DECLARE
TIMI-58 TIMI STUDY GROUP/HADASSAH MEDICAL ORG
Dapagliflozin Effect on Cardiovascular Events

TIMI

DECLARE – TIMI 58

Stephen D. Wiviott, MD

for the DECLARE – TIMI 58 Investigators

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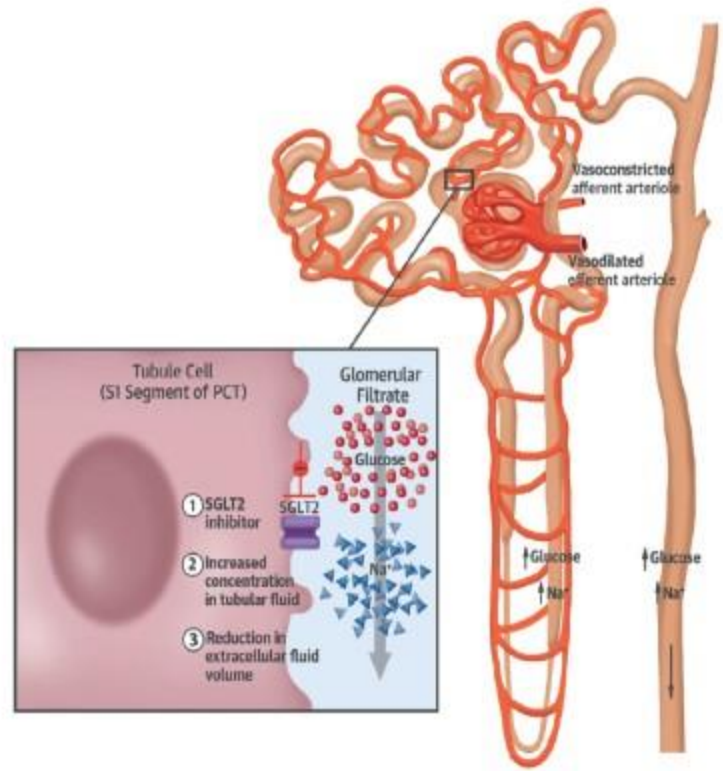
Background

- **Patients with type 2 DM are at high risk for development of atherosclerotic CV events and heart failure.**

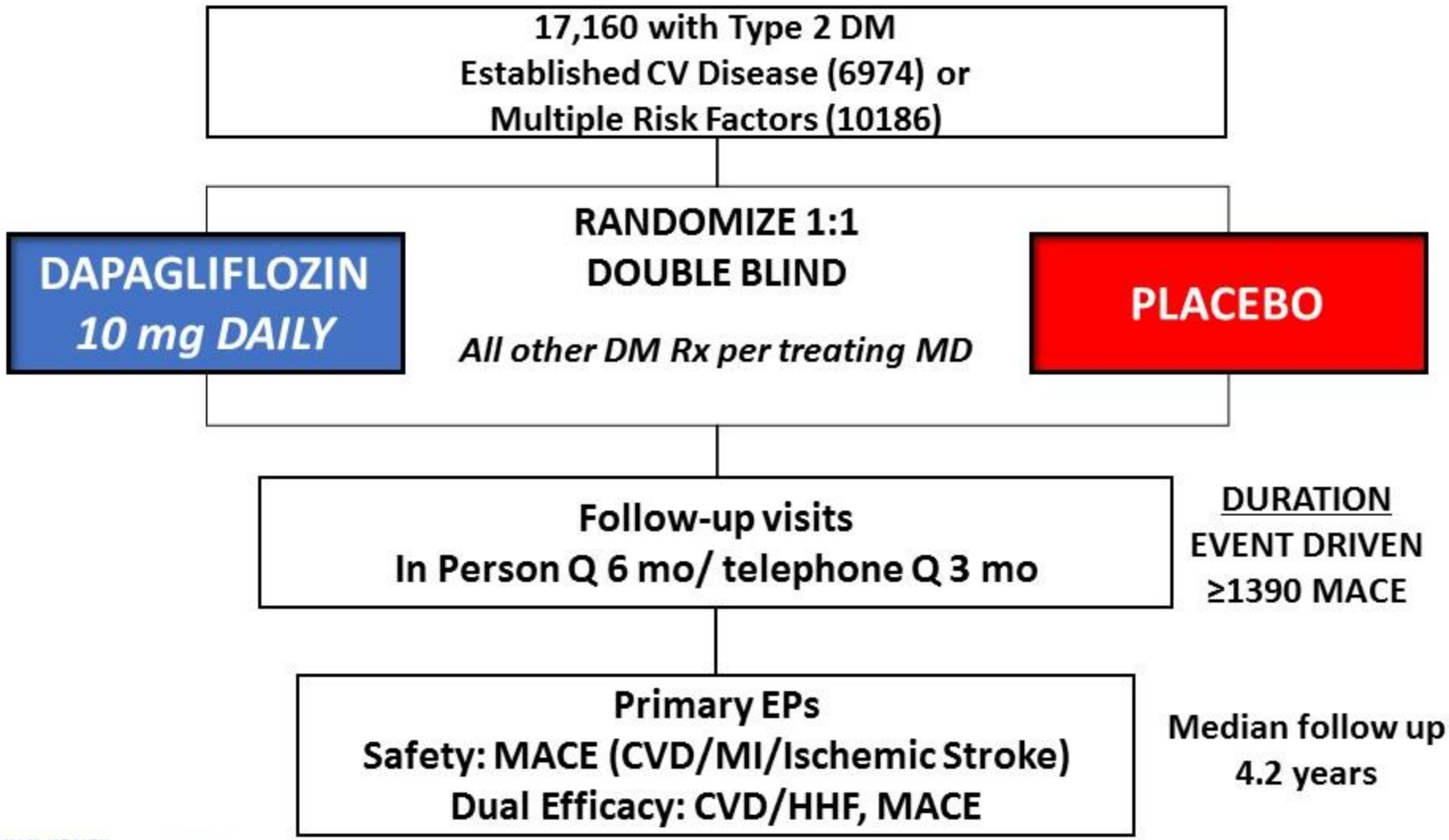
- **Dapagliflozin is a selective SGLT2 inhibitor which blocks glucose and sodium resorption in the kidney, and thereby ↓ blood sugar, BP & weight.**

