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Top HF Trials to Impact Your Practice

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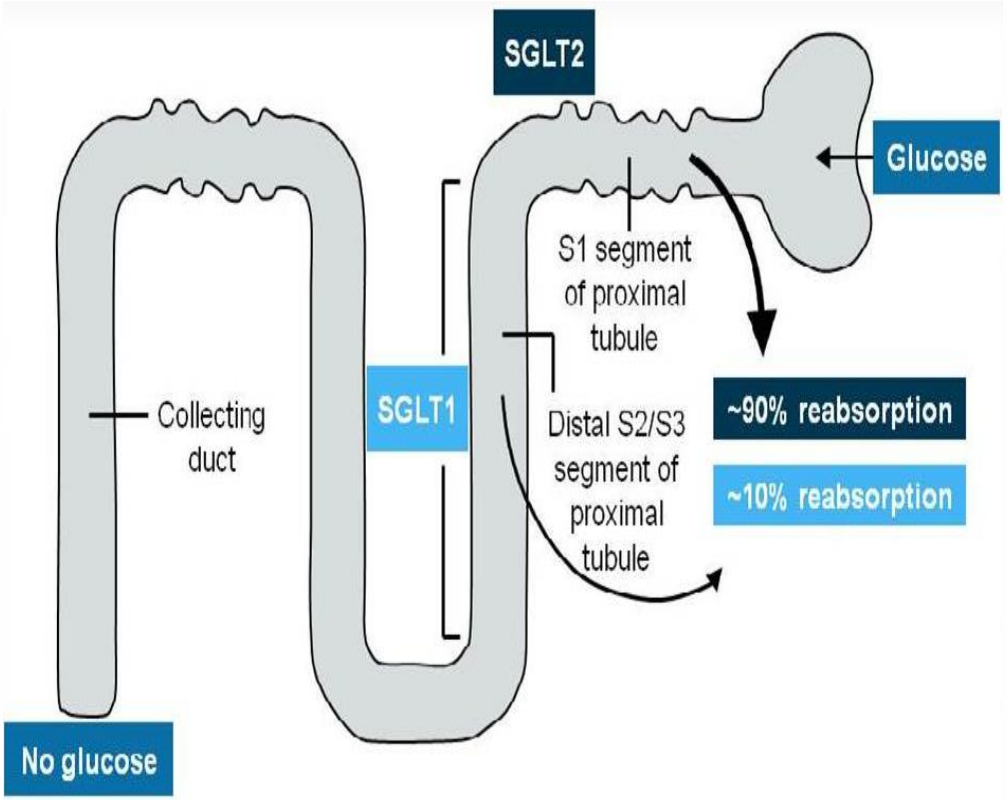
Sodium–glucose cotransporter inhibitors (SGLT-2i)

Canagliflozin

Dapagliflozin

Empagliflozin

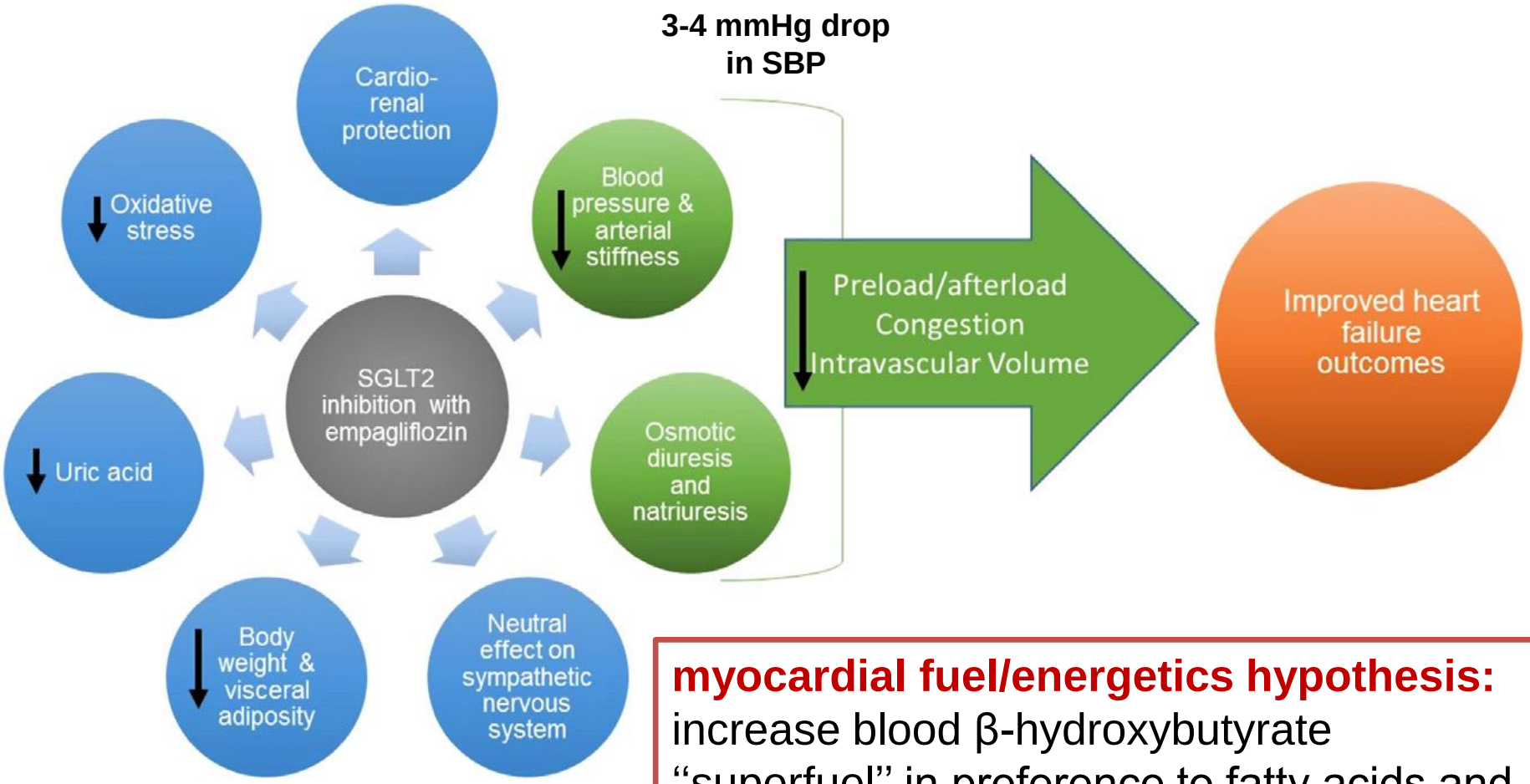


↑ urinary glucose excretion

↓ plasma glucose

sodium–glucose cotransporter inhibitors reduce renal glucose reabsorption, increase urinary glucose ,
HAS MILD NATRIURETIC DIURETIC EFFECT AND RESULTS IN WEIGHT LOSS
increases in hemoglobin and hematocrit concentrations

Potential Mechanisms of SGLT2i for Benefit in HF



myocardial fuel/energetics hypothesis: increase blood β-hydroxybutyrate ‘‘superfuel’’ in preference to fatty acids and glucose

