Professor Russell Scott

Professor of Medicine

Christchurch School of Medicine & Health Sciences

University of Otago

Sunday, August 11, 2019

(Plenary)

7:15 - 8:25 Novartis Breakfast Session - Practical strategies for improving T2D control

Important Updates on CVD and Heart Failure and Type 2 DM

Russell SCOTT

AUGUST 2019

Simple case

- Male aged 62: weight 74 kg (BMI 31) and unchanged for years; ethnicity Asian; real estate
- DM 12 years
  - Detected on health check at 50 yrs
    - metformin 2 g/day + Gliclazide now at 160 mg/day in divided doses
  - BP systolic 130-160 mmHg usually
  - keeps active in house but doesn't do much other activity.. To busy; not enjoyable
  - No maculopathy or retinopathy (retinal screening); annual reviews fine
  - Non smoker, no alcohol
- HbA1c always around 60 mmol/mol, improved with the increase of the SU 2 years ago.
- on atorvastatin (LDL 1.8 mmol/l); cilazapril 2.5 mg/day; takes aspirin
- U Alb 20-35 g/mol crn (fluctuates, negative at Dx)
- eGFR 50 ml/min (stage 3a, but dropping slowly)
- Abnormal ECG with non r wave progression V2-V4; ?anteroseptal
- Never been in hospital

Case continued:

- Summary: DM 12 years with CKD, albuminuria, CAD likely and high BP

Prevent, delay and treat complications in this man with type 2 DM: what we do

- Glucose control is a prime focus in diabetes care from outset
    - Close relationship to microvascular complications of eye, nerve and renal change
- But what do the studies tell us about HbA1c control as it relates to cardiovascular health

Glucose intensification and CVD outcomes

- There are 3 main long term (5-7.5 years) glucose intensification trials in those with established DM.
  - VADT
  - ACCORD
  - ADVANCE

- And UKPDS in those with recently diagnosed DM

- Non significant CVD benefit at end of trials
  - though event separation did occur, particularly UKPDS

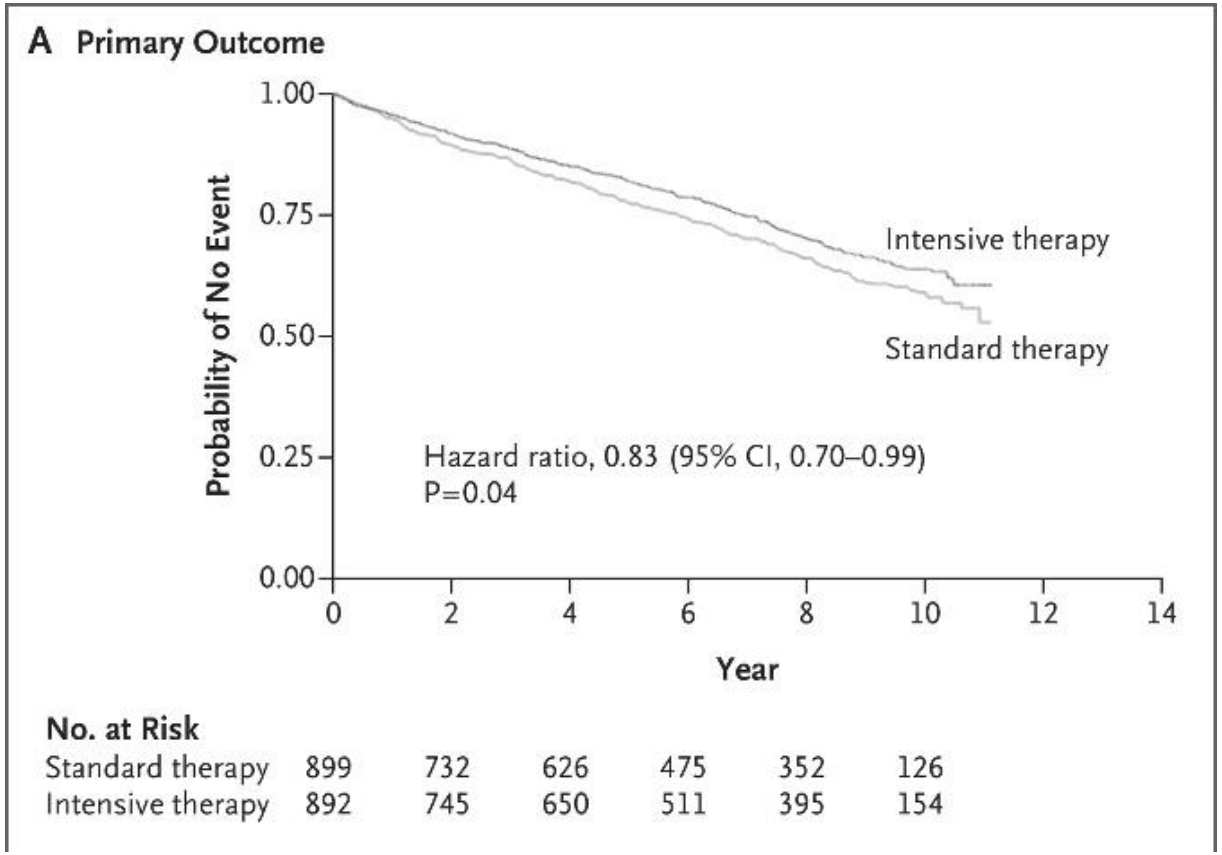
- Extended follow-up of CVD outcomes for all trials available

VA Diabetes trial follow up for CVD events (median 9.8 yrs)

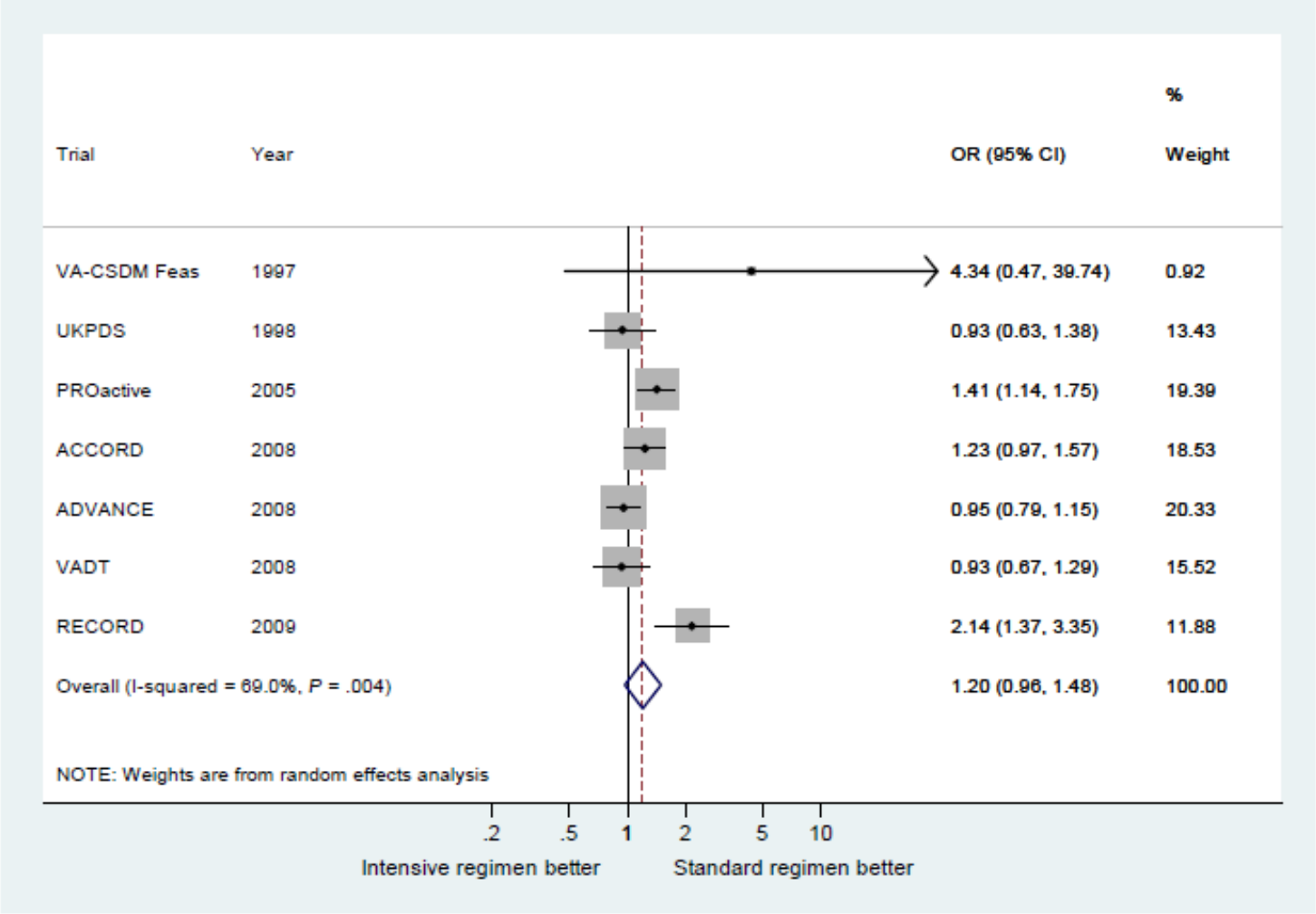
VA DM: primary outcome = time to the first major cardiovascular event (a composite of MI, stroke, new or worsening congestive heart failure, amputation for ischemic gangrene, or death from cardiovascular causes).

