Updates in the management of heart failure and reduced ejection fraction

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Disclosures

- AHA Strategically Focused Research Network

- ESC Young Investigator Research Grant

- Bayer-Vascular Canadian Cardiovascular Society grant

- Roche Diagnostics

- Takeda

- BMS-Pfizer

- B.I-CVCT Fellow

- Boeringer-Ingelhiem

- Novartis

Agenda

- Current paradigm to chronic heart failure management
- ARNI- impact and evidence in HFrEF
- SGLT inhibitors and heart failure – new kids on the block
- Future paradigm

What is Heart Failure

Typical Symptoms + Physical Signs + Structural

☐ Shortness of breath at rest
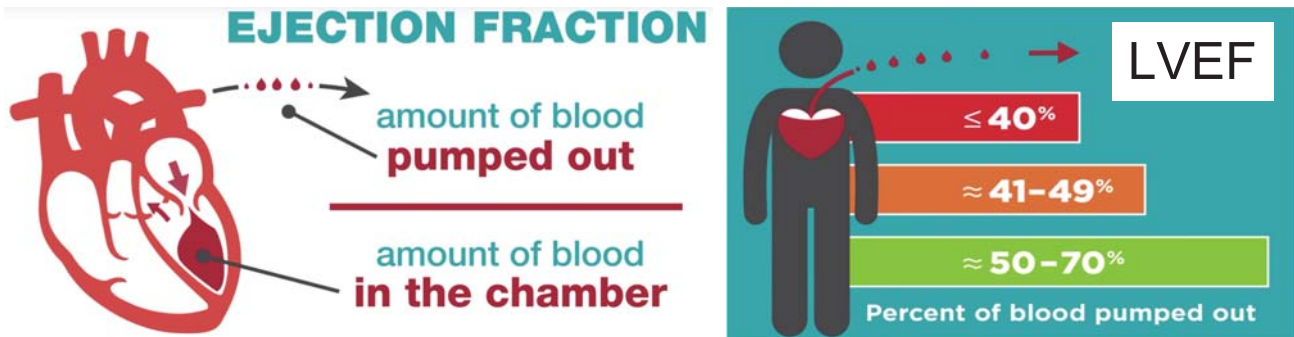☐ Increased discomfort or swelling in the lower body
☐ Sudden weight gain of more than 2-3 lbs in a 24 hour period (or 5 lbs in a week)

1. Rise AboveHF.org; 2. https://www.medicalnewstoday.com/articles/321773.php; 3. *EHJ (47);27:14:2129-2200*

What is Heart Failure - Terminology

What is Heart Failure - Terminology

| Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%

	3	–	1. Elevated levels of natriuretic peptides[b];
			2. At least one additional criterion:
			    a. relevant structural heart disease (LVH and/or LAE),
			    b. diastolic dysfunction (for details see Section 4.3.2).
				1. Elevated levels of natriuretic peptides[b];
				2. At least one additional criterion:
				    a. relevant structural heart disease (LVH and/or LAE),
				    b. diastolic dysfunction (for details see Section 4.3.2).

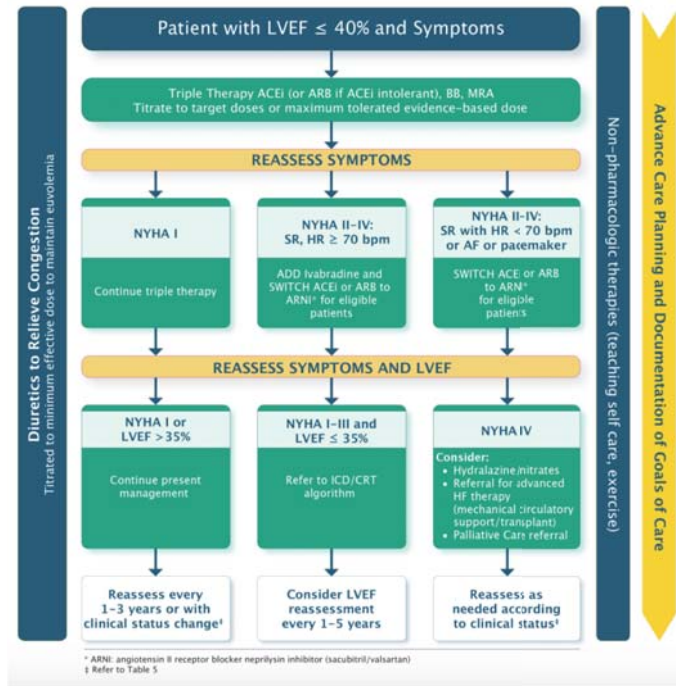# Mortality and Heart Failure Risk
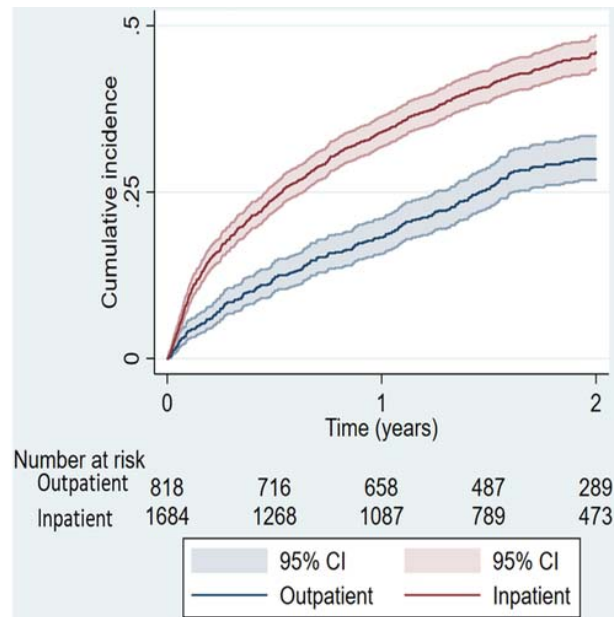
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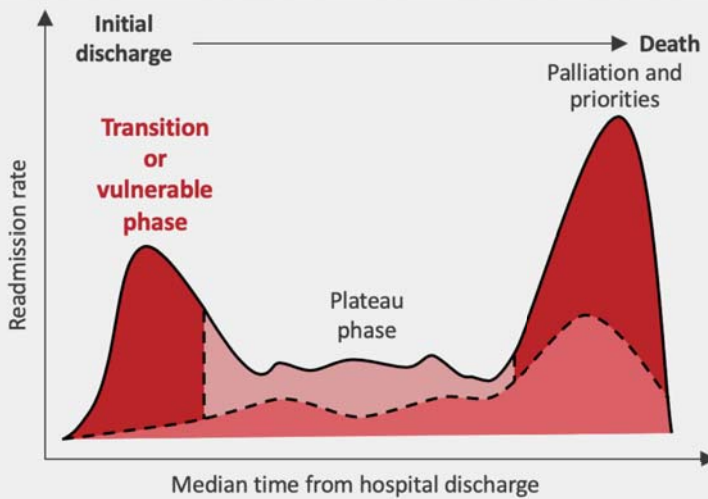
Red indicates period of highest risk for readmission immediately after discharge and just before death

