Scompenso cardiaco e diabete

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Disclosure

Il sottoscritto prof. Alberto Maria Marra dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

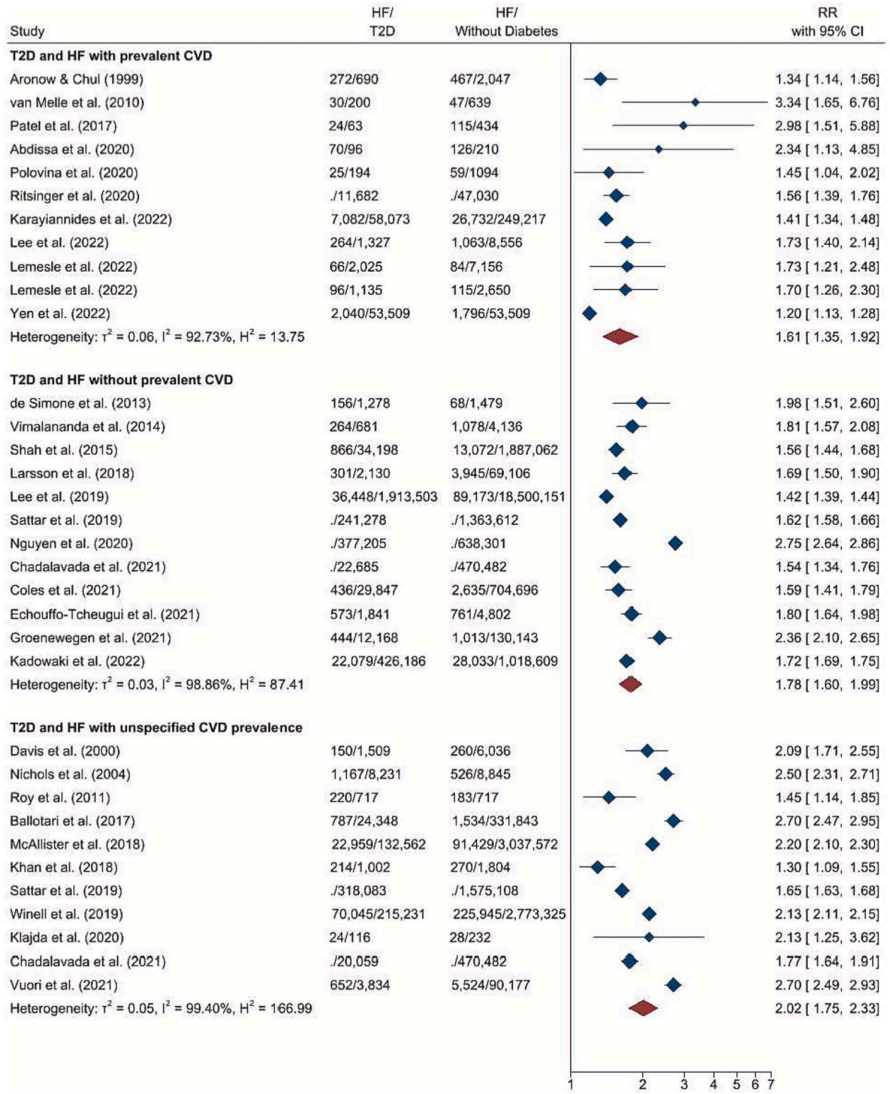
-Advisory Board for MSD

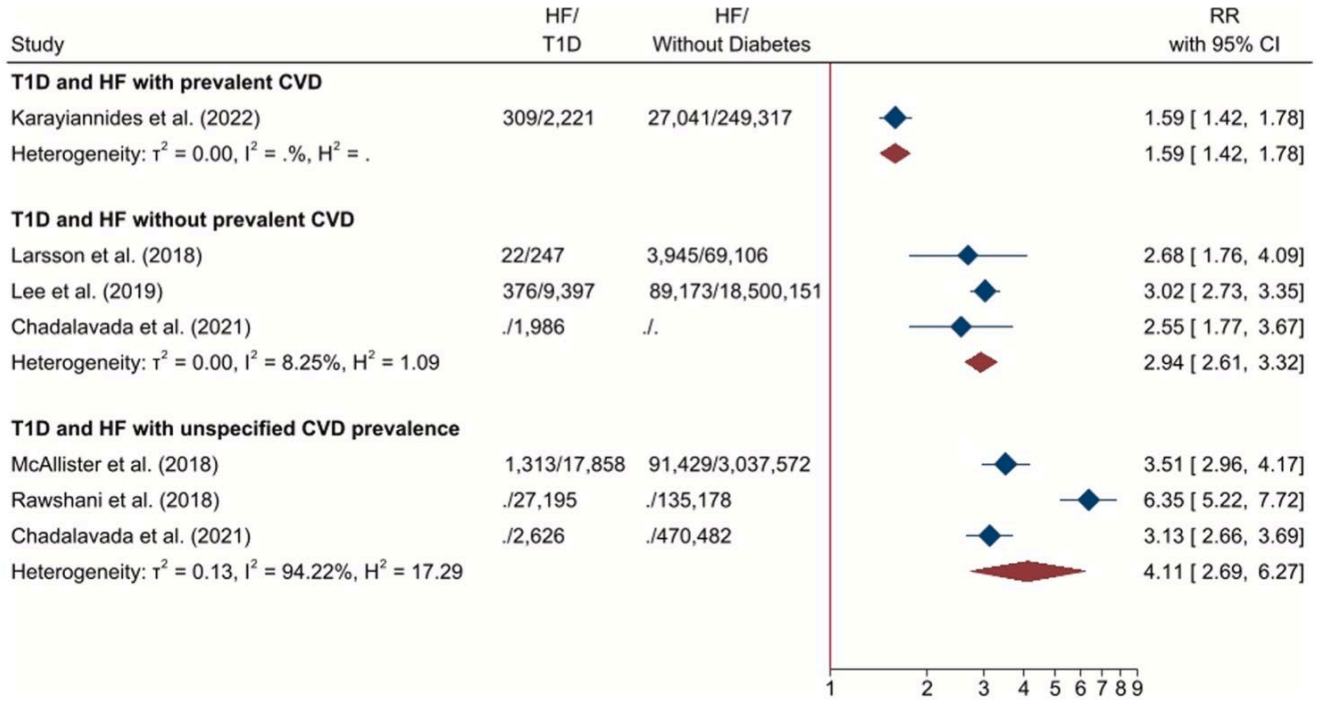
- Lecture Fees for Bruno Farmaceutici s.p.a.

- Unrestricted Research Grant from Farmagens Healthcare

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.).

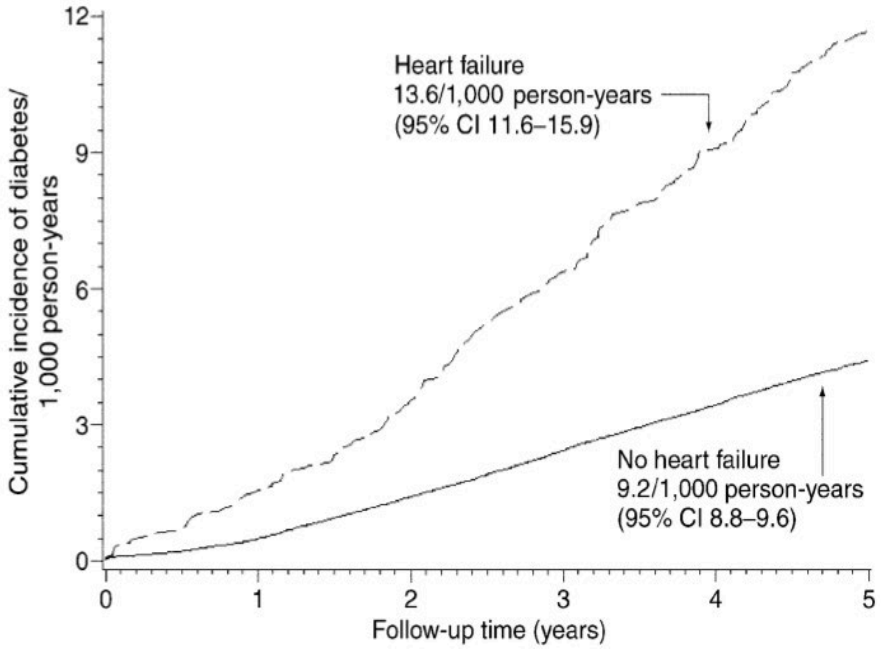
From Diabetes to Heart Failure: one way





Panchal K et al. Diab Res and Clin Pract 2018

From Heart Failure to Diabetes: the way back



58,056 *non-diabetic adults* aged ≥30 years with no evidence of diabetes.

Heart failure was independently associated with **an increase in diabetes incidence of 48%** (95% CI 27– 73%)

	Wald χ^2	*P*	OR (95% CIs)
A1C	51.6	<0.0001	1.78 (1.52–2.08)
BMI	26.6	<0.0001	1.64 (1.36–1.98)
Lipid-lowering therapy	12.1	0.0005	2.05 (1.37–3.07)
Serum creatinine	9.7	0.0018	0.68 (0.54–0.87)
Diuretic therapy	8.6	0.0033	4.81 (1.69–13.69)
Digoxin therapy	5.2	0.0221	1.65 (1.08–2.54)
ALT	4.9	0.0269	1.15 (1.02–1.31)
Age	3.9	0.0476	0.81 (0.65–1.00)

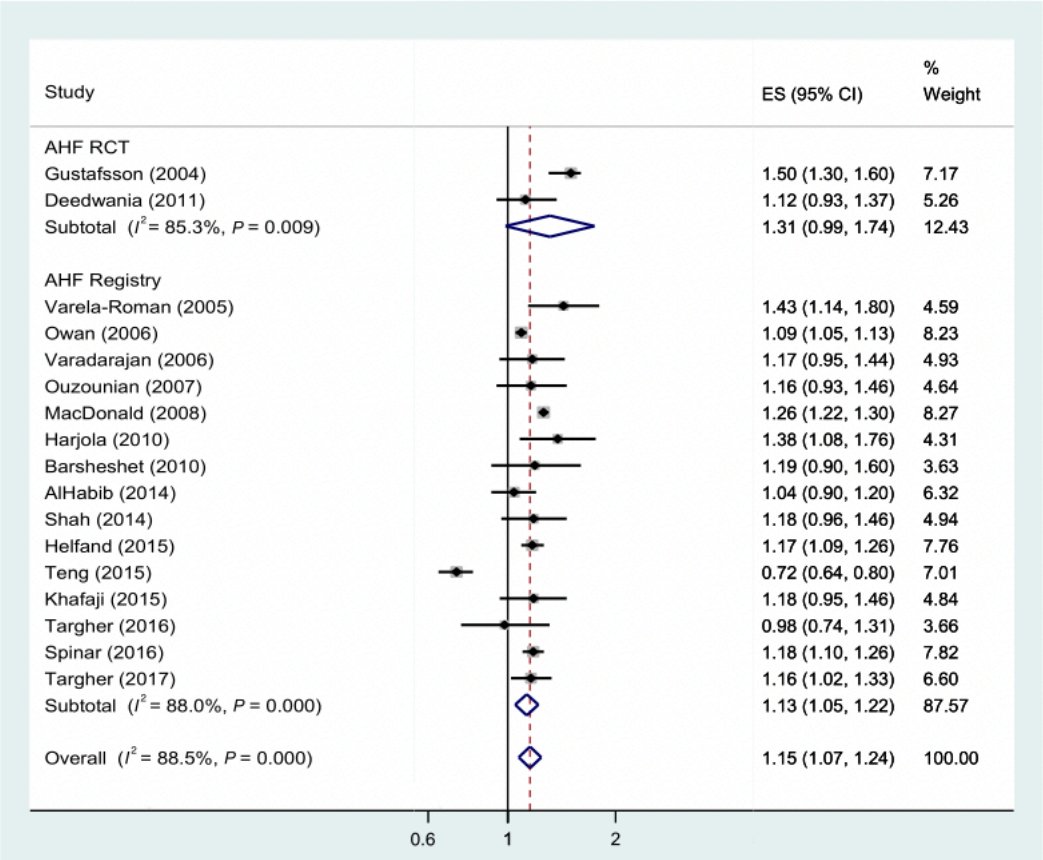
ORs are expressed per 1 SD change in age, BMI, ALT, A1C, and creatinine.

