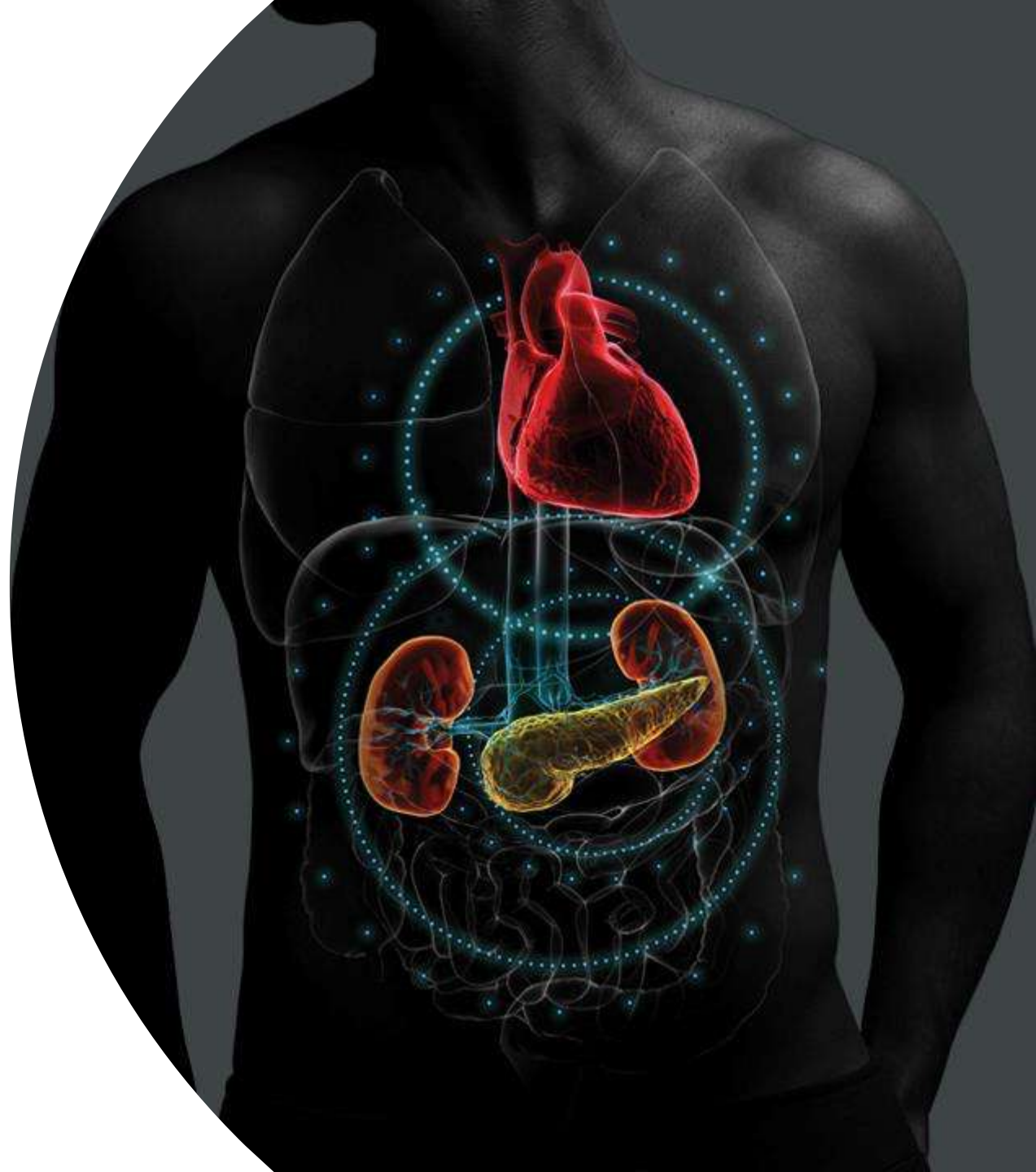


# 心腎共病的最新臨床治療策略 －以糖尿病合併心衰竭為例

國立臺灣大學醫學院附設醫院  
吳卓鎔 醫師

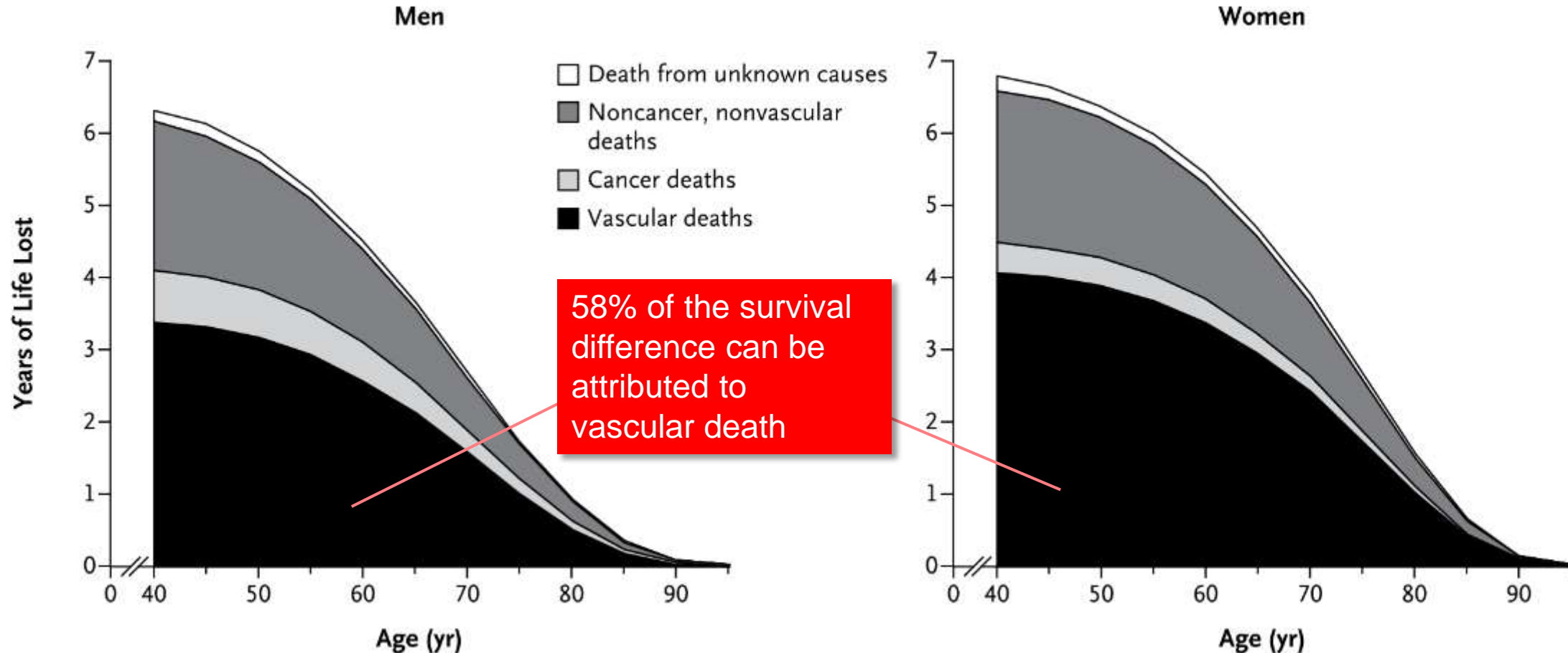


# Diabetes and heart failure

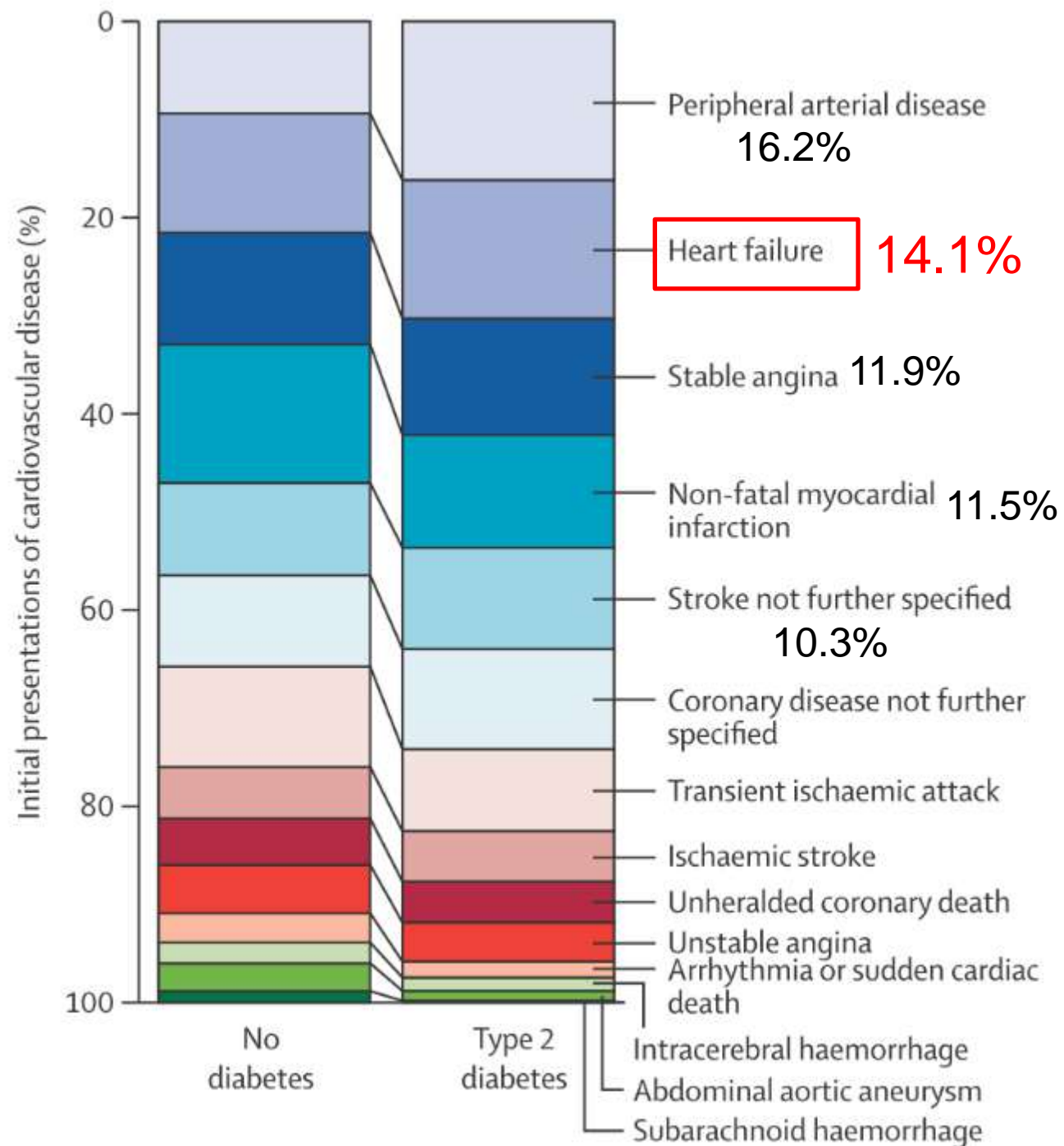


# Diabetes is associated with significant loss of life years

Estimated Future Years of Life Lost Owing to Diabetes

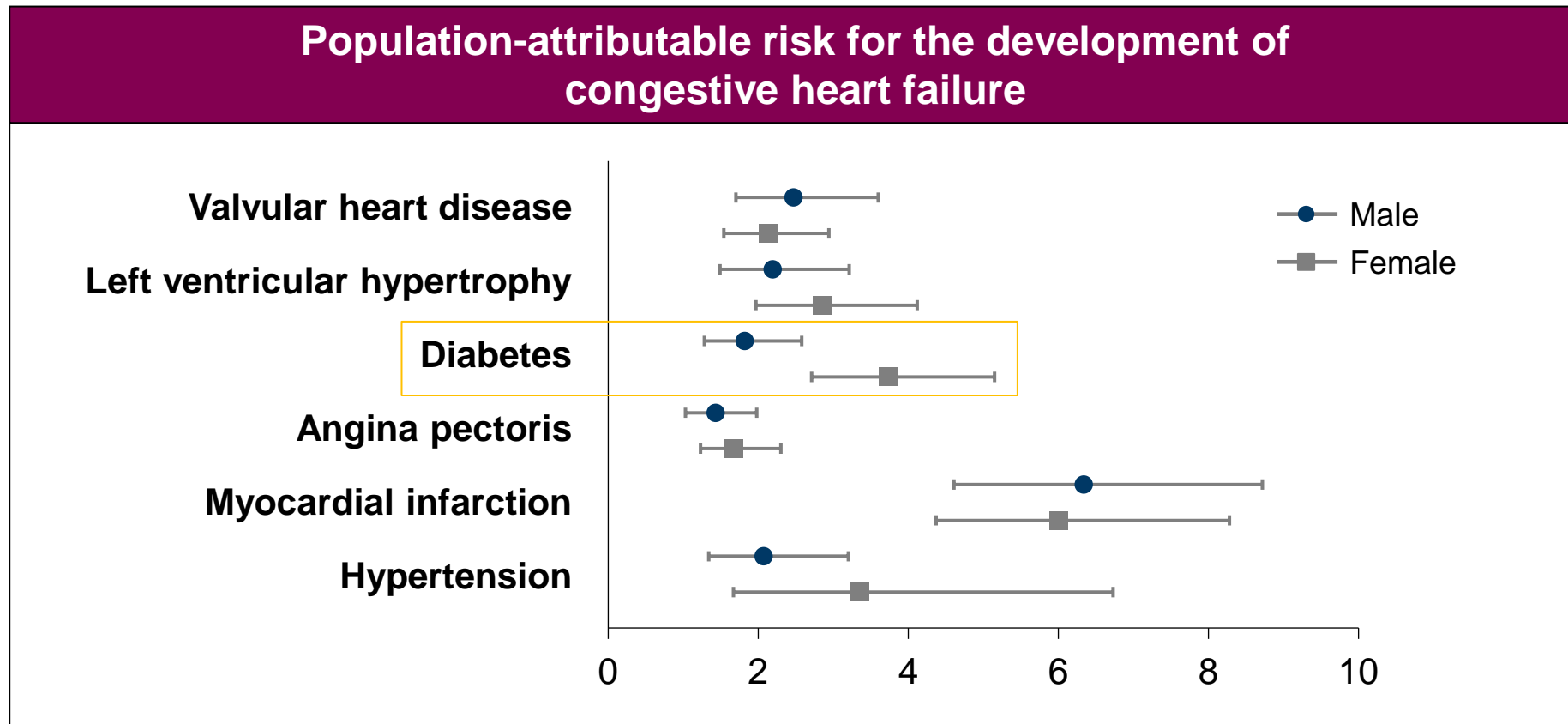


At 40, 50, and 60 years of age, men with diabetes would incur about 6.3, 5.8, and 4.5 years of life lost. At 40, 50, and 60 years of age, women with diabetes would incur about 6.8, 6.4, and 5.4 years of life lost



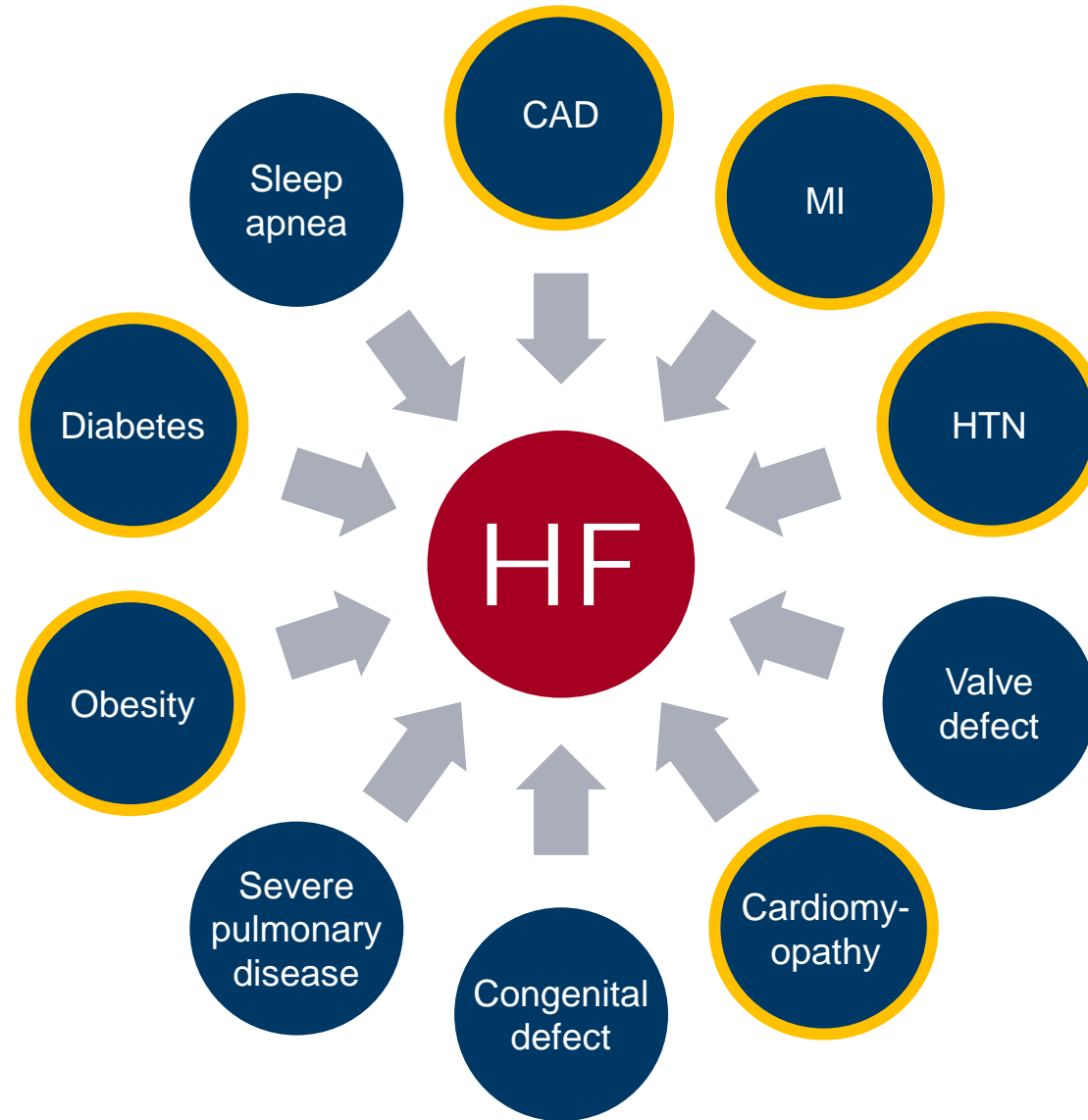
**Heart failure** and peripheral arterial disease are the most common initial manifestations of cardiovascular disease in type 2 diabetes.

# A number of risk factors for the development of heart failure have been identified



Analysis based on dynamic model with reclassification of hypertension and risk factors at each follow-up.  
Adjustments made for angina pectoris, myocardial infarction, diabetes, left ventricular hypertrophy, and valvular heart disease.  
The Framingham Heart Study: age- and risk-factor-adjusted hazard ratios.  
Levy D, et al. *JAMA*. 1996;275(20):1557–1562.

# A number of medical conditions can contribute to HF

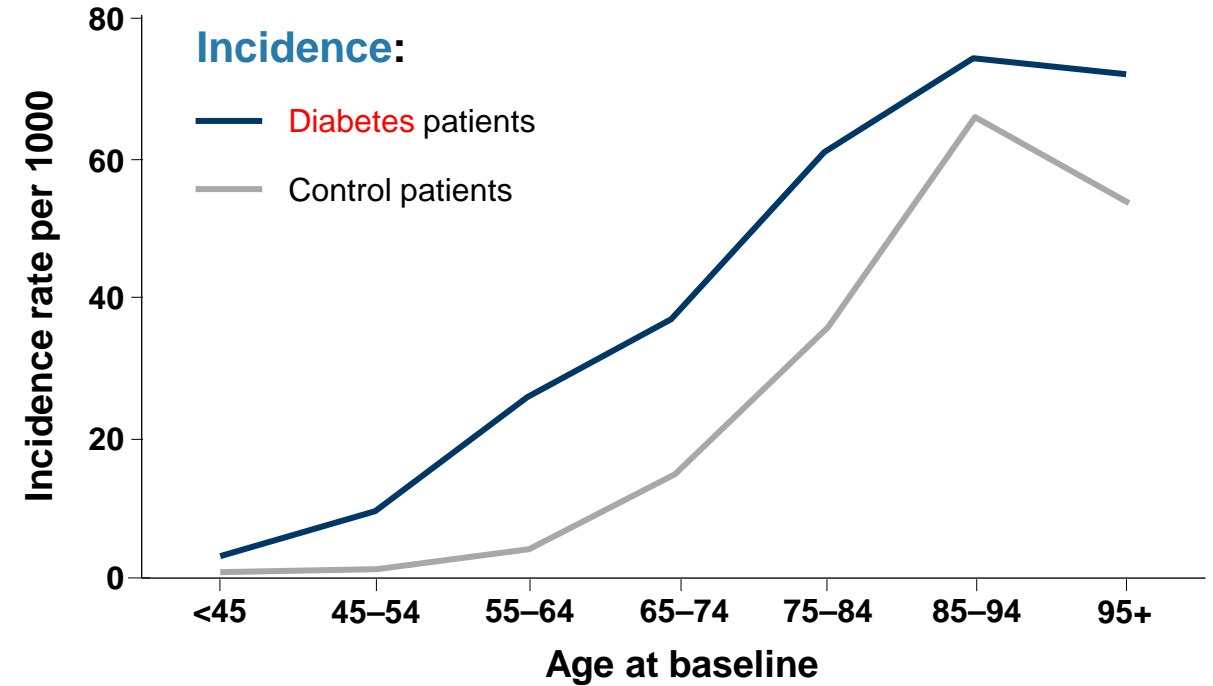
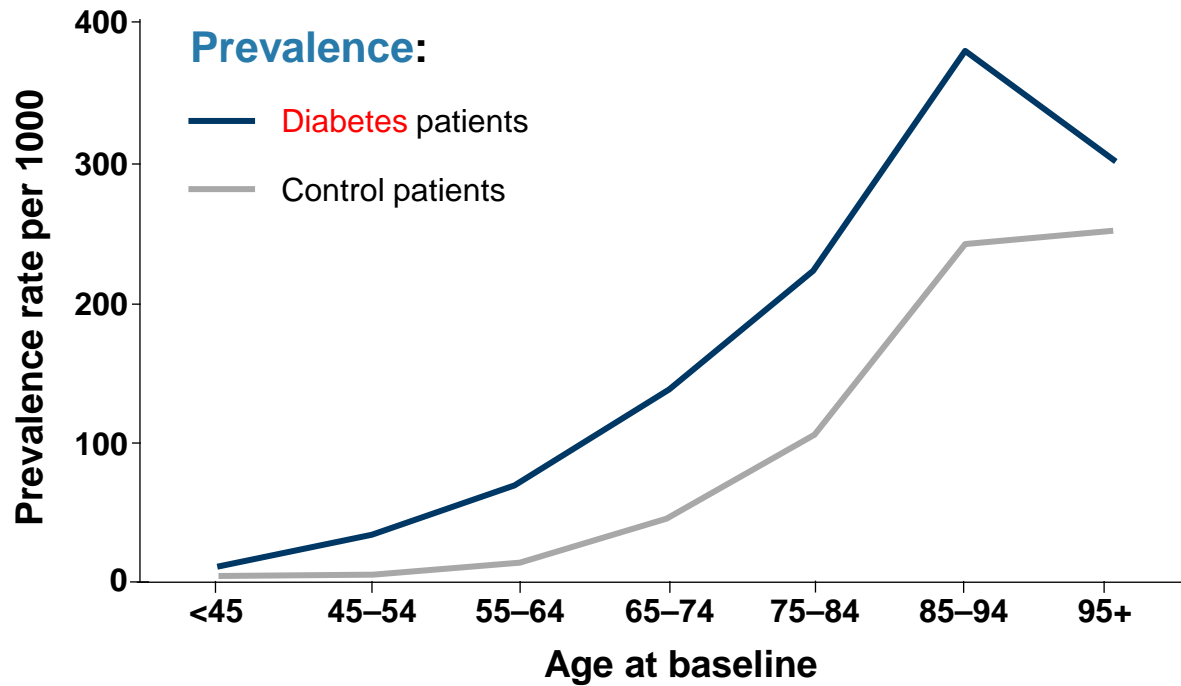


CAD, coronary artery disease; HF, heart failure; HTN, hypertension; MI, myocardial infarction.

American Heart Association. Causes of heart failure. [http://www.heart.org/HEARTORG/Conditions/HeartFailure/CausesAndRisksForHeartFailure/Causes-of-Heart-Failure\\_UCM\\_477643\\_Article.jsp](http://www.heart.org/HEARTORG/Conditions/HeartFailure/CausesAndRisksForHeartFailure/Causes-of-Heart-Failure_UCM_477643_Article.jsp). Update May 8, 2017. Accessed April 30, 2018.

# Diabetes is an independent risk factor for HF

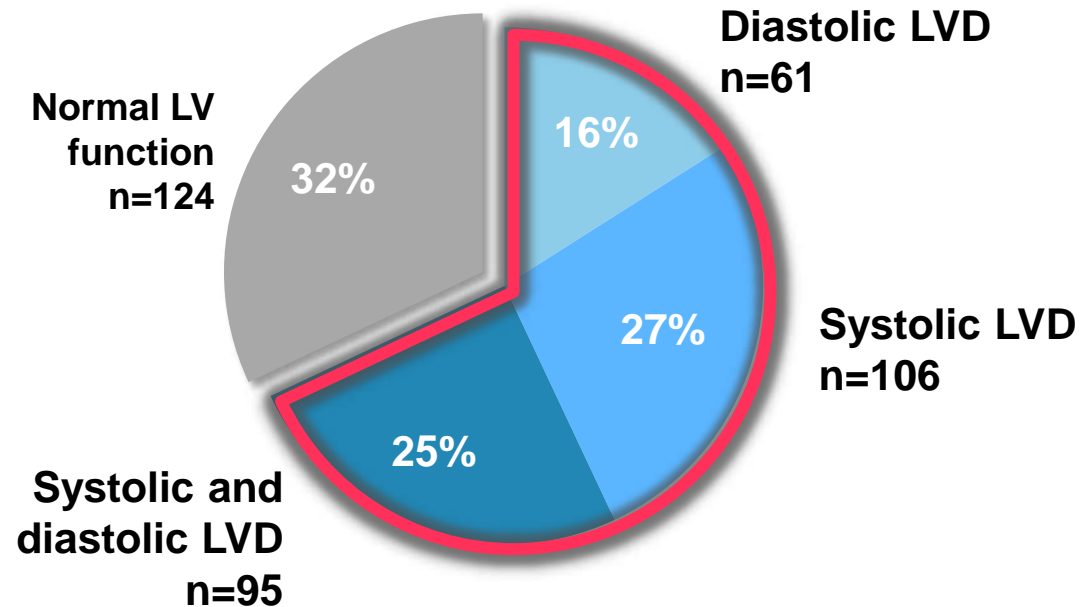
HF was more common in subjects with diabetes than in age- and sex-matched control group



Diabetes appeared to add a constant risk of HF, independent of age

# Left ventricular dysfunction can also occur in T2DM with the absence of atherosclerosis

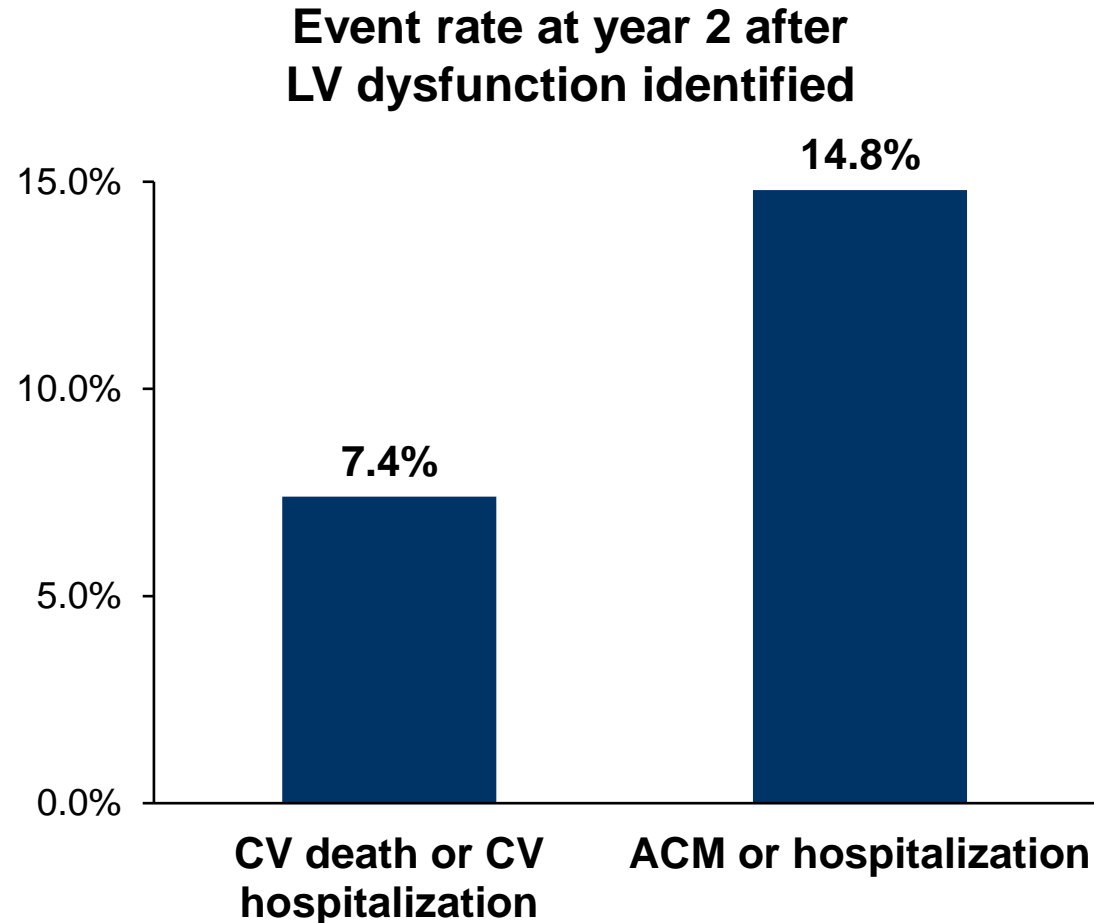
**68%** of patients with T2DM had evidence of LV dysfunction **5 years** after T2D diagnosis<sup>1</sup>



- Multicentre study evaluating clinical and echocardiographic characteristics of individuals with T2D (n=386)
- Patients had no evidence of inducible ischaemia by stress testing at baseline
- This suggests the earliest defect in the diabetic heart is that of diastolic dysfunction, not atherothrombosis<sup>2</sup>

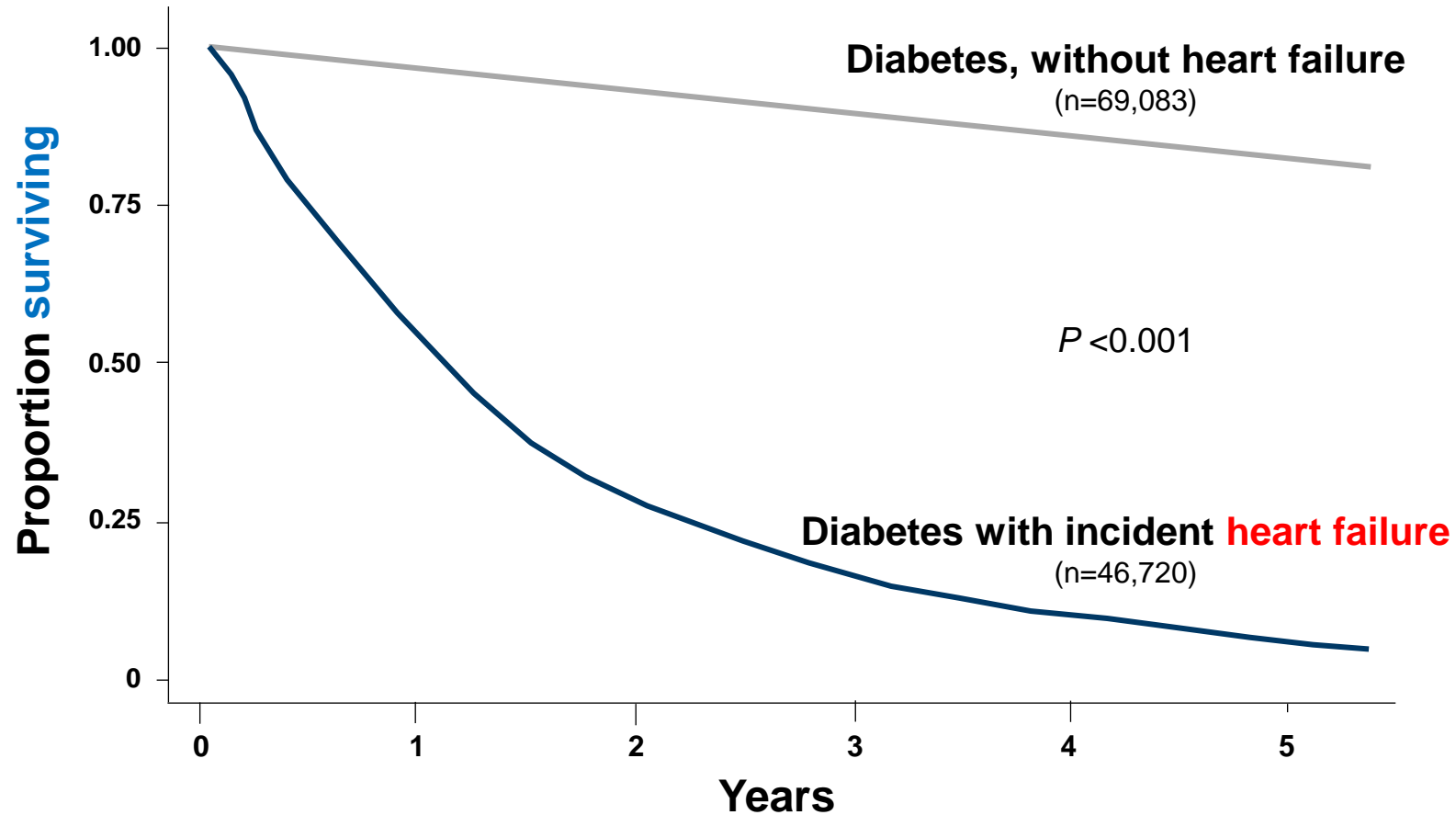


# Progression from asymptomatic LV dysfunction to a CV event occurred quickly



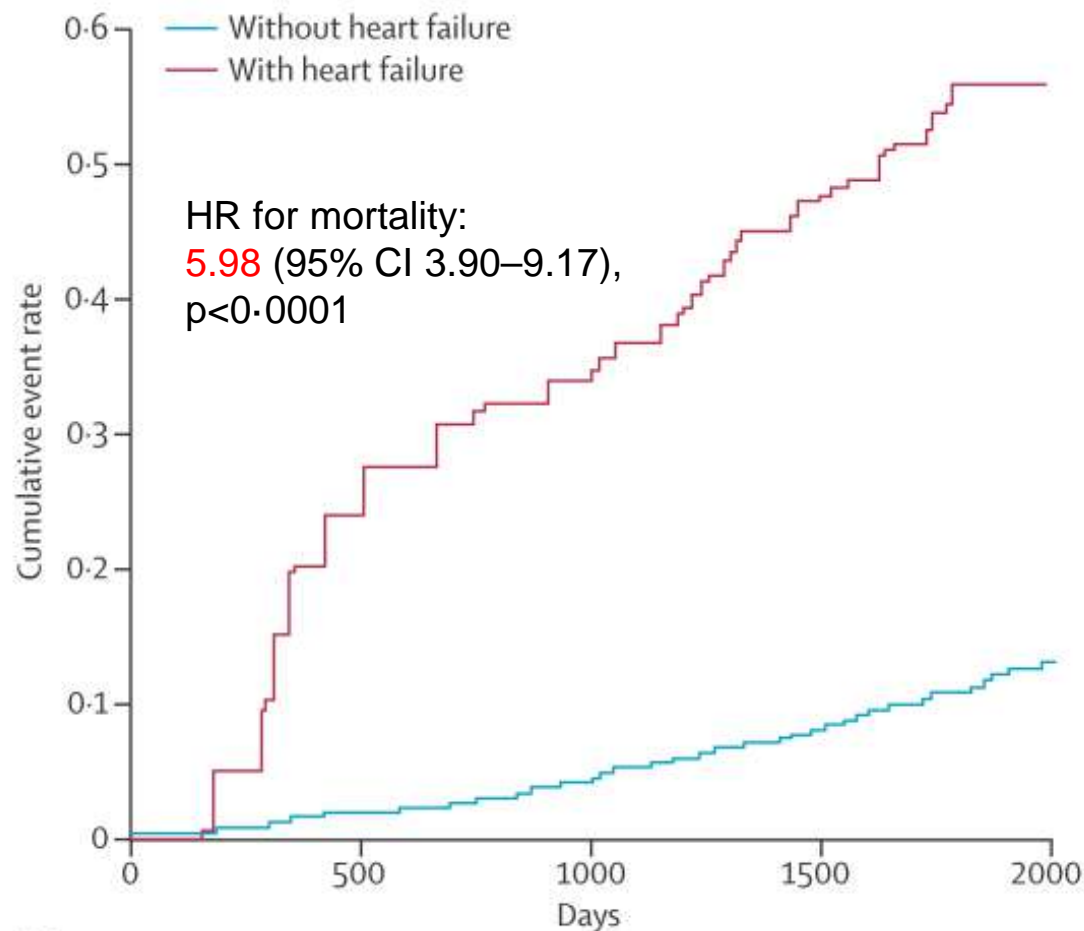
- Patients with T2D and no evidence of coronary disease in the DYDA study who had LV dysfunction identified by transthoracic echocardiography were assessed for the incidence of clinical events at a 2-year follow-up
- The incidence of a combined outcome measure of all-cause death and hospitalizations at 2-year follow-up was 14.8%

