AstraZeneca
What science can do

Farxiga's DAPA-HF trial at ESC

Conference call for investors and analysts

1st September 2019

Forward-looking statements

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Presenters

Pascal Soriot
Executive Director and
Chief Executive Officer

Professor John McMurray
MB ChB (Hons), MD, FRCP, FESC,
FACC, FAHA, FRSE, FmedSci, OBE
University of Glasgow, UK

Available for Q&A

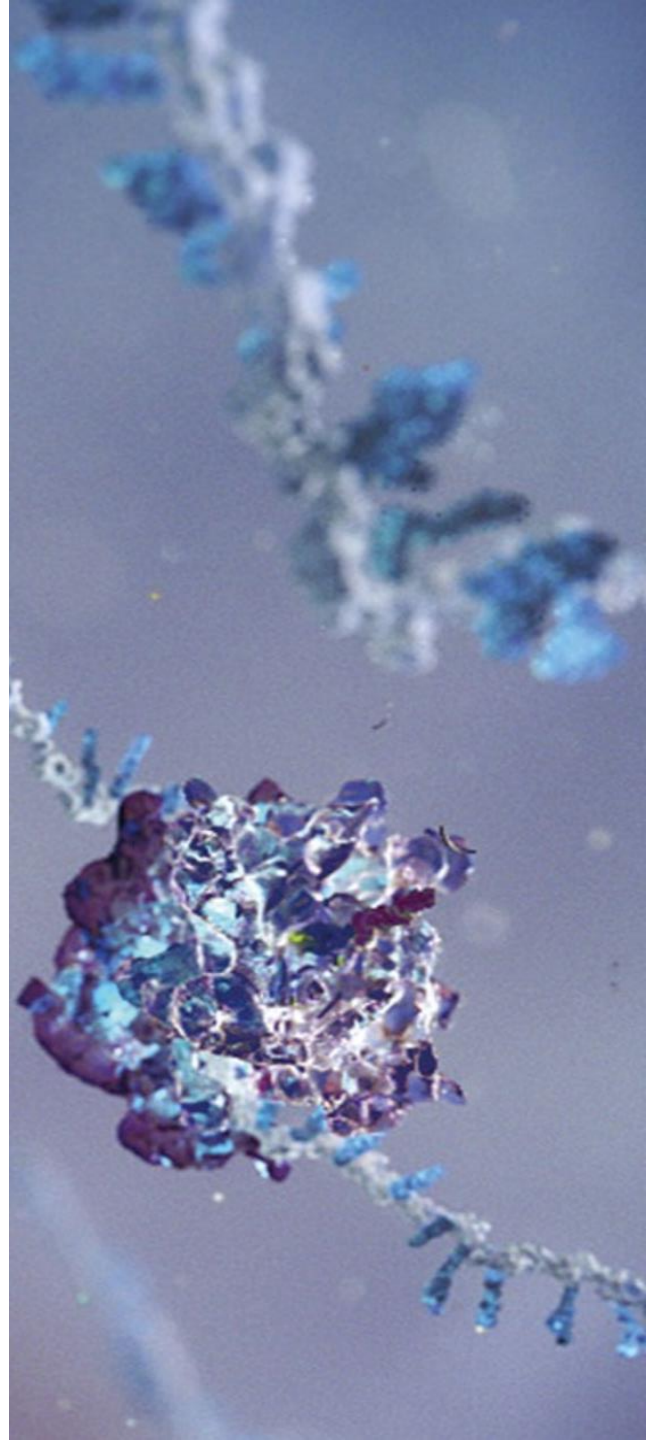
Mene Pangalos
Executive Vice President,
BioPharmaceuticals R&D

Ruud Dobber
Executive Vice President,
BioPharmaceuticals Business Unit

Elisabeth Björk
Senior Vice President,
Late CVRM

Agenda for today's conference call

1. Introduction by Pascal Soriot
2. DAPA-HF presentation by Prof. John McMurray
3. Closing and Q&A



AstraZeneca @ ESC 2019

DAPA-HF another important milestone for *Farxiga*
THEMIS builds on positive *Brilinta* momentum

Farxiga

- Positive DECLARE data in a broad patient population in **type-2 diabetes**
- Ground breaking results in **heart failure** (HFrEF) in both patients with and without type-2 diabetes
- DELIVER (HFpEF), data 2020+
- US FDA Fast Track Designation in **CKD**

Brilinta

- **THEMIS** shows statistically significant benefit for *Brilinta* in patients with CAD and type-2 diabetes
  Positive risk/benefit in PCI subgroup