Picture from: Desai AS and Stevenson LW. Circulation 2012;126(4):501-6;
1. A.P. Maggioni et al. Eur J Heart Fail. 2013 Jul;15(7):808-17.; 2. Yancy et al. Circulation. 2013;128:e240-e327, originally published October 14, 2013.

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PARADIGM-HF Trial

A **Primary End Point**

Hazard ratio, 0.80 (95% CI, 0.73–0.87)
P<0.001
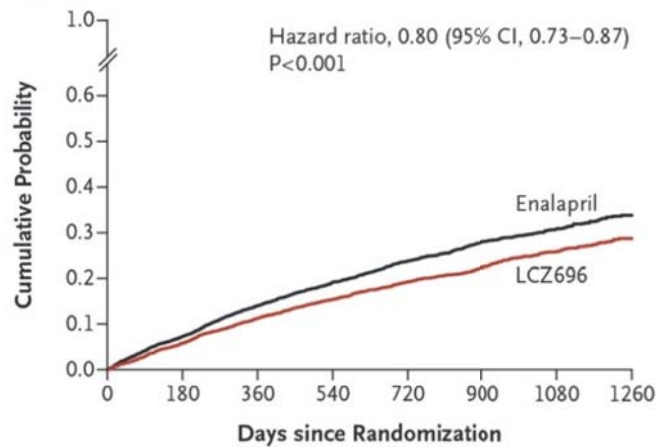
No. at Risk

LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

PIONEER-HF: Study Design

Hospitalized With Acute Decompensated HF With Reduced EF

Sacubitril/valsartan 97/103 mg twice daily **vs** Enalapril 10 mg twice daily

While hospitalized

In-hospital initiation
Study drug for 8 weeks

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Time-average proportional change of NT-proBNP from baseline

Enalapril

Sacubitril/Valsartan

Week since randomization

12

Cumulative incidence of rehospitalization for HF

Effect through Week 8
HR 0.61 (95% CI: 0.40, 0.93)
p = 0.021

30 Days

13.6%

7.0%

Enalapril

8.5%

5.1%

Sacubitril/Valsartan

Days from Randomization

NEJM 2019 Feb 7;380(6):539-548

Composite of death, HF re-hospitalization, LVAD, listing for transplant

Effect through Week 8
HR 0.58 (95% CI: 0.40, 0.85)
p = 0.005

16.3%

Enalapril

9.8%

Sacubitril/Valsartan

Days from Randomization

13

Rapid and significant reduction of NT-proBNP was observed, with majority of reduction within the first 2 weeks

sacubitril/valsartan

Geometric mean plasma NT-proBNP (pg/mL)

