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New Drugs For Diabetes: It's More Than Just The Blood Sugar

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DISCLOSURES

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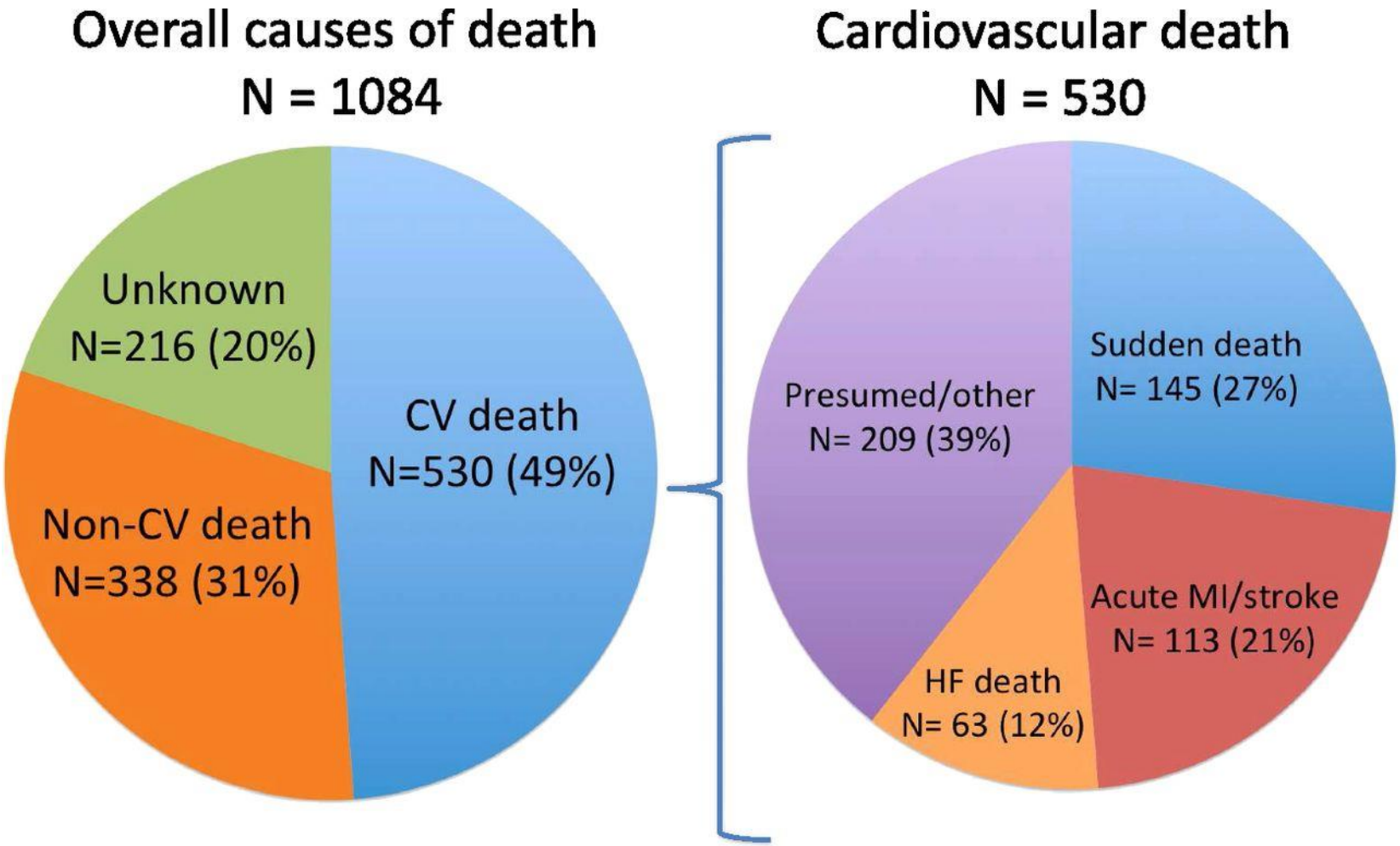
Research Grants: AstraZeneca, Novo Nordisk, Fractyl, Aspire Bariatrics

Distribution of causes of mortality in patients with T2DM (TECOS)



Abhinav Sharma et al. Dia Care 2017;40:1763-1770

American Diabetes Association.

CASE 1: 62 YO MAN

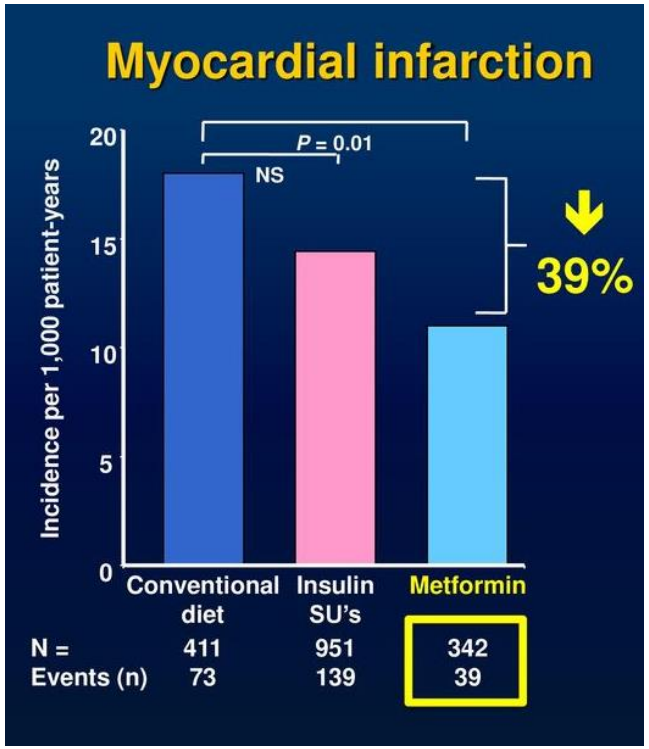
- BMI 36
- T2DM x 5 years, HTN x 20 years, NYHA 2 HF
- FHx: T2DM, HTN and CHF in mother
- A1c 7.8%

Metfomin 1000 mg bid

- BP 142/88

Valsartan, Carvedilol, Furosemide

- eGFR 50



Goals of Care

- Reduction of CV mortality and morbidity
  - Glycemic control
  - BP control
  - Preservation of kidney function
  - Weight reduction

