9-24-2020

Journal Club - DAPA-HF trial

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Journal Club

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DAPA-HF trial

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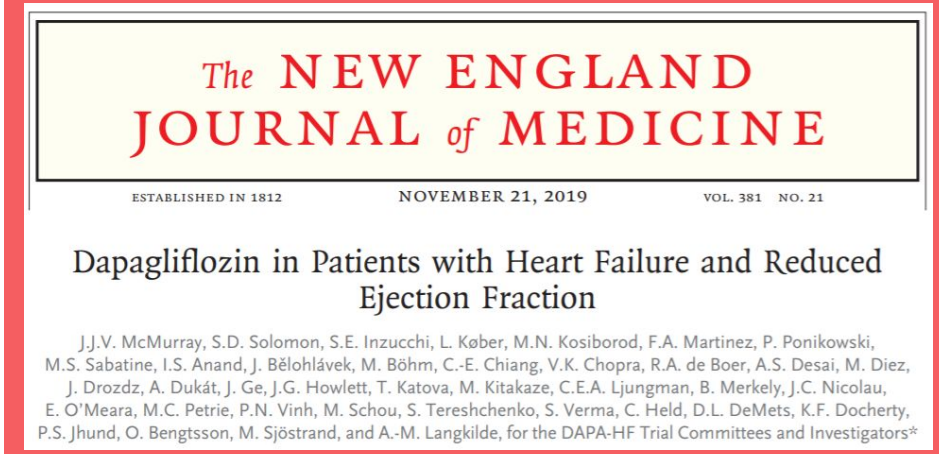
9/24/20



Disclosures

I have no disclosures

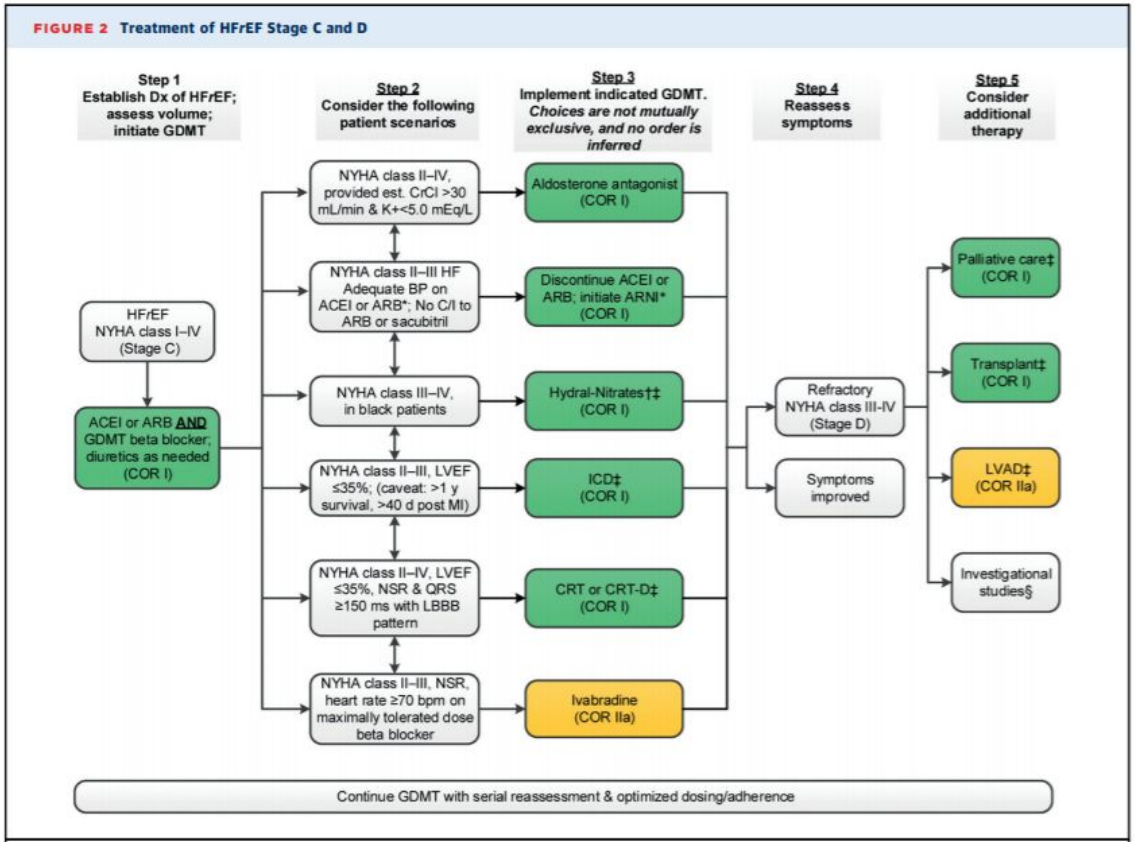
Outline

- 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



AMERICAN COLLEGE of CARDIOLOGY

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

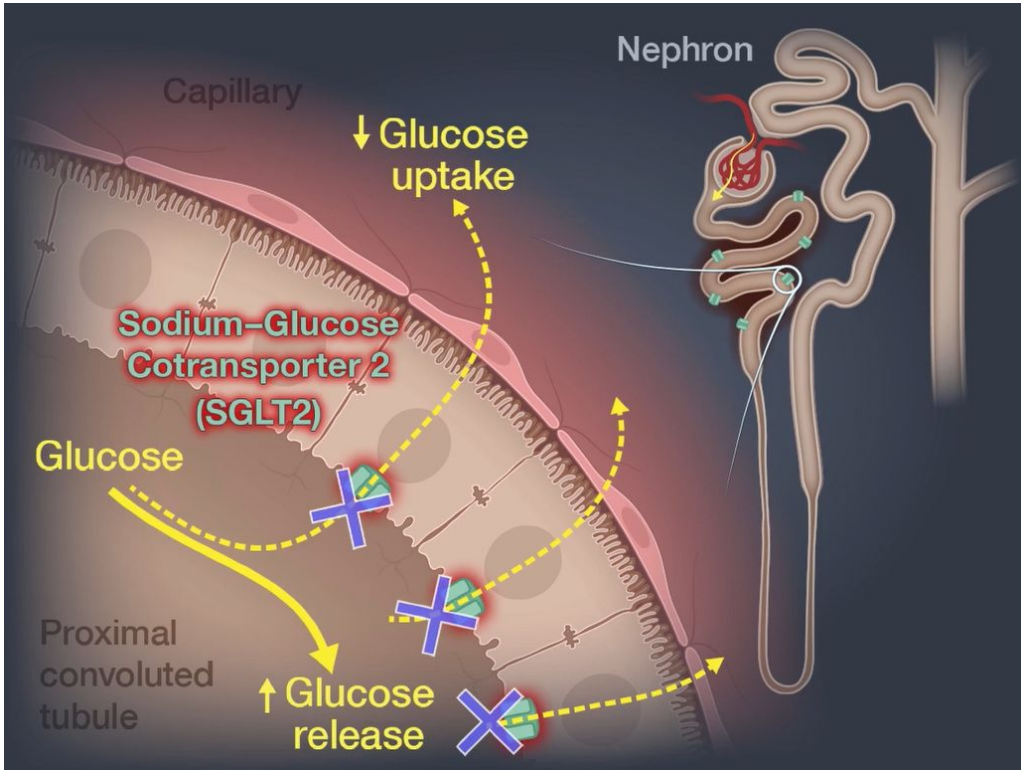
B: Structural heart failure but without symptoms

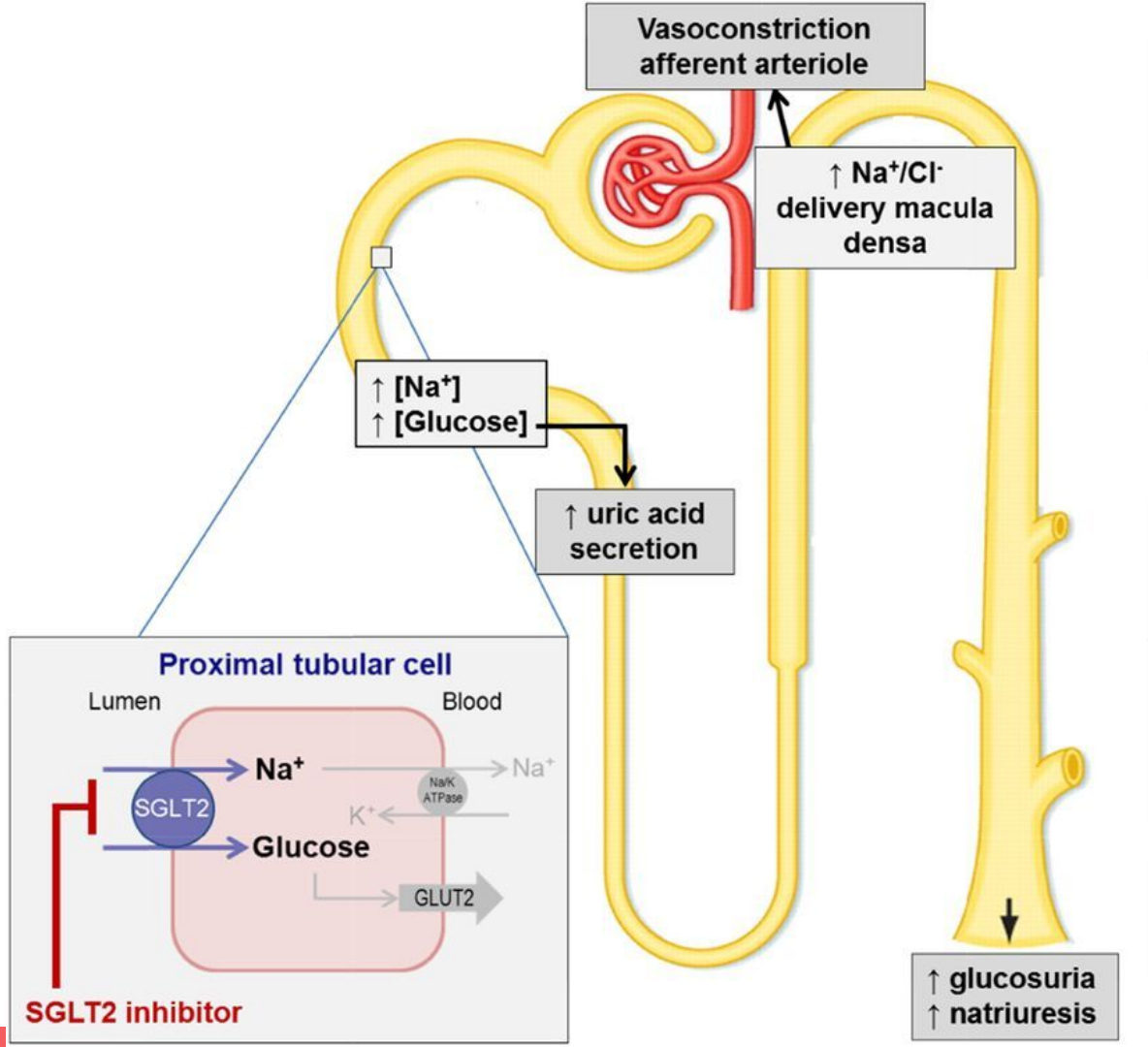
C: Structural heart failure with current or prior symptoms

