PHARMACY VISION 2020

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Disneyland RESORT

CardioRenal Outcomes in Type 2 Diabetes

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DISCLOSURE

- Nathan A. Painter has no potential conflict of interest (COI)

Learning Objectives

- Review Standards of Care as it relates to medication management
- Identify studies with cardiorenal outcomes
- Use case scenarios to identity patients who may benefit from medications based on non-glucose lowering outcomes.

TEST QUESTION #1

A 65-year old man presents to your clinic for diabetes management. He has hypertension, dyslipidemia, and diabetes. He also currently smokes 1 pack per day (PPD). The patient has previously controlled his diabetes with diet and exercise and metformin but A1C recently increased to 8.5%. He is adamantly against injections. Which one of the following oral agents is best to recommend for this patient's MACE?

A. Semaglutide

B. Sitagliptin

C. Canagliflozin

D. Glipizide

TEST QUESTION #2

A.J., a 48-year-old man, presents to your CV risk reduction clinic. A.J. was diagnosed with diabetes based on an A1C of 9.5% and was started on metformin and alogliptin. Which one of the following best evaluates the cardiovascular safety and efficacy of A.J.'s current therapy?

A. Alogliptin has demonstrated neutral effects on MACE outcomes in patients post-acute coronary syndrome (ACS).

B. Alogliptin has been shown to significantly decrease MACE in patients with established CVD.

C. Other DPP-4 inhibitors have shown superiority with regard to reduction in MACE.

D. Other classes besides DPP-4 inhibitors have shown significant reductions in MACE in patients immediately post-ACS.

TEST QUESTION #3

A 56-year-old woman has a medical history of diabetes, HTN, stroke, and dyslipidemia. Her home drugs include metformin 1000 mg BID. Her HTN and dyslipidemia are well-controlled. Her most recent A1C is 7.6%. Which one of the following is the best adjunctive therapy to recommend for this patient?

A. Dapagliflozin

B. Glipizide

C. Sitagliptin

D. Dulaglutide

Diabetes Facts

More than 30 million people in the US have diabetes

More than 84 million US adults—1 in 3—have prediabetes

Prediabetes is a risk factor for type 2 diabetes. Being overweight, being age 45 or older, and being physically active less than 3 times a week are risk factors for prediabetes and type 2 diabetes.

In 2017, the total estimated cost of diagnosed diabetes was $327 billion.

National Center for Chronic Disease Prevention and Health Promotion

ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD)

ASCVD manifests as coronary artery disease (CAD), ischemic stroke, peripheral artery disease (PAD), and Heart Failure (HF) and tends to be more severe and occur at an earlier age in patients with type 2 diabetes.

Several factors including hyperglycemia, insulin resistance, inflammation, endothelial dysfunction, hypercoagulability, and vascular calcification lead to increased plaque formation and narrower coronary arteries.

Low-Wang 2016, ADA 2018

DEFINING MAJOR ADVERSE CARDIAC EVENT (MACE)

3-POINT MACE

1. CV death
2. Nonfatal myocardial infarction (MI)
3. Nonfatal stroke

4-POINT MACE

1. CV death
2. Nonfatal myocardial infarction (MI)
3. Nonfatal stroke
4. Hospitalization for unstable angina

Marx, N, Diabetes Care. 2017 Sept.

Kidney Disease

Kidney disease, a major risk factor for Cardiovascular disease, affects about 37% of patients with diabetes.

Diabetes is currently the leading cause of chronic (CKD) and end-stage kidney disease (ESRD), accounting for 38.5% of cases.

The presence of kidney disease in patients with diabetes increases risk of mortality by 23.4%.

CDC Stats report 2020, Afkarian 2013

GUIDELINES

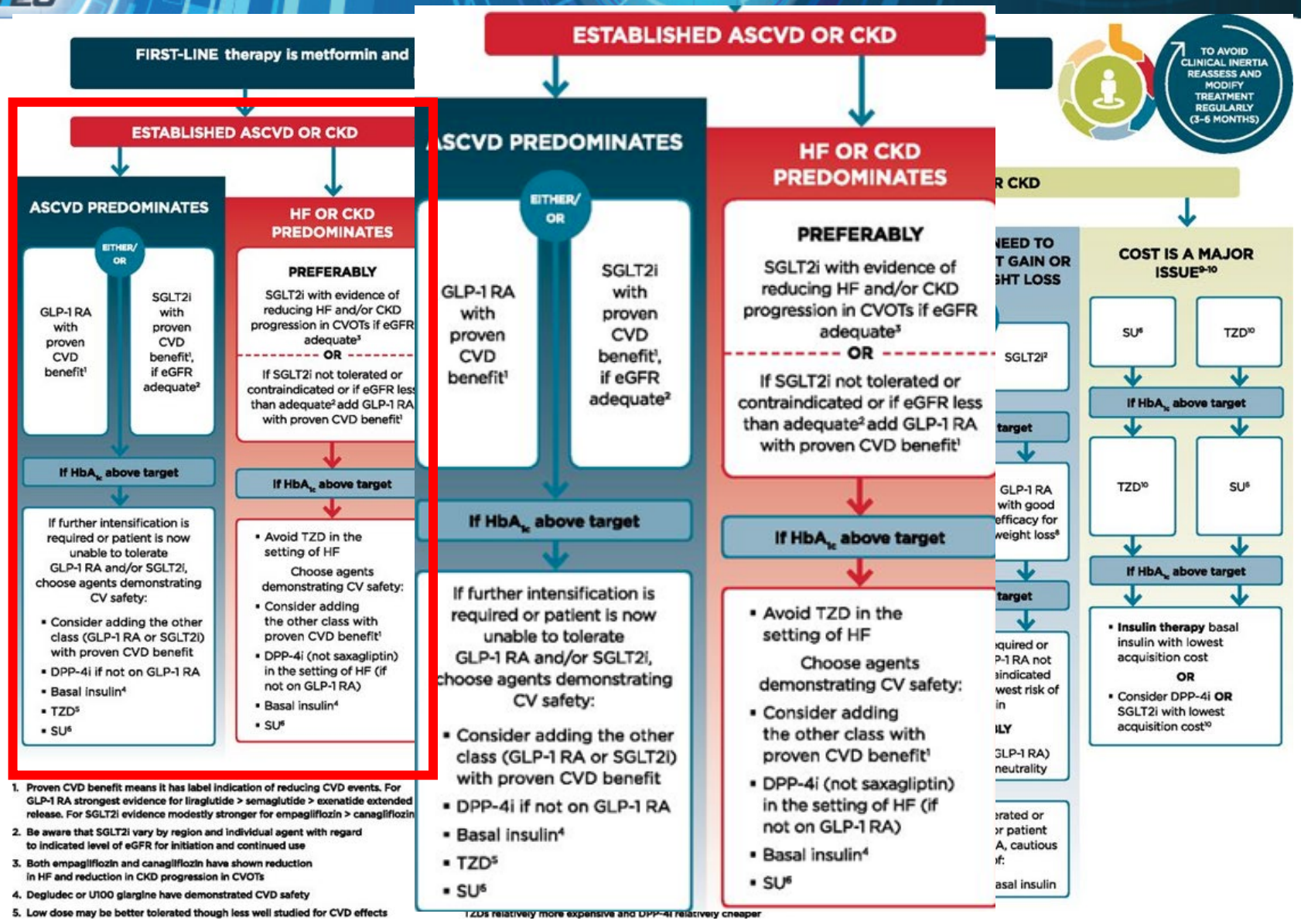
Major guidelines related to the management of diabetes have shifted from a standard algorithm to a patient-centered, individualized approach.

Many guidelines continue to recommend metformin as first-line therapy

Considerations for selecting an adjunctive medication included

- Glycemic control
- Risk of hypoglycemia
- Weight
- Side effects
- Cost

ADA guidelines, AACE/ACE guidelines, ADA/EASD guidelines



American Diabetes Association. Diabetes Care 2019 Jan; 42(Supplement 1): S90-S102.

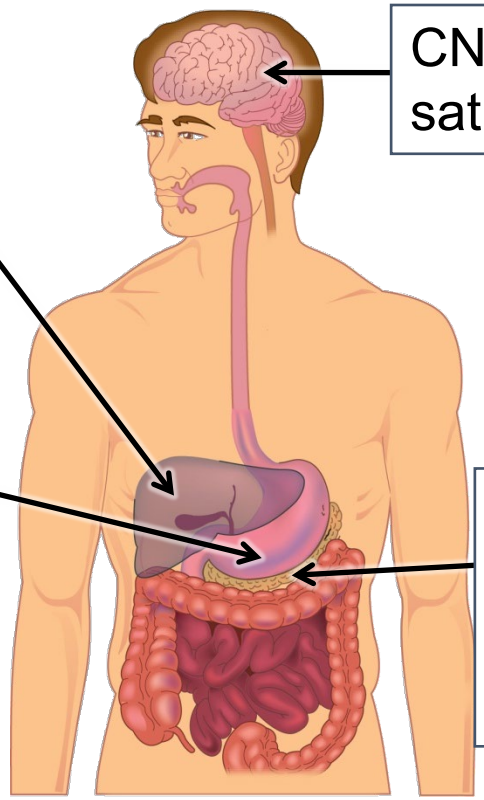
METFORMIN AND CKD

- Contraindicated eGFR < 30 mL/min
- Starting with eGFR 30-45 mL/min is not recommended
- Obtain eGFR at least annually
  - More often if at risk to develop of renal impairment
- If eGFR later falls below 45 mL/min assess risks vs benefits
- Discontinue if eGFR later falls below 30 mL/min
- The National Kidney Foundation recommends using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Equation to estimate GFR

http://www.fda.gov/Drugs/DrugSafety/ucm493244.htm
Levey 2009

GLP-1 Receptor Agonists

GLP-1 RA: MOA



CNS: Increases satiety

Liver: Reduces hepatic glucose output

Stomach: Slows gastric emptying

β cell: Increases insulin secretion in a glucose-dependent manner

GLP-1 Receptor Agonists

GLP-1 is thought to exert CV protective effects including

- improved glycemic control
- improved endothelial function
- vasodilation
- improved blood flow

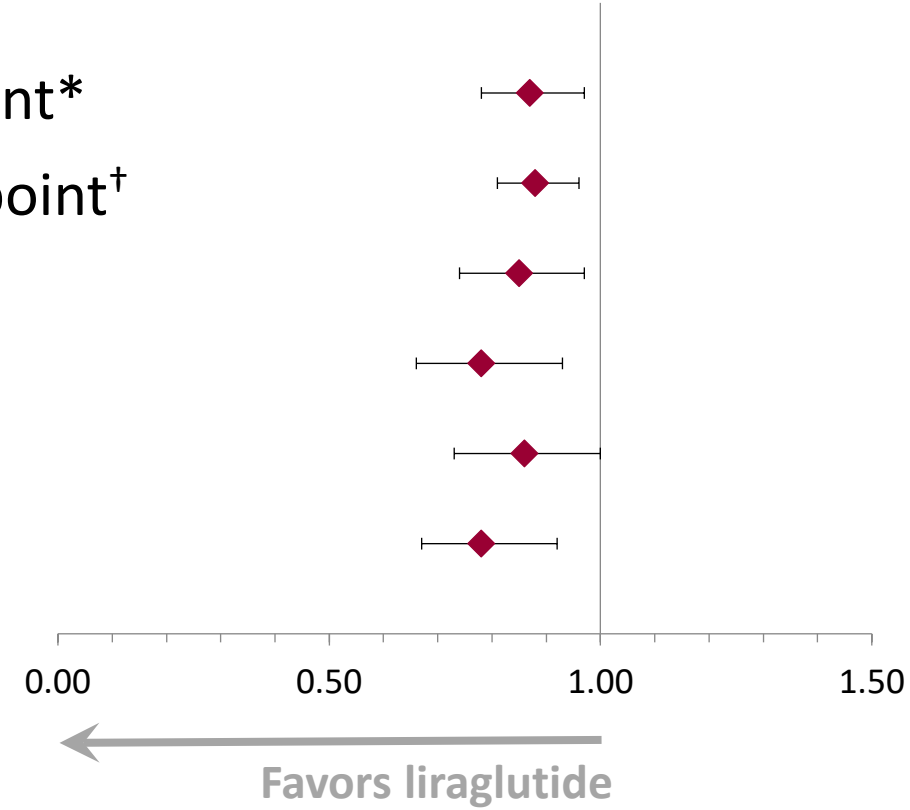
Reductions in

- fatty acid utilization
- body weight
- BP and lipids
- natriuresis resulting in decreased blood volume

Ussher 2014, Scheen 2018

OUTCOMES WITH LIRAGLUTIDE

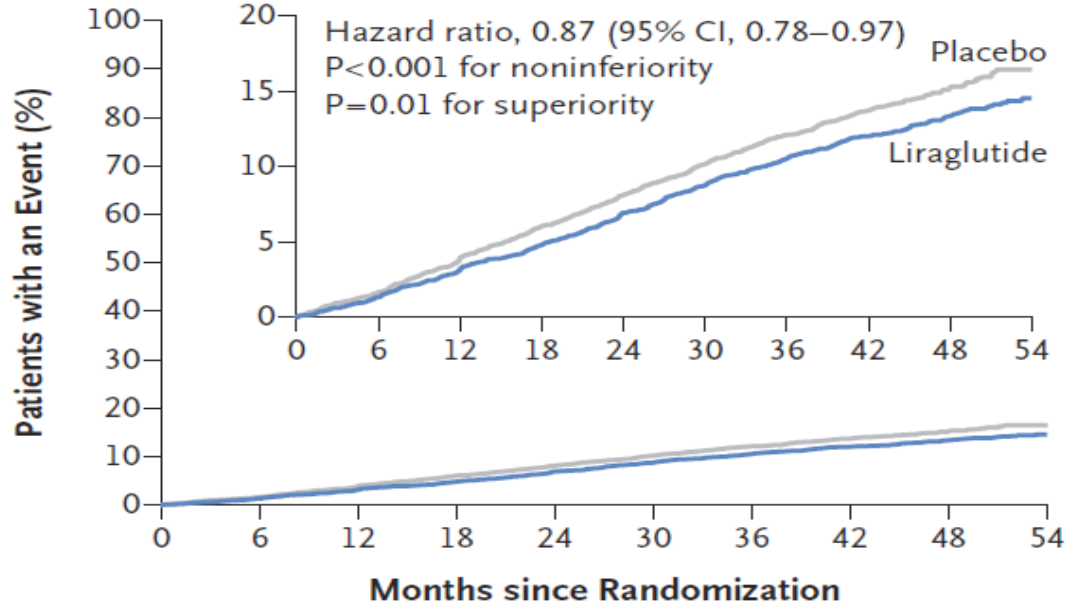
	Hazard ratio (95% CI)	*P* value
Primary composite endpoint*	0.87 (0.78-0.97)	0.01
Expanded composite endpoint†	0.88 (0.81-0.96)	0.005
Death from any cause	0.85 (0.74-0.97)	0.02
CV death	0.78 (0.66-0.93)	0.007
Fatal or nonfatal MI	0.86 (0.73-1.00)	0.046
Nephropathy	0.78 (0.67-0.92)	0.003



