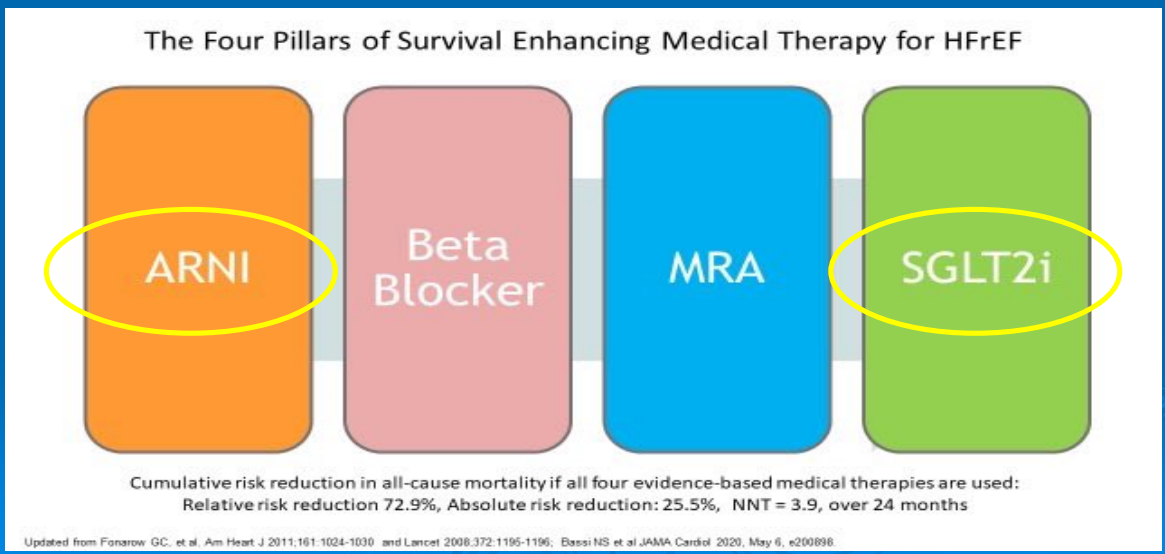
HFrEF in 2020: Optimal Therapies and Beyond

Michelle M. Kittleson, M.D., Ph.D.
Professor of Medicine
Smidt Heart Institute at Cedars-Sinai
Los Angeles, California
@MKittlesonMD

1

#QuadrupleTherapy

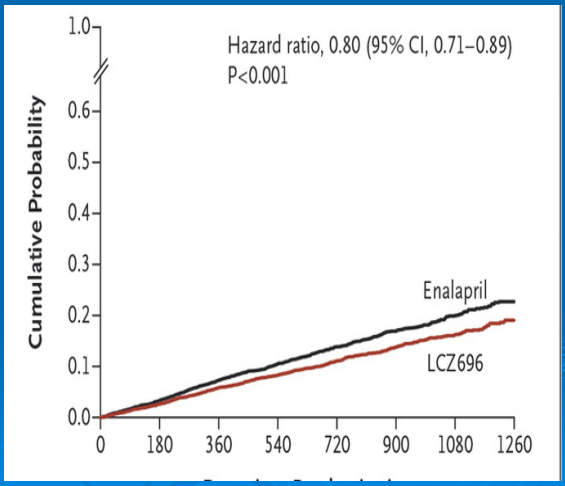


Courtesy of Gregg Fonarow MD

2

PARADIGM-HF

- ~8400 patients
  - EF ≤ 35%
  - One HF hosp or ↑ BNP
- Sacubitril/valsartan vs enalapril
- Outcomes
  - CV deaths: 17% → 13%
  - HF hosp: 16% → 13%



McMurray J et al. NEJM 2014; 371: 993-1004.

