SGLT2 ANTAGONISTS:
A FOUNDATION OF HEART FAILURE TREATMENT FOR ALL?

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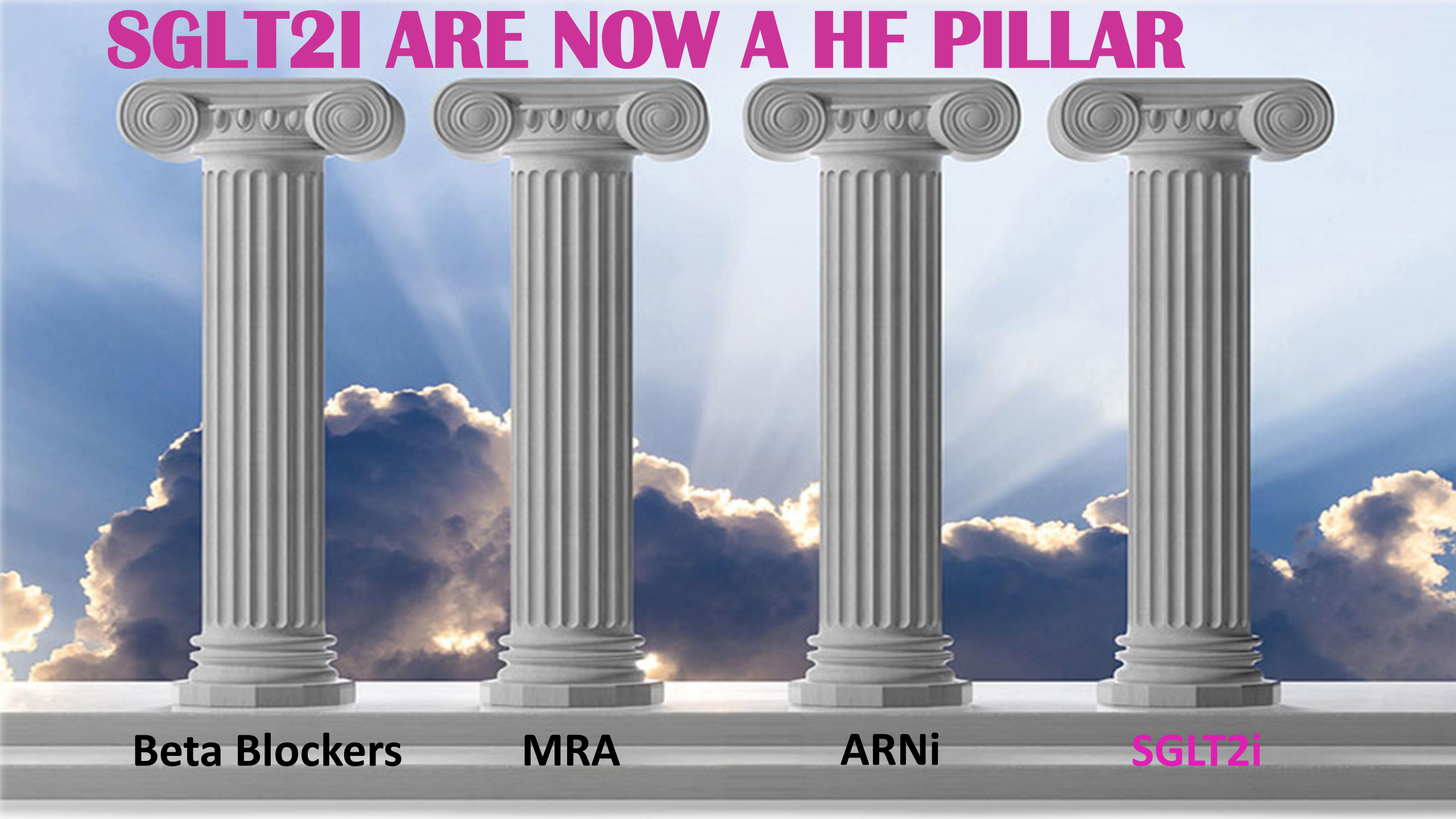
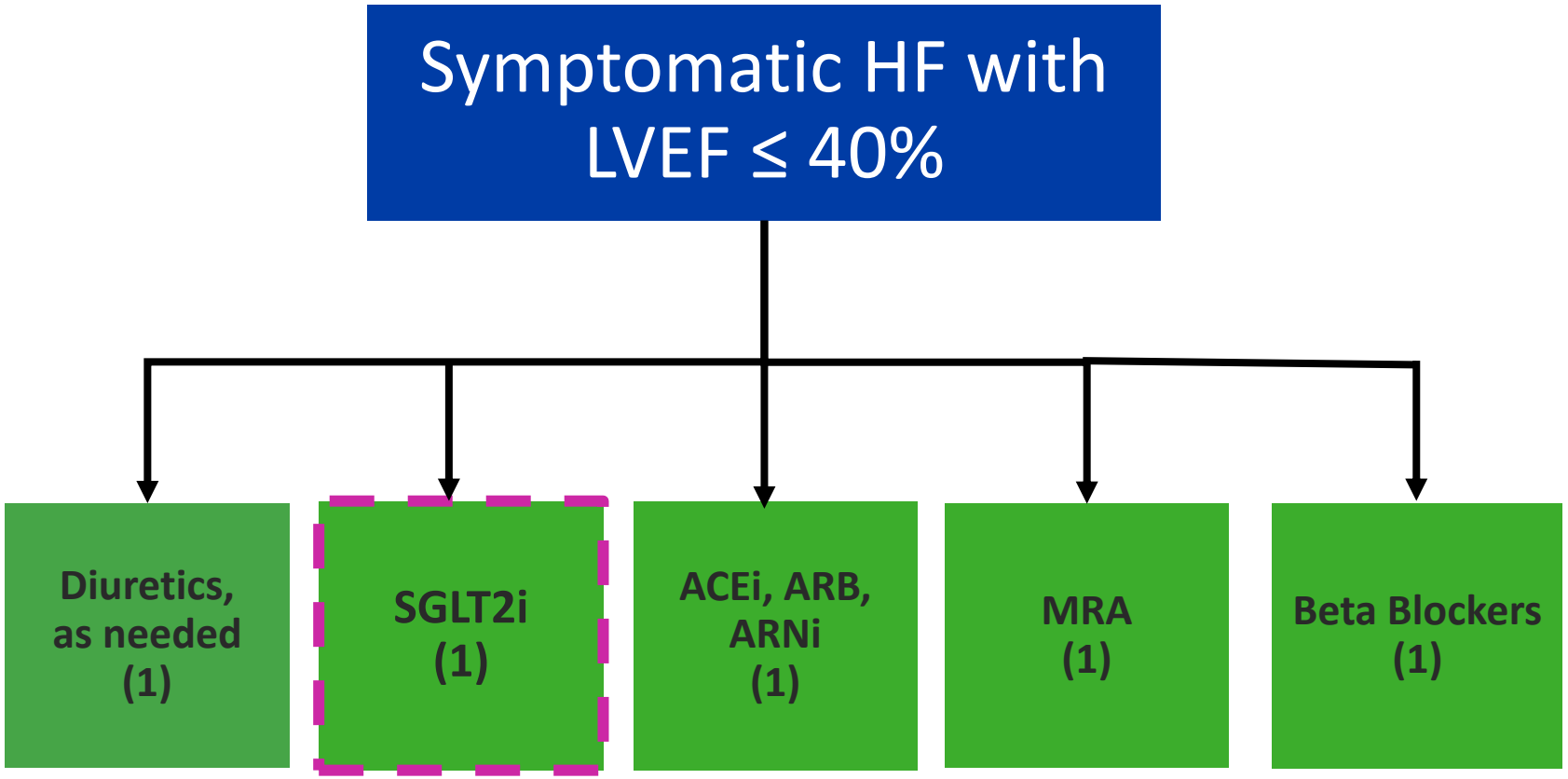
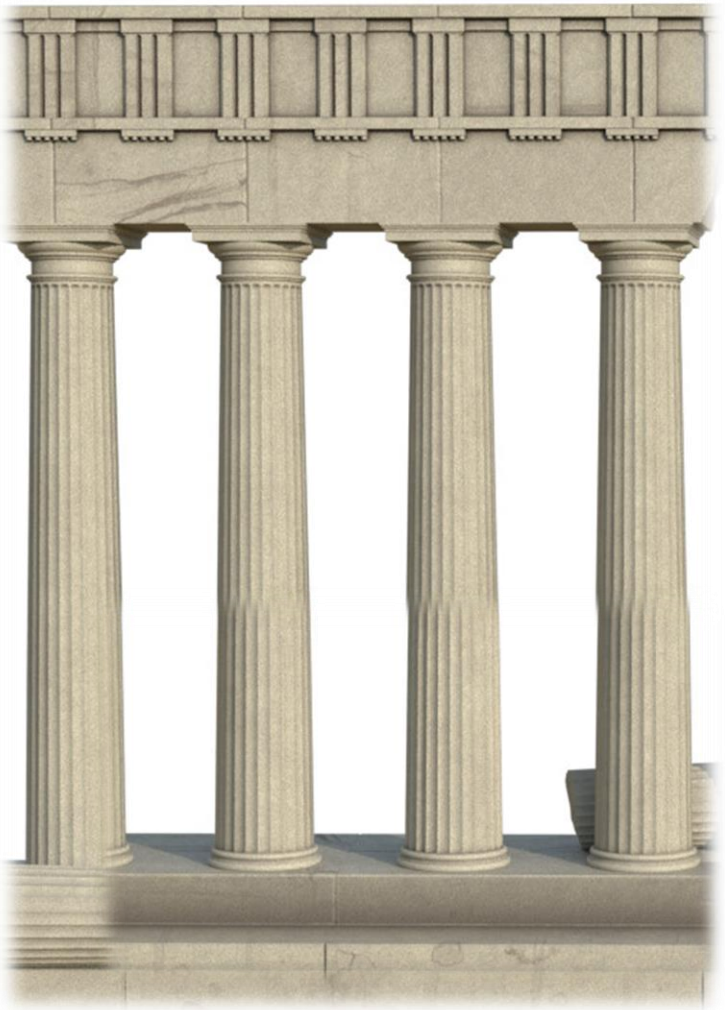
Cardiovascular Institute

