Cardiometabolic Disease and Novel Therapies: SGLT2 Inhibitors and GLP1 Receptor Agonists

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Scripps

Disclosures

- Advisor

Eli Lilly, Boehringer-Ingelheim, Novo Nordisk, Sanofi, Janssen, Aztra Zeneca, Abbott, CorceptPharma

- Clinical Research

Eli Lilly, DexCom, Mylan, Novo Nordisk, Sanofi, Aztra Zeneca, Janssen, Boehringer Ingelheim, Teva, CorceptPharma

- Start-ups

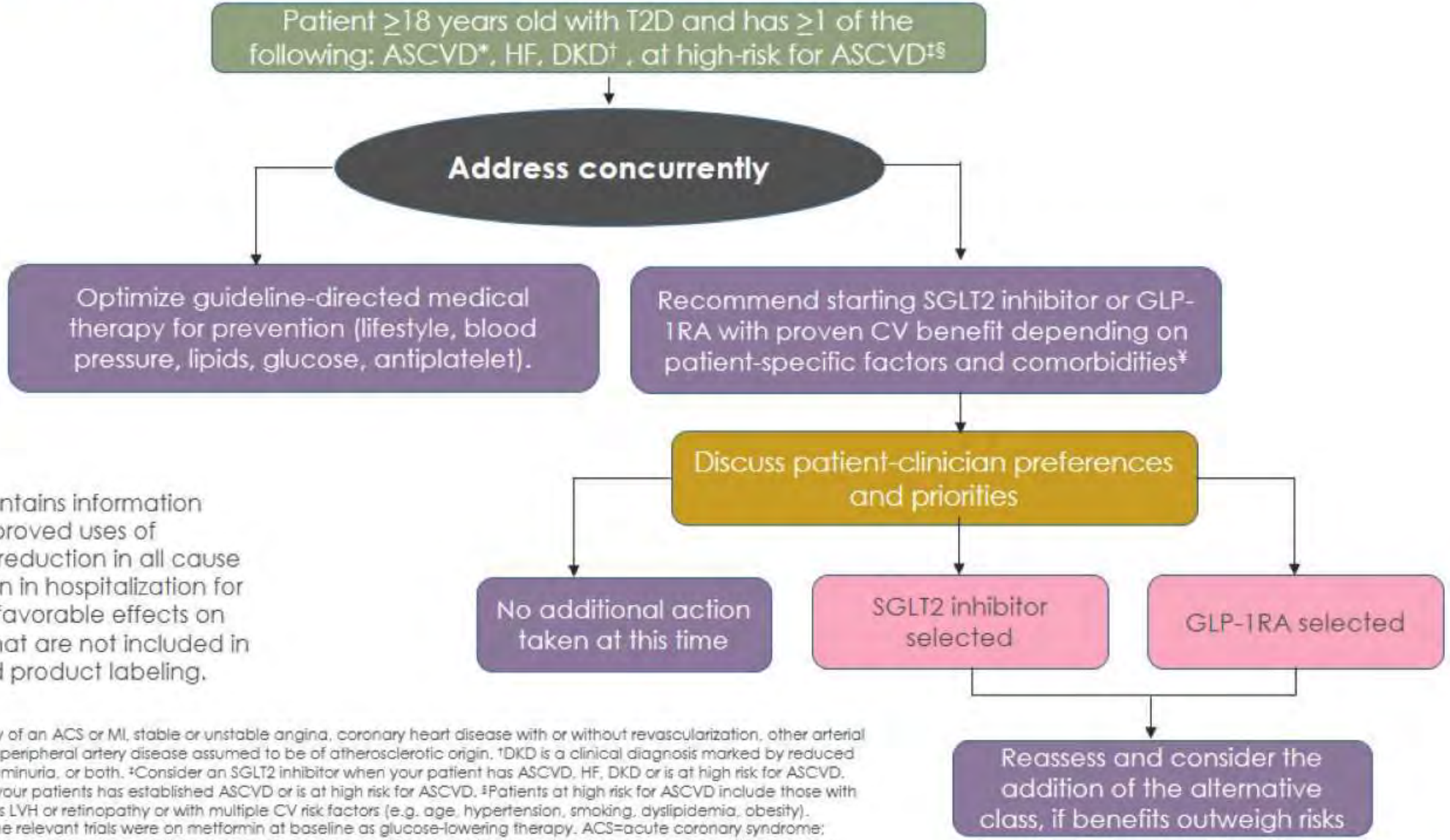
Epitracker, Glysens, Intuity Medical

- Speaker

Abbott, Novo Nordisk, Eli Lilly, Boehringer-Ingelheim

Start with the punchline:

ACC 2020 Expert Consensus Decision Pathway on Novel Therapies for CV Risk Reduction in Patient with Type 2 Diabetes



The ACC ECDP contains information concerning unapproved uses of empagliflozin (i.e. reduction in all cause mortality, reduction in hospitalization for heart failure, and favorable effects on kidney function) that are not included in the FDA-approved product labeling.

*ASCVD is defined as history of an ACS or MI, stable or unstable angina, coronary heart disease with or without revascularization, other arterial revascularization, stroke, or peripheral artery disease assumed to be of atherosclerotic origin. †DKD is a clinical diagnosis marked by reduced eGFR, the presence of albuminuria, or both. ‡Consider an SGLT2 inhibitor when your patient has ASCVD, HF, DKD or is at high risk for ASCVD. Consider a GLP-1RA when your patients has established ASCVD or is at high risk for ASCVD. §Patients at high risk for ASCVD include those with end organ damage such as LVH or retinopathy or with multiple CV risk factors (e.g. age, hypertension, smoking, dyslipidemia, obesity). ¥Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy. ACS=acute coronary syndrome; ASCVD=atherosclerotic cardiovascular disease; DKD=diabetic kidney disease; HF=heart failure; eGFR=estimated glomerular filtration rate; LVH=left ventricular hypertrophy; MI=myocardial infraction; T2D=type2 diabetes. Das SR et al. JACC 2020 Online 1 September.

Scripps Was Among the First - Tom Heywood "Gets It"

- September 2015 – Stockholm presentation of empa-reg: first SGLT2i CVOT
- November 2015 – Scripps grand rounds – "what do we do with this new data?" – Tom has an intellectual grand mal
- We agonize over not "jumping the gun" while not "missing the boat" over what to do about this new data
- January 2016 – Tom reconvenes the whole cardiology department to hear the data
- April 2016 – Tom convenes hospital cardiology section meeting to act on the data
- January 2017 – AACE/ACE Diabetes guidelines begin to change to reflect the data
- January 2018 – AACE/ACE Diabetes guidelines actually change
- January 2019 – ADA, ACC join in the major changes
- January 2020 – ADA, ACC change their guidelines
- January 2021 – ADA, ACC, (AHA joins in)
- "A cardiologist an endocrinologist, and a real doctor walk into a bar…"

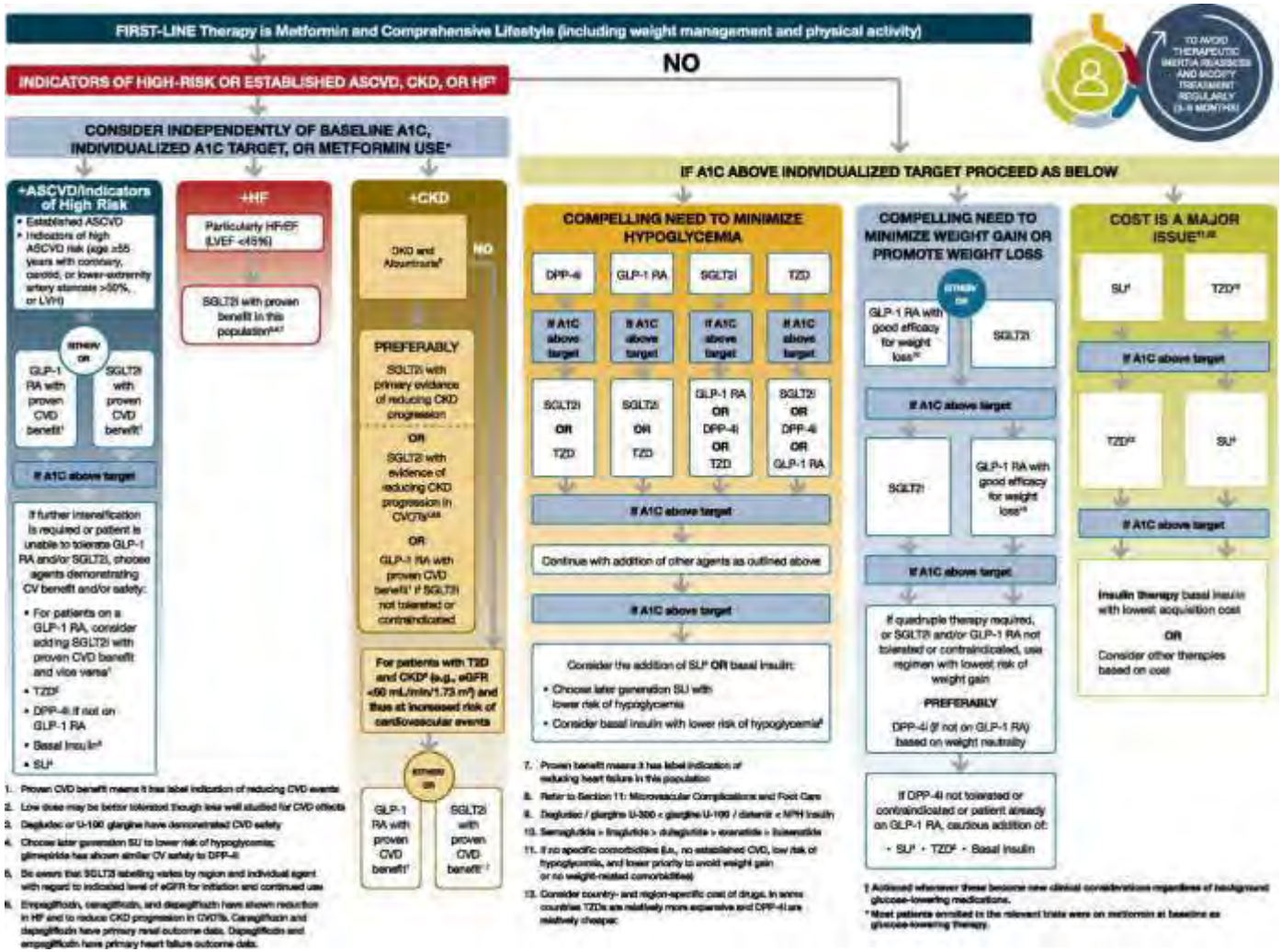
Evolution of the Diabetes Guidelines for SGLT2i's and GLP1-RA's
Changes So Fast There Was No Longer Any Point in Annual Printing

- To lower A1c – after lifestyle rx and metformin and ***after*** possible other meds
- To lower A1c – after lifestyle and metformin ***before*** any other meds
- To lower A1c – in combination with above ***right away***
- To ***lower CVD risks*** – in diabetics with elevated A1c

- To Lower CVD risks - in diabetics ***independent of A1c***

- To lower CVD (and renal) risk – ***independent of having diabetes*** at all

Glucose-lowering medication in type 2 diabetes: 2021 ADA Professional Practice Committee (PPC) adaptation of Davies et al.



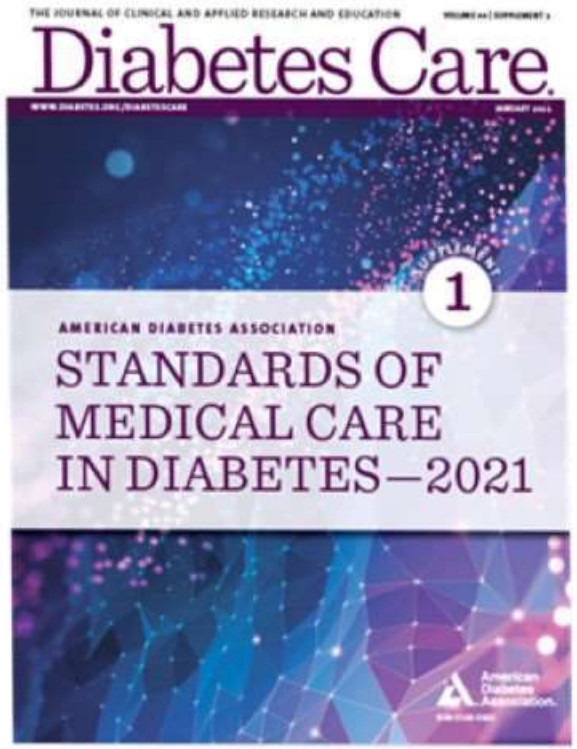
American Diabetes Association Dia Care 2021;44:S111-S124

American Diabetes Association.

ADA Standards of Medical Care in Diabetes – Jan 2021

Section 9. Pharmacologic approaches to glycemic treatment

Pharmacologic Therapy for Type 2 Diabetes



9.9 "Among patients with **T2D who have established ASCVD or established kidney disease, or indicators of high ASCVD risk†, established kidney disease, or heart failure, an SGLT2 inhibitor or GLP-1 RA with demonstrated CV disease benefit** is recommended as **part of the glucose-lowering regimen independent of A1C** and in consideration of patient-specific factors" (A)*

"For patients **without** established ASCVD, indicators of high ASCVD risk, heart failure or CKD, **the choice of a second agent to add to metformin is not yet guided by empiric evidence.** Rather, drug choice is based upon avoidance of side effects, particularly hypoglycaemia, weight gain, cost and patient preferences."

† **Indicators of high ASCVD risk; age ≥ 55 years with coronary carotid or lower extremity artery stenosis > 50%, or LVH**
*Description of evidence-grading system is provided at the end of this slide deck
ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium-glucose co-transporter-2
American Diabetes Association. *Diabetes Care* 2021;44:S1-S222.

Critical Caveats

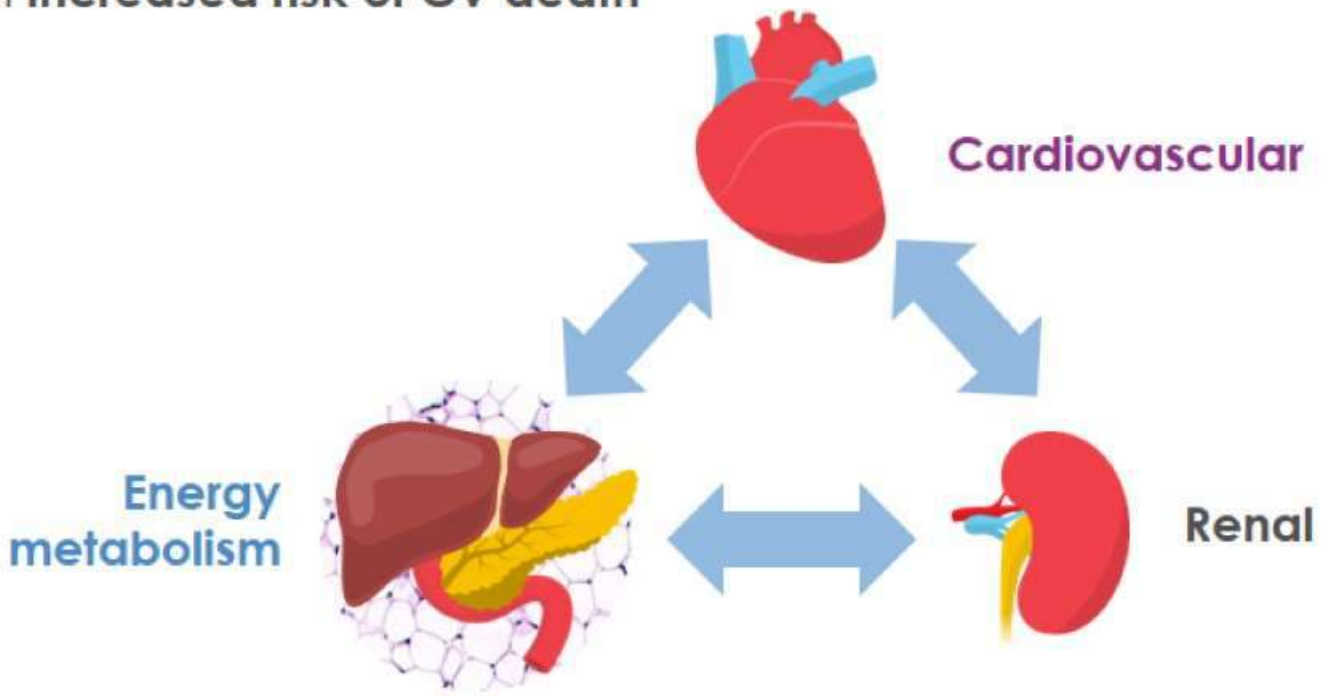
- "Established ASCVD" is not defined in the FDA label – clinician decides
  - Now includes "multiple risk factors"
  - Now includes primary as well as secondary prevention

- "Heart failure" is not defined in the FDA label
  - Most of beneficiaries in the trials did not have known HF (rEF or pEF)

- "Chronic Kidney Disease" is not defined in the FDA label
  - eGFR < 60 is standard but not absolute
  - Role of Cystatin-C eGFR in 45-60, 30-45

Dysfunction of the heart, kidneys or metabolism may contribute to the dysfunction of the others[1,2]

- Diseases in the components of the CRM systems share many of the **same risk factors**[3]
- Dysfunction in one system can set off a **cascade of multisystem dysfunction**[4]
- This can lead **to interrelated diseases** such as **T2D**, **CV disease, HF, and CKD**, which in turn leads to an **increased risk of CV death**[5]



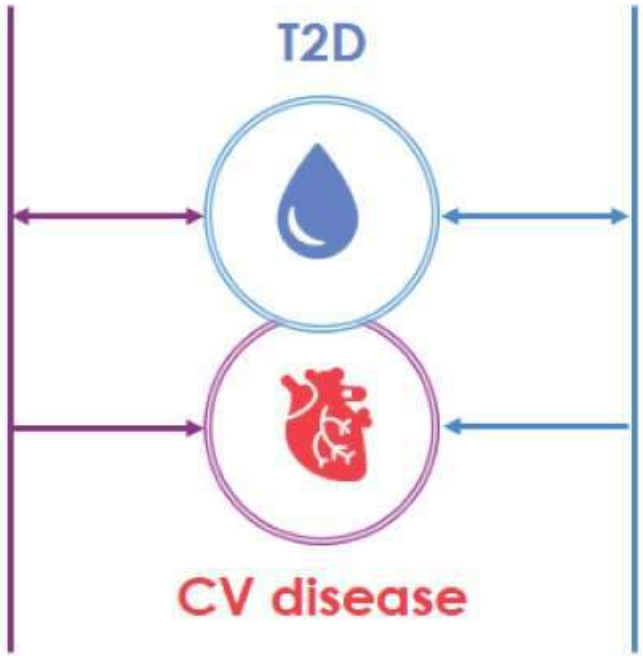
CKD, chronic kidney disease; CRM, cardio-renal-metabolic; CV, cardiovascular; HF, heart failure; T2D, type 2 diabetes
CRM, cardio-renal-metabolic; CV, cardiovascular; HF, heart failure; T2D, type 2 diabetes
1. García-Donaire JA & Ruilope LM. Int J Nephrol 2011;2011:975782; 2. Thomas G et al. Clin J Am Soc Nephrol 2011;6:2364; 3. Sarafidis PA et al. J Cardiometab Syndr 2006:58; 4. Ronco C et al. Contrib Nephrol 2010;165:54; 5. Leon BM and Maddox TM. World J Diabetes 2015;6:1246

The pathophysiology of CV disease in patients with T2D is complex

T2D shares common risk factors with CV disease and contributes to vascular damage

Risk factors for T2D and CV disease

- Physical inactivity
- High blood pressure
- Poor diet
- Smoking
- Obesity
- Dyslipidaemia
- Metabolic syndrome



Direct effects of hyperglycaemia

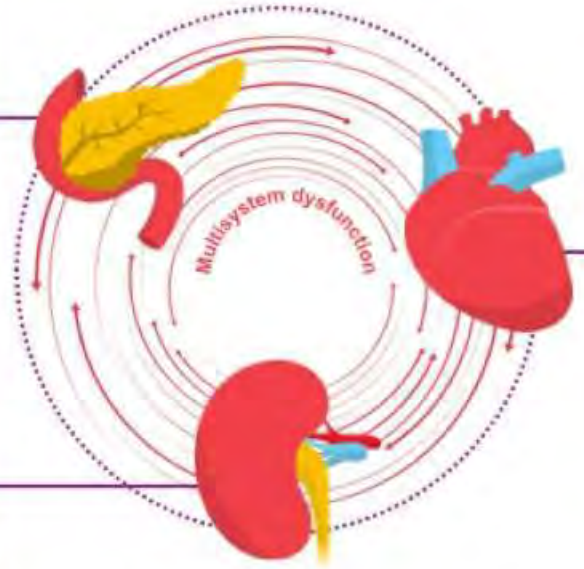
- Arterial stiffness
- Endothelial dysfunction
- Oxidative stress
- Platelet activation
- Inflammation
- Metabolic syndrome
- Metabolic dysfunction

CV, cardiovascular; T2D, type 2 diabetes
Newman JD *et al. J Am Coll Cardiol* 2017;70:883

Disorders of the Cardio-Renal-Metabolic (CRM) systems often co-exist

~One-third of patients with T2D have CV disease[1,2]

Patients with diabetes have a **2- to 5-fold higher risk of HHF**[3]



2× increased risk of death with a history of MI, stroke or diabetes[6]

20–67% of patients with HF are estimated to have CKD[7]

Presence of CKD in patients with HF **increases risk of mortality by ~25–28%**[8]

CKD affects up to **50% of patients with T2D** globally[4]

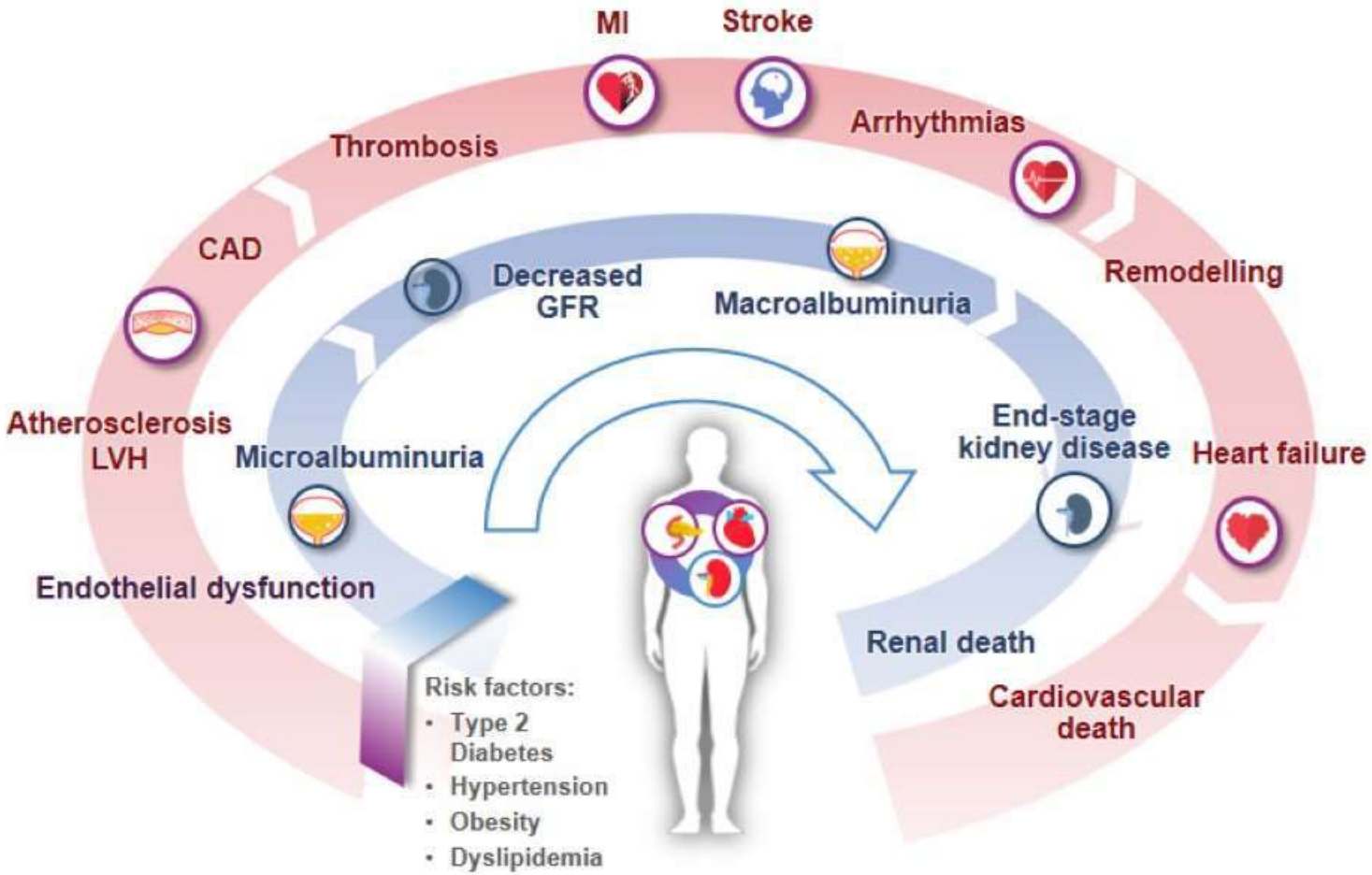
Diabetes and/or hypertension is the cause of **>80% of ESKD** cases worldwide[2]

Established risk factors for CKD include CV disease, high blood pressure, obesity and diabetes[5]

CKD, chronic kidney disease; CV, cardiovascular; ESKD, end-stage kidney disease; HF, heart failure; HHF, hospitalisation for heart failure; MI, myocardial infarction; T2D, type 2 diabetes

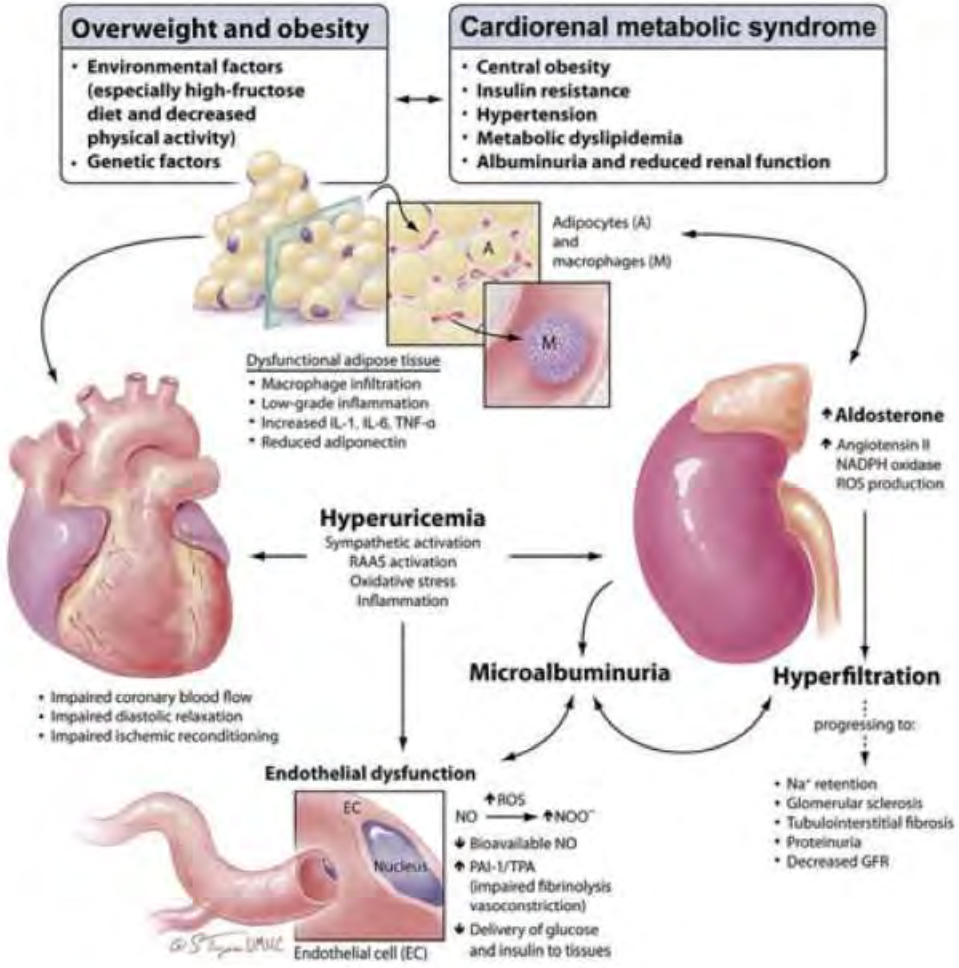
1.Einarson TR *et al. Cardiovasc Diabetol* 2018;17:83 2. International Diabetes Federation. IDF Diabetes Atlas. 9th edn. 2019. https://www.diabetesatlas.org/ (accessed March 2020). 3.Kannel WB *et al. Am J Cardiol* 1974;34:29 4. Thomas M et al. Nat Rev Nephrol 2016;12:73. 5. Siemens Healthineers. Chronic kidney disease: a global crisis. 2018. www.siemens-healthineers.com/en-uk/news/chronic-kidney-disease.html (accessed March 2020) 6. The Emerging Risk Factors Collaboration. *JAMA* 2015;314:52. 7. Sarraf M *et al. Clin J Am Soc Nephrol* 2009;4:2013. 8. Ather M et al. J Am Coll Cardiol 2012;59:998–1005.

