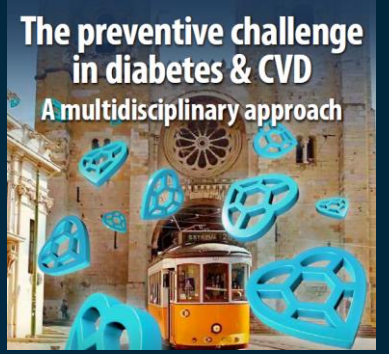


Type 2 Diabetes & CV outcomes: More than Glucose management? - lessons from GLP1-ra trials

Stephan Jacob, MD
Tübingen, Germany

EBAC accredited satellite symposium held during EuroPrevent
April 11, 2019 - Lisbon, Portugal

Cardio-Metabolic-Institute

Deutsche Diabetes Gesellschaft

AG Herz und Diabetes

Type 2 Diabetes & CV outcomes: More than glucose management? - Lessons from GLP-1 RA trials

Eberhard-Karls-Universität Tübingen

Prof. Dr. Stephan Jacob

Internist, endocrinologist, diabetologist, clinical hypertension specialist ESH

Cardio-Metabolic-Institute Villingen-Schwenningen

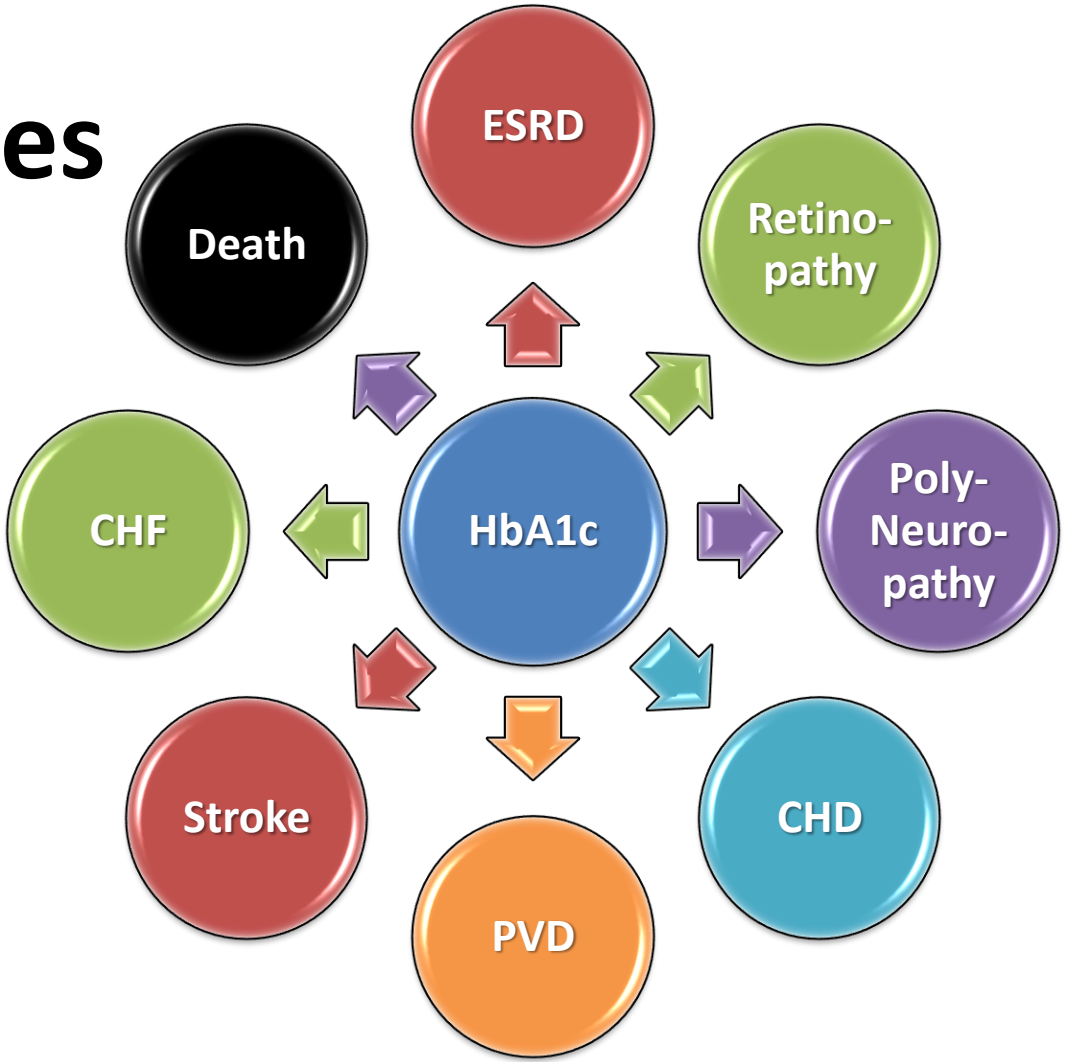
I have received honoraria, research support and consulting fees of the following companies

