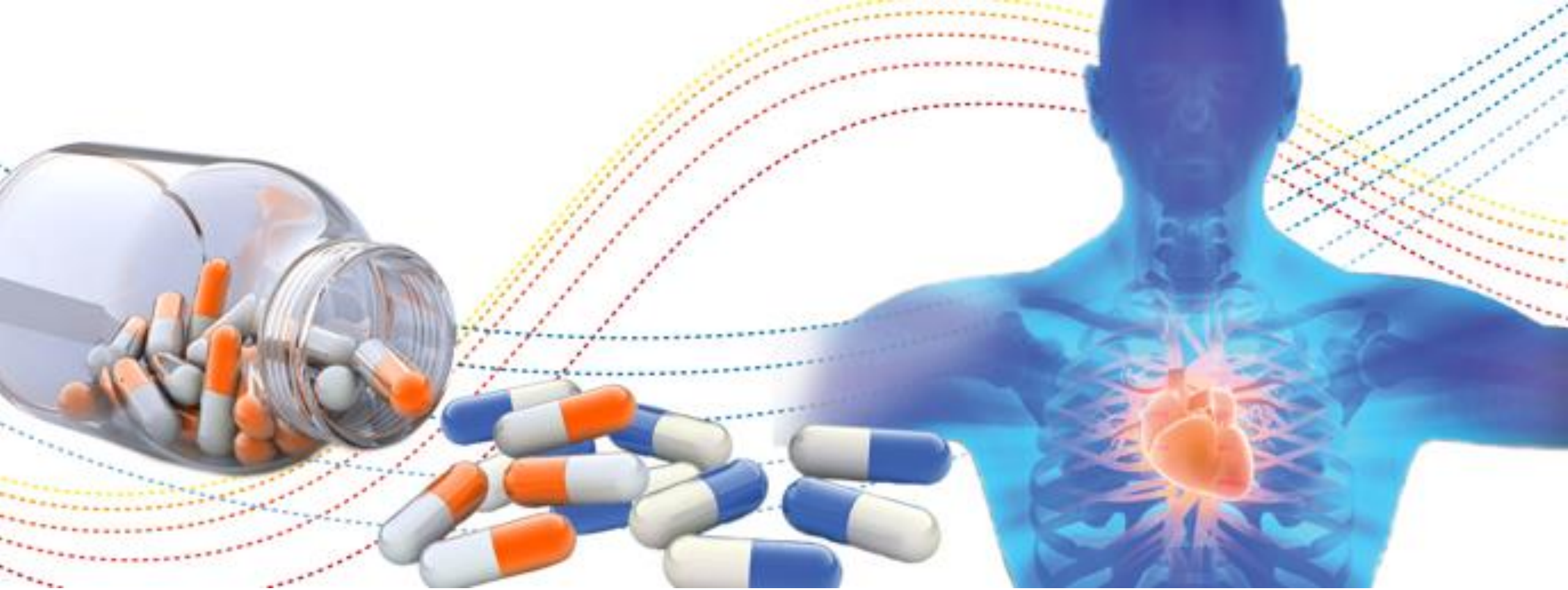


Cardiovascular Outcome Trials

YANERY'S AGOSTO VARGAS, MD

ENDOCRINOLOGY FELLOW

SAN JUAN CITY HOSPITAL

LEARNING OBJECTIVES

- Review the evidence on trials of cardiovascular outcomes with antihyperglycemic agents.
- Discuss the FDA requirements to conduct a cardiovascular safety trial in all antihyperglycemic medications.
- Discuss the impact of intensive glucose lowering on cardiovascular outcomes.
- Review the cardiovascular safety with glucose lowering agents.
- Analyze positive CV outcomes found in trials designed to prove safety and validity of positive effects.
- Discuss other study endpoints that could have an impact on CV outcomes beyond glucose lowering.
- Discuss the impact of these evidence on clinical practice guidelines.

The NE AND
JOUR L of ME CINE

ESTABLISHED IN 1812 14, 2007 VOL. 356 NO. 24

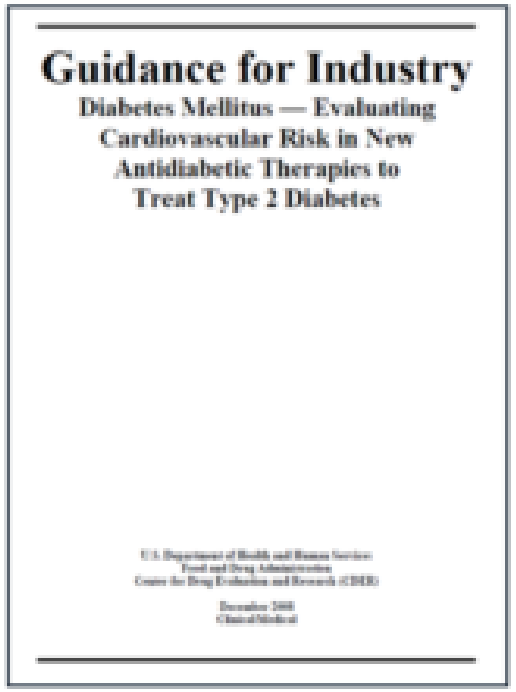
Effect of Rosig one on th of My dial Infarction And h from Car cul uses

S issen, M.D., and Kat .

CONCLUSIONS

Rosiglitazone was associated with a sig se in the risk of myocardial infarction and with an increase in the risk of death…that had borderline significance.

FDA requirements for CV outcome studies for new anti-diabetic agents


Guidance for Industry

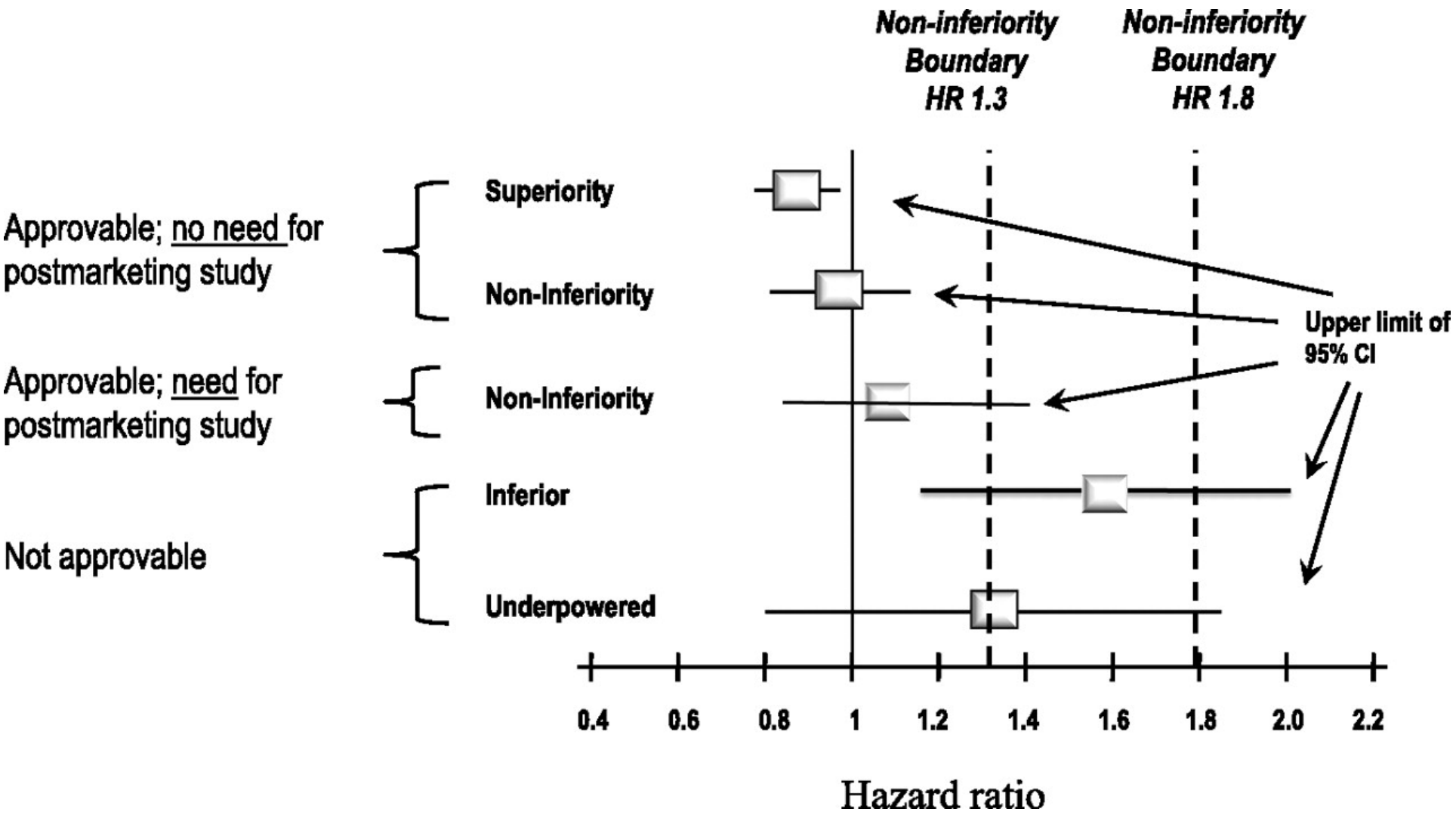
Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

2008 FDA guidelines substantially raised the threshold for approval of antidiabetes drugs from proof of glucose lowering to robust assessment of cardiovascular safety

CV risk assessment on phase 2/3 data for all marketed and pipeline antidiabetes treatments: requisite upper bound of two-sided 95% CI for estimated risk ratio

>1.8:	the data are inadequate to support approval; a large safety trial should be conducted
1.3–1.8:	potential for CV harm might still exist; an adequately powered and designed post-marketing trial is necessary to show an upper bound <1.3
<1.3:	overall risk-benefit analysis supports approval; a post-marketing trial is generally not necessary

FDA Guidance for Industry. Diabetes mellitus – evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. Available from: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf [Accessed July 2014]


Non-inferiority Boundary HR 1.3
Non-inferiority Boundary HR 1.8
Approvable; no need for postmarketing study
Approvable; need for postmarketing study
Not approvable
Superiority
Non-Inferiority
Non-Inferiority
Inferior
Underpowered
Upper limit of 95% CI
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2.0
2.2
Hazard ratio

FDA REQUIEREMENT

Patient selection

- Focus on high-risk populations including those with advanced disease, elderly and those with renal impairment

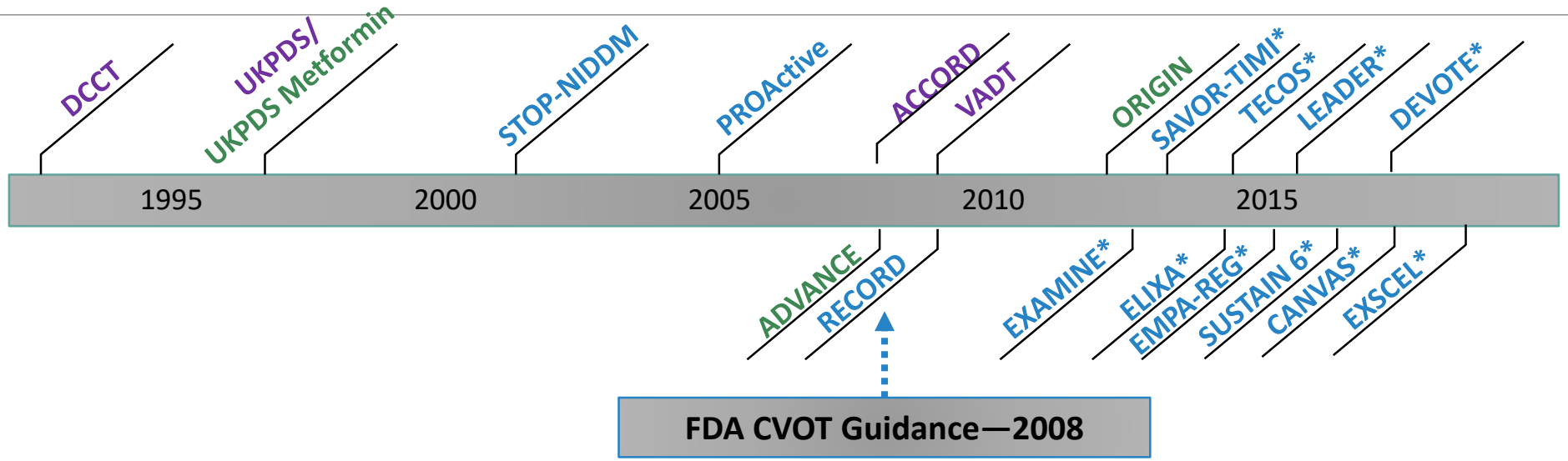
• Duration

- At least 2 years of CV safety data

• Endpoints

- A prospective independent adjudication of CV events in phase 2 and 3 studies must also be performed including most important cardiovascular events

Timeline of Major Diabetes Outcomes Trials



Purple = Intensive vs standard control using same set of glucose-lowering agent(s)
Green = Intensive control with a specific agent vs standard care
Blue = Placebo- or active-controlled study
* = FDA-mandated cardiovascular safety trial

ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; CANVAS, Canagliflozin Cardiovascular Assessment Study; DCCT, Diabetes Control and Complications Trial; DEVOTE, Trial Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events; EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; EMPA-REG, EMPA-REG OUTCOME trial; Exenatide Study of Cardiovascular Event Lowering; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; ORIGIN, Outcome Reduction with an Initial Glargine Intervention; PROActive, Prospective Pioglitazone Clinical Trial in Macrovascular Events; RECORD, Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes; SAVOR-TIMI, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction; STOP-NIDDM, Study to Prevent Non-Insulin-Dependent Diabetes Mellitus; SUSTAIN, Trial to Evaluate Cardiovascular and Other Long-Term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

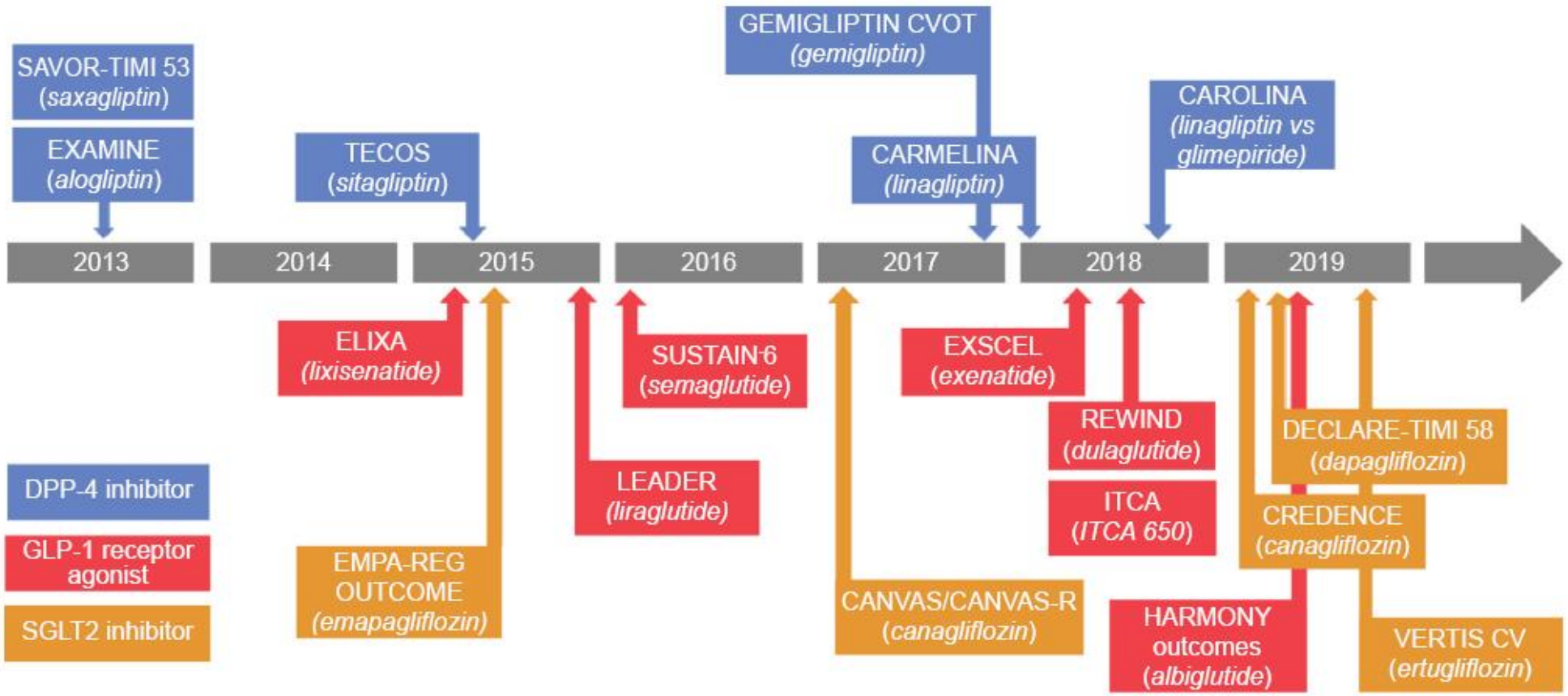


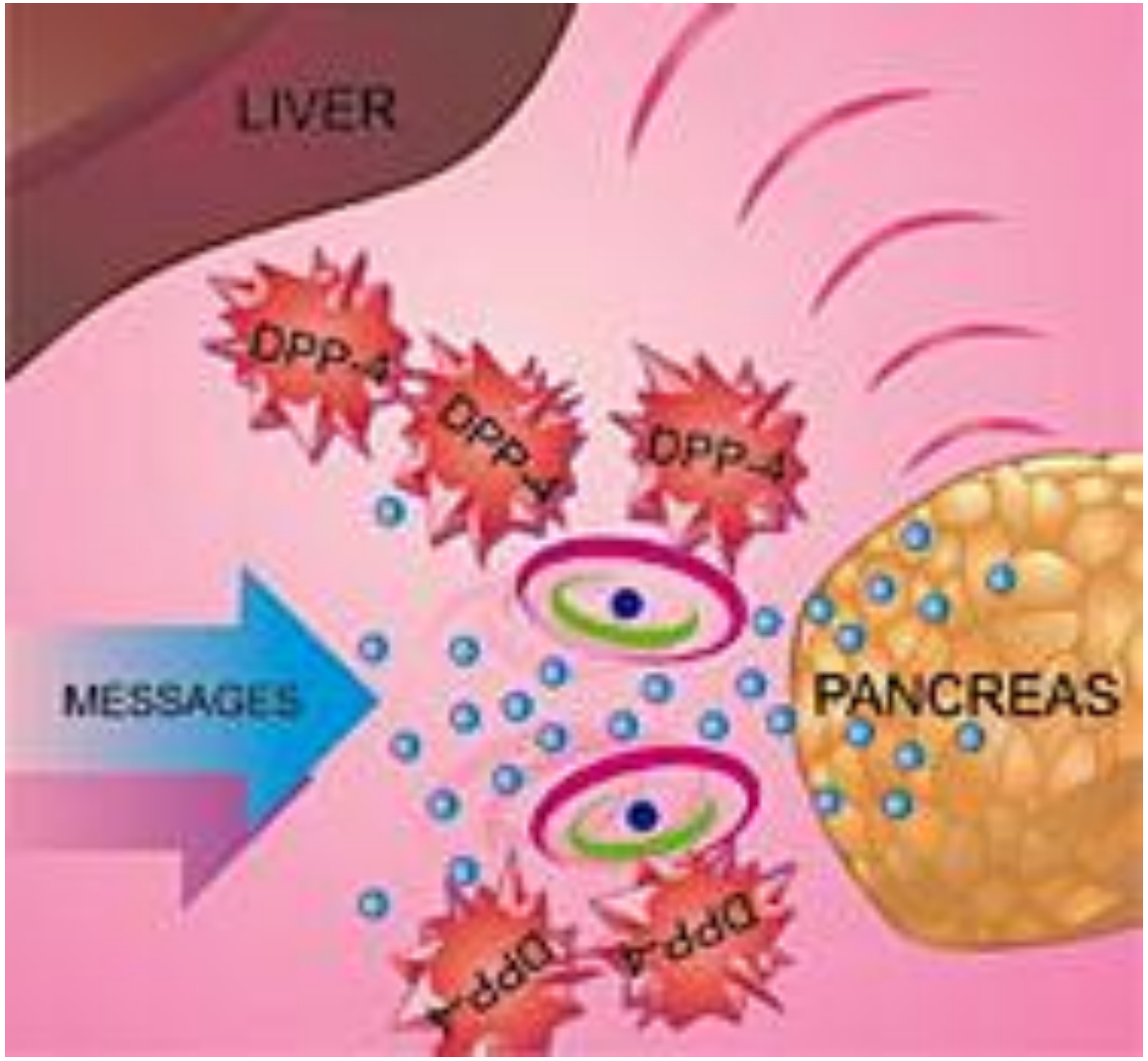
Figure 1 Completed and ongoing cardiovascular outcome trials in type 2 diabetes.
Note: This figure was produced based on trials referenced at clinicaltrials.gov.[62]
Abbreviations: CVOT, cardiovascular outcome trial; SGLT2, sodium/glucose cotransporter 2.

Schernthaner G, Jarvis S, Lotan C, Prazny M, Wanner C, Wascher TC. Advances in the management of cardiovascular risk for patients with type 2 diabetes: perspectives from the Academy for Cardiovascular Risk, Outcomes and Safety Studies in Type 2 Diabetes. Ther Clin Risk Manag. 2017;13:69–79

Drug Class	Trial	Drug	Primary Endpoint	N
DPP-4 inhibitors	TECOS	Sitagliptin	MACE + UA	14,671
	SAVOR-TIMI 53	Saxagliptin	MACE	16,492
	EXAMINE	Alogliptin	MACE	5,380
	CAROLINA	Linagliptin	MACE + UA	6,000
	CARMELINA	Linagliptin	CV risk	8,300
GLP-1 RA	LEADER	Liraglutide	MACE	9,340
	SUSTAIN-6	Semaglutide	MACE	3,297
	ELIXA	Lixisenatide	MACE	6,068
	EXSCEL	Exenatide	MACE	14,000
	ITCA 650	Exenatide	MACE	4,000
	REWIND	Dulaglutide	MACE	9,622
	HARMONY	Albiglutide	MACE	9,400
SGLT2 inhibitors	EMPA-REG	Empagliflozin	MACE	7,020
	CANVAS	Canagliflozin	MACE	4,407
	DECLARE-TIMI 58	Dapagliflozin	MACE	17,150
	VERTIS CV	Ertugliflozin	MACE	8,000
Insulin	DEVOTE	Degludec	MACE	7,500

MACE = major adverse cardiac events (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke UA= hospitalization for unstable angina

et al. *Diabetes Care*. 2016; 39:738-742; Jayawardene D, et al. *Heart Lung Circ*. 2014;23:997-1008.



