SGLT2 Inhibitors:
Expanding Therapeutic Niche in Clinical Practice

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Abbreviation	Meaning
ACEi	Angiotensin converting enzyme inhibitor
ADR	Adverse drug reaction
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor/neprilysin inhibitor
ASCVD	Atherosclerotic cardiovascular disease
BNP	Brain natriuretic peptide
CKD	Chronic kidney disease
CV	Cardiovascular
eGFR	Estimated glomerular filtration rate
EF	Ejection fraction
ESKD	End stage kidney disease
GLP-1 RA	GLP-1 receptor agonist
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction

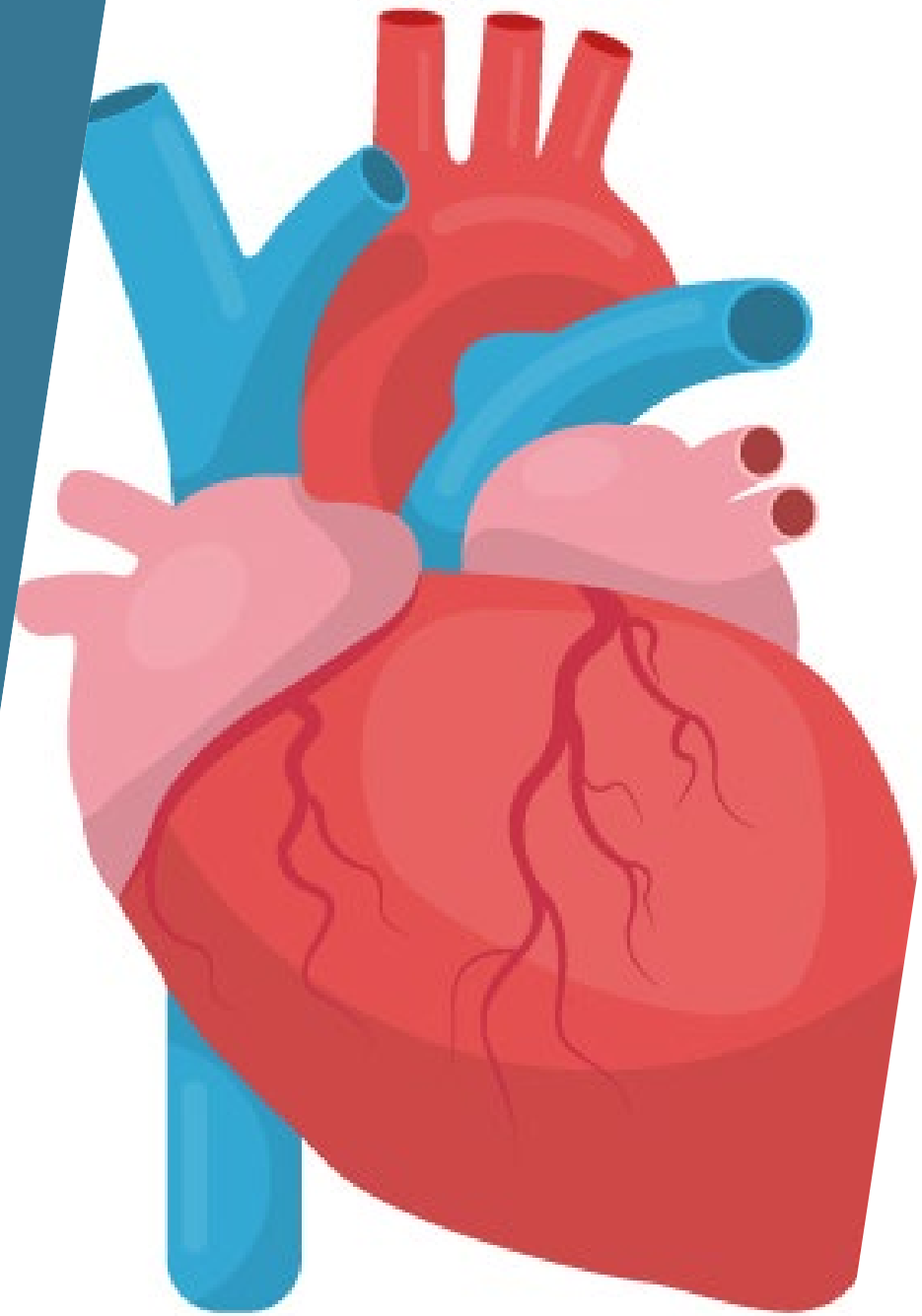
Abbreviation	Meaning
IV	Intravenous
MI	Myocardial infarction
MRA	Mineralocorticoid receptor antagonist
MGI	Mycotic genital infection
NYHA	New York Heart Association
Pt	Patient
RAAS	Renin angiotensin aldosterone system
UACR	Urine albumin-to-creatinine ratio
UTI	Urinary tract infection
yo	Years old

SGLT2 Inhibitors

Agent	Dosing	Cost (30 days)	Type 2 Diabetes	CKD	HF	CV Risk Reduction
Bexagliflozin	20 mg daily	$47.85	X			
Canagliflozin	100-300 mg	$580-620	X			
Dapagliflozin	5-**10** mg daily	$241-390	X	X	X	
Empagliflozin	**10**-25 mg daily	$595-620	X	X	X	
Ertugliflozin	5-15 mg daily	$352-360	X			
Sotagliflozin*	200-400 mg daily	$330-613			X	X