SGLT2 INHIBITORS: MECHANISMS

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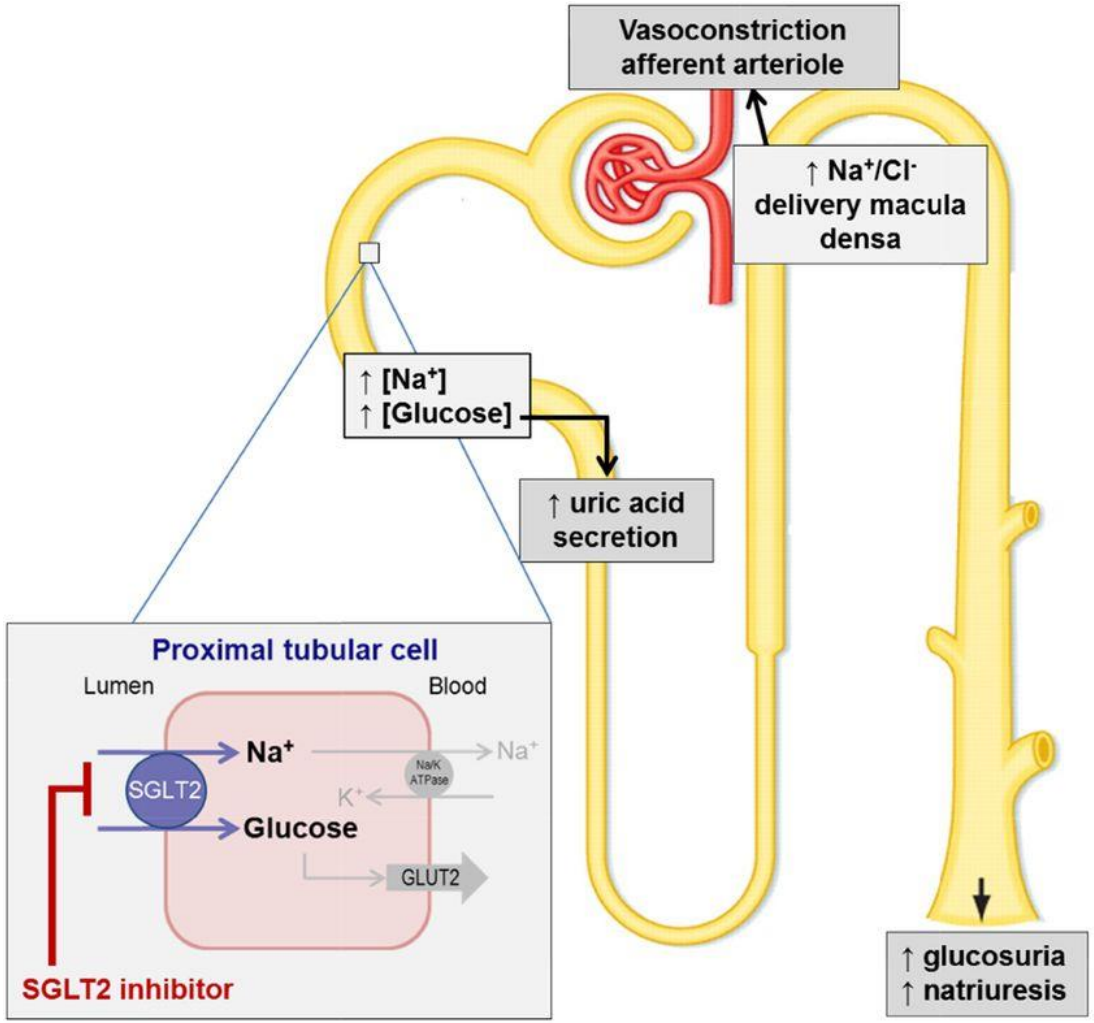

Clinical findings

- ↓ Plasma glucose
- ↓ Body weight
- ↓ Blood pressure
- ↓ Plasma uric acid
- ↓ Glomerular hyperfiltration

