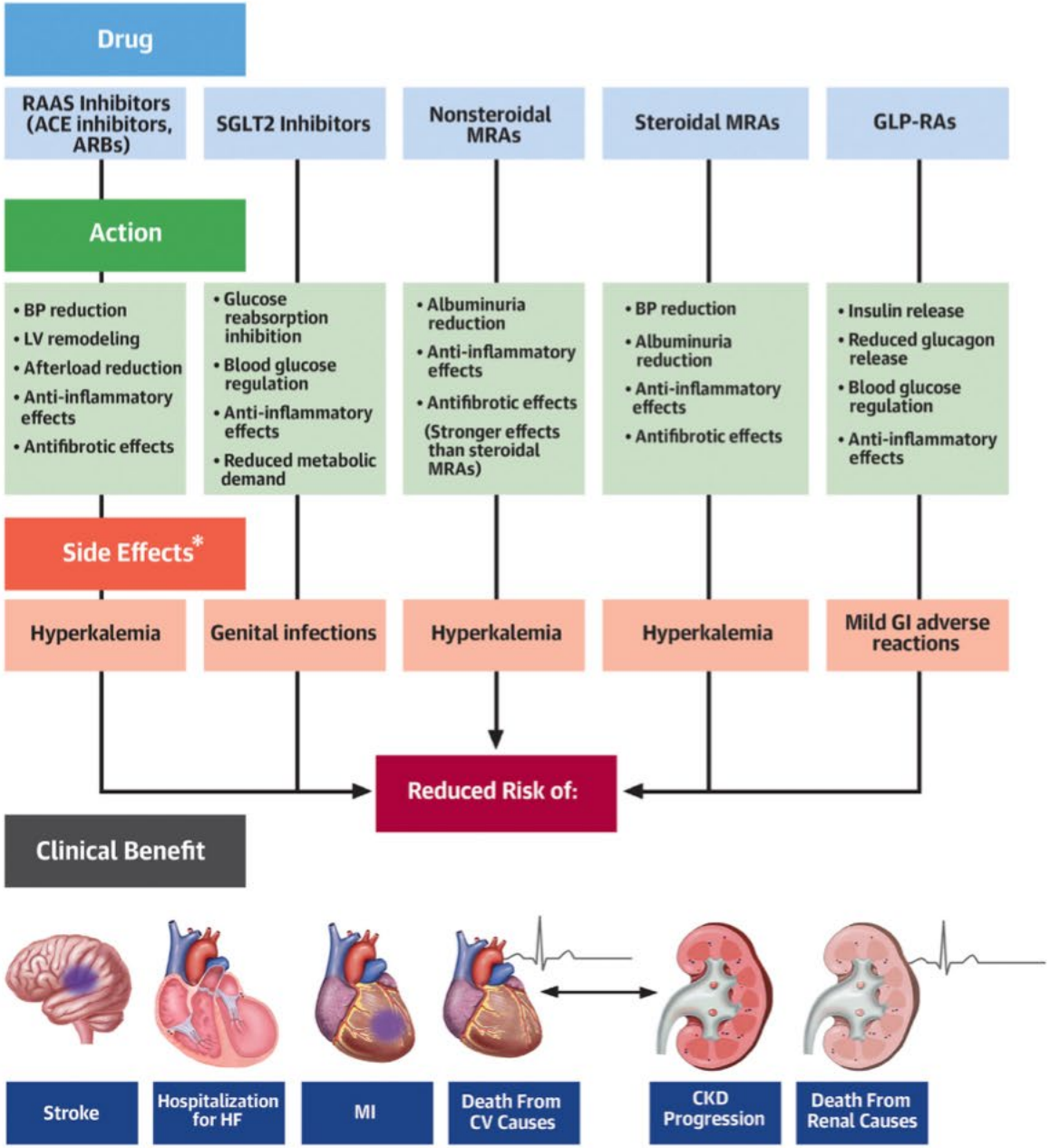
Javier Morales, MD,[a] Yehuda Handelsman, MD[b]

JACC 2023, july 11

TABLE 1 Comparative Efficacy of Cardiovascular Therapies in Patients With CKD of Diabetes vs Placebo

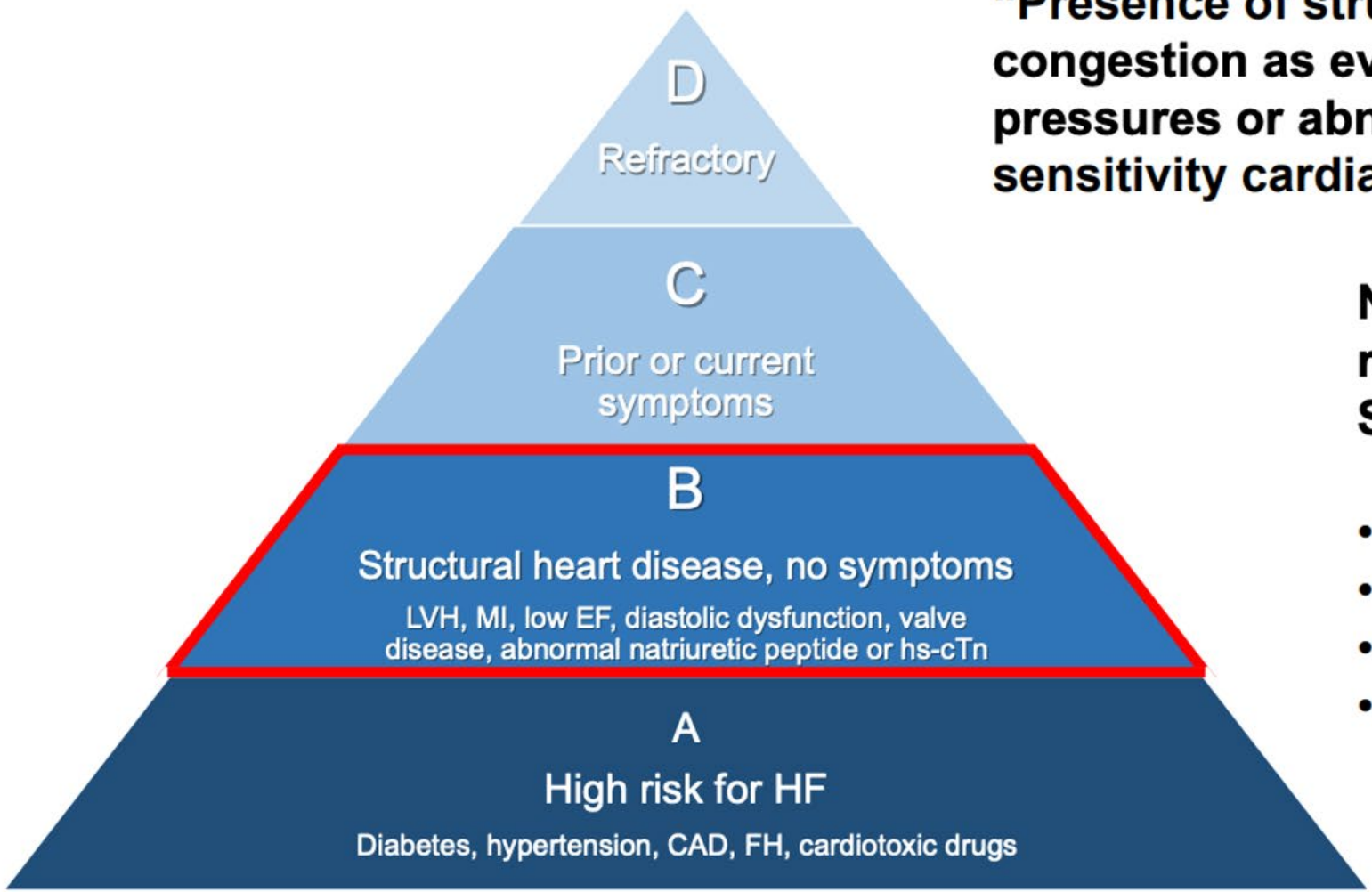
Drug Class	First Author, Study Type	No. of Trials	N	Population	Efficacy on MACE (95% CI)
ACE inhibitors	Zhang et al,[17] meta-analysis	30	34,538[a]	CKD ± T2D	OR: 0.73 (0.64-0.84)
				CKD and T2D	OR: 0.89 (0.74-1.07)
ARBs	Zhang et al,[17] meta-analysis	30	34,538[a]	CKD ± T2D	OR: 0.83 (0.70-0.98)
				CKD and T2D	OR: 0.87 (0.75-1.01)
SGLT2 inhibitors	Kaze et al,[24] meta-analysis	8	26,106	CKD and T2D	HR: 0.83 (0.75-0.93)
GLP-1 RAs	Sattar et al,[35] meta-analysis	8	60,080	T2D ± CKD	HR: 0.86 (0.80-0.93)
			12,060	T2D and CKD	HR: 0.88 (0.77-1.01)
Nonsteroidal MRAs	Agarwal et al,[47] FIDELITY pooled analysis	2	13,026	CKD and T2D	HR: 0.86 (0.78-0.95)

Morales S, Handelsman Y. JACC 2023, july 11



Morales S, Handelsman Y.
JACC 2023, july 11

Stages of heart failure: Stage B (pre-HF)



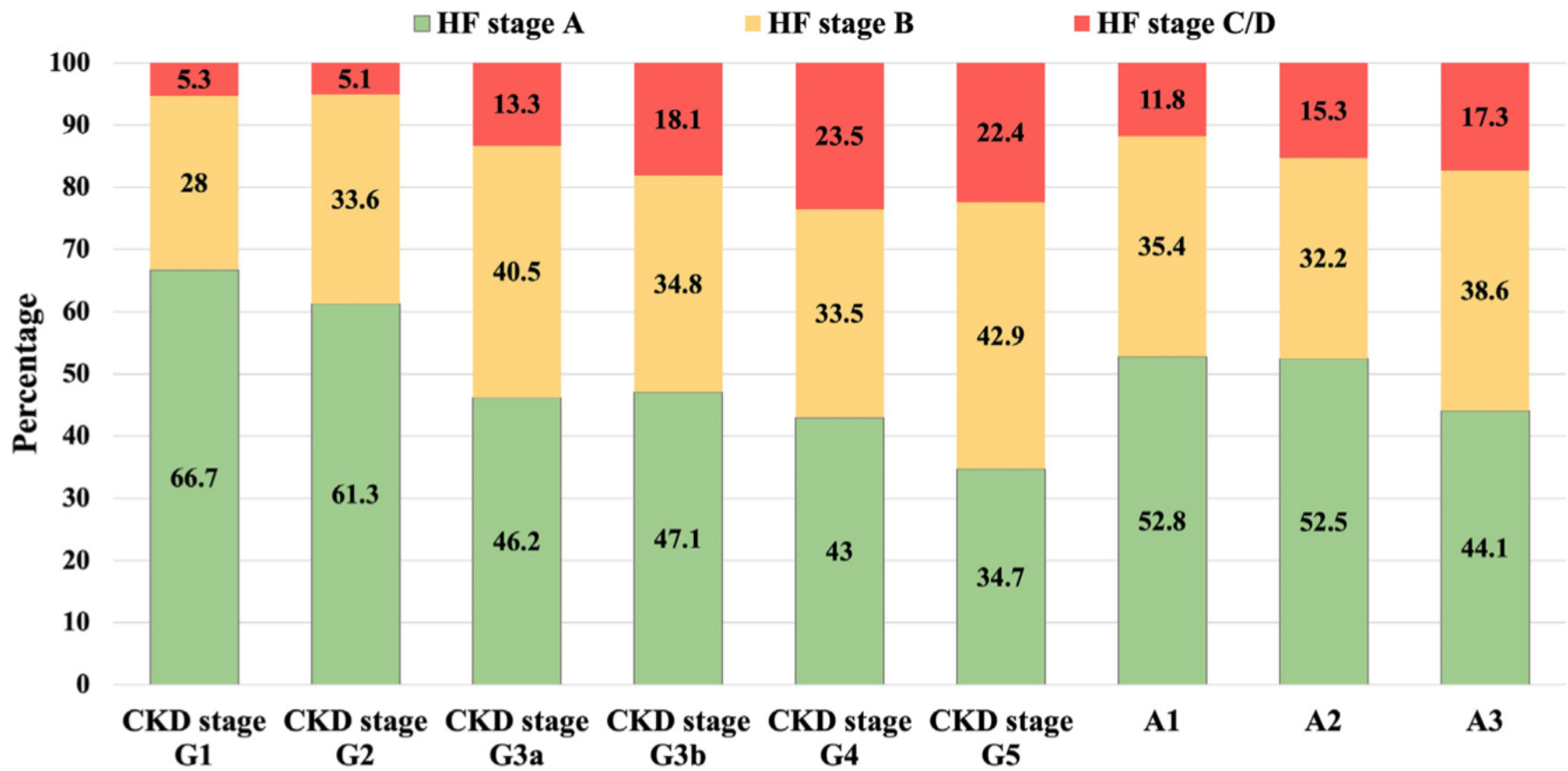
"Presence of structural heart disease and/or congestion as evidenced by elevated filling pressures or abnormal natriuretic peptide or high sensitivity cardiac troponin"

