



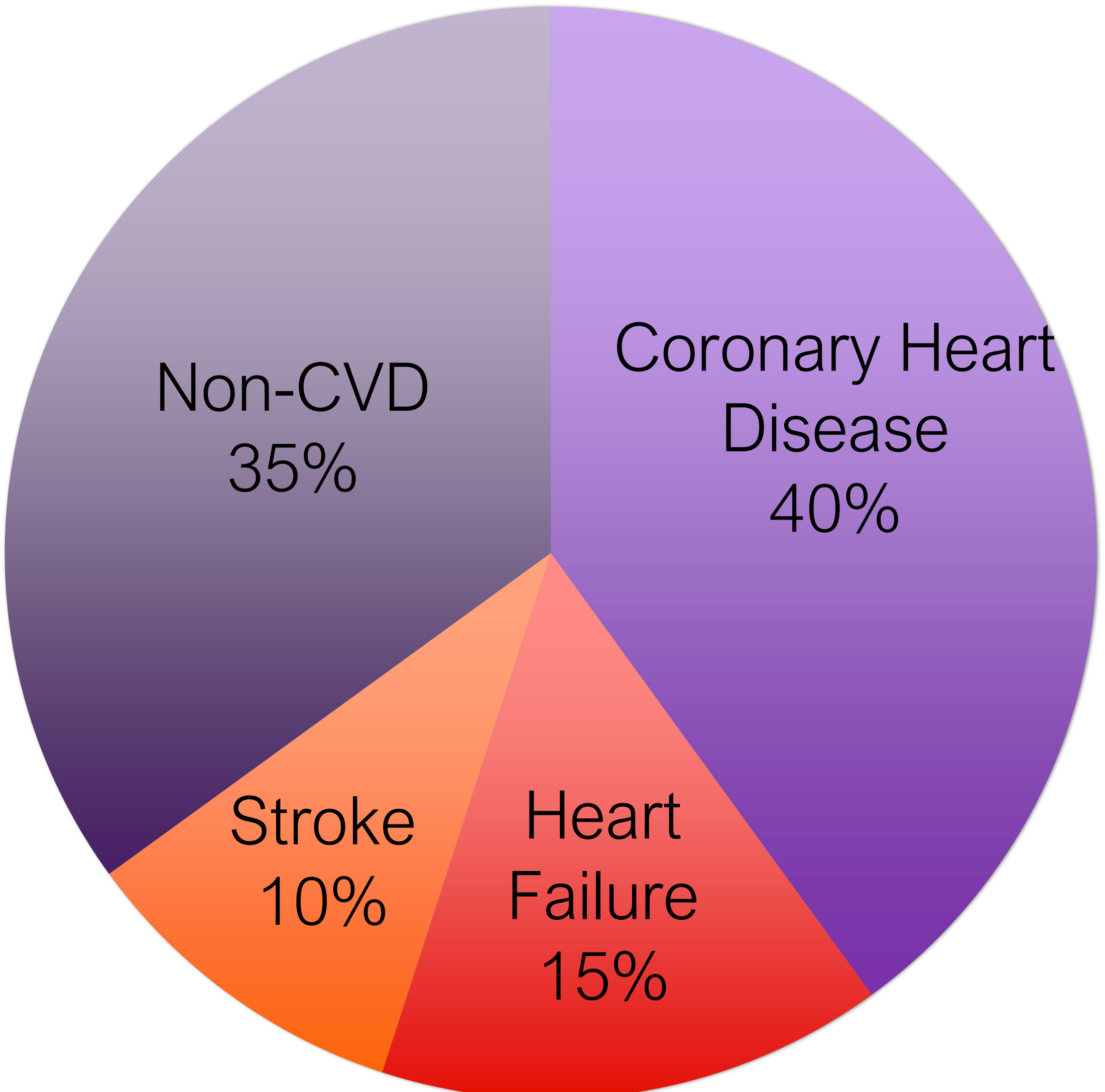
# *Rationale use of SGLT2 Inhibitors in Diabetes*

***Prakash Deedwania, MD, FACC, FACP, FAHA, FESC, FHFS***

**Professor of Medicine, UCSF School of Medicine, San Francisco,  
Director, Cardiovascular Research, UCSF Program, Fresno, CA  
Clinical Professor of Medicine, Stanford University, Palo Alto, CA**

A 50-year old with Diabetes dies ~6 years earlier than an individual without Diabetes.

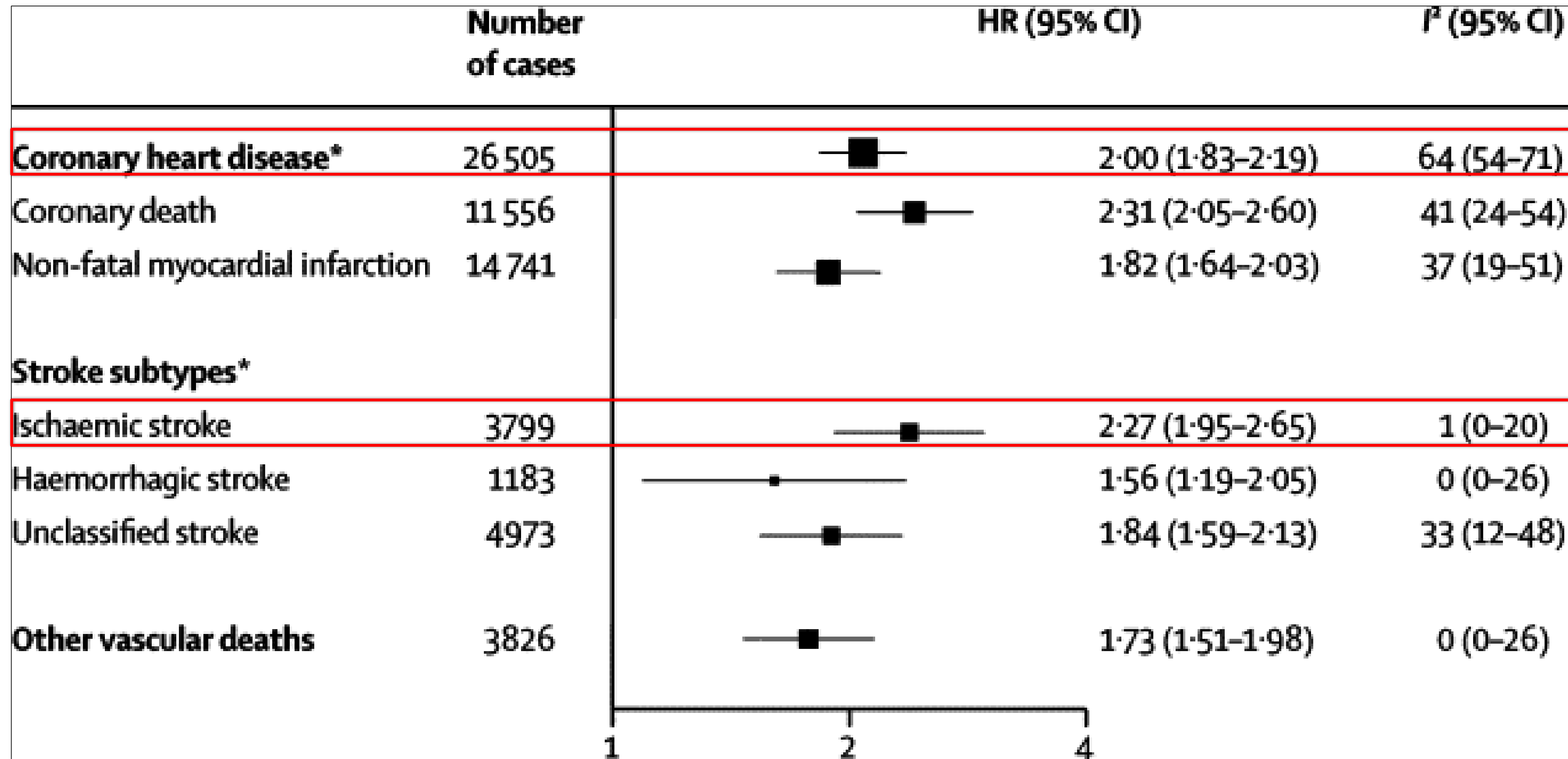
### Causes of Death in Diabetes



Emerging Risk Factors Collaboration NEJM 2011. 364: 829-841.  
Wang et al. Circulation 2016. 133: 2459-2502.



# Diabetes increases the risk of CHD and Stroke.



CHD  
HR 2.00

Ischemic  
Stroke  
HR 2.27



# Diabetes increases the risk of Heart Failure.

## Role of Diabetes in Congestive Heart Failure: The Framingham Study

WILLIAM B. KANNEL, MD, FACC  
MARTHANA HJORTLAND, PhD\*  
WILLIAM P. CASTELLI, MD

Framingham, Massachusetts  
Bethesda, Maryland

The incidence of congestive heart failure was determined in relation to prior diabetic status in 5,209 men and women aged 30 to 62 years followed up for 18 years in the Framingham study. Men aged 45 to 74 years had more than twice the frequency of congestive failure as their nondiabetic cohorts, and diabetic women had a fivefold increased risk. This excessive risk appears to be caused by factors other than accelerated atherogenesis and coronary heart disease. Even when patients with prior coronary or rheumatic heart disease were excluded, the diabetic subjects had a four- to fivefold increased risk of congestive heart failure. In women (but not men) with prior coronary disease, diabetes also imposed a threefold increased risk of congestive failure. Furthermore, the increased risk of heart failure in the diabetic patients persisted after taking into account age, blood pressure, weight and cholesterol values as well as coronary heart disease. Women with diabetes appeared to be especially vulnerable and, irrespective of coronary disease status, had twice the frequency of congestive heart failure as men. The excessive risk of heart failure among diabetic subjects was confined to those treated with insulin. The data suggest that diabetes is another discrete cause of congestive heart failure and that some form of cardiomyopathy is associated with diabetes, as a result of either small vessel disease or metabolic disorders.

Congestive heart failure is a common end stage of heart disease due to a variety of causes. The incidence is far from trivial. The annual rate is 2.3/1,000 men and 1.4/1,000 women aged 30 years and over.<sup>1</sup> Despite the availability of potent glycosides and diuretic agents, congestive heart failure continues to be a lethal process, and half of the patients die within 5 years of onset.<sup>1</sup> Previous study<sup>1</sup> revealed that hypertension and coronary heart disease were the dominant causes, but 14 percent of men and 26 percent of women with congestive failure also had diabetes, an apparent excess. The purpose of this report is to explore the role of diabetes in the development of congestive heart failure and to assess its contribution taking into account the presence of coronary heart disease and atherogenic factors such as hypertension, high serum cholesterol levels, overweight and increased age.

### Methods

The Framingham study was initiated in 1949 to explore the epidemiology of cardiovascular disease in a general population sample of 5,209 men and women aged 30 to 62 years. These subjects have been followed up for the development of cardiovascular disease including congestive heart failure. At every biennial examination each participant has had, in addition to a history and physical evaluation, a 13 lead electrocardiogram, a chest X-ray film, tests of vital capacity, urinalysis, measurements of blood sugar, uric acid and cholesterol levels and determinations of Framingham relative body weight.

Detailed descriptions of the sampling procedure, response rate, methods of examination and laboratory procedures and the criteria for the outcome of disease have been reported previously.<sup>2</sup>

From the Framingham Heart Disease Epidemiology Study, Framingham, Mass., and the National Heart and Lung Institute,\* National Institutes of Health, Bethesda, Md. Manuscript accepted February 27, 1974.

Address for reprints: William B. Kannel, MD, Framingham Heart Disease Epidemiology Study, 123 Lincoln St., Framingham, Mass. 01701.

July 1974 The American Journal of CARDIOLOGY Volume 34 29

TABLE IV

## Risk of Congestive Heart Failure According to Sex and Diabetic Status at Each Biennial Examination: 18 Year Follow-Up Study

Diabetic Status	Person Years At Risk	Incidence		Relative Risk
		Crude Annual per 10,000	Age-Adjusted* per 10,000	
Men Aged 45 to 74 years				
Nondiabetic	26,988	31.87	32.14	2.36†
Diabetic	1,226	89.72	75.98	
Women Aged 45 to 74 years				
Nondiabetic	35,322	19.53	19.75	5.14‡
Diabetic	1,190	142.85	101.60	

\* Indirect method.

† Significant at  $P < 0.05$  (chi square = 6.50).

‡ Significant at  $P < 0.01$  (chi square = 12.53).

