SGLT2 inhibitors: Delivering benefits beyond glycemic control

Prof. Prafulla Kerkar

15th Best of ACC Conference Chennai, 28 Sep 2022

SGLT2 inhibitors: DELIVERing benefits beyond glycemic control

Prof. Prafulla Kerkar

15th Best of ACC Conference Chennai, 28 Sep 2022

ESC European Society of Cardiology

European Heart Journal (2022) **43**, 1029–1030
https://doi.org/10.1093/eurheartj/ehab765

CARDIOPULSE

Braunwald's Corner

SGLT2 inhibitors: the statins of the 21st century

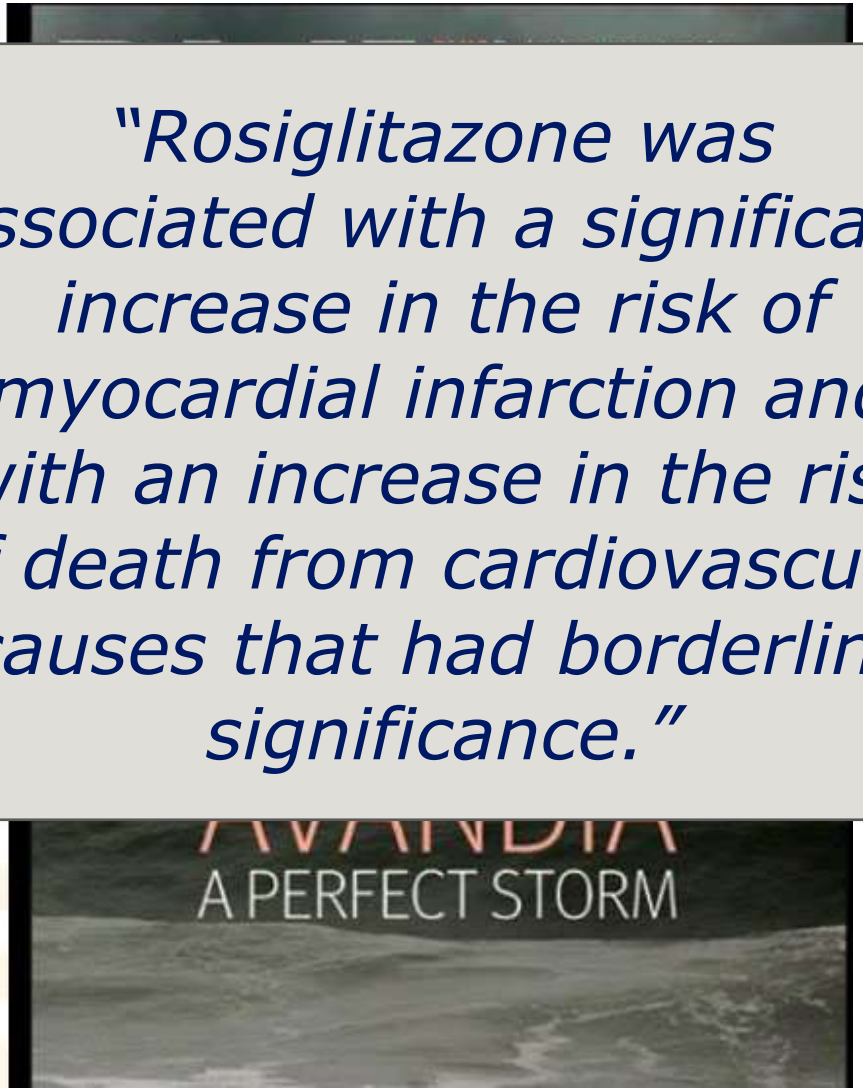
Eugene Braunwald [1,2]*

[1]TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Hale Building for Transformative Medicine, Suite 7022, 60 Fenwood Road, Boston, MA 02115, USA; and [2]Department of Medicine, Harvard Medical School, Boston, MA, USA

A relatively small number of drugs have been responsible for major advances in medical practice. The discovery, development, and elucidation of the mechanisms of action of aspirin, penicillin, and statins are remarkable success stories, each with some surprises and each crowned by a Nobel Prize. The sodium glucose co-transporter inhibitors have been proven effective in the treatment of type 2 diabetes mellitus, various forms of heart failure, and kidney failure and represent *the, or one of the*, major pharmacological advances in cardiovascular medicine in the 21st century.

Diabetes and CVD: A perfect storm!

Overall			1.43 (1.03–1.98)	0.03
Death from cardiovascular causes				
Small trials combined	25/6,845 (0.36)	7/3980 (0.18)	2.40 (1.17–4.91)	0.02
DREAM	12/2,635 (0.46)	10/2634 (0.38)	1.20 (0.52–2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2895 (0.17)	0.80 (0.17–3.86)	0.78
Overall			1.64 (0.98–2.74)	0.06



"Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance."

Nissen SE, Wolski K. N Engl J Med 2007; 356: 2457-2471

Regulatory Requirements

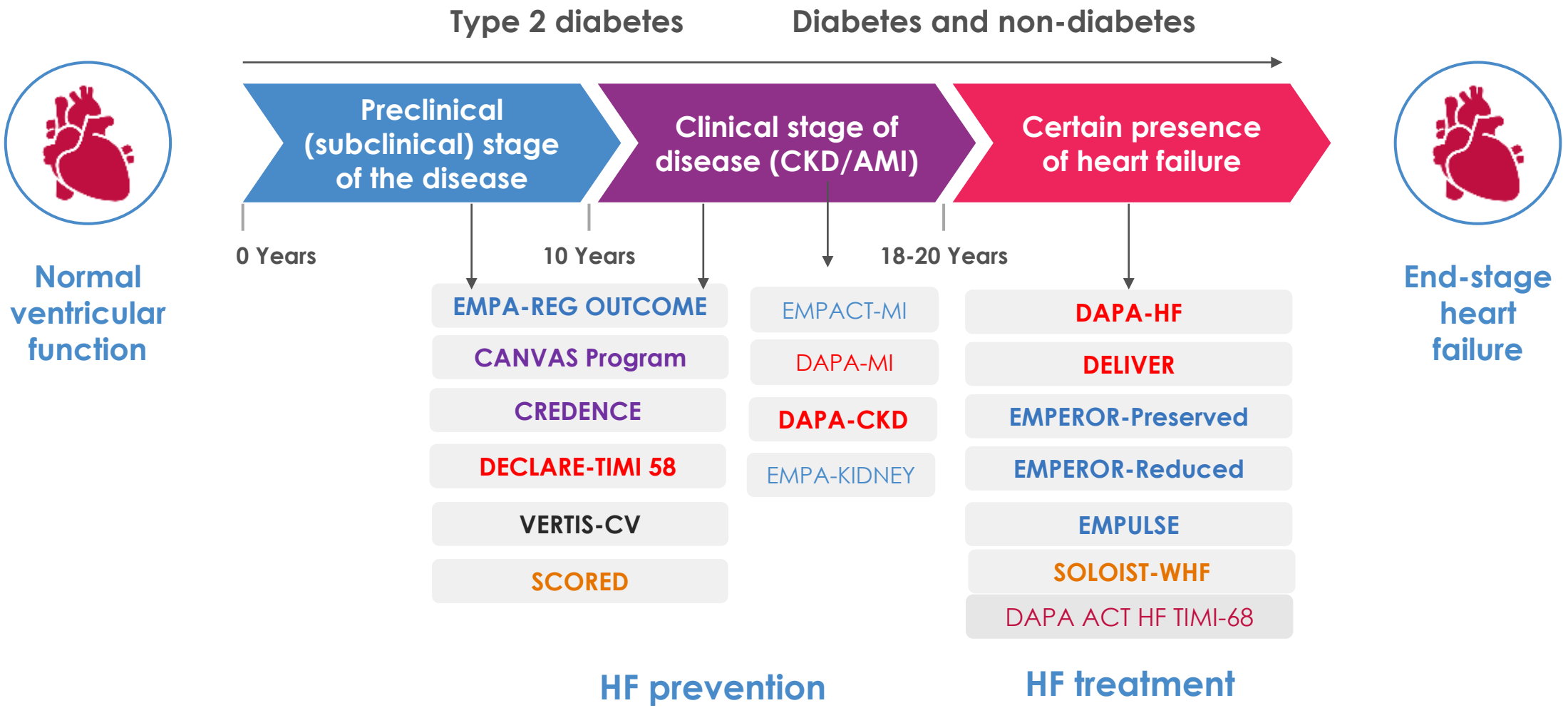
European Medicines Agency (EMA) and US Food and Drug Administration (FDA): Need for CV Outcomes Studies

- 'Demonstrate that a new anti-diabetic therapy is not associated with **unacceptable increase** in cardiovascular risk'

EMA. 2012. http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500129256&mid=WC0b01ac058009a3dc.
FDA. 2008. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf

Story of SGLT2 inhibition in T2DM

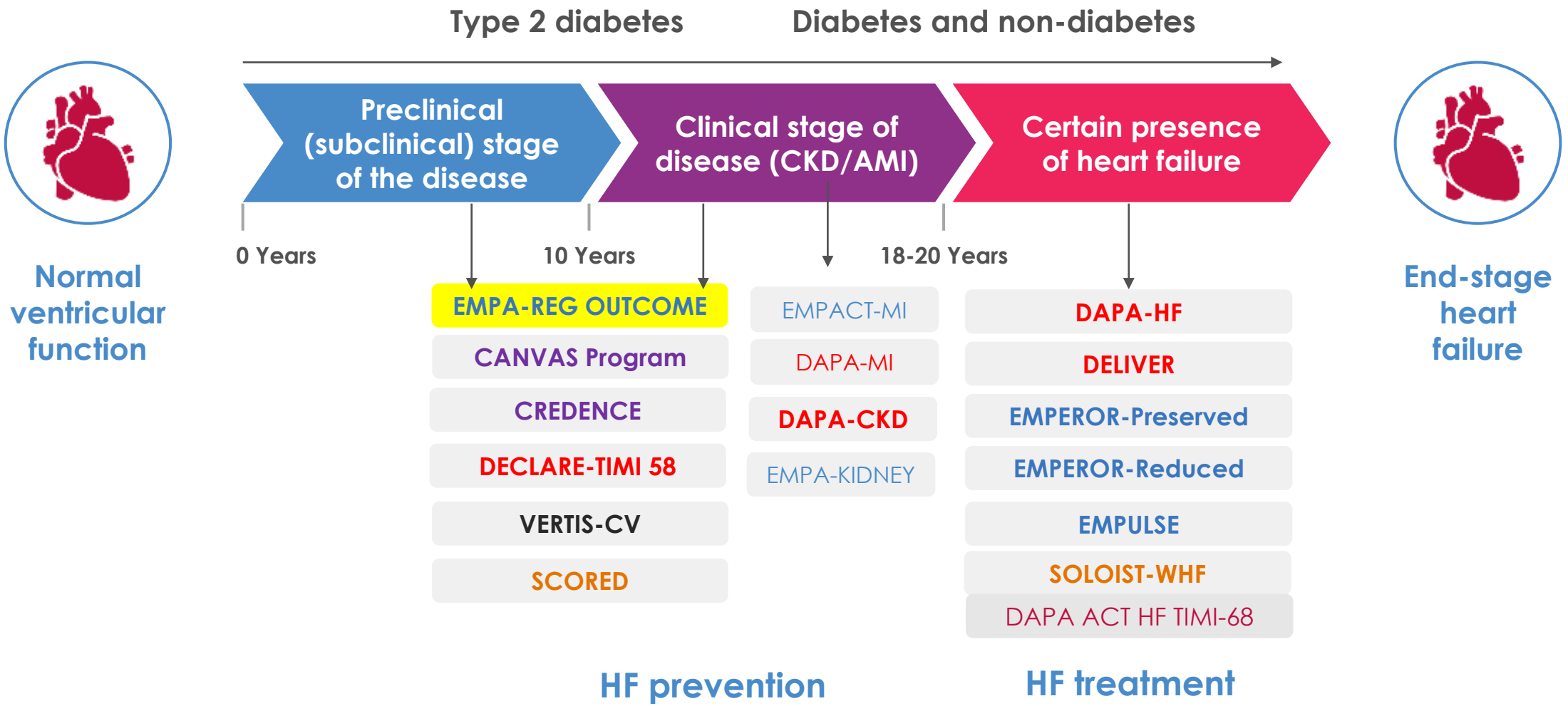
-- across the whole spectrum of CV disease in T2DM --



Adapted from Bhatt DL *et al. Cell Metab*. 2019 Courtesy Prof. Stefan Anker

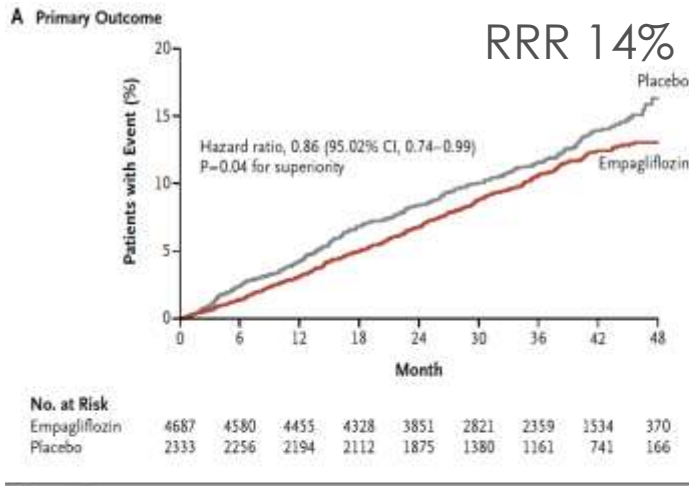
Story of SGLT2 inhibition in T2DM

-- across the whole spectrum of CV disease in T2DM --



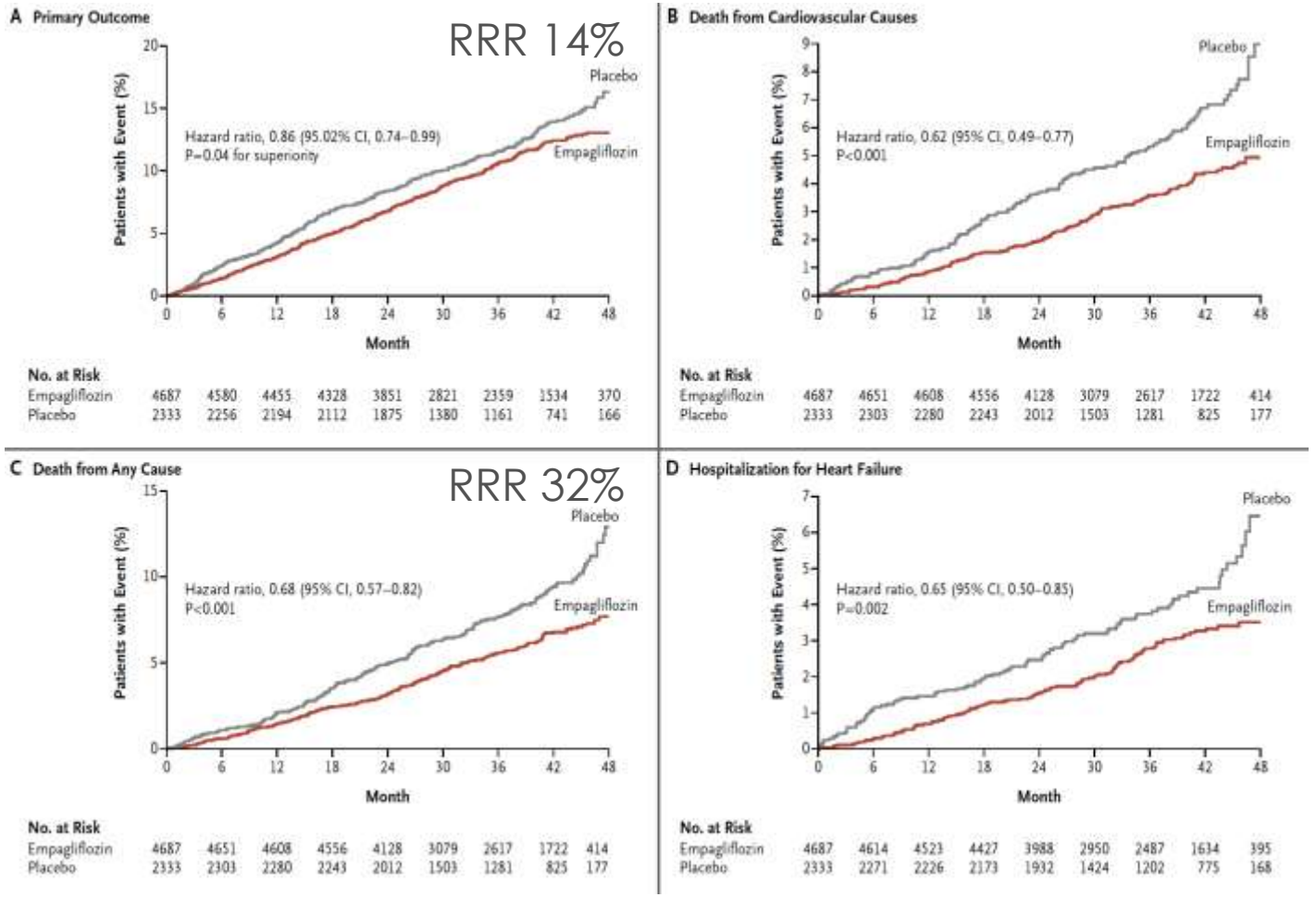
Adapted from Bhatt DL *et al. Cell Metab*. 2019 Courtesy Prof. Stefan Anker

EMPA-REG Outcome: CV outcomes and all cause death



Zinman et al.N Engl J Med 2015; 373:2117-28

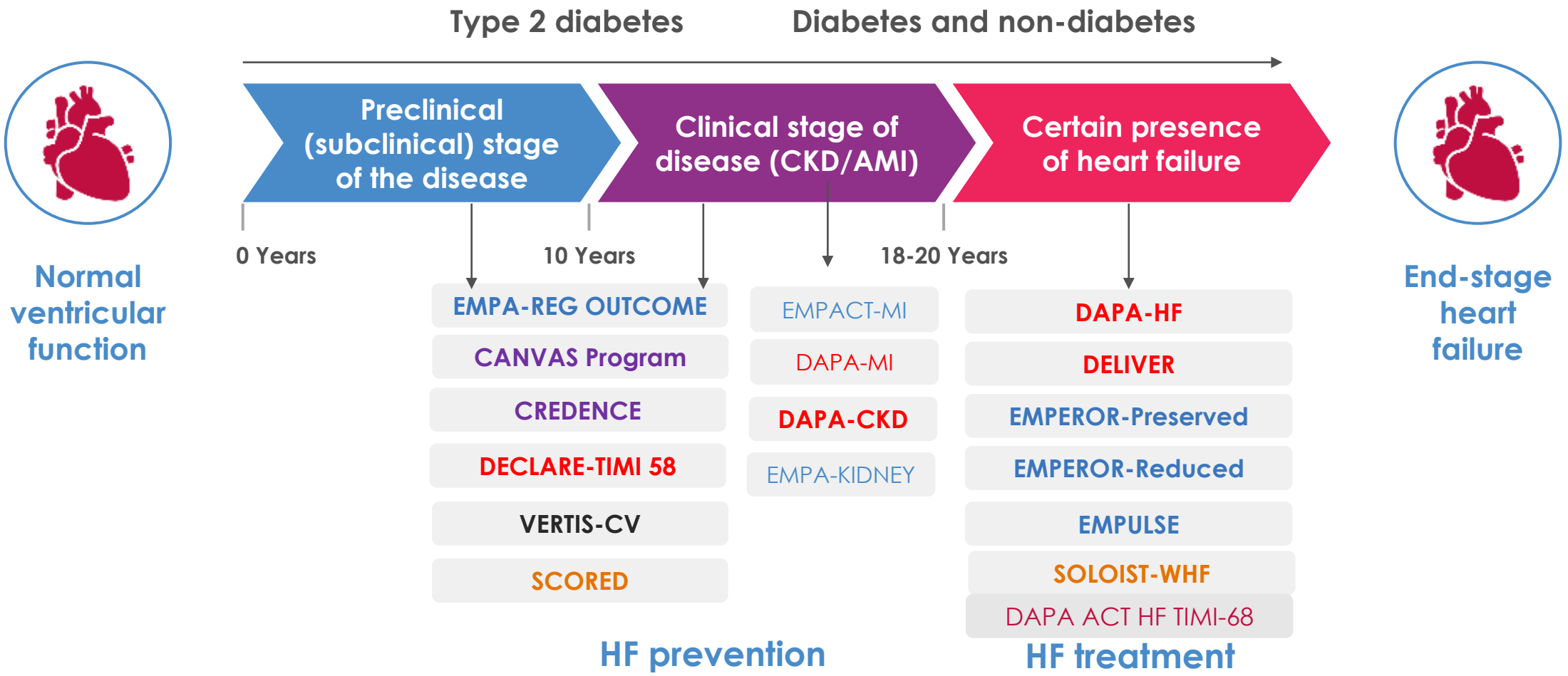
EMPA-REG Outcome: CV outcomes and all cause death



Zinman et al.N Engl J Med 2015; 373:2117-28

Story of SGLT2 inhibition in T2DM

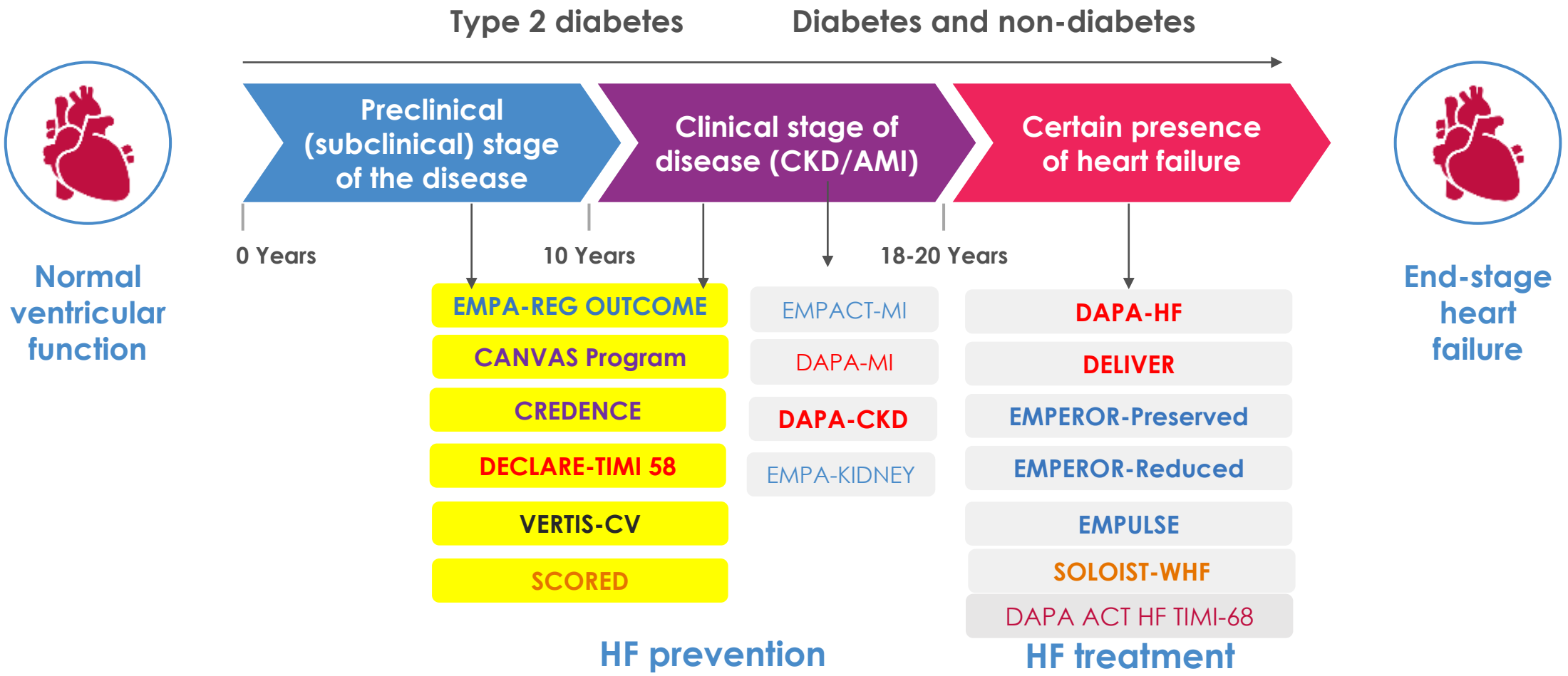
-- across the whole spectrum of CV disease in T2DM --