Abbott, Astra Zeneca, Bayer, Berlin Chemie,

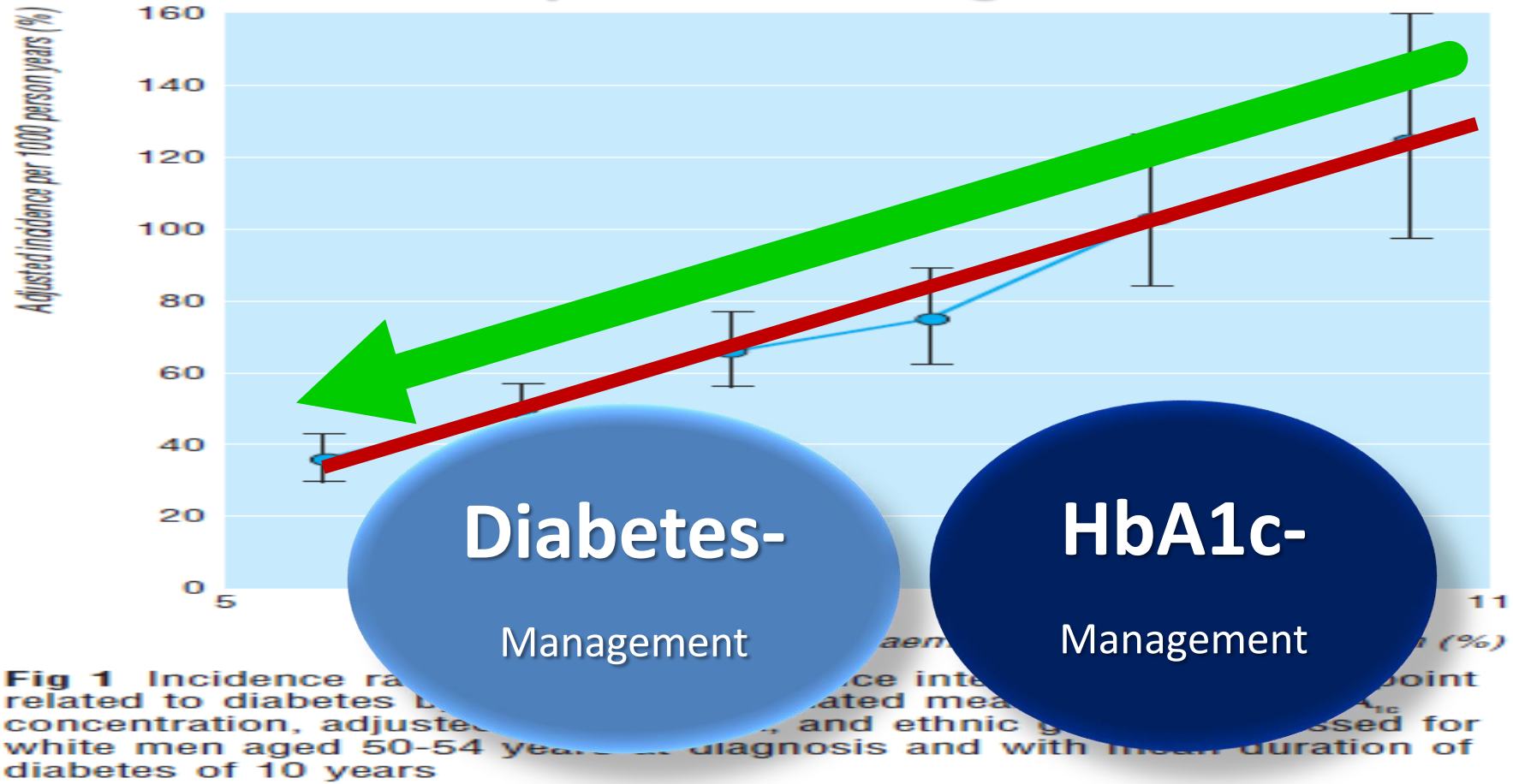
Boehringer Ingelheim, Lilly, Medcon, Merck, MSD, Novo Nordisk, Novartis, Roche, Sanofi-Aventis, Servier,

Simplified view

Typ 2 Diabetes



Epidemiologie



Diabetes-

Management

HbA1c-

Management

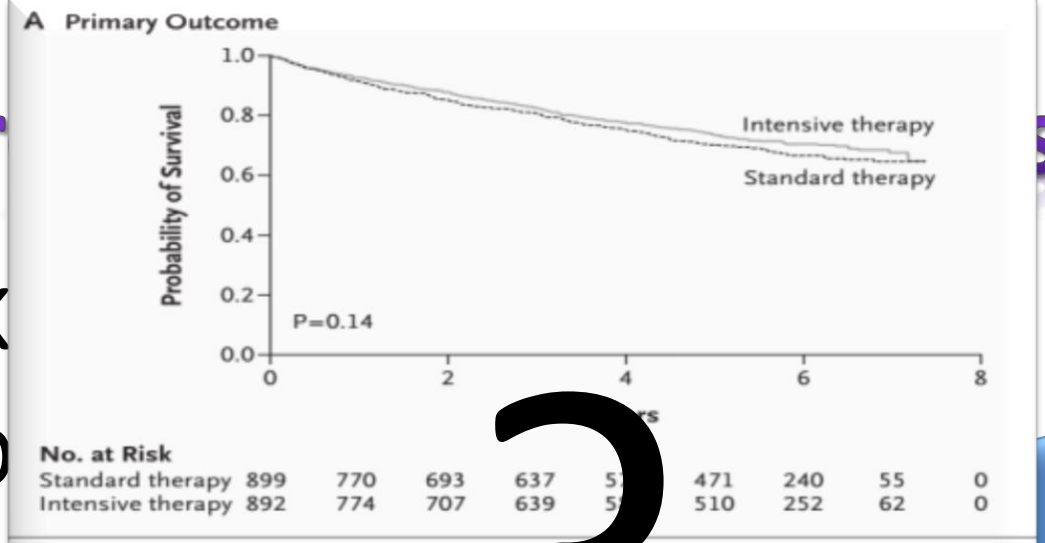
Fig 1 Incidence ra ce inte oint related to diabetes l ated mea $_{1c}$ concentration, adjuste , and ethnic g ssed for white men aged 50-54 yea diagnosis and with mean duration of diabetes of 10 years

Reference category (hazard ratio 1.0) is HbA_{1c} <6% with log linear scales. CV, cardiovascular; MI, myocardial infarction; PVD, peripheral vascular disease

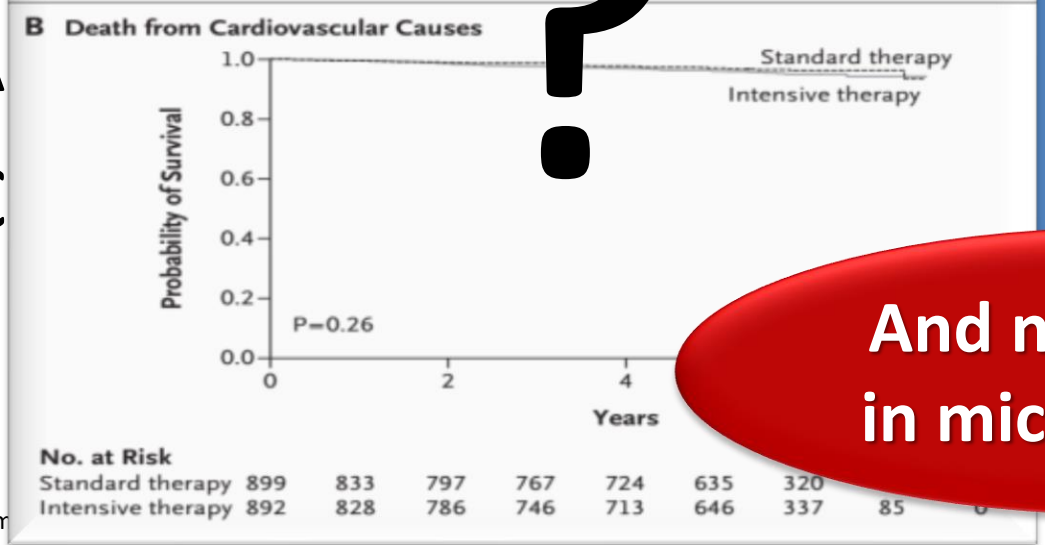
Stratton IM et al. *BMJ* 2000;321:405–412.

Is r successful?

- UK
- AD
- VA
- AC



?



MAX diff. 1.5%

And no reduction in microvascular!!

