New Drugs (SGLT2 Inhibitors) for Heart Failure Management: Where Do They Fit In?

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Faculty/Presenter Disclosure

- **Faculty:** Ricky Turgeon
- **Relationships with commercial interests:**
  - **Grants/Research Support:** Vancouver Coastal Health Research Institute-Research Challenge (work unrelated to this presentation).
  - **Speakers Bureau/Honoraria:** None.
  - **Consulting Fees:** None.
  - **Other:** None.

Mitigating Potential Bias

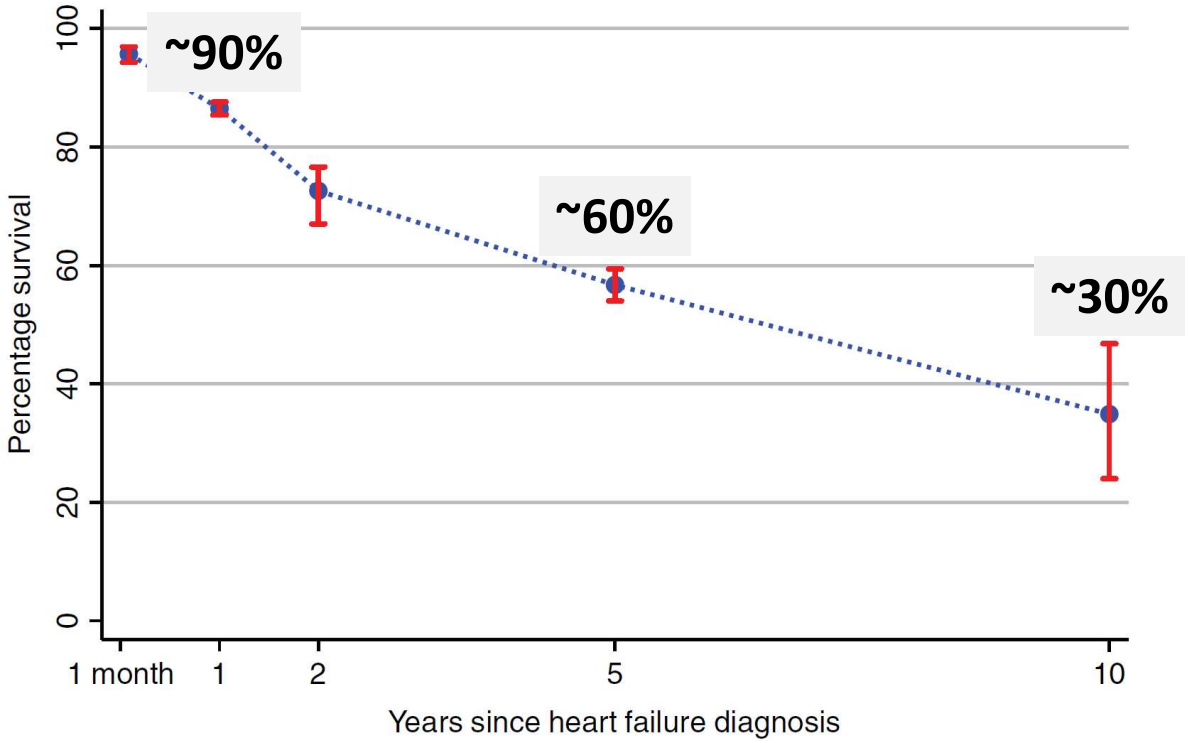
- I will limit my discussion to pharmacotherapy that is supported by high-quality randomized controlled trials and meta-analyses
- I will explicitly state when use of therapy is considered off-label

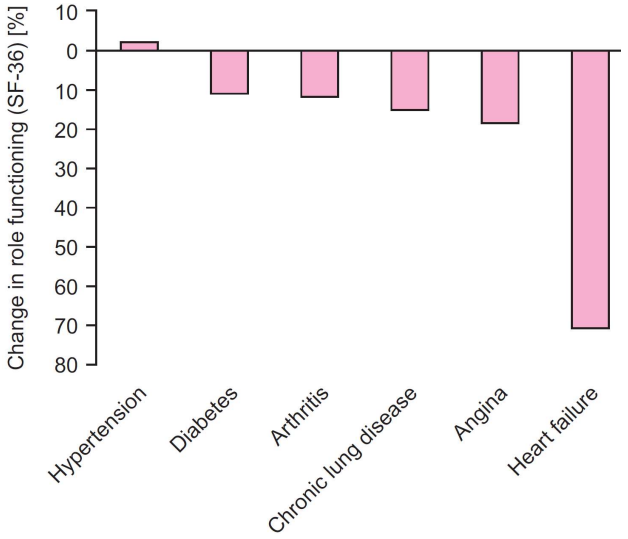
Summary: SGLT2 inhibitors for heart failure

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) in heart failure with reduced ejection fraction (HFrEF):

1. ↓ death & HF hospitalizations
2. Improve health-related quality of life (QoL)
3. Acutely ↓ eGFR, but improve long-term kidney outcomes
4. Have similar efficacy/safety:
   - With or without T2DM
   - Regardless of other HF meds
   - With “low BP”
   - During/soon after acute HF