The ACCORD trial showed a significant reduction in the rate of nonfatal cardiovascular events in a follow-up of its study population, but that benefit was offset by an increase in mortality in the original trial.

In contrast, no reduction in the rate of cardiovascular events or in mortality was found in a follow-up of the ADVANCE trial.



Intensive glucose control has no impact on risk of heart failure; 7 studies. Am Heart J: 2011;162, 938



Probability of HF-related events with intensive glucose-lowering versus standard treatment. The size of the markers (squares) is approximately proportional to the statistical weight of each trial.

Summary: Tight glucose control and CVD

- Treating intensively gives disappointing CVD outcomes even out to 10 years
  - Legacy effect of hyperglycemia
  - Adverse effects of lipids, renal disease, hypertension, high body weight, diet, exercise lack ….

- Take away message:

  HbA1c control <u>still</u> needs to be done

  get the best control you can from the onset of DM

  Think of composite Renal, Eye, Nerve, CVD, psychological gains

What about treatment with agents not used in those earlier trials?

Pioglitazone and cardiovascular outcomes

Nine trials with 12,026 participants in meta-analysis.

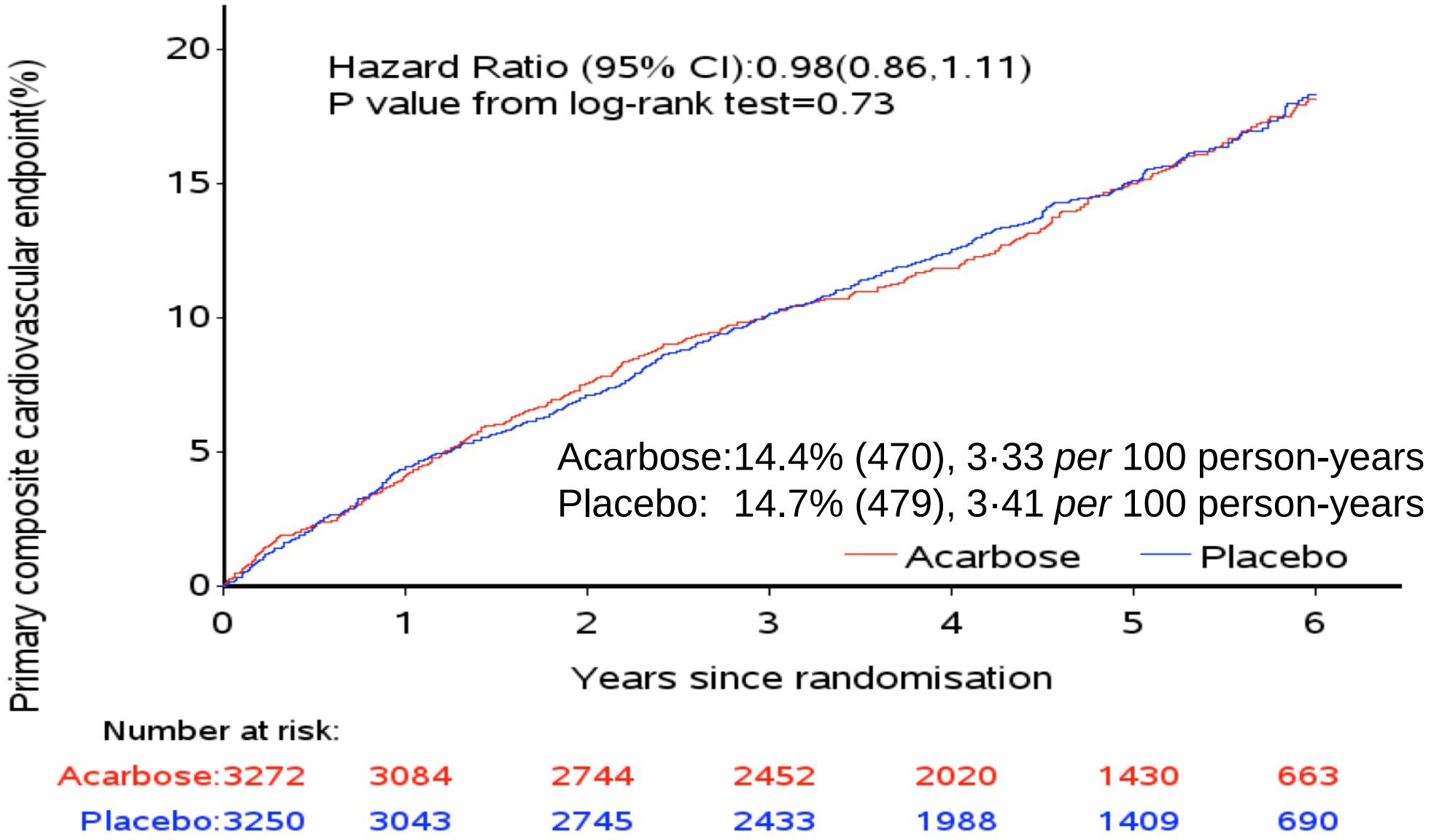
Pioglitazone therapy was associated with a lower risk of MACE in patients with diabetes (RR 0.83, 95% CI 0.72 to 0.97) pre-diabetes or insulin resistance (RR 0.77, 95% CI 0.64 to 0.93).
BUT:

Heart failure (RR 1.32; CI 1.14 to 1.54)
Bone fracture (RR 1.52, 95% CI 1.17 to 1.99)
Oedema (RR, 1.63; CI 1.52 to 1.75)
weight gain (RR 1.60; CI 1.50 to 1.72)

- All worse in pioglitazone group.