HbA_{1c}, glycosylated haem

Recent long term f/up studies in DM2

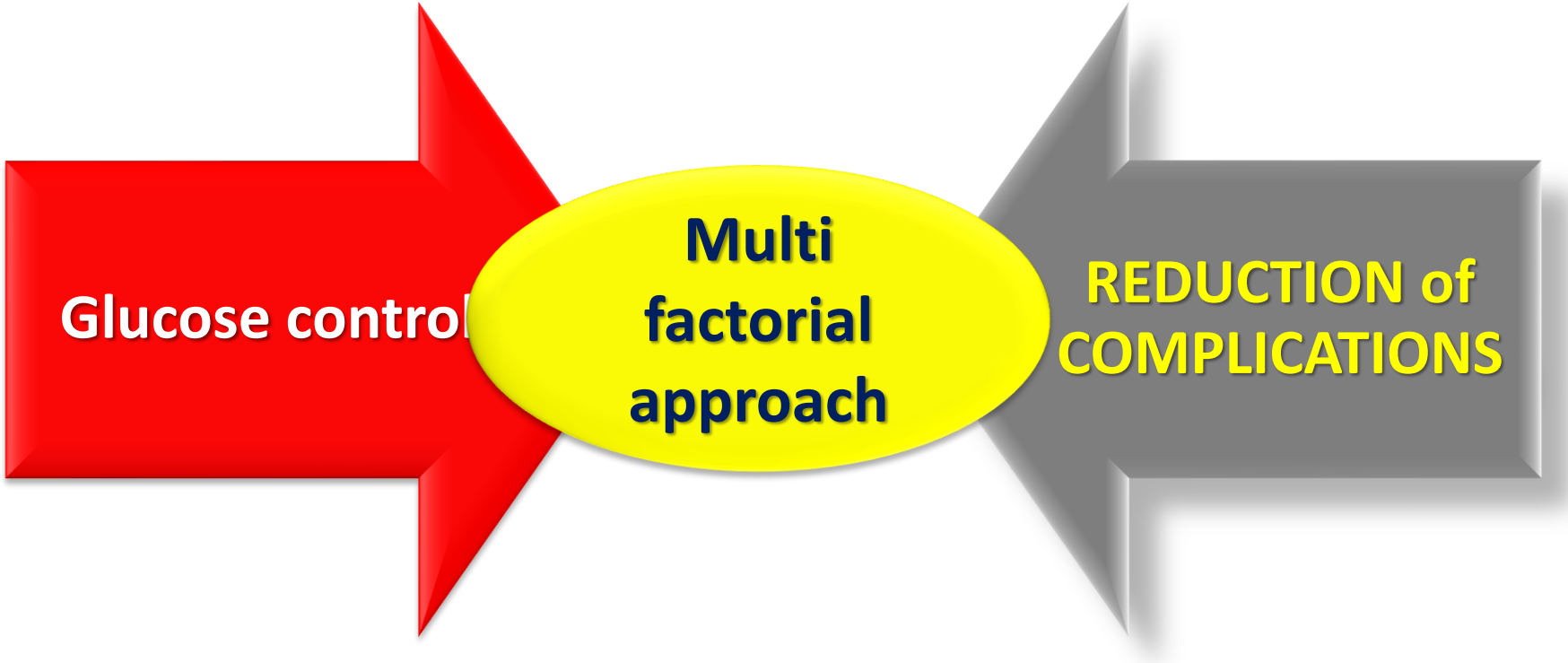
	HbA1c Diff	Yrs RX			P	LEGACY
ACCORDION	0,9%					
Composite CVD						
CV death						

Is Legacy only a legend?

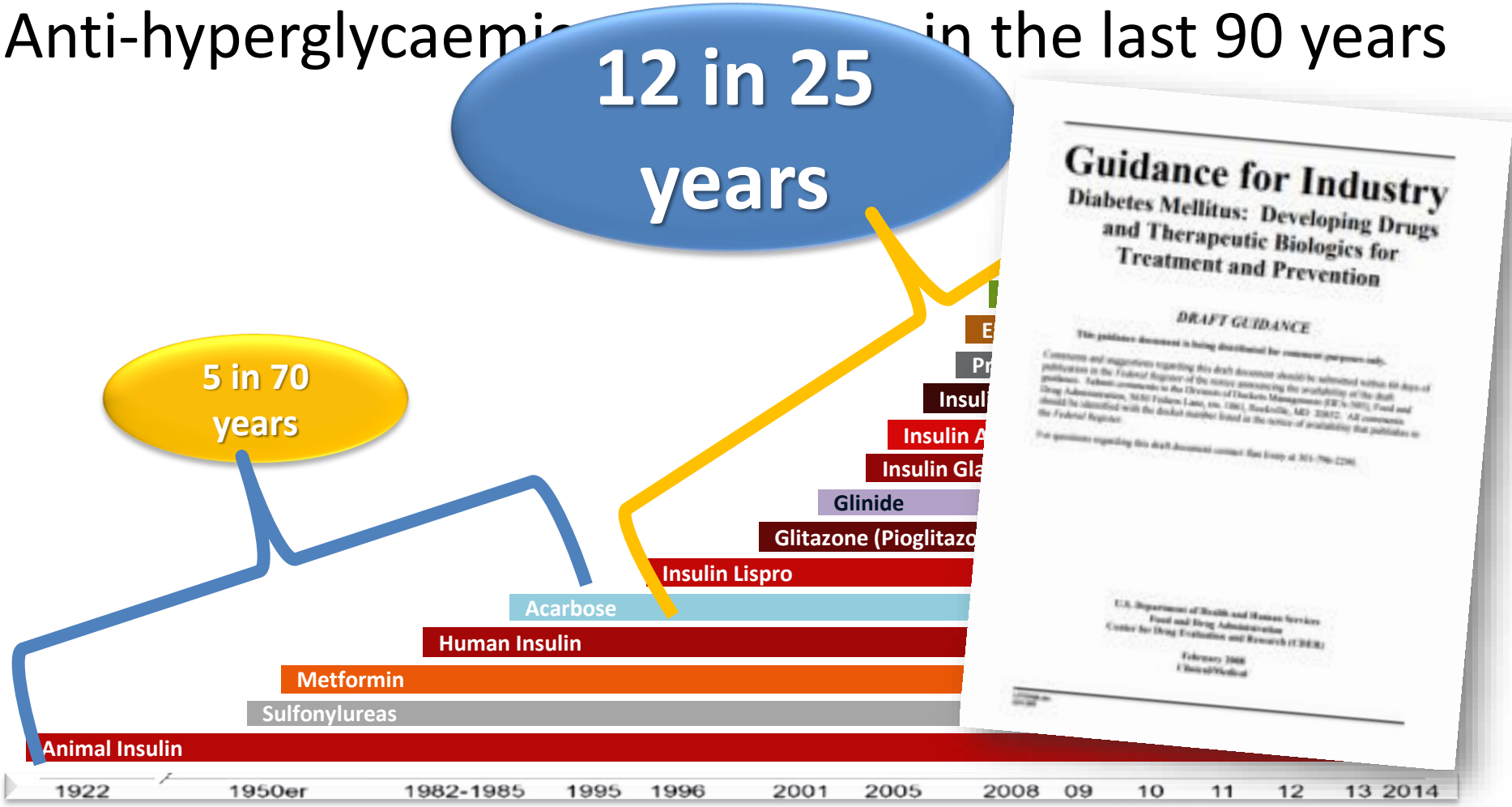
Facts

- Type 2 diabetes is associated with a high morbidity and mortality
- Tackling glucose only was not successful in reducing MACE and mortality
- Treatment induced adverse events (weight gain and hypoglycemia) were thought to wipe off benefits of glycemic control