Interconnectivity of CRM systems exists throughout the CV and renal risk continuum



LVH, left ventricular hypertrophy; MI, myocardial infarction
Adapted from Dzau VJ et al. Circulation 2006;114:2850–2870

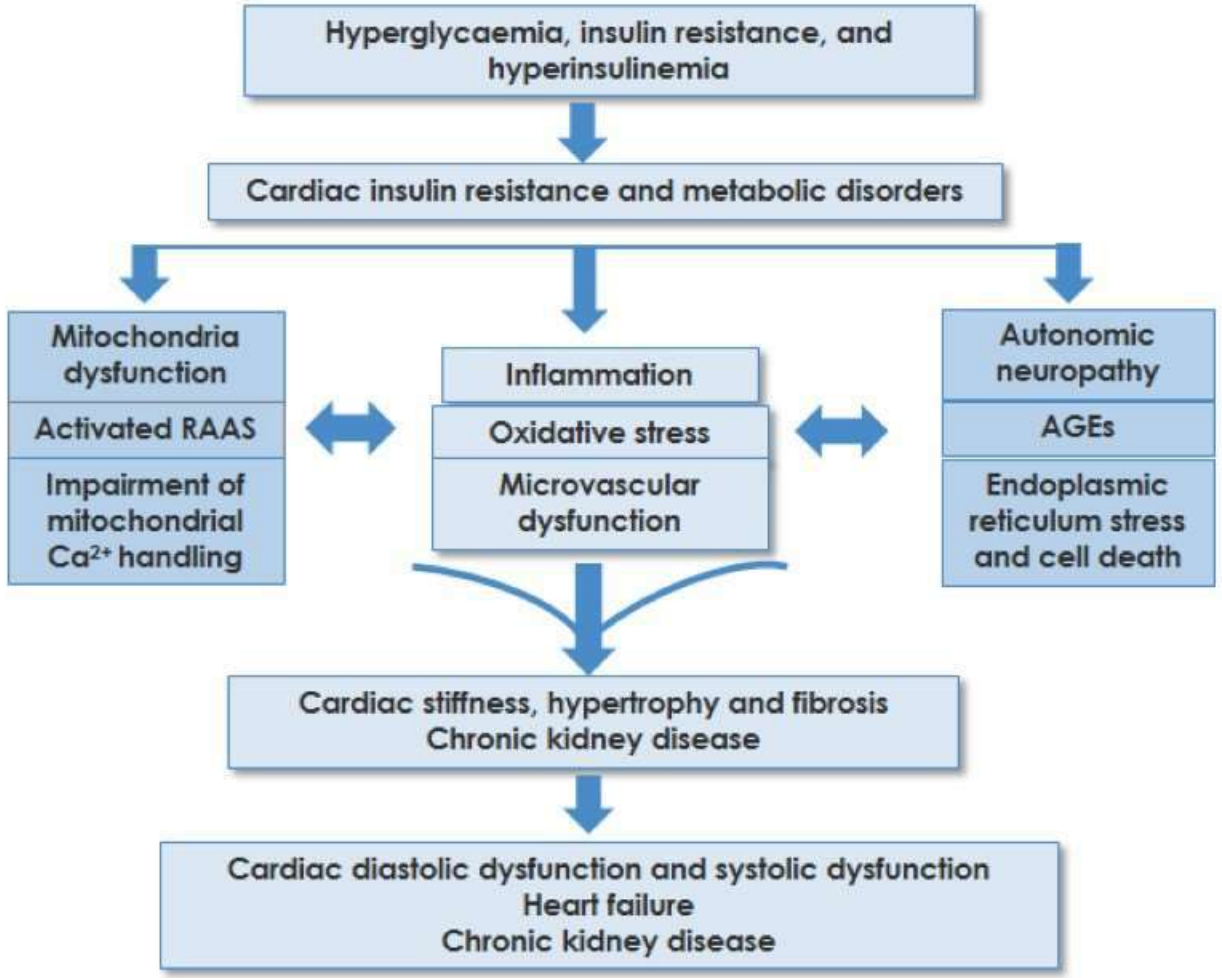
The interrelationship between adiposity and maladaptive changes in the heart and kidney in CRM systems



Presence of a ***constellation of interactive cardiac and renal risk factors***, including overweight/obesity, hypertension, insulin resistance, hyperinsulinemia, dyslipidemia, microalbuminuria and/or reduced renal function, constitute the cardiorenal metabolic syndrome

Sowers JR et al. Cardiorenal Med 2011;1:5–12.

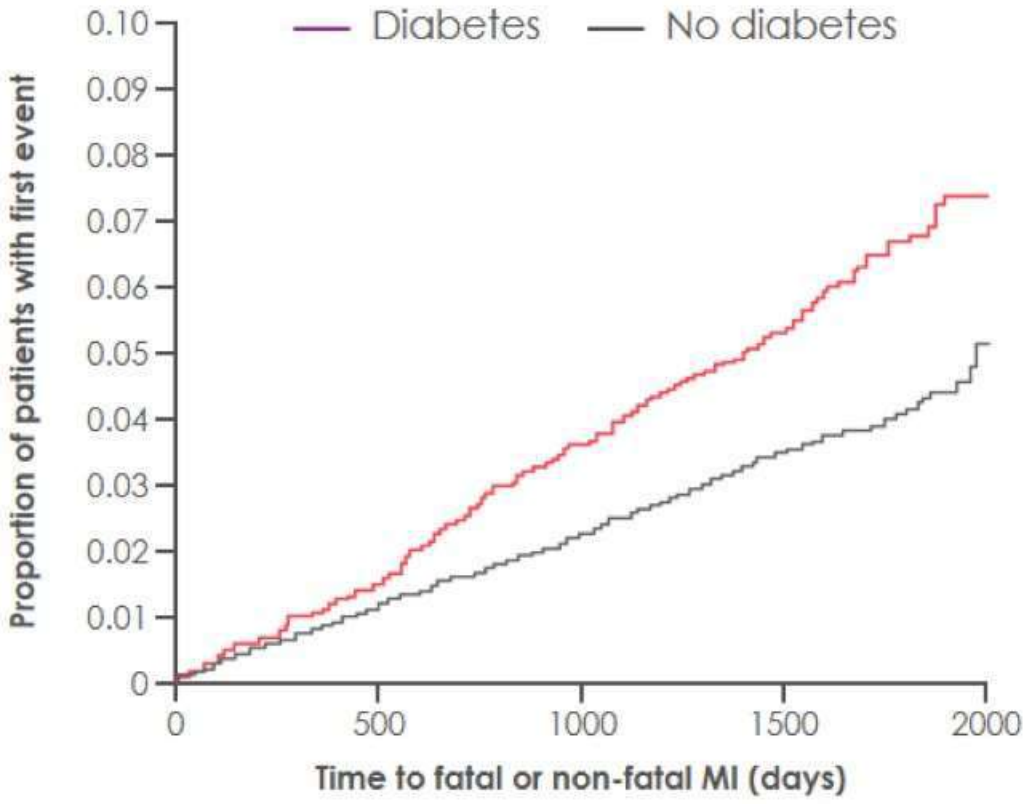
Metabolic disorders contributes to the progression of HF and CKD



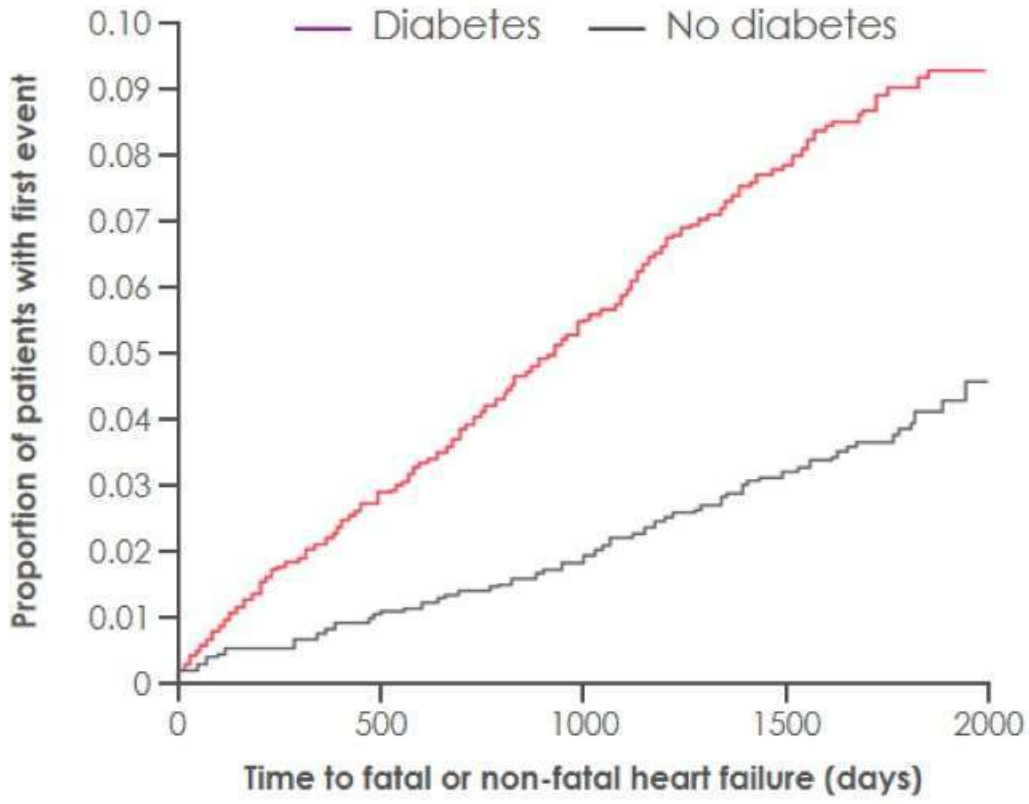
HF, Heart Failure; CKD, Chronic Kidney Disease; AGEs, advanced glycation end-products; RAAS, renin-angiotensin-aldosterone system
Diagram adapted from: Jia G et al. Circ Res 2018;122:624; 2. Borgetti G et al. Front Physiol 2018;9:1514

Diabetes accelerates the time to first CV event

Time to first MI



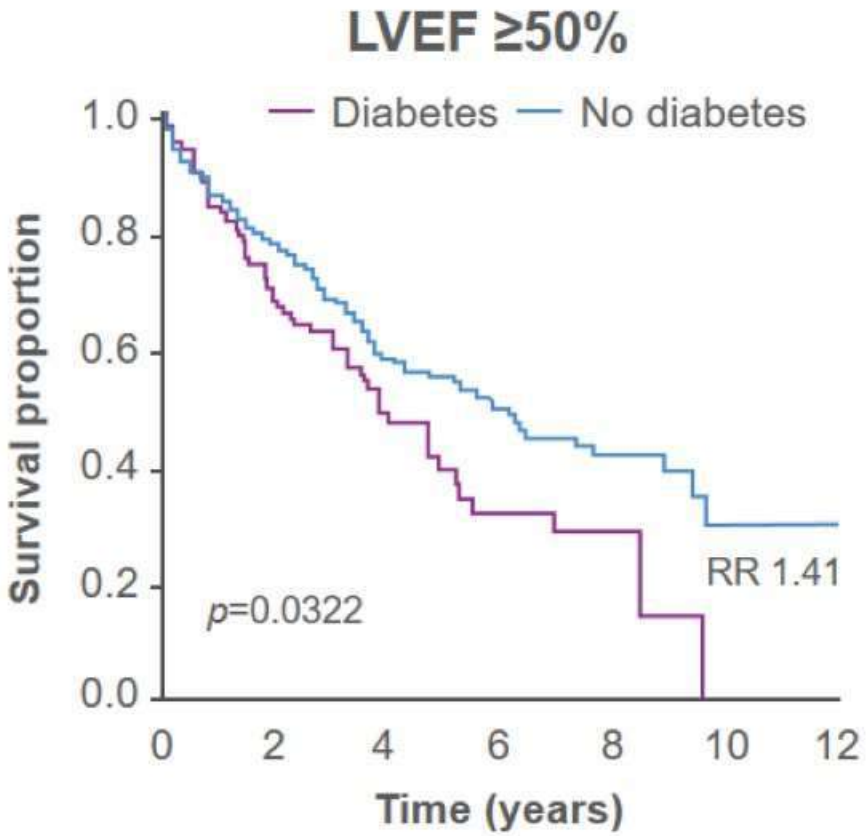
Time to first hospitalisation for heart failure

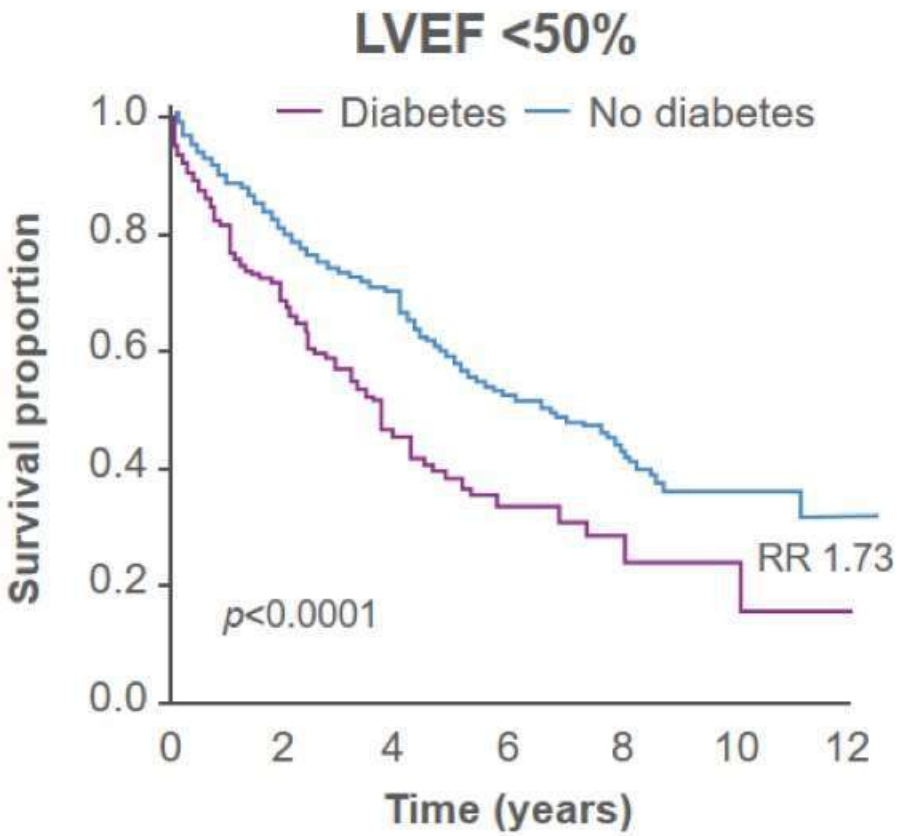


CV, cardiovascular; MI, myocardial infarction
McMurray JJV *et al. Lancet Diabetes Endocrinol* 2014;2:843

Diabetes as a comorbidity is associated with a worse prognosis for patients with heart failure

Survival of patients with HF hospitalised with LVEF ≥50% (n=498) or <50% (n=754)

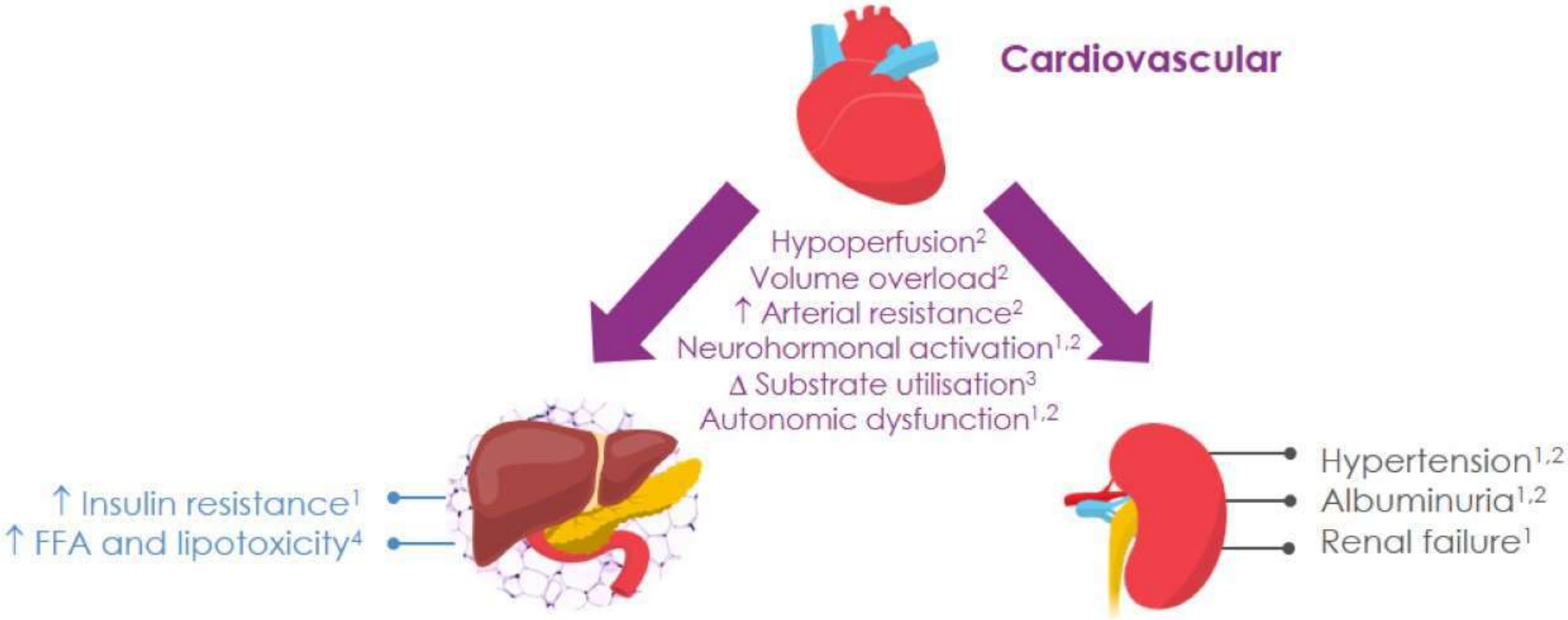




HF, heart failure; LVEF, left ventricular ejection fraction; RR, relative risk
Varela-Roman A et al. Eur J Heart Failure 2005;7:859

Cardiac dysfunction adds to the renal/metabolic burden[1,2]

Cardiac abnormalities affect renal/metabolic disease progression and outcomes[1,2]



FFA, free fatty acids

1. Connell AW & Sowers JR. J Am Soc Hypertens 2014;8:604; 2. Ronco C et al. J Am Coll Cardiol 2008;52:1527; 3. Ronco C et al. J Am Coll Cardiol 2008;52:1527
4. Lopashuk GD & Ussher JR. Circ Res 2016;119:1173

2007: The Avandia Affair

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.

Rosiglitazone compared with the control:

Odds ratio for **myocardial infarction: 1.43** (95% CI, 1.03 to 1.98; P=0.03)

OR for **death from cardiovascular causes: 1.64** (95% CI, 0.98 to 2.74; P=0.06)

"Urgent need for comprehensive evaluations to clarify the cardiovascular risks of rosiglitazone

Our data suggest a cardiovascular risk associated with the use of rosiglitazone

Until more precise estimates of the cardiovascular risk of this treatment can be delineated in patients with diabetes, patients and providers should carefully consider the potential risks of rosiglitazone in the treatment of type 2 diabetes"

FDA Guidance for Industry to Evaluate CV Risk in New Antihyperglycemic Medications[1] July 2008

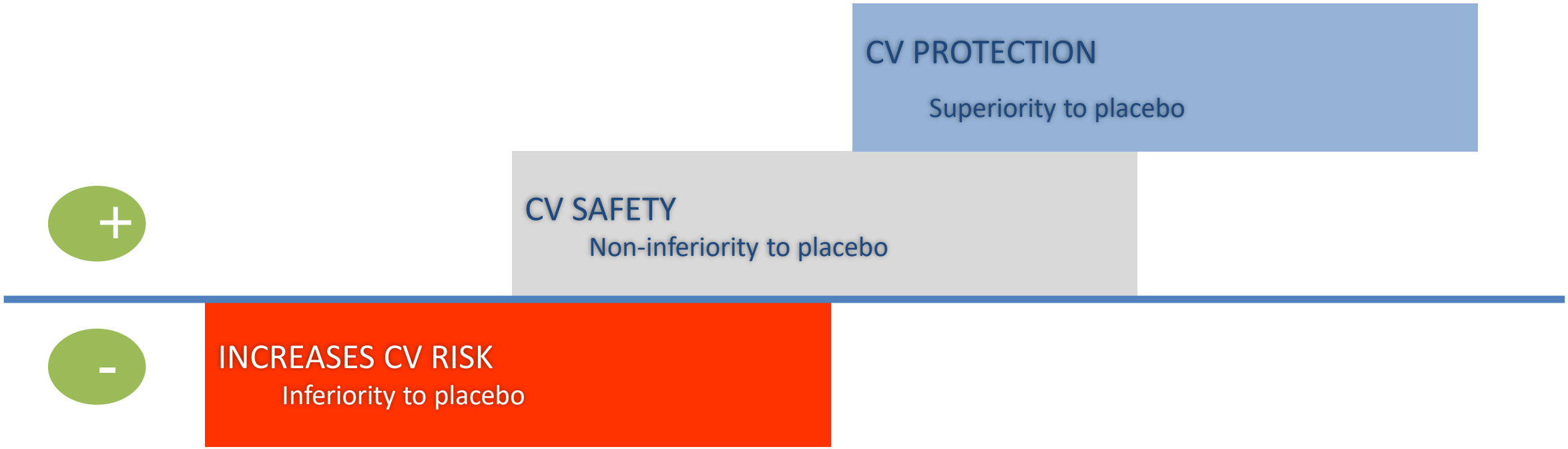
- In order ***to establish the safety*** of a new antihyperglycemics
  - ***Effects on CV risk*** to be more thoroughly addressed during antihyperglycemic medication development
  - Demonstrate that therapy ***will not result in unacceptable increase in CV risk***
  - Key areas to be addressed: inclusion of patients with a higher risk of CV events
    - e.g. patients with advanced CV disease, elderly patients, and patients with impaired renal function
    - study duration ≥2 years

http://www.fda.gov/downloads/Drugs

CVOTs (double-blind, randomized, placebo-controlled) - 3 possible results

CV outcome trials PRIMARY ENDPOINT

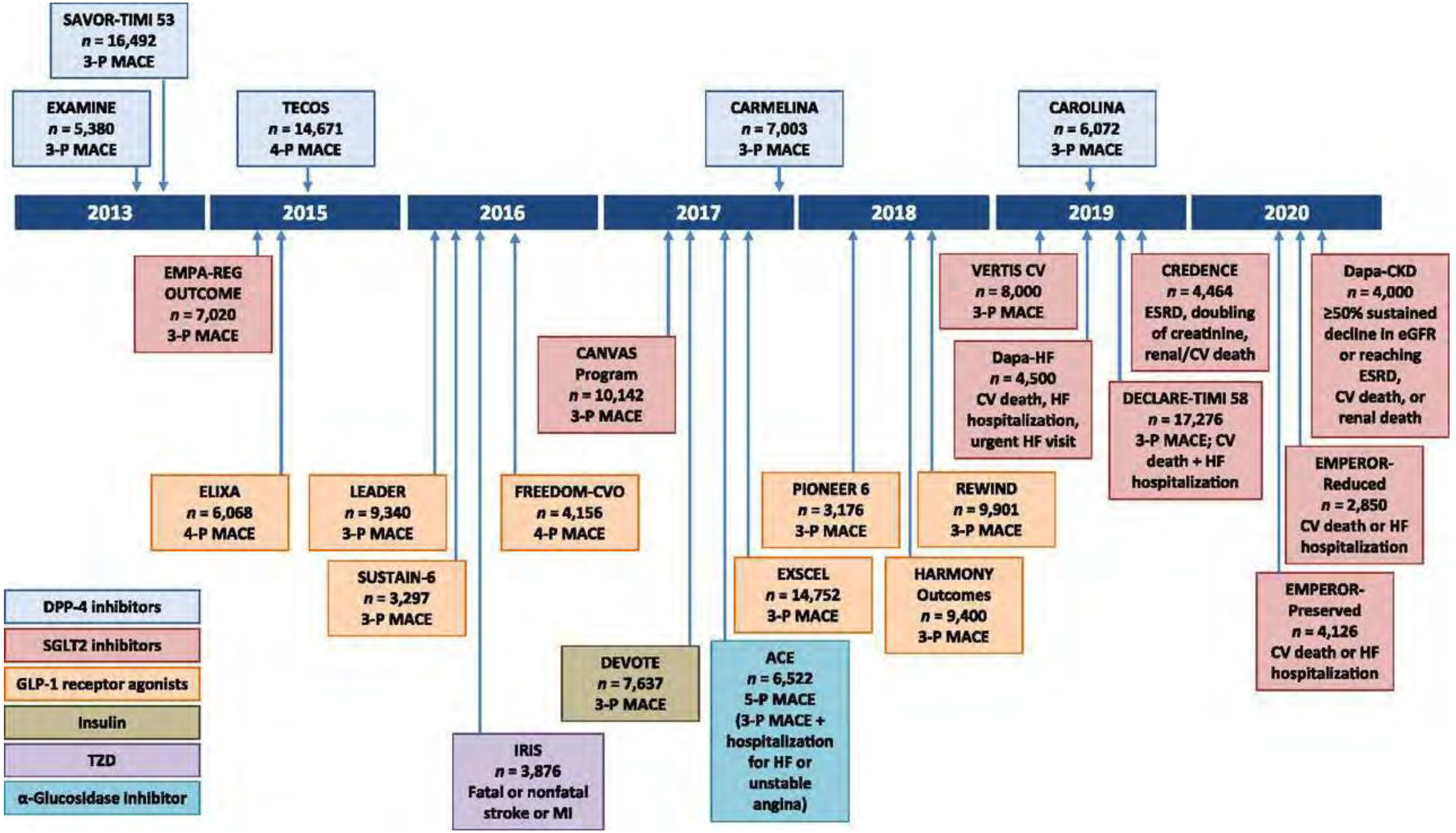
3P-MACE: CV death, nonfatal MI, nonfatal stroke