# The presence of HF in patients with diabetes is associated with an increased risk of death

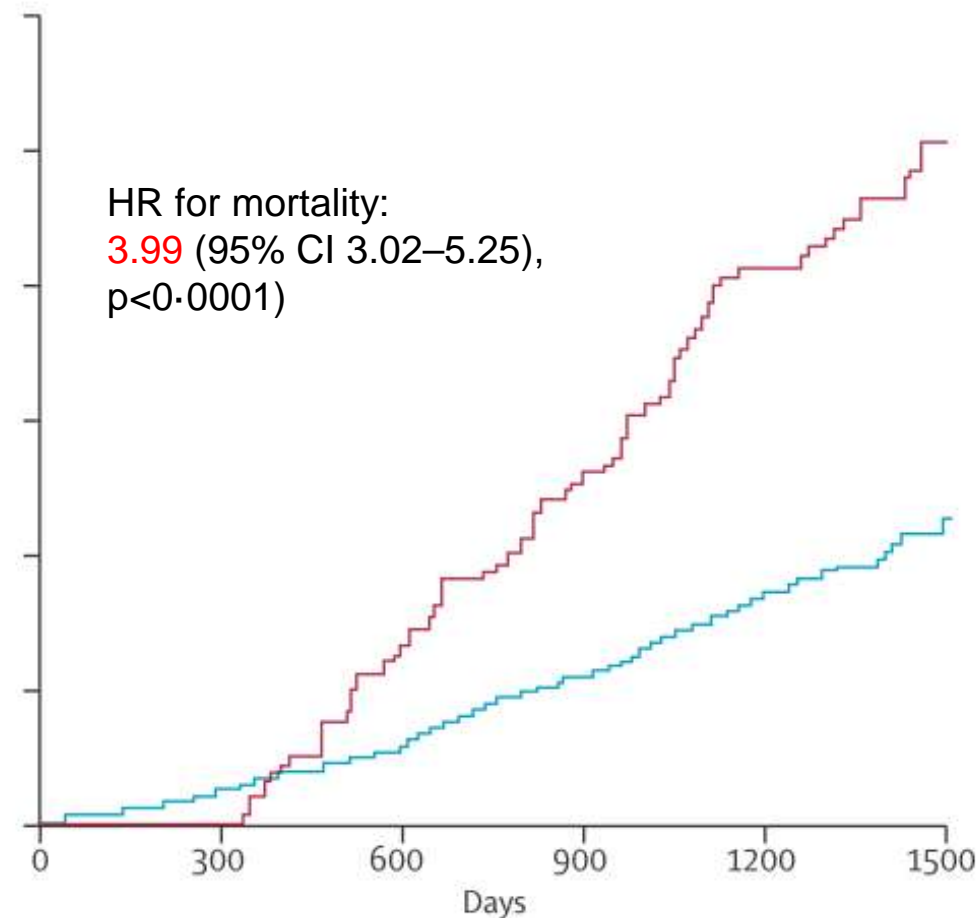


- 115,803 adults 65 years and older in fee-for-service Medicare without a prior HF claim were followed for 5 years
- Incident HF was determined using DRG codes
- Survival was significantly lower in those who developed HF compared with those without HF

# Mortality in diabetic patients with and without heart failure in LIFE and RENAAL trial



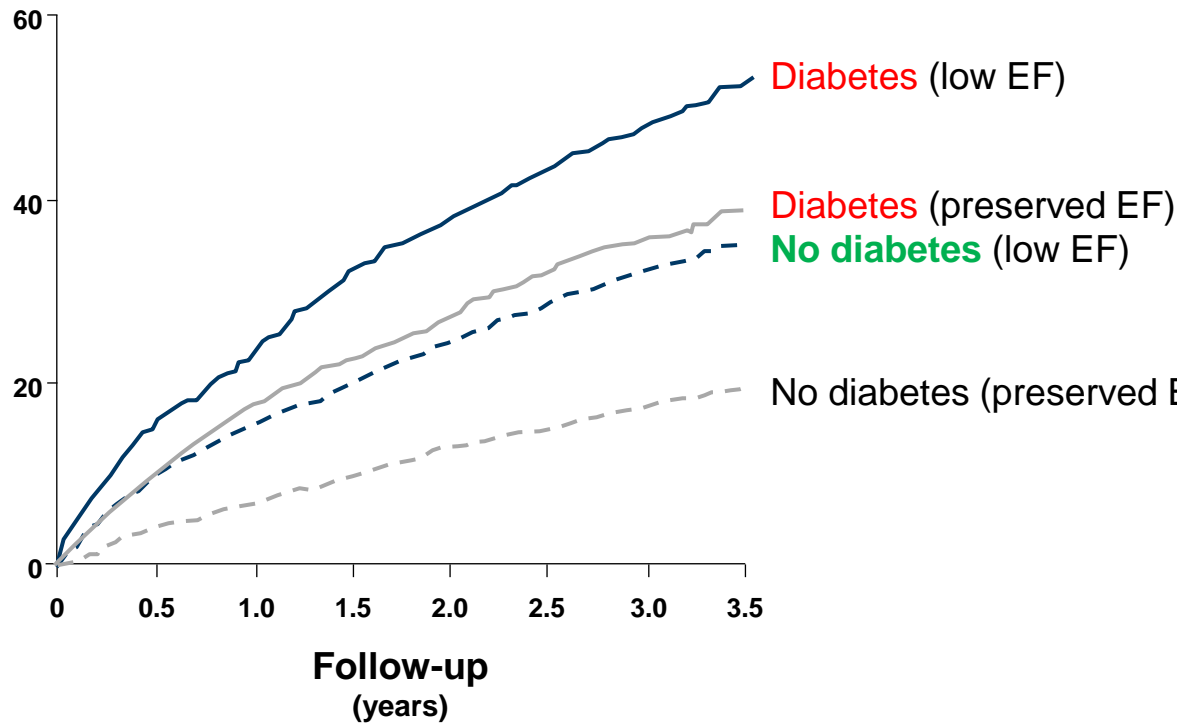
Number at risk		Days				
Without heart failure	1147	1088	1032	961	195	
With heart failure	0	22	46	60	9	



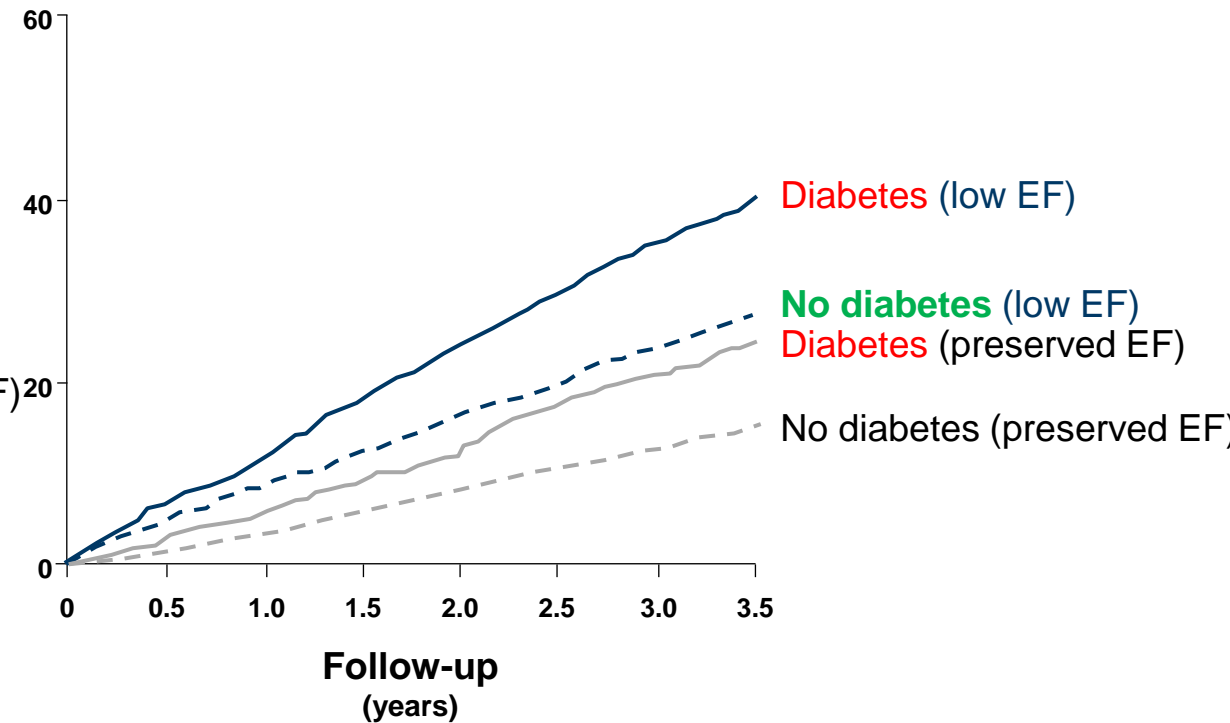
Number at risk		Days				
Without heart failure	1431	1348	1259	1107	544	77
With heart failure	0	46	83	108	76	15

# Conversely, the presence of diabetes in both HFrEF and HFpEF increased the risk of CV events and death

**CV death or hospitalization due to HF**  
(Cumulative incidence, %)

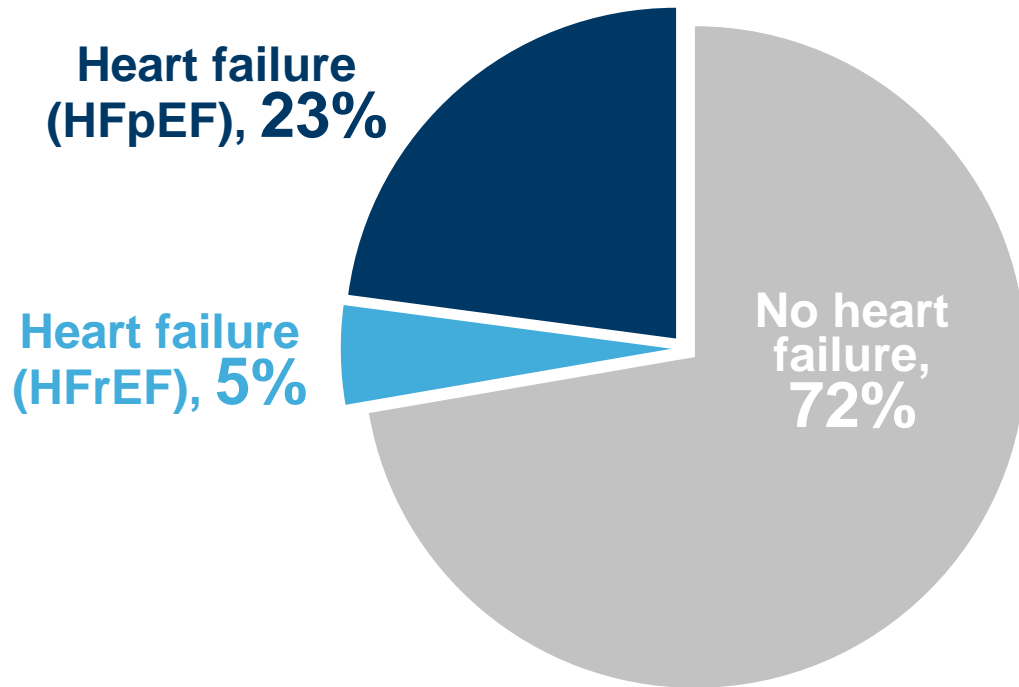


**All-cause mortality**  
(Cumulative incidence, %)



# HF remains **under-diagnosed** in patients with T2D, suggesting a high index of suspicion is warranted

**28%** of a T2D population  
had undiagnosed HF



- The majority of newly detected HF had HFpEF
- The prevalence of undiagnosed HF was higher:
  - With increasing age
  - In females
  - In patients with BMI  $\geq 30$  kg/m<sup>2</sup>
  - In patients with dyspnea
  - In patients complaining of fatigue
  - In patients with hypertension
- The authors suggest that screening of patients with T2D should be considered given the high prevalence of previously unknown HF

# Although presentations vary, patients with HF present with a number of “classic” symptoms

## Classic **symptoms** of heart failure<sup>1</sup>

- Shortness of breath
- Difficulty breathing at night when recumbent
  - Orthopnea
  - Paroxysmal nocturnal dyspnea
- Reduced exercise tolerance
- Fatigue
- Tiredness
- Swelling in feet

The New York Heart Association (NYHA)<sup>2</sup> functional classification is based on the severity of symptoms

### NYHA functional class

I	No symptoms
II	Symptomatic with moderate exertion
III	Symptomatic with minimal exertion
IV	Symptomatic at rest

1. McMurray JJV et al. *Eur Heart J*. 2012;33:1787–1847. 2. New York Heart Association/Little Brown and Company, 1964.

Adapted from: Farrell MH, et al. *JAMA*. 2002;287(7):890–897.

# Evidence of volume overload is a common physical finding of heart failure<sup>1</sup>

- **Neck exam<sup>2</sup>**
  - Elevated jugular venous pressure
- **Auscultation of the lungs<sup>2</sup>**
  - Rales or crackles
- **Auscultation of the heart<sup>2,3,4</sup>**
  - Third or fourth heart sound (S3 or S4) sometimes called a gallop rhythm
  - Murmur
- **Edema in dependent areas<sup>2</sup>**
  - Sacrum
  - Feet/ankles/lower legs

Elevated jugular venous pressure



Pitting edema of the ankle

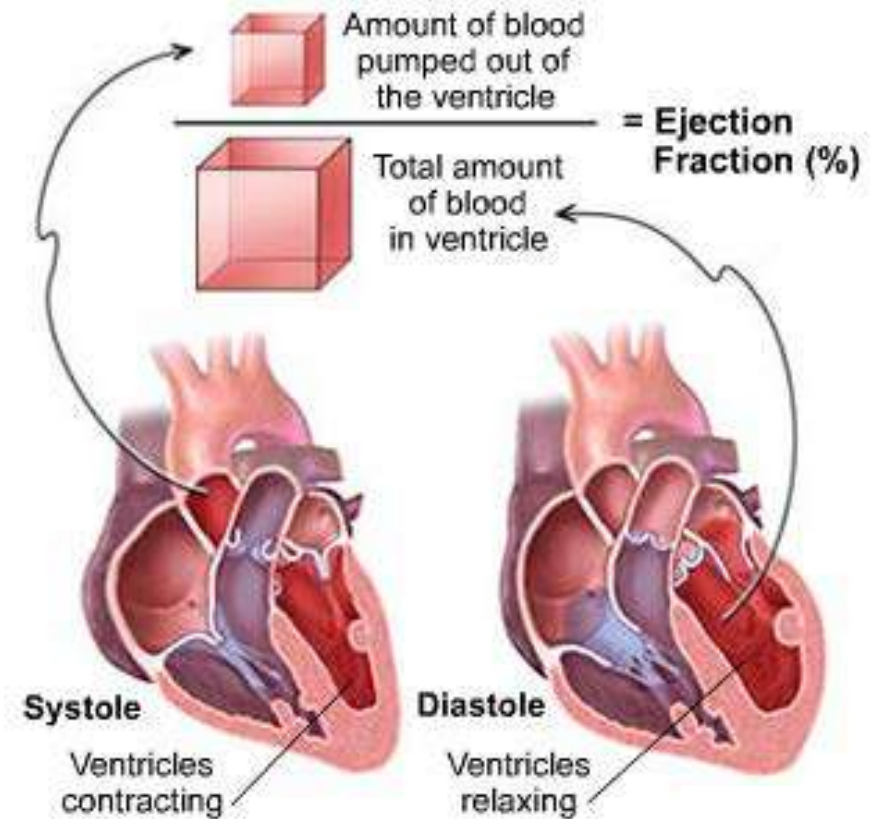


1. McMurray JJ, et al. *Eur Heart J*. 2012;33:1787–1847. 2. Yancy CW, et al. *Circulation*. 2013;128:1810–1852. 3. Hunt SA et al. *J Am Coll Cardiol*. 2005;46(6)e1-82;

4. Jessup M, Brozena S. *N Engl J Med*. 2003;348:2007–2018.

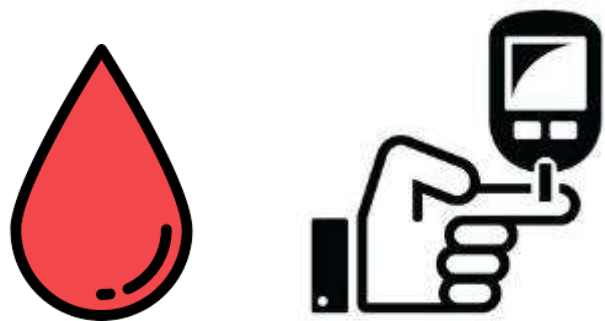
# Ejection fraction (EF) is a key criteria in heart failure management

- **EF** is the percentage of blood that is pumped out of the heart during each beat
- A normal EF is  $\geq 50\%$
- Heart failure with an EF  $\leq 40\%$  is known as **heart failure with reduced ejection fraction (HFrEF)**
- Heart failure in the setting of a normal EF is known as **heart failure with preserved ejection fraction (HFpEF)**





# Glycemic control and risk of heart failure



Each 1% increase in HbA1c was associated with a **12-23%** increased risk of heart failure<sup>1,2</sup>



## In patients with stable CAD

Each 1% increase in A1C concentration was associated with a **36%** increased HR of heart failure hospitalization.<sup>3</sup>

CAD: coronary artery disease

# Tight **blood pressure** control reduce the risk of heart failure



Each 10 mmHg reduction in SBP was associated with an

**15-56%**

decreased risk of heart failure<sup>1,2</sup>



Baseline Characteristics		Proportional hazards model of observational analyses (n=3642)	Clinical trial of tight v less tight blood pressure control policy (n=1148)
Haemoglobin A <sub>1c</sub> (%)		7.1 (1.8)	7.0 (1.7)
Systolic blood pressure (mm Hg)		135 (19)	159 (19)

Observational analyses				Clinical trial (less tight v tight policy) <sup>1</sup>		
Baseline SBP		Updated mean SBP		No of events	Decrease in risk (%) / 10 mm Hg difference in SBP (95% CI)	P value
Decrease in risk (%) / 10 mm Hg reduction (95% CI)	P value	Decrease in risk (%) / 10 mm Hg reduction (95% CI)	P value			
14 (5 to 21)	0.0016	15 (4 to 19)	<0.0001	45	56 (6 to 80)	0.0043

# Higher risk for the development of HF in T2DM patients with higher BMI<sup>1,2</sup>



Diabetic patients with BMI  $\geq 30$  kg/m<sup>2</sup> have a **significantly increased** risk of HF when compared with those with BMI 25 to 29.9 kg/m<sup>2</sup>.

Overweight: BMI  $\geq 25$   
Obese: BMI  $\geq 30$

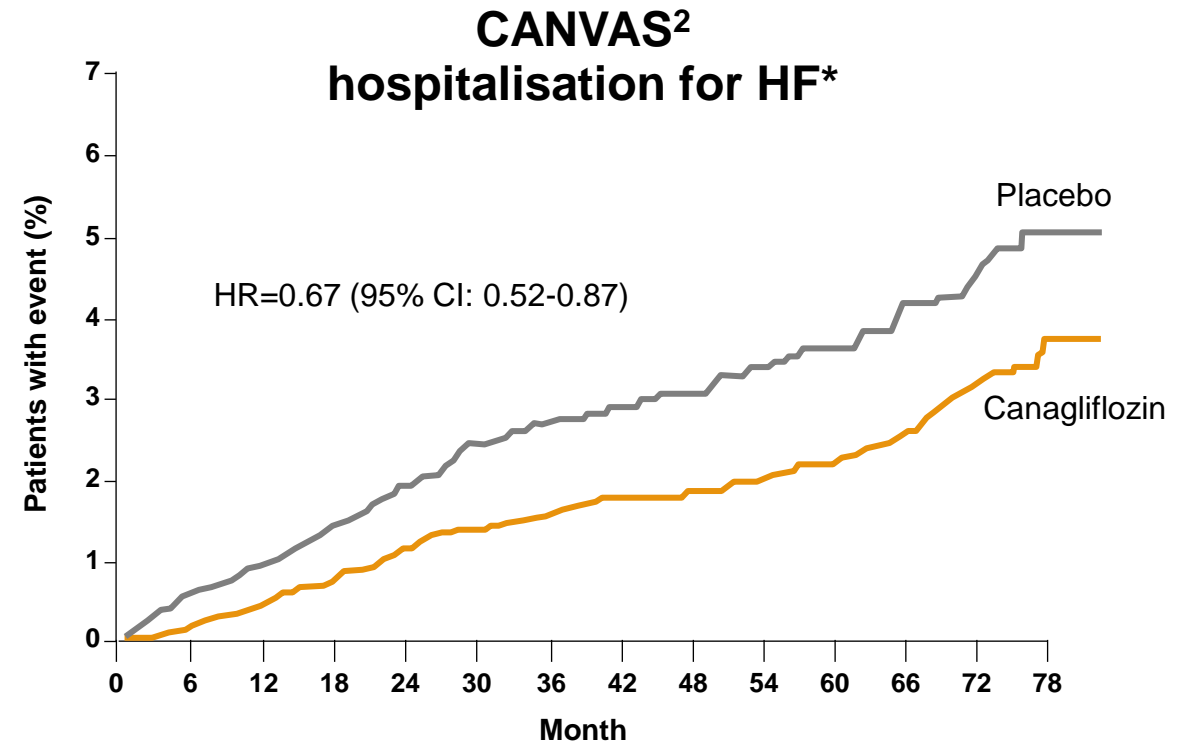
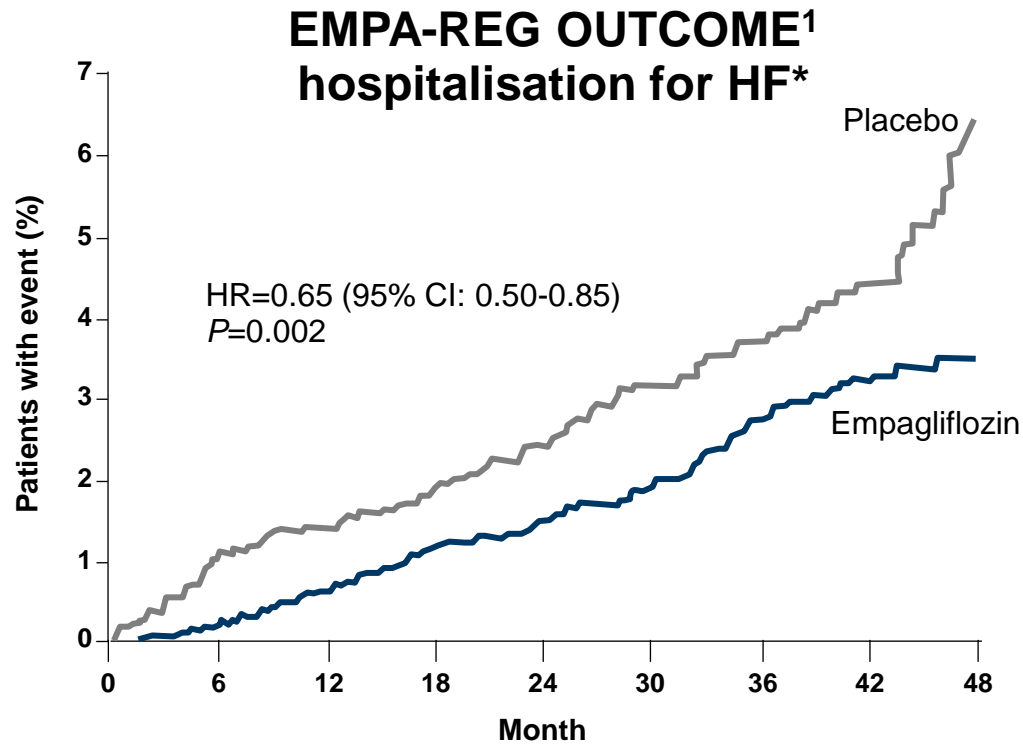
		BMI, kg/m <sup>2</sup>					
		<23	23–24.9	25–29.9	30–34.9	35–39.9	$\geq 40$
Baseline							
Total heart failure							
Men		0.95 (0.78–1.15)	1.00 (0.84–1.19)	1.00	1.16 (1.04–1.29)	1.64 (1.45–1.85)	2.02 (1.79–2.29)
Women		1.16 (1.00–1.37)	1.16 (0.97–1.38)	1.00	1.23 (1.11–1.37)	1.55 (1.39–1.73)	2.01 (1.81–2.23)

BMI: body mass index

# SGLT-2 inhibitors and heart failure

- SGLT-2 inhibitors are a class of drugs that inhibit the sodium-glucose cotransporter 2 (SGLT-2) in the proximal tubule of the kidney. They are used to treat type 2 diabetes and have been found to have beneficial effects on heart failure.
- The mechanism of action of SGLT-2 inhibitors is to block the reabsorption of glucose and sodium in the proximal tubule, leading to increased urinary excretion of glucose and sodium. This results in a diuretic effect, which can help to reduce fluid overload and improve heart function.
- SGLT-2 inhibitors have been shown to improve clinical outcomes in patients with heart failure, including reducing the risk of hospitalization and mortality. They are now recommended as first-line therapy for patients with heart failure and type 2 diabetes.
- The most commonly used SGLT-2 inhibitors are empagliflozin, dapagliflozin, and canagliflozin. These drugs are available as oral tablets and are generally well-tolerated.
- However, there are some potential side effects associated with SGLT-2 inhibitors, including an increased risk of urinary tract infections, genital infections, and dehydration. It is important for patients to be monitored for these side effects and to stay hydrated while taking these drugs.
- In conclusion, SGLT-2 inhibitors are a promising class of drugs for the treatment of heart failure, particularly in patients with type 2 diabetes. They offer a novel mechanism of action and have been shown to improve clinical outcomes. Further research is needed to fully understand the long-term benefits and risks of these drugs.

# New insights into HF prevention have emerged from trials examining SGLT2 inhibitor use in T2D



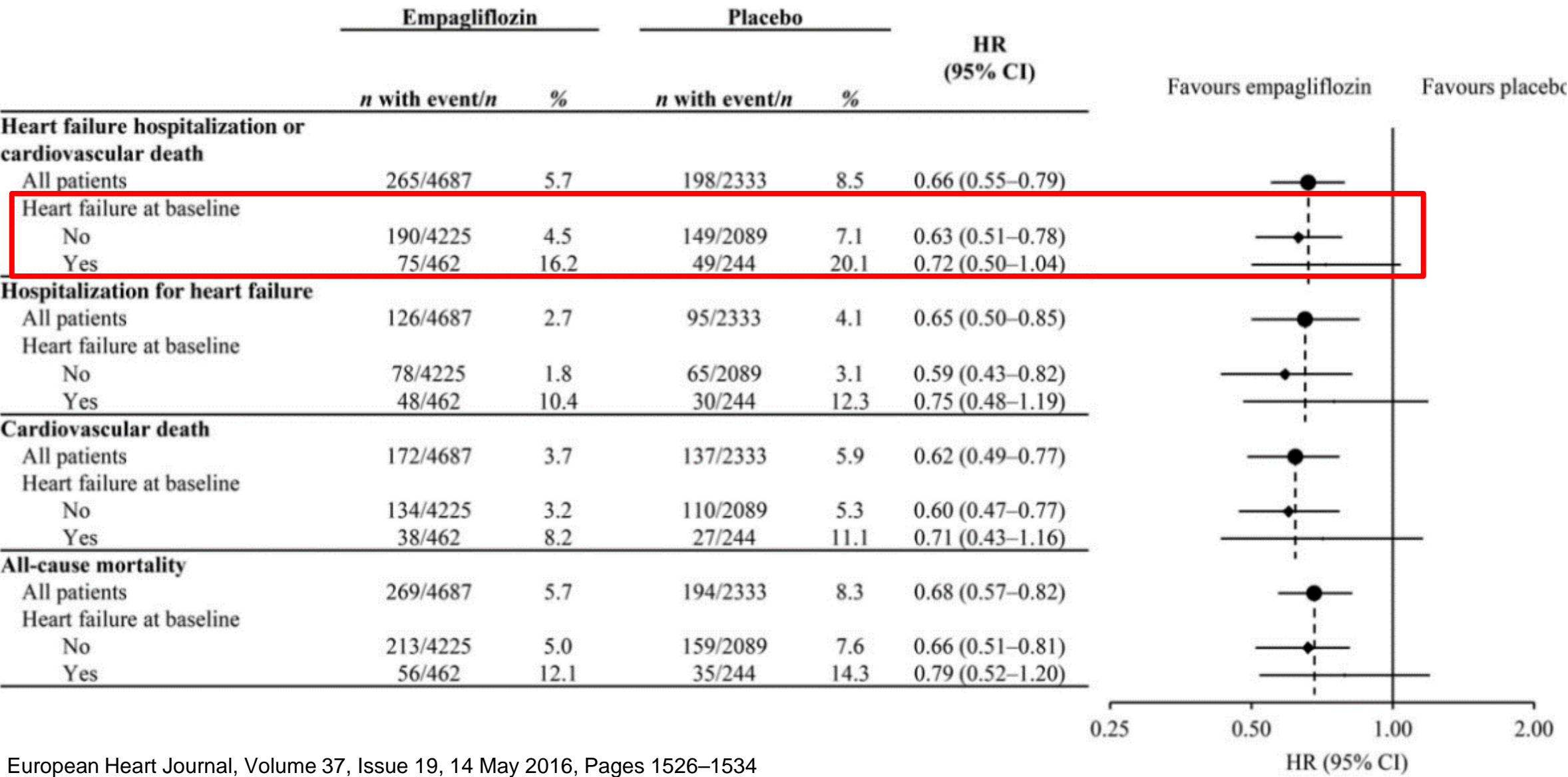
**These hypothesis generating exploratory analyses\* will need to be confirmed in future trials**

\*hHF is an exploratory end point in both studies. In the EMPA-REG OUTCOME protocol it was considered an exploratory end point. In CANVAS, after the MACE end point, the hierarchical testing started with all-cause mortality. This did not meet statistical significance thus no additional testing was done. Therefore the HF end point is considered exploratory.

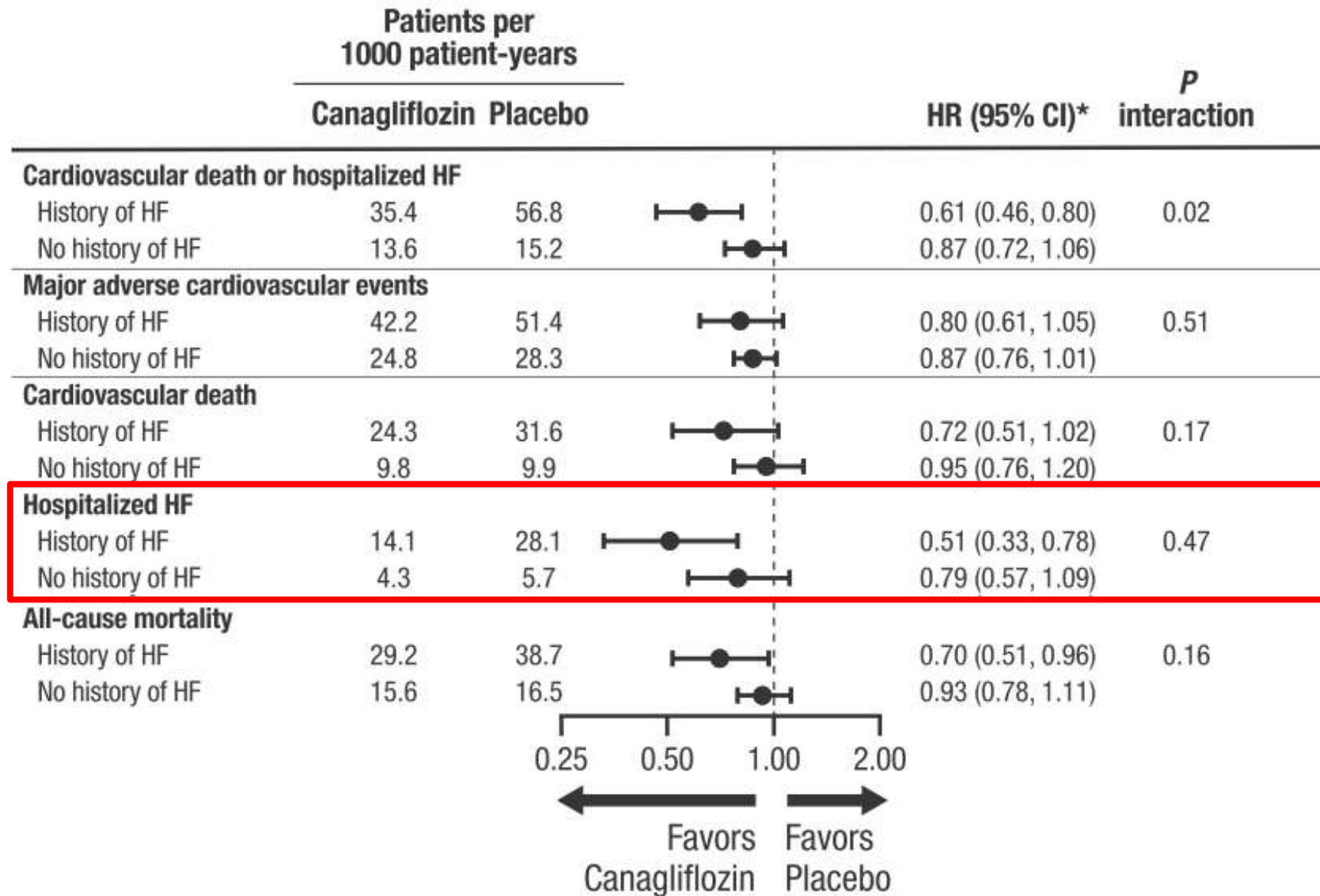
CI, confidence interval; CV, cardiovascular; HF, heart failure; hHF, hospitalisation for heart failure; HR, hazard ratio; MACE, major adverse cardiovascular events; SGLT2, sodium-glucose cotransporter-2; T2D, type 2 diabetes.

1. Zinman B, et al. *N Engl J Med*. 2015;373:2117–2128. 2. Neal B, et al. *N Engl J Med*. 2017;377:644-657.

# Heart failure outcomes in EMPA-REG trial



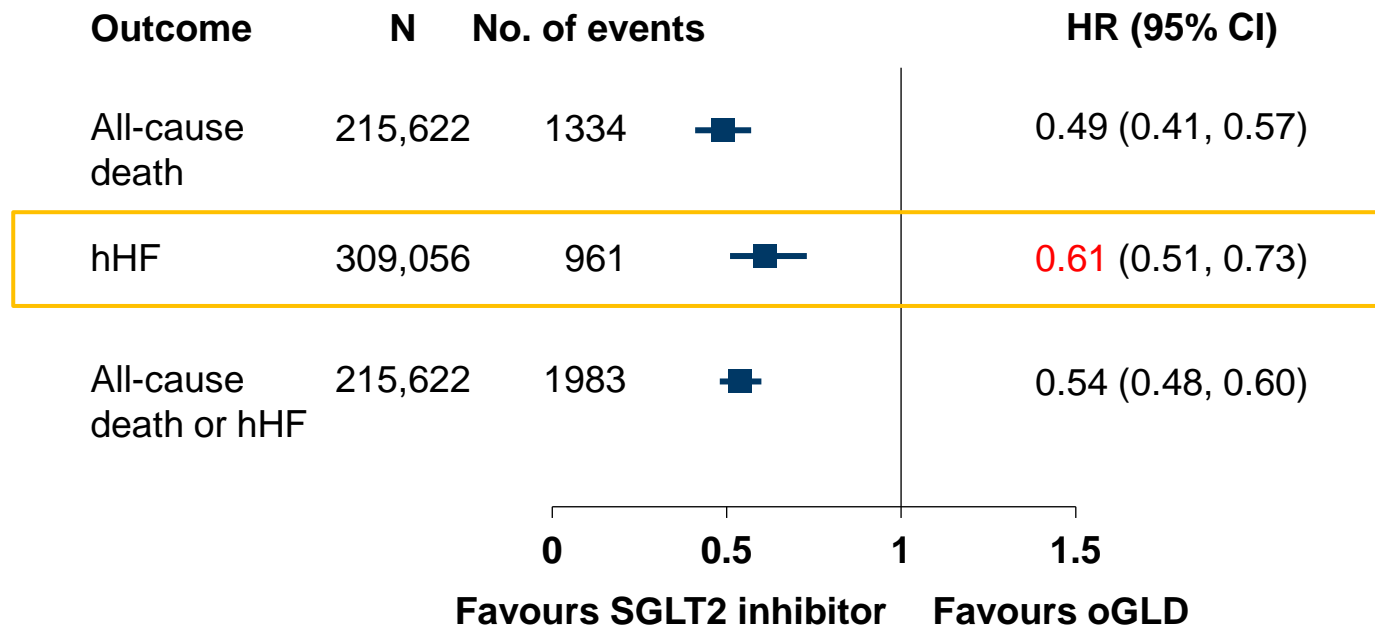
# Heart failure outcomes in CANVAS trial





# In CVD-REAL, a real-world study, SGLT2 inhibitors were associated with reductions in hHF compared to oGLDs

## All-cause death and hHF for SGLT2 inhibitors vs oGLDs<sup>1</sup>



- 13% of patients had established CVD\*
- **3.1%** of patients has **established HF**
- Compared to oGLDs, SGLT2 inhibitors were associated with a **39%** reduction in hHF



\*Previous event of myocardial infarction, stroke, unstable angina, heart failure or atrial fibrillation.

