Dapagliflozin in patients with HFmrEF/HFpEF treated with an MRA or sacubitril/valsartan

A pre-specified analysis from the DELIVER trial

Mingming Yang, MD PhD
BHF Cardiovascular Research Centre, University of Glasgow, Glasgow, Scotland, UK.

University of Glasgow

DELIVER

Brigham and Women's Hospital
Founding Member, Mass General Brigham

Disclosures

Relevant financial relationships:

Travel grant from AstraZeneca

Relevant nonfinancial relationships

Nothing to disclose

Background: Treatment of HFmrEF/HFpEF

- The 2022 AHA/ACC/HFSA heart failure guidelines recommended the use of a mineralocorticoid receptor antagonist (MRA; Class 2b) and the angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril/valsartan (Class 2b) in patients with heart failure and a LVEF >40%, noting that benefit was greater in patients with a LVEF closer to 50%.
- These guidelines gave a stronger recommendation (Class 2a) for an SGLT2 inhibitor based on the results of the EMPEROR-Preserved trial, likely to strengthened by the recent positive results of the DELIVER trial.
- Therefore, the efficacy and tolerability/safety of combinations of these different therapies is a key question for physicians treating patients with HFmrEF/HFpEF. We examined these in the DELIVER trial.

DELIVER Study Design

Randomized, double-blind, placebo-controlled trial testing the hypothesis that dapagliflozin would reduce cardiovascular death or worsening heart failure in patients with heart failure and mildly reduced or preserved ejection fraction

Eligibility Criteria

- Age ≥40 years
- NYHA class II-IV
- LVEF >40%
- (including prior LVEF ≤ 40%)

- Structural Heart Disease
- (LVH or LA Enlargement)
- Elevated Natriuretic Peptides Either Ambulatory or Hospitalized for Heart Failure

N=6,263

Double-blind treatment period

Dapagliflozin 10mg once daily

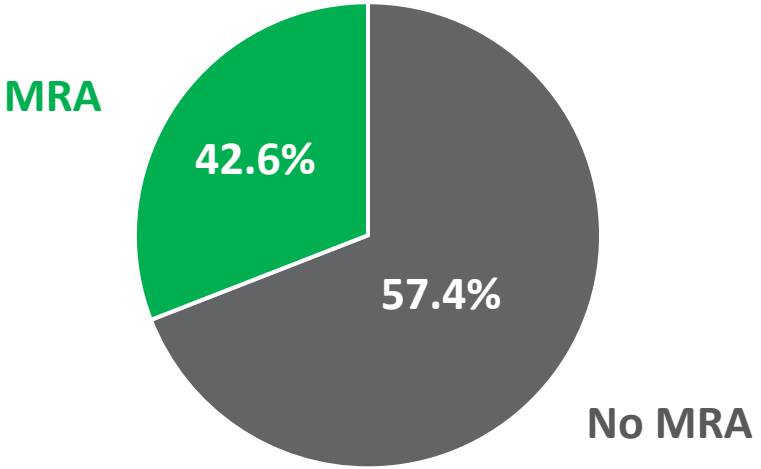
Placebo

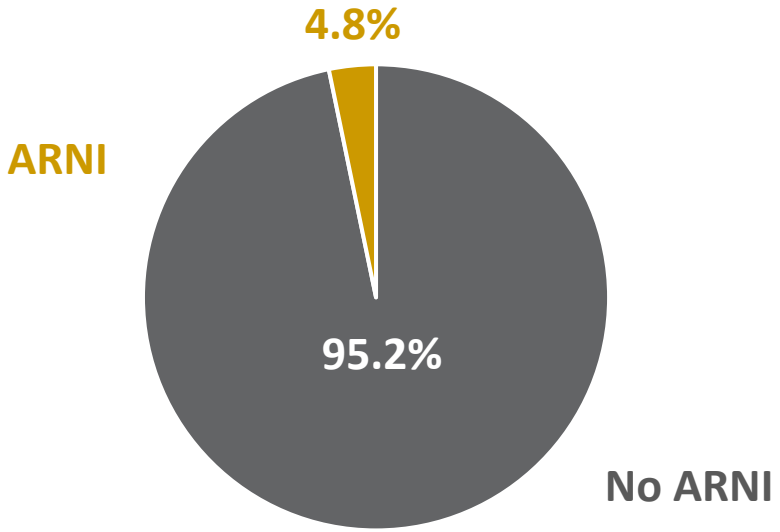
Primary outcome: Worsening HF event or CV death

