AstraZeneca
What science can do

American Heart Association Scientific Sessions 2018

Investor science conference call

12 November 2018

Forward-looking statements

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Speakers

Stephen D. Wiviott, MD, FACC
Senior Investigator, TIMI Study Group

Elisabeth Björk
Vice President, Head of CVRM, Global Medicines Development

Mark Mallon
Executive Vice President, Global Products & Portfolio Strategy, Global Medical Affairs, Corporate Affairs

Klaus Hinterding
Global Medicine Leader, Oral Diabetes Franchise

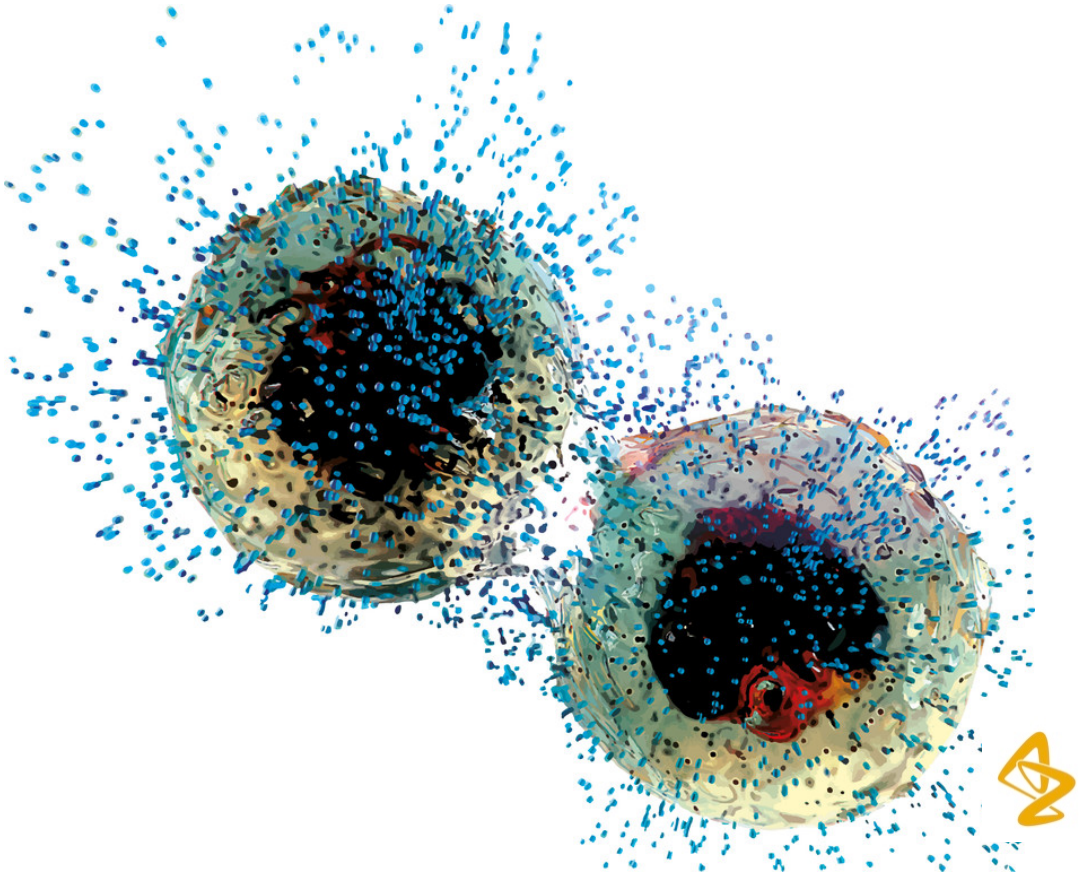
Agenda

Introduction

DECLARE-TIMI 58 trial

Farxiga perspective

Q&As



DECLARE – TIMI 58

Stephen D. Wiviott, MD

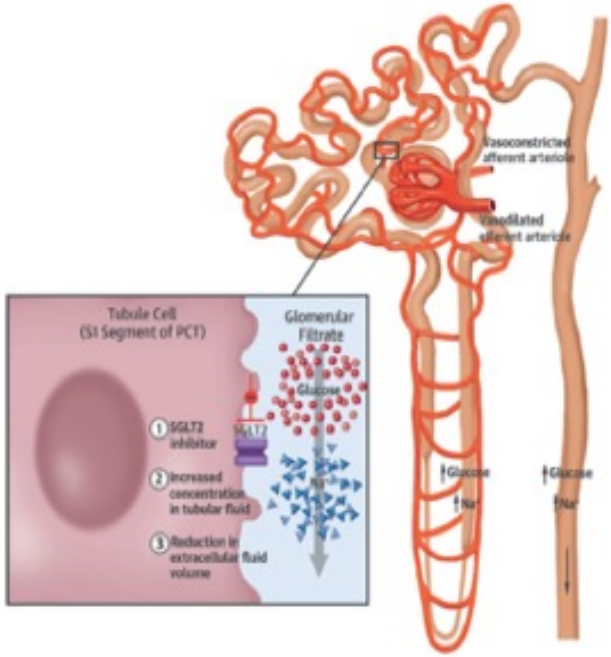
for the DECLARE – TIMI 58 Investigators

American Heart Association, Scientific Sessions

November 10, 2018

Background

- Patients with type 2 DM are at high risk for development of atherosclerotic CV events and heart failure.
- Dapagliflozin is a selective SGLT2 inhibitor which blocks glucose and sodium resorption in the kidney, and thereby ↓ blood sugar, BP & weight.
- Prior CV outcomes trials with other SGLT2i have shown reductions in CV and renal events predominantly in *secondary prevention* patients, though questions have been raised related to amputation, stroke and DKA.



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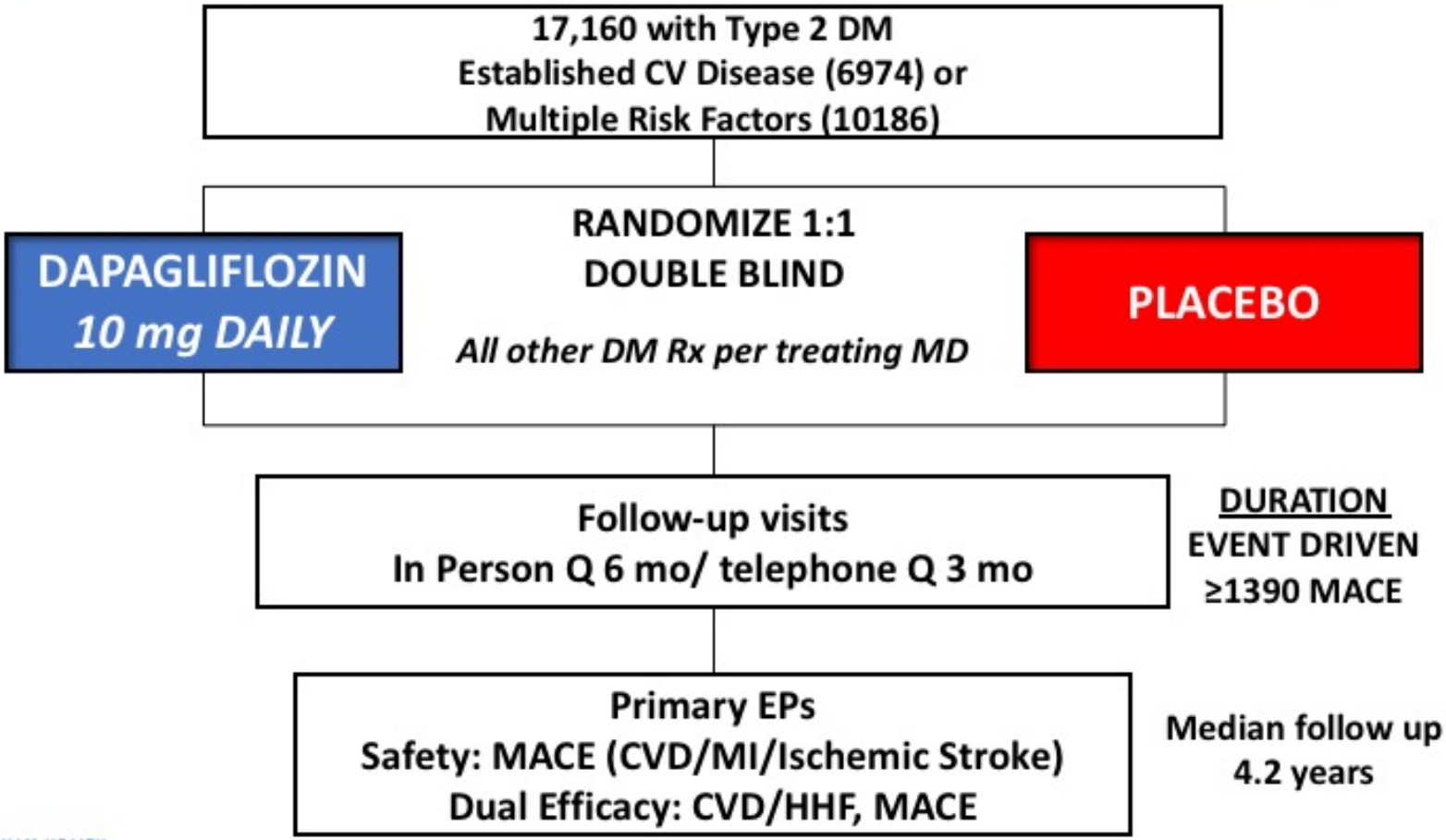
Zelniker TA, Braunwald E *JACC* 2018