Numerous therapies exist to reduce risk of progression from Stage B→Stage C

- **RAAS inhibitors**
- **Beta blockers**
- **SGLT2i**
- **GLP-1RA**

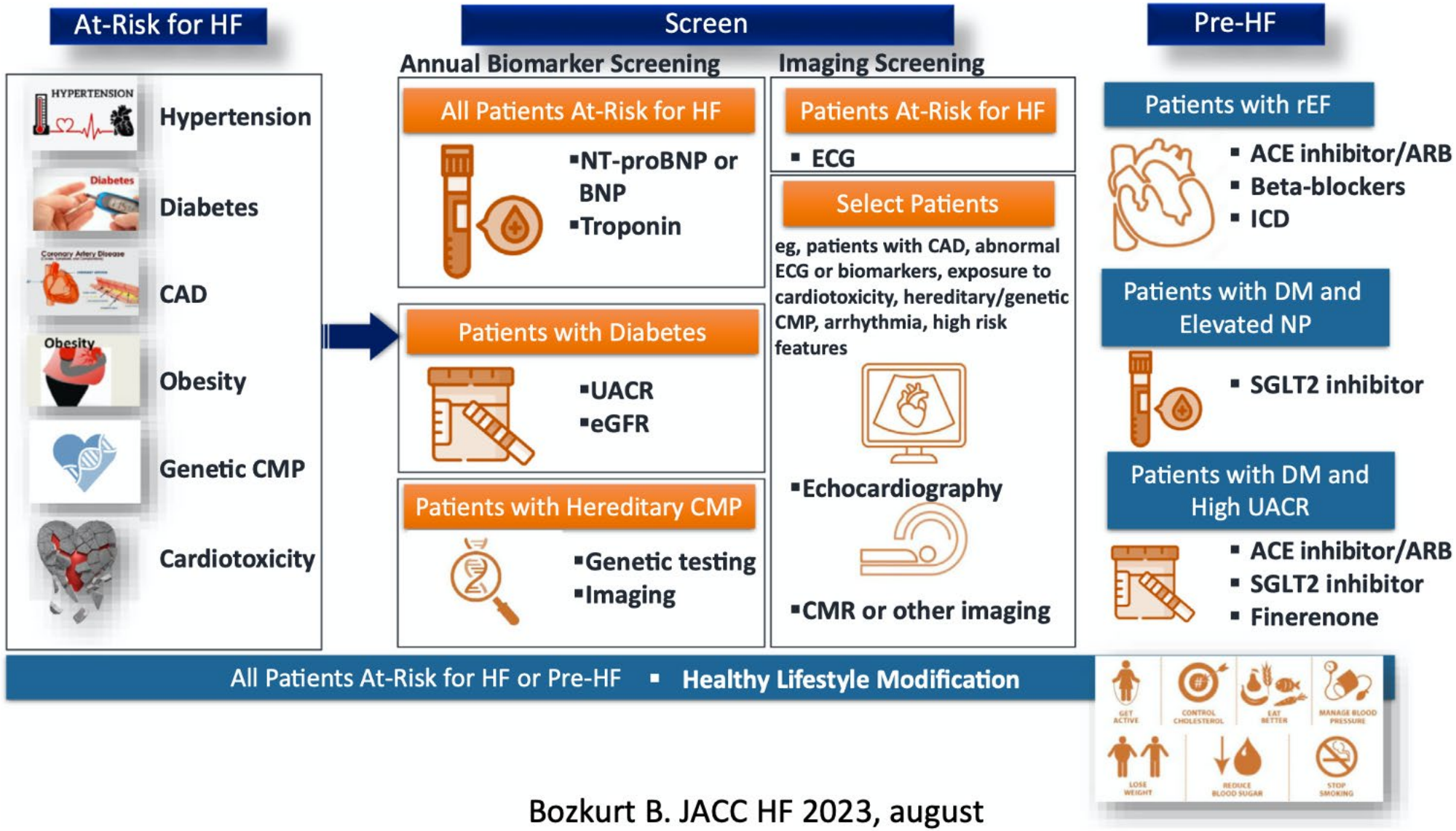
MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

FIGURE 1 Distribution of HF Stages According to Kidney Disease Improving Global Outcomes CKD Stages and Albuminuria Categories

