Declaring the New Landscape of Type 2 Diabetes Mellitus in the Primary Care Setting

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AHA SFRN in Peripheral Vascular Disease

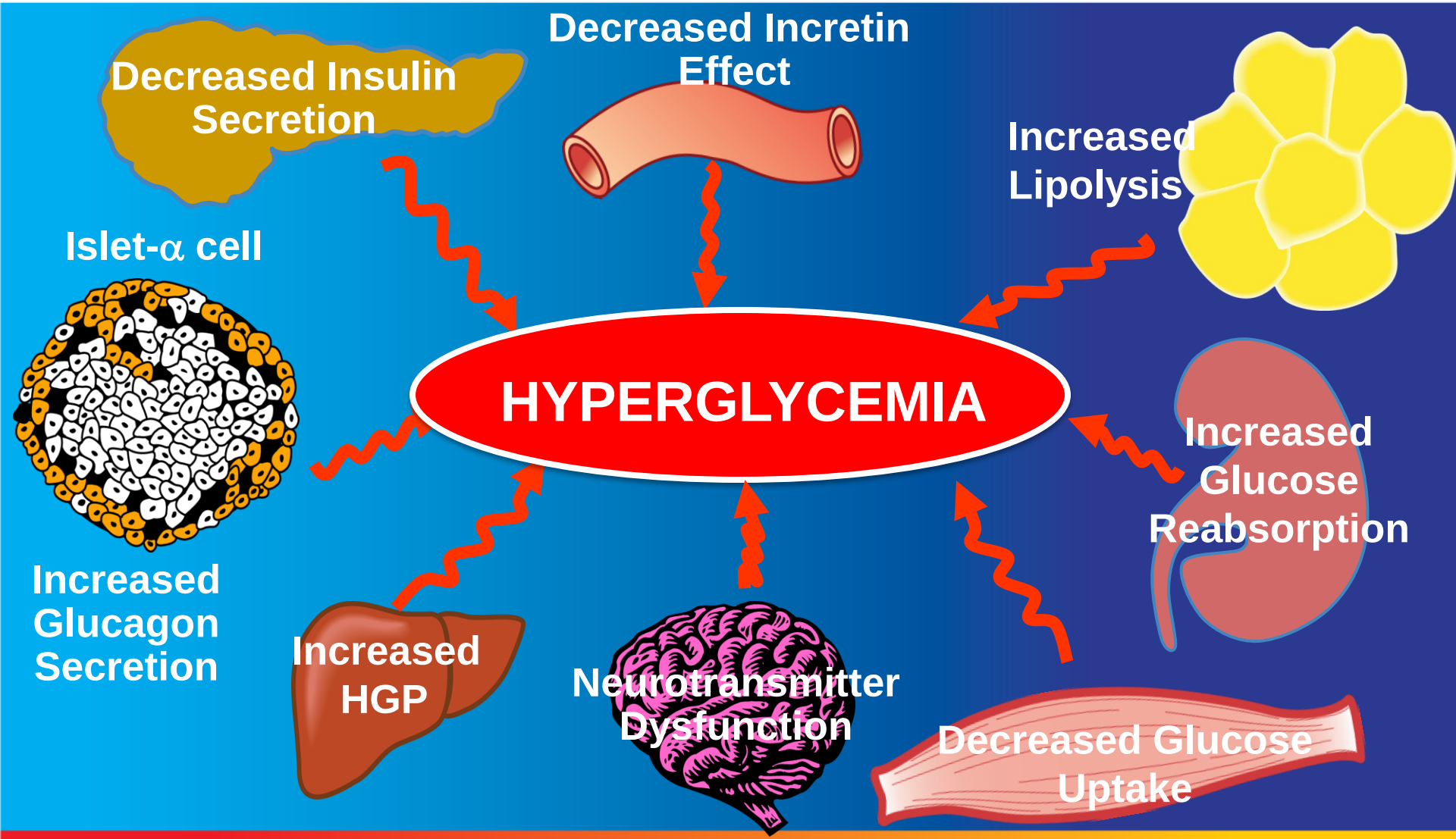
Harvard University, Boston

Disclosures

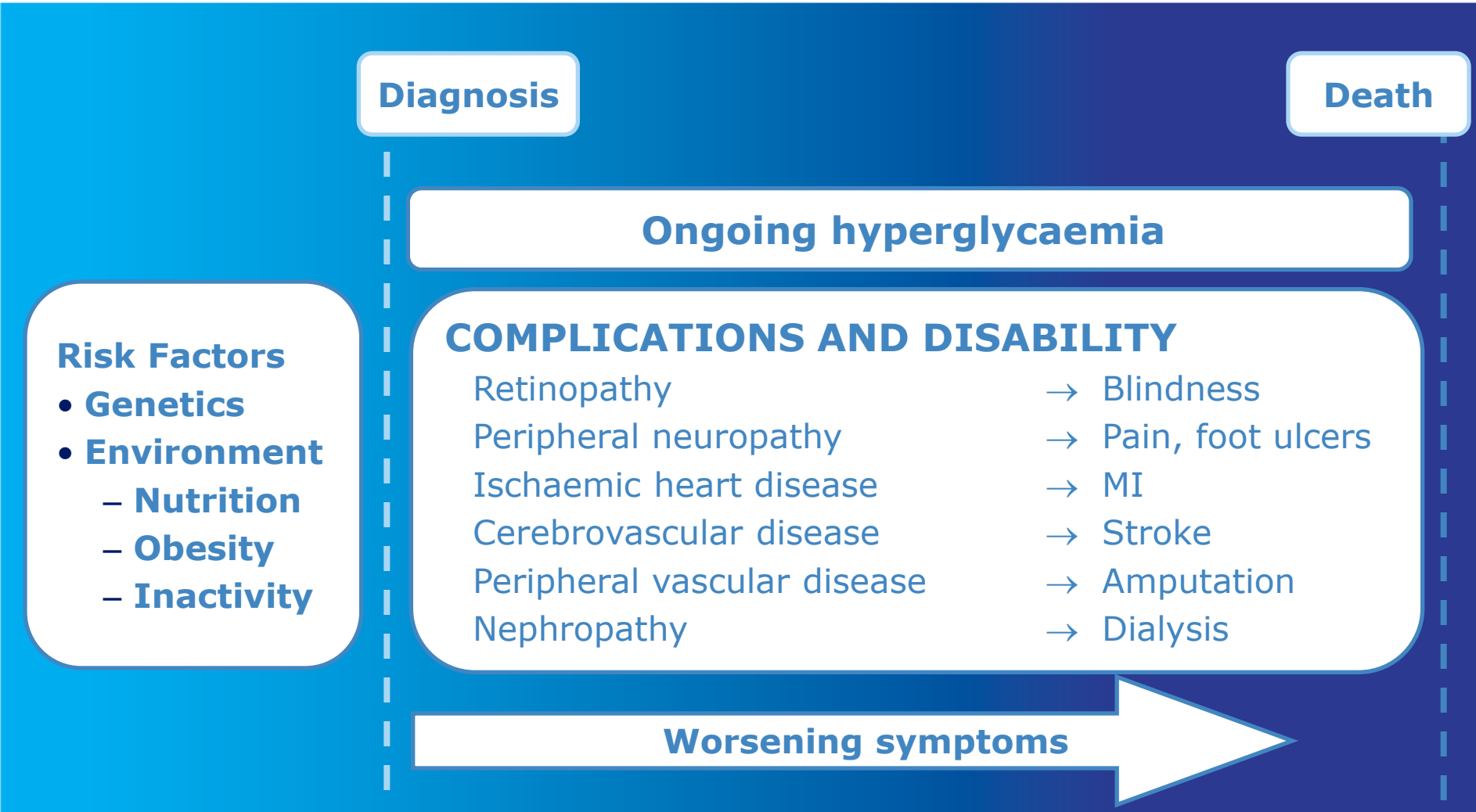
Grant Support to BWH from AstraZeneca

Consulting from AstraZeneca, Janssen, Bayer

Ominous Octet



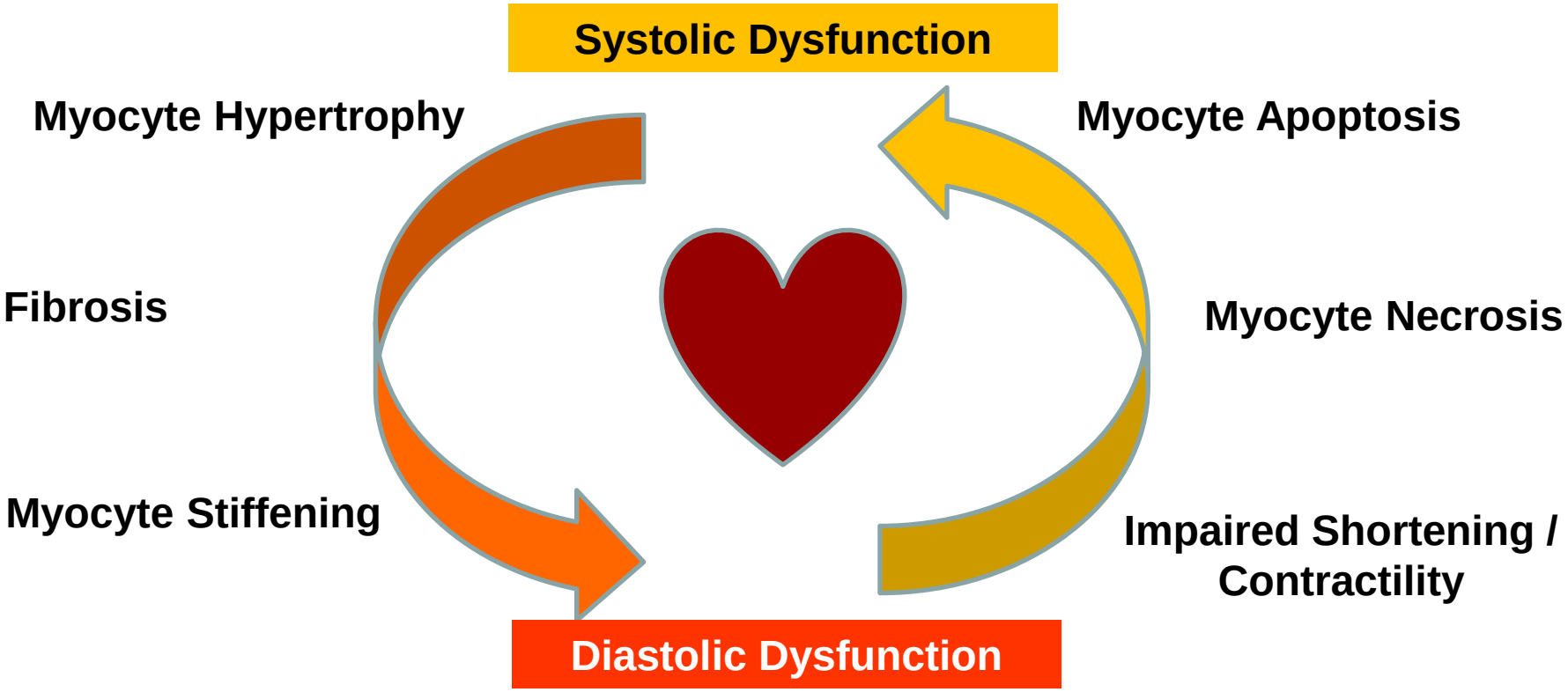
Micro and Macro Vascular Complications are Associated with T2DM



Adapted from: Brown *et al. Diabetes Obes Metab* 2000;2(Suppl):S11–18

Diabetes and Heart Failure
A “Special” Relationship

~2/3 of Patients with T2DM have evidence of LV dysfunction (diastolic or systolic) 5 years from diagnosis (without ischemia!)

