ADA 2020 CHICAGO AND ADA VIRTUAL 2021

CARDIOVASCULAR PROTECTION OF SGLT2-INHIBITORS AND GLP1-AGONISTS: STRONG PLAYERS ALONE OR AS A POWERFUL TEAM

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PROGRAM

- Introduction
- Overview
- SGLT-2I in HF
- SGLT-2I and Kidney
- Cardiorenal Protection
- GLP-1-RA
  - Rewind
  - Pioneer
  - Sustain 6
  - Award 7
- AMPLITUDE-O and new insights
- Combination of SGLT-2I and GLP-1-RA
- E-Posters in short
- Where are we now?
- Two outlayers
- An Oldie

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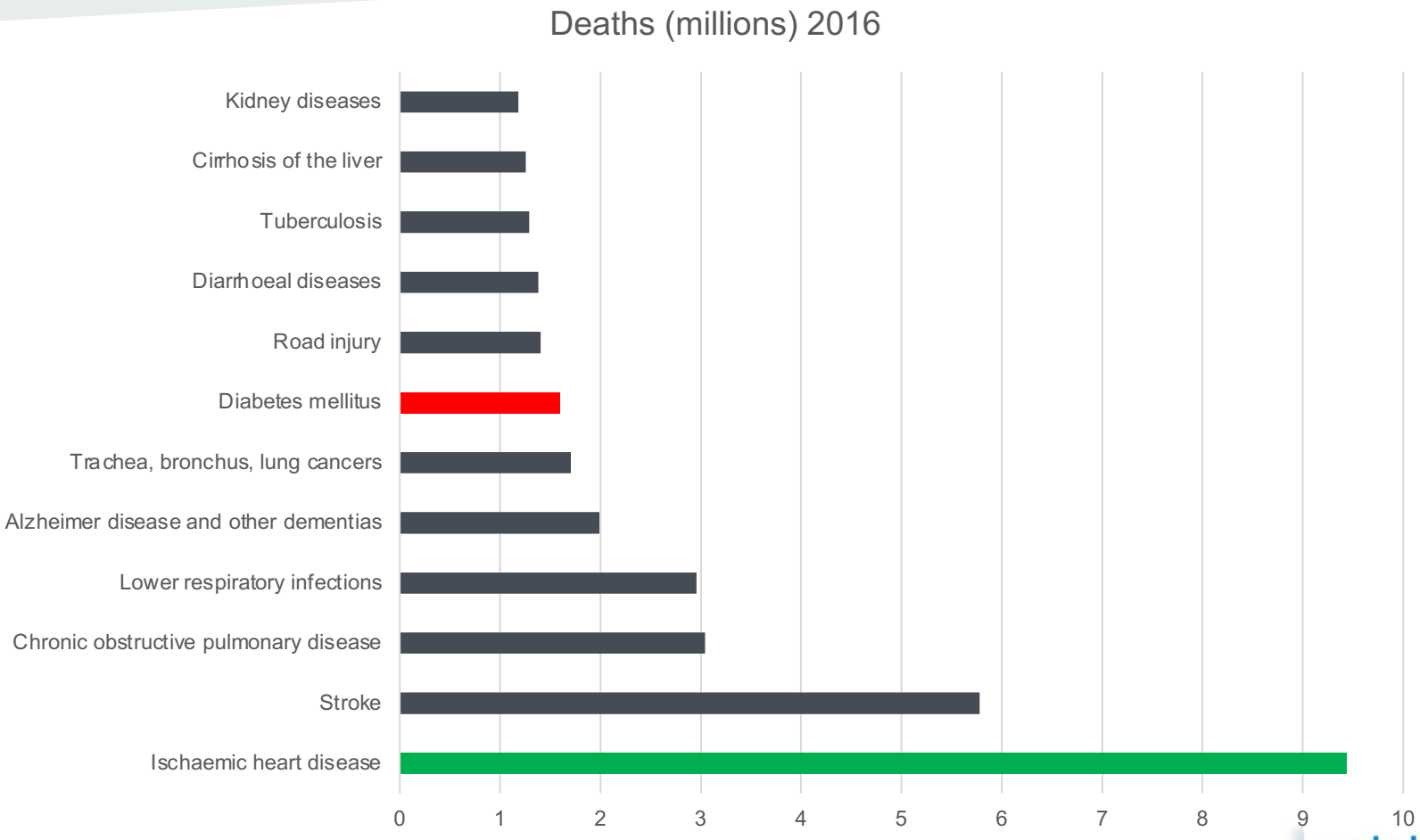
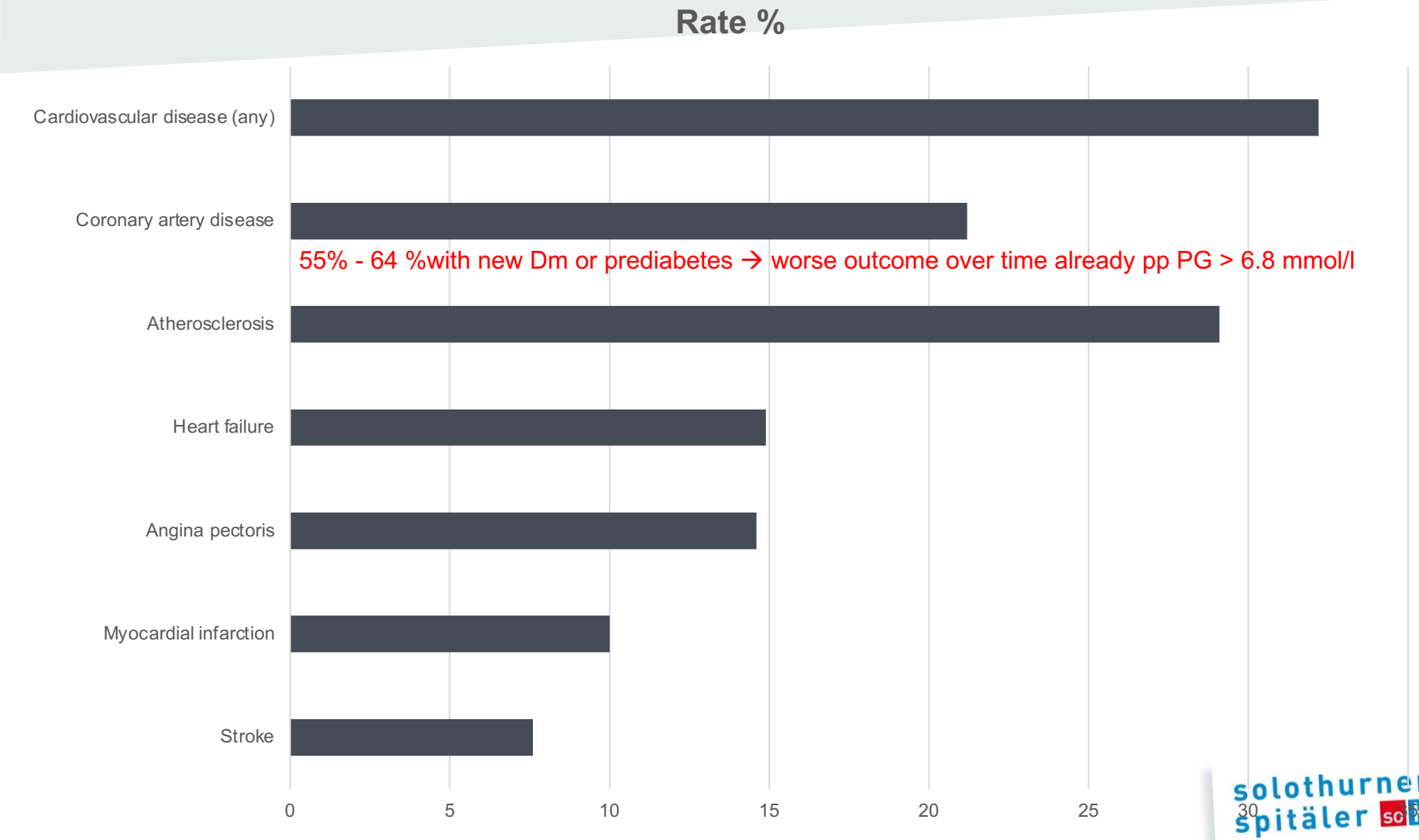
LEADING CAUSES OF DEATH WORLDWIDE



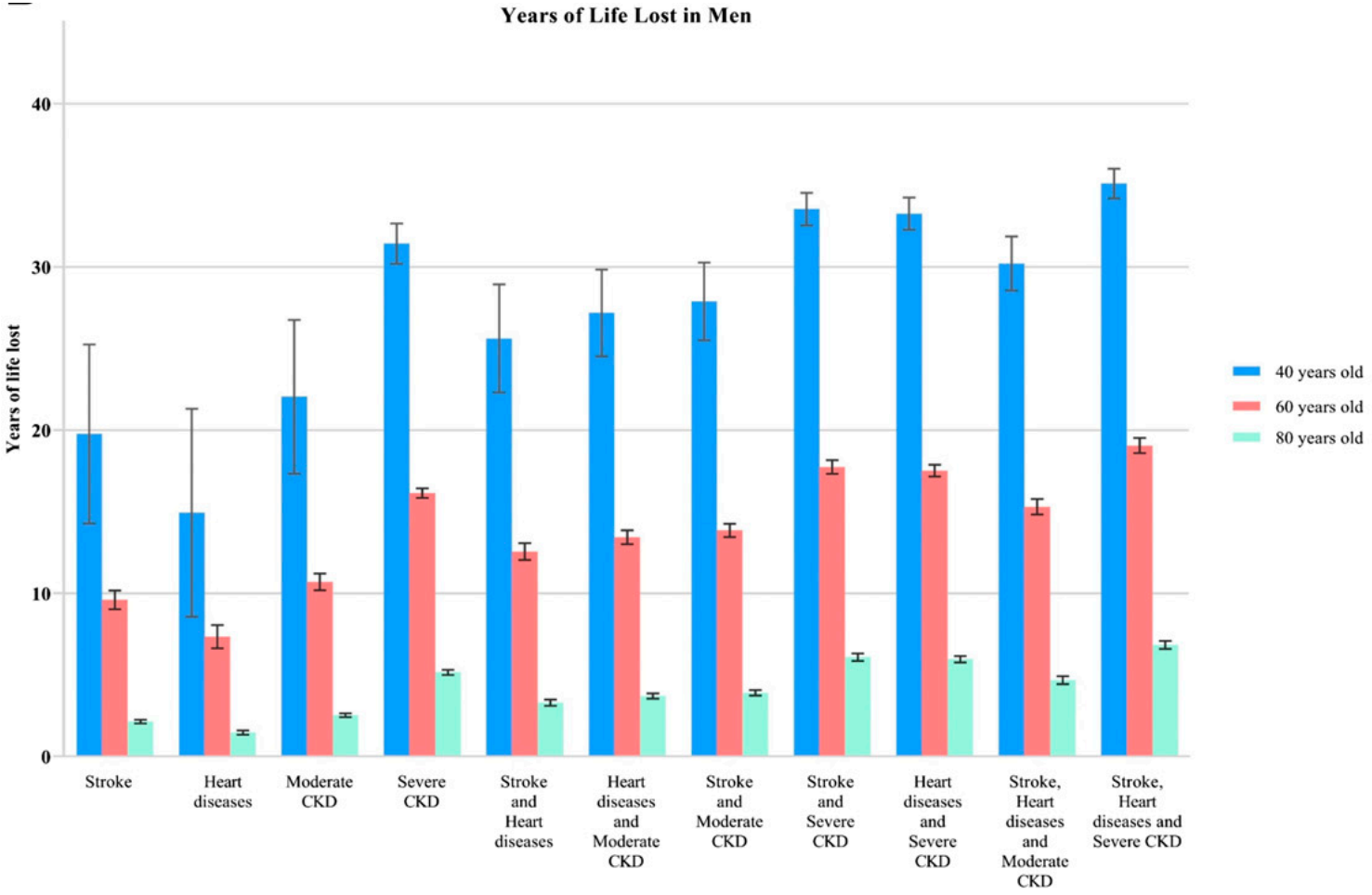
WHO 2018

PREVALENCE OF CARDIOVASCULAR DISEASE IN TYPE 2 DIABETES



Einarson et al. Cardiovasc Diabetol (2018) 17:83

THE IMPACT OF CARDIOVASCULAR DISEASE AND CHRONIC KIDNEY DISEASE ON LIFE EXPECTANCY AND DIRECT MEDICAL COST IN A 10-YEAR DIABETES COHORT STUDY



Diabetes Care 2020;43:1750–1758

N Engl J Med 2017;376:1407-18; Diabetes Care 2021 Mar; 44(3): 699-706

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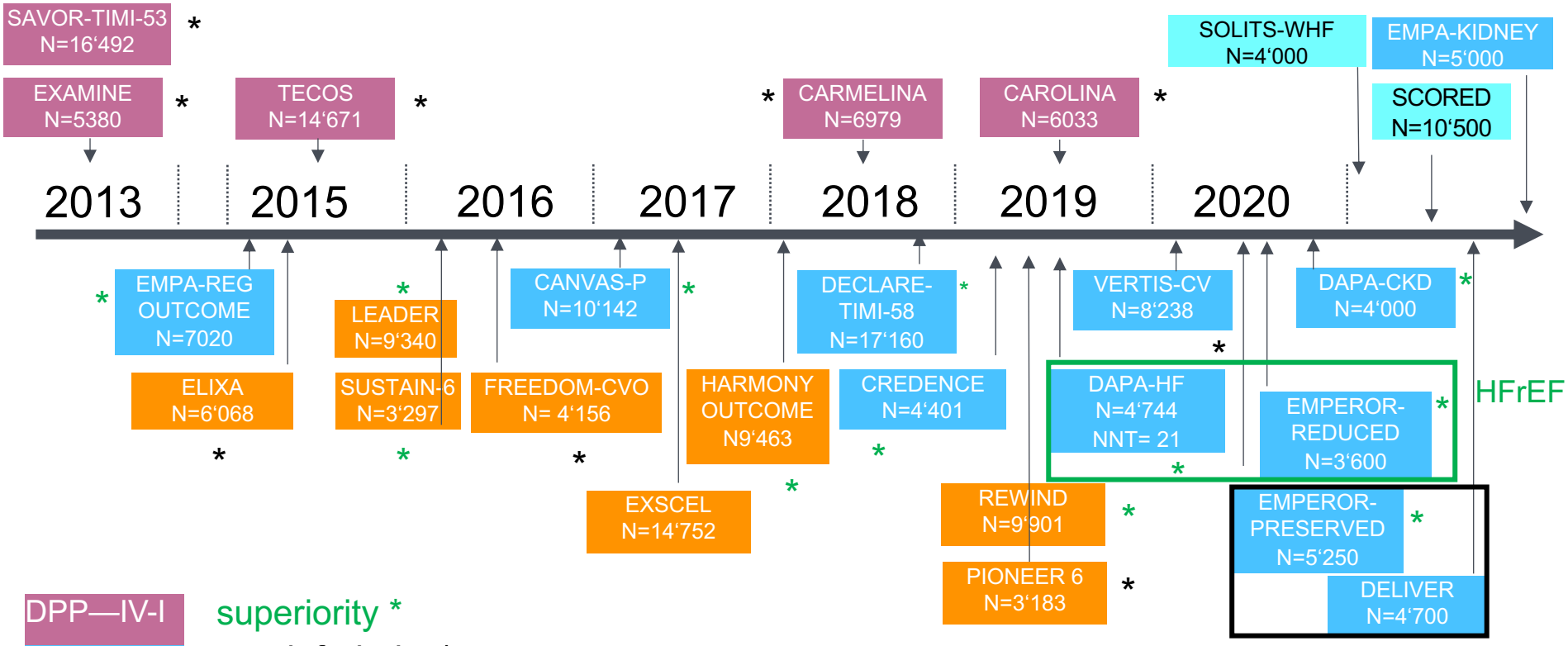
CVOT IN T2D
26 TRIALS: N=197‘832 PATIENTS



DPP—IV-I
SGLT-2-I
SGLT-1/2-I
GLP-1-RA

superiority *

non-inferiority *

To fullfill FDA safety guidelines: trail with 7-15‘000 patients with 3-5 y follow-up!

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Adapted DC 2018; 41:14-31

BASELINE CHARACTERISTICS IN COMPLETED CVOTS IN TYPE 2 DM

	SGLT-2 I				GLP-1 RA						
	EMPA_REG OUTCOME	CANVAS	DECLARE-TIMI 58	VERTIS	ELIXA	LEADER	SUSTAIN 6	PIONEER 6	EXSCEL	REWIND	HARMMONY
Age (y)	63	63	64	64	60	64	65	66	62	66	64
BMI (kg/m²)	31	32	32	32	30	33	33	32	32	32	32
Female sex (%)	28	36	37	30	31	36	39	32	38	46	31
Diabetes duration (y)	8	14	12	13	9	13	14	15	12	10	14
History of CVD (%)	99	66	41	100	100	81	83	85	73	31	100
HbA1c (%)	8.1	8.2	8.3	8.2	7.7	8.7	8.7	8.2	8.0	7.3	8.7

NEJM 2015, 2016, 2017
Lancet 2019
Diabetes Obes Metab 2018, 2019
ADA 2020

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HEART FAILURE:
THE MOST COMMON AND IMPORTANT CV COMPLICATION AND HOSPITALIZATION OF DIABETES MELLITUS

HFpEF and epidemiological associations

- Age (~ 75 %)
- Female gender
- Hypertension (US: 115 mio)
- Diabetes (US: 30/92 mio)
- Renal failure (~ 25%)
- Anemia (~20%)
- Obesity (US: 100 mio)
- Atrial fibrillation
- OSAS
- COPD (~22%)

HFrEF

- Younger
- More males
- Less hypertension
- More diabetes
- More CAD

Death by 80-85% CV reasons

Death by CV reasons and almost equally non CV causes

For every increase of 1% HbA1c → 8% increased risk of HF

Mortality rate (%) after 1 y and 2 y after hospitalization: 29% resp. 40%!