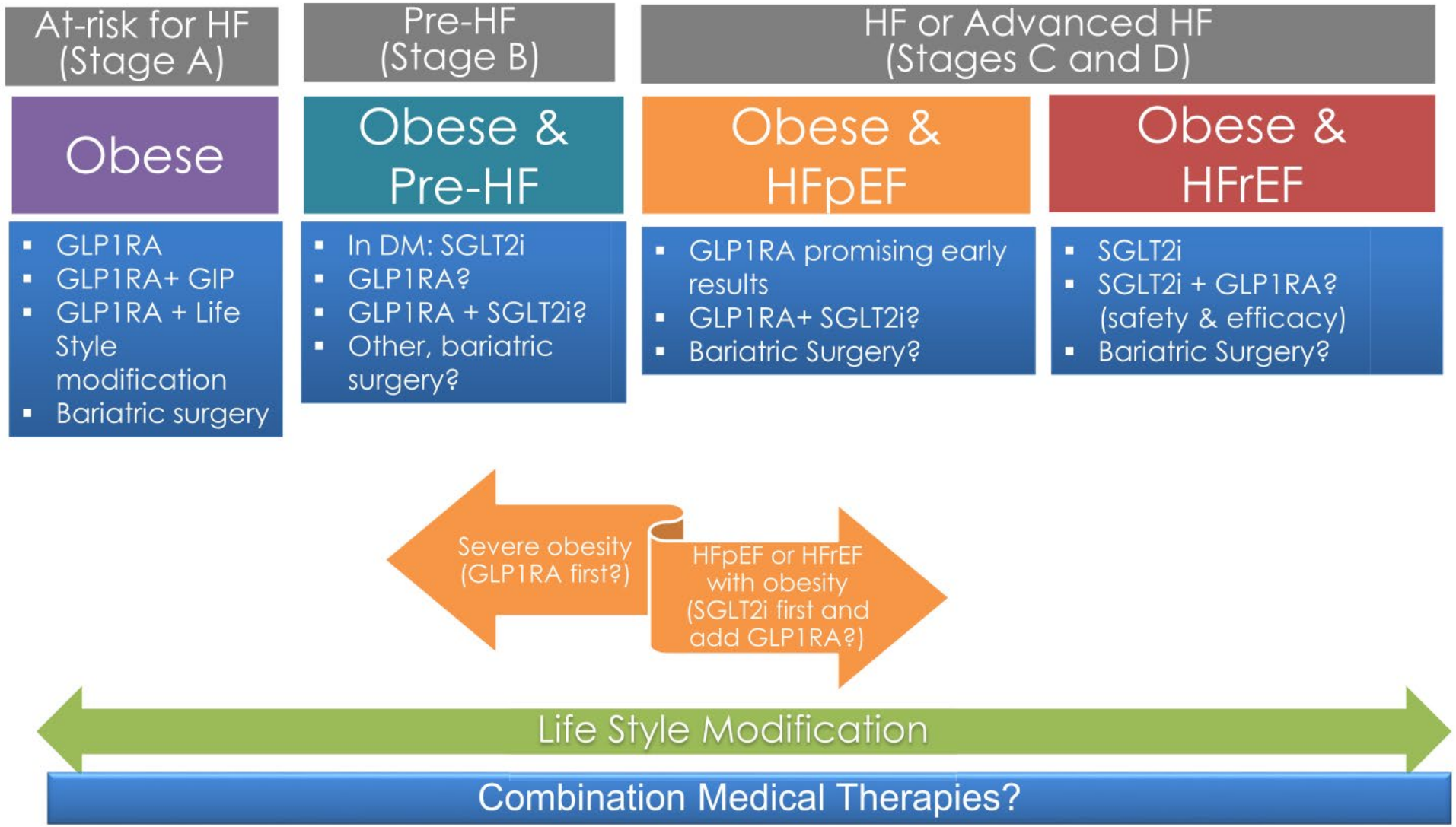


Lauridsen A et al. JACC HF 2024, august

FIGURE 1 **Strategies for Screening for and Treatment of Pre-HF**

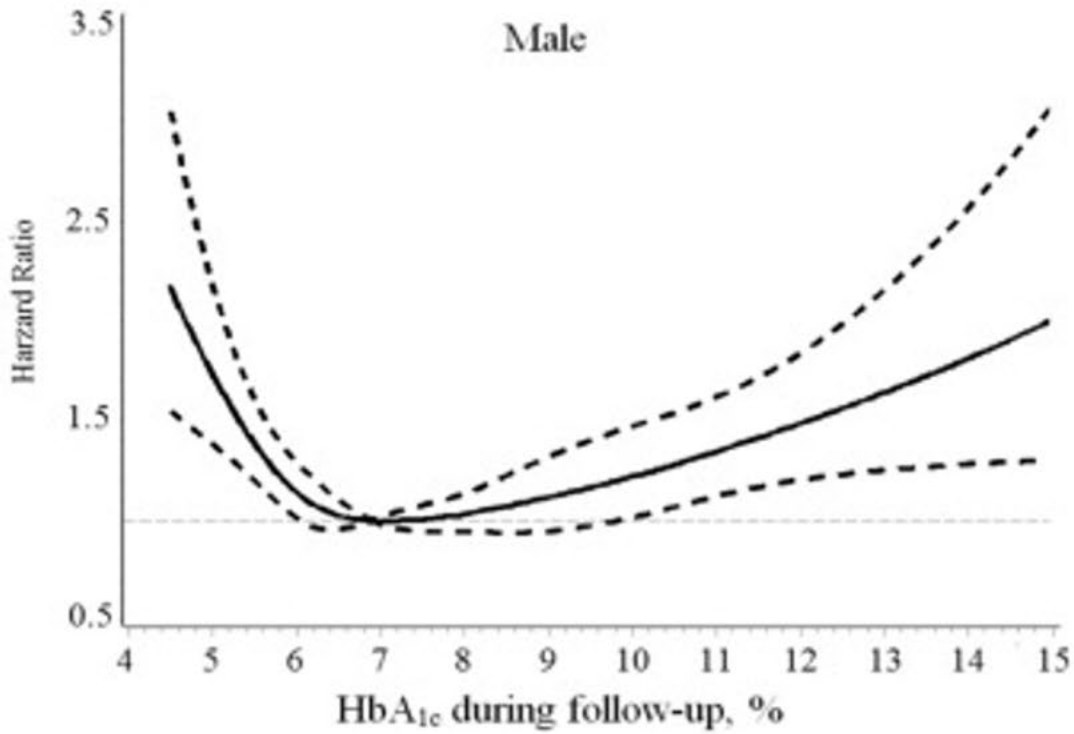


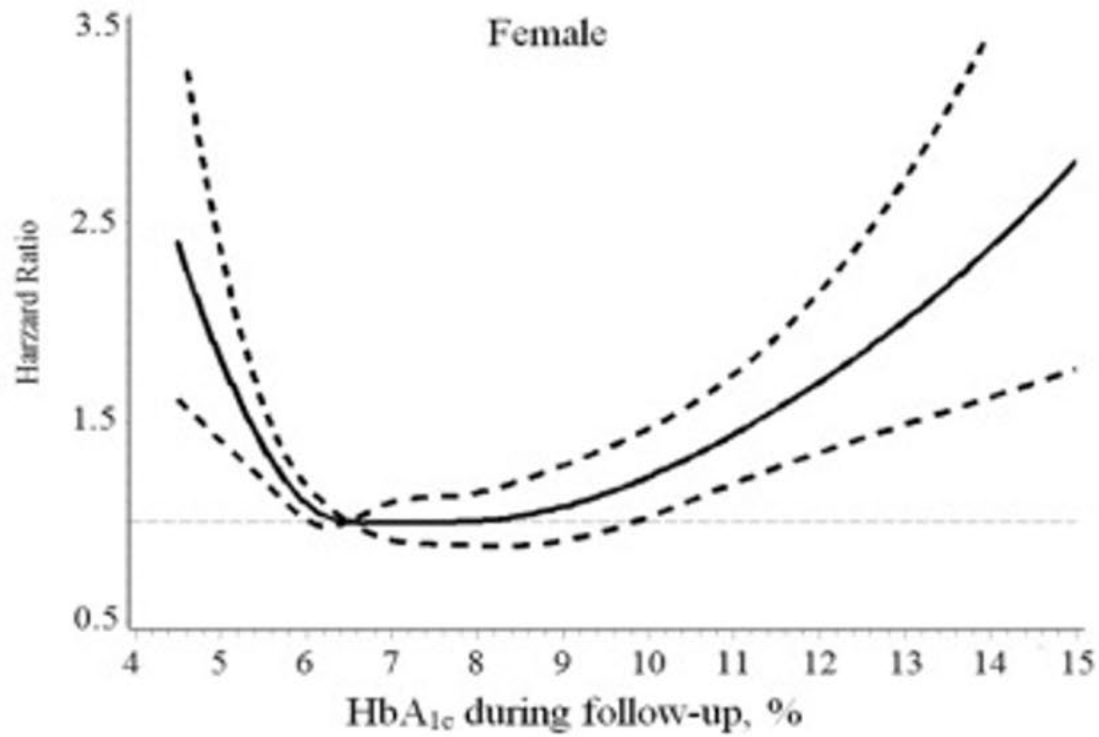
Bozkurt B. JACC HF 2023, august



Bozkurt B. JACC HF 2024, july

When HbA1c is predictive of cardiovascular events





Lind M et al. Diabetes Care 2021; 44: 2231-7

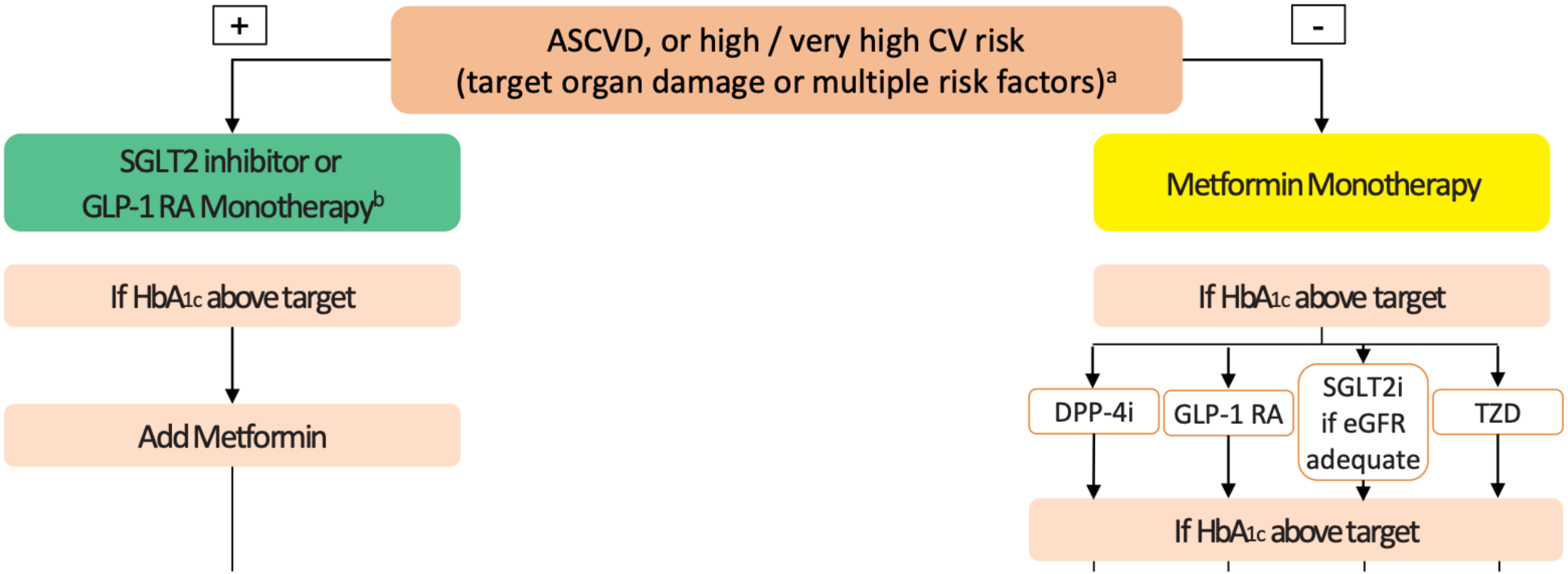
	ACCORD	ADVANCE	VADT
Major Endpoints	CV death, Non-fatal MI/Stroke	CV death, Non-fatal MI/Stroke, macrovacs event	CV death, Non-fatal MI/Stroke, CHF macrovacs event
Study	RCT	RCT	RCT
design	Glucose Intensive vs Standard Arm 2x2 BP control +/-fenofibrate v placebo	Glucose Intensive vs Standard Arm 2x2 Perindopril +indamide v placebo	Glucose Intensive vs Standard Arm 2x1 All received BP and Lipid Rx

	ACCORD	ADVANCE	VADT
# Participants	10,251	11,140	1,791
population	North America	Europe /Asia	US
Male	62%	58%	97%
Age group mean age	40-79 62.2	>55 yrs 66	>40yrs 60.5
Non-Hispanic White Ethnic Representation	27% Hispanic, African Am	37% Asian	38% Hispanic, African Am, Native Am

	ACCORD*	ADVANCE	VADT
A1C (%) (Intensive vs. Std)	6.4 vs.7.5 †	6.4 vs. 7.0 †	6.9 vs. 8.4 †
Nonfatal MI (%) (Intensive vs. Std)	3.6 vs 4.6% †	2.7 vs.2.8	6.3 vs. 6.1
CV Death (%) (Intensive vs. Std)	2.6 vs. 1.8 † (1.35 Hazard Ratio)	4.5 vs. 5.2	2.1 vs.1.7
Microvascular	-	nephropathy ↓ 21% retinopathy ↓ 5% NS	-
Take home	↓ risk MIs, but ↑ risk death in intensive arm	Glucose control has no impact on CV events, but ↓ Microvascular risk	Glucose control has no impact on CV events

Treatment algorithm in patients with T2DM and ASCVD or high/very high CV risk - drug naïve (1)

ESC European Society of Cardiology



ESC Guidelines on Diabetes, pre-diabetes and cardiovascular diseases in collaboration with EASD (European Heart Journal 2019 - doi/10.1093/eurheartj/ehz486)

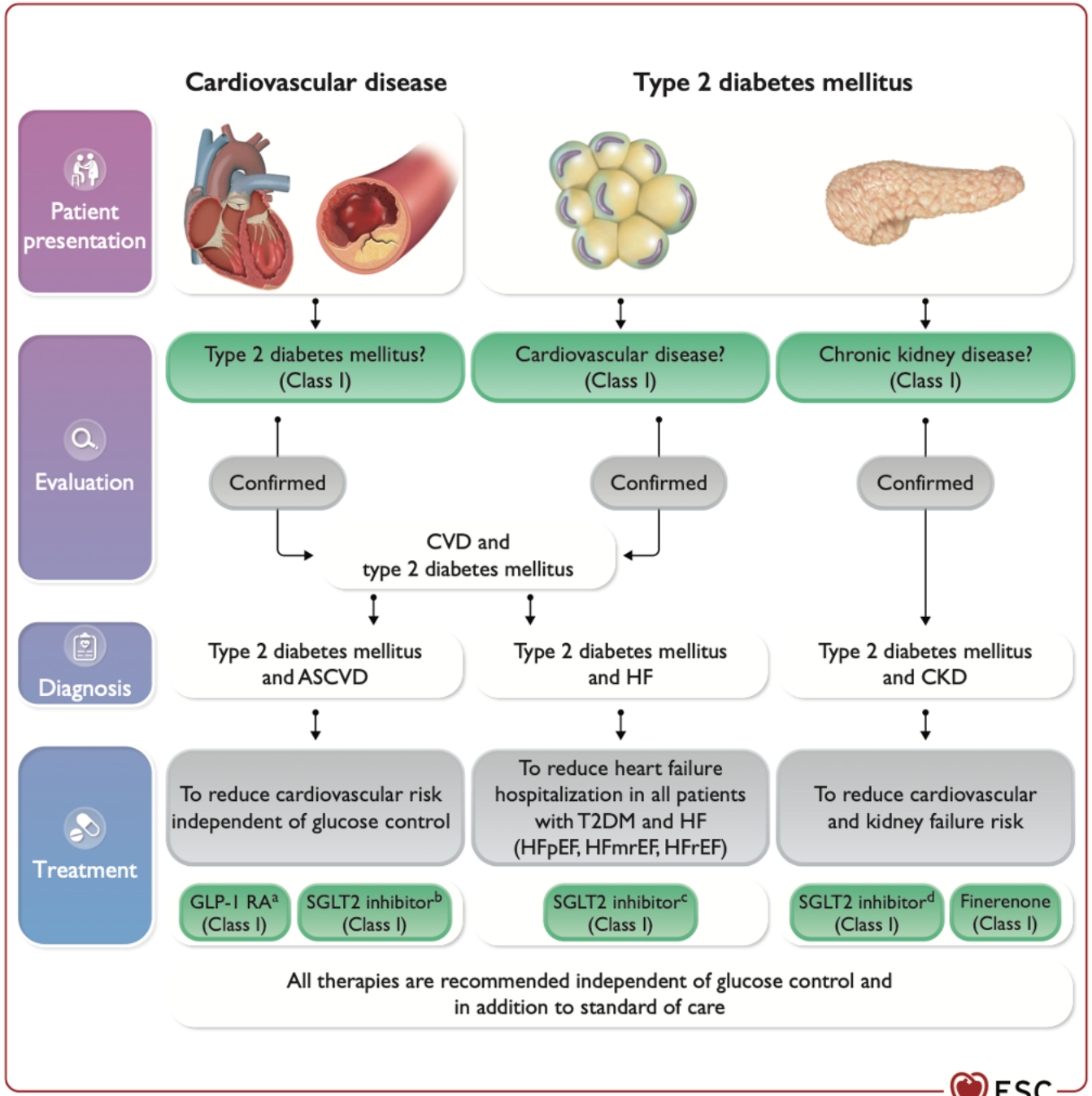
ESC European Society of Cardiology
European Heart Journal (2023) **44**, 4043–4140
https://doi.org/10.1093/eurheartj/ehad192

ESC GUIDELINES

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes

Developed by the task force on the management of cardiovascular disease in patients with diabetes of the European Society of Cardiology (ESC)

Authors/Task Force Members: Nikolaus Marx *†, (Chairperson) (Germany), Massimo Federici *†, (Chairperson) (Italy), Katharina Schütt ‡, (Task Force Co-ordinator) (Germany), Dirk Müller-Wieland ‡, (Task Force Co-ordinator) (Germany), Ramzi A. Ajjan (United Kingdom), Manuel J. Antunes (Portugal), Ruxandra M. Christodorescu (Romania), Carolyn Crawford (United Kingdom), Emanuele Di Angelantonio (United Kingdom/Italy), Björn Eliasson (Sweden), Christine Espinola-Klein (Germany), Laurent Fauchier (France), Martin Halle (Germany), William G. Herrington (United Kingdom), Alexandra Kautzky-Willer (Austria), Ekaterini Lambrinou (Cyprus), Maciej Lesiak (Poland), Maddalena Lettino (Italy), Darren K. McGuire (United States of America), Wilfried Mullens (Belgium), Bianca Rocca (Italy), Naveed Sattar (United Kingdom), and ESC Scientific Document Group



GLP-1A in patients with diabetes mellitus

	Main analysis with all 8 CVOTs (HR; I^2)	Sensitivity analyses minus ELIXA (HR; I^2)
MACE	0.86 (0.80 to 0.93) 45%	0.85 (0.80 to 0.90) 15%
CV death	0.87 (0.80 to 0.94) 13%	0.85 (0.78 to 0.93) 12%
MI	0.90 (0.83 to 0.98) 27%	0.88 (0.81 to 0.96) 16%
All-cause mortality	0.88 (0.82 to 0.94) 10%	0.87 (0.81 to 0.94) 17%
Incident HHF	0.89 (0.82 to 0.98) 3%	0.88 (0.79 to 0.98) 12%
Kidney composite (+ albuminuria)	0.79 (0.73 to 0.87) 48%	0.78 (0.71 to 0.87) 57%
Worsening kidney function (eGFR)	0.86 (0.72 to 1.02) 43%	0.82 (0.69 to 0.98) 40%

Marx N, Sattar N et al. Circulation 2022; 146: 1882-84

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 14, 2023 VOL. 389 NO. 24

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

A. Michael Lincoff, M.D., Kirstine Brown-Frandsen, M.D., Helen M. Colhoun, M.D., John Deanfield, M.D., Scott S. Emerson, M.D., Ph.D., Sille Esbjerg, M.Sc., Søren Hardt-Lindberg, M.D., Ph.D., G. Kees Hovingh, M.D., Ph.D., Steven E. Kahn, M.B., Ch.B., Robert F. Kushner, M.D., Ildiko Lingvay, M.D., M.P.H., Tugce K. Oral, M.D., Marie M. Michelsen, M.D., Ph.D., Jorge Plutzky, M.D., Christoffer W. Tornøe, Ph.D., and Donna H. Ryan, M.D., for the SELECT Trial Investigators*

METHODS

In a multicenter, double-blind, randomized, placebo-controlled, event-driven superiority trial, we enrolled patients 45 years of age or older who had preexisting cardiovascular disease and a body-mass index (the weight in kilograms divided by the square of the height in meters) of 27 or greater but no history of diabetes. Patients were randomly assigned in a 1:1 ratio to receive once-weekly subcutaneous semaglutide at a dose of 2.4 mg or placebo. The primary cardiovascular end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke in a time-to-first-event analysis. Safety was also assessed.