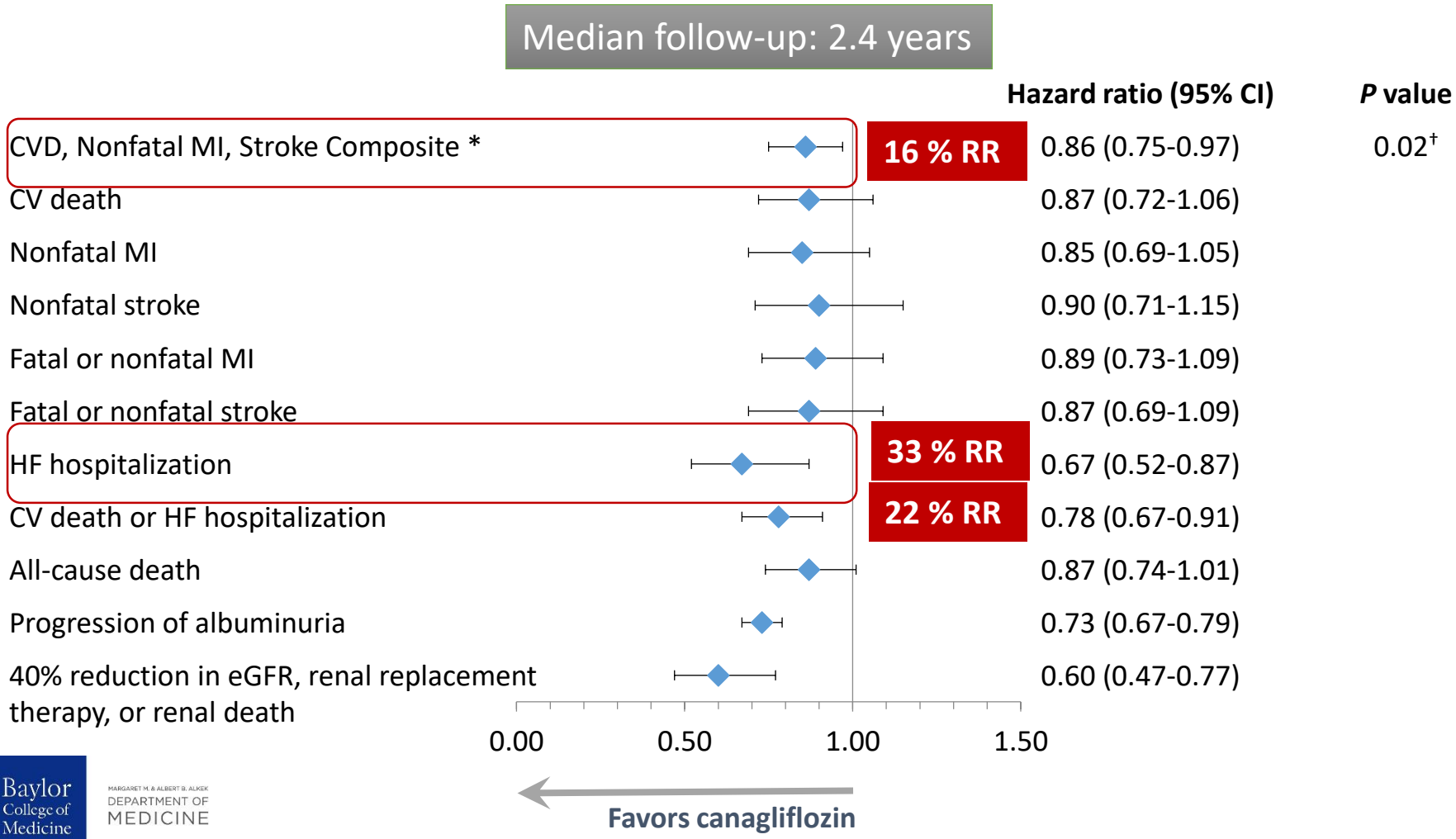
From Pham D. et al. Trends in Cardiovascular Medicine Aug 4, 2016, Ferrannini et al., 2016; Mudaliar et al., 2016, Tahara et al.,2014, Aubert et al., 2016

CANVAS Trials

(Canagliflozin on CV, renal, and safety outcomes)

- CANVAS Program : 10,142 participants with DM II & high CV risk, canagliflozin vs placebo
- Primary : Composite CVD, nonfatal MI, or nonfatal stroke
- Mean age 63.3 years, 35.8% were women
- 66% had a hx of CVD, 14 % had hx of HF
- HF patients were more frequently women, white, and hypertensive and had a history of prior CVD. Usually treated with β-blockers , RAS antagonists, diuretics

Clinical Outcomes with Canagliflozin : CANVAS Program (N=10,142) CVD and Renal



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*CV death, nonfatal MI, or nonfatal stroke. †Superiority.

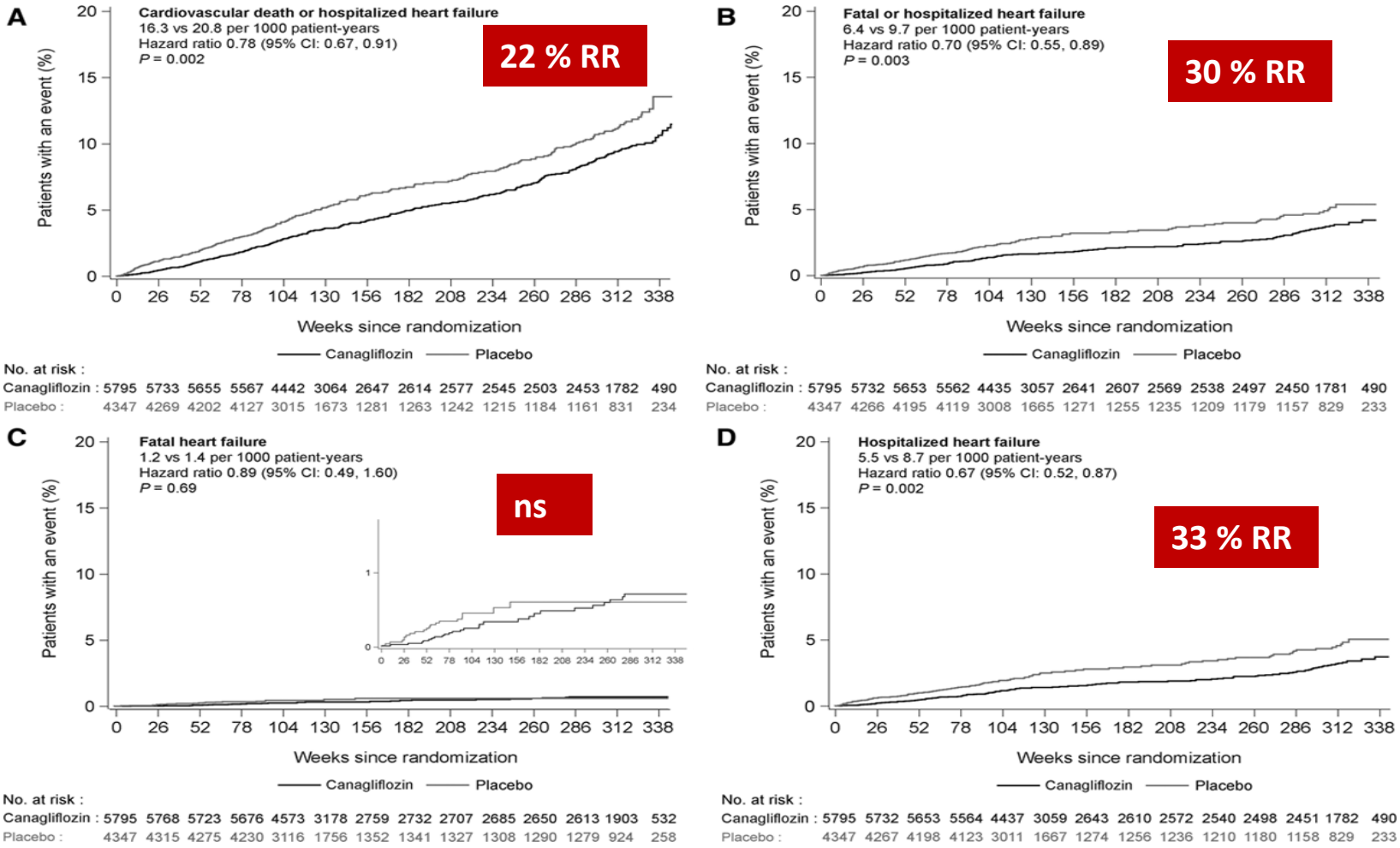
Neal B et al. N Engl J Med ; 377:644-657