All patients receive standard-of-care treatment in addition to the study drug or placebo

MACE: major adverse cardiac events

Cardiovascular Outcome Trials in Diabetes



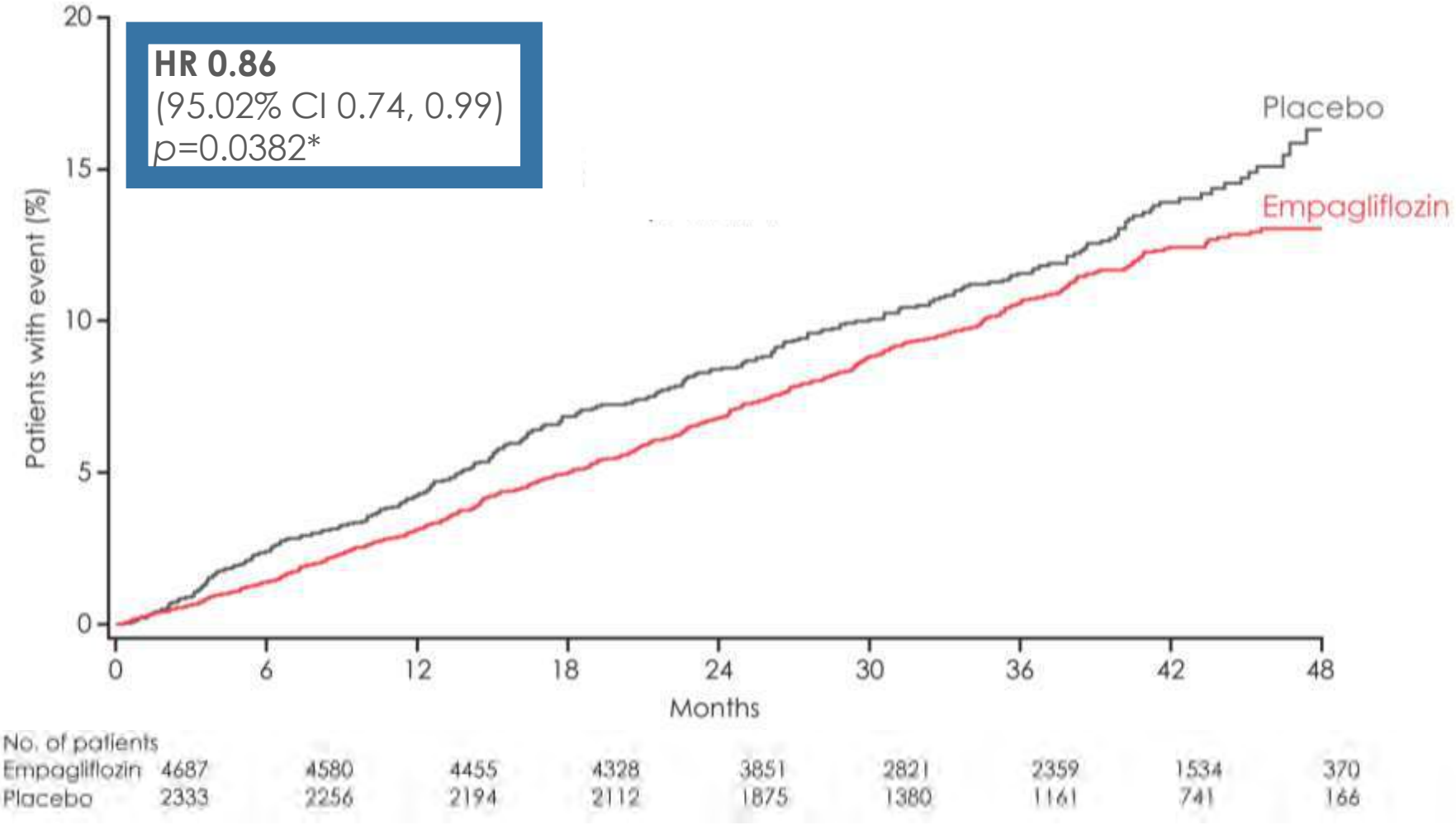
Cardiovascular Outcome Trials

SGLT2 inhibitors


Stockholm, September 17, 2015
Empagliflozin CV outcomes
51st ANNUAL
MEETING
EASD
14 - 18 SEPTEMBER
STOCKHOLM 2015

Primary outcome: 3-point MACE

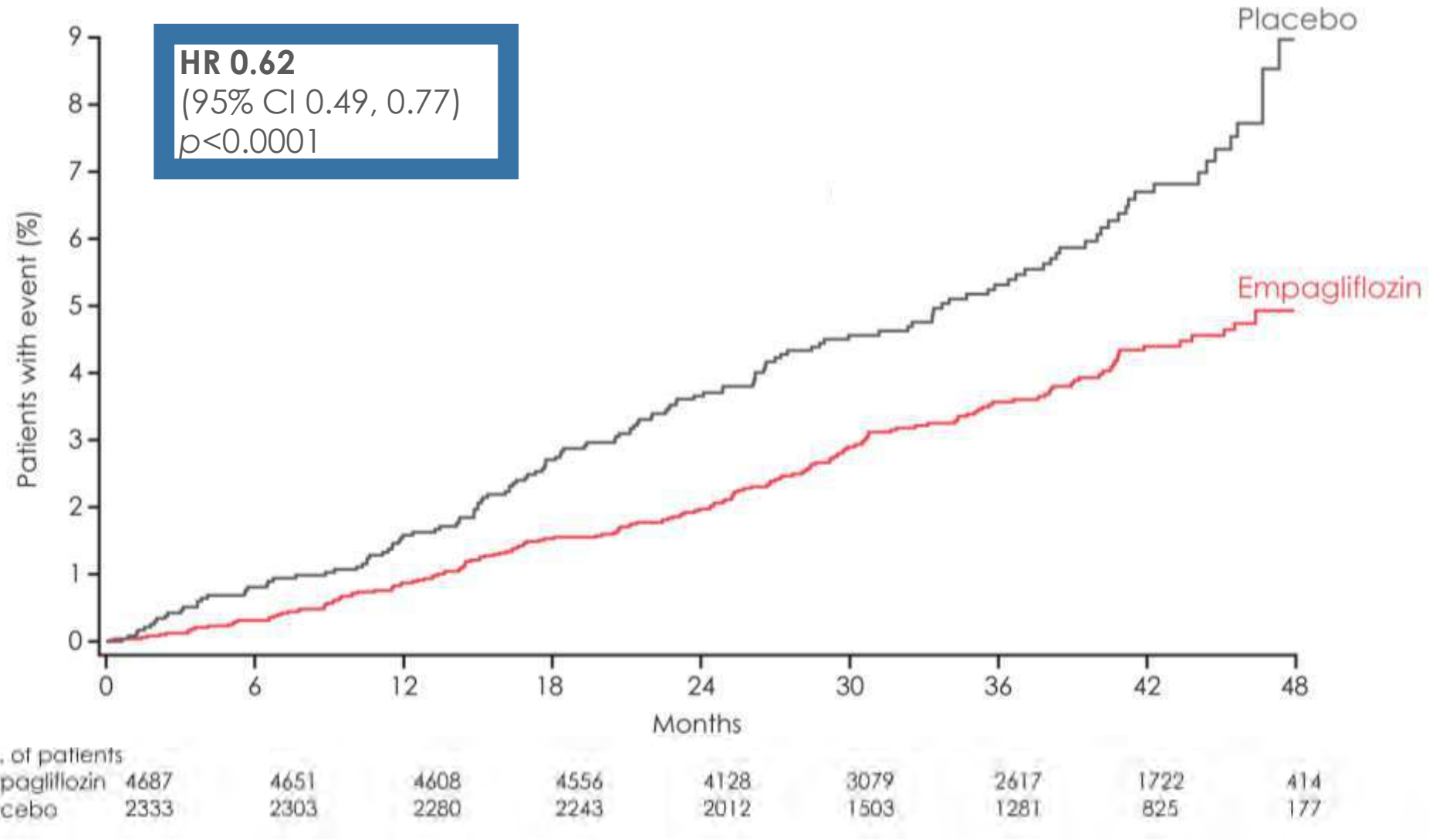
Empagliflozin



Cumulative incidence function. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio.
* Two-sided tests for superiority were conducted (statistical significance was indicated if p≤0.0498)

Zinman B et al. NEJM 2015; 373:2117-2128

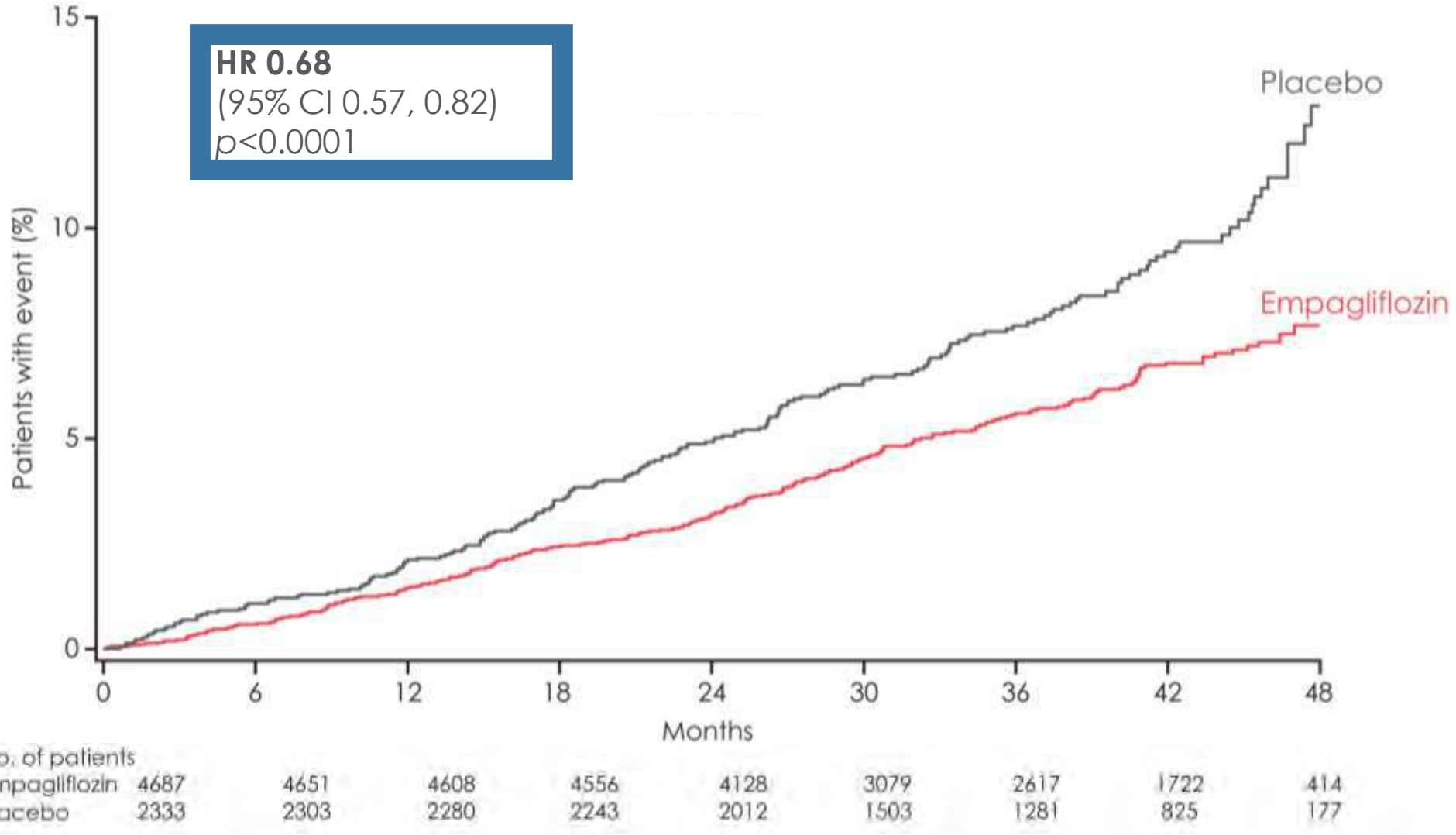
CV death



Cumulative incidence function. HR, hazard ratio

Zinman B et al. NEJM 2015;373:2117-2128

All-cause mortality



Kaplan-Meier estimate. HR, hazard ratio

Zinman B et al. NEJM 2015;373:2117-2128

FDA Approves Indications for empagliflozin (Jardiance)

2016 Update

1. as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

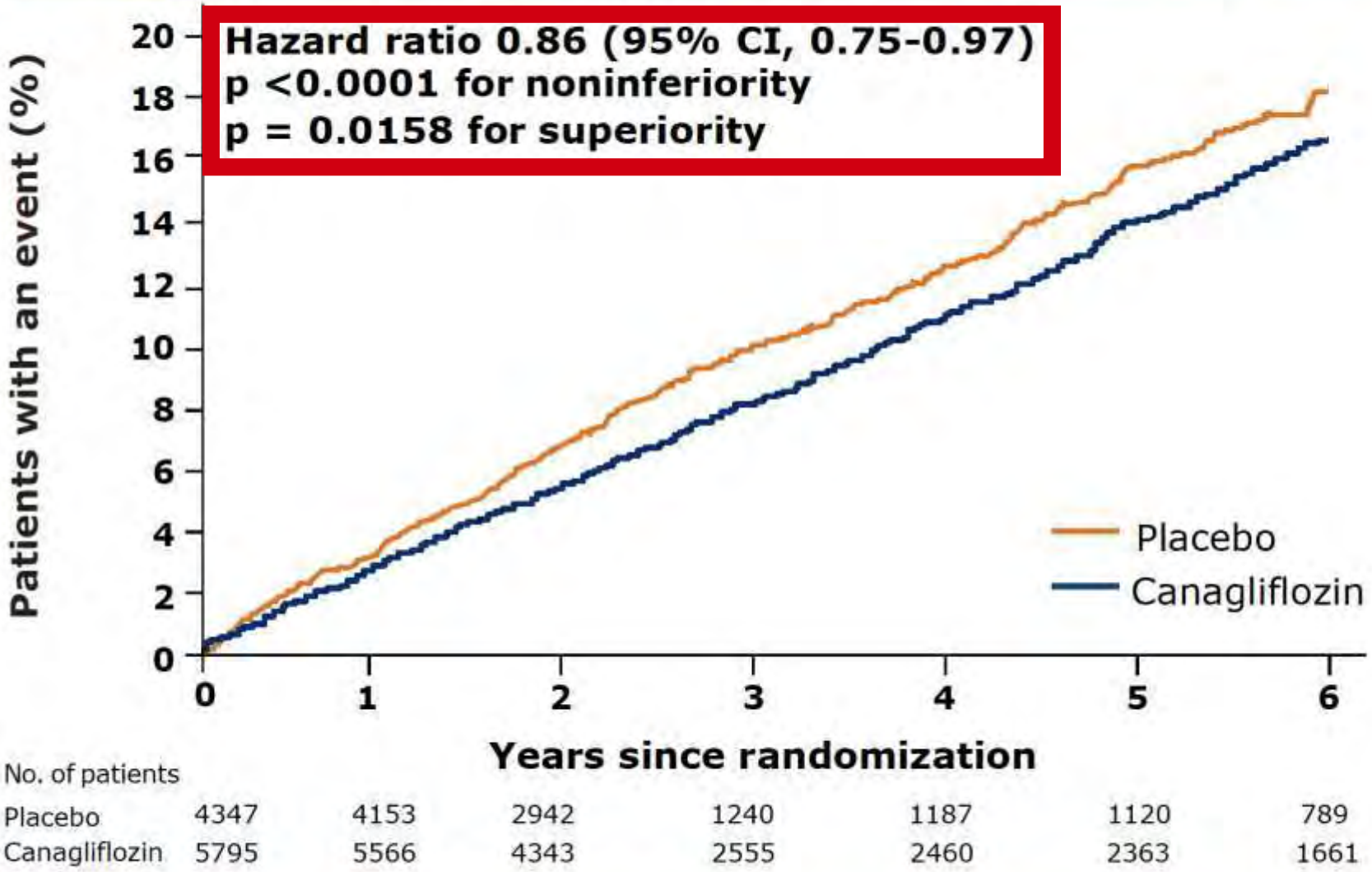
2. to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease

Is This a Class Effect?

Primary MACE Outcome

CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke

Canagliflozin



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

Intent-to-treat analysis

CANVAS Program

FDA approves CV events indication for canagliflozin (Invokana)

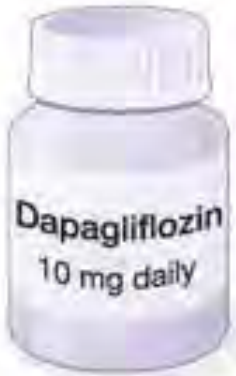
October 31, 2018

- To reduce the risk of **major adverse cardiovascular events** in adults with type 2 diabetes who have **established cardiovascular disease**

DECLARE-TIMI 58: Dapagliflozin reduces risk of hospitalization for heart failure in patients who have type 2 diabetes and established, or risk for, atherosclerotic cardiovascular disease

Patients (N=17,160; aged ≥40 years) with type 2 diabetes mellitus who had established, or had multiple risk factors for, atherosclerolc cardiovascular disease

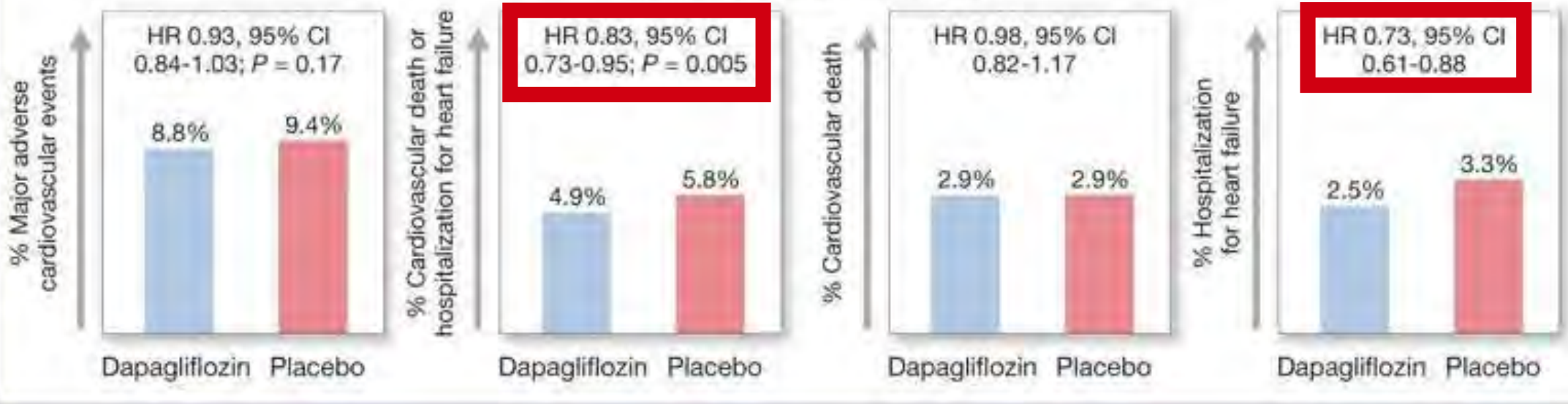
+



OR

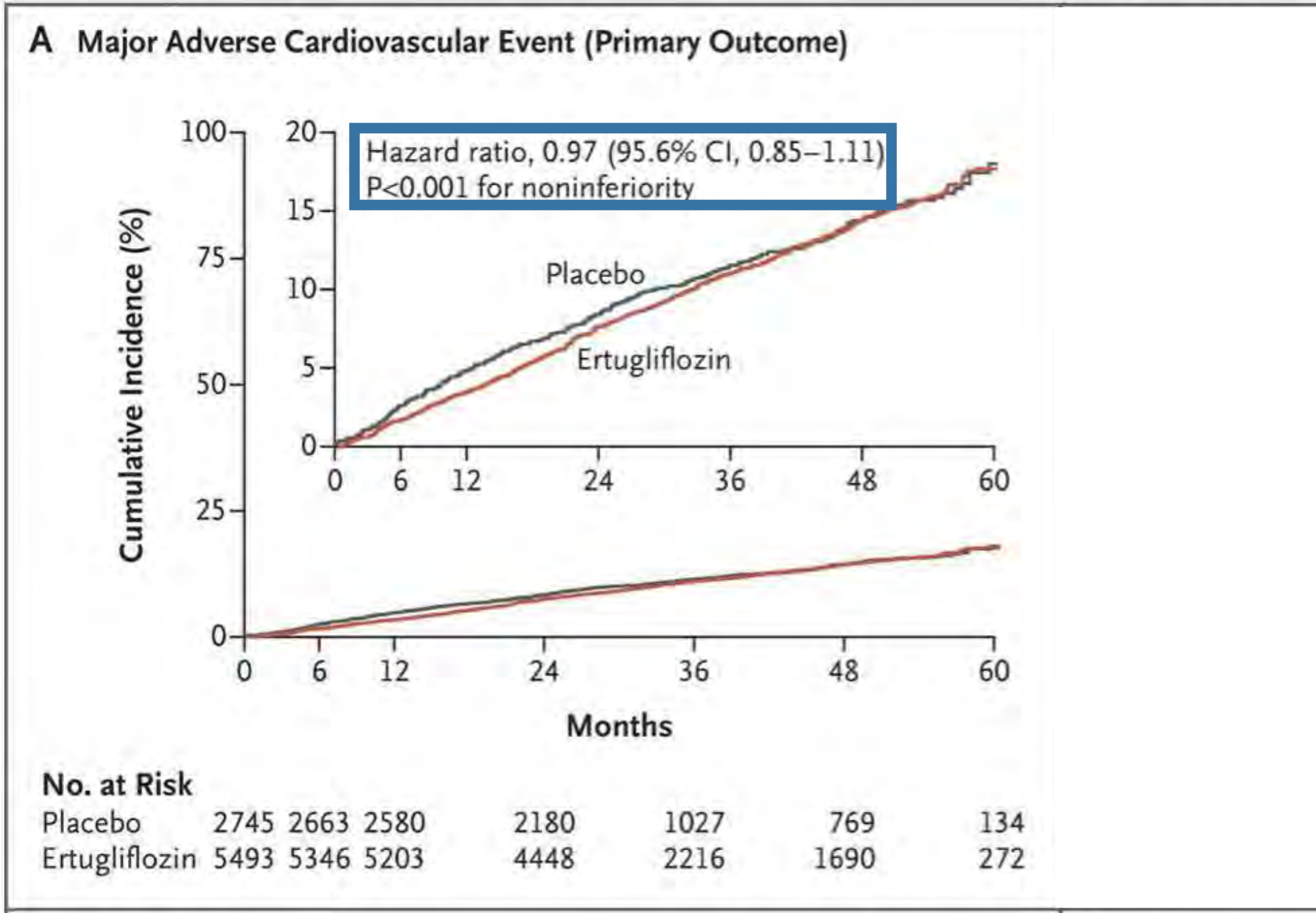
Primary endpoint (MACE) missed

Median 4.2 years follow-up



N Engl J Med 2019; 380:347-357

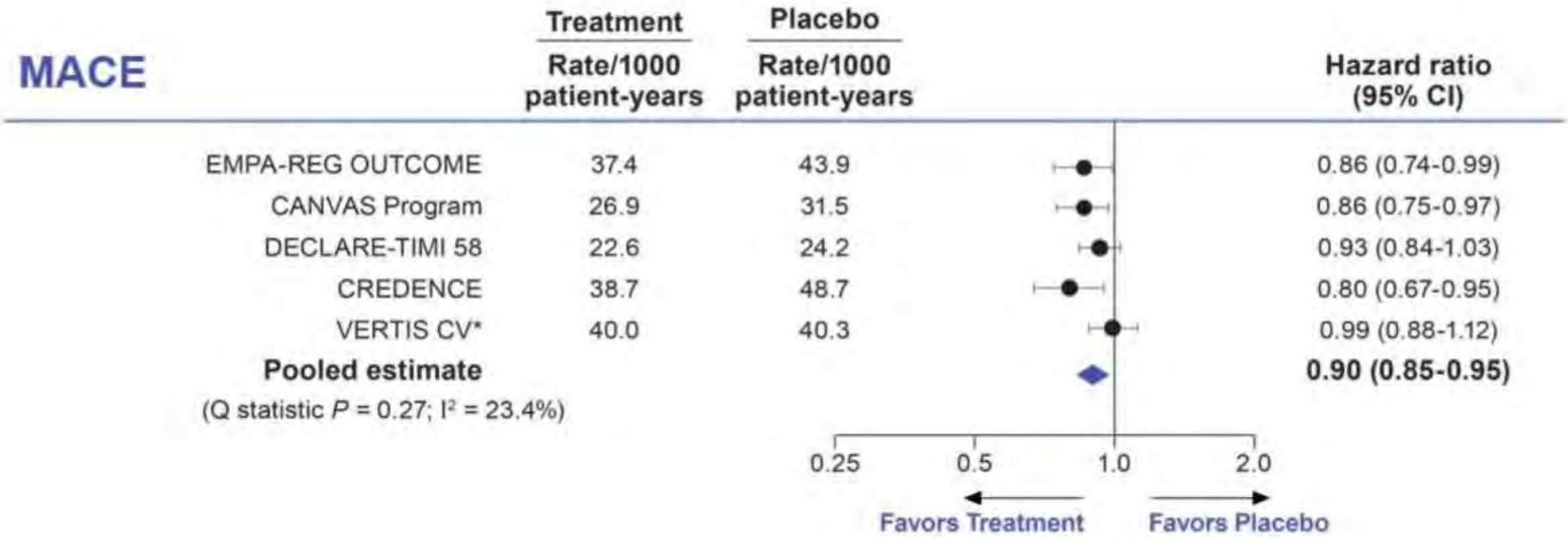
Ertugliflozin CVOT (VERTIS CV)