SELECT trial, NEJM 2023

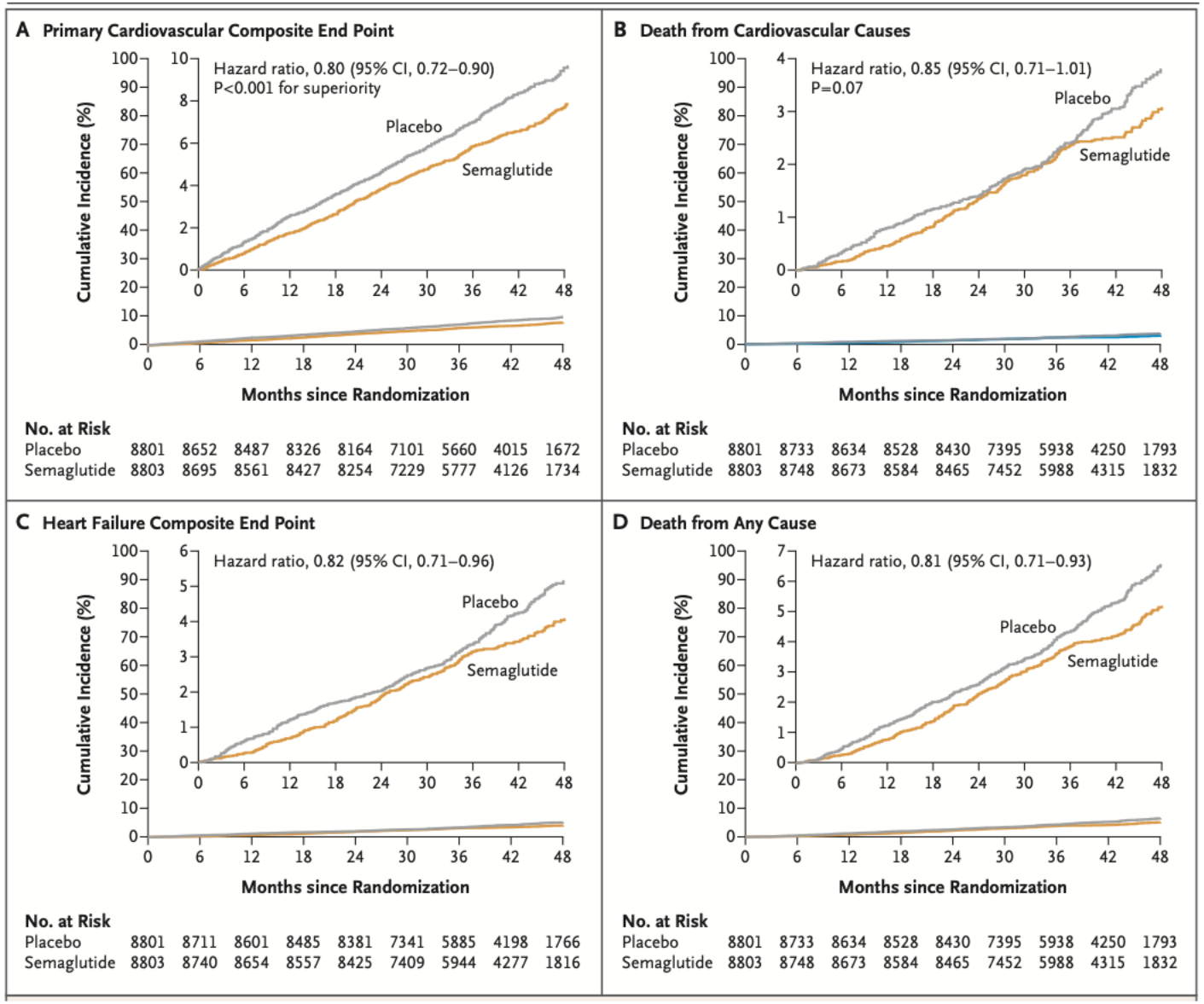
Table 1. Baseline Characteristics of the Patients.*

Characteristic	Semaglutide (N=8803)	Placebo (N=8801)
Age — yr	61.6±8.9	61.6±8.8
Male sex — no. (%)	6355 (72.2)	6377 (72.5)
Race or ethnic group — no. (%)†		
White	7387 (83.9)	7404 (84.1)
Asian	720 (8.2)	727 (8.3)
Black	348 (4.0)	323 (3.7)
Other	253 (2.9)	273 (3.1)
Hispanic or Latino	914 (10.4)	908 (10.3)
Body weight — kg	96.5±17.5	96.8±17.8
BMI‡	33.3±5.0	33.4±5.0
Waist circumference — cm	111.3±13.1	111.4±13.1
Glycated hemoglobin level — %	5.78±0.34	5.78±0.33
Distribution — no. (%)		
<5.7%	2925 (33.2)	2980 (33.9)
≥5.7%	5877 (66.8)	5819 (66.1)
Median high-sensitivity CRP level (IQR) — mg/liter	1.87 (0.89–4.18)	1.80 (0.86–4.06)

SELECT trial, NEJM 2023

Cardiovascular inclusion criteria — no. (%)		
Myocardial infarction only	5962 (67.7)	5944 (67.5)
Stroke only	1578 (17.9)	1556 (17.7)
Peripheral arterial disease only	376 (4.3)	401 (4.6)
Two or more inclusion criteria	718 (8.2)	719 (8.2)
Other§	169 (1.9)	181 (2.1)
eGFR — ml/min/1.73 m^2	82.4±17.5	82.5±17.3
Median lipid level (IQR) — mg/dl		
Total cholesterol	153 (131–182)	153 (131–183)
HDL cholesterol	44 (37–52)	44 (37–52)
LDL cholesterol	78 (61–102)	78 (61–102)
Triglycerides	134 (99–188)	135 (100–190)
Systolic blood pressure — mm Hg	131.0±15.6	130.9±15.3
Diastolic blood pressure — mm Hg	79.4±10.0	79.2±9.9

SELECT trial, NEJM 2023



SELECT trial, NEJM 2023

Table 2. Primary and Secondary Time-to-First-Event Efficacy End Points.*

End Point	Semaglutide (N=8803)	Placebo (N=8801)	Hazard Ratio (95% CI)	P Value
	number of patients (percent)			
Primary cardiovascular composite end point†	569 (6.5)	701 (8.0)	0.80 (0.72 to 0.90)	<0.001
Confirmatory secondary end points‡				
Death from cardiovascular causes	223 (2.5)	262 (3.0)	0.85 (0.71 to 1.01)	0.07
Heart failure composite end point§	300 (3.4)	361 (4.1)	0.82 (0.71 to 0.96)	NA
Death from any cause	375 (4.3)	458 (5.2)	0.81 (0.71 to 0.93)	NA
Supportive secondary end points¶				
Cardiovascular expanded composite end point‖	873 (9.9)	1074 (12.2)	0.80 (0.73 to 0.87)	NA
Cardiovascular composite end point with death from any cause**	710 (8.1)	877 (10.0)	0.80 (0.72 to 0.88)	NA
Nonfatal myocardial infarction	234 (2.7)	322 (3.7)	0.72 (0.61 to 0.85)	NA
Nonfatal stroke	154 (1.7)	165 (1.9)	0.93 (0.74 to 1.15)	NA
Hospitalization or urgent medical visit for heart failure	97 (1.1)	122 (1.4)	0.79 (0.60 to 1.03)	NA
Coronary revascularization	473 (5.4)	608 (6.9)	0.77 (0.68 to 0.87)	NA
Unstable angina leading to hospitalization	109 (1.2)	124 (1.4)	0.87 (0.67 to 1.13)	NA
Glycated hemoglobin level ≥6.5%††	306 (3.5)	1059 (12.0)	0.27 (0.24 to 0.31)	NA
Nephropathy composite end point‡‡	155 (1.8)	198 (2.2)	0.78 (0.63 to 0.96)	NA
Glycated hemoglobin level ≥5.7% among patients with baseline glycated hemoglobin <5.7%§§	623 (21.3)	1501 (50.4)	0.33 (0.30 to 0.36)	NA

SELECT trial, NEJM 2023

Table 3. Supportive Binary and Continuous Secondary End Points.*

End Point	Semaglutide (N=8803)	Placebo (N=8801)	Difference (95% CI)†
Glycated hemoglobin level of <5.7% among patients with baseline glycated hemoglobin level of ≥5.7% — no./total no. (%)‡			
At week 52	3848/5831 (66.0)	1136/5748 (19.8)	10.15 (9.18 to 11.23)
At week 104	3775/5750 (65.7)	1211/5663 (21.4)	8.74 (7.91 to 9.65)
Mean change from randomization to week 104			
Body weight — %	−9.39±0.09	−0.88±0.08	−8.51 (−8.75 to −8.27)
Waist circumference — cm	−7.56±0.09	−1.03±0.09	−6.53 (−6.79 to −6.27)
Glycated hemoglobin level — percentage points	−0.31±0.00	0.01±0.00	−0.32 (−0.33 to −0.31)
Systolic blood pressure — mm Hg	−3.82±0.16	−0.51±0.16	−3.31 (−3.75 to −2.88)
Diastolic blood pressure — mm Hg	−1.02±0.10	−0.47±0.10	−0.55 (−0.83 to −0.27)
Heart rate — beats/min	3.79±0.11	0.69±0.11	3.10 (2.80 to 3.39)
EQ-5D-5L index score§	0.01±0.00	−0.01±0.00	0.01 (0.01 to 0.02)
EQ-5D-VAS score§	2.52±0.16	0.92±0.16	1.60 (1.16 to 2.04)
High-sensitivity CRP level — %	−39.12	−2.08	−37.82 (−39.70 to −35.90)
Total cholesterol level — %	−4.63	−1.92	−2.77 (−3.37 to −2.16)
HDL cholesterol level — %	4.86	0.59	4.24 (3.70 to 4.79)
LDL cholesterol level — %	−5.25	−3.14	−2.18 (−3.22 to −1.12)
Triglyceride level — %	−18.34	−3.20	−15.64 (−16.68 to −14.58)

SELECT trial, NEJM 2023

The NEW ENGLAND JOURNAL of MEDICINE

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Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity

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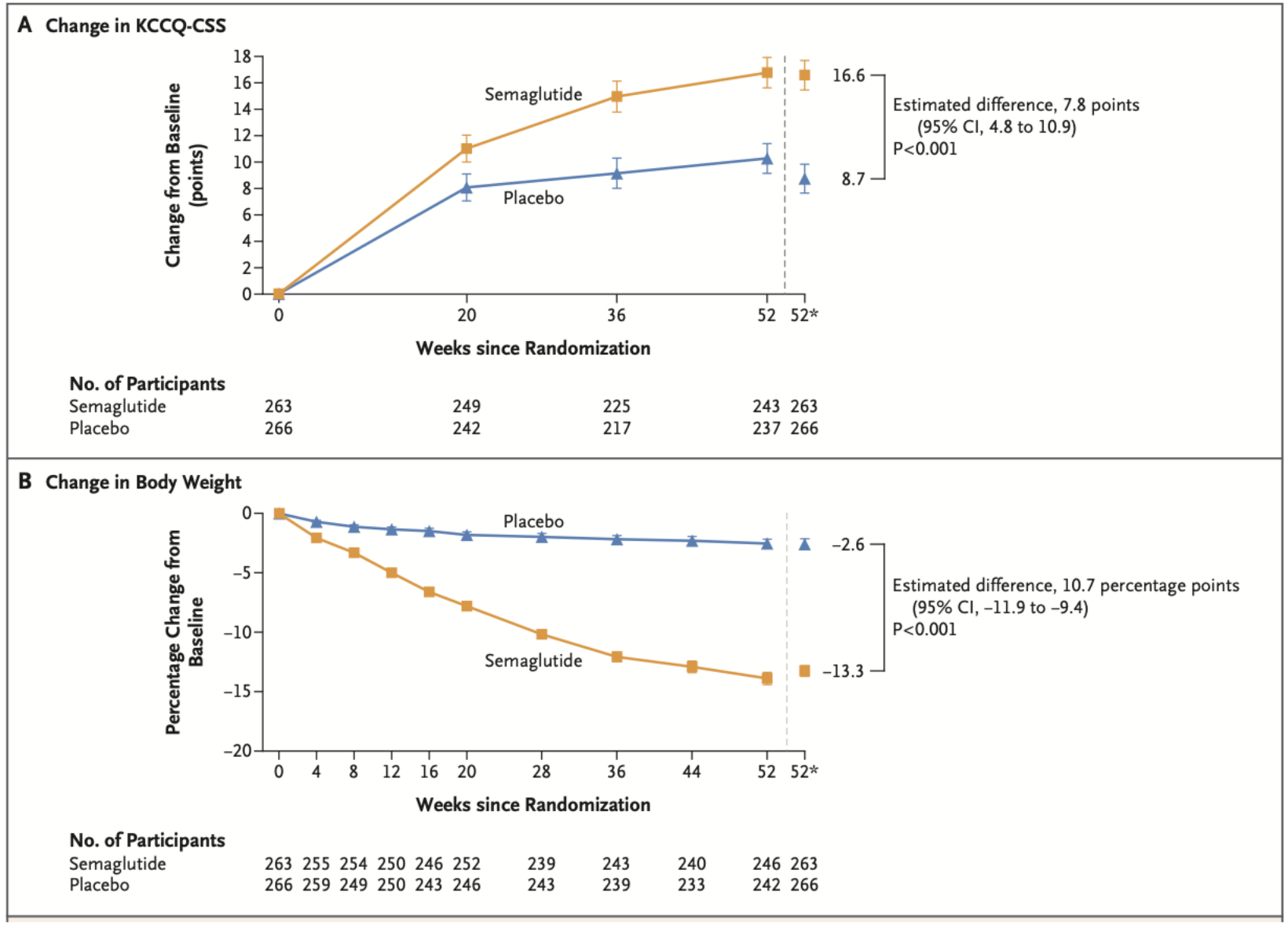
Table 1. Baseline Demographic and Clinical Characteristics of the Participants.*

Characteristic	Semaglutide (N=263)	Placebo (N=266)	Total (N=529)
Female sex — no. (%)	149 (56.7)	148 (55.6)	297 (56.1)
Median age (IQR) — yr	70 (62–75)	69 (62–75)	69 (62–75)
Ethnic group — no. (%)†			
Hispanic or Latino	15 (5.7)	21 (7.9)	36 (6.8)
Not Hispanic or Latino	248 (94.3)	245 (92.1)	493 (93.2)
Race — no. (%)†			
Black	8 (3.0)	13 (4.9)	21 (4.0)
White	255 (97.0)	252 (94.7)	507 (95.8)
Other	0	1 (0.4)	1 (0.2)
Median body weight (IQR) — kg	104.7 (92.4–120.1)	105.3 (92.4–122.0)	105.1 (92.4–120.8)
Median BMI (IQR)	37.2 (33.9–41.1)	36.9 (33.3–41.6)	37.0 (33.7–41.4)
BMI stratum — no. (%)			
30 to <35	89 (33.8)	91 (34.2)	180 (34.0)
≥35	174 (66.2)	175 (65.8)	349 (66.0)
Median waist circumference (IQR) — cm	119.0 (110.5–127.1)	120.0 (110.5–129.0)	119.4 (110.5–128.0)
Median systolic blood pressure (IQR) — mm Hg	133 (122–145)	132 (120–142)	133 (121–144)
Median NT-proBNP level (IQR) — pg/ml	414.4 (229.2–1014.0)	499.8 (204.7–1025.0)	450.8 (218.2–1015.0)
Median CRP level (IQR) — mg/liter	3.8 (1.9–7.0)	3.9 (2.0–8.4)	3.8 (1.9–7.7)