Marso SP 2016

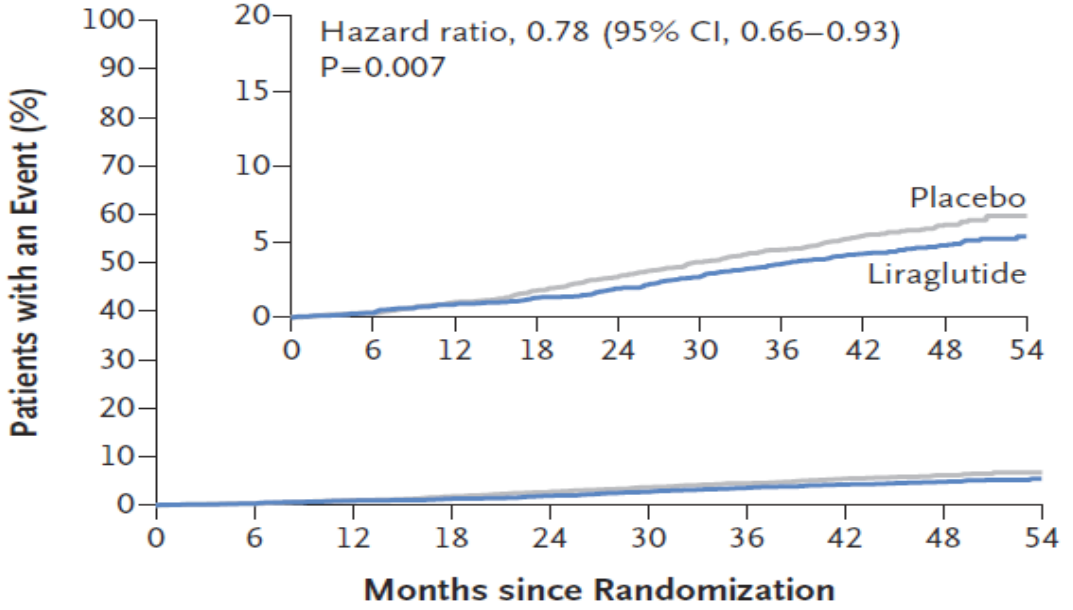
CLINICAL OUTCOMES WITH LIRAGLUTIDE

A Primary Outcome



No. at Risk										
Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

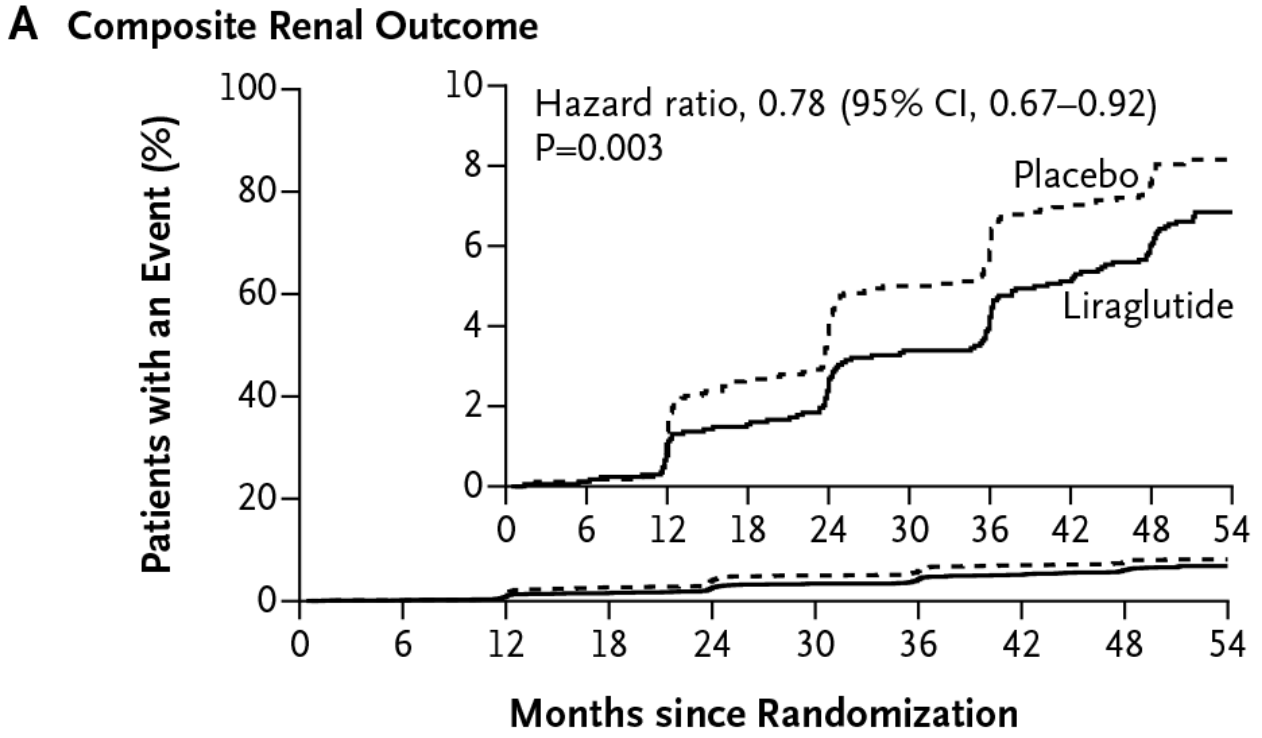
B Death from Cardiovascular Causes



No. at Risk										
Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

Marso 2016

LIRAGLUTIDE AND RENAL OUTCOMES IN TYPE 2 DIABETES



No. at Risk

Placebo	4672	4643	4540	4428	4316	4196	4094	3990	1613	433
Liraglutide	4668	4635	4561	4492	4400	4304	4210	4114	1632	454

Marso 2016

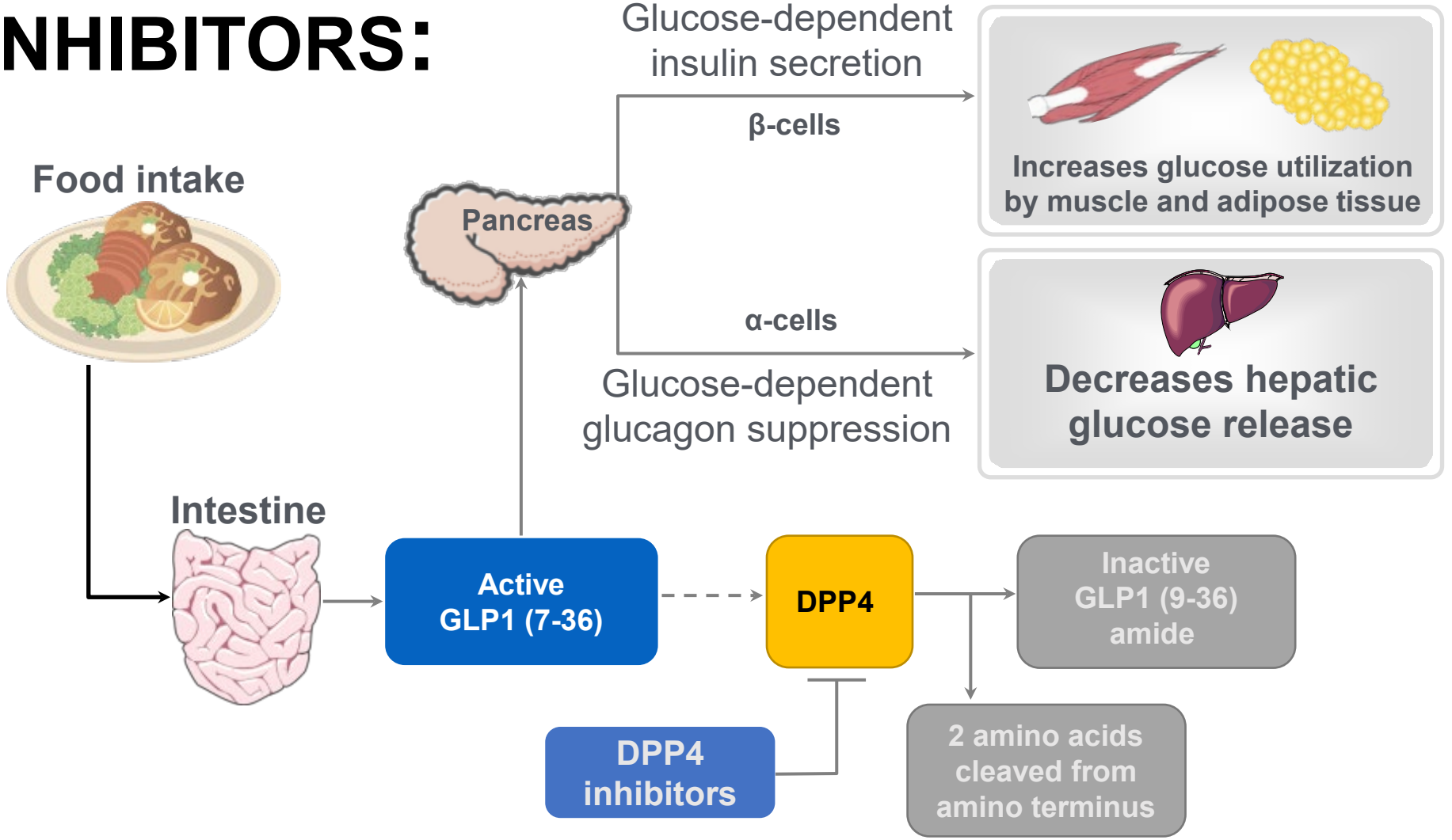
GLP-1 RA AND CV OUTCOMES

	LEADER (liraglutide)	SUSTAIN-6 (semaglutide)	ELIXA (lixisenatide)
Primary composite endpoint (CV death, MI, stroke)	HR = 0.87 (0.78, 0.97) P < .001	HR = 0/74 (0.58, 0.95) P < .001	HR = 1.02 (0.89, 1.17) p=.81
CV Death	HR = 0.78 (0.66, 0.93) P = .007	HR = 0.98 (0.65, 1.48) P +.92	HR = 0.98 (0.78, 1.22) P= .85
Nonfatal MI	HR = 0.86 (0.73, 1.00) P = .046	HR = 0.74 (0.51, 1.08) P = .12	HR = 1.03 (0.87, 1.22) P=.71
Nonfatal Stroke	HR = 0.86 (0.71, 1.06) P = .16	HR = 0.61 (0.38, 0.99) P = .04	HR = 1.12 (0.79, 1.58) P=.54