Pioglitazone and cardiovascular outcomes in patients with insulin resistance, pre-diabetes and type 2 diabetes: a systematic review and meta-analysis: BMJ Open 2017;7:e013927. doi:10.1136/bmjopen-2016-013927

ACE study with acarbose: CVD events



DPP-4 inhibitors
Vildagliptin funded in NZ

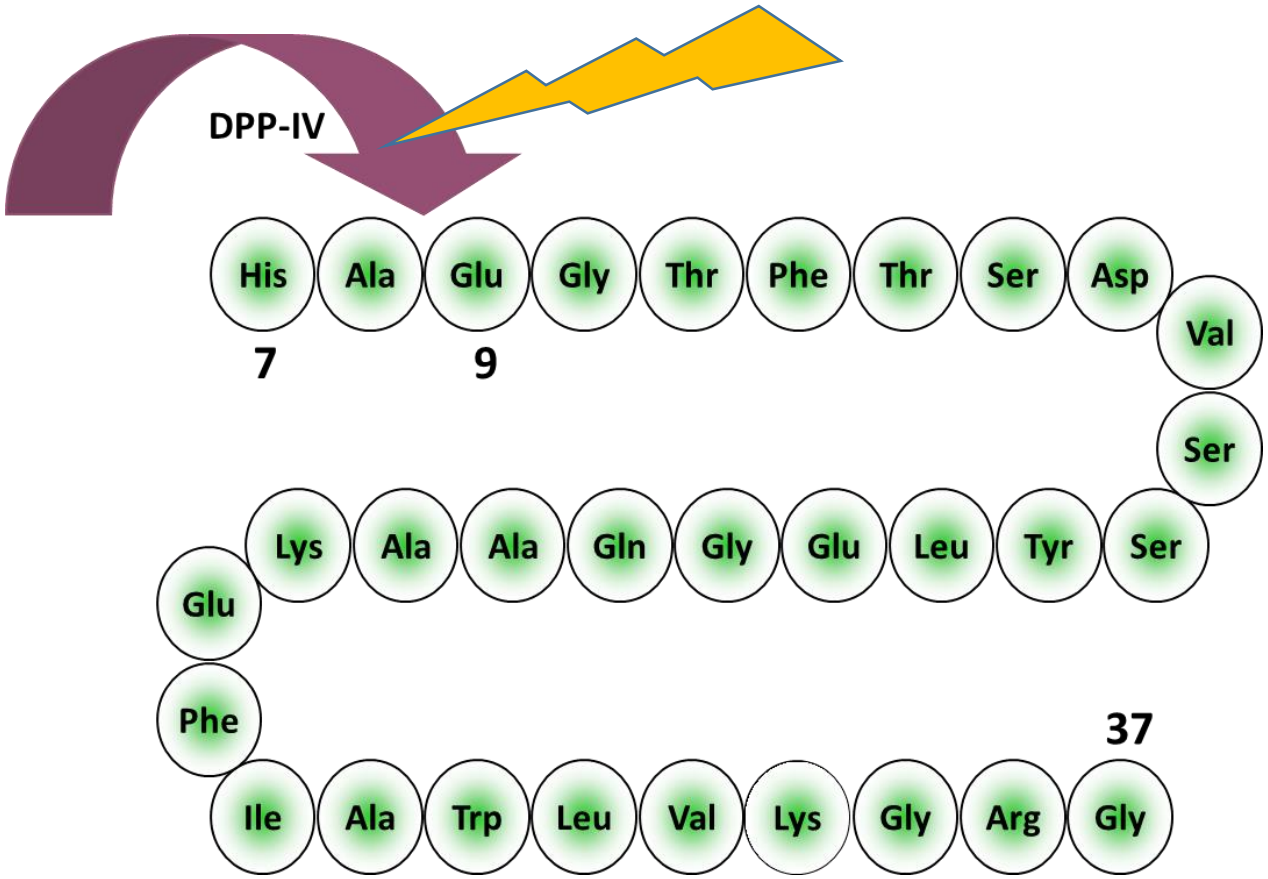
- This class has been around since 2006

- DPP4 agents have benefit over SU (no weight gain, no hypoglycaemia)

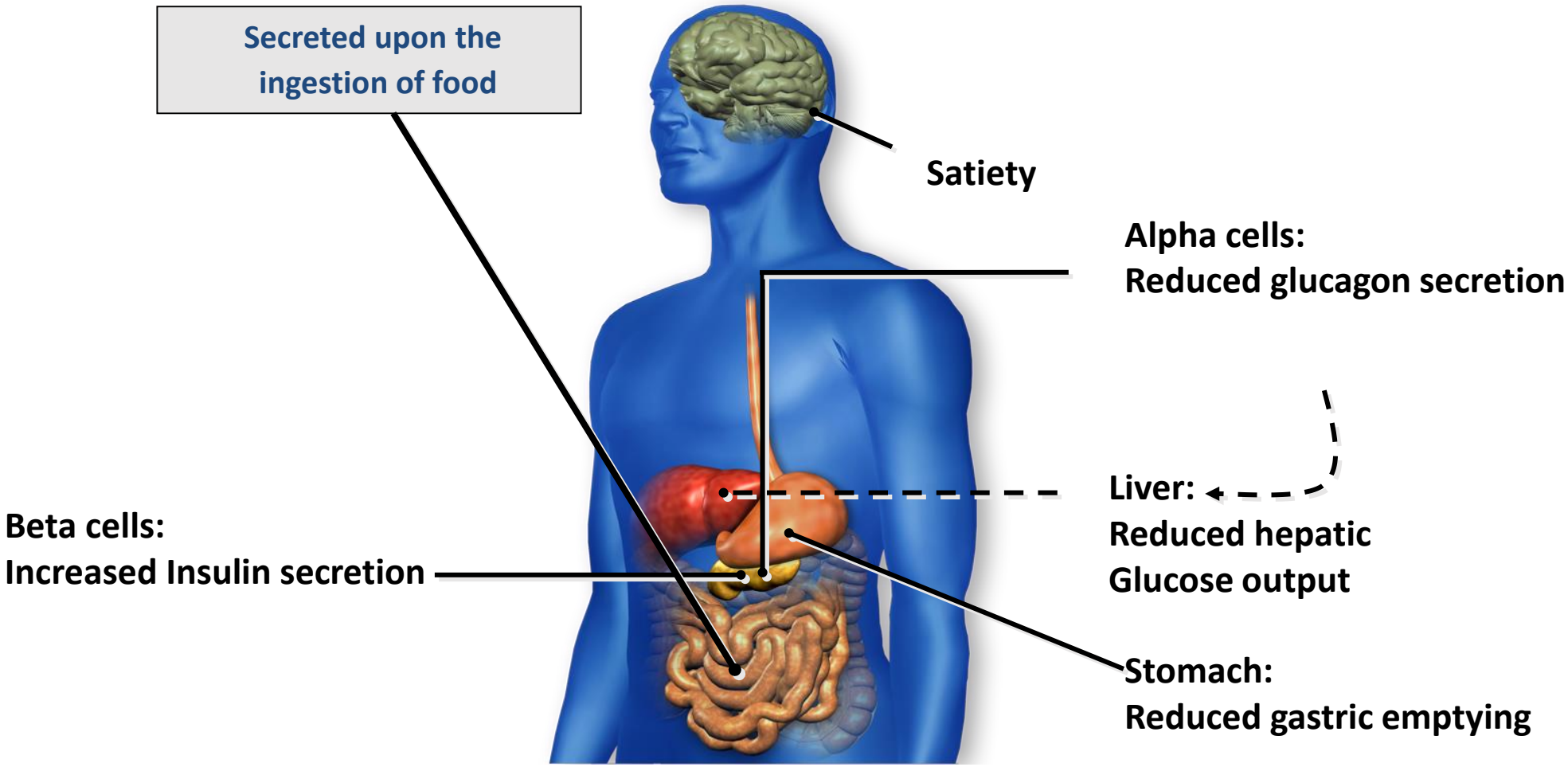
  SU do have suspicious CVD adversity but impossible to prove