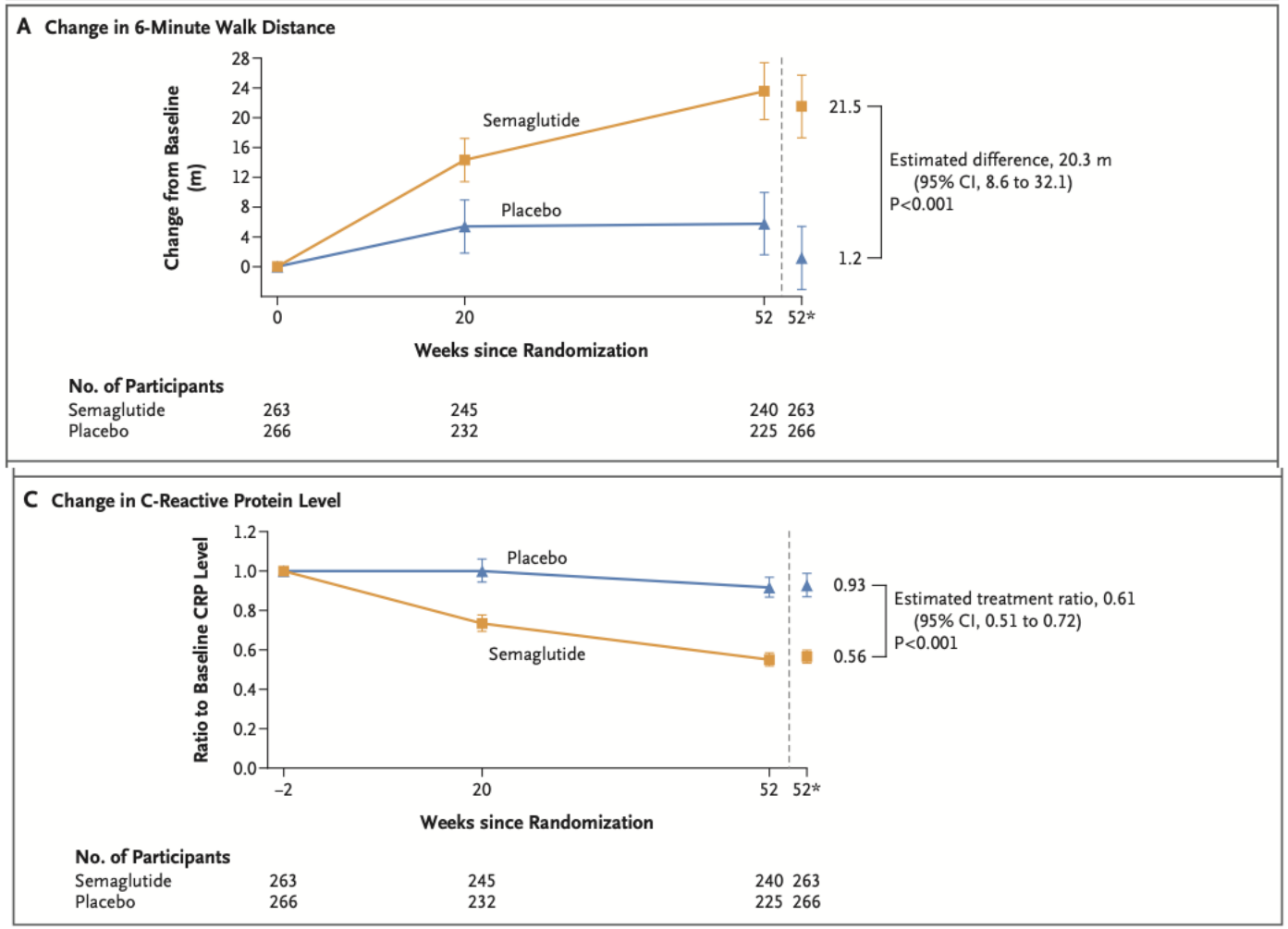
STEP-HFpEF trial, NEJM 2023

Median LVEF (IQR) — %	57.0 (50.0–60.0)	57.0 (50.0–60.0)	57.0 (50.0–60.0)
LVEF stratum — no. (%)			
45 to <50%‡	37 (14.1)	48 (18.0)	85 (16.1)
50 to 59%	113 (43.0)	102 (38.3)	215 (40.6)
≥60%	113 (43.0)	116 (43.6)	229 (43.3)
Median KCCQ-CSS (IQR) — points§	59.4 (42.7–72.9)	58.3 (40.5–72.9)	58.9 (41.7–72.9)
Median 6-minute walk distance (IQR) — m	316.0 (251.0–386.0)	325.8 (232.4–392.0)	320.0 (240.0–389.0)
Hospitalization for heart failure within 1 year — no. (%)	42 (16.0)	39 (14.7)	81 (15.3)
Coexisting conditions at screening — no. (%)			
Atrial fibrillation	135 (51.3)	140 (52.6)	275 (52.0)
Hypertension	216 (82.1)	217 (81.6)	433 (81.9)
Coronary artery disease	53 (20.2)	45 (16.9)	98 (18.5)
NYHA functional class — no. (%)			
II	183 (69.6)	167 (62.8)	350 (66.2)
III or IV	80 (30.4)	99 (37.2)	179 (33.8)
Concomitant medication — no. (%)			
Diuretic	207 (78.7)	220 (82.7)	427 (80.7)
Loop diuretic	158 (60.1)	171 (64.3)	329 (62.2)
Thiazide	40 (15.2)	50 (18.8)	90 (17.0)
MRA	89 (33.8)	95 (35.7)	184 (34.8)
ACEI, ARB, or ARNI	210 (79.8)	214 (80.5)	424 (80.2)
Beta-blocker	201 (76.4)	217 (81.6)	418 (79.0)
SGLT2 inhibitor	8 (3.0)	11 (4.1)	19 (3.6)

STEP-HFpEF trial, NEJM 2023

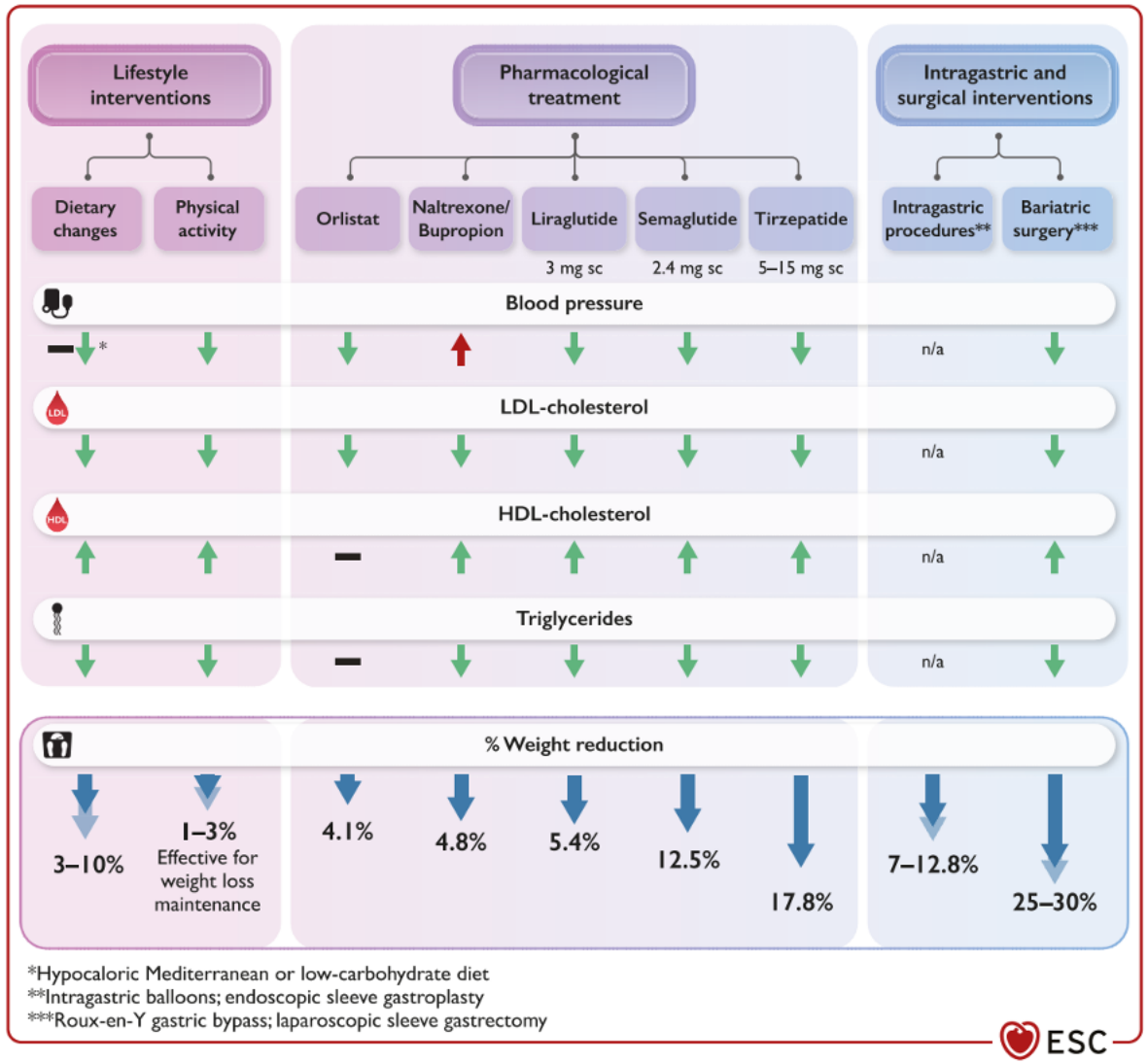


STEP-HFpEF trial, NEJM 2023



STEP-HFpEF trial, NEJM 2023

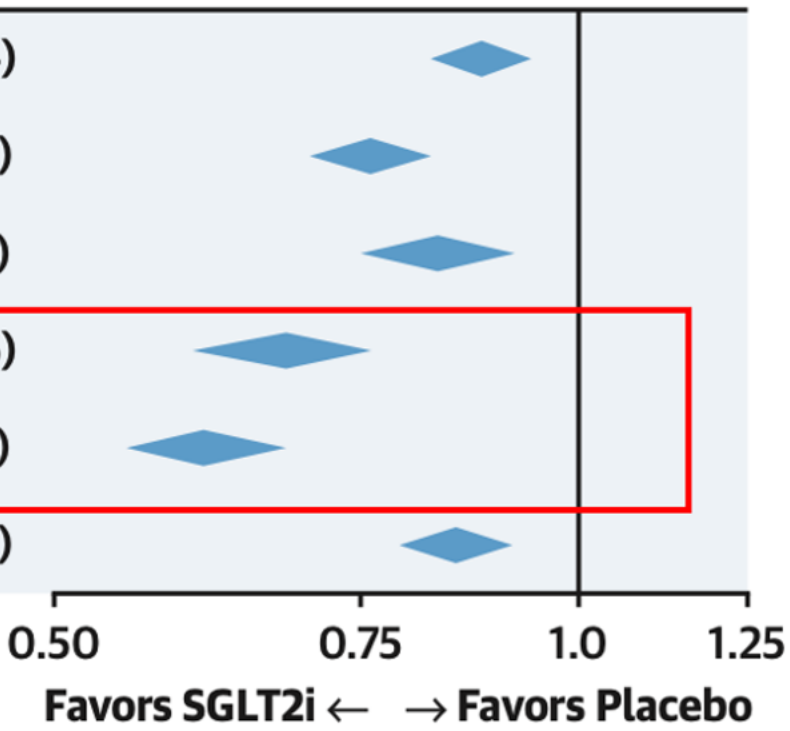
Obesity and cardiovascular disease: an ESC clinical consensus statement



Koskinas K et al.
Eur Heart J 2024; 45: 4063-98

SGLT2-i in patients with diabetes mellitus

Outcome	# Events	HR (95% CI)
MACE	3,828	0.88 (0.82-0.94)
CV death/HHF	2,460	0.76 (0.70-0.82)
CV death	1,506	0.83 (0.75-0.92)
HHF	1,192	0.68 (0.60-0.76)
Composite Renal Endpoint	1,351	0.61 (0.55-0.68)
All-cause Mortality	2,493	0.85 (0.79-0.92)



Zelniker TA and Braunwald EA, JACC 2020; february 4

Study	DAPA-HF[1]	EMPEROR-REDUCED[2]
SGLT2 -inhibitor	Dapagliflozin	Empagliflozin
Population	NYHA class II-IV, LVEF <40%, Elevated NT-proBNP	NYHA class II-IV, LVEF <40%, Elevated NT-proBNP
Primary endpoint	CV death / hHF / Urgent HF visit	CV death / hHF
Secondary endpoint(s)	CV death or hHF, > 50% sustained declined in eGFR, any cause death	Time to hHF, eGFR slope change, tme to dialysis, renal transplant or >40% sustained decline in eGFR
Glycemic status	With/without T2D	With/without T2D