Cannon CP et al. NEJM 2020; 383:1425-1435

Time to first MACE

SGLT2 Inhibitor CVOTs



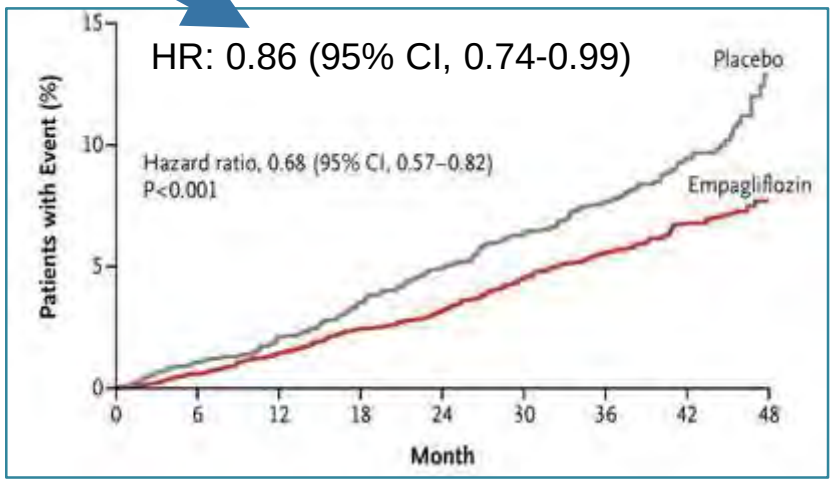
UT Southwestern Medical Center | Parkland

McGuire DK et al. *In press.*

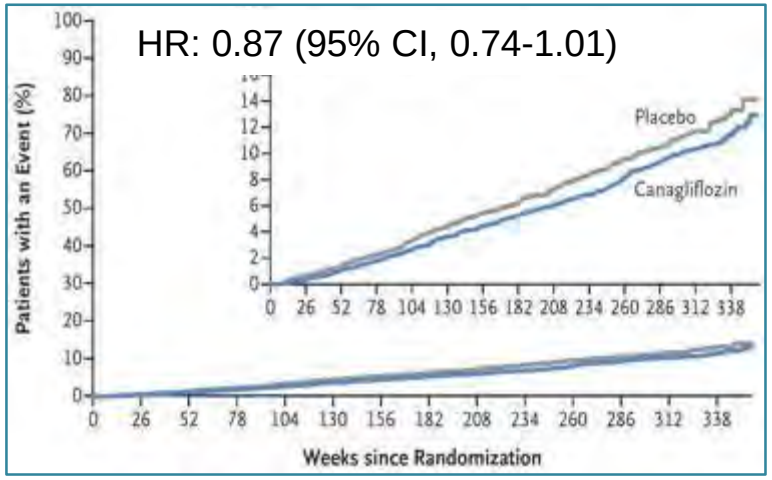
What About Other Effects of SGLT2 inhibitors?

All-cause Mortality

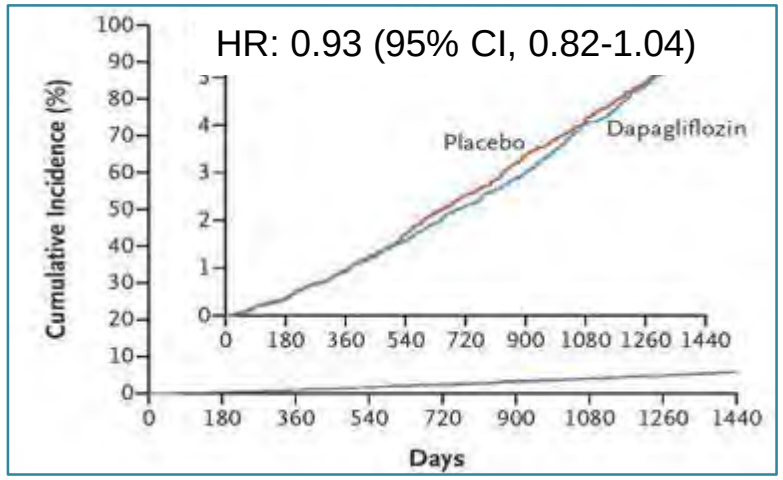
EMPA-REG (Empagliflozin)



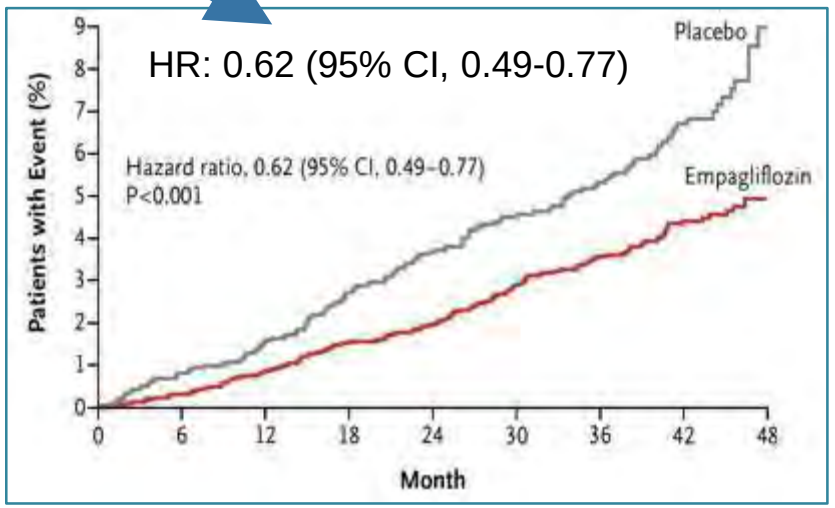
CANVAS (Canagliflozin)

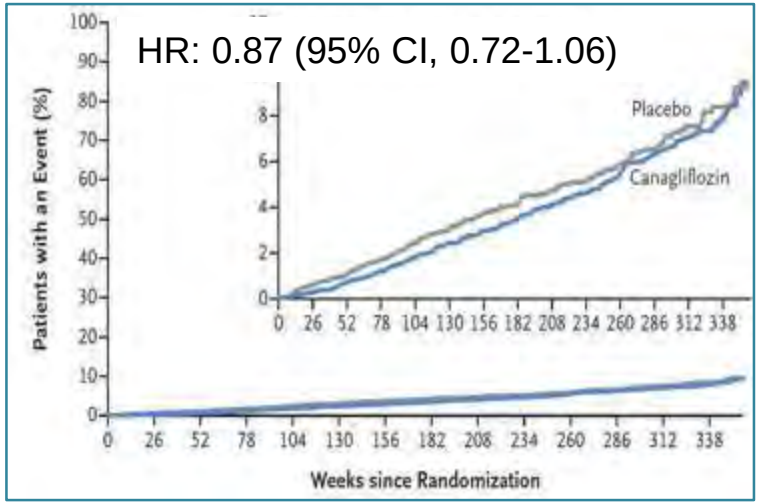


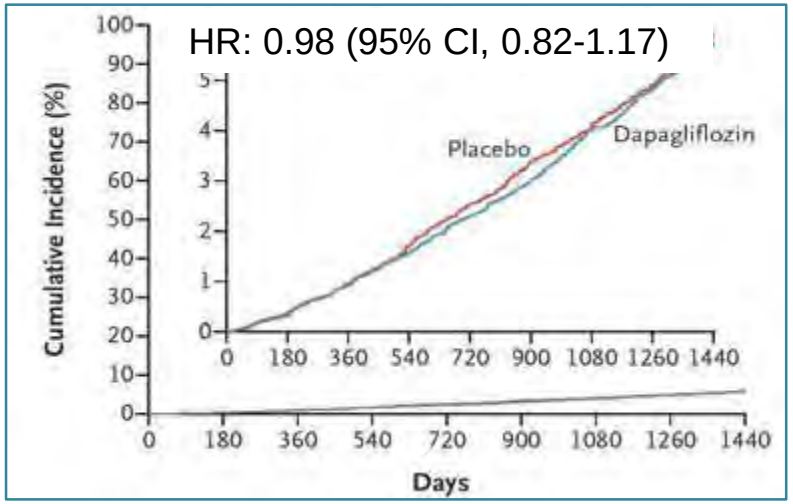
DECLARE (Dapagliflozin)



Cardiovascular Death

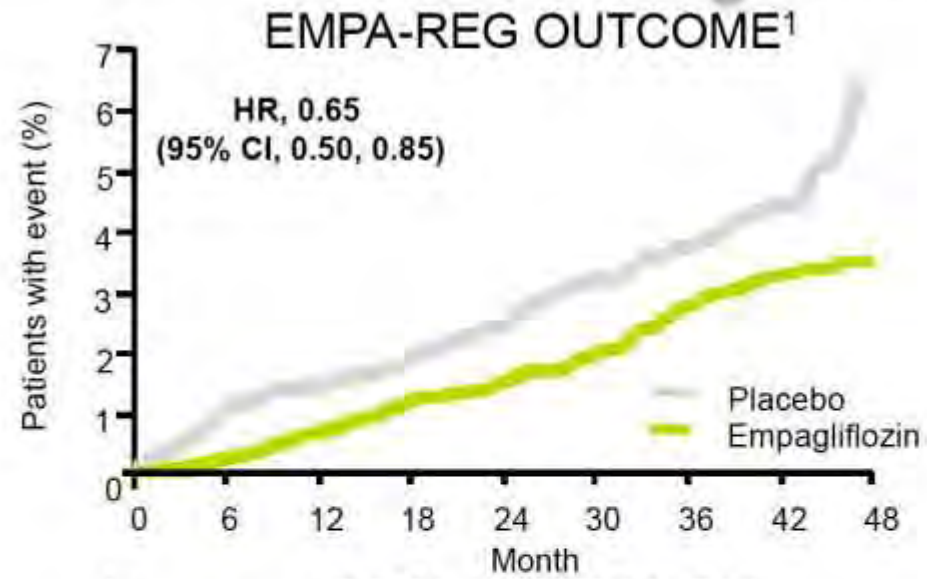


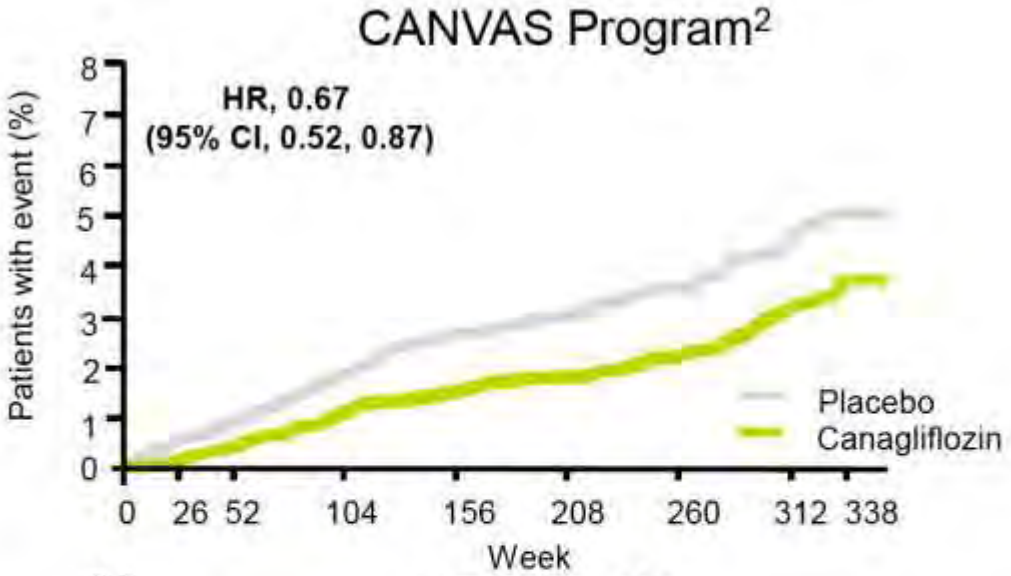


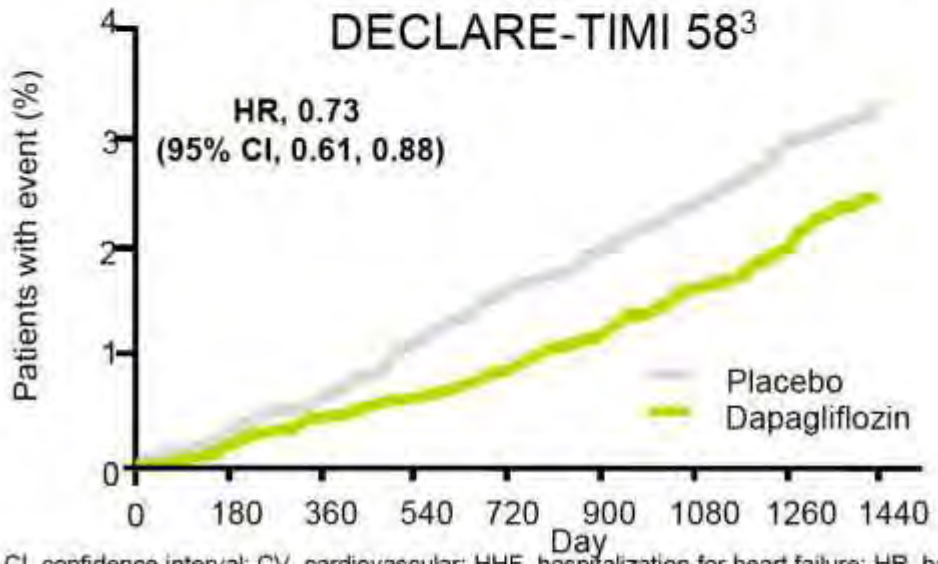


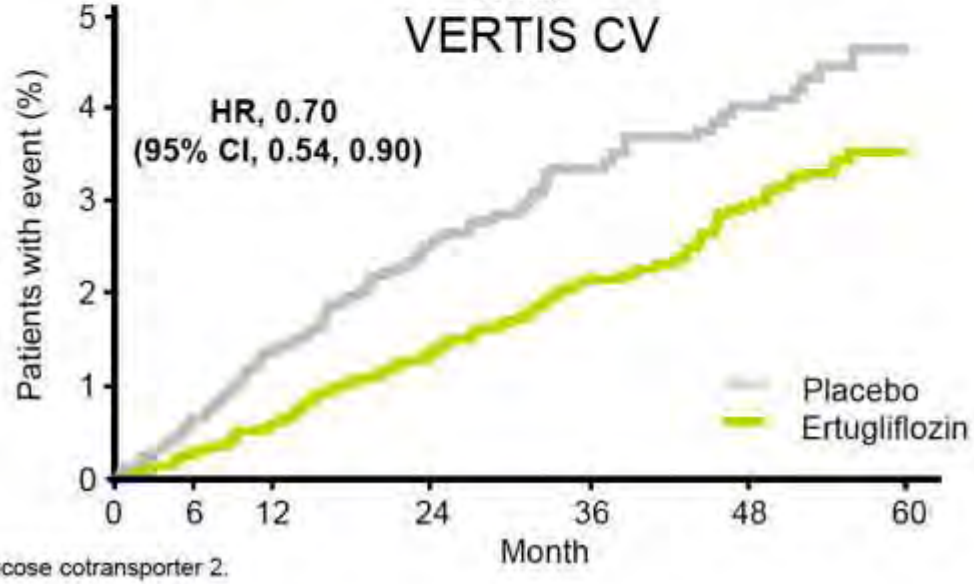
Hospitalization for Heart Failure: SGLT2-i CVOTs

All four drugs showed significant hazard risk reduction









CI, confidence interval; CV, cardiovascular; HHF, hospitalization for heart failure; HR, hazard ratio; SGLT2, sodium-glucose cotransporter 2.

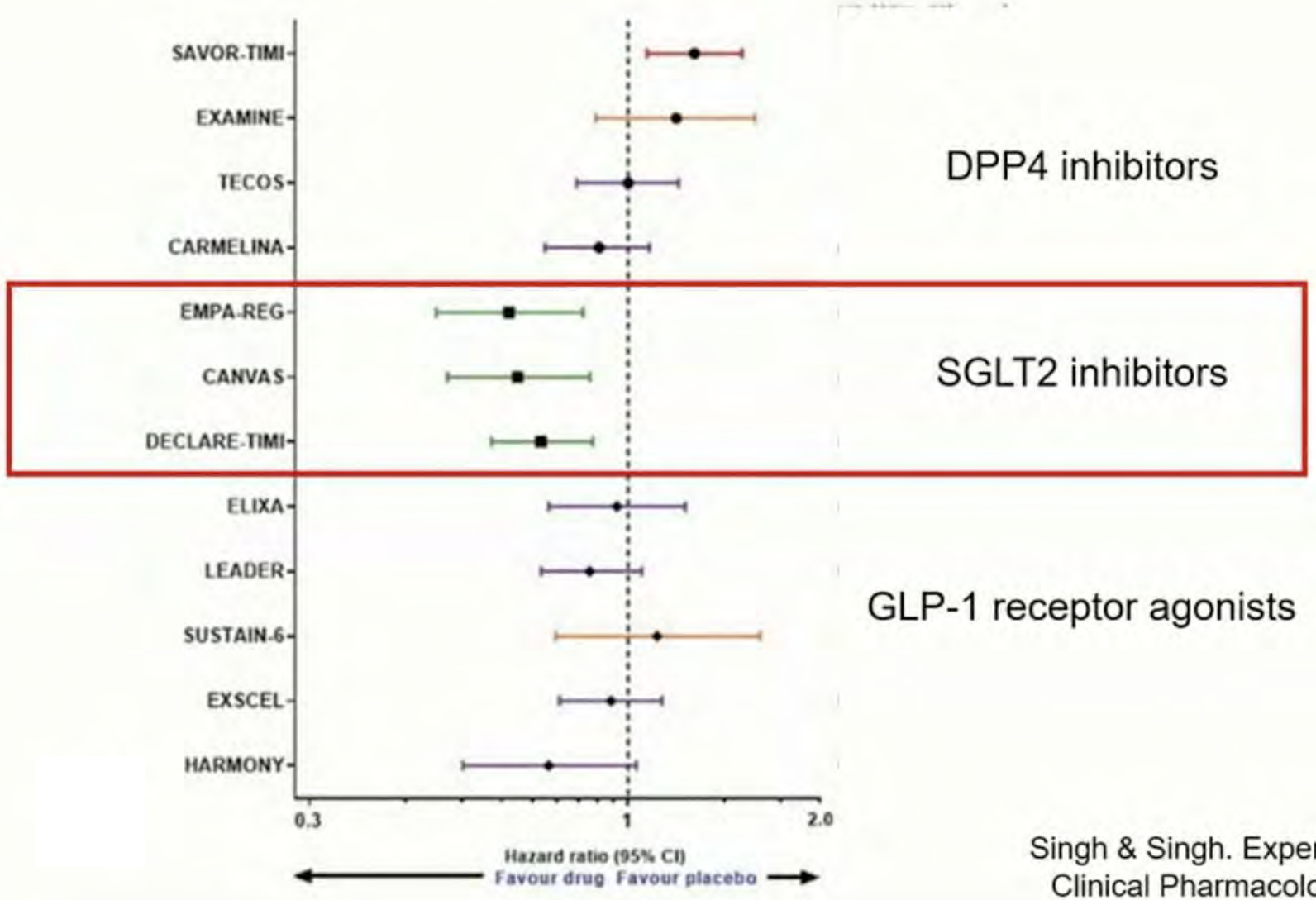
1. Zinman B et al. *N Engl J Med* 2015;373:2117-2128. 2. Neal B et al. *N Engl J Med* 2017;377:644-657.
3. Wiviott SD et al. *N Engl J Med* 2019;380:347-357 (figure provided by D.K. McGuire, with permission).

CV outcomes

	MACE HR (95% CI)	CV Death HR (95% CI)	HHF HR (95% CI)
EMPA-REG OUTCOME[1]	**0.86** (0.74, 0.99)	**0.62** (0.49, 0.77)	**0.65** (0.50, 0.85)
CANVAS Program[2]	**0.86** (0.75, 0.97)	**0.87** (0.72, 1.06)	**0.67** (0.52, 0.87)
DECLARE-TIMI 58[3]	**0.93** (0.84, 1.03)	**0.98** (0.82 ,1.17)	**0.73** (0.61, 0.88)
VERTIS CV	**0.97** (0.85, 1.11)	**0.92** (0.77, 1.11)	**0.70** (0.54, 0.90)

CV, cardiovascular; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events.
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* 2019;380:347-357.

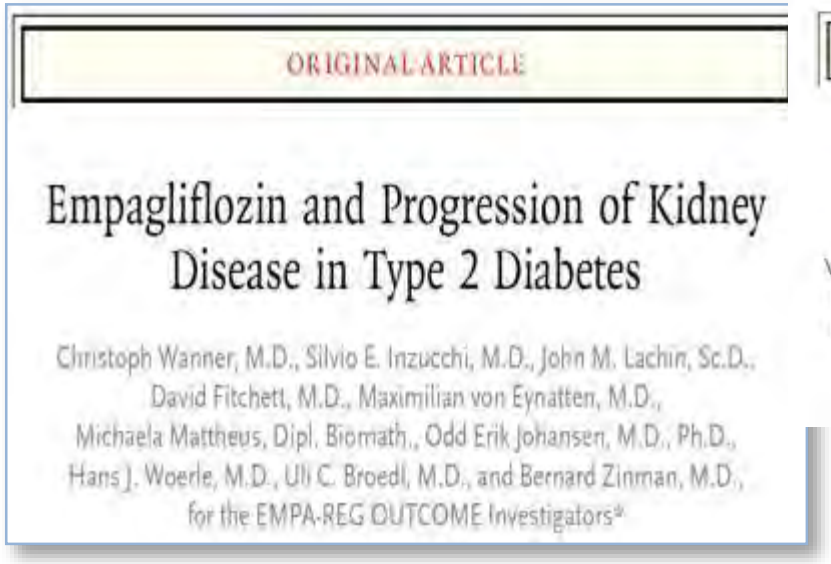
Effect of Antidiabetic Drugs on Heart Failure Hospitalizations



Singh & Singh. Expert Review of Clinical Pharmacology (2019)

SGLT-2 Inhibitors and Renal Outcomes

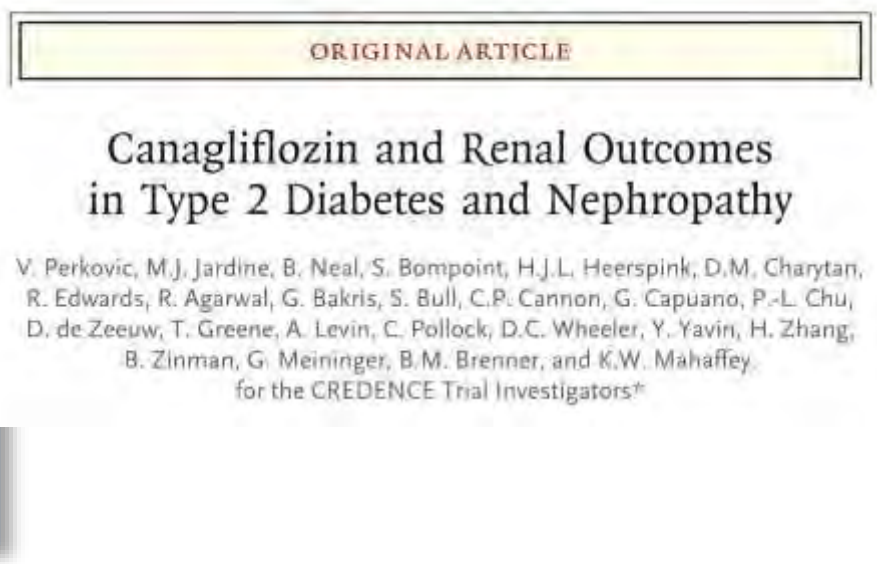
The NEW ENGLAND JOURNAL of MEDICINE



ORIGINAL ARTICLE

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

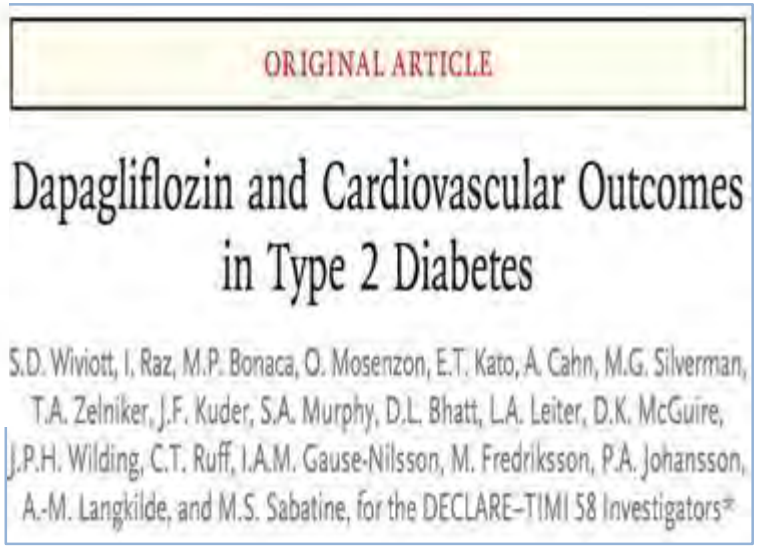
Christoph Wanner, M.D., Silvio E. Inzucchi, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Maximilian von Eynatten, M.D., Michaela Mattheus, Dipl. Biomath., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Bernard Zinman, M.D., for the EMPA-REG OUTCOME Investigators*



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*



ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, M.G. Silverman, T.A. Zelniker, J.F. Kuder, S.A. Murphy, D.L. Bhatt, L.A. Leiter, D.K. McGuire, J.P.H. Wilding, C.T. Ruff, I.A.M. Gause-Nilsson, M. Fredriksson, P.A. Johansson, A.-M. Langkilde, and M.S. Sabatine, for the DECLARE–TIMI 58 Investigators*

The EMPA-REG, CANVAS and DECLARE trials showed empagliflozin, canagliflozin and dapagliflozin were associated with ***slower progression of kidney disease and lower rates of clinically relevant renal events*** than was placebo when added to standard care.