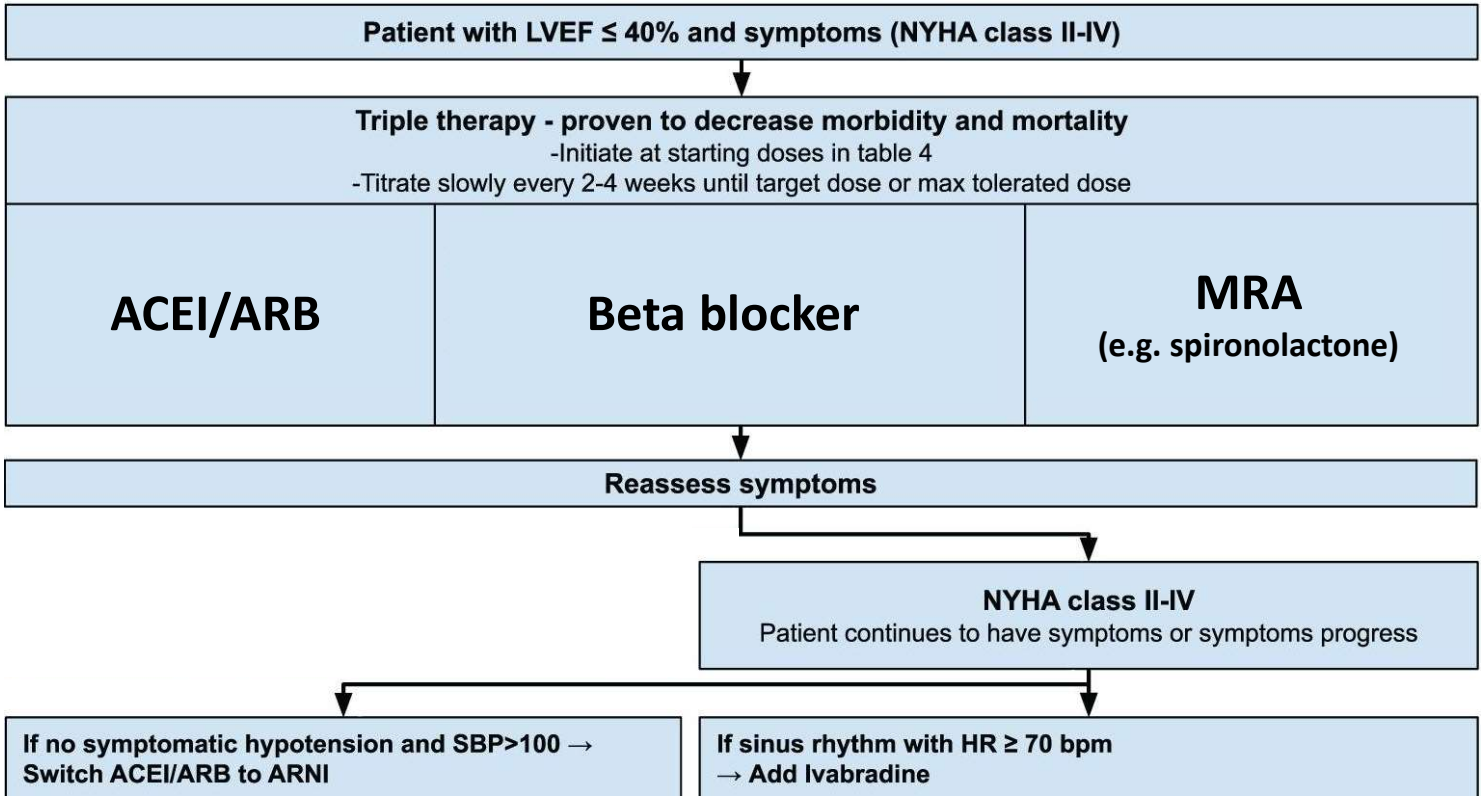
HF reduces quantity & quality of life





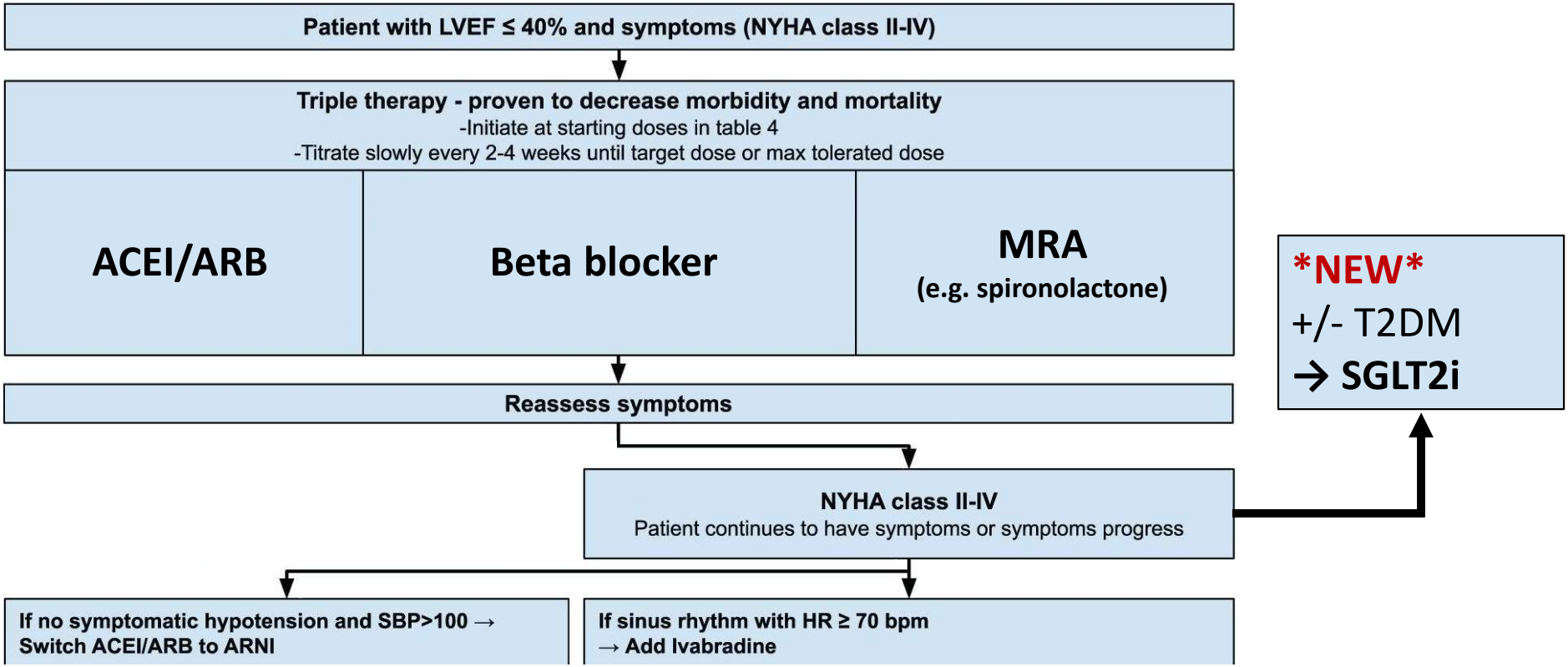
Eur J Heart Fail 2019;21:1306-25
Pharmacoeconomics 1999;16:247-71

Canadian HF guidelines 2017



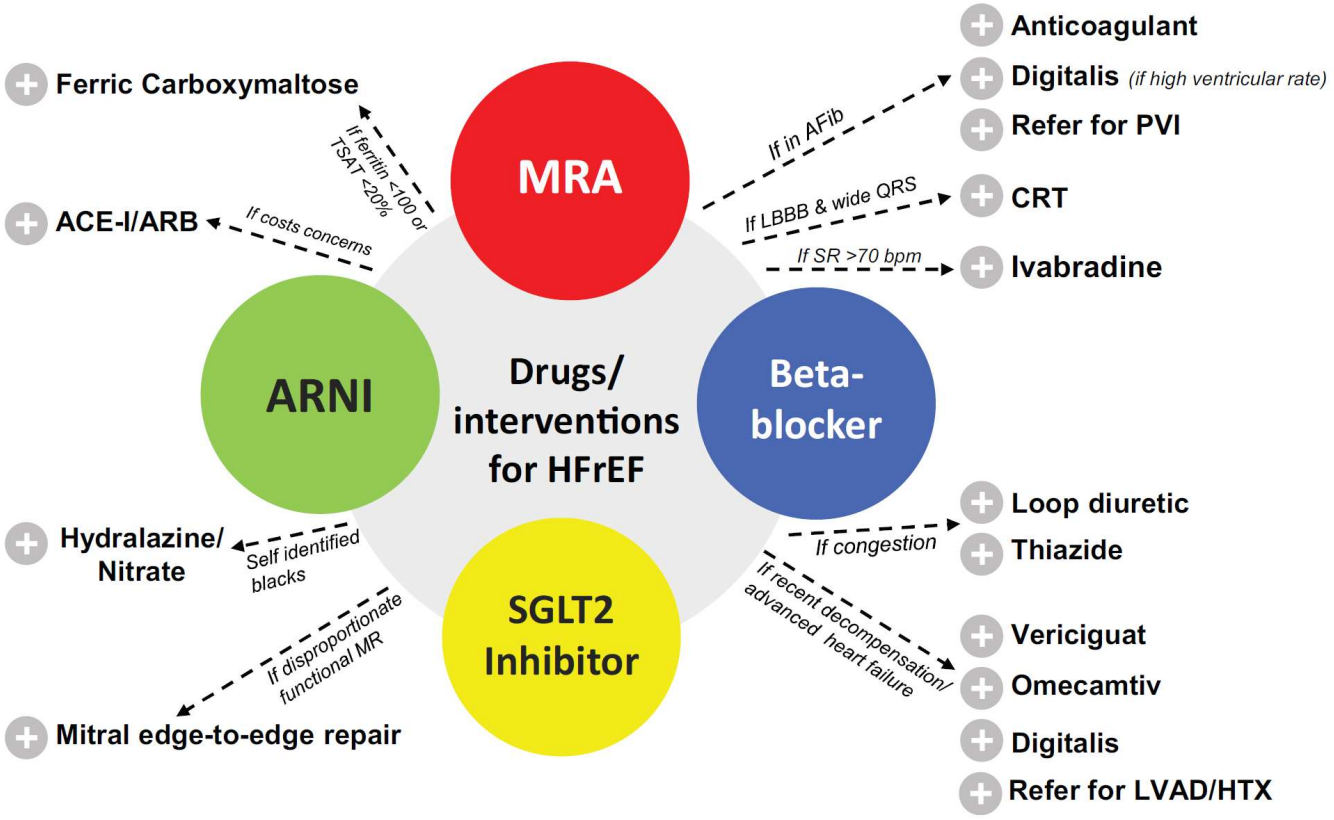
Can J Cardiol 2017;33:1342-433 Can Pharm J 2019;152:301-16

Canadian HF guidelines 2020



Can J Cardiol 2017;33:1342-433 Can Pharm J 2019;152:301-16 Can J Cardiol 2020;36:159-69

HFrEF treatment in 2021



https://doi.org/10.1093/eurheartj/ehaa1012

How did a diabetes drug become a HF drug?

All “thanks to” rosiglitazone

1999: Rosiglitazone approved based on glucose↓

2007: Rosiglitazone ↑ cardiovascular (CV) outcomes in meta-analyses

2008: FDA changed industry guidance

- Require large RCTs to prove new T2DM drugs don’t increase CV outcomes vs placebo

2015: EMPA-REG trial

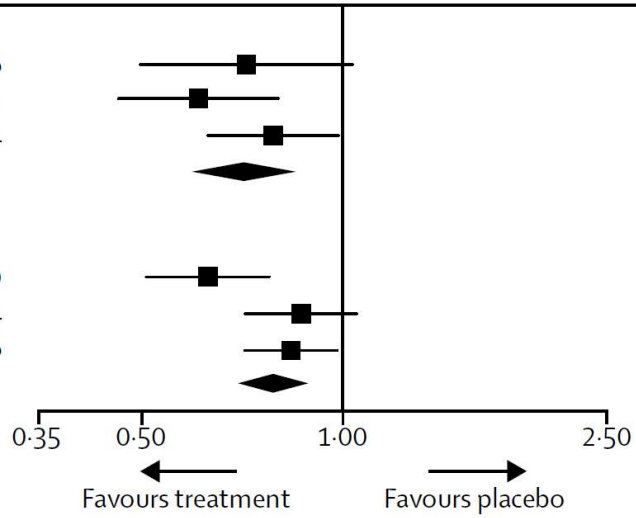
- Empagliflozin ↓ CV outcomes (surprisingly, ↓ HF hospitalizations)

≥2017: Other RCTs showing SGLT2i ↓ HF hospitalizations in T2DM

JACC 2018;72:1845-55

SGLT2i reduce HF hospitalization in T2DM

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo			
Patients with history of heart failure								
EMPA-REG OUTCOME	462	244	124	63·6	85·5	23·6		0·72 (0·50–1·04)
CANVAS Program	803	658	203	35·4	56·8	34·1		0·61 (0·46–0·80)
DECLARE-TIMI 58	852	872	314	45·1	55·5	42·4		0·79 (0·63–0·99)
Fixed effects model for history of heart failure (p<0·0001)								**0·71 (0·61–0·84)**
Patients with no history of heart failure								
EMPA-REG OUTCOME	4225	2089	339	15·5	24·9	30·0		0·63 (0·51–0·78)
CANVAS Program	4992	3689	449	13·6	15·2	32·4		0·87 (0·72–1·06)
DECLARE-TIMI 58	7730	7706	599	8·9	10·5	37·6		0·84 (0·72–0·99)
Fixed effects model for no history of heart failure (p<0·0001)								**0·79 (0·71–0·88)**



… What about in HF patients +/- T2DM?

Lancet 2019;393:31-9

DAPA-HF

D	**RCT with low overall risk of bias** (allocation concealed, all blinded, loss to follow-up <0.8%, intention-to-treat analysis)
P **n=4744**	• **Symptomatic HFrEF** (HF with NYHA class 2-4, ejection fraction ≤40%) • Elevated NT-proBNP • +/- T2DM • Max-tolerated background HFrEF therapy • eGFR ≥30 mL/min/1.73m^2 & systolic BP ≥95 mm Hg
I	**Dapagliflozin** 10 mg once daily
C	Matching **placebo**
O	Primary: Cardiovascular death, HF hospitalization, or urgent visit for HF resulting in IV therapy

NEJM 2019;381:1995-2008

EMPEROR-Reduced

D	**RCT with low overall risk of bias** (allocation concealed, all blinded, loss to follow-up 1.1%, intention-to-treat analysis)
P **n=3730**	• **Symptomatic HFrEF** (HF with NYHA class 2-4, ejection fraction ≤40%) • Elevated NT-proBNP • +/- T2DM • Max-tolerated background HFrEF therapy • eGFR ≥20 mL/min/1.73m^2 & systolic BP ≥100 mm Hg
I	**Empagliflozin** 10 mg once daily
C	Matching **placebo**
O	Primary: Cardiovascular death or HF hospitalization

NEJM 2020;383:1413-24

DAPA-HF & EMPEROR-Reduced: Closer look at study population

	DAPA-HF	EMPEROR-Reduced
Demographics	66 y, male (77%)	67 y, male (76%)
NYHA class	**2 (68%)**, 3 (32%), 4 (<1%)	**2 (75%)**, 3 (24%), 4 (0.5%)
LVEF	**31%**	**27%**
NT-proBNP	**~1400**	**~1900**
T2DM	46%	50%
SBP	122	122
eGFR	66	62
ACEI/ARB/ARNI (ARNI)	94% (**11%**)	89% (**19%**)
Beta-blocker	96%	95%
MRA	71%	71%

