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Journal Club - DAPA-HF trial

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Journal Club

—

DAPA-HF trial

Emma de Louw, PGY-3
9/24/20

The NEW ENGLAND
JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

NOVEMBER 21, 2019

VOL. 381 NO. 21

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F.A. Martinez, P. Ponikowski, M.S. Sabatine, I.S. Anand, J. Böhlhávek, M. Böhm, C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diez, J. Drozd, A. Dukát, J. Ge, J.G. Howlett, T. Katova, M. Kitakaze, C.E.A. Ljungman, B. Merkely, J.C. Nicolau, E. O'Meara, M.C. Petrie, P.N. Vinh, M. Schou, S. Tereshchenko, S. Verma, C. Held, D.L. DeMets, K.F. Docherty, P.S. Jhund, O. Bengtsson, M. Sjöstrand, and A.-M. Langkilde, for the DAPA-HF Trial Committees and Investigators*

Disclosures

I have no disclosures

Outline

- Heart failure background
- Overview SGLT-2 inhibitor
- Previous evidence
- DAPA-HF trial
 - Aim
 - Methods
 - Results
 - Limitations
 - Conclusion
- Future directions
- Translate to JFMA

Heart failure

- ~6.2 million adults in the US
- High costs: \$30.7 billion ('12)
- Treatment guidelines HFrEF (2017):

Beta blocker + diuretic +
ACEi/ARB/ARNI

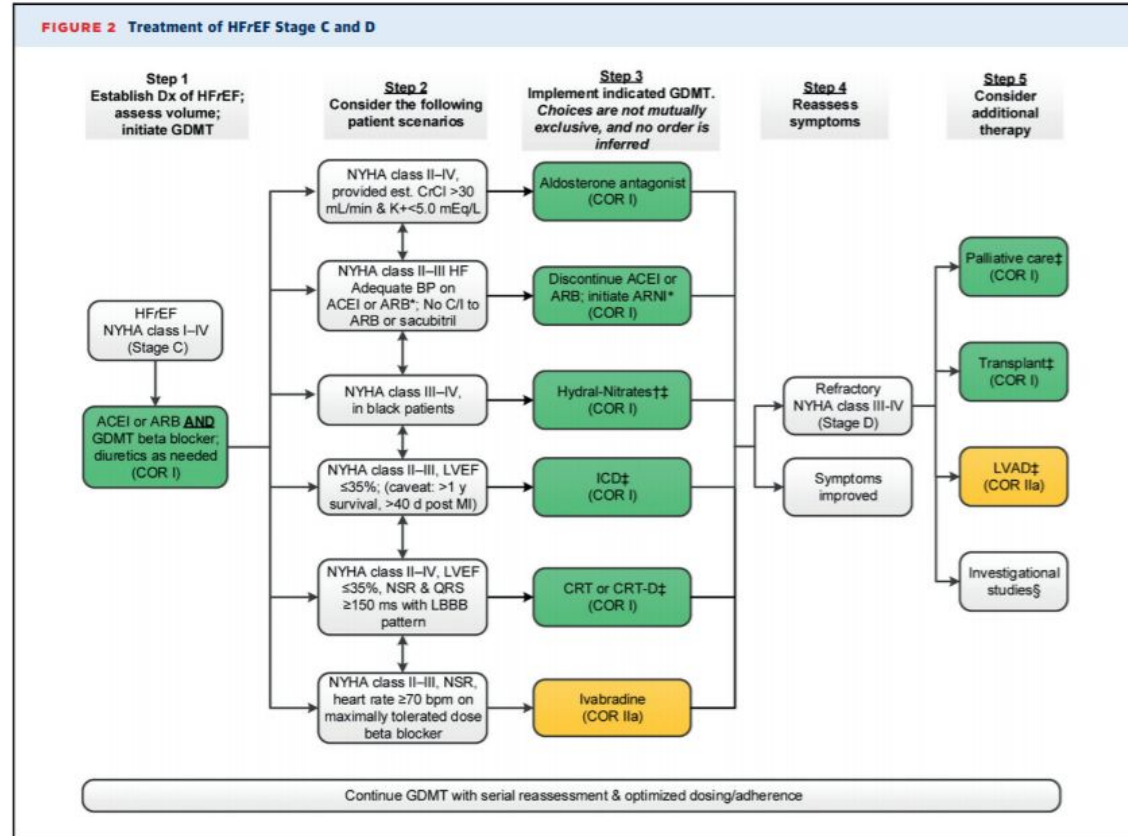


Table 1. Functional Classification Systems for Heart Failure

New York Heart Association classification

I: Asymptomatic

II: Minor symptoms, symptoms with modest exertion

III: Moderate symptoms, symptoms with minor exertion

IV: Symptoms at rest

American College of Cardiology/American Heart Association classification

A: At risk of heart failure but without structural disease

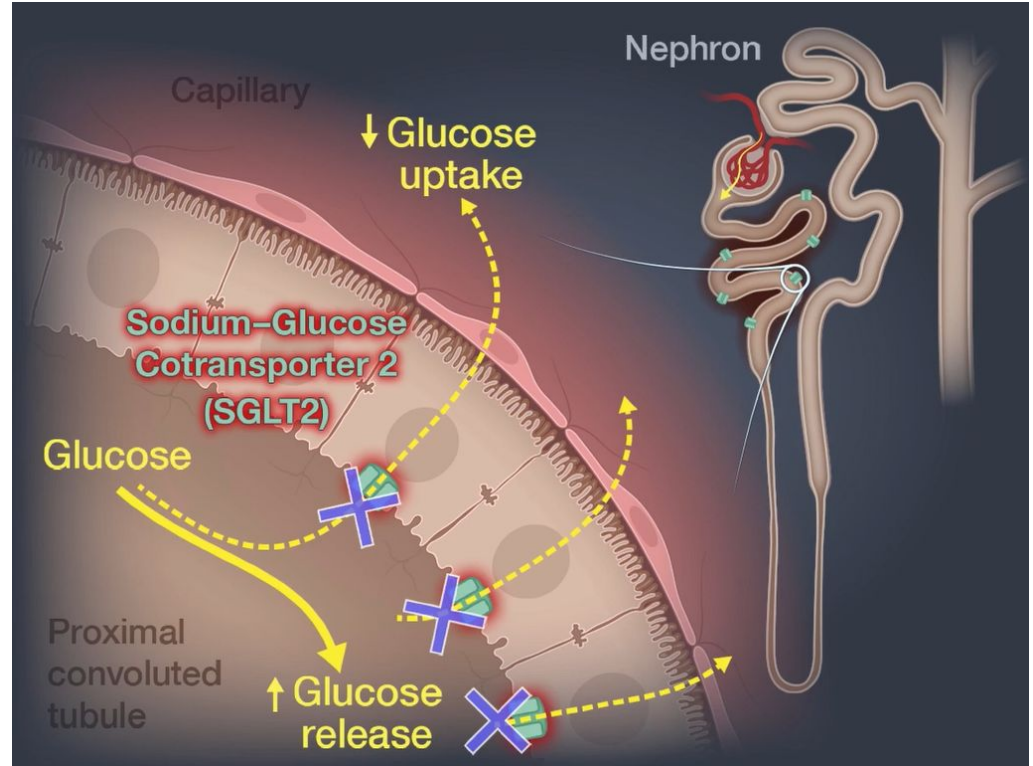
B: Structural heart failure but without symptoms

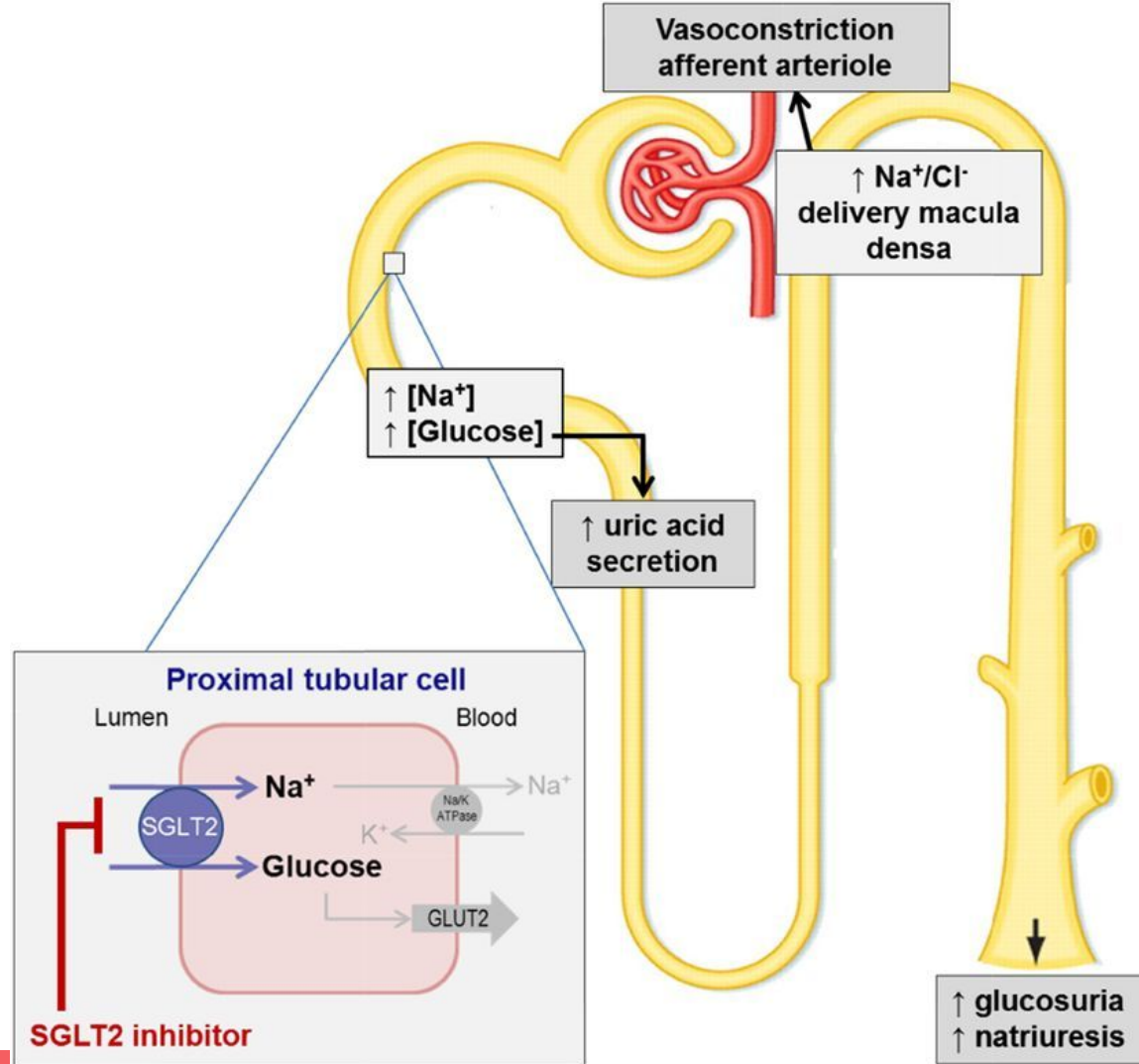
C: Structural heart failure with current or prior symptoms