Adapted from Bhatt DL *et al. Cell Metab*. 2019 Courtesy Prof. Stefan Anker

Story of SGLT2 inhibition in T2DM

-- across the whole spectrum of CV disease in T2DM --



Adapted from Bhatt DL *et al. Cell Metab*. 2019 Courtesy Prof. Stefan Anker

SGLT2i CVOTs in patients with T2DM

Table 1. Cardiovascular Outcome Trials Involving Patients with Type 2 Diabetes.*

Variable	EMPA-REG OUTCOME	CANVAS Program	CREDENCE	DECLARE–TIMI 58	VERTIS CV	SCORED	All
Drug	Empagliflozin	Canagliflozin	Canagliflozin	Dapagliflozin	Ertugliflozin	Sotagliflozin	
No. of patients	7020	10,142	4401	17,160	8246	10,584	57,553
Atherosclerotic cardiovascular disease — % of patients	100	65.6	50.4	40.6	100	48.6	63.0
History of heart failure — % of patients	10.1	14.4	14.8	10.0	23.7	31.0	17.0
Outcomes — hazard ratio (95% CI)†							
Major adverse cardiovascular events	0.86 (0.74–0.99)	0.86 (0.75–0.97)	0.80 (0.67–0.95)	0.93 (0.84–1.03)	0.99 (0.88–1.12)	0.77 (0.65–0.91)	0.89 (0.84–0.94)
Cardiovascular death	0.62 (0.49–0.77)	0.87 (0.72–1.06)	0.78 (0.61–1.00)	0.98 (0.82–1.12)	0.92 (0.77–1.10)	0.90 (0.73–1.12)	0.86 (0.79–0.93)
Hospitalization for heart failure	0.65 (0.50–0.85)	0.67 (0.52–0.87)	0.61 (0.47–0.80)	0.73 (0.61–0.88)	0.70 (0.54–0.90)	0.67 (0.55–0.82)	0.68 (0.62–0.75)

* Data sources for the individual trials are as follows: EMPA-REG OUTCOME, Zinman et al.[14]; CANVAS Program, Neal et al.[15]; CREDENCE, Perkovic et al.[16]; DECLARE–TIMI 58, Wiviott et al.[17]; VERTIS CV, Cannon et al.[18]; and SCORED, Bhatt et al.[19] Data are also based on a meta-analysis by McGuire et al.[20]

† Hazard ratios are based on a time-to-first event analysis, except for SCORED, which estimated hazard ratios for major adverse cardiovascular events and hospitalization for heart failure on the basis of a total-event analysis. CI denotes confidence interval.

Circulation

EDITORIAL

The Serendipitous Story of SGLT2 Inhibitors in Heart Failure

Articles, see p 2516 and p 2528

Subodh Verma, MD, PhD
John J.V. McMurray, MB ChB (Hons), MD

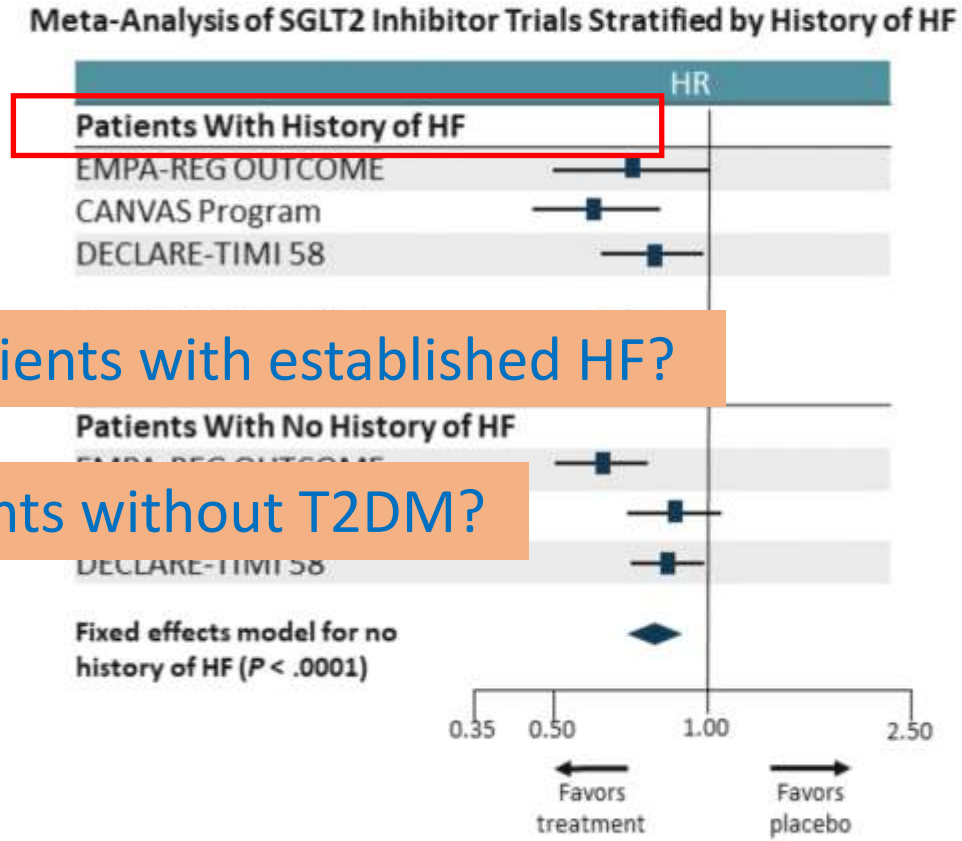
Diabetes mellitus intersects with cardiovascular disease at every level. Although there has been much focus on understanding atherosclerotic complications, less well appreciated is the relationship between diabetes mellitus and heart failure. In addition to being a key and independent risk factor for the development of heart failure,[1] diabetes mellitus is also one of the most important adverse prognostic factors in those with established heart failure with either reduced or preserved ejection fraction (EF).[1,2] Diabetes mellitus is associated with a high prevalence of unrecognized left ventricular diastolic and systolic dysfunction, and it accelerates the development of overt heart failure compared with similar patients without diabetes mellitus.[3] In addition to car-

CVOTs: SGLT2 Inhibitors Prevent HHF

	EMPA-REG	CANVAS	DECLARE-TIMI 58
Drug	Empa (10 or 25 mg once daily)	Cana (100 or 300 mg once daily)	Dapa (10 mg once daily)
N			
Follow-up, y	3.1	2.4	4.2
ASCVD, %			
History of HF, %	10.1	14.4	10
eGFR < 60 mL/min/1.73 m^2, %	25.9	20.1	7.4

Can SGLT2i be used to treat patients with established HF?

What about in HF patients without T2DM?

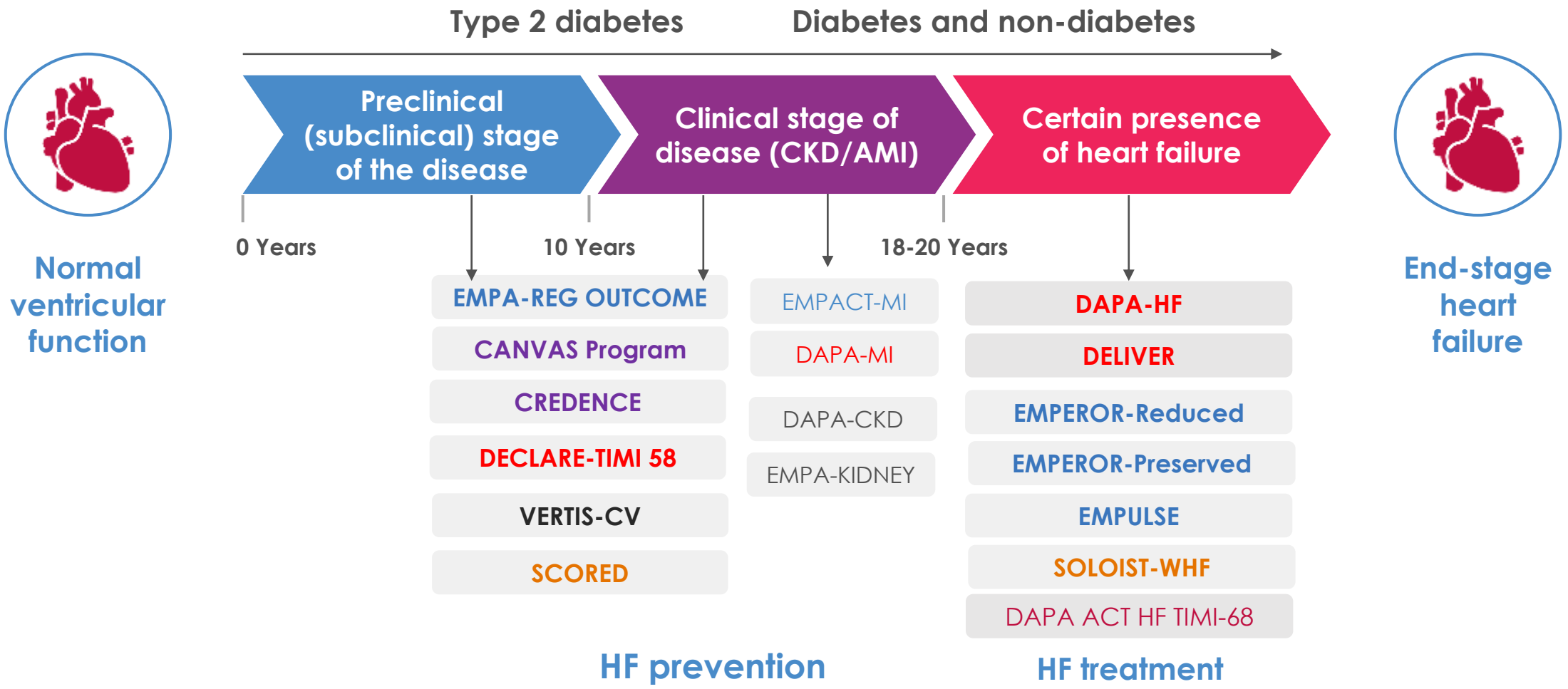


- In all CVOTs: mean age was ~63 y; ~30% or more participants were female

Zelniker TA, et al. *Lancet*. 2019;393:31-39.

Story of SGLT2 inhibition in heart failure – A full success

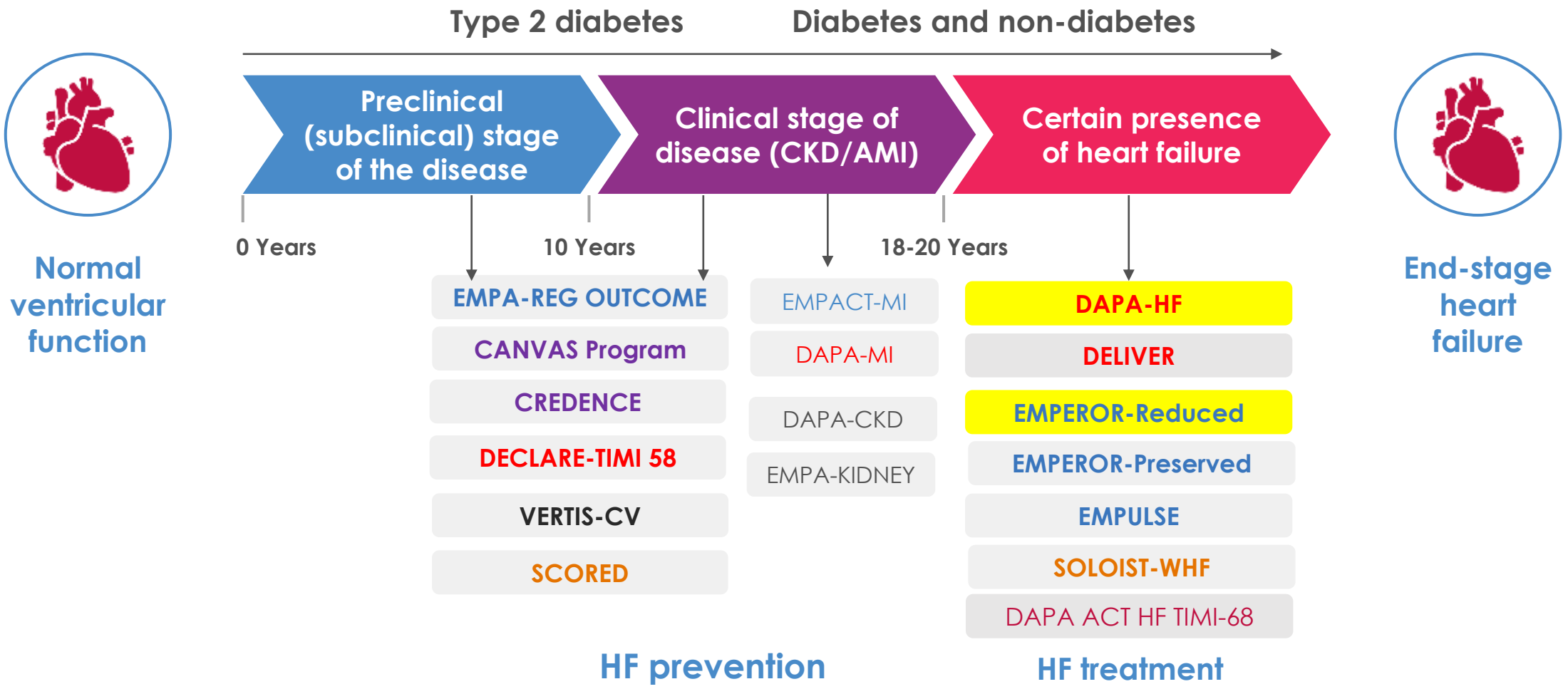
-- across the whole spectrum of LVEF --



Adapted from Bhatt DL *et al. Cell Metab*. 2019

Story of SGLT2 inhibition in heart failure – A full success

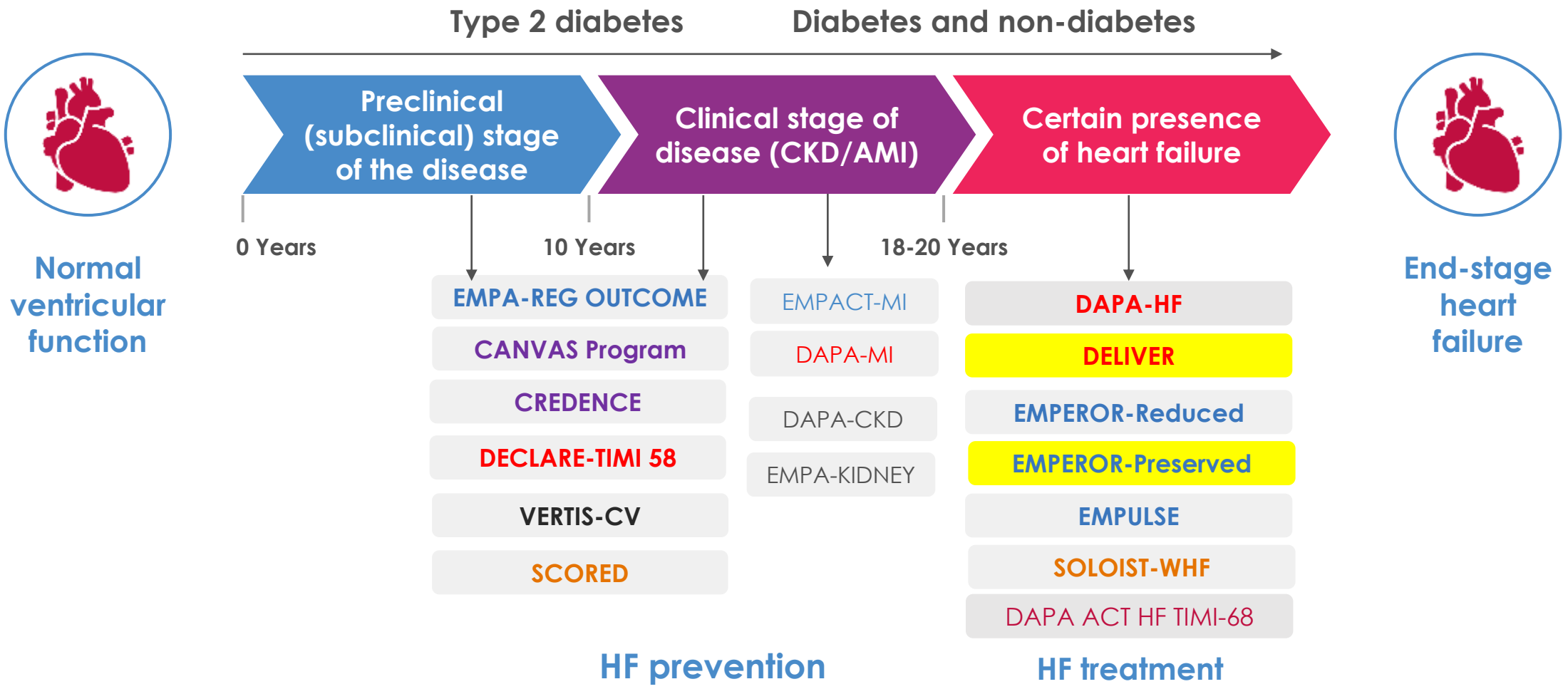
-- across the whole spectrum of LVEF --



Adapted from Bhatt DL *et al. Cell Metab*. 2019

Story of SGLT2 inhibition in heart failure – A full success

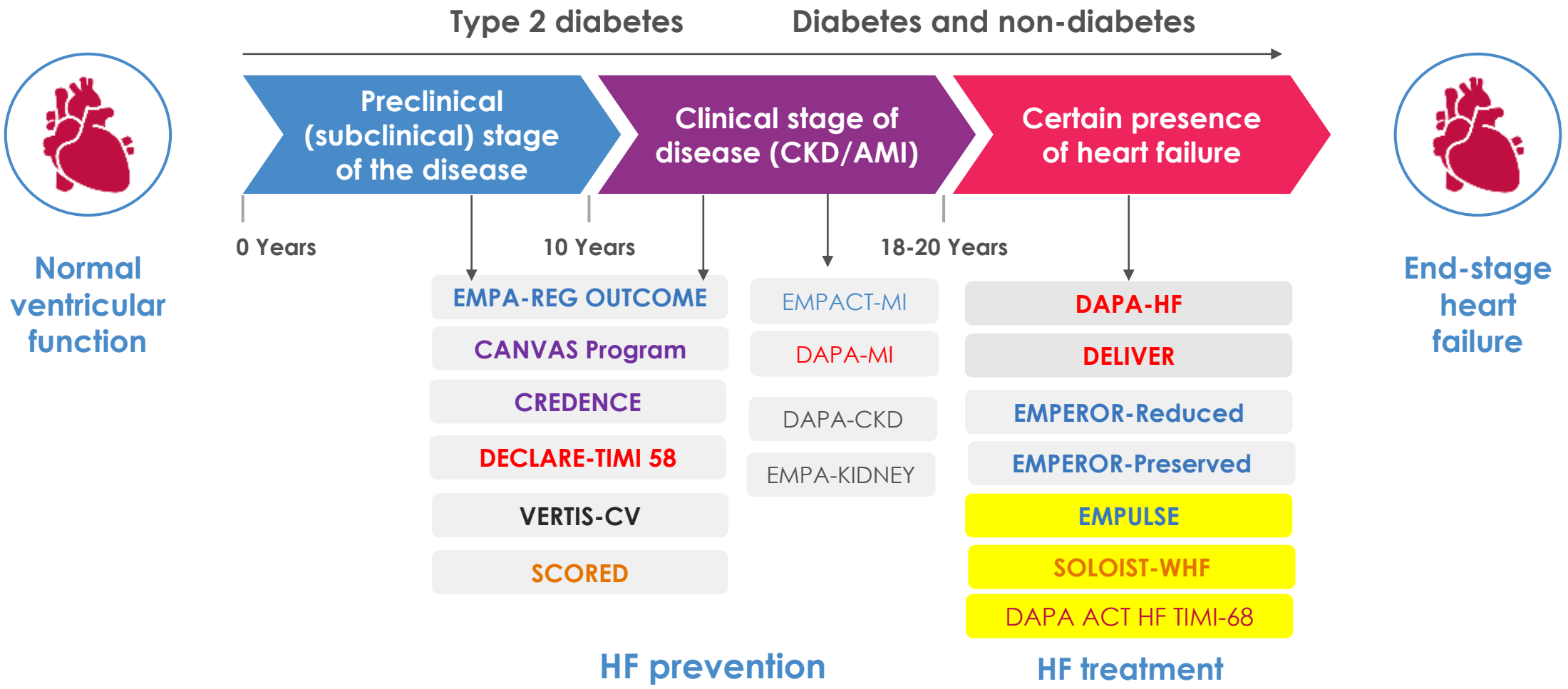
-- across the whole spectrum of LVEF --



Adapted from Bhatt DL *et al. Cell Metab*. 2019

Story of SGLT2 inhibition in heart failure – A full success

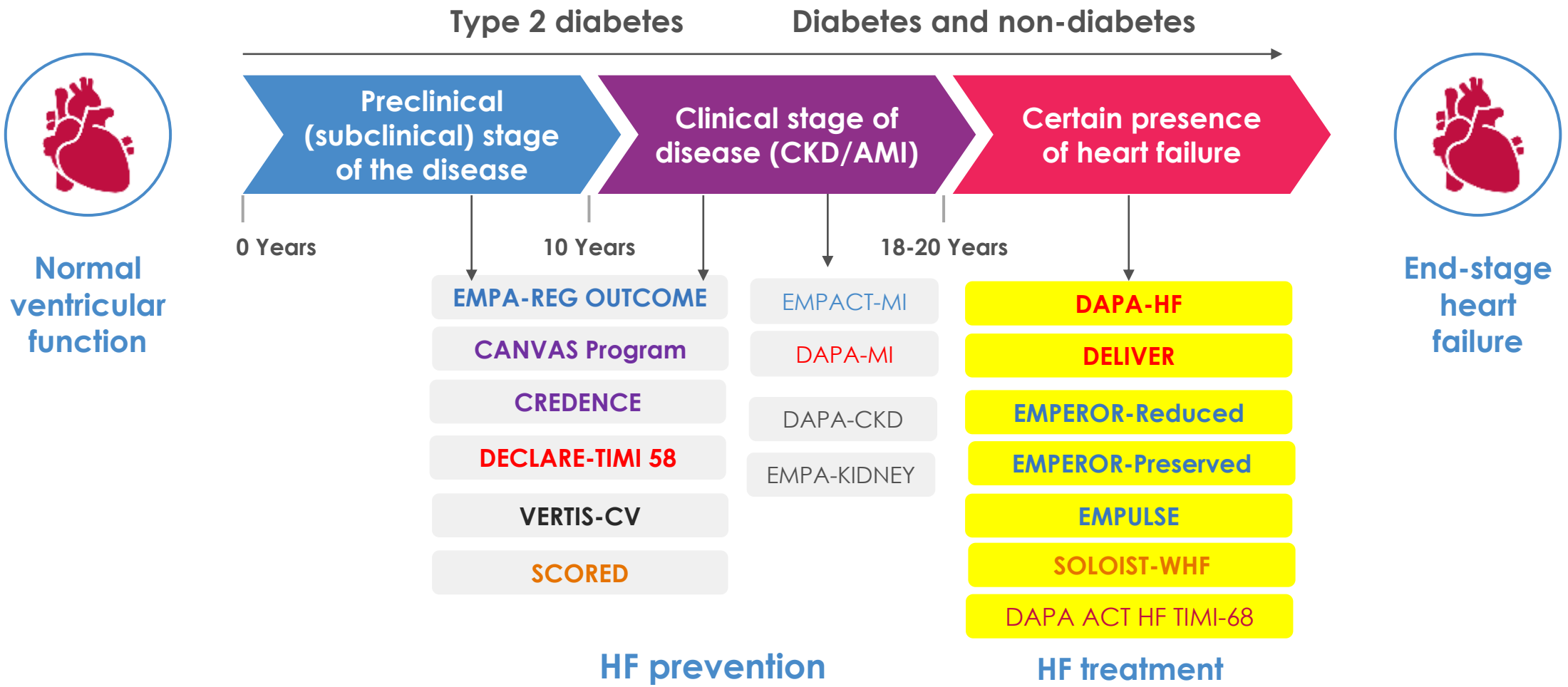
-- across the whole spectrum of LVEF --



Adapted from Bhatt DL *et al. Cell Metab*. 2019

Story of SGLT2 inhibition in heart failure – A full success

-- across the whole spectrum of LVEF --



Adapted from Bhatt DL *et al. Cell Metab*. 2019

Evidence in HFrEF (LVEF<40%):