Erik J.M. van Bommel et al. CJASN 2017;12:700-710

CJASN

EMPA-REG

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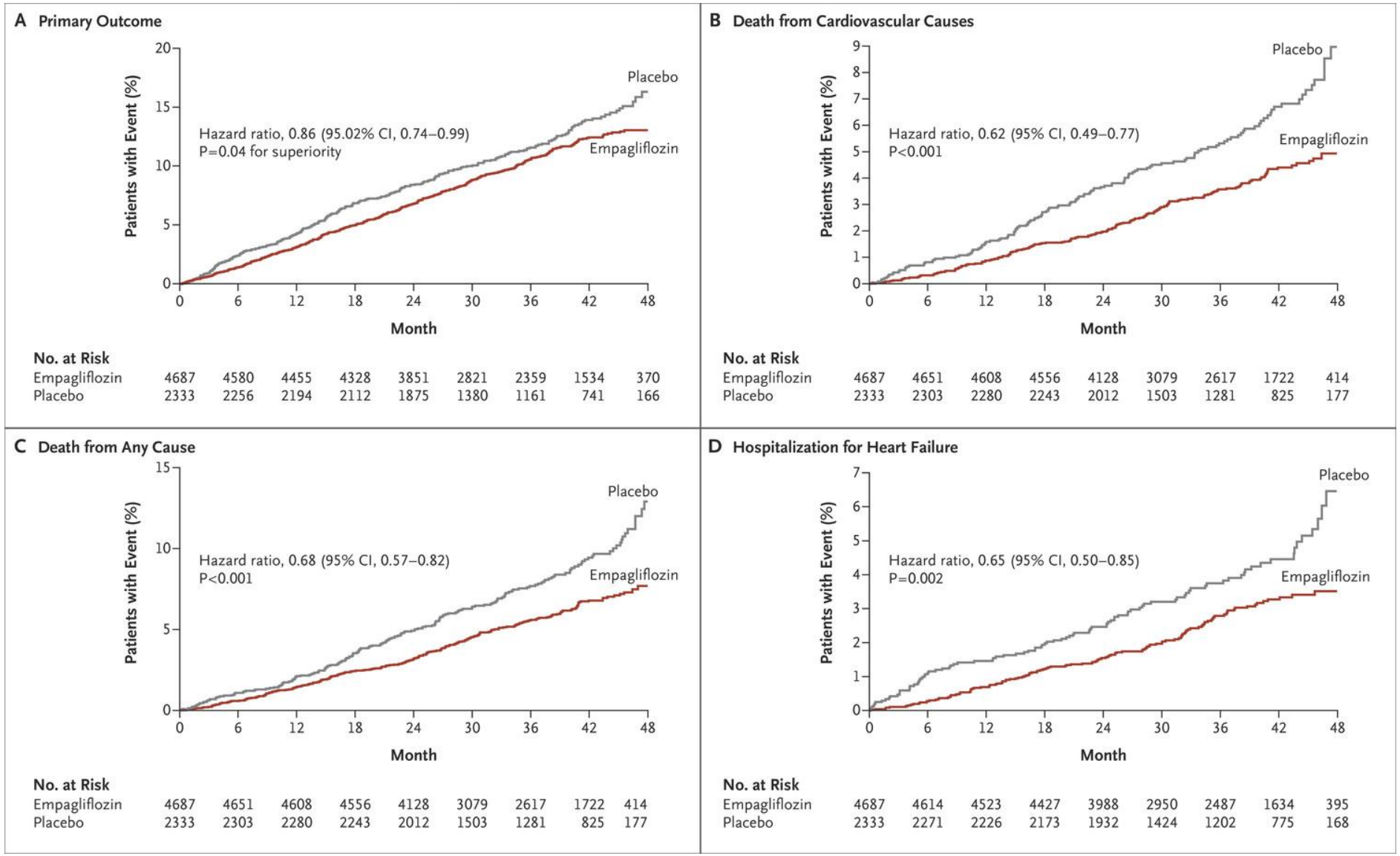
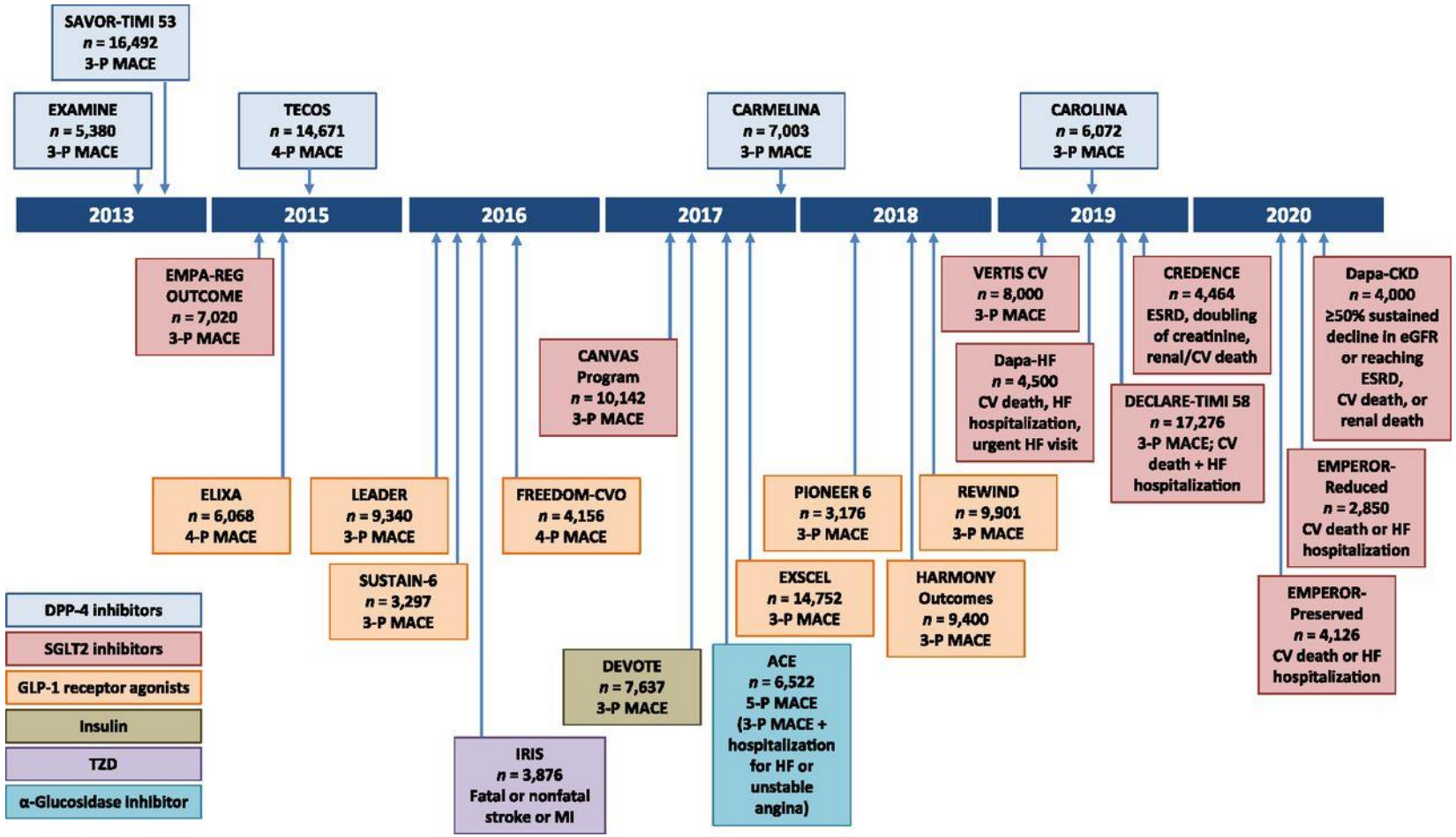


Zinman B et al. N Engl J Med 2015;373:2117-2128.

COMPLETED AND ONGOING CVOTs



William T. Cefalu et al. Dia Care 2018;41:14-31

EMPA-REG, CANVAS, DECLARE-TIMI 58

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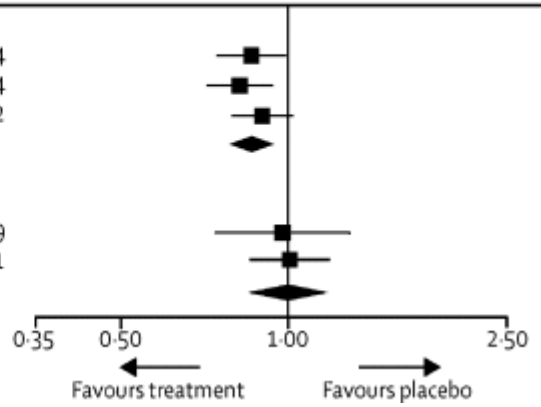
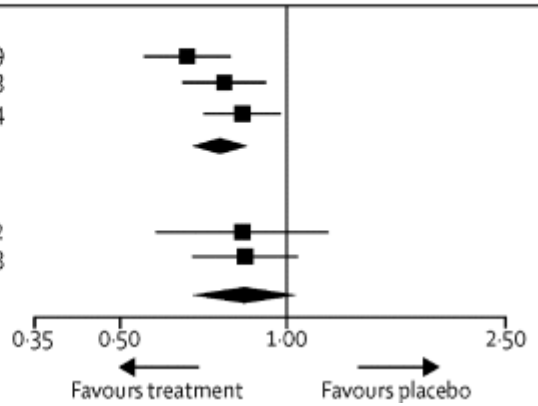
MACE