*SGLT1 and 2 inhibitor

http://online.lexi.com/ www.goodrx.com

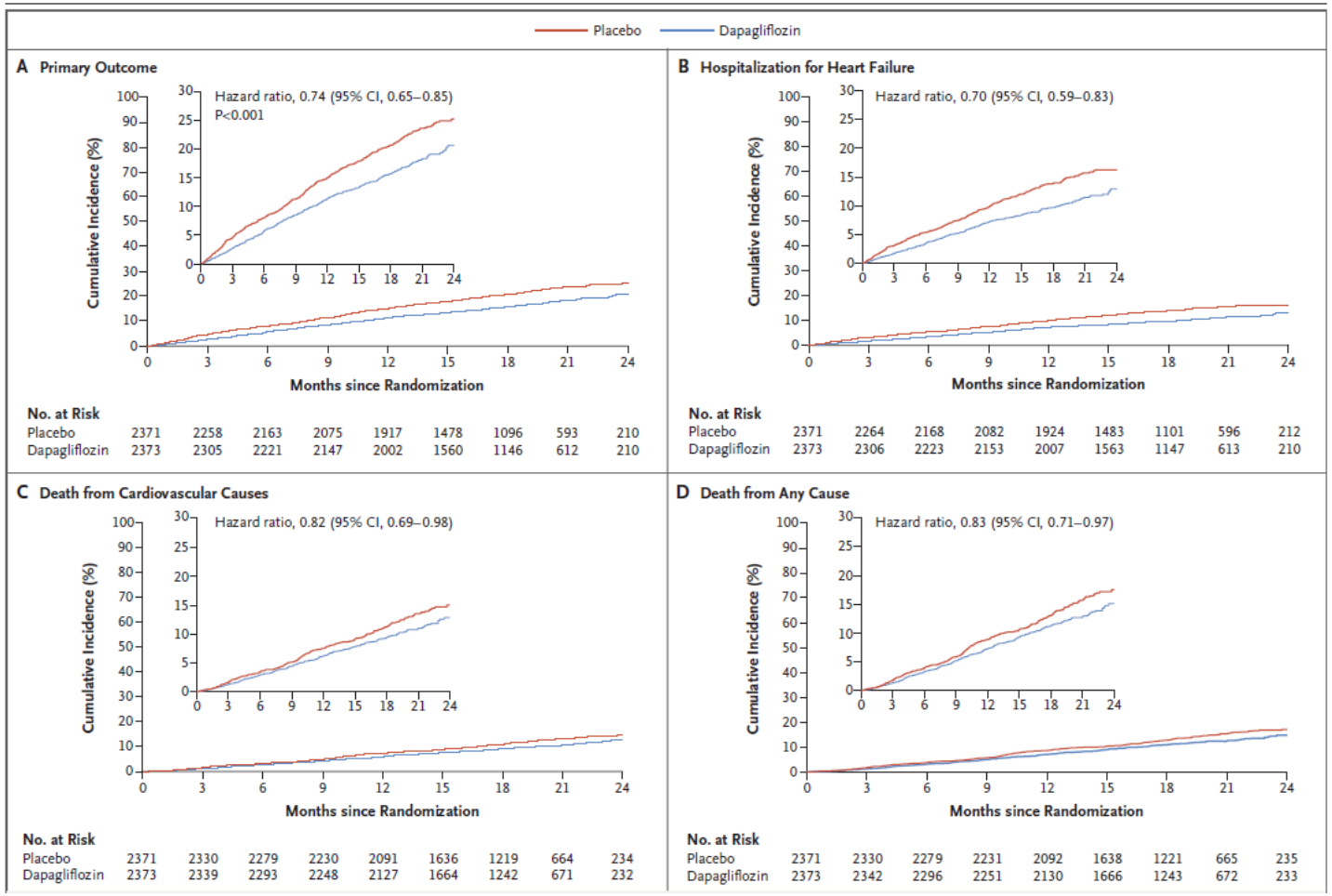


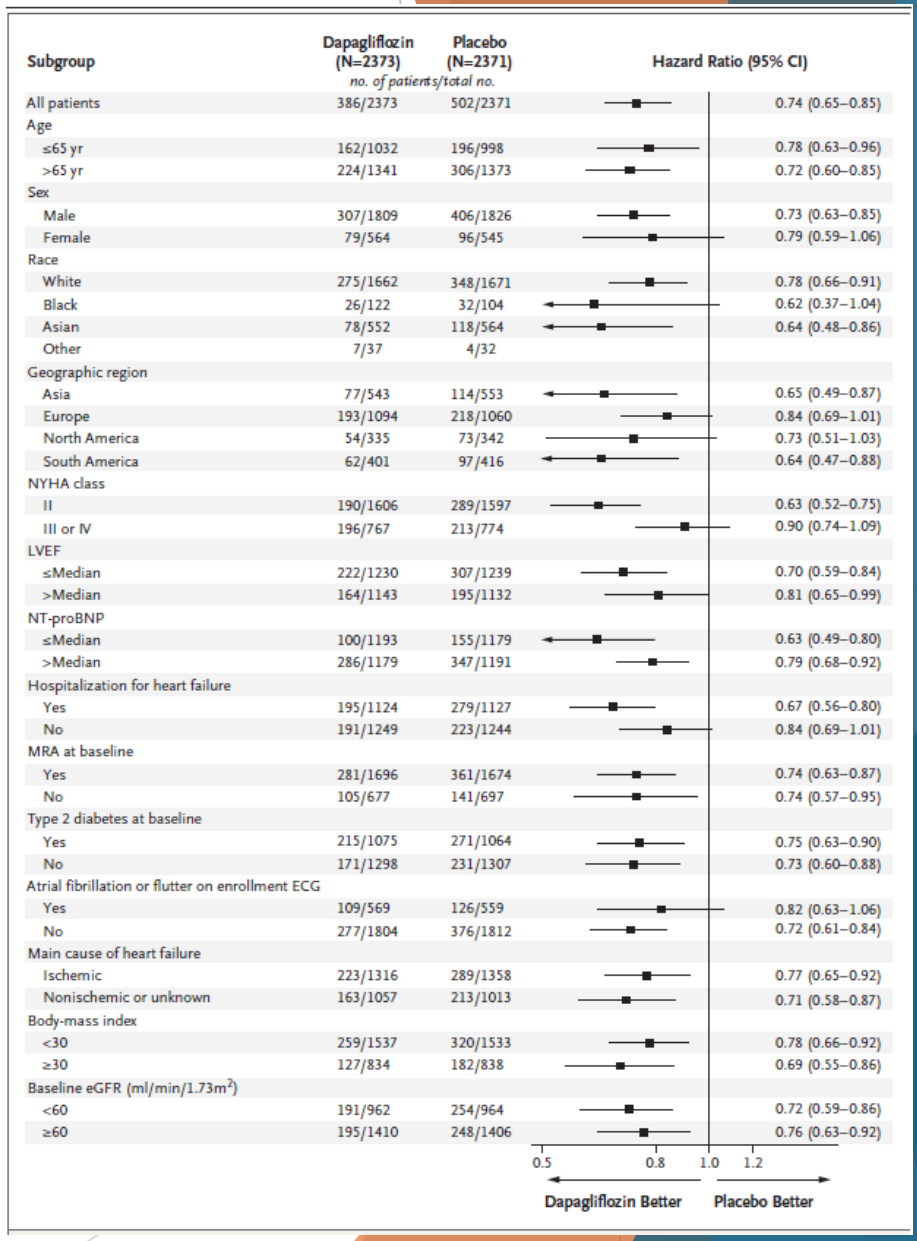
Heart Failure

Trial	DAPA-HF	EMPEROR-Reduced
Population	• EF ≤ 40% • NYHA II, III, or IV • Elevated NT-proBNP • Receiving HF therapy (ACEi/ARB/ARNi + beta-blocker, MRA encouraged)	• EF ≤40% • NYHA II, III, or IV • Elevated NT-proBNP • Receiving HF therapy (ACEi/ARB/ARNi, beta-blocker, MRA, diuretic, and ivabradine) • No change in diuretic management for 1 week
Intervention	Dapagliflozin 10 mg daily	Empagliflozin 10 mg daily
Comparator	Placebo	Placebo
Outcomes	• HF hospitalization or CV death: 16.3% vs 21.2% (p<0.001) ○ HF hospitalization: 9.7% vs 13.4% (HR 0.7 (0.59-0.83)) ○ CV death: 9.6% vs 11.5% (HR 0.82 (0.96-0.98)) • UTI: 0.9% vs. 1.2%	• HF hospitalization or CV death: 19.4% vs 24.7% (p<0.001) ○ HF hospitalization: 13.2% vs 18.3% (HR 0.69 (0.59-0.81)) ○ CV death: 10.0% vs 10.8% (HR 0.92 (0.75-1.12)) • UTI: 4.9% vs. 4.5% • MGI: 1.7% vs. 0.6%

N Engl J Med. 2019;381(21):1995-2008. N Engl J Med. 2020;383(15):1413-1424.

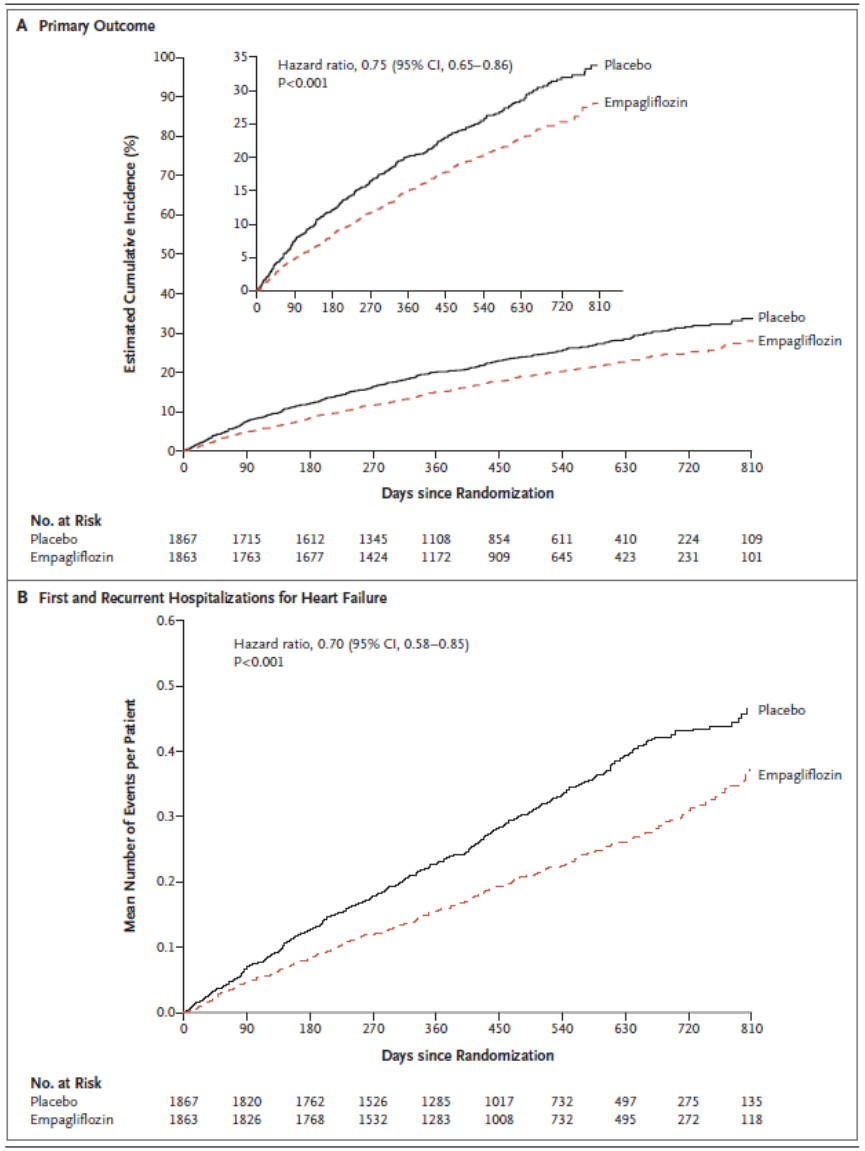
DAPA-HF





N Engl J Med. 2019;381(21):1995-2008.

