IMPACT OF DIABETES DRUGS ON CARDIOVASCULAR AND RENAL DISEASE IN TYPE 2 DIABETES
Roma, 2-3 febbraio 2018

Effetto dei nuovi farmaci sul cuore: GLP1-RA

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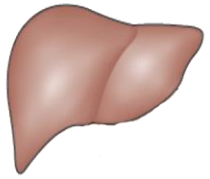
Disclosure Statement

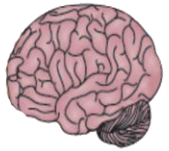
- Stefano Genovese, in the last three years, has received speaking and/or consulting fees from:
  - Abbott Diabetes Care
  - AstraZeneca
  - Boehringer Ingelheim
  - Bristol-Myers Squibb
  - Bruno Farmaceutici
  - Eli Lilly
  - Janssen
  - Lifescan
  - Merck Sharp & Dohme
  - Novartis
  - Novo Nordisk
  - Sanofi
  - Takeda
- and research grants from:
  - Novartis

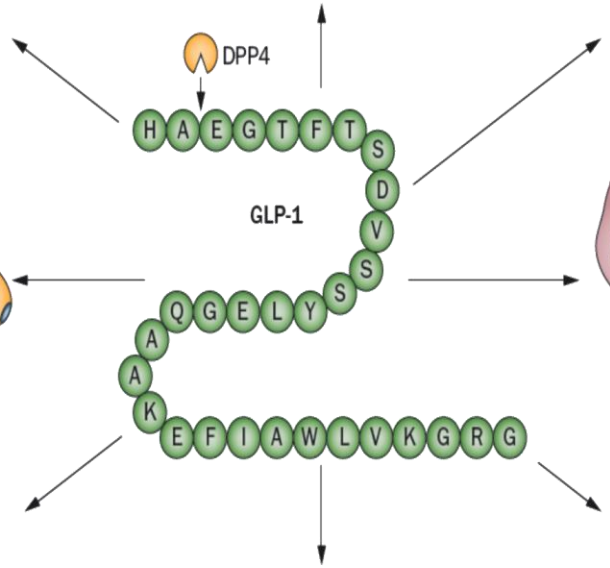
GLP-1: un ampio spettro di azioni biologiche

Fegato
↑ Immagazzinamento del glicogeno

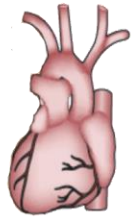


Cervello
↑ Neuroprotezione
↑ Memoria

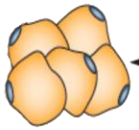




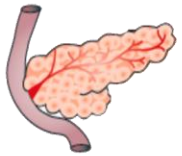
Cuore
↑ Contrattilità miocardica
↑ Frequenza cardiaca
↑ Captazione del glucosio a livello del miocardio
↓ Danno miocardico indotto da ischemia



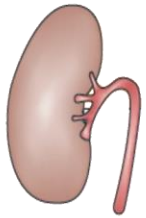
Cellule adipose
↑ Captazione del glucosio
↑ Lipolisi



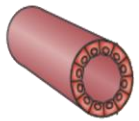
Pancreas
↑ Formazione di nuove cellule β
↓ Apoptosi delle cellule β
↑ Biosintesi dell'insulina



Rene
↑ Natriuresi



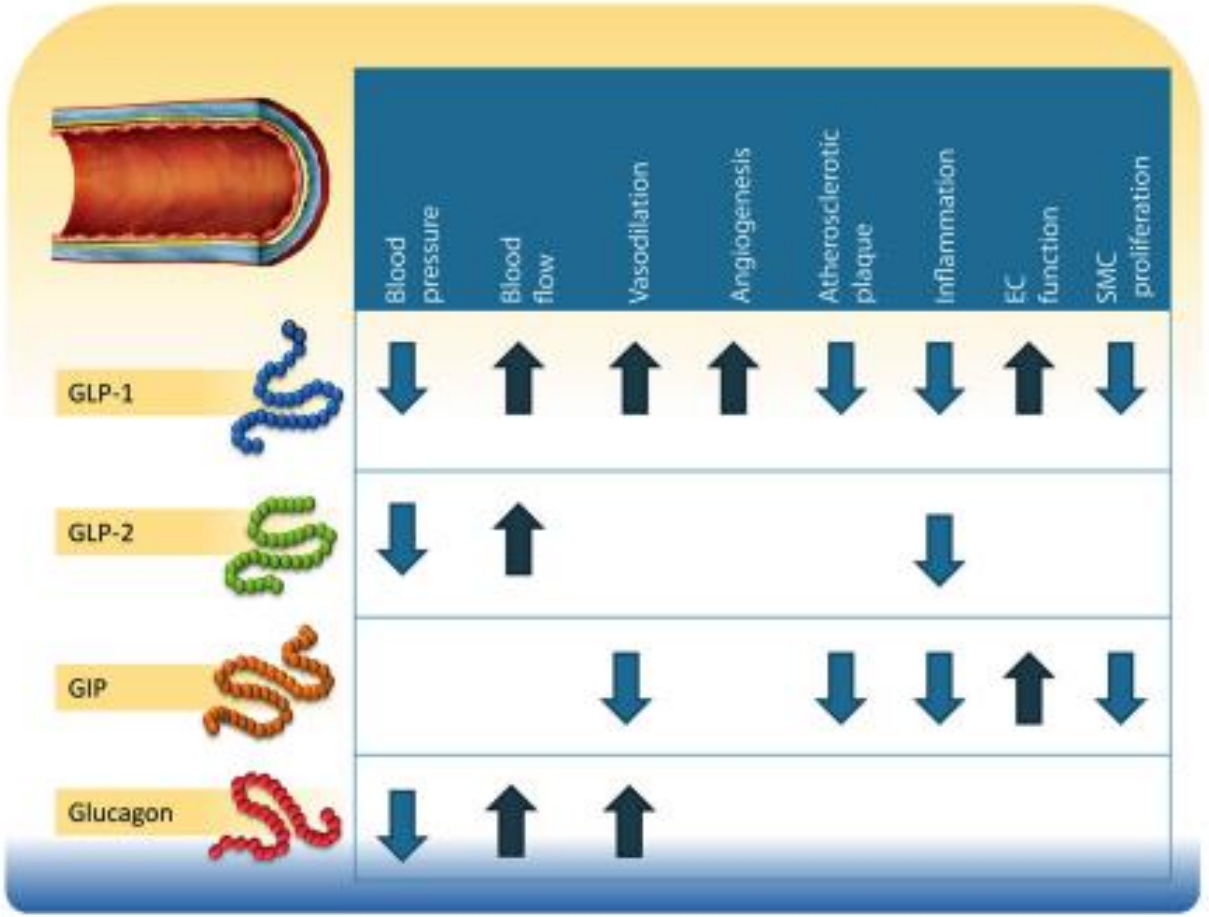
Vaso sanguigno
↑ Vasodilatazione endotelio-dipendente



Muscolo scheletrico
↑ Captazione del glucosio

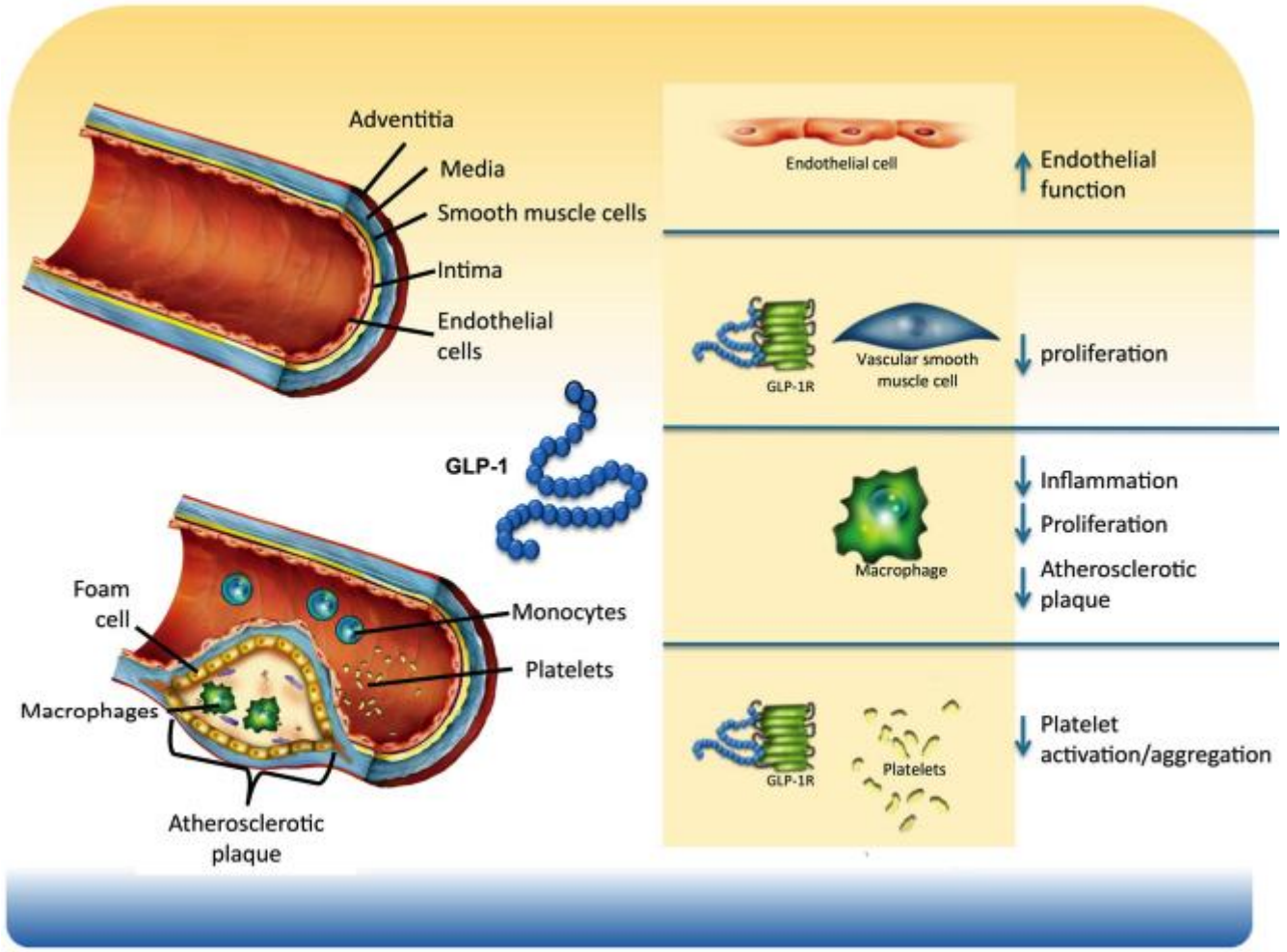
Meier JJ Nat rev endocrinol. 2012;8:728-42

