HFpEF Masterclasses
In centers of expertise

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FRANCE

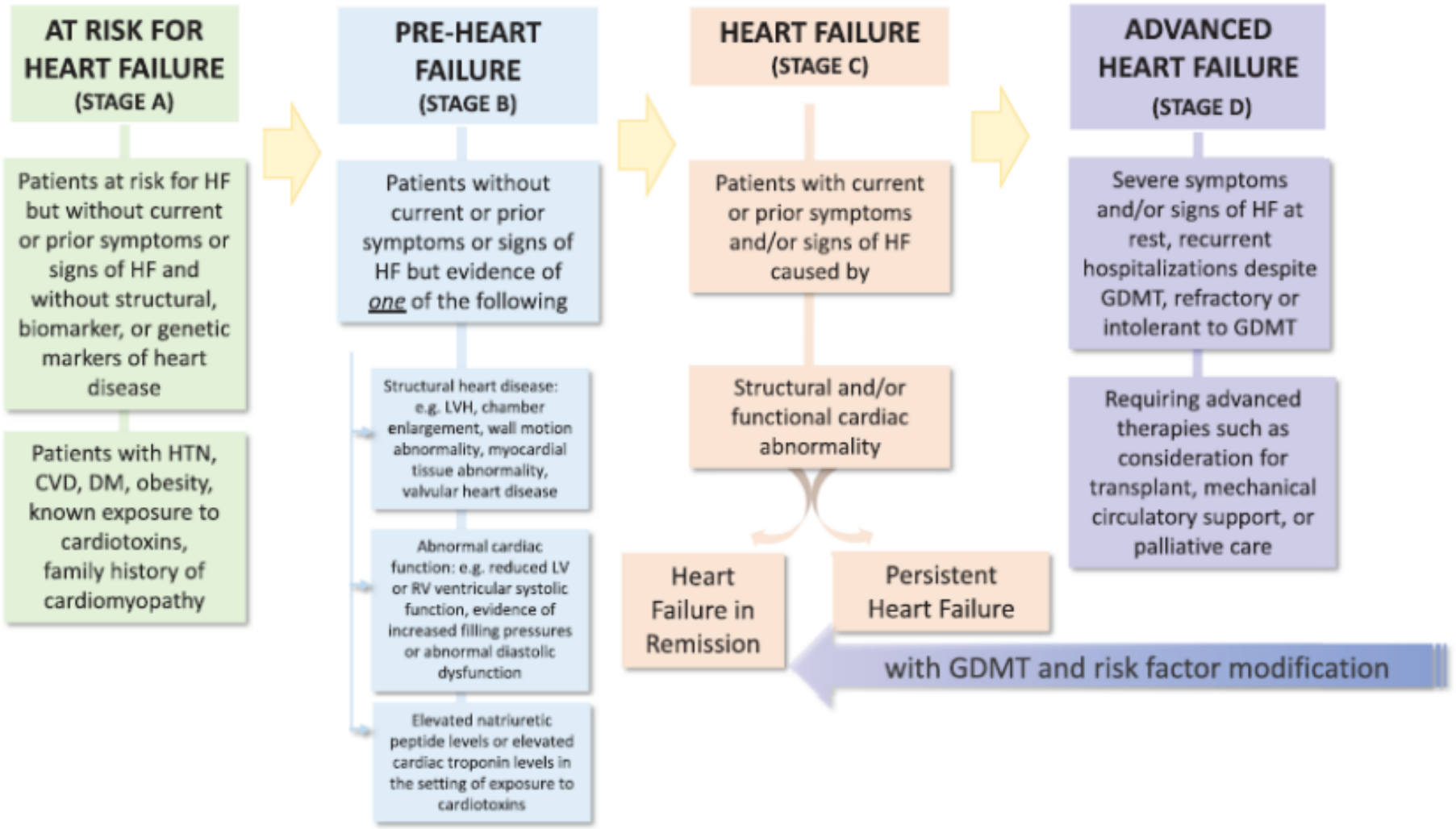
7th November 2024 - DAY 1
8th November 2024 - DAY 2

Dr Emmanuelle Berthelot

SGLT2i from prevention to the treatment of heart failure

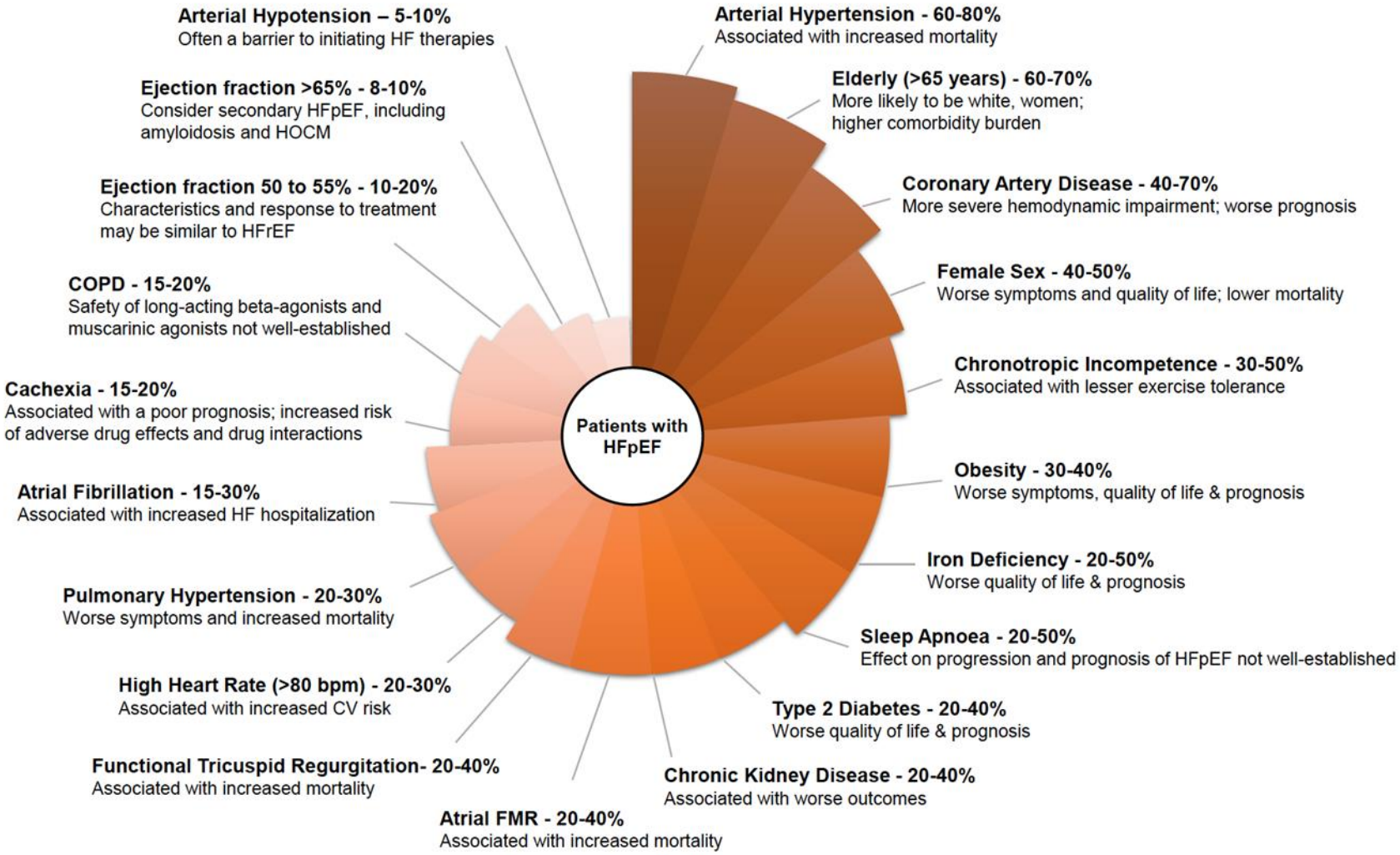
CHU Bicetre

Universal definition of HF



Heidenreich et al, Journal of Cardiac Failure 28.5 (2022): e1-e167.