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





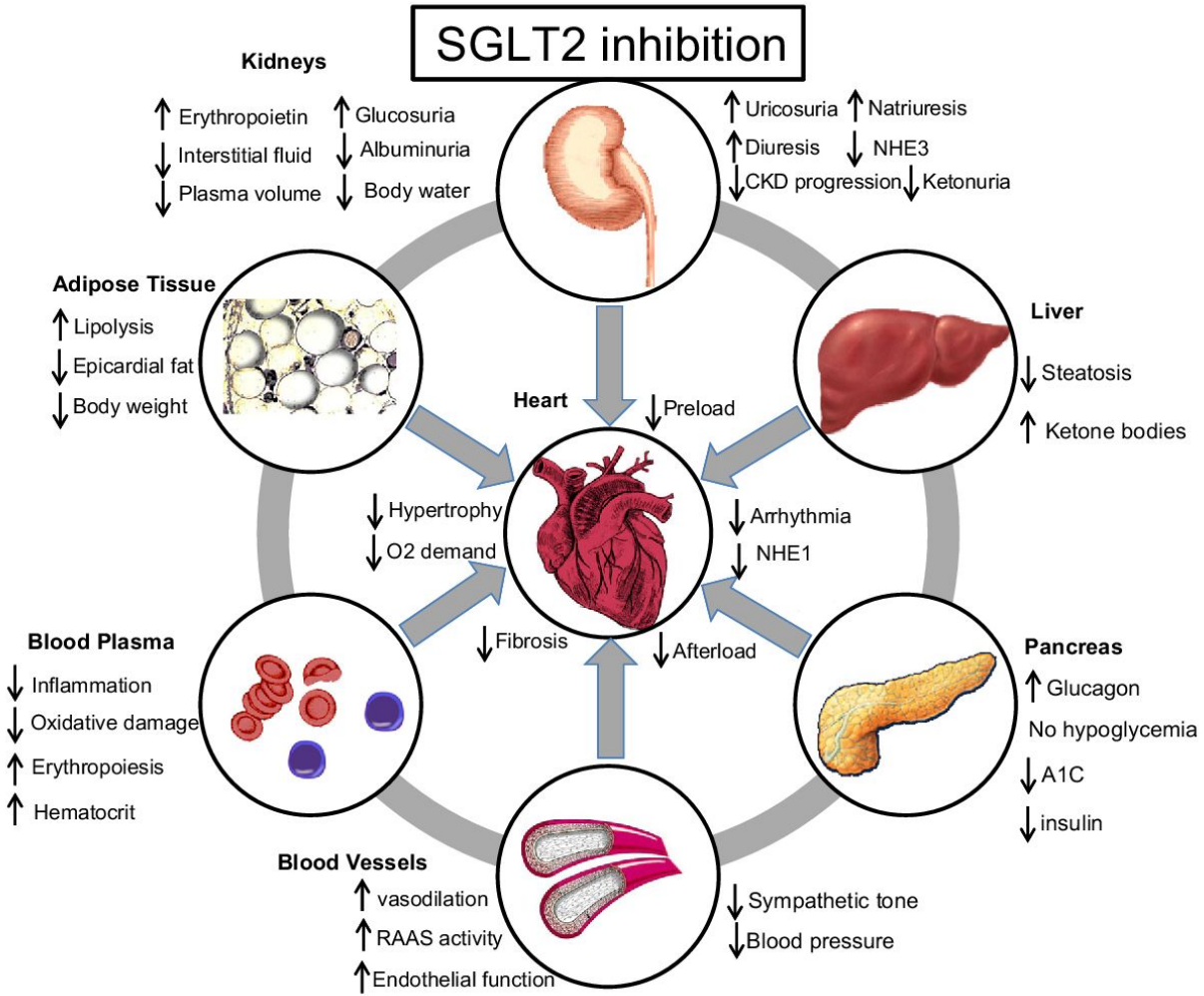
Clinical findings

- ↓ 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 Neal [1], Vlado Perkovic [1], Kenneth W Mahaffey [1], Dick de Zeeuw [1], Greg Fulcher [1], Ngozi Erondu [1], Wayne Shaw [1], Gordon Law [1], Mehul Desai [1], David R Matthews [1], 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 Zinman [1], 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 Wiviott [1], Itamar Raz [1], Marc P Bonaca [1], Ofri Mosenzon [1], Eri T Kato [1], Avivit Cahn [1], Michael G Silverman [1], Thomas A Zelniker [1], Julia F Kuder [1], Sabina A Murphy [1], Deepak L Bhatt [1], Lawrence A Leiter [1], Darren K McGuire [1], John P H Wilding [1], Christian T Ruff [1], Ingrid A M Gause-Nilsson [1], Martin Fredriksson [1], Peter A Johansson [1], Anna-Maria Langkilde [1], Marc S Sabatine [1], 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, MD[1]; Stefan D. Anker, MD[2,3]; Javed Butler, MD, MPH[4]; et al

» Author Affiliations

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

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. Bělohlávek, M. Böhm, C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diez, J. Drozdz, 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*

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

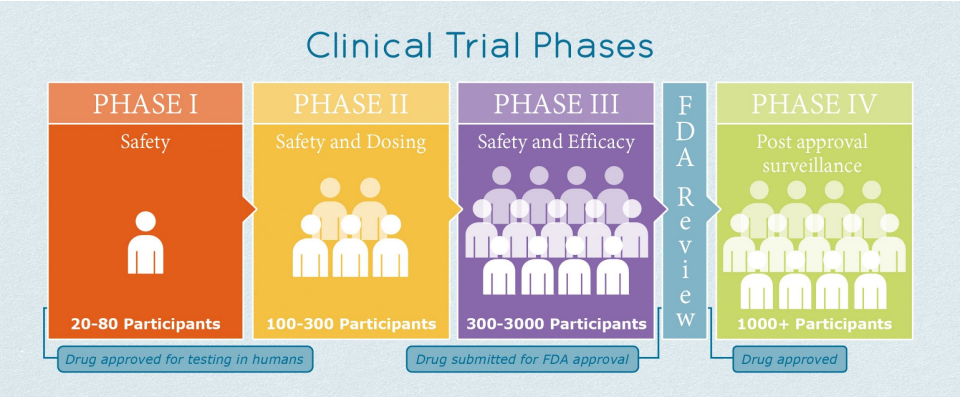
- Trial design
- Patients
- Outcomes
- Statistical analyses

