SEPTEMBER 11, 2021

SGLT2 inhibitors: Are you ready to prescribe?

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Disclosures

I have no financial relationships to disclose.

Objective

- Discuss the use of sodium glucose transport (SGLT2) inhibitors in the management of cardiovascular disease

Outline

- Drug Overview
- Role in heart failure
- Role in chronic kidney disease
- Practical Application

FDA and Diabetes Drugs

SGLT-2 Inhibitor CVOTs: Diabetes

3 pt MACE: CV death, MI, ischemic stroke

Study	Drug	N	% Pts with ASCVD	Primary Outcome
EMPA-REG OUTCOME	Empagliflozin	7,020	100	Significant ↓ in 3 pt MACE[1,2,3]
CANVAS	Canagliflozin	10,142	72.2	Significant ↓ in 3 pt MACE[1,4,5]
DECLARE-TIMI 58	Dapagliflozin	17,160	40.8	Significant ↓ in composite (CV death and HF hospitalization)[1]
VERTIS-CV	Ertugliflozin	8,246	100	No difference in 3 pt MACE[1]

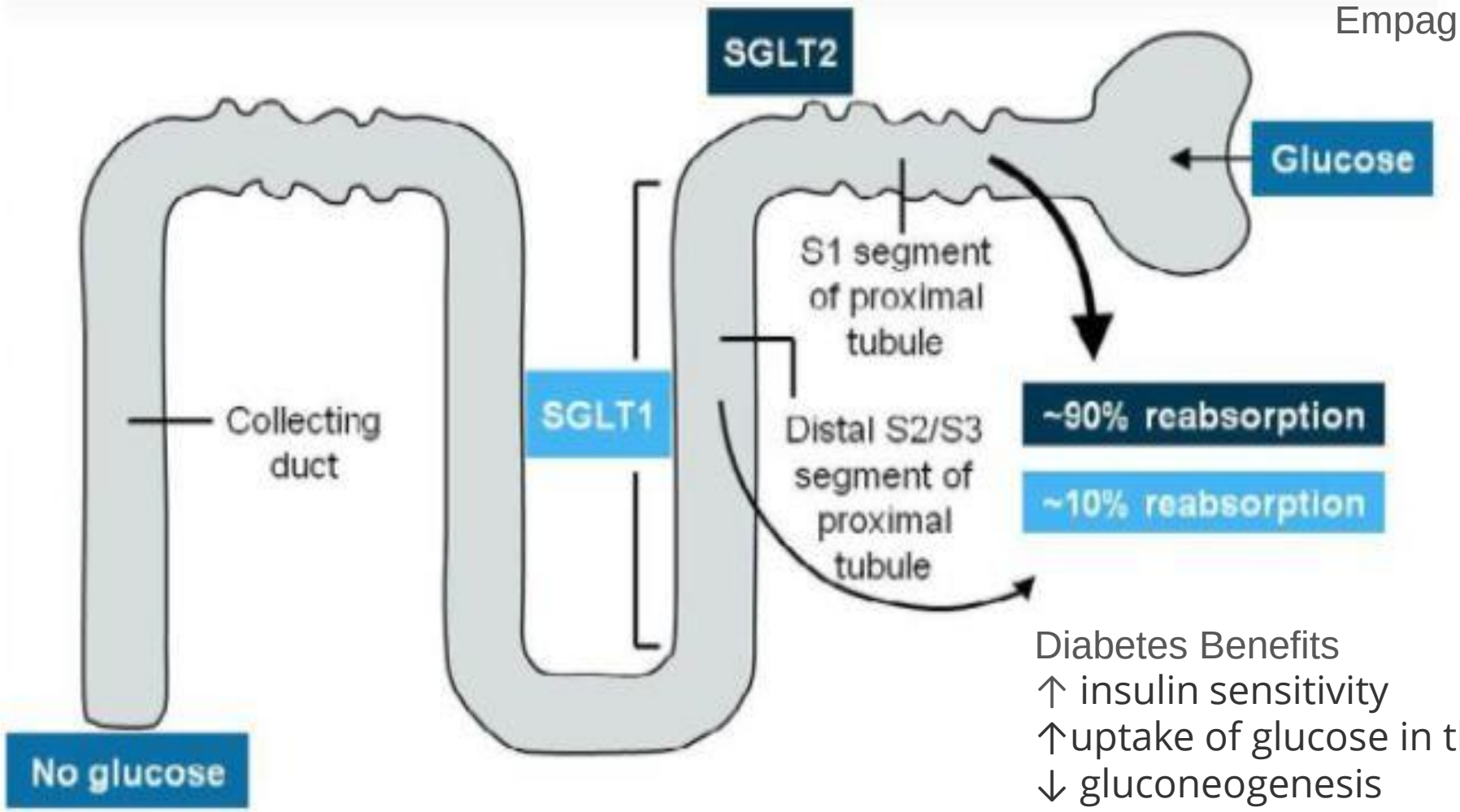
[1]**Signficant reduction in HF hospitalizations**
[2]Significant reduction in CV death
[3]Significant reduction in all-cause mortality
[4]Significant reduction in progression of albuminuria
[5]Significant reduction in need for renal-replacement therapy, 40% reduction in eGFR, or renal death

N Engl J Med 2015; 373:2117-2128.
N Engl J Med 2019; 380:347-357.
N Engl J Med 2017; 377:644-657
80th American Diabetes Association Virtual Scientific Sessions; June 16, 2020.