NEJM 2019;381:1995-2008
NEJM 2020;383:1413-24

DAPA-HF & EMPEROR-Reduced: Safety outcomes

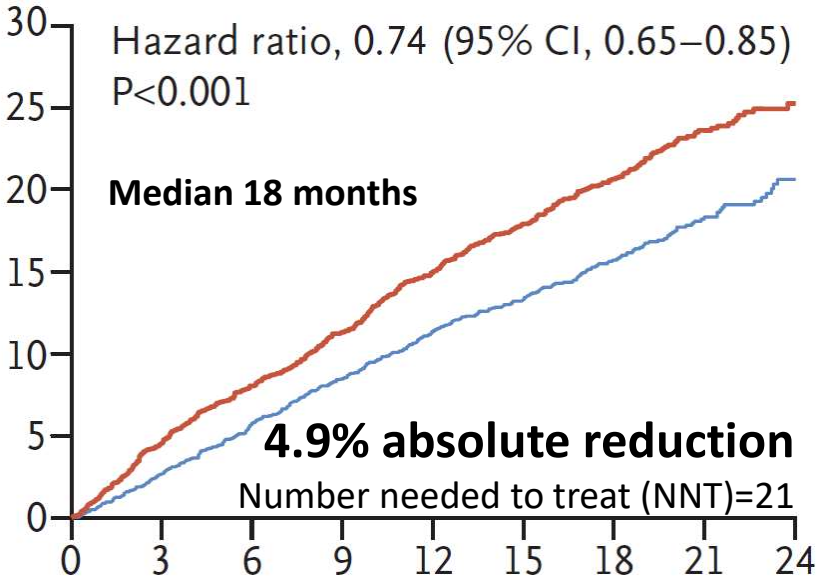
Absolute risk difference	DAPA-HF	EMPEROR-Reduced
Serious adverse events	**↓4.5%**	**↓6.7%**
Stop for adverse events	↔ (~5% both groups)	-
Genital infections	-	**↑1.1%**
Volume depletion	↔ (~7-10% both groups)	
Amputation	↔ (~0.5% both groups)	
Severe hypoglycemia	↔ (~0.3% both groups)	
Diabetic ketoacidosis (DKA)	↔ (≤0.1% both groups)	

NEJM 2019;381:1995-2008
NEJM 2020;383:1413-24

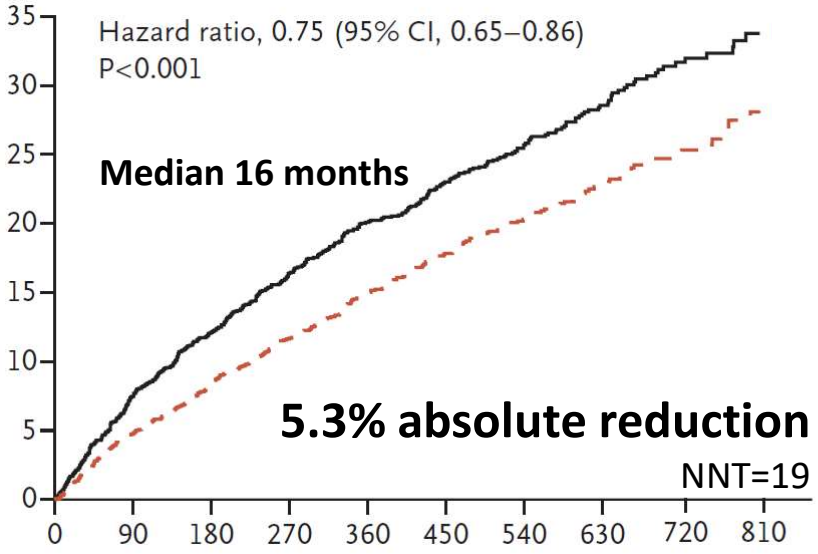
DAPA-HF & EMPEROR-Reduced

Primary outcome

DAPA-HF



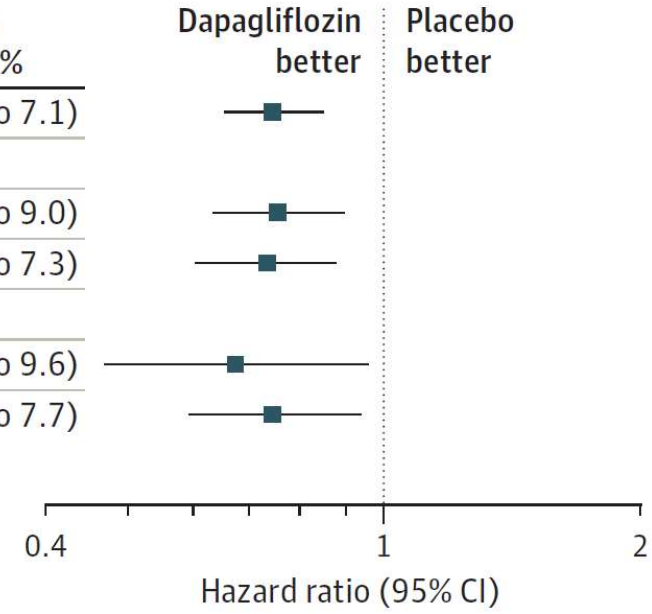
EMPEROR-Reduced



NEJM 2019;381:1995-2008
NEJM 2020;383:1413-24

Efficacy of SGLT2i in HFrEF
with or without diabetes

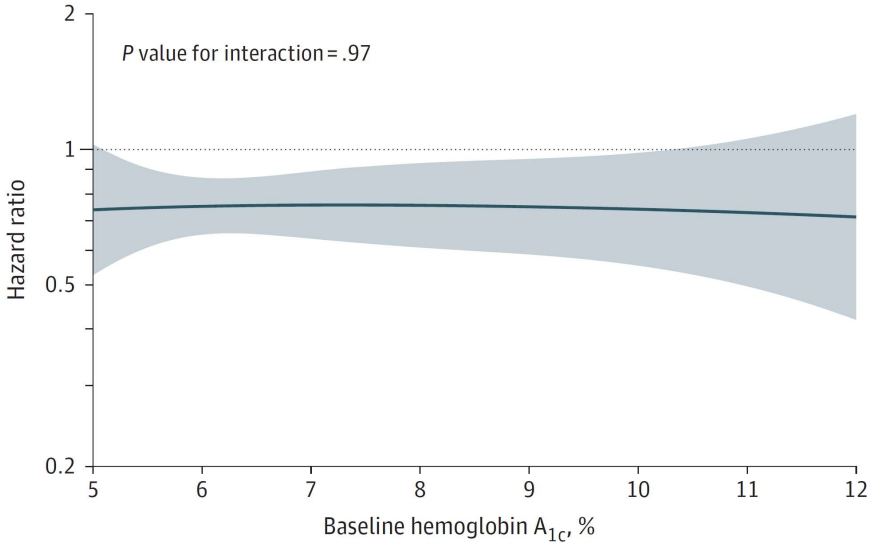
Primary composite outcome	Absolute risk reduction (95% CI), %	*P* value for interaction
Overall effect	4.9 (2.7 to 7.1)	
Type 2 diabetes at baseline[a]		
Yes	5.5 (1.9 to 9.0)	.80
No	4.5 (1.7 to 7.3)	
Patients without type 2 diabetes		
Normoglycaemic	4.8 (0.1 to 9.6)	.72
Prediabetes	4.3 (0.9 to 7.7)	



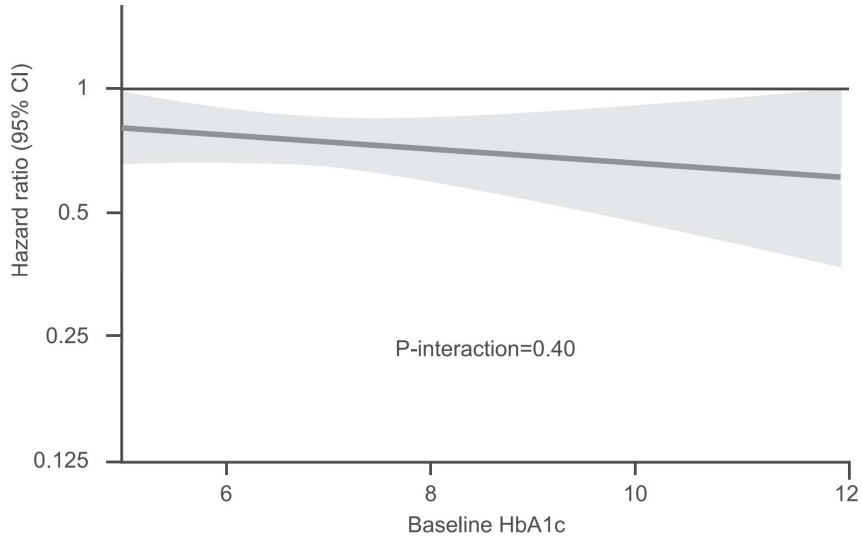
JAMA 2020;323:1353-68

Efficacy of SGLT2i in HFrEF
independent of A1c

DAPA-HF



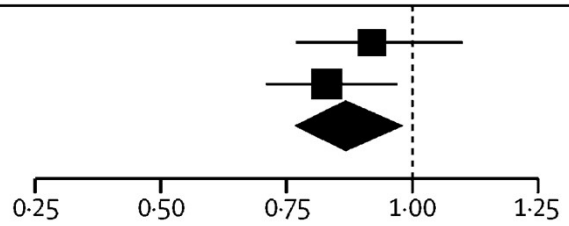
EMPEROR-Reduced



JAMA 2020;323:1353-68
Circulation 2021;143:337-49

Meta-analysis of all-cause mortality

	Number with event/number of patients (%)		HR (95% CI)
	SGLT2 inhibitor	Placebo	
EMPEROR-Reduced	249/1863 (13·4%)	266/1867 (14·2%)	0·92 (0·77–1·10)
DAPA-HF	276/2373 (11·6%)	329/2371 (13·9%)	0·83 (0·71–0·97)
Total			**0·87 (0·77–0·98)**
Test for overall treatment effect p=0·018			
Test for heterogeneity of effect p=0·39			