- ***increase with each hospitalization***

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Lewis JACC 2017, Udell: Lancet Diabet Endo 2015;3:356, McMurray: Lancet Diabet Endo 2014; 2: 843, Iribarren: Circulation 2001

HEART FAILURE:PREDICTORS

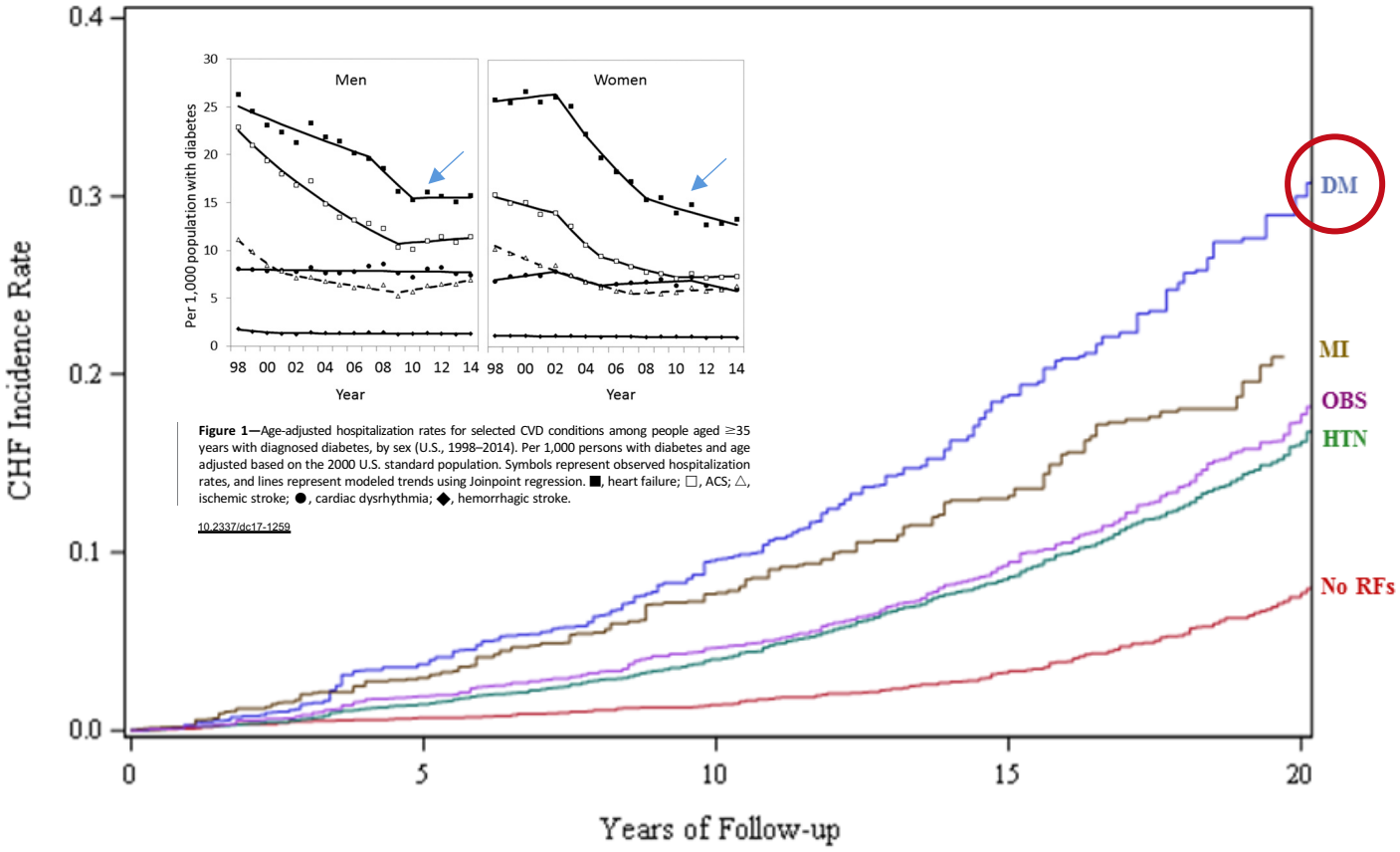

Figure 1—Age-adjusted hospitalization rates for selected CVD conditions among people aged ≥35 years with diagnosed diabetes, by sex (U.S., 1998–2014). Per 1,000 persons with diabetes and age adjusted based on the 2000 U.S. standard population. Symbols represent observed hospitalization rates, and lines represent modeled trends using Joinpoint regression. ■, heart failure; □, ACS; △, ischemic stroke; ●, cardiac dysrhythmia; ◆, hemorrhagic stroke.

10.2337/dc17-1259

https://doi.org/10.1016/j.ypmed.2019.105878

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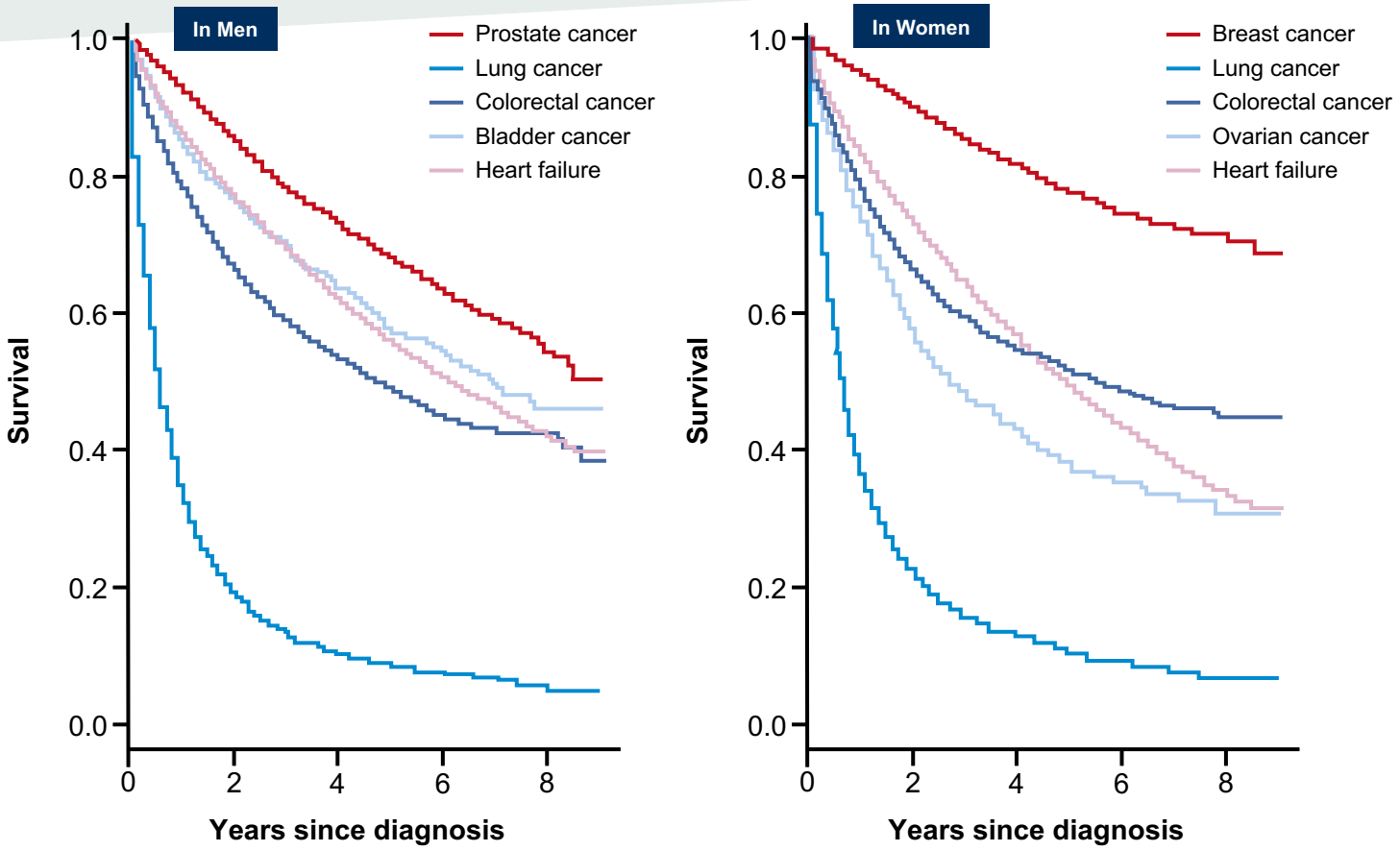
HF AS ‘MALIGNANT’ AS MANY CANCERS



HF, heart failure

Mamas MA. et al. Do patients have worse outcomes in heart failure than in cancer? A primary care-based cohort study with 10-year follow-up in Scotland *Eur J of Heart Failure* 2017.19:1095–1104

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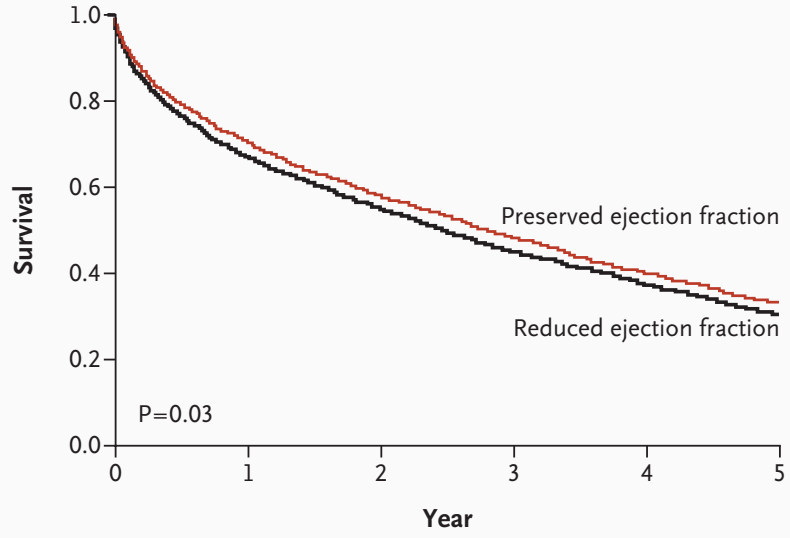
HEART FAILURE AND LVEF



No. at Risk

Reduced ejection fraction	2424	1637	1350	1049	813	604
Preserved ejection fraction	2166	1539	1270	1001	758	574

Figure 2. Kaplan–Meier Survival Curves for Patients with Heart Failure and Preserved or Reduced Ejection Fraction.

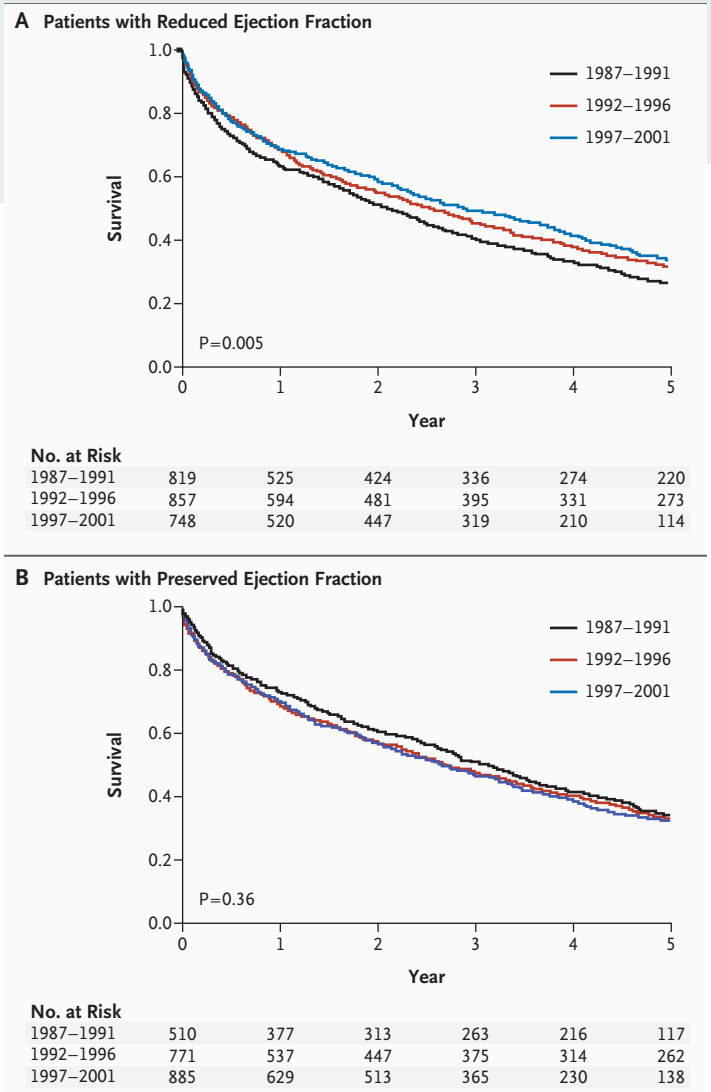
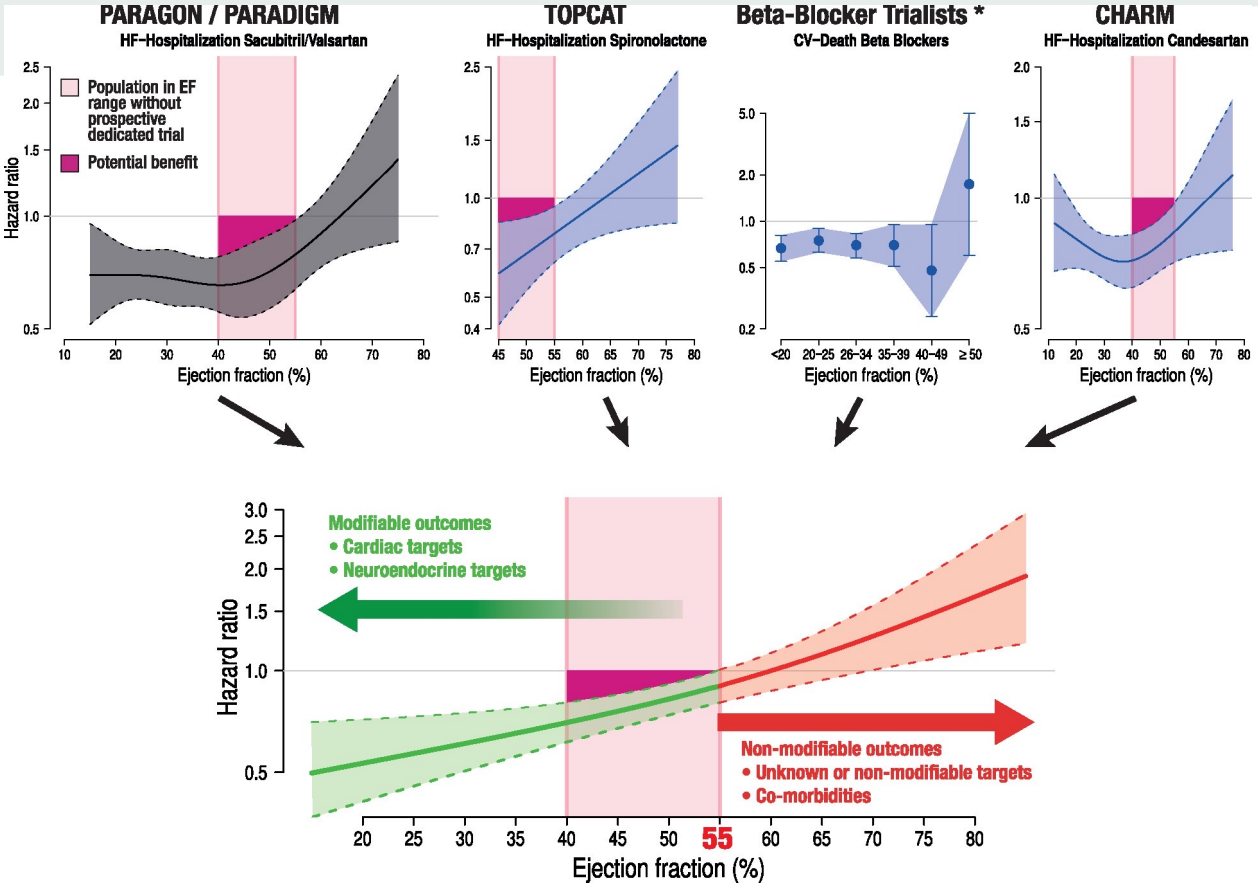


Figure 3. Secular Trends in Survival among Patients with Heart Failure and Preserved or Reduced Ejection Fraction.

Kaplan–Meier survival curves for three five-year periods according to the year of admission show that survival improved over time in patients with reduced ejection fraction (Panel A) but not in patients with preserved ejection fraction (Panel B).