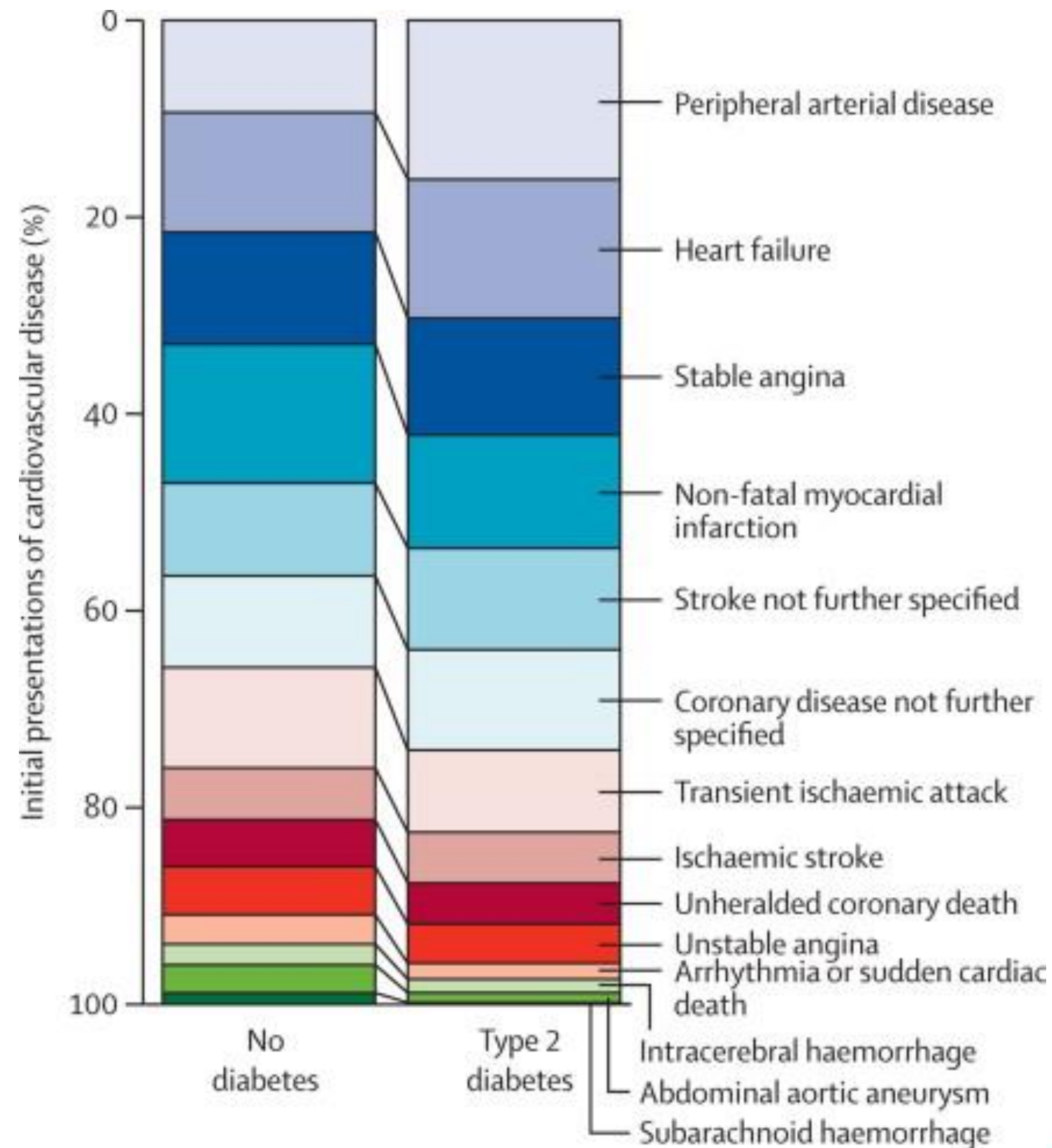
HF in Men  
HR 2.36

HF in Women  
HR 5.14





# Initial presentations of cardiovascular disease in patients with Diabetes.



# Competing risks of CHD, Stroke, and Heart Failure Deaths in Diabetes

Cardiovascular Cause of Death	HR (95% CI) (Ref: Non-diabetes)
Coronary Heart Disease	3.02 (2.38, 3.85)
Stroke	2.30 (1.63, 3.24)
Heart Failure	1.72 (1.05, 2.82)



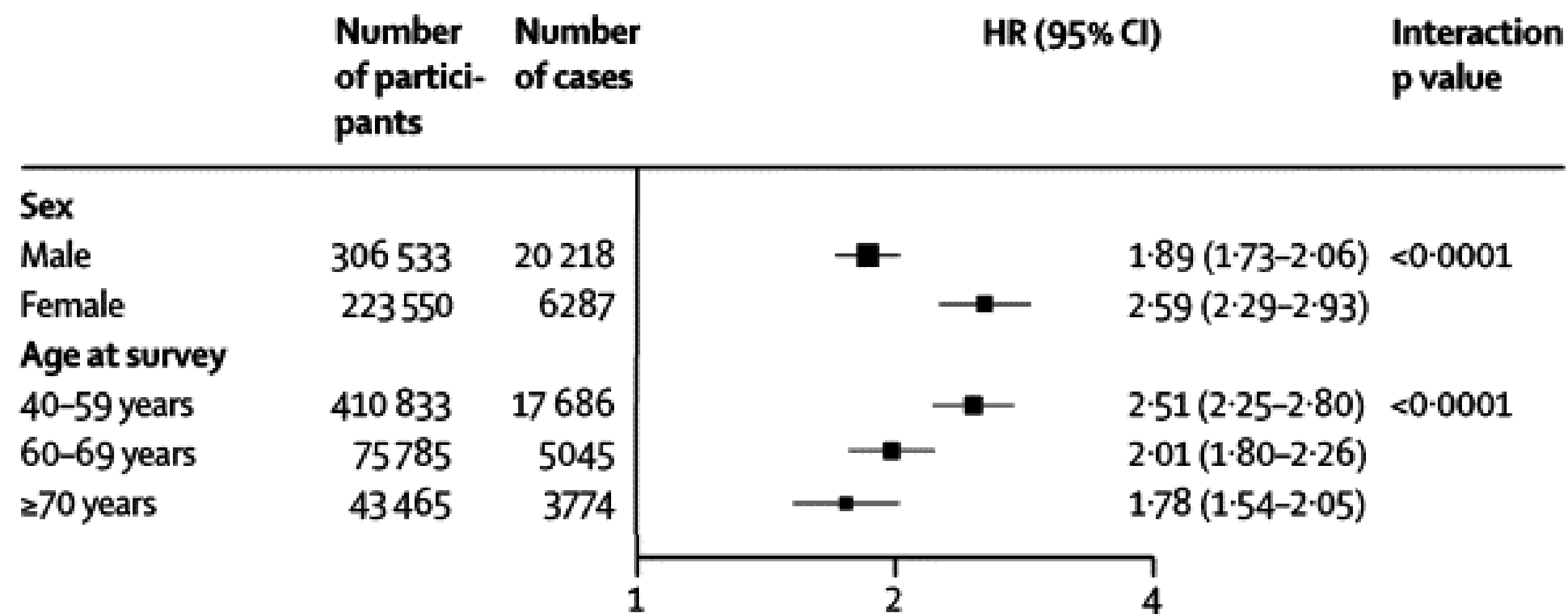
# Predictors of CHD, Stroke, and Heart Failure in Diabetes