Mechanism of Action

HgbA1C reduction: 0.5-1%

Canagliflozin
Dapagliflozin
Empagliflozin



Diabetes Benefits
↑ insulin sensitivity
↑uptake of glucose in the muscle cells
↓ gluconeogenesis
improved first phase insulin release from the beta cells.

Benefits beyond glucose

Proposed mechanisms:

- Osmotic diuresis /natriuresis → decreased preload
- Decreases in arterial pressure and stiffness → decreased afterload
- Decreased preload and afterload → ↓ hypertrophy (proven ↓ LV mass) / fibrosis → less remodeling
- Decreased LA enlargement in HFpEF
- Shift to ketone based myocardial metabolism → more energy for the heart muscle
- Protects kidney function
  - reduces intraglomerular pressure
  - Reduces NAG (biomarker for tubular injury)

Other benefits

- Decreases uric acid/gout
- Increased hemoglobin

Verma S, et al. JAMA Cardiol 2017;2:939-40, Shirakabe A, et al. Cric Rep 2020;2:565-75

SGLT2i Role in Heart Failure

HFrEF: DAPA HF and EMPEROR Reduced

Primary Outcome: CV death or worsening HF

Patient Inclusion

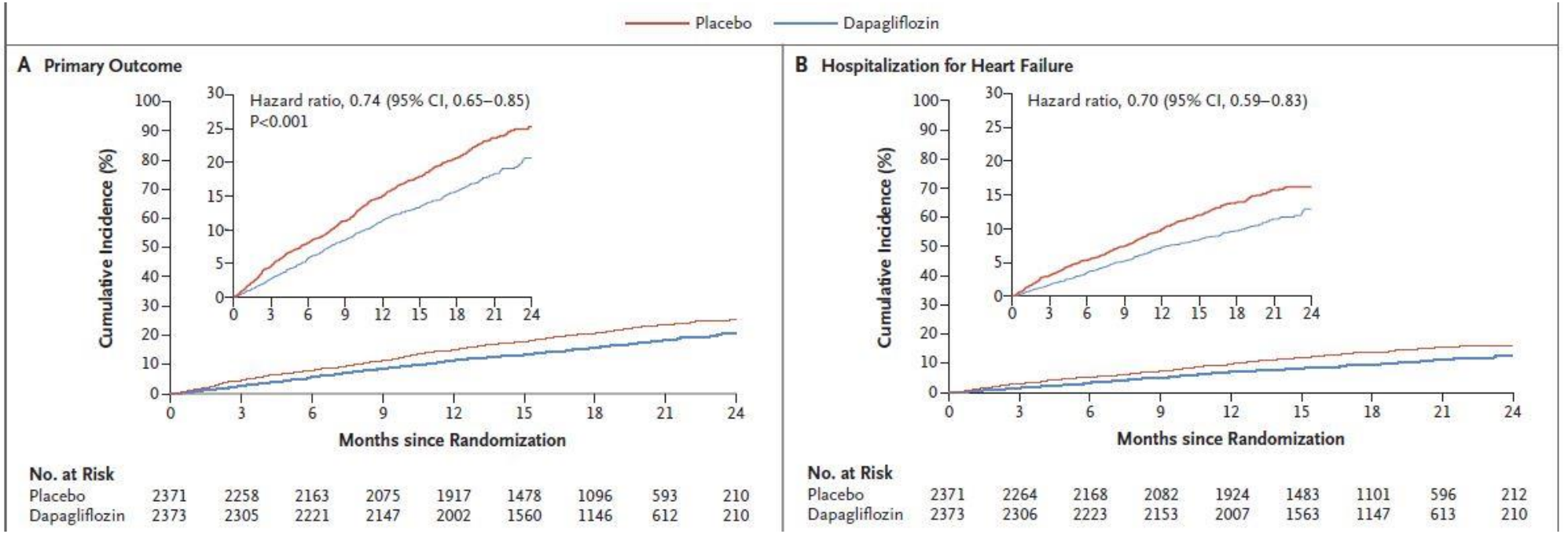
- Age ≥ 18 years
- Ejection fraction ≤ 40%
- NYHA class II- IV symptoms
- Elevated NT-proBNP
- Stable standard of care HF treatment
- eGFR > 30 ml/min/1.73 m^2 (dapa) or > 20 30 ml/min/1.73 m^2 (emperor)