Marso 2016, Pfeffer 2015

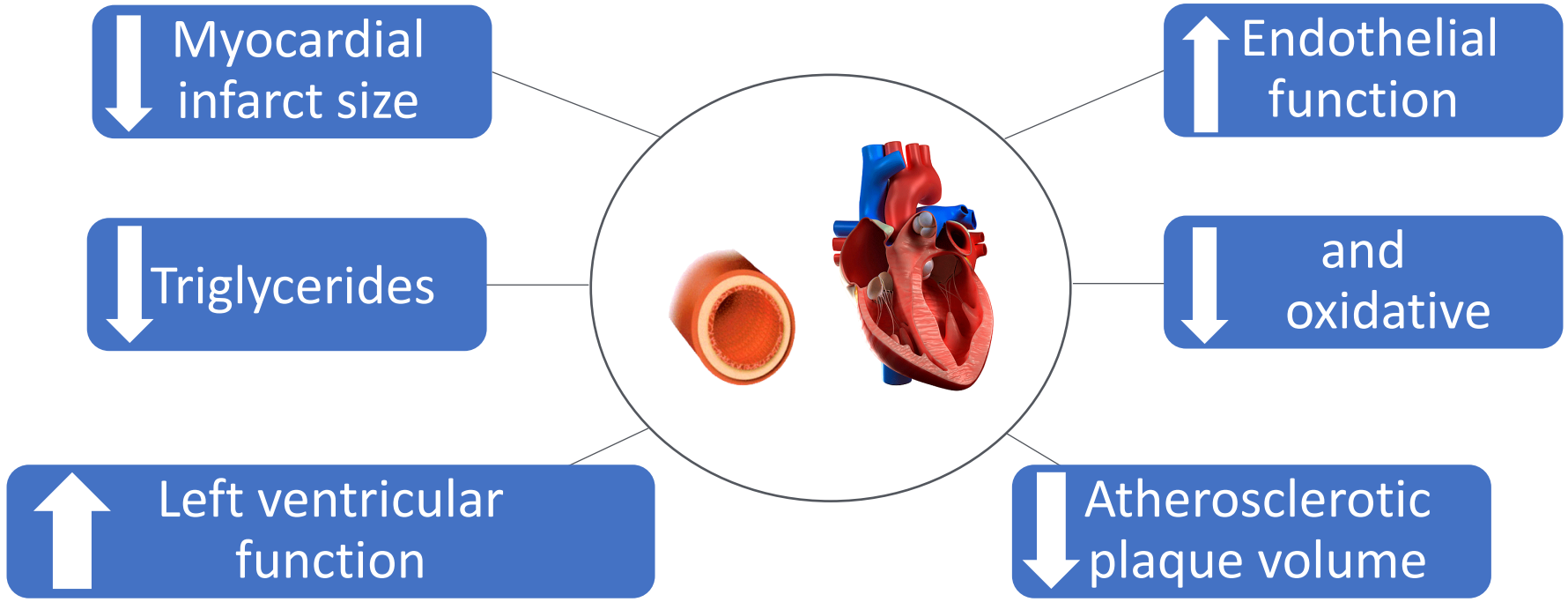
DPP-4 Inhibitors

DPP-4 INHIBITORS: MOA



Drucker 2003, Ahrén 2003

POTENTIAL CV EFFECTS OF THE DPP-4 INHIBITORS



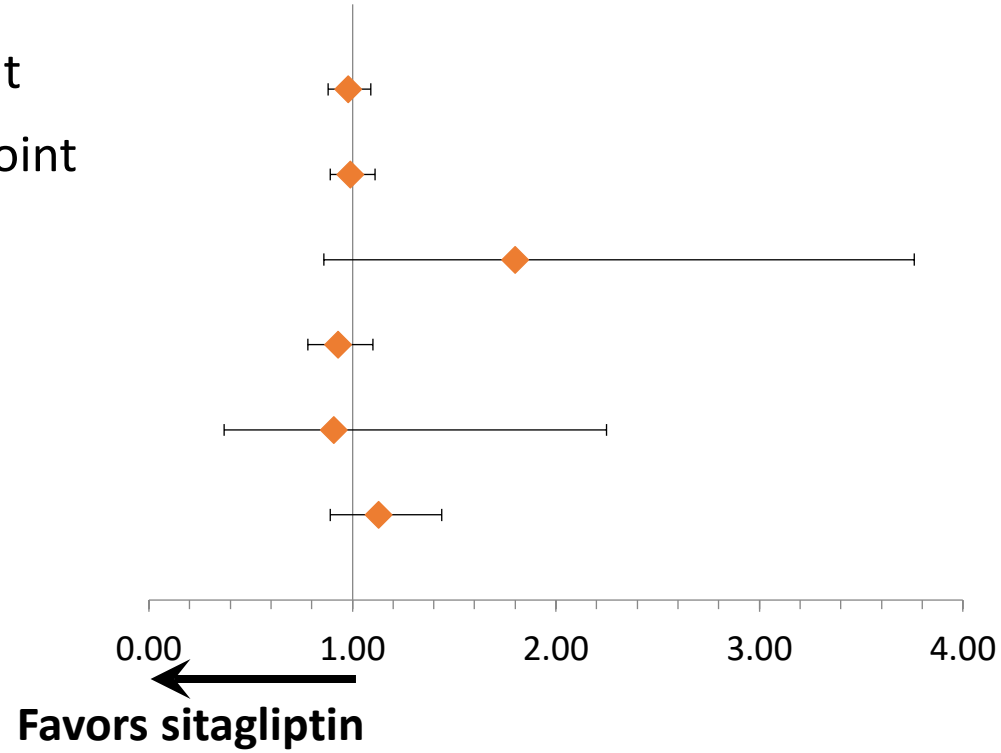
Ye 2010, Hocher 2013

DPP-4 Inhibitors CVD Outcomes

Trial	Agent	Study Population	# Patients	Median Trial Duration	Outcomes (95% CI)
TECOS (Green 2015)	Sitagliptin 50-100 mg daily	Age ≥ 50 years (mean 65 years) Established CVD	14,735	3 years	4-pt MACE (CV death, non-fatal MI or stroke, hospitalization for UA) HR: 0.98 (0.89-1.11)
EXAMINE (White 2013)	Alogliptin 6.25-25 mg daily	Median age: 61 years ACS within 15-90 days	5,380	18 months	3-pt MACE (CV death, non-fatal MI or stroke) HR: 0.96 (one-sided <1.17); p=0.32
SAVOR-TIMI 53 (Scirica 2013)	Saxagliptin 2.5-5 mg daily	Mean age: 65.1 years Age ≥ 40 years and established CVD (78.4%) or Age ≥ 55 years and multiple CV risk factors	16,492	2.1 years	3-pt MACE HR: 1.0 (0.89-1.12) HHF HR: 1.27 (1.07-1.51)
CARMELINA (Rosenstock 2019)	Linagliptin 5 mg daily	Mean age: 66.1 years High CV risk (established CVD 57%) or High renal risk (kidney disease 74%)	6,991	2.2 years	3-pt MACE HR: 1.02 (0.89-1.17)

PRIMARY AND SECONDARY OUTCOMES WITH SITAGLIPTIN

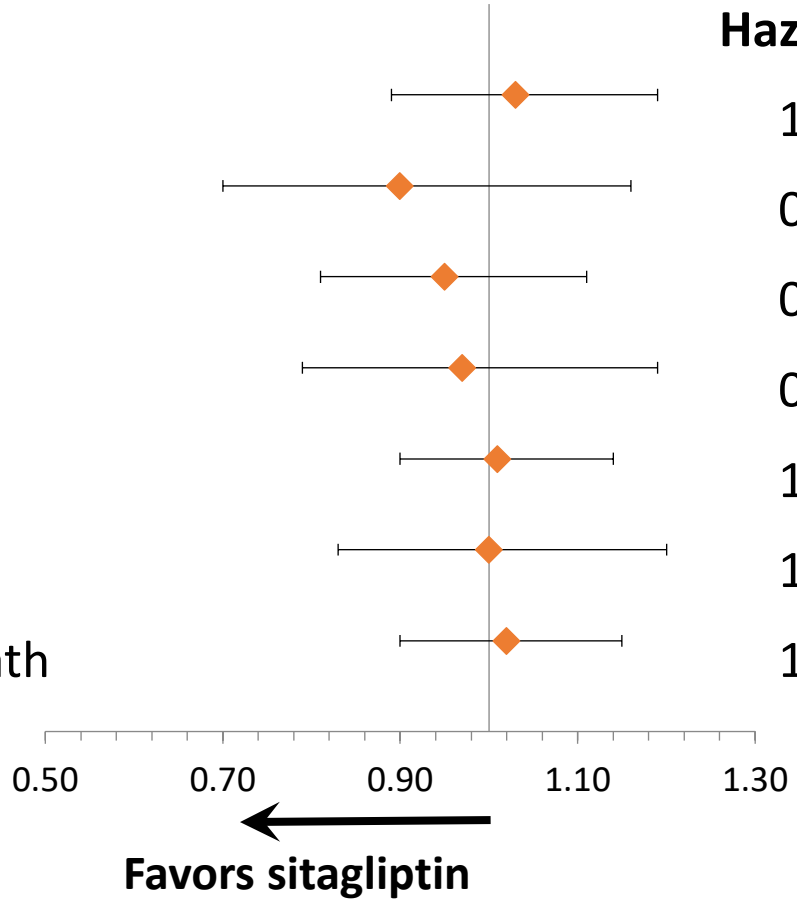
	Hazard ratio (95% CI)	*P* value
Primary composite endpoint	0.98 (0.88-1.09)	<0.001 (NF)
Secondary composite endpoint	0.99 (0.89-1.11)	<0.001 (NF)
Acute pancreatitis	1.80 (0.86-3.76)	0.12
Any cancer (except nonmelanoma skin cancer)	0.93 (0.89-1.44)	0.38
Pancreatic cancer	0.91 (0.37-2.25)	0.85
Severe hypoglycemia	1.13 (0.89-1.44)	0.31



Green 2015

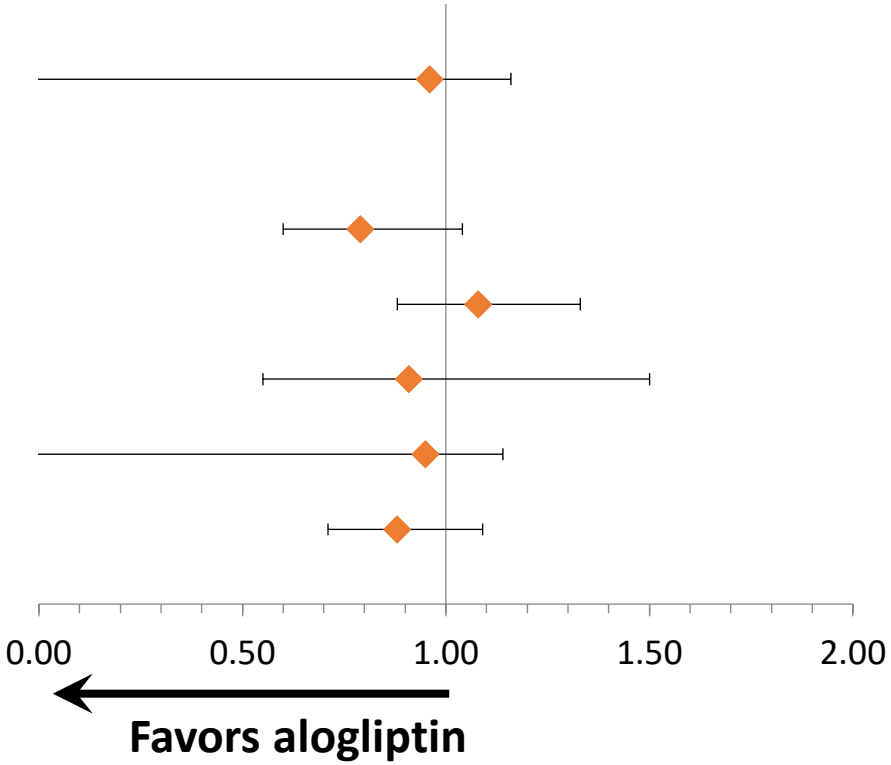
INDIVIDUAL SECONDARY OUTCOMES WITH SITAGLIPTIN

	Hazard ratio (95% CI)	*P* value
CV death	1.03 (0.89-1.19)	0.71
Hospitalization for unstable angina	0.90 (0.70-1.16)	0.42
Fatal or nonfatal MI	0.95 (0.81-1.11)	0.49
Fatal or nonfatal stroke	0.97 (0.79-1.19)	0.76
Death from any cause	1.01 (0.90-1.14)	0.88
Hospitalization for heart failure	1.09 (0.83-1.20)	0.98
Hospitalization for heart failure or CV death	1.02 (0.90-1.15)	0.74



Green 2015

CLINICAL OUTCOMES WITH ALOGLIPTIN



	Hazard ratio (95% CI)	*P* value
Primary composite	0.96 (≤1.16)	0.32
Primary endpoint components		
CV death	0.79 (0.6-1.04)	0.10
Nonfatal MI	1.08 (0.88-1.33)	0.47
Nonfatal stroke	0.91 (0.55-1.50)	0.71
Primary secondary endpoint	0.95 (≤1.14)	0.26
Death from any cause	0.85 (0.66-1.10)	0.21

White 2013

HEART FAILURE AND ALOGLIPTIN

Risk of HHF occurring as the first event in pre-specified exploratory extended MACE endpoint did not differ significantly between groups

	Alogliptin (n = 2701)	Placebo (n = 2679)	HR (95% CI)	p value
Hospitalization for HF	85 (3.1%)	79 (2.9%)	1.07 (0.79–1.46)	0.657

Risk of events assessed as component of post-hoc composite endpoint of CV death and HHF was not significantly different between groups

	Alogliptin (n = 2701)	Placebo (n = 2679)	HR (95% CI)	p value
Hospitalization for HF	106 (3.9%)	89 (3.3%)	1.19 (0.90–1.58)	0.220

Zannad 2015

Heart Failure and Sitagliptin

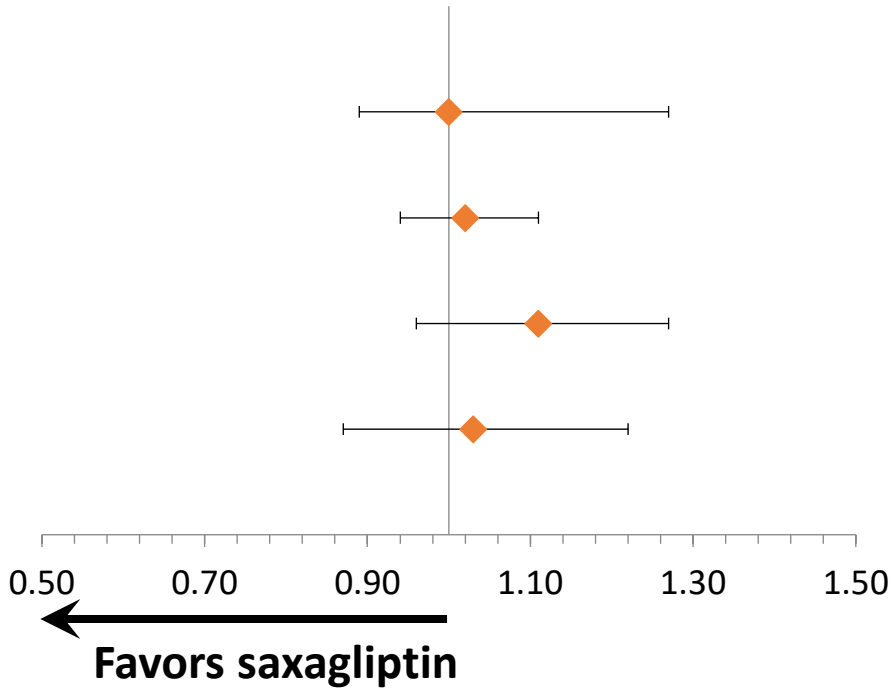
Outcome	Placebo	Sitagliptin	HR (95% CI)
HHF*	228 (3.1%)	228 (3.1%)	1.00 (0.83–1.20) p = 0.98
CV Death + HHF*	525 (7.2%)	538 (7.3%)	1.02 (0.90–1.15) p = 0.74

ITT population. Adjusted for history of heart failure at baseline *Pre-specified analyses

Green 2015

CLINICAL OUTCOMES WITH SAXAGLIPTIN

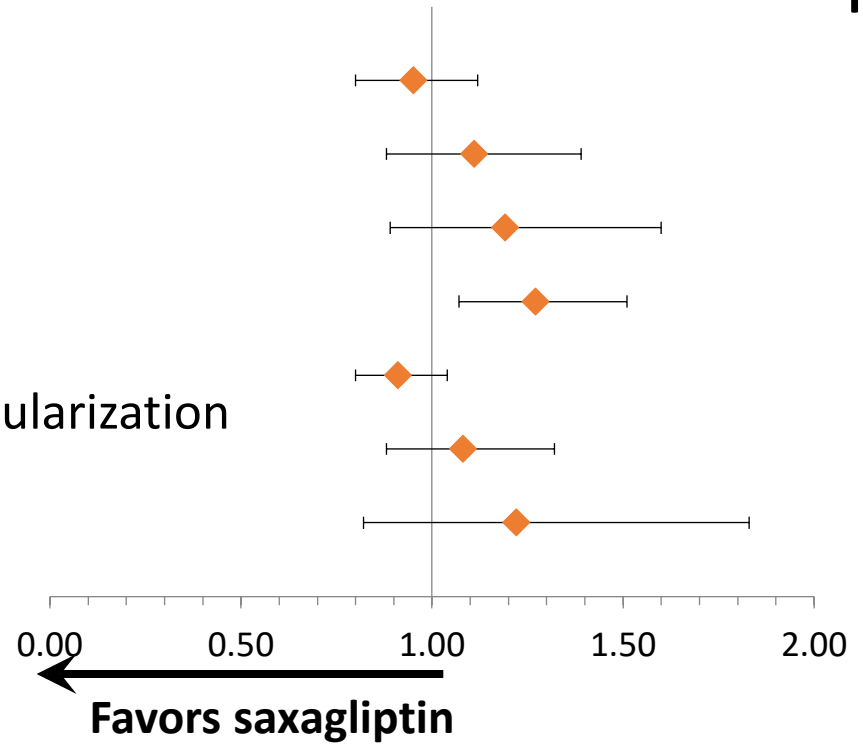
	Hazard ratio (95% CI)	*P* value
Primary composite endpoint*	1.00 (0.89-1.27)	0.99
Secondary composite endpoint†	1.02 (0.94-1.11)	0.66
Death from any cause	1.11 (0.96-1.27)	0.15
CV death	1.03 (0.87-1.22)	0.52



