Clinical Outcome Trials and Side Effects of Type 2 Diabetes Agents

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Outline

- Are there adverse safety signals for diabetic agents?
- Define cardiovascular risks for diabetes
- Determine when a CVD outcome trial is to be performed
- Define clinical outcome trials
- Depth of outcome trials
- Significance of the Empa Reg and Leader trials

Defining the risks of overtreatment

- Hypoglycemia
  - ? Adrenergic overdrive *(unproven)*
  - ? Causal pathway for mortality or macrovascular events *(unproven)*
- Off-target effects of therapeutic choices
  - Cardiovascular morbidity?
  - Fractures?
  - Cancer?
  - Pancreatitis? Pancreatic cancer?

SAFETY ISSUES

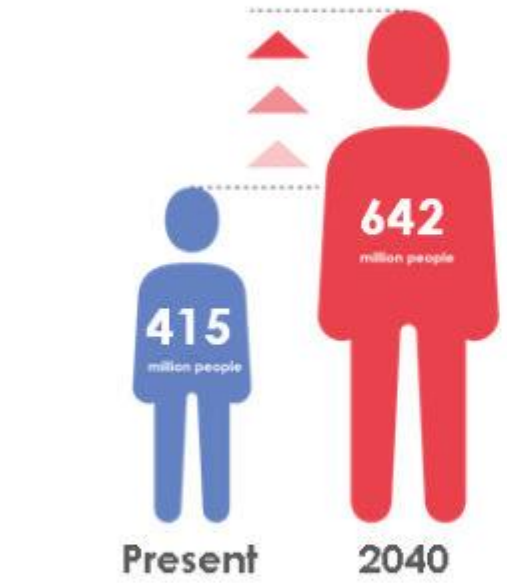
- Incretins: Pancreatic safety, CHF
- DPP-4 Inhibitors: polyarthralgias
- SGLT-2 Inhibitors : bone density, pyelonephritis, euglycemic DKA

Why CARDIOVASCULAR OUTCOME (CVOT) TRIALS?

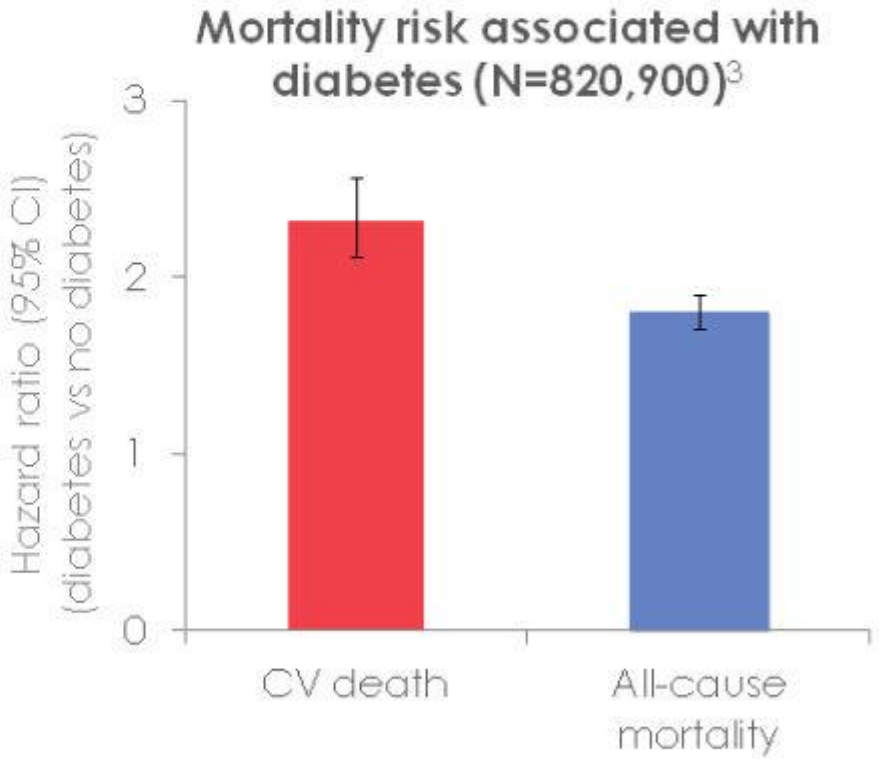
- What are they?
- What do we gain from them?

Type 2 diabetes is increasingly prevalent

- Globally, 415 million people are living with diabetes[1]
- At least 68% of people >65 years with diabetes die of heart disease[2]



This will rise to 642 million by 2040[1]



1. IDF Diabetes Atlas 7th Edition 2015 http://www.idf.org/diabetesatlas; 2. Centers for Disease Control and Prevention 2011 https://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf; 3. Seshasai et al. N Engl J Med 2011;364:829-41.

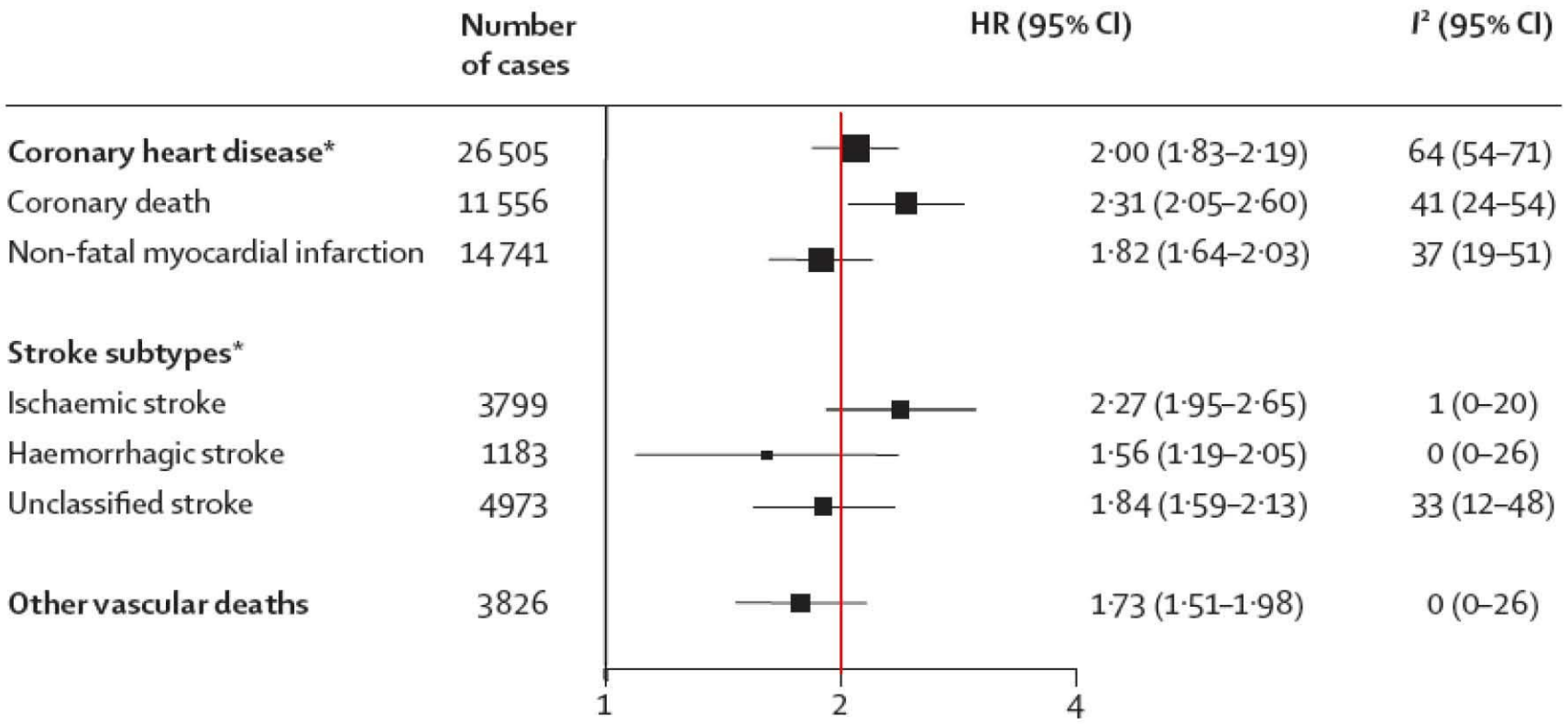
Association of A1C With CVD Outcomes in Subjects With No Baseline Diabetes or CVD History

Over 9.9 yrs median follow up:

- 20,840 fatal and nonfatal CVD outcomes (13,237 CHD; 7,603 stroke) in 294,998 subjects
- J-shaped associations seen between all glycemic measures (A1C and fasting, random, postload glucose) and CVD risk after adjustment for conventional CVD risk factors*
  - Slight change in HRs seen after adjustment for total cholesterol, triglycerides or eGFR; change attenuated after adjustment for HDL-C or C-reactive protein

*Models included age, sex, smoking, systolic BP level, total cholesterol, and HDL-C
Mean study levels: A1C=5.37%, fasting glucose=96 mg/dL, random glucose=99 mg/dL, postload glucose=125 mg/dL

Cardiovascular risk in diabetes



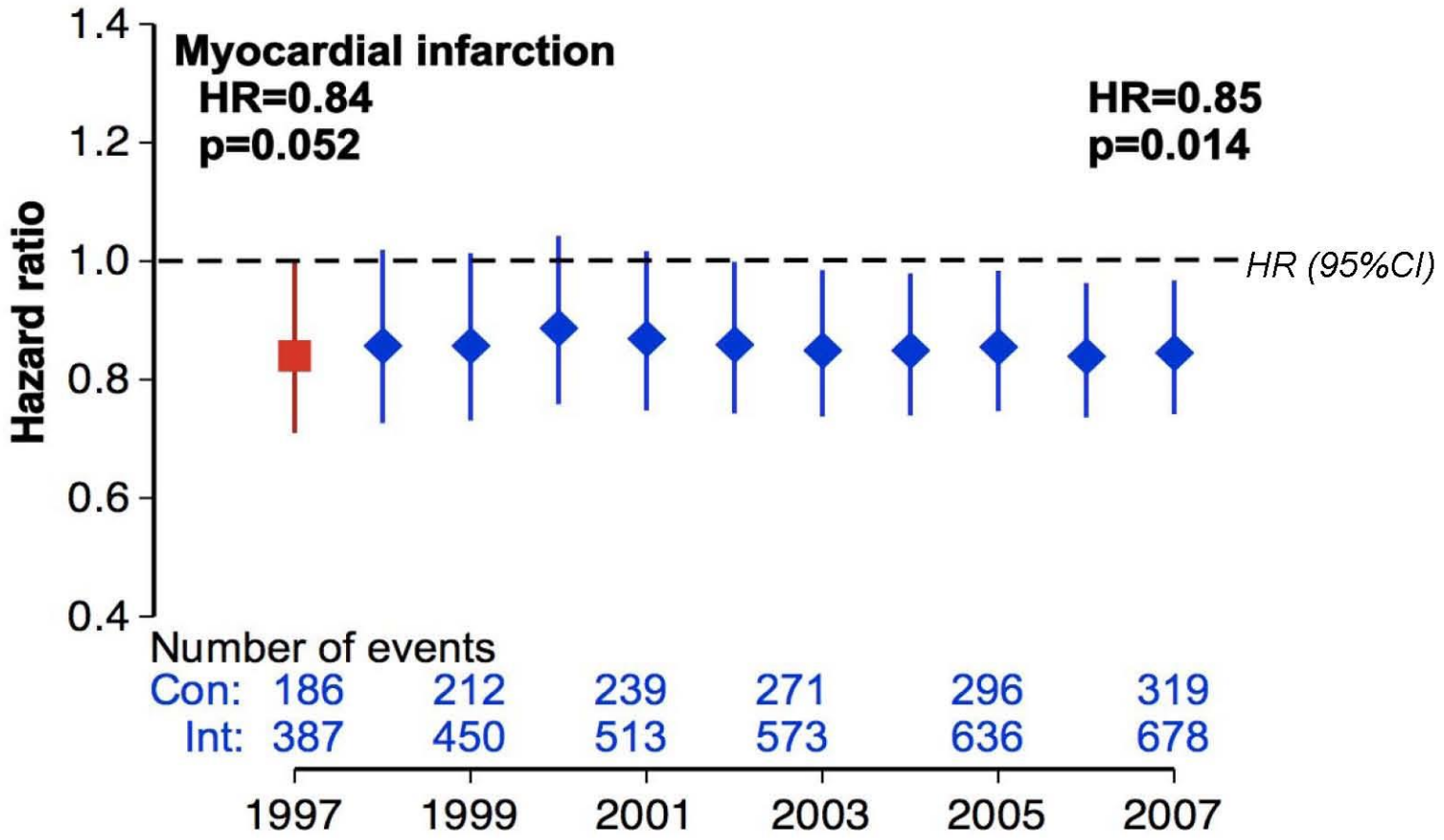
Analyses based on 530,083 participants from 102 prospective studies.
HRs adjusted for age, smoking status, body-mass index and systolic blood pressure, and, where appropriate, stratified by sex and trial arm.

Emerging Risk Factors Collaboration. *Lancet* 2010; 375: 2215-22

UKPDS-PTM: Myocardial Infarction Hazard Ratio

(fatal or non-fatal myocardial infarction or sudden death)

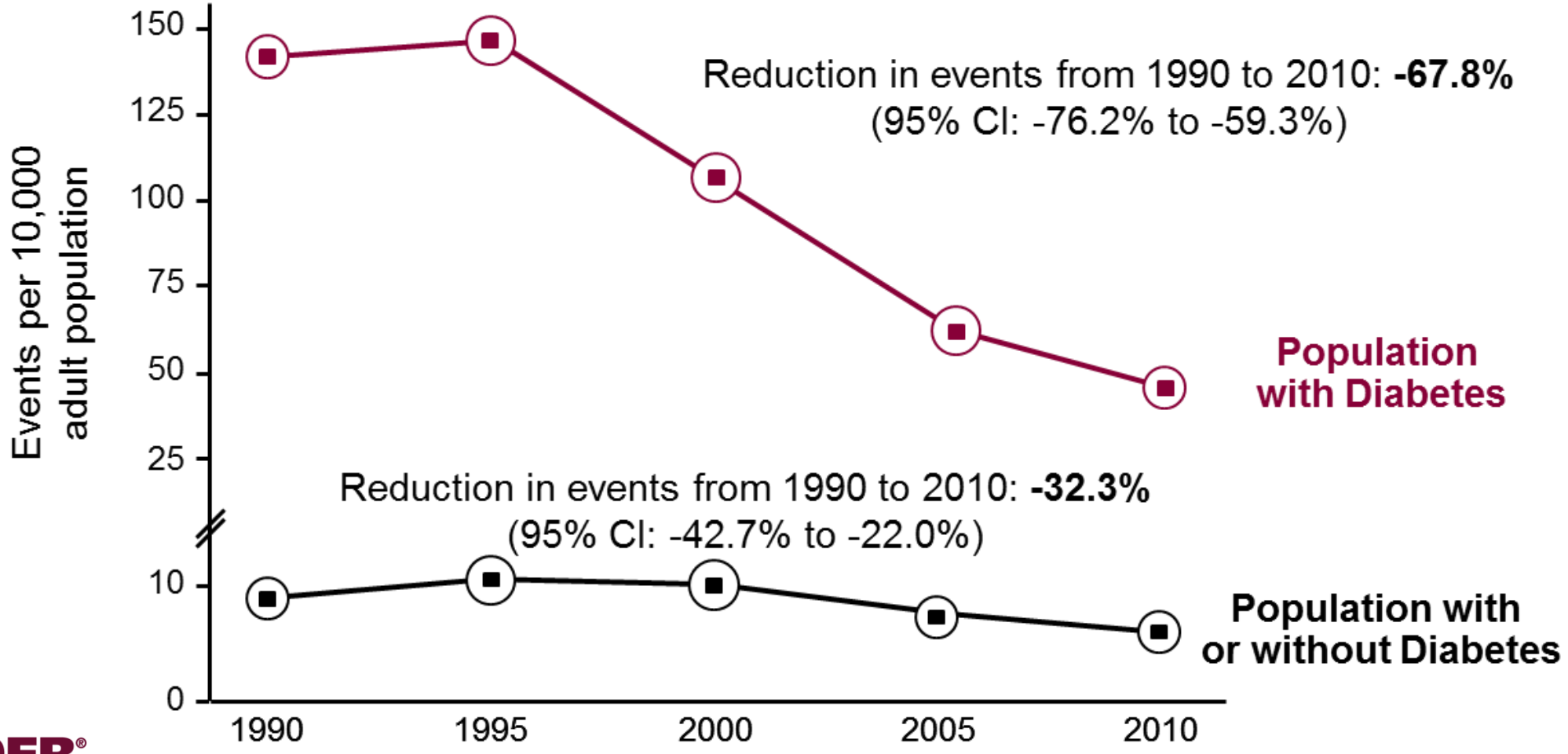
Intensive (SU/Ins) *vs.* Conventional glucose control



UKPDS 80. NEJM (2008); 359:1577-1589

Diabetes-related complications in the USA, 1990-2010

Acute myocardial infarction



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

Adapted from Gregg EW, et al. *N Engl J Med* 2014;370:1514–1523.
Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

Cardiovascular effects of incretin therapies

GLP-1 analogues

- SBP reduced 2-4 mmHg
- Weight loss
- ~5% total cholesterol, LDL reduction
- Reductions in CRP, BNP

DPP-4 Inhibitors

- SBP reduced 2-3 mmHg
- Weight neutral
- Small reductions in LDL (inconsistent finding)

Reducing risk for complications

- Microvascular
  - **Glucose**
  - **Blood pressure (esp retinopathy, nephropathy)**
  - Lipids
  - Smoking cessation
- Macrovascular
  - **Blood pressure**
  - **Lipids**
  - **Antiplatelet agents**
  - Smoking cessation
  - Glucose?

