

DIABETES AND HEART FAILURE

NEW INSIGHTS INTO METABOLIC AND CARDIORENAL WELLNESS IN PEOPLE
WITH DIABETES

Beth Israel Lahey Health



May, 2025

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Disclosures

- Scientific Advisory Board: Abiomed, Boston Scientific
- Consultant: NuPulseCV
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Learning Objectives

- Recognize the impact on prognosis of co-morbid DM and HF
- Review novel therapy for DM and its impact on HF
- Identify non-medical intervention for HF

Overview

- Impact of DM and HF as co-morbidities
- Medical Therapies for DM
- Other Therapeutic Interventions

Overview

- Impact of DM and HF as co-morbidities
- Medical Therapies for DM
- Other Therapeutic Interventions

Epidemiology of HF and DM

- DM frequently occurs concomitantly with both HFrEF and HFpEF
- Prevalence of DM in HF cohorts ranges from 10–47% and is higher in hospitalized HF patients
- 2 – 4 fold increased risk of HF among diabetics compared to non-diabetics
- Risk of HF increases with poor glycemic control

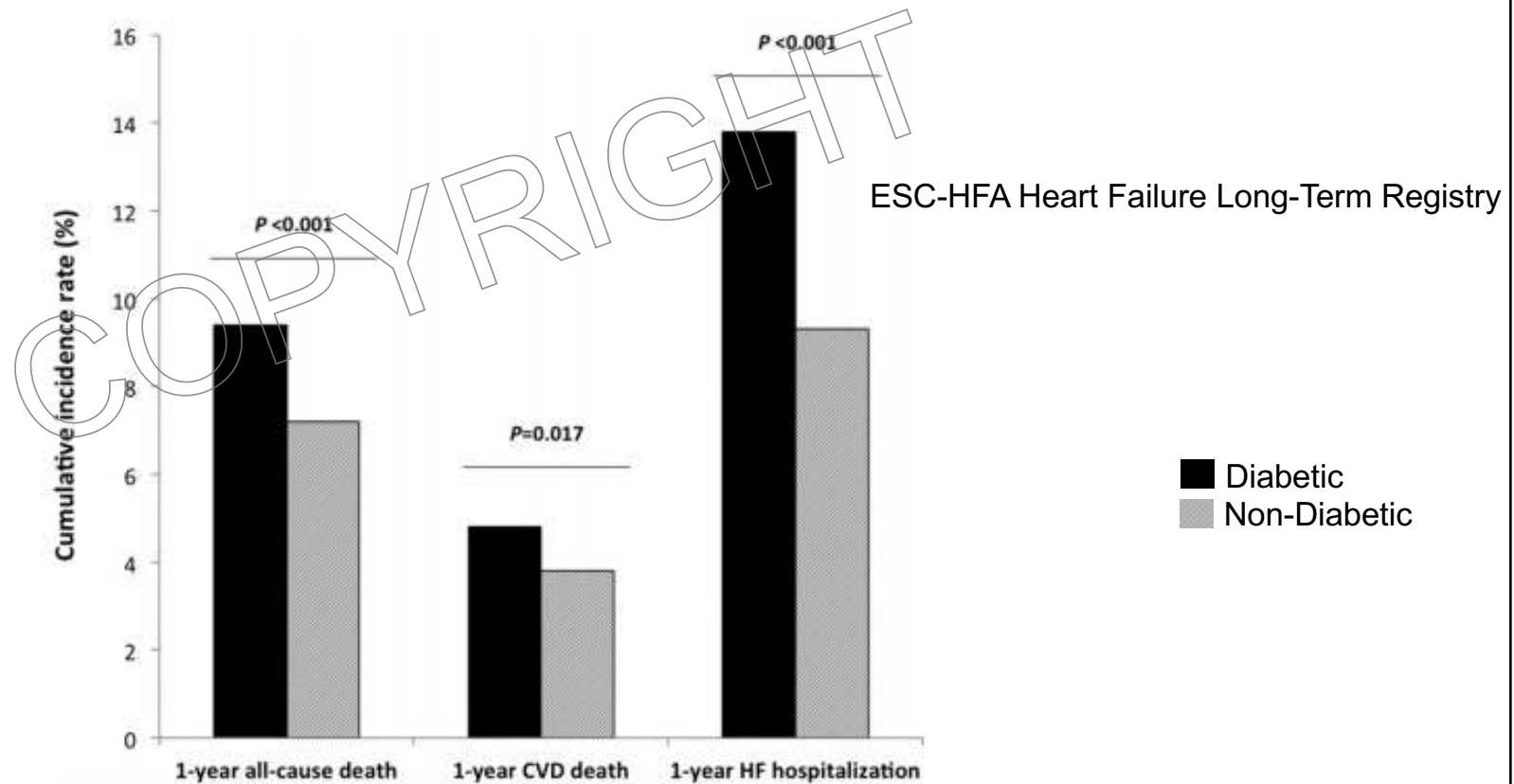
Dunlay SM, et al. Circulation 2019; 140:e294 – 324.

Risk of Incident DM in HF

- Insulin resistance present in up to 60% of HF patients
- Rate of incident DM in HF trials has ranged from 21 – 28 per 1000 person – years compared to ~10 in general population
- Risk factors include elevated BMI, tobacco use, higher systolic BP, longer HF duration, diuretic therapy, and more advanced NYHA functional class

Dunlay SM, et al. Circulation 2019; 140:e294 – 324.

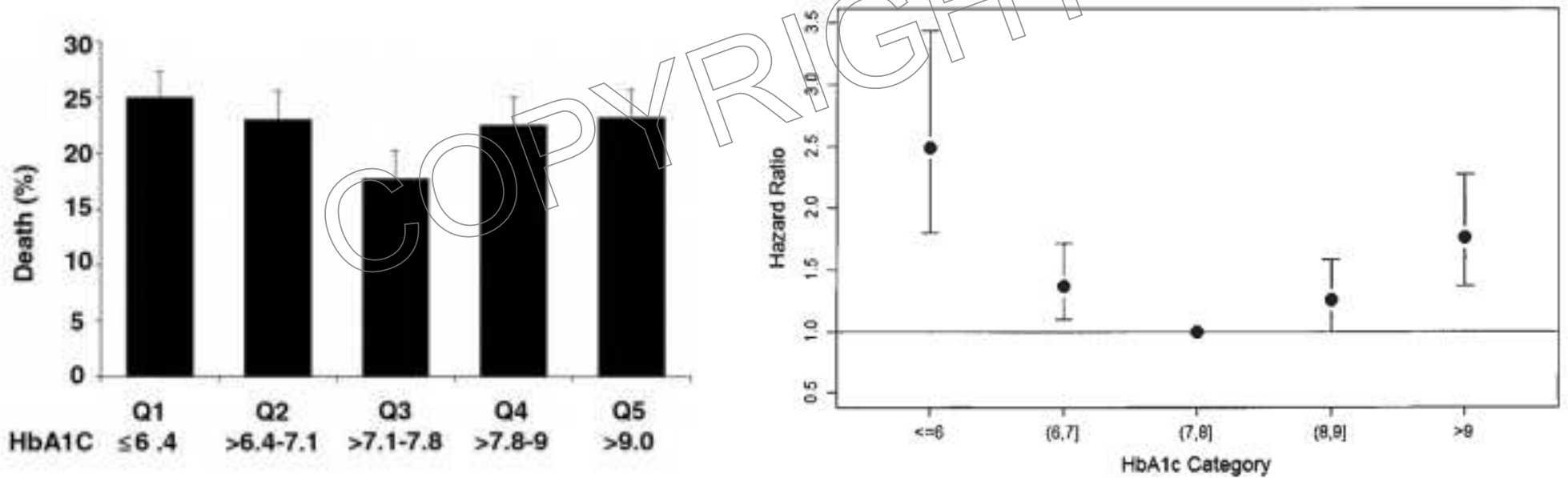
DM and HF: Impact on Outcomes



Dauriz M, et al. Diabetes Care. Diabetes Care 2017;40:671–678.