Trial Design



Wiviott SD, Raz I...Sabatine MA, *AHJ* 2018

Enrollment Criteria

Diagnosis of T2DM, HbA1c 6.5-12%, CrCl ≥60 ml/min

AND

Established ASCVD (Secondary prevention)

- Ischemic heart disease
- Cerebrovascular disease
- Peripheral Artery Disease

Or

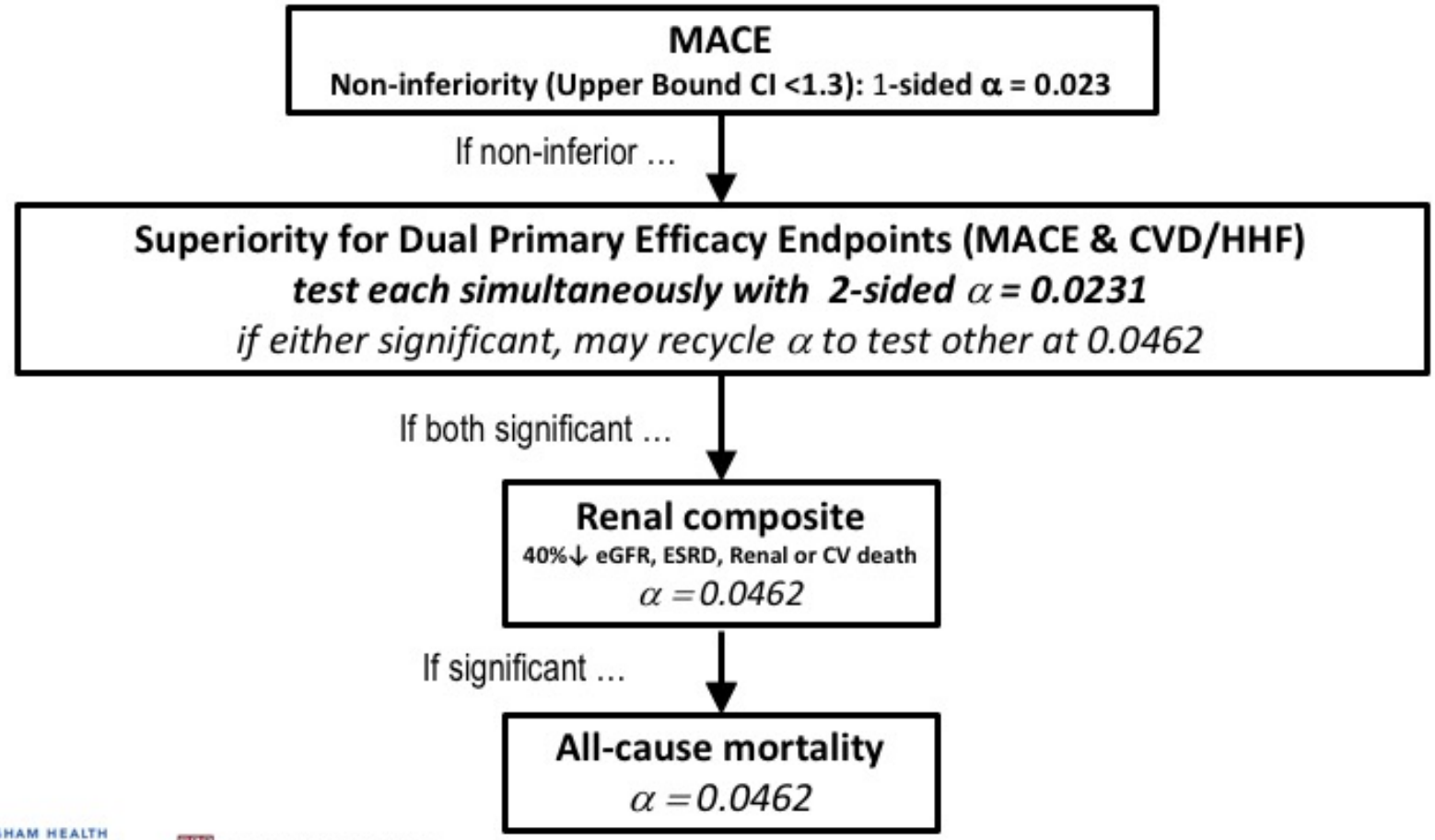
Multiple risk factors for ASCVD (Primary prevention)

Men ≥ 55 yrs and women ≥ 60 yrs with at least one additional risk factor:

- Dyslipidemia
- Hypertension
- Current Tobacco use

Wiviott SD, Raz I...Sabatine MA, *AHJ* 2018

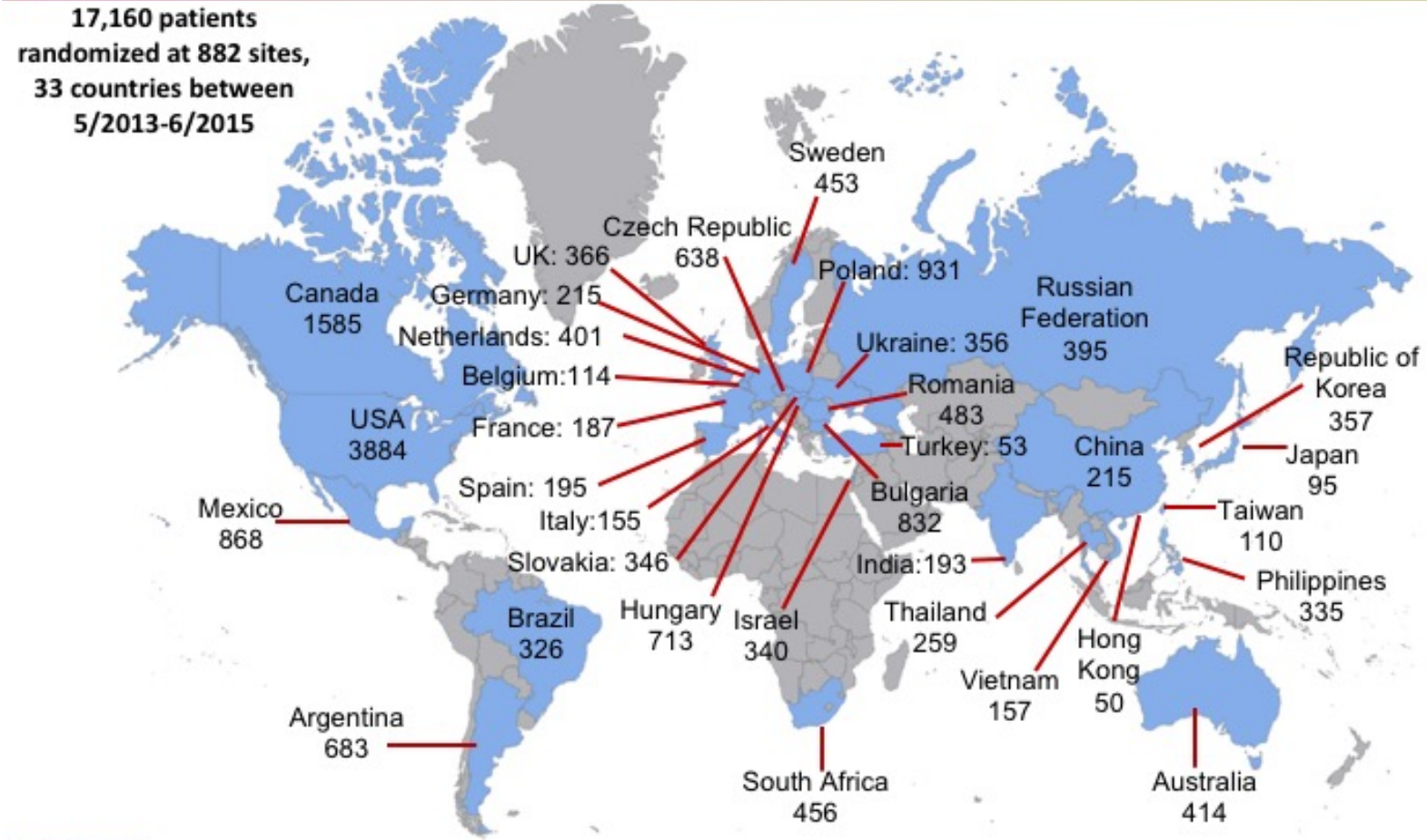
Analytic Plan



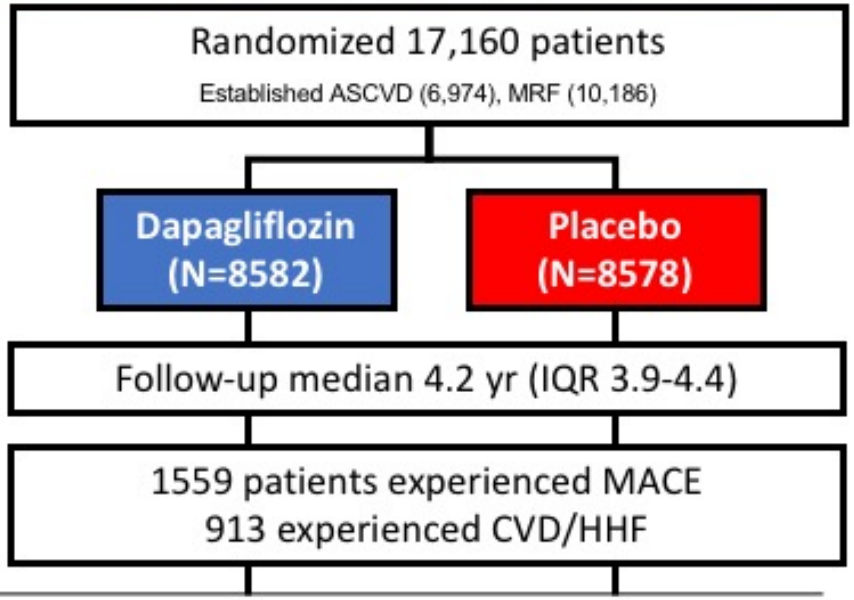
Wiviott SD, Raz I…Sabatine MA, *AHJ* 2018