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4687	2333	772	37·4	43·9	29·4		0·86 (0·74–0·99)
CANVAS Program	3756	2900	796	34·1	41·3	32·4		0·82 (0·72–0·95)
DECLARE-TIMI 58	3474	3500	1020	36·8	41·0	38·2		0·90 (0·79–1·02)
Fixed effects model for atherosclerotic cardiovascular disease (p=0·0002)								**0·86 (0·80–0·93)**
Patients with multiple risk factors								
CANVAS Program	2039	1447	215	15·8	15·5	25·9		0·98 (0·74–1·30)
DECLARE-TIMI 58	5108	5078	539	13·4	13·3	74·1		1·01 (0·86–1·20)
Fixed effects model for multiple risk factors (p=0·98)								**1·00 (0·87–1·16)**



HF Hospitalizations

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4687	2333	463	19·7	30·1	30·9		0·66 (0·55–0·79)
CANVAS Program	3756	2900	524	21·0	27·4	32·8		0·77 (0·65–0·92)
DECLARE-TIMI 58	3474	3500	597	19·9	23·9	36·4		0·83 (0·71–0·98
Fixed effects model for atherosclerotic cardiovascular disease (p<0·0001)								**0·76 (0·69–0·84)**
Patients with multiple risk factors								
CANVAS Program	2039	1447	128	8·9	9·8	30·2		0·83 (0·58–1·19)
DECLARE-TIMI 58	5108	5078	316	7·0	8·4	69·8		0·84 (0·67–1·04)
Fixed effects model for multiple risk factors (p=0·0634)								**0·84 (0·69–1·01)**



T. Zelniker, *The Lancet 2019*

DAPA-HF

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Subgroup	Dapagliflozin (N=2373) no. of patients/total no.	Placebo (N=2371)	Hazard Ratio (95% CI)
All patients	386/2373	502/2371	0.74 (0.65–0.85)
Age			
≤65 yr	162/1032	196/998	0.78 (0.63–0.96)
>65 yr	224/1341	306/1373	0.72 (0.60–0.85)
Sex			
Male	307/1809	406/1826	0.73 (0.63–0.85)
Female	79/564	96/545	0.79 (0.59–1.06)
Race			
White	275/1662	348/1671	0.78 (0.66–0.91)
Black	26/122	32/104	0.62 (0.37–1.04)
Asian	78/552	118/564	0.64 (0.48–0.86)
Other	7/37	4/32	
Geographic region			
Asia	77/543	114/553	0.65 (0.49–0.87)
Europe	193/1094	218/1060	0.84 (0.69–1.01)
North America	54/335	73/342	0.73 (0.51–1.03)
South America	62/401	97/416	0.64 (0.47–0.88)
NYHA class			
II	190/1606	289/1597	0.63 (0.52–0.75)
III or IV	196/767	213/774	0.90 (0.74–1.09)
LVEF			
≤Median	222/1230	307/1239	0.70 (0.59–0.84)
>Median	164/1143	195/1132	0.81 (0.65–0.99)
NT-proBNP			
≤Median	100/1193	155/1179	0.63 (0.49–0.80)
>Median	286/1179	347/1191	0.79 (0.68–0.92)
Hospitalization for heart failure			
Yes	195/1124	279/1127	0.67 (0.56–0.80)
No	191/1249	223/1244	0.84 (0.69–1.01)
MRA at baseline			
Yes	281/1696	361/1674	0.74 (0.63–0.87)
No	105/677	141/697	0.74 (0.57–0.95)
Type 2 diabetes at baseline			
Yes	215/1075	271/1064	0.75 (0.63–0.90)
No	171/1298	231/1307	0.73 (0.60–0.88)
Atrial fibrillation or flutter on enrollment ECG			
Yes	109/569	126/559	0.82 (0.63–1.06)
No	277/1804	376/1812	0.72 (0.61–0.84)
Main cause of heart failure			
Ischemic	223/1316	289/1358	0.77 (0.65–0.92)
Nonischemic or unknown	163/1057	213/1013	0.71 (0.58–0.87)
Body-mass index			
<30	259/1537	320/1533	0.78 (0.66–0.92)
≥30	127/834	182/838	0.69 (0.55–0.86)
Baseline eGFR (ml/min/1.73m²)			
<60	191/962	254/964	0.72 (0.59–0.86)
≥60	195/1410	248/1406	0.76 (0.63–0.92)

0.5 0.8 1.0 1.2

Dapagliflozin Better Placebo Better

All-cause death – 17% reduction
CV death – 18% reduction
HF hospitalization plus CV deaths – 25% reduction

NNT is 21 to prevent one primary endpoint during 18 months of treatment

JJ McMurray et al. *N Engl J Med 2019*

CASE 1: 62 YO MAN

- BMI 36
- T2DM x 5 years, HTN x 20 years, NYHA 2 HF
- FHx: T2DM, HTN and CHF in mother
- A1c 7.8%

MFM 1000 mg bid

- BP 142/88

Valsartan, Carvedilol, Furosemide

- eGFR 50

6 months later

- MFM 1000 bid, Dapagliflozin 10 mg daily
- BMI 34.5, weight loss 5%
- A1c 6.9%
- BP 130/80
- eGFR 51

CASE 2: 62 YO MAN

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- BMI 29.2
- T2DM x 12 years, HTN, HL, NAFLD
- FHx: CAD in father
- A1c 8.1%