D: Symptoms at rest

SGLT-2 inhibitors

- Block glucose reabsorption in blood
- Increased urinary glucose & sodium secretion
- Side effects:
 - Increased UTI
 - Genital mycotic infections
 - Increased risk of DKA
 - Fournier's gangrene
 - AKI
 - Hypotension, dehydration



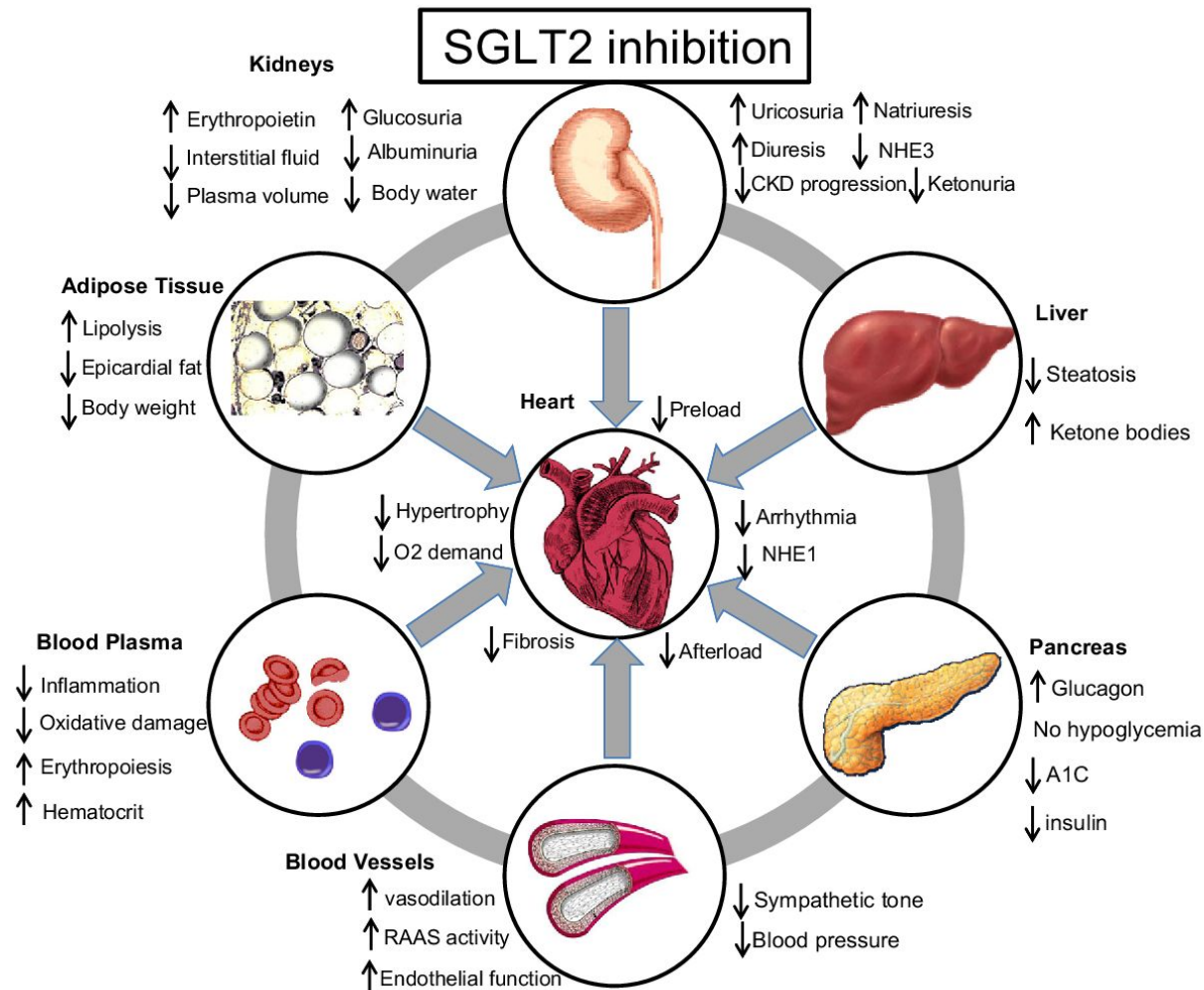


- Clinical findings**
- ↓ Plasma glucose
 - ↓ Body weight
 - ↓ Blood pressure
 - ↓ Plasma uric acid
 - ↓ Glomerular hyperfiltration

SGLT-2 inhibitors

“Gliflozins”:

- Canagliflozin (Invokana)
- Dapagliflozin (Farxiga)
- Empagliflozin (Jardiance)
- Ertugliflozin (Steglatro)



A schematic representation of the different mechanisms implicated in the cardiovascular benefits of SGLT2 inhibitors

Previous evidence

- SGLT2 inhibitors decrease risk of first hospitalization for heart failure in patients with DM2 (25 - 35%) = **prevention**
- CANVAS + EMPA-REG: mechanisms CV benefit likely driven by reduced HF death
- EMPA-REG OUTCOME: reduced risk of pump failure and sudden deaths
- DECLARE-TIMI 58: no reduction in major adverse CV events, but reduction in CV death or HF hospitalization (Esp. HFrEF)

→ Can SGLT-2 inhibitors treat HFrEF?

Randomized Controlled Trial > N Engl J Med. 2017 Aug 17;377(7):644-657.

doi: 10.1056/NEJMoa1611925. Epub 2017 Jun 12.

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal¹, Vlado Perkovic¹, Kenneth W Mahaffey¹, Dick de Zeeuw¹, Greg Fulcher¹, Ngozi Erondu¹, Wayne Shaw¹, Gordon Law¹, Mehel Desai¹, David R Matthews¹, CANVAS Program Collaborative Group

Randomized Controlled Trial > N Engl J Med. 2015 Nov 26;373(22):2117-28.

doi: 10.1056/NEJMoa1504720. Epub 2015 Sep 17.

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman¹, Christoph Wanner, John M Lachin, David Fitchett, Erich Bluhmki, Stefan Hantel, Michaela Mattheus, Theresa Devins, Odd Erik Johansen, Hans J Woerle, Uli C Broedl, Silvio E Inzucchi, EMPA-REG OUTCOME Investigators

Randomized Controlled Trial > N Engl J Med. 2019 Jan 24;380(4):347-357.

doi: 10.1056/NEJMoa1812389. Epub 2018 Nov 10.

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

Stephen D Wiviott¹, Itamar Raz¹, Marc P Bonaca¹, Ofri Mosenzon¹, Eri T Kato¹, Avivit Cahn¹, Michael G Silverman¹, Thomas A Zelniker¹, Julia F Kuder¹, Sabina A Murphy¹, Deepak L Bhatt¹, Lawrence A Leiter¹, Darren K McGuire¹, John P H Wilding¹, Christian T Ruff¹, Ingrid A M Gause-Nilsson¹, Martin Fredriksson¹, Peter A Johansson¹, Anna-Maria Langkilde¹, Marc S Sabatine¹, DECLARE-TIMI 58 Investigators

Previous evidence

- Benefits on HF could not be explained by diuretic or anti-hyperglycemic effects
- Benefits may be mediated by the inhibition of sodium-hydrogen exchange rather than the effect on glucose reabsorption
- Reduced cardiac injury, hypertrophy, fibrosis, systolic dysfunction

→ Will it work for patients without DM?

Effects of Sodium-Glucose Cotransporter 2 Inhibitors for the Treatment of Patients With Heart Failure

Proposal of a Novel Mechanism of Action

Milton Packer, MD¹; Stefan D. Anker, MD^{2,3}; Javed Butler, MD, MPH⁴; [et al](#)

» Author Affiliations

JAMA Cardiol. 2017;2(9):1025-1029. doi:10.1001/jamacardio.2017.2275

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Aim

“To prospectively evaluate the efficacy and safety of the SGLT2 inhibitor dapagliflozin in patients with heart failure and a reduced ejection fraction, regardless of the presence or absence of diabetes”

Methods

- Trial design
- Patients
- Outcomes
- Statistical analyses

Methods - Trial design

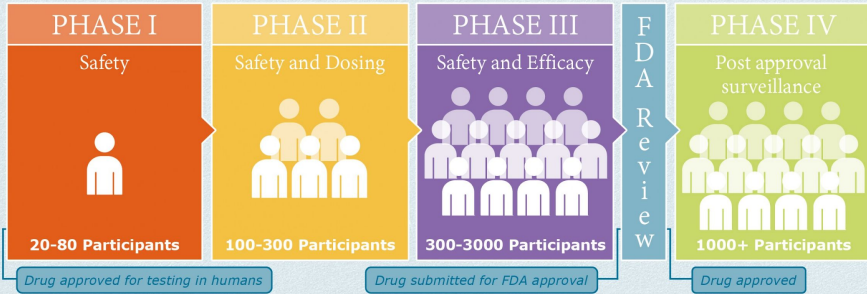
- Phase 3, Randomized, Double-Blinded
- Placebo-controlled
 - Dapagliflozin 10 mg vs Placebo
 - + Conventional HF therapy
- 410 centers in 20 countries
- N = 4744
- Stratification: DM2 (A1c \geq 6.5%)
- Median follow up time: 18.2 months
 - 14 days, 60 days, q4 months

- In collaboration with sponsor: AstraZeneca
 - Analyses replicated by independent academic group



Clinical Trials

Clinical Trial Phases



= 15 healthy participants
 = 15 participants with CF
 *number of participants varies based on study characteristics

= Number of months of participant involvement



CLINICAL TRIAL PROCESS

Phase	Length	Number of People*	Purpose		
Phase 1	1 month	10-20	Is it safe?	How does the body process it?	What are the side effects?
Phase 2	3 - 12 months	50-75	Is it safe?	How well is it working?	How much should be taken?
Phase 3	6 - 12 months	100-300	Is it safe?	How well is it working?	Does the benefit outweigh the risk?
FDA Approval (6-12 months)					
Application submitted → Application reviewed → Application Approved → Available to public					
Phase 4	3 - 12 months	100-300	Does it still appear to be safe?	Are there rare side effects?	Cost effectiveness & comparison to other similar drugs