SGLT2I ARE NOW A HF PILLAR



TREATMENT FOR HFrEF





TREATMENT FOR HFMREF

HFimpEF

GDMT should be continued, even in patients who may become asymptomatic. (1)

Symptomatic HF with LVEF 41-49%

- **Diuretics, as needed (1)**
- **SGLT2i (2a)**
- **ACEi, ARB, ARNi (2b)**
- **MRA (2b)**
- **Evidence-based beta blockers for HFrEF (2b)**

There are no specific RCTs for patients with HFmrEF.

TREATMENT FOR HFpEF

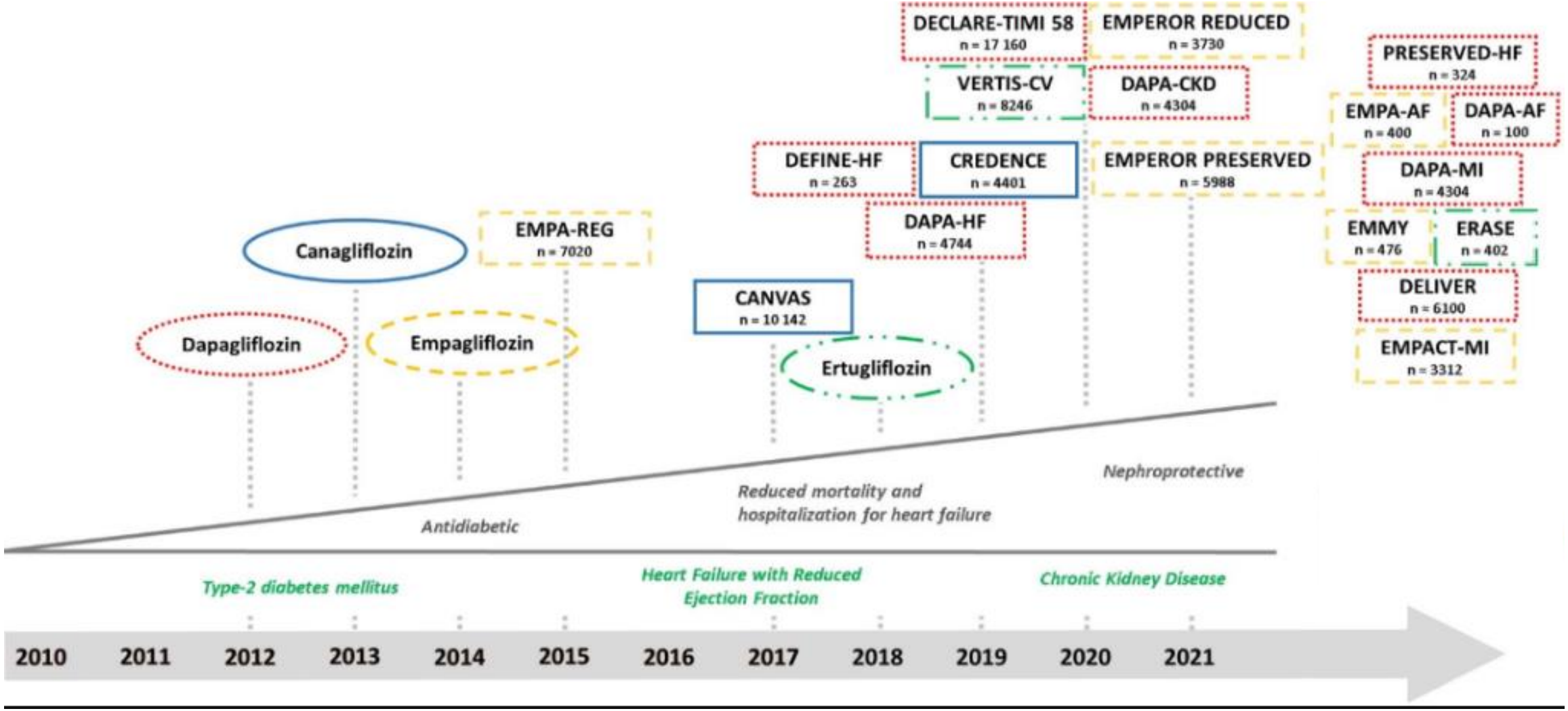
Use of nitrates
Class 3 – NO BENEFIT

Symptomatic HF with LVEF ≥ 50%

- **Diuretics, as needed (1)**
- **SGLT2i (2a)**
- **ARB * (2b)**
- **ARNi* (2b)**
- **MRA (2b)**