- **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.**



Zelniker TA, Braunwald E *JACC* 2018

Trial Design



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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

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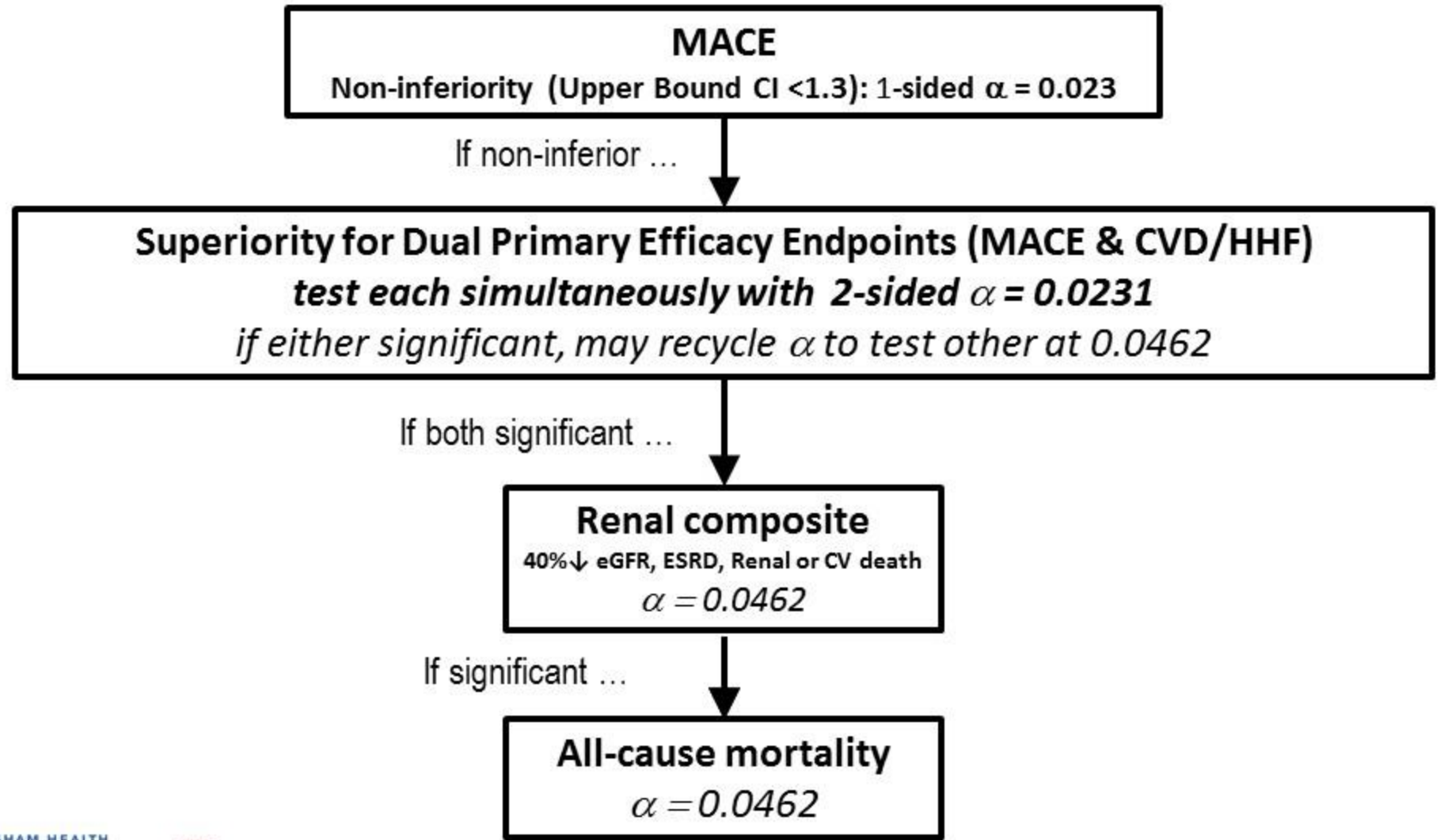
Analytic Plan