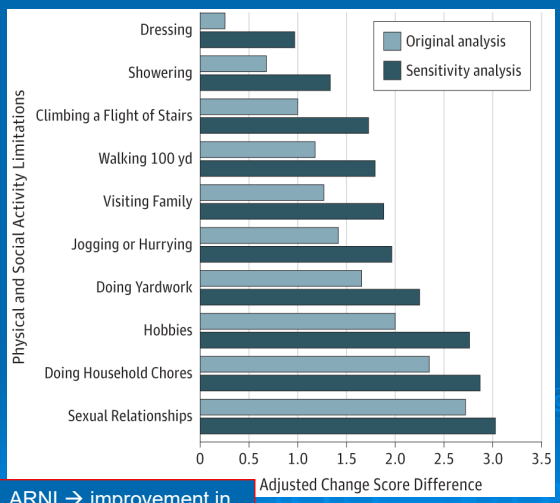
3

ARNI and QOL (it's not *just* about survival)

	Sacubitril/Valsartan		Enalapril		Difference	*P* Value
	N	LSM Estimates (SE)	n	LSM Estimates (SE)		
Overall summary score						
Visit						
Month 4	3583	1.10 (0.2)	3572	0.44 (0.2)	0.66 (0.31)	0.03
Month 8	3460	1.13 (0.25)	3421	−0.14 (0.25)	1.27 (0.35)	<0.001
Month 12	3325	1.17 (0.26)	3267	0.08 (0.27)	1.09 (0.37)	0.004
Month 24	2363	0.69 (0.33)	2279	−0.64 (0.34)	1.33 (0.47)	0.005
Month 36	1087	0.36 (0.51)	1091	−1.92 (0.51)	2.28 (0.73)	0.002
Overall		0.80 (0.20)		−0.39 (−0.20)	1.19 (0.28)	<0.001
Clinical summary score						
Visit						
Month 4	3583	0.69 (0.22)	3572	0.21 (0.22)	0.48 (0.31)	0.12
Month 8	3460	0.64 (0.25)	3421	−0.29 (0.25)	0.92 (0.35)	0.008
Month 12	3325	0.60 (0.26)	3267	−0.39 (0.26)	0.99 (0.37)	0.008
Month 24	2363	−0.05 (0.33)	2279	−1.40 (0.33)	1.30 (0.47)	0.005
Month 36	1087	−0.89 (0.52)	1091	−2.50 (0.51)	1.60 (0.73)	0.03
Overall		0.23 (0.20)		−0.76 (0.20)	0.99 (0.28)	<0.001

ARNI → sustained improvement in overall QOL

Lewis E et al. Circulation HF. 2017.



ARNI → improvement in physical/social QOL

Chandra A et al. JAMA Cardiol. 2018.

4

2016/2017 Heart Failure Focused Update: ARNI

- Class I
  - ACEI OR ARBs OR ARNI in conjunction with evidence-based BB and aldo antag recommended for pts w/HFrEF to reduce morbidity and mortality
  - In patients with chronic HFrEF NYHA class II or III who tolerate ACEI or ARB, *replacement by an ARNI is recommended to further reduce morbidity and mortality.*

What about NYHA Class I?

What about *de novo* ARNI?

Yancy CW et al. J Am Coll Cardiol. 2016.

5

De novo ARNI in HFrEF

- PIONEER- HF: ~900 pts
  - EF ≤ 40%
  - Hosp for ADHF with SBP > 100 mm Hg
  - 34% new HF diagnosis
  - 52% not on prior ACEI/ARB
- Sacubitril/valsartan vs enalapril st… during hospitalization

- TRANSITION-HF: ~1000 pts
  - EF ≤ 40%
  - Hosp for ADHF with SBP > 100 mm Hg
  - 29% new HF diagnosis
  - 24% not on prior ACEI/ARB
- …valsartan prior to discharge vs 1-…discharge (mostly 1d post d/c)

***De novo* inpatient ARNI initiation is safe**

No difference in:
- Worsening renal function
- Hyperkalemia
- Symptomatic hypotension
- Angioedema

Velazquez EJ et al. NEJM. 2019.

Wachter R et al. Eur Heart J. 2019.

6

The Important SGLT2i CV Trials (Thank you, Rosiglitazone)

Trial	Entry criteria	Number pts/ duration/ drug	Outcomes
EMPA-REG *NEJM* 2015	DM2 + ASCVD risk eGFR > 30	7020 pts/ 3.1y Empagliflozin	↓ 38% CV death ↓ 35% HF hosp
CANVAS *NEJM* 2017	DM2 + ASCVD risk eGFR > 30	2569 pts/ 3.6y Canagliflozin	↓ 14% CV death/MI/stroke ↓ 33% HF hosp
DECLARE-TIMI 58 *NEJM* 2019	DM2 + ASCVD risk eGFR > 60	17160 pts/ 4.2y Dapagliflozin	↓ 27% HF hosp
VERTIS-CV *ADA meeting June 2020*	DM2 + ASCVD eGFR > 30	8246 pts/ Ertugliflozin	↓ 14% CV death/MI/stroke ↓ 30% HF hosp