Dipeptidyl peptidase 4 inhibitor

Drug Name	Trade Name	Trial
Sitagliptin	Januvia	TECOS
Saxaglitpin	Onglyza	SAVOR-TIMI 53
Alogliptin	Nesina	EXAMINE
Linagliptin	Tradjenta	CARMELINA/CAROLINA

DPP4 Inhibitors

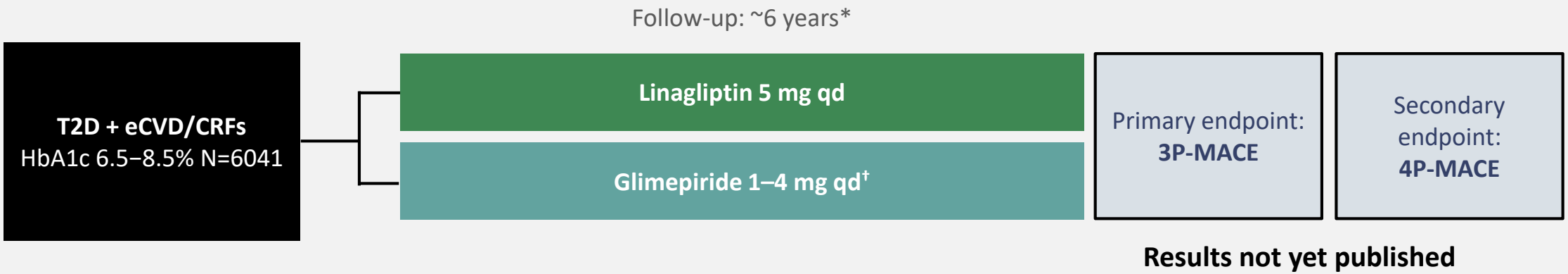
Summary of completed DPP-4 inhibitor CVOTs

SAVOR-TIMI 53[1]	**T2D + eCVD/CRFs** HbA1c 6.5–12.0% N=16,492	**Saxagliptin 5 mg qd*** **Placebo**	2.1-year median follow-up	Primary endpoint: **3P-MACE**	**HR 1.00** (95% CI 0.89, 1.12) ***p*<0.001/*p*=0.99**
EXAMINE[2]	**T2D + ACS** HbA1c 6.5–11.0% N=5380	**Alogliptin 25 mg qd**† **Placebo**	1.5-year median follow-up	Primary endpoint: **3P-MACE**	**HR 0.96** (upper CI‡ 1.16) ***p*<0.001/*p*=0.32**
TECOS[3]	**T2D + eCVD** HbA1c 6.5–8.0% N=14,671	3.0-year median follow-up **Sitagliptin 100 mg qd**§ **Placebo**		Primary endpoint: **4P-MACE**	**HR 0.98** (95% CI 0.89, 1.08) ***p*<0.001/*p*=0.65**
CARMELINA®[4]	**T2D + eCVD and/or prevalent CKD** HbA1c 6.5–10.0% N=6979	2.2-year median follow-up **Linagliptin 5 mg qd** **Placebo**		Primary endpoint: **3P-MACE**	**HR 1.02** (95% CI 0.89, 1.17) ***p*<0.001/*p*=0.74**

1. SCIRICA BM *ET AL. N ENGL J MED* 2013;369:1317; 2. WHITE WB *ET AL. N ENGL J MED* 2013;369:1327; 3. GREEN JB *ET AL. N ENGL J MED* 2015;373:232; 4. ROSENSTOCK J *ET AL. JAMA* 2019;321:69

Summary of completed DPP-4 inhibitor CVOTs

CAROLINA® (active comparator)[1,2]



Results not yet published

1. SCIRICA BM *ET AL. N ENGL J MED* 2013;369:1317; 2. WHITE WB *ET AL. N ENGL J MED* 2013;369:1327; 3. GREEN JB *ET AL. N ENGL J MED* 2015;373:232; 4. ROSENSTOCK J *ET AL. JAMA* 2019;321:69

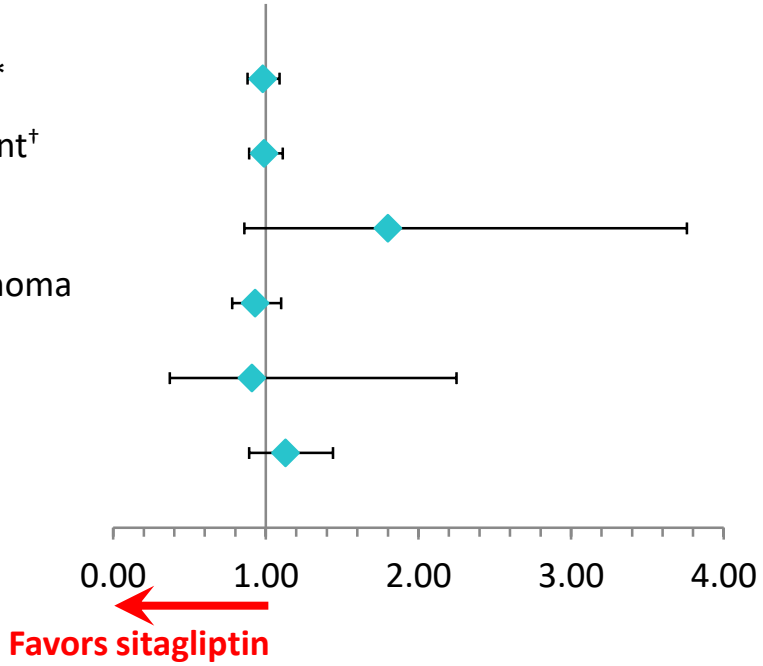
TECOS

TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

Primary and Secondary Outcomes with Sitagliptin

TECOS Per Protocol Analysis (n=14,523)

Median follow-up: 3.0 years



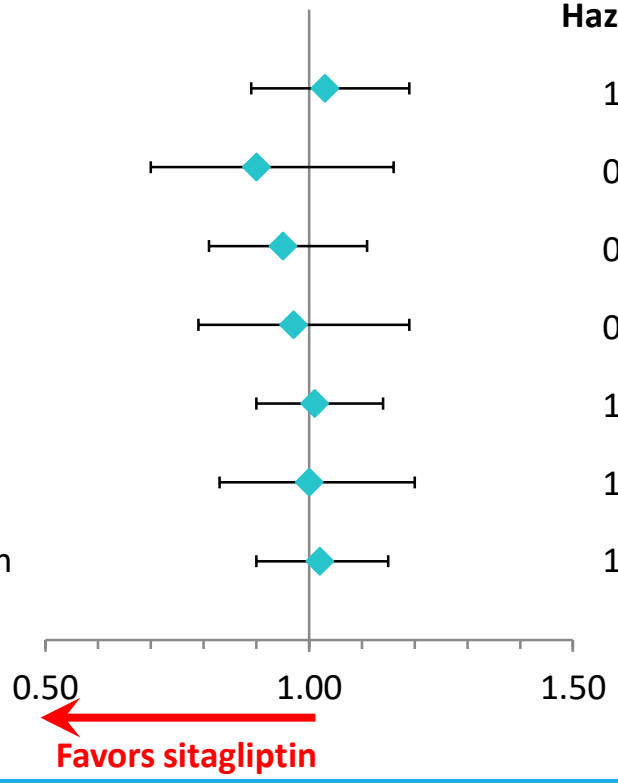
	Hazard ratio (95% CI)	*P* value
Primary composite endpoint*	0.98 (0.88-1.09)	<0.001 (NF)
Secondary composite endpoint†	0.99 (0.89-1.11)	<0.001 (NF)
Acute pancreatitis	1.80 (0.86-3.76)	0.12
Any cancer (except nonmelanoma skin cancer)	0.93 (0.89-1.44)	0.38
Pancreatic cancer	0.91 (0.37-2.25)	0.85
Severe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

Green JB, et al. *N Engl J Med*. 2015;373:232-242.

Individual Secondary Outcomes with Sitagliptin

TECOS Intent to Treat Analysis
(n=14,671)

Median follow-up: 3.0 years

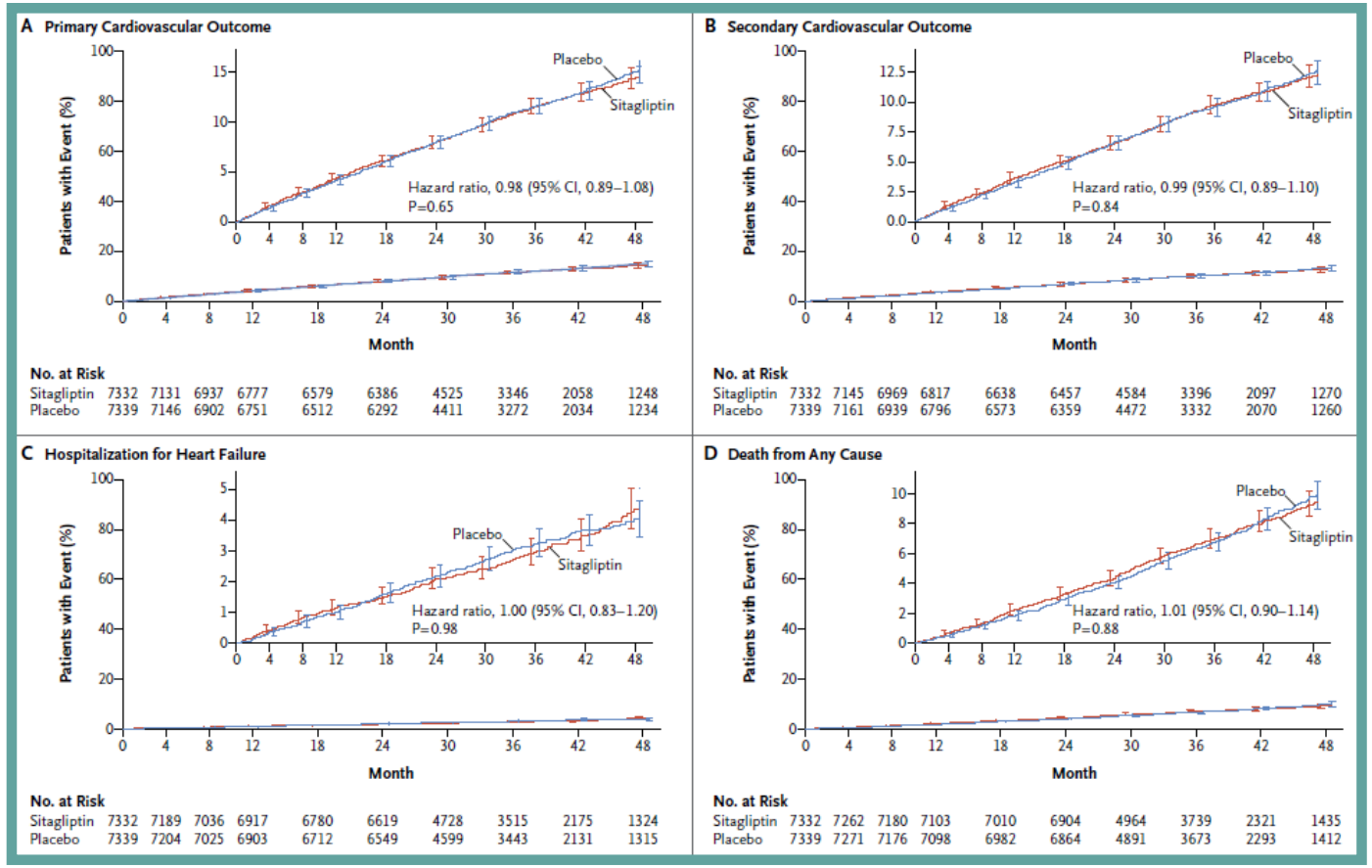


	Hazard ratio (95% CI)	*P* value
CV death	1.03 (0.89-1.19)	0.71
Hospitalization for unstable angina	0.90 (0.70-1.16)	0.42
Fatal or nonfatal MI	0.95 (0.81-1.11)	0.49
Fatal or nonfatal stroke	0.97 (0.79-1.19)	0.76
Death from any cause	1.01 (0.90-1.14)	0.88
Hospitalization for heart failure	1.09 (0.83-1.20)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

Green JB, et al. *N Engl J Med*. 2015;373:232-242

Clinical Outcomes with Sitagliptin

TECOS
(n=14,671)



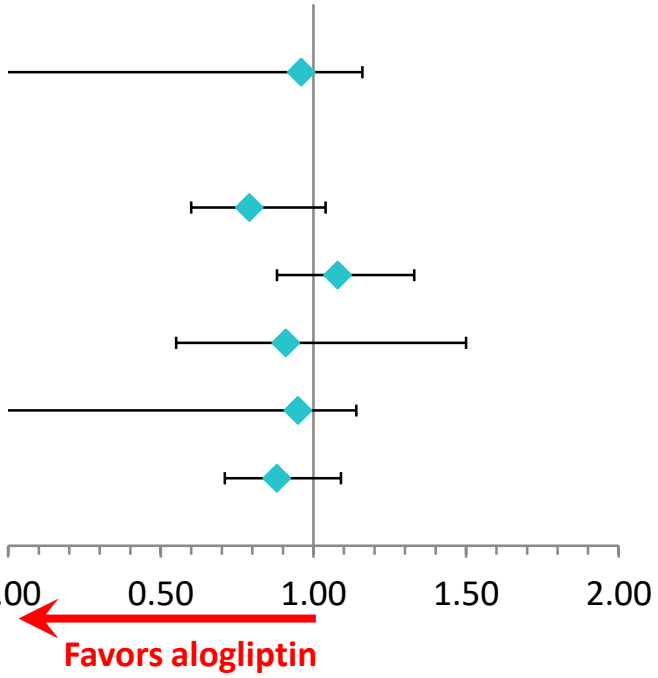
Green JB, et al. *N Engl J Med*. 2015;373:232-242.

(EXAMINATION OF CARDIOVASCULAR OUTCOMES WITH ALOGLIPTIN VERSUS STANDARD OF CARE)

Clinical Outcomes with Alogliptin

EXAMINE Safety Endpoints (n=5380)

Median follow-up: 18 months



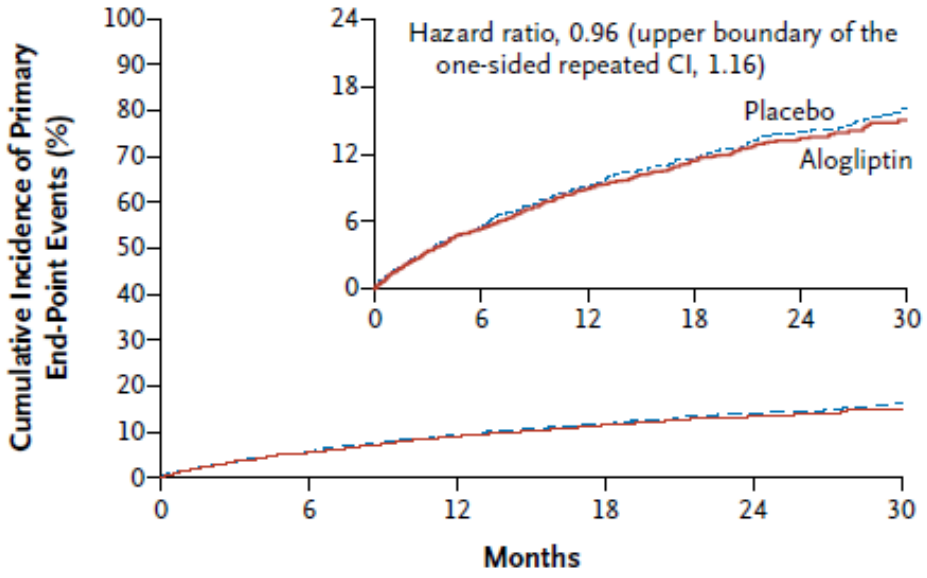
	Hazard ratio (95% CI)	*P* value
Primary composite	0.96 (≤1.16)*	0.32
Primary endpoint components		
CV death	0.79 (0.6-1.04)	0.10
Nonfatal MI	1.08 (0.88-1.33)	0.47
Nonfatal stroke	0.91 (0.55-1.50)	0.71
Primary secondary endpoint†	0.95 (≤1.14)*	0.26
Death from any cause	0.85 (0.66-1.10)	0.21

White W, et al. *N Engl J Med*. 2013;369:1327-1335.

Alogliptin CV Outcomes and Mortality

A

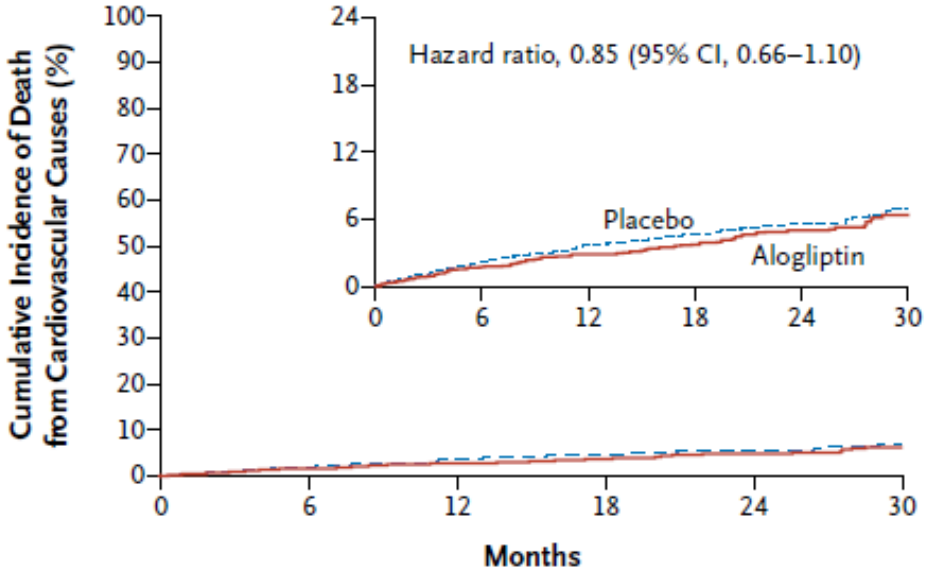
CV Death, Nonfatal MI, or Nonfatal Stroke



No. at Risk						
Placebo	2679	2299	1891	1375	805	286
Alogliptin	2701	2316	1899	1394	821	296

B

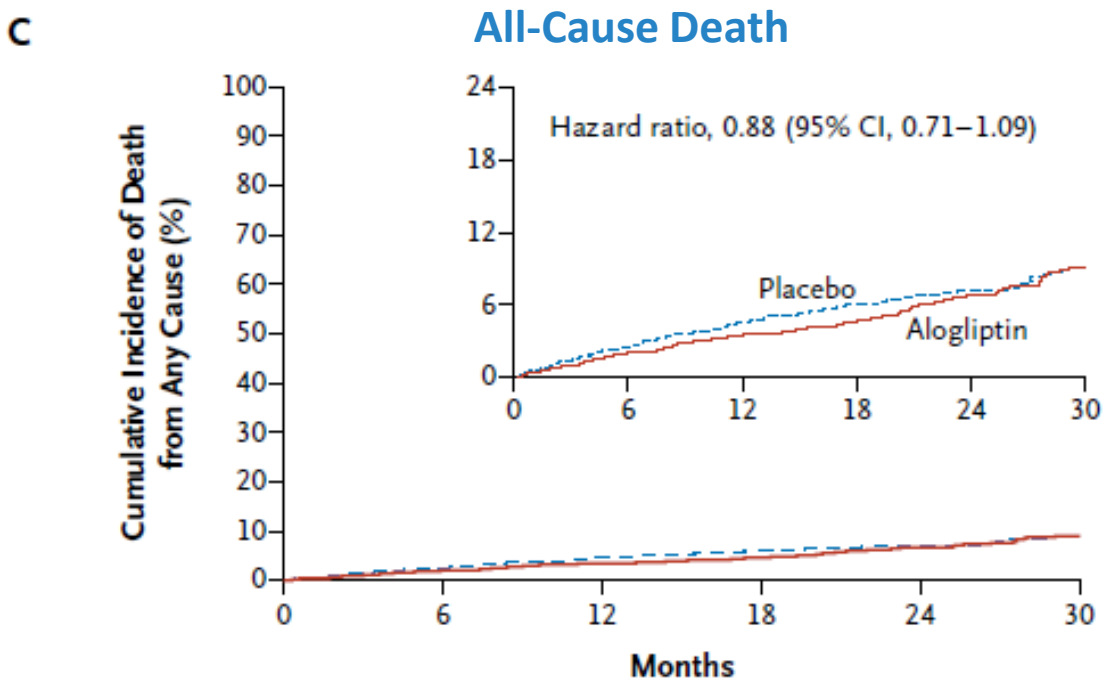
CV Death



No. at Risk						
Placebo	2679	2384	1996	1477	889	324
Alogliptin	2701	2402	2023	1504	894	320

White W, et al. *N Engl J Med*. 2013;369:1327-1335

Alogliptin CV Outcomes and Mortality



No. at Risk						
Placebo	2679	2384	1996	1477	889	324
Alogliptin	2701	2401	2023	1504	894	320

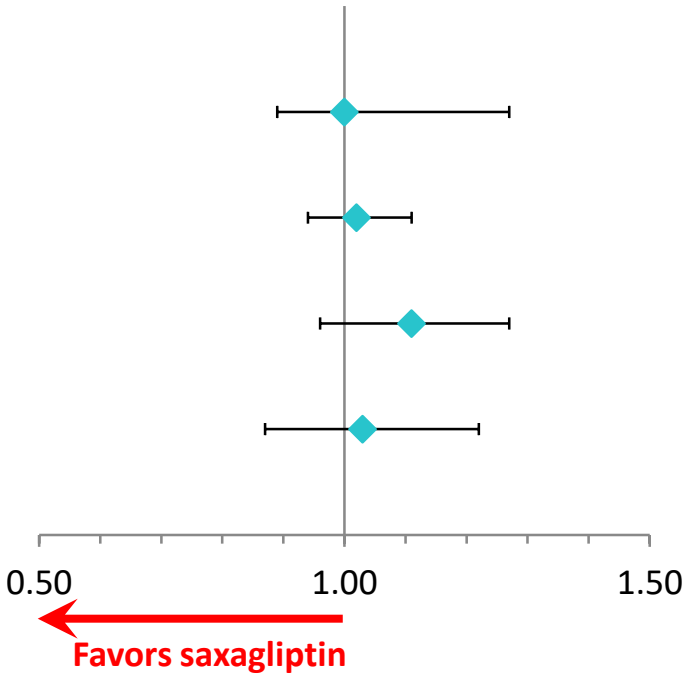
White W, et al. *N Engl J Med*. 2013;369:1327-1335

(SAXAGLIPTIN ASSESSMENT OF VASCULAR OUTCOMES RECORDED IN PATIENTS WITH DIABETES MELLITUS–THROMBOLYSIS IN MYOCARDIAL INFARCTION)

Clinical Outcomes with Saxagliptin

SAVOR-TIMI Prespecified Composite Endpoints and Mortality (n=16,492)

Median follow-up: 2.1 years



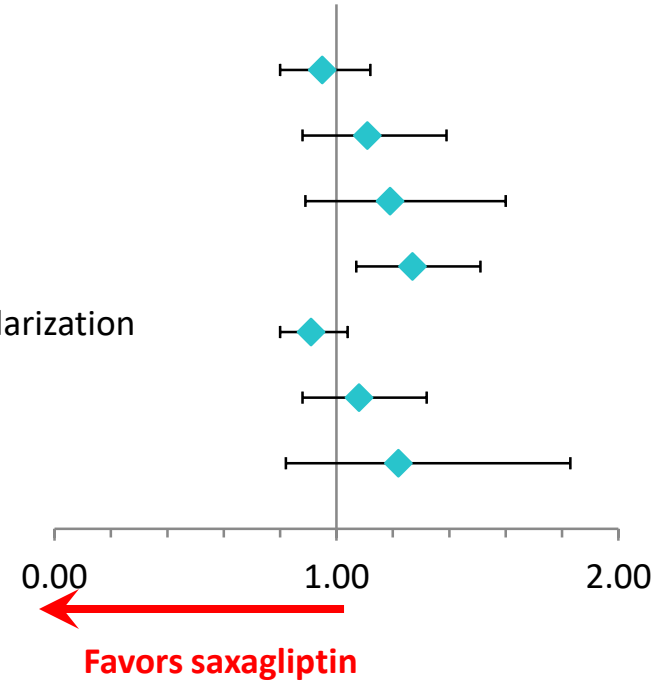
	Hazard ratio (95% CI)	*P* value
Primary composite endpoint*	1.00 (0.89-1.27)	0.99
Secondary composite endpoint†	1.02 (0.94-1.11)	0.66
Death from any cause	1.11 (0.96-1.27)	0.15
CV death	1.03 (0.87-1.22)	0.52

Scirica BM, et al. *N Engl J Med*. 2013;369,1317-1326.

Individual Secondary Outcomes with Saxagliptin

SAVOR-TIMI Prespecified Individual Endpoints (n=16,492)

Median follow-up: 2.1 years

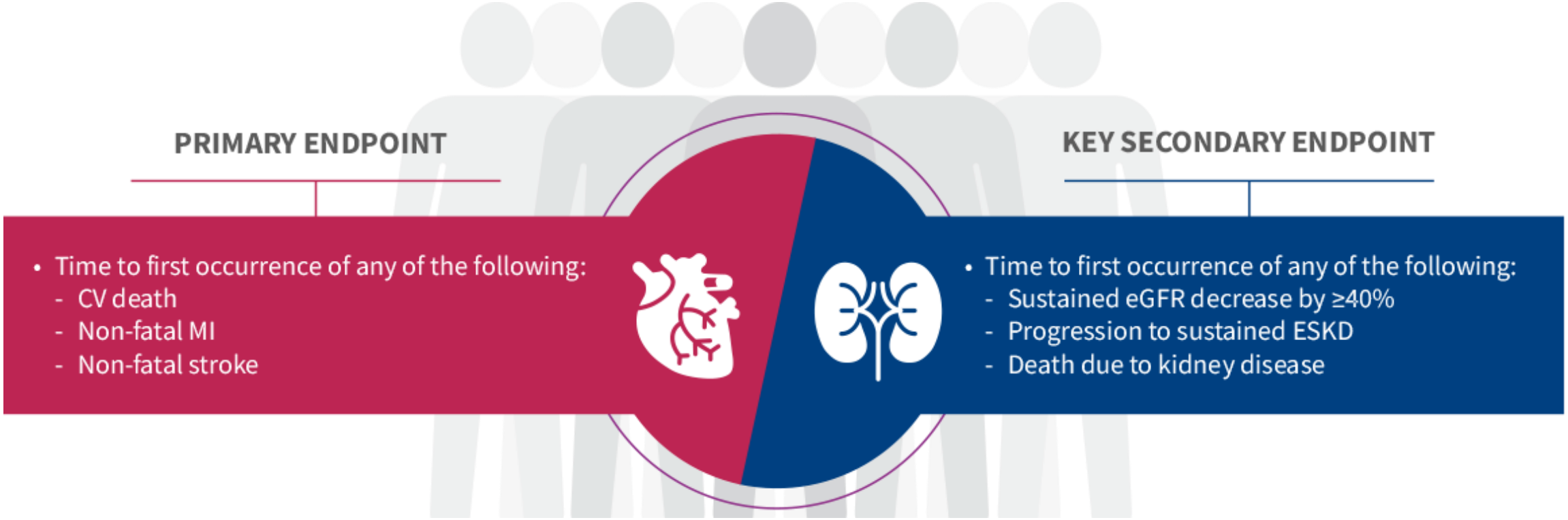


	Hazard ratio (95% CI)	*P* value
Myocardial infarction	0.95 (0.80-1.12)	0.52
Ischemic stroke	1.11 (0.80-1.12)	0.38
Hospitalization for unstable angina	1.19 (0.89-1.60)	0.24
Hospitalization for heart failure	**1.27 (1.07-1.51)**	**0.007**
Hospitalization for coronary revascularization	0.91 (0.80-1.04)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

Scirica BM, et al. *N Engl J Med*. 2013;369,1317-1326.