CI, confidence interval; CVD, cardiovascular disease; hHF, hospitalisation for heart failure; HR, hazard ratio; oGLD, other glucose-lowering drug.

SGLT2, sodium-glucose cotransporter-2.

Kosiborod M, et al. *Circulation*. 2017;136:249–259.



# SGLT-2 Inhibitors Tied to Less HF in CVD-REAL 2 study



**Table. Risk for Outcome, SGLT-2 Inhibitor vs Other Glucose-Lowering Drug**

Outcome	Patients (n)	Events (n)	Hazard Ratio (95% CI)	P Value
All-cause death <sup>a</sup>	470,128	5216	0.51 (0.37 - 0.70)	<.001
Hospitalization for HF	442,686	5997	0.64 (0.50 - 0.82)	.001
MI	442,686	2249	0.81 (0.74 - 0.88)	<.001
Stroke	442,686	6439	0.68 (0.55 - 0.84)	<.001

**87% Asian patients**

	N
South Korea	336,644
Japan	67,780
Singapore	2726
Israel	19,472
Canada	16,064
Australia	27,442
Total	470,128

- **27% of patients had established CVD\***
- **7% of patients has established HF**

## Data Sources

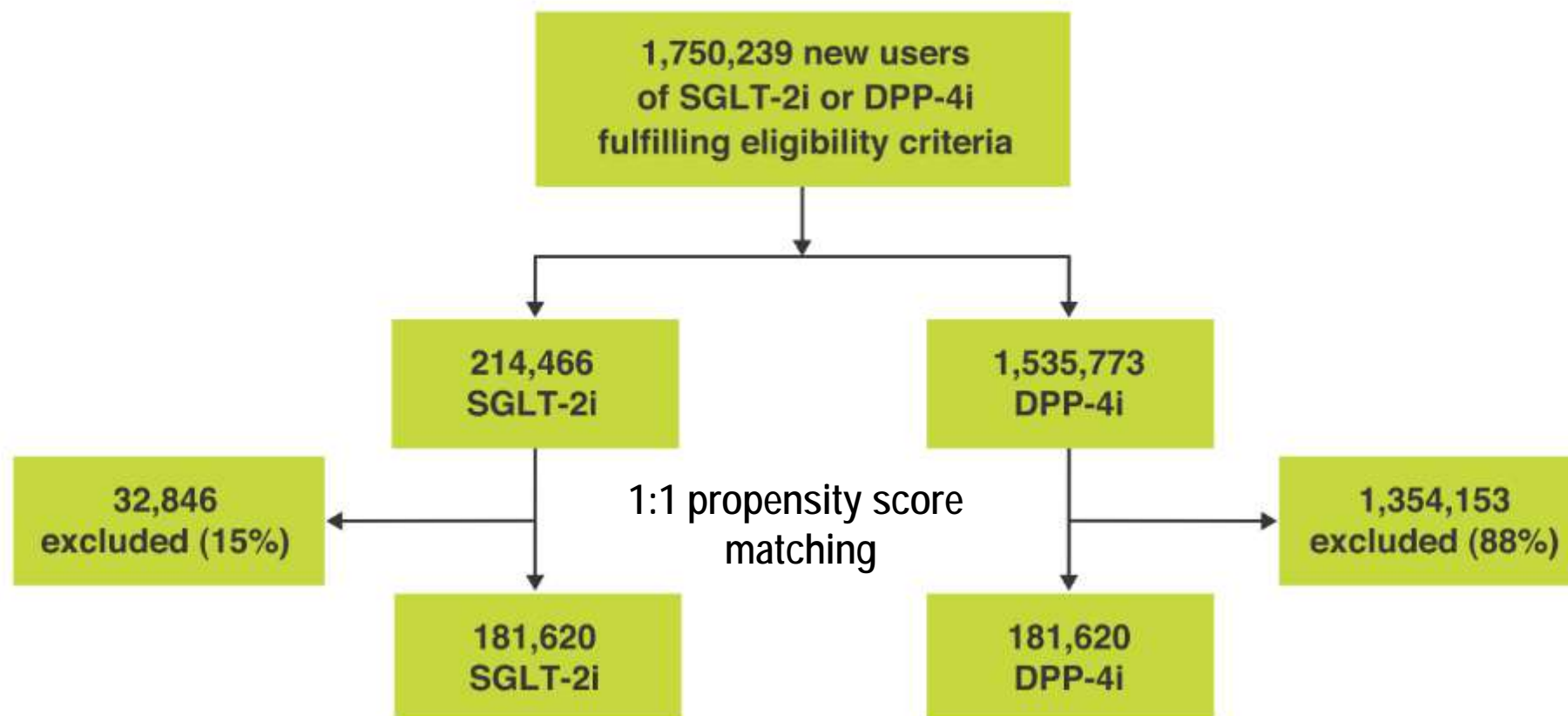
- Deidentified health records from 12 countries, South Korea, Japan, Singapore, Australia, USA, Canada, Denmark, Sweden, Norway, Spain, Israel and Germany, were analyzed



# Patient Cohort

- Patients with T2D newly initiated on either SGLT-2i or DPP-4i were selected from each data source between December 2012 and November 2017

**Figure 1. Study flow diagram**



# Baseline Characteristics

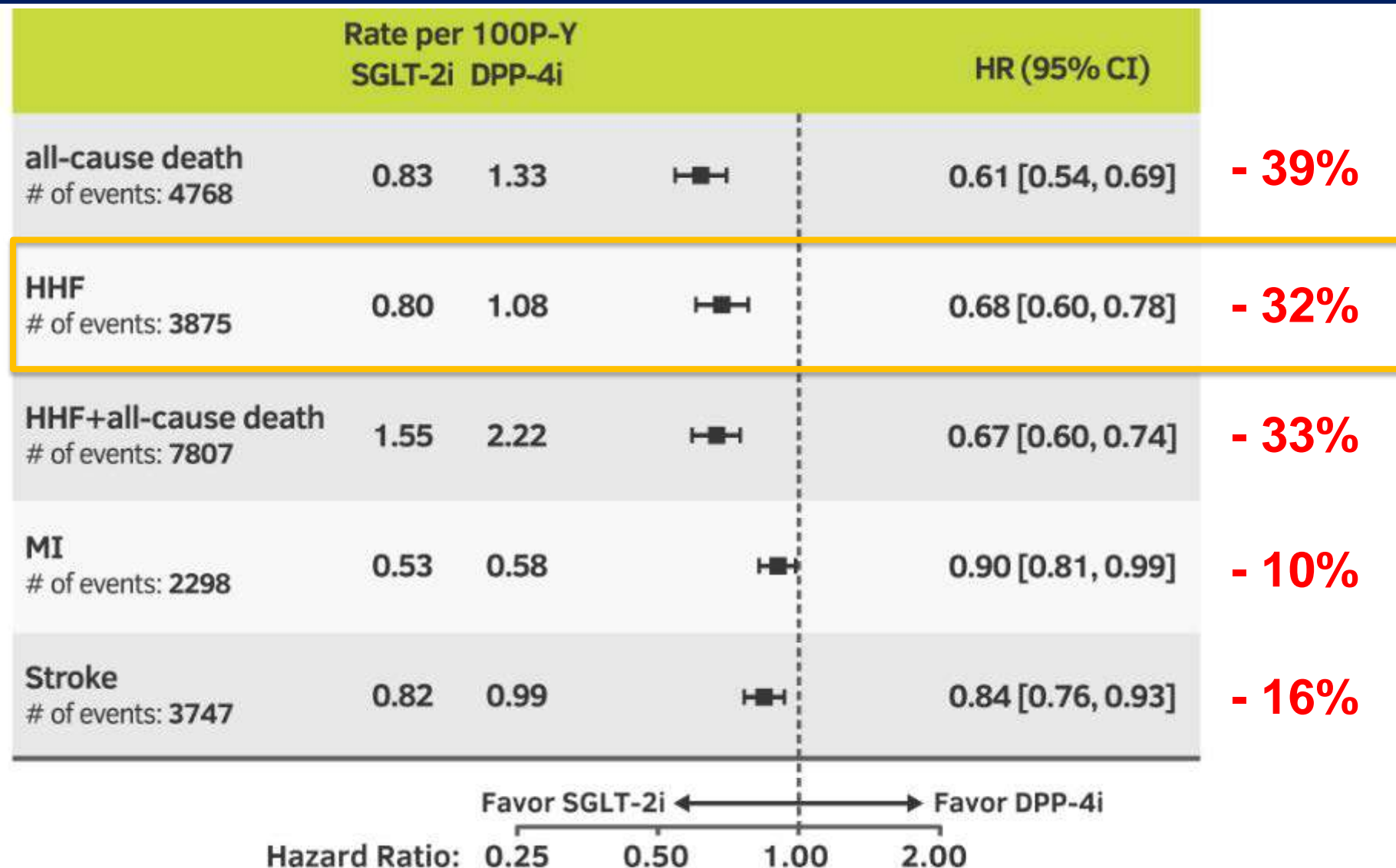


**Table 1. Baseline characteristics after propensity-score matching**

	<b>SGLT-2i (N=181,620)</b>	<b>DPP-4i (N=181,620)</b>	<b>Standardized difference*</b>
<b>Age, years (SD)</b>	57.6 (11.9)	57.5 (12.7)	1.1%
<b>Women</b>	79,898 (44.0)	79,959 (44.0)	0.1%
<b>Established CVD</b>	52,087 (29.8)	50,221 (28.8)	2.3%
<b>Metformin</b>	140,971 (77.6)	142,342 (78.4)	1.8%
<b>Sulphonylurea</b>	66,007 (36.3)	65,960 (36.3)	0.1%
<b>Thiazolidinedione</b>	14,784 (8.1)	14,480 (8.0)	0.6%
<b>GLP-1 receptor agonist</b>	12,523 (6.9)	11,096 (6.1)	3.2%
<b>Insulin</b>	44,963 (24.8)	43,781 (24.1)	1.5%



# All five outcomes



# Association Between Use of Sodium-Glucose Cotransporter 2 Inhibitors, Glucagon-like Peptide 1 Agonists, and Dipeptidyl Peptidase 4 Inhibitors With All-Cause Mortality in Patients With Type 2 Diabetes

## A Systematic Review and Meta-analysis

Sean L. Zheng, BM BCh, MA, MRCP; Alistair J. Roddick, BSc; Rochan Aghar-Jaffar, BMedSci, BMBS, MRCP; Matthew J. Shun-Shin, BM BCh, MRCP; Darrel Francis, MB BChir, FRCP, MD; Nick Oliver, MBBS, FRCP; Karim Meeran, MBBS, MD, FRCP, FRCPath

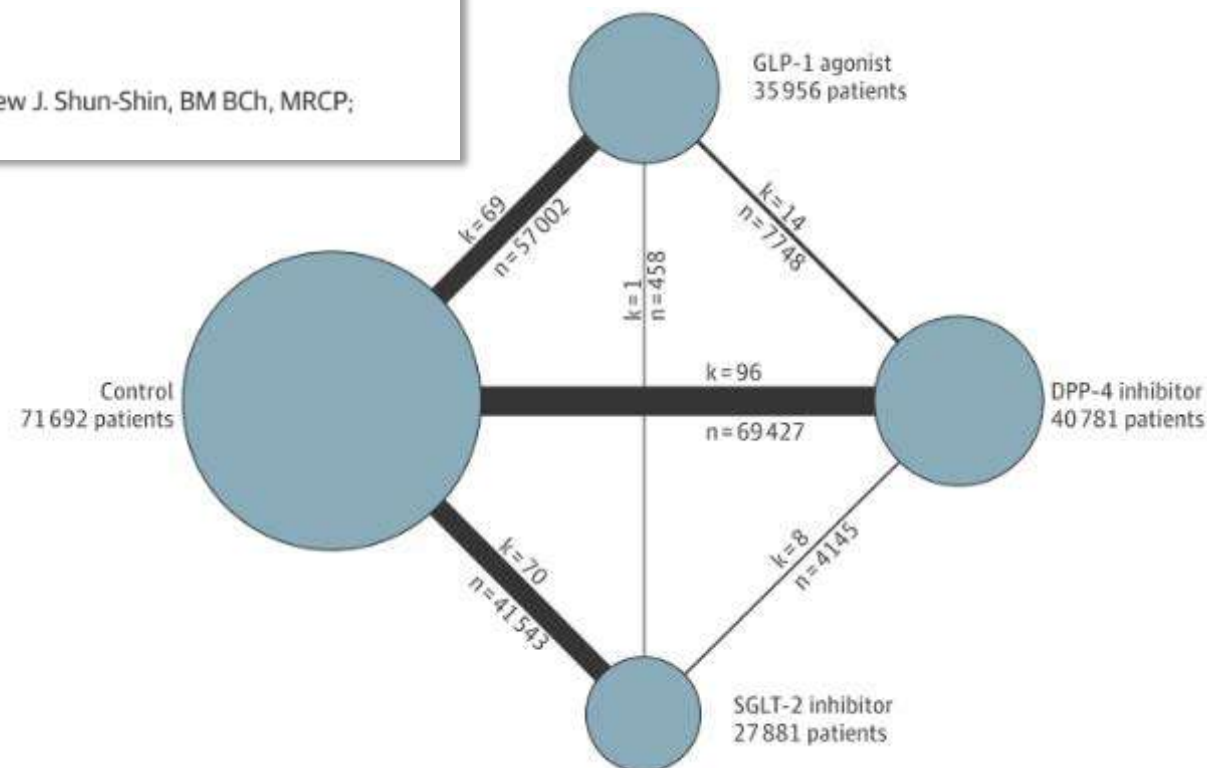
# JAMA<sup>®</sup>

The Journal of the American Medical Association

### 236 Randomized clinical trials included in analysis

- 65 SGLT-2 inhibitor vs control (40 009 participants, 76 133 participant-y)
- 65 GLP-1 agonist vs control (55 740 participants, 115 176 participant-y)
- 83 DPP-4 inhibitor vs control (67 958 participants, 106 970 participant-y)
- 23 Between drug classes (12 603 participants, 11 887 participant-y)

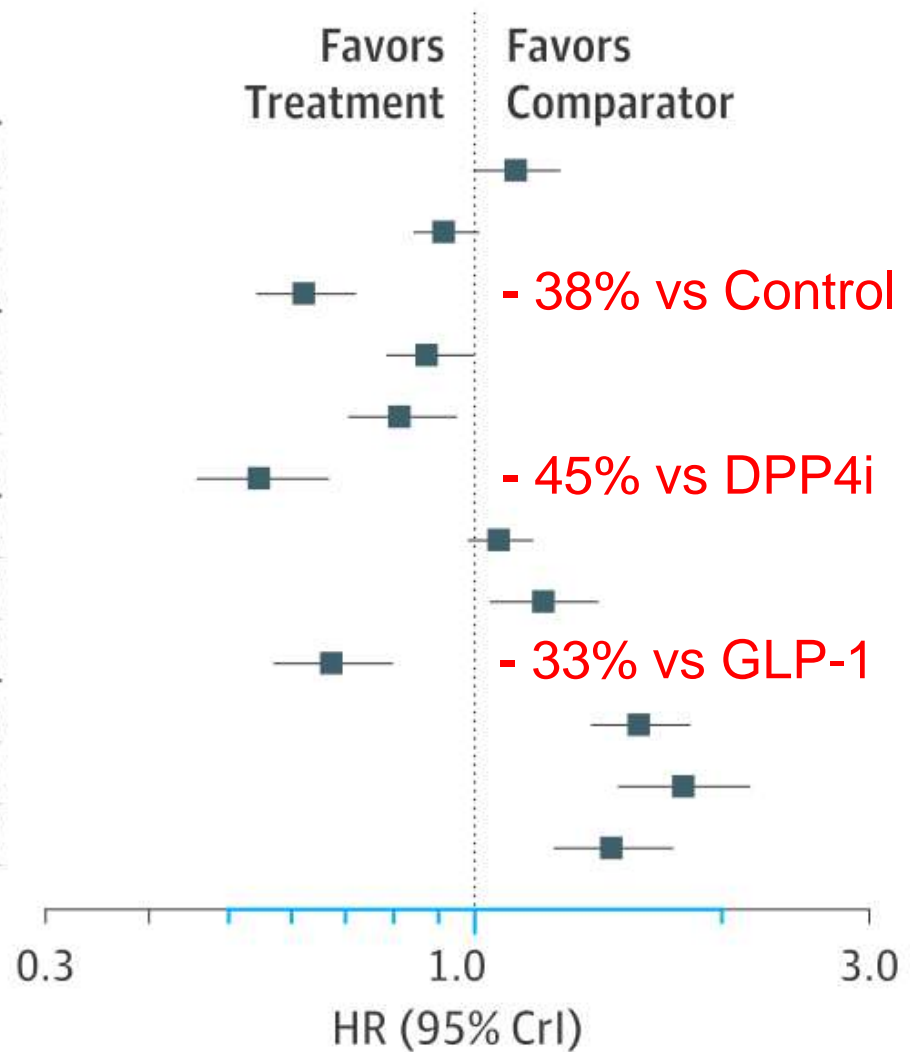
236 trials randomizing  
176 310 participants



# SGLT-2 inhibitors was associated with lower Heart Failure risk than control group & DPP-4 inhibitors & GLP-1 agonists

**C** Heart failure events, 58 trials;  $I^2 = 19\%$

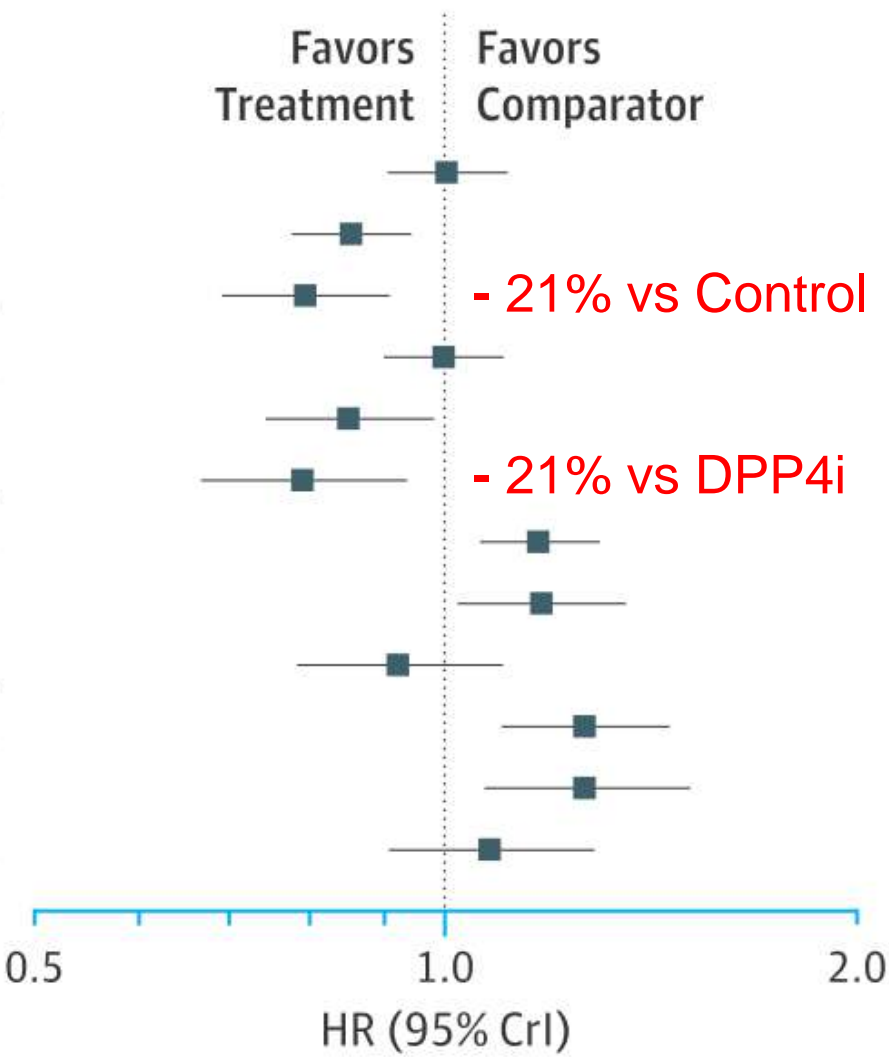
Treatment	Comparator	Absolute RD (95% CrI), %	HR (95% CrI)
DPP-4 inhibitor	vs Control	0.4 (0.0 to 0.8)	1.13 (1.00 to 1.28)
GLP-1 agonist		-0.2 (-0.5 to 0.1)	0.93 (0.84 to 1.02)
SGLT-2 inhibitor		-1.1 (-1.3 to -0.8)	0.62 (0.54 to 0.72)
Control	vs DPP-4 inhibitor	-0.3 (-0.5 to 0.0)	0.88 (0.78 to 1.00)
GLP-1 agonist		-0.4 (-0.7 to -0.1)	0.82 (0.70 to 0.95)
SGLT-2 inhibitor		-1.1 (-1.3 to -0.8)	0.55 (0.46 to 0.67)
Control	vs GLP-1 agonist	0.2 (-0.1 to 0.5)	1.08 (0.98 to 1.18)
DPP-4 inhibitor		0.6 (0.1 to 1.1)	1.22 (1.05 to 1.42)
SGLT-2 inhibitor		-0.9 (-1.2 to -0.5)	0.67 (0.57 to 0.80)
Control	vs SGLT-2 inhibitor	1.0 (0.6 to 1.4)	1.60 (1.39 to 1.84)
DPP-4 inhibitor		1.3 (0.8 to 2.0)	1.81 (1.50 to 2.18)
GLP-1 agonist		0.8 (0.4 to 1.3)	1.48 (1.25 to 1.76)



SGLT-2 inhibitors and GLP-1 agonists were associated with lower CV mortality than control group & DPP-4 inhibitors

**B** Cardiovascular mortality, 56 trials;  $I^2 = 19\%$

Treatment	Comparator	Absolute RD (95% CrI), %	HR (95% CrI)
DPP-4 inhibitor	vs Control	0.0 (-0.3 to 0.4)	1.00 (0.91 to 1.11)
GLP-1 agonist		-0.5 (-0.8 to -0.1)	0.85 (0.77 to 0.94)
SGLT-2 inhibitor		-0.8 (-1.1 to -0.3)	0.79 (0.69 to 0.91)
Control	vs DPP-4 inhibitor	0.0 (-0.3 to 0.3)	1.00 (0.90 to 1.10)
GLP-1 agonist		-0.5 (-0.8 to -0.1)	0.85 (0.74 to 0.98)
SGLT-2 inhibitor		-0.7 (-1.1 to -0.2)	0.79 (0.66 to 0.94)
Control	vs GLP-1 agonist	0.5 (0.2 to 0.9)	1.17 (1.06 to 1.30)
DPP-4 inhibitor		0.5 (0.1 to 1.1)	1.18 (1.02 to 1.36)
SGLT-2 inhibitor		-0.2 (-0.7 to 0.3)	0.93 (0.78 to 1.10)
Control	vs SGLT-2 inhibitor	0.8 (0.3 to 1.3)	1.27 (1.10 to 1.46)
DPP-4 inhibitor		0.8 (0.2 to 1.5)	1.27 (1.07 to 1.51)
GLP-1 agonist		0.2 (-0.3 to 0.8)	1.08 (0.91 to 1.29)

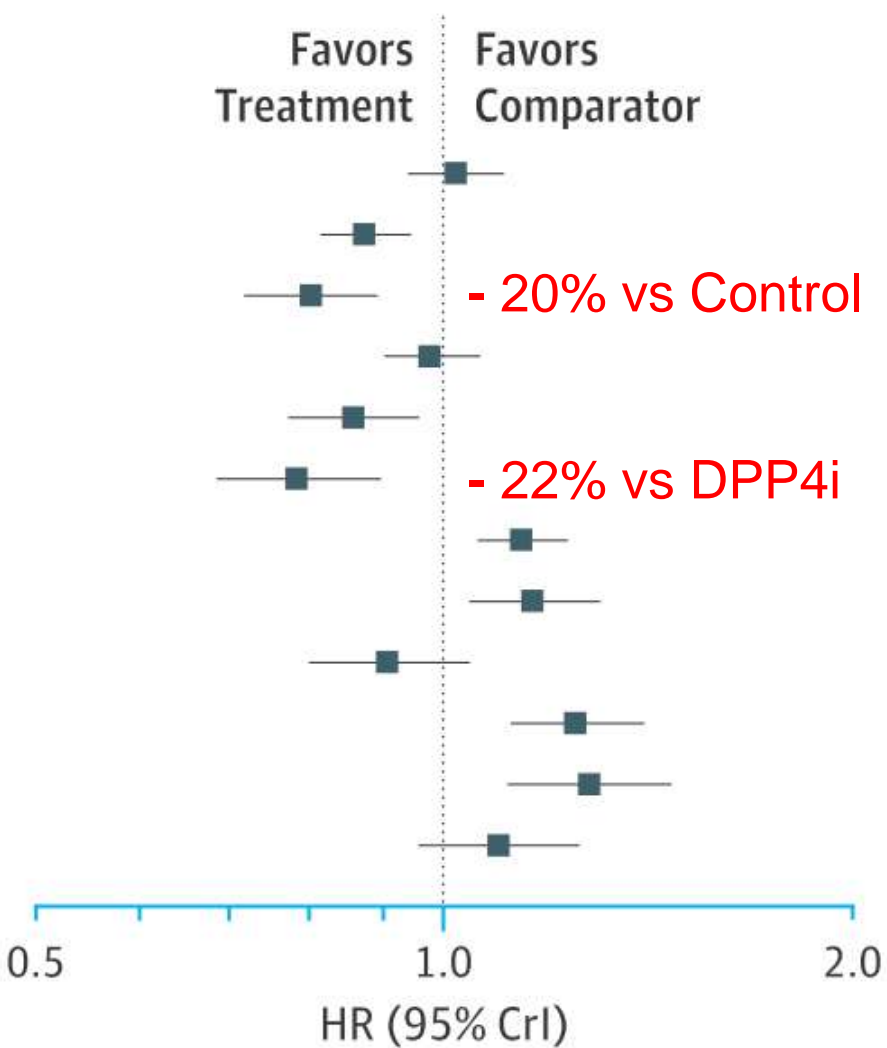




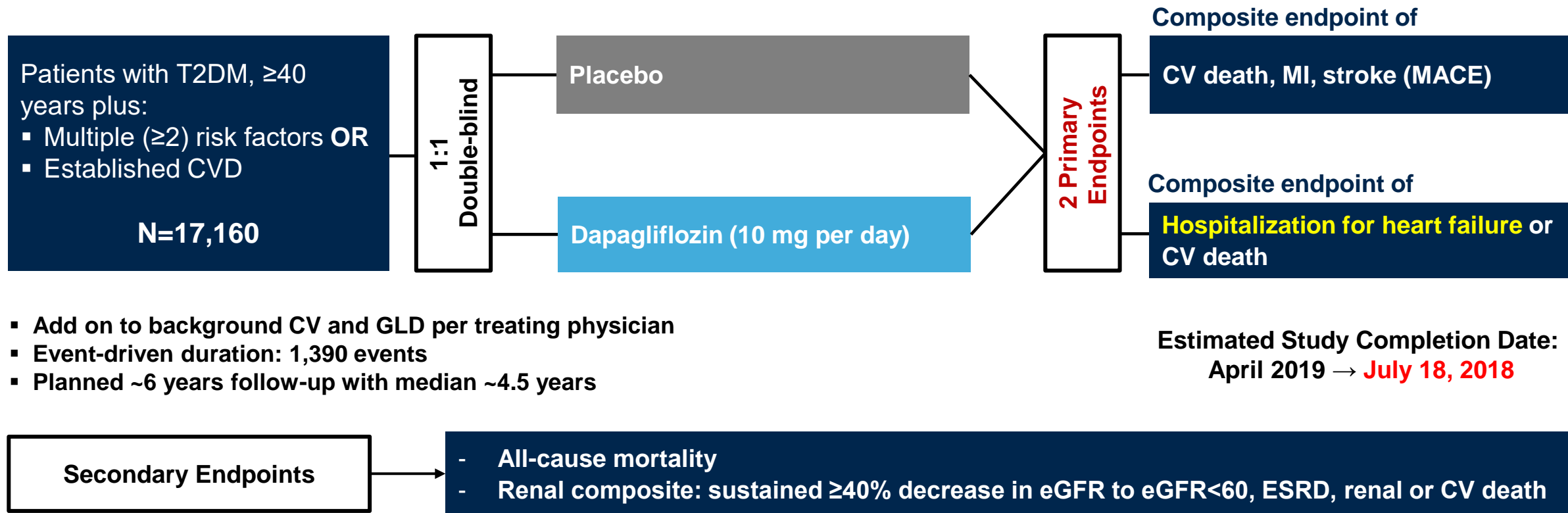
# SGLT-2 inhibitors and GLP-1 agonists were associated with lower mortality than control group & DPP-4 inhibitors

**A** Primary outcome: all-cause mortality, 97 trials; *I*<sup>2</sup> = 12%

Treatment	Comparator	Absolute RD (95% CrI), %	HR (95% CrI)
DPP-4 inhibitor	vs Control	0.1 (-0.3 to 0.6)	1.02 (0.94 to 1.11)
GLP-1 agonist		-0.6 (-1.0 to -0.3)	0.88 (0.81 to 0.94)
SGLT-2 inhibitor		-1.0 (-1.5 to -0.6)	0.80 (0.71 to 0.89)
Control	vs DPP-4 inhibitor	-0.1 (-0.4 to 0.2 )	0.98 (0.90 to 1.06)
GLP-1 agonist		-0.5 (-0.9 to -0.2)	0.86 (0.77 to 0.96)
SGLT-2 inhibitor		-0.9 (-1.2 to -0.4)	0.78 (0.68 to 0.90)
Control	vs GLP-1 agonist	0.6 (0.3 to 1.0)	1.14 (1.06 to 1.23)
DPP-4 inhibitor		0.7 ( 0.2 to 1.3 )	1.17 (1.04 to 1.30)
SGLT-2 inhibitor		-0.4 (-0.9 to 0.2 )	0.91 (0.79 to 1.04)
Control	vs SGLT-2 inhibitor	0.9 (0.4 to 1.5)	1.25 (1.12 to 1.40)
DPP-4 inhibitor		1.0 (0.4 to 1.7)	1.28 (1.11 to 1.47)
GLP-1 agonist		0.4 (-0.1 to 0.9 )	1.10 (0.96 to 1.26)



# DECLARE-TIMI 58: Broad CV risk population & 2 clinically important CV co-primary endpoints in Type 2 Diabetes



CV, cardiovascular; CVD, cardiovascular disease; 2, T2DM, type 2 diabetes mellitus; NF, non-fatal; MACE, major adverse cardiac event; hHF, hospitalization for heart failure. Raz I, et al. *Diabetes Obes Metab* 2018. <http://dx.doi.org/10.1111/dom.13217>; Wiviott SD, et al. *Am Heart J* 2018. <http://dx.doi.org/10.1016/j.ahj.2018.01.012>; ClinicalTrials.gov: <https://clinicaltrials.gov/ct2/show/NCT01730534>

# DECLARE-TIMI 58: Organization

Conducted together with the TIMI Study Group in Boston and the Hadassah University Hospital, Jerusalem, Israel with AstraZeneca as Sponsor

## **Executive Committee**

Marc Sabatine, Principal Investigator (chair, TIMI)

Steve Wiviott, Principal Investigator (TIMI)

Itamar Raz, Principal Investigator (Hadassah)

Lawrence Leiter, Diabetology

John Wilding, Diabetology

Deepak Bhatt, Cardiology

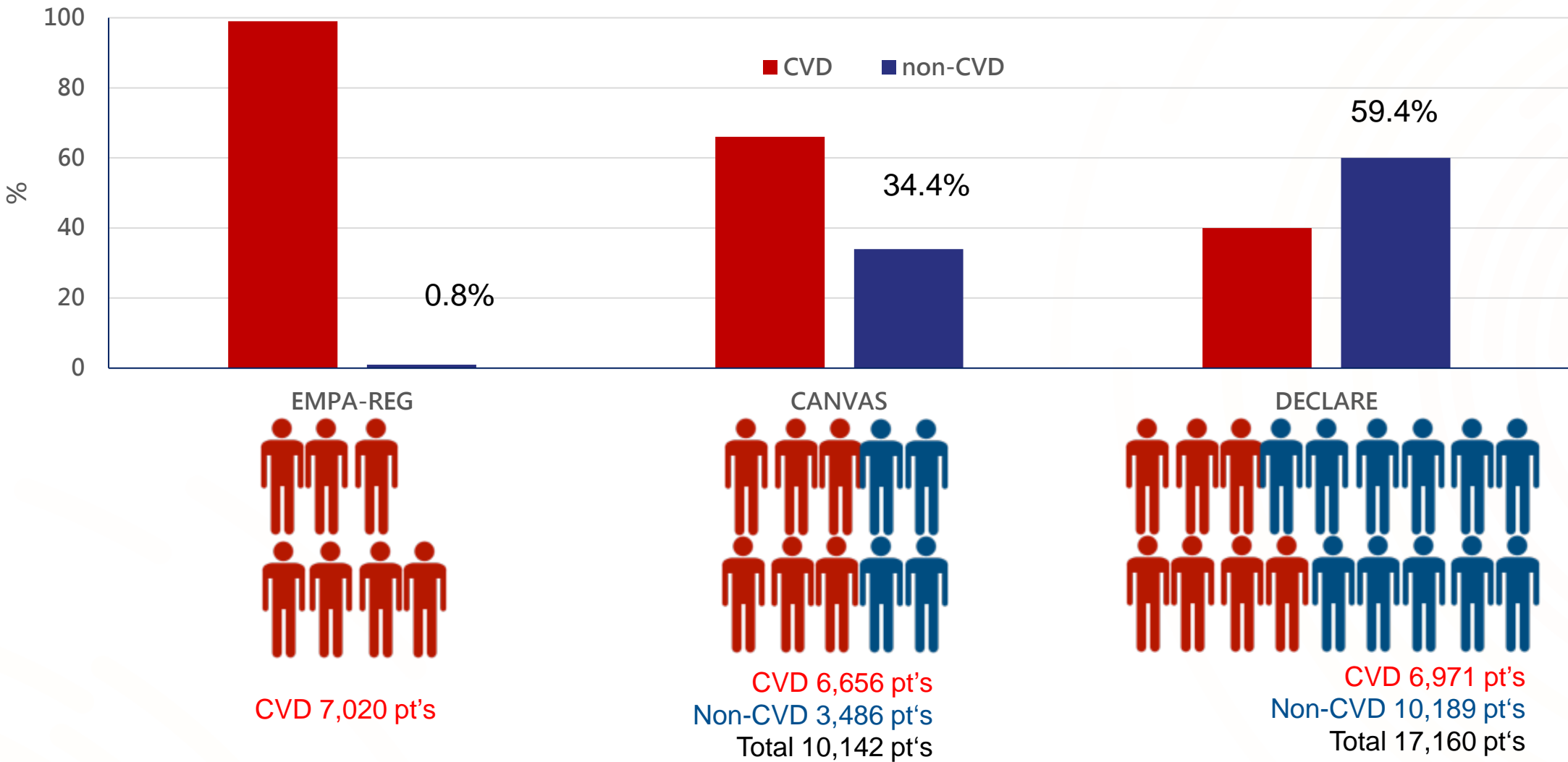
Darren McGuire, Cardiology

## **AstraZeneca non voting members**

Anna Maria Langkilde, Global Clinical Lead

Ingrid Gause-Nilsson, Senior Medical Lead

# CVD and Non-CVD proportion in 3 CVOTs of SGLT2i



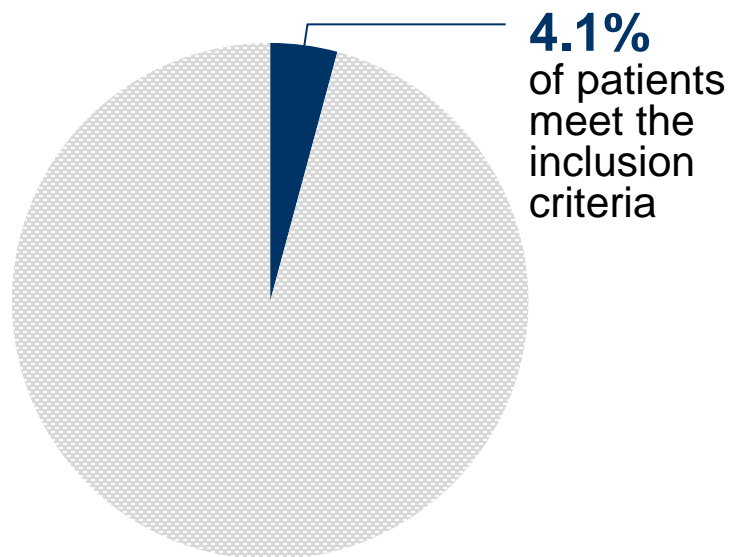
CVD, cardiovascular disease; CVOT, cardiovascular outcome trials; SGLT2i, sodium-glucose co-transporter 2 inhibitor; T2D, type 2 diabetes  
1. Zinman B, et al. Cardiovasc Diabetol. 2014 Jun 19;13:102.; 2. Neal B, et al. N Engl J Med. 2017 Aug 17;377(7):644-657;  
3. Raz I, et al. Diabetes Obes Metab. 2018 Jan 11. doi: 10.1111/dom.13217.