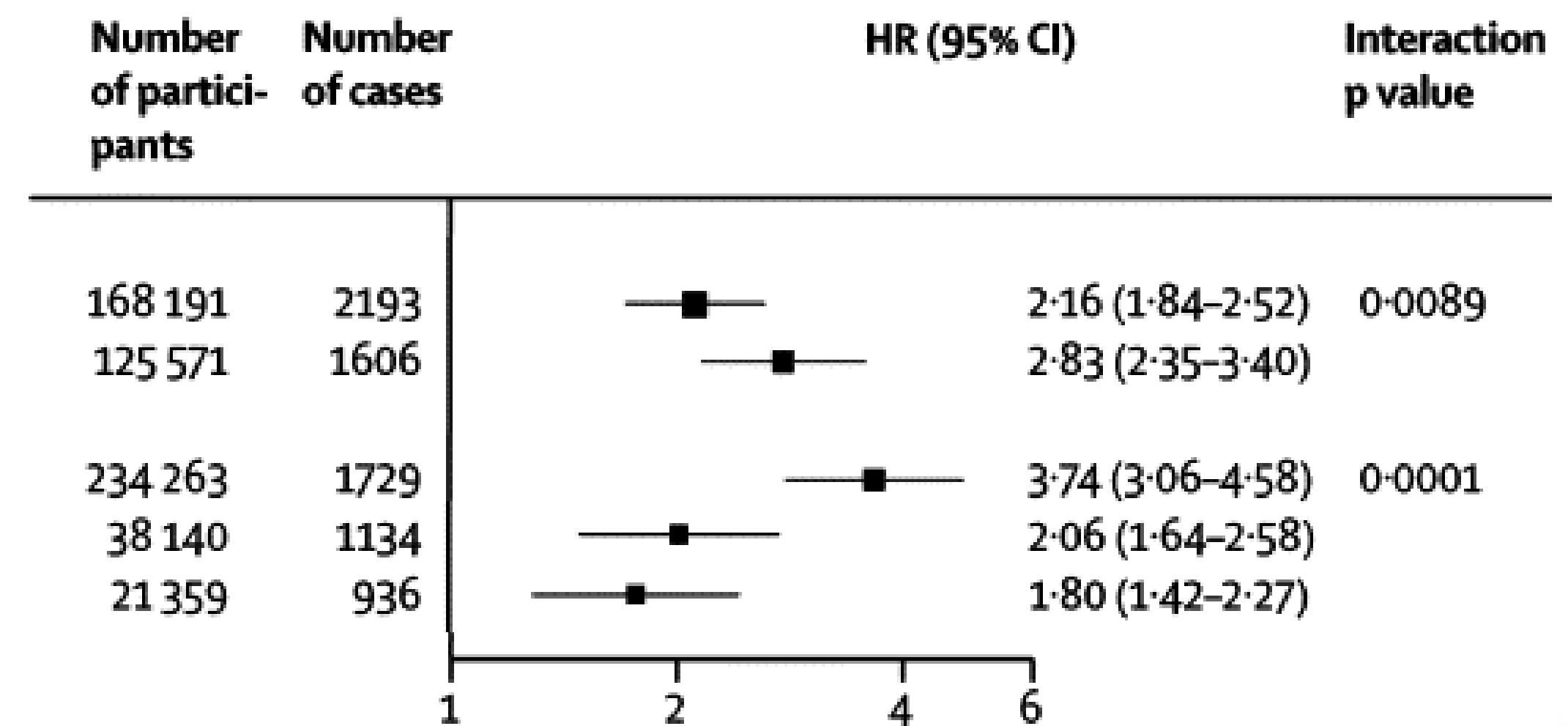


# Risks of CHD and Stroke vary by age and sex in Diabetes.

**A Coronary heart disease**



**B Ischaemic stroke**

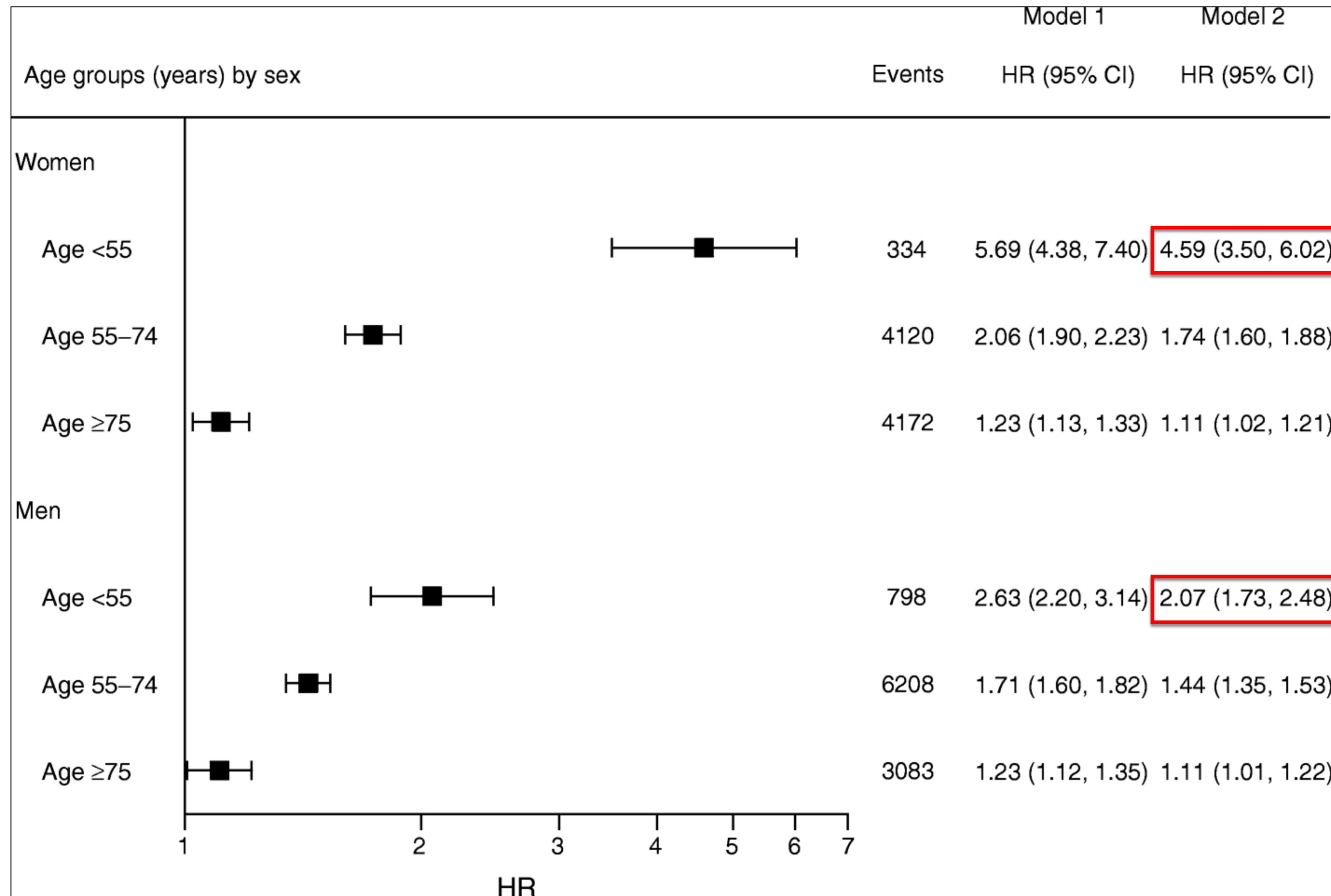


**Women and younger adults (40-59yo) have the highest risk of CHD and Stroke.**





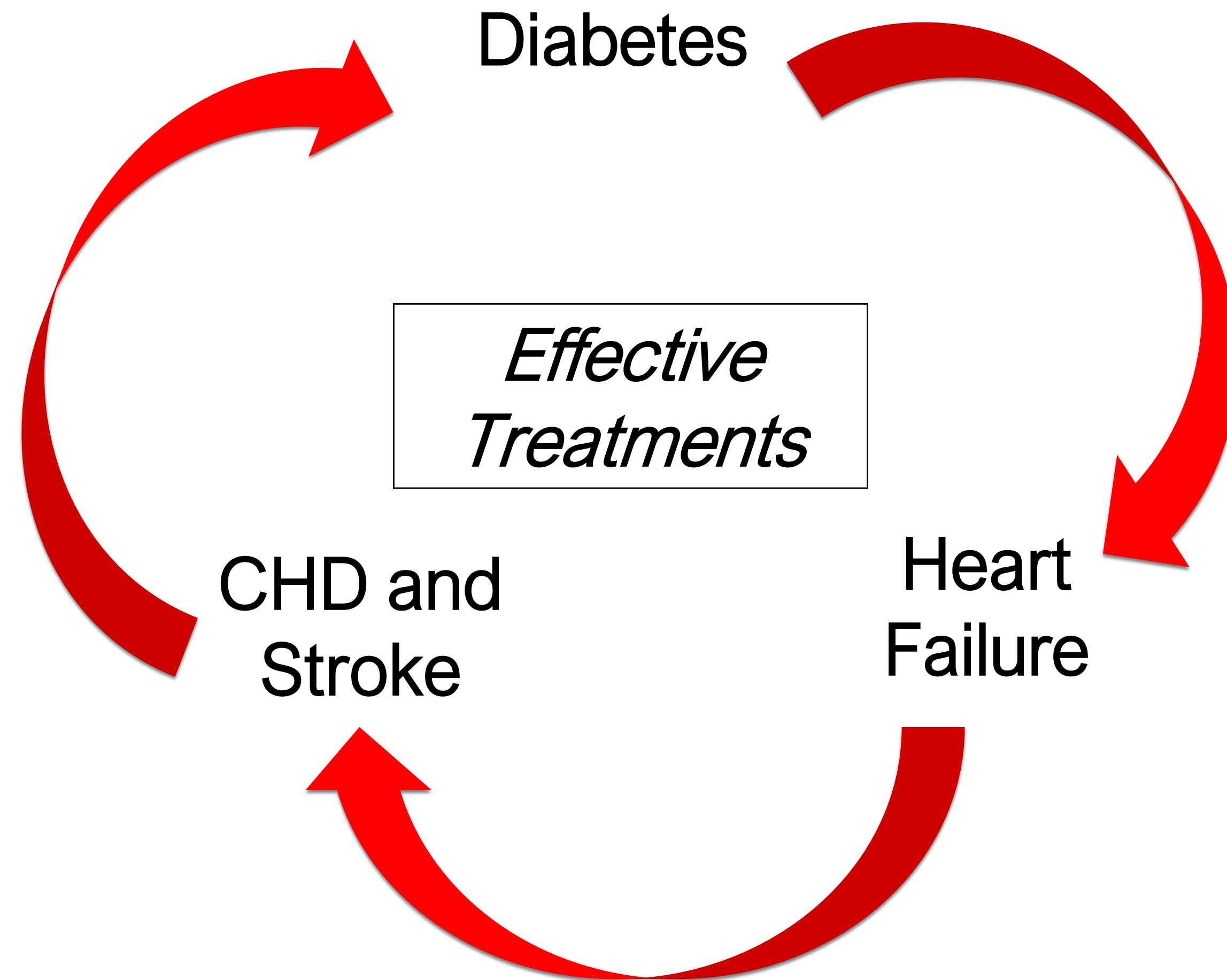
# Risk of Heart Failure varies by age and sex in Diabetes.



**Young women have the highest risk of Heart Failure.**

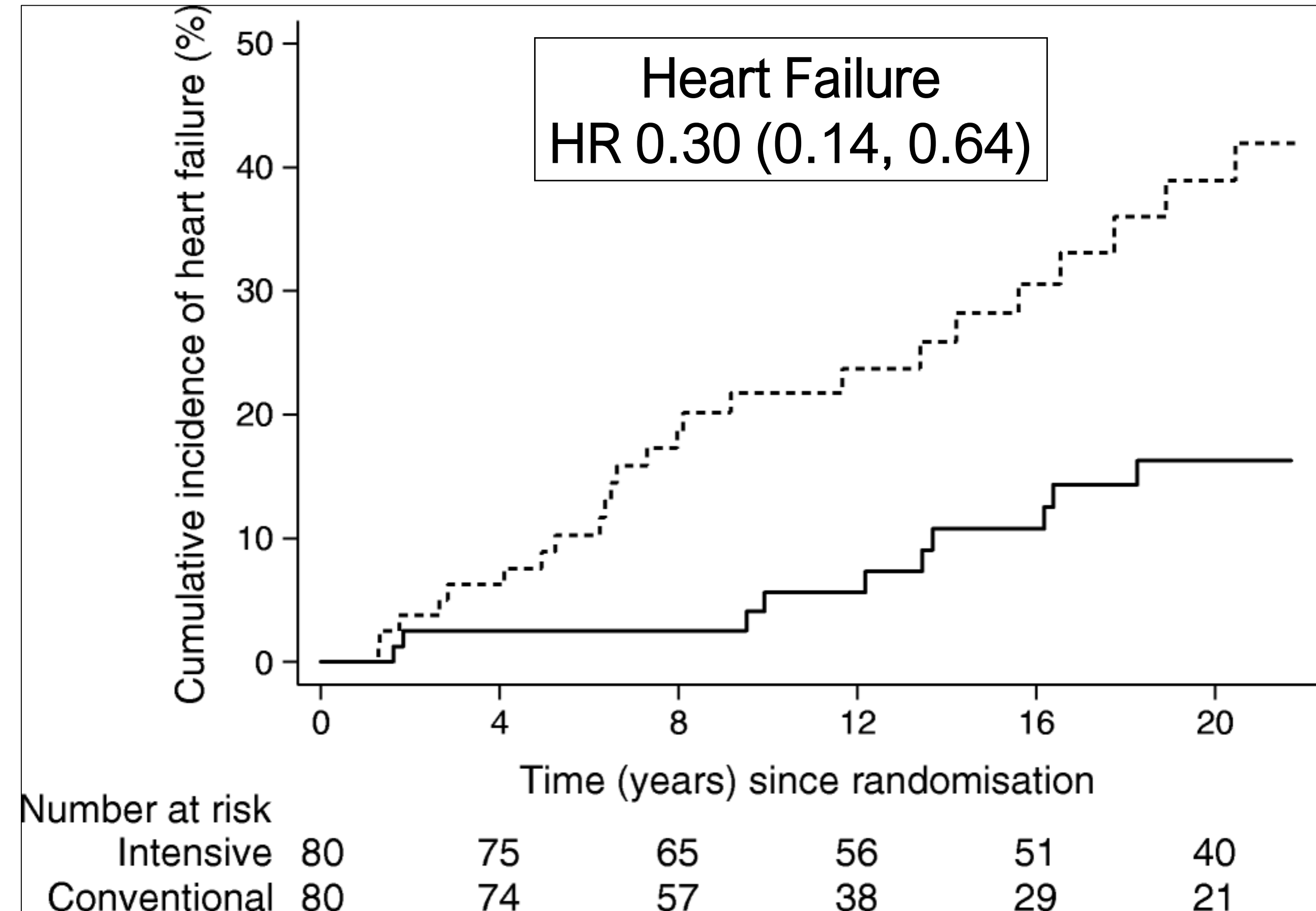
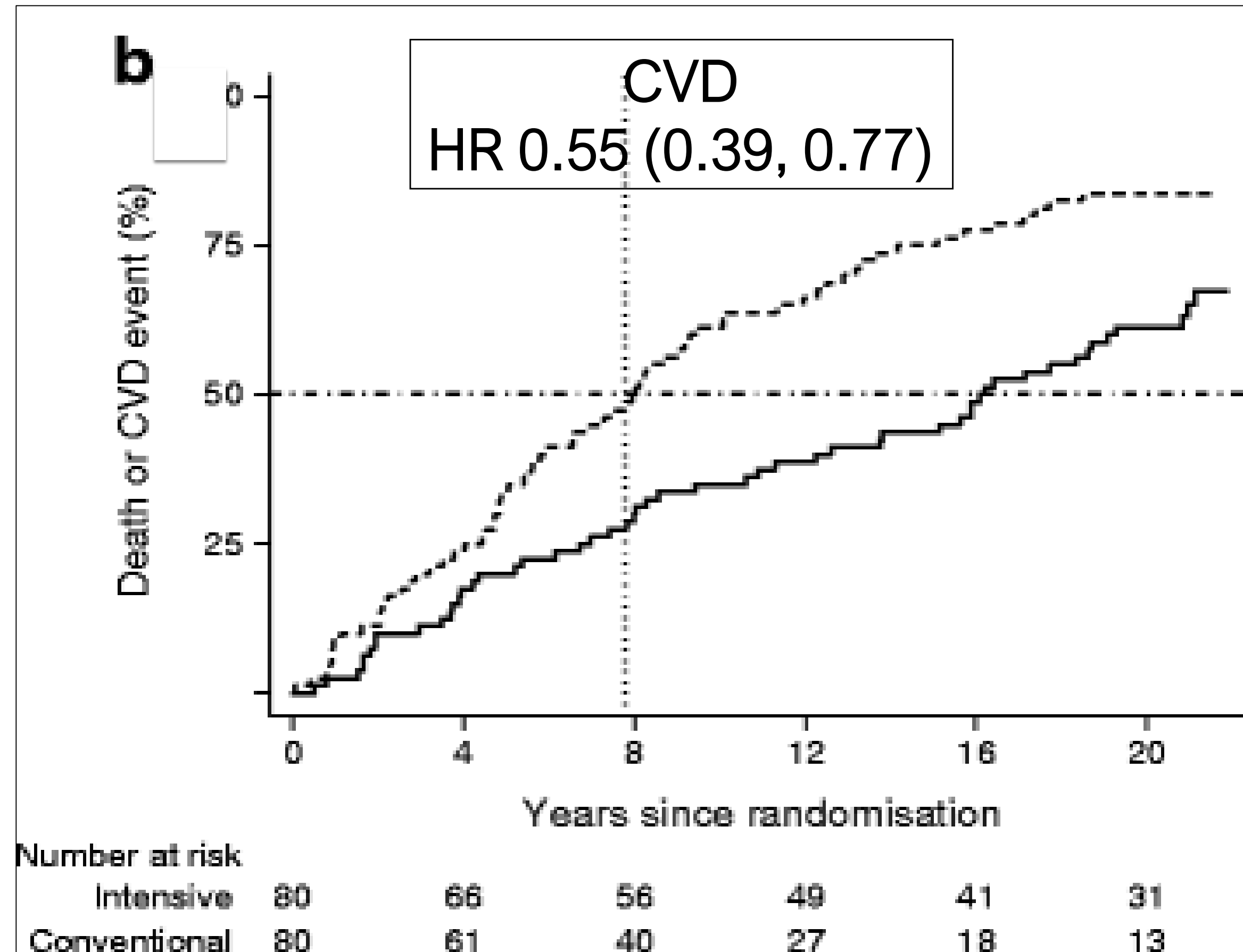


We need effective treatments to address all CV risks in Diabetes.





# Controlling traditional risk factors reduces CV risk.



# Large CV Outcomes Trials in Diabetes

Study	SAVOR	EXAMINE	TECOS	CARMELINA	CAROLINA
DPP-4-inhibitor	saxagliptin	alogliptin	sitagliptin	linagliptin	linagliptin
Comparator	placebo	placebo	placebo	placebo	sulfonylurea
n	16,500	5,400	14,000	6,900	6,000
Results	2013	2013	2015	2017	2019
	<b>NEUTRAL</b>	<b>NEUTRAL</b>	<b>NEUTRAL</b>	<b>NEUTRAL</b>	

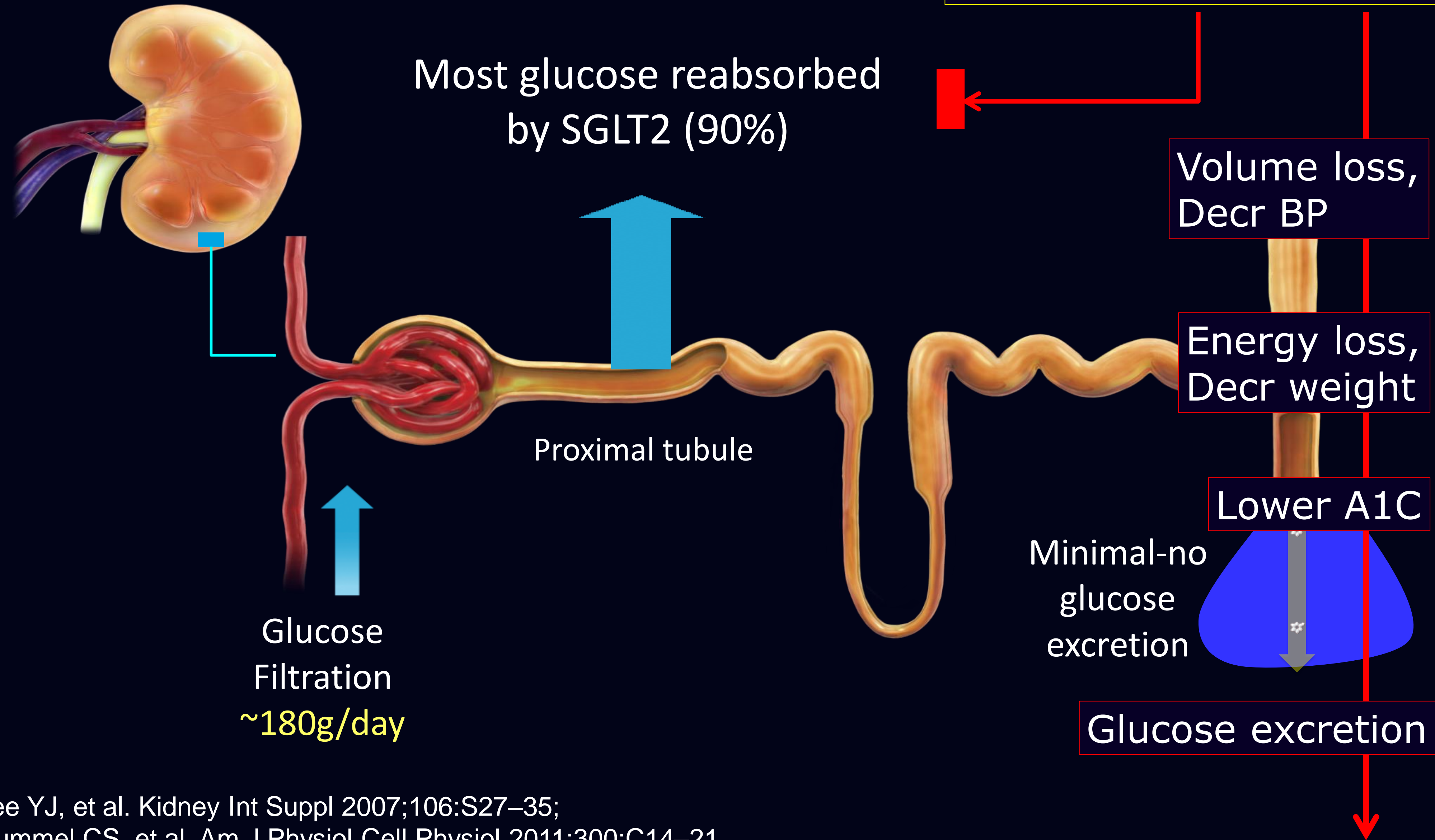
Study	EMPA-REG	CANVAS	DECLARE	VERTIS CV Study
SGLT-2 inhibitor	empagliflozin	canagliflozin	dapagliflozin	ertugliflozin
Comparator	placebo	placebo	placebo	placebo
n	7300	4,300	22,200	8,000
Results	2015	2017	2019	2019
	<b>CV BENEFIT</b>	<b>CV BENEFIT</b>	<b>CV BENEFIT</b>	