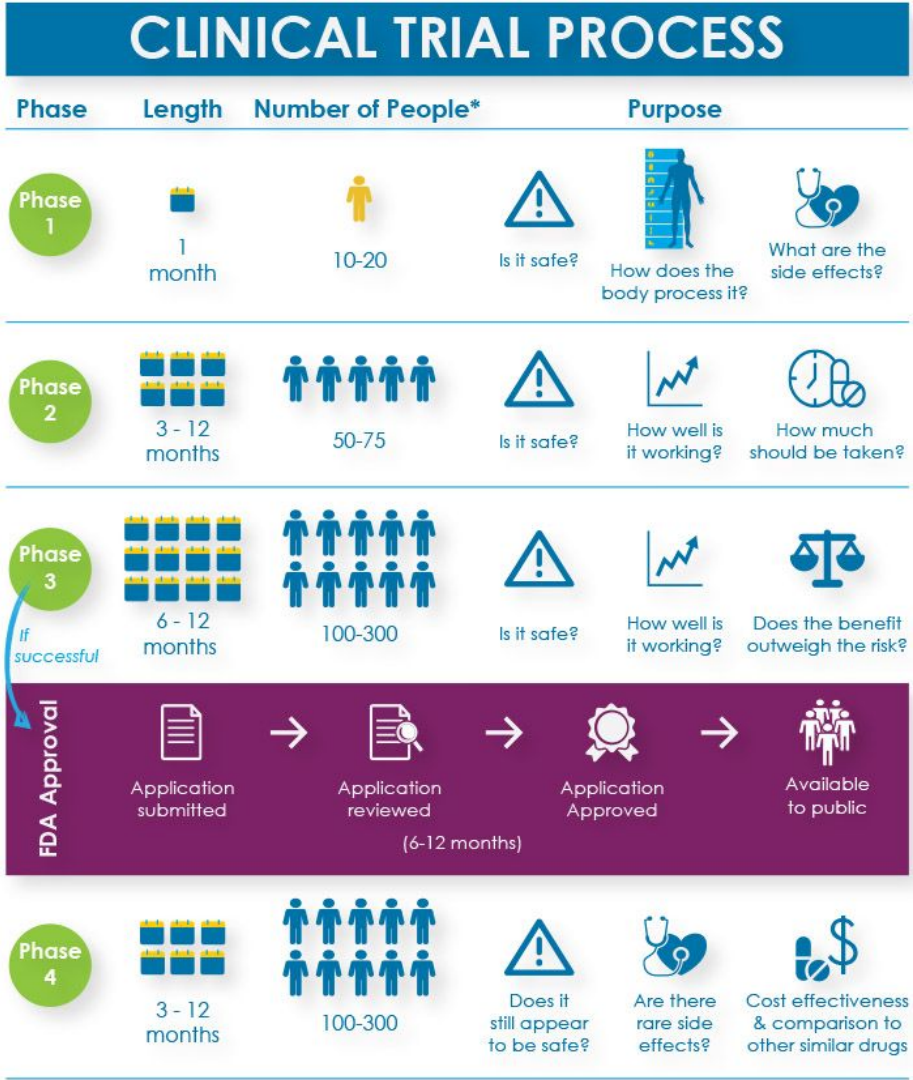
Methods - Trial design

- 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 ≥ 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





Methods - Patients

Inclusion criteria:

- Age ≥ 18 years
- EF ≤ 40%
- NYHA class II-IV
- NT-proBNP ≥ 600 pg/ml
  - or ≥ 400 pg/ml if HF hospitalization in previous 12 mo)
  - Afib or Aflutter: NT-proBNP ≥ 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 ≤ 30

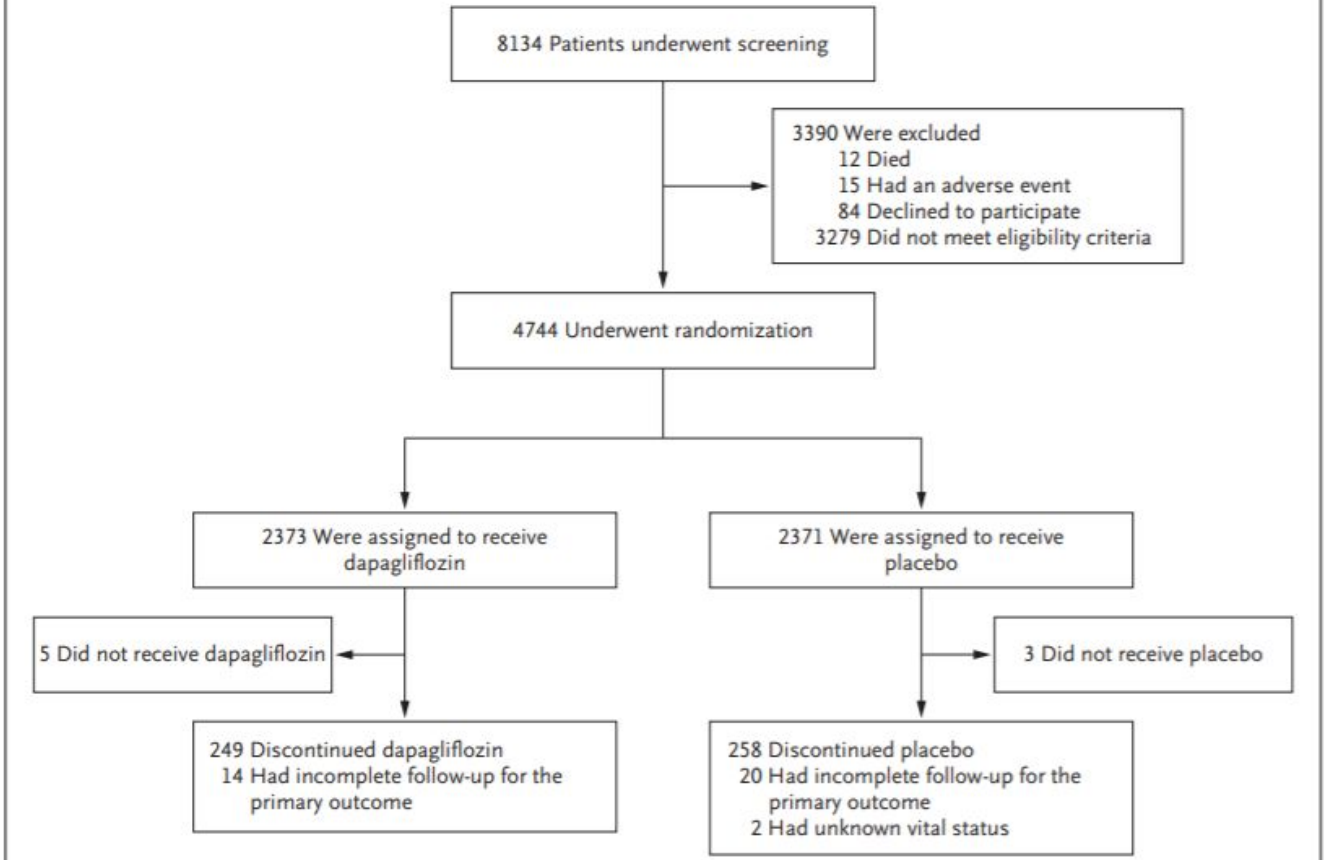


Figure 1. Enrollment and Follow-up.

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
  - ≥ 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 ea 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 ≠RR