Methods - Patients

Inclusion criteria:

- Age \geq 18 years
- EF \leq 40%
- NYHA class II-IV
- NT-proBNP \geq 600 pg/ml
 - or \geq 400 pg/ml if HF hospitalization in previous 12 mo)
 - Afib or Aflutter: NT-proBNP \geq 900 mg/ml
- Standard treatment for heart failure
 - Device: ICD, cardiac resynchronization therapy, or both
 - Meds: ACEi, ARB, sacubitril-valsartan + beta-blocker +/- mineralocorticoid receptor antagonist
- DM: continued to take glucose-lowering therapy
 - Doses could be adjusted as required (insulin, sulfonylurea)

Methods - Patients

Exclusion criteria:

- Recent treatment with SGLT2 inhibitor
- Unacceptable side effects associated with SGLT2 inhibitor
- DM type 1
- Symptomatic hypotension or SBP < 95 mmHg
- eGFR \leq 30

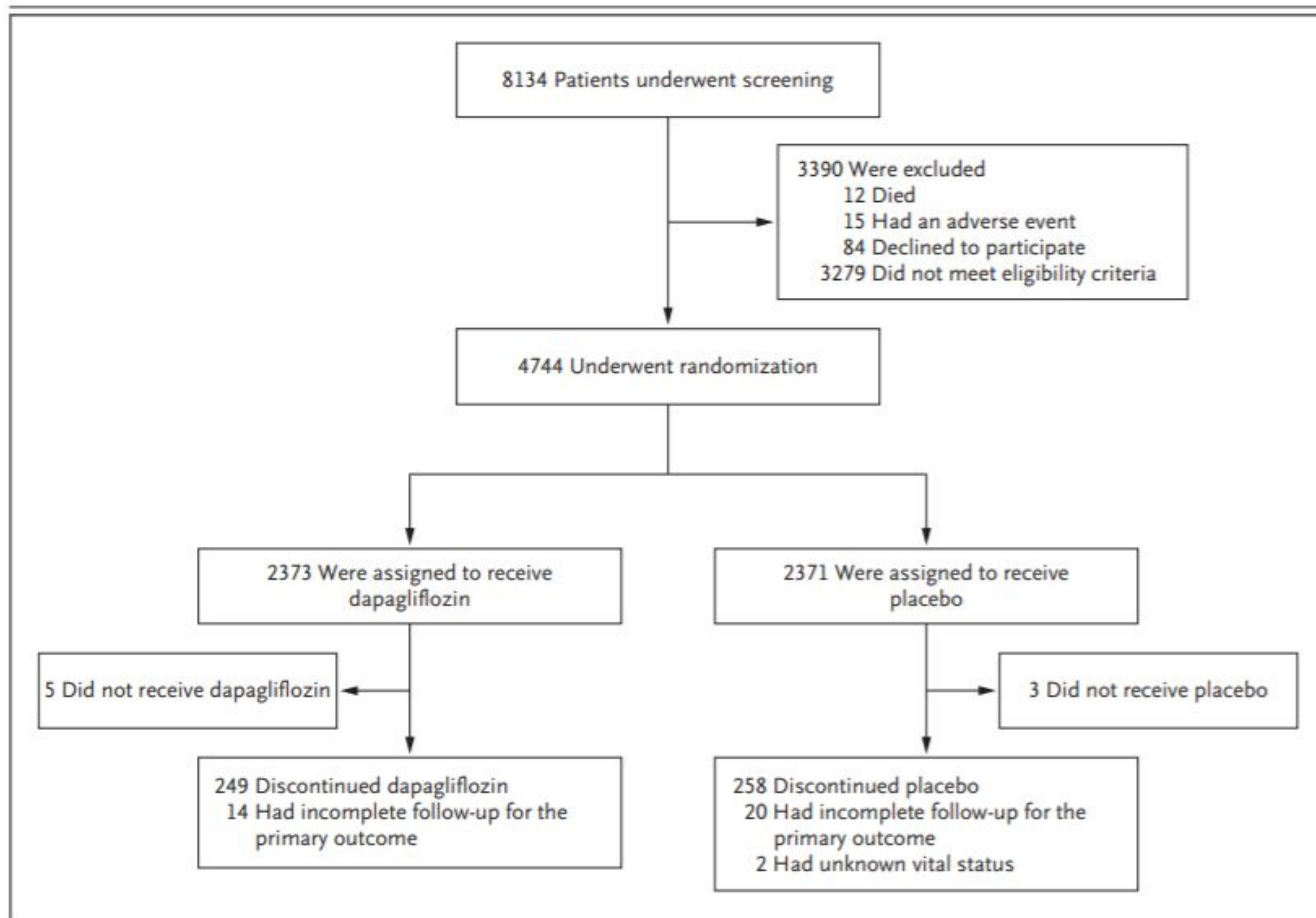


Figure 1. Enrollment and Follow-up.

All the patients who underwent randomization were included in the primary analysis. Patients who did not receive a dose of either dapagliflozin or placebo were excluded from the safety analysis.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Dapagliflozin (N = 2373)	Placebo (N = 2371)
Age — yr	66.2±11.0	66.5±10.8
Female sex — no. (%)	564 (23.8)	545 (23.0)
Body-mass index†	28.2±6.0	28.1±5.9
Race — no. (%)‡		
White	1662 (70.0)	1671 (70.5)
Black	122 (5.1)	104 (4.4)
Asian	552 (23.3)	564 (23.8)
Other	37 (1.6)	32 (1.3)
Region — no. (%)		
North America	335 (14.1)	342 (14.4)
South America	401 (16.9)	416 (17.5)
Europe	1094 (46.1)	1060 (44.7)
Asia-Pacific	543 (22.9)	553 (23.3)
NYHA functional classification — no. (%)		
II	1606 (67.7)	1597 (67.4)
III	747 (31.5)	751 (31.7)
IV	20 (0.8)	23 (1.0)
Heart rate — beats/min	71.5±11.6	71.5±11.8
Systolic blood pressure — mm Hg	122.0±16.3	121.6±16.3
Left ventricular ejection fraction — %	31.2±6.7	30.9±6.9
Median NT-proBNP (IQR) — pg/ml	1428 (857–2655)	1446 (857–2641)
Principal cause of heart failure — no. (%)		
Ischemic	1316 (55.5)	1358 (57.3)
Nonischemic	857 (36.1)	830 (35.0)
Unknown	200 (8.4)	183 (7.7)

Medical history — no. (%)		
Hospitalization for heart failure	1124 (47.4)	1127 (47.5)
Atrial fibrillation	916 (38.6)	902 (38.0)
Diabetes mellitus§	993 (41.8)	990 (41.8)
Estimated GFR		
Mean — ml/min/1.73 m ²	66.0±19.6	65.5±19.3
Rate of <60 ml/min/1.73 m ² — no./total no. (%)	962/2372 (40.6)	964/2371 (40.7)
Device therapy — no. (%)		
Implantable cardioverter–defibrillator¶	622 (26.2)	620 (26.1)
Cardiac resynchronization therapy	190 (8.0)	164 (6.9)
Heart failure medication — no. (%)		
Diuretic	2216 (93.4)	2217 (93.5)
ACE inhibitor	1332 (56.1)	1329 (56.1)
ARB	675 (28.4)	632 (26.7)
Sacubitril–valsartan	250 (10.5)	258 (10.9)
Beta-blocker	2278 (96.0)	2280 (96.2)
Mineralocorticoid receptor antagonist	1696 (71.5)	1674 (70.6)
Digitalis	445 (18.8)	442 (18.6)
Glucose-lowering medication — no./total no. (%)**		
Biguanide	504/993 (50.8)	512/990 (51.7)
Sulfonylurea	228/993 (23.0)	210/990 (21.2)
DPP-4 inhibitor	161/993 (16.2)	149/990 (15.1)
GLP-1 receptor agonist	11/993 (1.1)	10/990 (1.0)
Insulin	274/993 (27.6)	266/990 (26.9)

Methods - Outcomes

Primary outcome:

- Composite of worsening heart failure or death from cardiovascular causes
 - Hospitalization
 - Urgent visit resulting in IV therapy for HF

Methods - Outcomes

Secondary outcomes:

- Composite of hospitalization for heart failure or cardiovascular death
- Total number of hospitalizations for HF & cardiovascular deaths
- Change in symptoms
 - Kansas City Cardiomyopathy Questionnaire
- Composite of worsening renal function
 - $\geq 50\%$ decline in eGFR, ESRD (eGFR ≤ 15 for ≥ 28 days), renal death
- Death from any cause

Methods - Outcomes

Safety analysis:

- Serious adverse events
- Adverse events associated with discontinuation of a trial treatment
- Adverse events of interest
 - Volume depletion
 - Renal events
 - Major hypoglycemic events
 - Bone fractures
 - DKA
 - Amputations
 - Fournier's gangrene
- Abnormal lab findings of note

*Data on other adverse events not routinely collected given extensive previous collection on safety data regarding dapagliflozin (Wiviott et al 2019)

Methods – Statistical Analysis

- Intention-to-treat analysis
- Time-to-event data: Kaplan-Meier estimates & cox proportional-hazards models
- Incidence of adverse events: Fisher's exact test

Cox proportional hazards model

Relate several risk factors/exposures, considered simultaneously, to survival time

Effect measured: **Hazard rate** = Probability of an individual at time t has event happening at that time

Hazard Ratio = Probability of events in treatment group / probability of events in control group