Preiss D et al Diabetes Care 2009

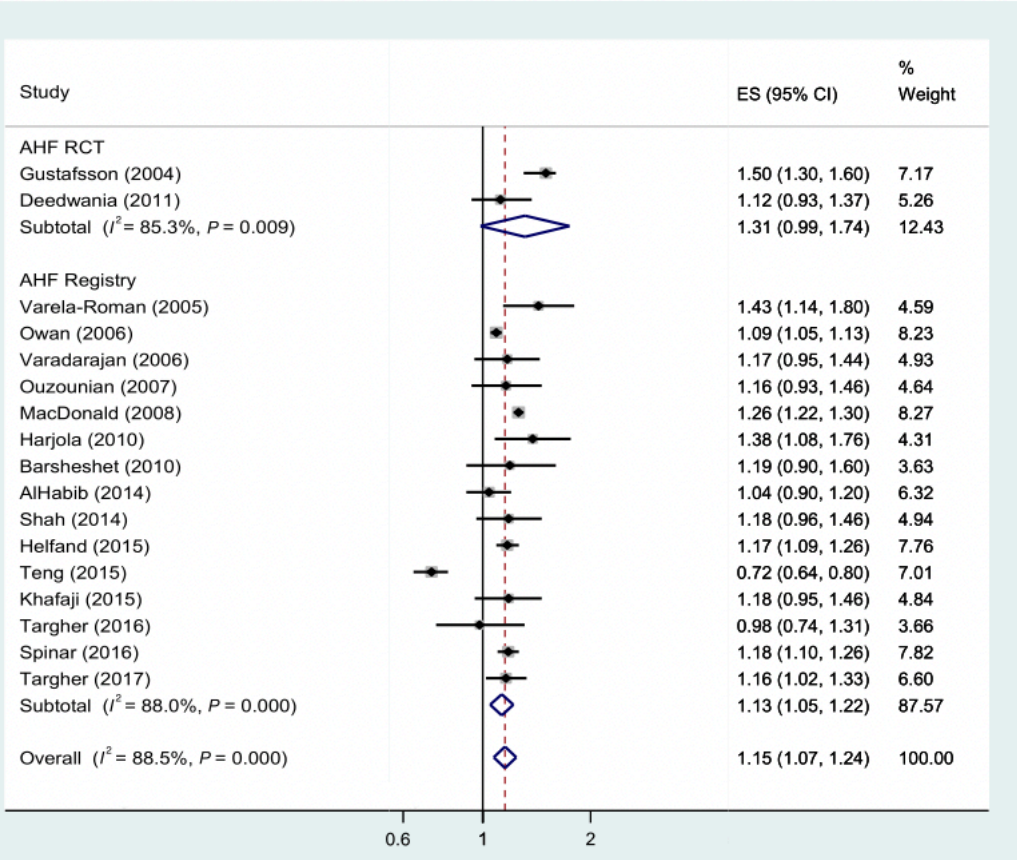
Nichols GA et al. Diabetologi 2011

Heart Failure and Diabetes: dangerous liaison

Acute Heart Failure



Chronic Heart Failure

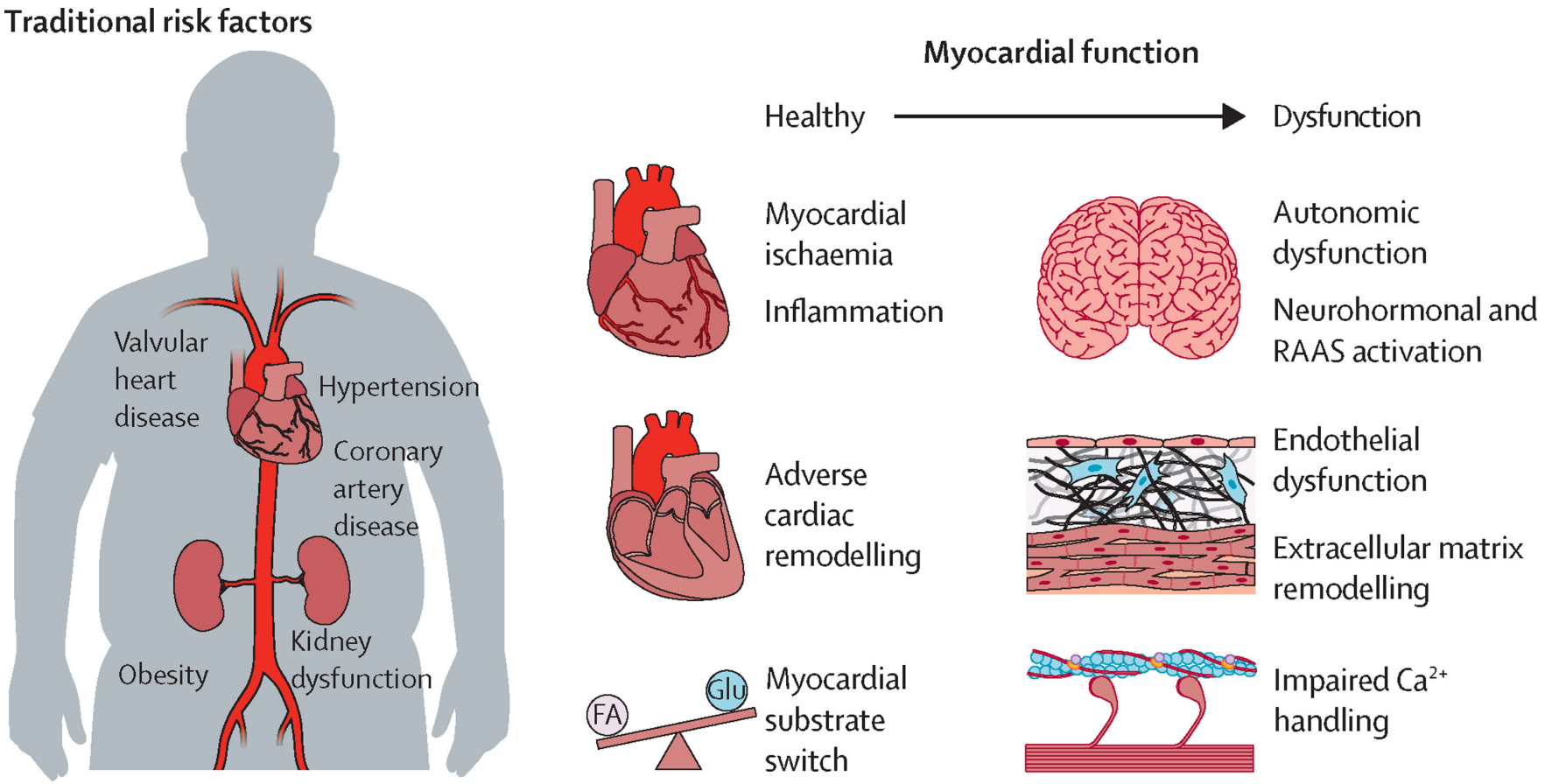


Dauriz M et al. Diabetes Care 2017

Heart Failure and Diabetes: a dangerous liaison

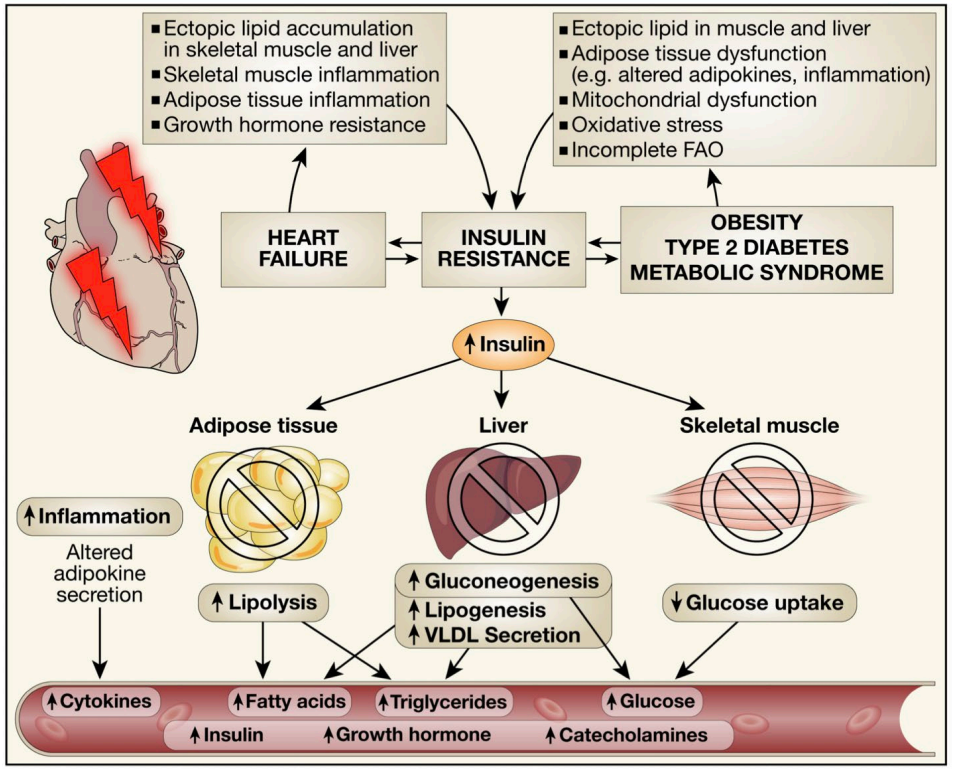
1. How to **prevent** development of Heart Failure in patients with Diabetes
2. How to **handle glycemic control** in Heart Failure patients
3. How to **manage Heart Failure** in patients with Diabetes

From Diabetes to Heart Failure: one way

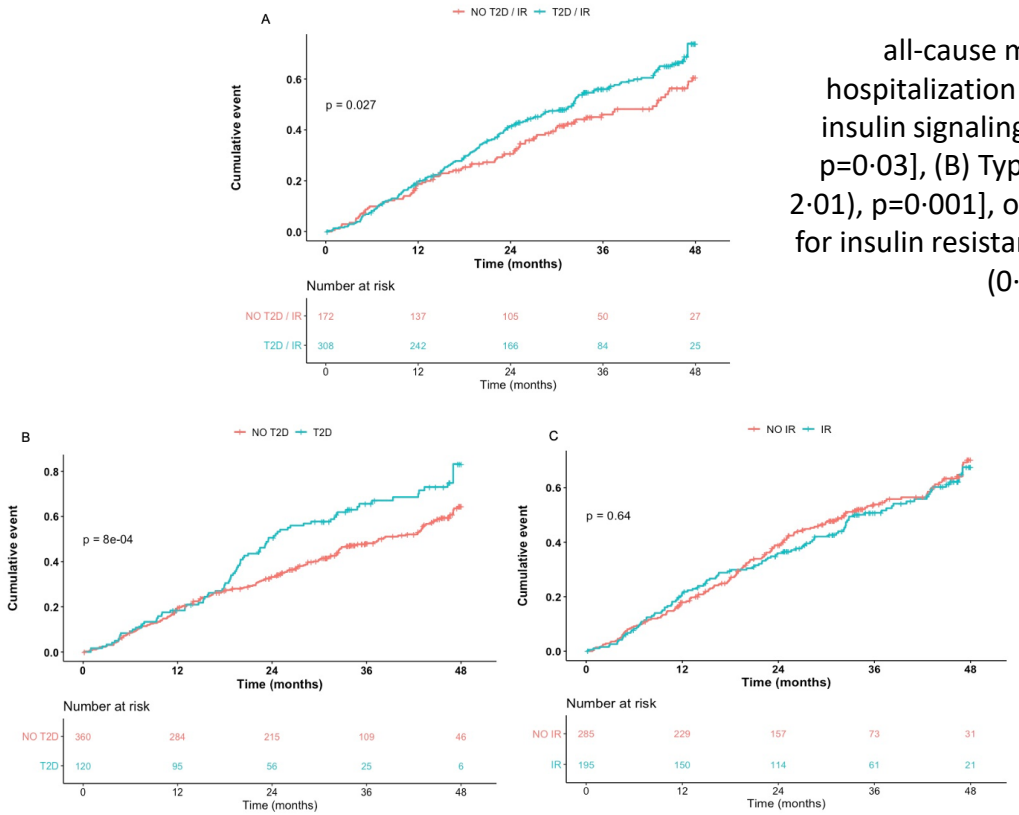


Pandey A et al. Lancet Endocrinol & Metab 2023

Insulin-Resistance is (one of?) the link



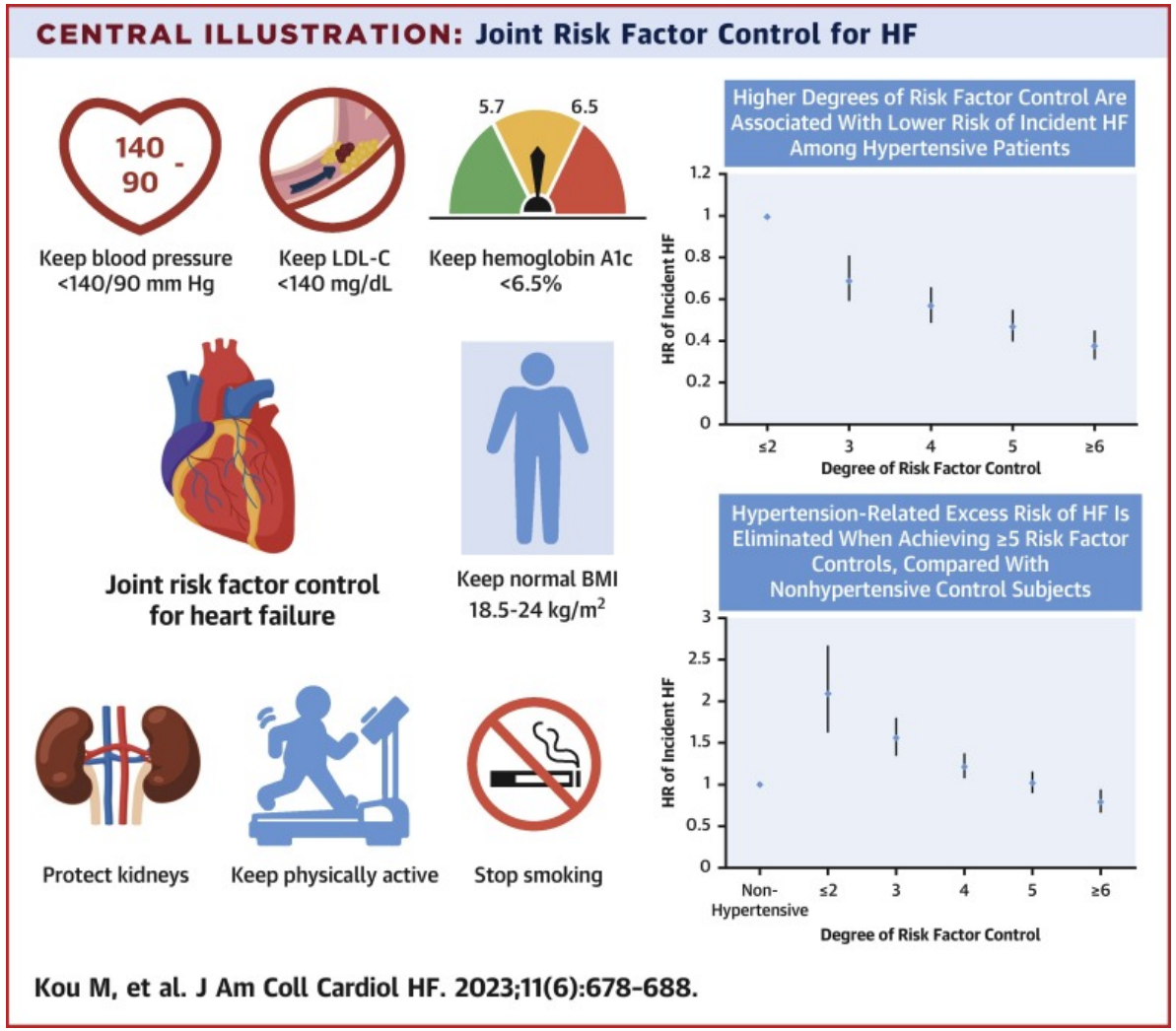
Riehle C et al. Cardiovasc Res 2016



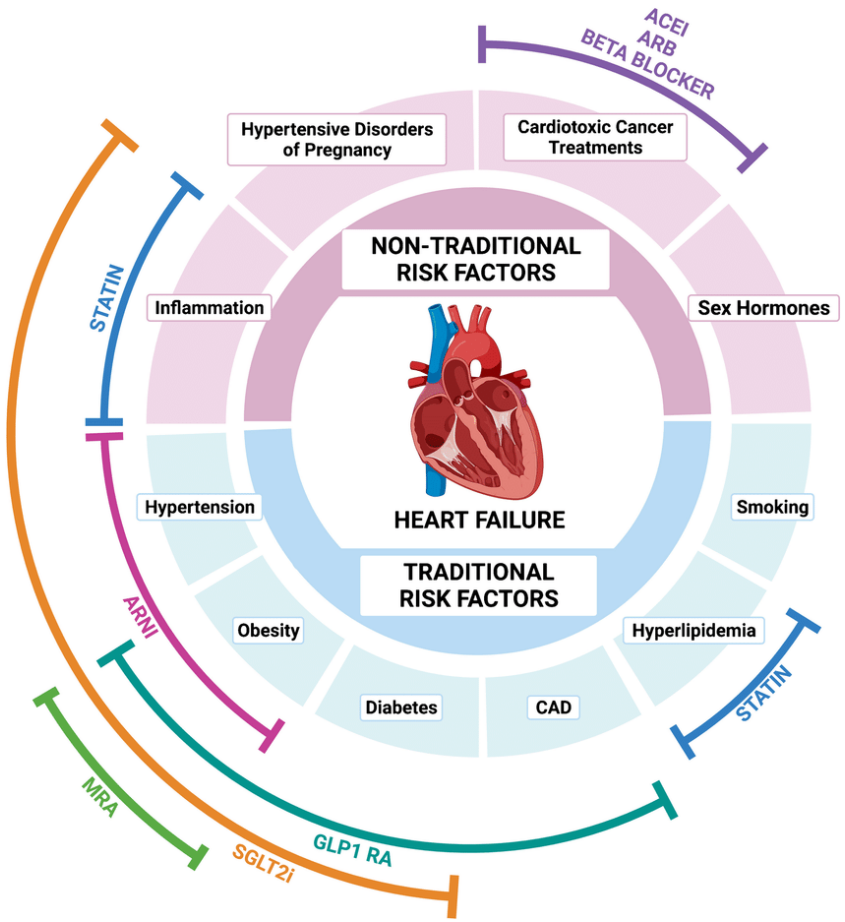
Cittadini A et al. Eur J Prev Cardiol 2022

all-cause mortality or Cardiovascular hospitalization in patients with or without (A) insulin signaling impairment [1·34 (1·03-1·73), p=0·03], (B) Type 2 Diabetes (T2D) [1·55 (1·20-2·01), p=0·001], or Homeostatic model assessment for insulin resistance (HOMA-IR) impairment [0·94 (0·74-1·20), p=0·64].

Risk factors for Heart Failure



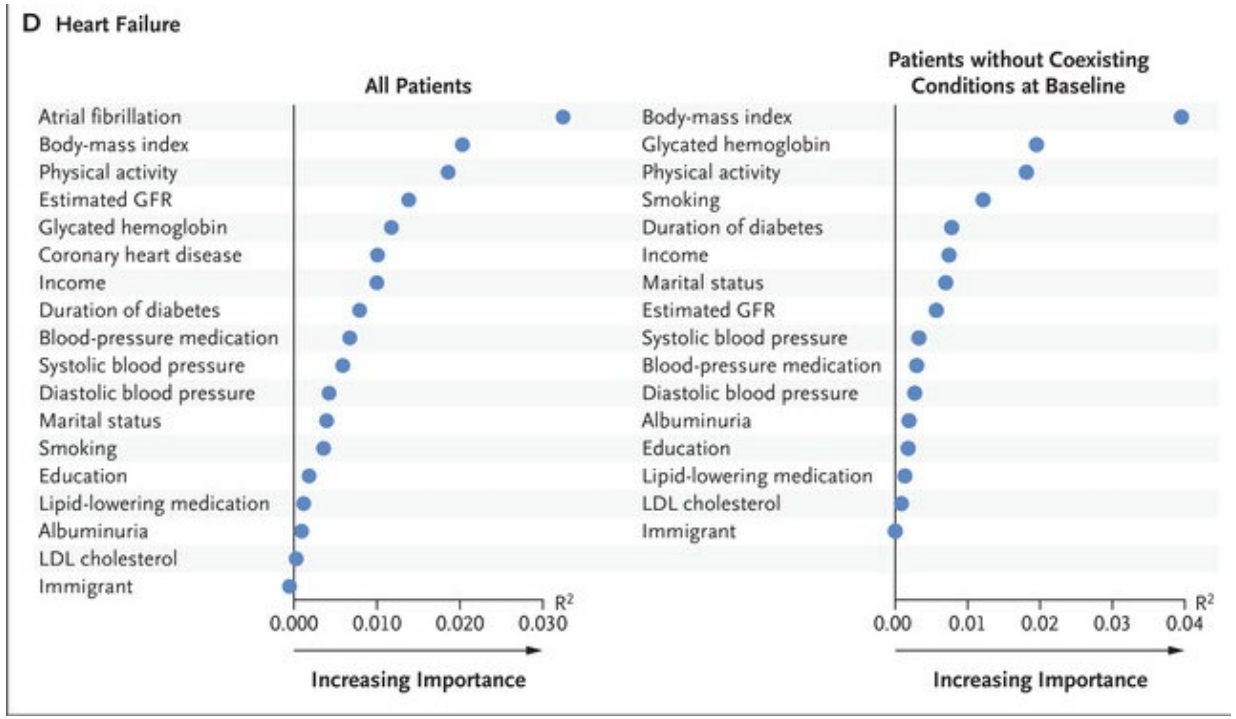
Kou M, et al. J Am Coll Cardiol HF. 2023;11(6):678-688.



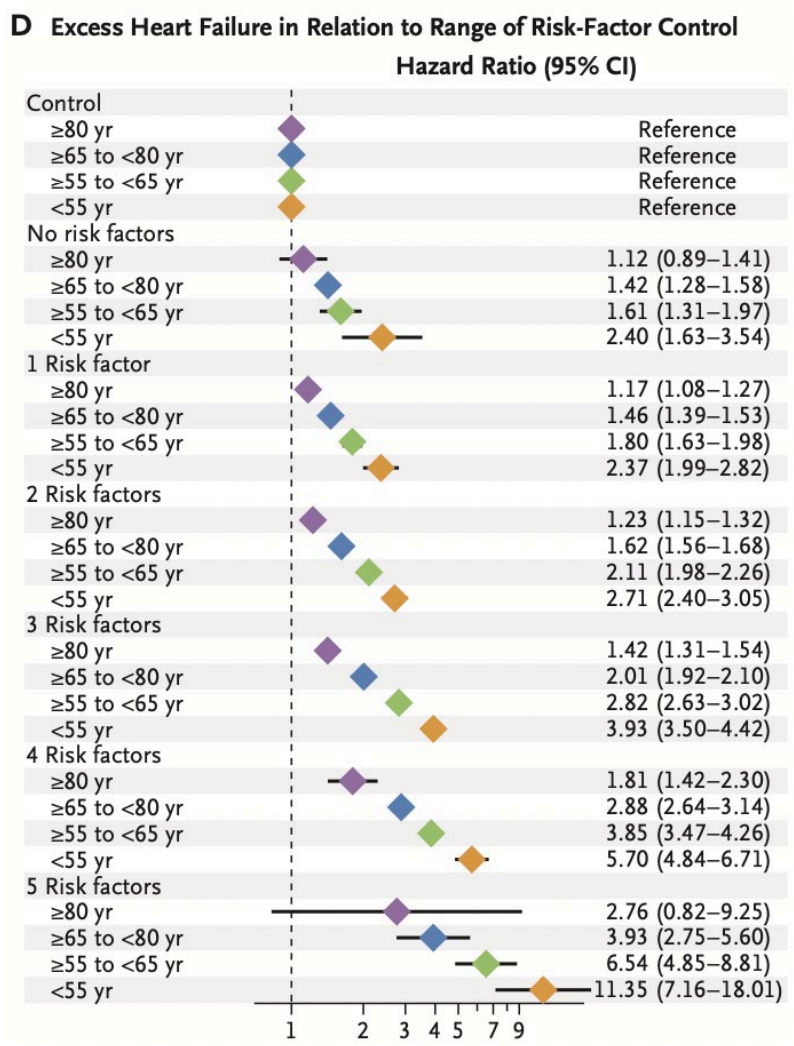
Everit IK et al. Curr Ateroscl Rep 2022

Importance of difference risk factors

271,174 patients with type 2 diabetes who were reg- istered in the Swedish National Diabetes Register and matched them with 1,355,870 controls



Rawshani A et al. NEJM 2018



1) glycated hemoglobin level (≥7.0 %)
2) systolic and diastolic blood pressure (SBP ≥140 mm Hg or DBP ≥80 mmHg)
3) Micro-albuminuria (or albuminuria)
4) smoking
5) LDL cholesterol level (≥ 97 mg/dl).