Solomon et al. Eur J Heart Fail 2021

DELIVER: Baseline use of MRA and ARNI

Overall n=6263





MRA *and* ARNI=197 (3.1%)

Background MRA therapy

Baseline characteristics according to background MRA therapy

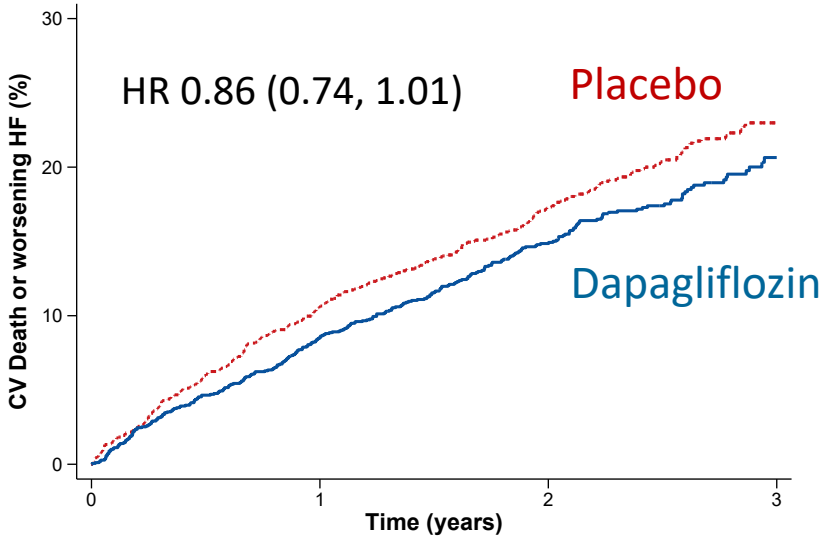
	Not on MRA N=3596	On MRA N=2667	*P-Value*
Age (years), mean	72.8	70.2	*<0.001*
Male sex, %	54.9	57.8	*0.024*
SBP (mmHg), mean	130.1	125.7	*<0.001*
BMI (kg/m^2), mean	30.0	29.6	*0.003*
Atrial fibrillation, %	55.6	55.0	*0.66*
Myocardial infarction, %	23.4	29.9	*<0.001*
eGFR (mL/min/1.73m^2), mean	60.2	62.1	*<0.001*
Previous HF hospitalization, %	37.2	45.0	*<0.001*
Enrollment ≤30 days after HF hospitalization, %	8.7	12.8	*<0.001*
NYHA III/IV, %	23.4	26.6	*0.003*

Baseline characteristics according to background MRA therapy

	Not on MRA N=3596	On MRA N=2667	*P-Value*
KCCQ-TSS, mean	70.0	70.1	*0.79*
NT-proBNP (pg/ml), median	989	1050	*0.001*
LVEF (%), mean	55.3	52.7	*<0.001*
Prior LVEF ≤ 40, %	15.9	21.7	*<0.001*
Diuretics, %	96.1	100.0	*<0.001*
Loop diuretic, %	79.2	73.6	*<0.001*
Thiazide diuretic, %	17.4	6.7	*<0.001*
Beta-blocker, %	80.3	85.9	*<0.001*
ICD, %	1.5	2.2	*0.037*