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 et al. NEJM 2018, on line November 2018

DAPA-HF

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

Background

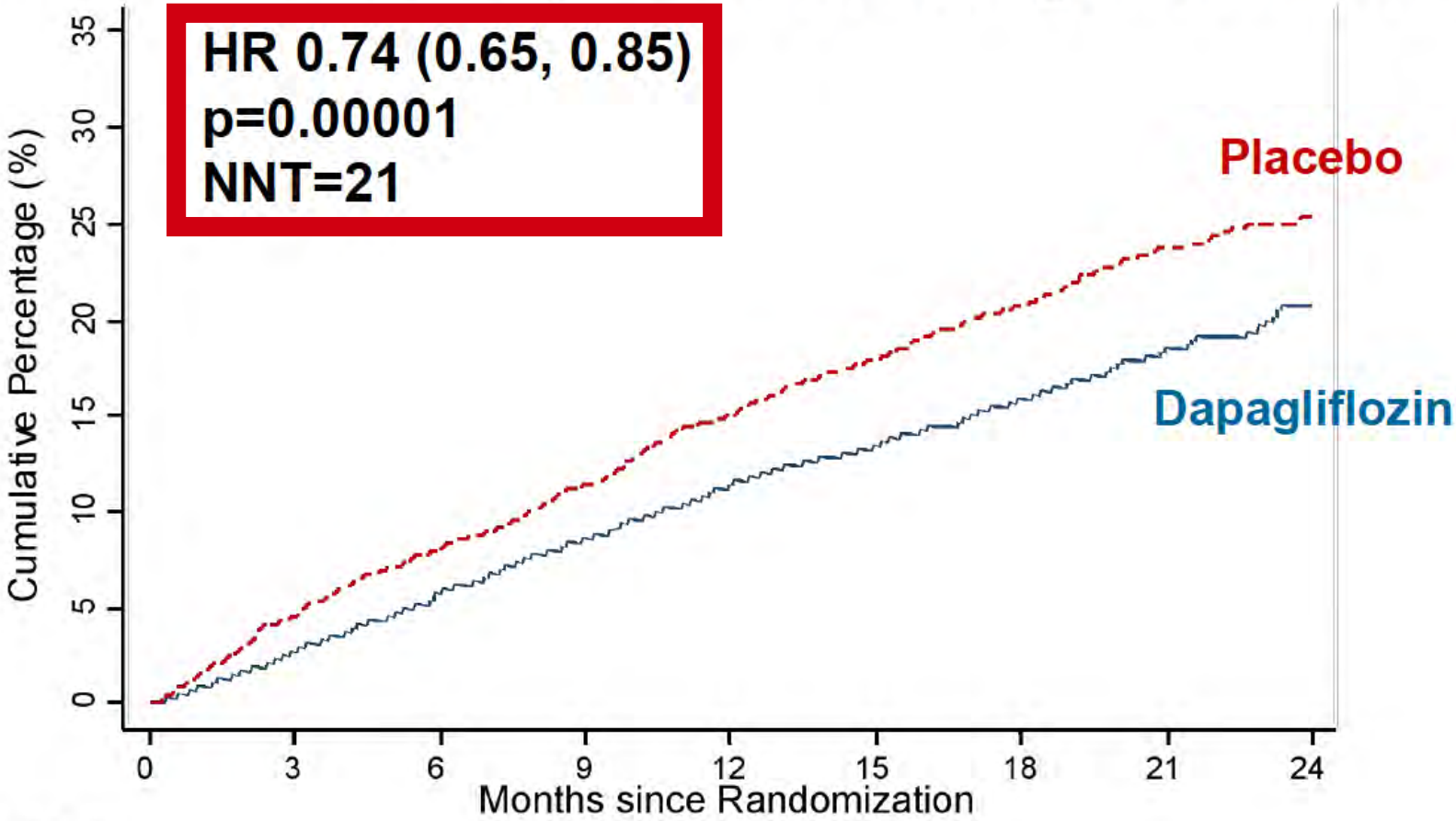
- Sodium-glucose co-transporter 2 (SGLT2) inhibitors ***prevent*** the development of heart failure in patients with type 2 diabetes (T2D). Can they be used to ***treat*** patients with established heart failure?
- The benefits of SGLT2 inhibitors may be glucose-independent. Can SGLT2 inhibitors be used to treat patients ***without*** T2D?
- We tested the SGLT2 inhibitor dapagliflozin,10 mg once daily, added to standard therapy, in patients with heart failure and reduced ejection fraction (HFrEF) both ***with and without*** T2D

McMurray JJV et al. N Engl J Med 2019; 381:1995-2008

DAPA-HF

Primary composite outcome

CV Death/HF hospitalization/Urgent HF visit



Number at Risk

Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

McMurray JJV et al. N Engl J Med 2019; 381:1995-2008

Indications for the Use of dapafliflozin (Farxiga)

October 21, 2019 Update

as an adjunct to diet and exercise to improve *glycemic control* in adults with type 2 diabetes mellitus

- to *reduce the risk of hospitalization for heart failure* in adults with type 2 diabetes mellitus *and* established cardiovascular disease *or* multiple cardiovascular risk factors

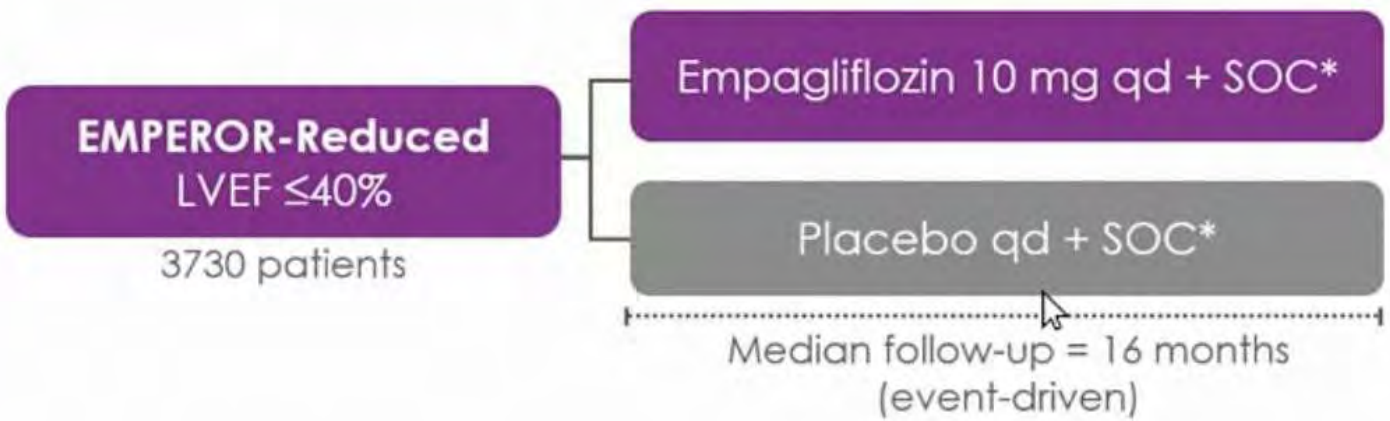
EMPEROR-Reduced

Phase III randomised double-blind placebo-controlled trial

Aim: To investigate the safety and efficacy of empagliflozin versus placebo on top of guideline-directed medical therapy in patients with heart failure with **reduced ejection fraction**

Population: T2D and non-T2D, aged ≥18 years, chronic HF (NYHA class II–IV)

Study design[1-3]



Confirmatory endpoints[1,2]

COMPOSITE PRIMARY ENDPOINT

Time to first event of adjudicated CV death or adjudicated HHF

SECONDARY ENDPOINTS

- **First and recurrent adjudicated HHF events**
- **Slope of change in eGFR (CKD-EPI) from baseline**

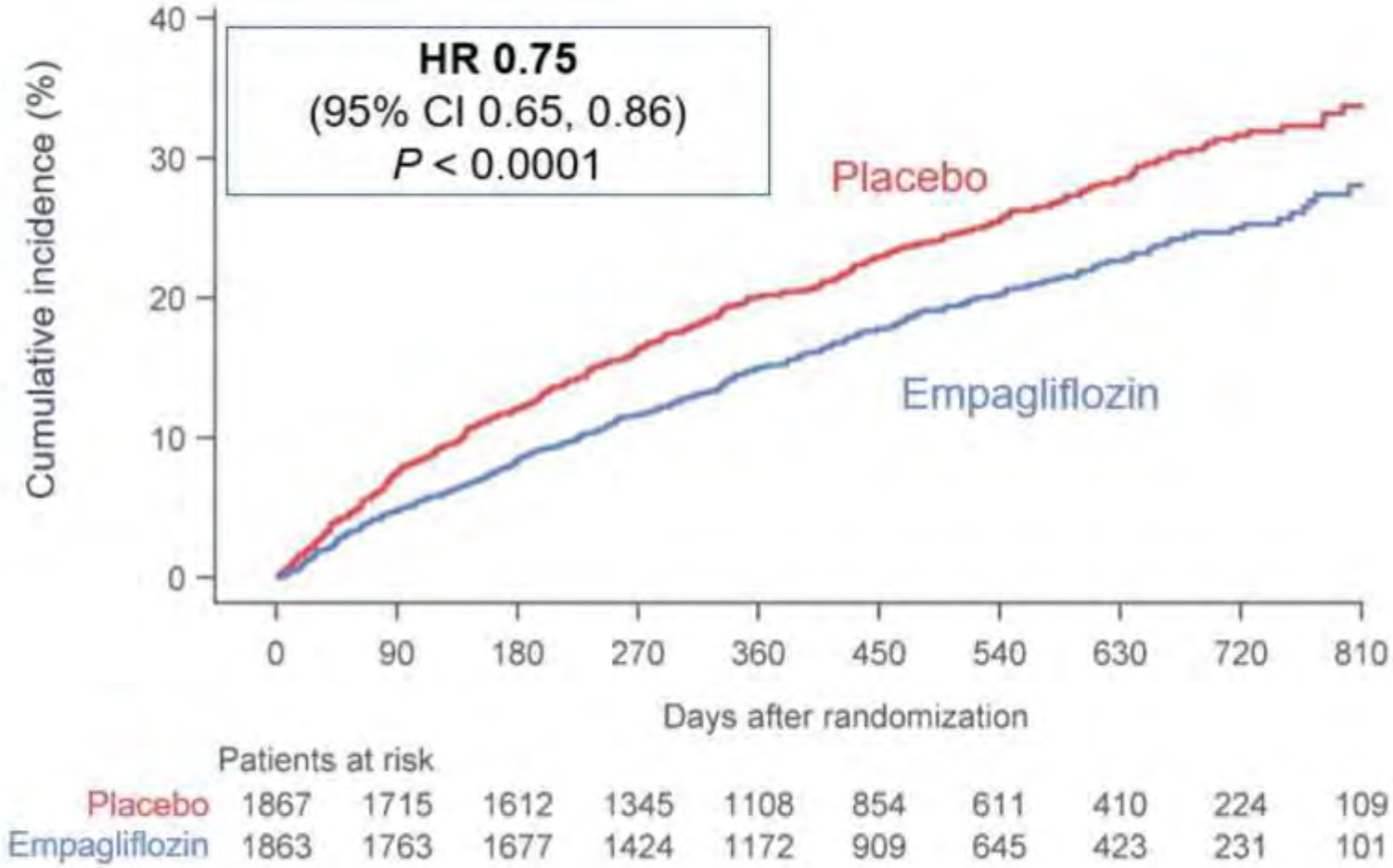
*Guideline-directed medical therapy

CV, cardiovascular; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HF, heart failure; HHF, hospitalisation for heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; qd, once daily; SOC, standard of care; T2D, type 2 diabetes

1. ClinicalTrials.gov. NCT03057977 (accessed Aug 2020); 2. Packer M et al. Eur J Heart Fail 2019;21:1270; 3. Date on file

EMPEROR-Reduced: Primary Composite Outcome

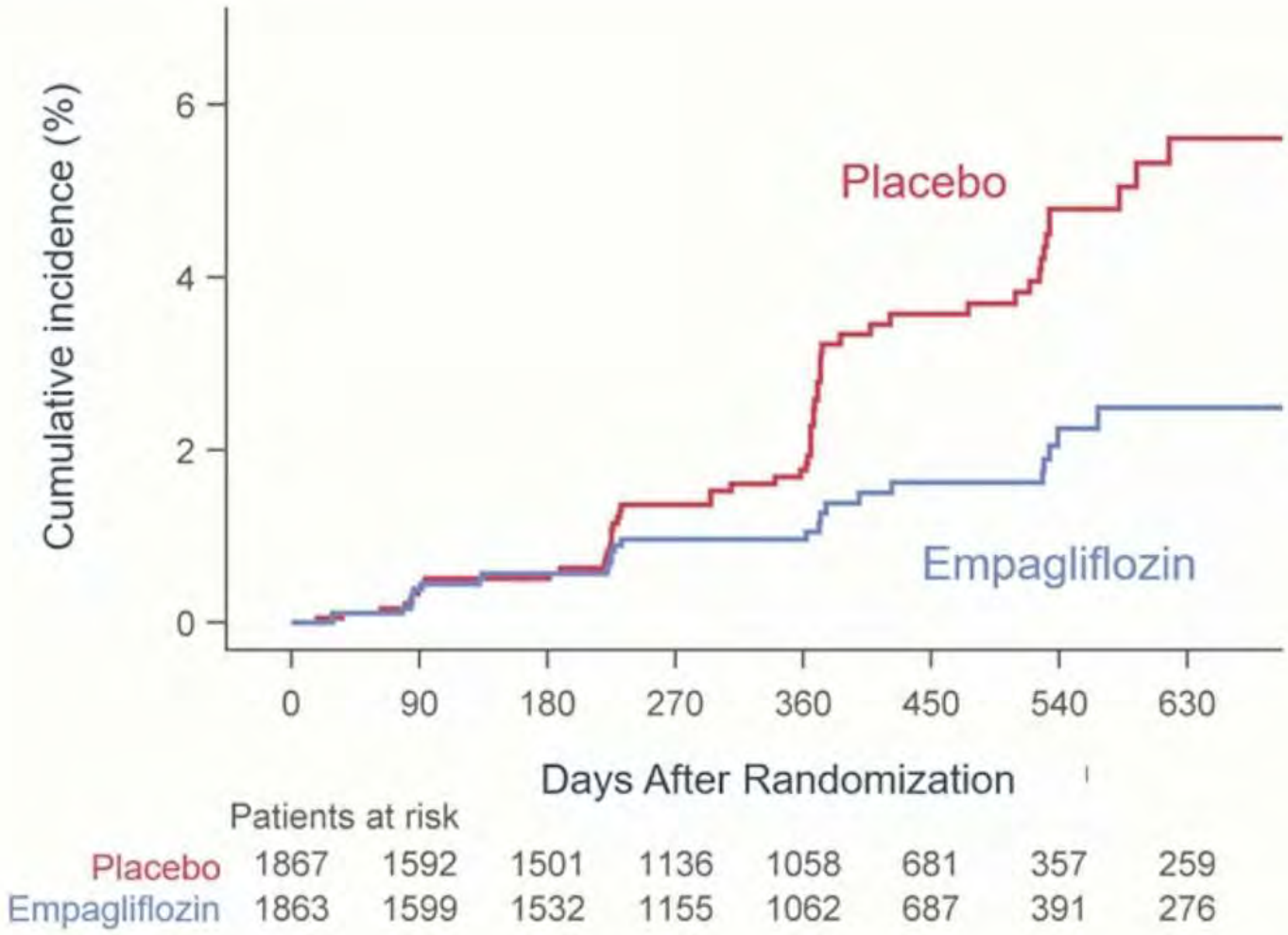
N=3730
EF ≤40%
eGFR ≥20
empa 10mg vs. Plac
F/U 16 months



UT Southwestern Medical Center
Parkland

Packer M, et al. N Engl J Med 2020; DOI: 10.1056/NEJMoa2022190

EMPEROR-Reduced: Composite Renal Endpoint



58 patients with event
Rate: 3.1/100 patient-years

30 patients with event
Rate: 1.6/100 patient-years

HR 0.50
(95% CI 0.32, 0.77)

Packer et al. Under review

SGLT2 Inhibition With Empagliflozin Is Effective in Heart Failure With a Reduced Ejection Fraction With or Without Diabetes

Primary Endpoint
Composite of cardiovascular death or heart failure hospitalization

25% ↓ in risk
P < 0.001

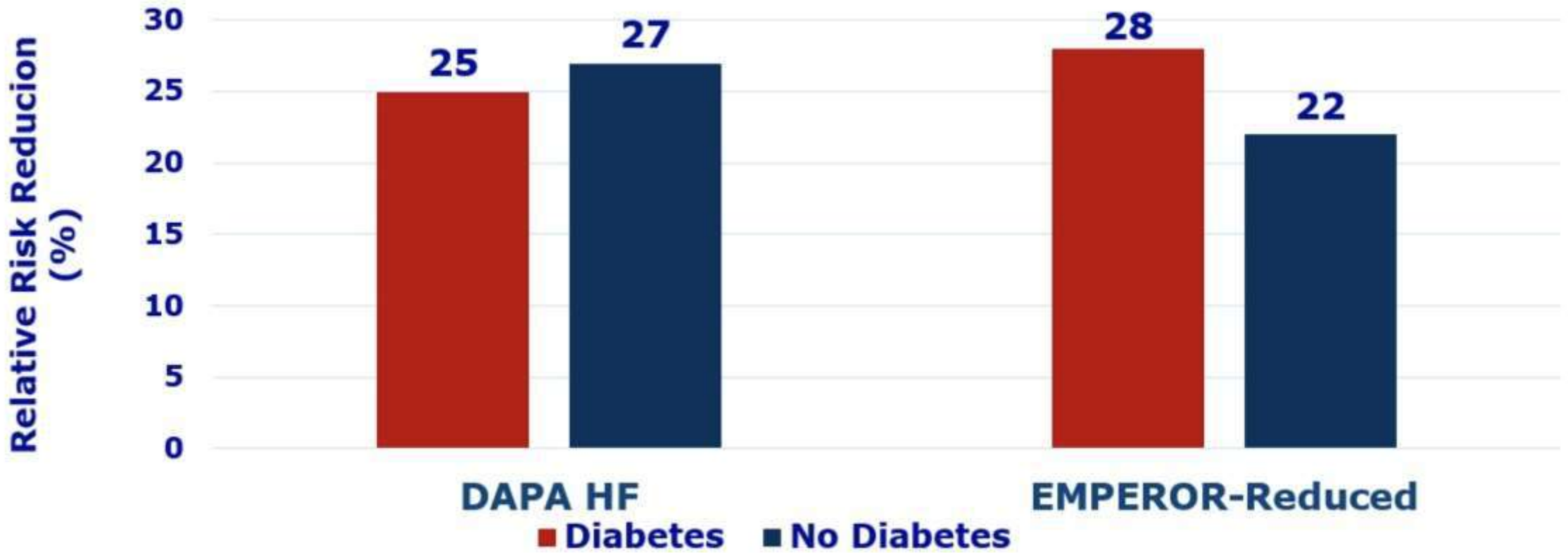
First Secondary Endpoint
Total (first and recurrent) heart failure hospitalizations

30% ↓ in risk
P < 0.001

Second Secondary Endpoint
Slope of decline in glomerular filtration rate over time

P < 0.001
(50% ↓ in renal events)

SGLT2 inhibitors in HFrEF with or without Diabetes: Effects on primary composite outcomes



UT Southwestern Medical Center
Parkland

McMurray, J. J. V., et al. N Engl J Med 2019; 381: 1995-2008
Packer M, et al. N Engl J Med 2020; DOI: 10.1056/NEJMoa2022190

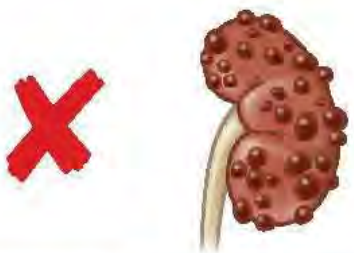
RCT Protocol

Dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD)

Rationale and trial protocol

Multicentre ~ 400
Target n = 4300
Patients with and without type 2 diabetes

≥ 18 years
25–75 ml/min/1.73 m^2
uACR ≥ 200 mg/g



Polycystic kidney disease
Lupus nephritis
ANCA vasculitis
Type I diabetes

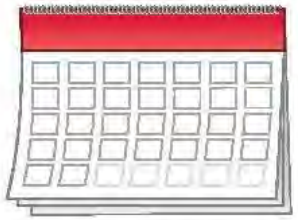
Interventions

Dapagliflozin 10 mg

1:1

Placebo

Follow-up

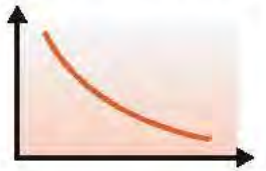


~ 45 months

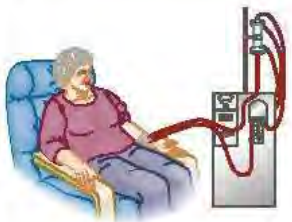
Event-driven (681 events)

Primary outcome

Composite renal endpoint



≥ 50% decline in eGFR



End-stage kidney disease

Renal or cardiovascular death

ndt NEPHROLOGY DIALYSIS TRANSPLANTATION

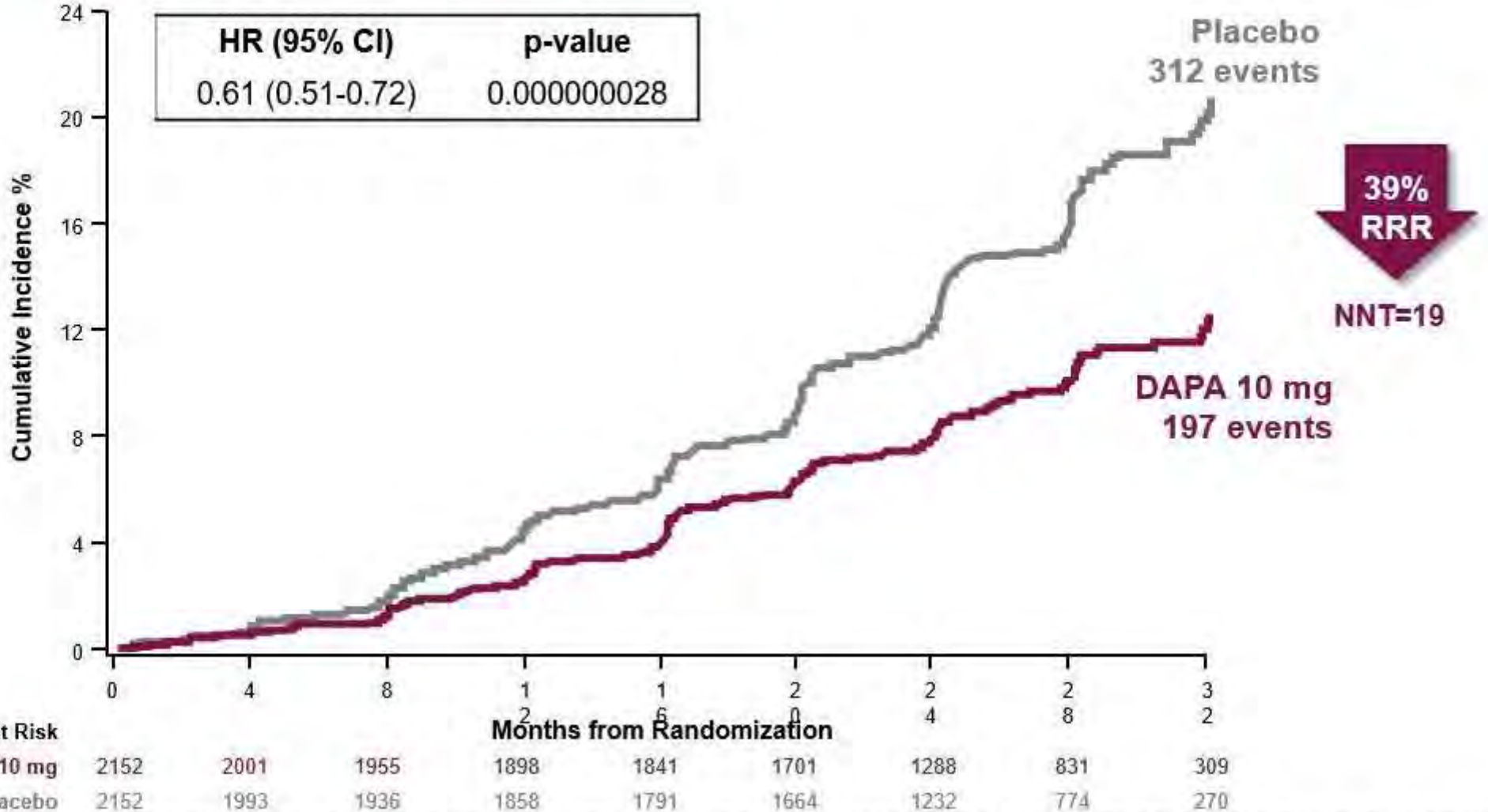
Heerspink HJL et al. NDT (2019)
@NDTSocial

AstraZeneca Stops DAPA-CKD Phase 3 trial Early After Dapagliflozin Shows Efficacy in Patients with Chronic Kidney Disease

Farxiga Phase III DAPA-CKD trial will be stopped early after overwhelming efficacy in patients with chronic kidney disease

Primary Composite Outcome: Sustained ≥50% eGFR Decline, ESKD, Renal or CV Death (similar in T2D vs. non-T2D)

Heerspink HJL et al. NEJM 2020;383:1436-1446



[a]ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15mL/min/1.73m^2 for at least 28 days. Renal death was defined as death due to ESKD when dialysis treatment was deliberately withheld for any reason.[2] CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; ; NNT = number needed to treat; RRR = relative risk reduction.

1. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020. 2. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282.

