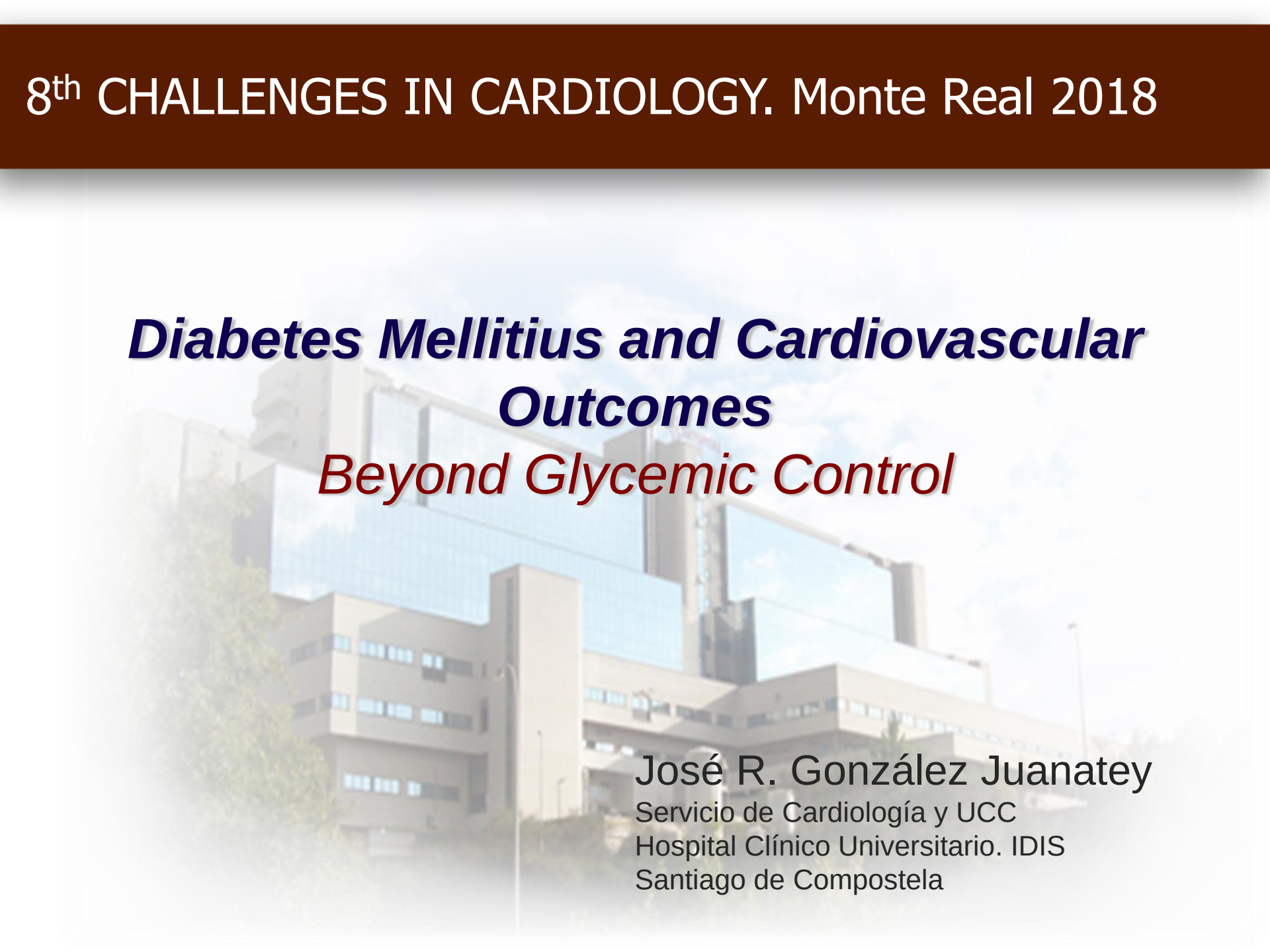
Diabetes Mellitius and Cardiovascular Outcomes

Beyond Glycemic Control



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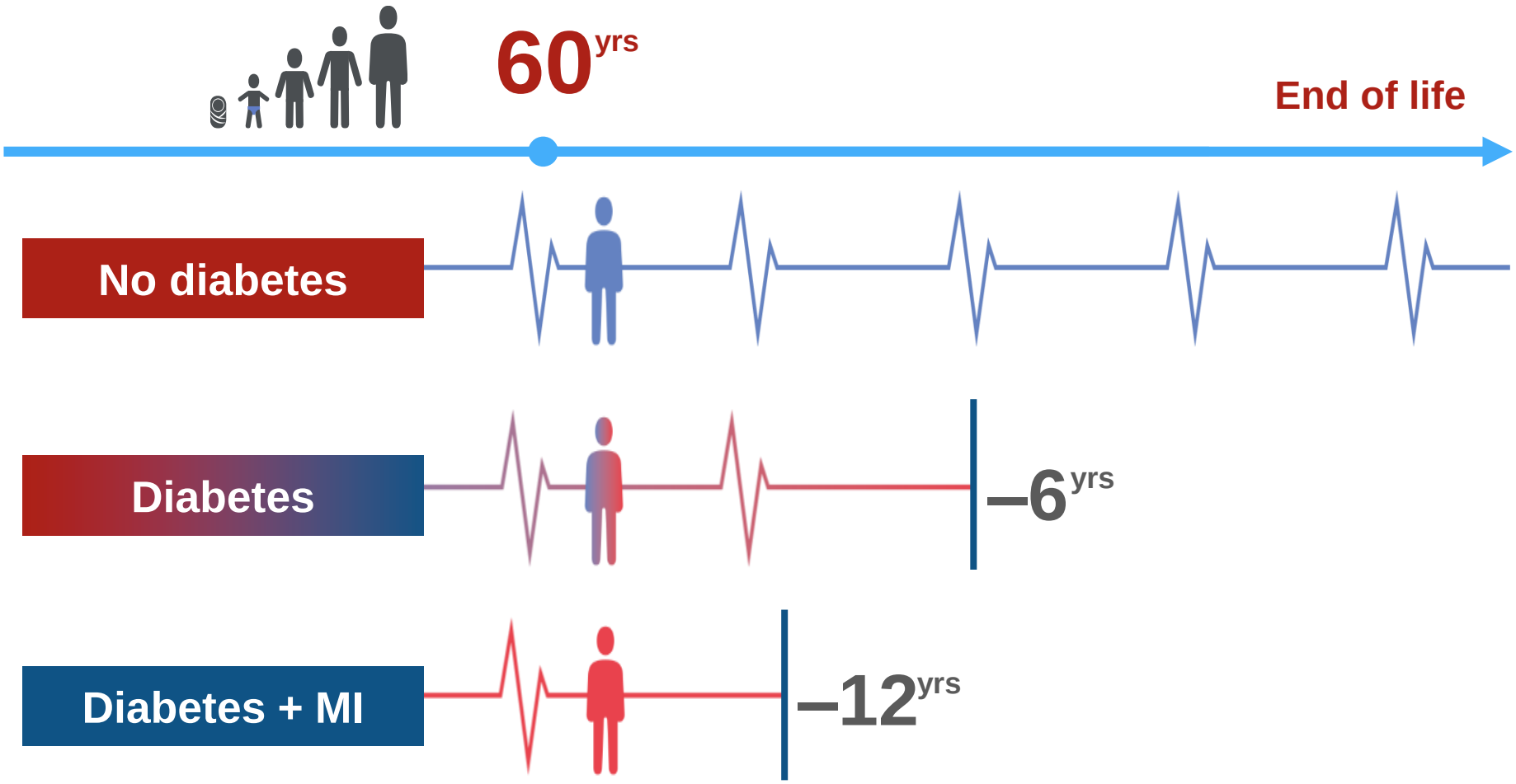
Santiago de Compostela

Disclosures:

Research Grants: AZ, Boehringer Ingelheim, Pfizer, Novartis, Daichii-Sankyo, Sanofi-Aventis, Bayer, MSD, Servier, Ferrer

Consultant/Honorarium. AZ, Boehringer-Ingelheim, Bayer, Pfizer, BMS, MSD, Daichii-Sankyo, Servier, Menarini, Ferrer, Angem

A 60-year-old man with CVD and T2D may die 12 years younger than someone without CVD and T2D



In this case, CV disease is represented by MI or stroke

*Male, 60 years of age with history of MI or stroke

The Emerging Risk Factors Collaboration. JAMA 2015

ESC 2016 Guidelines.
Multifactorial approach T2D

Life style modification

Glycaemic control

Antiplatelet therapy

Primary Prevention?

Reducing CV risk in T2D requires a multifactorial approach

Blood pressure control

Lipid control

Is Hemoglobin A1c the right outcome in Diabetes?

VIEWPOINT

Is Hemoglobin A_{1c} the Right Outcome for Studies of Diabetes?

Kasia J. Lipska, MD, MHS
Section of Endocrinology and Metabolism, Department of Internal Medicine, Yale School of

The goals of treatment of type 2 diabetes are to reduce the risk of diabetic complications and, as a result, improve the quality and, possibly, duration of life. For several decades, authoritative guidelines instructed clinicians to strictly control glucose levels of patients with diabetes to accomplish these goals. In addition, in the 1990s, the US Food and Drug Administration (FDA) be-

Moreover, intensive glucose control had minimal, if any, effects on hard microvascular complications, such as vision loss or renal failure.[1] Around the same time, a meta-analysis indicated the possibility that a certain glucose-lowering drug (ie, rosiglitazone) was paradoxically associated with increased cardiovascular risk. As a result, in 2008, the FDA began to require postapproval trials

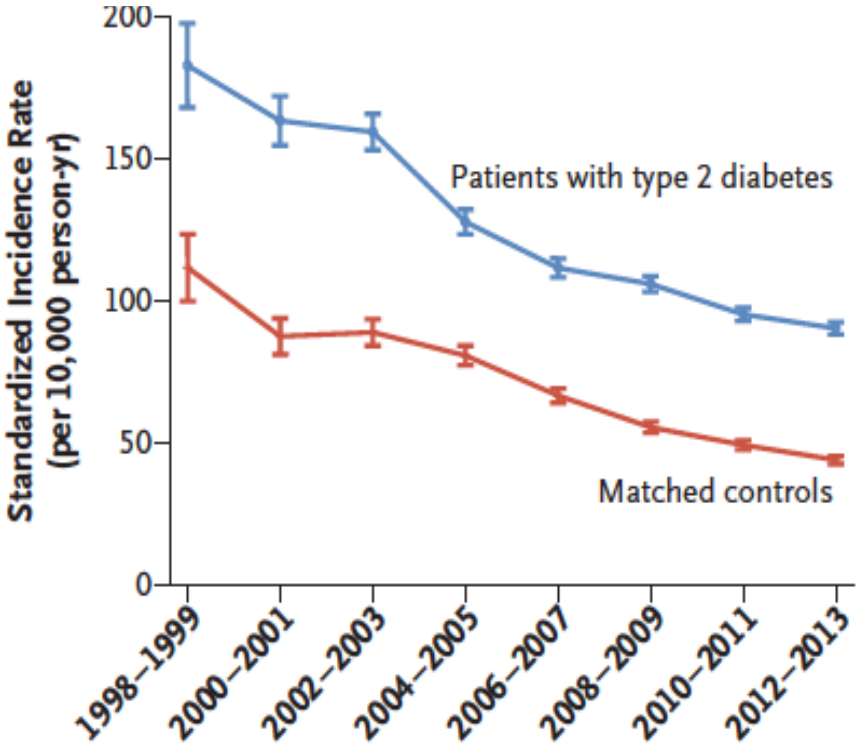
Trials that use outcomes based solely on glycemic parameters are no longer acceptable for clinical decision making. Clinicians and patients need evidence about outcomes associated with different drug classes and likely with different agents within a class. Investments in pragmatic studies of existing agents are needed to understand the impact on outcomes of all treatment options.