DPP-4 inhibitors

- Prevent rapid degradation of the gut peptide GLP-1 (amongst others)



GLP-1, GIP …. gut peptides and glucose metabolism



DPP4 inhibitor cardiovascular outcome trials ….. huge disappointment

- The main CVD outcome studies were not superior

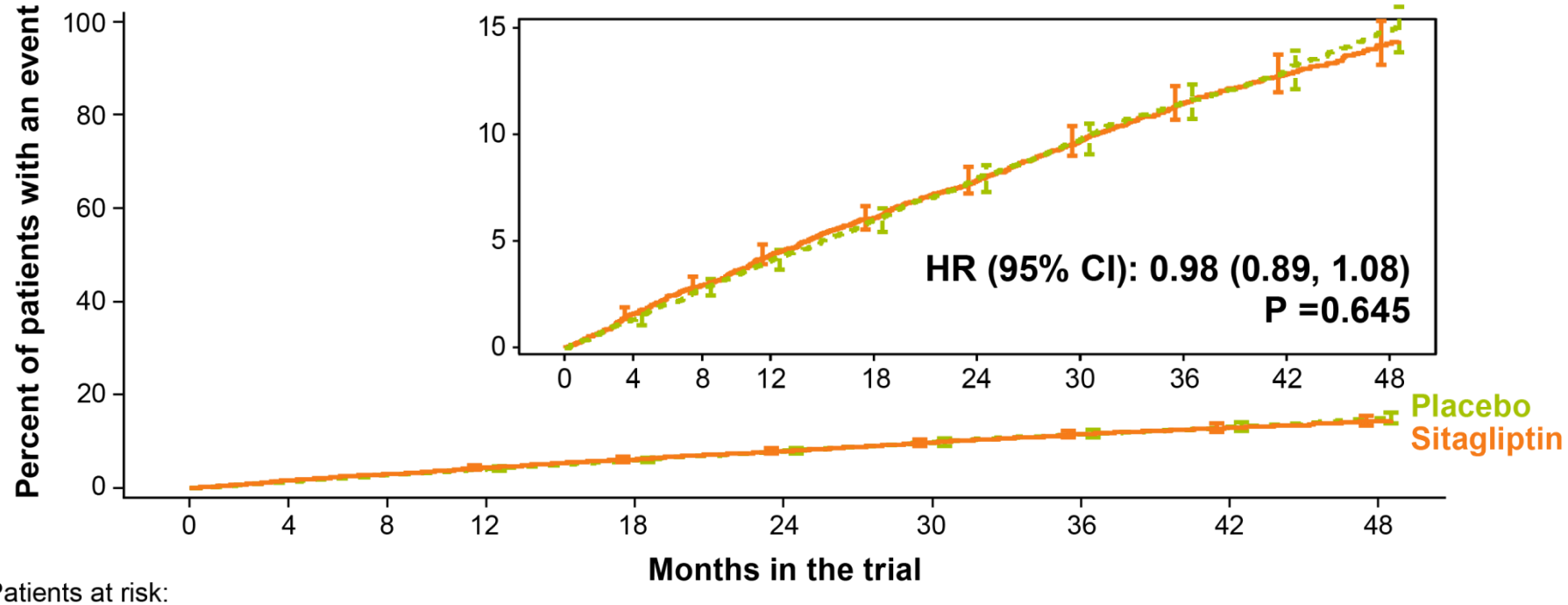
  (Yes: non inferior ….. comparing to standard of care but not the result needed after decades of expectant hope for a new CVD diabetes drug)

  - TECOS (sitagliptin)
  - EXAMINE (alogliptin)
  - CAROLINA (linagliptin)
  - CARMELINA (linagliptin)

  - And in SAVOR-TIMI (saxagliptin) CHF event rates actually increased (3.4 vs 2.6%)

TECOS: Primary Composite Cardiovascular Outcome*

ITT Analysis for Superiority



Patients at risk:										
Sitagliptin	7,332	7,131	6,937	6,777	6,579	6,386	4,525	3,346	2,058	1,248
Placebo	7,339	7,146	6,902	6,751	6,512	6,292	4,411	3,272	2,034	1,234

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

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

So: the big brother of GLP1 oral agonist: LIZARD SPIT

Exenatide

Synthetic version of salivary protein found in the Gila monster

~ 50% amino acid sequence identity with human GLP-1

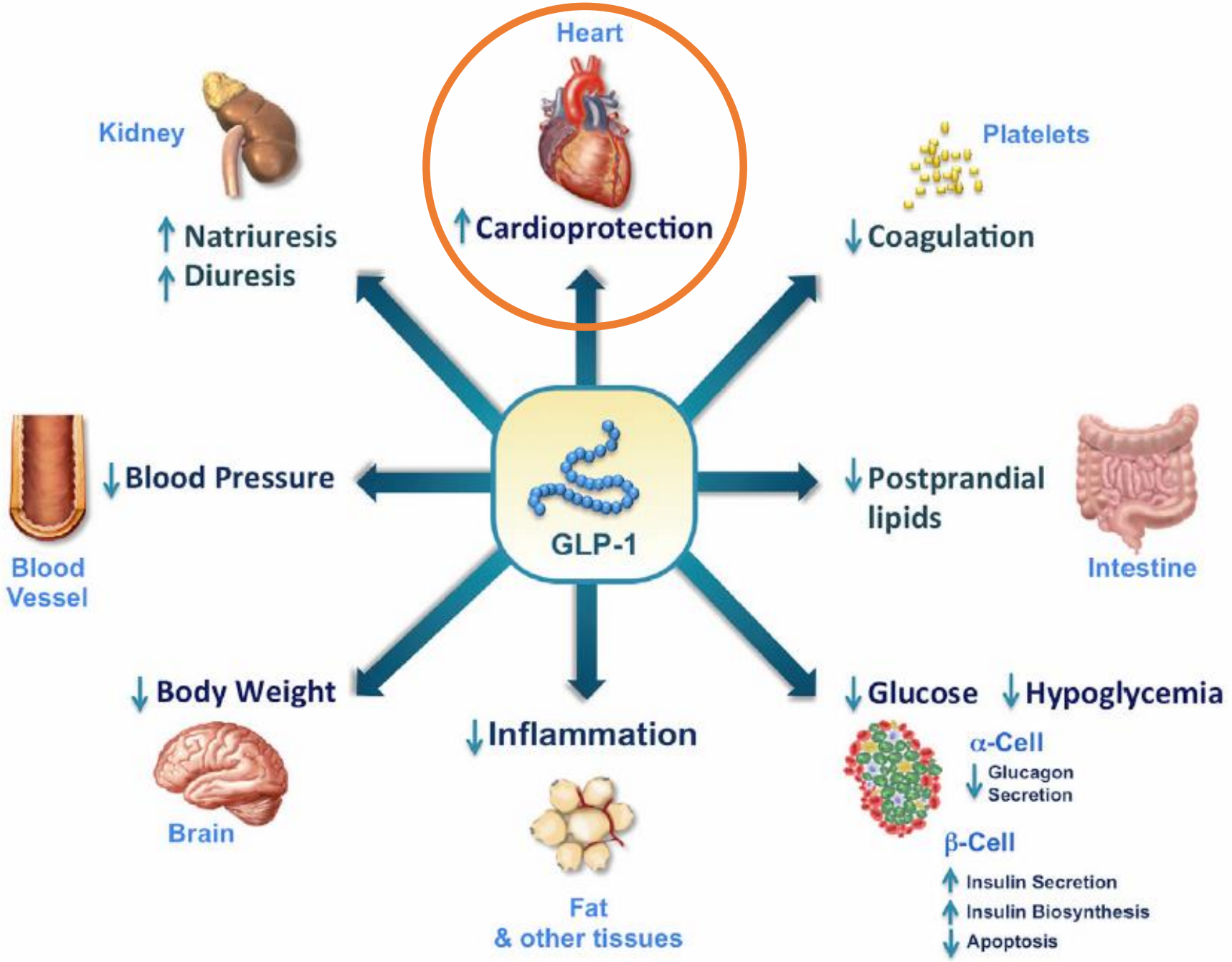
Binds to known human GLP-1 receptors on beta cells and other tissues including heart and brain