CV effects of incretins



Pujadas et al. End Rev 2016

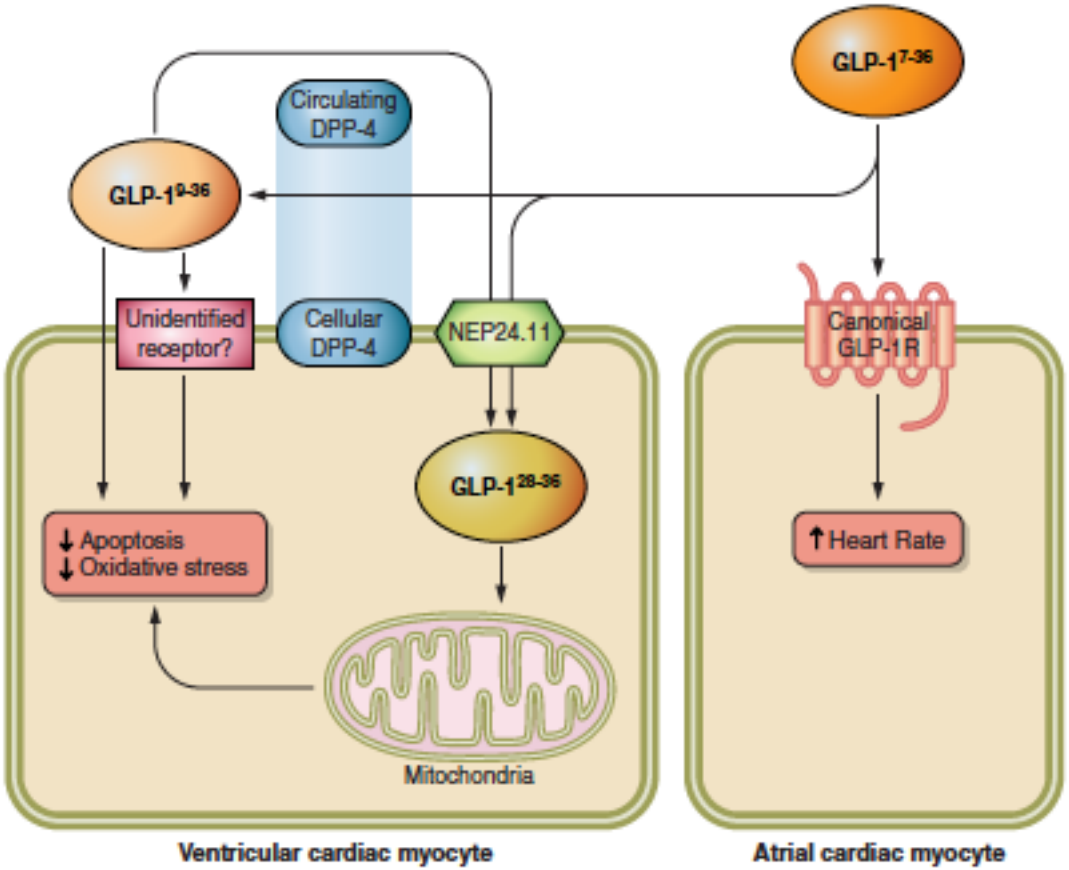
Effects of GLP-1 on atherosclerosis



Pujadas et al. End Rev 2016

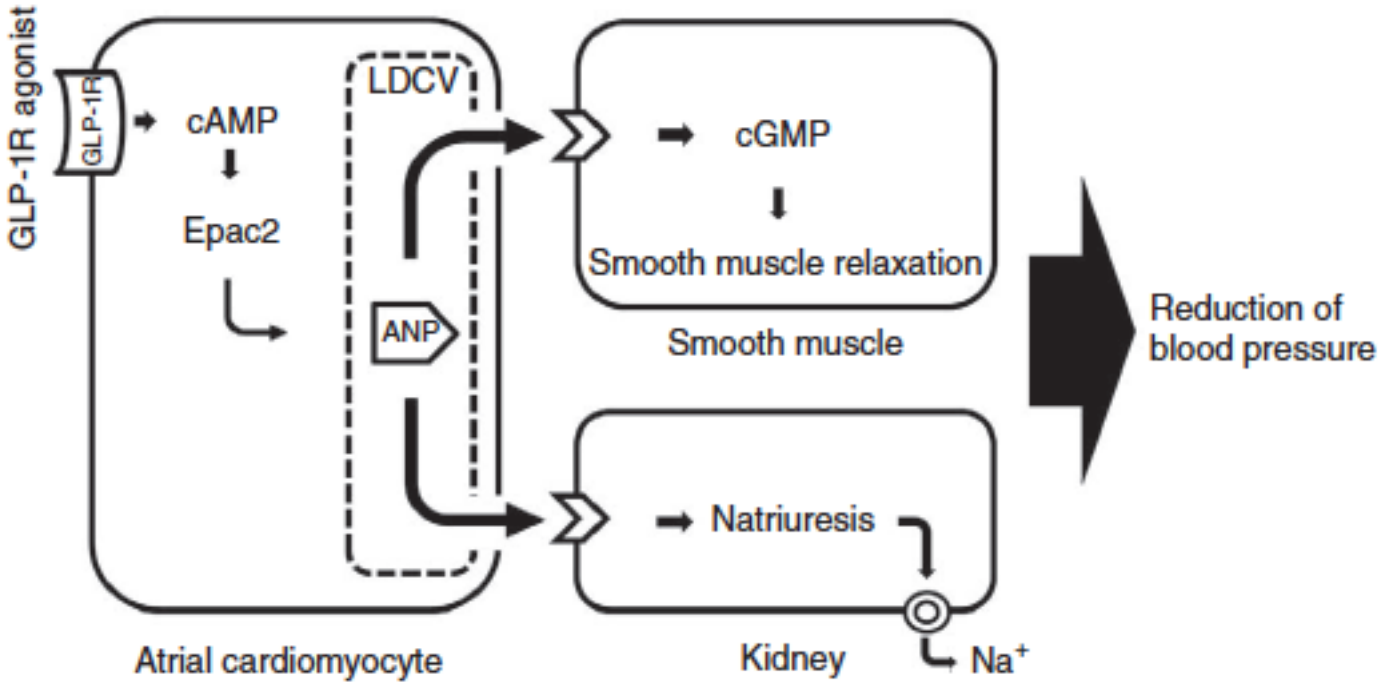
Myocardial effect of GLP 1

Potential GLP-1-mediated actions in atrial and ventricular cardiac myocytes



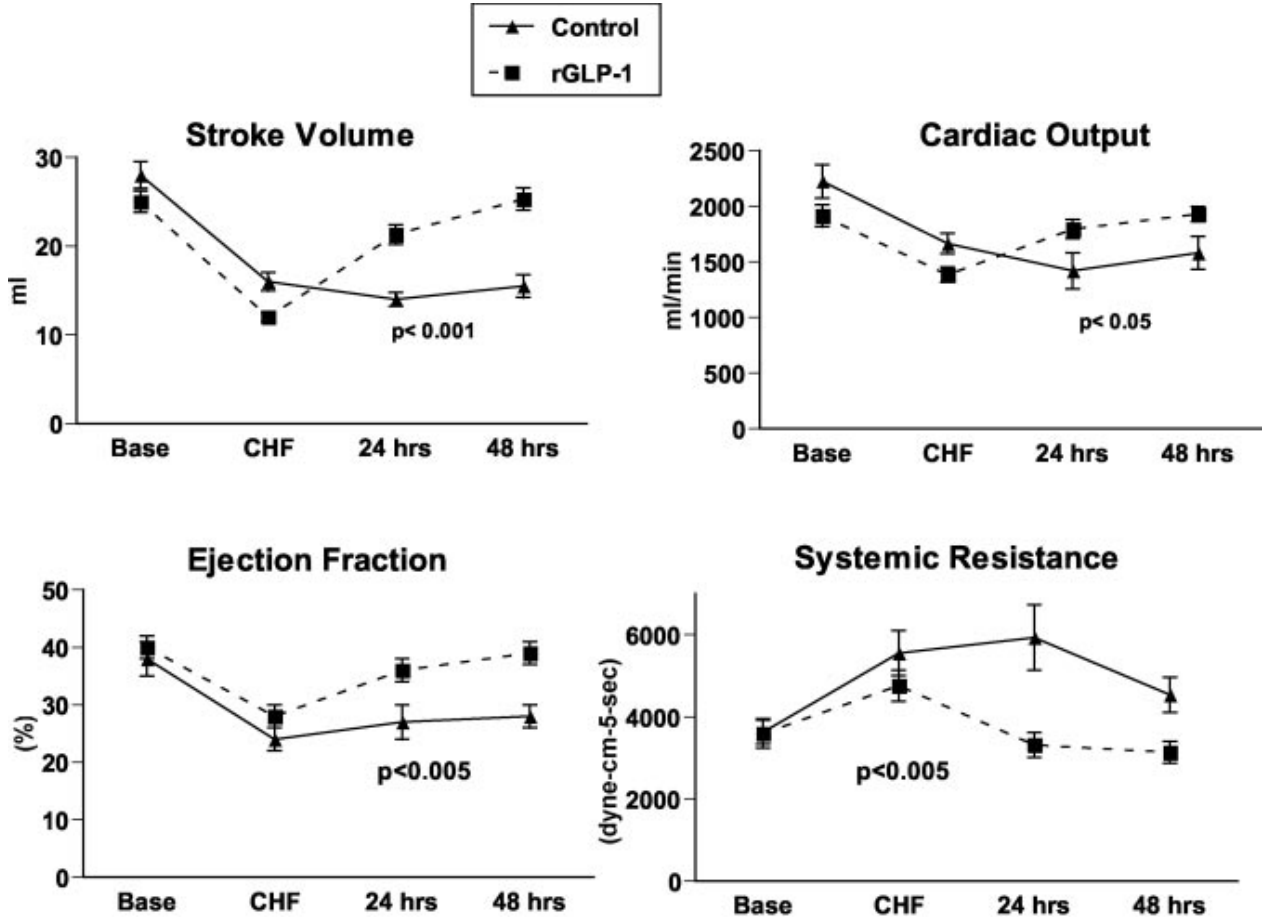
Ussher JR, Am J Physiol Heart Circ Physiol. 2014

GLP-1 receptor activation and Epac2 link atrial natriuretic peptide secretion to control of blood pressure



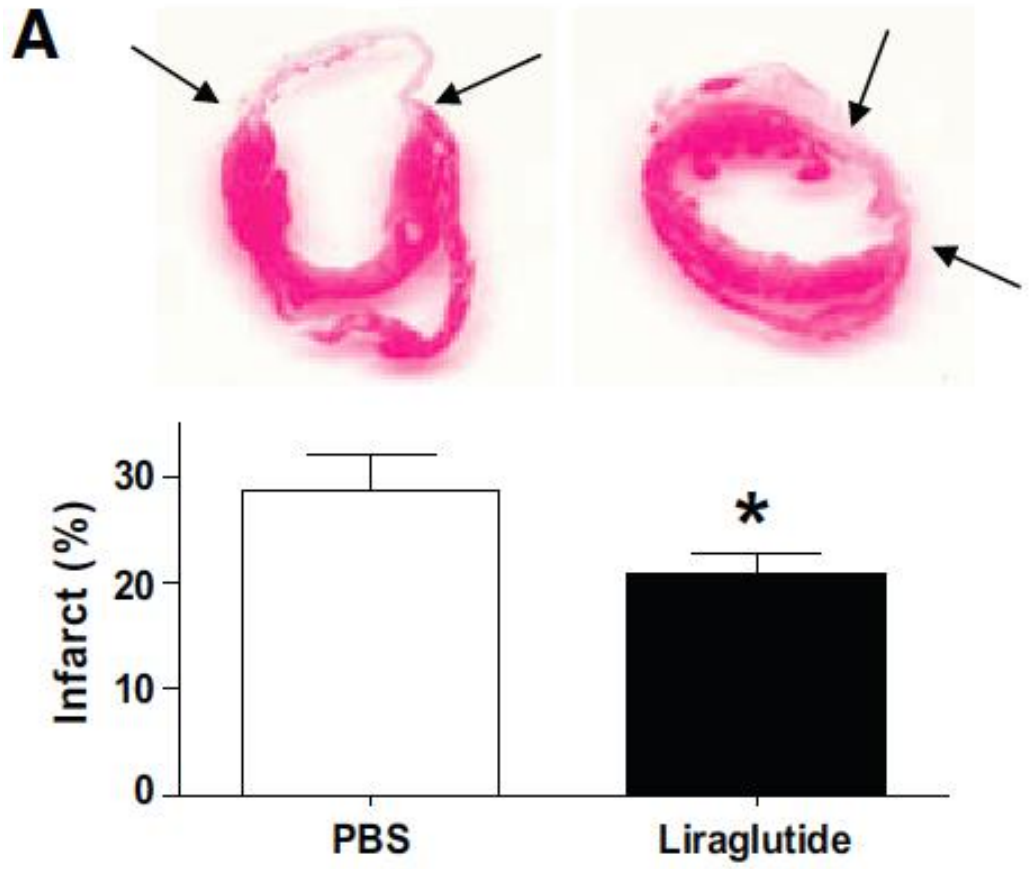
M. Kim Nat Med. 2013 May;19(5):567-75

Effects of rGLP-1 on cardiac function in dogs with pacing-induced dilated cardiomyopathy