Circulation

ORIGINAL RESEARCH ARTICLE

Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus

Results From the CANVAS Program



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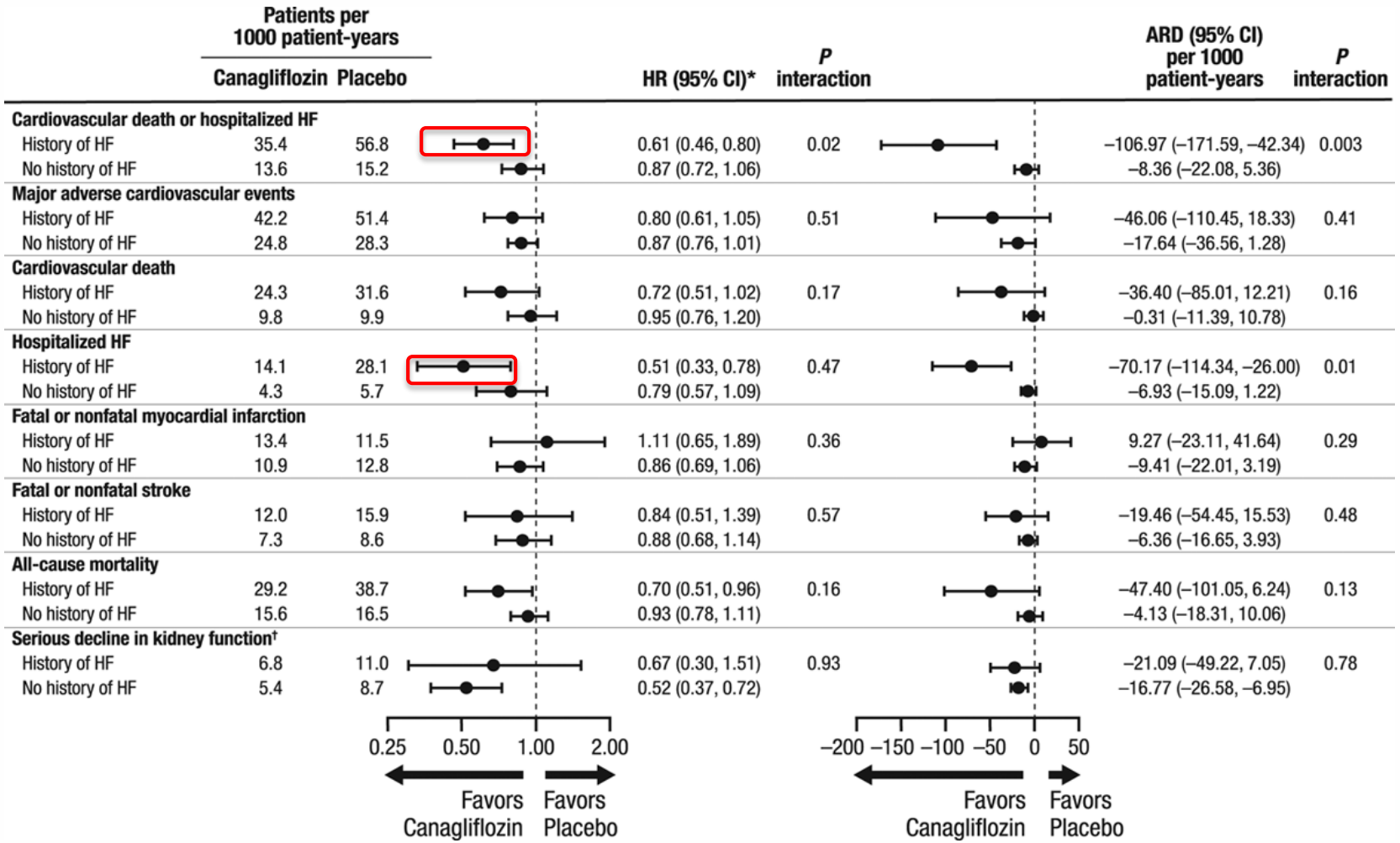
Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus, Volume: 138, Issue: 5, Pages: 458-468, DOI: (10.1161/CIRCULATIONAHA.118.034222)

Benefits Greater with History of HF



Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus, Volume: 138, Issue: 5, Pages: 458-468, DOI: (10.1161/CIRCULATIONAHA.118.034222)

Adverse Events with Canagliflozin

CANVAS Program* Safety Results

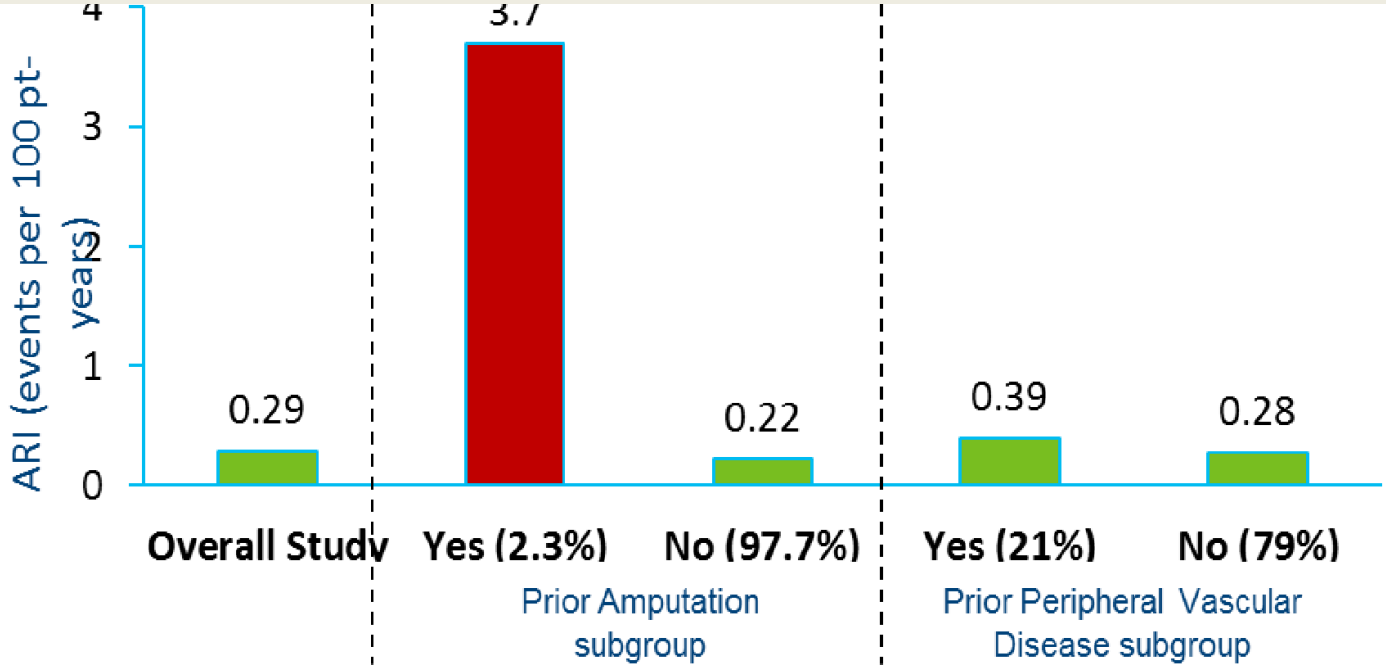
Event	Canagliflozin	Placebo	P value
	Events / 1000-patient years		
All serious adverse events	104.3	120.0	0.04
A/E leading to discontinuation	35.5	32.8	**0.07**
Diabetic ketoacidosis (adjudicated)	0.6	0.3	0.14
Events of interest occurring in significantly more canagliflozin-treated patients			
Amputation	6.3	3.4	<0.001
Bone fracture (adjudicated)			
All	15.4	11.9	0.02
Low trauma	11.6	9.2	0.06
Infection of male genitalia	34.9	10.8	<0.001
Osmotic diuresis†	34.5	13.3	<0.001
Volume depletion†	26.0	18.5	0.009
Mycotic genital infection in women†	68.8	17.5	<0.001

*Includes patients from CANVAS and CANVAS-R (N=10,142). †CANVAS-only population (n=4330).

CANVAS Program

Absolute Amputation Risk Increase: Overall and in Subgroups

Overall amputation risk : **HR: 1.97**; 95% CI 1.41 to 2.75; compared to placebo
Amputations were primarily at the level of the toe or metatarsal



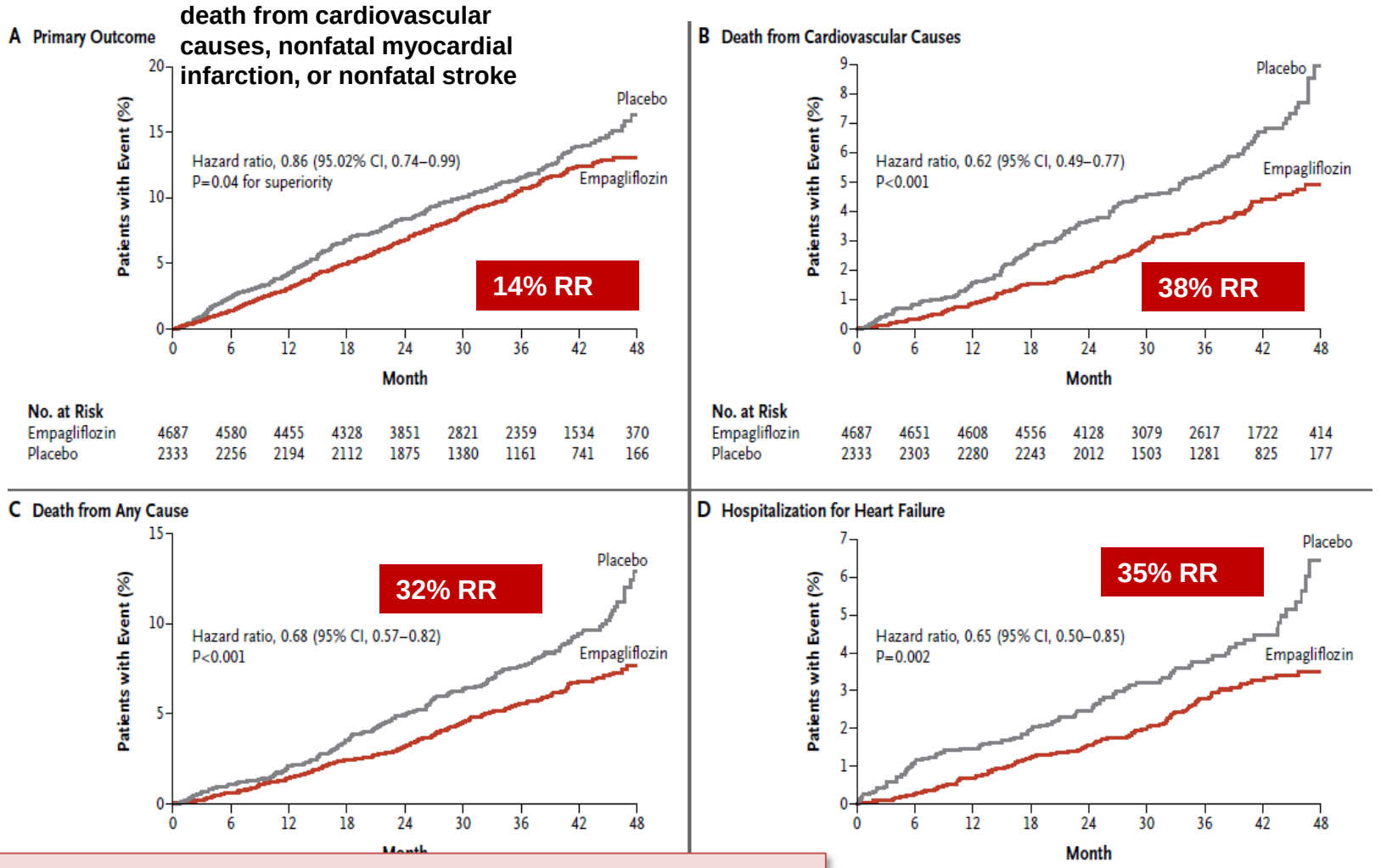
ARI (Absolute risk increase (difference between canagliflozin and placebo amputation event rates per 100 patient years), adapted from Neal B et al. NEJM