Global Enrollment

17,160 patients randomized at 882 sites, 33 countries between 5/2013-6/2015



Follow-up



Premature perm. drug discontinuation	5.2%/yr	6.2%/yr
Withdrew consent	0.28%/yr	0.37%/yr
Lost to follow-up	12 patients	18 patients

Baseline Characteristics

	Full Trial Cohort N = 17160
Age, yrs, Mean (SD)	64 (7)
Female Sex (%)	37
BMI, Mean (SD)	32 (6)
Duration of T2DM, yrs, Median (IQR)	11 (6, 16)
HbA1c (%), Mean (SD)	8.3 (1.2)
eGFR (CKD-EPI), Mean (SD)	85 (16)
Region (%): North America	32
Europe	44
Latin America	11
Asia Pacific	13
Established CV Disease (%)	41
History of Heart Failure (%)	10

P=NS for all between treatment arm comparisons

Baseline Characteristics: Medication Use

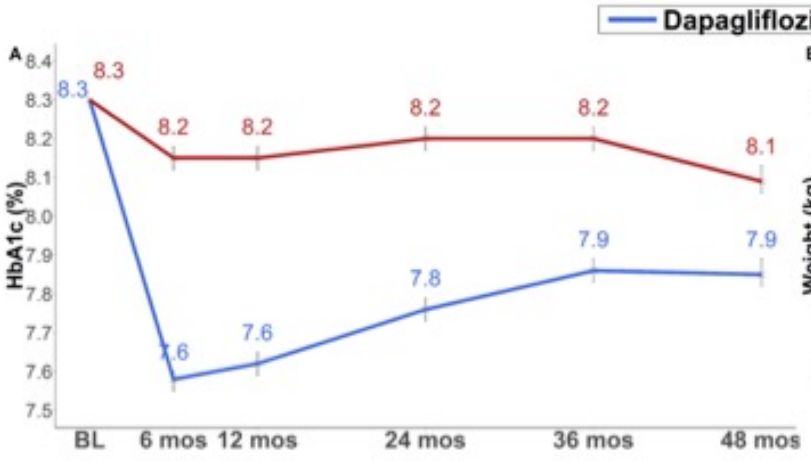
	Full Trial Cohort N = 17160
Glucose lowering therapies (%)	
Metformin	82
Insulin	41
Sulfonylurea	43
DPP4i	17
GLP-1 RA	4
Cardiovascular therapies (%)	
Antiplatelet	61
ACEI/ARB	81
Beta-blocker	53
Statin or Ezetimibe	75

P=NS for all between treatment arm comparisons

Cardiovascular Risk Factors

HbA1c

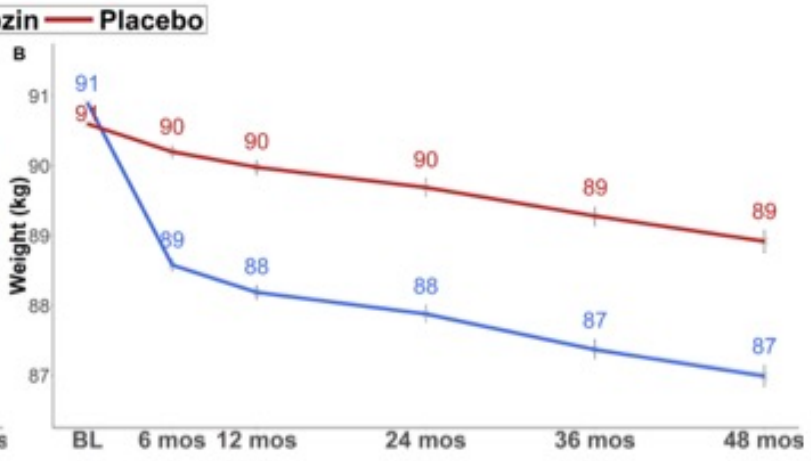
LSM Difference 0.42% (95% CI 0.40-0.45)



All P-values (except BL) <0.001

Weight

LSM Difference 1.8 kg (95% CI 1.7-2.0)

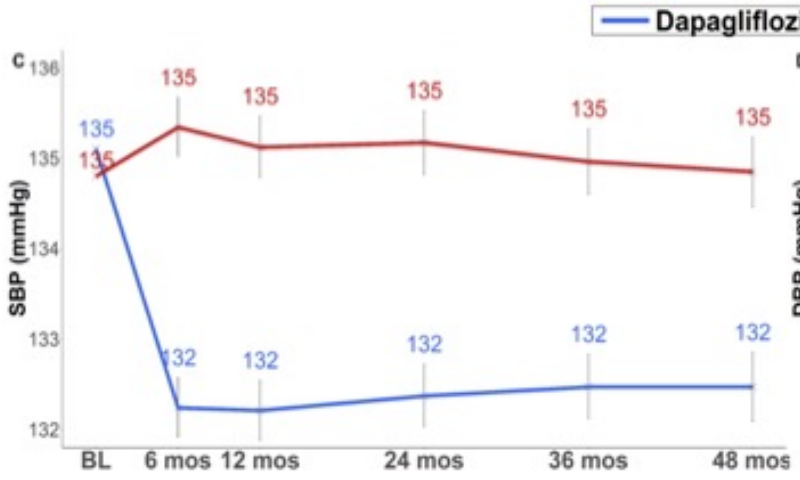


All P-values (except BL) <0.001

Cardiovascular Risk Factors

SBP

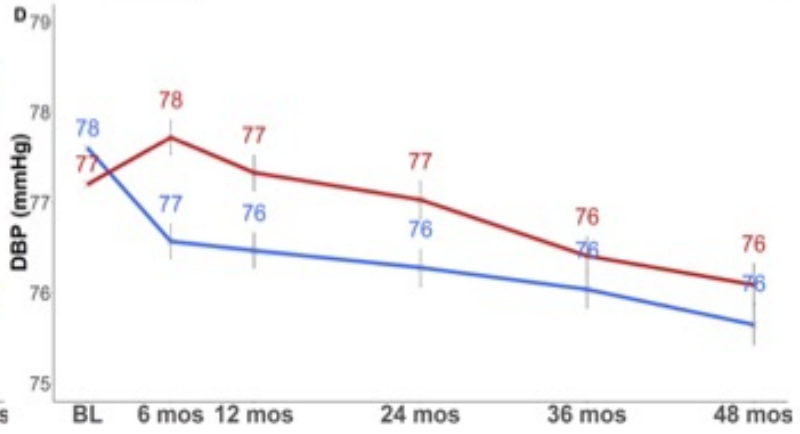
LSM Difference 2.7 mmHg (95% CI 2.4-3.0)



All P-values (except BL) <0.001

DBP

LSM Difference 0.7mmHg (95% CI 0.6-0.9)



All P-values (except BL) <0.001

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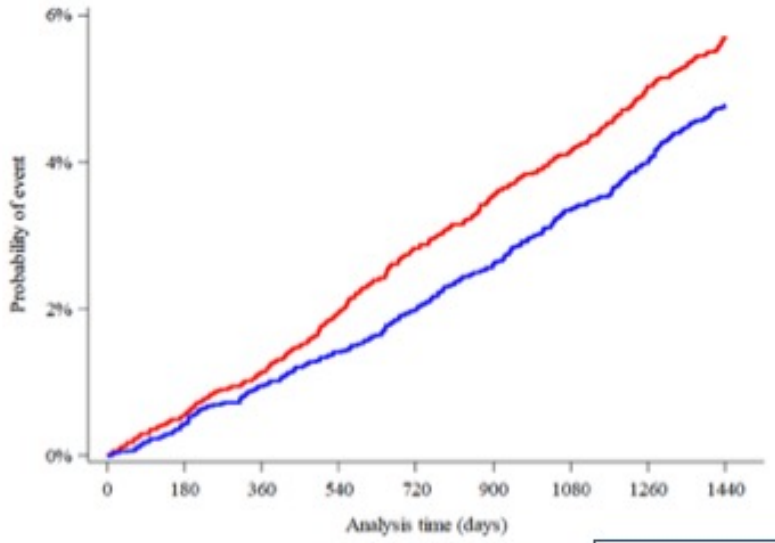
Primary Endpoints