EUR HEART J, VOLUME 41, ISSUE 25, 1 JULY 2020, PAGES 2363–2365, HTTPS://DOI.ORG/10.1093/EURHEARTJ/EHAA281

SGLT-2-I IN HF TRIALS

Trial	Inclusion criteria	N pts/duration/drug	Outcome
DAPA-HF NEJM 2019	EF ≤ 40% NYHA II-IV NT-proBNP > 600 No DM requirement	4744 pts 18 months Dapagliflozin	↓ CV death: 9.6% vs 11.5% ↓ HF hosp : 10.0% vs 13.7%
EMPEROR-HF NEJM 2020	EF≤ 30 % EF 31-40% if HF hosp/BNP ↑ No DM requirement	3730 pts 16 months Empagliflozin	NS CV death: 10.0% vs 10.8% ↓ HF Hosp: 13.2% vs 18.3%
SOLOIST-WHF NEJM 2021	DM type 2 HF Hospitalization No EF requirement	1222 pts 9 months Sotagliflozin	NS CV death: 10.6 vs 12.5 per 100 pt-years ↓ HF Hosp/visits: 194 vs 297 per 100 pt-years

DAPA-HF (EF≤ 40%, GFR ≥ 30ML/MIN

Benefit: With and without Dm in any age

Beyond of MRA and ARNI

Same baseline Tx

No difference in AE

- DKA and amputation
- More kidney AEs in the placebo group

Less new onset Dm (p=0.019)

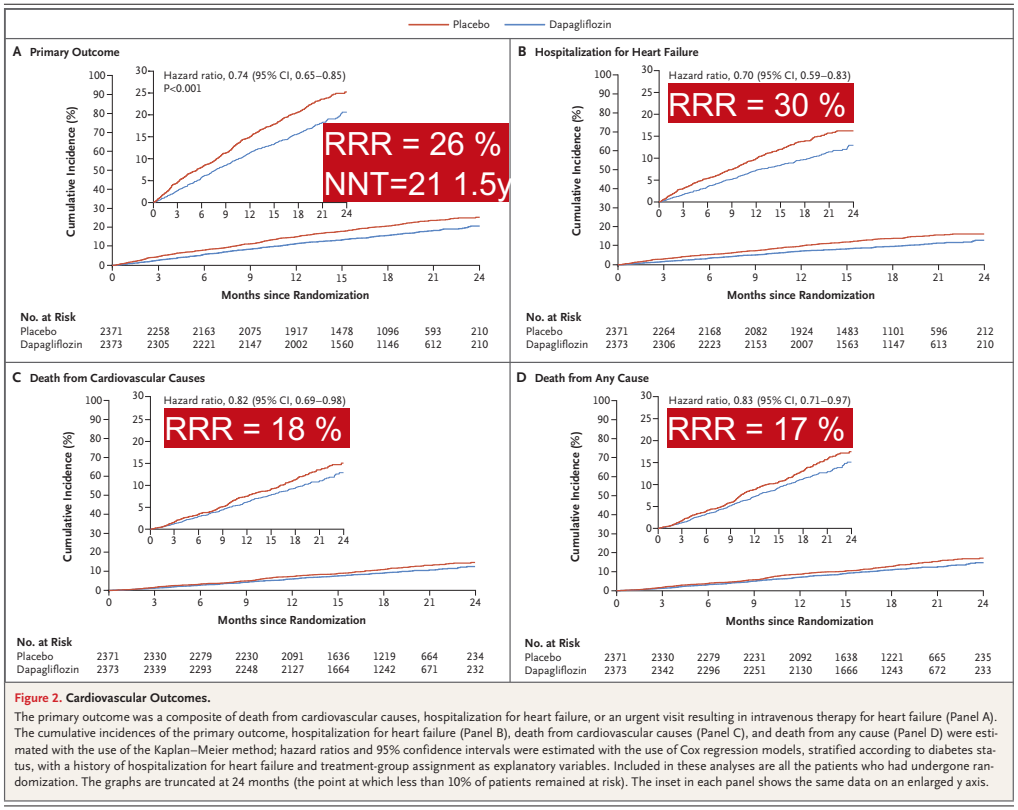


Figure 2. Cardiovascular Outcomes.

The primary outcome was a composite of death from cardiovascular causes, hospitalization for heart failure, or an urgent visit resulting in intravenous therapy for heart failure (Panel A). The cumulative incidences of the primary outcome, hospitalization for heart failure (Panel B), death from cardiovascular causes (Panel C), and death from any cause (Panel D) were estimated with the use of the Kaplan–Meier method; hazard ratios and 95% confidence intervals were estimated with the use of Cox regression models, stratified according to diabetes status, with a history of hospitalization for heart failure and treatment-group assignment as explanatory variables. Included in these analyses are all the patients who had undergone randomization. The graphs are truncated at 24 months (the point at which less than 10% of patients remained at risk). The inset in each panel shows the same data on an enlarged y axis.

(US 25‘594 less death in US [JAMA Cardiol. 2020])

DOI: 10.1056/NEJMoa1911303; Inzucchi Diabetes Care 2021 Feb;44(2); Docherty Eur Heart J. 2020 Jul 1; 41(25)

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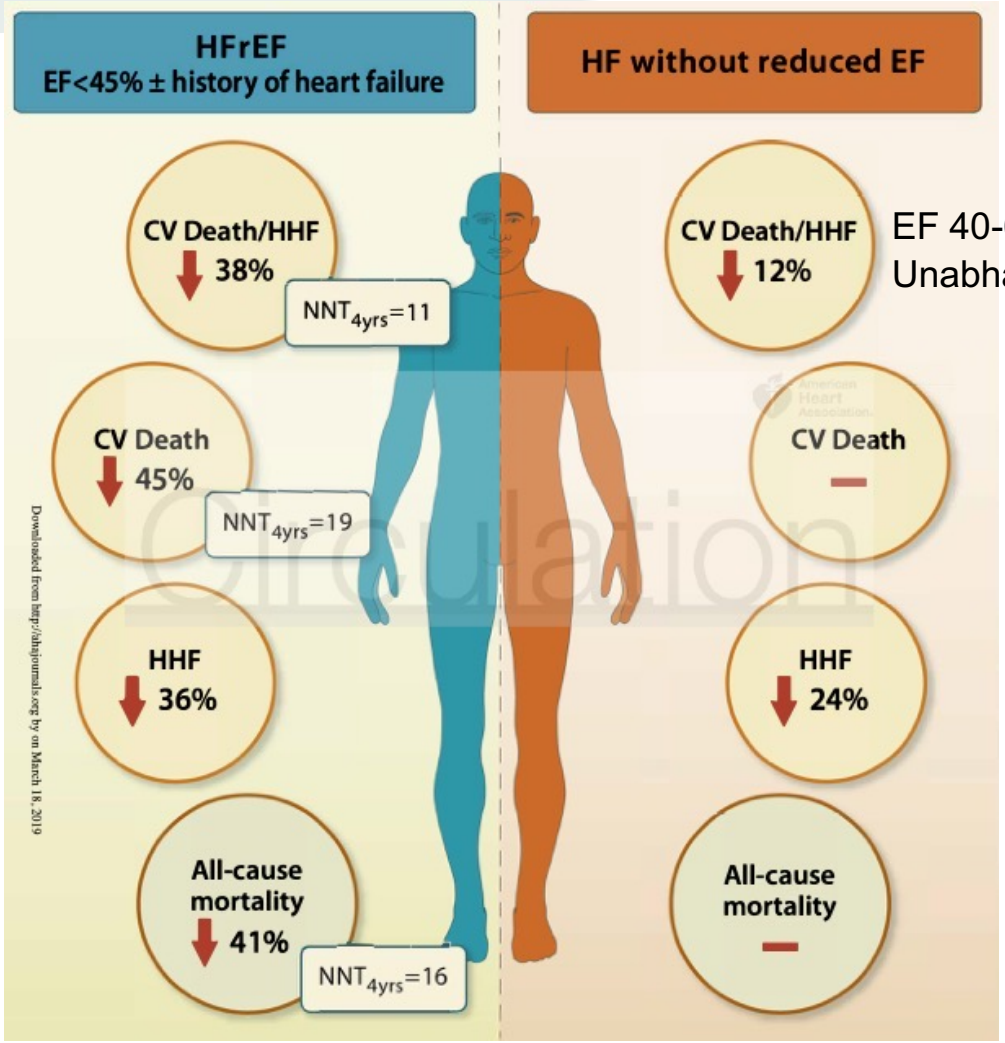
DAPA-HF BASED ON EJECTION FRACTION



EF 40-60%
Unabhängig vom Dm

10.1161/CIRCULATIONAHA.119.040514

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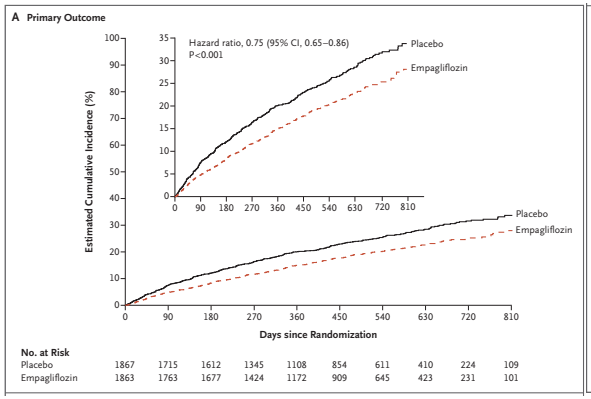
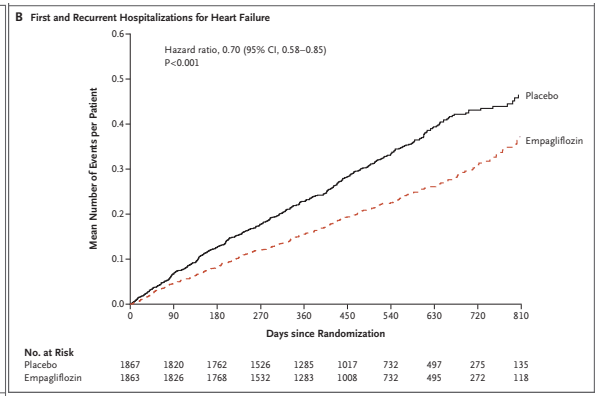
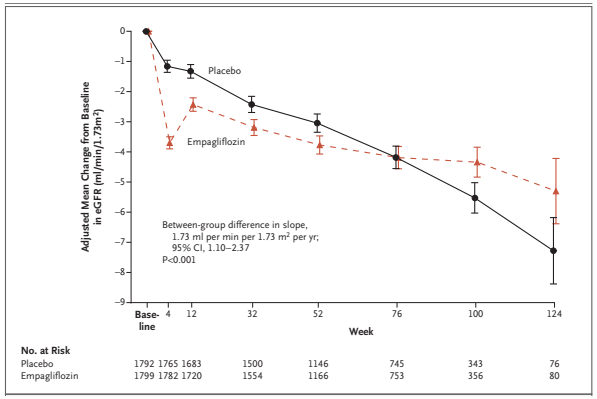
CARDIOVASCULAR AND RENAL OUTCOMES WITH EMPAGLIFLOZIN IN HEART FAILURE (EMPEROR-REDUCED)

Primary endpoint: Composite CV death or HHF
First secondary endpoint: HHF
Second secondary endpoint: slope of decline in GFR







25 % reduction, p=<0.001

30 % reduction, p=<0.001

p=<0.001, delta 3.1 ml/min

Day 12 first statistical signifiance, up day 34 sustained

Equally SAE, benefit in all subgroups

N Engl J Med 2020;383:1413-24.

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EMPAGLIFLOZIN IN HEART FAILURE WITH A PRESERVED EJECTION FRACTION

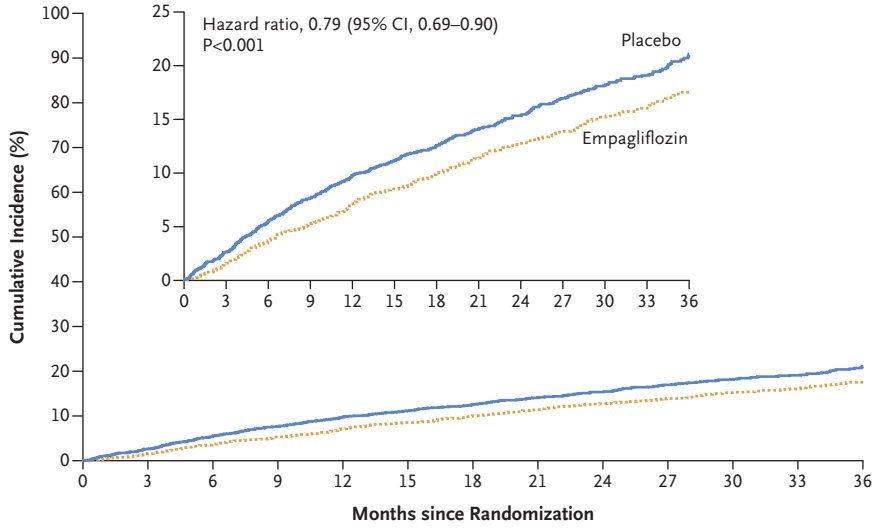

Figure 1. Primary Outcome, a Composite of Cardiovascular Death or Hospitalization for Heart Failure.

The estimated cumulative incidence of the primary outcome in the two groups is shown. The inset shows the same data on an expanded y axis.

DOI: 10.1056/NEJMoa2107038

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EMPAGLIFLOZIN IN HEART FAILURE WITH A PRESERVED EJECTION FRACTION

Table 2. Primary and Secondary Cardiovascular Outcomes.*

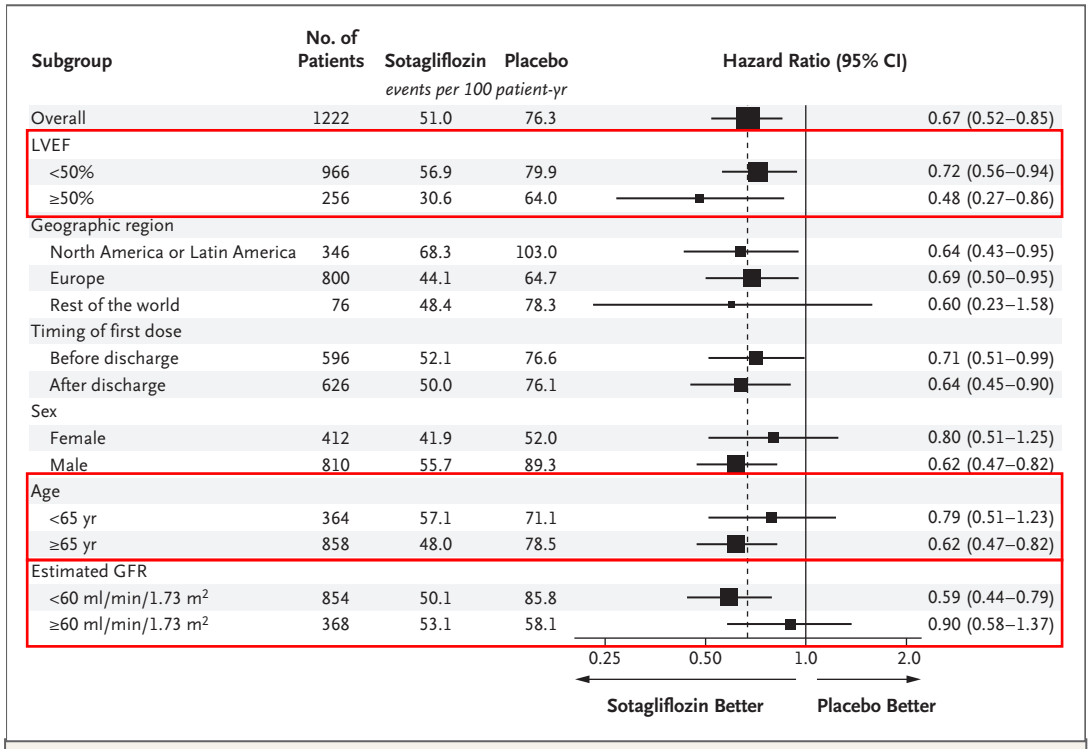
Variable	Empagliflozin (N=2997)		Placebo (N=2991)		Hazard Ratio or Difference (95% CI)	P Value
		events per 100 patient-yr		*events per 100 patient-yr*		
Primary composite outcome — no. (%)	415 (13.8)	6.9	511 (17.1)	8.7	0.79 (0.69–0.90) s: NNT: 31	<0.001
Hospitalization for heart failure	259 (8.6)	4.3	352 (11.8)	6.0	0.71 (0.60–0.83) s: NNT: 32	
Cardiovascular death	219 (7.3)	3.4	244 (8.2)	3.8	0.91 (0.76–1.09) ns: NNT: 118	
Secondary outcomes specified in hierarchical testing procedure						
Total no. of hospitalizations for heart failure	407	—	541	—	0.73 (0.61–0.88)	<0.001
eGFR (CKD-EPI) mean slope change per year — ml/min/1.73 m^2†	−1.25±0.11	—	−2.62±0.11	—	1.36 (1.06–1.66)	<0.001
Other prespecified analyses						
Change in KCCQ clinical summary score at 52 wk‡	4.51±0.31	—	3.18±0.31	—	1.32 (0.45–2.19)	
Total no. of hospitalizations for any cause	2566	—	2769	—	0.93 (0.85–1.01)	
Composite renal outcome — no. (%)	108 (3.6)	2.1	112 (3.7)	2.2	0.95 (0.73–1.24) ns	
Onset of new diabetes in patients with prediabetes — no. (%)	120 (12.0)	6.1	137 (14.0)	7.4	0.84 (0.65–1.07) ns	
Death from any cause — no. (%)	422 (14.1)	6.6	427 (14.3)	6.7	1.00 (0.87–1.15) ns	

EMPAGLIFLOZIN IN HEART FAILURE WITH A PRESERVED EJECTION FRACTION

- For the primary outcome, the benefit was similar among patients with or without type 2 diabetes. The benefit appeared somewhat attenuated among patients with EF ≥60%.
- Pooled analysis of EMPEROR-Reduced and EMPEROR-Preserved on renal outcomes: profound and sustained decreases in eGFR or renal replacement therapy), total n = 9,718: 2.8% vs. 3.5% for empagliflozin vs. placebo, with significant heterogeneity between both trials (p = 0.016 for interaction).