High unmet medical need

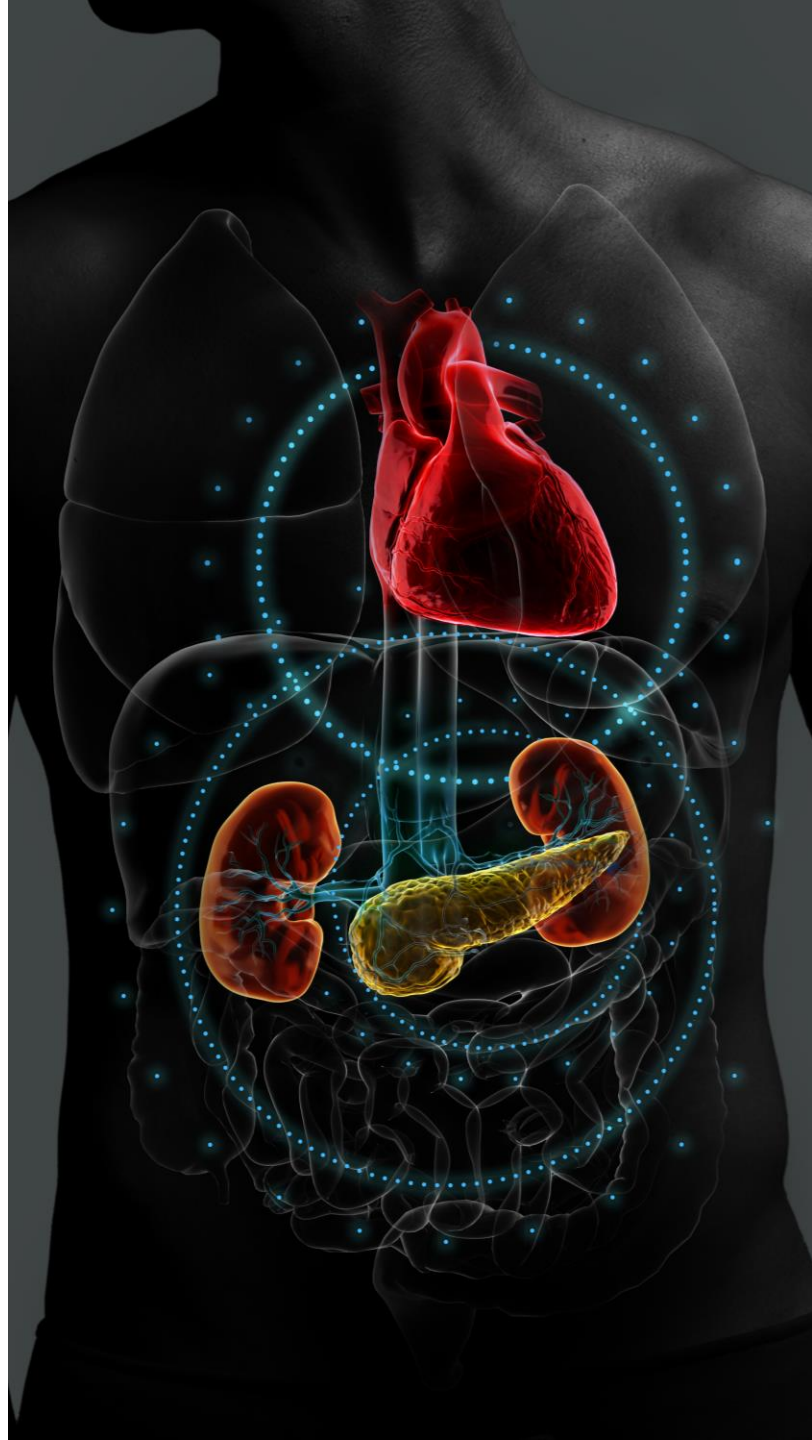
425m people affected with diabetes

64m people with HF

$31bn estimated costs in the US alone in 2012

17.9m CV deaths per year

200m people with chronic kidney disease



Sources; 1. World Health Organization. Cardiovascular diseases (CVDs). 2016. http://www.who.int/mediacentre/factsheets/fs317/en/. Accessed 30 August 2019. 2. International Diabetes Federation. About Diabetes. 2018. https://idf.org/52-about-diabetes.html. Accessed 30 August 2019. 3. Ojo A. Addressing the global burden of chronic kidney disease through clinical and translational research. Trans Am Clin Climatol Assoc. 2014;125:229-43; discussion 243-6. 4. Vos T et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. The Lancet 2017; 390(10100):1211-59. 5. Heidenreich P.A. et.al, Forecasting the Impact of Heart Failure in the United States: A Policy Statement From the American Heart Association. Circ Heart Fail. 2013 May; 6(3): 606–619.

Innovative, complementary CVRM portfolio

Diabetes

farxiga (dapagliflozin) 5mg tablets

BRILINTA ticagrelor tablets

Roxadustat roxadustat

Once-weekly BYDUREON® BCise™ exenatide extended-release injectable suspension 2 mg

Heart Failure

farxiga (dapagliflozin) 5mg tablets

LOKELMA™▼* powder for oral suspension Sodium zirconium cyclosilicate

Cardiovascular

farxiga (dapagliflozin) 5mg tablets

BRILINTA ticagrelor tablets

once daily epanova omega-3-carboxylic acids

Data 2020

Kidney Disease

farxiga (dapagliflozin) 5mg tablets

Data 2020+

LOKELMA™▼ powder for oral suspension Sodium zirconium cyclosilicate

Roxadustat roxadustat

* Enabling effective treatment for HF

Farxiga's Dapa-HF trial at ESC 2019

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

John McMurray
BHF Cardiovascular Research Centre,
University of Glasgow & Queen Elizabeth
University Hospital, Glasgow

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Trial leadership and data analysis

Executive Committee

John J.V. McMurray MD (Chairman), David L. DeMets, Silvio E. Inzucchi, Lars Køber, Mikhail N. Kosiborod, Anna Maria Langkilde, Felipe A. Martinez, Piotr Ponikowski, Marc S. Sabatine, Mikaela Sjöstrand, Scott D. Solomon

AstraZeneca leadership

Anna Maria Langkilde, Olof Bengtsson, Mikaela Sjöstrand, Kinga Kazanowska, Mikael Forsby, Ywonne Fox

Data analysis

Olof Bengtsson, Folke Folkvaljon, Samvel Gasparyan (AstraZeneca); Pardeep Jhund, Kieran Docherty, Alice Jackson, Jim Lewsey (University of Glasgow)

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Background

- Sodium-glucose co-transporter 2 (SGLT2) inhibitors ***prevent*** the development of heart failure in patients with type 2 diabetes (T2D). Can they be used to ***treat*** patients with established heart failure?
- The benefits of SGLT2 inhibitors may be glucose-independent. Can SGLT2 inhibitors be used to treat patients ***without*** T2D?
- We tested the SGLT2 inhibitor dapagliflozin,10 mg once daily, added to standard therapy, in patients with heart failure and reduced ejection fraction (HFrEF) both ***with and without*** T2D

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Trial Design

- **Key inclusion criteria:** Symptomatic HF; EF ≤40%; NT-proBNP ≥600 pg/ml (if hospitalized for HF within last 12 months ≥400 pg/mL; if atrial fibrillation/flutter ≥900 pg/mL)
- **Key exclusion criteria:** eGFR <30 ml/min/1.73 m^2; symptomatic hypotension or SBP <95 mmHg; type 1 diabetes mellitus
- **Primary endpoint:** Worsening HF event or cardiovascular death (worsening HF event = unplanned HF hospitalization or an urgent heart failure visit requiring intravenous therapy)