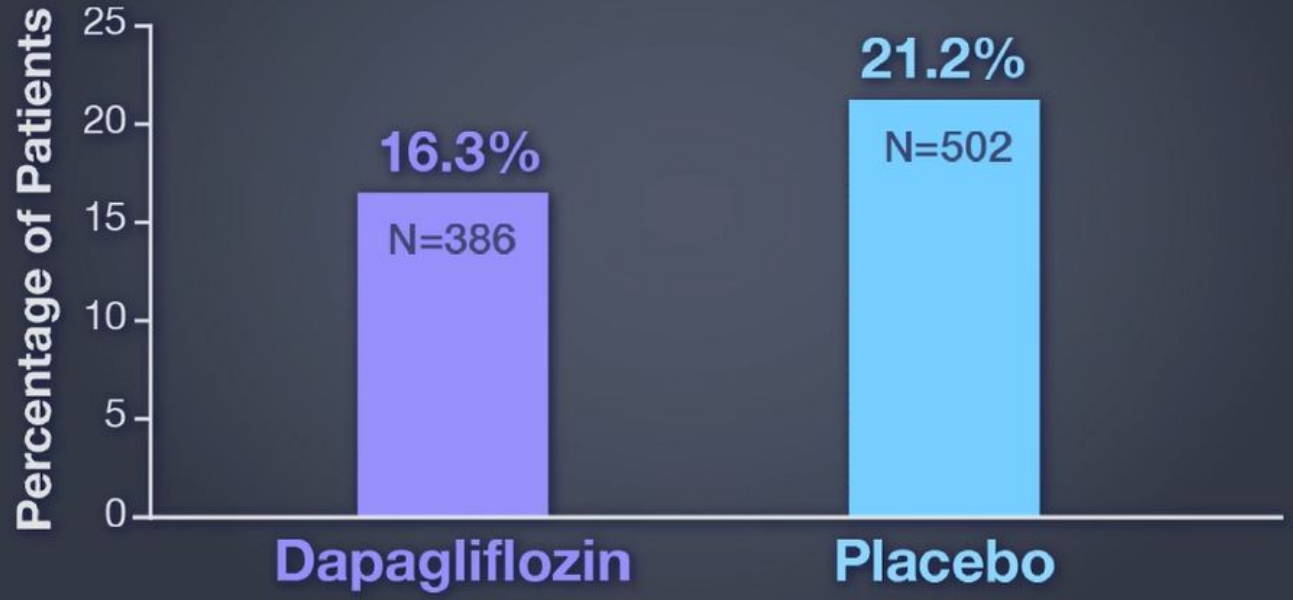
→ Time to event

Results

- Efficacy Outcomes
- Safety Outcomes

Primary Outcome

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



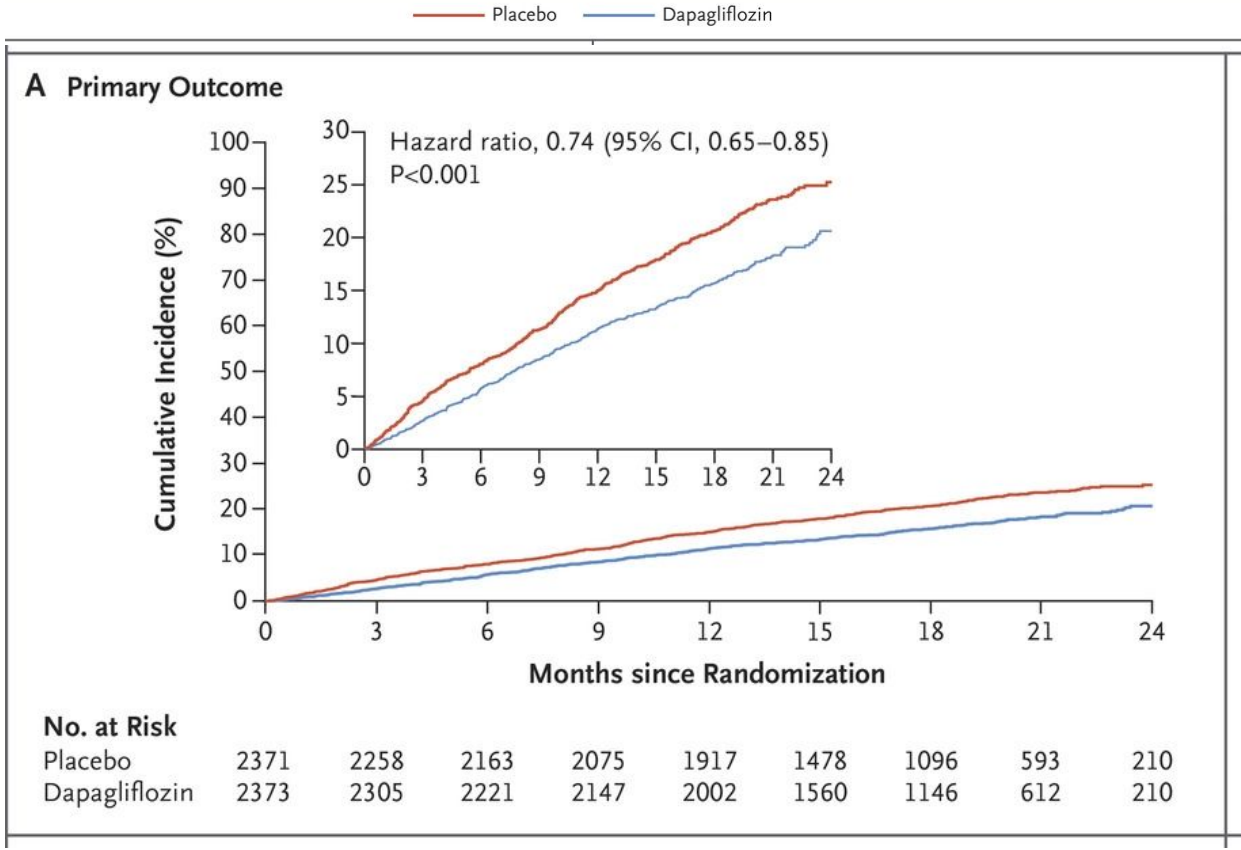
Hazard Ratio, 0.74; 95% CI, 0.65 to 0.85; P<0.001