Baseline Characteristics*	DAPA	EMPEROR
DM	42%	50%
White	70%	71%
Age	66 years	67 years
NYHA FC II	68%	75%
ACEi or ARB	84.5%	70.5%
ARNI	10.5%	18.3%
Beta-blocker	96%	95%
MRA	71.5%	70.1%

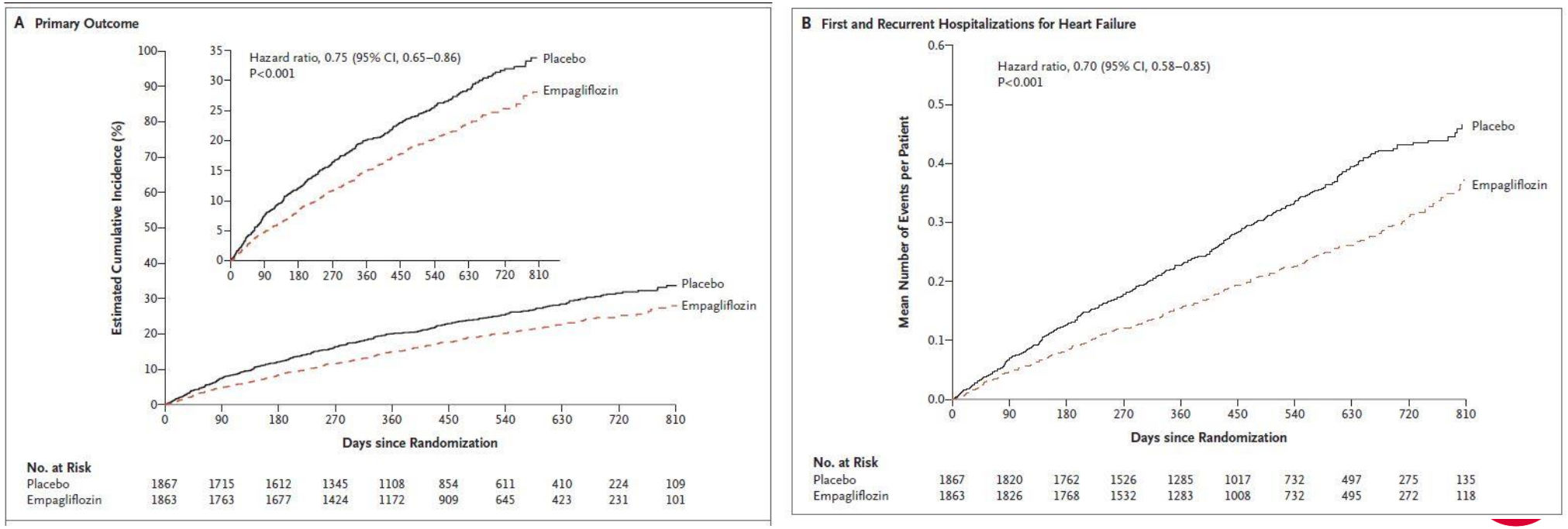
* In treatment arm. Placebo evenly matched

Packer M, et al. N Engl J Med 2020;383:1413-24, McMurray JJV et al. N Engl J Med 2019; 380:347-357