MFM 2000 mg/day and Glipizide 10 mg bid

- BP 132/77

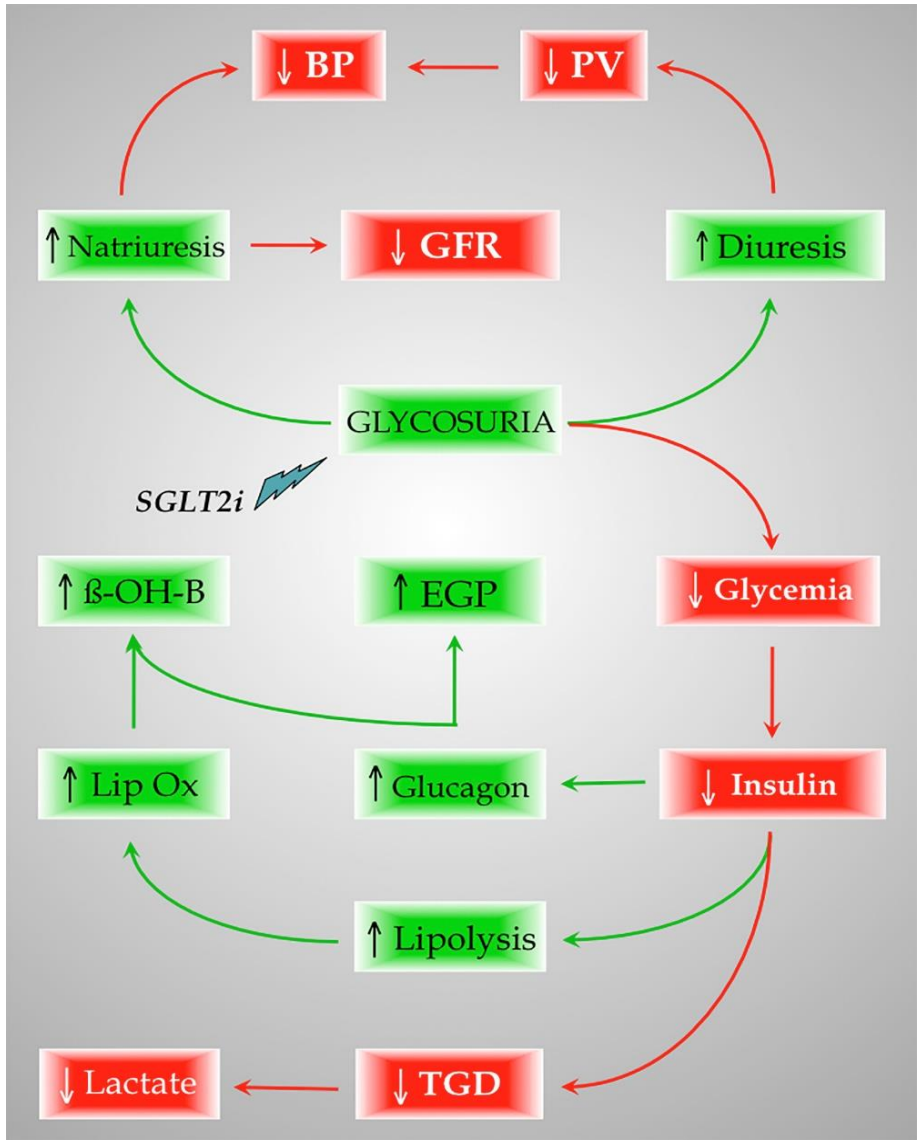
Lisinopril, HCTZ/triamterene

- ALT 68, AST 26
- eGFR 66
- AFRAID OF NEEDLES

2 months later

- MFM 1000 mg bid and Canagliflozin 300
- BMI 28.6, weight loss 3%
- Hospitalization for cholecystectomy
- DM meds stopped 24 hours prior to surgery
- POD 1: BG 146, AG 20, CO2 17, BHB 4.6, Glucosuria >1000 mg/dl
- Insulin Gtt at 0.5 -1.0 u/hr and D5 1/2NS
- POD 2: AG10, transitioned to basal-bolus and started PO intake, glucosuria >1000 mg/dl

SGLT2 INHIBITORS: EUGLYCEMIC DKA +



Ele Ferrannini, *Cell Metabolism, 2017*

SIDE EFFECTS and CONSIDERATIONS:

- EUGLYCEMIC DKA
  - If uncontrolled on SU or receiving insulin
  - Prolonged fasting
- HYPOGLYCEMIA
  - If receiving insulin or sulfonylurea
- Polyuria, frequency
- Dehydration, orthostasis
  - Consider adjusting diuretic, monitor BP
- Genital mycotic infections
  - Educate, fluconazole
- Risk of UTI
  - Studies do not show

CASE 3: 47 YO MAN

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- BMI 38, weight gain
- T2DM x 2 years, HTN, NAFLD
- H/o Vtach 10 years ago, non-obstructive CAD
- FHx of CAD in father
- A1c 7.8%