SGLT2i and CKD

	Renal-related Composite Outcomes	HR (95% CI)
EMPA-REG OUTCOME[1]	Doubling of the serum creatinine level, initiation of renal-replacement therapy, or death from renal disease	**0.54 (0.40, 0.75)**
CANVAS Program[2]	Sustained 40% reduction in eGFR, renal- replacement therapy (dialysis or transplantation),or death from renal causes	**0.60 (0.47, 0.77)**
DECLARE-TIMI 58[3]	Sustained ≥40% decrease in eGFR to <60 mL/min/1.73 m^2 and/or end-stage renal disease and/or renal or CV death	**0.53 (0.43, 0.66)**
VERTIS CV[4]	Renal death, dialysis/transplant, or doubling of serum creatinine from baseline	**0.81 (0.64, 1.03)**
CREDENCE[5]	Sustained doubling of serum creatinine level and/or end-stage renal disease and or renal or cardiovascular death	**0.70 (0.59, 0.82)**
DAPA-CKD[6]	Sustained ≥50% eGFR decline and/or end-stage renal disease and or renal or cardiovascular death	**0.61 (0.51, 0.72)**

CV, cardiovascular; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

1. Wanner C et al. *N Engl J Med* 2016. 2. Neal B et al. *N Engl J Med* 2017. 3. Wiviott SD et al. *N Engl J Med* 2019. 4. Mc Murray J. et al. Presented at the American Diabetes Association 2020; 5. Perkovic V. et al *N Engl J Med* 2019. 6. Heerspink H. et al. *N Engl J Med* 2020

Ongoing Large HF & CKD Trials with SGLT2 Inhibitors

Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved)

- Chronic HF (NYHA II-IV)
- LVEF >40%
- ↑ NT-proBNP
- eGFR >20
- N=5988
- 1°: HHF / CV death
- Est. completion: 2021

Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction HF (DELIVER)

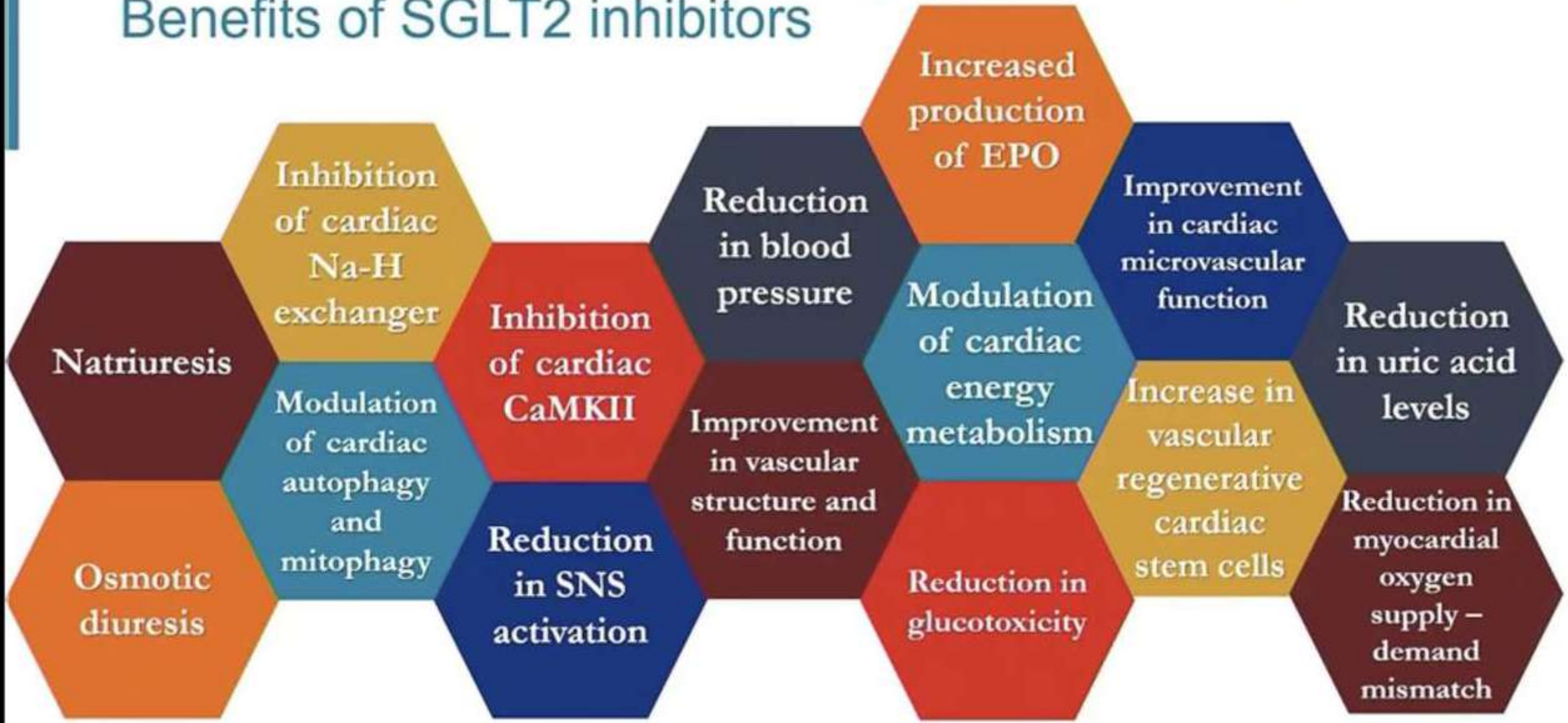
- Chronic HF (NYHA II-IV)
- LVEF >40%
- ↑ NT-proBNP
- eGFR ≥25
- N=6100
- 1°: Worsening HF/CV death
- Completion: 2021

EMPA-KIDNEY (The Study of Heart and Kidney Protection With Empagliflozin)

- eGFR 20-45 or 45-90 + UACR >500
- N=6000
- Outcome: ESKD, renal or CV death or 40% ↓ in eGFR
- Completion: 2022

www.clinicaltrials.gov (accessed 9/19/20)

Proposed Mechanisms Underlying the Heart Failure Benefits of SGLT2 inhibitors



What's likely off the table 2020

- Glucose lowering
- Plaque regression
- Blood pressure
- Increased ketone oxidation
- Weight reduction
- Just a diuretic

What's on the table 2020

- Sustained natriuresis and differential diuresis
- Cardiac energetics
- EPO
- SNS inhibition
- NHE-1 and NLRP3
- 2* to renal function

Cardiovascular Outcome Trials

GLP-1 Receptor Agonists

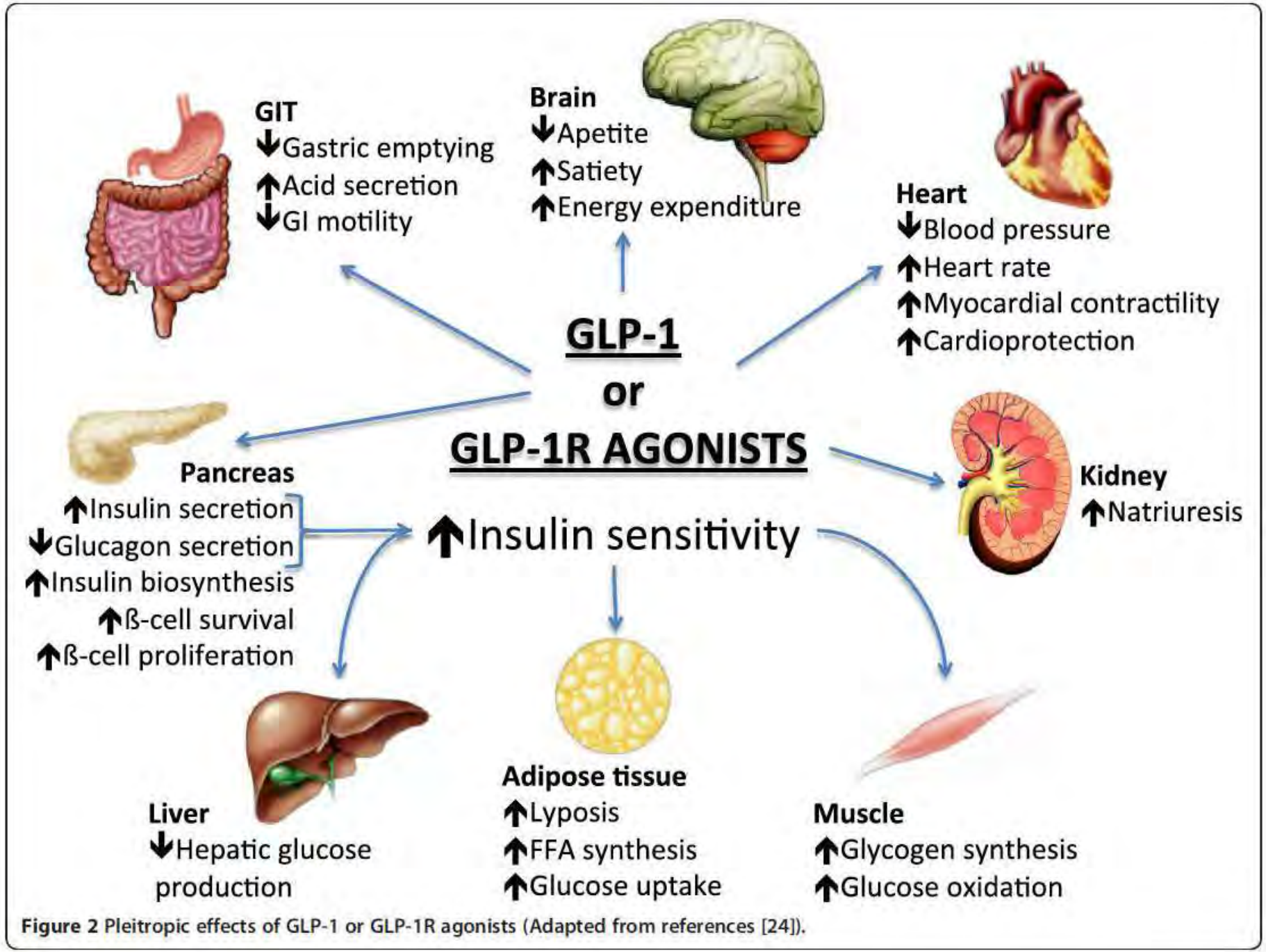
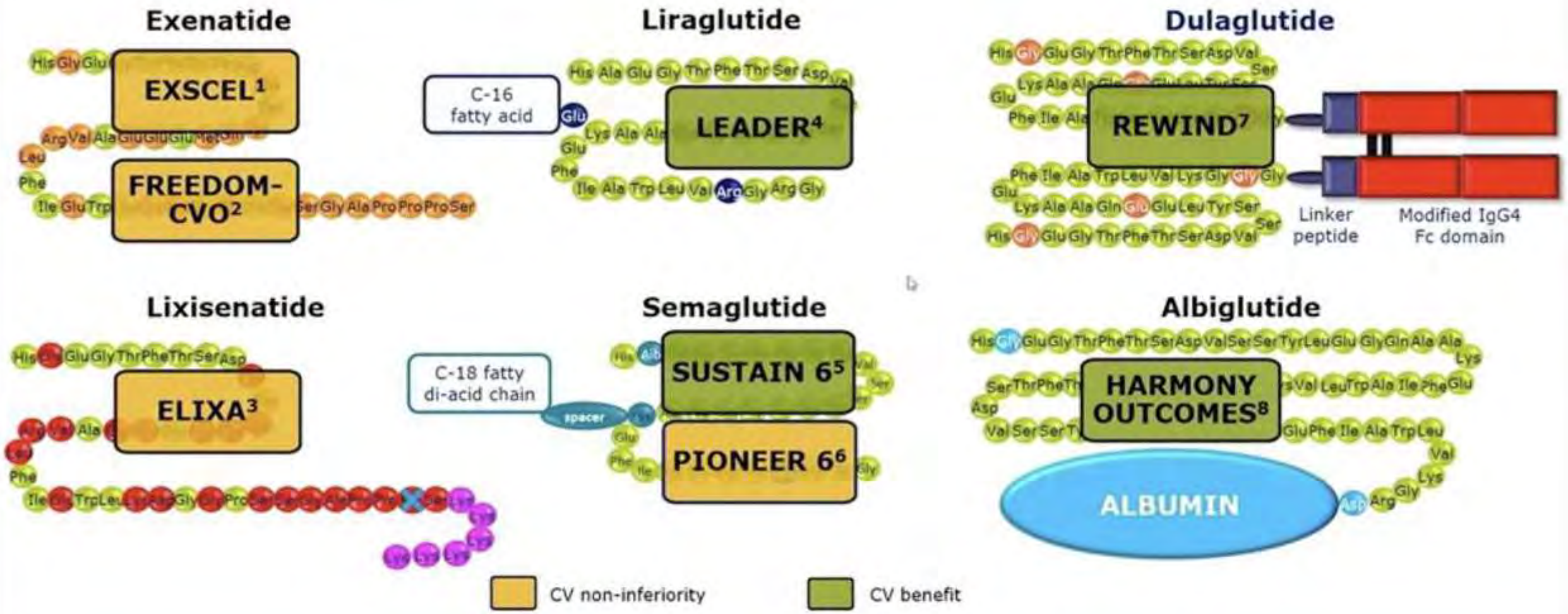


Figure 2 Pleitropic effects of GLP-1 or GLP-1R agonists (Adapted from references [24]).

Sussman et al.: Physiol Rev 2011, 91:1023–1070.

GLP-1RAs have different structures

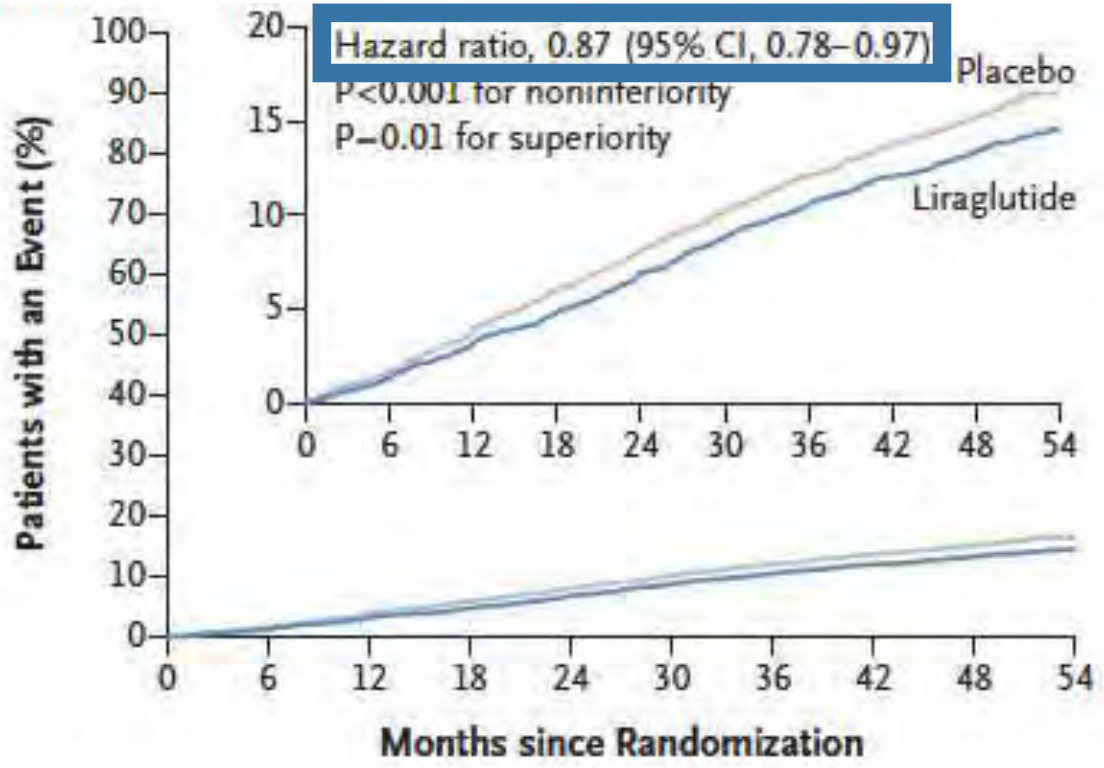


CV, cardiovascular; GLP-1, glucagon-like peptide-1; GLP-1RA, glucagon-like peptide-1 receptor agonist; Ig, immunoglobulin
1. Holman RR *et al. N Engl J Med* 2017;377:1228–39; 2. FREEDOM-CVO. Intarcia Therapeutics, Inc May 2016 press release http://prn.to/1SVcaXg; 3. Pfeffer MA *et al. N Engl J Med* 2015;373:2247–57; 4. Marso SP *et al. N Engl J Med* 2016;375:311–22; 5. Marso SP *et al. N Engl J Med* 2016;375:1834–44; 6. Husain M *et al. N Engl J Med* 2019;381:841-51; 7. Gerstein HC *et al. Diabetes Obes Metab* 2017;20:42–9; 8. Hernandez AF *et al. Lancet* 2018; 203:30–8

LEADER TRIAL

Liraglutide and Cardiovascular Outcomes in T2D

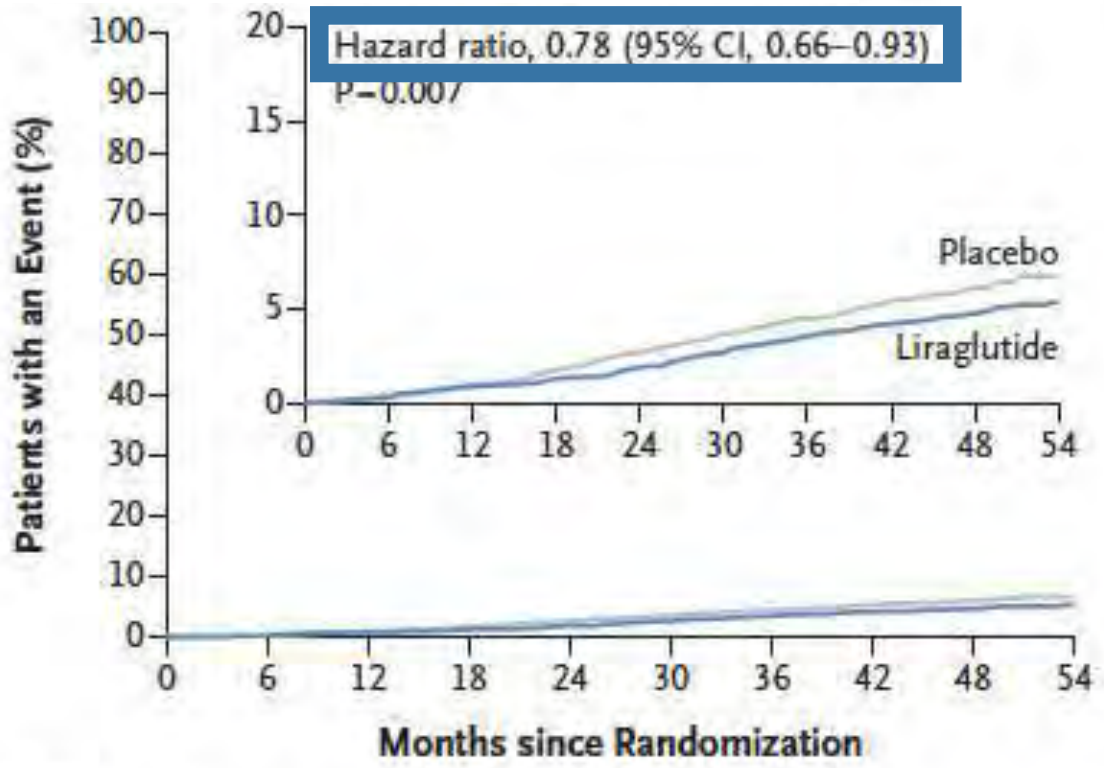
MACE: primary outcome



No. at Risk

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

Death from Cardiovascular causes



No. at Risk

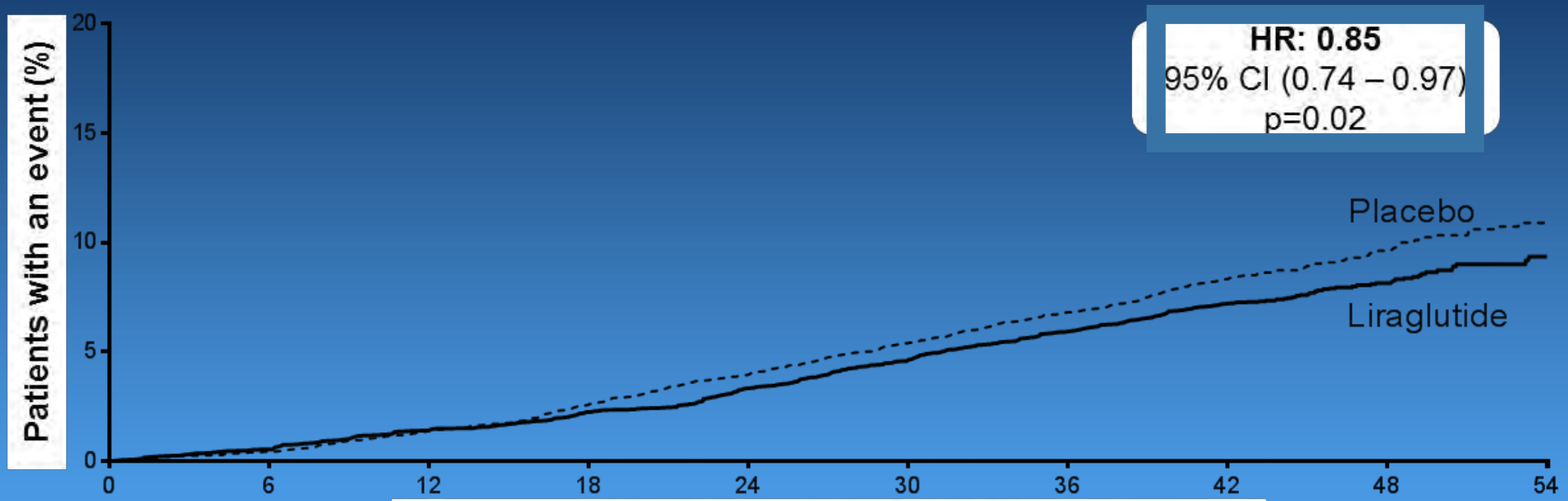
Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

Primary outcome: first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke

Marso SP et al. N Engl J Med 2016;375:311-22

All-cause death

LEADER®



Patients at risk

Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4268	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; HR: hazard ratio.

Marso SP et al. N Engl J Med 2016;375:311-22

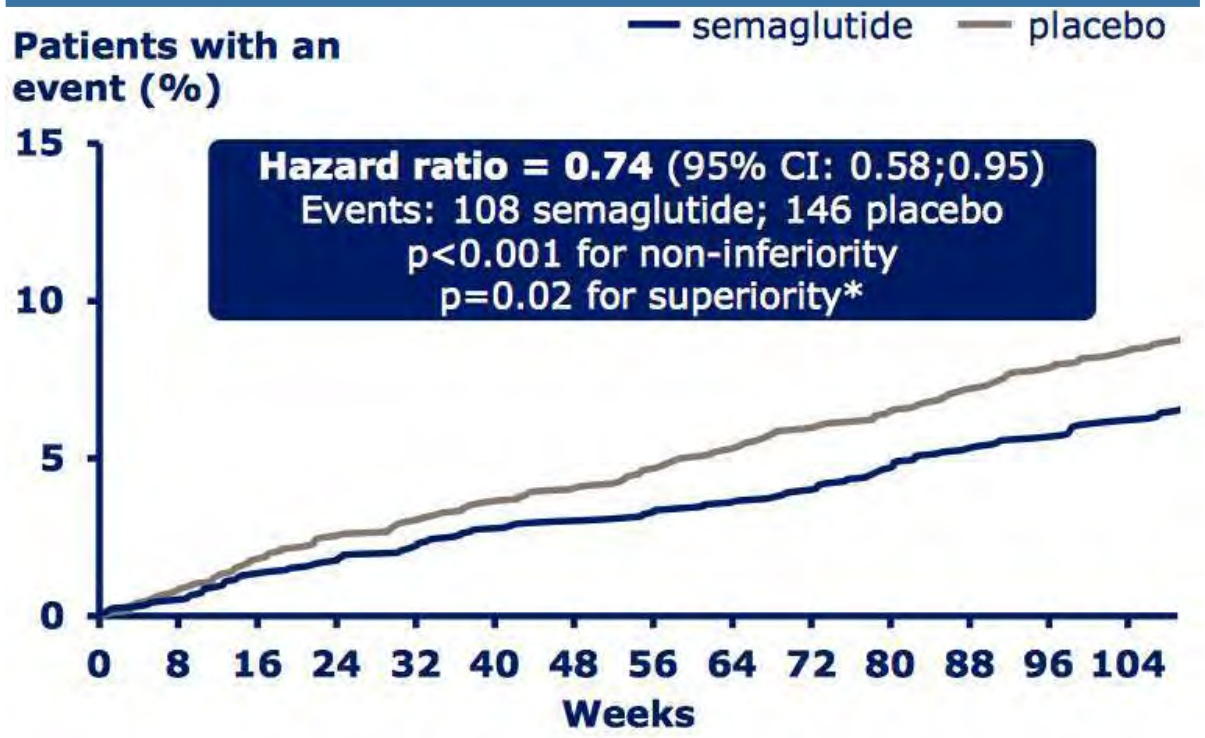
Liraglutide (Victoza) Indications

as an adjunct to diet and exercise ***to improve glycemic control*** in adults with type 2 diabetes mellitus, and

- to reduce the risk of ***major adverse cardiovascular events*** (CV death, non-fatal myocardial infarction, or non-fatal stroke) in adults with *type 2 diabetes mellitus* ***and established CV disease***

Semaglutide significantly reduced the risk of major cardiovascular events in the SUSTAIN 6 trial

Semaglutide demonstrated 26% reduction in composite CV outcome compared with placebo