SGLT-2-I IN HF TRIALS: SOLOIST

SOTAGLIFOLZIN



Subgroup	No. of Patients	Sotagliflozin	Placebo	Hazard Ratio (95% CI)
		events per 100 patient-yr		
Overall	1222	51.0	76.3	0.67 (0.52–0.85)
LVEF				
<50%	966	56.9	79.9	0.72 (0.56–0.94)
≥50%	256	30.6	64.0	0.48 (0.27–0.86)
Geographic region				
North America or Latin America	346	68.3	103.0	0.64 (0.43–0.95)
Europe	800	44.1	64.7	0.69 (0.50–0.95)
Rest of the world	76	48.4	78.3	0.60 (0.23–1.58)
Timing of first dose				
Before discharge	596	52.1	76.6	0.71 (0.51–0.99)
After discharge	626	50.0	76.1	0.64 (0.45–0.90)
Sex				
Female	412	41.9	52.0	0.80 (0.51–1.25)
Male	810	55.7	89.3	0.62 (0.47–0.82)
Age				
<65 yr	364	57.1	71.1	0.79 (0.51–1.23)
≥65 yr	858	48.0	78.5	0.62 (0.47–0.82)
Estimated GFR				
<60 ml/min/1.73 m^2	854	50.1	85.8	0.59 (0.44–0.79)
≥60 ml/min/1.73 m^2	368	53.1	58.1	0.90 (0.58–1.37)

Benefit > 50%, ns

DOI: 10.1056/NEJMoa2030183

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SGLT-2 INHIBITOR IN CARDIOVASCULAR OUTCOME TRIALS IN TYPE 2 DM

	MACE	CV DEATH	HHF
	HR (95% CI)	HR (95% CI)	HR (95% CI)
EMPA-REG OUTCOME	0.86 (0.74, 0.99) P=0.04	0.62 (0.49,0.77) P<0.001	0.65 (0.50,0.85) P<0.001
CANVAS Program	0.86 (0.75, 0.97) P<0.02	0.87 (0.72, 1.06) P=0.04	0.67 (0.52, 0.87) P<0.001
DECLARE-TIMI 58	0.93 (0.84, 1.03) P=0.17	0.98 (0.82, 1.17) NS	0.73 (0.61, 0.88) P<0.005
VERTIS CV	0.97 (0.85, 1.11) P<0.001 f. Non-inferiority	0.82 (0.77, 1.11) P=0.39	0.70 (0.54, 0.90) P=0.006
SOLOIST	0.67 (0.52, 0.85) P<0.001	0.84 (0.58, 1.22) 0.36	0.64 (0.49, 0.83) P<0.001

NEJM 2015, 2017, 2018, ADA

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SGLT-2 INHIBITOR: RENAL OUTCOME IN TYPE 2 DM

	Renal-related composite outcomes	HR (95% CI)
EMPA-REG OUTCOME	Doubling of serum creatinine, initiation of renal-replacement tx or death from renal disease	0.54 (0.40, 0.75)
CANVAS Program	Sustained 40 % reduction in eGFR, renal-replacement tx (dialysis or transplantation) or death from renal causes	0.6 (0.47, 0.77)
DECLARE-TIMI 58	Sustained ≥ 40 % decrease in eGFR to < 60 ml/min/1.73m2 and/or end-stage renal disease and/or renal or CV death	0.53 (0.43, 0.66)
VERTIS CV	Renal death, dialysis/transplant or doubling of serum creatinine	0.81 (0.64, 1.03) P=0.08
DAPA-CKD	Composite outcome of sustained ≥ 50% eGFR decline, eSKD, renal or cv death	0.61 (0.51, 0.72) For any cause

NNT=19

KIDNEY CREDENCE (CANAGLIFLOZIN)

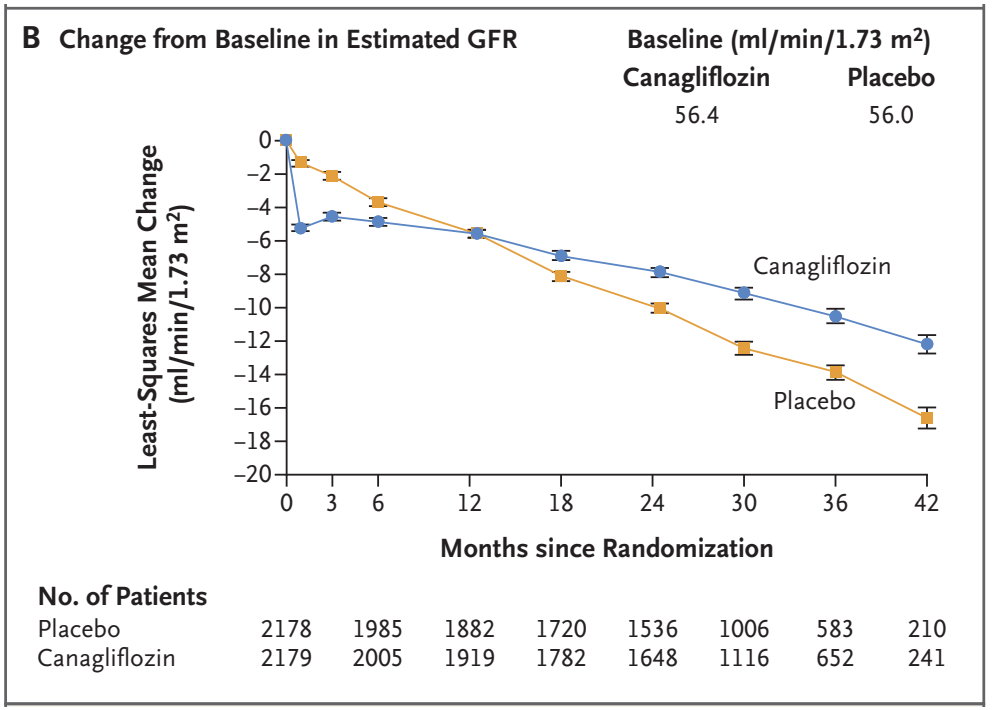
CV death or HHF: HR 0.69 (0.57,0.83) p< 0.001
- CV death: HR 0.78 (0.61,1.00) p=0.05
- HHF: HR 0.61 (0.47,0.80) p< 0.001

NNT for renal and CV outcome over 2.5 years

- Primary composite outcome: NNT=22
- ESKD: NNT=43
- ESKD, doubling of serum creatinine or kidney disease death: NNT=28
- HHF: NNt=46
- CV death, MI, stroke: NNT=40

- Older patients without HF have a decrease of eGFR > 10%

Reduction of hyperfiltration



PERKOVIC, NEJM 2019

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KIDNEY POOLED

SGLT2 INHIBITORS FOR THE PREVENTION OF KIDNEY FAILURE IN PATIENTS WITH TYPE 2 DIABETES: A SYSTEMATIC REVIEW AND META-ANALYSIS

DECLARE-TIMI 58, CANVAS-P, CREDENCE, EMPA-REG OUTCOME

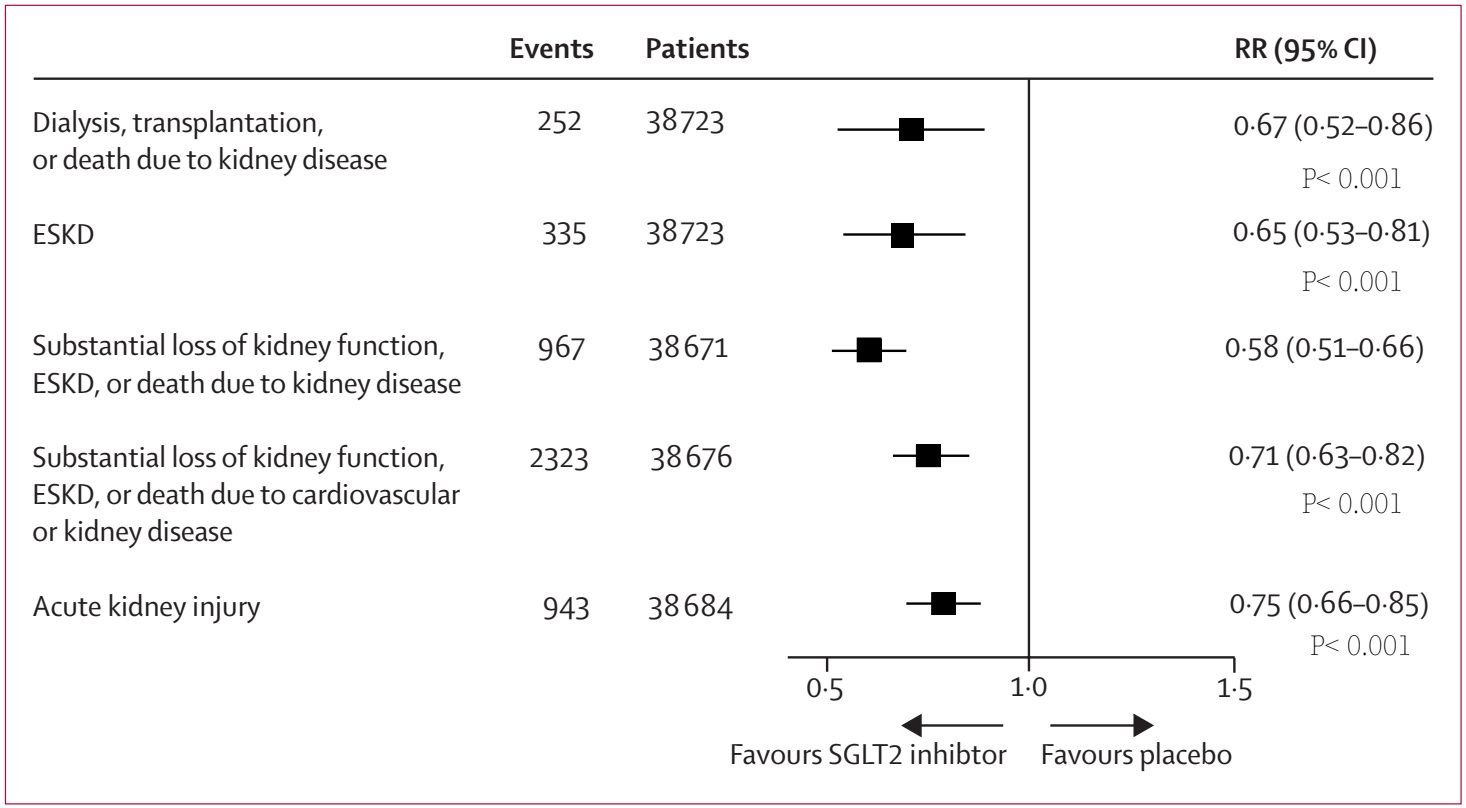

Figure 4: **Summary of the effects of SGLT2 inhibition on major kidney outcomes**
ESKD=end-stage kidney disease. SGLT2=sodium-glucose co-transporter-2. RR=relative risk.

NEUEN ET AL LANCET DIABETES ENDOCRINOLOGY 2019

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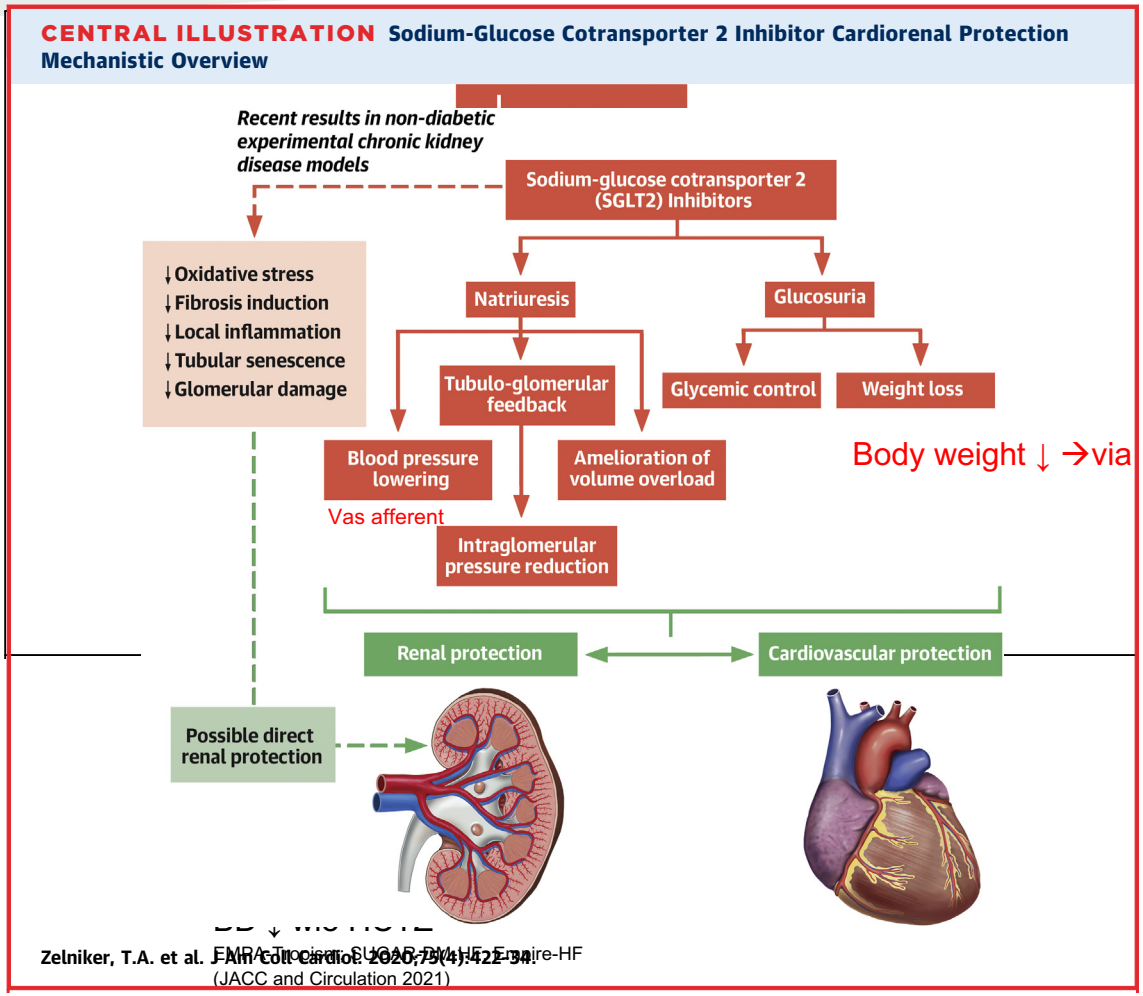
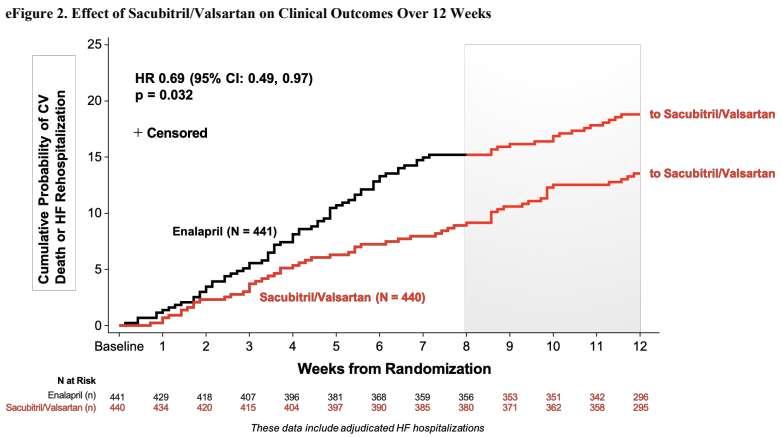
CARDIORENAL PROTECTION IN SGLT-2-I

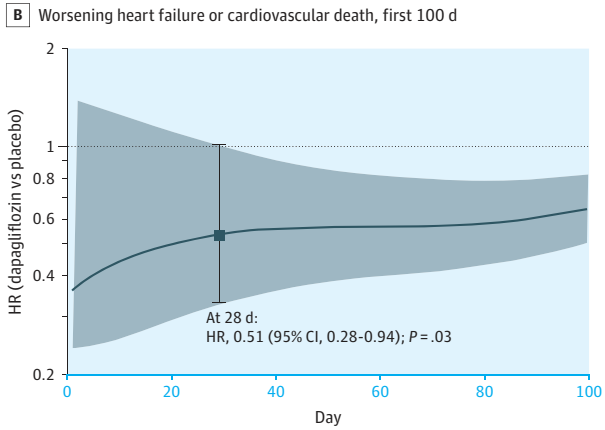


Body weight ↓ →via NAFLD ↓ → CV death ↓

Kidney International (2018) 94, 26–39

SAVED LIVES





Trial	RR	2-Year Mortality in HFrEF
None		35 %
ARNI	↓ 28%	25%
+ Betablocker	↓ 35%	16%
+ MRA	↓ 30%	11.5%
+ SGLT-2-i	↓ 17%	9.5 %