EMPEROR-Reduced



Subgroup	Empagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of patients with events/total no.		
Overall	361/1863	462/1867	0.75 (0.65–0.86)
Baseline diabetes status			
Diabetes	200/927	265/929	0.72 (0.60–0.87)
No diabetes	161/936	197/938	0.78 (0.64–0.97)
Age			
<65 yr	128/675	193/740	0.71 (0.57–0.89)
≥65 yr	233/1188	269/1127	0.78 (0.66–0.93)
Sex			
Male	294/1426	353/1411	0.80 (0.68–0.93)
Female	67/437	109/456	0.59 (0.44–0.80)
Race			
White	264/1325	289/1304	0.88 (0.75–1.04)
Black	24/123	48/134	0.46 (0.28–0.75)
Asian	62/337	99/335	0.57 (0.41–0.78)
Other	5/51	14/63	0.41 (0.15–1.14)
Baseline body-mass index			
<30	226/1263	322/1300	0.70 (0.59–0.83)
≥30	135/600	140/567	0.85 (0.67–1.08)
Baseline eGFR (CKD-EPI)			
≥60	159/969	224/960	0.67 (0.55–0.83)
<60	202/893	237/906	0.83 (0.69–1.00)
HF hospitalization in ≤12 mo			
No	208/1286	285/1293	0.71 (0.60–0.85)
Yes	153/577	177/574	0.79 (0.64–0.99)
Cause of heart failure			
Ischemic	207/983	236/946	0.82 (0.68–0.99)
Nonischemic	154/880	226/921	0.67 (0.55–0.82)
Baseline NYHA class			
II	220/1399	299/1401	0.71 (0.59–0.84)
III or IV	141/464	163/466	0.83 (0.66–1.04)
Heart failure physiology			
LVEF ≤30% and NT-proBNP <median	80/699	115/724	0.70 (0.53–0.93)
LVEF ≤30% and NT-proBNP ≥median	169/631	249/661	0.65 (0.53–0.79)
LVEF >30%	108/526	97/475	0.99 (0.76–1.31)
Baseline use of MRA			
No	118/557	132/512	0.76 (0.59–0.97)
Yes	243/1306	330/1355	0.75 (0.63–0.88)
Baseline use of ARNi			
No	310/1523	369/1480	0.77 (0.66–0.90)
Yes	51/340	93/387	0.64 (0.45–0.89)

0.125 0.25 0.5 1.0 2.0 4.0 8.0

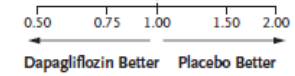
Empagliflozin Better | Placebo Better

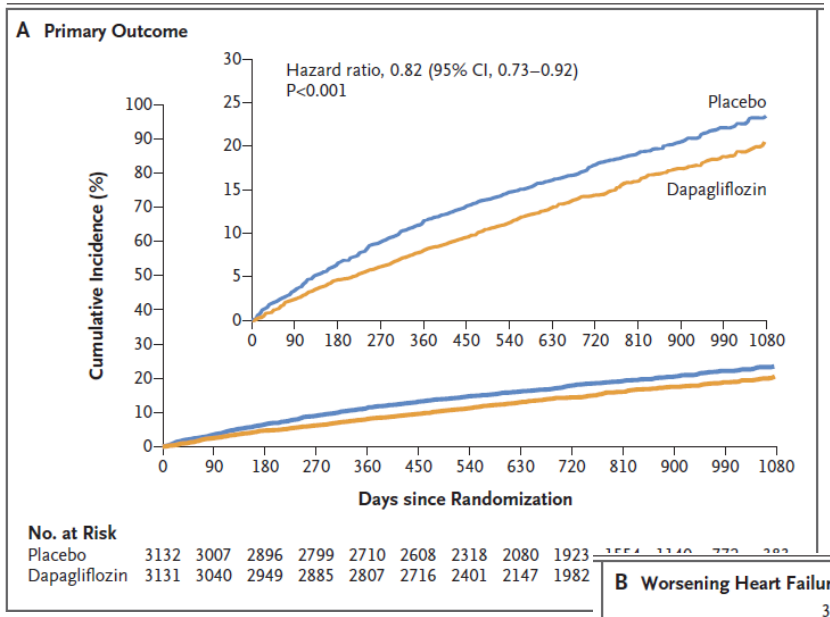
N Engl J Med. 2020;383(15):1413-1424.

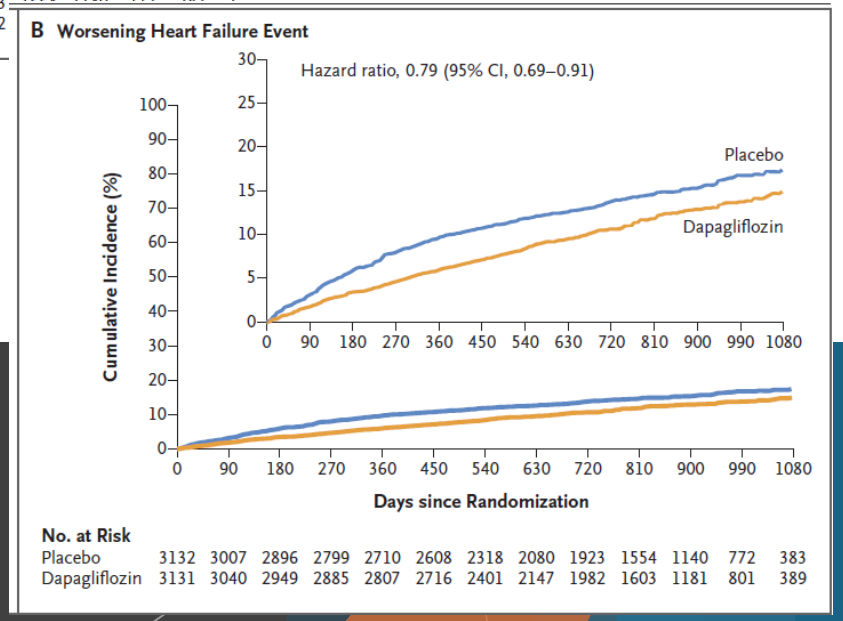
Trial	DELIVER	EMPEROR-Preserved
Population	• Stabilized HF ± type 2 diabetes • EF > 40% • Inpatient or outpatient at randomization, but off IV HF therapies for ≥ 12 hours • Elevated BNP or NT-proBNP	• Patients with chronic HF + NYHA class II-IV • Chronic HF + EF > 40% • Elevated BNP or NT-proBNP
Intervention	Dapagliflozin 10 mg daily	Empagliflozin 10 mg daily
Comparator	Placebo	Placebo
Outcomes	• HF hospitalization or CV death: 16.4% vs 19.5% (p<0.001) ○ HF hospitalization: 10.5% vs 13.3% (HR 0.77 (0.67-0.89)) ○ CV death: 7.4% vs 8.3% (HR 0.88 (0.74-1.05)) • UTI: 1% vs. 1%	• HF hospitalization or CV death: 6.9/100 pt years vs 8.7/100 pt years (p<0.001) ○ HF hospitalization: 4.3/100 pt years vs 6.0/100 pt years (HR 0.71 (0.60-0.83)) ○ CV death: 3.4/100 pt years vs 3.8/100 pt years (HR 0.91 (0.76-1.09)) • UTI: 9.9% vs. 8.1% • MGI: 2.2% vs. 0.7%

N Engl J Med. 2022;387(12):1089-1098. N Engl J Med. 2021;385(16):1451-1461.

