

New Considerations in Heart Failure: New
Roles for SGLT-2 Inhibitors

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Disclosures

Andrew Buelt D.O.

No relevant financial relationship(s) with ineligible companies to disclose.



QUESTioning
medicine

Conflicts of Interest

- Bay Pines Veterans Affairs Hospital
- Right On Prime Education
- All Care Family Medical
- Multiple Medical Speaking Engagements

NOTE: none of my employers have ever given me money for a particular opinion that was not my own....EVER



**WE WANT YOUR
FEEDBACK!**

Learning Objectives:

- Evaluate the evidence supporting the use of SGLT2 inhibitors in the management of heart failure, including their impact on cardiovascular outcomes
- Discuss the limitations in the trials used for FDA approval of the SGLT2 inhibitors
- Understand the difference in benefit with SGLT2 inhibitors between systolic and diastolic dysfunction

SGLT2 inhibitors are miracles!

*Decrease mortality in CHF



:KD

ney disease with proteinuria even if there is no

**First generic October 2025!

**(Dapagliflozin)

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

“In the rosiglitazone group, as compared with the control group, the odds ratio for myocardial infarction was 1.43 (95% confidence interval [CI], 1.03 to 1.98; $P=0.03$)”

UNITED STATES SENATE
COMMITTEE ON FINANCE

Grassley, Baucus Release Committee Report on Avandia

*Senators Express Concern About FDA's Role in Protecting Patients in
Ongoing Avandia Study*



Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes



The NEW ENGLAND
JOURNAL of MEDICINE

N Engl J Med 2015; 373:2117-2128

Trial Design: Double Blind Placebo Control RCT

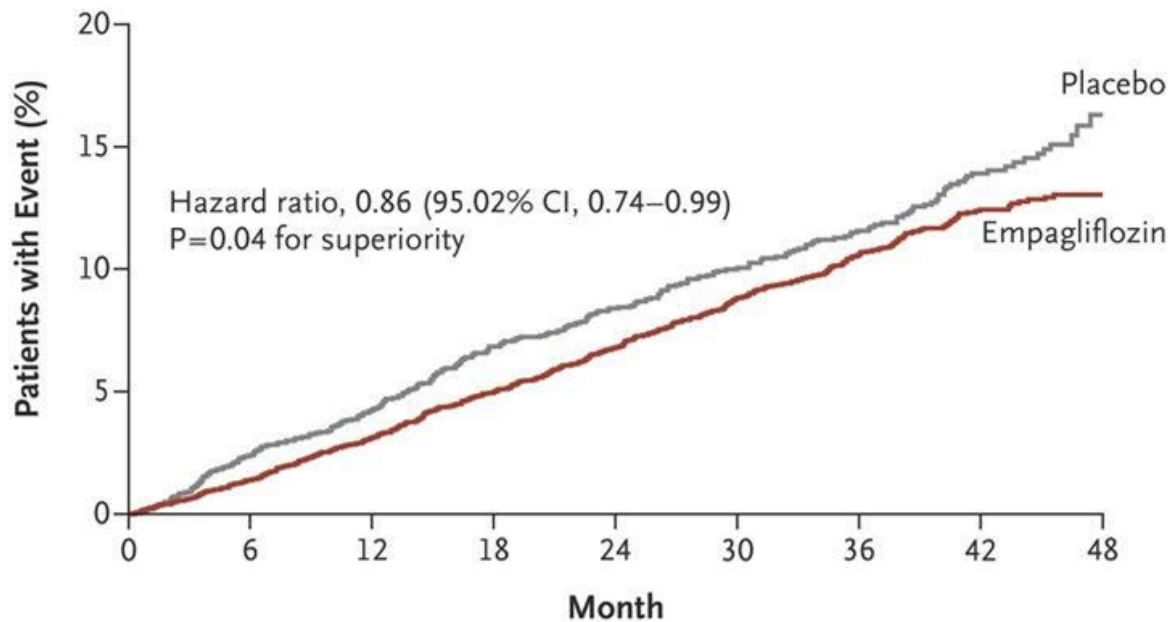
Population: DM2, GFR>30, History of CVD

Intervention: Empagliflozin 10mg or 25mg or placebo

Primary Outcome: composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke

Follow up: 3.1yrs

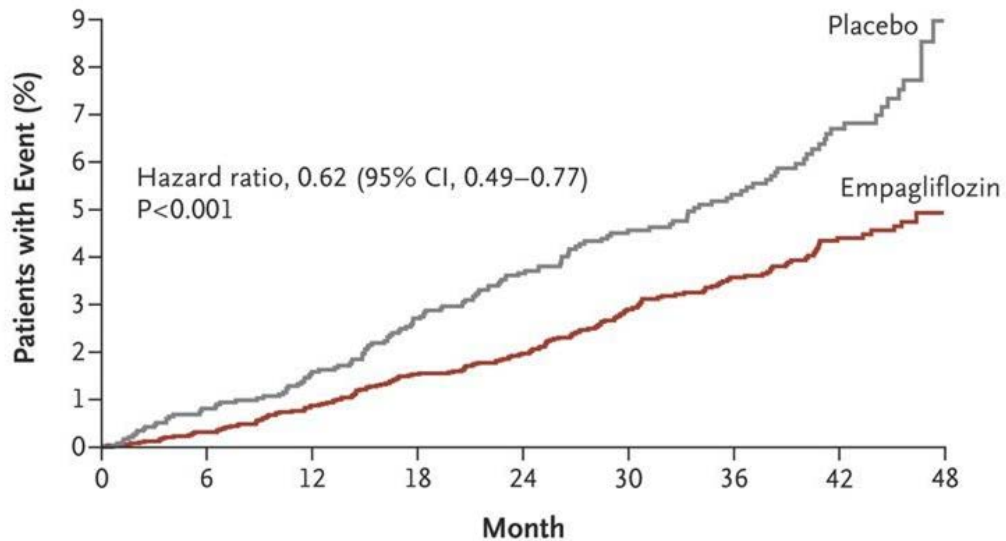
A Primary Outcome



No. at Risk

Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

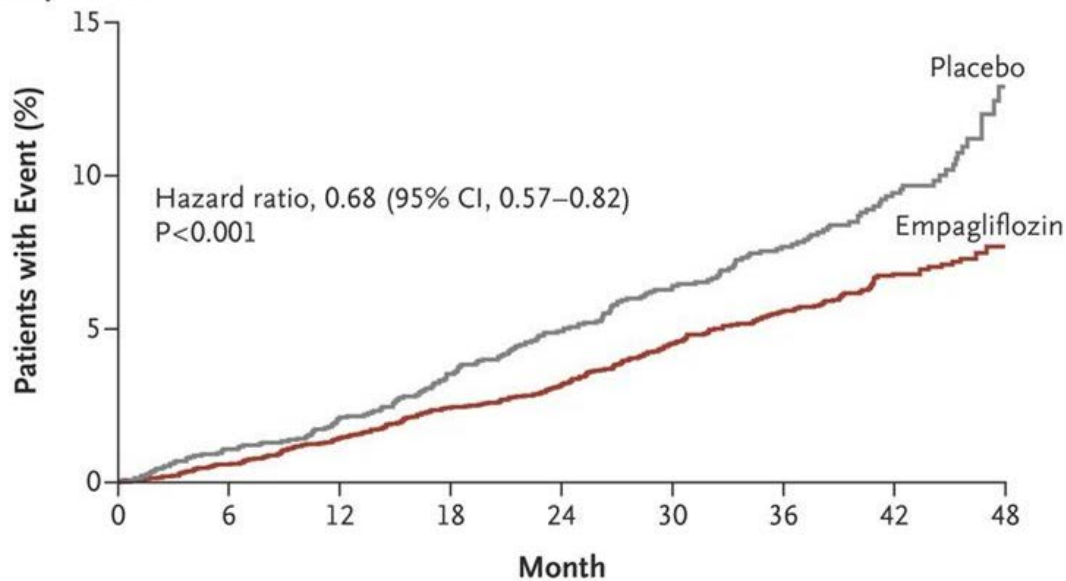
B Death from Cardiovascular Causes



No. at Risk

Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

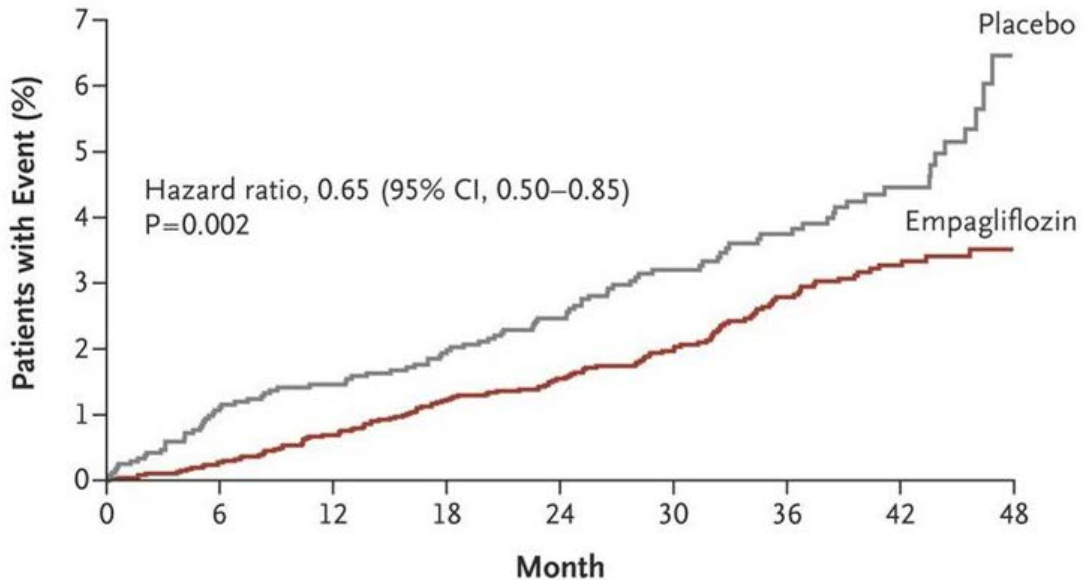
C Death from Any Cause



No. at Risk

Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

D Hospitalization for Heart Failure



No. at Risk

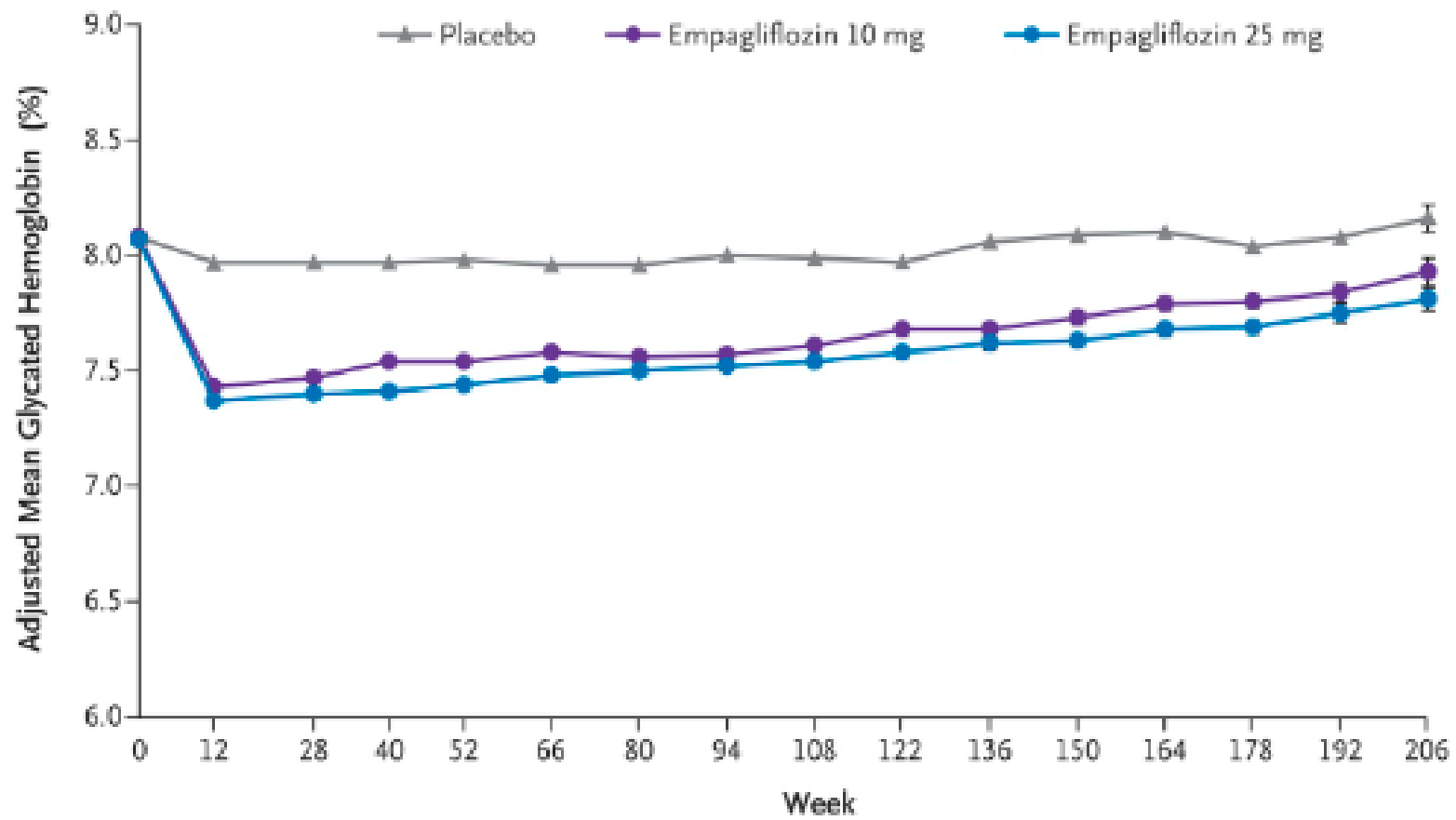
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

Primary Outcome:

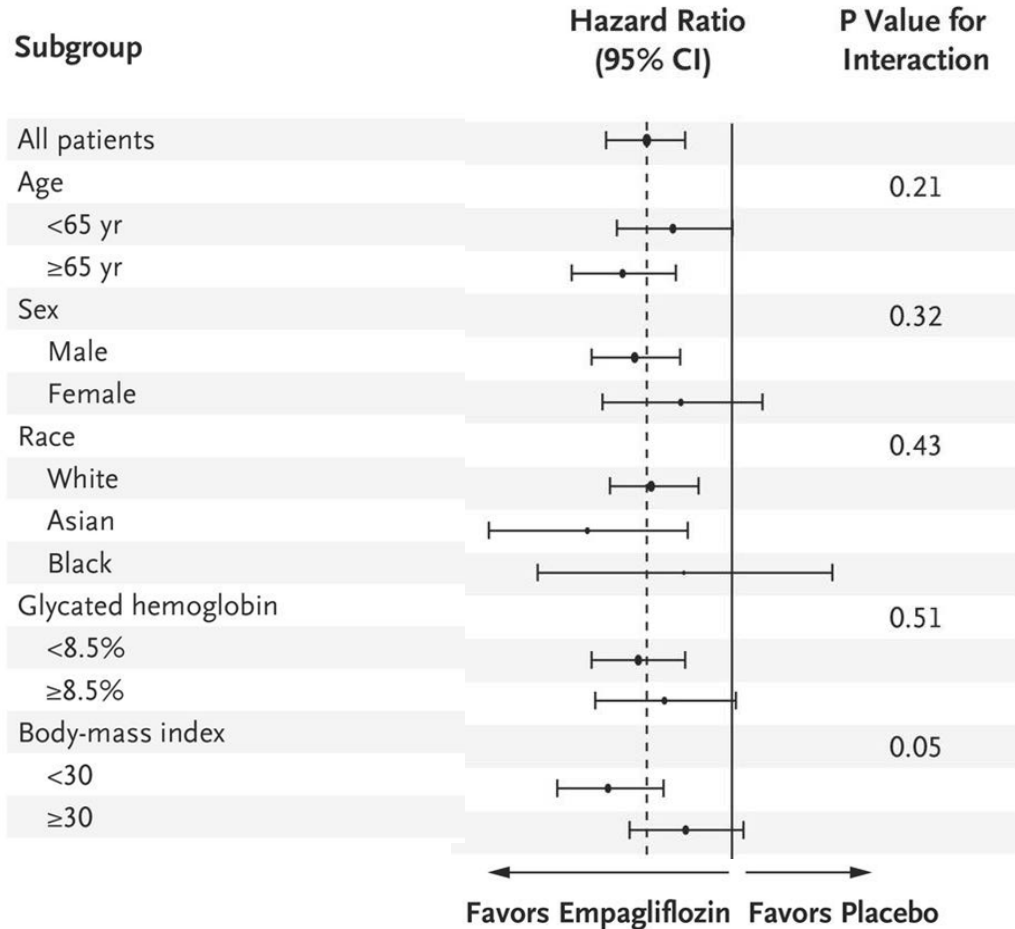
Death from cardiovascular causes: NNT 46 per 3.1 yrs (at \$600 a month, 1 million dollars per life saved)

Nonfatal myocardial infarction: NS ∞

Nonfatal stroke: NS ∞



Death from Cardiovascular Causes



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GAME PLAN FOR THIS LECTURE

- *Evidence Around Heart Failure with Preserved Ejection Fraction

- *Evidence Around Heart Failure with Reduced Ejection Fraction

- *What this means for your practice and what to do Monday Morning

HF PRESERVED EF

N Engl J Med 2021; 385:1451-1461

ORIGINAL ARTICLE

Empagliflozin in Heart Failure with a Preserved Ejection Fraction



The NEW ENGLAND
JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

N Engl J Med 2022; 387:1089-1098

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

N Engl J Med 2021; 385:1451-1461

CONCLUSIONS

Empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart failure in patients with heart failure and a preserved ejection fraction, regardless of the presence or absence of diabetes. (Funded by Boehringer Ingelheim and Eli Lilly; EMPEROR-Preserved ClinicalTrials.gov number, [NCT03057951](#)).