JAMA Cardiol. doi:10.1001/jamacardio.2019.4665

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SUMMERY
SGLT-2 INHIBITOR IN CARDIOVASCULAR OUTCOME TRIALS IN TYPE 2 DM

- Reduce risk of major adverse CVD events
  - Decrease macroalbuminuria, slower decline in eGFR and ESKD
- CVD and CKD benefits in patients with pre-existing CV and CKD
- EMPA-RESPONSE-AHF: save in AHF! (European Journal of Heart Failure (2020) 22, 713–722)
- DKA with SGLT-2-i
  - DARE-19: 0.3%
  - Diabetic CVOT: < 0.1-0.3%
  - DAPA-HF: 0.1%
  - EMPEROR-reduced: 0%
  - SOLOIST-WHF: 0.3% vs 0.7 placebo

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GLP1-RA

	Trail	Endpoint	HR (95% CI)	Trail population	P-value (superiority)
GLP-1-RA	LEADER	3-POINT-MACE	0.87 (0.78; 0.97)	9‘340	0.01
	SUSTAIN 6	3-POINT-MACE	0.74 (0.58; 0.95)	3‘297	0.02
	PIONEER 6	3-POINT-MACE	0.79 (0.57; 1.11)	3‘183	0.17
	HARMONY	3-POINT-MACE	0.78 (0.68; 0.90)	9‘463	0.0006
	REWIND	3-POINT-MACE	0.88 (0.79; 0.99)	9‘901	0.026
SGLT-2-In	EMPA-REG-OUTCOME	3-POINT-MACE	0.86 (0.74; 0.99)	7‘020	0.04
	CANVAS	3-POINT-MACE	0.86 (0.75; 0.97)	10‘142	0.001
	DECLARE-TIMI-58	3-POINT-MACE	0.93 (0.84; 1.03)	17‘160	0.17
	SCORED	3-POINT-MACE	0.74 (0.63; 0.88)	10‘584	<0.001

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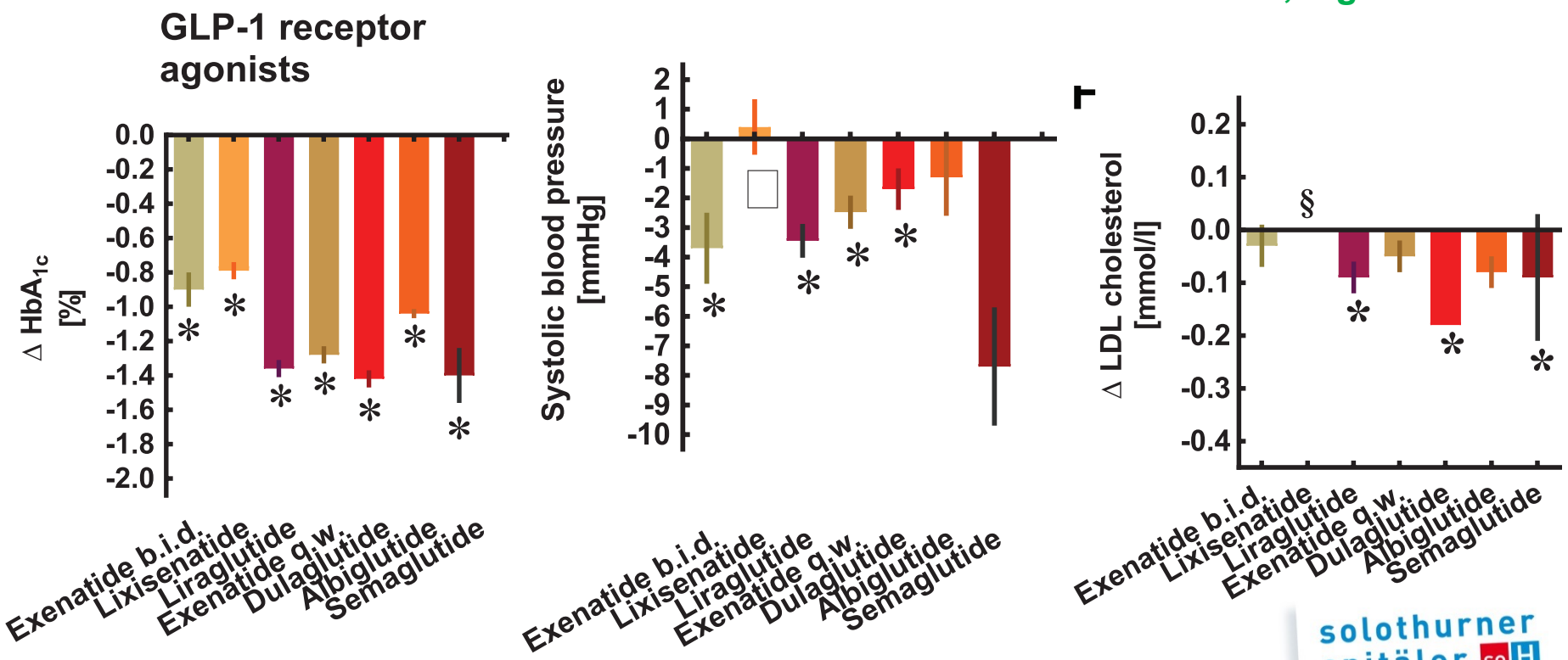
GLP1-RA
HBA1C, SBP, LDL

HbA1c: 0.8-1.4 % lower
Weight: 3-4 kg less
SBP: 3-6 mmHg
Lower LDL, higher HDL



Circulation. 2017;136:849–870

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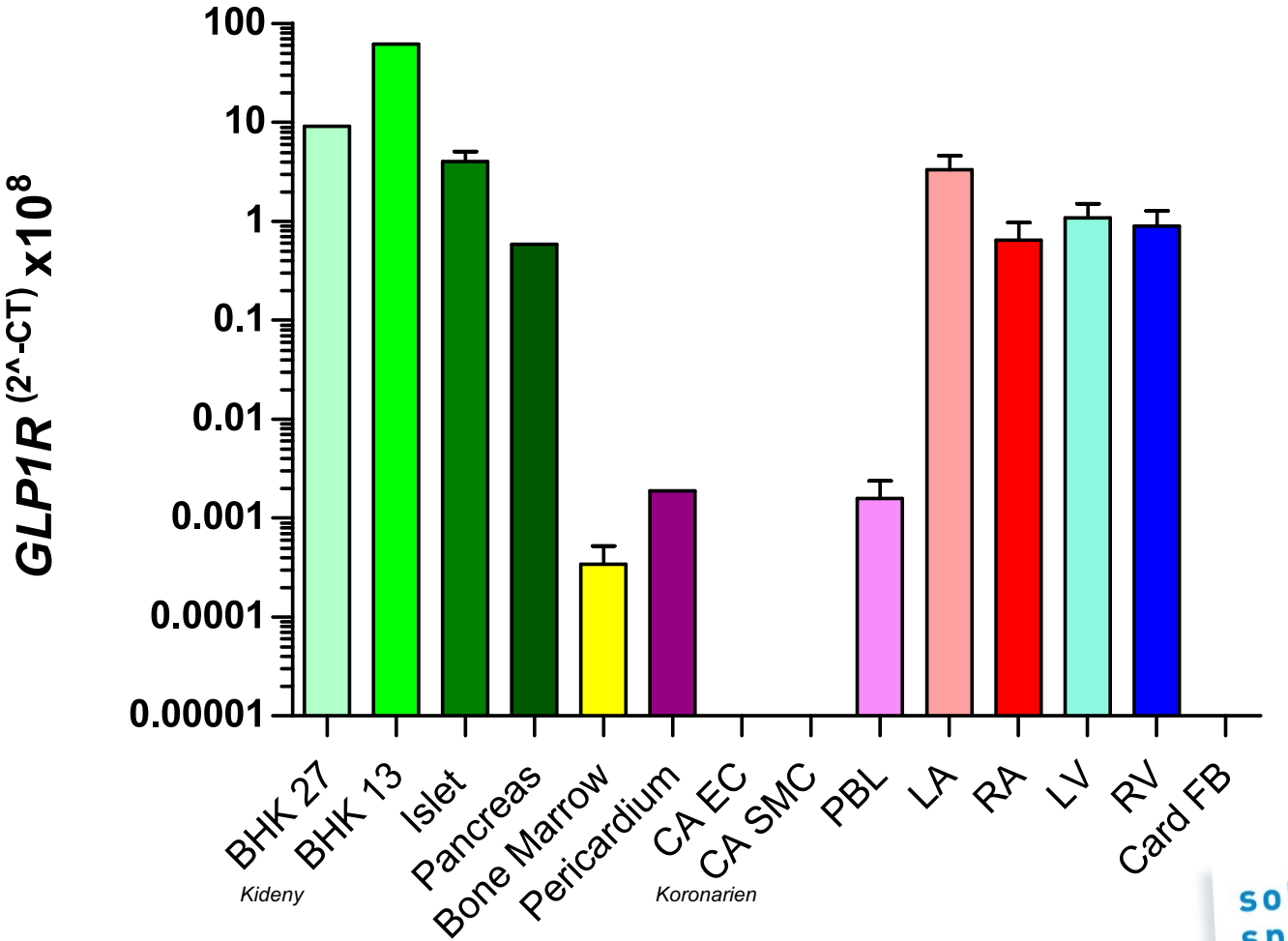
HUMAN CARDIAC GLP-1 RECEPTOR EXPRESSION



Endocrinology, April 2018, 159(4):1570–1584

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THE CARDIOVASCULAR BIOLOGY OF GLUCAGON-LIKE PEPTIDE-1

HTTPS://DOI.ORG/10.1016/J.AHJ.2020.07.008
http://dx.doi.org/10.1016/j.cmet.2016.06.009

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GLP-1-RA AND ATHEROSCLEROSIS

- GLP-1 RA reduce atherosclerosis in animal models
- Reduce inflammation
- GLP-1 cleavage peptides have metabloc and cardioprodective effects
  - GLP-9-36 on the liver (reduced Gluconeogenesis and steatosis)
  - GLP-9-36 and GLP-28-36 on the heart (post MI Remodeling)
- Exenatide reduce infarct size in STEMI (benefit 6 months: higher LVEF)
- Improves biomarker of CV risk as: PAI-1, HOMA-IR, CRP, Triglycerides and UACR (JAMA. 2015;314(7):687-699)
- Reduction of BP, decreased post-prandial TG, VLDL and CM Remnants
- Better endothelial function

Tomas et al. Regul Pept. 2011
Ban K. et al. Circulation 2008
Siraj et al. J Clin Invets 2020
Lønborg J Eur Heart j. 2012
Clin Lipidol. 2015
Drucker DK Cell Metabolism 2016

REWIND (DULAGLUTIDE) BASELINE CHARACTERISTICS

	All N=9901	Dulaglutide N=4949	Placebo N=4952
Age (y)	**66.2**	66.2	66.2
Females (%)	**46.3**	46.6	46.1
White (%)	**75.7**	75.9	75.6
Current tabacco	**14.2**	14.0	14.4
Prior CV disease (%)	**31.5**	31.5	31.4
Prior MI or ischemic stroke (%)	**20.6**	20.8	20.3
Prior stroke or TIA	**9.1**	9.0	9.2
Prior AF	**6.4**	6.6	6.2
Prior hypertension (%)	**93.2**	93.0	93.3
Prior HF (%)	**8.6**	8.5	8.7

Follow up time, retention, Adherence

Median follow-up period: 5.4 y

Person years of follow-up: 51‘820

Retention: 97.1%

Vital status: 99.7%

Adherence (F/U time on drug): 82 % dulaglutide; 83 % placebo

Stopped due to adverse event: 11% dulaglutide; 7.5 % placebo

Gerstein et la. Lancet 2019

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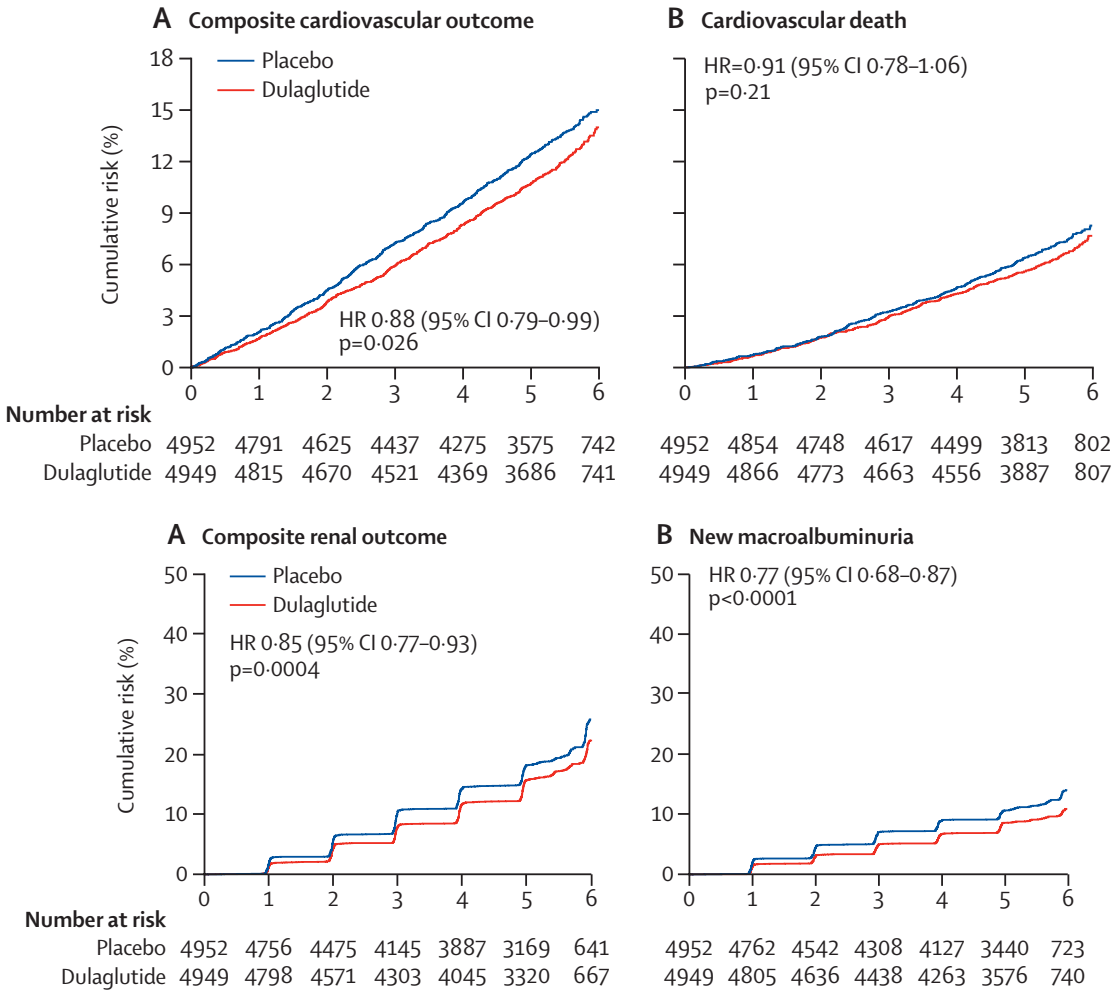
REWIND (DULAGLUTIDE)
OUTCOME



Gerstein et la. Lancet 2019

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REWIND OUTCOME AND KIDNEY
DULAGLUTIDE

	Dulaglutide (n=4949)		Placebo (n=4952)		Hazard ratio (95% CI)	p value
	Number of patients (%)	Incidence rate (number of events per 100 person-years)	Number of patients (%)	Incidence rate (number of events per 100 person-years)		
Main analyses of renal effect						
Composite renal outcome	848 (17·1%)	3·47	970 (19·6%)	4·07	0·85 (0·77–0·93)	0·0004
Components of composite renal outcome						
New macroalbuminuria	441 (8·9%)	1·76	561 (11·3%)	2·29	0·77 (0·68–0·87)	<0·0001
Sustained decline in eGFR of ≥30%	453 (9·2%)	1·79	500 (10·1%)	2·00	0·89 (0·78–1·01)	0·066
Chronic renal replacement therapy	16 (0·3%)	0·06	21 (0·4%)	0·08	0·75 (0·39–1·44)	0·39
Serious renal adverse event*	84 (1·7%)	0·32	93 (1·9%)	0·36	0·90 (0·67–1·20)	0·46
Sensitivity analyses of renal effect						
Sustained decline in eGFR of ≥40%	169 (3·4%)	0·66	237 (4·8%)	0·93	0·70 (0·57–0·85)	0·0004
Composite renal outcome with this decline	587 (11·9%)	2·36	751 (15·2%)	3·10	0·76 (0·68–0·84)	<0·0001
Sustained decline in eGFR of ≥50%	61 (1·2%)	0·24	108 (2·2%)	0·42	0·56 (0·41–0·76)	0·0002
Composite renal outcome with this decline	496 (10·0%)	1·99	649 (13·1%)	2·66	0·74 (0·66–0·84)	<0·0001

eGFR=estimated glomerular filtration rate. *Based on a search of the REWIND database for any reported adverse event linked to acute renal failure.