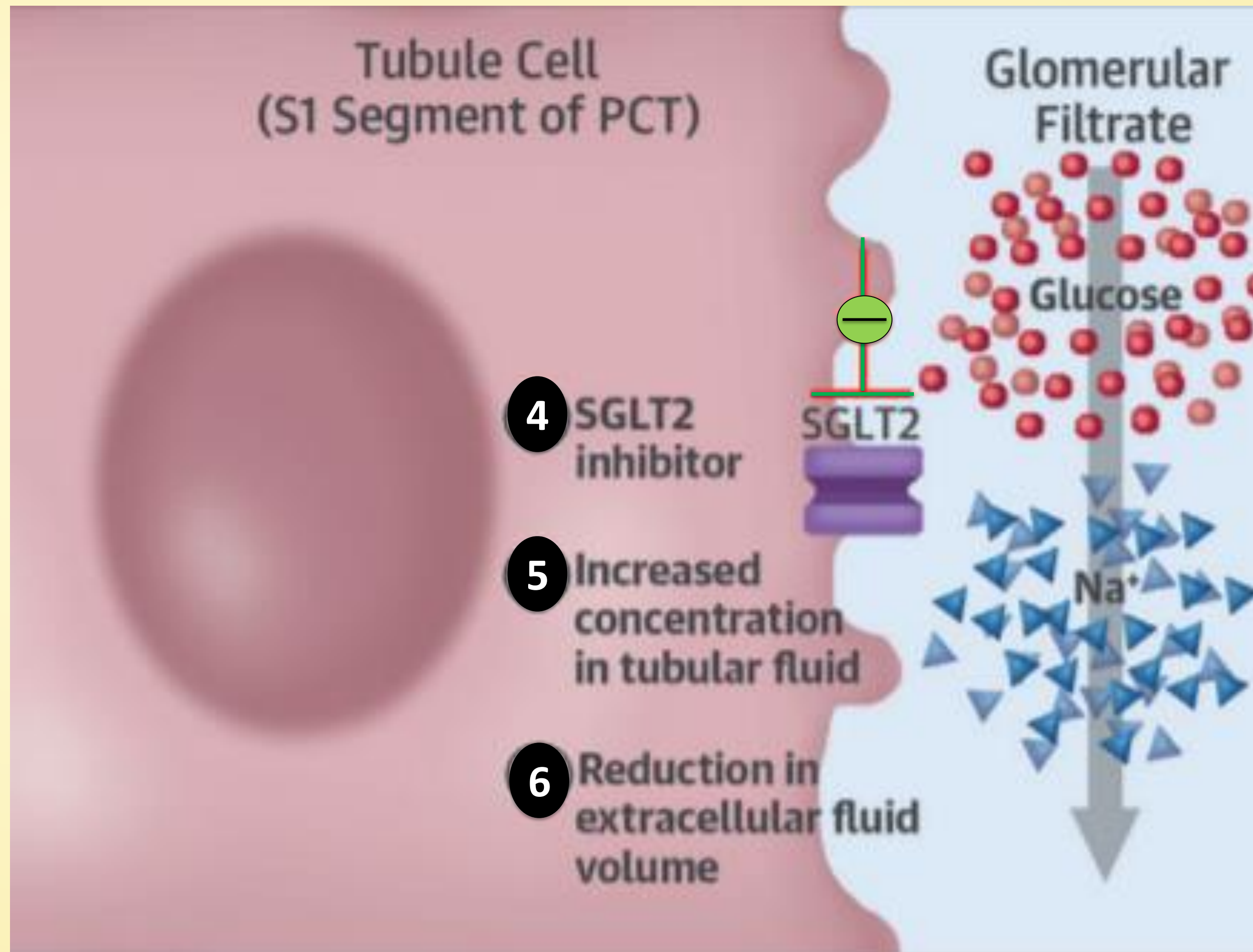
Study	LEADER	ELIXA	SUSTAIN 6	EXSCEL	REWIND
GLP-1 RA	liraglutide	lixisenatide	semaglutide	exenatide LR	dulaglutide
Comparator	placebo	placebo	placebo	placebo	placebo
n	16,500	14,000	6,000	5,400	8,300
Results	2015	2015	2016	2017	2019
	<b>CV BENEFIT</b>	<b>NEUTRAL</b>	<b>CV BENEFIT</b>	<b>NEUTRAL</b>	



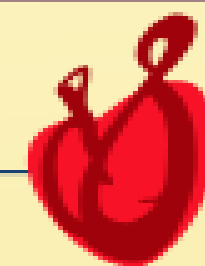
# SGLT2 Inhibitors



# Renal effects of SGLT2 inhibition (1)

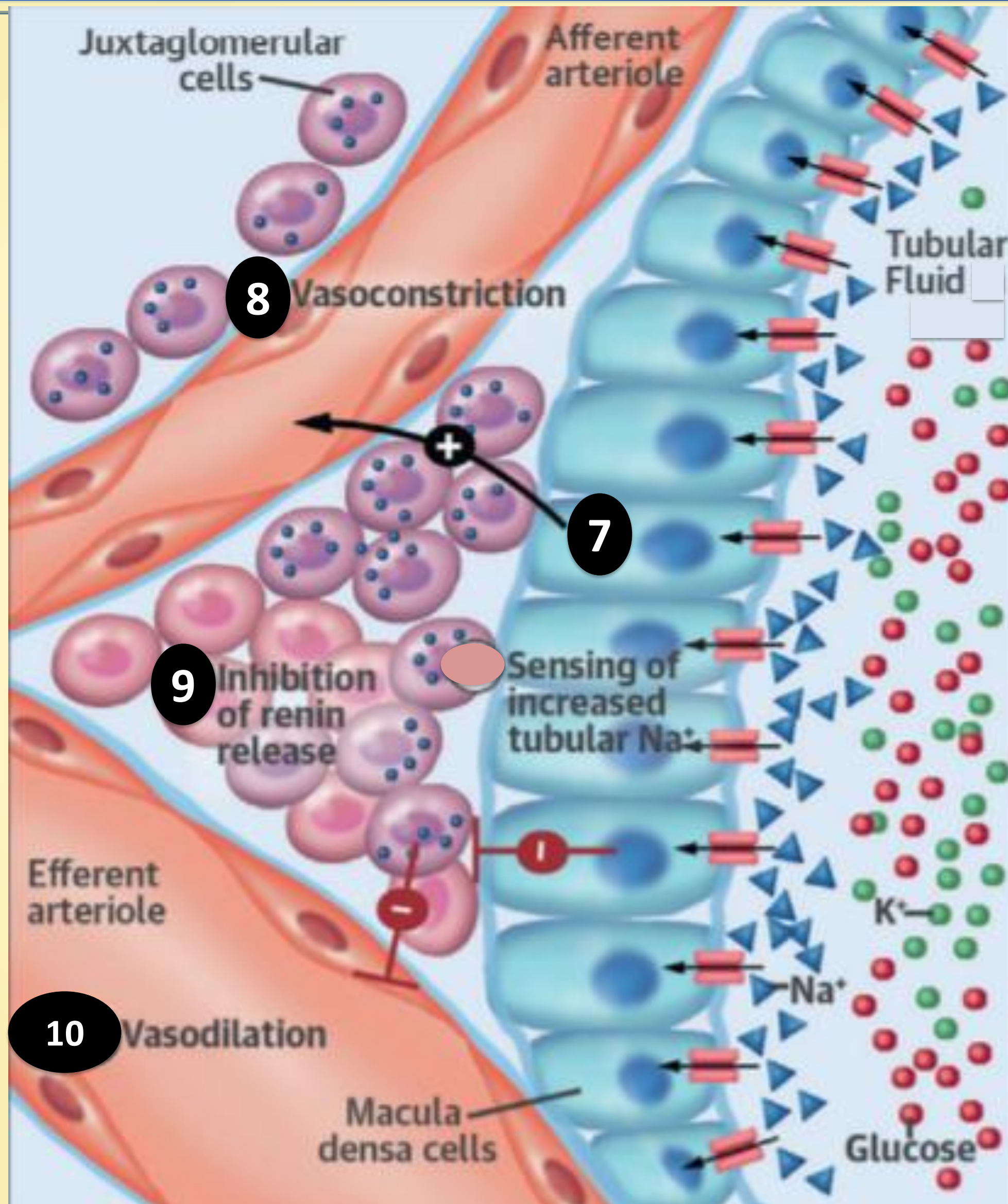


Zelniker TA, Braunwald E.  
JACC 2018;72:1845

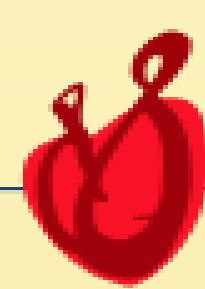




# Renal effects of SGLT2 inhibition (2)

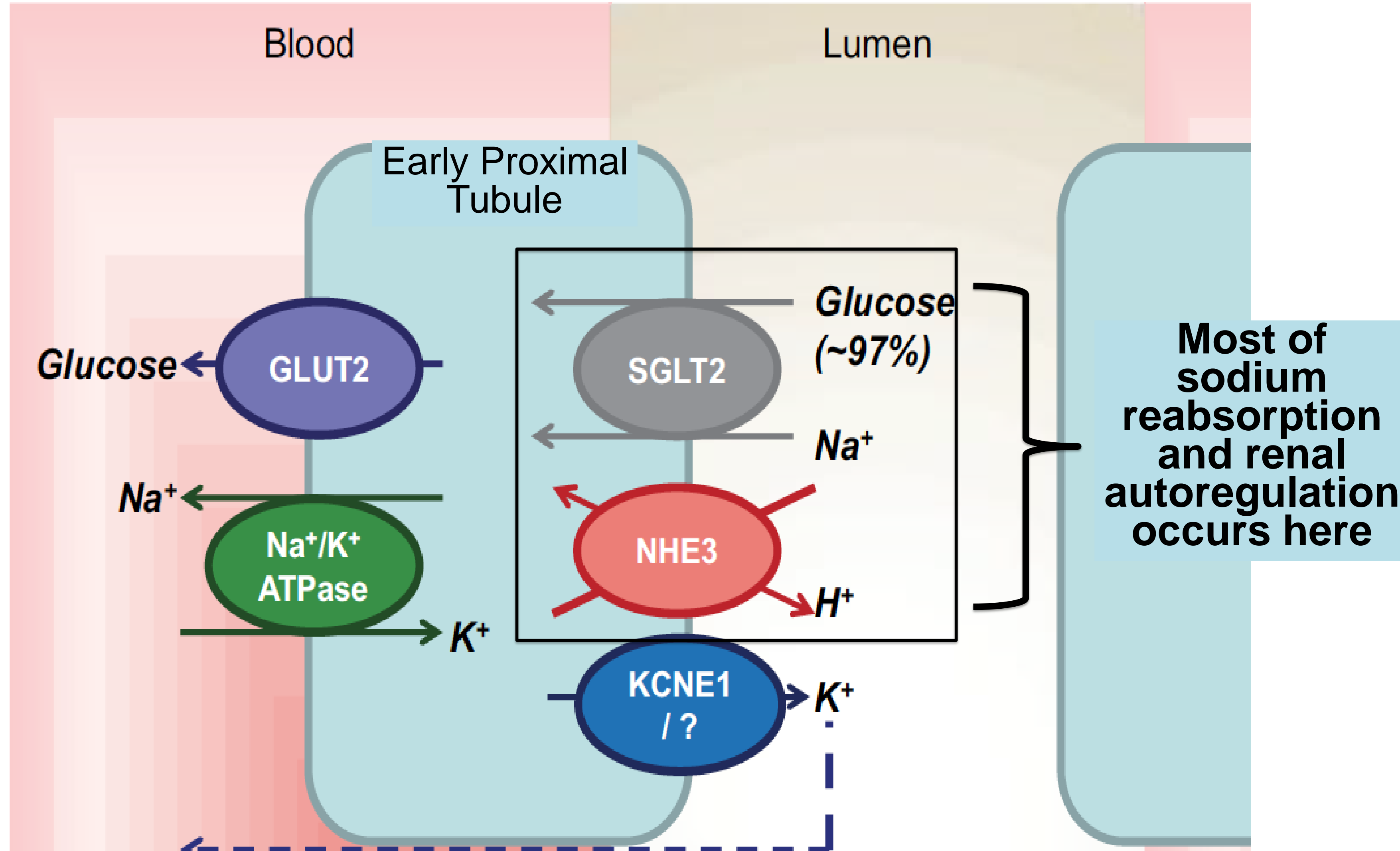


- 7 MD senses  $\uparrow[\text{Na}^+]$  in tubular fluid  $\rightarrow \uparrow$  TG feedback  $\rightarrow$
  - 8 Constriction of afferent arteriole
  - 9 MD  $\downarrow$  renin release from JG cells  $\rightarrow$
  - 10 Dilatation of efferent arterioles
- $\rightarrow \downarrow$  intraglomerular press.  $\rightarrow$  renal protection