Global distribution of participants

Study	US/Canada	WE	EE	Middle East	Africa	Australasia	LatinAmerica
Pre-FDA Guidance							
ADVANCE	X		X			X	
Proactive		X	X				
HEART2D	X	X	X	X	X		
SPREADDIMCAD						X	
Aleglitazar(term.)							
Acarbose						X	
Phantom	X						
RECORD		X	X			X	
Post-FDA Guidance							
TOSCA-IT		X					
TECOS	X	X	X	X	X	X	X
ACE						X	
EXAMINE	X	X	X	X	X	X	X
TIDE	X	X	X	X	X	X	X
SAVOR-TIMI53	X	X	X	X	X	X	X
EXSCEL	X	X	X	X		X	X
ELIXA	X	X	X	X	X	X	X
LEADER	X	X	X	X	X	X	X
CAROLINA	X	X	X	X	X	X	X
Taspog	X	X	X	X	X	X	X
CANVAS	X	X	X	X		X	X
BI10773	X	X	X	X	X	X	X
AAA						X	
RASCIN	X						
ALECARDIO	X	X	X	X		X	X

Cardiovascular risk in type 2 diabetes: Summary of randomized trials

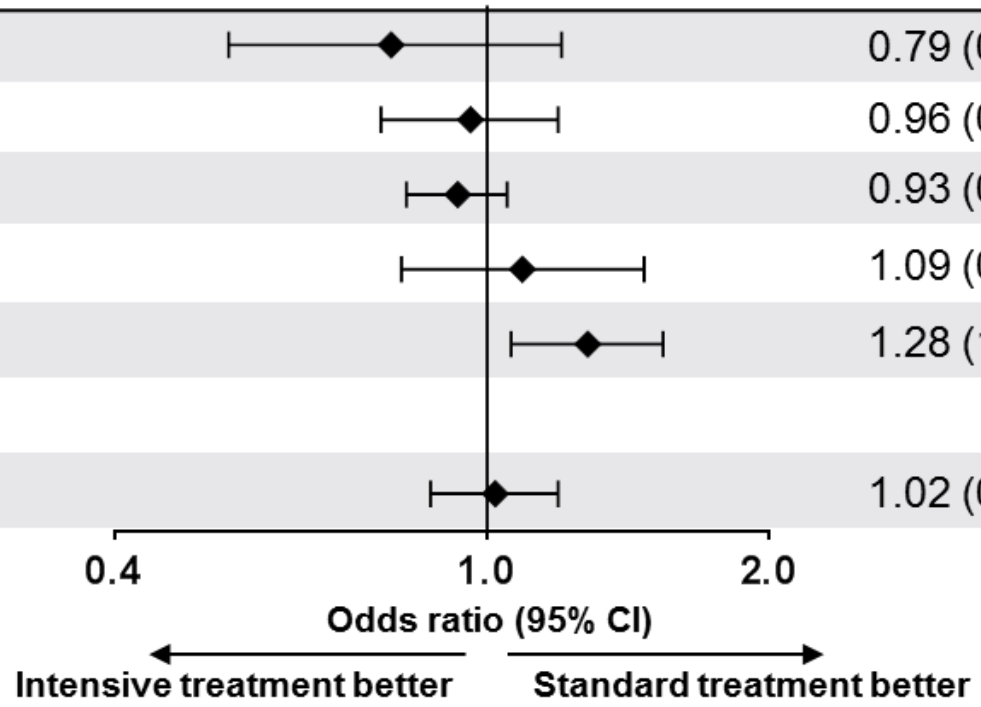
	Cardiovascular events	Mortality
Intensive vs less intensive glycemic control[1]		
ACCORD	↔	↑
ADVANCE	↔	↔
UKPDS	↔	↔
VADT	↔	↔
Individual glucose-lowering drug vs placebo (since 2008 FDA guidance)		
ELIXA[2]	↔	↔
EXAMINE[3]	↔	↔
SAVOR[4]	↔	↔
TECOS[5]	↔	↔
EMPA-REG OUTCOME[6]	↓	↓
LEADER[7]	↓	↓

1. Bergenstal RM et al. Am J Med 2010;123:374.e18; 2. Pfeffer MA et al. N Engl J Med 2015;373:2247-57; 3. White WB et al. N Engl J Med 2013;369:1327-35; 4. Scirica BM et al. N Engl J Med 2013;369:1317-26; 5.Green JB et al. N Engl J Med 2015;373:232-42; 6. Zinman B et al. N Engl J Med 2015;373:2117-28; 7. Marso SP et al. N Engl J Med 2016; epub ahead of print.

All Cause Mortality

Intensive vs Standard Glucose Lowering

Trial	Odds ratio (95% CI)	Intensive treatment/ standard treatment: Participants	Events	Weight of study size
UKPDS	0.79 (0.53 – 1.20)	3071/1549	539/302	10.1%
PROactive	0.96 (0.77 – 1.19)	2605/2633	177/186	21.5%
ADVANCE	0.93 (0.82 – 1.05)	5571/5569	498/533	29.4%
VADT	1.09 (0.81 – 1.47)	892/899	102/95	15.5%
ACCORD	1.28 (1.06 – 1.54)	5128/5123	257/203	23.6%
Overall	1.02 (0.87 – 1.19)	17267/15773	1573/1319	100%



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

CI: confidence interval; HR: hazard ratio.

Ray KK et al *Lancet* 2009;373:1765–1772.
Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

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FDA guidance: confidence intervals for meta-analysis

Upper bound of a 2-sided 95% confidence interval for estimated CV risk	
>1.8	The data are inadequate to support approval. A large safety trial should be conducted
1.3 – 1.8	The potential for CV harm may still exist. An adequately powered and designed post-marketing trial is necessary to show an upper bound < 1.3*
<1.3	A post-marketing trial is generally not needed*

*with a reassuring point estimate for overall CV risk

FDA Guidance for Industry: Diabetes Mellitus – Evaluating CV risk in new antidiabetic therapies to treat type 2 diabetes. www.fda.gov

What is MACE?

- “Major Adverse Cardiac Events”
- Three point MACE all cause mortality, non fatal MI, non fatal stroke.
- Four point MACE adds hospitalization for CHF or angina.

Overview of ongoing CV outcomes trials in diabetes

Drug class	Existing evidence	Outcomes trials	Number of patients
Metformin	UKPDS, meta-analysis suggests benefit	?	?
Glitazones/Glitazars	Meta-analysis suggests increased risk of CV morbidity for some	TOSCA-IT ALECARDIO	>11,000
DPP-4 inhibitor	Favorable effects on CV risk factors	EXAMINE TECOS SAVOR CAROLINA	>35,000
GLP-1 analogue	Favorable effects on CV risk factors	ELIXA EXSCEL LEADER REWIND	>33,000
SGLT-2 inhibitor	Favorable effects on CV surrogate markers	BI 10773 CANVAS	>8500

CV outcome trials in type-2 diabetes mellitus: GLP-1 analogues

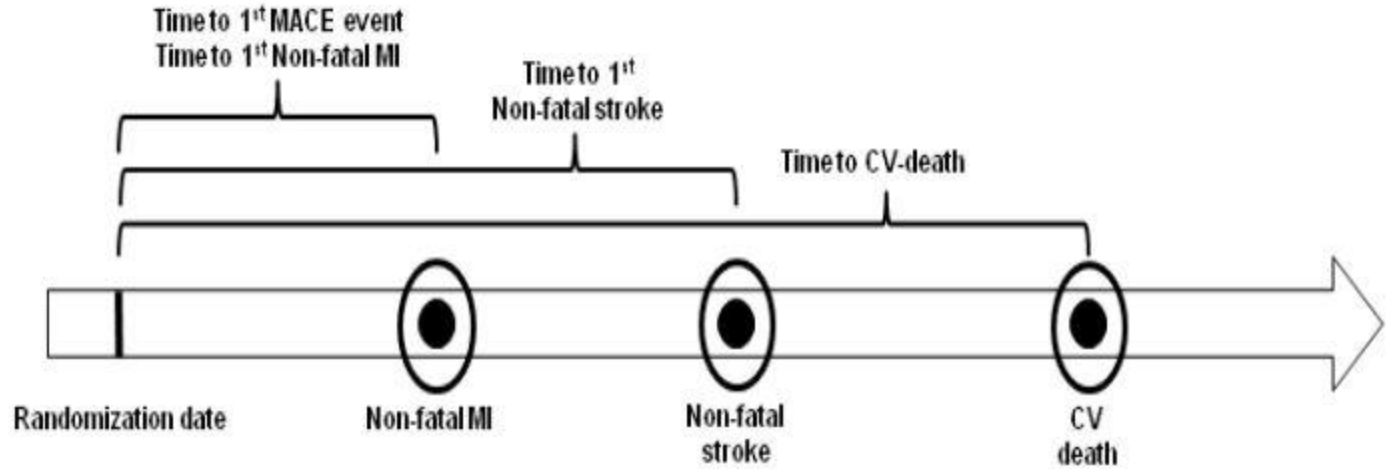
Trial	Treatment	Inclusion criteria	Primary endpoint	Number of patients
ELIXA	Placebo Lixisenatide	T2DM HbA1c 6.0% - 10.0% ACS	CV death, MI, UA or stroke	6000
EXSCEL	Placebo Exenatide	T2DM HbA1c 7.0% - 10.0% CVD in 60%	CV death, MI or stroke	9500
LEADER	Placebo Liraglutide	T2DM HbA1c ≥ 7.0% ≥50 years + CVD ≥60 years + CV risk factors	CV death, MI or stroke	8754
REWIND	Placebo Dulaglutide Add-on: 2 oral agents +/- GLP-1 analogue/insulin	T2DM ≥50 years + CVD ≥55 years + subclinical CVD ≥60 years + CV risk factors HbA1c ≤9.5%	CV death, MI or stroke	9600

CV Outcome Trials in type-2 diabetes mellitus: DPP4 Inhibitors ("Gliptins")

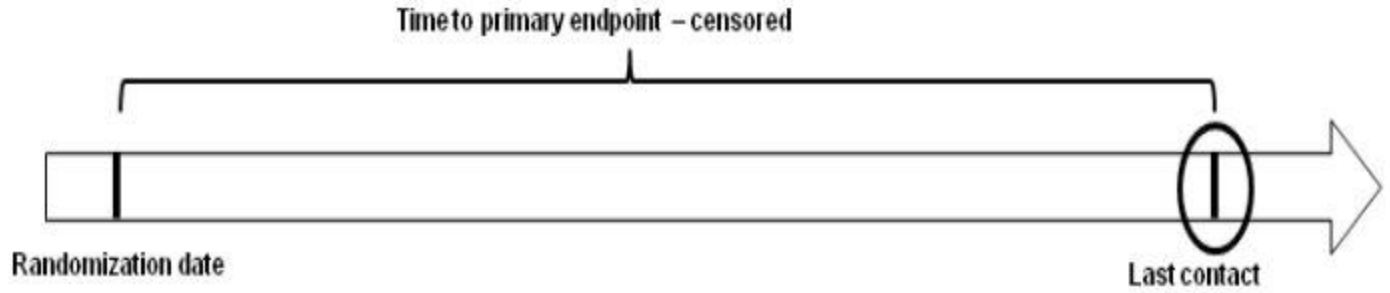
Trial	Treatment	Inclusion criteria	Primary endpoint	Number of patients
EXAMINE	Placebo Alogliptin	T2DM HbA1c 6.5 – 11.0% ≥ 18 years ACS	CV death, MI or stroke	5400
TECOS	Placebo Sitagliptin	T2DM HbA1c 6.5 – 8.0% ≥ 50 years CVD	CV death, MI, UA or stroke	14000
SAVOR (TIMI-53)	Placebo Saxagliptin	T2DM HbA1c ≥ 6.5% ≥ 40 years CVD/CV risk factors	CV death, MI or stroke	12000
CAROLINA	Glimepiride Linagliptin	T2DM HbA1c 6.5-8.5% 40-85 years CVD/CV risk factors/ diabetes end organ damage	CV death, MI, UA or stroke	6000

Analyses of MACE and time to first event

Patient with events



Patient without event



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

CV: cardiovascular; MACE: major adverse cardiovascular event; MI: myocardial infarction.

Confirmatory statistical analysis

Primary statistical analysis	Cox proportional hazard model with treatment as a covariate
Test hierarchy for the primary outcome	**1. Test of non-inferiority** • Confirmed if upper bound of the 2-sided 95% CI of the hazard ratio is below **1.30** **2. Test of superiority** • Confirmed if upper bound of the 2-sided 95% CI of the hazard ratio is below **1.00**

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

CI: confidence interval; CV: cardiovascular; MACE: major adverse cardiovascular event; MI: myocardial infarction.

Primary outcome

Time to first MACE composed of:	• CV death • Non-fatal MI • Non-fatal stroke

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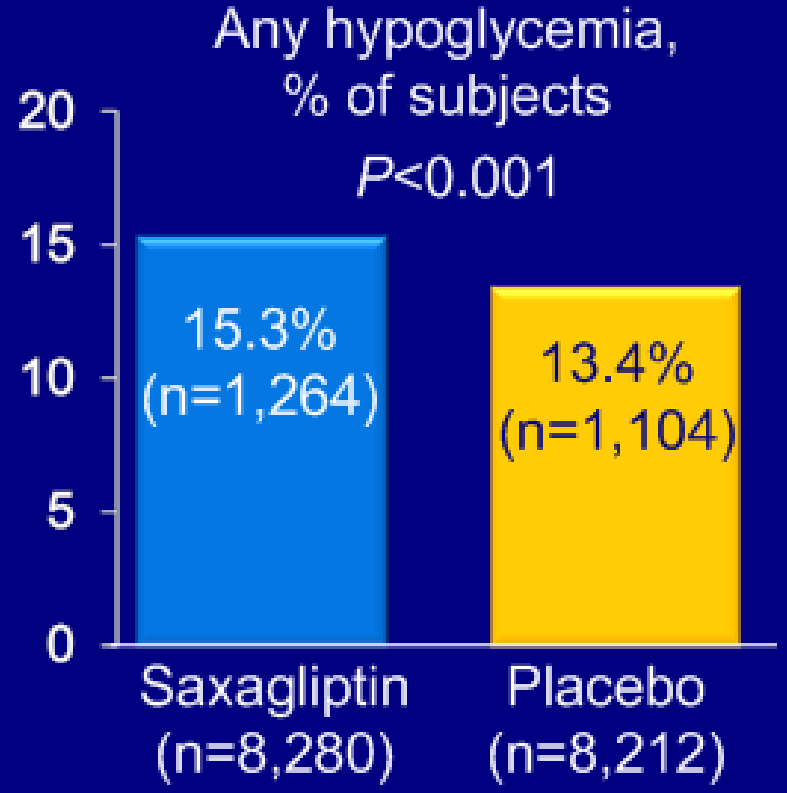
Savor Trial (Saxagliptin)

SAVOR-TIMI 53: Safety Endpoints

- More hypoglycemia with saxagliptin
- Similar rates in both groups
  - Pancreatitis
  - Thrombocytopenia
  - Lymphocytopenia
  - Infections
  - Hypersensitivity/skin reactions
  - Bone fractures
  - Liver abnormalities
- Cancer rate similar between groups; no excess of pancreatic cancer with saxagliptin
  - 12 cases of pancreatic cancer in placebo group vs 5 cases in saxagliptin group; *P*=0.095

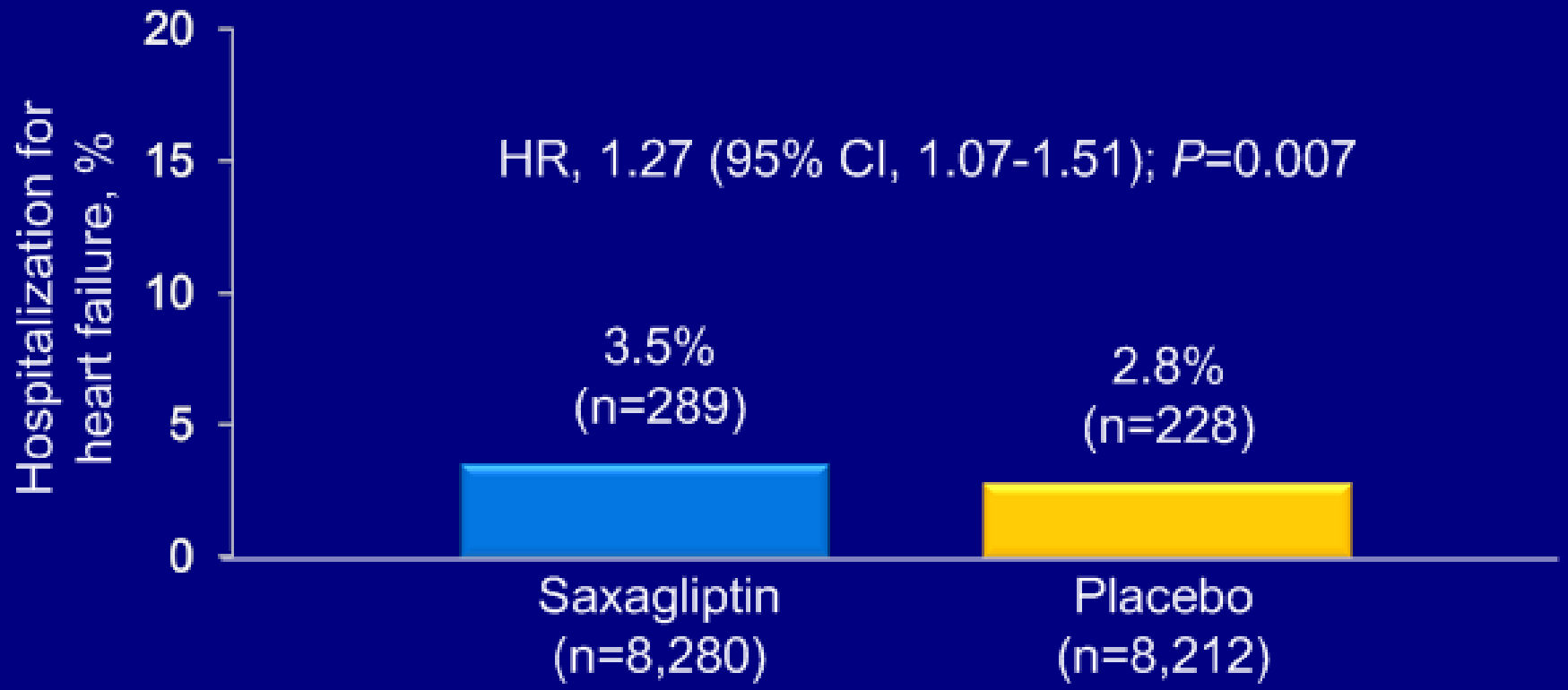


Saxagliptin is not FDA approved for cardiovascular risk reduction.

SAVOR-TIMI 53=Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53

Scirica BM et al; for the SAVOR-TIMI 53 Steering Committee and Investigators.

SAVOR-TIMI 53: Saxagliptin Increased Hospitalization for Heart Failure



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Scirica BM et al; for the SAVOR-TIMI 53 Steering Committee and Investigators.

Pancreatitis and Pancreatic Cancer With Saxagliptin or Placebo in Patients With or At Risk for CVD in SAVOR-TIMI 53

- Results from SAVOR-TIMI 53[1]
  - Similar rates of pancreatitis in saxagliptin and placebo groups
  - No excess of pancreatic cancer with saxagliptin
- Current SAVOR-TIMI 53 analysis determined incidence of pancreatitis and pancreatic cancer
  - Pancreatitis history not a contraindication for trial participation
- Reported cases classified as definite acute pancreatitis, possible acute pancreatitis, chronic pancreatitis, unlikely to be pancreatitis
- Outcome measures: total number of adjudicated pancreatitis cases and reported pancreatic cancer cases

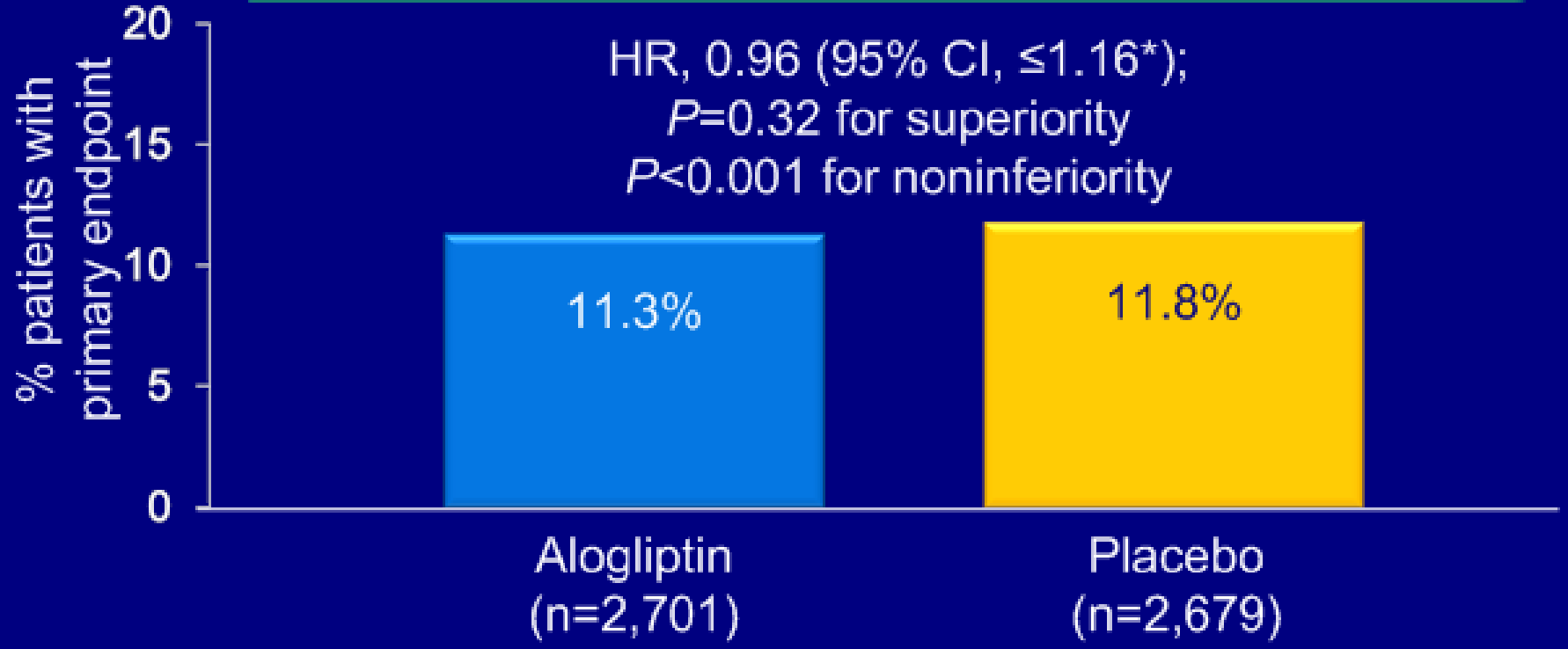
SAVOR-TIMI 53=Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53

1. Scirica BM, et al; for the SAVOR-TIMI 53 Steering Committee and Investigators. *N Engl J Med*. 2013;369(14):1317-1326.