CARMELINA

(Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus)


PRIMARY ENDPOINT
• Time to first occurrence of any of the following:
- CV death
- Non-fatal MI
- Non-fatal stroke
KEY SECONDARY ENDPOINT
• Time to first occurrence of any of the following:
- Sustained eGFR decrease by ≥40%
- Progression to sustained ESKD
- Death due to kidney disease

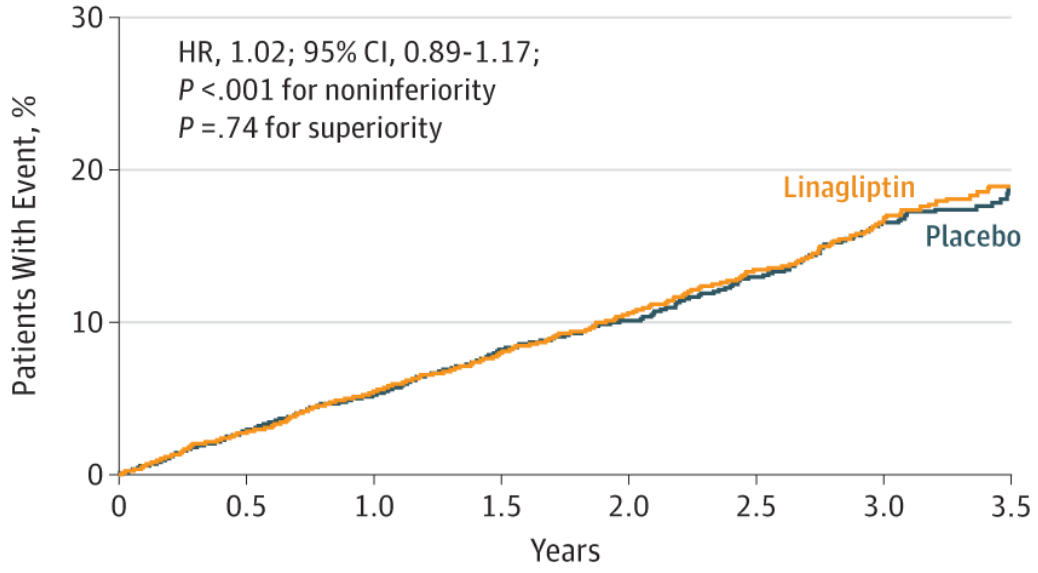
CARMELINA

JAMA Network™

From: **Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial**

JAMA. 2019;321(1):69-79. doi:10.1001/jama.2018.18269

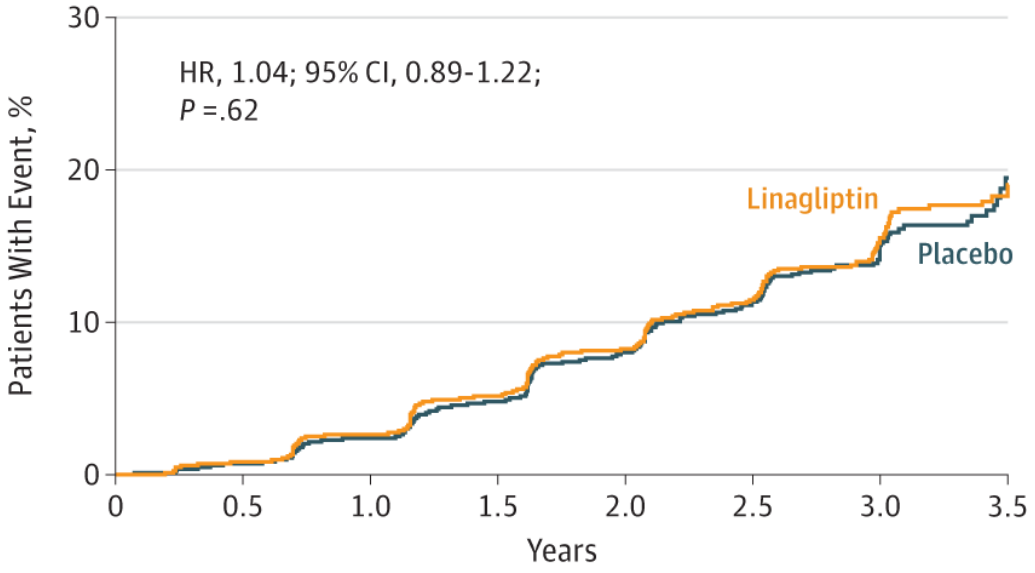
A Time to primary 3-point MACE outcome



No. of patients

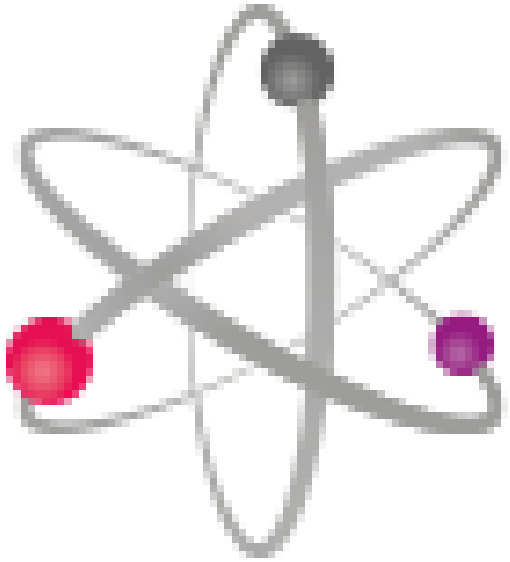
Placebo	3485	3353	3243	2625	1931	1285	758	251
Linagliptin	3494	3373	3254	2634	1972	1306	778	269

B Time to secondary kidney outcome



No. of patients

Placebo	3485	3213	2995	2298	1608	1005	496	103
Linagliptin	3494	3227	3018	2345	1675	1040	518	109



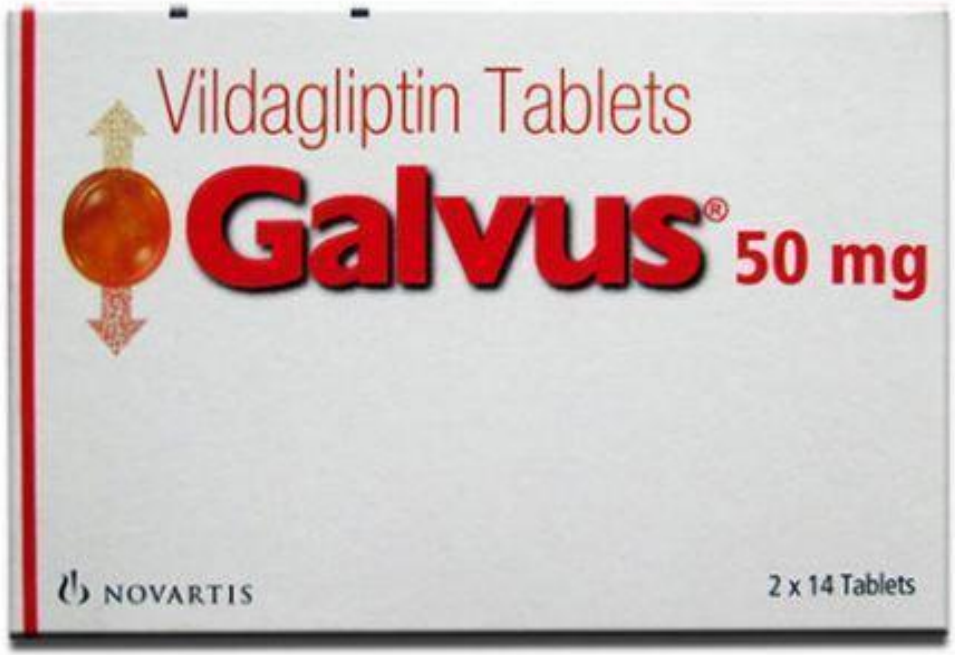
CAROLINA

(CARDIOVASCULAR OUTCOME STUDY OF LINAGLIPTIN VERSUS GLIMEPIRIDE IN PATIENTS WITH TYPE 2 DIABETES)

CAROLINA TOPLINE

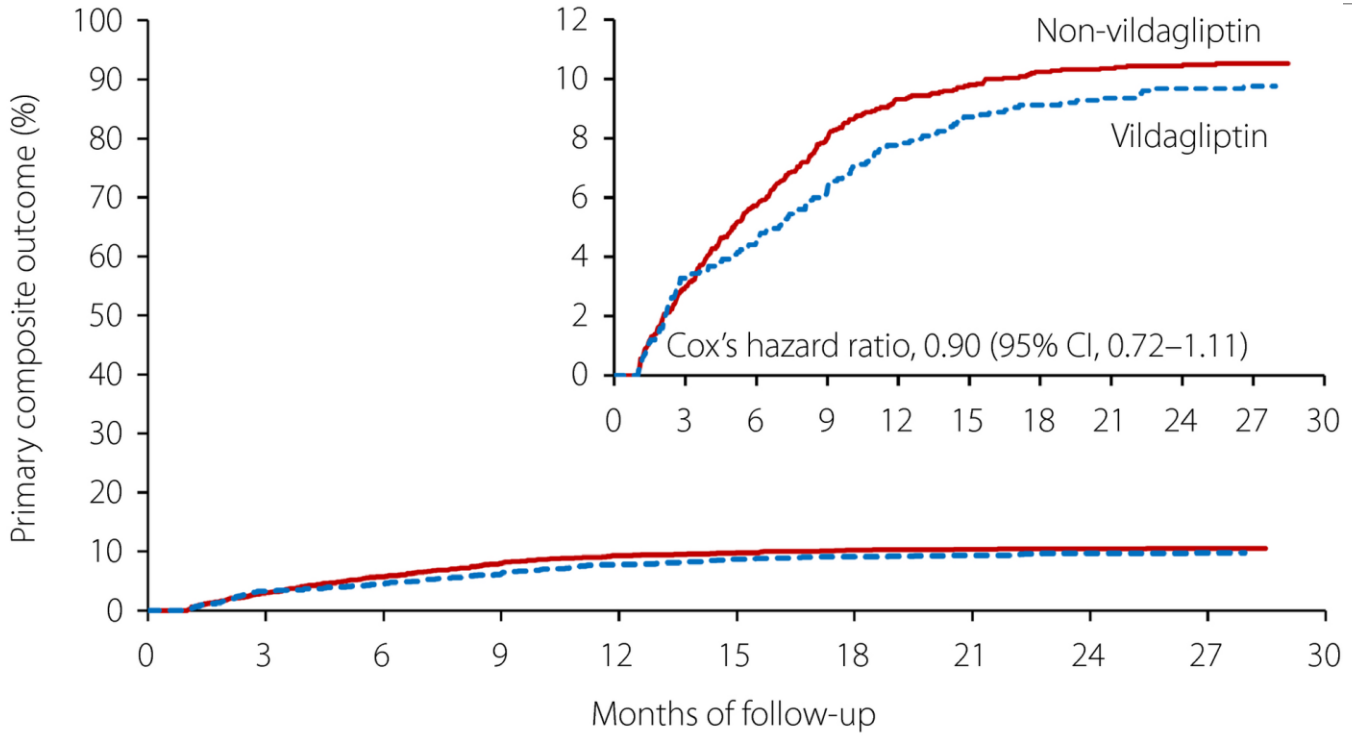
CAROLINA® met its primary endpoint, defined as non-inferiority of linagliptin versus glimepiride in time to first occurrence of CV death, non-fatal MI or non-fatal stroke (3P-MACE)

The overall safety profile of linagliptin in CAROLINA® was consistent with previous data, and no new safety signals were observed


Vildagliptin Tablets
Galvus® 50 mg
NOVARTIS
2 x 14 Tablets

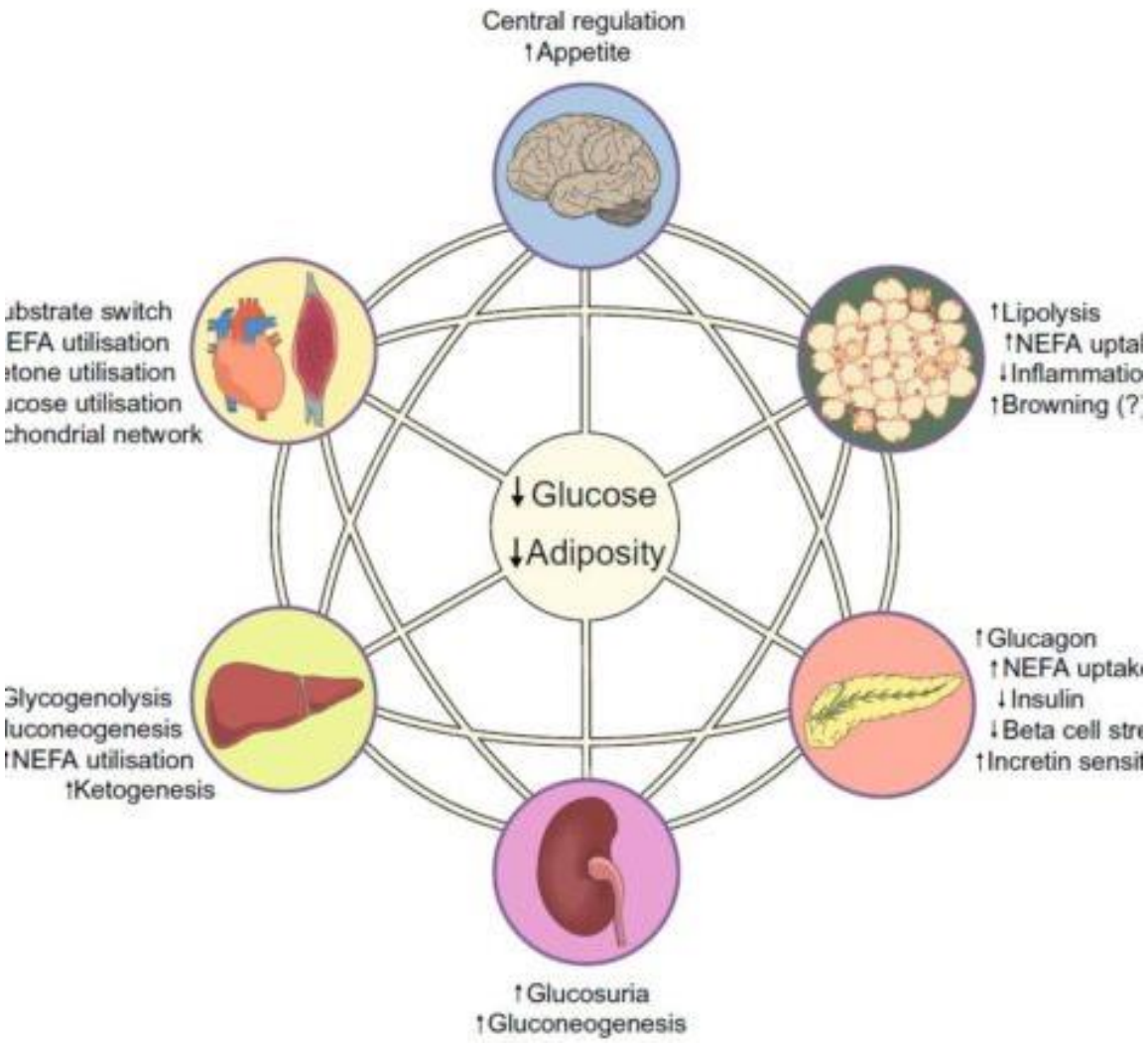

AMIGOZ
AMICLOVIR 1000
10 Tablets
Vildagliptin Tablets 50mg
AMIVILDA 50
AMIGOZ
Lifesciences

Cardiovascular outcomes of vildagliptin in patients with type 2 diabetes mellitus after acute coronary syndrome or acute ischemic stroke: Primary composite



No. at risk:						
Non-vildagliptin	2,500	1,546	741	237	51	0
Vildagliptin	1,250	803	387	132	27	0

Journal of Diabetes Investigation, First published: 22 May 2019, DOI: (10.1111/jdi.13078)



SGLT2

SODIUM GLUCOSE COTRANSPORTER 2 INHIBITORS

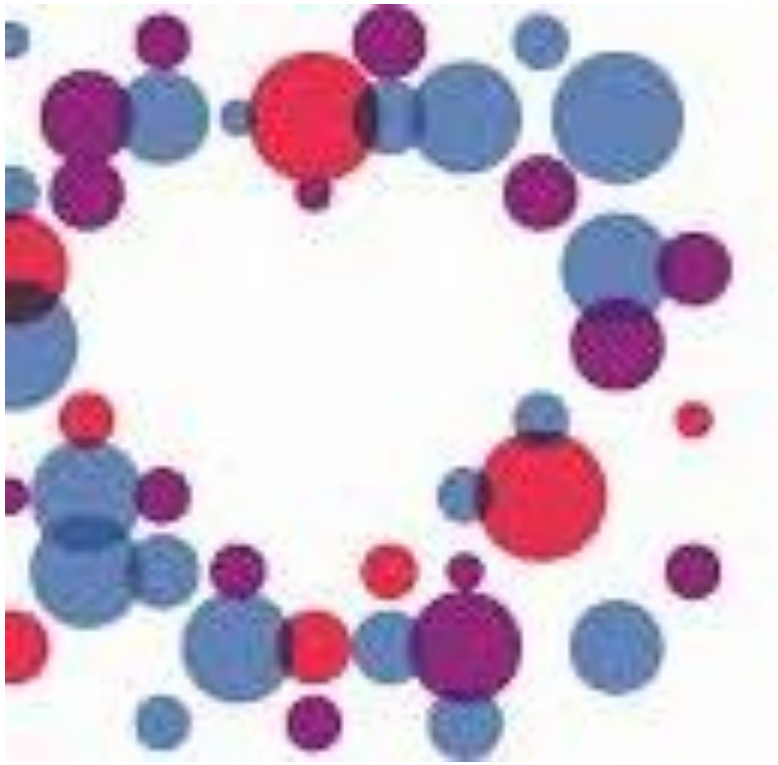
Drug Name	Trade Name	Trial
Empaglifloxin	Jardiance	EMPA-REG
Canaglifloxin	Invokana	CANVAS/CANVAS R
Dapaglufloxin	Farxiga	DECLARE-TIMI 58
Ertuglifloxin	Steglatro	VERTIS CV
Sotagliflozin ***	Zynquista	SCORED

SGLT2

Comparative characteristics of SGLT2 inhibitor CVOTs

Variable	EMPA-REG OUTCOME [13]	CANVAS Program[a] [16]	DECLARE [19]
Drug	Empagliflozin	Canagliflozin	Dapagliflozin
Population (*n*)	7020	10,142	17,160
Follow-up (years)	3.1	3.6[b]	4.2
Known atherosclerotic CVD	99	66	41
Renal impairment[b]	26	20	7
Female sex	29	36	37
HbA_{1c} (%)	8.1 ± 0.8	8.2 ± 0.9	8.3 ± 1.2
HbA_{1c} (mmol/mol)	65 ± 9	66 ± 10	67 ± 13
Insulin therapy			
Baseline	48	50	41
Any time	8	NG	NG
Ethnicity			
Asian	22	13	13
Black	5	3	3
Hispanic	18	NG	15
Failed to finish on medication	25	30	23
CV events, first MACE (*n*)[c]	772	1011	1559
Placebo event rate (%/year)	4.4	3.2	2.4

HOME, P. DIABETOLOGIA. JAN 2019.



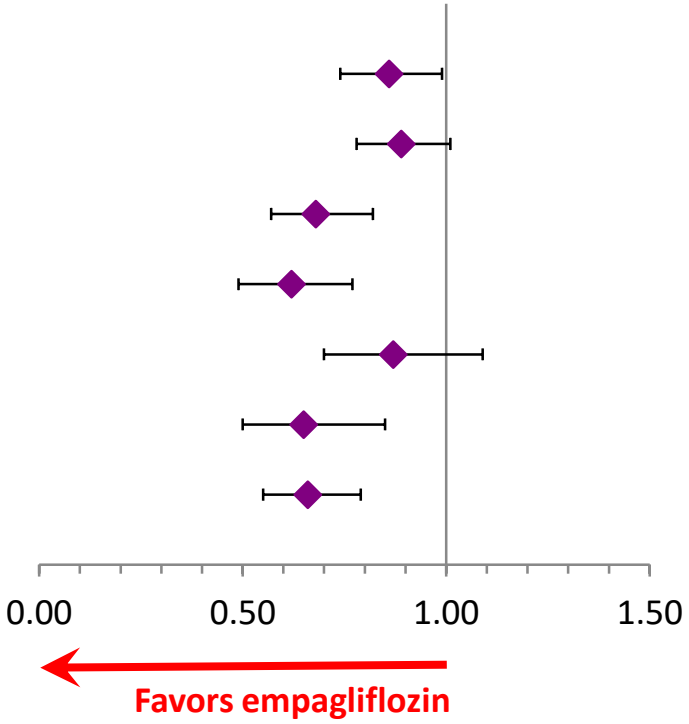
EMPA-REG OUTCOME®

(EMPAGLIFLOZIN CARDIOVASCULAR OUTCOME EVENT TRIAL IN TYPE 2 DIABETES MELLITUS PATIENTS)

Clinical Outcomes with Empagliflozin

EMPA-REG OUTCOME Pooled Analysis (N=7020)

Median follow-up: 3.1 years



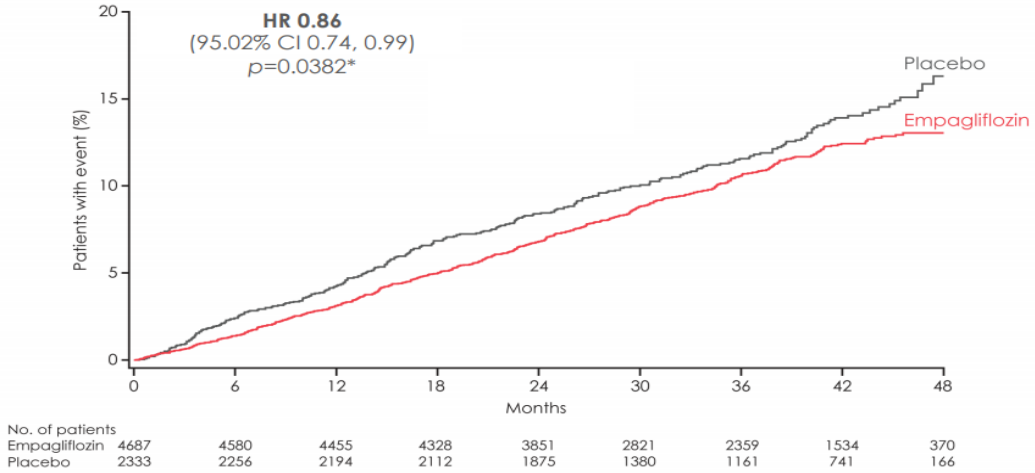
	Hazard ratio (95% CI)	*P* value
Primary composite endpoint*	0.86 (0.74-0.99)	0.04
Secondary composite endpoint†	0.89 (0.78-1.01)	0.08
Death from any cause	0.68 (0.57-0.82)	<0.001
CV death	0.62 (0.49-0.77)	<0.001
Fatal or nonfatal MI	0.87 (0.70-1.09)	0.23
Hospitalization for HF	0.65 (0.50-0.85)	0.002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

Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128.