Baseline Day 14 Day 30 Day 45 Month 2 Month 3 Month 6 Month 9 Month 12

ESC Congress World Congress
Paris 2019 of Cardiology

Together with

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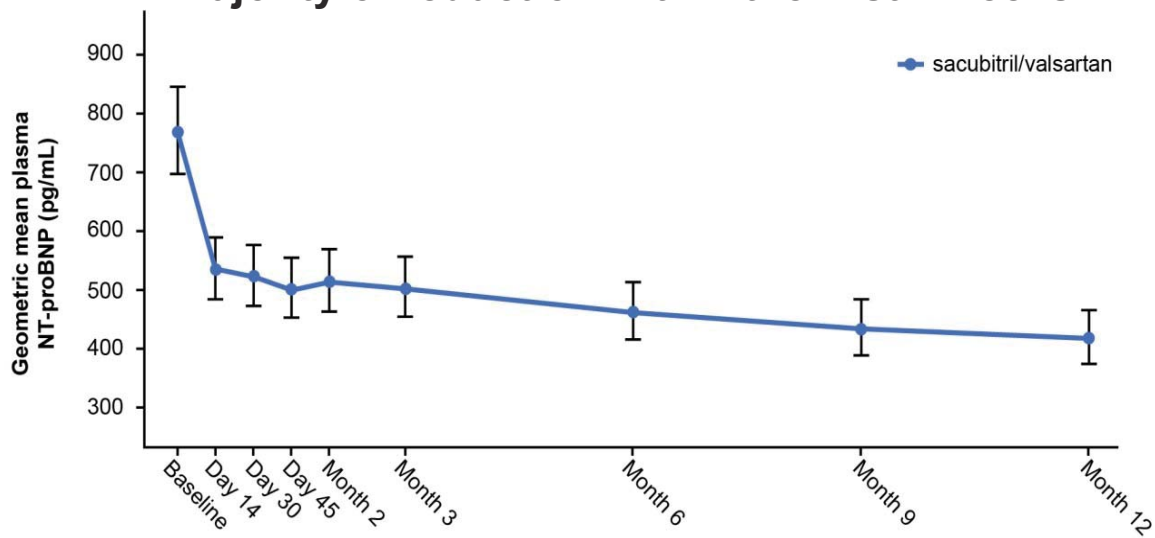
CCS/CHFS Heart Failure Guidelines Update: Defining a New Pharmacologic Standard of Care for Heart Failure With Reduced Ejection Fraction

Primary Panel: Michael McDonald, MD (Co-chair) • Sean Virani, MD (Co-chair) • Michael Chan, MBBS • Anique Ducharme, MD 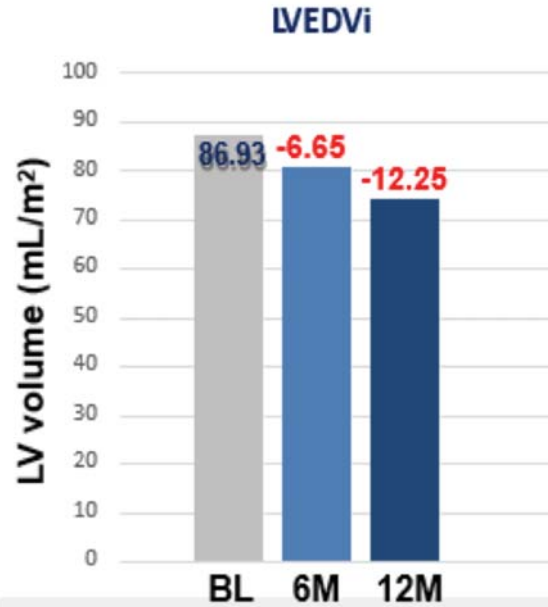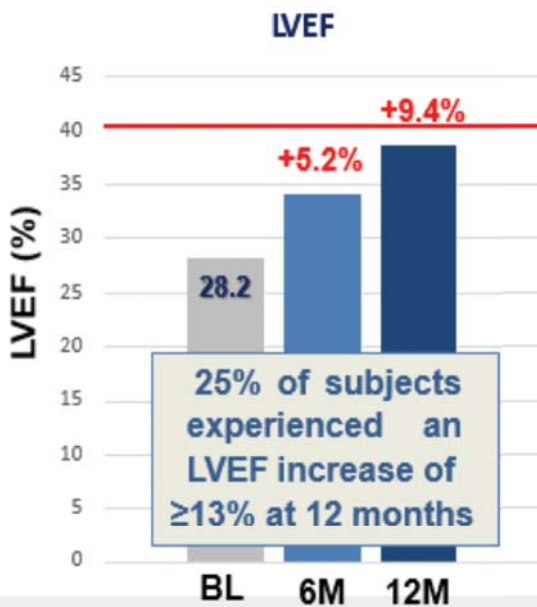• Justin A. Ezekowitz, MBBCh • Nadia Giannetti, MD • George A. Heckman, MD • Jonathan G. Howlett, MD • Sheri L. Koshman, Pharm D • Serge Lepage, MD • Lisa Mielniczuk, MD • Gordon W. Moe, MD • Eileen O'Meara, MD • Elizabeth Swiggum, MD • Mustafa Toma, MD • Shelley Zieroth, MD **Secondary Panel:** Kim Anderson, MD • Sharon A. Bray, EdD • Brian Clarke, MD • Alain Cohen-Solal, MD • Michel D'Astous, MD • Margot Davis, MD • Sabe De, MD • Andrew D.M. Grant, MD • Adam Grzeslo, MD • Jodi Heshka, MD • Sabina Keen, MD • Simon Kouz, MD • Douglas Lee, MD, PhD • Frederick A. Masoudi, MD MSPH • Robert McKelvie, MD • Marie-Claude Parent, MD • Stephanie Poon, MD • Miroslaw Rajda, MD • Abhinav Sharma, MD • Kyla Siatecki, MN, NP • Kate Storm, NP • Bruce Sussex, MBBS • Harriette Van Spall, MD MPH • Amelia Ming Ching Yip, MD • Show less