EXAMINE (Alogliptin)

EXAMINE: No Increase in CV Events with Alogliptin *Primary Endpoint*

Primary endpoint: composite of CV death, nonfatal MI, or nonfatal stroke



*Upper boundary of one-sided repeated CI
Median follow-up: 18 months
Alogliptin is not FDA approved for cardiovascular risk reduction.
EXAMINE=Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care
CV=cardiovascular; MI=myocardial infarction

EXAMINE: Adverse Events

- No significant between-group difference in occurrence of serious adverse events
  - 33.6% with alogliptin, 35.5% with placebo (*P*=0.14)
- Similar rates for:
  - Hypoglycemia
  - Acute and chronic pancreatitis (no fatal cases)
  - Changes in eGFR and dialysis initiation
- No significant between-group difference in cancer incidence
  - No reports of pancreatic cancer

EXAMINE=Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care
eGFR=estimated glomerular filtration rate

Primary Results

8th June 2015

Primary Composite Cardiovascular Outcome

Time to first occurrence of:

- Cardiovascular-related death
- Nonfatal myocardial infarction
- Nonfatal stroke
- Hospitalization for unstable angina

A Clinical Endpoints Committee, blinded to therapy allocation, reviewed all potential CVD endpoints independently.

Green JB et al. NEJM 2015; DOI: 10.1056/NEJMoa1501352

Major Inclusion Criteria

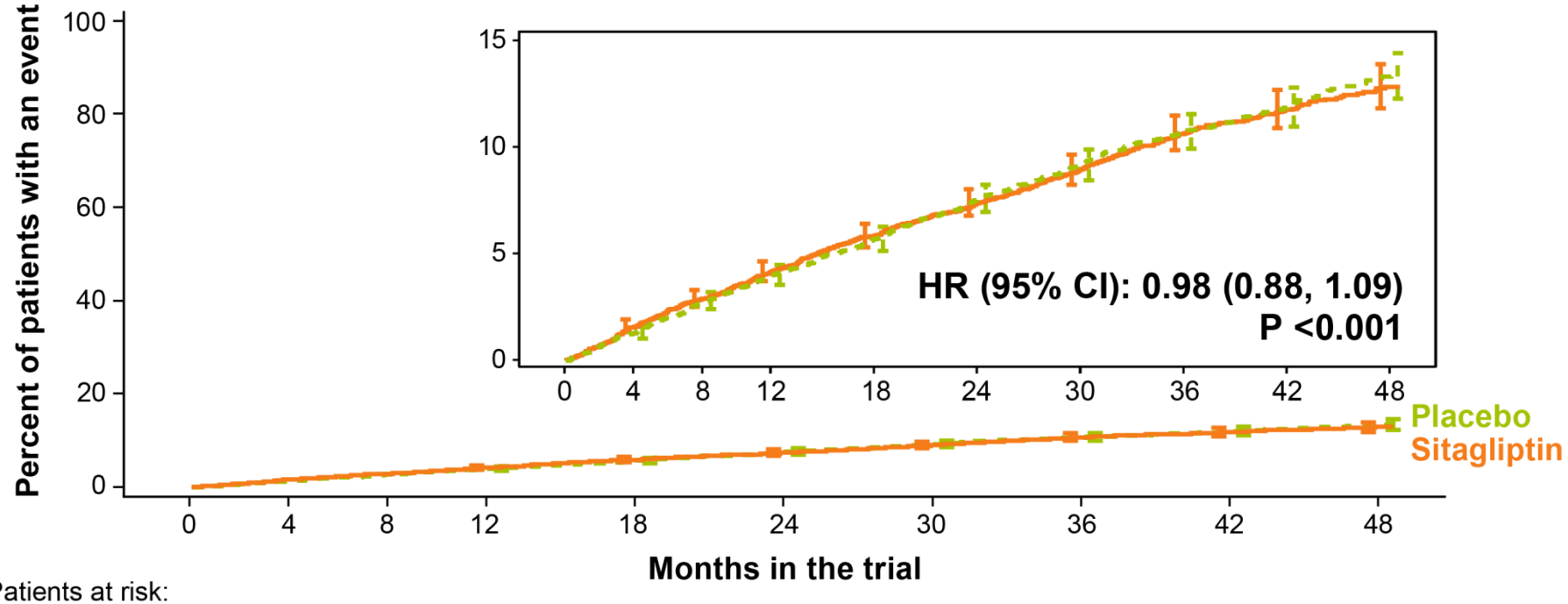
- **Type 2 diabetes** (A1c ≥6.5% and ≤8.0%)
  - Stable monotherapy OR dual combination therapy with metformin, pioglitazone, or sulfonylurea or *stable dose of insulin with or without metformin
- **≥50 years old**
- **Preexisting vascular disease** defined as having:
  - History of myocardial infarction
  - Prior coronary revascularization
  - Coronary angiography with at least one ≥50% stenosis
  - History of ischemic stroke
  - Carotid arterial disease with ≥50% carotid stenosis
  - Peripheral arterial disease with objective evidence
- **Able to see usual care provider at least twice yearly**

**Amended 13Sept2010*

Green JB et al. NEJM 2015; DOI: 10.1056/NEJMoa1501352

Primary Composite Cardiovascular Outcome*

PP Analysis for Non-inferiority



Patients at risk:

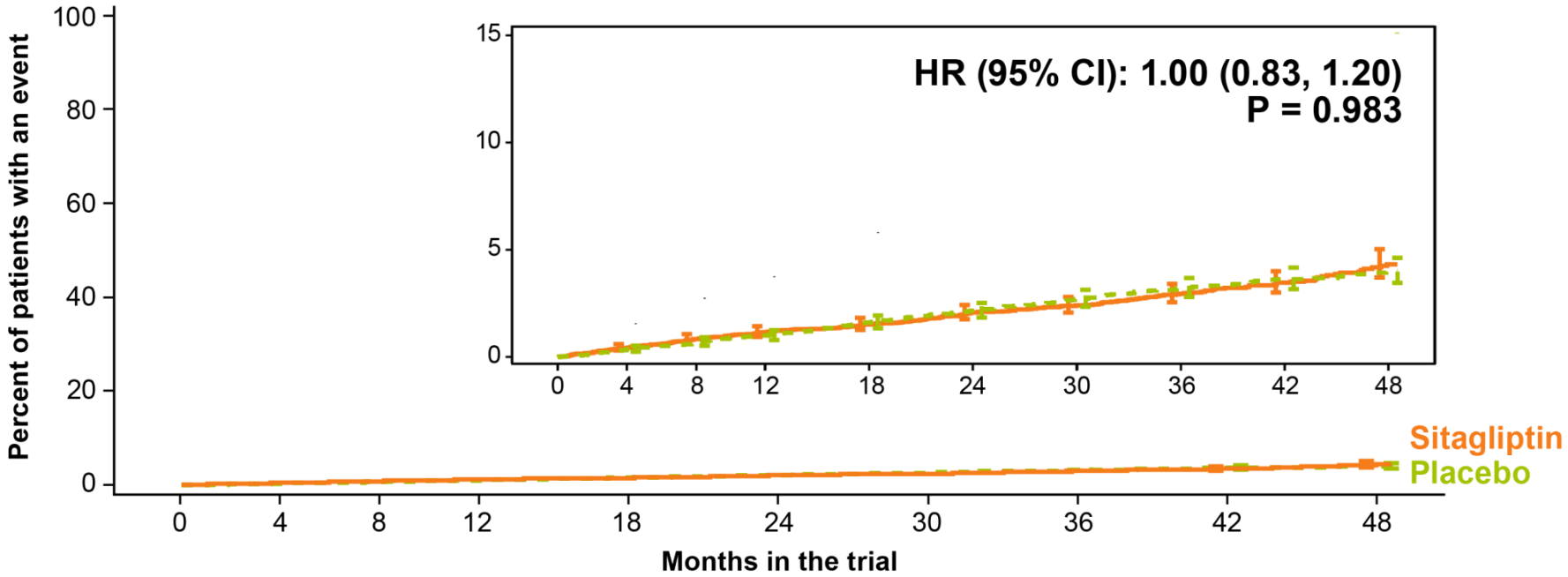
Sitagliptin	7,257	6,857	6,519	6,275	5,931	5,616	3,919	2,896	1,748	1,028
Placebo	7,266	6,846	6,449	6,165	5,803	5,421	3,780	2,743	1,690	1,005

** CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina*

Green JB et al. NEJM 2015; DOI: 10.1056/NEJMoa1501352

Hospitalization for Heart Failure*

ITT Analysis



Patients at risk:										
Sitagliptin	7,332	7,189	7,036	6,917	6,780	6,619	4,728	3,515	2,175	1,324
Placebo	7,339	7,204	7,025	6,903	6,712	6,549	4,599	3,443	2,131	1,315

** Adjusted for history of heart failure at baseline*

Green JB et al. NEJM 2015; DOI: 10.1056/NEJMoa1501352

Summary of Results (1)

- *For the primary composite cardiovascular outcome* (CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina) sitagliptin, compared with placebo, was *noninferior, and not superior*
- *For the secondary composite cardiovascular outcome* (CV death, nonfatal MI, or nonfatal stroke) sitagliptin, compared with placebo, was *noninferior, and not superior*
- The rate of *hospitalization for heart failure* did not differ between sitagliptin and placebo treatment groups
- The incidence of *severe hypoglycemia* did not differ between sitagliptin and placebo treatment groups

Green JB et al. NEJM 2015; DOI: 10.1056/NEJMoa1501352

Summary of Results (2)

- The rates of *infections, and deaths from infection,* did not differ between sitagliptin and placebo treatment groups
- The incidence of *overall malignancies* did not differ between sitagliptin and placebo treatment groups
- Overall, confirmed events of *acute pancreatitis* were uncommon, but numerically more frequent in the sitagliptin group
- Overall, confirmed events of *pancreatic cancer* were uncommon, but numerically more frequent in the placebo group

Green JB et al. NEJM 2015; DOI: 10.1056/NEJMoa1501352

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

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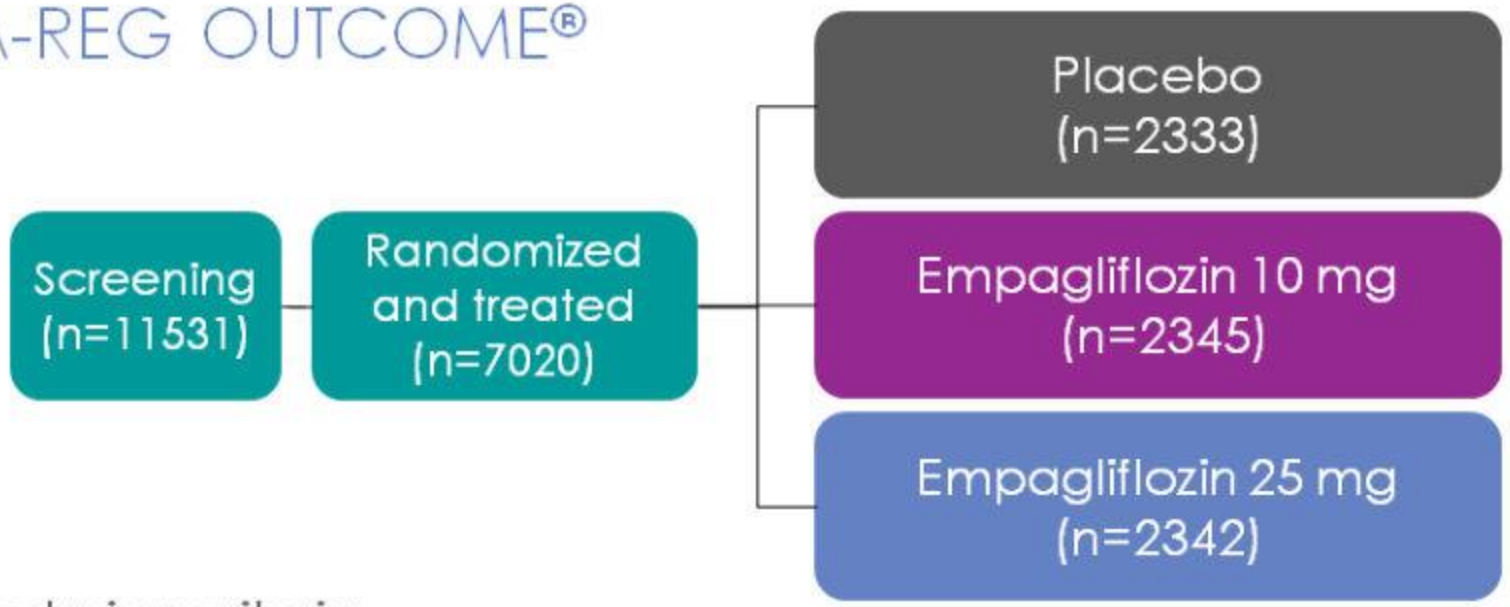
Evaluation of cardiovascular outcome Results

EMPA-REG OUTCOME®



- Key inclusion criteria
  - Adults with type 2 diabetes and established cardiovascular disease
    - At baseline, 75.6% of patients had coronary artery disease, 23.3% had a history of stroke, 20.8% had peripheral artery disease,10.1% had heart failure*
  - BMI ≤45 kg/m^2; HbA1c 7–10%; eGFR ≥30 mL/min/1.73m^2 (MDRD)
- Study medication was given in addition to standard of care

*Based on narrow standardized MedDRA query (SMQ) "cardiac failure".
eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.
Zinman B et al. N Engl J Med 2015;373:2117-28.

EMPA-REG OUTCOME®

CV risk factor management at baseline

Glycemic management	HbA1c, %	8.07 ± 0.85
	Any metformin	74.0%
	Any insulin	48.2%
Blood pressure management	SBP/DBP, mmHg	136/77
	SBP <140 and DBP <90 mmHg	61.3%
	Any BP-lowering drug	95.0%
	ACE inhibitor/ARB	80.7%
Lipid management	LDL-cholesterol, mg/dL	85.6 ± 35.7
	Statin	77.0%
Anti-platelet therapies	Acetylsalicylic acid	82.7%

Data are mean ± SD or % in 7020 patients treated with ≥1 dose of study drug.

Zinman B et al. N Engl J Med 2015;373:2117-28.

EMPA-REG OUTCOME®

EASD 2015

EMPA-REG OUTCOME: Design and Baseline Characteristics

- CVOT for the SGLT2 inhibitor, empagliflozin
- 7,020 subjects with type 2 diabetes at high CV risk on standard care randomized to:

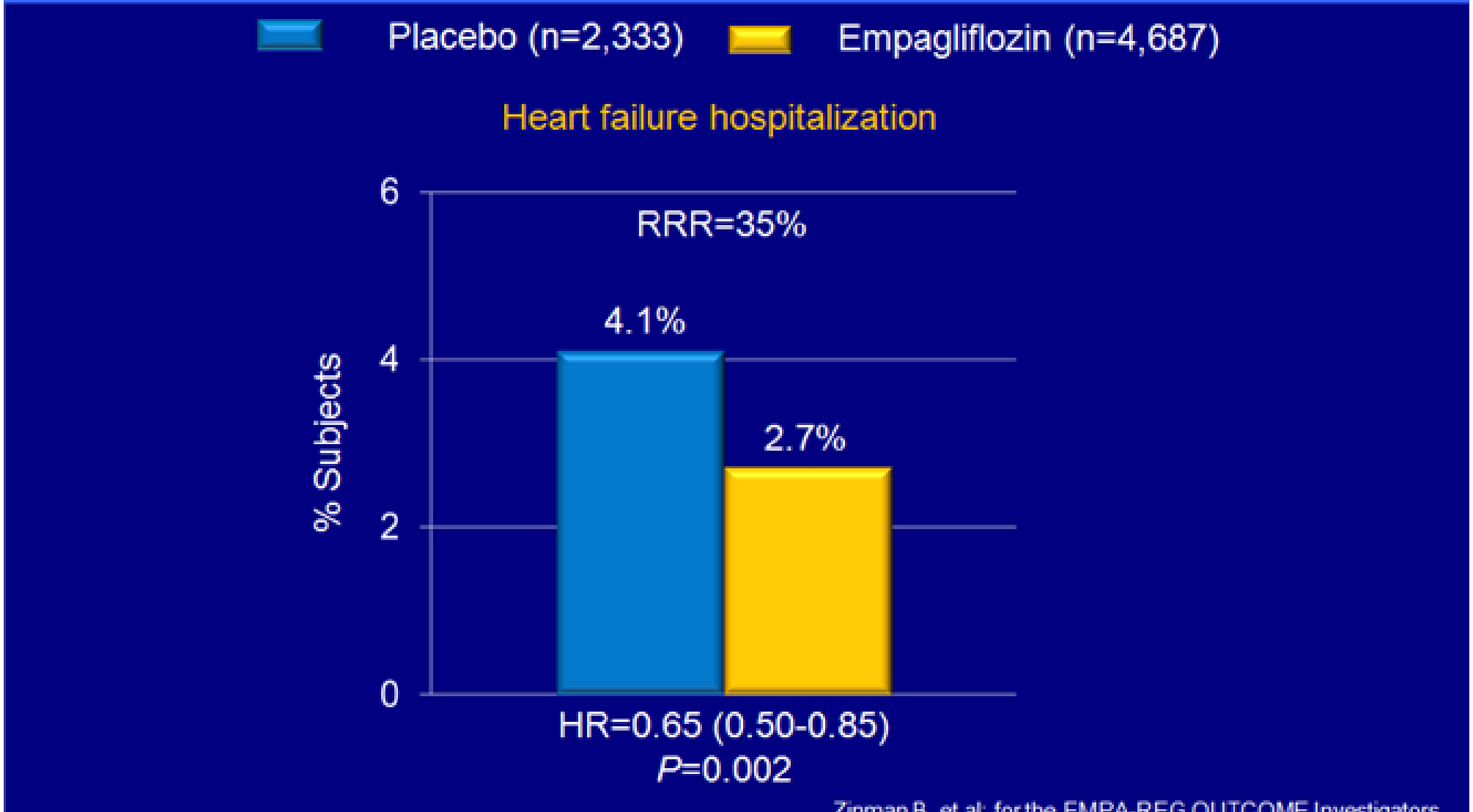
  Empagliflozin 10 mg • Empagliflozin 25 mg • Placebo
- Primary composite endpoint: CV mortality, nonfatal MI, nonfatal stroke
- Key secondary composite outcome: Primary plus hospitalization for UA
- Median 3.1-yr follow-up