Comorbidities in HFpEF



Patient characteristics in patients with LVEF >40% in recent clinical trials

TABLE 4 Comparison of Baseline Characteristics in Various Trials in Heart Failure With LVEF >40%

	DELIVER (n = 6,263)	EMPEROR-Preserved (n = 5,988)	PARAGON-HF (n = 4,822)	TOPCAT-Americas (n = 1,767)	I-PRESERVE (n = 4,128)	CHARM-Preserved (n = 3,023)
Age, y	72 ± 10	72 ± 9	73 ± 8	72 (64 to 79)	72 ± 7	67 ± 11
Women, %	44	45	52	50	60	40
NYHA functional class, %						
II	75	82	77	59	22	61
III	25	18	27	35	77	38
IV	0.3	0.3	0.6	1	3	2
Type 2 diabetes, %	45	49	43	45	27	28
Smoker, %	8	7	7	7		14
History of MI, %	26	29	22	20	23.5	44
History of AFF, %	56	52	52	42	29	29
AFF at screening, %	42	35	32	34	29	29
Stroke, %	9 (stroke/TIA)	10	10	9	10	9
Prior HF hospitalization, %						
Within 6 mo						
Within 12 mo	26	23	48			
Any prior hospitalization	40			59	23	68
Subacute	10					
LVEF, mean %	54	54	58	58	60	54
eGFR, mean mL/min/1.73 m^2	61	61	62	61	73	72
NT-proBNP, median, pg/mL	1,011	974	885	900	339	–
ACEi, %	33	40	40	50	26	19
ARB, %	34	39	45	31	–	–
ARNI, %	4	2	–	–	–	–
MRA, %	39	37	24	–	15	12

Values are mean ± SD or n.

COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; TIA = transient ischemic attack; other abbreviations as in Table 1.

Solomon S et al. JACC HF 2022

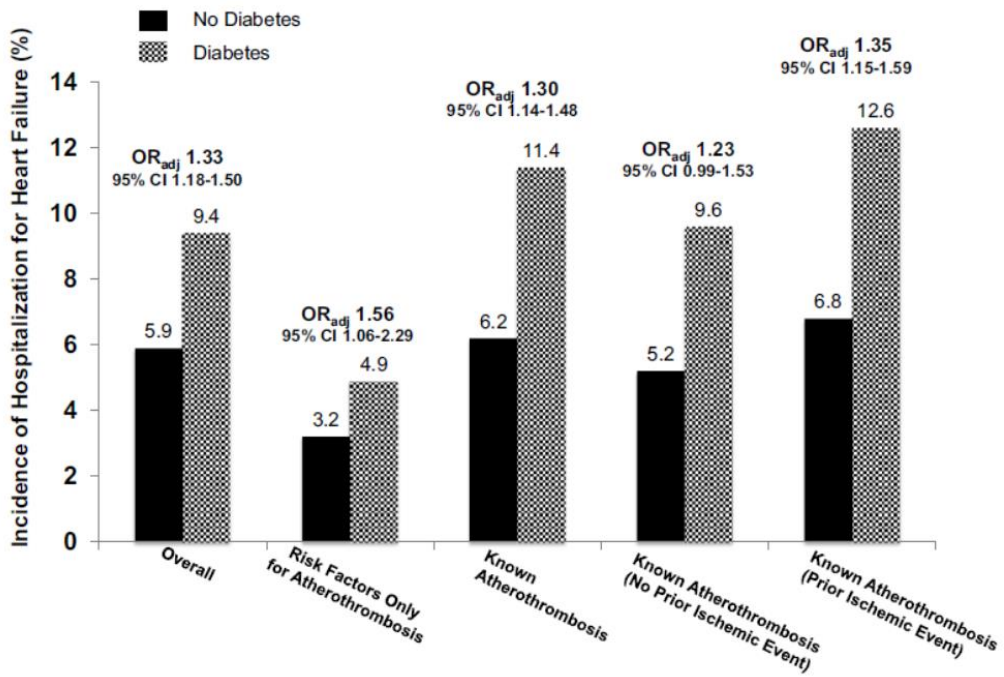
Diabete and HF

HF common complication of diabetes : prévalence 22 %

HF may develop in DM patients even in the absence of HTN IHD or VHD

HF is the first CV presentation in T2DM

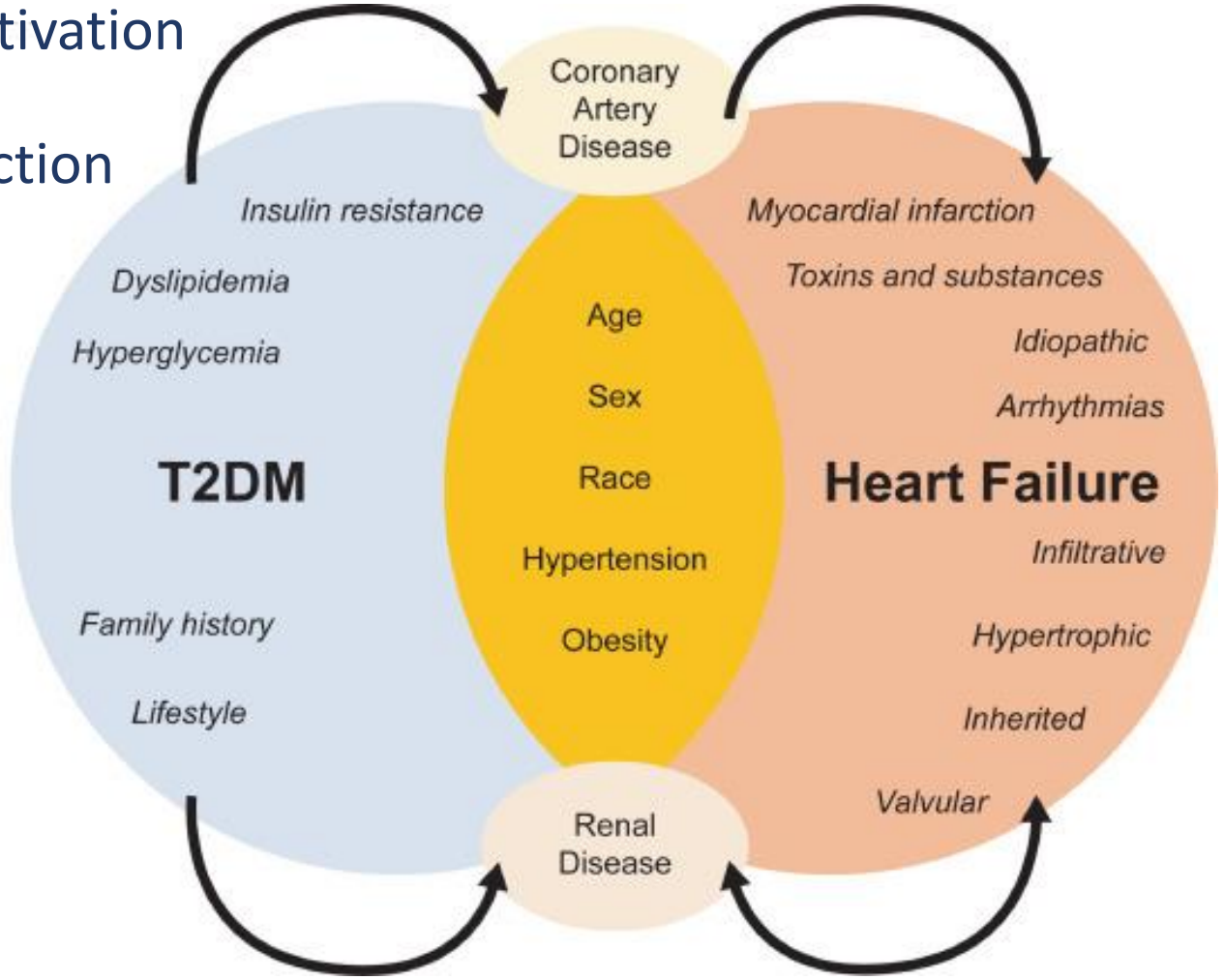
Risk factors of HF : T2D and T1D include DM duration and others risks factors.



Diabetes Care 2022; 45 (7): 1670-169
Ohkuma T et al. Diabetologia 2019;62:1550-60
Shah et al. Endocrinol 2015;3:105-113

Mecanisms

Neurohormonal activation
Cytokines
Endothelial dysfonction



How to prevent HF in DM patients ?

Tight glycemic control ?