New paradigm
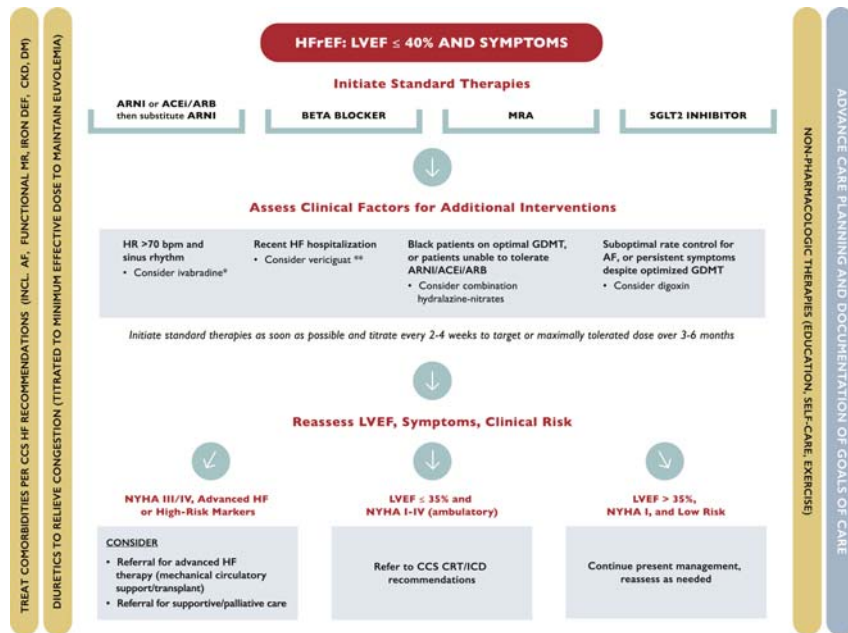
Sodium glucose co-transporter-2 inhibitors and HF

EMPA-REG OUTCOME: Effect of Empagliflozin vs Placebo on HF Hospitalization

HF Hospitalization

HR: 0.65
95% CI: 0.50-0.85
P = .0017

35% RRR

Placebo

Empagliflozin

Patients With Event, %

Time, mo
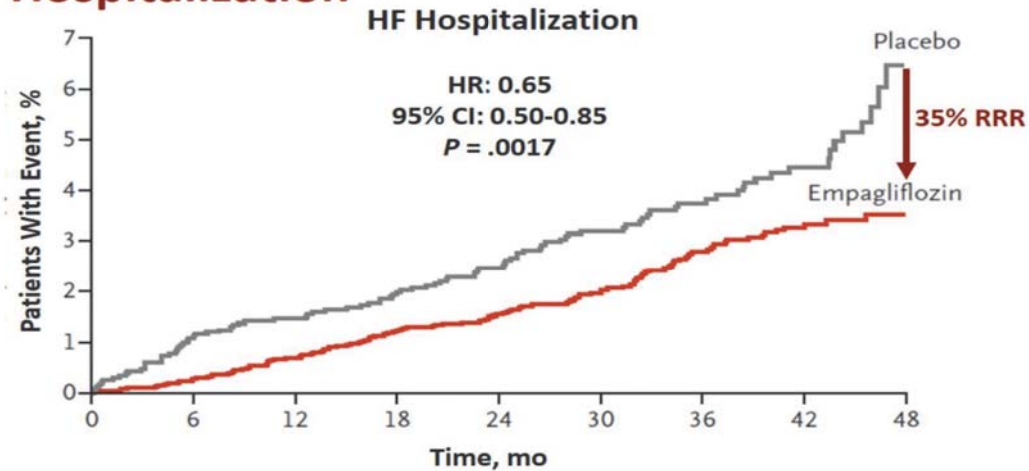
From New England Journal of Medicine, Zinman et al, Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes, 373(22):2117-28, Copyright© (2015) MMS. Reprinted with permission from Massachusetts Medical Society

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DAPA-HF trial

- SGLT-2 inhibitors can reduce the risk of HF development among patients with T2DM and CV disease or CV risk factors

- Can SGLT-2 inhibitors reduce the risk of CV death or HF hospitalization among patients with established HF and reduced ejection fraction ?

- Is this benefit independent of of the presence of diabetes ?

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Trial design

Patient disposition

Median follow-up 18.2 months

8134 patients screened

3390 patients not randomized
Death 12
Adverse event 15
Participant choice 84
Eligibility criteria not met 3279

4744 patients randomized

2373 assigned to dapagliflozin

5 patients did not receive drug

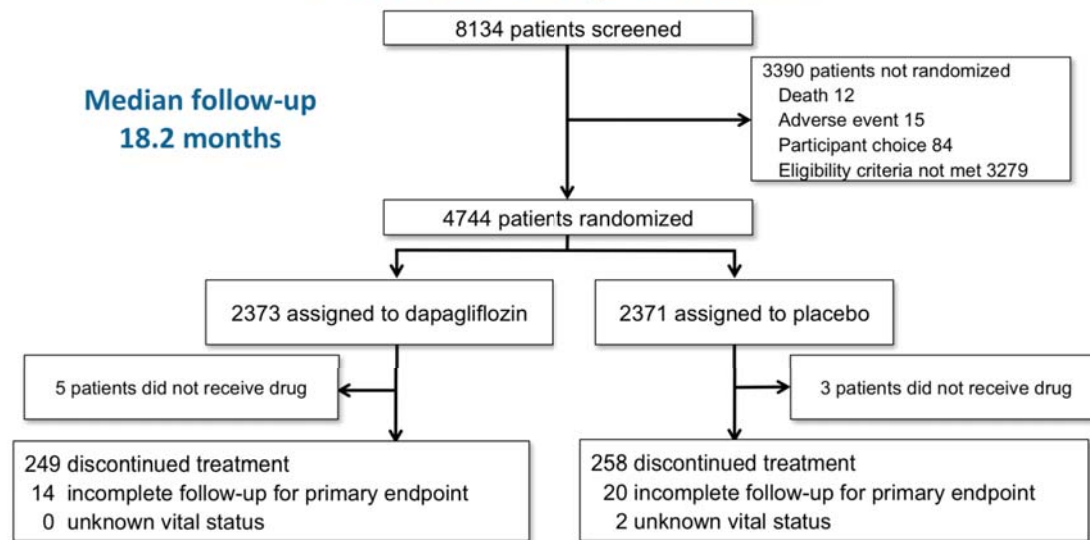249 discontinued treatment
14 incomplete follow-up for primary endpoint
0 unknown vital status