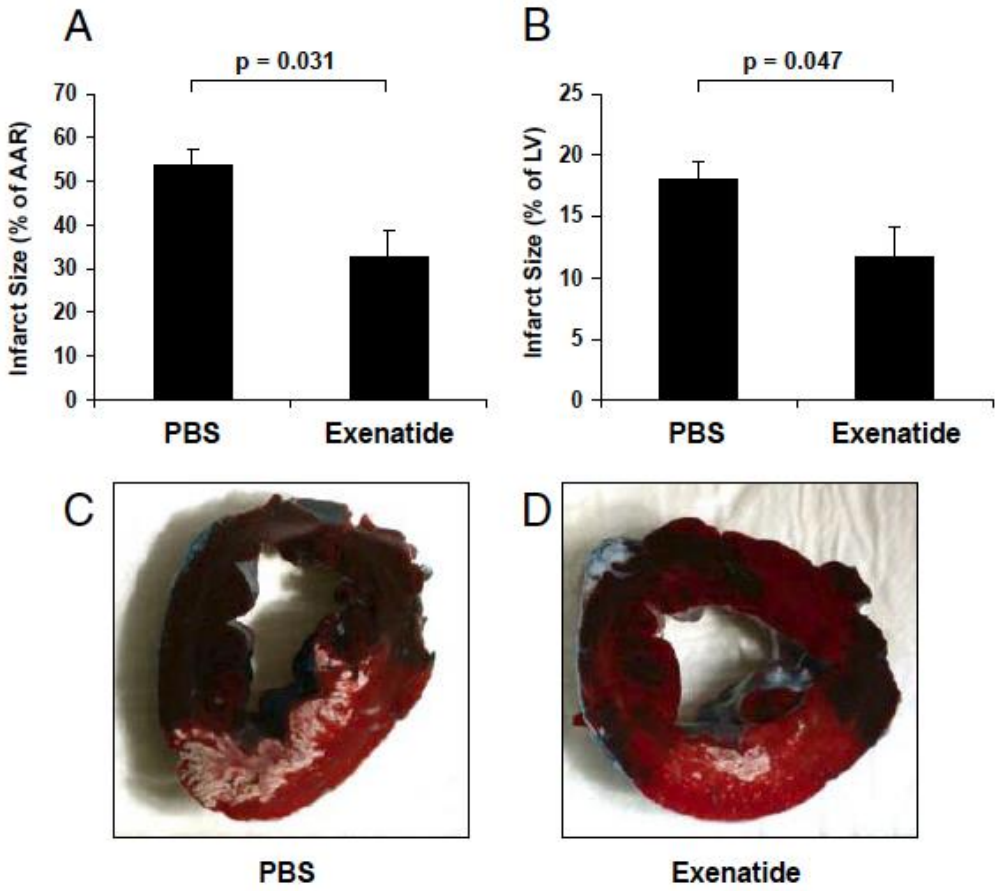
NIkolaidis LA et al. Circulation 2004

Effects of liraglutide pretreatment on infarct size in mice with experimental MI



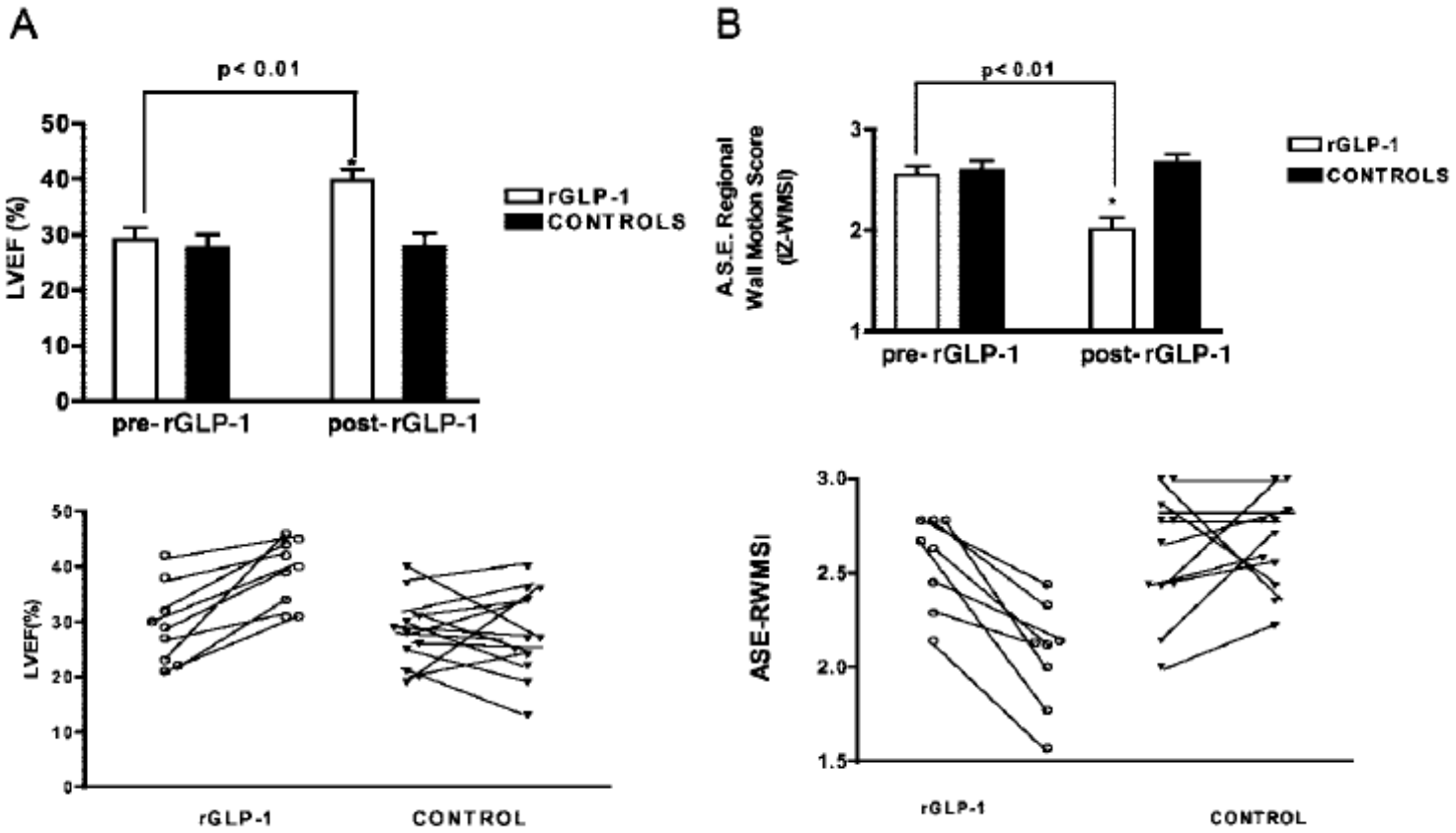
Noyan- Ashraf MH et al. Diabetes 58:975–983, 2009

Exenatide reduces infarct size and improves cardiac function in a porcine model of ischemia and reperfusion injury



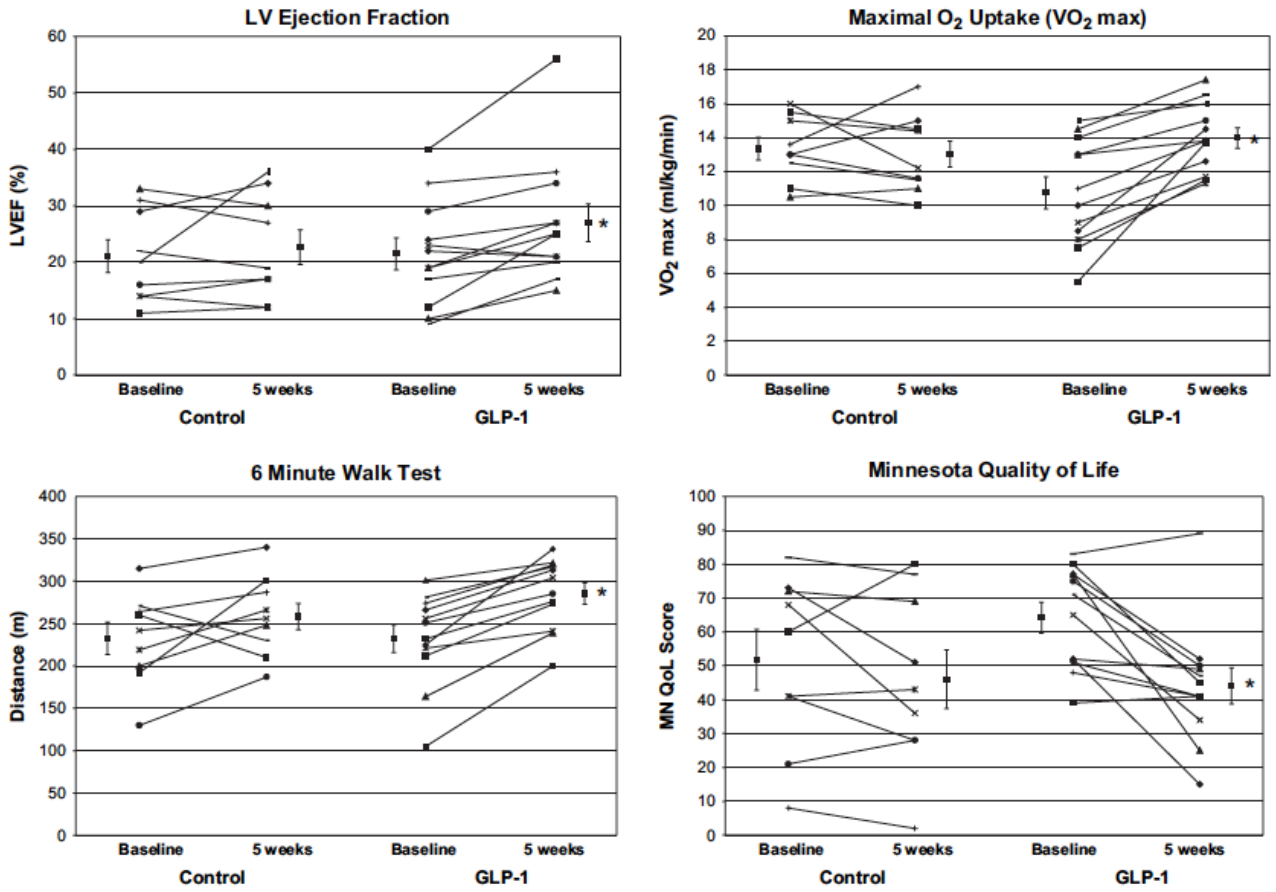
Timmers L et al. JACC Vol. 53, No. 6, 2009

Effects of GLP-1 in patients with AMI and LV dysfunction after successful reperfusion



Nikolaidis LA et al. Circulation. 2004;109:962-965

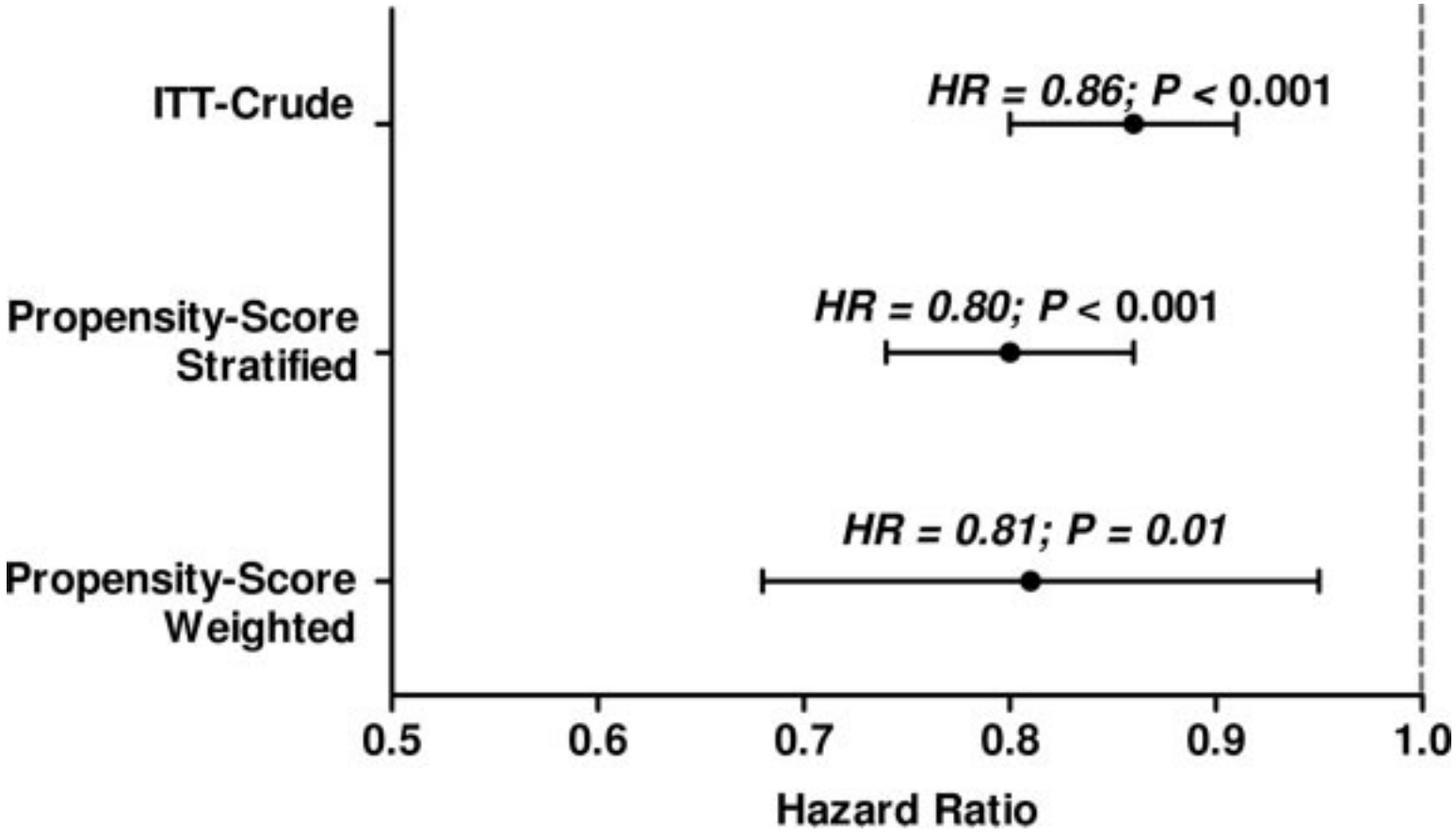
GLP-1 infusion improves LV ejection fraction and functional status in non diabetic patients with CHF



Sokos GG et al. Journal of Cardiac Failure Vol. 12 No. 9 2006

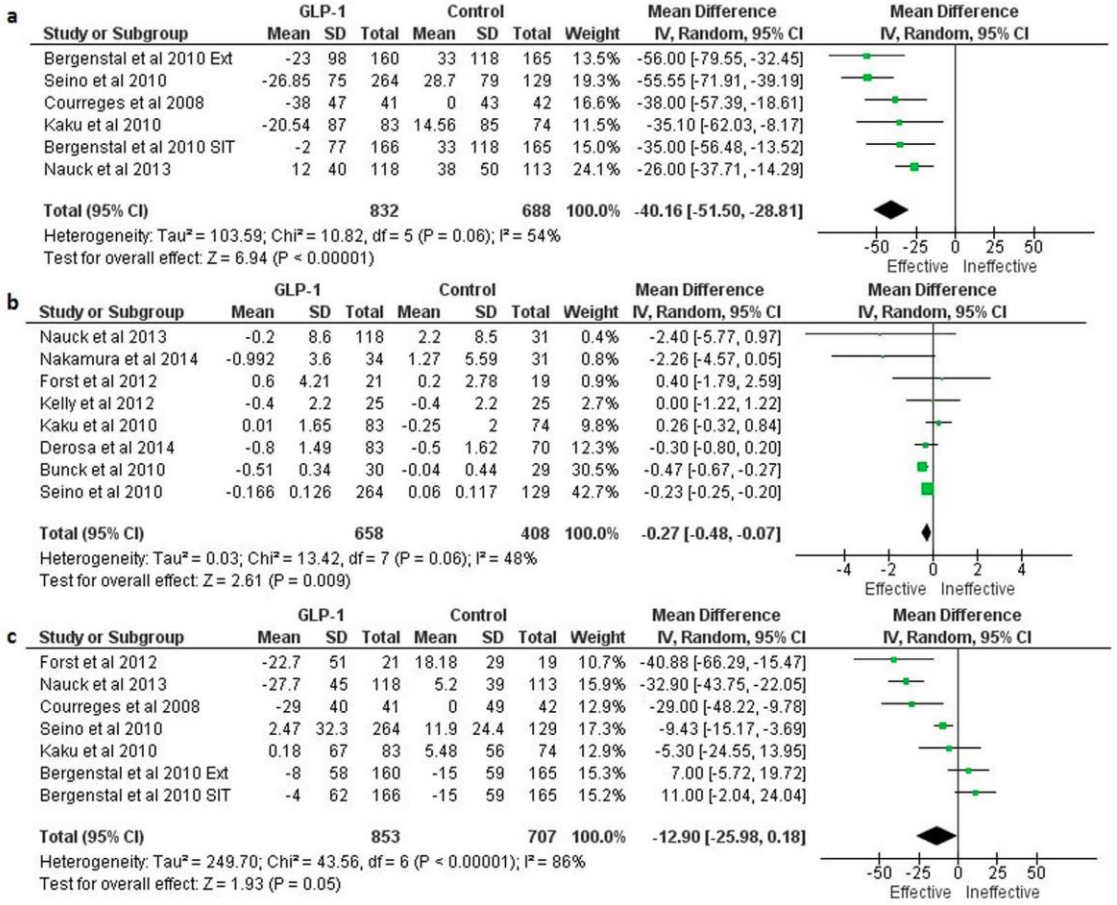
Risk of CVD events in T2DM patients treated with exenatide: a retrospective analysis of the LifeLink database

exenatide (n=21,754)
other drugs (n=361,771)



