Effect of dapagliflozin on the incidence of diabetes: A prespecified exploratory analysis from DAPA-HF

Silvio E. Inzucchi MD
Yale University School of Medicine
Yale-New Haven Hospital
New Haven, Connecticut, USA

Yale University
School of Medicine

DAPAHF

Disclosures

- **Grant funding:** NIDDK
- **Consultant / Clinical Trial Committees:** Astra Zeneca, Boehringer-Ingelheim, Sanofi/Lexicon, Novo Nordisk, vTv Therapeutics, Abbott, Merck

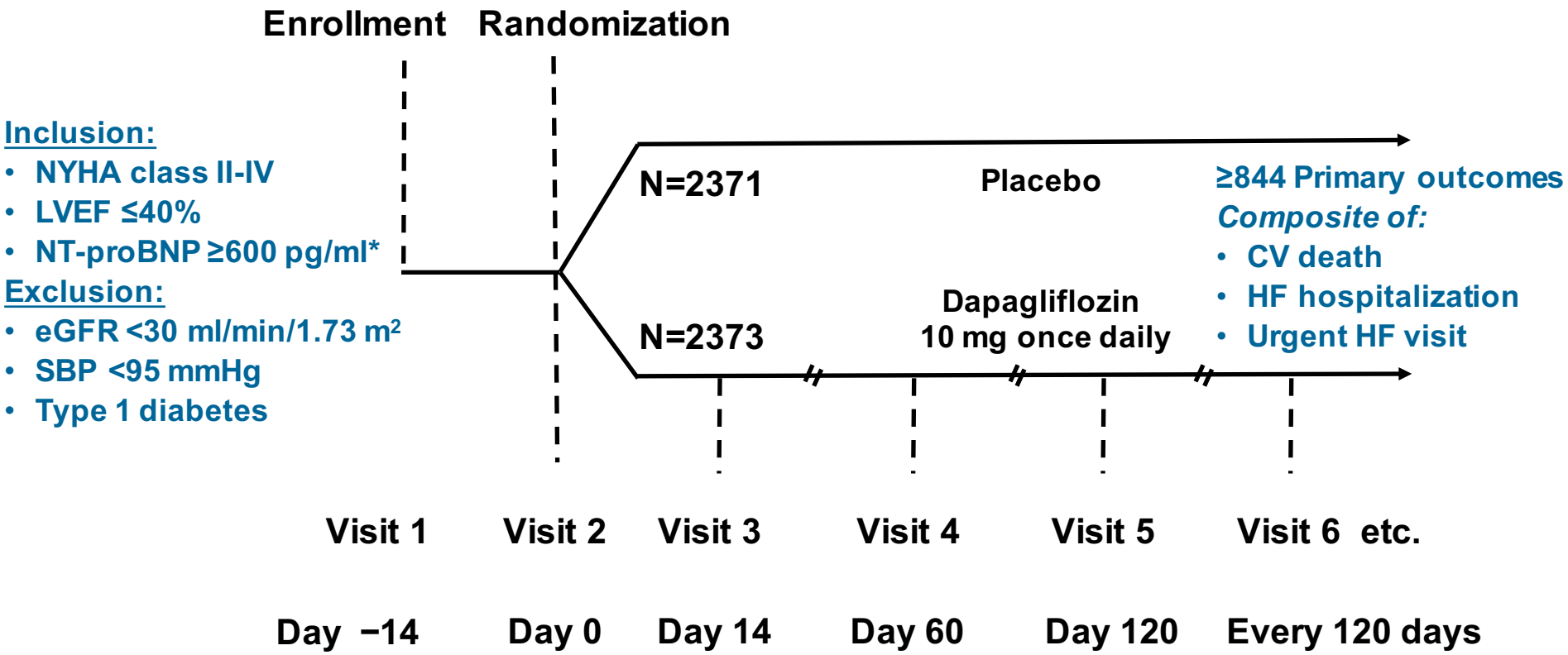
Background - 1

- Incidence of type 2 diabetes (T2D) continues to increase globally.
- Once established, diabetes can lead to micro- and macrovascular complications, increasing mortality and healthcare costs.
- T2D prevention has therefore been of keen interest to the medical community for many years.
- Prior studies show that lifestyle change and certain medications (glucose-lowering, anti-obesity) reduce the incidence of T2D.
- It remains controversial whether preventing diabetes will have any other beneficial health effects (*i.e.,* prevention/delay of complications, reduction in mortality.)