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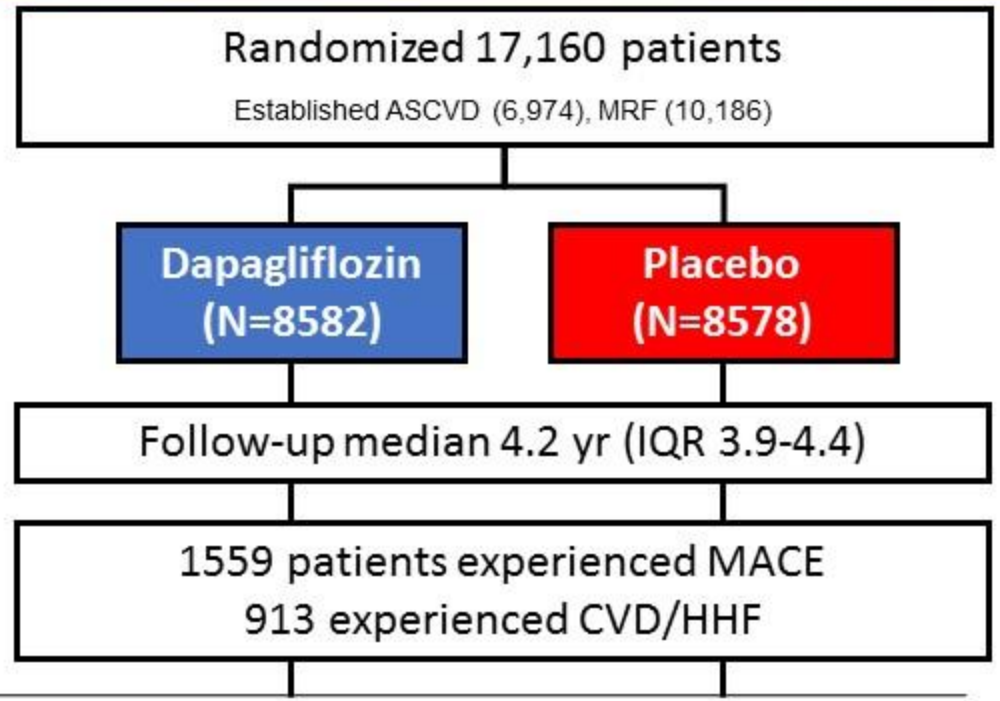
Follow-up



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

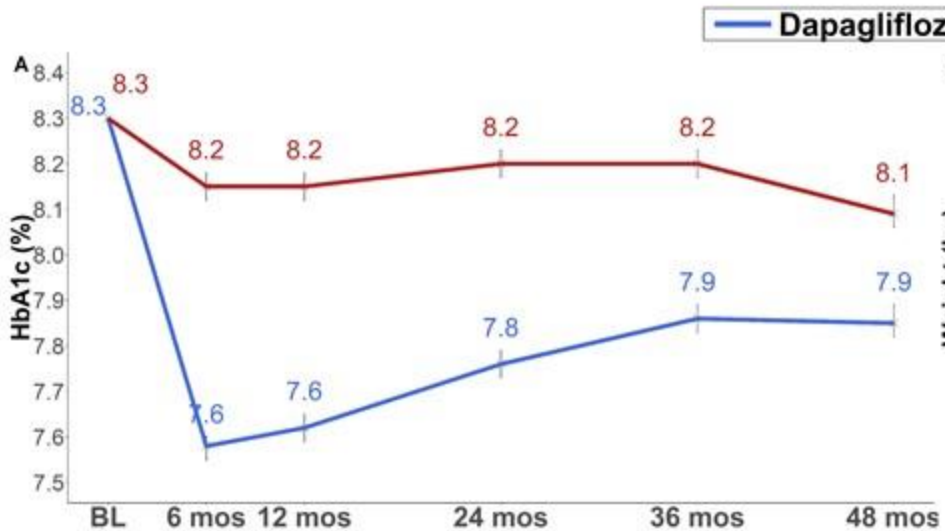
	Full Trial Cohort N = 17160
Glucose lowering therapies (%)	
Metformin	82
Insulin	41
Sulfonylurea	43
DPP4i	17
GLP-1 RA	4
Cardiovascular therapies (%)	
Antiplatelet	61
ACEI/ARB	81
Beta-blocker	53
Statin or Ezetimibe	75