1- McMurray JJV, et al. N Engl J Med 2019

2- Packer M, et al. N Engl J Med 2020

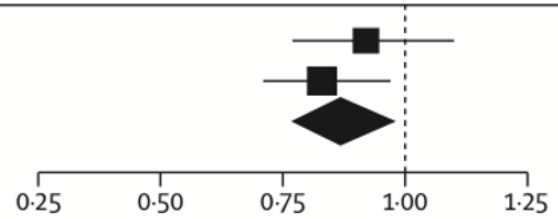
➢ 70% of pts
FE ≤ 30%

	EMPEROR-Reduced		DAPA-HF	
	Empagliflozin	Placebo	Dapagliflozin	Placebo
Number of participants	1863	1867	2373	2371
Age, years	67·2 (10·8)	66·5 (11·2)	66·2 (11·0)	66·5 (10·8)
Sex				
Men	1426 (76.5%)	1411 (75·6%)	1809 (76·2%)	1826 (77·0%)
Women	437 (23·5%)	456 (24·4%)	564 (23·8%)	545 (23·0%)
NYHA functional classification				
II	1399 (75·1%)	1401 (75·0%)	1606 (67·7%)	1597 (67·4%)
III	455 (24·4%)	455 (24·4%)	747 (31·5%)	751 (31·7%)
IV	9 (0·5%)	11 (0·6%)	20 (0·8%)	23 (1·0%)
Mean LVEF, %	27·7 (6·0)	27·2 (6·1)	31·2 (6·7)	30·9 (6·9)
NT-pro BNP, pg/mL	1887 (1077–3429)	1926 (1153–3525)	1428 (857–2655)	1446 (857–2641)
Medical history				
Hospitalisation for heart failure*	577 (31·0%)	574 (30·7%)	1124 (47·4%)	1127 (47·5%)
Diabetes†	927 (49·8%)	929 (49·8%)	1075 (45·3%)	1064 (44·9%)
eGFR, mL/min per 1·73 m²‡	61·8 (21·7)	62·2 (21·5)	66·0 (19·6)	65·5 (19·3)
Heart failure medications				
ACE inhibitor	867 (46·5%)	836 (44·8%)	1332 (56·1%)	1329 (56·1%)
ARB	451 (24·2%)	457 (24·5%)	675 (28·4%)	632 (26·7%)
Mineralocorticoid receptor antagonist	1306 (70·1%)	1355 (72·6%)	1696 (71·5%)	1674 (70·6%)
ARNI	340 (18·3%)	387 (20·7%)	250 (10·5%)	258 (10·9%)
Device therapy				
ICD or CRT-D	578 (31·0%)	593 (31·8%)	622 (26·2%)	620 (26·1%)
CRT-D or CRT-P	220 (11·8%)	222 (11·9%)	190 (8·0%)	164 (6·9%)

Zannad F et al. Lancet 2020, published online august 30

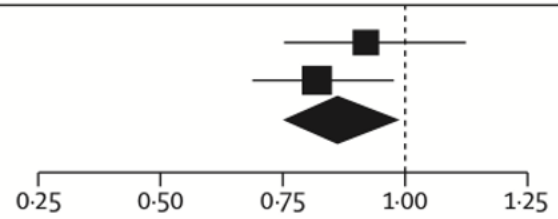
A All-cause mortality

	Number with event/number of patients (%)		HR (95% CI)
	SGLT2 inhibitor	Placebo	
EMPEROR-Reduced	249/1863 (13·4%)	266/1867 (14·2%)	0·92 (0·77–1·10)
DAPA-HF	276/2373 (11·6%)	329/2371 (13·9%)	0·83 (0·71–0·97)
Total			**0·87 (0·77–0·98)**
Test for overall treatment effect p=0·018			
Test for heterogeneity of effect p=0·39			



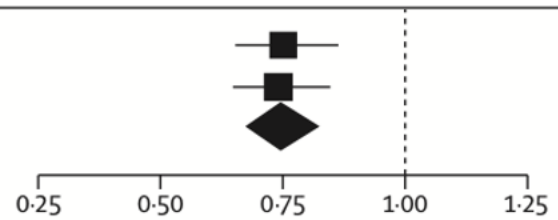
B Cardiovascular death

	Number with event/number of patients (%)		HR (95% CI)
	SGLT2 inhibitor	Placebo	
EMPEROR-Reduced	187/1863 (10·0%)	202/1867 (10·8%)	0·92 (0·75–1·12)
DAPA-HF	227/2373 (9·6%)	273/2371 (11·5%)	0·82 (0·69–0·98)
Total			**0·86 (0·76–0·98)**
Test for overall treatment effect p=0·027			
Test for heterogeneity of effect p=0·40			



C First hospitalisation for heart failure or cardiovascular death

	Number with event/number of patients (%)		HR (95% CI)
	SGLT2 inhibitor	Placebo	
EMPEROR-Reduced	361/1863 (19·4%)	462/1867 (24·7%)	0·75 (0·65–0·86)
DAPA-HF	386/2373 (16·3%)	502/2371 (21·2%)	0·74 (0·65–0·85)
Total			**0·74 (0·68–0·82)**
Test for overall treatment effect p<0·0001			
Test for heterogeneity of effect p=0·89			



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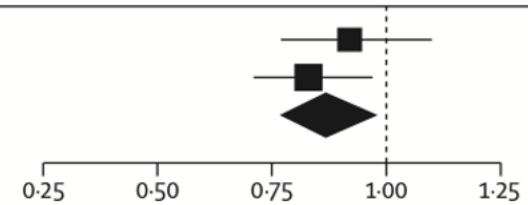

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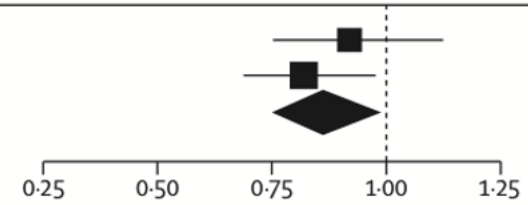

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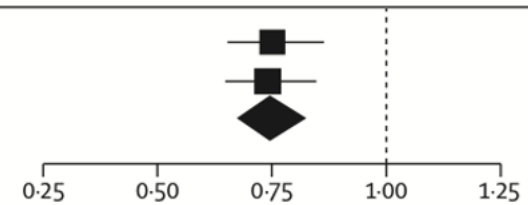

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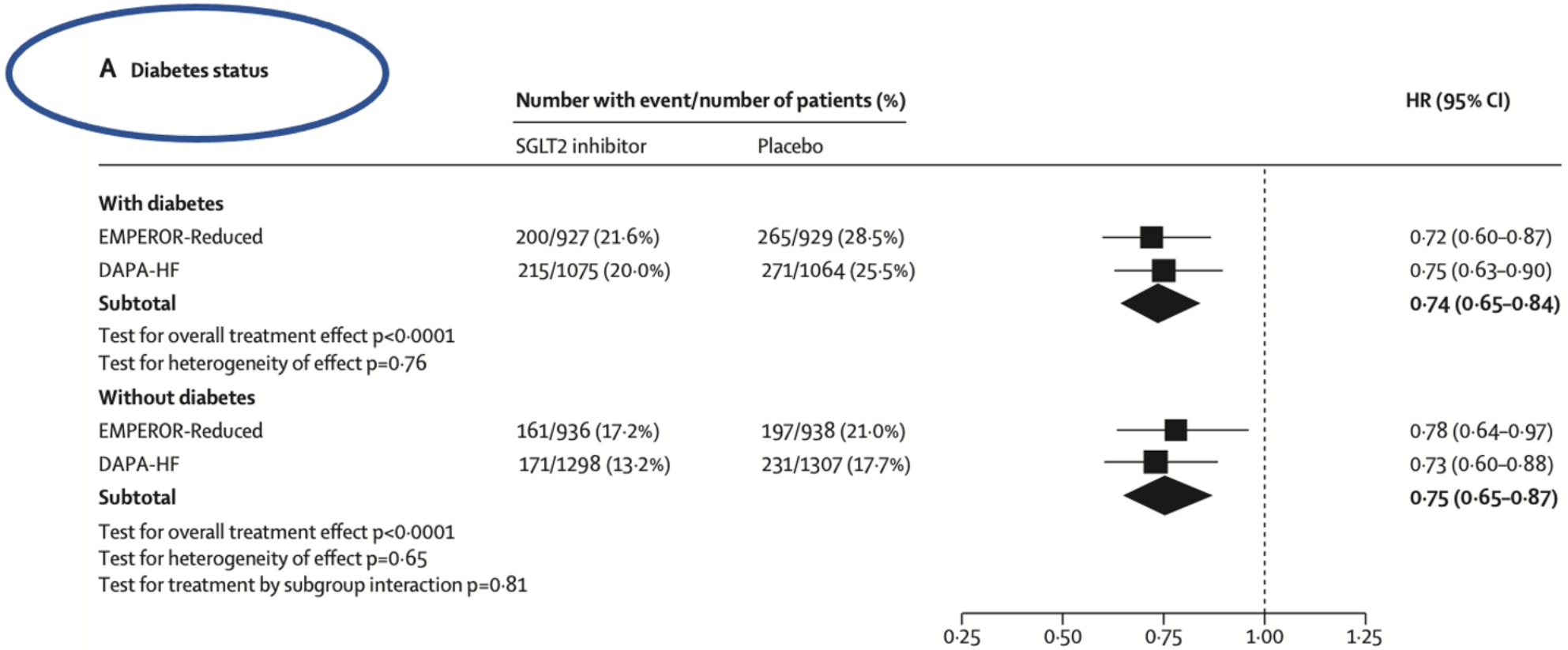

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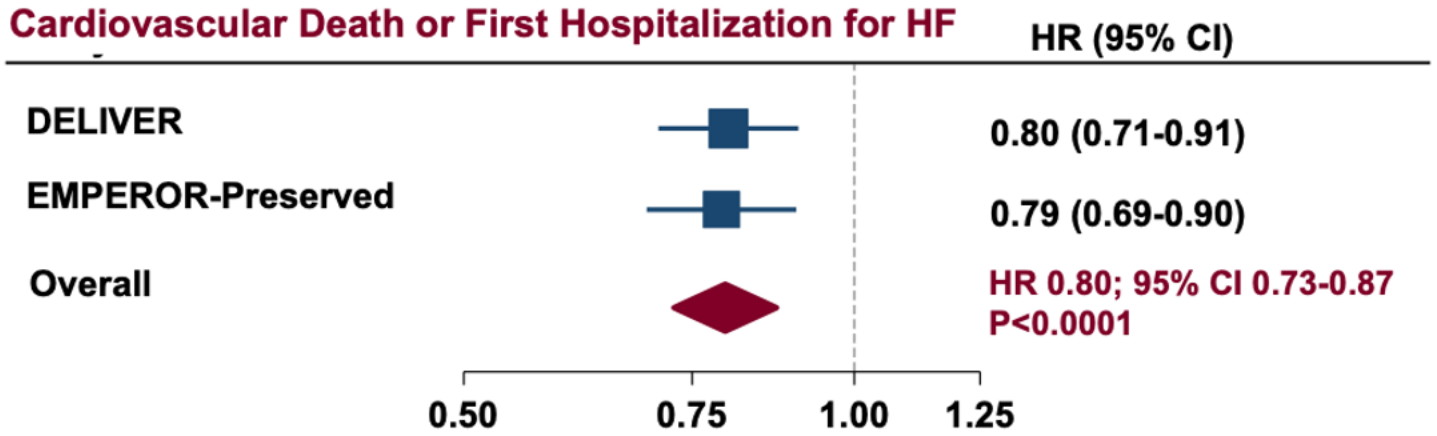
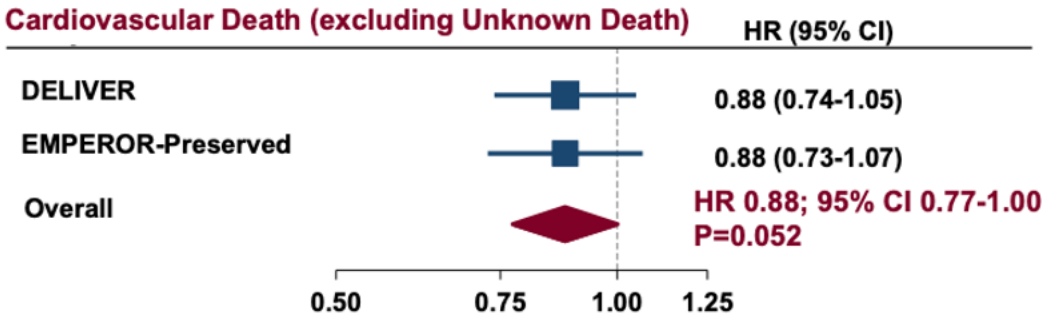
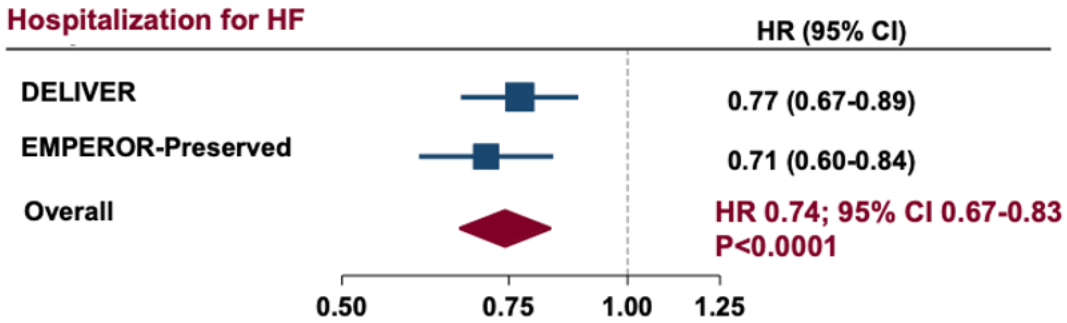
DELIVER and EMPEROR-Preserved Meta-Analysis:
↓ 20% (13-27%) Relative Risk Reduction of Primary Endpoint with Consistent Reductions in Both Components