# What Are We Missing in the Proximal Renal Tubule?



# SGLT-2 Inhibitors for Treatment of T2DM

## SGLT-2 inhibitors

block reabsorption of filtered glucose in kidneys  
leads to glycosuria, improved glycemic control

### Benefits

- Insulin-independent action
- Calorie loss – possible weight loss
- Low hypoglycemia
- Complement action of other anti-diabetic agents
- Can be used regardless of diabetes duration

### Side effects

- Recurrent UTI
- Genital fungal infection
- Decreased blood pressure
- Worsening of renal function<sup>#</sup>
- Increased hematocrit<sup>\*</sup>
- Increased LDL-C<sup>\*</sup>

<sup>#</sup> Specific considerations for individuals with existing renal insufficiency, the elderly, and those receiving loop diuretics

<sup>\*</sup> Significance on patient outcomes is unclear at this time



# The SGLT-2 Inhibitor Studies

ORIGINAL ARTICLE

## Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christopher  
David Fitchett, M.D., Eric  
Michaela Mattheus, Dipl. Bio  
Odd Erik Johansen, M.D., Ph.D.,  
and Silvio E. Inzucchi, M.D.,

ORIGINAL ARTICLE

## Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Christoph Wanner, M.D., Silvio  
David Fitchett, M.D.,  
Michaela Mattheus, Dipl. Bio  
Hans J. Woerle, M.D., Uli C. B  
for the EMPA-REG

ORIGINAL ARTICLE

## Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D.,  
Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D.,  
Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D.,  
Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch.,  
for the CANVAS Program Collaborative Group\*

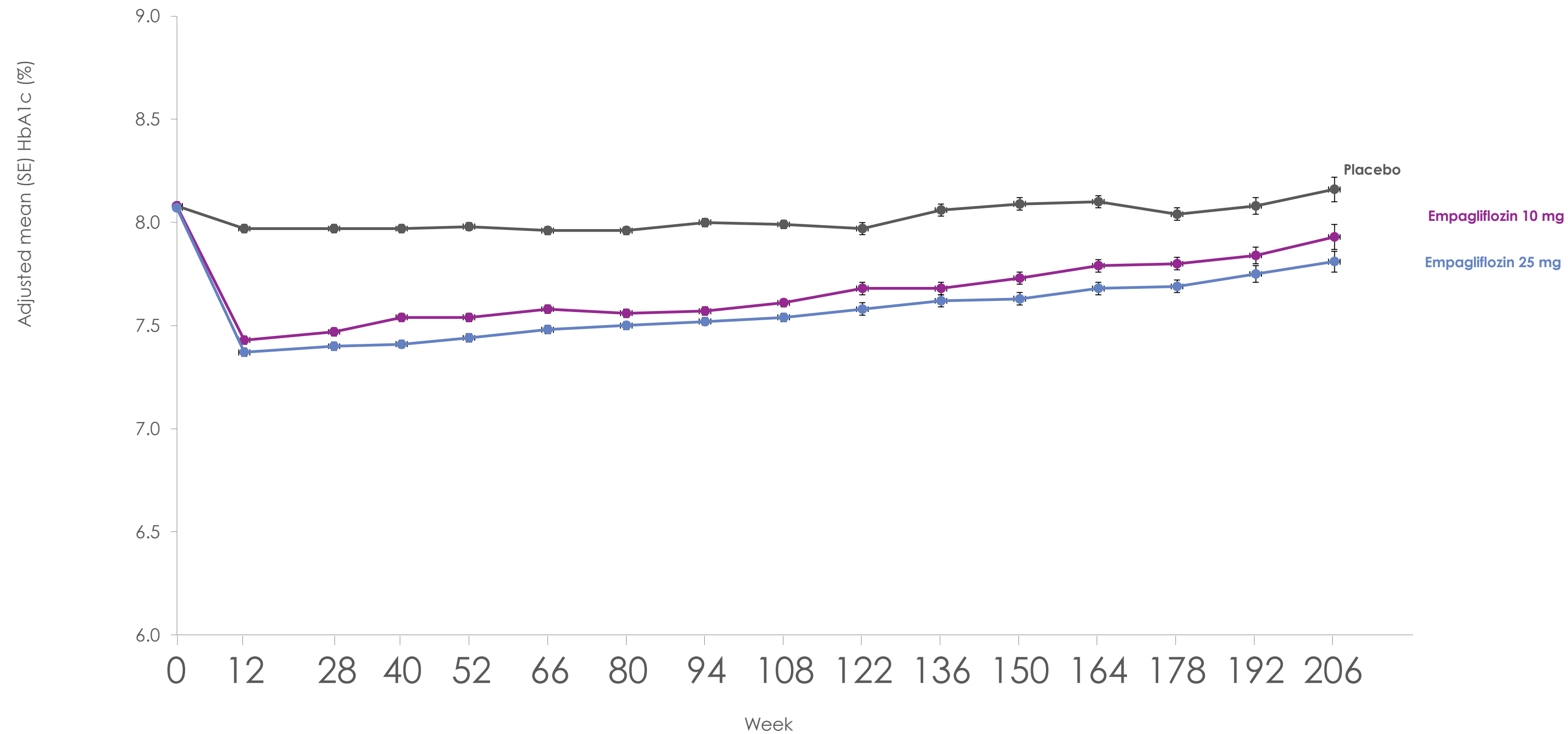
- The EMPA-REG and CANVAS trials showed that the SGLT-2 inhibitors empagliflozin and canagliflozin reduced the risk of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.<sup>1,2</sup>
- Empagliflozin also was associated with slower progression of kidney disease and lower rates of clinically relevant renal events.<sup>3</sup> In patients receiving canagliflozin, the composite outcome of sustained 40% reduction in eGFR, need for renal-replacement therapy, or death from renal causes occurred less frequently compared with placebo (CANVAS-R trial).<sup>2</sup>

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.

3. Wanner C, et al. *N Engl J Med.* 2016;375:323-334.

# HbA1c in EMPA-REG OUTCOME Trial

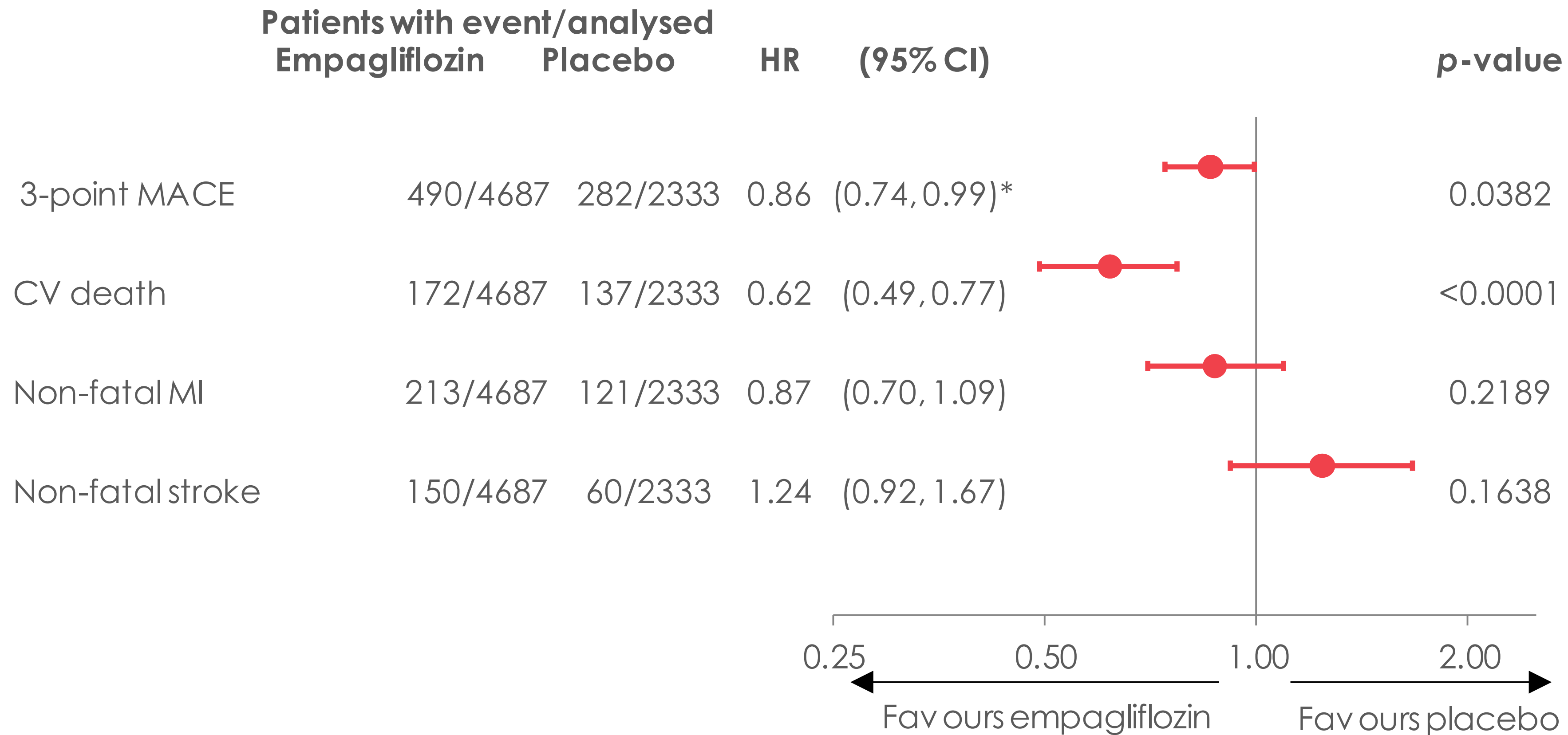


Placebo	2294	2272	2188	2133	2113	2063	2008	1967	1741	1456	1241	1109	962	705	420	151
Empagliflozin 10 mg	2296	2272	2218	2150	2155	2108	2072	2058	1805	1520	1297	1164	1006	749	488	170
Empagliflozin 25 mg	2296	2280	2212	2152	2150	2115	2080	2044	1842	1540	1327	1190	1043	795	498	195

All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent-to-treat) X-axis: timepoints with reasonable amount of data available for pre-scheduled measurements

Zinman B *et al.* *N Engl J Med* 2015;373:2117

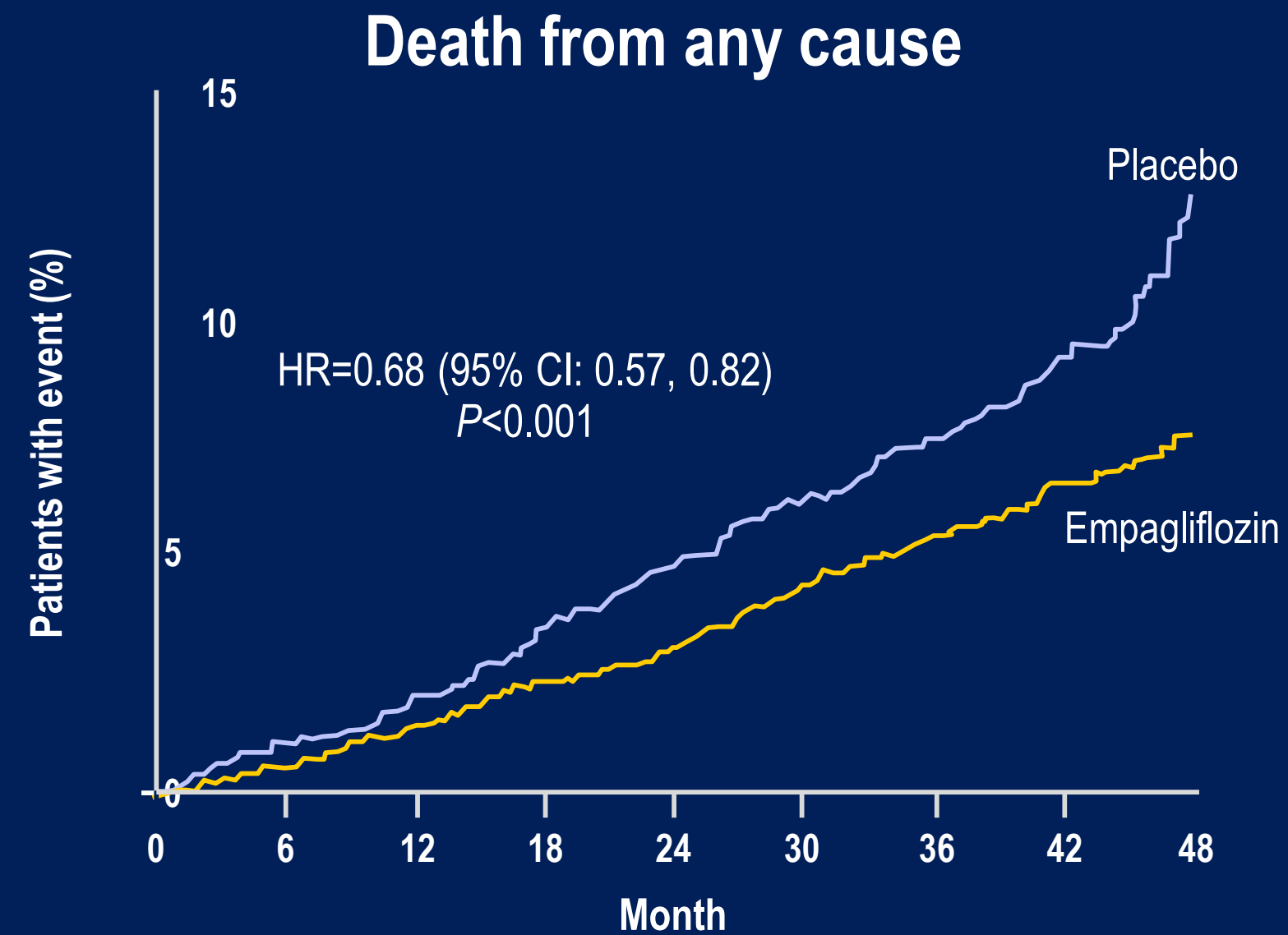
# EMPA-REG OUTCOME Primary outcome: 3-point MACE