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

N Engl J Med 2021; 385:1451-1461

- 11,583 patients were screened for eligibility, 5988 patients randomized to empagliflozin (2997 patients) or placebo (2991 patients)
 - **51% inclusion rate**

INCLUSION CRITERIA

- New York Heart Association Class II–IV heart failure
- EF \geq 40%
- NT-proBNP level greater than 300 pg/mL (> 900 pg/mL if the patient had atrial fibrillation) (**78% of those excluded did not meet this criteria**)

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

N Engl J Med 2021; 385:1451-1461

Trial Design: Double Blind Placebo Control RCT

Population: Mean age 72yrs, EF \geq 40%

Intervention: Empagliflozin 10 mg daily or placebo

Primary Outcome: Composite of cardiovascular death or hospitalization for heart failure

Follow up: 26 Months

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

N Engl J Med 2021; 385:1451-1461

CONCLUSIONS

Empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart failure in patients with heart failure and a preserved ejection fraction, regardless of the presence or absence of diabetes. (Funded by Boehringer Ingelheim and Eli Lilly; EMPEROR-Preserved ClinicalTrials.gov number, [NCT03057951](#)).

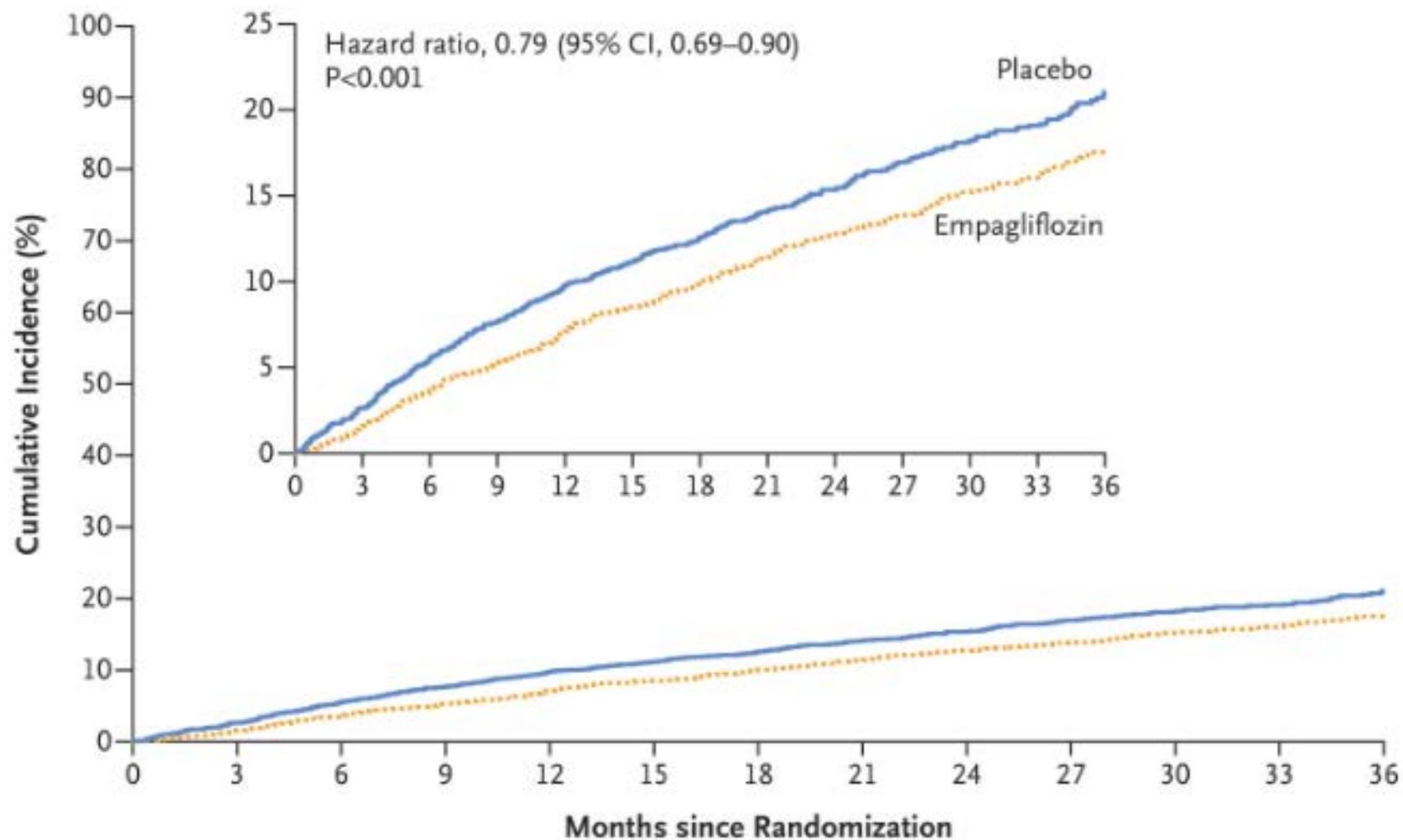


Table 2. Primary and Secondary Cardiovascular Outcomes.*

Variable	Empagliflozin (N=2997)		Placebo (N=2991)		Hazard Ratio or Difference (95% CI)	P Value
	no. (%)	<i>events per 100 patient- yr</i>	no. (%)	<i>events per 100 patient- yr</i>		
Primary composite outcome — no. (%)	415 (13.8)	6.9	511 (17.1)	8.7	0.79 (0.69–0.90)	<0.001
Hospitalization for heart failure	259 (8.6)	4.3	352 (11.8)	6.0	0.71 (0.60–0.83)	
Cardiovascular death	219 (7.3)	3.4	244 (8.2)	3.8	0.91 (0.76–1.09)	

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

N Engl J Med 2021; 385:1451-1461

CONCLUSIONS

Empagliflozin reduced ~~the combined risk of cardiovascular death or~~ hospitalization for heart failure in patients with heart failure and a preserved ejection fraction, regardless of the presence or absence of diabetes. (Funded by Boehringer Ingelheim and Eli Lilly; EMPEROR-Preserved ClinicalTrials.gov number, [NCT03057951](#)).

Hospitalization for heart failure occurred in 8.6% of patients in the empagliflozin group and 11.8% patients in the placebo group (hazard ratio, 0.71; 95% CI, 0.60 to 0.83)

Number Needed to Treat [NNT] = 32 per 26 months

HF PRESERVED EF

N Engl J Med 2021; 385:1451-1461

ORIGINAL ARTICLE

Empagliflozin in Heart Failure with a Preserved Ejection Fraction



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ORIGINAL ARTICLE

Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

N Engl J Med 2022; 387:1089-1098

Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

N Engl J Med 2022; 387:1089-1098

CONCLUSIONS

Dapagliflozin reduced the combined risk of worsening heart failure or cardiovascular death among patients with heart failure and a mildly reduced or preserved ejection fraction. (Funded by AstraZeneca; DELIVER ClinicalTrials.gov number, [NCT03619213](#).)

Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

N Engl J Med 2022; 387:1089-1098

- 10,418 patients were screened for eligibility, 6263 patients randomized to Dapagliflozin (3131 patients) or placebo (3132 patients)
 - 60% inclusion rate

INCLUSION CRITERIA

- New York Heart Association Class II–IV heart failure
- ejection fraction $\geq 40\%$
- NT-proBNP level greater than 300 pg/mL (**> 600 pg/mL** if the patient had atrial fibrillation) **(Didn't give inclusion failure breakdown)**

Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

N Engl J Med 2022; 387:1089-1098

Trial Design: Double Blind Placebo Control RCT

Population: Mean age 72yrs, EF \geq 40%

Intervention: Dapagliflozin 10 mg daily or placebo

Primary Outcome: Composite of worsening heart failure (defined as an unplanned hospitalization for heart failure or urgent visit for heart failure) or cardiovascular death

Follow up: 2.3 years

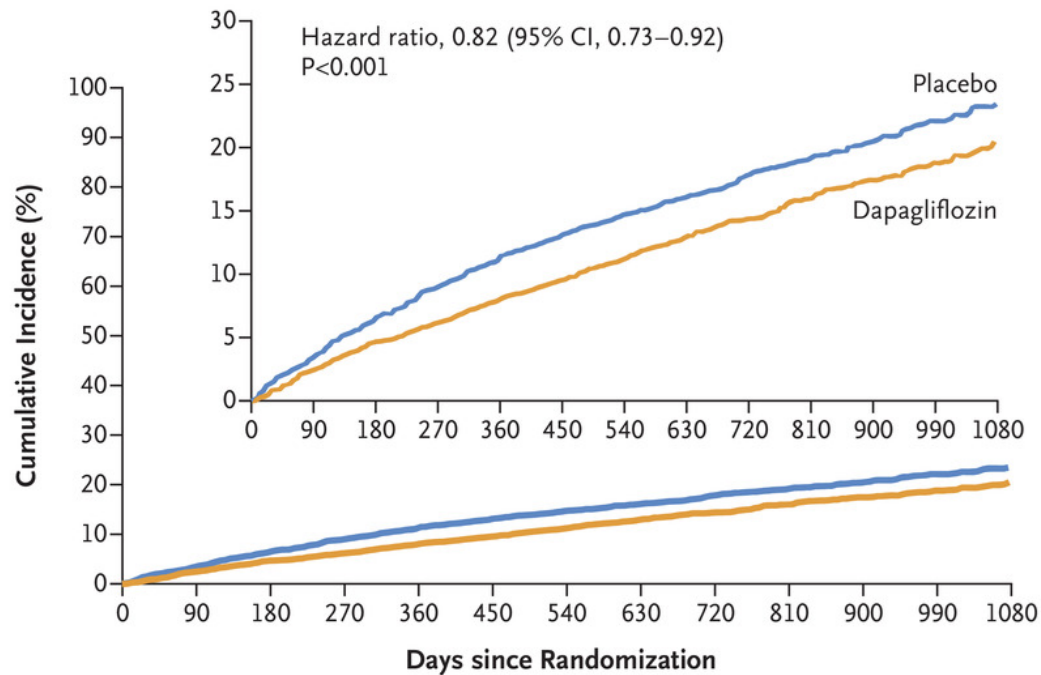
Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

N Engl J Med 2022; 387:1089-1098

CONCLUSIONS

Dapagliflozin reduced the combined risk of worsening heart failure or cardiovascular death among patients with heart failure and a mildly reduced or preserved ejection fraction. (Funded by AstraZeneca; DELIVER ClinicalTrials.gov number, [NCT03619213](#).)

A Primary Outcome



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

Variable	Dapagliflozin (N=3131)		Placebo (N=3132)		Hazard or Rate Ratio or Win Ratio (95% CI)
	<i>values</i>	<i>events/ 100 patient-yr</i>	<i>values</i>	<i>events/ 100 patient-yr</i>	
Efficacy outcomes					
Primary composite outcome — no. (%)	512 (16.4)	7.8	610 (19.5)	9.6	0.82 (0.73–0.92)
Hospitalization for heart failure or an urgent visit for heart failure	368 (11.8)	5.6	455 (14.5)	7.2	0.79 (0.69–0.91)
Hospitalization for heart failure	329 (10.5)	5.0	418 (13.3)	6.5	0.77 (0.67–0.89)
Urgent visit for heart failure	60 (1.9)	0.9	78 (2.5)	1.1	0.76 (0.55–1.07)
Cardiovascular death†	231 (7.4)	3.3	261 (8.3)	3.8	0.88 (0.74–1.05)

Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

N Engl J Med 2022; 387:1089-1098

CONCLUSIONS

Dapagliflozin reduced the ~~combined~~ risk of worsening heart failure ~~or cardiovascular~~ ~~death~~ among patients with heart failure and a mildly reduced or preserved ejection fraction. (Funded by AstraZeneca; DELIVER ClinicalTrials.gov number, **NCT03619213**.)

Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

Hospitalization for heart failure (10.5% vs 13.3%; HR 0.77; 0.67 - 0.89;

NNT = 36 over 2.3 years

Empagliflozin NNT = 32 per 26 mths to prevent one hospitalization

Dapagliflozin NNT = 36 over 2.3 yrs to prevent one hospitalization

*****LET'S AGREE--ABOUT 35 PER 26 MONTHS*****

35 patients HFpEF x 26 months x \$400 per month =
\$364,000 to prevent one hospitalization

GAME PLAN FOR THIS LECTURE

*Evidence Around Heart Failure with Preserved Ejection Fraction

*Evidence Around Heart Failure with Reduced Ejection Fraction

*What this means for your practice and what to do Monday Morning

ORIGINAL ARTICLE

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

ORIGINAL ARTICLE

Sotagliflozin in Patients with Diabetes and Recent Worsening
Heart Failure

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction



The NEW ENGLAND
JOURNAL of MEDICINE

CONCLUSIONS

Among patients with heart failure and a reduced ejection fraction, the risk of worsening heart failure or death from cardiovascular causes was lower among those who received dapagliflozin than among those who received placebo, regardless of the presence or absence of diabetes. (Funded by AstraZeneca; DAPA-HF ClinicalTrials.gov number, NCT03036124.)

8134 Patients underwent screening

3390 Were excluded
12 Died
15 Had an adverse event
84 Declined to participate
3279 Did not meet eligibility criteria

4744 Underwent randomization

(HA) class II, III, IV

er or ≥ 400 pg if

hospitalized for heart failure in the previous 12mths

If atrial fibrillation or atrial flutter on EKG, BNP level of at least 900pg

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction



The NEW ENGLAND
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N Engl J Med 2019; 381:1995-2008

Trial Design: Double Blind Placebo Control RCT

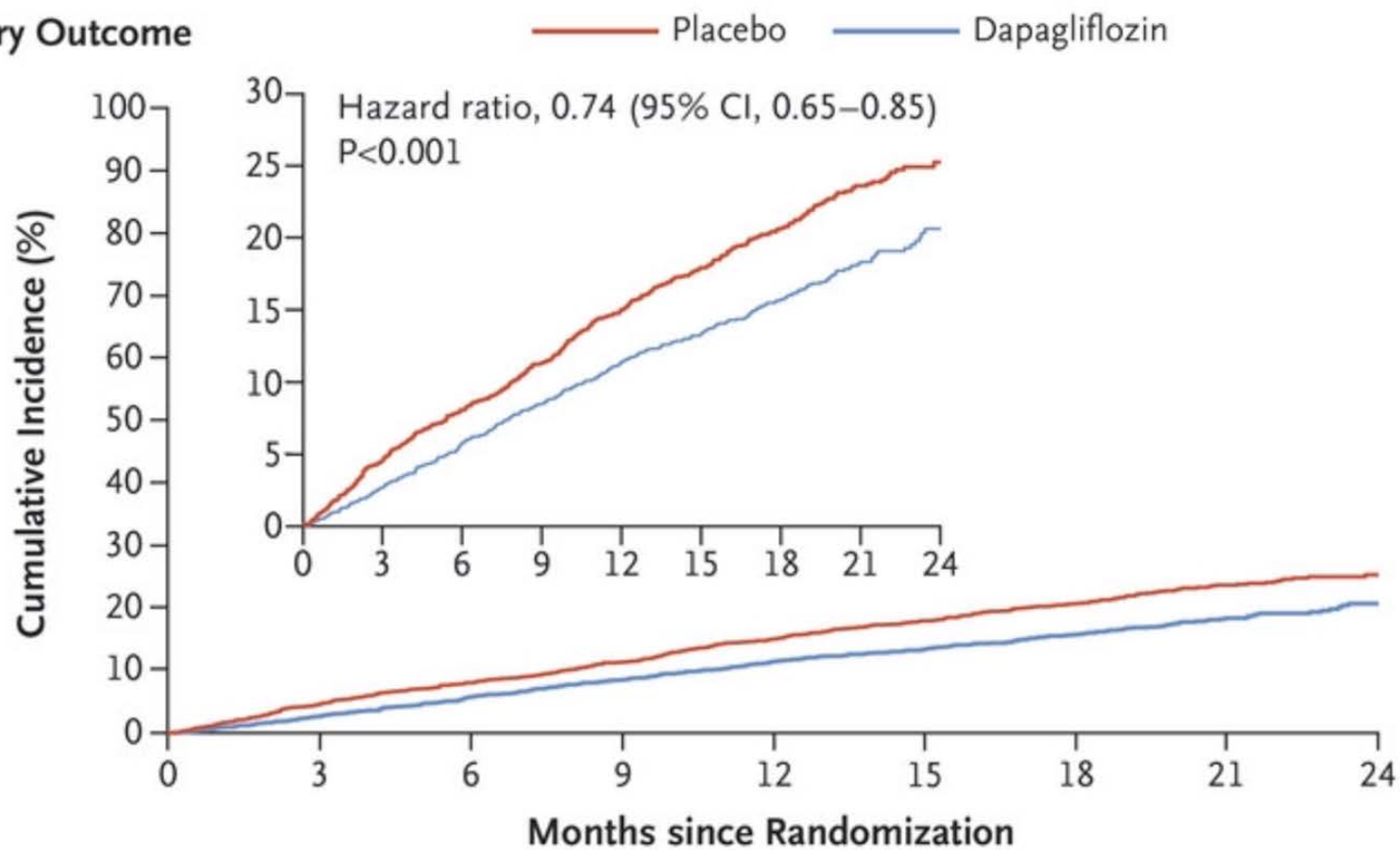
Population: HFrEF EF \leq 40%, and NYHA II-IV symptoms