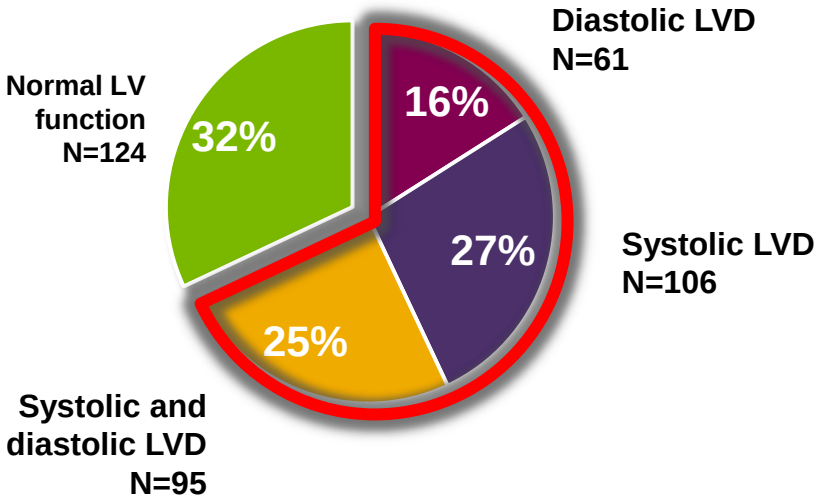


LV, left ventricular; LVD, LV dysfunction

Faden G, et al. *Diabetes Res Clin Res.* The increasing detection of asymptomatic left ventricular dysfunction in patients with type 2 diabetes mellitus without overt cardiac disease: data from the SHORTWAVE study 2013101;309-316; Seferović PM, Paulus WJ. *Eur Heart J.* 2015;36:1718-27, 1727a-1727c

Diabetes and Heart Failure
A “Special” Relationship

68% of patients with T2D had evidence of LV dysfunction 5 years after T2D diagnosis

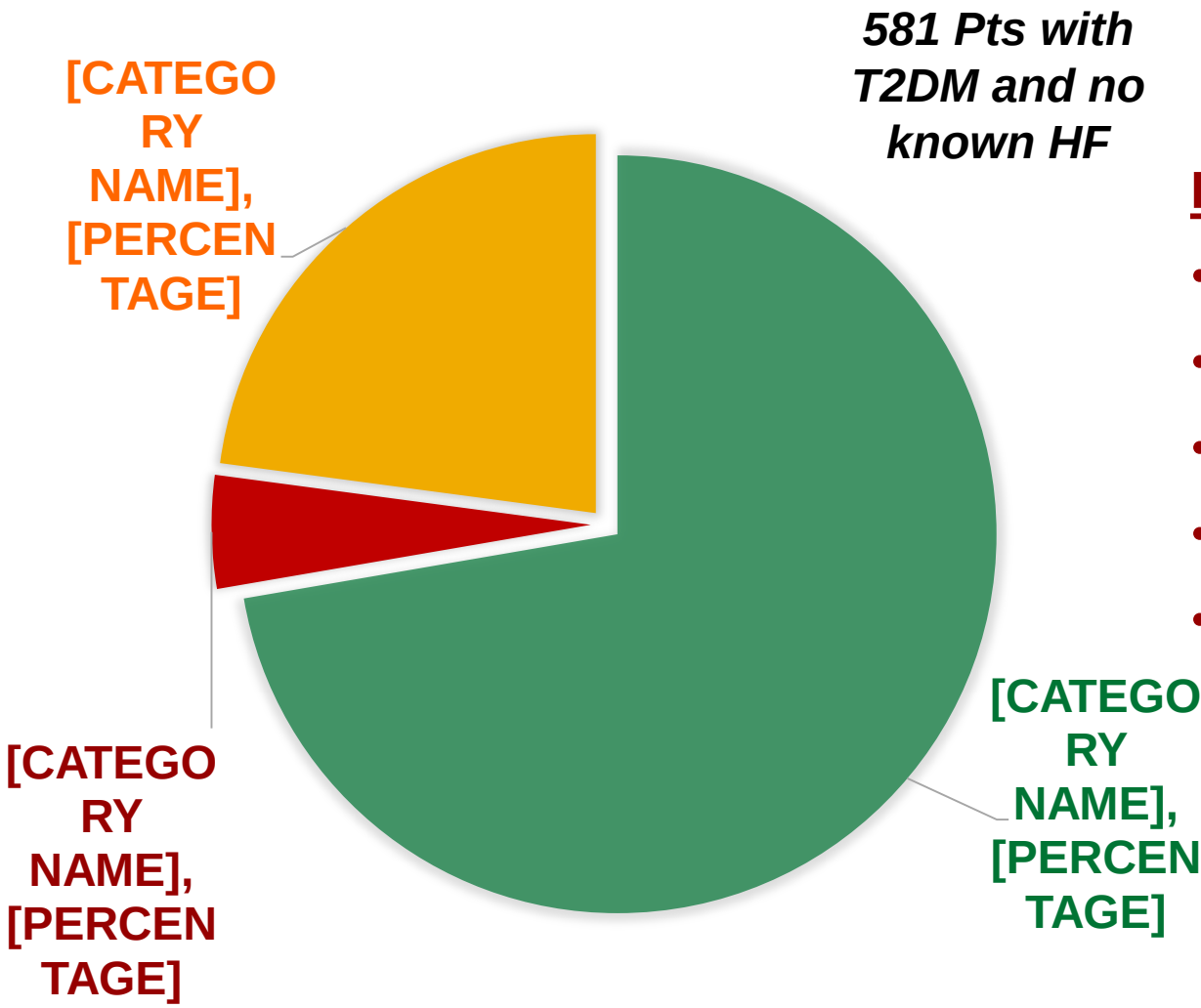


This suggests the earliest defect in the diabetic heart may be diastolic dysfunction rather than atherothrombosis

LV, left ventricular; LVD, LV dysfunction

Faden G, et al. *Diabetes Res Clin Res.* The increasing detection of asymptomatic left ventricular dysfunction in patients with type 2 diabetes mellitus without overt cardiac disease: data from the SHORTWAVE study 2013101;309-316; Seferović PM, Paulus WJ. *Eur Heart J.* 2015;36:1718-27, 1727a-1727c

Many Patients with T2DM have HF and Don't Know It "Subclinical HF"



581 Pts with T2DM and no known HF

Risk Factors

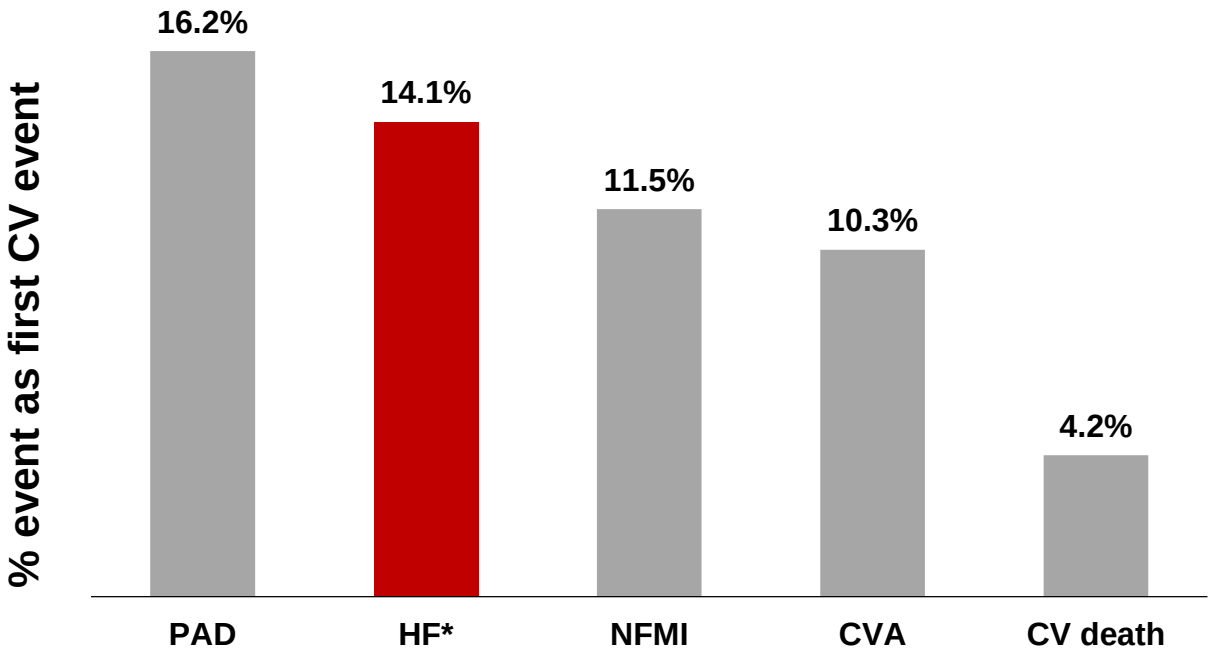
- **Age**
- **Females**
- **BMI ≥30 kg/m^2**
- **Hypertension**
- **Complaints of Dyspnea or Fatigue**

HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; T2DM, Type 2 diabetes mellitus

Boonman-de Winter LJ, et al High prevalence of previously unknown heart failure and left ventricular dysfunction in patients with type 2 diabetes. *Diabetologia* 2012;55:2154–2162

Heart Failure is one of the Earliest Manifestations of Cardiovascular Disease in Patients with T2DM

Cohort study of patients (n= 1.9 million) with T2DM and incidence of CV disease



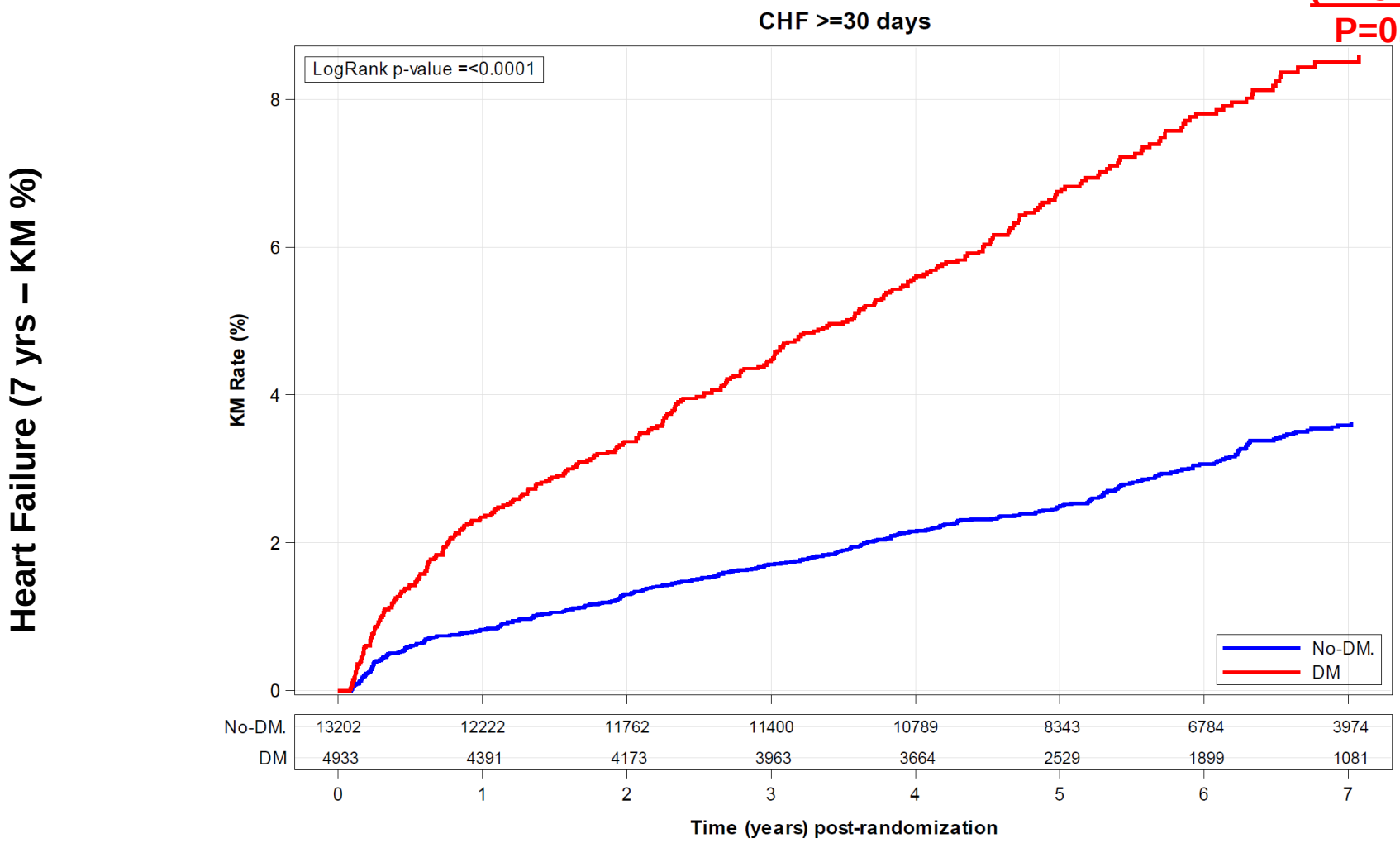
*Heart failure post MI was not included in this definition of HF

CV, cardiovascular; CVA, cerebrovascular accident; HF, heart failure; NFMI, nonfatal myocardial infarction; PAD, peripheral arterial disease; T2D, type 2 diabetes.

Shah AD, et al. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1·9 million people. Lancet Diabetes Endocrinol. 2015;3:105-113, Appendix.