2371 assigned to placebo

3 patients did not receive drug

258 discontinued treatment
20 incomplete follow-up for primary endpoint
2 unknown vital status

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Key Baseline Criteria

Characteristic	Dapagliflozin (n=2373)	Placebo (n=2371)
Mean age (yr)	66	67
Male (%)	76	77
NYHA class II/III/IV (%)	68/31/1	67/32/1
Mean LVEF (%)	31	31
Median NT pro BNP (pg/ml)	1428	1446
Mean systolic BP (mmHg)	122	122
Ischaemic aetiology (%)	55	57
Mean eGFR (ml/min/1.73m^2)	66	66
Prior diagnosis T2D (%)	42	42
Any baseline T2D (%)*	45	45

*includes 82 dapagliflozin and 74 placebo patients with previously undiagnosed diabetes i.e. two HbA1c ≥6.5% (≥48 mmol/mol)

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CV Death/HF hospitalization/Urgent HF visit

HR 0.74 (0.65, 0.85)
p=0.00001
NNT=21
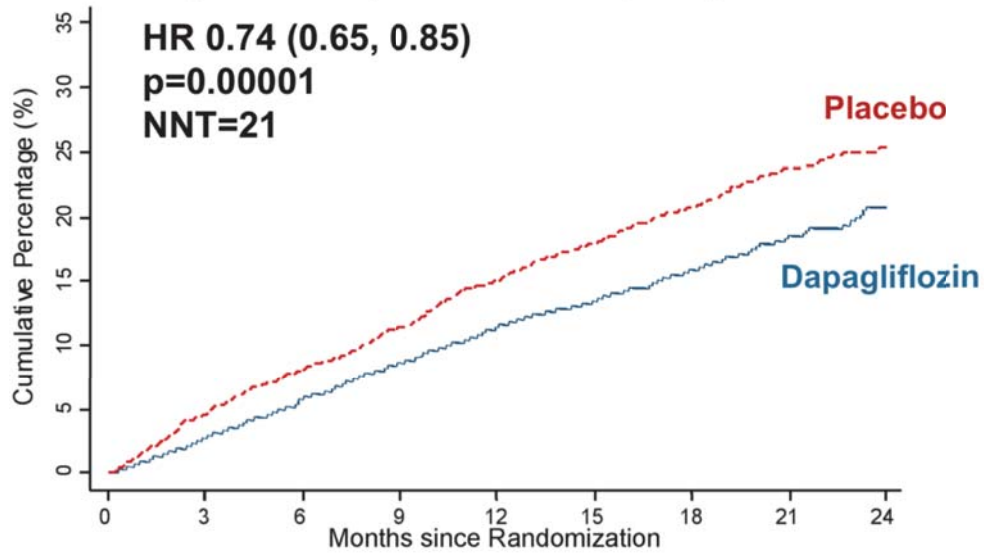
Number at Risk

	0	3	6	9	12	15	18	21	24
Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

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Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

Milton Packer, M.D., Stefan D. Anker, M.D., Ph.D., Javed Butler, M.D., Gerasimos Filippatos, M.D., Stuart J. Pocock, Ph.D., Peter Carson, M.D., James Januzzi, M.D., Subodh Verma, M.D., Ph.D., Hiroyuki Tsutsui, M.D., Martina Brueckmann, M.D., Waheed Jamal, M.D., Karen Kimura, Ph.D., et al., for the EMPEROR-Reduced Trial Investigators*

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EMPEROR REDUCED (Empagliflozin)

- 3730 patients with class II, III, or IV heart failure
- Ejection fraction of 40% or less to receive empagliflozin (10 mg once daily) or placebo, in addition to recommended therapy.

The primary outcome :cardiovascular death or hospitalization for worsening heart failure

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Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Empagliflozin (N=1863)	Placebo (N=1867)
Age — yr	67.2±10.8	66.5±11.2
Female sex — no. (%)	437 (23.5)	456 (24.4)
Race — no. (%)†		
White	1325 (71.1)	1304 (69.8)
Black	123 (6.6)	134 (7.2)
Asian	337 (18.1)	335 (17.9)
Other or missing	78 (4.2)	94 (5.0)
Region — no. (%)		
North America	212 (11.4)	213 (11.4)
Latin America	641 (34.4)	645 (34.5)
Europe	676 (36.3)	677 (36.3)
Asia	248 (13.3)	245 (13.1)
Other	86 (4.6)	87 (4.7)
NYHA functional class — no. (%)		
II	1399 (75.1)	1401 (75.0)
III	455 (24.4)	455 (24.4)
IV	9 (0.5)	11 (0.6)
Body-mass index‡	28.0±5.5	27.8±5.3
Heart rate — beats/min	71.0±11.7	71.5±11.8
Systolic blood pressure — mm Hg	122.6±15.9	121.4±15.4
Left ventricular ejection fraction		
Mean value	27.7±6.0	27.2±6.1
Value of ≤30% — no. (%)	1337 (71.8)	1392 (74.6)