For full details see McMurray JJV et al Eur J Heart Fail. 2019;21:665-675

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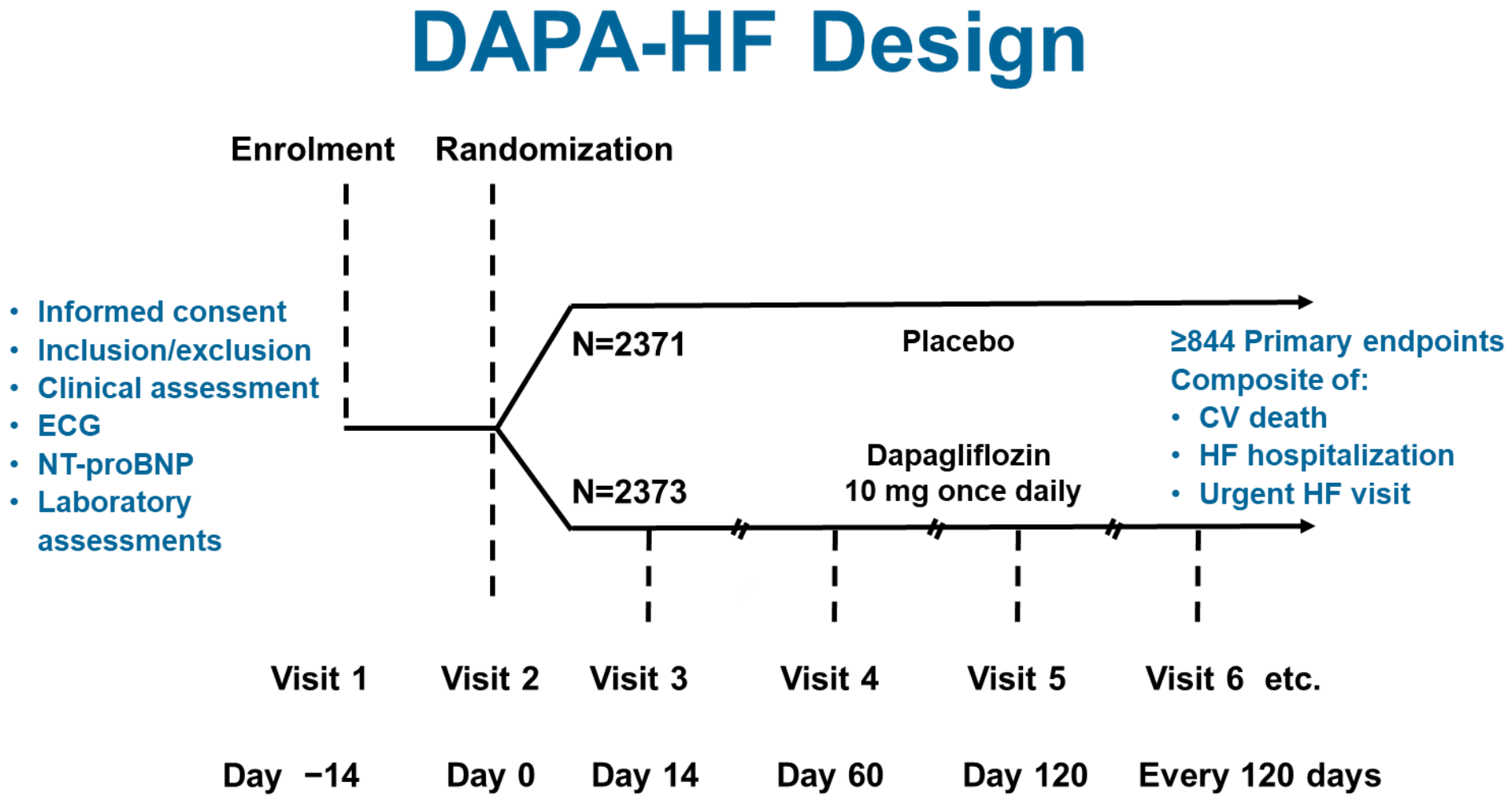

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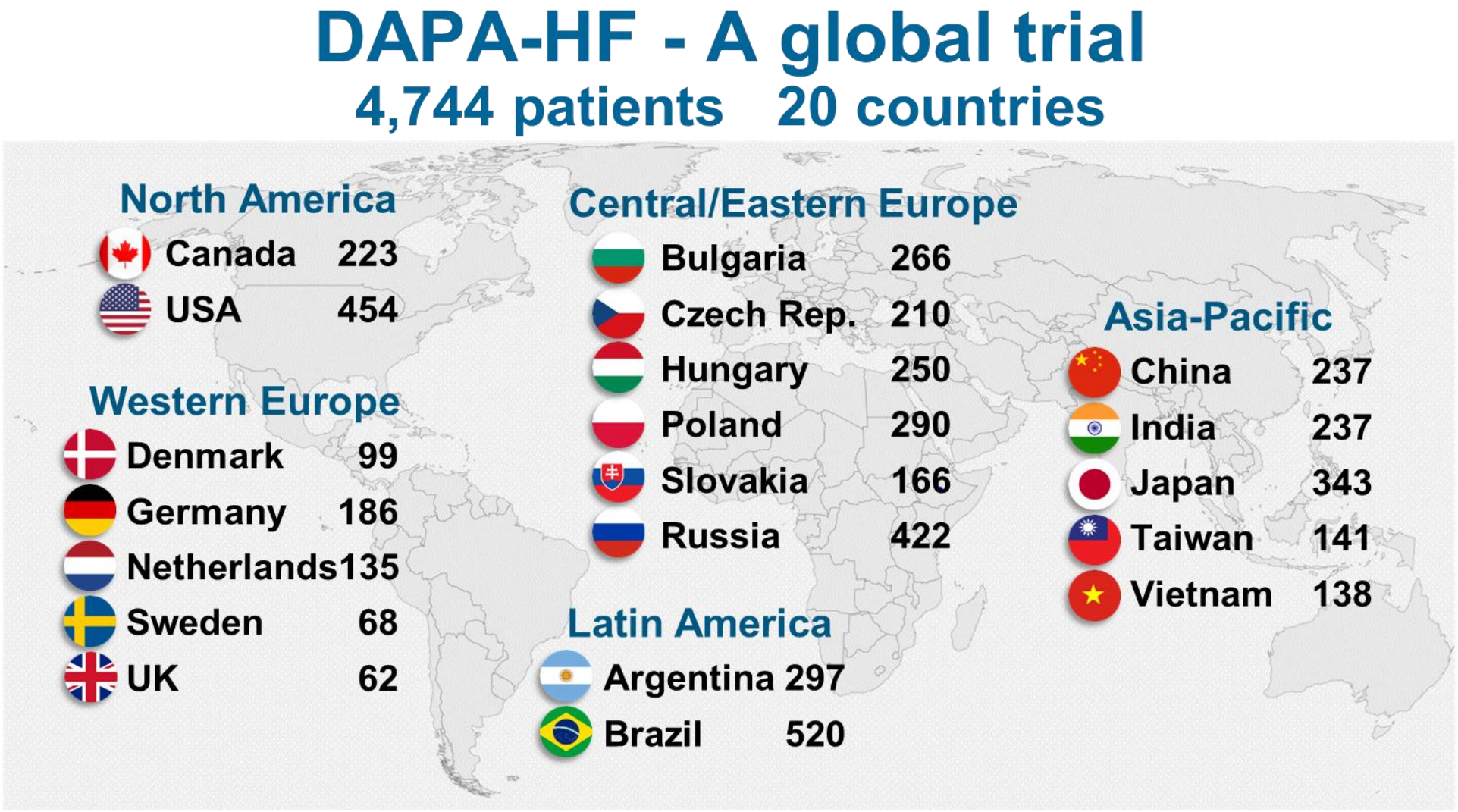

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Key baseline characteristics

Characteristic	Dapagliflozin (n=2373)	Placebo (n=2371)
Mean age (yr)	66	67
Male (%)	76	77
NYHA class II/III/IV (%)	68/31/1	67/32/1
Mean LVEF (%)	31	31
Median NT pro BNP (pg/ml)	1428	1446
Mean systolic BP (mmHg)	122	122
Ischaemic aetiology (%)	55	57
Mean eGFR (ml/min/1.73m^2)	66	66
Prior diagnosis T2D (%)	42	42
Any baseline T2D (%)*	45	45