Clinical Outcome with Empagliflozin

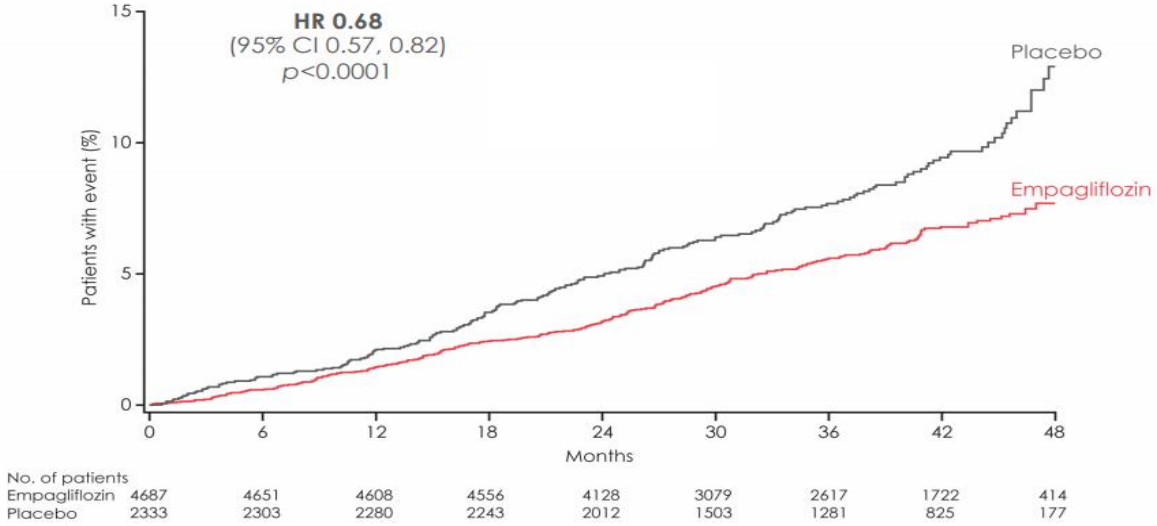
Primary outcome: 3-point MACE

10.5% vs 12.1% i empa (10+25mg) vs placebo, **ARR: 1.6%**

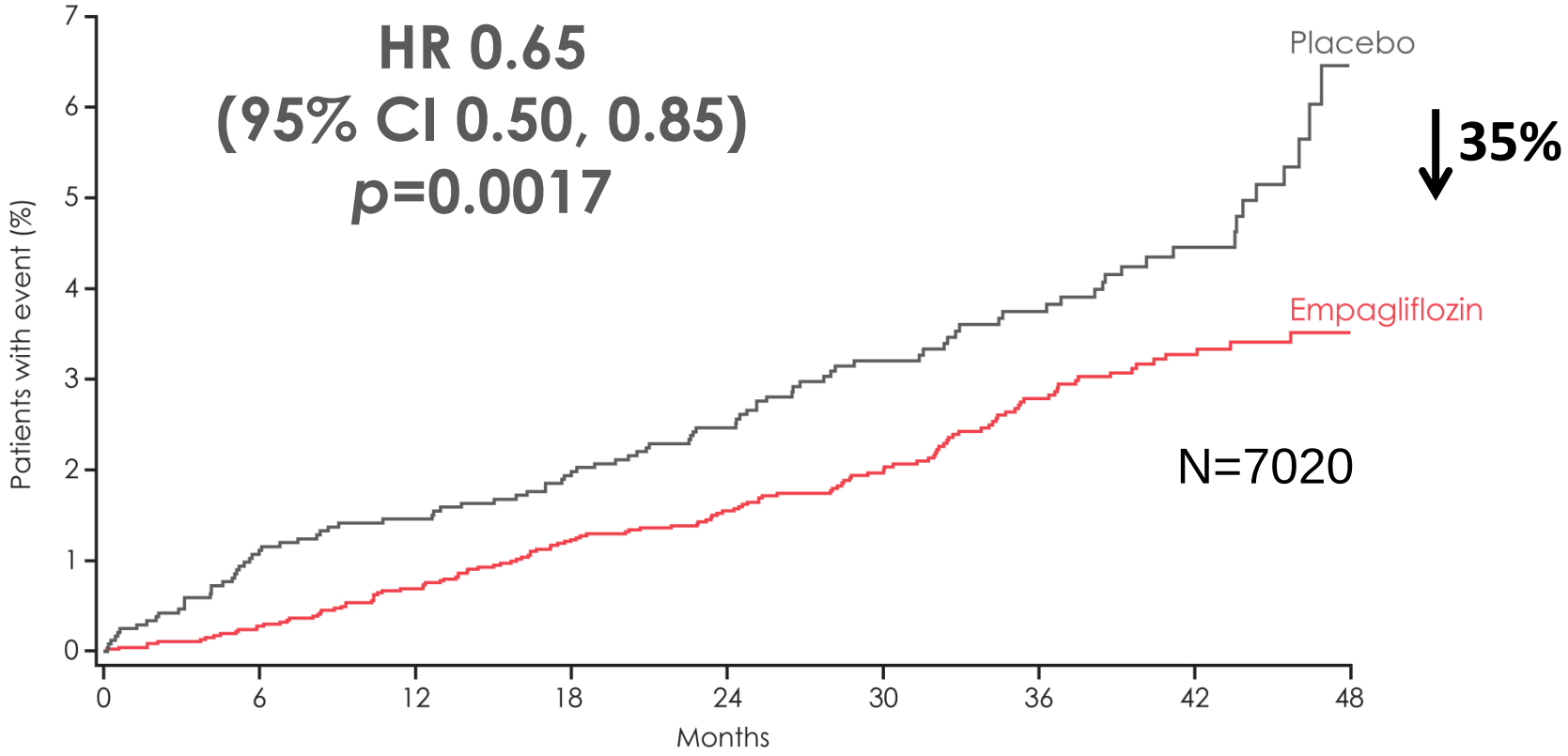


All-cause mortality

All-cause mortality: 5.7% vs 8.3%, **ARR 2.6%**



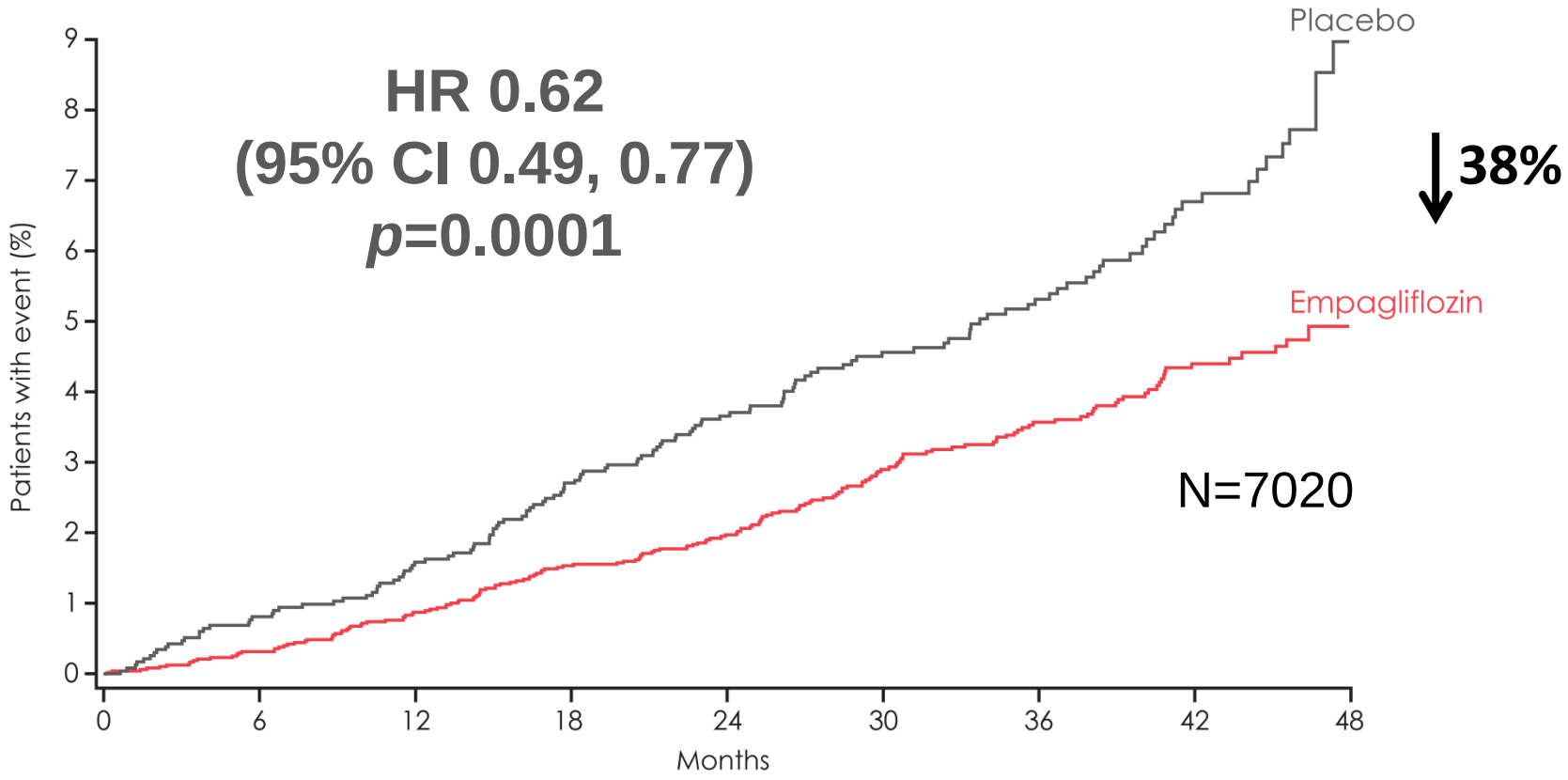
EMPA-REG OUTCOME: Hospitalization for heart failure



No. of patients									
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128.

EMPA-REG OUTCOME: Cardiovascular death



No. of patients									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128

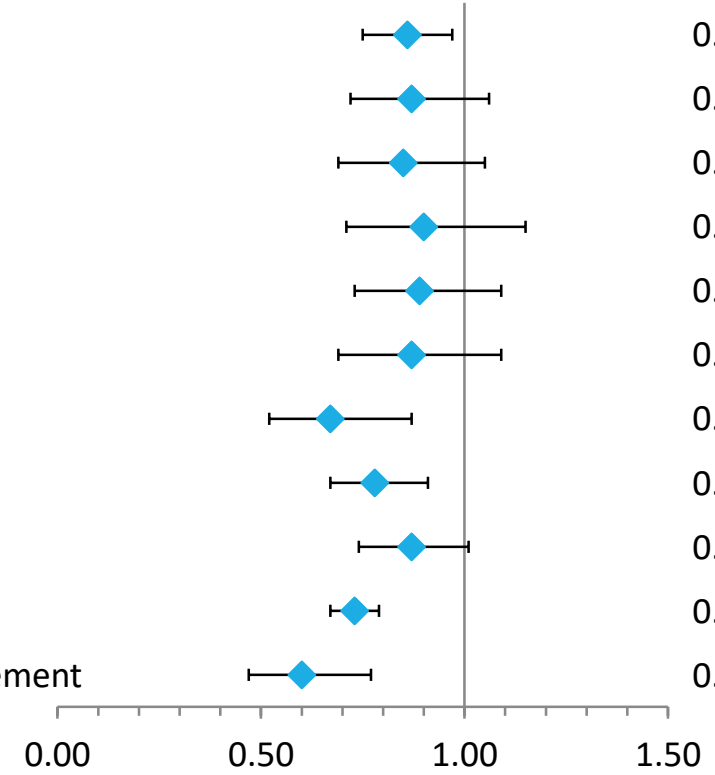
CANVAS Program

(CANAGLIFLOZIN CARDIOVASCULAR ASSESSMENT STUDY)

Clinical Outcomes with Canagliflozin

CANVAS Program
(N=10,142)

Median follow-up: 3.6 years

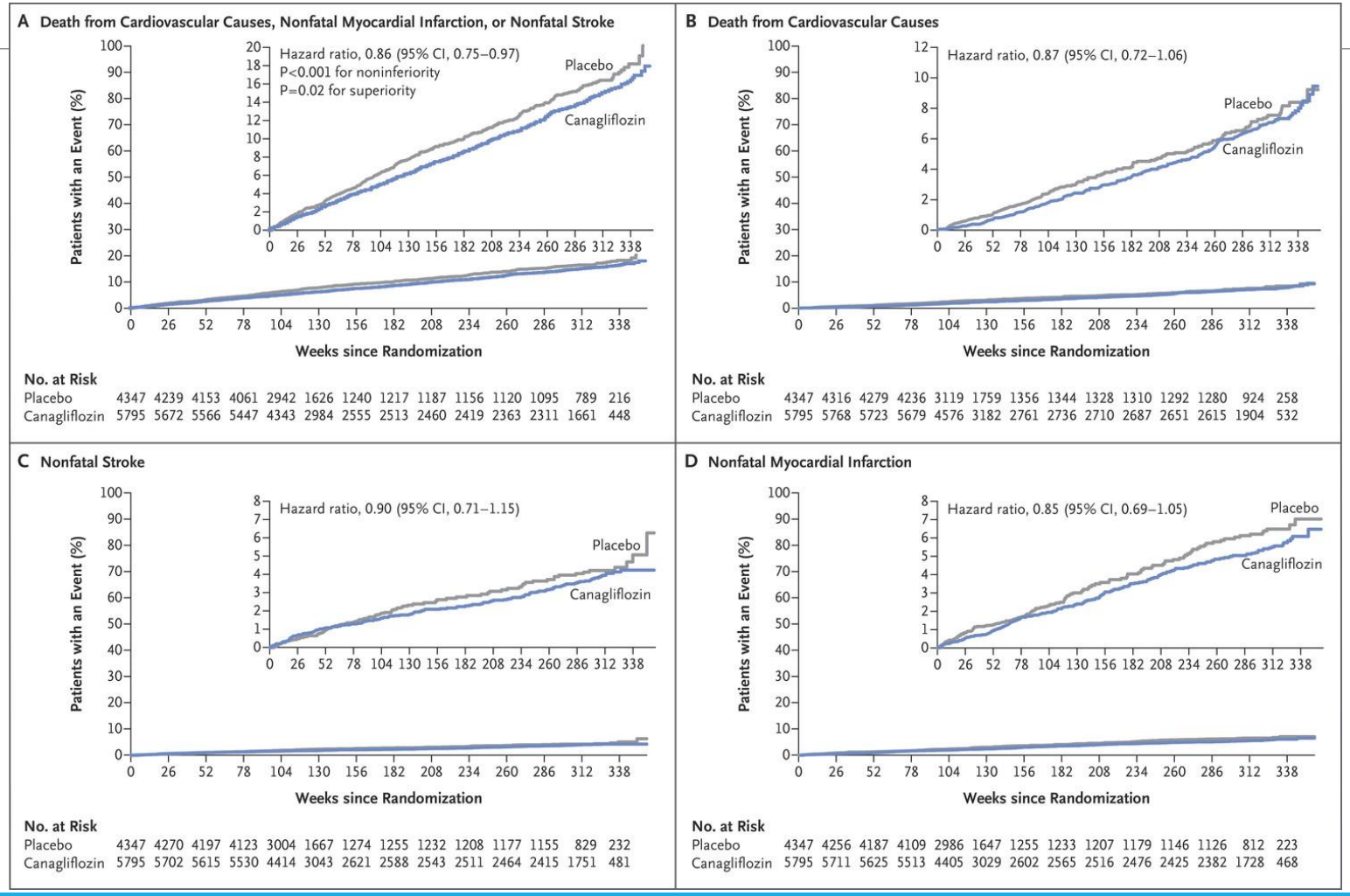


	Hazard ratio (95% CI)	*P* value
Primary composite endpoint*	0.86 (0.75-0.97)	0.02†
CV death	0.87 (0.72-1.06)	
Nonfatal MI	0.85 (0.69-1.05)	
Nonfatal stroke	0.90 (0.71-1.15)	
Fatal or nonfatal MI	0.89 (0.73-1.09)	
Fatal or nonfatal stroke	0.87 (0.69-1.09)	
HF hospitalization	0.67 (0.52-0.87)	
CV death or HF hospitalization	0.78 (0.67-0.91)	
All-cause death	0.87 (0.74-1.01)	
Progression of albuminuria	0.73 (0.67-0.79)	
40% reduction in eGFR, renal replacement therapy, or renal death	0.60 (0.47-0.77)	

Favors canagliflozin

Neal B, et al. *N Engl J Med*. 2017 Jun 12 [epub ahead of print].

Cardiovascular Outcomes in the Integrated CANVAS Program



Neal B et al. N Engl J Med 2017;377:644-657.

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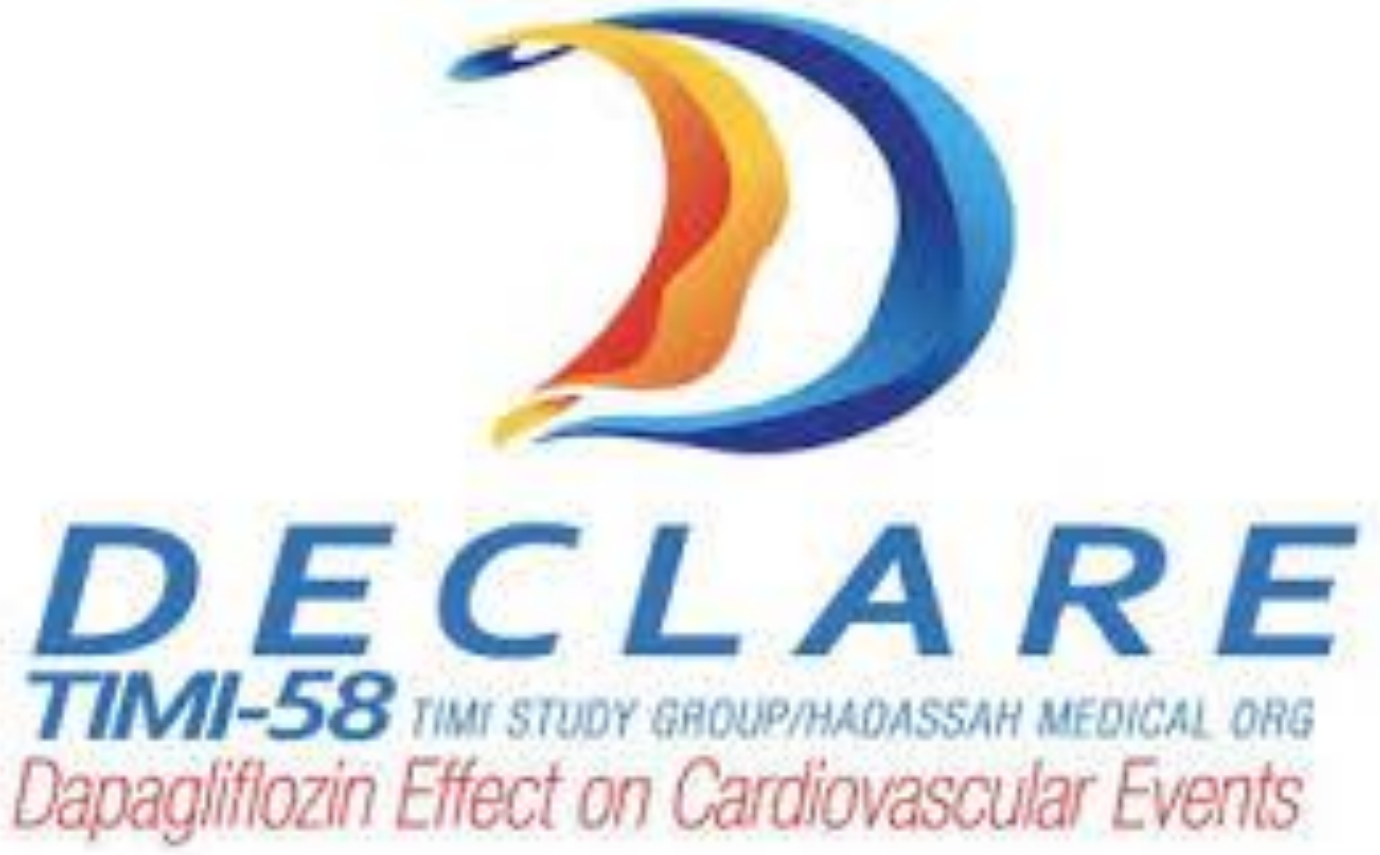
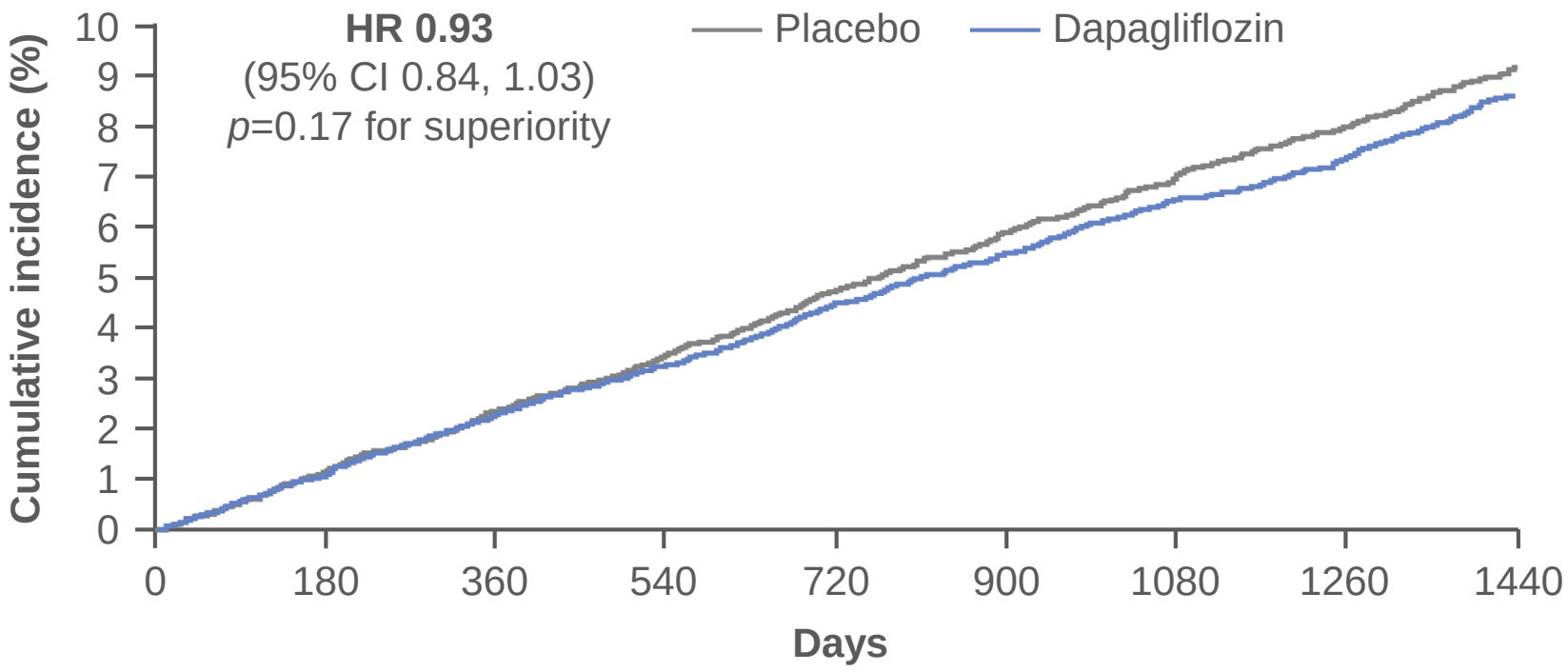


DAPAGLIFLOZIN EFFECT ON CARDIOVASCULAR EVENTS–THROMBOLYSIS IN MYOCARDIAL INFARCTION 58)

DECLARE-TIMI 58: 3P-MACE co-primary outcome

Dapagliflozin demonstrated non-inferiority, but did not show superiority for 3P-MACE



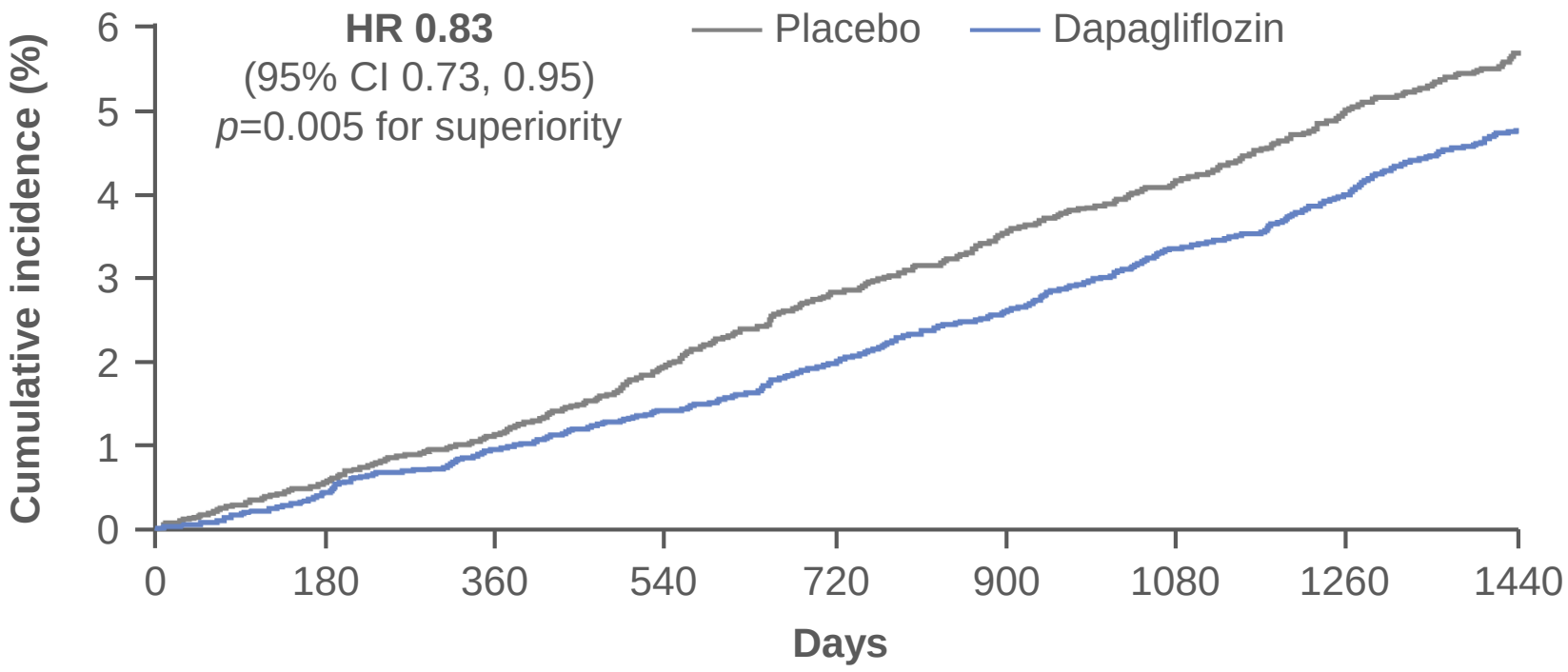
No. at risk									
Placebo	8578	8433	8281	8129	7969	7805	7649	7137	5158
Dapagliflozin	8582	8466	8303	8166	8017	7873	7708	7237	5225

3P-MACE, 3-point major adverse cardiovascular events; CV, cardiovascular; MI, myocardial infarction