Some medications might increase the risk of HF

- Gliflozin (iSGLT2)
- Analogue GLP1
- Insuline
- Metformine
- Inh DPP4 : Saxagliptine
- Sulfamides hypoglycémiants

Tzoulaki I, BMJ. 2009; 339:b4731.
Gerstein HC, N Engl J Med. 2012;367:319-28.
SAVOR TIMI 53, TECOS (iDPP4)
LEADER, SUSTAIN 6 (GLP1)

Prevention of HF in DM

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo			
Patients with history of heart failure								
EMPA-REG OUTCOME	462	244	124	63·6	85·5	23·6		0·72 (0·50–1·04)
CANVAS Program	803	658	203	35·4	56·8	34·1		0·61 (0·46–0·80)
DECLARE-TIMI 58	852	872	314	45·1	55·5	42·4		0·79 (0·63–0·99)
Fixed effects model for history of heart failure (p<0·0001)								**0·71 (0·61–0·84)**
Patients with no history of heart failure								
EMPA-REG OUTCOME	4225	2089	339	15·5	24·9	30·0		0·63 (0·51–0·78)
CANVAS Program	4992	3689	449	13·6	15·2	32·4		0·87 (0·72–1·06)
DECLARE-TIMI 58	7730	7706	599	8·9	10·5	37·6		0·84 (0·72–0·99)
Fixed effects model for no history of heart failure (p<0·0001)								**0·79 (0·71–0·88)**

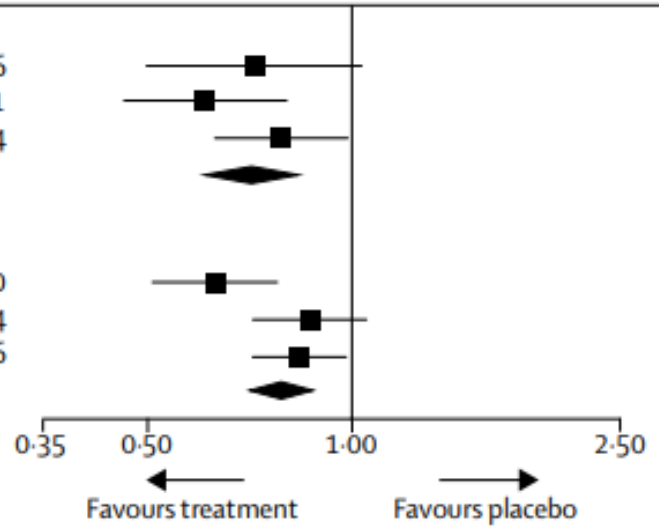


***Figure 3*: Meta-analysis of SGLT2i trials on hospitalisation for heart failure and cardiovascular death stratified by history of heart failure**
History of heart failure: Q statistic=2·02, p=0·37, I^2=0·8%; no history of heart failure: Q statistic=5·89, p=0·0527, I^2=66%. The p value for subgroup differences was 0·51. Tests for subgroup differences were based on F tests in a random effect meta-regression estimated using restricted maximum likelihood and Hartung Knapp adjustment. HR=hazard ratio. SGLT2i=sodium-glucose cotransporter-2 inhibitors.

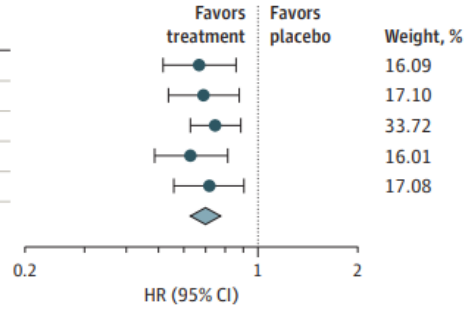
Zelniker TA. Lancet. 2019 Jan 5;393(10166):31-39.

Prevention of HF in DM patients : iSGLT2

Figure 3. Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Hospitalization for Heart Failure

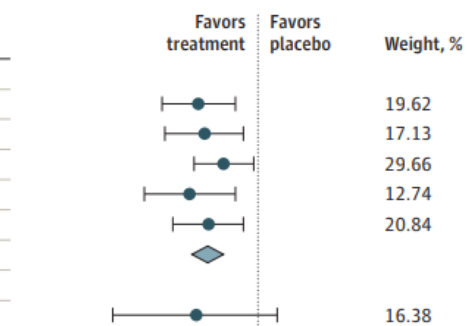
A Overall HHF

	Treatment		Placebo				
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)	Favors treatment / Favors placebo	Weight, %
EMPA-REG OUTCOME	126/4687	9.4	95/2333	14.5	0.65 (0.50-0.85)		16.09
CANVAS program	NA/5795	5.5	NA/4347	8.7	0.67 (0.52-0.87)		17.10
DECLARE-TIMI 58	212/8582	6.2	286/8578	8.5	0.73 (0.61-0.88)		33.72
CREDENCE	89/2202	15.7	141/2199	25.3	0.61 (0.47-0.80)		16.01
VERTIS CV	139/5499	7.3	99/2747	10.5	0.70 (0.54-0.90)		17.08
Fixed-effects model ($Q = 1.39$; $df = 4$; $P = .85$; $I^2 = 0.0\%$)					0.68 (0.61-0.76)		



B HHF by ASCVD status

	Treatment		Placebo				
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)	Favors treatment / Favors placebo	Weight, %
Patients with ASCVD							
EMPA-REG OUTCOME	126/4687	9.4	95/2333	14.5	0.65 (0.50-0.85)		19.62
CANVAS program	NA/3756	7.3	NA/2900	11.3	0.68 (0.51-0.90)		17.13
DECLARE-TIMI 58	151/3474	11.1	192/3500	14.1	0.78 (0.63-0.97)		29.66
CREDENCE	59/1113	20.6	92/1107	33.2	0.61 (0.44-0.85)		12.74
VERTIS CV	139/5499	7.3	99/2747	10.5	0.70 (0.54-0.90)		20.84
Fixed-effects model ($Q = 1.97$; $df = 4$; $P = .74$; $I^2 = 0.0\%$)					0.70 (0.62-0.78)		
Patients without ASCVD							
CANVAS program	NA/2039	2.6	NA/1447	4.2	0.64 (0.35-1.15)		16.38
DECLARE-TIMI 58	61/5108	3.0	94/5078	4.6	0.64 (0.46-0.88)		55.07
CREDENCE	30/1089	10.6	49/1092	17.5	0.61 (0.39-0.96)		28.56
Fixed-effects model ($Q = 0.03$; $df = 2$; $P = .99$; $I^2 = 0.0\%$)					0.63 (0.50-0.80)		



ASCVD indicates atherosclerotic cardiovascular disease; CANVAS, Canagliflozin ... EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in

McGuire D., JAMA cardiol 2021. ;6(2):148-158

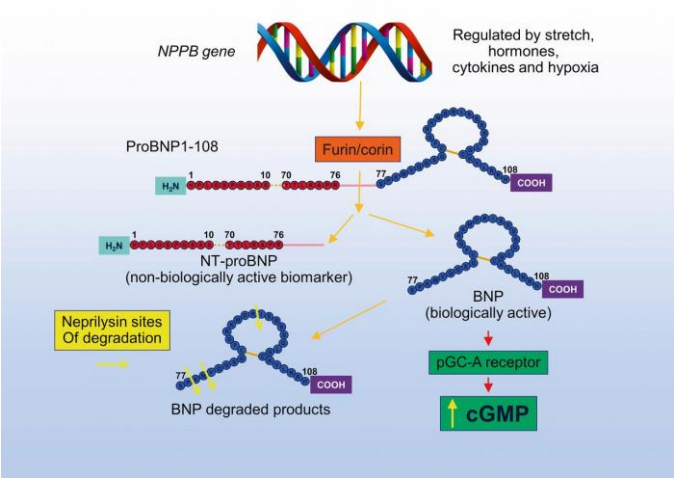
Healthy plan for Diabetes management = healthy life style

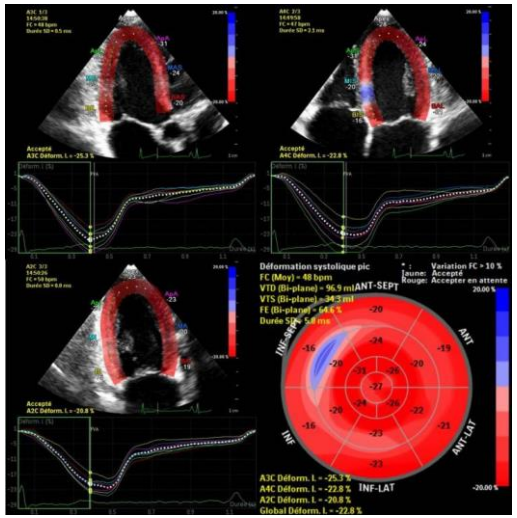
Davis et al. Diabetes Care 2022;45:484–494

How to screen ?

- Natriuretic peptides : in addition, easy and inexpensive, a standard of care and may help refine HF prediction.