*includes 82 dapagliflozin and 74 placebo patients with previously undiagnosed diabetes i.e. two HbA1c ≥6.5% (≥48 mmol/mol)

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Baseline treatment

Treatment (%)	Dapagliflozin (n=2373)	Placebo (n=2371)
Diuretic	93	94
ACE-inhibitor/ARB/ARNI+	94	93
ACE inhibitor	56	56
ARB	28	27
Sacubitril/valsartan	11	11
Beta-blocker	96	96
MRA	71	71
ICD*	26	26
CRT**	8	7

+ARNI = angiotensin receptor neprilysin inhibitor
*ICD or CRT-D **CRT-P or CRT-D

For full details see McMurray JJV et al Eur J Heart Fail.2019 Jul 15. doi: 10.1002/ejhf.1548

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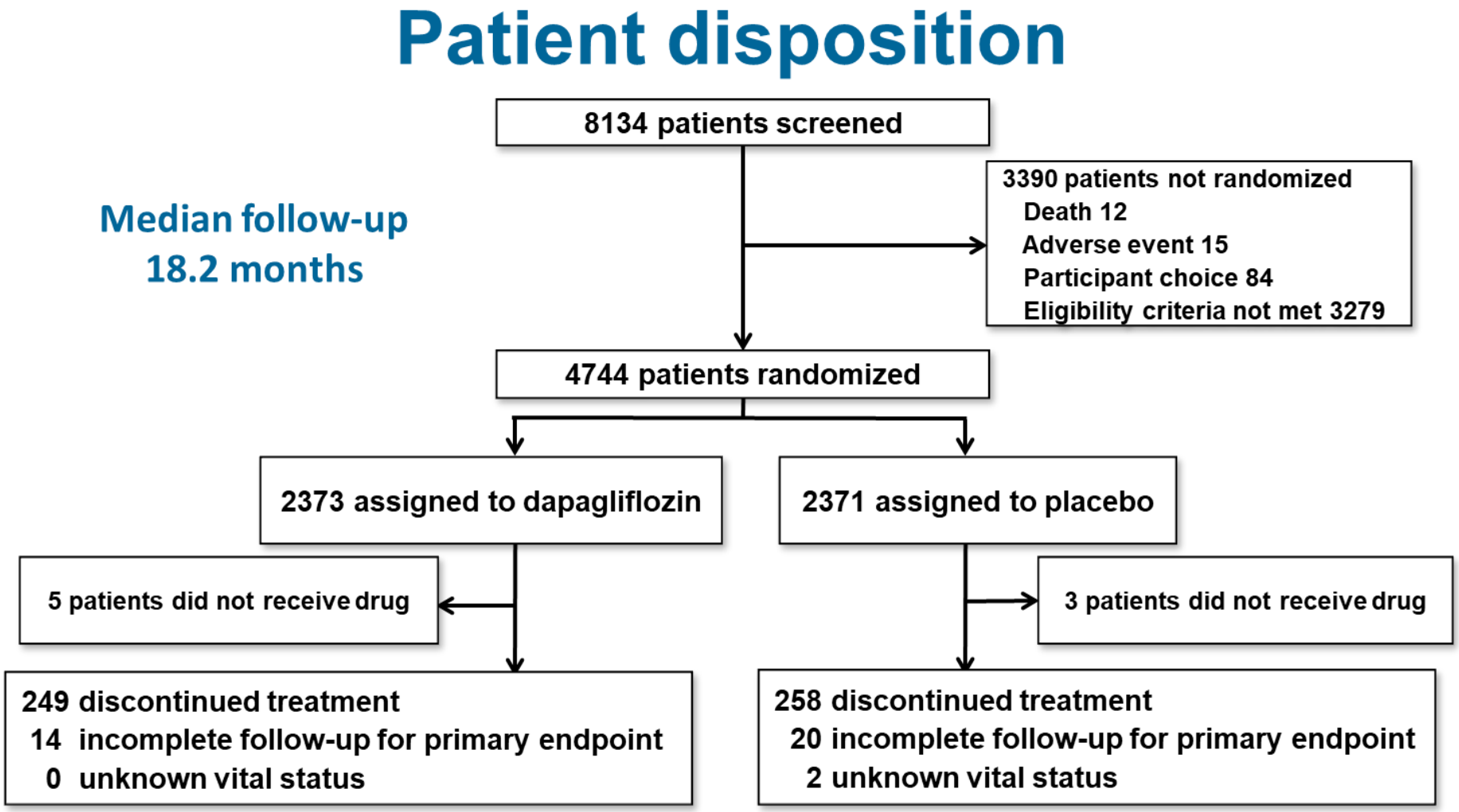

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Primary outcome

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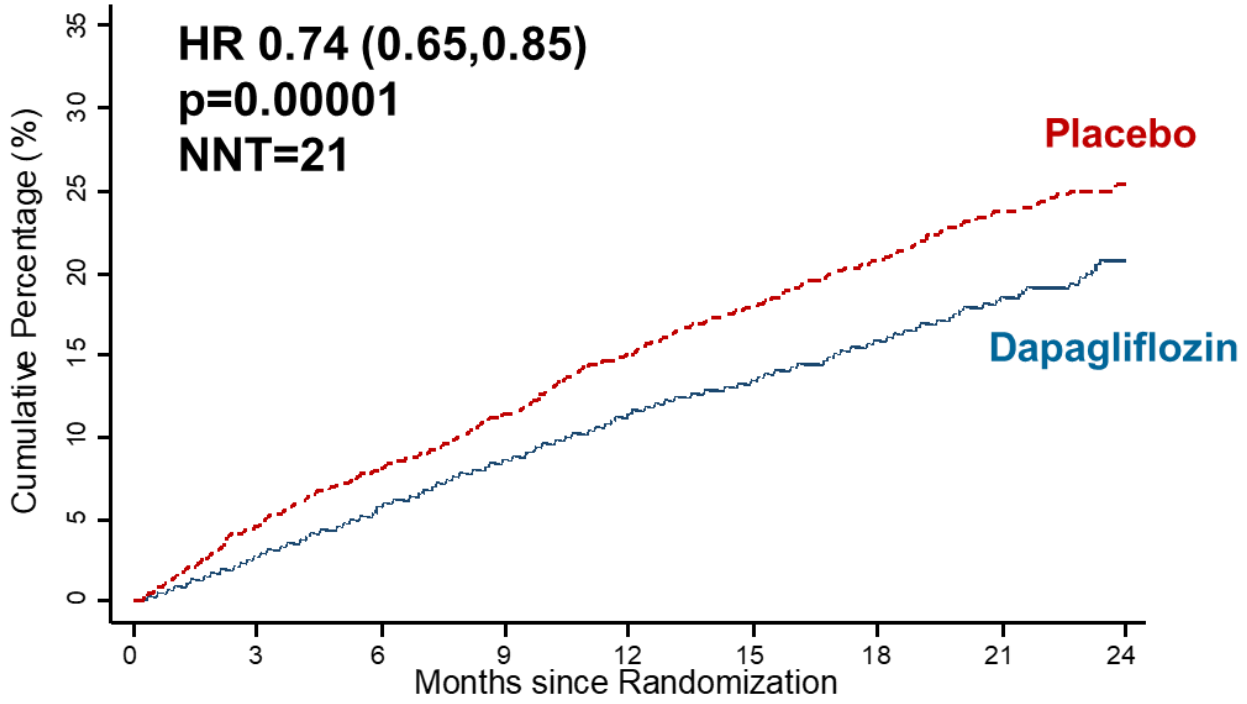
Primary composite outcome