DELIVER: Primary outcome according to background treatment with an MRA

Not on MRA

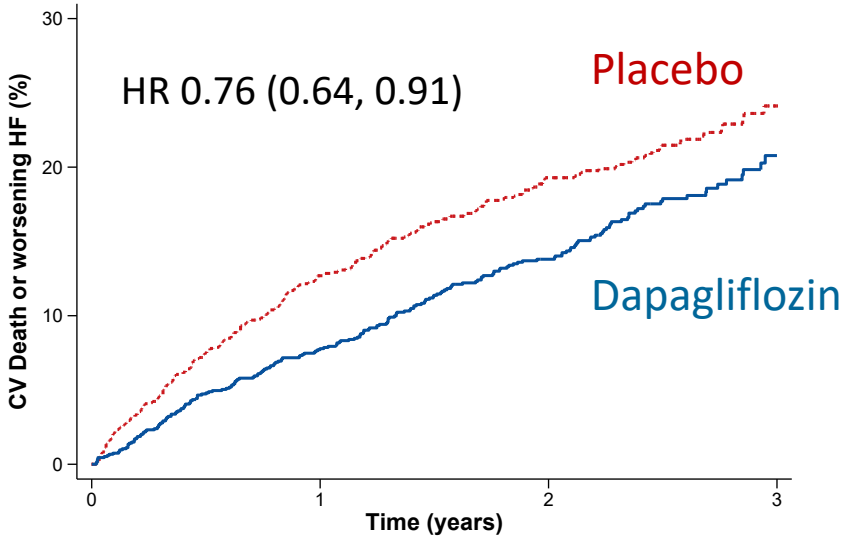


No. at risk

Placebo	1805	1570	1118	200
Dapagliflozin	1791	1598	1125	196

Interaction
P-value=0.30

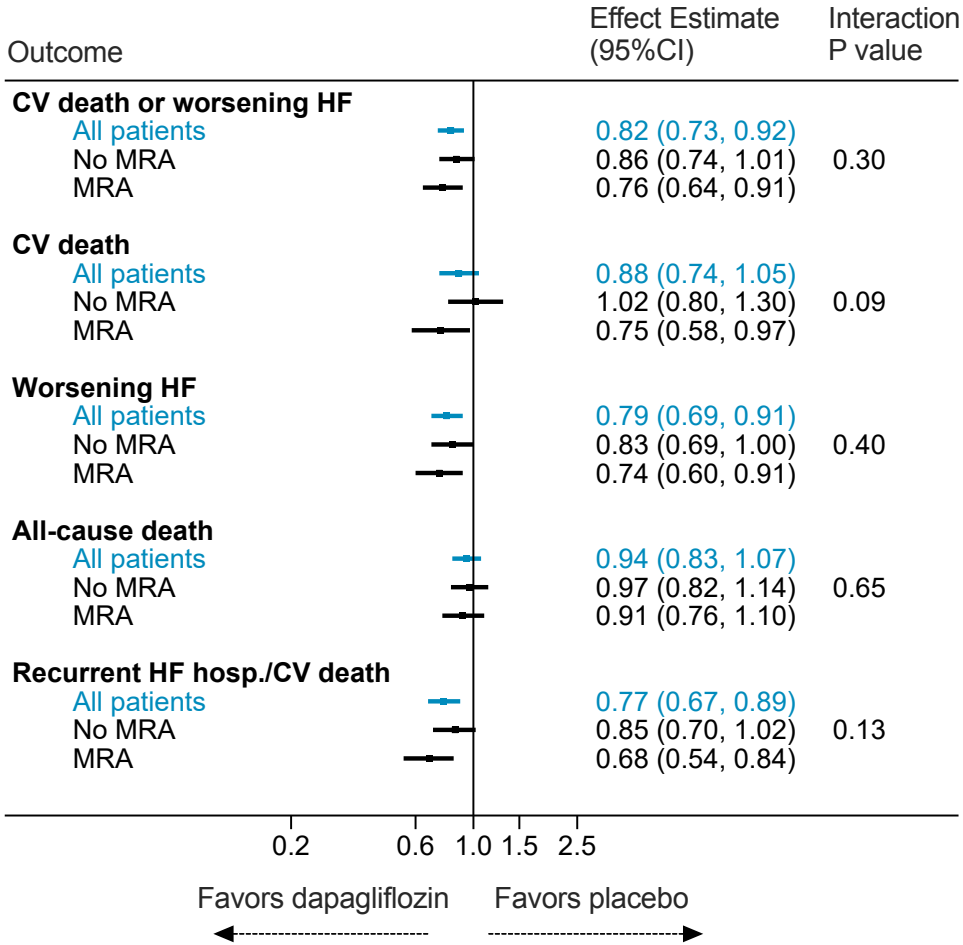
On MRA