7

The SGLT2i in HF

- DAPA- HF: ~4700 pts
  - EF ≤ 40%
  - NYHA II-IV
  - NT-proBNP > 600
  - ***DM2 not required***
- Dapagliflozin vs placebo

9/1/19: DAPA-HF presented at ESC

5/6/20: Dapa approved by FDA for HFrEF *without DM*

- Outcomes
  - ↓ CV death: 9.6% vs 11.5%
  - ↓ HF hosp: 10.0% vs 13.7%

McMurray J et al. NEJM 2019.

- EMPEROR-Reduced: ~3700 patients
  - EF ≤ 30%
  - EF 31-40% if HF hosp/↑BNP
  - NYHA II-IV
  - ***DM2 not required***
- Empagliflozin vs placebo

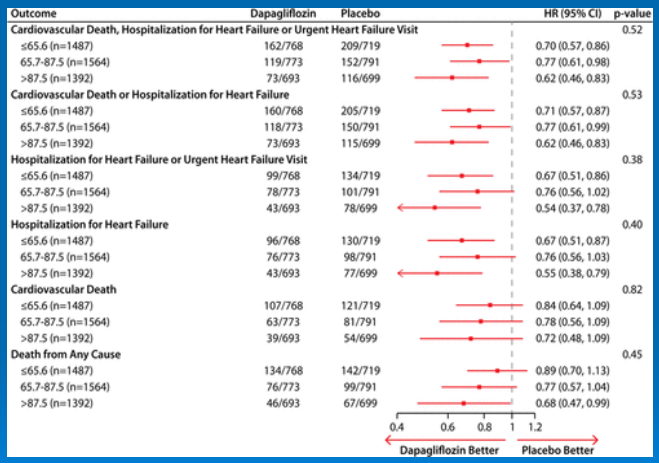
Is it a class effect?

- Outcomes
  - NS CV death: 10.0% vs 10.8%
  - ↓ HF hosp: 13.2% vs 18.3%

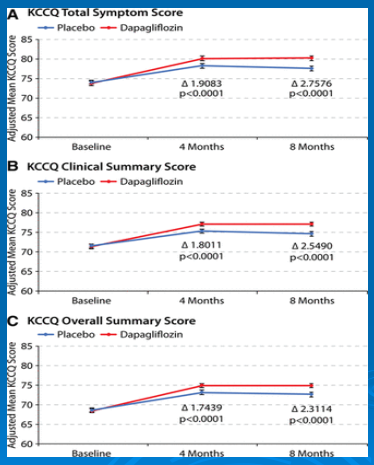
Packer M et al. NEJM 2020.

8

SGLT2i and QOL



Benefit of dapa is independent of baseline KCCQ

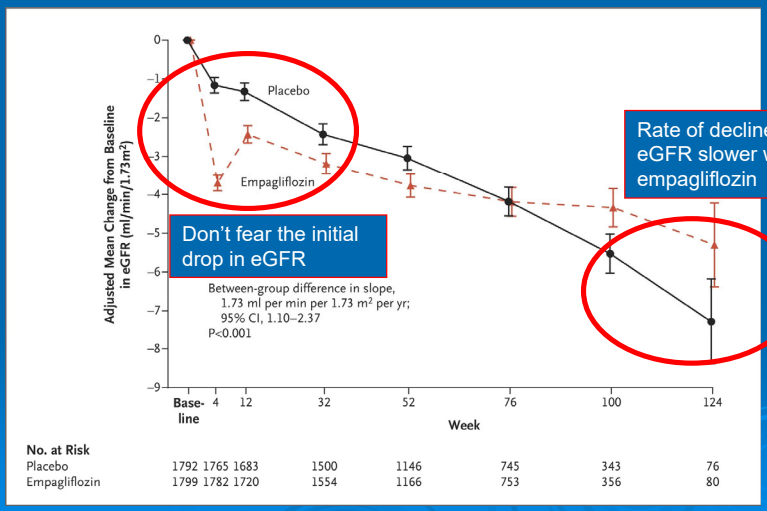


Greater KCCQ improvement with dapa

Kosiborod M et al. Circulation 2020.