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

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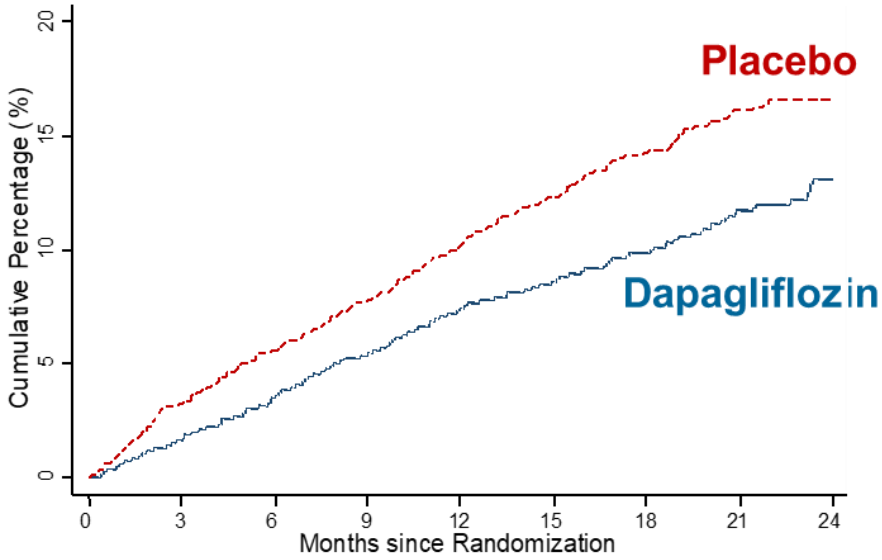
Components of primary outcome

Worsening HF event

HR 0.70 (0.59, 0.83); p=0.00003

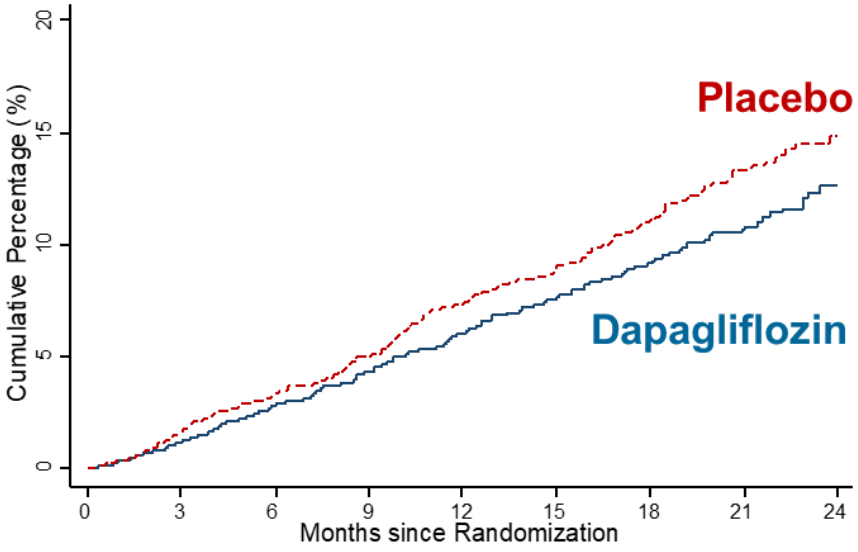


Number at Risk

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

Cardiovascular death

HR 0.82 (0.69, 0.98); p=0.029



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

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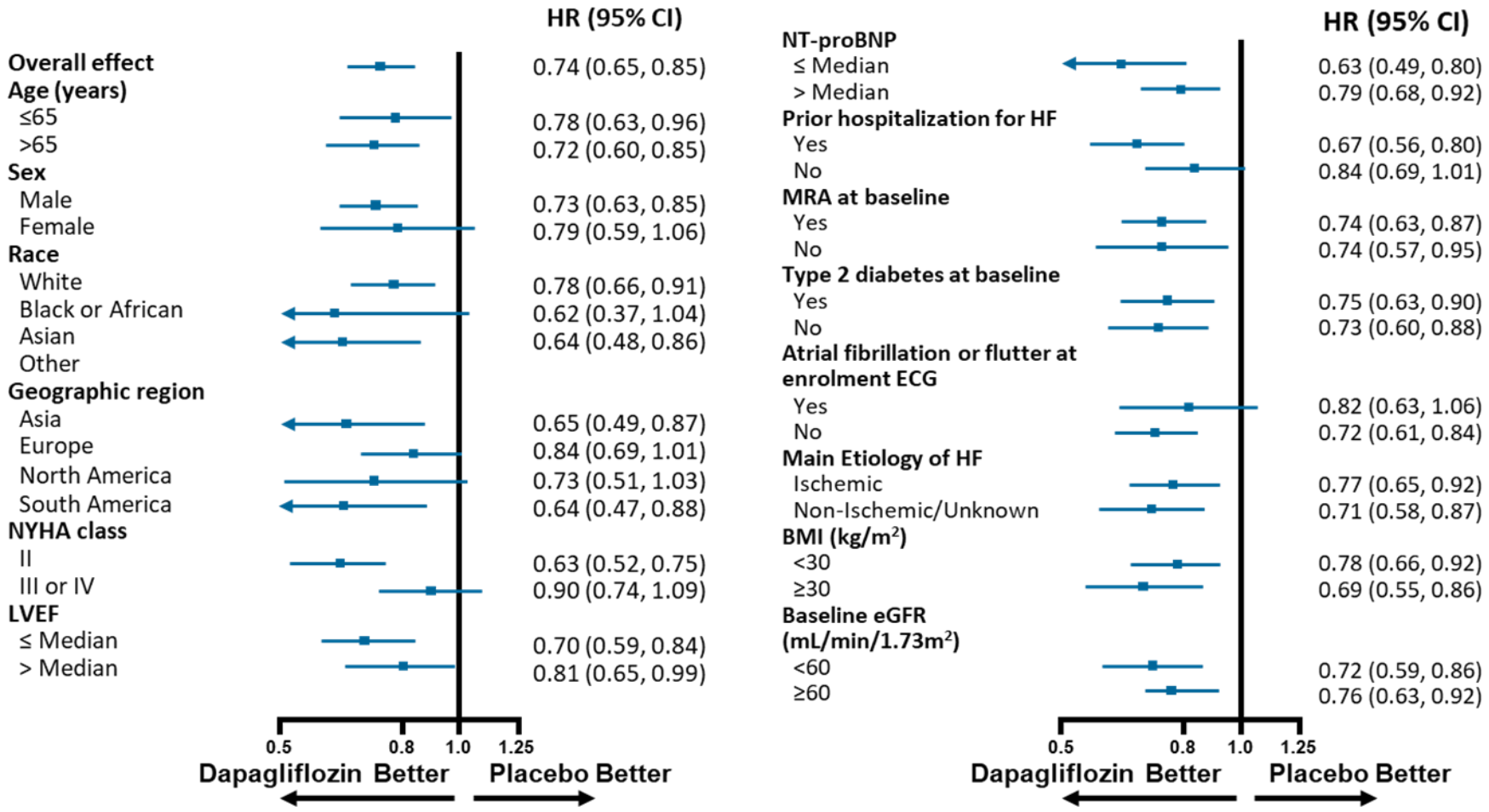
Primary Endpoint: Prespecified subgroups



