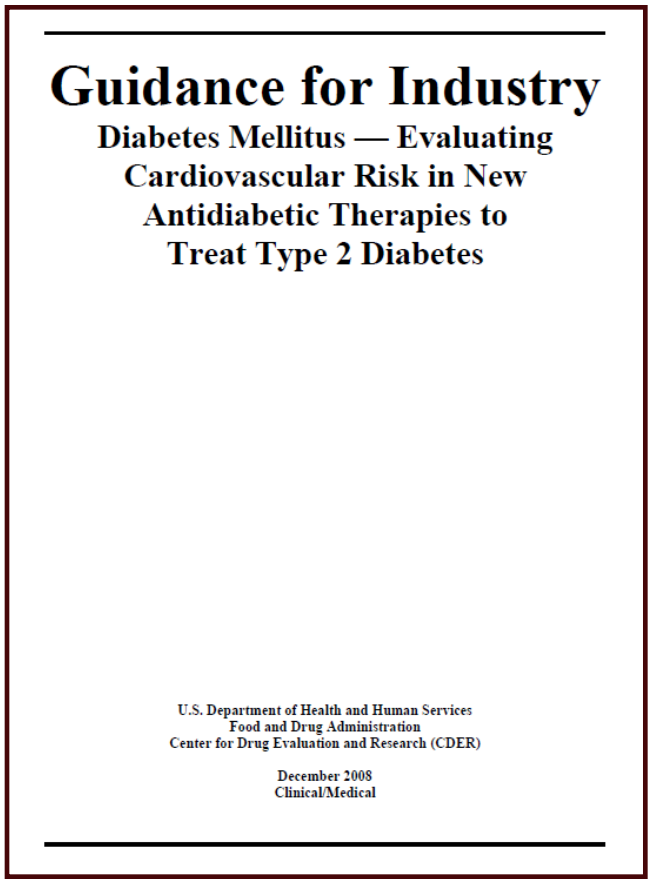
Possibili meccanismi di differenti risultati dei trials di outcome.

Antonio Ceriello

**Institut d'Investigacions Biomèdiques
August Pi i Sunyer (IDIBAPS)
Barcelona, Spain and
IRCCS MultiMedica Milan, Italy**

IDIBAPS
Institut
D'Investigacions
Biomèdiques
August Pi i Sunyer

FDA Requirements for Cardio-Vascular Outcome (CVOT) Studies for New Antidiabetic Agents


Guidance for Industry

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

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2008
Clinical/Medical

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

CV, cardiovascular; CI, confidence interval.

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 2016].

The primary objectives of the three major CVOTs for DPP4 inhibitors were different

EXAMINE[1] Alogliptin

Demonstrate the **non-inferiority of MACE on alogliptin versus placebo** in a **high-risk CV patients with T2D**

SAVOR-TIMI[2] Saxagliptin

Determine if **saxagliptin** as add on is **non-inferior to placebo for the composite endpoint** of CV death, non-fatal MI, or non-fatal ischaemic stroke

TECOS[3] Sitagliptin

Demonstrate that the **risk of CV events** with **sitagliptin** in addition to usual care was **non-inferior** to the treatment without

1. White WB, et al. *N Engl J Med.* 2013;369:1327–1335; 2. Scirica BM, et al. *N Engl J Med.* 2013;369:1317–1326;
3. Green JB, et al. *Am Heart J.* 2013;166:983–989.e7; 4. Bentley-Lewis R, et al. *Am J Heart* 2015;0:1–8.

Primary end points were not the same

EXAMINE[1]

Time from randomization to the first occurrence of any event in the primary MACE composite:

- CV death
- Nonfatal myocardial infarction (MI)
- Nonfatal stroke

SAVOR-TIMI[2]

Composite of nonfatal MI, nonfatal ischemic stroke, or CV death

TECOS[3]

Time from randomization to the first confirmed CV-related death, nonfatal MI, nonfatal stroke, or unstable angina requiring hospitalization

1. White WB, et al. N Engl J Med. 2013;369:1327–1335; 2. Scirica BM, et al. N Engl J Med. 2013;369:1317□1326;
3. Green JB, et al. Am Heart J. 2013;166:983–989.e7.

Only EXAMINE specifically studied post ACS patients

EXAMINE[1]

History of ACS within 15 to 90 days prior to randomization

SAVOR-TIMI[2]

History of established CV disease

- ≥40 yrs
- Documented atherosclerosis (coronary, cerebrovascular, peripheral vascular disease)

OR

Multiple risk factors

- ≥55 yrs (male) or ≥60 yrs (female)
- ≥1 additional risk factor (dyslipidemia, hypertension, smoking)

TECOS[3]

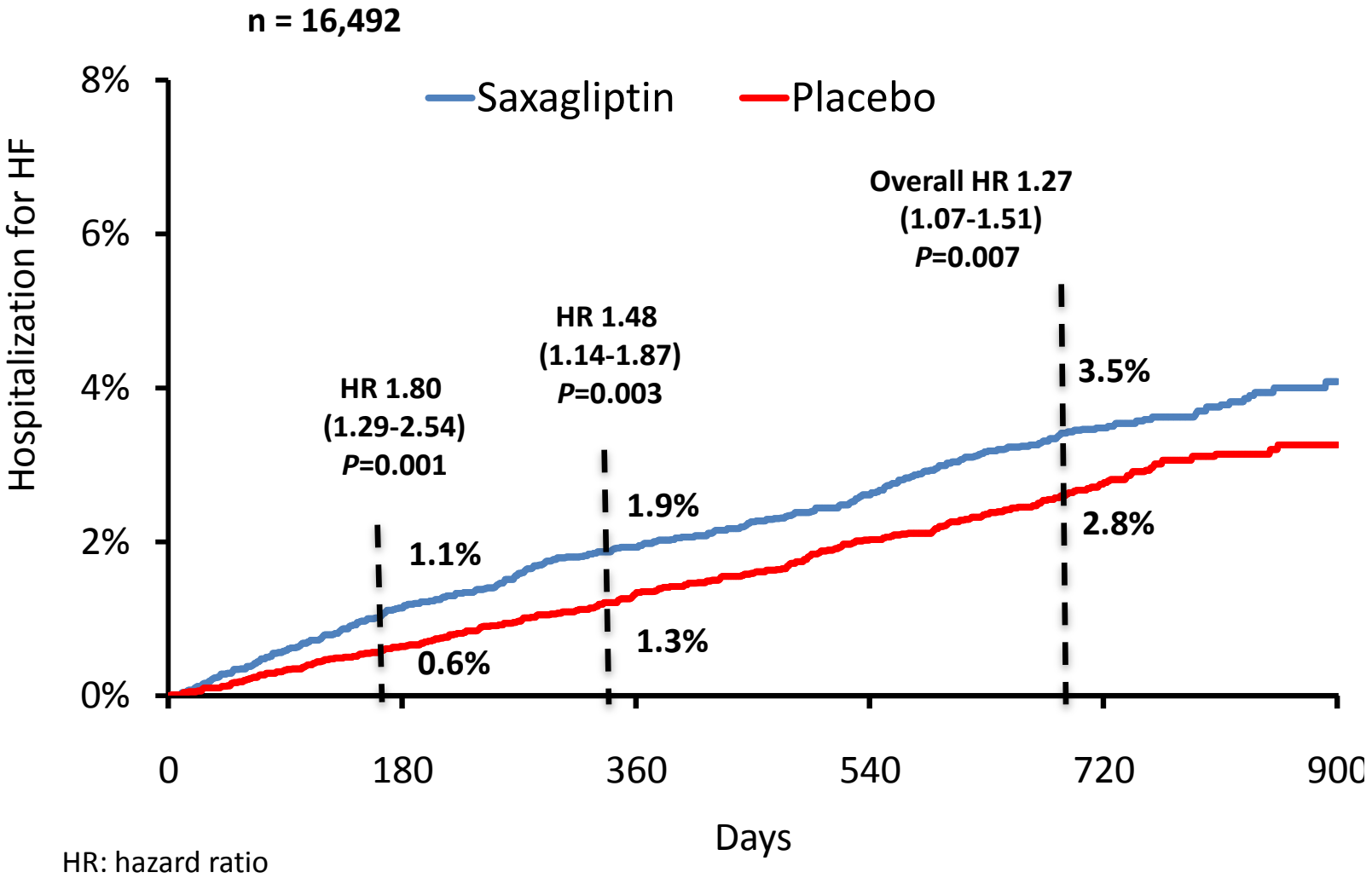
Pre-existing vascular disease defined as having:

- 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

CV, cardiovascular; T2D, type 2 diabetes

1. White WB, et al. N Engl J Med. 2013;369:1327–1335; 2. Scirica BM, et al. N Engl J Med. 2013;369:1317–1326;
3. Green JB, et al. Am Heart J. 2013;166:983–989.e7.

Rates of Risk of Hospitalization for HF Over Time



HR: hazard ratio

Scirica BM, et al. *American Heart Association Scientific Sessions.* November 2013.