DAPA HF

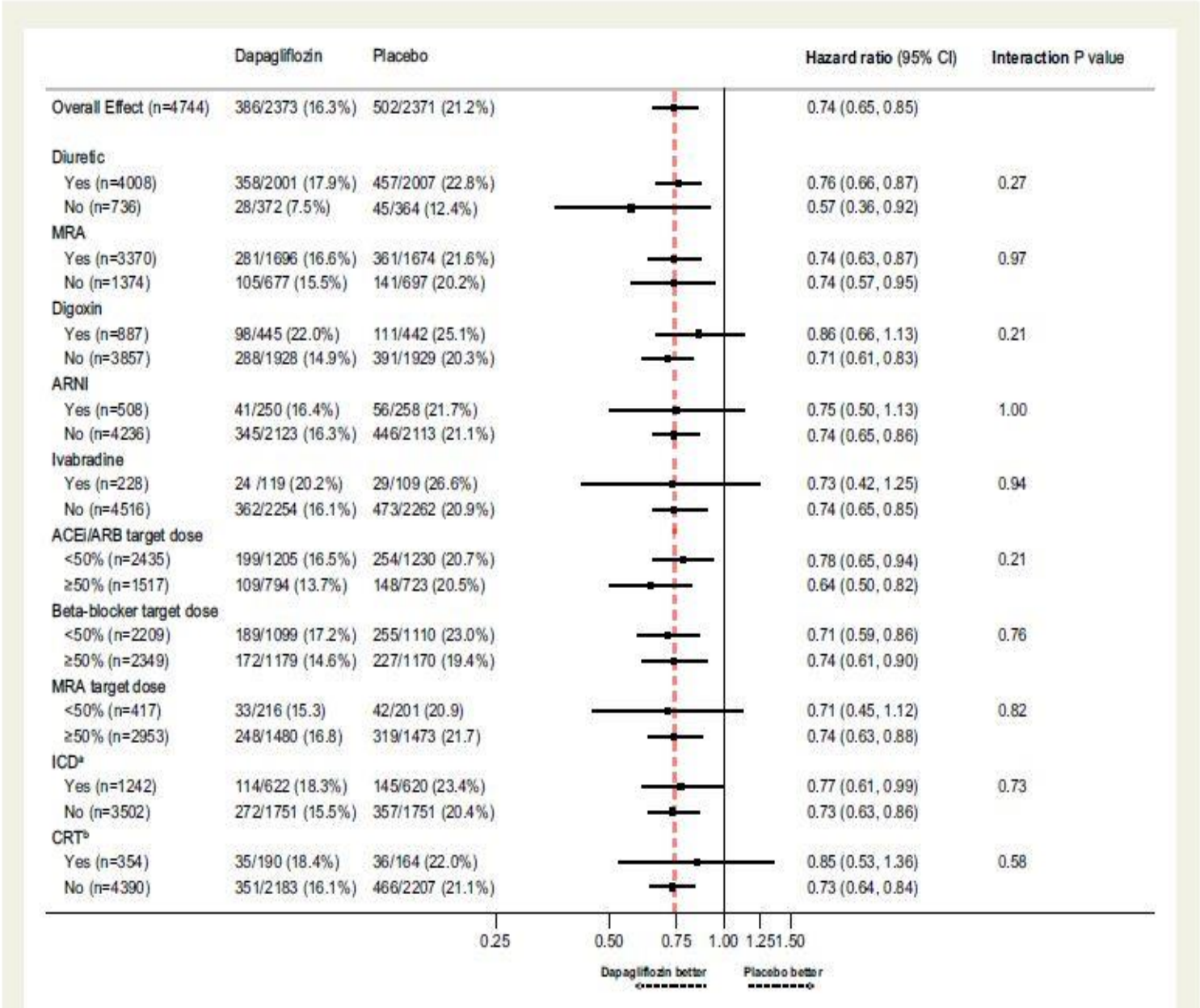


EMPEROR REDUCED



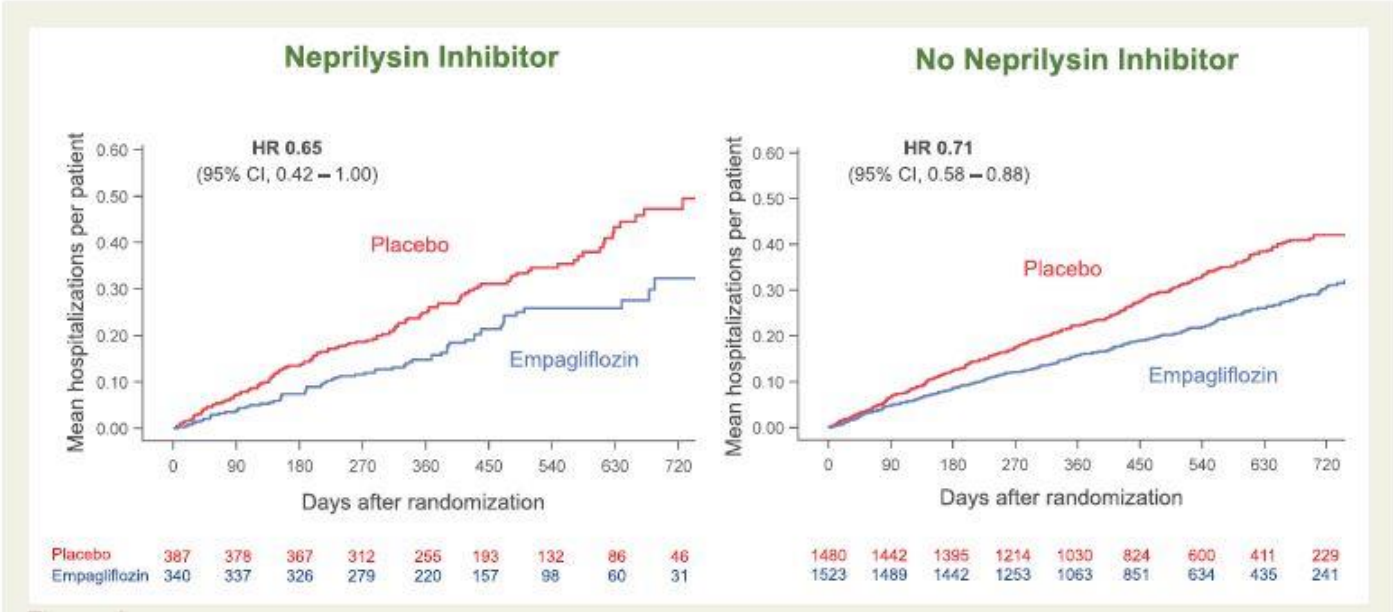
McMurray JJV et al. N Engl J Med 2019; 380:347-357,
Packer M, et al. N Engl J Med 2020;383:1413-24