Adverse Events

- Similar risk of amputation with canagliflozin in population based studies (Easel Study, Udell JA, et al. Circulation 117.031227, Duelle JA, et al. Circulation. 2017)
- Not seen in EMPA-REG OUTCOME trial of empagliflozin
- Mechanism unclear : Reduced tissue perfusion, hypovolemia ?

EMPA-REG OUTCOME TRIAL
Empagliflozin, CV Outcomes and Mortality in Type 2 Diabetes

7028 patients with DM with CV Risk (history of MI or stroke, CAD with USA, ischemia and PAD).
76 % CAD, majority on ACEI, ARB, BB.



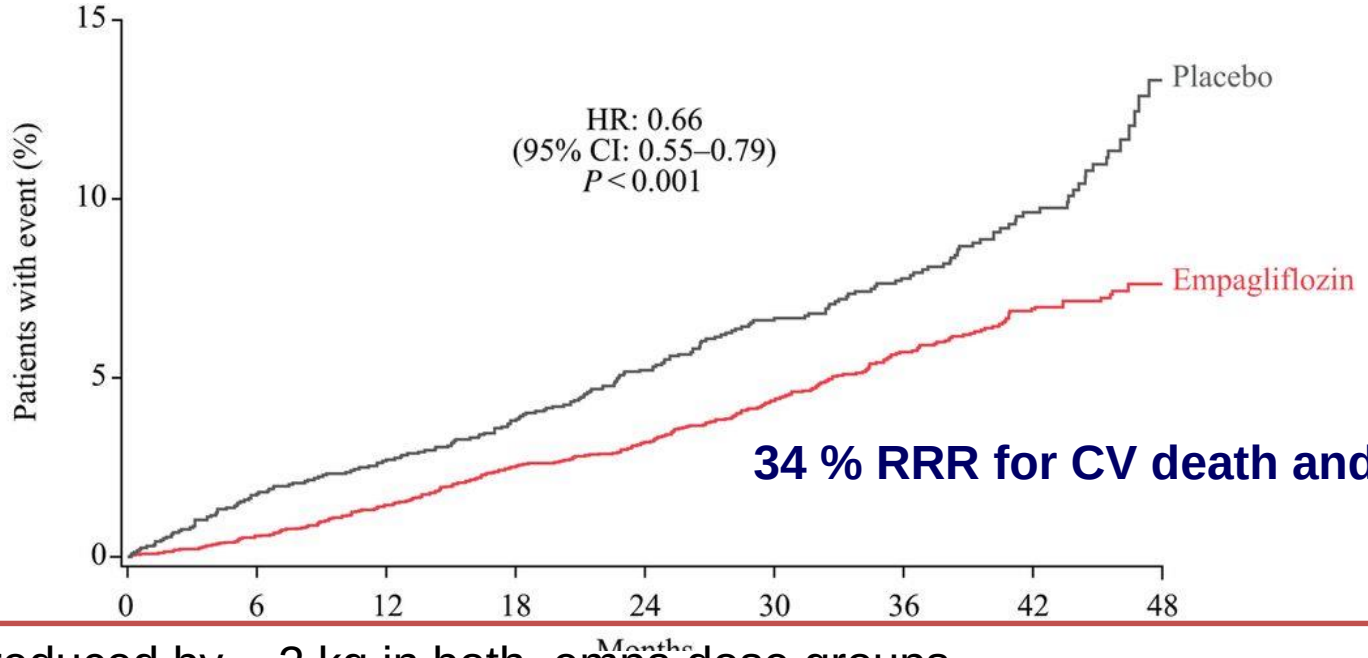
outcome curves diverged early – hemodynamic effects rather than glucose control effects?

N Engl J Med. 373:2117-28.

HF Outcomes-EMPA-REG OUTCOME TRIAL

- **~ 10% had pre- existing HF, 43% on loop diuretics at baseline**

Time to first HFH or CVD



34 % RRR for CV death and HFH

- Weight reduced by ~2 kg in both empa dose groups
- ↓SBP and ↑ in hemoglobin and hematocrit with empagliflozin
- Introduction of loop diuretics lower in the empagliflozin (8.6% vs 13.3%, HR 0.62).

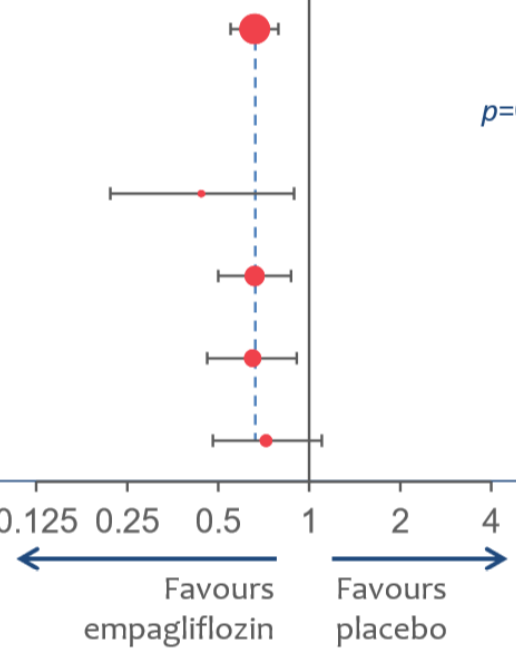
No measure of LVEF, no data on HFrEF vs HFpEF, or BNP

Fitchett et al. European Heart Journal 37, 1526–1534

Reduction in risk of HHF or CV death was consistent across subgroups by baseline HbA1c

HHF or CV death by HbA1c at baseline; post hoc analysis

	n with event/analysed (%)				Treatment by subgroup interaction
	Empagliflozin	Placebo	HR (95% CI)	HR (95% CI)	
All patients	265/4687 (5.7)	198/2333 (8.5)	0.66 (0.55, 0.79)		
HbA1c at baseline					*p*=0.6881
<7.0%	16/297 (5.4)	15/127 (11.8)	0.44 (0.22, 0.89)		
7.0% to <8.0%	114/2042 (5.6)	86/1029 (8.4)	0.66 (0.50, 0.87)		
8.0% to <9.0%	77/1534 (5.0)	60/795 (7.5)	0.65 (0.46, 0.91)		
≥9.0%	57/812 (7.0)	37/382 (9.7)	0.72 (0.48, 1.10)		



Indirect evidence suggests non-diabetes patients with heart failure may benefit from empagliflozin

Empagliflozin is not indicated in all countries for CV risk reduction, and is not indicated for the treatment of heart failure
HbA1c, glycated haemoglobin; HHF, hospitalisation for heart failure
Fitchett D. *ESC-HF* 2017; oral presentation