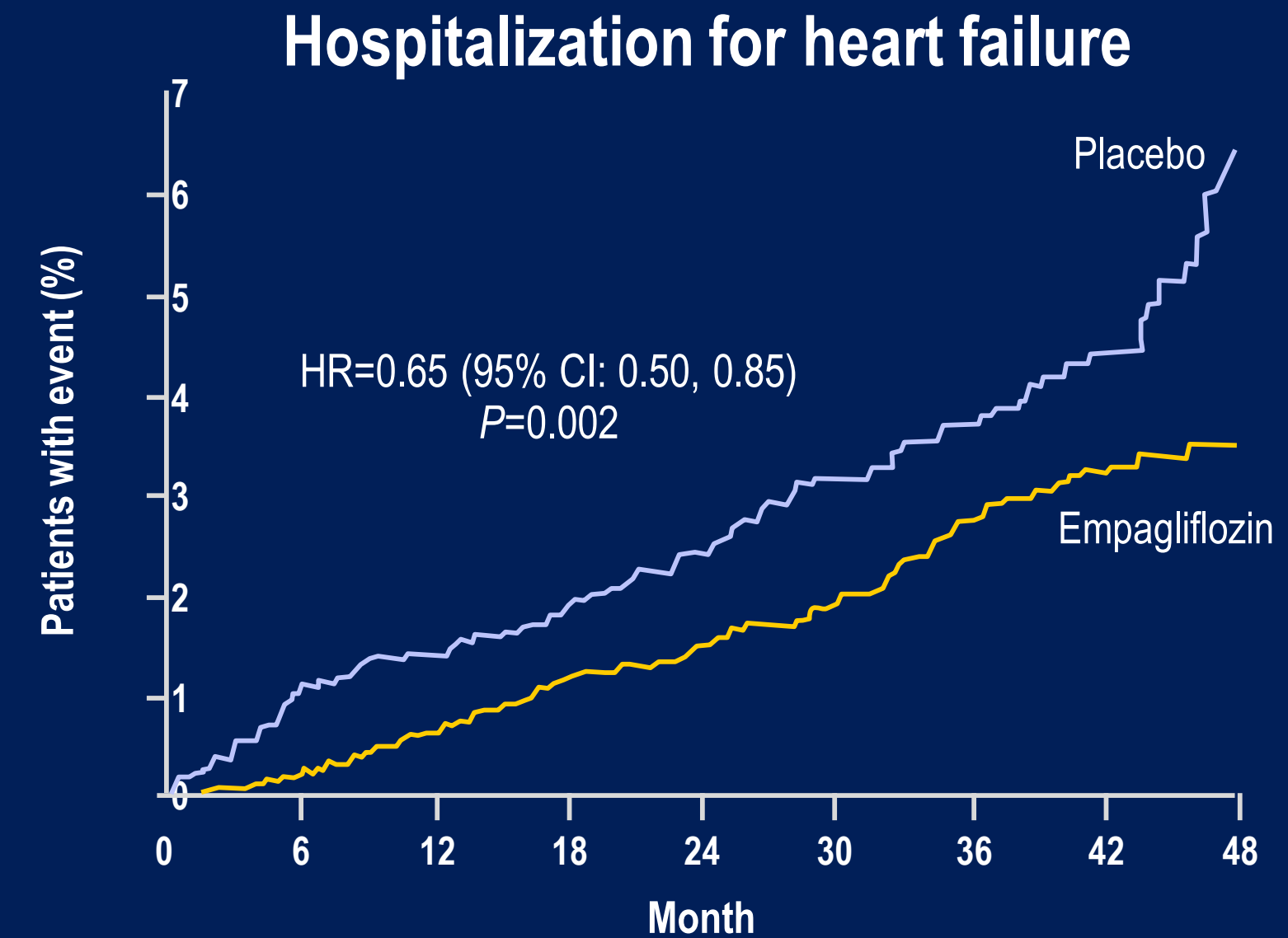


# EMPA-REG OUTCOMES

## *Empagliflozin and CV Outcomes*



No. at risk	0	6	12	18	24	30	36	42	48
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177



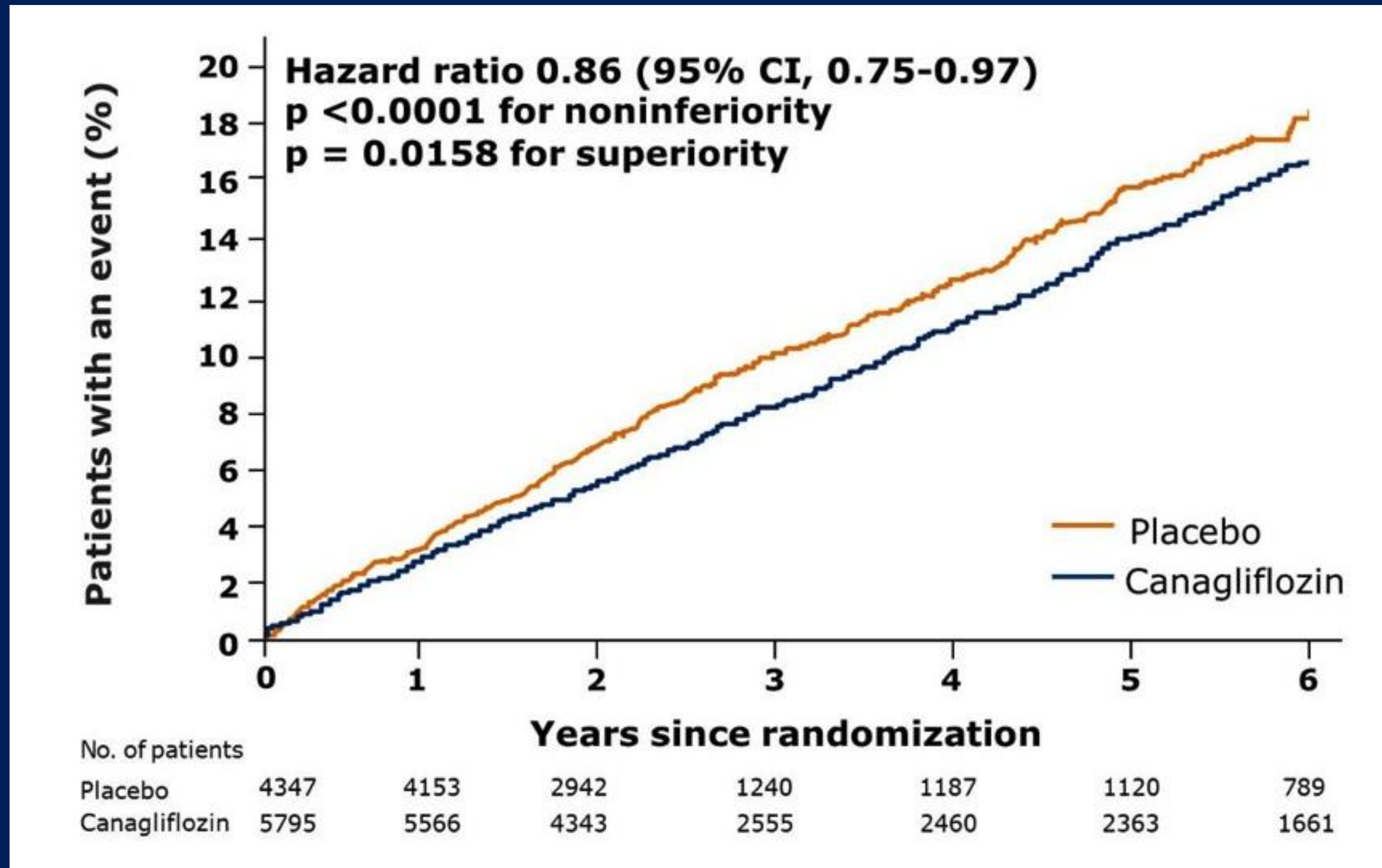
No. at risk	0	6	12	18	24	30	36	42	48
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

CI, confidence interval; CV, cardiovascular; HR, hazard ratio

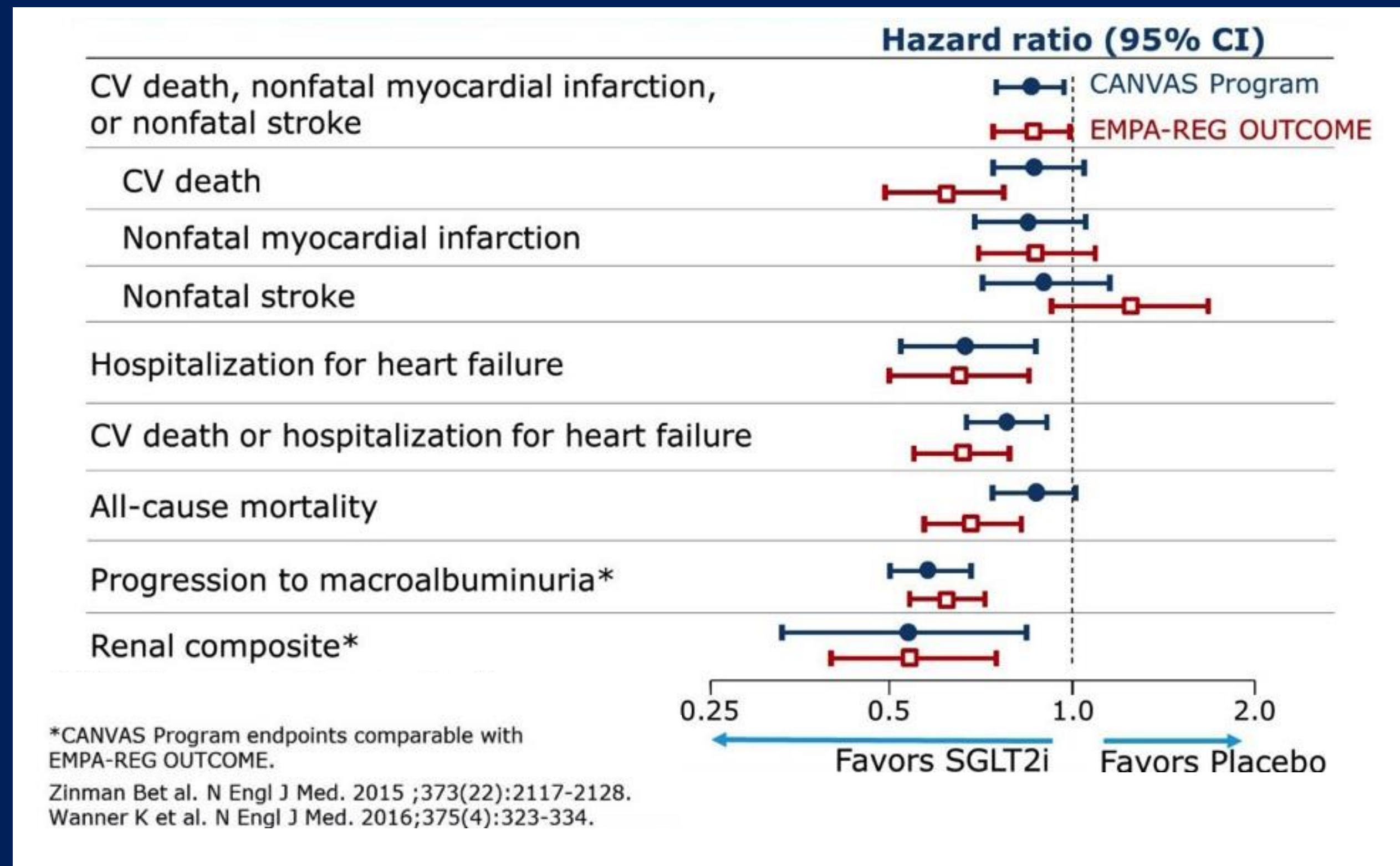
Zinman B, et al. *N Engl J Med.* 2015;373:2217-2128.

# CANVAS: MACE with Canagliflozin

*CV Death, Nonfatal Myocardial Infarction, or Nonfatal Stroke*



# CANVAS and EMPA-REG Outcomes



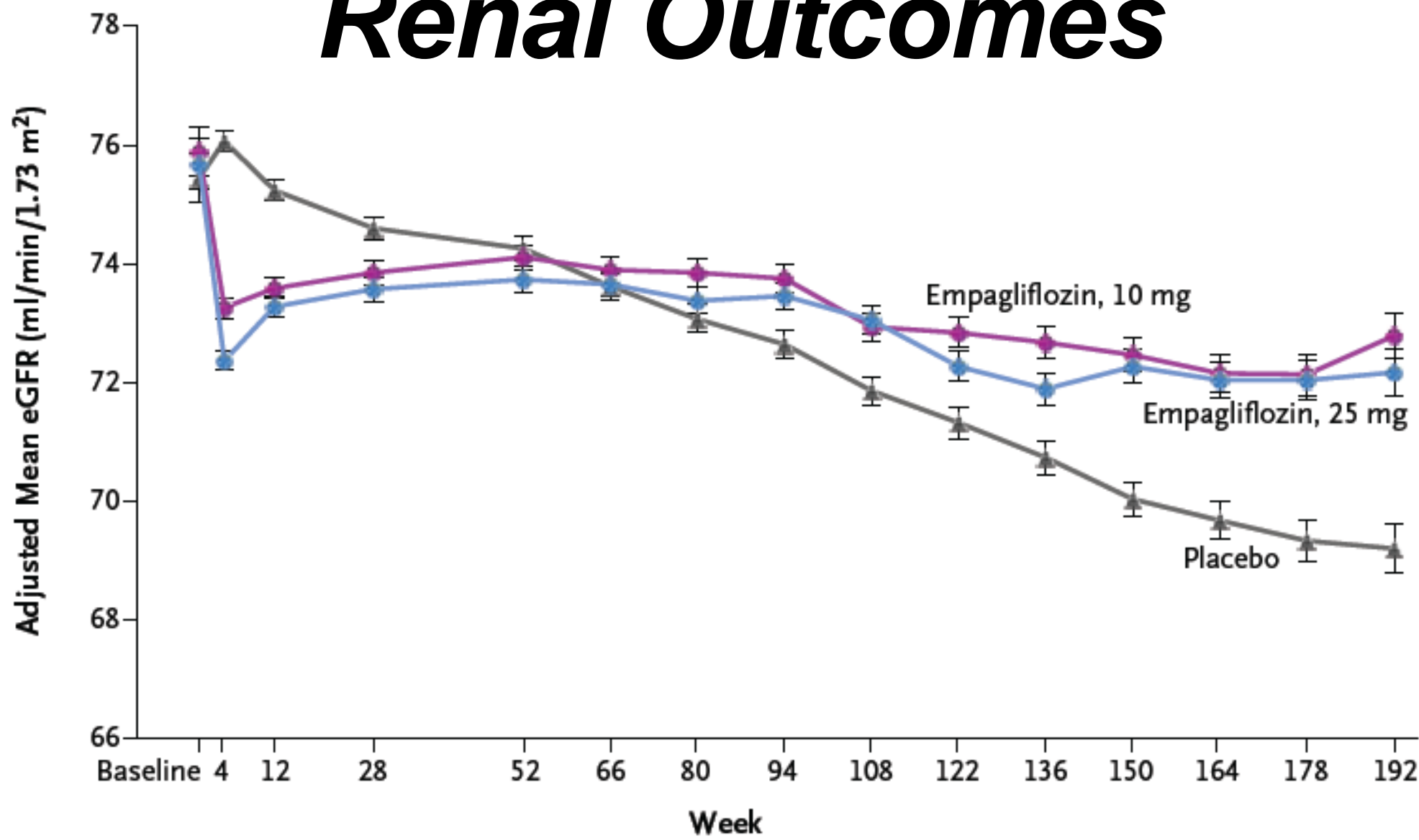
- CANVAS and CANVAS-R trial data showed increased risk of leg and foot amputations with canagliflozin vs placebo; higher fracture rate also observed with canagliflogizin<sup>1</sup>