Aim of Diabetes management



Anti-hyperglycaemi in the last 90 years



LAR, long-acting release; SGLT-2, sodium-glucose cotransporter-2. Adapted from: Schernthaner G. *Internist* 2012;53:1399–1410

Cardiovascular outcome trials

After years of frustrations...

EMPA-REG OUTCOME®

DECLARE

NVAS Program

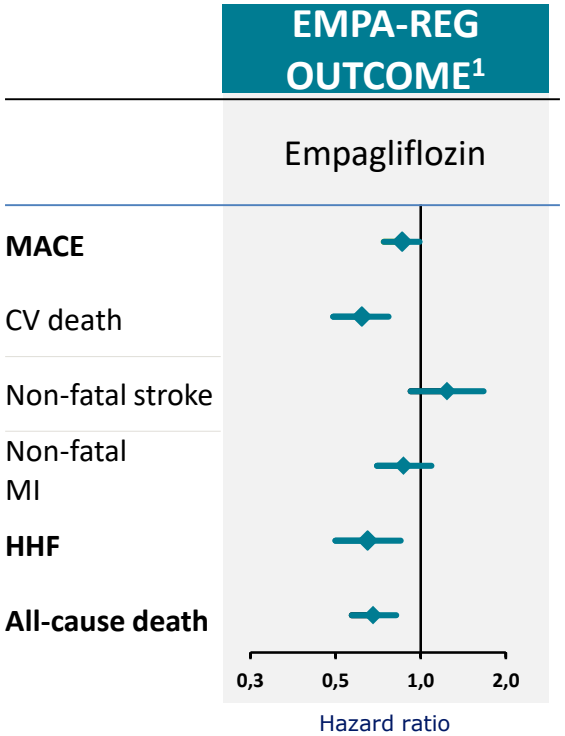
LEADER
Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

SUSTAIN
SEMAGLUTIDE UNABATED SUSTAINABILITY IN TREATMENT OF TYPE 2 DIABETES

HARMONY

Macrovascular risk reduction (=MACE)

SGLT-2 inhibitors



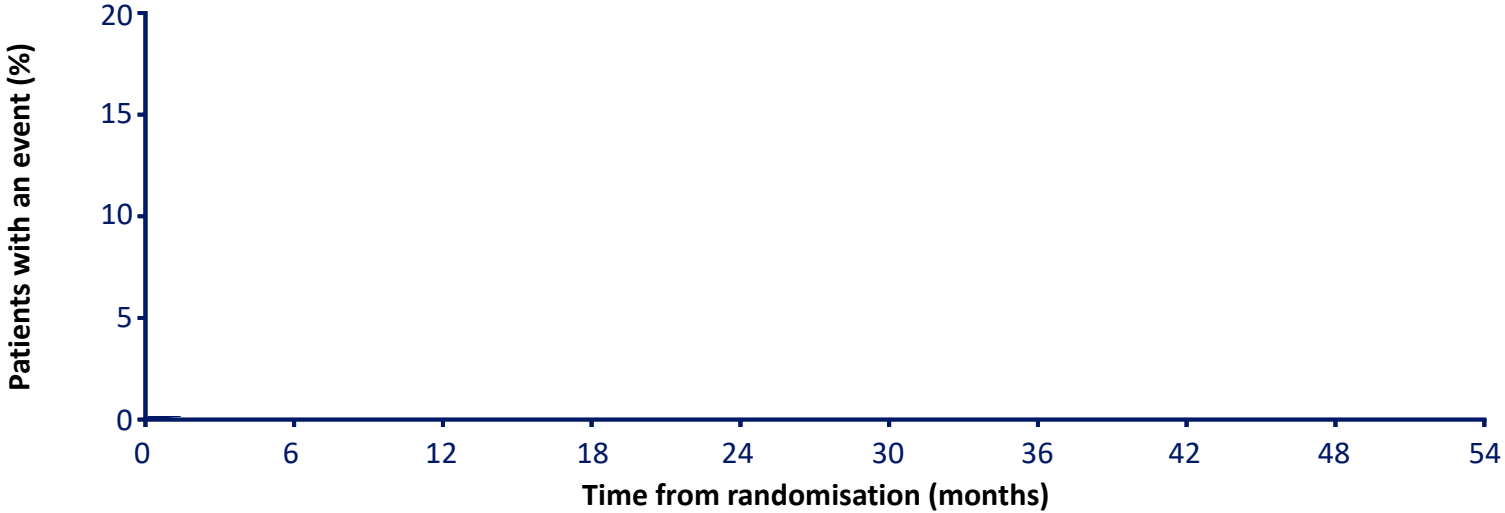
CV, cardiovascular; HHF, hospitalisation from heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction; SGLT-2, sodium–glucose co-transporter-2

1. Zinman B et al. *N Engl J Med* 2015;373:2117–2128; 2. Neal B et al. *N Engl J Med* 2017;377:644–657; 3. Wiviott SD et al. *N Engl J Med* 2018;doi: 10.1056/NEJMoa1812389 [Epub ahead of print]