Adverse events

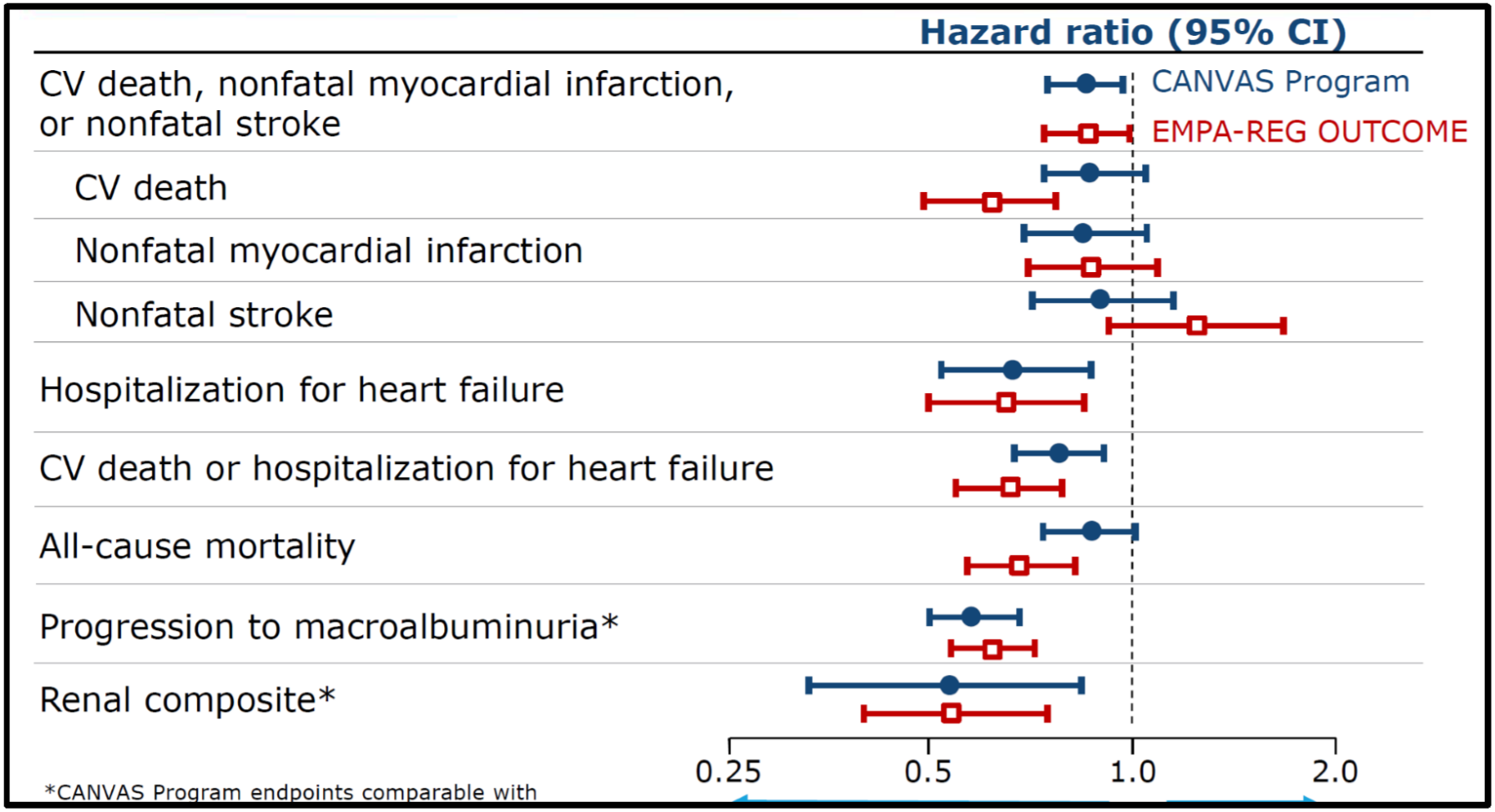
	Placebo	Empagliflozin	
Genital Infection	1.8 %	6.4 % *	↑
Complicated UTI	1.8 %	1.7%	ns
Edema	9.3% *	4.5 %	↓
Volume depletion	4.9 %	5.1 %	ns
ARF	6.6 % *	5.2 %	↓
Any AE	91.7 % *	90.2 %	↓
SAE	42.3 % *	38.2%	↓

Prescribing information :

- Possible increased risk of symptomatic hypotension or volume depletion in patients with renal impairment, elderly or lower SBP
- Increased risk for bone fractures associated with osteoporosis
- Restricted to patients with GFR >45 mL/min/1.73 m2

Zinman et al N Engl J Med 2015;373:2117-28
Fitchett et al. European Heart Journal (2016) 37, 1526–1534
Pham D. et al. Trends in Cardiovascular Medicine Aug 4, 2016

EMPA REG and CANVAS compared



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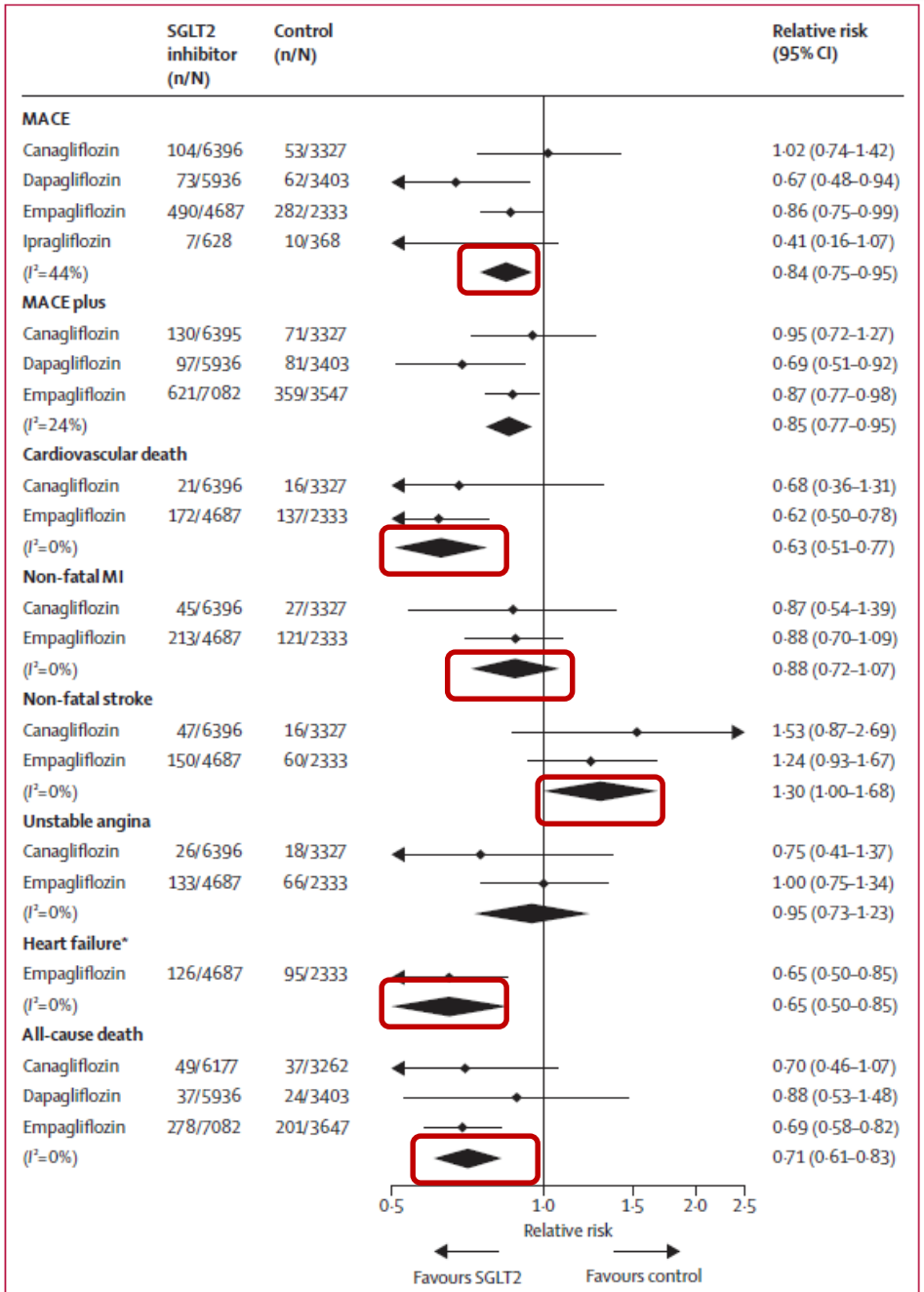
Zinman B et al. N Engl J Med; 373: 2117-28 Neal B et al. N Engl J Med; 377: 644-657