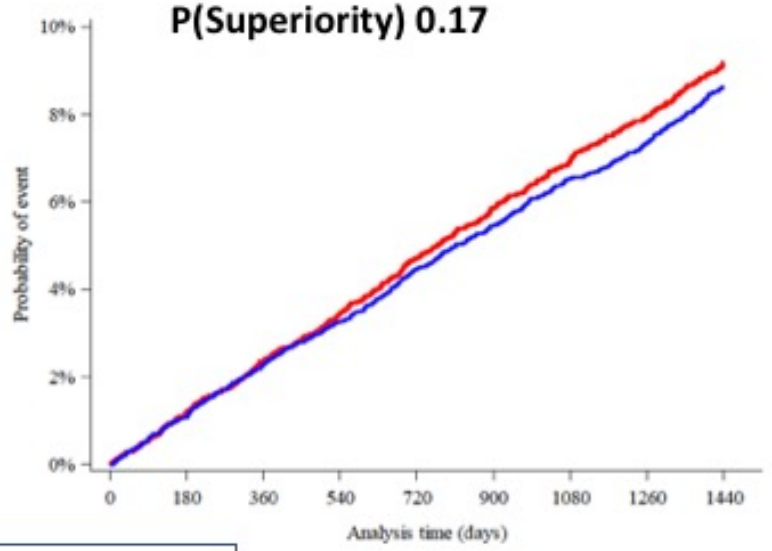
CVD/HHF

4.9% vs 5.8%
HR 0.83 (0.73-0.95)
P(Superiority) 0.005



MACE

8.8% vs 9.4%
HR 0.93 (0.84-1.03)
P(Noninferiority) <0.001
P(Superiority) 0.17

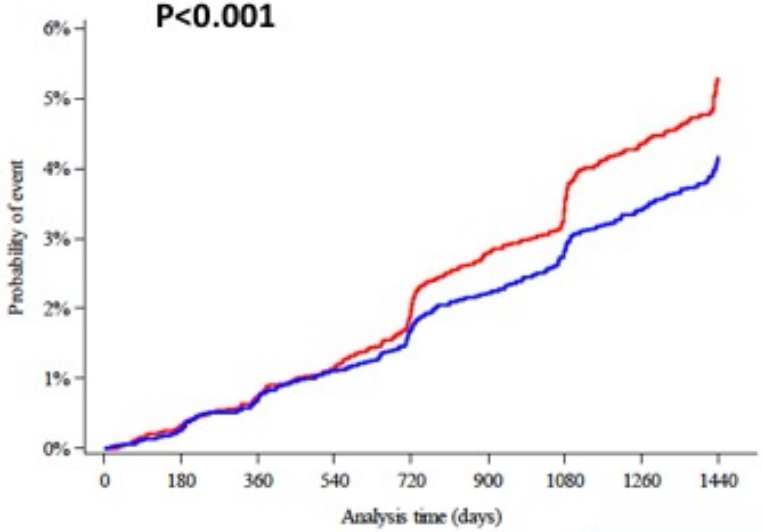


Secondary Endpoints

Renal Composite EP

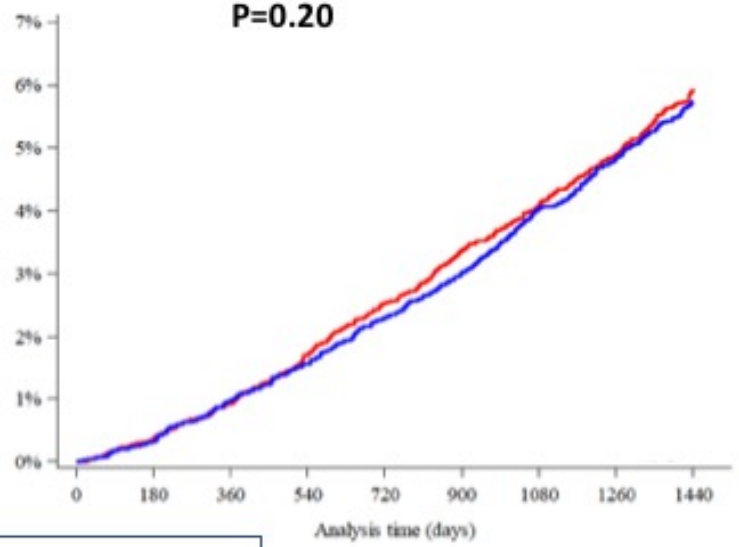
40%↓ eGFR, ESRD, Renal or CV death

4.3% vs. 5.6%
HR 0.76 (0.67-0.87)
P<0.001



All-Cause Mortality

6.2% vs 6.6%
HR 0.93 (0.82-1.04)
P=0.20



Dapagliflozin
Placebo

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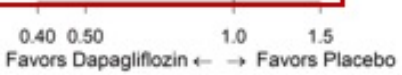
Endpoints and Components

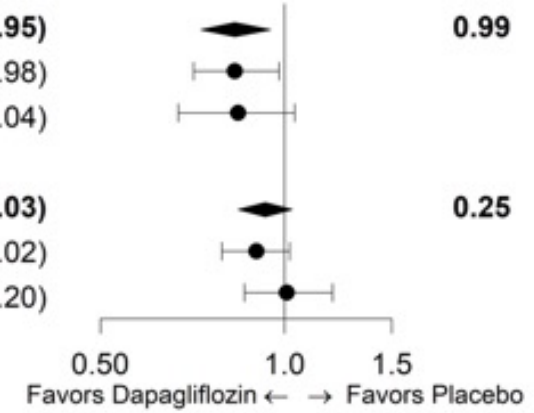
	Dapagliflozin rate/1000 patient-yr	Placebo rate/1000 patient-yr	Hazard Ratio (95% CI)	P value
CV death/HHF	12.2	14.7	0.83 (0.73-0.95)	0.005*
MACE	22.6	24.2	0.93 (0.84-1.03)	<0.001** 0.17*
40% decrease in eGFR to <60 ml/min/m2, ESRD, or renal or CV death	10.8	14.1	0.76 (0.67-0.87)	
All-cause death	15.1	16.4	0.93 (0.82-1.04)	
HHF	6.2	8.5	0.73 (0.61-0.88)	
Myocardial infarction	11.7	13.2	0.89 (0.77-1.01)	
Ischemic Stroke	6.9	6.8	1.01 (0.84-1.21)	
CV death	7.0	7.1	0.98 (0.82-1.17)	
Non-CV death	6.0	6.8	0.88 (0.73-1.06)	
40% decrease in eGFR to <60 ml/min/m2, ESRD, or renal death	3.7	7.0	0.53 (0.43-0.66)	



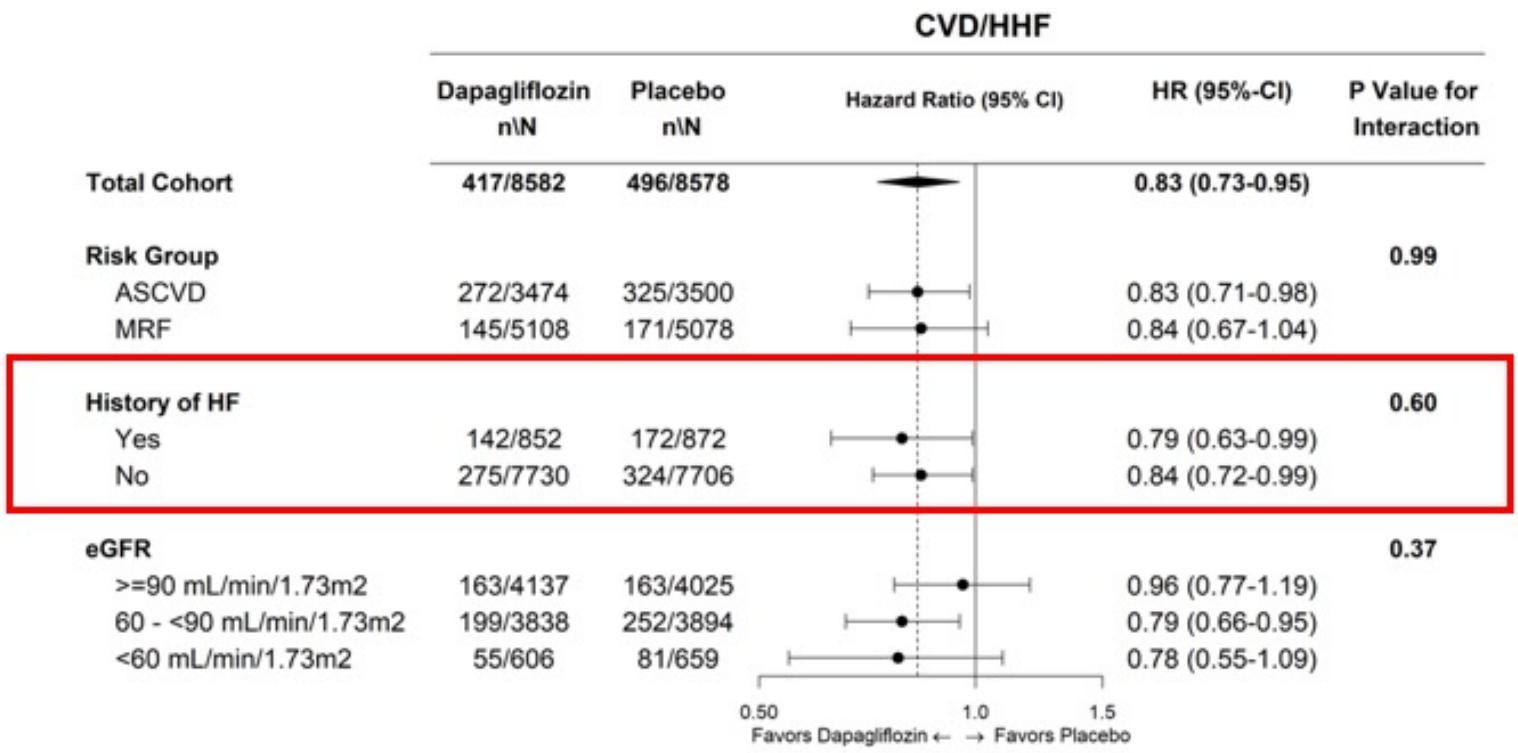
*P for superiority, **P for non-inferiority

Primary Efficacy Endpoints by Presence of ASCVD vs MRF

Outcomes	Dapagliflozin Events per 1000 pt years	Placebo Events per 1000 pt years	Hazard Ratio (95% CI)	P value for interaction
CV death/HHF	**12.2**	**14.7**	**0.83 (0.73-0.95)**	**0.99**
ASCVD	19.9	23.9	0.83 (0.71-0.98)	
MRF	7.0	8.4	0.84 (0.67-1.04)	
MACE	**22.6**	**24.2**	**0.93 (0.84-1.03)**	**0.25**
ASCVD	36.8	41.0	0.90 (0.79-1.02)	
MRF	13.4	13.3	1.01 (0.86-1.20)	