- Echocardiography : might identify signs of maladaptative heart. Recommanded for asymptomatic diabetic adults





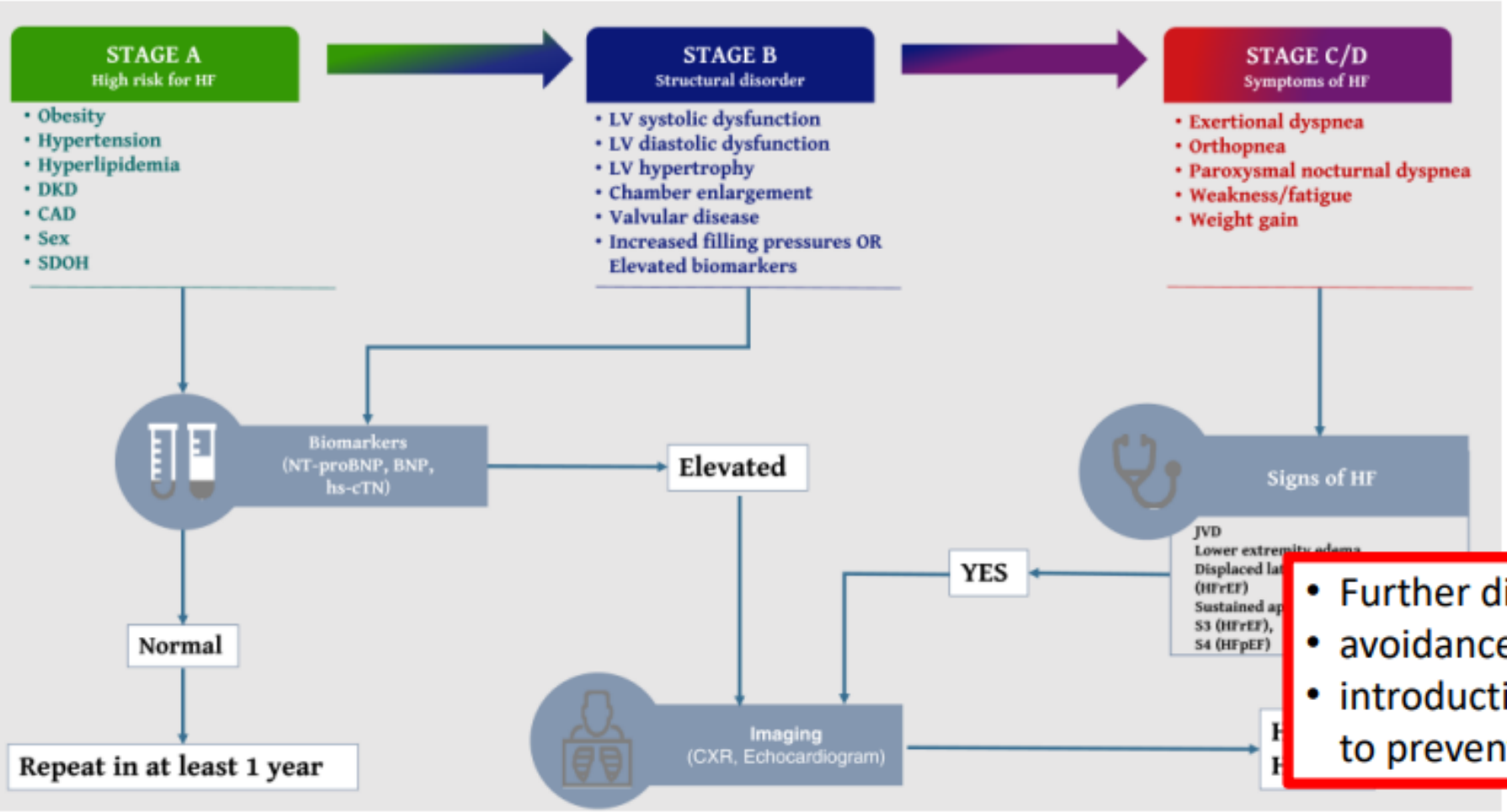
Prevention of HF in DM

- **PONTIAC (NT-proBNP selected prevention of cardiac events in a population of diabetic patients without a history of cardiac disease): a prospective randomized controlled trial**
  - NT-proBNP >125 pg/ml
  - Primary endpoint -hospitalization/death due to cardiac disease
  - Accelerated up-titration of RAS antagonists and beta-blockers to maximum tolerated dosages is an effective and safe intervention for the primary prevention of cardiac events for diabetic patients pre-selected using NT-proBNP.

Hospitalization Due to	All	Control	Intensified	p Value
Any reason	135 (45%)	77 (51%)	58 (39%)	0.02
Cardiovascular event	25 (8%)	18 (12%)	7 (5%)	0.02
Cardiac event	19 (6%)	14 (9%)	5 (3%)	0.03
Heart failure	8 (3%)	7 (5%)	1 (1%)	0.003

PONTIAC study, JACC 2013. 62 (15):1365-72

So : what to do ?



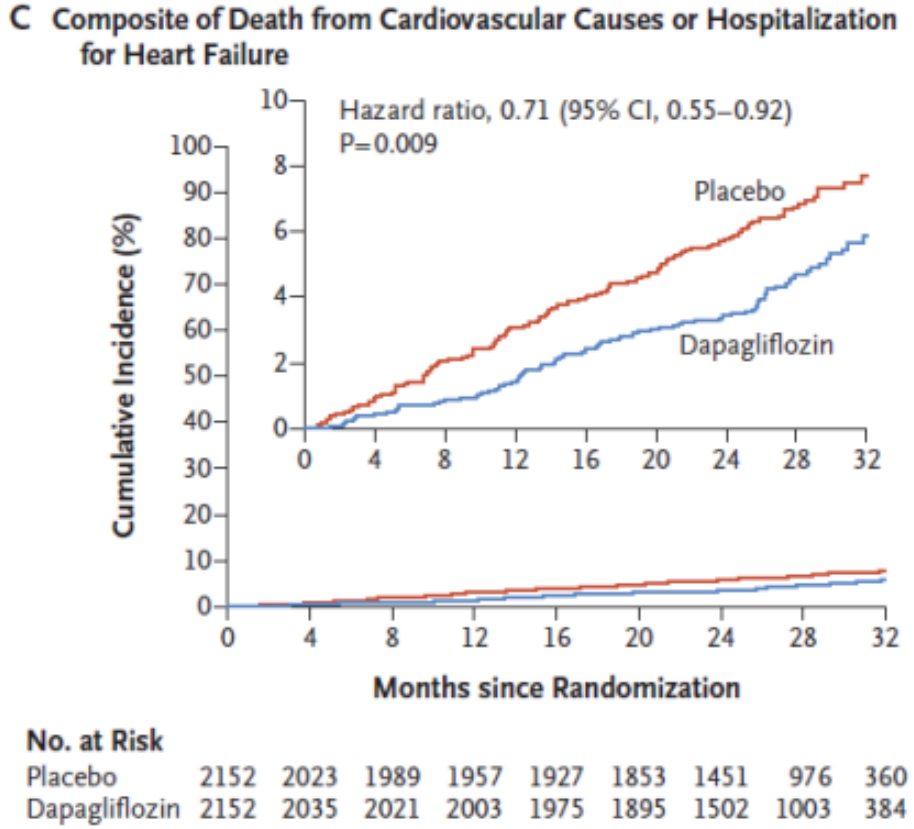
BNP>50 pg/mL
NT-proBNP >125 pg/mL
hs troponin >99th percei

- Further diagnostic studies,
- avoidance treatments that migh arm
- introduction of therapies with proof to prevent HF

Preventing HF in CKD

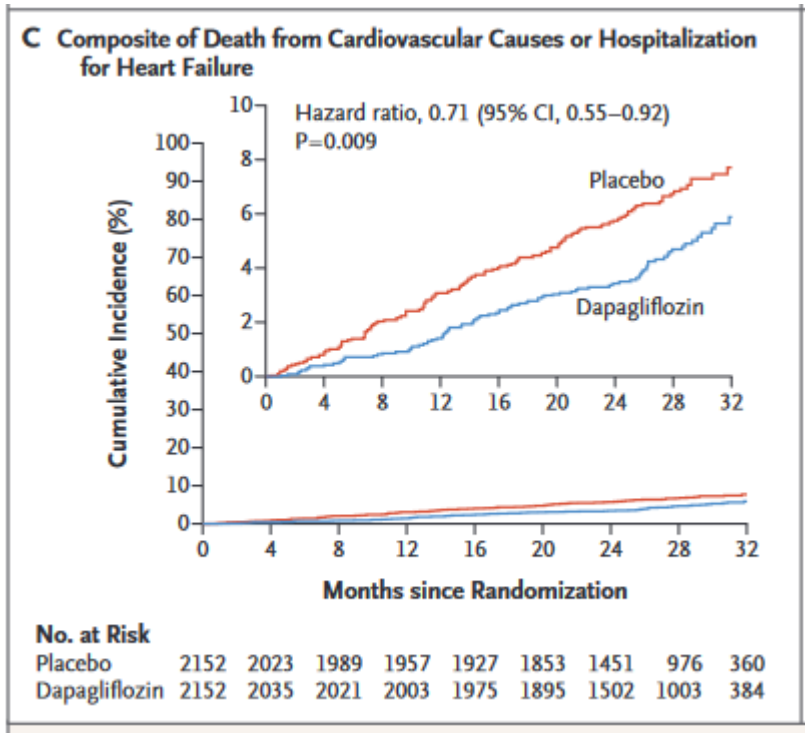
DAPA-CKD trial

- 4304 pts,
- eGFR of 25 to 75 ml/min/1.73 m2 BSA
- Urinary albumin-to-creatinine ratio of 200 to 5000
- Dapagliflozin 10 mg od or placebo.
- Primary outcome was a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes.