Intervention: Dapagliflozin 10 mg daily or placebo

Primary Outcome: Composite of worsening heart failure (defined as an unplanned hospitalization for heart failure or urgent visit for heart failure) or cardiovascular death

Follow up: 18.2 months

A Primary Outcome

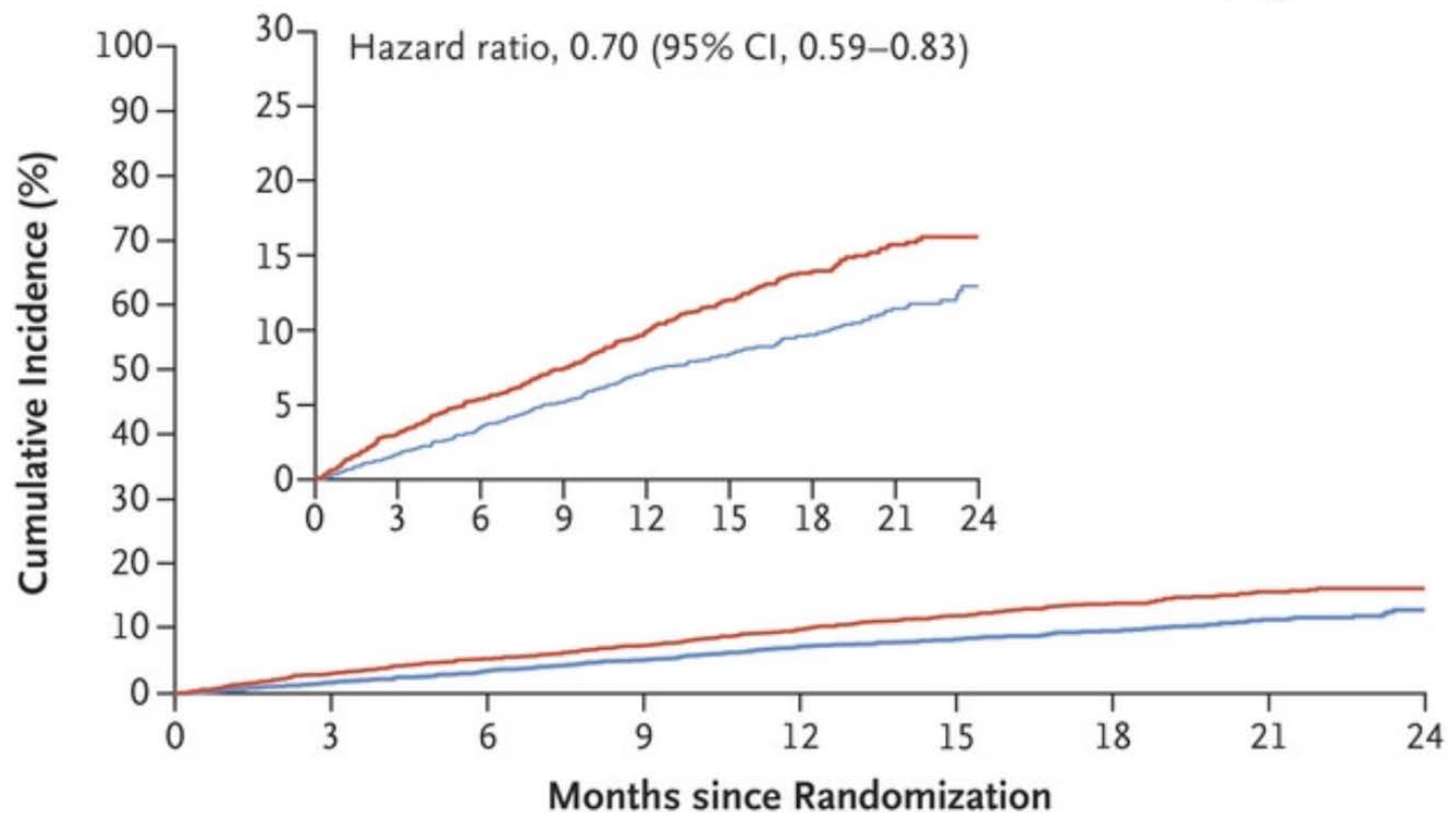


No. at Risk

Placebo	2371	2258	2163	2075	1917	1478	1096	593	210
Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210

B Hospitalization for Heart Failure

— Placebo — Dapagliflozin

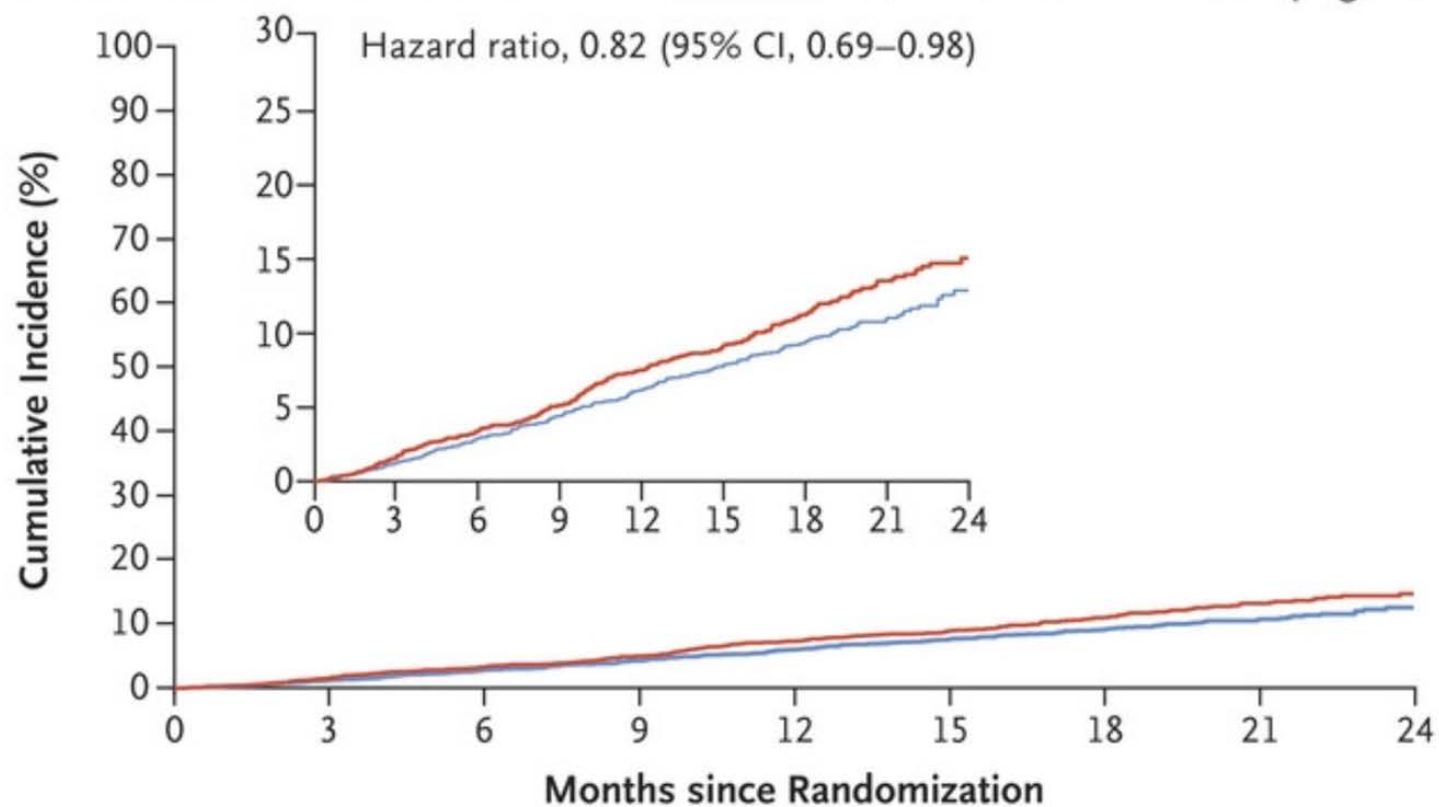
**No. at Risk**

Placebo	2371	2264	2168	2082	1924	1483	1101	596	212
Dapagliflozin	2373	2306	2223	2153	2007	1563	1147	613	210