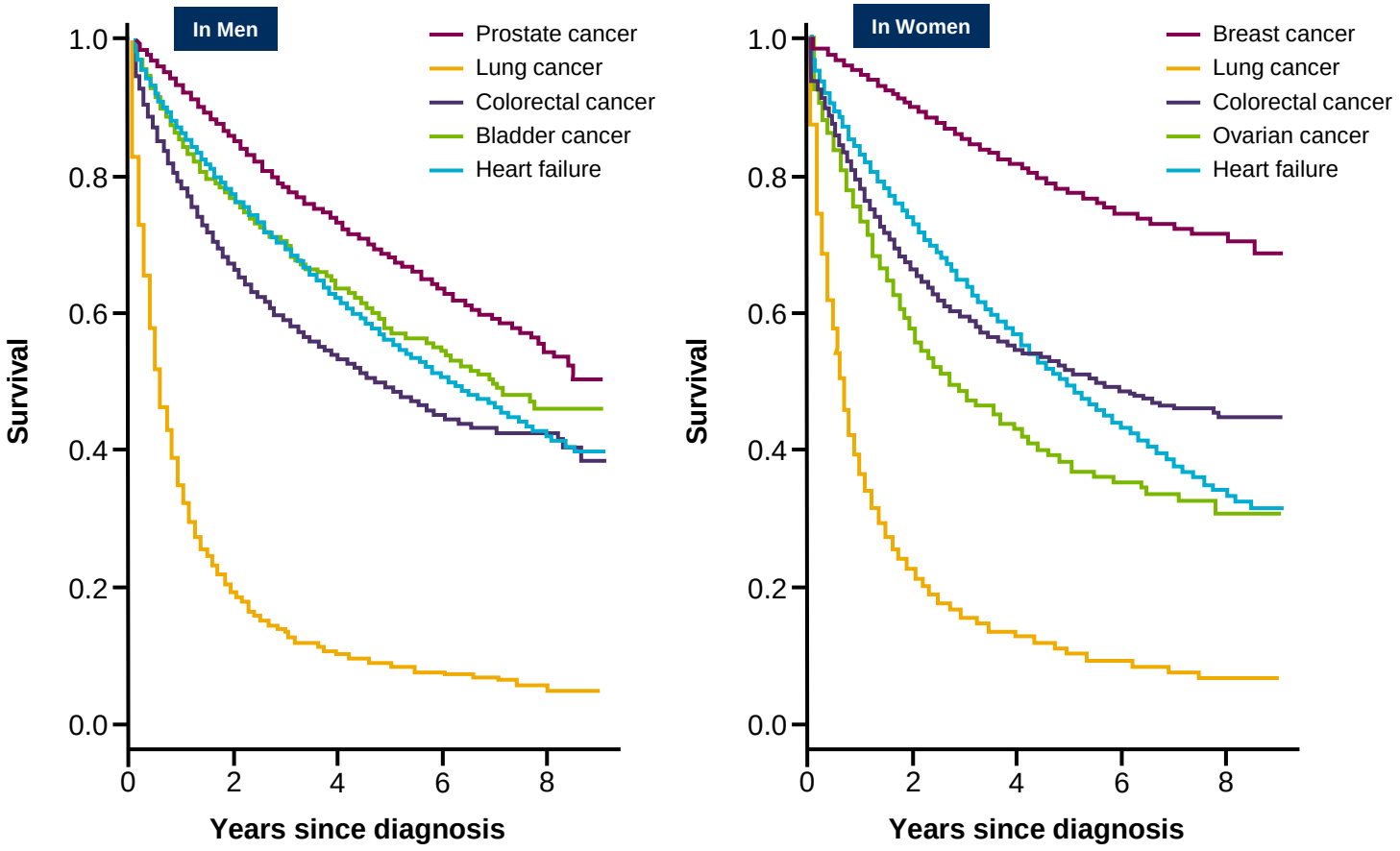
Concomitant T2DM Increases the Risk of HF by 70% after ACS

Adjusted HR 1.70 (1.23 – 2.34) P=0.0012



Bonaca et al. Lancet Diabetes & Endocrinology 2018

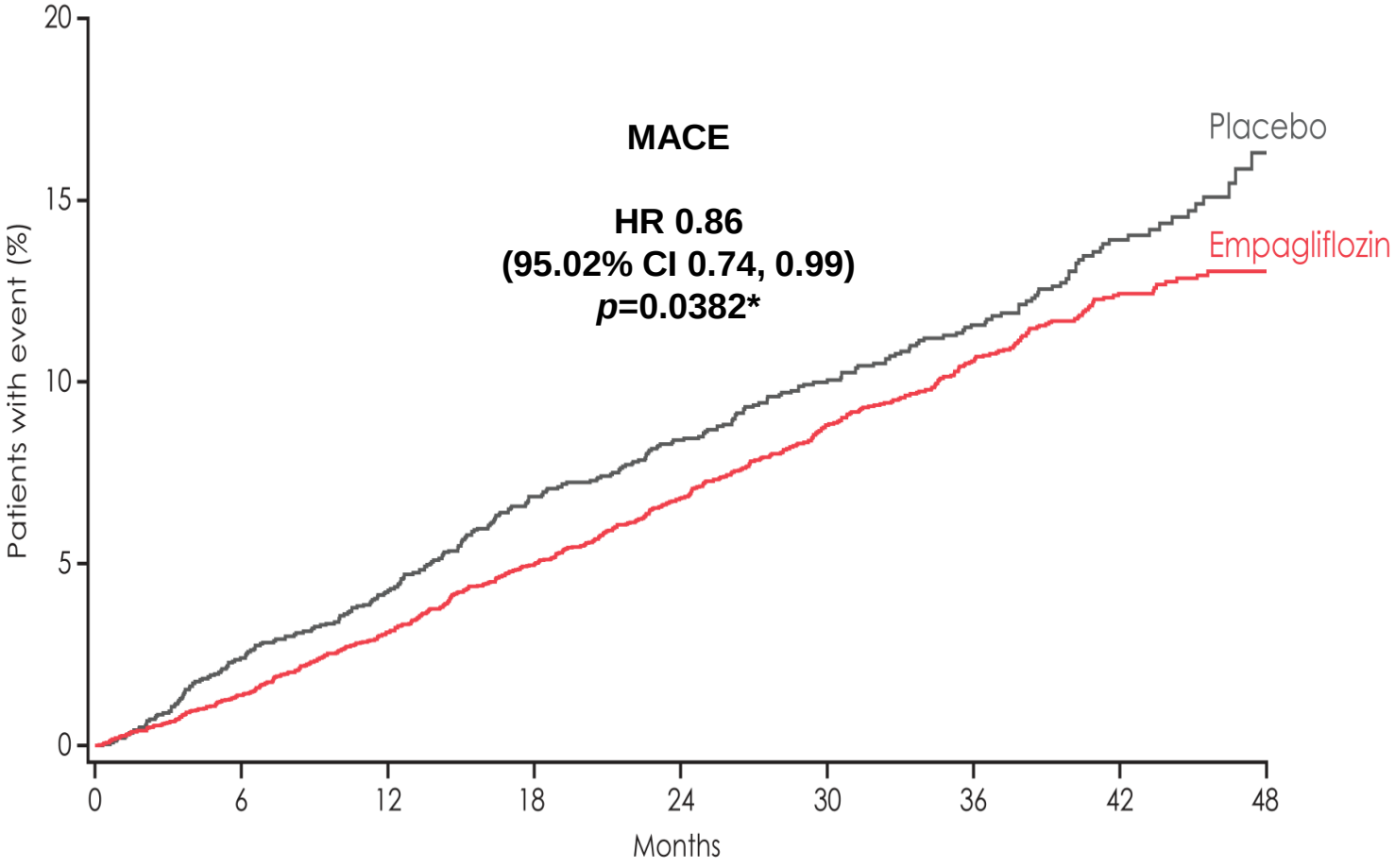
Prognosis in Patients with Heart Failure is Similar to Cancer



HF, heart failure

Mamas MA. et al. Do patients have worse outcomes in heart failure than in cancer? A primary care-based cohort study with 10-year follow-up in Scotland *Eur J of Heart Failure* 2017.19:1095–1104

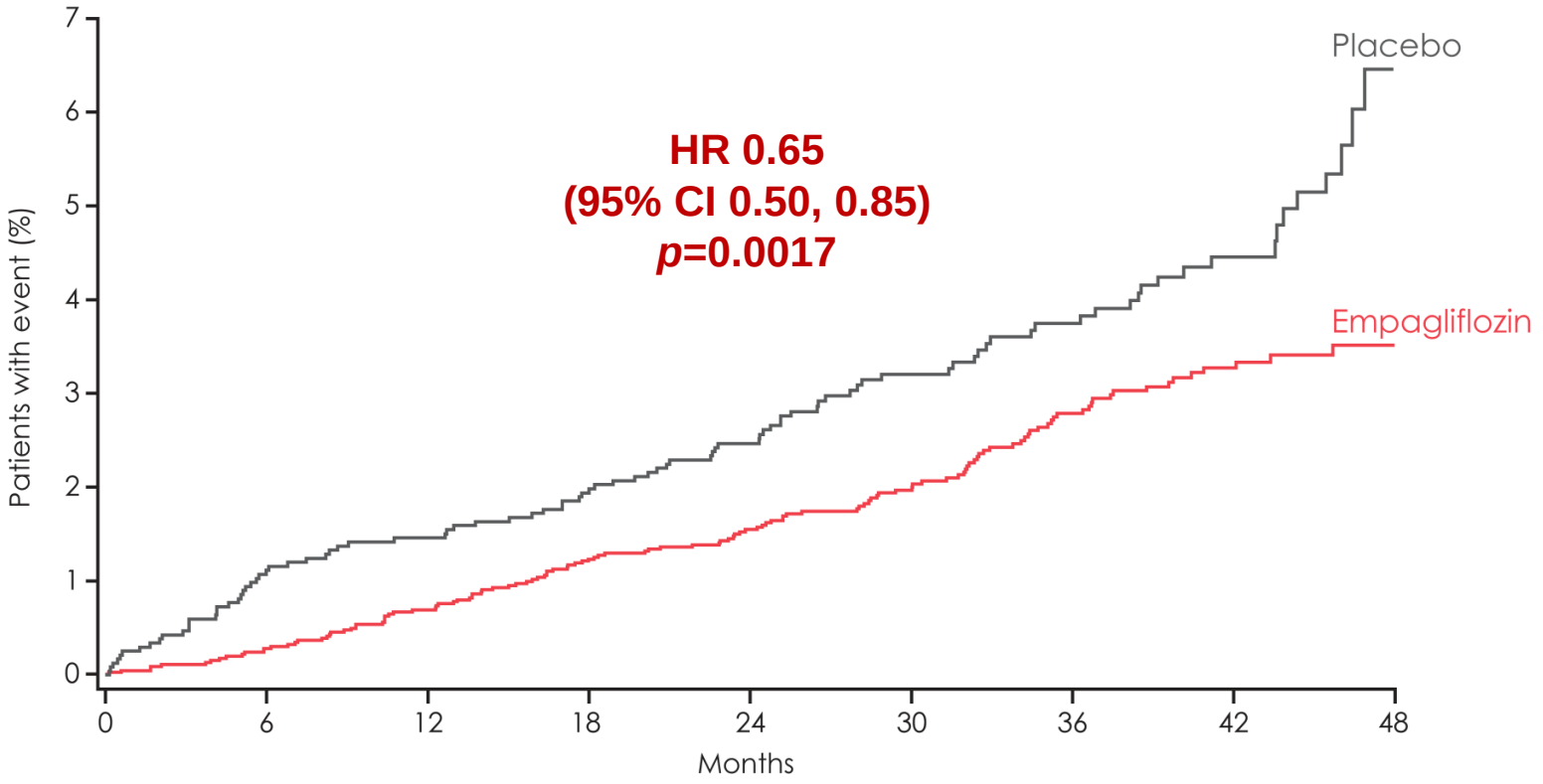
SGLT2i in Patients with Established CVD
Major Adverse Cardiovascular Events