MFM 1000 mg a day

Glimepiride 4 mg bid

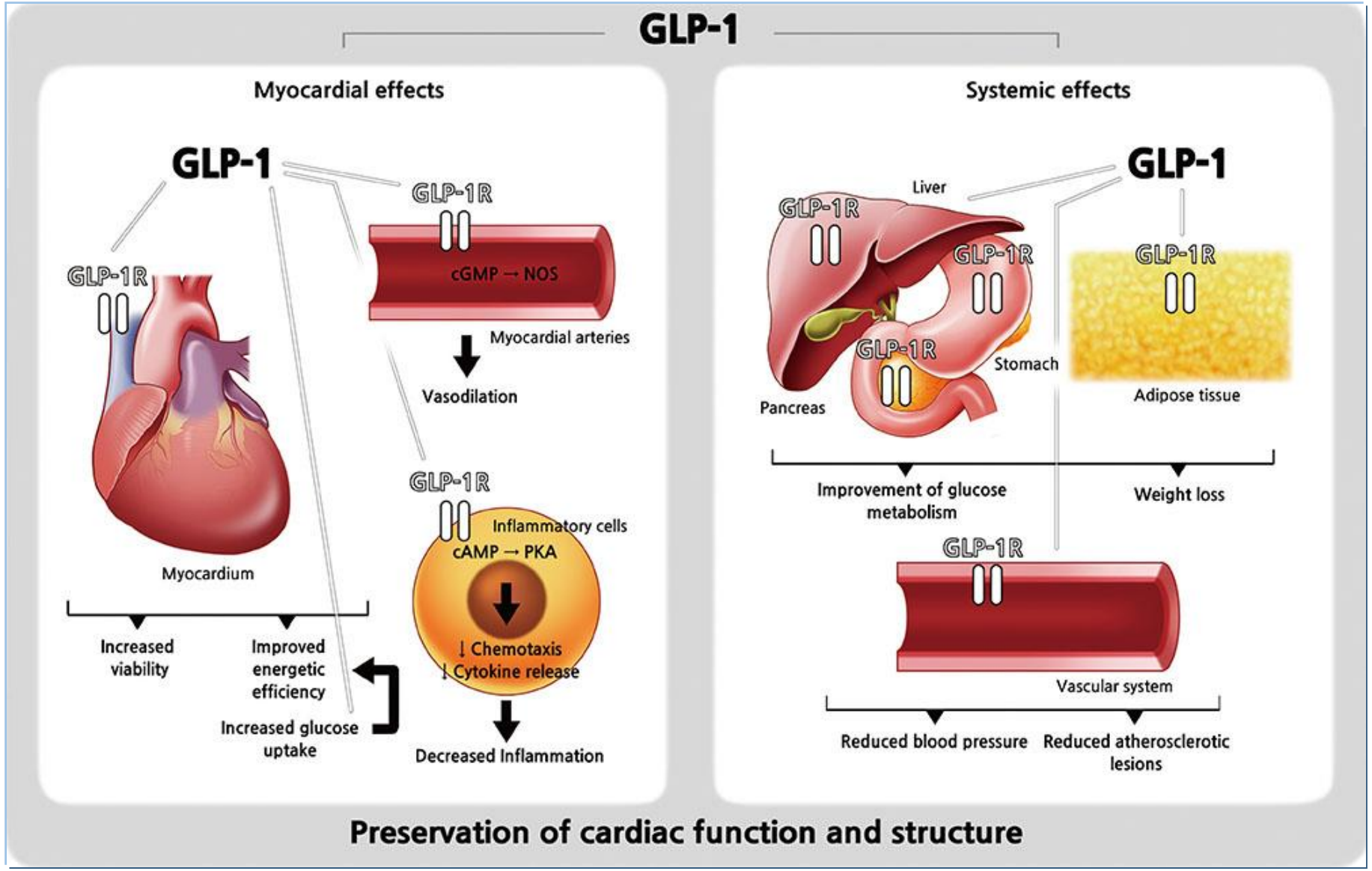
- BP 135/85

Amlodipine, Carvedilol, Lisinopril, HCTZ

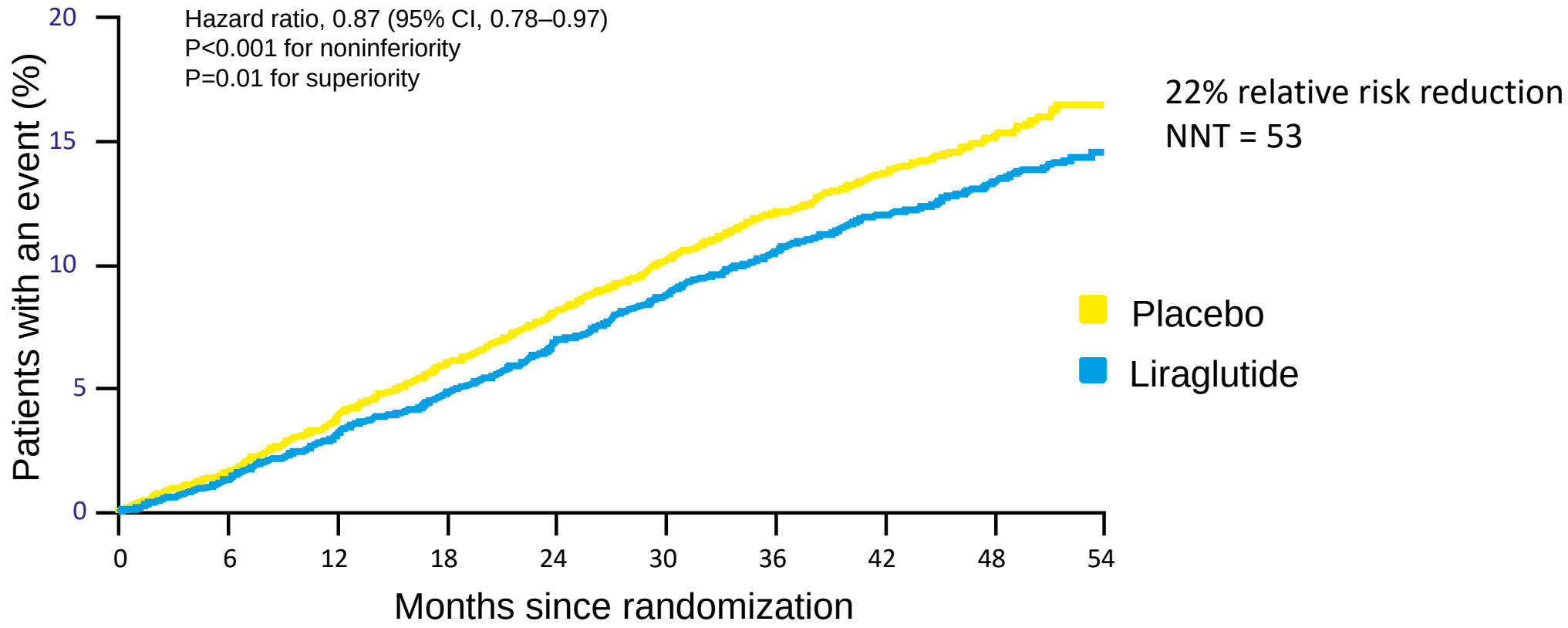
- GFR 85

- Obesity
- NAFLD
- ASCVD

GLP-1 RECEPTOR AGONISTS: MECHANISMS



First occurrence of CV death, nonfatal myocardial infarction, or nonfatal stroke in the time-to-event analysis in patients with type 2 diabetes and high CV risk