DAPA-CKD trial. NEJM 2020. 383:1436-46.

Preventing HF in CKD



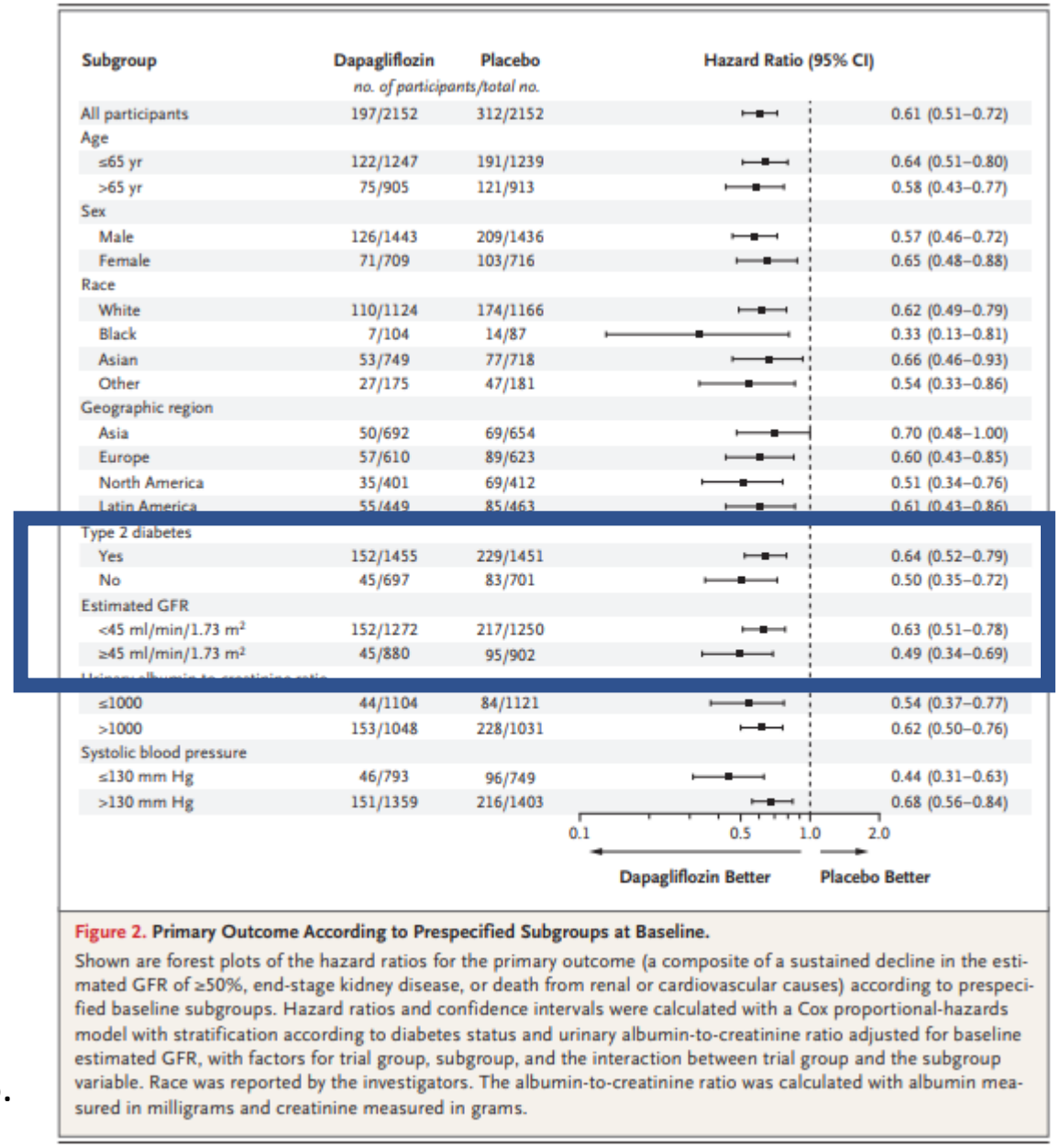


Figure 2. Primary Outcome According to Prespecified Subgroups at Baseline.

Shown are forest plots of the hazard ratios for the primary outcome (a composite of a sustained decline in the estimated GFR of ≥50%, end-stage kidney disease, or death from renal or cardiovascular causes) according to prespecified baseline subgroups. Hazard ratios and confidence intervals were calculated with a Cox proportional-hazards model with stratification according to diabetes status and urinary albumin-to-creatinine ratio adjusted for baseline estimated GFR, with factors for trial group, subgroup, and the interaction between trial group and the subgroup variable. Race was reported by the investigators. The albumin-to-creatinine ratio was calculated with albumin measured in milligrams and creatinine measured in grams.

DAPA-CKD trial. NEJM 2020. 383:1436-46.

Obesity

- Risk of HF development increases by 5-7% with each increment of 1 kg/m² in BMI

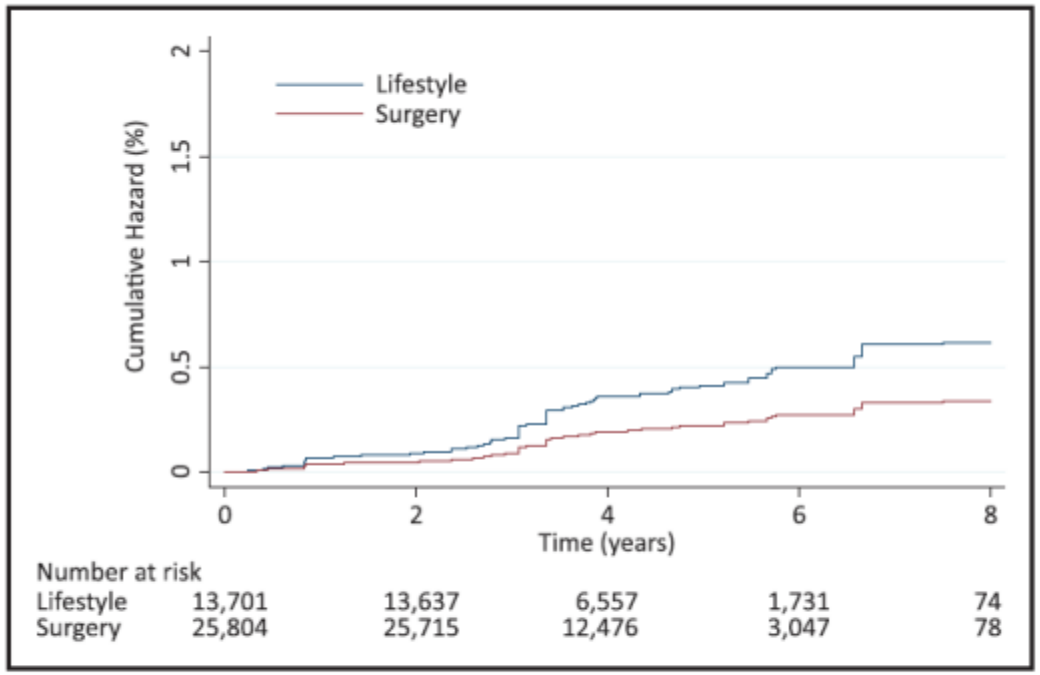
- Contribution of obesity (BMI > 30 kg/m²) to the development of HFpEF is greater than for HFrEF, BMI is a risk factor

- In a population from Rochester, Minnesota, obesity was present in 20,5% of newly diagnosed HF personns 1985-90 and 29,5 % from 1997-2002

- The population attributable risk (PAR) of obésity for incident HF was estimated at 12%

Kenchaiah S et al NEJM 2002; 305-313 and EJPC 2022 29, 275-300

Prevention of HF with bariatric surgery



Cumulative hazard of heart failure in individuals treated with lifestyle or gastric bypass surgery.