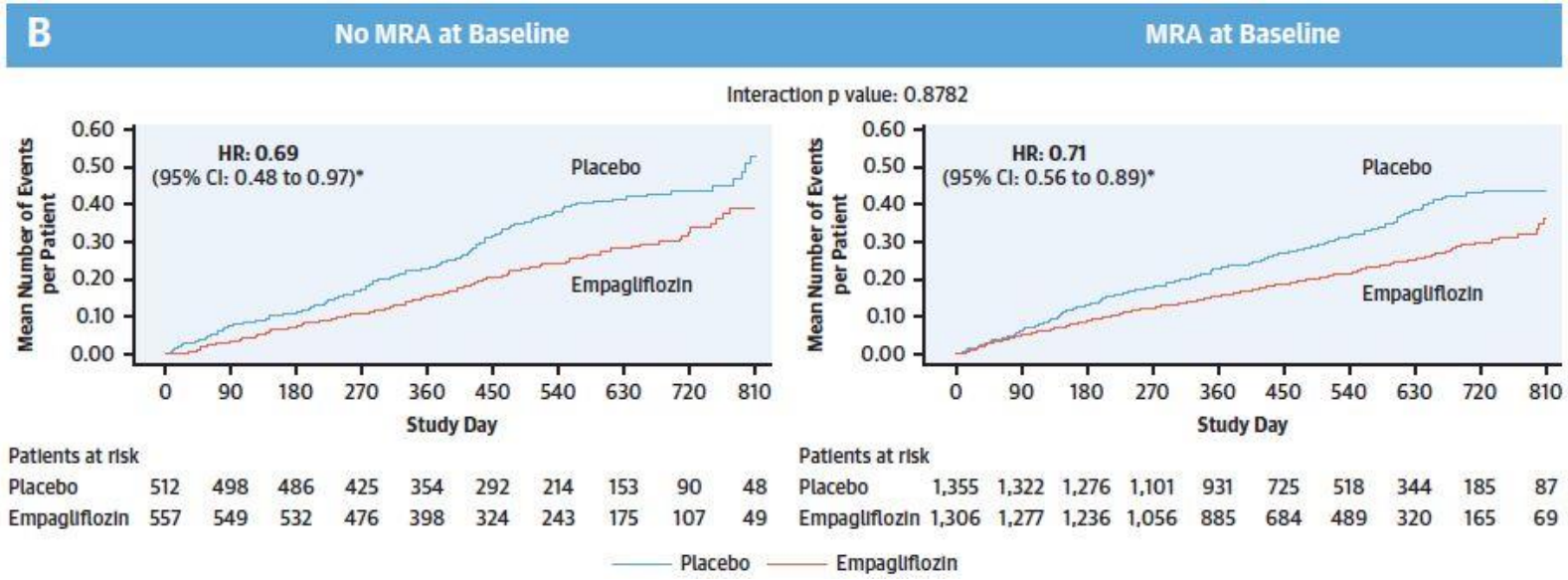
DAPAGLIFLOZIN BENEFICIAL WITH OTHER HF MEDS AT HIGH OR LOW DOSE



Docherty KF et al. European Heart Journal 2020;41:2379-92

EMPAGLIFLOZIN BENEFICIAL WITH OR WITHOUT ARNI OR MRA IN REDUCING HF HOSPITALIZATIONS





Packer M et al. European Heart Journal 2021;42:671-80.
Ferreira JP et al. J Am Coll Cardiol 2021;77:1397-407

Safety of Dapagliflozin + HF therapies

	Volume depletion			Renal adverse event		
	Dapagliflozin	Placebo	Interaction *P*-value	Dapagliflozin	Placebo	Interaction *P*-value
ACEi/ARB + beta-blocker + MRA						
Yes	104/1399 (7.4)	72/1363 (6.5)	0.02	79/1399 (5.6)	88/1363 (6.5)	0.76
No	74/969 (7.6)	90/1005 (9.0)		74/969 (7.6)	82/1005 (8.2)	
ACEi/ARB ≥50% + beta-blocker ≥50%						
Yes	45/521 (8.6)	22/451 (4.9)	0.03	43/521 (8.3)	26/451 (5.8)	0.03
No	133/1847 (7.2)	140/1917 (7.3)		110/1847 (6.0)	144/1917 (7.5)	
ACEi/ARB ≥50% + beta-blocker ≥50% + MRA						
Yes	39/371 (10.5)	11/339 (3.2)	<0.001	30/371 (8.1)	19/339 (5.6)	0.07
No	139/1997 (7.0)	151/2029 (7.4)		123/1997 (6.2)	151/2029 (7.4)	
ACEi/ARB ≥50% + beta-blocker ≥50% + ICD[a]						
Yes	15/134 (11.2)	4/109 (3.7)	0.04	7/134 (5.2)	9/109 (8.3)	0.46
No	163/2234 (7.3)	158/2259 (7.0)		146/2234 (6.5)	161/2259 (7.1)	
ARNI + beta-blocker + MRA						
Yes	18/161 (11.2)	20/171 (11.7)	0.63	15/161 (9.3)	16/171 (9.4)	0.77
No	160/2207 (7.2)	142/2197 (6.5)		138/2207 (6.3)	154/2197 (7.0)	