Diabetes and Heart Failure | May, 2025

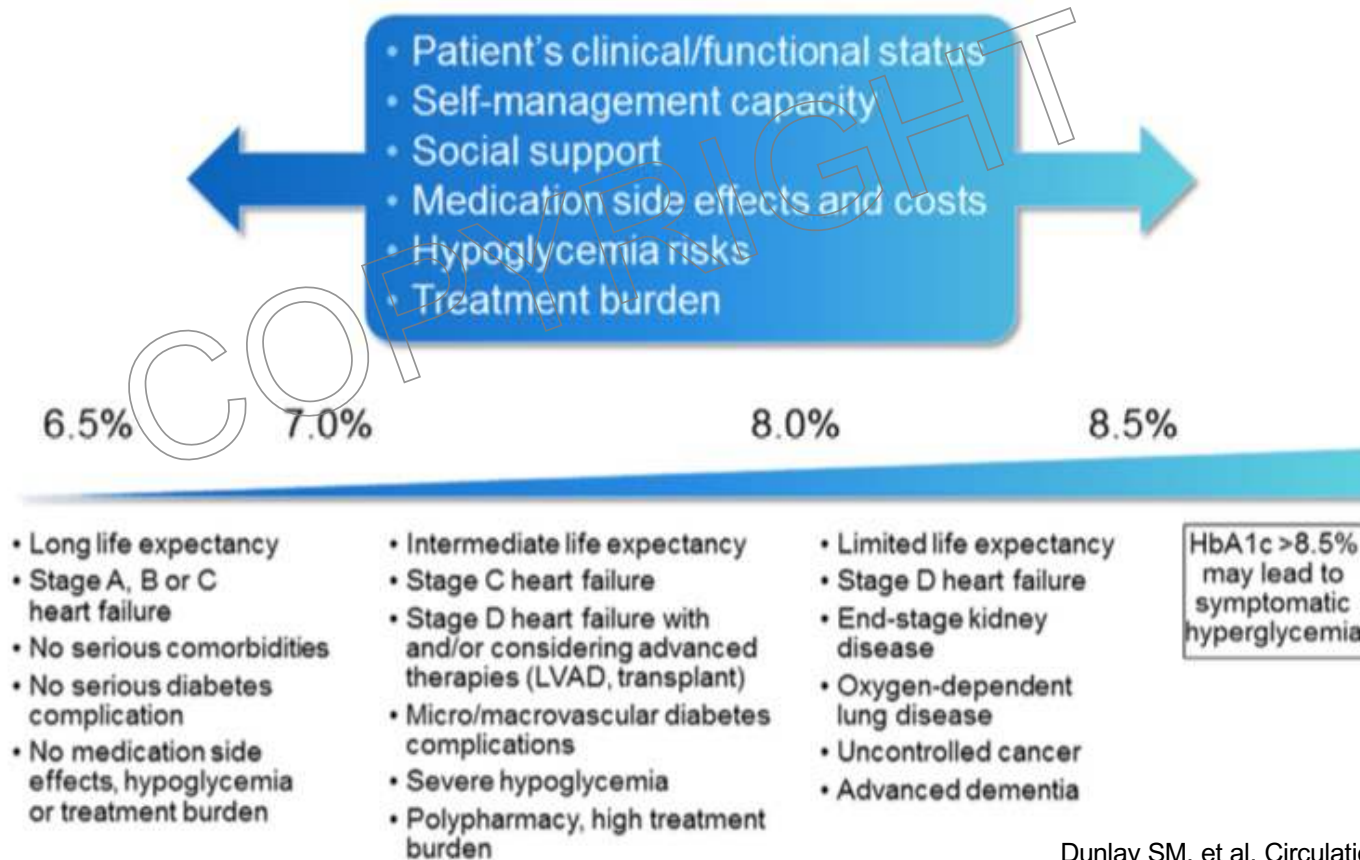
Glycemic Control and Mortality in HF



Aguilar D, et al. J Am Coll Cardiol 2009;54:422–8.

Elder DHJ, et al. Eur J Heart Fail 2016;18:94–102.

What is the Goal Glycemic Target in HF?



Dunlay SM, et al. Circulation 2019; 140:e294 – 324.

Overview

- Impact of DM and HF as co-morbidities
- **Medical Therapies for DM**
- Other Therapeutic Interventions

GLP – 1 Agonists

Medication Trial (Year)	Population	N	% HF	Median Follow-Up, y	Primary Outcome	Impact on Primary Cardiovascular End Point	Impact on HF Hospitalization
Lixisenatide - ELIXA (2015) ⁹³	Recent ACS	6068	22	2.1	Cardiovascular death, MI, UA, stroke	No difference in risk (HR, 1.02 [95% CI, 0.89–1.17])	No difference in risk (HR, 0.96 [95% CI, 0.75–1.23])
Liraglutide - LEADER (2016) ⁹¹	CVD or high risk	9340	14	3.8	Cardiovascular death, MI, stroke	Decreased risk (HR, 0.87 [95% CI, 0.78–0.97])	No difference in risk (HR, 0.87 [95% CI, 0.73–1.05])
Semaglutide - SUSTAIN-6 (2017) ⁹²	CVD or high risk	3297	24	2.1	Cardiovascular death, MI stroke	Decreased risk (HR, 0.74 [95% CI, 0.58–0.95])	No difference in risk (HR, 1.11 [95% CI, 0.77–1.61])
Exenatide - EXSCEL (2017) ¹⁰⁹	+/- CVD	14752	16	3.2	Cardiovascular death, MI, stroke	No significant difference* (HR, 0.91 [95% CI, 0.83–1.00])	No difference in risk (HR, 0.94 [95% CI, 0.78–1.13])

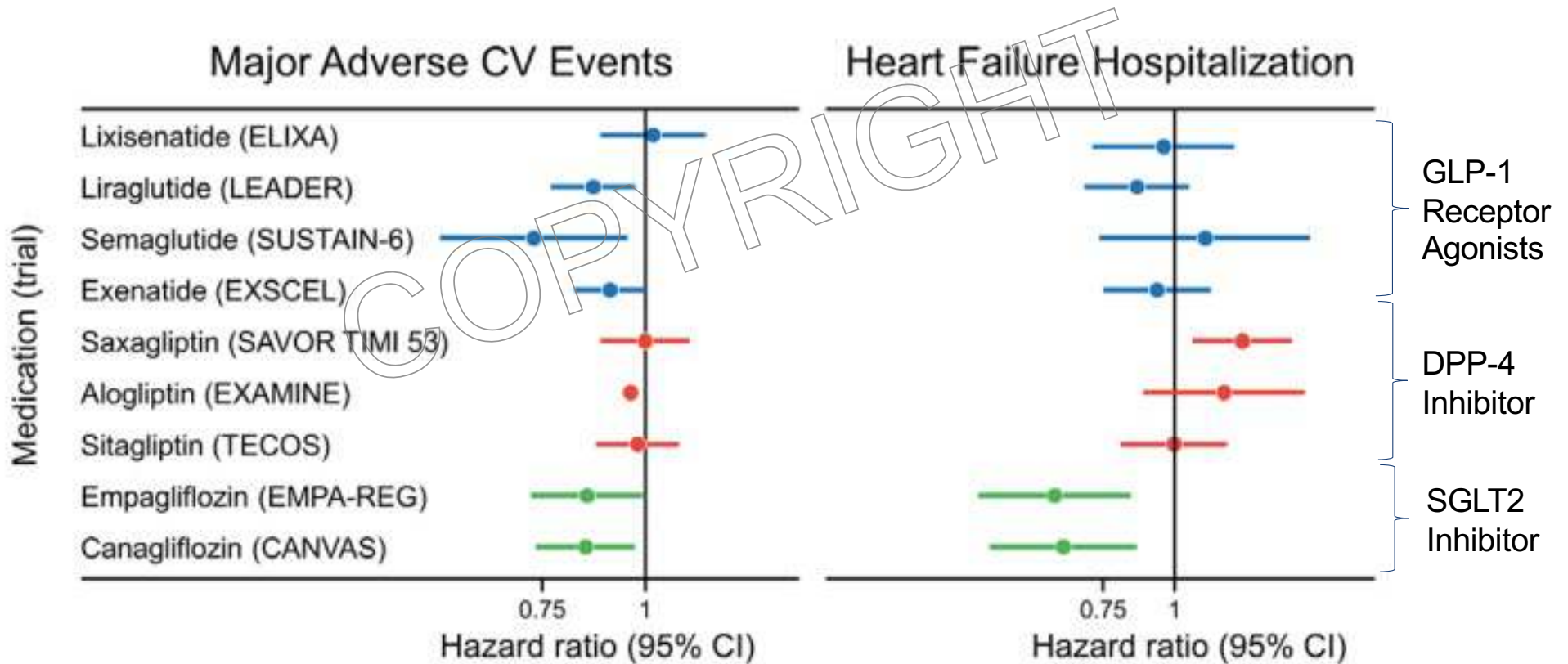
Dunlay SM, et al. Circulation 2019; 140:e294 – 324.

DPP – 4 Inhibitors

Medication Trial (Year)	Population	N	% HF	Median Follow-Up, y	Primary Outcome	Impact on Primary Cardiovascular End Point	Impact on HF Hospitalization
Saxagliptin - SAVOR TIMI-53 (2014) ^{90,97}	CVD or high risk	16492	13	2.1	Cardiovascular death, MI, stroke	No difference in risk (HR, 1.00 [95% CI, 0.89–1.12])	Increased risk of HF (HR, 1.27 [95% CI, 1.07–1.51])
Alogliptin - EXAMINE (2013) ⁹⁸	Recent ACS	5380	28	1.5	Cardiovascular death, MI, stroke	No difference in risk (HR, 0.96; $P < 0.001$ for noninferiority)	No difference in risk (HR, 1.19 [95% CI, 0.90–1.58])
Sitagliptin - TECOS (2016) ^{95,110}	CVD	14724	18	3.0	Cardiovascular death, MI, UA, stroke	No difference in risk (HR, 0.98 [95% CI, 0.88–1.09])	No difference in risk (HR, 1.00 [95% CI, 0.83–1.20])