Cause of heart failure — no. (%)		
Ischemic	983 (52.8)	946 (50.7)
Nonischemic	880 (47.2)	921 (49.3)
Cardiovascular history — no. (%)		
Hospitalization for heart failure in ≤12 mo	577 (31.0)	574 (30.7)
Atrial fibrillation	664 (35.6)	705 (37.8)
Diabetes mellitus	927 (49.8)	929 (49.8)
Hypertension	1349 (72.4)	1349 (72.3)
Estimated glomerular filtration rate		
Mean value — ml/min/1.73 m^2	61.8±21.7	62.2±21.5
Value of <60 ml/min/1.73 m^2 — no./total no. (%)	893/1862 (48.0)	906/1866 (48.6)

Table 1. (Continued.)

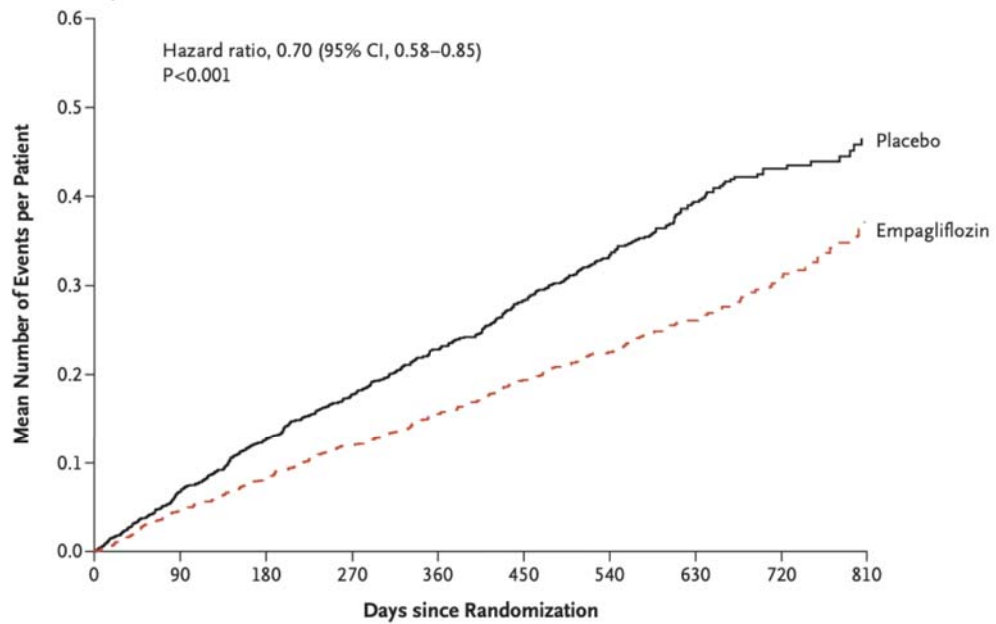| Characteristic	Empagliflozin (N=1863)	Placebo (N=1867)
Heart failure medication — no. (%)		
Renin–angiotensin inhibitor§		
Without neprilysin inhibitor	1314 (70.5)	1286 (68.9)
With neprilysin inhibitor	340 (18.3)	387 (20.7)
Mineralocorticoid receptor antagonist	1306 (70.1)	1355 (72.6)
Beta-blocker	1765 (94.7)	1768 (94.7)
Device therapy — no. (%)		
Implantable cardioverter–defibrillator¶	578 (31.0)	593 (31.8)
Cardiac resynchronization therapy‖	220 (11.8)	222 (11.9)

A Primary Outcome

Hazard ratio, 0.75 (95% CI, 0.65–0.86)
P<0.001

Estimated Cumulative Incidence (%)

Days since Randomization
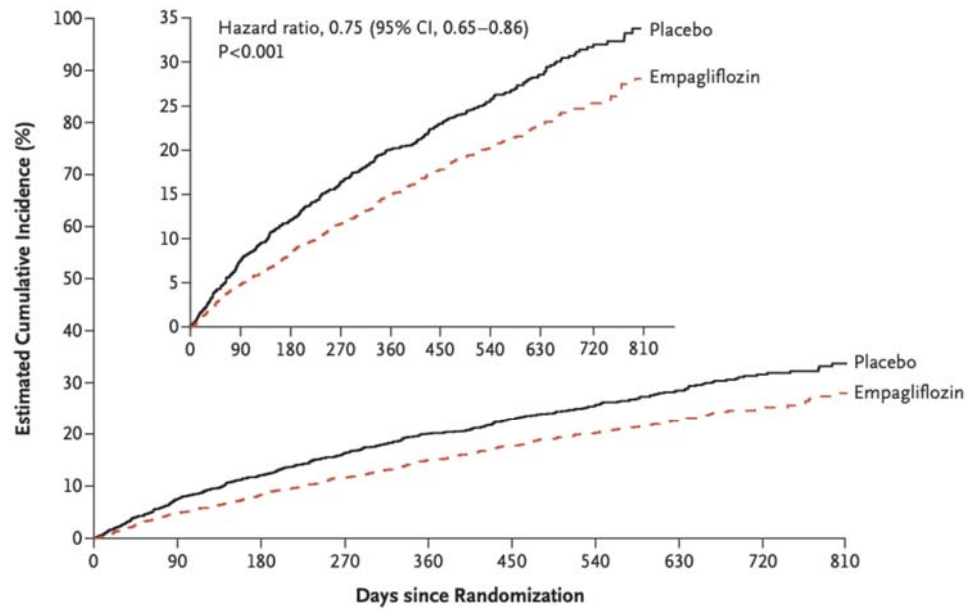
No. at Risk										
Placebo	1867	1715	1612	1345	1108	854	611	410	224	109
Empagliflozin	1863	1763	1677	1424	1172	909	645	423	231	101