Wiviott SD *et al. N Engl J Med* 2018;380:347

DECLARE-TIMI 58: composite of CV death or HHF co-primary outcome

Dapagliflozin demonstrated a 17% RRR in CV death or HHF

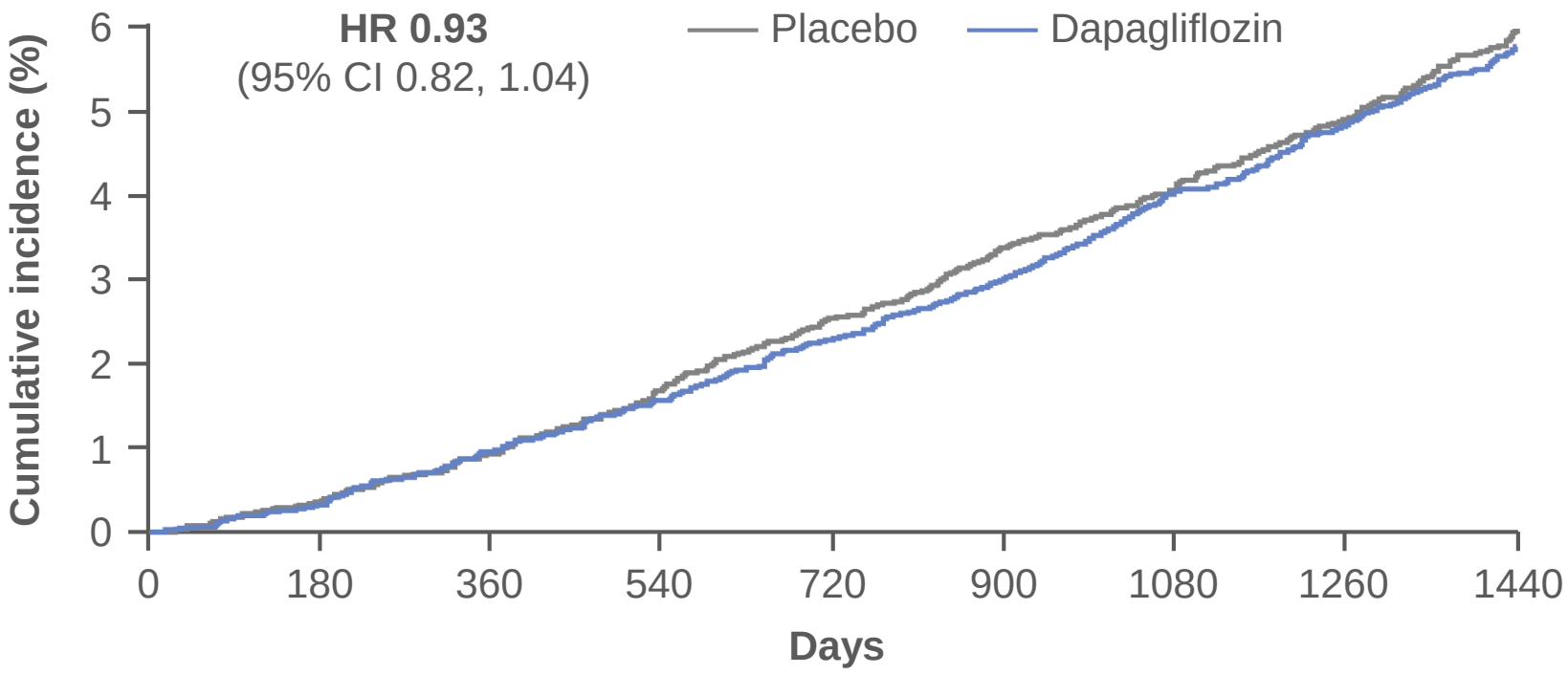


No. at risk									
Placebo	8578	8485	8387	8259	8127	8003	7880	7367	5362
Dapagliflozin	8582	8517	8415	8322	8224	8110	7970	7497	5445

CV, cardiovascular; HHF, hospitalisation for heart failure; RRR, relative risk reduction
Wiviott SD *et al. N Engl J Med* 2018;380:347

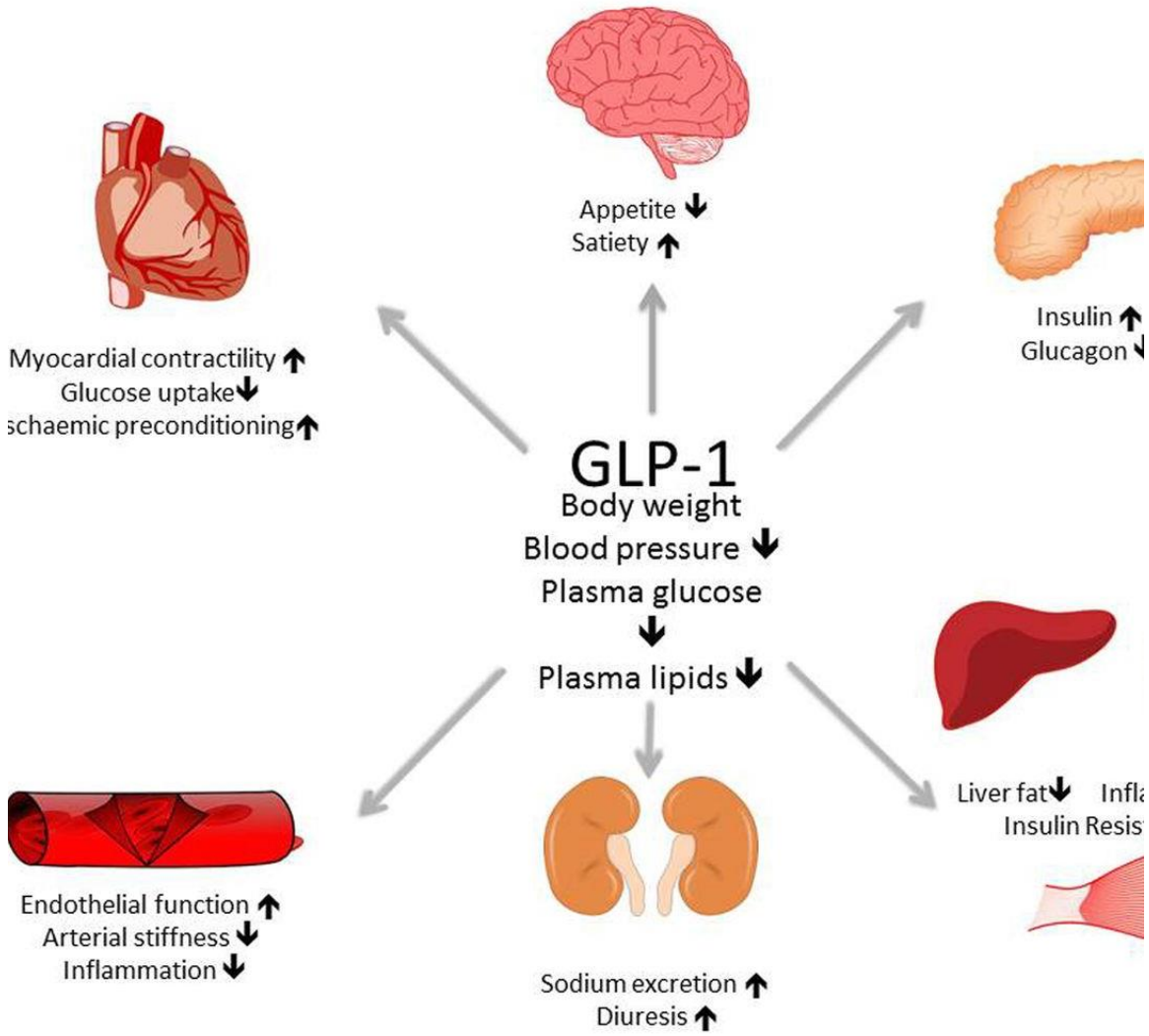
DECLARE-TIMI 58: all-cause mortality

Dapagliflozin demonstrated no effect on all-cause mortality



No. at risk									
Placebo	8578	8542	8484	8414	8337	8258	8184	7741	5715
Dapagliflozin	8582	8554	8495	8437	8369	8305	8207	7763	5715

Wiviott SD *et al. N Engl J Med* 2018;380:347



GLP-1 RA

GLUCAGON LIKE PEPTIDE RECEPTOR AGONIST

Drug Name	Trade Name	Trial
Lixisenatide	Adlyxin TM	ELIXA
Liraglutide	Victoza	LEADER
Semaglutide	Ozempic	SUSTAIN 6
Exenatide	Bydureon/Byetta	EXSCEL
Dulaglutide	Trulicity	REWIND
Albiglutide	Tanzeum	HARMONY
Semaglutide PO		PIONEER 6

GLP-1

Variable	LEADER [14]	SUSTAIN-6 [15]	EXSCEL [33]	Harmony [17]
Drug	Liraglutide	Semaglutide	Exenatide (MR)	Albiglutide
Population (*n*)	9340	3297	14,752	9463
Follow-up (years)	3.8	2.1	3.2	1.6
Known atherosclerotic CVD	81	71	73	100
Renal impairment[b]	23	24	22	23
Female sex	36	39	38	31
HbA_{1c} (mmol/mol)	72 ± 16	72 ± 16	64	72 ± 16
HbA_{1c} (%)	8.7 ± 1.5	8.7 ± 1.5	8.0	8.7 ± 1.5
Insulin therapy				
Baseline	45	58	14	59
Any time	81	75	26	62[c]
Ethnicity				
Asian	10	8	10	5
Black	8	7	6	2
Hispanic	12	15	21	21
Failed to finish on medication	NG	20	44	26
CV events, first MACE (*n*)[d]	1302	254	1744	766
Placebo event rate (%/year)	3.9	4.2	4.0	5.9

Comparative characteristics of GLP-1RA CVOTs

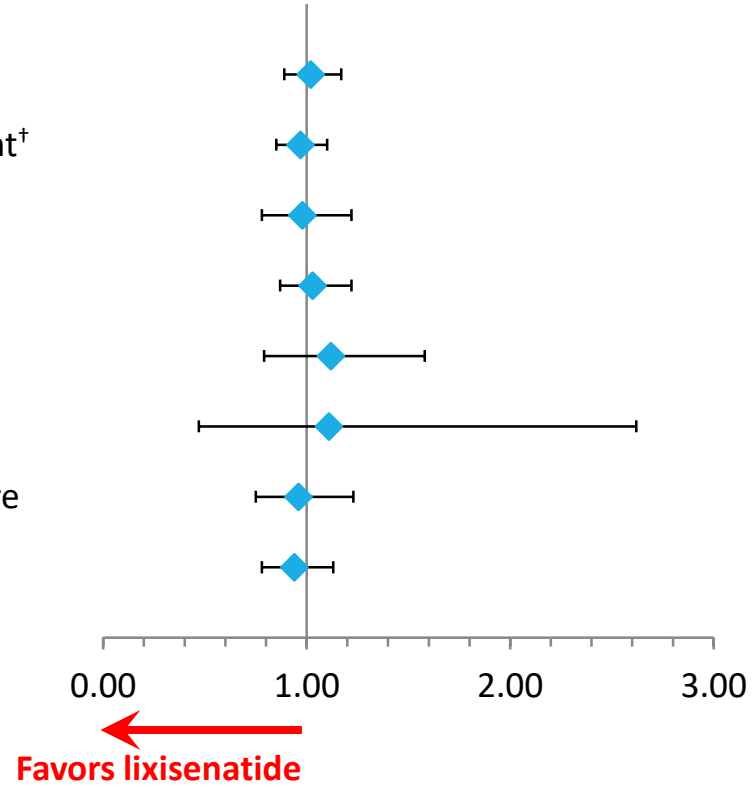
HOME, P. DIABETOLOGIA. JAN 2019.

ELIXA

(EVALUATION OF LIXISENATIDE IN ACUTE CORONARY SYNDROME)

Clinical Outcomes with Lixisenatide

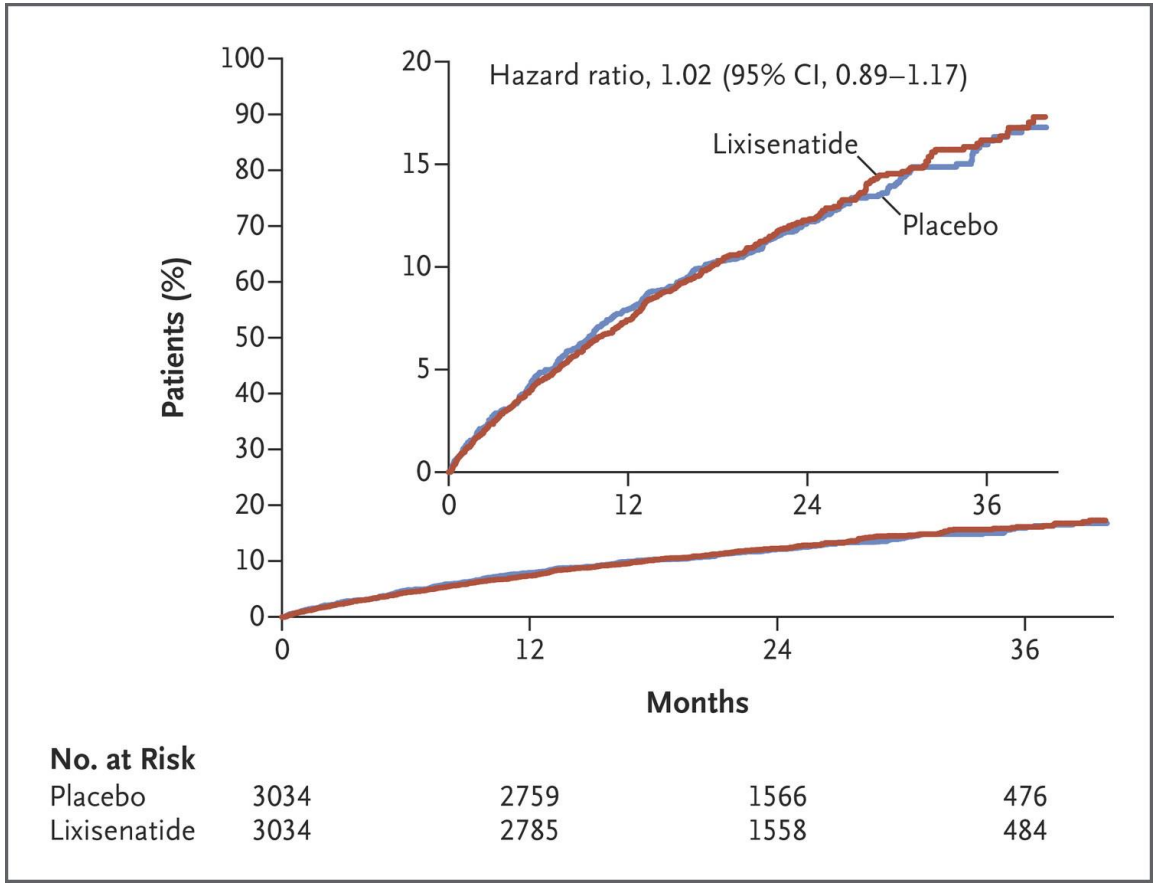
ELIXA
(Patients with T2D and CVD; N=6068)



	Hazard ratio (95% CI)	*P* value
Primary composite endpoint*	1.02 (0.89-1.17)	0.81
Secondary composite endpoint†	0.97 (0.85-1.10)	0.63
CV death	0.98 (0.78-1.22)	0.85
Fatal or nonfatal MI	1.03 (0.87-1.22)	0.71
Stroke	1.12 (0.79-1.58)	0.54
Unstable angina	1.11 (0.47-2.62)	0.81
Hospitalization for heart failure	0.96 (0.75-1.23)	0.75
Death from any cause	0.94 (0.78-1.13)	0.50

Pfeffer MA, et al. *N Engl J Med*. 2015;373:2247-2257.

Clinical Outcomes with Lixisenatide



Non inferiority:
P<0.001
Superiority:
P=0.81

Pfeffer MA et al. N Engl J Med 2015;373:2247-2257

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LEADER®

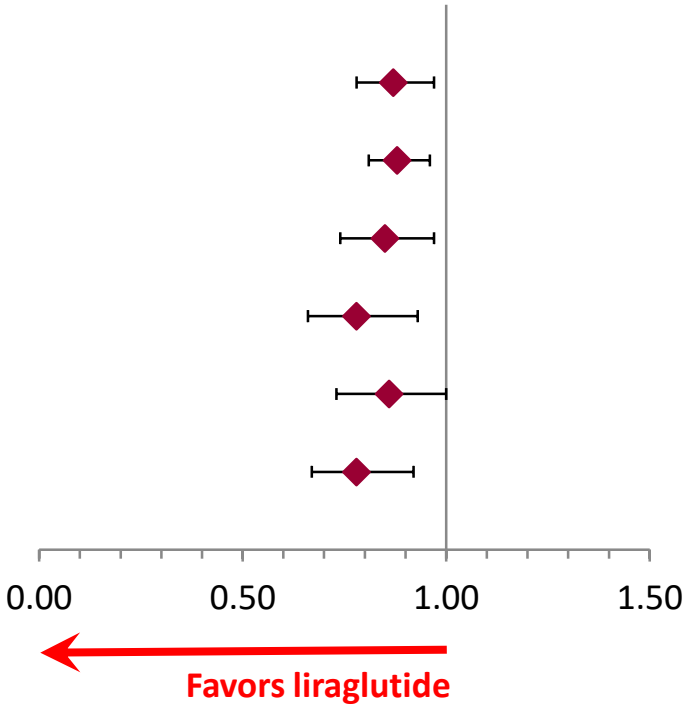
Liraglutide Effect and Action in Diabetes:
Evaluation of cardiovascular outcome Results

(LIRAGLUTIDE EFFECT AND ACTION IN DIABETES: EVALUATION OF CARDIOVASCULAR OUTCOME RESULTS)

Clinical Outcomes with Liraglutide

LEADER
(N=9340)

Median follow-up: 3.5 years

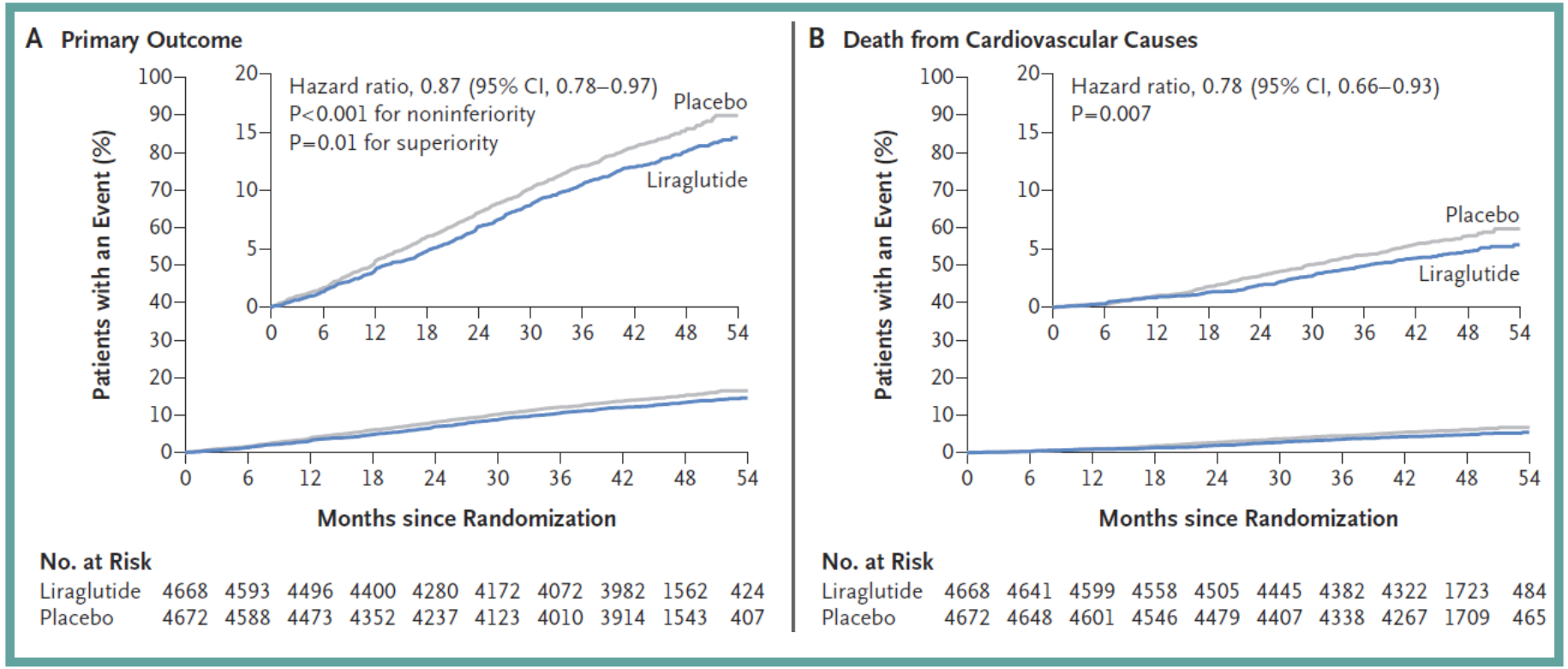


	Hazard ratio (95% CI)	*P* value
Primary composite endpoint*	0.87 (0.78-0.97)	0.01
Expanded composite endpoint†	0.88 (0.81-0.96)	0.005
Death from any cause	0.85 (0.74-0.97)	0.02
CV death	0.78 (0.66-0.93)	0.007
Fatal or nonfatal MI	0.86 (0.73-1.00)	0.046
Nephropathy	0.78 (0.67-0.92)	0.003

Marso SP, et al. *N Engl J Med*. 2016:375:311-322.

Clinical Outcomes with Liraglutide

LEADER
(N=9340)



Marso SP, et al. *N Engl J Med*. 2016:375:311-322.

EXSCEL

Exenatide Study of Cardiovascular Event Lowering

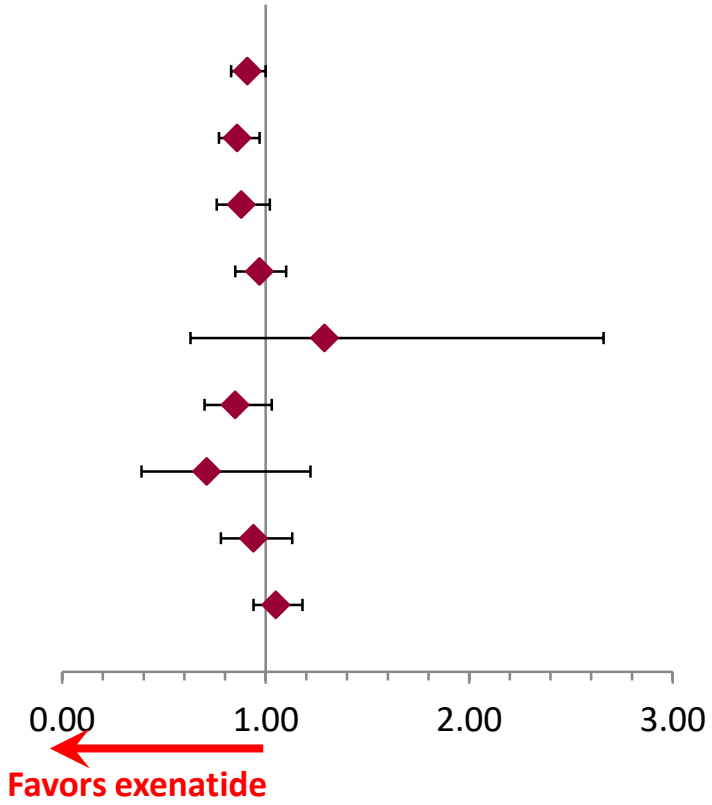
(EXENATIDE STUDY OF CARDIOVASCULAR EVENT LOWERING

Clinical Outcomes with Exenatide

EXSCEL

(N=14,752)

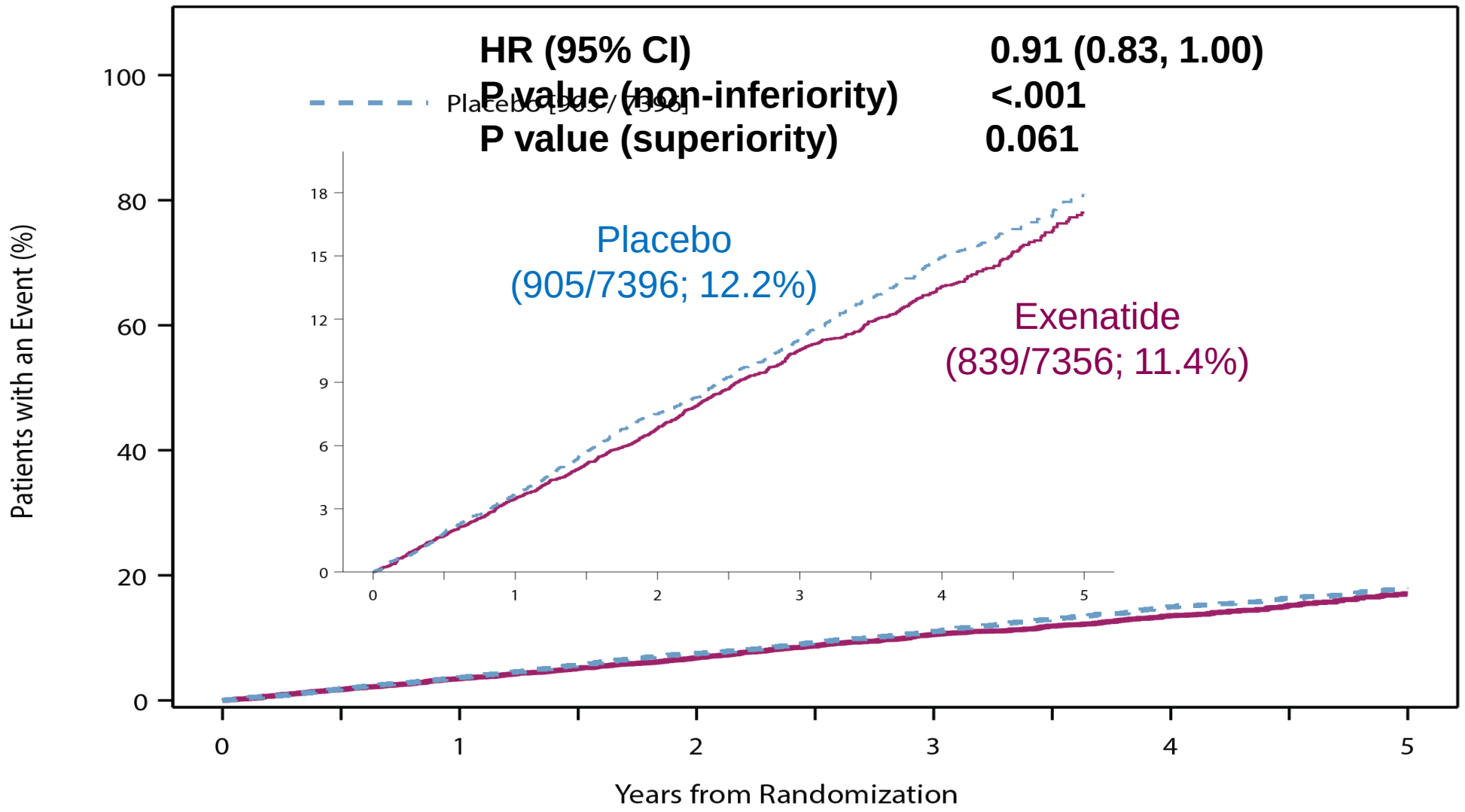
Median follow-up: 3.2 years



	Hazard ratio (95% CI)	*P* value†
Primary composite endpoint*	0.91 (0.83-1.00)	0.06
Death from any cause	0.86 (0.77-0.97)	NS
CV death	0.88 (0.76-1.02)	
Fatal or nonfatal MI	0.97 (0.85-1.10)	
Fatal MI	1.29 (0.63-2.66)	
Fatal or nonfatal stroke	0.85 (0.70-1.03)	
Fatal stroke	0.71 (0.39-1.30)	
Hospitalization for HF	0.94 (0.78-1.13)	
Hospitalization for ACS	1.05 (0.94-1.18)	

Holman RR, et al. *N Engl J Med*. 2017 Sept 14 [Epub before print].