*Greater benefit in patients with LVEF closer to 50%

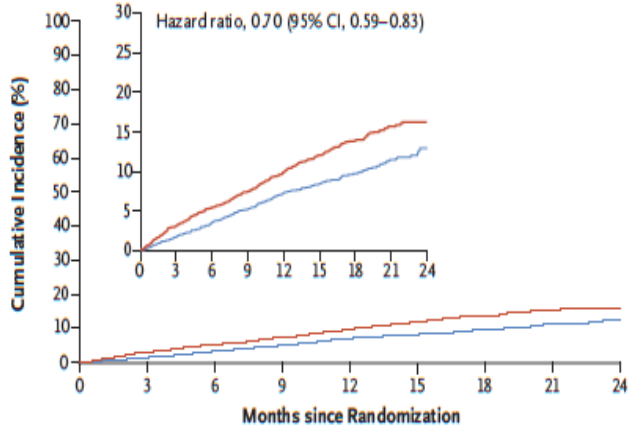
THE EVOLUTION OF SGLT1 AND 2 INHIBITORS



Kolesnik, et al. *Int. J. Mol. Sci.* **2022**, *23*, 1678

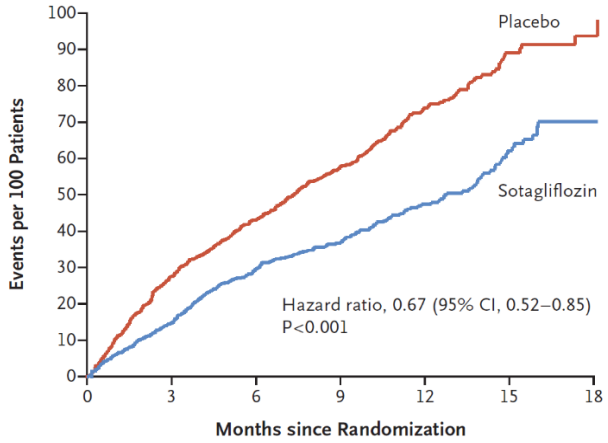
A REDUCTION IN HF HOSPITALIZATION (NOT CV DEATH)

DAPA- HF 2019



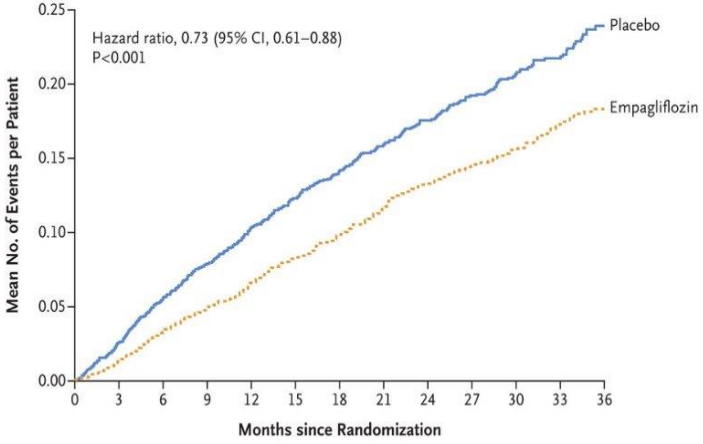
No. at Risk									
Placebo	2371	2264	2168	2082	1924	1483	1101	596	212
Dapagliflozin	2373	2306	2223	2153	2007	1563	1147	613	210

SOLOIST 2020



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

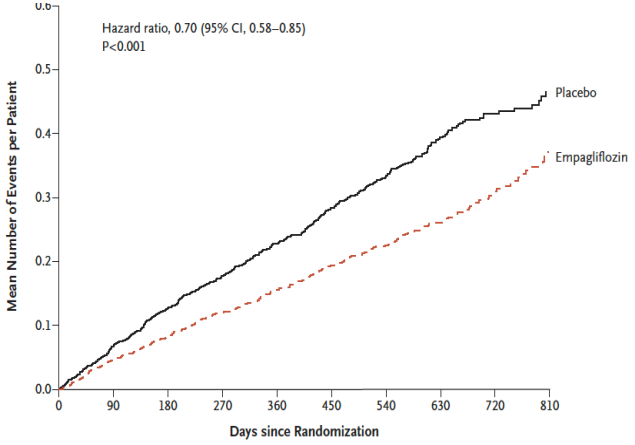
EMPEROR- Preserved 2021



No. at Risk													
Placebo	2991	2945	2901	2855	2816	2618	2258	1998	1695	1414	1061	747	448
Empagliflozin	2997	2962	2913	2869	2817	2604	2247	1977	1684	1429	1081	765	446

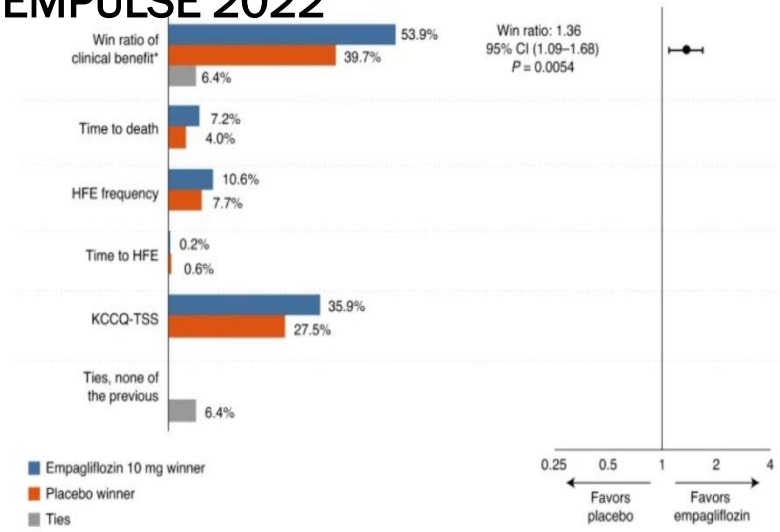
HFrEF — *Effects seen as early as 28 days & in hospital* — *HFpEF*

EMPEROR- Reduced 2020

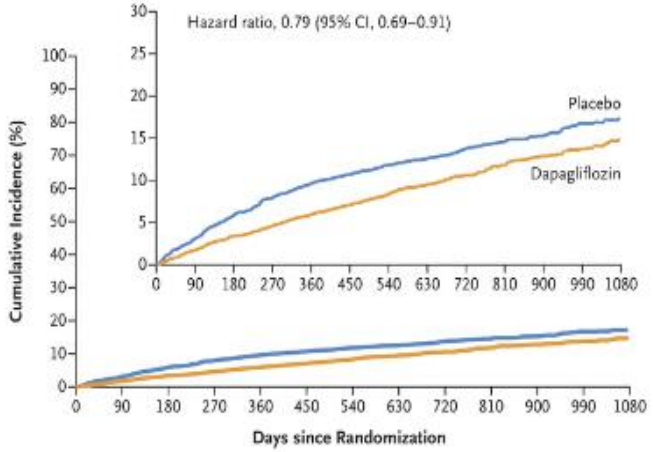


No. at Risk										
Placebo	1867	1820	1762	1526	1285	1017	732	497	275	135
Empagliflozin	1863	1826	1768	1532	1283	1008	732	495	272	118