Lipska K and Krumholz H. JAMA. 2017;317(10):1017-1018

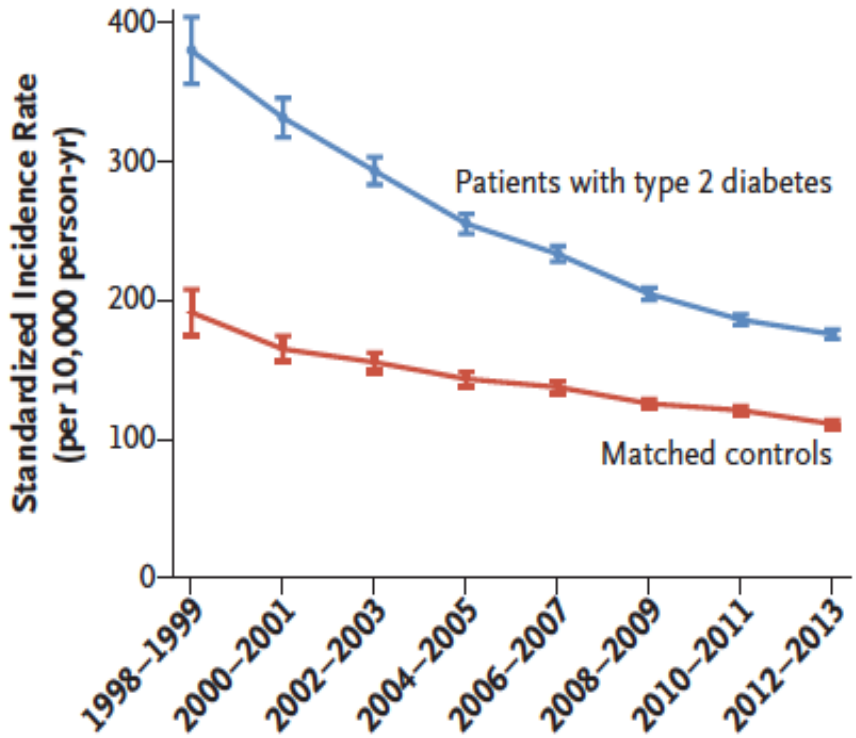
Mortality and CV Disease in Type 2 Diabetics

Swedish National Diabetes Registry

Death from CHD



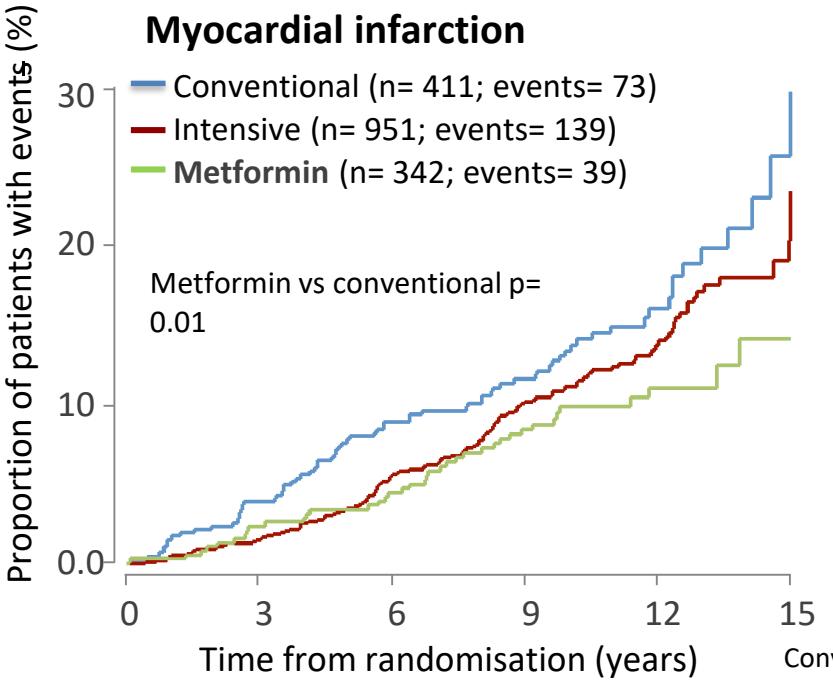
Hospitalization from CV Disease



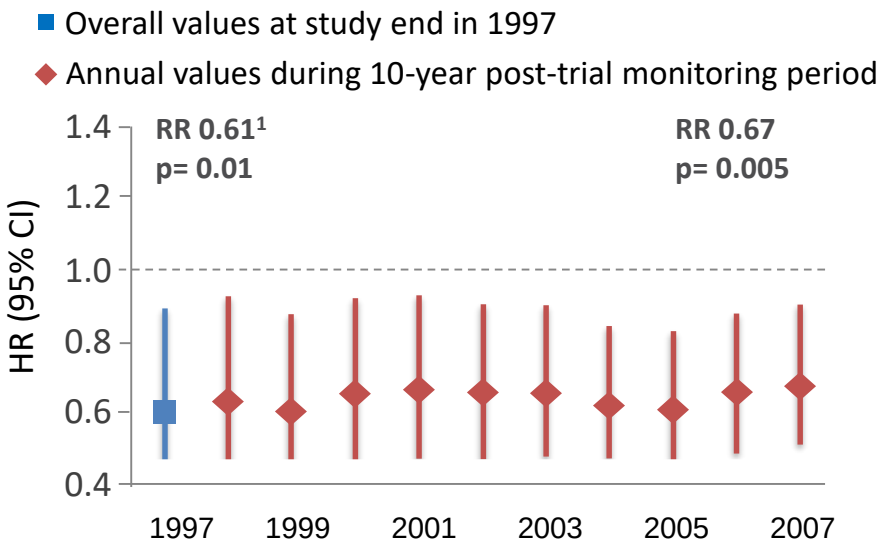
Rawshani A, et al. New Engl J Med 2017;376: 1407-18.

UKPDS 34 provides some evidence for beneficial CV effects of metformin in overweight patients

Risk of MI is 39% lower with metformin vs conventional therapy in obese patients[1,2]



Significant reduction in MI maintained over 10 years' follow-up[3]



No. of events:						
Conventional therapy	73	83	92	106	118	126
Metformin	39	45	55	64	68	81

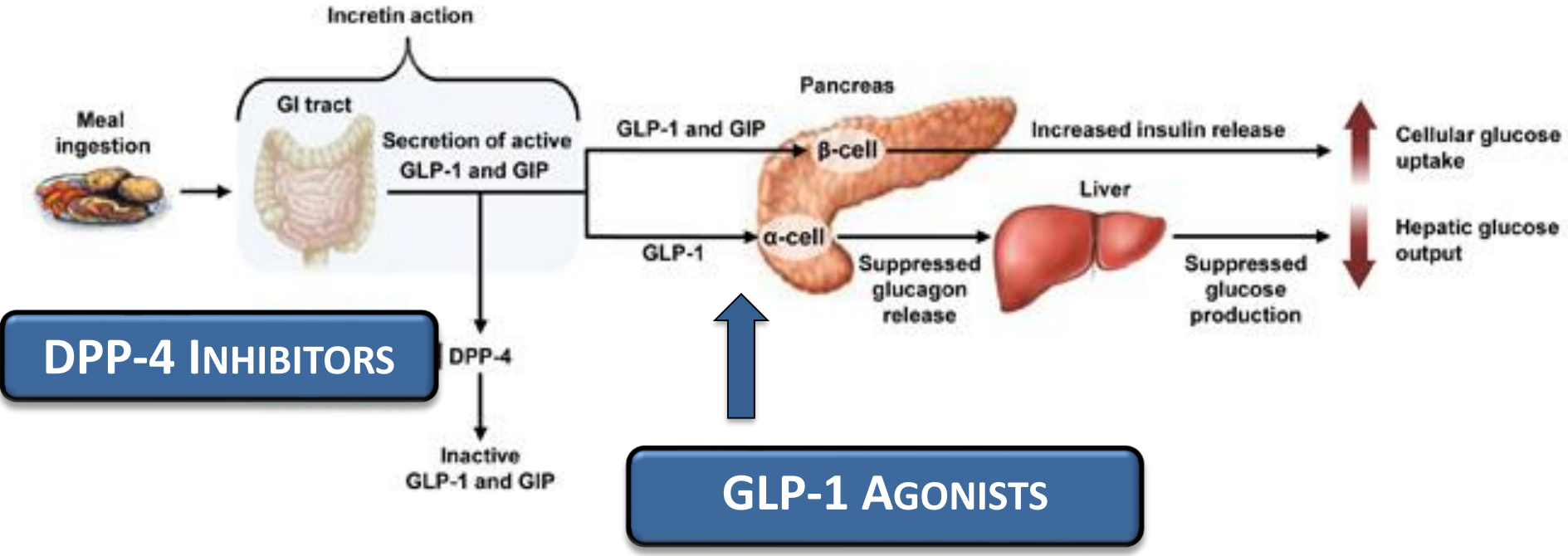
1. UKPDS 34. Lancet. 1998; 352: 854-865.
2. http://www.medicines.org.uk/emc/medicine/23244/SPC
3. Holman et al. N Engl J Med. 2008; 359: 1.577-1.589.

STUDIES WITH CARDIOVASCULAR ENDPOINTS OF ANTI-DIABETIC DRUGS

1) DPP4 INHIBITORS

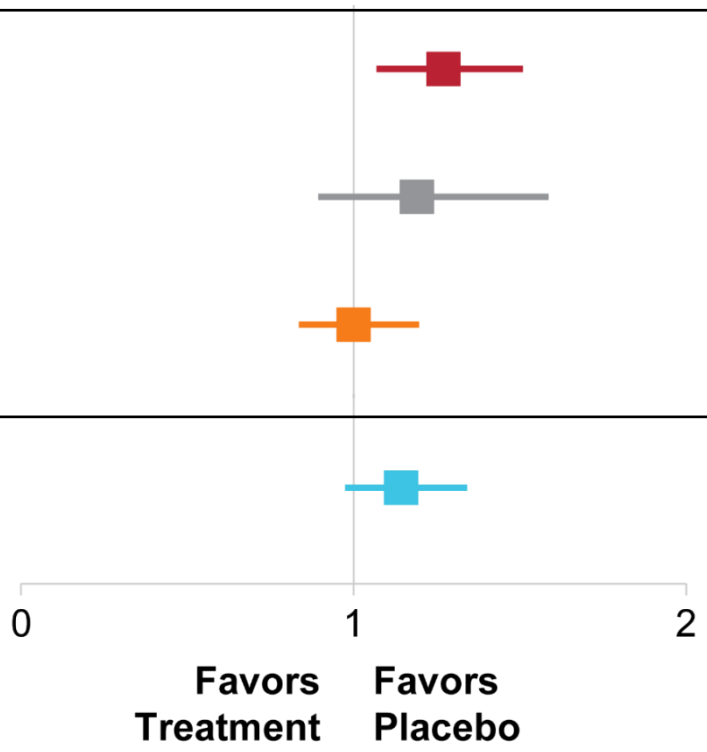
2) SGLT2 INHIBITORS

3) GLP-1 AGONISTS



SAVOR-TIMI 53, EXAMINE, and TECOS*: Hospitalization for Heart Failure

Trial	HR (95% CI)	P-Value
SAVOR-TIMI	1.27 (1.07–1.51)	0.007
EXAMINE	1.19 (0.89–1.59)	0.235
TECOS	1.00 (0.84–1.20)	0.99
SAVOR-TIMI + EXAMINE + TECOS	1.14 (0.97–1.34)	0.102