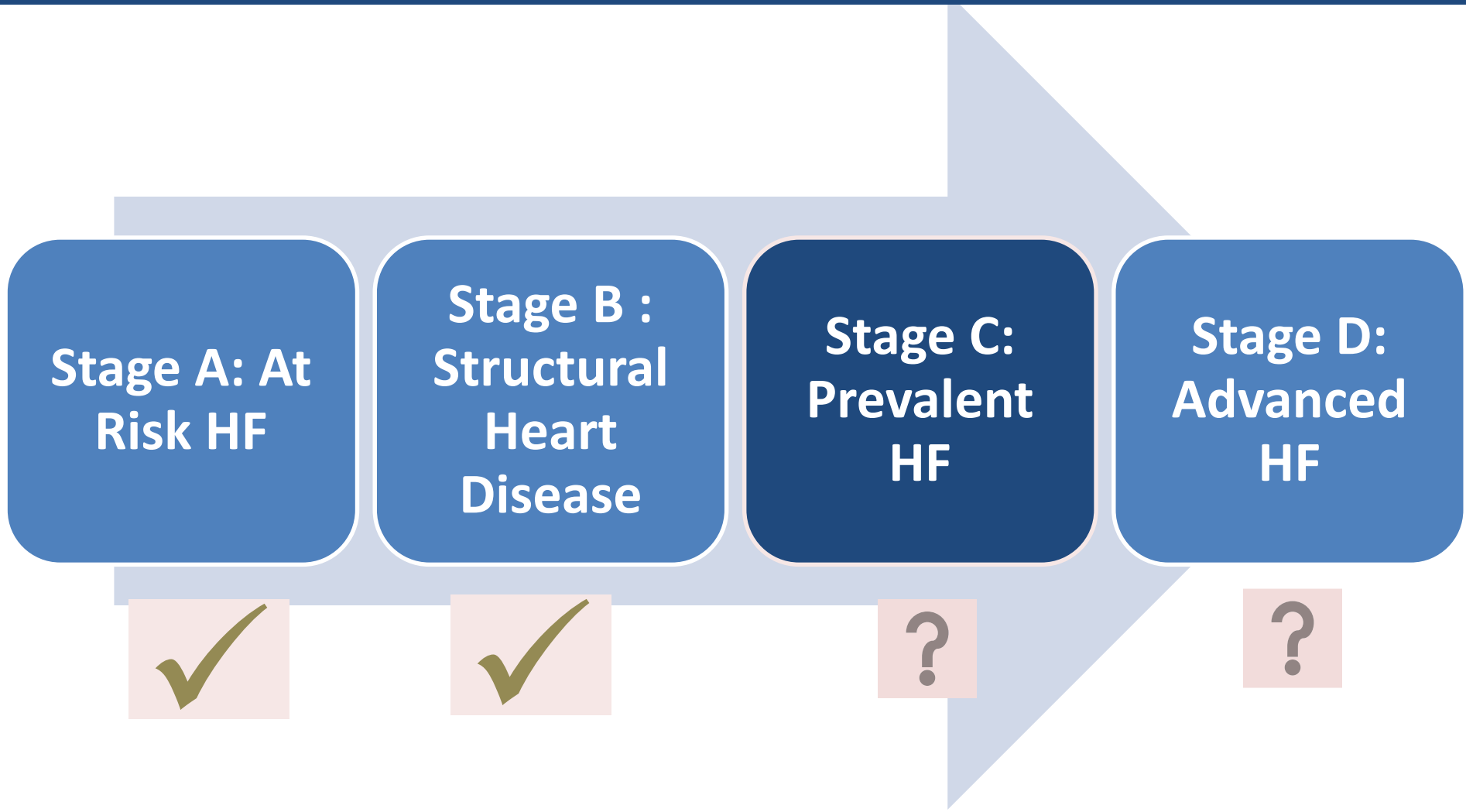
Meta-Analysis of GLT-2 Inhibitors on CV Events in DM



- Overall beneficial effects on MACE and CV death
- Effect on MI: ns
- Strong protective effect for HF

J.H. Wu, *et al.* Effects of sodium–glucose cotransporter-2 inhibitors on cardiovascular events, death, and major safety outcomes in adults with type 2 diabetes: a systematic review and meta-analysis . Lancet Diabetes Endocrinol, 4 (2016), pp. 411–419

Primary and Secondary Prevention of HF with SGLT2i



Ongoing SGLT2i Trials in HF

	EMPEROR-Preserved[1]	EMPEROR-Reduced[2]	Dapa-HF[3]	SOLOIST-WHF[4,5]
Sample size	4126	2850*	4500	4000[4] (6667 ?)[5]
Key inclusion criteria	• Chronic HF† • Elevated NT-proBNP • eGFR ≥20 ml/min/1.73 m²		• Symptomatic HFrEF† • Elevated NT-proBNP • eGFR ≥30 ml/min/1.73 m²	• Type 2 diabetes • Chronic HF • Elevated NT-proBNP • Hospital admission for worsening HF and haemodynamically stable
	HFpEF (LVEF >40%)	HFrEF (LVEF ≤40%)	HFrEF (LVEF ≤40%)	
Primary endpoint	• Time to first event of adjudicated CV death or adjudicated HHF		• Time to first occurrence of CV death, HHF or urgent HF visit	• Time to first event of CV death or HHF (both EF<50% and II)
Key secondary endpoints	• Individual components of primary endpoint • All-cause mortality • All-cause hospitalisation • Time to first occurrence of sustained reduction of eGFR • Change from baseline in KCCQ		• Total number of CV death or HHF • All-cause mortality • Composite of ≥50% sustained eGFR decline, ESRD or renal death • Change from baseline in KCCQ	• Total number of CV death, HHF or urgent HF visit • Composite of ≥50% sustained eGFR decline, chronic dialysis, renal transplant or sustained eGFR <15 ml/min/1.73 m²
Start date	March 2017	March 2017	February 2017	June 2018
Expected completion date	June 2020	June 2020	December 2019	January 2021

*NT-proBNP-based enrichment of the population with patients at higher severity of HF; †NYHA class II–IV

ESRD, end-stage renal disease; HHF, hospitalisation for heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide

1. ClinicalTrials.gov NCT03057951; 2. ClinicalTrials.gov NCT03057977; 3. ClinicalTrials.gov NCT03036124; 4. ClinicalTrials.gov NCT03521934; 5. EU Clinical Trials Register 2017-003510-16. Available at: https://www.clinicaltrialsregister.eu

sotagliflozin

Brief History – Glucose Lowering Drugs Approval

- 2008 FDA mandated assessment of CV safety of all antihyperglycemic agents in RCTs
  - noninferiority studies :study drug not associated with more MACE than placebo
  - (Some tested for superiority if noninferiority met)
  - Primary endpoint: composite of CVD, nonfatal MI, and nonfatal stroke
  - HF end points were not mandated

Summary

SGLT2i

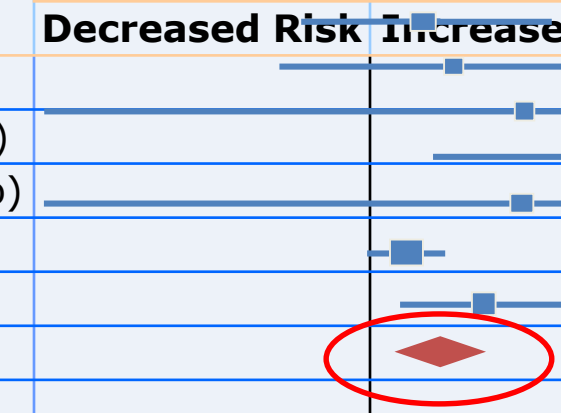
- 15% reduction in MACE
- 35% reduction in HF hospitalization
- Favorable effects on kidney function
- Potential PVD safety signal for canagliflozin