Zinman et al. NEJM 2015

Median 3.2 Yrs Follow up

SGLT2i in Patients with Established CVD
Hospitalization for Heart Failure

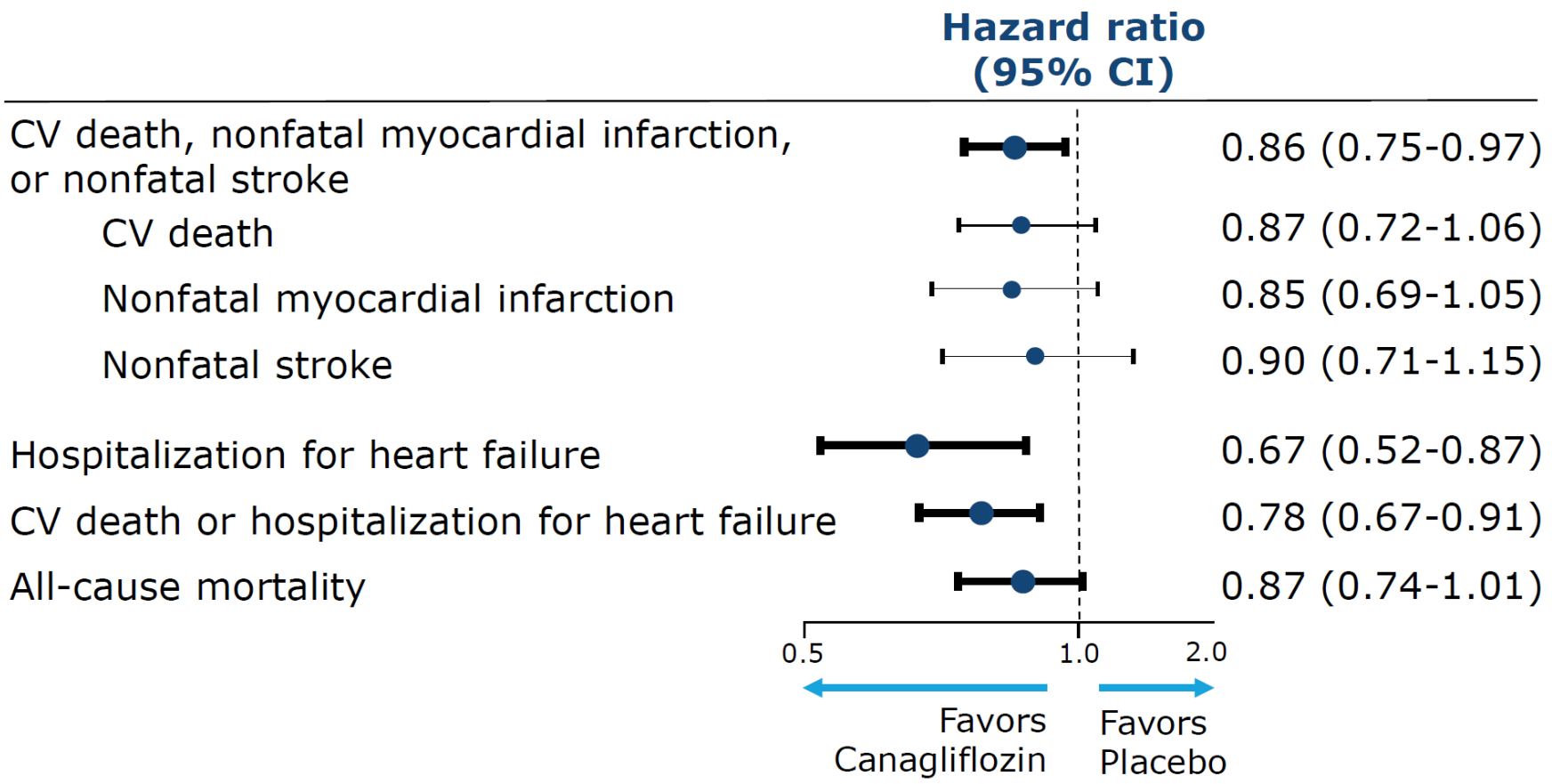


Zinman et al. NEJM 2015

Canagliflozin in T2DM

Other vascular events and death

T2DM with 2/3 having eCVD for ~3.5 yrs



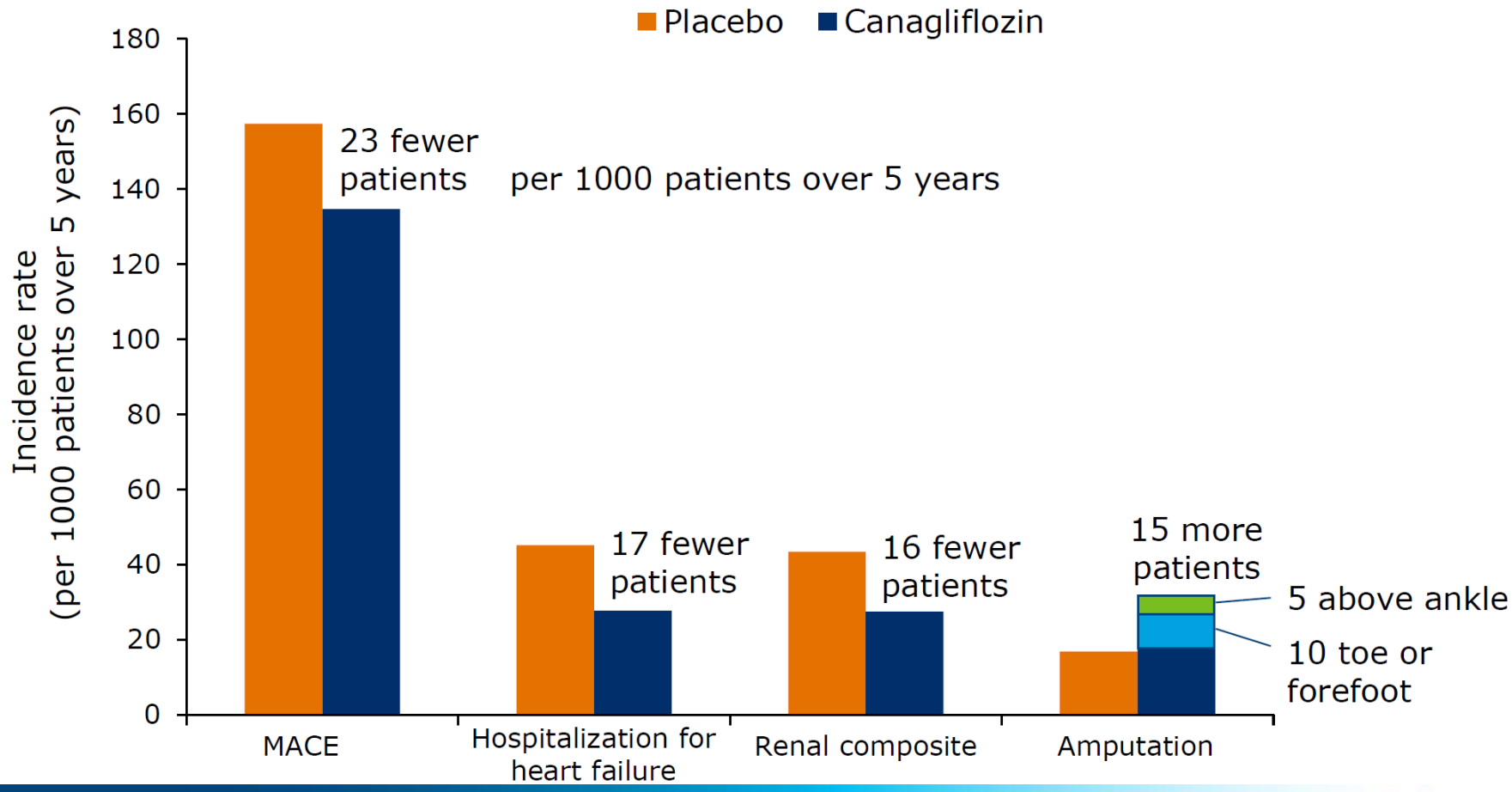
Intent-to-treat analysis

CANVAS Program

Neal et al. NEJM 2017

Canagliflozin in T2DM

Benefits and risk



CANVAS Program

Neal et al. NEJM 2017

Remaining Questions about SGLT2i In T2DM

Two trials for MACE reduction but are the benefits driven by HHF and renal endpoints?

Do the benefits extend to primary prevention?

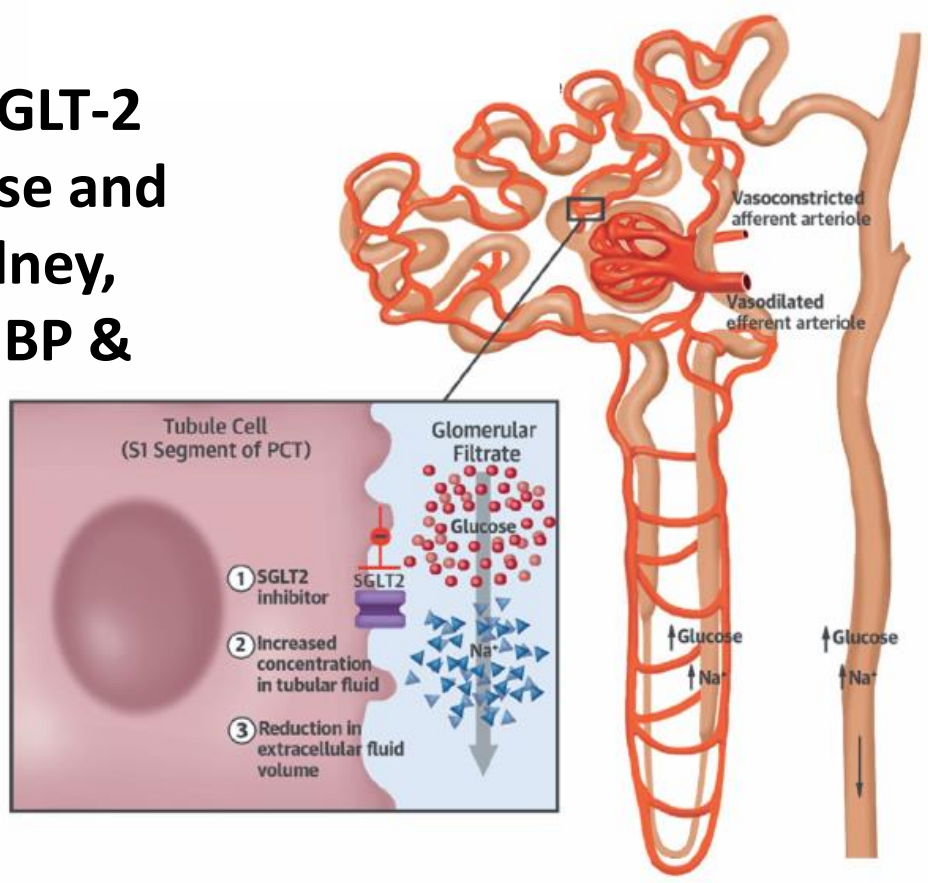
Is this a therapy for primary care or just subspecialties (e.g. endocrine, cardiology)?

What is the safety especially long-term?

- **Bladder cancer**
- **Fournier's gangrene**
- **Fractures**
- **Amputations**

Background

- **Patients with type 2 DM are at high risk for *development of* and *complications from* heart failure and atherosclerotic vascular disease.**
- **Dapagliflozin is a selective SGLT-2 inhibitor which blocks glucose and sodium resorption in the kidney, and thereby ↓ blood sugar, BP & weight.**



Zelniker TA, Braunwald E *JACC* 2018

Trial Design

17,160 with Type 2 DM
Established CV Disease (6974) or
Multiple Risk Factors (10186)

RANDOMIZE 1:1
DOUBLE BLIND

All other DM Rx per treating MD

DAPAGLIFLOZIN
10 mg DAILY

PLACEBO

Follow-up visits
In Person Q 6 mo/ telephone Q 3 mo

DURATION
EVENT DRIVEN
≥1390 MACE

Primary EPs
Safety: MACE (CVD/MI/Ischemic Stroke)
Dual Efficacy: CVD/HHF, MACE

Median follow up
4.2 years

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)

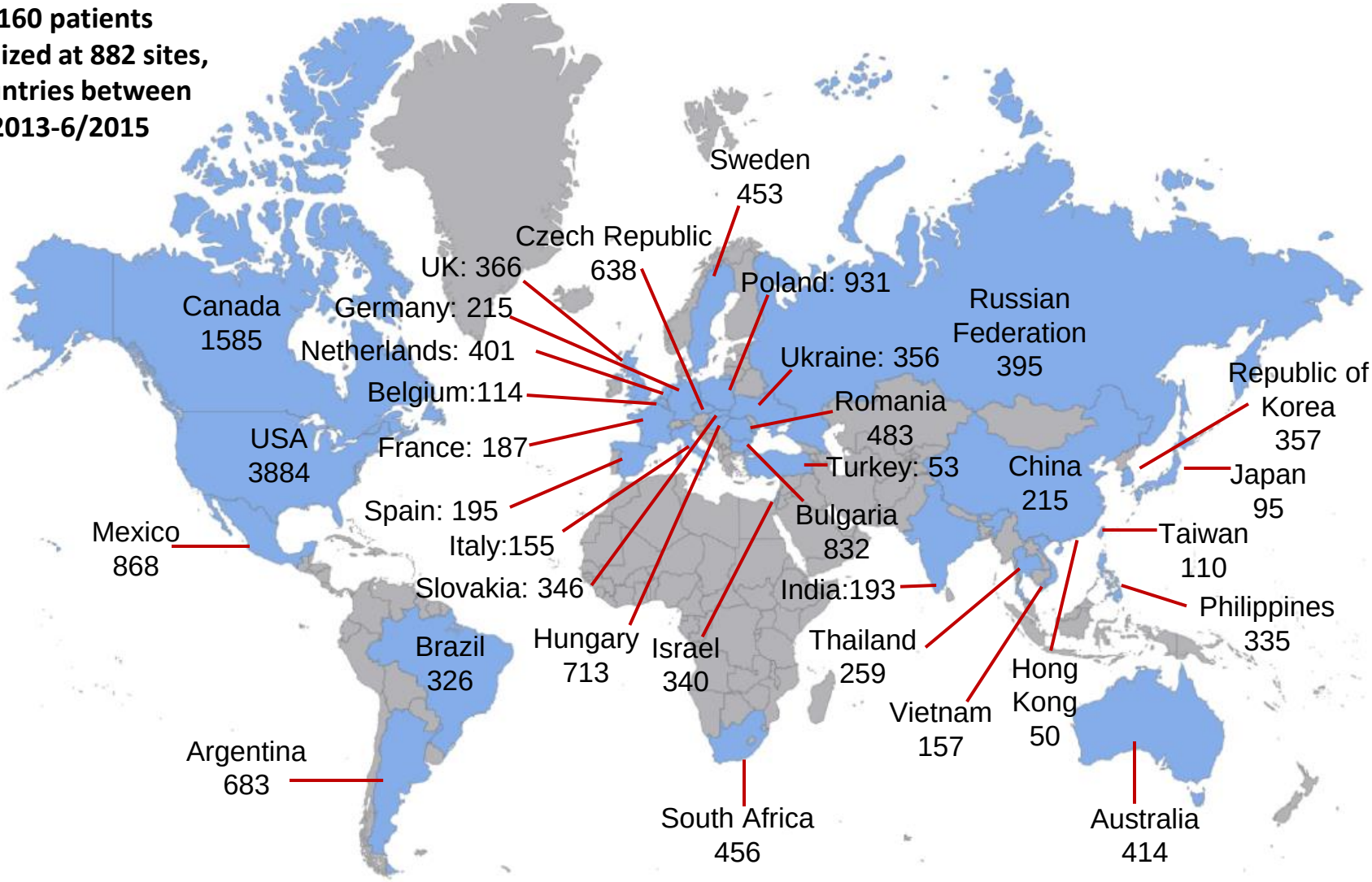
Men ≥ 55 yrs and women ≥ 60 yrs with at least one additional risk factor:

- Dyslipidemia
- Hypertension
- Current Tobacco use

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

Global Enrollment

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



Baseline Characteristics

	Full Trial Cohort N = 17160
Age , Mean (SD)	64 (7)
Female Sex (%)	37
BMI, Mean (SD)	32 (6)
Duration of T2DM, 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