1. Neal B, et al. *N Engl J Med* 2017;377:644-657.
2. Wanner C, et al. *N Engl J Med.* 2016;375:323-334.

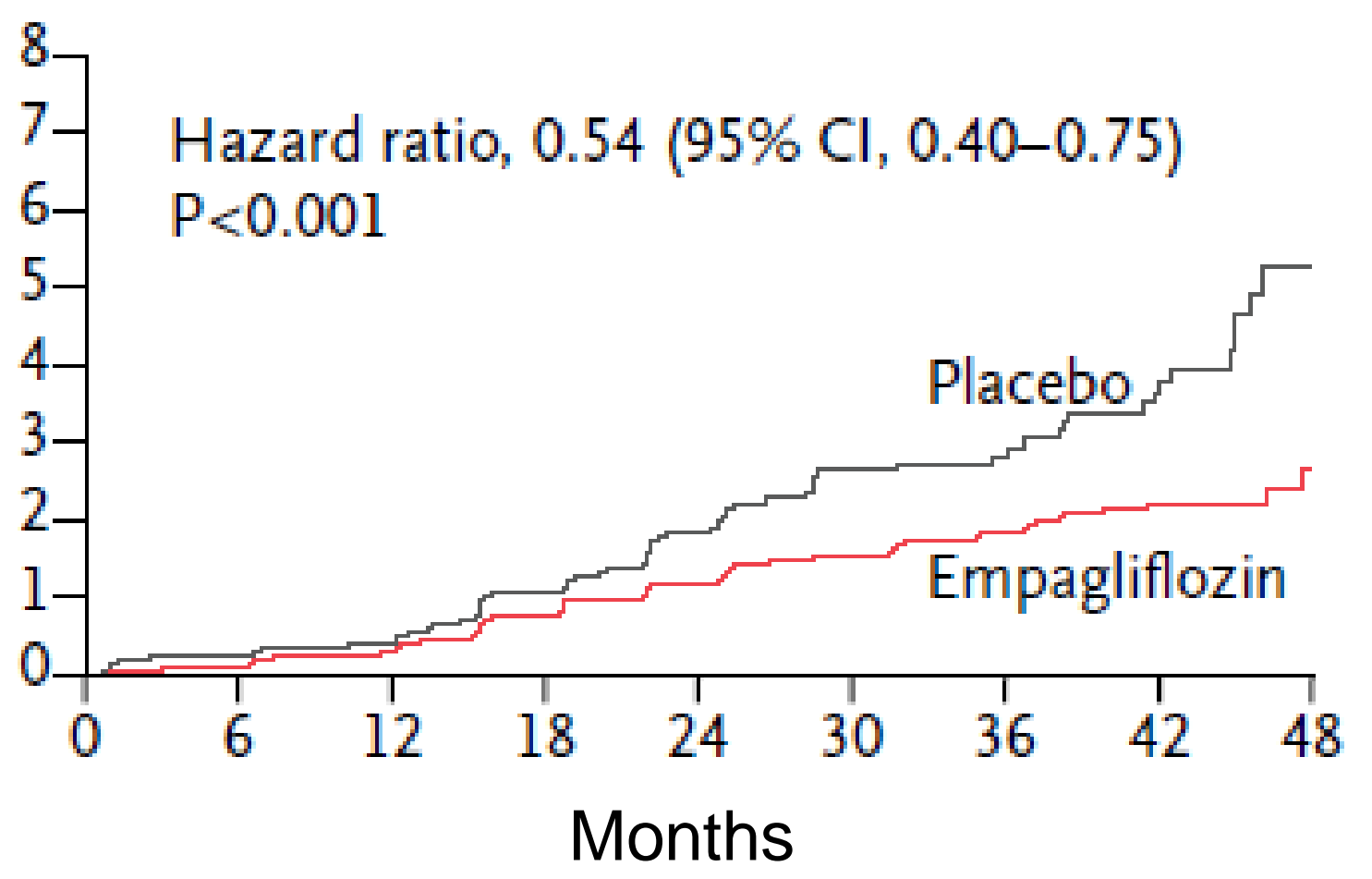


# EMPA-REG OUTCOME and CANVAS: *Renal Outcomes*

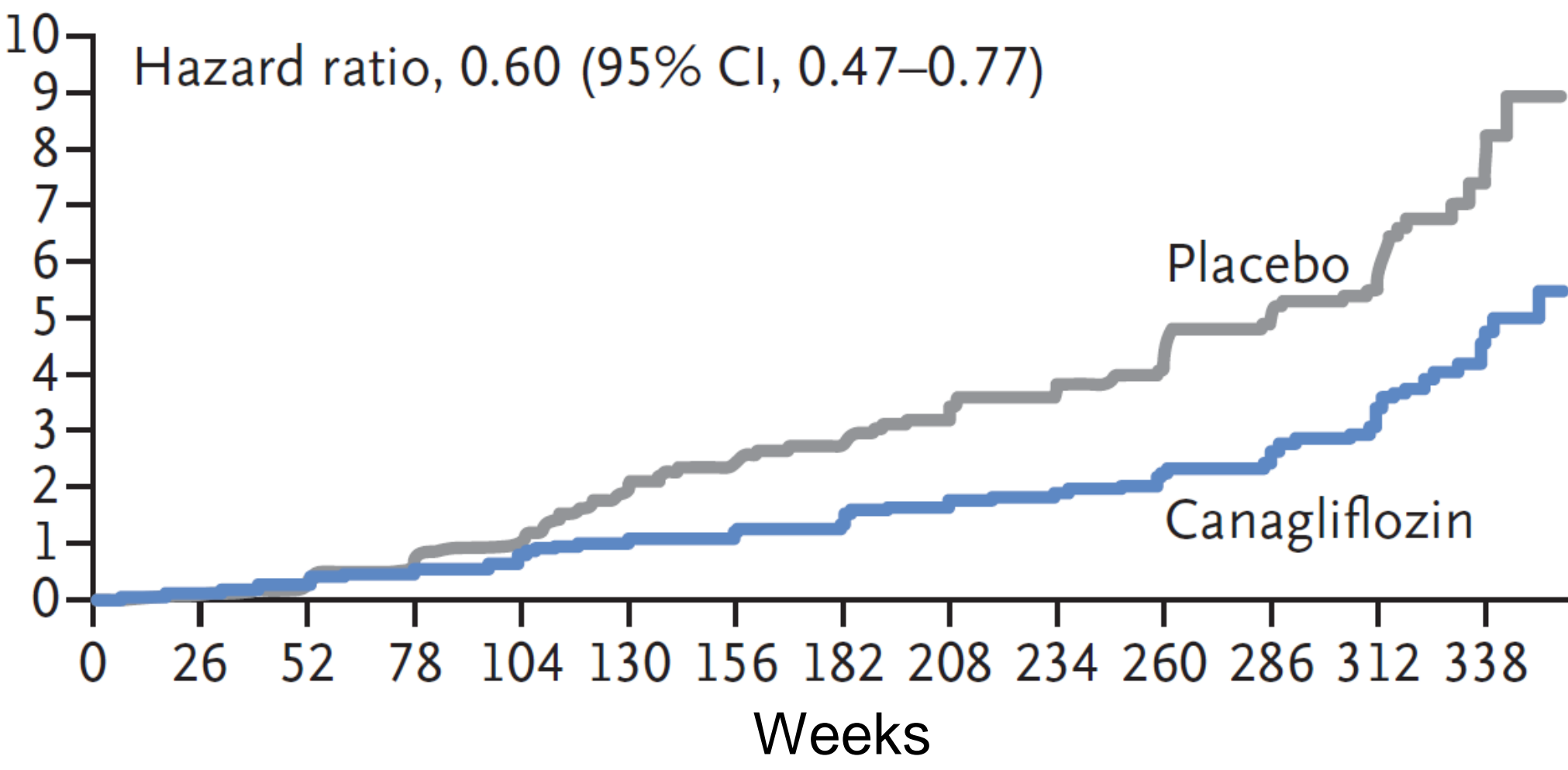
**RECENT RESULTS OF  
CREDENCE STUDY  
PROVIDES UNEQUIVOCAL  
EVIDENCE OF  
RENOPROTECTIVE EFFECTS  
OF CANAGLIFLOZINE**



**Doubling SCre, RRT, Renal Death**



**40%↓ eGFR, RRT, Renal Death**



Zinman B et al. N Engl J Med 2016; DOI: 10.1056/NEJMoa1515920

Neal B et al. N Engl J Med 2017. DOI: 10.1056/NEJMoa1611925

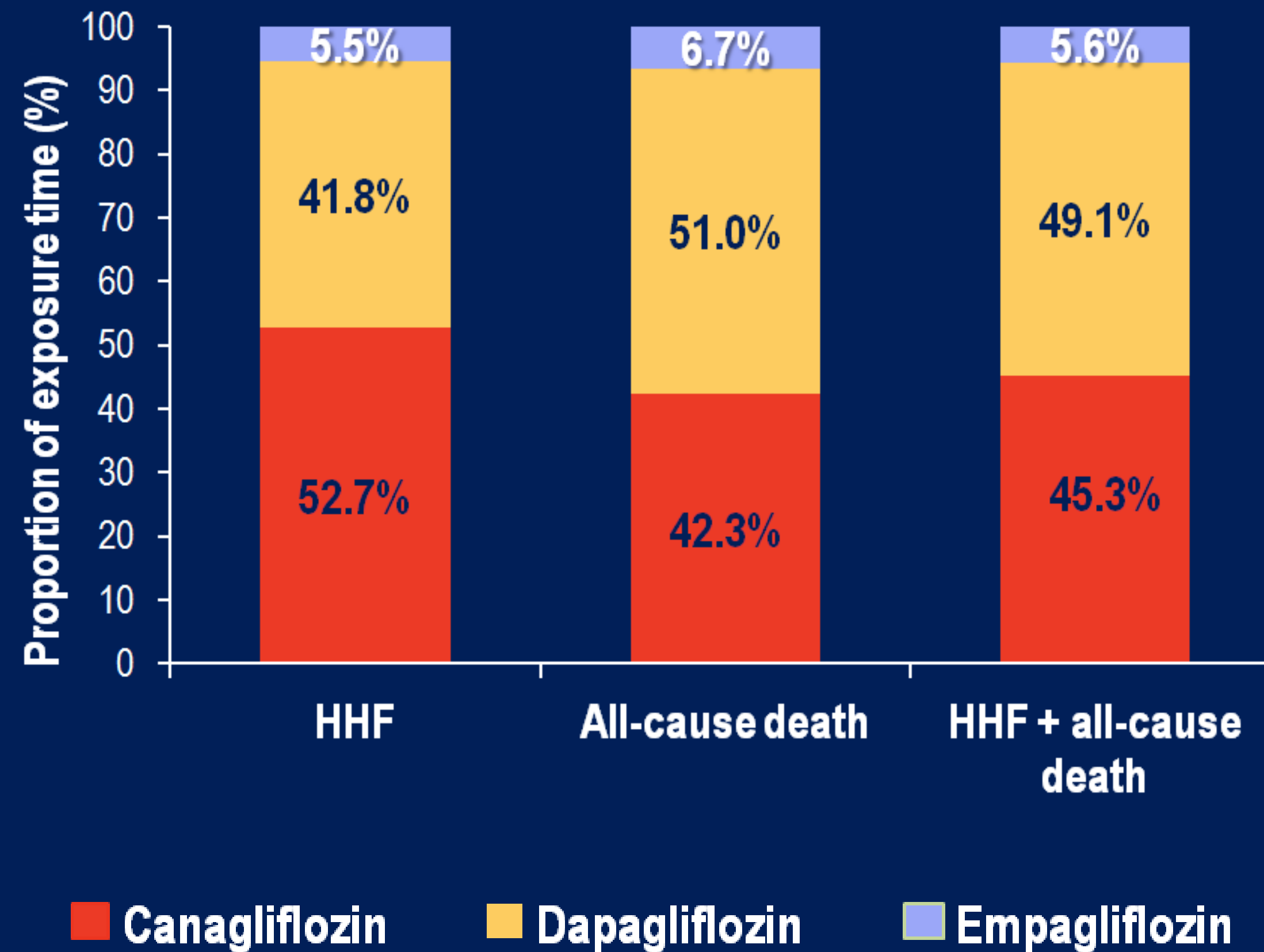
# CVD-REAL

## *How Do Data from Randomized Clinical Trials Compare with Real-world Clinical Practice?*

- Investigational multi-country observational study using real-world clinical practice records from six countries
  - United States, United Kingdom, Germany, Sweden, Norway, and Denmark
- Patients were followed from the index date until end of the index treatment (for the on-treatment analysis), migration/leaving the practice/database, last date of data collection, outcome date, or censoring date (range from September 2015 in the US to November 2016 in Sweden)
- The outcome of hospitalization for heart failure was evaluated for all six countries
- The outcome of all-cause death was evaluated for the US, Denmark, Norway, Sweden, and the UK