Primary Endpoint: CV Death, Non-fatal MI and Non-fatal stroke (MACE)



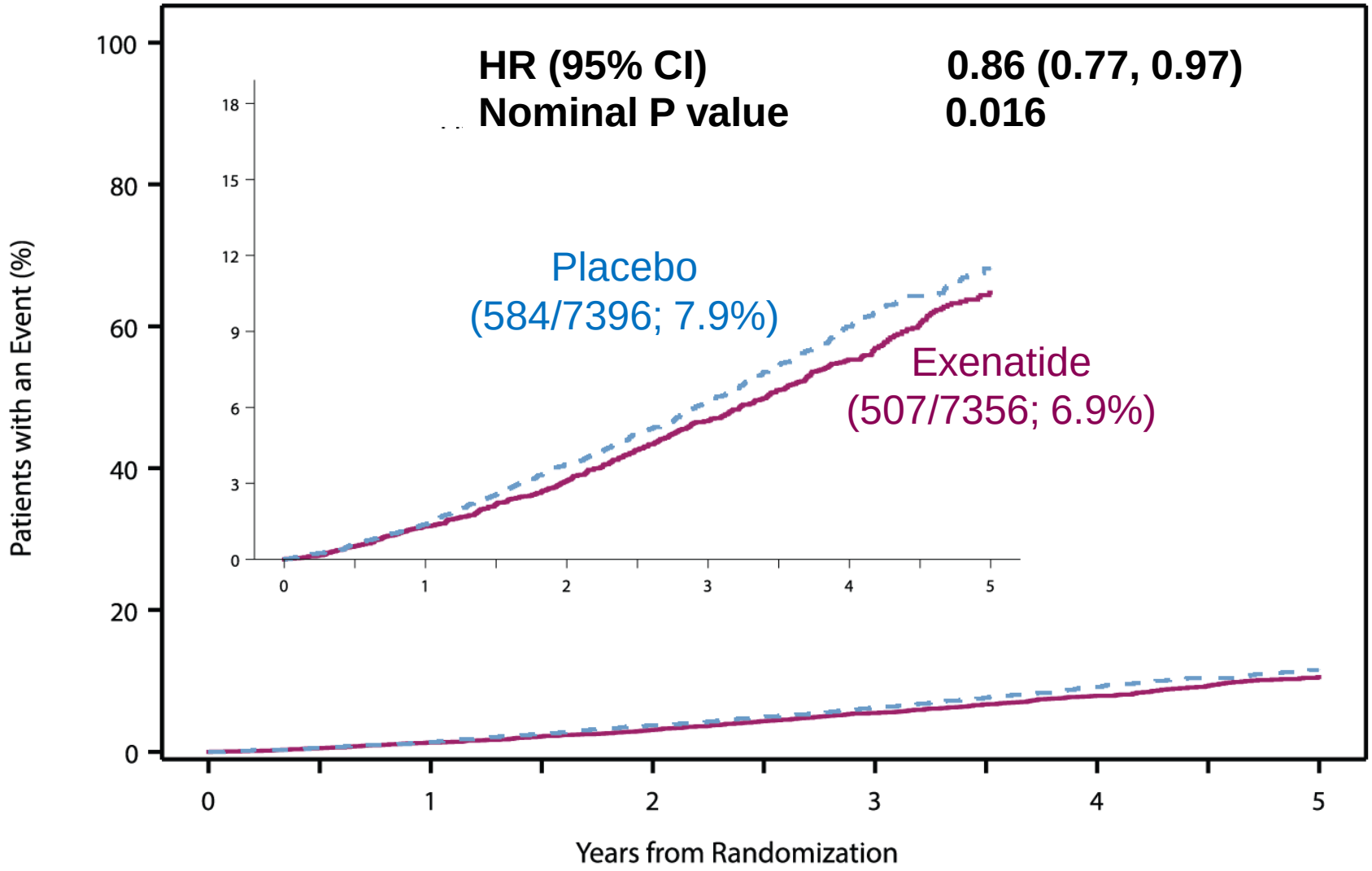
Median Follow-up= 3.2 yr (2.2-4.4)

No at Risk											
Exenatide	7356	7101	6893	6580	5912	4475	3595	3053	2281	1417	727
Placebo	7396	7120	6897	6565	5908	4468	3565	2961	2209	1366	687

Holman RR, *et al*. *NEJM* 2017;377(13):1228-1239.

EXSCEL

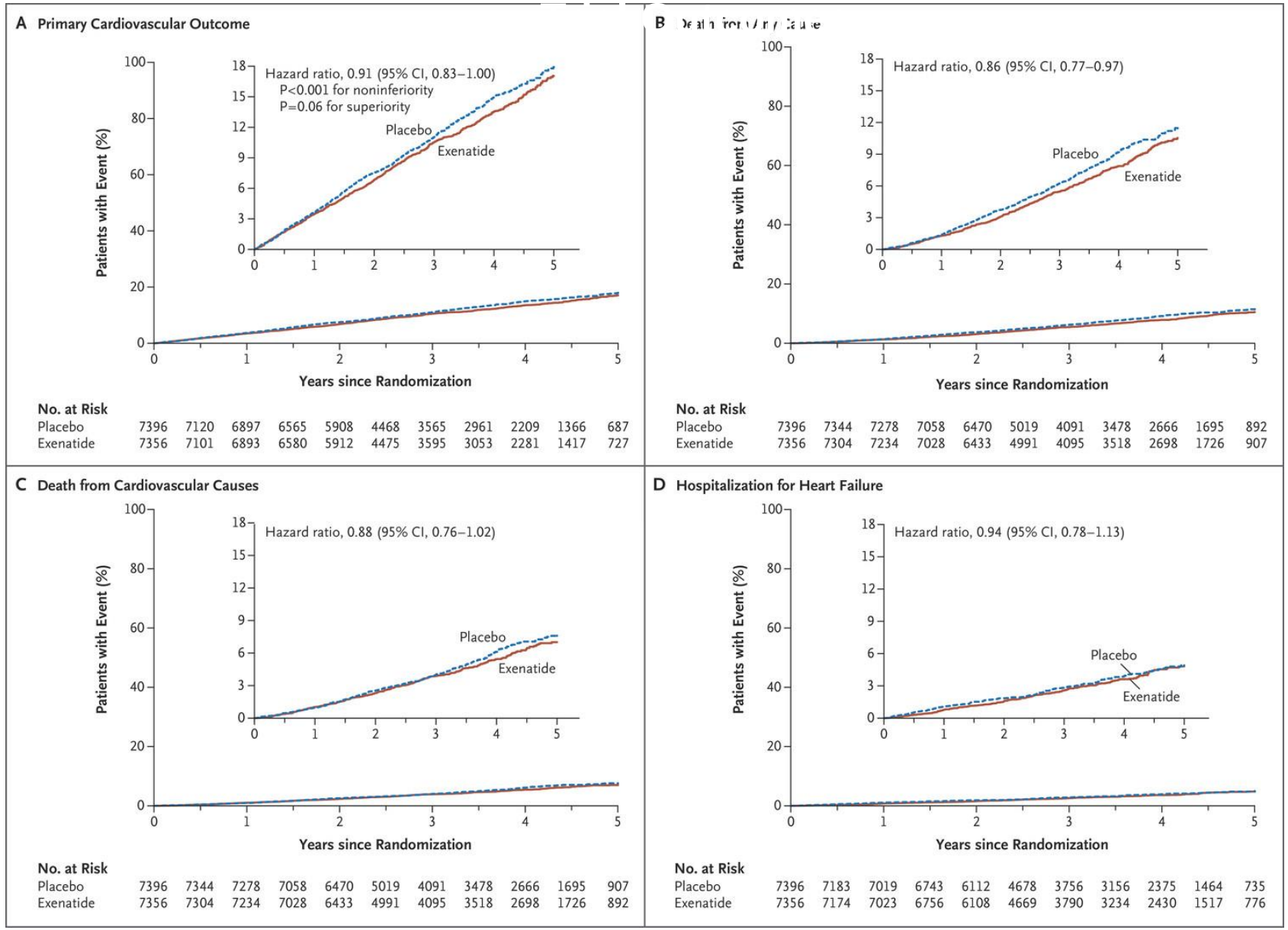
All-Cause Mortality



No at Risk											
Exenatide	7356	7304	7234	7028	6433	4991	4095	3518	2698	1726	907
Placebo	7396	7344	7278	7058	6470	5019	4091	3478	2666	1695	892

Holman RR, *et al*. *NEJM* 2017;377(13):1228-1239.

EXSCEL



Holman RR et al. N Engl J Med 2017;377:1228-1239.

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SUSTAIN™

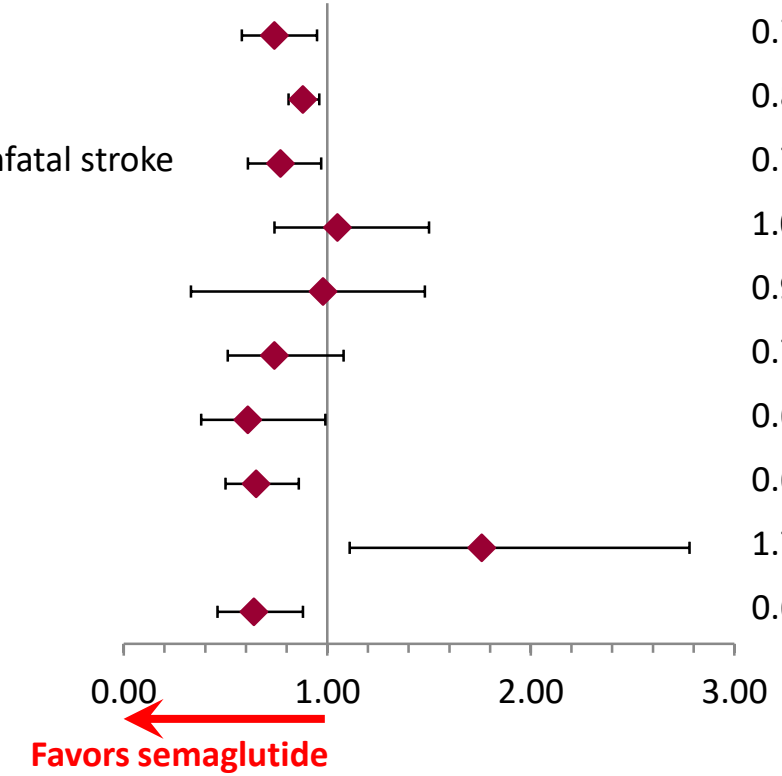
SEMAGLUTIDE UNABATED SUSTAINABILITY IN TREATMENT OF TYPE 2 DIABETES

(SEMAGLUTIDE AND CARDIOVASCULAR OUTCOMES IN PATIENTS WITH TYPE 2 DIABETES)

Clinical Outcomes with Semaglutide

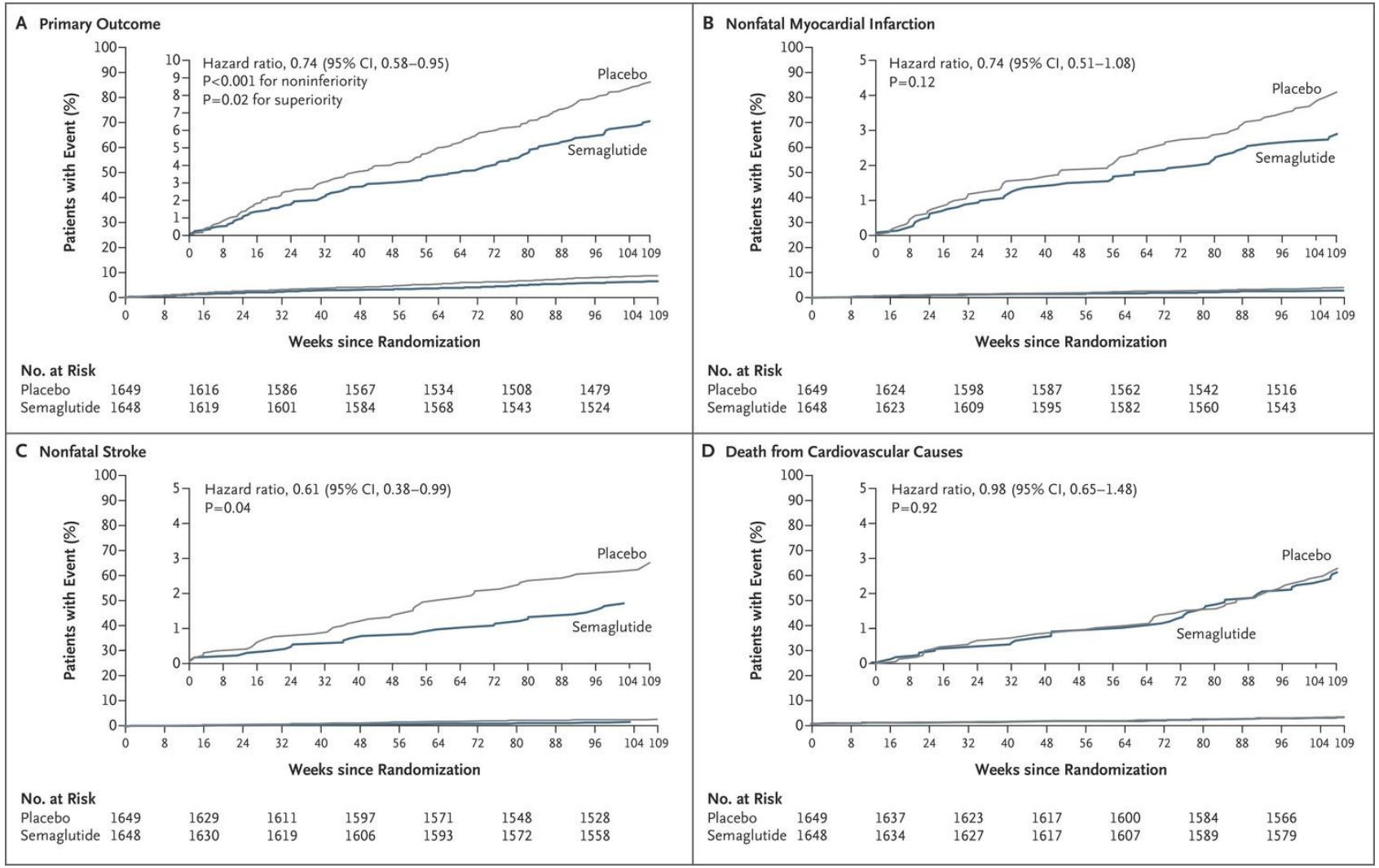
SUSTAIN 6 Results
(N=3297)

Median follow-up: 2.1 years



	Hazard ratio (95% CI)	*P* value
Primary composite endpoint*	0.74 (0.58-0.95)	0.02
Expanded composite endpoint†	0.88 (0.81-0.96)	0.002
All-cause death, nonfatal MI, nonfatal stroke	0.77 (0.61-0.97)	0.03
Death from any cause	1.05 (0.74-1.50)	0.79
CV death	0.98 (0.65-1.48)	0.92
Nonfatal MI	0.74 (0.51-1.08)	0.12
Nonfatal stroke	0.61 (0.38-0.99)	0.04
Revascularization	0.65 (0.50-0.86)	0.003
Retinopathy complications	1.76 (1.11-2.78)	0.02
New or worsening nephropathy	0.64 (0.46-0.88)	0.005

Marso SP, et al. *N Engl J Med*. 2016:375:1834-1844.

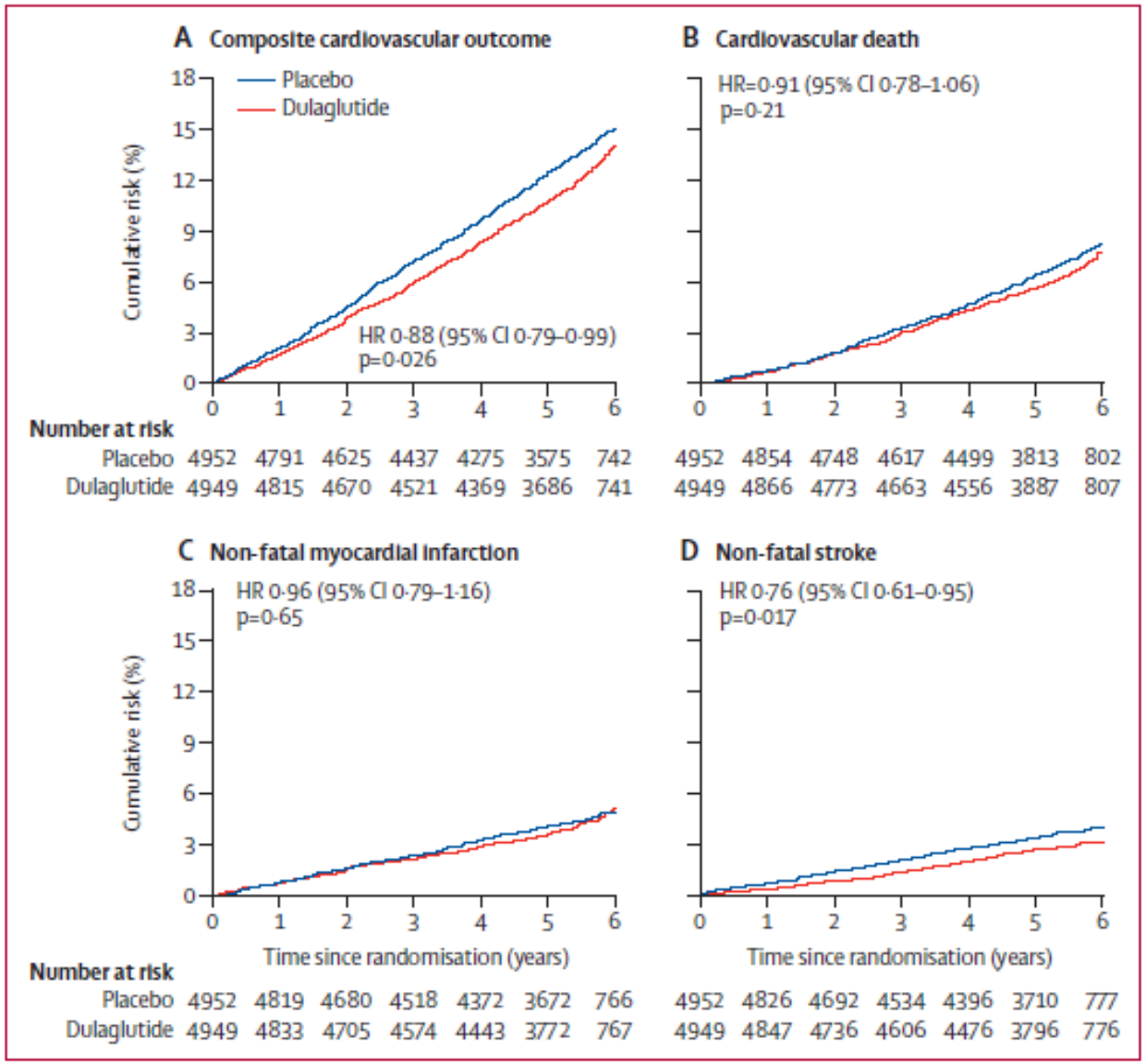


Marso SP et al. N Engl J Med 2016;375:1834-1844

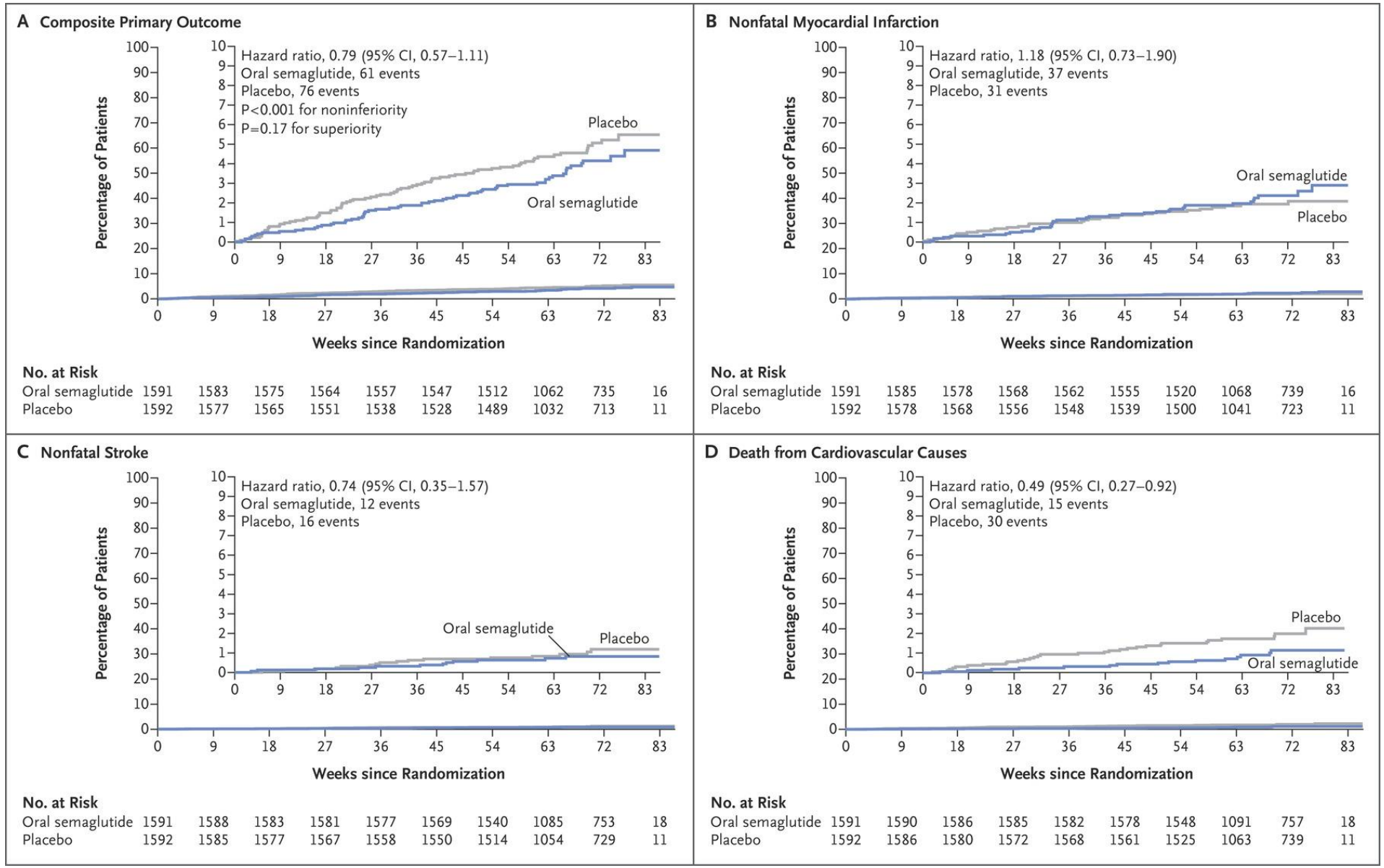
REWIND

Dulaglutide CV Outcomes Trial

(DULAGLUTIDE AND CARDIOVASCULAR OUTCOMES IN TYPE 2 DIABETES)


A Composite cardiovascular outcome
Placebo
Dulaglutide
Cumulative risk (%)
HR 0·88 (95% CI 0·79–0·99)
p=0·026
B Cardiovascular death
HR=0·91 (95% CI 0·78–1·06)
p=0·21
Number at risk
Placebo 4952 4791 4625 4437 4275 3575 742 4952 4854 4748 4617 4499 3813 802
Dulaglutide 4949 4815 4670 4521 4369 3686 741 4949 4866 4773 4663 4556 3887 807
C Non-fatal myocardial infarction
HR 0·96 (95% CI 0·79–1·16)
p=0·65
D Non-fatal stroke
HR 0·76 (95% CI 0·61–0·95)
p=0·017
Time since randomisation (years)
Number at risk
Placebo 4952 4819 4680 4518 4372 3672 766 4952 4826 4692 4534 4396 3710 777
Dulaglutide 4949 4833 4705 4574 4443 3772 767 4949 4847 4736 4606 4476 3796 776

(ORAL SEMAGLUTIDE AND CARDIOVASCULAR OUTCOMES IN PATIENTS WITH TYPE 2 DIABETES)


A Composite Primary Outcome
Hazard ratio, 0.79 (95% CI, 0.57–1.11)
Oral semaglutide, 61 events
Placebo, 76 events
P<0.001 for noninferiority
P=0.17 for superiority
Placebo
Oral semaglutide
Percentage of Patients
Weeks since Randomization
No. at Risk
Oral semaglutide 1591 1583 1575 1564 1557 1547 1512 1062 735 16
Placebo 1592 1577 1565 1551 1538 1528 1489 1032 713 11
B Nonfatal Myocardial Infarction
Hazard ratio, 1.18 (95% CI, 0.73–1.90)
Oral semaglutide, 37 events
Placebo, 31 events
Oral semaglutide
Placebo
Percentage of Patients
Weeks since Randomization
No. at Risk
Oral semaglutide 1591 1585 1578 1568 1562 1555 1520 1068 739 16
Placebo 1592 1578 1568 1556 1548 1539 1500 1041 723 11
C Nonfatal Stroke
Hazard ratio, 0.74 (95% CI, 0.35–1.57)
Oral semaglutide, 12 events
Placebo, 16 events
Oral semaglutide
Placebo
Percentage of Patients
Weeks since Randomization
No. at Risk
Oral semaglutide 1591 1588 1583 1581 1577 1569 1540 1085 753 18
Placebo 1592 1585 1577 1567 1558 1550 1514 1054 729 11
D Death from Cardiovascular Causes
Hazard ratio, 0.49 (95% CI, 0.27–0.92)
Oral semaglutide, 15 events
Placebo, 30 events
Placebo
Oral semaglutide
Percentage of Patients
Weeks since Randomization
No. at Risk
Oral semaglutide 1591 1590 1586 1585 1582 1578 1548 1091 757 18
Placebo 1592 1586 1580 1572 1568 1561 1525 1063 739 11

DEVOTE

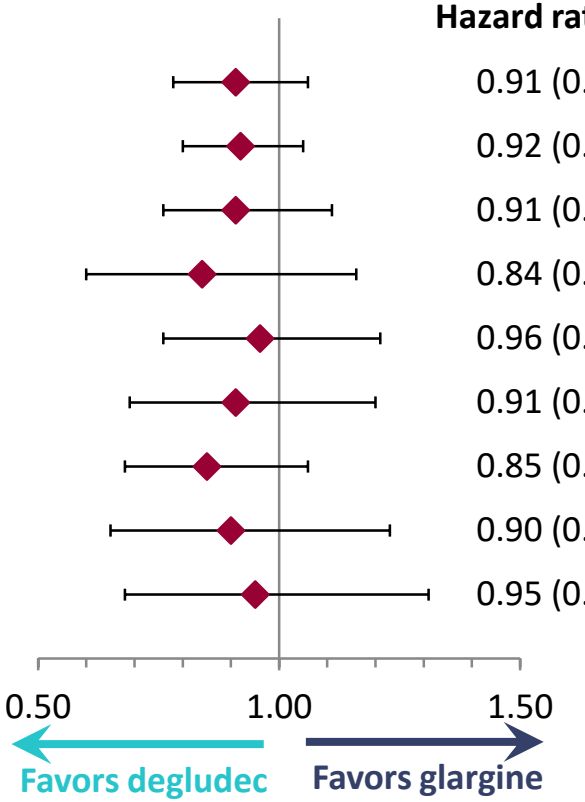
Degludec Cardiovascular Outcomes Trial

Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events

Clinical Outcomes with Insulin Degludec and Glargine

DEVOTE CV Outcomes (N=7637)

Median follow-up: 1.99 years



	Hazard ratio (95% CI)	*P* value
Primary composite endpoint*	0.91 (0.78-1.06)	<0.001 (NI)†
Expanded composite endpoint‡	0.92 (0.80-1.05)	0.22
All-cause death	0.91 (0.76-1.11)	0.35
Noncardiovascular death	0.84 (0.60-1.16)	0.28
CV death	0.96 (0.76-1.21)	0.71
CV death excluding undetermined cause of death	0.91 (0.69-1.20)	0.52
Nonfatal MI	0.85 (0.68-1.06)	0.15
Nonfatal stroke	0.90 (0.65-1.23)	0.50
Unstable angina hospitalization	0.95 (0.68-1.31)	0.74

Marso SP, et al. *N Engl J Med*. 2017;377:723-732.