Scirica 2013

INDIVIDUAL SECONDARY OUTCOMES WITH SAXAGLIPTIN

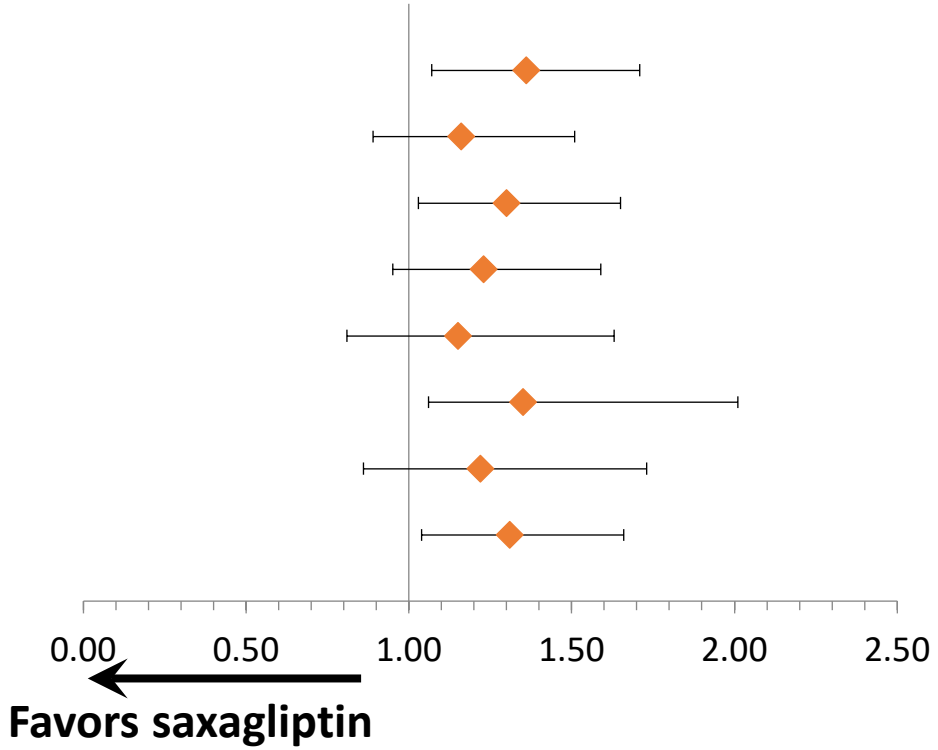
	Hazard ratio (95% CI)	*P* value
Myocardial infarction	0.95 (0.80-1.12)	0.52
Ischemic stroke	1.11 (0.80-1.12)	0.38
Hospitalization for unstable angina	1.19 (0.89-1.60)	0.24
Hospitalization for heart failure	**1.27 (1.07-1.51)**	**0.007**
Hospitalization for coronary revascularization	0.91 (0.80-1.04)	0.18
Renal endpoint*	1.08 (0.88-1.32)	0.46
Hospitalization for hypoglycemia	1.22 (0.82-1.83)	0.33



Scirica 2013

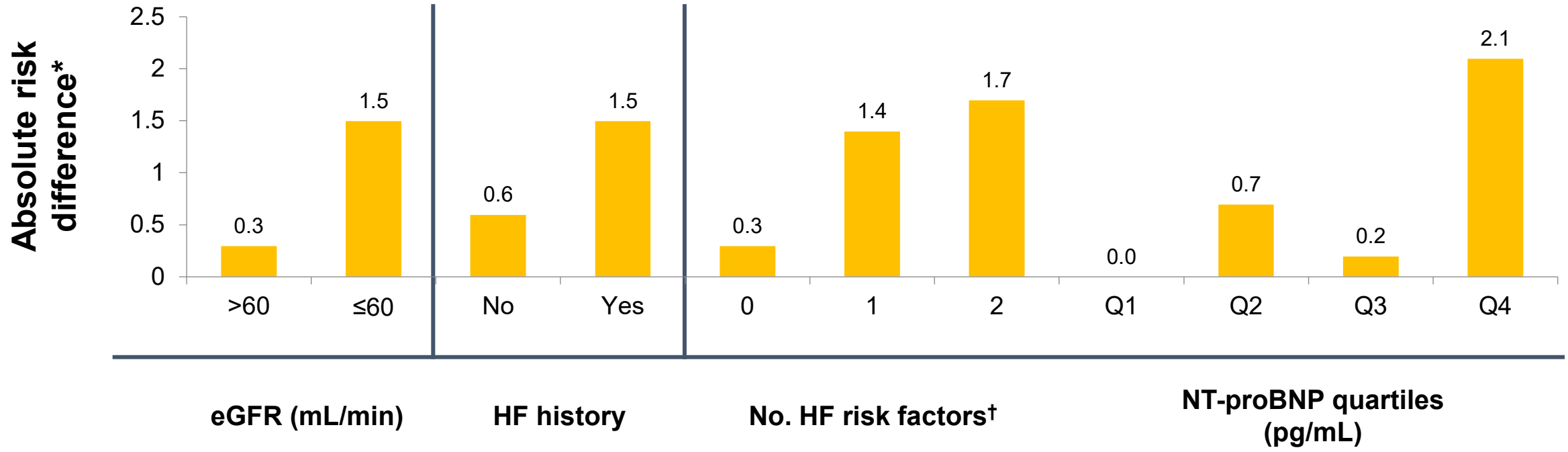
Baseline Characteristics and Risk of HF Hospitalization With Saxagliptin

	Hazard ratio (95% CI)	*P* value
eGFR ≤60 mL/min	**1.36 (1.07-1.71)**	**0.03**
eGFR >60 mL/min	1.16 (0.89-1.51)	0.27
No prior heart failure	**1.30 (1.03-1.65)**	**0.03**
Prior heart failure	1.23 (0.94-1.59)	0.13
No risk factors*	**1.15 (0.81-1.63)**	**0.03**
1 risk factor	**1.35 (1.06-1.72)**	**0.02**
2 risk factors	1.22 (0.86-1.73)	0.27
Q4 NT-proBNP (333-46,627 pg/mL)	**1.31 (1.04-1.66)**	**0.02**