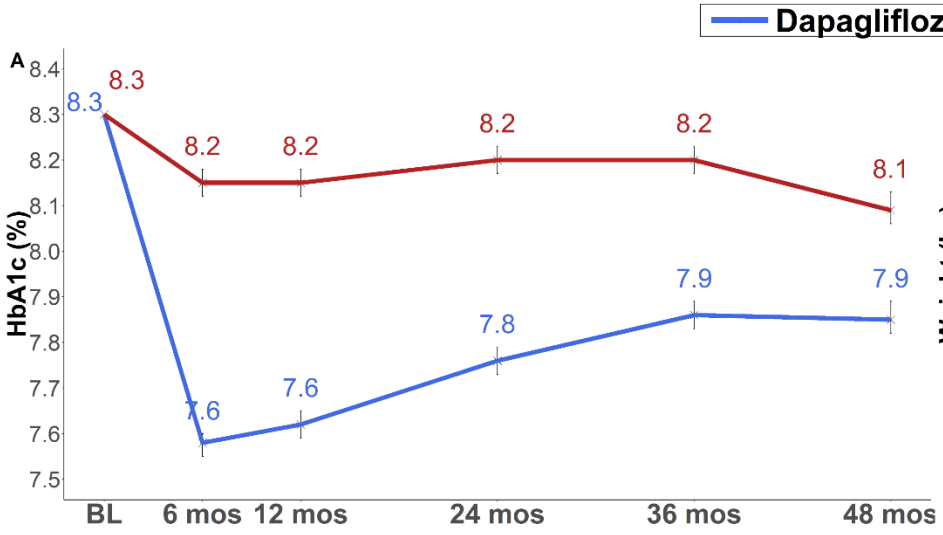
	Full Trial Cohort N = 17160
Glucose lowering therapies (%)	
Metformin	82
Insulin	41
Sulfonylurea	43
DPP4	17
GLP-1 RA	4
Cardiovascular Therapies (%)	
Antiplatelet	61
ACEI/ARB	81
Beta-blocker	53
Statin or Ezetimibe	75

P=NS for all between treatment arm comparisons

Cardiovascular Risk Factors

HbA1c

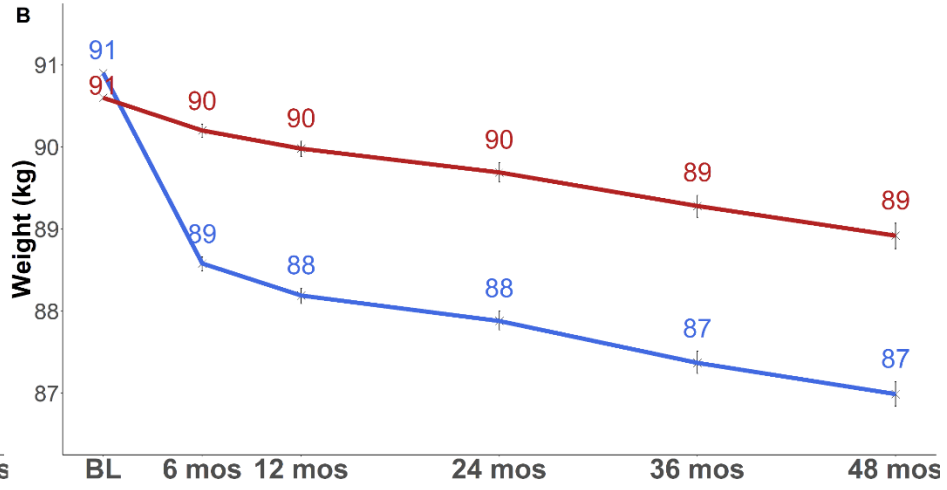
LSM Difference 0.42% (95% CI 0.40-0.45)



All P-values (except BL) <0.001

Weight

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

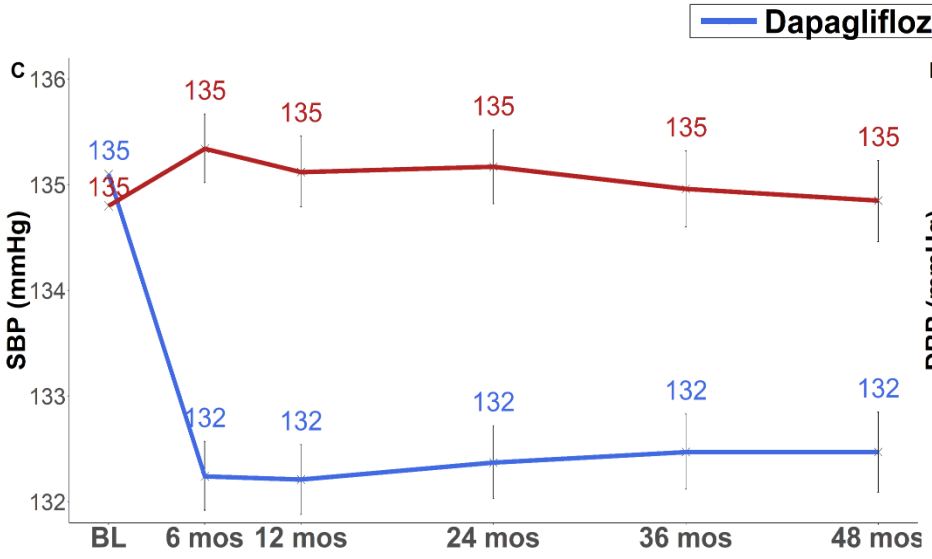


All P-values (except BL) <0.001

Cardiovascular Risk Factors

SBP

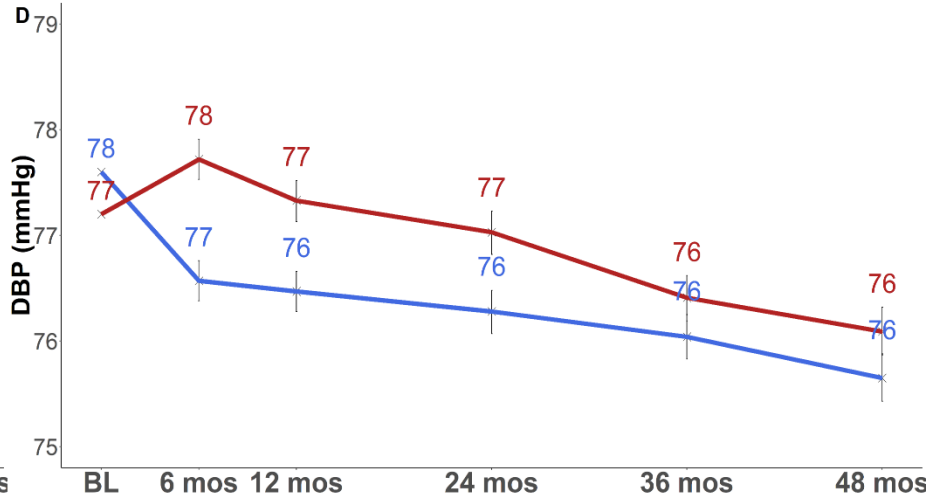
LSM Difference 2.7 mmHg (95% CI 2.4-3.0)



