Glycemic and non-glycemic effects of GLP-1 receptor agonist

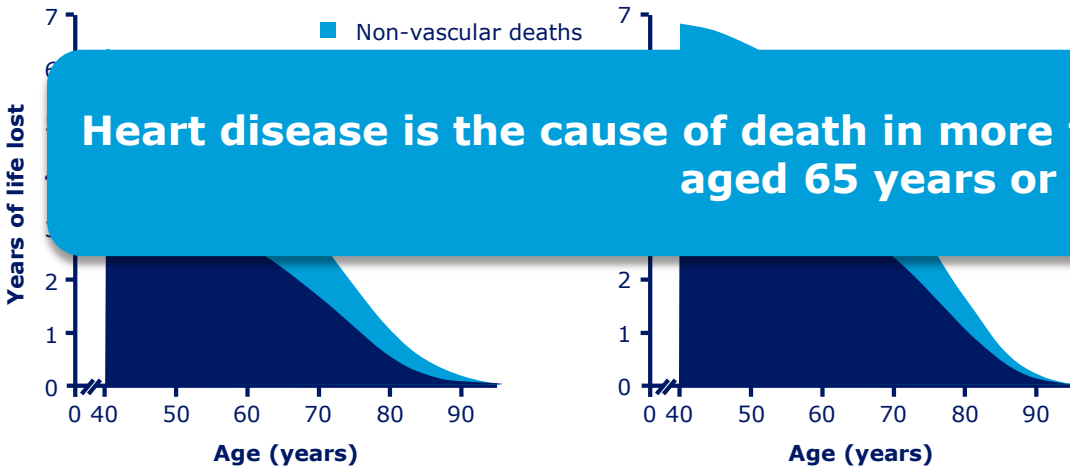
吳造中
台大醫院心臟內科

Burden of CVD in diabetes

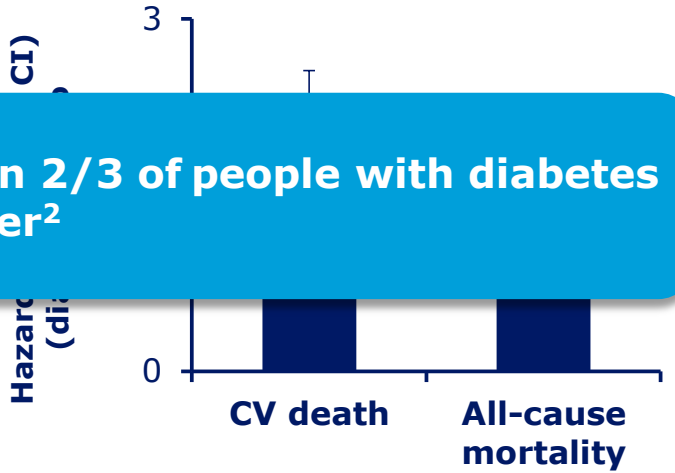
CVD, cardiovascular disease

CVD is the leading cause of death among people with diabetes

Years of life lost in people with diabetes* compared with non-diabetes peers[1]



Mortality risk associated with diabetes (n=820,900)[1]



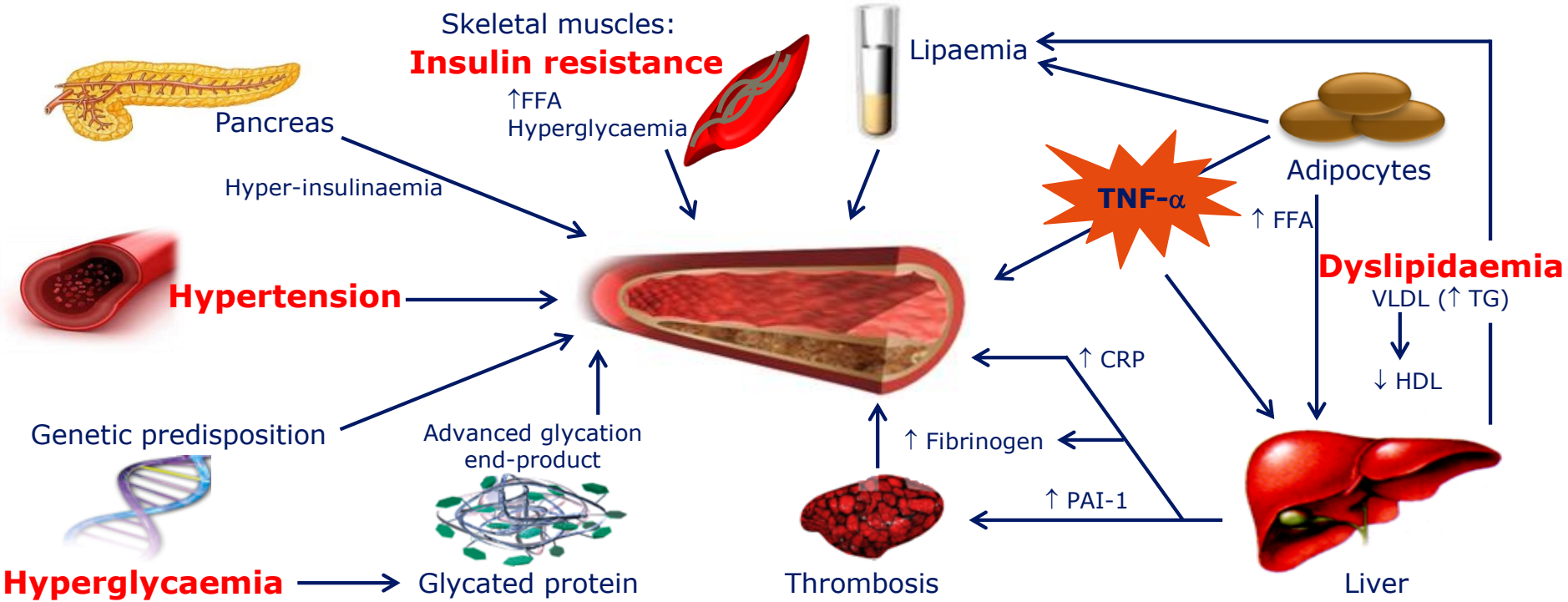
Heart disease is the cause of death in more than 2/3 of people with diabetes aged 65 years or older[2]

In high-income countries, up to 91% of adults with diabetes have type 2 diabetes[3]

*Information on diabetes type (i.e. type 1 or 2) was generally not available; however, the age of the participants suggests that the large majority with diabetes would have type 2
CI, confidence interval; CV, cardiovascular; CVD, CV disease

1. Seshasai SR et al. *N Engl J Med* 2011;364:829–841; 2. Centers for Disease Control and Prevention. National Diabetes Fact Sheet 2011. Available at: http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf; 3. International Diabetes Federation. *IDF Diabetes Atlas, 7th edn.* Brussels, Belgium: International Diabetes Federation, 2015. Available at: http://www.diabetesatlas.org

Many factors contribute to increased CV risk in T2DM



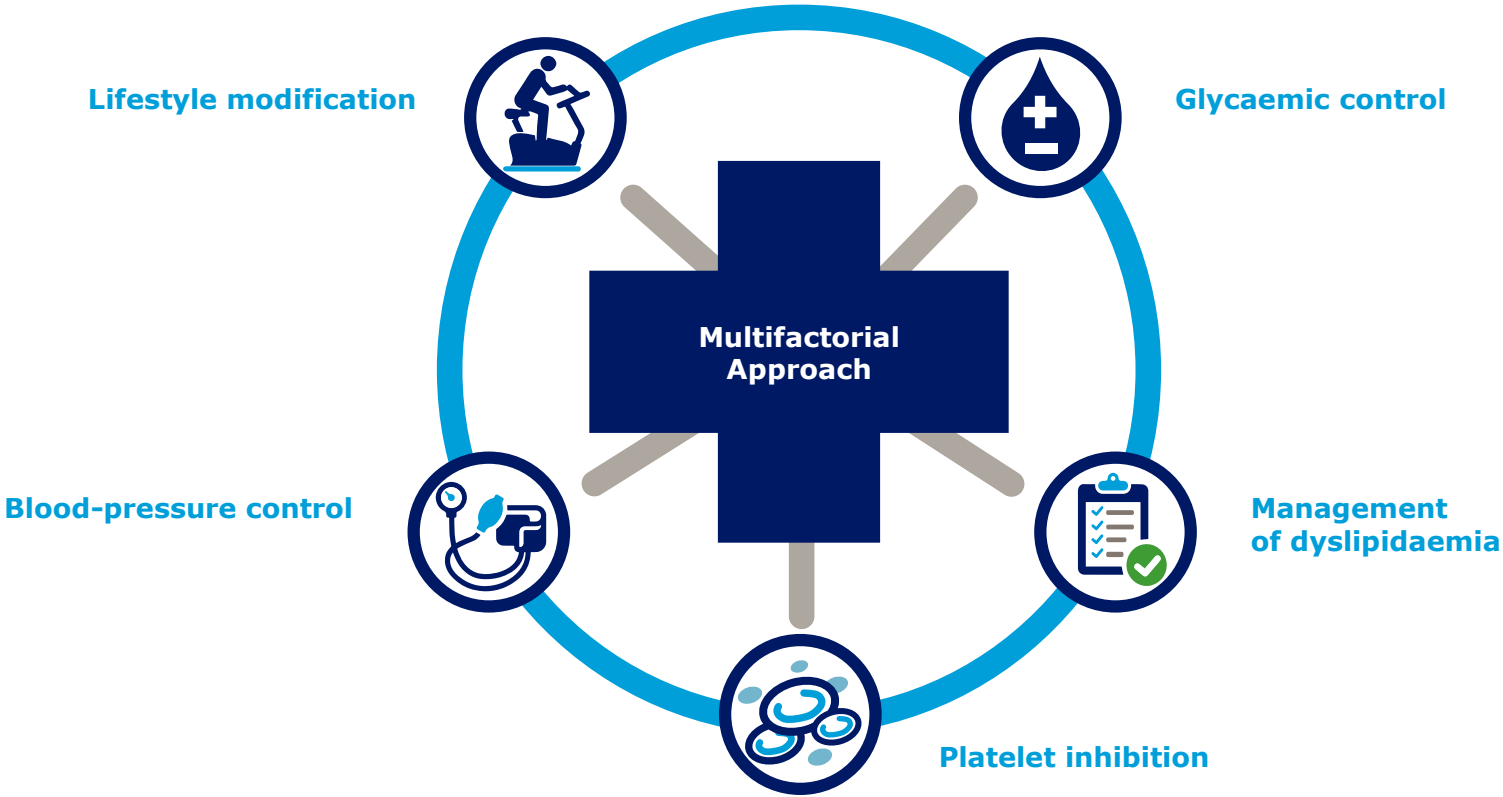
CRP, C-reactive protein; CV, cardiovascular; FFA, free fatty acid; HDL, high-density lipoprotein; IGT, impaired glucose tolerance; LDL, low-density lipoprotein; PAI-1, plasminogen activator inhibitor-1; T2DM, type 2 diabetes mellitus; TG, triglyceride; TNF-α, tumour necrosis factor-alpha; VLDL, very low-density lipoprotein.

Libby P, Plutzky J. *Circulation* 2002;106:2760–2763

How to manage CV risk in T2DM

CV, cardiovascular; T2DM, type 2 diabetes mellitus

How do we modify CV risk in T2DM?



CV, cardiovascular; T2DM, type 2 diabetes mellitus

1. Rydén L et al. *Eur Heart J* 2013;34:3035–3087; 2. Fox CS et al. *Diabetes Care* 2015;38:1777–1803; 3. Piepoli MF et al. *Eur Heart J* 2016;37:2315–2381

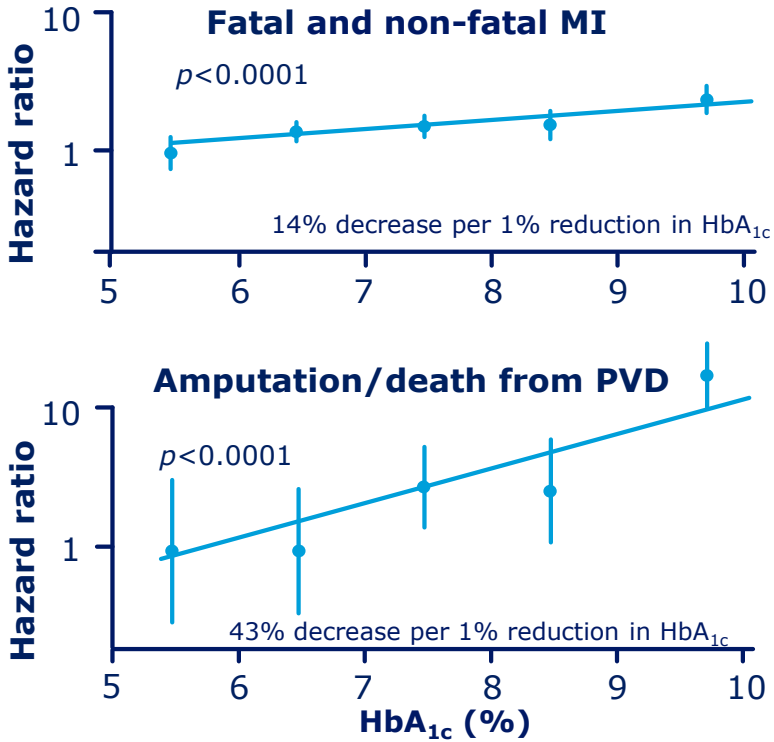
How do we modify CV risk in T2DM?

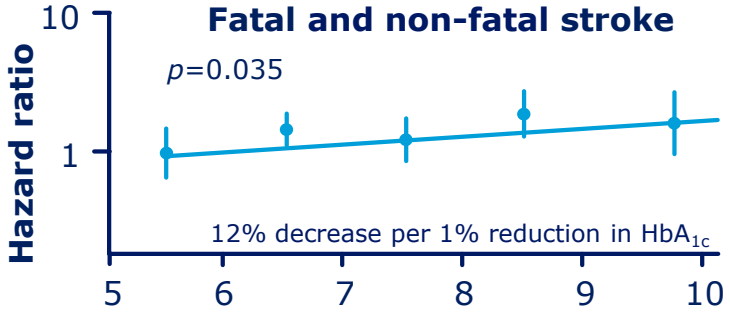
- Generally, HbA_{1c} <7.0%
- On an individual basis, <6.5–6.9% or above 7%

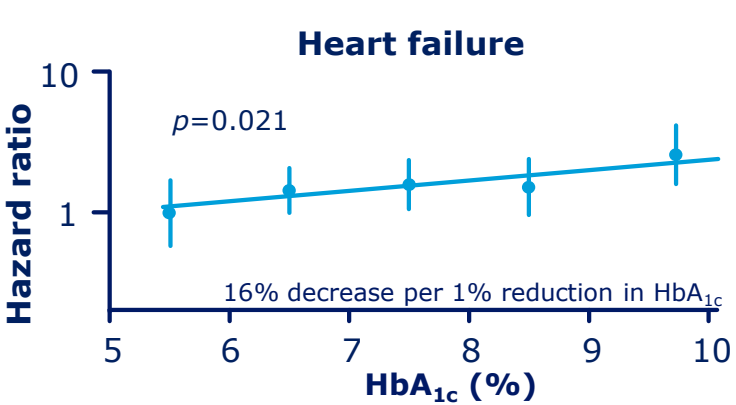
CV, cardiovascular; HbA_{1c}, glycosylated haemoglobin; T2DM, type 2 diabetes mellitus

1. Rydén L et al. *Eur Heart J* 2013;34:3035–3087; 2. Fox CS et al. *Diabetes Care* 2015;38:1777–1803; 3. Piepoli MF et al. *Eur Heart J* 2016;37:2315–2381

Higher HbA_{1c} predicts higher CV risk



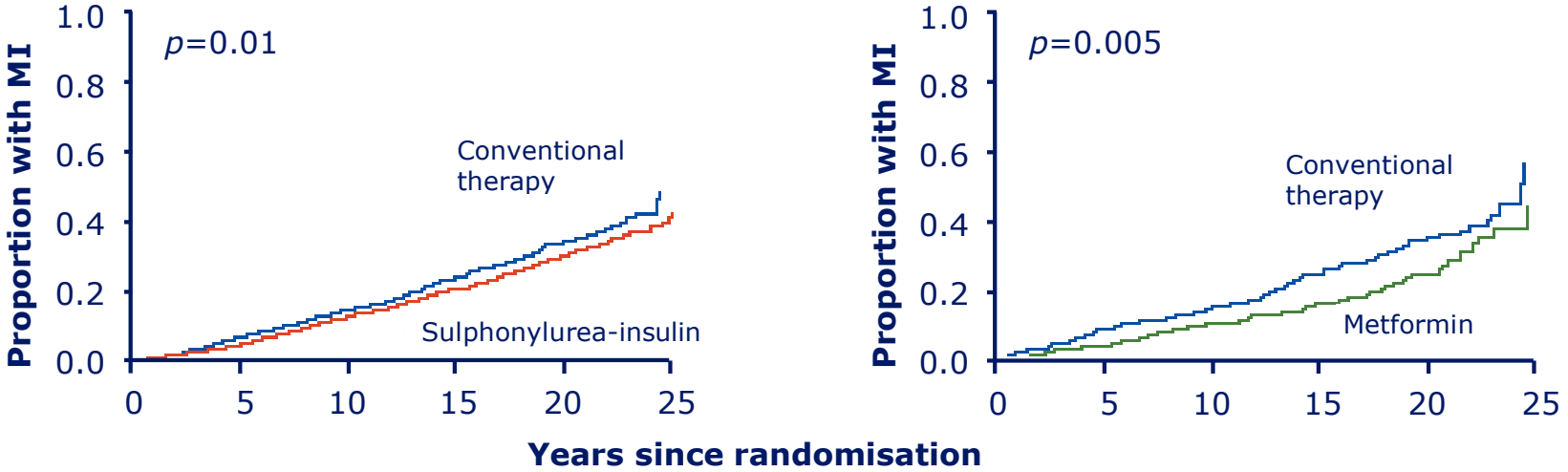




Reference category (hazard ratio 1.0) is HbA_{1c} <6% with log linear scales
CV, cardiovascular; HbA_{1c}, glycosylated haemoglobin; MI, myocardial infarction; PVD, peripheral vascular disease
Stratton IM et al. *BMJ* 2000;321:405–412

CV benefits of tight glycaemic control – 10 years

UKPDS



No. at risk						
Conventional:	1138	1013	857	578	221	20
SU/insulin:	2729	2488	2097	1459	577	66

No. at risk						
Conventional:	411	360	311	213	95	4
Metformin:	342	317	274	214	106	16

Patients were randomised to conventional glucose control (diet) or intensive glucose control (SU or insulin, or metformin if >120% of ideal body weight)
CV, cardiovascular; MI, myocardial infarction; SU, sulphonylurea; UKPDS, UK Prospective Diabetes Study
Holman RR et al. *N Engl J Med* 2008;359:1577–1589

Impact of intensive vs. conventional glucose-lowering therapy

Study (HbA_{1c} intensive vs. conventional)	Microvascular complications		CV complications		CV mortality	
UKPDS 33[1,2] (7.0% vs. 7.9%)	↓	↓	↔	↓	↔	↓†
ACCORD[3,4] (6.4% vs. 7.5%)	↓	↓	↔	↔	↑	↑
ADVANCE[5,6] (6.3% vs. 7.0%)	↓	↔*	↔	↔	↔	↔
VADT[7,8] (6.9% vs. 8.4%)	↓	N/R	↔	↓	↔	↔

Initial trial Long-term follow-up

*Significant improvement in end-stage renal disease was observed but no other difference in other microvascular end points. †Diabetes-related mortality
ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; CV, cardiovascular; HbA_{1c}, glycosylated haemoglobin; N/R, not reported; UKPDS, UK Prospective Diabetes Study; VADT, Veteran's Affairs Diabetes Trial

1. UKPDS Group. *Lancet* 1998;352:837–853; 2. Holman et al. *N Engl J Med* 2008;359:1565–1576; 3. Gerstein et al. *N Engl J Med* 2008;358:2545–2559; 4. ACCORD study group *Diabetes Care* 2016;39:701–708; 5. Patel et al. *N Engl J Med* 2008;358:2560–2572; 6. Zoungas et al. *N Engl J Med* 2014;371:1392–1406; 7. Duckworth et al. *N Engl J Med* 2009;360:129–139; 8. Hayward et al. *N Engl J Med* 2015;372:2197–2206

Cardiovascular outcomes trials in type 2 diabetes

TBD

CVOT background

CVOT, cardiovascular outcomes trial

Experience with rosiglitazone: Are diabetes medications associated with increased CV risk?

The NEW ENGLAND JOURNAL of MEDICINE

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

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

ABSTRACT

BACKGROUND

Rosiglitazone is widely used to treat patients with type 2 diabetes mellitus, but its effect on cardiovascular morbidity and mortality has not been determined.

METHODS

We conducted searches of the published literature, the Web site of the Food and Drug Administration, and a clinical-trials registry maintained by the drug manufacturer (GlaxoSmithKline). Criteria for inclusion in our meta-analysis included a study duration of more than 24 weeks, the use of a randomized control group not receiving rosiglitazone, and the availability of outcome data for myocardial infarction and death from cardiovascular causes. Of 116 potentially relevant studies, 42 trials met the inclusion criteria. We tabulated all occurrences of myocardial infarction and death from cardiovascular causes.

RESULTS

Data were combined by means of a fixed-effects model. In the 42 trials, the mean age of the subjects was approximately 56 years, and the mean baseline glycated hemoglobin level was approximately 8.2%. In the rosiglitazone group, as compared with the control group, the odds ratio for myocardial infarction was 1.43 (95% confidence interval [CI], 1.03 to 1.98; P=0.03), and the odds ratio for death from cardiovascular causes was 1.64 (95% CI, 0.98 to 2.74; P=0.06).

CONCLUSIONS

Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance. Our study was limited by a lack of access to original source data, which would have enabled time-to-event analysis. Despite these limitations, patients and providers should consider the potential for serious adverse car-

From the Cleveland Clinic, Cleveland. Address reprint requests to Dr. Nissen at the Department of Cardiovascular Medicine, Cleveland Clinic, 9500 Euclid Ave., Cleveland, OH 44195, or at nissens@ccf.org.

This article (10.1056/NEJMoa072761) was published at www.nejm.org on May 21, 2007.

N Engl J Med 2007;356:2457-71.

"Rosiglitazone was associated with a significant increase in the risk of MI and with an increase in the risk of CV death that had borderline significance"

CV, cardiovascular

Nissen SE et al. *N Engl J Med* 2007;156:2457–2471

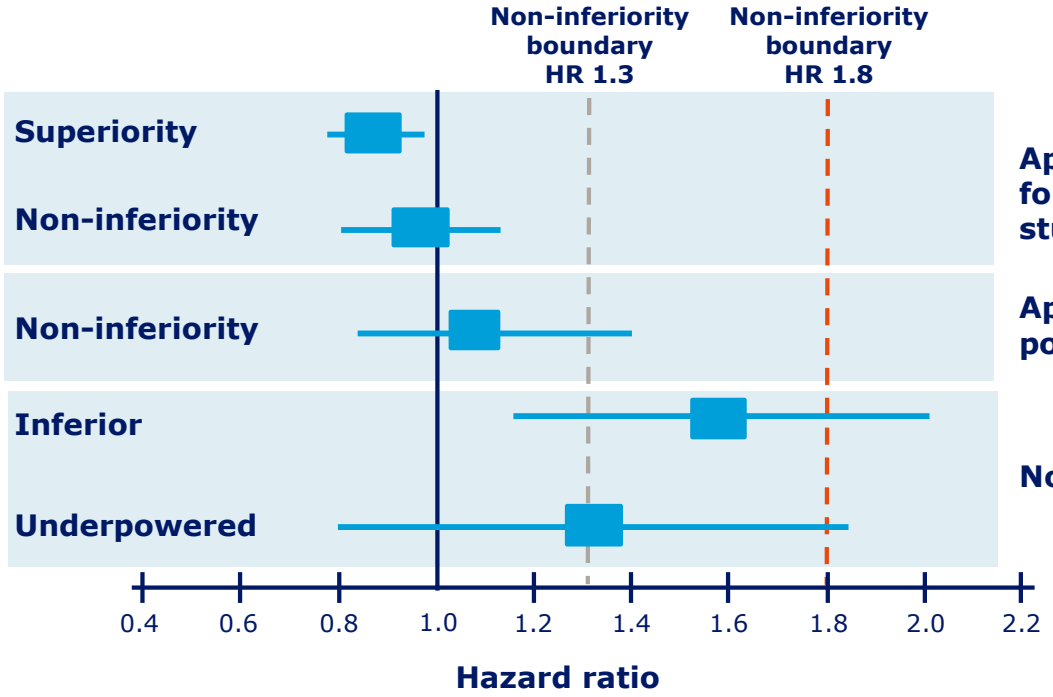
Addressing the need for CVOTs in T2DM

- Meta-analyses have raised the question of increased CV risk
- To date, clinical trial designs have not included CV outcomes assessments
- Need to assess non-inferiority versus placebo and versus standard of care

"Demonstrate that a new anti-diabetic therapy is not associated with **unacceptable increase** in cardiovascular risk"

CV, cardiovascular; CVOT, cardiovascular outcome trials; T2DM, type 2 diabetes mellitus
Hiatt WR et al. *N Engl J Med* 2013;369:1285–1287

FDA criteria for requirement of a postmarketing CV outcomes trial



Approvable: *No need* for postmarketing study

Approvable: *Need* for postmarketing study

Not approvable

All phase 2 and 3 studies should include a prospective independent adjudication of CV events

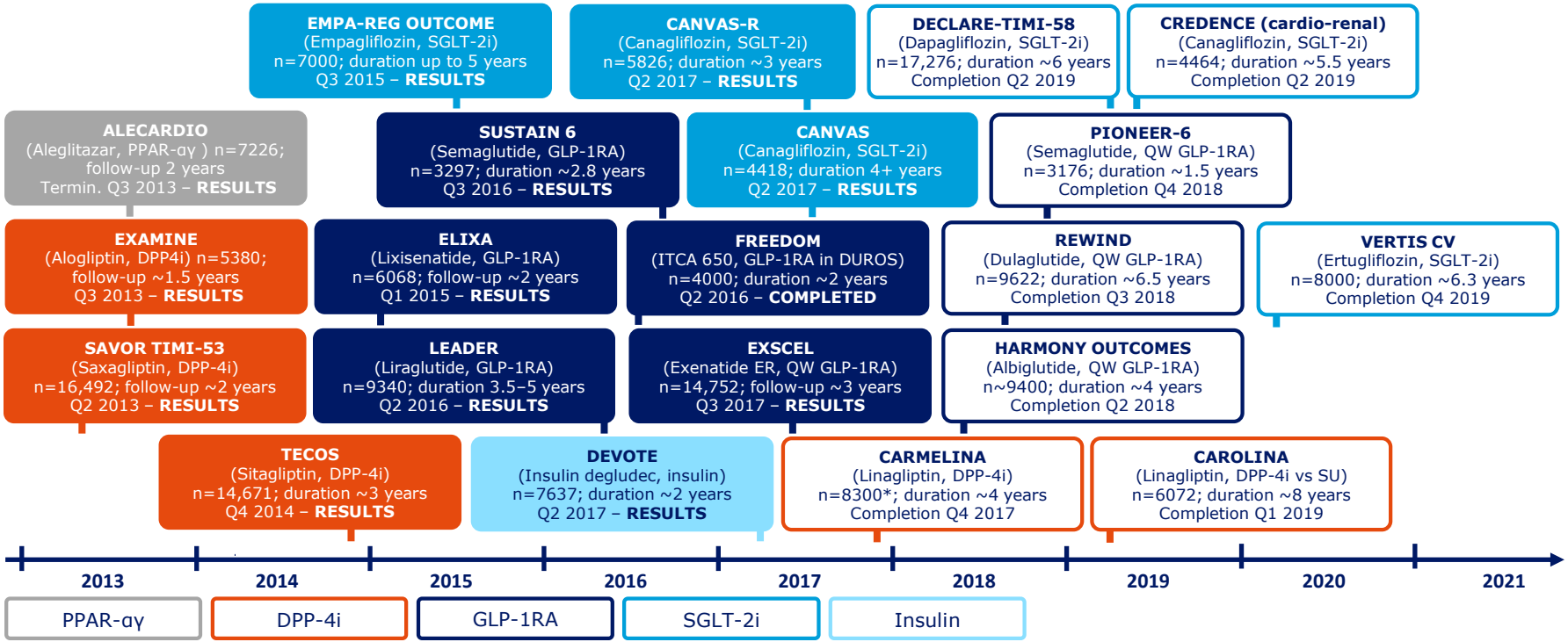
A minimum of 2 years' CV safety data must be provided