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

MACE in GLP1-RA

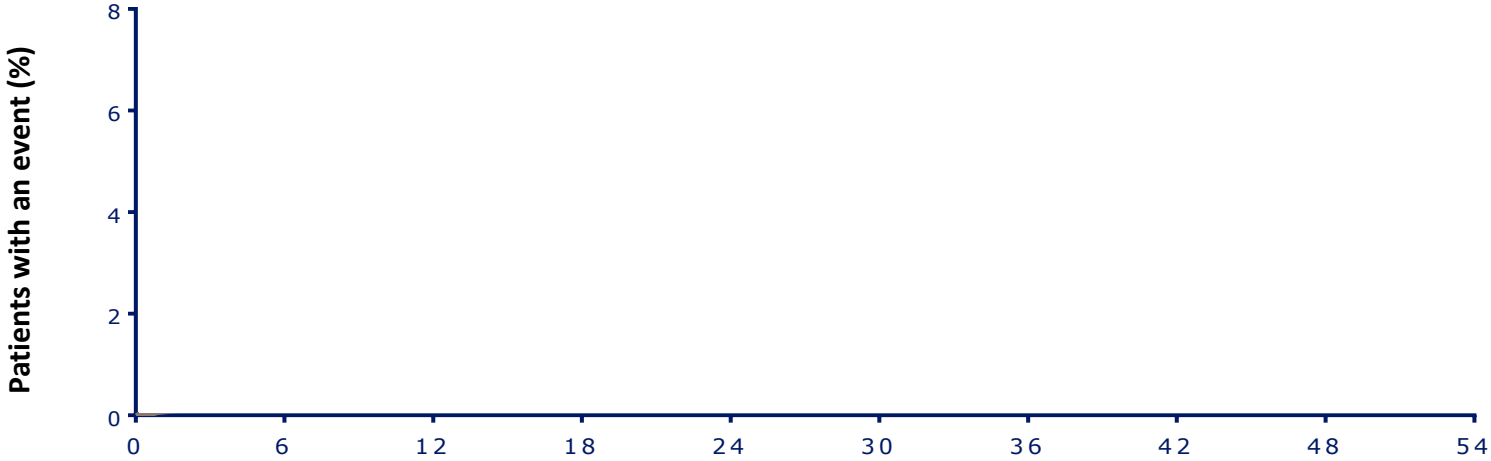
CV death, non-fatal myocardial infarction, or non-fatal stroke



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

The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months.
CI: confidence interval; CV: cardiovascular; HR: hazard ratio.
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

CV death



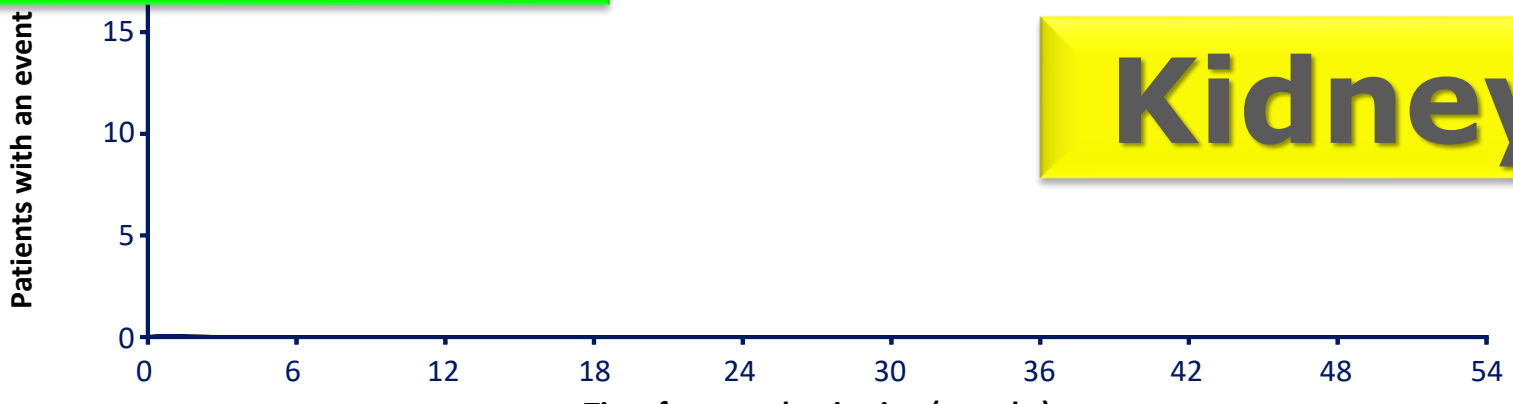
Patients at risk										
Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months.
CI, confidence interval; CV, cardiovascular; HR, hazard ratio.
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

All-cause death

SAFETY!

Kidney !



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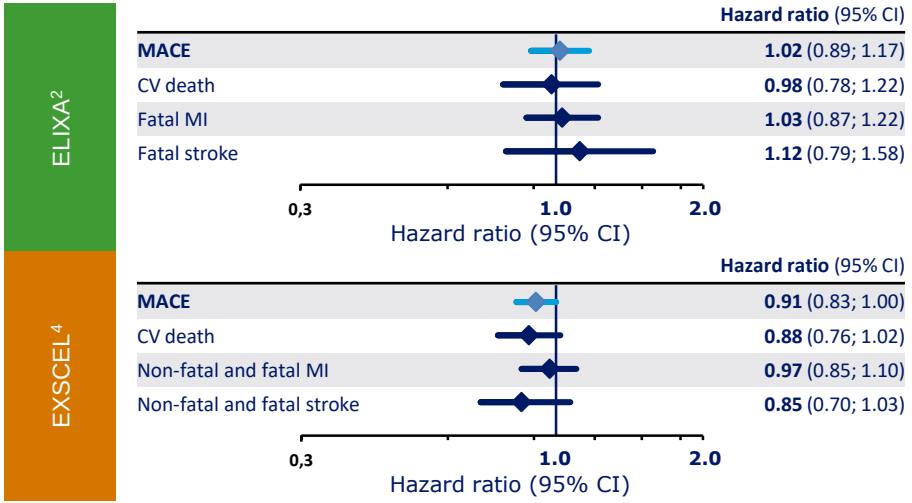
CI, confidence interval; HR, hazard ratio.
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

GLP-1 receptor agonists



CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction; NS, non significant

1. Marso SP et al. *N Engl J Med* 2016;375:311–322; 2. Pfeffer MA et al. *N Engl J Med* 2015;373:2247–2257; 3. Marso SP et al. *N Engl J Med* 2016;375:1834–1844; 4. Holman RR et al. *N Engl J Med* 2017;377:1228-39; 5. Hernandez AF et al. *Lancet* 2018;392:1519–1529; 6. Lilly press release (5th November 2018), available at: https://investor.lilly.com/node/39796/pdf; 7. Novo Nordisk press release (23rd November 2018), available from: https://www.novonordisk.com/media/news-details.2226789.html)