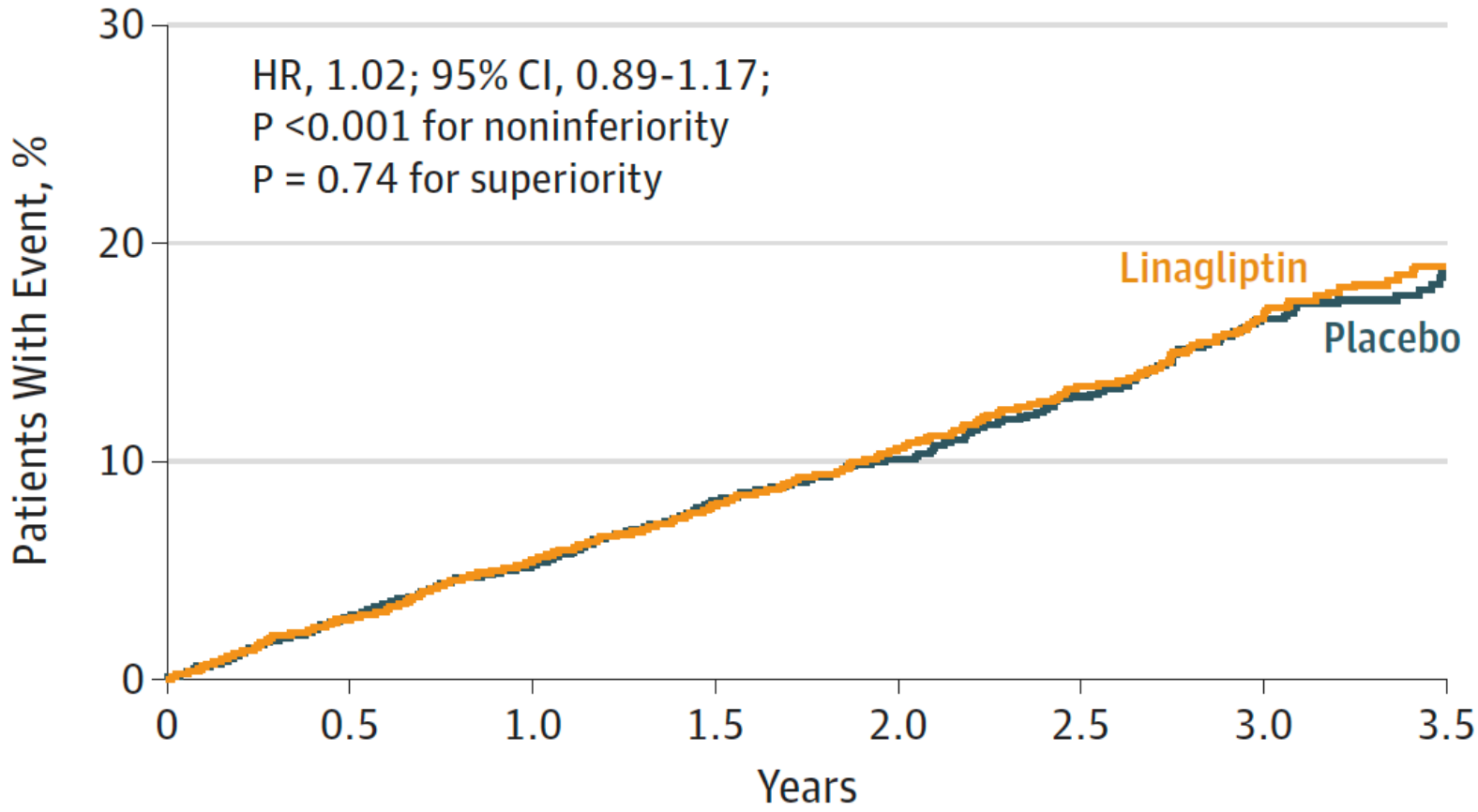
Scirica 2014

Risk of HF Hospitalization with Saxagliptin



Scirica 2014

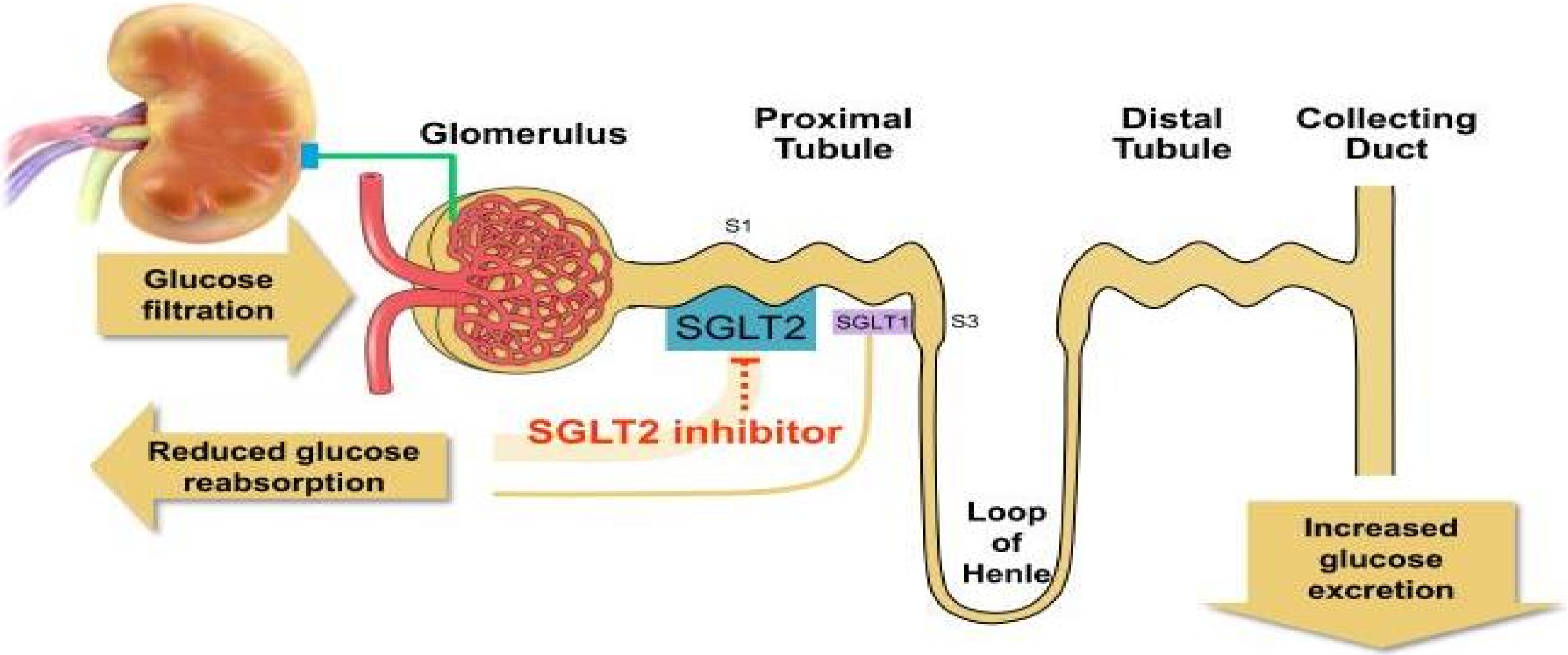
TIME TO PRIMARY 3P-MACE OUTCOME



No. of patients

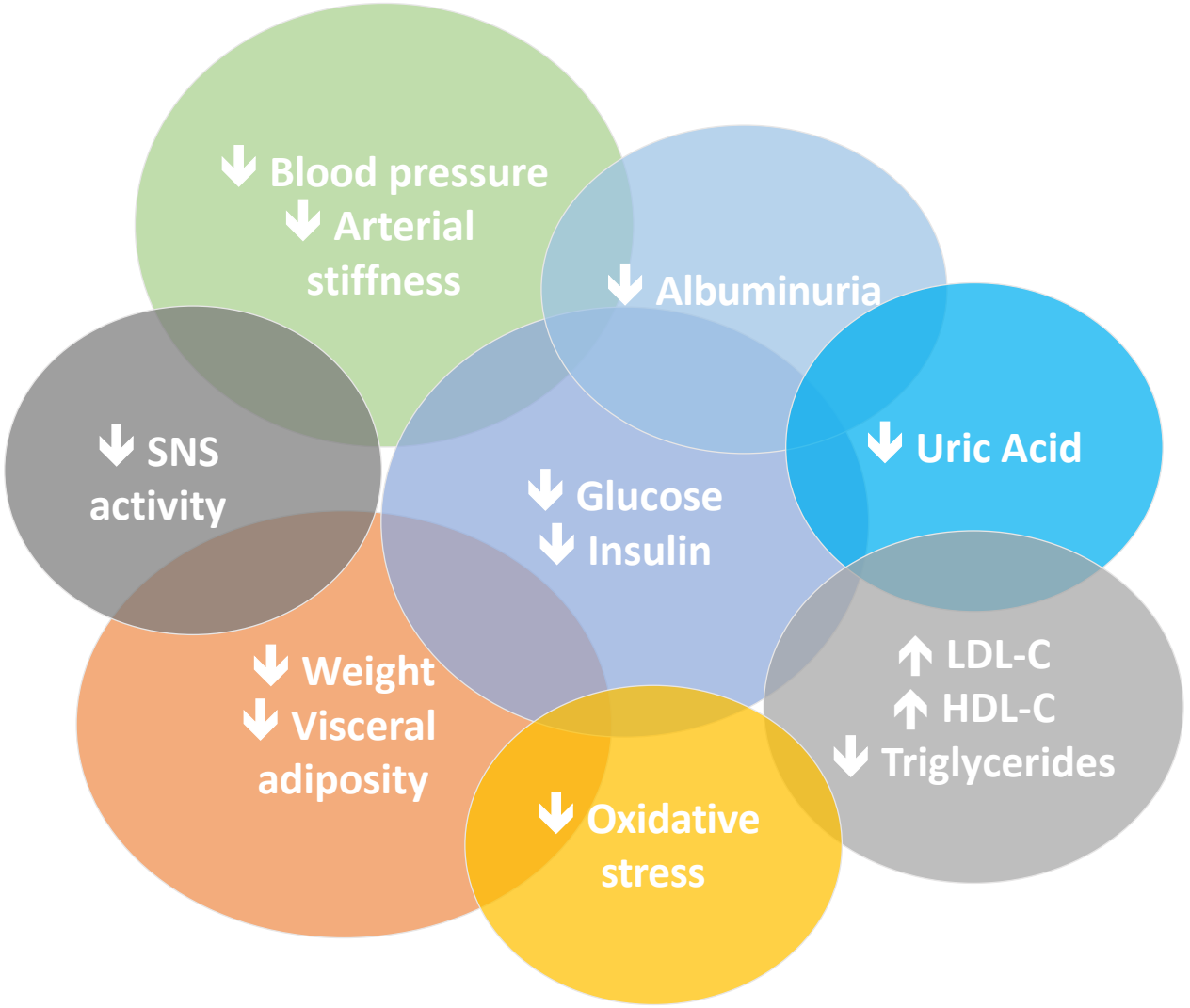
Placebo	3485	3353	3243	2625	1931	1285	758	251
Linagliptin	3494	3373	3254	2634	1972	1306	778	269

SGLT-2 INHIBITORS



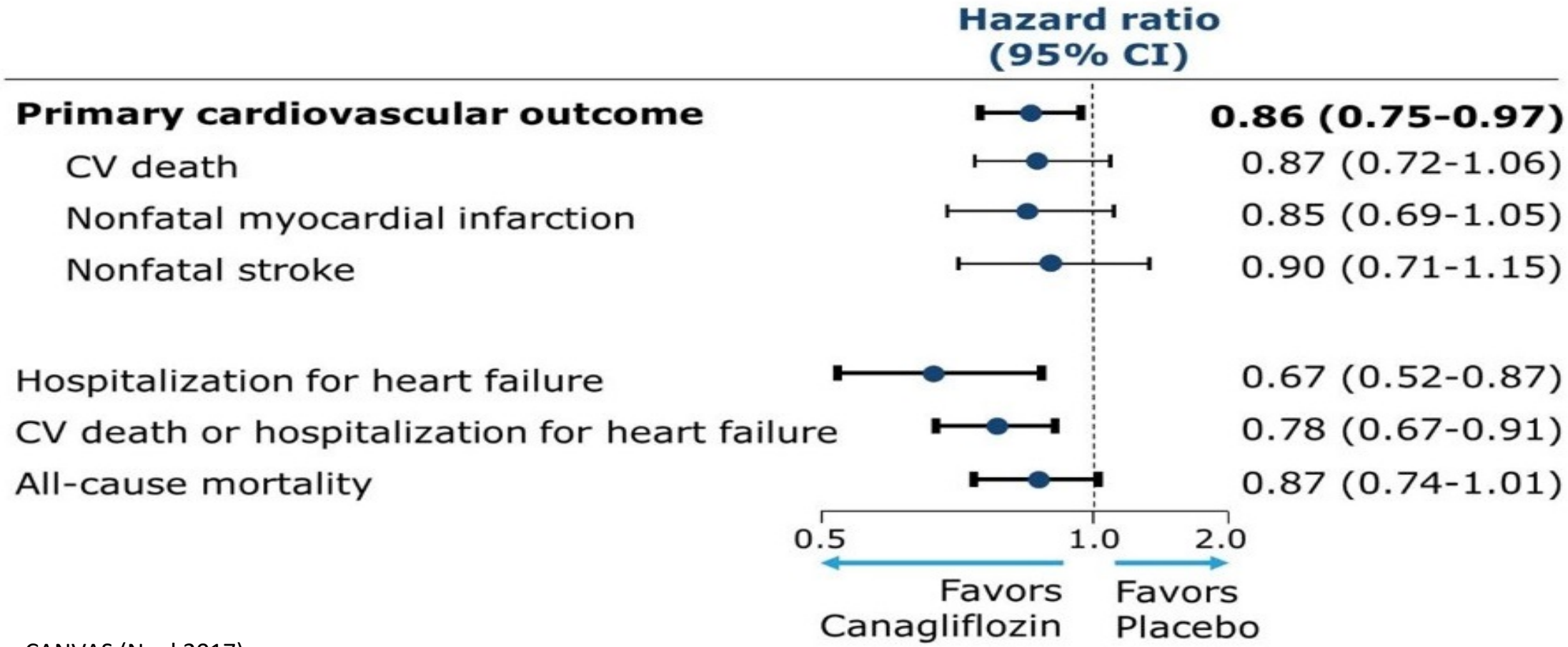
Wright, 2001, Taylor 2013

SGLT-2 Inhibitors Impact on factors related to CV risk



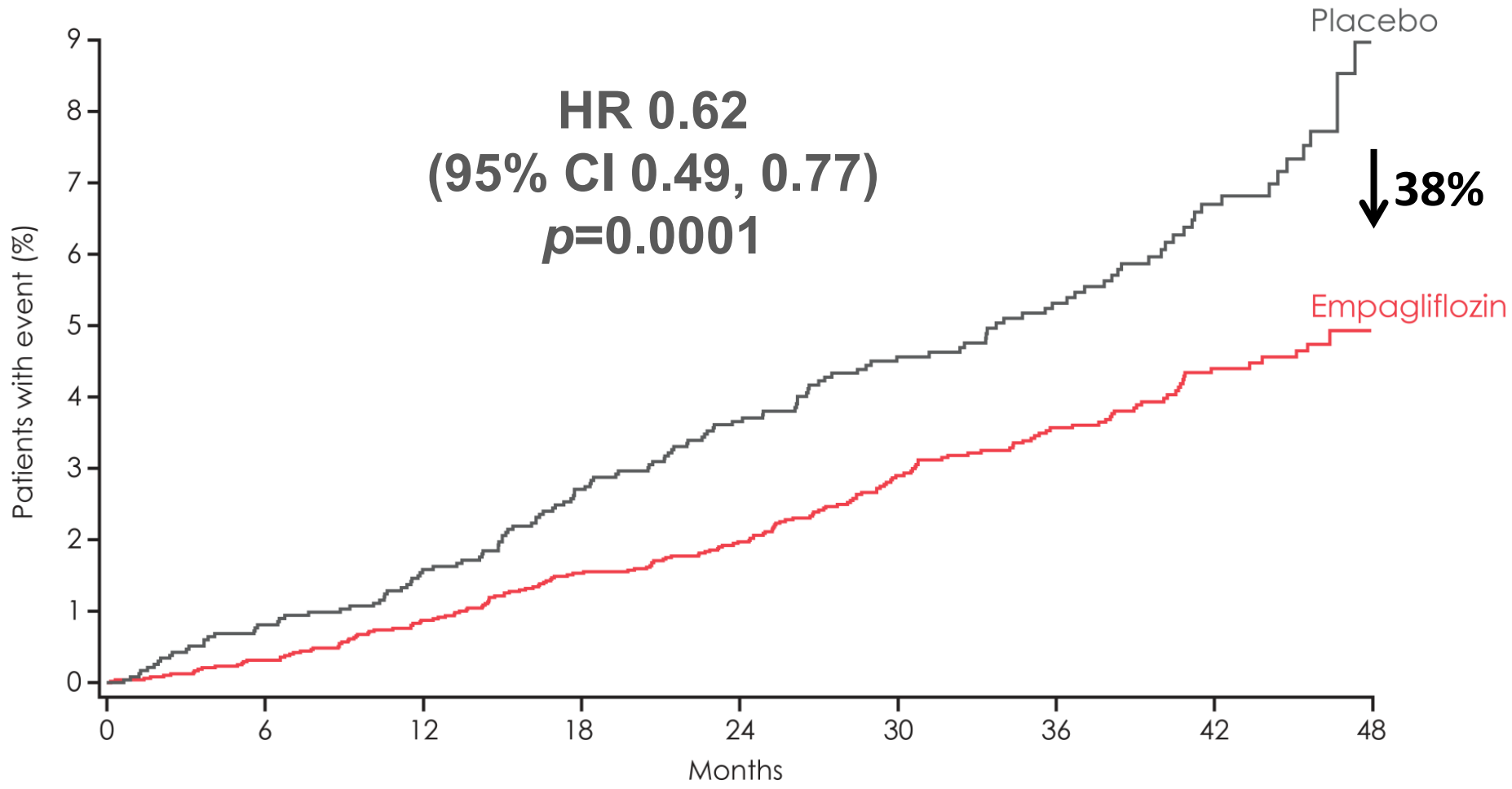
Inzucchi 2015

CV Outcomes with Canagliflozin



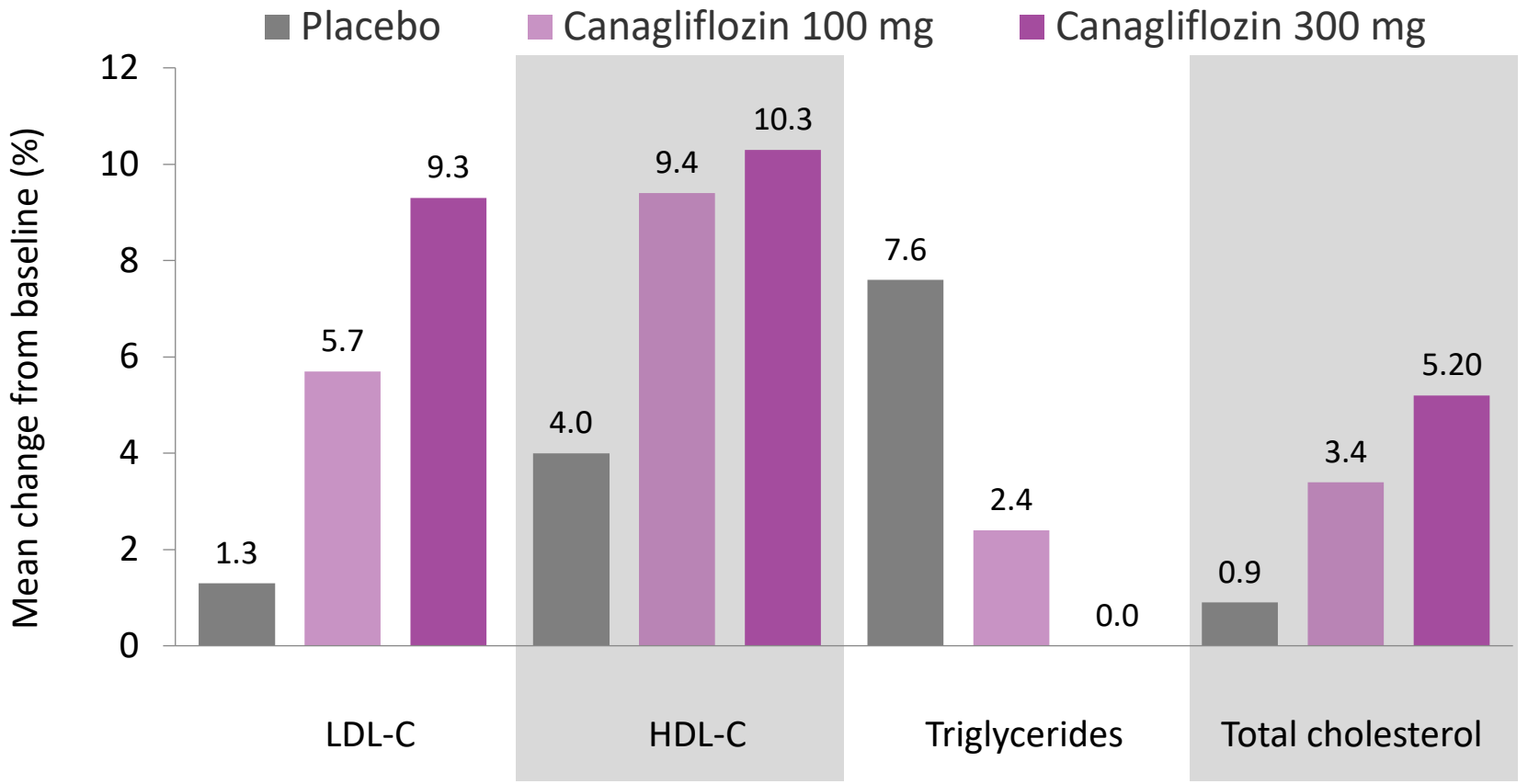
CANVAS (Neal 2017)