CI, confidence interval; CV, cardiovascular; FDA, US Food and Drug Administration; HR, hazard ratio
Hirshberg B, Raz I. *Diabetes Obes Metab* 2011;34(Suppl. 2):S101–S106

Overview of CVOT results in T2DM

CVOT, cardiovascular outcomes trial; T2DM, type 2 diabetes mellitus

CVOTs in T2DM

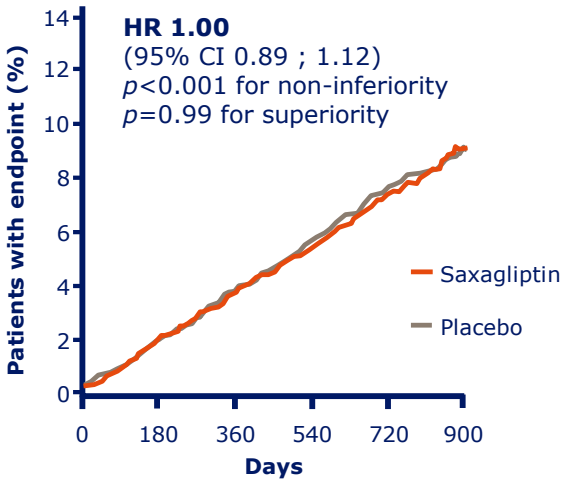


*Estimated enrolment
CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase-4 inhibitor; ER, extended release; GLP-1RA, glucagon-like peptide-1 receptor agonist; ITCA 650, continuous subcutaneous delivery of exenatide; PPAR- receptors-αγ, peroxisome proliferator-activated receptors-α and γ; QW, once weekly; SGLT-2i, sodium-glucose cotransporter 2 inhibitor; SU, sulphonylurea; T2DM, type 2 diabetes mellitus
ClinicalTrials.gov. Accessed 20 September 2017

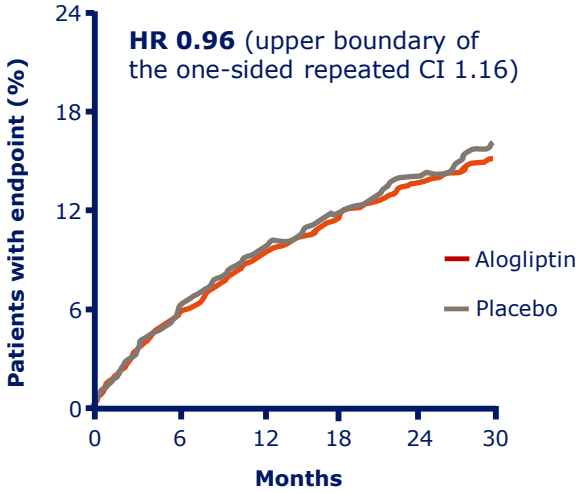
DPP-4i CVOTs

Time to first occurrence of CV death, non-fatal MI, or non-fatal stroke*

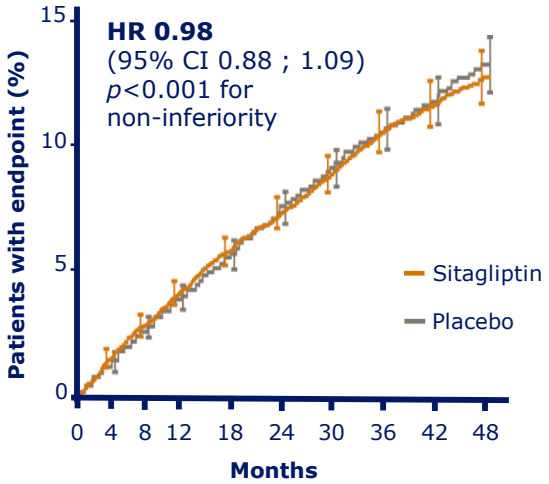
SAVOR-TIMI 53[1]



EXAMINE[2]



TECOS[3] †



*Ischaemic stroke for SAVOR-TIMI 53 and EXAMINE. †Primary outcome includes unstable angina requiring hospitalisation

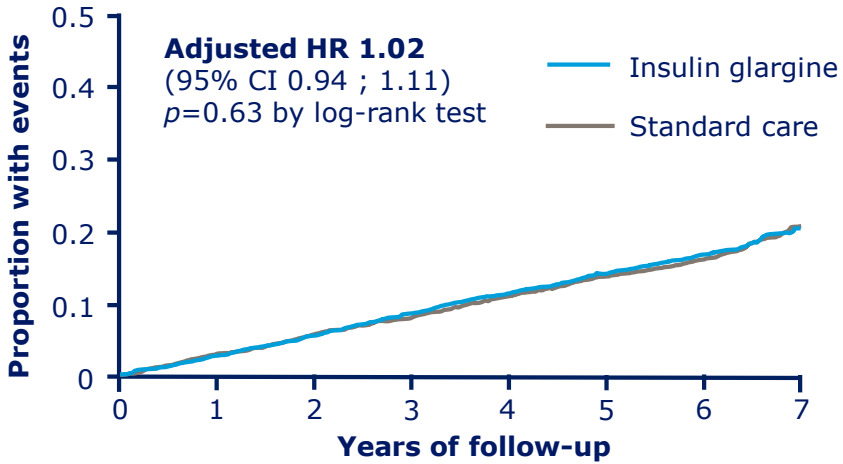
CI, confidence interval; CV, cardiovascular; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase-4 inhibitor; HR, hazard ratio; MI, myocardial infarction

1. Scirica BM et al. *N Engl J Med* 2013;369:1317–1326; 2. White WB et al. *N Engl J Med* 2013;369:1327–1335; 3. Green JB et al. *N Engl J Med* 2015;16;373:232–242

Insulin CVOTs

Time to first occurrence of CV death, non-fatal MI, or non-fatal stroke

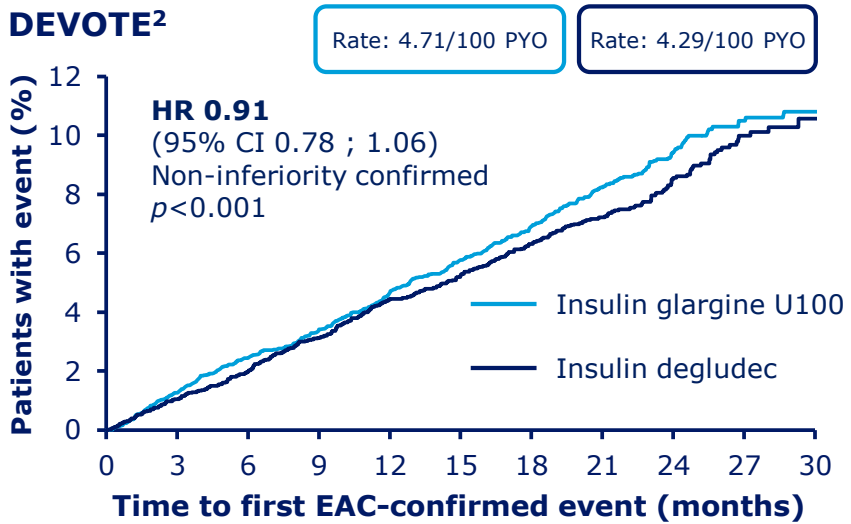
ORIGIN[1]*



No. at risk

IGlar	6264	6057	5850	5619	5379	5151	3611	766
SoC	6273	6043	5847	5632	5415	5156	3639	800

DEVOTE[2]



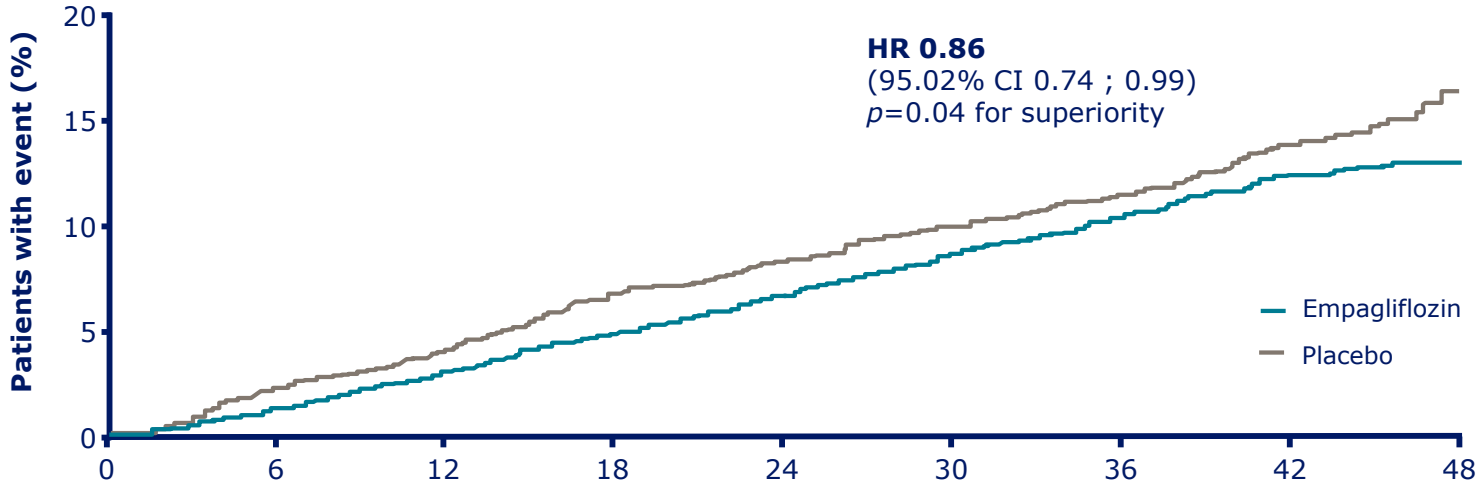
IDeg	3818	3765	3721	3699	3611	3563	3504	2851	1767	811	217
IGlar	3819	3758	3703	3655	3595	3530	3472	2832	1742	811	205

*Initiated before FDA requirements for mandatory CVOTs. CI, confidence interval; CV, cardiovascular; CVOT, cardiovascular outcomes trial; EAC, Event Adjudication Committee; FDA, US Food and Drug Administration; HR, hazard ratio; IDeg, insulin degludec; IGlar, insulin glargine; MACE, major adverse cardiac event; MI, myocardial infarction; SoC, standard of care; 100 PYO, per 100 patient-years of observation

1. The ORIGIN trial investigators *N Engl J Med* 2012;367:319–328; 2. Marso et al *N Engl J Med* 2017; Jun 12. doi: 10.1056/NEJMoa1615692 [Epub ahead of print]

SGLT-2i CVOT: EMPA-REG OUTCOME

Time to first occurrence of CV death, non-fatal MI*, or non-fatal stroke



No. at risk									
Empa	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

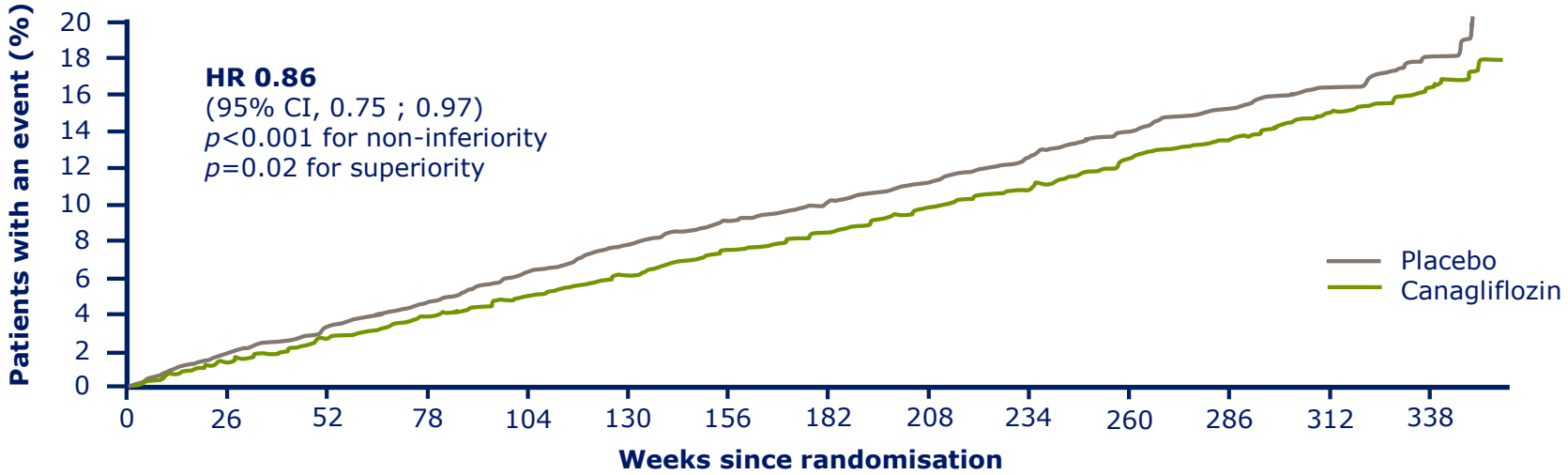
*Excluding silent MI. Background glucose-lowering therapy unchanged in first 12 weeks, then adjusted at the investigator's discretion to achieve desired glycaemic control

CI, confidence interval; CV, cardiovascular; CVOT, cardiovascular outcomes trial; Empa, empagliflozin; HR, hazard ratio; MI, myocardial infarction; SGLT-2i, sodium-glucose cotransporter-2 inhibitor

Zinman B et al. *Cardiovasc Diabetol* 2014;13:102; Zinman B et al. *N Engl J Med* 2015;373:2117–2128

SGLT-2i CVOT: CANVAS/CANVAS-R

Death from CV causes, non-fatal MI or non-fatal stroke



No. at risk														
Canagliflozin	5795	5672	5566	5447	4343	2984	2555	2513	2460	2419	2363	2311	1661	448
Placebo	4347	4239	4153	4061	2942	1626	1240	1217	1187	1156	1120	1095	789	216

HR and 95% CI for the primary outcome were estimated using Cox regression models with stratification according to trial and history of CVD for all canagliflozin groups combined versus placebo. Analyses are based upon the full integrated data set comprising all participants who underwent randomisation

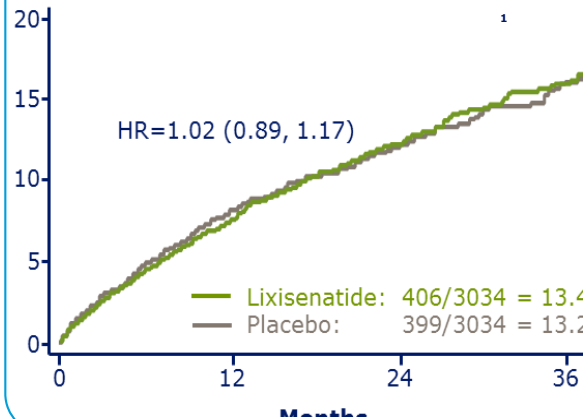
CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; HR, hazard ratio; MI, myocardial infarction; SGLT-2i, sodium-glucose cotransporter-2 inhibitor

Neal B et al. *N Engl J Med* 2017; doi: 10.1056/NEJMoa1611925

CVOTs for exendin-based GLP-1RA

ELIXA

Lixisenatide in acute coronary syndrome, a long-term cardiovascular end point trial of lixisenatide vs placebo[1]



FREEDOM

FREEDOM-CVO: Placebo-controlled cardiovascular outcomes study examining the safety of ITCA 650 vs placebo[2]


PRESS RELEASES

Intarcia Announces Successful Cardiovascular Safety Results in Phase 3 FREEDOM-CVO Trial for ITCA 650, an Investigational Therapy for Type 2 Diabetes

Company also Reports New $75 Million Financing for Manufacturing Scale-Up and Inventory Build for Anticipated Global Launch of ITCA 650

– FREEDOM-CVO Phase 3 safety trial in more than 4,000 patients meets its primary and secondary endpoints by demonstrating FDA required non-inferiority for pre-approval cardiovascular (CV) safety. Final data to be published and presented at major future medical meeting. –

– Comprehensive Phase 3 data and manufacturing data packages will be in hand during 3Q; Regulatory filing targeted for the end of 3Q 2016 in the U.S. –

Boston, MA – May 6, 2016 – Intarcia Therapeutics, Inc. today announced top-line results from its more than 4,000 patient Cardiovascular Safety Study (FREE… the global FREEDOM Phase 3 Clinical Tri… is targeted for end of … The Co… facilitate ongoing scale-up … of ITCA 650 in type 2 diabe…

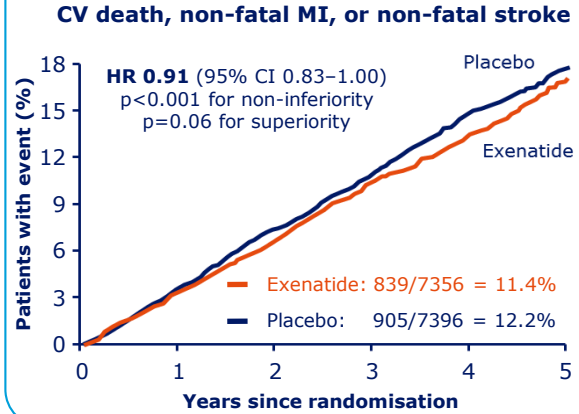
"The completion of our FREED… clinical milestones for Intarcia, ma… submissions for ITCA 650, said Dr. I… Therapeutics. "The FREEDOM-CVO tr… are pleased that it has achieved all of its… working closely with global health author… reviews."

Kurt Graves, Chairman, President and C… Clinical Trial Program for ITCA 650 has… receptor agonist category: A time when … when new medical evidence from larger… agonists may provide potential cardiova… growth trajectory and outlook for the GL…

"FREEDOM-CVO … meets its primary and secondary endpoints by demonstrating FDA required non-inferiority for pre-approval CV safety"

EXSCEL
Exenatide Study of Cardiovascular Event Lowering

A trial to evaluate cardiovascular outcomes after treatment with exenatide OW* vs placebo[3]



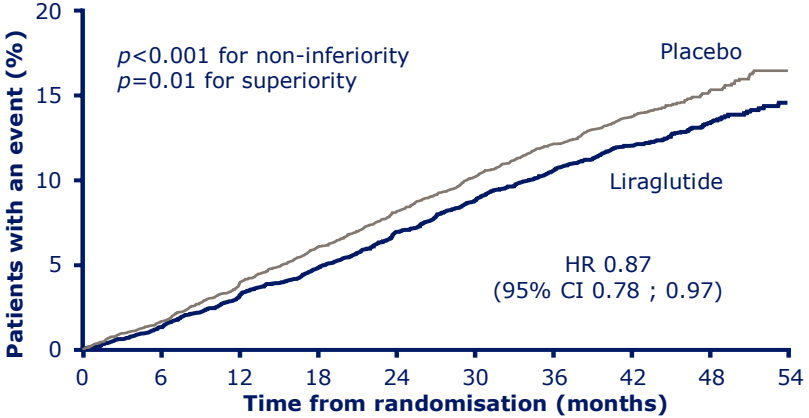
*Exenatide extended release. CV, cardiovascular; CVOT, cardiovascular outcomes trial; FDA, US Food and Drug Administration; GLP-1RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; ITCA 650, continuous subcutaneous delivery of exenatide; MACE, major adverse cardiac event; MI, myocardial infarction; OW, once weekly

1. Pfeffer M et al. *N Engl J Med* 2015;373:2247–2257; 2. Intarcia company announcement. Available at: http://www.intarcia.com/media/press-releases/2016-may-6-cardiovascular-safety.html accessed June 2017; 3. Holman RR et al. *N Engl J Med* 2017; DOI: 10.1056/NEJMoa1612917 [Epub ahead of print]

CVOTs for human GLP-1 analogues

LEADER[1]

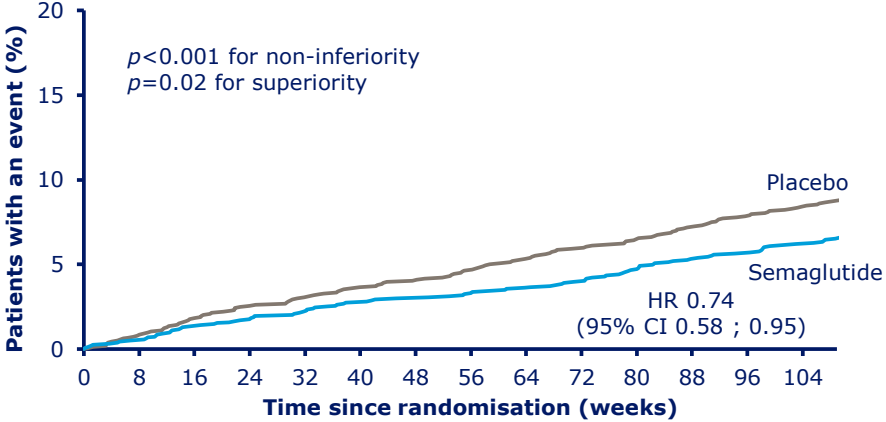
Time to first occurrence of CV death, non-fatal MI, or non-fatal stroke



LEADER is a post-approval CVOT with 1302 primary events

SUSTAIN 6[2]

Time to first occurrence of CV death, non-fatal MI, or non-fatal stroke



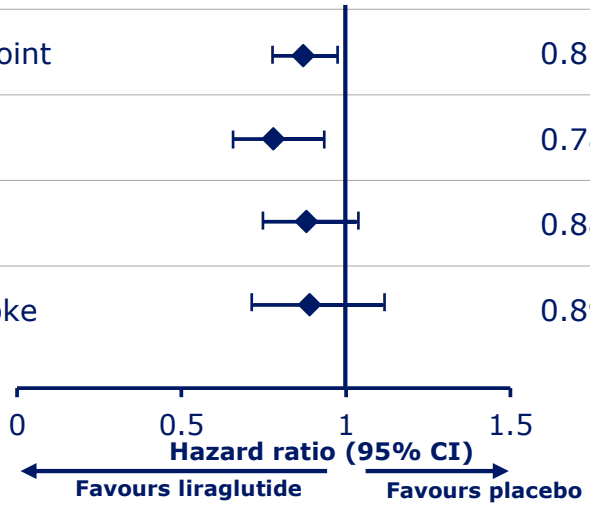
SUSTAIN 6 is a pre-approval CVOT with 254 primary events

CI, confidence interval; CV, cardiovascular; CVOT, cardiovascular outcomes trial; GLP-1, glucagon-like peptide-1; HR, hazard ratio; MI, myocardial infarction

1. Marso SP et al. *N Engl J Med* 2016;375:311–322; 2. Marso SP et al. *N Engl J Med* 2016;375:1834–1844

Individual components of the primary endpoint

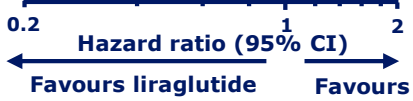
	Hazard ratio (95% CI)	*p*-value	Liraglutide			Placebo		
			N	%	R	N	%	R
Number of patients			**4668**	**100.0**	–	**4672**	**100.0**	–
Primary endpoint	0.87 (0.78 ; 0.97)	0.01	608	13.0	3.4	694	14.9	3.9
CV death	0.78 (0.66 ; 0.93)	0.007	219	4.7	1.2	278	6.0	1.6
Non-fatal MI	0.88 (0.75 ; 1.03)	0.11	281	6.0	1.6	317	6.8	1.8
Non-fatal stroke	0.89 (0.72 ; 1.11)	0.30	159	3.4	0.9	177	3.8	1.0



Hazard ratios and *p*-values were estimated using a Cox proportional-hazards model with treatment as a covariate
%, percentage of group; CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; N, number of patients; R, incidence rate per 100 patient-years of observation
Marso SP et al. *N Engl J Med* 2016;375:311–322

Primary outcome: Subgroup analyses (2/2)

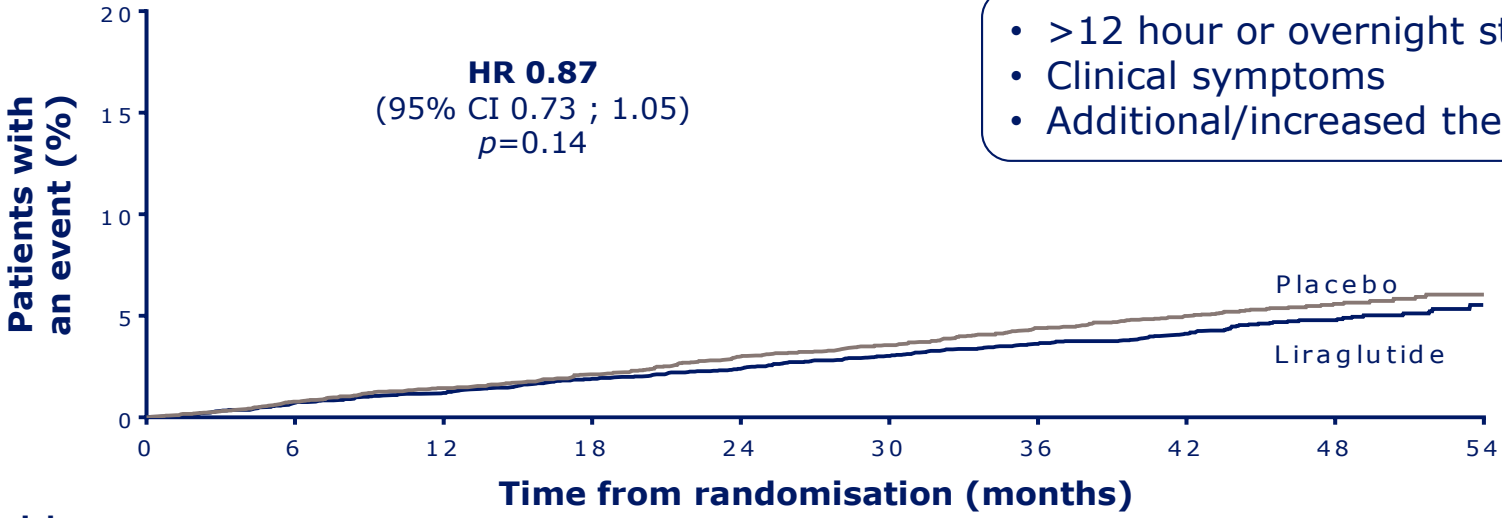
Subgroup	Hazard ratio (95% CI)	*p*-value for interaction	No. of patients	Liraglutide no. of events/no. of patients (%)	Placebo no. of events/no. of patients (%)
Primary analysis	**0.87 (0.78 ; 0.97)**		**9340**		
HbA_{1c}		0.58			
≤8.3%	0.89 (0.76 ; 1.05)		4768		
>8.3%	0.84 (0.72 ; 0.98)		4572		
Duration of diabetes		0.42			
≤11 years	0.82 (0.70 ; 0.97)		4429		
>11 years	0.90 (0.78 ; 1.04)		4892		
Risk of CVD		0.04			
Age ≥50 years and established CVD	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		
No	0.85 (0.76 ; 0.96)		8035		
Antidiabetic therapy		0.73			
1 OAD	0.75 (0.58 ; 0.98)		1818		
>1 OAD	0.95 (0.78 ; 1.16)		2997		
Insulin with OAD(s)	0.89 (0.74 ; 1.06)		3422		
Insulin without OAD	0.86 (0.63 ; 1.17)		737		
None	0.73 (0.42 ; 1.25)		366		
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)



The percentages of patients with a first primary outcome between the randomisation date and the date of last follow-up are shown. Race or ethnic group was self-reported. CI, confidence interval; CVD, cardiovascular disease; HbA_{1c}, glycosylated haemoglobin; OAD, oral antidiabetic drug

Marso SP et al. *N Engl J Med* 2016;375:311–322

Hospitalisation for heart failure



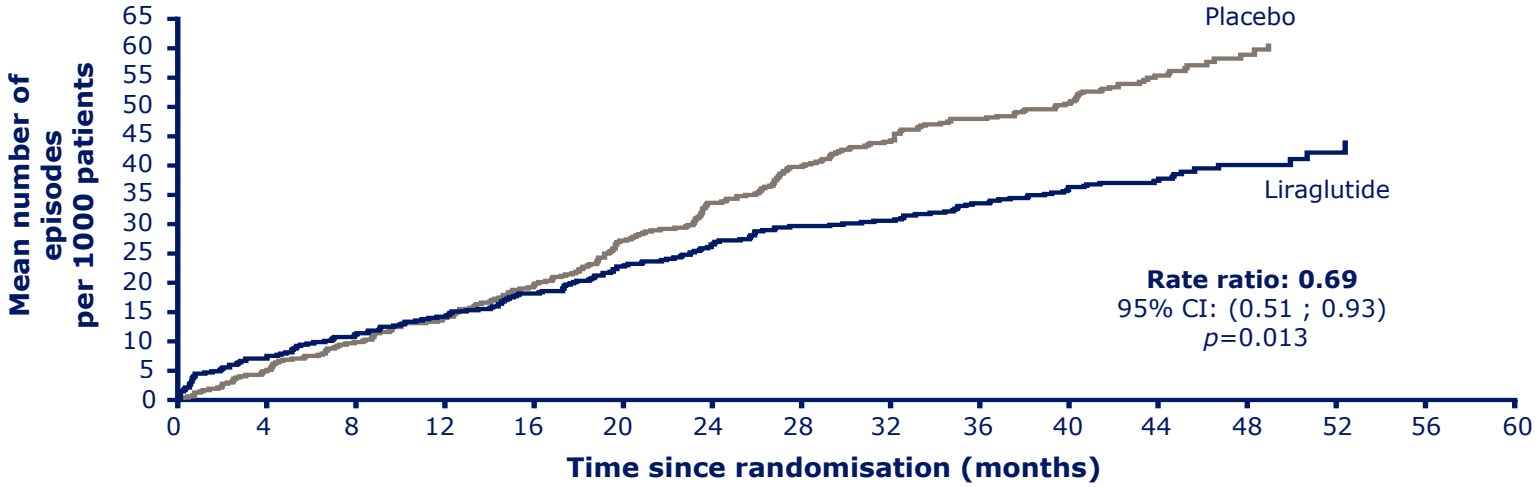
- >12 hour or overnight stay
- Clinical symptoms
- Additional/increased therapy