Heart Failure with reduced ejection fraction in patients with/without diabetes

SGLT2i CVOTs in patients with HF

Table 2. Cardiovascular Outcome Trials Involving Patients with Heart Failure.*

Variable	DAPA-HF	EMPEROR-Reduced	EMPEROR-Preserved	SOLOIST-WHF
Drug	Dapagliflozin	Empagliflozin	Empagliflozin	Sotagliflozin
No. of patients	4744	3730	5988	1222
Type 2 diabetes — % of patients	41.7	49.8	49.1	100
LVEF — %	31.1	27.4	54.3	35
Median NT-proBNP — pg/ml	1437	1907	970	1864
Mean eGFR — ml/min/1.73 m^2	65.7	62.0	60.6	49.9
Outcomes — hazard ratio (95% CI)				
Cardiovascular death or hospitalization for heart failure	0.74 (0.65–0.85)	0.75 (0.68–0.86)	0.79 (0.69–0.90)	0.67 (0.52–0.85)
Hospitalization for heart failure	0.70 (0.59–0.83)	0.69 (0.59–0.81)	0.73 (0.61–0.88)	0.64 (0.49–0.83)

* Data sources for the trials are as follows: DAPA-HF, McMurray et al.[24]; EMPEROR-Reduced, Packer et al.[25]; EMPEROR-Preserved, Anker et al.[26]; SOLOIST-WHF, Bhatt et al.[27] The abbreviation eGFR denotes estimated glomerular filtration rate, LVEF left ventricular ejection fraction, and NT-proBNP N-terminal pro–B-type natriuretic peptide.

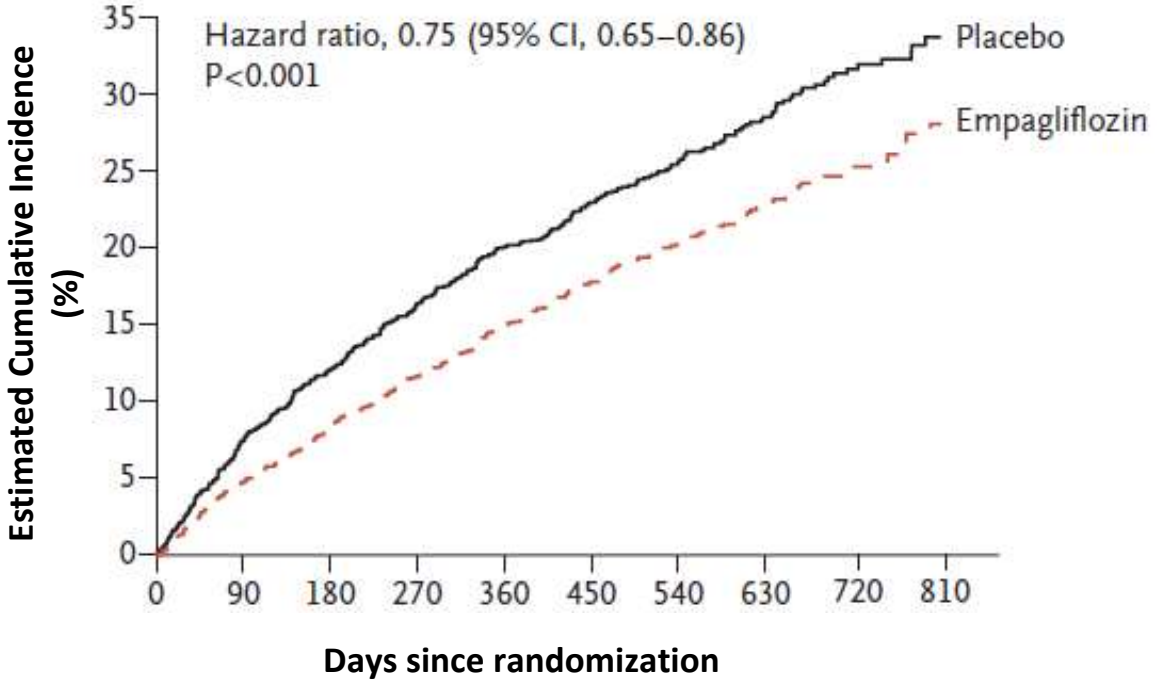
Results in HFrEF patients with/without diabetes:

Primary outcome-composite of CV death or hospitalization for heart failure

Benefits of SGLT2 inhibition are seen early in RCTs

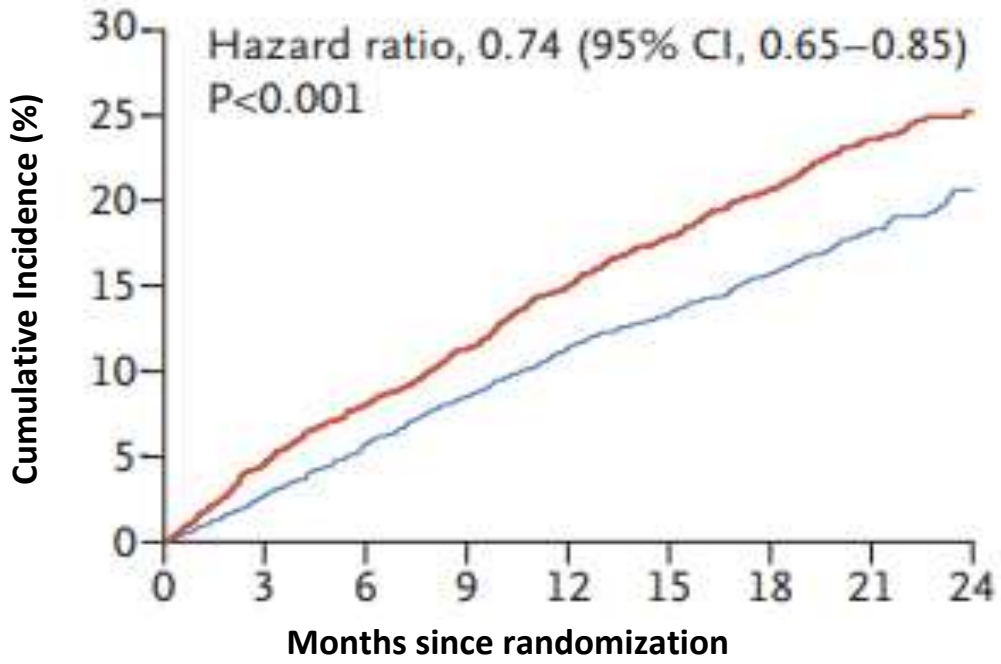
Benefits on top of excellent background therapy

EMPEROR-Reduced



25% risk reduction vs placebo

DAPA-HF

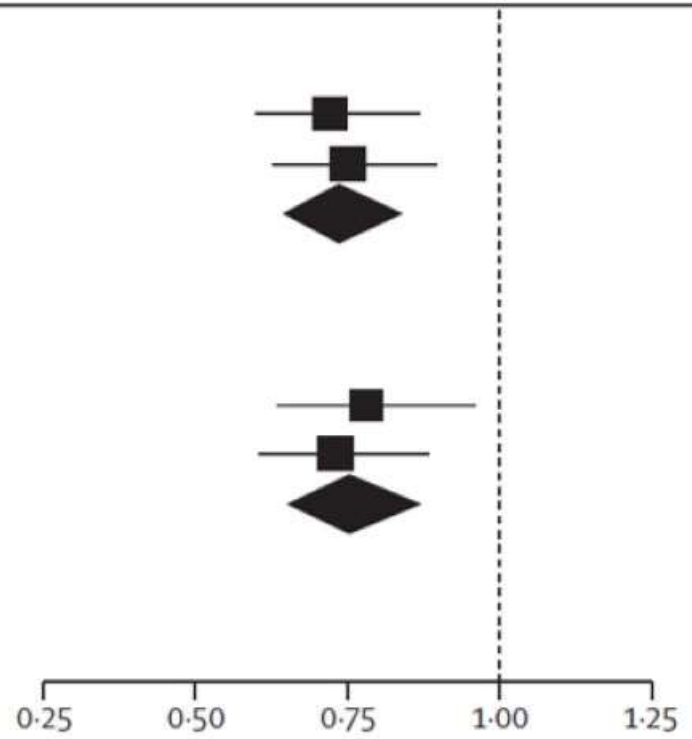


26% risk reduction vs placebo

Benefit of SGLT2 Inhibitors Independent of T2D Status

Meta-Analysis of DAPA-HF and EMPEROR-Reduced: First HHF or CV Death

	Number with event/number of patients (%)		HR (95% CI)
	SGLT2 inhibitor	Placebo	
With diabetes			
EMPEROR-Reduced	200/927 (21·6%)	265/929 (28·5%)	0·72 (0·60–0·87)
DAPA-HF	215/1075 (20·0%)	271/1064 (25·5%)	0·75 (0·63–0·90)
Subtotal			**0·74 (0·65–0·84)**
Test for overall treatment effect p<0·0001			
Test for heterogeneity of effect p=0·76			
Without diabetes			
EMPEROR-Reduced	161/936 (17·2%)	197/938 (21·0%)	0·78 (0·64–0·97)
DAPA-HF	171/1298 (13·2%)	231/1307 (17·7%)	0·73 (0·60–0·88)
Subtotal			**0·75 (0·65–0·87)**
Test for overall treatment effect p<0·0001			
Test for heterogeneity of effect p=0·65			
Test for treatment by subgroup interaction p=0·81			

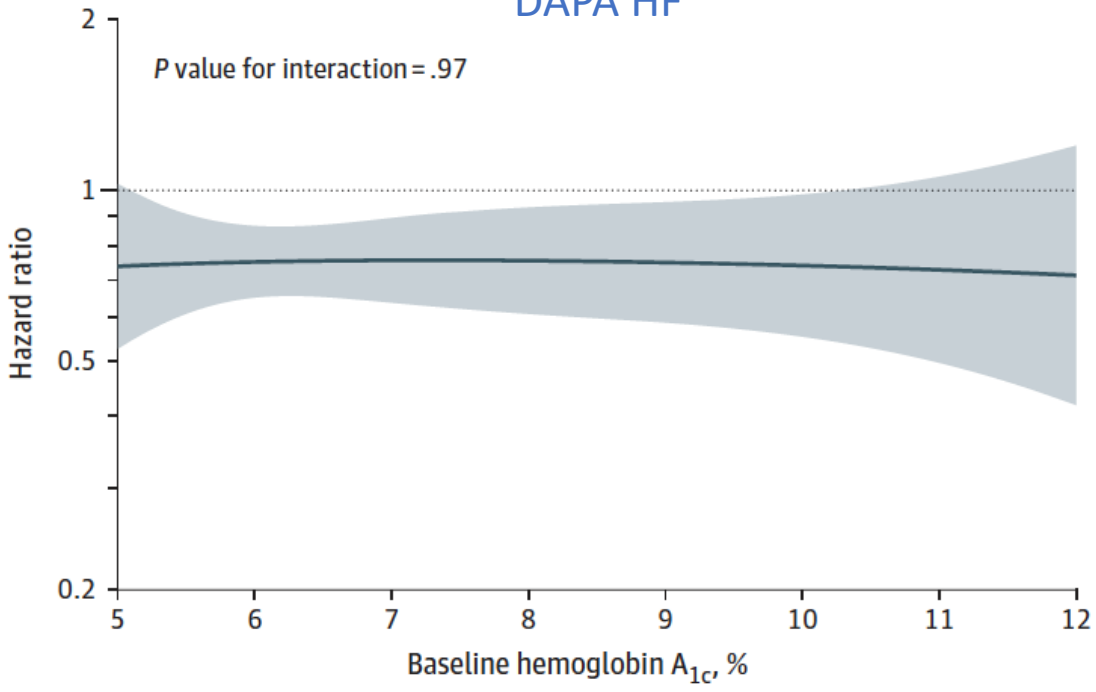


Zannad F, et al. Lancet. 2020;396:819-829.

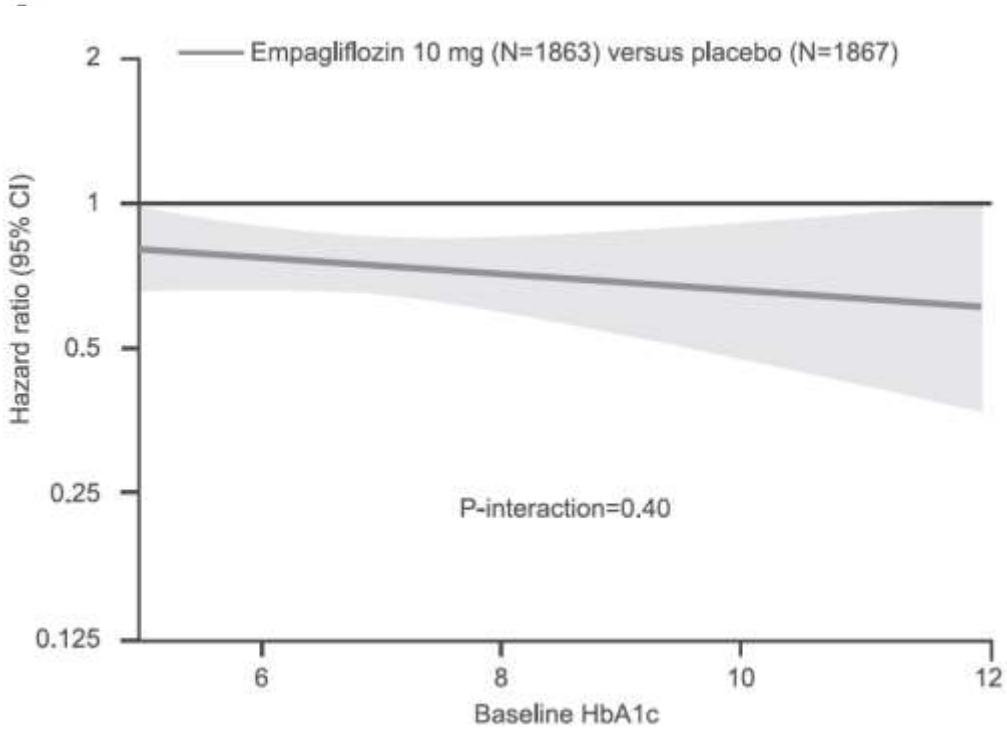
SGLT2 i: Baseline HbA1c Level Does Not Influence Treatment Effect

Primary outcome: Composite of CV death or hospitalization for heart failure

DAPA HF



EMPEROR Reduced



1. Petrie MC et al. JAMA. 2020;323(14):1353-1368 2. Anker SD et al Circulation. 2021;143:337–349.

Consistent Benefit of SGLT2 Inhibitors Across Prespecified Subgroups

Subgroups

- Age, sex, race
- NYHA Class, LVEF, NT-proBNP
- Previous hospitalization, HF etiology
- Baseline drug therapy
- T2D, AF, BMI, baseline eGFR

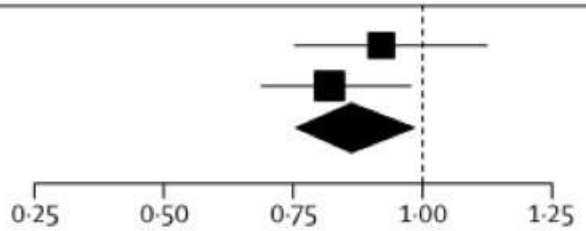
AF, atrial fibrillation; BMI, body mass index; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association.

McMurray JJ, et al. N Engl J Med. 2019;381:1995-2008; Packer M, et al. N Engl J Med. 2020;383:1413-1424.

SGLT2 Inhibitor HFrEF Trial Meta-Analysis
Components of the Primary Endpoint

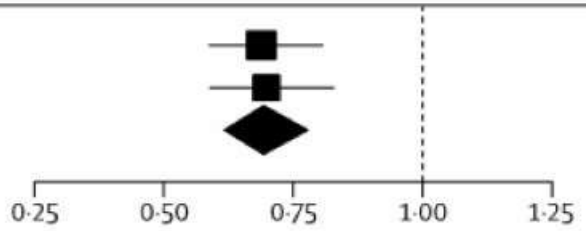
CV Death

	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			



First HHF

	Number with event/number of patients (%)		HR (95% CI)
	SGLT2 inhibitor	Placebo	
EMPEROR-Reduced	246/1863 (13·2%)	342/1867 (18·3%)	0·69 (0·59–0·81)
DAPA-HF	231/2373 (9·7%)	318/2371 (13·4%)	0·70 (0·59–0·83)
Total			**0·69 (0·62–0·78)**
Test for overall treatment effect p<0·0001			
Test for heterogeneity of effect p=0·90			

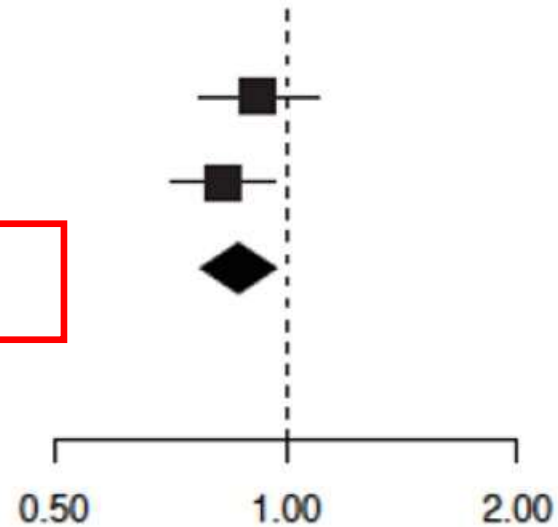


Zannad F, et al. Lancet. 2020;396:819-829.

SGLT2 Inhibitor HFrEF Trial Meta-Analysis:

All-Cause Death

	SGLT2I	Placebo	HR (95% CI)
	n with event/N analysed (%)		
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* = .018
Test for heterogeneity of effect, *P* = .39

Zannad F, et al. *Lancet*. 2020;396:819-829.

Goals of Therapy in HF

Make people feel better

- Improve symptoms/QoL or at least lower the rate of deterioration
- Allow them to continue to lead as normal and unrestricted of a life as possible

Stop them from being admitted to the hospital

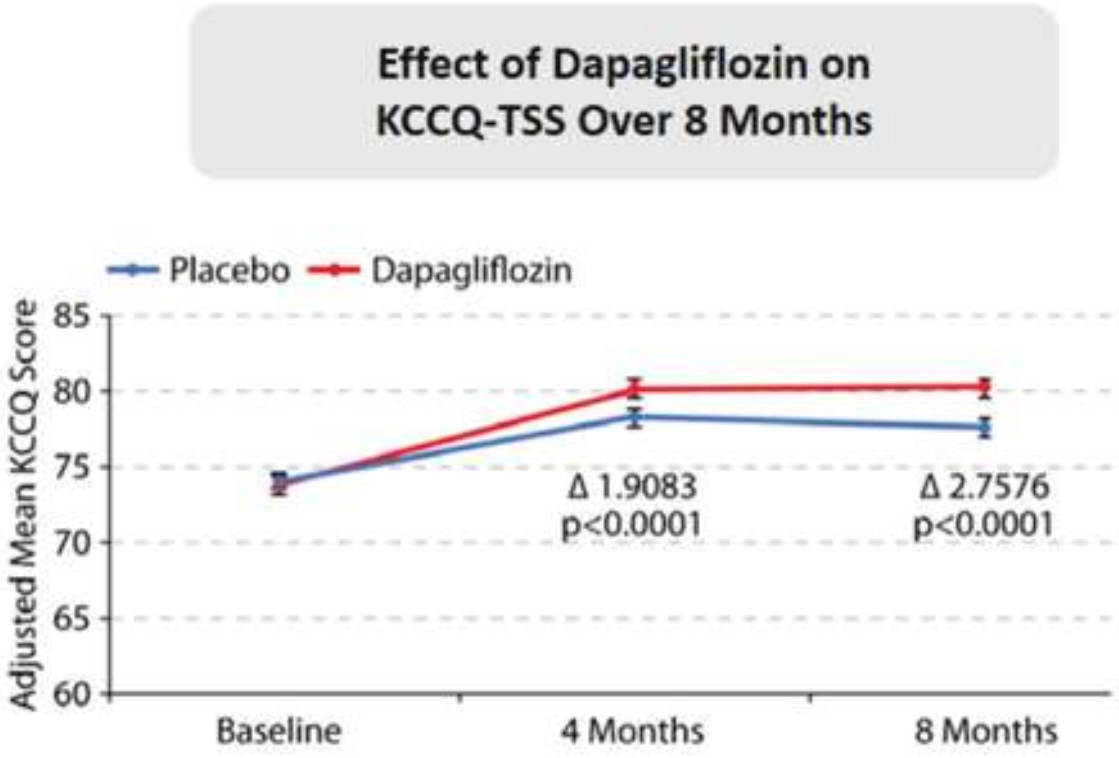
- Apart from being very unpleasant for patients, distressing for families, and costly, it is a bad prognostic development (which is also true of any episode of worsening HF requiring intensification of therapy)

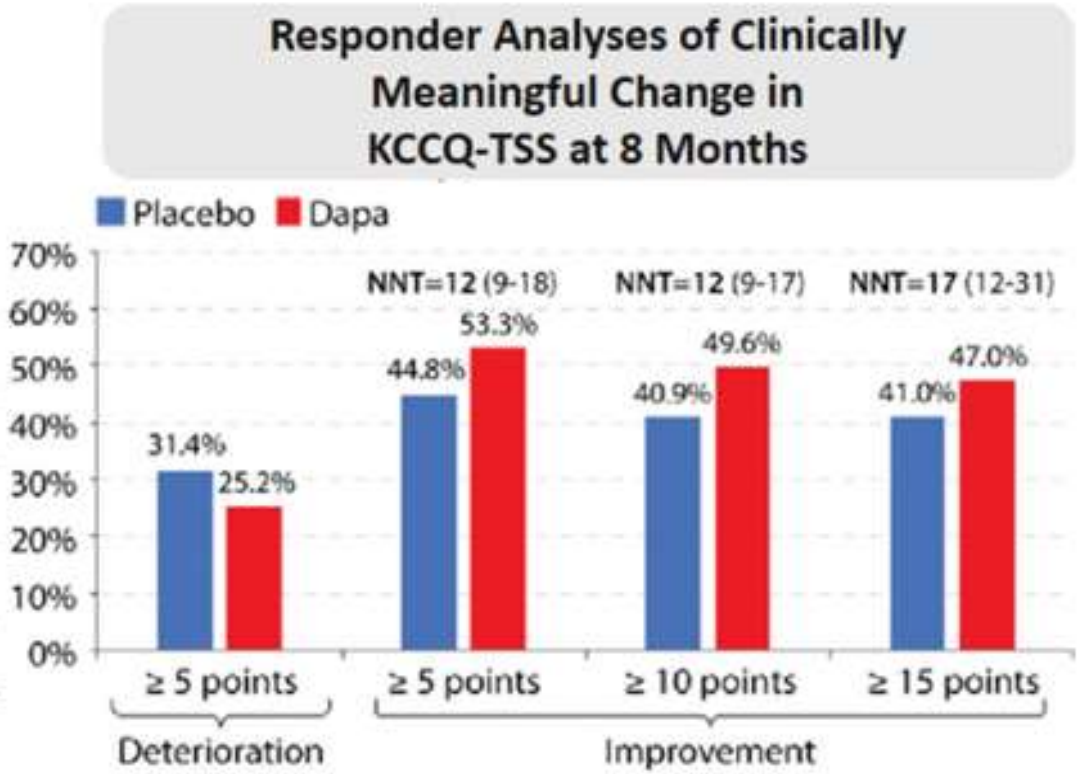
Increase longevity

- Reduce mortality/ premature death, ideally by reducing 2 main modes: sudden death and death from progressive HF (pump failure)

QoL, quality of life.
Personal communication, John J. V. McMurray, MD, FRCP, FESC, FACC, FAHA.

