XV CONGRESSO REGIONALE AMD MOLISE
22 OTTOBRE 2022

Diabete, Cuore e Rene: dalla Fisiopatologia alla Terapia

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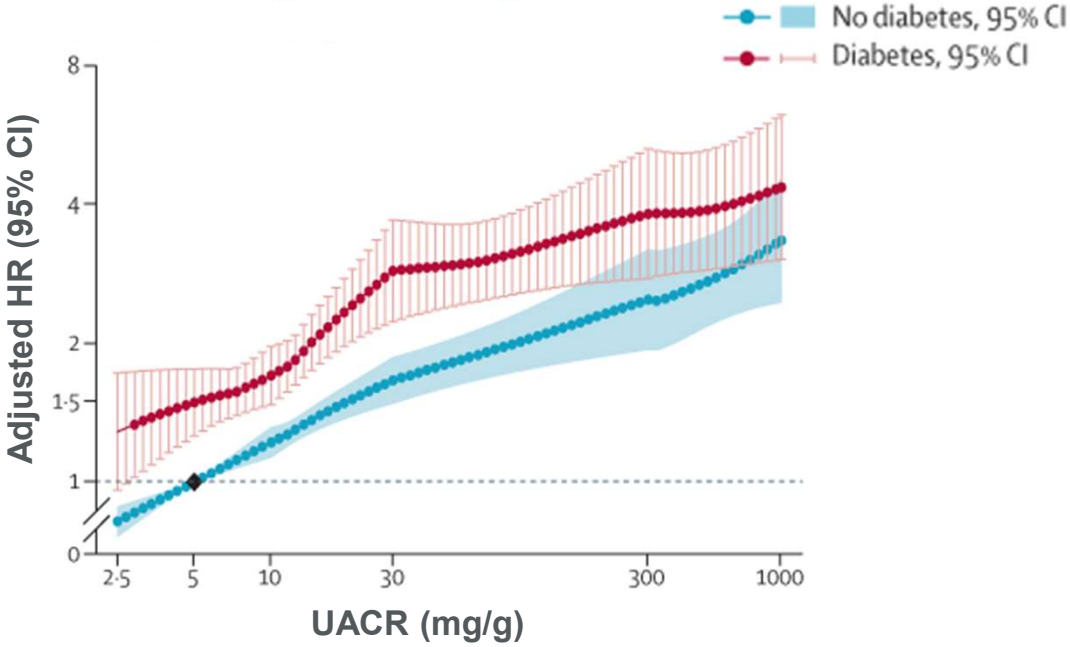
Cardio-renal prognosis by eGFR and albuminuria

in Diabetes Mellitus

CV risk increases as albuminuria progresses or eGFR declines
…and risk is constantly higher in DM vs no-DM