EXAMINE: HF & CV death in all patients & according to prior HF

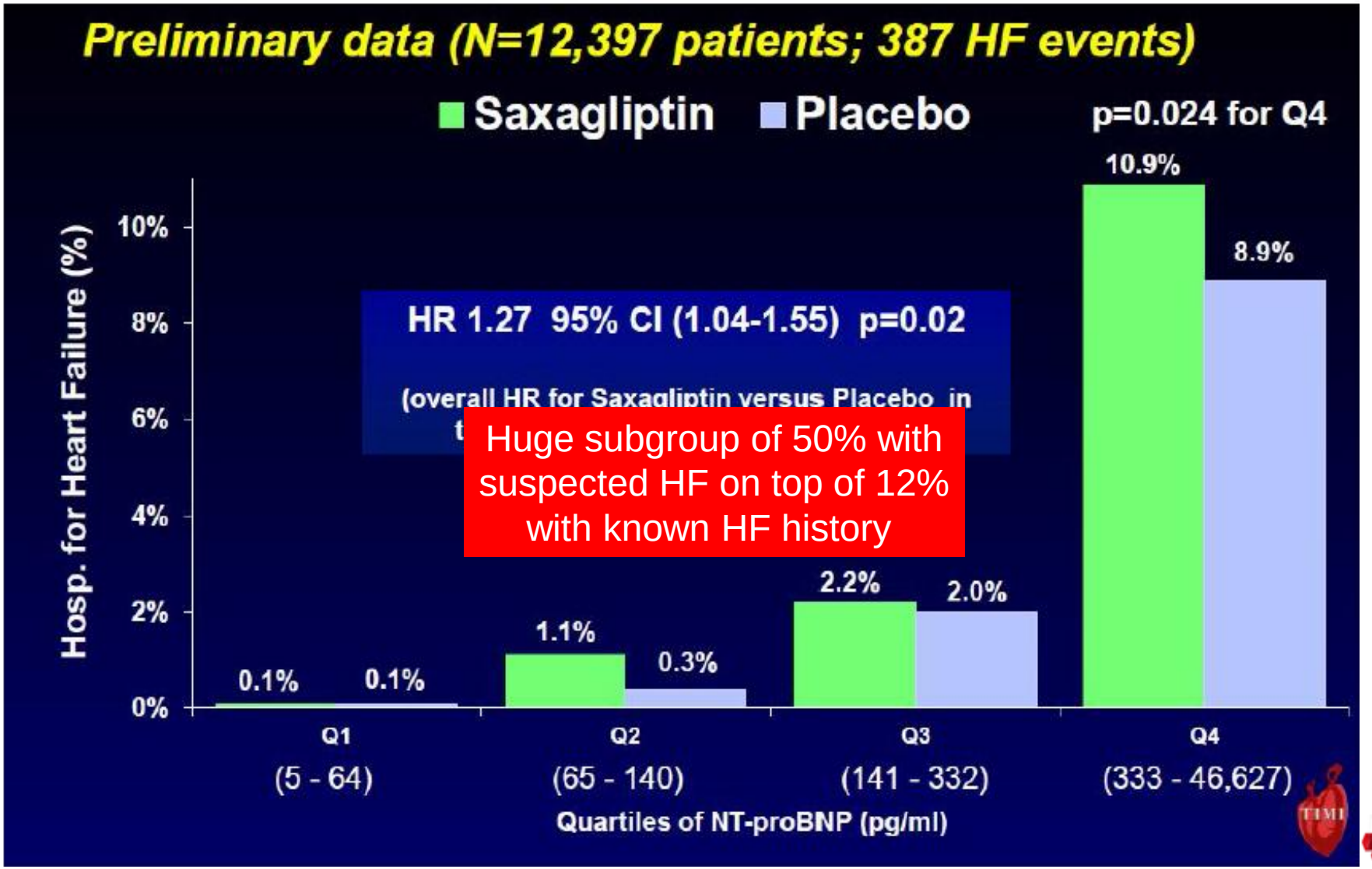
	All patients		History of heart failure prior to randomisation		No History of heart failure prior to randomisation	
	Alogliptin N=2701	Placebo N=2679	Alogliptin N = 771	Placebo N = 762	Alogliptin N = 1930	Placebo N = 1917
CV death and heart failure						
No. (%)	201 (7·4)	201 (7·5)	107 (13·9)	120 (15·7)	94 (4·9)	81 (4·2)
Hazard Ratio *(95% CI), P-value	1·00 (0·82, 1·21) p = 0·976		0·90, (0·70, 1·17) p= 0·446		1·14 (0·85, 1·54) p= 0·337	
CV Death[a]						
No. (%)	112 (4·1)	130 (4·9)	55 (7·1)	69 (9·1)	57 (3·0)	61 (3·2)

Patients without Hx of HF seem to contribute significantly to HF outcomes!
But what about undiagnosed HF?

Hospitalization for HF						
No. (%)	106 (3·9)	89 (3·3)	63 (8·2)	65 (8·5)	43 (2·2)	24 (1·3)
Hazard Ratio ***(95% CI), P-value	1·19 (0·90, 1·58) p = 0·220		1·00, (0·71, 1·42) p= 0·996		1·76 (1·07, 2·90) p= 0·026	

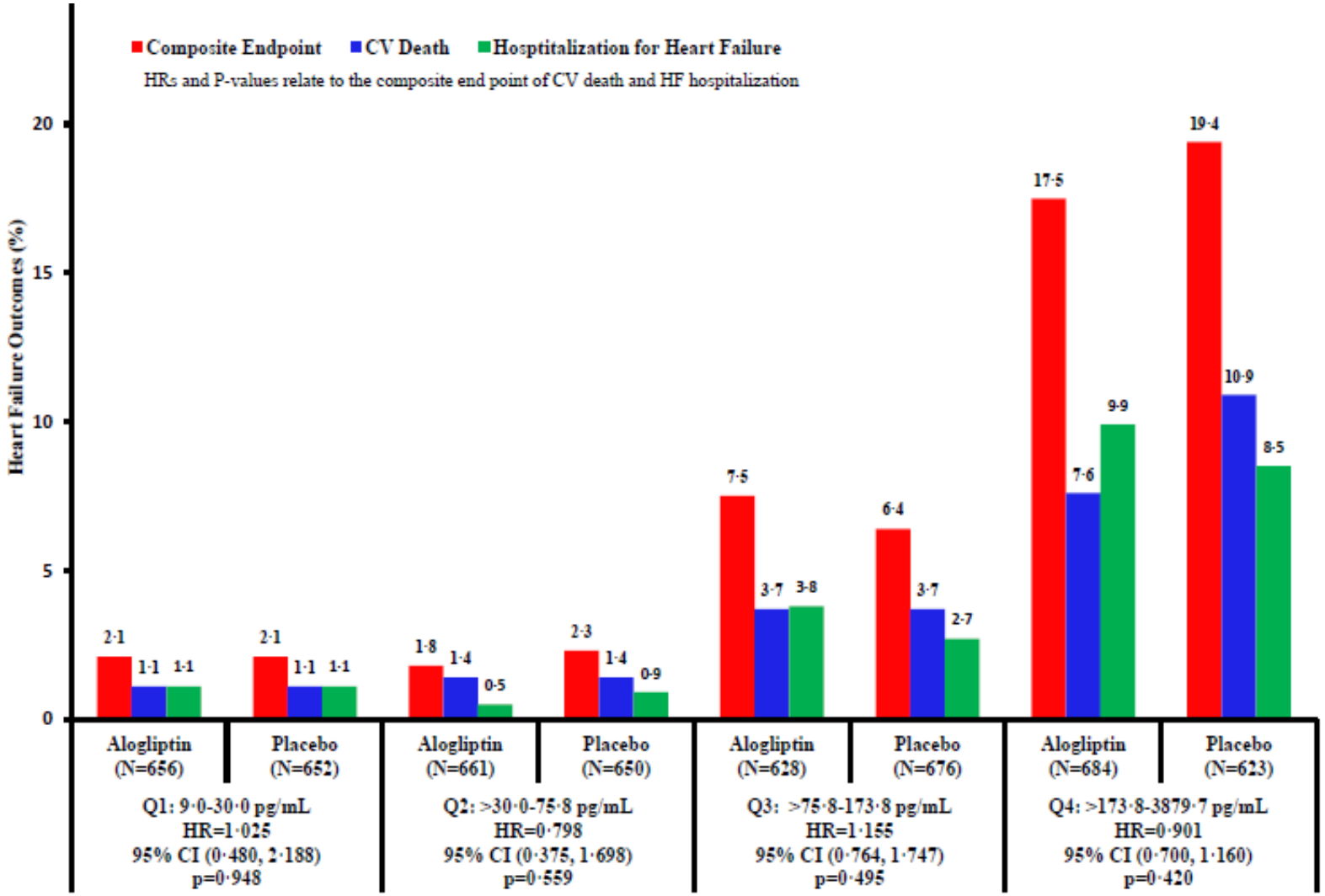
Zannad et al. Lancet 2015; 385:2067–76

Baseline NT-pro BNP and Hospitalization for Heart Failure



Scirica et al Circulation. 2014;130:1579-88

EXAMINE: Composite outcome of CV death & HF according to BNP levels at baseline



Zannad et al. Lancet 2015; 385:2067–76

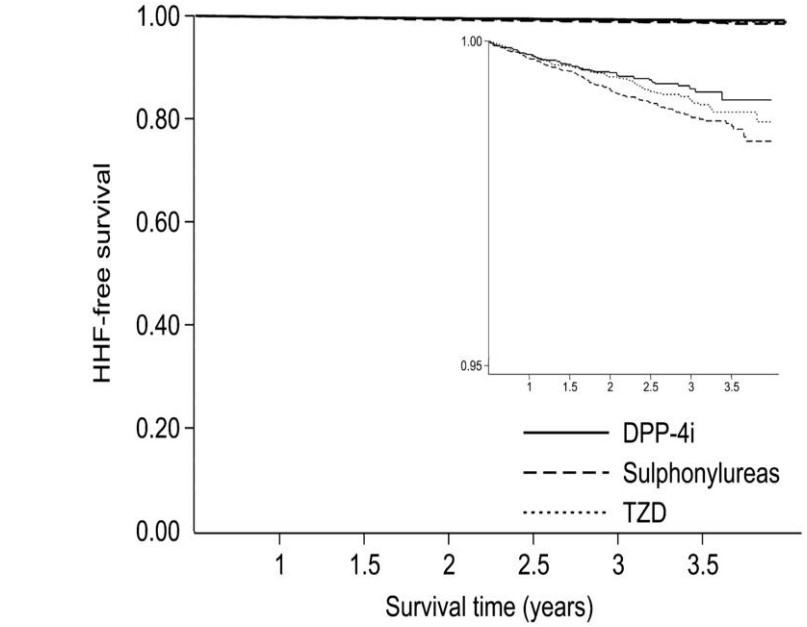
AHA

- **A meta-analysis of all randomized trials of vildagliptin, sitagliptin, saxagliptin, alogliptin, linagliptin, and dutogliptin found an elevated overall risk of acute HF in those patients taking any dipeptidyl peptidase-4 inhibitor (OR, 1.19; 95% CI, 1.03–1.37), suggesting a possible class effect.55**

The true mechanism of this potential increase in HF hospitalization remains unknown.