No. at risk

Placebo	1327	1132	750	111
Dapagliflozin	1340	1201	809	131

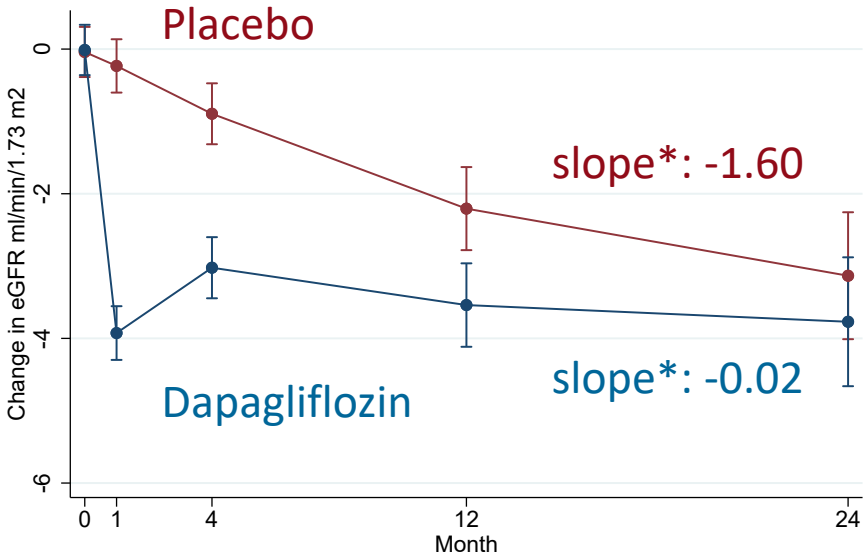
Effect of dapagliflozin according to background MRA therapy



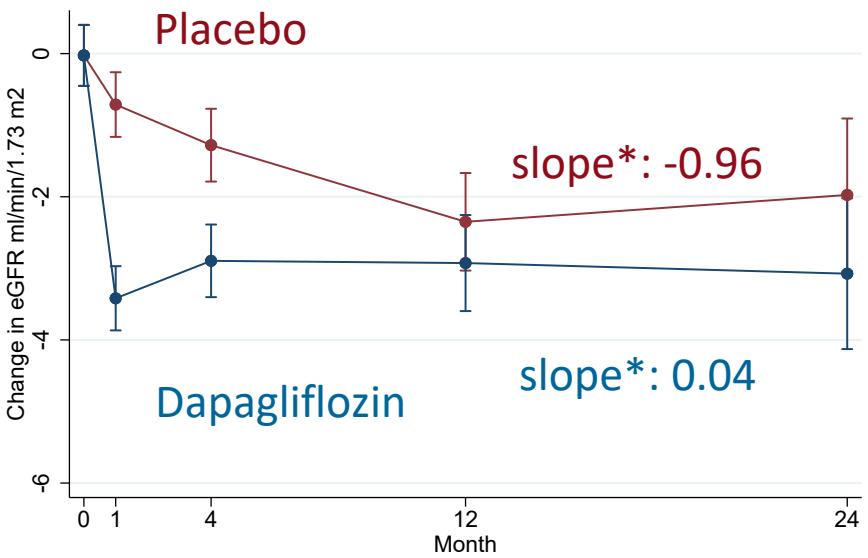
Changes in eGFR during follow-up by randomized treatment