Background - 2

- The SGLT2 inhibitors are glucose-lowering medications that work by inducing glucosuria. They also improve insulin action and secretion and don't increase the risk of hypoglycemia.
- Large CV outcome trials have shown that these agents reduce the risk of MACE, heart failure hospitalization, and CKD progression.
- DAPA-HF was the first trial to show the effectiveness of an SGLT2 inhibitor (dapagliflozin) to improve clinical outcomes in patients with HF with reduced ejection fraction (HFrEF) with/without T2D.
- We sought to determine whether dapagliflozin could **reduce the incidence of new onset T2D** in trial participants who did *not* have diabetes at baseline.

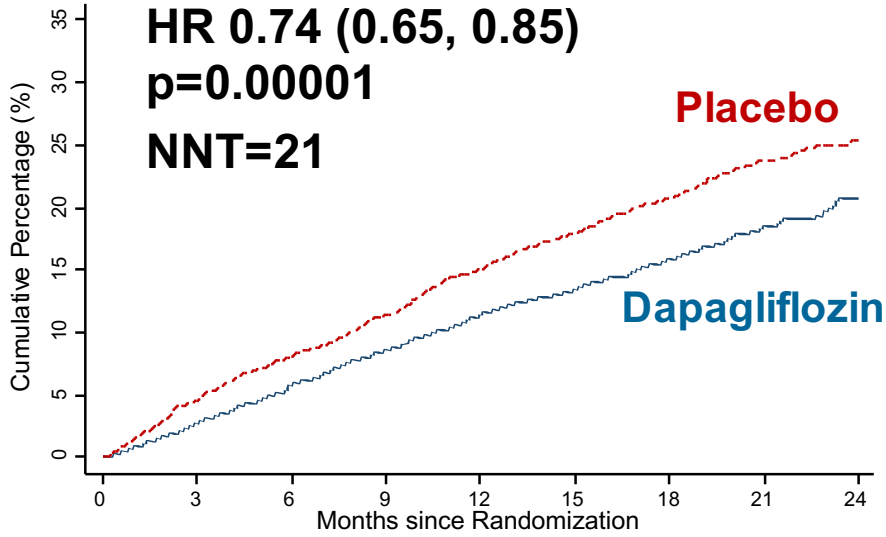
DAPA-HF Design



*≥400 pg/ml if HF hospitalization within ≤12 months; ≥900 pg/ml if atrial fibrillation/flutter

Dapagliflozin reduced worsening HF or CV death in patients with HFrEF

CV Death/HF hospitalization/Urgent HF visit

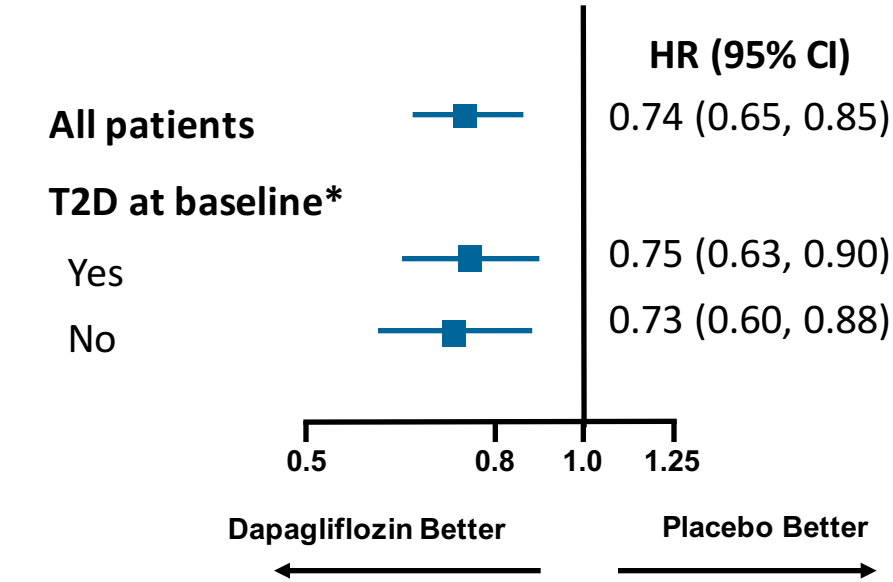


Number at Risk

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

McMurray et al. *N Engl J Med* 2019;38:1995-2008

Similar benefit in patients with and without T2DM



*Defined as history of type 2 diabetes or HbA1c ≥6.5% at both enrolment and randomization visits.