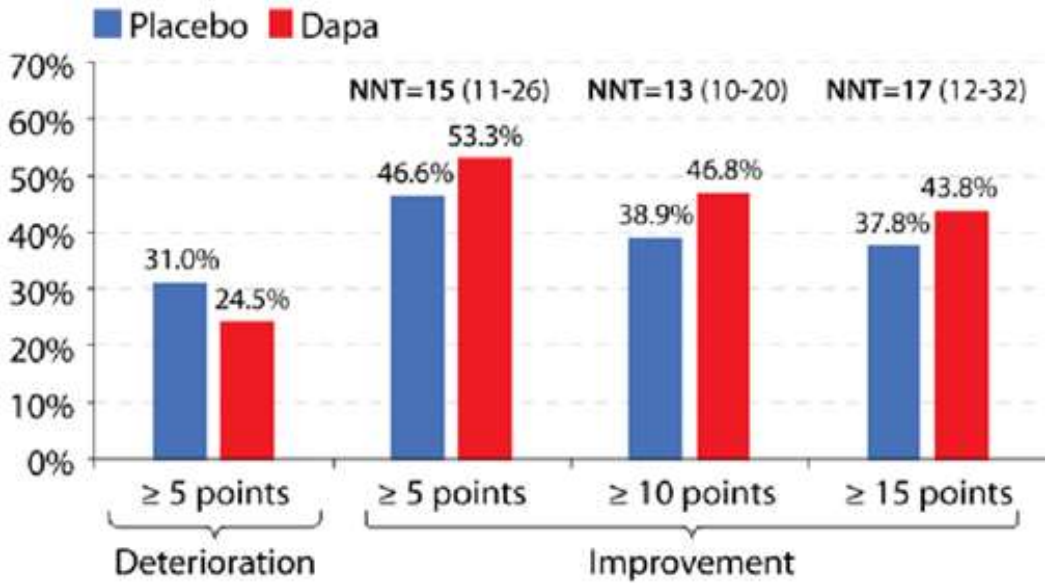
~1.6% absolute reduction

NNT=61 over 1.5 years

Lancet 2020;396:819-29

SGLT2i improve QoL (DAPA-HF)

HF-specific QoL measurement (0 to 100 scale, minimal important difference=5)

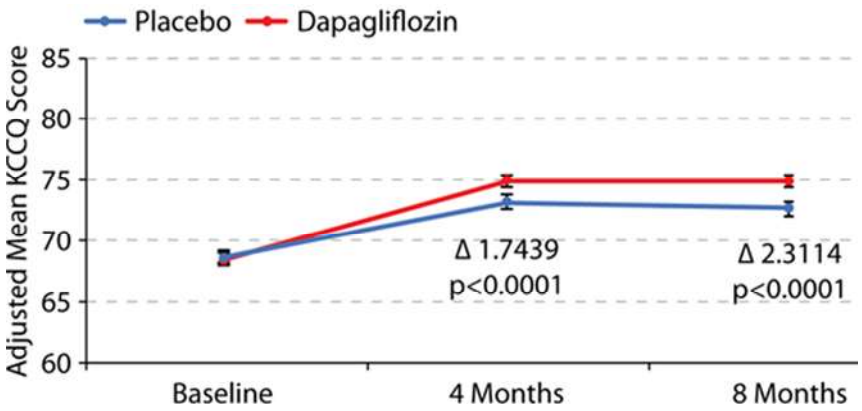


NNT 15 (~7 in 100) **for noticeable QoL improvement** at 8 months

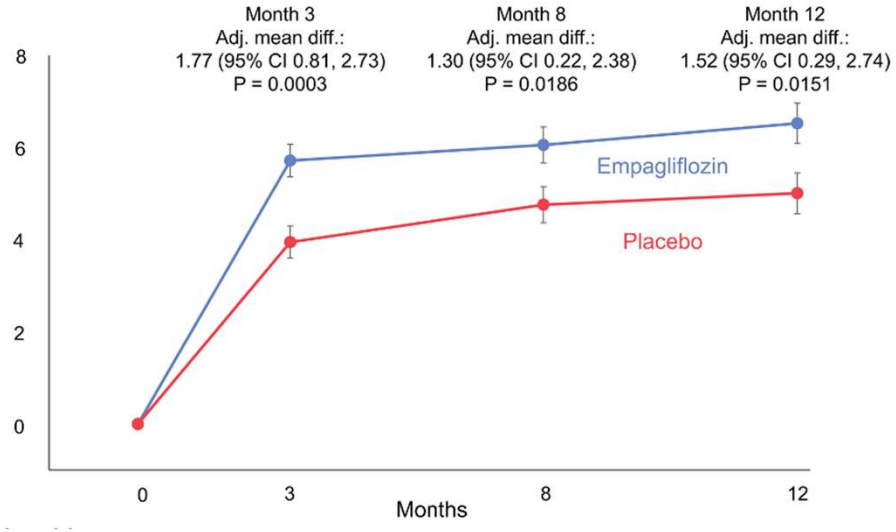
Circulation 2020;141:90-99

SGLT2i improve QoL within 3 months

DAPA-HF



EMPEROR-Reduced

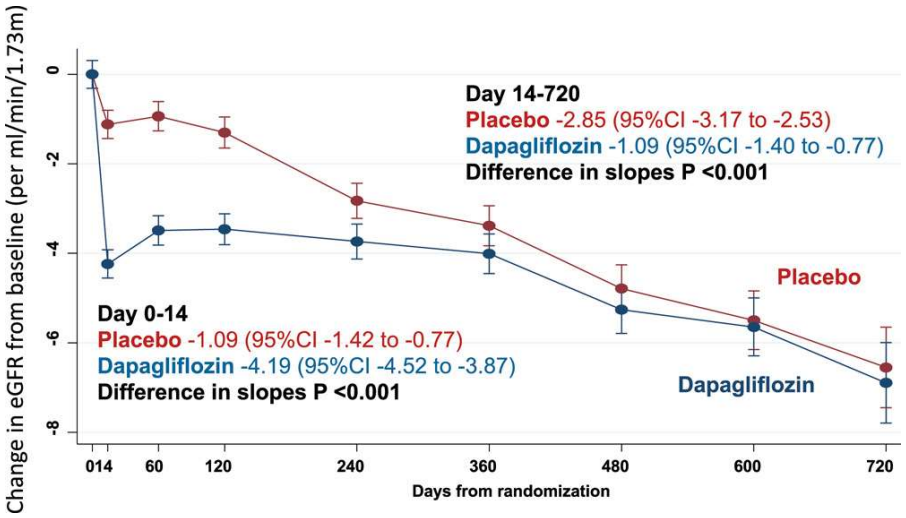


Circulation 2020;141:90-99
Butler J, et al. Eur Heart J 2021;[online ahead of print]

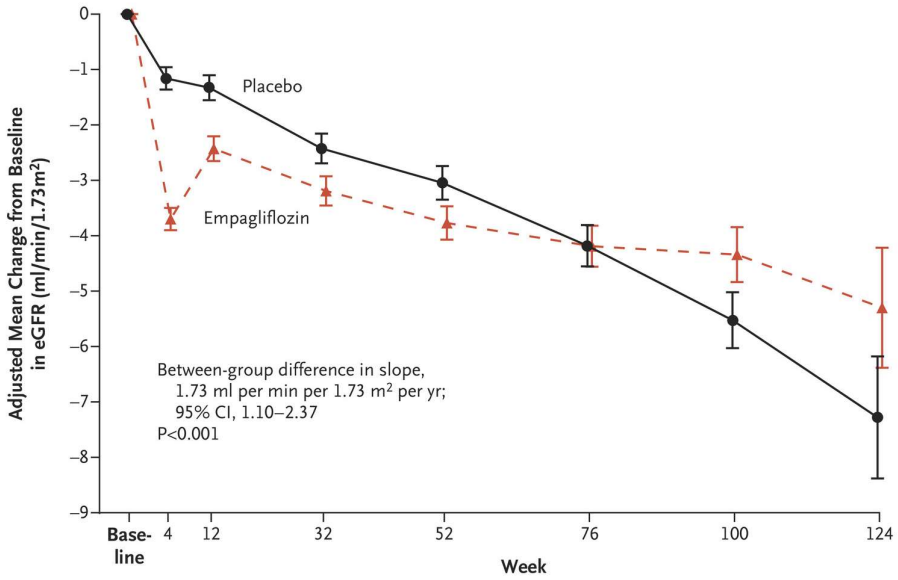
SGLT2i acutely ↓ eGFR (usually ≤10%)

eGFR ↓≤30% are expected & not concerning (similar to ACEI/ARB)

DAPA-HF



EMPEROR-Reduced

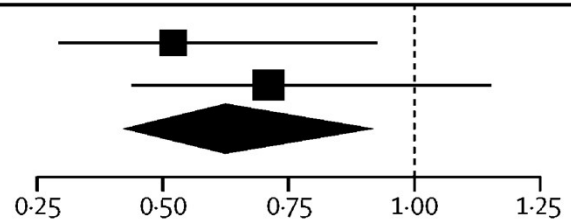


Circulation 2021;143:209-309
NEJM 2020;383:1413-24

SGLT2i improve long-term kidney outcomes

Composite of ↓ eGFR ≥50%, end-stage renal disease, or renal death

	Number with event/number of patients (%)		HR (95% CI)
	SGLT2 inhibitor	Placebo	
EMPEROR-Reduced	18/1863 (1·0%)	33/1867 (1·8%)	0·52 (0·29–0·92)
DAPA-HF	28/2373 (1·2%)	39/2371 (1·6%)	0·71 (0·44–1·16)
Total			**0·62 (0·43–0·90)**



~0.6% absolute reduction

NNT=167 over 1.5 years

Lancet 2020;396:819-29

SGLT2i efficacy & safety similar across subgroups

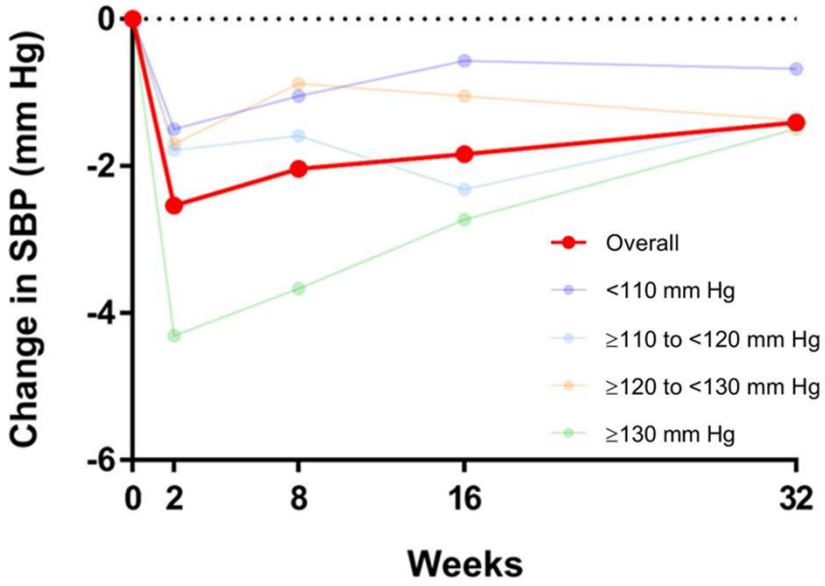
Irrespective of background HFrEF therapy