Risk of hospitalization for heart failure in patients with type 2 diabetes newly treated with DPP-4 inhibitors or other oral glucose-lowering medications: a retrospective registry study on 127,555 patients from the Nationwide OsMed Health-DB Database

Conclusion: In a very large observational study, the use of DPP-4i was associated with a reduced risk of HHF when compared with sulphonylureas.



At-risk							
DPP-4i	13 155	13 067	10 325	7424	5101	2136	667
Sulphonylureas	13 155	13 007	11 367	9338	7536	4342	2276
TZD	13 155	13 024	11 615	9826	8490	4863	1707

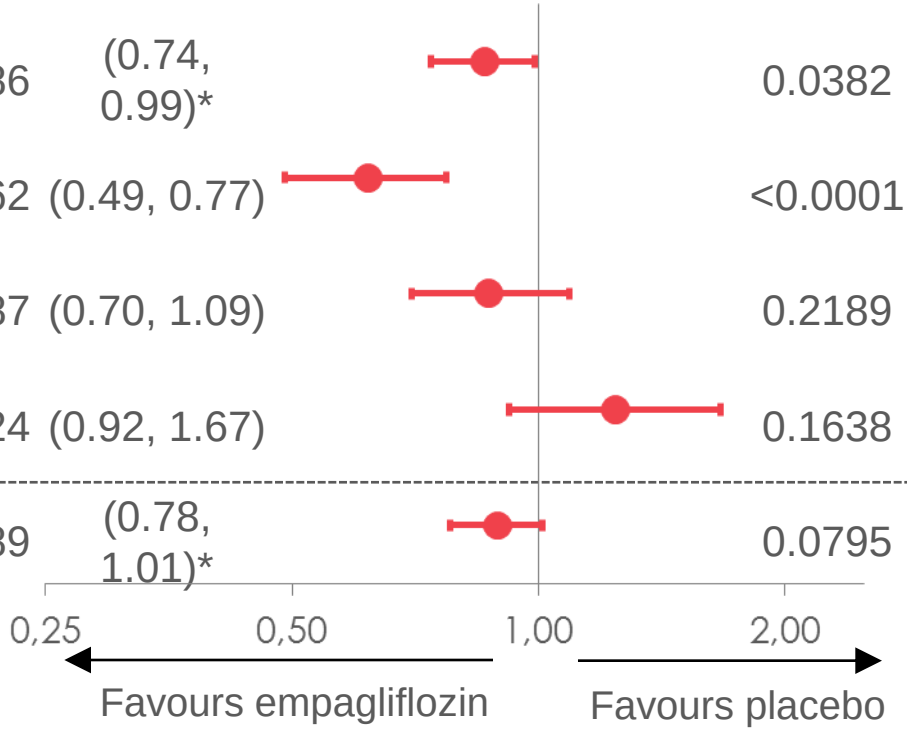
Kaplan–Meier curves showing HHF-free survival in the three groups of patients on DPP-4 inhibitors (DPP-4i), glitazones, or sulphonylureas in matched samples. Owing to the low absolute rate of HHF, curves are indistinguishable when the Y-axis is set from 0 to 1. The plot has been therefore exploded in the insert graph with Y-axis set from 0.95 to 1.00.

Fadini GP et al. Eur Heart J. 2015; 36:2454-62

EMPAREG OUTCOME TRIAL

3-point MACE and 4-point MACE

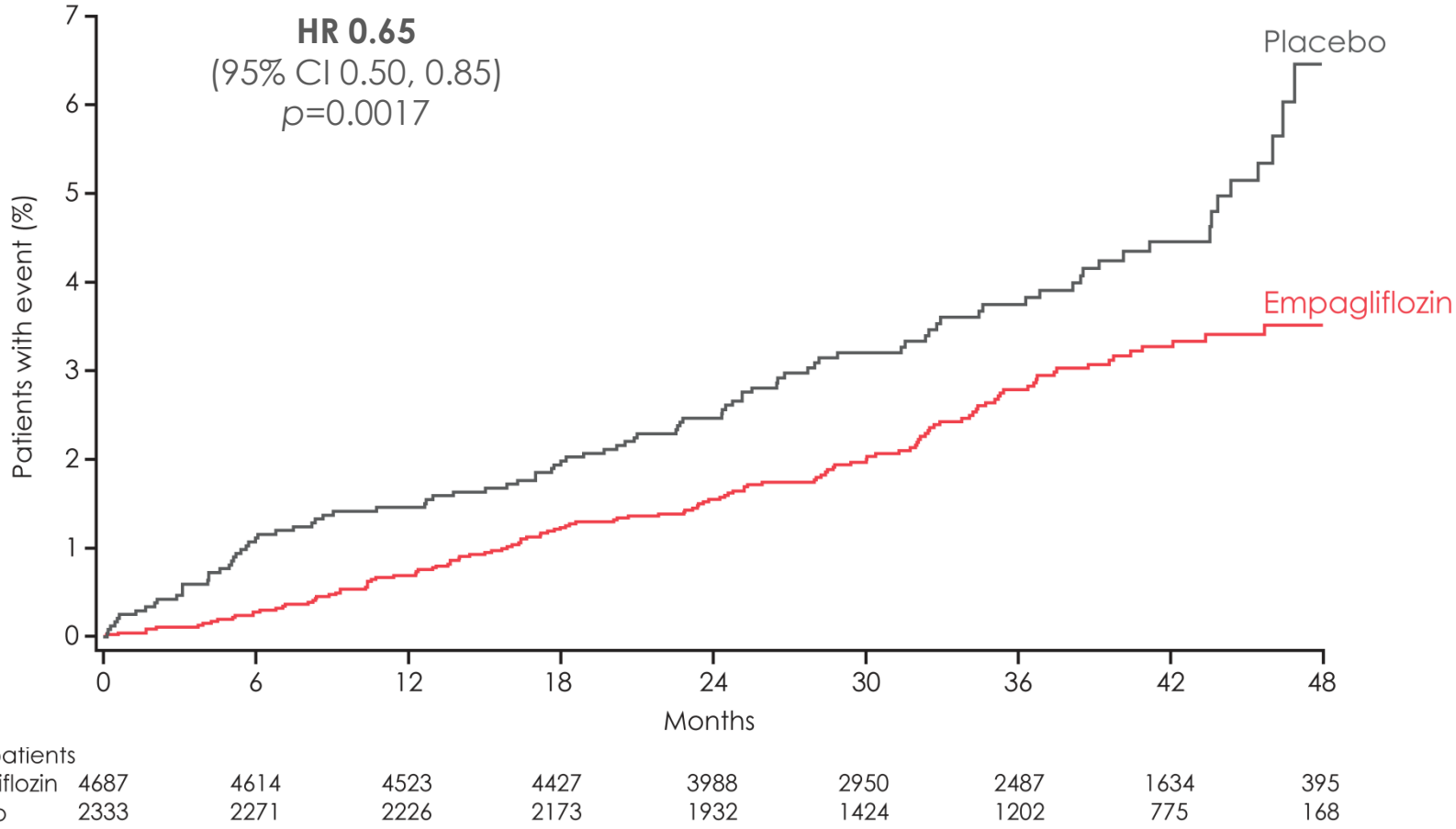
	Patients with event/analysed Empagliflozin	Placebo	HR	(95% CI)	*p*-value
3-point MACE	490/4687	282/2333	0.86	(0.74, 0.99)*	0.0382
CV death	172/4687	137/2333	0.62	(0.49, 0.77)	<0.0001
Non-fatal MI	213/4687	121/2333	0.87	(0.70, 1.09)	0.2189
Non-fatal stroke	150/4687	60/2333	1.24	(0.92, 1.67)	0.1638
4-point MACE	599/4687	333/2333	0.89	(0.78, 1.01)*	0.0795



Cox regression analysis. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio; CV, cardiovascular; MI, myocardial infarction
*95.02% CI