Prediction of T2DM in HF

WATCH-DM

Age (yrs)	
< 50	0
50 - 54	1
55 - 59	2
60 - 64	3
65 - 69	4
70 - 74	5
≥ 75	6

BMI (kg/m²)	
< 25	0
25 - 34	1
35 - 39	2
≥ 40	5

SBP (mmHg)	
< 100	0
100 - 139	1
140 - 159	2
≥ 160	3

FPG (mg/dL)	
< 125	0
125 - 199	1
200 - 299	2
≥ 300	3

QRS (ms)	
≥ 120	3
< 120	0

Serum Cr (mg/dL)	
< 1.0	0
1.0 - 1.49	2
≥1.50	5

DBP (mmHg)	
< 60	2
60 - 80	1
≥ 80	0

HDL-C (mg/dL)	
< 30	2
30 - 59	1
≥ 60	0

Prior MI	
Yes	3

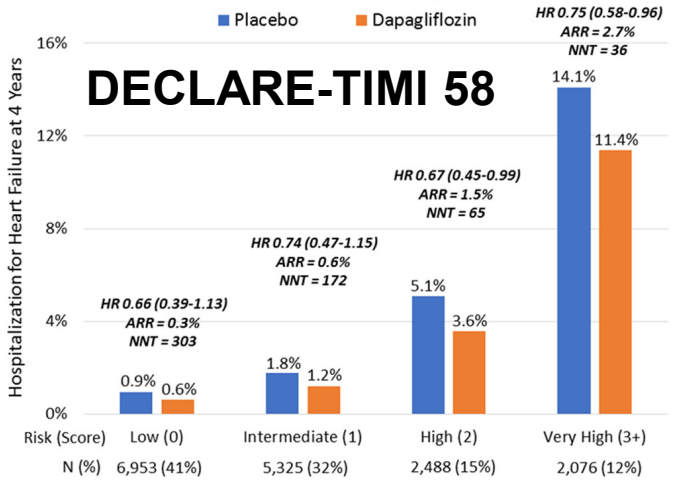
Prior CABG	
Yes	2

Risk Score	HF Risk Group	5-yr HF Risk
≤ 7 points	Very Low	1.1%
8-9 points	Low	3.6%
10 points	Average	4.7%
11-13 points	High	9.2%
≥ 14 points	Very High	17.4%

Segar MW et al. Diabetes Care 2019

TRS-HF$_{DM}$

Risk Indicator	Points
Prior heart failure	2
Atrial fibrillation	1
Coronary artery disease	1
eGFR <60 mL·min^{-1}·1.73 m^{-2}	1
Urine albumin-to-creatinine ratio	
>300 mg/g	2
30–300 mg/g	1



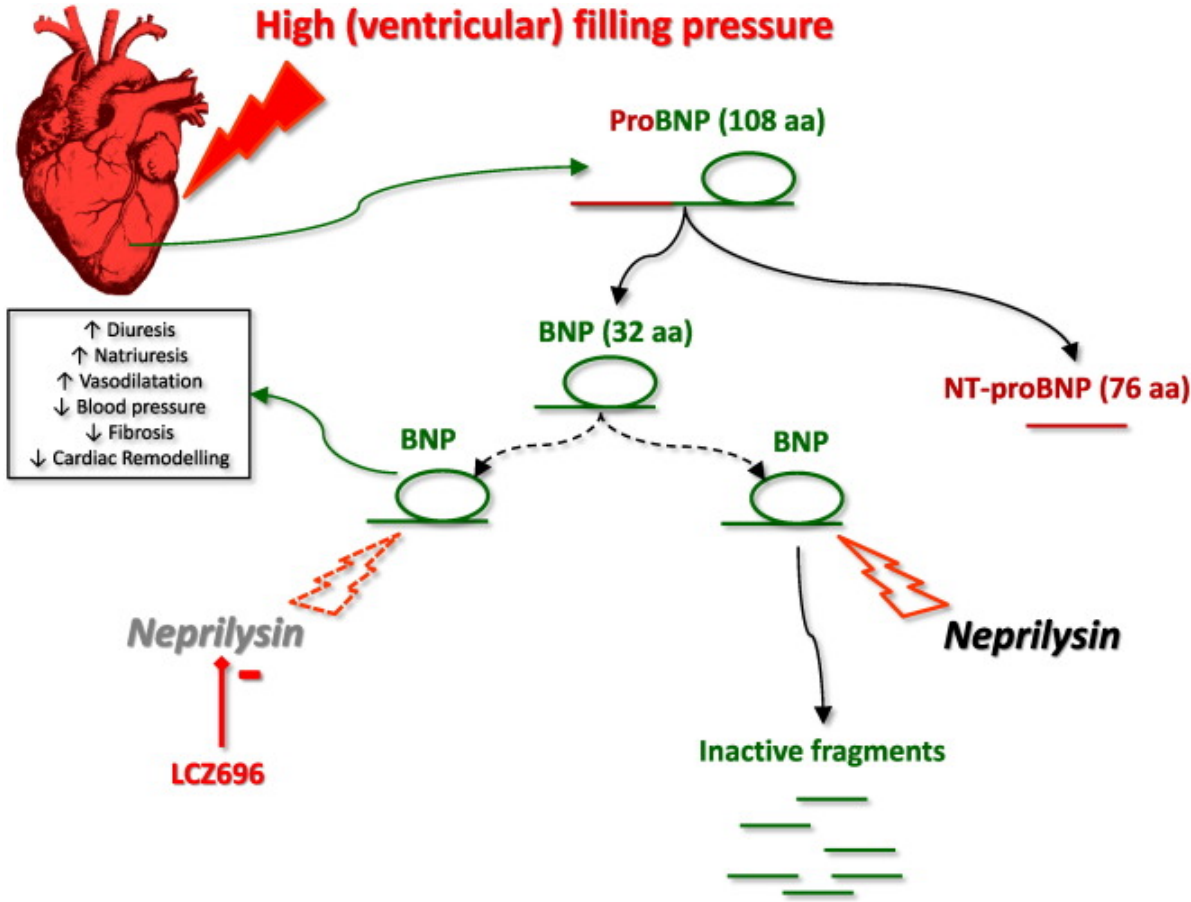
Berg D et al. Circulaltion 2019

Natriuretic peptides in T2DM

Table 1—Biomarkers and optimal cutoffs for incident HF in diabetes

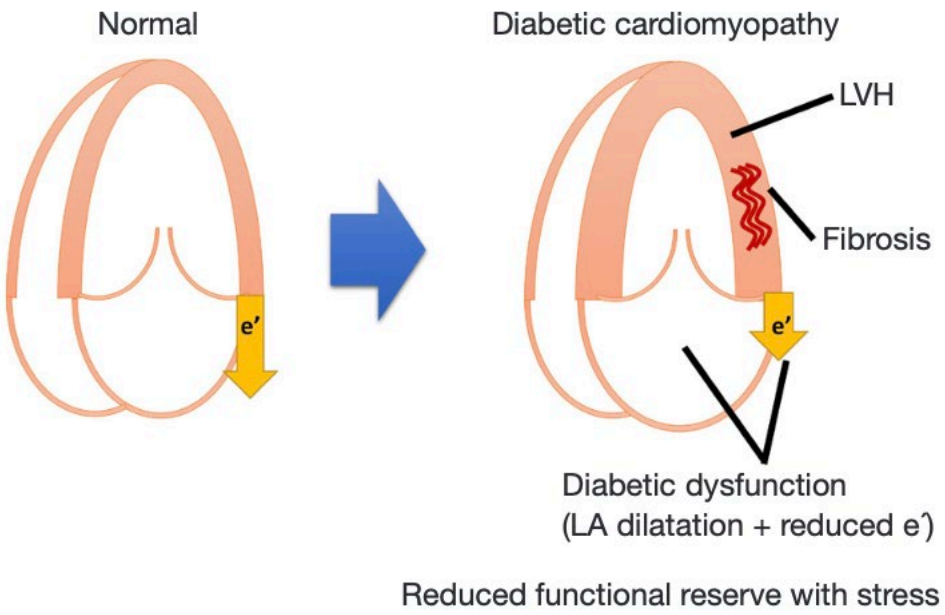
Cohort	Population studied	Biomarker(s) studied	Median follow-up	Outcome	Biomarker thresholds and results
Thousand & 1 Study (58)	1,093 individuals with T1D, ≥18 years old, with no known heart disease at baseline	NT-proBNP	6.3 years	Incident MACE* HF	**NT-proBNP >300 pg/mL:** 41 per 1,000 person-years **NT-proBNP <150 pg/mL:** 10 per 1,000 person-years
Pooled cohort from Atherosclerosis Risk in Communities (ARIC), Dallas Heart Study (DHS), and Multi-Ethnic Study of Atherosclerosis (MESA) (56)	6,799 individuals with dysglycemia (diabetes 33.2%, prediabetes 66.8%), and no CVD at baseline	NT-proBNP, hs-CRP, and hs-cTN	17 years	Incident HF: prediabetes vs. diabetes	hs-cTN ≥6 ng/L NT-proBNP ≥125 pg/mL hs-CRP ≥3mg/L **Biomarker score= 1** HR1.40 (1.09–1.80) vs. 1.82 (1.31–2.53) **Biomarker score = 2** HR 1.83 (1.37–2.45) vs. 2.42 (1.71–3.43) **Biomarker score ≥3** HR 3.68 (2.53–5.34) vs. 4.72 (3.16–7.04)
EXAMINE (57)	5,224 individuals with T2D and a recent acute coronary syndrome event	NT-proBNP	597 days	Incident HHF	**NT-proBNP 154.1–420.4:** HR 3.27 (1.20, 8.92) **NT-proBNP 420.4 to <1,084.0:** HR 7.24 (2.84–18.49) **NT-proBNP ≥1,084.0:** HR 29.3 (12.0–71.5)
St Vincent's Screening to Prevent Heart Failure (STOP-HF) (59)	1,374 participants at HF risk, ~20% with diabetes	BNP	4.2 years	LV dysfunction or newly diagnosed HF for intensive intervention vs. usual care	**At least one BNP >50 pg/mL** OR for intervention 0.55 (0.37–0.82); P =0.003
NT-proBNP Selected PreventiOn of cardiac eveNts in a populaTion of dIabetic patients without A history of Cardiac disease (PONTIAC) (60)	300 individuals with T2D with no history of CVD	NT-proBNP	2 years	HHF or death	**NT-proBNP >125 pg/mL** 65% risk reduction with intervention in primary endpoint 40% risk reduction in HHF
Canagliflozin Cardiovascular Assessment Study (CANVAS) (131,211)	4,330 individuals with T2D and either CVD or multiple risk factors	NT-proBNP	6 years	Incident HHF; HHF or death	**NT-proBNP ≥125 pg/mL** Incident HHF: HR 5.40 (2.67–10.9) HHF or death: HR: 3.52 (2.38–5.20)

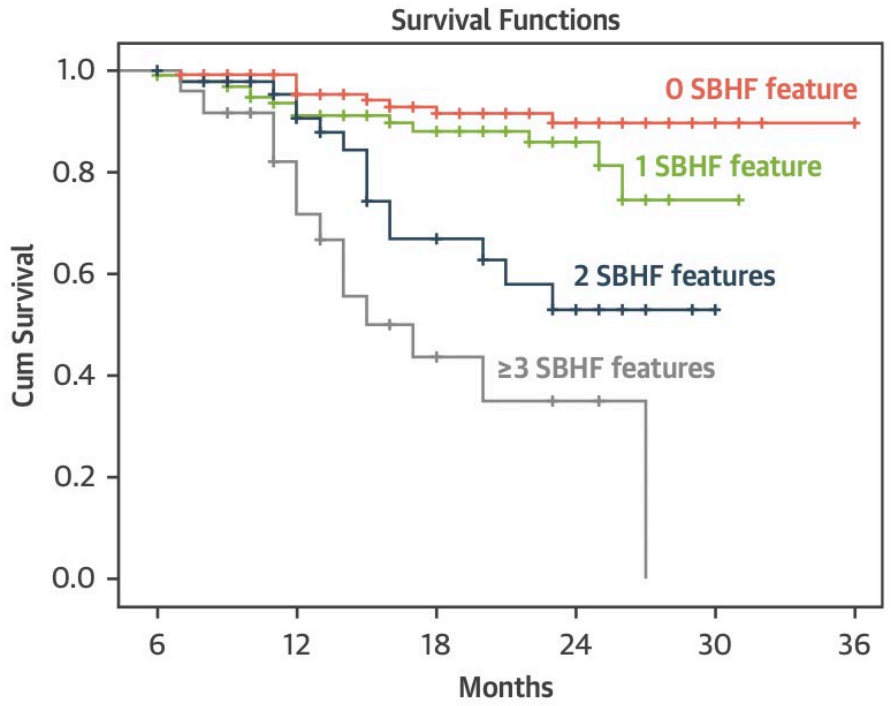
All HR and OR values are shown with 95% CI. HHF, hospitalization for HF; HR, hazard ratio; hs-cTN, high-sensitivity cardiac troponin; LV, left ventricular; OR, odds ratio. *MACE: hospital admissions for acute coronary syndrome, HF, stroke, and cardiac revascularization and death.



Pop-Busui R et al. Diabetes Care 2022

Diabetic Cardiomyopathy





0 SBHF feature	119	115	112	111	111	111
1 SBHF feature	96	92	87	87	85	85
2 SBHF features	47	43	37	34	34	34
=3 SBHF features	23	18	13	11	11	11

Patients with asymptomatic type 2 diabetes mellitus with preserved ejection fraction and no ischemic heart disease recruited from a community-based population. Features considered: left ventricular hypertrophy (LVH), LAE, DD (abnormal E/e0), and GLS (<16%).

Negishi K. Cardiovasc Diag Ther 2018

Wang Y et al. JACC Cardiovasc Imag 2018

Do the “Right” thing!

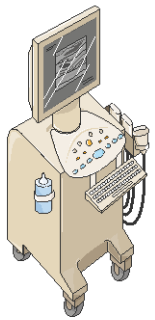
RIGHT-NET
RIGHT HEART INTERNATIONAL NETWORK

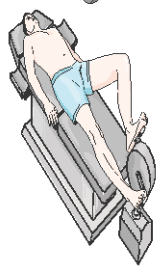
Resting and exercise echocardiography on a semirecumbent cycle ergometer

n.375
Healthy subjects

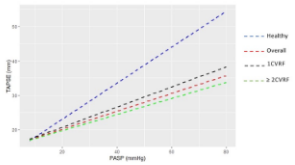
n.158
One CVRF

n.204
Two or more CVRFs

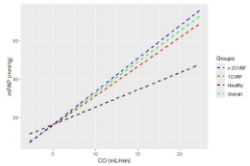




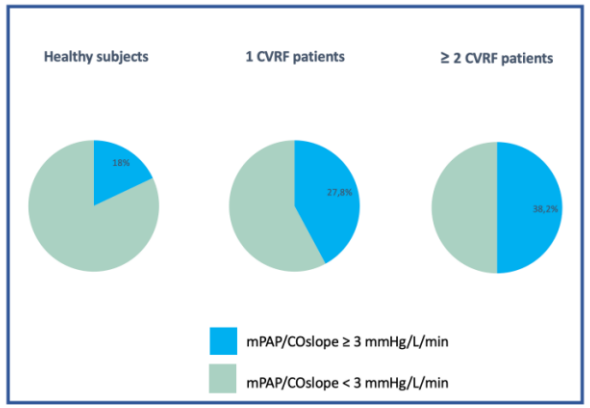
-22% peak TAPSE/PASP in CVRF



2.75-fold increase of mPAP/CO slope in CVRF



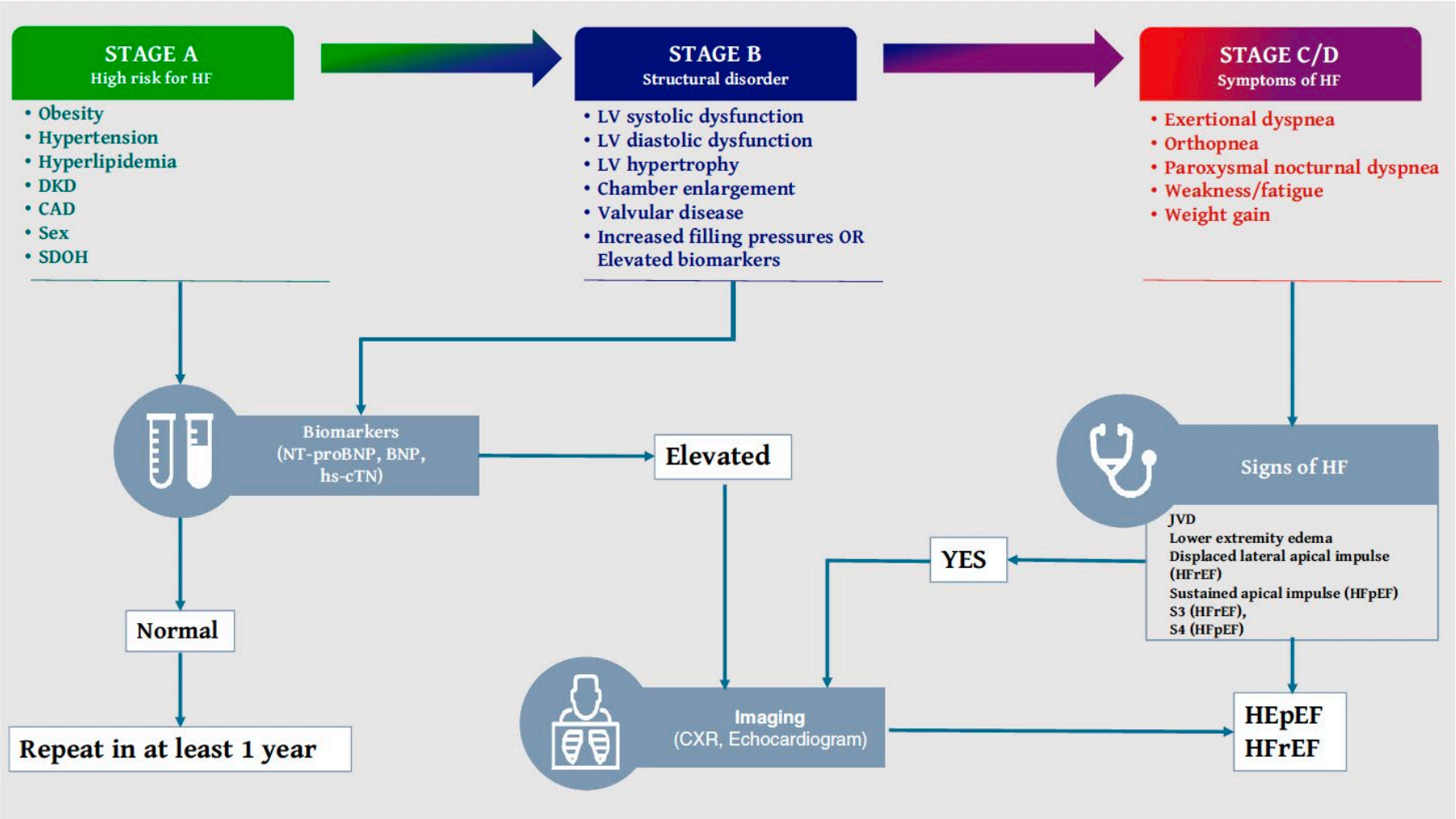
Incremental higher proportion of mPAP/CO slope ≥ 3 in CVRFs