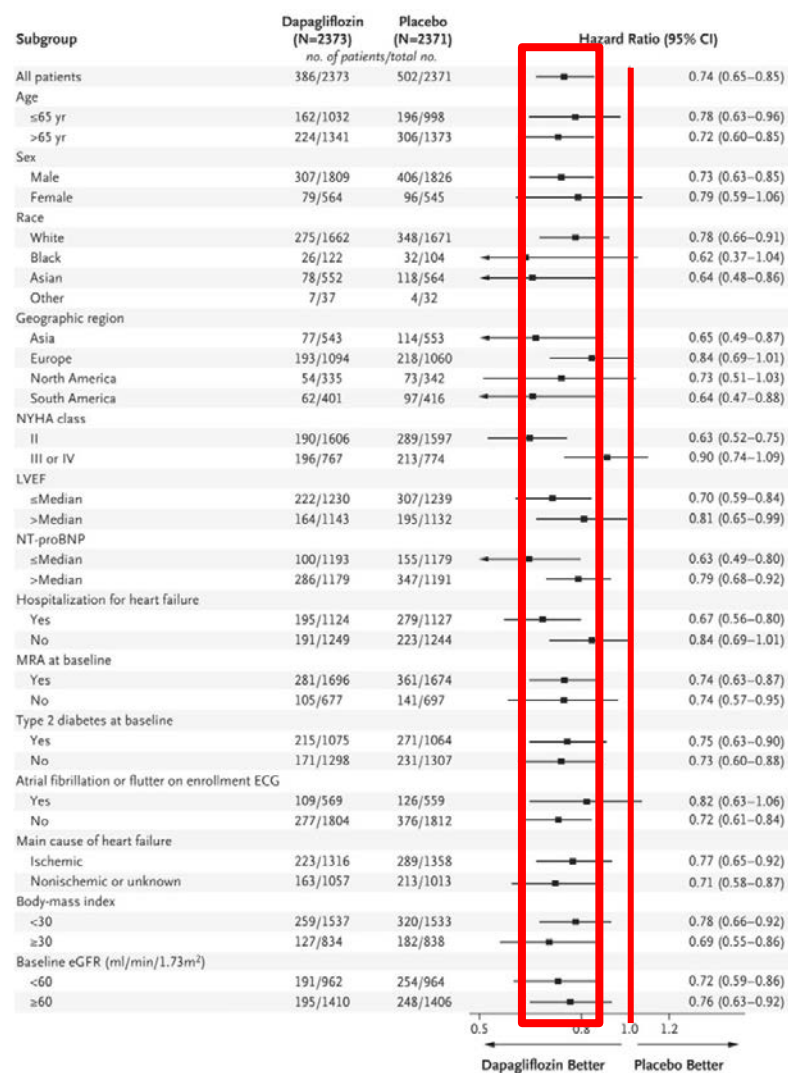
C Death from Cardiovascular Causes

— Placebo

— Dapagliflozin

**No. at Risk**

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



MONDAY MORNING PERSPECTIVE

NNT of 21 over 18 months to prevent a composite of worsening heart failure or cardiovascular death

NNT for hospitalization = 27

NNT for Cardiovascular Death = 53

ORIGINAL ARTICLE

~~Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction~~

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

ORIGINAL ARTICLE

Sotagliflozin in Patients with Diabetes and Recent Worsening
Heart Failure

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure



The NEW ENGLAND
JOURNAL of MEDICINE

N Engl J Med 2020; 383:1413-1424

CONCLUSIONS

Among patients receiving recommended therapy for heart failure, those in the empagliflozin group had a lower risk of cardiovascular death or hospitalization for heart failure than those in the placebo group, regardless of the presence or absence of diabetes. (Funded by Boehringer Ingelheim and Eli Lilly; EMPEROR-Reduced ClinicalTrials.gov number, [NCT03057977](https://clinicaltrials.gov/ct2/show/study/NCT03057977).)

7220 patients screened for eligibility

3730 were randomized

1863 assigned
to empagliflozin

1867 assigned
to placebo

Only 51% included!

LVEF \leq 40% with NYHA functional class II, III or IV **AND**

EF \geq 36% to \leq 40%: elevated NT-proBNP at Visit 1 \geq 2500 pg/ml

EF \geq 31% to \leq 35%: elevated NT-proBNP at Visit 1 \geq 1000 pg/ml

EF \leq 30%: elevated NT-proBNP at Visit 1 \geq 600 pg/m

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure



The NEW ENGLAND
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N Engl J Med 2020; 383:1413-1424

Trial Design: Double Blind Placebo Control RCT

Population: HFrEF EF \leq 40%, and NYHA II-IV symptoms

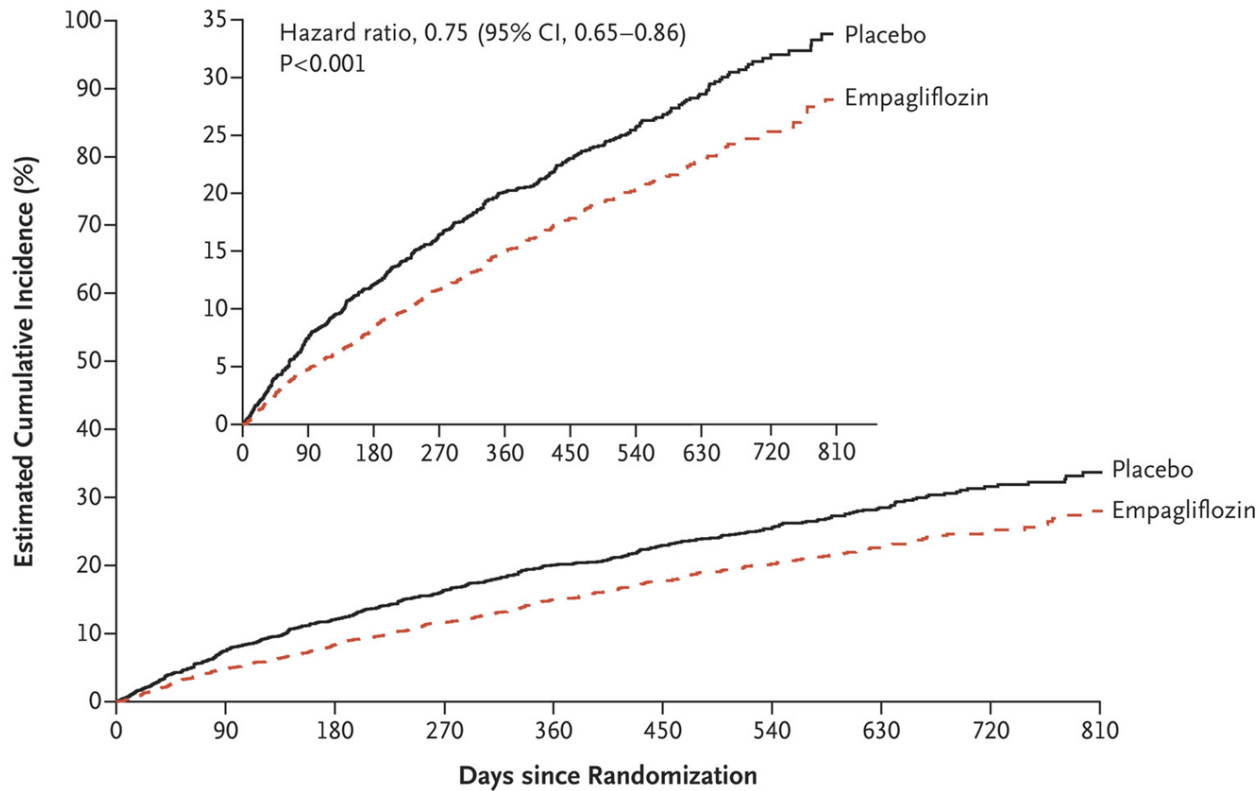
Intervention: Empagliflozin 10 mg daily or placebo