THESE ARE THE NEW FACTS

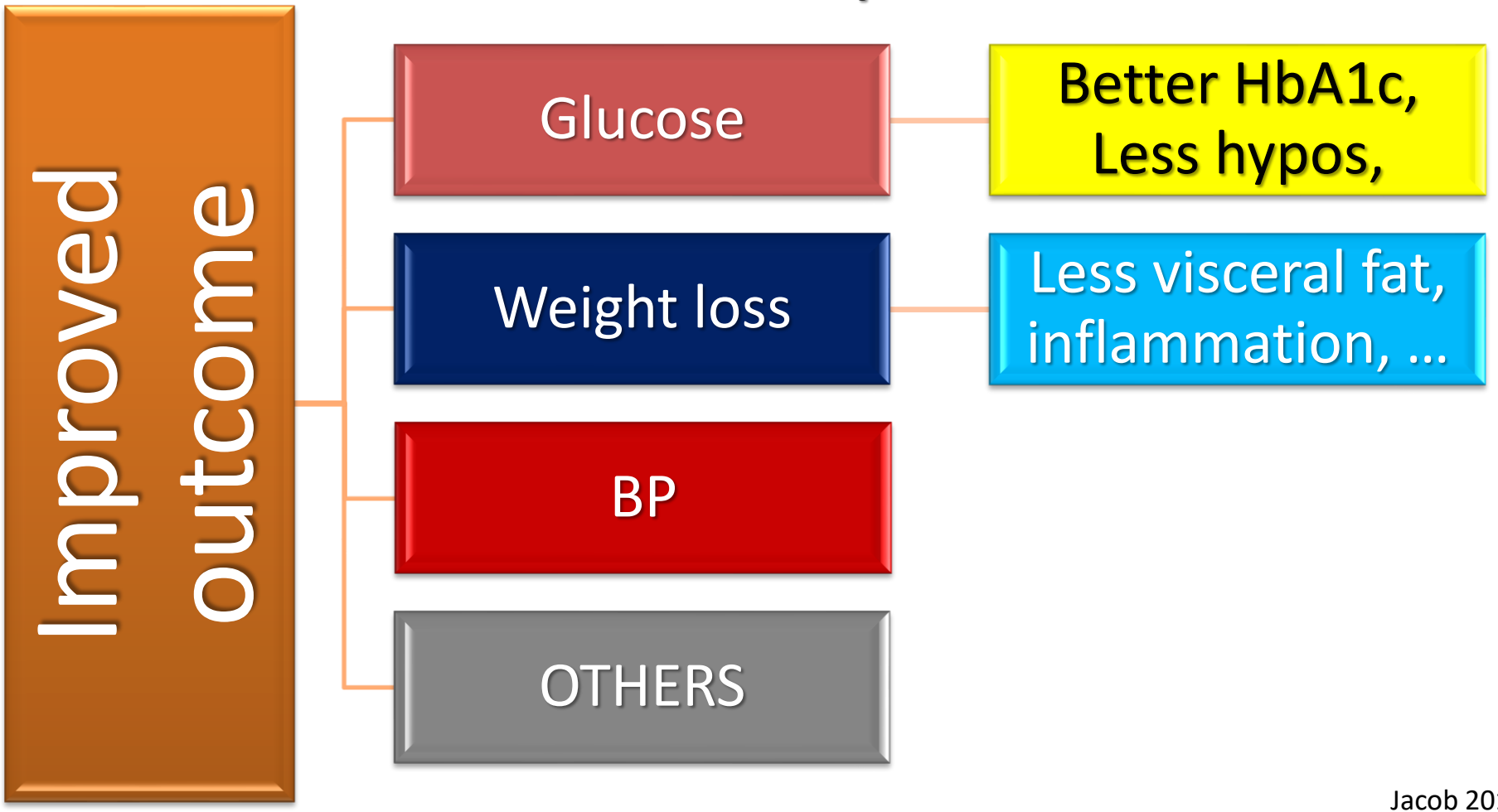
„Yes we can“ ….IMPROVE!

- ✓ ------ **MACE**
- ✓ ------ **CV and total mortality**
- ✓ ------ **Renal Outcome**

- In a short period of time
- In very sick people
- With best CV risk management
- And still elevated HbA1c…….

Jacob 2016

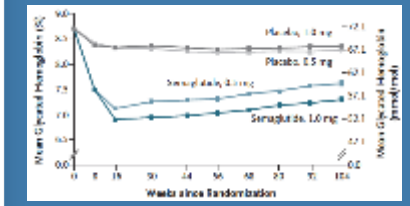
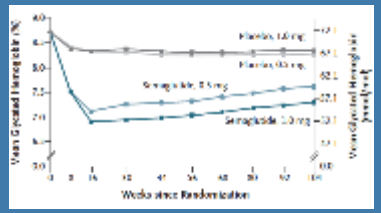
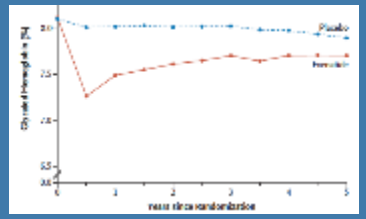
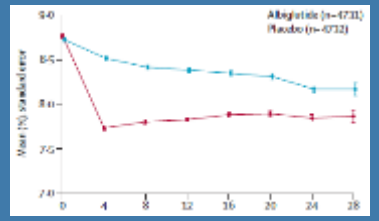
But HOW DO GLP1 RA improve outcome?



Jacob 2019

GLP-1 Receptor Agonists
Glycaemic control

HbA1c

Liraglutide	Semaglutide	Exenatide	Albiglutide
			
Treatment diff **– 0.4%** (95% CI – 0.45; – 0.34) *p*<0.001	Treatment diff **– 0.7%** (95% CI –0.80 ; –0.52) *p*<0.001	Treatment diff **– 0.5%** (95% CI – 0.57; – 0.50) *p*<0.001	Treatment diff **– 0.5%** (95% CI – 0.58; – 0.45)

TECOS-0,29%
EXAMINE-0,36%

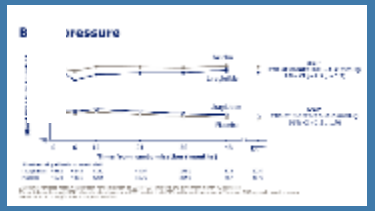
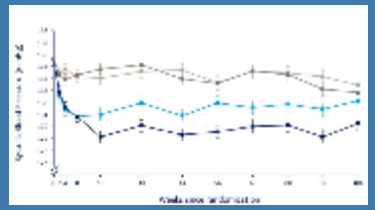
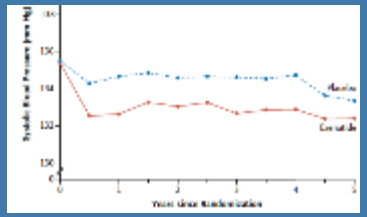
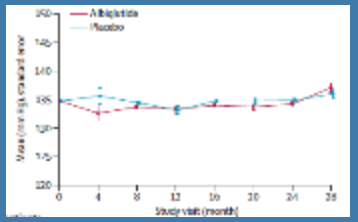
UKPDS, ACCORD, VADT, ADVANCE

Marso S P et al *N Engl J Med 2016; 375:311*
Marso S P et al *N Engl J Med 2016; 375:1834*
Holman R et al
Hernandez A F et al *N Engl J Med 2018; 392:1519*