9

The SGLT2i and the Kidney in HF



Don't fear the initial drop in eGFR

Rate of decline in eGFR slower with empagliflozin

Packer M et al. NEJM 2020.

10

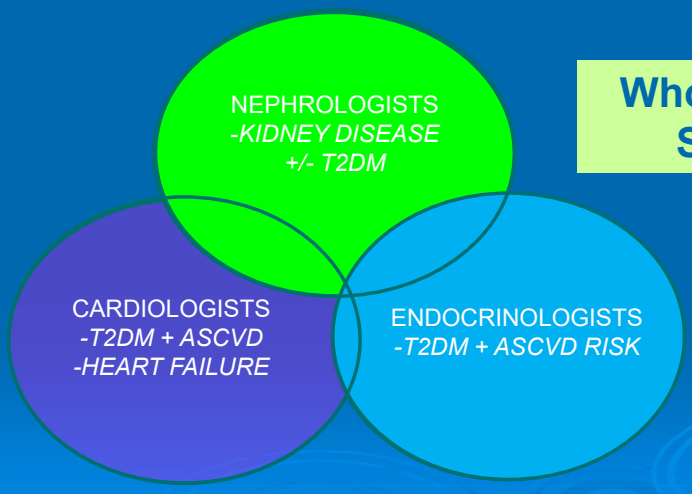
SGLT2i: A class effect?

	EMPEROR-Reduced		DAPA-HF
	Empagliflozin (n=1863)	Placebo (n=1867)	Dapagliflozin (n=2373)
Age (yr)	67.2 ± 10.8	66.5 ± 11.2	66.2 ± 11.0
Women (%)	437 (23.5)	456 (24.4)	564 (23.8)
Diabetes mellitus (%)	927 (49.8)	929 (49.8)	993 (41.8)
Ischemic cardiomyopathy (%)	983 (52.8)	946 (50.7)	1316 (55.5%)
NYHA functional class II (%)	1399 (75.1)	1401 (75.0)	1606 (67.7%)
LV ejection fraction (%)	27.7 ± 6.0 (72% ≤30%)	27.2 ± 6.1 (75% ≤30%)	31.2±6.7
NT-proBNP (median, IQR), pg/mL	1887 (1077, 3429) (79% ≥1000)	1926 (1153, 3525) (80% ≥1000)	1428 (857-2655)
Hospitalization for heart failure within 12 months	577 (31.0)	574 (30.7)	1124 (47.4)
Atrial fibrillation	664 (35.6)	705 (37.8)	916 (38.6)
Glomerular filtration rate (ml/min/1.73 m^2)	61.8 ± 21.7	62.2 ± 21.5	66.0 ± 19.6
Treatment for heart failure			
RAS inhibitor without neprilysin inhibitor	1314 (70.5)	1286 (68.9)	2007 (84.6)
RAS inhibitor with neprilysin inhibitor	340 (18.3)	387 (20.7)	250 (10.5)
Mineralocorticoid receptor antagonist	1306 (70.1)	1355 (72.6)	1696 (71.5)
Beta blocker	1765 (94.7)	1768 (94.7)	2278 (96.0)
Implantable cardioverter-defibrillator	578 (31.0)	593 (31.8)	622 (26.2%)
Cardiac resynchronization therapy	220 (11.8)	222 (11.9)	190 (8.0%)

Packer M et al. NEJM 2020.

11

SGLT2is = Team Sport

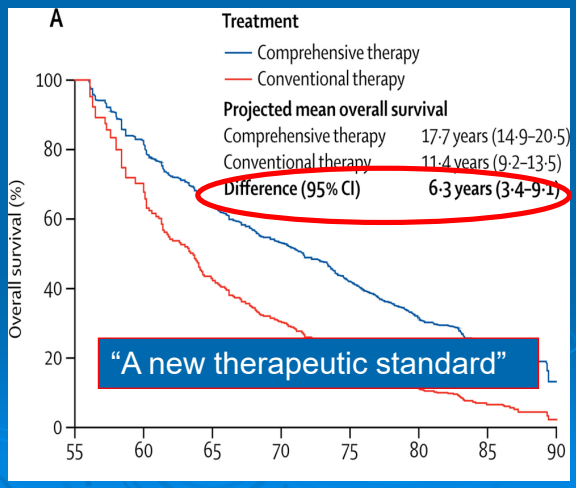


Who owns the SGLT2i?