Resistant to DPP-IV inactivation

inject twice daily or weekly with long acting version

GLP1 levels many times higher than achieved with DPP4 oral agents

GLP-1 agonist effects



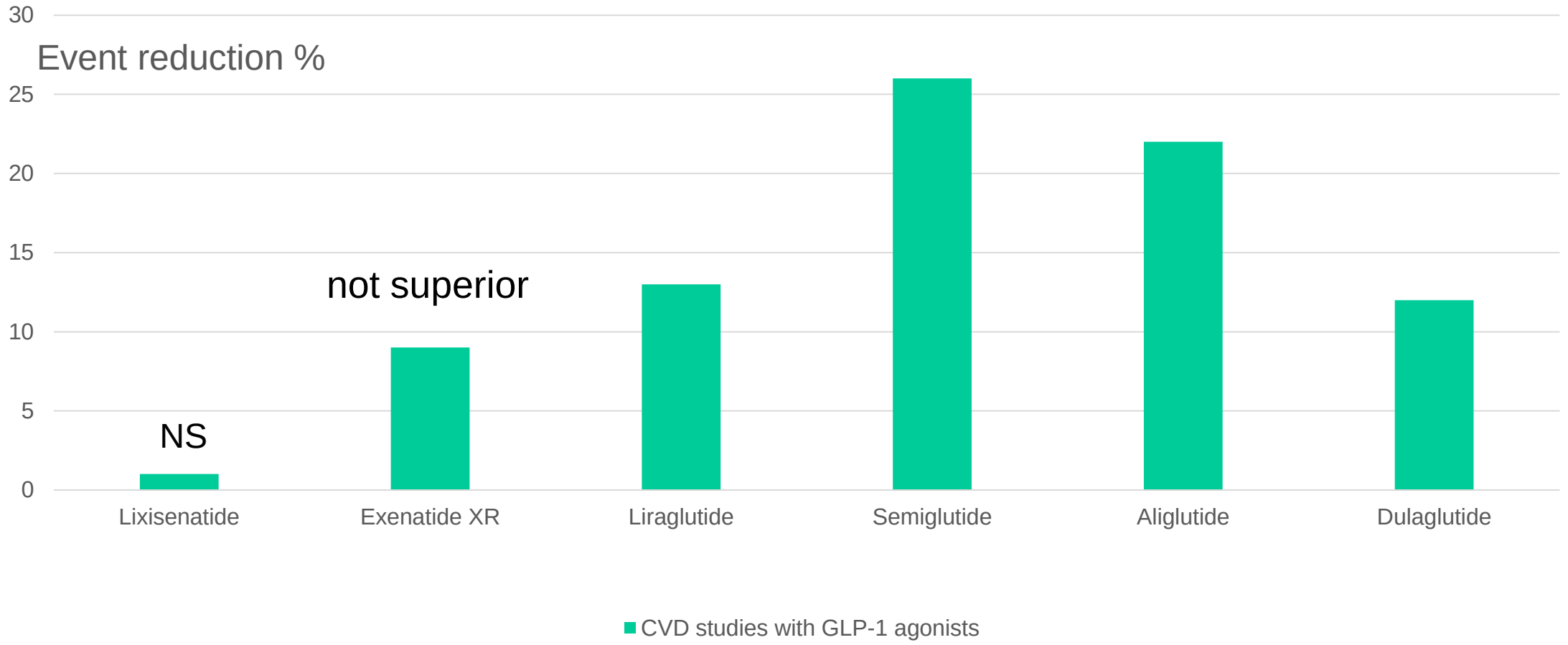
GLP-1 analogues of Lizard spit

- Exenatide (patients can develop high titre antibodies)
- Exenatide Long acting analogue
- Lixisenatide (not in stage 4 ckd)
- Liraglutide (long acting)
- Semaglutide (long acting; also available as oral agent now)
- Albuglutide (long acting 5-8 days)
- Dulaglutide (long half life)
- (Efpeglenatide)

  - 6 trials completed for CVD outcomes (all short duration)
  - Liraglutide licenced in UK for weight loss (called Saxenda)

2019 summary for GLP-1 trials:

MACE 3: CVD death, non fatal MI, non fatal stroke



NNT is 45-66 over 24-36 months

GLP-1 RA class effects

- No differences in
  - Heart Failure hospitalisation
  - Hypoglycaemia
  - Pancreatitis
  - Pancreatic cancer

2019: The guidelines change to reflect these data for GLP 1 agonists

A very strong statement from EASD and ADA

(to be detailed a few slides further on)

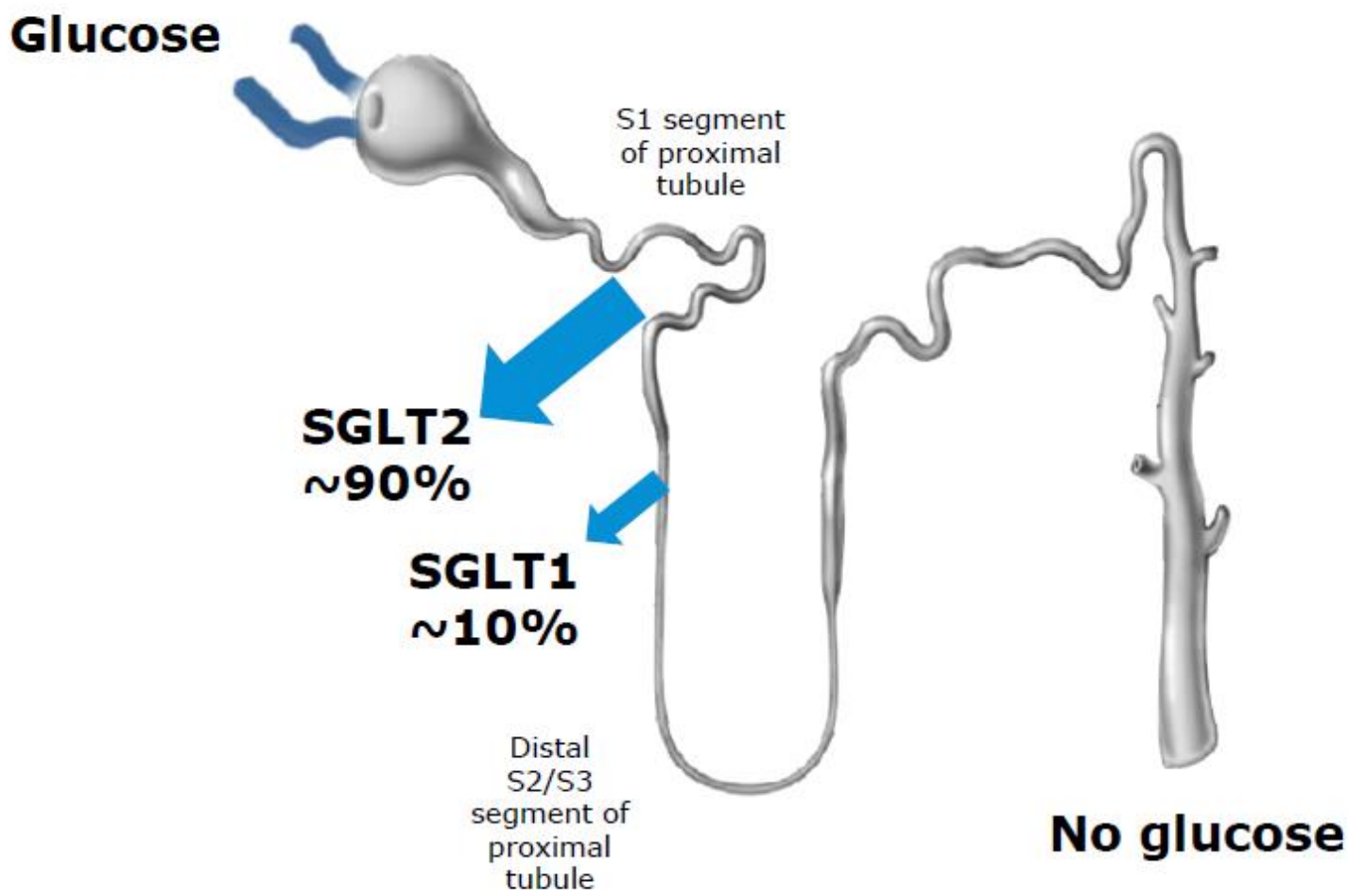
In NZ we have Exenatide immediate release and slow release Bydureon available non funded ($270-300 per month)