QoL is improved with SGLT2 inhibition in patients with HFrEF: DAPA HF

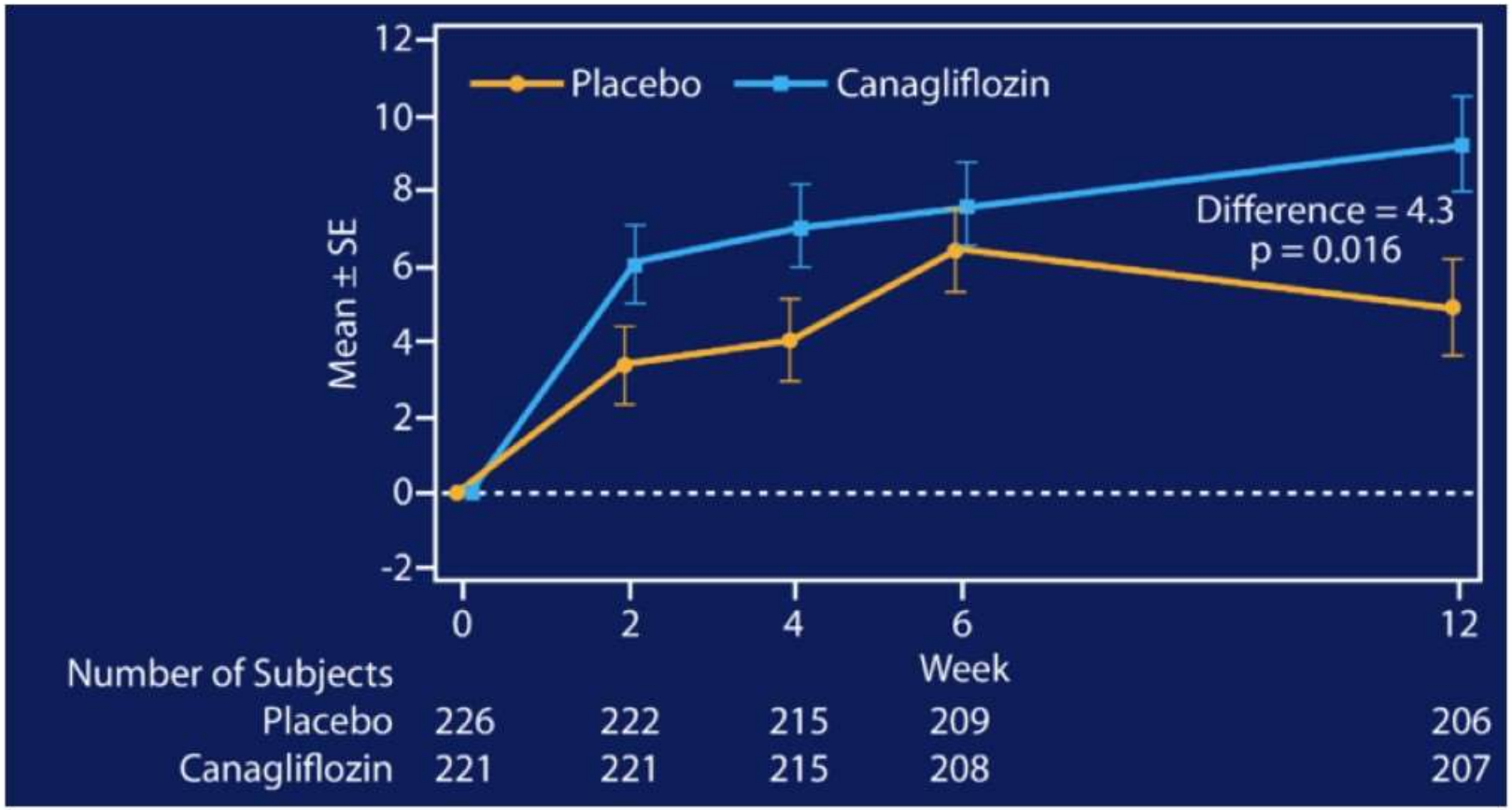




Kosiborod MN, et al. *Circulation*. 2020;141:90-99.

CHIEF-HF

Primary Results: KCCQ-TSS[a]



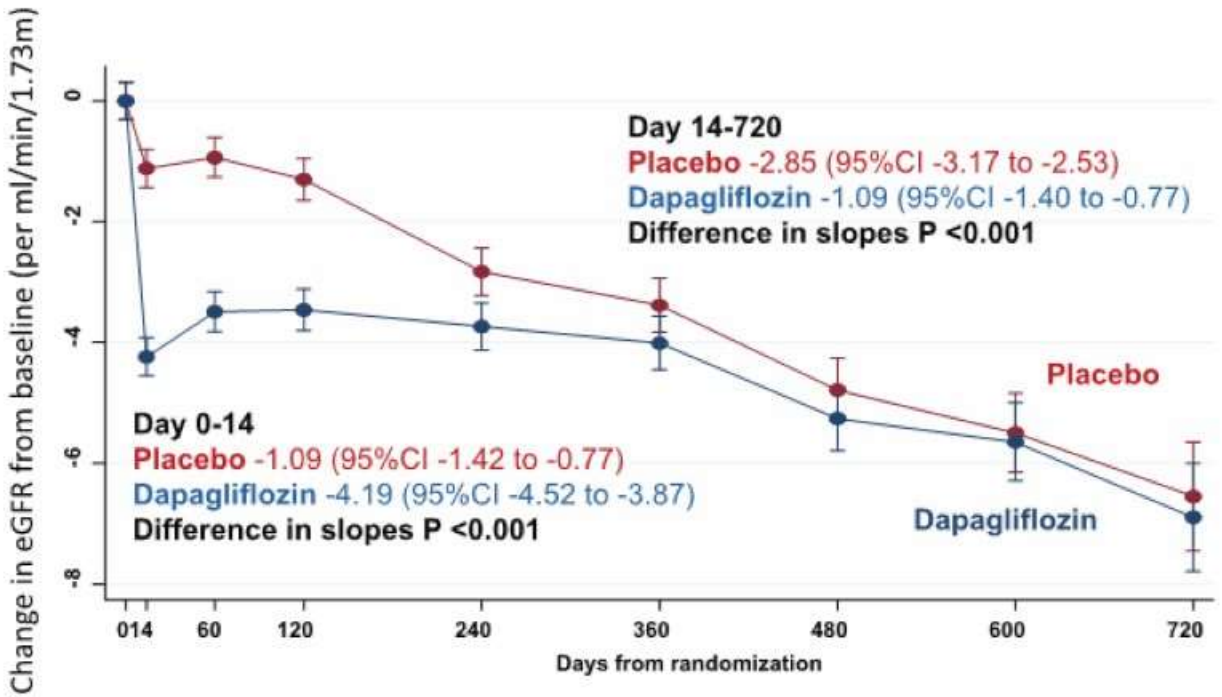
CHIEF-HF is a virtual RCT designed to evaluate the effect of canagliflozin vs placebo on function capacity and HRQoL[b]

TSS, Total Symptom Score.

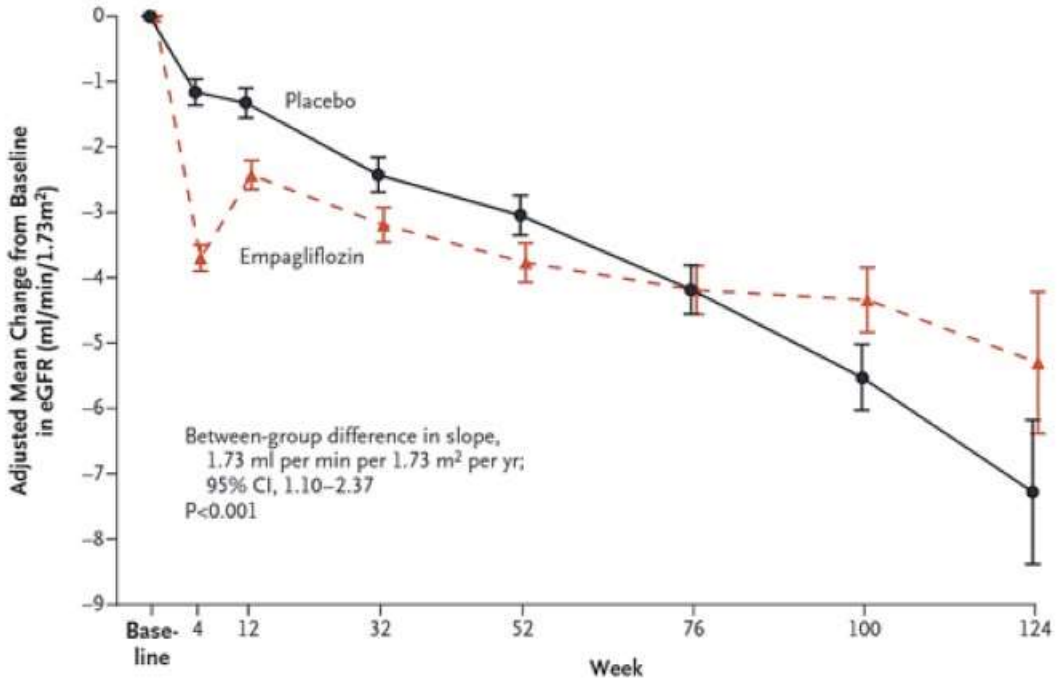
a. Spertus JA, et al. AHA Scientific Sessions; November 16-18, 2021; Virtual. Presentation LBS.05; b. Spertus JA, et al. Circ Heart Fail. 2021;14:e007767,

Preservation in Kidney Function: Change in eGFR From Baseline

DAPA-HF[a]



EMPEROR-Reduced[b]



No. at Risk							
Placebo	1792	1765	1683	1500	1146	745	343	76
Empagliflozin	1799	1782	1720	1554	1166	753	356	80

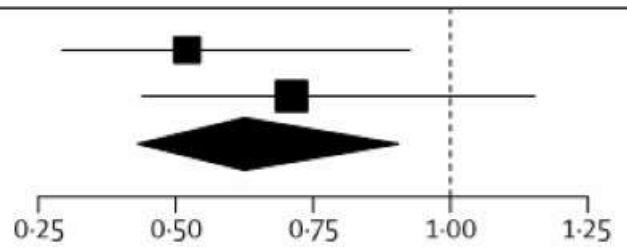
a. Jhund P, et al. Circulation. 2021;143:298-309; b. Packer M, et al. N Engl J Med. 2020;383:1413-1424.

SGLT2 Inhibitor HFrEF Trial Meta-Analysis
Hard Kidney Outcomes

First Kidney Outcome Composite*

	Number with event/number of patients (%)		HR (95% CI)
	SGLT2 inhibitor	Placebo	
EMPEROR-Reduced	18/1863 (1·0%)	33/1867 (1·8%)	0·52 (0·29–0·92)
DAPA-HF	28/2373 (1·2%)	39/2371 (1·6%)	0·71 (0·44–1·16)
Total			**0·62 (0·43–0·90)**

Test for overall treatment effect p=0·013
Test for heterogeneity of effect p=0·42



*Kidney composite was defined as time to first occurrence of any of the components of ≥ 50% sustained decline in eGFR, end-stage kidney disease, or kidney death. End-stage kidney disease was defined as either sustained eGFR < 15 mL/min/1.73 m², chronic dialysis treatment, or receiving a kidney transplant.
Zannad F, et al. Lancet. 2020;396:819-829.

SGLT2 Inhibition in Patients With HFrEF

- High-quality evidence from 2 large RCTs
  - DAPA-HF
  - EMPEROR-Reduced
- Consistent evidence that that SGLT2 inhibitors improve hard outcomes in patients with HFrEF
  - Benefits observed were in addition to standard care; add to all other HF treatments available
- Is overall well tolerated

RCT, randomized controlled trial.

SGLT2 Inhibitor HFrEF Trial Meta-Analysis

Safety

	EMPEROR-Reduced		DAPA-HF	
	Empagliflozin (n=1863)	Placebo (n=1867)	Dapagliflozin (n=2373)	Placebo (n=2371)
Serious adverse events	772 (41·4%)	896 (48·1%)	846 (35·7%)	951(40·2%)
Any renal adverse event	175 (9·4%)	192 (10·3%)	141 (6·0%)	158 (6·7%)
Volume depletion	197 (10·6%)	184 (9·9%)	170 (7·2%)	153 (6·5%)
Ketoacidosis	0	0	3 (0·1%)	0
Severe hypoglycaemic events	6 (0·3%)	7 (0·4%)	4 (0·2%)	4 (0·2%)
Bone fractures	45 (2·4%)	42 (2·3%)	48 (2·0%)	47 (2·0%)
Lower limb amputation	13 (0·7%)	10 (0·5%)	13 (0·5%)	12 (0·5%)
Fournier's Gangrene	1 (0·1%)	0	0	1 (0·1%)

Zannad F, et al. Lancet. 2020;396:819-829.

Guideline Recommendations for SGLT2 Inhibitors in Patients With HFrEF

2021 ESC Guidelines[a]

- Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death (grade IA)

2022 AHA/ACC/HFSA Guidelines[b]

- In patients with symptomatic chronic HFrEF, SGLT2 inhibitors are recommended to reduce hospitalization for HF and CV mortality, irrespective of the presence of T2D (grade IA)

ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; HFSA, Heart Failure Society of America.
a. McDonagh TA, et al. Eur Heart J. 2021;42:3599-3726; b. Heidenreich PA, et al. Circulation. 2022;145:e895-e1032.

Case 2. Suboptimal HFrEF Rx in Cardiology OPD

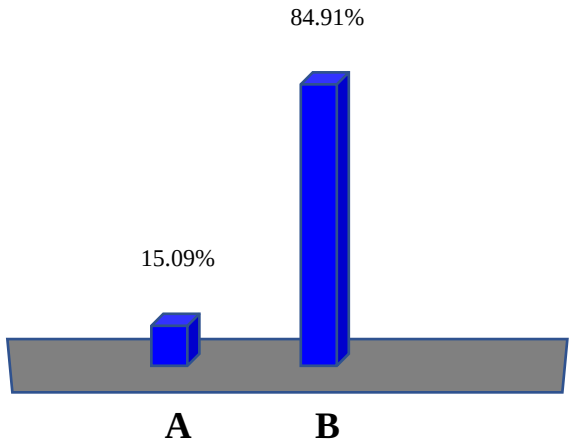
73 y/o woman

- **Complaint:** SOB and ankle edema
- **Past History:** Previous MI, COPD, AF
- **LVEF:** 35%
- **eGFR:** 40/mL/min
- **HF Medications:** Furosemide 40 mg OD, Ramipril 2.5 mg BID, Carvedilol 6.25 mg BID, Apixaban, ASA, Atorva
- **Vitals:** BP: 110/62, HR: 78/m
  - **Currently treated with RAASi, BB, and a diuretic**
  - **Missing MRA and SGLT2I**

Would you uptitrate existing medications? Or Add the missing 2?

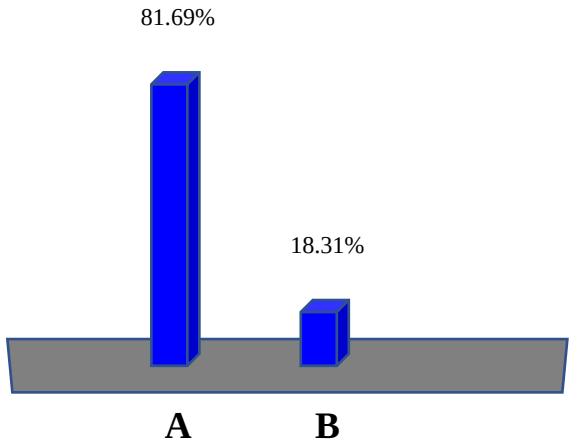
Options

- A. Uptitrate existing medications
- B. Add the missing MRA and SGLT2i

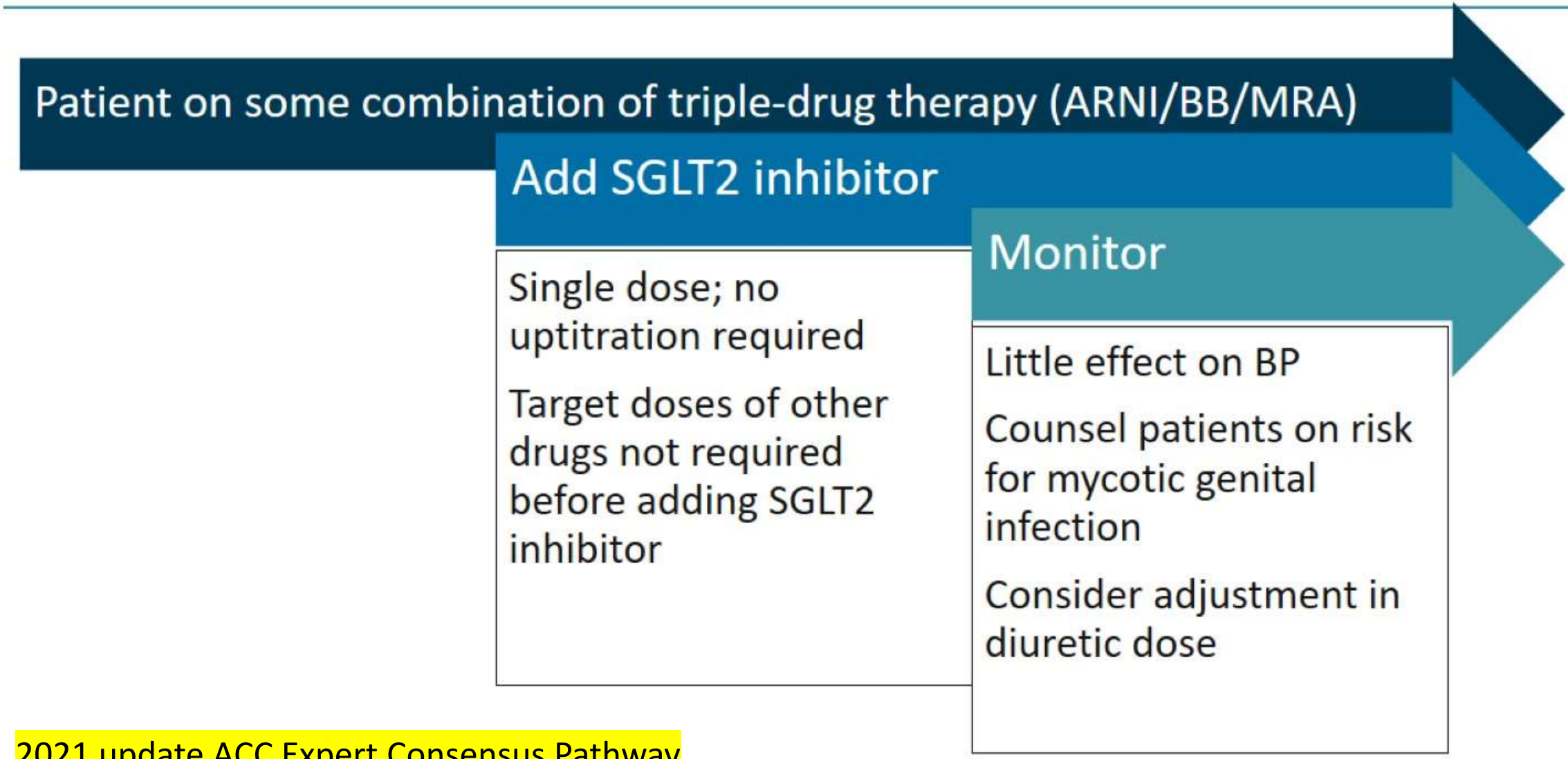


In which order will you give the other two?

- A: SGLT2i first
- B: MRA first



Starting an SGLT2 Inhibitor



2021 update ACC Expert Consensus Pathway

Maddox TM, et al. *J Am Coll Cardiol*. 2021;77:772-810.