Select baseline characteristics		
	Placebo (n=2,333)	Empagliflozin (n=4,687)
Age, yrs	63.2	63.1
CV history	2,307 (98.9%)	4,657 (99.4%)
A1C	8.08%	8.07%
Dual glucose-lowering therapy	1,148 (49.2%)	1,380 (29.4%)

Lower Heart Failure Hospitalization With Empagliflozin Vs Placebo in High-Risk Patients

EASD 2015

EMPA-REG OUTCOME

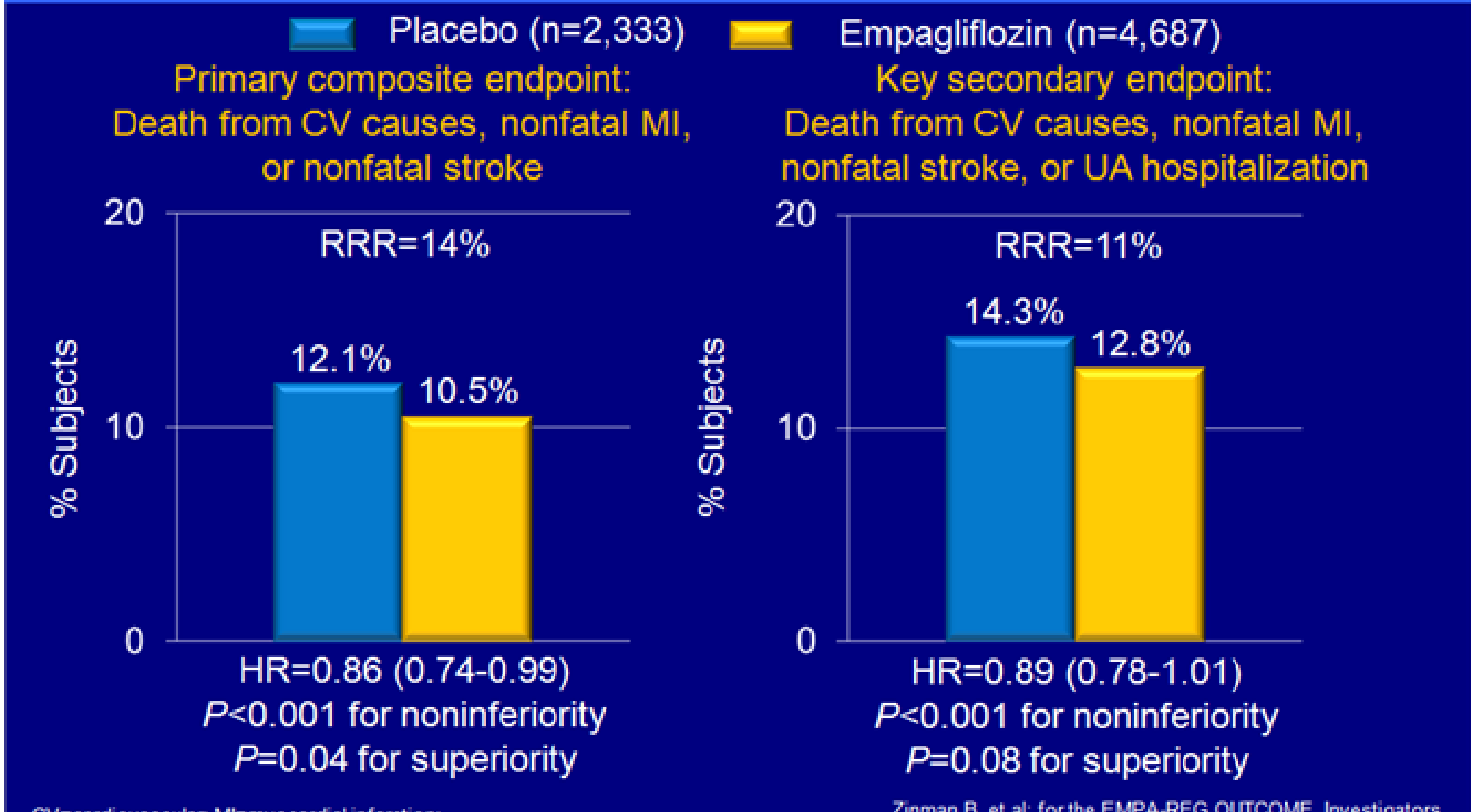


Zinman B, et al; for the EMPA-REG OUTCOME Investigators

Empagliflozin Reduces CV Events & Mortality in High-Risk Type 2 Diabetes

EASD 2015

EMPA-REG OUTCOME



Zinman B, et al; for the EMPA-REG OUTCOME Investigators

Safety of Empagliflozin Vs Placebo in High-Risk Patients With Type 2 Diabetes

EASD 2015

EMPA-REG OUTCOME

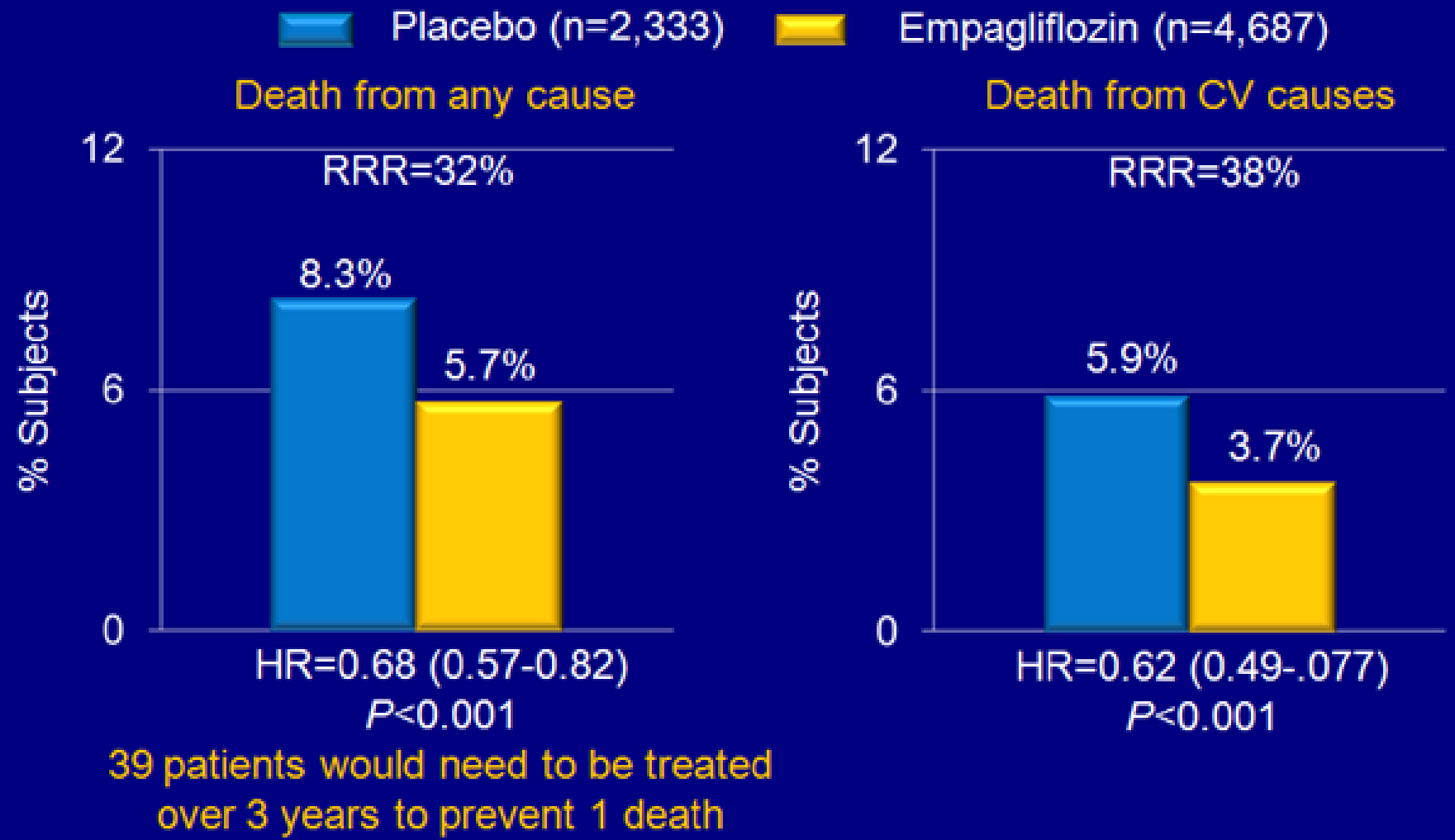
- Adverse events, serious AEs, and AEs leading to discontinuation were similar for empagliflozin and placebo
- Rate of genital infections was higher for empagliflozin

	Placebo (n=2,333)	Empagliflozin* (n=4,687)
Any AE	2,139 (91.7%)	4,230 (90.2%)
Serious AE	988 (42.3%)	1,789 (38.2%)
AE leading to discontinuation	453 (19.4%)	813 (17.3%)
Hypoglycemic AE	650 (27.9%)	1,303 (27.8%)
Volume depletion event	115 (4.9%)	239 (5.1%)
Acute renal failure	155 (6.6%)	346 (5.2%)
Bone fracture	91 (3.9%)	179 (3.8%)

Lower All-Cause & CV Mortality With Empagliflozin Vs Placebo in High-Risk Patients

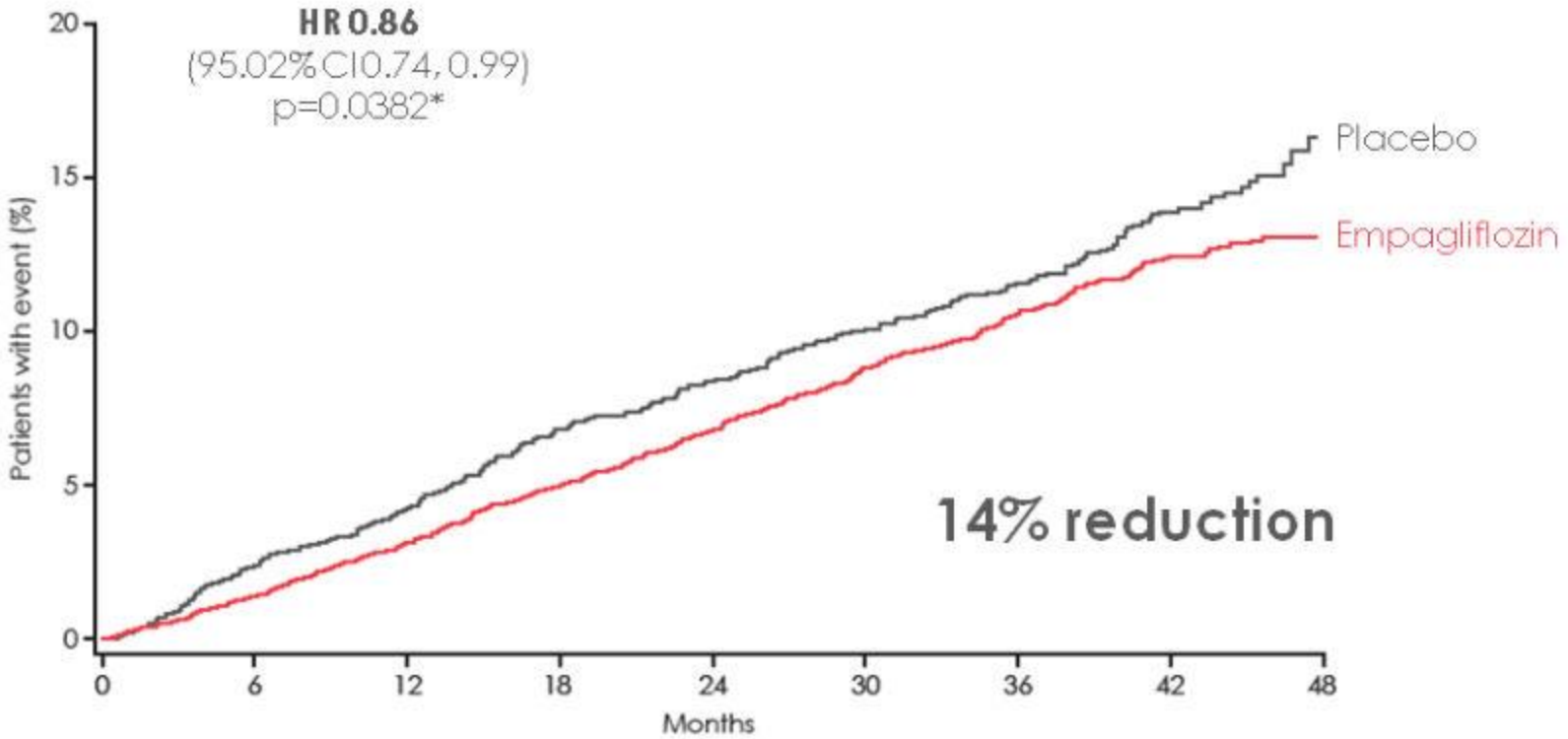
EASD 2015

EMPA-REG OUTCOME



Zinman B, et al; for the EMPA-REG OUTCOME Investigators

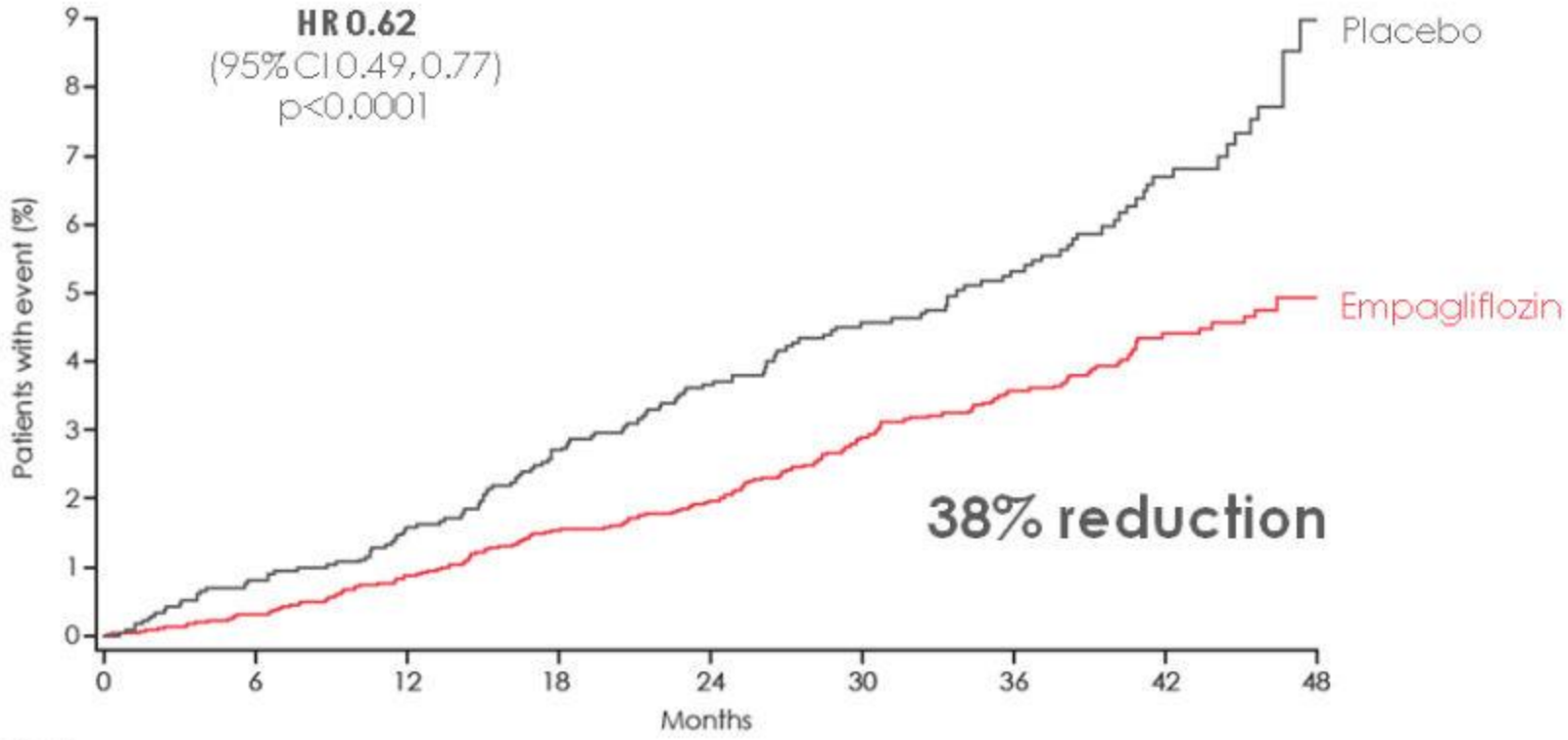
Primary outcome: 3-point MACE



Cumulative incidence function. *Two-sided tests for superiority were conducted (statistical significance was indicated if p≤0.0498).
Zinman B et al. N Engl J Med 2015;373:2117-28.

EMPA-REG OUTCOME®

CV death

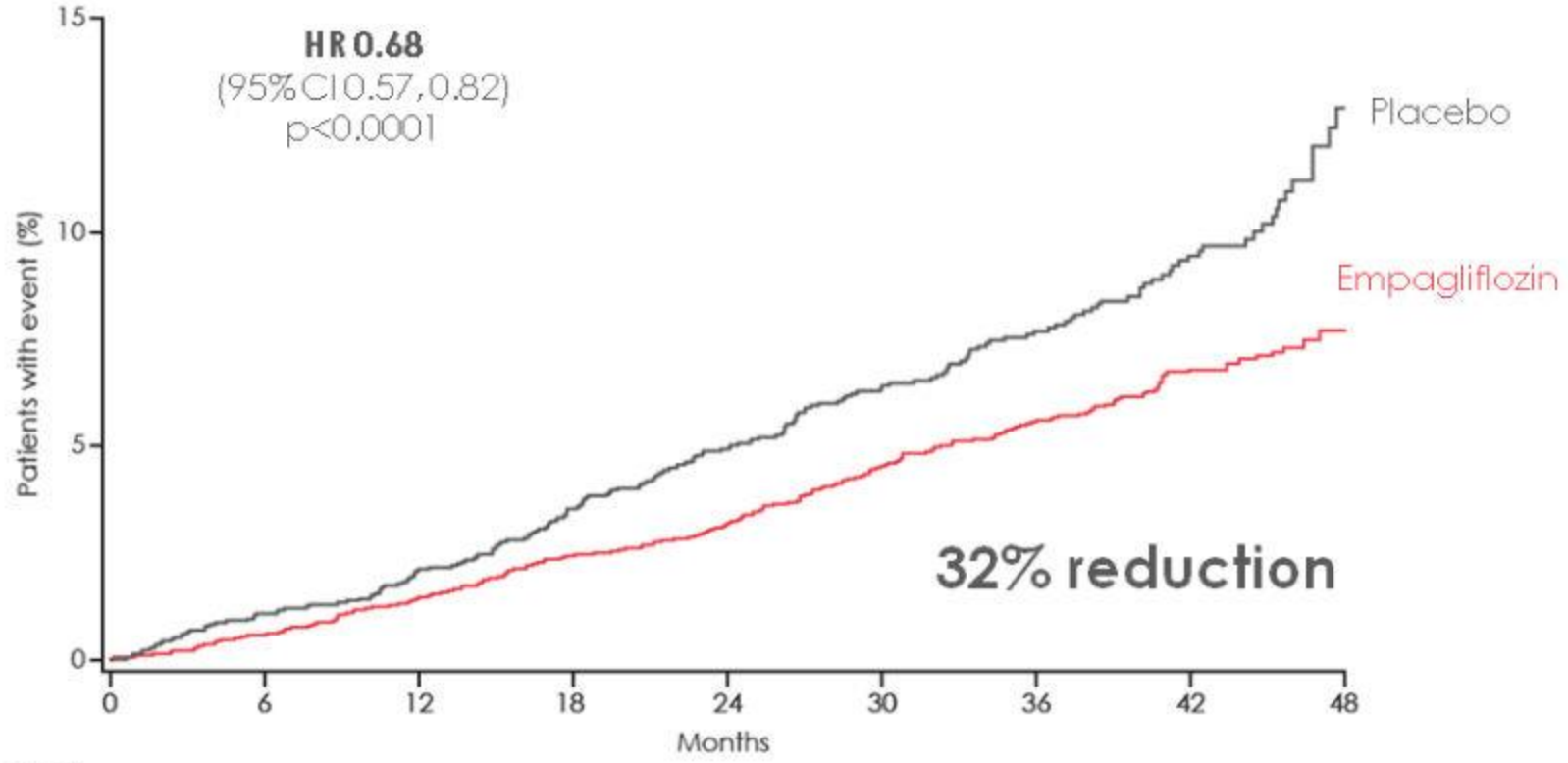


No. of patients									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Cumulative incidence function.
Zinman B et al. N Engl J Med 2015;373:2117-28.