McGuire DK, et al. JAMA Cardiology 2016, 1: 126-135

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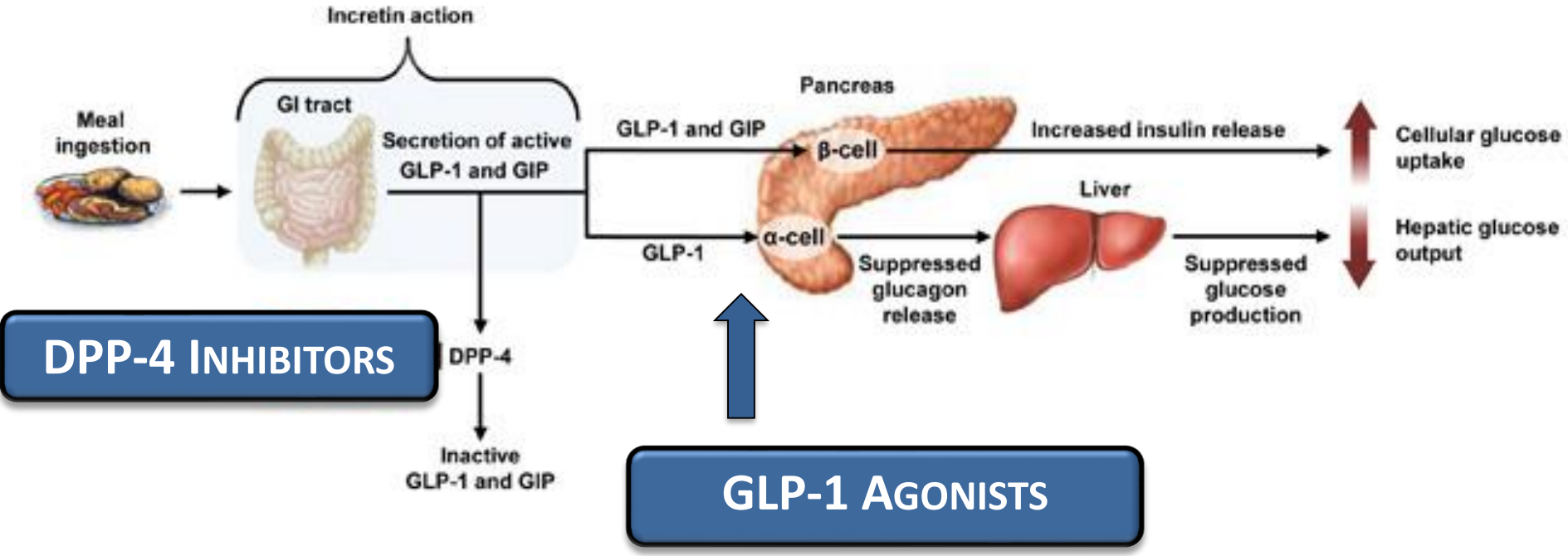
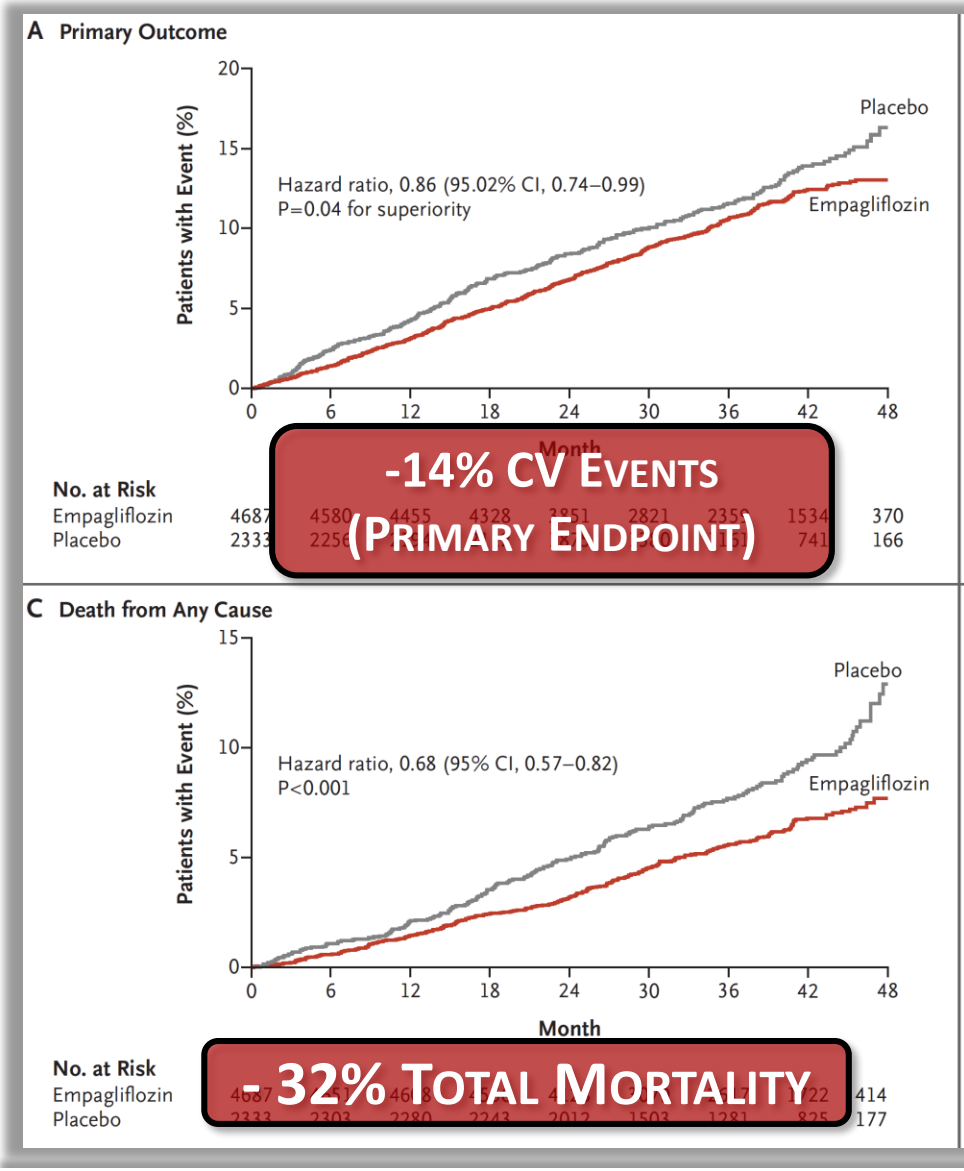
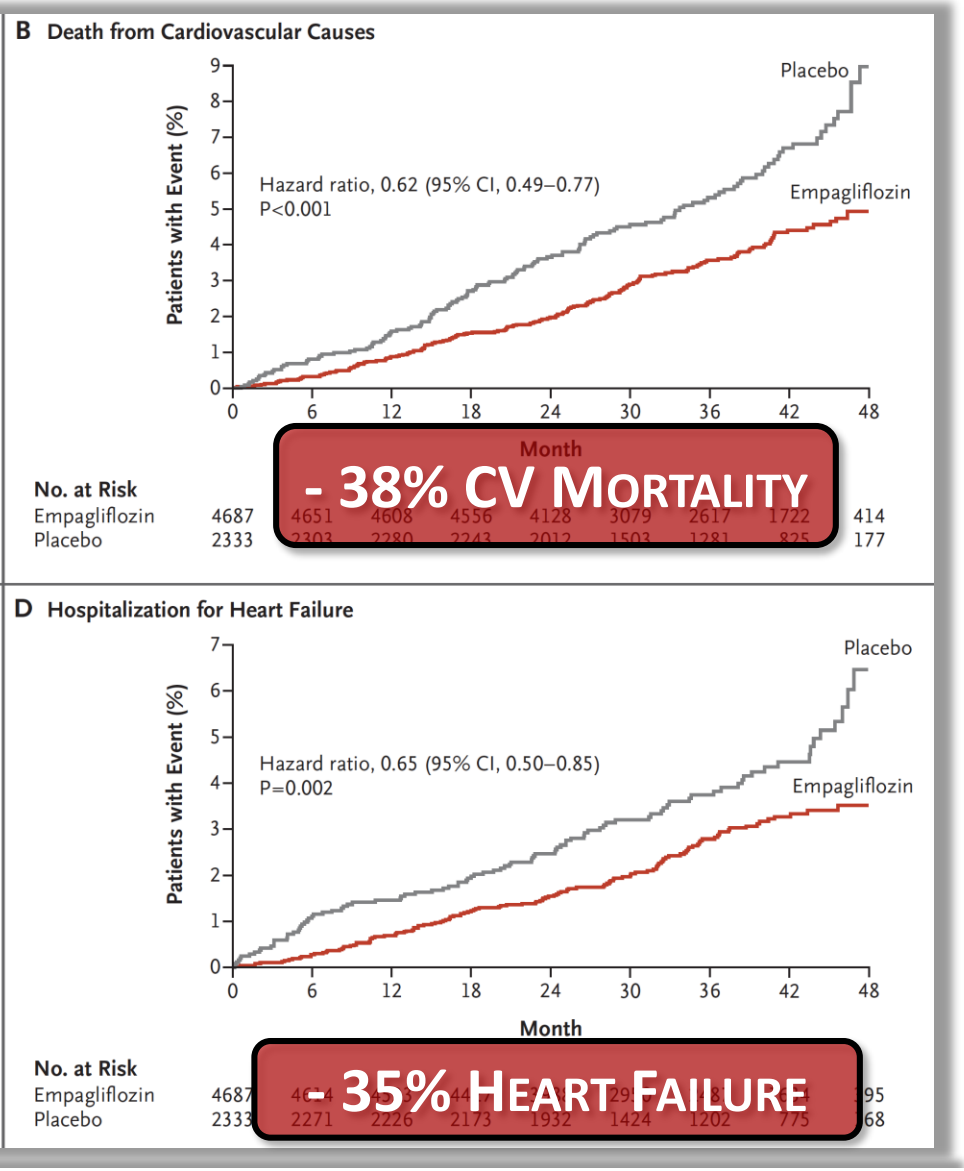