Averaged over the whole follow-up period

HR \neq RR

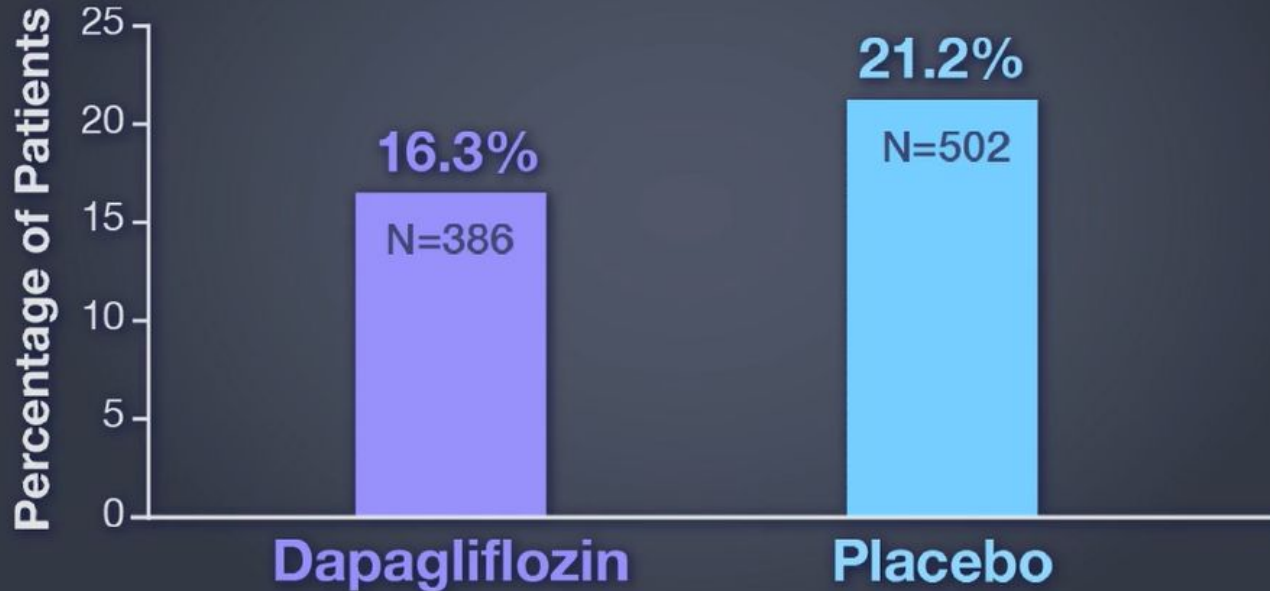
→ Time to event

Results

- Efficacy Outcomes
- Safety Outcomes

Primary Outcome

Composite of a First Episode of Worsening Heart Failure or Cardiovascular Death



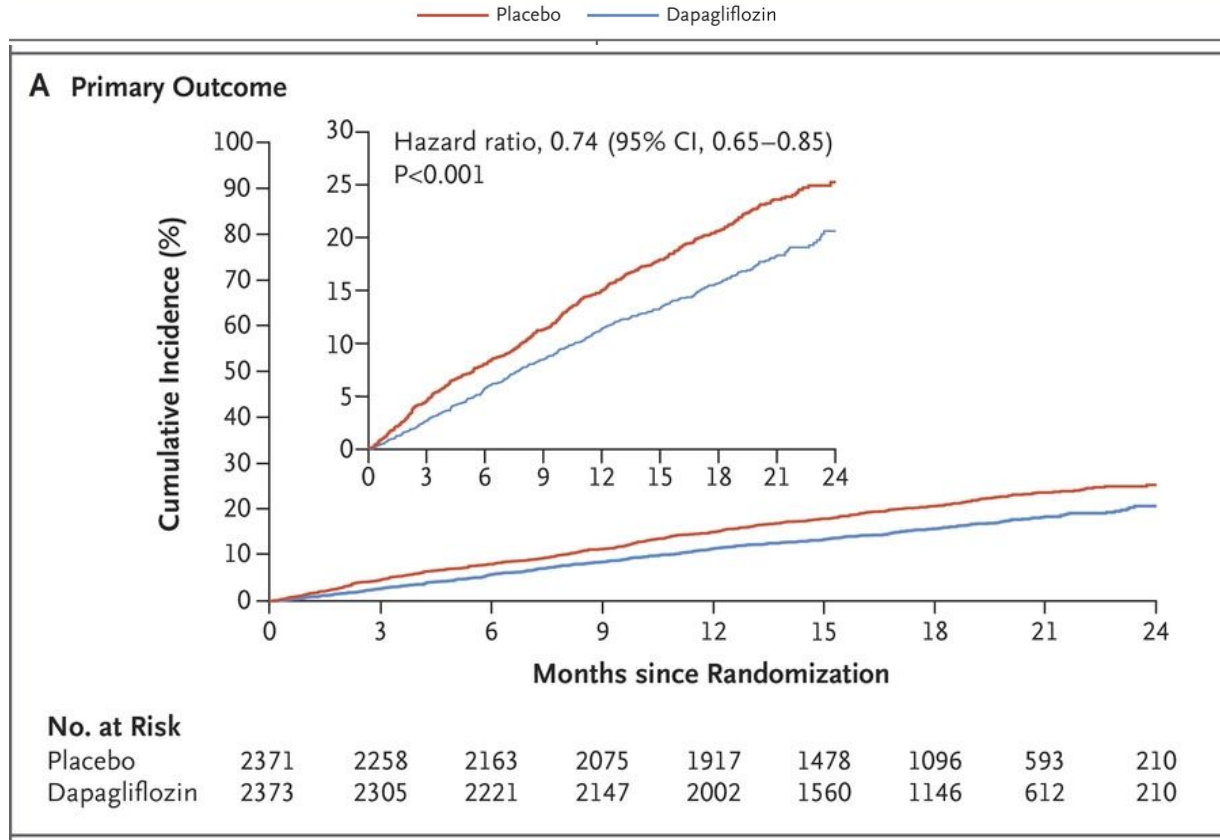
Hazard Ratio, 0.74; 95% CI, 0.65 to 0.85; P < 0.001

Primary outcome - Worsening HF or CV death

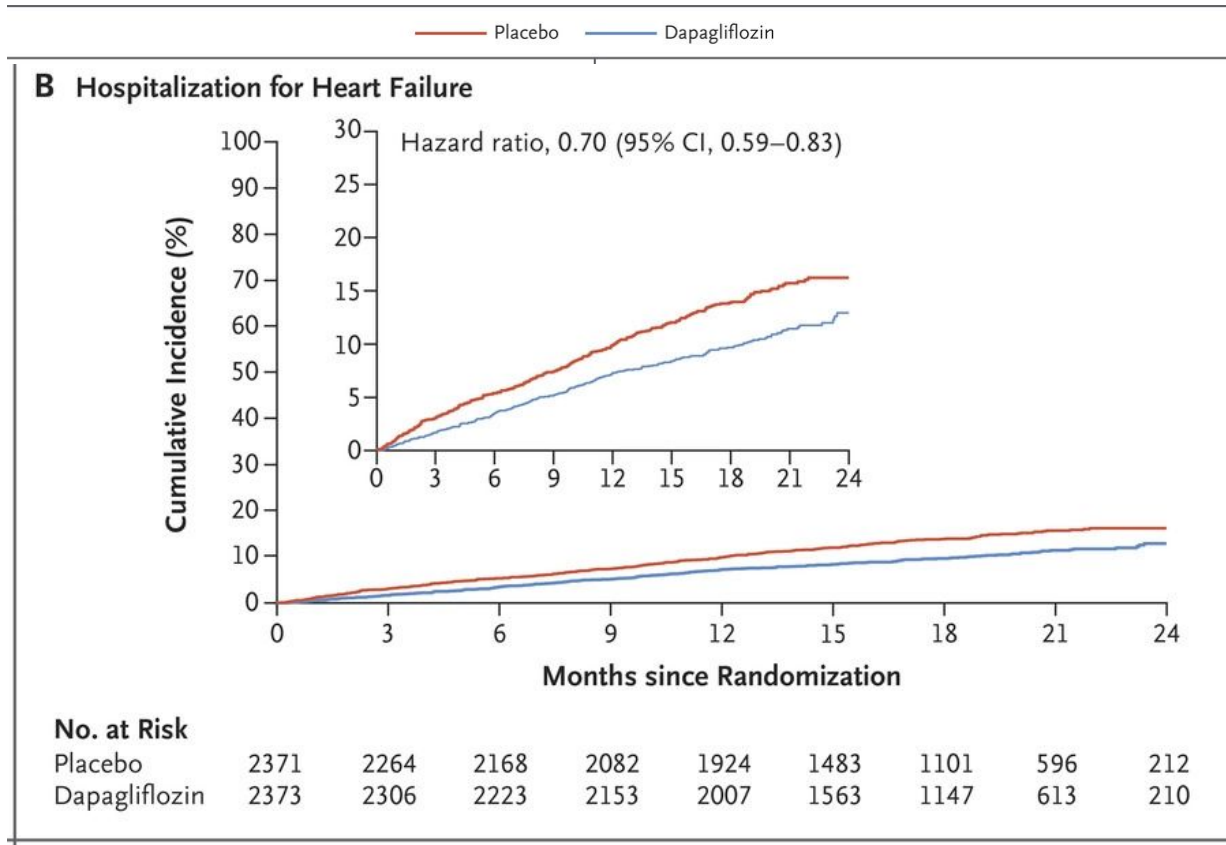
HR 0.74

Dapa → 26% less risk of developing worsening HF or CV death, at any time

NNT = 21



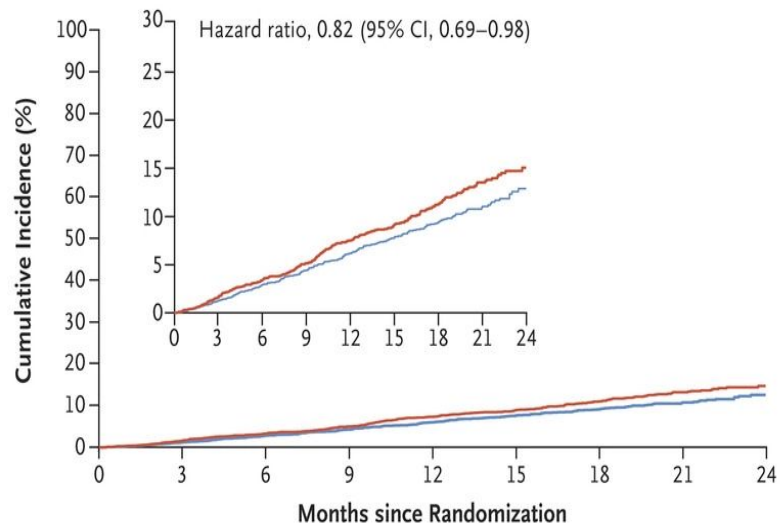
Secondary outcome - HF hospitalization



Secondary outcome - mortality

— Placebo — Dapagliflozin

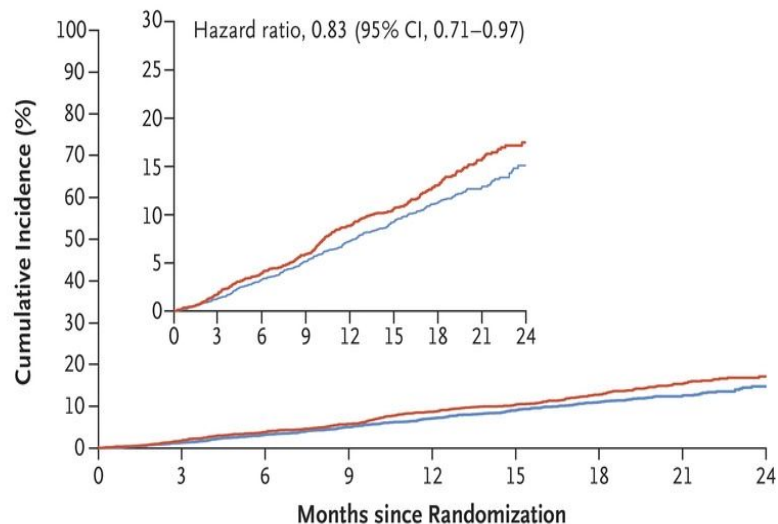
C Death from Cardiovascular Causes



No. at Risk

Placebo	2371	2330	2279	2230	2091	1636	1219	664	234
Dapagliflozin	2373	2339	2293	2248	2127	1664	1242	671	232