P for interaction = 0.942

Not on MRA



On MRA



**chronic slope, months 1-24*
ml/min/1.73m²

Background ARNI therapy

Baseline characteristics according to background ARNI therapy

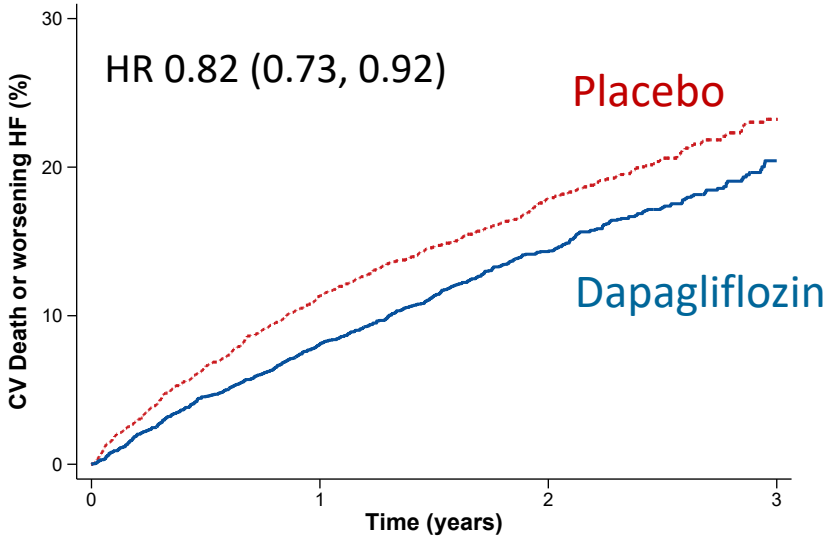
	Not on ARNI N=5962	On ARNI N=301	*P-Value*
Age (years), mean	71.8	68.7	*<0.001*
Male sex, %	55.5	69.1	*<0.001*
SBP (mmHg), mean	128.7	119.8	*<0.001*
BMI (kg/m^2), mean	29.9	28.6	*<0.001*
Atrial fibrillation, %	55.7	47.2	*0.004*
Myocardial infarction, %	26.0	29.6	*0.17*
eGFR (mL/min/1.73m^2), mean	61.0	61.9	*0.40*
Previous HF hospitalization, %	40.1	48.8	*0.003*
Enrollment ≤30 days after HF hospitalization, %	10.5	9.6	*0.64*
NYHA III/IV, %	24.6	27.9	*0.19*

Baseline characteristics according to background ARNI therapy

	Not on ARNI N=5962	On ARNI N=301	*P-Value*
KCCQ-TSS, mean	69.6	78.4	*<0.001*
NT-proBNP (pg/ml), median	1012	974	*0.73*
LVEF (%), mean	54.5	48.3	*<0.001*
Prior LVEF ≤ 40, %	**16.8**	**50.5**	*<0.001*
Diuretics, %	97.9	96.0	*0.035*
Loop diuretic, %	76.8	78.1	*0.60*
Thiazide diuretic, %	13.3	4.0	*<0.001*
Beta-blocker, %	82.6	84.1	*0.51*
ICD, %	1.5	8.0	*<0.001*