- Loop diuretic dose
- Triple therapy (ACEI/ARB + BB + MRA)
- Target dose of ACEI/ARB + BB
- Sacubitril-valsartan vs ACEI/ARB
- Device (ICD +/- cardiac resynchronization therapy)

Circulation 2020;142:1040-54
Eur Heart J 2020;41:2379-92
JACC Heart Fail 2020;8:811-8
Eur Heart J 2021;Jan 11;ehaa968

SGLT2i efficacy & safety similar across subgroups

- Asymptomatic hypotension
  - Baseline SBP as low as 95-100 mm Hg in DAPA-HF/EMPEROR-Reduced
- During HF hospitalization
  - Recurrent HF hospitalization NNT=7 in SOLOIST-WHF without symptomatic hypotension/AKI/DKA
- Duration of HF
  - From HF duration of 2 months to 5+ years in DAPA-HF

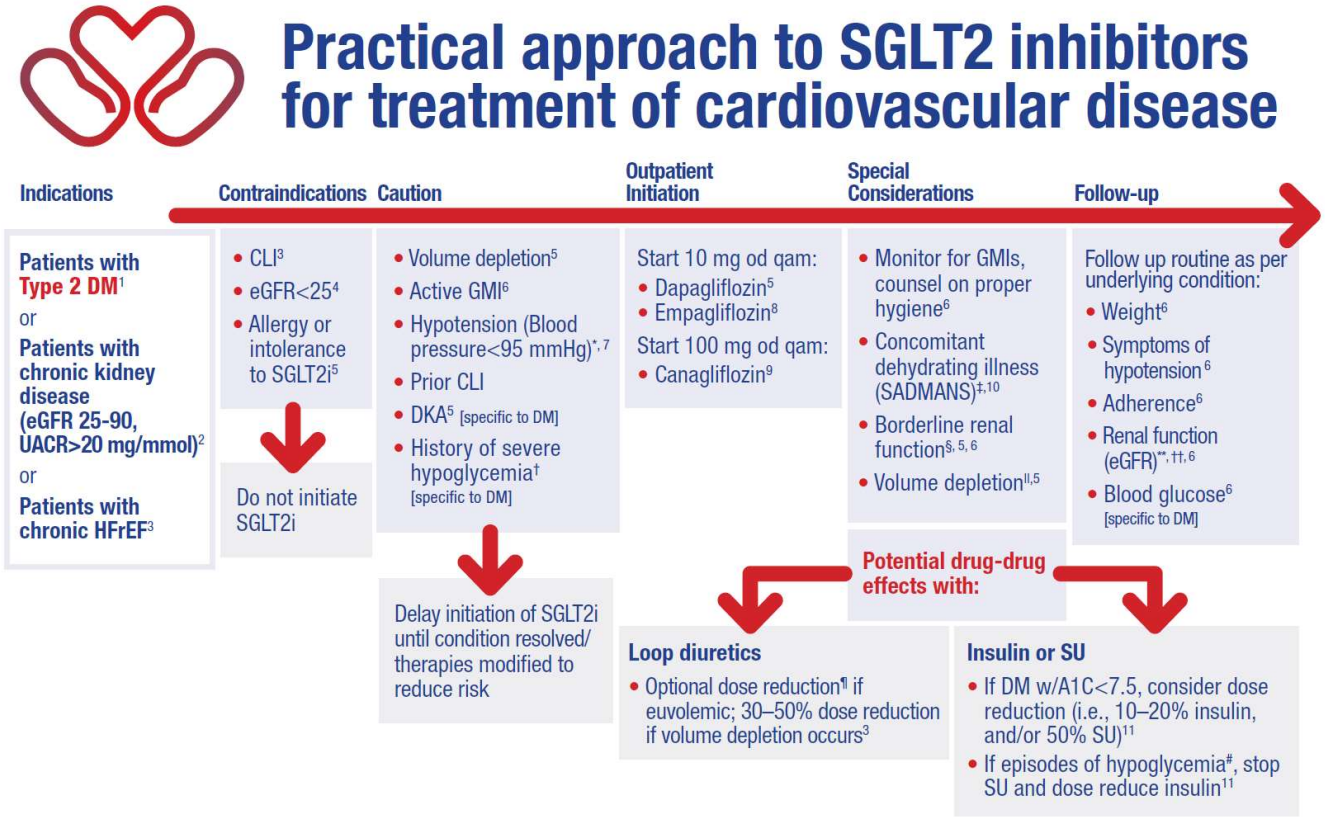


Eur Heart J 2020;41:3402-18
NEJM 2021;384:129-39
Circ Heart Fail. 2020;13:e007879

Practical tips for how to use SGLT2i in HFrEF

1. **Save patients $550/y by Rx'ing empagliflozin 12.5 mg daily**
   - Empa 10 mg = 25 mg = dapa 10 mg = $1100/y
2. **Sick-day management education to minimize ketoacidosis risk**
   - e.g. SADMANS Diabetes Canada handout
3. **Consider reducing loop diuretic dose if euvolemic & low BP**
   - If euvolemic: Empirically ↓ furosemide by 20-40 mg (or 30-50%)
   - If volume depletion develops: ↓ loop diuretic by 30-50%
4. **Genital fungal infections → topical antifungal/fluconazole**
   - Uncommon (especially without T2DM): Incidence ~1%/year in EMPEROR-Reduced

Canadian HF Society (CHFS) SGLT2i prescribing guide



https://heartfailure.ca/sites/default/files/chfs_practical_approach_algorithm_sglt2i_0.pdf

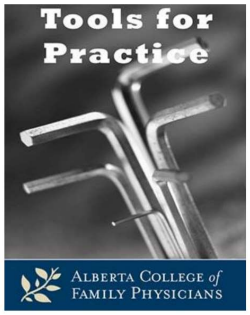
Bottom line: SGLT2i in HFrEF

	Per 100 treated for 1.5 years:
↓ death & HF hospitalizations	• 2 fewer deaths • 4 fewer HF hospitalizations
Improve health-related QoL	• 7 more with clinically important QoL improvement
Acutely ↓ eGFR, but improve long-term kidney outcomes	• 0.6 fewer renal events
Have similar efficacy/safety with/without T2DM, regardless of other HF meds, with “low BP”, & can be started during/soon after acute HF	• 15 fewer HF hospitalizations over 9 months if started during/shortly after HF hospitalization

Detailed summaries of the included studies

- DAPA-HF nerdcat.org/studysummaries/dapa-hf
- EMPEROR-Reduced nerdcat.org/studysummaries/emperor-reduced
- SOLOIST-WHF nerdcat.org/studysummaries/soloist-whf

PEER PATIENTS EXPERIENCE EVIDENCE RESEARCH



Should a 'flozin be chosen to play a part for a failing heart?
[coming soon]

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Questions & Answers

Question cluster 1:
When to start SGLT2i in the HFrEF medication sequence?

- Better to use low/sub-target doses of all 4 therapies (ACE/ARB/ARNI + BB + MRA + SGLT2i) vs target doses of 2-3 therapies?
- Better to start triple therapy prior to starting SGLT2 inhibitor?
- Better to optimize the doses of triple therapy prior to starting SGLT2i?
- Brand-new HFrEF admitted to our ward, what order of initiating HFrEF therapy would you go about it?

Answer 1:
When to start SGLT2i in the HFrEF medication sequence?

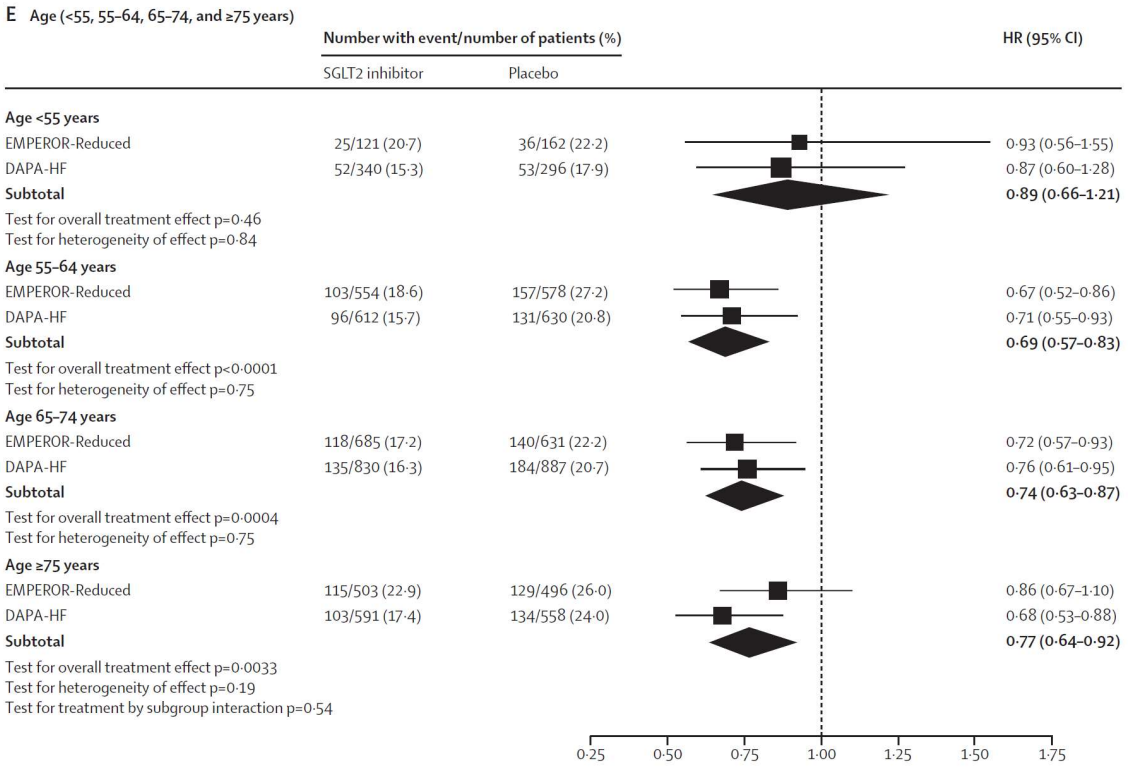
My general approach is to initiate sequence as low-dose ACEI/ARB/ARNI + beta-blocker + MRA over 2 weeks, then start SGLT2i, & once on all 4, titrate

- e.g. ramipril 2.5 mg/d + bisoprolol 2.5 mg/d + spironolactone 12.5 mg/d started at once or sequentially over 2 weeks; then 2 weeks later start empagliflozin 12.5 mg/d
- Main considerations:
  - Benefit in HFrEF of start SGLT2i > titrating other therapies (PubMedID:30817783)
  - SGLT2i efficacy consistent regardless of background meds
  - SGLT2i adverse events similar to placebo (no increase in symptomatic hypotension, hyperkalemia)

Question 2:

What was the age distribution in these HFrEF trials? Is there benefit in very elderly/frail patients?