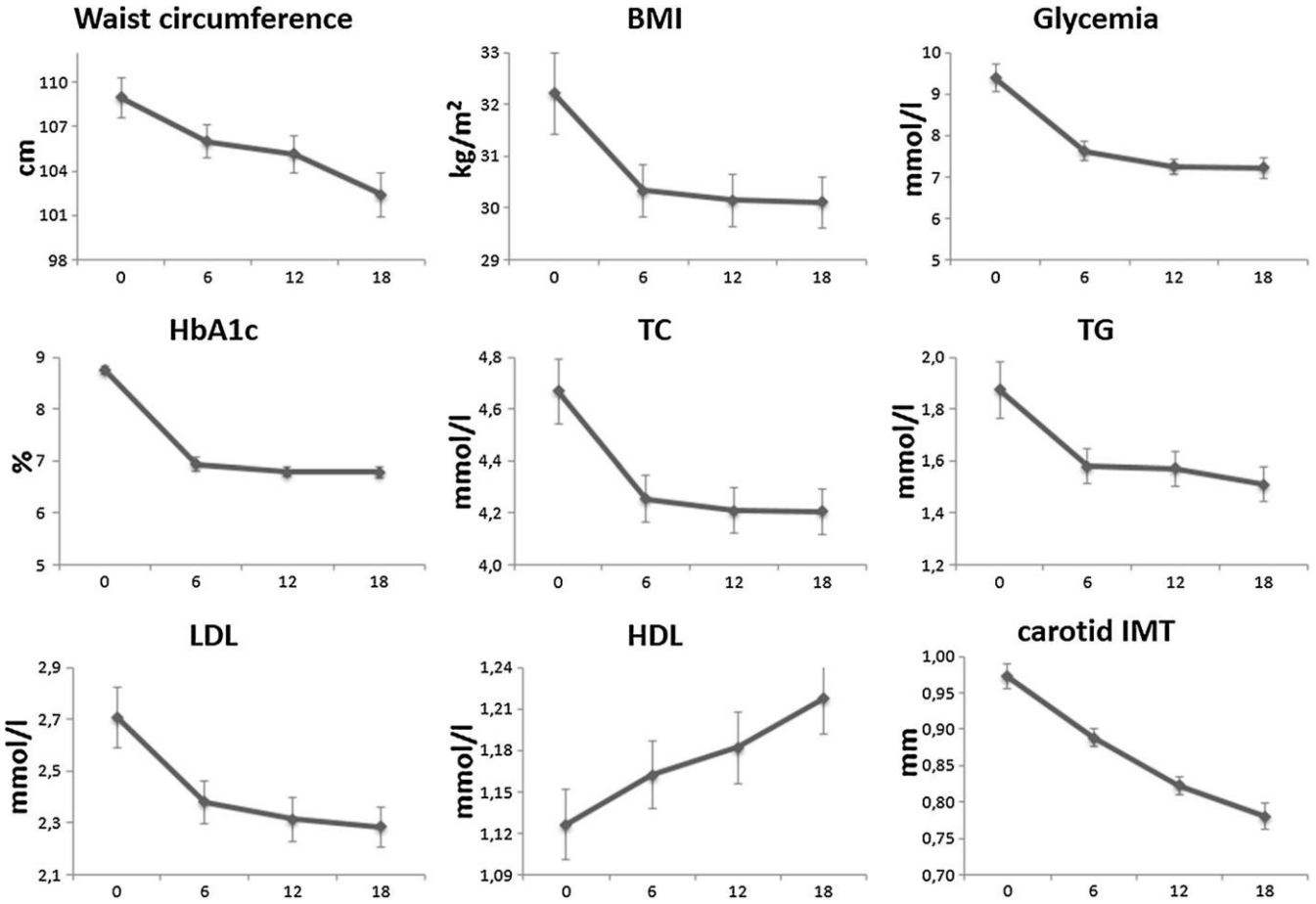
Best JH et al. Diabetes Care 34:90–95, 2011

The effects of GLP-1 based therapies on: BNP, hsCRP and PAI-1



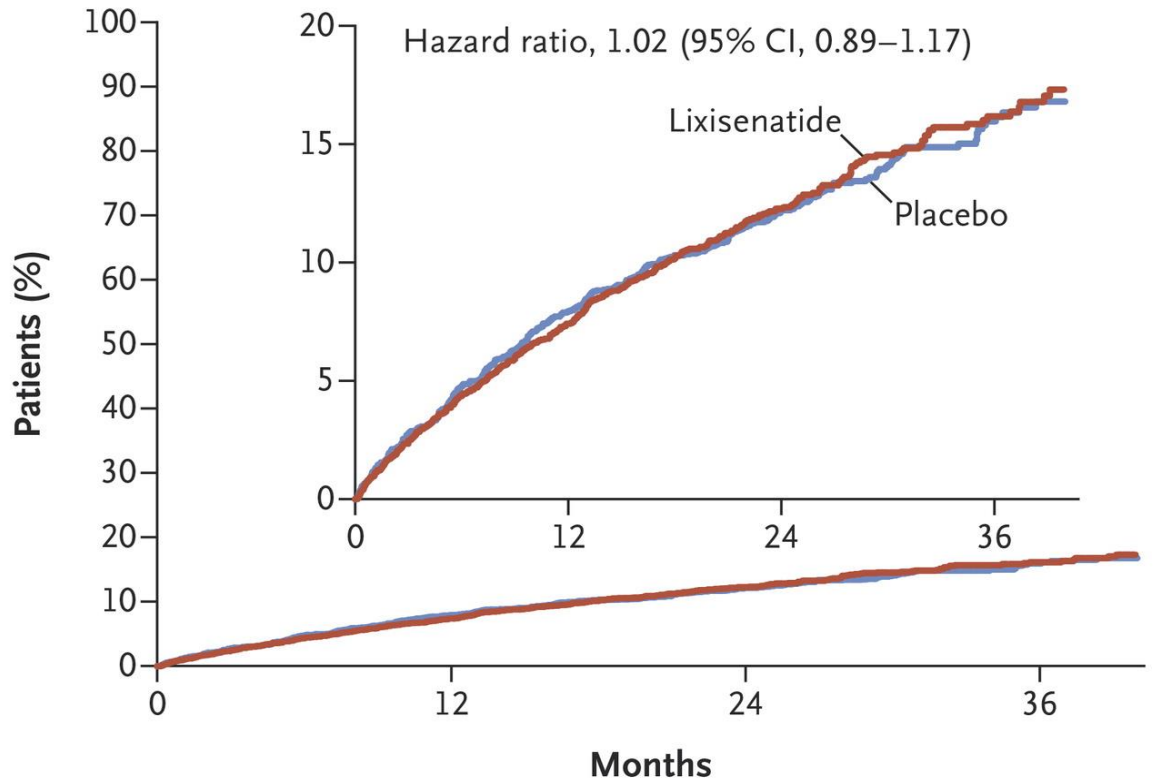
Song X et al. Sci Rep 2015

Changes in cardio-metabolic parameters with liraglutide: 18-month prospective, real-world study



Rizzo et al. Cardiovasc Diabetol (2016) 15:162

Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome



No. at Risk

Placebo	3034	2759	1566	476
Lixisenatide	3034	2785	1558	484

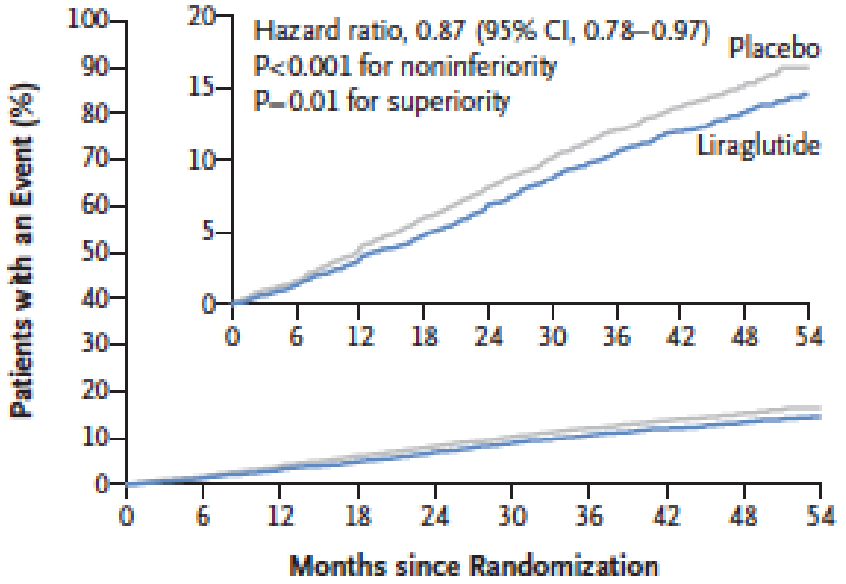
Pfeffer MA et al. N Engl J Med 2015;373:2247-2257.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

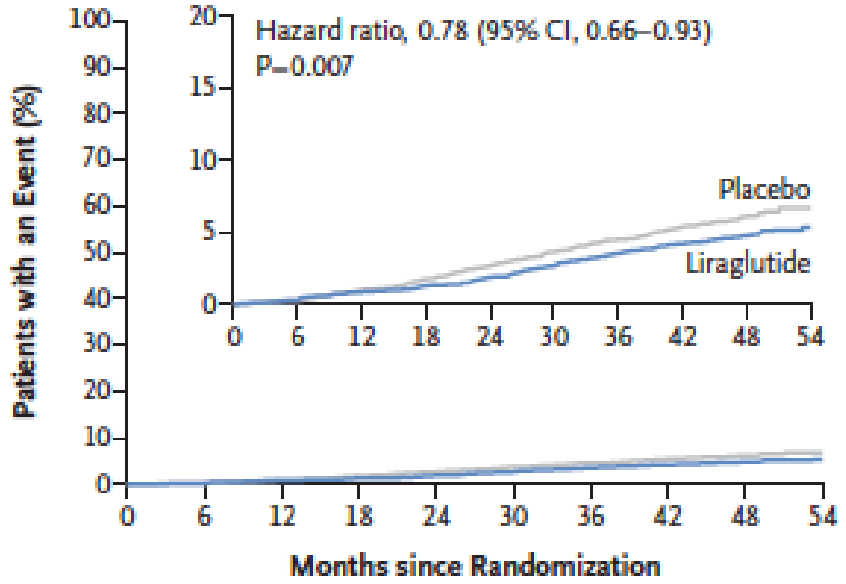
Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