EMPA-REG OUTCOME: CV DEATH



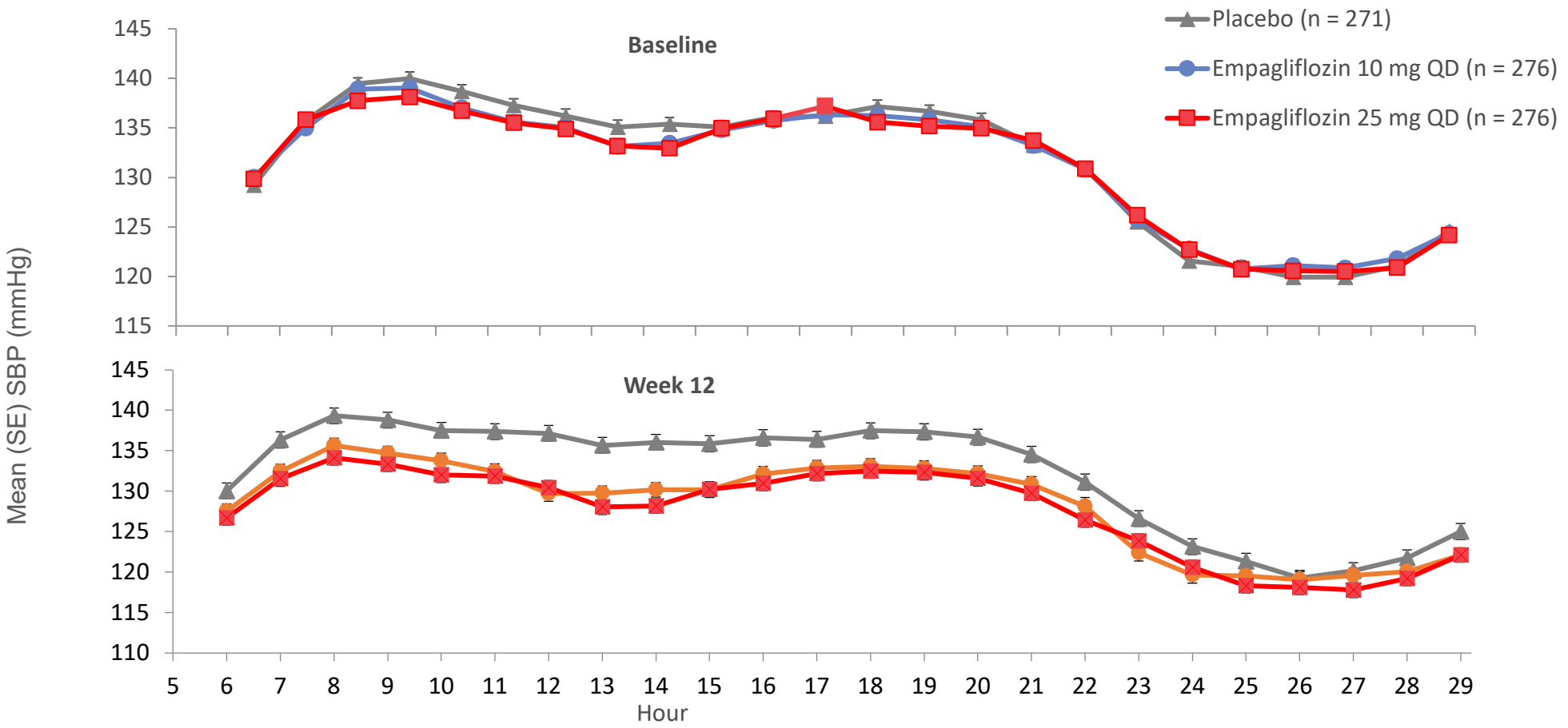
Zinman 2015

CANAGLIFLOZIN LIPID PROFILE



Mahaffey 2018

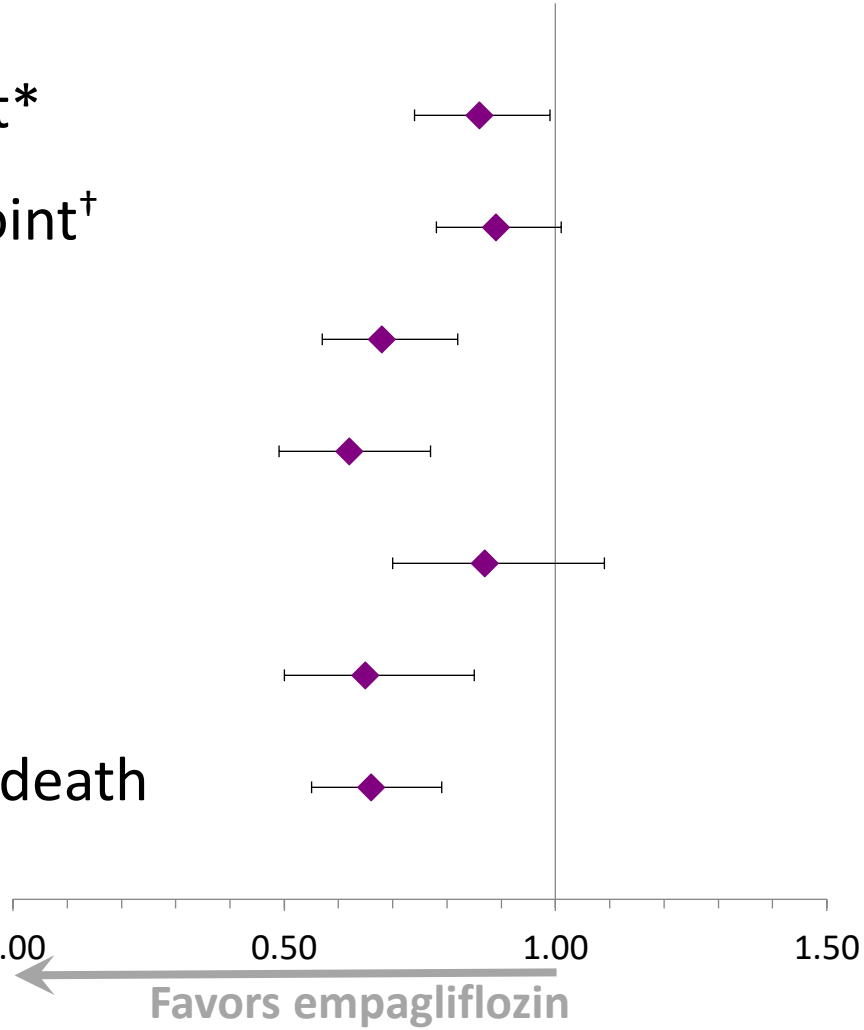
EMPAGLIFLOZIN IN PATIENTS WITH T2D AND HYPERTENSION



Tikkanen 2015

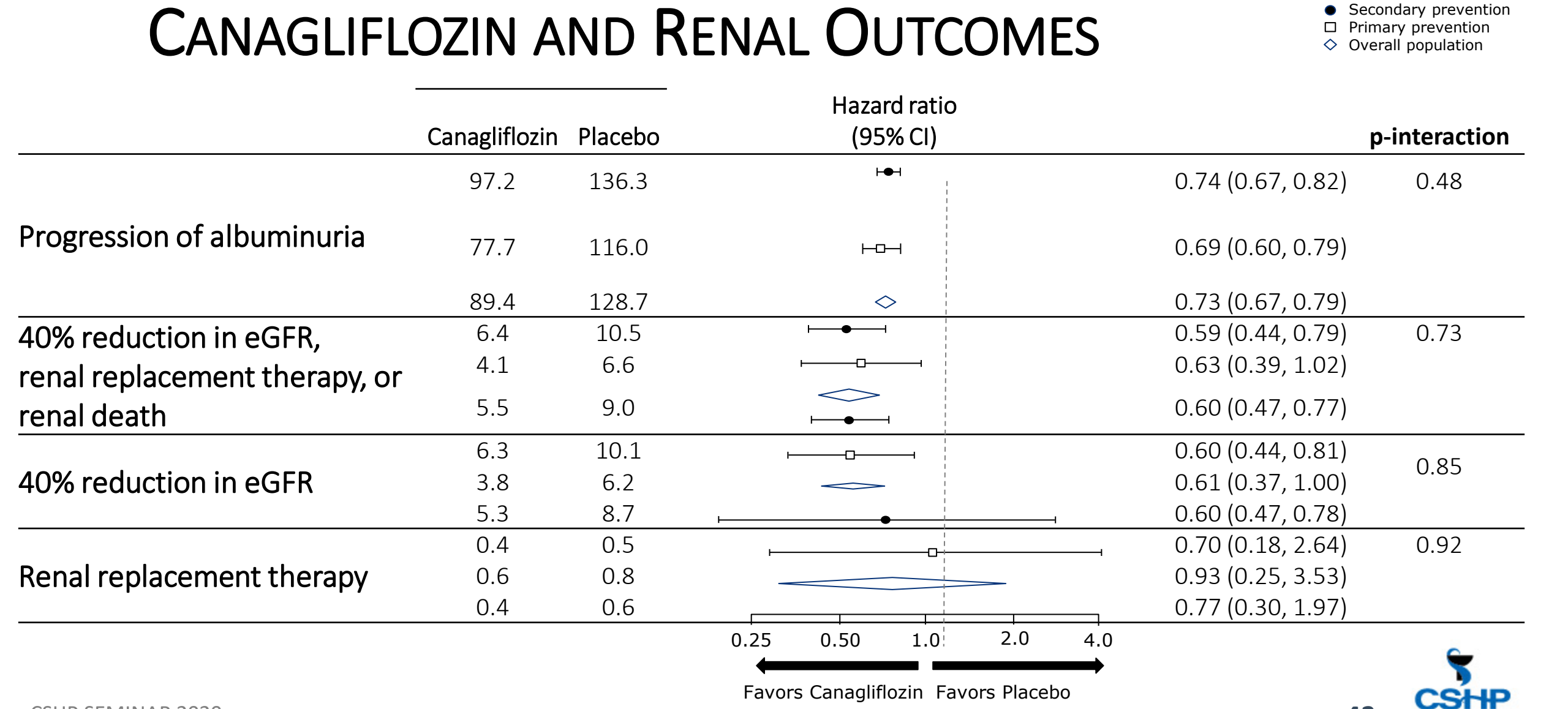
CLINICAL OUTCOMES WITH EMPAGLIFLOZIN

	Hazard ratio (95% CI)	*P* value
Primary composite endpoint*	0.86 (0.74-0.99)	0.04
Secondary composite endpoint†	0.89 (0.78-1.01)	0.08
Death from any cause	0.68 (0.57-0.82)	<0.001
CV death	0.62 (0.49-0.77)	<0.001
Fatal or nonfatal MI	0.87 (0.70-1.09)	0.23
Hospitalization for HF	0.65 (0.50-0.85)	0.002
Hospitalization for HF or CV death	0.66 (0.55-0.79)	<0.001



Zinman 2015

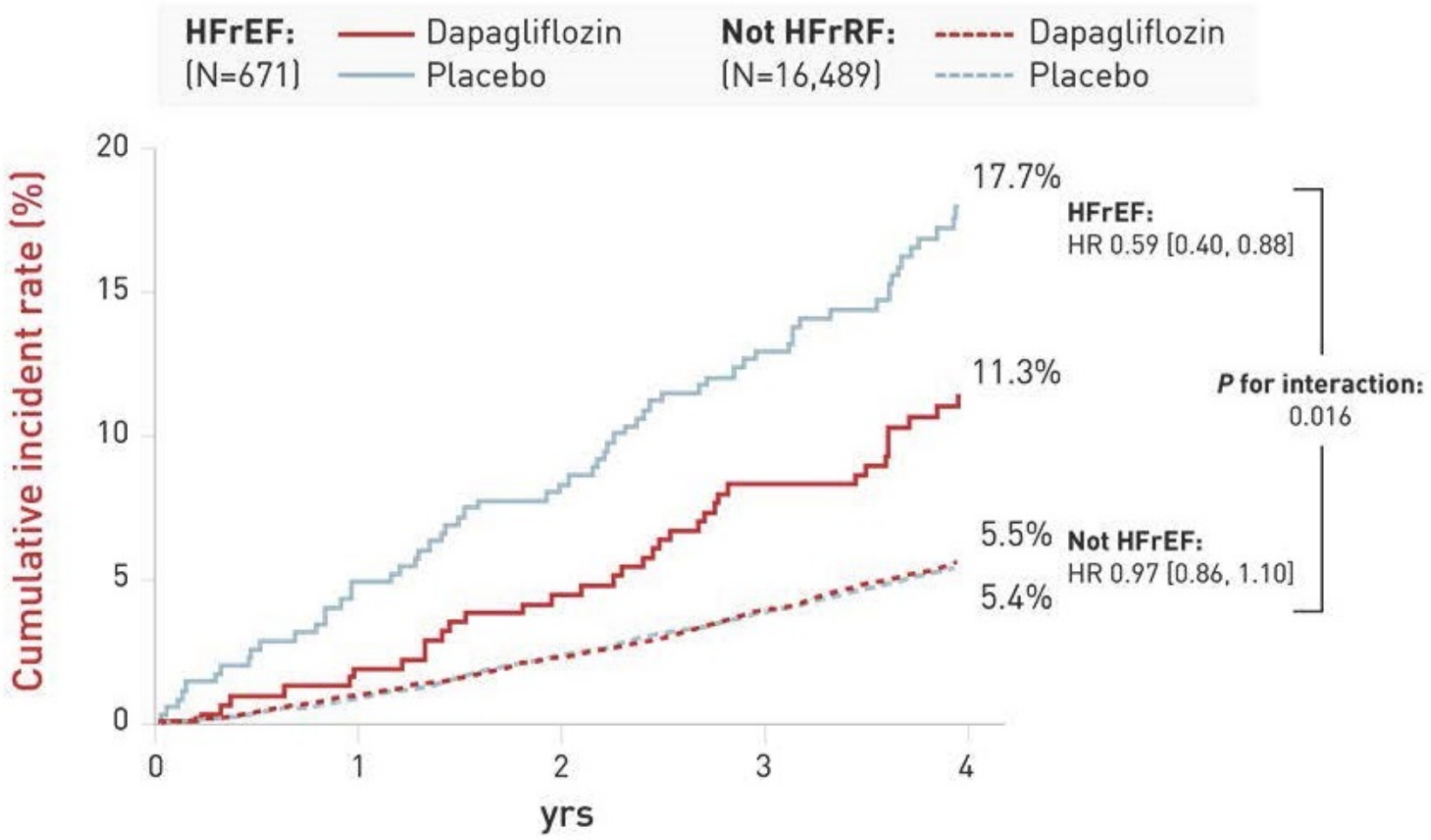
CANAGLIFLOZIN AND RENAL OUTCOMES



	Canagliflozin	Placebo	Hazard ratio (95% CI)	p-interaction
Progression of albuminuria	97.2	136.3	0.74 (0.67, 0.82)	0.48
	77.7	116.0	0.69 (0.60, 0.79)	
	89.4	128.7	0.73 (0.67, 0.79)	
40% reduction in eGFR, renal replacement therapy, or renal death	6.4	10.5	0.59 (0.44, 0.79)	0.73
	4.1	6.6	0.63 (0.39, 1.02)	
	5.5	9.0	0.60 (0.47, 0.77)	
40% reduction in eGFR	6.3	10.1	0.60 (0.44, 0.81)	0.85
	3.8	6.2	0.61 (0.37, 1.00)	
	5.3	8.7	0.60 (0.47, 0.78)	
Renal replacement therapy	0.4	0.5	0.70 (0.18, 2.64)	0.92
	0.6	0.8	0.93 (0.25, 3.53)	
	0.4	0.6	0.77 (0.30, 1.97)	