Table 2: **Effect of treatment allocation on renal outcomes**

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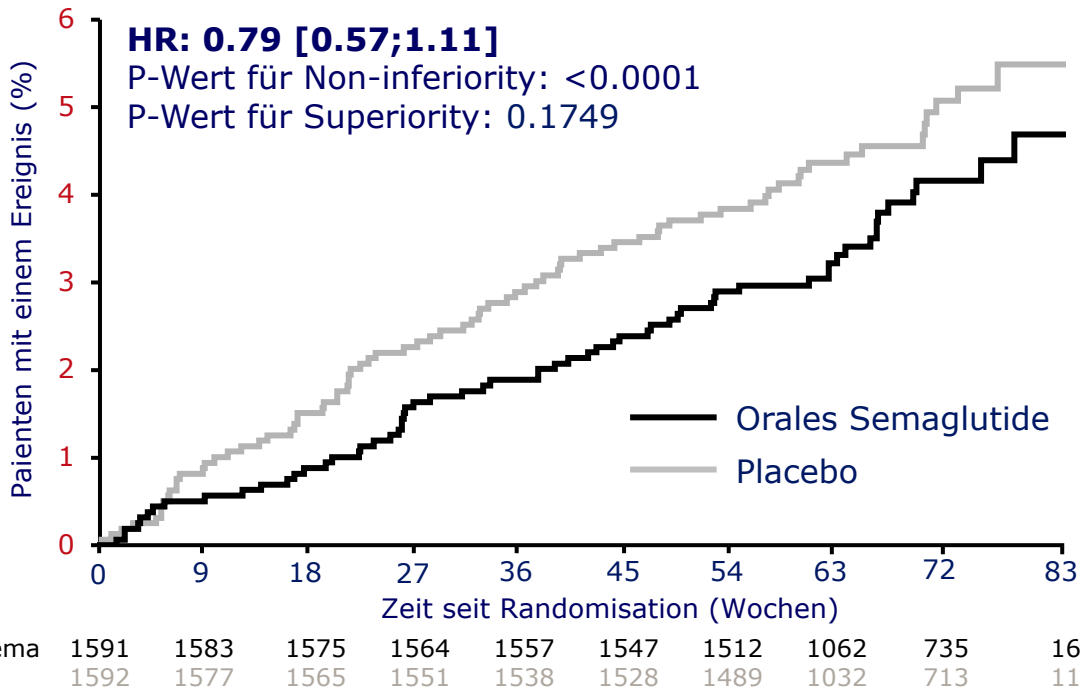
PIONEER 6: FIRST MACE – PRIMARY ENDPOINT

SEMAGLUTIDE ORAL

Composite primary Outcome



76 Ereignisse
Rate: 3.7 Ereignisse pro 100 Patienten–Jahre

61 Ereignisse
Rate: 2.9 Ereignisse pro 100 Patienten–Jahre

Alle Ereignisse von EAC bestätigt. CV, kardiovaskulär; EAC, Event Adjudication Committee; HR, Hazard Ratio; MACE, schwerwiegendes unerwünschtes kardiovaskuläres Ereignis; MI, Herzinfarkt.

Husein et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2019;381(9):841-51.

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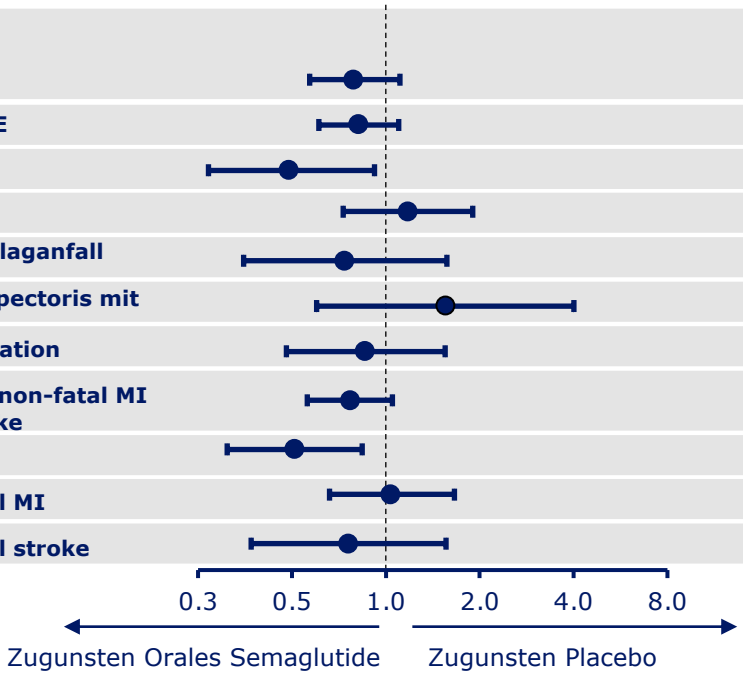
PIONEER 6: FIRST EVENT

SEMAGLUTIDE
SECONDARY ENDPOINTS



	Hazard Ratio (95% CI)	Orales Sema		Placebo	
		N	E	N	E
Primäre Analyse					
MACE	0.79 [0.57; 1.11]	1591	61	1592	76
Erweiterter MACE	0.82 [0.61; 1.10]	1591	83	1592	100
CV Tod	0.49 [0.27; 0.92]*	1591	15	1592	30
Nicht-fataler MI	1.18 [0.73; 1.90]	1591	37	1592	31
Nicht-fataler Schlaganfall	0.74 [0.35; 1.57]	1591	12	1592	16
Instable Angina pectoris mit Hospitalisation	1.56 [0.60: 4.01]	1591	11	1592	7
HI mit Hospitalisation	0.86 [0.48; 1.55]	1591	21	1592	24
All-cause death/non-fatal MI or non-fatal stroke	0.77 [0.56; 1.05]	1591	69	1592	89
All-cause death	0.51 [0.31; 0.84]*	1591	23	1592	45
Fatal or non-fatal MI	1.04 [0.66; 1.66]	1591	37	1592	35
Fatal or non-fatal stroke	0.76 [0.37; 1.56]	1591	13	1592	17

All events confirmed by EAC. Hazard ratio with 95% confidence intervals, Cox proportional hazards model with treatment as factor, 'p-value': unadjusted two-sided p-value for test of no difference from 1.
CI, confidence interval; EAC, event adjudication committee; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.
Husein et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2019;381(9):841-51.

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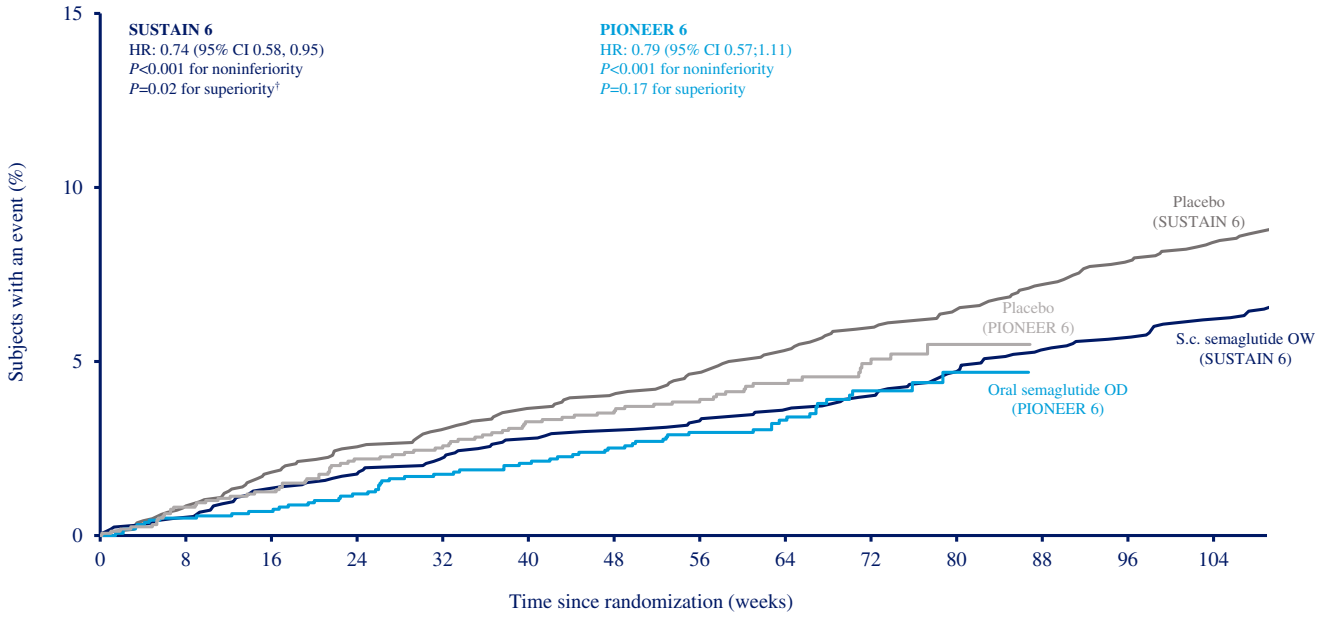
SUSTAIN 6 AND PIONEER 6
S/C VS ORAL SEMAGLUTIDE

significant benefit for pat without HF!



Number of subjects at risk

Week	0	16	32	48	64	80	96
S.c. semaglutide OW	1,648	1,619	1,601	1,584	1,568	1,543	1,524
Placebo	1,649	1,616	1,586	1,567	1,534	1,508	1,479

Week	0	9	18	27	36	45	54	63	72	83
Oral semaglutide OD	1,591	1,583	1,575	1,564	1,557	1,547	1,512	1,062	735	16
Placebo	1,592	1,577	1,565	1,551	1,538	1,528	1,489	1,032	713	11

DOI: 10.1111/dom.13955

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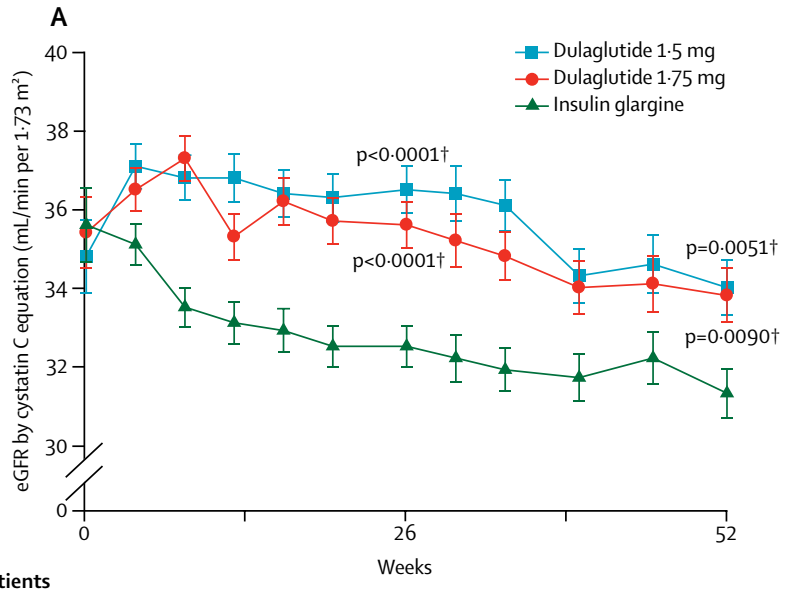
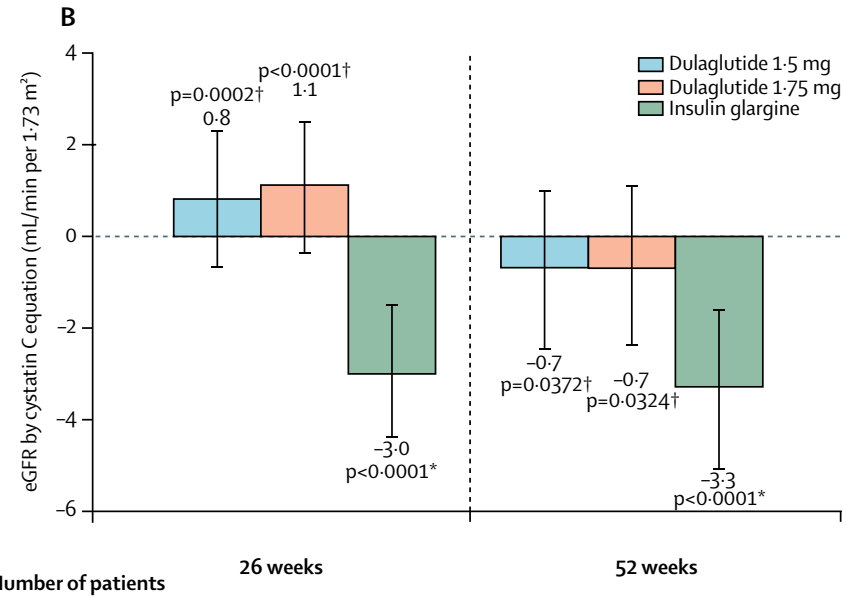
AWARD-7 OUTCOME AND KIDNEY

DULAGLUTIDE



Number of patients			
Dulaglutide 1·5 mg	192	163	157
Dulaglutide 0·75 mg	190	167	160
Insulin glargine	194	174	164



Number of patients	26 weeks			52 weeks		
Endpoint	163	167	174	157	160	164
Baseline	192	190	194	192	190	194

- * versus baseline
- † versus glargine

http://dx.doi.org/10.1016/S2213-8587(18)30104-9

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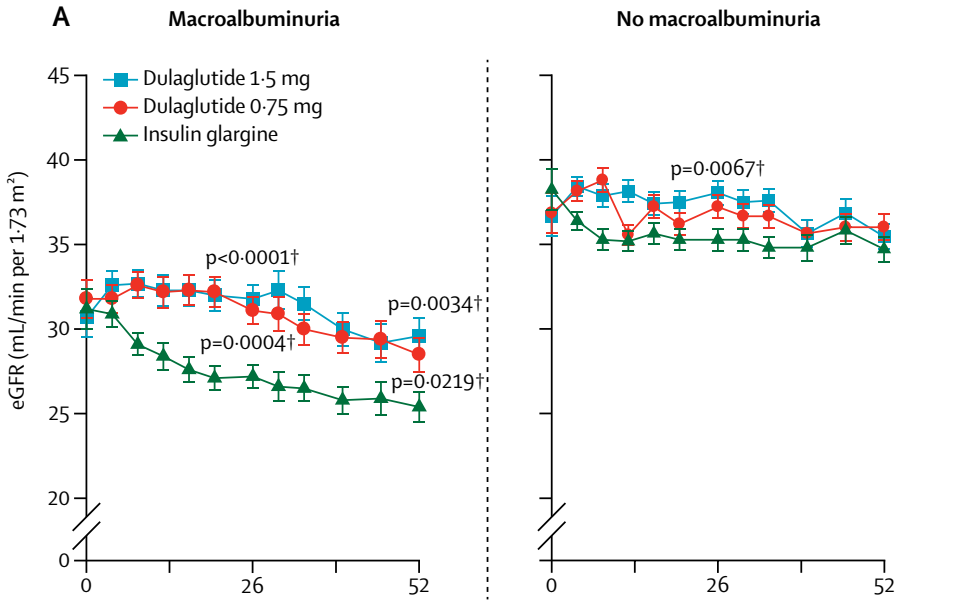
AWARD-7 OUTCOME AND KIDNEY

DULAGLUTIDE



Number of patients						N
Dulaglutide 1·5 mg	84	70	64	108	93	93
Dulaglutide 0·75mg	84	71	67	106	96	93
Insulin glargine	90	77	69	104	97	95

C Macroalbuminuria No macroalbuminuria

http://dx.doi.org/10.1016/S2213-8587(18)30104-9

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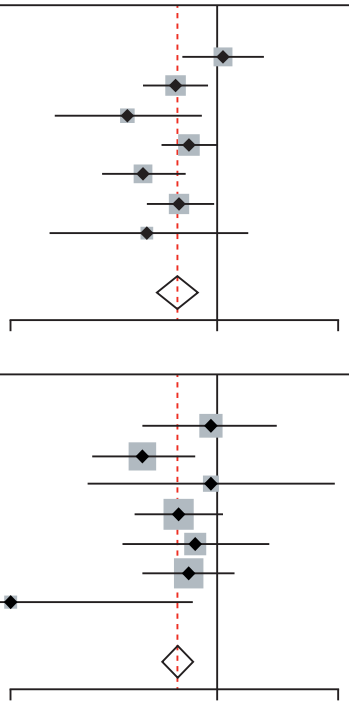
CARDIOVASCULAR, MORTALITY, AND KIDNEY OUTCOMES WITH GLP-1 RECEPTOR AGONISTS IN PATIENTS WITH TYPE 2 DIABETES