A Primary Outcome



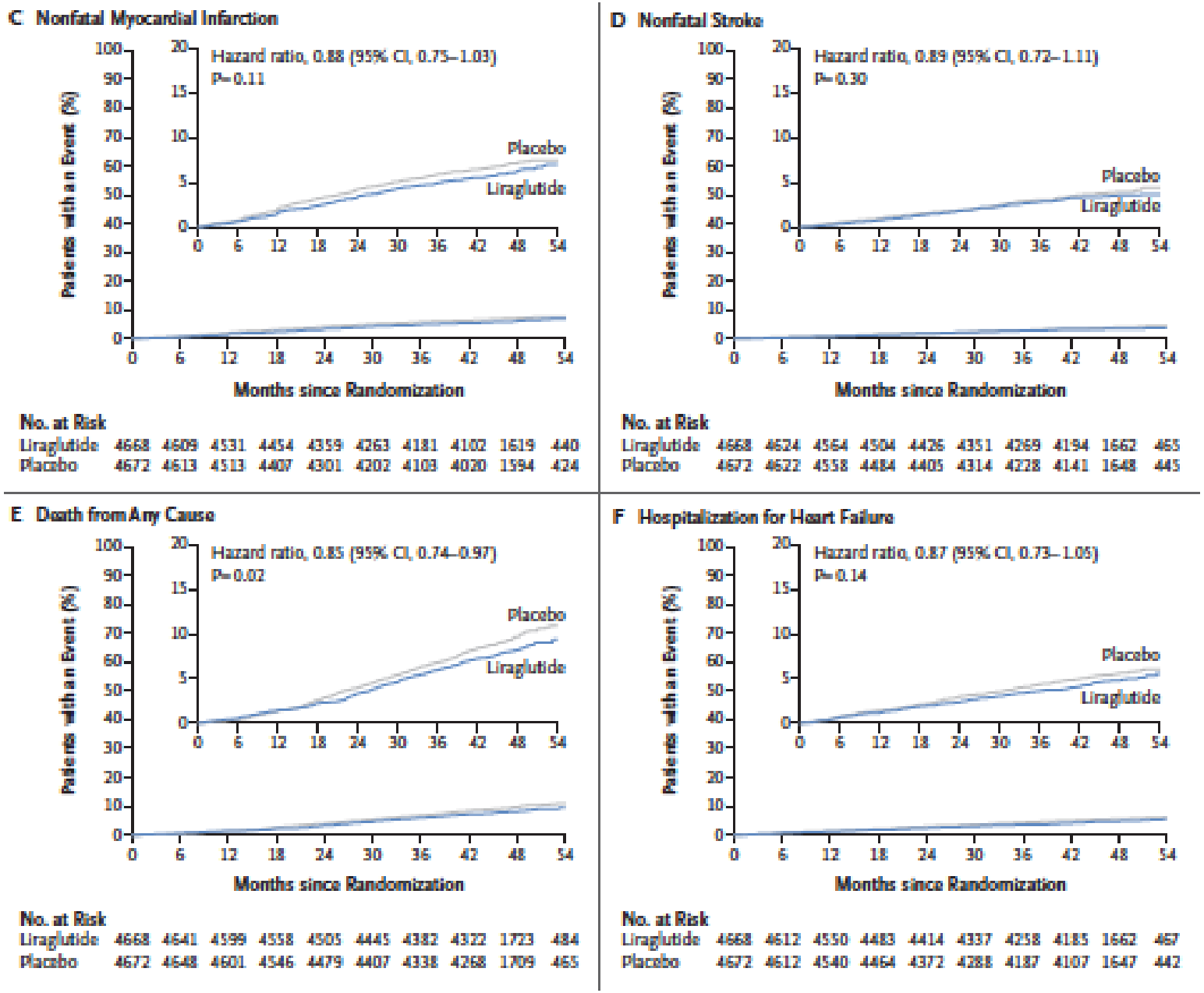
No. at Risk										
Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

B Death from Cardiovascular Causes

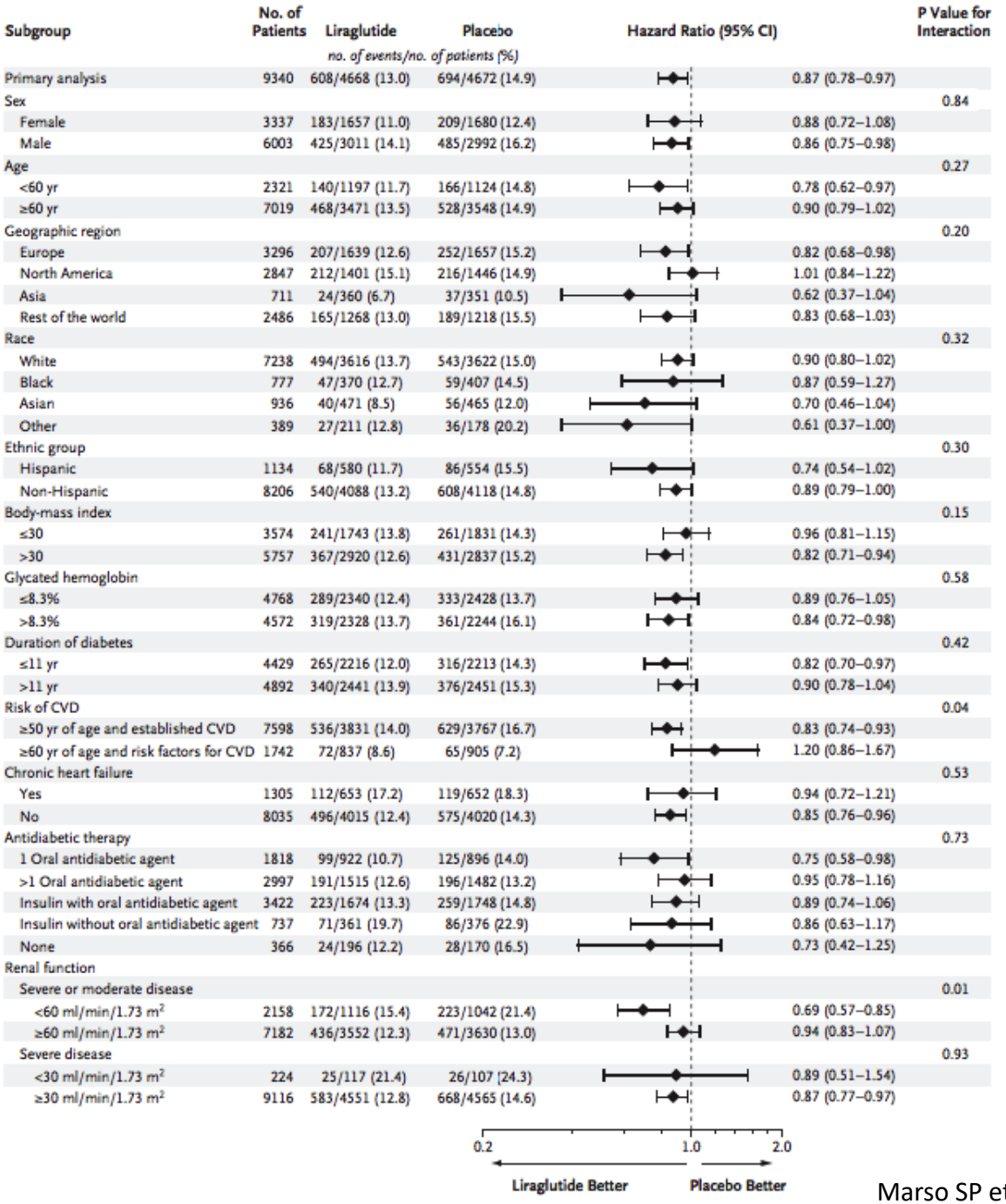


No. at Risk										
Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

Marso SP et al N Engl J Med. 2016 Sep 15. [Epub ahead of print]



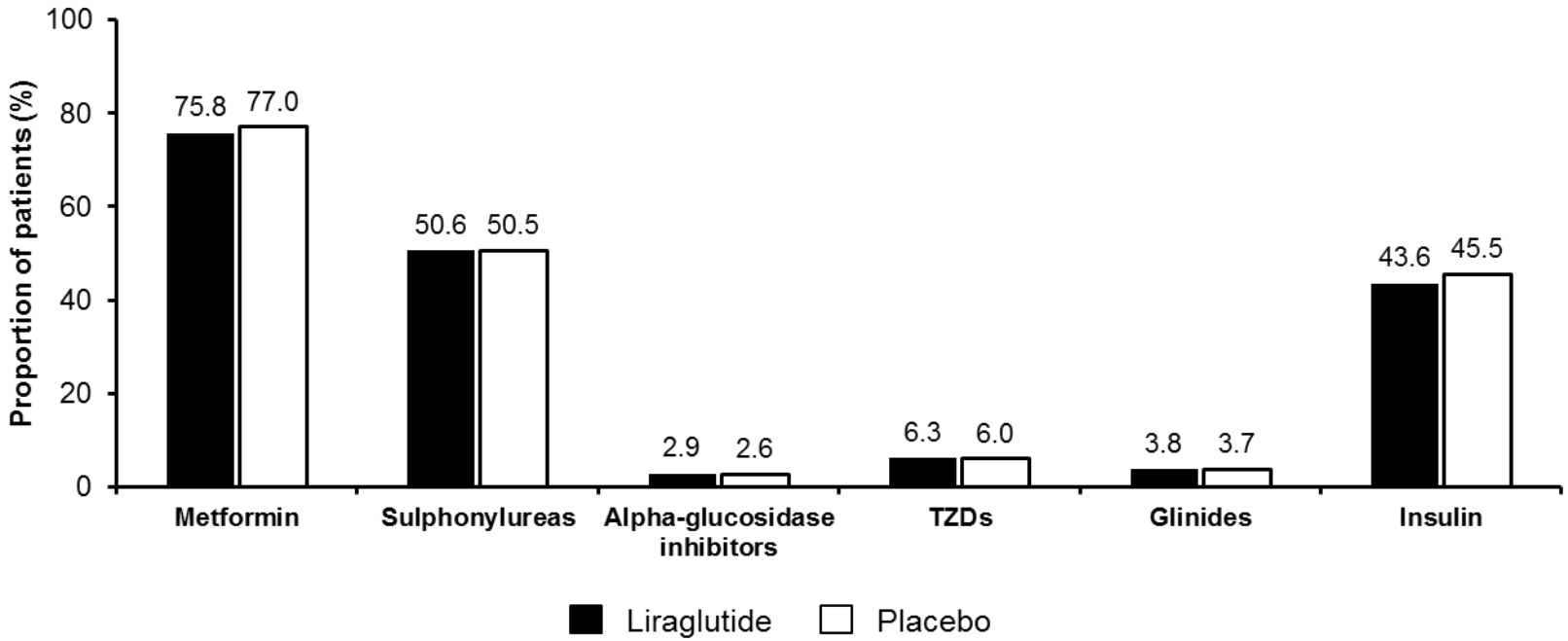
Marso SP et al N Engl J Med. 2016 Sep 15. [Epub ahead of print]



Marso SP et al N Engl J Med. 2016 Sep 15. [Epub ahead of print]

LEADER Study

Anti-hyperglycemic medication at baseline

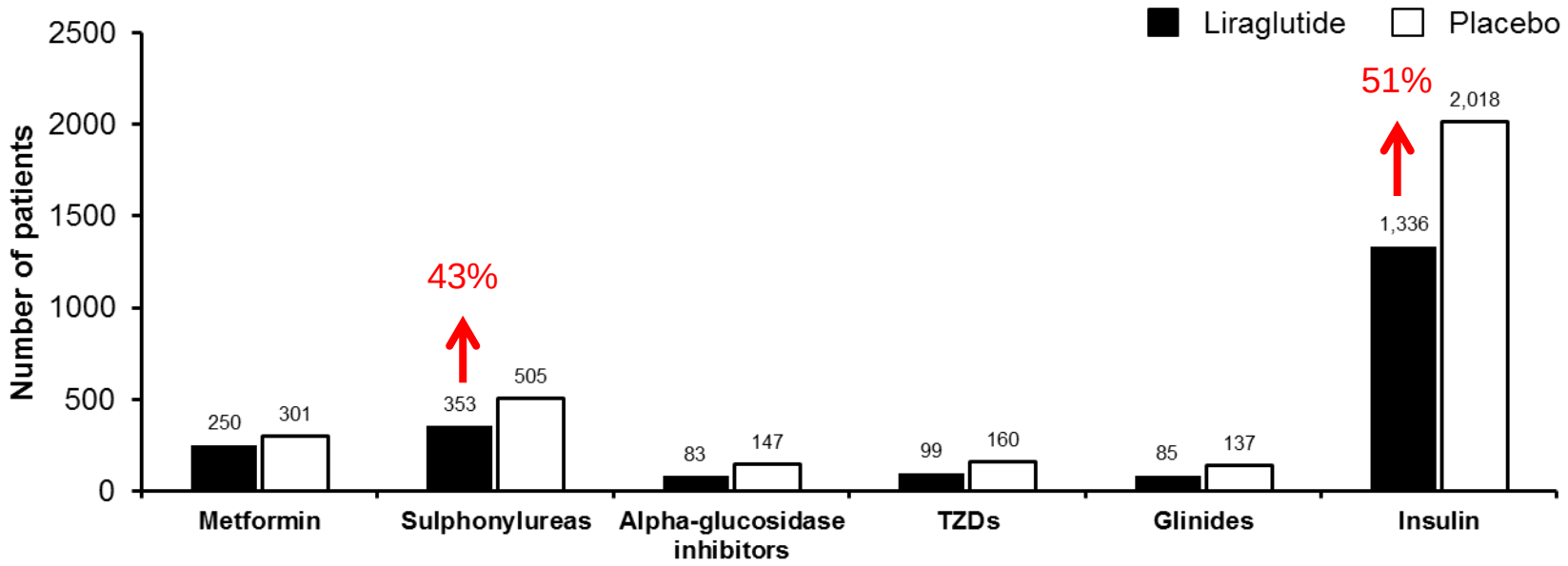


TZD: thiazolidinediones.