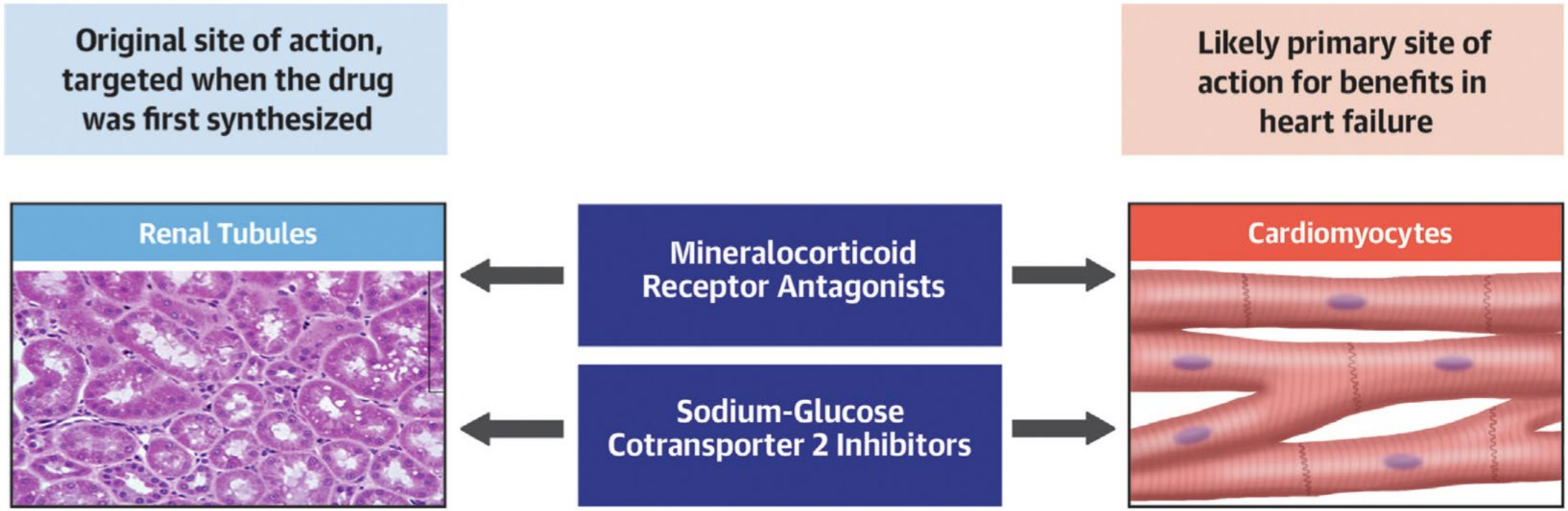






$P_{heterogeneity}$ >0.40 for all endpoints

FIGURE 1 Contrasts Between Originally Targeted and Currently Proposed Sites of Action



Packer M, JACC 2023

Association between BMI and Efficacy of SGLT2 Inhibitors in Patients with Heart Failure or at Risk of Heart Failure: A Meta-Analysis Based on Randomized Controlled Trials

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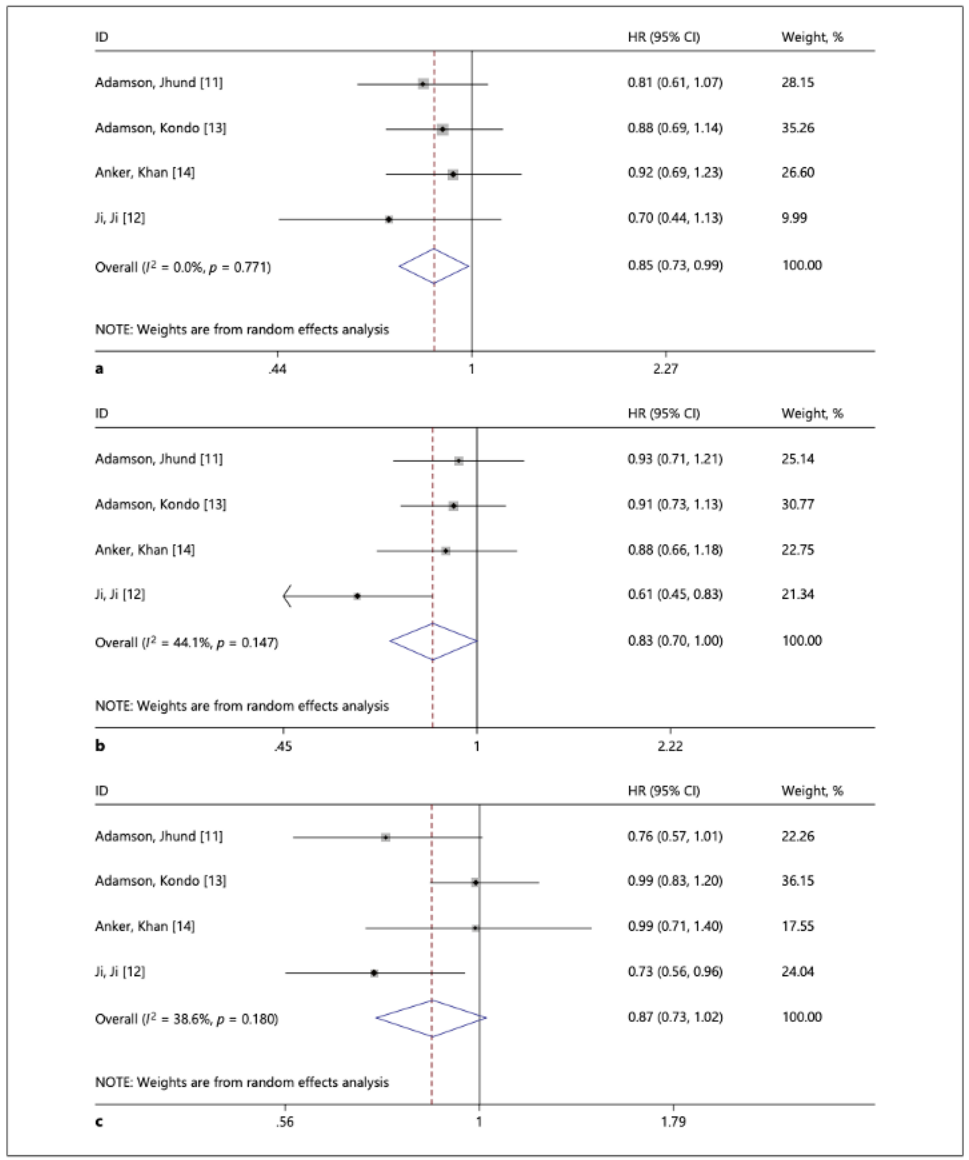
Cardiology 2024; 149: 104-116