CVRF: Cardiovascular Risk Factors → Hypertension · Diabetes · Dyslipidemia

De Luca M.…Marra AM. Eur J Prev Cardiol 2024

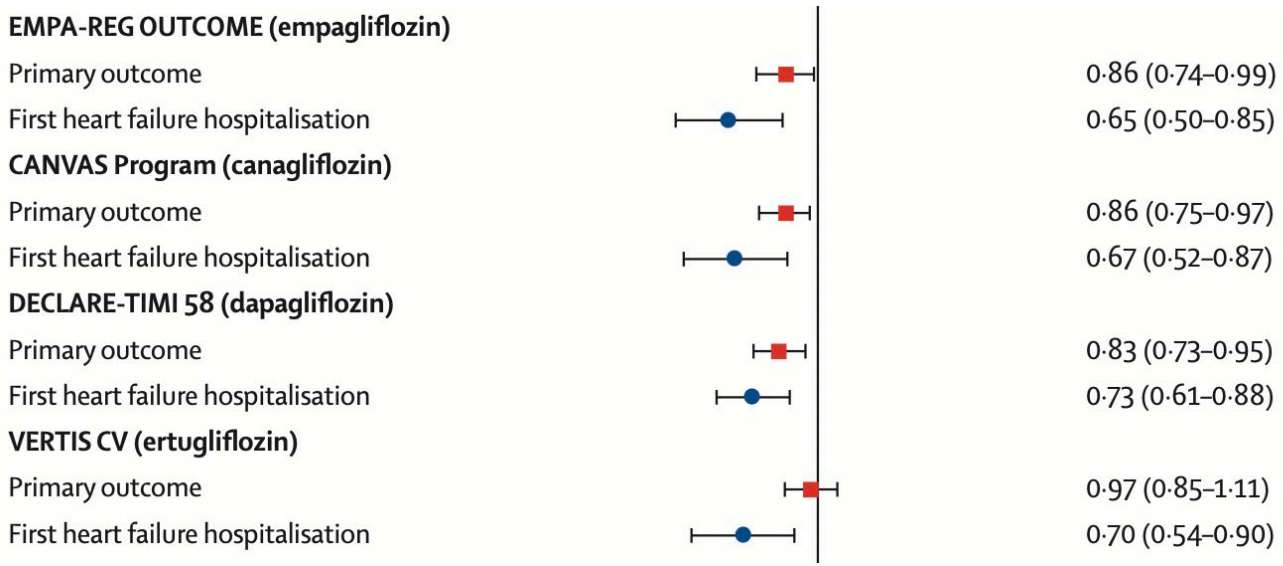
A practical approach



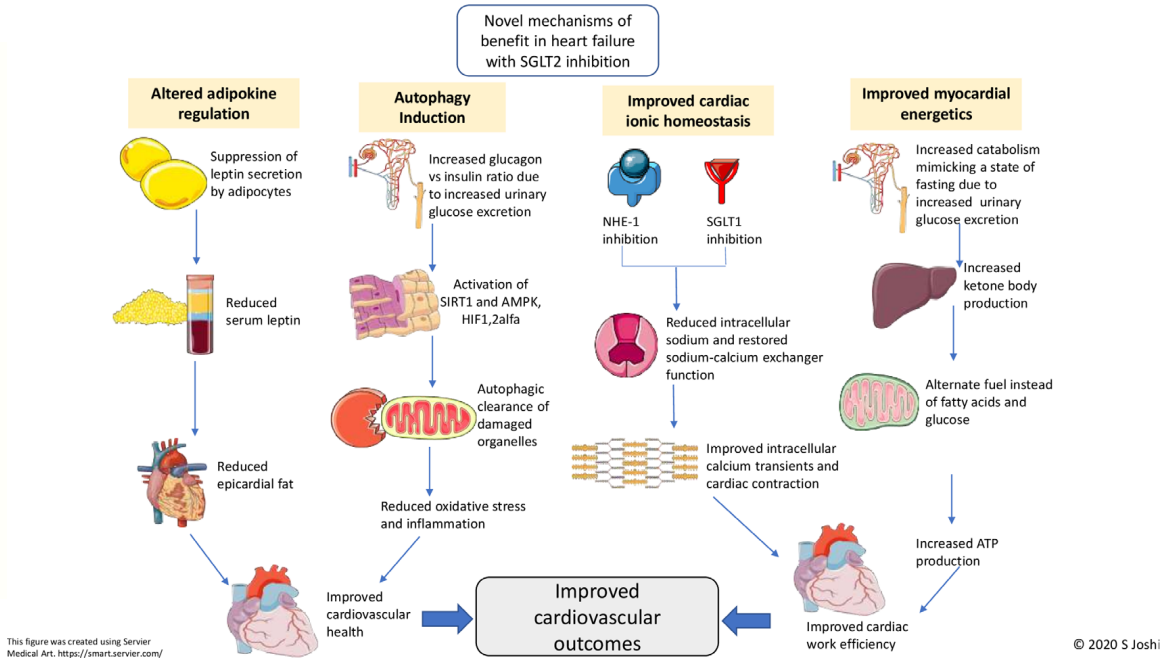
- Measurement of a natriuretic peptide or high-sensitivity cardiac troponin on at least a yearly basis is recommended to identify the presence of stage B HF and to determine risk for progression to symptomatic HF.

Pop-Busui R et al. Diabetes Care 2022

SGLT2i : don’t even need to talk about it!

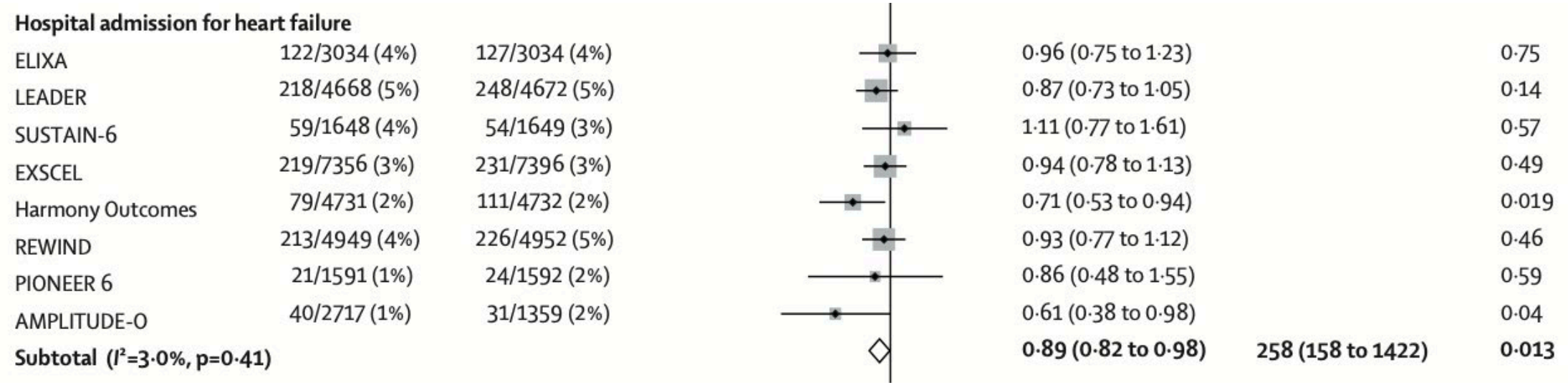


Pandey A et al Lancet 2023



Joshi SS et al. Heart 2021

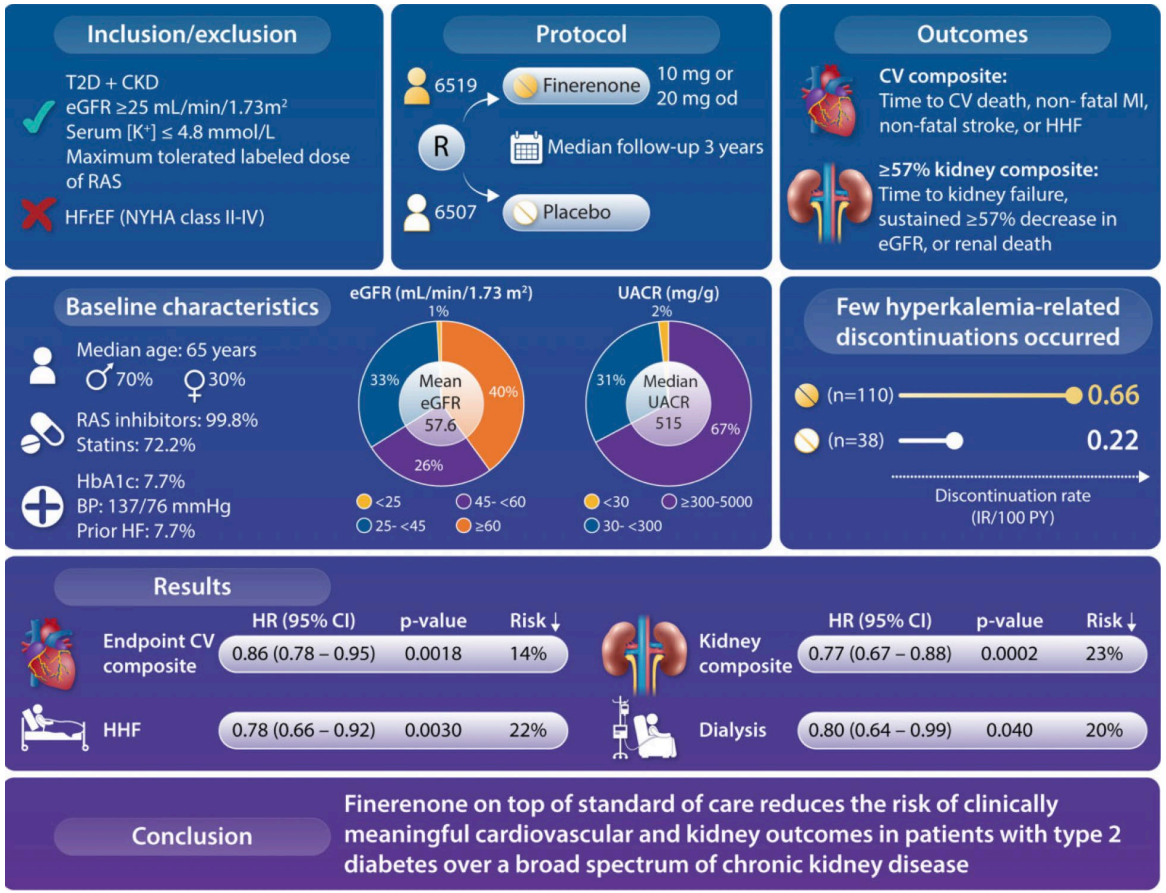
GLP-1ra and HF prevention



Reduction of first hospital admission for heart failure by 11% (HR 0·89 [95% CI 0·82–0·98]; p=0·013)

Joshi SS Sattar N Lancet Diabetes Endocrinol 2021

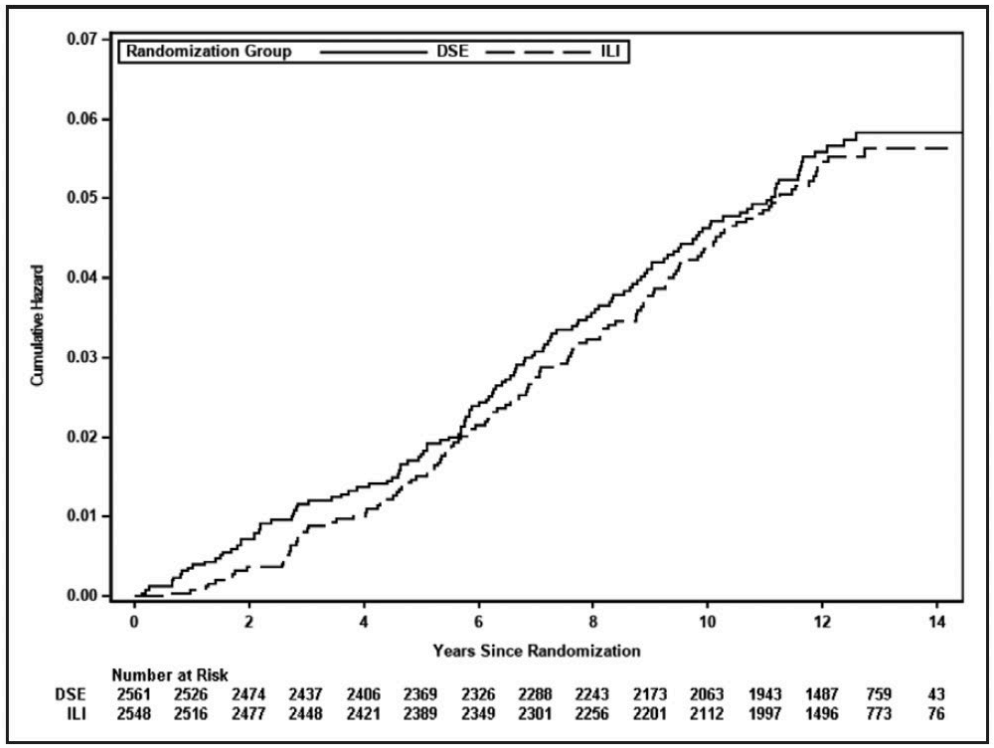
Mineralcorticoid Receptor Antagonists



10.14 Patients with hypertension who are not meeting blood pressure targets on three classes of antihypertensive medications (including a diuretic) should be considered for mineralocorticoid receptor antagonist therapy. **B**