S. Marso, *N Engl J Med 2016*

GLP-1 RECEPTOR AGONISTS: CVOTs

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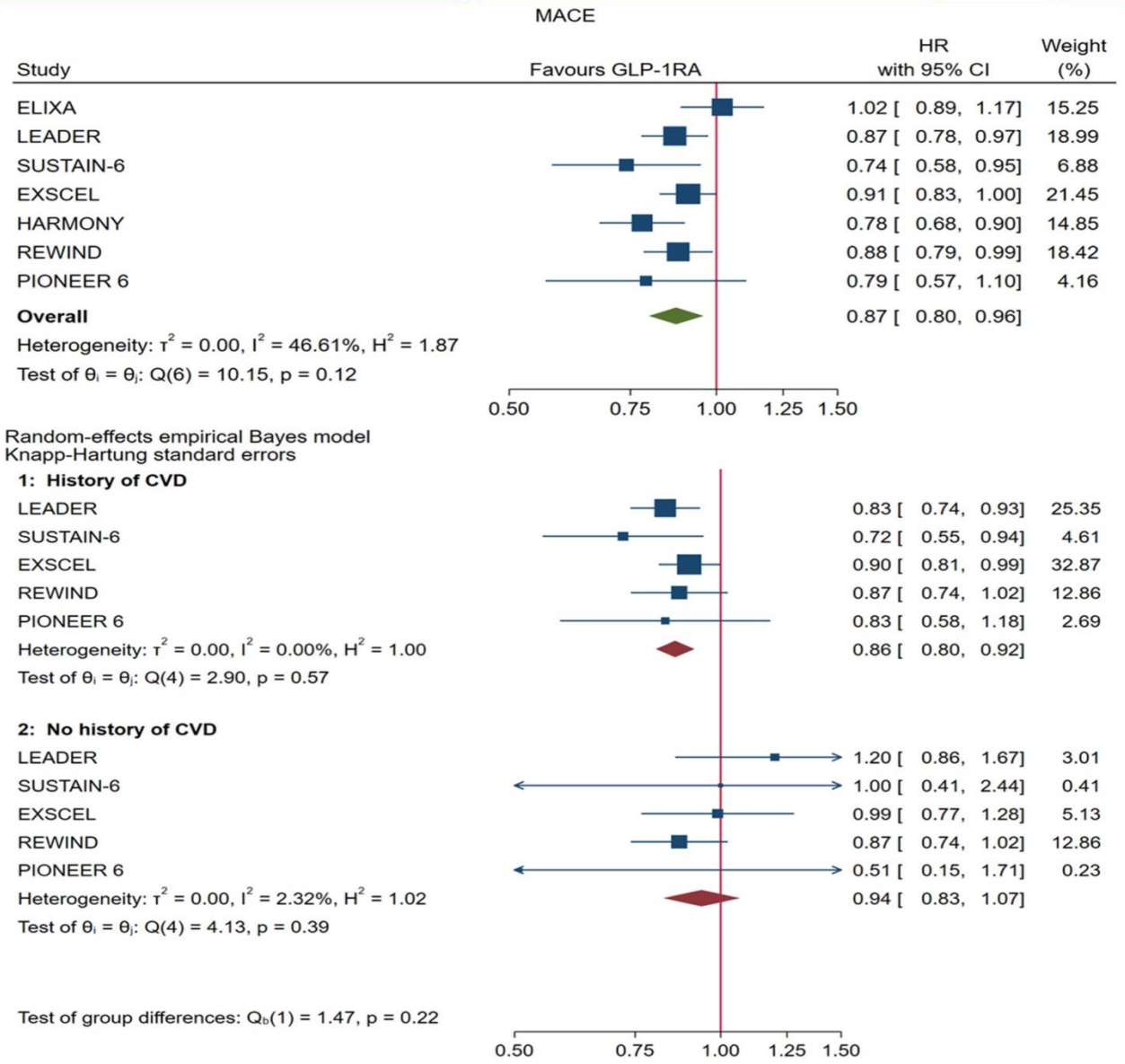

Diabetes, Obesity and Metabolism, August 2019

CASE 3: 47 YO MAN

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- BMI 38, weight gain
- T2DM x 2 years, HTN, NAFLD
- H/o Vtach 10 years ago, non-obstructive CAD
- FHx of CAD in father
- A1c 7.8%

MFM 1000 mg a day

Glimepiride 4 mg bid

- BP 135/85

Amlodipine, Carvedilol, Lisinopril, HCTZ

- GFR 85

6 months later

- MFM 2000 mg a day, Liraglutide 1.8
- Lifestyle modifications
- BMI 33, weight loss 15%
- A1c 5.8%
- BP 125/75

Amlodipine and HCTZ reduced

GLP-1 RA SIDE EFFECTS AND CONSIDERATIONS

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- Injectable medication, teaching is needed
- Nausea and Vomiting
  - Start at the lowest dose
  - Titrate slowly ever 2-4 weeks
- Hypoglycemia
  - In presence of insulin or SU
- Proliferative Retinopathy
  - Signal in Semaglutide studies only
- Pancreatitis and pancreatic cancer
  - No evidence of risk increase in humans
- Medullary thyroid cancer
  - No evidence in humans. Do not Rx to patients with FHx of MEN 1 or medullary thyroid cancer