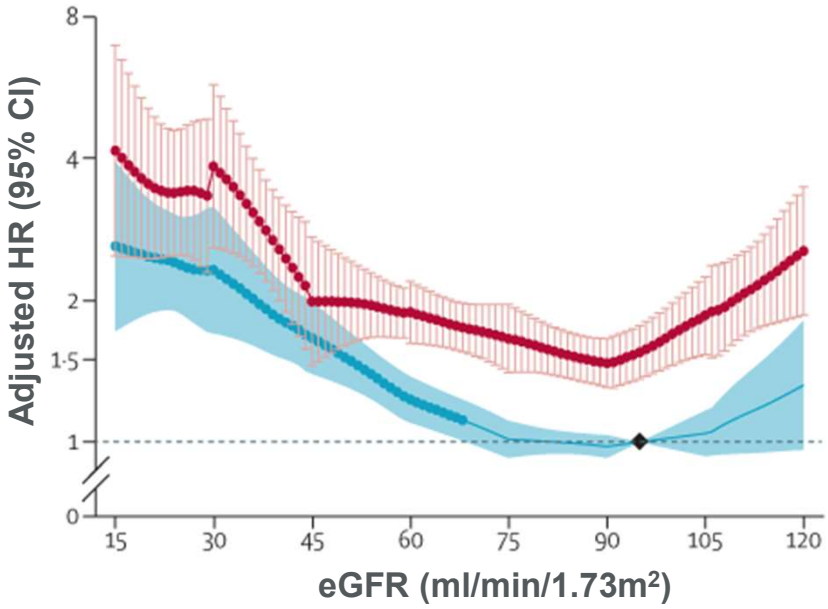
MA including 1,024,977 patients

CV mortality according to UACR



Risk of CV death is significantly increased as UACR rises above 10 mg/g

CV mortality according to eGFR



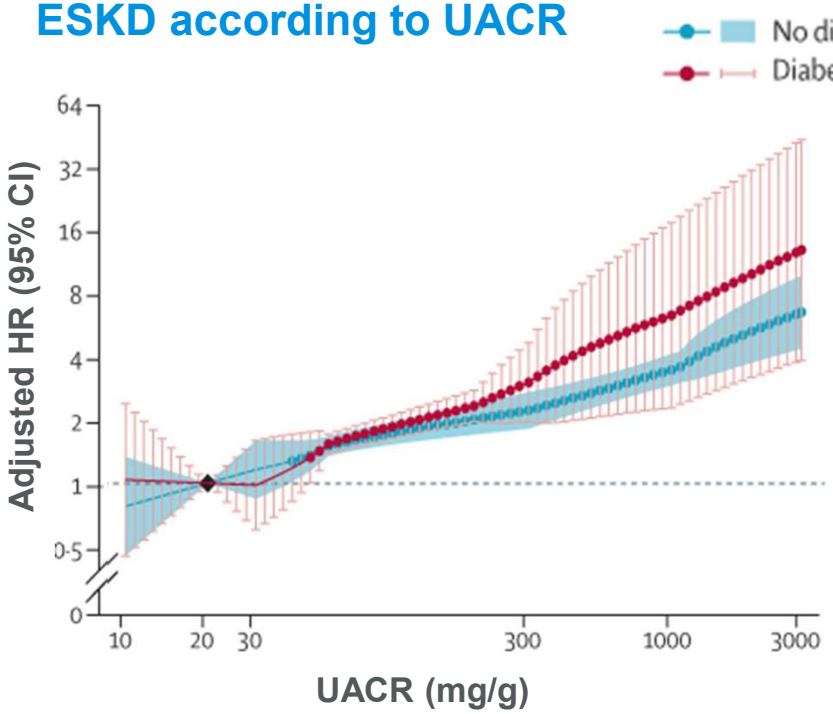
Risk of CV death is significantly increased as eGFR falls below 75 ml/min/1.73 m2

Fox CS, CKD Prognosis Consortium, Lancet 2012

ESKD risk increases as albuminuria progresses or eGFR declines
…and risk is constantly higher in DM vs no-DM