EMPA-REG OUTCOME®

All-cause mortality



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

Kaplan-Meier estimate.
Zinman B et al. N Engl J Med 2015;373:2117-28.

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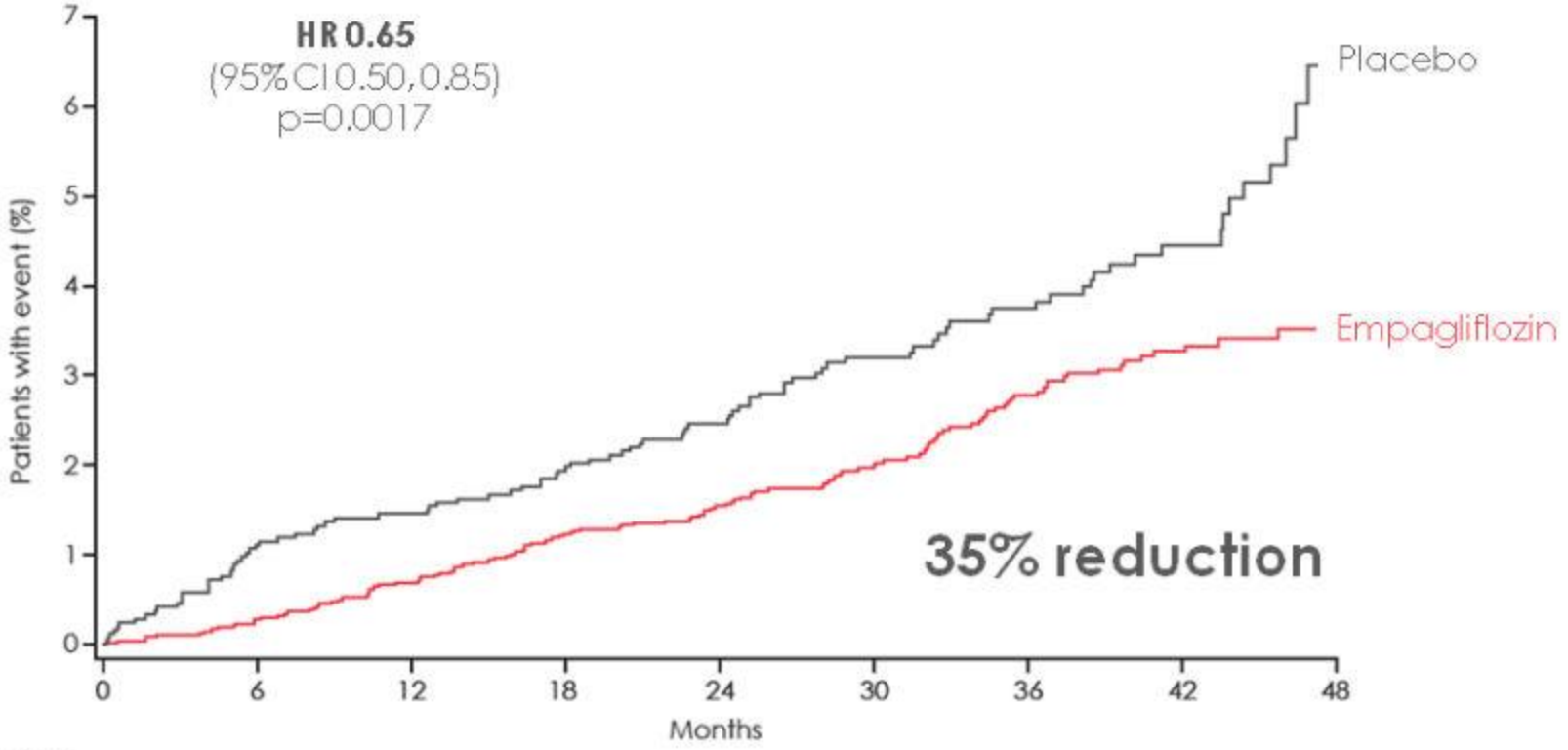
Hospitalization for heart failure

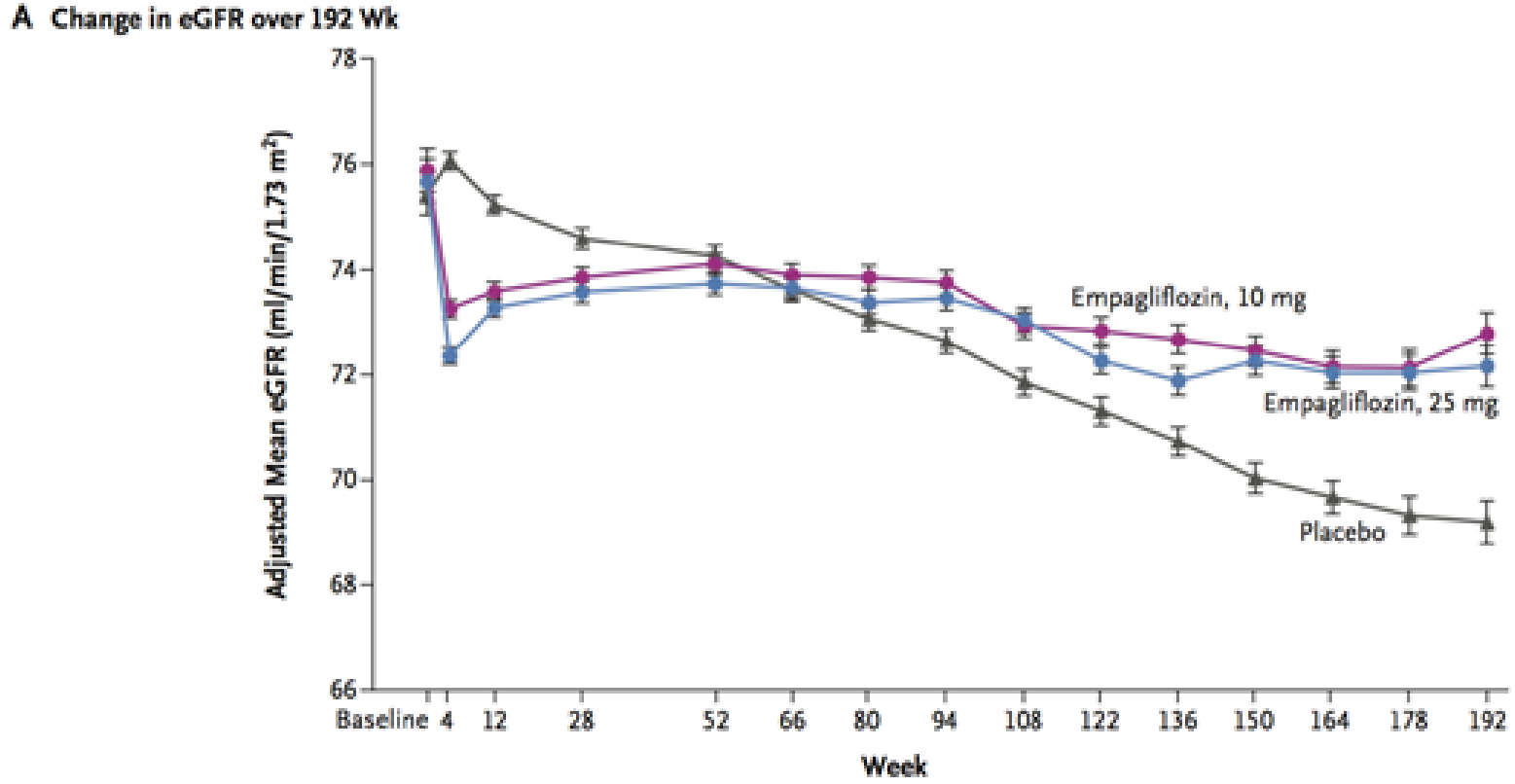


No. of patients									
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

Cumulative incidence function.
Zinman B et al. N Engl J Med 2015;373:2117-28.

EMPA-REG OUTCOME®

Empaglaflozin and change in GFR over 3.5 years



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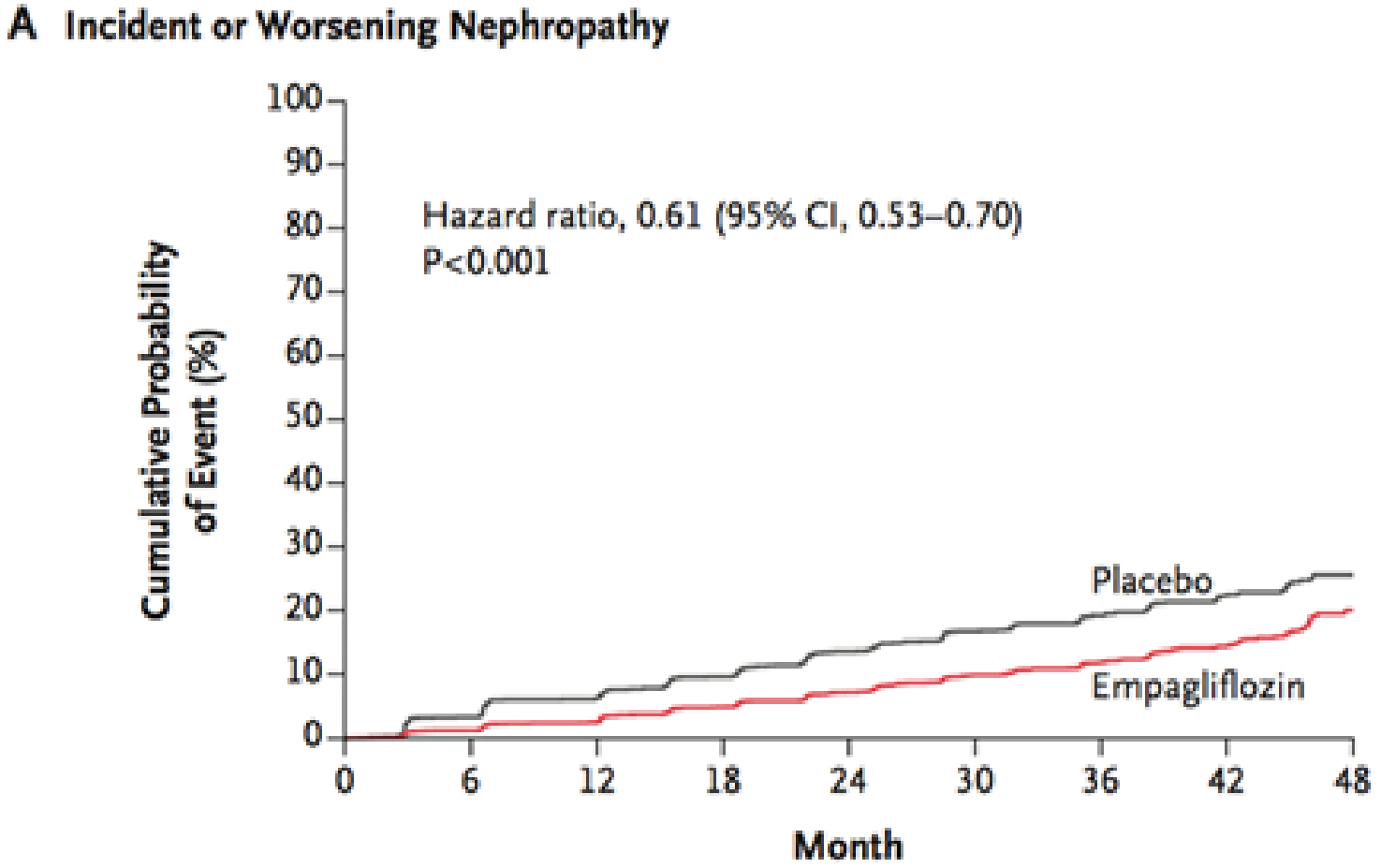
Liraglutide Effect and Action in Diabetes:
Evaluation of cardiovascular outcome Results

Empaglaflozin slows progression of renal disease



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Evaluation of cardiovascular outcome Results

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 28, 2016 VOL. 375 NO. 4

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

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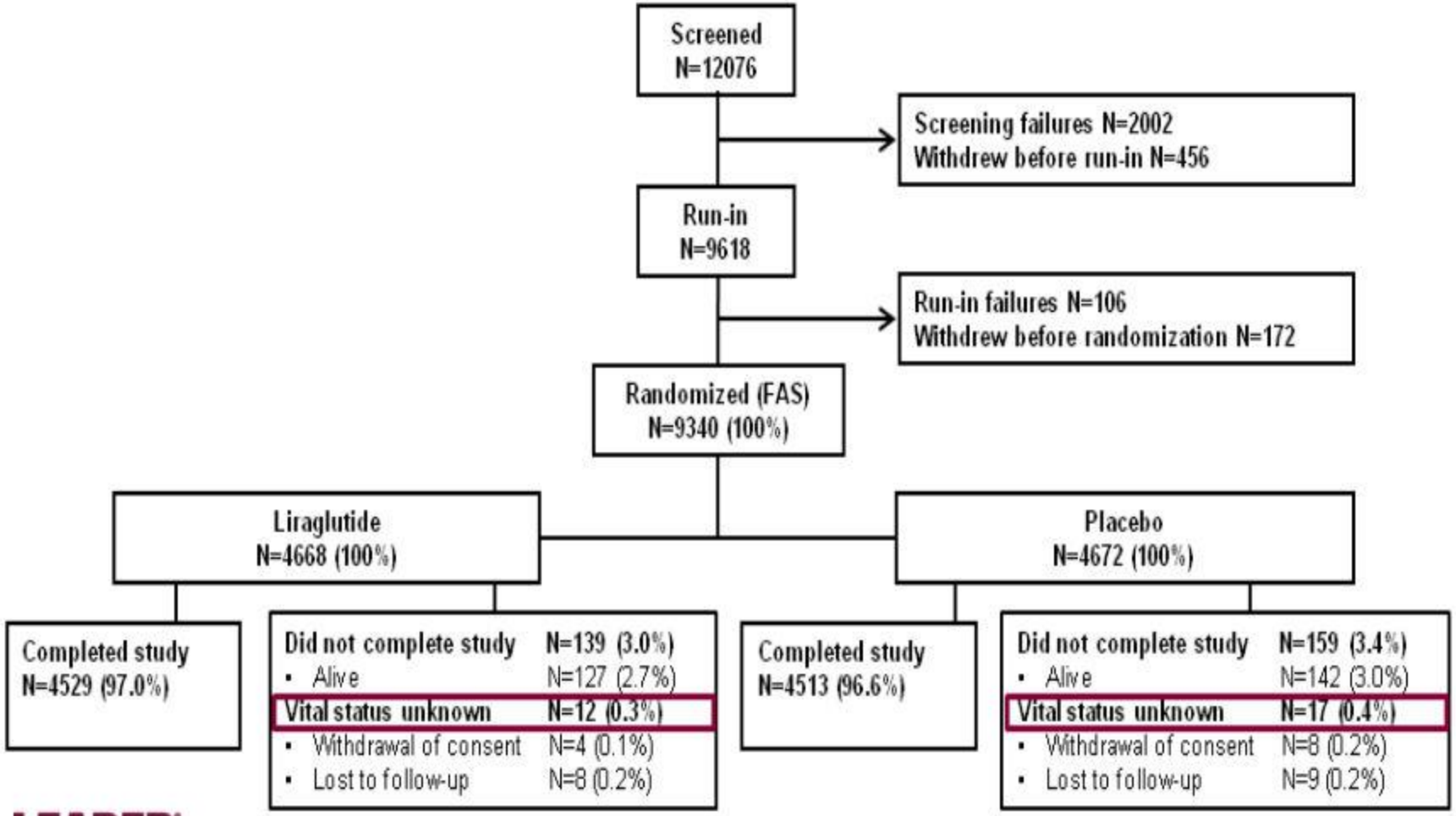
Evaluation of cardiovascular outcome Results

Study patient disposition



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FAS: full analysis set.

Baseline characteristics

(mean ± SD unless stated)

	Liraglutide (N=4668)	Placebo (N=4672)
Male sex, N (%)	3011 (64.5)	2992 (64.0)
Age, years	64.2 ± 7.2	64.4 ± 7.2
Diabetes duration, years	12.8 ± 8.0	12.9 ± 8.1
HbA_{1c}, %	8.7 ± 1.6	8.7 ± 1.5
BMI, kg/m^2	32.5 ± 6.3	32.5 ± 6.3
Body weight, kg	91.9 ± 21.2	91.6 ± 20.8
Systolic blood pressure, mmHg	135.9 ± 17.8	135.9 ± 17.7
Diastolic blood pressure, mmHg	77.2 ± 10.3	77.0 ± 10.1
Heart failure*, N (%)	835 (17.9)	832 (17.8)

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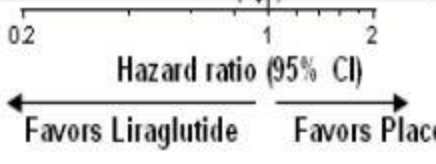
Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

*Heart failure includes New York Heart Association class I, II and III. BMI: body mass index; HbA_{1c}: glycated hemoglobin.

Primary outcome: Subgroup analyses

Subgroup	Hazard ratio (95% CI)	p-value for interaction	No. of patients	Liraglutide no. of events/no. of patients (%)	Placebo no. of events/no. of patients (%)
Primary analysis	**0.87 (0.78–0.97)**		**9340**	**608/4668 (13.0)**	**694/4672 (14.9)**
Glycated hemoglobin		0.58			
</=8.3%	0.89 (0.76–1.05)		4768	289/2340 (12.4)	333/2428 (13.7)
>8.3%	0.84 (0.72–0.98)		4572	319/2328 (13.7)	361/2244 (16.1)
Duration of diabetes		0.42			
</=11 years	0.82 (0.70–0.97)		4429	265/2216 (12.0)	316/2213 (14.3)
>11 years	0.90 (0.78–1.04)		4892	340/2441 (13.9)	376/2451 (15.3)
Risk of CVD		0.04			
Age >/=50 years and established CVD/CKD	0.83 (0.74–0.93)		7598	536/3831 (14.0)	629/3767 (16.7)
Age >/=60 years and risk factors for CVD	1.20 (0.86–1.67)		1742	72/837 (8.6)	65/905 (7.2)
Chronic heart failure		0.53			
Yes	0.94 (0.72–1.21)		1305	112/653 (17.2)	119/652 (18.3)
No	0.85 (0.76–0.96)		8035	496/4015 (12.4)	575/4020 (14.3)
Antidiabetic therapy		0.73			
1 OAD	0.75 (0.58–0.98)		1818	99/922 (10.7)	125/896 (14.0)
>1 OAD	0.95 (0.78–1.16)		2997	191/1515 (12.6)	196/1482 (13.2)
Insulin with OAD(s)	0.89 (0.74–1.06)		3422	223/1674 (13.3)	259/1748 (14.8)
Insulin without OAD	0.86 (0.63–1.17)		737	71/361 (19.7)	86/376 (22.9)
None	0.73 (0.42–1.25)		366	24/196 (12.2)	28/170 (16.5)
Renal function		0.01			
<60 mL/min/1.73 m^2	0.69 (0.57–0.85)		2158	172/1116 (15.4)	223/1042 (21.4)
>/=60 mL/min/1.73 m^2	0.94 (0.83–1.07)		7182	436/3552 (12.3)	471/3630 (13.0)



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

Prespecified Cox proportional-hazard regression analyses were performed for subgroups of patients with respect to the primary outcome (first occurrence of death from CV causes, nonfatal MI, or nonfatal stroke). P values signify tests of homogeneity for between-group differences with no adjustment for multiple testing. The percentages of patients with a first primary outcome between the randomization date and the date of last follow-up are shown. There were missing data for BMI in 5 patients in the liraglutide group and 4 in the placebo group and for the duration of diabetes in 11 patients in the liraglutide group and 8 in the placebo group.