Marso SP et al N Engl J Med. 2016 Sep 15. [Epub ahead of print]

LEADER Study

Anti-hyperglycemic medications introduced during trial



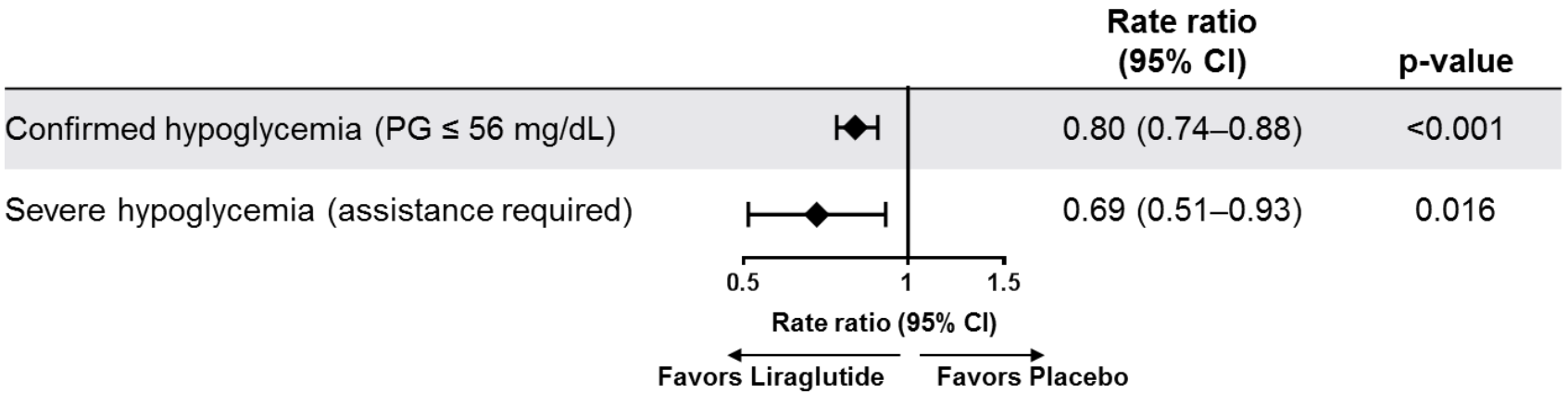
Additional classes added	Liraglutide	Placebo
DPP-4 inhibitors	149	170
GLP-1RAs	87	139
SGLT-2 inhibitors	100	130

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

Marso SP et al N Engl J Med. 2016 Sep 15. [Epub ahead of print]

LEADER Study

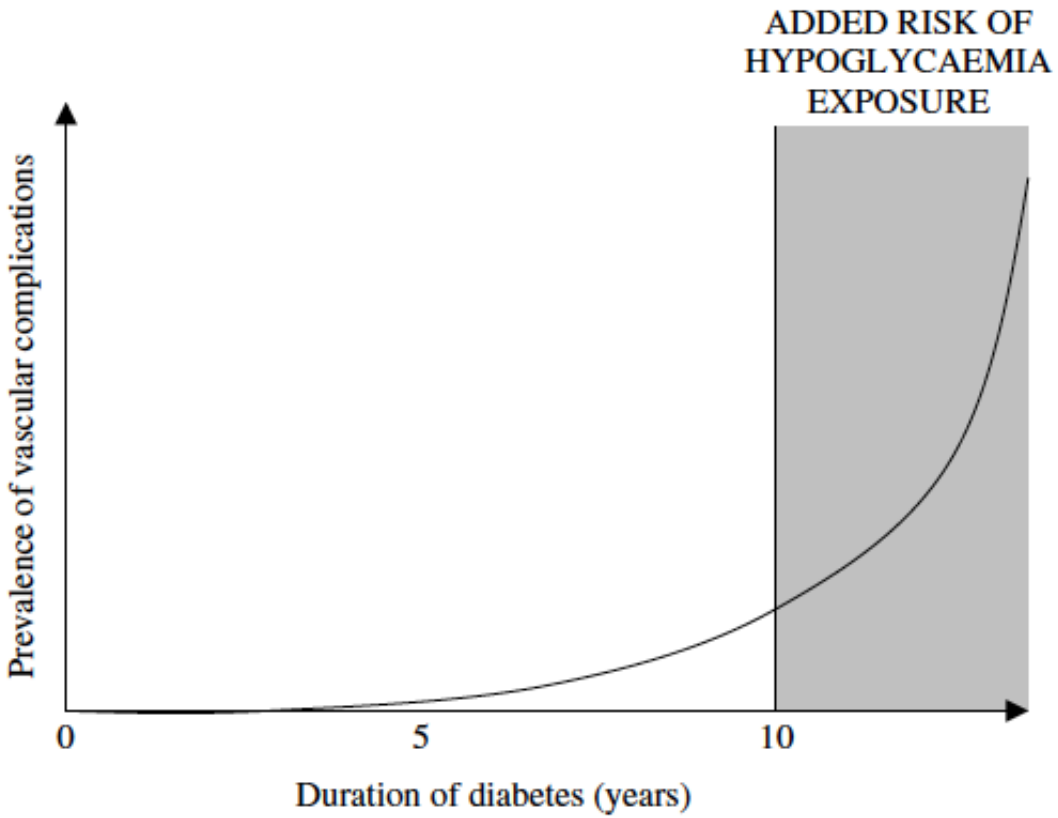
Hypoglycemia

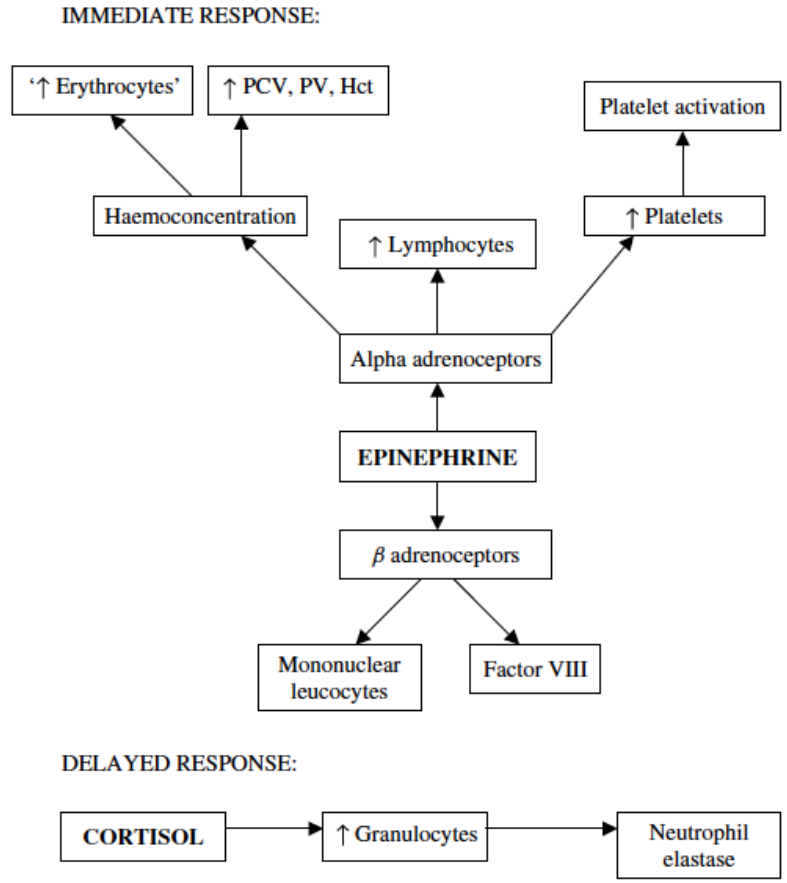


Confirmed hypoglycemia was defined as plasma glucose level of less than 56 mg per deciliter (3.1 mmol per liter) or a severe event. Severe hypoglycemia was defined as hypoglycemia for which the patient required assistance from a third party. Analyzed using a negative binomial regression model.
CI: confidence interval; PG: plasma glucose.

Marso SP et al N Engl J Med. 2016 Sep 15. [Epub ahead of print]

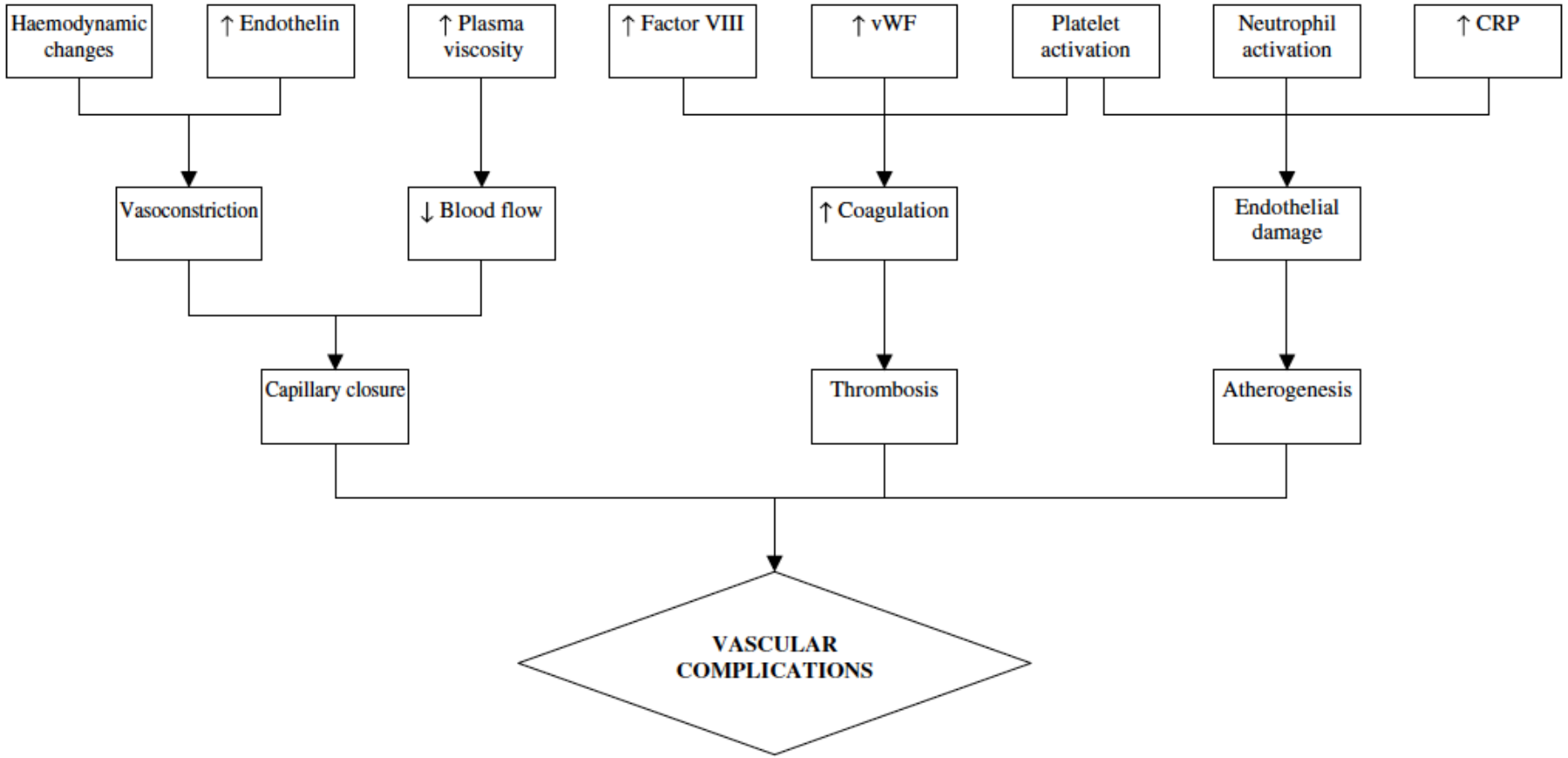
Hypoglycaemia and CV morbidity





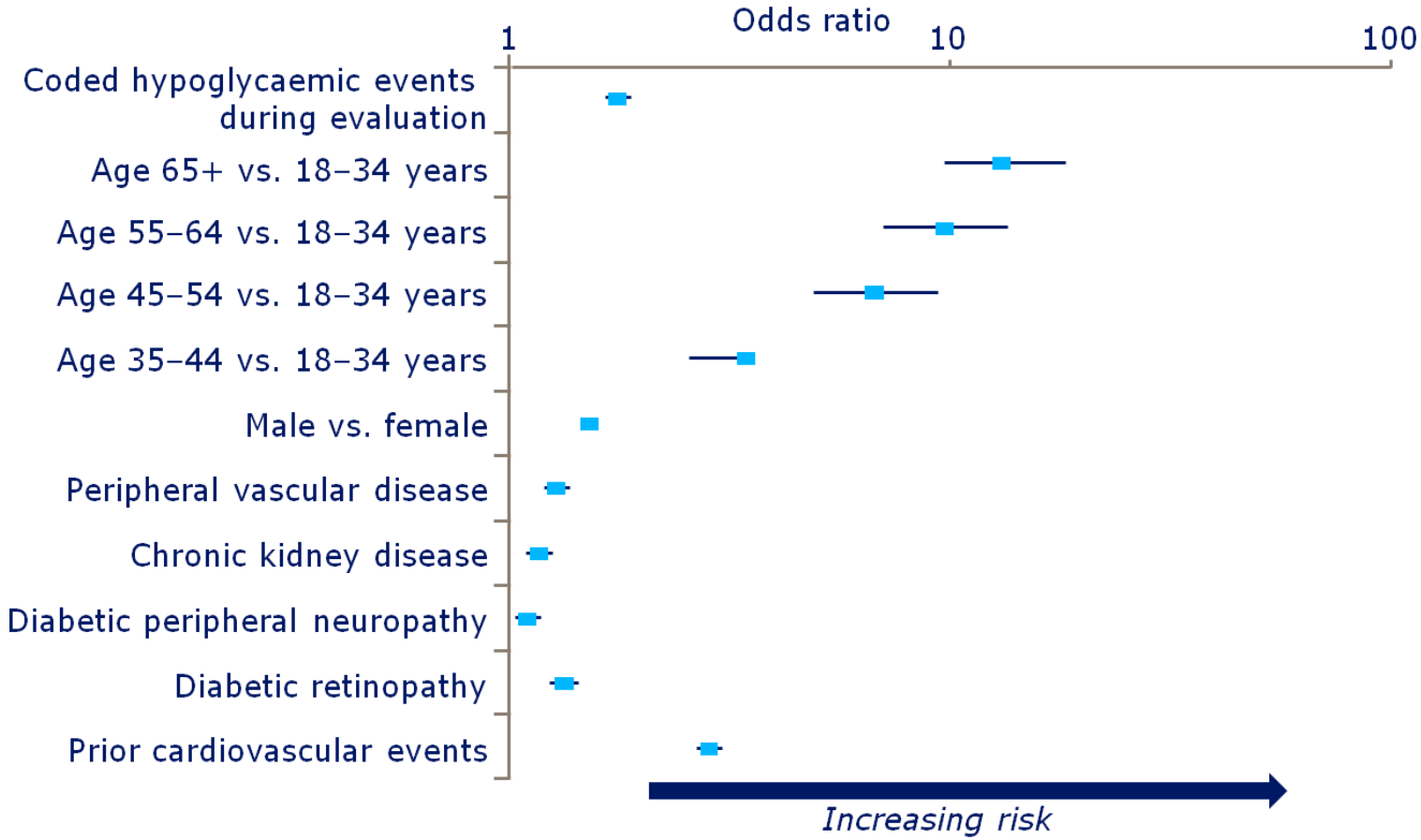
Wright RJ and Frier B Diabetes Metab Res Rev 2008; 24: 353–363.