DELIVER: Primary outcome according to background treatment with an ARNI

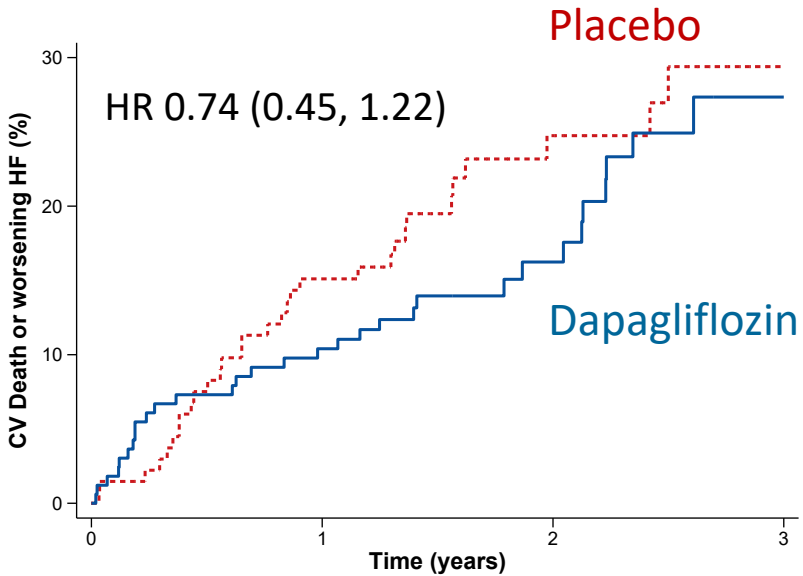
Not on ARNI



No. at risk				
Placebo	2996	2592	1820	302
Dapagliflozin	2966	2657	1870	316

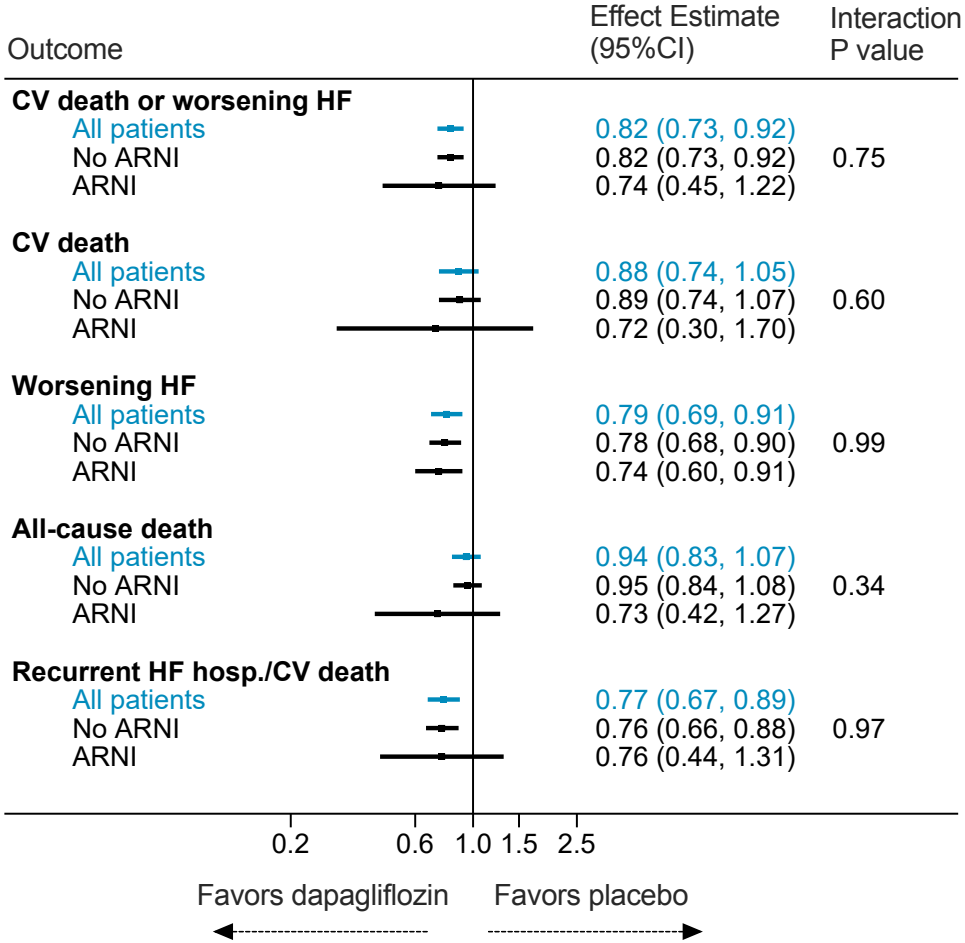
Interaction
P-value=0.75

On ARNI



No. at risk				
Placebo	136	110	48	9
Dapagliflozin	165	142	64	11

Effect of dapagliflozin according to background ARNI therapy



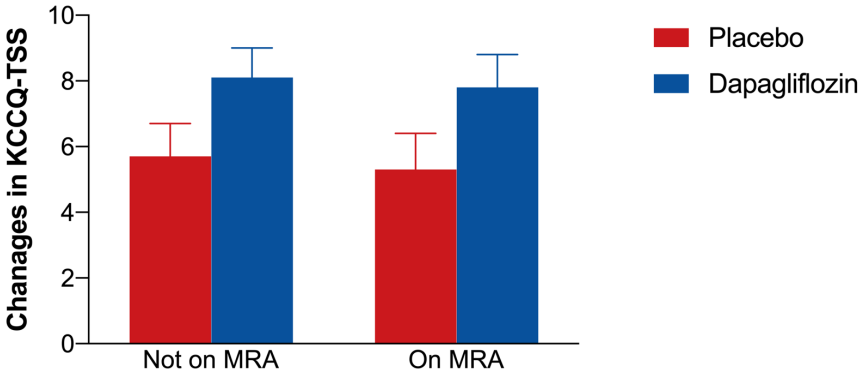
Symptoms, blood pressure and safety/tolerability