Subgroup	Dapagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of patients with events/total no.		
All patients	512/3131	610/3132	0.82 (0.73–0.92)
Age			
≤72 yr	247/1545	306/1604	0.82 (0.69–0.97)
>72 yr	265/1586	304/1528	0.81 (0.69–0.96)
Sex			
Female	195/1364	243/1383	0.81 (0.67–0.97)
Male	317/1767	367/1749	0.82 (0.71–0.96)
Race			
Asian	97/630	106/644	0.91 (0.69–1.21)
Black	21/81	19/78	1.08 (0.58–2.01)
White	372/2214	461/2225	0.79 (0.69–0.90)
Other	22/206	24/185	0.83 (0.46–1.48)
Geographic region			
Europe or Saudi Arabia	261/1494	309/1511	0.83 (0.70–0.98)
Asia	92/607	103/619	0.89 (0.67–1.18)
Latin America	70/602	87/579	0.78 (0.57–1.07)
North America	89/428	111/423	0.75 (0.57–1.00)
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)
Atrial fibrillation or flutter at enrollment ECG			
No	285/1803	339/1814	0.82 (0.70–0.96)
Yes	227/1327	271/1317	0.81 (0.68–0.97)
Body-mass index at enrollment			
<30	275/1734	302/1736	0.89 (0.75–1.04)
≥30	236/1395	308/1392	0.74 (0.63–0.88)
Estimated GFR at enrollment			
<60 ml/min/1.73 m^2	289/1516	355/1554	0.81 (0.69–0.94)
≥60 ml/min/1.73 m^2	223/1615	255/1577	0.84 (0.70–1.00)
Systolic blood pressure at randomization			
≤128 mm Hg	280/1568	300/1590	0.93 (0.79–1.10)
>128 mm Hg	232/1563	310/1542	0.71 (0.60–0.85)
Previous LVEF ≤40%			
No	420/2559	491/2553	0.84 (0.73–0.95)
Yes	92/572	119/579	0.74 (0.56–0.97)