	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
Three-component MACE					
ELIXA	400/3034 (13%)	392/3034 (13%)	1·02 (0·89–1·17)		0·78
LEADER	608/4668 (13%)	694/4672 (15%)	0·87 (0·78–0·97)		0·015
SUSTAIN-6	108/1648 (7%)	146/1649 (9%)	0·74 (0·58–0·95)		0·016
EXSCEL	839/7356 (11%)	905/7396 (12%)	0·91 (0·83–1·00)		0·061
Harmony Outcomes	338/4731 (7%)	428/4732 (9%)	0·78 (0·68–0·90)		<0·0001
REWIND	594/4949 (12%)	663/4952 (13%)	0·88 (0·79–0·99)		0·026
PIONEER 6	61/1591 (4%)	76/1592 (5%)	0·79 (0·57–1·11)		0·17
Overall (I^2=40·9%, p=0·118)	**2948/27977 (11%)**	**3304/28027 (12%)**	**0·88 (0·82–0·94)**	**75 (50–151)**	**<0·0001**
Cardiovascular death					
ELIXA	156/3034 (5%)	158/3034 (5%)	0·98 (0·78–1·22)		0·85
LEADER	219/4668 (5%)	278/4672 (6%)	0·78 (0·66–0·93)		0·007
SUSTAIN-6	44/1648 (3%)	46/1649 (3%)	0·98 (0·65–1·48)		0·92
EXSCEL	340/7356 (5%)	383/7396 (5%)	0·88 (0·76–1·02)		0·096
Harmony Outcomes	122/4731 (3%)	130/4732 (3%)	0·93 (0·73–1·19)		0·58
REWIND	317/4949 (6%)	346/4952 (7%)	0·91 (0·78–1·06)		0·18
PIONEER 6	15/1591 (1%)	30/1592 (2%)	0·49 (0·27–0·92)		0·021
Overall (I^2=13·5%, p=0·327)	**1277/27977 (5%)**	**1471/28027 (5%)**	**0·88 (0·81–0·96)**	**163 (103–489)**	**0·003**



http://dx.doi.org/10.1016/S2213-8587(19)30249-9

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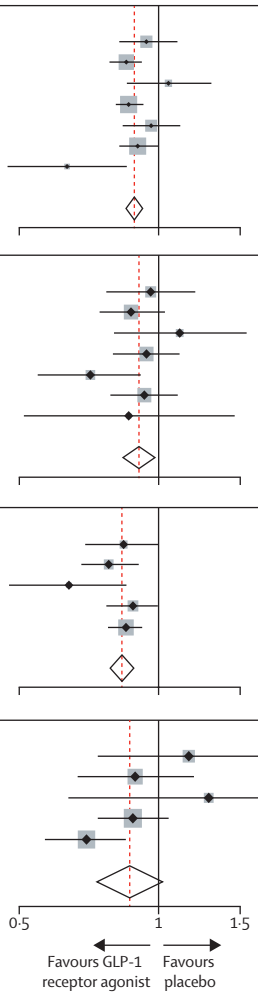
CARDIOVASCULAR, MORTALITY, AND KIDNEY OUTCOMES WITH GLP-1 RECEPTOR AGONISTS IN PATIENTS WITH TYPE 2 DIABETES

	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
All-cause mortality					
ELIXA	211/3034 (7%)	223/3034 (7%)	0·94 (0·78–1·13)		0·50
LEADER	381/4668 (8%)	447/4672 (10%)	0·85 (0·74–0·97)		0·02
SUSTAIN-6	62/1648 (4%)	60/1649 (4%)	1·05 (0·74–1·50)		0·79
EXSCEL	507/7356 (7%)	584/7396 (8%)	0·86 (0·77–0·97)		0·016*
Harmony Outcomes	196/4731 (4%)	295/4732 (4%)	0·95 (0·79–1·16)		0·64
REWIND	536/4949 (11%)	592/4952 (12%)	0·90 (0·80–1·01)		0·067
PIONEER 6	23/1591 (1%)	45/1592 (3%)	0·51 (0·31–0·84)		0·008
Overall (I^2=16·5%, p=0·304)	**1916/27977 (7%)**	**2246/28027 (8%)**	**0·88 (0·83–0·95)**	**108 (77 to 260)**	**0·001**
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)	**936/27977 (3%)**	**1016/28027 (4%)**	**0·91 (0·83–0·99)**	**312 (165 to 2810)**	**0·028**
Composite kidney outcome including macroalbuminuria					
ELIXA	172/2639 (6%)	203/2647 (6%)	0·84 (0·68–1·02)		0·083
LEADER	268/4668 (6%)	337/4672 (7%)	0·78 (0·67–0·92)		0·003
SUSTAIN-6	62/1648 (4%)	100/1649 (6%)	0·64 (0·46–0·88)		0·006
EXSCEL	366/6256 (6%)	407/6222 (7%)	0·88 (0·76–1·01)		0·065
REWIND	848/4949 (17%)	970/4952 (20%)	0·85 (0·77–0·93)		0·0004
Overall (I^2=0·0%, p=0·413)	**1716/20160 (9%)**	**2017/20142 (10%)**	**0·83 (0·78–0·89)**	**62 (48 to 96)**	**<0·0001**
Worsening of kidney function					
ELIXA	35/3032 (1%)	41/3031 (1%)	1·16 (0·74–1·83)		0·51
LEADER	87/4668 (2%)	97/4672 (2%)	0·89 (0·67–1·19)		0·43
SUSTAIN-6	18/1648 (1%)	14/1649 (1%)	1·28 (0·64–2·58)		0·48
EXSCEL	246/6456 (4%)	273/6458 (4%)	0·88 (0·74–1·05)		0·16
REWIND	169/4949 (3%)	237/4952 (5%)	0·70 (0·57–0·85)		0·0004
Overall (I^2=42·7%, p=0·137)	**555/20753 (3%)**	**662/20762 (3%)**	**0·87 (0·73–1·03)**	**245 (118 to –1064†)**	**0·098**



http://dx.doi.org/10.1016/S2213-8587(19)30249-9

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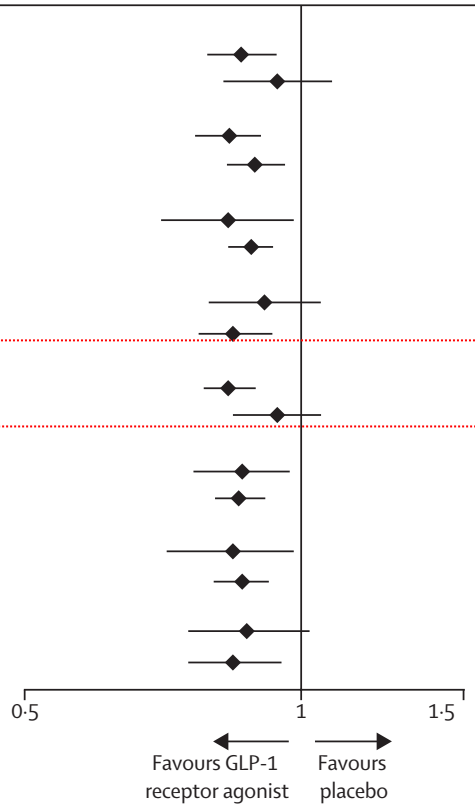
CARDIOVASCULAR, MORTALITY, AND KIDNEY OUTCOMES WITH GLP-1 RECEPTOR AGONISTS IN PATIENTS WITH TYPE 2 DIABETES

	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	$p_{interaction}$
Established cardiovascular disease				0·22
Yes	2431/21253 (11%)	2755/21202 (13%)	0·86 (0·79–0·94)	
No	480/6428 (7%)	518/6555 (8%)	0·95 (0·83–1·08)	
Baseline HbA_{1c}*				0·20
High	1645/14507 (11%)	1865/14298 (13%)	0·84 (0·78–0·91)	
Low	1300/13407 (10%)	1442/13661 (11%)	0·90 (0·84–0·97)	
Median duration of follow–up				0·53
<3 years	907/11004 (8%)	1042/11007 (9%)	0·84 (0·71–1·00)	
≥3 years	2041/16973 (12%)	2262/17020 (13%)	0·89 (0·84–0·94)	
Drug dosing				0·34
Daily	1069/9293 (12%)	1162/9298 (12%)	0·92 (0·80–1·05)	
Weekly	1879/18684 (10%)	2142/18729 (11%)	0·85 (0·78–0·93)	
Human GLP–1 homology				0·06
Yes	1709/17587 (10%)	2007/17597 (11%)	0·84 (0·79–0·90)	
No	1239/10390 (12%)	1297/10430 (12%)	0·95 (0·85–1·06)	
BMI, kg/m²				0·87
<30†	1254/11752 (11%)	1403/11904 (12%)	0·87 (0·77–0·98)	
≥30†	1679/16116 (10%)	1892/16011 (12%)	0·86 (0·81–0·92)	
Age, Years				0·79
<65	1249/14195 (9%)	1346/13948 (10%)	0·85 (0·72–0·99)	
≥65	1705/13782 (12%)	1965/14079 (14%)	0·87 (0·81–0·93)	
Baseline eGFR, mL/min per m²				0·72
<60	771/5341 (14%)	865/5432 (16%)	0·88 (0·76–1·03)	
≥60	1576/17653 (9%)	1773/17598 (10%)	0·85 (0·76–0·96)	



http://dx.doi.org/10.1016/S2213-8587(19)30249-9

AMPLITUDE O TRAIL (WEEKLY OR MONTHLY!)

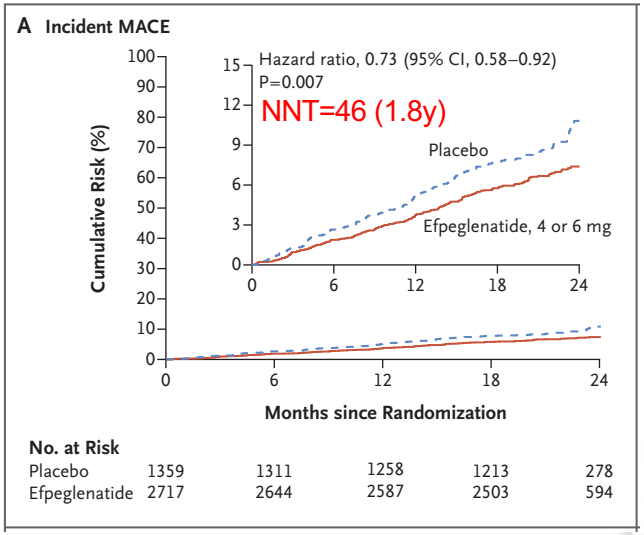
EXENDIN-4 BASED
N=4076

Dm Type 2, HbA1c > 7%

- >18 j with prior CVD
- Age ≥ 50, eGFR 25-59 ml/min & either
  - BMI ≥ 35 kg/m2
  - High LDL or low HDL on statin in prior 6 m
  - Current smoking
  - Albuminuria
  - SBP 140 or DBP >90 mmHg despite drugs
  - CAD in first degree relative

Age	64.5 years
Tobacco use	16%
Diabetes duration	15. 4 (8.8) y
Prior CVD	90 %
eGFR < 60 ml/min	32%
Prior CVD and eGFR < 60 ml/min	22%
HF	18%
Hypertension	91%
DR	33 %
Albuminuria	49%
BMI	32.7 (6.2) kg/m2

	Efpeglenatide n (%)	Placebo
Had a final visit	2715	1358
Metformin	1975 (72.7)	991 (73.0)
SUH	652 (24)	354 (26.1)
Insulin	1723 (63.5)	884 (65.1)
DPP-IV-I	24 (0.9)	26 (1.9)
SGLT-2I	475 (17.5)	288 (21.2)
ACE or ARB	2161 (79.6)	1085 (79.9)
Statin	2222 (81.8)	1098 (80.9)
Betablocker	1842 (67.9)	896 (66.0)



for all subgroups also for SGLT-2I

N Engl J Med 2021;385:896-907

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SUMMERY:
GLP-1 RA AND CVOT'S IN TYPE2 DM

- Reduce risk of major adverse CVD events
  - Atherosclerotic events
  - CVD death (liraglutide, semaglutide, [efpeglenatide])
- Decrease macroalbuminuria
- Reduce eGFR decline from early to late stage CKD
  - Lira- und Dulaglutide
- CVD and CKD benefits and safety in patients with pre-existing CKD

- GLP-1-RA CV effectiveness may be better in women (Raparelli. J Am Heart Assoc 2020; 9(1))
- Class effect

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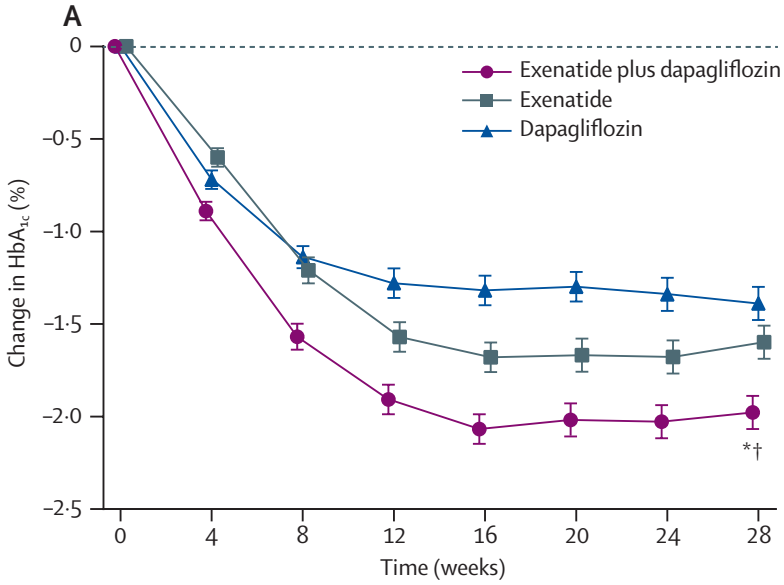
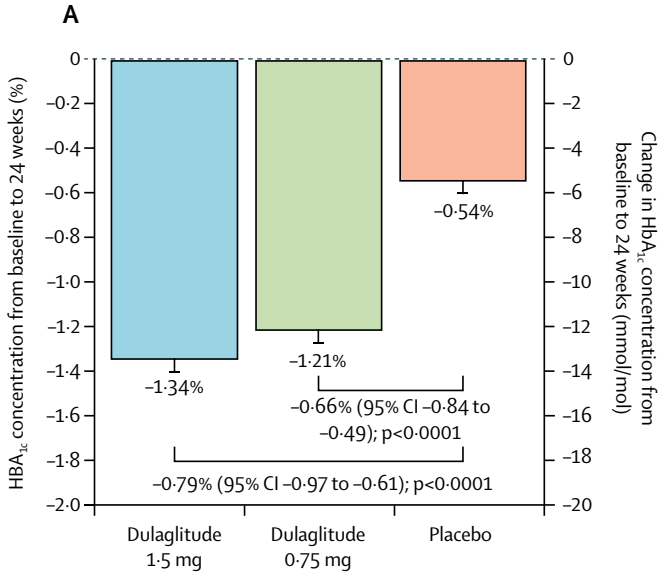
COMBINATION OF SGLT-2-I AND GLP-1 RA DURATION-8 AND AWARD-10*

DURATION 8
Exenatide and Dapagliflozin vs Placebo



AWARD-10
(Dulaglutide added to an SGLT-2-I)



- **PIONEER 4: SGLT-2i and GLP-1RA**

*Zelniker et al. Lancet 2019, Frias et al. Lancet Diabetes Endocrinol. 2016

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COMBINATION OF SGLT-2-I AND GLP-1 RA DURATION-8 AND AWARD-10*

Risk of cv outcomes in type 2 Dm following additon of SGLT-2-i vs SU to basline GLP-1 RA

	Prior to Propensity score matching		After propensity score matching	
	SGLT 2-I (N= 32‘221)	SU (N=26‘894)	SGLT 2-I (N= 12‘584)	SU (N=12‘584)
	Composite cv endpoint			
Events (IR per 1‘000 person-years)	258 (9.5)	374 (14.6)	107(9.9)	129(13.0)
Mean follow up in months	10.1	11.3	10.4	9.4
Database specific HR(95% CI)				
Optum	0.64 (0.49; 0.84)		0.76 (0.51; 1.13)	
MarketScan	0.77 (0.59; 1.01)		0.71 (0.43; 1.18)	
Medicare	0.69 (0.51; 0.93)		0.81 (0.52; 1.26)	
Pooled HR (95%CI)	**0.70 (0.60; 0.82)**		**0.76 (0.59; 0.98)**	
	HF hospitalizations			
Events (IR per 1‘000 person-years)	324 (11.9)	581 (22.9)	141 (13.0)	206 (20.8)
Mean follow up in months	10.1	11.3	10.3	9.4
Database specific HR(95% CI)				
Optum	0.58 (0.45; 0.74)		0.79 (0.56; 1.11)	
MarketScan	0.48 (0.38; 0.61)		0.51 (0.33; 0.79)	
Medicare	0.66 (0.52; 0.84)		0.61 (0.42; 0.87)	
Pooled HR (95%CI)	**0.57 (0.49; 0.65)**		**0.65 (0.52; 0.80)***	