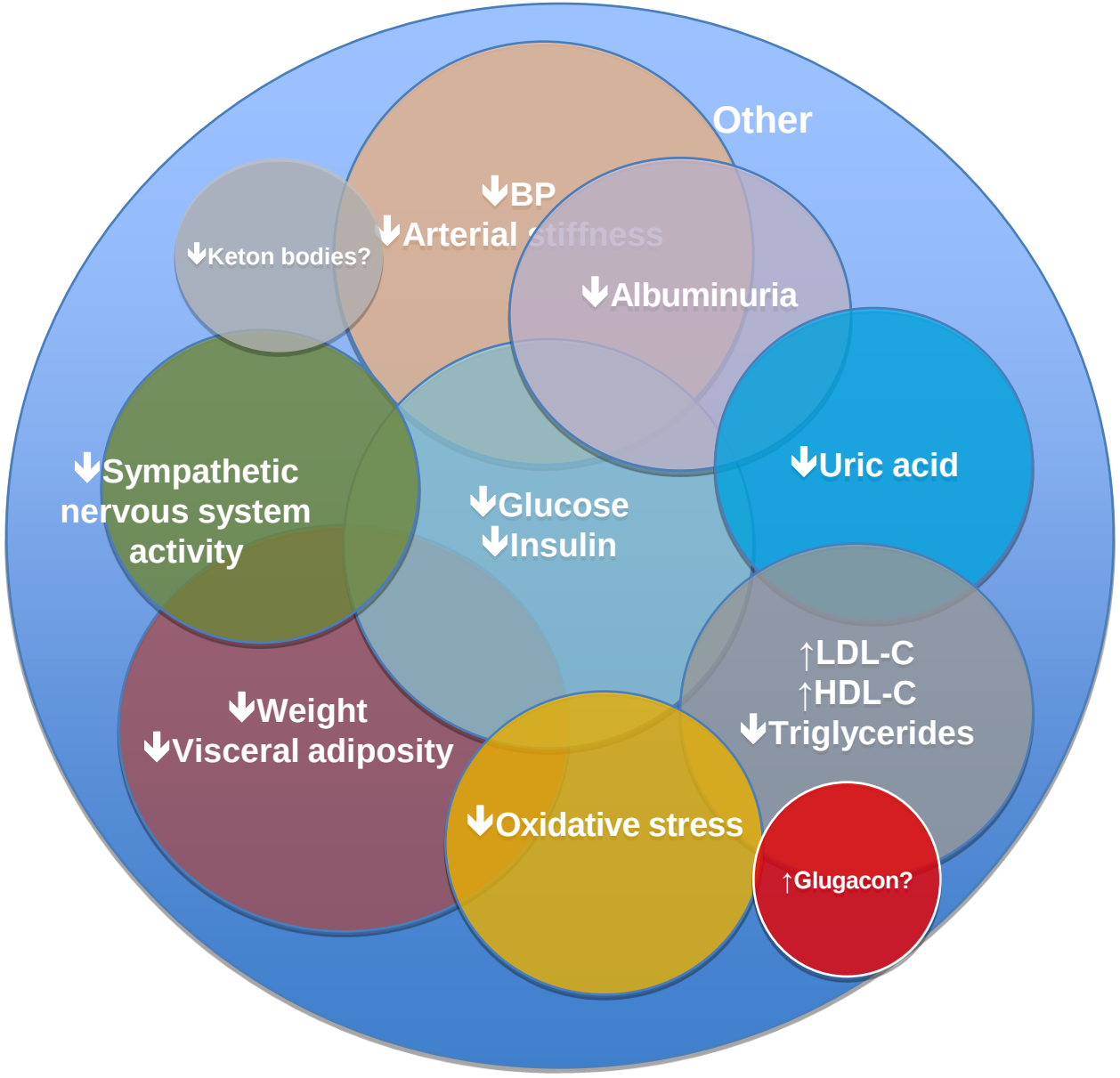
Zinman at al. published on September 17, 2015, at NEJM.org.DOI: 10.1056/NEJMoa1504720

EMPA-REG OUTCOME®
Hospitalization for heart failure



Cumulative incidence function. HR, hazard ratio

Possible explanation? Need to be explored!



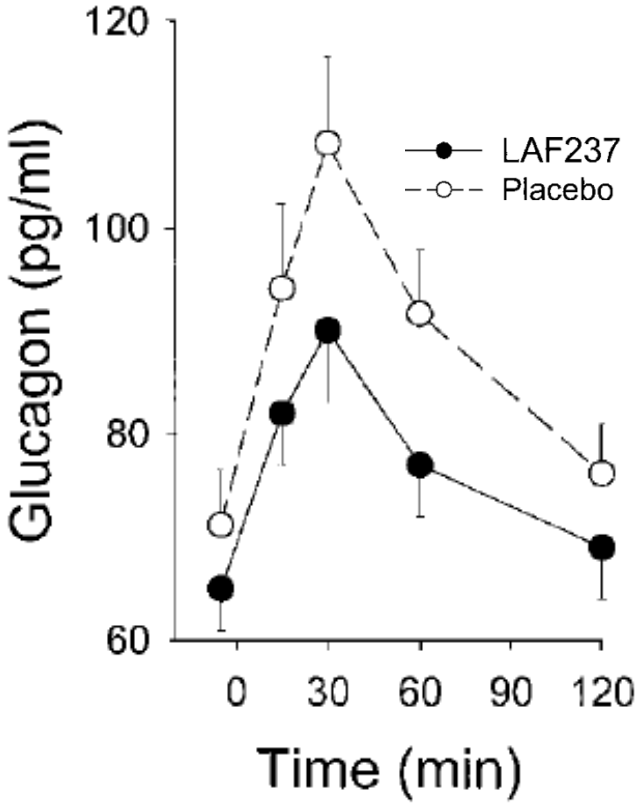
Adapted from Inzucchi SE,Zinman, et al. Diab Vasc Dis Res 2015;12:90-100, Ceriello A, et al. Lancet Diabetes Endocrinol. 2015;3:929-30, Ferrannini E, et al.CV Protection in the EMPA-REG OUTCOME Trial: A "Thrifty Substrate" Hypothesis. Diabetes Care 2016 Jun 11. pii: dc160330. [Epub ahead of print]

1. Ferrannini E, Mark M, Mayoux E. CV Protection in the EMPA-REG OUTCOME Trial: A "Thrifty Substrate" Hypothesis. Diabetes Care 2016 Jun 11. pii: dc160330. [Epub ahead of print].

2. Mudaliar S, Alloju S, Henry RR. Can a Shift in Fuel Energetics Explain the Beneficial Cardiorenal Outcomes in the EMPA-REG OUTCOME Study? A Unifying Hypothesis. Diabetes Care 2016 Jun 11. pii: dc160542. [Epub ahead of print].

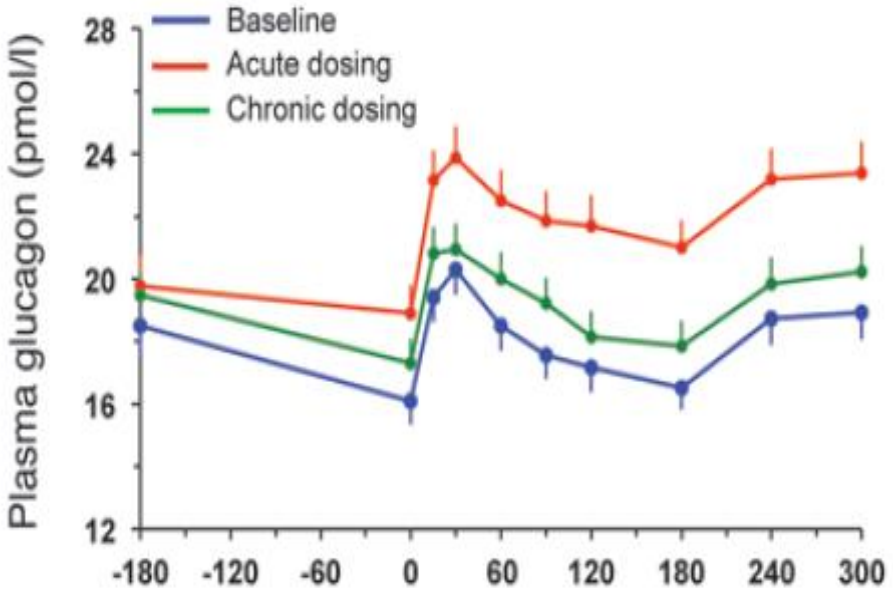
Divergent action of DPP4i and SGLT2i on Glucagon

DPP4i



Ahrén *B* *et al. J Clin Endocrinol Metab.* 1.2004 May;89(5):2078-84

Empagliflozin



Ferrannini E *et al. J Clin Invest* 2014; 124: 499-508. Erratum in: *J Clin Invest 2014;124:1868*

Glucagon and its effects on the heart

-Key hormone in glucose metabolism in cardiomyocites[1]
-Inotropic effect mediated through cAMP[2]
-Chronotropic and natriuretic effects[2,3]

For these reasons, glucagon was used in the 60'-70' in the treatment of heart failure, acute MI and cardiogenic shock[4].

1. **Harney JA** et al. *Am J Physiol Endocrinol Metab* 2008; 295: E155–E161. 2. **Jones BJ** *et al*. *Endocrinology.* 2012; 153: 1049-54. 3. **Parving HH** *et al.*. 1980 Oct;19(4):350-4. **Murtagh JG** *et al. British Heart Journal 1970;70:307-315*

Understanding EMPA-REG OUTCOME

Ceriello A, Genovese S, Mannucci E, Gronda E.

The reduced risk of hospitalization for heart failure with empagliflozin can be partly explained by a direct enhancement of myocardial function, determined by the increased levels of glucagon.

In addition, the beneficial effect of glucagon on disturbances of cardiac rhythm could be partly responsible for the reduction of cardiovascular mortality with empagliflozin.

In the case of the DPPIV inhibitors, a reduction of circulating levels of glucagon could precipitate a heart failure in in individuals with unstable hemodynamic compensation,

Lancet Diabetes Endocrinol. 2015;3:929-30.

Bewsher PD, Ashmore J.
Ketogenic and lipolytic effects of glucagon on liver.
Biochem Biophys Res Commun 1966 Aug 12;24(3):431-6

Bewsher PD, Ashmore J.
Ketogenic and lipolytic effects of glucagon on liver.
Biochem Biophys Res Commun 1966 Aug 12;24(3):431-6

EMPA-REG, The Thrifty Hypothesis and Glucagon.