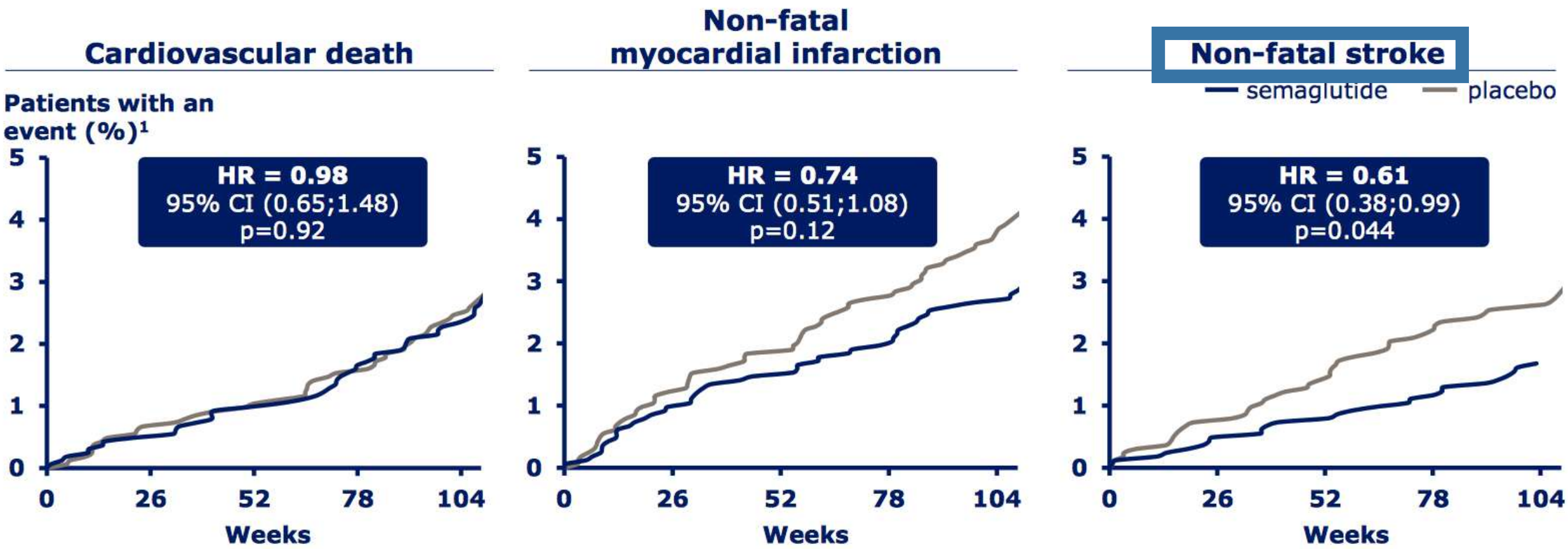
Note: p-value is two-sided, pooled data reported for both semaglutide and placebo
MACE: Major adverse cardiovascular event; 3-point MACE comprises cardiovascular death, non-fatal myocardial infarction and non-fatal stroke; CI: Confidence interval
* No adjustment for multiple tests
Source: Marso SP, Bain SC, Consoli A, *et al.* Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *The New England journal of medicine*. 2016

Key results

- Non-inferiority of semaglutide compared to placebo was confirmed for time to first MACE
- Semaglutide reduced the risk of composite cardiovascular outcome, ie time from randomisation to first occurrence of CV death, non-fatal MI or non-fatal stroke, by 26% compared to placebo
- The result was consistent across sensitivity analyses

Marso SP et al. NEJM 2016;375:1834-1844

The MACE risk reduction was driven by non-fatal MI and non-fatal stroke in the SUSTAIN 6 trial



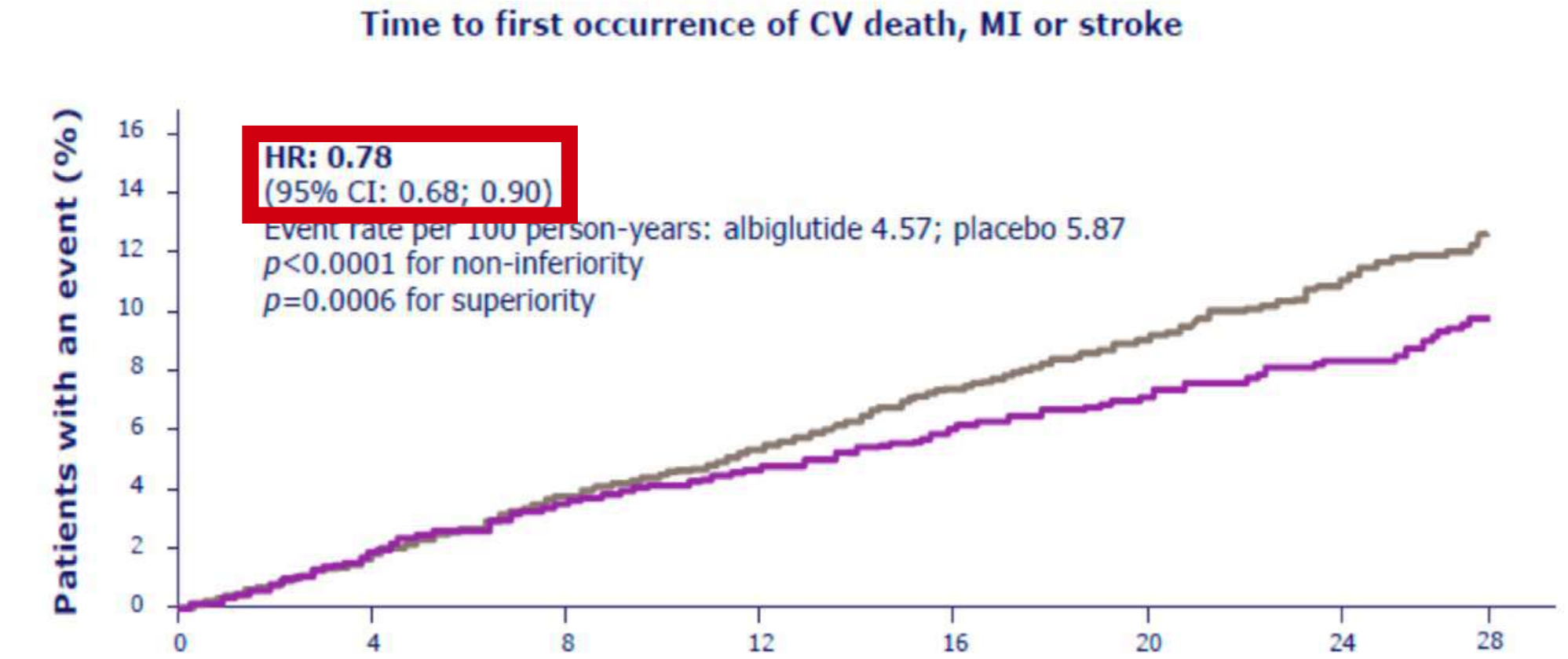
Semaglutide (Ozempic®) Indications

- As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM)

- To reduce risk of **major adverse cardiovascular events** (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke) in adults with **T2DM and established cardiovascular disease**

Albiglutide: HARMONY outcomes

2018

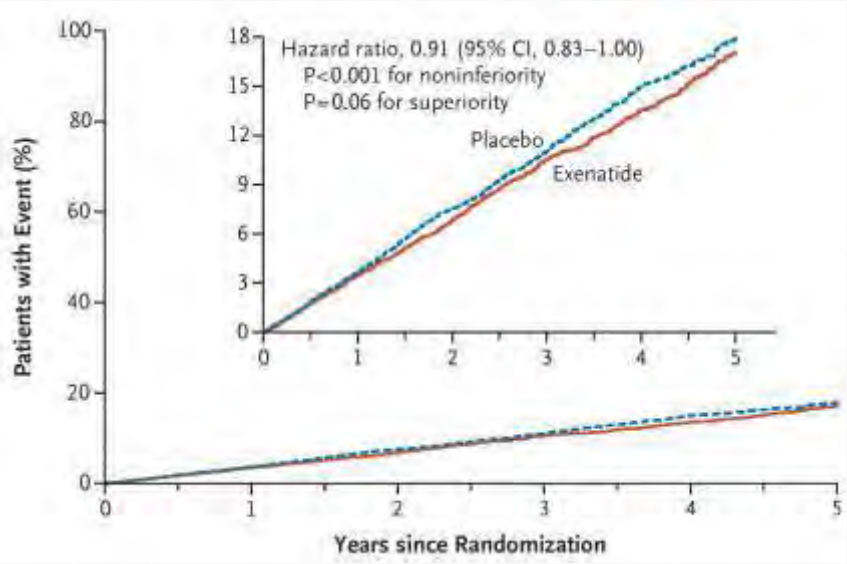


No. at risk							
Albiglutide	4731	4613	4503	4239	3148	2142	1064	-
Placebo	4732	4603	4460	4208	3074	2077	1030	-

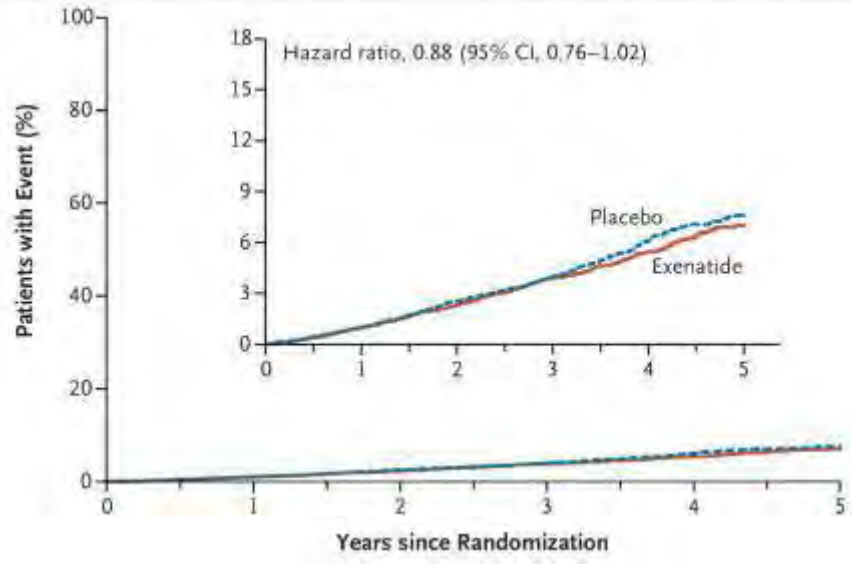
Hernandez et al. Lancet 2018; 392(10157): 1519-1529

EXSCEL Trial: Weekly Exenatide

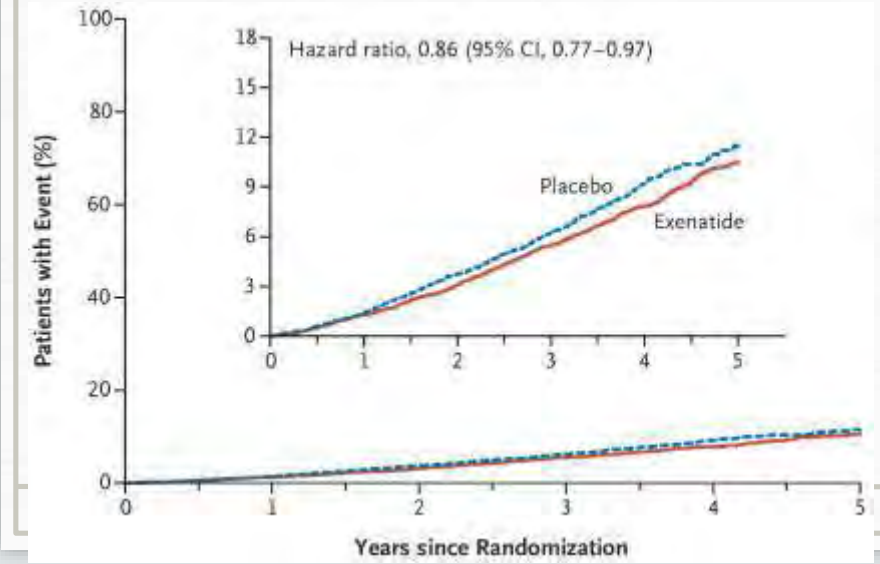
Primary CV outcome



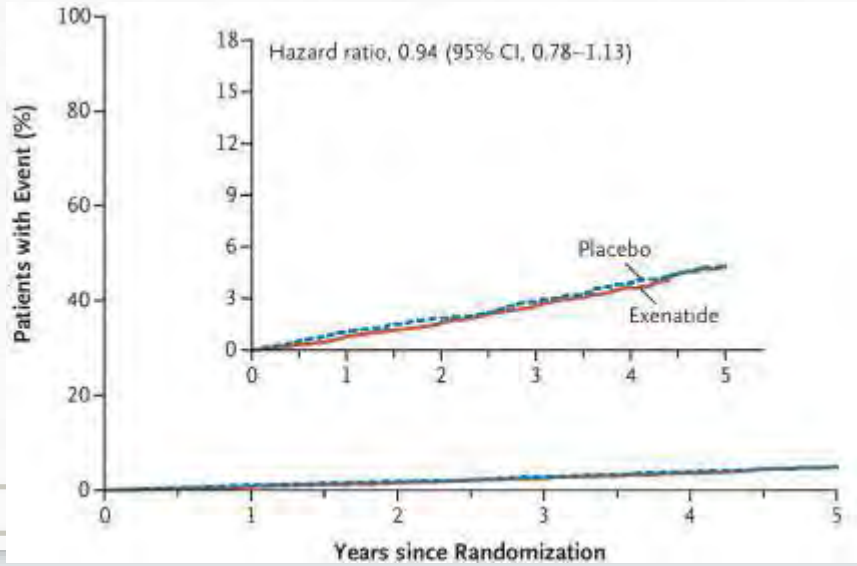
CVDeath



Death from Any Cause



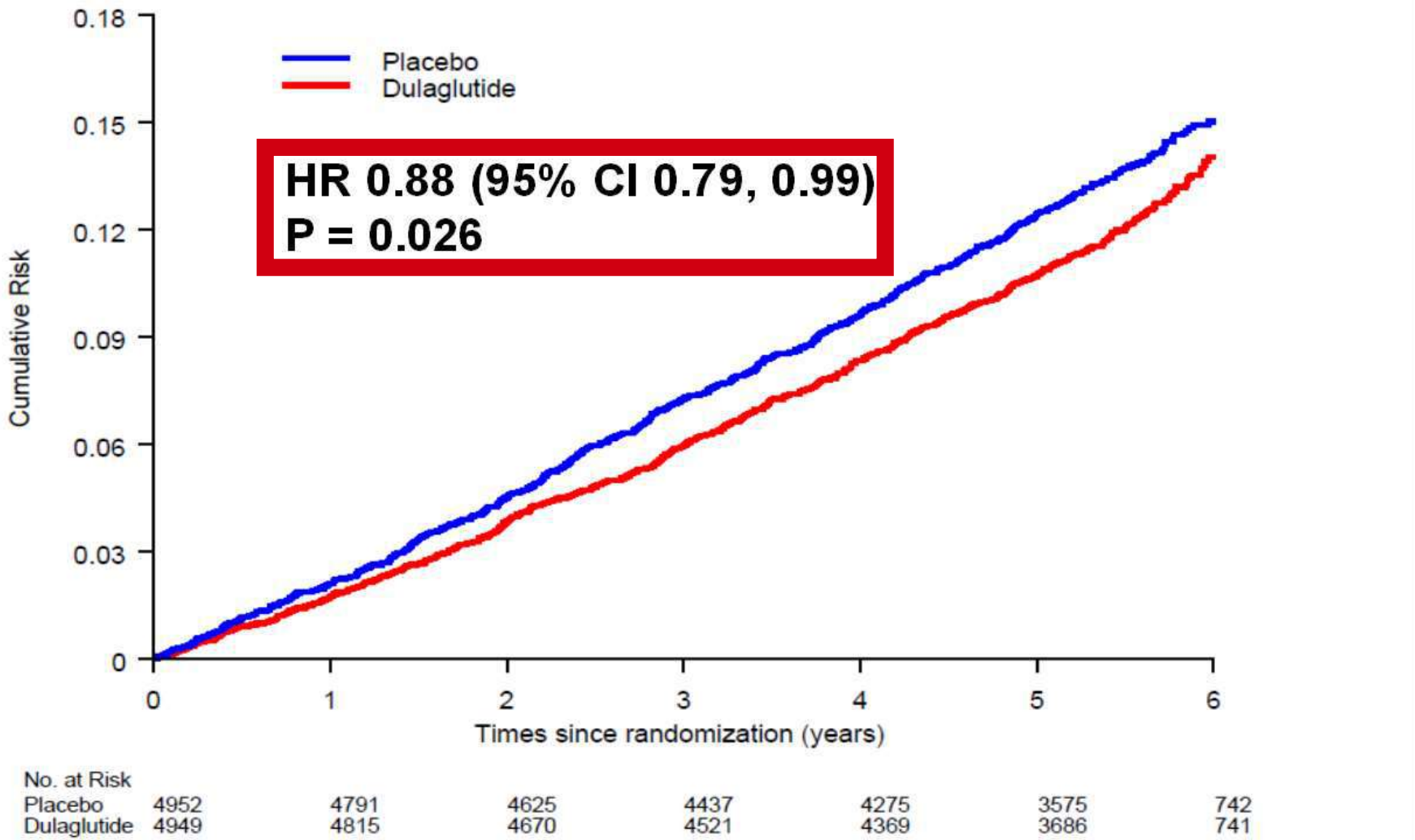
Hospitalization for Heart Failure



N Engl J Med 2017; 377:1228-1239

Dulaglutide Effect on the CV Composite

Primary Outcome: 1st Occurrence of Nonfatal MI, Nonfatal Stroke, CV Death



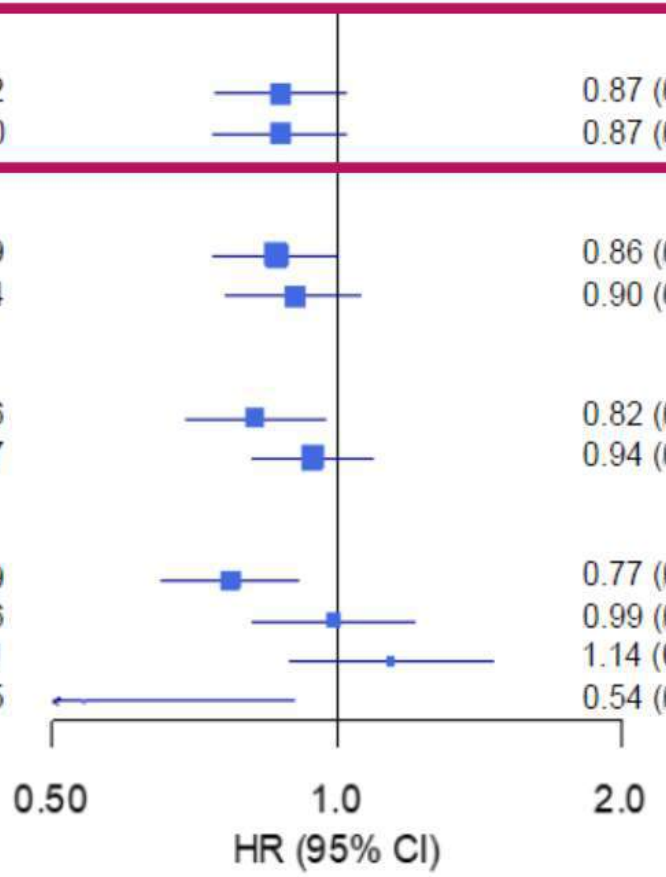
erstein's Slide deck: https://professional.diabetes.org/scientific-sessions-weekly-dulaglutide-and-major-cardiovascular-eventsresults-of-the-rewind-trialltstronggt

Lancet. 2019 Jul 13;394(10193):121-130

REWIND (Dulaglutide)

CV Composite in Prespecified Subgroups

Subgroups	Dulaglutide Events/Total (%)	Dulaglutide Rate/100 py	Placebo Events/Total (%)	Placebo Rate/100 py	Hazard Ratio 95% CI	P value for Interaction
History of CVD						
Prior CVD	280 /1560 (17.9)	3.7	315 /1554 (20.3)	4.2	0.87 (0.74-1.02)	
No Prior CVD	277 /3093 (8.9)	1.7	317 /3128 (10.1)	2.0	0.87 (0.74-1.02)	0.970
Baseline HbA1c						
≥ 7.2%	328 /2610 (12.6)	2.5	373 /2603 (14.3)	2.9	0.86 (0.74-1.00)	
< 7.2%	263 /2329 (11.3)	2.2	289 /2334 (12.4)	2.4	0.90 (0.76-1.06)	0.746
BMI (kg/m^2)						
≥ 32	254 /2281 (11.1)	2.1	308 /2302 (13.4)	2.6	0.82 (0.69-0.96)	
< 32	340 /2667 (12.7)	2.5	355 /2650 (13.4)	2.7	0.94 (0.81-1.09)	0.214
Region						
Europe	248 /2174 (11.4)	2.2	315 /2165 (14.5)	2.9	0.77 (0.65-0.90)	
Latin America	191 /1511 (12.6)	2.6	190 /1510 (12.6)	2.6	0.99 (0.81-1.21)	
USA/Canada	132 /1032 (12.8)	2.4	117 /1039 (11.3)	2.1	1.14 (0.89-1.47)	
Asia Pacific	23 / 232 (9.9)	1.9	41 / 238 (17.2)	3.5	0.54 (0.32-0.89)	0.008



ein's Slide deck: https://professional.diabetes.org/scientific-sessions-weekly-dulaglutide-and-major-cardiovascular-eventsresults-of-the-rewind-trialltstronggt

Lancet. 2019 Jul 13;394(10193):121-130

Implications of the REWIND Findings

	ELIXA	LEADER	SUSTAIN 6	EXSCEL	HARMONY	REWIND
N	6068	9340	3297	14752	9463	9901
Drug Tested	Lixi/d	Lira/d	Sema/wk	Exena/d	Albig/wk	Dula/wk
Prior CVD	10					31%
Mean Age	60					66 y
Women	30					46%
Median F/U	2.1					5.4 y
DM Duration	9.2					10.5 y
Baseline A1c	7.7					7.3%
Baseline eGFR	76	~75	~75	76	79	77
Insulin Use	39%	45%	58%	46%	59%	24%

Participants were similar to the sorts of ambulatory patients with type 2 DM & CV risk factors who are routinely seen in clinical practice

Professor Gerstein's Slide deck: https://professional.diabetes.org/scientific-sessions-weekly-dulaglutide-and-major-cardiovascular-eventsresults-of-the-rewind-trialltstronggt

Lancet. 2019 Jul 13;394(10193):121-130

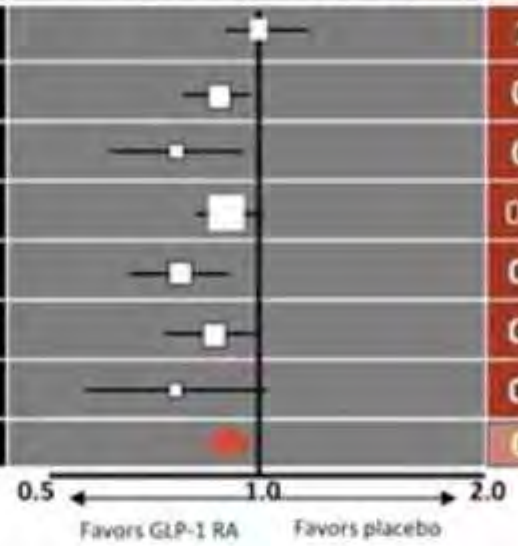
Dulaglutide (Trulicity®) Indications

as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

- to reduce the risk of **major adverse cardiovascular events** (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) in adults with type 2 diabetes mellitus who have **established cardiovascular disease or multiple cardiovascular risk factors**

Meta-analysis of GLP-1Ra Trials: 3P-MACE Updated Analysis

Study	GLP-1 RA	Placebo	Point Estimate CI	HR (95% CI)	*P* value
ELIXA (n=6068)	400/3034 (13%)	392/3034 (13%)		1.02 (0.89, 1.17)	0.776
LEADER (n=9340)	608/4668 (13%)	694/4672 (15%)		**0.87 (0.78, 0.97)**	**0.015**
SUSTAIN 6 (n=3327)	108/1648 (7%)	146/1649 (9%)		**0.74 (0.58, 0.95)**	**0.016**
EXSCEL (n=14,752)	839/7356 (11%)	905/7396 (12%)		0.91(0.83, (1.00)	0.061
HARMONY (n=9463)	333/4731	428/4732		**0.75 (0.61-0.90)**	**0.003**
REWIND (n=9901)	594 (4949)	663 (4952)		**0.88 (0.79-0.99)**	**0.026**
PIONEER 6 (n=3183)	61/1591	76/1592		**0.79 (0.59-1.11)**	**P=0.02**
Overall (n=42,950)				**0.84 (0.82, 0.94)**	**P<0.001**



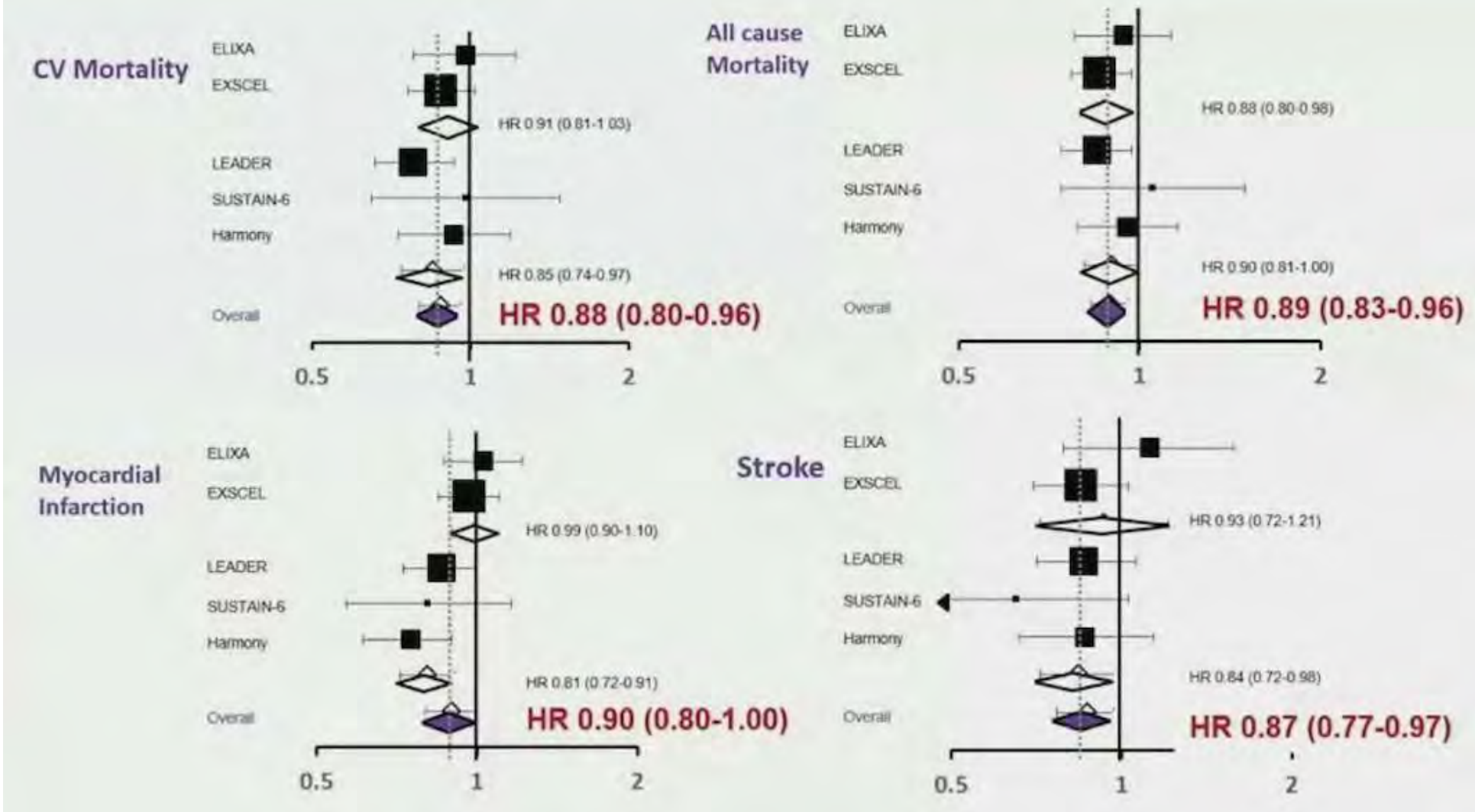
3P-MACE: composite of cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke; 3P-MACE, 3-pPtONoPOint major adverse cardiac events; CI, confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio

16% RR in MACE with GLP-1Ra

Heterogeneity; I^2=46.61%; H^2=1.87

Adapted from Giugliano, Dario et al. Diabetes Obes Metab. 2019;1–5.