Agarwal R et al. Eur Heart J 2022

Prevent HF in T2DM: lifestyle intervention



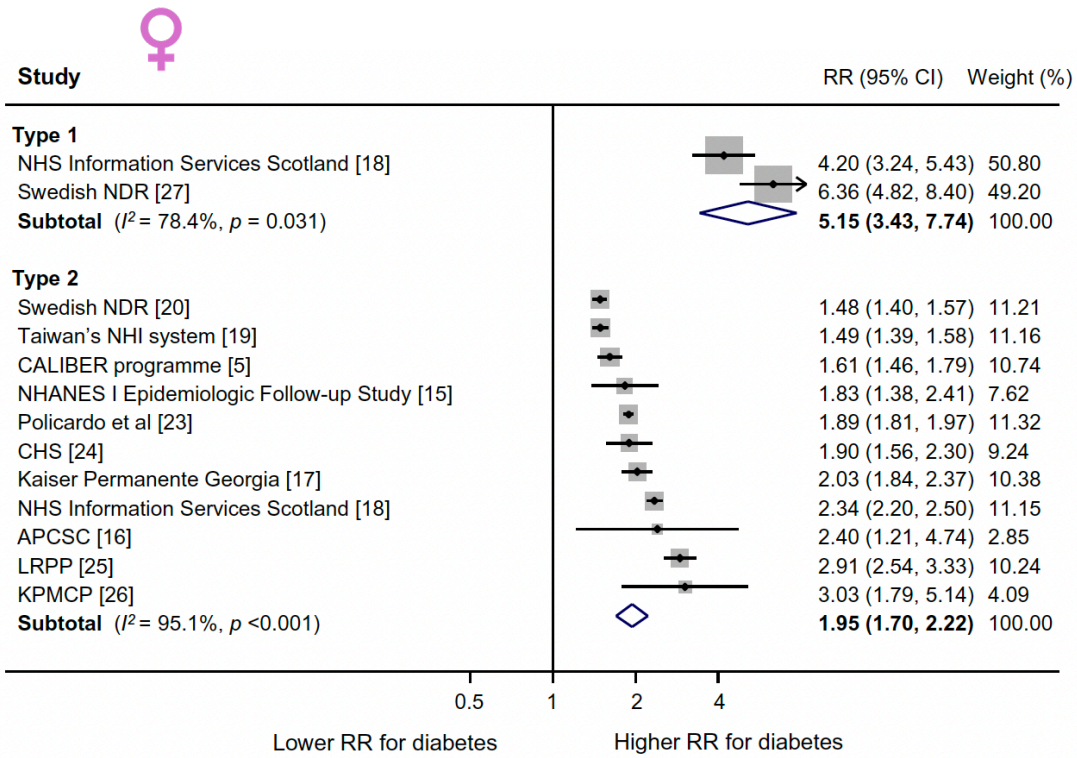
Pandey A et al. Circulation 2020

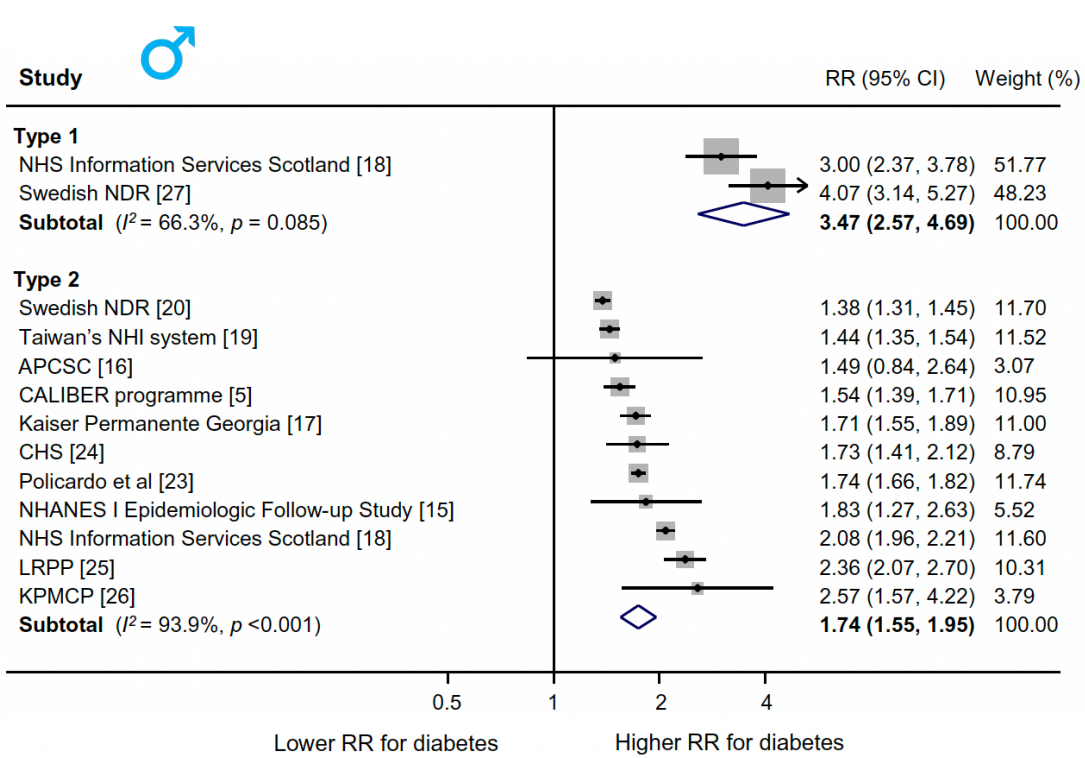
	Person-years	Event rate per 1000 person-years	Model 1		Model 2	
			HR (95% CI)	*P* value	HR (95% CI)	*P* value
Per 10% decrease in predicted fat mass from baseline to 1-year follow-up						
Overall HF	55 847	4.19	0.74 (0.64–0.86)	<0.001	0.80 (0.68–0.95)	0.01
HFpEF	55 715	2.08	0.72 (0.58–0.89)	0.002	0.78 (0.61–0.996)	0.046
HFrEF	55 715	1.72	0.72 (0.57–0.90)	0.004	0.76 (0.59–0.97)	0.03
Per 10% decrease in predicted lean mass from baseline to 1-year follow-up						
Overall HF	55 847	4.19	0.64 (0.50–0.81)	<0.001	0.75 (0.55–1.02)	0.06
HFpEF	55 715	2.08	0.57 (0.40–0.81)	0.002	0.68 (0.44–1.06)	0.09
HFrEF	55 715	1.72	0.72 (0.49–1.04)	0.08	0.88 (0.54–1.42)	0.60
Per 10% decrease in waist circumference from baseline to 1-year follow-up						
Overall HF	55 845	4.19	0.75 (0.61–0.93)	0.007	0.77 (0.62–0.95)	0.02
HFpEF	55 713	2.08	0.62 (0.46–0.83)	0.002	0.61 (0.44–0.83)	0.002
HFrEF	55 713	1.72	0.86 (0.62–1.18)	0.34	0.89 (0.64–1.24)	0.49

Patel KV et al. Circulation 2020

Type 1 Diabetes is even more dangerous

Data from 47 cohorts, involving 12,142,998 individuals





Ohkuma T et al. Diabetologia 2019

Type 1 Diabetes prompts attention

Table 3. Adjusted Hazard Ratios for All Outcomes.*

Outcome	Patients with Type 1 Diabetes	Matched Controls	Patients with Type 1 Diabetes vs. Matched Controls		Patients with Type 2 Diabetes	Matched Controls	Patients with Type 2 Diabetes vs. Matched Controls	
	Hazard Ratio during a 10-Year Period		Hazard Ratio†	P Value for Interaction‡	Hazard Ratio during a 10-Year Period		Hazard Ratio†	P Value for Interaction‡
Death								
From any cause	0.71 (0.66–0.78)	0.77 (0.72–0.83)	1.08 (0.99–1.18)	0.09	0.79 (0.78–0.80)	0.69 (0.68–0.70)	0.87 (0.85–0.89)	<0.001
From cardiovascular disease	0.58 (0.50–0.68)	0.62 (0.53–0.72)	1.06 (0.89–1.26)	0.53	0.54 (0.52–0.55)	0.50 (0.49–0.52)	0.94 (0.90–0.98)	0.004
From coronary heart disease	0.56 (0.48–0.67)	0.55 (0.46–0.65)	0.97 (0.80–1.18)	0.74	0.52 (0.50–0.53)	0.48 (0.46–0.50)	0.94 (0.89–0.98)	0.009
Hospitalization								
For cardiovascular disease	0.64 (0.56–0.72)	0.91 (0.82–1.01)	1.43 (1.25–1.62)	<0.001	0.56 (0.54–0.57)	0.71 (0.68–0.73)	1.27 (1.22–1.32)	<0.001
For acute myocardial infarction	0.63 (0.55–0.73)	0.87 (0.75–1.00)	1.37 (1.16–1.62)	<0.001	0.50 (0.48–0.52)	0.62 (0.59–0.65)	1.24 (1.18–1.31)	<0.001
For coronary heart disease	0.56 (0.50–0.64)	0.78 (0.70–0.87)	1.39 (1.22–1.58)	<0.001	0.55 (0.53–0.57)	0.67 (0.65–0.69)	1.22 (1.17–1.27)	<0.001
For stroke	0.65 (0.55–0.77)	0.95 (0.82–1.10)	1.47 (1.22–1.76)	<0.001	0.61 (0.59–0.63)	0.76 (0.73–0.79)	1.24 (1.18–1.31)	<0.001
For heart failure	0.87 (0.74–1.01)	1.01 (0.86–1.18)	1.16 (0.97–1.40)	0.10	0.71 (0.69–0.73)	0.84 (0.81–0.87)	1.18 (1.12–1.23)	<0.001

* The analysis based on Cox regression was adjusted for time-updated age, time-updated time period, sex, and interaction terms.
† Values are ratios of hazard ratios for patients with type 1 diabetes or type 2 diabetes as compared with controls, during a 10-year time period. A value above 1 means a greater event-rate reduction, and a value below 1 a lesser event-rate reduction, in the patients with diabetes than in the matched controls (see the Supplementary Appendix).
‡ The P value is for the interaction between time period and group — that is, patients with either type 1 diabetes or type 2 diabetes and matched controls.

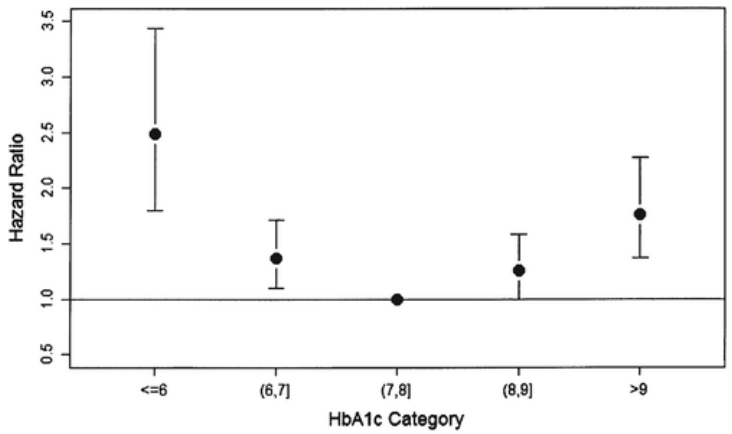
1) Lack of specific risk stratification
2) Lack of data on biomarkers
3) Warning on SGLT2i

Rawshani A et al. New Engl J Med 2017

Heart Failure and Diabetes: a dangerous liaison

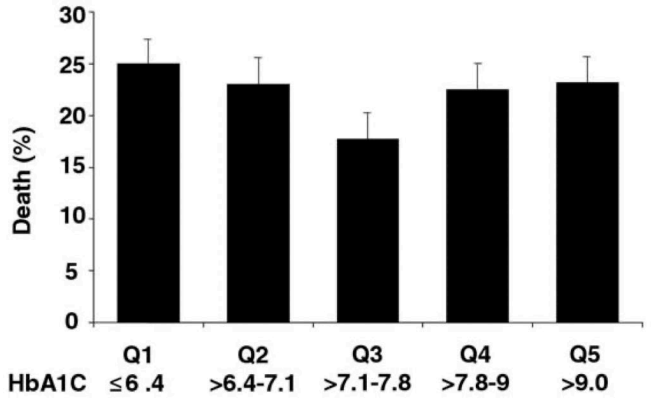
1. How to **prevent** development of Heart Failure in patients with Diabetes
2. How to **handle glycemic control** in Heart Failure patients
3. How to **manage Heart Failure** in patients with Diabetes

Glycemic control in HF and Diabetes



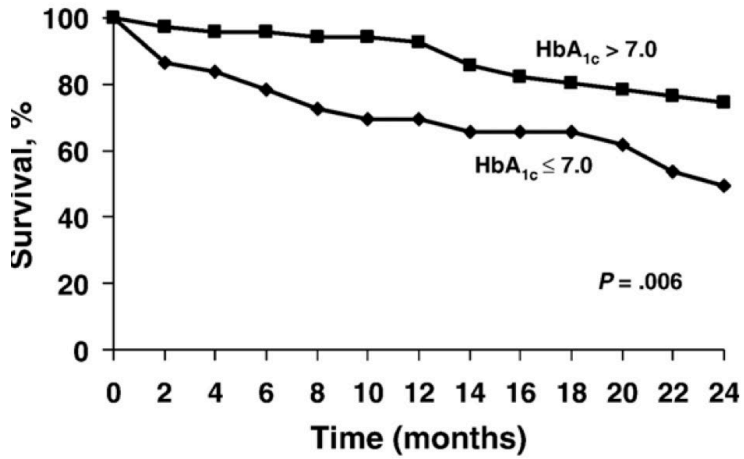
1447 patients
NYHA I-III

Elder DJH et al. Eur J Heart Fail 2015



21,794 patients
NYHA I-III

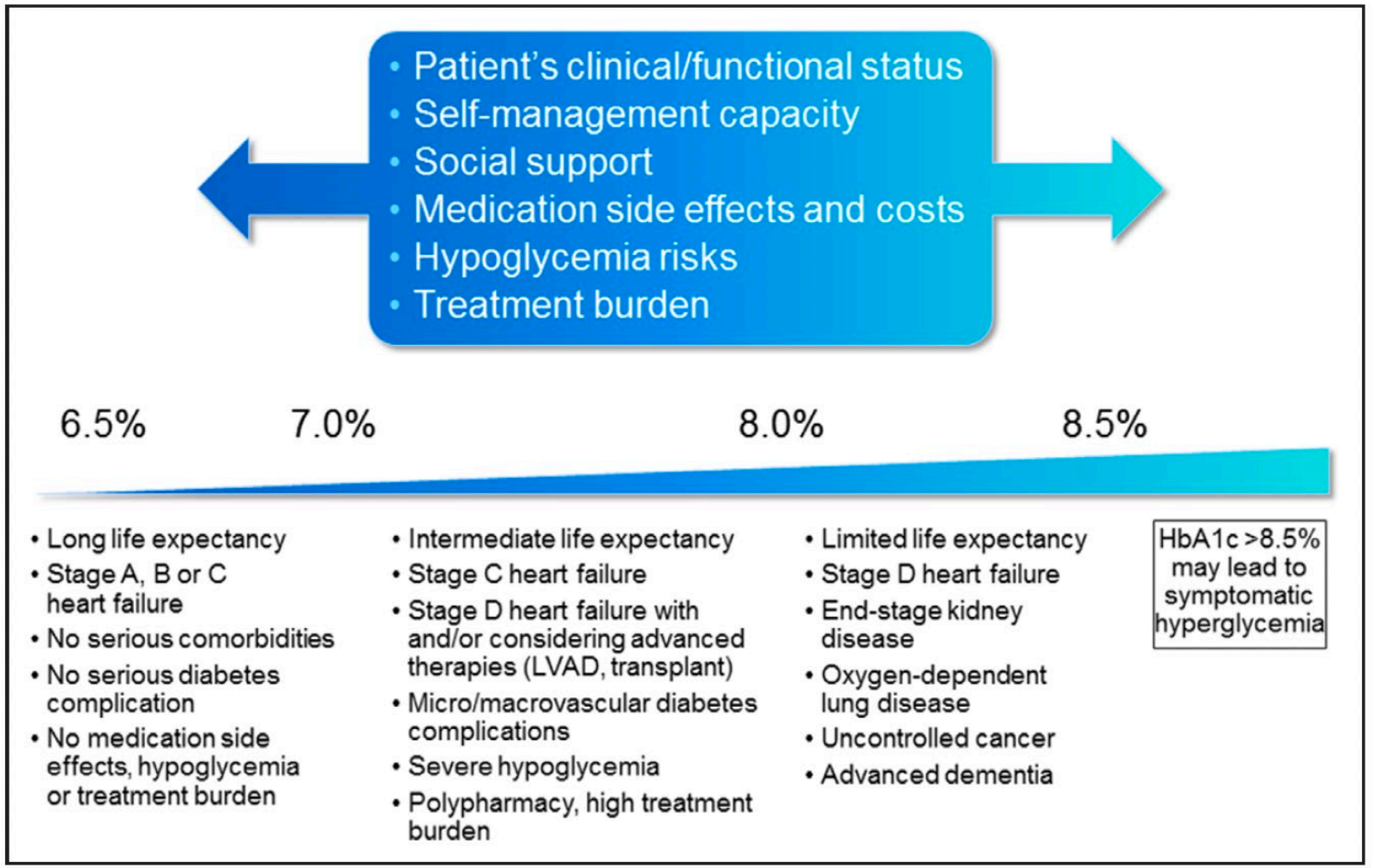
Aguillar D et al. J Am Coll Cardiol 2009



127 advanced HF

Eshaghian S et al. Am Heart J 2006

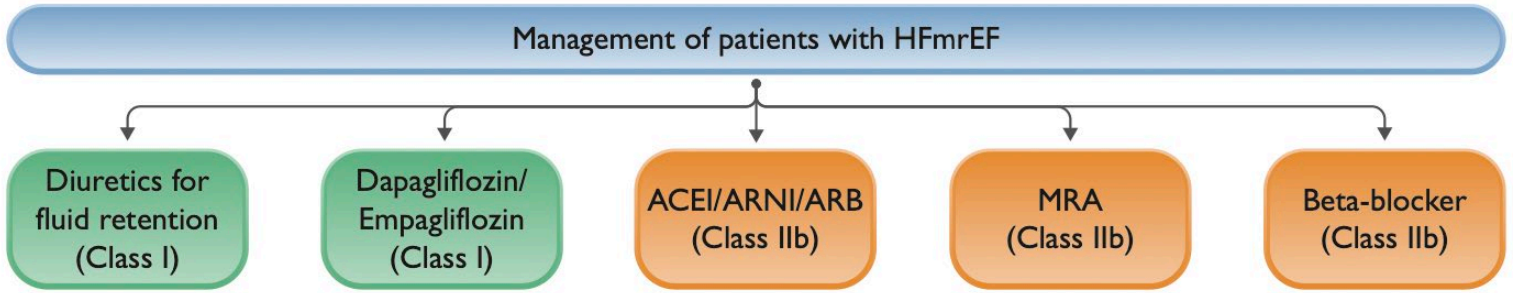
Glycemic control in HF and Diabetes



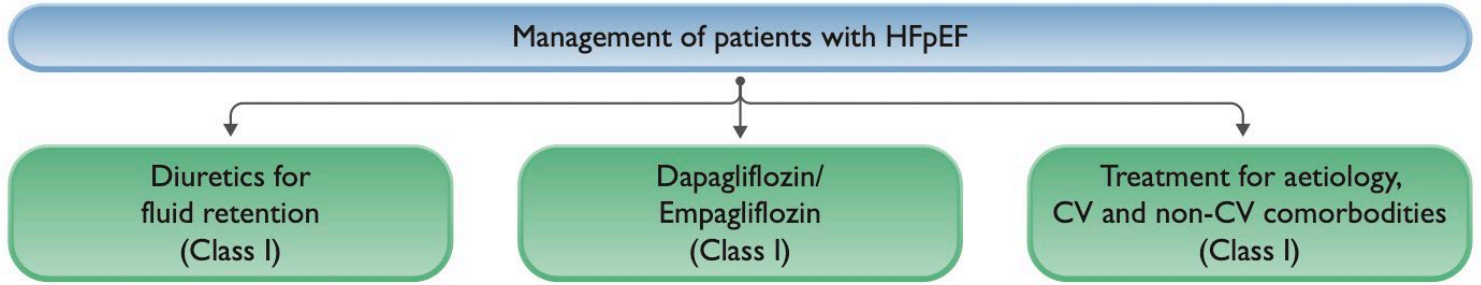
Dunlay SM et al. AHA Statement on Diabetes in Heart Failure Circulation 2019

SGLT2i: should we really talk about them?

Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[108,109]	I	A	**2021**

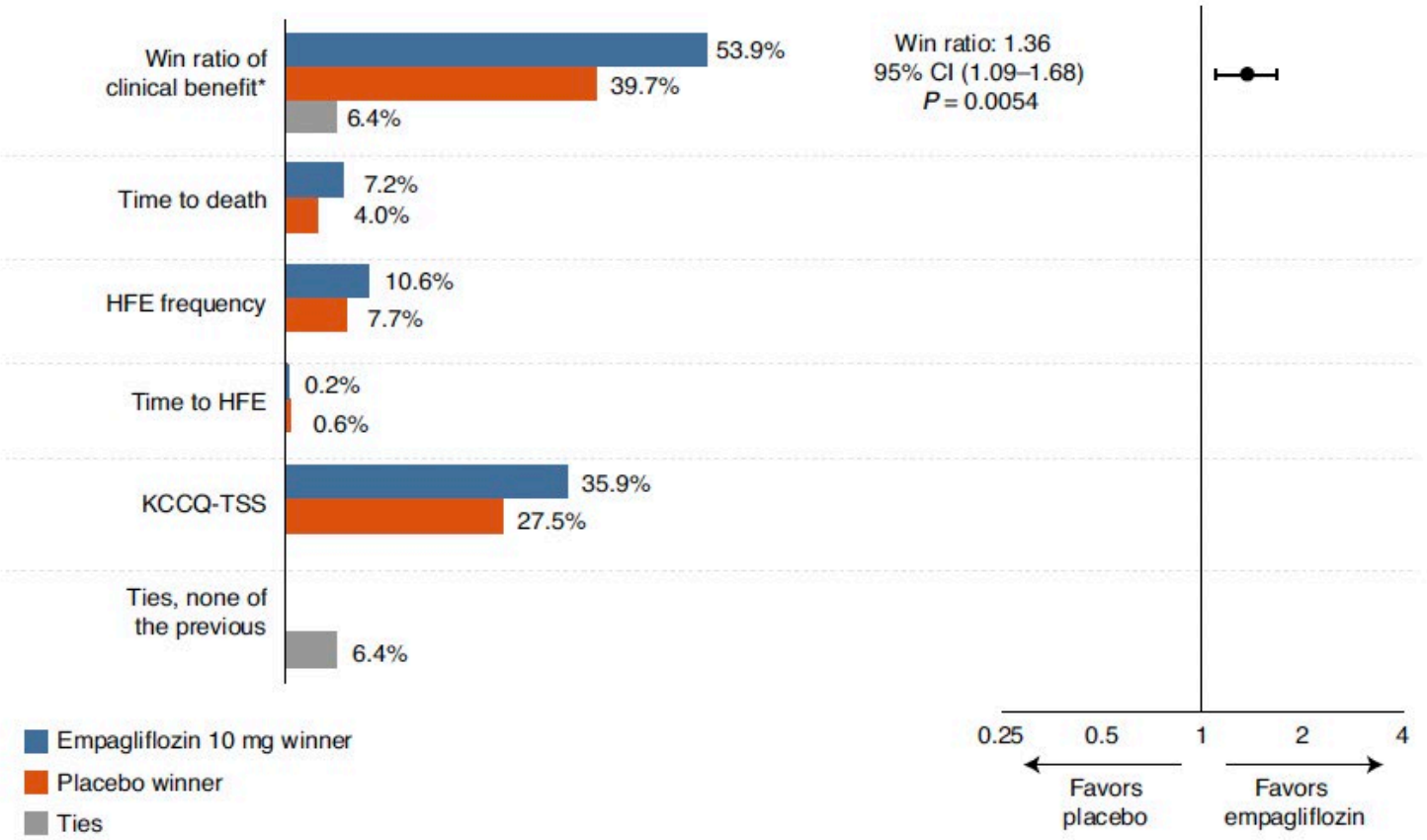


2023



2023

SGLT2i in HF: When? ASAP!



530 patients with a **primary diagnosis of acute de novo** or **decompensated chronic heart failure** regardless of left ventricular ejection fraction were randomly assigned to receive **empagliflozin 10 mg once daily or placebo**. Patients were randomized in-hospital when clinically stable and were treated for up to 90 days. The **primary outcome** of the trial was clinical benefit, defined as a hierarchical composite (**win ratio**).

Voors AA et al. Nature Medicine 2022

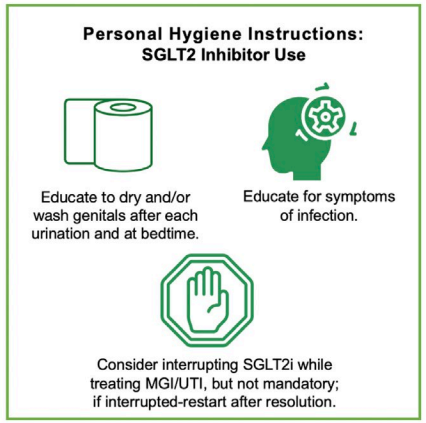
SGLT2i: should we really talk about them?

Table 1 Major SGLT2i trials in patients with HF and reported incidence of UTIs/MGIs

Trial	DAPA-HF[3]		DELIVER[4]		EMPEROR-Reduced[2]		EMPEROR-Preserved[1]		SOLOIST-WHF[5]		EMPULSE[6]	
	SGLT2i	Placebo	SGLT2i	Placebo	SGLT2i	Placebo	SGLT2i	Placebo	SGLT2i	Placebo	SGLT2i	Placebo
EF (%)	≤40%		>40%		≤40%		>40%		Any LVEF		Any LVEF	
Participants	2373	2371	3131	3132	1863	1867	2997	2991	605	611	265	265
Age (yrs)	66±11	67±11	72±10	72±10	67±11	67±11	72±9	72±10	69 (63–76)	70 (64–76)	71 (62–78)	70 (59–78)
Female (%)	24	23	44	44	24	24	45	45	33	35	33	35
BMI (kg/m^2)	28±6	28±6	30± 6	30 ± 6	28±6	28±5	30±6	30±6	30 (26–34)	31 (27–35)	28 (25–33)	29 (25–34)
eGFR (ml/min/1.73 m^2)	66±20	66±19	61±19	61±19	62±22	62±22	61±20	61±20	49 (40-34)	51 (41-65)	50 (36–65)	54 (39–70)
HF Hospitalization (%)	9.7	13.4	10.5	13.3	13.2	18.3	8.6	11.8	40.4	63.9	5.3**	4.5**
CV death (%)	9.6	11.5	7.4	8.3	10	10.8	7.3	8.2	10.6	12.5	12.8*	18.5*
Death from any cause (%)	11.6	13.9	15.9	16.8	13.4	14.2	14.1	14.3	13.5	16.3	4.2	8.3
Diabetes (%)	42	42	45	45	50	50	49	49	100	100	47	44
Exclusion for Hx of UTI/MGI	No		No		No		No		No		No	
MGI AEs (%)	-	-	-	-	1.7	0.6	2.2	0.7	0.8	0.2	-	-
Complicated MGI AEs (%)	-	-	-	-	0.3	0.3	0.3	0.3	-	-	-	-
UTI AEs (%)	0.9	1.2	1	1	4.9	4.5	9.9	8.1	8.6	7.2	4.2	6.4
Complicated UTI AEs (%)	-		-	-	1	0.8	1.9	1.5	-	-	-	-
UTI/MGI Causing Discontinuation (%)			0.4	0.2	-	-	-	-	-	-	2.3	1.5

*CV death or HF event until end-of-trial visit, (%).

**Hospitalizations for heart failure until 30 days after initial hospital discharge (%).AE, adverse event; BMI, body mass index; CV, cardiovascular; EF, ejection fraction; eGFR, estimated glomerular filtration rate; Hx, history; MGI, mycotic genital infections; UTI, urinary tract infection.Complicated UTI and MGI were based on a narrow BlcMQ (Boehringer Ingelheim customized MedDRA query) as defined in EMPEROR-Preserved and EMPEROR-Reduced protocols and included prespecified terms sensitive to capturing possible UTI/MGI events. The analyses of adverse events were based on the number of patients with AEs and not on the number of AEs.[1,2]



Assessing Risk of MGI and UTI Before Starting SGLT2 Inhibitors

Initiate:*	Do Not Initiate:
Demographics	Current UTI/MGI infection
- Female* - Uncircumcised male*	ADPKD
- Obesity - Older Individuals - Non-white	Recurrent MGI or UTI (special attention to MDRO)Δ
Increased Estrogen Levels	ΔRefer to specialist for guidance
- Postmenopausal Estrogen Therapy	
Medications	
- Antimicrobials - Corticosteroids	
Immunosuppression	
- HIV - Chemotherapy/Steroids	
Urologic Procedures	
- Orthotopic Bladder Substitution* - Urinary Outlet Obstruction*	
- Artificial Urinary Sphincter - Implantable Penile Prosthesis	
Type 2 Diabetes Mellitus*	
History of Fournier's Gangrene	

*Risk Factors for UTI/MGI from SGLT2 inhibitor Use
*Practice Shared Decision Making

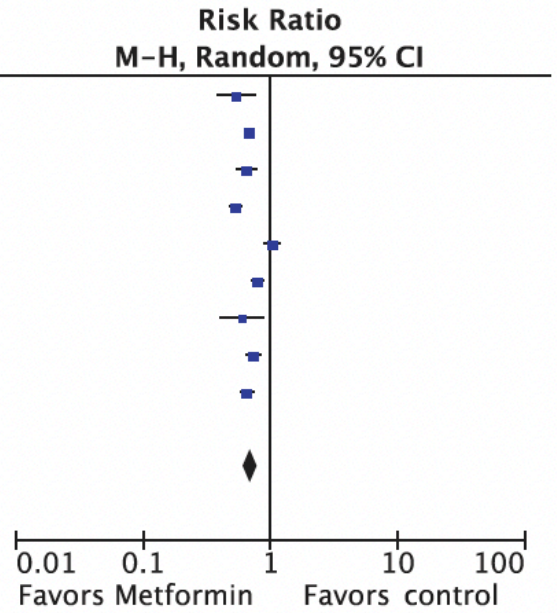
Duvalyan A et al. J Cardiac Fail 2022

Back to the future: Metformin!

Study or Subgroup	Metformin Events	Metformin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Eurich	29	208	200	773	7.0%	0.54 [0.38, 0.77]	2005
Masoudi	460	1861	4345	12069	13.3%	0.69 [0.63, 0.75]	2005
Inzucchi	93	406	768	2184	11.0%	0.65 [0.54, 0.79]	2005
Andersson	239	688	2344	3615	12.9%	0.54 [0.48, 0.60]	2010
Roussel	221	1220	488	2790	12.0%	1.04 [0.90, 1.20]	2010
Evans	137	205	183	217	12.8%	0.79 [0.71, 0.89]	2010
Shah	22	99	112	302	6.2%	0.60 [0.40, 0.89]	2010
MacDonald	155	376	733	1306	12.4%	0.73 [0.65, 0.84]	2010
Aguilar	246	1561	1117	4624	12.5%	0.65 [0.58, 0.74]	2011
Total (95% CI)		**6624**		**27880**	**100.0%**	**0.69 [0.61, 0.79]**	
Total events	1602		10290				

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 63.59$, df = 8 ($P < 0.00001$); $I^2 = 87\%$

Test for overall effect: $Z = 5.45$ ($P < 0.00001$)



34 504 patients with diabetes mellitus and HF

Eurich DT et al. Circ Heart Fail 2013

GLP1-ra (Liraglutide) in HFrEF

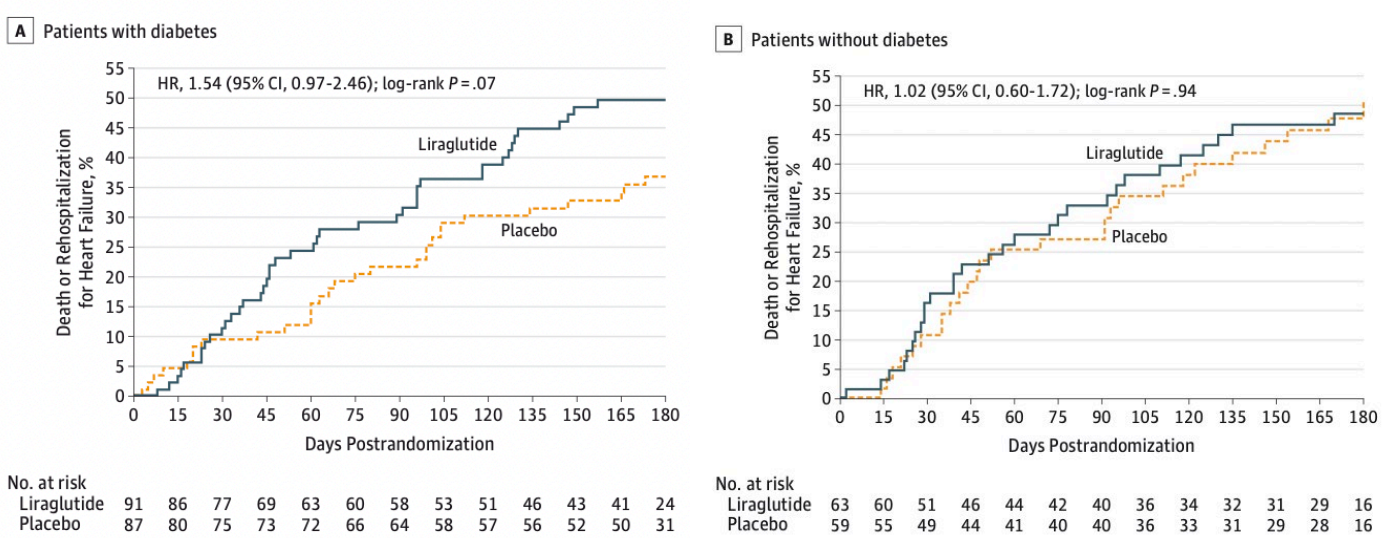
LIVE trial (247 HFrEF pt)

	Liraglutide *n* (%)	Placebo *n* (%
Cardiac		
Death due to ventricular tachycardia	1	0
Ventricular tachycardia	3	1
Atrial fibrillation (DC-converted)	4	2
Acute coronary syndrome	3	0
Worsening of CHF	1	0
Subtotal	12 (10)*	3 (3)
Gastrointestinal		
Gastritis	0	1
Subtotal	0	1 (1)
Central nervous system		
Apoplexy	1	2
TCI	1	0
Dizziness	0	1
Subtotal	2 (2)	3 (3)

*p <0.05

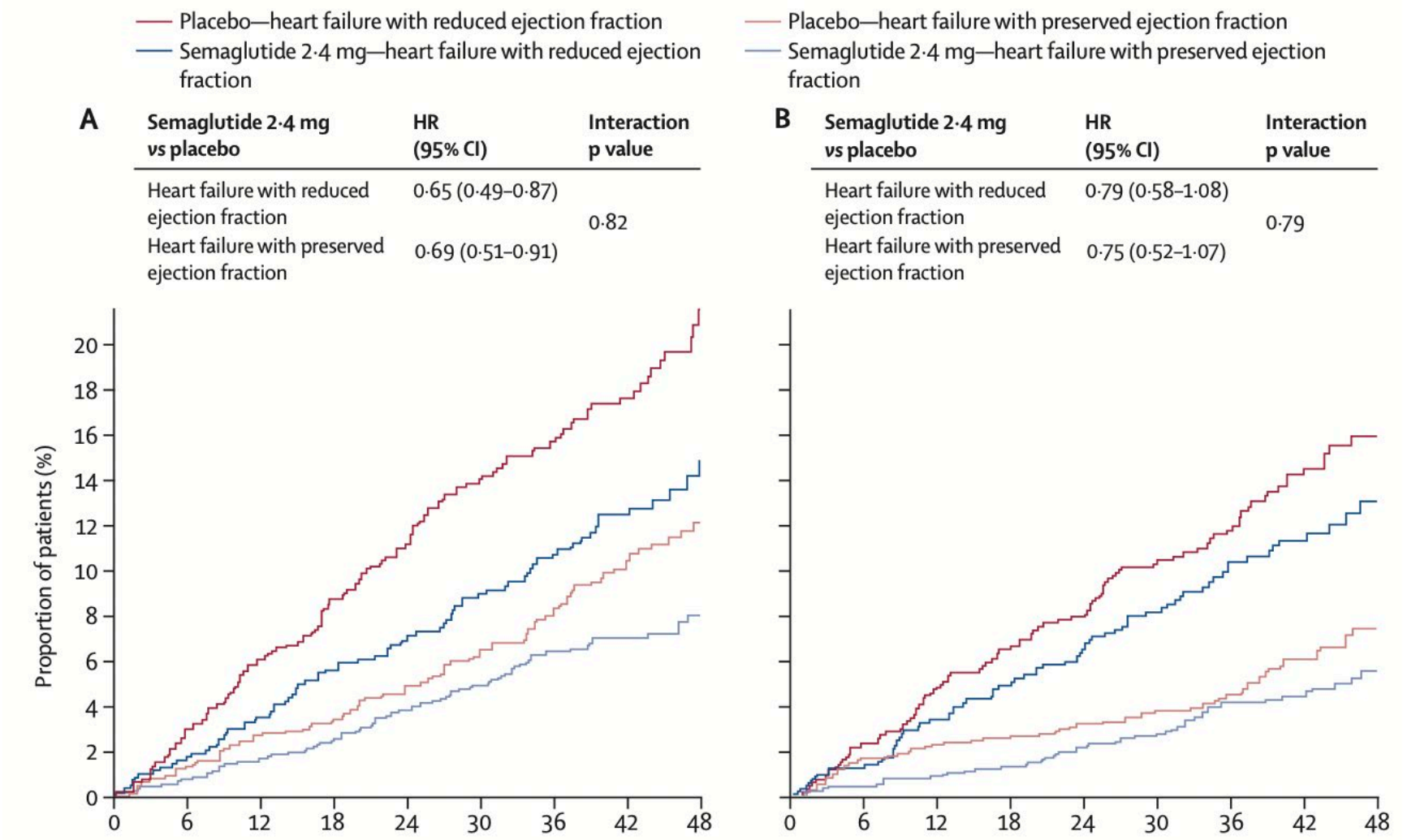
Jorsal A et al. Eur J Heart Fail 2016

FIGHT trial (300 HFrEF pt)



Magullies K et al JAMA2016

GLP1-ra (Semaglutide) in HFrEF



Treatment with **semaglutide** resulted in improved outcomes in both the **heart failure with reduced ejection fraction** (HR 0·65, 95% CI 0·49–0·87 for MACE; 0·79, 0·58–1·08 for the composite heart failure endpoint) and **heart failure with preserved ejection fraction groups** (0·69, 0·51–0·91 for MACE; 0·75, 0·52–1·07 for the composite heart failure endpoint)

Deanfield J et al. Lancet 2024

GLP1-ra (Semaglutide) in HFpEF: The STEP-HF trials

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

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

Kosiborod MN et al. DOI: 10.1056/NEJMoa2306963

CLINICAL PROBLEM

Patients with heart failure with preserved ejection fraction often have obesity, a condition that is associated with a greater burden of heart failure–related symptoms, worse functional capacity, and more impaired quality of life. Whether therapies that target obesity in such patients can alleviate symptoms and physical limitations is unknown.