D Death from Any Cause



No. at Risk

Placebo	2371	2330	2279	2231	2092	1638	1221	665	235
Dapagliflozin	2373	2342	2296	2251	2130	1666	1243	672	233

Efficacy outcomes

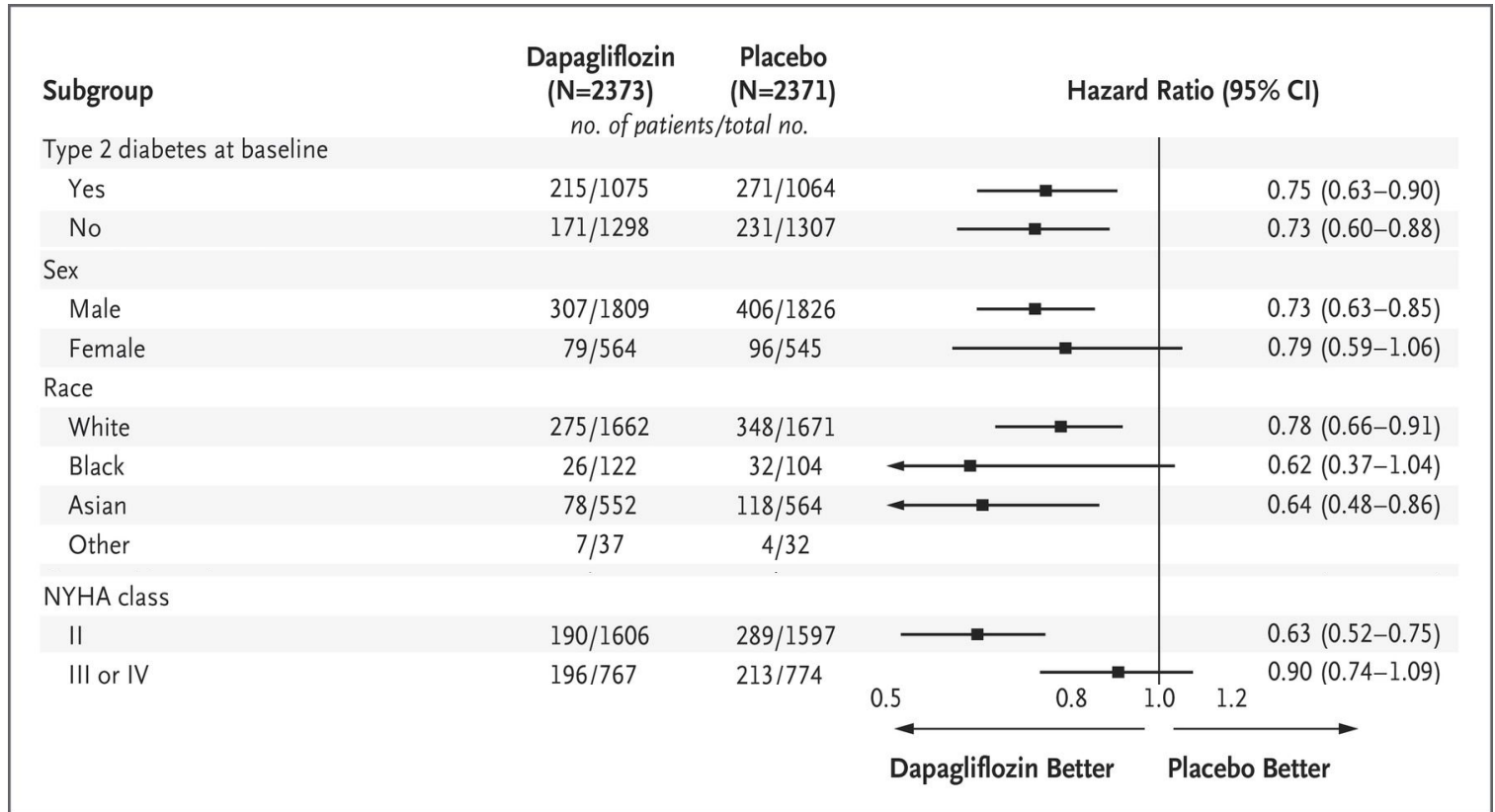
Table 2. Primary and Secondary Cardiovascular Outcomes and Adverse Events of Special Interest.*

Variable	Dapagliflozin (N=2373)		Placebo (N=2371)		Hazard or Rate Ratio or Difference (95% CI)	P Value
	values	events/100 patient-yr	values	events/100 patient-yr		
Efficacy outcomes						
Primary composite outcome — no. (%) [†]	386 (16.3)	11.6	502 (21.2)	15.6	0.74 (0.65 to 0.85)	<0.001
Hospitalization or an urgent visit for heart failure	237 (10.0)	7.1	326 (13.7)	10.1	0.70 (0.59 to 0.83)	NA
Hospitalization for heart failure	231 (9.7)	6.9	318 (13.4)	9.8	0.70 (0.59 to 0.83)	NA
Urgent heart-failure visit	10 (0.4)	0.3	23 (1.0)	0.7	0.43 (0.20 to 0.90)	NA
Cardiovascular death	227 (9.6)	6.5	273 (11.5)	7.9	0.82 (0.69 to 0.98)	NA
Secondary outcomes						
Cardiovascular death or heart-failure hospitalization — no. (%)	382 (16.1)	11.4	495 (20.9)	15.3	0.75 (0.65 to 0.85)	<0.001
Total no. of hospitalizations for heart failure and cardiovascular deaths [‡]	567	—	742	—	0.75 (0.65 to 0.88)	<0.001
Change in KCCQ total symptom score at 8 mo [§]	6.1±18.6	—	3.3±19.2	—	1.18 (1.11 to 1.26)	<0.001
Worsening renal function — no. (%) [¶]	28 (1.2)	0.8	39 (1.6)	1.2	0.71 (0.44 to 1.16)	NA
Death from any cause — no. (%)	276 (11.6)	7.9	329 (13.9)	9.5	0.83 (0.71 to 0.97)	NA

Primary outcome - subgroup analysis

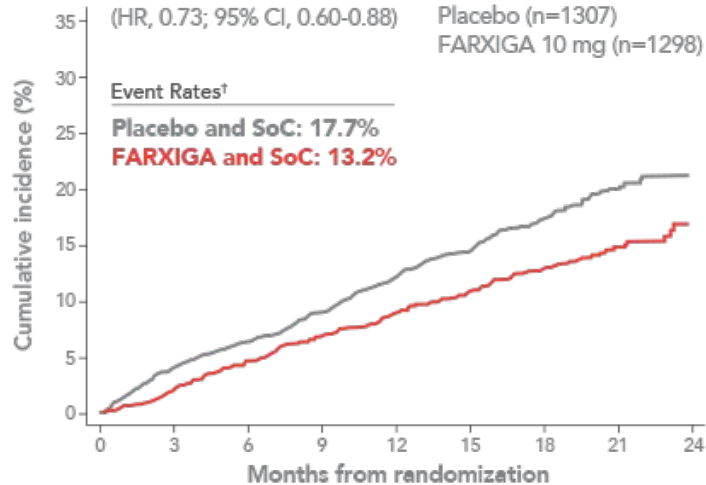
Subgroup	FARXIGA 10 mg (n=2373)	Placebo (n=2371)		Hazard ratio (95% CI)
	<i>number of patients/total number</i>			
All patients	386/2373	502/2371		0.74 (0.65-0.85)
Type 2 diabetes at baseline				
Yes	215/1075	271/1064		0.75 (0.63-0.90)
No	171/1298	231/1307		0.73 (0.60-0.88)

Effect by subgroups



Subgroup analysis - DM vs no DM

Patients without DM2 (n=2605)

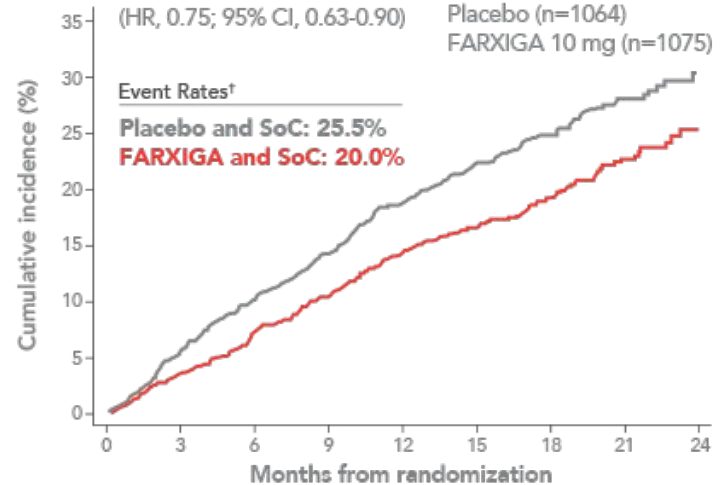



NNT=23

27%
RRR

▼4.5%
ARR

Patients with DM2 (n=2139)