GLP-1 Receptor Agonists

Impact on blood pressure

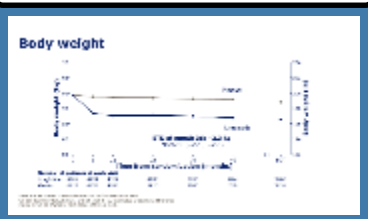
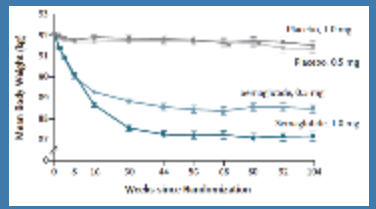
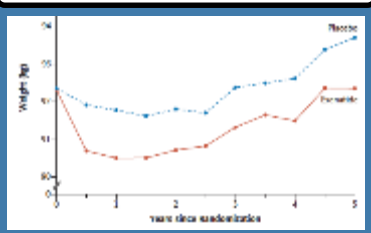
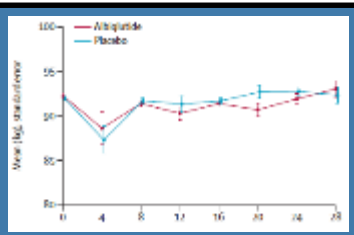
Systolic blood pressure

Liraglutide	Semaglutide	Exenatide	Albiglutide
			
Treatment diff **– 1.2 mmHg** (95% CI – 1.9; – 0.5) *p*<0.001	Treatment diff **– 2.6 mmHg** (95% CI –4.09 ; –1.08) *p*<0.001	Treatment diff **– 1.6 mmHg** (95% CI – 1.9; – 1.2) *p*<0.001	Treatment diff **– 0.7 mmHg** (95% CI – 1.40; – 0.06)

Marso S P et al *N Engl J Med 2016; 375:311*
Marso S P et al *N Engl J Med 2016; 375:1834*
Holman R et al *N Engl J Med 2017; 1228*
Hernandez A F et al *N Engl J Med 2018; 392:1519*

GLP-1 Receptor Agonists
Weight reduction

Impact on body weight

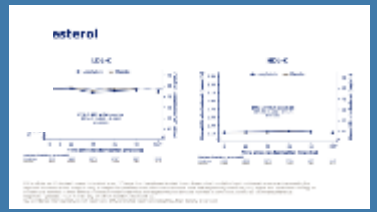
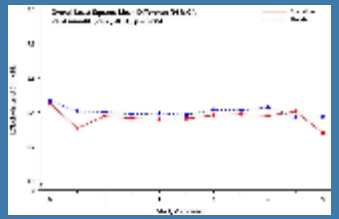
Liraglutide	Semaglutide	Exenatide	Albiglutide
			
Treatment diff **– 2.3 kg** (95% CI – 2.54; – 1.99) *p*<0.001	Treatment diff **– 4.3 kg** (95% CI –4.94 ; –3.75) *p*<0.001	Treatment diff **– 1.3 kg** (95% CI –1.4; –1.1) *p*<0.001	Treatment diff **– 0.8 kg** (95% CI - 1,06; – 0.60)

Marso S P et al *N Engl J Med 2016; 375:311*
Marso S P et al *N Engl J Med 2016; 375:1834*
Holman R et al *N Engl J Med 2017; 1228*
Hernandez A F et al *N Engl J Med 2018; 392:1519*

GLP-1 Receptor Agonists

Impact on dyslipidaemia

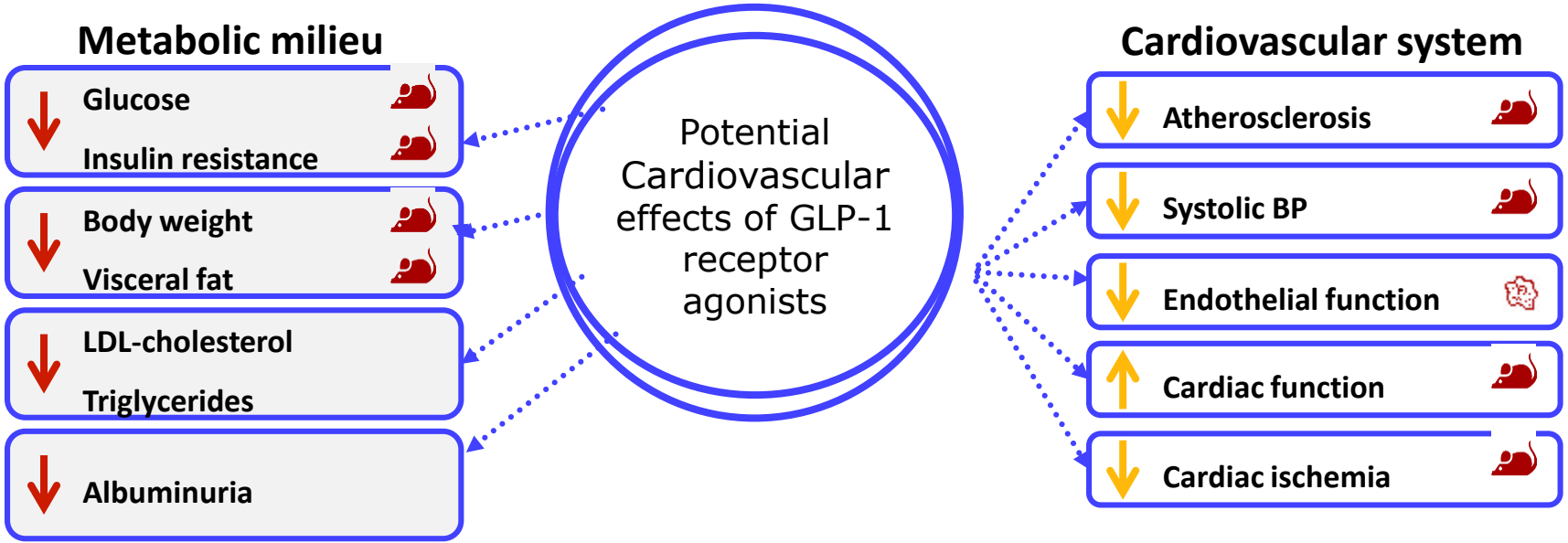
IMPROVED blood lipids

Liraglutide	Semaglutide	Exenatide	Albiglutide
			
Small decrease TC, LDL-C and TGs **Small increase** HDL-C	**Small decrease** TC, LDL-C and TGs **Small increase** HDL-C	**Small decrease** LDL-C and TGs HDL-C **No information**	**Not measured**

Marso S P et al *N Engl J Med 2016; 375:311*
Marso S P et al *N Engl J Med 2016; 375:1834*
Holman R et al *N Engl J Med 2017; 1228*
Hernandez A F et al *N Engl J Med 2018; 392:1519*

So ….what are the mechanisms?