- Mean age in the trials was ~66-67 years
- 2148/8474 (~25%) of patients ≥75 years old
- Similar efficacy regardless of age
  - No subgroup interaction by age
  - Relative risk reduction for primary outcome similar across age groups (see graph ->)



Lancet 2020;396:819-29

Question 3:

What were the exclusion criteria in DAPA-HF & EMPEROR-Reduced & how many were excluded?

DAPA-HF

- Key exclusion criteria: T1DM; symptomatic hypotension or SBP <95 mm Hg; eGFR <30 mL/min/1.73m^2
- 42% excluded during screening (did not meet inclusion criteria – details not provided)

EMPEROR-Reduced

- Key exclusion criteria: T1DM; symptomatic hypotension or SBP <100 mm Hg; eGFR <20 mL/min/1.73m2
- 46% (3314/7220) excluded during screening
  - ~80% of these for not meeting NYHA, LVEF or NT-proBNP criteria

In US population-based study of patients hospitalized for HFrEF:

44% eligible for SGLT2i based on DAPA-HF inclusion/exclusion criteria

JAMA Cardiol. doi:10.1001/jamacardio.2020.5864

Question 4: Are high BNP/NT-proBNP levels important to select who benefits most?

- Both DAPA-HF & EMPEROR-Reduced required elevated natriuretic peptide for inclusion
  - DAPA-HF: NT-proBNP range >400-900 pg/mL depending on AF & HF hospitalization history
  - EMPEROR-Reduced: NT-proBNP ≥600-5000 depending on AF & LVEF
- Rationale: Used to select higher risk patients for the trial
  - ↑BNP/NT-proBNP associated with ↑death & HF hospitalization
  - But not the only determinant/predictor of risk, & risk of many patients without elevated NT-proBNP still high relative to non-HF patients
- Subgroup analysis showed similar efficacy in both trials across NT-proBNP range

Bottom line:

- **BNP/NT-proBNP is a useful prognostic tool in HFrEF, but is only one piece in the puzzle to determine risk & potential benefit from medications.**
- **Don't use on its own for prognosis; consider along with other patient factors as part of a risk calculator (e.g. http://ww2.bcnbiohfcalculator.org/web/en/disclaimer)**

Question 5:

If starting SGLT2i in a patient on loop diuretic, would you decrease loop diuretic dose first, or only after monitoring?

- SGLT2i have a weak diuretic effect that is synergistic with loop diuretics
  - In HFrEF, may be limited to first 6-12 weeks
  - Long-term wt ↓ 1 kg vs placebo, but most not due to fluid loss
- For most patients, no need to change loop diuretic before starting SGLT2i
  - In DAPA-HF & EMPEROR-Reduced:
    - No mandated change to loop diuretic
    - No difference vs placebo in % of patients requiring change to loop diuretic or mean loop diuretic dose over time

My approach:

- **No empiric change to loop diuretic dose when starting SGLT2i**
- **Regardless: Follow-up at 1-2 weeks to assess symptoms & volume status**
- **If volume depletion develops: ↓ loop diuretic by ≤50% (usually ↓20-40 mg/d)**

Lancet Diabetes Endocrinol;doi.org/10.1016/S2213-8587(20)30382-X
Circulation. 2020;142:1028–39
Circulation. 2020;142:1040-54

Question 6: If patient experiences euglycemic DKA / genital mycotic infection / UTI with SGLT2i, would you ever re-challenge?

Prior ketoacidosis with SGLT2i:

- No evidence zone (as far as I'm aware); most ketoacidosis with SGLT2i associated with 1 or more reversible factors
- My approach: Rechallenge if possible to correct reversible factors (acute illness, hypovolemia, surgery, insufficient insulin if diabetes) & ensure sick-day management

Genital mycotic infection/UTI with SGLT2i:

- Genital mycotic infection recurrence uncommon following 1st episode with SGLT2i (especially without diabetes)
- Overall evidence unclear if SGLT2i increase UTI risk
- My approach: Continue/restart SGLT2i & treat (infrequent) recurrences with anti-infectives, unless systemic infection

CMAJ 2018;190:E766-E768
Ann Pharmacother 2020; https://doi.org/10.1177/1060028020951928

Question 7: Can we break empagliflozin 25-mg tablets (or other SGLT2i tablets)?

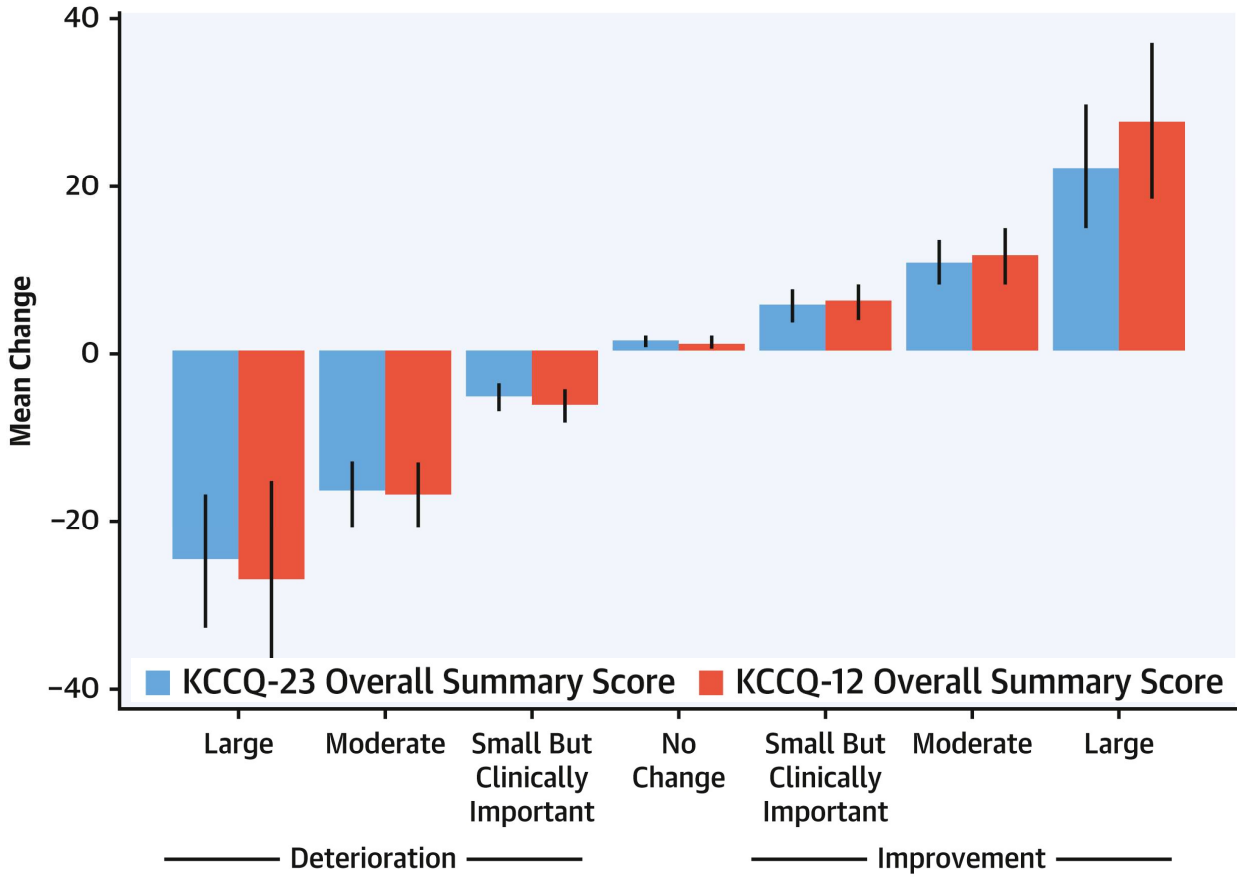
- All SGLT2i available as sugar-coated tablets without any biopharmaceutical concerns
  - Product monographs may state not to split/crush; however, no formulation-specific concerns of doing so

Bottom line: Splitting empagliflozin tablets feasible & safe

Pill splitting: Making the most of meds in a time of need. Therapeutics letter March 2020
https://www.ti.ubc.ca/wordpress/wp-content/uploads/2020/03/TL-SE.pdf

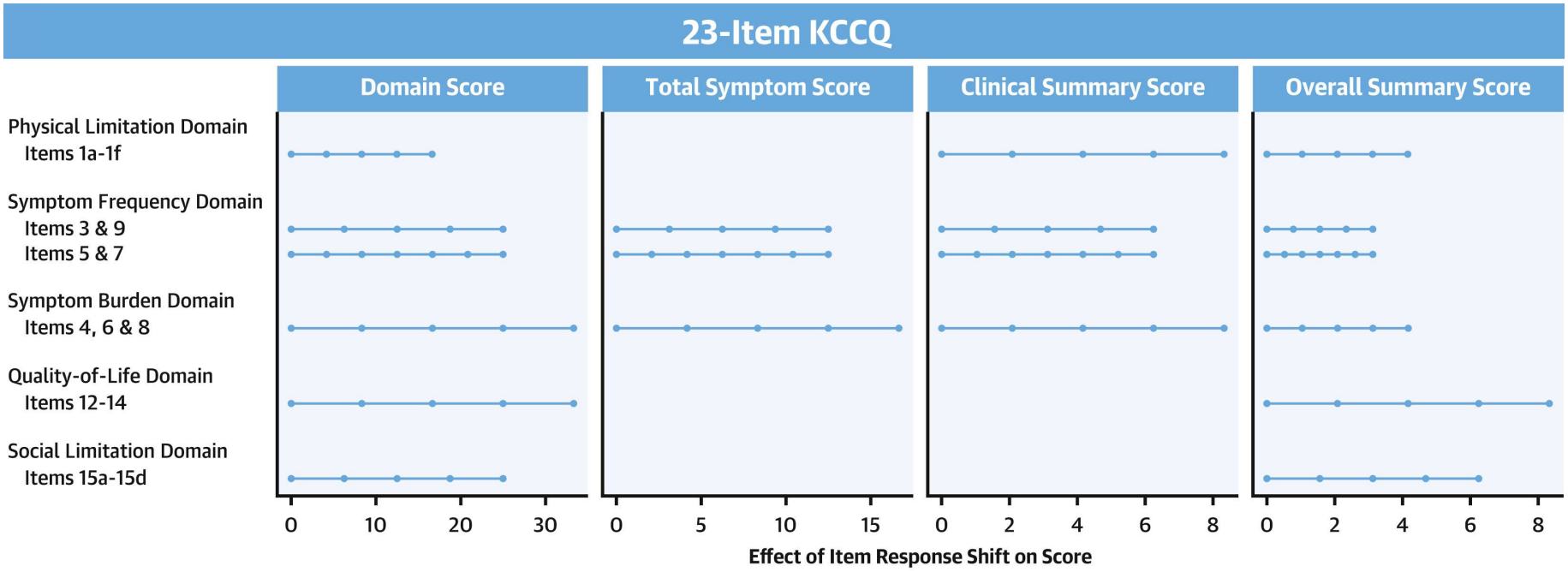
Bonus slides

Clinically important difference in HF-specific QoL: Kansas City Cardiomyopathy Questionnaire (KCCQ)