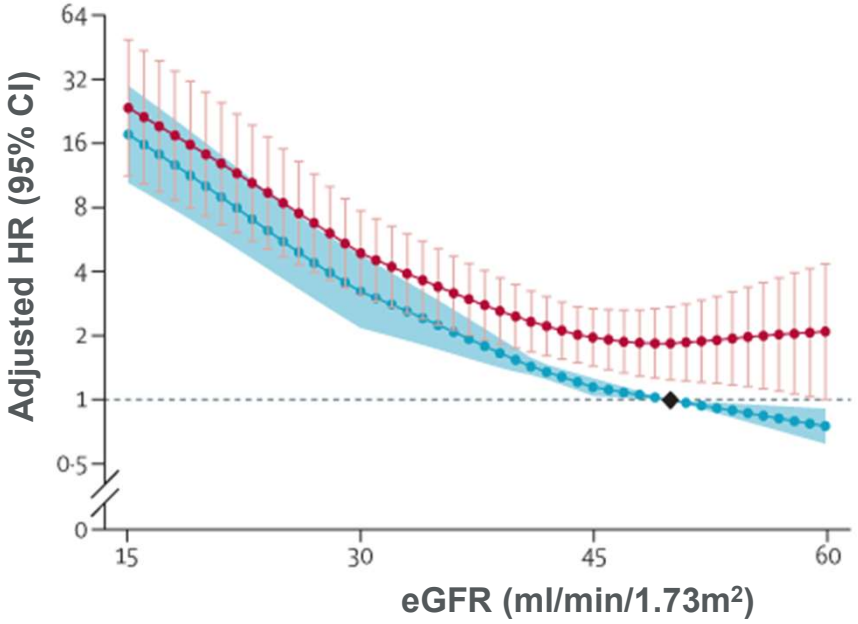
MA including 1,024,977 patients

ESKD according to UACR



Risk of ESKD is significantly increased as UACR rises above 100 mg/g

ESKD according to eGFR



Risk of ESKD is significantly increased as eGFR falls below 45 ml/min/1.73 m²

Fox CS, CKD Prognosis Consortium, Lancet 2012

Categorie di rischio Cardio-Renale nel DM tipo 2

(Linee Guida ESC-EASD 2019)

Molto alto	• **Diagnosi di malattia cardiovascolare** ***oppure*** • **Presenza di danno d'organo**, almeno uno tra: – proteinuria o albuminuria severa* (proteinuria >500 o albuminuria >300, o almeno un + all'esame urine) – $eGFR_{MDRD}$ ≤30 ml/min/1.73 m^2 – ipertrofia ventricolare sinistra – retinopatia ***oppure*** • **almeno tre fattori di rischio maggiori tra:** – età ≥50 anni – ipertensione arteriosa – dislipidemia – fumo – obesità
Alto	• **Durata di diabete mellito ≥10 anni <u>senza</u> danno d'organo <u>ma con almeno un fattore di rischio</u>:** – età ≥50 anni – ipertensione arteriosa – dislipidemia – fumo – obesità – $eGFR_{MDRD}$ 60-30 ml/min/1.73 m^2 – proteinuria o albuminuria moderata* (proteinuria 150-500 o albuminuria 30-300, o "tracce" all'esame urine)
Moderato	• **Età <50 anni con durata diabete mellito <10 anni e senza fattori di rischio**