Potential mechanisms of cardiovascular benefits of glucagon-like peptide-1 receptor agonists



BP, blood pressure; GLP-1, glucagon-like peptide-1; LDL, low-density lipoprotein

Adapted from: Lim et al. *Trends Endocrinol Metab* 2018;29:238–47

Cardiovascular Actions and Clinical Outcomes With Glucagon-Like Peptide-1 Receptor Agonists and Dipeptidyl Peptidase-4 Inhibitors

ABSTRACT: Potentiation of glucagon-like peptide-1 (GLP-1) action through selective GLP-1 receptor (GLP-1R) agonism or by prevention of enzymatic degradation by inhibition of dipeptidyl peptidase-4 (DPP-4) promotes glycemic reduction for the treatment of type 2 diabetes mellitus by glucose-dependent control of insulin and glucagon secretion. GLP-1R agonists also decelerate gastric emptying, reduce body weight by reduction of food intake and lower circulating lipoproteins, inflammation,

Michael A. Nauck, MD
Juris J. Meier, MD
Matthew A. Cavender, MD, MPH
Mirna Abd El Aziz, MD
Daniel J. Drucker, MD

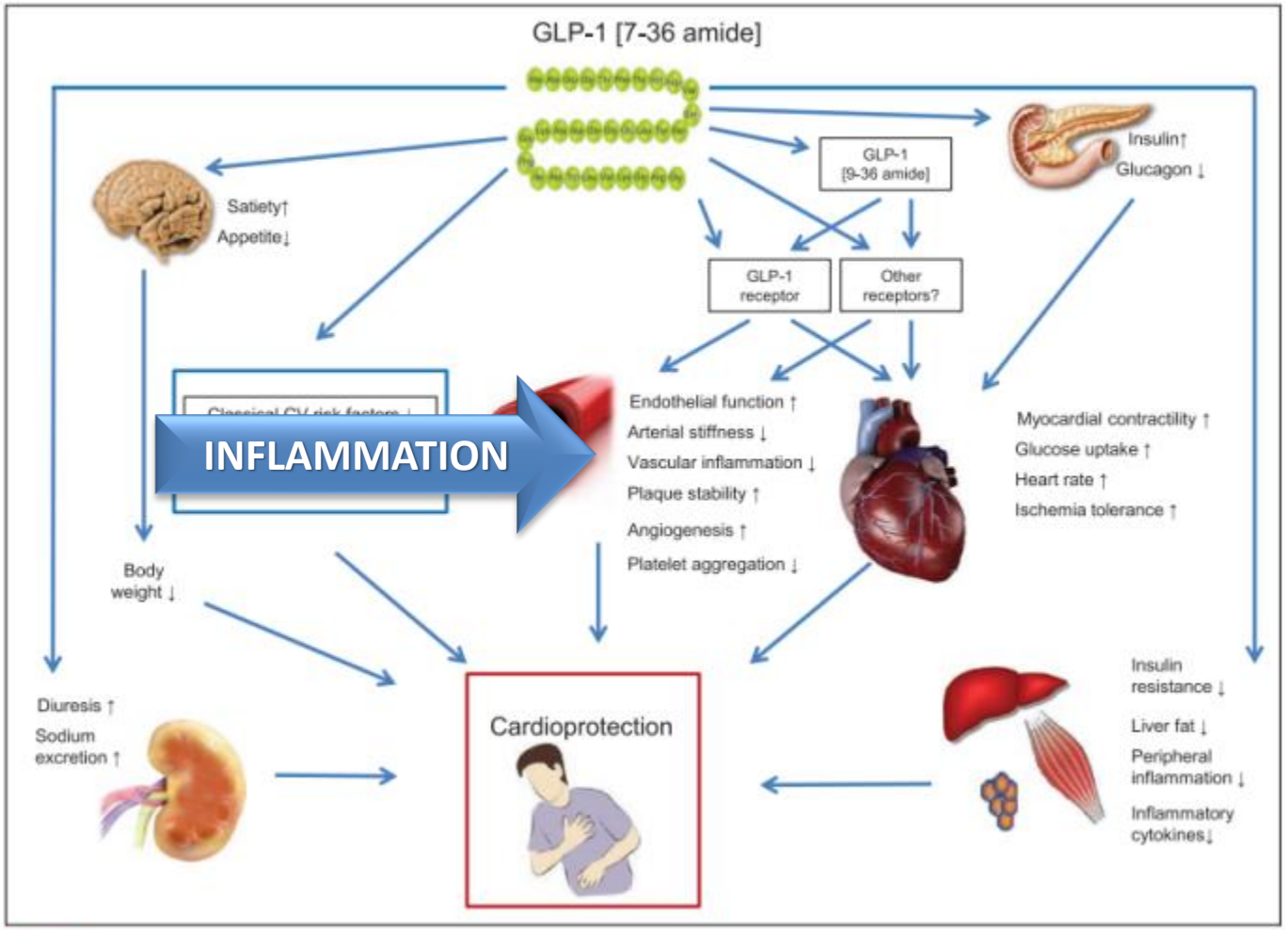


Figure 3. Potential mechanisms mediating a beneficial effect of glucagon-like peptide-1 (GLP-1) receptor agonists on reducing cardiovascular events.

Diabetologia
https://doi.org/10.1007/s00125-018-4729-5

CONSENSUS REPORT

Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Melanie J. Davies[1,2] · David A. D'Alessio[3] · Judith Fradkin[4] · Walter N. Kernan[5] · Chantal Mathieu[6] · Geltrude Mingrone[7,8] · Peter Rossing[9,10] · Apostolos Tsapas[11] · Deborah J. Wexler[12,13] · John B. Buse[14]

Established CVD

Hypos

Weight management

CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD) OR CHRONIC KIDNEY DISEASE (CKD)

NIAD before Insulin

Use principles in Figure 1

TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

Use metformin unless contraindicated or not tolerated

If not at HbA_{1c} target:

- Continue metformin unless contraindicated (remember to adjust dose/stop metformin with declining eGFR)
- Add SGLT2i or GLP-1 RA with proven cardiovascular benefit[1] (See below)

If at HbA_{1c} target:

- If already on dual therapy, or multiple glucose-lowering therapies and not on an SGLT2i or GLP-1 RA, consider switching to one of these agents with proven cardiovascular benefit[1] (See below)

OR reconsider/lower individualised target and introduce SGLT2i or GLP-1 RA

OR reassess HbA_{1c} at 3 month intervals and add SGLT2i or GLP-1 RA if HbA_{1c} goes above target

Take home message

OLD view

MAIN AIM
Early and strict control of HbA1c (…does not matter HOW, the lower the better)

BUT

No EVIDENCE for a better OUTCOME

„GLUCO-CENTRIC“

NEW

Improvement of CV, renal outcome, reduced mortality!... Better life expectancy

So far only a few substrates could show that

„Outcome-oriented“

It does not matter
HOW LOW WE GO

But it matters
HOW WE GO LOW

Change of paradigm needed

TREAT THE PATIENT
NOT HIS SUGAR
REDUCE THE CV RISK
NOT ONLY THE HBA1C

Ralph de Fronzo