No. at risk

Liraglutide	4668	4612	4550	4483	4414	4337	4258	4185	1662	467
Placebo	4672	4612	4540	4464	4372	4288	4187	4107	1647	442

The cumulative incidences were estimated using the Kaplan–Meier method, and the hazard ratios using 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
Marso SP et al. *N Engl J Med* 2016;375:311–322

Severe hypoglycaemia over time

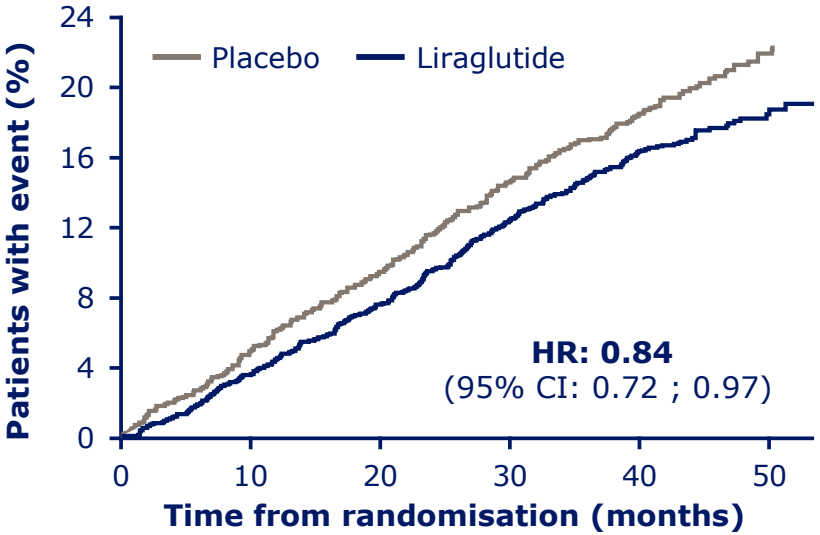


	Liraglutide	Placebo
Number of patients with severe hypoglycaemia (%)	114 (2.4)	153 (3.4)

Full analysis set. Mean number of severe hypoglycaemic episodes. Number of events analysed using a negative binomial regression model using a log link and the logarithm of the observation time (100 years) as offset. Treatment, sex, region and antidiabetic therapy at baseline included as fixed effects and age at baseline included as covariates
CI, confidence interval
Pratley R, presented at the American Diabetes Association 77th Scientific Sessions, Session 1-AC-SY13. 11 June 2017, San Diego, CA, USA

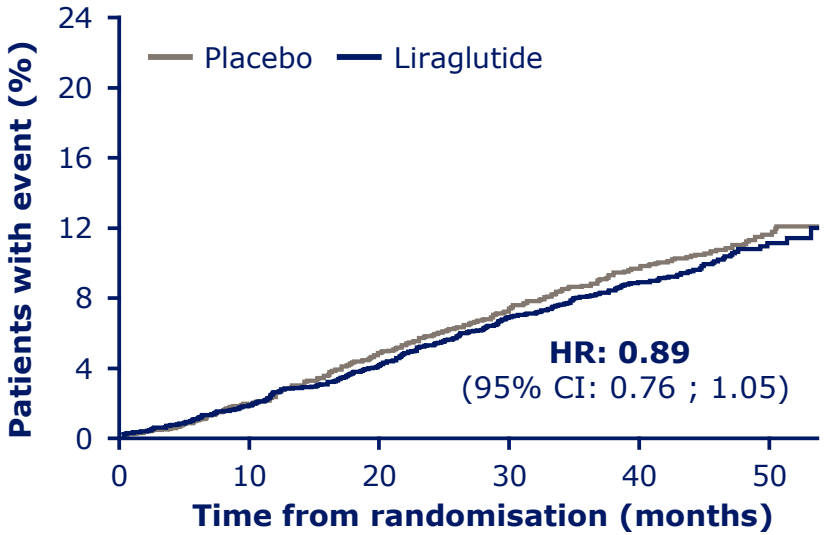
Primary outcome stratified by prior MI or stroke

Patients with prior MI/stroke



Patients at risk						
Liraglutide	1865	1791	1709	1603	1519	363
Placebo	1827	1733	1645	1545	1459	359

Patients without prior MI/stroke



Patients at risk						
Liraglutide	2803	2740	2662	2569	2487	588
Placebo	2845	2781	2674	2578	2486	551

CI, confidence interval; HR, hazard ratio; MI, myocardial infarction

Poulter N et al. Abstract 86477, presented at the European Society of Cardiology Congress, Barcelona, 28 August 2017

Guideline: GLP-1RA as 1st or 2nd line option for glycemic control

2018 ADA Guideline[1]

A1C is less than 9%, **consider Monotherapy.**

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy — Lifestyle Management + Metformin

Initiate metformin therapy if no contraindications* (See Table 8.1)

A1C at target after 3 months of monotherapy?

Yes: - Monitor A1C every 3–6 months

No: - Assess medication-taking behavior
- Consider Dual Therapy

Dual Therapy — Lifestyle Management + Metformin + Additional Agent

ASCVD?

Yes: - Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with * on p. S75 and **Table 8.1**) GLP-1RA, SGLT2i

No: - Add second agent after consideration of drug-specific effects and patient factors (See Table 8.1)

AACE/ACE Glycemic Control Algorithm

INDIVIDUALIZE GOALS

A1C ≤ 6.5% For patients without concurrent serious illness and at low hypoglycemic risk

A1C > 6.5% For patients with co illness and at risk fo

LIFESTYLE THERAPY (Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

Entry A1C ≥ 7.5%

Entry A

MONOTHERAPY*

- ✓ Metformin
- ✓ GLP-1RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ⚠ TZD
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to Dual Therapy

DUAL THERAPY*

MET or other 1st-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ⚠ TZD
- ⚠ Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*

MET or other 1st-line agent + 2nd-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ⚠ TZD
- ⚠ Basal insulin
- ✓ DPP-4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to or intensify

SYM

NO

DUAL Therapy

OR

TRIPLE Therapy

ADD OR INS

Refer to Ins

LE

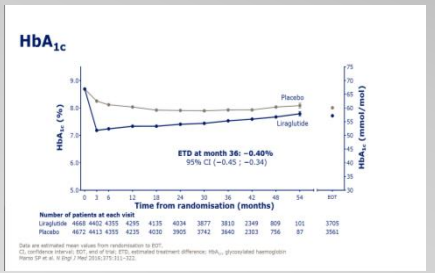
✓ Few adv possible

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength

Clinical and metabolic outcomes

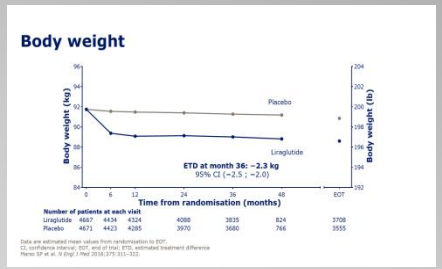
Summary of efficacy results at 3 years

HbA_{1c}



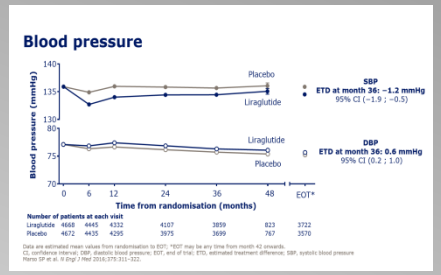
Treatment Difference
−0.4%
95% CI (−0.45 ; −0.34)
p<0.001

Body Weight



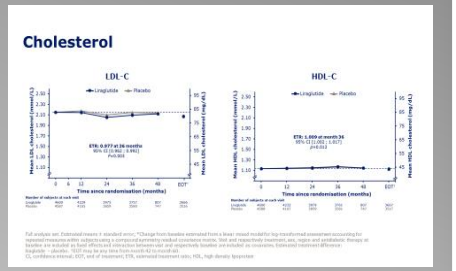
Treatment Difference
−2.3 kg
95% CI (−2.54 ; −1.99)
p<0.001

SBP



Treatment Difference
−1.2 mmHg
95% CI (−1.9 ; −0.5)
p<0.001

Lipids



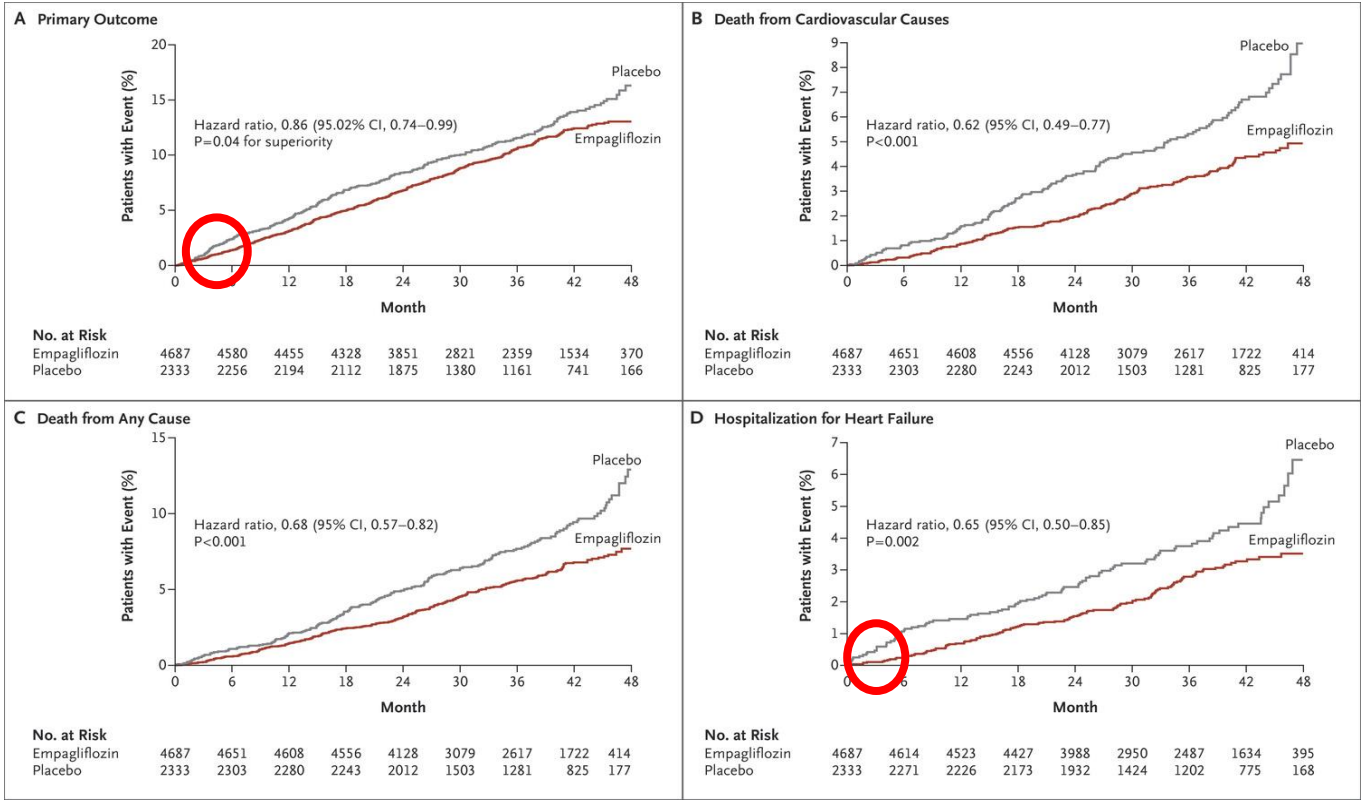
Small decreases in TC, LDL-C and TGs

Small increase in HDL-C

Mean change from baseline is to Month 36
DBP, diastolic blood pressure; ETD, estimated treatment difference; HbA_{1c}, glycosylated haemoglobin; HDL-C, low-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides; TC, total cholesterol
Marso SP et al. *N Engl J Med* 2016;375:311–322; Presented at American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. 13 June 2016, New Orleans, LA, USA

Clinical Outcomes with Empagliflozin

EMPA-REG OUTCOME Pooled Analysis (N=7020)



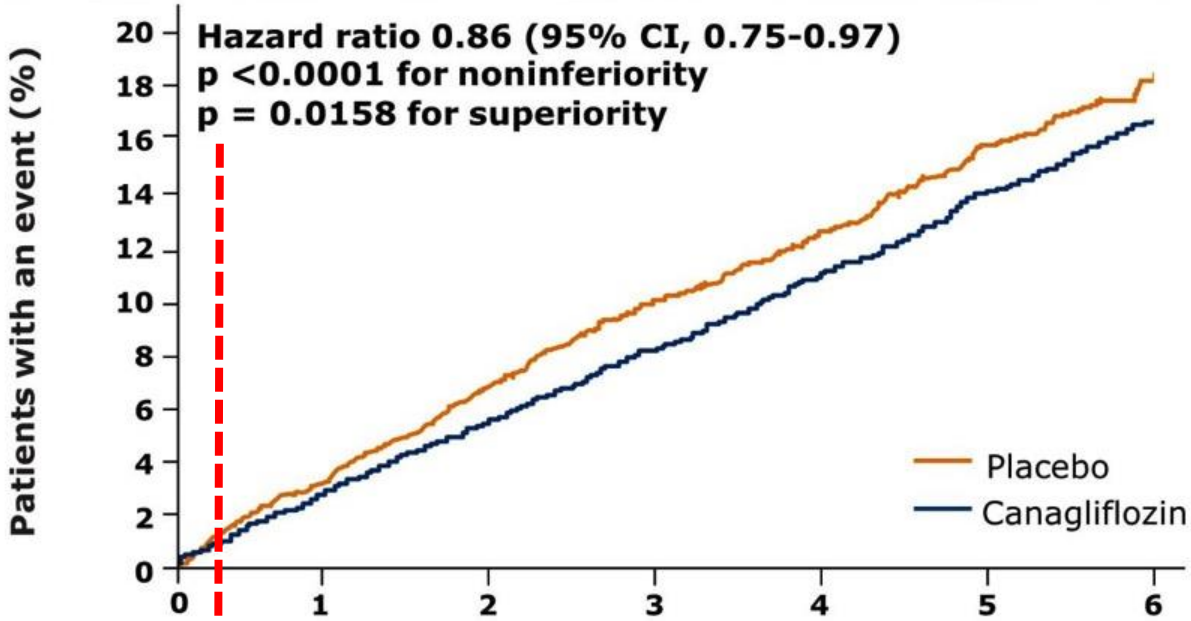
*CV death, nonfatal MI (excluding silent MI), or nonfatal stroke; †CV death, nonfatal MI (excluding silent MI), nonfatal stroke, and hospitalization for unstable angina.

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

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

Primary MACE Outcome

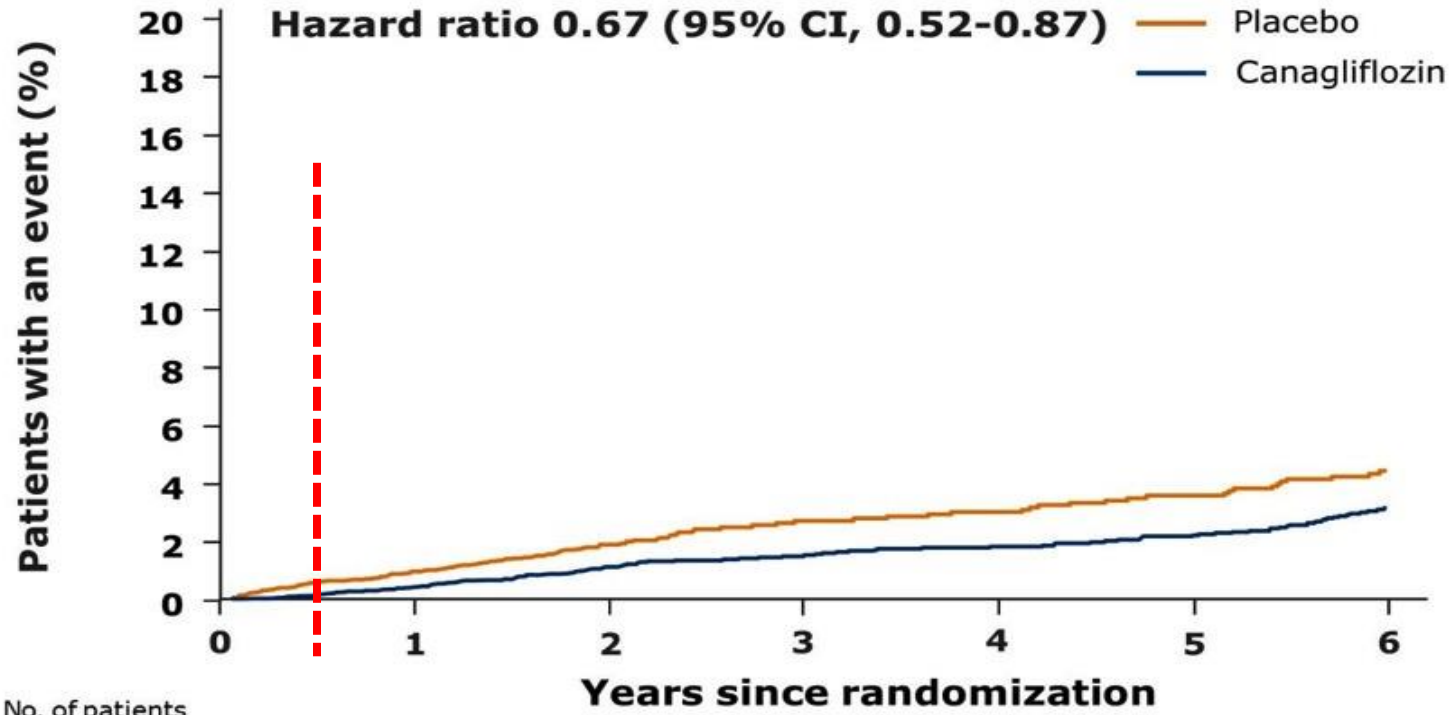
CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke



No. of patients							
Placebo	4347	4153	2942	1240	1187	1120	789
Canagliflozin	5795	5566	4343	2555	2460	2363	1661

Intent-to-treat analysis

Hospitalization for Heart Failure



No. of patients

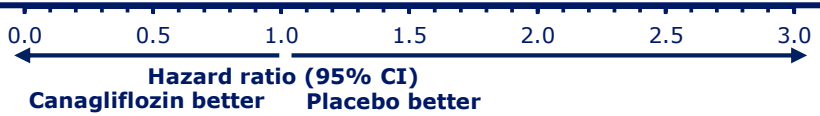
Placebo	4347	4198	3011	1274	1236	1180	829
Canagliflozin	5795	5653	4437	2643	2572	2498	1782

Intent-to-treat analysis

SGLT-2i CVOT: CANVAS/CANVAS-R

Effects of canagliflozin on CV, hospitalisation and death events

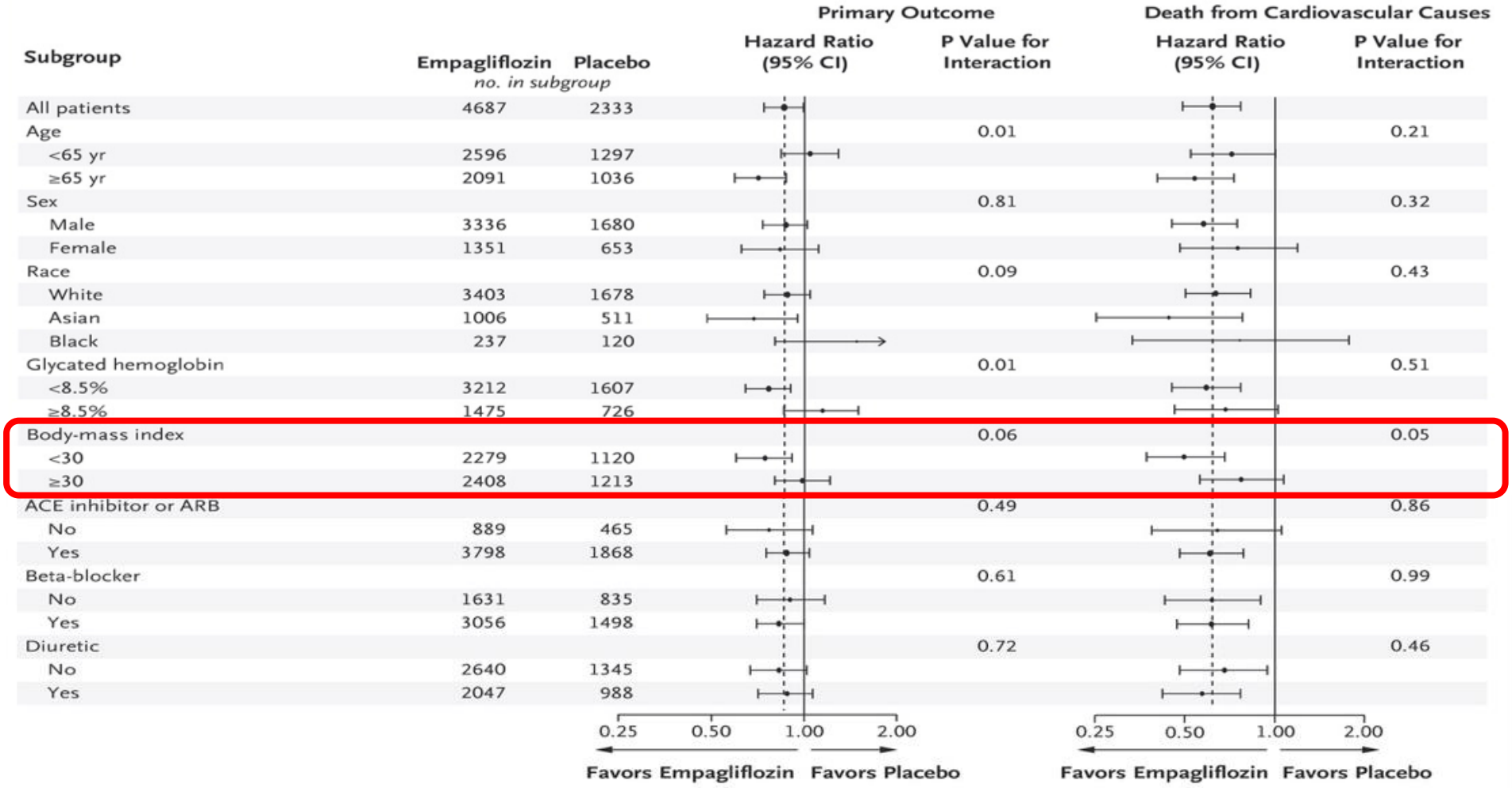
Outcome	No. of participants per 1000 PY: Canagliflozin (N=5795)	No. of participants per 1000 PY: Placebo (N=4347)	HR (95% CI)
CV death, non-fatal MI or non-fatal stroke	26.9	31.5	0.86 (0.75 ; 0.97)
CV death	11.6	12.8	0.87 (0.72 ; 1.06)
Non-fatal MI	9.7	11.6	0.85 (0.69 ; 1.05)
Non-fatal stroke	7.1	8.4	0.90 (0.71 ; 1.15)
Hospitalisation for HF	5.5	8.7	0.67 (0.52 ; 0.87)
Amputations	6.3	3.4	1.97 (1.41 ; 2.75)



- HR and 95% CI were estimated using Cox regression models with stratification according to trial and history of CVD for all canagliflozin groups combined versus placebo. CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; PY, person-years; SGLT-2i, sodium-glucose cotransporter-2 inhibitor
- Neal B et al. *N Engl J Med* 2017; doi: 10.1056/NEJMoa1611925

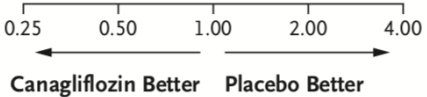
EMPA-REG OUTCOME Pooled Analysis (N=7020)

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



Effects of Canagliflozin on Primary CV Outcome in Subgroups

Subgroup	Canagliflozin	Placebo	Hazard Ratio (95% CI)	P Value
	no. of participants per 1000 patient-yr			
All patients	26.9	31.5	0.86 (0.75–0.97)	
Study				0.60
CANVAS	26.9	30.4	0.88 (0.75–1.03)	
CANVAS-R	27.1	33.0	0.82 (0.66–1.01)	
Age				0.26
<65 yr	22.0	23.6	0.91 (0.76–1.10)	
≥65 yr	33.8	42.3	0.80 (0.67–0.95)	
Sex				0.80
Male	29.8	35.1	0.86 (0.74–1.00)	
Female	21.7	25.0	0.84 (0.66–1.06)	
Race				0.40
White	29.1	34.2	0.84 (0.73–0.96)	
Black	18.6	37.0	0.45 (0.19–1.03)	
Asian	18.8	18.4	1.08 (0.72–1.64)	
Other	25.3	24.5	1.01 (0.57–1.80)	
BMI				0.29
<30	25.6	27.8	0.97 (0.79–1.20)	
≥30	27.8	34.0	0.79 (0.67–0.93)	
Glycated hemoglobin				0.29
<8%	24.7	26.9	0.94 (0.77–1.15)	
≥8%	28.8	35.3	0.80 (0.68–0.94)	
eGFR				0.20
30 to <60 ml/min/1.73 m^2	36.4	49.3	0.70 (0.55–0.90)	
60 to <90 ml/min/1.73 m^2	26.8	29.0	0.95 (0.80–1.13)	
≥90 ml/min/1.73 m^2	20.8	23.6	0.84 (0.62–1.12)	
RAAS inhibitor use				0.38
Yes	27.6	31.4	0.88 (0.76–1.01)	
No	24.4	31.8	0.77 (0.58–1.03)	
Beta-blocker use				0.01
Yes	29.5	39.0	0.75 (0.64–0.88)	
No	24.2	23.2	1.04 (0.85–1.28)	
Diuretic use				<0.001
Yes	27.6	41.0	0.66 (0.56–0.79)	
No	26.4	24.0	1.11 (0.93–1.34)	



CANVAS. N Engl J Med 2017;377:644-57.