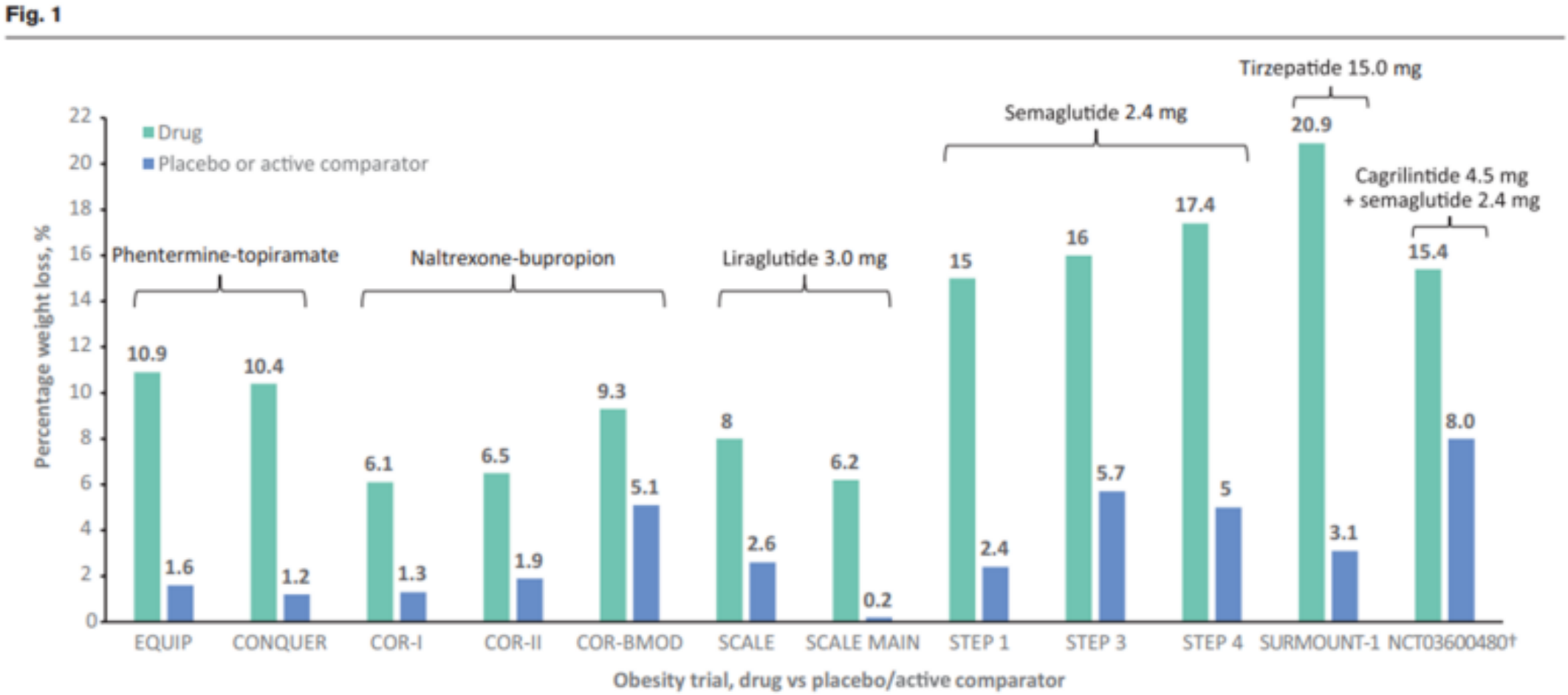
Swedish nationwide registry of people treated **w**ith structured intensive lifestyle program and the **Sc**andinavian **Obesity Surgery Registry**

25 804 individuals were treated with gastric bypass surgery and 13 701 with lifestyle modification.

Gastric bypass surgery was associated with a **ne**arly **halved incidence of heart failure** compared with intensive lifestyle modification

Circulation 2017. 135:1577-1585.

Weight loss achieved with anti-obesity medications



Ryan DH et al. Cardiovasc Endocr Metab 2023. 7;12(1):e0279

Preventing HF in Obesity

	Number of events/analysed participants		Incidence rate per 100 person-years (semaglutide:placebo)	Hazard ratio (95% CI)	p value
	Semaglutide	Placebo			
Composite of cardiovascular death or worsening heart failure event					0·0045
SELECT	53/1174	66/1099	1·4/1·8	0·75 (0·52–1·07)	
FLOW	40/167	40/158	8·1/9·2	0·87 (0·56–1·36)	
STEP-HFpEF	1/263	12/266	0·3/4·2	0·08 (0·00–0·42)	
STEP-HFpEF DM	9/310	20/306	2·7/6·2	0·46 (0·20–0·98)	
Overall	**103/1914**	**138/1829**	**2·1/3·0**	**0·69 (0·53–0·89)**	
Worsening heart failure event					0·0019
SELECT	17/1174	27/1099	0·4/0·7	0·58 (0·31–1·06)	
FLOW	29/167	29/158	5·9/6·7	0·88 (0·53–1·48)	
STEP-HFpEF	1/263	12/266	0·3/4·2	0·08 (0·00–0·42)	
STEP-HFpEF DM	7/310	18/306	2·1/5·5	0·40 (0·15–0·92)	
Overall	**54/1914**	**86/1829**	**1·1/1·8**	**0·59 (0·41–0·82)**	
Cardiovascular death*					0·25
SELECT	40/1174	43/1099	1·0/1·2	0·87 (0·56–1·34)	
FLOW	17/167	19/158	3·2/4·0	0·78 (0·40–1·51)	
STEP-HFpEF DM	2/310	4/306	0·6/1·2	0·49 (0·07–2·53)	
Overall	**59/1914**	**67/1829**	**1·2/1·4**	**0·82 (0·57–1·16)**	

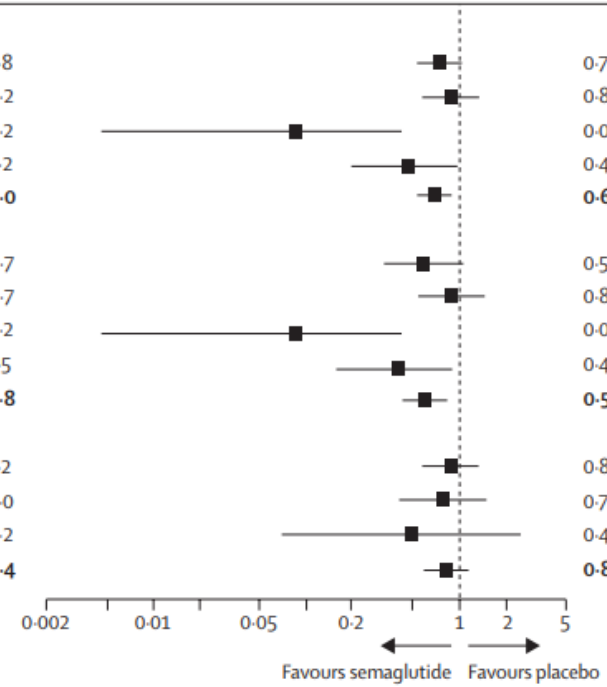


Figure 2: **Time from randomisation to first endpoint of interest (composite of cardiovascular death or worsening heart failure event, worsening heart failure event, and cardiovascular death), overall and by trial**

Data from the in-trial period. Heart failure events were defined as hospitalisation or urgent emergency department or outpatient visit due to heart failure. The overall analysis of the time from randomisation to relevant endpoint was performed with a Cox proportional hazards model with treatment as a fixed factor, stratified by study. The by-study analyses of the time from randomisation to relevant endpoint were done with a Cox proportional hazards model with treatment as a fixed factor, stratified by randomisation strata (if applicable). *There was only one cardiovascular death in STEP-HFpEF; the individual study analysis was not included for this endpoint.

Kosiborod, et al. *The Lancet* 404.10456 (2024): 949-961.