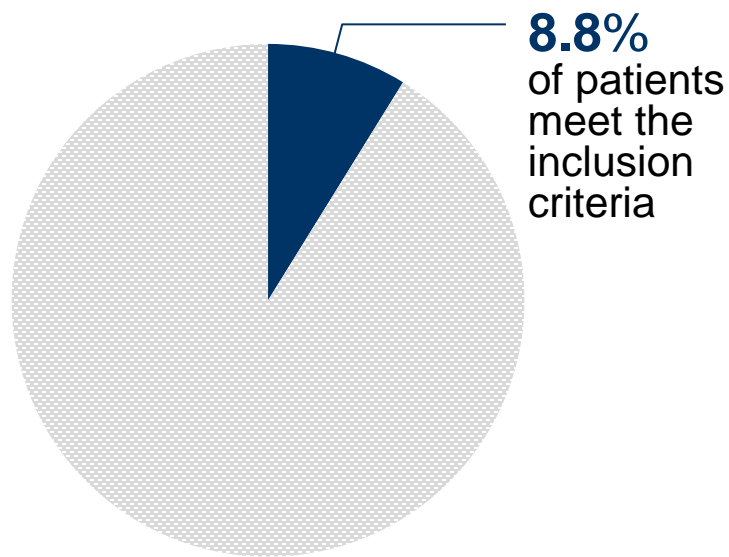
# DECLARE is the most inclusive SGLT2i CV outcomes trial to date<sup>1,2</sup>

The generalizability of the eligibility criteria of the 3 SGLT2 inhibitor CV outcome studies was assessed in the 2009–2010 and 2011–2012 National Health and Nutrition Examination Survey (NHANES) databases

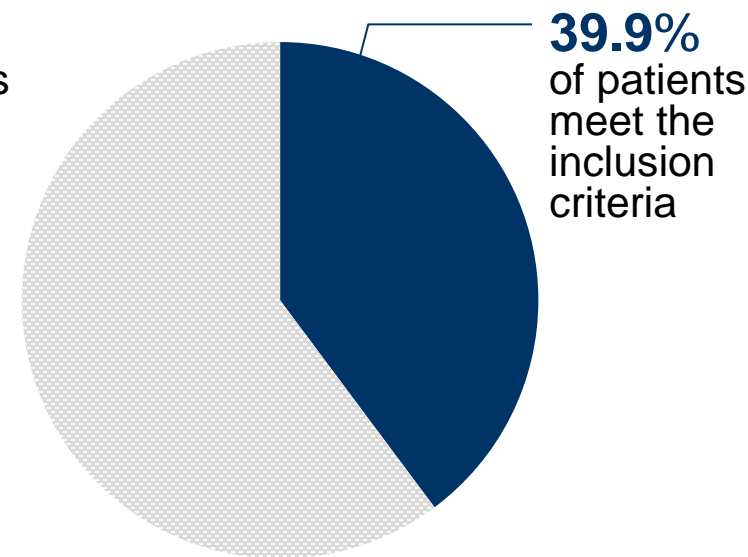
EMPA-REG OUTCOME



CANVAS



DECLARE



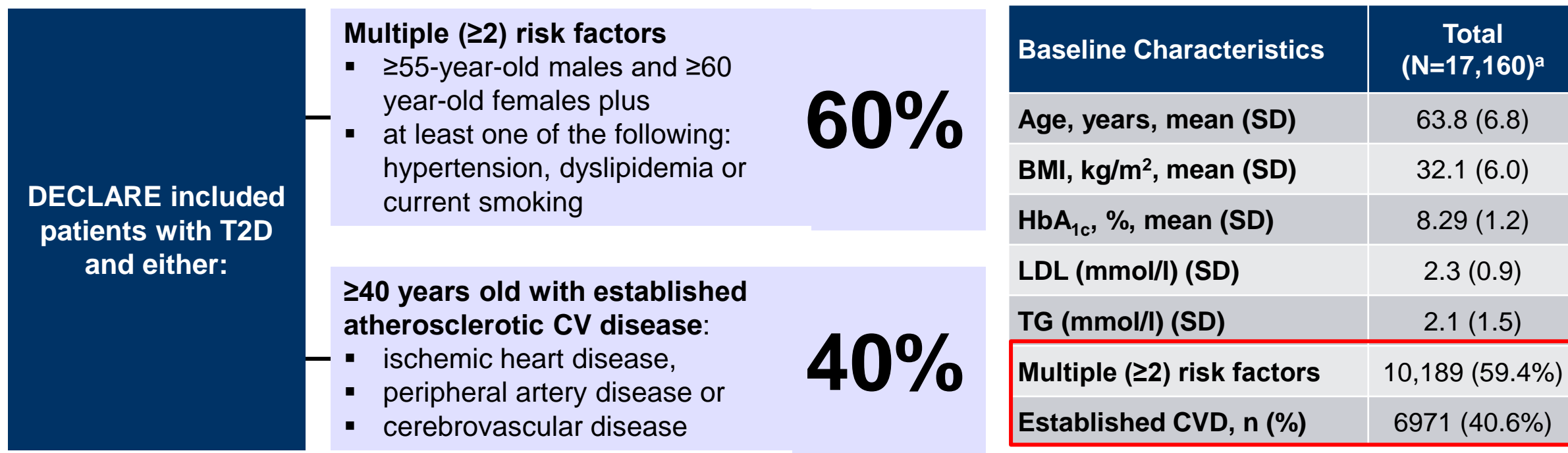
**As the most inclusive study, DECLARE is poised to provide guidance on how to reduce risk in a population of patients with type 2 diabetes and a broader CV risk profile**

CV, cardiovascular; SGLT2, sodium glucose co-transporter 2; T2D, type 2 diabetes.

1. Wittbrodt. Presented at the 15th Annual World Congress on Insulin Resistance, Diabetes & Cardiovascular Disease 2017;

2. Am J Manag Care. 2018;24:S138-S145

# The majority of the type 2 diabetes patients in DECLARE-TIMI 58 are in an earlier stage of the CV risk continuum



**DECLARE will provide results for the broad population enrolled**

BMI, body mass index; CABG, coronary artery bypass graft; CV, cardiovascular; CVD, cardiovascular disease; HbA<sub>1c</sub>, glycated hemoglobin; MRF, multiple risk factor; PCI, percutaneous coronary intervention; SD, standard deviation

Raz I, et al. Diabetes Obes Metab 2018. <http://dx.doi.org/10.1111/dom.13217>; Wiviott SD, et al. Am Heart J 2018. <http://dx.doi.org/10.1016/j.ahj.2018.01.012>

# Inclusion criteria of 3 CV outcome trials of SGLT-2 inhibitors

## EMPA-REG

- Patients with T2DM, age  $\geq 18$  years
- **HbA1c 7.0-10%**
- **eGFR  $\geq 30$  mL/min/1.73 m<sup>2</sup>**
- Establish CV disease (100%)
  - Prior MI, CAD, stroke, unstable angina, or occlusive PAD

## DECLARE

- Patients with T2DM
- **HbA1c 6.5-12%**
- **CrCl  $\geq 60$  mL/min**
- Age  $\geq 40$  years and prior CV event (40%)
- OR
- Age  $\geq 55$  years (men);  $\geq 60$  years (women) with  $\geq 1$  CV risk factors
  - CV risk factors: dyslipidemia, hypertension, tobacco use

## CANVAS program

Patients with T2DM

**HbA1c 7.0-10.5%**

**eGFR  $\geq 30$  mL/min/1.73 m<sup>2</sup>**

Age  $\geq 30$  years and prior CV event (65%)

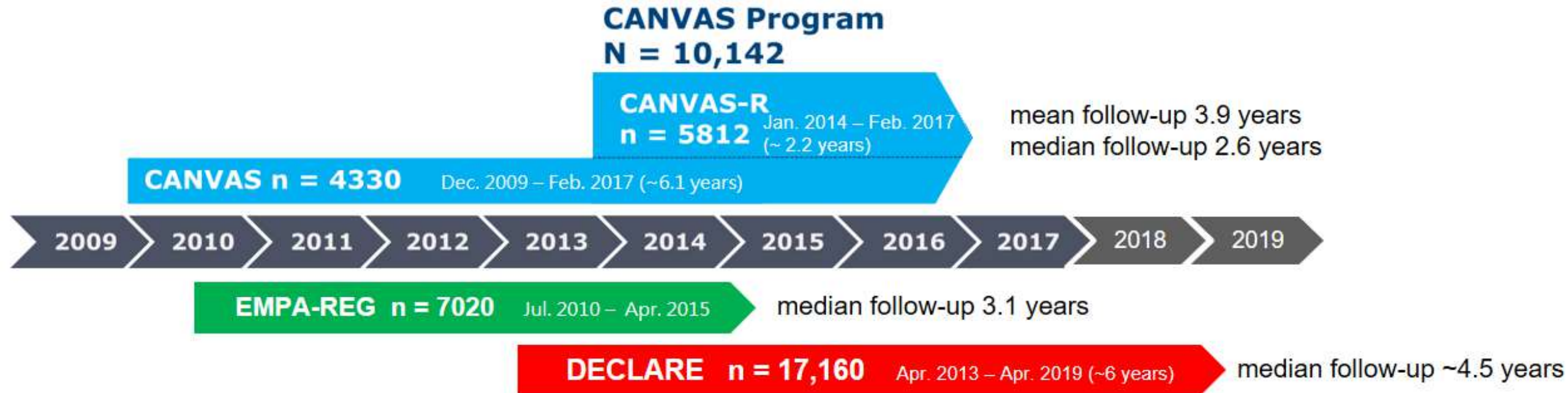
OR

Age  $\geq 50$  years with  $\geq 2$  CV risk factors

CV risk factors: diabetes duration  $\geq 10$  years, SBP  $> 140$  mmHg on  $\geq 1$  medication, current smoker, micro- or macroalbuminuria, or HDL cholesterol  $< 1$  mmol/L



# DECLARE is the CV outcome trial with longest time period



CVD, cardiovascular disease; CVOT, cardiovascular outcome trials; SGLT2i, sodium-glucose co-transporter 2 inhibitor; T2D, type 2 diabetes

1. Zinman B, et al. Cardiovasc Diabetol. 2014 Jun 19;13:102.; 2. Neal B, et al. N Engl J Med. 2017 Aug 17;377(7):644-657;

3. Raz I, et al. Diabetes Obes Metab. 2018 Jan 11. doi: 10.1111/dom.13217.



# DECLARE baseline & design publications are out in :

**DIABETES, OBESITY AND METABOLISM**  
A JOURNAL OF PHARMACOLOGY AND THERAPEUTICS  
[Explore this journal >](#)

ORIGINAL ARTICLE

**Declare-Timi 58: Participants' Baseline Characteristics**

Itamar Raz , Ofri Mosenzon, Marc P Bonaca, Avivit Cahn, Eri T Kato, Michael G Silverman, Deepak L Bhatt, Lawrence A. Leiter, Darren K. McGuire, John Wilding, Ingrid AM Gause-Nilsson, Anna Maria Langkilde, Peter A. Johansson, Marc S. Sabatine, Stephen D. Wiviott

Accepted manuscript online: 11 January 2018 [Full publication history](#)

DOI: 10.1111/dom.13217 [View/save citation](#)

Accepted: 5 January 2018, Published: 14 February 2018

Accepted Manuscript

**AHJ**  
American Heart Journal

The Design and Rationale for the Dapagliflozin Effect on Cardiovascular Events (DECLARE) – TIMI 58 Trial

Stephen D. Wiviott, Itamar Raz, Marc P Bonaca, Ofri Mosenzon, Eri T Kato, Avivit Cahn, Michael G Silverman, Sameer Bansilal, Deepak L Bhatt, Lawrence A. Leiter, Darren K. McGuire, John PH Wilding, Ingrid AM Gause-Nilsson, Anna Maria Langkilde, Peter A. Johansson, Marc S. Sabatine

**AHJ**  
American Heart Journal

Accepted: 28 January 2018

Link to the publications:

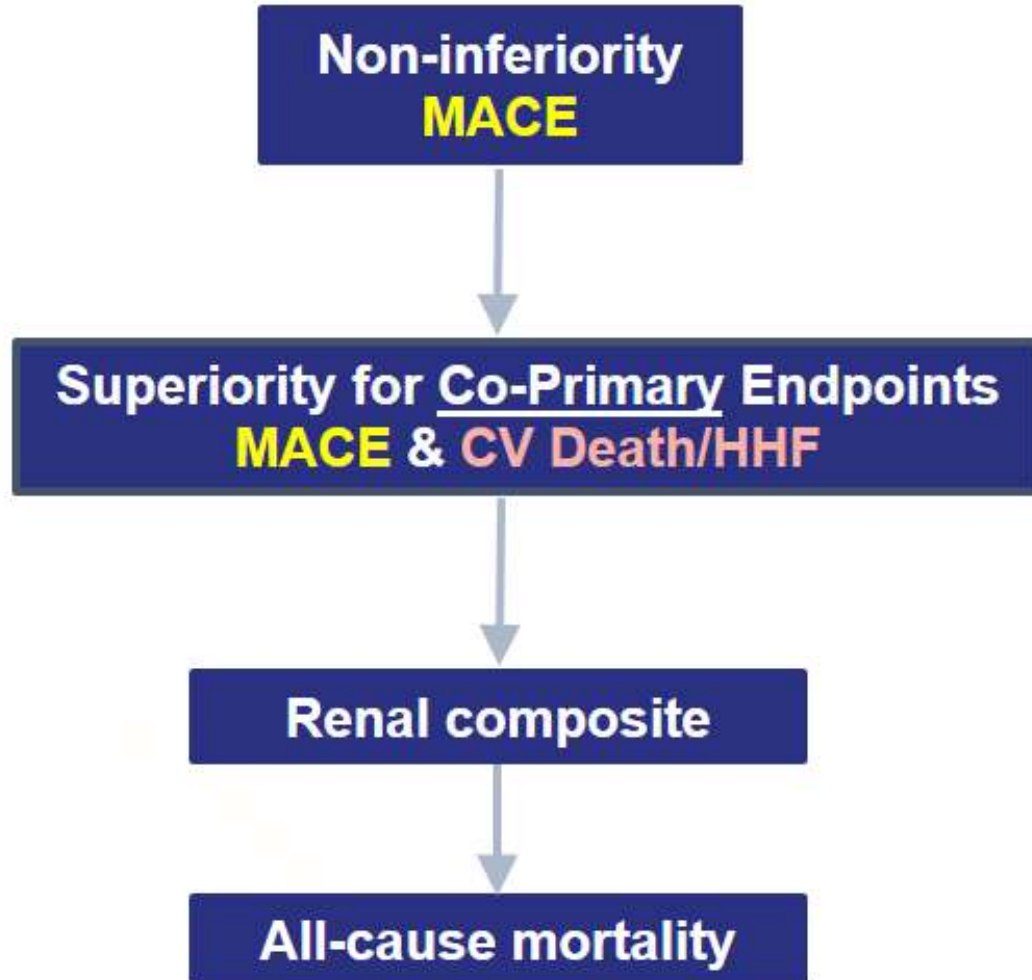
<http://onlinelibrary.wiley.com/doi/10.1111/dom.13217/full>

<https://www.sciencedirect.com/science/article/pii/S0002870318300383>

Link to additional materials/background information:

<https://az.box.com/s/wtdokd1a7nxgjba48kyrkbtgdglhw510>

# Design and Rationale of DECLARE



The **Design and Rationale** for the Dapagliflozin Effect on Cardiovascular Events (DECLARE) – TIMI 58 Trial

Stephen D. Wiviott, Itamar Raz, Marc P Bonaca, Ofri Mosenzon, Eri T Kato, Avivit Cahn, Michael G Silverman, Sameer Bansilal, Deepak L Bhatt, Lawrence A. Leiter, Darren K. McGuire, John PH Wilding, Ingrid AM Gause-Nilsson, Anna Maria Langkilde, Peter A. Johansson, Marc S. Sabatine



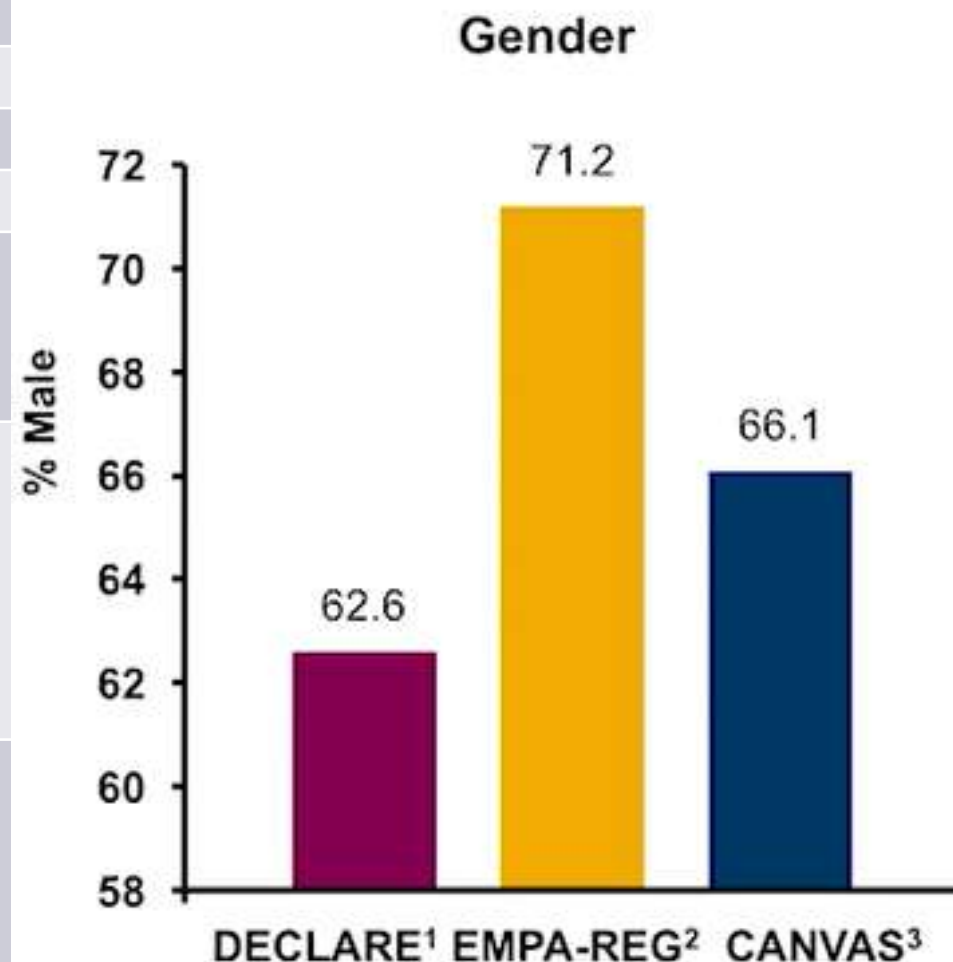
Accepted: 28 January 2018

American Heart Journal, Available online 7 February 2018,  
<https://doi.org/10.1016/j.ahj.2018.01.012>



# DECLARE-TIMI 58: Baseline Characteristics

	Total (N=17,160)*	ECVD (N=6971)	MRF (N=10,189)
<b>Gender, Male, n (%)</b>	10,738 (62.6)		
<b>Age, years, mean (SD)</b>	63.8 (6.8)		
<b>BMI, kg/m<sup>2</sup>, mean (SD)</b>	32.1 (6.0)		
<b>HbA1c, %, mean (SD)</b>	8.29 (1.2)		
<b>Cardiovascular risk factors, n (%)</b>			
LDL-C >130 mg/dL within last 12 months	3174 (18.5)		
Hypertension	15,343 (89.4)		
Tobacco use	2488 (14.5)		
<b>Cardiac history, n (%)</b>			
Angina pectoris	2802 (16.3)		
Heart failure	1698 (9.9)		
Atrial fibrillation/flutter	1110 (6.5)		
Myocardial infarction	3580 (20.9)		
Percutaneous coronary intervention	3655 (21.3)		
Coronary artery bypass grafting	1678 (9.8)		
<b>Investigator-reported history of microvascular complications, n (%)</b>			
Retinopathy	2131 (12.4)		
Laser treatment	587 (3.4)		
Nephropathy	1393 (8.1)		



\*116 subjects were omitted after randomization due to duplication or GCP violation.

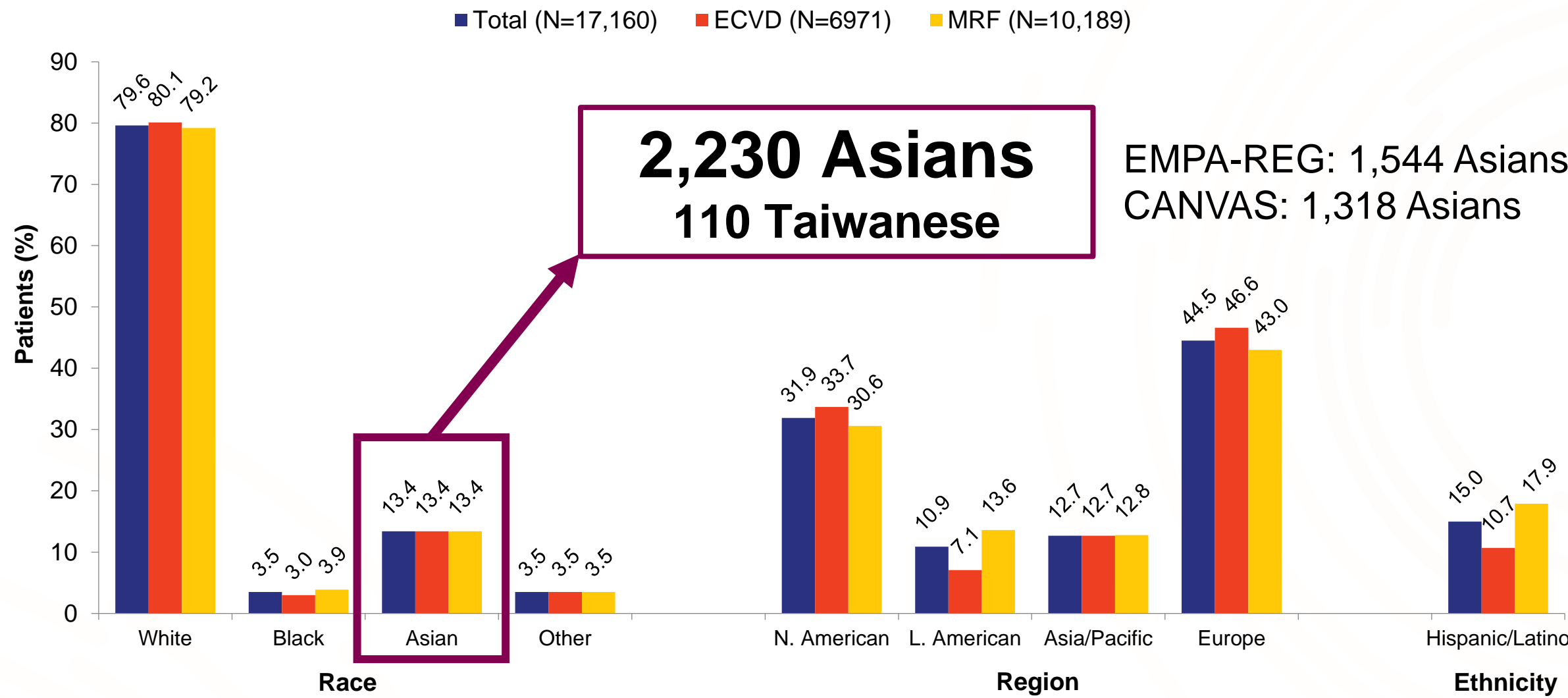
BMI, body mass index; ECVD, established cardiovascular disease; GCP, good clinical practice; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; MRF, multiple risk factors; SD, standard deviation.

1. Raz I et al. Poster presented at: 77<sup>th</sup> Scientific Sessions of the American Diabetes Association; June 9-13, 2017; San Diego, CA. Poster 1245-P; Raz I et al. Poster presented at: 53<sup>rd</sup> Annual Meeting of the European Association for the Study of Diabetes; September 11-15, 2017; Lisbon, Portugal. Poster 1129. 2. Zinman B, et al. Cardiovasc Diabetol. 2014 Jun 19;13:102; 3. Neal B, et al. N Engl J Med. 2017 Aug 17;377(7):644-657

# Comparison of baseline characteristics of SGLT2i CVOTs

		DECLARE (N=17,160)	CANVAS (N=10,142)	EMPA-REG (N=7020)
Gender (%)	Male	62.6%	64.2%	71.5%
Age (years)	mean± SD	63.8 (6.8)	63.3 (6.8)	63.1 (6.8)
BMI (kg/m <sup>2</sup> )	mean± SD	32.1 (6.0)	32.0 (5.9)	30.7 (5.3)
HbA1c (%)	mean± SD	8.3 (1.2)	8.2 (0.9)	8.1 (0.8)
Race (%)	White	79.6%	78.3%	72.4%
	Other	20.4%	21.7%	27.6%
ECVD	n (%)	6,971 (40.6%)	6,656 (65.6%)	7,020 (100%)
MRF	n (%)	10,189 (59.4%)	3,486 (34.4%)	0 (0%)
eGFR ml/min/1.73 m <sup>2</sup>		86.1 (21.8)	76.5 (20.5)	74.1 (21.4)
ACR- %	Normo-albuminuria (<30 mg/g)	67.9%	69.8%	59.4%
	Micro-albuminuria (30 - ≤ 300 mg/g)	23.4%	22.6%	28.7%
	Macro-albuminuria (>300 mg/g)	6.8%	7.6%	11.0%

# DECLARE with more Asian patients than other CVOTs of SGLT2i



ECVD, established cardiovascular disease; MRF, multiple risk factors.  
Raz I et al. Poster presented at: 77<sup>th</sup> Scientific Sessions of the American Diabetes Association; June 9-13, 2017; San Diego, CA. Poster 1245-P; Raz I et al. Poster presented at: 53<sup>rd</sup> Annual Meeting of the European Association for the Study of Diabetes; September 11-15, 2017; Lisbon, Portugal. Poster 1129.



# DECLARE timeline update on clinicaltrials.gov

Study completion date for DECLARE has been updated to July 18<sup>th</sup>, 2018:

## Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI58)

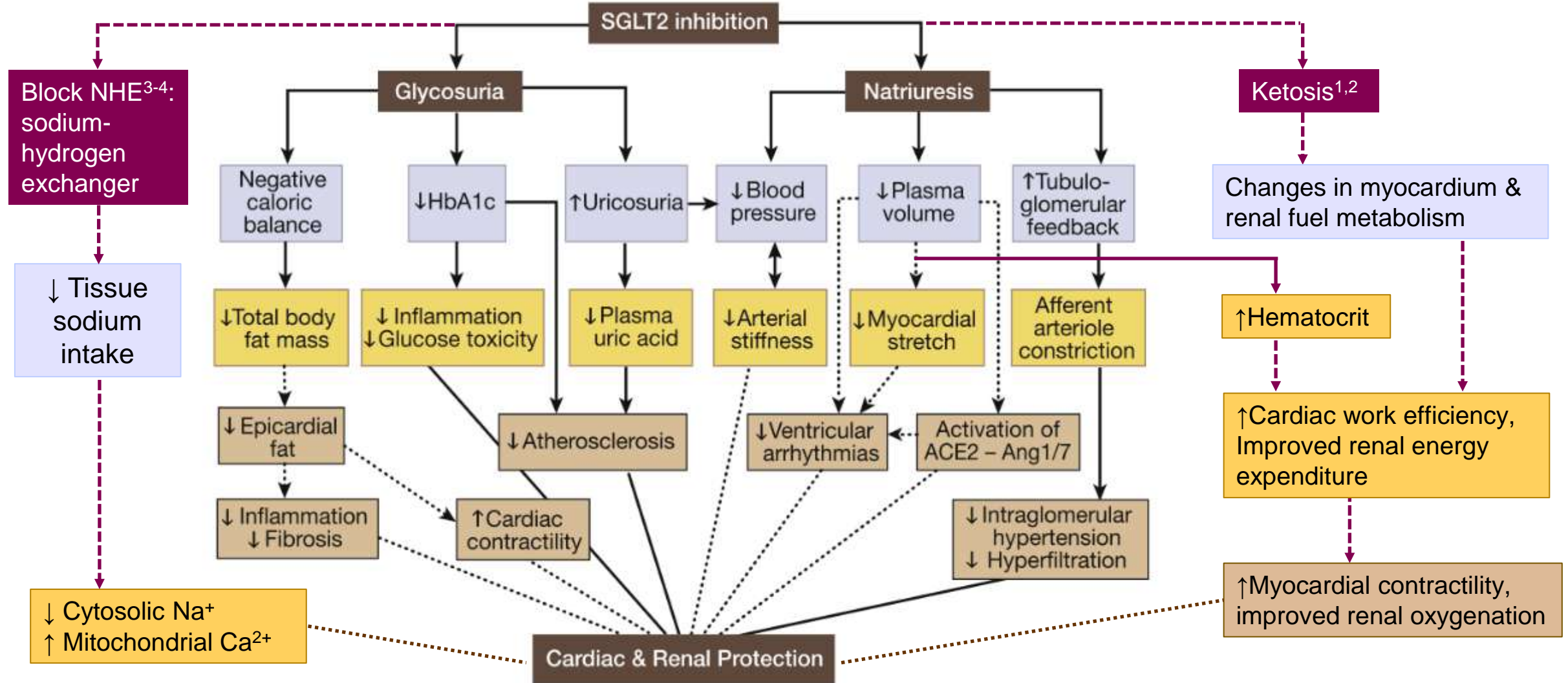
### Study Design

Study Type ⓘ : Interventional (Clinical Trial)  
Actual Enrollment ⓘ : 17276 participants  
Allocation: Randomized  
Intervention Model: Parallel Assignment  
Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)  
Primary Purpose: Treatment  
Official Title: Dapagliflozin Effect on Cardiovascular Events A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Dapagliflozin 10 mg Once Daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischemic Stroke in Patients With Type 2 Diabetes  
Actual Study Start Date ⓘ : April 25, 2013  
Estimated Primary Completion Date ⓘ : July 18, 2018  
Estimated Study Completion Date ⓘ : July 18, 2018

NIH U.S. National Library of Medicine  
*ClinicalTrials.gov*

<https://clinicaltrials.gov/ct2/show/NCT01730534?term=declare&rank=2>

# Proposed Mechanisms of CV & Renal Benefits of SGLT-2 inhibitors



The figure adapted from Kidney Int. 2016 Mar;89(3):524-6., with additional ketosis and NHE hypothesis depicted based on data from

1. Diabetes Care 2016;39:1115-1122., 2. Diabetes Care 2016;39:1108-1114., 3. JAMA Cardiol. 2017 Sep 1;2(9):1025-1029. 4. Cardiovasc Res. 2018 Jan 1;114(1):12-18.



# Diabetes treatment guideline and heart failure

Diabetes treatment guideline		Heart failure	
1	2	3	4
5	6	7	8
9	10	11	12
13	14	15	16
17	18	19	20
21	22	23	24
25	26	27	28
29	30	31	32
33	34	35	36
37	38	39	40
41	42	43	44
45	46	47	48
49	50	51	52
53	54	55	56
57	58	59	60
61	62	63	64
65	66	67	68
69	70	71	72
73	74	75	76
77	78	79	80
81	82	83	84
85	86	87	88
89	90	91	92
93	94	95	96
97	98	99	100



# 最新2023 ADA 第2型糖尿病藥物治療流程圖 延續ADA/EASD共識

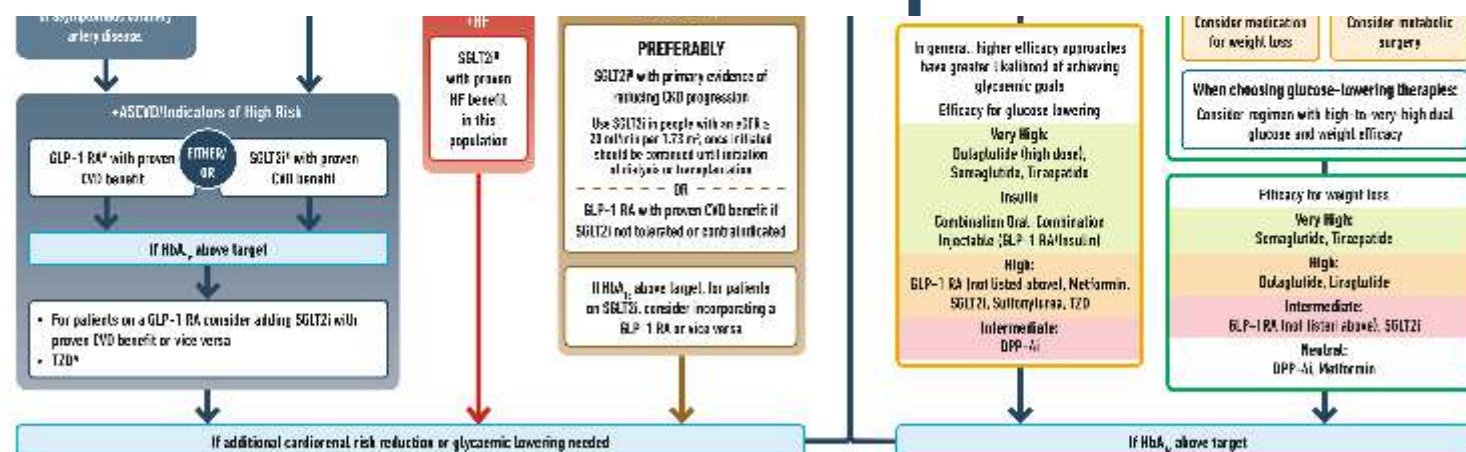
## USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIOURS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

TO AVOID  
THERAPEUTIC  
INERTIA REASSESS  
AND MODIFY TREATMENT  
REGULARLY  
(3-6 MONTHS)

**Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (In addition to comprehensive CV risk management)\***

**Goal: Achievement and Maintenance of Glycaemic and Weight Management Goals**

[illegible]

\* Intraplate (6.5–9.0), shallow (0–20) km, high-latitude, low-velocity, low-strain-rate ( $\sim 10^{-14}$  s $^{-1}$ ) plate-SHTs occur beneath all major independent tectonic and orogenic belts, including convergent margins with both compressional and extensional tectonics. They are also observed beneath the Pacific with both compressional and extensional tectonics. In contrast, plate-SHTs are absent beneath the mid-ocean ridges and the oceanic crust. The plate-SHTs occur beneath the Pacific and the Atlantic, but are absent beneath the Indian Ocean. The plate-SHTs occur beneath the Pacific and the Atlantic, but are absent beneath the Indian Ocean. The plate-SHTs occur beneath the Pacific and the Atlantic, but are absent beneath the Indian Ocean.