Mahaffey 2018

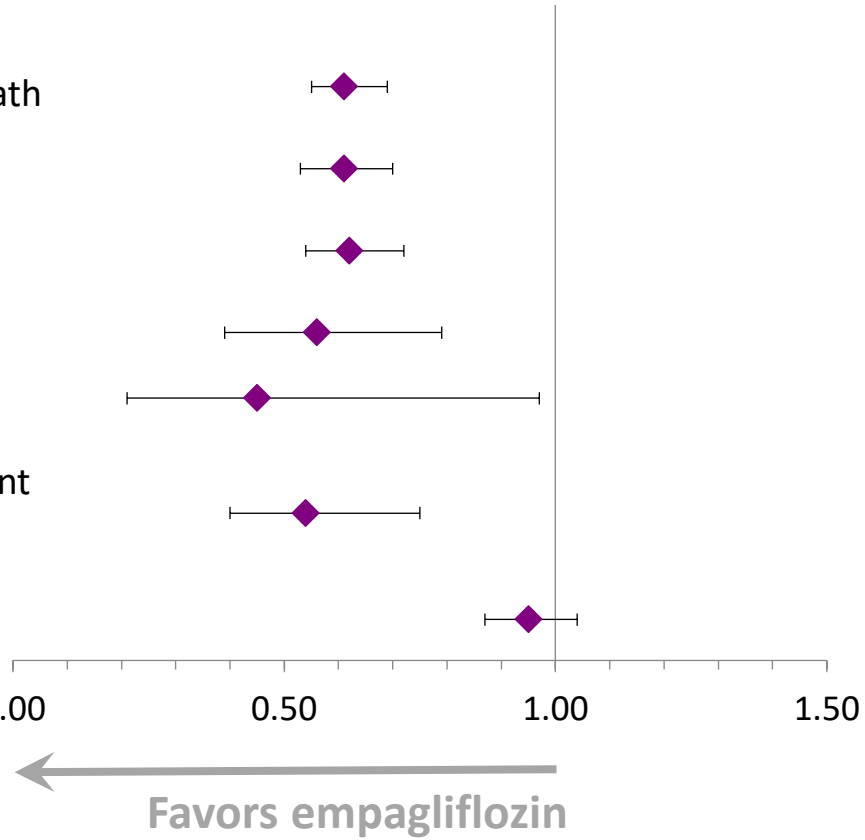
HEART FAILURE AND DAPAGLIFLOZIN



Zelniker 2018

Renal Outcomes with Empagliflozin

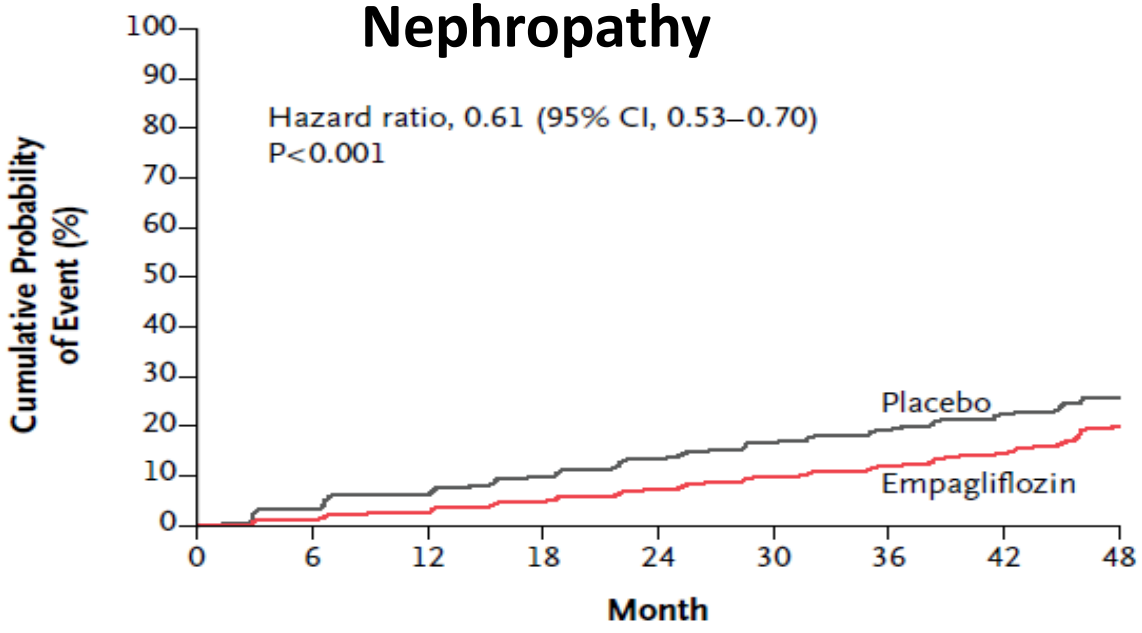
	Hazard ratio (95% CI)	*P* value
Incident or worsening nephropathy or CV death	0.61 (0.55-0.69)	<0.001
Incident or worsening nephropathy	0.61 (0.53-0.70)	<0.001
Progression to macroalbuminuria	0.62 (0.54-0.72)	<0.001
Doubling of SCr + eGFR ≤45	0.56 (0.39-0.79)	<0.001
Initiation of renal replacement therapy	0.45 (0.21-0.97)	0.04
Doubling of SCr + eGFR ≤45, renal replacement therapy, or renal disease death	0.54 (0.40-0.75)	<0.001
Incident albuminuria*	0.95 (0.87-1.04)	0.25



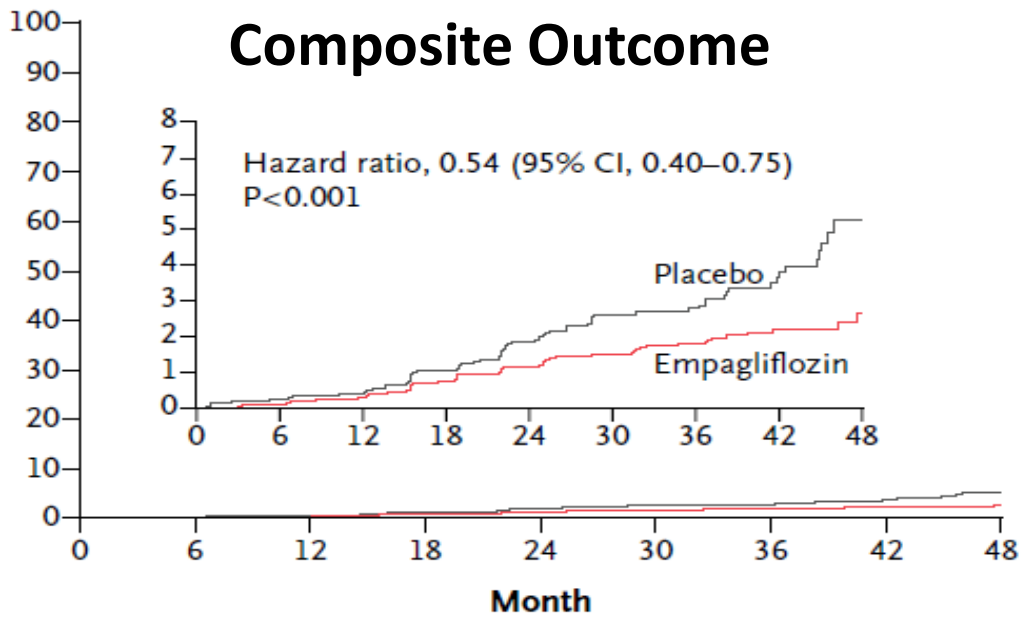
Wanner 2016

RENAL OUTCOMES WITH EMPAGLIFLOZIN

Incident or Worsening Nephropathy



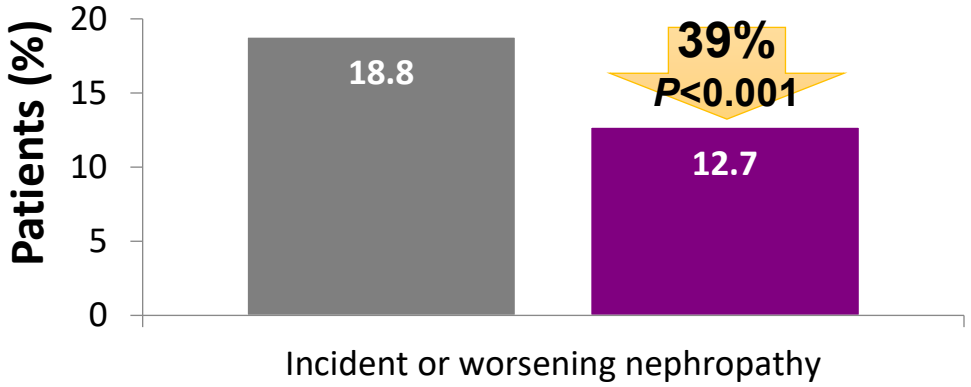
Post-hoc Renal Composite Outcome



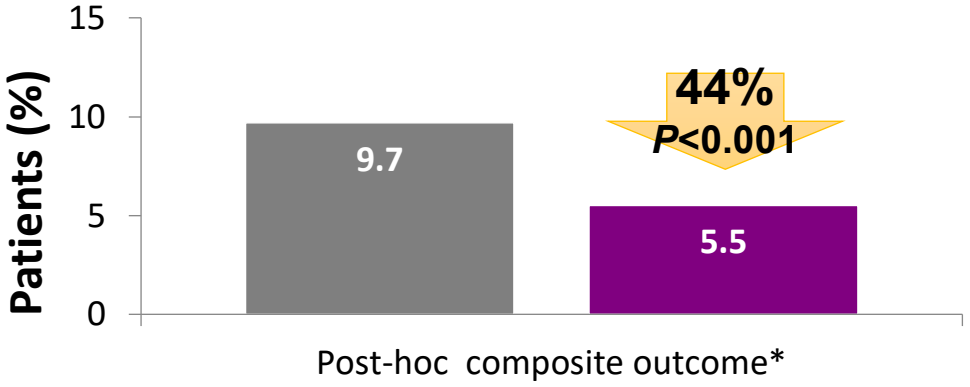
No. at Risk																	
Empagliflozin	4124	3994	3848	3669	3171	2279	1887	1219	290	4645	4500	4377	4241	3729	2715	2280	1496	360
Placebo	2061	1946	1836	1703	1433	1016	833	521	106	2323	2229	2146	2047	1771	1289	1079	680	144