Primary outcome - Worsening HF or CV death

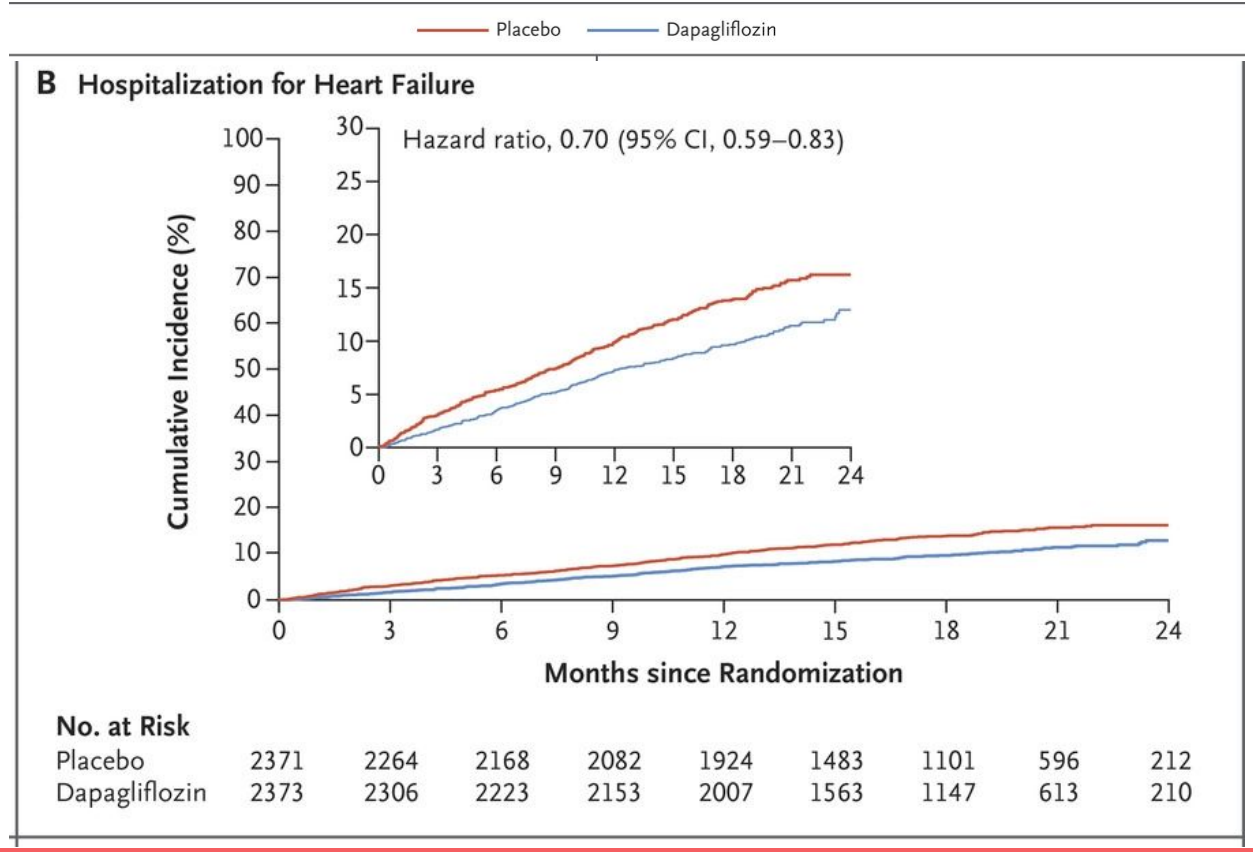
HR 0.74

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

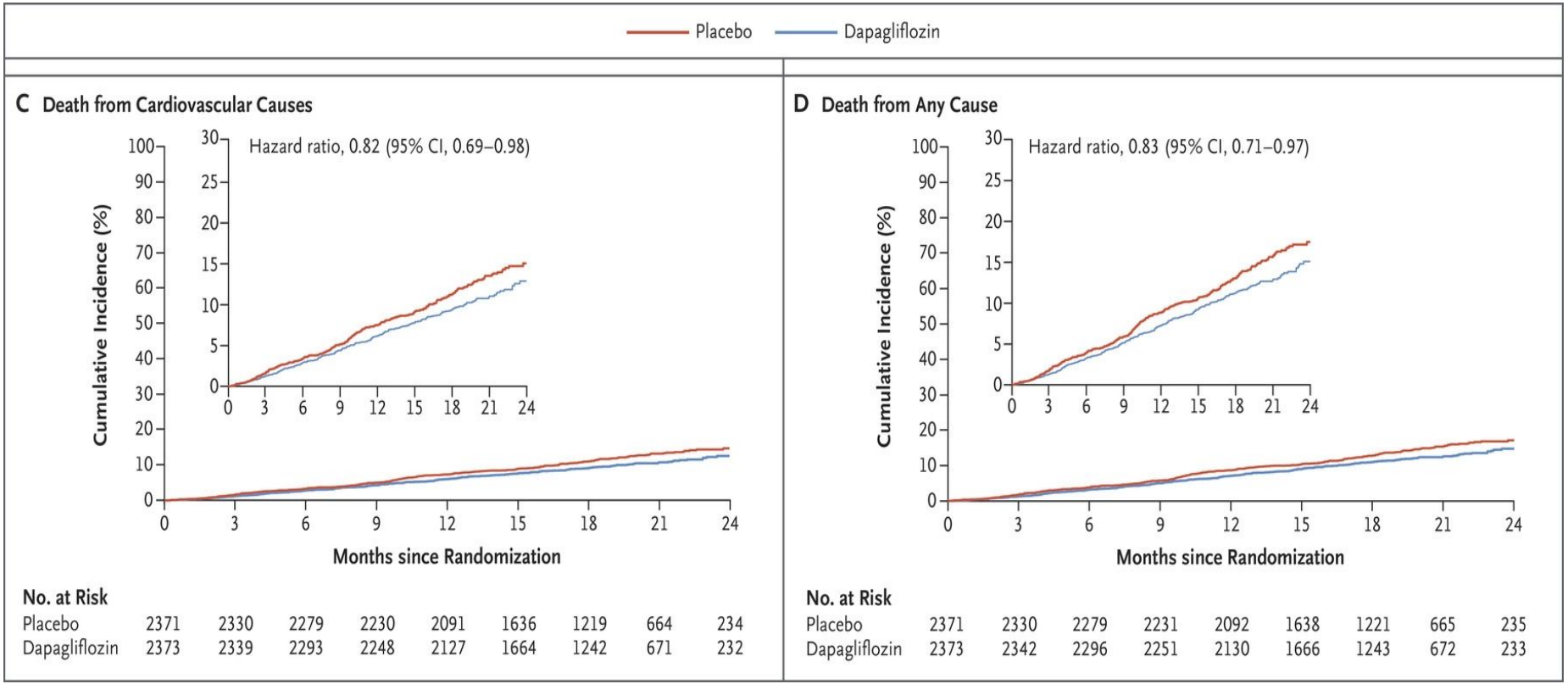
NNT = 21



Secondary outcome - HF hospitalization



Secondary outcome - mortality



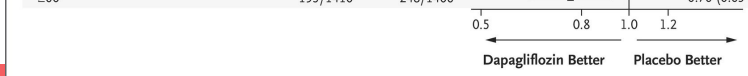
Efficacy outcomes

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

Effect by subgroups

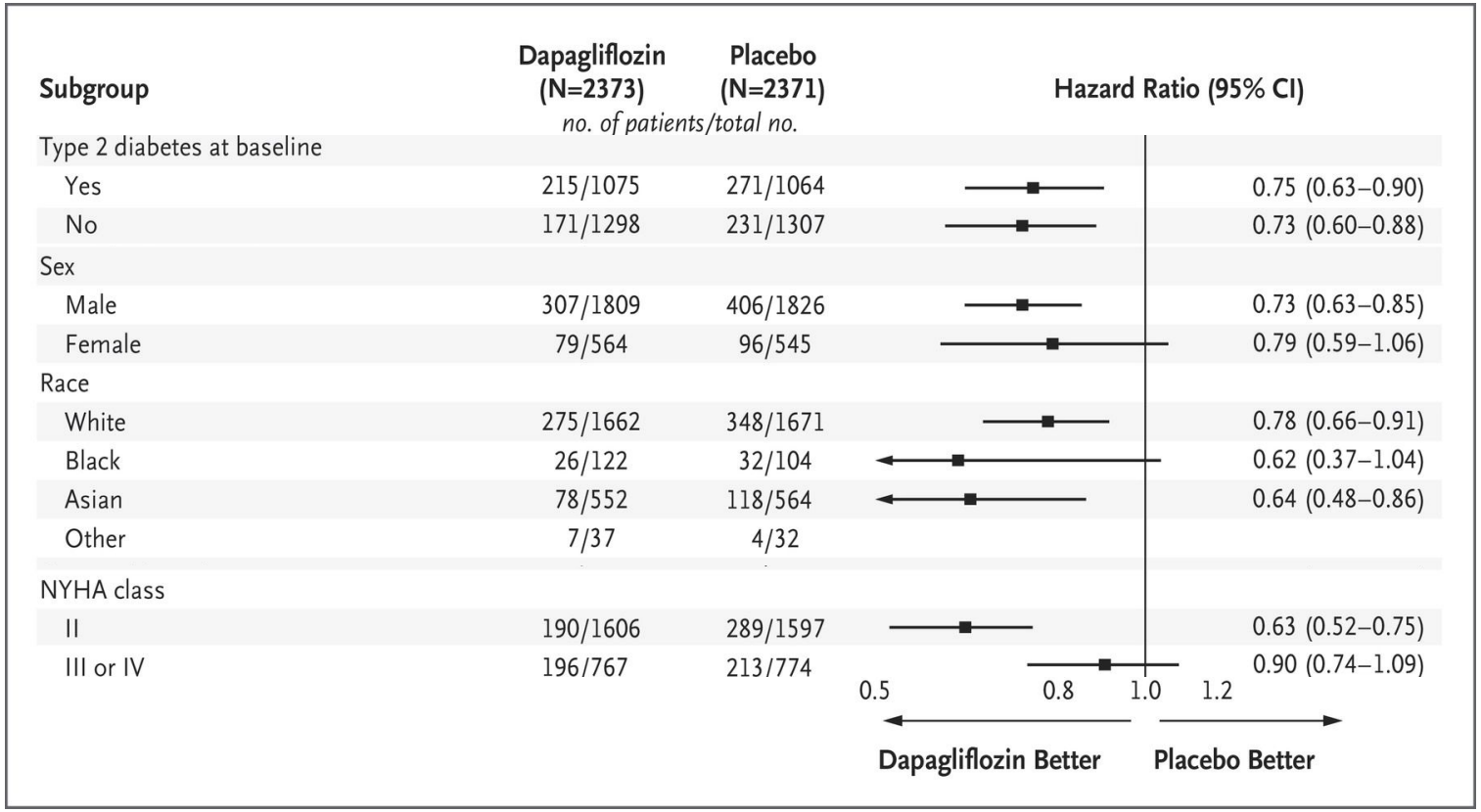
Subgroup	Dapagliflozin (N=2373)	Placebo (N=2371)	Hazard Ratio (95% CI)
	no. of patients/total no.		
All patients	386/2373	502/2371	0.74 (0.65–0.85)
Age			
≤65 yr	162/1032	196/998	0.78 (0.63–0.96)
>65 yr	224/1341	306/1373	0.72 (0.60–0.85)
Sex			
Male	307/1809	406/1826	0.73 (0.63–0.85)
Female	79/564	96/545	0.79 (0.59–1.06)
Race			
White	275/1662	348/1671	0.78 (0.66–0.91)
Black	26/122	32/104	0.62 (0.37–1.04)
Asian	78/552	118/564	0.64 (0.48–0.86)
Other	7/37	4/32	
Geographic region			
Asia	77/543	114/553	0.65 (0.49–0.87)
Europe	193/1094	218/1060	0.84 (0.69–1.01)
North America	54/335	73/342	0.73 (0.51–1.03)
South America	62/401	97/416	0.64 (0.47–0.88)
NYHA class			
II	190/1606	289/1597	0.63 (0.52–0.75)
III or IV	196/767	213/774	0.90 (0.74–1.09)
LVEF			
≤Median	222/1230	307/1239	0.70 (0.59–0.84)
>Median	164/1143	195/1132	0.81 (0.65–0.99)
NT-proBNP			
≤Median	100/1193	155/1179	0.63 (0.49–0.80)
>Median	286/1179	347/1191	0.79 (0.68–0.92)
Hospitalization for heart failure			
Yes	195/1124	279/1127	0.67 (0.56–0.80)
No	191/1249	223/1244	0.84 (0.69–1.01)
MRA at baseline			
Yes	281/1696	361/1674	0.74 (0.63–0.87)
No	105/677	141/697	0.74 (0.57–0.95)
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)
Atrial fibrillation or flutter on enrollment ECG			
Yes	109/569	126/559	0.82 (0.63–1.06)
No	277/1804	376/1812	0.72 (0.61–0.84)
Main cause of heart failure			
Ischemic	223/1316	289/1358	0.77 (0.65–0.92)
Nonischemic or unknown	163/1057	213/1013	0.71 (0.58–0.87)
Body-mass index			
<30	259/1537	320/1533	0.78 (0.66–0.92)
≥30	127/834	182/838	0.69 (0.55–0.86)
Baseline eGFR (ml/min/1.73m^2)			
<60	191/962	254/964	0.72 (0.59–0.86)
≥60	195/1410	248/1406	0.76 (0.63–0.92)



Primary outcome – subgroup analysis

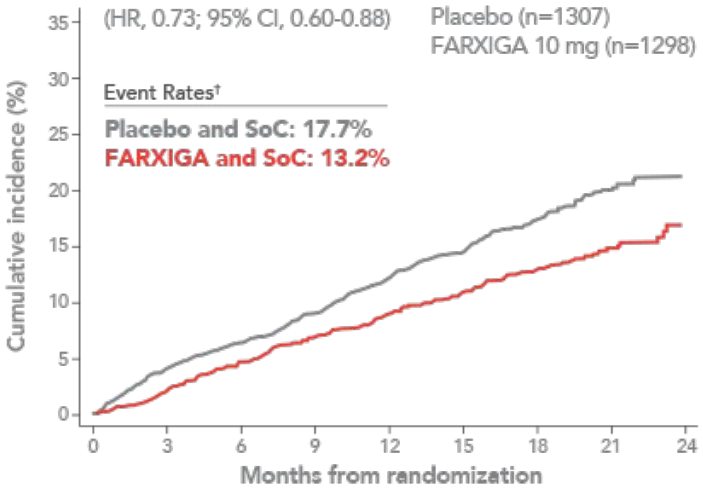
Subgroup	FARXIGA 10 mg (n=2373)	Placebo (n=2371)	Hazard ratio (95% CI)
	number of patients/total number		
All patients	386/2373	502/2371	0.74 (0.65-0.85)
Type 2 diabetes at baseline			
Yes	215/1075	271/1064	0.75 (0.63-0.90)
No	171/1298	231/1307	0.73 (0.60-0.88)

Effect by subgroups



Subgroup analysis - DM vs no DM

Patients without DM2 (n=2605)

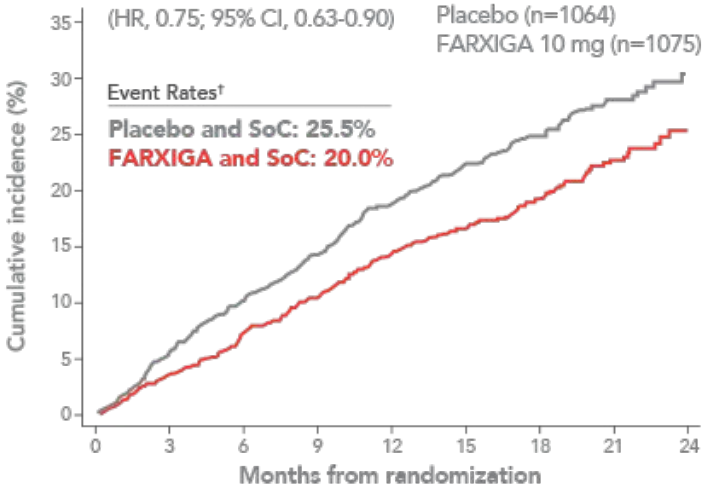


NNT=23

27% RRR

▼4.5% ARR

Patients with DM2 (n-2139)