SIC-SIN Consensus, G ITAL CARDIOL Oct 2022

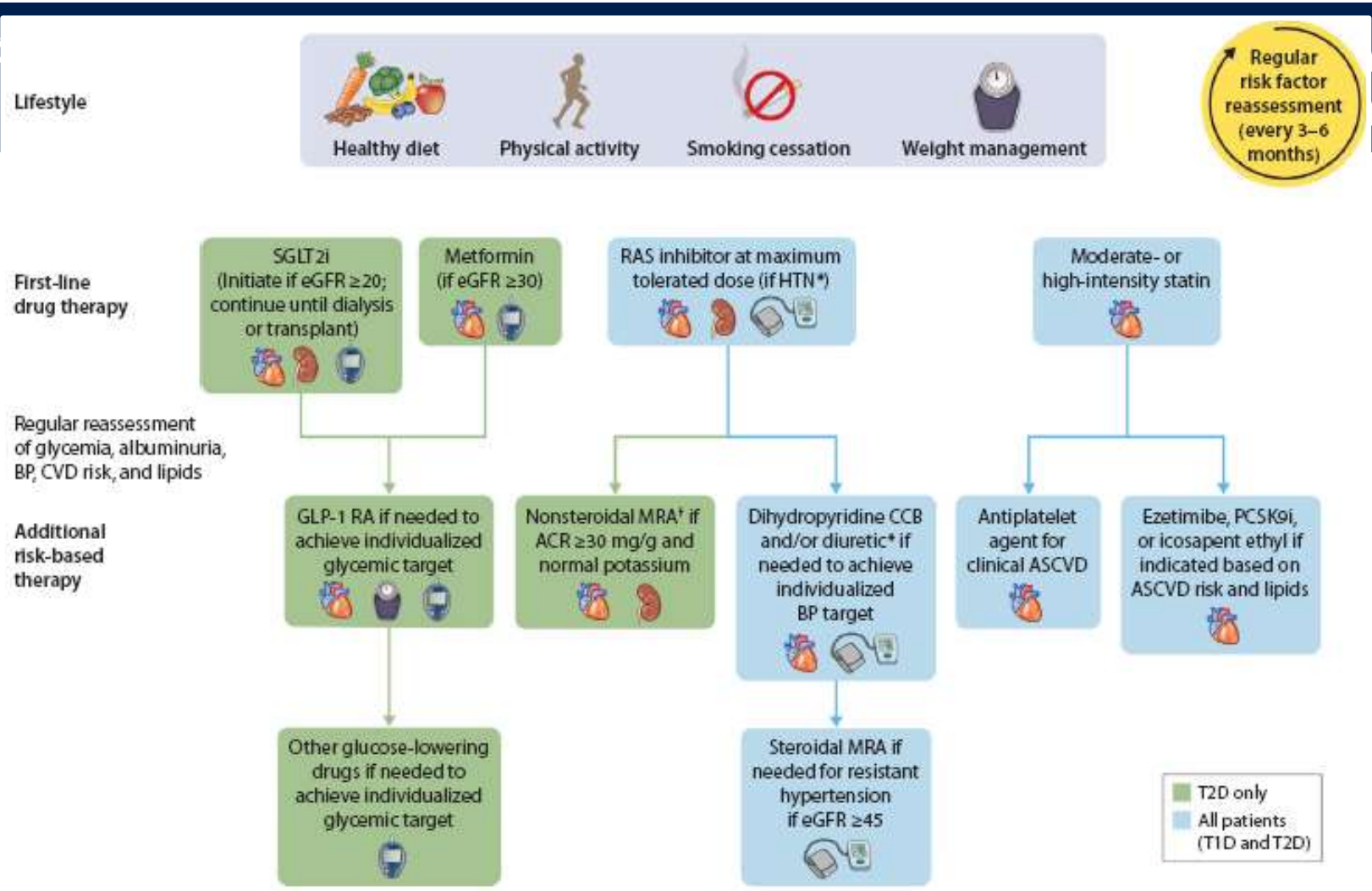
Novel approach to the high risk Diabetic CKD

Prevention of Target Organ Damage

…more than control of glycemia

Consensus report by ADA-KDIGO:
Diabetes management in chronic kidney disease

…Comp… kidney … prove … lthy lifestyle



Kidney Int, 19 Oct 2022

Consensus report by ADA-KDIGO:
Diabetes management in chronic kidney disease

	Progression of CKD	ASCVD	Heart failure	Glucose-lowering efficacy	Hypoglycemia risk	Weight effects
Metformin	Neutral	Potential benefit	Potential benefit	High	Low	Neutral
SGLT2 inhibitors	Benefit[a]	Benefit[c]	Benefit	Intermediate	Low	Loss
GLP-1 receptor agonists	Benefit[b]	Benefit[c]	Potential benefit	High	Low	Loss
DPP-4 inhibitors	Neutral	Neutral	Potential risk[c] (saxagliptin)	Intermediate	Low	Neutral
Insulin	Neutral	Neutral	Neutral	Highest	High	Gain
Sulfonylureas	Neutral	Neutral	Neutral	High	High	Gain
Thiazolidinediones	Neutral	Potential benefit (pioglitazone)	Increased risk	High	Low	Gain
α-Glucosidase inhibitors	Neutral	Neutral	Neutral	Intermediate	Low	Neutral