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B First and Recurrent Hospitalizations for Heart Failure

Hazard ratio, 0.70 (95% CI, 0.58–0.85)
P<0.001

Mean Number of Events per Patient

Days since Randomization

No. at Risk										
Placebo	1867	1820	1762	1526	1285	1017	732	497	275	135
Empagliflozin	1863	1826	1768	1532	1283	1008	732	495	272	118
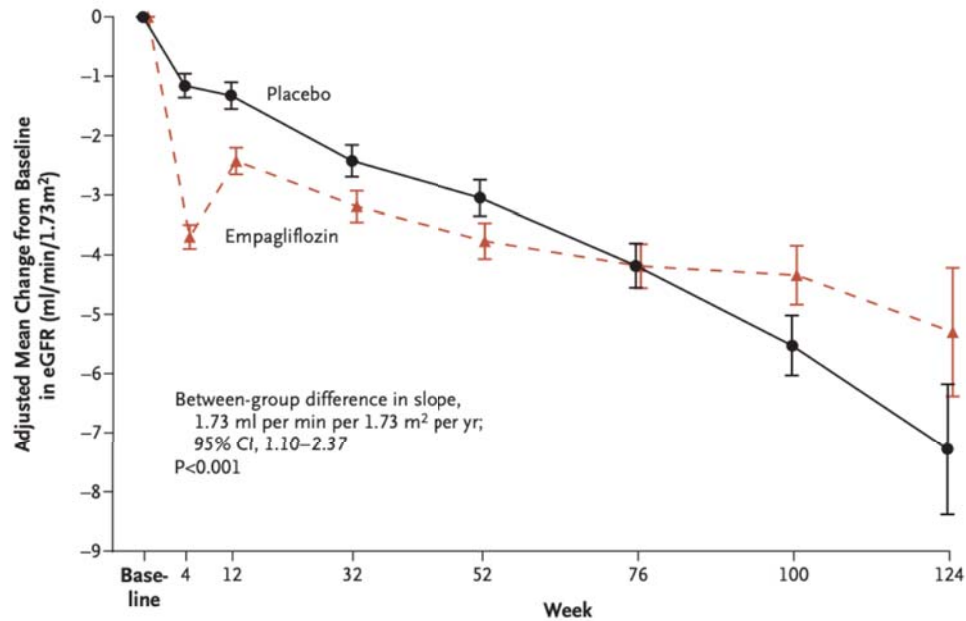
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SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials
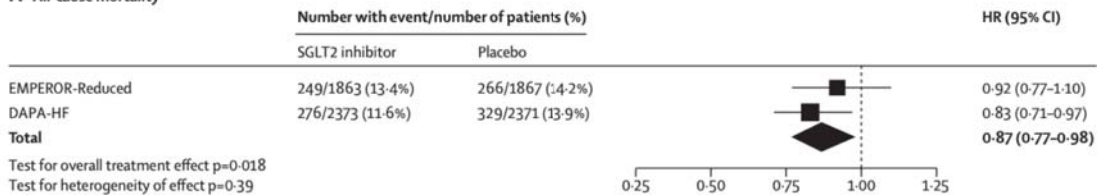
Faiez Zannad, João Pedro Ferreira, Stuart J Pocock, Stefan D Anker, Javed Butler, Gerasimos Filippatos, Martina Brueckmann, Anne Pernille Ofstad, Egon Pfarr, Waheed Jamal, Milton Packer
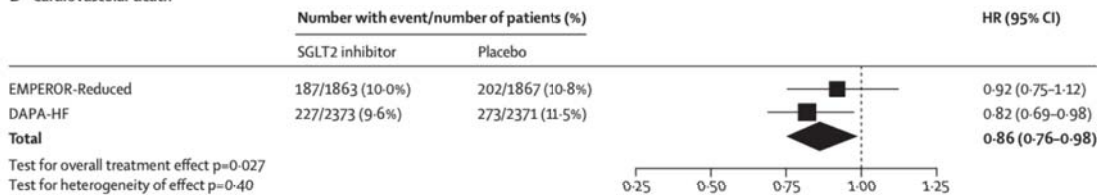
	EMPEROR-Reduced		DAPA-HF	
	Empagliflozin	Placebo	Dapagliflozin	Placebo
Number of participants	1863	1867	2373	2371
Age, years	67·2 (10·8)	66·5 (11·2)	66·2 (11·0)	66·5 (10·8)
Sex				
Men	1426 (76·5%)	1411 (75·6%)	1809 (76·2%)	1826 (77·0%)
Women	437 (23·5%)	456 (24·4%)	564 (23·8%)	545 (23·0%)
NYHA functional classification				
II	1399 (75·1%)	1401 (75·0%)	1606 (67·7%)	1597 (67·4%)
III	455 (24·4%)	455 (24·4%)	747 (31·5%)	751 (31·7%)
IV	9 (0·5%)	11 (0·6%)	20 (0·8%)	23 (1·0%)
Mean LVEF, %	27·7 (6·0)	27·2 (6·1)	31·2 (6·7)	30·9 (6·9)
NT-pro BNP, pg/mL	1887 (1077–3429)	1926 (1153–3525)	1428 (857–2655)	1446 (857–2641)
Medical history				
Hospitalisation for heart failure*	577 (31·0%)	574 (30·7%)	1124 (47·4%)	1127 (47·5%)
Diabetes†	927 (49·8%)	929 (49·8%)	1075 (45·3%)	1064 (44·9%)
eGFR, mL/min per 1·73 m²‡	61·8 (21·7)	62·2 (21·5)	66·0 (19·6)	65·5 (19·3)
Heart failure medications				
ACE inhibitor	867 (46·5%)	836 (44·8%)	1332 (56·1%)	1329 (56·1%)
ARB	451 (24·2%)	457 (24·5%)	675 (28·4%)	632 (26·7%)
Mineralocorticoid receptor antagonist	1306 (70·1%)	1355 (72·6%)	1696 (71·5%)	1674 (70·6%)
ARNI	340 (18·3%)	387 (20·7%)	250 (10·5%)	258 (10·9%)
Device therapy				
ICD or CRT-D	578 (31·0%)	593 (31·8%)	622 (26·2%)	620 (26·1%)
CRT-D or CRT-P	220 (11·8%)	222 (11·9%)	190 (8·0%)	164 (6·9%)