Primary outcome: Subgroup analyses

Subgroup	Hazard ratio (95% CI)	p-value for interaction	No. of patients	Liraglutide no. of events/no. of patients (%)	Placebo no. of events/no. of patients (%)
Primary analysis	**0.87 (0.78–0.97)**		**9340**	**608/4668 (13.0)**	**694/4672 (14.9)**
Glycated hemoglobin		0.58			
</=8.3%	0.89 (0.76–1.05)		4768	289/2340 (12.4)	333/2428 (13.7)
>8.3%	0.84 (0.72–0.98)		4572	319/2328 (13.7)	361/2244 (16.1)
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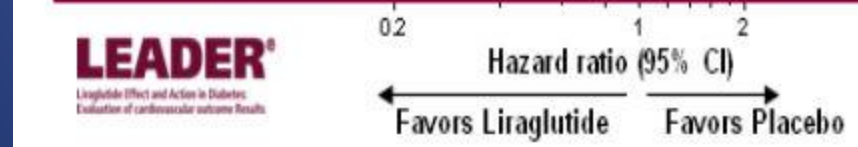

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Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

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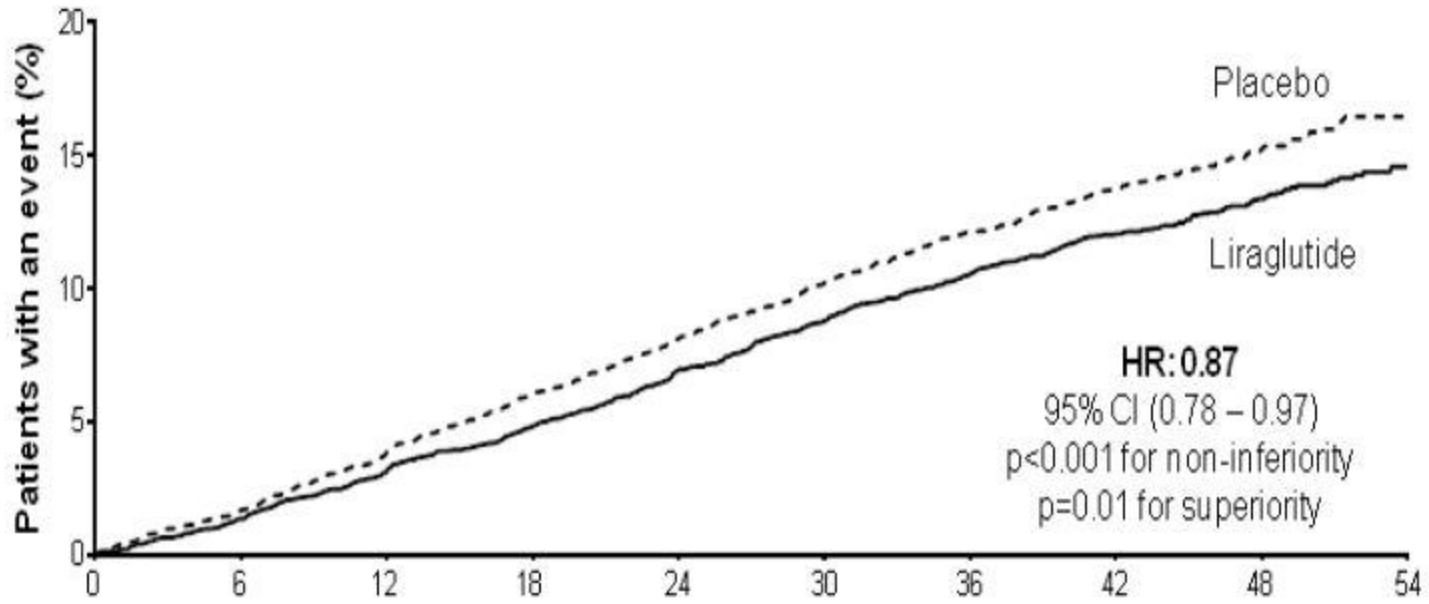
Primary outcome

CV death, non-fatal myocardial infarction, or non-fatal stroke



Patients at risk

Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

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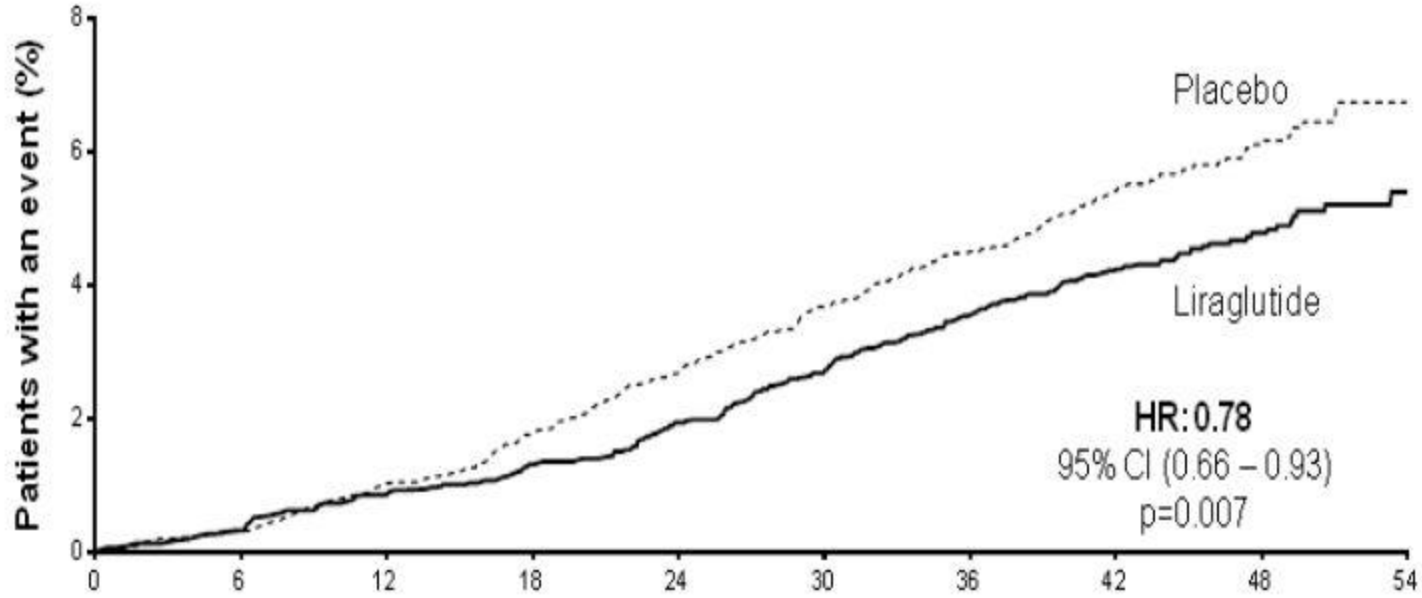
Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; CV: cardiovascular; HR: hazard ratio.

CV death



Patients at risk										
Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

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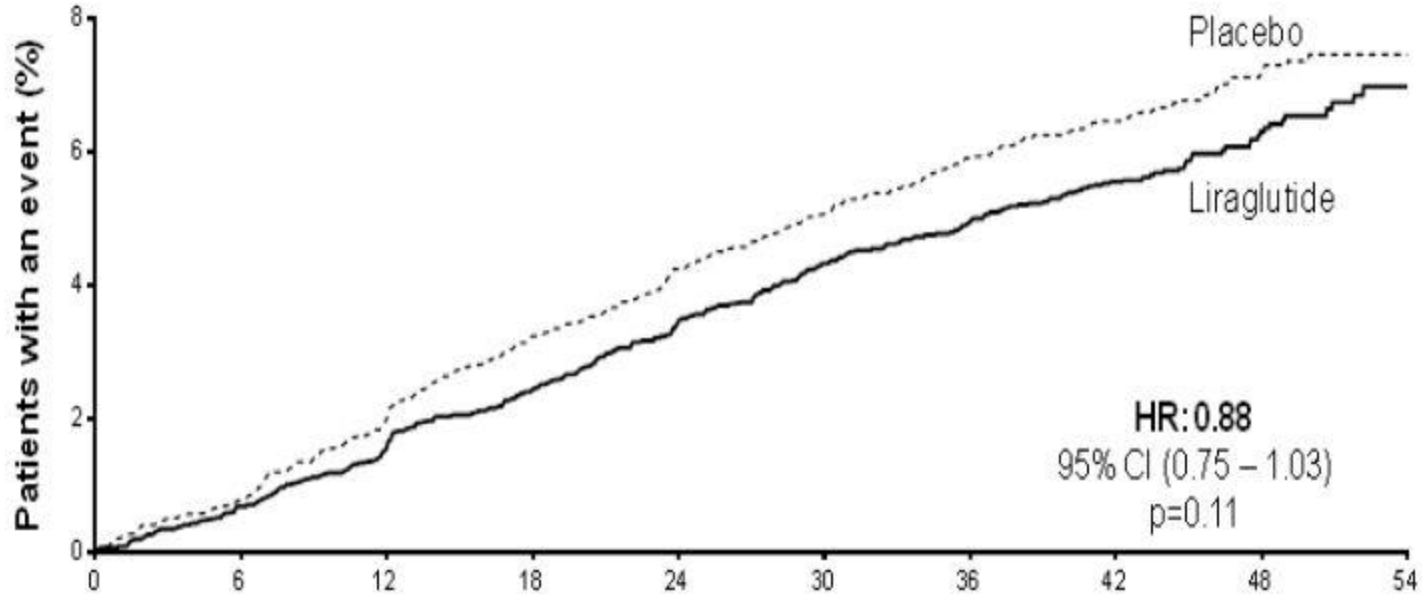
Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months.
CI: confidence interval; CV: cardiovascular; HR: hazard ratio.

Time to non-fatal myocardial infarction



Patients at risk

Liraglutide	4668	4609	4531	4454	4359	4263	4181	4102	1619	440
Placebo	4672	4613	4513	4407	4301	4202	4103	4020	1594	424

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

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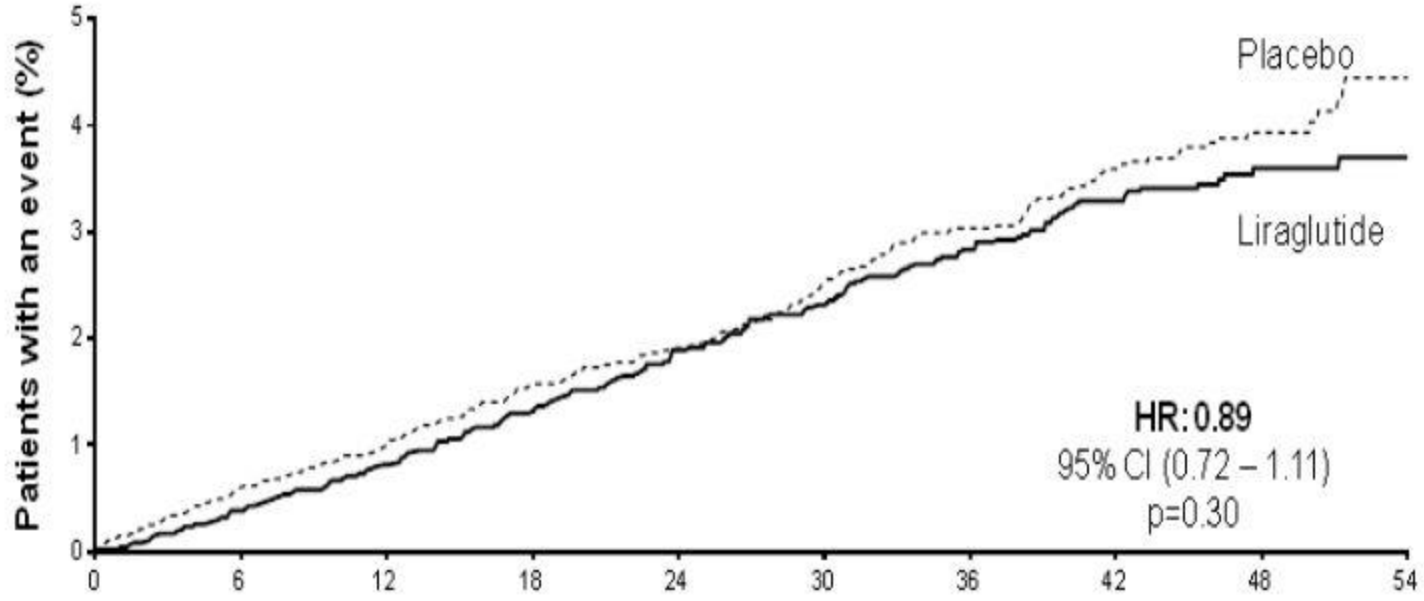
CI: confidence interval; HR: hazard ratio.

Time to non-fatal stroke



Patients at risk										
Liraglutide	4668	4624	4564	4504	4426	4351	4269	4194	1662	465
Placebo	4672	4622	4558	4484	4405	4314	4228	4141	1648	445

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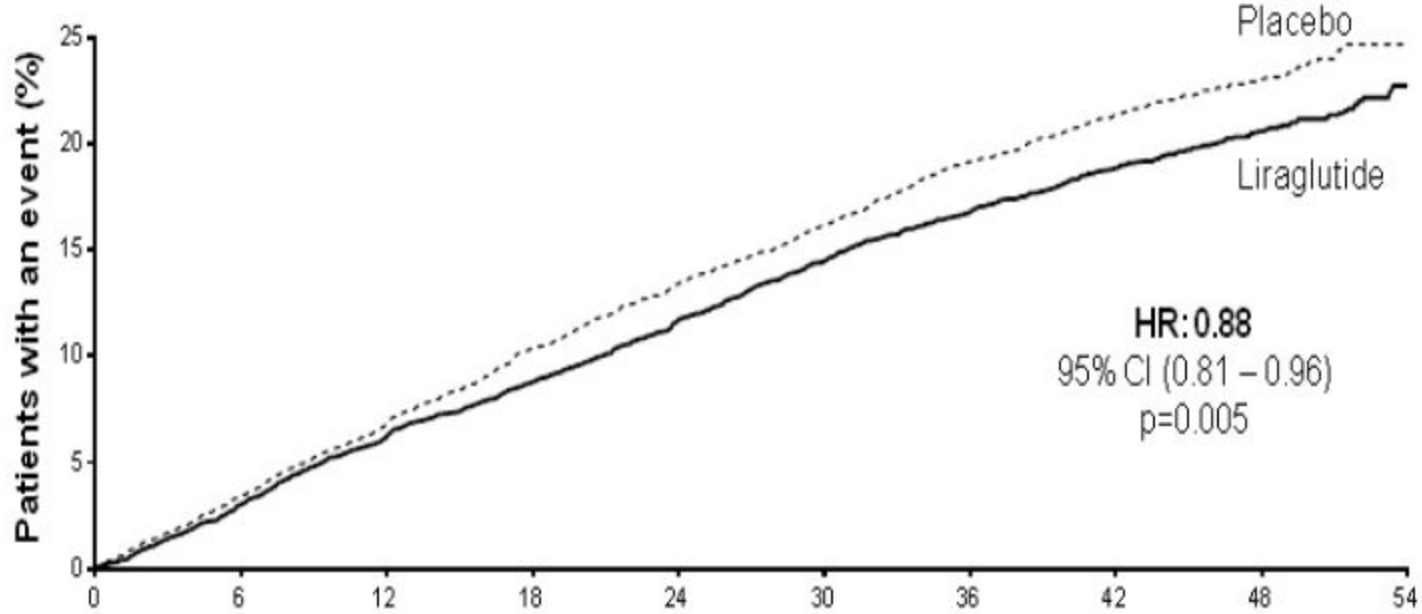
Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months.
CI: confidence interval; HR: hazard ratio.

Expanded MACE

CV death, non-fatal MI, non-fatal stroke, coronary revascularization, or hospitalization for unstable angina pectoris or heart failure



Patients at risk										
Liraglutide	4668	4515	4356	4221	4063	3914	3793	3682	1452	395
Placebo	4672	4506	4336	4157	4002	3857	3697	3581	1410	366

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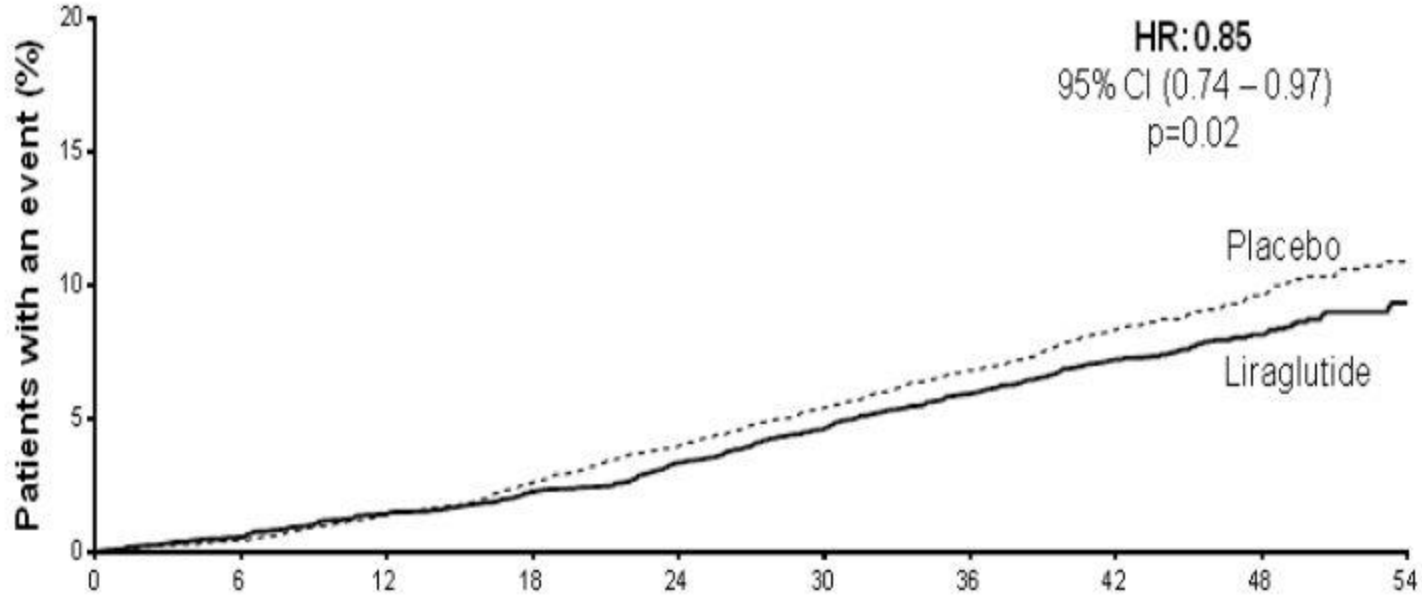
Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months.
CI: confidence interval; CV: cardiovascular; HR: hazard ratio; MACE: major adverse cardiovascular event; MI: myocardial infarction.