P=NS for all between treatment arm comparisons

Cardiovascular Risk Factors

HbA1c

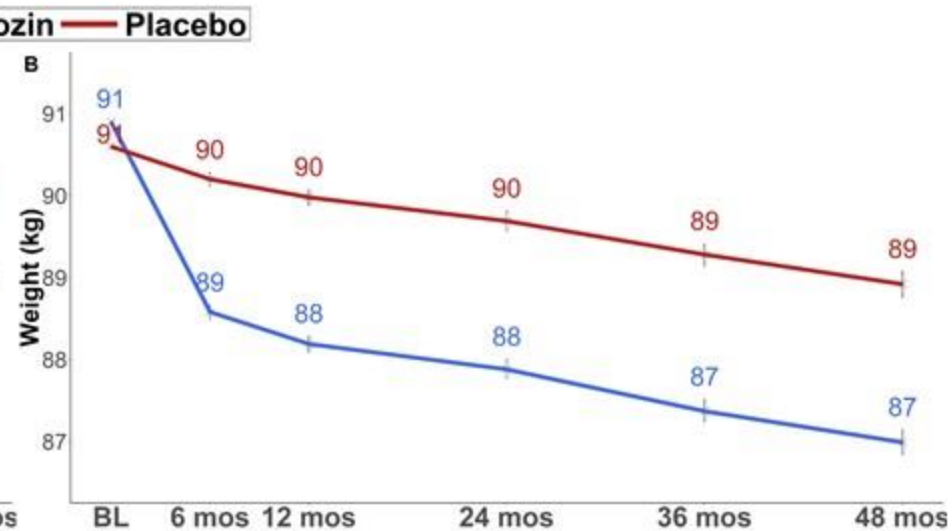
LSM Difference 0.42% (95% CI 0.40-0.45)



All P-values (except BL) <0.001

Weight

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

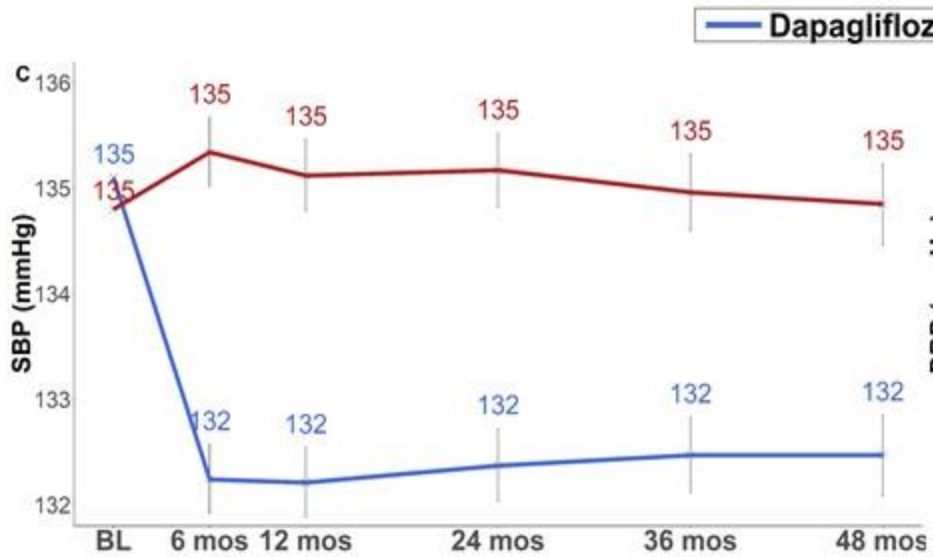


All P-values (except BL) <0.001

Cardiovascular Risk Factors

SBP

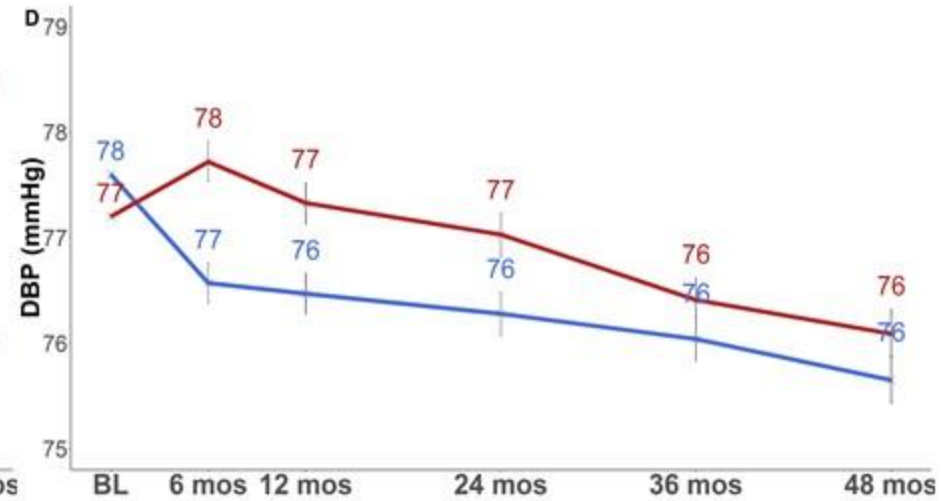
LSM Difference 2.7 mmHg (95% CI 2.4-3.0)