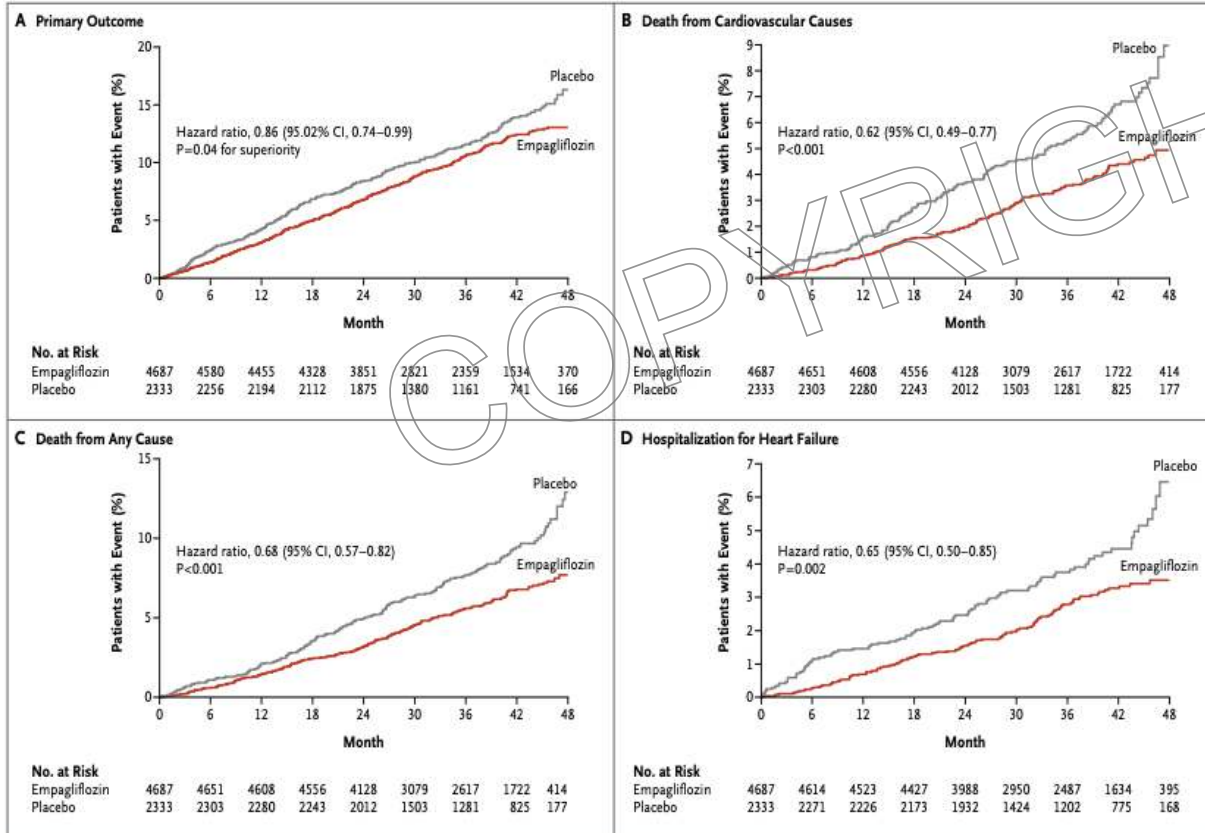
Dunlay SM, et al. Circulation 2019; 140:e294 – 324.

Effect on HF Hospitalization by Drug Class



Dunlay SM, et al. Circulation 2019; 140:e294 – 324.

EMPA – REG OUTCOME

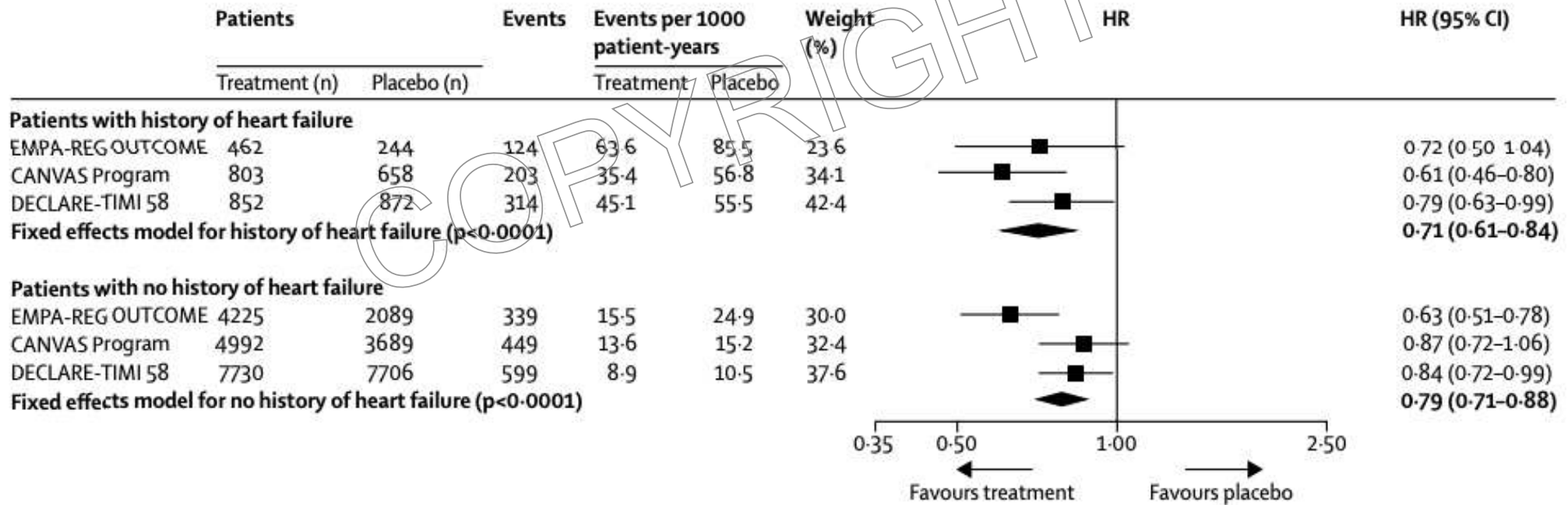


- 7020 patients with DM
- Empagliflozin vs placebo
- Primary outcome: CVD, nonfatal MI, or nonfatal stroke

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

Preventing Heart Failure?

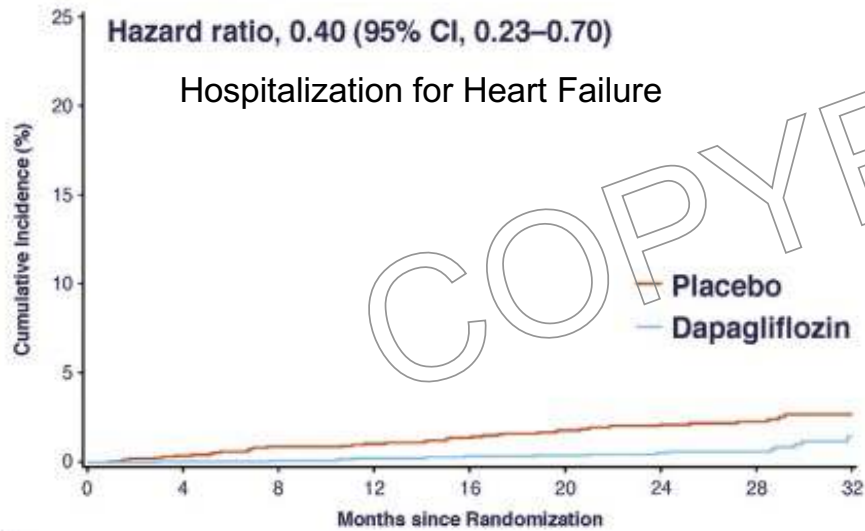
Composite of CVD and HHF



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

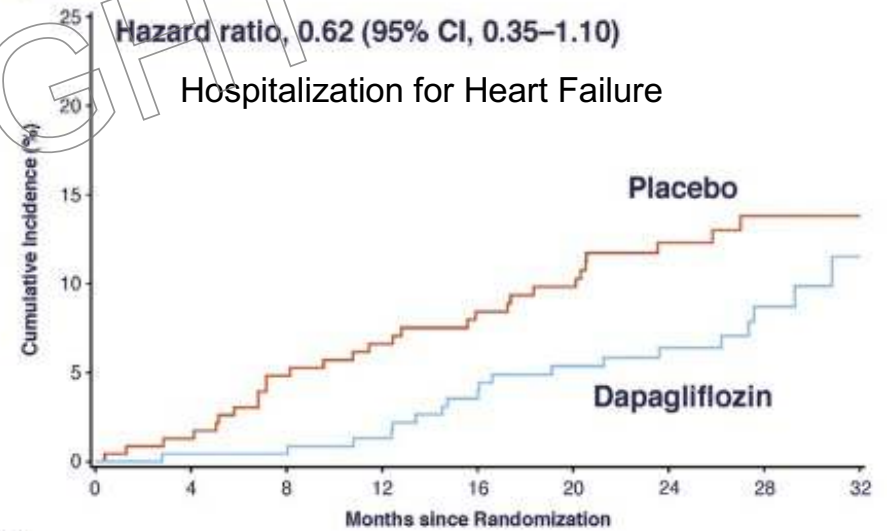
Preventing Heart Failure?