All-cause death



Patients at risk										
Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4268	1709	465

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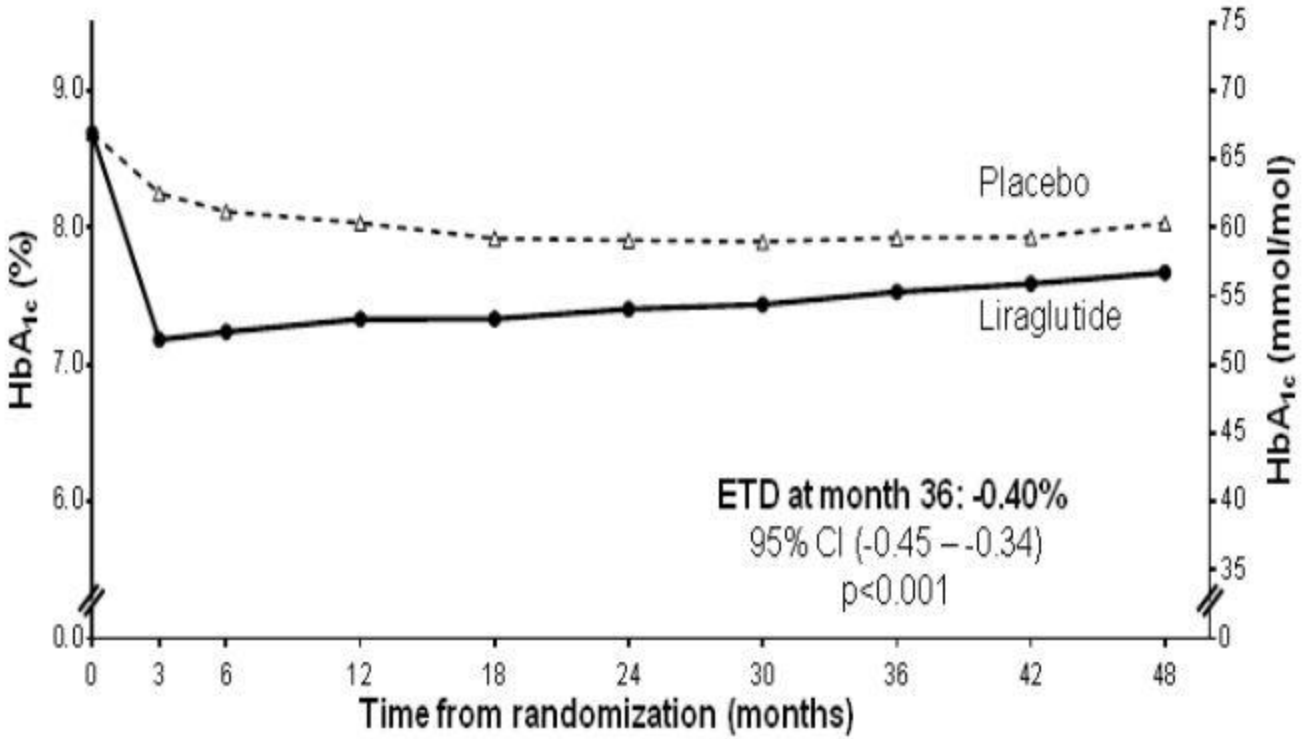
Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; HR: hazard ratio.

HbA_{1c}



Number of patients at each visit

Liraglutide	4668	4402	4355	4295	4135	4034	3877	3810	2349	809
Placebo	4672	4413	4355	4235	4030	3905	3742	3640	2303	756

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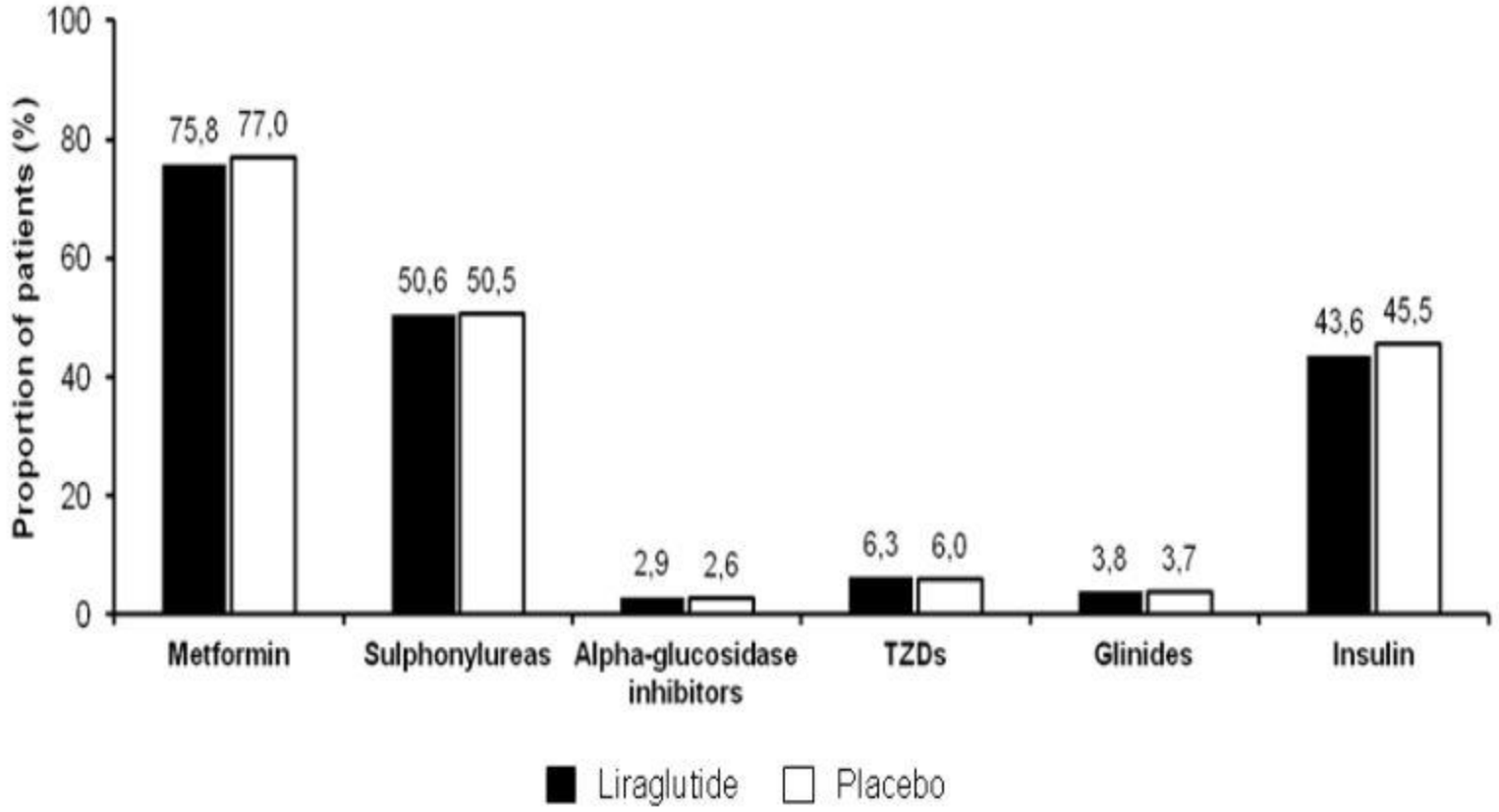
Data are estimated mean values from randomization to month 48.
CI: confidence interval; ETD: estimated treatment difference; HbA_{1c}: glycated hemoglobin.

Antihyperglycemic medication at baseline



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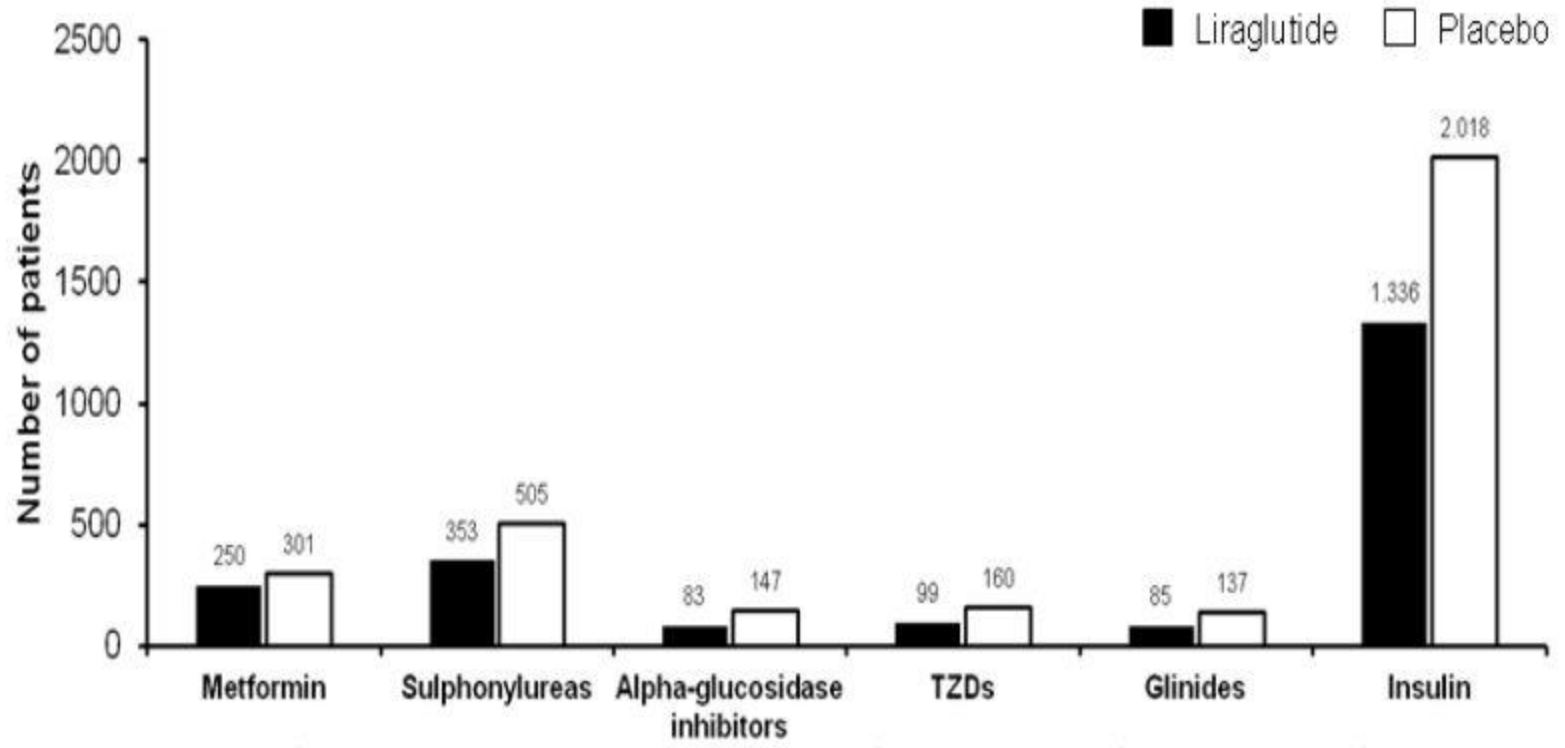
TZD: thiazolidinediones.

Antihyperglycemic medications introduced during trial



Additional classes added	Liraglutide	Placebo
DPP-4 inhibitors	149	170
GLP-1RAs	87	139
SGLT-2 inhibitors	100	130

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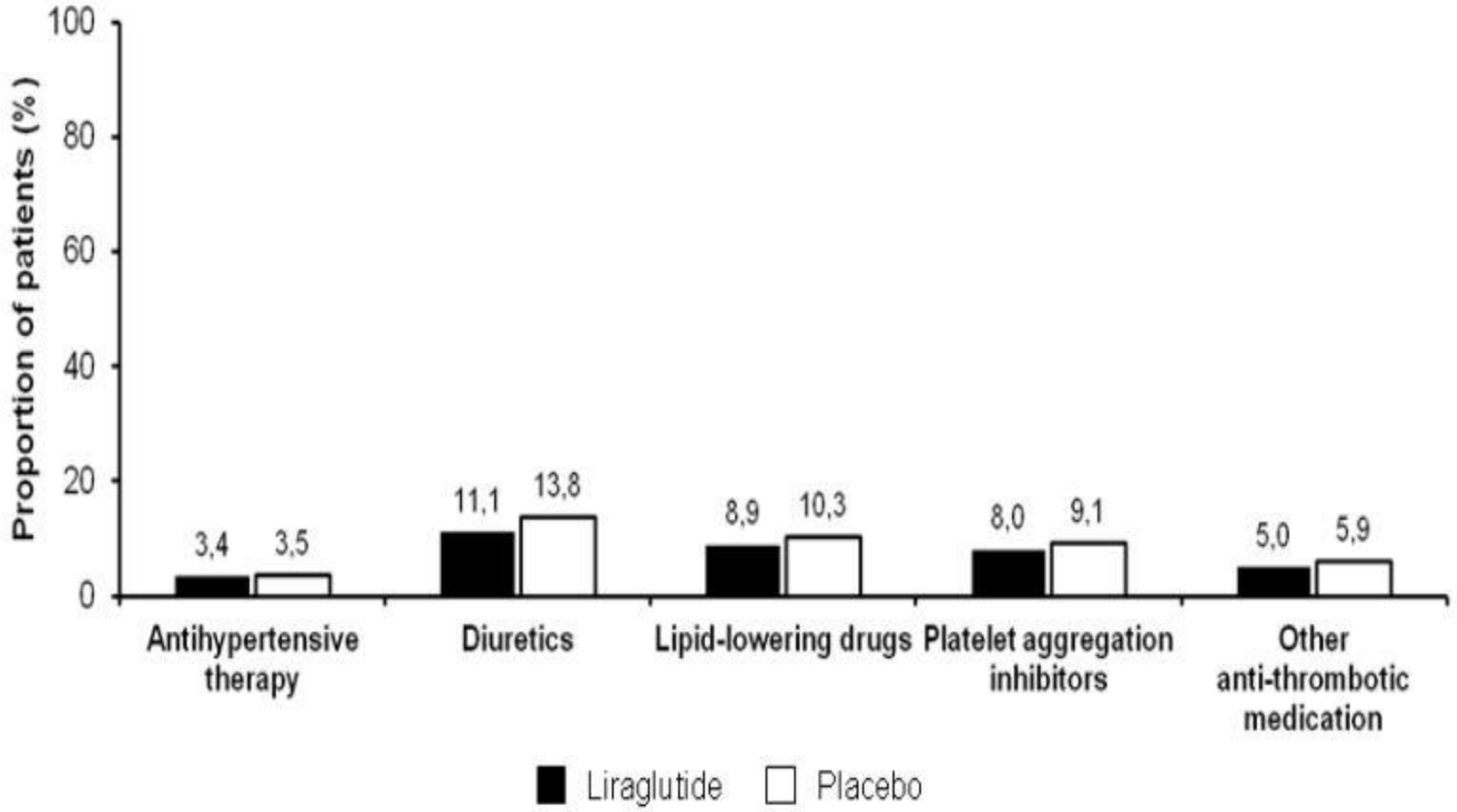
DPP-4: dipeptidyl peptidase-4; GLP-1RA: glucagon-like peptide-1 receptor agonist; SGLT-2: sodium-glucose co-transporter-2; TZD: thiazolidinedione.

Cardiovascular medication introduced during trial



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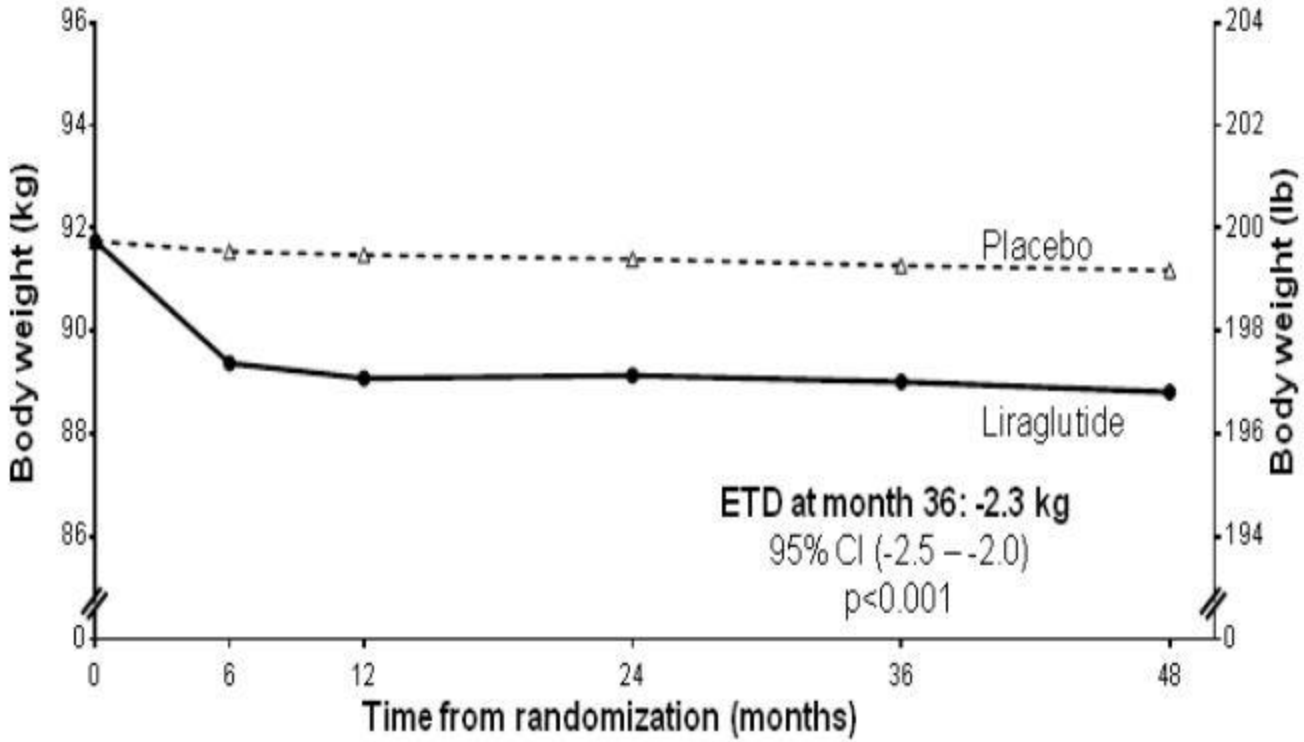
Body weight



Number of patients at each visit

Liraglutide	4667	4434	4324	4088	3835	824
Placebo	4671	4423	4285	3970	3680	766

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

Data are estimated mean values from randomization to last scheduled visit for body weight measurement (month 48).
CI: confidence interval; ETD: estimated treatment difference.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