Kidney Int, 19 Oct 2022

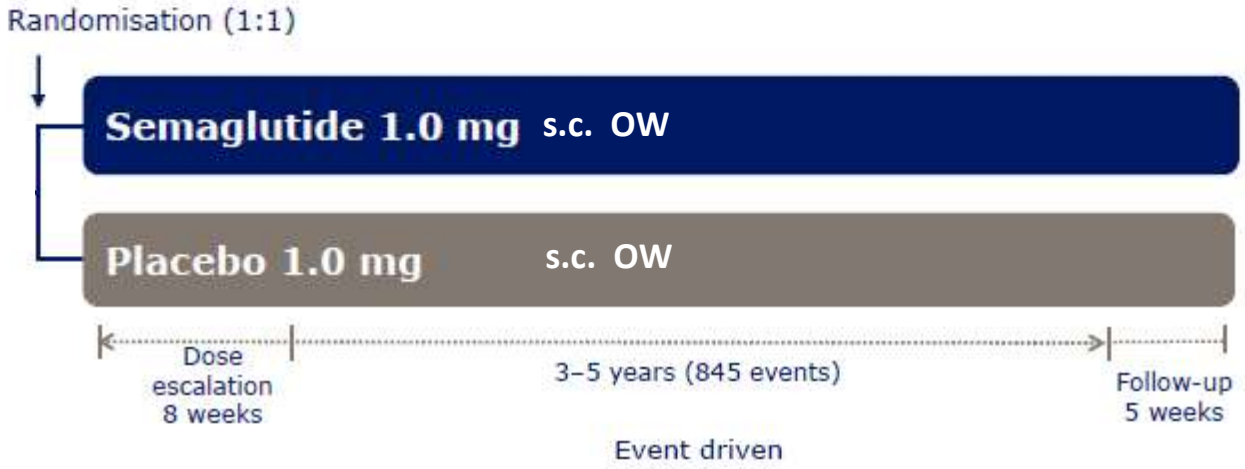
Consensus report by ADA-KDIGO:
Diabetes management in chronic kidney disease

	Stage 3b (eGFR 30–44 mL/min/1.73 m²)	Stage 4 (eGFR 15–29 mL/min/1.73 m²)	Stage 5 (eGFR <15 mL/min/1.73 m²)
SGLT2 inhibitors*			
Canagliflozin	Maximum 100 mg daily	Initiation not recommended; may continue 100 mg daily if tolerated for kidney and CV benefit until dialysis	
Dapagliflozin	10 mg daily†	Initiation not recommended with eGFR <25 mL/min/1.73 m²; may continue if tolerated for kidney and CV benefit until dialysis	
Empagliflozin	10 mg daily‡	Initiation not recommended with eGFR <20 mL/min/1.73 m²; may continue if tolerated for kidney and CV benefit until dialysis	
Ertugliflozin	Use not recommended with eGFR <45 mL/min/1.73 m²		
GLP-1 receptor agonists§			
Exenatide	Caution initiating or increasing dose; avoid once-weekly formulation	Use not recommended	
Dulaglutide	No dose adjustment required		
Liraglutide	No dose adjustment required		
Lixisenatide	No dose adjustment required		Use not recommended
Semaglutide	No dose adjustment required		

Kidney Int, 19 Oct 2022

FLOW trial (semaglutide):
first dedicated* GLP1-RA renal outcome trial

>3,000 patients with type 2 DKD under RAAS blockade



From Jun 2019 to Aug 2024 (expected)

***DKD as inclusion criterion:**

- **eGFR 50–75 mL/min + UACR 300–5000 mg/g**
- **eGFR 25–50 mL/min + UACR 100–5000 mg/g**

***Renal Primary Objective:**

Time to first occurrence of a composite of persistent eGFR decline ≤50%, reaching ESRD, death from kidney disease or death from CV disease

CV outcome in “survivors” with DM-CKD

Time in Fashion

Editorial

Heart Failure, Diabetes Mellitus, and Chronic Kidney Disease

A Clinical Conundrum

David Aguilar, MD

Type 2 DM occurs in 25% of patients with chronic HF ⇨ **worse outcome**
and in 40% of those hospitalized with acute HF ⇨ **worse outcome**

Presence of HF complicates the pharmacological treatment of hyperglycemia:

- **Thiazolidinediones are associated with greater rates of HF hospitalization**
- **Sulfonylureas and insulin increase the risk of hypoglycemia**