Methods - 1

- HbA1c testing at baseline and each post-randomization study visit (Bio-Rad Variant II HMT370 ion-exchange HPLC assay)
- **Incident diabetes (new-onset diabetes)**: HbA1c ≥6.5% on 2 consecutive study visits *OR* a diagnosis of T2DM by a patient's personal physician with a glucose lowering medication prescribed
- Baseline characteristics were compared using Kruskal-Wallis test for continuous variables and the χ^2 test for categorical variables.
- Change in HbA1c over time was analyzed using a mixed model for repeated measurements.*

* adjusted for baseline values, visit, randomized treatment and interaction of treatment and visit with a random intercept and slope per patient

DAPAHF

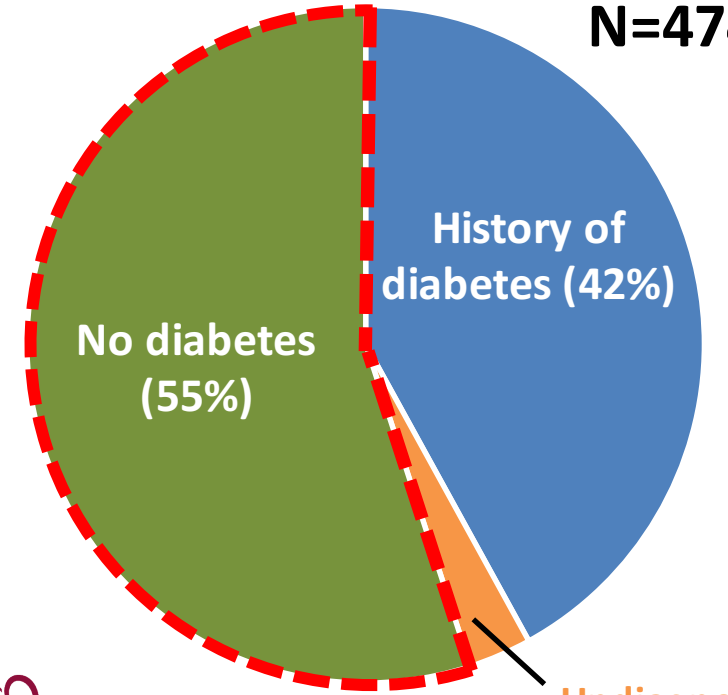
Methods - 2

- Effect of dapagliflozin on incident T2D was assessed using a Cox proportional hazards model with treatment allocation as the sole factor. (Sensitivity analysis using Fine & Gray technique to account for the competing risk of death.)
- Mortality following new onset T2D was also examined in a Cox proportional hazards model, with the indicator for T2D diagnosis entered as a time-updated covariate. The model was repeated, adjusted for treatment allocation and baseline features.*
- Analysis was repeated for HF hospitalizations (+recurrent) or CV death by means of a semiparametric proportional-rates model.

* Age, sex, region, race, NYHA class, LVEF, BMI, HR, SBP, SCr, log NT-proBNP, AFib, stroke, MI, hHTN, ischemic etiology of HF, use of ICD and/or CRT

DAPAHF

Distribution of Patients by Glycemic Status: A Typical HFrEF Population



45%

History of diabetes (n=1983)

- Provided by investigators

Undiagnosed diabetes (n=156)

- HbA1c ≥6.5% at Visits 1 and 2 in patients without diabetes history

55%

No diabetes (n=2605)

- HbA1c <6.5% at Visits 1 and 2

DAPAHF

Petrie MC *et al. JAMA* 2020;323:1353-68

Baseline characteristics by glycemic subgroups

	No Diabetes N=2605	Pre-diabetes N=1748 (67%)	Normoglycemic N=857 (33%)	p-value
Age, yr	66.2 ±11.6	67.1 ±11.1	64.5 ±12.5	<0.001
Sex, no (%)				0.44
Female	632 (24.3)	432 (24.7)	200 (23.3)	
Male	1,973 (75.7)	1,316 (75.3)	657 (76.7)	
Race, no. (%)				0.77
White	1,844 (70.8)	1,242 (71.1)	602 (70.2)	
Asian	625 (24.0)	419 (24.0)	206 (24.0)	
Black/African American	98 (3.8)	61 (3.5)	37 (4.3)	
Other	38 (1.5)	26 (1.5)	12 (1.4)	
BMI (kg/m^2)	27.2 ±5.7	27.4 ±5.8	26.8 ±5.6	0.023
HbA1c (%)	5.8 ±0.4	6.0 ±0.3	5.3 ±0.2	<0.001
eGFR ($ml/min/1.73m^2$)	67.8 ±19.2	67.1 ±18.8	69.2 ±20.0	0.010
eGFR < 60, no. (%)	944 (36.3)	643 (36.8)	301 (35.2)	0.43