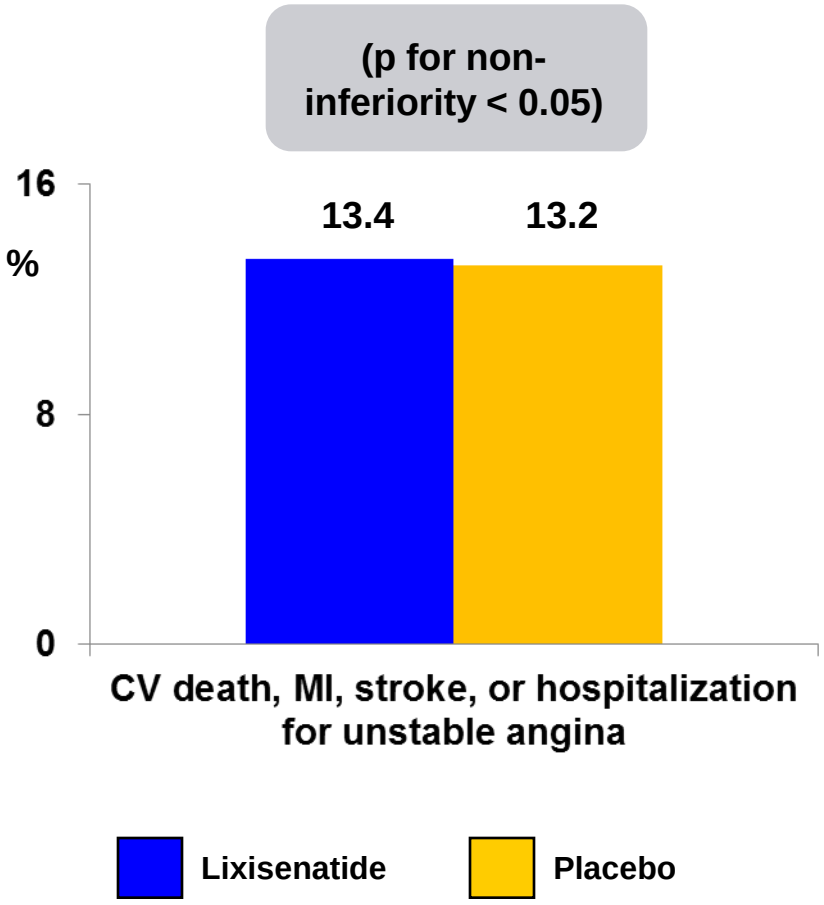
Ceriello A et al, Diabetes Care, in press

GLUCAGON and HEART in Type 2 Diabetes: New Perspectives.

Ceriello A et al, Cardiov Diabetol, 2016 Aug 27;15:123.

ELIXA

Trial design: Patients with type 2 diabetes and prior acute coronary syndrome were randomized to daily injection of lixisenatide vs. placebo.



Results

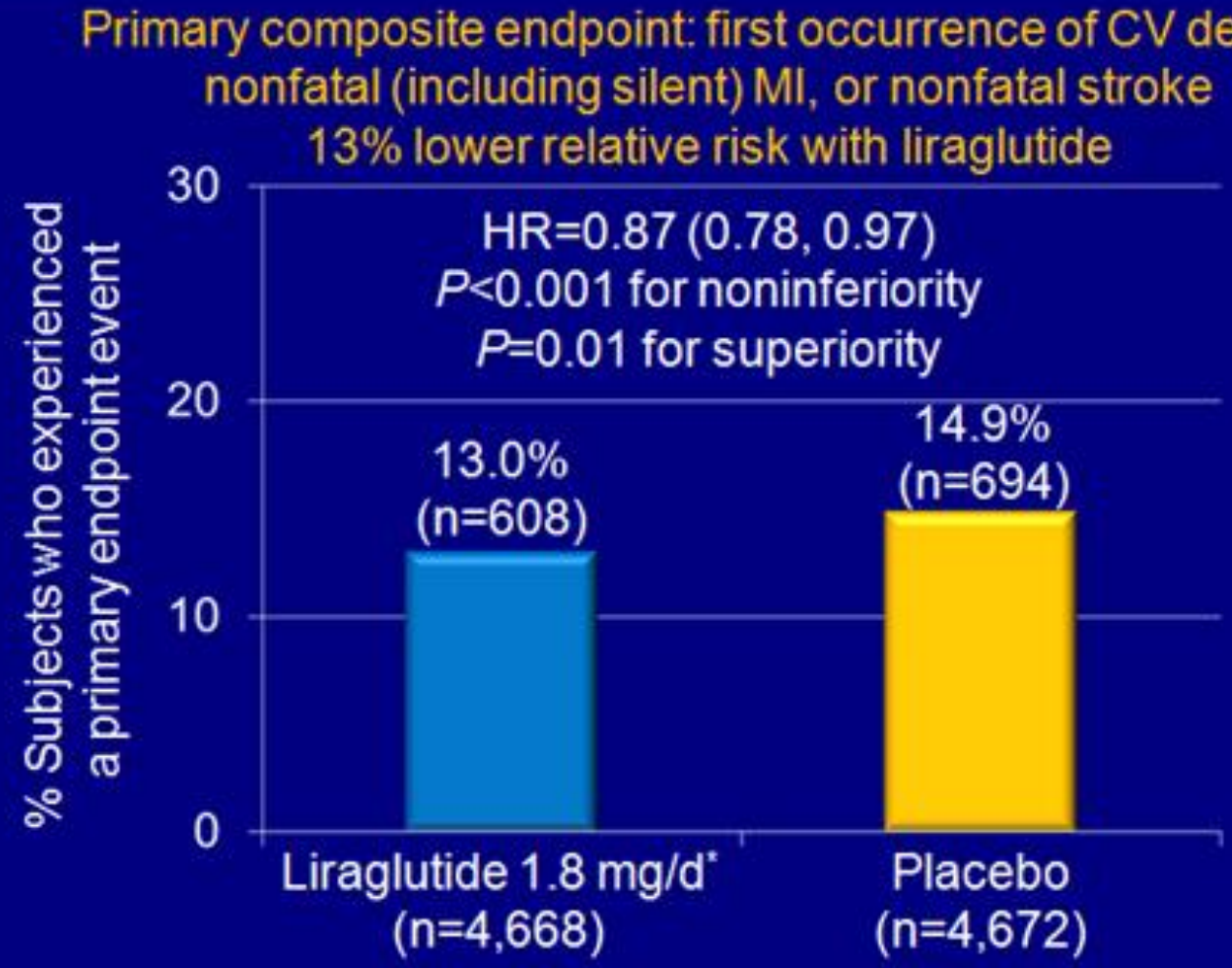
- CV death, MI, stroke, or hospitalization for unstable angina: 13.4% of the lixisenatide group vs. 13.2% of the placebo group (p for non-inferiority < 0.05; p for superiority = NS)

Conclusions

- Among patients with type 2 diabetes and prior acute coronary syndrome, lixisenatide was noninferior to placebo
- While this agent failed to demonstrate superiority compared with placebo, cardiovascular safety for this agent was established

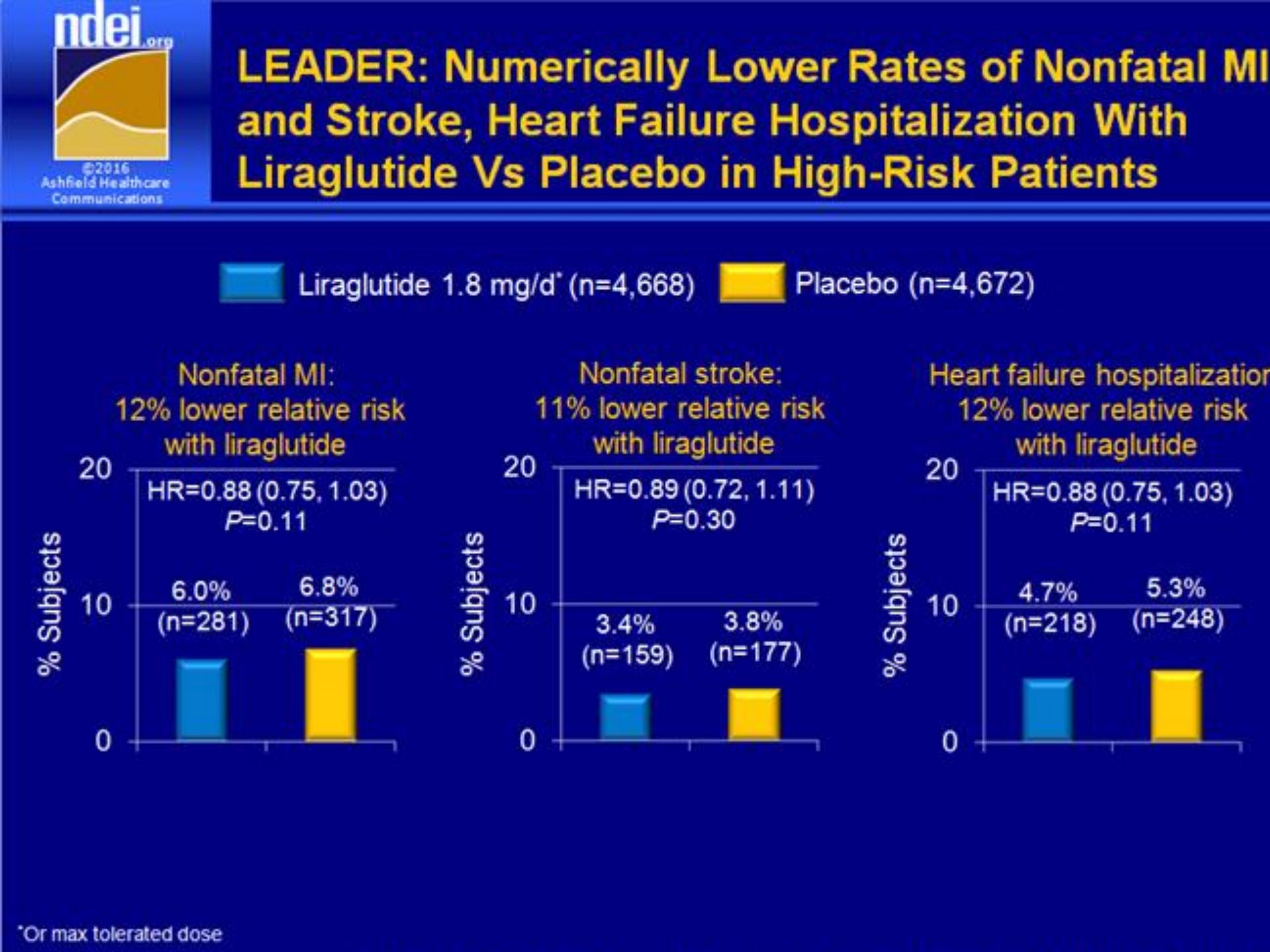
Pfeffer MA et al.N Engl J Med. 2015; 373: 2247-57