Hypoglycaemia and CV morbidity



Wright RJ and Frier B Diabetes Metab Res Rev 2008; 24: 353–363.

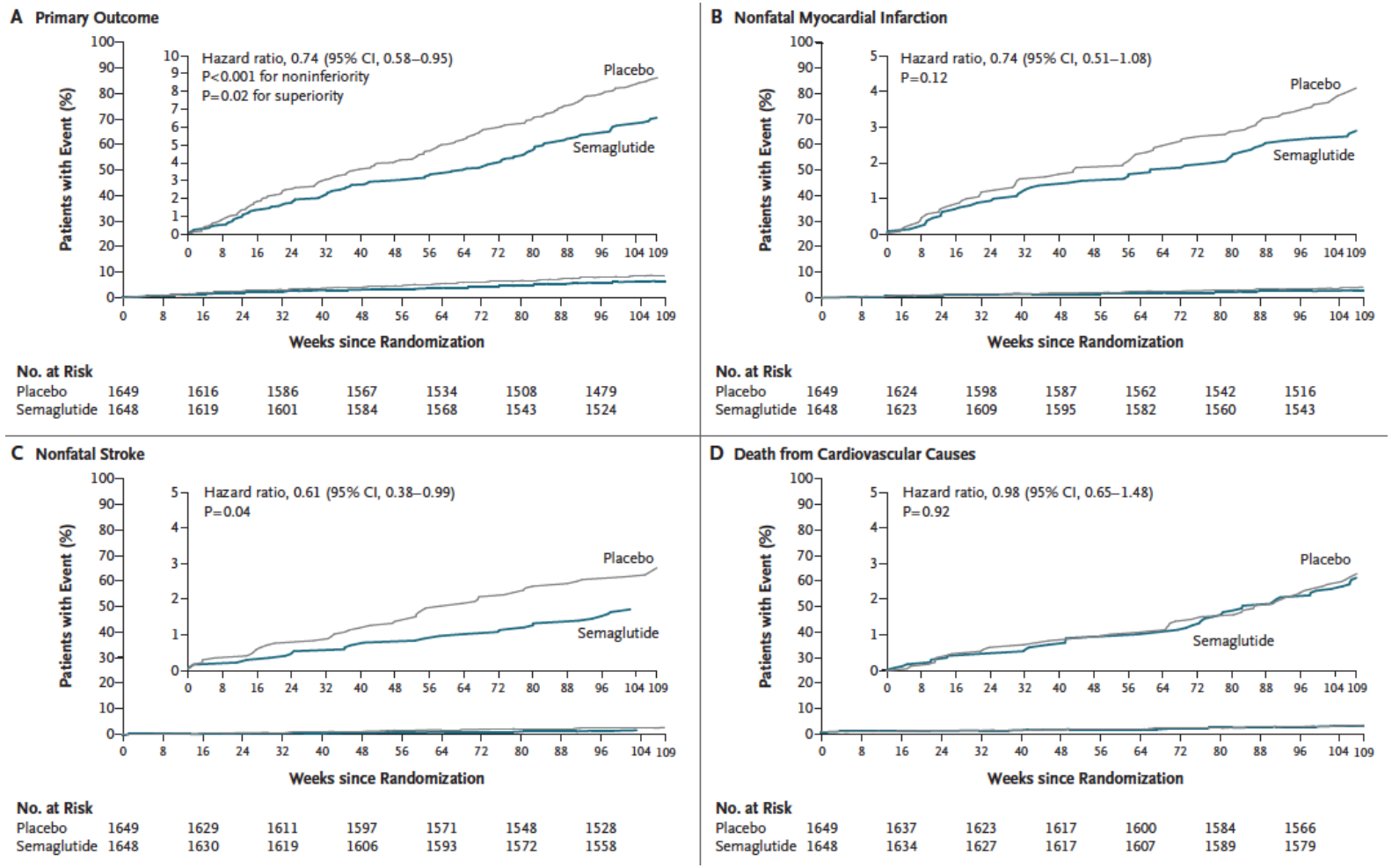
Hypoglycemic events and increased risk of acute cardiovascular events in T2DM patients



Johnston SS et al. Diabetes Care 34:1164–1170, 2011

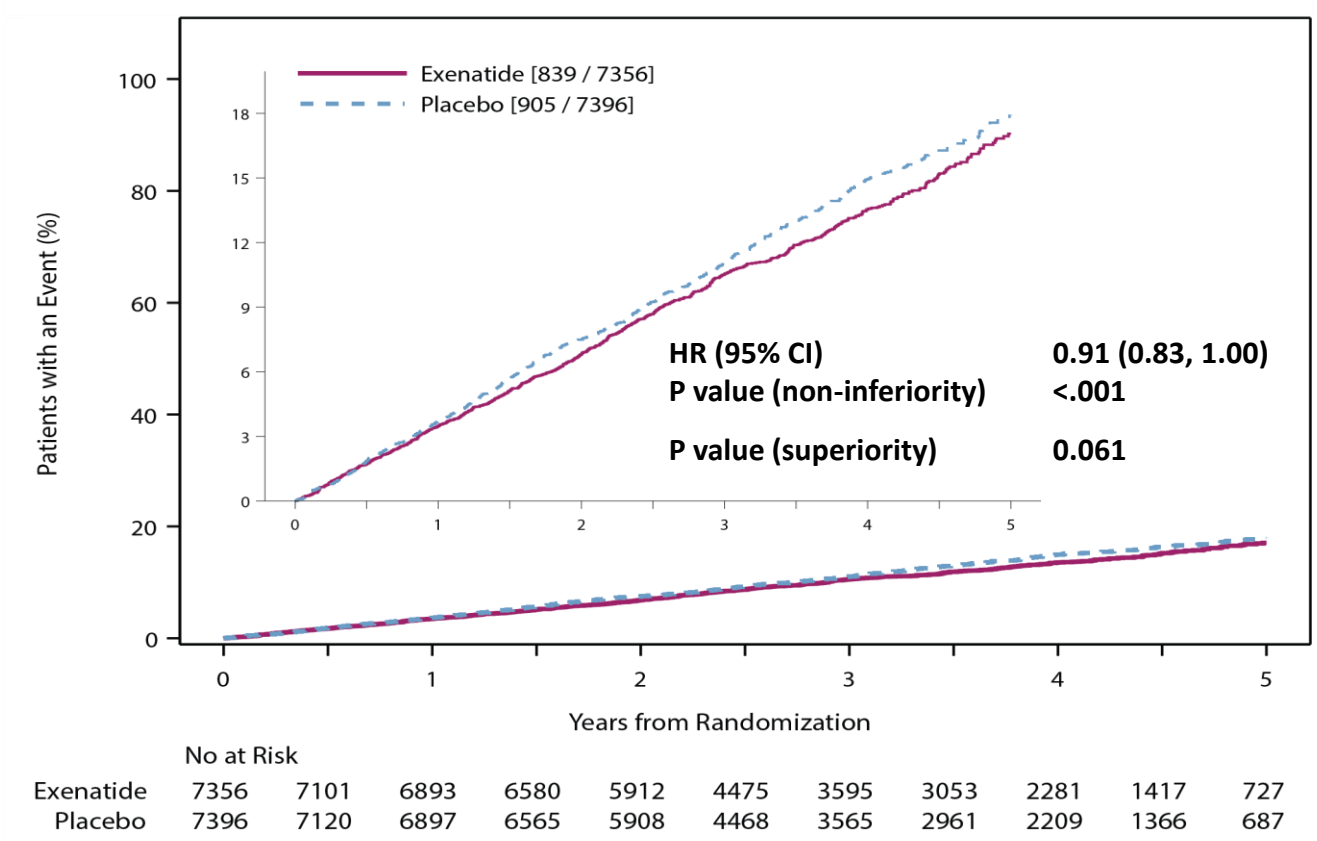
Semaglutide and CV risk

SUSTAIN-6 trial



Marso SP et al N Engl J Med. 2016 Sep 15. [Epub ahead of print]

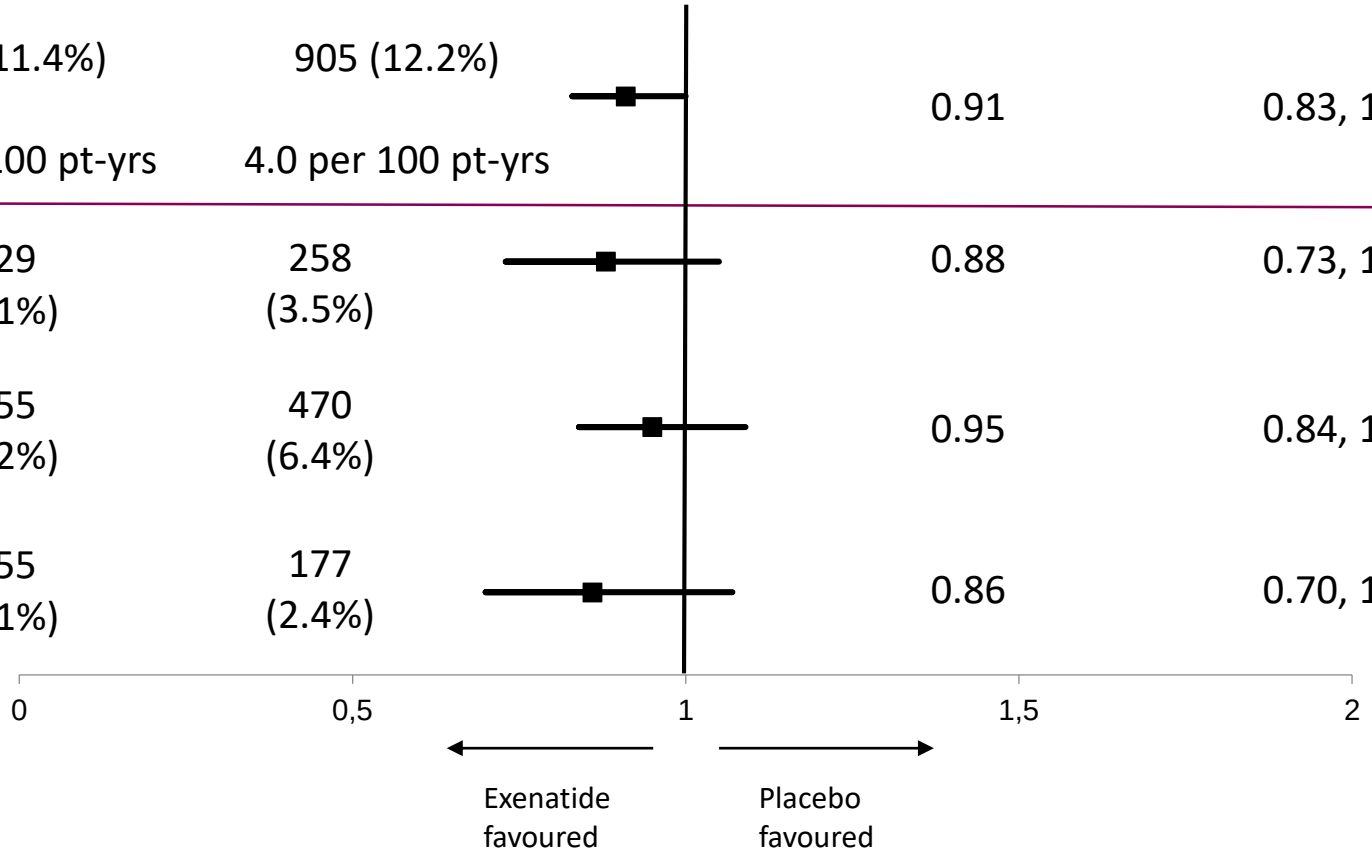
EXSCEL Study: Primary Composite Cardiovascular Outcome
Intention-to-Treat Analysis for Non-inferiority and Superiority