Wanner 2016

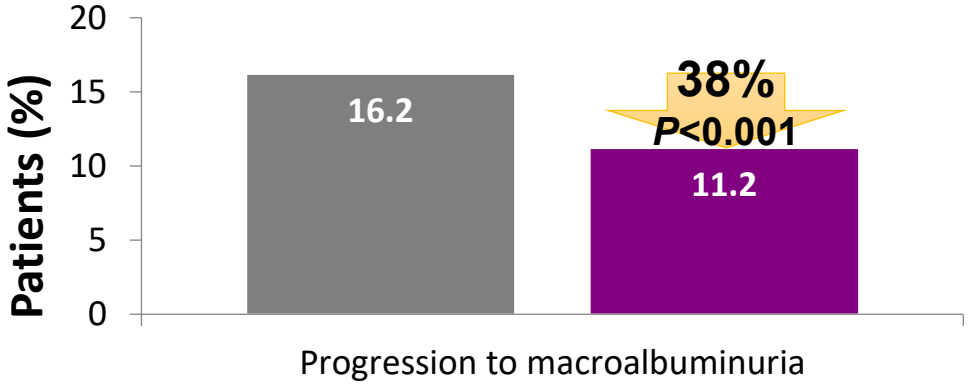
RENAL OUTCOMES WITH EMPAGLIFLOZIN



Incident or worsening nephropathy



Post-hoc composite outcome*

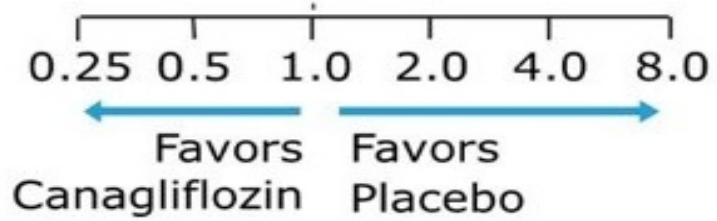


Progression to macroalbuminuria

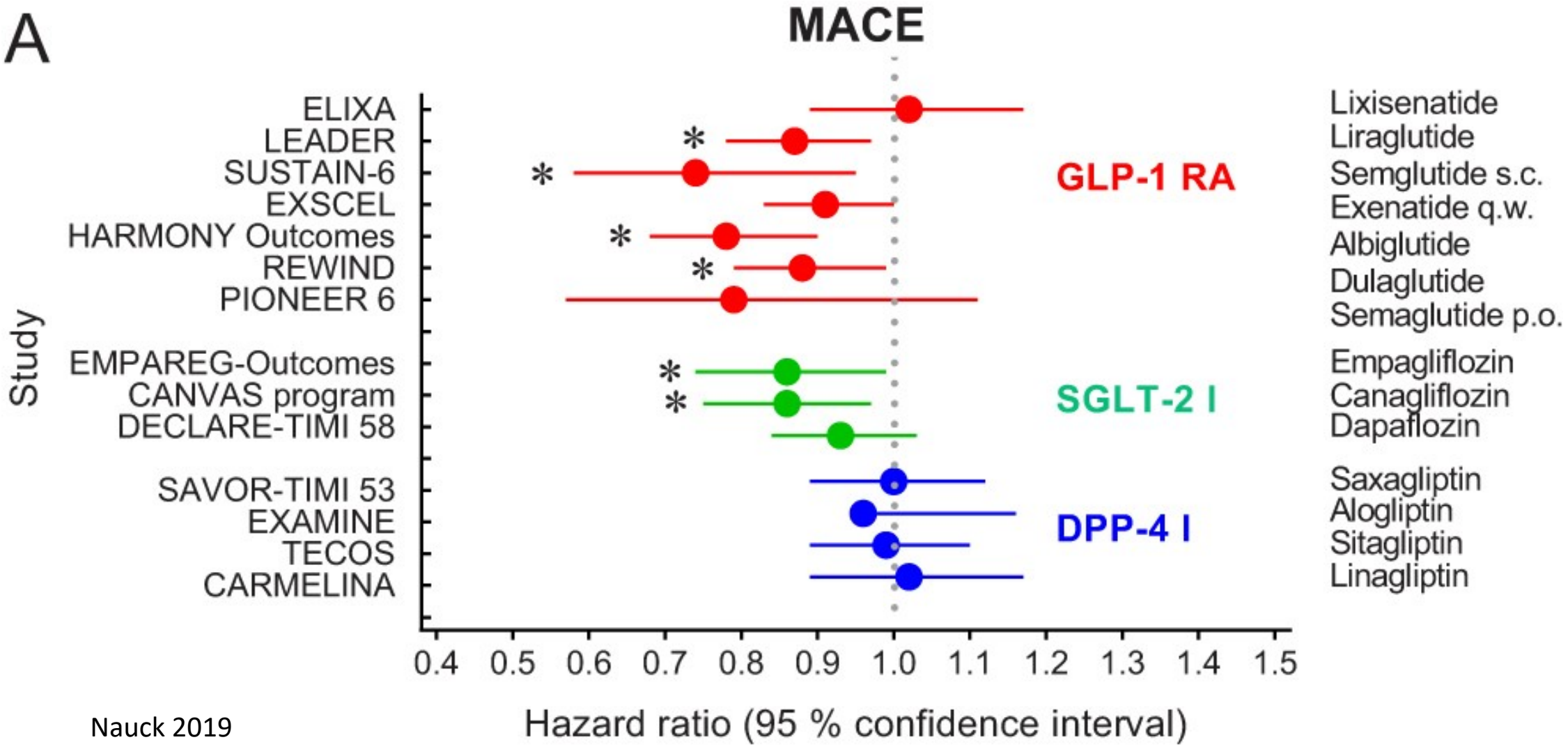
Wanner 2016

CANAGLIFLOZIN ADRS OF

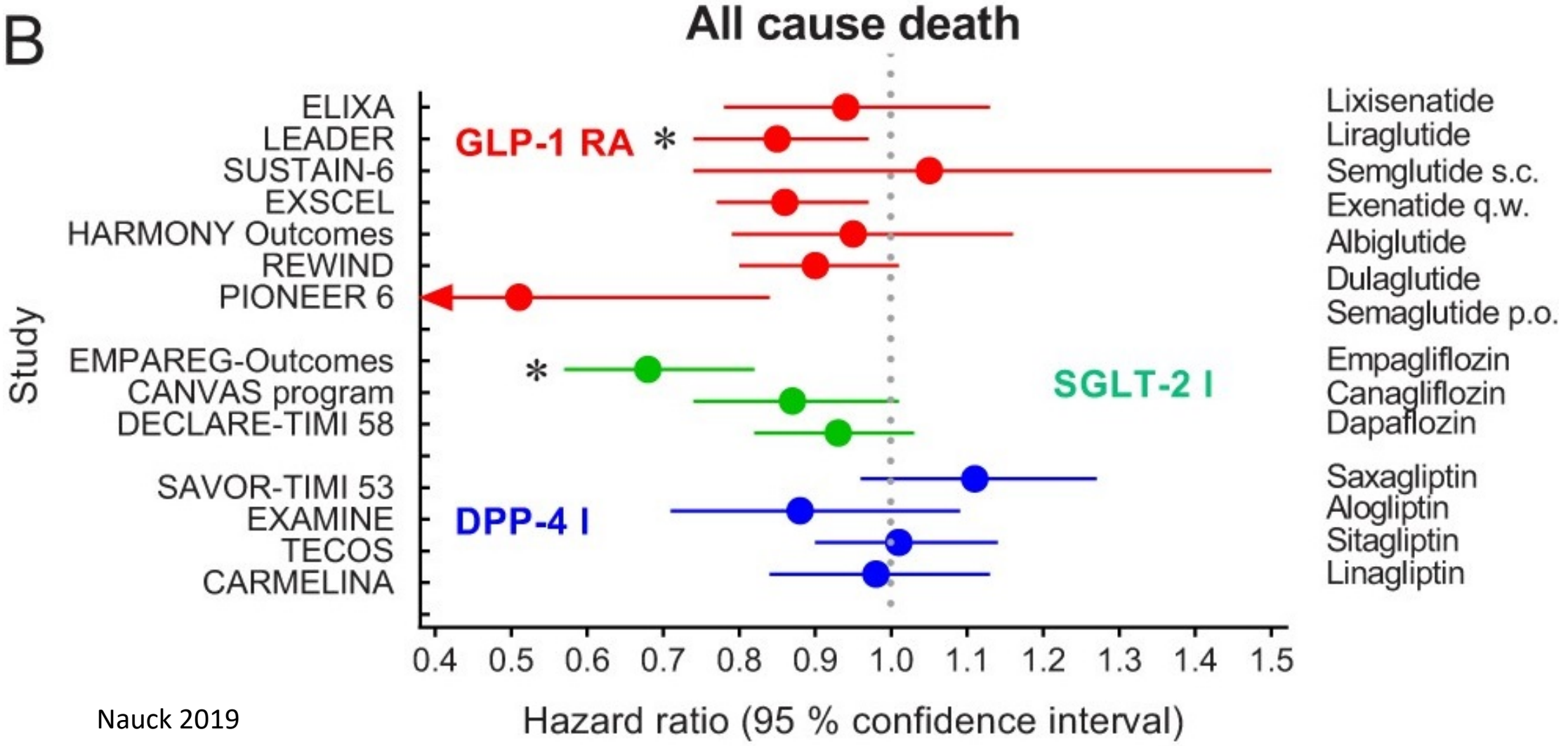
	Event rate per 1000 patient-years		Hazard ratio (95% CI)
	Canagliflozin	Placebo	
Male genital mycotic infection (n = 503)	35	11	3.76 (2.91-4.86)
Venous thromboembolic events (n = 50)	1.7	1.7	0.96 (0.54-1.71)
Photosensitivity (n = 22)	1.0	0.3	2.71 (0.92-8.03)
Adjudicated diabetic ketoacidosis (n = 18)	0.6*	0.3	2.33 (0.76-7.17)
Adjudicated acute pancreatitis (n = 13)	0.5	0.4	1.34 (0.40-4.41)



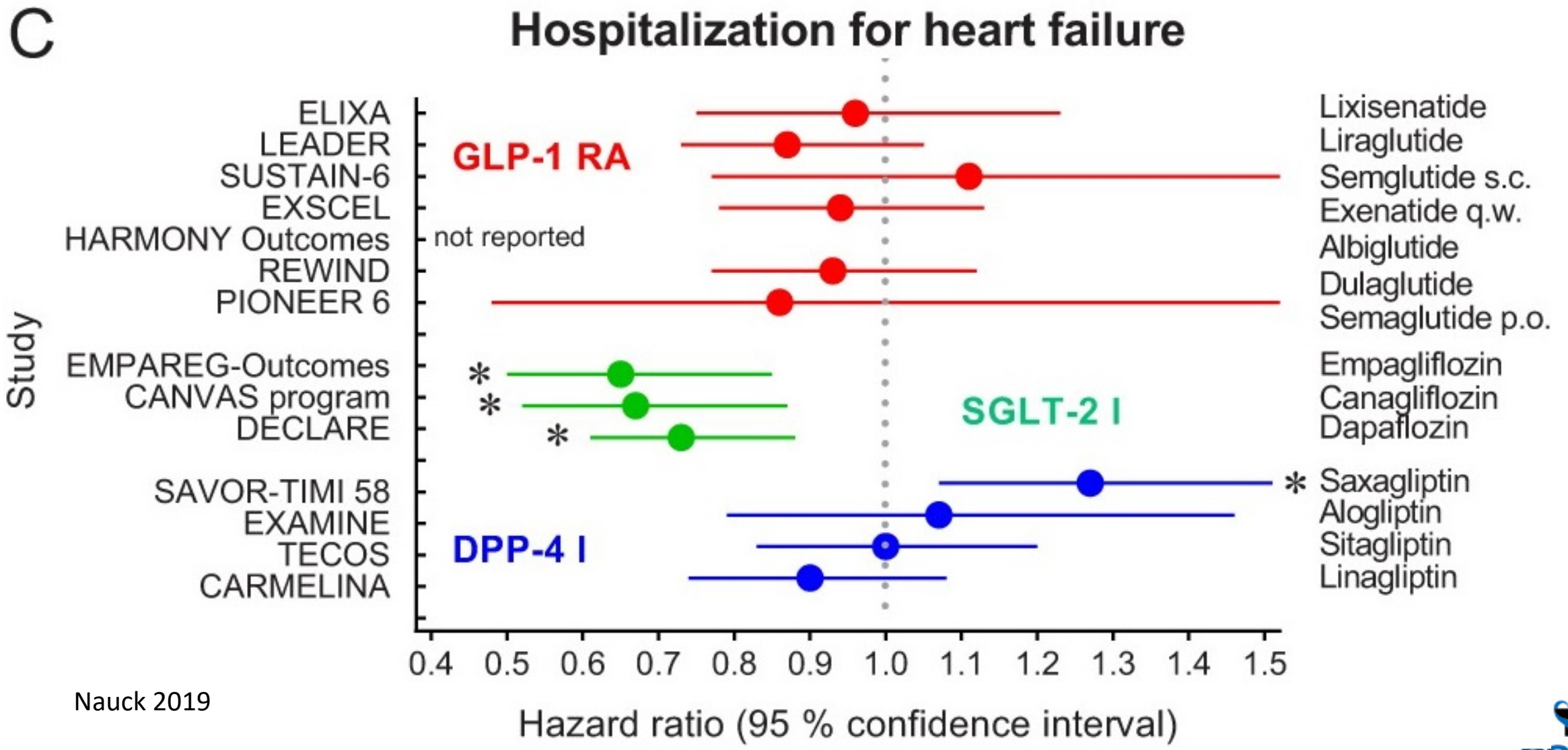
CANVAS (Neal 2017)


A
MACE
ELIXA
LEADER
SUSTAIN-6
EXSCEL
HARMONY Outcomes
REWIND
PIONEER 6
EMPAREG-Outcomes
CANVAS program
DECLARE-TIMI 58
SAVOR-TIMI 53
EXAMINE
TECOS
CARMELINA
Study
GLP-1 RA
SGLT-2 I
DPP-4 I
Lixisenatide
Liraglutide
Semglutide s.c.
Exenatide q.w.
Albiglutide
Dulaglutide
Semaglutide p.o.
Empagliflozin
Canagliflozin
Dapaflozin
Saxagliptin
Alogliptin
Sitagliptin
Linagliptin
0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.1 1.2 1.3 1.4 1.5
Hazard ratio (95 % confidence interval)

Nauck 2019


B
All cause death
ELIXA
LEADER
SUSTAIN-6
EXSCEL
HARMONY Outcomes
REWIND
PIONEER 6
GLP-1 RA
*
Lixisenatide
Liraglutide
Semglutide s.c.
Exenatide q.w.
Albiglutide
Dulaglutide
Semaglutide p.o.
Study
EMPAREG-Outcomes
CANVAS program
DECLARE-TIMI 58
*
SGLT-2 I
Empagliflozin
Canagliflozin
Dapaflozin
SAVOR-TIMI 53
EXAMINE
TECOS
CARMELINA
DPP-4 I
Saxagliptin
Alogliptin
Sitagliptin
Linagliptin
0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.1 1.2 1.3 1.4 1.5
Hazard ratio (95 % confidence interval)

Nauck 2019


C
Hospitalization for heart failure
ELIXA
LEADER
SUSTAIN-6
EXSCEL
HARMONY Outcomes
REWIND
PIONEER 6
GLP-1 RA
not reported
Lixisenatide
Liraglutide
Semglutide s.c.
Exenatide q.w.
Albiglutide
Dulaglutide
Semaglutide p.o.
Study
EMPAREG-Outcomes
CANVAS program
DECLARE
SGLT-2 I
Empagliflozin
Canagliflozin
Dapaflozin
SAVOR-TIMI 58
EXAMINE
TECOS
CARMELINA
DPP-4 I
Saxagliptin
Alogliptin
Sitagliptin
Linagliptin
0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.1 1.2 1.3 1.4 1.5
Hazard ratio (95 % confidence interval)

Nauck 2019

CASE 1

SS is a 56 yo Hispanic female with T2DM & HTN for 2 yrs, h/o stable CHF, PUD, sun sensitivity with sulfonylureas. Does not want injections. Exercising 3 x per week, eating more greens.

DM Med regimen: Metformin 1000 mg BID

A1C= 8.6%, FPG= 1700, Cr= 1.1, others WNL, wt 60 kg, 4’11”

CASE 2

48 year old African American Male

- Office manager
- Married with 2 teenage sons
- PMH: type 2 diabetes for 3 years, HTN for 5 years, dyslipidemia for 5 years, ED, osteoarthritis, obesity.
- Quit smoking 3 years ago when diagnosed with diabetes

Current Medications:

- Metformin 1000 mg BID
- Rosuvastatin 10 mg daily
- Lisinopril/HCTZ 10/25 mg daily
- Acetaminophen 500 mg TID
- Sildenafil 50 mg PRN

CASE 3

54 year old white male

PMH: T2DM, HTN, hyperlipidemia with CAD, morbid obesity, sleep apnea, GERD, microalbuminuria

Meds: metformin 1gm BID, glipizide 10mg BID, lisinopril 20mg QD, atorvastatin 20mg QD, omeprazole 20mg QD

Other: No SMBG, afraid of needles, married, works as an accountant

TEST QUESTION #1

A 65-year old man presents to your clinic for diabetes management. He has hypertension, dyslipidemia, and diabetes. He also currently smokes 1 pack per day (PPD). The patient has previously controlled his diabetes with diet and exercise and metformin but A1C recently increased to 8.5%. He is adamantly against injections. Which one of the following oral agents is best to recommend for this patient's MACE?

A. Semaglutide

B. Sitagliptin

C. Canagliflozin

D. Glipizide

TEST QUESTION #2

A.J., a 48-year-old man, presents to your CV risk reduction clinic. A.J. was diagnosed with diabetes based on an A1C of 9.5% and was started on metformin and alogliptin. Which one of the following best evaluates the cardiovascular safety and efficacy of A.J.'s current therapy?

A. Alogliptin has demonstrated neutral effects on MACE outcomes in patients post-acute coronary syndrome (ACS).

B. Alogliptin has been shown to significantly decrease MACE in patients with established CVD.

C. Other DPP-4 inhibitors have shown superiority with regard to reduction in MACE.

D. Other classes besides DPP-4 inhibitors have shown significant reductions in MACE in patients immediately post-ACS.

TEST QUESTION #3

A 56-year-old woman has a medical history of diabetes, HTN, stroke, and dyslipidemia. Her home drugs include metformin 1000 mg BID. Her HTN and dyslipidemia are well-controlled. Her most recent A1C is 7.6%. Which one of the following is the best adjunctive therapy to recommend for this patient?

A. Dapagliflozin

B. Glipizide

C. Sitagliptin

D. Dulaglutide

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