Evidence in HFmrEF (LVEF=40-50%)/ HFpEF (LVEF >50%)

- Heart Failure with preserved ejection fraction in patients with/without diabetes

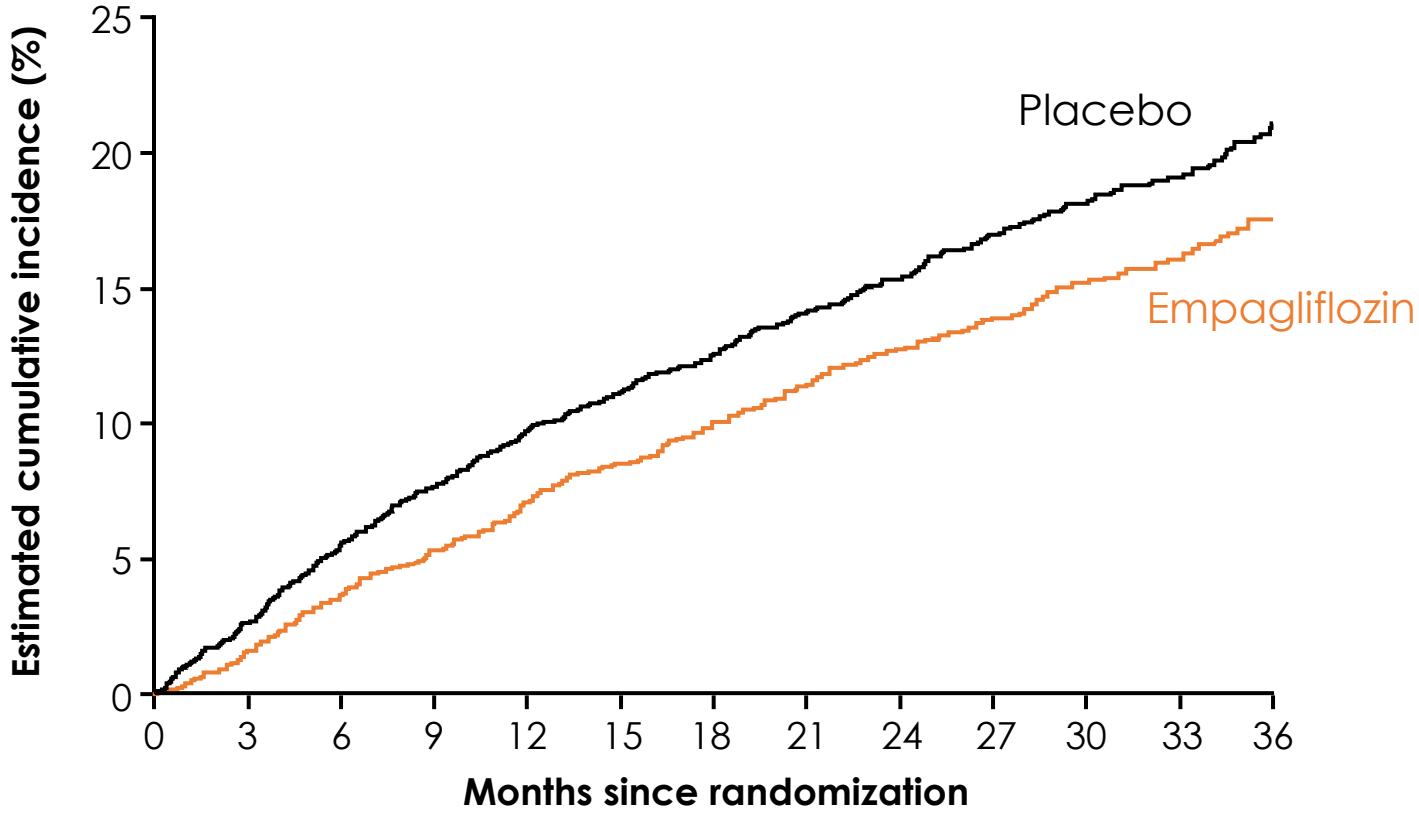
EMPEROR-Preserved
Key Baseline Characteristics

	Empagliflozin (n = 2997)	Placebo (n = 2991)
Age, mean ± SD, y	71.8 ± 9.3	71.9 ± 9.6
Women, No. (%)	1338 (45)	1338 (45)
NYHA functional Class II, No. (%)	2432 (81)	2451 (82)
LVEF, mean ± SD, %	54.3 ± 8.8	54.3 ± 8.8
NT-proBNP, median (IQR), pg/mL	994 (501-1740)	946 (498-1725)
HHF in previous 12 mo, No. (%)	699 (23)	670 (22)
Ischemic HF, No. (%)	1079 (36)	1038 (35)
Diabetes mellitus, No. (%)	1466 (49)	1472 (49)
AF	1543 (52)	1514 (51)
GFR, mean ± SD, mL/min/1.73 m^2	60.6 ± 19.8 (50% < 60)	60.6 ± 19.9 (50% < 60)
Medical treatment, No. (%)		
RAASi ± ARNI	2428 (81)	2404 (80)
MRA	1119 (37)	1125 (38)
β-Blocker	2598 (87)	2569 (86)

ARNI, angiotensin receptor neprilysin inhibitor; GFR, glomerular filtration rate; IQR, interquartile range; MRA, mineralocorticoid receptor antagonist; RAASi, renin-angiotensin-aldosterone system inhibitor.

Anker SD, et al. N Engl J Med. 2021;385:1451-1461.

Empagliflozin Demonstrated a Clinically Meaningful 21% RRR in the Composite Primary Endpoint of CV Death or HHF



Patients at risk

Placebo	2991	2888	2786	2706	2627	2424	2066	1821	1534	1278	961	681	400
Empagliflozin	2997	2928	2843	2780	2708	2491	2134	1858	1578	1332	1005	709	402

NNT*=31

RRR 21%

ARR 3.3%

HR: 0.79
(95% CI: 0.69, 0.90)
p<0.001

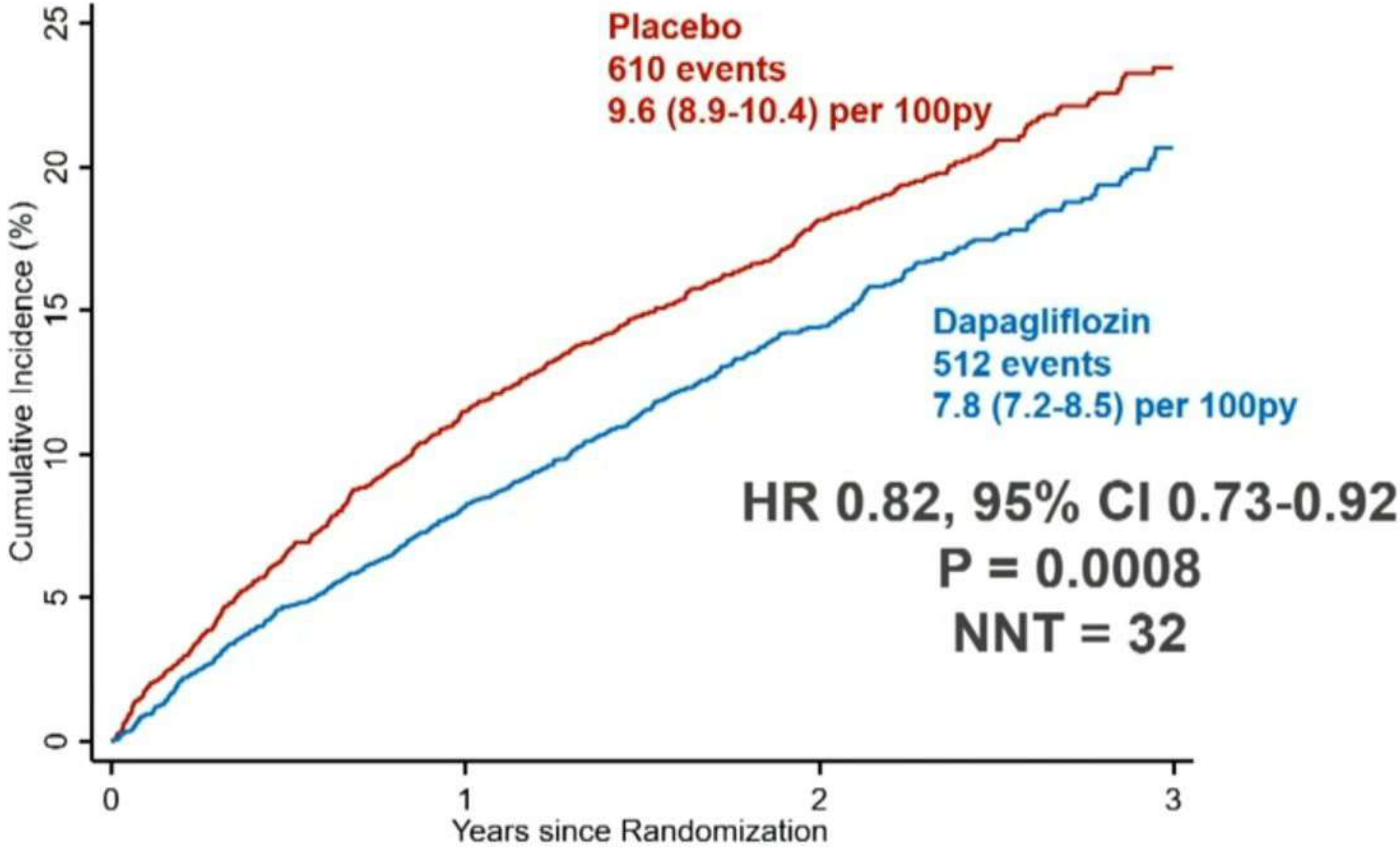
Empagliflozin:
415 (13.8%) patients with event
Rate: 6.9/100 patient-years

Placebo:
511 (17.1%) patients with event
Rate: 8.7/100 patient-years

*During a median trial period of 26 months. ARR, absolute risk reduction; CI, confidence interval; HR, hazard ratio; NNT, number needed to treat; RRR, relative risk reduction. Anker S *et al. N Engl J Med*. 2021;XX:XXX.

Primary Endpoint: CV Death or Worsening HF

Full Population

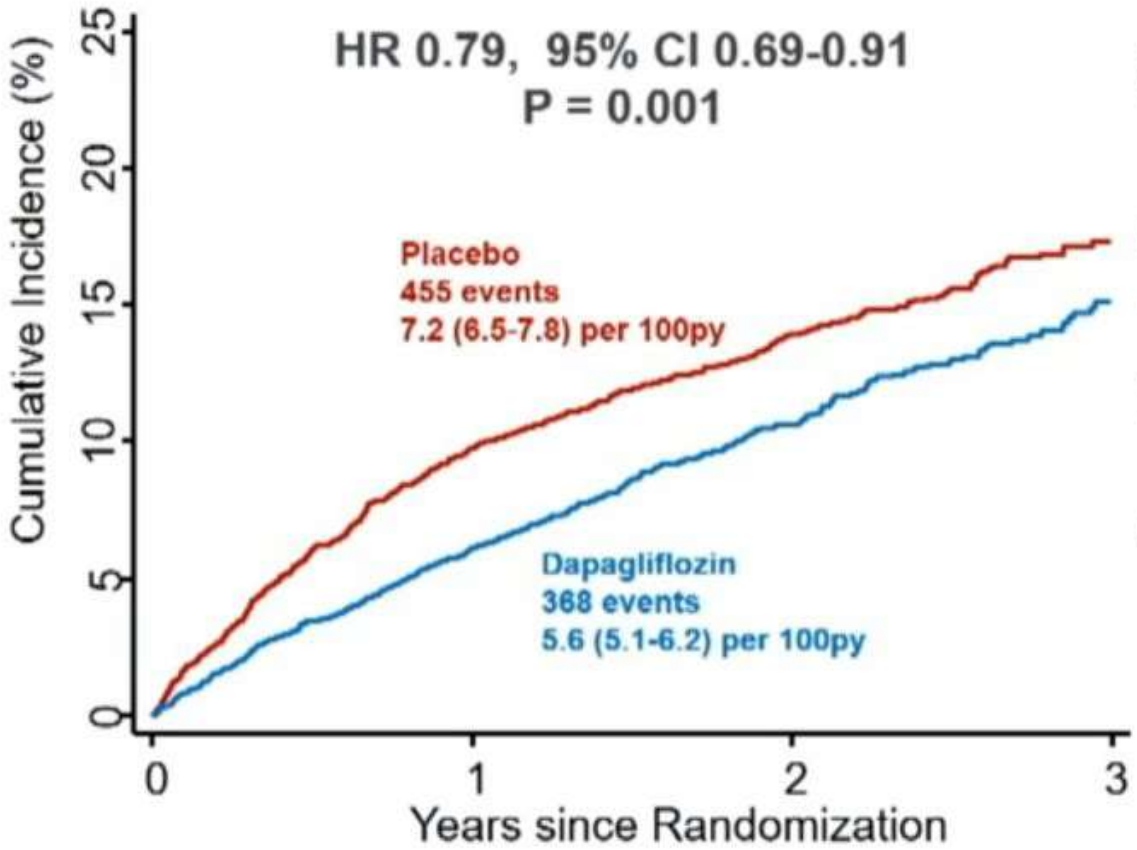


Components of Primary Endpoint

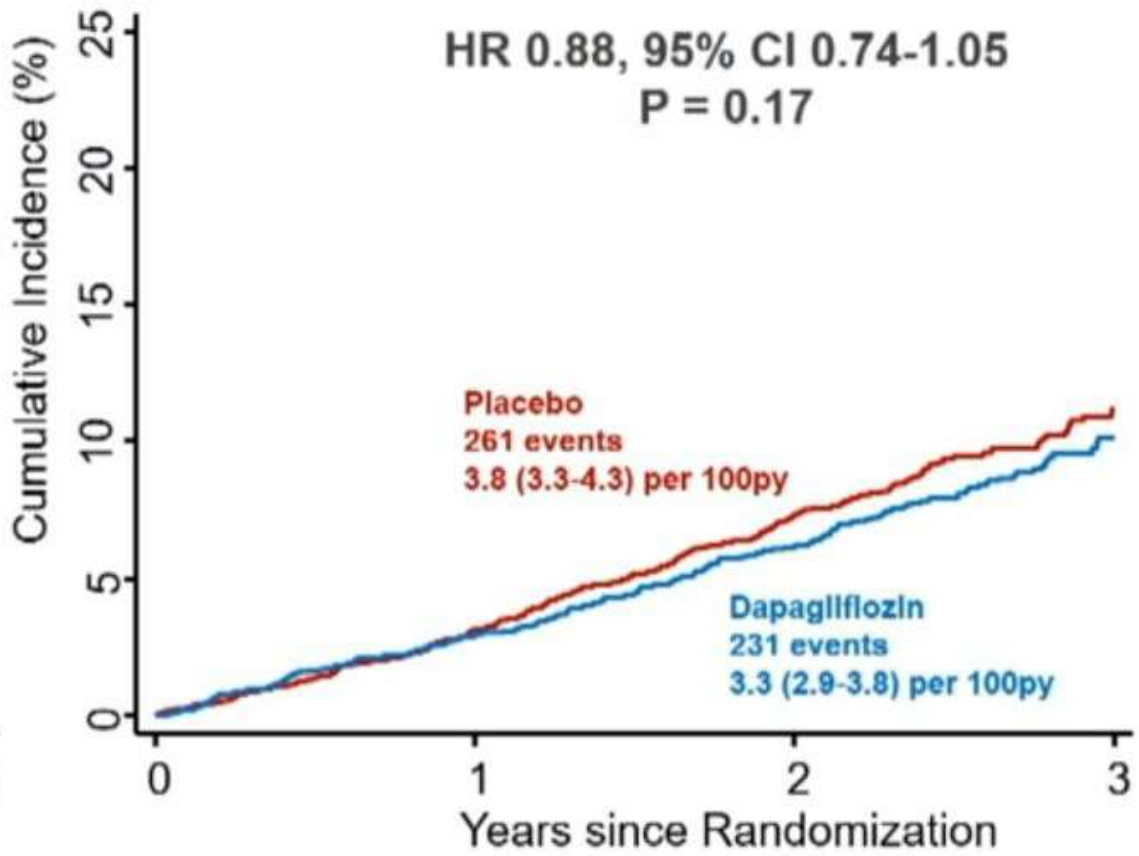
Full Population

DELIVER

Worsening Heart Failure (HF Hospitalization + Urgent HF Visit)



Cardiovascular Death



EMPEROR-Preserved
Safety

	Empagliflozin (n = 2996), No. (%)	Placebo (n = 2989), No. (%)
Serious AEs	1436 (47.9)	1543 (51.6)
Selected AEs of special interest		
Hypotension	311 (10.4)	257 (8.6)
Symptomatic hypotension	197 (6.6)	156 (5.2)
Hypoglycemia	73 (2.4)	78 (2.6)
Ketoacidosis	4 (0.1)	5 (0.2)
Bone fractures	134 (4.5)	126 (4.2)
Lower-limb amputations	16 (0.5)	23 (0.8)
Urinary tract infections	297 (9.9)	243 (8.1)
Genital infections	67 (2.2)	22 (0.7)

AE, adverse event.

Anker SD, et al. N Engl J Med. 2021;385:1451-1461.

Adverse Events*

AE data collection of Serious Adverse Events, Adverse Events leading to treatment discontinuation and other selected adverse events

	Dapagliflozin* n=3126	Placebo* n=3127
Any SAE (including death)	1361 (43.5%)	1423 (45.5%)
Any AE leading to treatment discontinuation	182 (5.8%)	181 (5.8%)
Any AE leading to treatment interruption	436 (13.9%)	494 (15.8%)
Any amputation	19 (0.6%)	25 (0.8%)
Any definite or probable diabetic ketoacidosis	2 (0.1%)	0 (0.0%)
Any major hypoglycemic event	6 (0.2%)	7 (0.2%)
Events related to volume depletion	42 (1.3%)	32 (1.0%)
Renal Events	73 (2.3%)	79 (2.5%)

*On treatment (in patients receiving at least one dose and up to 30 days following last dose of IP)

ESC European Society of Cardiology
European Heart Journal (2022) **43**, 416–426
https://doi.org/10.1093/eurheartj/ehab798

CLINICAL RESEARCH
Heart failure and cardiomyopathies

Effect of empagliflozin in patients with heart failure across the spectrum of left ventricular ejection fraction

Javed Butler [1*†], Milton Packer[2*†], Gerasimos Filippatos [3], Joao Pedro Ferreira [4], Cordula Zeller [5], Janet Schnee [6], Martina Brueckmann [7], Stuart J. Pocock[8], Faiez Zannad[4], and Stefan D. Anker[9]

[1]Department of Medicine, University of Mississippi School of Medicine, Jackson, MS, USA; [2]Baylor Heart and Vascular Institute, 621 North Hall Street, Dallas, TX 75226, USA; [3]National and Kapodistrian University of Athens School of Medicine, Athens University Hospital Attikon, Chaidari, Greece; [4]Université de Lorraine, Inserm INI-CRCT, CHRU, Nancy, France; [5]Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany; [6]Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT, USA; [7]Boehringer Ingelheim International GmbH, Ingelheim, Germany and Faculty of Medicine Mannheim, University of Heidelberg, Mannheim, Germany; [8]Department of Medical Statistics, London School of Hygiene & Tropical Medicine, London, UK; and [9]Department of Cardiology (CVK), Berlin Institute of Health Center for Regenerative Therapies (BCRT), German Centre for Cardiovascular Research (DZHK) partner site Berlin, Charité – Universitätsmedizin Berlin, Berlin, Germany

Received 18 August 2021; revised 23 September 2021; editorial decision 8 November 2021; accepted 23 November 2021; online publish-ahead-of-print 8 December 2021

See the editorial comment for this article 'Re-emergence of heart failure with a normal ejection fraction?', by Toru Kondo and John J.V. McMurray, https://doi.org/10.1093/eurheartj/ehab828.

Aims No therapy has shown to reduce the risk of hospitalization for heart failure across the entire range of ejection fractions seen in clinical practice. We assessed the influence of ejection fraction on the effect of the sodium–glucose cotransporter 2 inhibitor empagliflozin on heart failure outcomes.

Methods and results A pooled analysis was performed on both the EMPEROR-Reduced and EMPEROR-Preserved trials (9718 patients; 4860 empagliflozin and 4858 placebo), and patients were grouped based on ejection fraction: <25% ($n = 999$), 25–34% ($n = 2230$), 35–44% ($n = 1272$), 45–54% ($n = 2260$), 55–64% ($n = 2092$), and ≥65% ($n = 865$). Outcomes assessed included (i) time to first hospitalization for heart failure or cardiovascular mortality, (ii) time to first heart failure hospitalization, (iii) total (first and recurrent) hospitalizations for heart failure, and (iv) health status assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ). The risk of cardiovascular death and hospitalization for heart failure declined progressively as ejection fraction increased from <25% to ≥65%. Empagliflozin reduced the risk of cardiovascular death or heart failure hospitalization, mainly by reducing heart failure hospitalizations. Empagliflozin reduced the risk of heart failure hospitalization by ≈30% in all ejection fraction subgroups, with an attenuated effect in patients with an ejection fraction ≥65%. Hazard ratios and 95% confidence intervals were: ejection fraction <25%: 0.73 (0.55–0.96); ejection fraction 25–34%: 0.63 (0.50–0.78); ejection fraction 35–44%: 0.72 (0.52–0.98); ejection fraction 45–54%: 0.66 (0.50–0.86); ejection fraction 55–64%: 0.70 (0.53–0.92); and ejection fraction ≥65%: 1.05 (0.70–1.58). Other heart failure outcomes and measures, including KCCQ, showed a similar response pattern. Sex did not influence the responses to empagliflozin.

Conclusion The magnitude of the effect of empagliflozin on heart failure outcomes was clinically meaningful and similar in patients with ejection fractions <25% to <65%, but was attenuated in patients with an ejection fraction ≥65%.

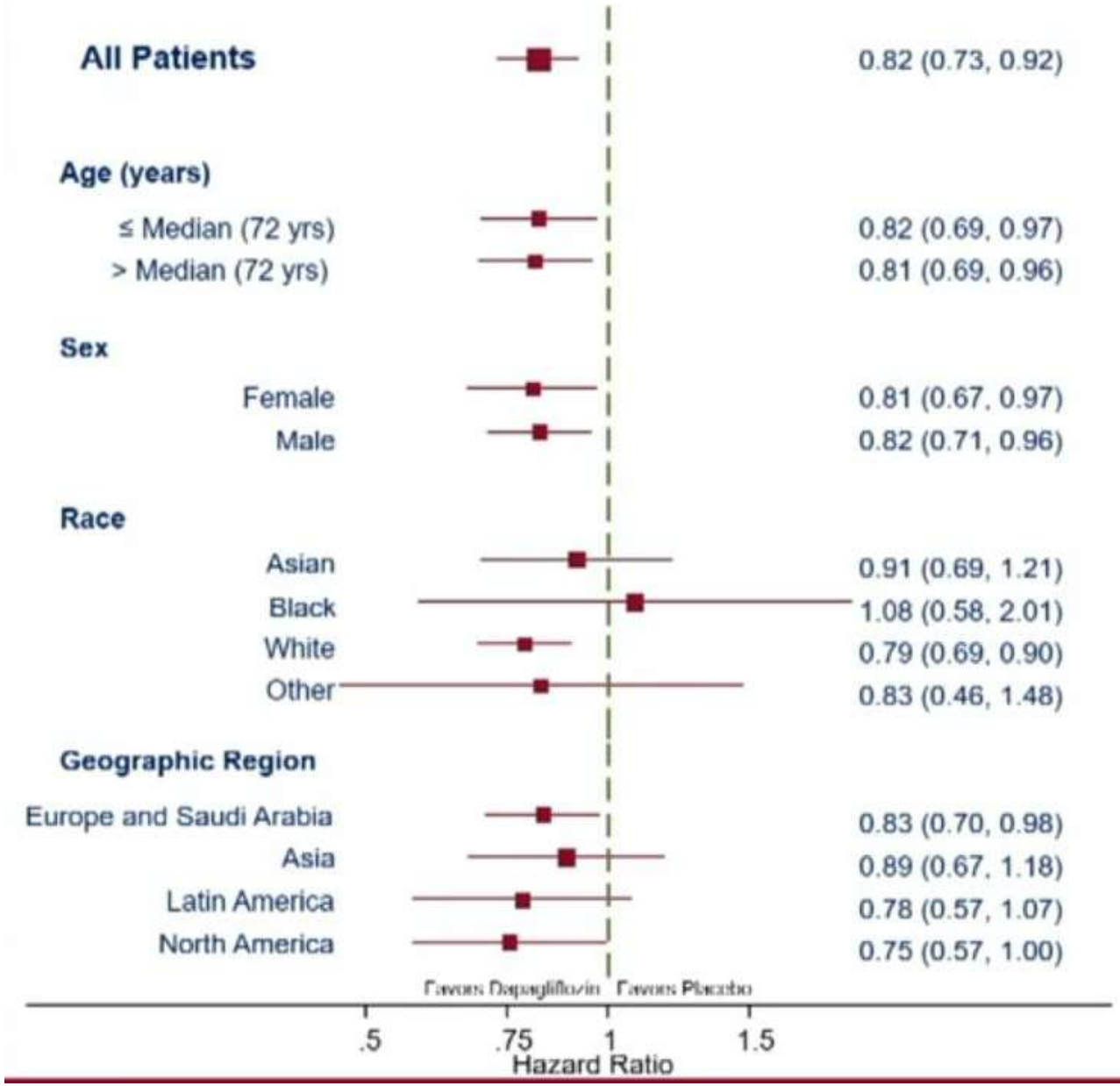
* Corresponding authors. Tel: +1 601 984 5600, Email: jbutler4@umc.edu (J.B.); Tel: +1 214 820 7500, Email: milton.packer@baylorhealth.edu (M.P.)
† These authors contributed equally to the study.