ACC CONSENSUS GUIDELINES 2018

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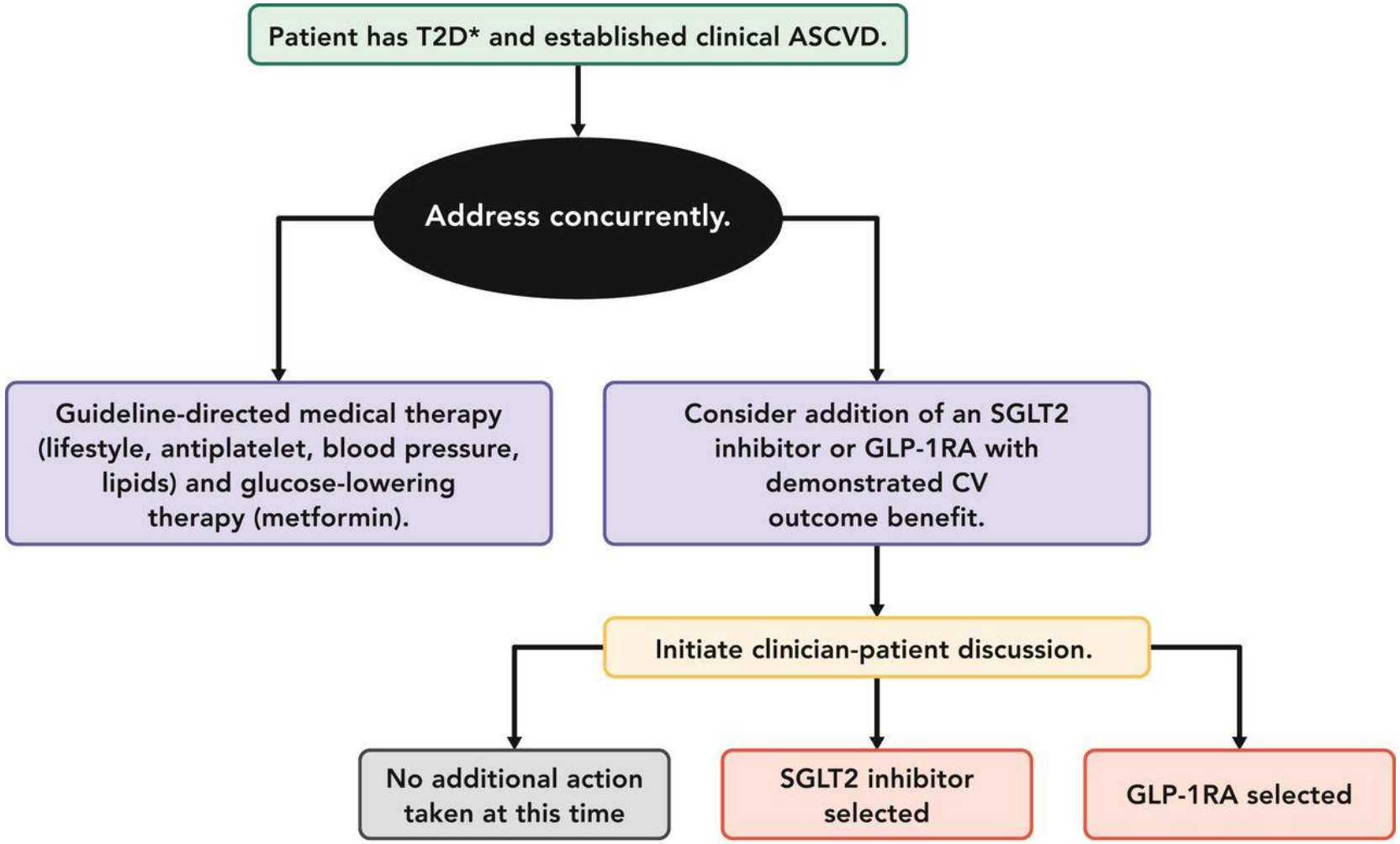

*Most trials of SGLT2i and GLP-1RA required baseline A1C ≥7% (Example: EXSCEL Trial required HbA1c ≥ 6.5%), and most patients were already on metformin as first-line therapy if tolerated and not contraindicated

ADA STANDARD OF CARE 2019

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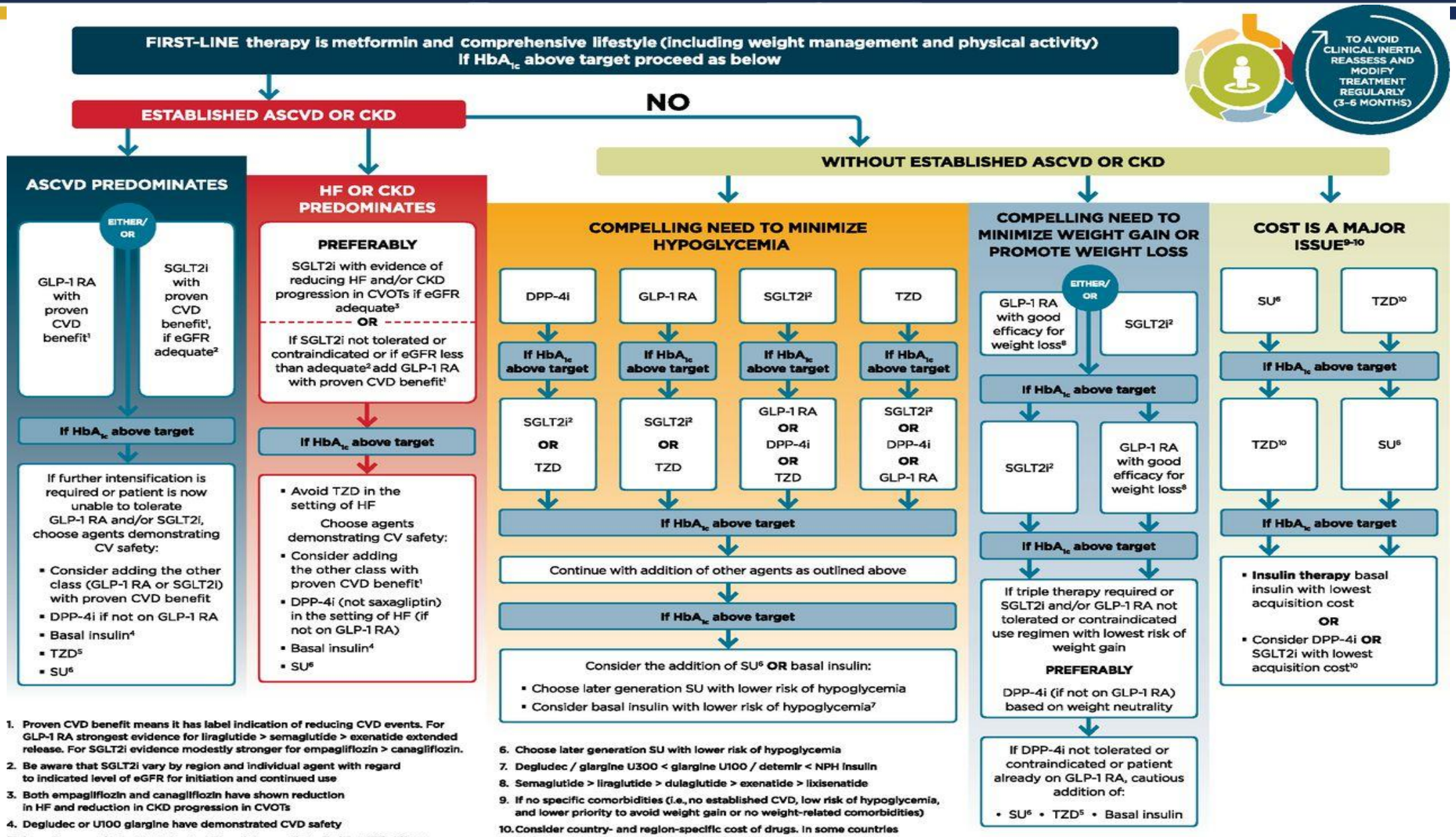

1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

The Next Decade

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- Paradigm shift in T2DM management from glycemic control alone to comprehensive CV risk reduction

- Cardiologists and nephrologists will take a more active role in T2DM management