No history of heart failure



No. at Risk	0	4	8	12	16	20	24	28	32
Dapagliflozin	1917	1804	1792	1780	1762	1691	1335	899	345
Placebo	1919	1798	1775	1750	1727	1664	1304	882	320

History of heart failure



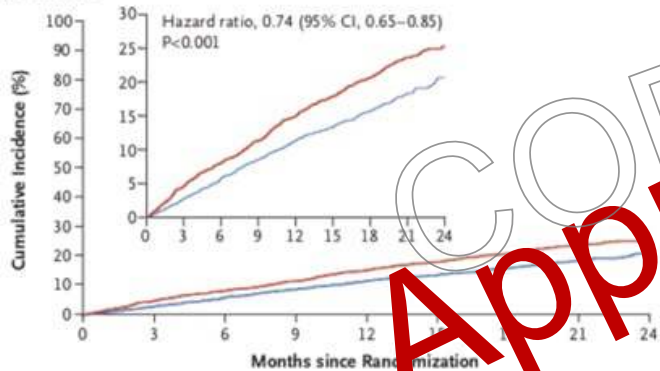
No. at Risk	0	4	8	12	16	20	24	28	32
Dapagliflozin	235	231	229	223	213	204	167	104	39
Placebo	233	225	214	207	200	192	147	94	40

- 4304 patients with CKD
- Randomized to dapagliflozin vs placebo
- 11% of patients had history of HF

McMurray JV, et al. J Am Coll Cardiol: HF 2021.

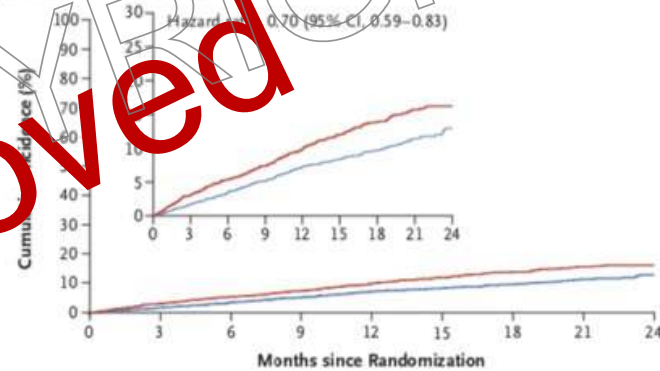
DAPA – HF

A Primary Outcome



No. at Risk	0	3	6	9	12	15	18	21	24
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210
Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210

B Hospitalization for Heart-Failure



No. at Risk	0	3	6	9	12	15	18	21	24
Placebo	2371	2264	2168	2082	1924	1483	1101	596	212
Dapagliflozin	2373	2306	2223	2153	2007	1563	1147	613	210

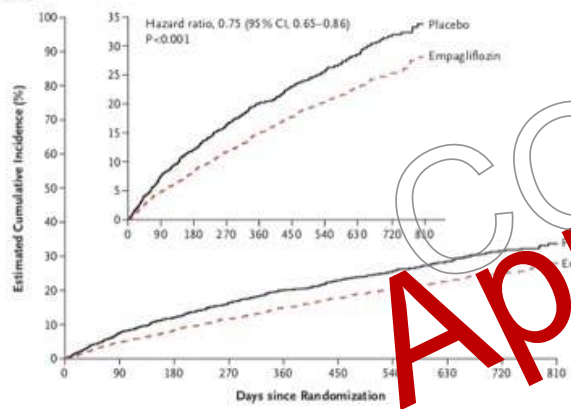
- 4744 patients with HFrEF (LVEF ≤ 40%), NYHA II-IV symptoms with or WITHOUT DM
- Dapagliflozin vs placebo
- Primary outcome: worsening HF or CVD
- Findings similar in those with and without DM
- Findings similar regardless of ARNI use
- HR at 28d = 0.51 (0.28 – 0.94)

McMurray JJV, et al. N Engl J Med 2019;381:1995-2008.

Berg DD, et al. JAMA Cardiol 2021;6:499-5-7.

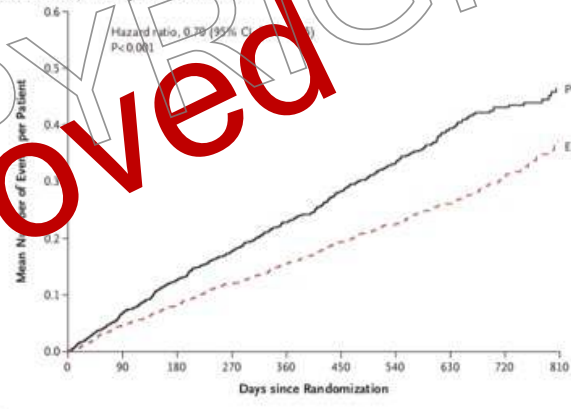
EMPEROR – Reduced

A Primary Outcome



No. at Risk	0	90	180	270	360	450	540	630	720	810
Placebo	1867	1715	1612	1345	1108	854	611	410	224	109
Empagliflozin	1863	1763	1677	1424	1172	909	645	423	231	101

B First and Recurrent Hospitalizations for Heart-Failure



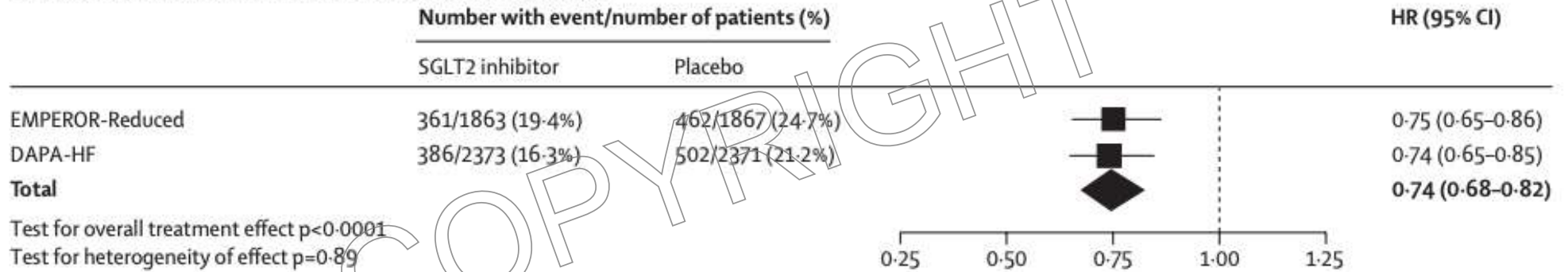
No. at Risk	0	90	180	270	360	450	540	630	720	810
Placebo	1867	1820	1762	1526	1285	1017	732	497	275	135
Empagliflozin	1863	1826	1768	1532	1283	1008	732	495	272	118

- 3730 patients with HFrEF and Class II-IV symptoms with or WITHOUT DM
- Empagliflozin vs placebo
- Primary outcome: CVD or Hospitalization for worsening HF
- Annual rate of decline in eGFR was slower in the empagliflozin group

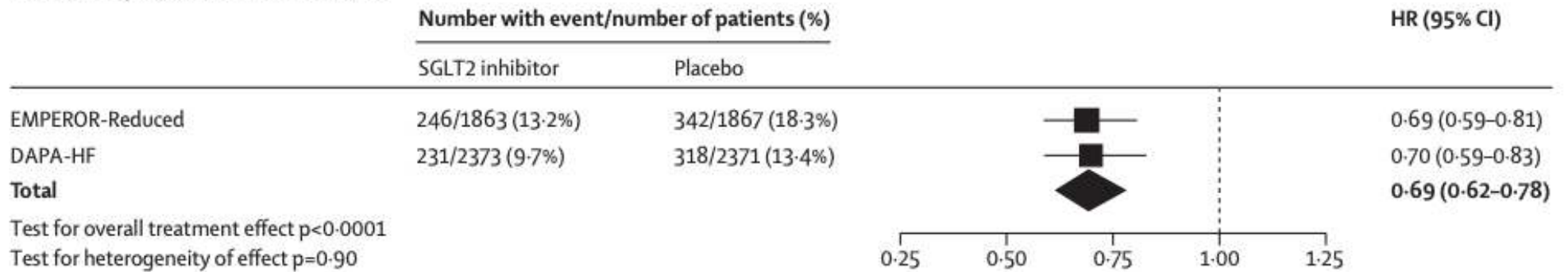
Packer M, et al. N Engl J Med 2020.