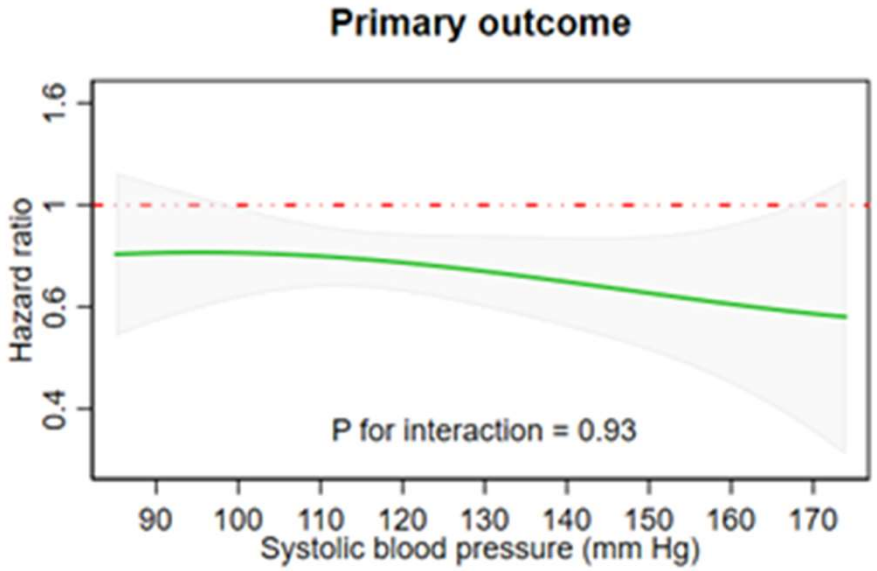
J Am Coll Cardiol 2020;76:2379-90

KCCQ: Interpreting change



J Am Coll Cardiol 2020;76:2379-90

DAPA-HF: Efficacy independent of baseline BP (if anything, lower BP is marker of higher risk)



Baseline systolic BP, mm Hg	Absolute risk reduction
<110	↓6.6%
110-119	↓5.6%
120-129	↓4.8%
≥130	↓5.0%

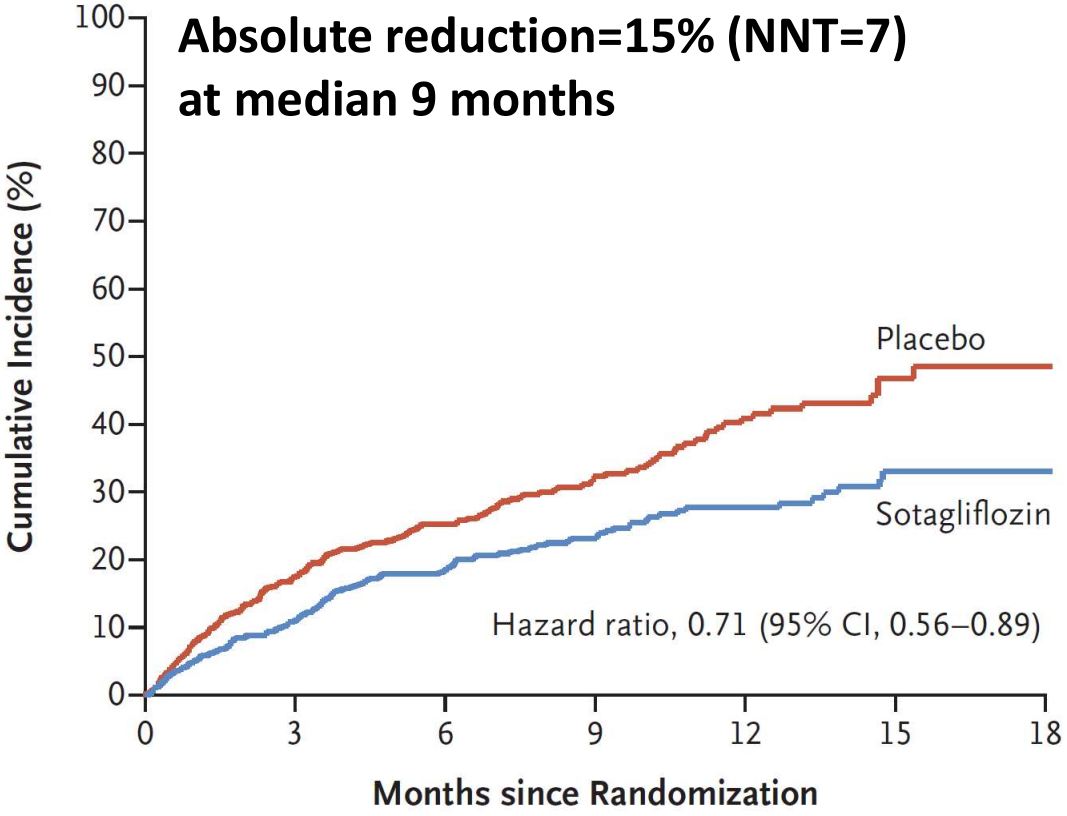
Eur Heart J 2020;41:3402-18

SOLOIST-WHF

D	**RCT with low overall risk of bias** (allocation concealed, all blinded, loss to follow-up ~3%, intention-to-treat analysis)
P **n=4744**	• **Acute HF: During admission to ≤3 days from discharge** • Any ejection fraction (mean 35%; 21% had LVEF ≥50%) • T2DM (mean HbA1c 7.1%) • Age 70 y, 76% male • Mean SBP 122 mm Hg, eGFR 50 • ACEI/ARB/ARNI 97%, beta-blocker 92%, MRA 65%
I	**Sotagliflozin** 200-400 mg once daily
C	Matching **placebo**
O	Primary: CV death or HF hospitalization

NEJM 2021;384:129-39

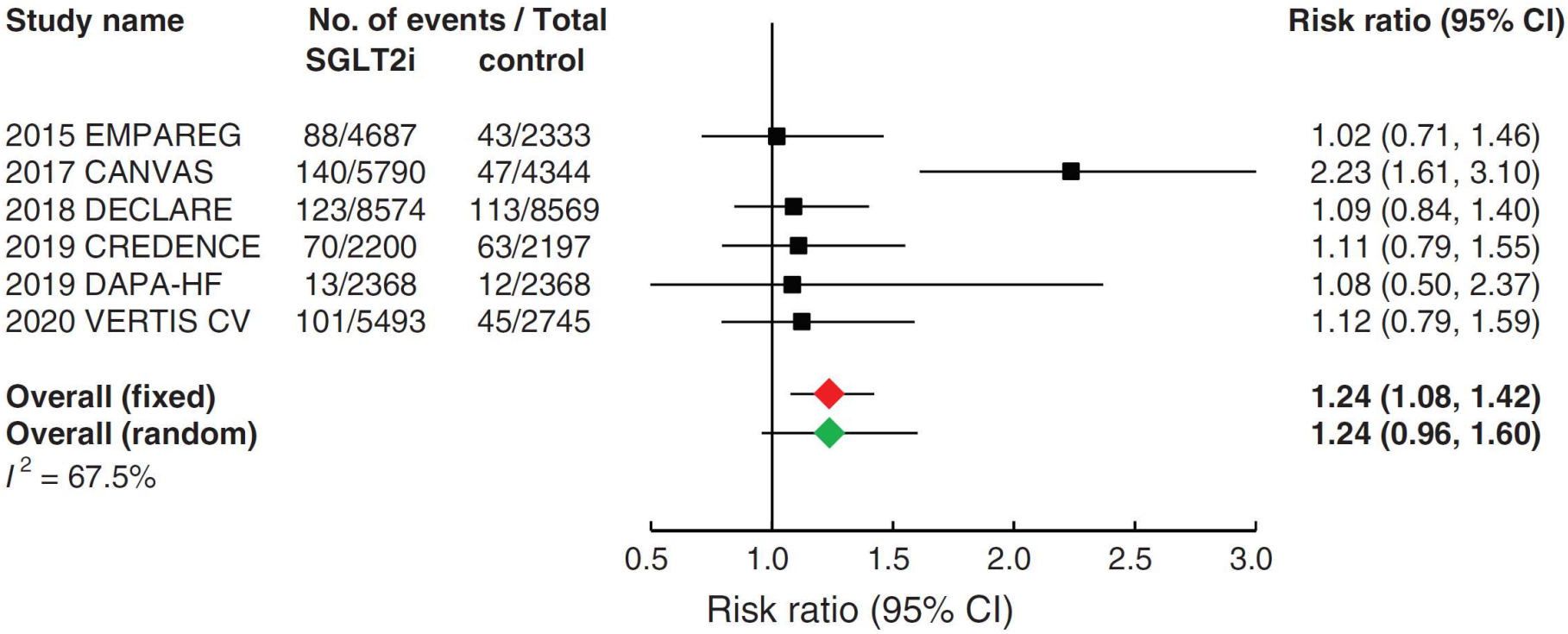
SOLOIST-WHF results



	Absolute risk difference
Diarrhea	↑2.7%
Severe hypoglycemia	↑1.2%
Hypotension	
Acute kidney injury	↔
DKA	