Liraglutide can also be obtained but I haven’t tried to get it yet.

Sodium Glucose Co-transporter 2 (SGLT2) inhibition:

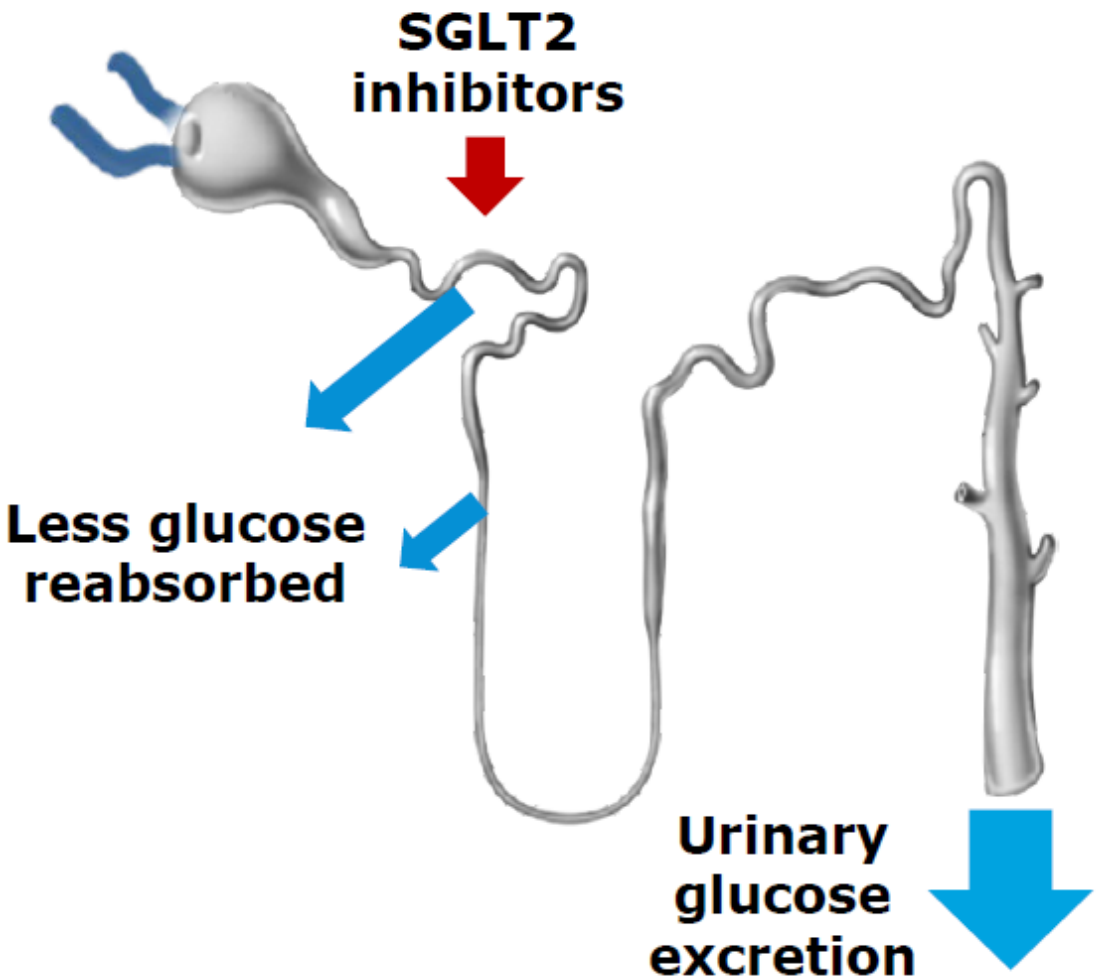
A newer oral therapy that will further change our practice in type 2 DM

Normal Renal Glucose Metabolism



Adapted from Bays H. *Curr Med Res Opin*. 2009;25(3):671-681.

SGLT2 Inhibition



- Combined blockade
- SGLT2 plus partial SGLT1
  - Sotaglifozin

Known actions

- Lowers glucose similar to other agents but more durable
- Lowers BP
- Reduces inflammatory markers and alters organ fibrotic change
- Change lipids
- Lowers weight
- Lowers uric acid
- Natriuretic effect without intravascular contraction.
- Increases Erythropoetin
- Less arterial stiffness
- Reduces albuminuria and preserves eGFR