- Consider DSM-5 criteria to support self-efficacy in achievement of goals
- Consider technology (e.g., diagnostic GDM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact on achievement of goals

# 「評估患者個人化情況」 兩大治療目標：降低心腎風險、血糖與體重控制

## USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIOURS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)



Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (In addition to comprehensive CV risk management)\*

Goal: Achievement and Maintenance of Glycaemic and Weight Management Goals



目標：

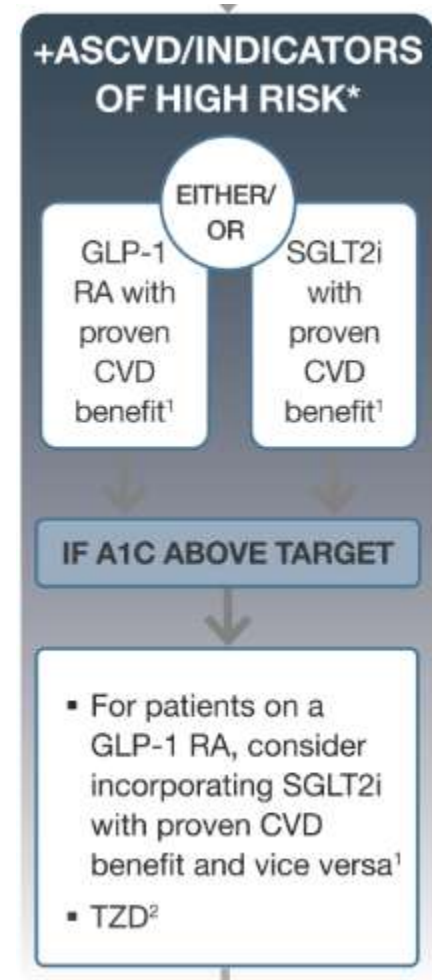
降低患有第二型糖尿病之(心腎)  
高風險病人之心腎風險  
(在全面的心血管風險管理之下)

目標：

達成及維持血糖與體重控制目標

# 2023 ADA Guideline: 心血管疾病及高風險族群

## 2022 ADA guideline

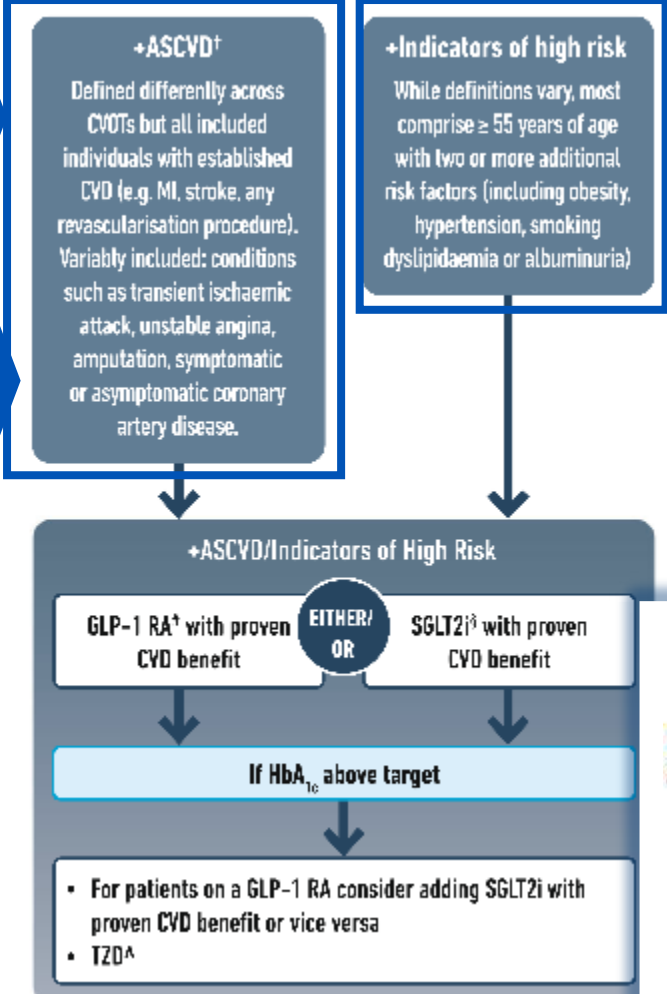


1  
依據試驗收納族群詳列疾病定義

2  
高風險族群定義趨向簡單化、符合臨床判定需求


\*Refer to Section 10: Cardiovascular Disease and Risk Management.

## 2023 ADA guideline



1  
動脈粥樣硬化心血管疾病/高風險指標定義隨不同試驗有所差異  
**ASCVD:**  
所有試驗皆包含:心肌梗塞、中風、任何血管重建手術; 部分試驗包含:暫時性腦缺血、不穩定型心絞痛、截肢、有無症狀之冠狀動脈疾病

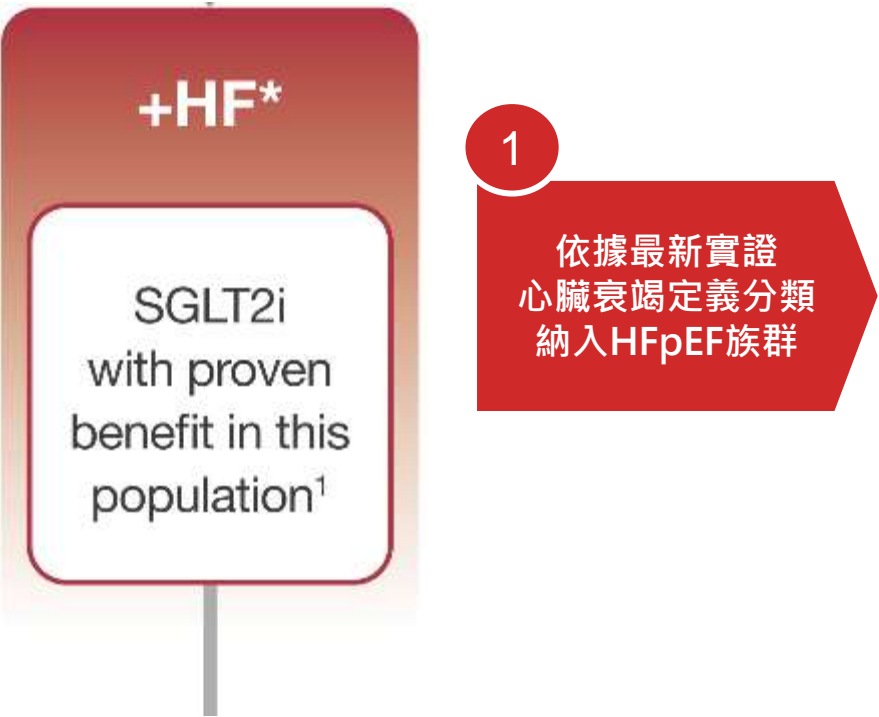
2  
**Indicators of high risk:**  
大多為≥55歲帶有兩項以上風險因子(肥胖、高血壓、抽菸、血脂異常或蛋白尿)

 **多重風險因子族群(MRF)收納條件:**  
**T2DM 患者合併**

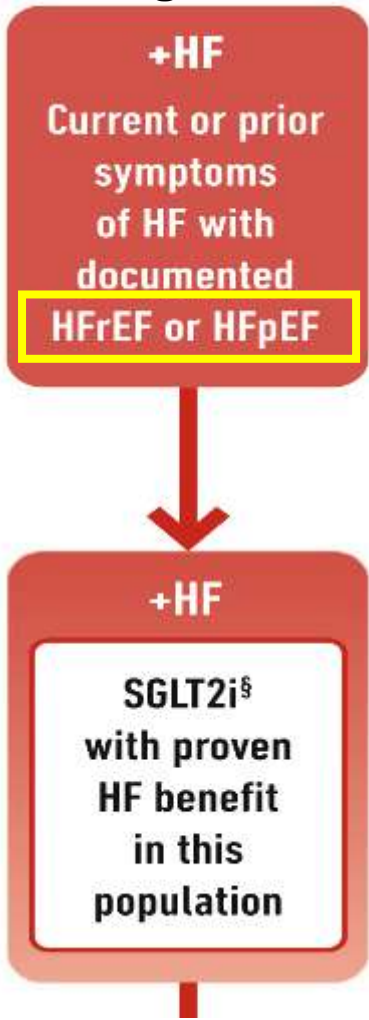
- 男性 ≥ 55 歲、女性 ≥ 60 歲
- 且合併 1 項以上的心血管風險因子
  - 血脂異常
  - 高血壓
  - 抽菸

# 2023 ADA guideline: 心臟衰竭

## 2022 ADA guideline



## 2023 ADA guideline





# 2023 ADA guideline: 根據患者情況， 兩大治療目標: 降低心腎風險、血糖與體重控制

## USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIOURS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)



Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (In addition to comprehensive CV risk management)\*

Goal: Achievement and Maintenance of Glycaemic and Weight Management Goals

**目標:**  
降低患有第二型糖尿病之(心腎)  
高風險病人之心腎風險  
(在全面的心血管風險管理之下)

**目標:**  
達成及維持血糖與體重控制目標

# 2023 ADA

## 第2型糖尿病藥物治療流程圖



If additional cardiorenal risk reduction or glycaemic lowering needed

If HbA<sub>1c</sub> above target



Identify barriers to goals:

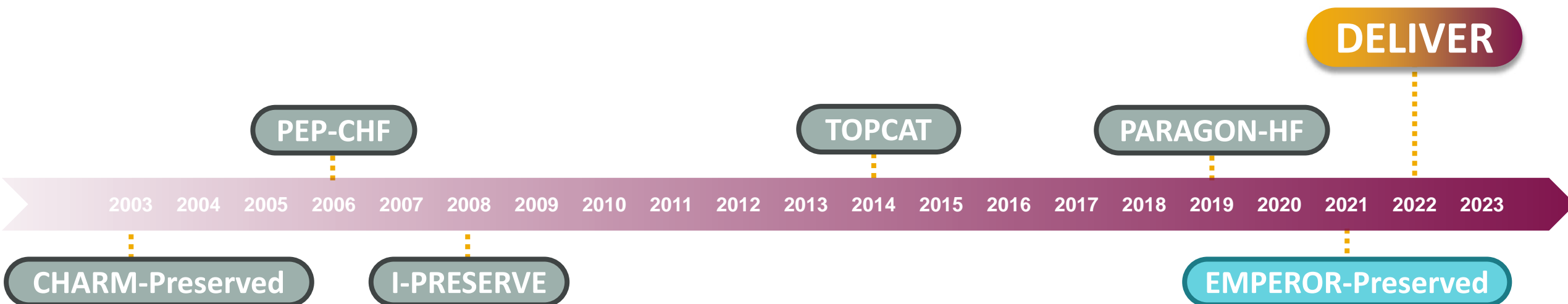
- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (e.g. diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact on achievement of goals

ACEi, Angiotensin-Converting Enzyme Inhibitor; ACR, Albumin/Creatinine Ratio; ARB, Angiotensin Receptor Blocker; ASCVD, Atherosclerotic Cardiovascular Disease; CGM, Continuous Glucose Monitoring; CKD, Chronic Kidney Disease; CV, Cardiovascular; CVD, Cardiovascular Disease; CVOT, Cardiovascular Outcomes Trial; DPP-4i, Dipeptidyl Peptidase-4 Inhibitor; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; HFpEF, Heart Failure with preserved Ejection Fraction; HFrEF, Heart Failure with reduced Ejection Fraction; HHF, Hospitalisation for Heart Failure; MACE, Major Adverse Cardiovascular Events; MI, Myocardial Infarction; SDOH, Social Determinants of Health; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes; TZD, Thiazolidinedione.

\* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin;† A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details;‡ Low-dose TZD may be better tolerated and similarly effective;§ For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF and renal outcomes in individuals with T2D with established/high risk of CVD;# For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke and renal endpoints in individuals with T2D with established/high risk of CVD.

\*在有心衰竭,慢性腎病,心血管疾病或多重風險因子病人, **使用有實證好處的GLP-1 RA或SGLT-2i的決定應該獨立於metformin使用與否**  
†對心血管疾病病患強力推薦,而對高心血管風險的則推薦力度較低;另外,更高的絕對風險下降和更低的需治人數(NNT)在較高的基礎風險族群較易觀察到,應該納入決策考量之一  
§對於**SGLT-2i**來說,心血管/腎臟終點結果的試驗展現了這類藥在**主要不良心血管事件、心血管死亡、全因性死亡、心肌梗塞、心衰竭住院以及腎臟結果**的降風險療效;這些數據是在患有**第二型糖尿病的心血管疾病/高風險族群**觀察得來  
#對於**GLP-1 RA**來說,心血管/腎臟終點結果的試驗展現了這類藥在**主要不良心血管事件、心血管死亡、全因性死亡、心肌梗塞、中風以及腎臟結果**的降風險療效;這些數據是在患有**第二型糖尿病的心血管疾病/高風險族群**觀察得來

# What's News about SGLT2i Treatment on HF



**Table 3 Comparison of DELIVER and other trials in heart failure with left ventricular ejection fraction >40%**

	CHARM-Preserved <sup>22</sup>	PEP-CHF <sup>23</sup>	I-PRESERVE <sup>24</sup>	TOPCAT <sup>25</sup>	PARAGON-HF <sup>17</sup>	EMPEROR-Preserved <sup>26</sup>	DELIVER
Patients, <i>n</i>	3023	850	4128	3445	4800	5988	6200
Treatment arms	Candesartan vs. placebo	Perindopril vs. placebo	Irbesartan vs. placebo	Spironolactone vs. placebo	Sacubitril/valsartan vs. valsartan	Empagliflozin vs. placebo	Dapagliflozin vs. placebo
Key inclusion criteria	NYHA class II–IV, prior CV hospitalization	Clinical diagnosis of DHF with ≥signs/symptoms of HF, ≥2 of the following: LAE/LVH/impaired left ventricular filling/AF	NYHA class II–IV + any corroborating evidence (e.g. HF sign), LVH or LAE considered optional corroborating evidence, HFH required unless in NYHA class III–IV	≥1 HF symptom + ≥1 HF sign, elevated NP or HFH	NYHA class II–IV, elevated NT-proBNP (adjusted for AF and higher if no recent HF hospitalization), structural heart disease (LAE or LVH)	NYHA class II–IV, elevated NT-proBNP	NYHA class II–IV, elevated NT-proBNP (adjusted for AF), structural heart disease (LAE or LVH)
LVEF cutpoint	>40%	>40%	≥45%	≥45%	≥45%	>40%	>40%
Endpoint	First of either CV death or HFH	First of either all-cause death or HFH	First of either all-cause death or hospitalization for a CV cause	First of either CV death, HFH, or RSD	CV death and total HFH (first and recurrent)	CV death or HFH	CV death or HFH either in the full population or in patients with LVEF <60%

AF, atrial fibrillation; CV, cardiovascular; DHF, diastolic heart failure; HF, heart failure; HFH, heart failure hospitalization; LAE, left atrial enlargement; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; NP, natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.






# Before We DELIVER...

## Questions that remained:

- **Attenuation** of benefit in the highest LVEF range?
  - EMPEROR-Preserved

Primary endpoint (CV death or hHF) by LVEF at baseline

LVEF at baseline					
<50%	145/995	193/988			0.71 (0.57–0.88)
≥50% to <60%	138/1028	173/1030			0.80 (0.64–0.99)
≥60%	132/974	145/973			0.87 (0.69–1.10)

- Benefit in **hospitalized** or **recently hospitalized** patients?
- Benefit in patients with prior LVEF ≤40% that had improved to >40%
  - **HF with improved LVEF** – Excluded from all prior outcome trials?

# **Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction The DELIVER Trial**

**Scott D. Solomon, MD**

**Brigham and Women's Hospital  
Harvard Medical School**

**on behalf of the DELIVER Committees, Investigators, Sponsor and  
Participants**



# DELIVER: Study Design

## RCT Protocol

## Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure (DELIVER)



Multicenter: 350 site  
n = 6263  
Patients with/without T2DM



Age  $\geq 40$  years  
NYHA class II-IV  
Structural heart disease

- LVH or LA enlargement
- LVEF  $>40\%$
- **Improved EF** included

**Ambulatory or Hospitalized**



Elevated NT-proBNP

- $>300$  pg/mL
- $>600$  pg/mL in AFF

eGFR  $>25$  mL/min/1.73 m<sup>2</sup>

### Interventions



Dapagliflozin  
10 mg

1:1



Placebo

### Follow-up



~ 27 months



Event-driven  
(1117 events)

### Primary outcome

Composite CV endpoint

#### Duo primary endpoint

- **Full population**
- **LVEF  $<60\%$**



Heart failure  
hospitalization




Urgent HF  
visit



CV death

# Study design of HFpEF outcome trials

	DELIVER	EMPEROR-Preserved
Number of patients	6263 (318 in TW) 	5989 (not in TW)
Intervention	Dapagliflozin 10 mg vs PBO	Empagliflozin 10 mg vs PBO
Key inclusion criteria	<ul style="list-style-type: none"> <li>NYHA II-IV ≥ 6 wk with intermittent diuretics</li> <li>LVEF &gt; 40% (<b>IMPROVED EF included</b> [18%])</li> <li>Structural heart disease documented within last 12M</li> <li>NT-proBNP ≥ 300 pg/mL (≥ 600 pg/mL if AF)</li> <li>eGFR ≥ 25 mL/min/1.73m<sup>2</sup></li> <li><b>Ambulatory or Hospitalized</b> [10%]; if hospitalized for HF, must be off IV HF therapy for ≥ 24 hr</li> </ul>	<ul style="list-style-type: none"> <li>NHYA II-IV</li> <li>LVEF &gt; 40%</li> <li>Structural heart disease within 6M or hHF within 12M</li> <li>NT-proBNP &gt; 300 pg/mL (&gt; 900 pg/mL if AF)</li> <li>eGFR ≥ 20 mL/min/1.73m<sup>2</sup></li> </ul>
Key exclusion criteria	<ul style="list-style-type: none"> <li>T1D</li> <li>MI, UA, stroke, TIA, or CV procedure/surgery within last 12wk</li> <li>SBP ≥ 160 or &lt; 95 mmHg</li> </ul>	<ul style="list-style-type: none"> <li><b>Acute decompensated HF</b></li> <li>MI, CABG, other major CV surgery, stroke, or TIA within 90 days</li> <li>SBP ≥ 180 or &lt; 100 mmHg or symptomatic hypotension</li> </ul>
Primary endpoint	CV death, hHF, or Urgent HF visit <ul style="list-style-type: none"> <li>Full population</li> <li><b>Subpopulation with LVEF &lt; 60%</b></li> </ul>	CV death or hHF
Estimated completion	April 2022	April 2021 Readout in ESC 2021

The Largest, The Broadest

"Please note that as head-to-head studies were not conducted between these products, it is inappropriate to draw any comparisons and/or make any conclusions as the study design, demographics and other criteria may be different."



# Global Randomization Across 350 Sites in 20 Countries



Country	Enrollment (# of Patients)
Poland	572
USA	552
Bulgaria	493
Hungary	466
Japan	422
Brazil	405
Russia	401
Argentina	320
<b>Taiwan</b>	<b>318</b>
China	310
Spain	308
Canada	299
Czech Republic	274
Peru	240
Mexico	216
Saudi Arabia	190
Netherlands	176
Vietnam	176
Belgium	64
Romania	61

# DELIVER Baseline Characteristics

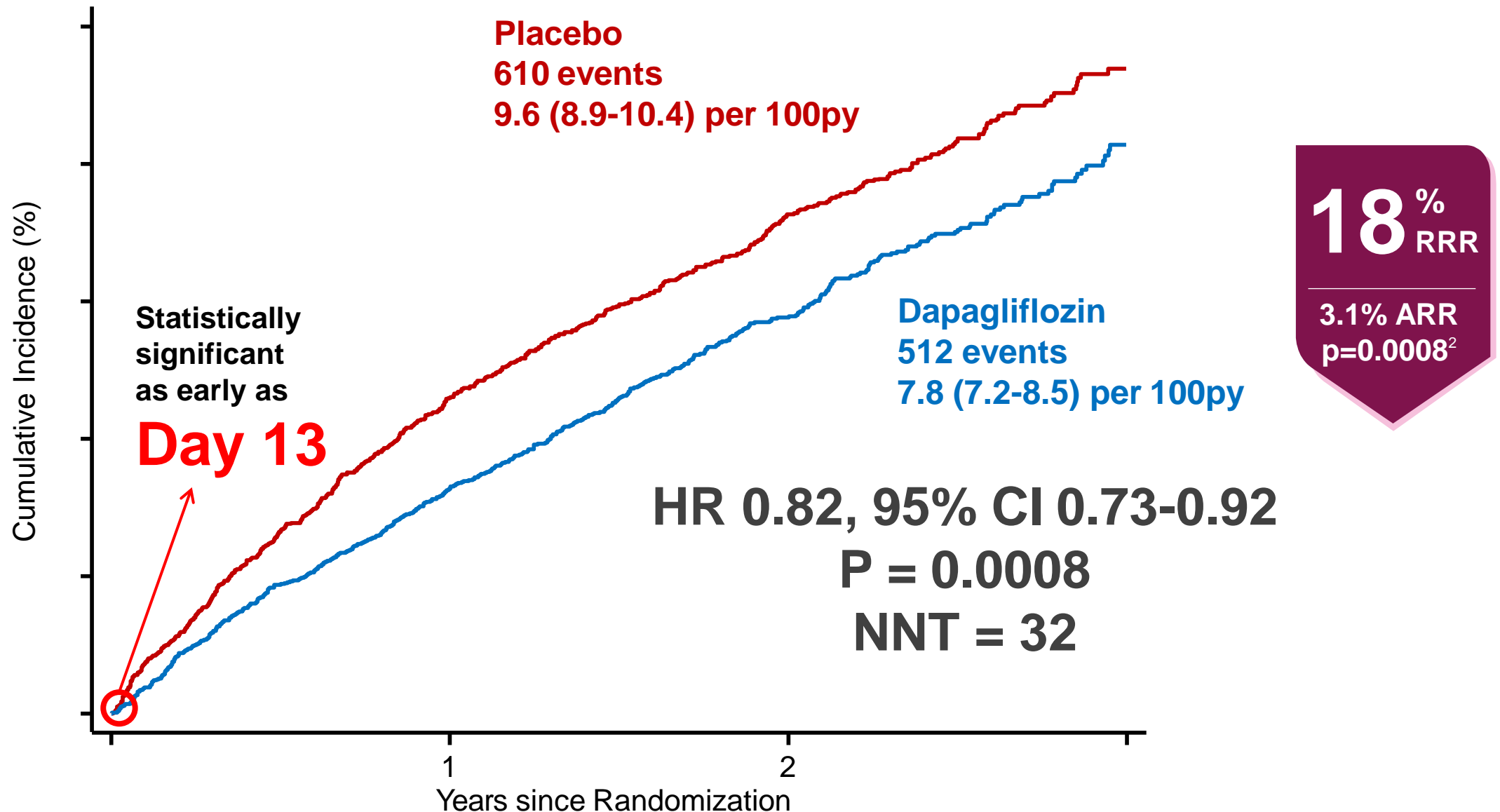
## Well Balanced Between Treatment Groups

	Dapagliflozin N=3131	Placebo N=3132		Dapagliflozin N=3131	Placebo N=3132
Age (years)	71.8 ± 9.6	71.5 ± 9.5	NT-proBNP when no AFF (ECG) (pg/ml)	729 [472, 1299]	704 [467, 1265]
Female Sex	43.6%	44.2%	NT-proBNP in AFF (ECG) (pg/ml)	1408 [956, 2256]	1387 [966, 2180]
Baseline LVEF (%)	54.0 ± 8.6	54.3 ± 8.9	Prior HF Hospitalization	40.6%	40.5%
LVEF < 60%	70.3%	69.3%	Atrial Fibrillation/Flutter at Enrollment	42.4%	42.1%
HF with Improved EF (Prior LVEF ≤ 40%)	18.3%	18.5%	Type 2 Diabetes	44.7%	44.9%
<u>Race</u>			eGFR (mL/min/1.73m <sup>2</sup> )	61.2 ± 19.0	60.9 ± 19.3
White	70.7%	71.0%	eGFR < 60 mL/min/1.73m <sup>2</sup>	48.4%	49.6%
Black	2.6%	2.5%			
Asian	20.1%	20.6%	<u>Medications</u>		
Other	6.6%	5.9%	Loop diuretics	76.7%	76.9%
<u>Geographic Region</u>			Renin-angiotensin-aldosterone system inhibitors(RAASi)	78%	77.4%
Europe and Saudi Arabia	47.7%	48.2%	Angiotensin converting enzyme inhibitors (ACEi)	36.5%	36.7%
Asia	19.4%	19.8%	Angiotensin receptor blocker (ARB)	36.2%	36.4%
Latin America	19.2%	18.5%	Sacubitril-valsartan	5.3%	4.3%
North America	13.7%	13.5%	β-blocker	82.8%	82.5%
<u>NYHA Class at Baseline</u>			Mineralocorticoid receptor antagonist (MRA)	42.8%	42.4%
II	73.9%	76.6%			
III/IV	26.1%	23.4%			
KCCQ Total Symptom Score	70 ± 23	70 ± 22			



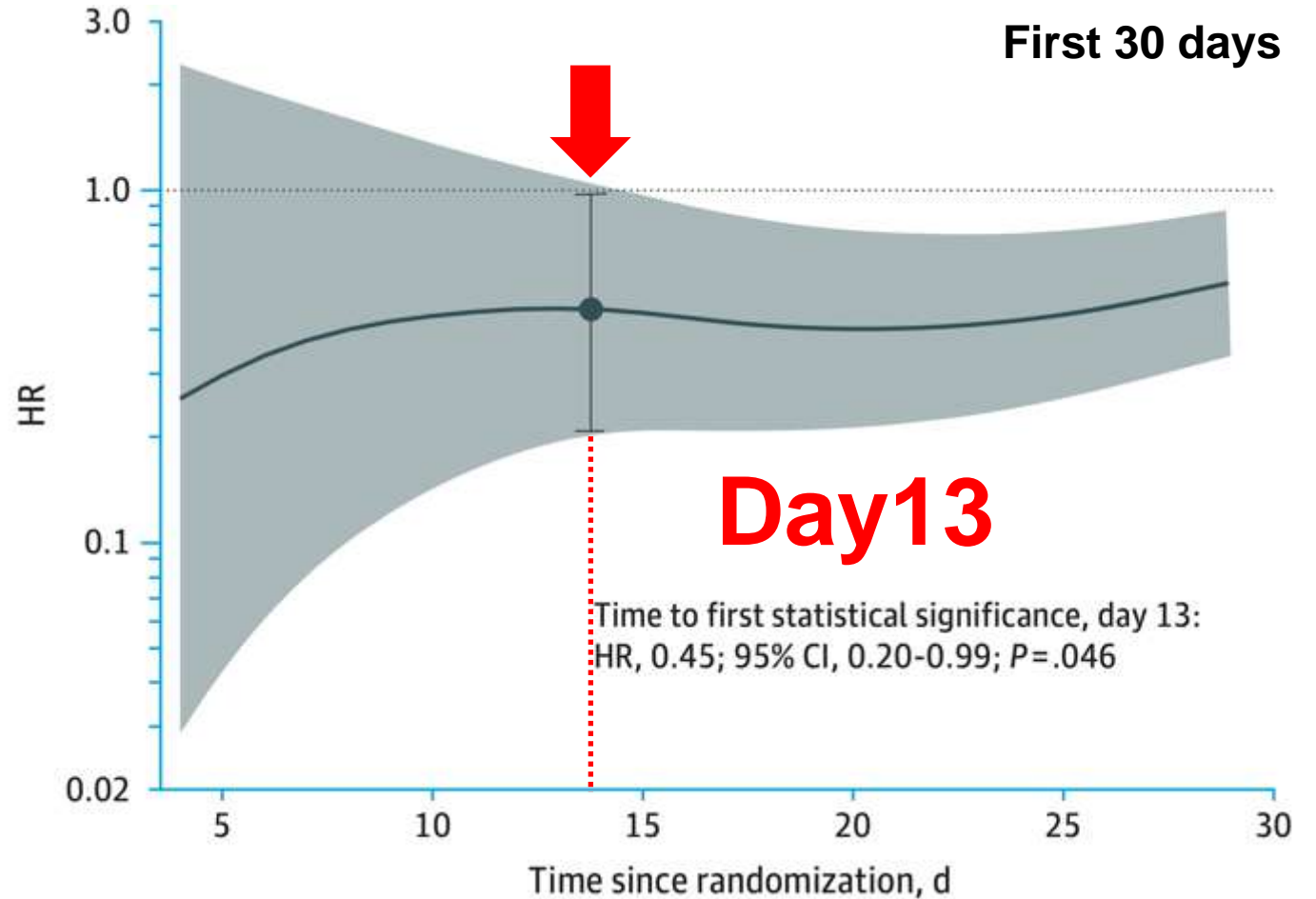
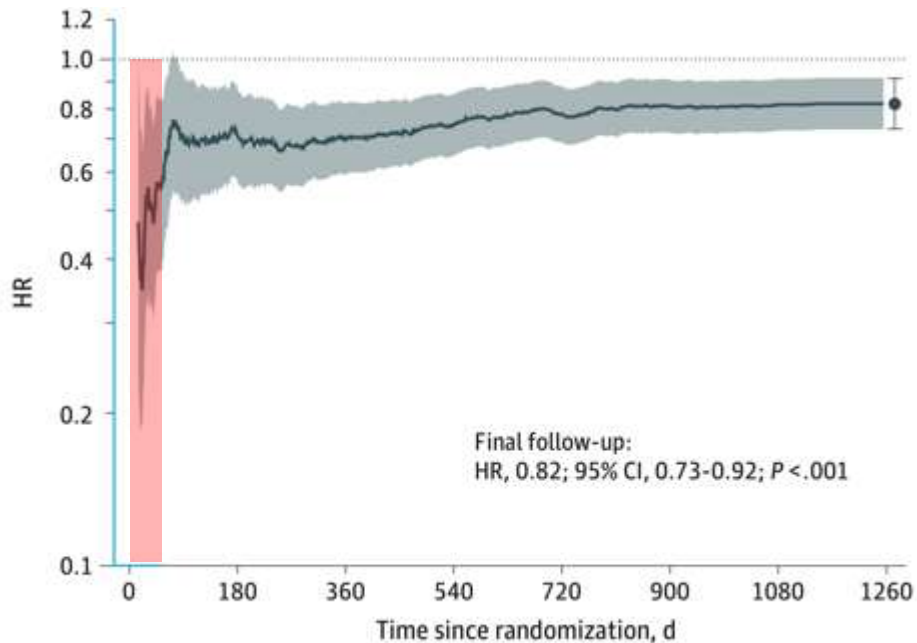
# Primary Endpoint: CV Death or Worsening HF

Full Population



# Time to First Nominal Statistical Significance Reached by Day 13

**Primary endpoint**  
CV death or Worsening HF events



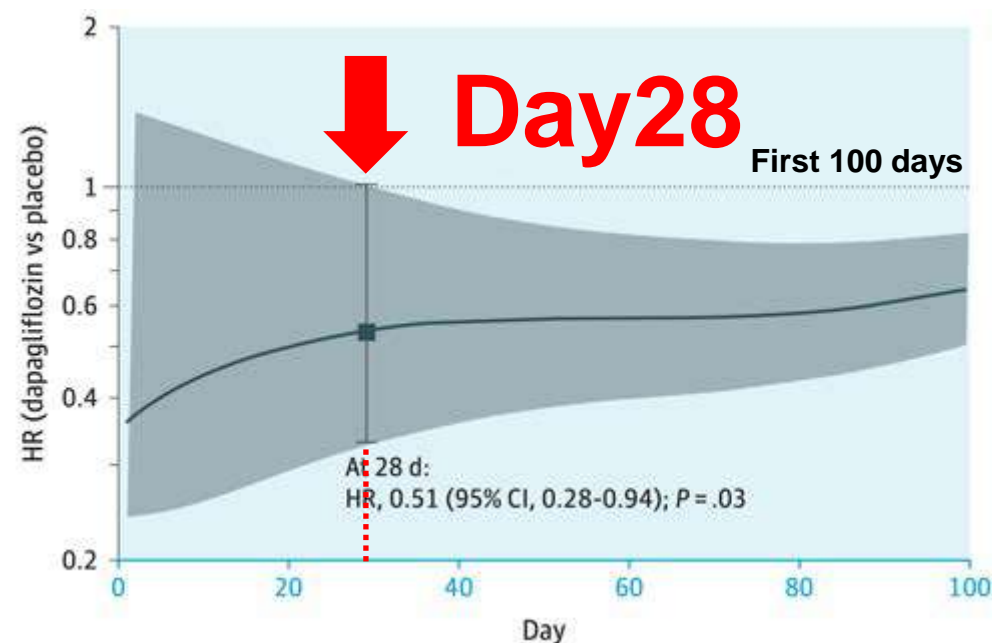
**Significance was sustained from day 15 onwards**

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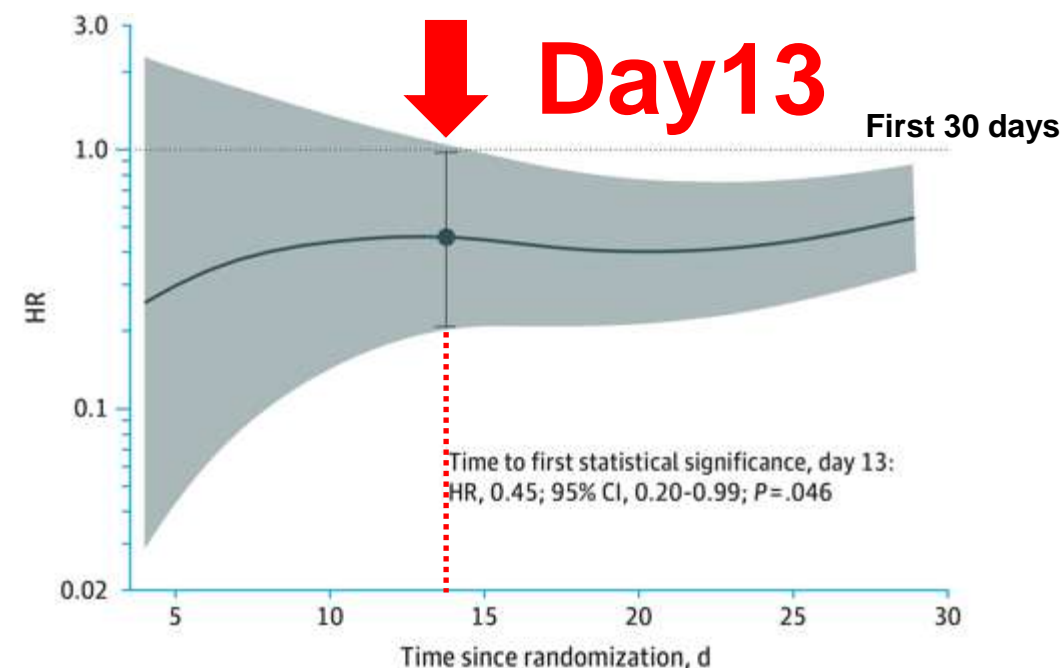
# Time to Clinical Benefit of Dapagliflozin in HF trials



CV death or Worsening HF events



CV death or Worsening HF events



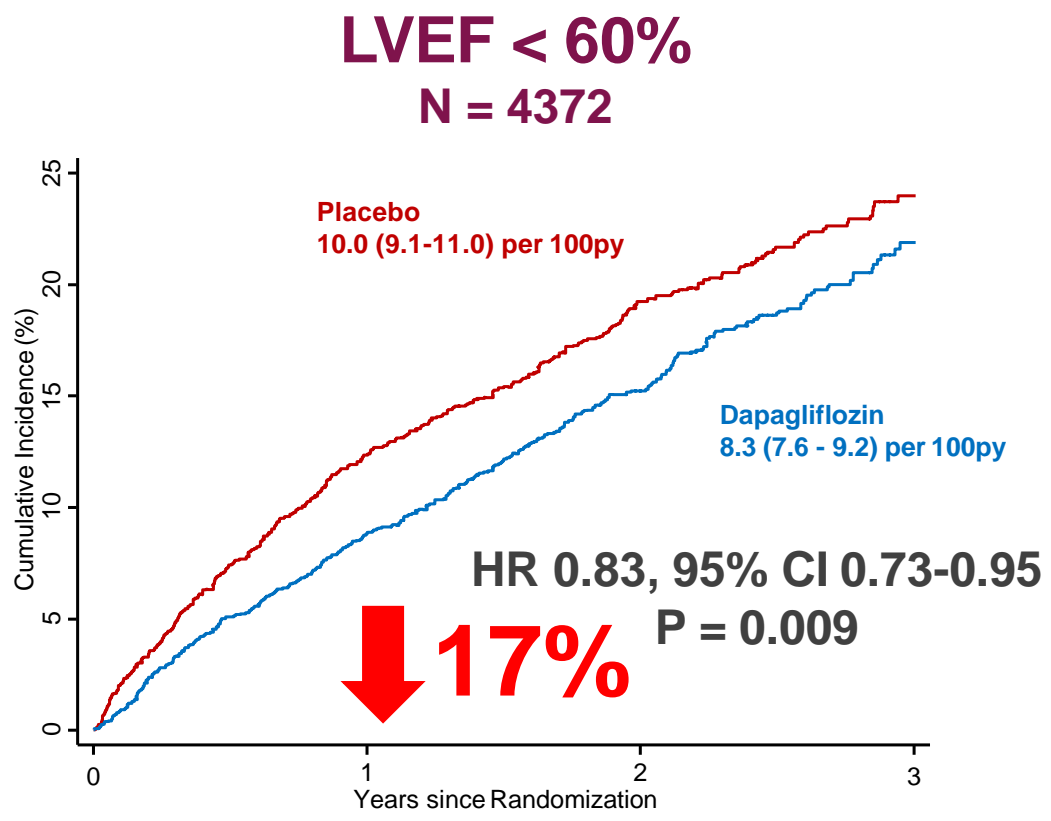
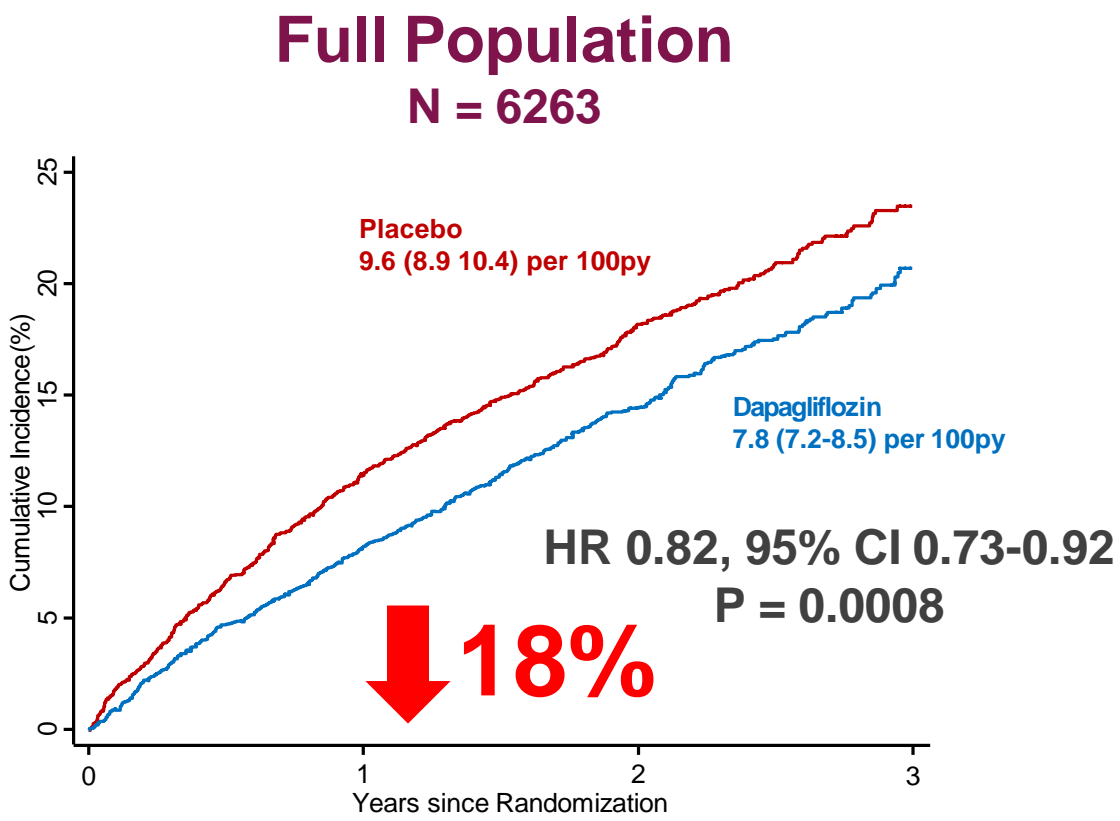
Early and sustained reduction in clinical event in patient with HF