LEADER: Fewer CV Events With Liraglutide Vs Placebo in High-Risk Patients



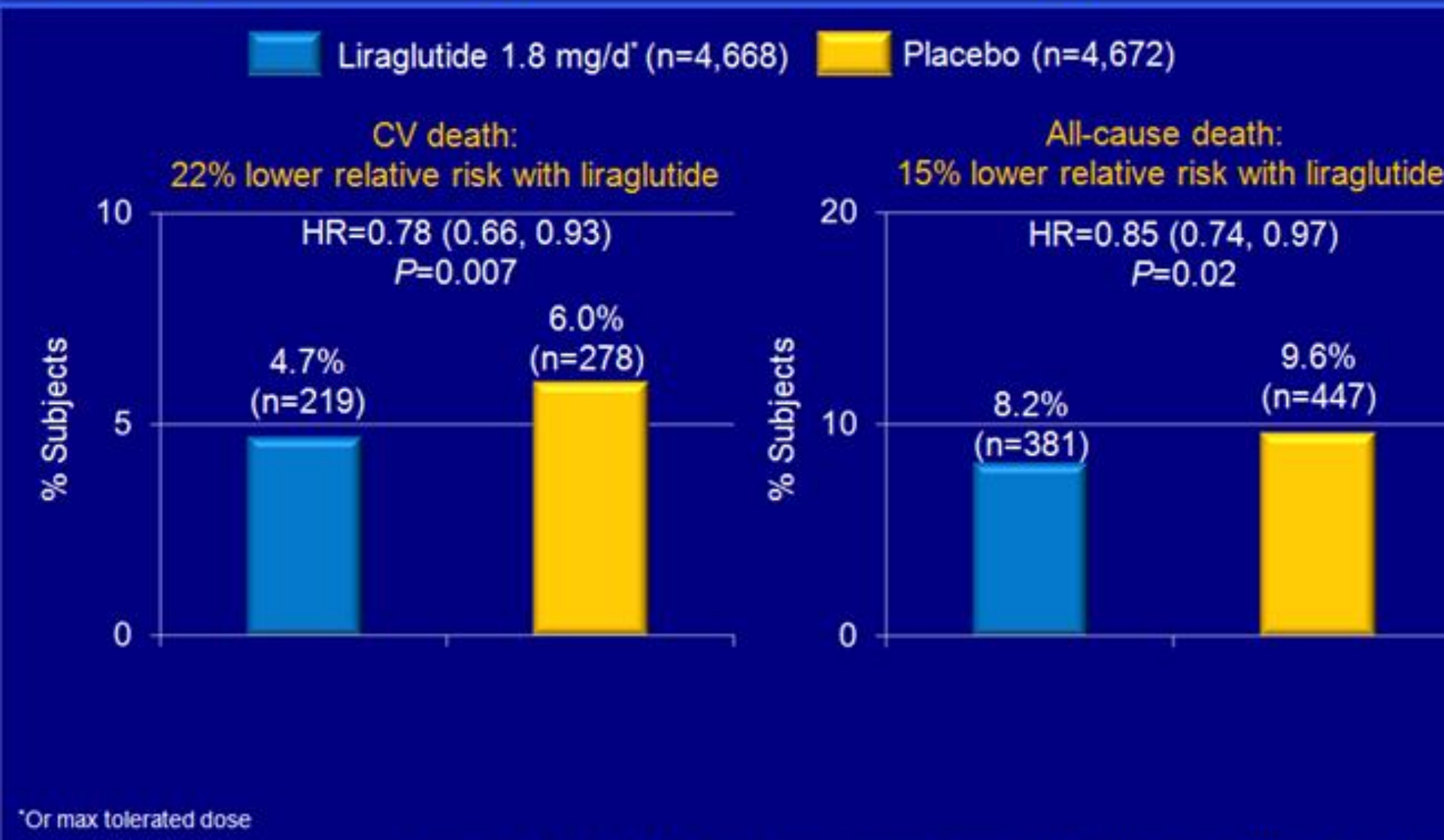
*Or max tolerated dose

LEADER: Numerically Lower Rates of Nonfatal MI and Stroke, Heart Failure Hospitalization With Liraglutide Vs Placebo in High-Risk Patients



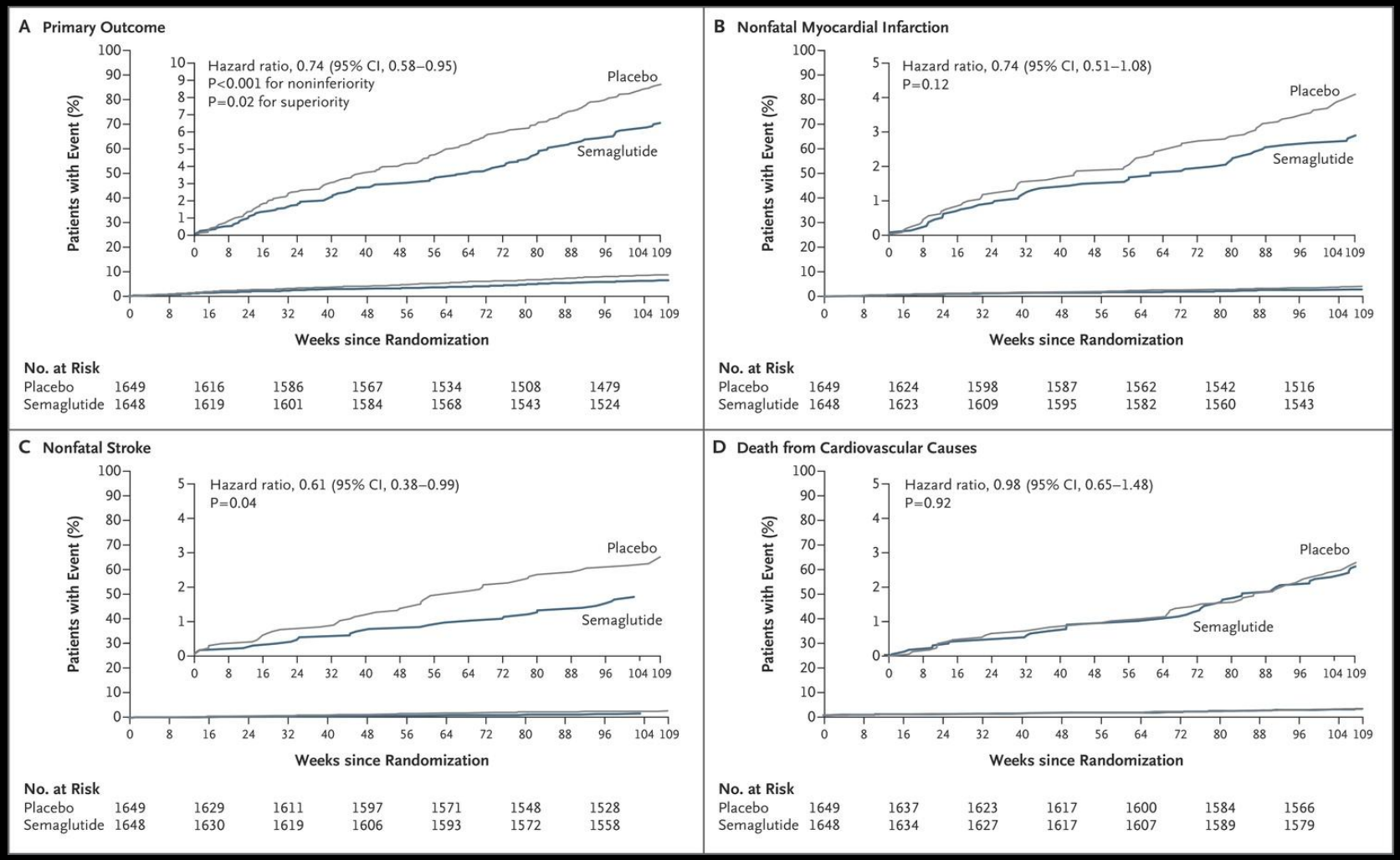
*Or max tolerated dose

LEADER: Rates of CV and All-Cause Death Lower With Liraglutide Vs Placebo in High-Risk Patients



*Or max tolerated dose

Cardiovascular Outcomes.



Marso SP et al. N Engl J Med 2016. DOI: 10.1056/NEJMoa1607141

The NEW ENGLAND JOURNAL of MEDICINE

Characteristics of the Patients at Baseline.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Semaglutide (N=1648)		Placebo (N=1649)		Total (N=3297)
	0.5 mg (N=826)	1.0 mg (N=822)	0.5 mg (N=824)	1.0 mg (N=825)	
Age — yr	64.6±7.3	64.7±7.1	64.8±7.6	64.4±7.5	64.6±7.4
Male sex — no. (%)	495 (59.9)	518 (63.0)	482 (58.5)	507 (61.5)	2002 (60.7)
Body weight — kg	91.8±20.3	92.9±21.1	91.8±20.3	91.9±20.8	92.1±20.6
Type 2 diabetes					
Duration — yr	14.3±8.2	14.1±8.2	14.0±8.5	13.2±7.4	13.9±8.1
Glycated hemoglobin — %	8.7±1.4	8.7±1.5	8.7±1.5	8.7±1.5	8.7±1.5
Cardiovascular risk factors					
Systolic blood pressure — mm Hg	136.1±18.0	135.8±17.0	135.8±16.2	134.8±17.5	135.6±17.2
Diastolic blood pressure — mm Hg	77.1±9.8	76.9±10.2	77.5±9.9	76.7±10.2	77.0±10.0
Low-density lipoprotein cholesterol — mg/dl†	81.6±47.1	83.3±41.2	80.9±48.1	83.6±45.9	82.3±45.6
Never smoked — no. (%)	390 (47.2)	364 (44.3)	391 (47.5)	348 (42.2)	1493 (45.3)
History of cardiovascular disease — no. (%)					
Ischemic heart disease	493 (59.7)	495 (60.2)	510 (61.9)	496 (60.1)	1994 (60.5)
Myocardial infarction	266 (32.2)	264 (32.1)	267 (32.4)	275 (33.3)	1072 (32.5)
Heart failure	201 (24.3)	180 (21.9)	190 (23.1)	206 (25.0)	777 (23.6)
Ischemic stroke	89 (10.8)	89 (10.8)	96 (11.7)	109 (13.2)	383 (11.6)
Hemorrhagic stroke	28 (3.4)	24 (2.9)	27 (3.3)	29 (3.5)	108 (3.3)
Hypertension	772 (93.5)	771 (93.8)	756 (91.7)	760 (92.1)	3059 (92.8)