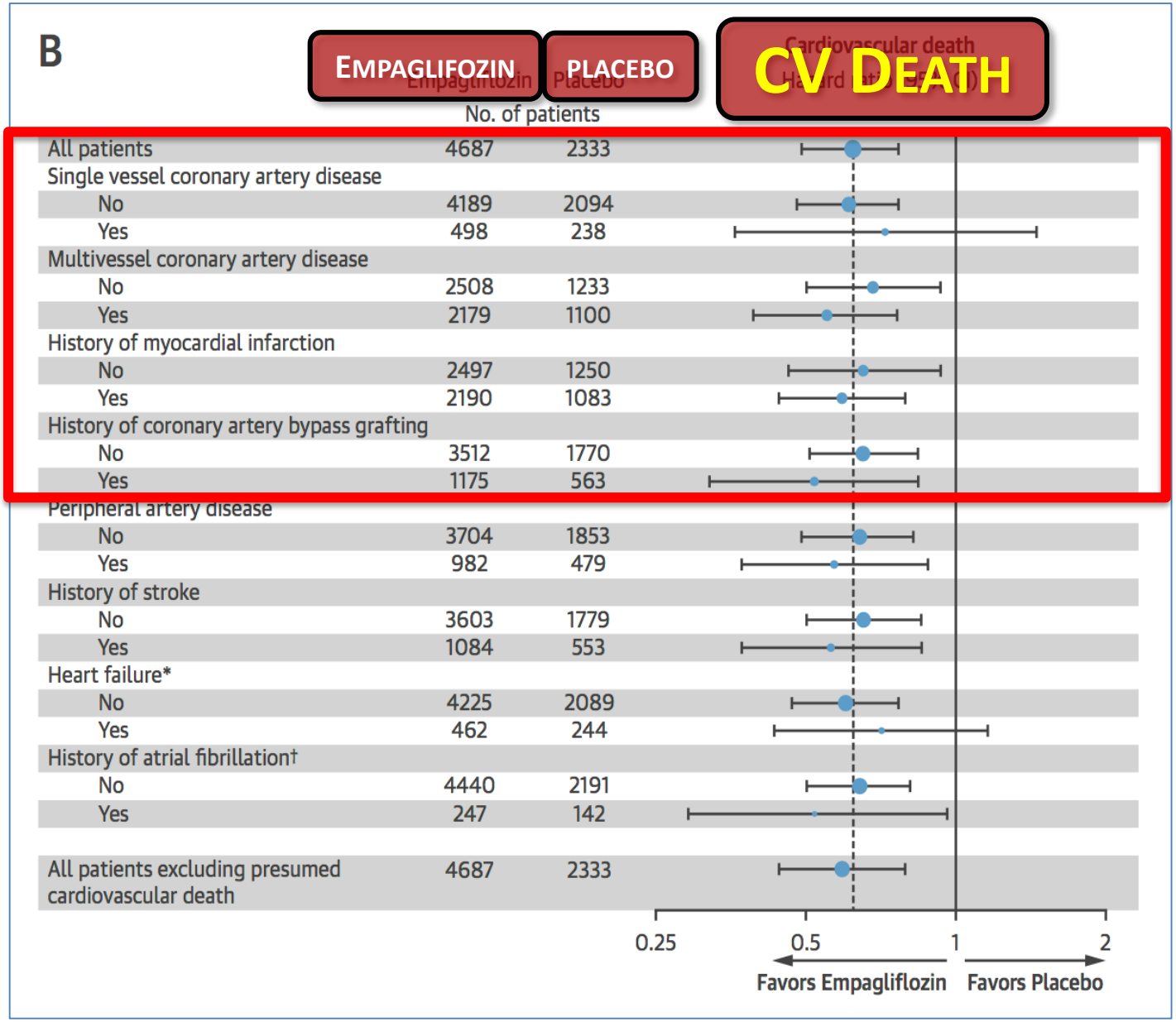
EMPA-REG OUTCOME :
CAN A ANTI-DIABETIC DRUG REDUCE CARDIOVASCULAR EVENTS?





Zinman et al. N Engl J Med 2015;373:2117

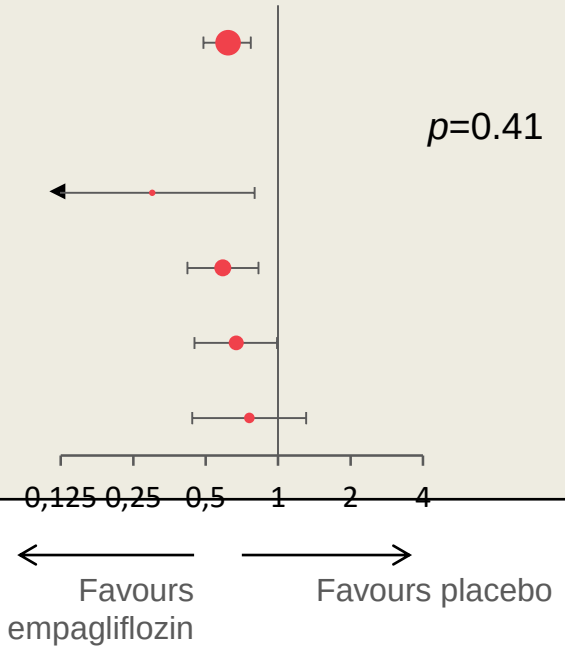
CV MORTALITY WITH EMPAGLIFOZIN IN PATIENTS CON T2D AND CV DISEASE. EMPA-REG



Fitchett D et al. JACC 2017;71:363

Reduced risk of ***CV death*** was not dependent on baseline HbA1c

	n with event/analyzed (%)			
	Empagliflozin	**Placebo**	**HR (95% CI)**	***p*-value for interaction**
All patients	172/4687 (3.7)	137/2333 (5.9)	0.62 (0.49, 0.77)	
HbA1c at baseline				*p*=0.41
<7.0%	7/297 (2.4)	10/127 (7.9)	0.30 (0.12, 0.80)	
7.0% to <8.0%	75/2042 (3.7)	63/1029 (6.1)	0.59 (0.42, 0.83)	
8.0% to <9.0%	56/1534 (3.7)	43/795 (5.4)	0.67 (0.45, 0.99)	
≥9.0%	34/812 (4.2)	21/382 (5.5)	0.76 (0.44, 1.31)	



Cox regression analysis in patients treated with ≥1 dose of study drug. Inzucchi et al. ADA 2017

What does someone with established CVD and T2D potentially gain with empagliflozin*?

Using data from the EMPA-REG OUTCOME trial and actuarial methods, empagliflozin was estimated to improve survival by up to ***4.5 years*** in patients with T2D and established CV disease

A 60 year old living with T2D and CVD could gain ***~2.5 additional years*** of life*

*assuming they are appropriate to receive an SGLT2 inhibitor as per local label

Claggett B. et al., 2017 3rd CVOT Summit of the D&CVD EASD Study Group, Munich, Germany Oct 26-27 2017

Clinical Implications Of EMPA-REG OUTCOME

1) What mechanisms can Explain the reduction in Cardiovascular Endpoints?

2) Is This a Class Effect of SGLT2 Inhibitors?

3) Can these results be extended to patients with a lower baseline CV risk?

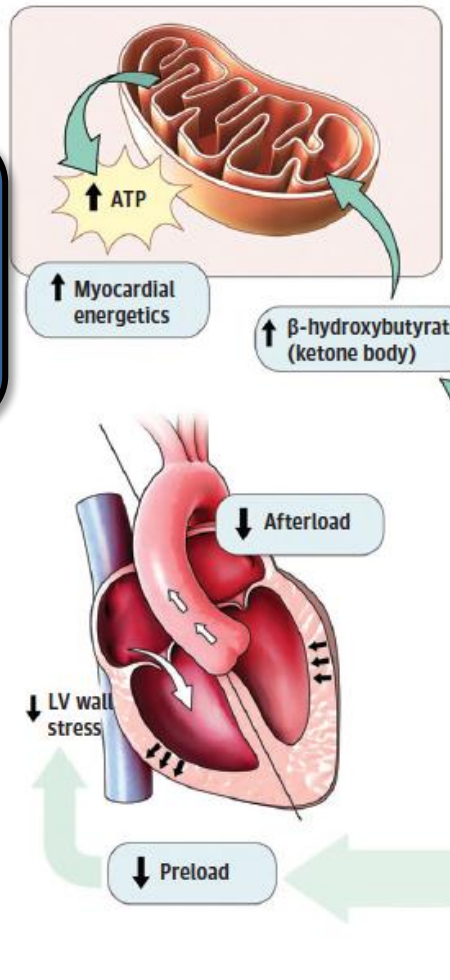
4) Will these agents work in patients with heart Failure (without Diabetes)?

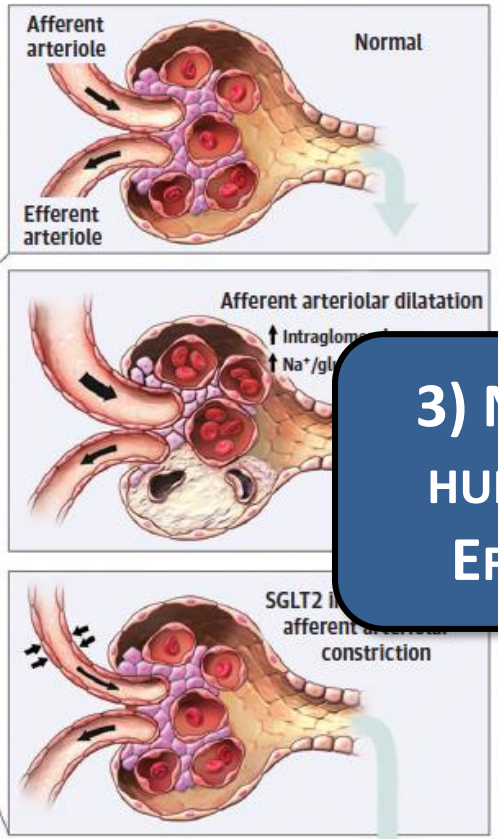
Mechanisms Responsible for the Reduction in CV and Renal Outcomes

"Pleiotropic Effects" of SGLT2 Inhibition?

(Non HbA1c related; Non-Atherotrombotic Effect)

1) Metabolic Effects





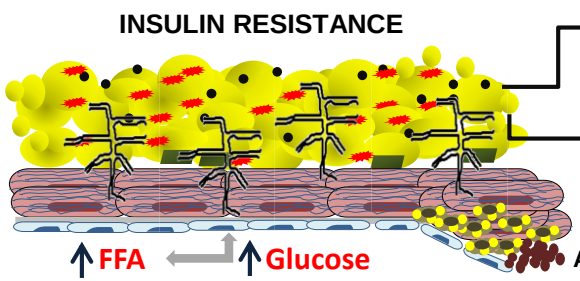
3) Neuro-humoral Effects

2) Hemodynamic Effects

Verma et al. JAMA Cardiol. 2017;2(9):939-940.