Effect on CVD/HHF in Key Subgroups



Key Safety Events

	Dapagliflozin (%)	Placebo (%)	Between Group Comparison
Treatment emergent SAE	34.1	36.2	P<0.001
Treatment emergent AE leading to drug D/C	8.1	6.9	P=0.01
Major Hypoglycemia	0.7	1.0	P=0.02
Diabetic Ketoacidosis* (DKA)	0.3	0.1	P=0.02
Amputation	1.4	1.3	NS
Fracture	5.3	5.1	NS
Acute Kidney Injury	1.5	2.0	P=0.002
Symptoms of volume depletion	2.5	2.4	NS
Genital infection (SAE, DAE)	0.9	0.1	P<0.001
Urinary tract infection (SAE, DAE)	1.5	1.6	NS
Fournier's Gangrene	0.01	0.08	NS
Cancer of Bladder*	0.3	0.5	P=0.02

*CEC Adjudicated

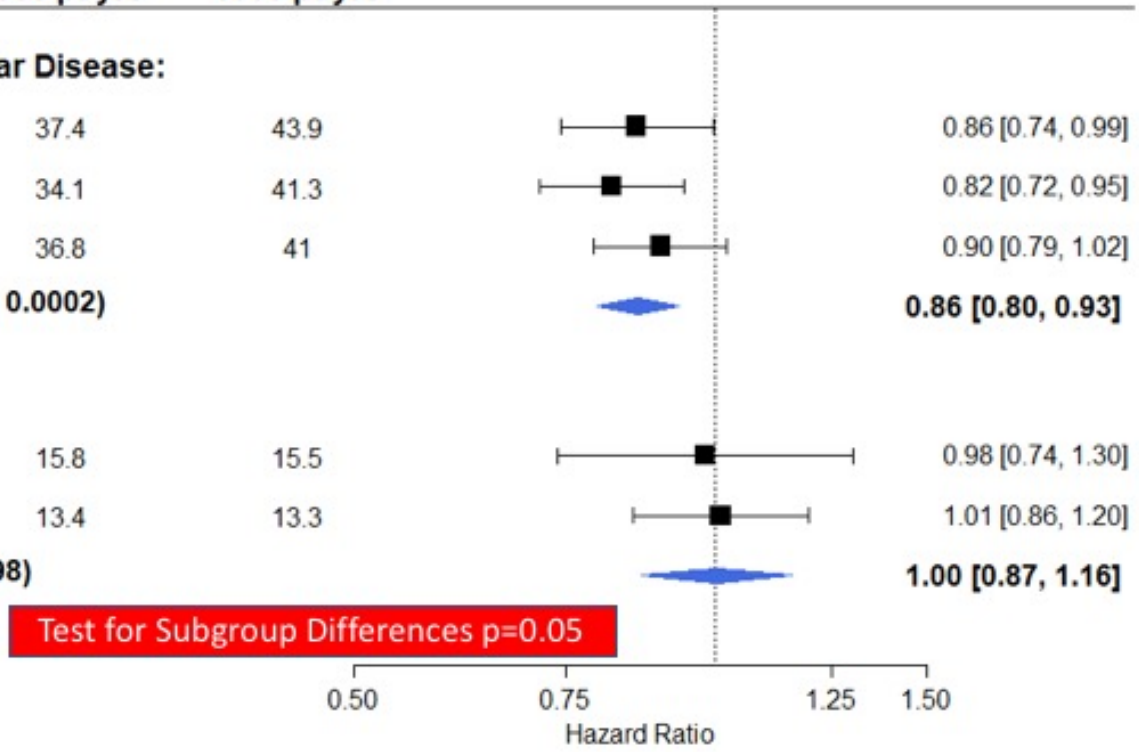
Summary

In DECLARE – TIMI 58, the largest SGLT2i trial, which included a broad representation of 1° and 2° prevention patients:

- **Dapagliflozin reduced CVD/HHF, was safe with regard to MACE and appeared to reduce renal events**
  - **↓ CVD/HHF was consistent regardless of baseline ASCVD or HF**
- **Dapagliflozin was safe and generally well-tolerated**
  - **↑ Genital infections & DKA**
  - **No difference in: amputation, fracture, or stroke**
  - **↓ Hypoglycemia, AKI, bladder Ca**

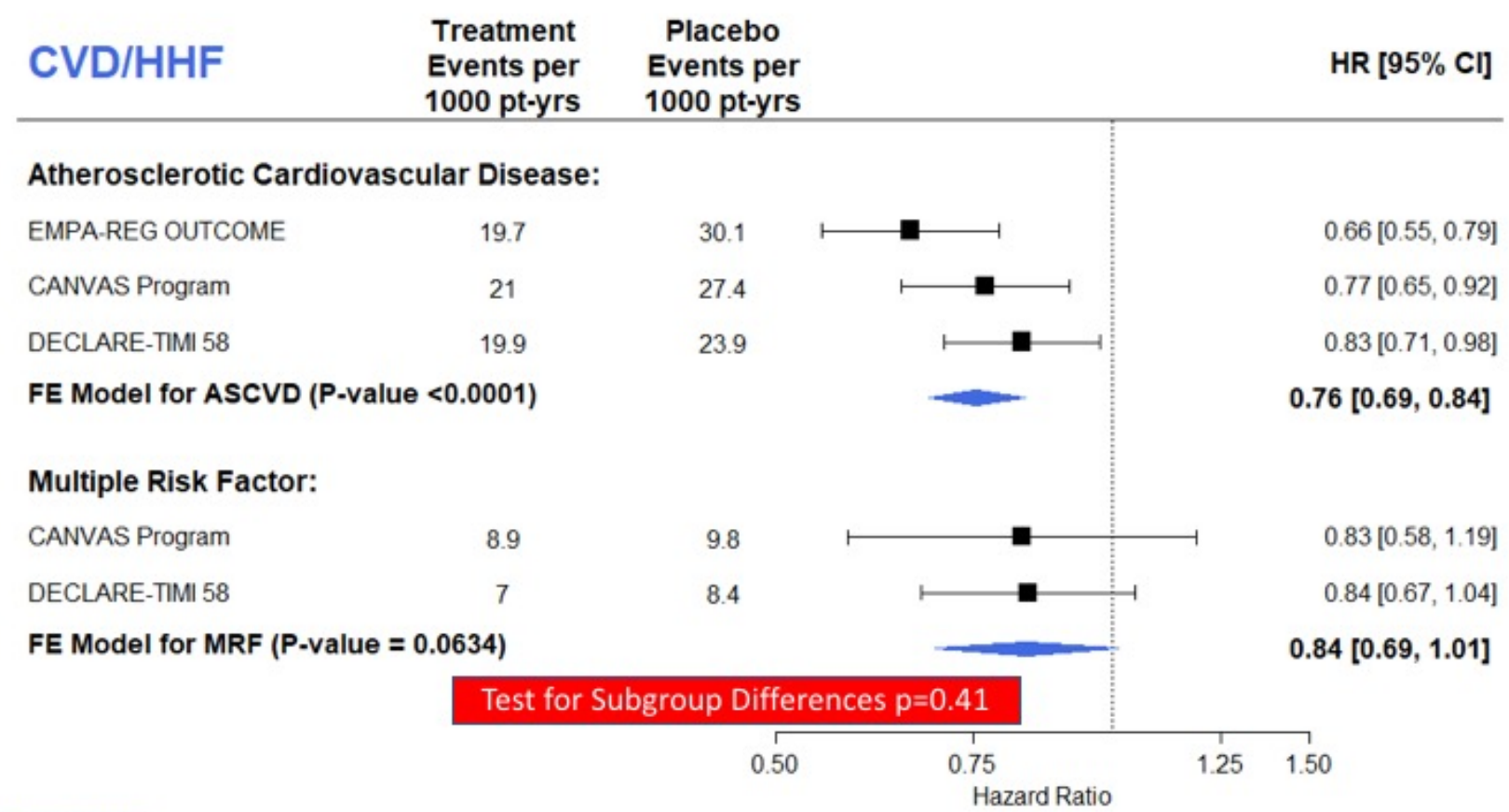
Meta-Analysis of CVOTs: MACE by Presence of ASCVD

MACE	Treatment Events per 1000 pt-yrs	Placebo Events per 1000 pt-yrs	HR [95% CI]
Atherosclerotic Cardiovascular Disease:			
EMPA-REG OUTCOME	37.4	43.9	0.86 [0.74, 0.99]
CANVAS Program	34.1	41.3	0.82 [0.72, 0.95]
DECLARE-TIMI 58	36.8	41	0.90 [0.79, 1.02]
FE Model for ASCVD (P-value = 0.0002)			**0.86 [0.80, 0.93]**
Multiple Risk Factor:			
CANVAS Program	15.8	15.5	0.98 [0.74, 1.30]
DECLARE-TIMI 58	13.4	13.3	1.01 [0.86, 1.20]
FE Model for MRF (P-value = 0.98)			**1.00 [0.87, 1.16]**



Zelniker TA, Wiviott SD...Sabatine MA, Lancet 2018

Meta-Analysis of CVOTs: CVD/HHF by Presence of ASCVD



Zelniker TA, Wiviott SD...Sabatine MA, Lancet 2018

Conclusions

Now with the context of 3 large CVOTs:

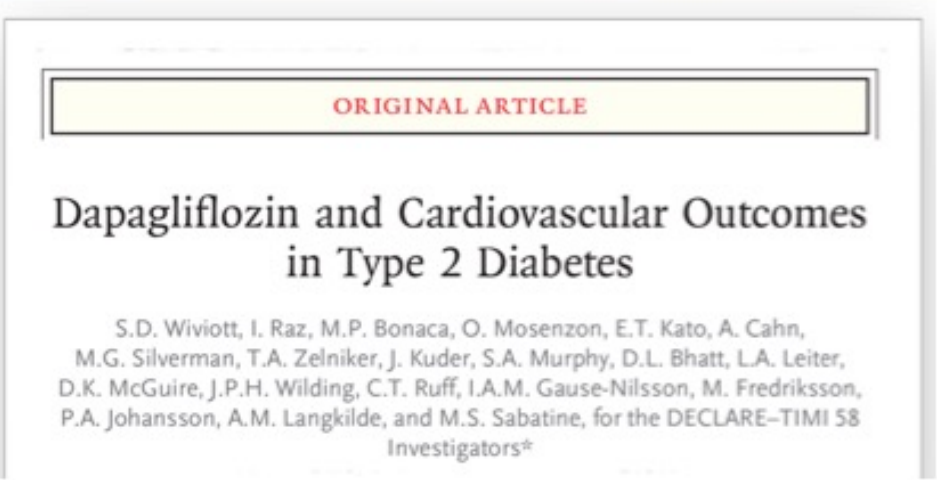
- ***SGLT2i have moderate benefits on atherosclerotic MACE that appear confined to those with established ASCVD***

- ***SGLT2i have robust effects on reducing the risk of heart failure and renal outcomes which do not appear dependent on baseline atherosclerotic risk or prior HF***

These data with dapagliflozin from DECLARE - TIMI 58 extend the benefit of SGLT2i to a broader population of patients for primary and secondary prevention

Additional Information

LBCT slides available:
www.timi.org



ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, M.G. Silverman, T.A. Zelniker, J. Kuder, S.A. Murphy, D.L. Bhatt, L.A. Leiter, D.K. McGuire, J.P.H. Wilding, C.T. Ruff, I.A.M. Gause-Nilsson, M. Fredriksson, P.A. Johansson, A.M. Langkilde, and M.S. Sabatine, for the DECLARE–TIMI 58 Investigators*

THE LANCET

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcomes trials

Thomas A Zelniker, Stephen D Wiviott, Itamar Raz, Kyungah Im, Erica L Goodrich, Marc P Bonaca, Ofri Mosenzon, Eri T Kato, Avivit Cahn, Remo H M Furtado, Deepak L Bhatt, Lawrence A Leiter, Darren K McGuire, John P H Wilding, Marc S Sabatine

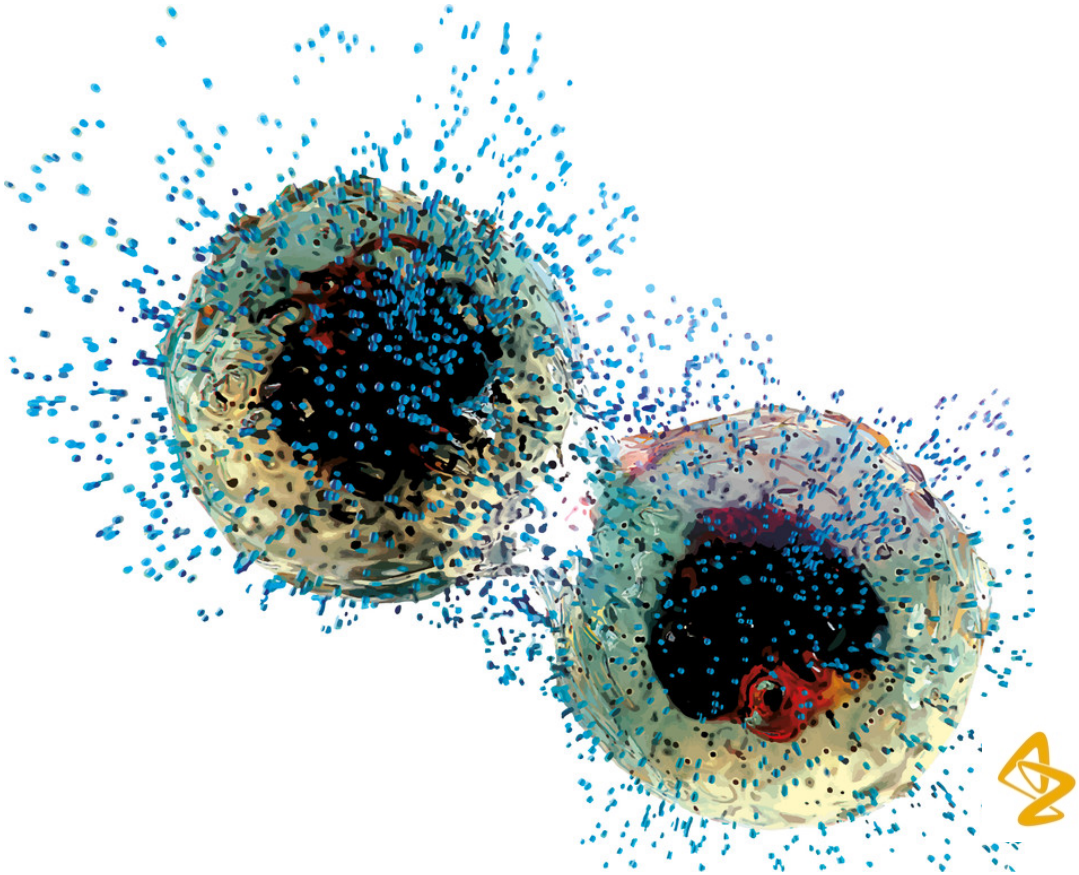
Agenda

Introduction

DECLARE-TIMI 58 trial

Farxiga perspective

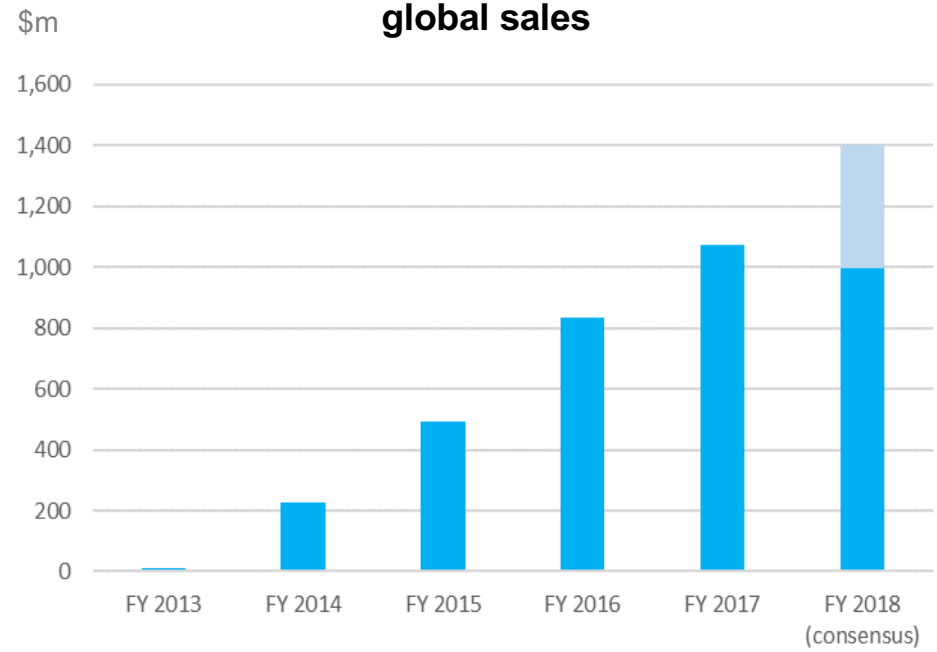
Q&As



Farxiga: steady growth five years into launch

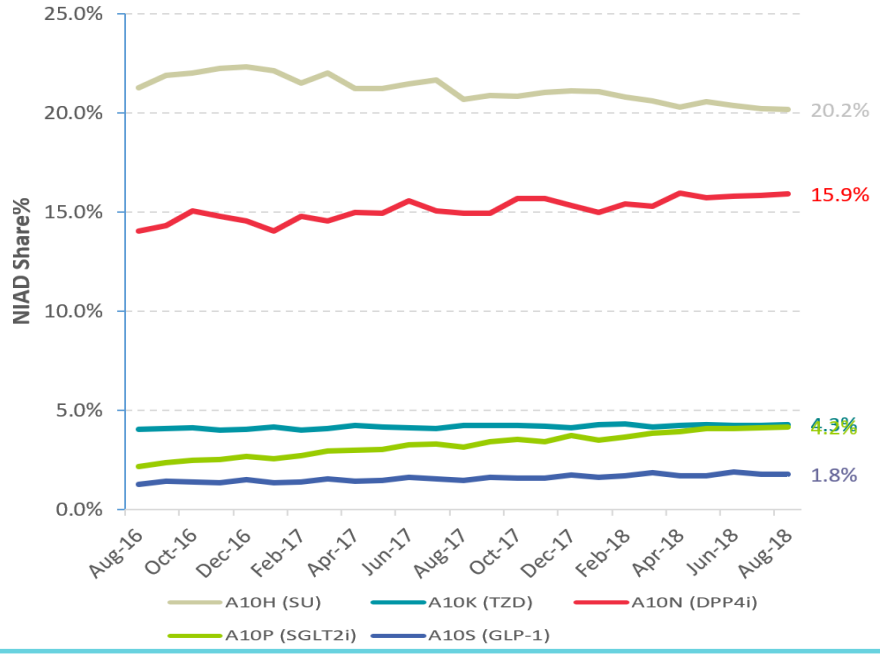
Market leader by volume in the fastest-growing class

Farxiga global sales



Absolute values at actual exchange rates.
Source: AstraZeneca financials and company-collected consensus.