Change in KCCQ total symptom score (KCCQ-TSS) according to background therapy

MRA

Changes in KCCQ-TSS from baseline to 8 months (mean and 95% CI, P_{int}=0.93)

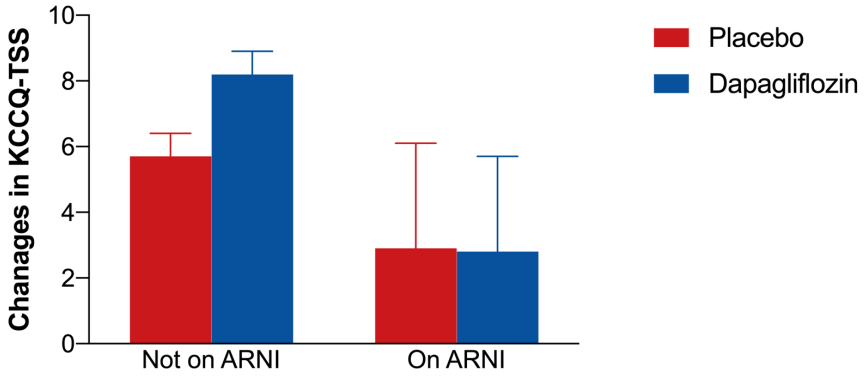
Placebo-corrected change at 8 month
- Not on MRA: 2.3 (1.0-3.6)
- On MRA: 2.4 (0.9-3.9)



ARNI

Changes in KCCQ-TSS from baseline to 8 months (mean and 95% CI, P_{int}=0.32)

Placebo-corrected change at 8 month
- Not on ARNI: 2.5 (1.5-3.5)
- On ARNI: -0.1 (-4.4 to 4.2)



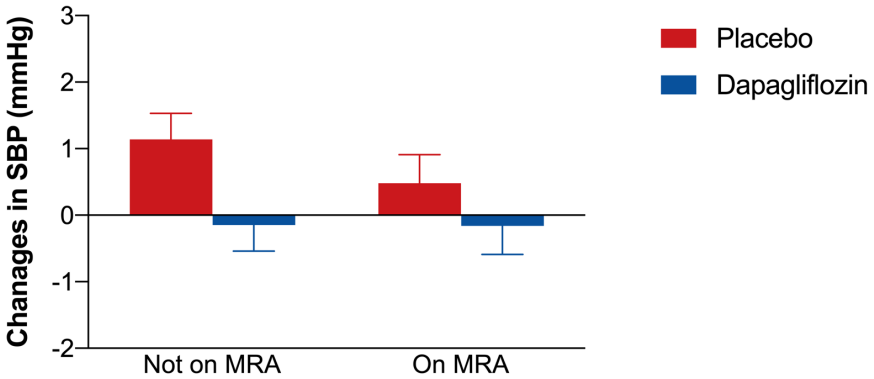
Effect of dapagliflozin on physiologic measures: Systolic blood pressure

MRA

Changes in SBP from baseline to 12 months (mean and SD, P_{int}=0.42)

Difference at 12 months

- Not on MRA: -1.29 (-2.37 to -0.21)
- On MRA: -0.64 (-1.83 to 0.55)