- Effect attenuates with renal compromise

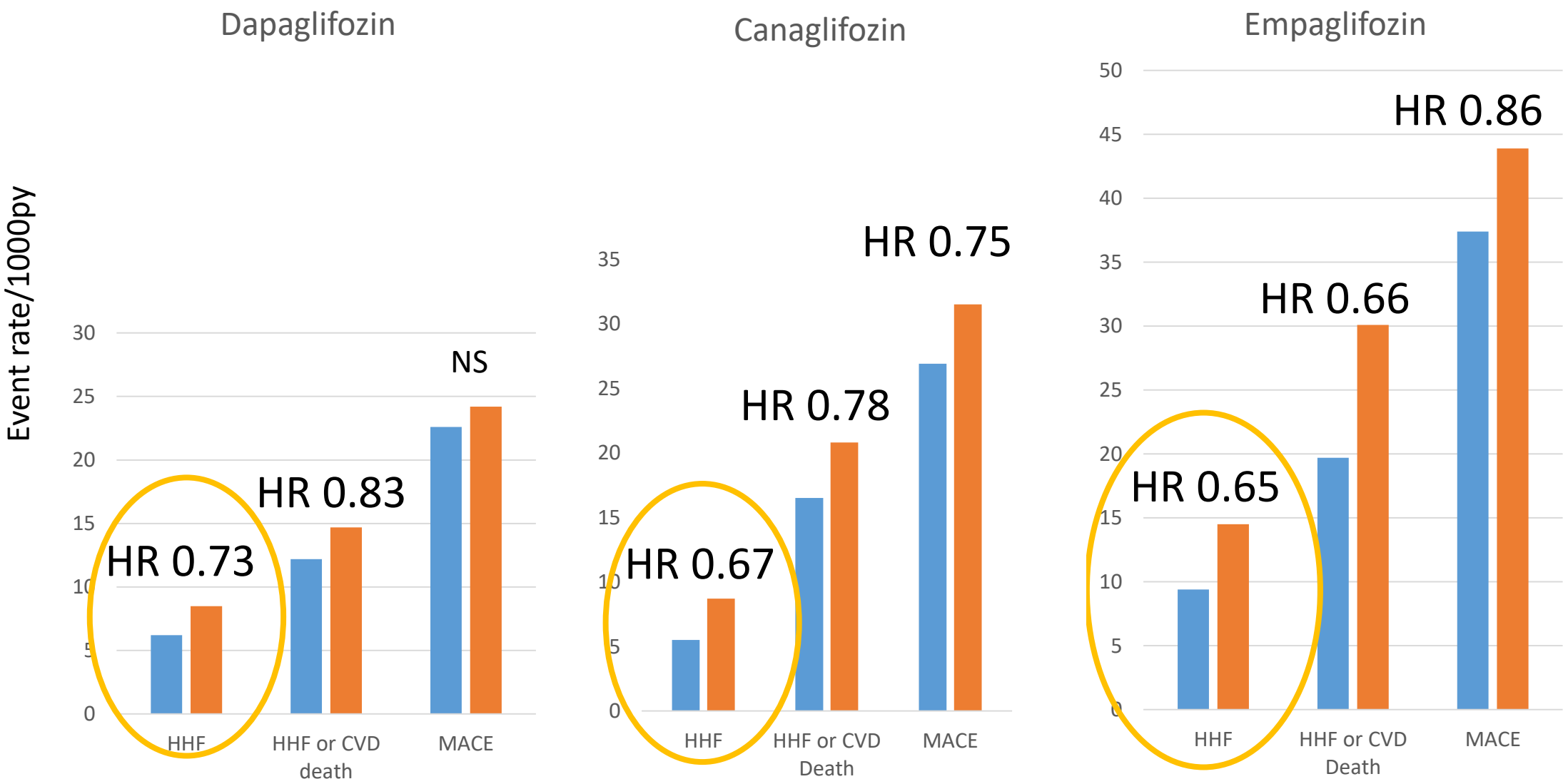
SGLT2 CV outcome Trials

- Canvas (canaglifozin)
- Empa Reg (empaglifozin)
- Declare-TIMI (dapaglifozin: largest trial)

  dapaglifozin available in NZ

- And just last month Credence study

MACE and Heart Failure results



Cardiorenal Outcomes in the CANVAS, DECLARE-TIMI 58, and EMPA-REG OUTCOME Trials: A Systematic Review (Rev. Cardiovasc. Med. 2018; 19(2): 41--49

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

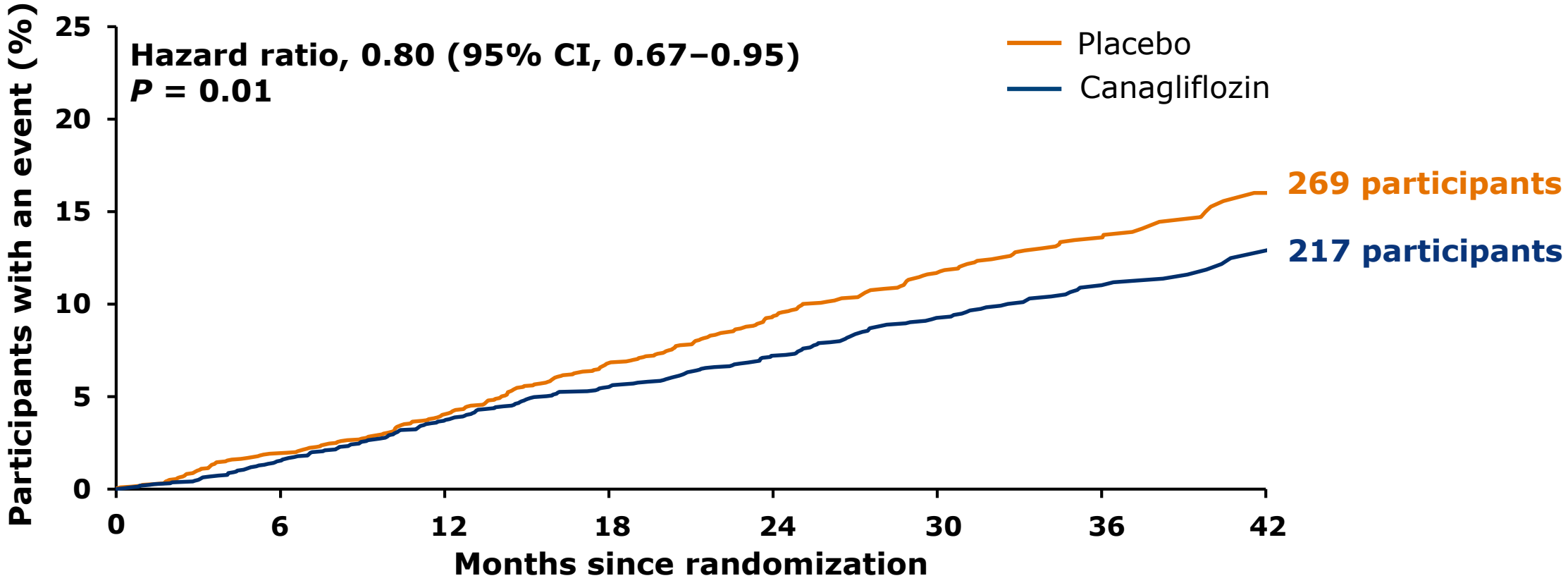
V. Perkovic, M.J. Jardine, B. Neal, S. Bompoint, H.J.L. Heerspink, D.M. Charytan, R. Edwards, R. Agarwal, G. Bakris, S. Bull, C.P. Cannon, G. Capuano, P.-L. Chu, D. de Zeeuw, T. Greene, A. Levin, C. Pollock, D.C. Wheeler, Y. Yavin, H. Zhang, B. Zinman, G. Meininger, B.M. Brenner, and K.W. Mahaffey, for the CREDENCE Trial Investigators*

Slides available at www.georgeinstitute.org and http://med.stanford.edu/sccr.html

Paper and editorial available at www.nejm.org

CREDENCE

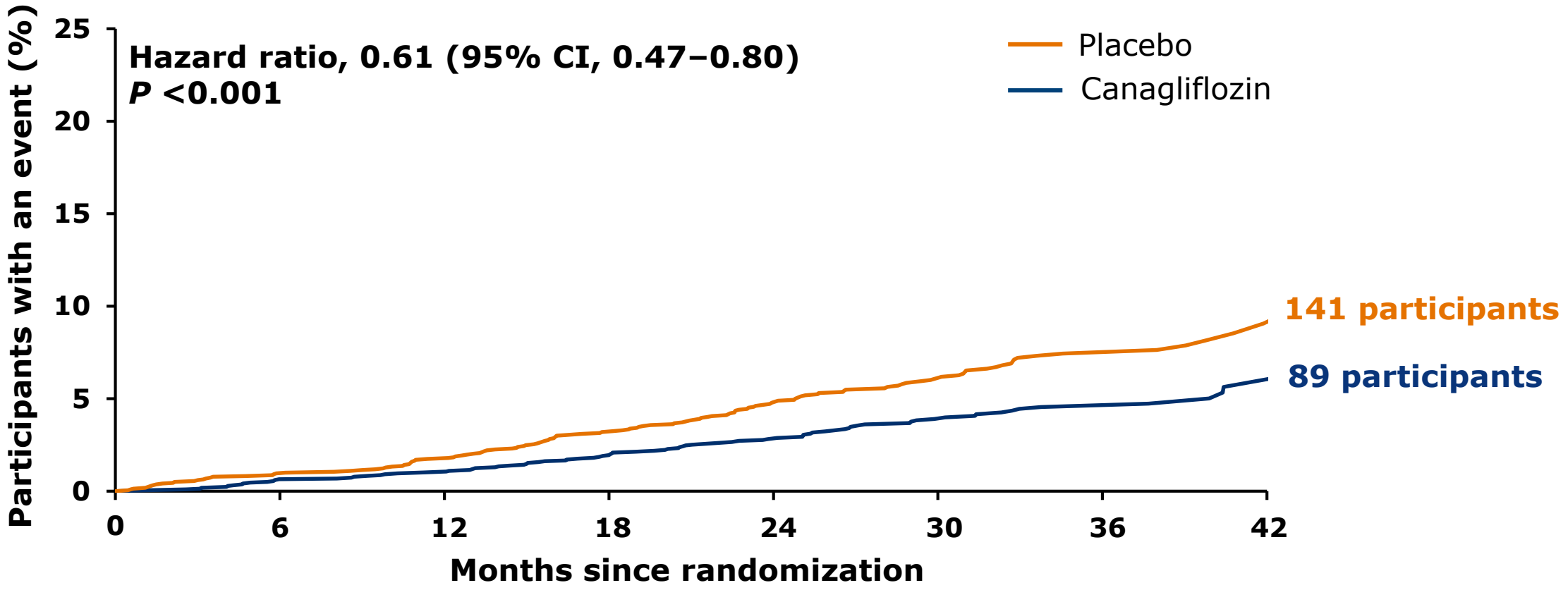
Major Cardiovascular Events: CV Death, MI, or Stroke