EMPULSE 2022



DELIVER 2022

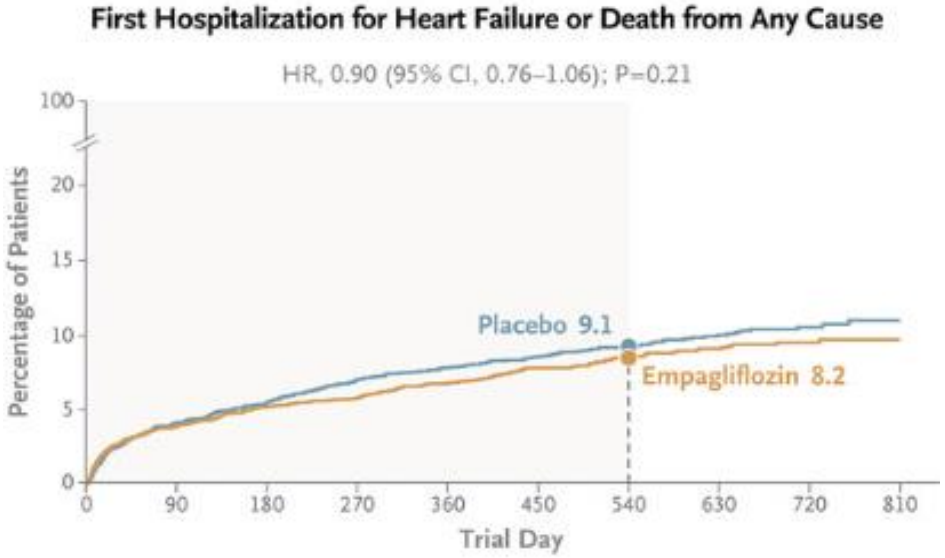


No. at Risk													
Placebo	3132	3007	2896	2799	2710	2608	2318	2080	1923	1554	1140	772	383
Dapagliflozin	3131	3040	2949	2885	2807	2716	2401	2147	1982	1603	1181	801	389

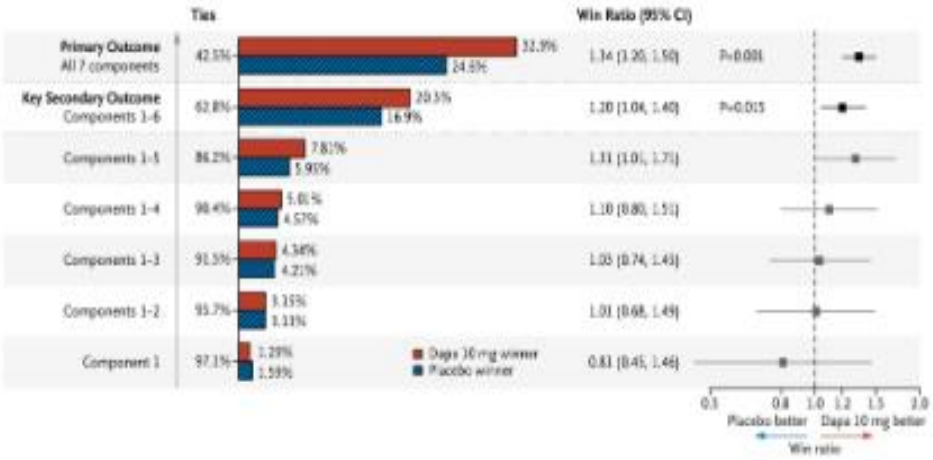
EXPANDED INDICATIONS & NEW HORIZONS

POST MI

EMPACT-MI, 2024	DAPA-MI, 2024
STEMI or NSTEMI, LVEF < 45% or HF symptoms	STEMI/NSTEMI/Q wave MI with LV dysfunction
Within 14 days	Within 10 day
INCLUDES pts with ≥ 1 enrichment factor: - DM1 and DM2, eGFR < 60, elevated BNP/uric acid/RVSP, CAD, PAD	EXLCUDES - DM1/2 and EGFR < 20
Mean age 63, F 24%, STEMI 75%, F/U 17.9 mths	Mean age 63, F 20%, STEMI 72%, F/U 24 mths



Composite HFH and all-cause mortality



All-cause mortality: 2.0% vs. 1.7% (p > 0.05)