NNT=19

25%
RRR

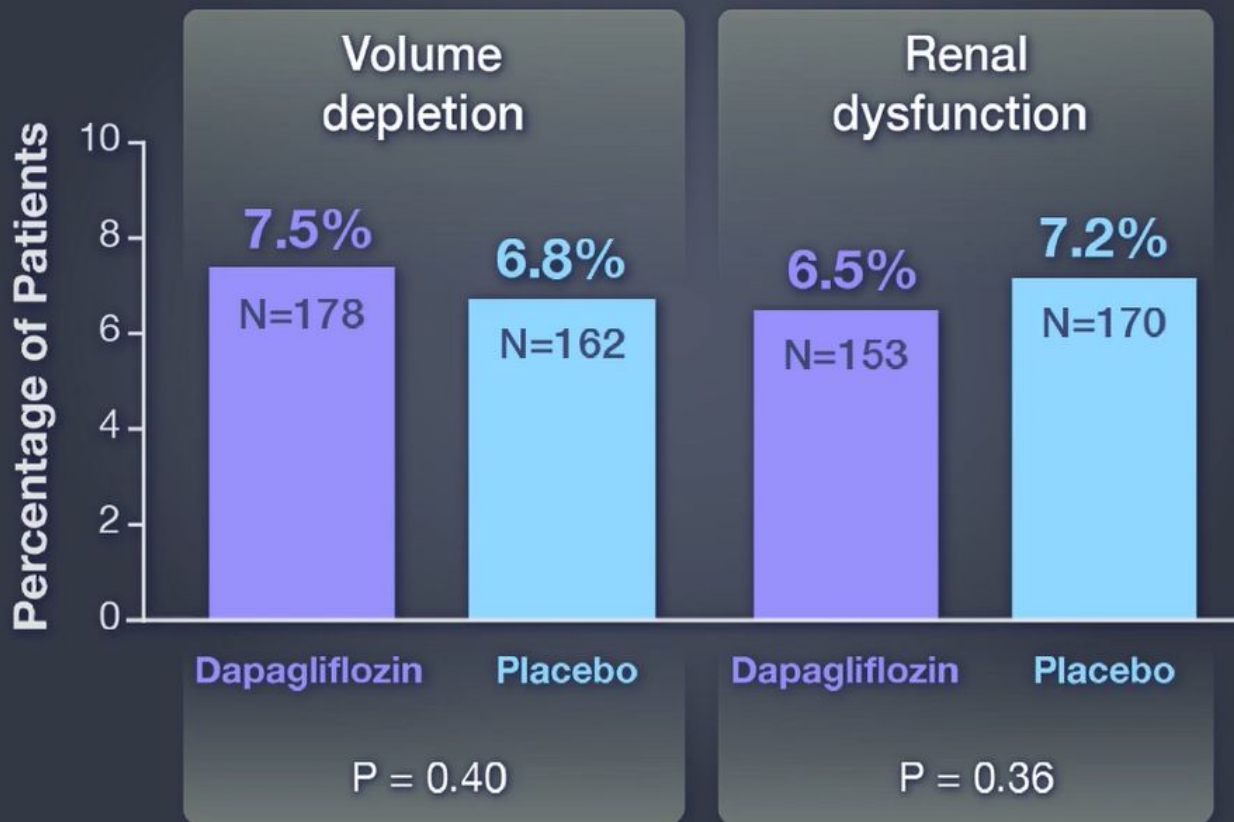
▼5.5%
ARR

Table 2. Primary and Secondary Cardiovascular Outcomes and Adverse Events of Special Interest.*

Variable	Dapagliflozin (N = 2373)		Placebo (N = 2371)		Hazard or Rate Ratio or Difference (95% CI)	P Value
	values	events/100 patient-yr	values	events/100 patient-yr		
Safety outcomes						
Discontinuation due to adverse event — no./total no. (%)	111/2368 (4.7)	—	116/2368 (4.9)	—	—	0.79
Adverse events of interest — no./total no. (%)						
Volume depletion	178/2368 (7.5)	—	162/2368 (6.8)	—	—	0.40
Renal adverse event	153/2368 (6.5)	—	170/2368 (7.2)	—	—	0.36
Fracture	49/2368 (2.1)	—	50/2368 (2.1)	—	—	1.00
Amputation	13/2368 (0.5)	—	12/2368 (0.5)	—	—	1.00
Major hypoglycemia**	4/2368 (0.2)	—	4/2368 (0.2)	—	—	NA
Diabetic ketoacidosis††	3/2368 (0.1)	—	0	—	—	NA
Fournier's gangrene	0	—	1/2368 (<0.1)	—	—	NA
Laboratory and other measures						
Change from baseline to 8 mo‡‡						
Glycated hemoglobin — %§§	-0.21±1.14	—	0.04±1.29	—	-0.24 (-0.34 to -0.13)	<0.001
Creatinine — mg/dl	0.07±0.24	—	0.04±0.25	—	0.02 (0.01 to 0.03)	<0.007
Hematocrit — %	2.31±3.90	—	-0.19±3.81	—	2.41 (2.21 to 2.62)	<0.001
NT-proBNP — pg/ml	-196±2387	—	101±2944	—	-303 (-457 to -150)	<0.001
Weight — kg	-0.88±3.86	—	0.10±4.09	—	-0.87 (-1.11 to -0.62)	<0.001
Systolic blood pressure — mm Hg	-1.92±14.92	—	-0.38±15.27	—	-1.27 (-2.09 to -0.45)	0.002

Safety Outcome

Rates of Adverse Events



Discussion

- Summary of findings
- Strengths
- Limitations

Discussion

- When added to standard therapy, dapagliflozin reduced the risk of worsening HF events and CV death, and improved symptoms in patients with HFrEF, both **with and without DM**
- Benefits occurred early after randomization
- Dapagliflozin was well tolerated
 - <8% volume depletion or worsening kidney function
- Rate of treatment discontinuation due to adverse event was low (<5%)

→ **Dapagliflozin offers new approach to treatment of HFrEF in patients with and without DM**

- 
- A group of seven blue silhouettes of human figures of various heights and builds, standing in a loose cluster. They are positioned on the left side of the image, behind the text.
- Heart failure
 - Reduced ejection fraction

& Appears to be safe

A large, blue, pill-shaped bottle with a white label. The label contains the text 'Dapagliflozin 10 mg Daily' and a list of risks. The bottle is surrounded by several gold-colored pills with a vertical score line. The background is dark blue.

Dapagliflozin

10 mg Daily

Reduced the risk of:

- Worsening heart failure
- Cardiovascular death

Even in patients without diabetes

Discussion - Strengths

- RCT
- Large patient population
- Multicenter trial across different countries
 - Increased external validity
- Independent analyses from sponsor
- Follow up time 24 months

Discussion - Limitations

- Limited generalizability due to specific inclusion and exclusion criteria
- <5% black patients
- Few very elderly patients with multiple coexisting illnesses
- Few NYHA III or IV
- Women ~ 25%
- Mean BMI ~ 28
- Not included in AE: UTI's, yeast infx

Mechanism of action?

Hypotheses:

- SGLT2 inhibitors mitigate glycemia-related cardiotoxicity
- Enhanced ketogenesis contributes to the benefit of heart failure
- Renal sodium excretion
- Increase in hematocrit favorable for CAD
 - Increase in hematocrit did not affect clinical course of pts with HF

DAPA-HF did not support the above hypotheses

FDA approval

FDA approves new treatment for a type of heart failure

- May 5 2020
- Dapagliflozin approved specifically for the treatment of patients with heart failure and a reduced ejection fraction

MEDICATION GUIDE
FARXIGA® (FAR-SEE-GUH)
(dapagliflozin)
tablets, for oral use

What is FARXIGA?

FARXIGA is a prescription medicine used in adults with:

- **Type 2 diabetes to:**
 - improve blood sugar (glucose) control along with diet and exercise
 - reduce the risk of hospitalization for heart failure in people who also have known cardiovascular disease or multiple cardiovascular risk factors
- **Heart failure when the heart is weak and cannot pump enough blood to the rest of your body to:**
 - reduce the risk of cardiovascular death, hospitalization for heart failure

FARXIGA is not for people with type 1 diabetes.

FARXIGA is not for people with diabetic ketoacidosis (increased ketones in your blood or urine).

It is not known if FARXIGA is safe and effective in children younger than 18 years of age.

New Guidelines

Canadian Journal of Cardiology 36 (2020) 159–169

Society Guidelines

CCS/CHFS Heart Failure Guidelines: Clinical Trial Update on Functional Mitral Regurgitation, SGLT2 Inhibitors, ARNI in HFpEF, and Tafamidis in Amyloidosis

8. New. We recommend SGLT2 inhibitors, such as dapagliflozin be used in patients with mild to moderate HF due to reduced LVEF ($\leq 40\%$) and concomitant type 2 diabetes, to improve symptoms and quality of life and to reduce the risk of hospitalization and cardiovascular mortality (Strong Recommendation, High-Quality Evidence).

9. New. We recommend SGLT2 inhibitors, such as dapagliflozin be used in patients with mild to moderate HF due to reduced LVEF ($\leq 40\%$) and without concomitant diabetes, to improve symptoms and quality of life and to reduce the risk of hospitalization and cardiovascular mortality (Conditional Recommendation, High-Quality Evidence).

Future directions

- EMPEROR-Reduced trial (NEJM, Aug 2020): empagliflozin, more severe HF
 - Similar results

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

Milton Packer, M.D., Stefan D. Anker, M.D., Ph.D., Javed Butler, M.D., Gerasimos Filippatos, M.D., Stuart J. Pocock, Ph.D., Peter Carson, M.D., James Januzzi, M.D., Subodh Verma, M.D., Ph.D., Hiroyuki Tsutsui, M.D., Martina Brueckmann, M.D., Waheed Jamal, M.D., Karen Kimura, Ph.D., et al., for the EMPEROR-Reduced Trial Investigators*

- RCT dapagliflozin vs empagliflozin
- Most effective dosage
- Mechanism of action





European Journal of Heart Failure (2019) 21, 1279–1287
doi:10.1002/ejhf.1596

TRIAL DESIGN

Evaluation of the effects of sodium–glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality in patients with chronic heart failure and a preserved ejection fraction: rationale for and design of the EMPEROR-Preserved Trial

Practice implications for JFMA

- Dapagliflozin 10mg seems to be effective & safe for patients with mild-mod HFrEF in reducing worsening HF and death
- Additional data needed
 - More severe HF
 - More diverse patient population
 - Higher BMI
 - More comorbidities
- How to explain to our patients?
- High costs
 - Discount not for Medicare/Medicaid

		Instant Savings on FARXIGA		GET FREE COUPON
		Simply download your coupon and present it at your pharmacy. Subject to eligibility. Restrictions apply.		Sponsored
Walmart	\$607 retail Save 15%	\$509.78 with free discount	GET FREE DISCOUNT	Exclusive! Restrictions apply
Costco	\$595 retail Save 14%	\$509.78 with free discount	GET FREE DISCOUNT	Exclusive! Restrictions apply
CVS Pharmacy 	\$593 retail Save 14%	\$509.78 with free discount	GET FREE DISCOUNT	Exclusive! Restrictions apply

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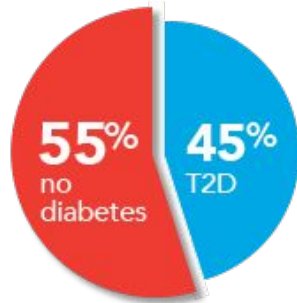
Anker SD, Butler J, Filippatos GS, et al. Evaluation of the effects of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality in patients with chronic heart failure and a preserved ejection fraction: rationale for and design of the EMPEROR-Preserved Trial. *Eur J Heart Fail*. 2019;21(10):1279-1287. doi:10.1002/ejhf.1596

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Questions?