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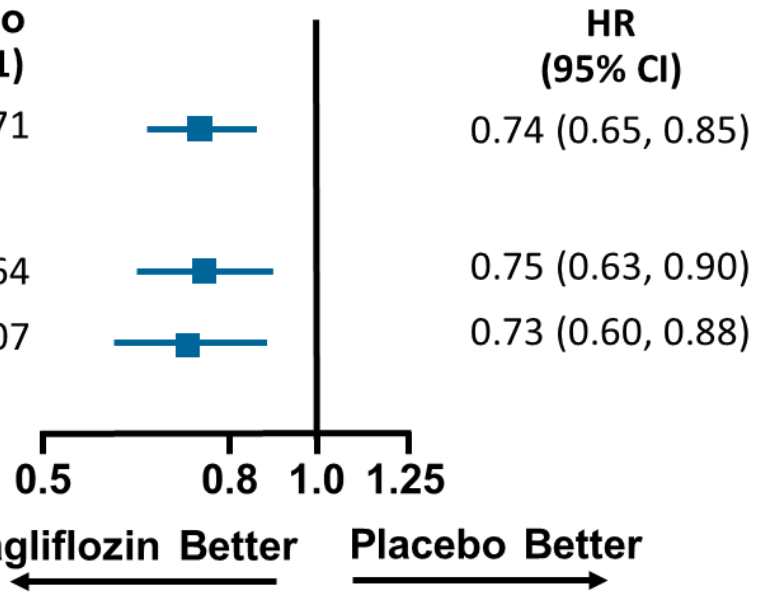
No diabetes/diabetes subgroup: Primary endpoint

	Dapagliflozin (n=2373)	Placebo (n=2371)	HR (95% CI)
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)



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

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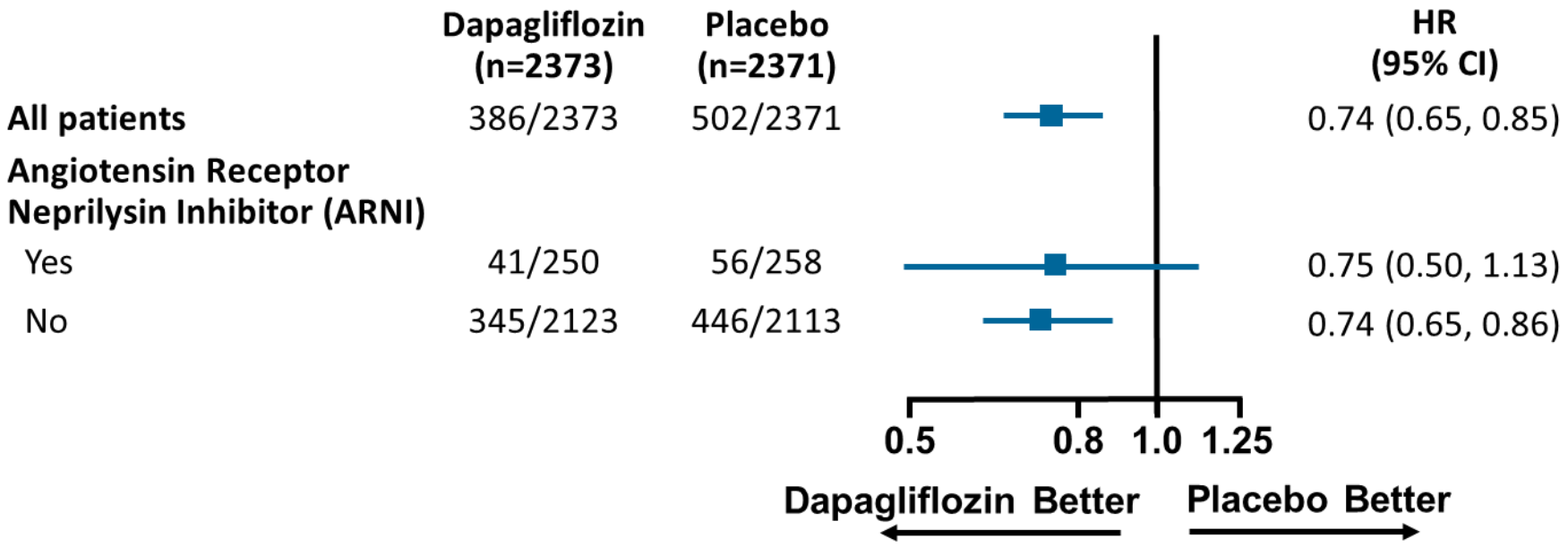
ARNI/no ARNI *post hoc* subgroup: Primary endpoint