MRA and finerenone

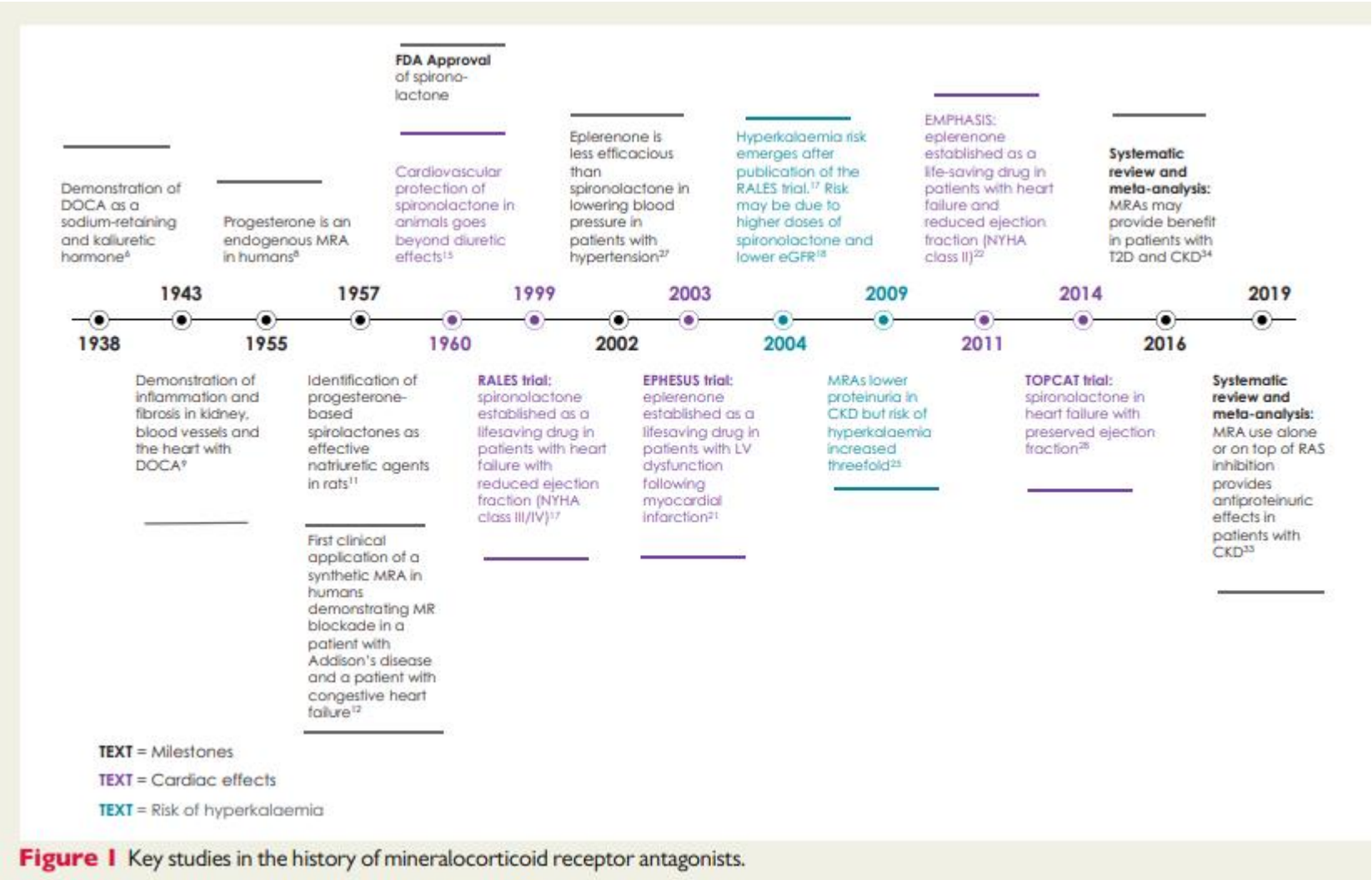


Figure 1 Key studies in the history of mineralocorticoid receptor antagonists.

European Heart Journal (2021) 42, 152–161

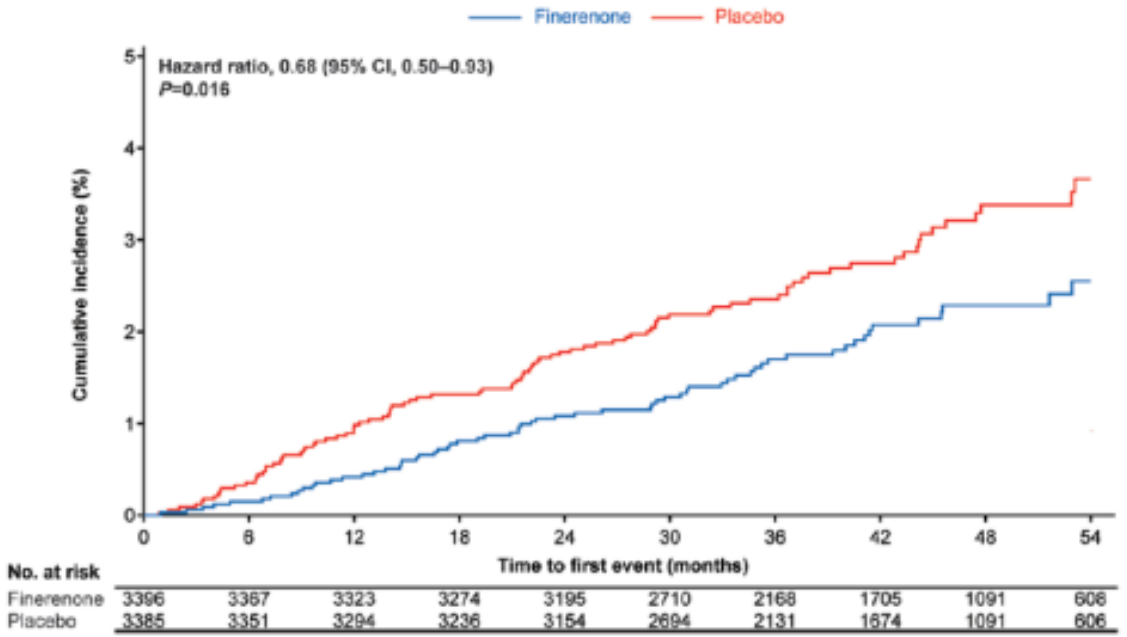
Finerenone in CKD + type 2 DM : FIGARO CKD

Finerenone -a selective, nonsteroidal mineralocorticoid receptor antagonist

FIDELIO-DKD -in CKD and DM T2, treatment with finerenone resulted in lower risks of CKD progression and cardiovascular events than placebo.

FIGARO-DKD - Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease
7352 patients

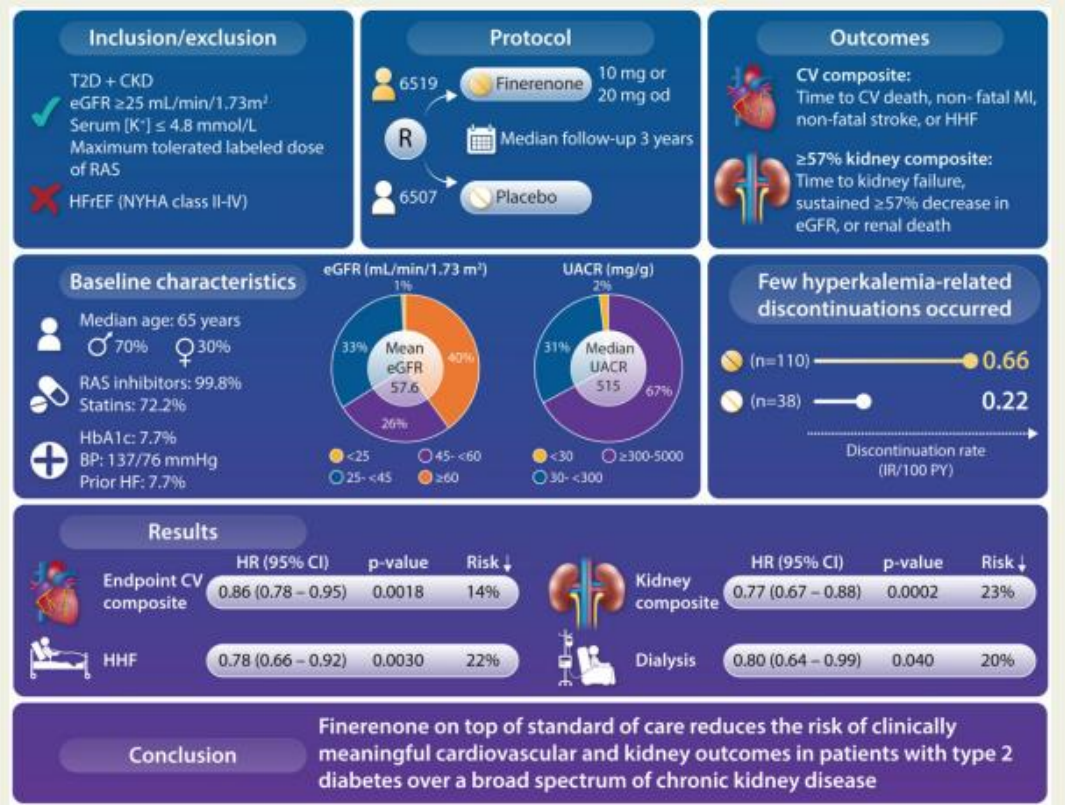
Improved CV outcomes in patients with albuminuric CKD and type 2 diabetes.