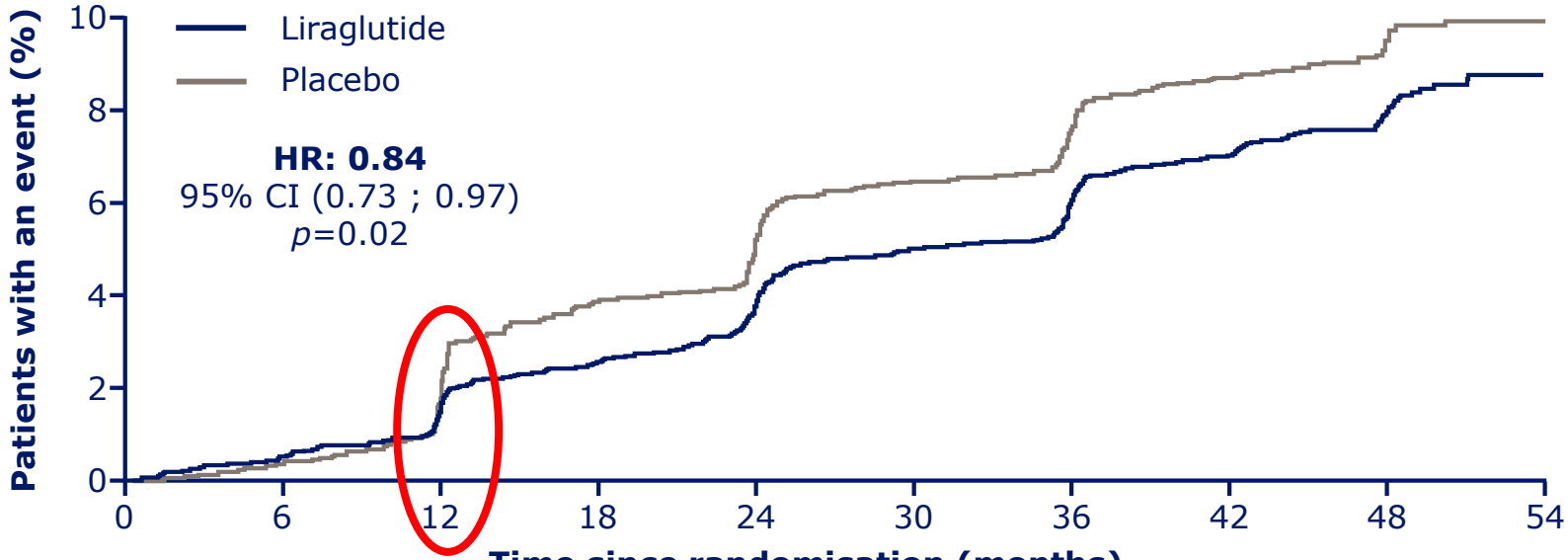
Microvascular outcomes

Microvascular event definitions

Event type		Event definition – one or more of the below
Microvascular events	**Renal**	• New onset of persistent macroalbuminuria • Persistent doubling of serum creatinine* • Need for continuous renal replacement therapy • Death due to renal disease
	Eye	• Need for retinal photocoagulation or treatment with intravitreal agents • Vitreous haemorrhage • Diabetes-related blindness

*and eGFR ≤45 mL/min/1.73 m^2 per MDRD
eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease
Marso SP et al. *N Engl J Med* 2016;375:311–322

Time to first microvascular outcome



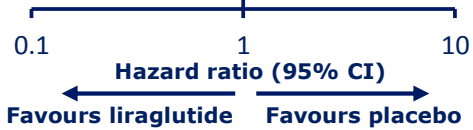
No. at risk										
Liraglutide	4668	4618	4530	4446	4344	4234	4137	4038	1603	444
Placebo	4672	4631	4504	4373	4260	4134	4030	3921	1589	422

Cumulative incidences estimated using the Kaplan–Meier method, and hazard ratios using the Cox proportional-hazard regression model. Data analyses are truncated at 54 months, as <10% of the patients had an observation time >54 months. CI, confidence interval, HR: hazard ratio

Marso SP et al. *N Engl J Med* 2016;375:311–322; Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA

Time to first microvascular outcomes

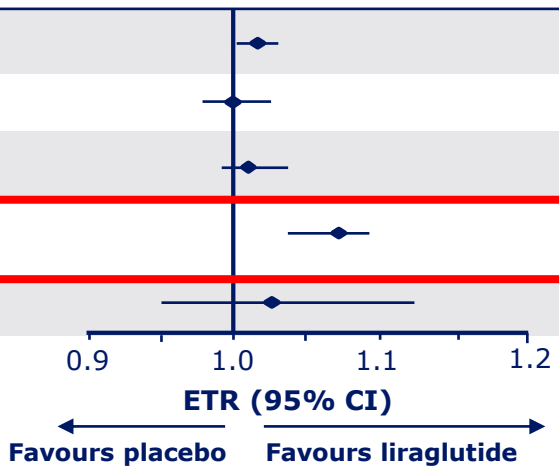
	Hazard ratio (95% CI)	Liraglutide N	Liraglutide %	Placebo N	Placebo %
Total number of patients		**4668**	**100**	**4672**	**100**
Microvascular outcome	**0.84 (0.73 ; 0.97)**	**355**	**7.6**	**416**	**8.9**
Renal outcomes	**0.78 (0.67 ; 0.92)**	**268**	**5.7**	**337**	**7.2**
New onset of persistent macroalbuminuria*	0.74 (0.60 ; 0.91)	161	3.4	215	4.6
Persistent doubling of serum creatinine†	0.89 (0.67 ; 1.19)	87	1.9	97	2.1
Need for continuous renal replacement therapy	0.87 (0.61 ; 1.24)	56	1.2	64	1.4
Death due to renal disease	1.59 (0.52 ; 4.87)	8	0.2	5	0.1
Eye outcomes	**1.15 (0.87 ; 1.52)**	**106**	**2.3**	**92**	**2.0**
Vitreous haemorrhage	1.45 (0.84 ; 2.50)	32	0.7	22	0.5
Treatment with photocoagulation or intravitreal agent	1.16 (0.87 ; 1.55)	100	2.1	86	1.8
Diabetes-related blindness	N/A	0	0	1	<0.001



Full analysis set. Cox proportional-hazards regression model adjusted for treatment. Development of diabetes-related blindness was not analysed as an individual component as only one event was observed. *New onset of persistent macroalbuminuria: urine albumin ≥300 mg/g creatinine. †Persistent doubling of serum creatinine level and eGFR ≤45 mL/min/1.73m^2 per MDRD. %: proportion of patients; CI: confidence interval; EAC: event adjudication committee; MDRD: modification of diet in renal disease; N: number of patients; N/A: not applicable

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

eGFR: Ratio to baseline at 3 years, stratified according to baseline eGFR



	No. of patients*	ETR (95% CI)
Total	**9340**	**1.02 (1.00 ; 1.03)†**
eGFR ≥90	3275	1.00 (0.98 ; 1.02)
eGFR 60–89	3907	1.01 (0.99 ; 1.03)
eGFR 30–59	1934	1.07 (1.04 ; 1.10)†
eGFR <30	224	1.03 (0.95 ; 1.12)

*Full analysis set; †Statistically significant, $p<0.001$
CI, confidence interval; eGFR, estimated glomerular filtration rate; ETR, estimated trial-group ratio; MDRD, modification of diet in renal disease
Mann JFE et al. *N Engl J Med* 2017;377:839–848.

Overall LEADER summary

Liraglutide significantly reduced the risk of:

1° CV endpoint	CV death	All-cause death	Severe hypoglycaemia	Microvascular event	Renal event
↓ 13%	↓ 22%	↓ 15%	↓ 31%	↓ 16%	↓ 22%
p=0.01	*p*=0.04	*p*=0.02	*p*=0.013	*p*=0.02	*p*=0.003

CV events

- All 3 components of MACE contributed to the risk reduction of the primary outcome
- No increased risk of HHF
- Risk reduction was independent of:
  - Baseline insulin or CV medication use
  - Insulin or SU/TZD introduced during the trial
  - Experiencing a severe hypoglycaemic episode

Clinical and metabolic outcomes

- Significant reductions in HbA_{1c}, body weight, SBP and lipids
- CV risk reduction could be partially explained by these variables

Microvascular outcomes

- Reduction in composite microvascular endpoint*
- Driven by reduced new-onset persistent macroalbuminuria

Safety outcomes

- Generally well tolerated
- Associated with GI side effects, increases in pancreatic enzymes and heart rate, in line with previous trials
- No increased risk of pancreatitis
- Increased risk of acute gallstone disease

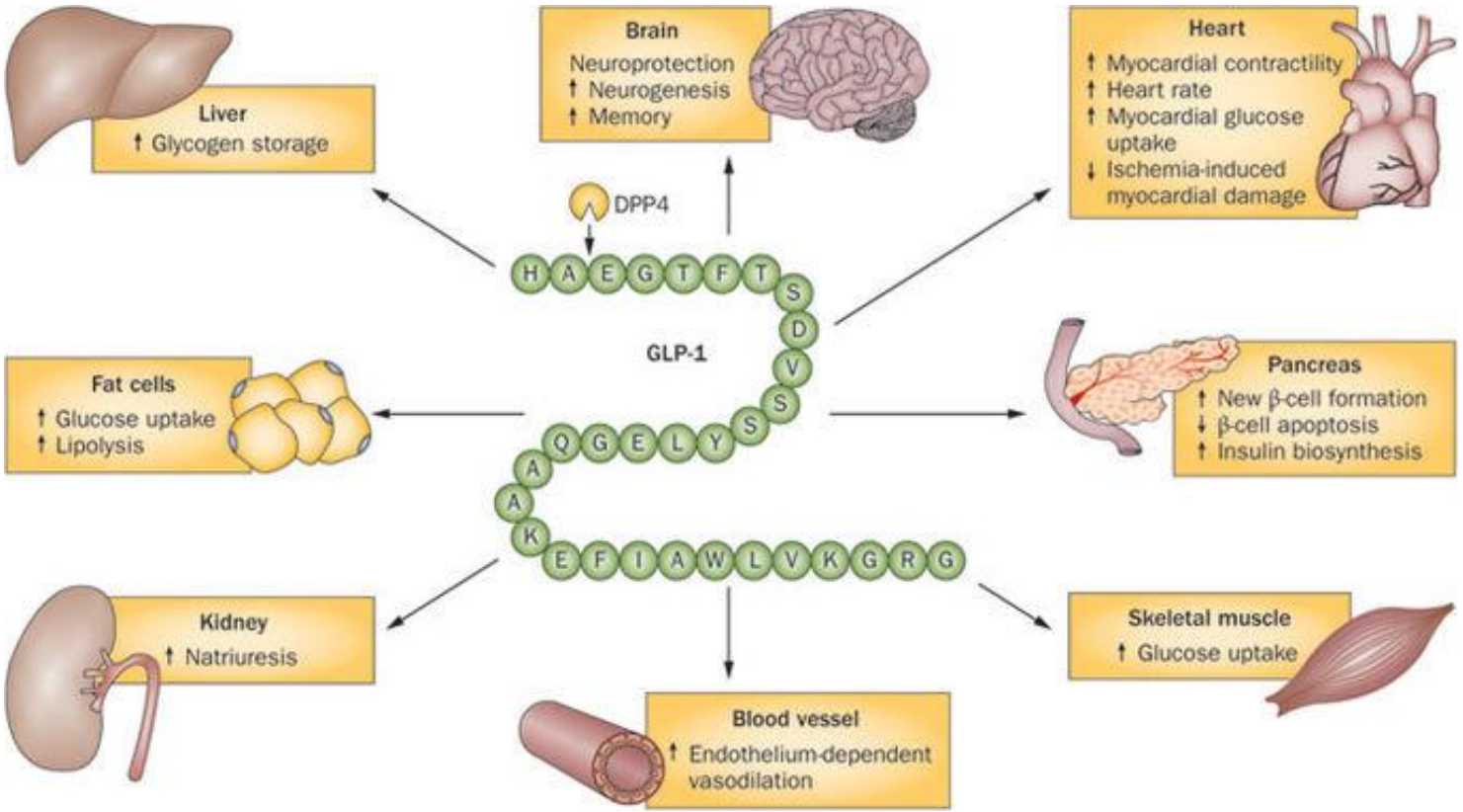
*Composite of renal and eye events

1°, primary; CV, cardiovascular; GI, gastrointestinal; HbA_{1c}, glycosylated haemoglobin; HHF, hospitalisation for heart failure; SBP, systolic blood pressure; SU, sulphonylurea; TZD, thiazolidinedione

Marso SP et al. *N Engl J Med* 2016;375:311–322

Effects on cardiovascular risk factors

Reported pleiotropic effects of GLP-1



Meier JJ. Nat Rev Endocrinol. 2012;8(12):728–42.

Liraglutide is an analog with 97% homology to human GLP-1[1,2]

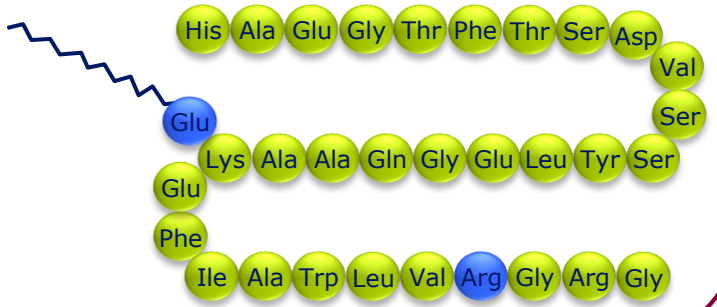
Molecular Structure

Human GLP-1[1]

Molecular Structure

Liraglutide [2]

C-16 fatty acid (Palmitic acid)



1. Knudsen LB ,et al. J Med Chem. 2000;43:1664–1669; 2. Nauck M, et al. Diabetes care.2009;32(1): 84-90.

2017ADA Guideline recognized the CV benefit of GLP-1 RA

American Diabetes Association.

GLP-1RA

Drugs	Cellular mechanism	Pharmacological Effects	Benefit
• Exenatide • Liraglutide • Semaglutide • Albiglutide • Lixisenatide • Dulaglutide	Activate GLP-1R	↑ Insulin secretion(glucose-dependent) ↓ glucagon secretion(glucose-dependent) ↓ gastric emptying ↑ Sotiety	Less hypoglycemia ↓ Body weight ↓ Postprandial glucose fluctuation ↓ CV risk ↓ MACE and mortality in CVD patients (LEADER & SUSTAIN 6)

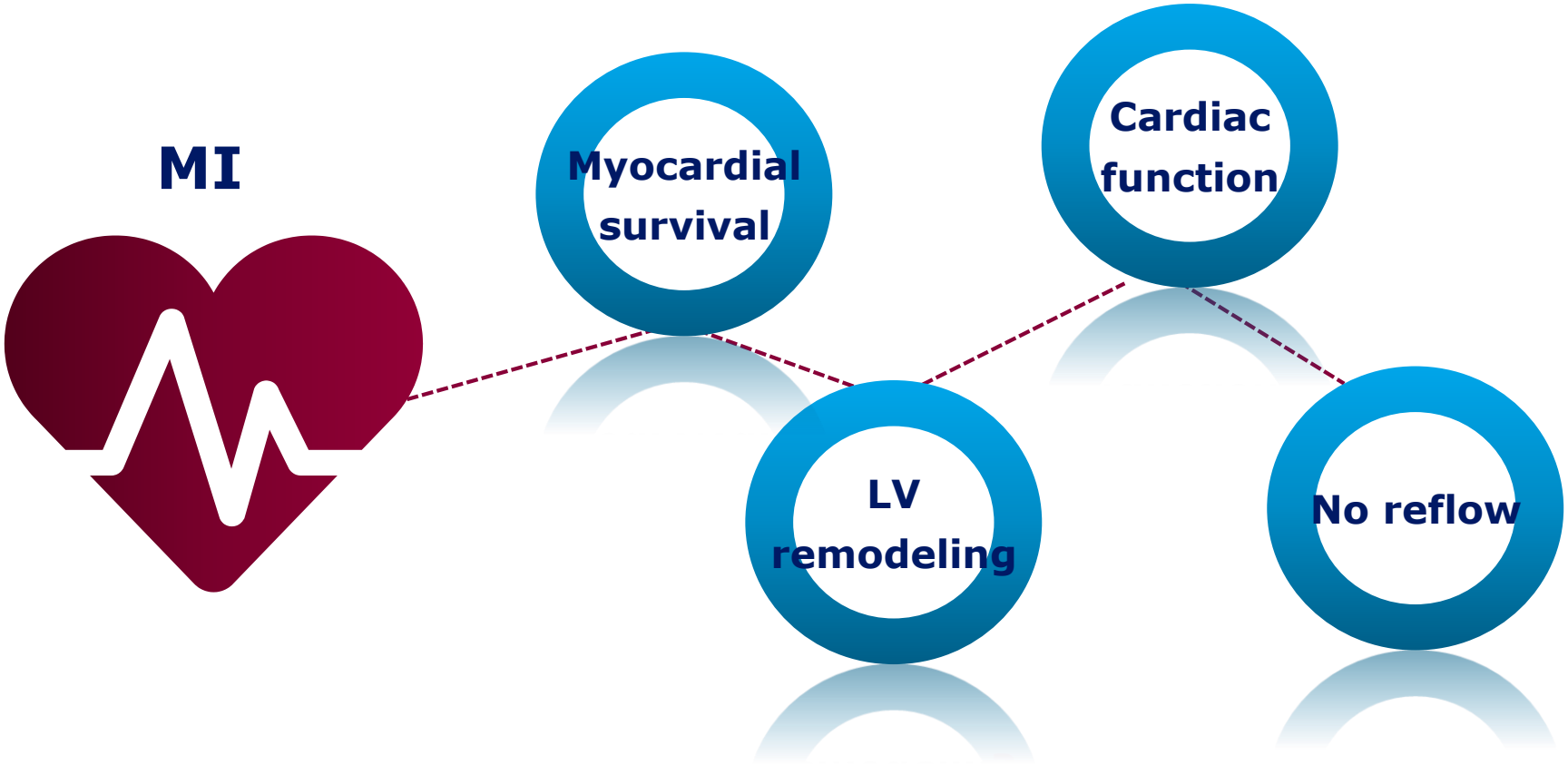
American Diabetes Association.Diabetes .Diabetes Care 2017; 40(Suppl.1): S1-S135.

Liraglutide has the latest evidence of cardiovascular benefits

	Researcher	Year	Country	Study design	Observation object	Measurement indicator
MI	Chen W R, et al.	2016	China	Single-center, randomized, double-blind, placebo-controlled study	Patient with STEMI	Myocardial survival index
	Nozue T,et al.	2016	Japan	Clinical trial	T2DM with AMI	Left ventricular remodeling
	Sassoon D J, et al.	2017	US	Basic animal research	Myocardial infarction in a obese Pig Model	Cardiac function
	Chen W R, et al.	2015	China	Single-center, randomized, double-blind, placebo-controlled study	Patient with STEMI	Left ventricular function
	Chen W R, et al.	2016	China	Single-center, randomized, double-blind, placebo-controlled	Patient with NSTEMI	Left ventricular function
HF	Zhang J Y,et al.	2017	China	Single-center, prospective, interventional study	Patient with HF	Cardiac function
	Arturi F,et al.	2017	Italy	Single-center, open, randomized, active drug control, parallel intervention study	T2DM patient with chronic HF	Cardiac function
	Scholten B J, et al.	2017	Denmark	Randomized, double-blind, placebo-controlled crossover study	T2DM patient with albuminuria	Heart failure risk markers
High CV risk	Rizzo M, et al.	2016	Italy	Prospective, real-world study	T2DM patient with metabolic syndrome	CV risk markers
	Marso SP,et al.	2016	US	Multicenter, double-blind, placebo-controlled study	T2DM patient with high CV risk	CVOT

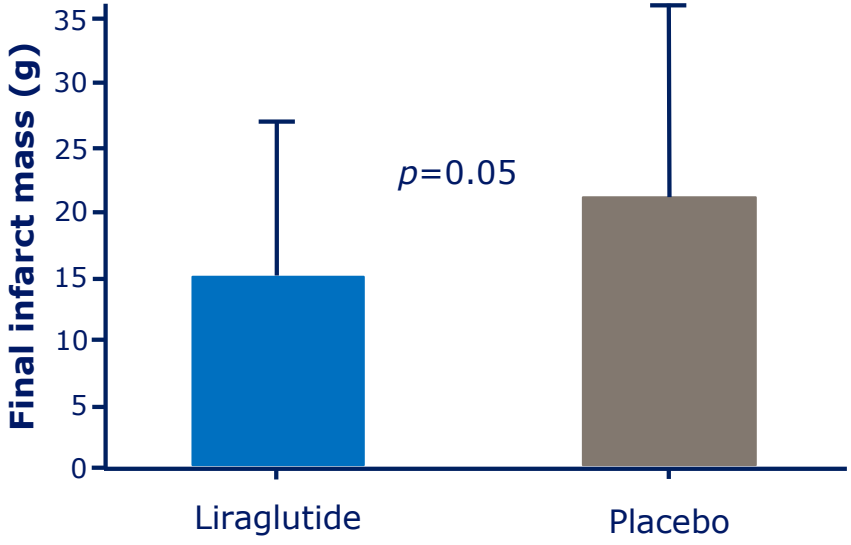
STEMI: ST-segment elevation myocardial infarction;
NSTEMI:non-ST-segment elevation myocardial infarction

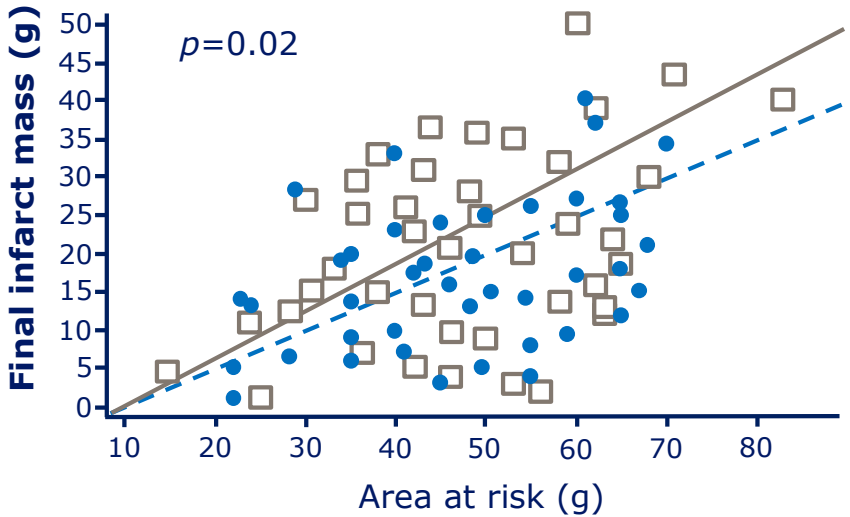
GLP-1 RA can improve myocardial infarction (MI)



Liraglutide improves infarct size (by MRI) after ST-segment-elevation MI

- China single center, radomized double blind, placebo control study, 96 **STEMI** pts, 30′ before PCI, Randomly divided into 2 groups, receiving LG (1.8mg) or Placebo, respectively for 7 days (0.6mg, 2days; 1.2mg, 2days; 1.8mg, 3days), followed up at 6 M's

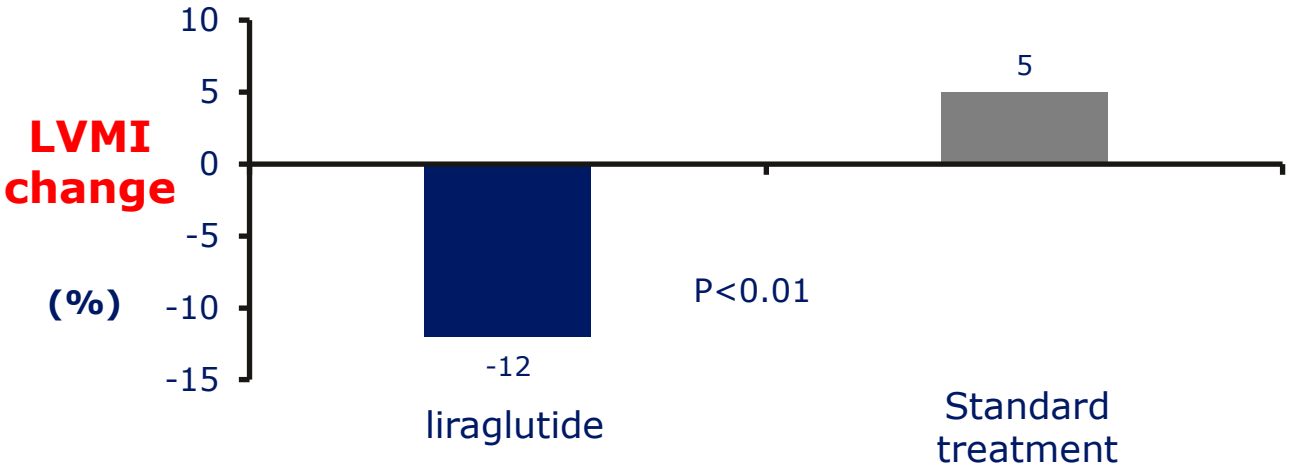




Chen WR et al. *Circ Cardiovasc Imaging* 2016;9:pii: e005146

Liraglutide (LG) decrease LVMI after PCI in T2DM pts

- Japan, 15 **T2DM** with **AMI** patients with successful PCI, divided into LG (n=6) and STD (n=9), LVMI after 6 months

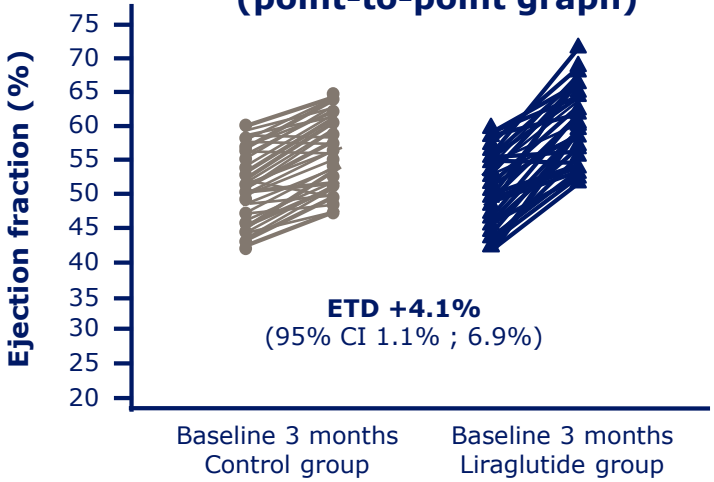


Nozue T, et al. Heart and vessels, 2016, 31(8): 1239-1246.

Greater increase in LV ejection fraction with liraglutide vs placebo in patients with STEMI undergoing primary PCI[1]

- China, A single-center, randomized, double-blind, placebo-controlled study, 92 **STEMI pts**, after PCI, receiving placebo and LG for 7 days, respectively

LV ejection fraction before and after 3 months' treatment (point-to-point graph)

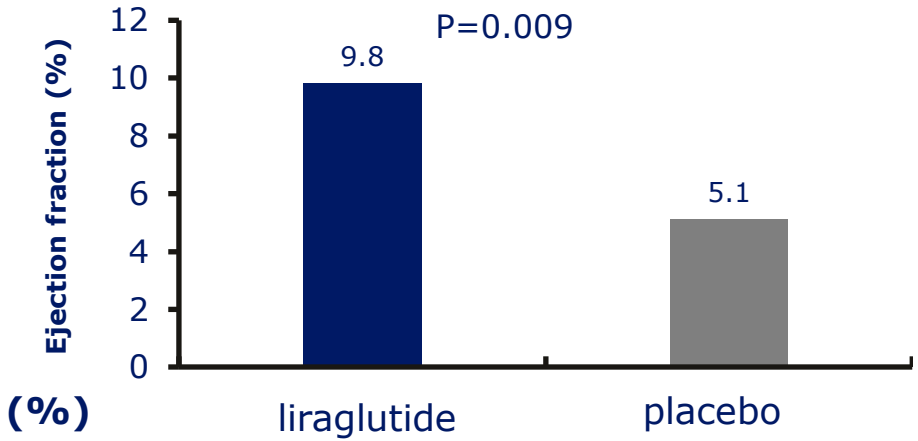


Similar results were seen in non-STEMI patients[2]
ETD 4.7% (95% CI 0.7% ; 9.2%)

Chen W R, et al. American heart journal.2015;170(5): 845-854.

Liraglutide (LG) increase LV ejection fraction in NSTEMI pts

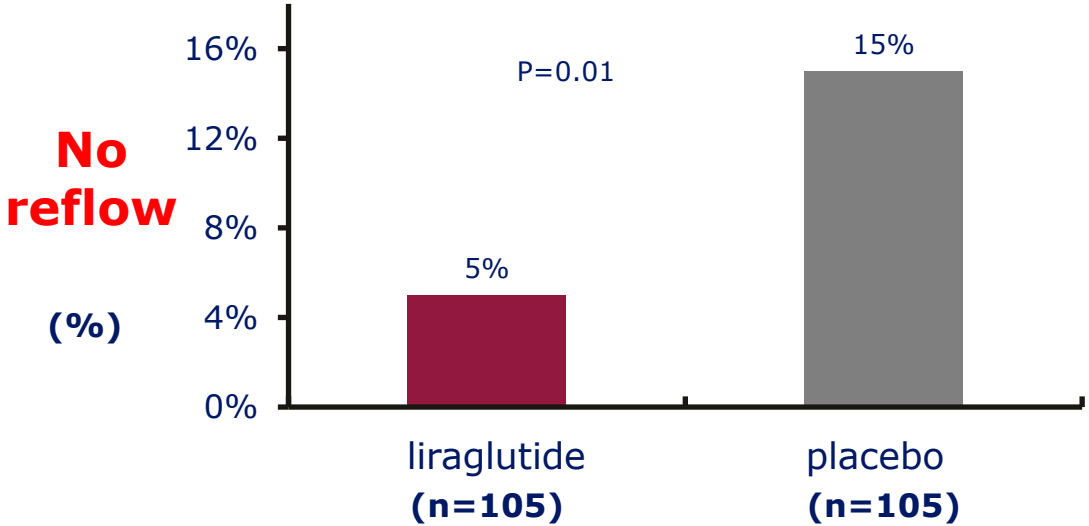
- China, A single-center, randomized, double-blind, placebo-controlled study. 90 **NSTEMI** pts, Randomly receiving LG (0.6mg,2d; 1.2mg, 2d; 1.8mg, 3d) or placebo for 7 days, followed up for 3 months



Chen W R, et al. Endocrine.2016;52(3): 516-526.