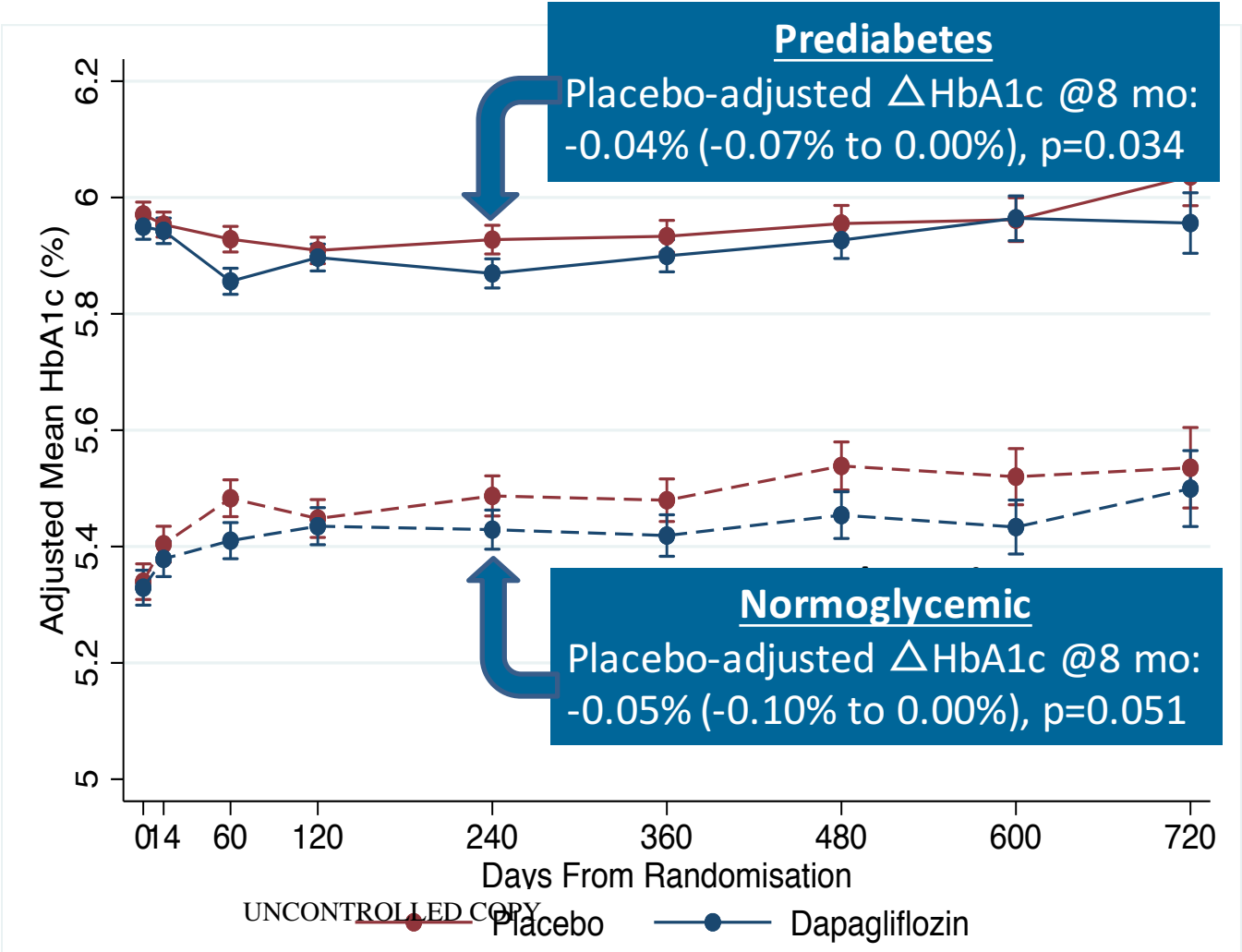
P values presented are for the comparison between prediabetes and normoglycemia. Data presented as mean (SD) unless otherwise indicated. Percentages may not total 100 because of rounding.

Baseline characteristics by glycemic subgroups

	No Diabetes N=2,605	Pre-diabetes N=1,748	Normoglycemic N=857	p-value
NYHA classification, no. (%)				0.048
II	1,841 (70.7)	1,232 (70.5)	609 (71.1)	
III	743 (28.5)	507 (29.0)	236 (27.5)	
IV	21 (0.8)	9 (0.5)	12 (1.4)	
LV ejection fraction, %	30.9 ±6.9	30.9 ±6.9	31.0 ±6.8	0.83
NT-proBNP (pg/ml), median (IQR)	1413 (828-2493)	1439 (832-2616)	1360 (819-2342)	0.094
KCCQ-TSS, median (IQR)	79.2 (61.5-91.7)	79.2 (60.4-91.7)	79.2 (62.5-93.8)	0.11
Principal cause of HF, no. (%)				0.013
Ischemic	1,341 (51.5)	935 (53.5)	406 (47.4)	
Non-ischemic	1,033 (39.7)	666 (38.1)	367 (42.8)	
Unknown	231 (8.9)	147 (8.4)	84 (9.8)	

P values presented are for the comparison between prediabetes and normoglycemia. Data presented as mean (SD) unless otherwise indicated. Percentages may not total 100 because of rounding.