All P-values (except BL) <0.001

DBP

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

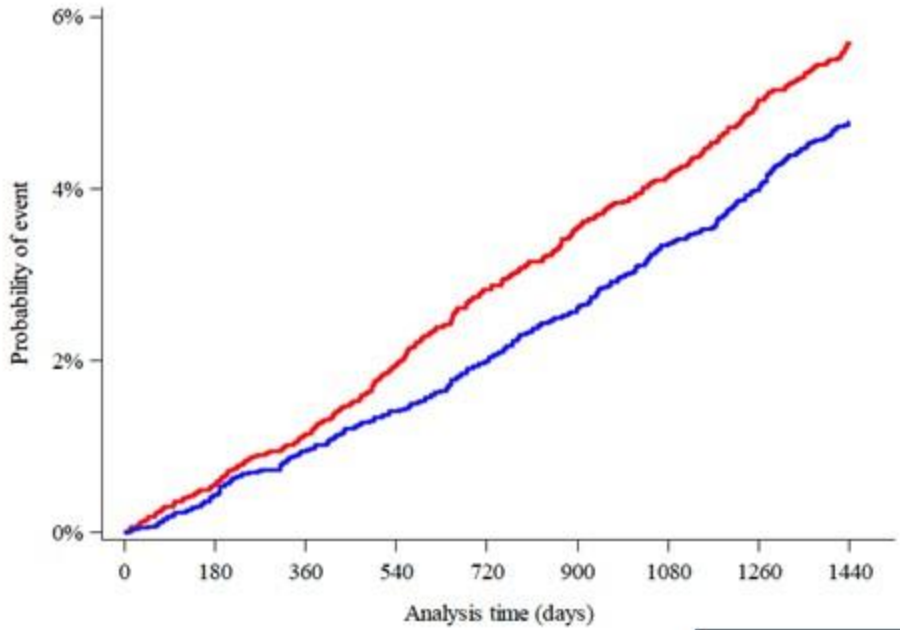


All P-values (except BL) <0.001

Primary Endpoints

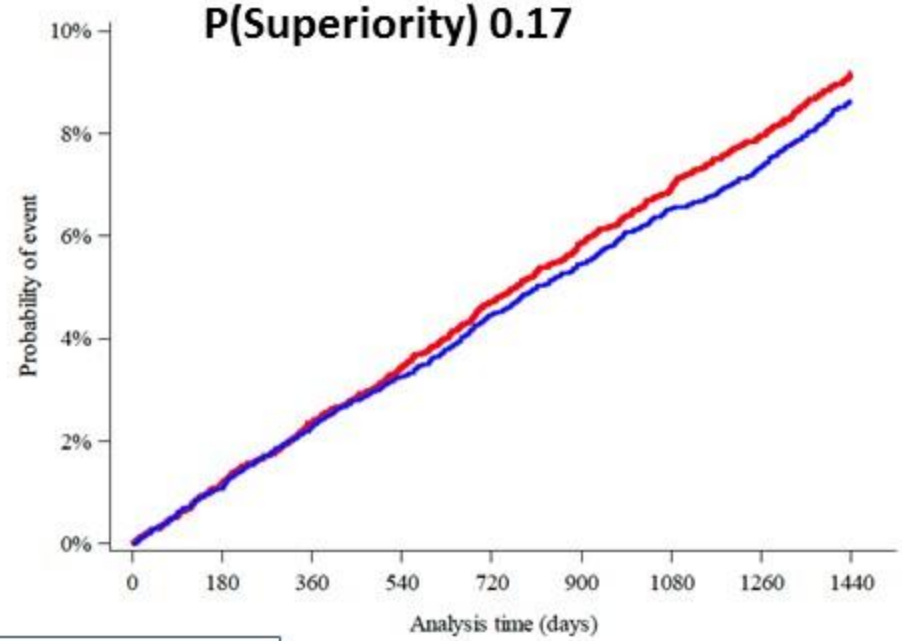
CVD/HHF

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



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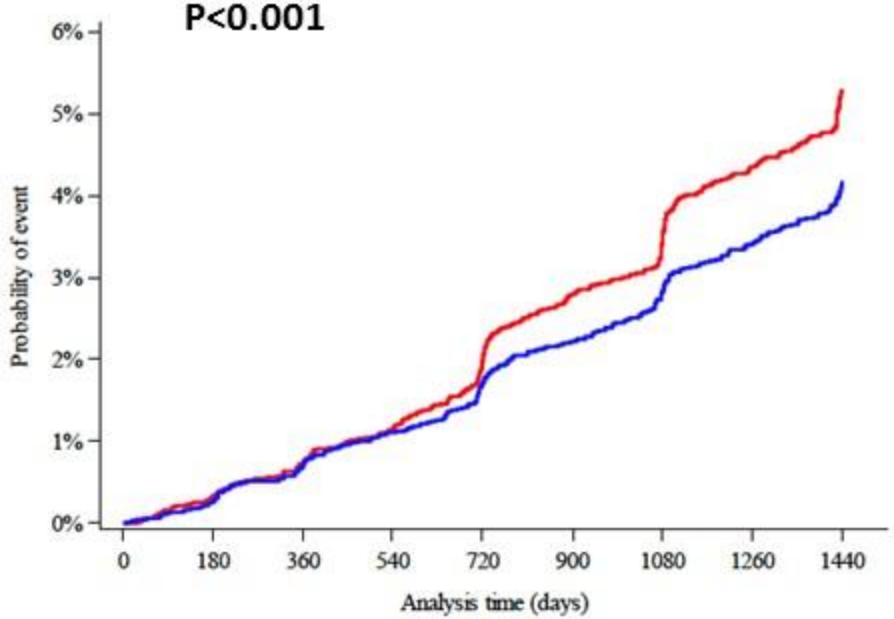
Secondary Endpoints

Renal Composite EP

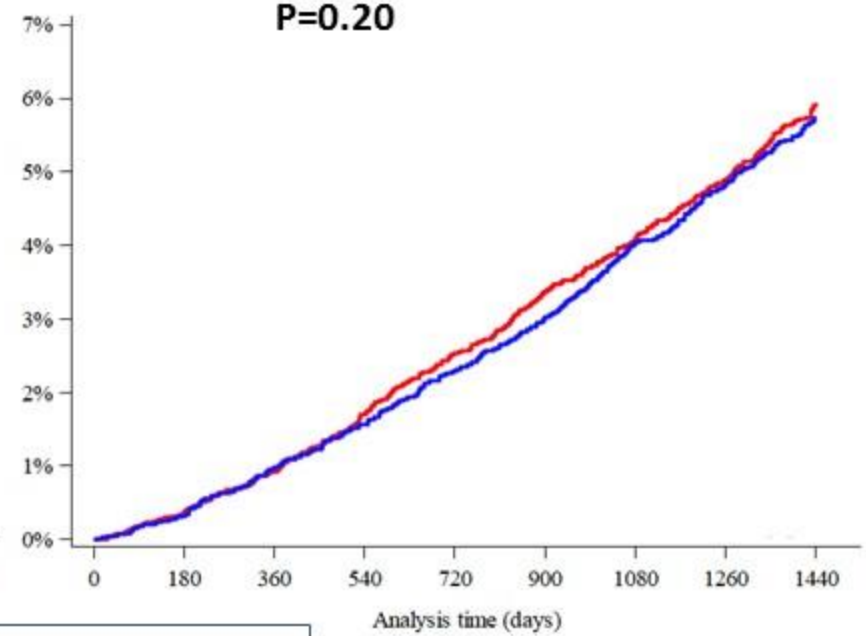
40%↓ eGFR, ESRD, Renal or CV death

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