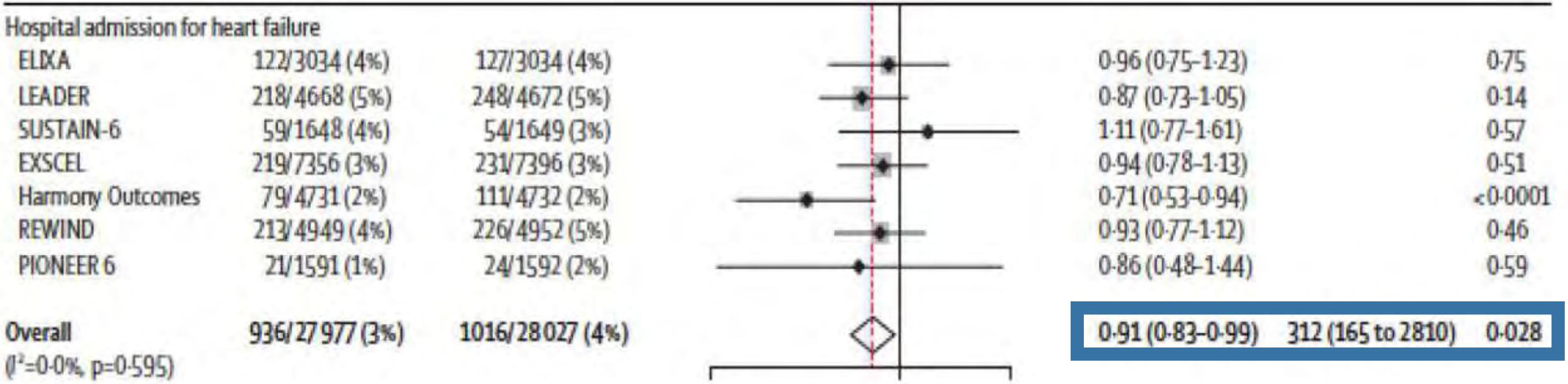
GLP-1R Agonist CV Outcome Trials:
[0.88 (0.82 to 0.94) MACE]



Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

Søren L Kristensen, Rasmus Rørth, Pardeep S Jhund, Kieran F Docherty, Naveed Sattar, David Preiss, Lars Køber, Mark C Petrie, John J V McMurray

GLP-1 RA and Hospitalizations for Heart Failure



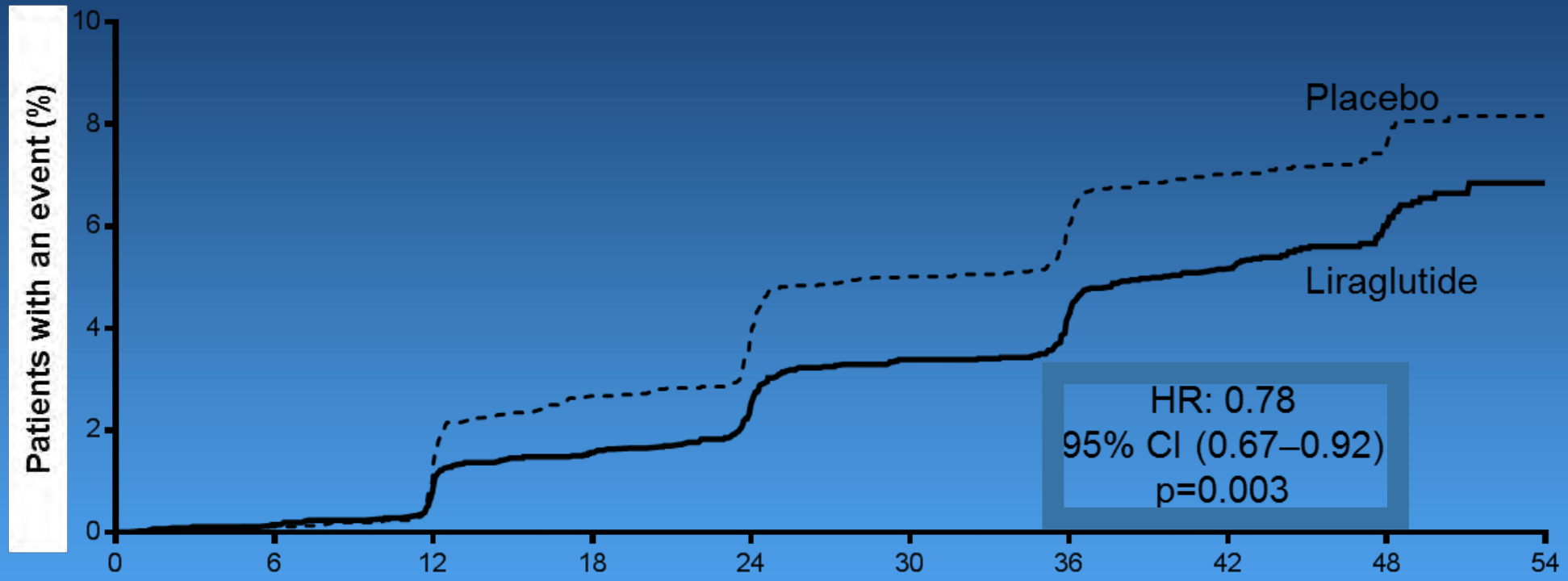
Hospital admission for heart failure					
ELIXA	122/3034 (4%)	127/3034 (4%)	0·96 (0·75–1·23)		0·75
LEADER	218/4668 (5%)	248/4672 (5%)	0·87 (0·73–1·05)		0·14
SUSTAIN-6	59/1648 (4%)	54/1649 (3%)	1·11 (0·77–1·61)		0·57
EXSCEL	219/7356 (3%)	231/7396 (3%)	0·94 (0·78–1·13)		0·51
Harmony Outcomes	79/4731 (2%)	111/4732 (2%)	0·71 (0·53–0·94)		<0·0001
REWIND	213/4949 (4%)	226/4952 (5%)	0·93 (0·77–1·12)		0·46
PIONEER 6	21/1591 (1%)	24/1592 (2%)	0·86 (0·48–1·44)		0·59
Overall (I^2=0·0%, p=0·595)	936/27 977 (3%)	1016/28 027 (4%)	**0·91 (0·83–0·99)**	**312 (165 to 2810)**	**0·028**

Lancet Diab Endocrinol 2019;7:776-785

Time to first renal event

Macroalbuminuria, doubling of serum creatinine, ESRD, renal death

LEADER®

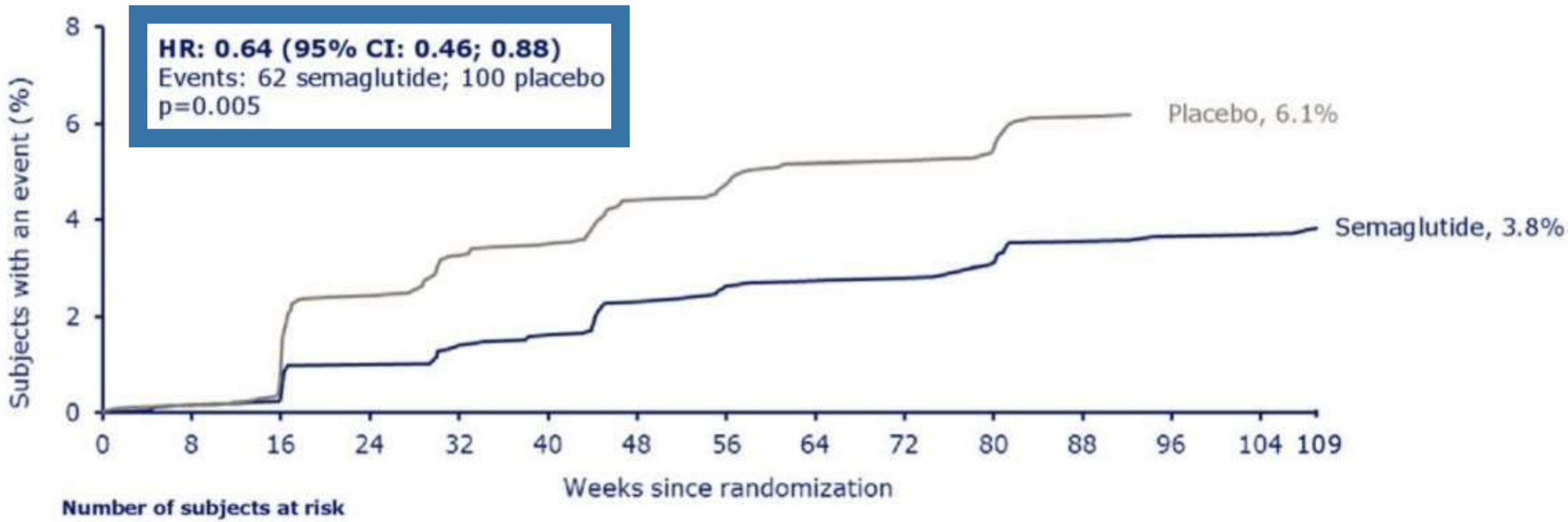


Patients at risk										
Liraglutide	4668	4635	4561	4492	4400	4304	4210	4114	1632	454
Placebo	4672	4643	4540	4428	4316	4196	4094	3990	1613	433

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; ESRD: end-stage renal disease; HR: hazard ratio.

Marso SP et al. N Engl J Med 2016;375:311-22

SUSTAIN 6: New or worsening nephropathy



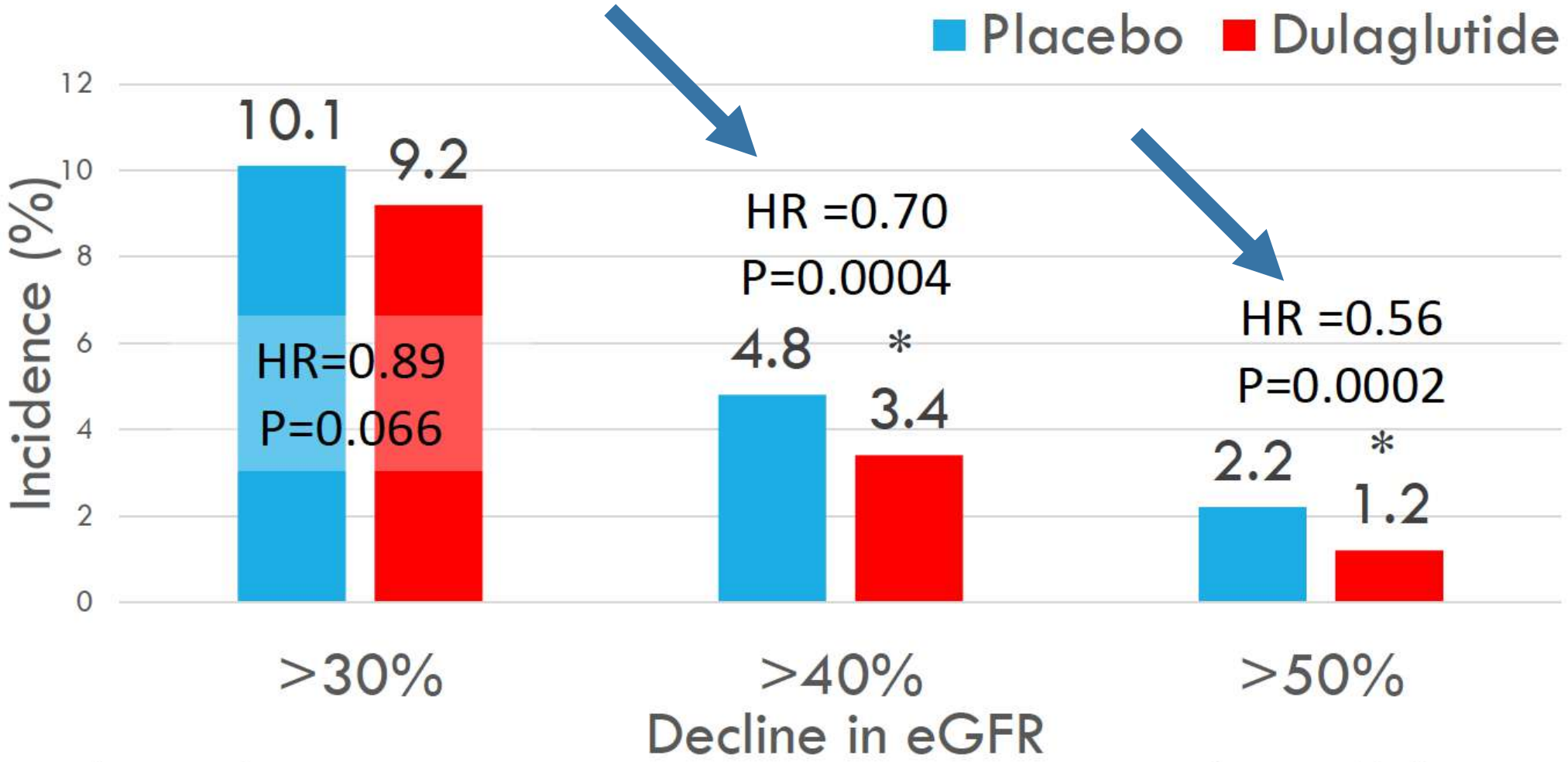
Number of subjects at risk

Semaglutide	1648	1630	1605	1580	1563	1541	1525	1518
Placebo	1649	1629	1570	1545	1518	1498	1471	1465

Kaplan–Meier plot for time from randomization to first (external) event adjudication committee–confirmed new or worsening nephropathy using "in-trial" data from subjects in the full analysis set. HR is from a proportional hazard model.
Marso SP *et al. N Engl J Med.* 2016;375(19):1834–1844.
HR, hazard ratio; CI, confidence interval.

REWIND
Dulaglutide CV Outcomes Trial

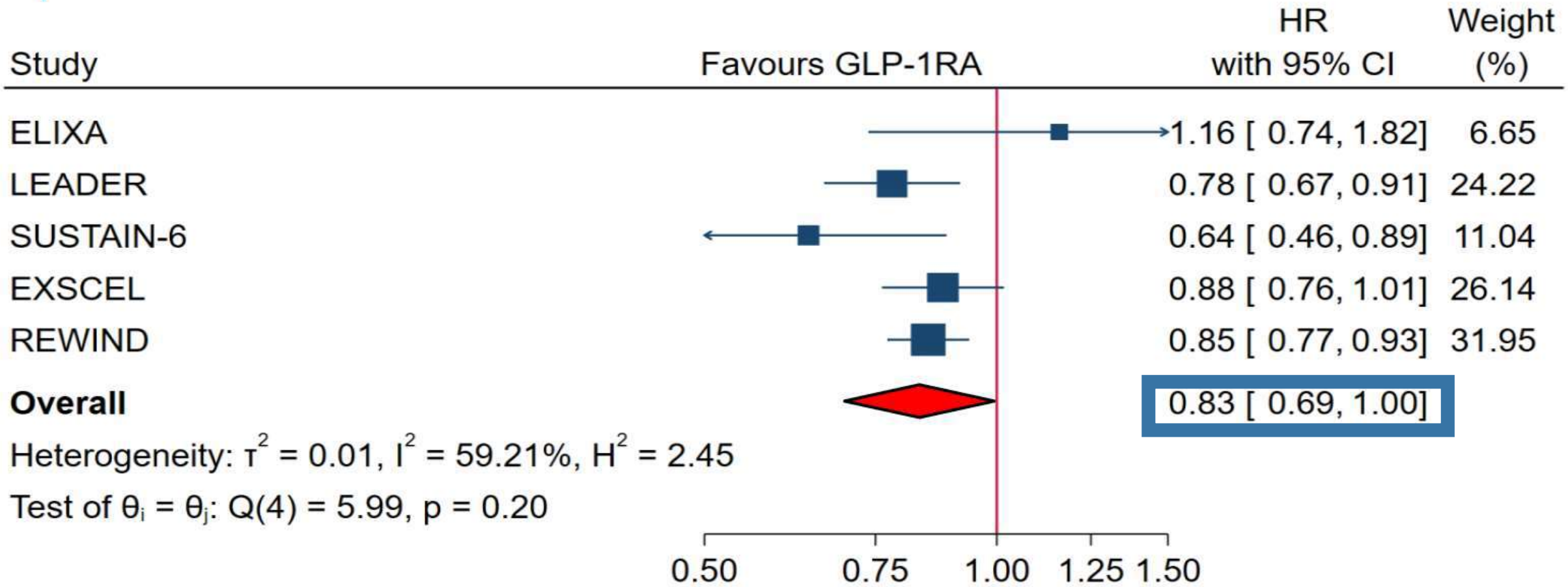
Dulaglutide on renal decline*



*sensitivity analysis – exploratory

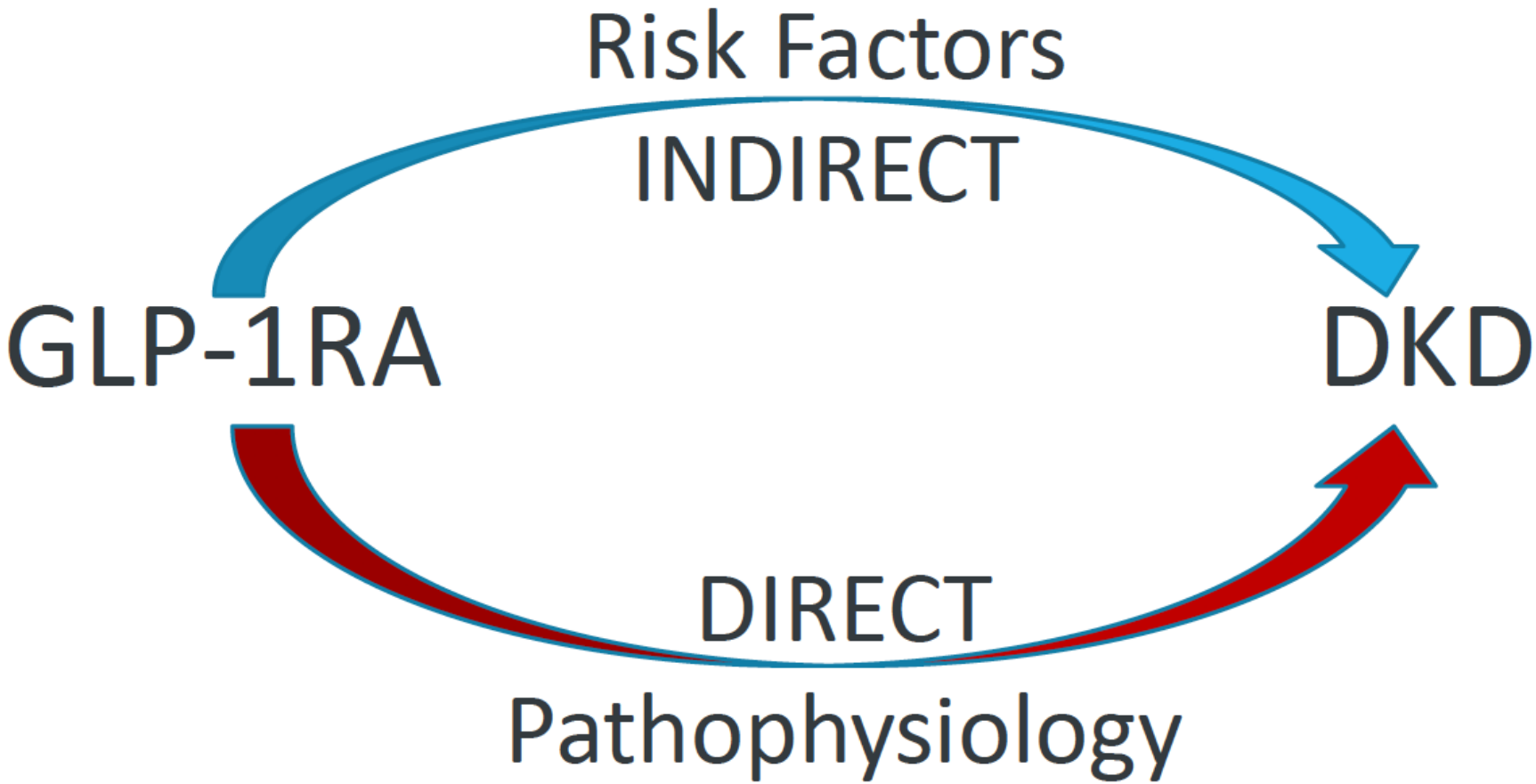
Gerstein et al. Lancet (2019)

RENAL ENDPOINTS **INCLUDING** ΔMACROALBUMINURIA



Giugliano et al. DOM (2019)

HOW MIGHT GLP-RA HAVE ACTIONS IN DKD?

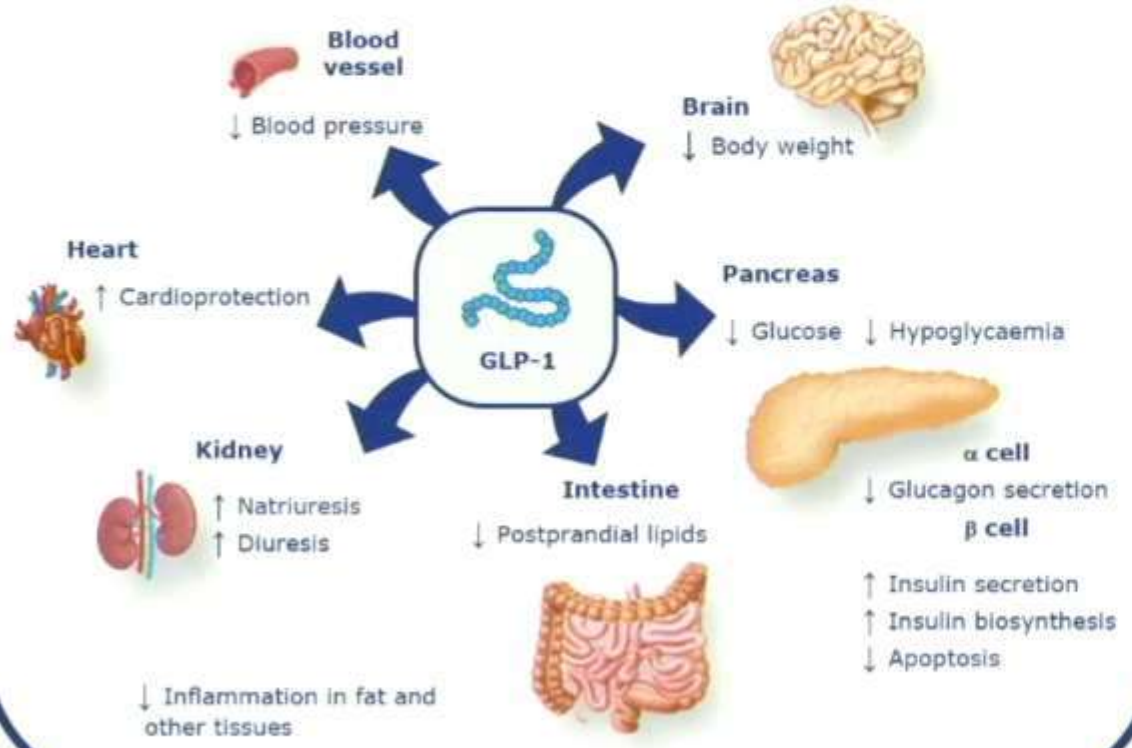


Thomas MC. Diabetes & Metabolism (2017)

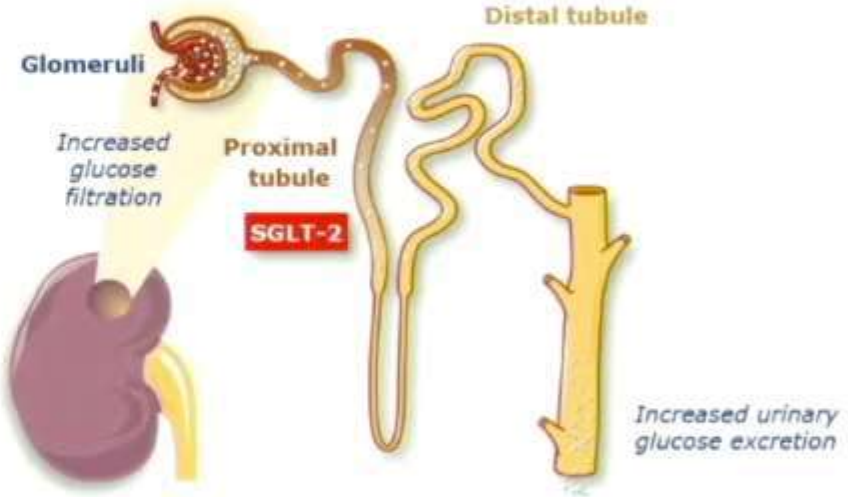
Could Their Effects Be Synergistic or Additive?

Mode of action of GLP-1RAs and SGLT-2is

GLP-1RAs[1]



SGLT-2is[2,3]



Proposed modes of action:

- Fluid reduction
- Haemodynamic effects
- Heart metabolism
- Renal effects

Dark-blue arrows indicate main mode of action of GLP-1 analogues.
GLP-1, glucagon-like peptide-1; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT-2, sodium–glucose cotransporter-2; SGLT-2i, sodium–glucose cotransporter-2 inhibitor.
1. Drucker DJ. *Cell Metab* 2016;24:15–30; 2. Zinman B et al. *N Engl J Med* 2015;373:2117–28; 3. Abdelgadir E et al. *J Clin Med Res* 2018;10:615–25.

Thank You!