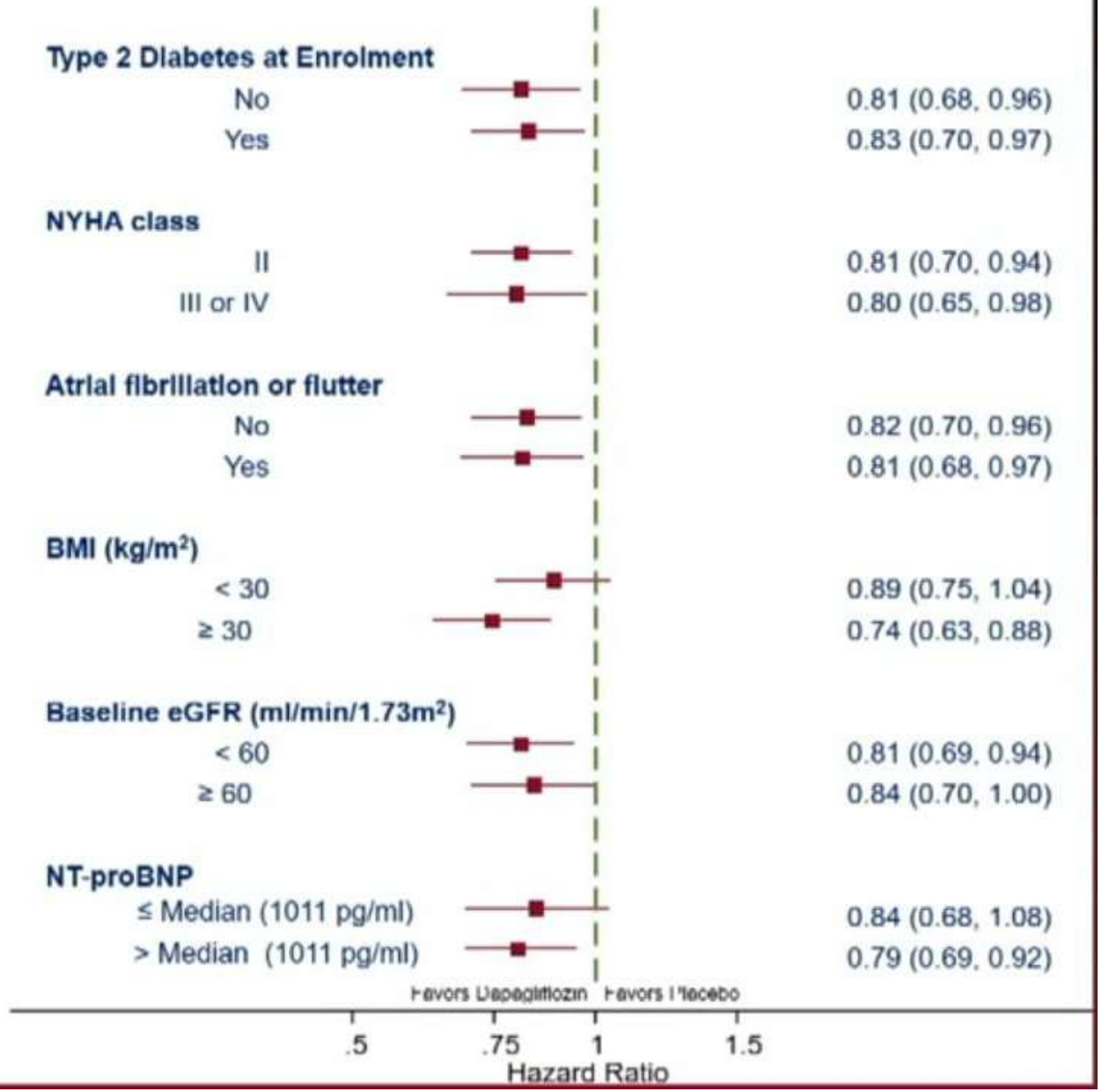
Pooled analysis of EMPEROR-Reduced and EMPEROR-Preserved trials

"Empagliflozin reduced risk of CV death or HoHF, mainly by reducing heart failure hospitalizations by 30% in all EF subgroups, with an attenuated effect in patients with an EF greater than 65%"

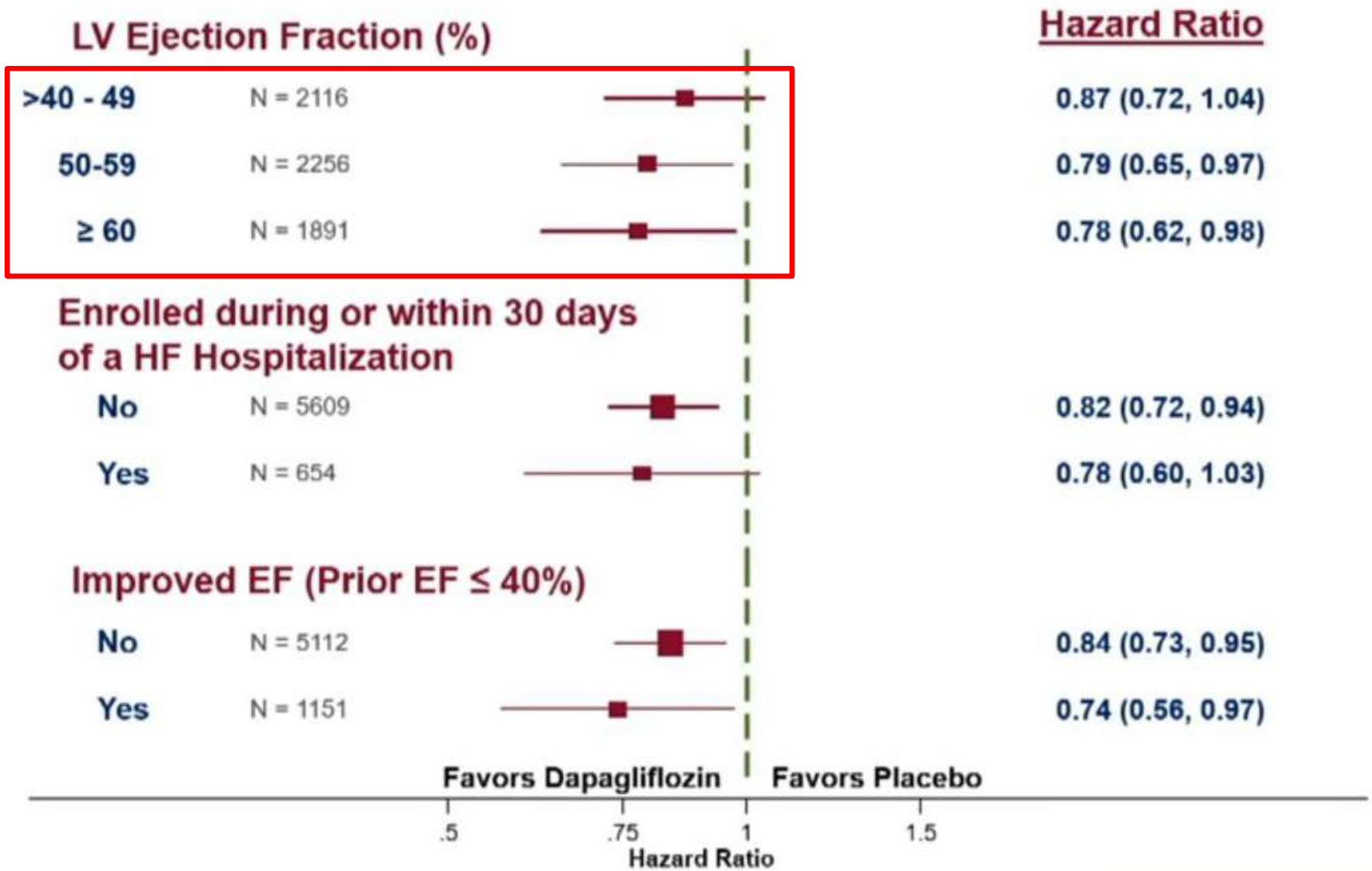
Primary Endpoint in Prespecified Subgroups

DELIVER





Primary Endpoint in Prespecified Subgroups

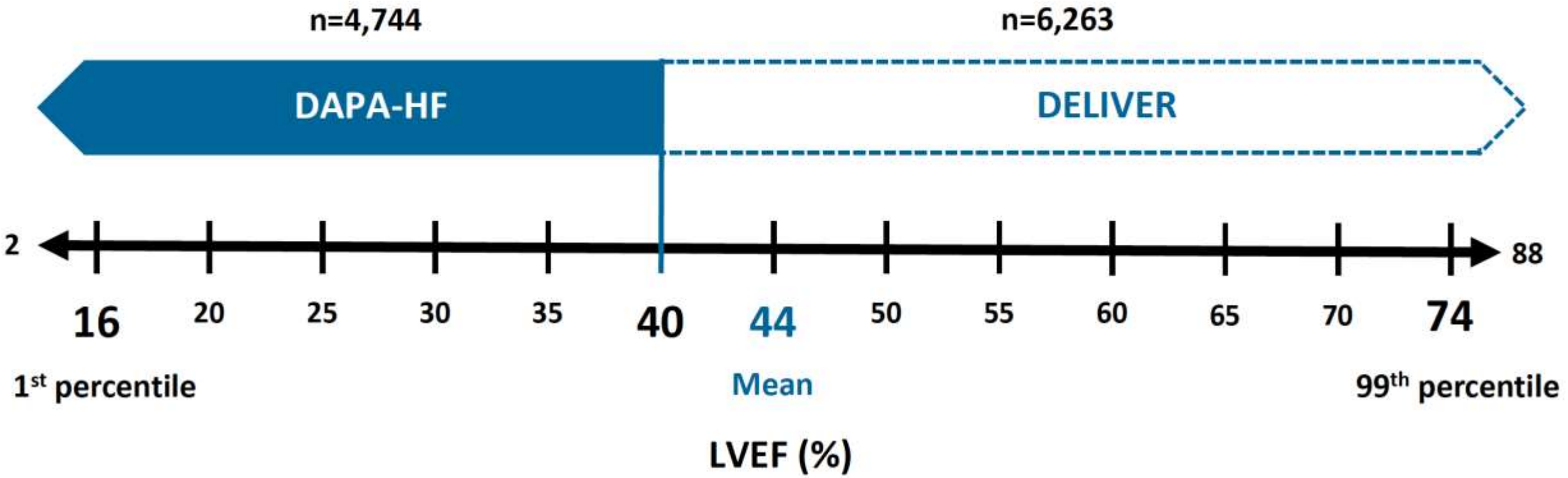


DAPA-HF and DELIVER pooled dataset

Dapagliflozin 10mg once daily vs placebo

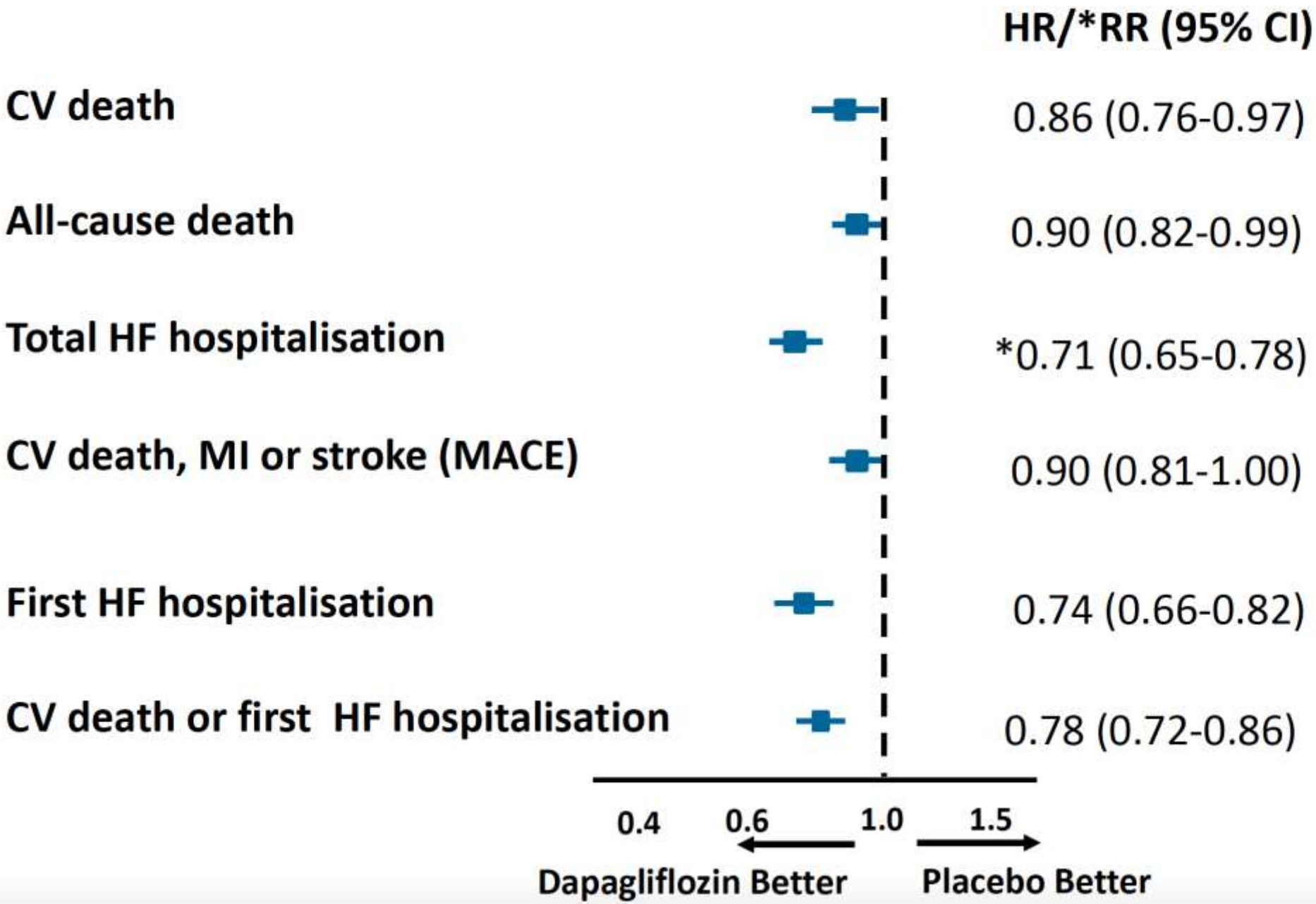
Median follow-up = 22 (IQR 17-30) months

Pooled dataset n=11,007



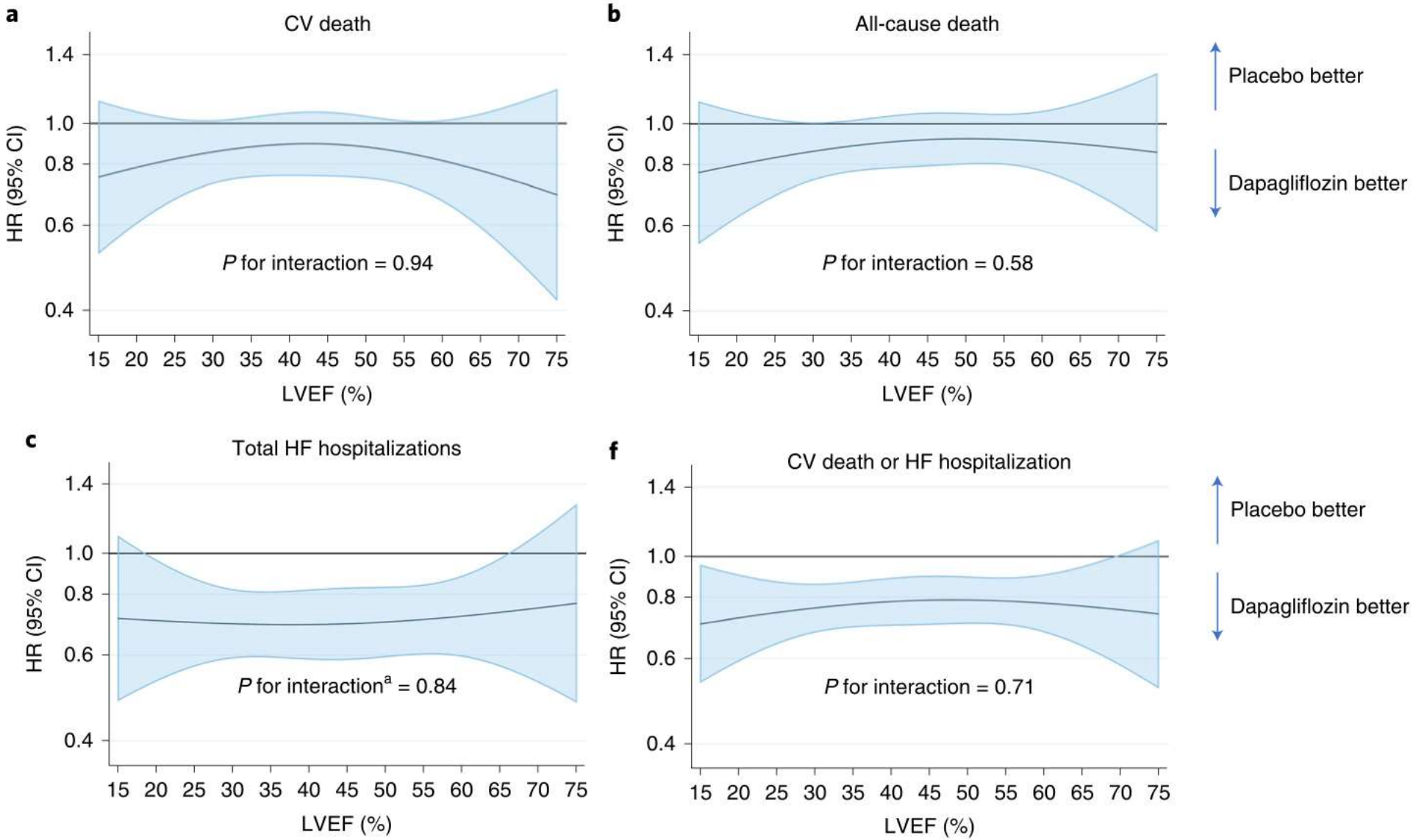
McMurray JJV et al Eur J Heart Fail. 2019;21:665-675 and Solomon SD et al Eur J Heart Fail 2021;23:1217-1225

DAPA-HF & DELIVER pooled: Outcome hierarchy



Efficacy across EF range: DAPA-HF/DELIVER

Jhund P, et al. Nature Med 2022



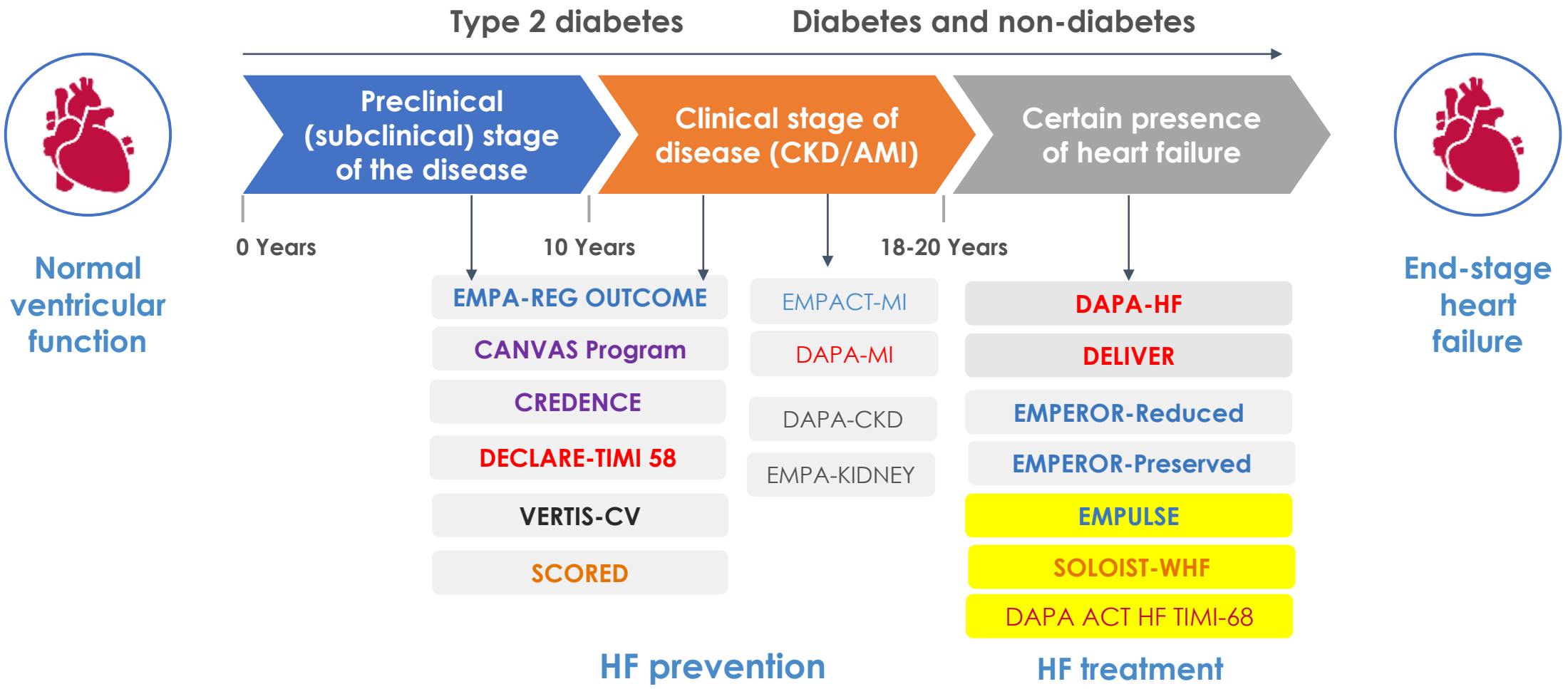
DAPA-HF & DELIVER pooled: Summary and conclusions