Kaplan-Meier estimate of **time to new-onset HF** (first hospitalization for HF in patients without a history of HF at baseline).

N Engl J Med. 2020;383(23):2219-2229.
N Engl J Med. 2021;385(24):2252-2263
Eur Heart J. 2022;43(6):474-48
Circulation 2022; 145:437-447

Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis



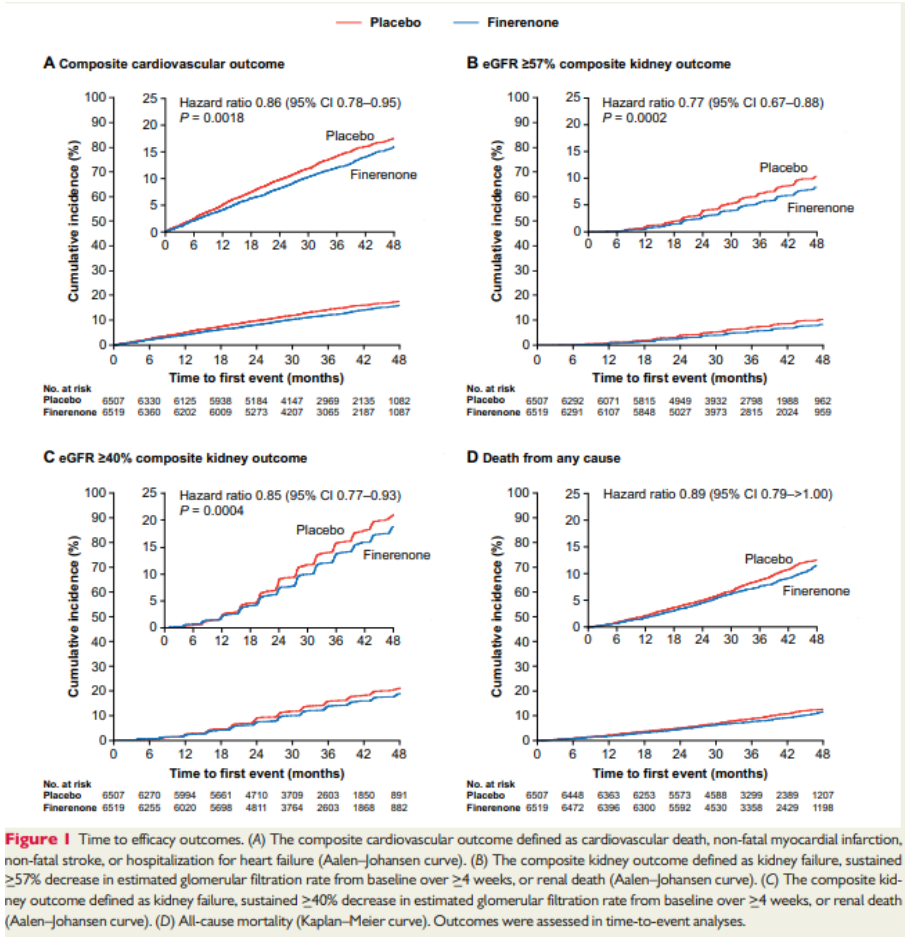
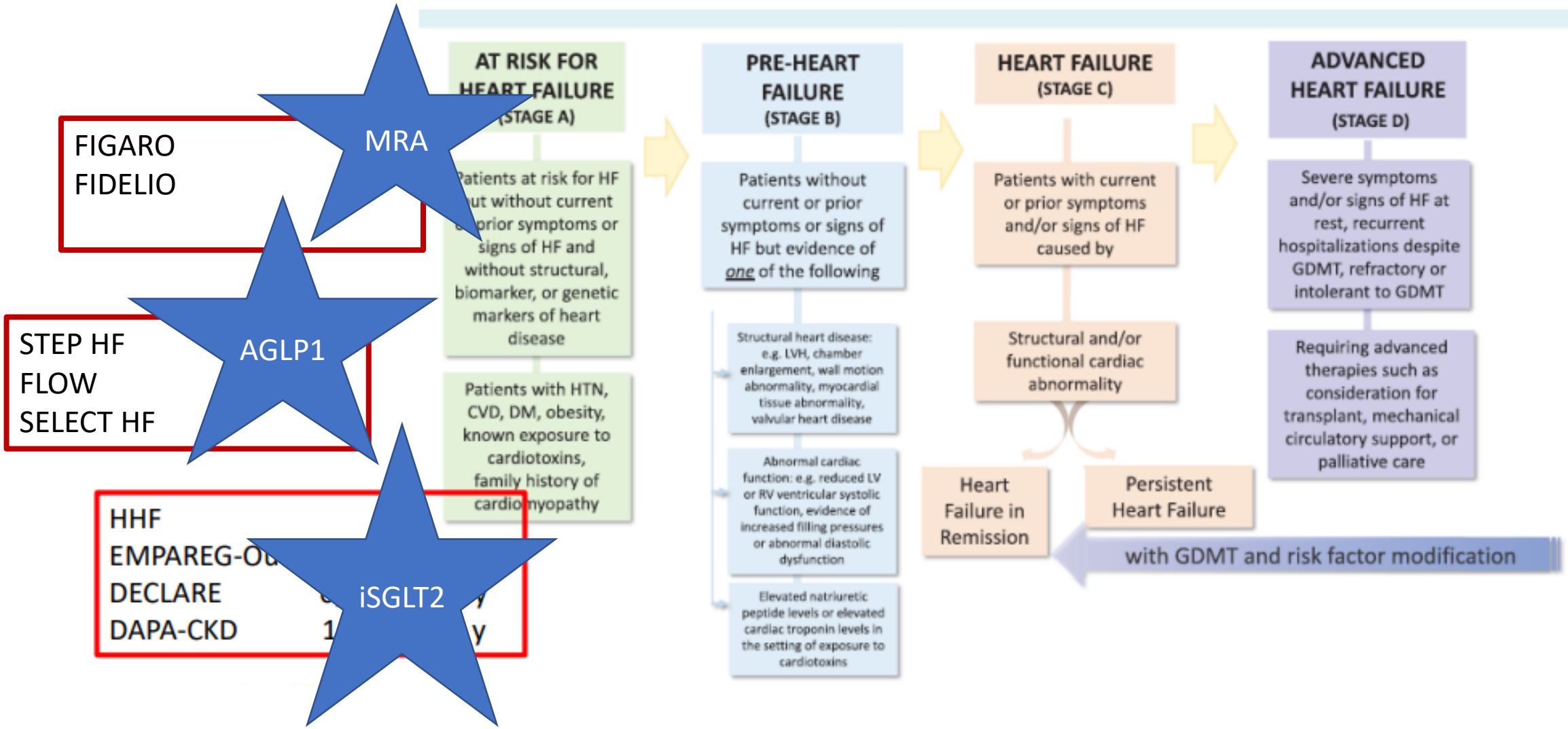


Figure 1 Time to efficacy outcomes. (*A*) The composite cardiovascular outcome defined as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure (Aalen–Johansen curve). (*B*) The composite kidney outcome defined as kidney failure, sustained ≥57% decrease in estimated glomerular filtration rate from baseline over ≥4 weeks, or renal death (Aalen–Johansen curve). (*C*) The composite kidney outcome defined as kidney failure, sustained ≥40% decrease in estimated glomerular filtration rate from baseline over ≥4 weeks, or renal death (Aalen–Johansen curve). (*D*) All-cause mortality (Kaplan–Meier curve). Outcomes were assessed in time-to-event analyses.

Argawal et al. European Heart Journal (2022) 43, 474–484

Universal definition of HF



Prevention of HFpEF …

In DM

- SGLT2 inhibitors for most patients
- If high risk (HTN, dyslipidemia, PAD,…) screen with NP
  - If NT-ProBNP > 125ng/ml – consider ACEi and Beta-blockers

Obesity

- Weight loss…..bariatric surgery
- Future – Semaglutide? Tirzepatide? (results from SELECT and SURMOUNT-MMO)

CKD (non-DM)

- SGLT2 Inhibitors

CKD in DM pts

- SGLT2 Inhibitors
- Finerenone