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Secondary outcomes

In order of hierarchical testing

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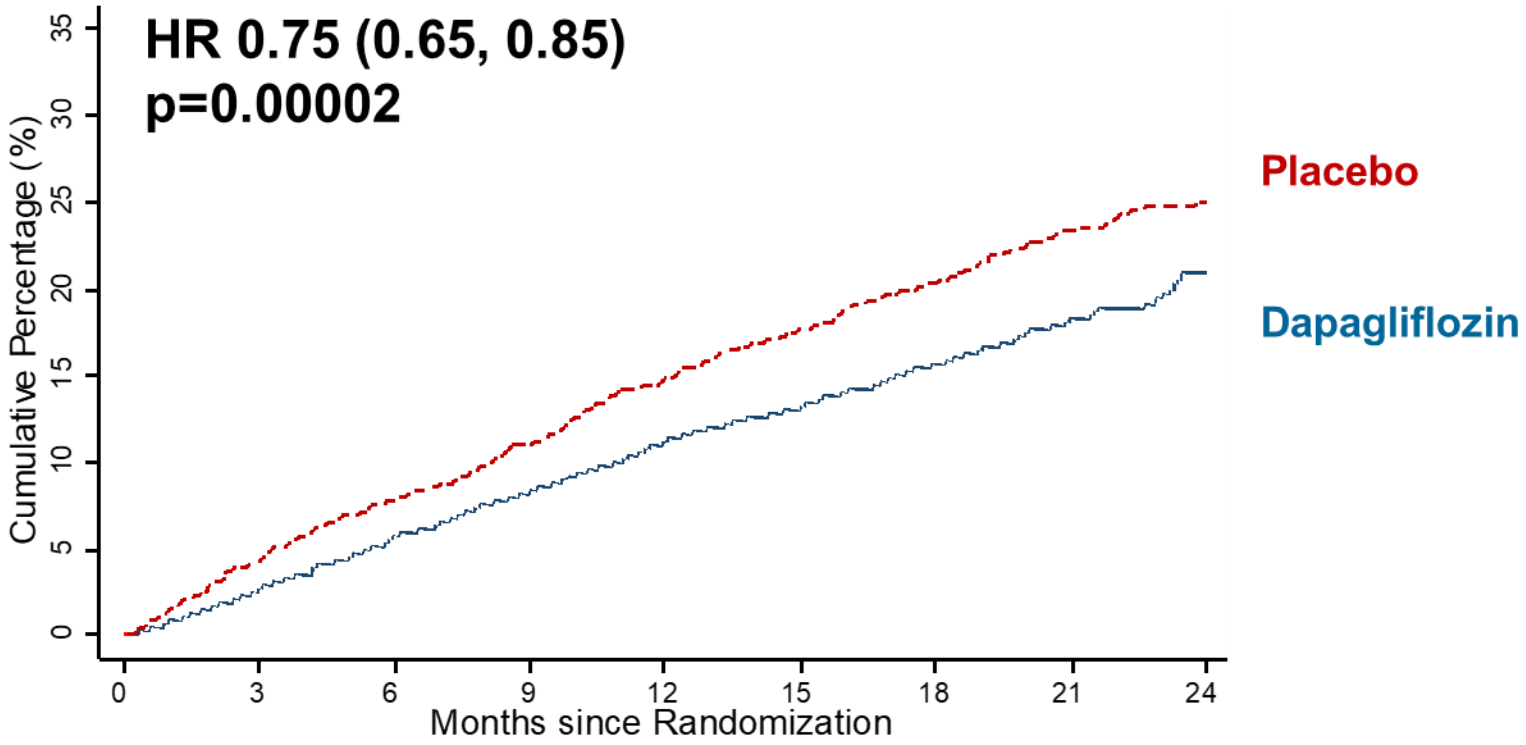
CV death or HF hospitalization



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

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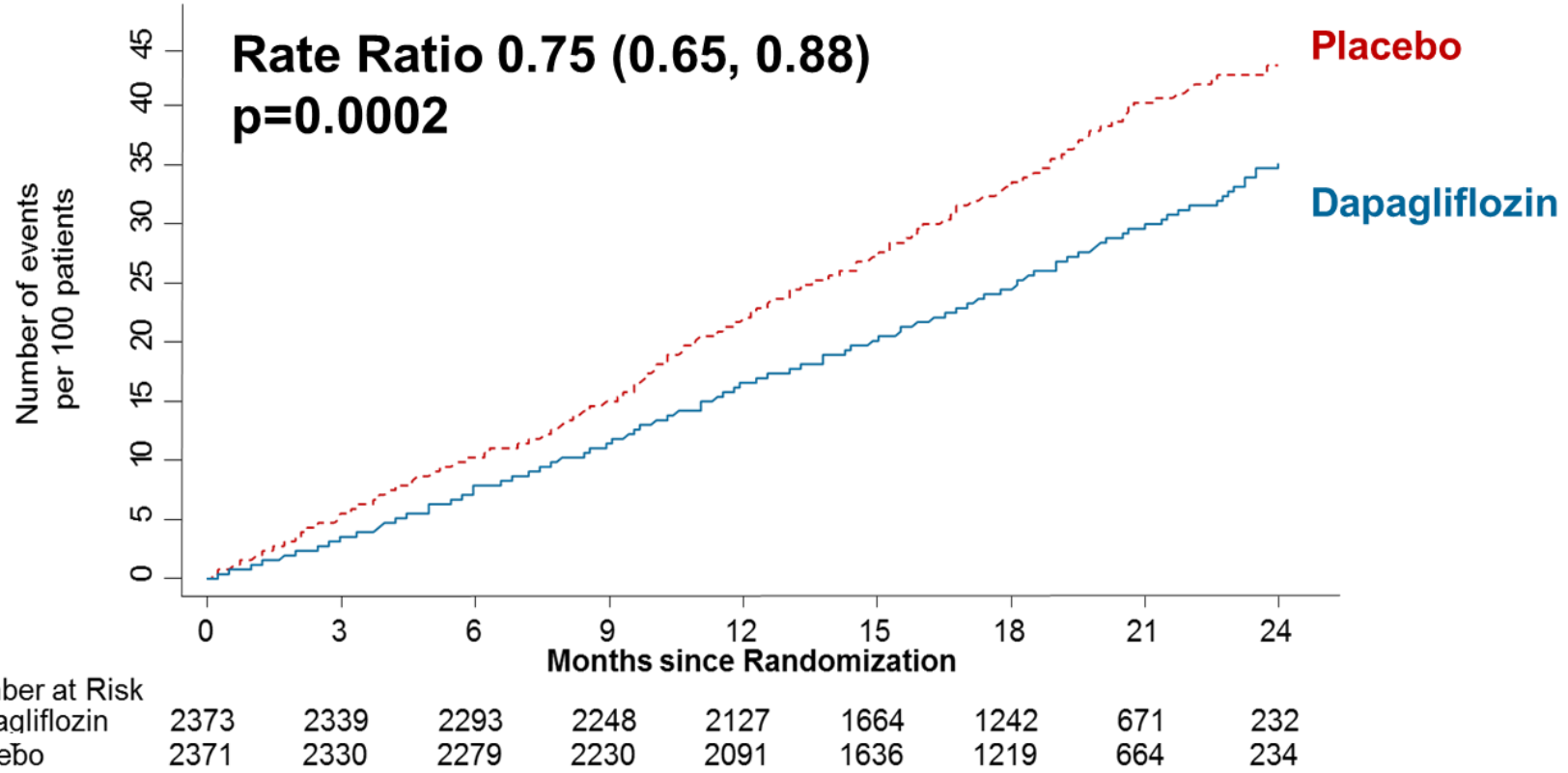
Total HF hospitalizations and CV death