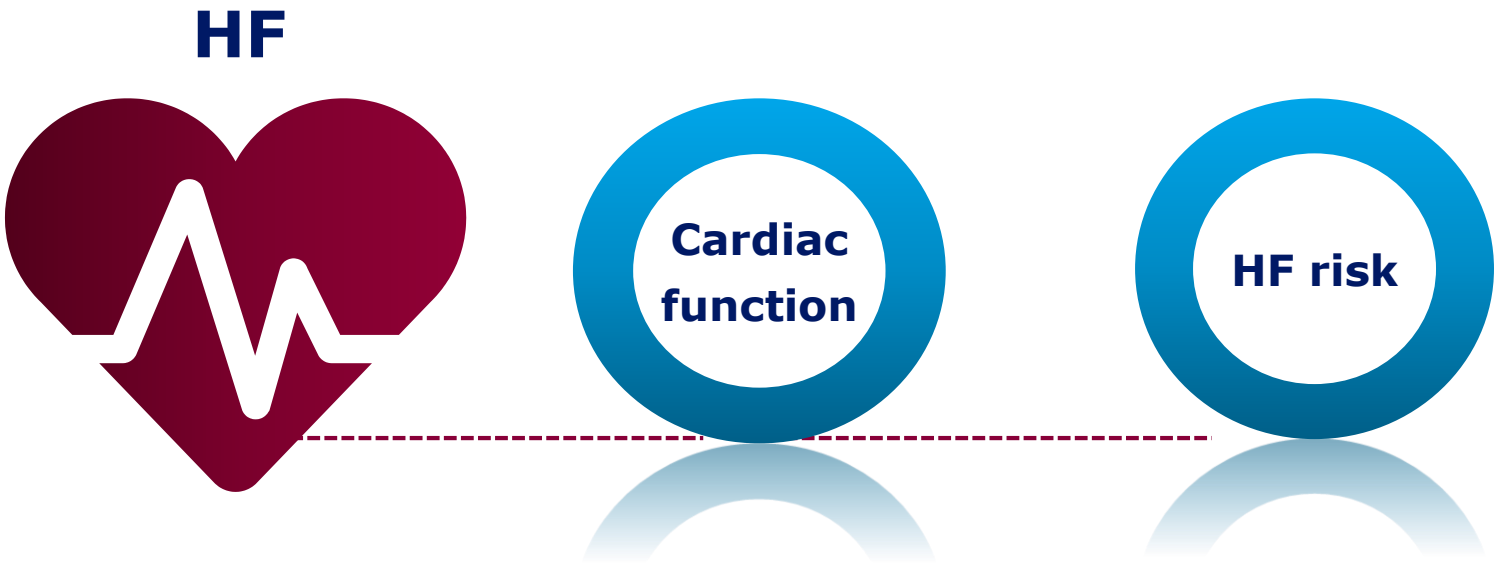
Liraglutide (LG) decreases the No-reflow after PCI in STEMI Pts

- China A single-center, prospective, interventional study, 284 **STEMI pts**, randomized divided into placebo and LG 2 groups, 30 mins before PCI, receiving placebo and 1.8mg LG, follow-up at 3 M's



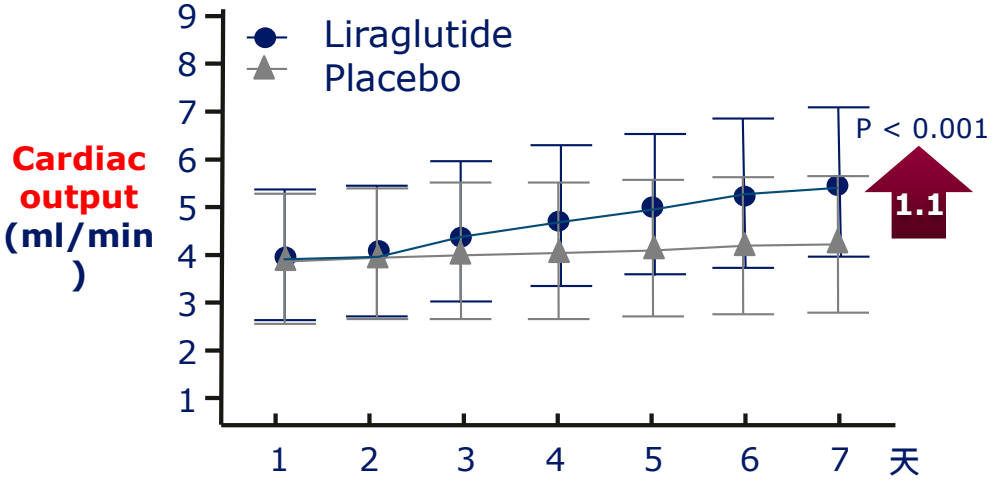
Chen W R, et al. International journal of cardiology.2016;208: 109-114.

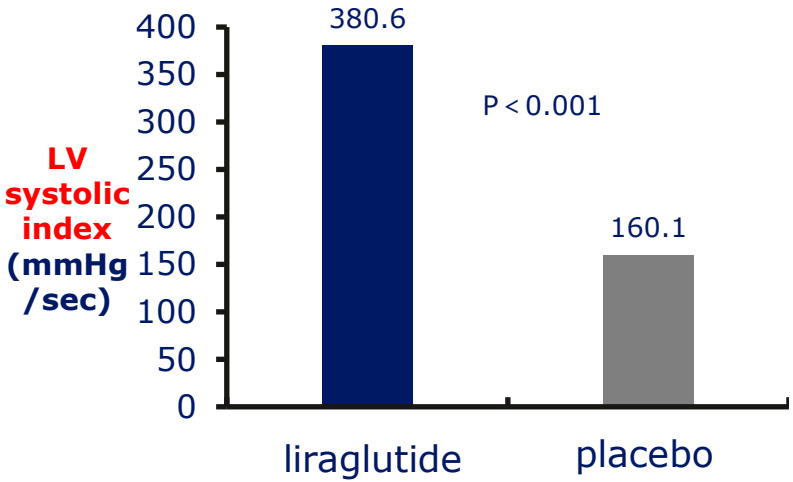
GLP-1 RA can improve the cardiac function and decrease CV risk in Heart Failure patients



GLP-1 RA increases CO and LVSI in Pts with HF

- China, A single-center, prospective, interventional study, 52 pts with **HF**, randomized to give LG or placebo for 7 days

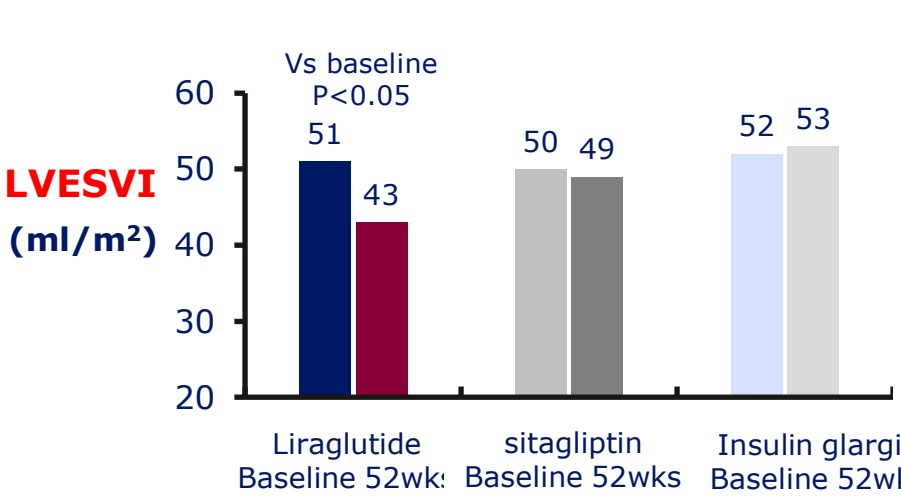


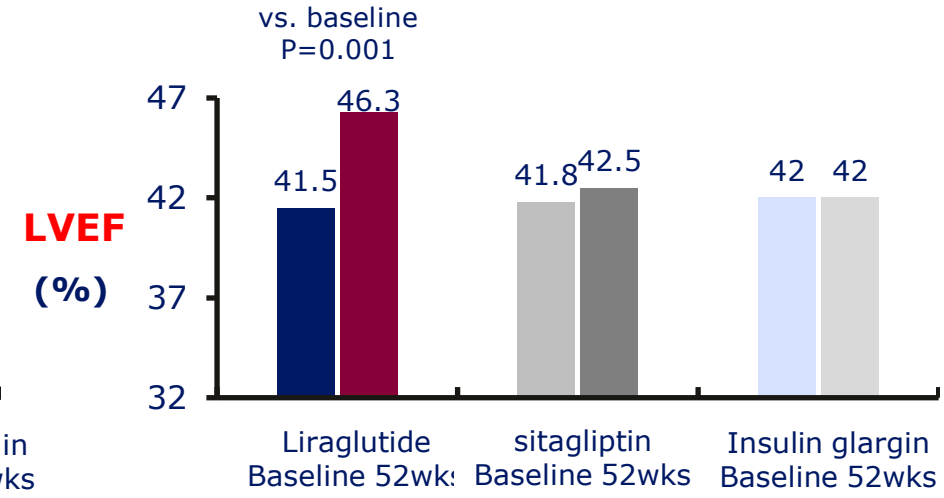


Zhang J Y,et al.Oncotarget.2017;8(37): 62693-702

GLP-1 RA can improve LV function in T2DM with chronic HF

- Italy, single center, open, random, 52 weeks, active drug control, parallel preliminary study
- 32 **Ischemic chronic HF** (FCC Ⅱ **or** Ⅲ) or **LVEF≤45%, T2DM,** randomized divided into 3 groups with LG (0.6-1.8mg), Sitagliptin and Glargine Insulin for 52 weeks

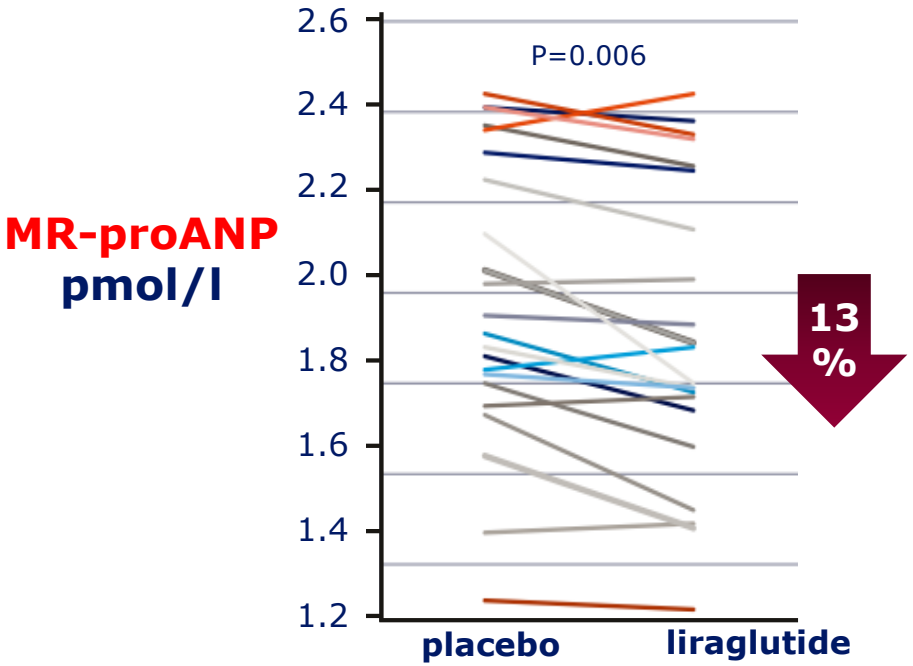




Arturi F, et al. Endocrine.2017;57(3): 464-73.

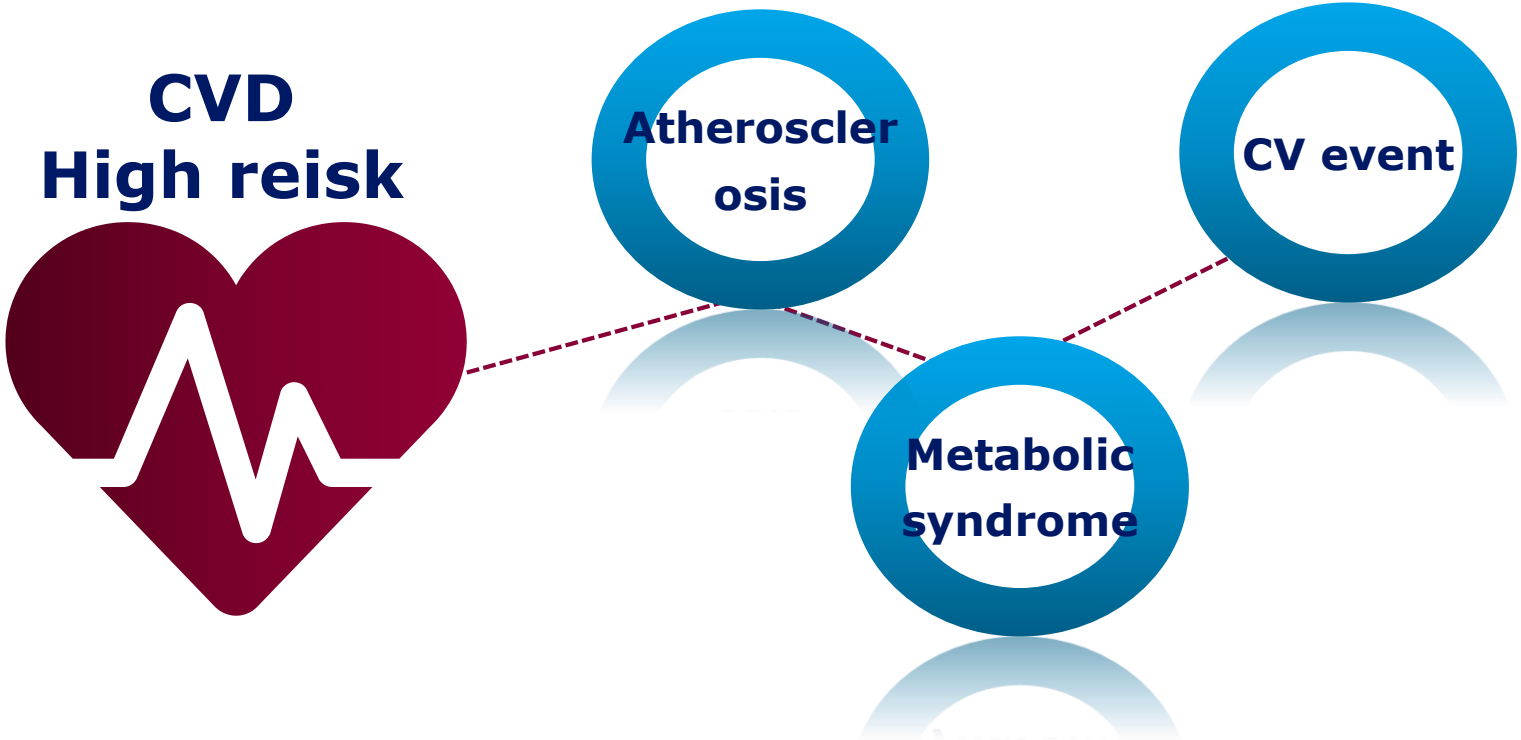
GLP-1 RA decreases HF risk in T2DM with albuminuria

- Denmark, A randomized, double-blind, placebo-controlled, crossover study, 32 **T2DM patient with albuminuria** (UACR > 30mg/g; eGFR ≥ 30ml/min/1.73m^2), randomly receiving LG (1.8 mg/day) or placebo 12weeks



Scholten B J, et al. Diabetes, Obesity and Metabolism.2017;19(6): 901-5.

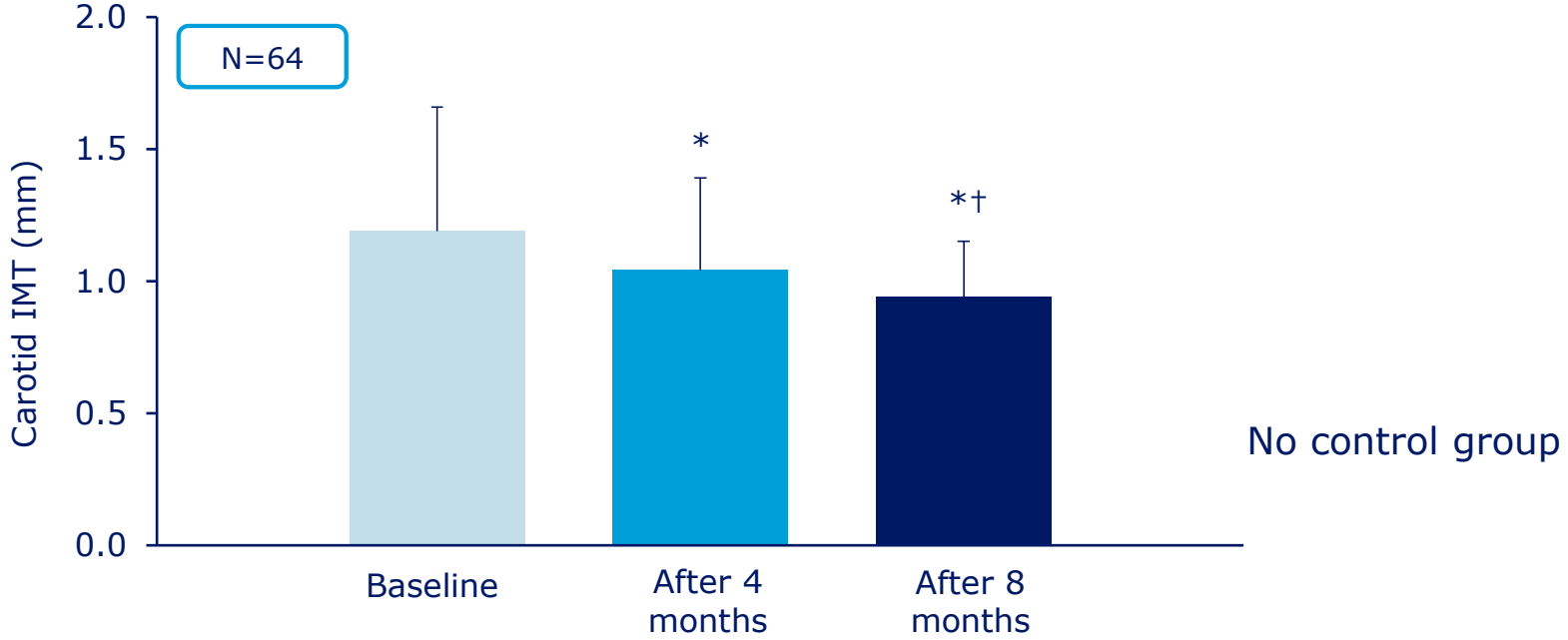
GLP-1 RA could reduce the CV event rate in the patients with high risk CVD



Liraglutide reduced carotid IMT

Effects of 8 months of liraglutide therapy in subjects with T2DM

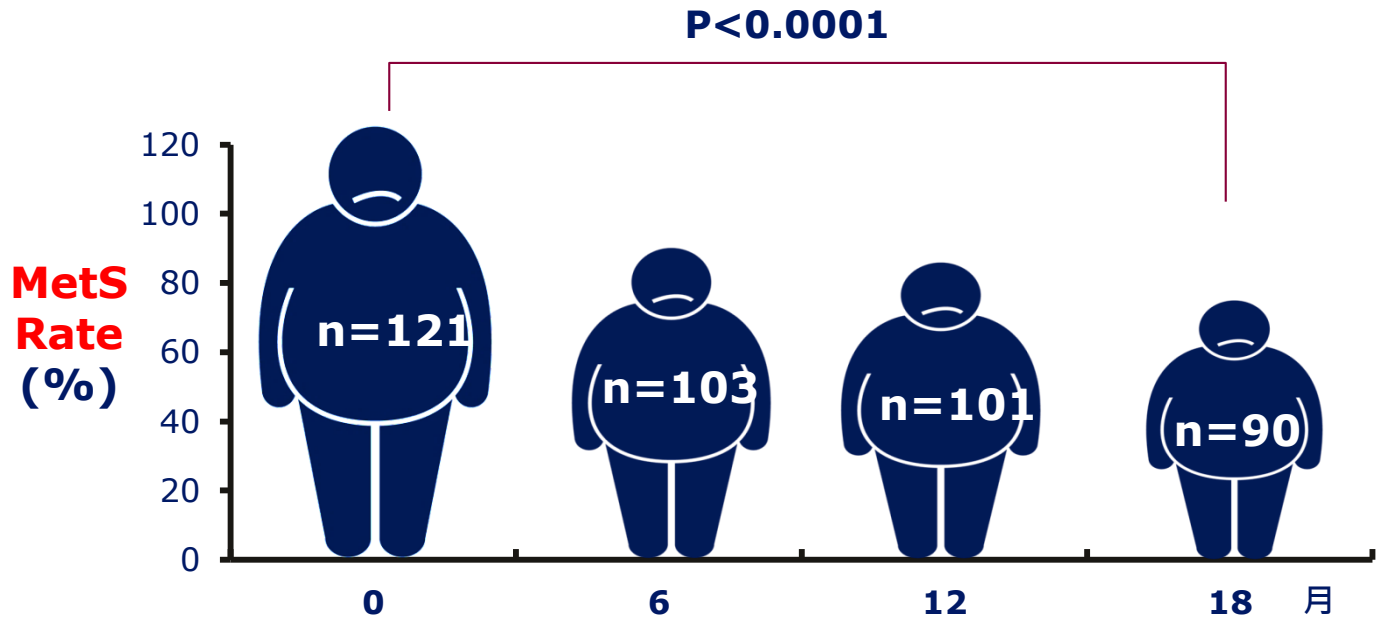
- A prospective, real-world study in Italy. 121 T2DM with MetS (71 M and 50 F; 62±9 y/o; poor controlled with metformin), treated with LG + Metformin for 8 M's



Rizzo M, et al. Cardiovascular diabetology.2016;15(1): 162.

Liraglutide reduced 26% of metabolic syndrome

- Italy a prospective, real-world study, 121 T2DM with MetS (71 M and 50 F; 62±9 y/o; poor controlled with metformin), receiving LG + Metformin for 18 M's



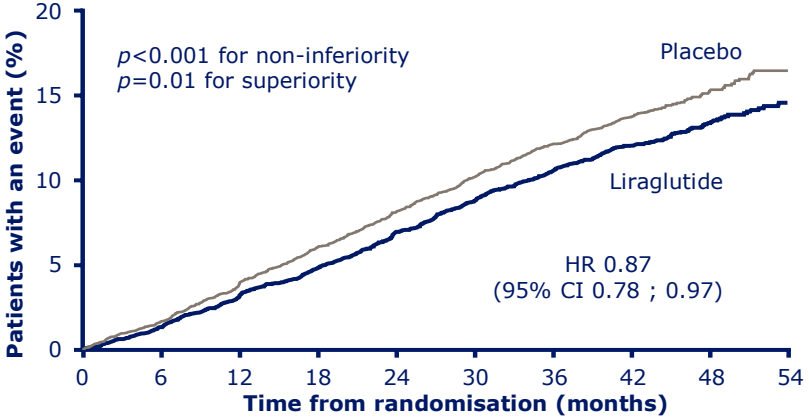
MetS: Metabolic syndrome

Rizzo M, et al. Cardiovascular diabetology.2016;15(1): 162.

CVOTs for human GLP-1 analogues

LEADER[1]

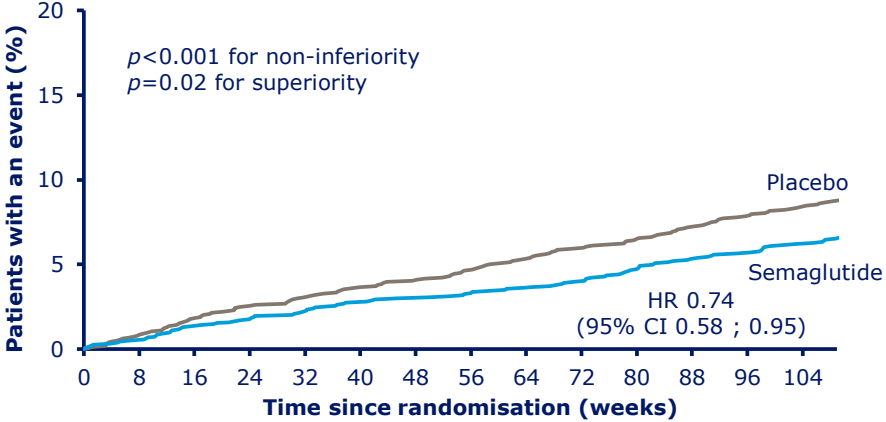
Time to first occurrence of CV death, non-fatal MI, or non-fatal stroke



LEADER is a post-approval CVOT with 1302 primary events

SUSTAIN 6[2]

Time to first occurrence of CV death, non-fatal MI, or non-fatal stroke



SUSTAIN 6 is a pre-approval CVOT with 254 primary events

CI, confidence interval; CV, cardiovascular; CVOT, cardiovascular outcomes trial; GLP-1, glucagon-like peptide-1; HR, hazard ratio; MI, myocardial infarction

1. Marso SP et al. *N Engl J Med* 2016;375:311–322; 2. Marso SP et al. *N Engl J Med* 2016;375:1834–1844

Application of GLP-1RA in CVD

MI

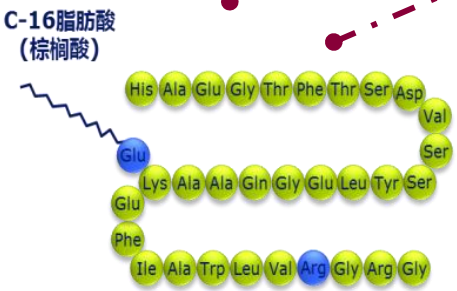
- Improve **LV function** after PCI in STEMI or NSTEMI patients
- Improve **myocardial survival** after STEMI, decrease "**No-Reflow**"
- Prevent **LV remodeling after** after PCI in patients with DM and AMI

HF

- Improve **cardiac function** in patients with T2DM and HF
- Decrease the **risk of HF**

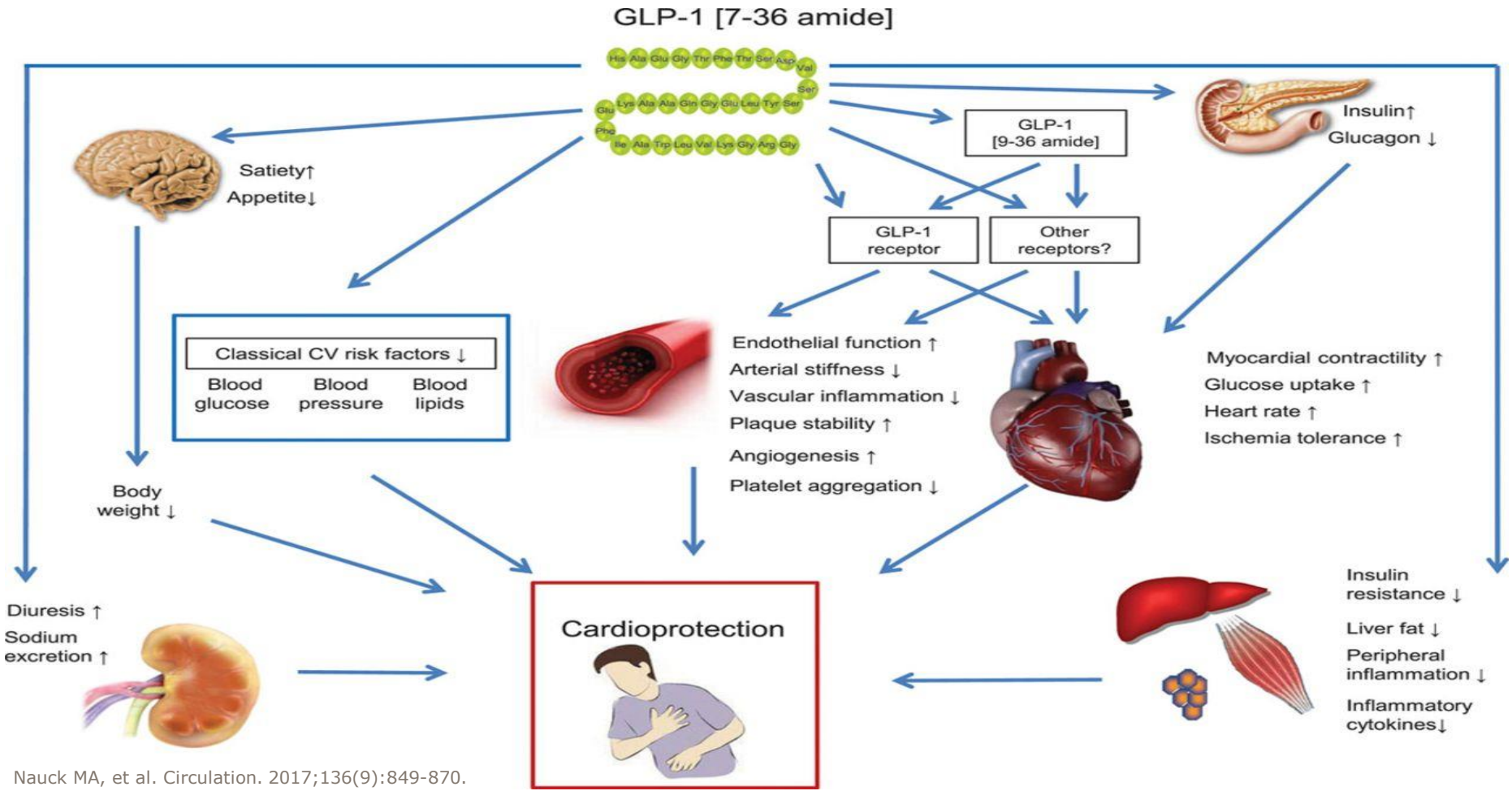
CVD High risk

- Decrease risk factors for CVD: **CIMT**, **MetS**
- Decrease **MACE** in T2DM patients



利拉鲁肽

GLP-1RA can achieve myocardial protection by regulating multiple targets



Nauck MA, et al. Circulation. 2017;136(9):849-870.