TRANSTHYRETIN AMYLOID

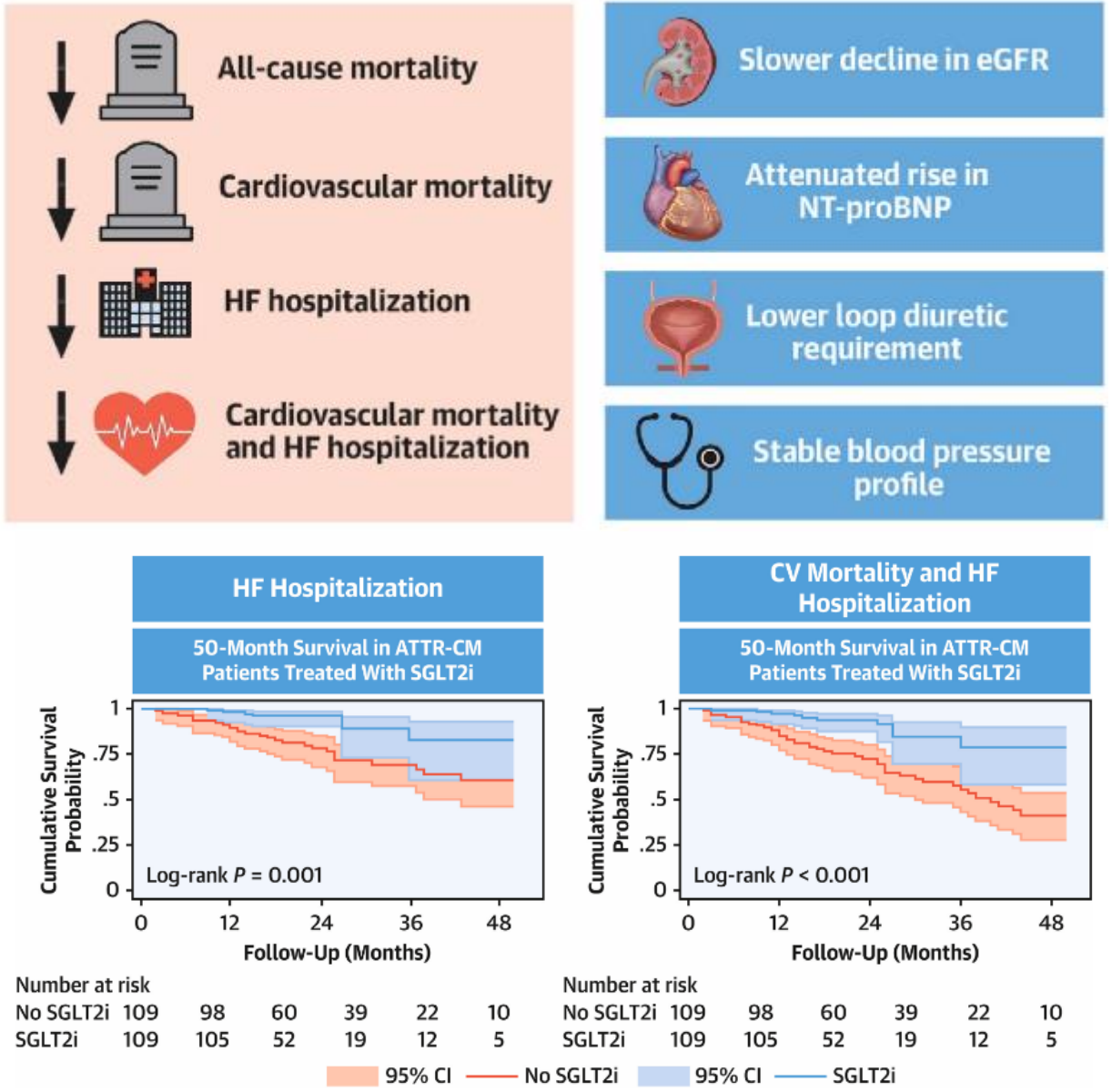
Porcari et al, 2024

2356 propensity matched patients with TTR amyloid

- Dapagliflozin (n = 148; 67.3%)
- Empagliflozin (n = 71; 32.3%)
- Canagliflozin (n = 1; 0.4%)

All patients were prescribed 100% of the target dose

Safe treatment: 4.5% discontinuation rate over 28months



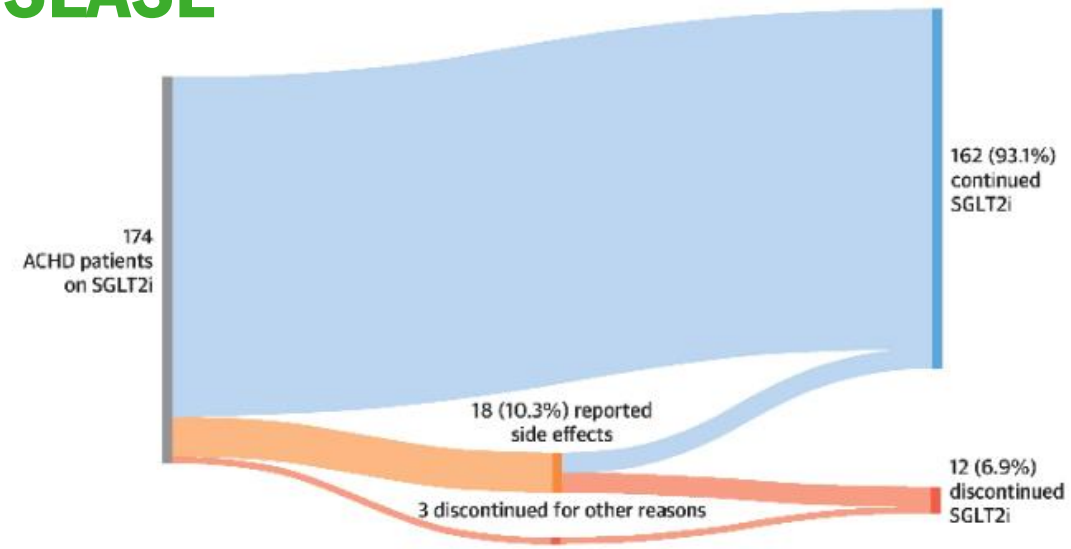
Porcari et al. *JACC* 2024; 83:2411-2422.

ADULTS WITH CONGENITAL HEART DISEASE

- Retrospective study at 4 European ACHD centers
- 174 patients, mean age 48.7, 41% Females
- Ten (5.7%) patients had mild, 75 (43.1%) moderate, and 89 (51.1%) severe CHD.

- Indication for starting SGLTi2i:
  - CHF 93.1%, DM 26.3%, CKD 0.6%.
- Follow-up 7.7 months

- Significant reduction in HFH was observed from 6 months before to 6 months after starting SGLT2i (relative rate = 0.30; 95% CI: 0.14-0.62; *P* = 0.001).



Neijenhuis RML., et al. J Am Coll Cardiol. 2024;83(15):1403-1414.