CKD is common in HF (40% to 50%) and severity of renal dysfunction
is associated with a **graded increase of death risk**

***Circ Heart Fail*. 2016**

The kidney in the **early stages** of HF

Intrarenal Determinants of Sodium Retention in Mild Heart Failure

Massimo Volpe, Paola Magri, Maria A. E. Rao, Sara Cangianiello, Luca De Nicola

- **10 untreated asymptomatic HF patients (NYHA class I, LVEF 29.7±2 %) with normal renal function (sCreat 1.0 ± 0.06)**
- **10 matched normal controls (similar age, BMI, BP, sCreat and salt intake)**
- **8 days of high salt intake (15 g/day) vs low salt intake (6 g/day)**
- **24h UNaV (salt intake), renal clearances (renal hemodynamics and tubular function)**
- **Effects of 6-week treatment with Enalapril 5 mg/day**

Hypertension 1997

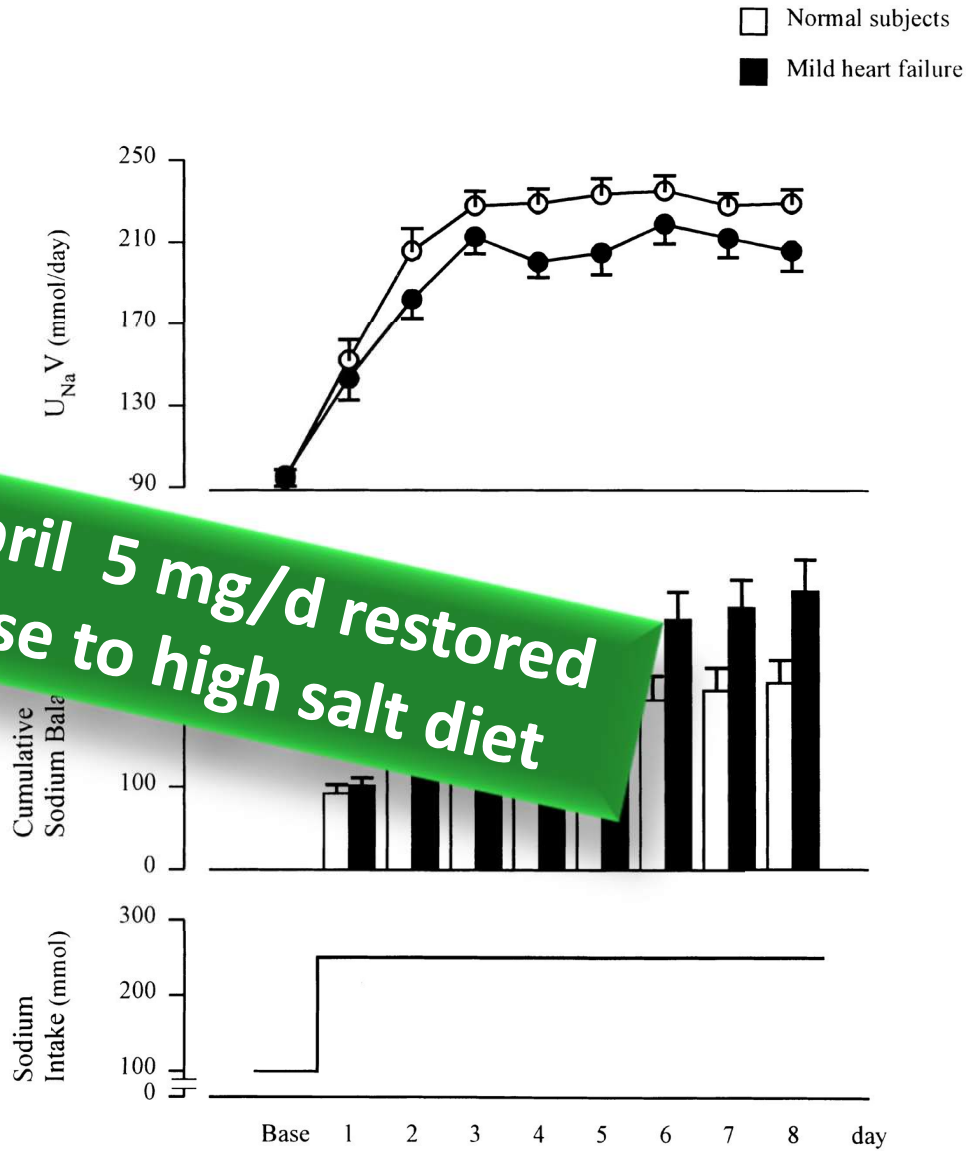
Intrarenal determinants of Na retention in mild HF