Holman RR et al. N Engl J Med. 2017 Sep 28;377(13):1228-1239

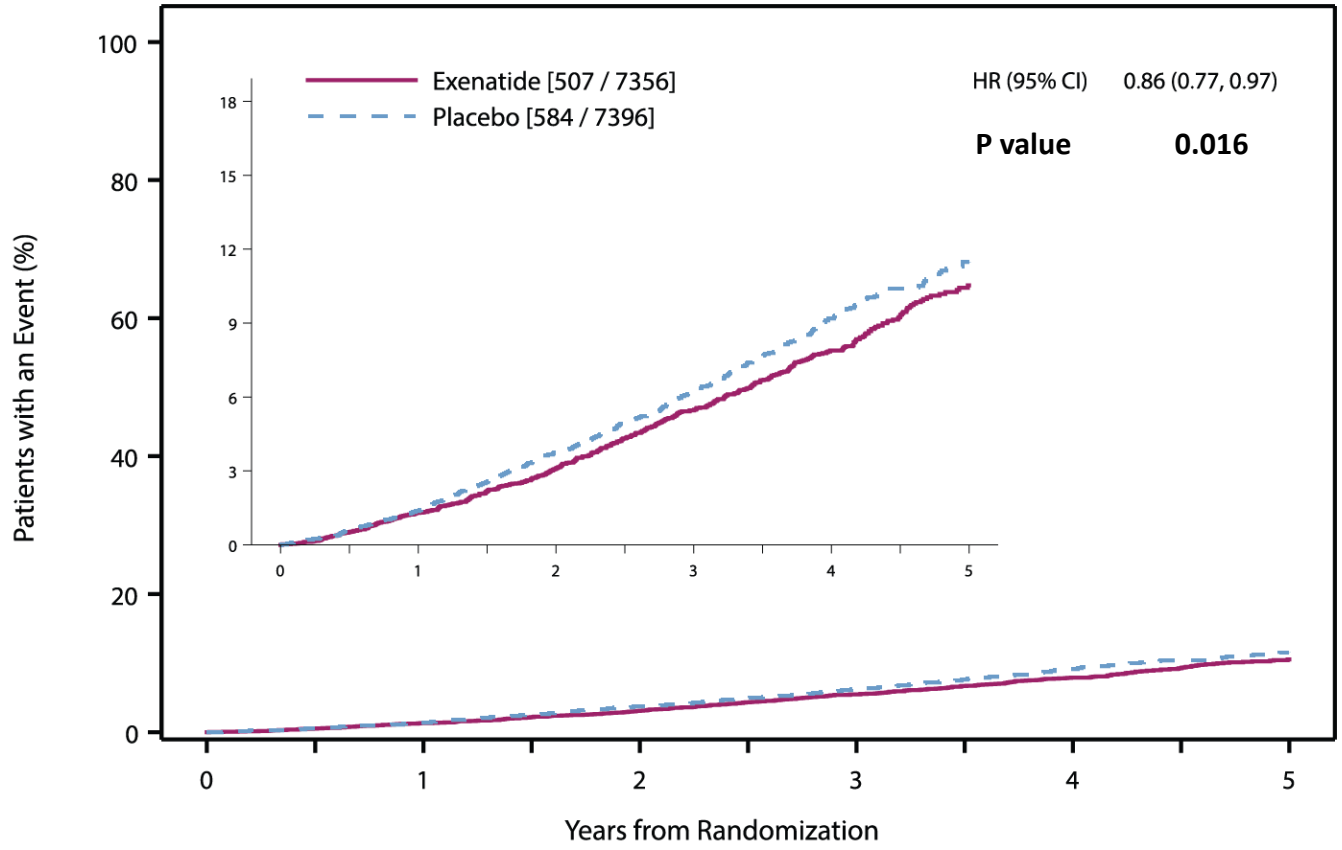
Primary Composite Cardiovascular Outcome Intention-to-Treat Analysis

	Exenatide N=7356	Placebo N=7396	Hazard Ratio	95% CI	P value
MACE	839 (11.4%) 3.7 per 100 pt-yrs	905 (12.2%) 4.0 per 100 pt-yrs	0.91	0.83, 1.00	**<.001 (non-inferiority)** **0.061 (superiority)**
CV-death	229 (3.1%)	258 (3.5%)	0.88	0.73, 1.05	
Non-fatal MI	455 (6.2%)	470 (6.4%)	0.95	0.84, 1.09	**0.628 (homogeneity among components)**
Non-fatal stroke	155 (2.1%)	177 (2.4%)	0.86	0.70, 1.07	



Holman RR et al. N Engl J Med. 2017 Sep 28;377(13):1228-1239

All-Cause Mortality
Intention-to-Treat Analysis



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. N Engl J Med. 2017 Sep 28;377(13):1228-1239

Two Broad Categories of Clinical Trial Designs

- In 1967, Schwartz and Lellouch differentiated clinical trials into pragmatic versus explanatory approaches.[1]
- There is a continuum rather than a dichotomy between the two approaches.[2]

Key Differences Between Trials With Explanatory and Pragmatic Designs[2-4]

	Explanatory	Pragmatic
Objective	Evaluates if a treatment will work under optimal conditions	Evaluates if a treatment will work under routine practice conditions
Validity	High internal validity[a]	High external validity[b]
Sample size	Smaller	Larger
Patient population	Homogenous, highly selected	Heterogeneous, little or no selection
Design/setting	Sophisticated design with well-defined controlled environment	Simple design with broad diverse setting
Intervention	Comparison to placebo	Comparison to usual care/standard of care
Phase of trial	Mostly Phase II to III	Mostly Phase IV
Relevance to practice	Indirect—little effort to match trial design to the usual setting in which intervention will be used	Direct—trial designed to match the setting in which intervention will be used

[a]Ability to determine cause-effect relationships; [b]Ability to generalize the results in extended populations and clinical settings.

1. Schwartz D et al. J Chronic Dis 1967;20:637-648;
2. Zwarenstein M et al. BMJ. 2008;337: a2390;
3. Patsopoulos NA. Dialogues Clin Neurosci. 2011;13:217-224;
4. Alford L. NZ J Physiother. 2007;35:12-16.

EXSCEL (Pragmatic Trial) Versus LEADER (Exploratory Trial)

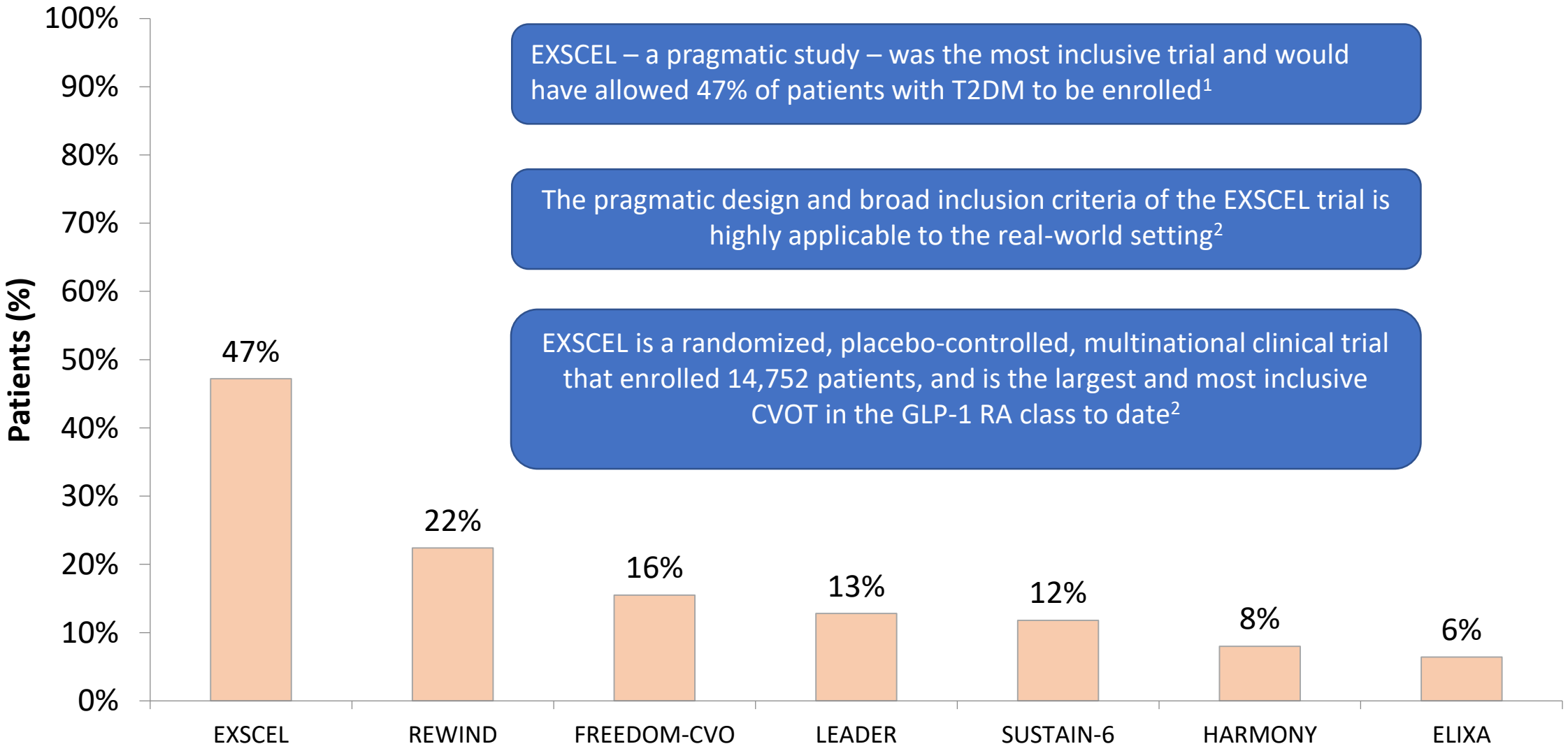
	EXSCEL[1,2] (exenatide once weekly)	LEADER[3,4] (liraglutide)
Study design	Pragmatic, randomized, parallel-group, placebo-controlled, international trial	Randomized, double-blind, placebo-controlled, multicenter, international trial
Population	T2DM patients ≥18 years, HbA1c 6.5% to 10%, with or without CV risk factors or prior CV events • Key exclusion: T1DM; history of ketoacidosis, gastroparesis, pancreatitis; prior/current GLP-1 RA use; planned/anticipated revascularization procedure; pregnancy; ESRD or eGFR <30 mL/min/1.73m^2; familial/personal history of medullary thyroid cancer or MEN2 or baseline calcitonin level >40 ng/L	T2DM patients, HbA1c ≥7.0%, ≥50 years with CVD or ≥60 years with 1 or more CV risk factors • Key exclusion: T1DM; use of GLP-1 RA, DPP-4i, pramlintide, rapid-acting insulin; familial/personal history of MEN2 or medullary thyroid cancer, acute coronary or cerebrovascular event (≤14 days); calcitonin ≥50 ng/L; end-stage liver disease; current continuous renal replacement therapy
Study treatments	EQW 2 mg + usual care[a] OR Placebo QW + usual care[a]	2-week run-in period with daily placebo injections followed by: Liraglutide 0.6 to 1.8 mg QD + standard of care[b] OR Placebo QD + standard of care[b]
Add-on glycemic therapy	Any glucose-lowering agent such as insulin, TZD, SU, α-GI, DPP-4i, or SGLT-2i	Insulin, TZD, SU, or α-GI
Patients, N	14,752	9340
Study duration	1360 confirmed primary composite CV endpoint events	60 months (max) + ≥611 primary composite CV endpoint events
Primary CV endpoint	Composite of • CV death • Nonfatal MI • Nonfatal stroke	Composite of • CV death • Nonfatal MI • Nonfatal stroke

[a]Patients were managed by their usual care provider and treated according to local standards of care for diabetes and cardiovascular risk factor management; [b]Standard of care guidelines were developed by the LEADER global expert panel and national study leaders in participating countries and included a protocol for the treatment of risk factors and concomitant use of medications.

α-GI = α-glucosidase inhibitor; CV = cardiovascular; CVD = cardiovascular disease; DPP-4i = dipeptidyl peptidase-4 inhibitor; eGFR = estimated glomerular filtration rate; EQW = exenatide once weekly; ESRD = end-stage renal disease; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HbA1c = glycated hemoglobin; MEN2 = multiple endocrine neoplasia type 2; MI = myocardial infarction; QW = once weekly; SGLT-2i = sodium-glucose co-transporter-2 inhibitor; SU = sulfonylurea; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione.

1. Holman RR et al. Article and supplementary appendix. *Am Heart J*. 2016;174:103-110; 2. Mentz RJ et al. *Am Heart J.* 2017;187:1-9; 3. Marso SP et al. Article, online protocol, and supplementary appendix. *N Engl J Med*. 2016; 375:311-322; 4. Marso SP et al. *Am Heart J*. 2013;166:823-830.e5.

US Patients With T2DM Who Meet the Eligibility Criteria for GLP-1 RA CVOTs[1]



EXSCEL – a pragmatic study – was the most inclusive trial and would have allowed 47% of patients with T2DM to be enrolled[1]

The pragmatic design and broad inclusion criteria of the EXSCEL trial is highly applicable to the real-world setting[2]

EXSCEL is a randomized, placebo-controlled, multinational clinical trial that enrolled 14,752 patients, and is the largest and most inclusive CVOT in the GLP-1 RA class to date[2]

CVOT = cardiovascular outcomes trial; GLP-1 RA = glucagon-like peptide-1 receptor agonist; T2DM = type 2 diabetes mellitus.

1. Wittbrodt ET et al. Poster presented at: 77th American Diabetes Association Scientific Sessions; June 9-13, 2017; San Diego, CA. Poster 1515-P; 2. Mentz RJ et al. *Am Heart J.* 2017;187:1-9.

Conclusioni

- La malattia cardiovascolare è la causa più frequente di morbilità e mortalità nel paziente affetto da diabete mellito di tipo 2

- Il GLP-1 svolge importanti effetti cardiovascolari dimostrati sia in modelli sperimentali sia nell'uomo

- Nei CVOT i GLP-1 RA si sono dimostrati superiori al placebo nella protezione cardiovascolare e nella riduzione della mortalità

Thank you for your attention

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