No effect on BP or creatinine change

Docherty KF et al. European Heart Journal 2020;41:2379-92

Safety of Empagliflozin + HF therapies

Empagliflozin + ARNI (n = 727) vs no ARNI (n = 3003)

- **No difference** in BP reduction, hypotension or hyper/hypokalemia
- Numerical ↑ in volume depletion and ↓ in frequency of worsening renal function

Empagliflozin + MRA (n=2661) vs no MRA (n = 1069)

- (-) MRA, less likely to start / (+) MRA, less likely to d/c
- **No effect** on BP, renal outcomes
- **Less** hyperkalemia

Packer M et al. European Heart Journal 2021;42:671-80.
Ferreira JP et al. J Am Coll Cardiol 2021;77:1397-407

HFpEF Trials:

RAAS antagonists:

- ARB = mixed results (CHARM-Preserved and I-Preserve)
- ACEi = no benefit (PEP-CHF)
- MRA = ↓decreased hospitalization for HF (TOPCAT)

Neprilysin Inhibition (ARNI)

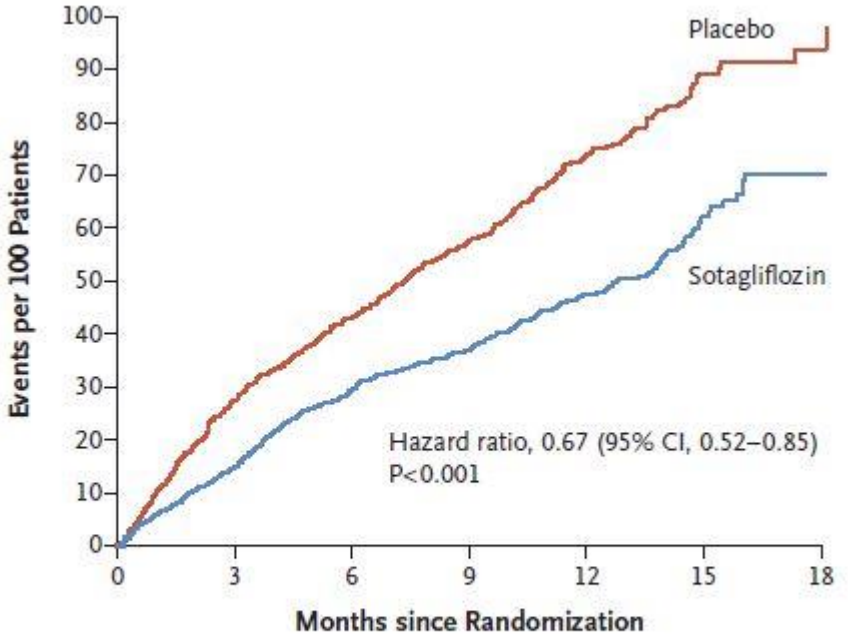
- PARAGON trial: HF hospitalization or CV death p = 0.06
- Less decline in renal function / More patients had improvement in NYHA FC
- Subgroup analysis: + benefit in women or EF ≤ 57% (median for trial)
- FDA label for sacubitril/valsartan updated in 2021
  - ENTRESTO is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal.

Pfeffer YS, et al. Lancet 2003;362:777-81. Massie BM, et al. N Engl J Med. 2008;359:2456-67. Cleland JGF, et al. European Heart J 2006;27:2338-45. Pitt B, et al. N Engl J Med. 2014;370:1383-92. Solomon SD, et al. N Engl J Med. Solomon SD, et al. N Engl J Med. 2019;1609-20.

HFpEF: SOLOLIST WHF

Study Design:

- DM
- Hospitalization or emergency treatment for HF (Randomized during admit or within 3 days)
- Elevated NT-proBNP
- Hemodynamically stable
- Transitioning to oral diuretic
- No EF requirement
- Sotaliflozin (SGLT2 + GI SGLT1 inhibition) vs placebo
- 1º Endpoint: CV death or HF hospitalization/urgent visit



No. at Risk							
Placebo	614	524	416	305	195	100	25
Sotagliflozin	608	540	430	310	209	97	29

Subgroup	No. of Patients	Sotagliflozin	Placebo	Hazard Ratio (95% CI)
		events per 100 patient-yr		
Overall	1222	51.0	76.3	0.67 (0.52–0.85)
LVEF				
<50%	966	56.9	79.9	0.72 (0.56–0.94)
≥50%	256	30.6	64.0	0.48 (0.27–0.86)