Data are n (%), mean (SD), or median (IQR). ACE=angiotensin converting enzyme. ARB=angiotensin receptor blocker. ARNI=angiotensin receptor neprilysin inhibitor. CRT-D=cardiac resynchronisation therapy defibrillator. CRT-P=cardiac resynchronisation therapy pacemaker. eGFR=estimated glomerular filtration rate. ICD=implantable cardiac defibrillator. LVEF=left ventricular ejection fraction. NT-pro BNP=N-terminal pro B-type natriuretic peptide. NYHA=New York Heart Association. *For EMPEROR-Reduced: preceding 12 months. †Determined by a combination of medical history and pre-treatment glycated haemoglobin. ‡Chronic Kidney Disease Epidemiology Collaboration formula.
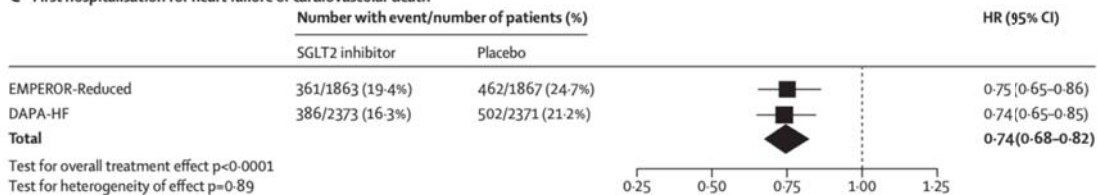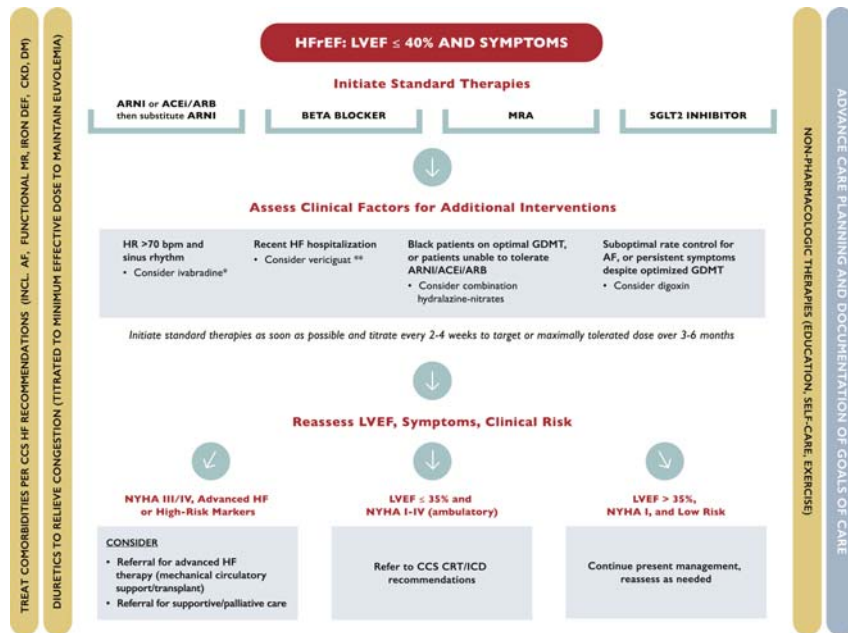

A All-cause mortality

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

Test for overall treatment effect p=0·018
Test for heterogeneity of effect p=0·39

B Cardiovascular death

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

Test for overall treatment effect p=0·027
Test for heterogeneity of effect p=0·40

C First hospitalisation for heart failure or cardiovascular death

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

Test for overall treatment effect p<0·0001
Test for heterogeneity of effect p=0·89

New paradigm

Conclusion

- Risk of mortality and HF hospitalization is high in acutely hospitalized and chronic stable patients with HFrEF

- Robust evidence for use of ARNI +SGLT2i + BB + MRA in patients with HFrEF

Thank you!