* Plus–minus values are means ±SD unless otherwise indicated. Differences in baseline characteristics were assessed with the use of analysis of covariance for continuous characteristics and logistic regression for categorical characteristics. There were no significant differences between the groups except for the duration of type 2 diabetes (P=0.048). To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

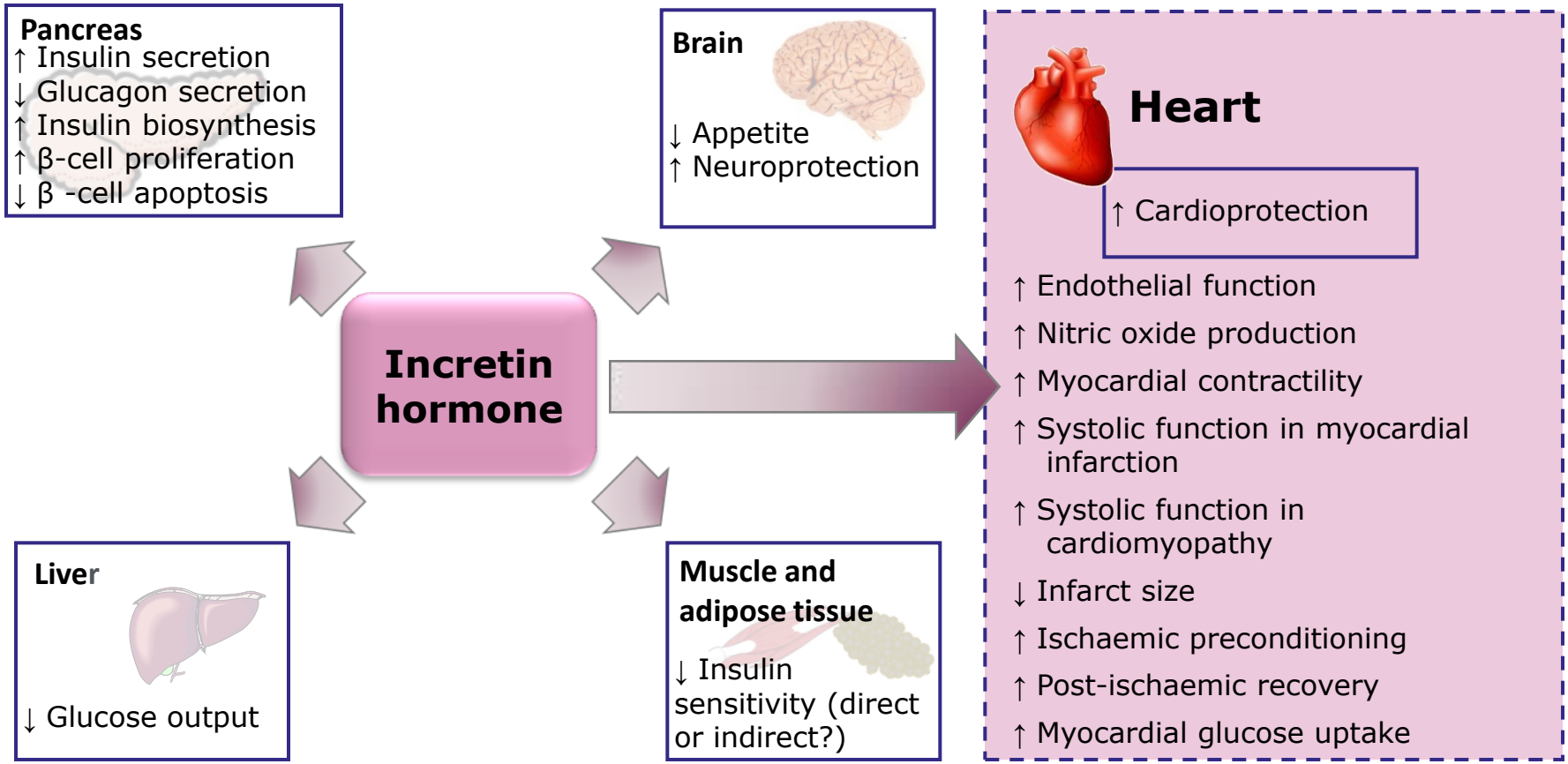
† Values are geometric means and coefficients of variation.

Marso SP et al. N Engl J Med 2016. DOI: 10.1056/NEJMoa1607141

The NEW ENGLAND JOURNAL of MEDICINE

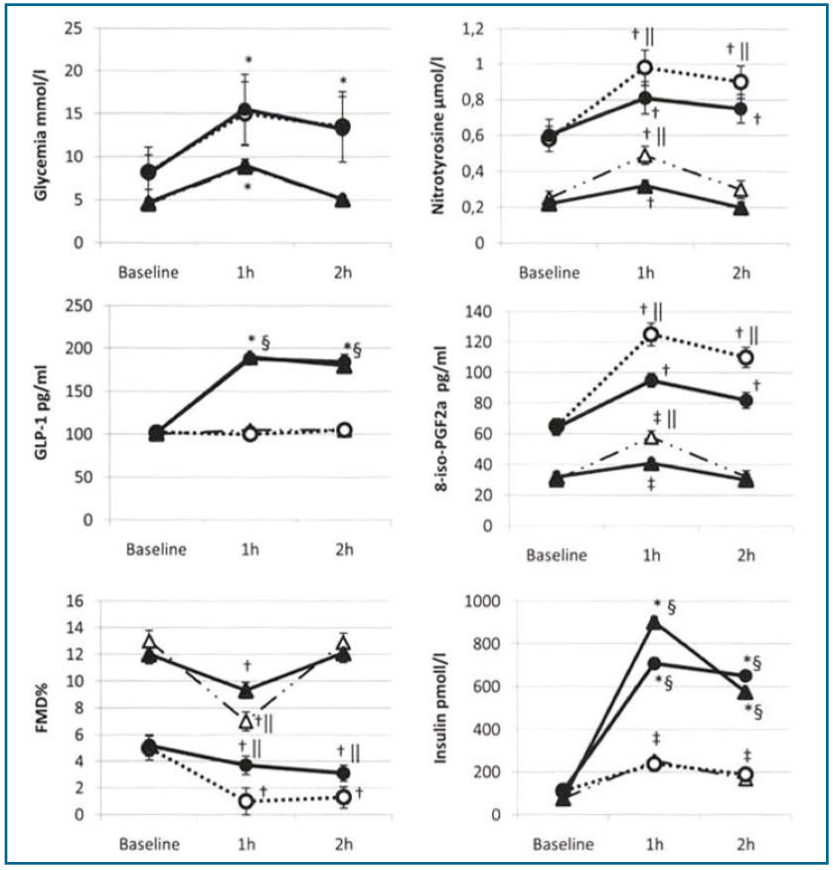
GLP-1 has various potential effects on the cardiovascular system

Potential impact of DPP4 inhibition and the incretin system on various organs



Jax T. *Clin Res Cardiol.* 2009;98:75–79;
Grieve DJ. *Br J Pharmacol*. 2009;157:1340–1351 (modified).

Protective effect of GLP-1 during both hypoglycemia and hyperglycemia in T1DM



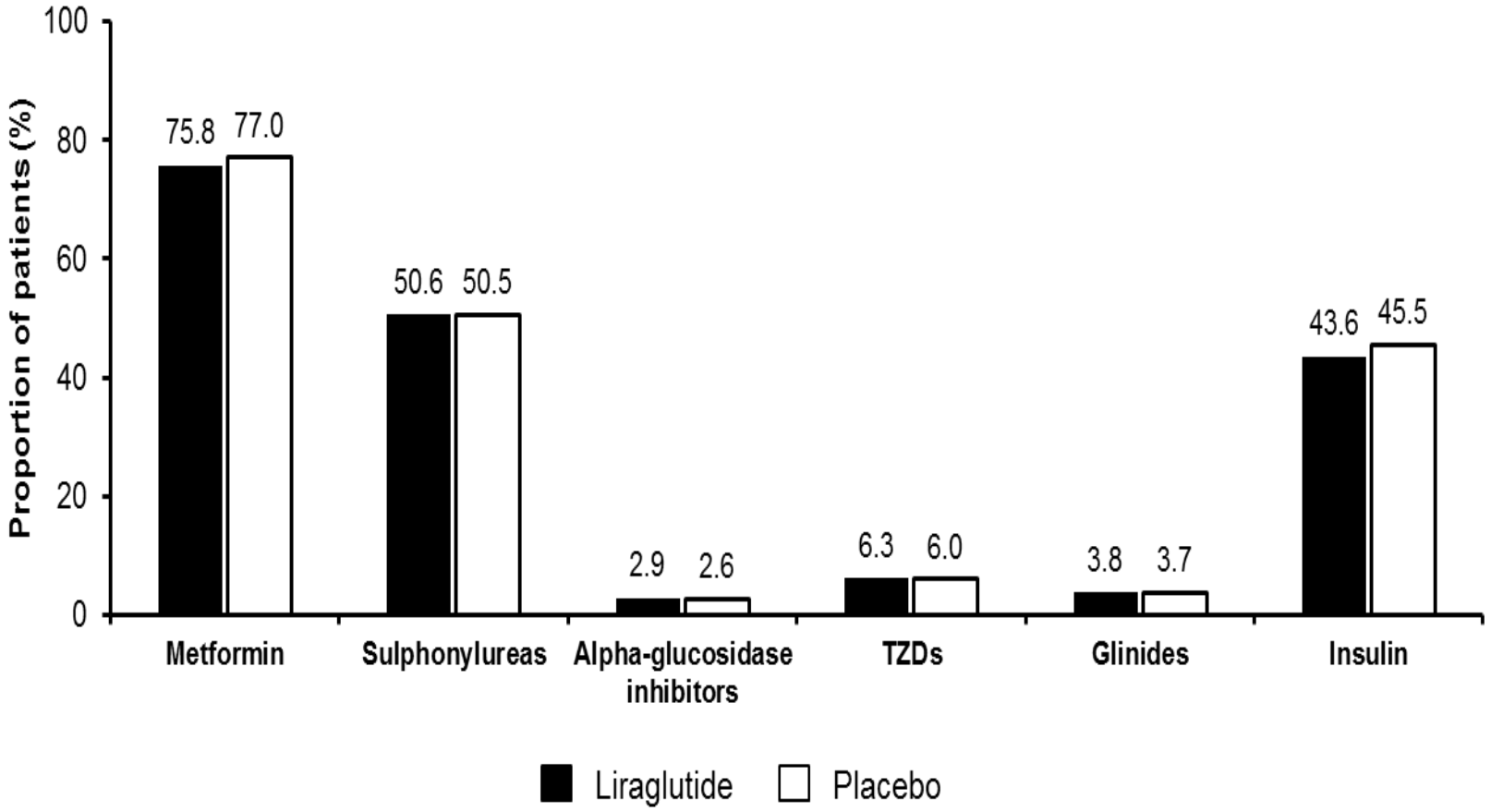
Both hyperglycemia and hypoglycemia acutely induced oxidative stress, inflammation and endothelial dysfunction.