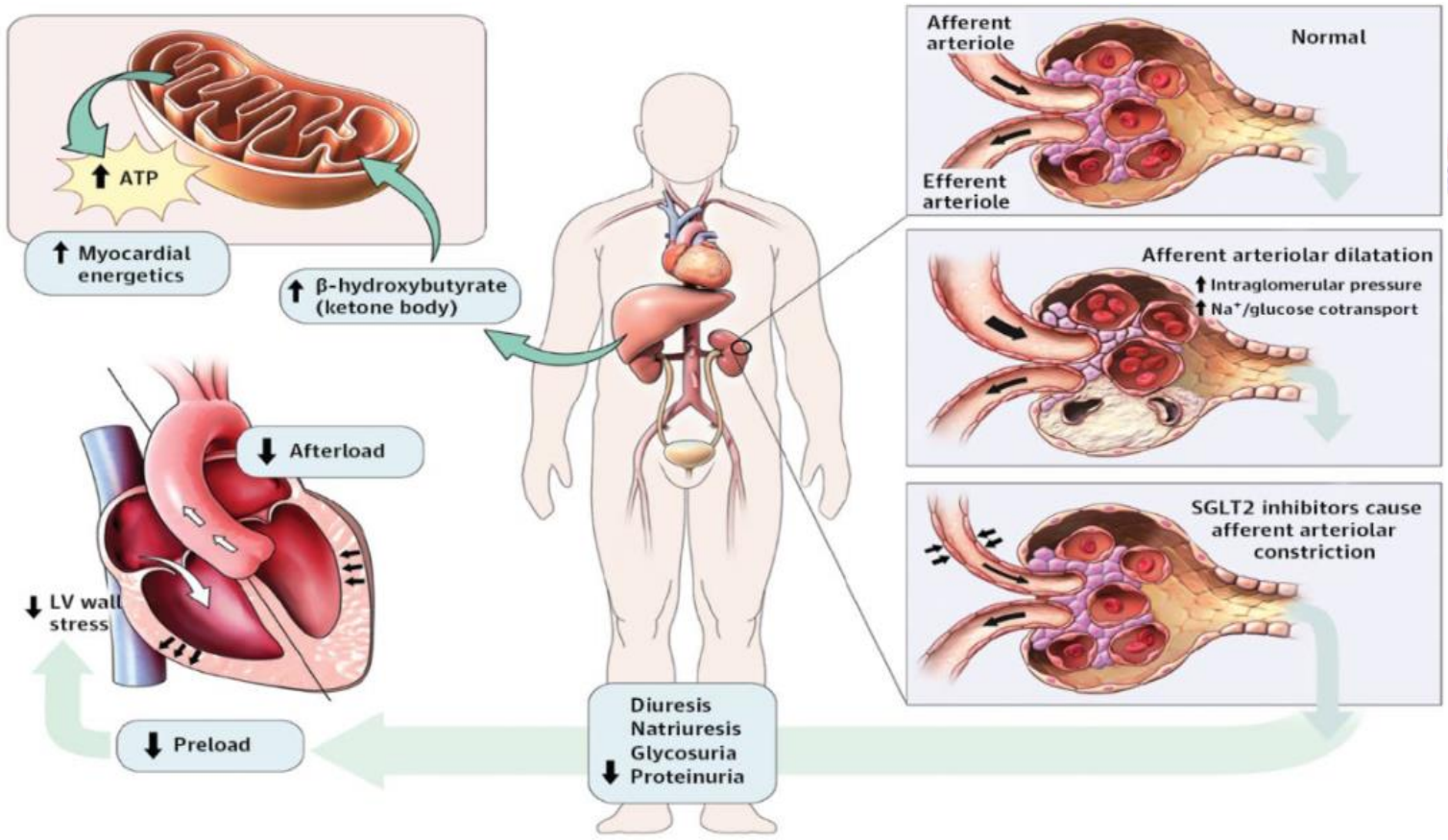
HYPERTROPHIC CARDIOMYOPATHY

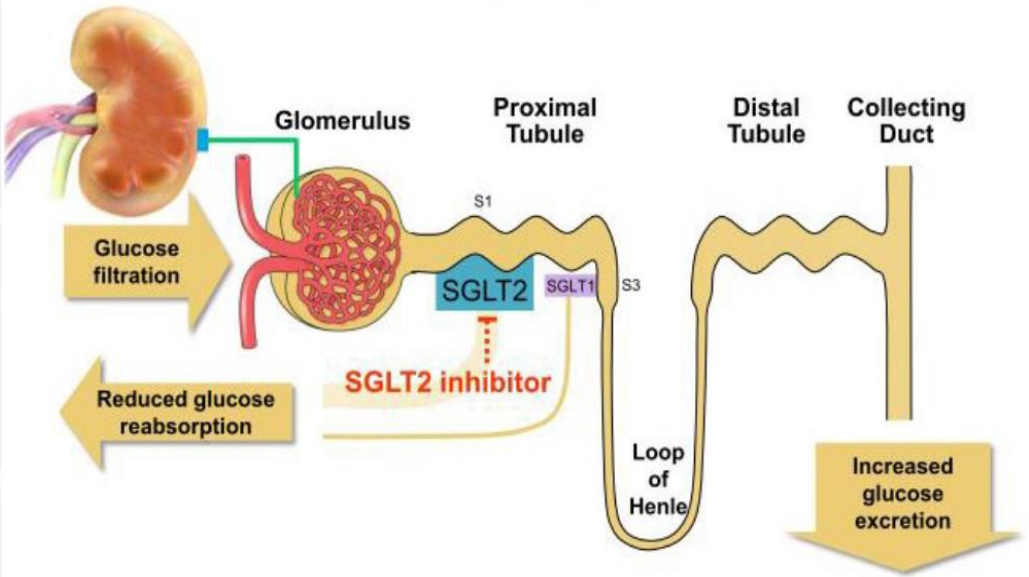
SONATA- HCM Trial

Upcoming study, to be enrolling at Northwell Health…

Effect of sotagliflozin (dual SLGT1 and 2 inhibitor) in symptomatic and non-symptomatic hypertrophic cardiomyopathy patients.

MECHANISM OF ACTION

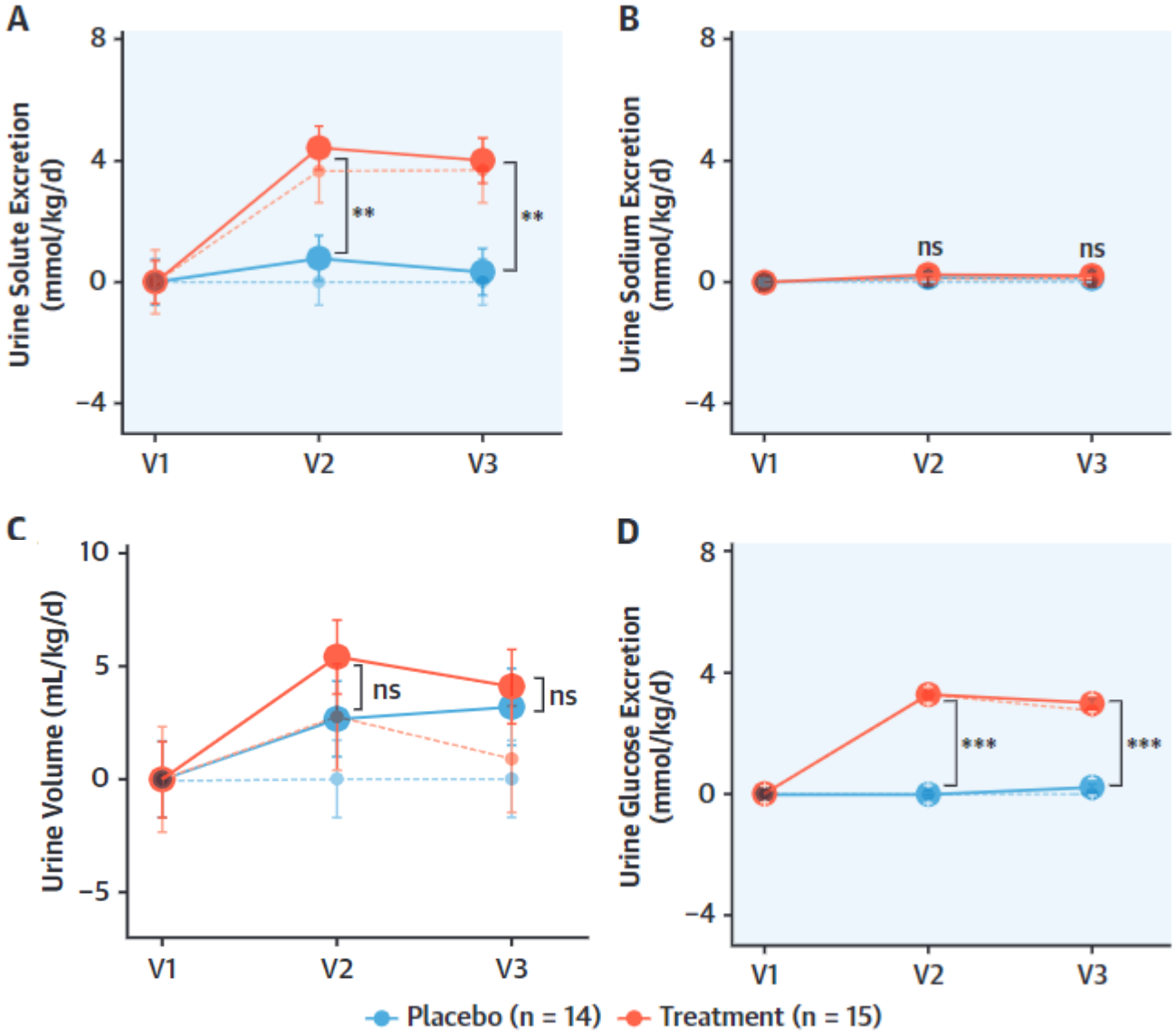




Work in the proximal tubule, responsible for 90% (SGLT2) and 10% (SGLT1) of glucose reabsorption.

In non- DM pts, induce a glucose excretion of 40-80g/d. This is greater in DM2 patients.

NEITHER A DIURETIC OR A NATURETIC… (MILTON PACKER, JACC, 2024)



DAPA- SHUTTLE, 2024

Water conservation over osmotic diuresis

- Current theory ignores the distal nephron!
- Expected mechanism opposed by ADH
- Decrease in free H2O clearance @ 24 hrs

Starvation Mimicry

Upregulates Autophagy

Cardiomyocte Housekeeping

Marton A, et al. J Am Coll Cardiol. 2024;83(15):1386–1398.