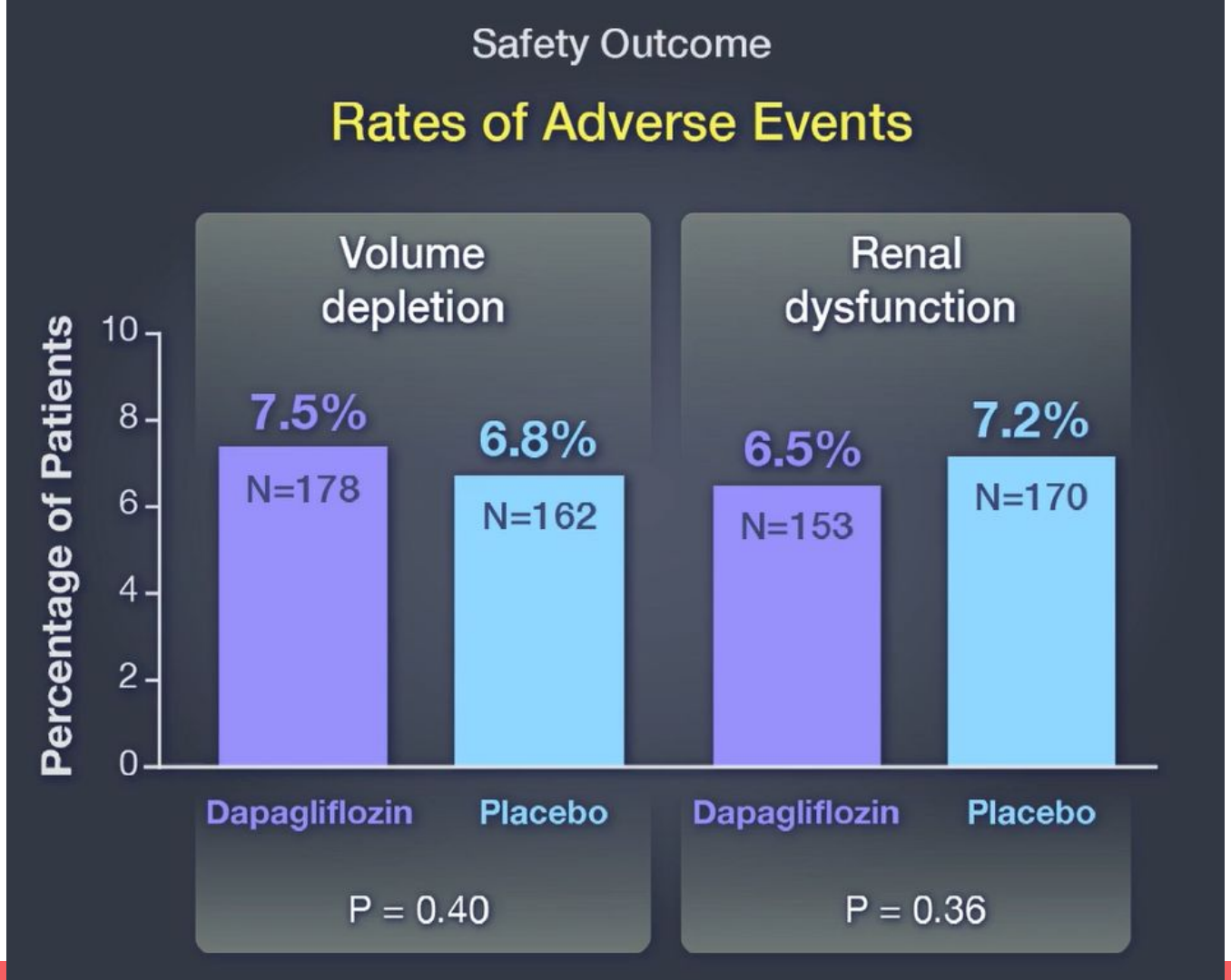
NNT=19

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
Volume depletion
Renal dysfunction
Percentage of Patients
10
8
6
4
2
0
7.5%
N=178
6.8%
N=162
6.5%
N=153
7.2%
N=170
Dapagliflozin
Placebo
Dapagliflozin
Placebo
P = 0.40
P = 0.36

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


• Heart failure
• Reduced ejection fraction
Dapagliflozin
10 mg Daily
Reduced the risk of:
• Worsening heart failure
• Cardiovascular death
Even in patients without diabetes
& Appears to be safe

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

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

FDA NEWS RELEASE

FDA approves new treatment for a type of heart failure

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

CJC Canadian Journal of Cardiology
Journal canadien de cardiologie

8. **New.** We recommend SGLT2 inhibitors, such as dapagliflozin be used in patients with mild to moderate HF due to reduced LVEF (≤ 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 (≤ 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

ESC European Society of Cardiology

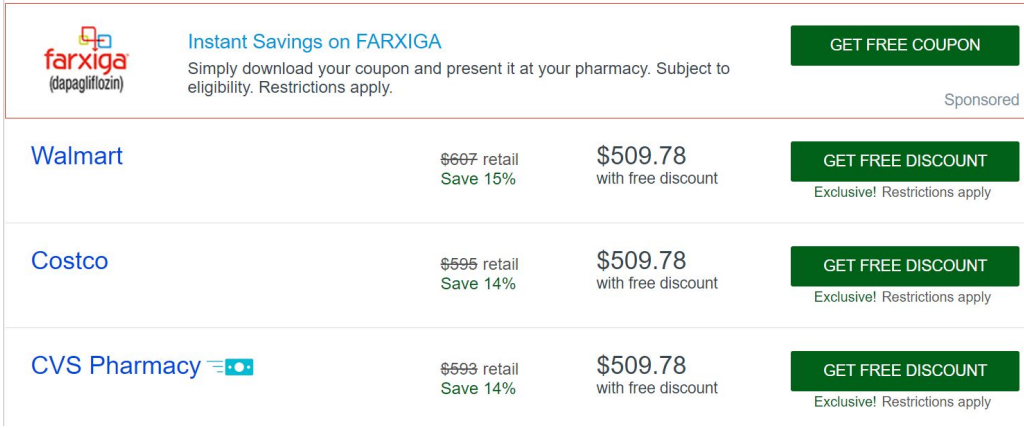
European Journal of Heart Failure (2019) 21, 1279–1287
doi:10.1002/ejhf.1596

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



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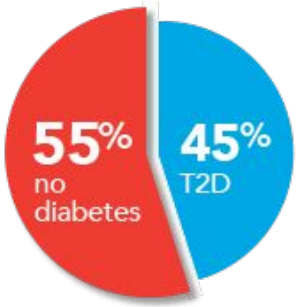
Questions?



ELIGIBILITY CRITERIA

- ≥18 years of age
- Diagnosis of symptomatic HFrEF (NYHA class II-IV)
- LVEF ≤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

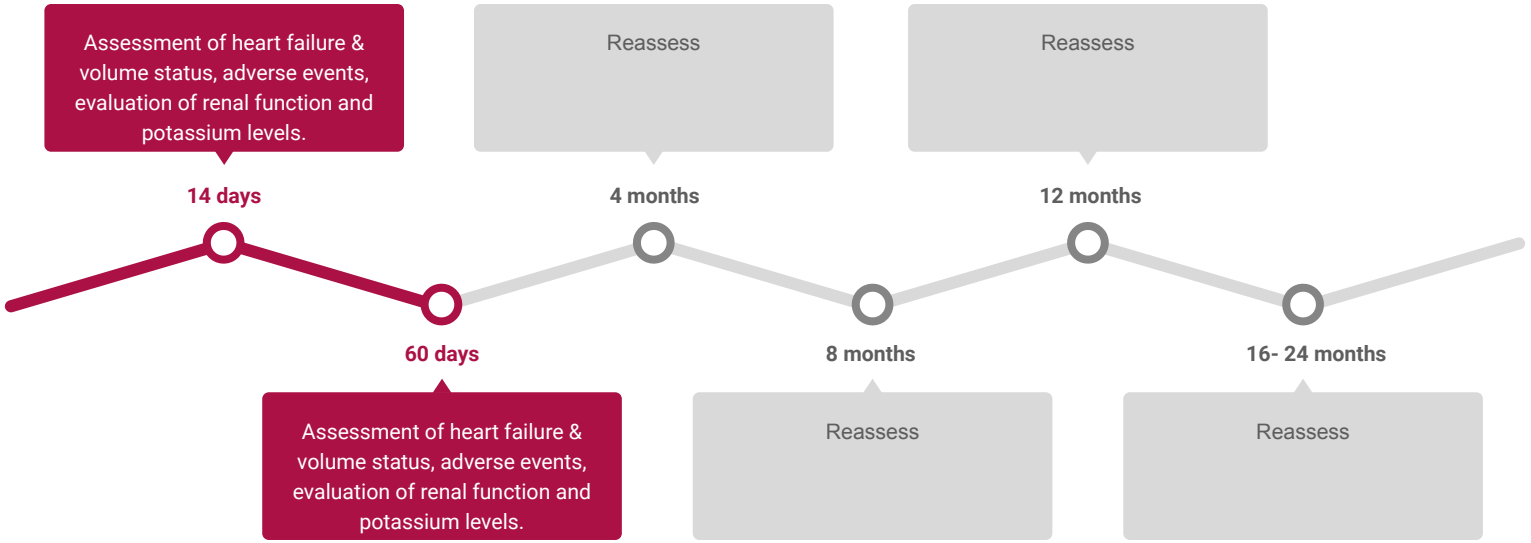
FARXIGA 10 mg and standard of care (n=2373)	Placebo and standard of care (n=2371)