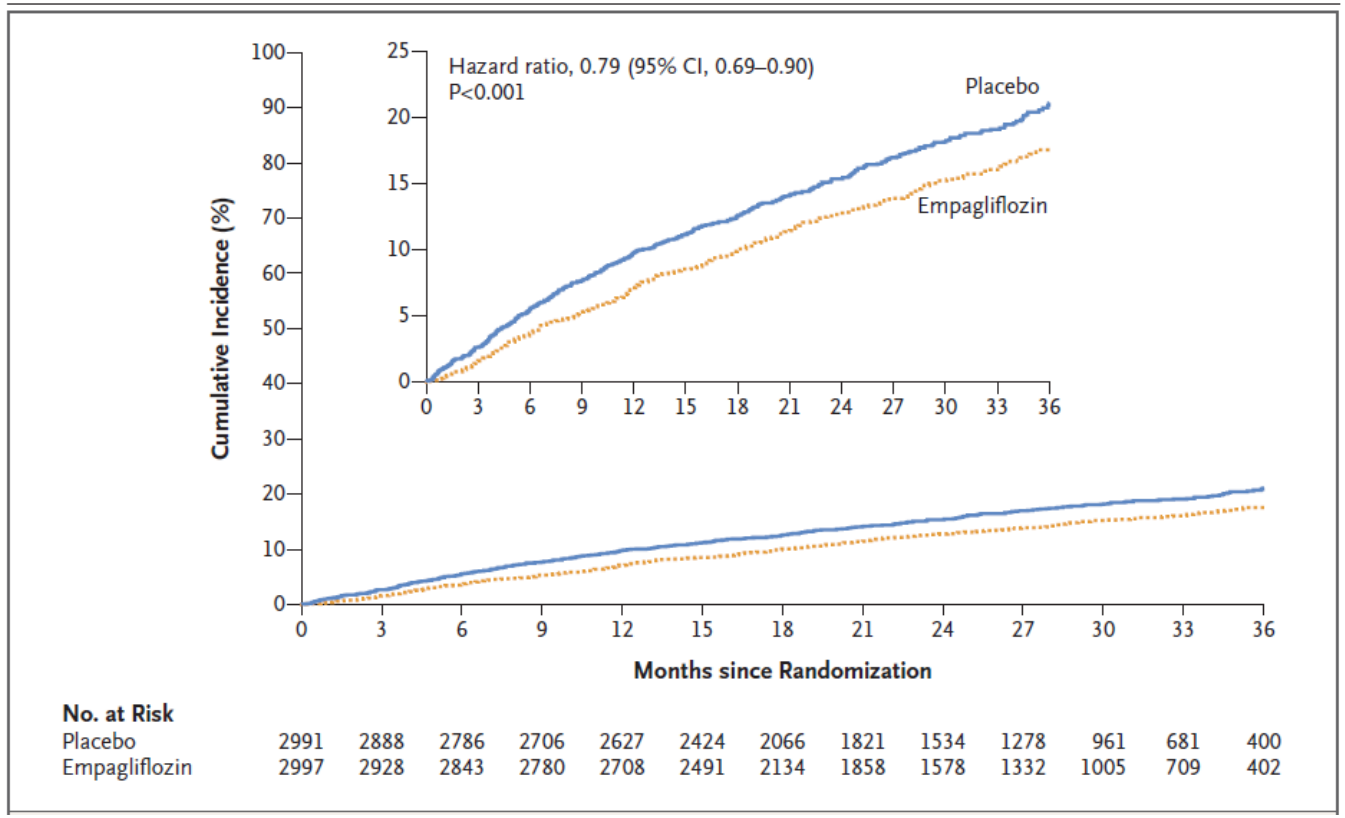


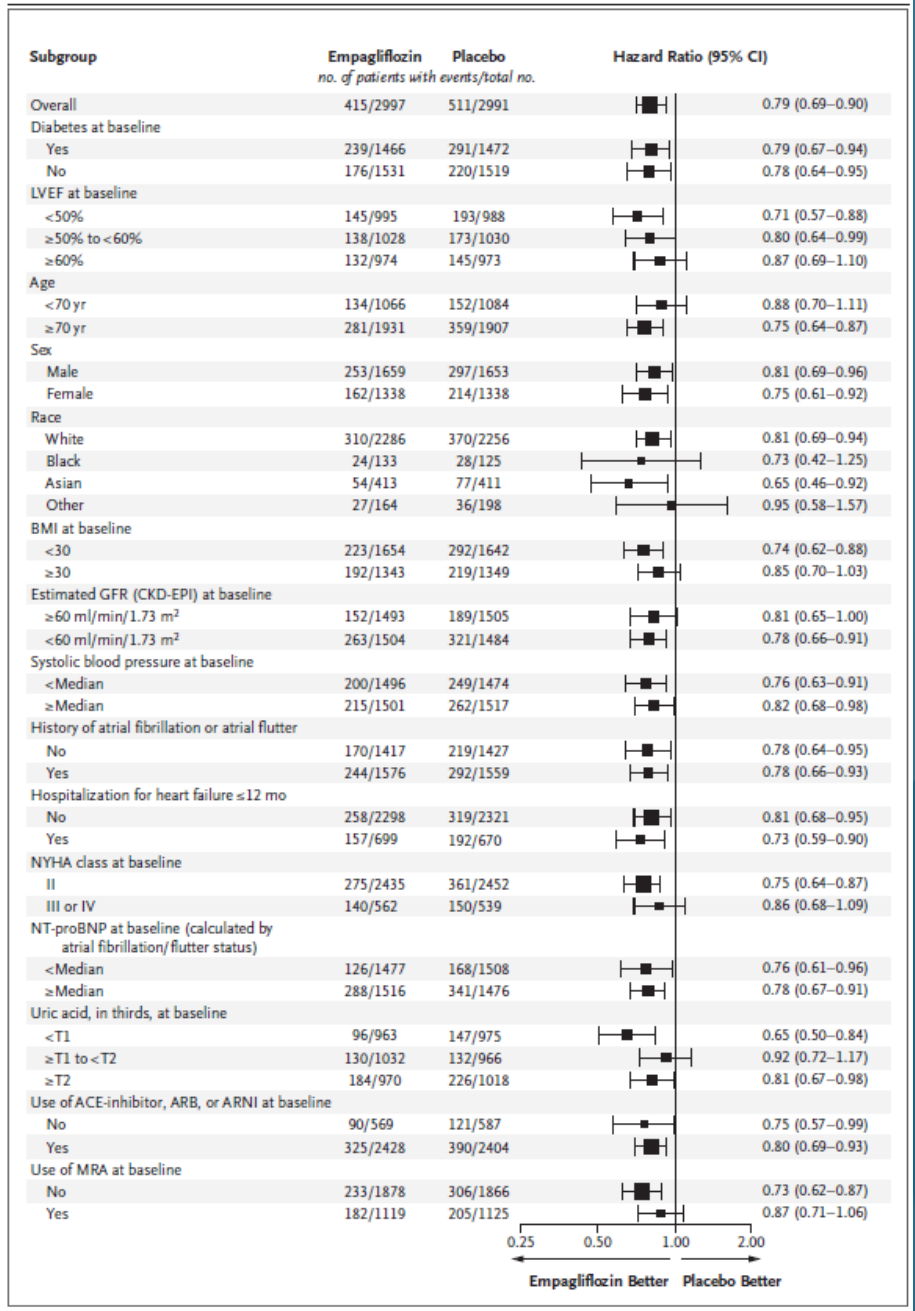




DELIVER

EMPEROR-Preserved



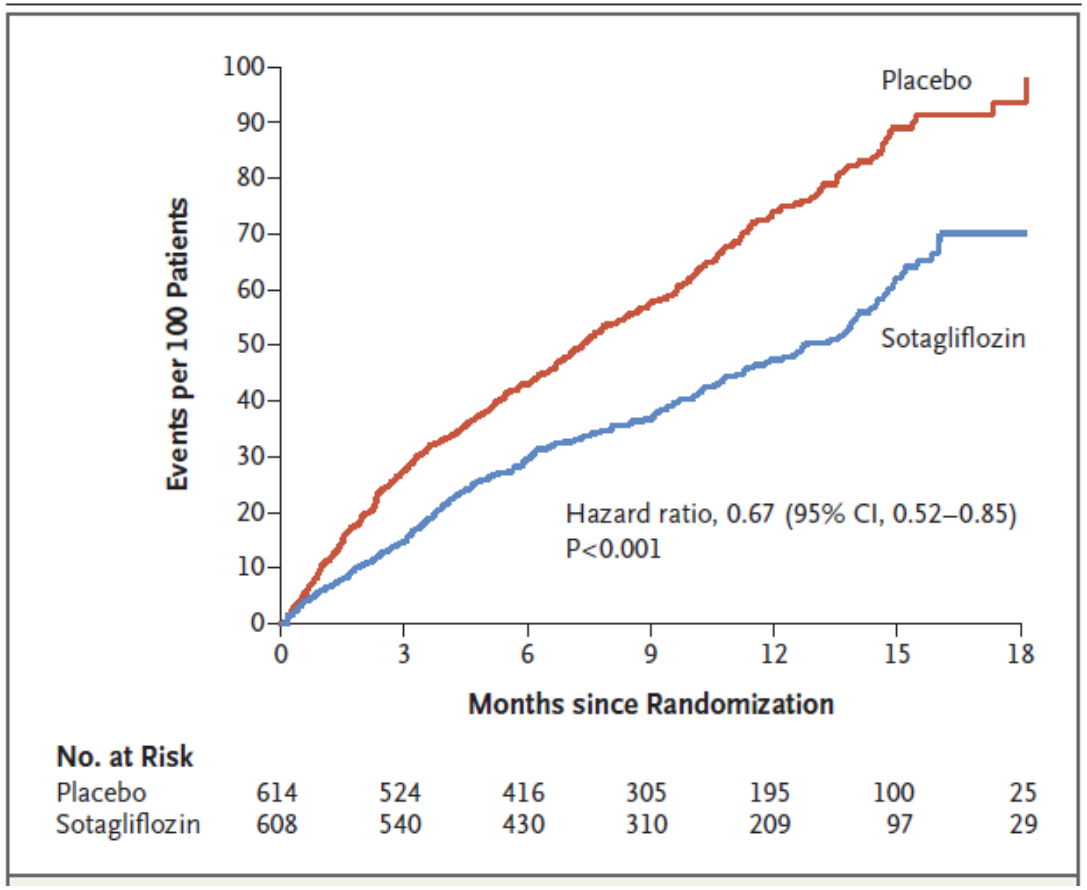


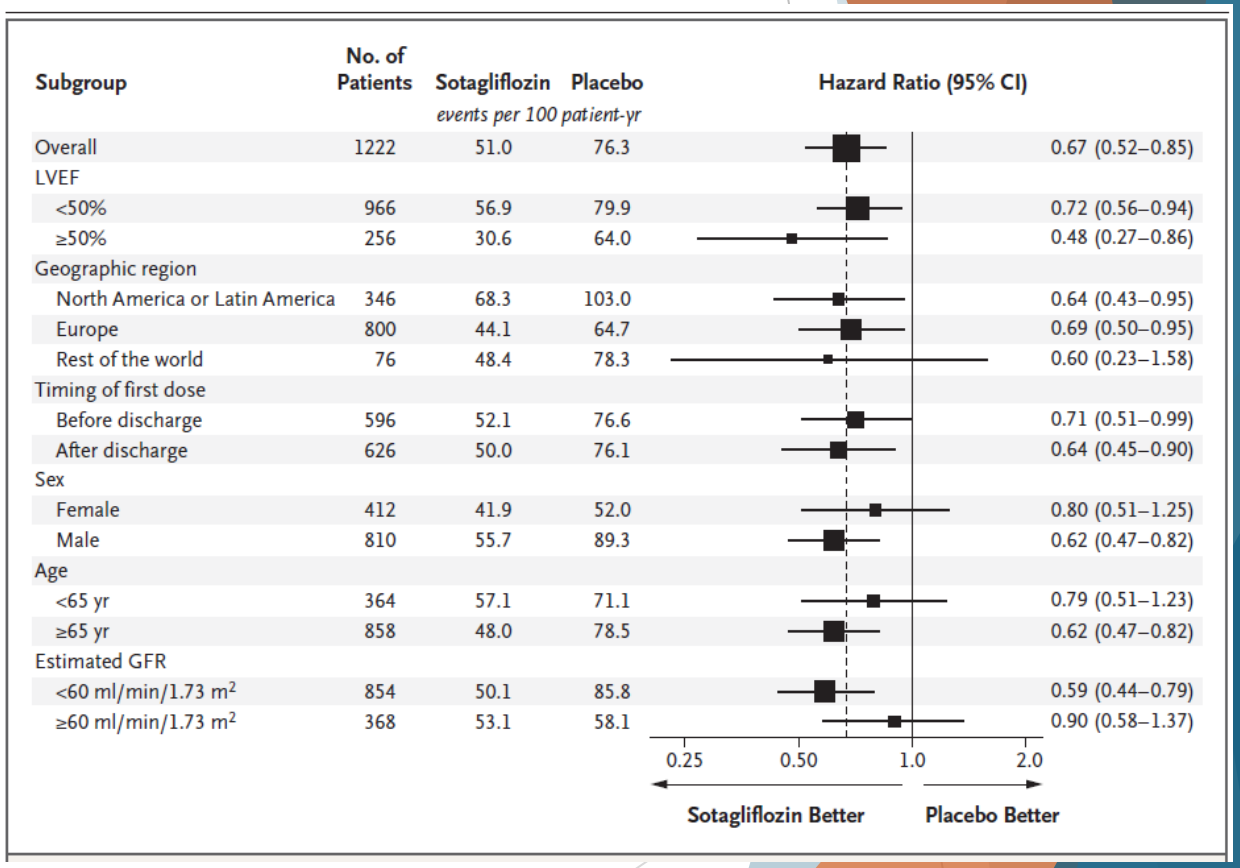
N Engl J Med. 2021;385(16):1451-1461.

Trial	SOLOIST-WHF
Population	• HF hospitalization (no EF cut point) + IV diuretic therapy • Type 2 diabetes • Elevated NT-proBNP
Intervention	Sotagliflozin 200-400 mg daily
Comparator	Placebo
Outcomes	• HF hospitalization or CV death: 51.0% vs. 76.3% (p<0.001) ○ HF hospitalization/uregent HF visit: 40.4% vs 63.9% (p<0.001) ○ CV death: 10.6% vs 12.5% (p=0.36) • UTI: 4.8% vs. 5.1%