CLINICAL TRIAL

Design: A multinational, double-blind, randomized, placebo-controlled trial evaluated whether treatment with semaglutide — a glucagon-like peptide 1 receptor agonist approved for long-term weight management — would reduce heart failure–related symptoms and improve physical function, in addition to inducing weight loss, in adults with heart failure with preserved ejection fraction and obesity.

Intervention: 529 patients with a body-mass index of ≥30 were assigned to receive subcutaneous semaglutide (2.4 mg) or placebo once weekly for 52 weeks. The dual primary end points were the change in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS), which quantifies heart failure–related symptoms and physical function, and the change in body weight from baseline to week 52.

RESULTS

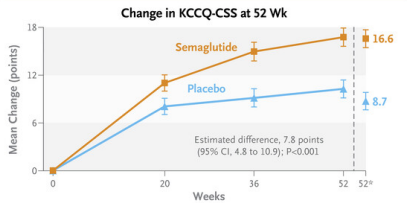
Efficacy: The mean change in KCCQ-CSS and the mean percentage change in body weight were significantly greater with semaglutide than with placebo.

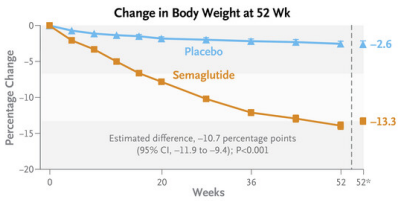
Safety: Serious adverse events occurred less often with semaglutide than with placebo, primarily because fewer cardiac disorders occurred in the semaglutide group. Adverse events leading to treatment discontinuation were more common with semaglutide.

LIMITATIONS AND REMAINING QUESTIONS

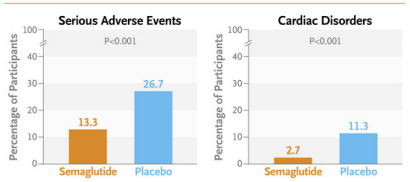
- The number of non-White trial participants was low.
- The trial was not sufficiently powered to evaluate the effects of semaglutide on clinical events, such as hospitalization for heart failure.
- Whether the observed effects of semaglutide would last beyond 1 year is unknown.

Links: Full Article | NEJM Quick Take | Editorial





Week 52 data are based on ANCOVA and imputation of missing data.



CONCLUSIONS

In adults with heart failure with preserved ejection fraction and obesity, once-weekly treatment with semaglutide was associated with greater reductions in heart failure–related symptoms and physical limitations and greater weight loss than placebo over 52 weeks.

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Semaglutide in Patients with Obesity-Related Heart Failure and Type 2 Diabetes

Kosiborod MN et al. DOI: 10.1056/NEJMoa2313917

CLINICAL PROBLEM

In patients with heart failure with preserved ejection fraction and obesity, but without type 2 diabetes, semaglutide treatment has led to larger reductions in heart failure–related symptoms and physical limitations and greater weight loss than placebo. However, the efficacy of the glucagon-like peptide-1 receptor agonist in patients with obesity-related heart failure with preserved ejection fraction and type 2 diabetes is unknown.

CLINICAL TRIAL

Design: A multinational, double-blind, randomized, controlled trial assessed the efficacy and safety of semaglutide in adults with heart failure with preserved ejection fraction, a body-mass index ≥30, and type 2 diabetes.

Intervention: 616 participants were randomly assigned to receive once-weekly subcutaneous semaglutide (2.4 mg) or placebo for 52 weeks. The first primary end point was the change in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS), which ranges from 0 to 100, with higher scores indicating fewer symptoms and physical limitations. The second primary end point was the change in body weight.

RESULTS

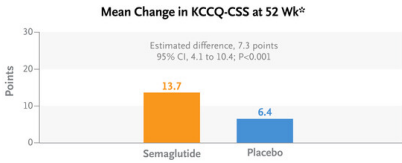
Efficacy: Treatment with semaglutide was associated with a significantly greater improvement in the KCCQ-CSS and with greater weight loss at week 52 than placebo.

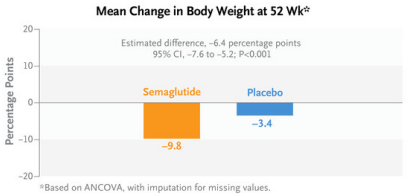
Safety: The placebo group had a higher incidence of serious adverse events than the semaglutide group.

LIMITATIONS AND REMAINING QUESTIONS

- Non-White participants were underrepresented in the trial, thus limiting generalizability.
- The trial was not designed to evaluate clinical events such as hospitalizations and urgent visits for heart failure.
- The trajectory of the effects of semaglutide suggested persistent improvements over time as compared with placebo, but the durability of these effects beyond 1 year is unknown.

Links: Full Article | NEJM Quick Take





*Based on ANCOVA, with imputation for missing values.

CONCLUSIONS

In patients with type 2 diabetes and heart failure with preserved ejection fraction, once-weekly semaglutide led to fewer heart failure–related symptoms and physical limitations and greater weight loss than placebo at 1 year.

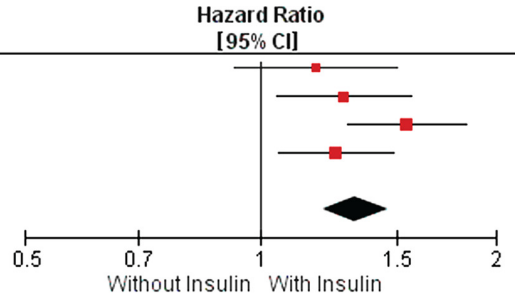
Insulin in Heart Failure patients

24 012 patients with HF from four large randomized trials

A

Study	log[Hazard Ratio]	SE	Weight	Hazard Ratio [95% CI]
Val-HeFT	0.1655	0.1219	15.8%	1.18 [0.93, 1.50]
CORONA	0.2469	0.101	23.0%	1.28 [1.05, 1.56]
GISSI-HF	0.4318	0.0892	29.4%	1.54 [1.29, 1.83]
ATMOSPHERE	0.2231	0.0858	31.8%	1.25 [1.05, 1.47]
Total (95% CI)			**100.0%**	**1.32 [1.20, 1.46]**

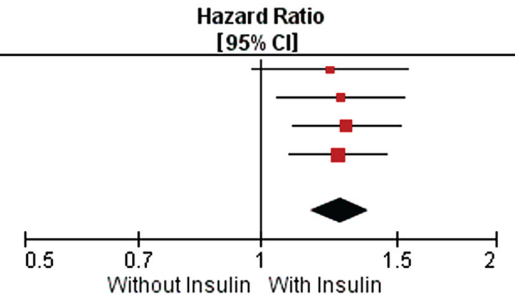
Heterogeneity: $Chi^2 = 4.33$, $df = 3$ ($P = 0.23$); $I^2 = 31\%$
Test for overall effect: $Z = 5.80$ ($P < 0.00001$)



B

Study	log[Hazard Ratio]	SE	Weight	Hazard Ratio [95% CI]
Val-HeFT	0.207	0.117	14.0%	1.23 [0.98, 1.55]
CORONA	0.239	0.096	20.7%	1.27 [1.05, 1.53]
GISSI-HF	0.2546	0.0808	29.3%	1.29 [1.10, 1.51]
ATMOSPHERE	0.2311	0.0728	36.0%	1.26 [1.09, 1.45]
Total (95% CI)			**100.0%**	**1.27 [1.16, 1.38]**

Heterogeneity: $Chi^2 = 0.12$, $df = 3$ ($P = 0.99$); $I^2 = 0\%$
Test for overall effect: $Z = 5.41$ ($P < 0.00001$)



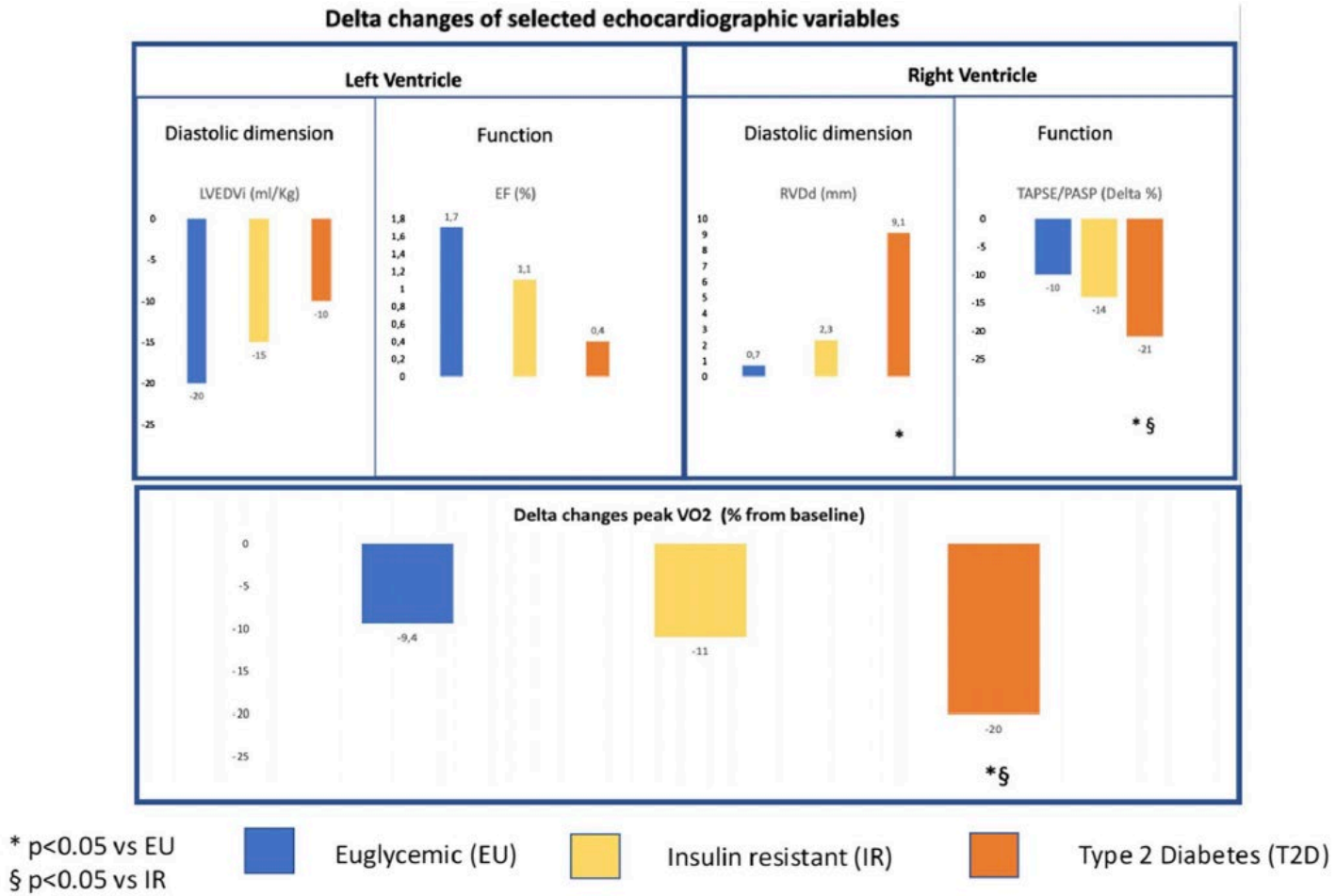
Logistic regression analysis showed that insulin prescription was associated with a significantly higher risk of all-cause death [odds ratio (OR) 2.02, 95% confidence interval (CI) 1.87–2.19] and rehospitalization for HF (OR 1.42, 95% CI 1.32–1.53).

Cosmi F et al. Eur J Heart Fail 2018

Heart Failure and Diabetes: a dangerous liaison

1. How to **prevent** development of Heart Failure in patients with Diabetes
2. How to **handle glycemic control** in Heart Failure patients
3. How to **manage Heart Failure** in patients with Diabetes

Diabetes accelerates disease progression in HF



Salzano A , Marra AM, Cittadini A Cardiovasc Diabetol 2022

The four Pillars in HFrEF

McDonagh T et al.
ESC Heart Failure Guidelines.
Eur Heart J 2021

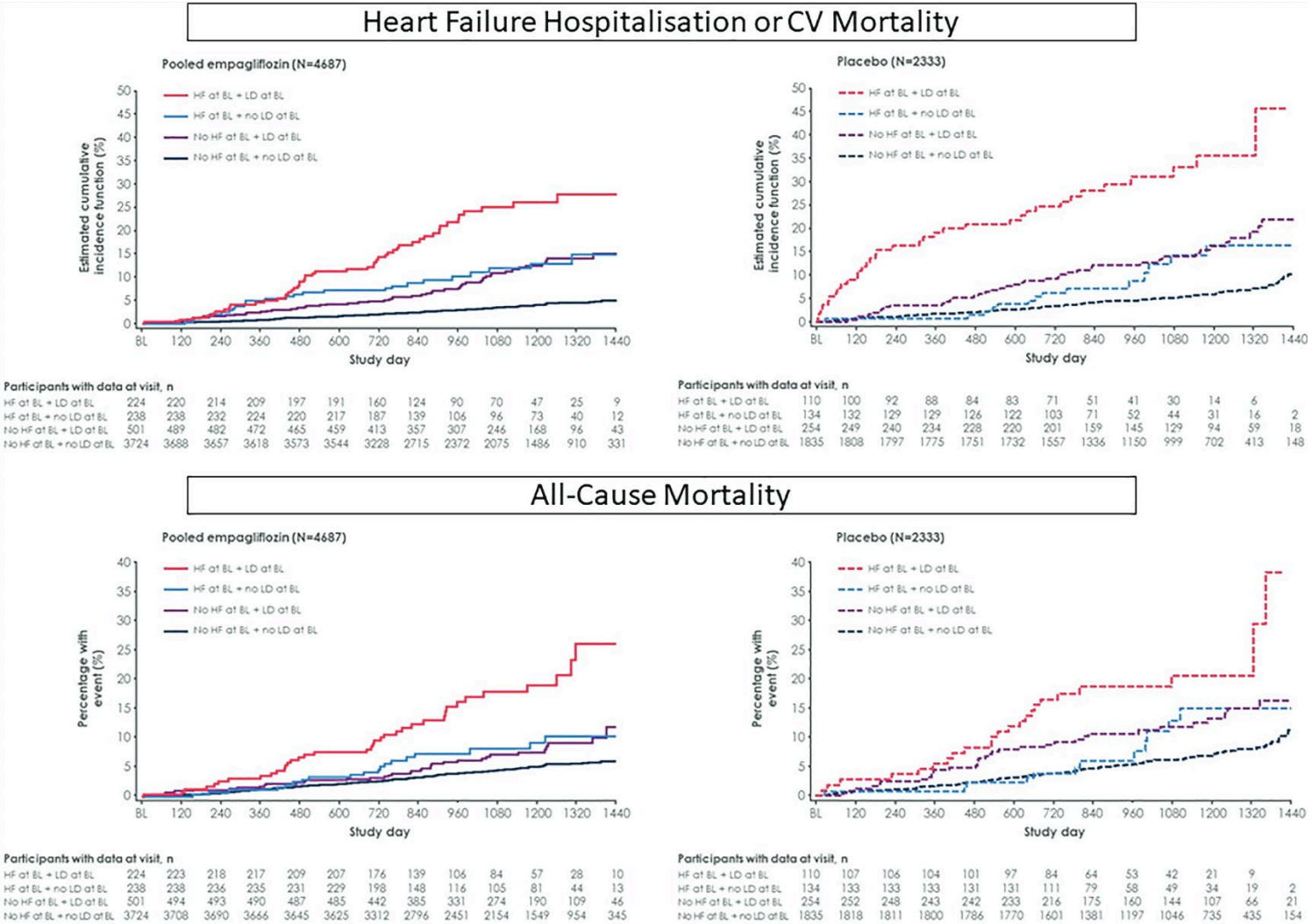
Trial and Year	Drug/Device Studied	Patient Population	N	% With DM	Treatment Effects by DM Status
ACE inhibitor					
CONSENSUS[175] 1987	Enalapril	NYHA IV	253	22	From meta-analysis[174]: mortality RR of 0.64 (95% CI, 0.46–0.88) in non-DM vs 1.06 (95% CI, 0.65–1.74) in DM
SAVE[176] 1992	Captopril	Recent MI EF ≤40% No overt HF	2231	22	No interaction by DM status (P=0.45) Benefit of captopril was similar among non-DM (HR, 0.80 [95% CI, 0.64–0.94]) and DM (HR, 0.83 [95% CI, 0.63–0.87])[132]
SOLVD-Treatment[177] 1991	Enalapril	Chronic HF EF ≤35%	2569	26	From meta-analysis[174]: mortality RR of 0.84 (95% CI, 0.74–0.95) in non-DM vs 1.01 (95% CI, 0.85–1.21) in DM
TRACE[178] 1995	Trandolapril	NYHA IIIB-IV EF ≤25%	1749	14	Multivariable analysis[179]: interaction analysis (P=0.3). Mortality RR of 0.82 (95% CI, 0.69–0.97) in non-DM vs 0.64 (95% CI, 0.45–0.91) in DM
ARB					
Val-HeFT[180] 2001	Valsartan	NYHA class II-IV EF <40%	5010	25	Primary text: "Valsartan improved the composite outcome in those with and without diabetes" For overall trial, combined end-point mortality and morbidity, 3.3% ARR (28.8% vs 32.1%; RRR, 13%; P=0.009)
HEAAL[181] 2009	Losartan 150 mg vs 50 mg daily (target doses)	NYHA classes II-IV EF ≤40% Intolerant of ACE inhibitors	3846	31	No interaction by DM status (P=0.35) Death or HF admission: 0.87 (95% CI, 0.77–0.98) in non-DM vs HR 0.96 (95% CI, 0.82–1.12) in DM for 150 mg vs 50 mg
VALIANT[182] 2003	Valsartan vs valsartan plus captopril vs captopril	MI complicated by LVSD, HF, or both within past 10 d	14 703	23	A prespecified subgroup analysis found that patients with DM experienced similar treatment effects as patients without DM for death and cardiovascular death, reinfarction, or hospitalization for HF. Overall trial found no difference in mortality for valsartan vs captopril (HR, 1.00 [97.5% CI, 0.90–1.11]; P=0.98).
CHARM-Program 2008	Candesartan	Multiple trials: CHARM-Alternative, Added, and Preserved	7599	28	Summary paper from the CHARM Program[76]: the effect of candesartan was not modified by DM status (P=0.09 test for interaction).
ARNI					
PARADIGM-HF[183] 2014	Sacubitril-valsartan vs enalapril	NYHA II-IV EF ≤40%	8442	35	Primary paper: ARR of 4.7% in cardiovascular death or HF hospitalization with sacubitril/valsartan vs enalapril. Primary end-point interaction for DM subgroup not significant (P=0.40). The interaction P value for cardiovascular mortality was 0.05. Secondary paper: the benefit of sacubitril-valsartan was consistent across the range of HbA_{1c}[184]