HF should be a safety and efficacy outcome in DM trials

Background
Safety and Efficacy with Other Glucose Lowering Medications in HF

Risk of HF is Increased With Thiazolidinediones

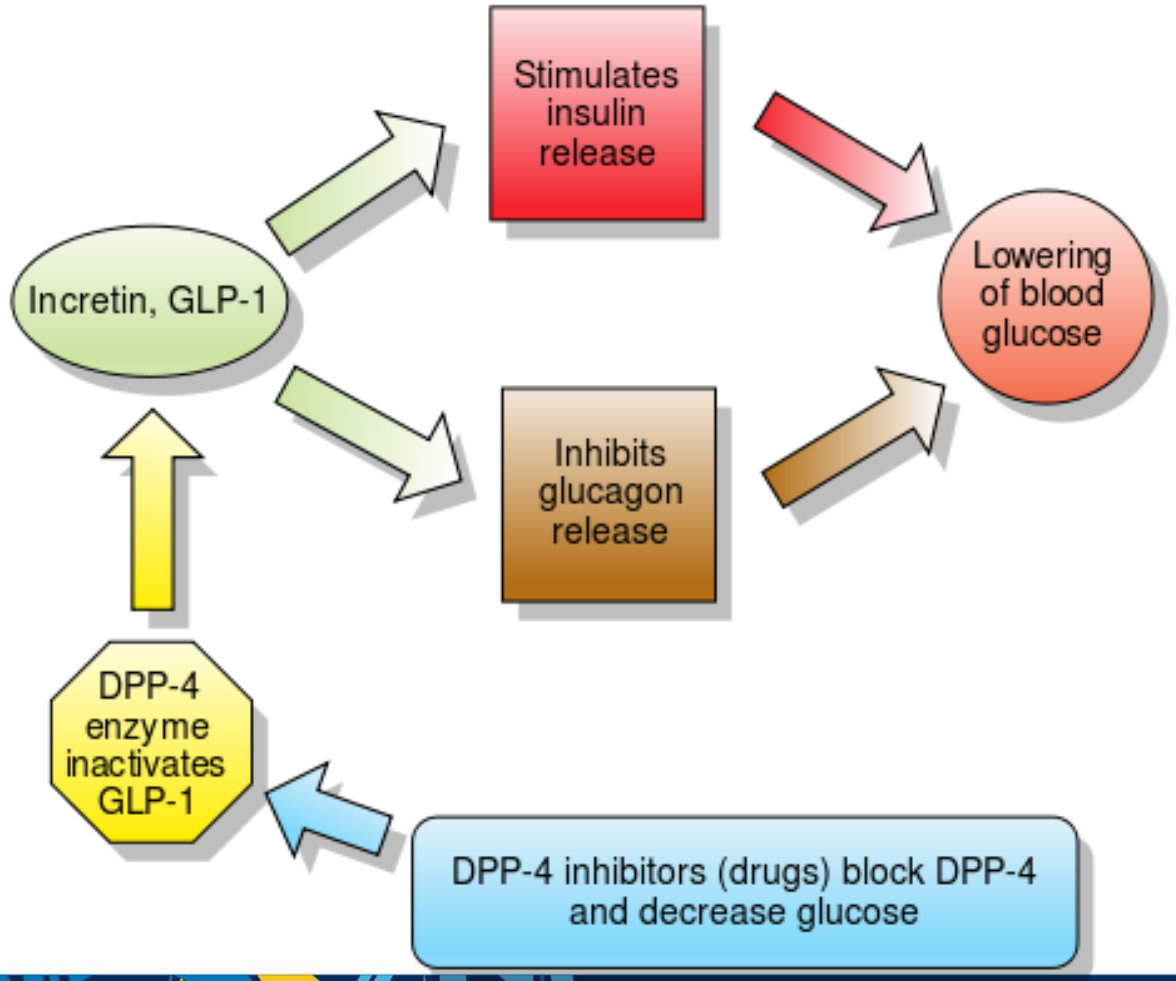
Risk of CHF	Risk Ratio (95% Confidence Interval) Decreased Risk / Increased Risk	Weight	Risk Ratio (95% CI)
ADOPT (RSG)		12.0%	1.49 (0.62, 3.53)
Dargie et al. (RSG)		7.3%	1.81 (0.55, 6.02)
Mazzone et al. (Pio)		1.1%	2.97 (0.12, 72.63)
DREAM (RSG)		5.0%	7.00 (1.59, 30.76)
PPAR (RSG)		1.2%	2.88 (0.12, 69.94)
PROactive (Pio)		49.0%	1.31 (1.03, 1.67)
RECORD (RSG)		23.5%	2.24 (1.27, 3.96)
TOTAL		**100.0%**	**1.72 (1.21, 2.42)**



Test for overall effect: $p = 0.002$

Lago RM, et al. *Lancet.* 2007; 370:1129–1136

Glucagon Like Peptide 1 (GLP-1)



DPP-4 Inhibitor Trials

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SAVOR TIMI 53

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

Benjamin M. Scirica, M.D., M.P.H., Deepak L. Bhatt, M.D., M.P.H., Eugene Braunwald, M.D., P. Gabriel Steg, M.D., Jaime Davidson, M.D., Boaz Hirshberg, M.D., Peter Ohman, M.D., Robert Frederich, M.D., Ph.D., Stephen D. Wiviott, M.D., Elaine B. Hoffman, Ph.D., Matthew A. Cavender, M.D., M.P.H., Jacob A. Udell, M.D., M.P.H., Nihar R. Desai, M.D., M.P.H., Ofri Mosenzon, M.D., Darren K. McGuire, M.D., Kausik K. Ray, M.D., Lawrence A. Leiter, M.D., and Itamar Raz, M.D., for the SAVOR-TIMI 53 Steering Committee and Investigators*

⇧ HF Hospitalization
- **3.5% vs 2.8% over median 2.1 yrs**
- **HR 1.27 (95% CI 1.01 to 1.51,p=0.007)**

Previous HF, estimated GFR <60 ml/min, elevated BNP, and albumin/creatinine ratio were the strongest predictors of HF hospitalization

N Engl J Med 2013; 369, p: 1317-1326

EXAMINE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

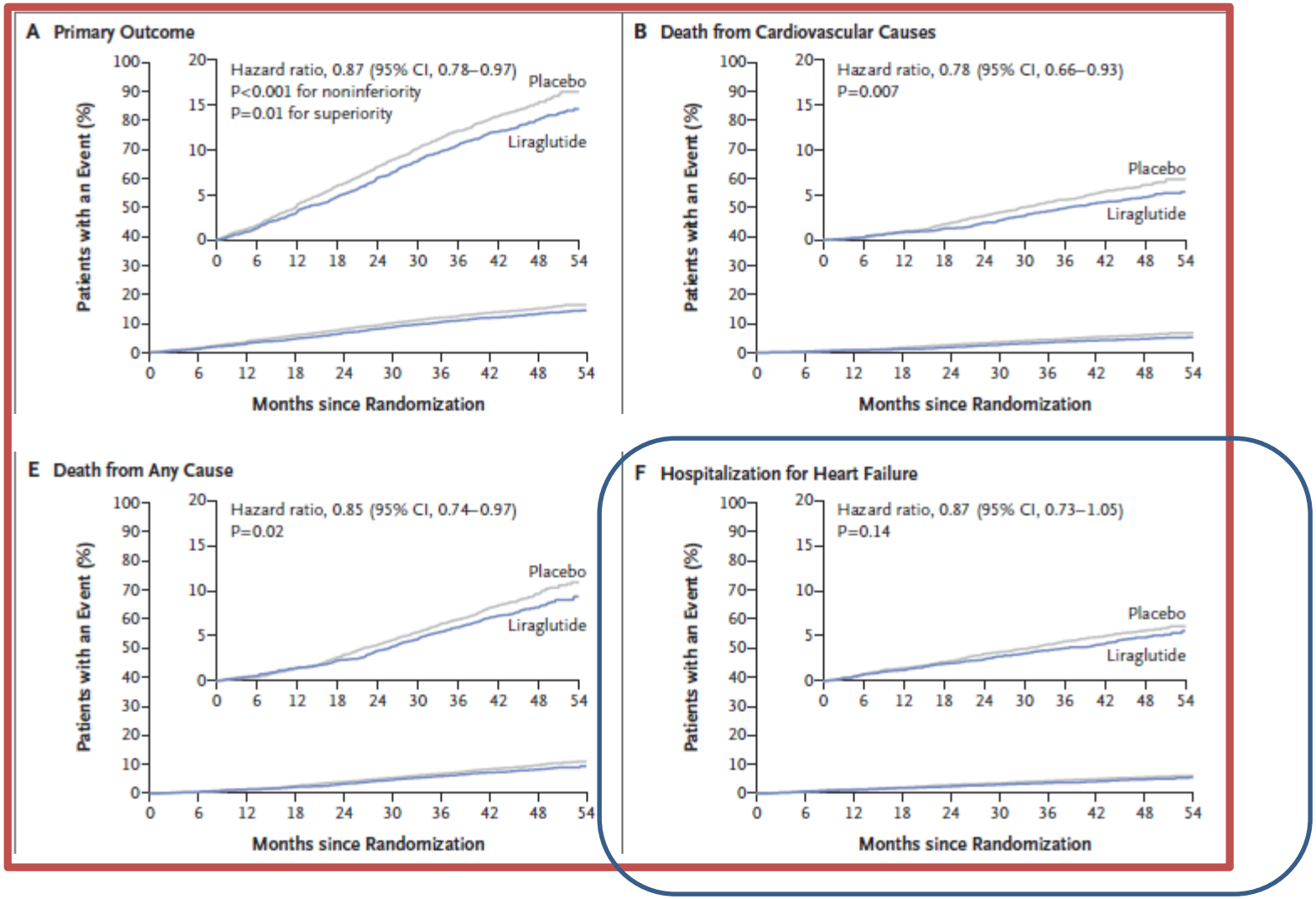
Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes

William B. White, M.D., Christopher P. Cannon, M.D., Simon R. Heller, M.D., Steven E. Nissen, M.D., Richard M. Bergenstal, M.D., George L. Bakris, M.D., Alfonso T. Perez, M.D., Penny R. Fleck, M.B.A., Cyrus R. Mehta, Ph.D., Stuart Kupfer, M.D., Craig Wilson, Ph.D., William C. Cushman, M.D., and Faiez Zannad, M.D., Ph.D., for the EXAMINE Investigators*

HF not reported in main manuscript, Posthoc analysis : HFH or CVD and HFH not different

N Engl J Med, 369 2013, p. 1327–1335
F. Zannad, Lancet, 2015 23;385(9982):2067-76.