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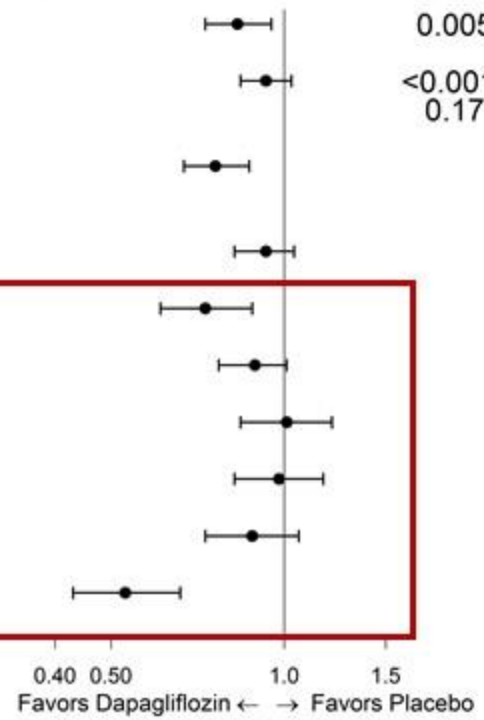
Endpoints and Components

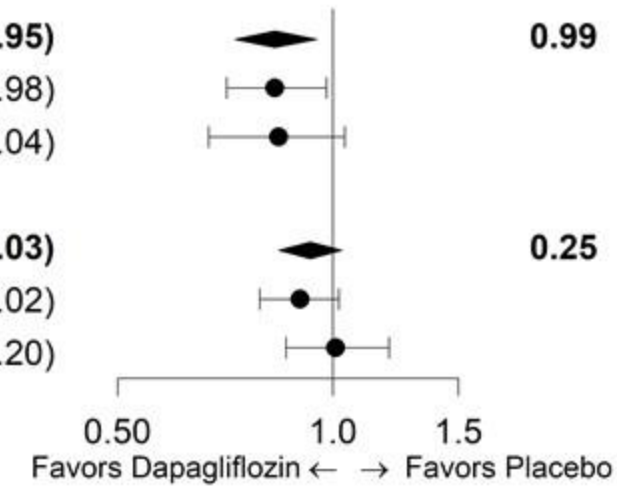
	Dapagliflozin rate/1000 patient-yr	Placebo rate/1000 patient-yr	Hazard Ratio (95% CI)	P value
CV death/HHF	12.2	14.7	0.83 (0.73-0.95)	0.005*
MACE	22.6	24.2	0.93 (0.84-1.03)	<0.001** 0.17*
40% decrease in eGFR to <60 ml/min/m2, ESRD, or renal or CV death	10.8	14.1	0.76 (0.67-0.87)	
All-cause death	15.1	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