Primary Outcome: Composite of hospitalization for heart failure or cardiovascular death

Follow up: 16 months

Variable	Empagliflozin (N=1863)		Placebo (N=1867)		Hazard Ratio or Absolute Difference (95% CI) [†]	P Value
	no. (%)	<i>events/100 patient-yr</i>	no. (%)	<i>events/100 patient-yr</i>		
Primary composite outcome — no. (%)	361 (19.4)	15.8	462 (24.7)	21.0	0.75 (0.65 to 0.86)	<0.001
Hospitalization for heart failure	246 (13.2)	10.7	342 (18.3)	15.5	0.69 (0.59 to 0.81)	
Cardiovascular death	187 (10.0)	7.6	202 (10.8)	8.1	0.92 (0.75 to 1.12)	

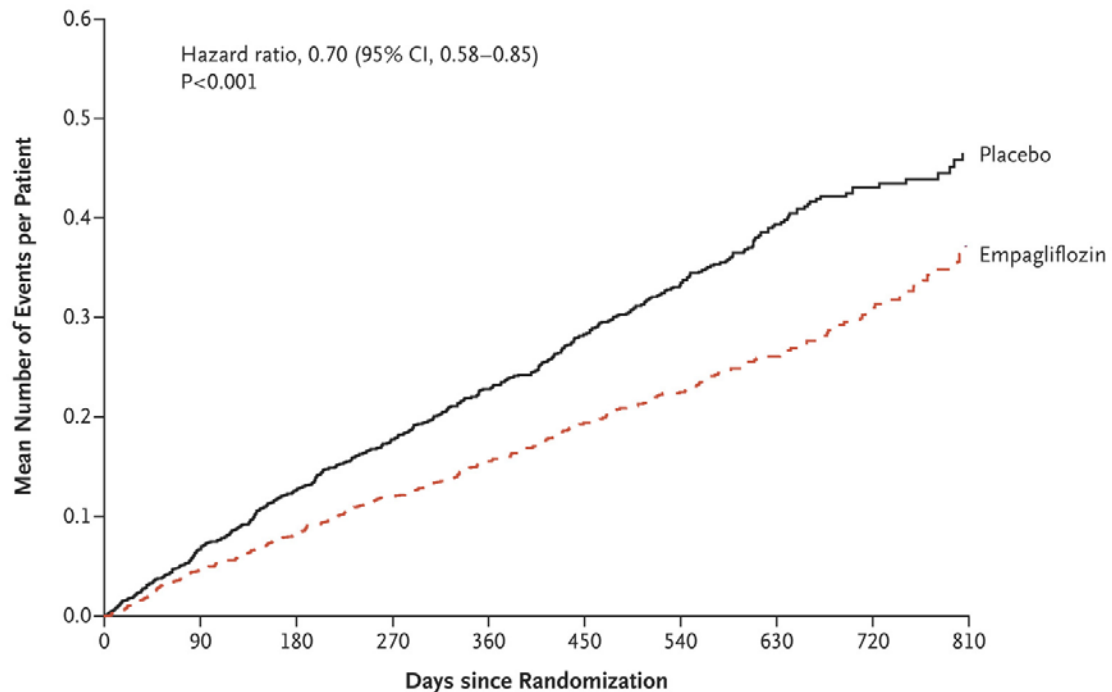
A Primary Outcome



No. at Risk

Placebo	1867	1715	1612	1345	1108	854	611	410	224	109
Empagliflozin	1863	1763	1677	1424	1172	909	645	423	231	101

B First and Recurrent Hospitalizations for Heart Failure



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

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure



The NEW ENGLAND
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N Engl J Med 2020; 383:1413-1424

CONCLUSIONS

Among patients receiving recommended therapy for heart failure, those in the empagliflozin group had a lower risk of ~~cardiovascular death or~~ hospitalization for heart failure than those in the placebo group, regardless of the presence or absence of diabetes. (Funded by Boehringer Ingelheim and Eli Lilly; EMPEROR-Reduced ClinicalTrials.gov number, [NCT03057977](https://clinicaltrials.gov/ct2/show/study/NCT03057977).)

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure



The NEW ENGLAND
JOURNAL of MEDICINE

N Engl J Med 2020; 383:1413-1424

NNT of 20 to prevent 1 hospitalization at
16 months of follow up

ORIGINAL ARTICLE

~~Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction~~

~~Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure~~

ORIGINAL ARTICLE

Sotagliflozin in Patients with Diabetes and Recent Worsening
Heart Failure

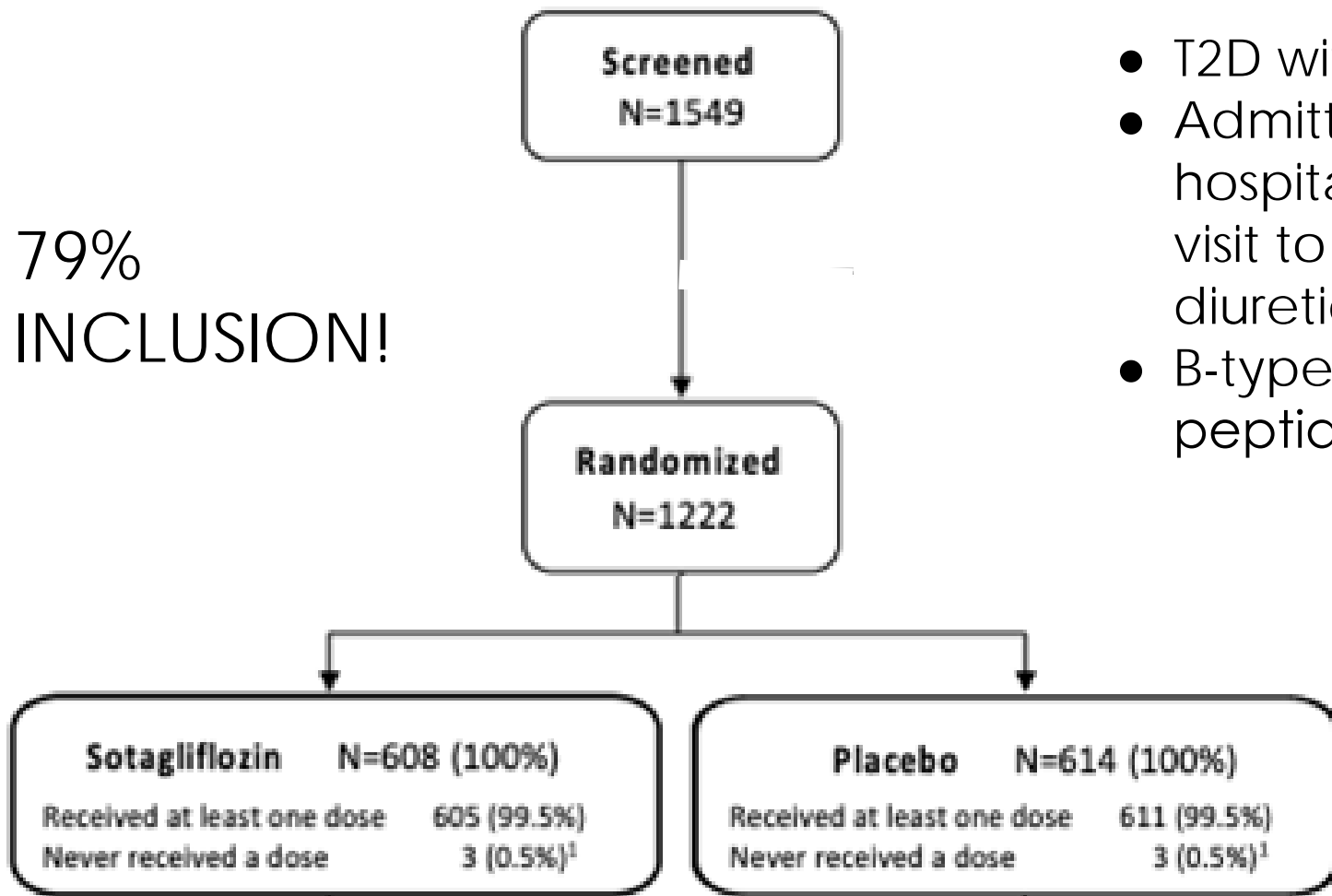
Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure

N Engl J Med 2021; 384:117-128

CONCLUSIONS

In patients with diabetes and recent worsening heart failure, sotagliflozin therapy, initiated before or shortly after discharge, resulted in a significantly lower total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure than placebo. (Funded by Sanofi and Lexicon Pharmaceuticals; SOLOIST-WHF ClinicalTrials.gov number, [NCT03521934](https://clinicaltrials.gov/ct2/show/study/NCT03521934).)