SGLT2 Inhibitor Effects in HF

C First hospitalisation for heart failure or cardiovascular death



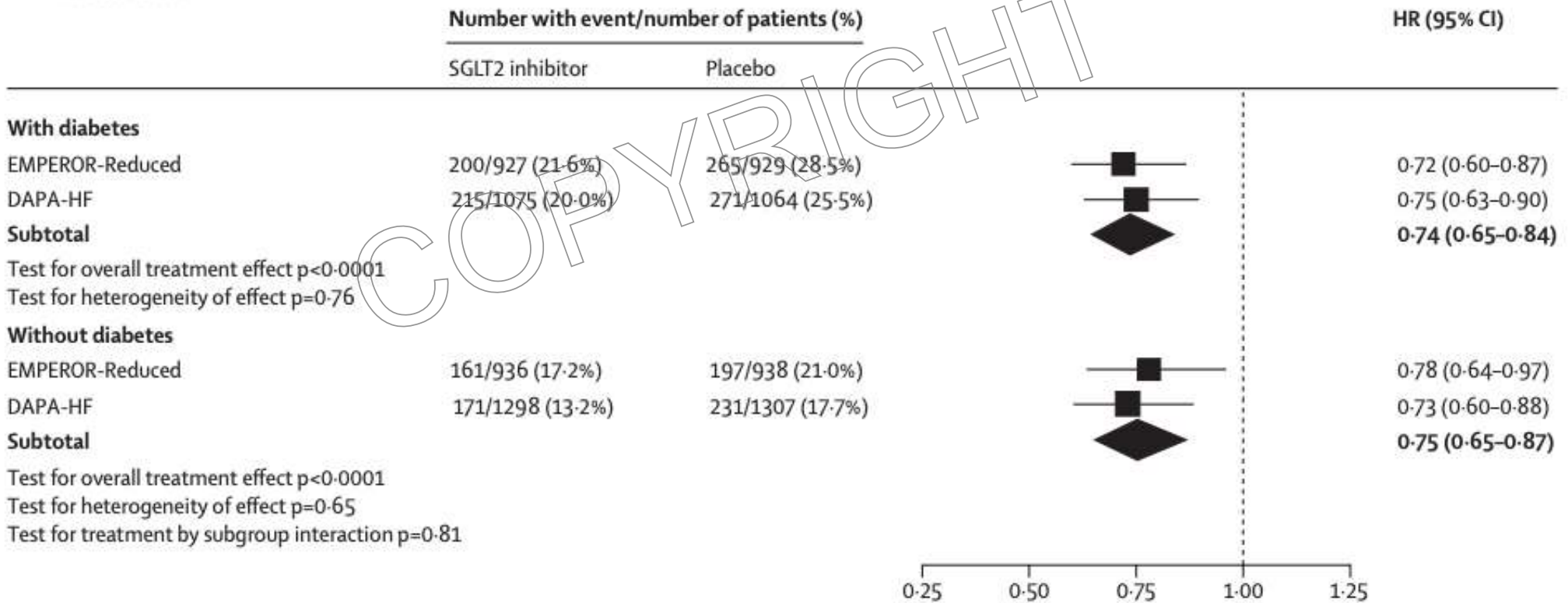
D First hospitalisation for heart failure



Zannad F, et al. Lancet 2020; 396: 819–29.

Benefits Irrespective of Diabetes

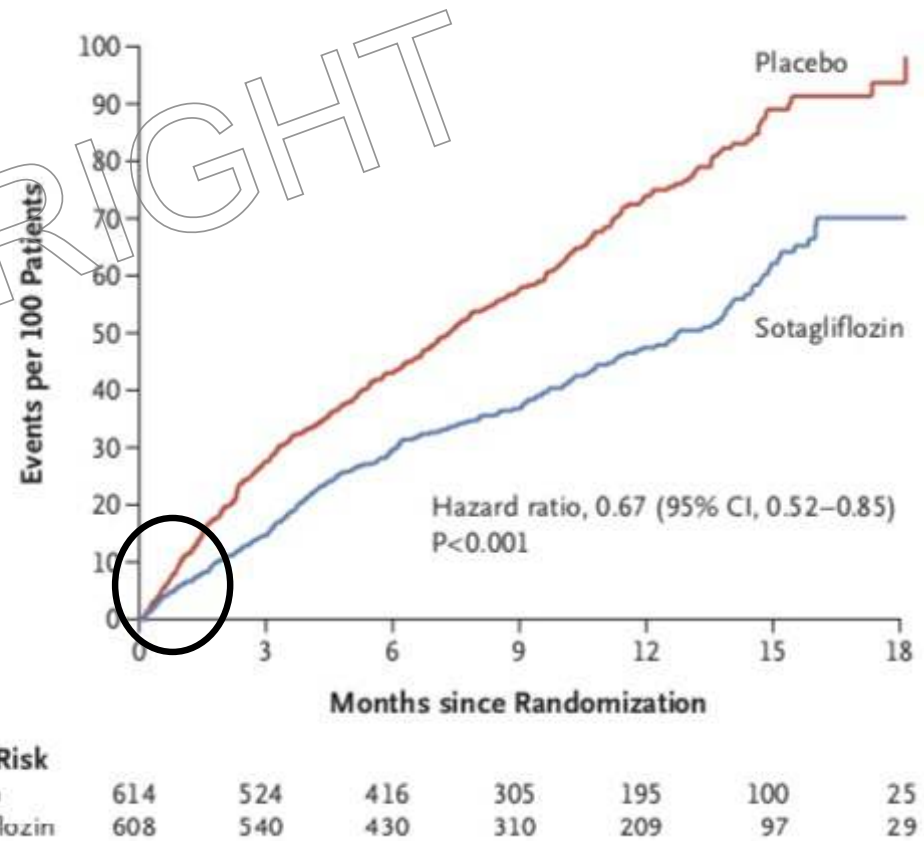
A Diabetes status



Zannad F, et al. Lancet 2020; 396: 819–29.

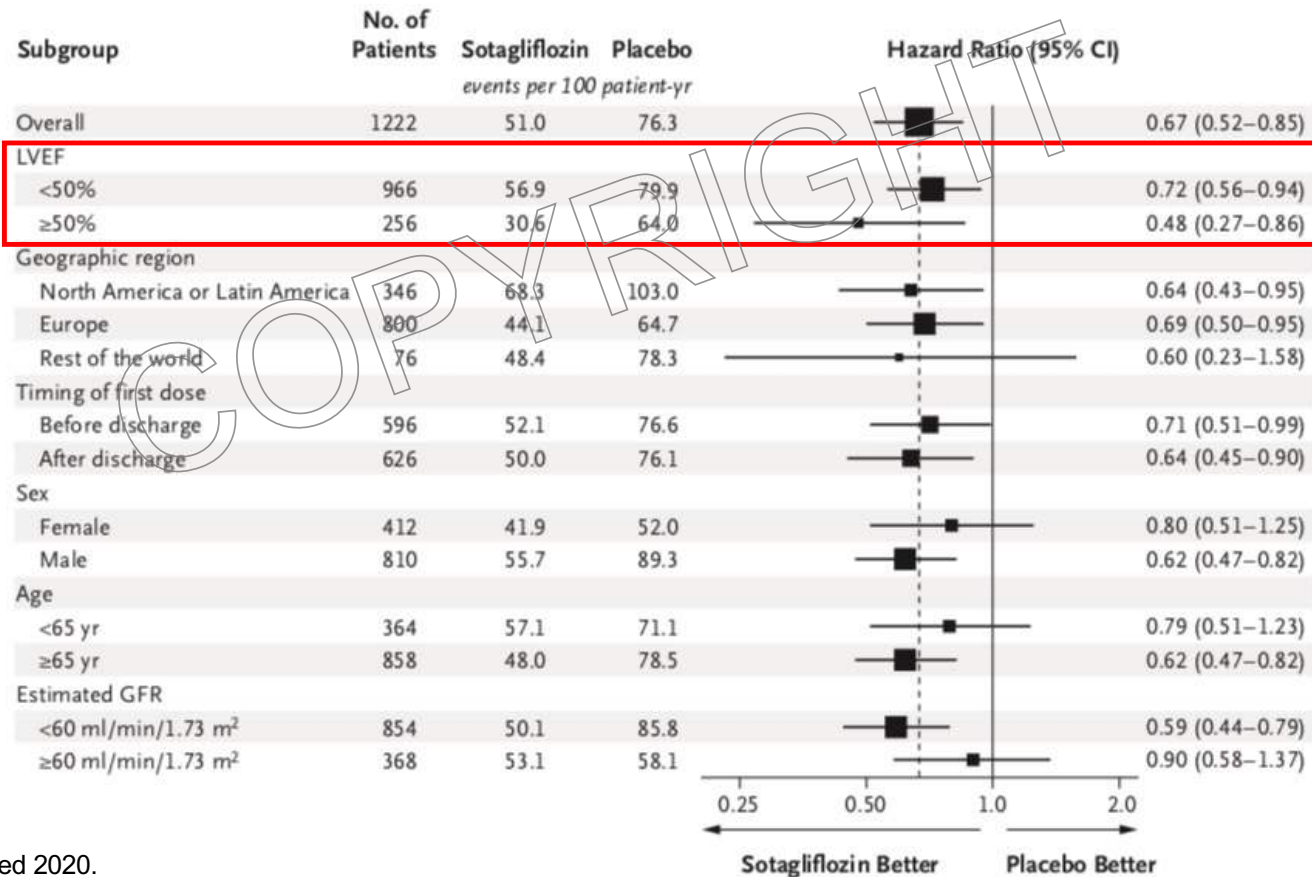
SOLOIST – WHF

- 1222 patients with DM and worsening (i.e. hospitalization for) HF (EF not specified)
- Randomized to sotagliflozin (combined SGLT1 and SGLT2 inhibitor) vs placebo (initiated before or shortly after discharge)
- Primary outcome: composite of CV death, hospitalization or urgent visit for HF
- Additional concern: safety of initiation early after episode of worsening HF (risk of hypotension or AKI)



Bhatt DL, et al. N Engl J Med 2020.