SGLT2 inhibitors is the fastest-growing non-insulin antidiabetic class (global volume, days of therapy)

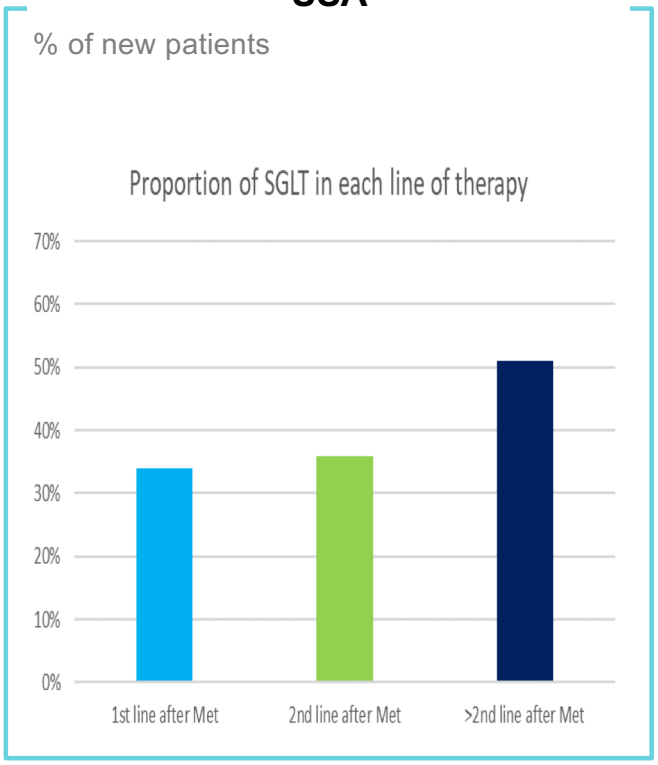


Source: IQVIA, pharmacy sales, retail and hospital where available, YTD August 2018.

Farxiga: opportunity to move into earlier use

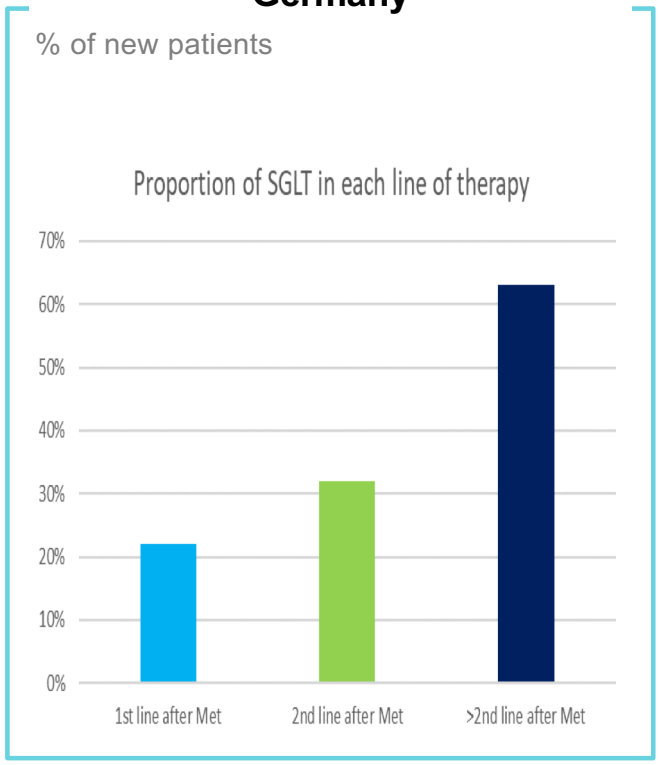
Meaningful CV benefit with opportunity for early use

USA



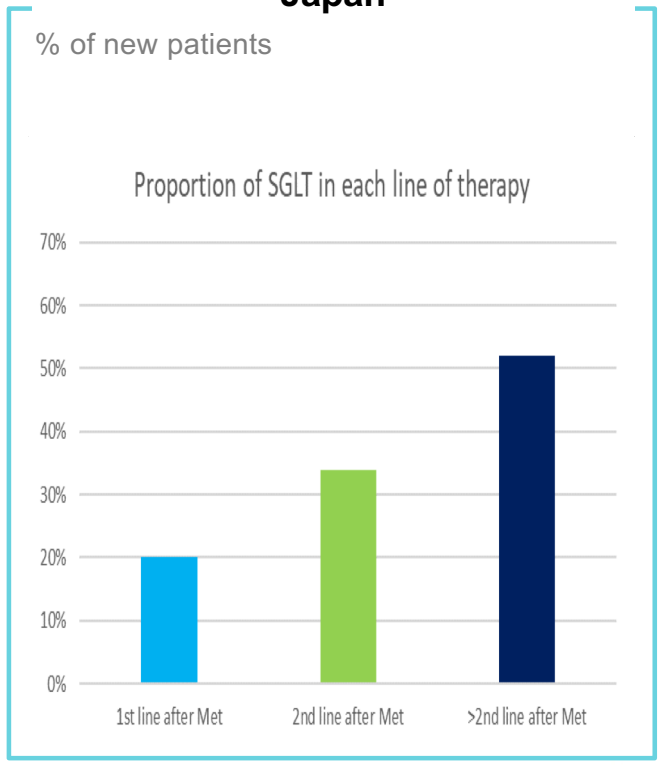
Source: IQVIA APLD, patients starting therapy in June to August 2017 and tracking until July 2018.

Germany



Source: IQVIA LRx, SGLT2 use, Q2 2018.

Japan

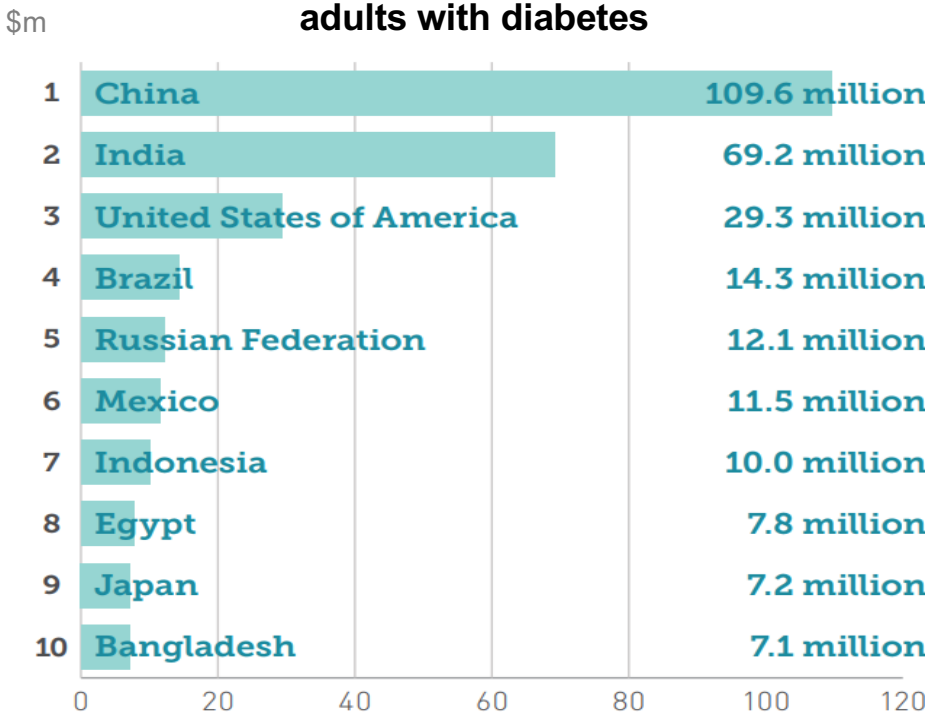


Source: IQVIA NPA, custom report, October 2018.

Farxiga: potential in Emerging Markets

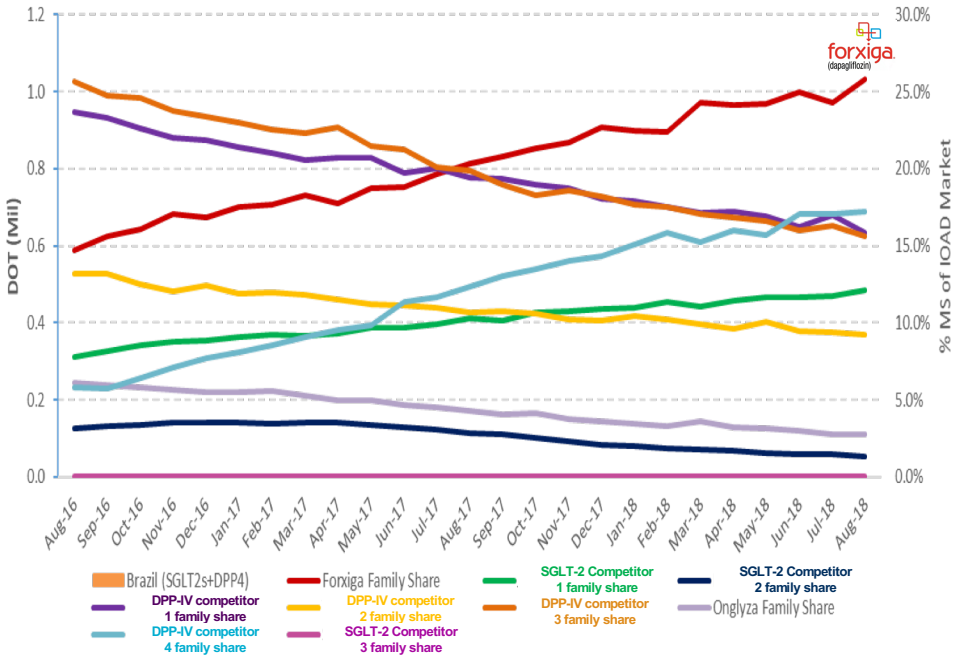
Potential to leverage AstraZeneca's presence

Top-ten countries of adults with diabetes



Source: IDF, Diabetes Atlas, 2015.