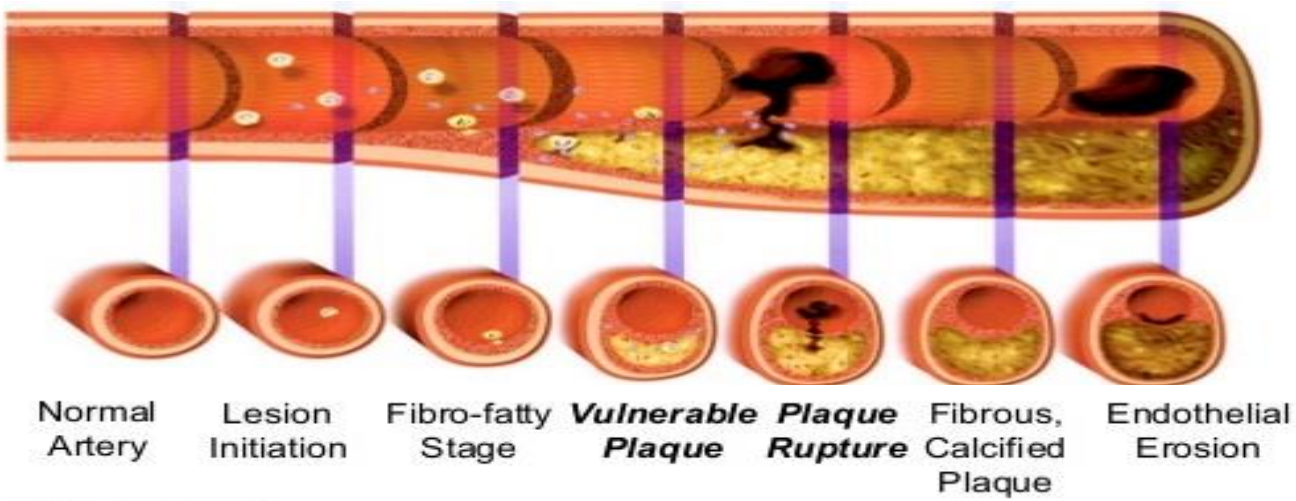
The pathological mechanism of the development of CVD before myocardial injury

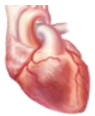
Hyperglycemia, hypertension, obesity, hyperlipidemia and other factors

Oxidative stress (ROS)

NO bioavailability ↓

endothelial dysfunction → Foam cell formation inflammatory response simulates migration and proliferation of VSMC → coagulation factor Thrombosis formation → deterioration

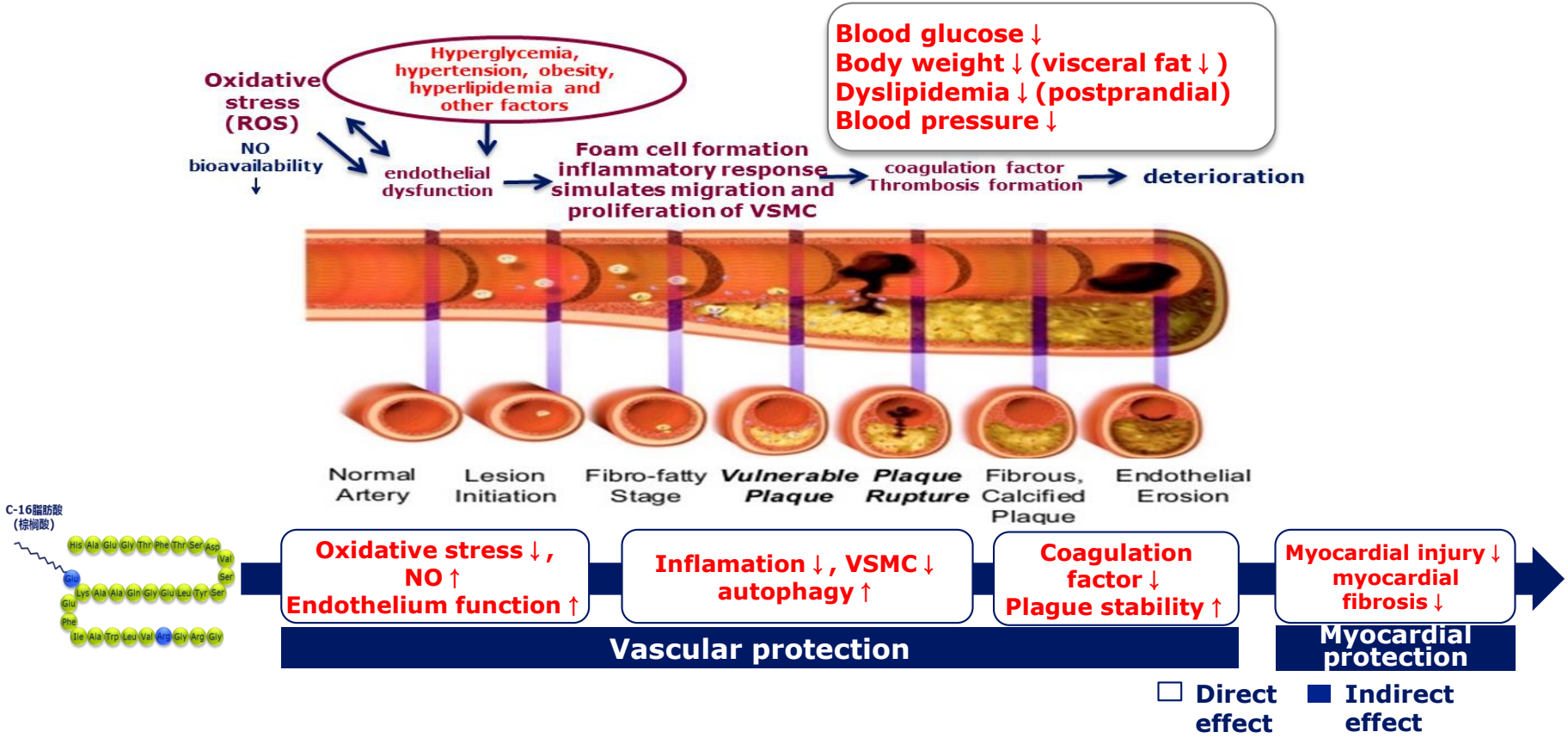




Myocardial injury / myocardial fibrosis

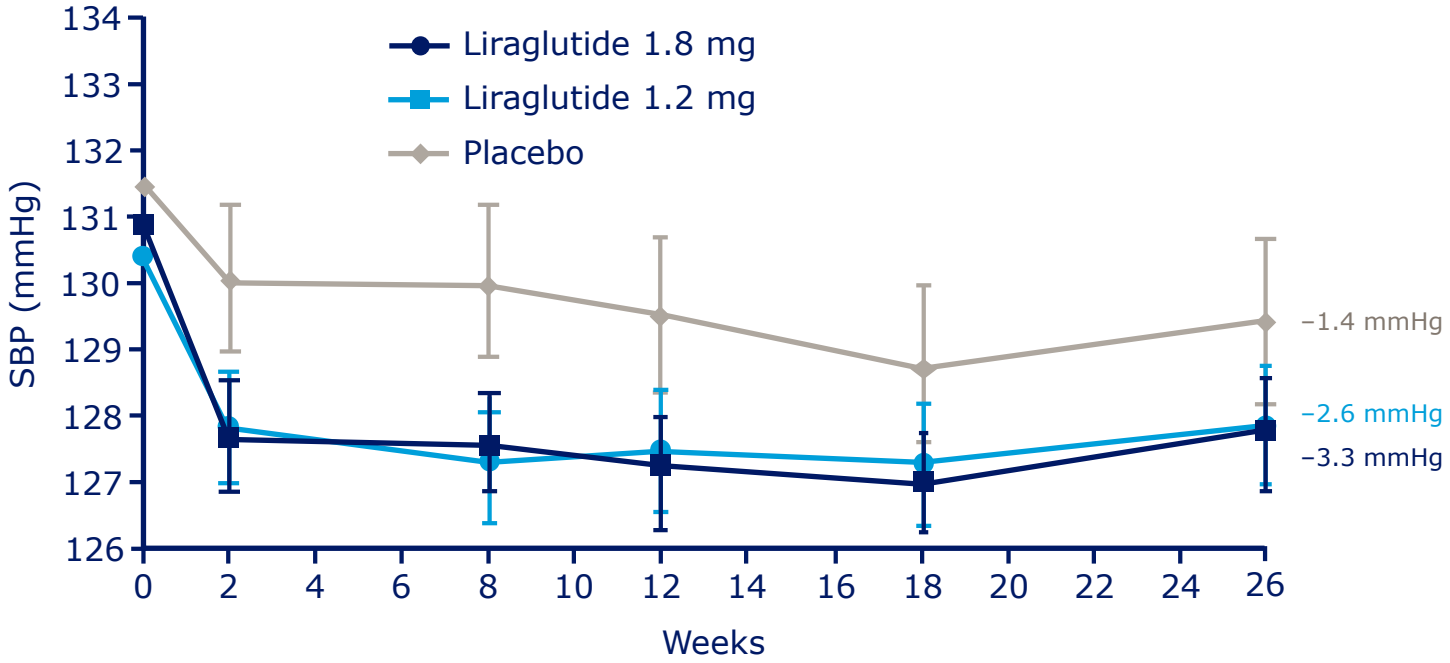
1.Libby P.Circulation.2001;104(3):365-72 2. Bauersachs J, et al. Pharmacological Reports.2008;60(1):119-26.

GLP-1RA effects on the progression of CVD



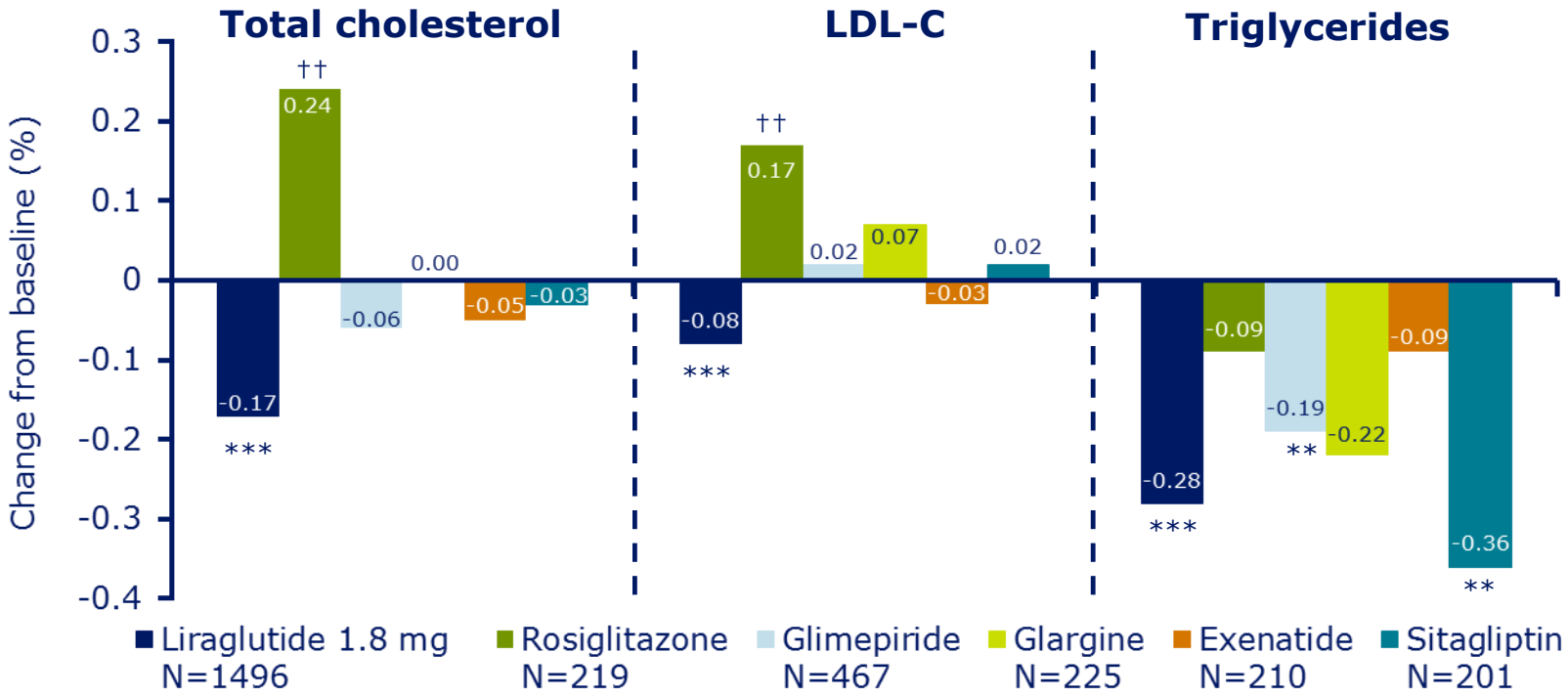
1.Libby P.Circulation.2001;104(3):365-72 . 2. Bauersachs J, et al. Pharmacological Reports.2008;60(1):119-26.
3. Hirano T, at al. Journal of diabetes investigation.2016;7(S1): 80-86. 4.Okerson T,et al.Cardiovascular therapeutics.2012;30(3):e146–e155.

Liraglutide reduced SBP in LEAD 1–6



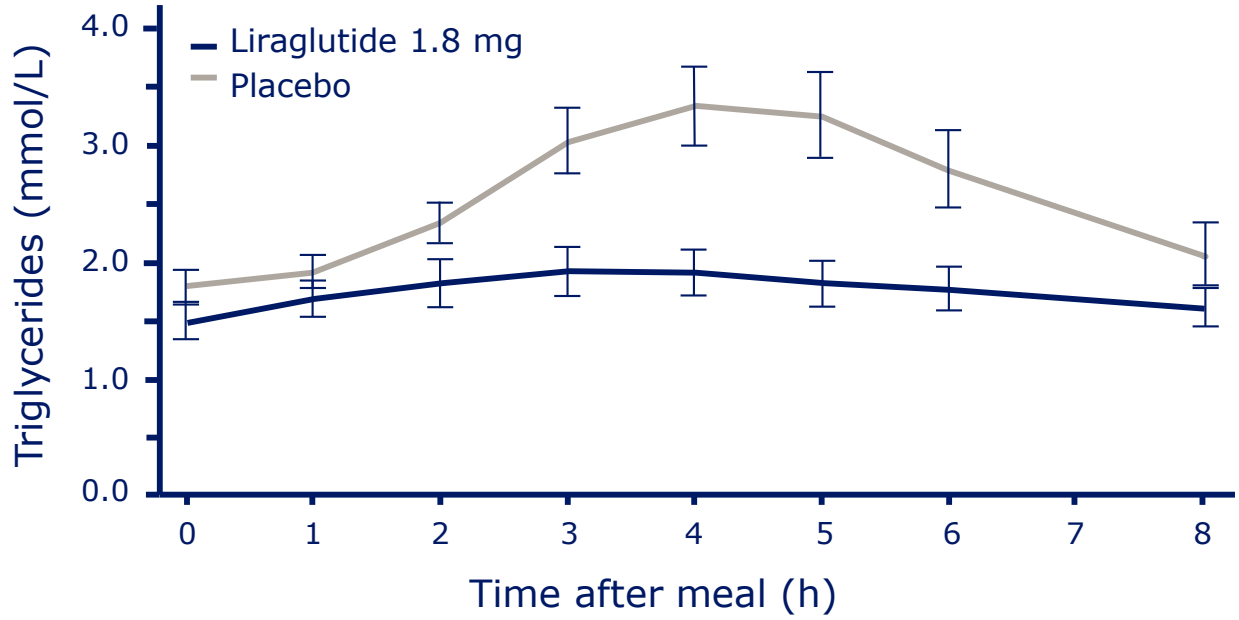
Data are last observation carried forward for the ITT population and expressed as least squares ± confidence intervals. Patient-level pooled analysis of six randomised clinical trials (LEAD 1–6)
ITT, intention-to-treat; SBP, systolic blood pressure
Adapted from: Fonseca VA et al. *J Diabetes Complications* 2014;28:399–405

Liraglutide effect on fasting lipid levels



LEAD 1–6: Meta-analysis. $^{**}p<0.01$; $^{***}p<0.0001$; all indicate a significant decrease vs baseline; † is used instead of * to indicate a significant increase from baseline
LDL-C, low-density lipoprotein cholesterol
Fonseca VA et al. International Diabetes Federation 21st World Diabetes Congress, 4–8 December 2011, Dubai, UAE

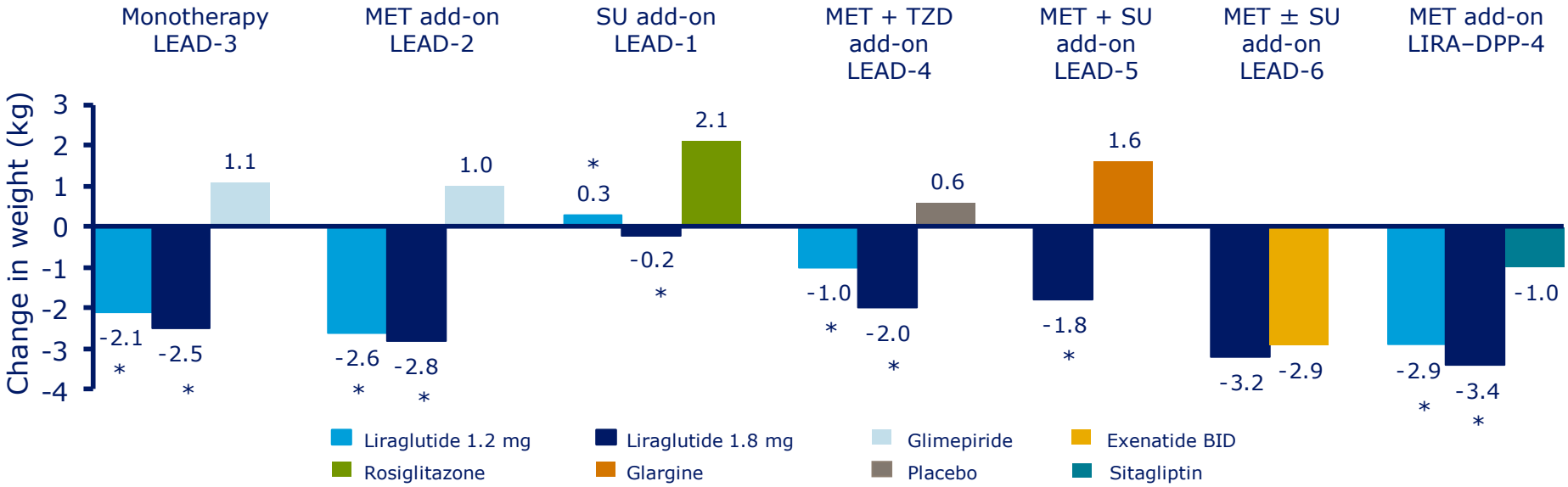
Effect of liraglutide on postprandial TG



AUC_{0-8h}
Treatment ratio 0.72
(95% CI 0.62 to 0.83)
p=0.0004

Data are mean ± SEM
AUC, area under the curve; CI, confidence interval; SEM, standard error of the mean
Hermansen K et al. *Diabetes Obes Metab* 2013;15:1040–1048

Liraglutide reduced body weight in people with T2DM



*Significant vs comparator
BID, twice daily; DPP-4, dipeptidyl peptidase-4; MET, metformin; SU, sulphonylurea; T2DM, type 2 diabetes mellitus; TZD, thiazolidinedione
Marre M et al. *Diabet Med* 2009;26:268–278 (LEAD-1); Nauck M et al. *Diabetes Care* 2009;32:84–90 (LEAD-2); Garber A et al. *Lancet* 2009;373:473–481 (LEAD-3); Zinman B et al. *Diabetes Care* 2009;32:1224–1230 (LEAD-4); Russell-Jones D et al. *Diabetologia* 2009;52:2046–2055 (LEAD-5); Buse JB et al. *Lancet* 2009;374:39–47 (LEAD-6); Pratley RE et al. *Lancet* 2010;375:1447–1456 (LIRA–DPP-4)

GLP-1RAs cause a small increase in heart rate

- Small but statistically significant increases in heart rate have been observed with liraglutide and exenatide OW[1–5]

	Exenatide 10 µg BID[4,6]	Exenatide 2 mg OW[5]	Liraglutide 1.2 mg OD[1–4,9]	Liraglutide 1.8 mg OD[1–4,9]	Albiglutide 50 mg[7]	Dulaglutide 1.5 mg[8]	Lixisenatide 20 µg[9]
Increase in heart rate (bpm)	1–2	4	2–4	2–4	1–2	2–4	3

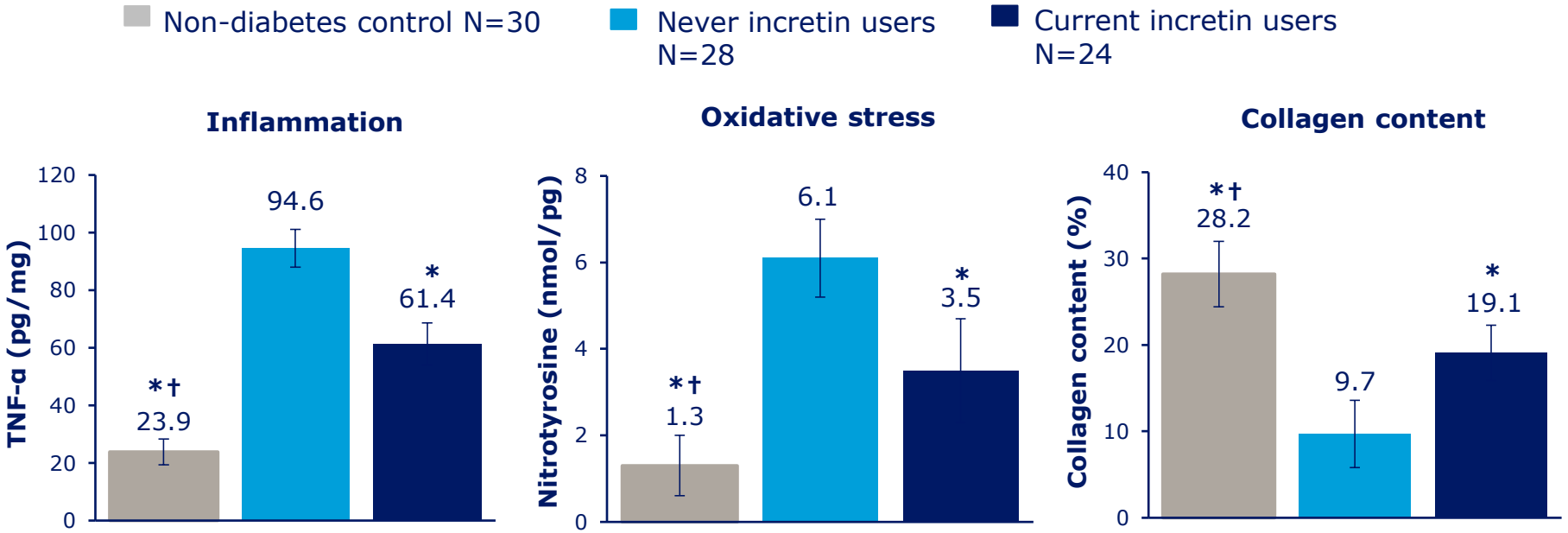
BID, twice daily; bpm, beats per minute; GLP-1RA; glucagon-like peptide-1 receptor agonist; OD, once daily; OW, once weekly

1. Marre M et al. *Diabet Med* 2009;26:268–278; 2. Nauck MA et al. *Diabetes Care* 2009;32:84–89; 3. Zinman B et al. *Diabetes Care* 2009;32:1224–1230; 4. Buse JB et al. *Lancet* 2009;374:39–47; 5. Diamant M et al. *Lancet* 2010;26;375:2234-2243; 6. Gill A et al. *Cardiovasc Diabetol* 2010;9:6; 7. Albiglutide Summary of Product Characteristics August 2016. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002735/WC500165117.pdf accessed June 2017; 8. Dulaglutide Summary of Product Characteristics March 2016. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002825/WC500179470.pdf accessed June 2017; 9. Meier JJ et al. *Diabetes Care* 2015;38:1263–1273

Studies show the cardioprotective mechanism of liraglutide

	Researcher	Year	Country	Observation objects	Study indicator
Vascular protection	Nana Li,et al.	2016	China	Endothelial cells	Endothelial function
	Jing Ke,et al.	2017	China	Endothelial cells High fat diet (HFD)-fed ApoE−/− mice	Endothelial function
	Xianwei Wang,et al.	2016	China	myocardial ischemia/reperfusion mice	Oxidative stress Inflammation
	Teruo Jojima,et al.	2017	Japan	ApoE$^{-/-}$mice	Smooth muscle proliferation
	Gleizes C,et al.	2014	France	B-Cells were submitted to oxidative stress conditions	procoagulant tissue factor
	Gaspari T,et al.	2013	Australia	ApoE$^{-/-}$mice	Plaque Stability
Cardiac protection	Ya Zhang,et al.	2017	China	Zucker diabetic fatty rat	Autophagy
	Noha A. T. Abbas,et al.	2017	Egypt	Doxorubicin-induced cardiotoxicity in rat	Myocardial injury
	Shun-Ying HU,et al.	2017	China	Cardiomyocytes	Myocardial injury
	Tracey Gaspari, et al.	2015	Australia	obesity- and age-induced cardiac fibrosis model in mice	Cardiac fibrosis

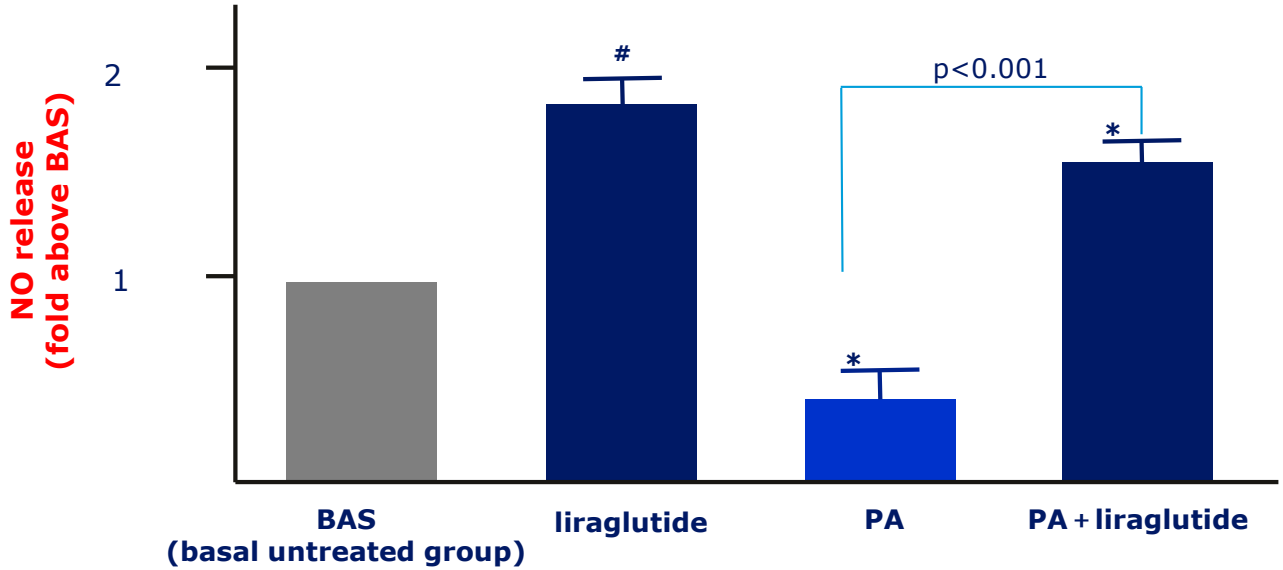
Incretin therapy improves indicators of plaque stability in patients with T2DM



*p<0.05 vs never users group; †p<0.05 vs current users group
Atherosclerotic plaques from patients undergoing carotid endarterectomy; patients included patients without diabetes and patients with T2DM ± incretin therapy
TNF-α, tumour necrosis factor-α; T2DM, type 2 diabetes mellitus
Balestrieri ML et al. *Diabetes* 2015;64:1395–1406

Liraglutide can improve NO release and endothelial function

- Human umbilical vein endothelial cells (HUVECs) were incubated with PA for 16 h and then were treated with liraglutide for 30 min.