JAMA Cardiology



# Primary Endpoint in Full Population and LVEF < 60%

## Dual Primary Analyses



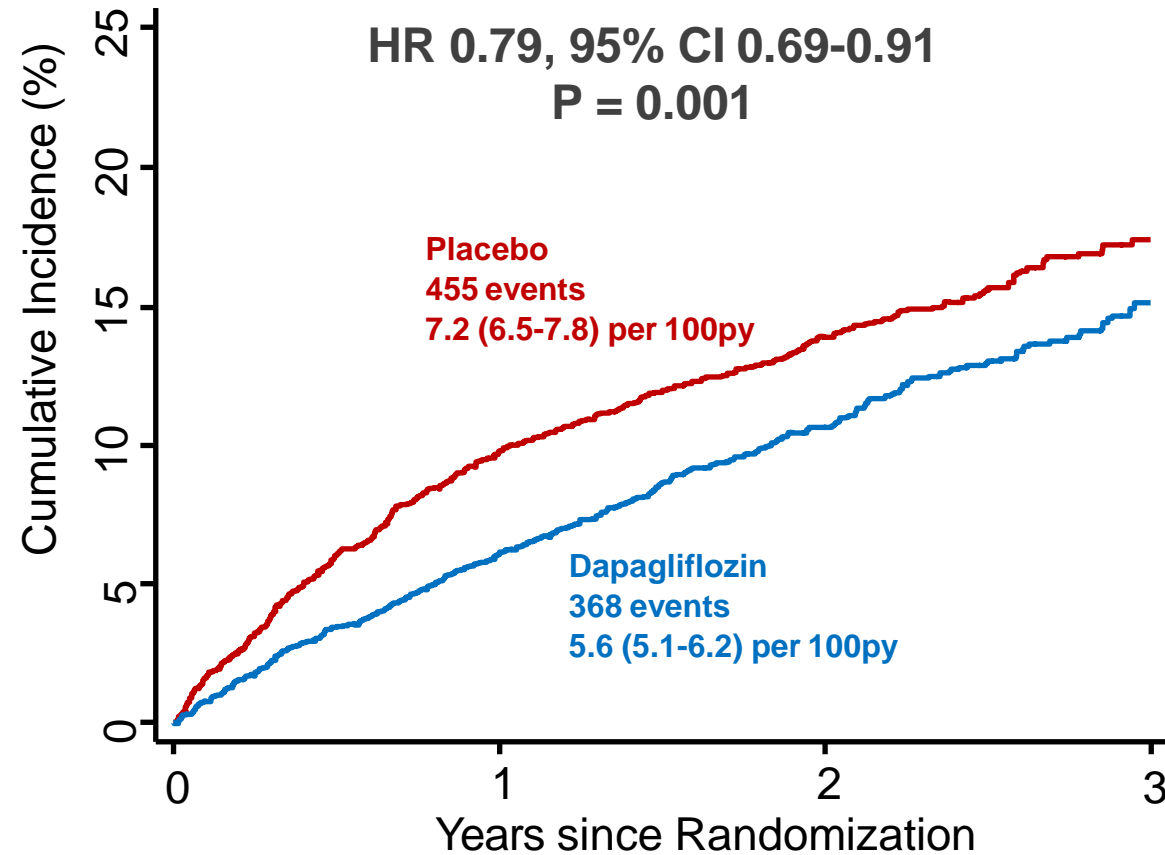
Consistency in full population and LVEF <60%

# Components of Primary Endpoint

## Full Population

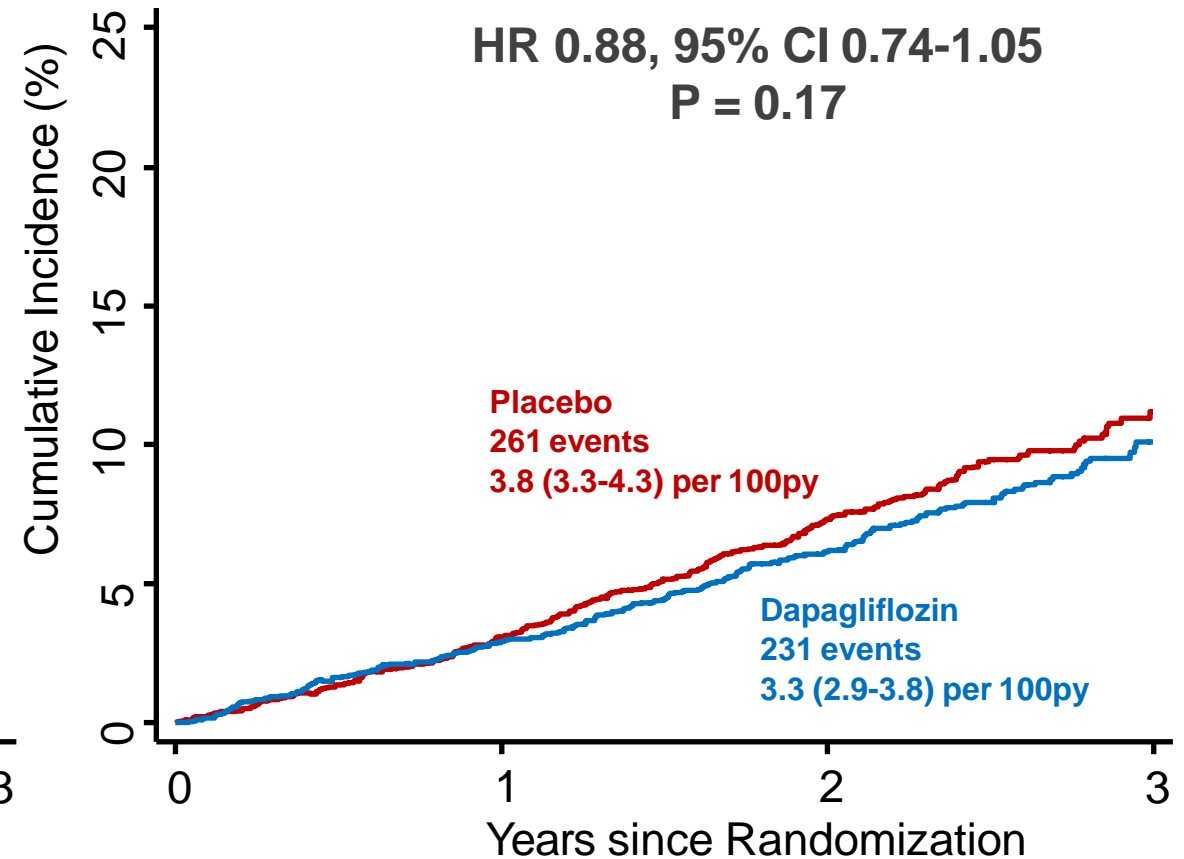
### Worsening Heart Failure (HF Hospitalization + Urgent HF Visit)

HR 0.79, 95% CI 0.69-0.91  
P = 0.001

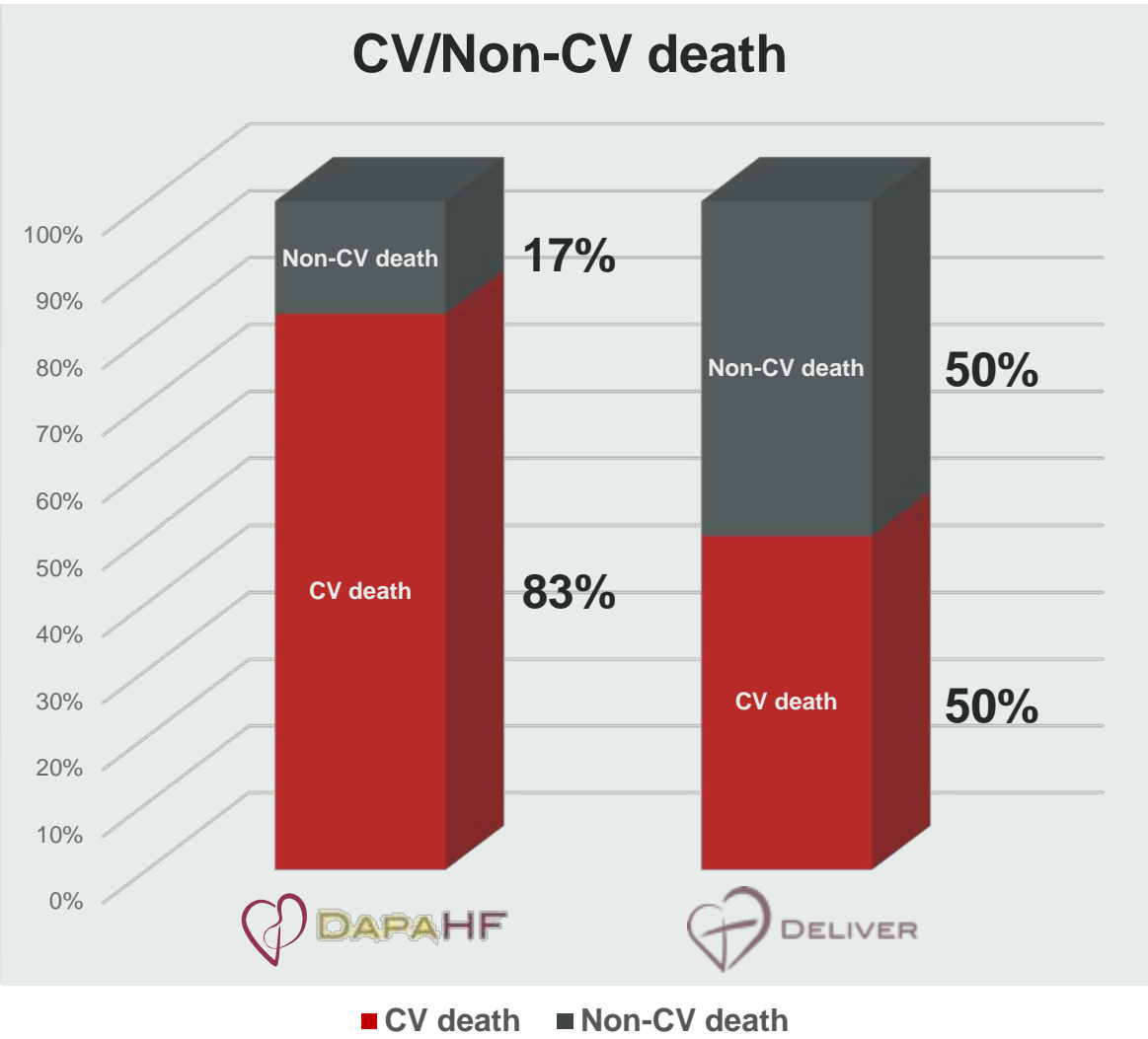
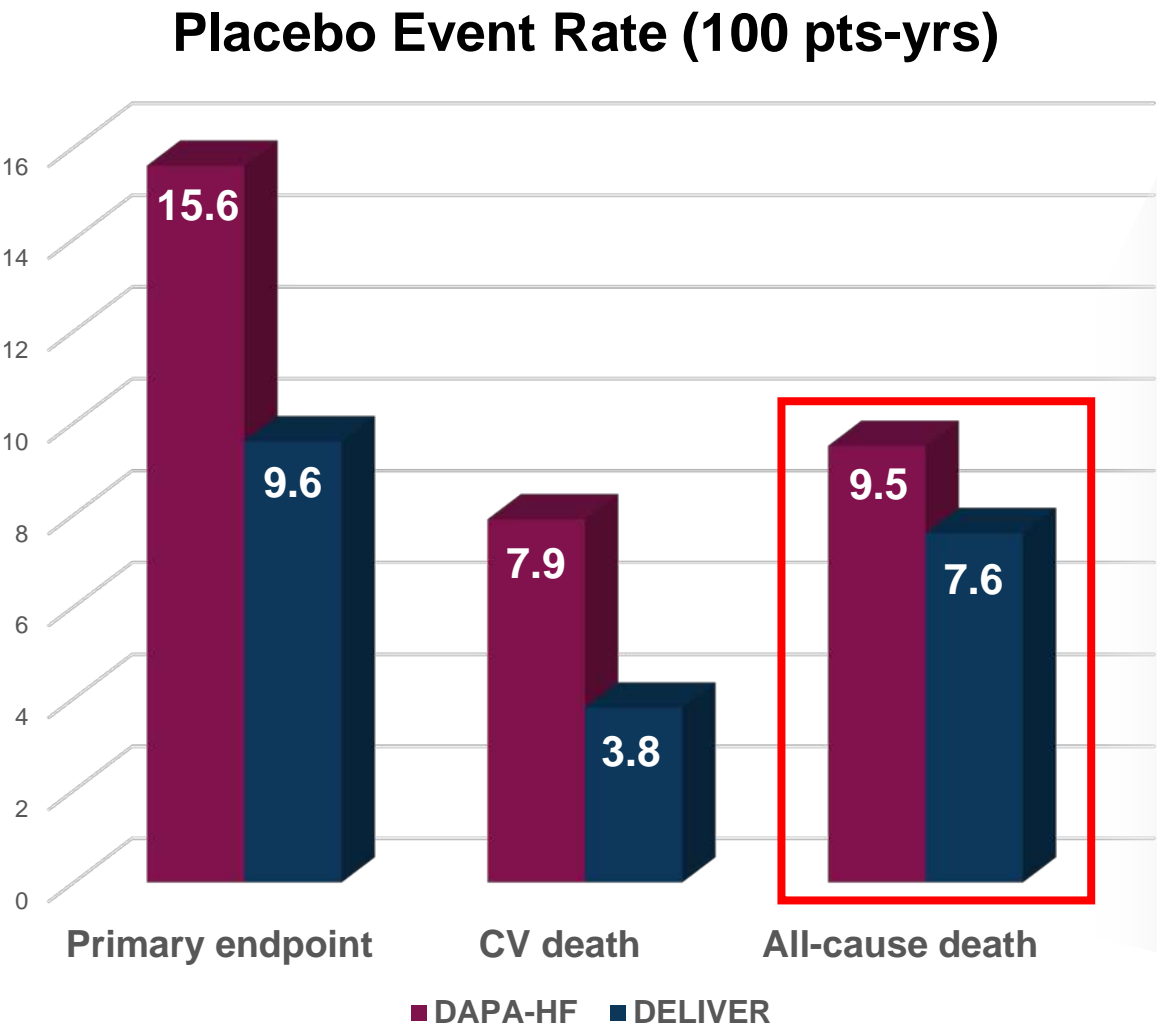


### Cardiovascular Death

HR 0.88, 95% CI 0.74-1.05  
P = 0.17



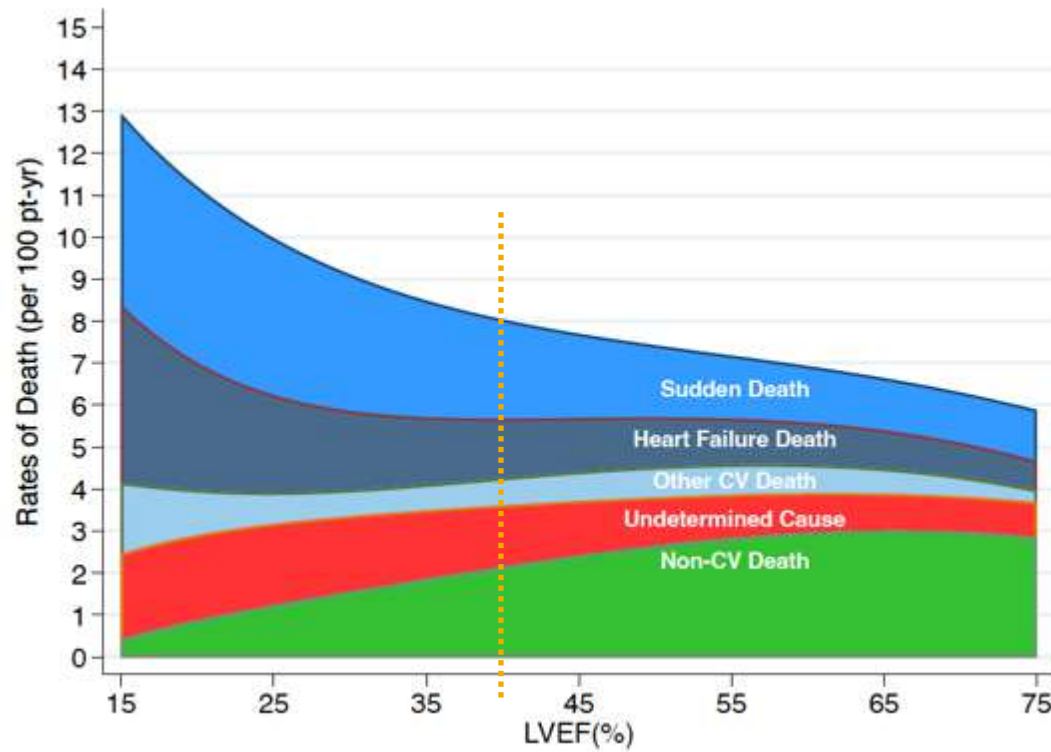
# Placebo Event Rate: Comparison of DAPA-HF and DELIVER



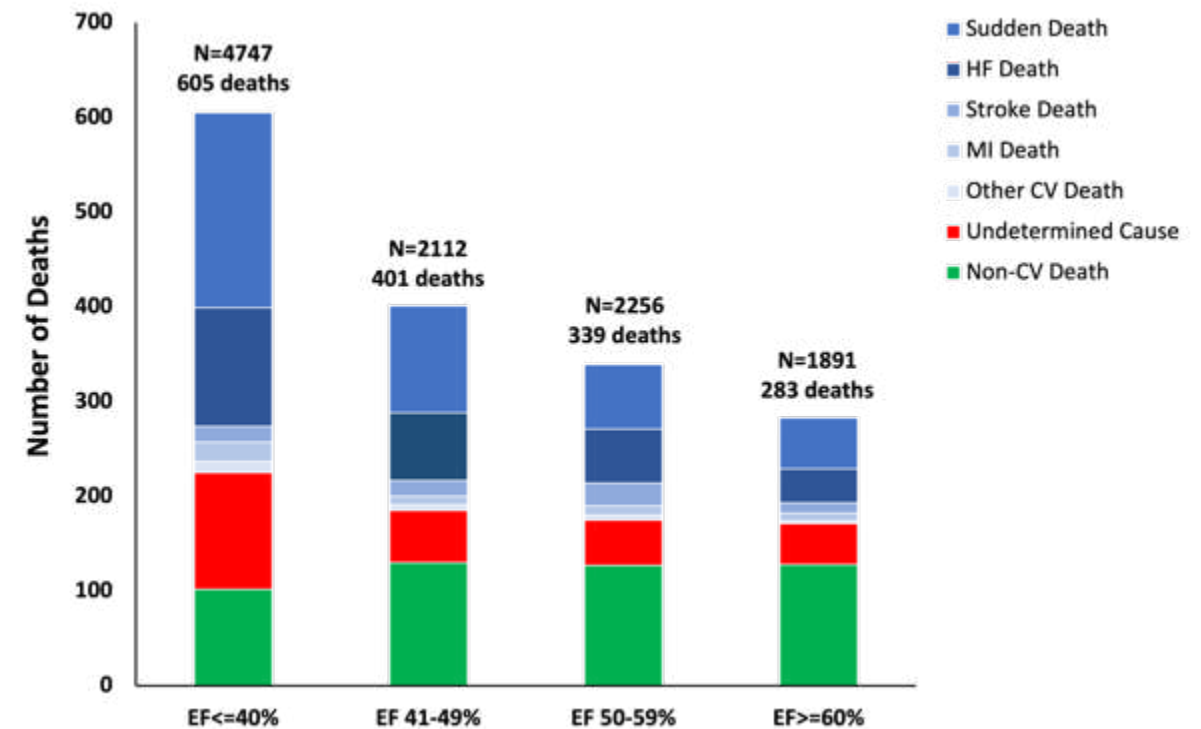


# Mode of Death by Cause in DAPA-HF & DELIVER

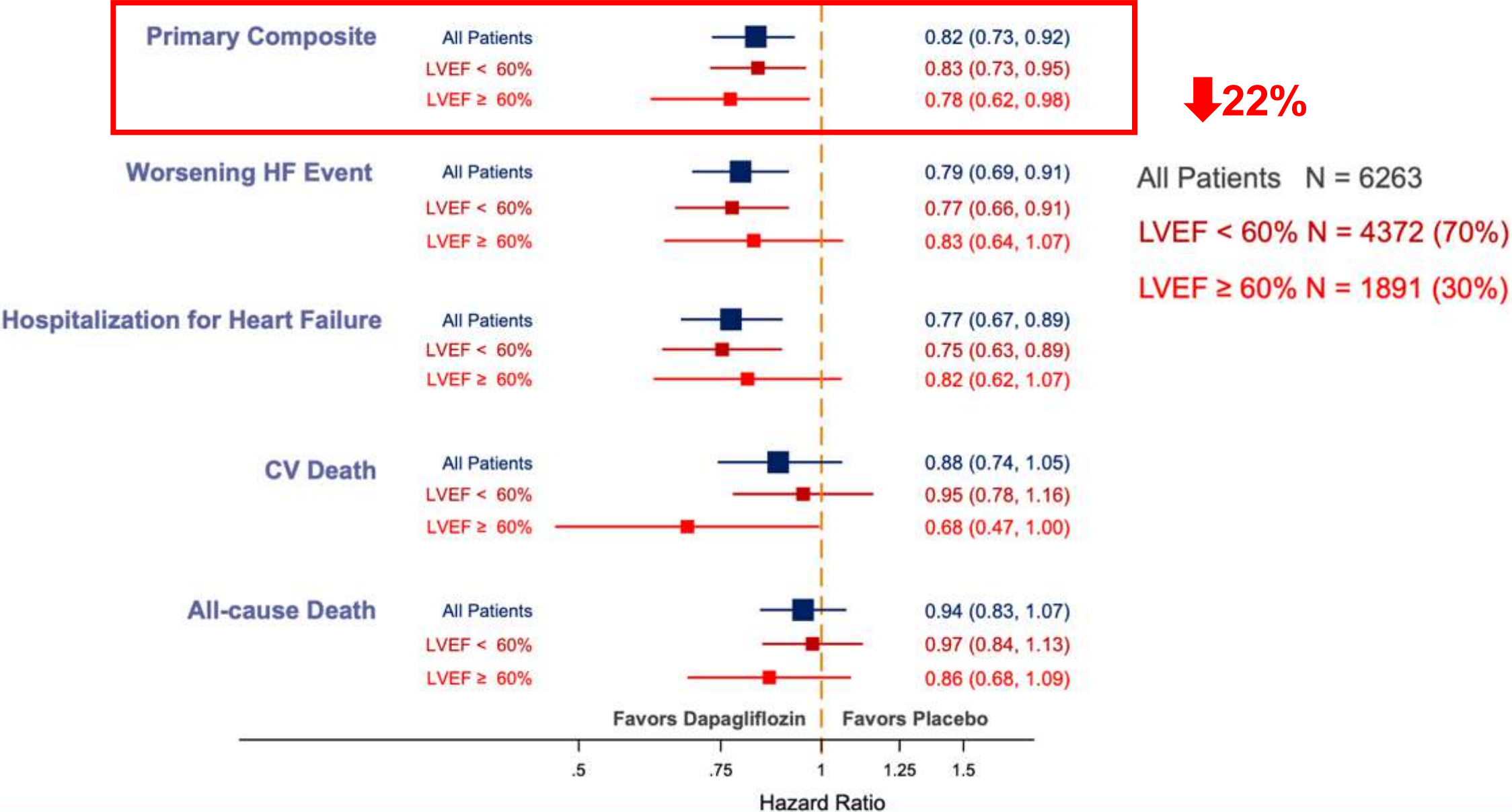
## Variation in incidence rates of death by cause and continuous LVEF



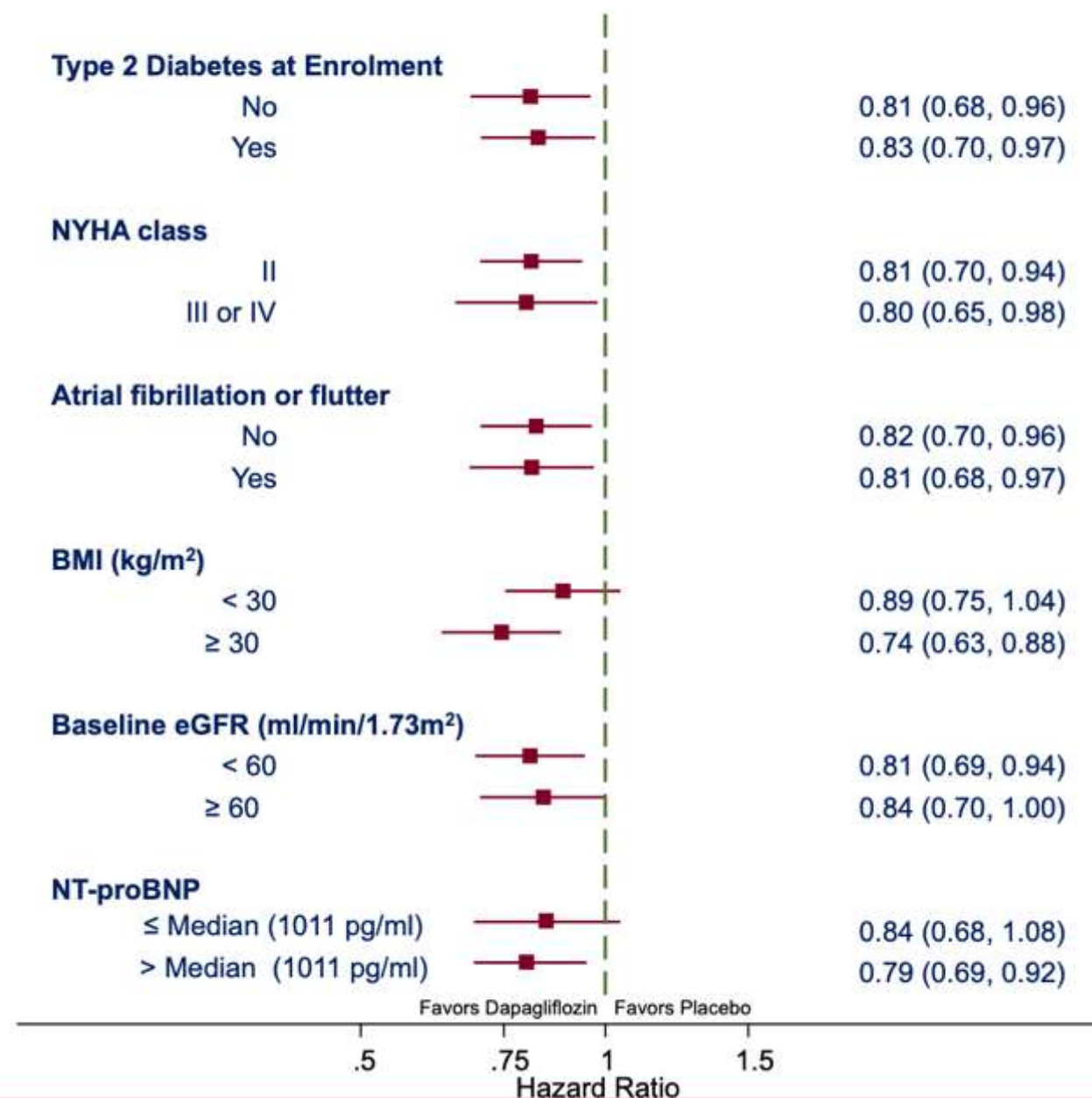
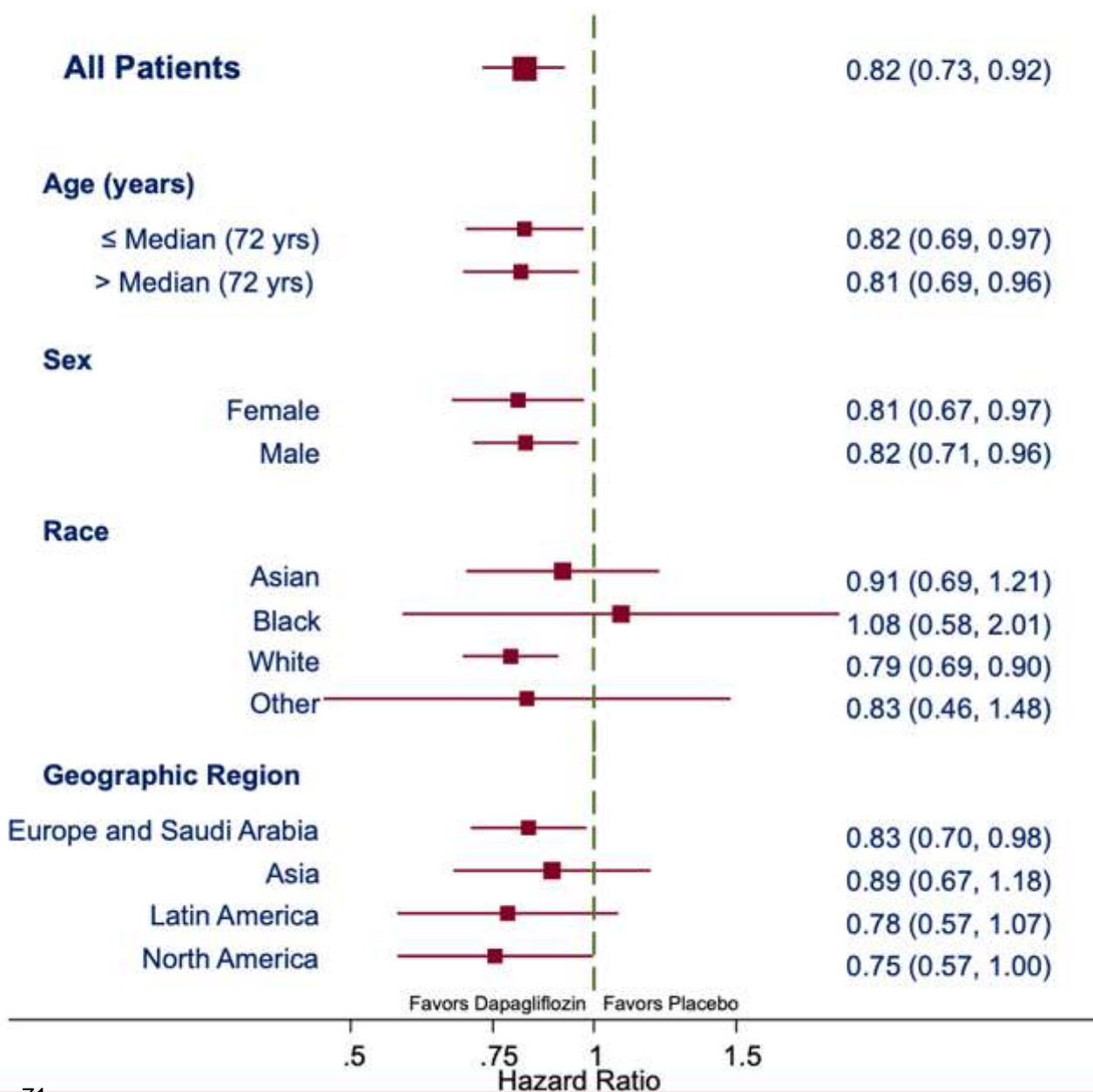
## Number of deaths by adjudicated cause and EF category