Harmony Outcomes

(ALBIGLUTIDE AND CARDIOVASCULAR OUTCOME IN PATIENTS WITH TYPE 2 DIABETES AND CARDIOVASCULAR DISEASE)

Harmony Outcomes: primary and secondary outcomes

Primary outcomes

Non-inferiority for 3P-MACE*

Superiority for 3P-MACE†

If non-inferiority met, superiority can be assessed

Secondary CV outcomes

- 4P-MACE‡
- CV death
- Fatal or non-fatal MI
- Fatal or non-fatal stroke
- CV death or HHF
- Microvascular event composite§

Secondary metabolic outcomes

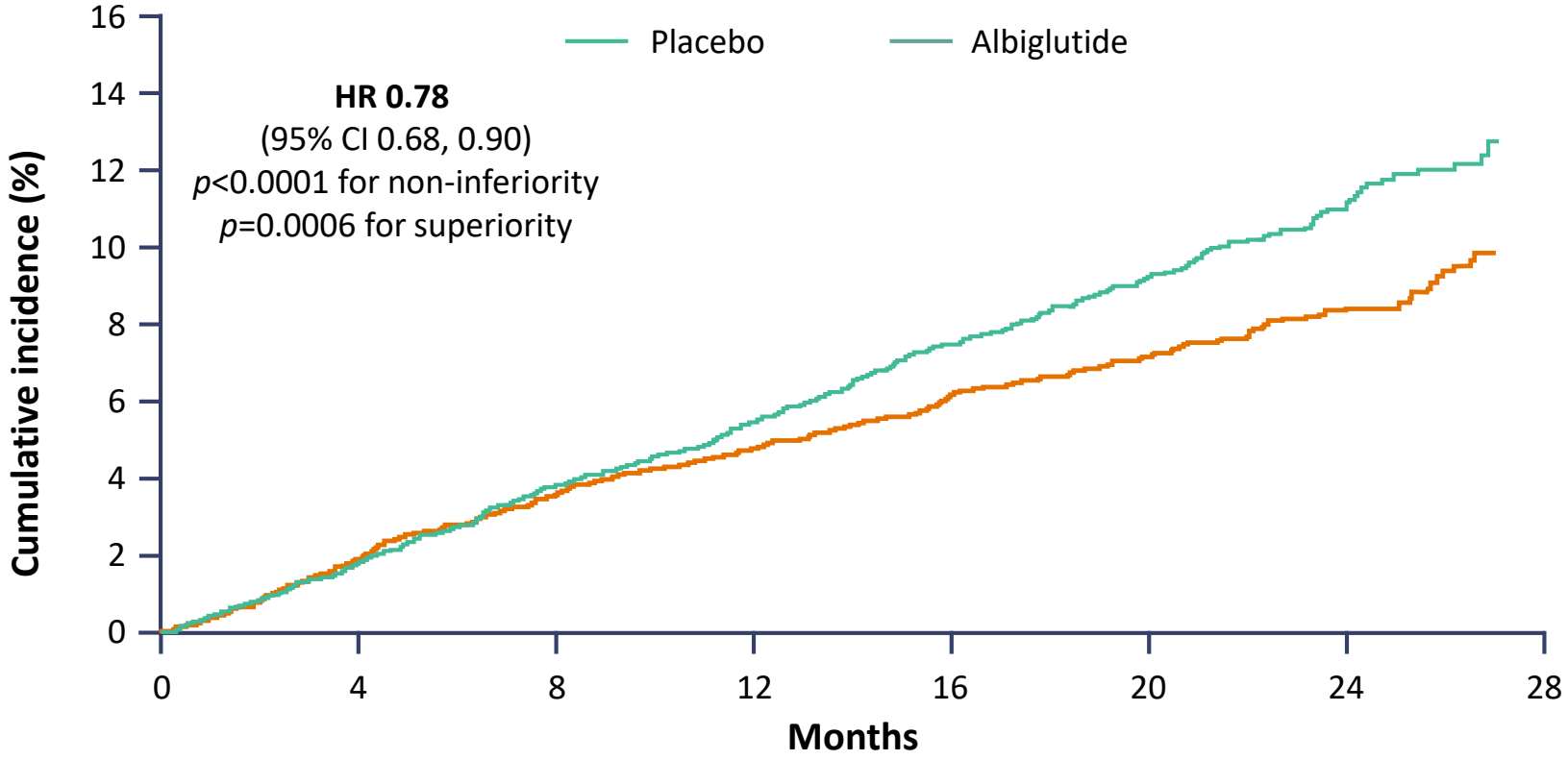
- Time to initiation of chronic insulin therapy
- Change in HbA1c
- Change in body weight
- Metabolic composite outcome:
  - HbA1c ≤7% at final visit
  - Absence of severe hypoglycaemic event
  - Weight gain <5% body weight

GREEN JB *ET AL. AM HEART J* 2018;203:30; HERNANDEZ AF *ET AL. LANCET* 2018;392:1519;

Harmony Outcomes: primary outcome 3P-MACE (time to first occurrence of CV death, MI or stroke)

ACROSS T2D

Albiglutide demonstrated superiority for 3P-MACE



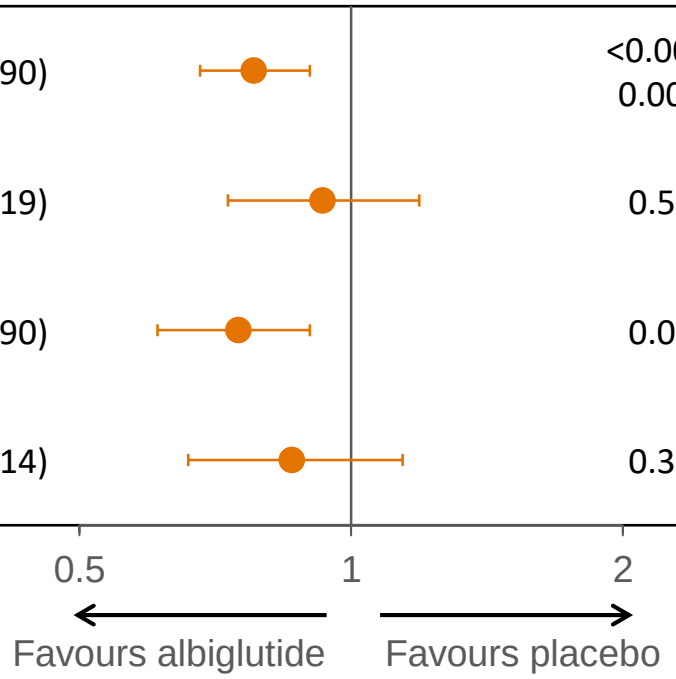
No. at risk								
Placebo	4732	4603	4460	4208	3074	2077	1030	..
Albiglutide	4731	4613	4503	4239	3148	2142	1064	..

HERNANDEZ AF *ET AL. LANCET* 2018;392:1519

Harmony Outcomes: components of 3P-MACE

The effect of albiglutide on 3P-MACE was driven by a 25% relative risk reduction in fatal or non-fatal MI

	Albiglutide		Placebo			
	n with event/ N analysed (%)	Rate/ 100 PY	n with event/ N analysed (%)	Rate/ 100 PY	HR (95% CI)	*p*-value
3P-MACE	338/4731 (7)	4.57	428/4732 (9)	5.87	0.78 (0.68, 0.90)	<0.0001* 0.0006†
CV death	122/4731 (3)	1.61	130/4732 (3)	1.72	0.93 (0.73, 1.19)	0.578‡
Fatal or non-fatal MI	181/4731 (4)	2.43	240/4732 (5)	3.26	0.75 (0.61, 0.90)	0.003‡
Fatal or non-fatal stroke	94/4731 (2)	1.25	108/4732 (2)	1.45	0.86 (0.66, 1.14)	0.300‡

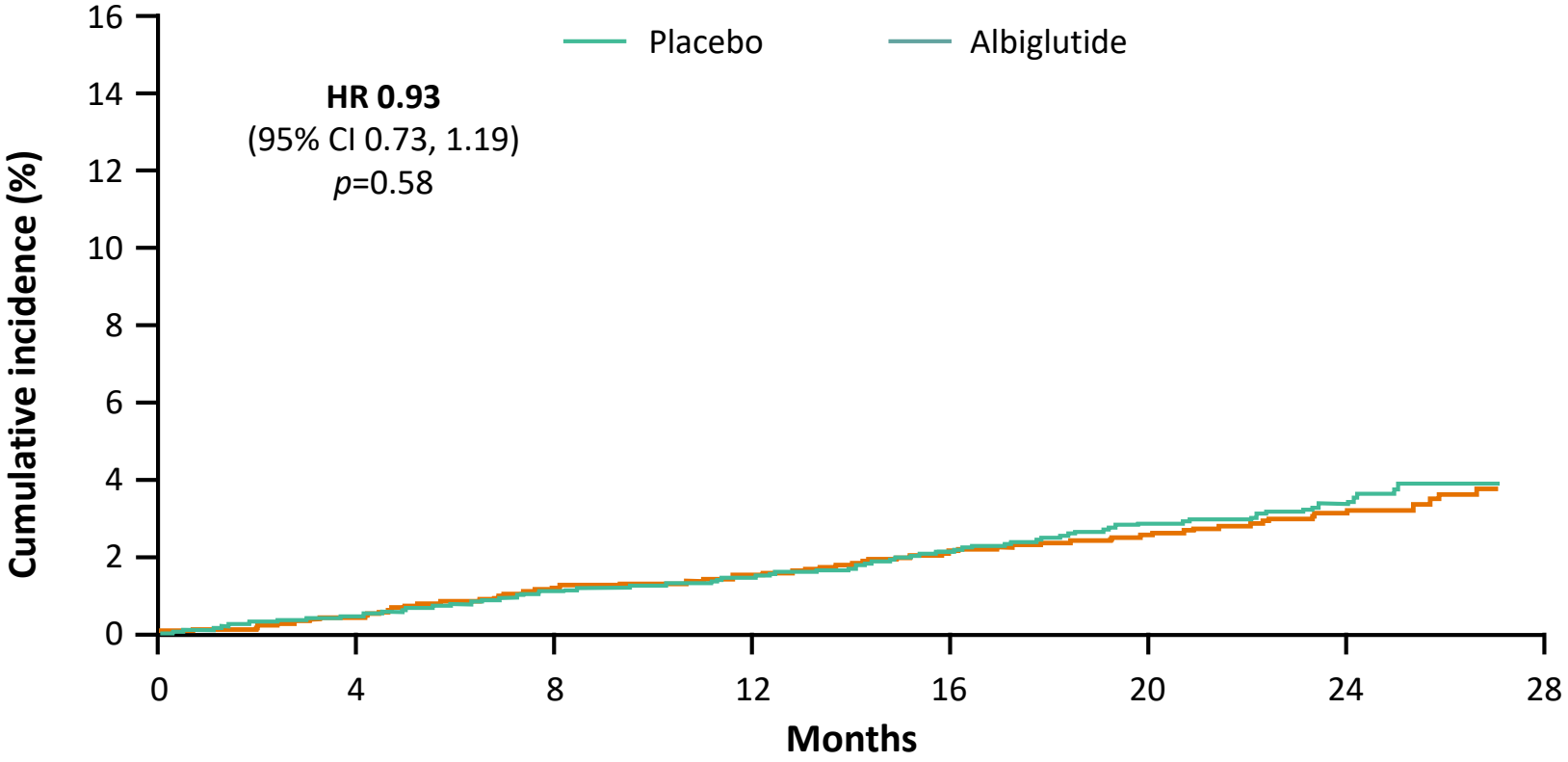


HERNANDEZ AF *ET AL. LANCET* 2018;392:1519

Harmony Outcomes: CV death

ACROSS T2D

Albiglutide had no significant effect on CV death

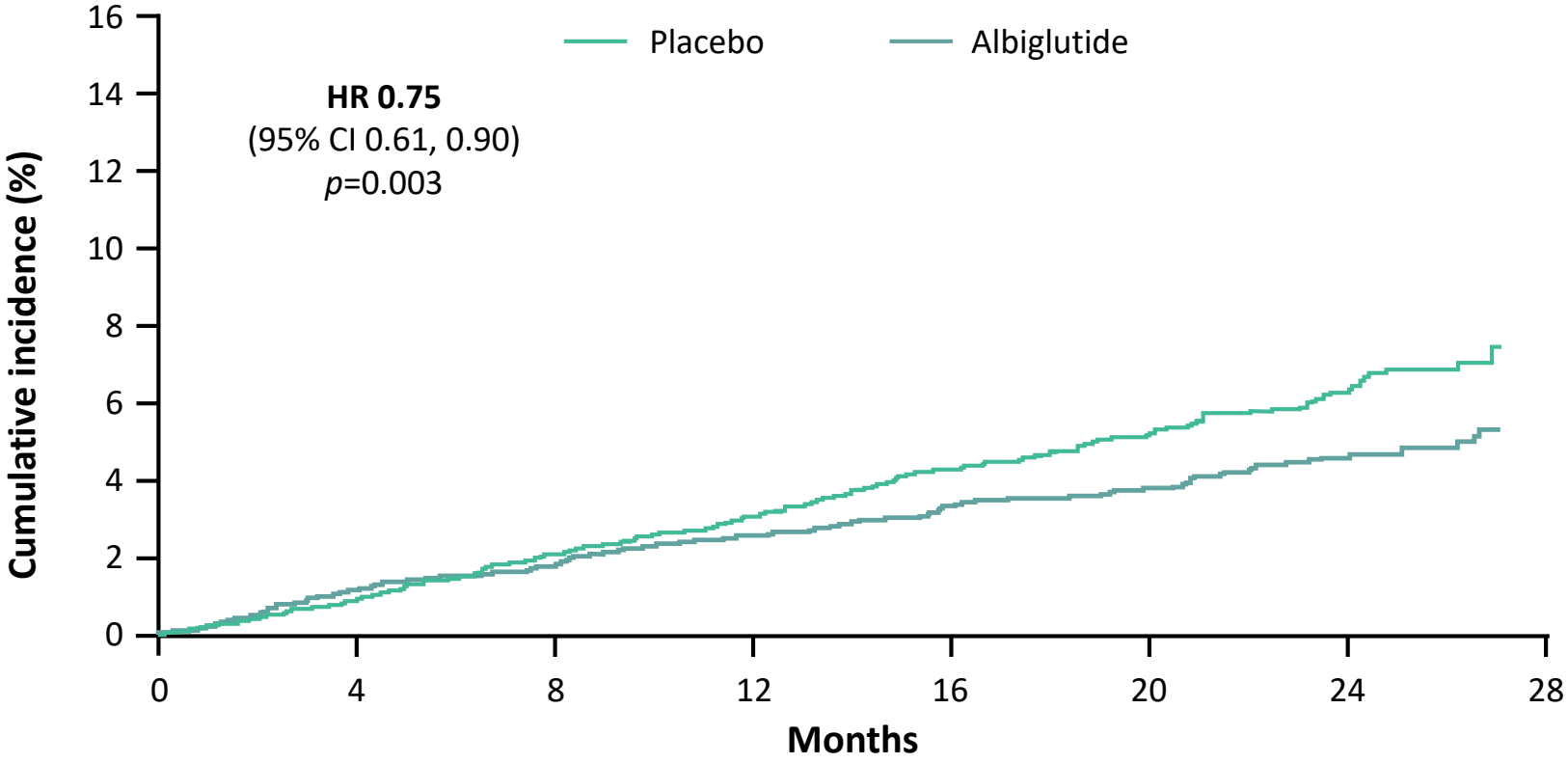


Hernandez AF *et al. Lancet* 2018;392:1519

Harmony Outcomes: MI

ACROSS T2D

Albiglutide demonstrated a 25% relative risk reduction in fatal or non-fatal MI

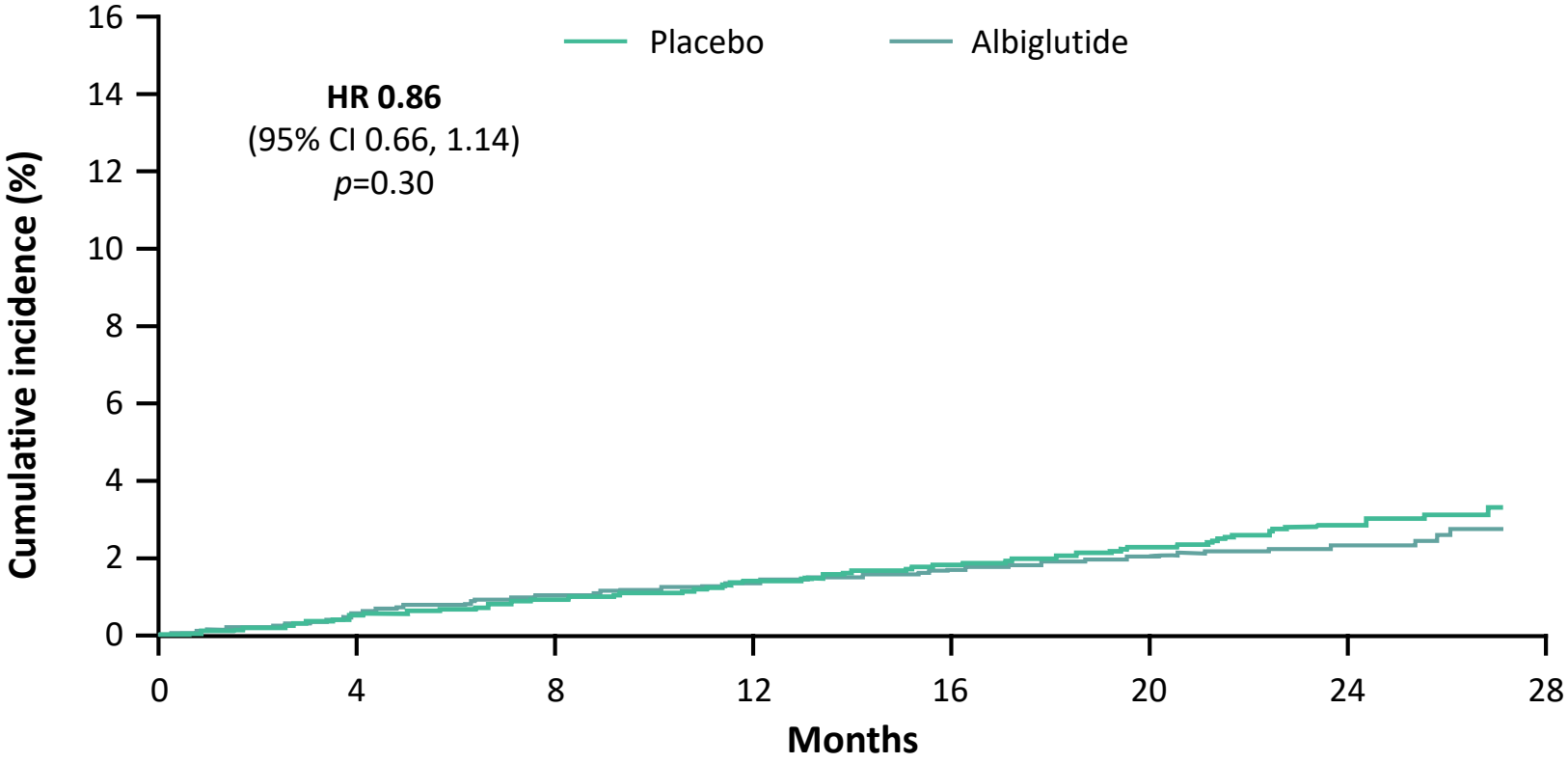


No. at risk								
Placebo	4732	4624	4496	4262	3124	2122	1056	..
Albiglutide	4731	4635	4543	4286	3184	2167	1080	..

Hernandez AF *et al. Lancet* 2018;392:1519

Harmony Outcomes: stroke

Albiglutide had no significant effect on fatal or non-fatal stroke

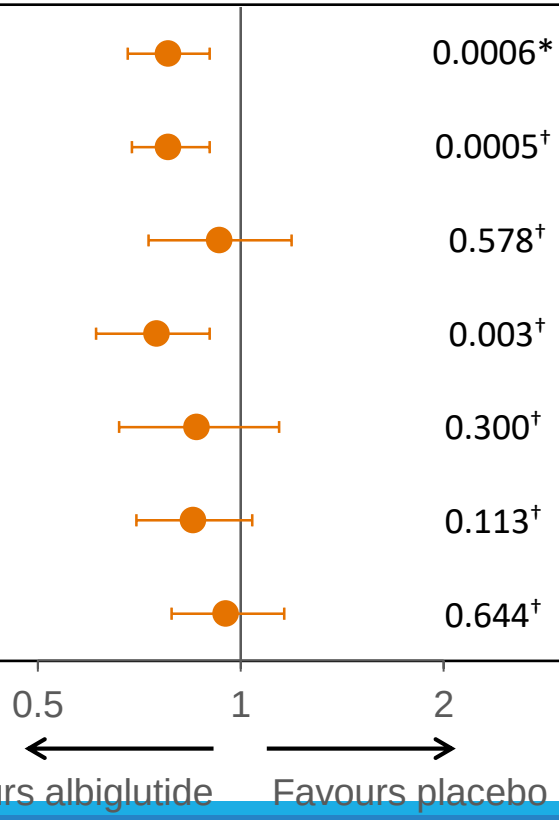


No. at risk								
Placebo	4732	4640	4543	4318	3194	2178	1093	..
Albiglutide	4731	4658	4570	4328	3233	2205	1103	..