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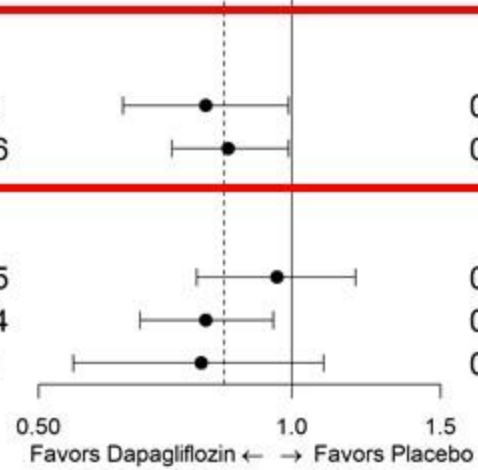
CVD/HHF

	Dapagliflozin n\N	Placebo n\N	HR (95%-CI)	P Value for Interaction
Total Cohort	**417/8582**	**496/8578**	**0.83 (0.73-0.95)**	
Risk Group				**0.99**
ASCVD	272/3474	325/3500	0.83 (0.71-0.98)	
MRF	145/5108	171/5078	0.84 (0.67-1.04)	
History of HF				**0.60**
Yes	142/852	172/872	0.79 (0.63-0.99)	
No	275/7730	324/7706	0.84 (0.72-0.99)	
eGFR				**0.37**
>=90 mL/min/1.73m2	163/4137	163/4025	0.96 (0.77-1.19)	
60 - <90 mL/min/1.73m2	199/3838	252/3894	0.79 (0.66-0.95)	
<60 mL/min/1.73m2	55/606	81/659	0.78 (0.55-1.09)	



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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