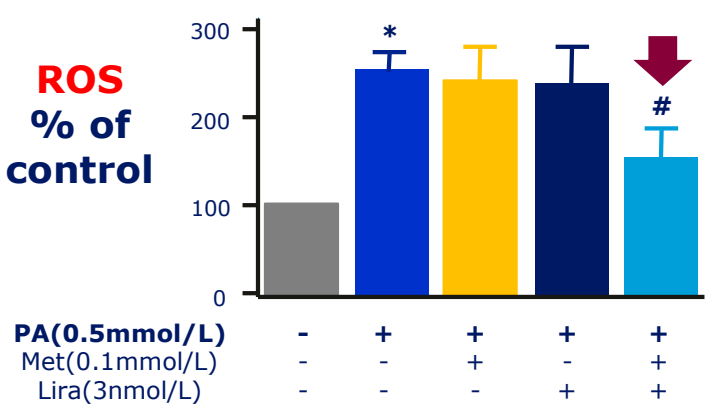
Compared to BAS,*p < 0.05,#p<0.001

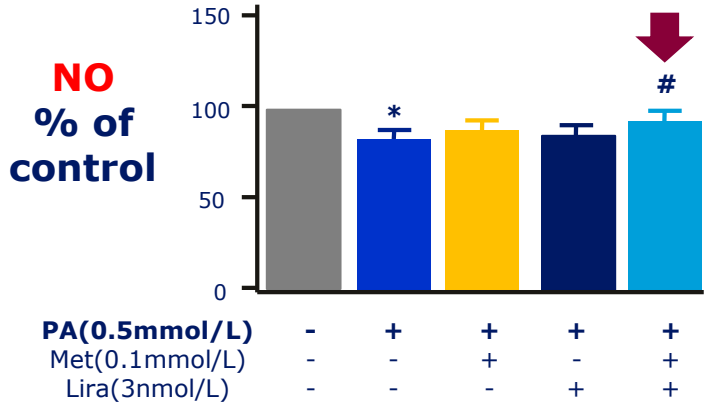
NO: Nitric oxide NO, known as endothelium-derived relaxing factor before. It participates in several biological processes such as vasodilatation and platelet aggregation inhibition

Li N, et al.Biochemical and biophysical research communications.2016;478(1): 46-52.

Liraglutide+Metformin decrease ROX and increase NO

- Human umbilical vein endothelial cells (HUVECs), exposed to palmitic acid (PA) to induce endothelial dysfunction, were incubated with metformin, liraglutide or their combination



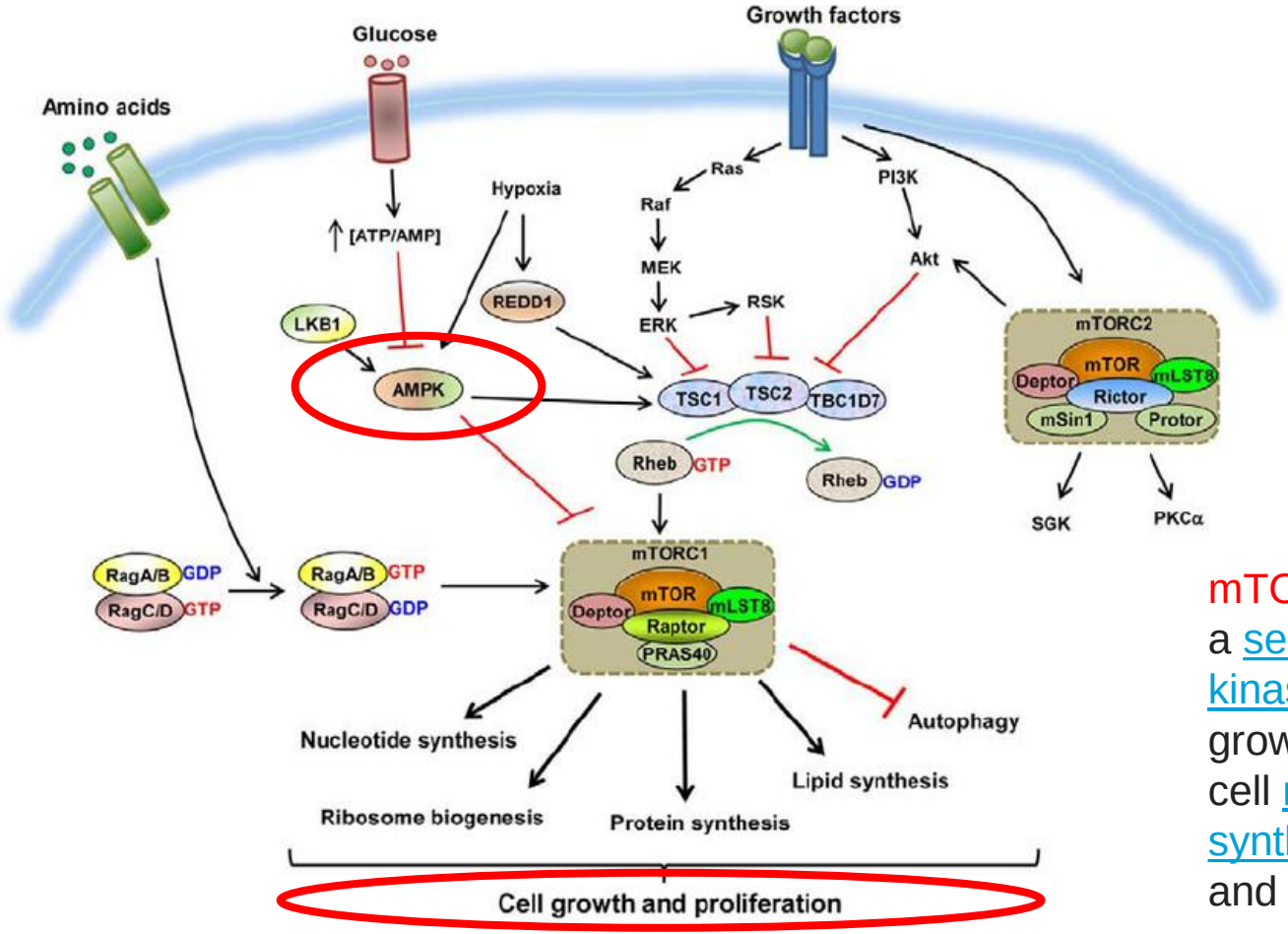


*P<0.05 (vs. control);
#P<0.05 (vs. PA)

ROS, reactive oxygen species; PA, palmitic acid, Met, metformin; Lira, liraglutide

Ke J, et al. Scientific Reports.2017;7: 41085.

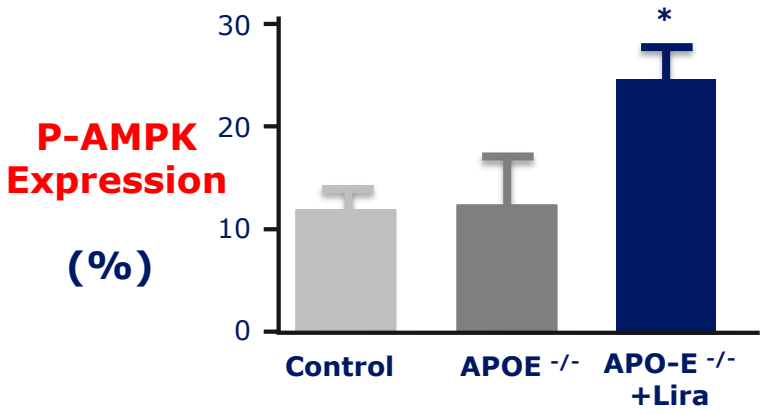
The AMPK/mTOR signaling pathway

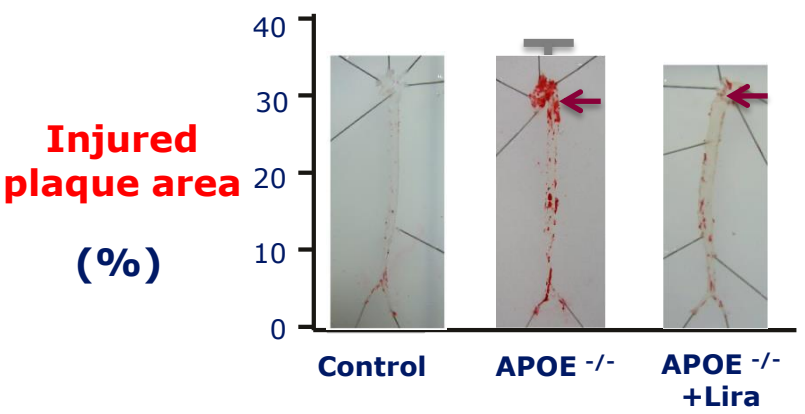


mTOR functions as a serine/threonine protein kinase that regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis, autophagy, and transcription.

Liraglutide activates AMPK, inhibits VSMCs proliferation

- We investigated whether liraglutide could:
  - prevent the development of atherosclerosis in apolipoprotein E knockout mice (ApoE-/-) on a high-fat diet.
  - have the influence on angiotensin II-induced proliferation of rat vascular smooth muscle cells (VSMCs) via enhancement of AMP-activated protein kinase (AMPK) signaling and regulation of cell cycle progression





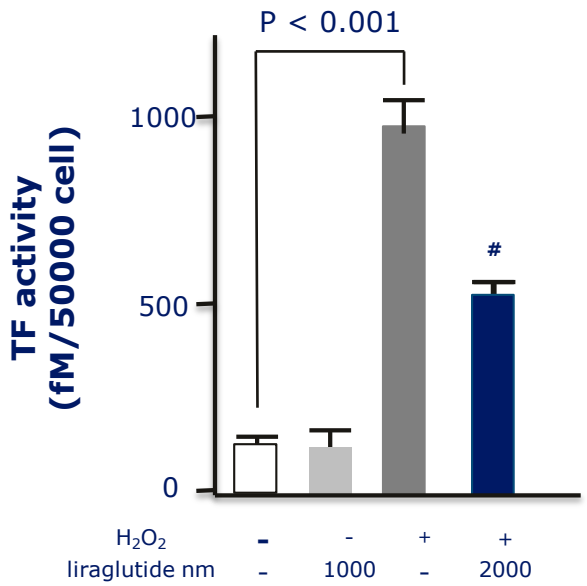
* compared with the vehicle-treated ApoE KO mice $P < 0.05$

Jojima T, et al. Atherosclerosis.2017;261: 44-51.

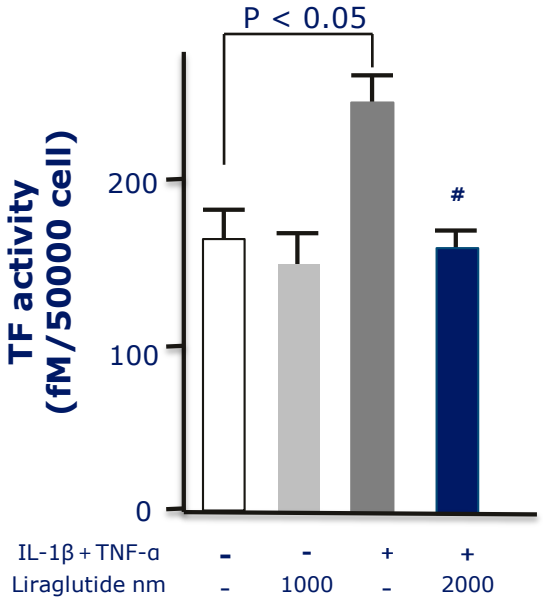
Liraglutide can inhibit the tissue thromboplastin activity under oxidant stress and inflammation

- Rin-m5f rat β cells were stimulated by H_2O_2 or a combination of IL-1β and TNF-α. To mimic the oxidative and inflammatory conditions. The cells were pretreated by 1 μm liraglutide for 4 h to access the modulation effect of liraglutide

Oxidant stress



Inflammation

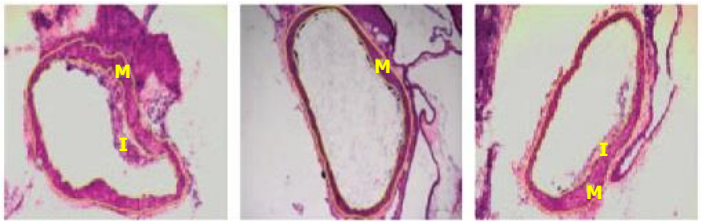


TF: tissue factor

Gleizes C, et al.Transplant International.2014;27(7):733-740.

Liraglutide inhibits progression of early, low-burden atherosclerotic lesion development in ApoE−/− mice

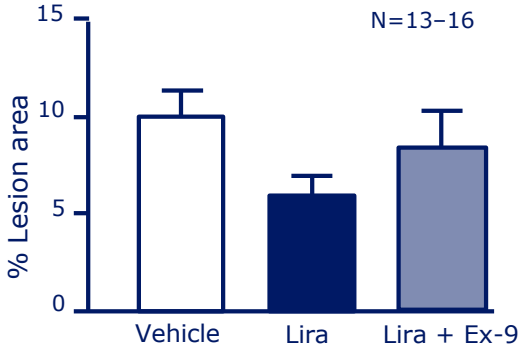
Lesion development



Vehicle | Lira | Lira + Ex-9

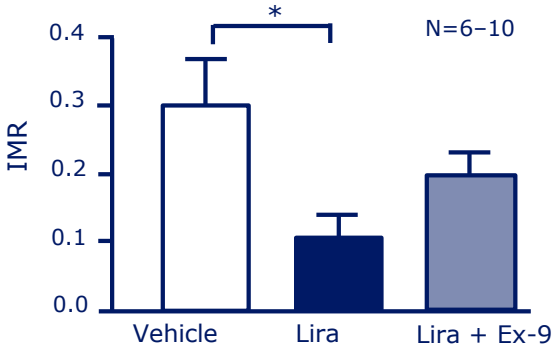
Haemotoxylin and eosin staining in the aortic arch

Lipid deposition



Oil red O staining performed in the aorta

Intima/media ratio (IMR)

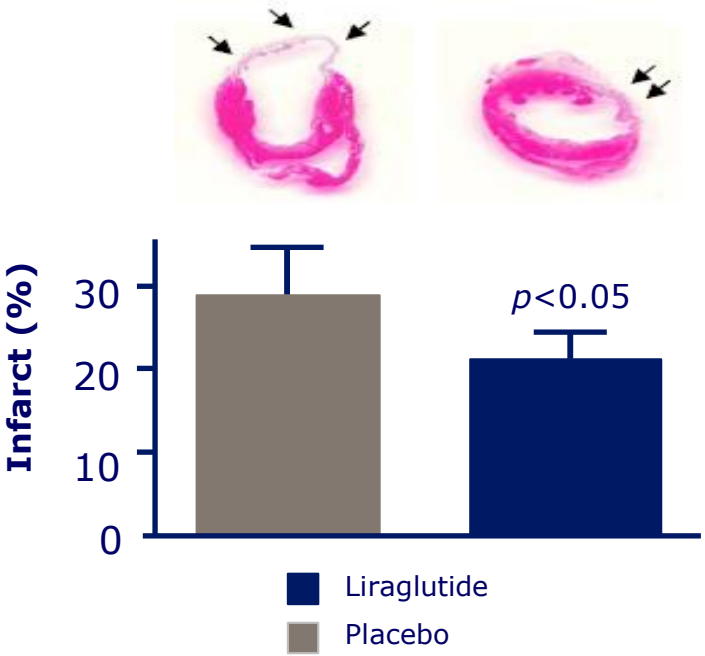


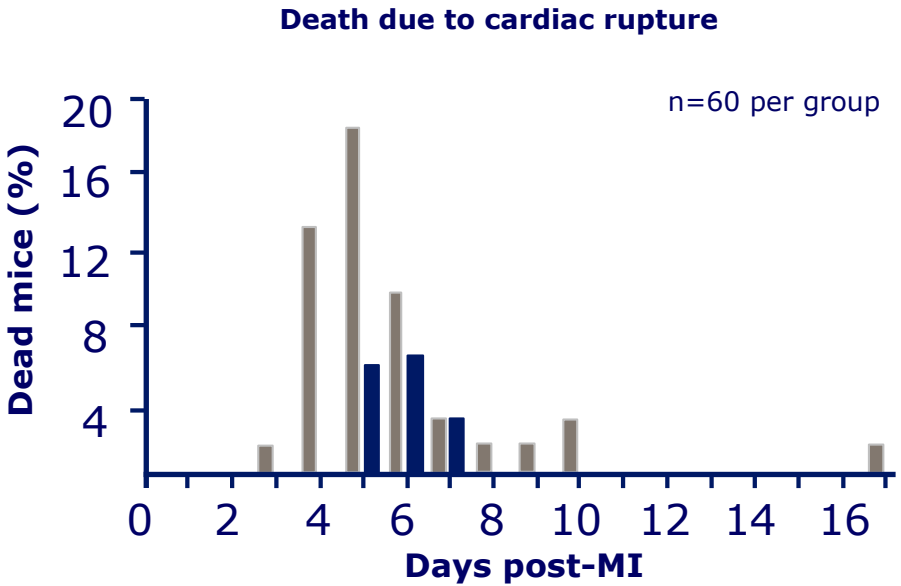
IMR analysis performed in the aortic arch

*p<0.05 vs vehicle by one-way ANOVA; data are mean ± SEM; performed in ApoE$^{-/-}$ mice with early, low-burden atherosclerotic lesions
ApoE$^{-/-}$, apolipoprotein E knockout; ANOVA, analysis of variance; Ex-9, exendin-9; IMR, intima-media ratio; Lira, liraglutide; SEM, standard error of the mean

Gaspari T et al. *Diab Vasc Dis Res* 2013;10:353–360

Liraglutide reduced infarct size and improved survival in mice following LAD artery ligation





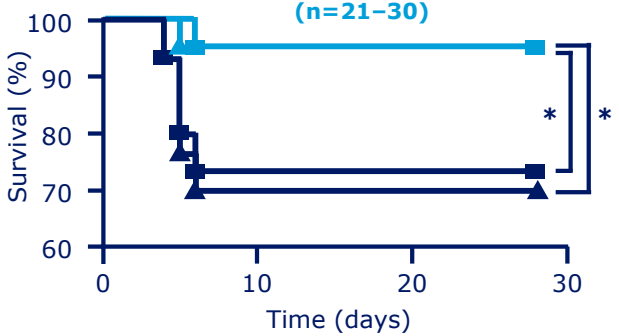
LAD, left anterior descending; MI, myocardial infarction

Noyan-Ashraf M et al. *Diabetes* 2009;58:975–983

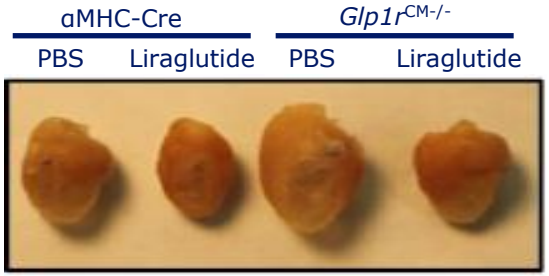
Cardiac GLP-1R is not required for post-MI benefits of liraglutide *in vivo*

▲ αMHC-Cre + PBS
▲ αMHC-Cre + Liraglutide
■ *Glp1r*$^{CM-/-}$ + PBS
■ *Glp1r*$^{CM-/-}$ + Liraglutide

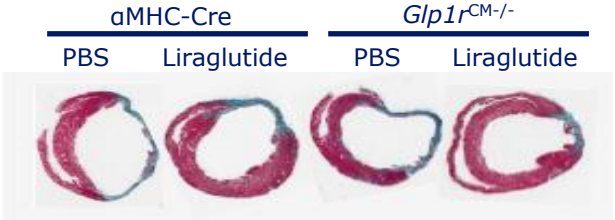
Survival following LAD coronary artery occlusion (n=21–30)



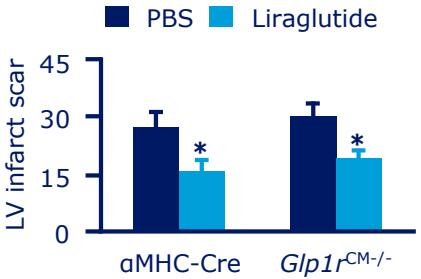
Cardiac hypertrophy



Representative Masson's Trichrome stained heart sections depicting % LV infarct scar formation and LV infarct wall thickness



% LV infarct scar formation



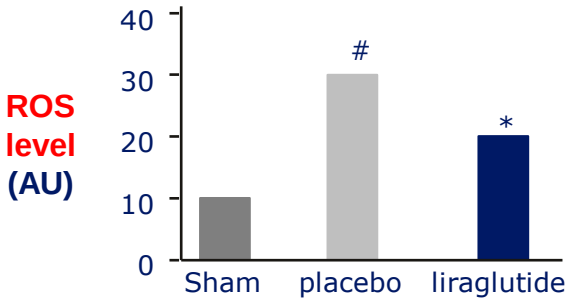
*30 mg/kg BW i.p. twice daily for 1 week. αMHC-Cre, α-myosin heavy chain-Cre mice; GLP-1R, glucagon-like peptide-1 receptor; *Glp1r*$^{CM-/-}$, *Glp1r* deficient mice; i.p., intraperitoneal; LAD, left anterior descending; LV, left ventricular; MI, myocardial infarction; PBS, phosphate-buffered saline

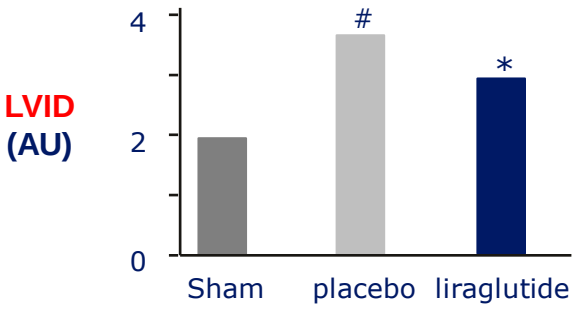
Ussher JR et al. *Mol Metab* 2014;3:507–517

Liraglutide can improve ROS, inflammation and LV remodeling

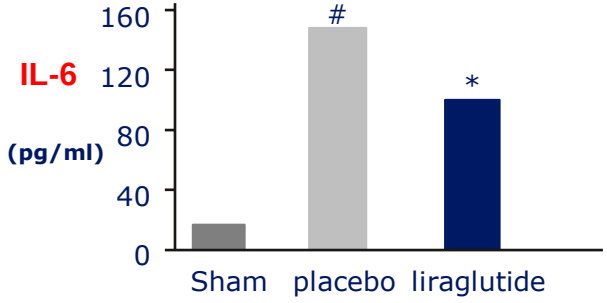
- C57BL/6 mice were treated with liraglutide for 5 days, and then subjected to LCA occlusion (1 h) and reperfusion (3 h)

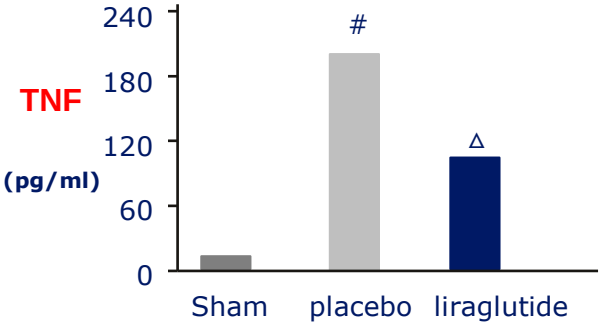
ROS





Inflamatory markers

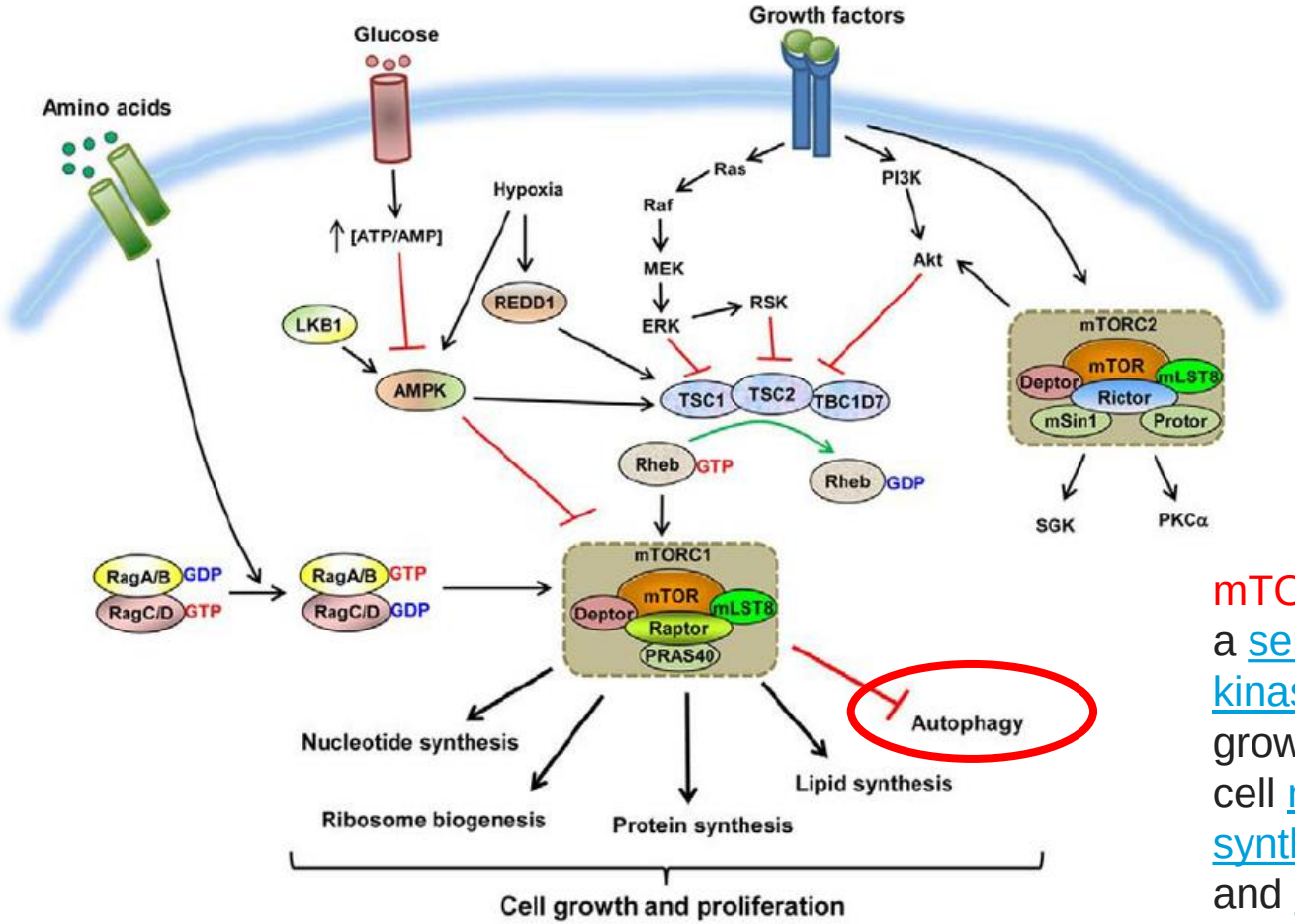




Compared to Sham,#P<0.01
Compared to placebo,*P<0.05,ΔP<0.01

Wang X, et al. Clinical Science.2016;130(15): 1353-62.