All P-values (except BL) <0.001

DBP

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

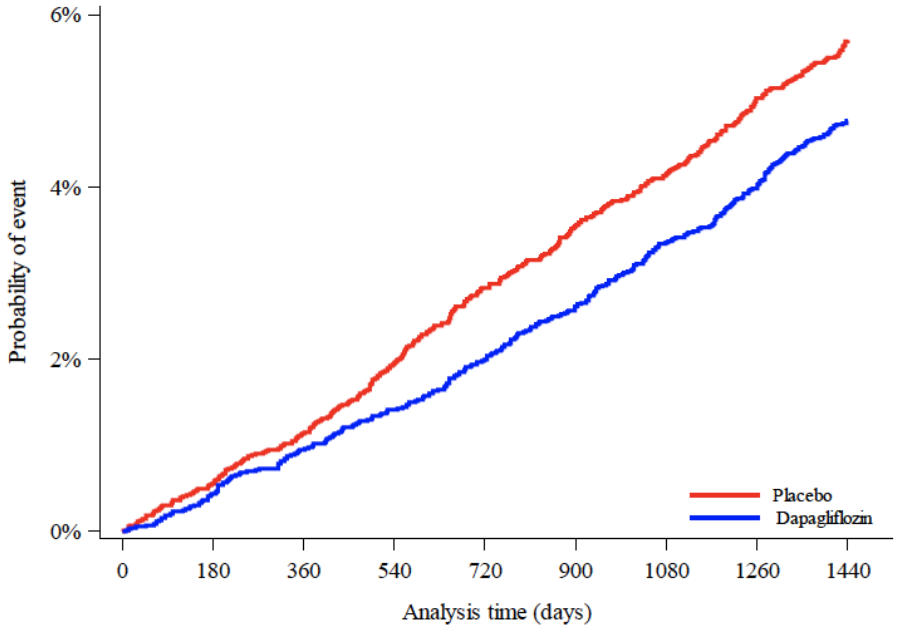


All P-values (except BL) <0.001

Primary Endpoints

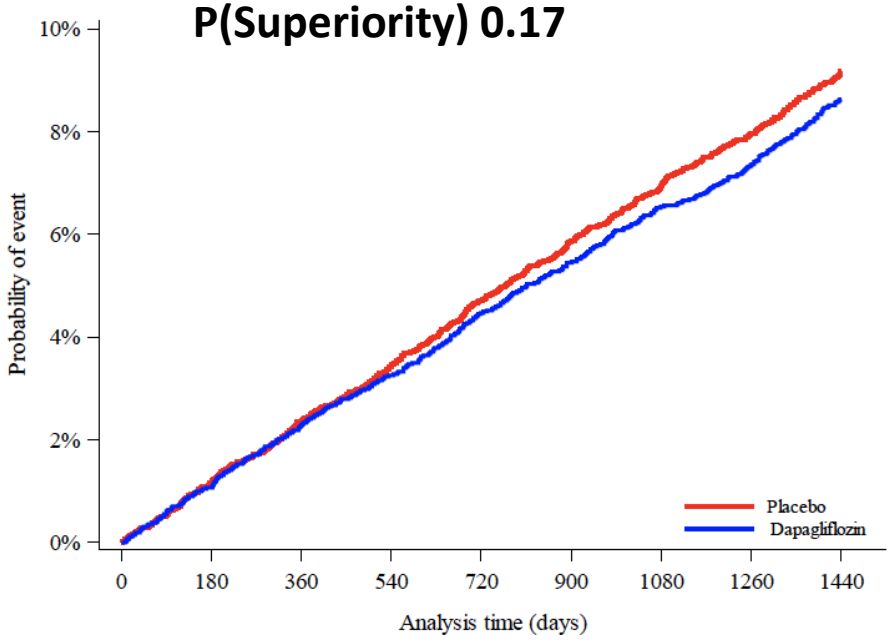
CVD/HHF

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

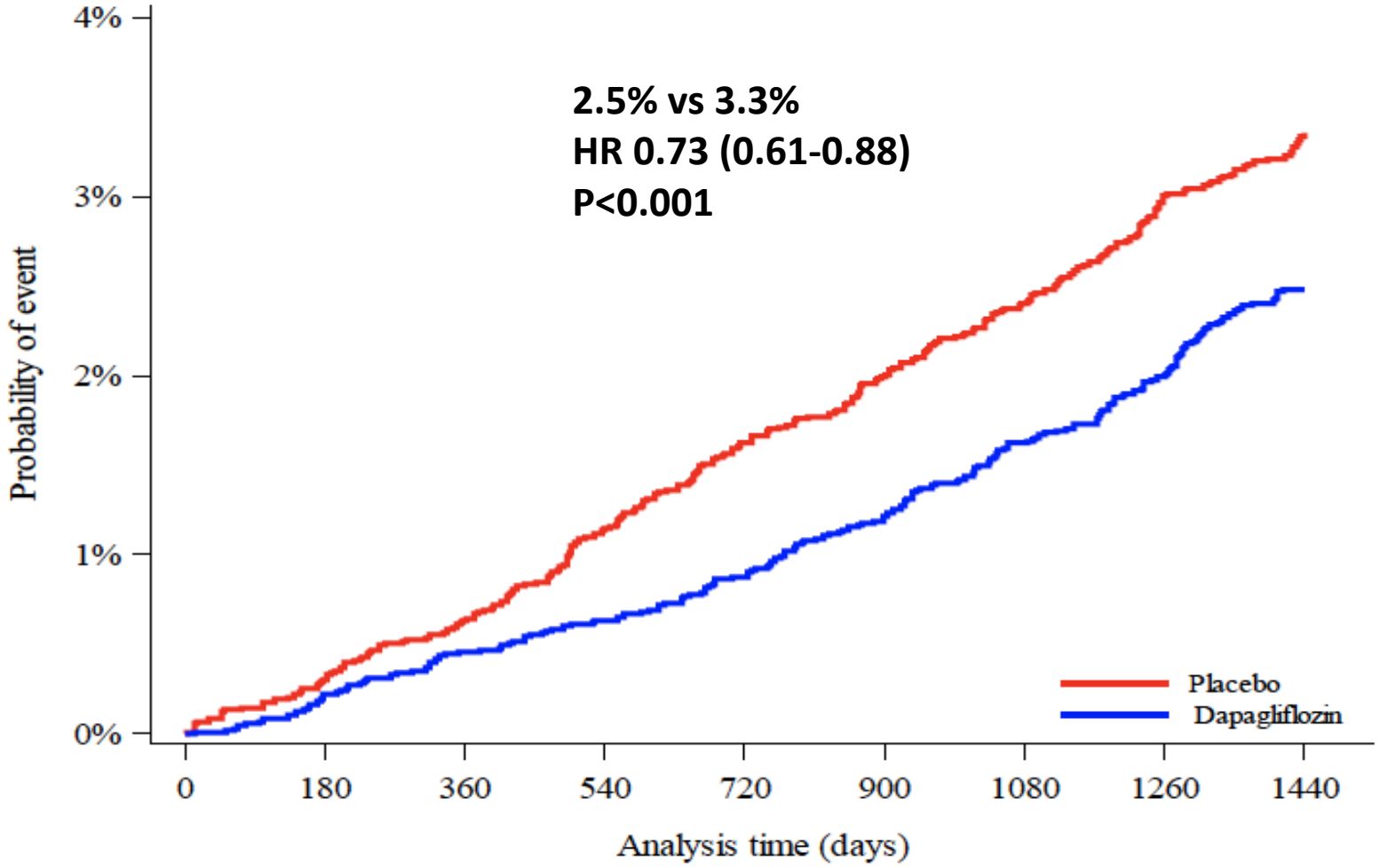


MACE

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



Hospitalization for Heart Failure

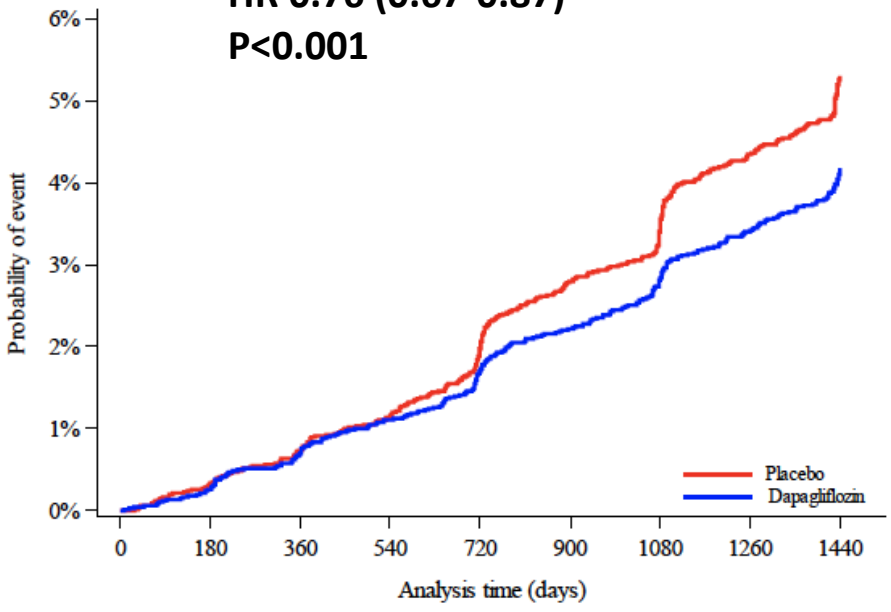


Secondary Endpoints

1st Renal Composite EP

40%↓ eGFR, ESRD, Renal or CV death

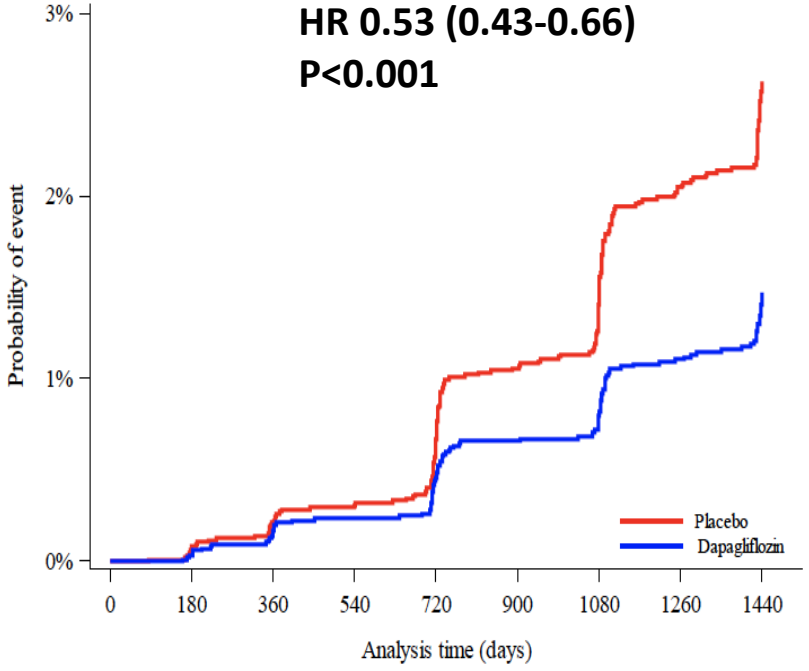
4.3% vs. 5.6%
HR 0.76 (0.67-0.87)
P<0.001



2nd Renal Composite EP

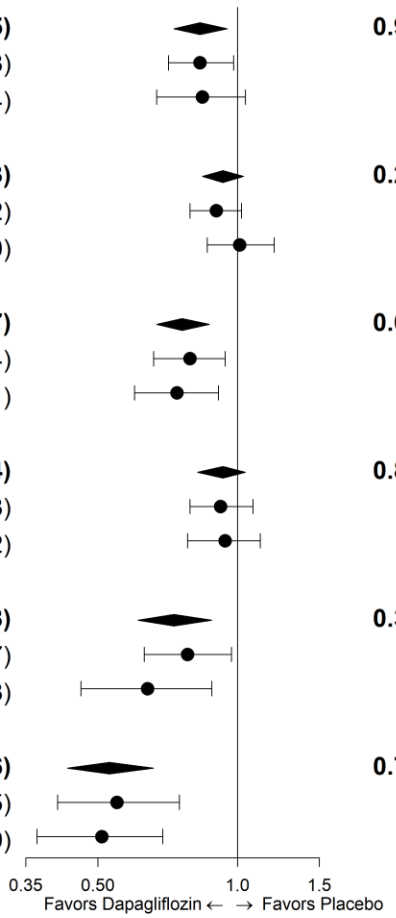
40%↓ eGFR, ESRD, Renal death

1.5% vs. 2.8%
HR 0.53 (0.43-0.66)
P<0.001



Outcomes by ASCVD vs. Primary Prevention

Outcomes	Dapagliflozin n/N	Placebo n/N	Hazard Ratio (95% CI)	P value for interaction
CV death/HHF	**2**	**78**	**0.83 (0.73-0.95)**	**0.99**
ASCVD	272/3474	325/3500	0.83 (0.71-0.98)	
MRF	145/5108	171/5078	0.84 (0.67-1.04)	
MACE	**756/8582**	**803/8578**	**0.93 (0.84-1.03)**	**0.25**
ASCVD	483/3474	537/3500	0.90 (0.79-1.02)	
MRF	273/5108	266/5078	1.01 (0.86-1.20)	
40% decrease in eGFR, ESRD, or renal or CV death	**370/8582**	**480/8578**	**0.76 (0.67-0.87)**	**0.67**
ASCVD	216/3474	275/3500	0.79 (0.66-0.94)	
MRF	154/5108	205/5078	0.74 (0.60-0.91)	
All-cause death	**529/8582**	**570/8578**	**0.93 (0.82-1.04)**	**0.87**
ASCVD	299/3474	327/3500	0.92 (0.79-1.08)	
MRF	230/5108	243/5078	0.94 (0.78-1.12)	
HHF	**212/8582**	**286/8578**	**0.73 (0.61-0.88)**	**0.30**
ASCVD	151/3474	192/3500	0.78 (0.63-0.97)	
MRF	61/5108	94/5078	0.64 (0.46-0.88)	
40% decrease in eGFR, ESRD, or renal death	**127/8582**	**238/8578**	**0.53 (0.43-0.66)**	**0.72**
ASCVD	65/3474	118/3500	0.55 (0.41-0.75)	
MRF	62/5108	120/5078	0.51 (0.37-0.69)	

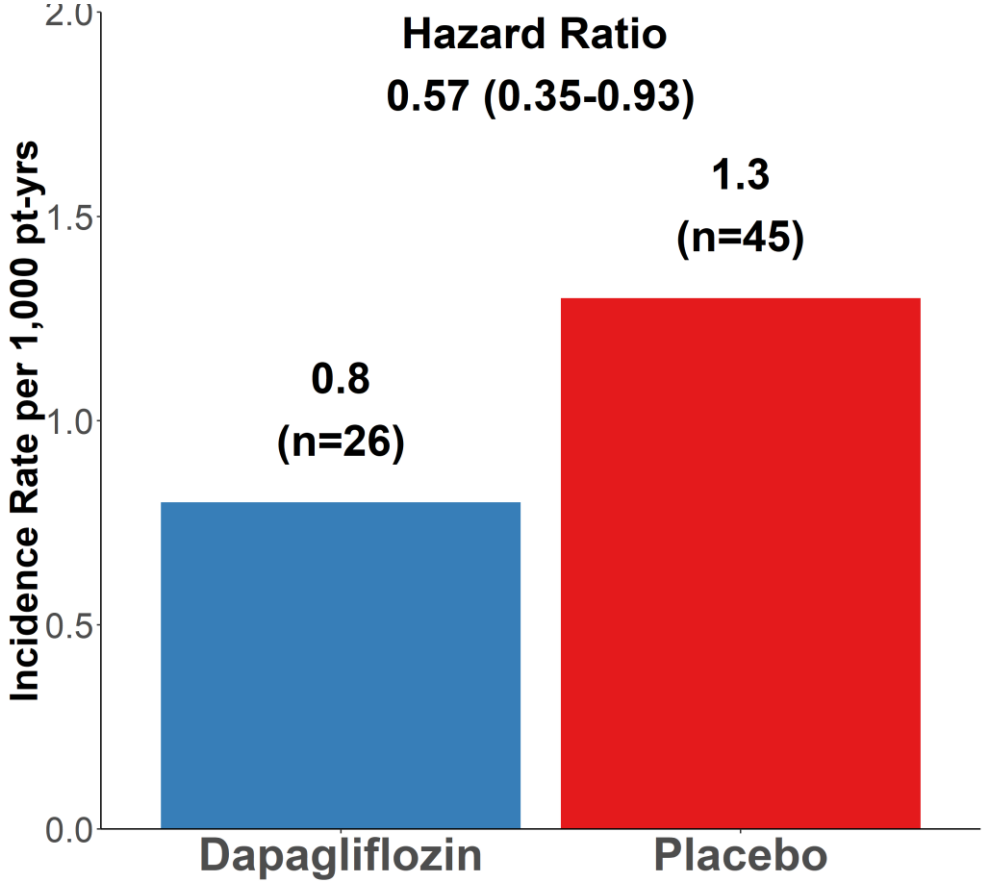


Key Safety Events

	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
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	0.0	0.1	NS
Malignancy event*	5.6	5.7	NS
Cancer of Bladder*	0.3	0.5	P=0.02
Hepatic event*	1.0	1.0	NS

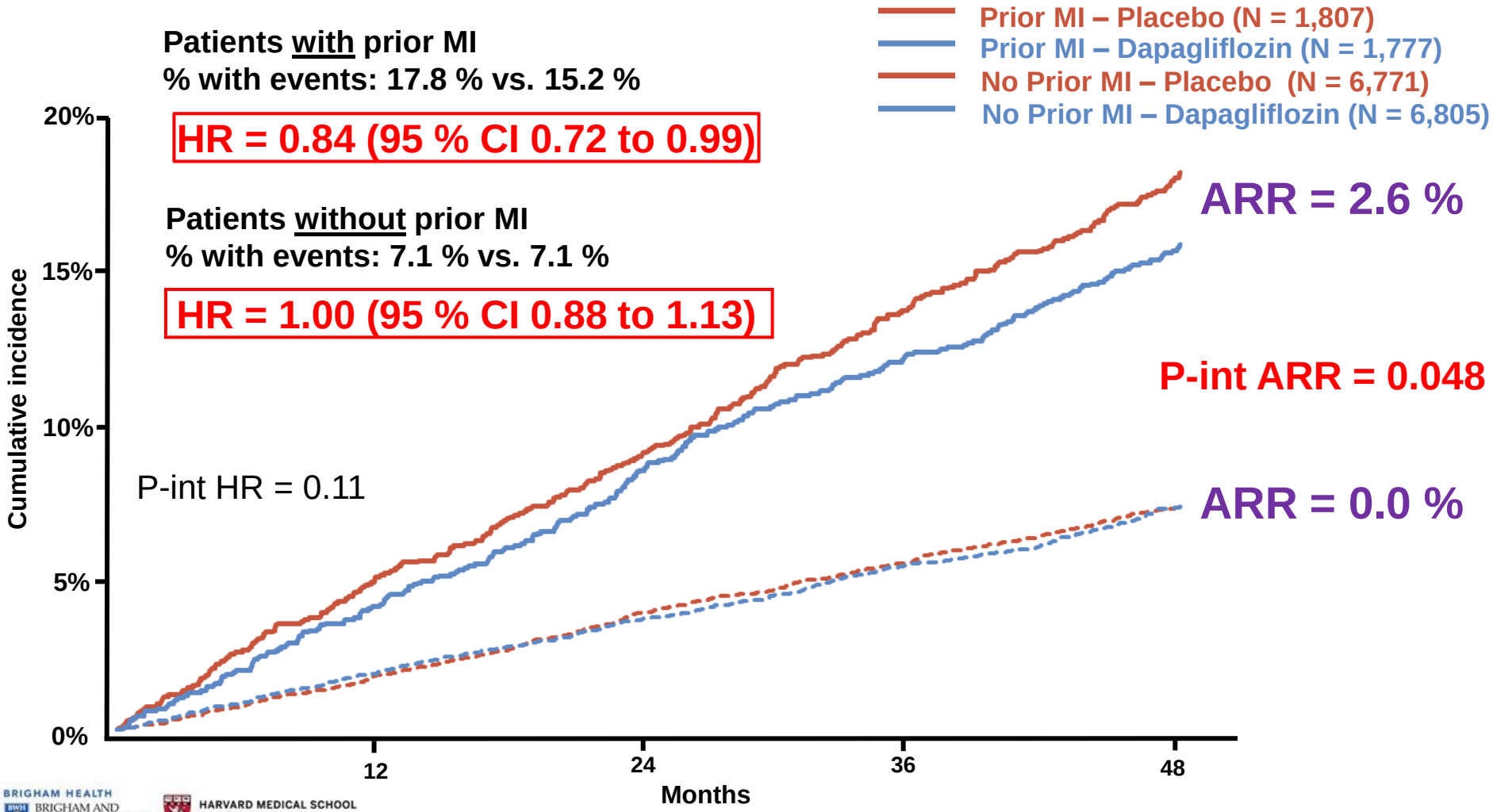
*CEC Adjudicated

Bladder Cancer (CEC adjudicated)