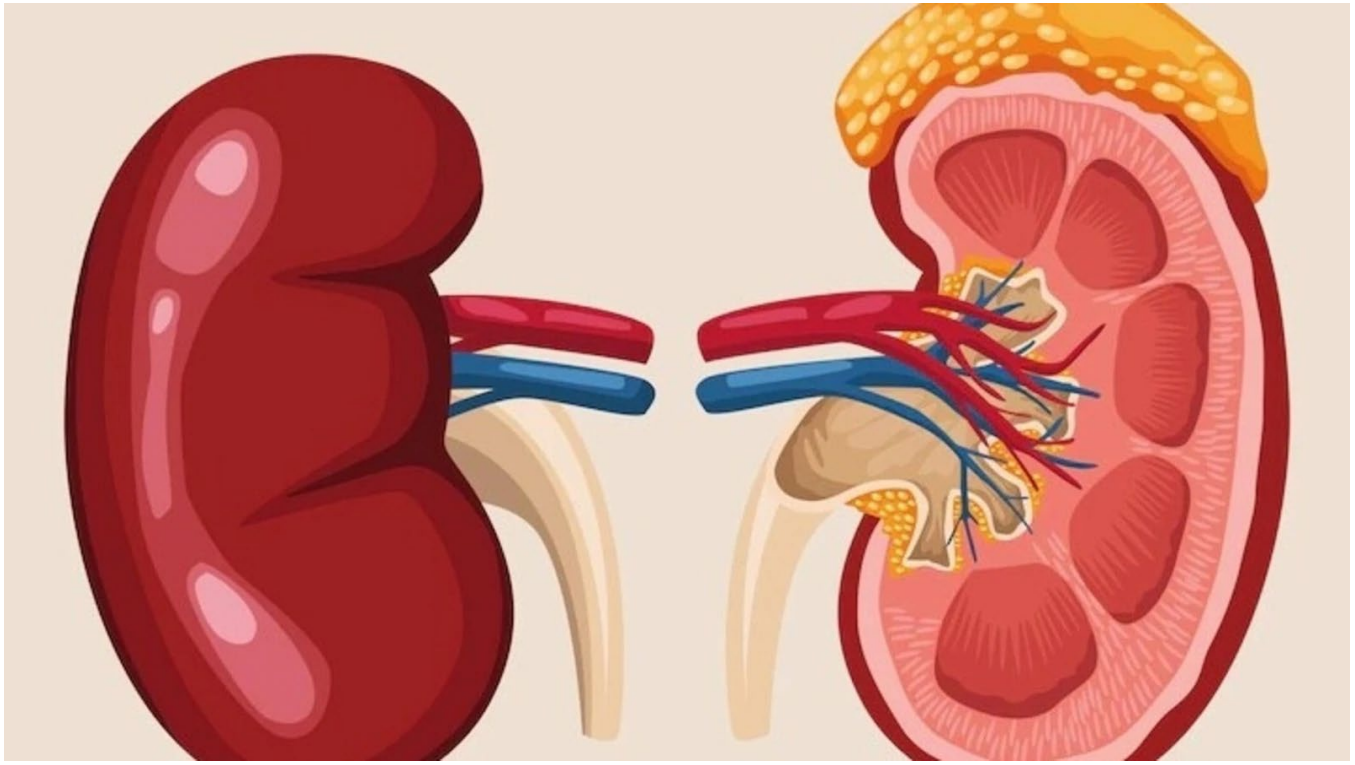
N Engl J Med. 2021;384(2):117-128.

SOLOIST-WHF





N Engl J Med. 2021;384(2):117-128.