Results: HbA1c levels over time in dapa vs. placebo groups



DAPAHF

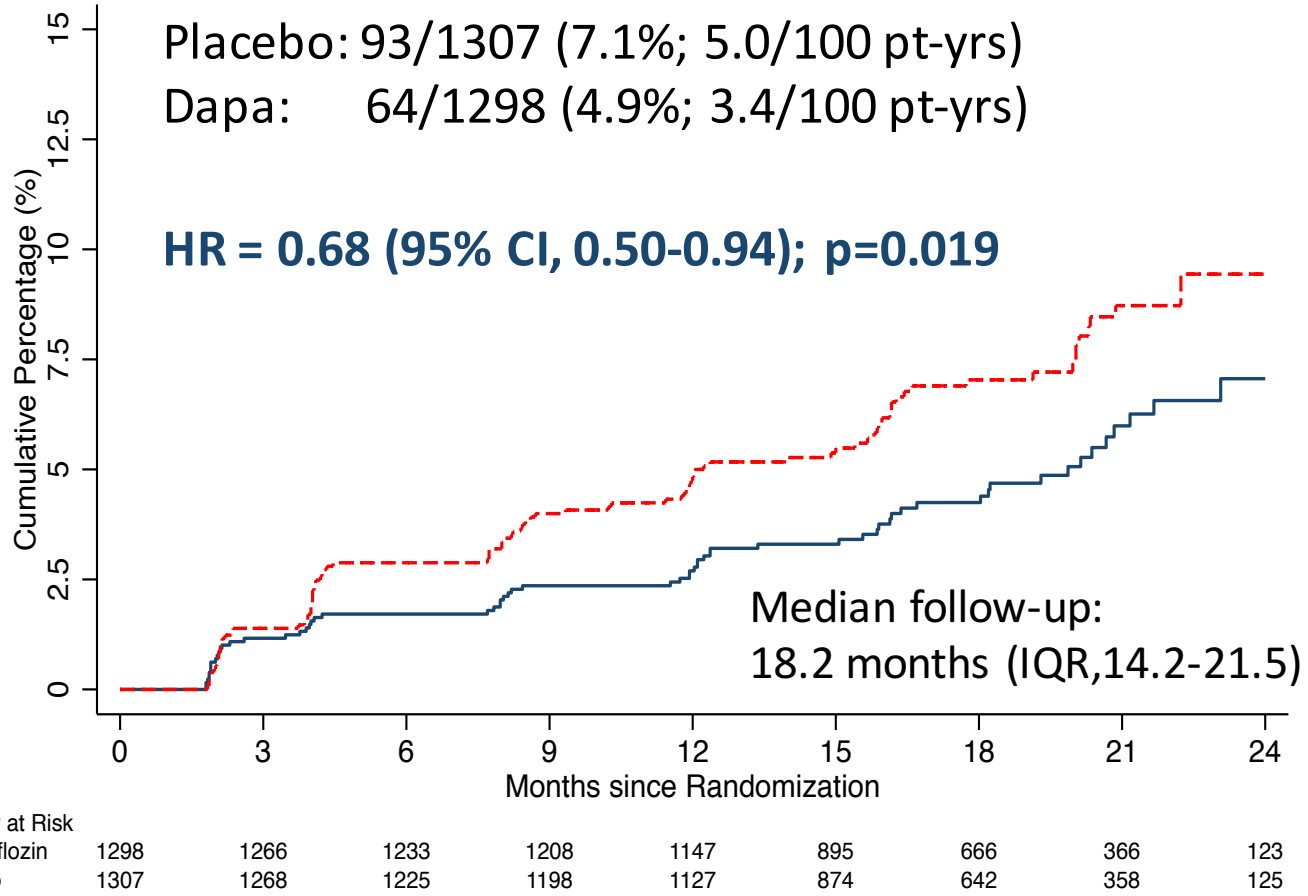
Results

- Amongst the 2605 trial participants without diabetes at baseline, 157 or **6.0%** developed T2D during the trial.

- 150 / 157 or **95.5%** of those with new-onset diabetes had prediabetes at baseline, based on the ADA definition of a HbA1c of 5.7-6.4%.

- 136 / 157 or **86.6%** of those with new-onset diabetes had prediabetes at baseline, using the more restrictive HbA1c criterion of the International Expert Committee (6.0-6.4%.)