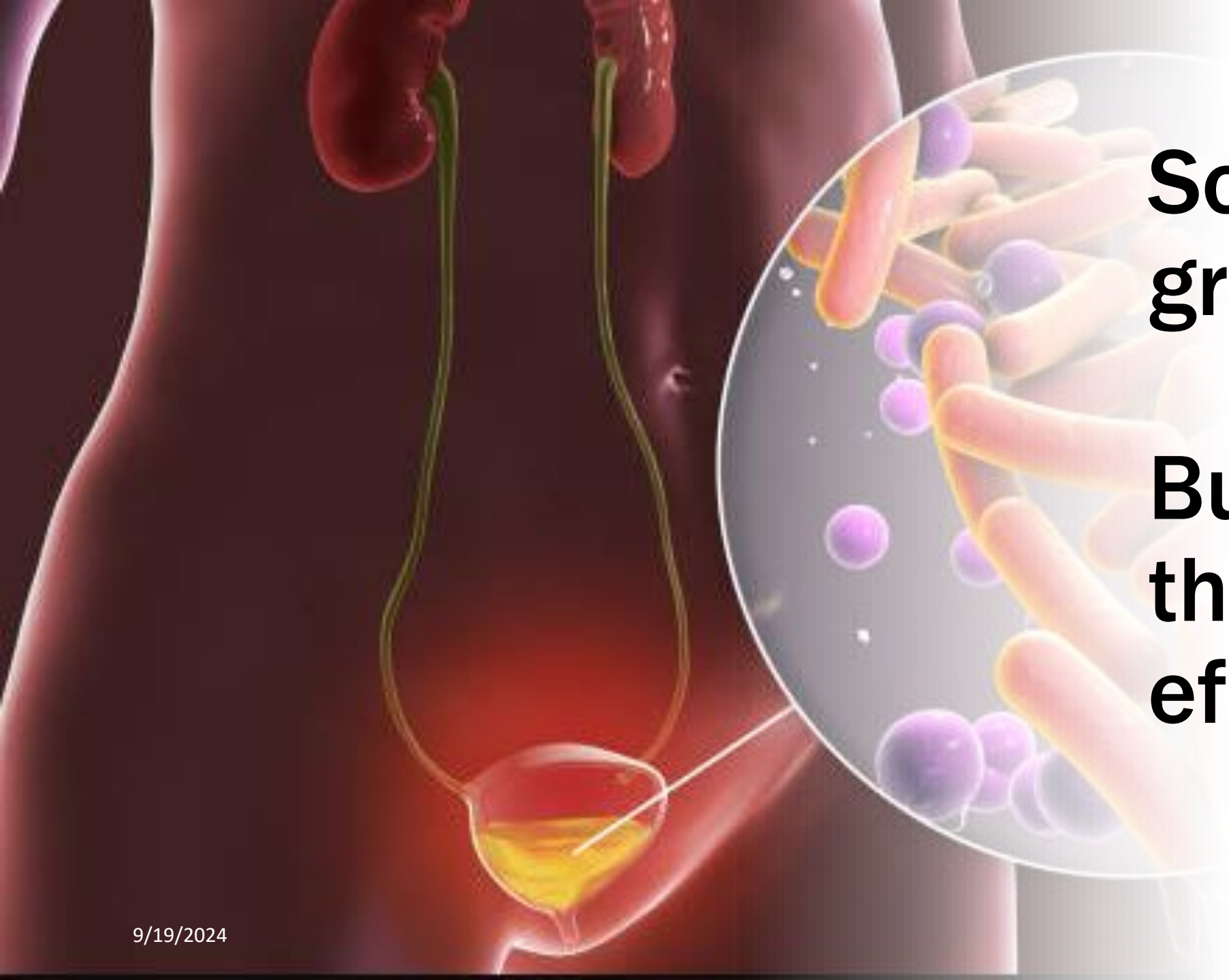
SGLT2I DOSING

DRUG	DOSE	RENAL CUT-OFF
Dapagliflozin (Farxiga)	10mg once daily	eGFR ≥ 30 mL/min/1.73 m2
Empagliflozin (Jardiance)	10mg once daily	eGFR ≥ 30 mL/min/1.73 m2
Sotagliflozin (Inpefa)	200-400mg once daily	eGFR ≥ 25 mL/min/1.73 m2

Important notes:

DAPA-CKD trial: Dapagliflozin 10 mg daily was utilized in patients with an eGFR down to 25 mL/min/1.73 m2 which resulted in superior renal outcomes than placebo.

No data for HD patients.



Sounds great….

But what are the side effects?

ADVERSE EFFECTS

- Genitourinary (GU) infections are thought to be a result of pharmacologically induced glucosuria

- In vitro studies – addition of glucose to urine samples has been shown to promote the growth of E coli and Candida Albicans

Two FDA Warnings

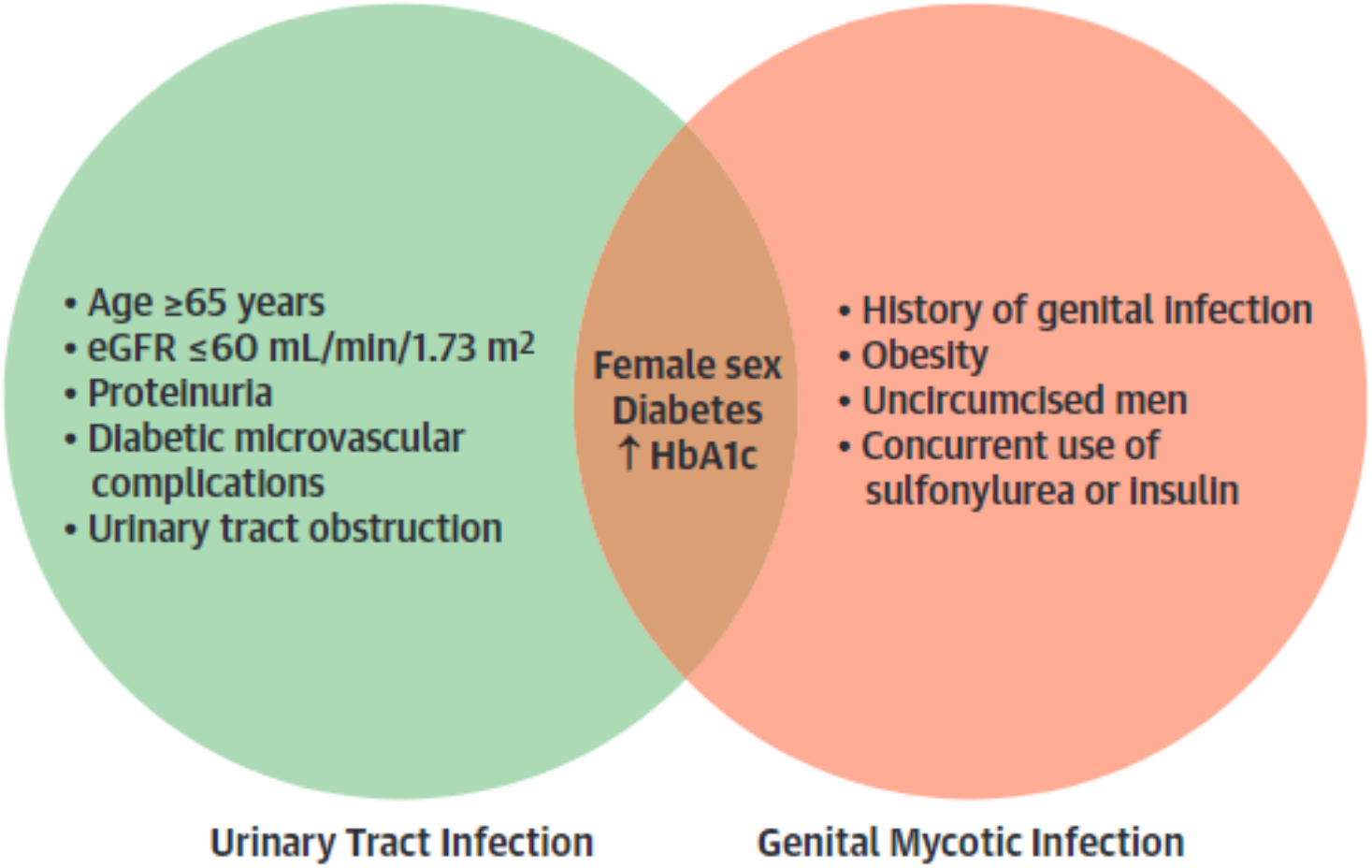
- **2015 - increased risk of serious UTI** – 19 cases of life- threatening urosepsis and pyelonephritis
- **2018 – increased risk of necrotizing fasciitis of the perineum (Fournier's gangrene)** - 12 cases