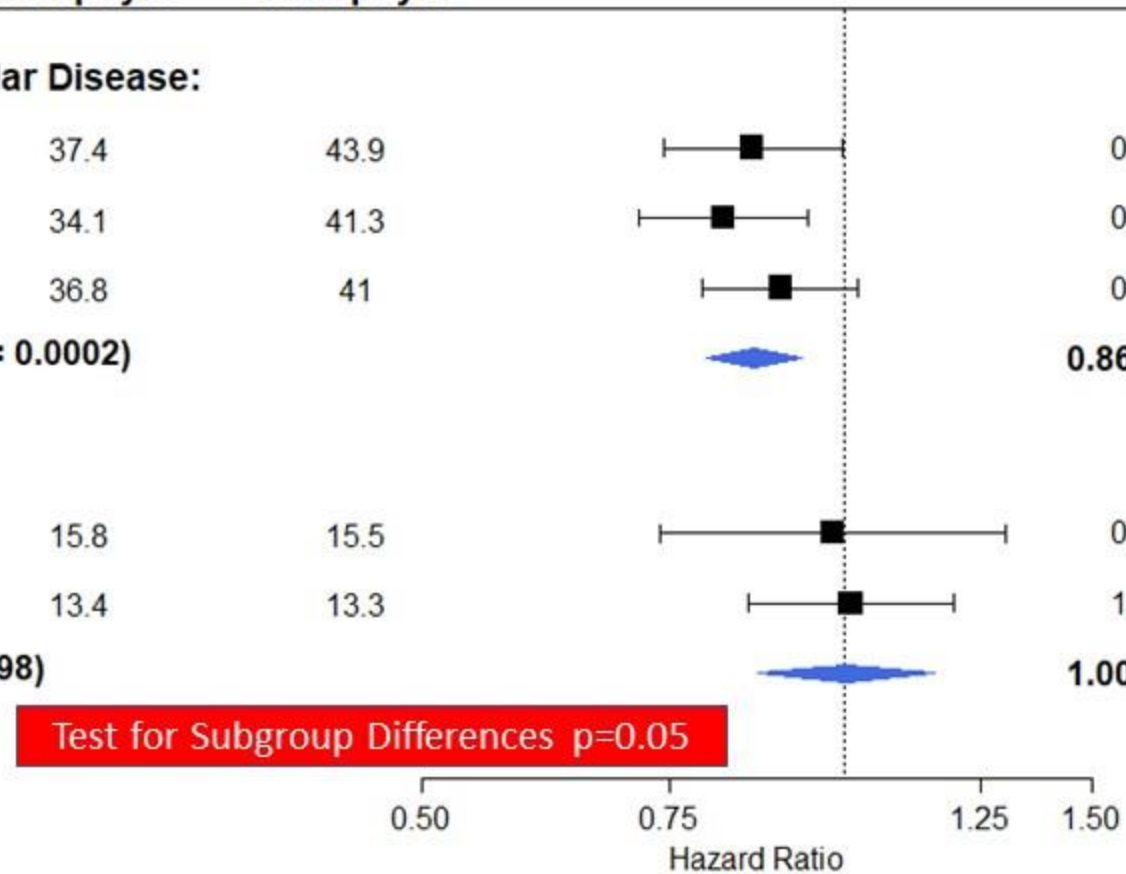
Summary

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]**



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

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

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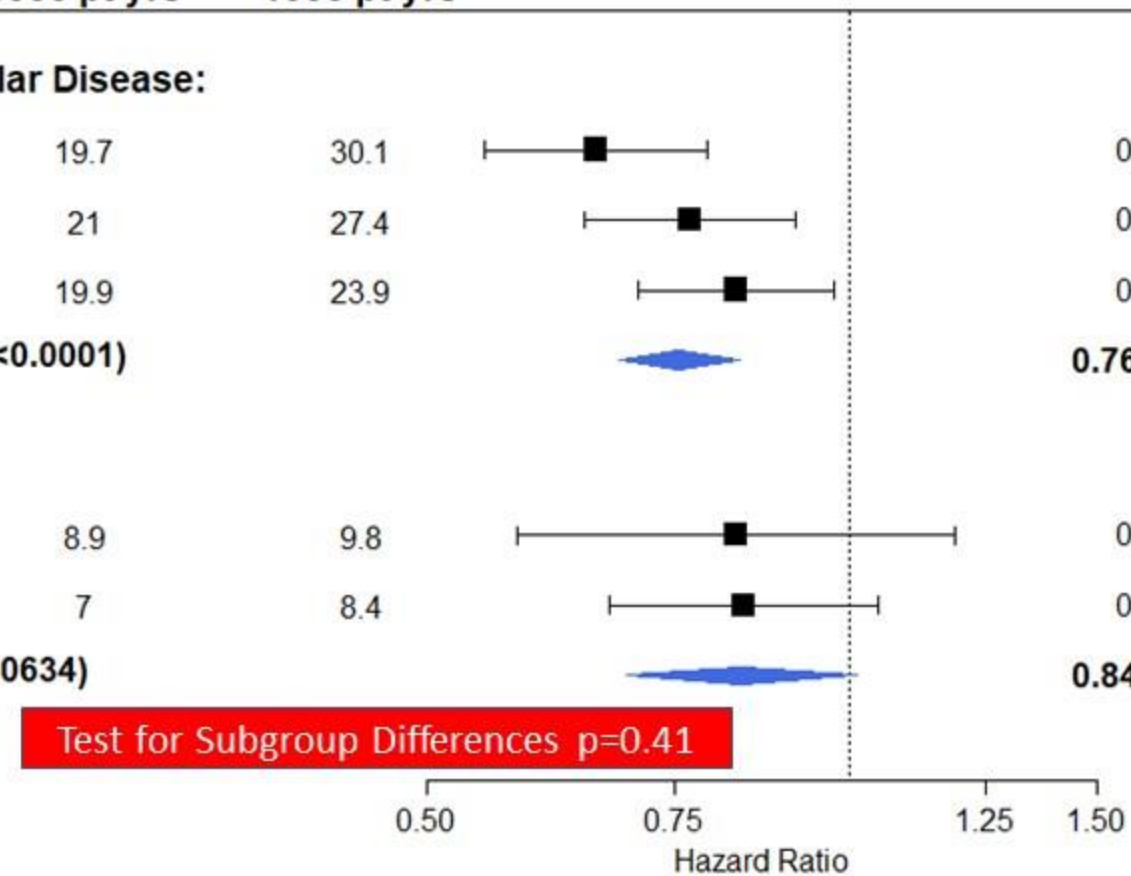
CVD/HHF	Treatment Events per 1000 pt-yrs	Placebo Events per 1000 pt-yrs	HR [95% CI]
Atherosclerotic Cardiovascular Disease:			
EMPA-REG OUTCOME	19.7	30.1	0.66 [0.55, 0.79]
CANVAS Program	21	27.4	0.77 [0.65, 0.92]
DECLARE-TIMI 58	19.9	23.9	0.83 [0.71, 0.98]
FE Model for ASCVD (P-value <0.0001)			**0.76 [0.69, 0.84]**
Multiple Risk Factor:			
CANVAS Program	8.9	9.8	0.83 [0.58, 1.19]
DECLARE-TIMI 58	7	8.4	0.84 [0.67, 1.04]
FE Model for MRF (P-value = 0.0634)			**0.84 [0.69, 1.01]**



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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