Liraglutide and CV Outcomes in DM with CVD Risk: LEADER



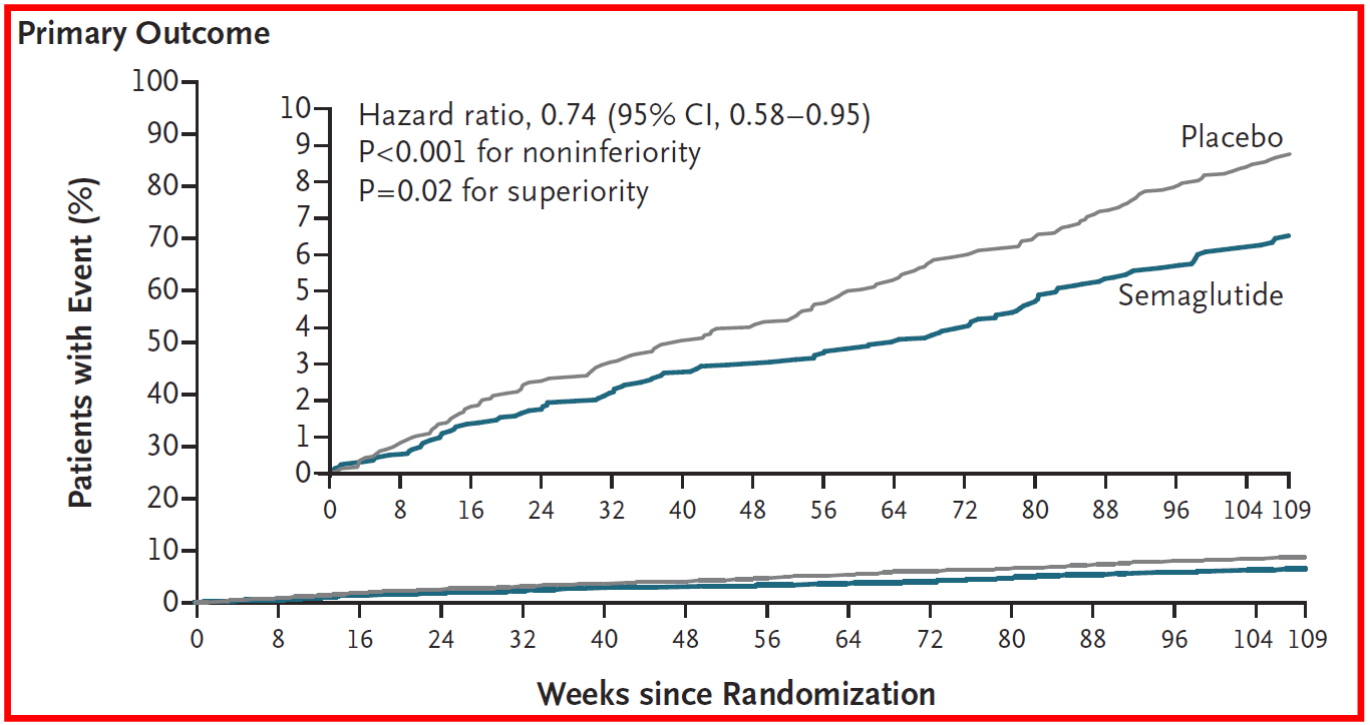
Reduced CV death, nonfatal MI or stroke. HFH Not Different

Marso et al. New Engl J Med July 28 2016

SUSTAIN-6 : Longer Acting GLP-1 agonist (sc/week) semaglutide ; also with CVD benefit , no effect on HFH

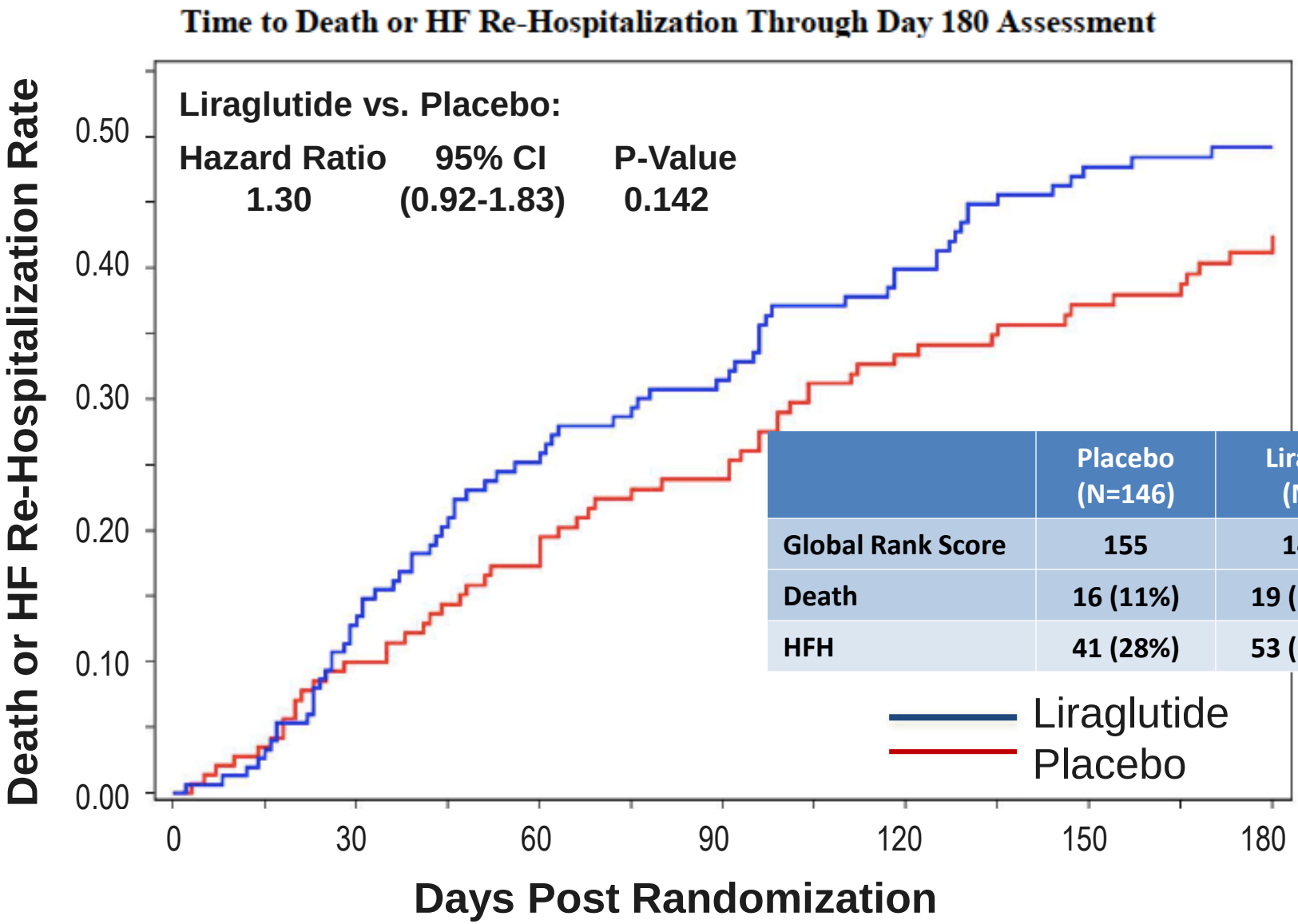
- Approximately 24 % patients with hx of HF
- 26% lower risk CV death, nonfatal MI or nonfatal stroke
  - 39% decrease in nonfatal stroke
  - 26% reduction in nonfatal MI (ns)
- **HFH not different**

CV death, nonfatal MI or nonfatal stroke



Marso S. et al . September 16, 2016, NEJM

GLP-1 post ADHF (FIGHT): NHLBI HF Network: Trend for Increase in Death or HFH



	Placebo (N=146)	Liraglutide (N=154)
Global Rank Score	155	146 (ns)
Death	16 (11%)	19 (12%) (ns)
HFH	41 (28%)	53 (34%) (ns)

Marguiles K et al. JAMA. 2016;316(5):500-508.