Hernandez AF *et al. Lancet* 2018;392:1519

Harmony Outcomes: CV outcomes

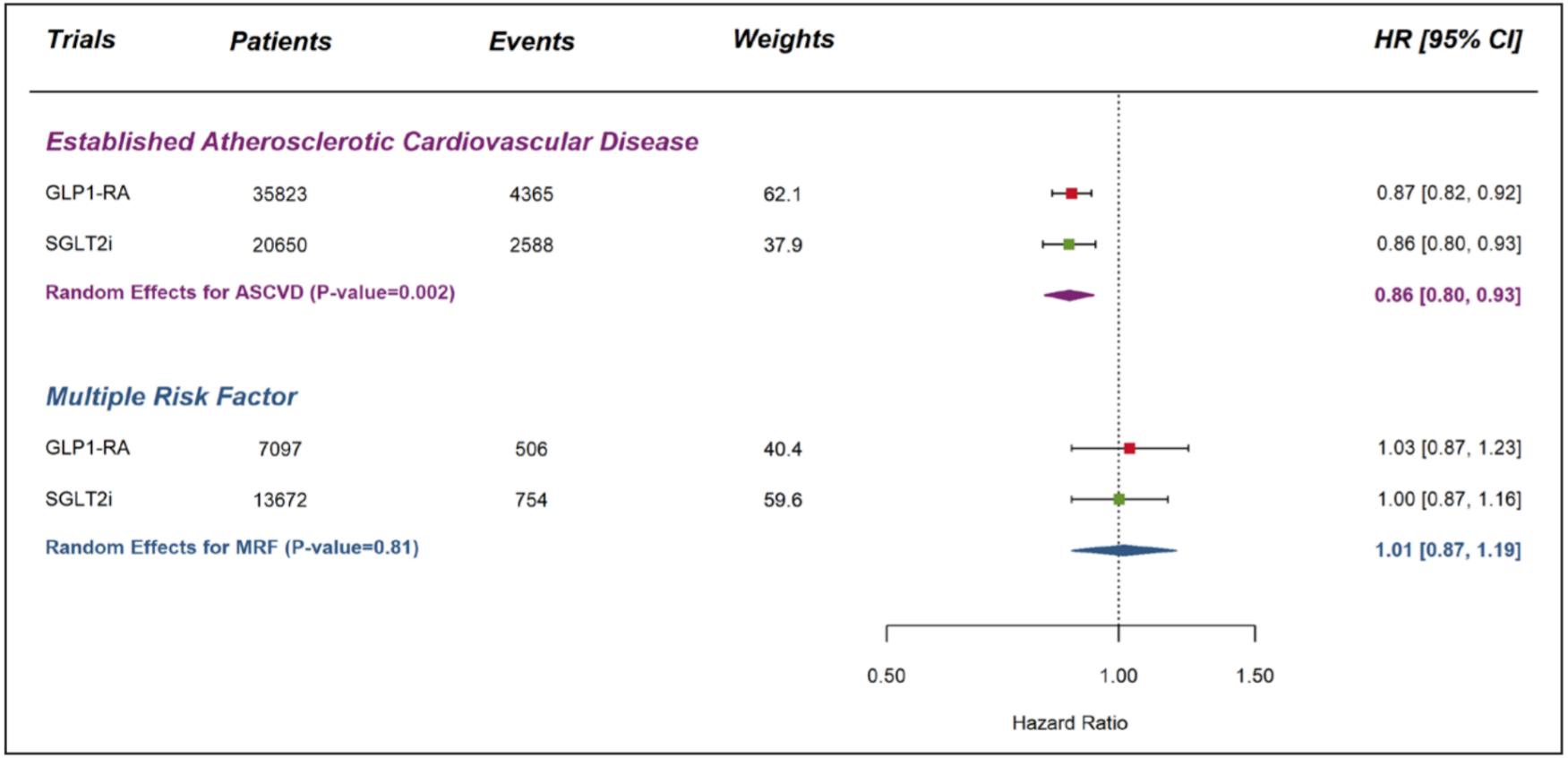
	Albiglutide		Placebo			
	n with event/ N analysed (%)	Rate/ 100 PY	n with event/ N analysed (%)	Rate/ 100 PY	HR (95% CI)	*p*-value
3P-MACE	338/4731 (7)	4.57	428/4732 (9)	5.87	0.78 (0.68, 0.90)	0.0006*
4P-MACE	373/4731 (8)	5.06	468/4732 (10)	6.45	0.78 (0.69, 0.90)	0.0005†
CV death	122/4731 (3)	1.61	130/4732 (3)	1.72	0.93 (0.73, 1.19)	0.578†
Fatal or non-fatal MI	181/4731 (4)	2.43	240/4732 (5)	3.26	0.75 (0.61, 0.90)	0.003†
Fatal or non-fatal stroke	94/4731 (2)	1.25	108/4732 (2)	1.45	0.86 (0.66, 1.14)	0.300†
CV death or HHF	188/4731 (4)	2.49	218/4732 (5)	2.92	0.85 (0.70, 1.04)	0.113†
All-cause mortality‡	196/4731 (4)	2.44	205/4732 (4)	2.56	0.95 (0.79, 1.16)	0.644†



Hernandez AF *et al. Lancet* 2018;392:1519

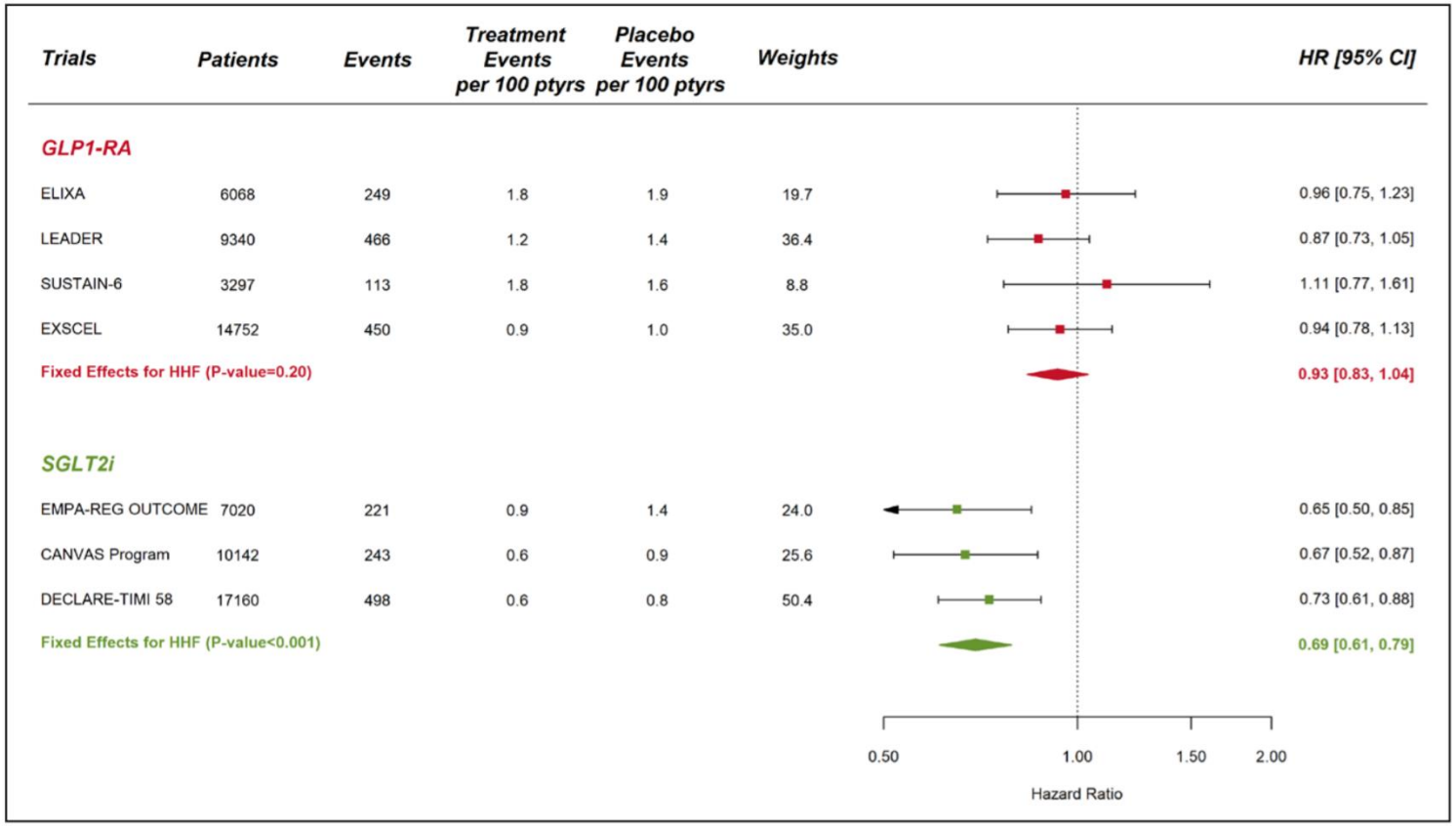

meta-analysis
encyclopedic
argued
statistical
methodologically
inverse
outcome
publication
difference
research
underlying
drawer
smaller
sampling
reported
combinatorial
randomization
sources
include
result
single
variability
error
effect
findings
evidence
medicine
unpublished
technique
methodological

Meta-analysis of GLP1-RA and SGLT2i trials on the composite of myocardial infarction, stroke, and cardiovascular death stratified by the presence of atherosclerotic cardiovascular disease.



ZELNIKER, T. ET AL. CIRCULATION. 2019;139:2022–2031.

Meta-analysis of GLP1-RA and SGLT2i trials on hospitalization for heart failure stratified by drug class.



ZELNIKER, T. ET AL. CIRCULATION. 2019;139:2022–2031.

GLP-1RA CVOTs with the best confidence for superiority and worst confidence for inferiority (excluding ELIXA) by MACE, MACE components and all-cause death

	Best upper CI[a]		Worst upper CI[b]	
Variable	Study	HR (95% CI)	Study	HR (95% CI)
MACE[c]	Harmony	0.78 (0.68, 0.90)	EXSCEL	0.91 (0.83, 1.00)
MI[d]	Harmony	0.75 (0.61, 0.90)	EXSCEL	0.97 (0.85, 1.10)
Stroke[d]	SUSTAIN-6	0.61 (0.38, 0.99)	Harmony	0.86 (0.66, 1.14)
CV death	LEADER	0.78 (0.66, 0.93)	SUSTAIN-6	0.98 (0.65, 1.48)
All death	LEADER	0.85 (0.74, 0.97)	SUSTAIN-6	1.05 (0.74, 1.50)
	EXSCEL	0.86 (0.77, 0.97)		

The chosen criteria will be affected by study power and play of chance, as well as underlying medication efficacy

[a] Lowest upper 95% CI

[b] Highest upper 95% CI

[c] MACE: CV death, MI, stroke

[d] Fatal and non-fatal

Source: Harmony [17]; SUSTAIN-6 [15]; LEADER [14]; EXSCEL [33]

HOME, P. DIABETOLOGIA. JAN 2019.

Table 2 HR and 95% CI for CV and kidney endpoints and all death for DPP4 inhibitor, GLP-1RA and SGLT2 inhibitor studies (excludes post-ACS studies)

Study	Medication	MACE[a]	MACE+[a]	MI[b]	Stroke[b]	CV death	Heart failure	All death	Kidney endpoint[c]	Reference
DPP4 inhibitor studies										
SAVOR	Saxagliptin	1.00 (0.89, 1.12)	1.02 (0.94, 1.11)	0.95 (0.80, 1.12)	1.11 (0.88, 1.39)	1.03 (0.87, 1.22)	1.27 (1.07, 1.51)	1.11 (0.96, 1.27)	1.08 (0.96, 1.22)	[12]
TECOS	Sitagliptin	0.99 (0.89, 1.10)	0.98 (0.88, 1.09)	0.95 (0.81, 1.11)	0.97 (0.79, 1.19)	1.03 (0.89, 1.19)	1.00 (0.83, 1.20)	1.01 (0.90, 1.14)	NG	[10]
CARMELINA	Linagliptin	1.02 (0.89, 1.17)	1.00 (0.88, 1.13)	1.12 (0.90, 1.40)	0.91 (0.67, 1.23)	0.96 (0.81, 1.14)	0.90 (0.74, 1.08)	0.98 (0.84, 1.13)	1.04 (0.89, 1.22)	[18]
GLP-1RA studies										
LEADER	Liraglutide	0.87 (0.78, 0.97)	NG	0.88 (0.75, 1.03)	0.89 (0.72, 1.11)	0.78 (0.66, 0.93)	0.87 (0.73, 1.05)	0.85 (0.74, 0.97)	NG	[14]
SUSTAIN-6	Semaglutide (s.c.)	0.74 (0.58, 0.95)	NG	0.74 (0.51, 1.08)	0.61 (0.38, 0.99)	0.98 (0.65, 1.48)	1.11 (0.77, 1.61)	1.05 (0.74, 1.50)	NG	[15]
EXSCEL	Exenatide (MR)	0.91 (0.83, 1.00)	NG	0.97 (0.85, 1.10)	0.85 (0.70, 1.03)	0.88 (0.76, 1.02)	0.94 (0.78, 1.13)	0.86 (0.77, 0.97)	NG	[33]
Harmony	Albiglutide	0.78 (0.68, 0.90)	0.78 (0.69, 0.90)	0.75 (0.61, 0.90)	0.86 (0.66, 1.14)	0.93 (0.73, 1.19)	NG	0.95 (0.79, 1.16)	NG	[17]
SGLT2 inhibitor studies										
EMPA-REG OUTCOME	Empagliflozin	0.86 (0.74, 0.99)	0.89 (0.78, 1.01)	0.87 (0.70, 1.09)	1.18 (0.89, 1.56)	0.62 (0.49, 0.77)	0.65 (0.50, 0.85)	0.68 (0.57, 0.82)	0.54 (0.40, 0.75)	[13]
CANVAS Program[d]	Canagliflozin	0.86 (0.75, 0.97)	NG	0.85 (0.69, 1.05)	0.90 (0.71, 1.15)	0.90 (0.71, 1.15)	0.67 (0.52, 0.87)	0.87 (0.74, 1.01)	0.60 (0.47, 0.77)	[16]
DECLARE	Dapagliflozin	0.93 (0.84, 1.03)	NG	0.89 (0.77, 1.01)	1.01 (0.84, 1.21)	0.98 (0.82, 1.17)	0.73 (0.61, 0.88)	0.93 (0.82, 1.04)	0.53 (0.43, 0.66)	[19]

HR findings are derived from intention-to-treat analyses

[a] MACE: CV death, MI, stroke; MACE+: CV death, MI, stroke, acute coronary event

[b] Fatal and non-fatal

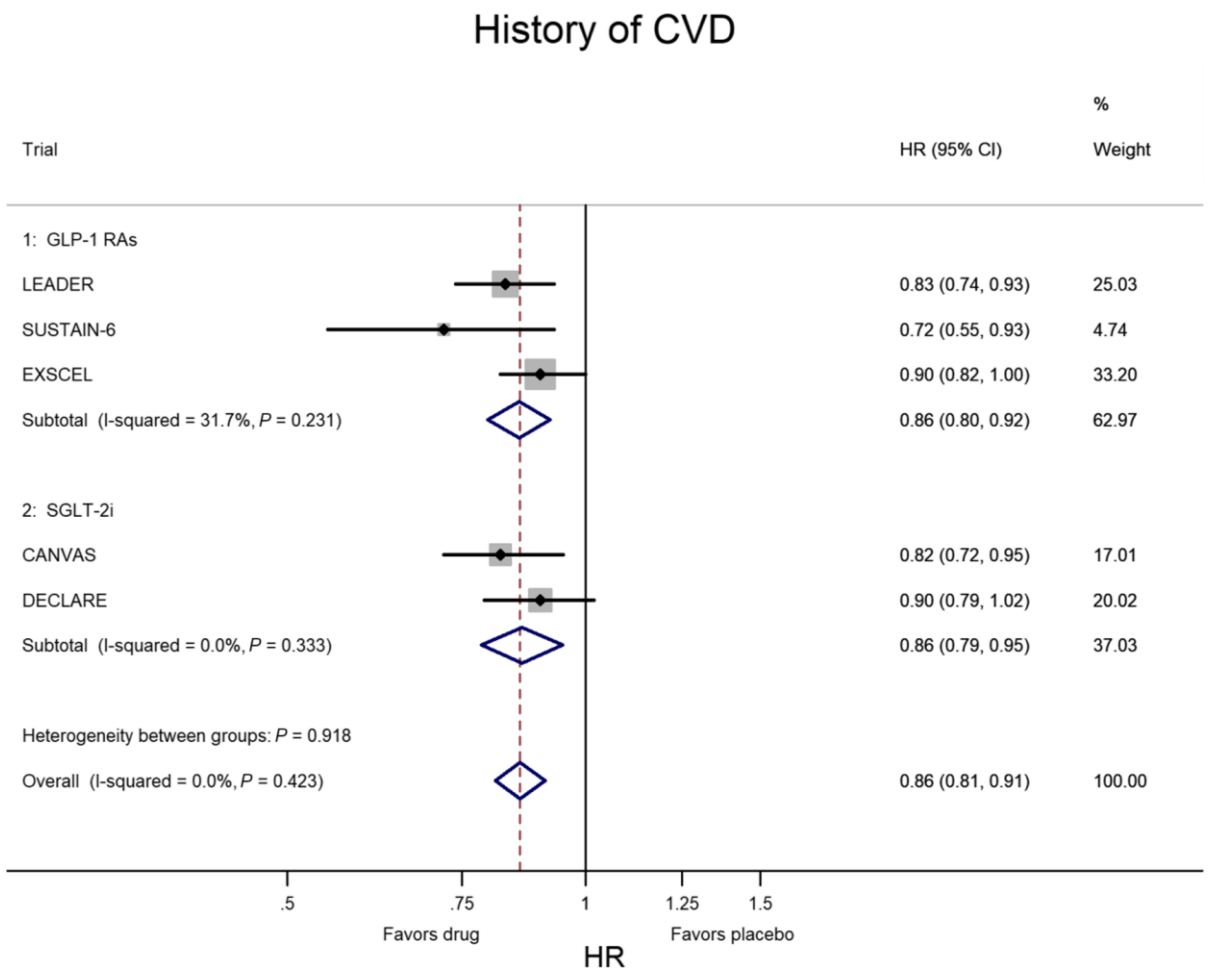
[c] Composite of variables, not including albuminuria

[d] Composed of two studies

MR, modified release (long-acting); NG, not given

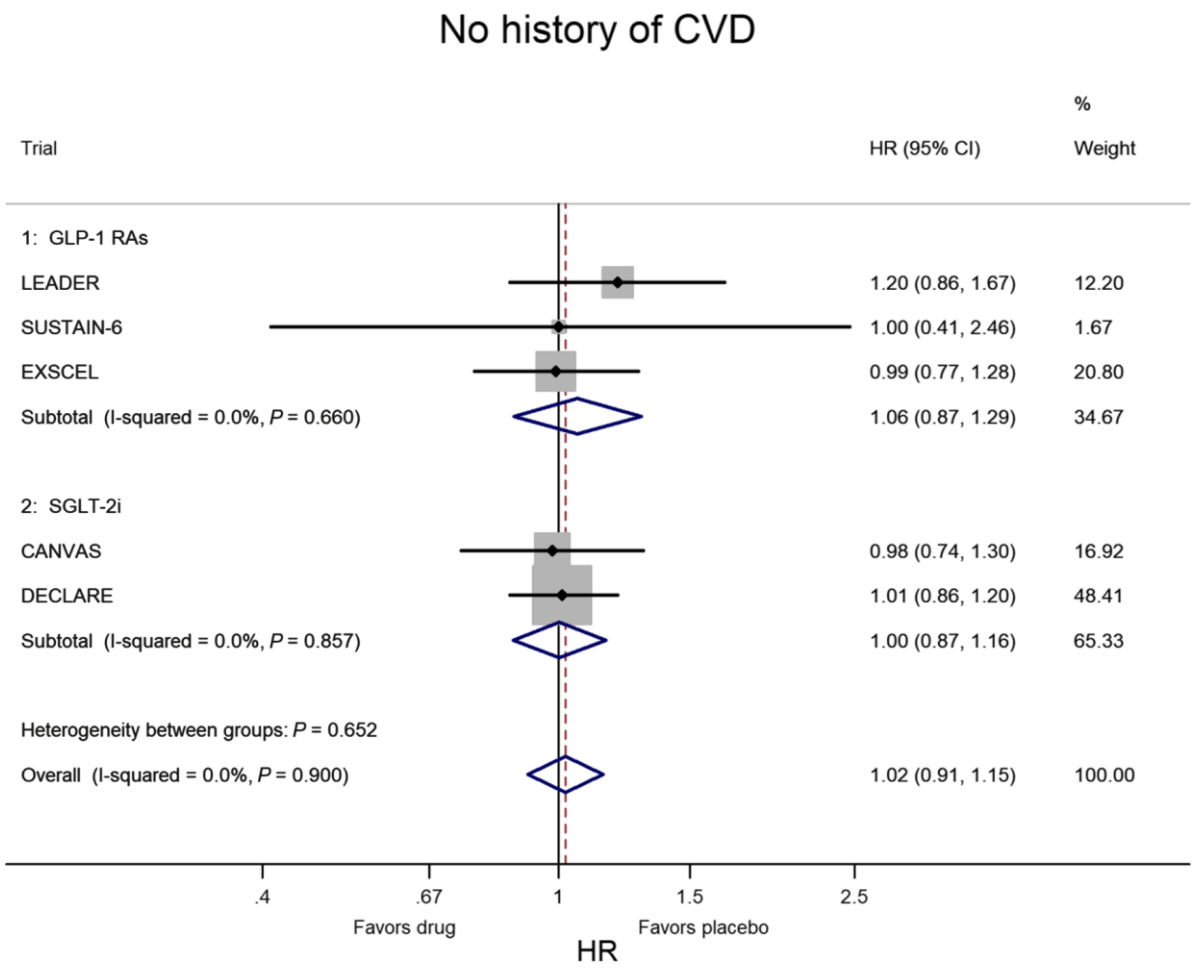
HOME, P. DIABETOLOGIA. JAN 2019.

Glycemic Control, Preexisting Cardiovascular Disease, and Risk of Major Cardiovascular Events in Patients with Type 2 Diabetes Mellitus: Systematic Review With Meta-Analysis of Cardiovascular Outcome Trials and Intensive Glucose Control Trials

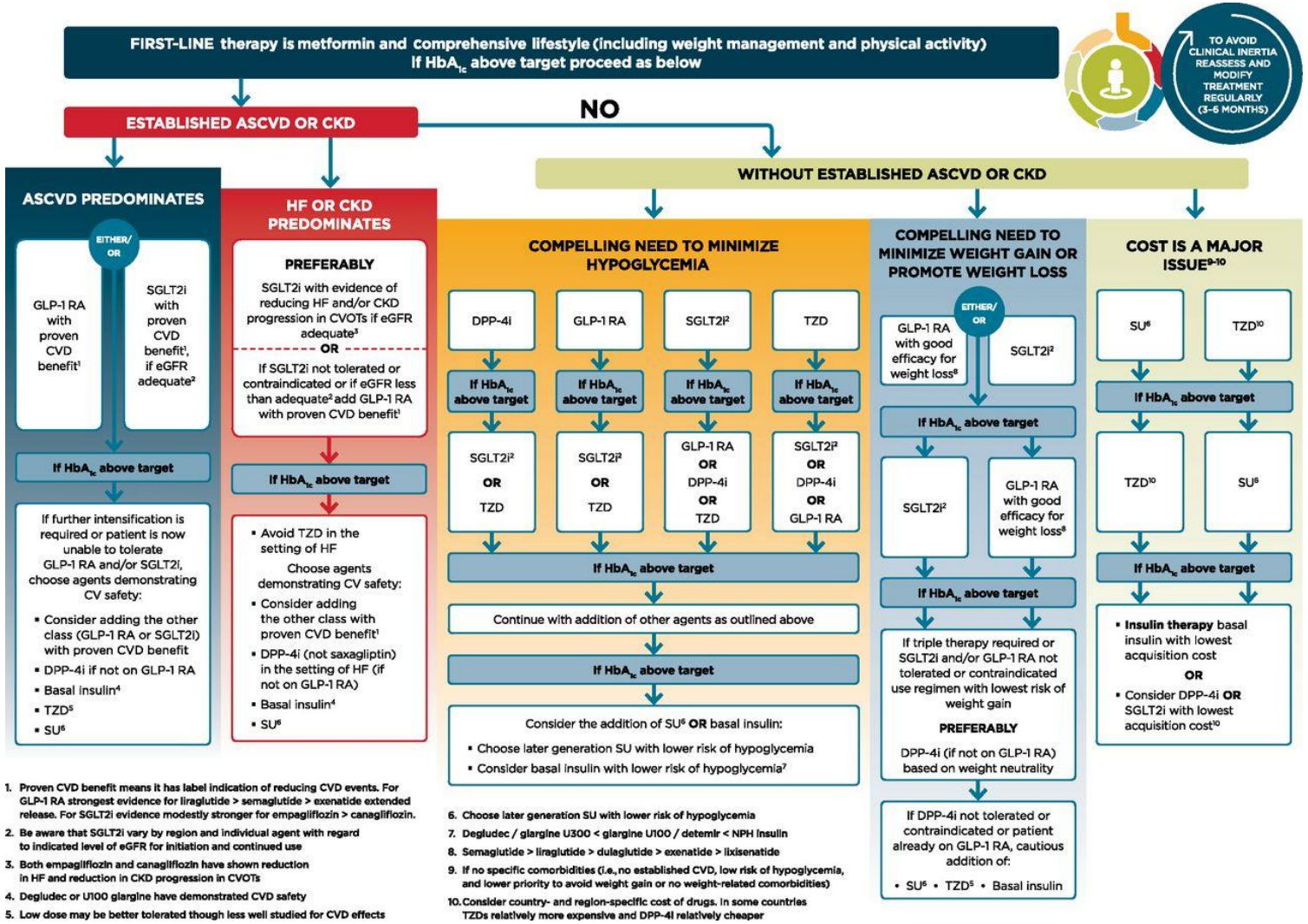


Giuliano D. Journal of the American Heart Association. 2019.

Glycemic Control, Preexisting Cardiovascular Disease, and Risk of Major Cardiovascular Events in Patients with Type 2 Diabetes Mellitus: Systematic Review With Meta-Analysis of Cardiovascular Outcome Trials and Intensive Glucose Control Trials



Giuliano D. Journal of the American Heart Association. 2019.



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

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