Dapagliflozin in Patients with Prior MI

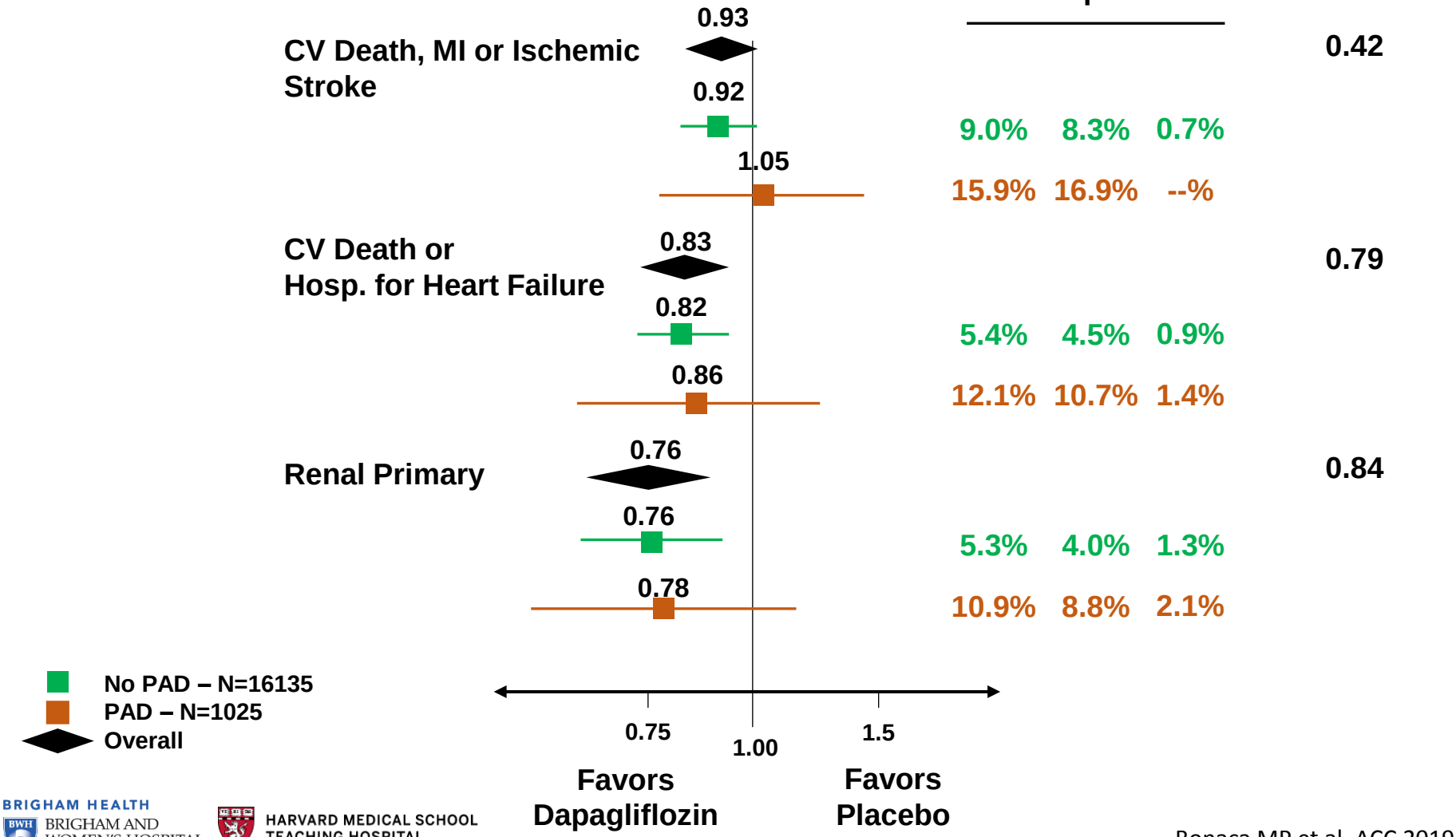
MACE – CV death, MI or ischemic stroke



BRIGHAM HEALTH
BRIGHAM AND WOMEN'S HOSPITAL
HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

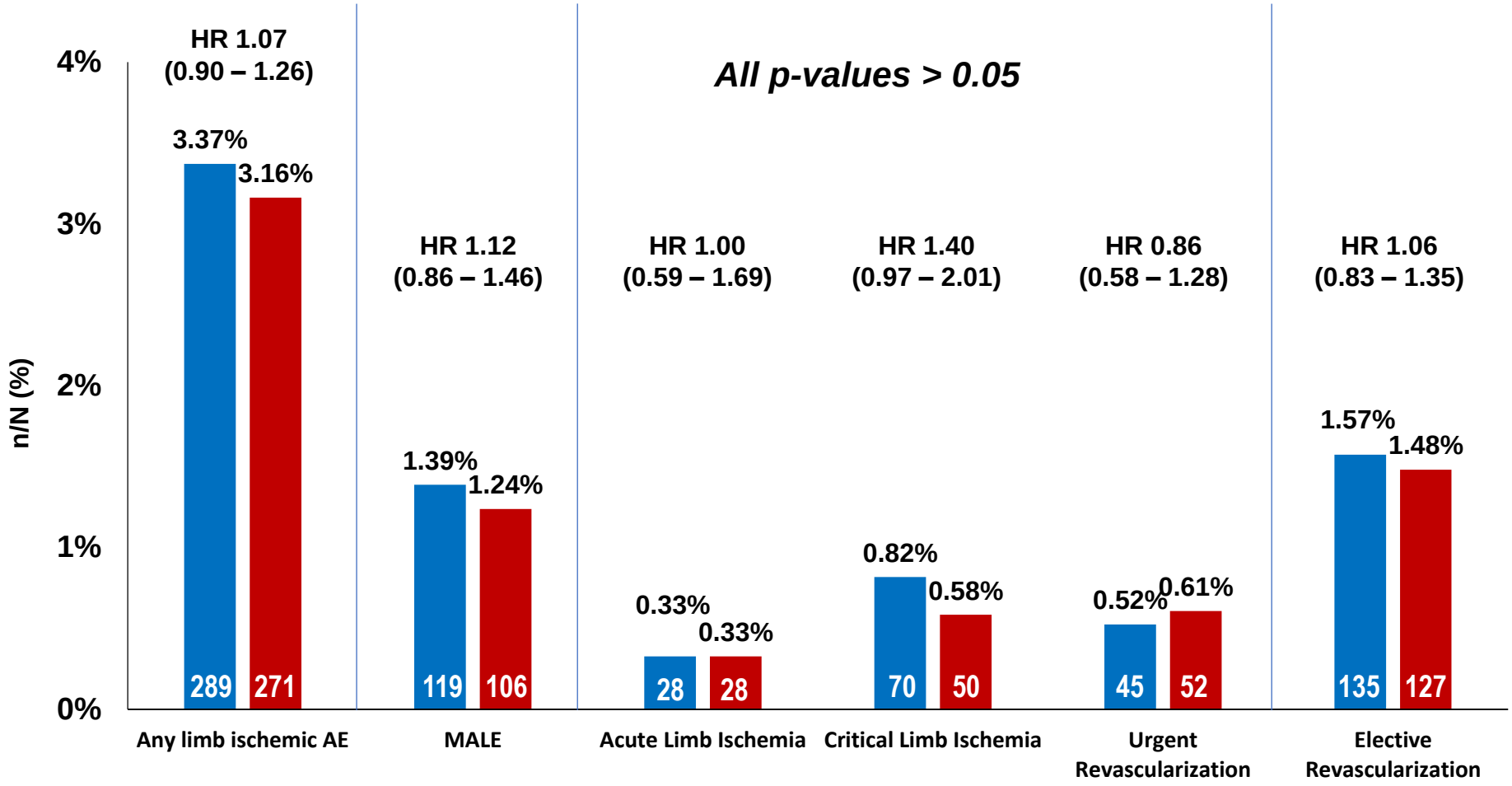
Furtado RHM, Bonaca MP, …Wiviott SD *Circulation* 2019

Consistent Benefit of Dapagliflozin in Patients with and without PAD



Bonaca MP et al. ACC 2019

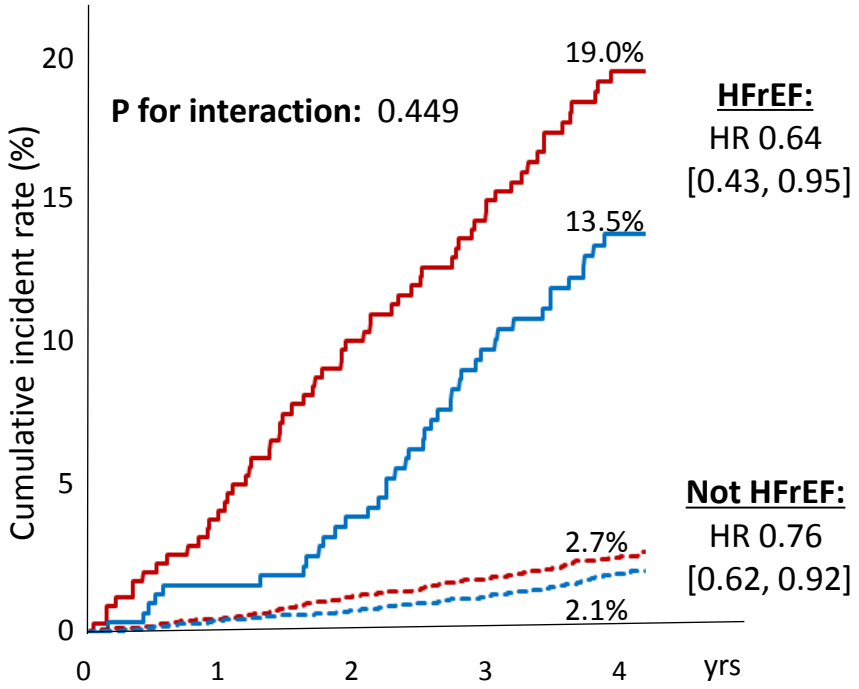
Dapagliflozin and Limb Outcomes
All Patients

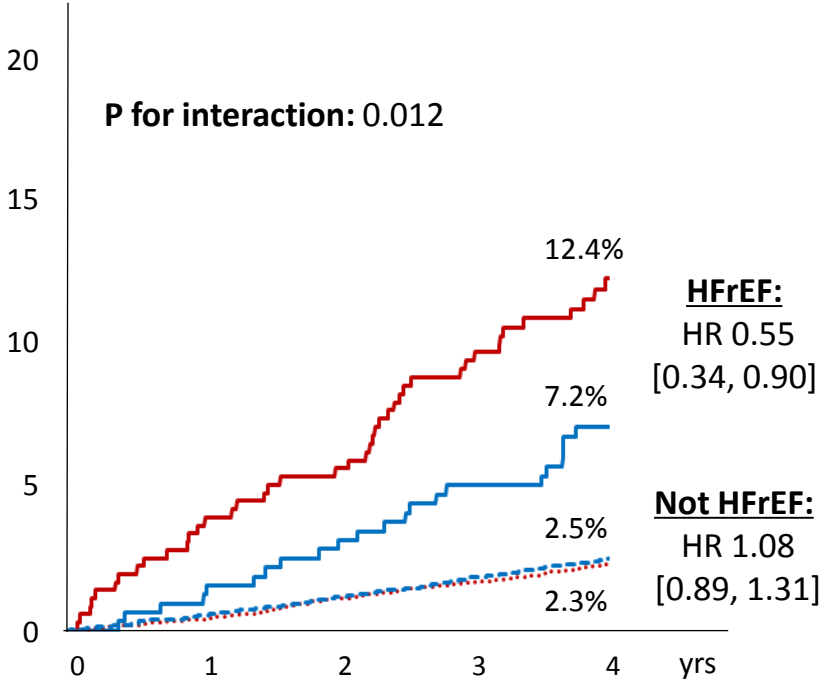


Bonaca MP et al. ACC 2019

MALE Defined as ALI, CLI, amputation for ischemia or Urgent Revascularization for Ischemia