E. Patorno, ADA Scientific Sessions 2020

*Zelniker et al. Lancet 2019, Frias et al. Lancet Diabetes Endocrinol. 2016

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EPOSTER IN SHORT

- Combination therapy of SGLT2i and GLP-1 RA confers the highest CV risk mitigation when compared to isolated therapy (50% reduction in relative risk). 987 P-2021.
- addition of a GLP-1RA to SGLT-2i treatment was associated with further reductions in HbA1c, BW and SBP without additional safety concerns. 647-P 2021
- Liraglutide might have synergistic renal protection effects with SGLT2i in rapidly progressive DKD. 402-P 2021
- Triple combination therapy with metformin - GLP1-analog - SGLT2-inhibitor has the greatest effectiveness in weight loss and in improving liver biochemistry. The renal improvement seen with these drugs appears to be driven by a decrease in UACR for SGLT-2inhibitors and an increase in eGFR for GLP1-analogues in this retrospective 24-month study 88-LB 2021
- Early vs. Late Initiation of SGLT2i and GLP-1RA for Cardiometabolic Risk Factor Control: the earlier the better (1207-P)
- Outcomes of Type 2 Diabetes (T2D) Clustering Replicated in the DEVOTE and LEADER Trials: high A1c low BMI → shorter time to MACE and CV-death (8-LB)
- the combination GLP-1ra-SGLT2i reduces UACR, especially if macroalbuminuria is present and is correlated to improvement in either HbA1c, weight and SBP (523-P)

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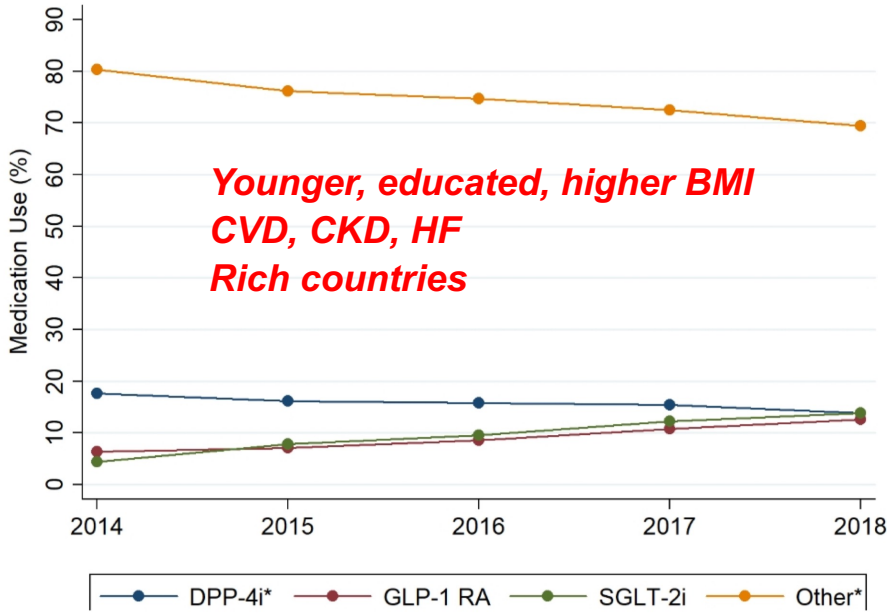
SITUATION TODAY

Only few patients in the US are on new drugs

GOULD*: within 12 mts from 7% to 8%!. Especially in Blacks and Medicare recipients (1211-P around 11%). 12.8 % with both drugs in patients who recieve GLP-1A or SGLT-2i;

Main reasons not choosinα: Economic considerations • Unfamiliarity with use



	SGLT2i	GLP-1-RA
DCR 2014-2016: USA	5%	6%
GOULD 2016-2018: USA	9%	8%
CAPTURE 2018-2019: 13 Countries	15%	9%

Arnold Eur J Prev Cardiol 2017
Arnold Circulation 2019
Vencio EASD 2020

1578-P and 16 B, 1429-P*

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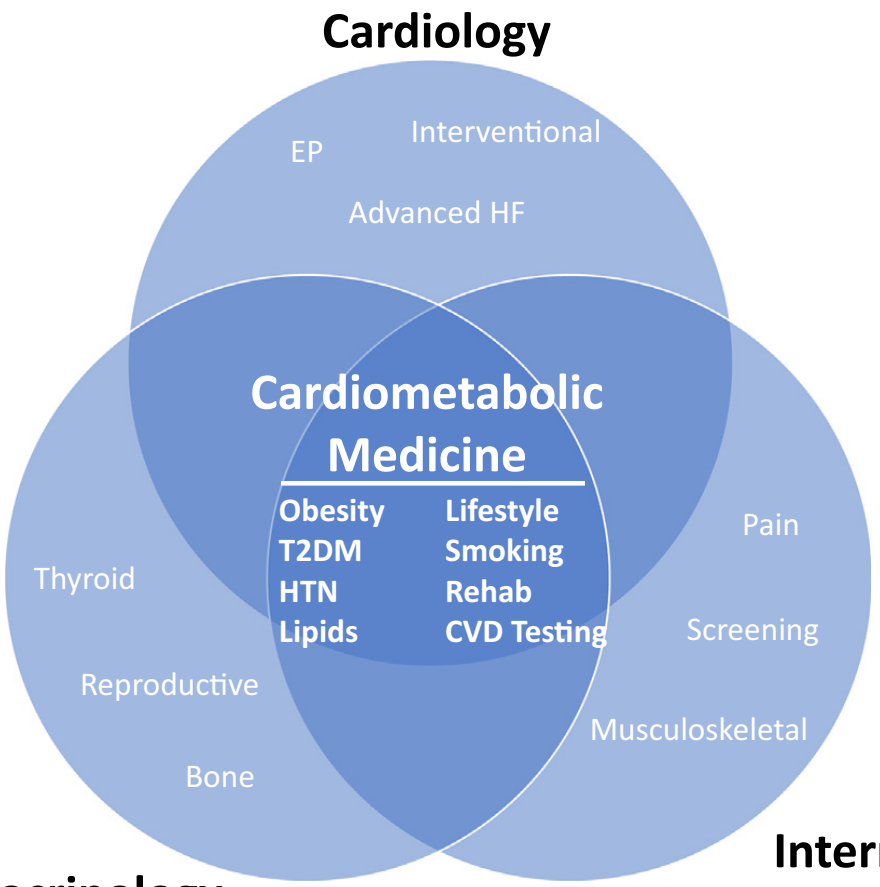
THE FUTURE FOR CV HIGH RISK PATIENTS INDEPENDET OF BASELINE HBA1C!



Life style modification

\+

HF risk	SGLT-2-I and treat all other risks
ASCVD risk	SGLT-2-I or GLP-1 RA and treat all other risks
Renal risk	SGLT-2-I and treat all other risks

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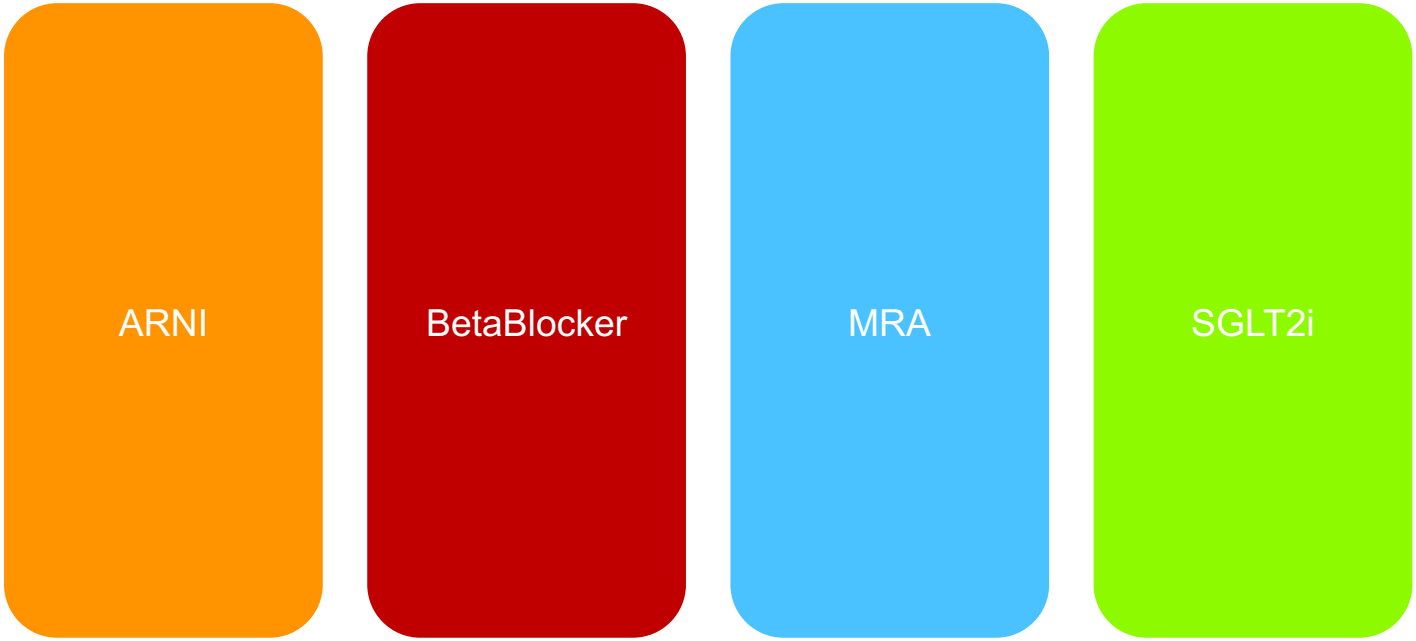
The American Journal of Medicine, Vol 132, No 7, July 2019

QUADRIGA



Cumulative risk reduction in all-cause mortality with all 4
RR 72.9%, ARR: 25.5%, NNT=3.9 over 24 months

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Am. Heart J 2011, 161;1024, Lancet 2008;372:1196, JAMA Cardio 2020 May 4

STEP SEMAGLUTIDE 2.4 MG ONCE WEEKLY

FDA approved by June 4, 2021

STEP-Program
- STEP 1: WM
- STEP 2: WM IN TYPE 2
- STEP 3: WM WITH BEHAVIORAL THERAPY
- STEP 4: SUSTAINED WM
- STEP 5: LONG-TERM WM
- STEP 6: EAST ASIAN

STEP-Program
- STEP 7: CHINA
- STEP 8: H2H VS LIRAGLUTIDE
- STEP TEENS
- SELECT: CVOT
- STEP: HFpEF
- STEP 9: KNEE OSTEOARTHRITIS

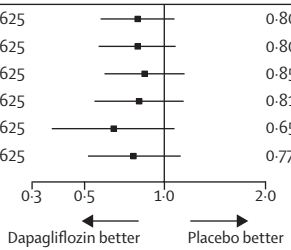
Mean weight loss of 15-17% in non-Dm and 10% in Dm Type 2 (1/3 more than 20% weight loss, 10% > 30 % weight loss, BUT 10 % without and 30% with Dm fail, women> men)
- Waist: -9.4 cm
- BD syst: -3.9 mmHg
- HDL: + 7 mg/dl, LDL:0 mg/dl, VLDL -21 mg/dl, TC: -22 mg/dl
- 29 % weniger Glc-lowering-Tx, HbA1c – 1.6%
- Non DM
  - Ongoing in the SELECT Trail
- NASH ongoing

ADA 2021

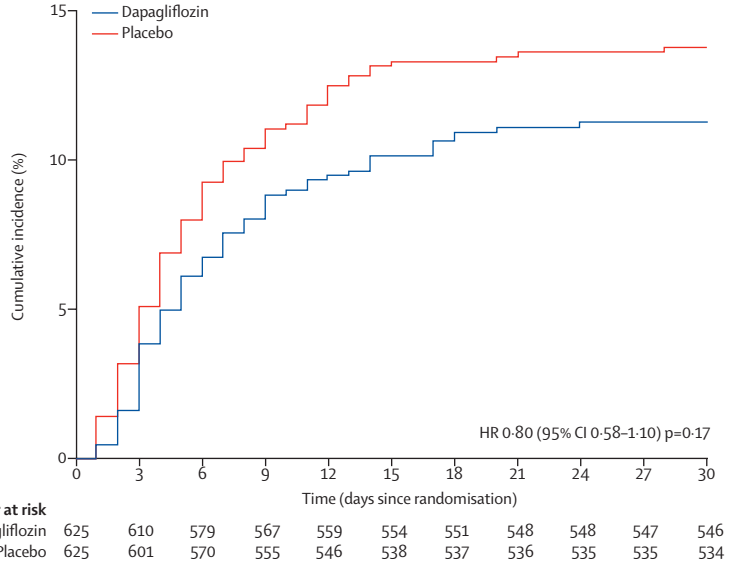
DARE-19 TRAIL: SGLT2I IN COVID 19 PATIENTS: ≥ RISK FACTOR: HTN, DM, ASCVD, HF, CKD

A

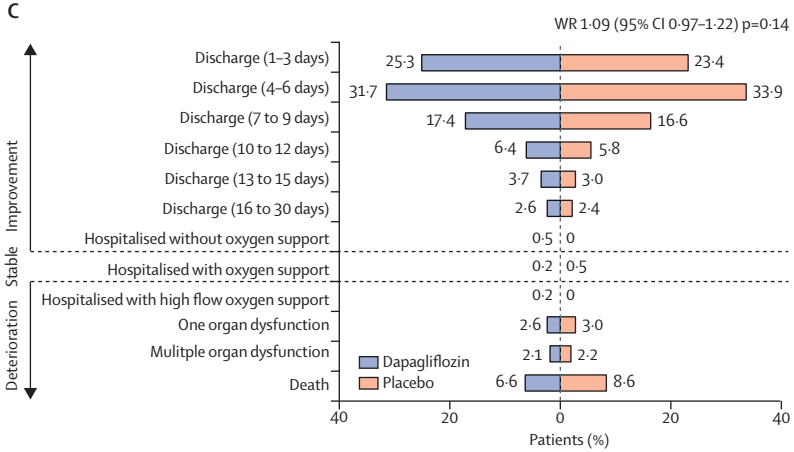
	Dapagliflozin n/N	Placebo n/N	HR (95% CI)
Primary composite outcome	70/625	86/625	0·80 (0·58–1·10)
New or worsening organ dysfunction	64/625	80/625	0·80 (0·57–1·11)
Respiratory decompensation	58/625	70/625	0·85 (0·60–1·20)
Cardiac decompensation	47/625	58/625	0·81 (0·55–1·19)
Kidney decompensation	24/625	35/625	0·65 (0·38–1·10)
Death from any cause	41/625	54/625	0·77 (0·52–1·16)



B



C



Keine Zusammenhang zum Dm-Status
SAE ausgeglichen
META: weniger Pneumonien unter SGLT2i

Lancet Diabetes Endocrinol 2021; 9: 586–94

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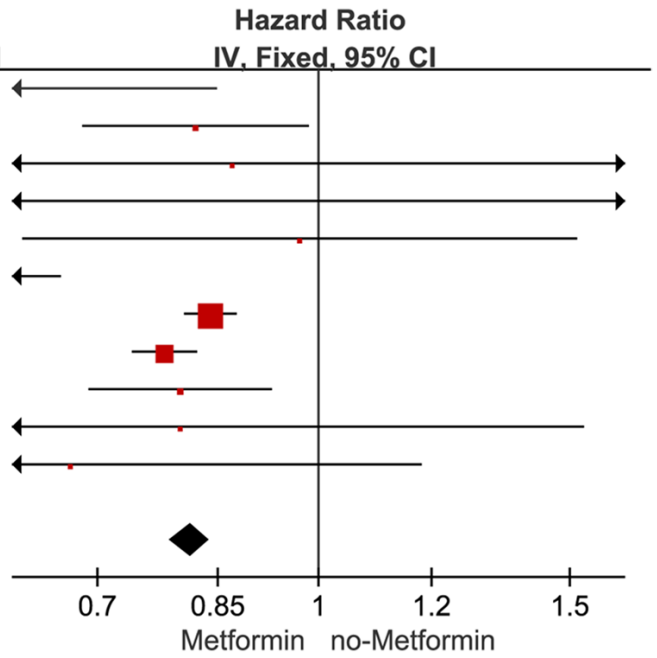
The end of metformin?

Hazard ratio of **cardiovascular mortality** among patients with metformin therapy vs no-metformin therapy

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Evans 2006	-0.5276	0.1857	0.7%	0.59 [0.41, 0.85]
Johnson 2005	-0.1985	0.0933	3.0%	0.82 [0.68, 0.98]
Liu 2016	-0.1393	0.3364	0.2%	0.87 [0.45, 1.68]
Preiss	1.1217	1.6415	0.0%	3.07 [0.12, 76.63]
Rachmani 2002	-0.0305	0.2284	0.5%	0.97 [0.62, 1.52]
Raee 2017	-2.1203	0.8698	0.0%	0.12 [0.02, 0.66]
Retwinski 2018	-0.1744	0.0217	54.8%	0.84 [0.80, 0.88]
Romero 2013	-0.2485	0.0269	35.7%	0.78 [0.74, 0.82]
Schramm 2011	-0.2231	0.0755	4.5%	0.80 [0.69, 0.93]
Shah 2010	-0.2231	0.3324	0.2%	0.80 [0.42, 1.53]
Sillars 2010	-0.4005	0.2893	0.3%	0.67 [0.38, 1.18]
Total (95% CI)			**100.0%**	**0.81 [0.79, 0.84]**

Heterogeneity: Chi² = 14.25, df = 10 (P = 0.16); I² = 30%

Test for overall effect: Z = 12.88 (P < 0.00001)



Action of metformin: effects on gut AMPK, brain and liver with

- Lower inflammation
- Reduced lipogenesis and gluconeogenesis
- Higher Glc utilisation

https://doi.org/10.1186/s12933-019-0900-7
Rena et al. Diabetologia (2017); 60:1577-1585

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Thank you for your attention

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