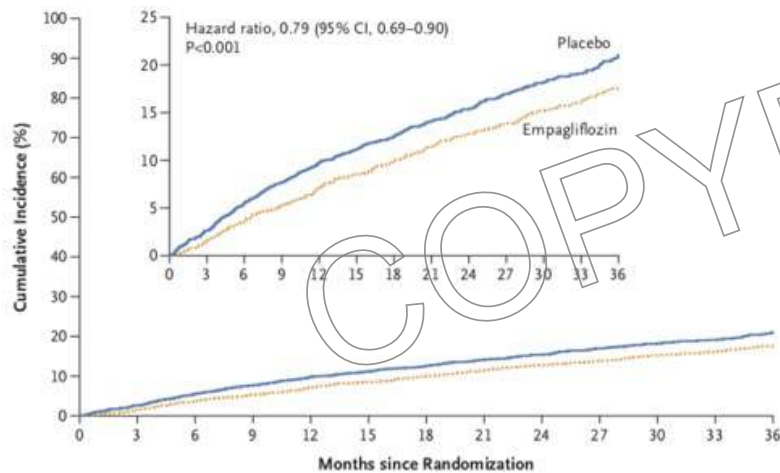
SOLOIST – WHF



Bhatt DL, et al. N Engl J Med 2020.

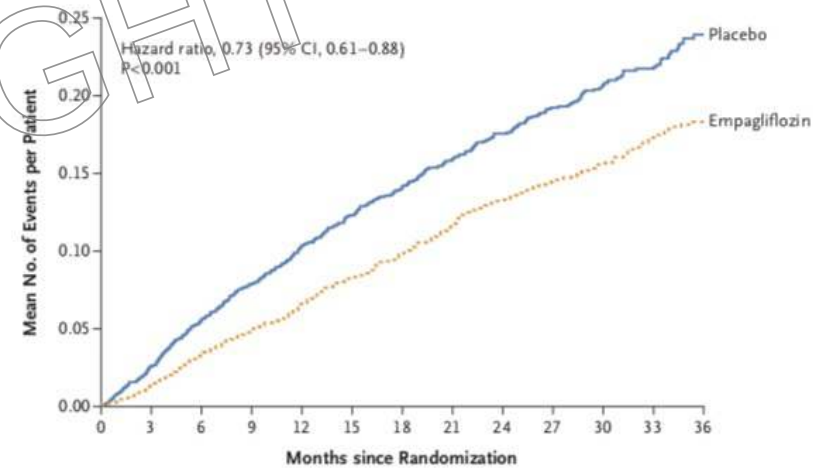
EMPEROR – Preserved

Primary Outcome



No. at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36
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

Hospitalization for HF



No. at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36
Placebo	2991	2945	2901	2855	2816	2618	2258	1998	1695	1414	1061	747	448
Empagliflozin	2997	2962	2913	2869	2817	2604	2247	1977	1684	1429	1081	765	446

- 5988 patients with NYHA class II – IV HF
- LVEF > 40%

- Primary outcome: composite of CV death or hospitalization for HF

Anker SD, et al. New Engl J Med 2021

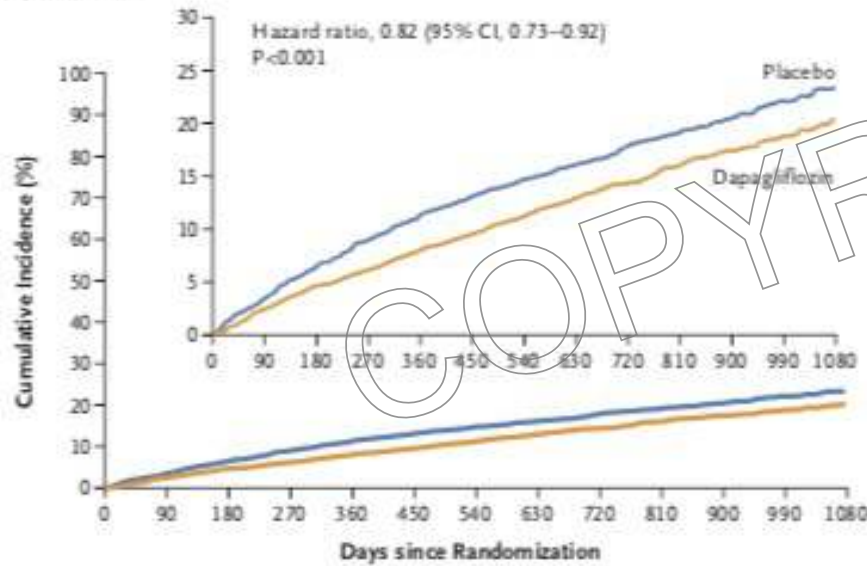
EMPEROR – Preserved

Subgroup	Empagliflozin <i>no. of patients with events/total no.</i>	Placebo <i>no. of patients with events/total no.</i>	Hazard Ratio (95% CI)
Overall	415/2997	511/2991	0.79 (0.69–0.90)
Diabetes at baseline			
Yes	239/1466	291/1472	0.79 (0.67–0.94)
No	176/1531	220/1519	0.78 (0.64–0.95)
LVEF at baseline			
<50%	145/995	193/988	0.71 (0.57–0.88)
≥50% to <60%	138/1028	173/1030	0.80 (0.64–0.99)
≥60%	132/974	145/973	0.87 (0.69–1.10)
Age			
<70 yr	134/1066	152/1084	0.88 (0.70–1.11)
≥70 yr	281/1931	359/1907	0.75 (0.64–0.87)
BMI at baseline			
<30	223/1654	292/1642	0.74 (0.62–0.88)
≥30	192/1343	219/1349	0.85 (0.70–1.03)
Estimated GFR (CKD-EPI) at baseline			
≥60 ml/min/1.73 m ²	152/1493	189/1505	0.81 (0.65–1.00)
<60 ml/min/1.73 m ²	263/1504	321/1484	0.78 (0.66–0.91)

Anker SD, et al. New Engl J Med 2021

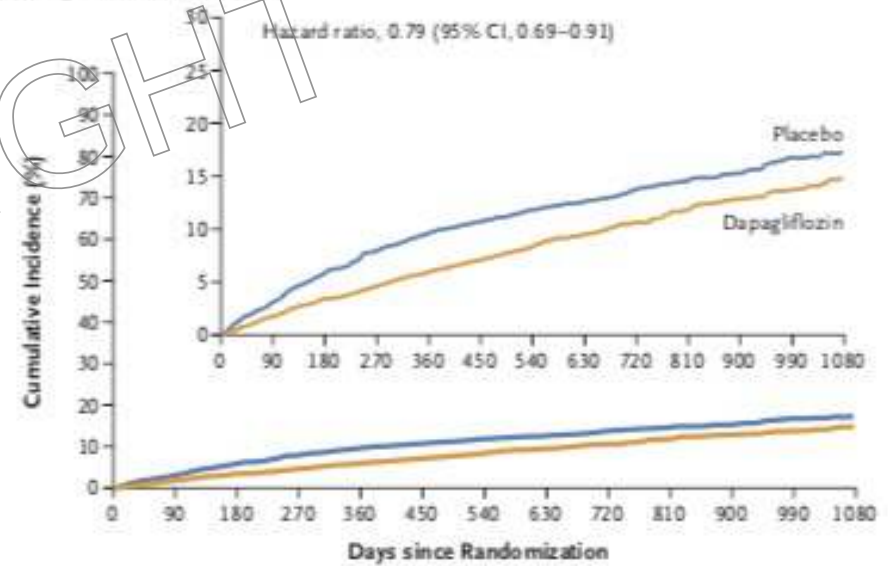
DELIVER

A Primary Outcome



No. at Risk		0	90	180	270	360	450	540	630	720	810	900	990	1080
Placebo		3132	3007	2896	2799	2710	2608	2318	2080	1923	1554	1140	772	383
Dapagliflozin		3131	3040	2949	2885	2807	2716	2401	2147	1982	1603	1181	801	389

B Worsening Heart Failure Event



No. at Risk		0	90	180	270	360	450	540	630	720	810	900	990	1080
Placebo		3132	3007	2896	2799	2710	2608	2318	2080	1923	1554	1140	772	383
Dapagliflozin		3131	3040	2949	2885	2807	2716	2401	2147	1982	1603	1181	801	389