# CVD-REAL: Contribution of SGLT-2 Inhibitors

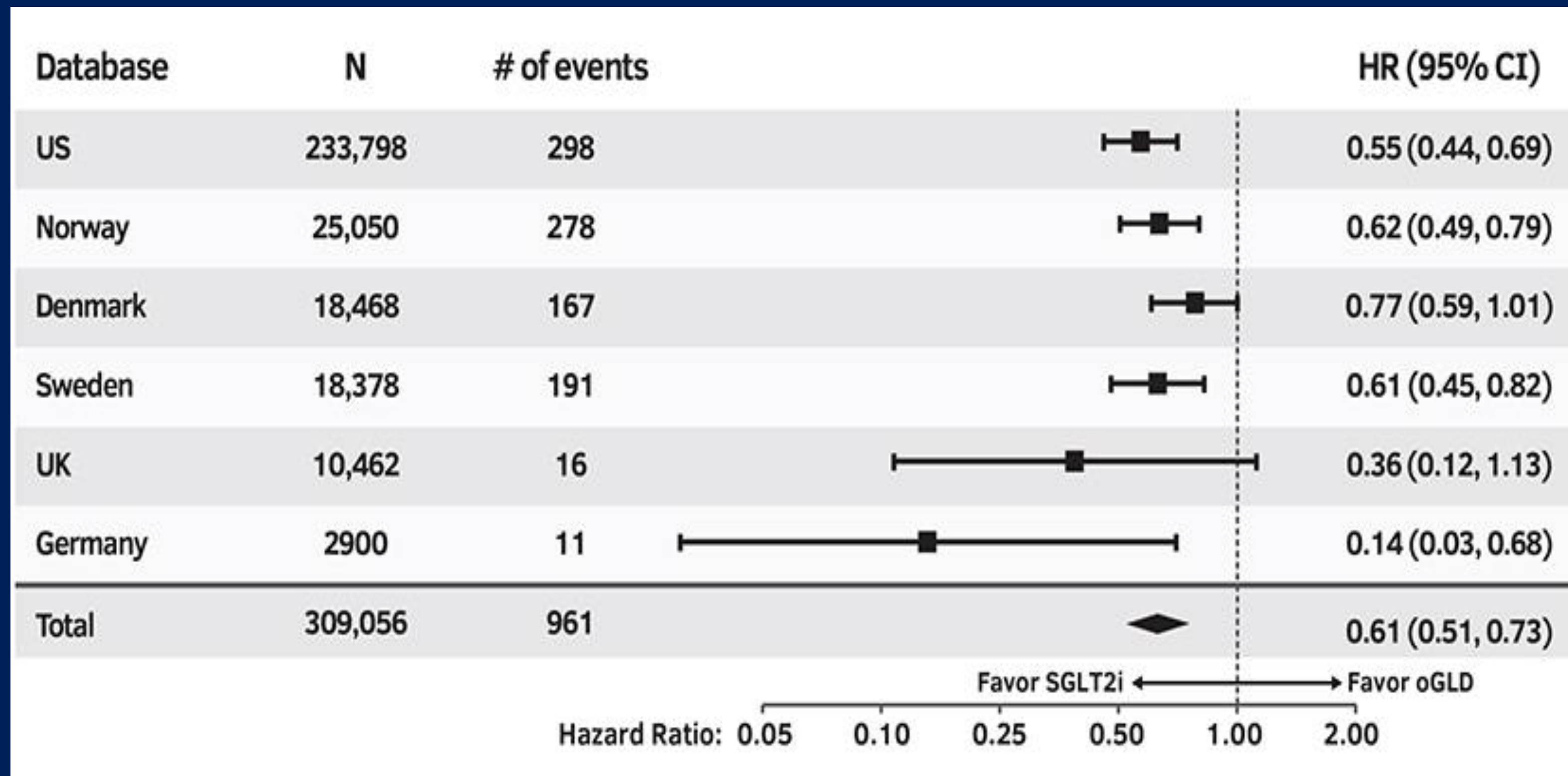
*All Countries Combined*





# CVD-REAL: Hospitalization for Heart Failure

## Primary Analysis



**P-value for SGLT-2 inhibitor vs other glucose-lowering drug: <0.001**

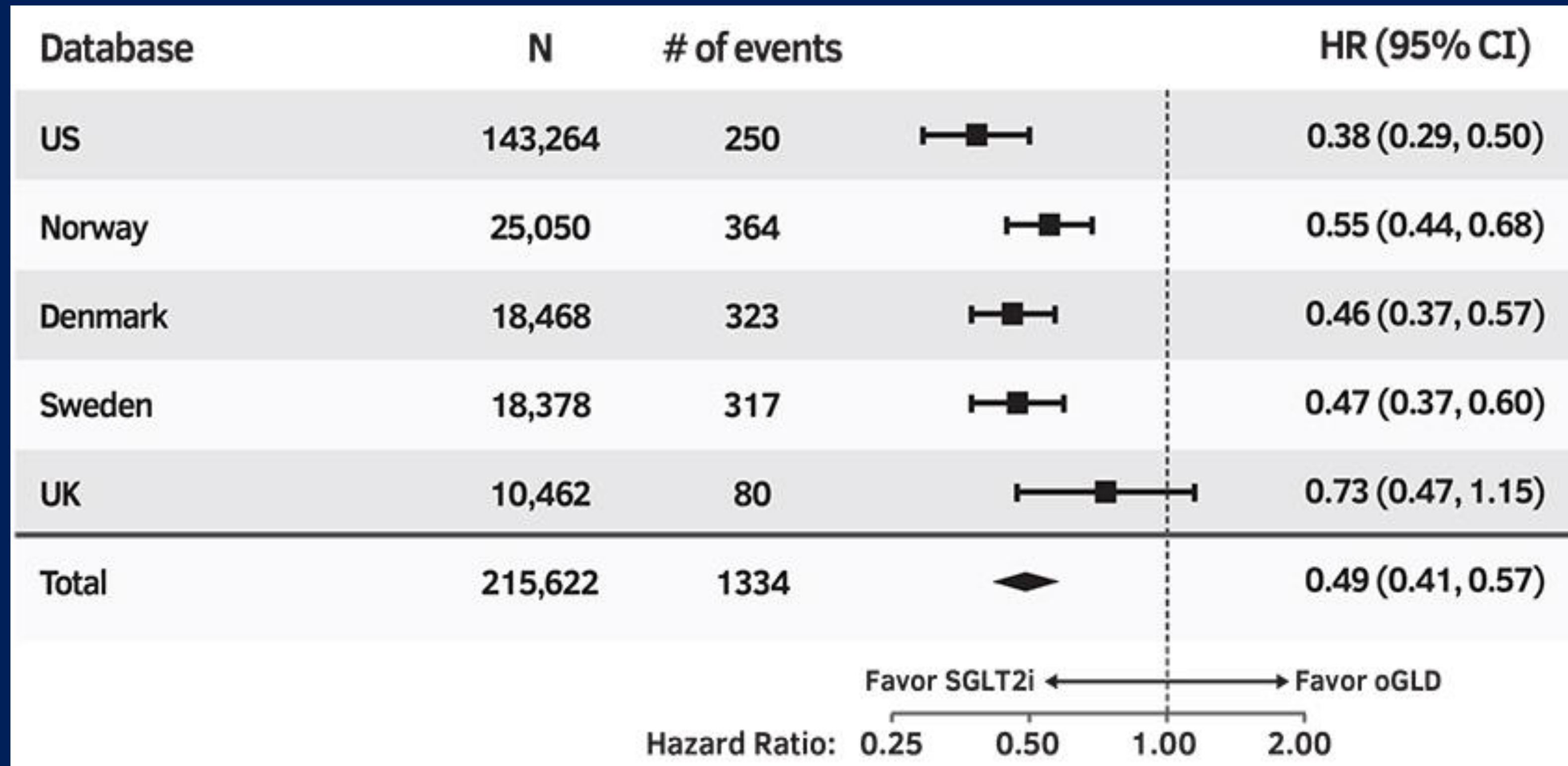
**Heterogeneity P-value=0.169**

Data are on treatment, unadjusted.

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

# CVD-REAL: All-cause Death

## Primary Analysis



**P-value for SGLT-2 inhibitor vs other glucose-lowering drug: <0.001**

**Heterogeneity P-value=0.089**

Data are on treatment, unadjusted.

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

# SLGT2 Inhibitors in DM & CV Disease

- Mechanism for striking decrease in CV mortality?
  - Not anti-atherosclerotic effect?
  - Hemodynamic effects likely : Diuresis
  - Lowers BP
  - CHF effect (including subclinical)? Diuresis plus?
    - ? Direct Myocardial Effects (Remodelling/Energetics)
  - Weight loss?
  - Arrhythmia/sudden death effect?
  - Other action? Decreased uric acid
- Therapeutic role in treating CVD in diabetes?
  - CHF (HF-pEF or rEF?) EMPEROR Trials
  - Suboptimal BP control
- Therapeutic role in treating CVD w/o diabetes?
  - No hypoglycemia
- Class effect? Very likely at least for DM and CHF

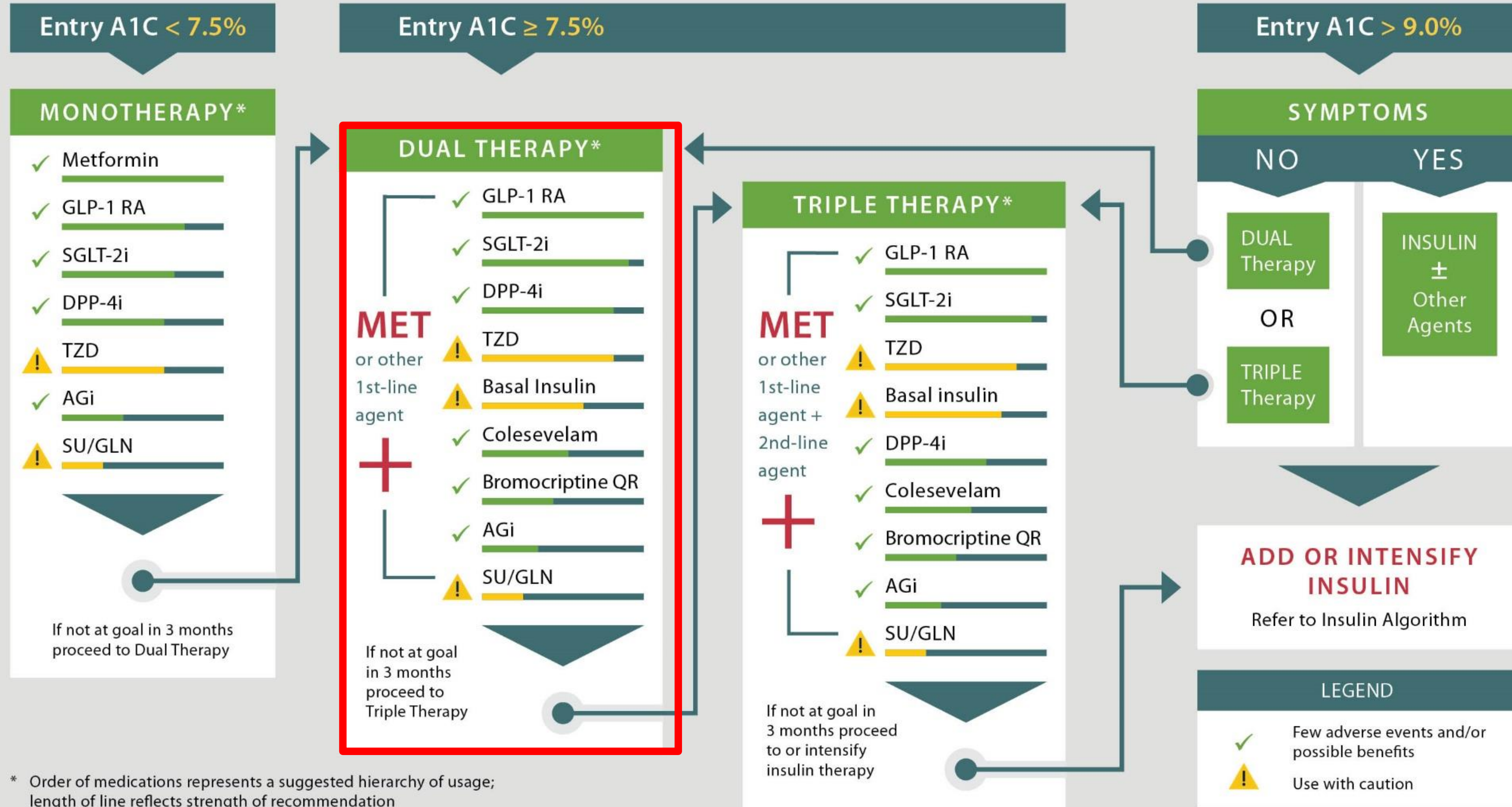




# GLYCEMIC CONTROL ALGORITHM



## AACE LIFESTYLE THERAPY (Including Medically Assisted Weight Loss)



\* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation


## PROGRESSION OF DISEASE

# Take Away Points

- Risks of CHD, Stroke, and Heart Failure are very high in patients with diabetes, especially in younger women
- Newer drugs such as SGLT2i are safe and highly effective in reducing most CV complications, specially HFH and Renal failure which are increasing in DM pts.
- Comprehensive risk factor control & use of these newer drugs should improve the CV outcomes in DM.







*THANK YOU!*