INCIDENCE OF GU INFECTION IN SGLT2I TRIALS

- Incidence of UTIs varies significantly based on variable reporting in trials
  - Different definitions of UTIs
  - UTI or pylenonephritis at the primary cause of hospitalization and UTI with urosepsis (< 2% in all trials)

- No significant difference vs. placebo in all but 2 trials
- EMPEROR – PRESERVED – empagliflozin 9.9 vs 8.1 % *(Anker et al 2021)*
- VERTIS CV – ertugliflozin tx from DM2 patients with vascular disease (12 vs. 10.2%). *Cannon et al 2020*

RISK FACTORS FOR SGLT2I ASSOCIATED GU INFECTIONS



There is no current evidence to suggest differences in infections across different SGLT2is.

CLINICAL IMPLICATIONS

Should risk factors for GU infections prevent prescription of SGLT2i?

No, a history of uncomplicated GU is not a C/I. Caution in patients with recurring infection. Underlying etiology must be investigated and if resolved ok to use.

Should I get a UA prior to prescribing SGT2i?

No, asymptomatic bacteriuria is not a C/I.

CLINICAL IMPLICATIONS

Should I discontinue an SGLT2i in the setting of a GU infection?

No! In contrast to euglycemic DKA, the FDA label does not advise routine discontinuation of SGLT2i in the setting of mild – moderate and clinically stable GU infections. This was not done in SGLt2i trials. Discontinuation may be warranted in the setting of life-threatening infections.

CLINICAL IMPLICATIONS

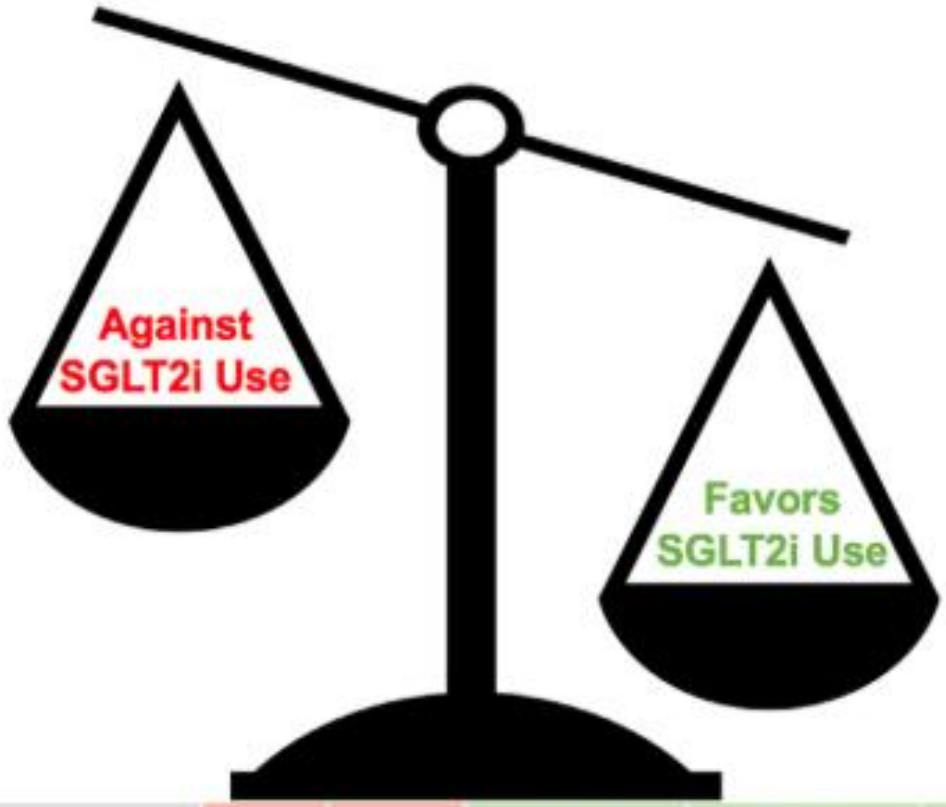
RISK vs. BENEFIT of Withdrawal

- Genital Myocitic infections result in a withdrawal rate of 32% over 1 year. *(McGovern et al 2020)*

- The withdrawal rate following UTI in routine practice is unknown.

- As early as 30 days post withdrawal there was an increase in CV death and HFH (HR 1.75) as seen in EMPEROR – PRESERVED.

CLINICAL IMPLICATIONS



	MGI	UTI	HF admission	CV mortality	Total Mortality
Absolute Risk Reduction (%)	-0.3	-0.2	5.6	1.1	1.3
NNT-H/NNT-B	356	557	18	93	76

Duvalyan et al. SGLT2is and Mycotic Genital or Urinary Tract Infections in Heart Failure. J Card Fail. 2024 Apr 25:S1071-9164(24)00145-3.

CLINICAL IMPLICATIONS

Should SGLT2i be re-initiated post GU infections?

Yes, however no recommend exists as to how long after infection these can be resumed.

Rate of recurrence is highest in the first 2 weeks post re-initiation.

Recurrent UTI occurred in 28% of patients with risk factors including CAD and eGFR < 45.

TAKE HOME POINTS

- SGLT2i are now an established pillar of care in heart failure.
- Expanded areas of use now include: Post MI, TTR amyloid, ACHD and possibly HCM.
- Shifting mechanism of action paradigm…neither a diuretic or a naturetic
- Risk of side effects higher in women and diabetic patients (with higher HBA1C)
- Withdrawal of SGLT2i has shown a worse HFH and CV death rate in as early as 30 days post withdrawal. Stop only in setting of severe GU infections.

THANK YOU

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