Results:
Incidence of new onset T2D in dapa vs. placebo groups



Fine & Gray: HR 0.69 (0.50-0.95)
LR adjusted for baseline HbA1c: OR 0.72 (0.51, 1.02)

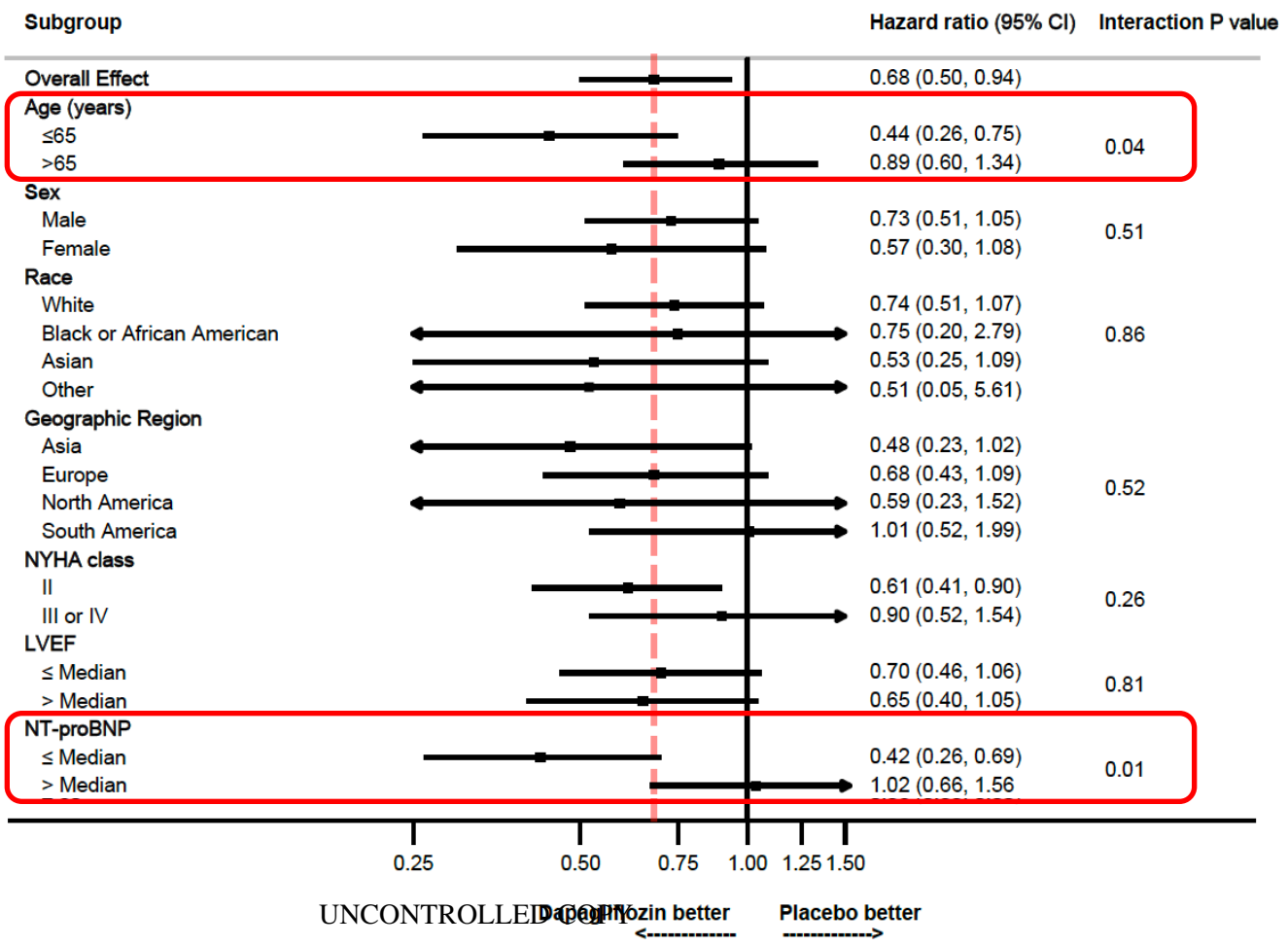
Baseline characteristics by new onset T2D status