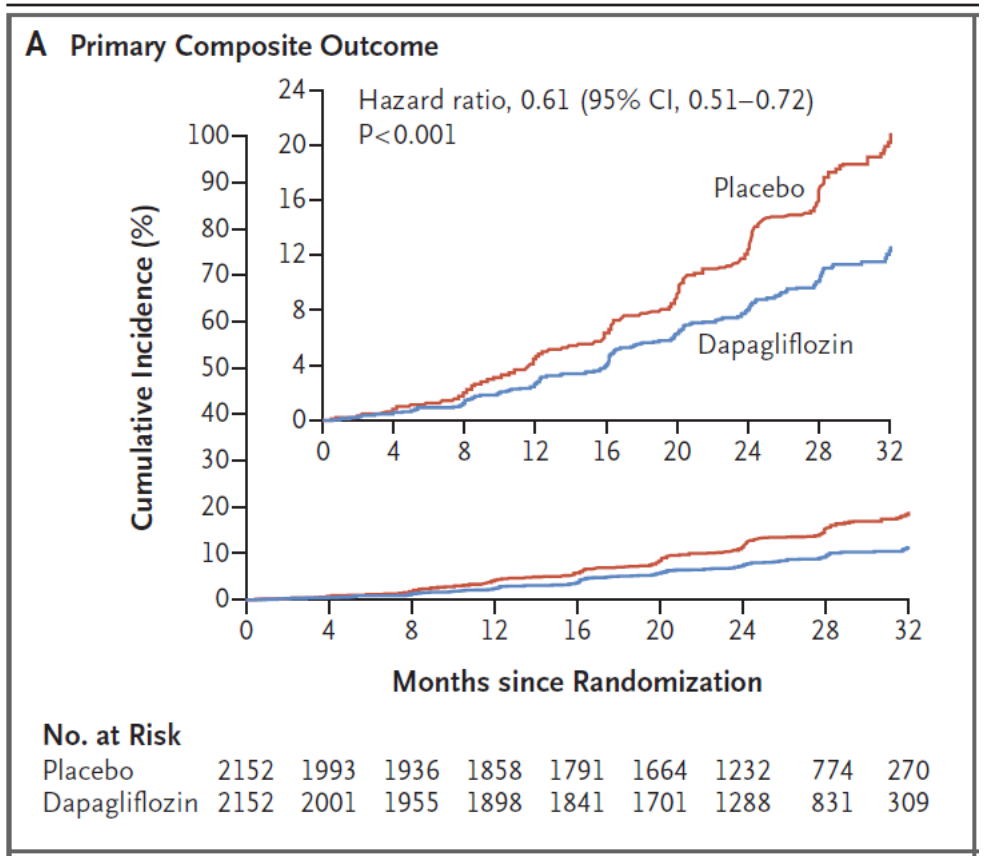


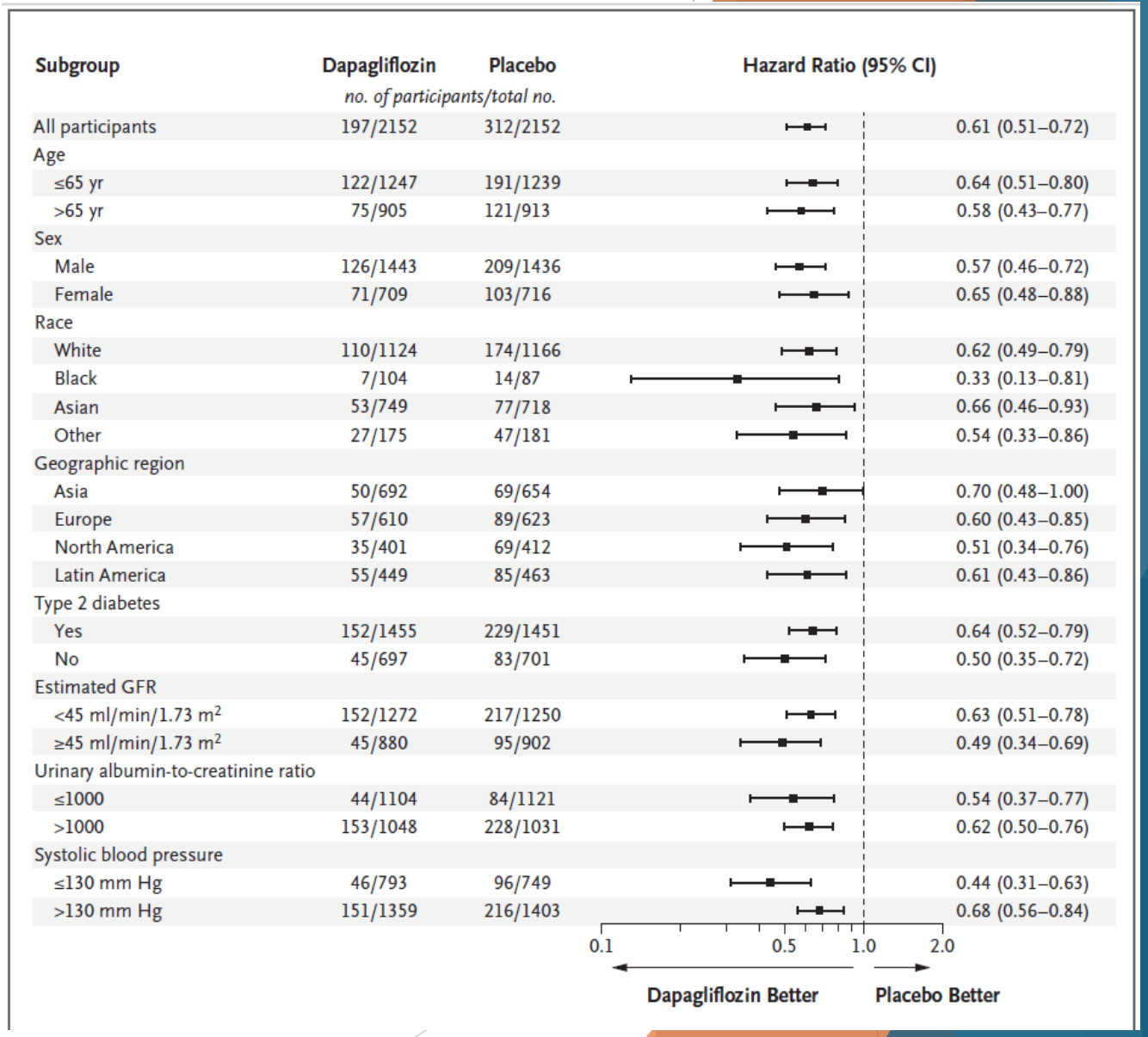
Chronic Kidney Disease

Trial	DAPA-CKD	EMPA-Kidney
Population	• eGFR 25-75 mL/min/1.73 m^2 • UACR 200-5000 • Stable ACEi/ARB dose	• eGFR 20-44 mL/min/1.73 m^2 **OR** 45-89 mL/min/1.73 m^2 + UACR ≥ 200 • UACR 200-5000 • Stable RAAS inhibitor dose
Intervention	Dapagliflozin 10 mg daily	Empagliflozin 10 mg daily
Comparator	Placebo	Placebo
Outcomes	• ≥50% decline in eGFR, ESKD, or death from renal or CV cause: 9.2% vs. 14.5% (p<0.001) ○ ≥50% decline in eGFR: 5.2% vs. 9.3% (HR 0.53 (0.42-0.67)) ○ ESKD: 5.1% vs. 7.5% (HR 0.64 (0.50-0.82)) ○ Renal death: <0.1% vs. 0.3% ○ CV death: 3.0% vs. 3.7% (HR 0.81 (0.58-1.12)) • Death from any cause: 4.7% vs. 6.8% (p=0.01)	• Progression of kidney disease (≥40% decline in eGFR or ESKD), or death from renal or CV cause: 13.1 vs. 16.9% (p<0.001) ○ Progression of kidney disease: 11.6% vs. 15.2% (HR 0.71 (0.62-0.81) ○ CV death: 1.8% vs. 2.1% (HR 0.84 (0.60-1.19)) • Death from any cause: 4.5% vs. 5.1% (p=0.21)

N Engl J Med. 2020;383(15):1436-1446. N Engl J Med. 2023;388(2):117-127.

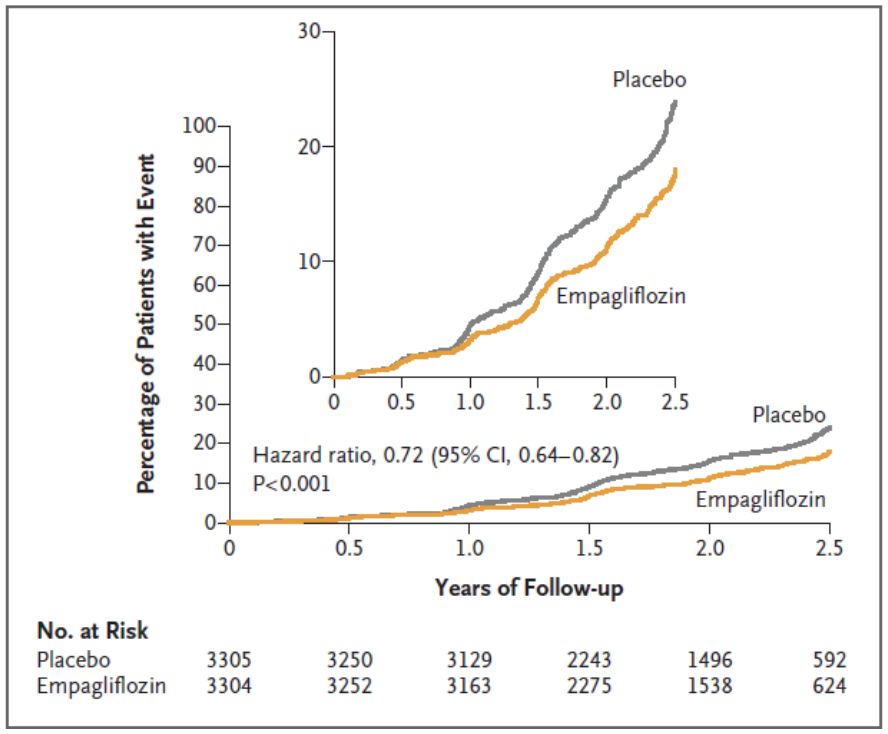
DAPA-CKD

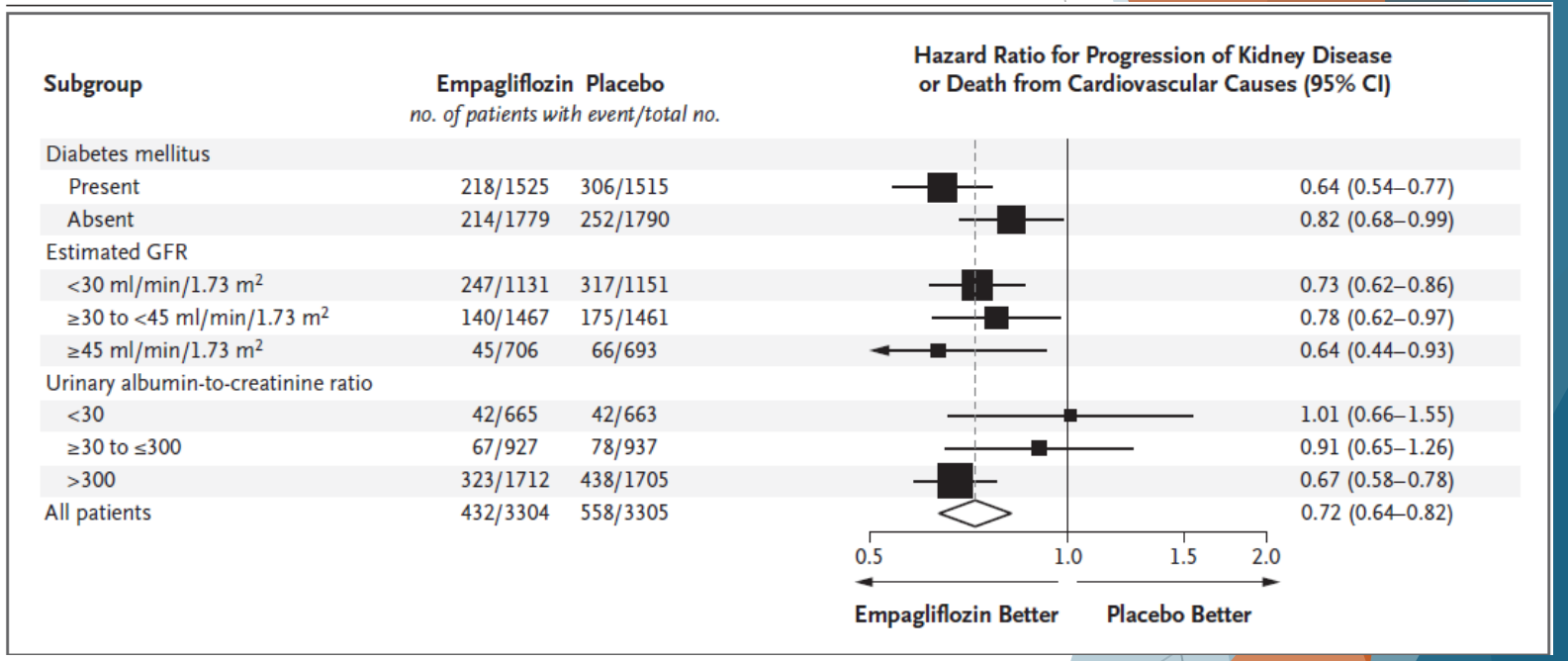




N Engl J Med. 2020;383(15):1436-1446.

EMPA-Kidney





N Engl J Med. 2023;388(2):117-127.

Trial	SCORED
Population	• Type 2 diabetes + A1c ≥7% • eGFR 25-60 mL/min/1.73m^2 • ≥ 1 major CV risk factor if ≥ 18 yo **OR** ≥ 2 minor CV risk factors if ≥ 55 yo
Intervention	Sotagliflozin 200-400 mg daily
Comparator	Placebo

Outcomes	• CV death, HF hospitalization, urgent HF visit: 400/100 pt years vs. 530/100 pt years (p<0.001)
	  ○ HF hospitalization/urgent HF visit: 245/100 pt years vs. 360/100 pt years (p<0.001)
	  ○ CV death: 155/100 pt years vs. 170/100 pt years (p=0.35)
	• UTI: 11.5 vs. 11.1% (p=0.45)
	• MGI: 2.4% vs. 0.9% (p<0.001)
	• Diarrhea: 8.5% vs. 6.0% (p><0.001)

N Engl J Med. 384(2):129-139.