Example: in Brazil, *Farxiga* is the largest oral, innovative anti-diabetic medicine

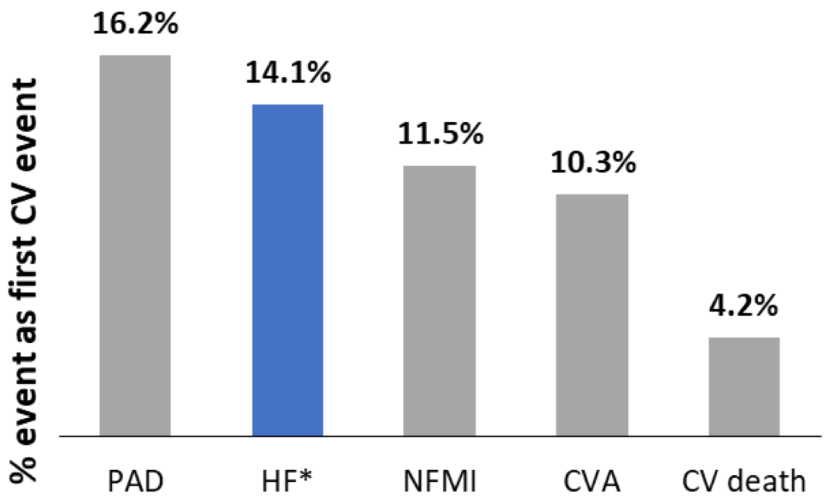


Source: IQVIA, pharmacy sales, retail and hospital where available, YTD August 2018.

Farxiga: heart failure remains a large unmet need

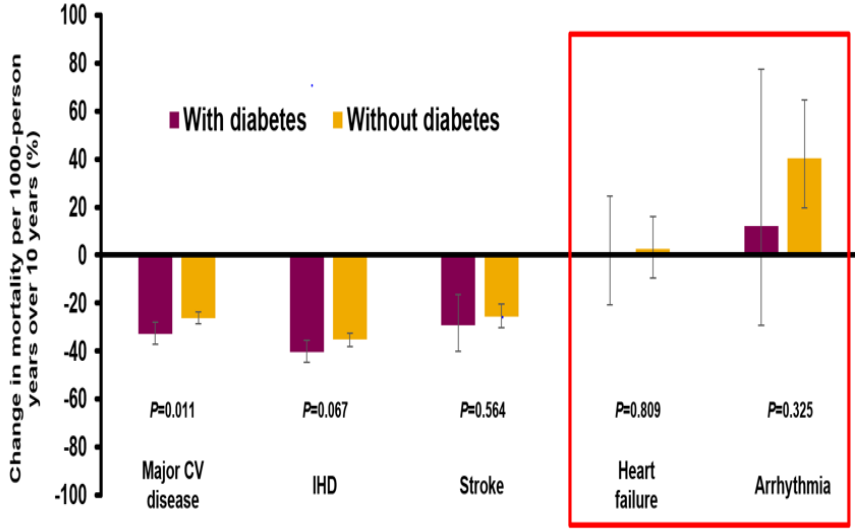
Very frequent T2D complication; no progress in a decade

First CV event in type-2 diabetes patients (selected events, 6,137 events total)



PAD=peripheral arterial disease NFMI=non-fatal myocardial infarction CVA=cerebrovascular accident.
*Heart failure post MI was not included in this definition of HF.
Source: Shah AD, et al., Lancet Diabetes Endocrinol 2015;3:105–113.

Heart failure: no reduction in mortality over the last decade



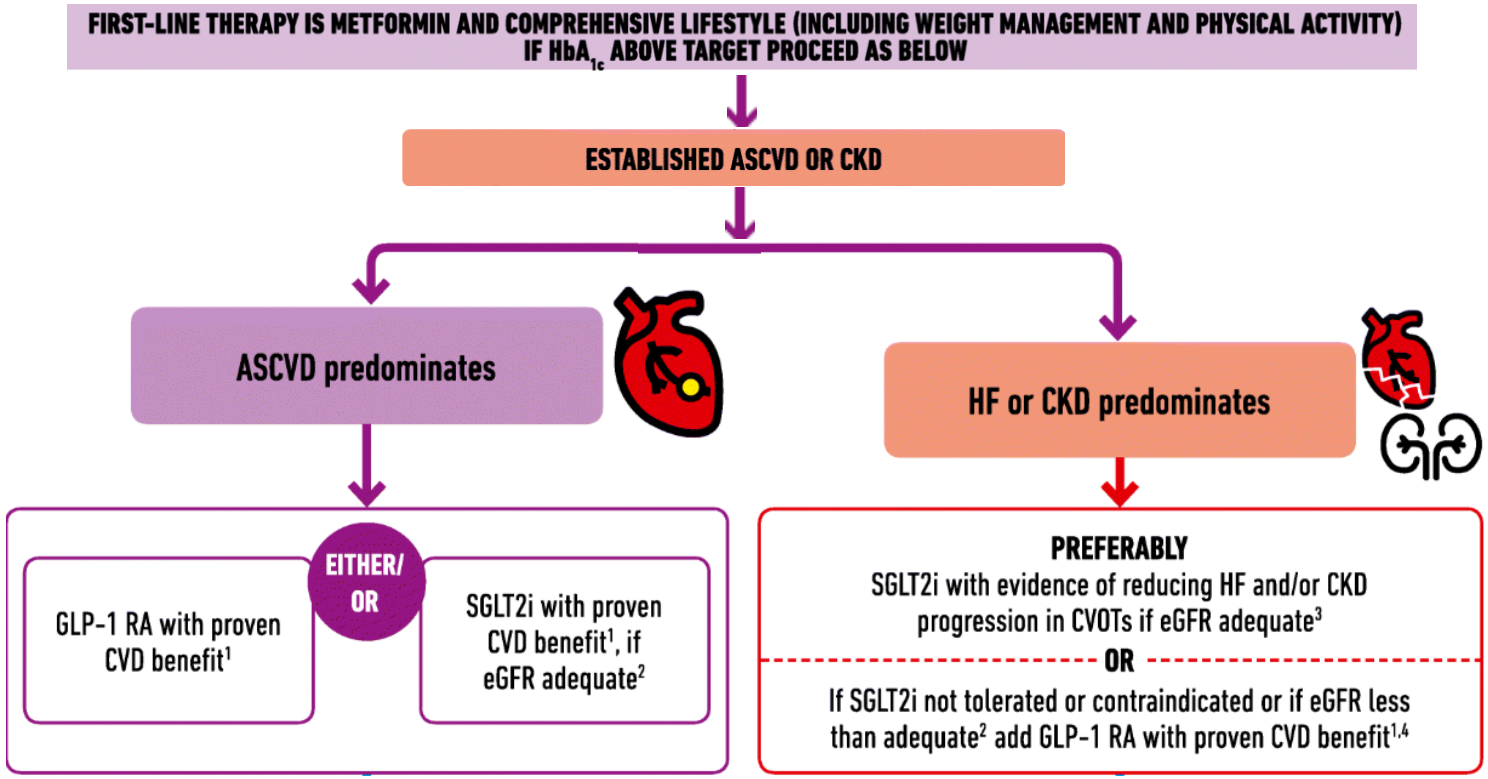
Source: Cheng YJ, et al., online ahead of print, Diabetes Care 2018;doi:10.2337/dc18-0831.

New: 2018 ADA-EASD T2D consensus report reflects emerging evidence from CV outcomes trials

DECLARE results were not yet available when consensus report was written

CONSENSUS RECOMMENDATIONS

- **Patients with T2D who have established ASCVD:** SGLT2 inhibitors or GLP-1 RAs with proven CV benefit recommended
- **Patients with ASCVD in whom HF coexists or is of special concern:** SGLT2 inhibitors recommended
- **Patients with T2D and CKD, with or without CVD:** Consider an SGLT2 inhibitor shown to reduce CKD progression or, if contraindicated/not preferred, GLP-1 RA shown to reduce CKD progression



1. Proven CVD benefit means label indication of reducing CVD events. For GLP-1 strongest evidence for liraglutide>semaglutide>exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin>canagliflozin.
2. SGLT2i vary by region and individual medicine with regard to indicated level of eGFR for initiation and continued use.
3. Both empagliflozin and canagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs.
4. Caution with GLP-1 in ESRD.

Source: Davies MJ, et al., online ahead of print, Diabetologia, 2018;https://doi.org/10.1007/s00125-018-4729-5.

Farxiga: lifecycle plans aim at extending benefits beyond type-2 diabetes

DAPACKD

CKD Outcome Trial

DECLARE TIMI-58 TIMI STUDY GROUP/HADASSAH MEDICAL ORG

CV Outcome Trial

DELIVER

HFpEF Outcome Trial

DAPAHF

HF Outcome Trial


Q&A

Use of AstraZeneca conference call, webcast and presentation slides