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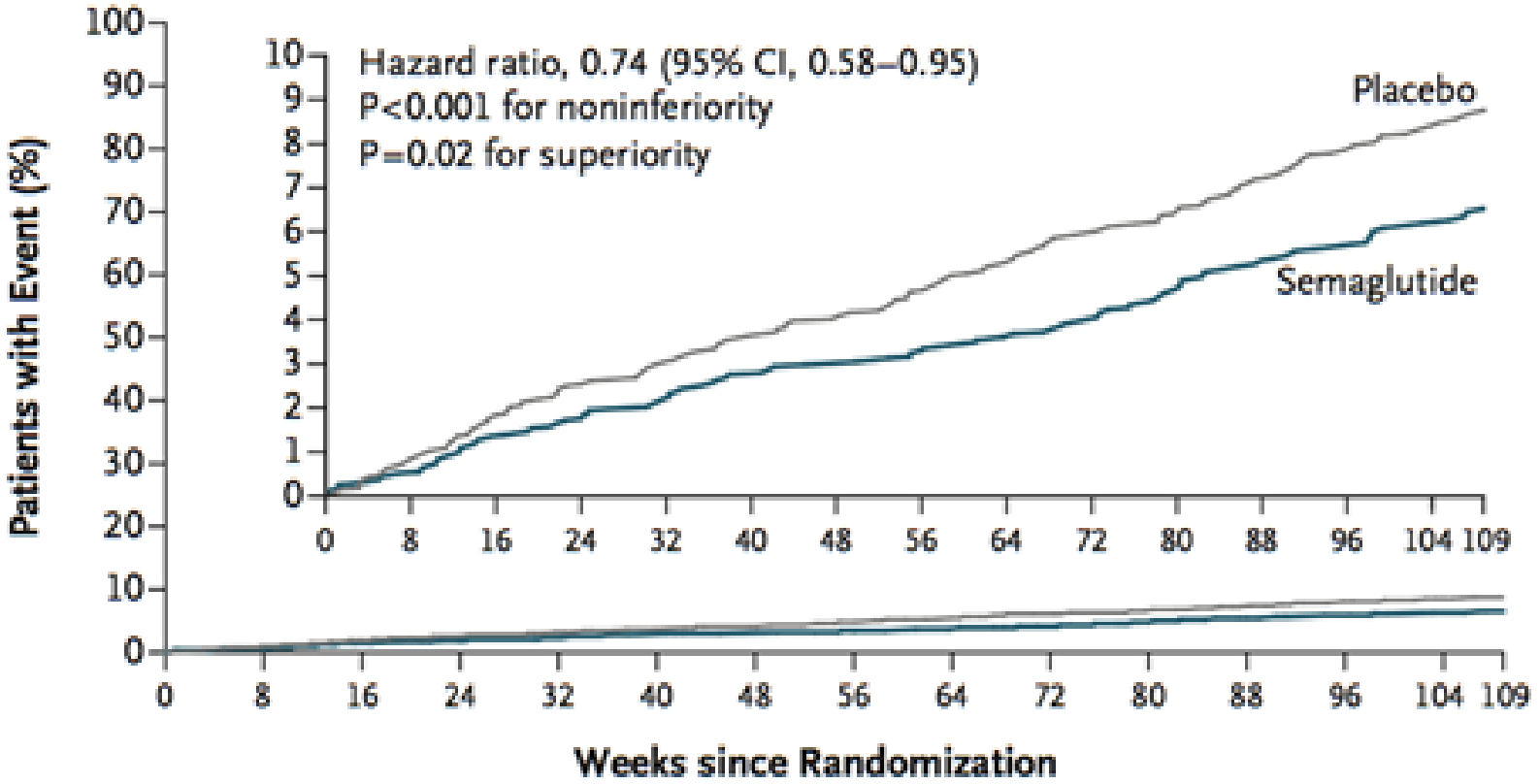
Liraglutide Effect and Action in Diabetes:
Evaluation of cardiovascular outcome Results

A Primary Outcome



No. at Risk

Placebo	1649	1616	1586	1567	1534	1508	1479
Semaglutide	1648	1619	1601	1584	1568	1543	1524

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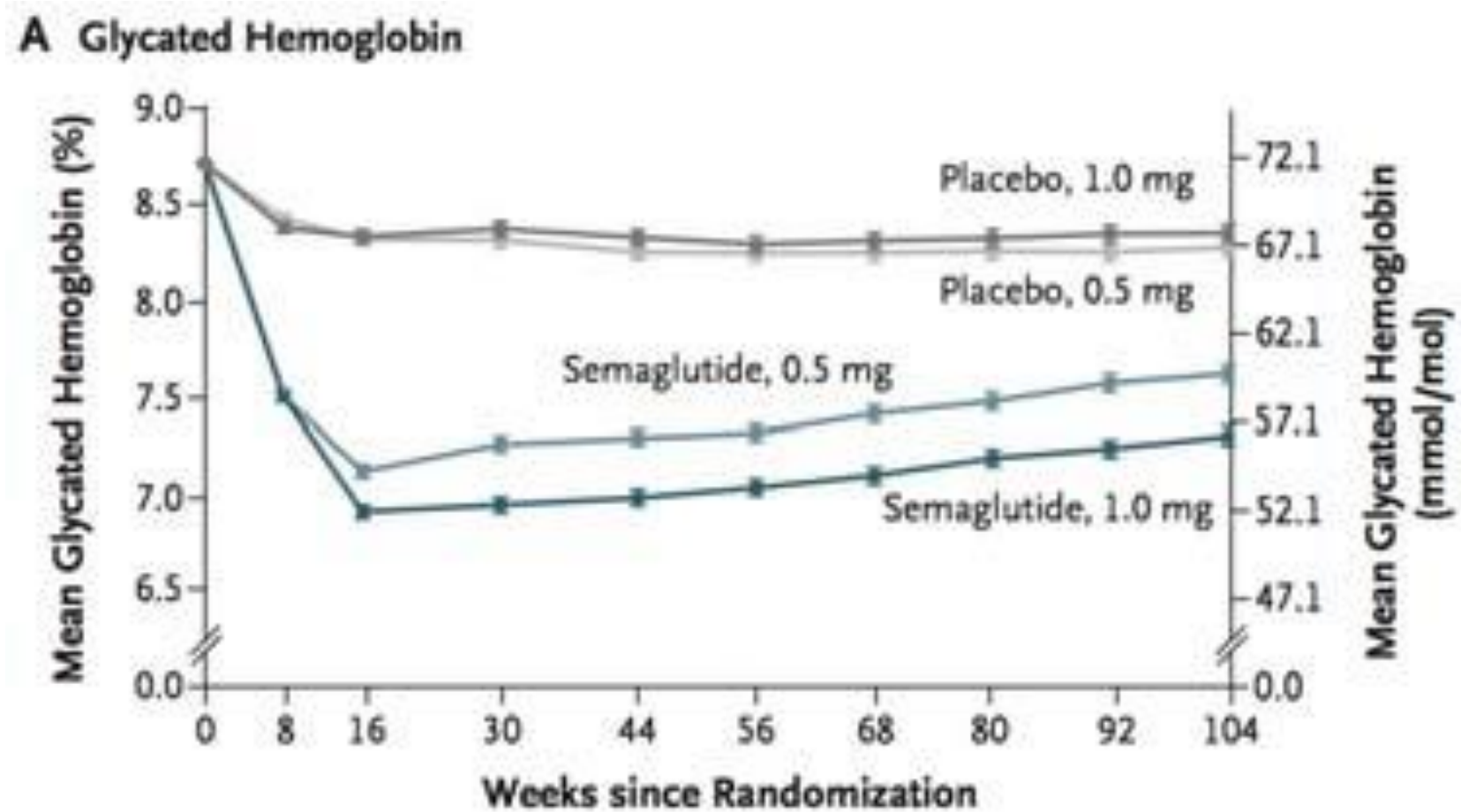

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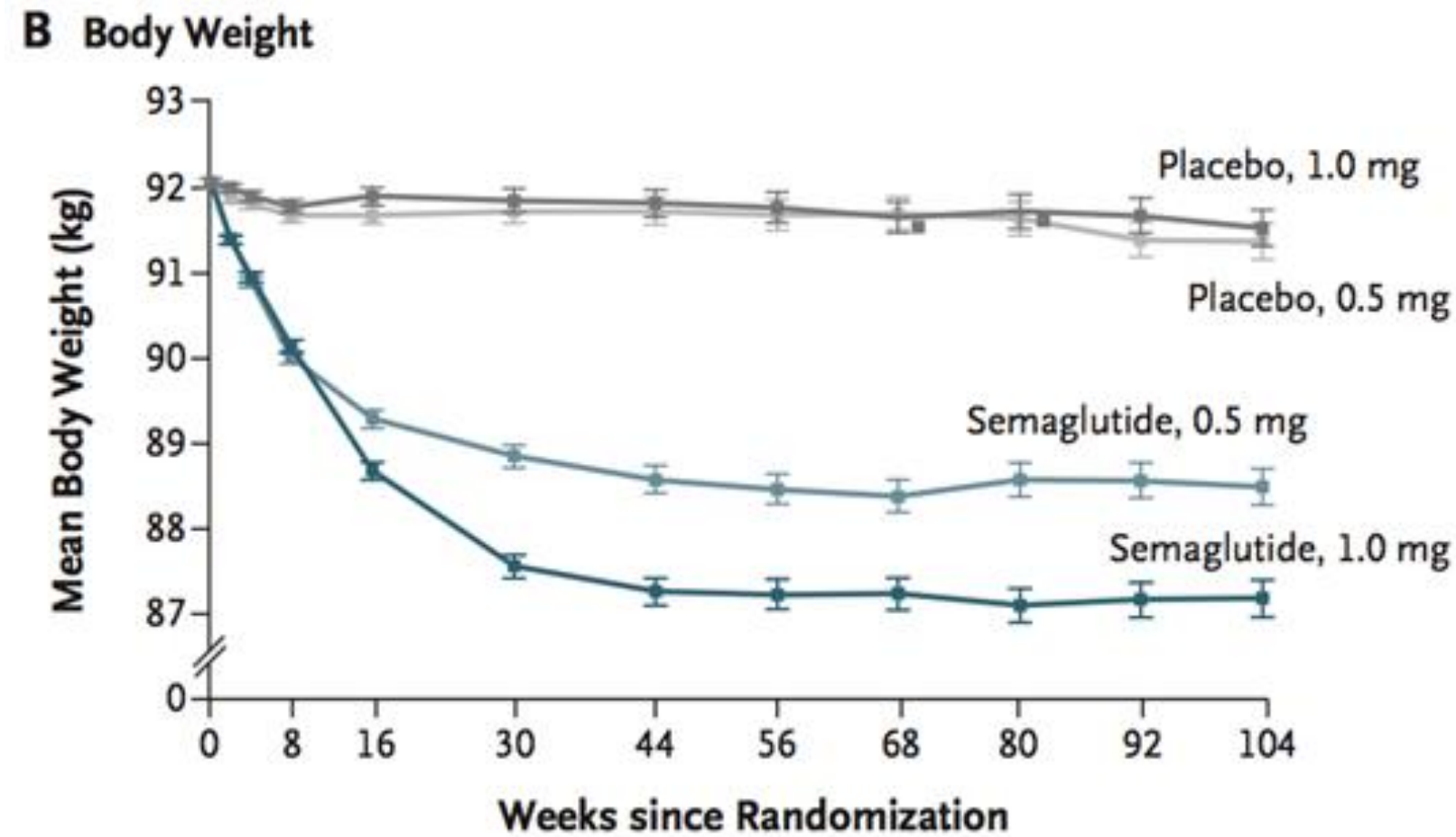

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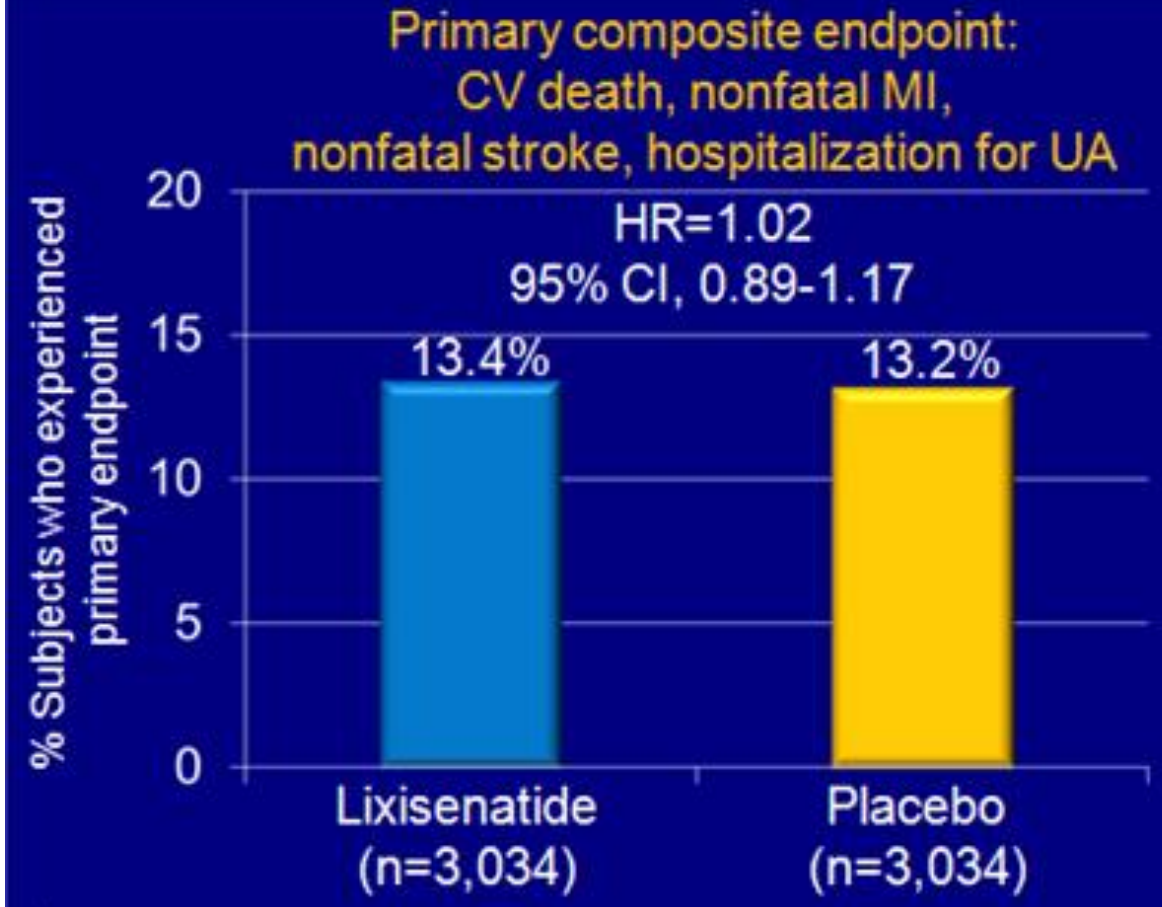
ELIXIA(Lixisenatide)

ELIXA: No Cardiovascular Risks or Benefits With Lixisenatide Vs Placebo



About ELIXA

- First events-driven CV outcomes study to provide data for a GLP-1 receptor agonist
- Randomized, double-blind, placebo-controlled trial
- N=6,068 subjects with type 2 diabetes and recent ACS event
- Randomization:
  - Lixisenatide 10 mcg/d*
  - Placebo

*Up- or down-titrated to maximum 20 mcg/d

ELIXA=Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With Lixisenatide

HR=hazard ratio; UA=unstable angina

Lixisenatide is an investigational agent; not yet FDA

Pfeffer MA, et al. Presented at the American Diabetes Association 75th

ELIXA: Cardiovascular Outcomes for Lixisenatide Vs Placebo

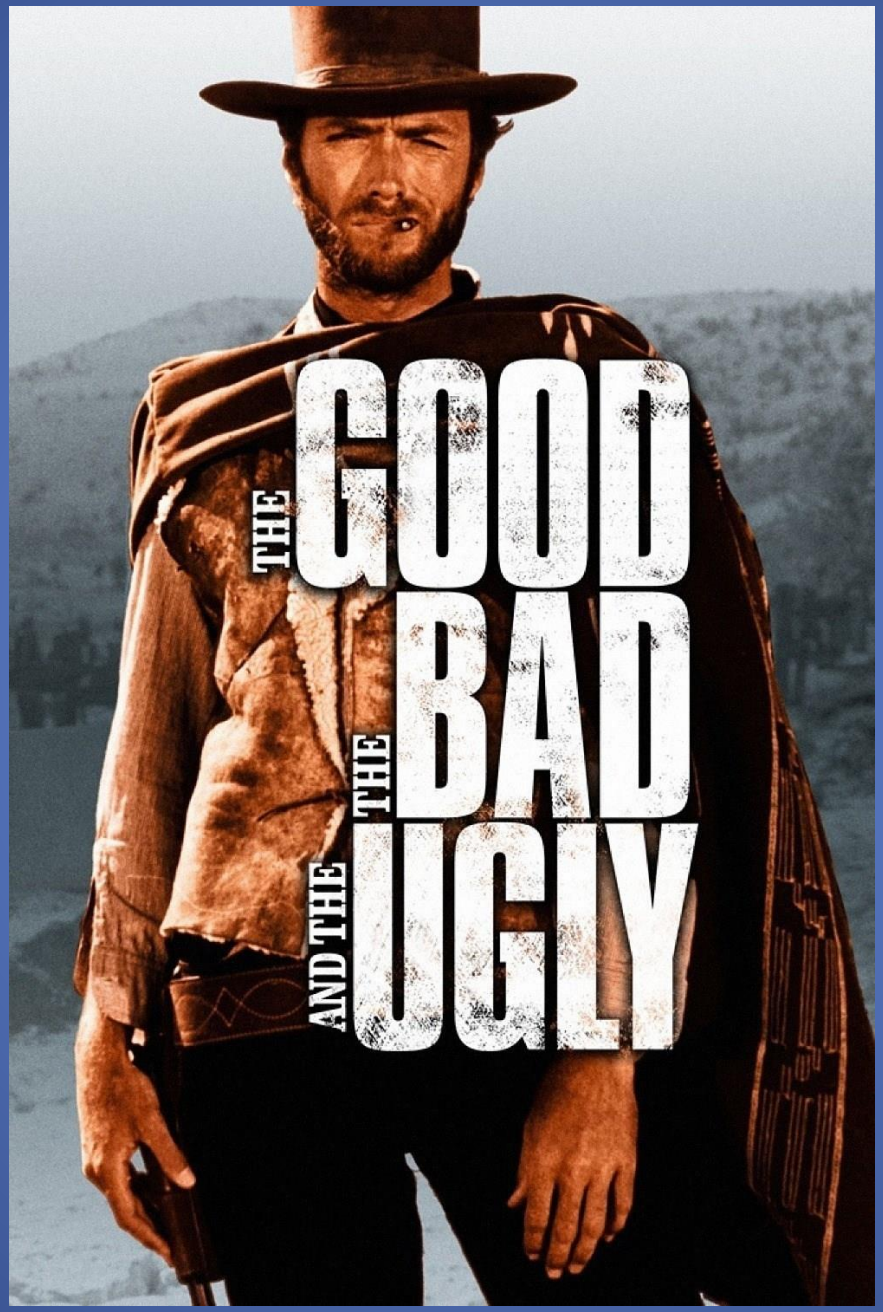
No increased risk for lixisenatide vs placebo for:

Primary composite outcome: CV death, nonfatal MI, nonfatal stroke, hospitalization for UA	Lixisenatide 13.4%	Placebo 13.2%
	HR=1.02 (95% CI: 0.89-1.17)	
Primary outcome plus hospitalization for heart failure	HR=0.97 (95% CI: 0.85-1.10)	
Hospitalization for heart failure	HR=0.96 (95% CI: 0.75-1.23)	
All-cause mortality	HR=0.94 (95% CI: 0.78-1.13)	

ELIXA=Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With Lixisenatide
HR=hazard ratio

SUMMARY

- CVD outcome trials potentially establishes safety of diabetes agents
- CVD outcome trials potentially establishes efficacy of agents
- These outcome trials and others will hopefully change the scope of therapeutic diabetes including modifying clinical paths and teach our future physicians and patients the impact of CVD, diabetes and safety.


THE GOOD
THE BAD
AND THE UGLY