	No New Onset T2D	New Onset T2D	p-value
	N=2448	N=157	
Age – yr	66.2±11.7	66.7±10.7	0.55
Sex - no (%)			0.86
Female	593 (24.2)	39 (24.8)	
Male	1,855 (75.8)	118 (75.2)	
Race – no. (%)			0.41
White	1,731 (70.7)	113 (72.0)	
Asian	593 (24.2)	32 (20.4)	
Black or African American	89 (3.6)	9 (5.7)	
Other	35 (1.4)	3 (1.9)	
Body-mass index	27.1±5.7	28.5±5.9	0.003
HbA1c – %	5.7±0.4	6.2±0.3	<0.001
Estimated GFR			
Mean – ml/min/1.73 m^2	68.2±19.3	61.5±17.4	<0.001
Rate < 60 ml/min/1.73 m^2 – no. (%)	868 (35.5)	76 (48.4)	0.001
Systolic Blood Pressure – mmHg	120.6±16.0	120.8±17.3	0.84

Baseline characteristics by new onset T2D status

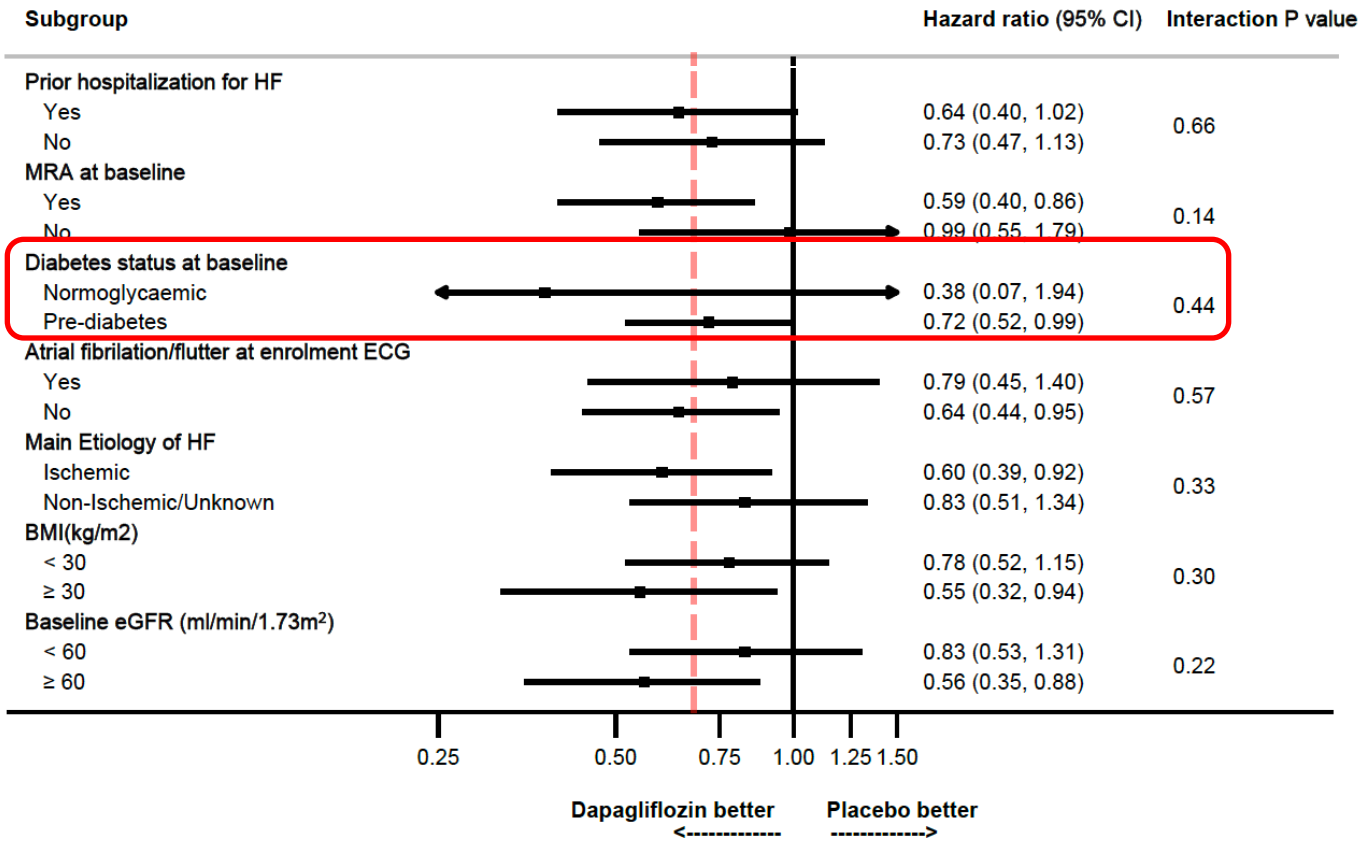
	No New Onset T2D	New Onset T2D	p-value
	N=2448	N=157	
NYHA functional classification – no. (%)			0.40
II	1,737 (71.0)	104 (66.2)	
III/IV	692 (28.3)/19 (0.8)	51 (32.5)/2 (1.3)	
Left ventricular ejection fraction – %	30.9±6.9	30.5±6.8	0.42
Median NT-proBNP (IQR) – pg/ml	1406 (828-2463)	1585 (832-2984)	0.20
Median KCCQ-TSS (IQR)	79.2 (61.5-92.7)	75.0 (60.4-88.5)	0.049
Principal cause of heart failure – no. (%)			0.12
Ischemic	1,249 (51.0)	92 (58.6)	
Non-ischemic/unknown	983 (40.2)/216 (8.8)	50 (31.8)/15 (9.6)	
Heart failure medication – no (%)			
Diuretic	2,256 (92.2)	149 (94.9)	0.21
ACE-inhibitor/ARB	1,402 (57.3)/645 (26.3)	87 (55.4)/47 (29.9)	0.65
Sacubitril-valsartan	266 (10.9)	13 (8.3)	0.31
Beta-blocker	2,338 (95.5)	153 (97.5)	0.25
Mineralocorticoid receptor antagonist	1,728 (70.6)	113 (72.0)	0.71
Digitalis	421 (17.2)	37 (23.6)	0.042