SGLT2I ON EPICARDIAL FAT

Dysfunctional epicardial adipose tissue from patients with CVD



Inflammatory cytokines

Stromal vascular cells (SVC) low differentiation ability

Atherogenesis

Dapagliflozin

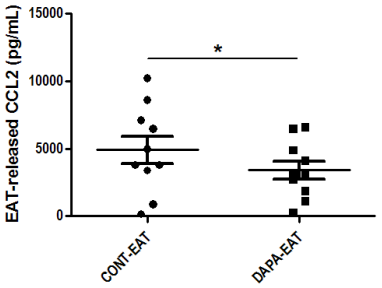
Dapagliflozin

Dapagliflozin

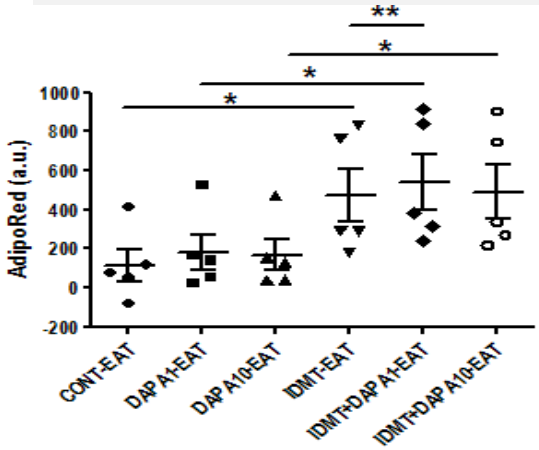
Dapagliflozin

Vasa vasorum
Adipocytes
Mesenchymal cells
Macrophages
Lymphocytes
Smooth muscle cells
Endothelial cells

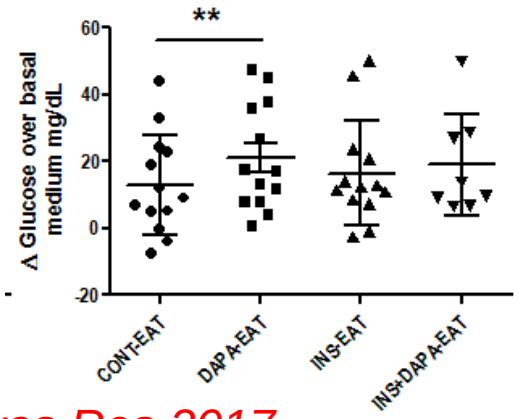
Reduced chemokines secretion levels



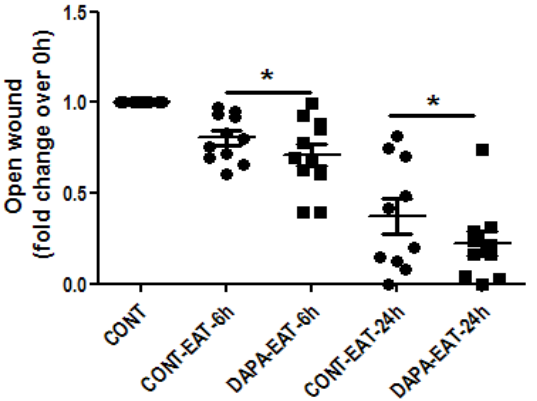
Improved differenciation of SVC



Improved glucose uptake



EAT- released products with benefits on coronary endothelial cells



Eiras S, et al Cardiovas Res 2017

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- Empagliflozin
- Canagliflozin
- Dapagliflozin

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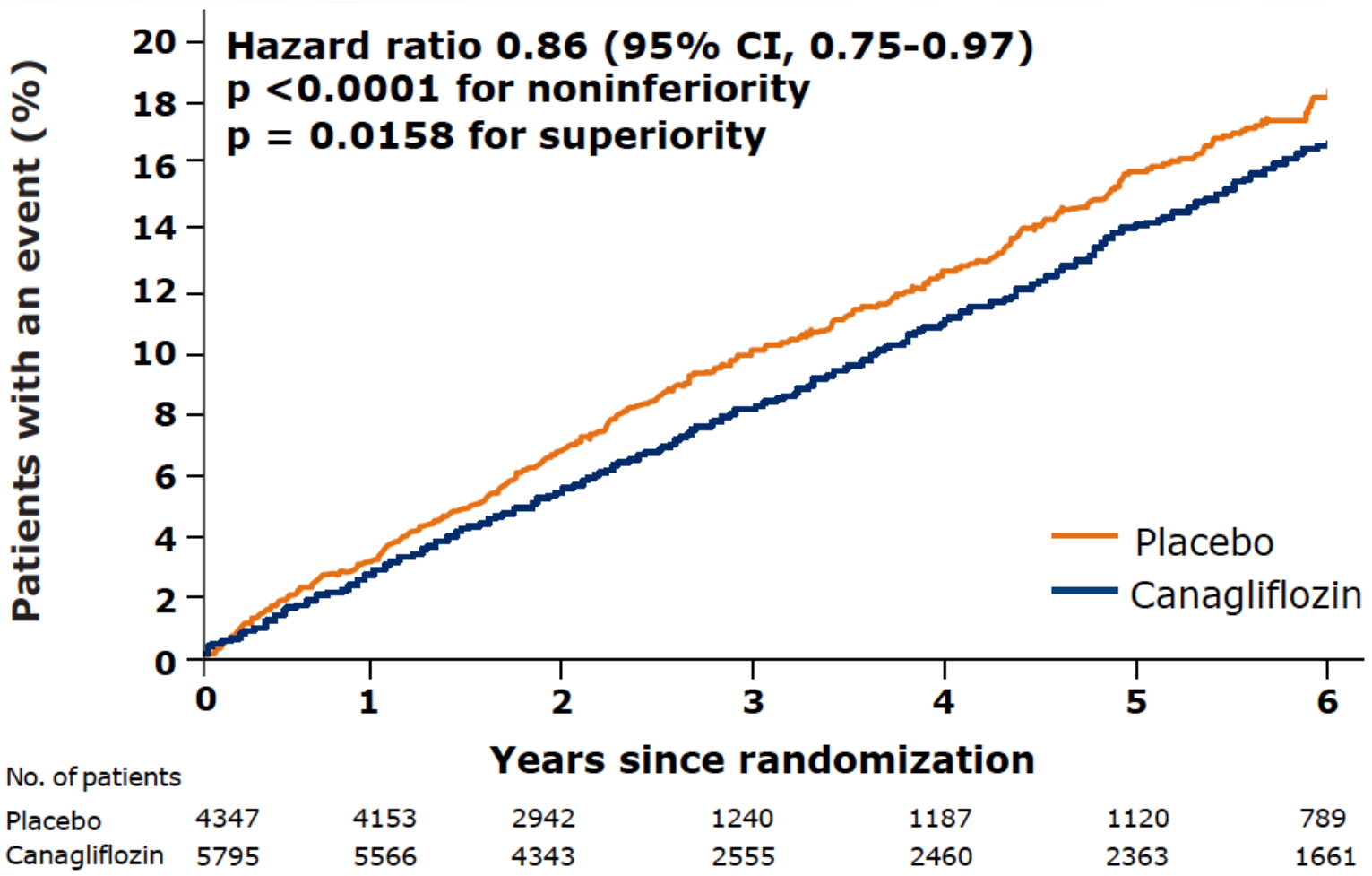
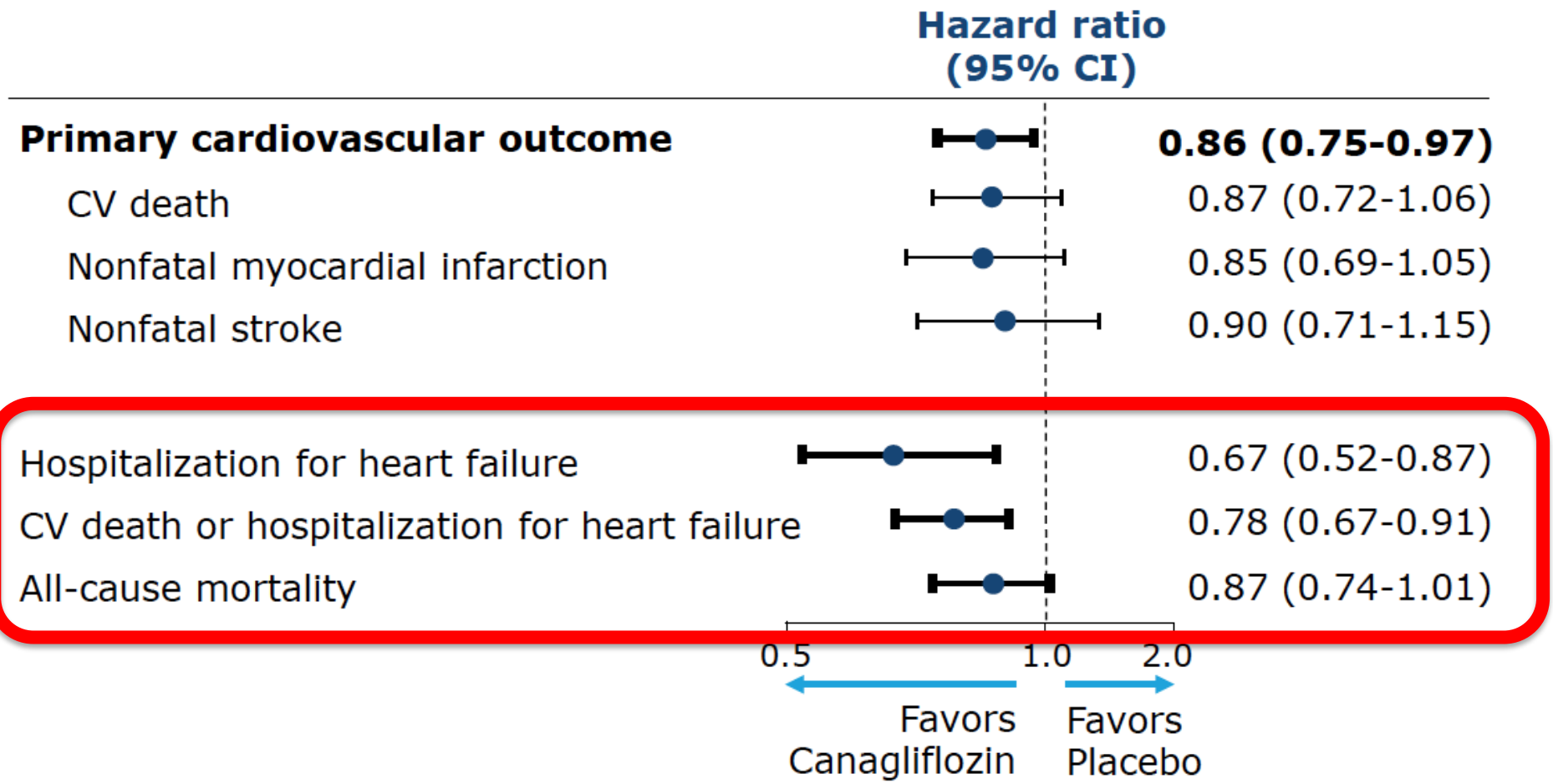
CANVAS PROGRAM - CANAGLIFLOZIN

MAJOR ADVERSE CV EVENTS (PRIMARY ENDPOINT)



Neal et al. N Engl J Med 2017; 377:644-657

CANVAS PROGRAM - CANAGLIFLOZIN



Neal et al. N Engl J Med 2017; 377:644-657

The *CANVAS* Alone/Program Collaborative Group. Adverse Events. A "class effect" finding?

Event	Canagliflozin	Placebo	P Value†
	event rate per 1000 patient-yr		
All serious adverse events	104.3	120.0	0.04
Adverse events leading to discontinuation	35.5	32.8	0.07
Amputation	6.3	3.4	<0.001
Fracture			
All	15.4	11.9	0.02
Low-trauma	11.6	9.2	0.06
Venous thromboembolic events	1.7	1.7	0.63
Infection of male genitalia§	34.9	10.8	<0.001
Mycotic genital infection in women	68.8	17.5	<0.001
Osmotic diuresis	34.5	13.3	<0.001
Volume depletion	26.0	18.5	0.009
Hypoglycemia	50.0	46.4	0.20

Neal B, et al. NEJM 2017; June 12.