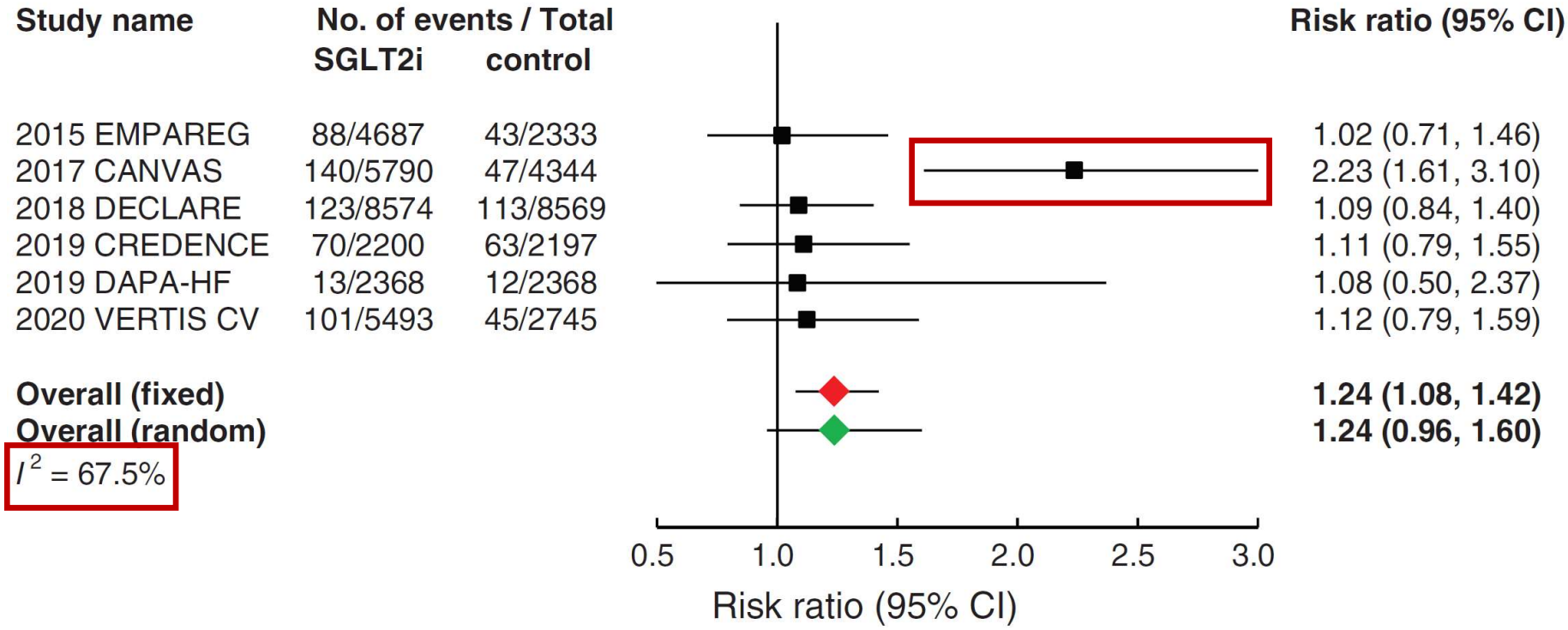
NEJM 2021;384:129-39

SGLT2i & amputations



Diabetes Obes Metab 2020;22:2348-55

SGLT2i & amputations



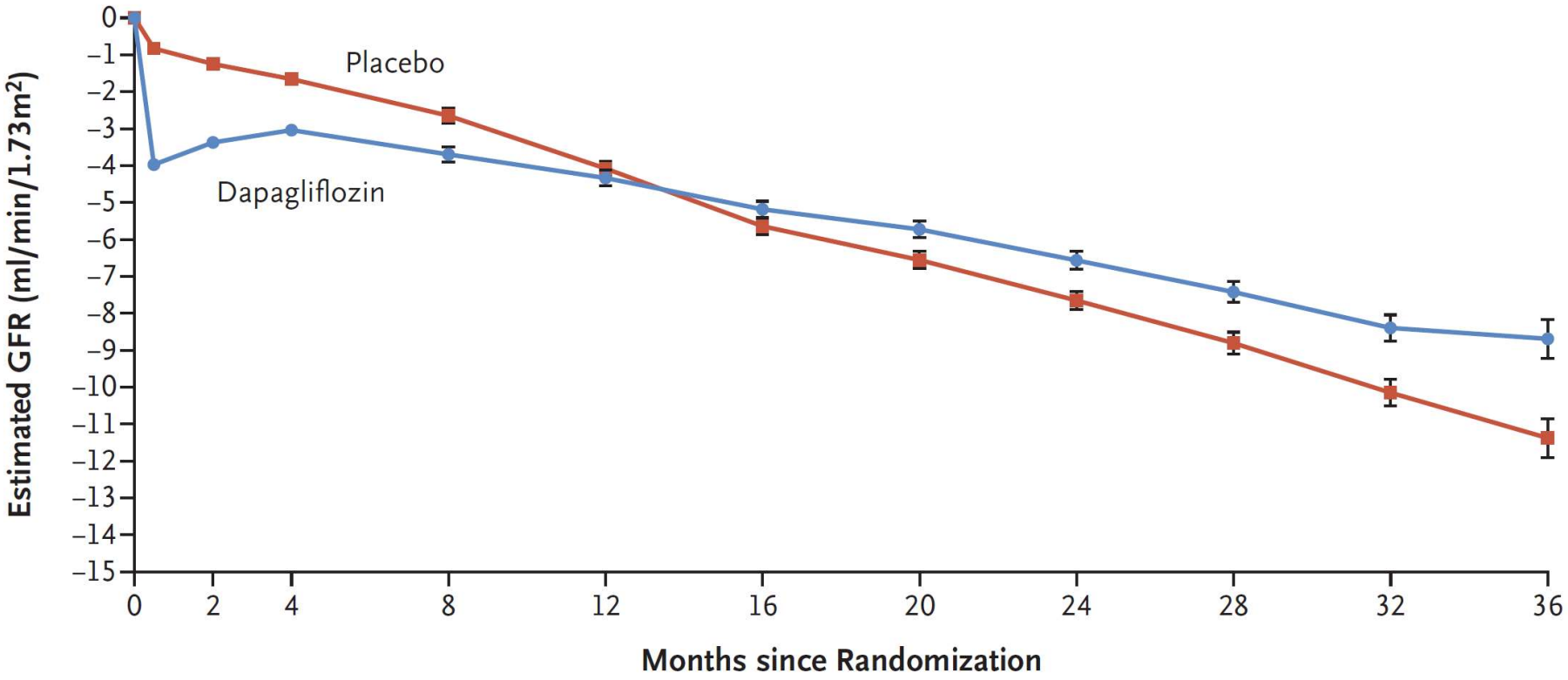
Diabetes Obes Metab 2020;22:2348-55

DAPA-CKD

D	**RCT with low overall risk of bias** (allocation concealed, all blinded, loss to follow-up 0.1%, intention-to-treat analysis)
P **n=4304**	• eGFR 25-75 mL/min/1.73m^2 + uACR 200-5000 mg/g • +/- T2DM • Stable ACEI/ARB ≥4 weeks or intolerant of ACEI/ARB
I	**Dapagliflozin** 10 mg once daily
C	Matching **placebo**
O	Primary: Sustained ↓eGFR by ≥50%, ESRD, renal/CV death • ↓5.3% (NNT=19); HR 0.61 (0.51-0.72)
T	Median 2.4 years

NEJM 2020;383:1436-46

DAPA-CKD

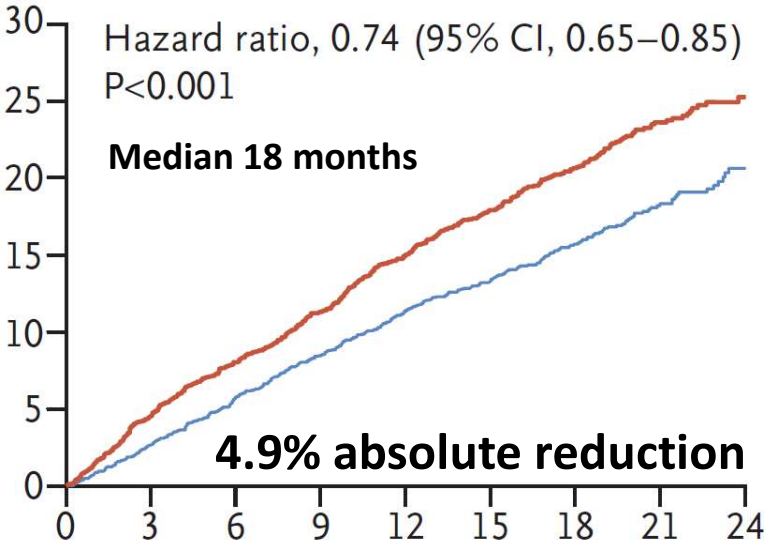


NEJM 2020;383:1436-46

DAPA-HF vs DAPA-CKD

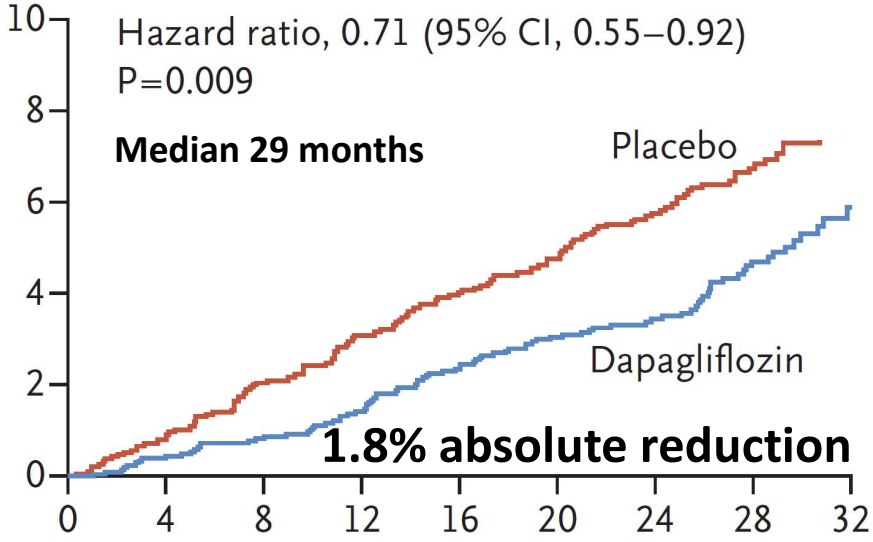
DAPA-HF

CV death, HF hospitalization, or urgent visit for HF resulting in IV therapy



DAPA-CKD

CV death or HF hospitalization



NEJM 2019;381:1995-2008
NEJM 2020;383:1436-46