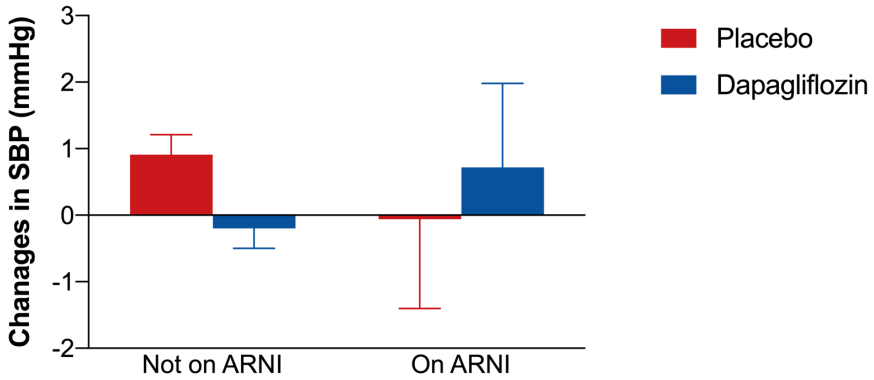


ARNI

Changes in SBP from baseline to 12 months (mean and SD, P_{int}=0.27)

Difference at 12 months

- Not on ARNI: -1.11 (-1.93 to -0.29)
- On ARNI: 0.79 (-2.82 to 4.40)



DELIVER: Effect of dapagliflozin on safety outcomes

	Not on MRA		On MRA		
	Placebo (n=1805)	Dapagliflozin (n=1791)	Placebo (n=1327)	Dapagliflozin (n=1340)	p Value for interaction
Any discontinuation	14.5	16.0	13.6	11.8	0.07
AE leading to treatment discontinuation (DAE)	6.1	6.7	5.4	4.8	0.29
Volume depletion SAE or DAE	1.4	1.5	0.9	1.7	0.18
Renal SAE or DAE	2.9	3.1	2.9	2.2	0.29
Hyperkalemia SAE	0.1	0.6	0.2	0.1	0.09

SAE: Serious adverse event DAE: Adverse event leading to discontinuation of randomized treatment

DELIVER: Effect of dapagliflozin on safety outcomes

	Not on ARNI		On ARNI		
	Placebo (n=2996)	Dapagliflozin (n=2966)	Placebo (n=136)	Dapagliflozin (n=165)	p Value for interaction
Any discontinuation	14.0	14.2	16.2	14.6	0.68
AE leading to treatment discontinuation (DAE)	5.7	5.9	8.1	4.2	0.14
Volume depletion SAE or DAE	1.1	1.6	2.9	1.2	0.14
Renal SAE or DAE	2.8	2.7	5.9	1.8	0.07
Hyperkalemia SAE	0.1	0.4	0.0	0.0	N/A

SAE: Serious adverse event DAE: Adverse event leading to discontinuation of randomized treatment

Conclusions: Dapagliflozin added to an MRA or ARNI in patients with HFmrEF/HFpEF

- The efficacy and safety of dapagliflozin were similar, regardless of background treatment with an MRA or ARNI
- The clinical decision to initiate SGLT2 inhibitors in patients with HFmrEF/HFpEF should not be contingent on the background use of an MRA or ARNI

ESC European Society of Cardiology

European Journal of Heart Failure (2022)
doi:10.1002/ejhf.2722

RESEARCH ARTICLE

Dapagliflozin in patients with heart failure with mildly reduced and preserved ejection fraction treated with a mineralocorticoid receptor antagonist or sacubitril/valsartan

Mingming Yang[1,2], Jawad H. Butt[1,3], Toru Kondo[1,4], Karola S. Jering[5], Kieran F. Docherty[1], Pardeep S. Jhund[1], Rudolf A. de Boer[6], Brian L. Claggett[5], Akshay S. Desai[5], Adrian F. Hernandez[7], Silvio E. Inzucchi[8], Mikhail N. Kosiborod[9], Carolyn S.P. Lam[10], Anna Maria Langkilde[11], Felipe A. Martinez[12], Magnus Petersson[11], Sanjiv J. Shah[13], Muthiah Vaduganathan[5], Ulrica Wilderäng[11], Scott D. Solomon[5], and John J.V. McMurray[1]*

For more information and presentation please visit www.delivertrial.org

THANK YOU

American Heart Association.

Scientific Sessions

#AHA22