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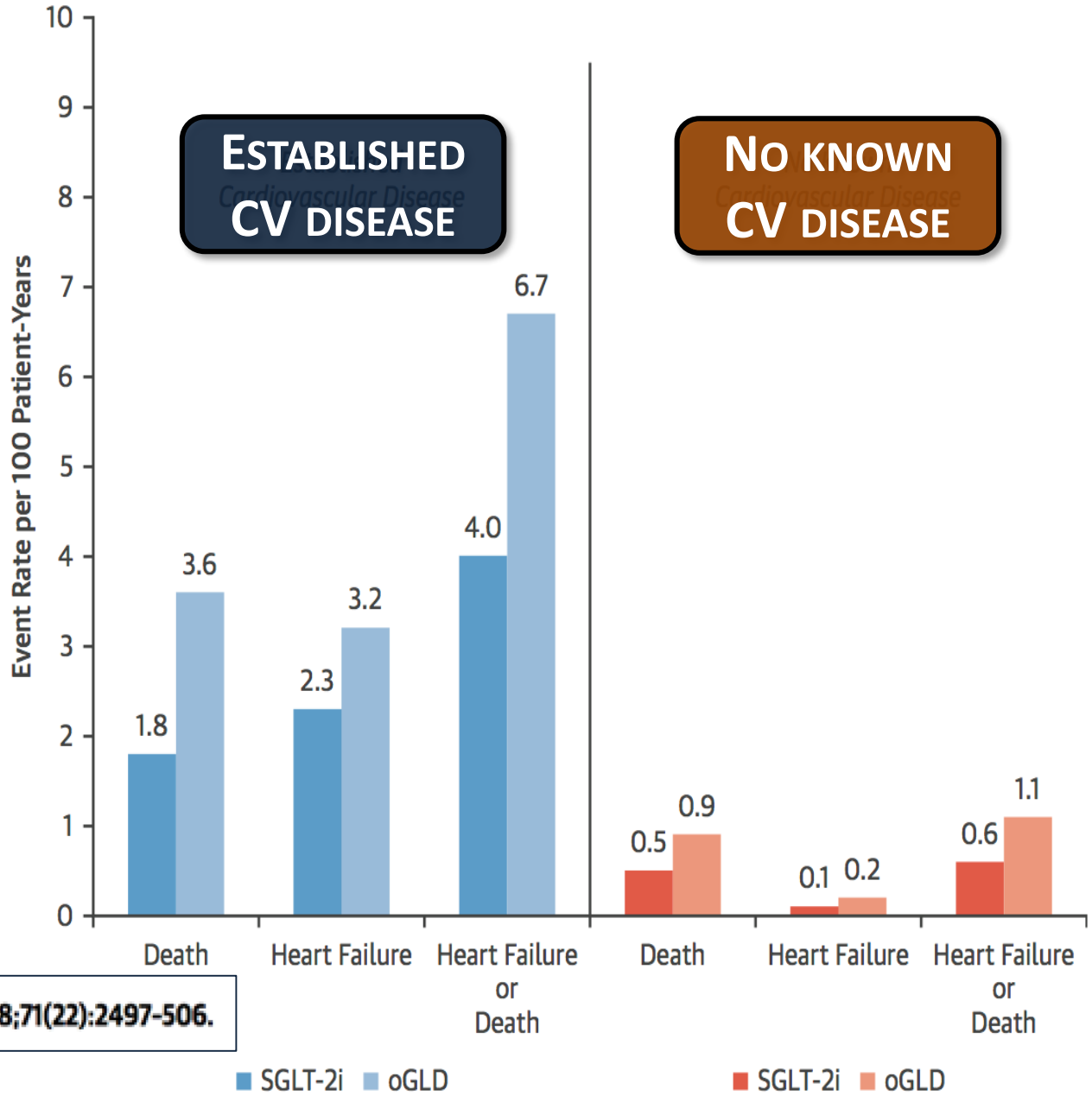
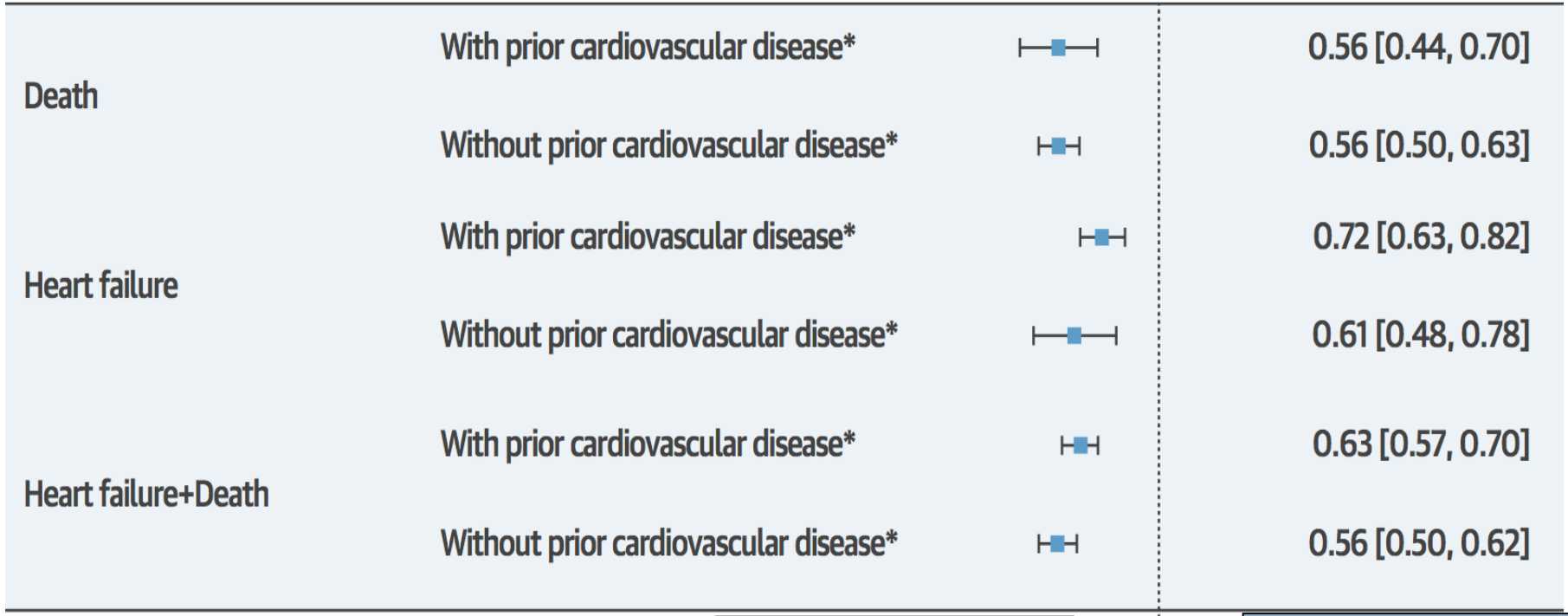
SLGT2 Inhibitors In The "Real World" in patients with and without CV disease. CVD-REAL



ITT cohort; p < *0.001 for all comparisons*

Cavender, M.A. et al. J Am Coll Cardiol. 2018;71(22):2497-506.

SLGT2 Inhibitors In The "Real World" in patients with and without CV disease. CVD-REAL



*Diagnosis of AMI, unstable angina, stroke, heart failure, transient ischemic attack, coronary revascularization (CABG or PCI) or occlusive peripheral artery disease prior to index drug initiation

Cavender, M.A. et al. J Am Coll Cardiol. 2018;71(22):2497-506.

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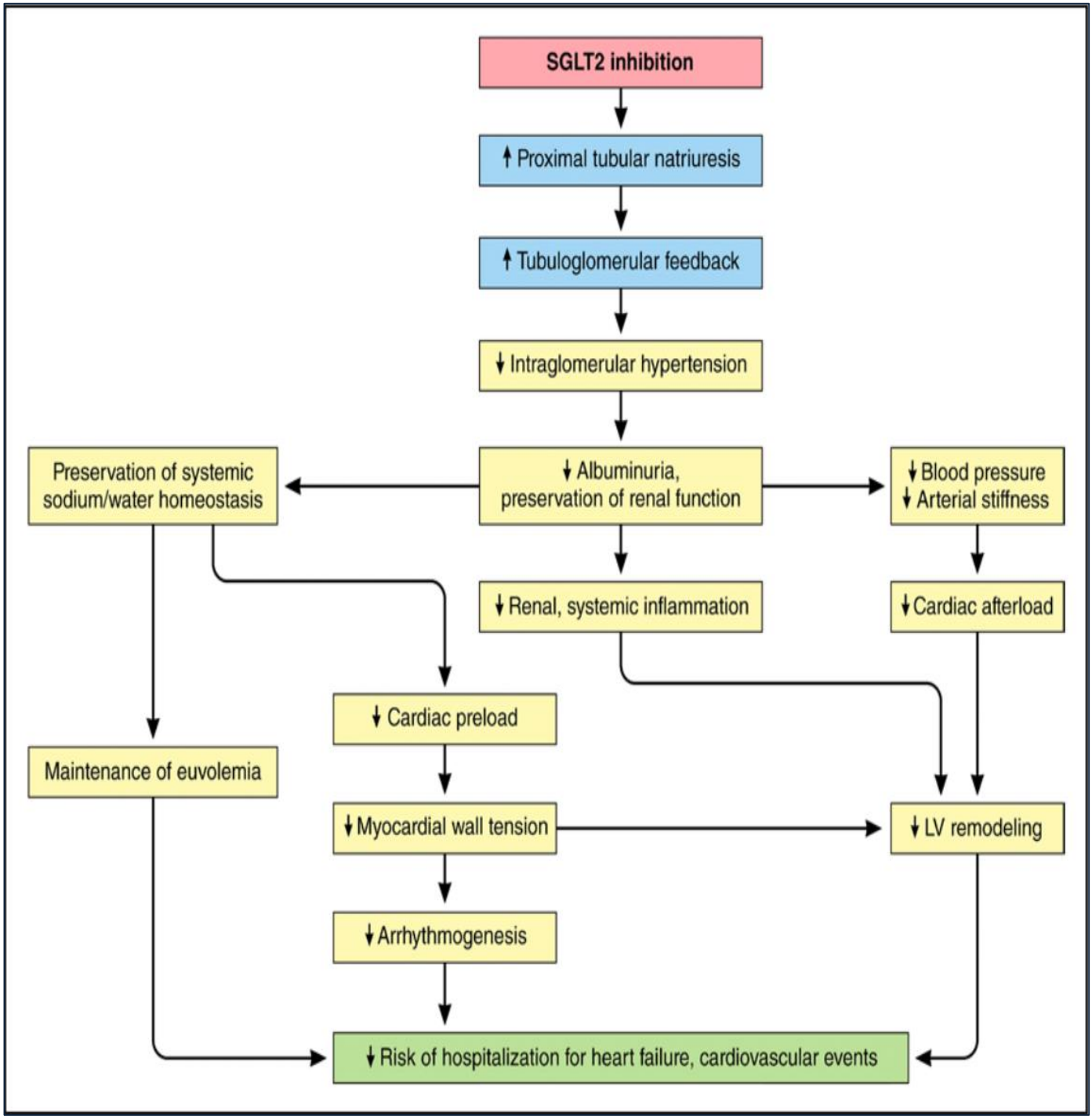
"Mechanistic Effects" of SGLT2 Inhibition?