ELIGIBILITY CRITERIA

- ≥ 18 years of age
- Diagnosis of symptomatic HFrEF (NYHA class II-IV)
- LVEF $\leq 40\%$
- Elevated NT-proBNP ≥ 600 pg/mL (or ≥ 400 pg/mL if hospitalized for heart failure within the past 12 months)
- eGFR ≥ 30 mL/min/1.73 m²

1:1
Randomization

FARXIGA 10 mg and
standard of care
(n=2373)

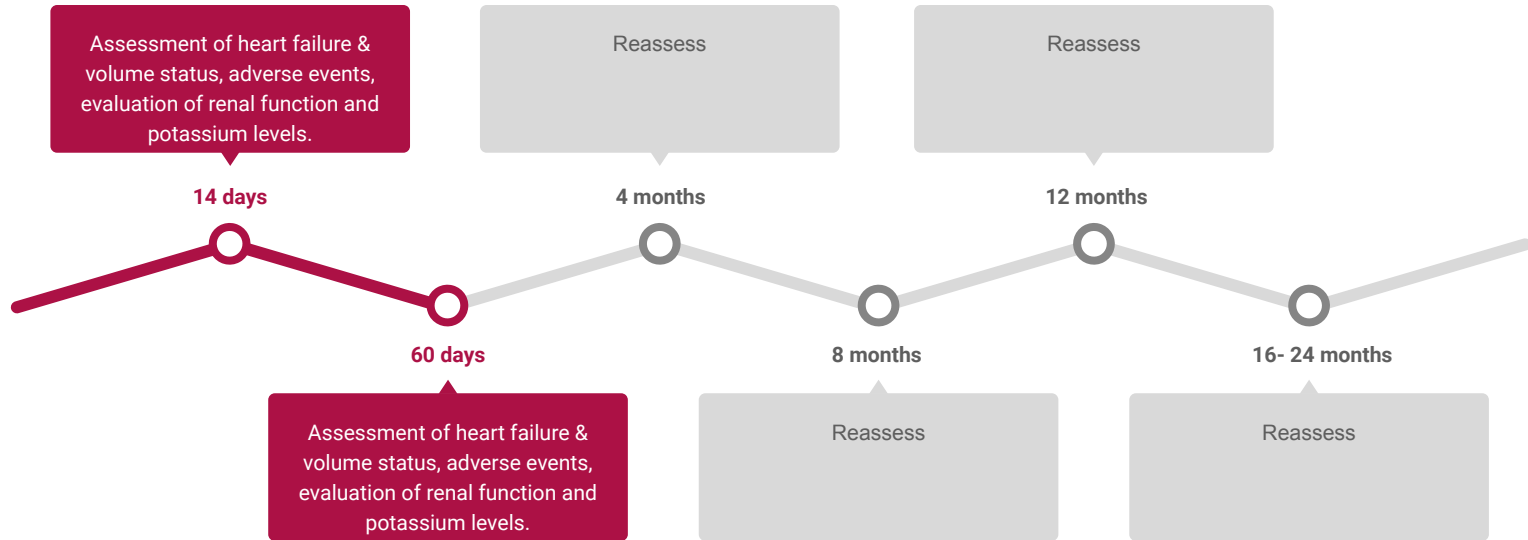
Placebo and
standard of care
(n=2371)

MEDIAN FOLLOW-UP: 18.2 MONTHS

Methods - Procedures

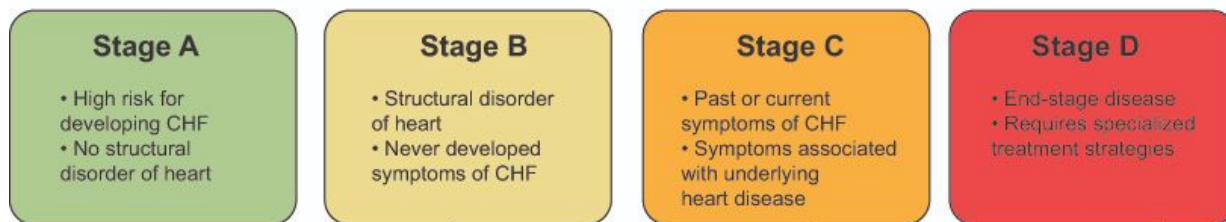
- 14 day screening period: baseline criteria, in- and exclusion criteria
- Random assignment to treatment vs placebo group
 - Dapagliflozin 10mg once daily
- Randomization: sequestered, fixed-randomization schedule; use of balanced blocks → 1:1 ratio
-

Methods - Procedures

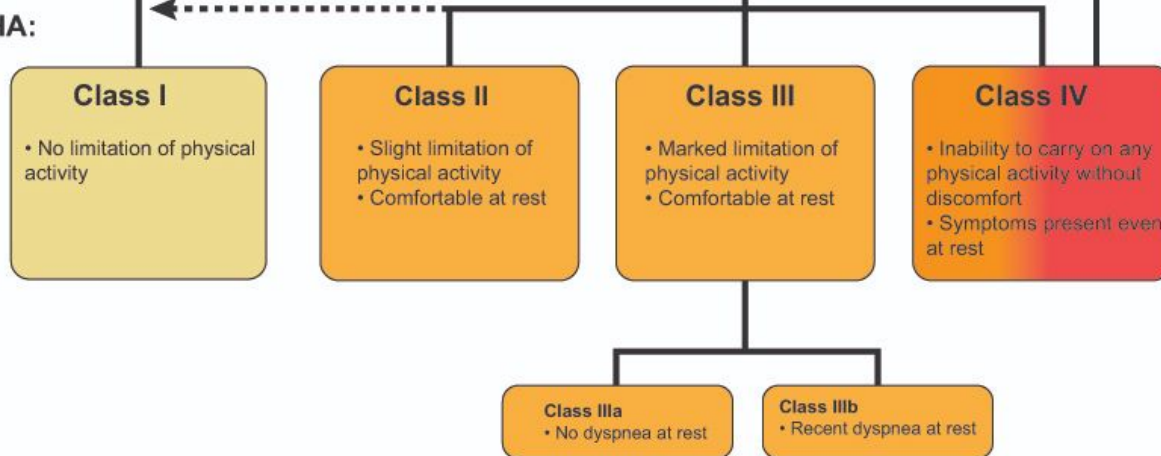


- Dapagliflozin or placebo discontinued if pregnancy, DKA
- Dose reduction or temporary discontinuation: if acute unexpected decline in eGFR, volume depletion or hypotension

ACC/AHA:



NYHA:



SGLT2 Inhibitor



- ↑ Natriuresis
- ↑ Diuresis
- ↑ Glycosuria
- ↓ Intraglomerular pressure



- ↑ Metabolic efficiency
- ↑ Oxygen supply
- ↓ Oxidative stress
- ↓ Fibrosis
- ↓ Epicardial fat
- ↓ Neurohormonal stimulation