Bhatt DL et al. N Eng J Med. 2021;384:117-28

HFpEF: EMPEROR Preserved

Study Design

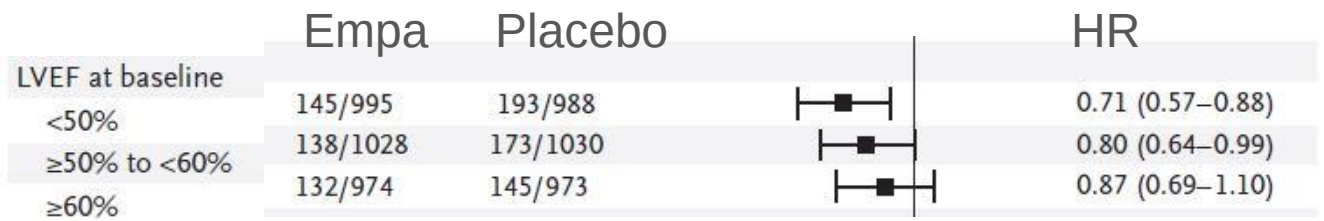
- NYHA FC II-IV HF with EF >40%
- Elevated NT-proBNP
- HF hospitalization within 12 months
- 1º Endpoint: CV death or HF hospitalization

Patient Population

- 76% white
- 82% NYHA FC II
- Mean LVEF: 54.3%
- 49% with DM
- 50% with eGFR <60 ml/min/1.73m^2
- 51% with Afib

	Empa N=2997	Placebo N=2991	Hazard Ratio
1º Outcome	13.8%	17.1%	0.79 (0.69-0.90)
Hospitalization	8.6%	11.8%	**0.71 (0.63-0.83)**
CV Death	7.3%	8.2%	0.91 (0.76-1.09)
Total HF hosp.	407	541	0.73 (0.61-0.88)
eGFR*	-1.25	-2.62	1.36 (1.06-1.66)

* Mean slope change/year ml/min/1.73m^2



Anker SD, et al. N Engl J Med 2021: **DOI: 10.1056/NEJMoa2107038**

Role in CKD

CKD Trials

Trial	CREDENCE (Canagliflozin)	DAPA-CKD (Dapagliflozin)	EMPEROR REDUCED (Empagliflozin)	SCORED (Sotagliflozin)
DM	+	+/-	+/-	+
eGFR (ml/min/1.73m^2)	30-<90 (≥ 60 limited to 40% of patients)	25-75 / (≥ 60 limited to 10% of patients)		25-60
Urinary Alb:Cr Ratio	927	965	Not reported	74
1^o Endpoint	Renal composite or CV death **HR 0.7 (0.59-0.82)**	Renal composite or CV death **HR 0.61 (0.51-.072)**	CV death or HF HR 0.75 (0.65-0.86)	CV death or HF HR 0.74 (0.63-0.88)
2^o Endpoint	CV death or HF HR 0.69 (0.57-0.83)	Renal composite **HR 0.56 (0.45-0.68)** CV composite HR 0.71 (0.55-0.92)	Renal composite **HR 0.5 (0.32-0.7)**	Renal composite **HR 0.71 (0.83-1.18)**

Renal Composite: decline in eGFR or rise in serum creatine (various definitions), dialysis, transplant or renal death

Add references

Practical Considerations

SGLT2i Dosing for HF/CV risk reduction

Drug	DM type II	No DM	Renal eGFR
Canagliflozin* (Invokana®)	100-300 mg daily	-----	30-59 ml/min: 100 mg daily <30 ml/min: avoid^
Dapagliflozin (Farxiga®)	10 mg daily	10 mg daily	<30 ml/min: avoid
Empagliflozin (Jardiance®)	10 mg daily	10 mg daily	<20 ml/min: avoid

* CV risk reduction indication only

^ If already taking and eGFR < 30 with albuminuria >300 mg/day, can continue 100 mg daily

Contraindicated in Type I DM and Dialysis

SGLT2 inhibitors: Common Side Effects

Genitourinary infections

- ↑ Risk in patients with a history of urinary tract infections and genital mycotic infections
- ↑ Risk in uncircumcised males
- Counsel on importance of proper hygiene

↑ Serum Creatinine

- Expected within 2 weeks (small ↑ Creatinine or up to10% dip in eGFR)
- Resolves over time (about 12 weeks)
- Consider further evaluation for volume depletion if 30% increase in Creatinine

Polyuria

- Expected but also consider worsening hyperglycemia in diabetics
- Adjustment of fluid restrictions in HF, as necessary

Farxiga [package insert]. Bristol-Myers Squibb Company; 2020. Invokana [package insert]. Janssen Pharmaceuticals, Inc.; 2020. Jardiance [package insert]. Boehringer Ingelheim Pharmaceuticals, Inc.; 2020. Steglatro Whitehouse Station, NJ: Merck & Co., Inc.; 2020. Meraz-Muñoz AY. Kidney 360. doi:10.34067/KID.0001172021

SGLT2 inhibitors: Rare but serious side effects

↑ Risk of foot amputations and ↑ fracture risk (canagliflozin)

- Use with caution in patients with neuropathy, history of diabetic foot ulcers, those with or at risk for PVD, and those with a history of amputation
- Consider other factors that contribute to fracture risk

Necrotizing Fasciitis/Fournier's Gangrene

- Baseline risk in patients with diabetes
- Counsel on importance of proper hygiene

Farxiga [package insert]. Bristol-Myers Squibb Company; 2020. Invokana [package insert]. Janssen Pharmaceuticals, Inc.; 2020. Jardiance [package insert]. Boehringer Ingelheim Pharmaceuticals, Inc.; 2020. Steglatro Whitehouse Station, NJ: Merck & Co., Inc.; 2020.