GLP-1 significantly counterbalanced these effects.

Ceriello A, et al.Diabetes Care 2013 ; 36: 2346-50

Among the possible explanations, the most convincing one is linked to the half life of the molecules as currently used in the clinical practice: almost 24 hours for Liraglutide, 1 week for Semaglutide versus 2.7-4.3 hours for Lixisenatide.
Clearly the beneficial actions of the GLP-1 RAs on the cardiovascular system are linked to their presence in the bloodstream.

Antihyperglycemic medication at baseline

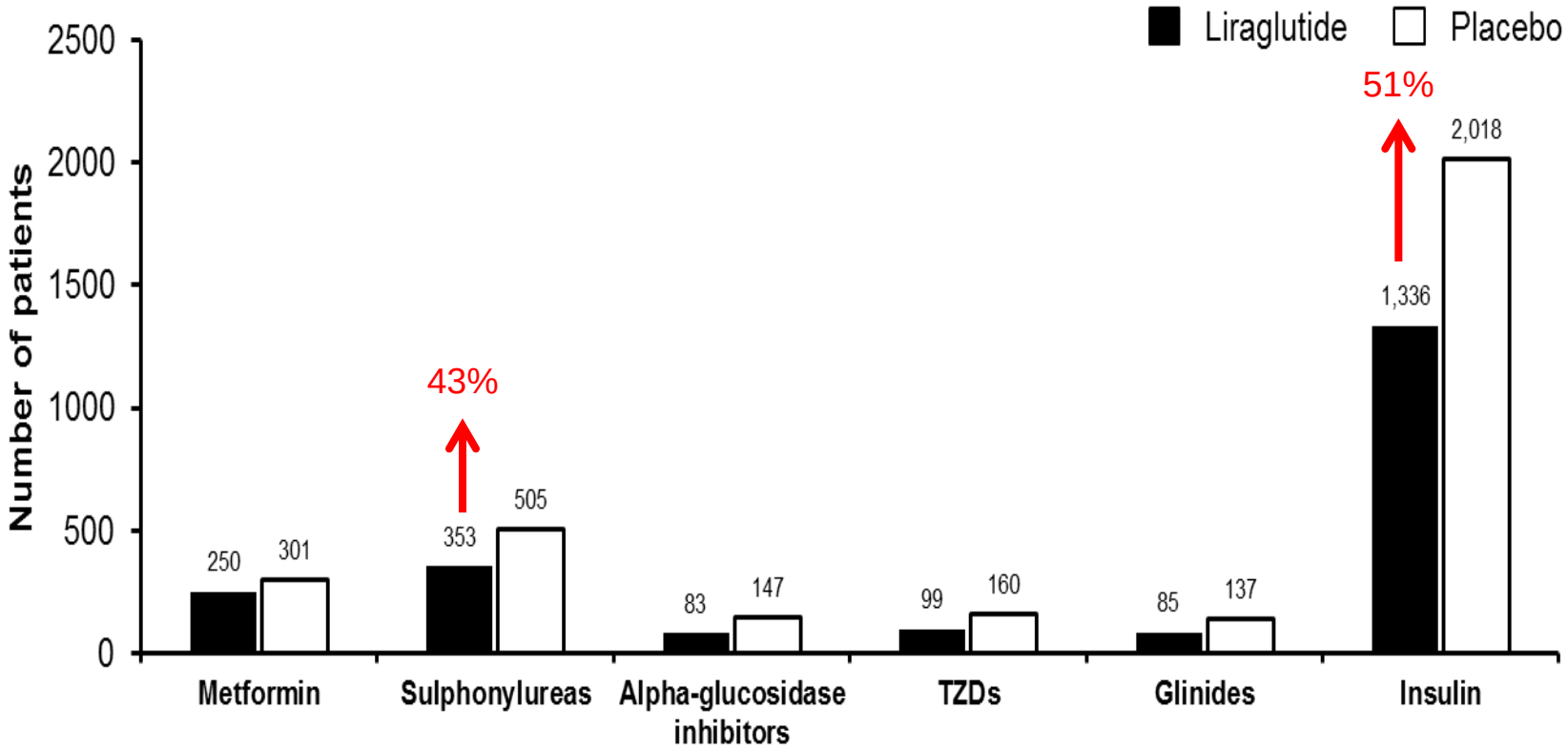


LEADER®
Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

TZD: thiazolidinediones.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

Antihyperglycemic medications introduced during trial



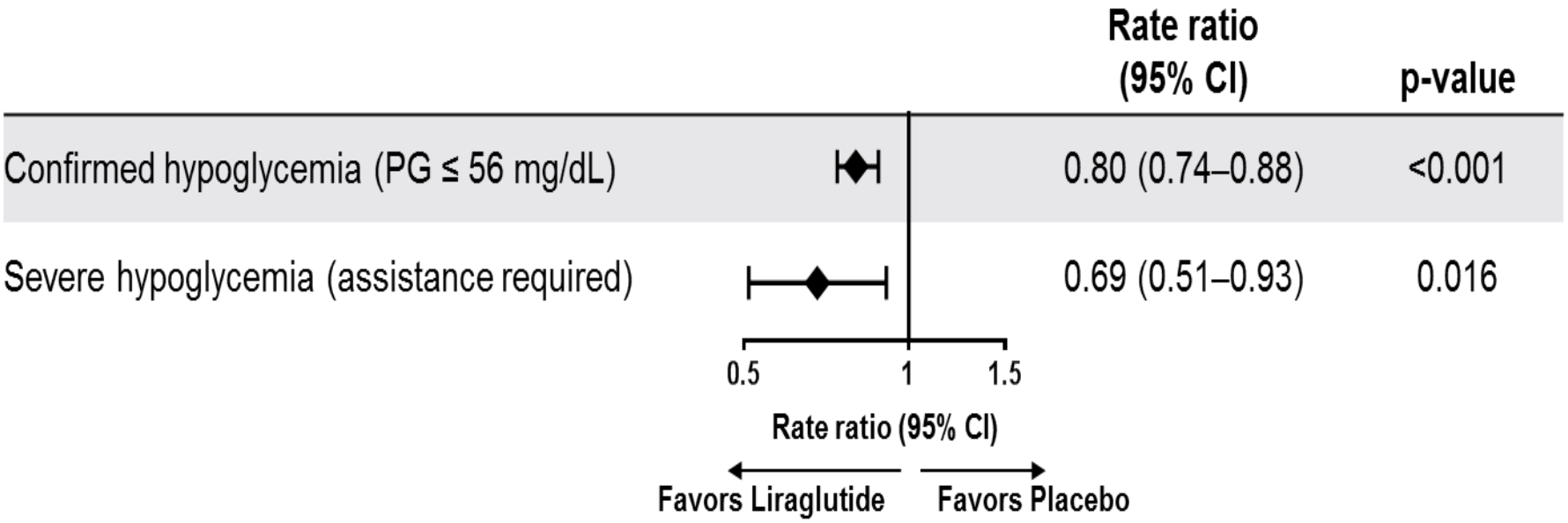
Additional classes added	Liraglutide	Placebo
DPP-4 inhibitors	149	170
GLP-1RAs	87	139
SGLT-2 inhibitors	100	130

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

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

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

Hypoglycemia



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

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.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

REVIEW Open Access

Current perspectives on cardiovascular outcome trials in diabetes

Oliver Schnell[1*], Lars Rydén[2], Eberhard Standl[1], Antonio Ceriello[3,4] and on behalf of the D&CVD EASD Study Group

Abstract

Cardiovascular disease (CVD) is one of the most common diabetes-associated complications, as well as a leading cause for death in type 2 diabetes patients (T2D). Despite the well-known correlation between the two, up until the 2008 FDA industry guidance for licensing of new anti-hyperglycemic drugs, which required an investigation of cardiovascular outcomes (CVO) of glucose-lowering agents, only a few studies had looked into the relationship between glucose lowering drugs and cardiovascular (CV) risk. Thereafter, CVOT design has focused on non-inferiority short-term studies on high-risk patient populations aiming at capturing CV safety issues. Despite the wealth of information and useful data provided by CVOTs, this approach still suffers from certain limitations. The present review will condense the main results of the most recently completed CVOTs, reflect on the lessons learned, discuss on the issues presented by current CVOT design and offer some suggestions for improvement.

Keywords: Cardiovascular risk, Diabetes, CVOT, Non-inferiority, Cardiovascular safety

Grazie!