Other Considerations

Adverse Effects

Proven

- UTI
- MGI
- Hypotension
- Volume depletion
- Weight loss

Debunked

- Bone fracture
- Acute kidney injury
- Ketoacidosis
- Amputations
- Hypoglycemia
- Symptomatic hypotension

Int J Cardiol. 2022;366:51-56. J Am Heart Assoc. 2024;13(3):e031805. *BMJ Open*. 2019;9(1):e022577.

Mycotic Genital and Urinary Tract Infections

- Low occurrence rate in clinical trials
- Occurrence most common in first 3-6 months of use
- Clinical trials
  - UTI: 1-10%
  - MGI: 1-2%
- 2022 meta-analysis of SGLT2 inhibitors in HF
  - MGI: 1.9% vs. 0.6% (OR 2.97 (2.02-4.36))
  - UTI: OR 1.18 (1.02-1.36)

Class effect?

Dose dependent?

Benefit >>> Risk

Int J Cardiol. 2022;366:51-56. J Card Fail. Published online April 25, 2024.

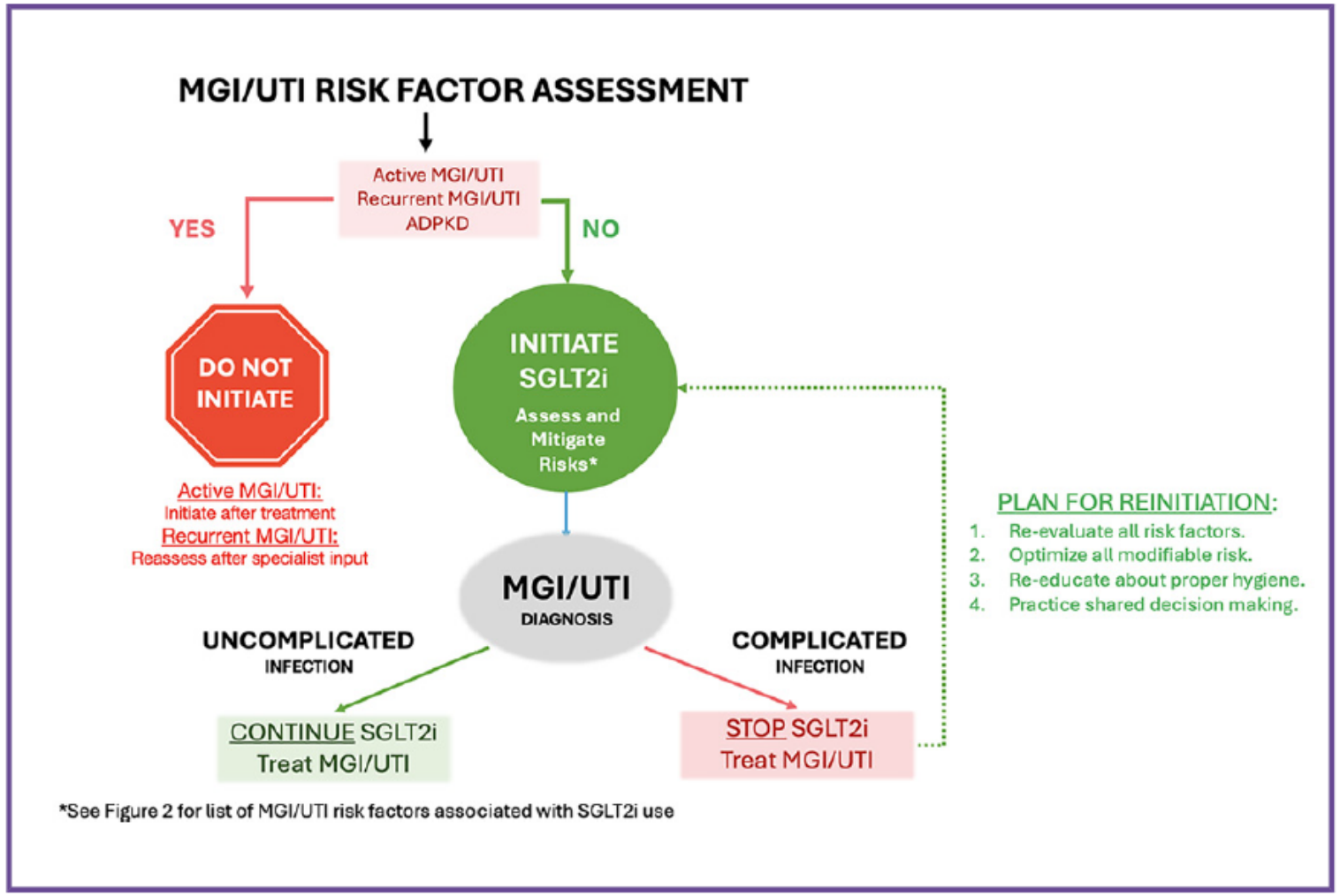
Considerations Before Initiation

History of MGI or UTI

Risk factors for MGI/UTI

- Female
- Age > 60
- Uncircumcised male
- Diabetes
- Prior MGI
- Lack of urinary hygiene
- Other urologic conditions

Counseling



Can consider changing agent if UTI/MGI occurs

MGI/UTI Initiation and Continuation

J Card Fail. Published online April 25, 2024.

Medication	eGFR (mL/min/1.73m^2)
Bexagliflozin	< 30
Canagliflozin	< 25-30
Dapagliflozin	<25
Empagliflozin	<20
Ertugliflozin	<45
Sotagliflozin	<15-25

eGFR Cut Point

http://online.lexi.com/

Guideline	Recommendation for SGLT2 Inhibitor	Rationale
American Diabetes Association Standards of Care (2024)	High risk of ASCVD, HF, or CKD	Reduce CVD and CKD risk
	HFrEF or HFpEF	Prevent HF hospitalization
	CKD (eGFR 20-60 mL/min/1.73m^2)	Prevent progression of CKD Reduce CV events Reduce HF hospitalization
	Established ASCVD	Reduce CV events
KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (2024)	Type 2 diabetes + eGFR ≥ 20	Prevent progression of CKD
	eGFR ≥ 20 + UACR ≥ 200 **OR** heart failure	Prevent progression of CKD Prevent HF hospitalization
	eGFR 20-45 + UACR <200	Prevent progression of CKD

Guideline Recommendations

Diabetes Care. 2024;47(Suppl 1):S158-S178.
Diabetes Care. 2024;47(Suppl 1):S179-S218.
Diabetes Care. 2024;47(Suppl 1):S219-S230.
Kidney Int. 2024;105(4S):S117-S314.

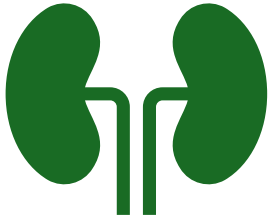
Additional Guideline Statements

ADA

Glycemic benefit reduced with eGFR < 45

eGFR < 30: consider GLP-1 RA

GLP-1 RA can be combined with SGLT2 inhibitor for additive CV event reduction and kidney event reduction



KDIGO

Can continue SGLT2 inhibitor if eGFR < 20 if tolerated

Hold SGLT2 inhibitor during prolonged fasting, surgery, or critical illness

Diabetes Care. 2024;47(Suppl 1):S158-S178.
Diabetes Care. 2024;47(Suppl 1):S219-S230.
Diabetes Care. 2024;47(Suppl 1):S179-S218.
Kidney Int. 2024;105(4S):S117-S314.

Guideline	Recommendation for SGLT2 Inhibitor	Rationale
AHA/ACC/HFSA Guideline for the Management of Heart Failure (2022)	HFrEF • Stage A if type 2 diabetes, ASCVD, or high risk of ASCVD • Stage C – all patients	• Prevent HF hospitalization • Reduce mortality and prevent HF hospitalization
	HFmrEF	Reduce mortality and prevent HF hospitalization
	HFpEF	Reduce mortality and **prevent HF hospitalization**

Guideline Recommendations

Circulation. 2022;145(18):e895-e1032.

Considerations

Generally well tolerated

Should be 1st line option for type 2 diabetes, heart failure, and CKD

Agent of choice depends on indication and patient access

Initiate early in patients with indications

Patient assistance programs available

Monitor ADRs and renal function

SGLT2 Inhibitors:
Expanding Therapeutic Niche in Clinical Practice

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