All cause mortality

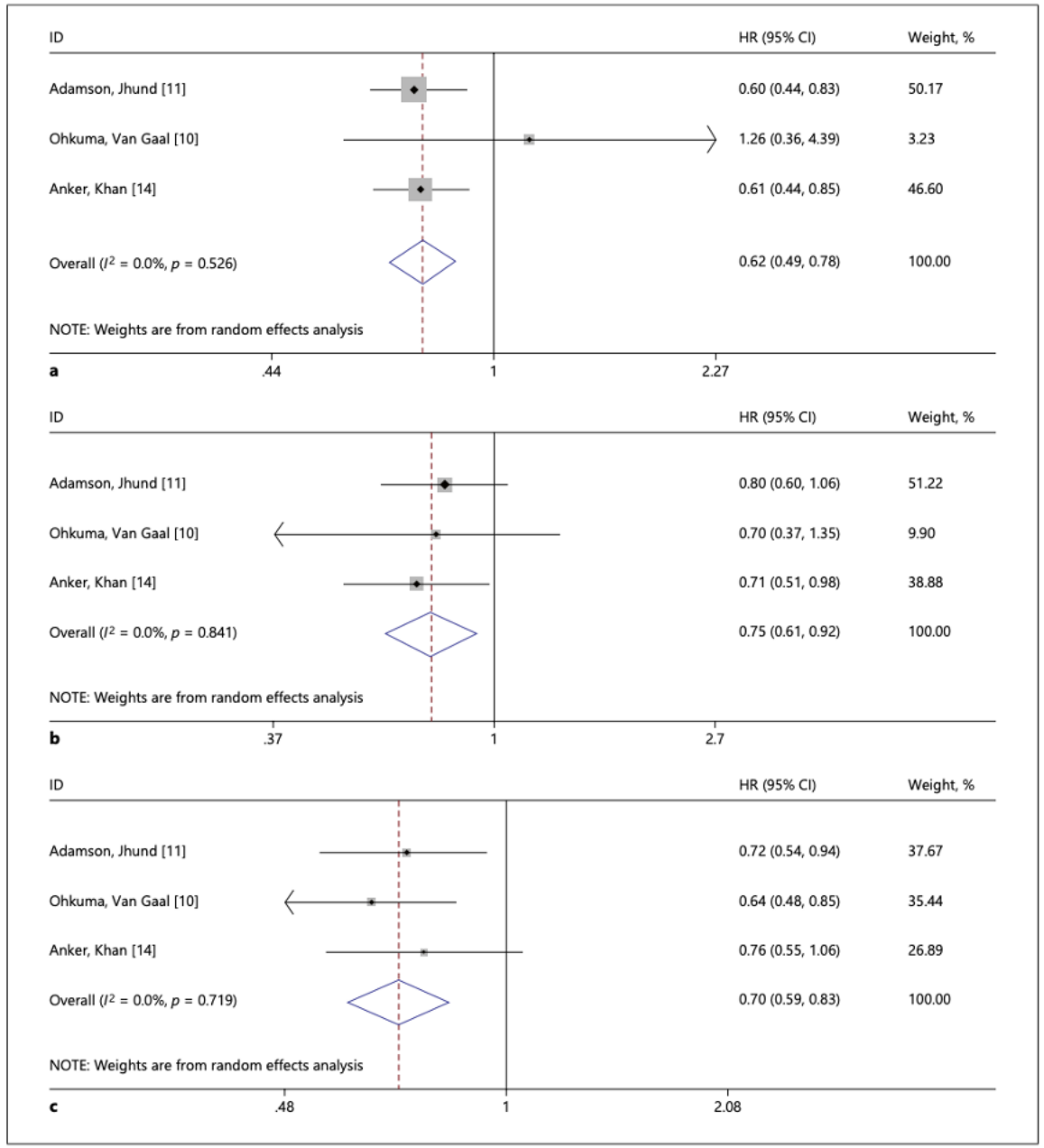


BMI < 25

BMI 25-30

BMI > 30

Zhou et al. Cardiology 2024; 149: 104-116



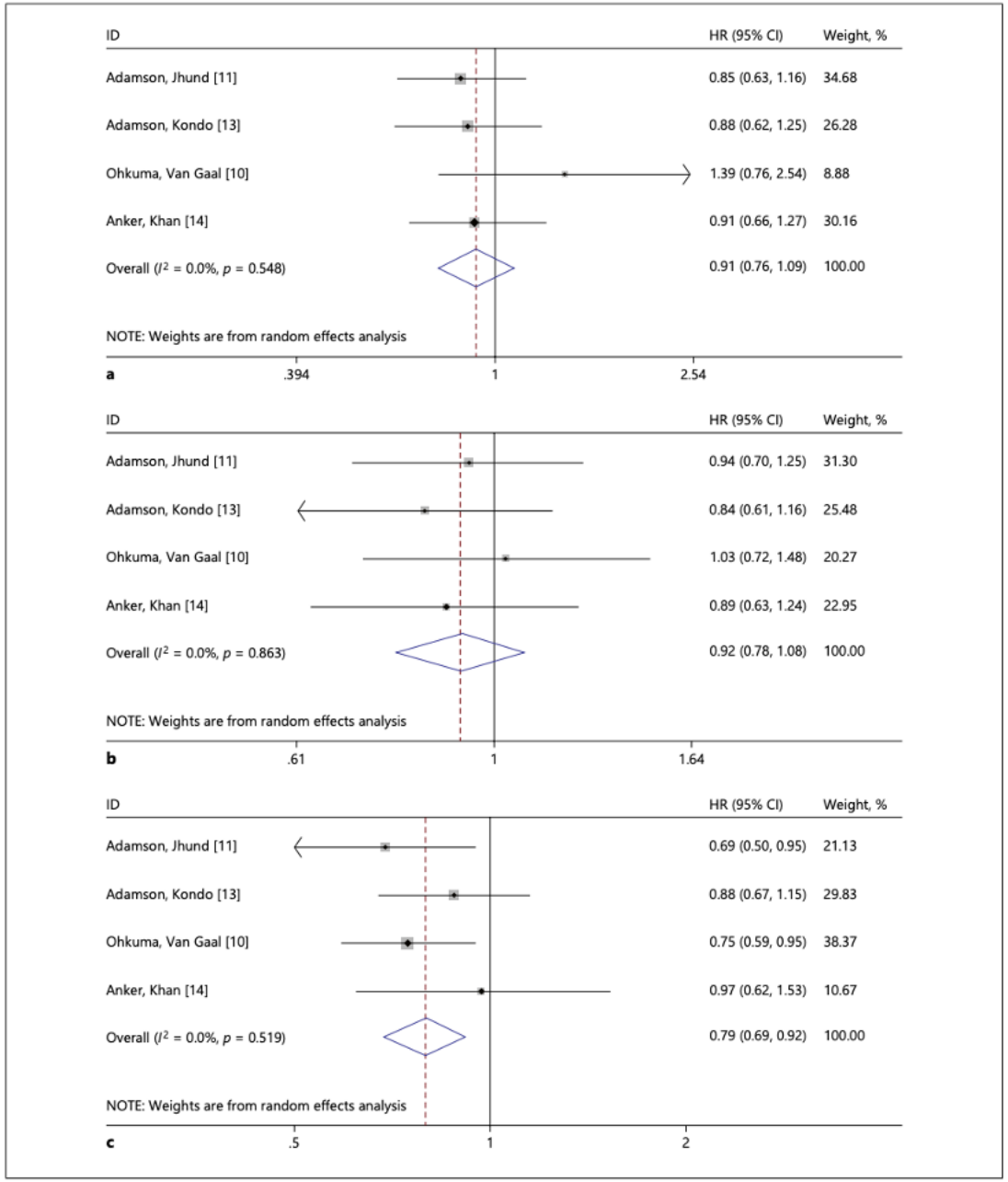
BMI < 25

BMI 25-30

BMI > 30

Hospitalization for heart failure

Zhou et al. Cardiology 2024; 149: 104-116



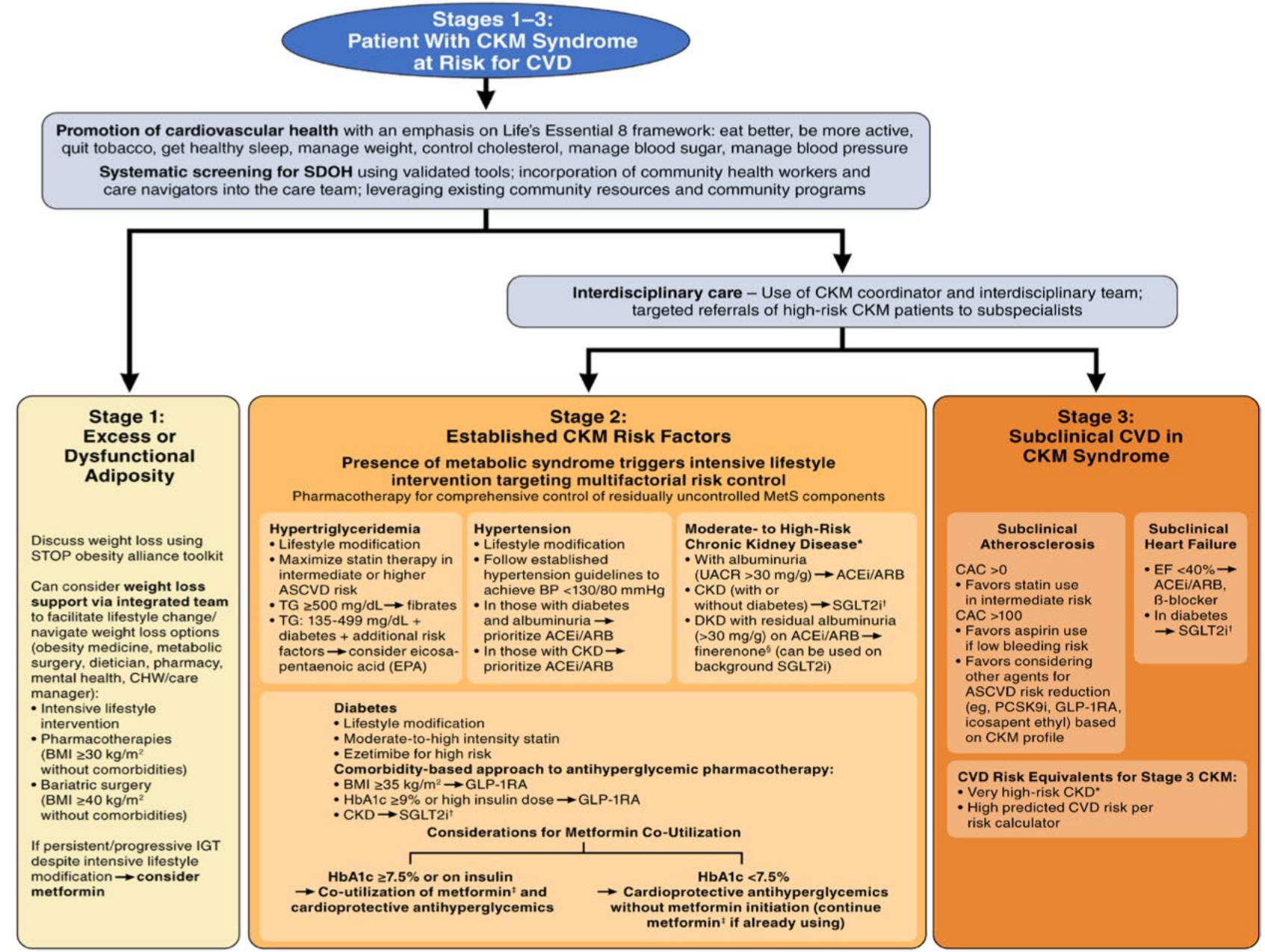
BMI < 25

BMI 25-30

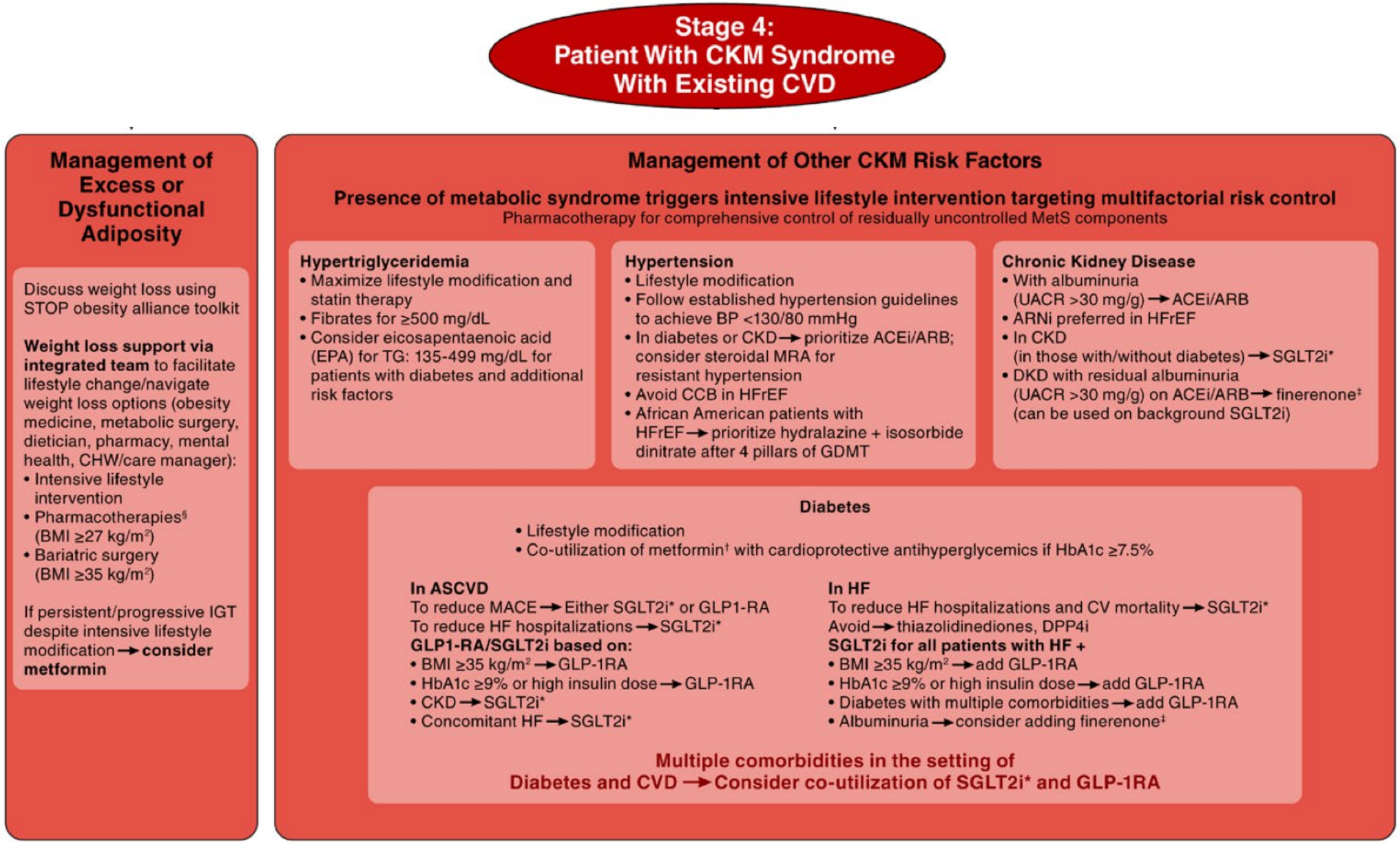
BMI > 30

CV mortality

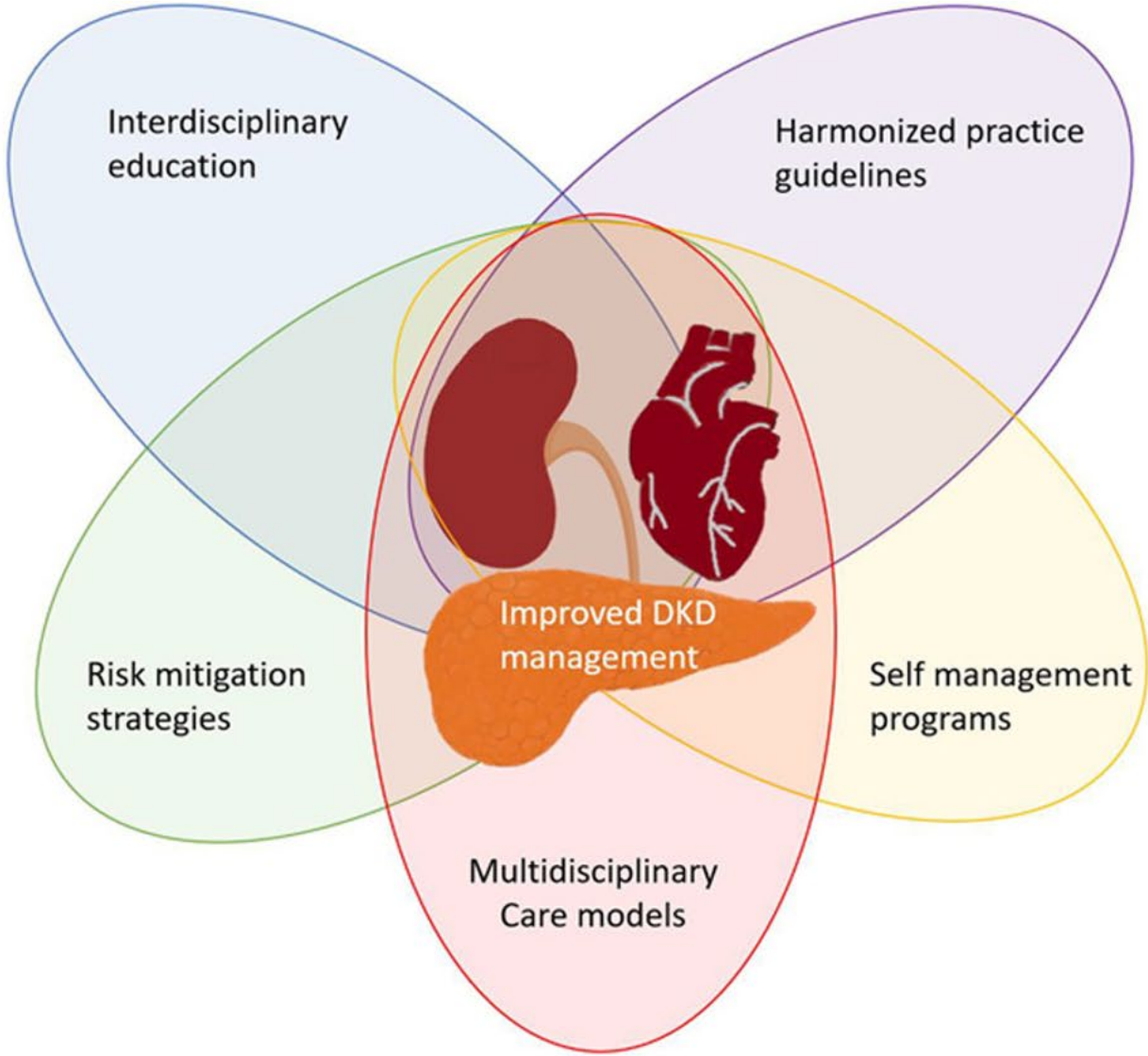
Zhou et al. Cardiology 2024; 149: 104-116



Ndumele C et al. AHA Advisory. Circulation 2023, november 14



Ndumele C et al. AHA Advisory. Circulation 2023, november 14



Cardio-renal-metabolic care model, Cardiovasc Qual Outcomes 2020, november