THE RENAL-CARDIO HYPOTHESIS

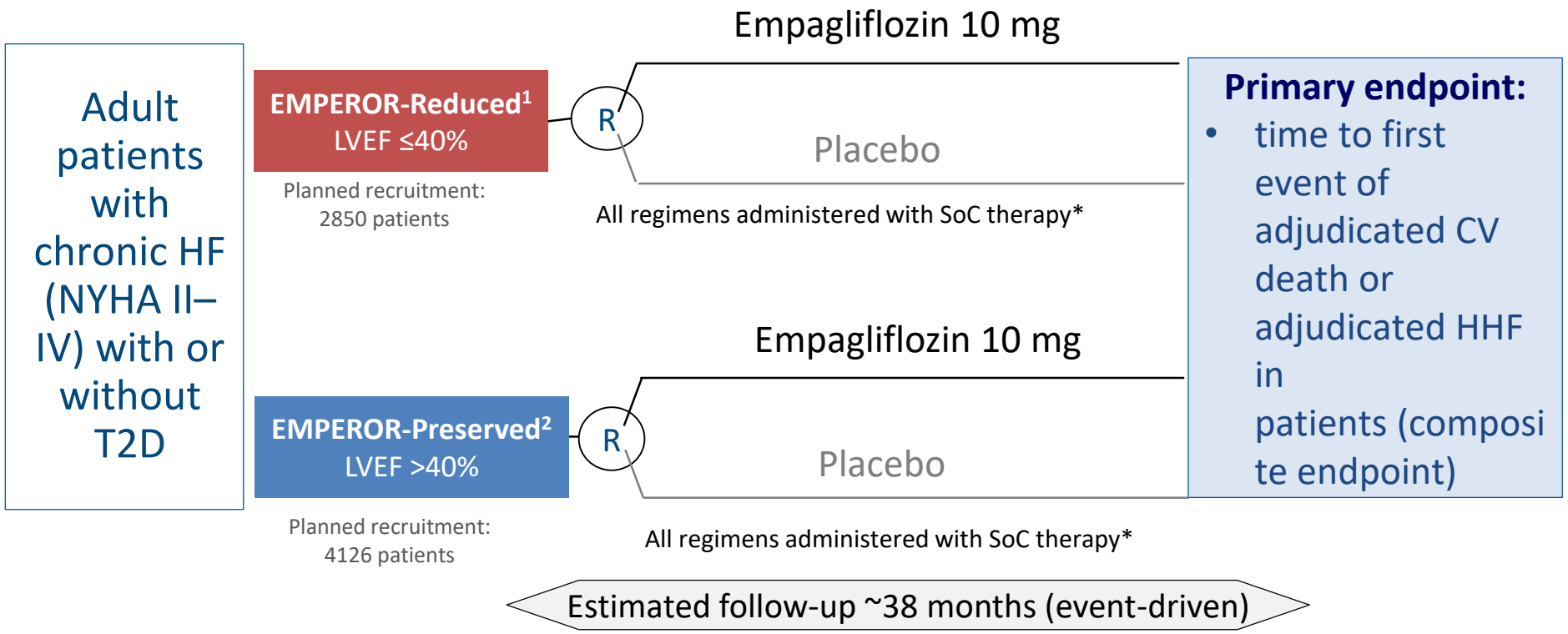


EMPEROR-Reduced and EMPEROR-Preserved HF outcome trials

investigated empagliflozin vs placebo on top of guideline-directed medical therapy

EMPEROR HEART FAILURE STUDIES

Phase III randomized double-blind placebo-controlled outcomes trials



*Guideline-directed medical therapy

HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; HHF, hospitalisation for heart failure. 1. ClinicalTrials.gov NCT03057977; 2. ClinicalTrials.gov NCT03057951

DAPAHF

~4,500 patients

Status: Currently recruiting participants

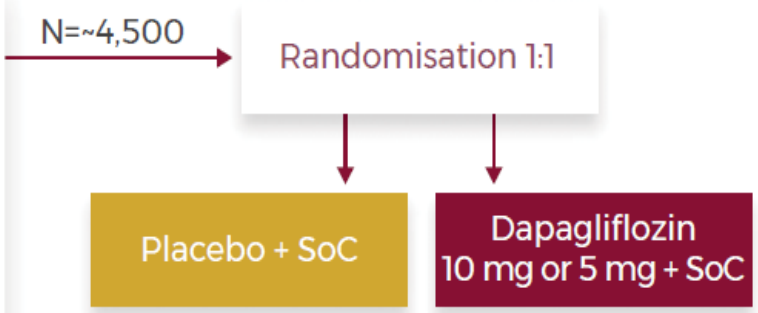
Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure (Dapa-HF)[12]

An international, multicentre, parallel group, event-driven, randomised, double-blind, placebo-controlled study in patients with chronic HFrEF, evaluating the effect of dapagliflozin versus placebo, given once daily in addition to background SoC therapy, for the prevention of CV death or reduction of HF events.

STUDY DESIGN

Population

- ≥18 years of age
- Established documented diagnosis of symptomatic HFrEF (NYHA functional Class II-IV) present ≥ 2 months
- LVEF ≤40%
- NTproBNP ≥600 pg/mL
- eGFR ≥30 mL/minute/1.73 m²*
- Stable SoC HFrEF treatment



DURATION

PRIMARY ENDPOINT

Time to first occurrence of any of the components of the composite: CV death, hHF or an urgent hHF visit.

SECONDARY ENDPOINTS

- Time to first occurrence of CV death of hHF. Total number of (first and recurrent) hHF and CV death.
- Change from BL in KCCQ at 8 months. Time to first occurrence of renal composite (≥50% sustained decline in eGFR, reaching ESRD or renal death). Time to death (any cause).

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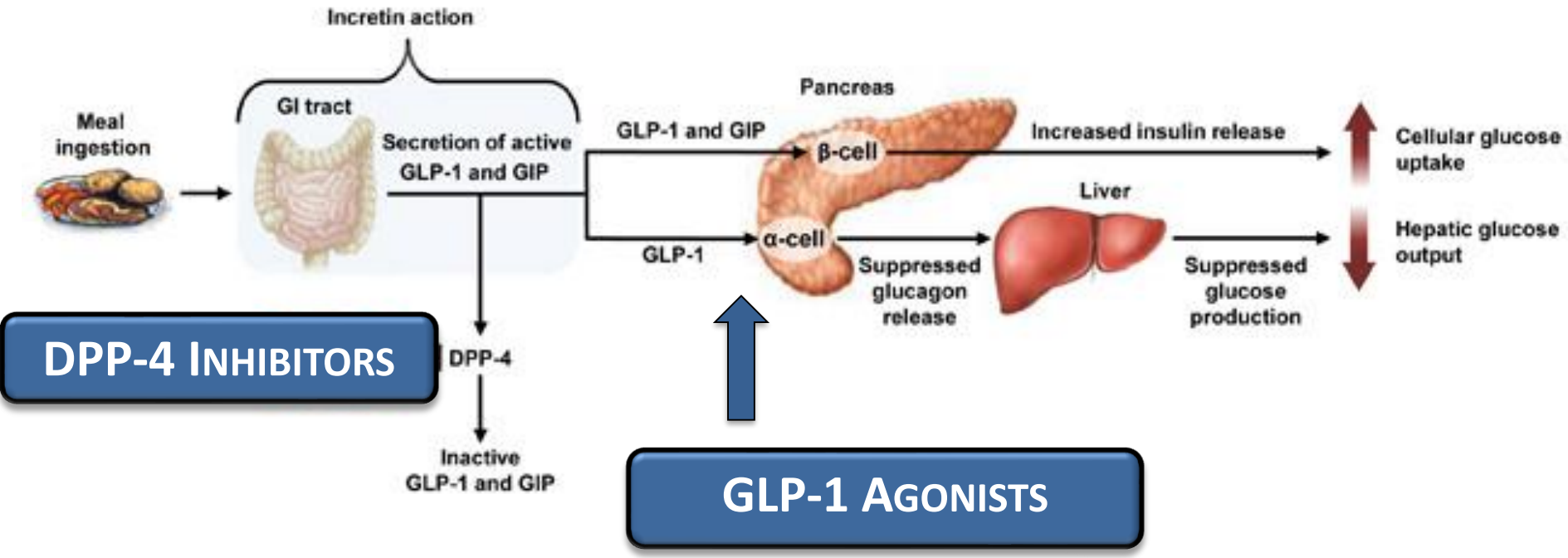
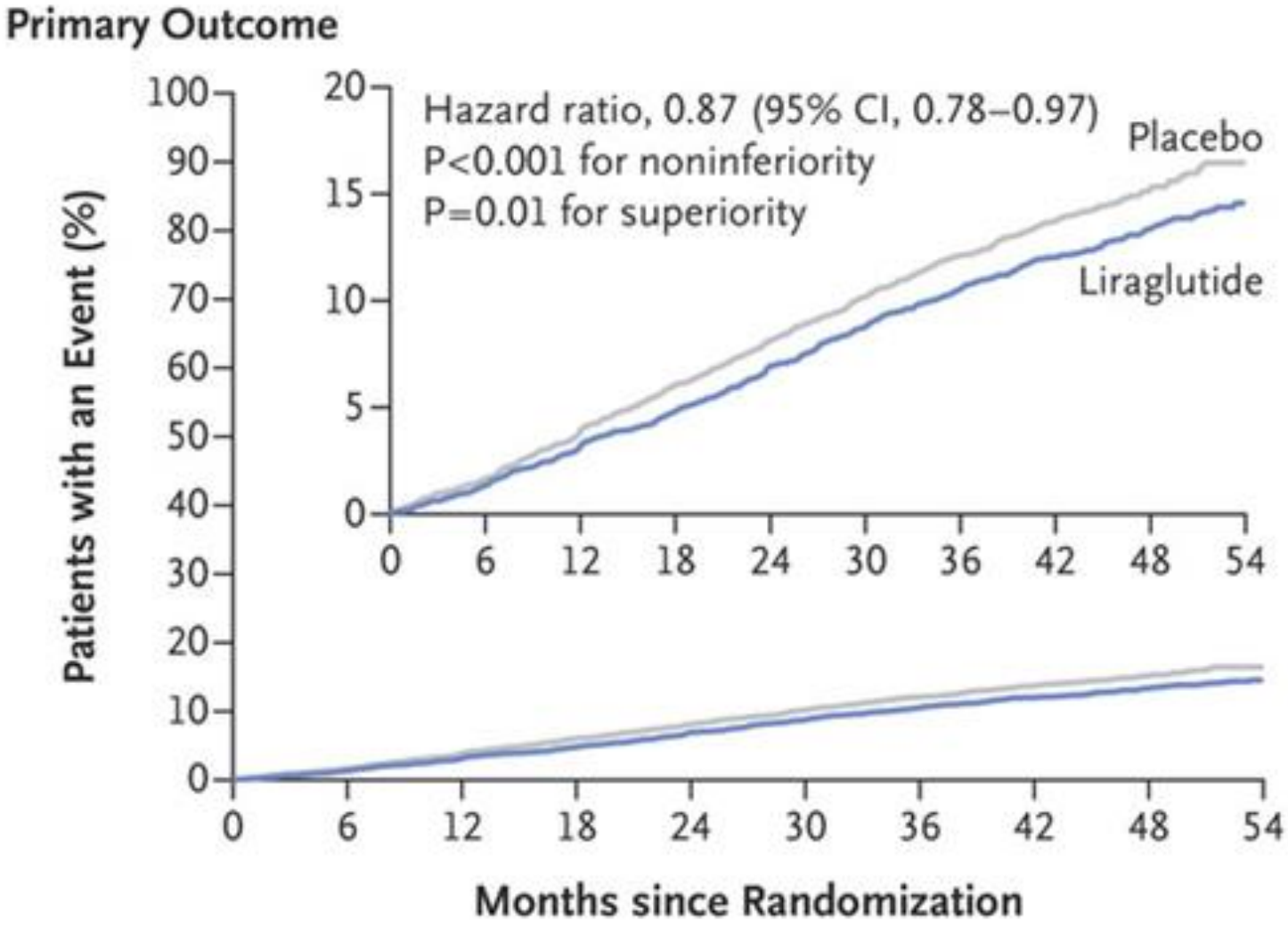