79%
INCLUSION!



- T2D with HF (any %)
- Admitted to the hospital or urgent HF visit to ED, receiving IV diuretics in prior 3 days
- B-type natriuretic peptide ≥ 150 pg/mL

Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure

N Engl J Med 2021; 384:117-128

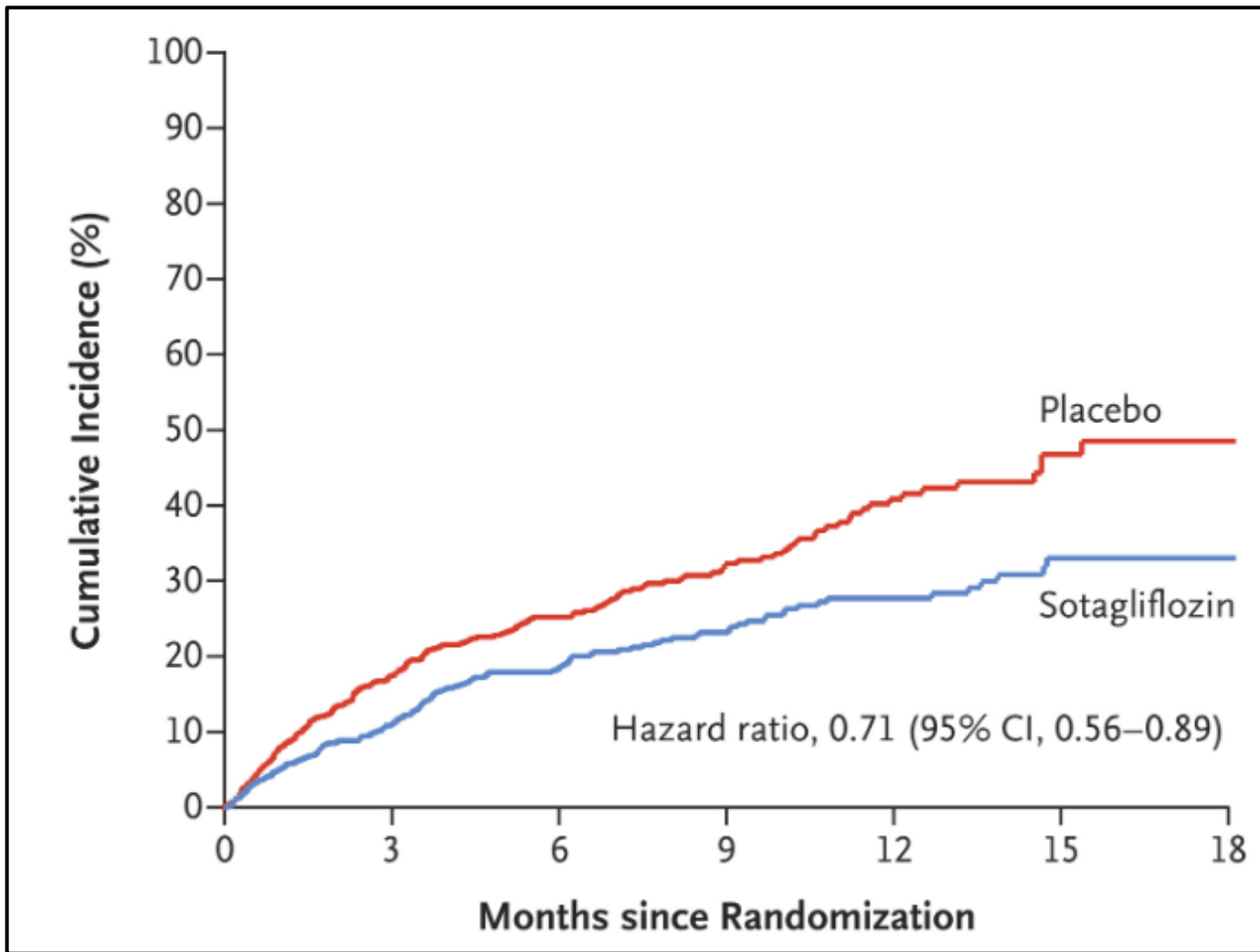
Trial Design: Double Blind Placebo Control RCT

Population: HF, T2D and Recent DC from hospital/ED/urgent clinic getting IV diuretics

Intervention: Sotagliflozin 200-400 mg once daily or placebo

Primary Outcome: Composite of deaths from cardiovascular causes or hospitalizations and urgent visits for heart failure

Follow up: 9 months



End Point	Sotagliflozin (N=608)	Placebo (N=614)	Hazard Ratio or Difference (95% CI)*	P Value
Primary end point: deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure — total no. of events (rate)†	245 (51.0)	355 (76.3)	0.67 (0.52 to 0.85)	<0.001

Secondary end points in order of hierarchical testing

Hospitalizations and urgent visits for heart failure — total no. of events (rate)†	194 (40.4)	297 (63.9)	0.64 (0.49 to 0.83)	<0.001
Deaths from cardiovascular causes — total no. of events (rate)†	51 (10.6)	58 (12.5)	0.84 (0.58 to 1.22)	0.36‡

Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure

N Engl J Med 2021; 384:117-128

CONCLUSIONS

In patients with diabetes and recent worsening heart failure, sotagliflozin therapy, initiated before or shortly after discharge, resulted in a significantly lower ~~total number of deaths from cardiovascular causes and~~ hospitalizations and urgent visits for heart failure than placebo. (Funded by Sanofi and Lexicon Pharmaceuticals; SOLOIST-WHF ClinicalTrials.gov number, [NCT03521934](https://clinicaltrials.gov/ct2/show/study/NCT03521934).)

Monday Morning Review!

NNT of 5-- However, results are not reported separately for hospitalizations, which is the more important component of this outcome.

The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial

NATURE MEDICINE

www.nature.com

Trial Design: Double Blind Placebo Control RCT

[Nat Med.](#) 2022; 28(3): 568–574.

Population: Patients admitted to the hospital with acute HF (any EF), N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥ 1600 pg/ml

Intervention: Empagliflozin 10 mg daily or placebo

Primary Outcome: composite of death from any cause, number of HF events and time to first HF event, or a 5 point or greater difference in change from baseline in the Kansas City Cardiomyopathy Questionnaire at 90 days assessed by win ratios

Follow up: 90 days

They combined HFpEF and HFrEF

They used win ratios

Individual trials didn't show mortality benefit but now there is?

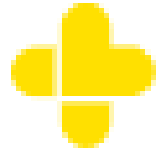
Monday Morning Summary Slide

Dapagliflozin 10 mg NNT for hospitalization = 27 at 18 mths
NNT for Cardiovascular Death = 53 at 18 mths

Empagliflozin 10 mg NNT of 20 for hospitalization at 16 mths
No mortality benefit

Sotagliflozin- Decreased hospitalizations or urgent visits but we don't know which one (NNT 5).

No mortality benefit



GoodRx

Dapagliflozin 10 mg - \$241 per month

Empagliflozin 10 mg- \$597 per month

Sotagliflozin- \$619 per month



Dapagliflozin 10 mg = \$241 per month x 18 months x
NNT 53 = **\$229,914 prevent one cardiovascular death** (\$117K
for hospitalization)

Empagliflozin 10 mg = \$597 per month x 20 months x
NNT 20 = **\$238,800 prevent one hospitalization**

Sotagliflozin = \$619 per month x 9 months x NNT 5 (for
hospitalization or urgent care we don't know) = **\$27,855**

KEY PRACTICE POINTS!!!!

KEY POINTS

Diabetic patient- Empagliflozin prevents death from cardiovascular causes: NNT 46 per 3.1 yrs (\$600 a month, 1 million dollars per life saved)

-HFpEF- SGLT2 inhibitors **do not prevent death** and cost roughly \$364,000 to prevent one hospitalization

-HFrEF -Using Cox models, **only Dapagliflozin has mortality benefit** (NNT 53) and comes at a cost of \$229,914 prevent one cardiovascular death. (117,126\$\$\$ dap for hospitalization)



Questions