- 6263 patients with NYHA class II – IV HF
- LVEF > 40%

- Primary outcome: composite of CV death or worsening HF

Solomon SD, et al. New Engl J Med 2022

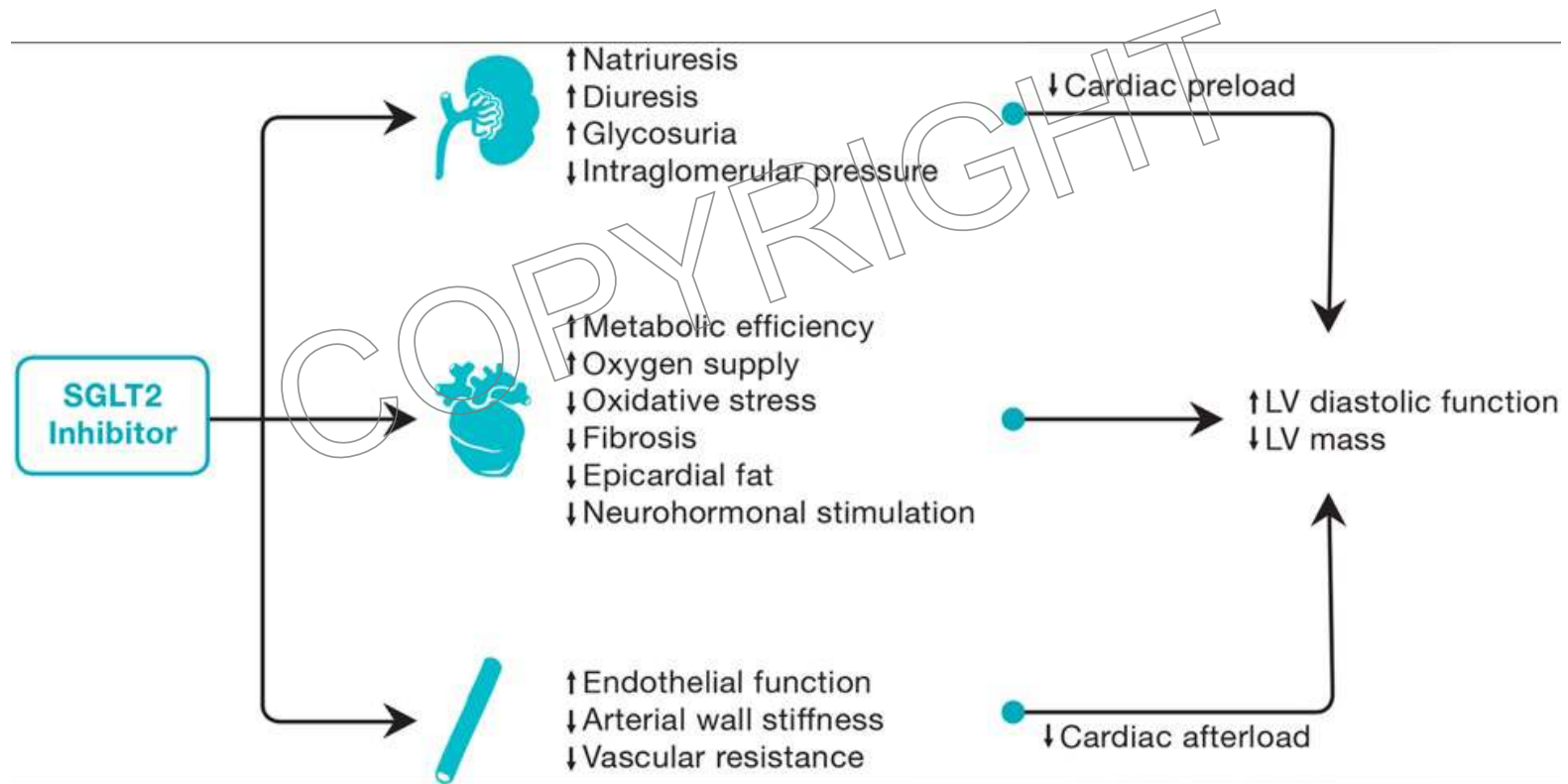
DELIVER

Subgroup	Dapagliflozin <i>no. of patients with events/total no.</i>	Placebo <i>no. of patients with events/total no.</i>	Hazard Ratio (95% CI)
NYHA class at enrollment			
II	331/2314	411/2399	0.81 (0.70–0.94)
III or IV	181/817	198/732	0.80 (0.65–0.98)
LVEF at enrollment			
≤49%	207/1067	229/1049	0.87 (0.72–1.04)
50–59%	174/1133	211/1123	0.79 (0.65–0.97)
≥60%	131/931	170/960	0.78 (0.62–0.98)
NT-proBNP at enrollment			
≤1011 pg/ml	173/1555	208/1578	0.84 (0.68–1.02)
>1011 pg/ml	339/1576	402/1553	0.79 (0.69–0.92)
Enrollment during or within 30 days after hospitalization for heart failure			
No	419/2803	497/2806	0.82 (0.72–0.94)
Yes	93/328	113/326	0.78 (0.60–1.03)
Type 2 diabetes mellitus at enrollment			
No	242/1730	293/1727	0.81 (0.68–0.96)
Yes	270/1401	317/1405	0.83 (0.70–0.97)

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Solomon SD, et al. New Engl J Med 2022

SGLT2 Inhibitor Mechanism in Heart Failure



Lan et al. ESC Heart Failure 2019.

SGLT2 Inhibitor Net Effect



Zelniker TA and Braunwald E. J Am Coll Cardiol. 2020;75:435-447.

SGLT2 Inhibitor – Practical Considerations



Patients with T2DM with or at High Risk for CV Disease, Already on Metformin

Below Individualized HbA1c Target:
Switch non-metformin oral therapies (e.g. sulfonylureas) to a SGLT2i

Above Individualized HbA1c Target:
Consider SGLT2i initiation

Drug Type
Canagliflozin, dapagliflozin, & empagliflozin with similar efficacy profile in reducing HF events

Starting Dose (once daily in AM)

- Canagliflozin (100mg)
- Dapagliflozin (5mg)
- Empagliflozin (10mg)
- Ertugliflozin (5mg)

Metformin+SGLT2i Combination Therapies
Consider to limit non-adherence and pill burden

Stable Hemodynamic and Clinical Status

Pre-Initiation eGFR must be above:

- ~~30~~ mL/min/1.73 m² 25 (dapagliflozin, ertugliflozin)
- ~~35~~ mL/min/1.73 m² 20 (canagliflozin, empagliflozin)

Anticipatory Guidance
Consider diuretic dose reduction

Patient Counseling

- Genital/perineal hygiene
- Orthostatic hypotension
- Regular foot exams
- Symptoms of DKA
- Avoid excessive alcohol

Multidisciplinary Care
Close communication with other providers, including PCPs and endocrinologists

Long-Term Continuation

Follow-up and Monitoring

- Serial assessment of renal function, body weights, blood pressure, and symptoms
- Dose uptitration guided by need for glycemic control
- Ensure adherence to SGLT2i, other therapies, and therapeutic lifestyle
- Multidisciplinary care team follow-up

Vardeny, O. et al. J Am Coll Cardiol HF. 2019;7(2):169-72.

More Help Coming?

529 patients randomized to semaglutide vs placebo

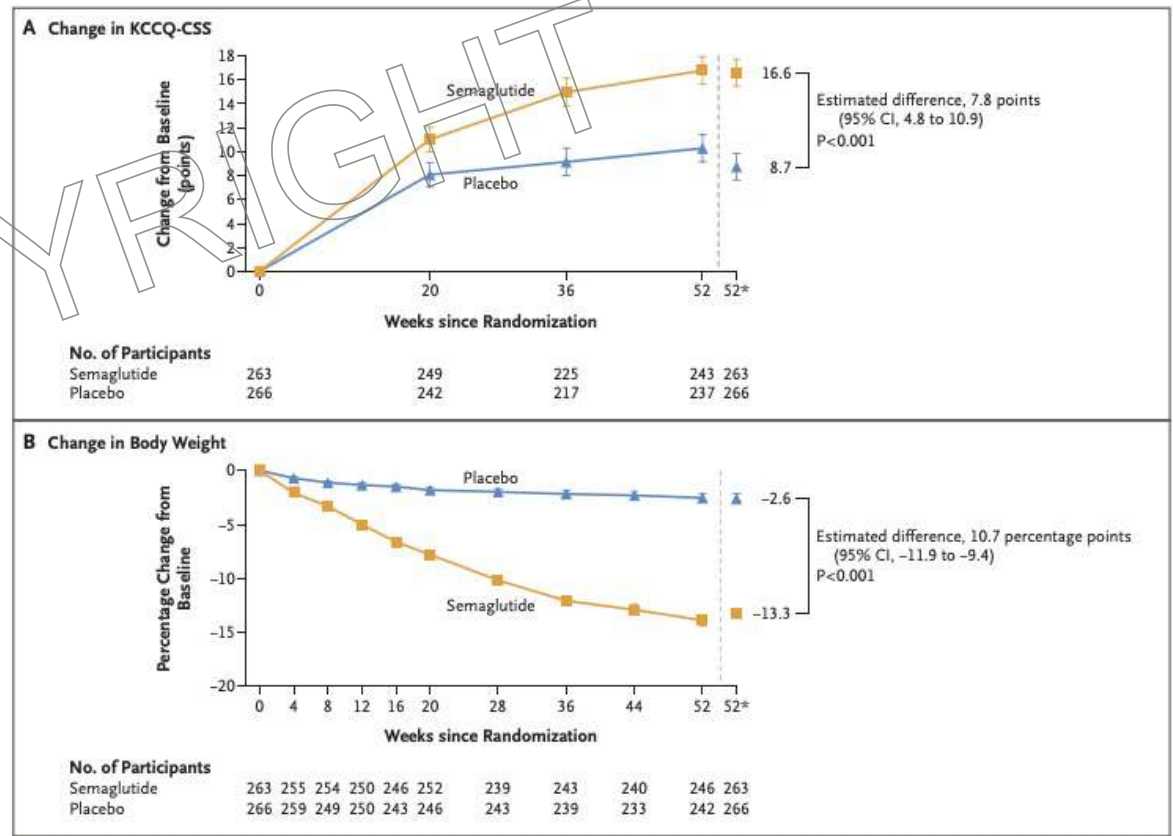
Inclusion Criteria:

- LVEF > 45%
- BMI > 30
- at least one of the following findings:
 - elevated LV pressures
 - elevated natriuretic peptide levels, or
 - HF hospitalization

Exclusion Criteria:

- Hgb A1c > 6.5

Kosiborod MN, et al. New Engl J Med 2023

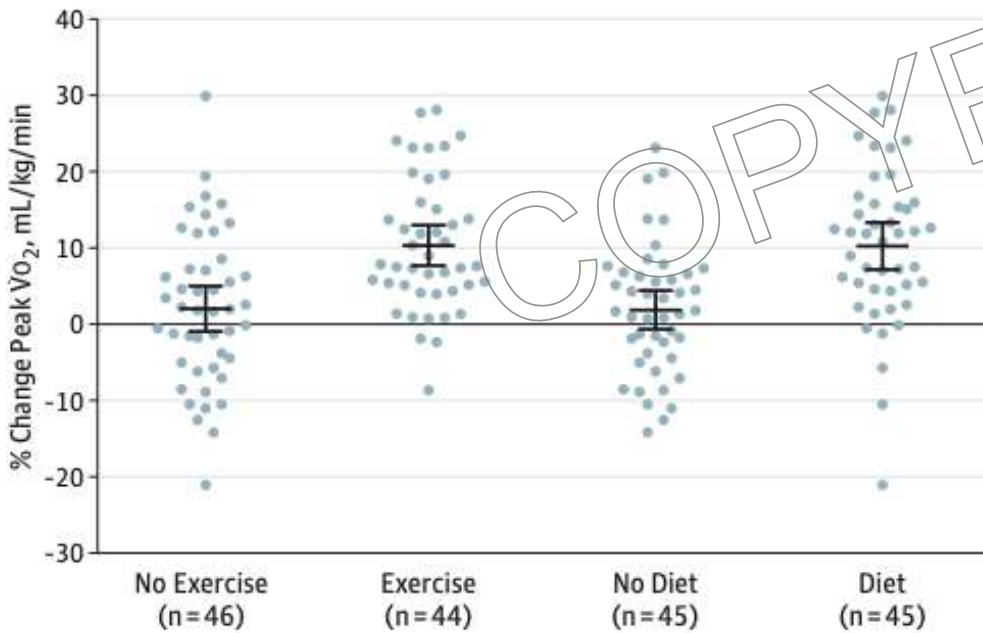


Overview

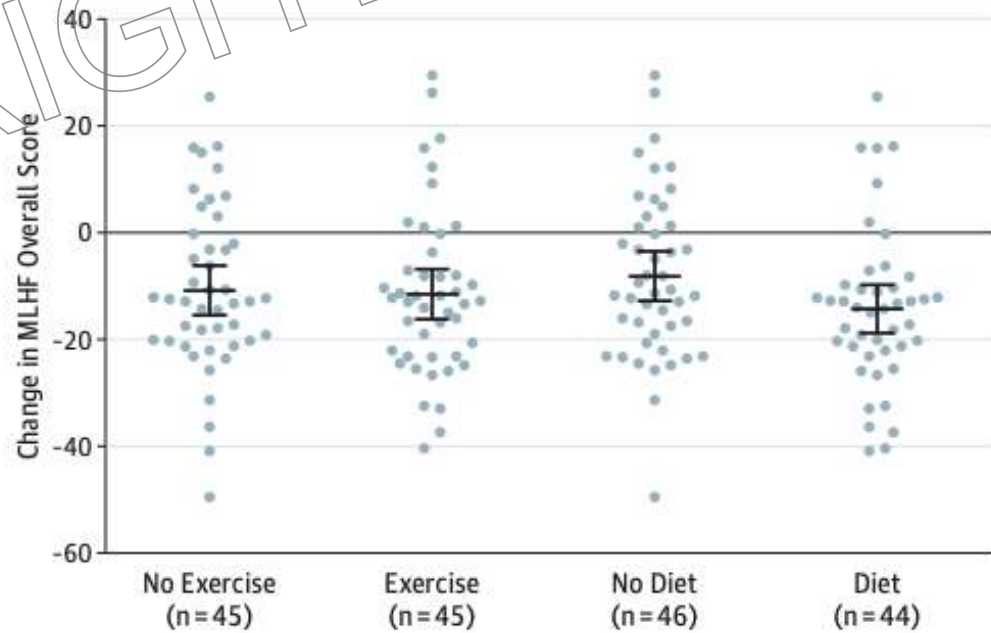
- Impact of DM and HF as co-morbidities
- Medical Therapies for DM
- **Other Therapeutic Interventions**

Lifestyle Modification

A Peak VO_2 percentage change from baseline

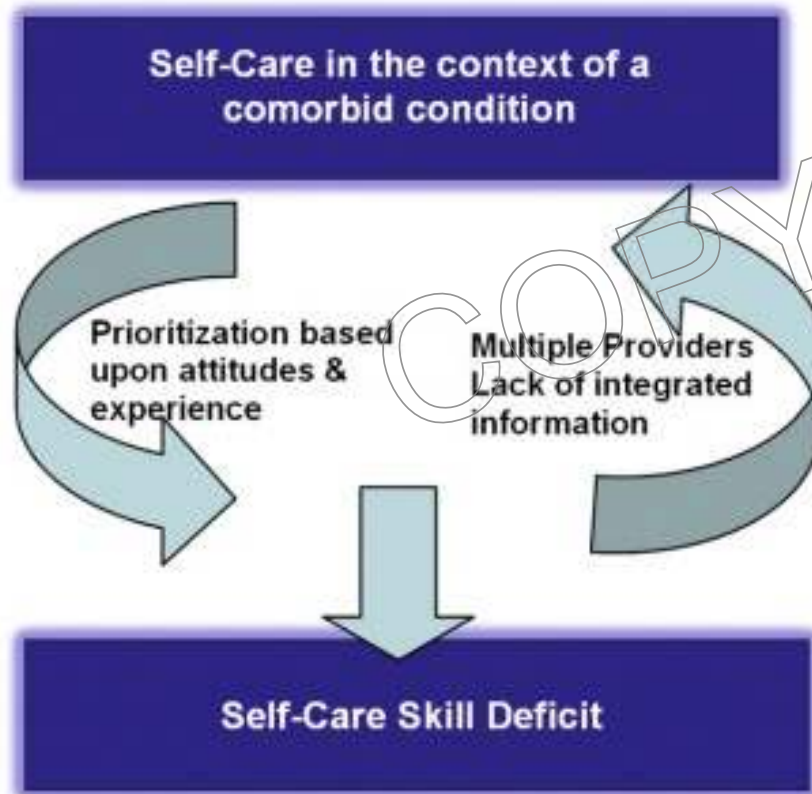


B Minnesota Living With Heart Failure (MLHF) score change from baseline



Kitzman DW, et al. JAMA. 2016;315(1):36-46.

Complexities of Managing DM and HF

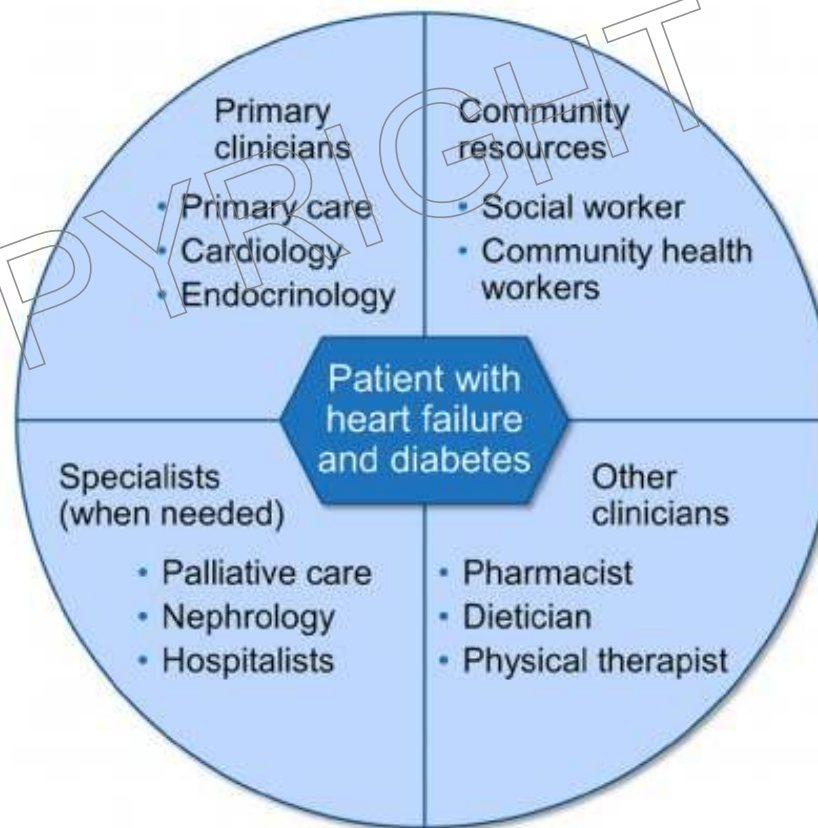


- 1) Attitudes drive self care prioritization
- 2) Fragmented self-care instruction leads to poor self-care integration

Dickson VV, et al. J Cardiac Fail 2011;17:413-419.

Coordination of Care

Communication between providers a necessity



Dunlay SM, et al. Circulation 2019; 140:e294 – 324.

Key Take Home Points

- Heart failure and DM are commonly co-morbid conditions
- Patients with co-morbid DM and HF have worse outcomes than their counterparts
- SGLT2 inhibitor therapy represents a novel therapy with major benefit to HF patients irrespective of the presence of DM or the phenotype of HF
- A comprehensive approach to co-management of these conditions is critical to optimizing outcomes for this patient population



Thank you

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