- In a large population with heart failure, dapagliflozin reduced the risk of cardiovascular and all-cause death, heart failure hospitalisations and cardiovascular death/MI/stroke
- The benefits of dapagliflozin were observed in all patients regardless of ejection fraction
- Patients with heart failure, regardless of ejection fraction, are likely to benefit from treatment with a SGLT2 inhibitor
- SGLT2 inhibitors could be initiated in patients with a clinical diagnosis of HF and no contraindications while awaiting a measurement of ejection fraction

Evidence in Acute/Worsening heart failure with ongoing or recent hospitalization

Story of SGLT2 inhibition in heart failure – A full success

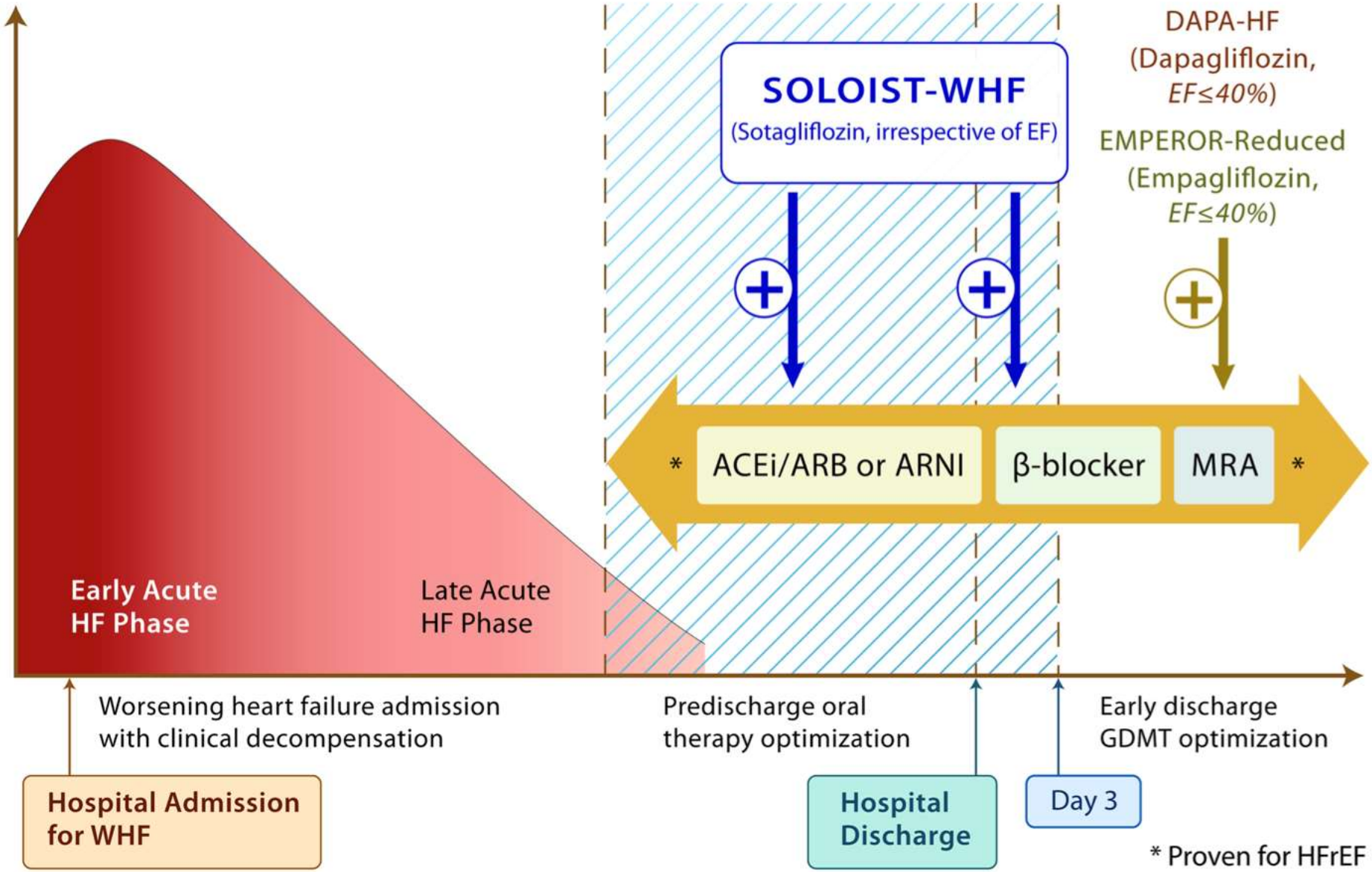
-- across the whole spectrum of LVEF --



Adapted from Bhatt DL *et al. Cell Metab*. 2019

Early initiation of SGLT2Is is important

Verma S, et al. Eur J Heart Failure



SOLOIST - WHF TRIAL

Bhatt DL et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. N Engl J Med. 2021;384(2):117-128.

SOTAGLIFLOZIN

inhibits

SGLT-2 → increases urinary glucose excretion

SGLT-1 → delays intestinal glucose absorption

QUESTION

In patients with diabetes and recently worsening HF, does SOTAGLIFLOZIN:

↓ CV mortality?

↓ HF urgent visits?

↓ HF hospitalizations?

INCLUSION

18 - 85 yo patients with diabetes hospitalized for signs or symptoms of HF and treatment with IV diuretics

1222 patients

TOTAL NO. OF EVENTS (RATE PER 100 PATIENT YEARS)

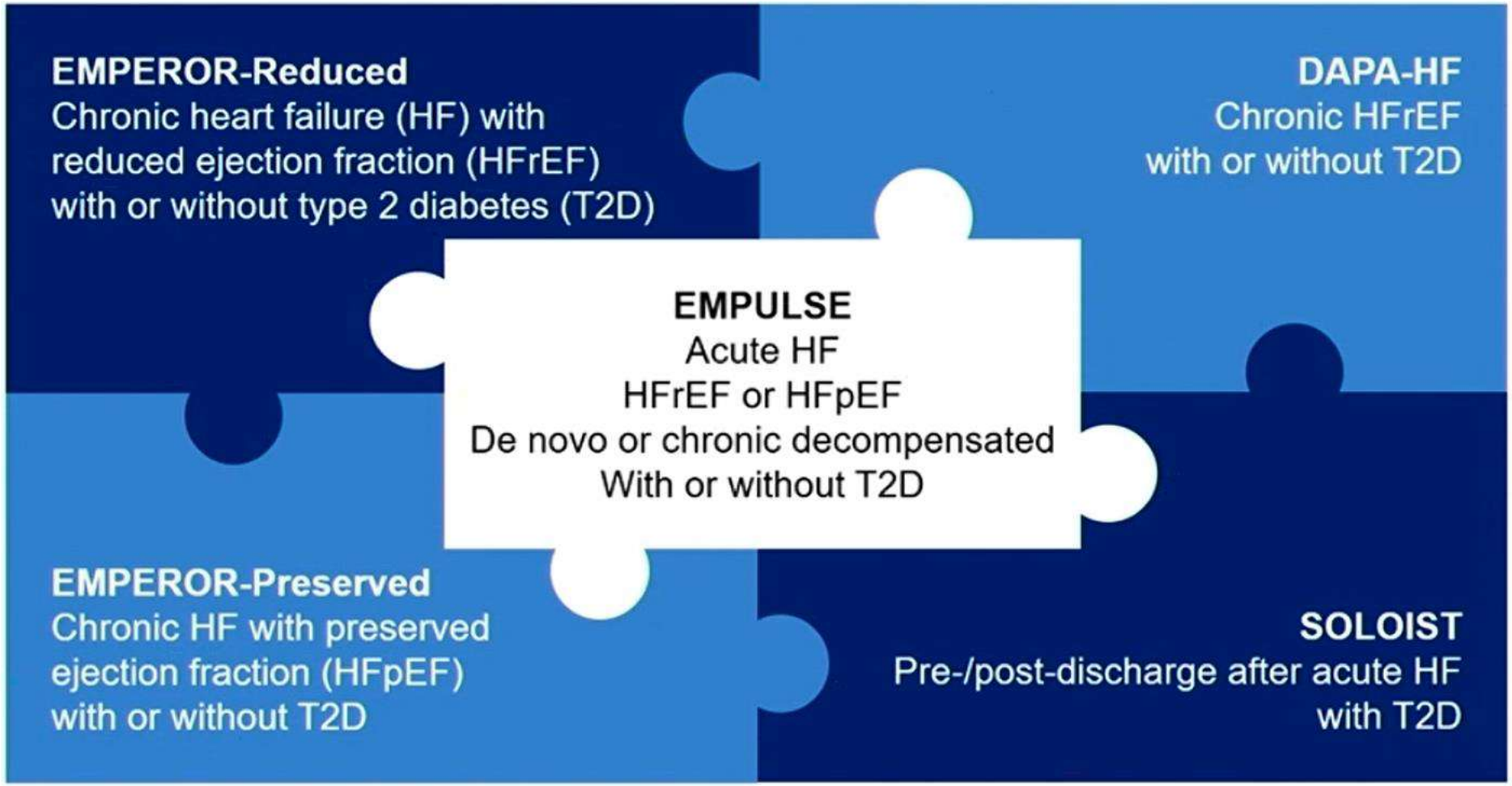
	PRIMARY OUTCOME: HF urgent visits + HF hospitalizations + CV Death	SECONDARY OUTCOME: HF urgent visits + HF hospitalizations	SECONDARY OUTCOME: CV Death
Sotagliflozin n=608	245 (51)	194 (40)	51 (11)
	HR 0.67 95% CI 0.52-0.85 p<0.001	HR 0.64 95% CI 0.49-0.83 p<0.001	HR 0.84 95% CI 0.58-1.22 p=0.36
Placebo n=614	355 (76)	297 (64)	58 (13)

CONCLUSION

In patients with diabetes with worsening HF, sotagliflozin significantly decreased CV deaths, HF urgent visits, and HF hospitalizations

Created by @TDonisan | @CardioNerdsJC

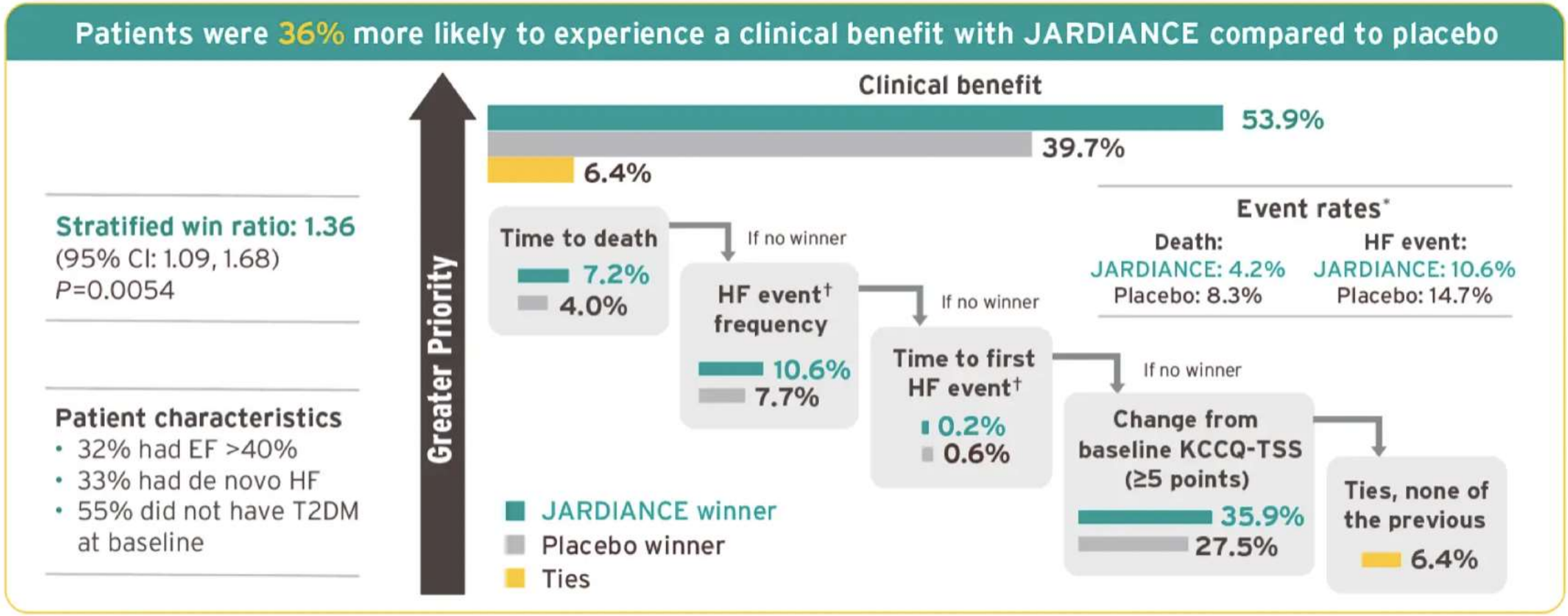
EMPULSE: the missing link



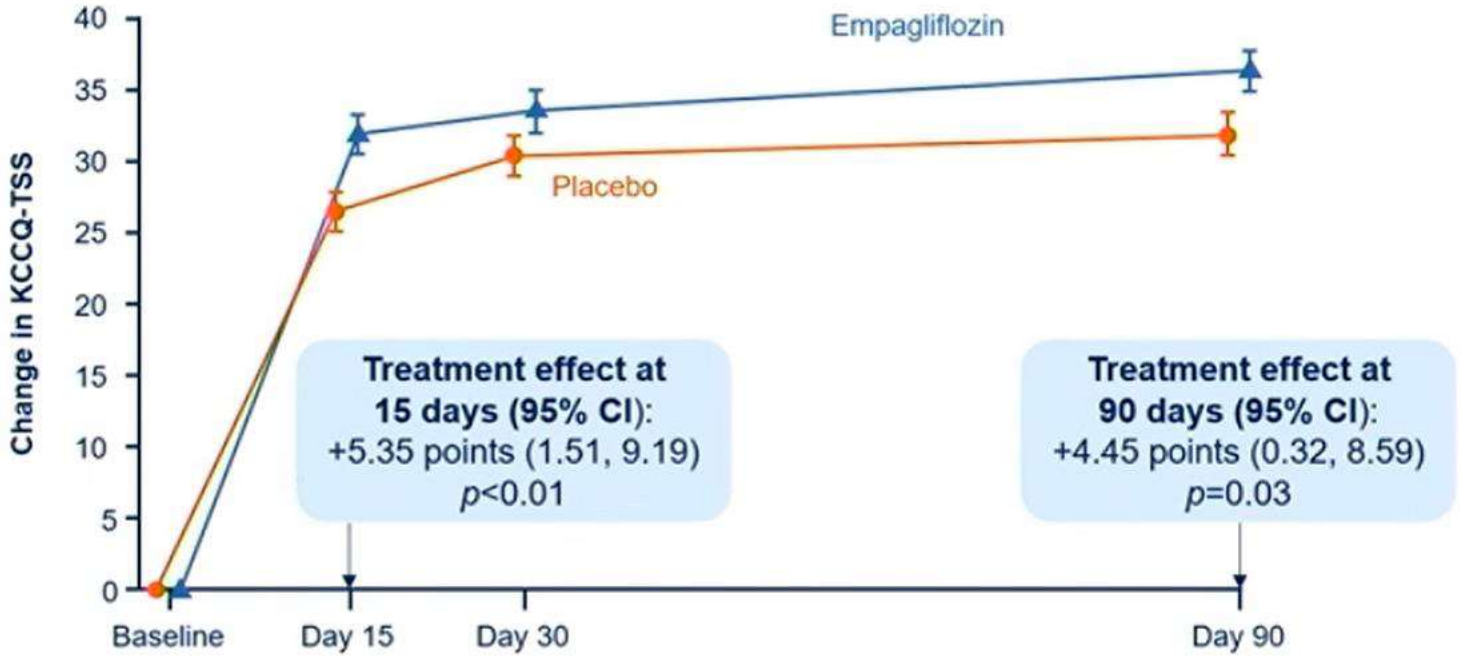
HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; T2D, type 2 diabetes.

EMPULSE: Results

N=524

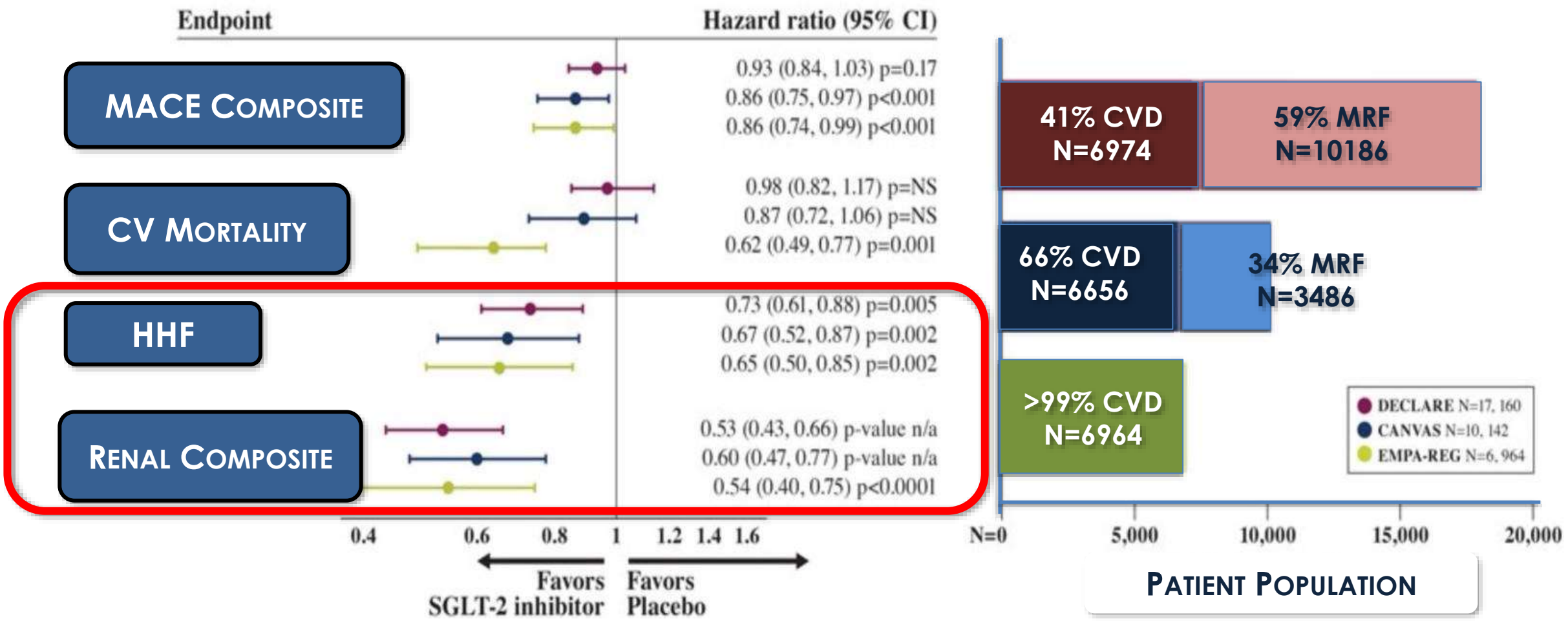


Effects of empagliflozin versus placebo on change in KCCQ-TSS



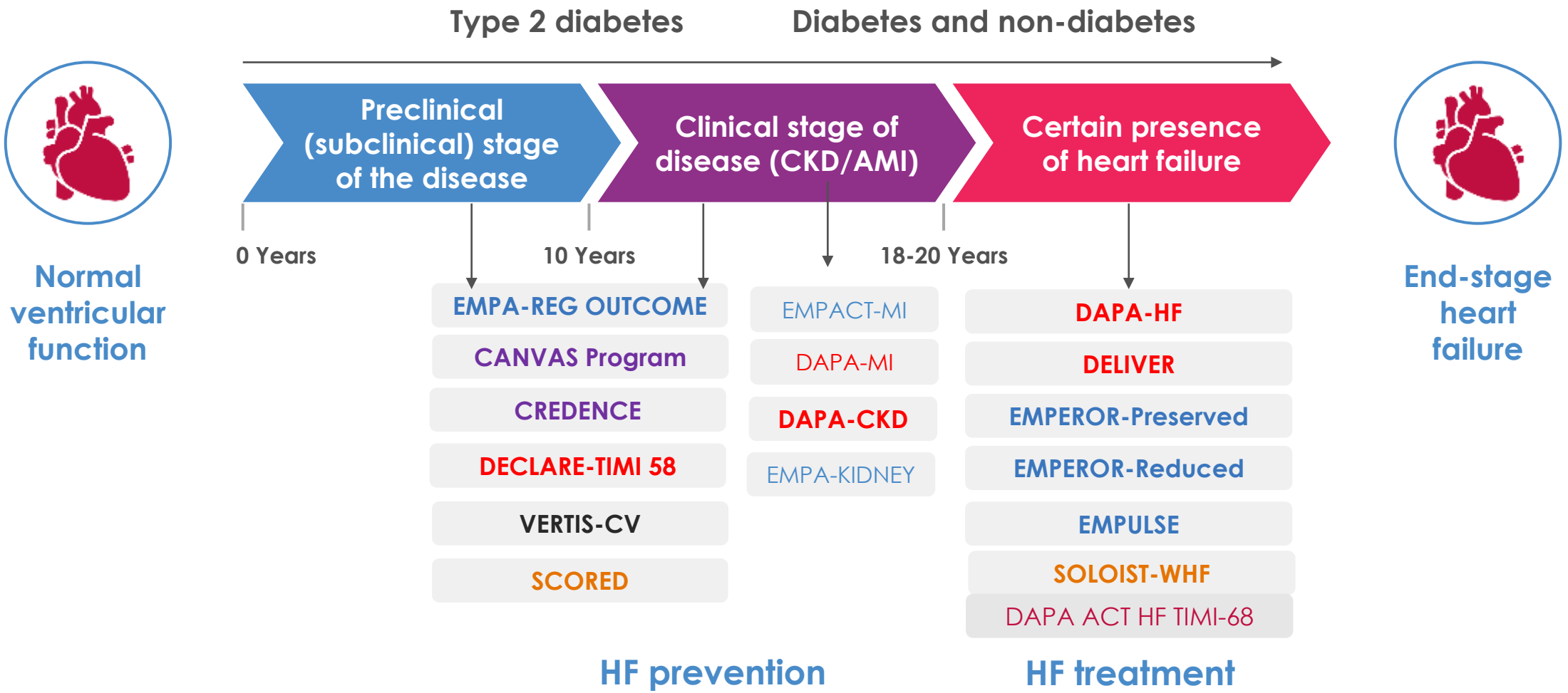
N with data at visit				
Placebo	250	240	234	221
Empagliflozin	245	233	237	230