β-Blocker					
CIBIS-II[185] 1999	Bisoprolol	NYHA III-IV EF ≤35%	2647	12	Primary paper: Interaction P=0.48 for mortality benefit by DM status Secondary paper: RR of mortality was 0.66 (95% CI, 0.54–0.81) in non-DM vs 0.81 (95% CI, 0.51–1.28) in DM[186]
COPERNICUS[187] 2001	Carvedilol	HF with EF ≤25%	2289	26	Data from meta-analysis[174]: Mortality RR of 0.67 (95% CI, 0.52–0.85) in non-DM vs 0.68 (95% CI, 0.47–1.00) in DM. RRR of 1.02 (95% CI, 0.65–1.61)
MERIT-HF[188] 1999	Metoprolol succinate	NYHA IIIB-IV EF ≤25%	3991	25	Primary paper with DM subgroup predefined; similar mortality in DM and non-DM Data from meta-analysis[174]: mortality RR of 0.62 (95% CI, 0.48–0.79) in non-DM vs 0.81 (95% CI, 0.57–1.15) in DM. RRR of 1.32 (95% CI, 0.86–2.02) Secondary paper: similar reductions for mortality and hospitalization in DM and non-DM[189]

MRA					
RALES[190] 1999	Spironolactone	NYHA III-IV EF ≤35%	1663	22	Not reported in primary paper; not one of the 6 prespecified subgroups of interest
EMPHASIS-HF[191] 2011	Eplerenone	NYHA II EF ≤35%	2737	32	No interaction by DM status Secondary paper: HR, 0.72 (95% CI, 0.58–0.88; P=0.002) in non-DM vs 0.54 (95% CI, 0.42–0.70; P<0.0001) in DM[192]
EPHESUS[193] 2003	Eplerenone	Acute MI complicated by LVSD (EF ≤40%) and HF	6632	32	No interaction of DM status with mortality (P=0.35) Secondary paper: RRR for cardiovascular death or cardiovascular hospitalization of 17% in DM (P=0.031); greater ARR hospitalization in DM cohort (5.1%) than non-DM (3%)[194]

Dunlay SM et al. AHA Statement on Diabetes in Heart Failure Circulation 2019

Diuretics and Diabetes



Compared to those with neither HF nor prescribed LD (reference group; placebo), **those with both HF and receiving LD had the highest rates for all-cause [hazard ratio (HR) (95% confidence interval) 3.19(2.03–5.01)] and cardiovascular mortality [3.83 [(2.28–6.44)], and HF hospitalizations [9.51 (5.61–16.14)].** Patients **without HF but prescribed LD** had **higher rates for all three outcomes [1.62 (1.10–2.39); 1.97 (1.26–3.08); 3.20(1.90–5.39)], which were similar to patients with HF who were not receiving LD [1.42 (0.78–2.57); 1.56 (0.78–3.11);3.00 (1.40–6.40)].**

Pellicori P et al Eur J Heart Fail 2021

Cardiac Rehabilitation in Diabetes and HF

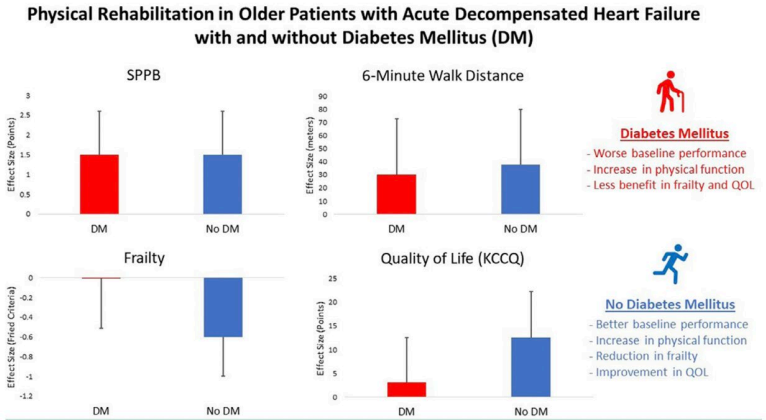


Figure Effect of the novel REHAB-HF intervention in patients with acute decompensated heart failure on outcomes at 3 months in participants with diabetes mellitus (shown in red) and without (shown in blue). SPPB = Short Physical Performance Battery; DM = diabetes mellitus; QOL = quality of life; KCCQ = Kansas City Cardiomyopathy Questionnaire.

Table 3 Physical Function Outcomes at 3 Months Stratified by Diabetes Status with Adjustment for Baseline Covariates*

3-Month Outcome	Diabetes Mellitus: Rehabilitation Intervention (n = 103)	Diabetes Mellitus: Attention Control (n = 83)	Diabetes Mellitus: Difference (95% CI)	Diabetes Mellitus: *P* for Difference	No Diabetes Mellitus: Rehabilitation Intervention (n = 72)	No Diabetes Mellitus: Attention Control (n = 91)	No Diabetes Mellitus: Difference (95% CI)	No Diabetes Mellitus: *P* for Difference	*P* for Interaction
SPPB score	7.8 (0.3)	6.2 (0.3)	1.5 (0.5-2.6)	< .001	8.3 (0.3)	6.8 (0.3)	1.5 (0.4-2.6)	< .001	.99
Balance score	3.0 (0.1)	2.5 (0.1)	0.5 (0.1-1.0)	.004	3.3 (0.2)	3.0 (0.1)	0.3 (-0.2-0.8)	.18	.32
4-meter walk score	2.8 (0.1)	2.3 (0.1)	0.4 (0.0-0.8)	.006	3.1 (0.1)	2.6 (0.1)	0.6 (0.1-1.0)	.001	.62
Chair rise score	1.9 (0.1)	1.4 (0.1)	0.6 (0.1-1.0)	.001	2.0 (0.2)	1.3 (0.1)	0.7 (0.2-1.2)	< .001	.69
6-minute walk distance (m)	281.3 (11.8)	252.5 (13.3)	28.8 (−13.1-70.7)	.076	286.7 (13.9)	248.0 (12.8)	38.7 (−3.8-81.2)	.019	.67
Gait speed (m/s)	0.8 (0.0)	0.7 (0.0)	0.1 (0.0-0.2)	.004	0.8 (0.0)	0.7 (0.0)	0.1 (0.1-0.2)	< .001	.22
Male grip strength (kg)	28.9 (1.0)	30.5 (1.3)	−1.6 (−5.6-2.5)	.32	32.2 (1.3)	30.9 (1.1)	1.4 (−2.6-5.4)	.37	.19
Female grip strength (kg)	20.9 (1.0)	21.9 (1.0)	−1.0 (−3.9-1.9)	.39	22.0 (0.9)	21.2 (0.9)	0.8 (−2.3-3.8)	.52	.29
Modified Fried frailty score	1.7 (0.1)	1.7 (0.2)	−0.0 (−0.5-0.5)	.99	1.2 (0.1)	1.8 (0.1)	−0.6 (−1.1, −0.1)	.001	.021
KCCQ overall	63.8 (2.6)	60.0 (2.9)	3.8 (−5.6-13.2)	.30	74.3 (3.1)	62.0 (2.8)	12.2 (2.3-22.1)	.002	.11
EQ5D VAS	69.4 (2.4)	62.2 (2.7)	7.2 (−1.5-15.8)	.033	72.2 (2.8)	64.8 (2.6)	7.4 (−1.8-16.6)	.038	.97
Cognition (MoCA Score)	22.4 (0.4)	22.4 (0.5)	−0.0 (−1.6-1.5)	.93	22.4 (0.5)	22.8 (0.4)	−0.4 (−2.0-1.2)	.52	.69
Depression (GDS-15 Score)	3.6 (0.3)	4.4 (0.3)	−0.8 (−2.0-0.3)	.050	3.4 (0.4)	4.1 (0.3)	−0.7 (−1.8-0.5)	.15	.77

Presented as mean (SE).
*Adjusted for baseline measure, age, sex, clinical site, and EF category (< vs. ≥45%).
BMI = body mass index; GDS-15 = Geriatric Depression Scale-15; GDS-15 = Geriatric Depression Scale-15; KCCQ = Kansas City Cardiomyopathy Questionnaire; EQ5D VAS = EuroQol visual analogue scale; MoCA = Montreal Cognitive Assessment; SPPB = Short Physical Performance Battery.

Outcomes	Group PT (n=90)	Group TELE (n=90)	P-value
SPPB score, primary outcomet			
At baseline	5.30 (1.62)	5.26 (1.55)	0.860
At 3 mo	8.09 (0.79)	8.12 (0.72)	0.781
At 6 mo	9.21 (0.61)	9.21 (0.66)	1.000

Murray EM et al. Am J Med 2022

Yuan M et al. Front Endocrinonl 2024

Diabetes And Heart Failure: Take Home Message

-The **bidirectional interplay** between Diabetes and Heart Failure cannot be neglected

-**Risk factor control** prevents development from Diabetes to Heart Failure

-**Yearly screening with natriuretic peptides is highly recommended**

-Patients with **Type 1 Diabetes have higher risk of Heart Failure** than Type 2

-Patients with Diabetes and HF Should be on a **moderate glycemic control (HB1AC 7-8%)**

-**SGLT2i** are nowadays a pillar of **HF therapy** regardless of EF (and of diabetic status too)

-**GLP1-RA** seems quite **promising in patients with HFpEF**

-**Insulin** is associated with a Risk of **poor outcomes in HF patients**

-**Cardiac Rehabilitation** might be helpful

Thanks for your Attention

From Diabetes to Heart Failure: one way

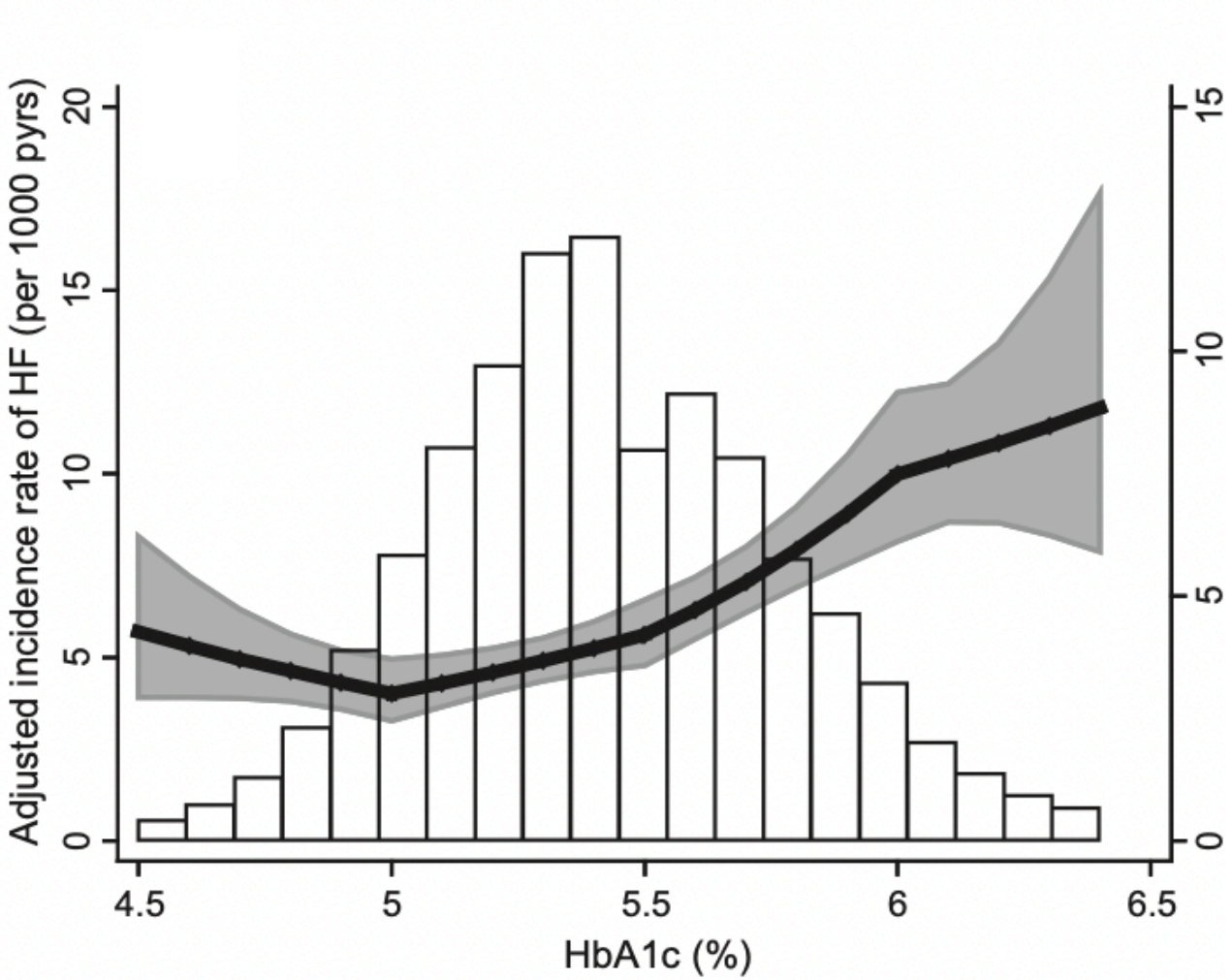
Study	Cohort	N	Follow-Up, y	Incidence of HF	Adjusted Risk of HF With vs Without DM	Population-Attributable Fraction
Framingham [1] (study sample included ages 45–74 y)	45–74 y	5209	Up to 20	Age-adjusted rates (person-years): DM (men): 7.6/1000 No DM (men): 3.5/1000 DM (women): 11.4/1000 No DM (women): 2.2/1000	RR (men): 1.82 RR (women): 3.75	Men: 7.7% Women: 18.0%
Cardiovascular Health Study [2]	>65 y	5888	Mean 5.5	Rates (person-years): DM (men): 44.6/1000 No DM (men): 22.9/100 DM (women): 32.5/1000 No DM (women): 12.1/1000	RR: 1.74 (95% CI, 1.38–2.19)	8.3%
Heart and Soul Study [3]	Stable CAD	839	Mean 4.1	Rates (person-years): DM: 36.6/1000 No DM: 17.9/1000	HR, 3.34 (95% CI, 1.65–6.76)	…
MESA [4]	4–84 y	6814	Median 4	…	HR, 1.99 (95% CI, 1.08–3.68)	DM-attributable risk: 19 per 1000
NHANES [5]	25–74 y	13643	Mean 19	Cumulative incidence at age 85 y: DM (men): 65.5% No DM (men): 36.9% DM (women): 61.8% No DM (women): 28.9%	RR, 1.85 (95% CI, 1.51–2.28) Similar in men and women	…
Retrospective cohort of Kaiser Permanente Northwest Database [6]		8231 +DM, 8845 no DM	Up to 6	Rates (person-years): DM: 30.9/1000 No DM: 12.4/1000 Rate ratio, 2.5 (95% CI, 2.3–2.7)	…	…

CAD indicates coronary artery disease; DM, diabetes mellitus; ellipses (…), not reported; HF, heart failure; HR, hazard ratio; MESA, Multi-Ethnic Study of Atherosclerosis; NHANES, National Health and Nutrition Examination Survey; and RR, relative risk.

1. Kannel WB et al. JAMA 1979
2. Gottdiener JS et al. JACC 2000
3. Van Melle JP et al. Diabetes Care 2010
4. Bahrami H et al. JACC 2008
5. He J et al. Arch Intern Med 2001
6. Nichols JA et al. Diabetes Care 2004

modified from Dunlay SM et al. AHA official statement on Diabetes and Heart Failure. Circulation 2022

Prevention of HF in Diabetic patients: glycemic control



Among individuals without type 2 diabetes, a **1% higher HbA1c** is associated with a **39% higher risk of heart failure** independent of other risk factors.

Matsushita K et al. Diabetes 2010