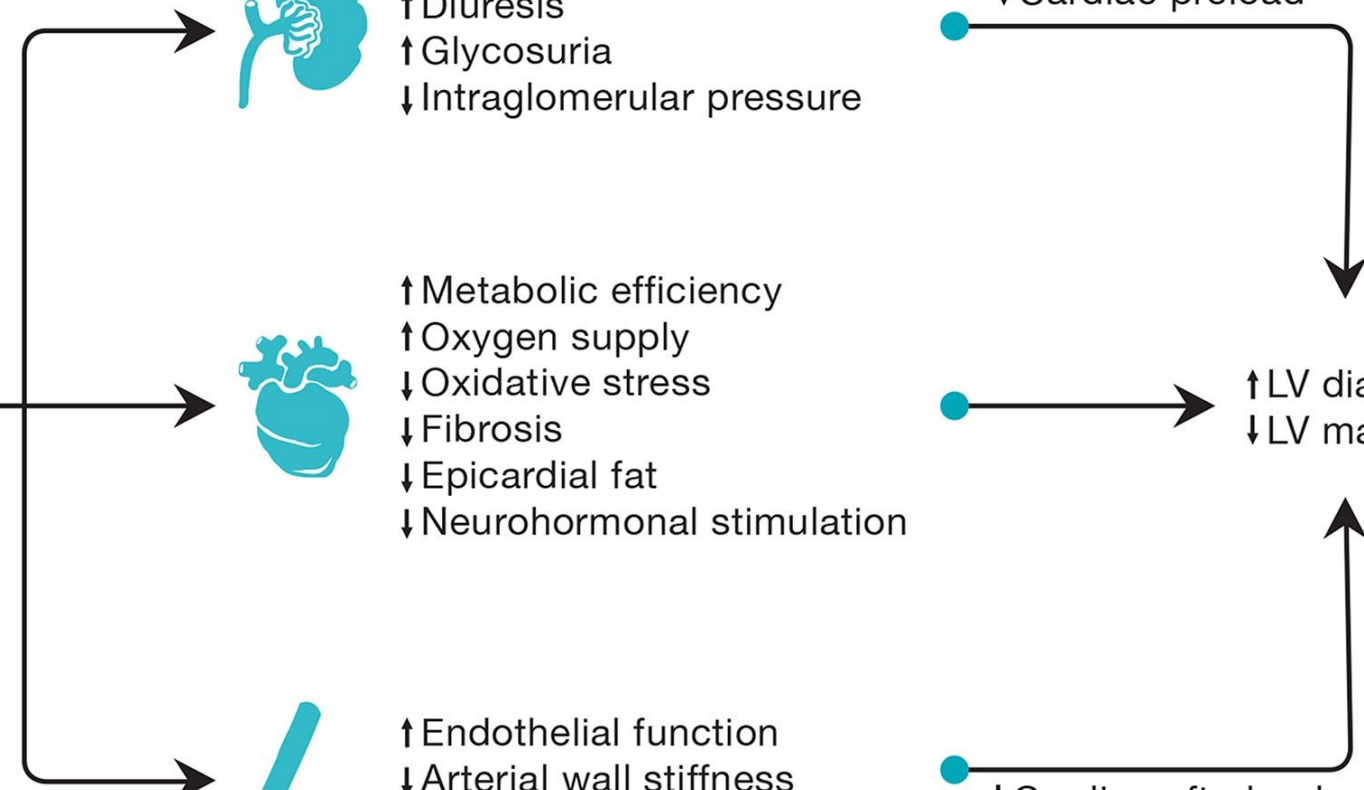


- ↑ Endothelial function
- ↓ Arterial wall stiffness
- ↓ Vascular resistance

↓ Cardiac preload

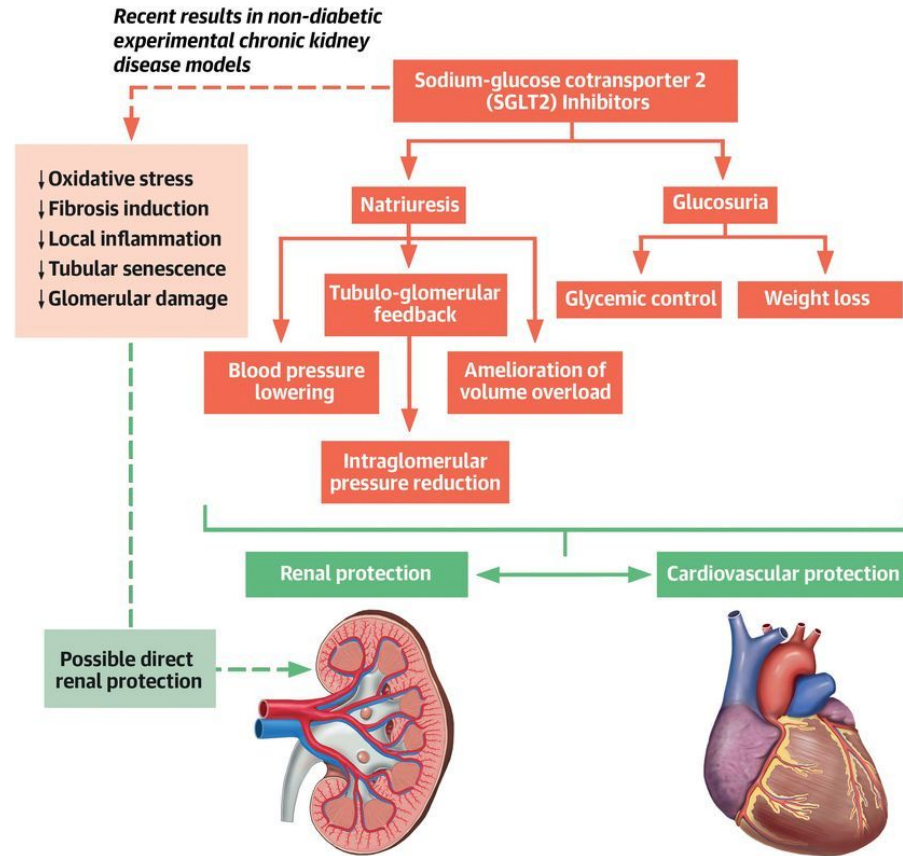
↑ LV diastolic function
↓ LV mass

↓ Cardiac afterload



MOA

CENTRAL ILLUSTRATION: Sodium-Glucose Cotransporter 2 Inhibitor Cardiorenal Protection Mechanistic Overview

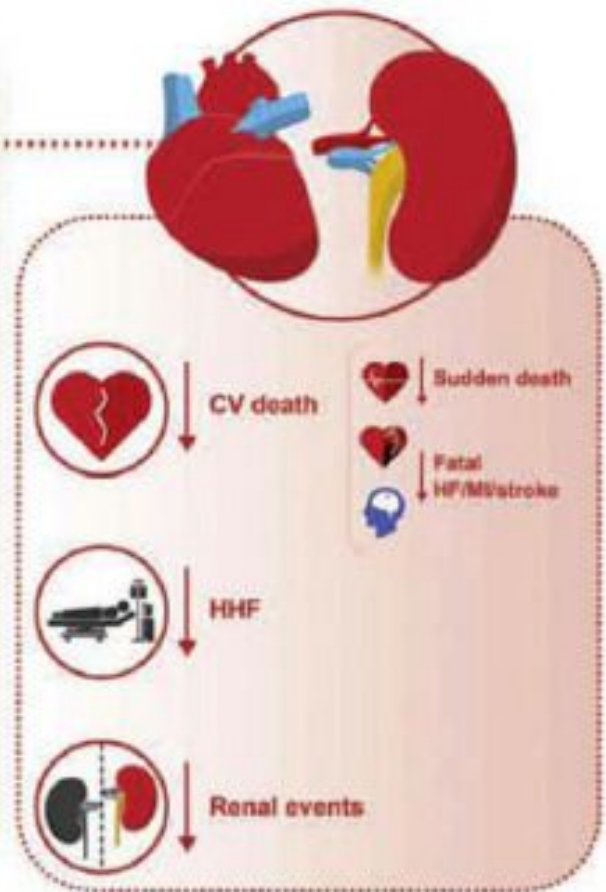
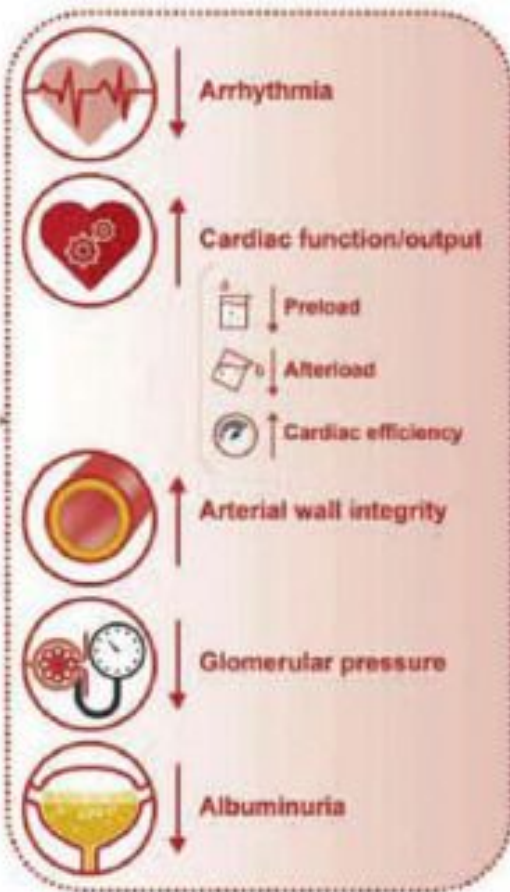
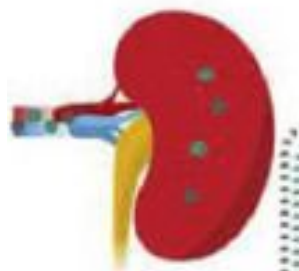


SGLT2i

Pathway

Possible cardio-renal benefits

CV/renal outcomes observed in
EMPA-REG OUTCOME®



Time to event

Hazard = instantaneous event rate

Probability of an individual at time t has event happening at that time

Hazard Ratio

Probability of events in treatment group / probability of events in control group

- $HR = 1$ (at any time, event rates similar in both arms)
- $HR 0.5$ (at any time, half as many patients in treatment group are having an event proportionally to comparison group)

$HR \neq RR$

Relative Risk (Risk Ratio) =

Risk (cumulative incidence) treatment group / risk placebo group

Relative Risk Reduction (efficacy) = 1-RR

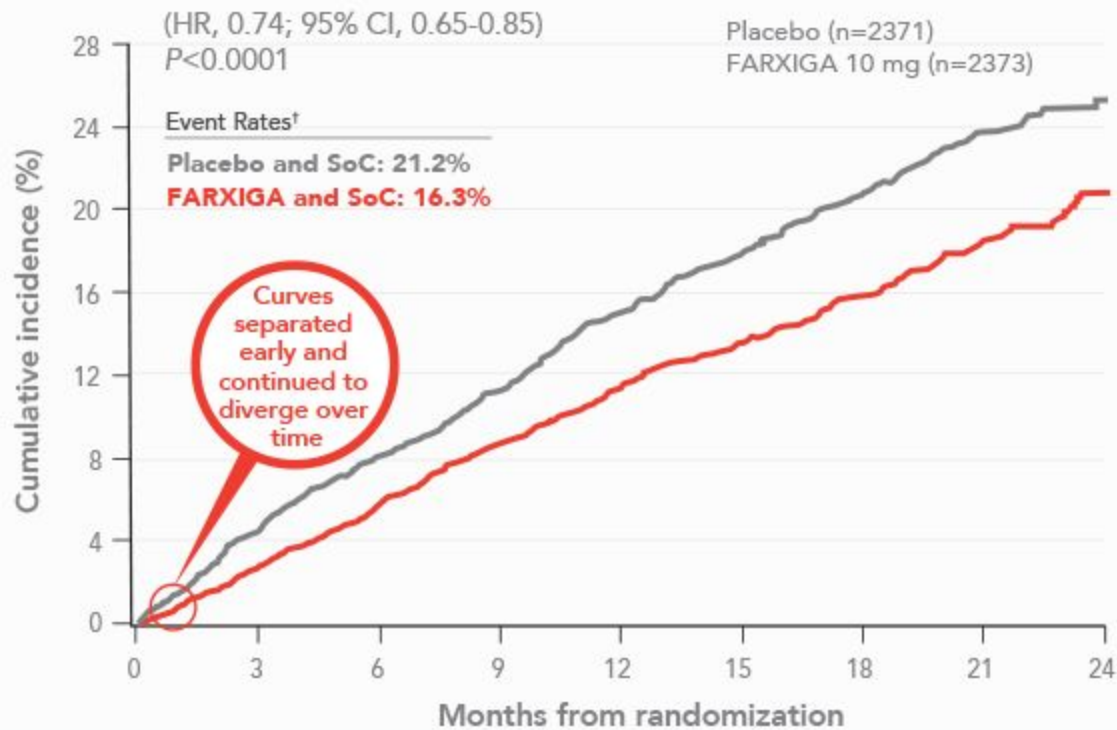
Relative decrease in risk of event in exposed group compared to unexposed group

Absolute Risk Reduction

Disease risk in placebo group - disease risk in treatment group

NNT = 1/ARR

How many patients need treatment before 1 patient benefits



26% RRR

▼ **4.9%** ARR



NNT=21