Results: Effect of dapa on incident T2D by relevant subgroups



DAPAHF

Results: Effect of dapa on incident T2D by relevant subgroups



DAPAHF

Key outcomes with the event of new-onset diabetes as a time-updated covariate

	Events/100PY	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
All-cause mortality			
No new-onset T2D (n=2448)	7.2 (6.4-8.1)	1.00	1.00
New-onset T2D (n=157)	16.6 (10.5-26.3)	**2.20 (1.36-3.55) p=0.001**	**1.70 (1.04-2.80) p=0.035**
Cardiovascular death			
No new-onset T2D (n=2448)	5.8 (5.1-6.7)	1.00	1.00
New-onset T2D (n=157)	14.7 (9.0-24.1)	**2.43 (1.46-4.06) p=0.001**	**1.77 (1.04-3.02) p=0.035**
Total HF hospitalizations (including recurrent) and cardiovascular death			
No new-onset T2D (n=2448)	14.6 (13.4-15.9)	1.00	1.00
New-onset T2D (n=157)	28.6 (20.1-40.6)	**1.90 (1.18-3.05)*** **p=0.008**	1.37 (0.83-2.24)* p=0.22

* Effect estimate displayed as a rate ratio

Limitations

- We did not assess FPG or OGTT, as is typically done in traditional diabetes prevention trials.
- Our findings apply only to patients with HFrEF.
- In this event-driven trial, due to a strong effect of dapagliflozin on the primary outcome, our follow-up was only 18 months. It is unknown if the effect of this medication on incident T2D would be durable over time.
- We also did not retest for diabetes after drug withdrawal at the conclusion of the trial.

Conclusions

- The SGLT2i dapagliflozin decreased the incidence of T2D by **32%** in 2605 participants in the DAPA-HF trial who did not have diabetes at baseline.
- This effect was principally driven by participants who had prediabetes.
- While the major role of dapagliflozin in patients with HFrEF is to reduce CV mortality and worsening of HF, decreasing the incidence of diabetes may be considered an additional benefit, especially since incident T2D is associated with greater mortality.

DAPAHF

Observations

- DAPA-HF is the first trial to demonstrate a “diabetes prevention” effect from an SGLT2 inhibitor.
- In contrast to other diabetes prevention trials with glucose lowering medications, HbA1c was minimally reduced by dapagliflozin in non-diabetic patients at baseline. This may dispel concerns about merely ‘masking’ the development of diabetes.
- Dapagliflozin is the first medication demonstrated to reduce *both* incident T2D and mortality in a single trial.

DAPAHF

Thanks to…

- **Co-Authors:** Kieran F Docherty, Lars Køber, Mikhail N Kosiborod, Felipe A Martinez, Piotr Ponikowski, Marc S Sabatine, Scott D Solomon, Subodh Verma, Jan Bělohlávek, Michael Böhm, Chern-En Chiang, Rudolf A. de Boer, Mirta Diez, Andre Dukát, Charlotta E.A. Ljungman, David L Demets, Olof Bengtsson, Anna Maria Langkilde, Mikaela Sjöstrand, Pardeep S Jhund, John JV McMurray
- **Investigators and coordinators at 410 sites**
- **8134 patients screened, 4744 patients randomized**

Effect of dapagliflozin on the incidence of diabetes: A prespecified exploratory analysis from DAPA-HF

Silvio E. Inzucchi MD
Yale University School of Medicine
Yale-New Haven Hospital
New Haven, Connecticut, USA

Yale University
School of Medicine

DAPAHF