12

Quadruple therapy saves lives!

- Cross-trial analysis
  - EMPHASIS-HF
  - PARADIGM-HF
  - DAPA-HF
- ARNI/BB/MRA/SGLT2i vs ACEI/BB



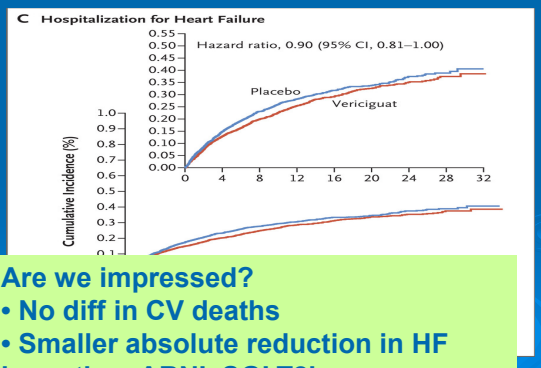
Vaduganathan et al. Lancet May 21, 2020 online.

13

VICTORIA Trial: Vericiguat in HFrEF

- 5050 pts
  - NYHA II-IV
  - EF < 45%
  - Elevated BNP
  - Recent hospitalization or IV diuretic therapy
- Vericiguat vs placebo
- Primary composite outcome met (death from CV cause + HF hosp) → driven by HF hosp
  - HF hosp 27.5% vs 29.5%

BASELINE MEDICAL THERAPY
- 60% on ACEI/ARB/ARNI + BB + MRA
- 15% on ARNI
- 32% on ICD, CRT, or both

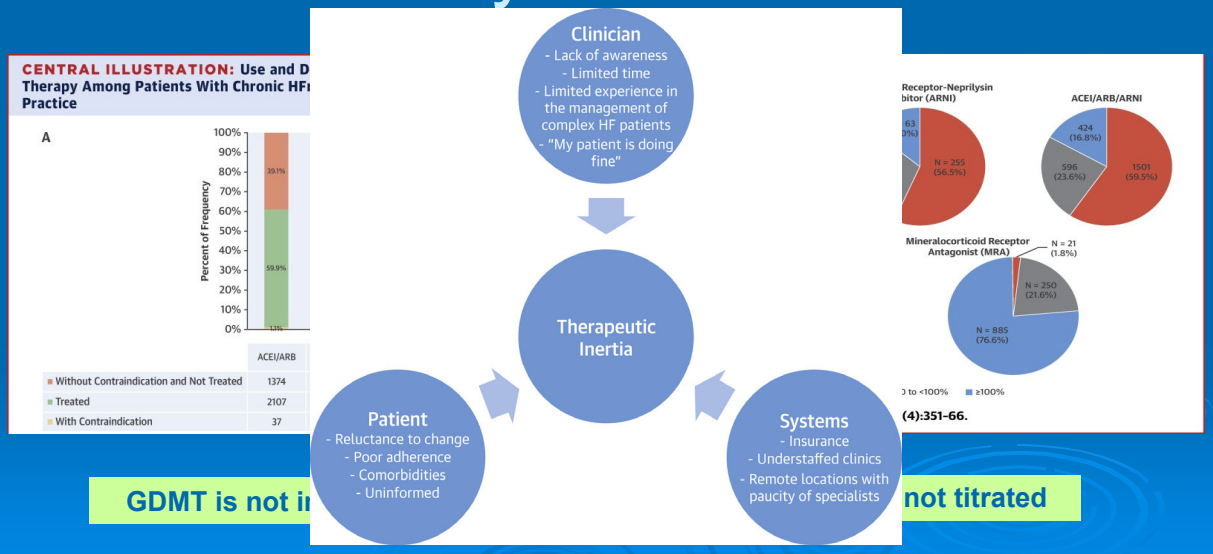


Are we impressed?
• No diff in CV deaths
• Smaller absolute reduction in HF hosp than ARNI, SGLT2i

Armstrong P et al. NEJM 2020.

14

Theory vs Practice



Greene SJ et al. JACC 2018; 72: 351-66 and Jefferies JL et al. JACC 2018; 72: 367-369.

15

The Finer Points

Quadruple therapy: Is NYHA Class I/II distinction important?

Is there an SGLT2i class effect?

Where will vericiguat fit in?

Great science + Implementation = Lives Saved

16