MEDIAN FOLLOW-UP: 18.2 MONTHS

Methods - Procedures

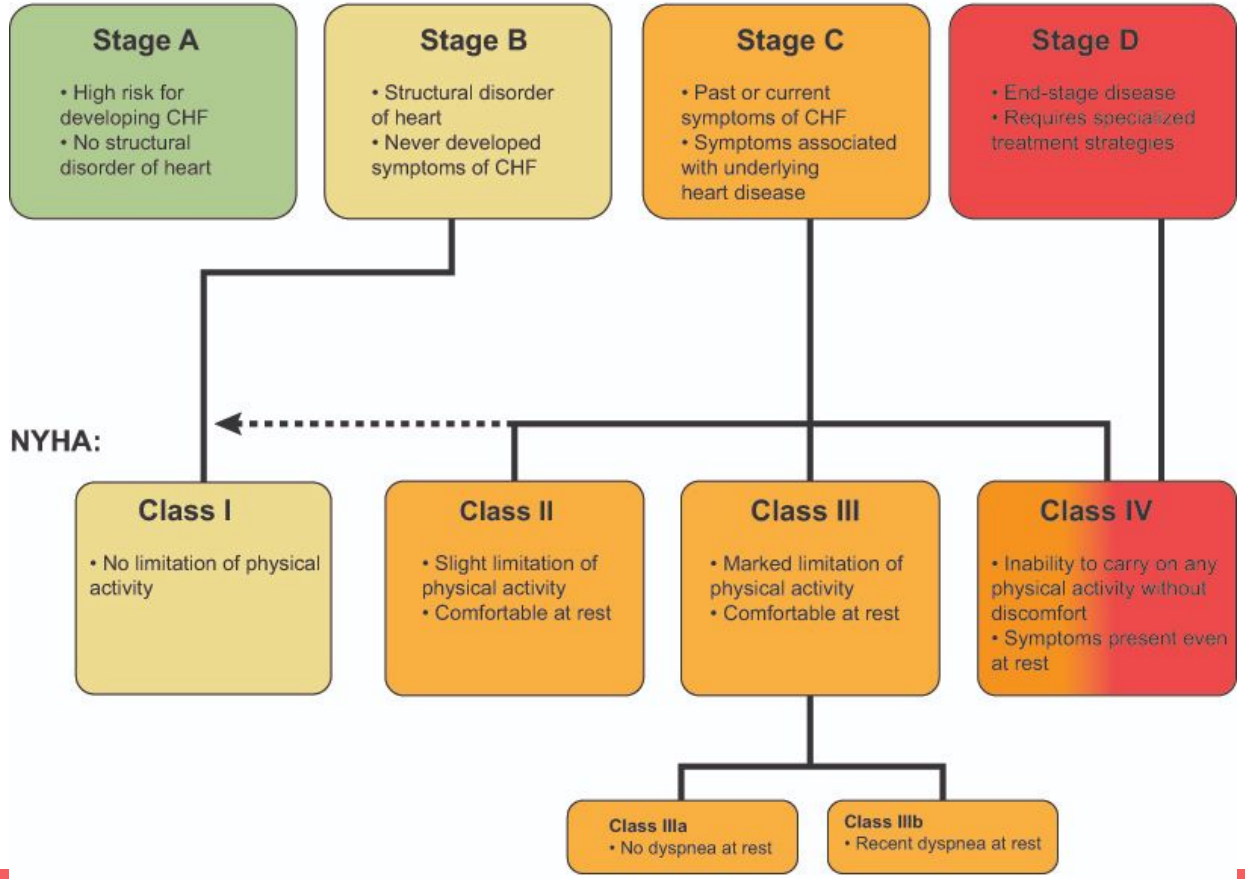
- 14 day screening period: baseline criteria, in- and exclusion criteria
- Random assignment to treatment vs placebo group
  - Dapagliflozin 10mg once daily
- Randomization: sequestered, fixed-randomization schedule; use of balanced blocks → 1:1 ratio
-