LEADER TRIAL RESULTS - LIRAGLUTIDE

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

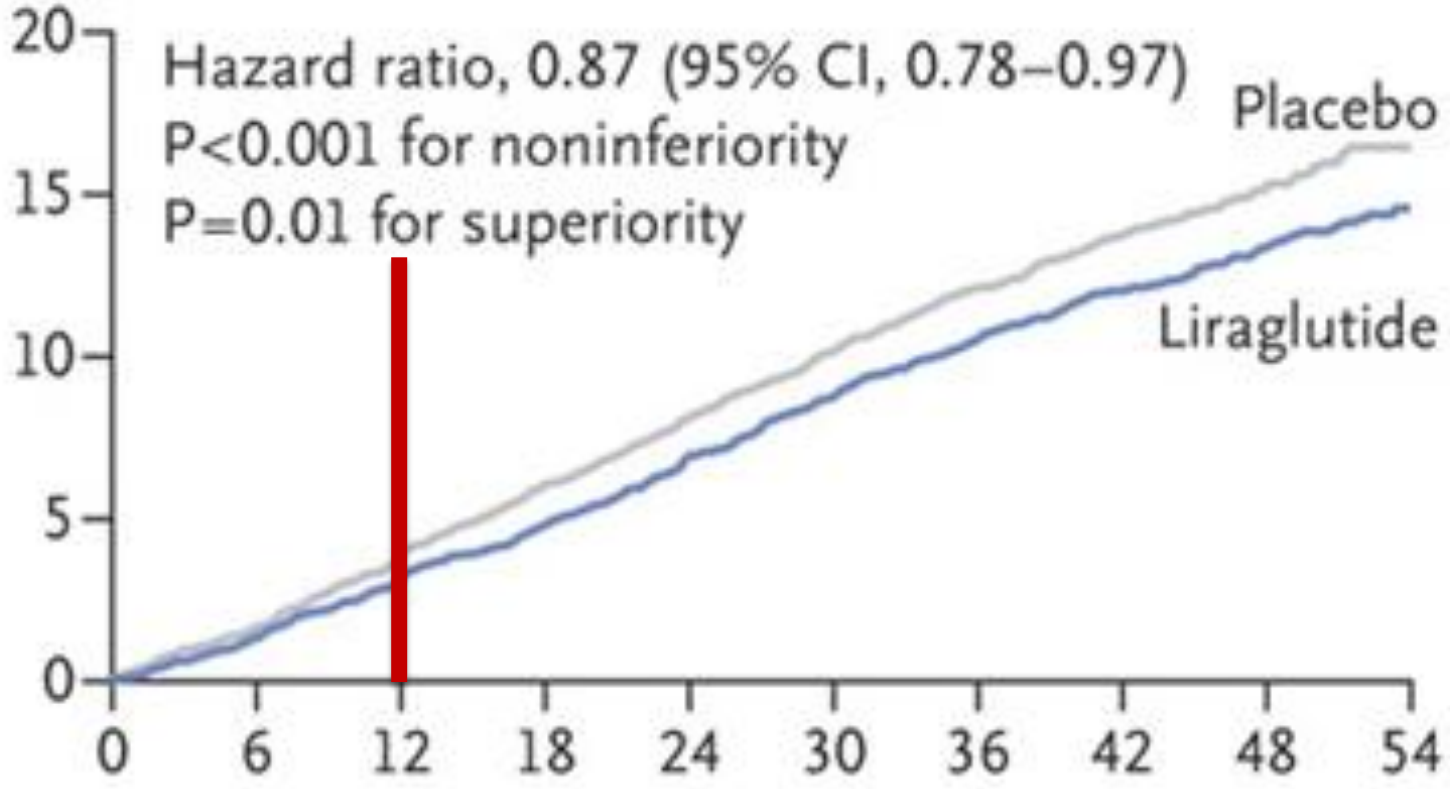


-13% RRR

Marso SP et al NEJM 2016; 375: 311-322

LEADER TRIAL RESULTS - LIRAGLUTIDE

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



SEPARATION OF SURVIVAL CURVES
ONLY AFTER 12 MONTHS OF TREATMENT

Marso SP et al NEJM 2016; 375: 311-322

Cardiovascular Outcomes Trials with GLP-1 Agonists

CVOT	Agent	Established CV Safety	Demonstrated Beneficial Effects on CV Endpoints
LEADER[a]	Liraglutide	Yes	Yes
ELIXA[b]	Lixisenatide	Yes	No
SUSTAIN-6[c]	Semaglutide	Yes	Yes
EXSCEL[d]	Exenatide once weekly	Yes	No

No Reduction in Cardiovascular Outcomes with Lixisenatide e Exenatide
(Not a Class Effect)

Facing a New Treatment Paradigm in Diabetes and Cardiovascular Disease?

NEW TREATMENT PARADIGM IN DIABETES

New Treatament Paradigm In Diabetics with High Cardiovascular Risk

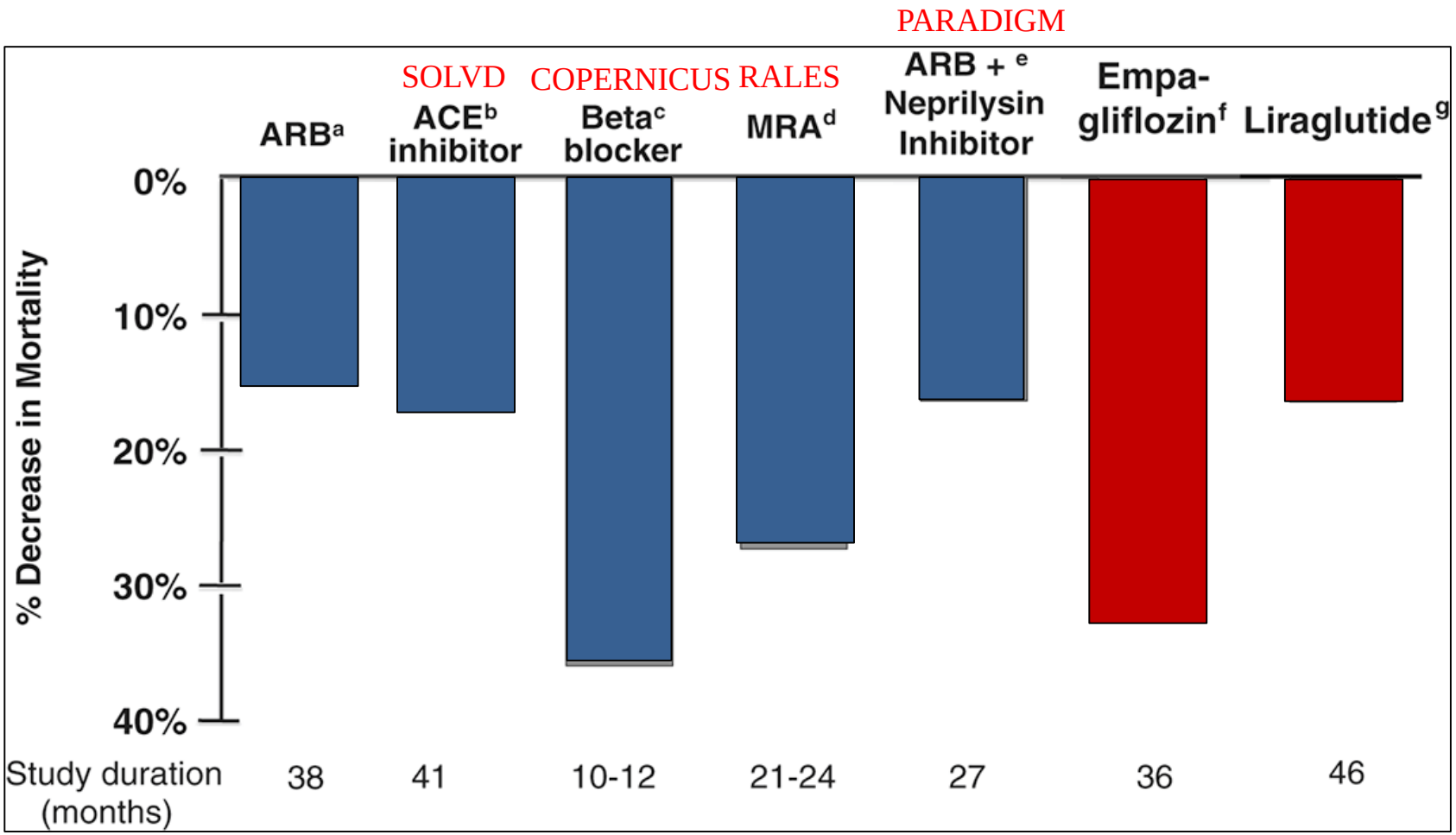
"Glucocentric" Approach

Hb A1c in the Center

(CV) Events Reduction Approach

MULTIFACTORIAL INTERVENTION

ALL-CAUSE MORTALITY IN SEVERAL CLINICAL TRIALS



CARDIOLOGIST COMMITMENT WITH CV CARE

Fitchett DH et al European Journal of Heart Failure 2016

Clinical Trials with Cardiovascular Outcomes
Effect in Total Mortality

Clinical Trial 4 S

Sinvastatin vs Placebo

→ **NNT of 30 over 5.4 years (to reduce 1 death)**

Clinical Trial HOPE

Ramipril vs Placebo

→ **NNT of 56 over 5 years (to reduce 1 death)**

Clinical Trial EMPA-REG

Empagliflozin vs Placebo

→ **NNT of 39 over 3 years (to reduce 1 death)**

Fitchett DH et al European Journal of Heart Failure 2016

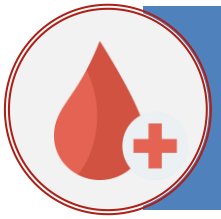
Cost-efficacy in Secondary Prevention 2018

EMPA-REG OUTCOME EMPAGLIFOCINA	PARADIGM SACUBUTRILO/VALSARTAN	FOURIER/ODISSEY EVOLOCUMAB/ALIROCUMAB
14% RRR	20% RRR	15% RRR
55.45 EUROS/MONTH	193.35 EUROS/MONTH	481,58 EUROS/MONTH

LEADER LIRAGLUTIDE	COMPASS RIVAROXABAN	CANTOS CANAKINUMAB
13% RRR	24% RRR	15% RRR
138 EUROS/MONTH	? EUROS/MONTH	? EUROS/MONTH

Clinical guideline updates following EMPA-REG OUTCOME

Diabetes



ADA and Diabetes Canada recommend empagliflozin to reduce major adverse CV events and CV mortality in patients with T2D and established CV disease[1,2]

CV disease

ESC recommend the use of an SGLT2 inhibitor early in the management of patients with T2D and CV disease to reduce CV and total mortality[3]

Heart failure

CCS and ESC suggest empagliflozin be considered for patients with T2D and established CV disease for the prevention or delay of heart failure[4,5]

American Diabetes Association; CCS, Canadian Cardiovascular Society; CV, cardiovascular; ESC, European Society of Cardiology; SGLT2, sodium glucose transporter 2; T2D, type 2 diabetes

1. American Diabetes Association. Diabetes Care 2018; 2. Canadian Diabetes Association. Can J Diabetes 2016; 3. Piepoli MF et al. Eur Heart J 2016; 4. Ezekowitz JA et al. Can J Cardiol 2017; 5. Ponikowski P et al. Eur Heart J 2016