No. at risk								
Placebo	2199	2152	2100	2022	1717	1143	635	168
Canagliflozin	2202	2163	2106	2047	1756	1196	642	198

CREDENCE

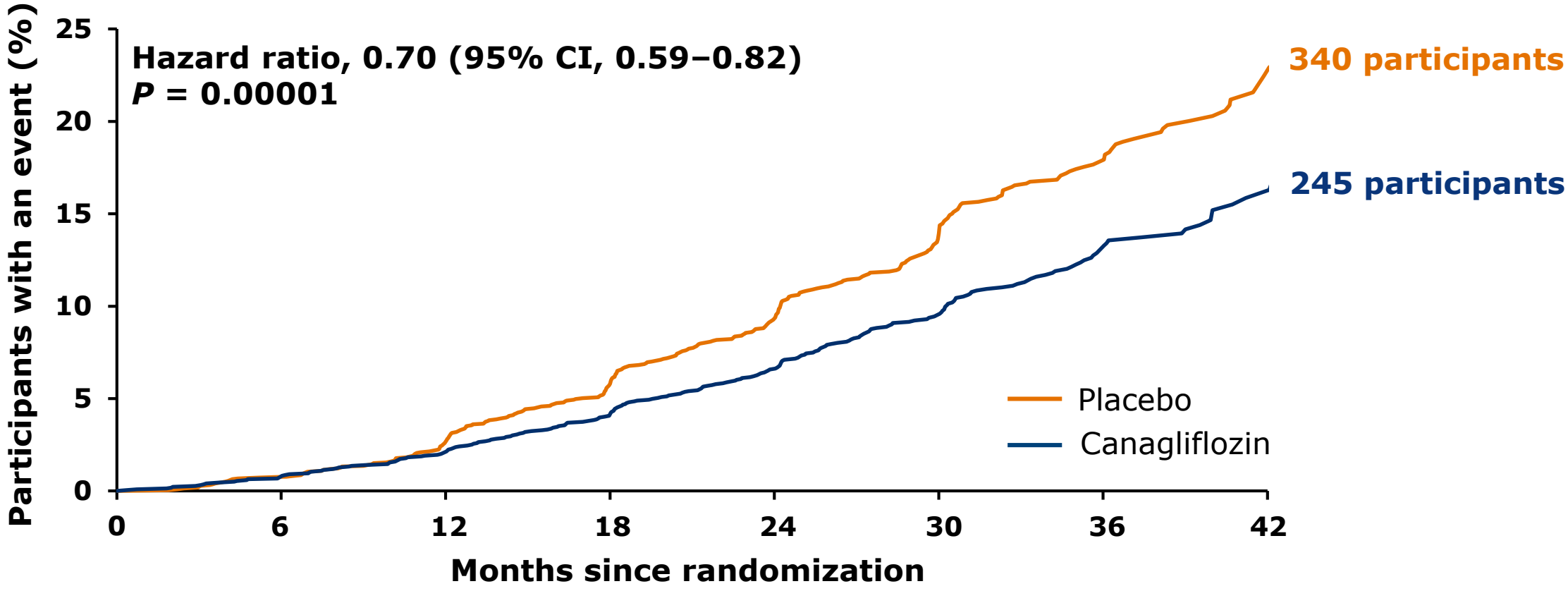
Hospitalization for Heart Failure



No. at risk								
Placebo	2199	2165	2122	2043	1735	1147	638	170
Canagliflozin	2202	2171	2131	2076	1789	1226	668	199

CREDENCE

Primary Outcome:
ESKD, Doubling of Serum Creatinine, or Renal or CV Death



No. at risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

CREDENCE

New EASD-ADA consensus guidelines on managing hyperglycaemia in type 2 diabetes:
ADA June 2019 and at EASD meeting later this year

Specific recommendations for SGLT2 and GLP-1

- Available EASD and ADA website

Snapshot of new EASD ADA guidelines

- **Metformin continues to be the first-line** recommended therapy for almost all patients with type 2 diabetes
- **The selection of medication added to metformin is based on patient preference and clinical characteristics**, including presence of cardiovascular disease, heart failure and kidney disease.
- **For patients with clinical cardiovascular disease,** a sodium–glucose cotransporter-2 (SGLT2) inhibitor or a glucagon-like peptide-1 (GLP-1) receptor agonist with **proven cardiovascular benefit is recommended**. Individual agents within these drug classes have been shown to have cardiovascular benefits.
- **For patients with chronic kidney disease (CKD) or clinical heart failure and atherosclerotic cardiovascular disease**, an SGLT2 inhibitor with proven benefit should be considered
- **GLP-1 receptor agonists are generally recommended as the first injectable** medication, except in settings where type 1 diabetes is suspected

Diabetologia 61; 2461, 2018

Diabetologia ADA EASD guidelines: Fig 3

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

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 individualized 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

Back to our case; your latest review

- 62 year old Male with diabetes, CAD, renal impairment, hypertension, albuminuria

- Limited with usual exercise last few weeks; nil else
  - BNP raised
  - HbA1c 54 mmol/mol

A clear position statement message here for this **patient with DM plus CVD or CKD….**

Consider withdrawing the SU

Then use GLP1 or SGLT2

HbA1c level is generally not relevant to this decision

Winning against CVD in type 2 DM: my 2019 summary

- We use metformin, DPP4 inhibitors, SU, Insulin etc to improve glucose levels and HbA1c as well as possible from outset to minimise the diabetes impact on well being, CVD, heart failure, renal disease, eyes, nerves, gut, tendons/joints/skin etc
- A multifactorial risk factor management approach works best and involves diet and lifestyle. This approach will include medication: lipids, BP, glucose, antiplatelet agents, reno protection, CVD protection etc
- Recognition and treatment of heart failure in diabetes is an important 2019 focus
  - SGLT2, Sacubritil/valsartan treatments
  - Certain patients with low risk of heart failure may be able to use pioglitazone
  - Hopefully the NZSSD CVD ESRF risk calculator will soon include a heart failure risk estimate as well.
- SGLT2 and GLP1 therapies (albeit yet unfunded) will be part of our treatment program in type 2 DM (prob non-DM as well) and we need to stop thinking of using them only in the context of a raised HbA1c in those at higher CVD risk, with or without CKD.

Russell Scott
August 2019