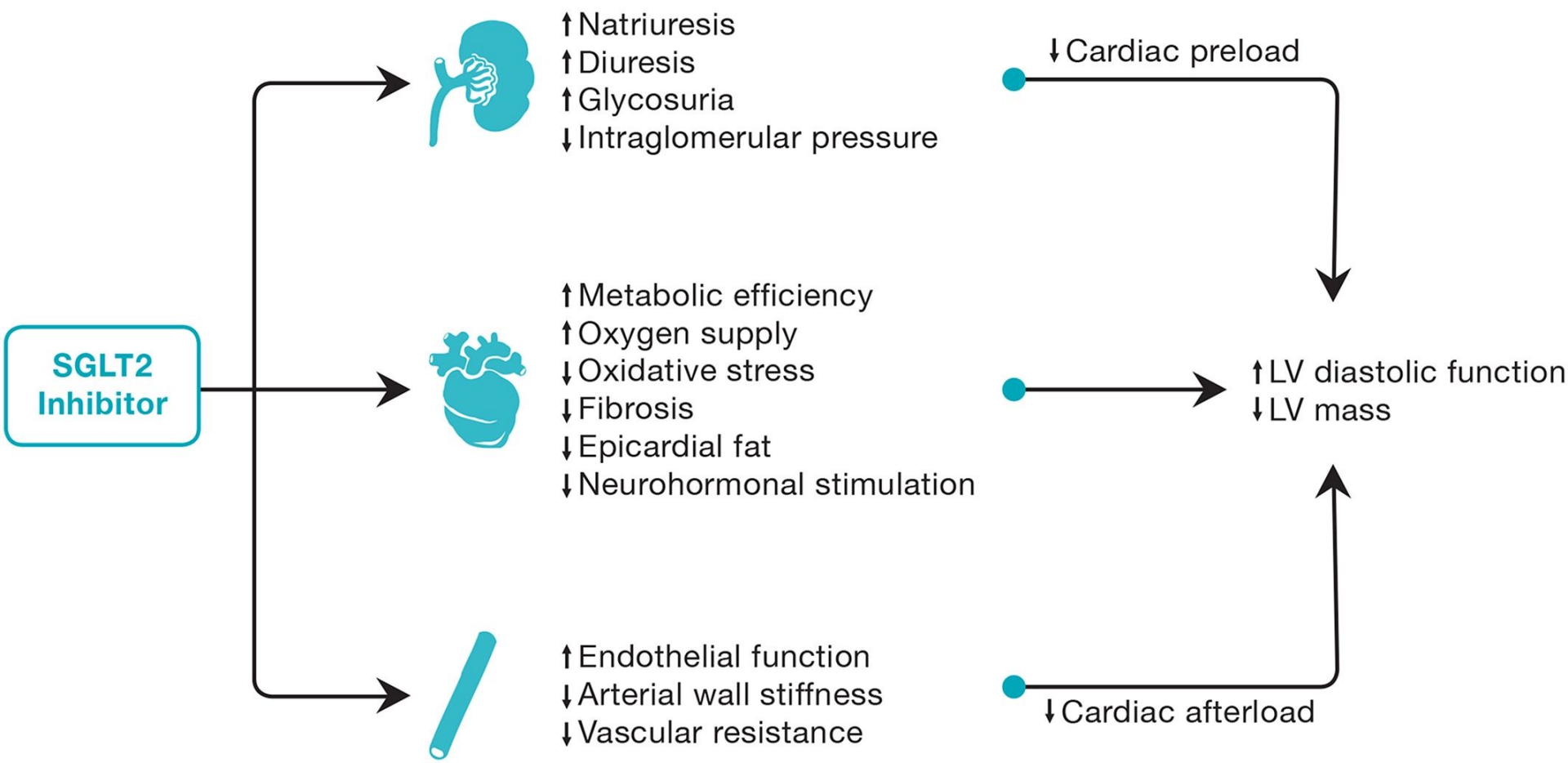
Methods - Procedures



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

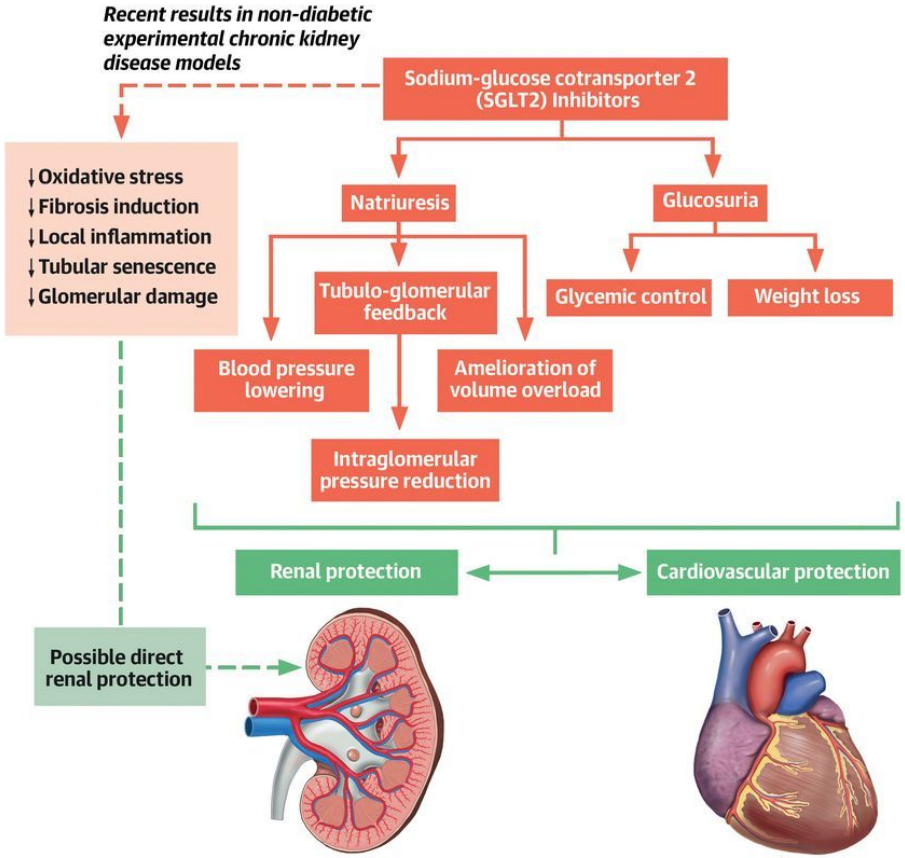
ACC/AHA:


Stage A
• High risk for developing CHF
• No structural disorder of heart
Stage B
• Structural disorder of heart
• Never developed symptoms of CHF
Stage C
• Past or current symptoms of CHF
• Symptoms associated with underlying heart disease
Stage D
• End-stage disease
• Requires specialized treatment strategies
NYHA:
Class I
• No limitation of physical activity
Class II
• Slight limitation of physical activity
• Comfortable at rest
Class III
• Marked limitation of physical activity
• Comfortable at rest
Class IV
• Inability to carry on any physical activity without discomfort
• Symptoms present even at rest
Class IIIa
• No dyspnea at rest
Class IIIb
• Recent dyspnea at rest


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
↓Cardiac afterload
↑LV diastolic function
↓LV mass

MOA

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



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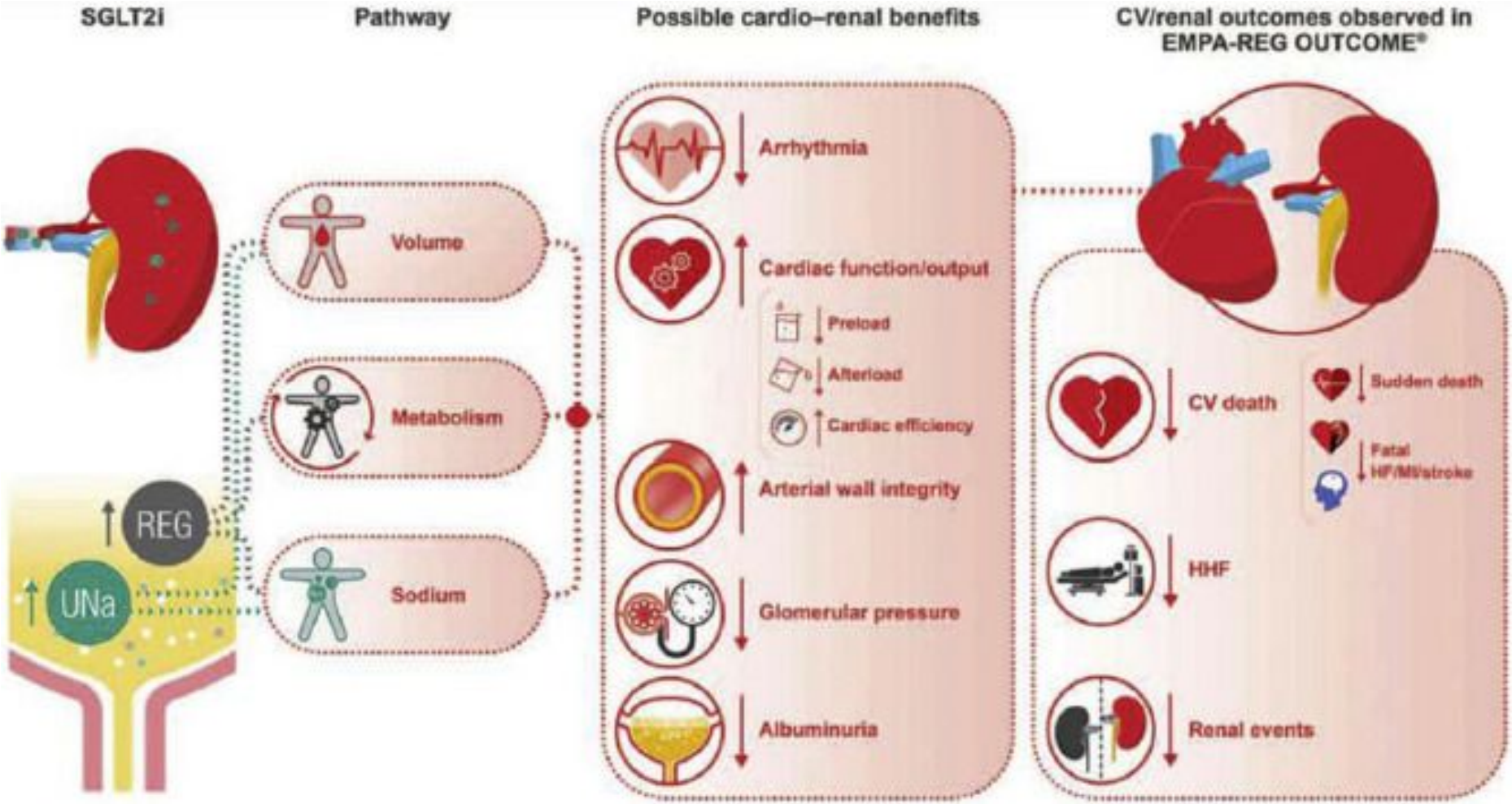

SGLT2i
Pathway
Possible cardio–renal benefits
CV/renal outcomes observed in EMPA-REG OUTCOME®
Volume
Metabolism
Sodium
REG
UNa
Arrhythmia
Cardiac function/output
Preload
Afterload
Cardiac efficiency
Arterial wall integrity
Glomerular pressure
Albuminuria
CV death
Sudden death
Fatal HF/MI/stroke
HHF
Renal events

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 ≠RR

Relative Risk (Risk Ratio) =

Risk (cumulative incidence) treatment group / risk placebo group

Relative Risk Reduction (efficacy) = 1-RR

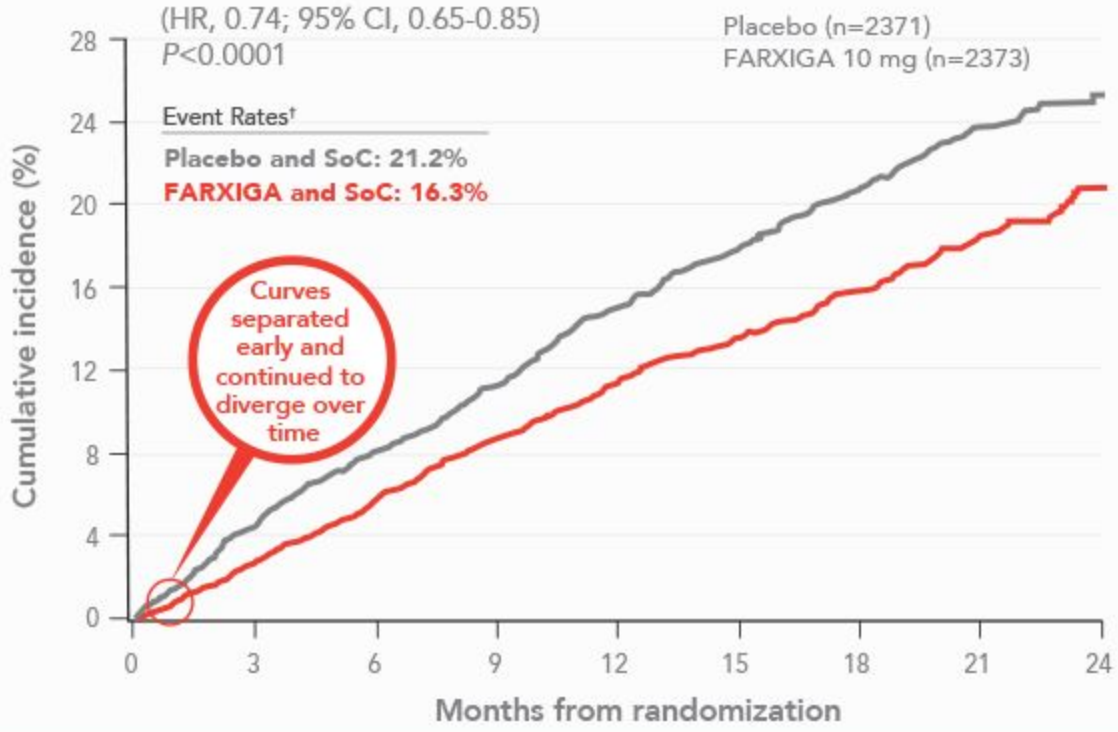
Relative decrease in risk of event in exposed group compared to unexposed group

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