# Outcomes by LVEF < 60% or LVEF ≥ 60%

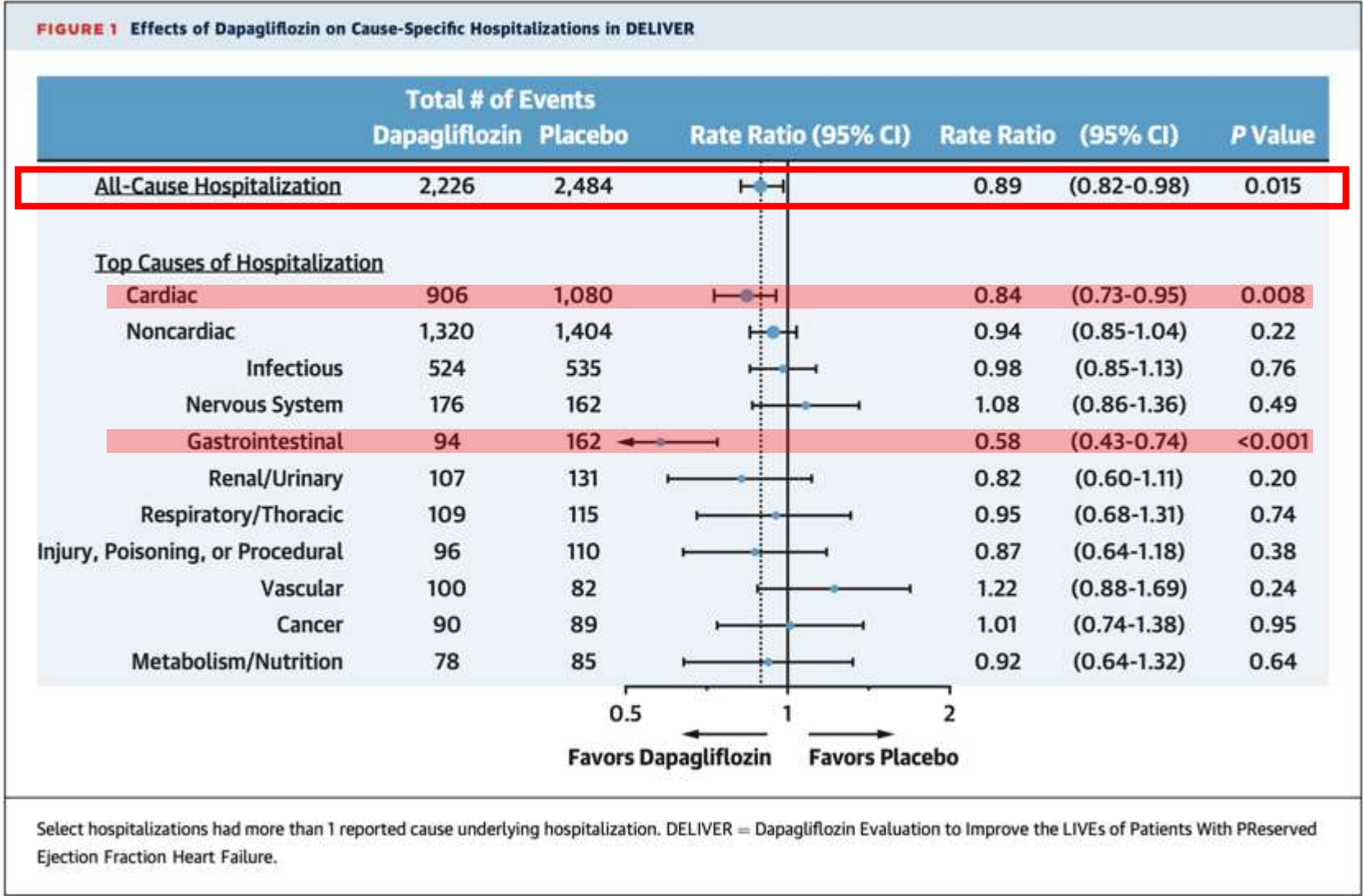



# Primary Endpoint in Prespecified Subgroups





# DELIVER trial: Dapagliflozin Significantly Reduce All-Cause Hospitalization

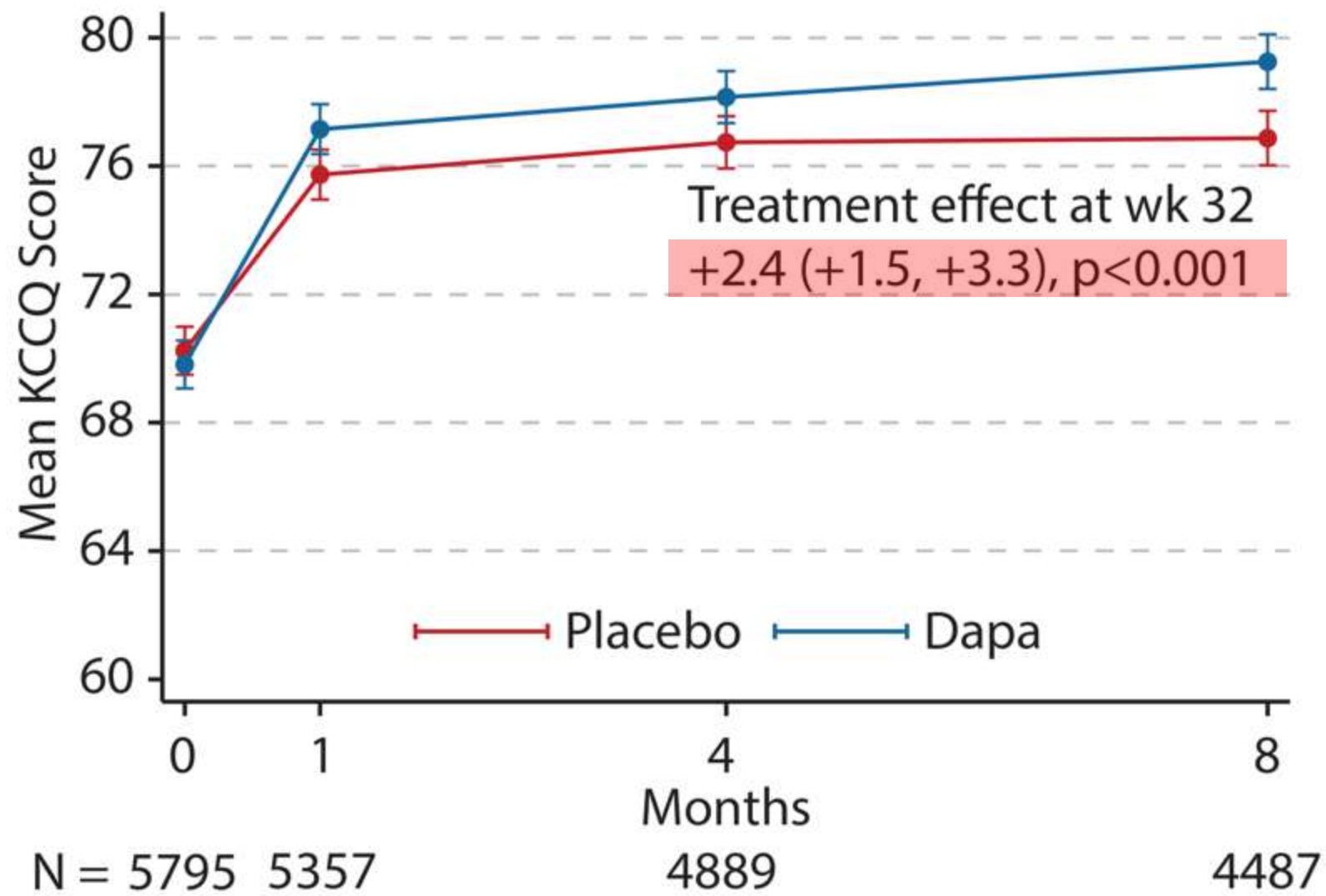


 **11%**  
**NNT = 26 patient-years**



**JACC**  
Journals

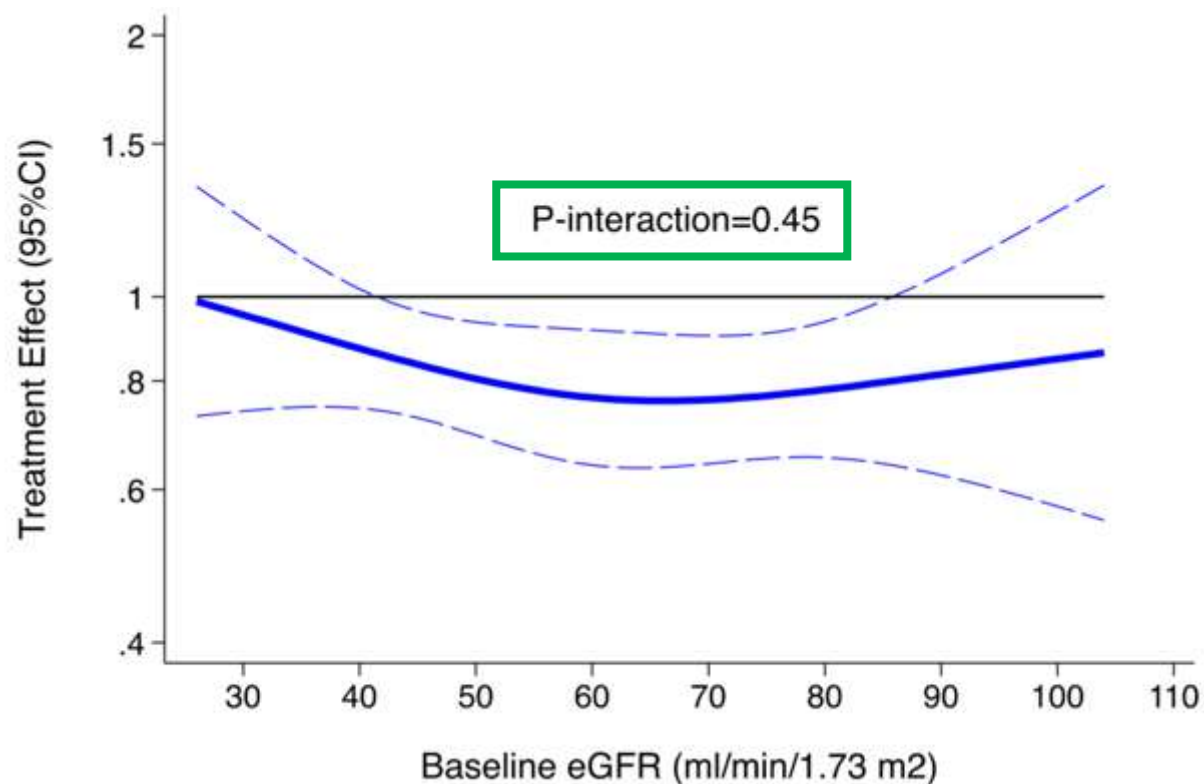
# Change in KCCQ-Total Symptom Score Over Time by Treatment Allocation



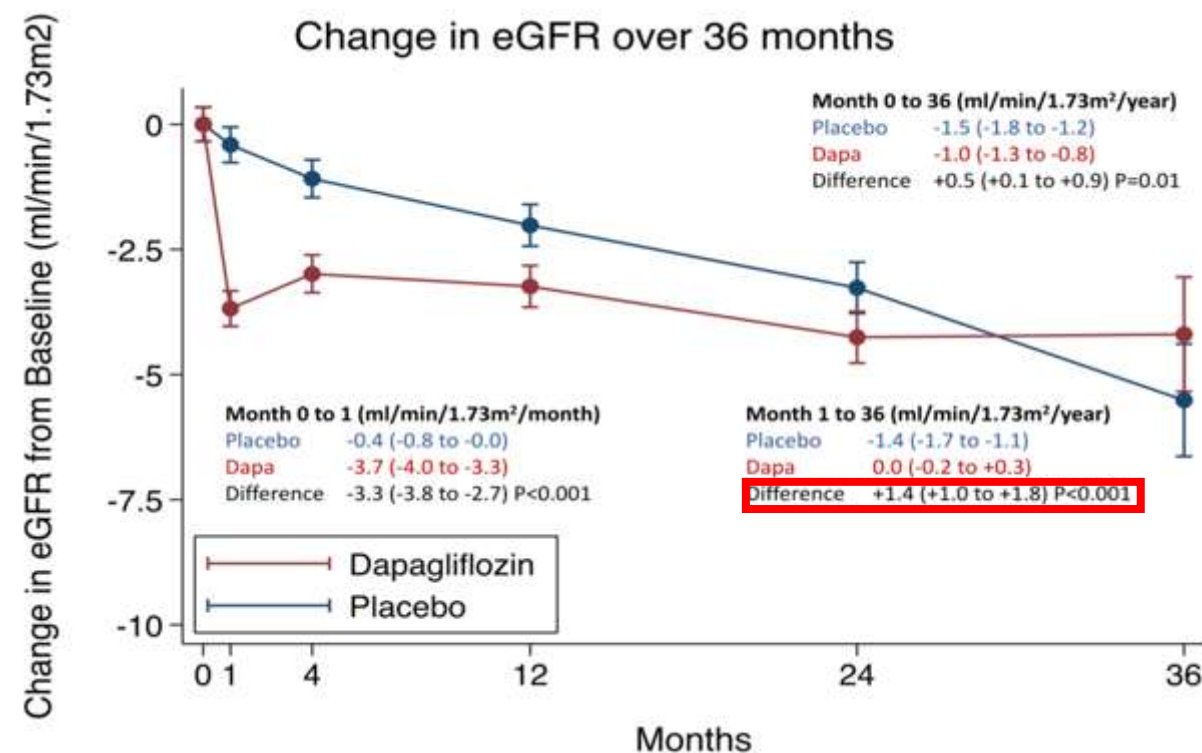
# Key Result From DELIVER:

Consistent Efficacy Regardless Baseline eGFR and Slow the Rate of Decline in eGFR

## CV Outcome By Baseline eGFR



## eGFR slope



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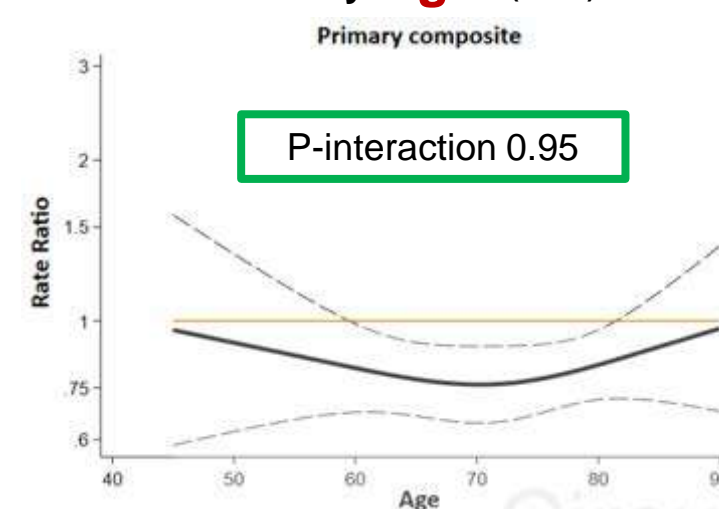
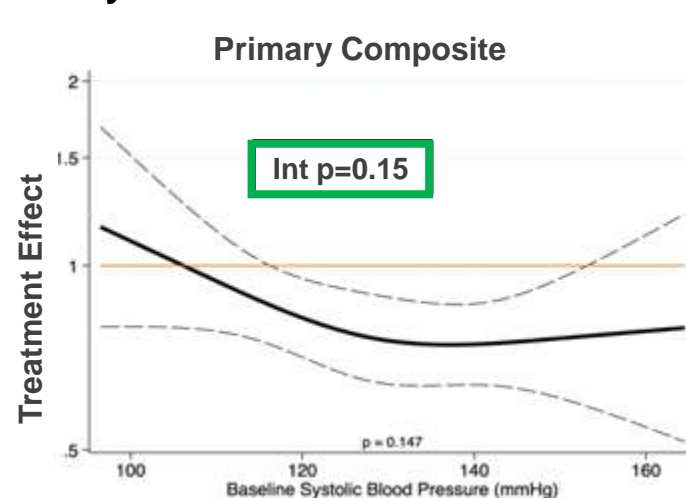
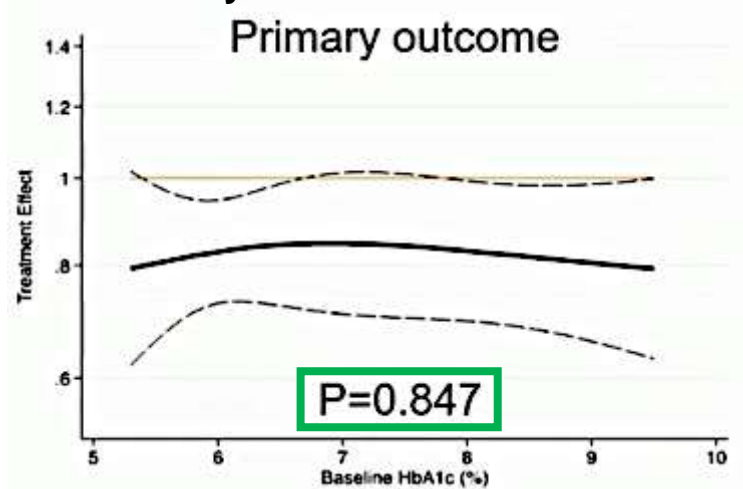
# Consistency Benefit Across Broad Patient Profile



By Baseline **HbA1C**<sup>1</sup>

By Baseline **Blood Pressure**<sup>2</sup>

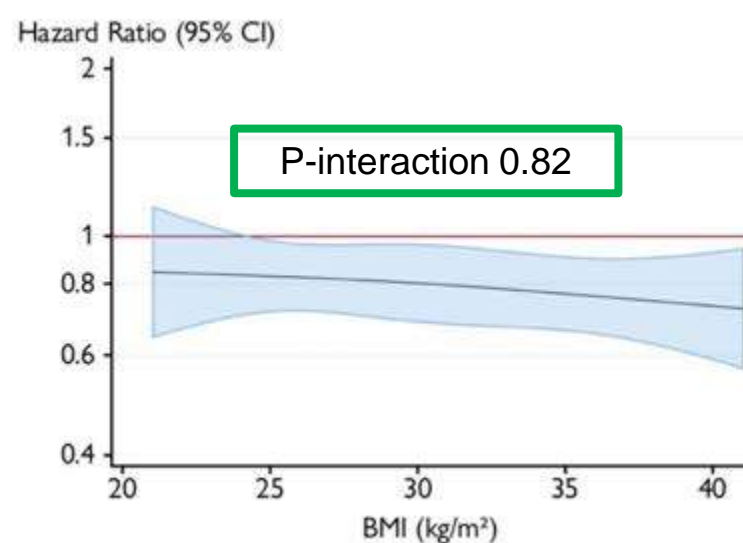
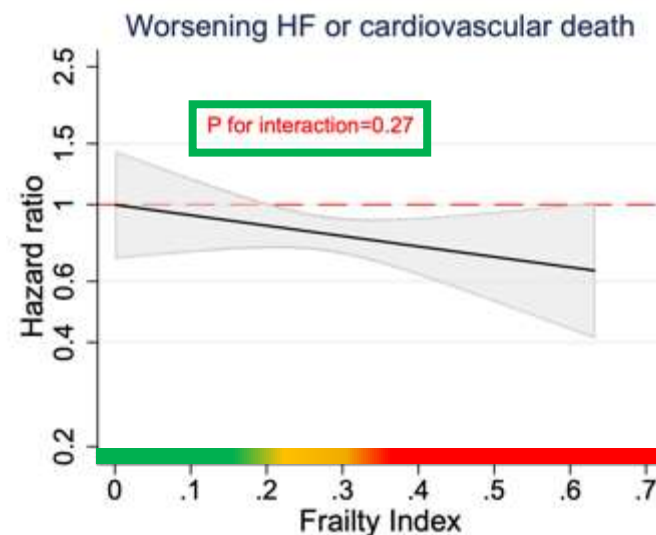
By **Age**<sup>3</sup> (40-99)



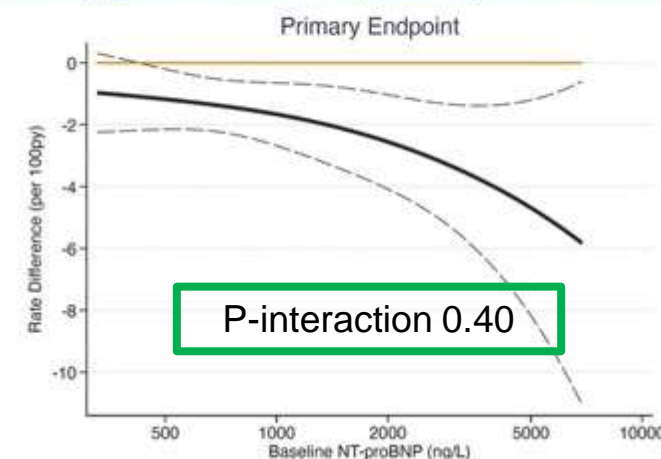
By **Frailty Index**<sup>4</sup>

By Baseline **BMI**<sup>5</sup>

By Baseline **NT-proBNP**<sup>6</sup>



Greater absolute benefits with dapagliflozin among patients with higher NT-proBNP levels



1. Lancet Diabetes Endocrinol. 2022 Nov 10;S2213-8587(22)00308-4. 2. J Am Coll Cardiol HF. Oct 02, 2022. Epub ahead of print. 3. Circulation. 2022 Aug 27. Online ahead of print.

4. Circulation. 2022 Aug 27. Online ahead of print. 5. Eur Heart J. 2022 Aug 27;ehac481. Online ahead of print. 6. J Am Coll Cardiol HF. Aug 27, 2022. Epub ahead of print.

# DELIVER analysis: Result according to Frailty Status



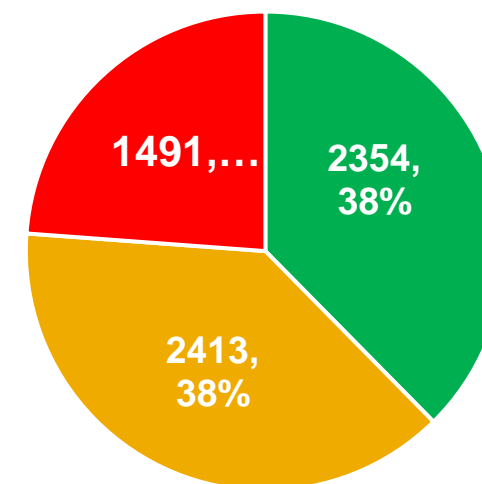
## Frailty Assessment (30 Items frailty index [FI])

共病症			生命徵象	實驗室檢驗	生活品質
心肌梗塞	節律器	昏厥	BMI	肌酸酐	自我照護
PCI or CABG	第二型糖尿病	睡眠呼吸中止	收縮壓		平常活動度
心絞痛	痛風	神經病變	舒張壓		疼痛/不適
周邊動脈疾病	腦中風	骨質疏鬆	脈壓		焦慮/憂鬱
心房顫動/撲動	癌症	高血脂			行動
心臟瓣膜疾病	慢性腎臟病	高血壓			
肺栓塞疾病	慢性肺阻塞疾病				

## Classification:

- **Not frail (FI ≤0.210)**
- **More frail (FI 0.211-0.310)**
- **Most frail (FI ≥0.311)**

■ Not frail ■ More Frail ■ Most frail

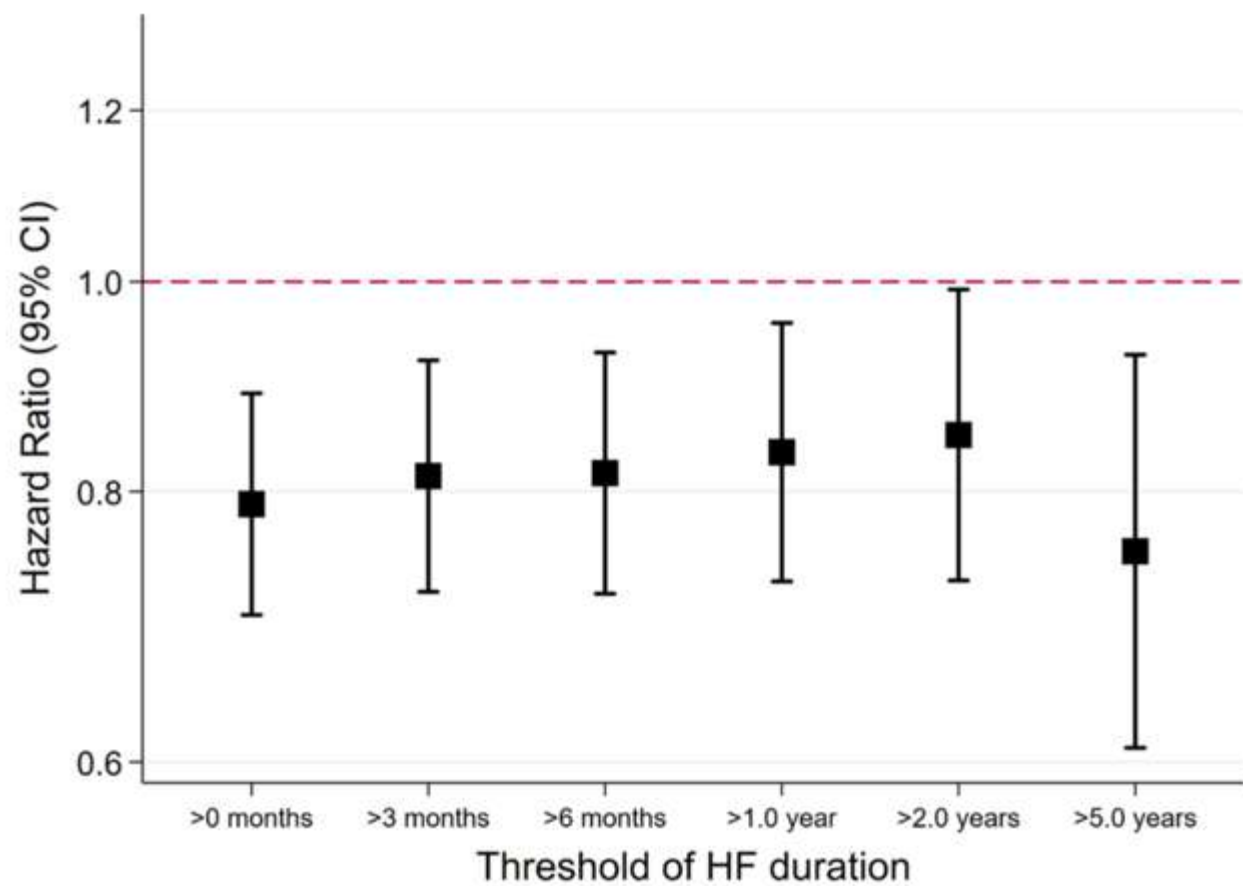


**Circulation**

- FI: Number of health deficits present / Number of health deficits measured

# Effect of Dapagliflozin on Primary Outcome According to **Threshold Duration of HF** in DELIVER Trial

It is **NEVER TOO EARLY** or **TOO LATE** to **START TREATMENT** in patients who have had a diagnosis of HF for some time and who may be considered “stable” survivors.

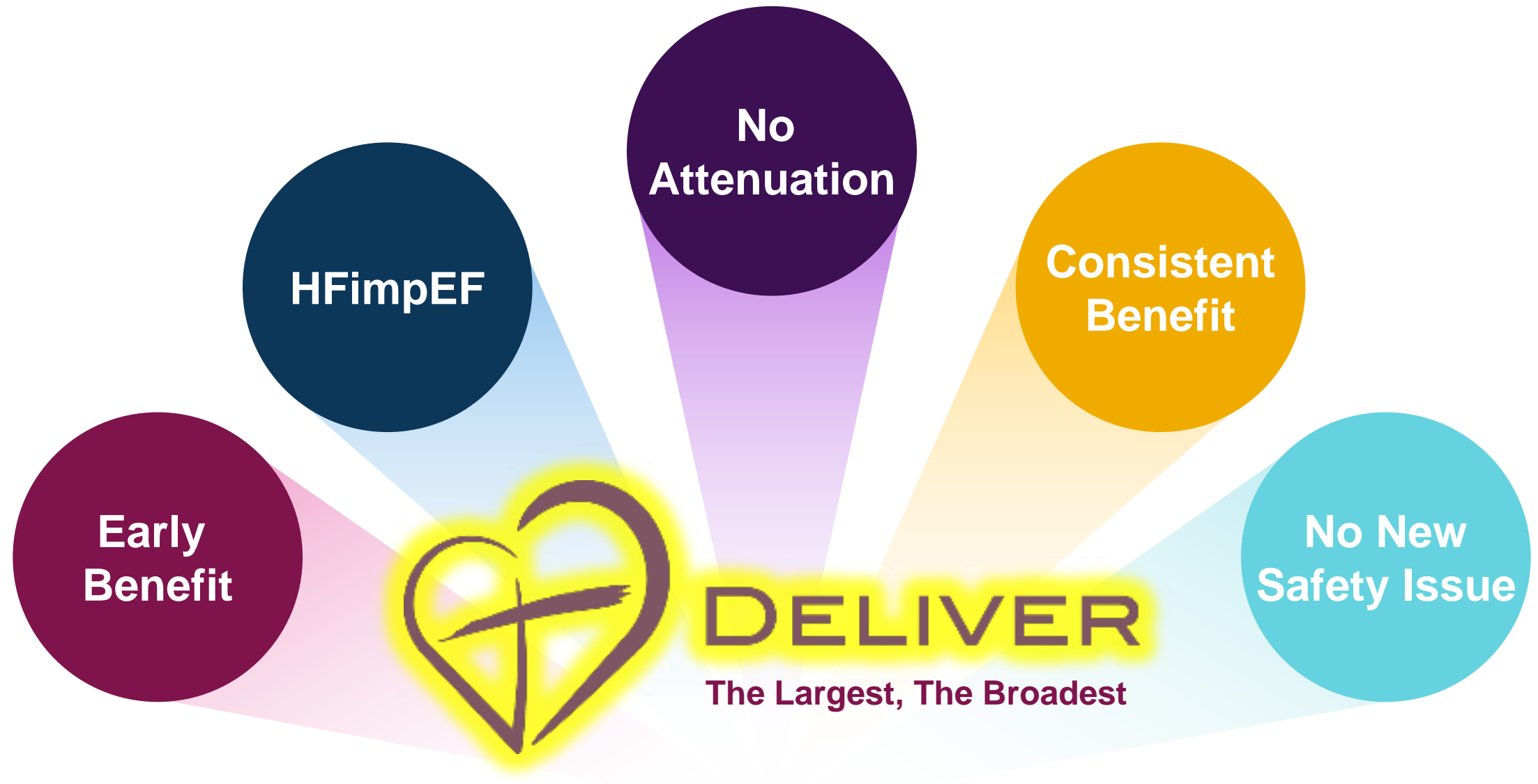


# Dapagliflozin was Well Tolerated in Patients Without T2D

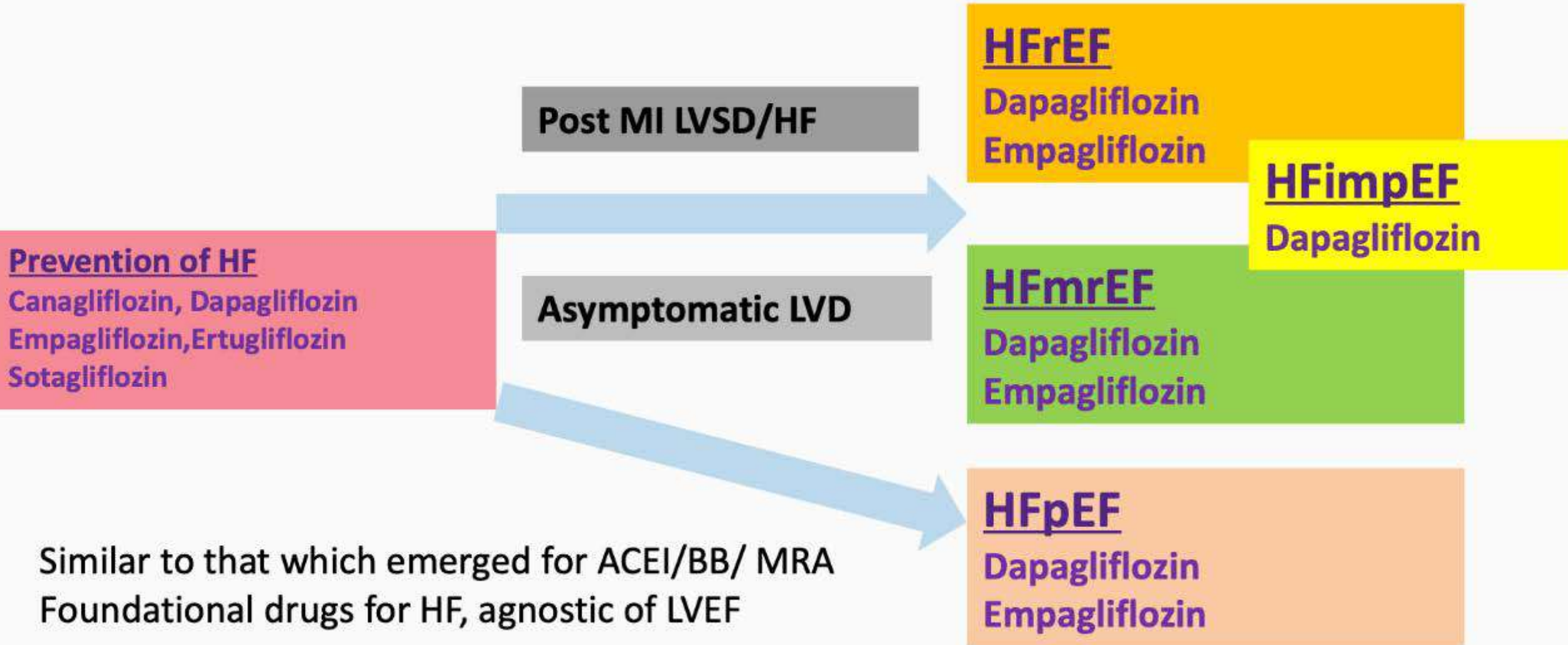


	T2D (45%)		No T2D (55%)		T2D (68%)		No T2D (32%)		T2D (50%)		No T2D (50%)	
Event,%	DAPA 10 mg (N=1075)	Placebo (N=1064)	DAPA 10 mg (N=1298)	Placebo (N=1307)	DAPA 10 mg (N=1453)	Placebo (N=1450)	DAPA 10 mg (N=696)	Placebo (N=699)	DAPA 10 mg (N=1576)	Placebo (N=1567)	DAPA 10 mg (N=1548)	Placebo (N=1558)
Any serious AE	41.7	48.3	34.6	36.9	33.2	38.8	21.6	23.9	45.9	49.1	41.2	41.8
AE leading to treatment discontinuation	4.0	5.4	5.3	4.5	5.6	6.5	5.2	4.1	5.3	5.9	6.3	5.6
AE of interest												
Volume depletion	7.8	7.8	7.3	6.1	6.3	4.9	5.0	2.7	1.3	0.8	1.4	1.2
Kidney AE	8.5	8.7	4.8	6.0	8.3	10.2	4.9	5.7	2.9	2.9	1.7	2.1
Fracture	2.1	2.4	2.1	1.9	4.5	3.5	2.9	2.6	NA	NA	NA	NA
Amputation	1.1	0.8	0.1	0.2	2.4	2.6	0	0.1	1.0	1.3	0.3	0.3
Major hypoglycemia	0.4	0.4	0	0	1.0	1.9	0	0	0.4	0.4	0	0
Diabetic ketoacidosis	0.3	0	0	0	0	0.1	0	0	0.1	0	0	0

# Five Strength that Make DELIVER Trial So Unique



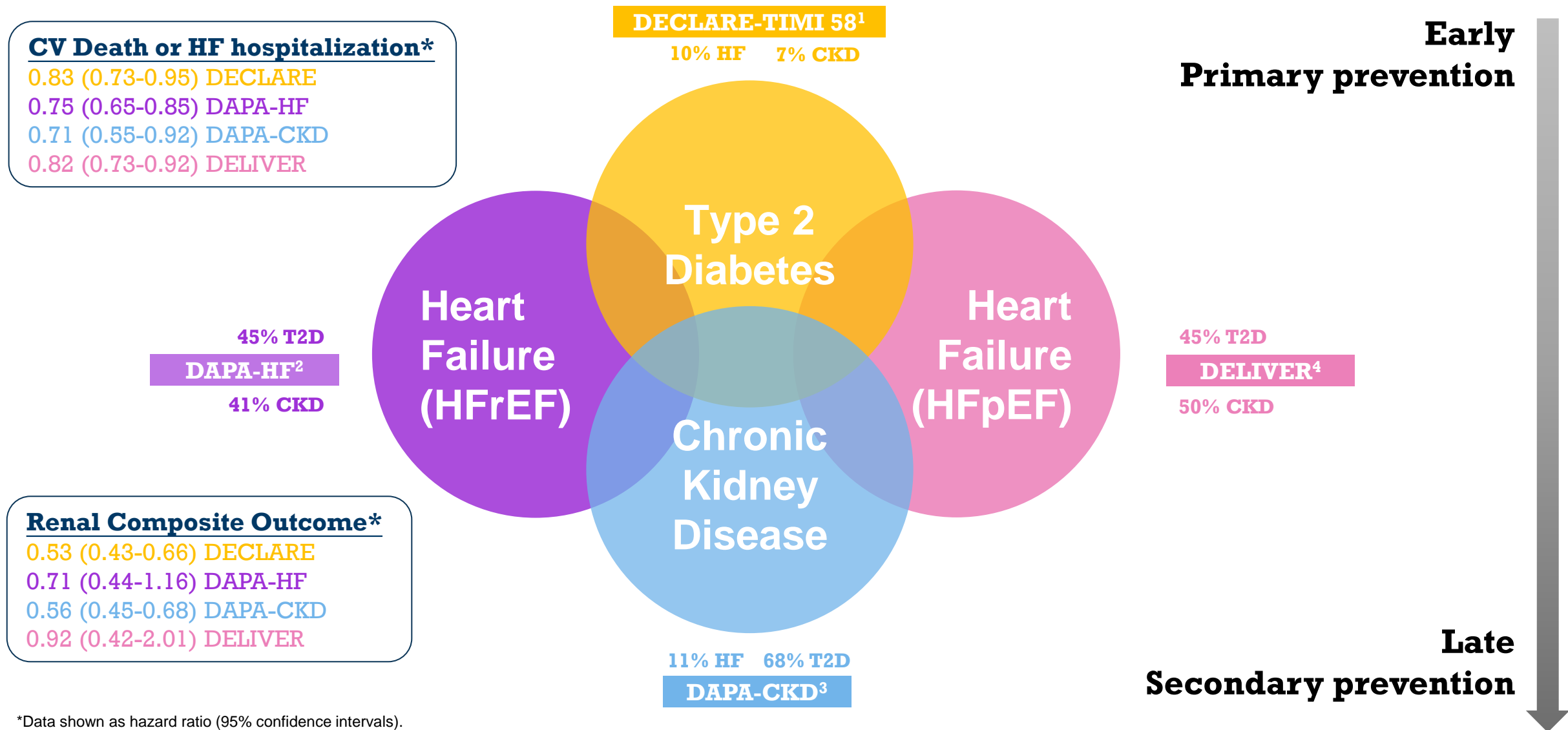
# Consistency Across the CHF Spectrum



Similar to that which emerged for ACEI/BB/ MRA  
Foundational drugs for HF, agnostic of LVEF



# Multiverse of SGLT2i, dapagliflozin

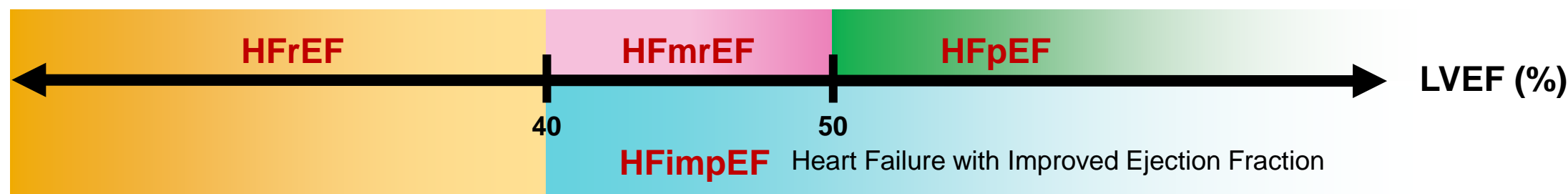


\*Data shown as hazard ratio (95% confidence intervals).