HHF and CV Death by HFrEF vs not HFrEF subgroups





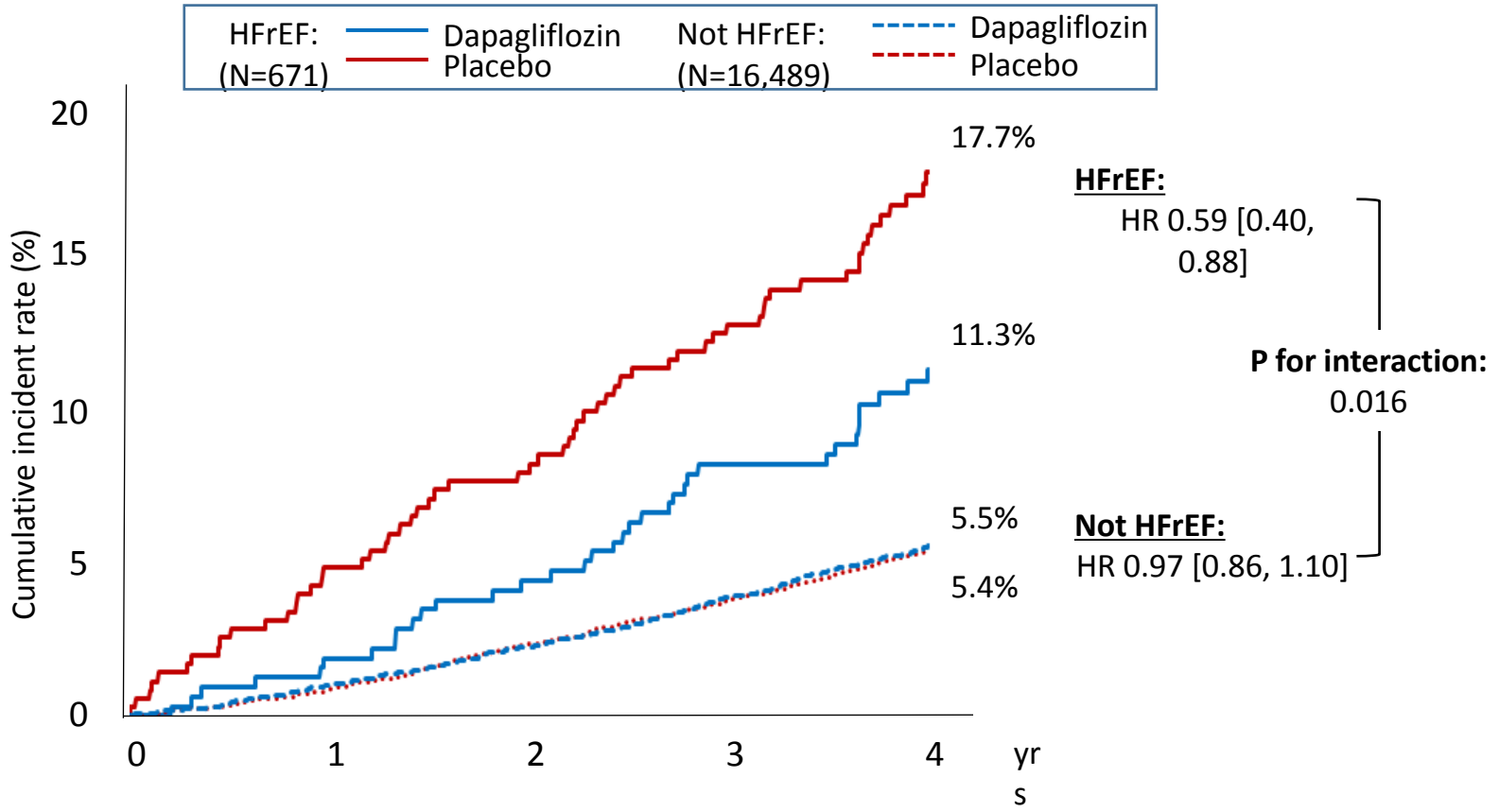
HFrEF: (N=671) — Dapagliflozin / Placebo

Not HFrEF: (N=16,489) — Dapagliflozin / Placebo

Not HFrEF defined as pts with HF without known reduced EF and pts without hx of HF

Kato ET et al. Circulation 2019

All Cause Mortality by HFrEF vs not HFrEF subgroups



Not HFrEF defined as pts with HF without known reduced EF and pts without hx of HF

Kato ET et al. Circulation 2019

Three Trials – Baseline Characteristics

	EMPA-REG OUTCOME	CANVAS Program	DECLARE-TIMI 58
Median Follow-Up Time (yrs)	3.1	2.4	4.2
Trial participants (n)	7020	10142	17160
Age (mean)	63.1	63.3	63.9
Female Sex	2004 (28.5%)	3633 (35.8%)	6422 (37.4%)
Established ASCVD	7020 (100%)	6656 (66%)	6974 (41%)
History of Heart Failure	706 (10.1%)	1461 (14.4%)	1724 (10.0%)
eGFR <60 ml/min/1.73 m^2	1819 (25.9%)	2039 (20.1%)	1265 (7.4%)

DECLARE – TIMI 58

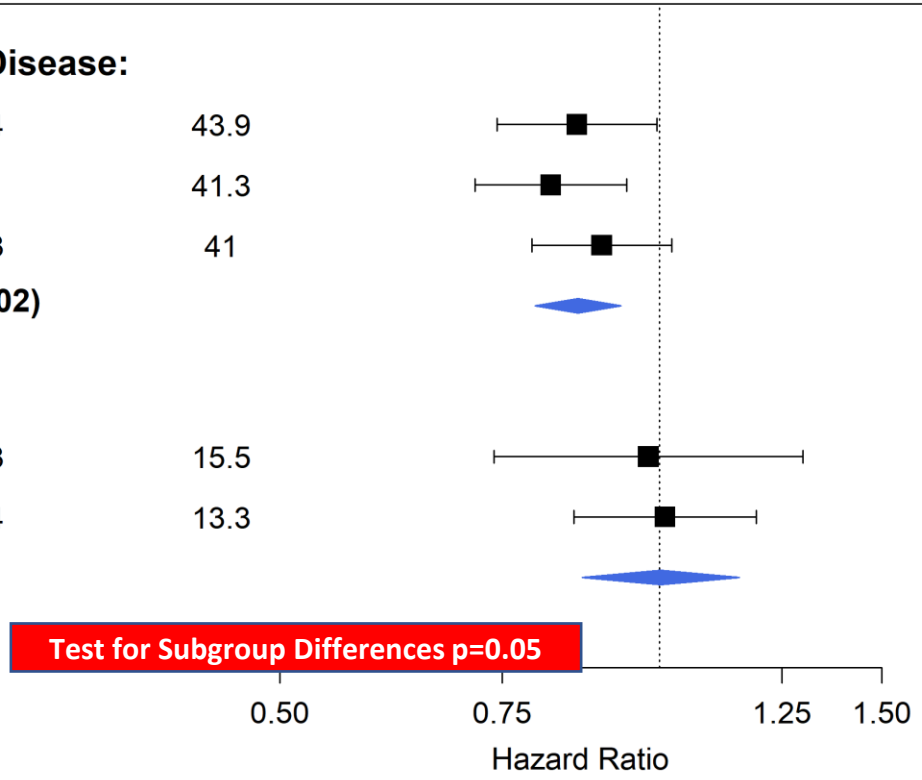
Largest

Longest exposure (important for safety)

More than 50% Primary Prevention

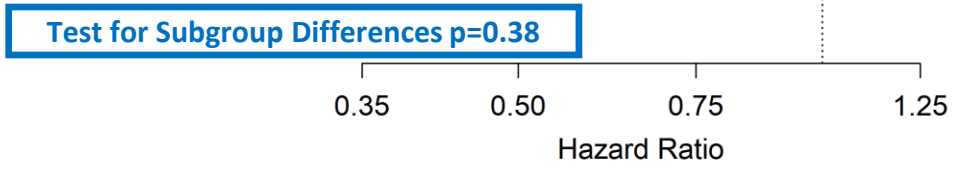
MACE Benefit Dependent on ASCVD

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]**



Heart Failure Benefit in All

HHF	Treatment Events per 1000 pt-yrs	Placebo Events per 1000 pt-yrs	HR [95% CI]
Atherosclerotic Cardiovascular Disease:			
EMPA-REG OUTCOME	9.4	14.5	0.65 [0.50, 0.85]
CANVAS Program	7.3	11.3	0.68 [0.51, 0.90]
DECLARE-TIMI 58	11.1	14.1	0.78 [0.63, 0.97]
FE Model for ASCVD (P-value <0.0001)			**0.71 [0.62, 0.82]**
Heterogeneity: Q=1.24, p=0.54, I^2=0.0%			
Multiple Risk Factor:			
CANVAS Program	2.6	4.2	0.64 [0.35, 1.15]
DECLARE-TIMI 58	3	4.6	0.64 [0.46, 0.88]
FE Model for MRF (P-value = 0.0021)			**0.64 [0.48, 0.85]**
Heterogeneity: Q=0.00, p=1.00, I^2=0.0%			



Summary

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

- **Dapagliflozin reduced CVD/HHF and neither increased nor decreased MACE**
  - **Reduction in CVD/HHF was consistent regardless of baseline ASCVD or HF**
- **Dapagliflozin was safe and generally well-tolerated**
  - **↑ Genital infections & DKA**
  - **no difference in: amputation, stroke, or fracture**
  - **↓ hypoglycemia, bladder Ca**

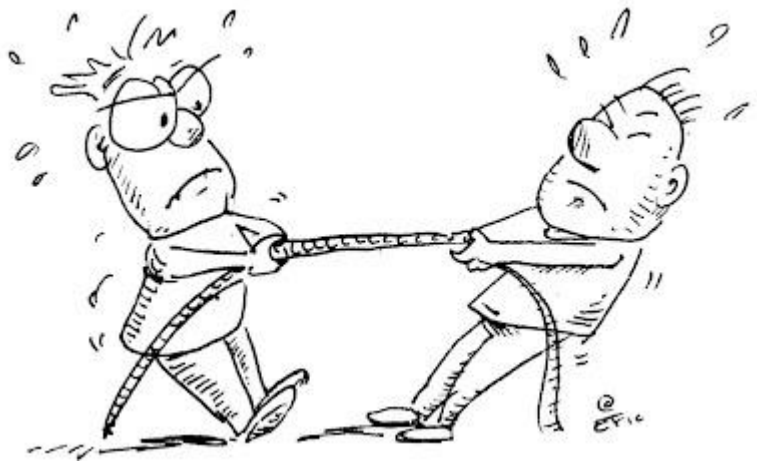
Translation to Practice

SGLT2i

A Drug to Prevent HF and Renal Dysfunction
(that happens to lower A1C)

A Drug to lower A1C
(that happens to reduce HF and renal dysfunction)

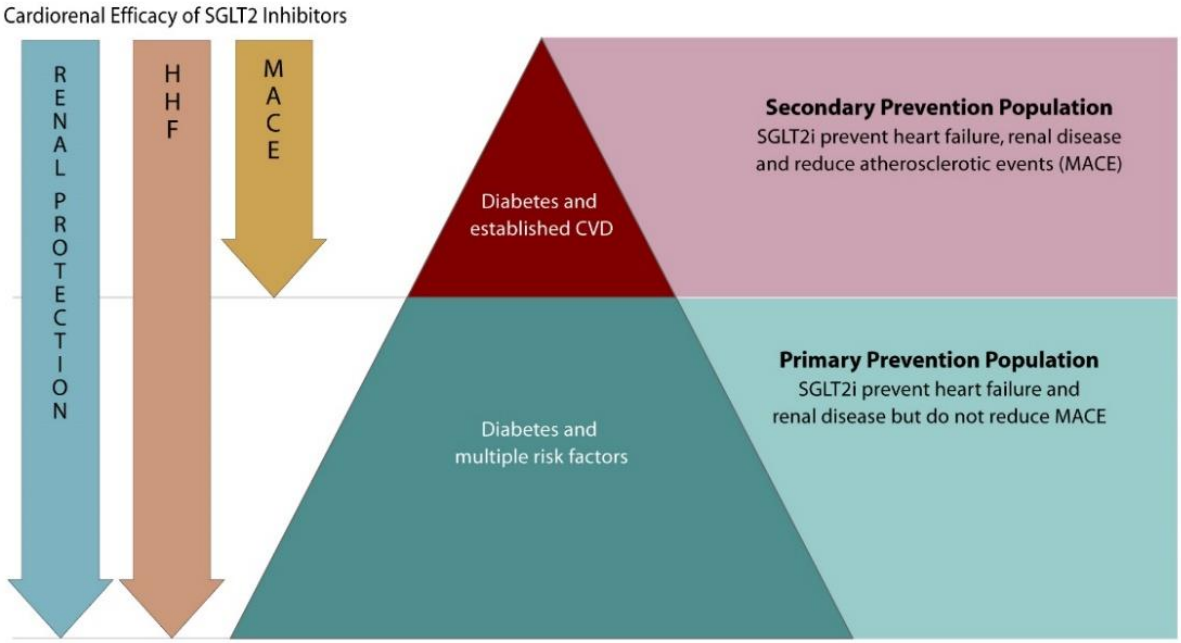
Challenges in Translation to Practice



Is this a drug with broad benefits in broad populations (e.g. like ACEi)?

Is this a specialty drug for endocrinologists and/or cardiologists for selected high risk patients?

Conclusion



Pump, Pipes and Filter: do SGLT2 inhibitors have it all covered?
Verma S, Jüni P, Mazer CD, The Lancet 2018

DECLARE- TIMI 58 extends the benefit of SGLT2i to a broader population of patients for <u>primary and secondary prevention</u>

ACC Guidelines for Primary Prevention

DECLARE-TIMI 58 most applicable to primary prevention

For adults with type 2 diabetes mellitus, lifestyle changes, such as improving dietary habits and achieving exercise recommendations, are crucial. If medication is indicated, metformin is first-line therapy, followed by consideration of a sodium-glucose cotransporter 2 inhibitor or a glucagon-like peptide-1 receptor agonist.

AMERICAN COLLEGE of CARDIOLOGY

A Multidisciplinary Cardio-metabolic Paradigm with the Patient at the Center

Primary Care

Cardiology / Vascular Medicine

Endocrinology

Podiatry

Ophthalmology

Nephrology

Conclusions

The SGLT2i are an exciting class that prevent HF and renal complications in patients with T2DM (primary and secondary prevention

Ongoing studies will explore efficacy outside of T2DM (HFpEF, HFrEF, CKD) and elucidate mechanisms

Optimal application will require focus on cardio-metabolic and renal risk through multidisciplinary framework but driven by primary care