Including first and repeat hospitalizations



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Kansas City Cardiomyopathy Questionnaire (KCCQ)

Total Symptom Score (TSS): Change from baseline to 8 months

Treatment	Change
Dapagliflozin	**+6.1** ± 18.6
Placebo	**+3.3** ± 19.2

Difference
2.8 points (95% CI 1.6, 4.0)
p<0.001*

Increase in score indicates an improvement

*Calculated from win ratio, incorporating death. Win ratio = 1.18 (CI 1.11, 1.26). Win ratio >1 indicates superiority of dapagliflozin over placebo

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Kansas City Cardiomyopathy Questionnaire (KCCQ)

Total Symptom Score: Proportion with ≥5 point change from baseline to 8 months*

Treatment	Dapagliflozin	Placebo	Odds ratio (95% CI)
≥5 point improvement	58%	51%	1.15 (1.08, 1.23) p<0.001
≥5 point deterioration	25%	33%	0.84 (0.78, 0.90) p<0.001

*Taking account of death

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Worsening renal function endpoint

Composite of: Sustained* ≥50% reduction in eGFR, end-stage renal disease (ESRD) or death from renal causes

Treatment	No. (%)
Dapagliflozin	28 (1.2)
Placebo	39 (1.6)

Hazard ratio (95% CI)
0.71 (0.44, 1.16)
p=0.17

ESRD consisted of sustained eGFR below 15 ml/min/1.73m^2, sustained dialysis or kidney transplantation

*Sustained = 28 days or more

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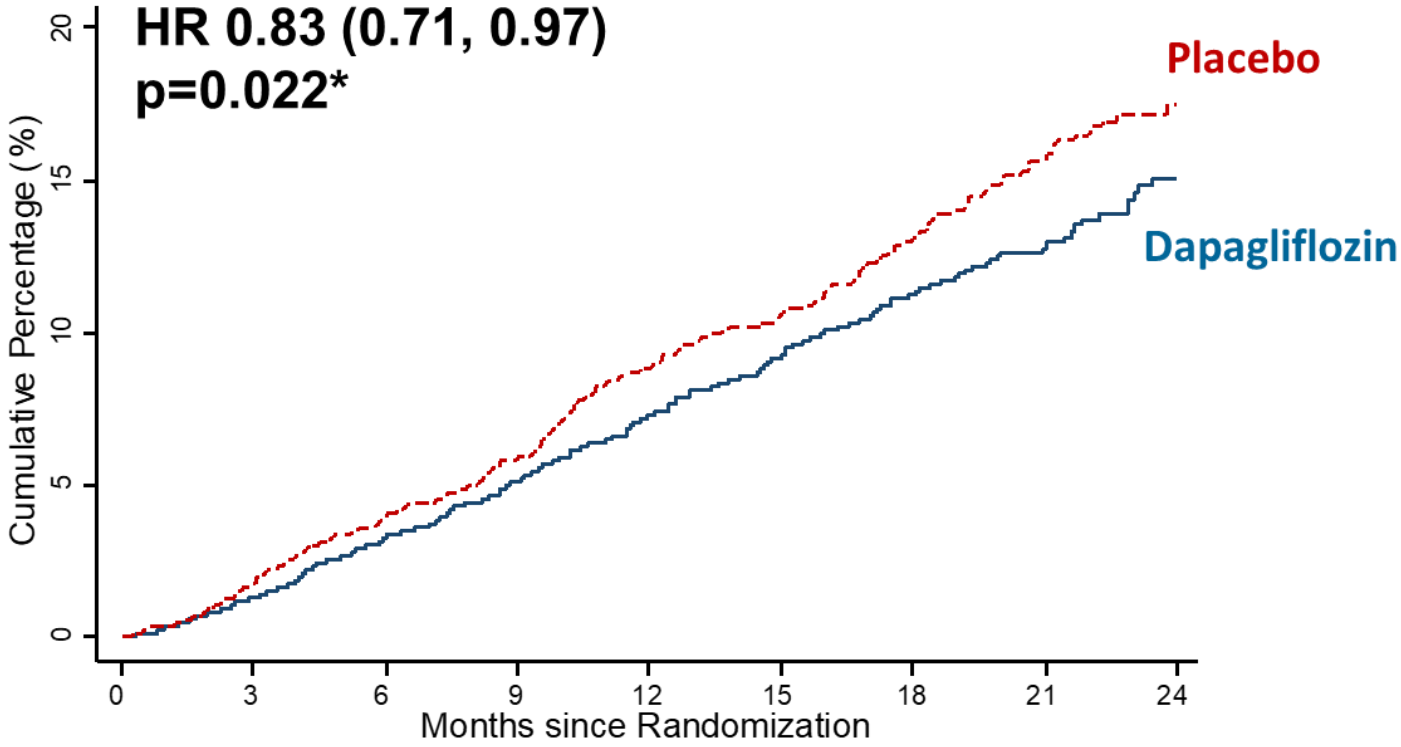
All-cause death



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

*Nominal p value

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Safety/adverse events

Patients exposed to at least one dose of study drug	Dapagliflozin (n=2368)	Placebo (n=2368)	p-value
Adverse events (AE) of interest (%)			
Volume depletion[+]	7.5	6.8	0.40
Renal AE[‡]	6.5	7.2	0.36
Fracture	2.1	2.1	1.00
Amputation	0.5	0.5	1.00
Major hypoglycaemia	0.2	0.2	-
Diabetic ketoacidosis	0.1	0.0	-
AE leading to treatment discontinuation (%)	4.7	4.9	0.79
Any serious adverse event (incl. death) (%)	38	42	<0.01

[+] Volume depletion serious AEs in 29 dapagliflozin patients (1.2%) and 40 placebo patients (1.7%), p=0.23

[‡] Renal serious AEs in 38 dapagliflozin patients (1.6%) and 65 placebo patients (2.7%), p=0.009

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Summary and conclusions

- Dapagliflozin reduced the risk of worsening heart failure events and cardiovascular death, and improved symptoms, in patients with HFrEF, when added to standard therapy
- The relative and absolute risk reductions in death and hospitalization were substantial, clinically important, and consistent across important subgroups, including patients ***without*** T2D
- Dapagliflozin was well tolerated and the rate of treatment discontinuation was low
- Dapagliflozin offers a new approach to the treatment of HFrEF

Q&A

Use of AstraZeneca conference call, webcast and presentation slides