SGLT2 Inhibitors in T2DM – Serendipitous Renal Benefit



Story of SGLT2 inhibition in CKD

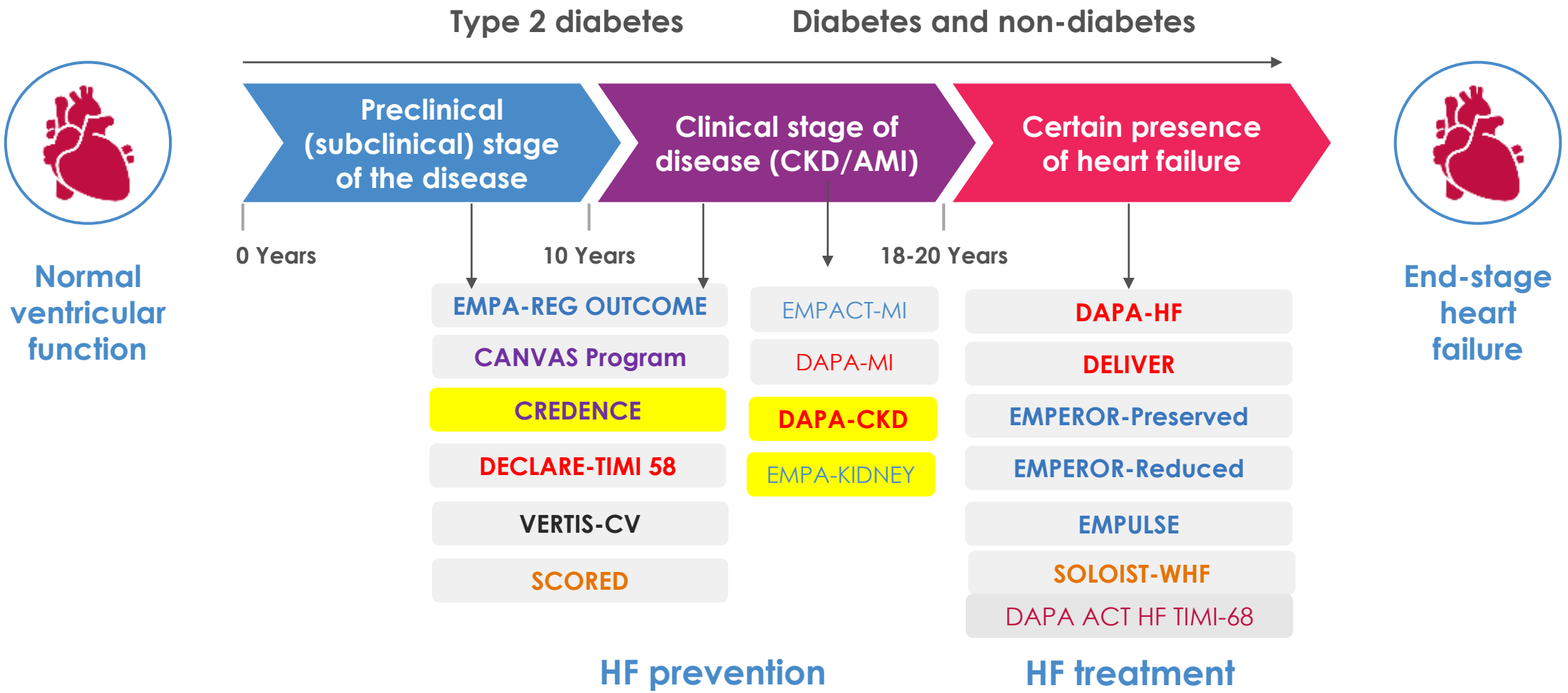
-- across the whole spectrum of eGFR--



Adapted from Bhatt DL *et al. Cell Metab*. 2019 Courtesy Prof. Stefan Anker

Story of SGLT2 inhibition in CKD

-- across the whole spectrum of eGFR--



Adapted from Bhatt DL *et al. Cell Metab*. 2019 Courtesy Prof. Stefan Anker

Randomized Controlled Trials of SGLT2 Inhibitors in CKD

	CREDENCE[a-c]	DAPA-CKD[d-f]	EMPA-KIDNEY[g-h]
Population	**DIABETIC KIDNEY DISEASE** ✓ T2D x Non-DM x Non-Albuminuric	**PROTEINURIC CHRONIC KIDNEY DISEASE** ✓ T2D ✓ Non-DM x Non-Albuminuric	**CHRONIC KIDNEY DISEASE** ✓ T2D ✓ Non-DM ✓ Non-Albuminuric
No. of patients	4401[b,c]	4304	~6000
Key inclusion criteria	eGFR ≥30 to <90 **and** UACR >300 mg/g	eGFR ≥25 to ≤75 **and** UACR ≥200 mg/g	eGFR ≥20 to <45 **or** eGFR ≥45 to <90 and UACR ≥200 mg/g
Primary composite outcome	ESKD, doubling of creatinine, or renal/ CV death	ESKD, ≥50% sustained eGFR decline, or renal/CV death	ESKD, or ≥40% sustained eGFR decline, or renal/CV death
Study start and stop date (announced or planned)	February 2014 [b] July 2018	February 2017 [d] March 2020	November 2018 [g] ~June 2022
Results	+ [c]	+ [f]	**TBD**

DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; TBD, to be determined; UACR, urinary albumin:creatinine ratio.

a. Jardine MJ, et al. Am J Nephrol. 2017;46:462-472; b. ClinicalTrials.gov. Accessed November 09, 2021. https://clinicaltrials.gov/ct2/show/NCT02065791; c. Perkovic V, et al. N Engl J Med. 2019;380:2295-2306; d. ClinicalTrials.gov. Accessed November 09, 2021. https://clinicaltrials.gov/ct2/show/NCT03036150; e. Heerspink HJL, et al. Nephrol Dial Transplant. 2020;35:274-282; f. Heerspink HJL, et al. N Engl J Med. 2020;383:1436-1446; g. ClinicalTrials.gov. Accessed November 09, 2021. https://clinicaltrials.gov/ct2/show/ NCT03594110; h. Herrington WG, et al. Clin Kidney J. 2018;11:749-761.

CREDENCE: DM + eGFR of 30 to <90 ml/min/1.73 m² and albuminuria (UACR >300 to 5000)

Perkovic V *et al. N Engl J Med* 2019;380:2995

Primary composite outcome

ESKD, doubling of serum creatinine, death from kidney causes or CV death

↓30% RRR
p=0.00001

Secondary outcomes

CV death or HHF

↓31% RRR
p<0.001

3P-MACE†

↓20% RRR
p=0.01

HHF

↓39% RRR
p<0.001

DAPA-CKD: noDM & DM + eGFR of 25 to <75 ml/min/1.73 m² and albuminuria (UACR >200 to 5000)

Primary composite outcome

Decline in eGFR ≥50%; ESKD*; renal or CV death

↓39% RRR
p=0.000000028

*Defined as eGFR <15 ml/min/1.73 m², need for chronic dialysis and/or renal transplantation

Secondary outcomes

≥50% sustained decline in eGFR or reaching ESRD or renal death

↓44% RRR
P=0.000000018

CV death or HHF

↓29% RRR
p=0.008

TOTAL death

↓31% RRR
p 0.0035

EMPA-Kidney

News > Medscape Medical News

Empagliflozin Scores Topline Win in EMPA-KIDNEY Trial

Mitchel L. Zoler, PhD

March 17, 2022

Add to Email Alerts

1

36

Researchers running the EMPA-KIDNEY trial that's been testing the safety and efficacy of the SGLT2 inhibitor empagliflozin (Jardiance) in about 6600 patients with chronic kidney disease (CKD) announced on March 16 that they had stopped the trial early because of positive efficacy that met the study's prespecified threshold for early termination.

Guidelines: SGLT2i in CKD

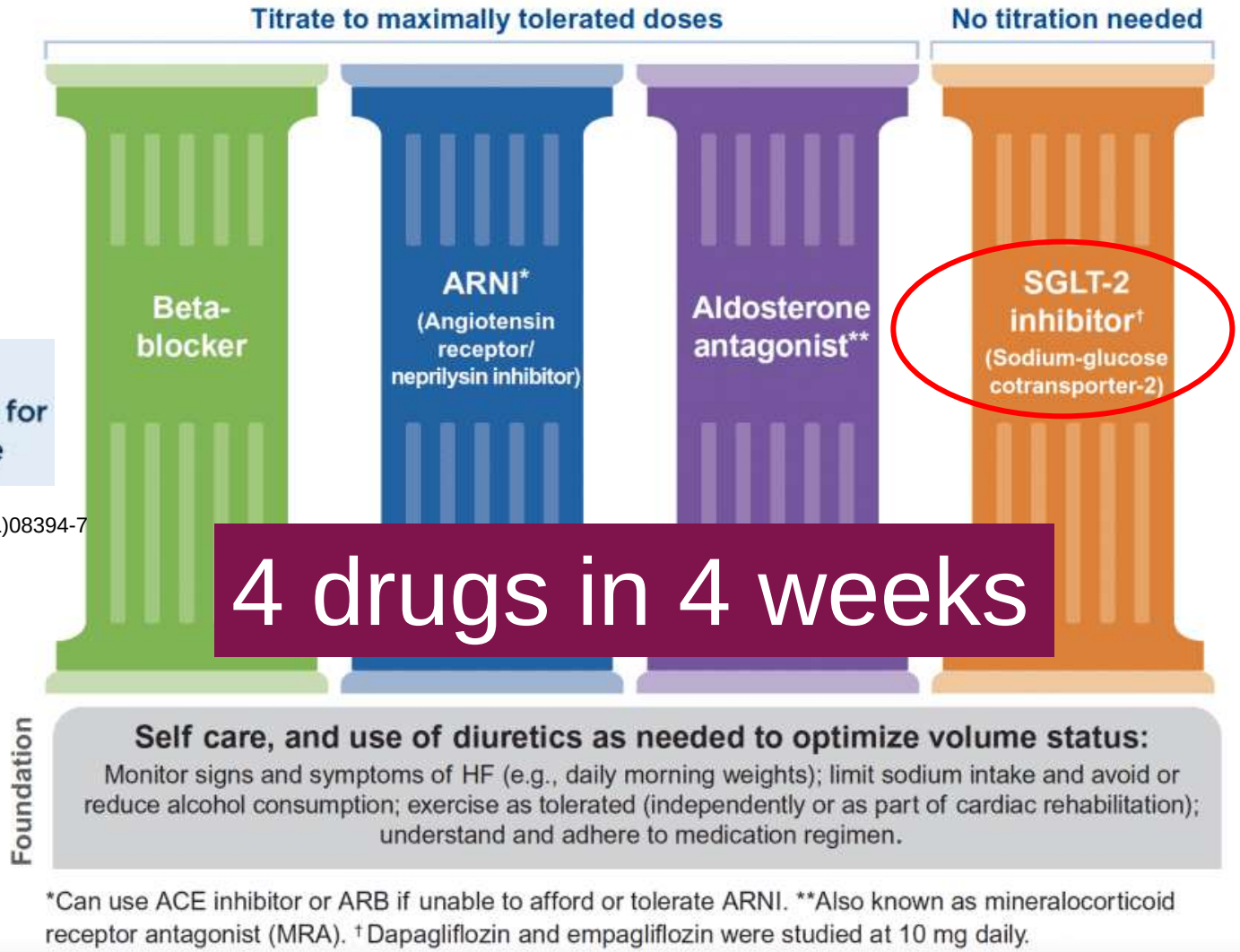
Guidelines	Population	Recommendation
KDIGO (2020)	CKD with eGFR ≥ 30	SGLT2i
ADA (2022)	DM2 + CKD with albuminuria (≥ 200 mg/g)	SGLT2i
	DM2 + CKD without albuminuria (if eGFR 25-60)	SGLT2i or GLP1 RA

Four Foundational Pillars of Survival Enhancing HF Rx

CLINICAL PRACTICE GUIDELINE: FULL TEXT

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

Heidenreich et al JACC 2022 Mar 24;S0735-1097(21)08394-7



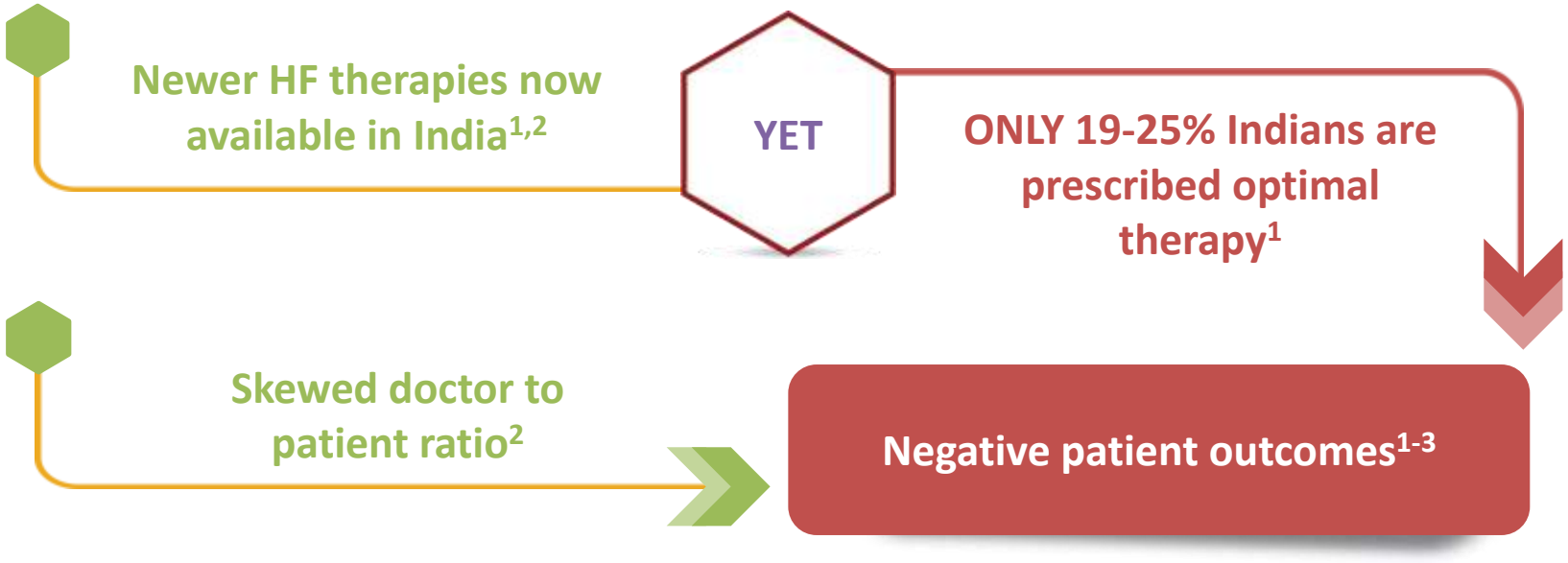
ESC European Society of Cardiology

ESC GUIDELINES

McDonagh TA et al. *Eur Heart J*. 2021

https://alosahealth.org/clinical-modules/heartfailure/

GDMT: Still a challenge in India



1. Seth S, et al. J Pract Cardiovasc Sci 2017;3:133-8. 2. Ponikowski P, et al. European Heart Journal 2016; 37: 2129–2200.
3. Pokharel Y, et al. Clin Cardiol. 2016 Mar;39(3):145-9.

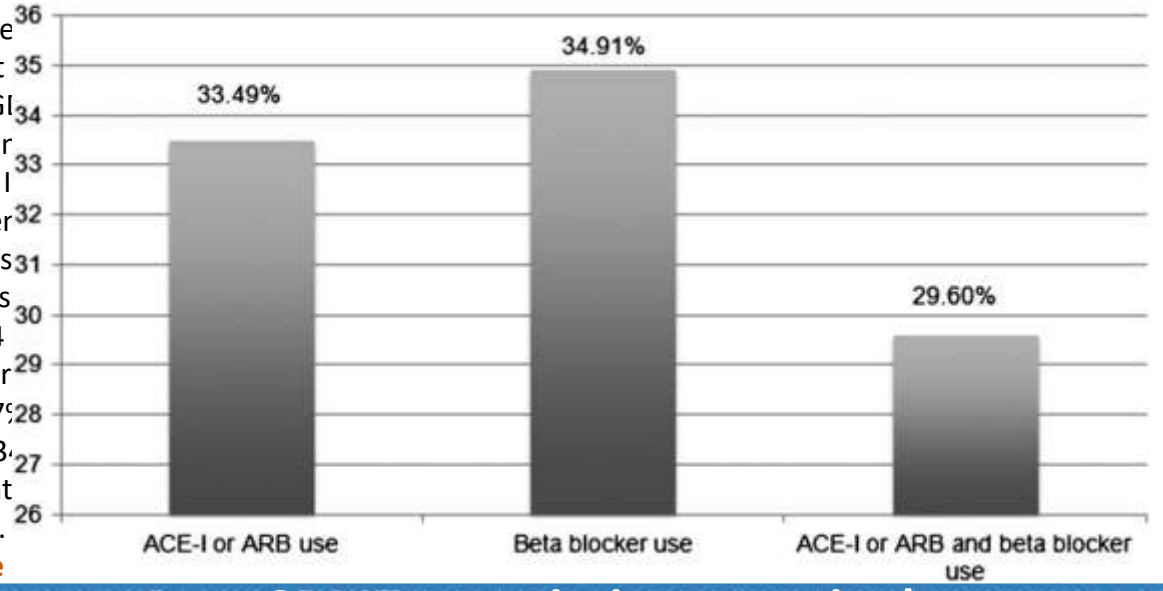
Guideline-Directed Medication Use in Patients With Heart Failure With Reduced Ejection Fraction in India: American College of Cardiology's PINNACLE India Quality Improvement Program

Address for correspondence:
Salim S. Virani, MD
Health Services Research and Development (152)
Michael E. DeBakey Veterans Affairs Medical Center
2002 Holcombe Boulevard
Houston, TX 77030
virani@bcm.edu

Yashashwi Pokharel, MD, MSCR; Jessica Wei, PhD; Ravi S. Hira, MD; Ankur Kalra, MD; Supriya Shore, MD, MSCS; Prafulla G. Kerkar, MD; Ganesh Kumar, MD; Samantha Risch, BS; Veronique Vicera, BS; William J. Oetgen, MD, MBA; Anita Deswal, MD, MPH; Mintu P. Turakhia, MD, MAS; Nathan Glusenkamp, MA; Salim S. Virani, MD, PhD

Little is known about the
failure with reduced left
understand the use of GI
Excellence (PINNACLE) Ir
quality improvement in I
January 2008 and Septer
enzyme inhibitors (ACEIs
outpatients with HFrEF s
in the PIQIP registry, 34
23% were female. Hyper
present in 37%, 23%, 27
documented in 33.5%, 3
higher in men, in patient
coronary artery disease.
patients enrolled in the
docume

India an



Poor GDMT prescriptions seen in the OPD setting in India

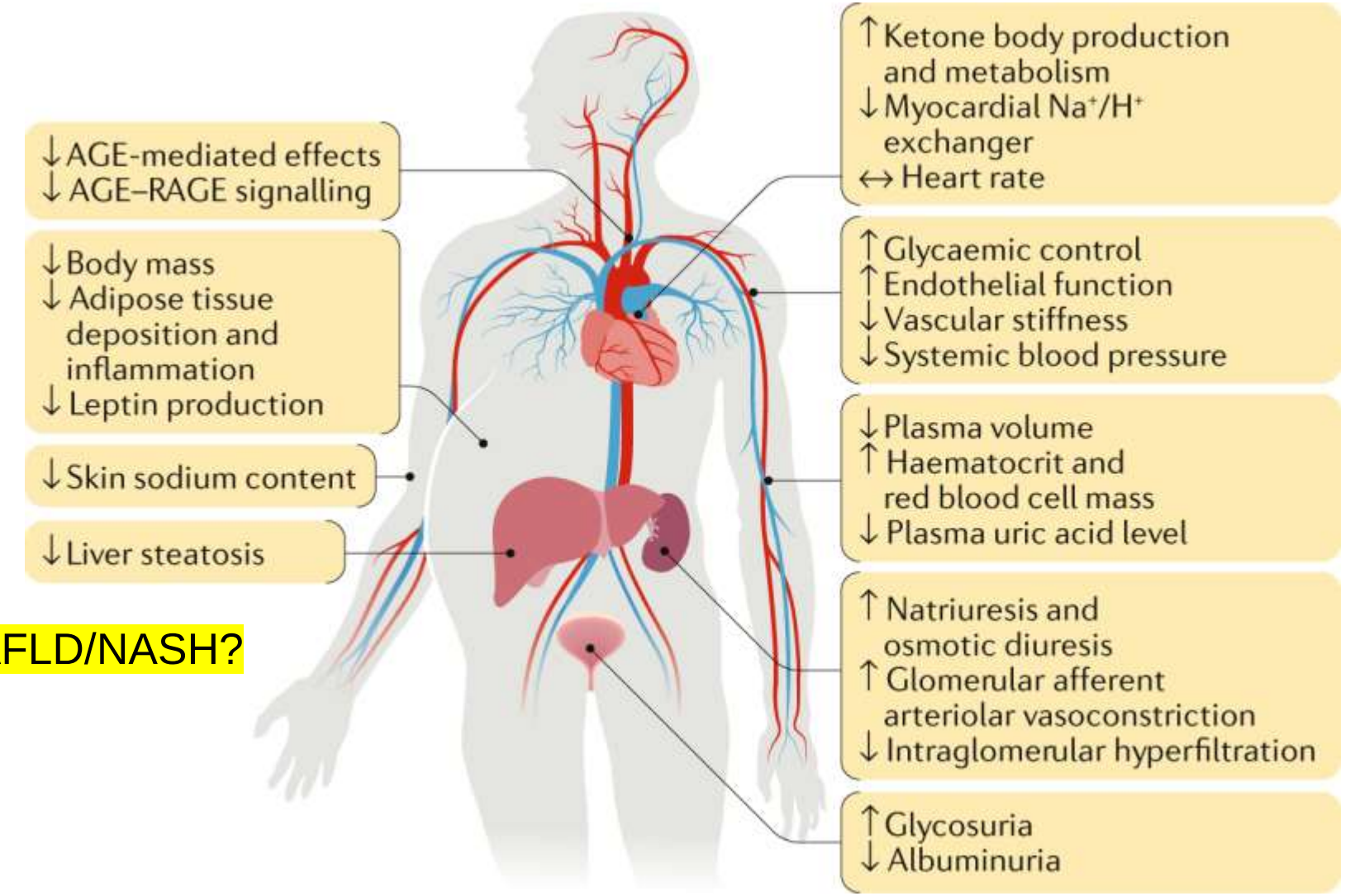
Clin. Cardiol. 39, 3, 145–149 (2016)

Take Home: Use a SGLT2 inhibitor early or even first !!

- Single dose, no titration
- Can be started in hospital or in the community
- Benefit within <28 days
- Outstanding tolerability (counsel about hygiene/genital mycosis)
- Negligible effect on blood pressure
- Preserve rather than worsen renal function *(do we even need to check blood chemistry for eGFR?)*
- Reduce risk of hyperkalaemia with MRAs *(concept: agents started earlier can enhance the safety of agents started later)*

Courtesy Stefan Anker

SGLT2 inhibitors: Mechanisms of Benefits beyond glycemic control



SGLT2i for NAFLD/NASH?

Cowie MR, Fisher M. Nature Reviews Cardiology. 2020 Dec;17(12):761-72.

SGLT2 inhibitors

“Many other possibilities exist, waiting to be discovered just like diamonds in the rough”
-Kosiborod M.

Thank You