The AMPK/mTOR signaling pathway

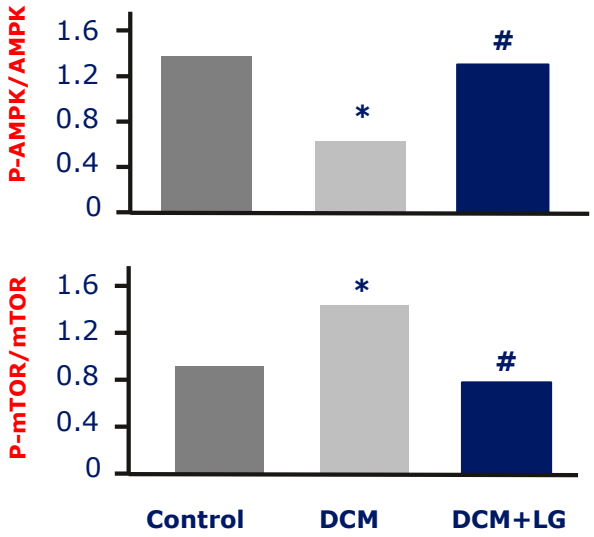


mTOR functions as a serine/threonine protein kinase that regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis, autophagy, and transcription.

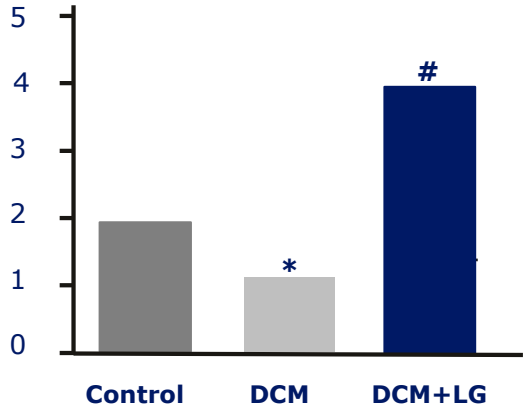
Liraglutide can increase autophagy and decrease myocardial injury

- The effect of liraglutide for myocardial fibrosis in the Zucker diabetic fatty (ZDF) rat model

  The ZDF rats were randomly divided into five groups: (1) normal group (Control); (2) DCM group; (3) DCM + LG group (200 μg/kg of LG, subcutaneous injection) group. LG was injected once a day for 8 weeks.



Autophagy vacuole number

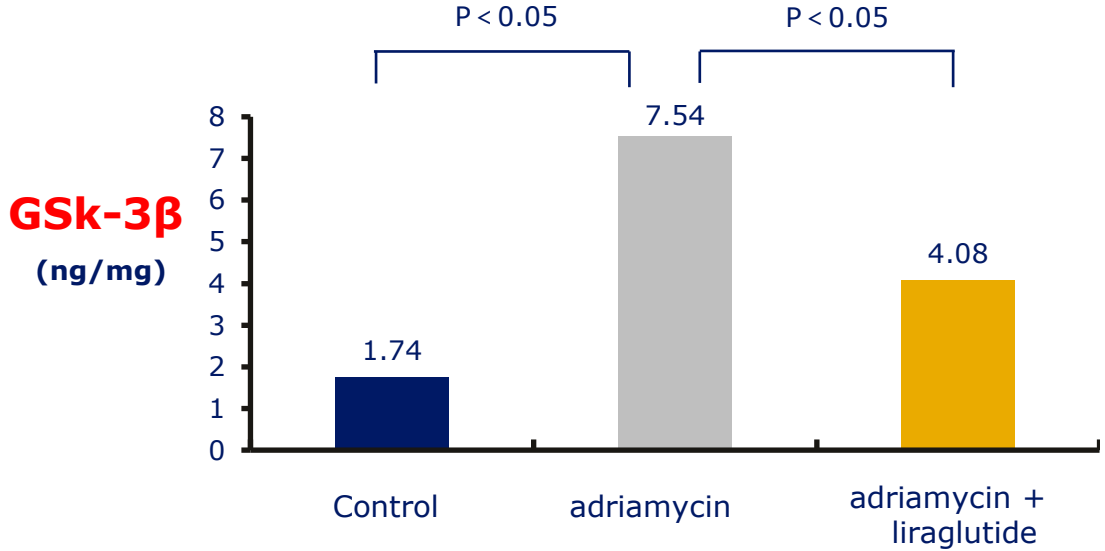


Vs control,*P<0.01; vs DCM,#P<0.05

DCM: Diabetic
LG: liraglutide

Zhang Y, et al. Molecular and Cellular Endocrinology.2017;448:98-107.

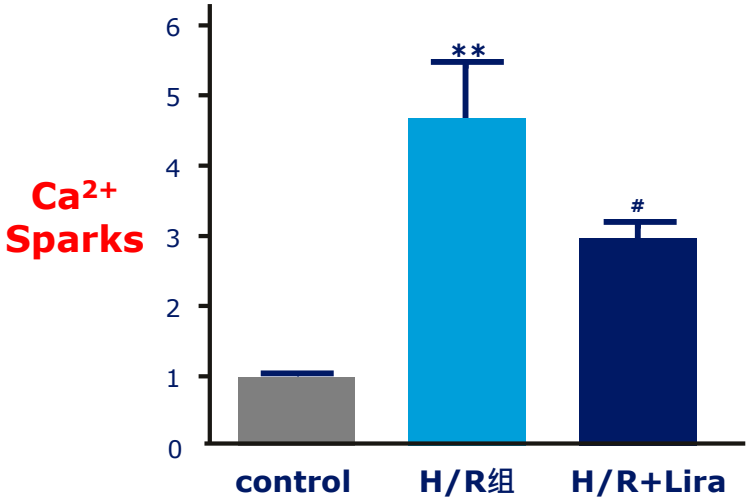
Liraglutide can inhibit gsk-3β to improve the cardiotoxicity induced by adriamycin

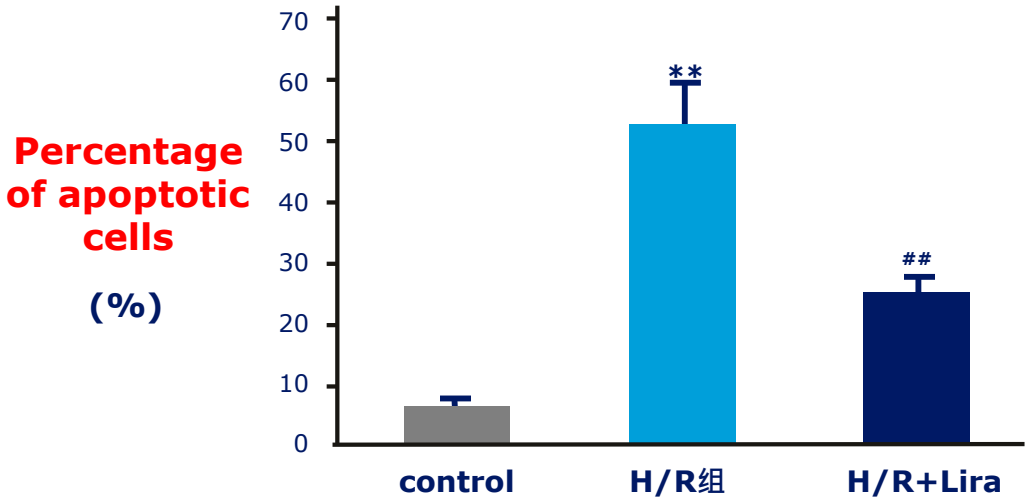


GSK-3β: Glycogen synthase kinase-3 (GSK-3) is a proline-directed serine-threonine kinase that was initially identified as a phosphorylating and an inactivating agent of glycogen synthase. Two isoforms, alpha (GSK3A) and beta, show a high degree of amino acid homology.[5] GSK3B is involved in energy metabolism, neuronal cell development, and body pattern formation.[9][10] It might be a new therapeutic target for ischemic stroke.

Abbas N A T, et al.Naunyn-Schmiedeberg's archives of pharmacology.2017;390(11):1145-53.

Liraglutide can decrease Ca^{2+} overload and prevent myocardial apoptosis in ischemia-reperfusion injury

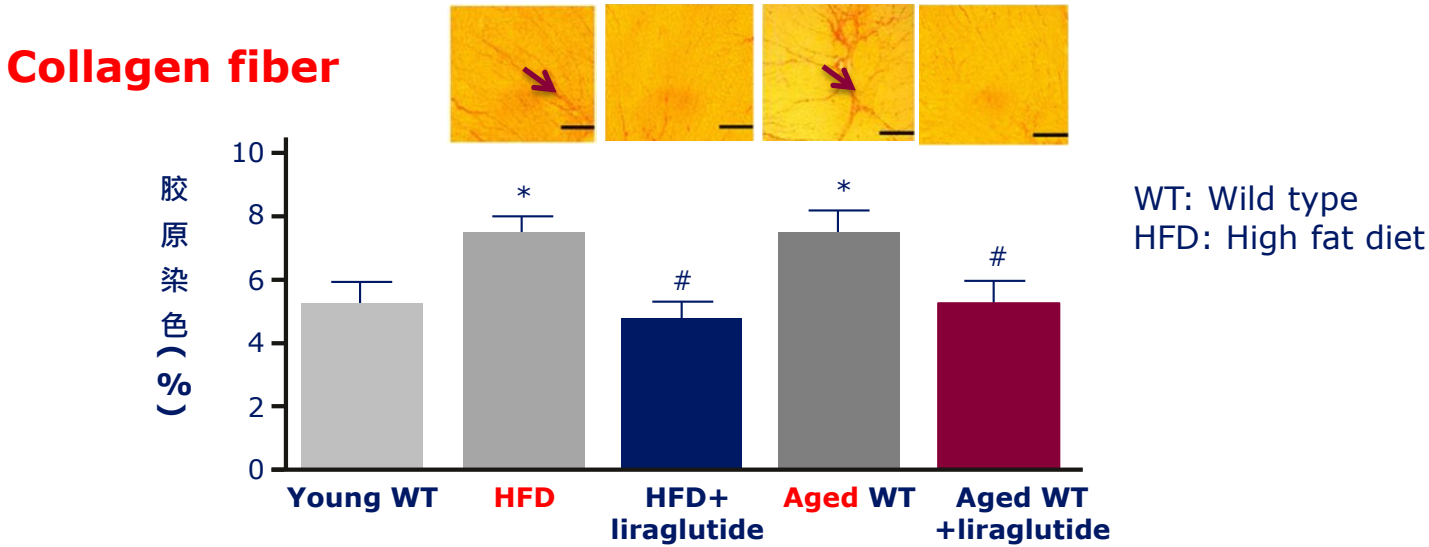




H/R:hypoxia/reoxygenatio; lira,liraglutide; Fura-2/AM:was used to measure intracellular Ca2+ concentration and calcium transient.

Hu S Y, et al. Journal of geriatric cardiology.2017;14(1): 57.

Liraglutide can improve myocardial fibrosis in aged rats or fed with high fat



WT: Wild type
HFD: High fat diet

Vs young WT,*P<0.01; vs HFD and aged WT,#P<0.01

Gaspari T, et al. Diabetes and Vascular Disease Research.2016;13(1): 56-68.

Possible Mechanisms of Beneficial Effects on CVS

Improve endoth. dysfunction
Anti-inflammation
Anti-oxidation
Inh. VSMC proliferation
Anti-coagulation
Stabilize unstable plaque
Augment autophagy

Anti-atherosclerosis

Improve myocardial injury & fibrosis

Blood glucose ↓
BW ↓ (Body fat decrease)
Dyslipidemia ↓
Hypertension ↓

GLP-1 RA

Decrease CV risk or mortality

Summary

Strong evidence for the important role of GLP-1 in T2DM treatment

All guidelines recognize the beneficial CV effects of GLP-1 RA

More and more researches to focus on the CV effect of GLP-1 RA

In addition to treat T2DM, GLP-1 RA may be used for the patients with MI, HF, or other high CVD risks to get beneficial effects

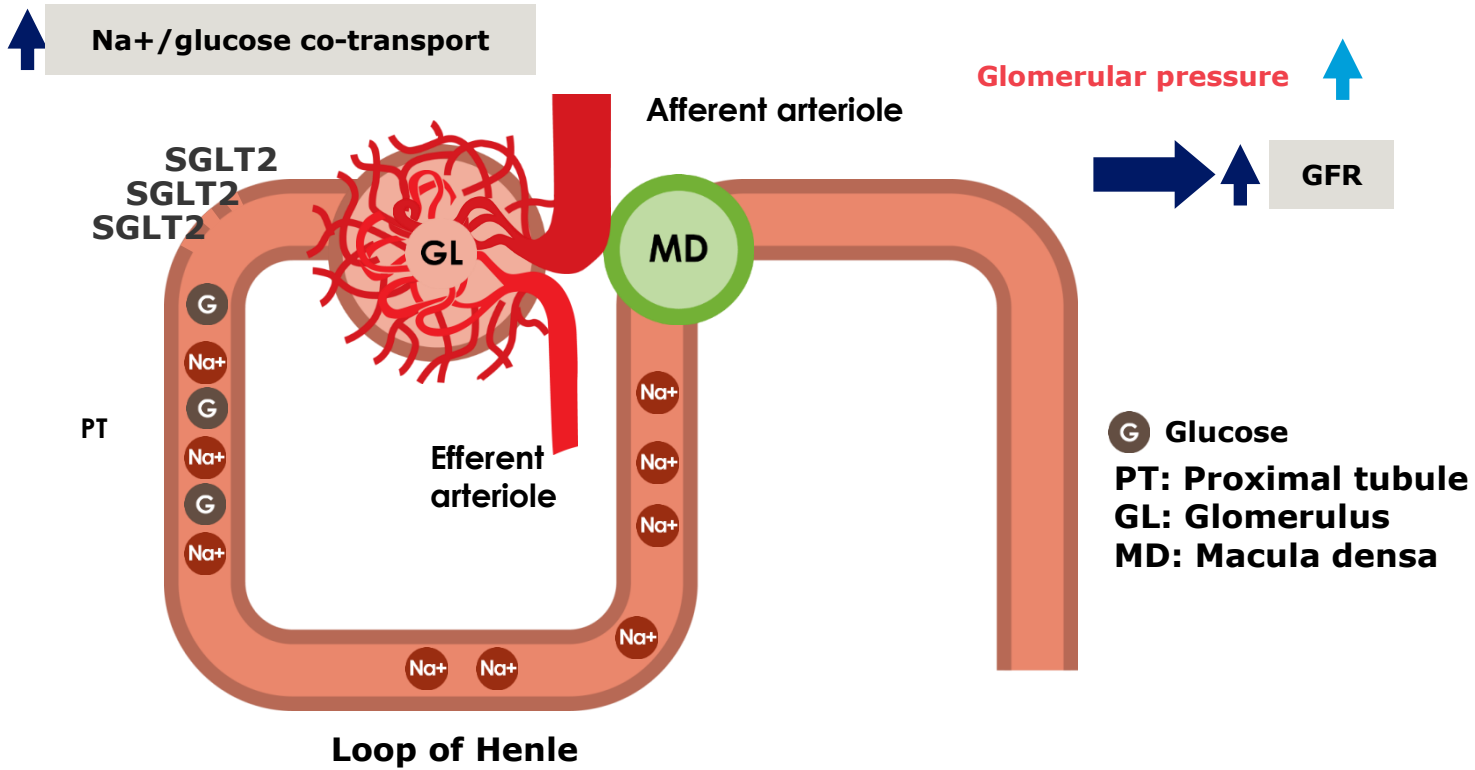
Liraglutide can effect in different stages of CVD to reduce CVD risk or mortality

Vascular protection			Myocardial protection
ROS ↓, NO ↑ Endoth. function ↑	Inflam. ↓, VSMC prolif. ↓ Apoptosis ↓	Coagulation ↓ Unstable plaque ↓	Myocardial injury ↓ Myocardial fibrosis ↓

CVD progression

THANKYOU

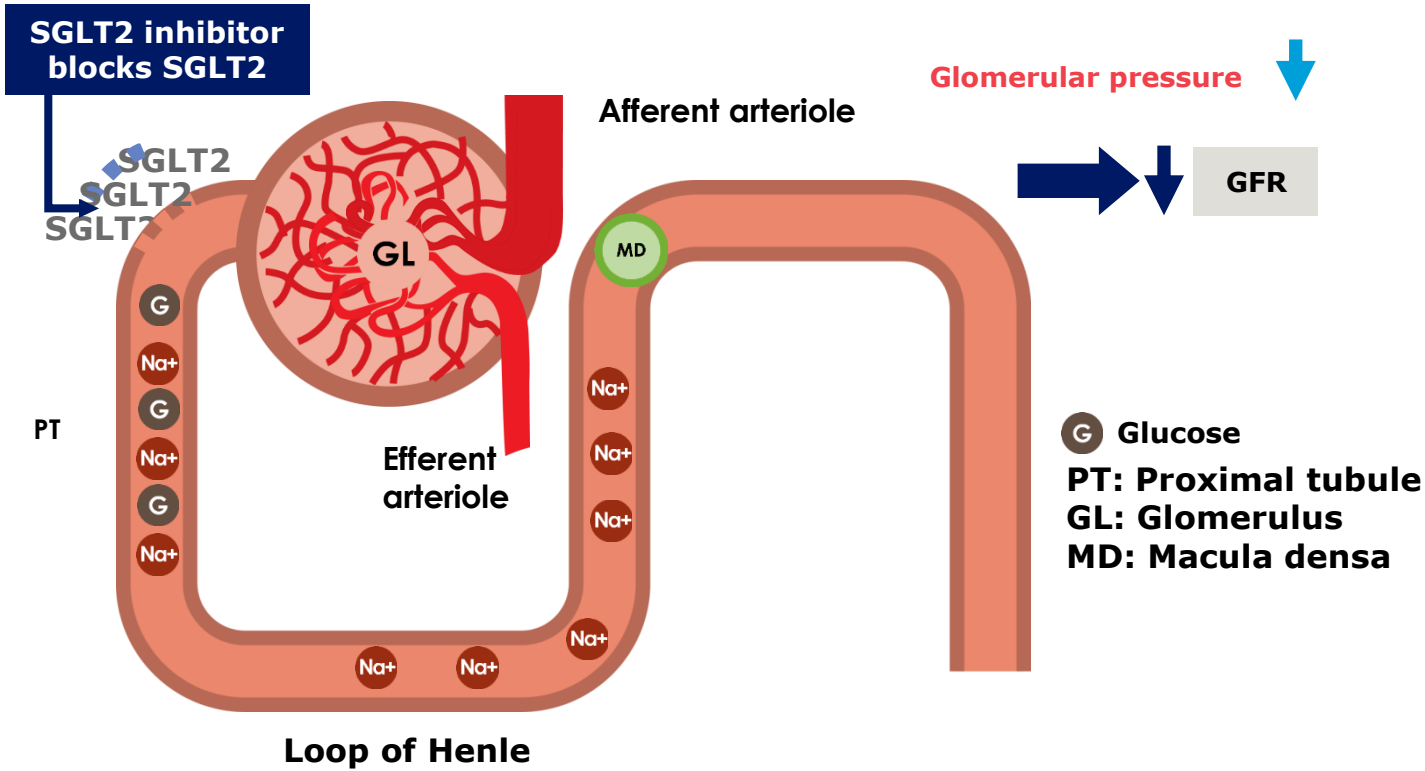
Diabetes causes glomerular hypertension



Renal hemodynamics under hyperglycemia

Adapted from: Cherney D et al. Circulation 2014;129:587

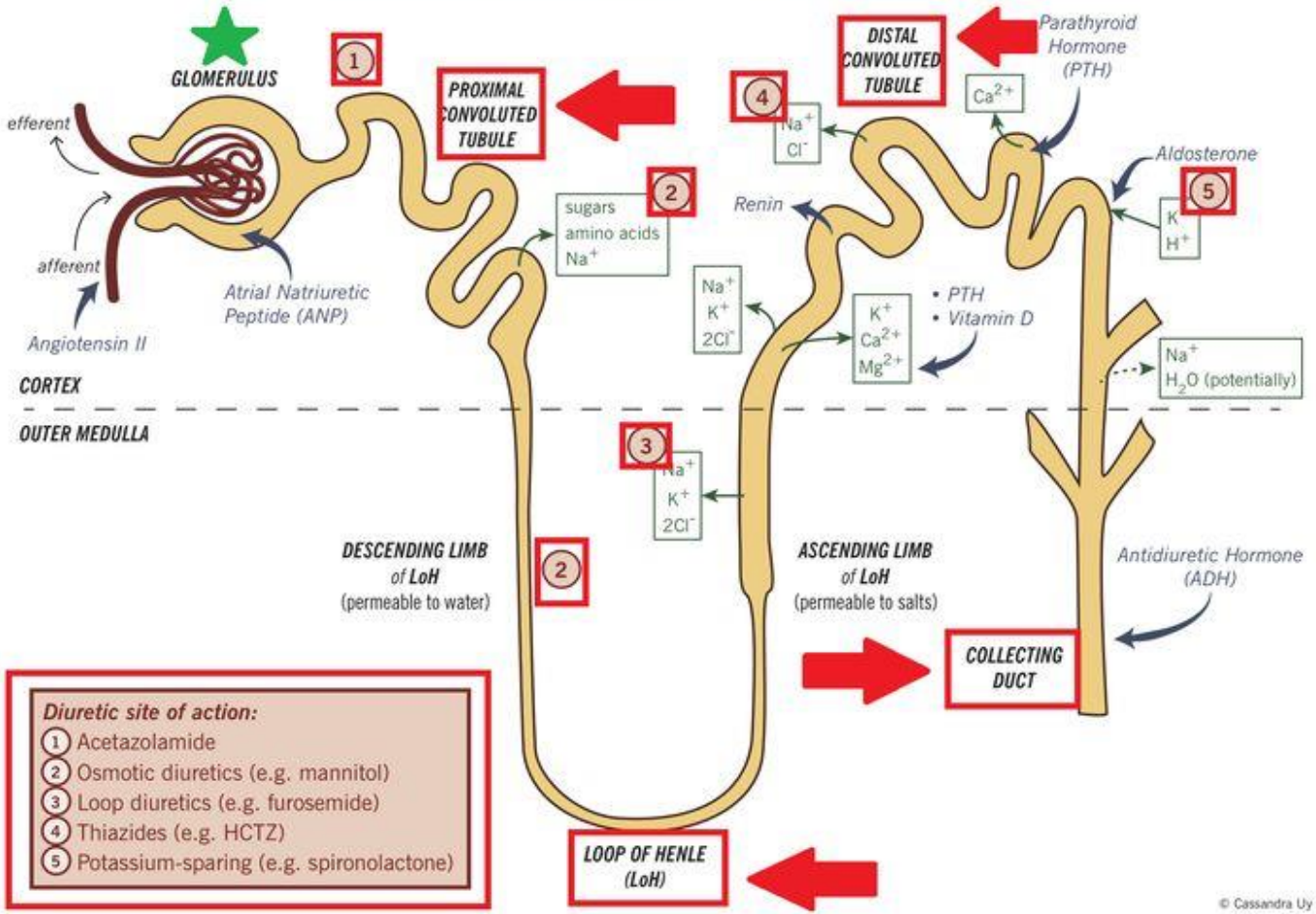
SGLT2 inhibitors lowers intra-glomerular pressure



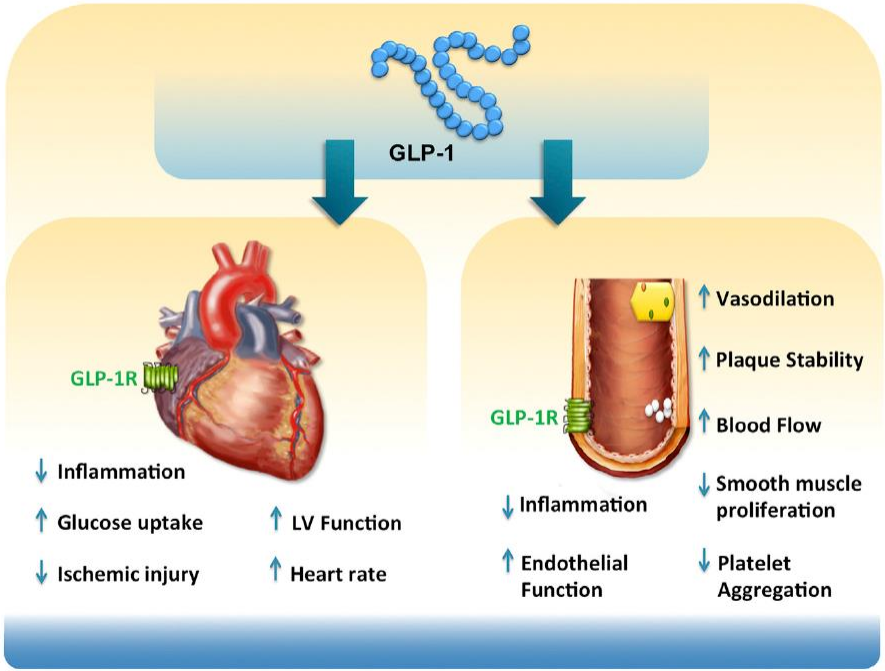
Renal hemodynamics with SGLT2 inhibitor

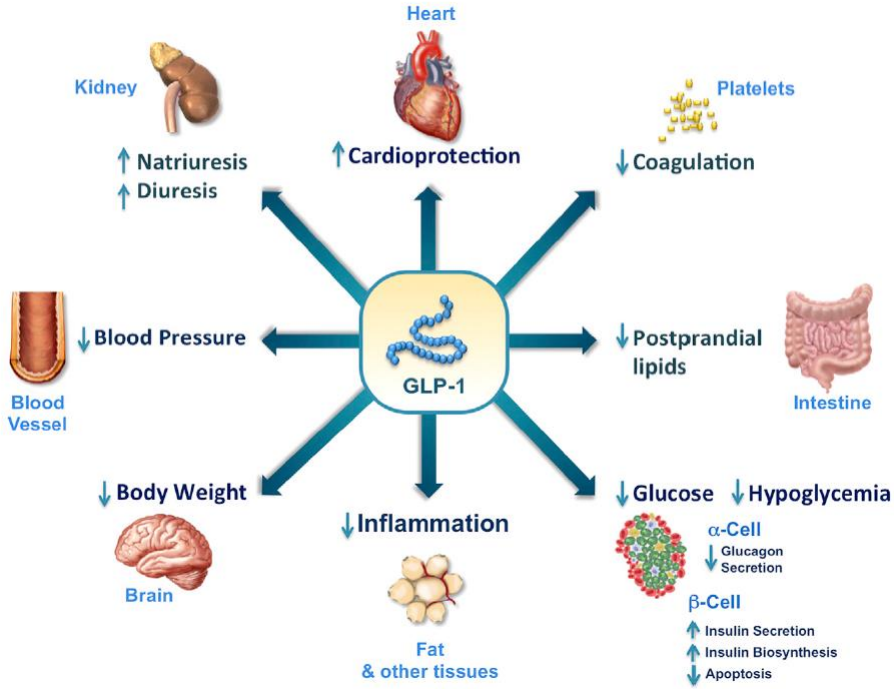
Adapted from: Cherney D et al. Circulation 2014;129:587

Hormones Acting on the Nephron / Diuretics and Their Site of Action



Potential mode of action for GLP-1 to impact cardiovascular disease





GLP-1, glucagon-like peptide-1; GLP-1R, glucagon-like peptide-1 receptor; LV, left ventricular
Drucker DJ. Cell Metab 2016;24:15–30

Summary: CV effects of GLP-1RAs

- GLP-1RAs, including liraglutide, have been shown to reduce SBP and lipid levels[1–3]
  - Improvement in these risk factors is associated with a reduced risk of adverse CV outcomes[4–7]
- Weight loss with GLP-1RAs may improve CV endpoints[8–11]
- GLP-1RAs have been reported to increase heart rate[1,12]
- Exploratory data in small cohorts suggest that GLP-1RAs potentially modify the progression of atherosclerotic vascular disease

CV, cardiovascular; GLP-1RA, glucagon-like peptide-1 receptor agonist

1. Fonseca VA et al. *J Diabetes Complications* 2014;28:399–405; 2. Fonseca VA et al. International Diabetes Federation 21st World Diabetes Congress, 4–8 December 2011, Dubai, UAE; 3. Hermansen K et al. *Diabetes Obes Metab* 2013;15:1040–1048; 4. Ettehad D et al. *Lancet* 2016;387:957–967; 5. Xie X et al. *Lancet* 2016;387:435–443; 6. Yusuf S et al. *N Engl J Med* 2016;374:2021–2031; 7. Nordestgaard BG, Varbo A. *Lancet* 2014;384:626–635; 8. Sjöström L et al. *N Engl J Med* 2004;351:2683–2693; 9. Dattilo AM, Kris-Etherton PM. *Am J Clin Nutr* 1992;56:320–328; 10. Dengo AL et al. *Hypertension* 2010;55:855–861; 11. Li G et al. *Lancet Diabetes Endocrinol* 2014;2:474–480; 12. Monami M et al. *Diabetes Obes Metab* 2014;16:38–47

Thank You For Your Attention