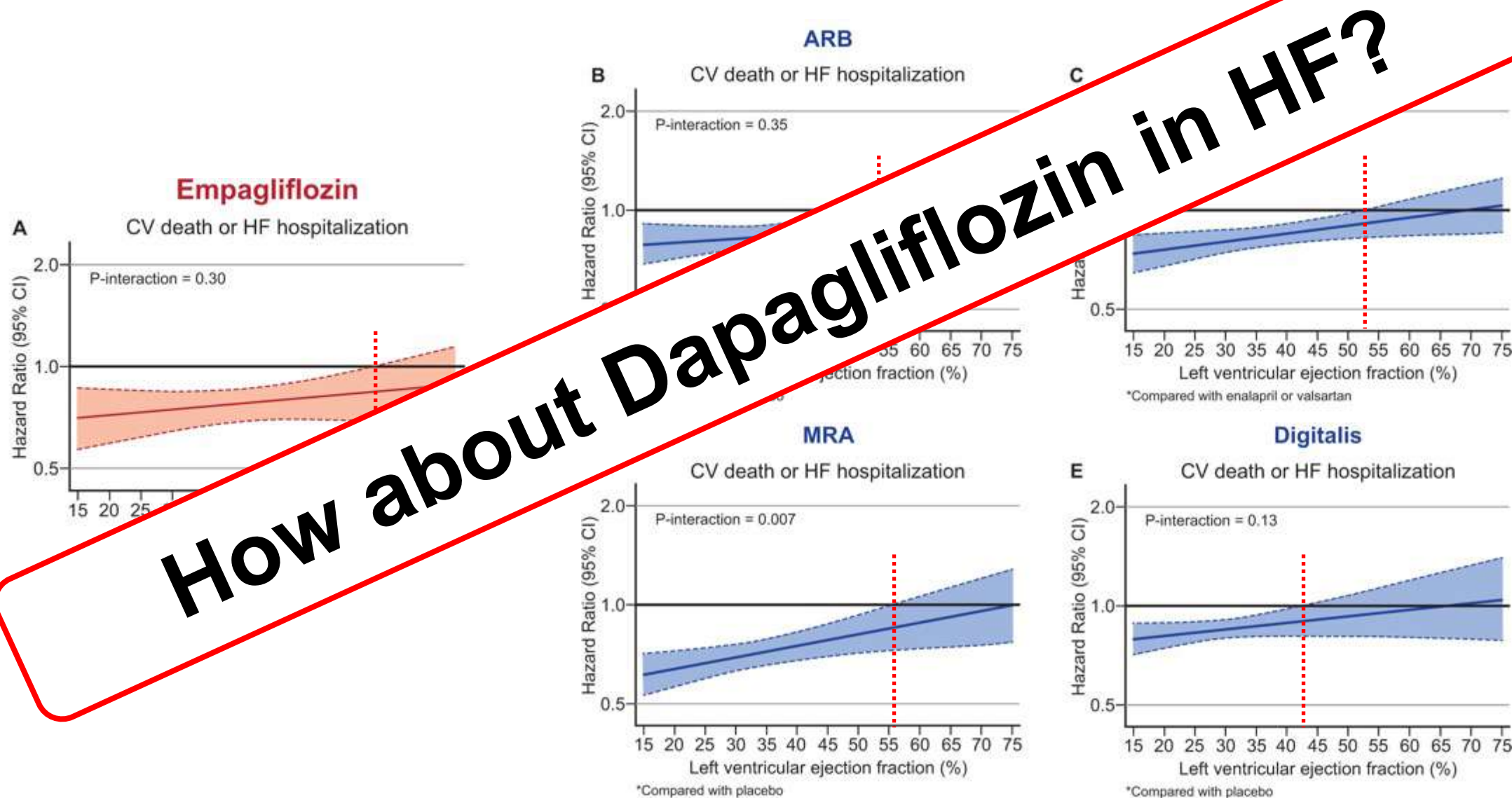
1. Wiviott SD, et al. N Engl J Med 2019; 380:347-357; 2. McMurray JJV, et al. N Engl J Med 2019; 381:1995-2008;

3. Heerspink HJL, et al. N Engl J Med 2020; 383:1436-1446. 4. Solomon, S.D. et al. N Engl J Med. 2022 Aug 27. doi: 10.1056/NEJMoa2206286.

# DAPA-HF + DELIVER Pooled Analysis



# Treatment Effect by Ejection Fraction

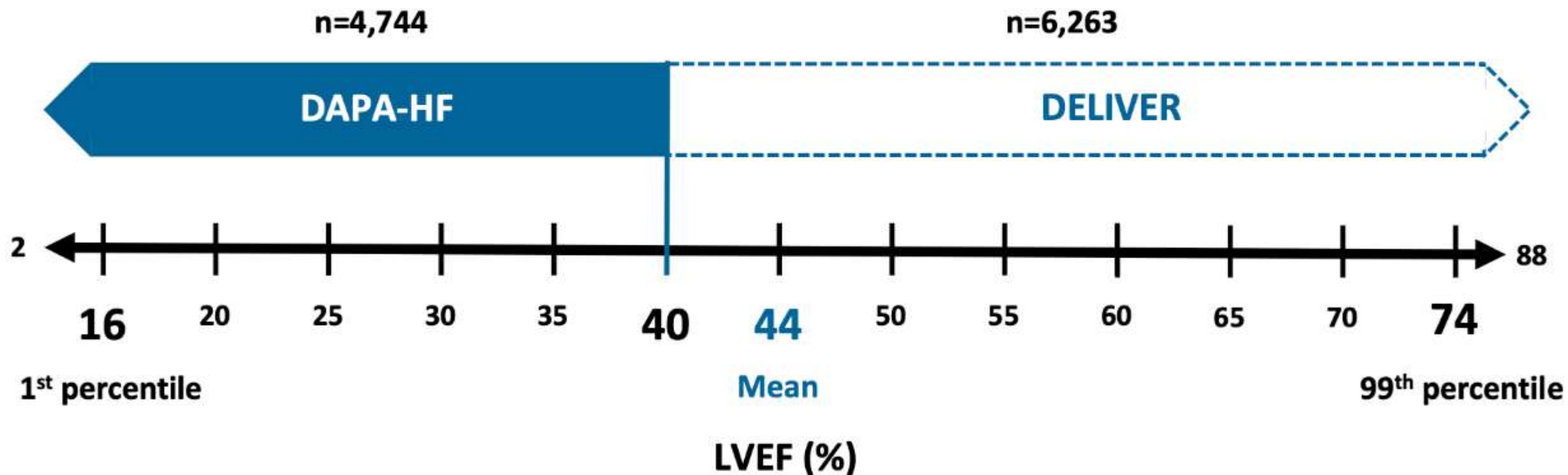


# DAPA-HF and DELIVER pooled dataset

Dapagliflozin 10mg once daily vs placebo

Median follow-up = 22 (IQR 17-30) months

Pooled dataset n=11,007

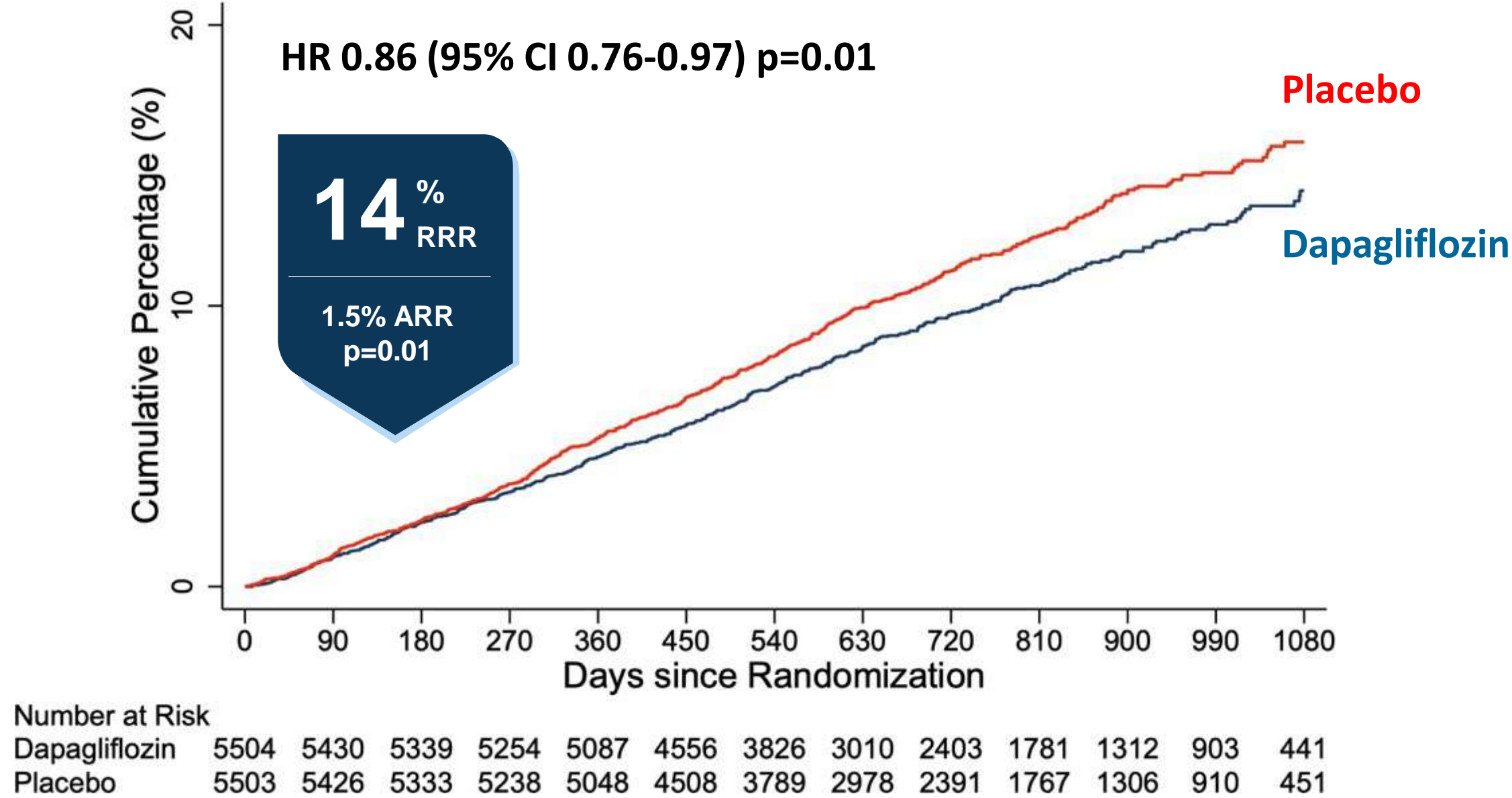


# DAPA-HF & DELIVER pooled analysis: Aims

- The following endpoints were studied in this pre-specified hierarchy to control alpha:
  - **CV Death** (pre-specified to include undetermined deaths from both trials)
  - **All cause death**
  - **Total (i.e., first and repeat) hospitalisations for HF** (with an additional supportive analysis of time to the first occurrence of hospital admissions for heart failure, outside alpha control)
  - **CV death/ myocardial infarction/ stroke** (i.e., “major adverse cardiovascular events” - MACE)
- To compare our findings with the analysis of the EMPEROR trials we also examined the composite of **CV death/ first HF hospitalisation**

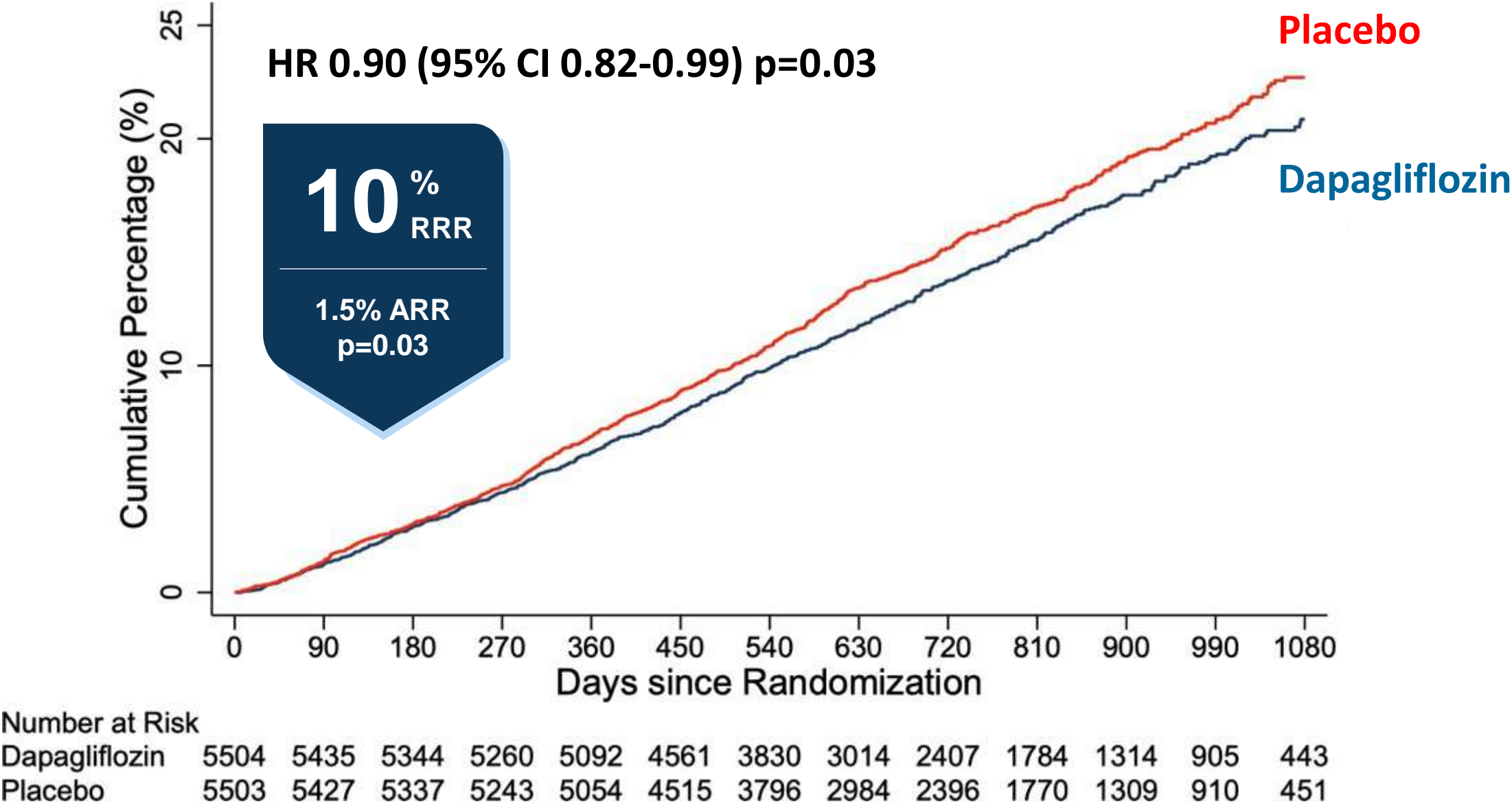


# DAPA-HF & DELIVER pooled: Cardiovascular death











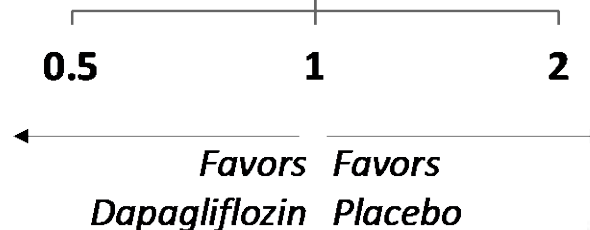


# DAPA-HF & DELIVER pooled: All-cause death

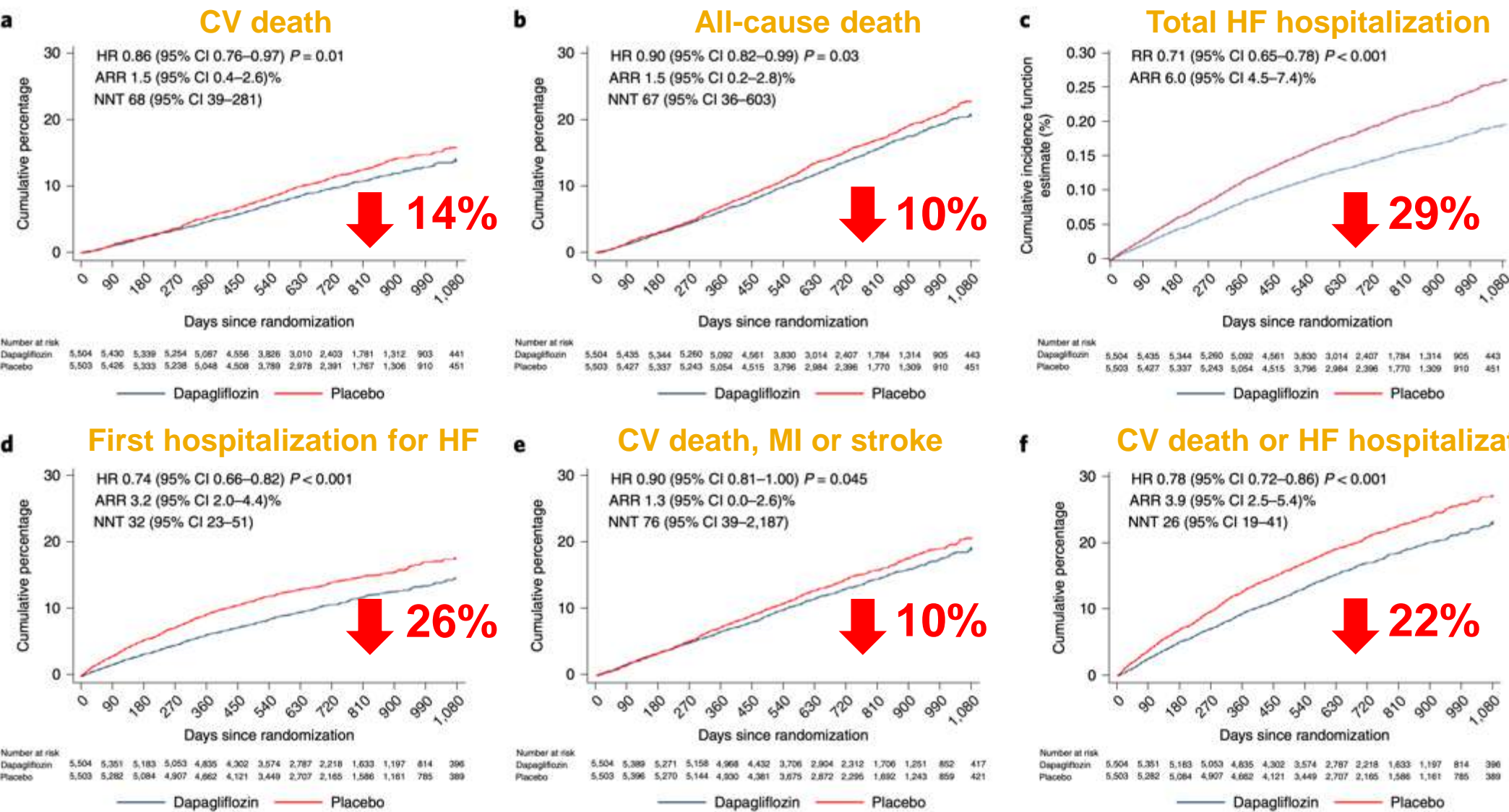


# Effect of Dapagliflozin on Cause-Specific Mortality

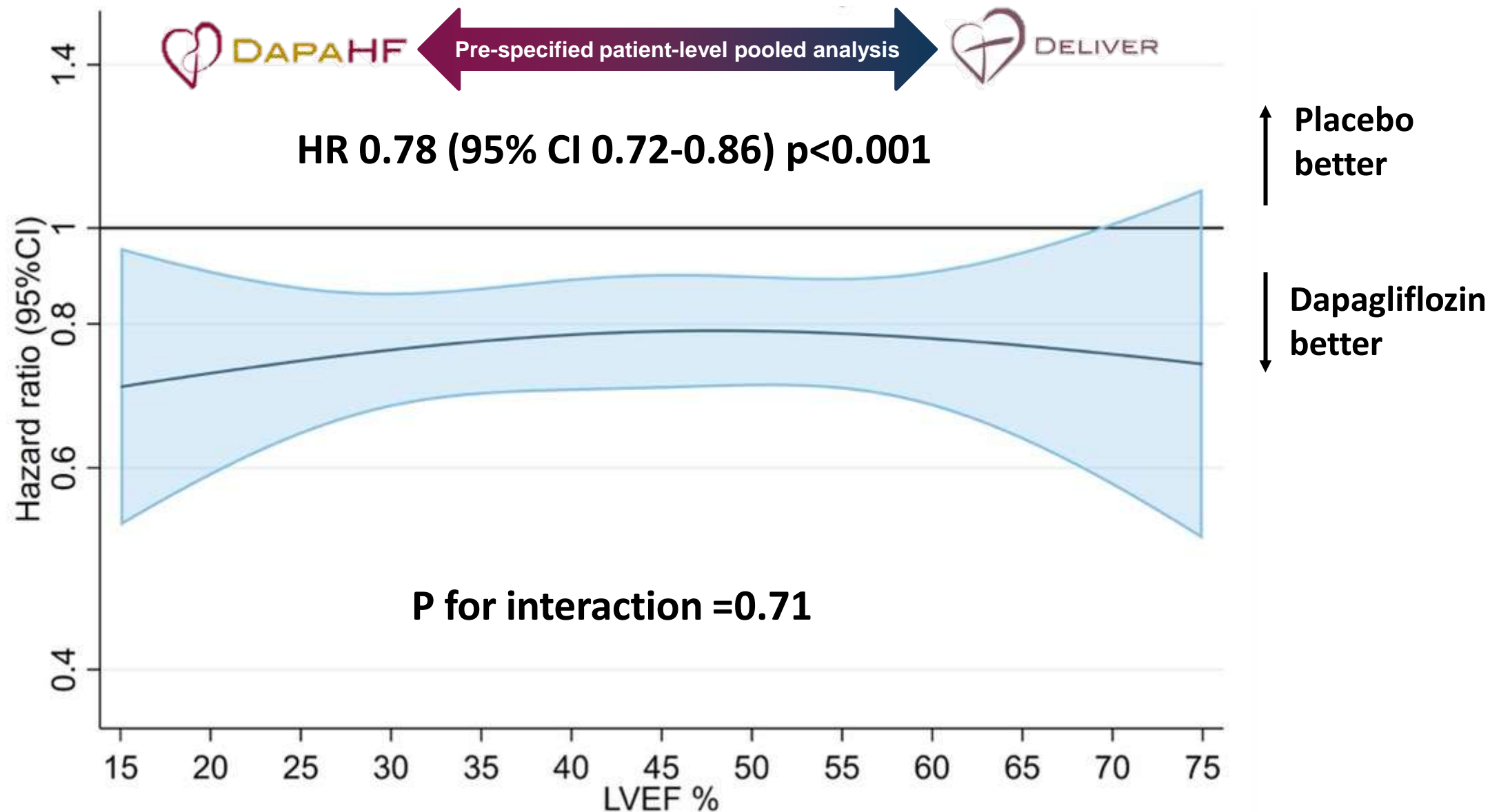
	Dapagliflozin Events (rate/100 pt-yr) (N=5504)	Placebo Events (rate/100 pt-yr) (N=5503)		HR (95% CI)	P
All-Cause Death	773 (7.4)	855 (8.3)		0.90 (0.82-0.99)	0.032
CV Death	404 (3.9)	468 (4.5)		0.86 (0.75-0.98)	0.024
HF Death	136 (1.3)	153 (1.5)		0.88 (0.70-1.11)	0.296
Sudden Death	202 (1.9)	239 (2.3)		0.84 (0.70-1.01)	0.067
Stroke Death	34 (0.3)	35 (0.3)		0.97 (0.60-1.55)	0.896
MI Death	23 (0.2)	24 (0.2)		0.95 (0.54-1.69)	0.870
Non-CV Death	245 (2.4)	242 (2.3)		1.01 (0.84-1.20)	0.937
Unknown Death	124 (1.2)	145 (1.4)		0.85 (0.67-1.08)	0.181



# Effect of Dapagliflozin on Key Clinical Outcomes in DAPA-HF+DELIVER



# DAPA-HF & DELIVER: CV death/HF hospitalisation



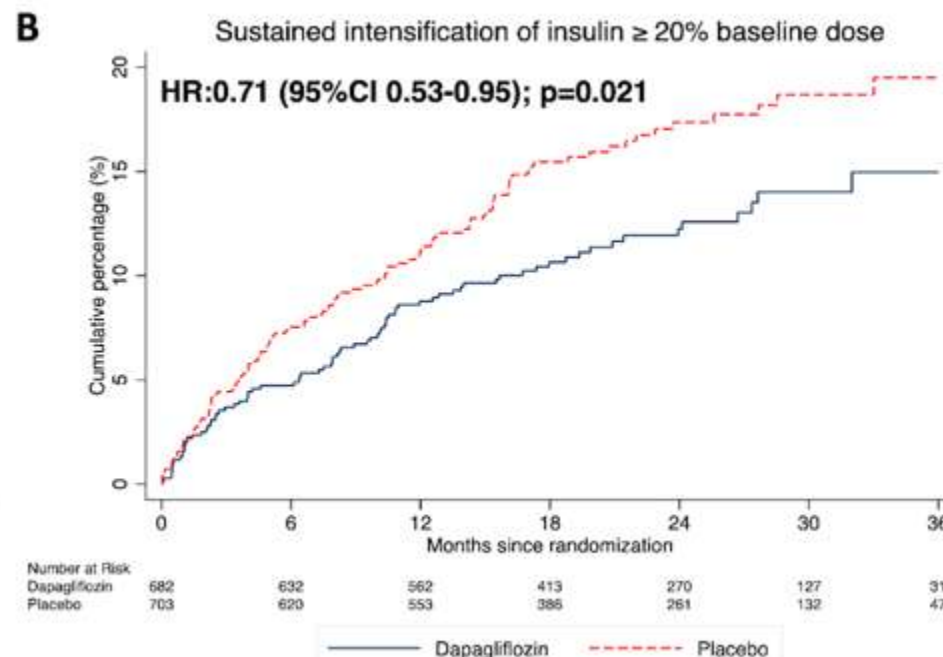
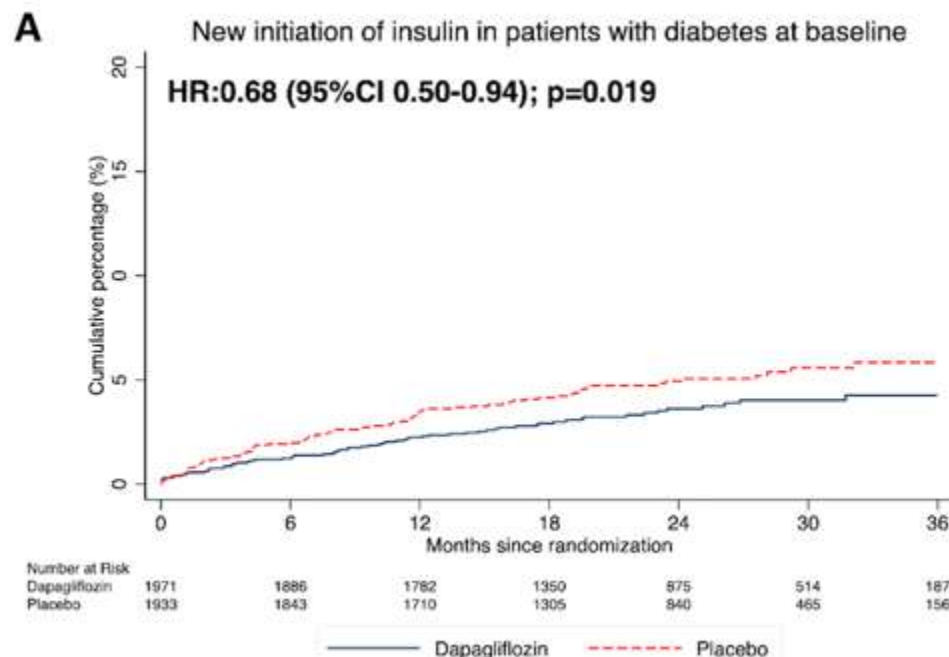
# Effect of DAPA on Insulin Use in HF with DM: Analysis from DAPA-HF and DELIVER Pooled Analysis



- DAPA-HF (N=4474) and DELIVER (N=6263)
- HF with DM patients, N=5289
- 1385 (26%) treated with insulin at baseline
- Primary endpoint:
  - ✓ Insulin initiation
  - or
  - ✓ Intensification of existing insulin therapy

Outcome	Insulin Rate per 100PY	No insulin Rate per 100PY	Adjusted HR (95%CI) insulin vs. no insulin
CV death or worsening HF	17.0	11.6	1.38 (1.20, 1.59)
CV death	7.1	5.8	1.24 (1.02, 1.50)
Worsening HF	12.0	7.5	1.43 (1.21, 1.69)
All-cause death	10.9	8.0	1.38 (1.17, 1.62)

Hazard ratio (95% CI)





# DAPA-HF + DELIVER Pooled Analysis

Death 

hHF 

CV death

All-cause death

First hHF

Total<sup>a</sup> hHF

14%  
RRR

1.5% ARR  
p=0.01

HR: 0.86  
95% CI: 0.76-0.97

10%  
RRR

1.5% ARR  
p=0.03

HR: 0.90  
95% CI: 0.82-0.99

HF  
Across  
Spectrum

26%  
RRR

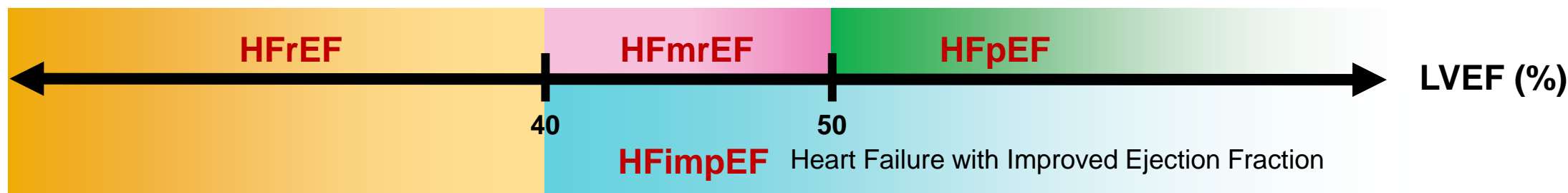
3.2% ARR  
p<0.001

HR: 0.74  
95% CI: 0.66-0.82

29%  
reduction

6.0% ARR  
p<0.001

RR: 0.71  
95% CI: 0.65-0.78



<sup>a</sup>First and repeat.

Jhund PS et al. Online ahead of print. *Nat Med.* 2022.



## Braunwald's Corner



# SGLT2 inhibitors: the statins of the 21<sup>st</sup> century

Eugene Braunwald  <sup>1,2\*</sup>

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A relatively small number of drugs have been responsible for major advances in medical practice. The discovery, development, and elucidation of the mechanisms of action of **aspirin, penicillin, and statins** are remarkable success stories, each with some surprises and each crowned by a Nobel Prize. The sodium glucose co-transporter inhibitors have been proven effective in the treatment of type 2 diabetes mellitus, various forms of heart failure, and kidney failure and represent *the, or one of the,* major pharmacological advances in cardiovascular medicine in the 21st century.

**T2DM**

**CVOT**

**EMPA-REG  
CANVAS  
DECLARE-TIMI58**

**HF**

**DAPA-HF  
EMPEROR-Reduced**

**CKD**

**CREDENCE  
DAPA-CKD  
EMPA-KIDNEY**

...what else?  
HFpEF, MI...?

**EMPEROR-Preserved  
DELIVER**

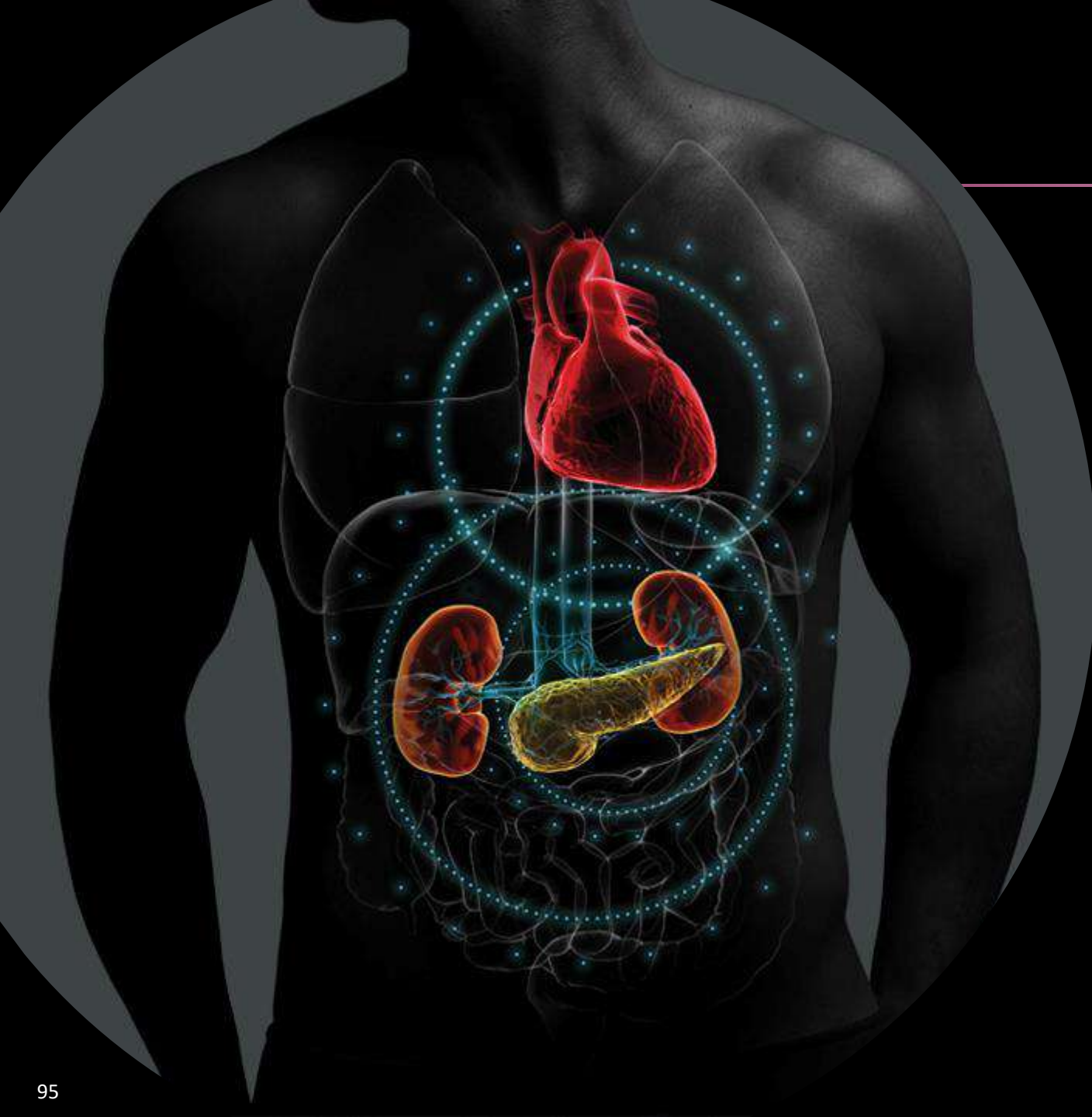
# FORXIGA顯著減少HFrEF死亡、一天一次不需調整劑量， 可同時治療CKD、T2D的優質治療選擇



In Heart Failure (HFrEF)	FORXIGA (dapagliflozin)	Empagliflozin	Sacubitril/ Valsartan	ACEI/ ARB	Beta Blockers	MRA
Composite endpoint of CV death or hospitalization for HF	✓	✓	✓	✓	✓	✓
CV death alone in RCT	✓	✗	✓	✓	✓	✓
Single dose/No titration	✓ 10 mg	✓ 10 mg	✗	✗	Depends <sup>#</sup>	✗
Once daily dose	✓	✓	✗	Depends <sup>#</sup>	✗	✓
Beyond Heart Failure <sup>#</sup>	FORXIGA (dapagliflozin)	Empagliflozin	Sacubitril/ Valsartan	ACEI/ ARB	Beta Blockers	MRA
Chronic kidney disease	✓	✗	✗	✓	✗	✗
Type 2 diabetes	✓	✓	✗	✗	✗	✗

<sup>#</sup>Depends on the specific agent in the class 1. FORXIGA仿單: 核准治療第二型糖尿病、心臟衰竭、慢性腎臟病 2. Empagliflozin 10 mg仿單: 核准治療第二型糖尿病、心臟衰竭 3. Sacubitril/valsartan仿單: 核准治療慢性心臟衰竭 4. Enalapril仿單: 核准治療高血壓、充血性心臟衰竭 5. Ramipril仿單: 核准治療高血壓、心肌梗塞後的心衰竭，降低因心血管疾病導致之心肌梗塞、中風及死亡的危險 6. Lisinopril仿單: 核准治療高血壓、充血性心臟衰竭、急性心肌梗塞 7. Candesartan仿單: 核准治療本態性高血壓、左心室射出分率≤40%之心臟衰竭 8. Valsartan仿單: 核准治療高血壓、心臟衰竭、心肌梗塞後左心室功能異常 9. Bisoprolol仿單: 核准治療狹心症、高血壓、穩定型慢性中度至重度心臟衰竭 10. Carvedilol仿單: 核准治療高血壓、鬱血性心臟衰竭 11. Spironolactone仿單: 核准治療利尿、高血壓、原發性醛固酮過多症 12. Eplerenone 50 mg仿單: 核准治療心肌梗塞後之心衰竭、NYHA第II級(慢性)心臟衰竭、高血壓





Thank you.