SGLT2 inhibitors: Rare but serious side effects

Euglycemic Diabetic Ketoacidosis (euDKA)

Risk Factors

- Insulin dose reductions
- Acute febrile illness
- Reduced caloric intake
- Surgery
- Pancreatic disorders resulting in insulin deficiency (e.g., T1D)
- Alcohol abuse
- Ketogenic diet

Presentation

- Nausea and vomiting
- Abdominal pain
- Generalized malaise
- Shortness of breath
- Hyperglycemia not required
  - Often <250 mg/dL
- Ketonemia

Risk Mitigation

- Educate on s/sx!
- Avoid off label use in T1D
- Prior to scheduled surgery:
  - Hold 3 days
    - Dapagliflozin
    - Empagliflozin
    - Canagliflozin
  - Hold 4 days
    - Ertugliflozin

Farxiga [package insert]. Bristol-Myers Squibb Company; 2020. Invokana [package insert]. Janssen Pharmaceuticals, Inc.; 2020. Jardiance [package insert]. Boehringer Ingelheim Pharmaceuticals, Inc.; 2020. Steglatro Whitehouse Station, NJ: Merck & Co., Inc.; 2020.

Loop Diuretic / Risk of Volume Depletion
To dose reduce or not?

Loop Diuretic and SGLT2i

Loop diuretic use with SGLT2i vs other DM meds

- HF + DM Medicare Claims
- SGLT2i matched to pts on other DM meds (750 pts ea)
- EF not reported
- ↓ **new loop** diuretics in SGLT2i patients
- **No change** in patterns of loop diuretic use @ 12 months

DAPA HF Diuretic Use

Empa and compensated HF

Weeda ER, et al. J of Diabetes and Its Complications. 2019;33:567-71. Jackson AM, McMurray JJV. Circulation. 2020;142:1040-54. Shirakabe A, et al. Circ Rep 2020;2:565-75.

Loop Diuretic and SGLT2i

Loop diuretic use with SGLT2i vs other DM meds

DAPA HF Diuretic Use

- Categorized at baseline in furosemide equivalents
- Mean daily dose: 60 mg
- Any dose change ↑ over time / >70% no change
- **Sig Diuretic dose ↓ D vs P**
- 6 mos: 10.4% vs 7.3%
- 12 mos: 12.4 vs 8.7%
- **Volume depletion: ↑ if on dapa and >40 mg/day**

Empa and compensated HF

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Loop Diuretic and SGLT2i

Loop diuretic use with SGLT2i vs other DM meds

DAPA HF Diuretic Use

Empa and compensated HF

- 58 patients with DM and compensated HF
- Empa vs not taking
- Median EF 55%
- **Median dose ↓ 40 to 20 mg in empa but ↑ in non-empa from 23 to 40mg**
- Dose decreased in only 15 of 28 patients on empa (5 for rise in creatinine)

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My Take: Routine decrease not necessary

Volume Depletion more frequent in patients taking >50% target dose RAASi and BB / > 40 mg/day of furosemide

- Consider dose decrease (BP, volume status)
- Close follow up with labs (2 weeks)
- Home weight and BP monitoring
- Counsel s/sx dehydration

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Considerations for HF Patient Selection

New HFrEF diagnosis along with **low doses** of RAASi, BB and MRA

No Titration Needed

Add to optimized HFrEF medications in patients who remain symptomatic

Add to HFrEF regimen in patients who can't tolerate or achieve >50% target doses of RAASi, BB or MRA

Add to reduce hospitalizations in HFpEF (HF mid range EF)

Prioritize use in patients with CKD (albuminuria)

Closely **monitor** volume status after initiation (multiple HF meds or higher dose loop diuretic)

Expect a small reduction in BP

Diabetes Patient Selection: ADA Guidelines:

FIRST-LINE = metformin* + comprehensive lifestyle modifications

Indicators of high CV risk or established ASCVD, HF or CKD?

Consider independently of baseline A1c or individualized A1c target

GLP1 Agonist or SGLT2i if ASCVD predominates

GLP1 agonist:
- + Weight loss
- Larger A1c Reduction
- + nausea/vomiting/diarrhea
- Caution if hx of pancreatitis
- Contraindicated: medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2

SGLT2i if HF or CKD predominates

(GLP1 agonist for CV risk reduction if SLGT2i not tolerated)

Diabetes Care. 2020;43:S1-S212.

Thank you, Questions?