Hypertension 1997

Effects of increased
on UNaV and Na+ bala

The two groups differed in cumulative Na+ balance with increased ECV of 1.6 L in normal and 2.4 L in MHF due to increased prox tubule reabsorption at high salt diet in mild HF
(P<.001)

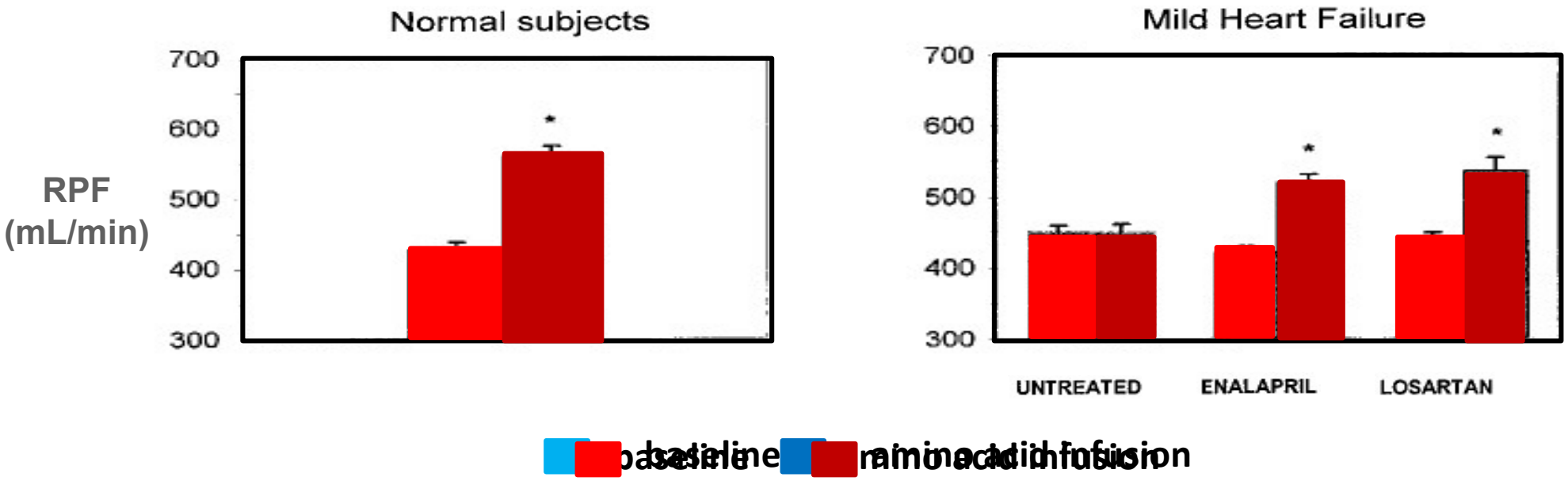
Six weeks of Enalapril 5 mg/d restored the normal response to high salt diet



Early Impairment of Renal Hemodynamic Reserve in Patients With Asymptomatic Heart Failure Is Restored by Angiotensin II Antagonism

Paola Magri, MD; Maria A.E. Rao, MD; Sara Cangianiello, MD; Vincenzo Bellizzi, MD; Rosaria Russo, MD; Alessandro F. Mele, MD; Michele Andreucci, MD; Bruno Memoli, MD; Luca De Nicola, MD; Massimo Volpe, MD

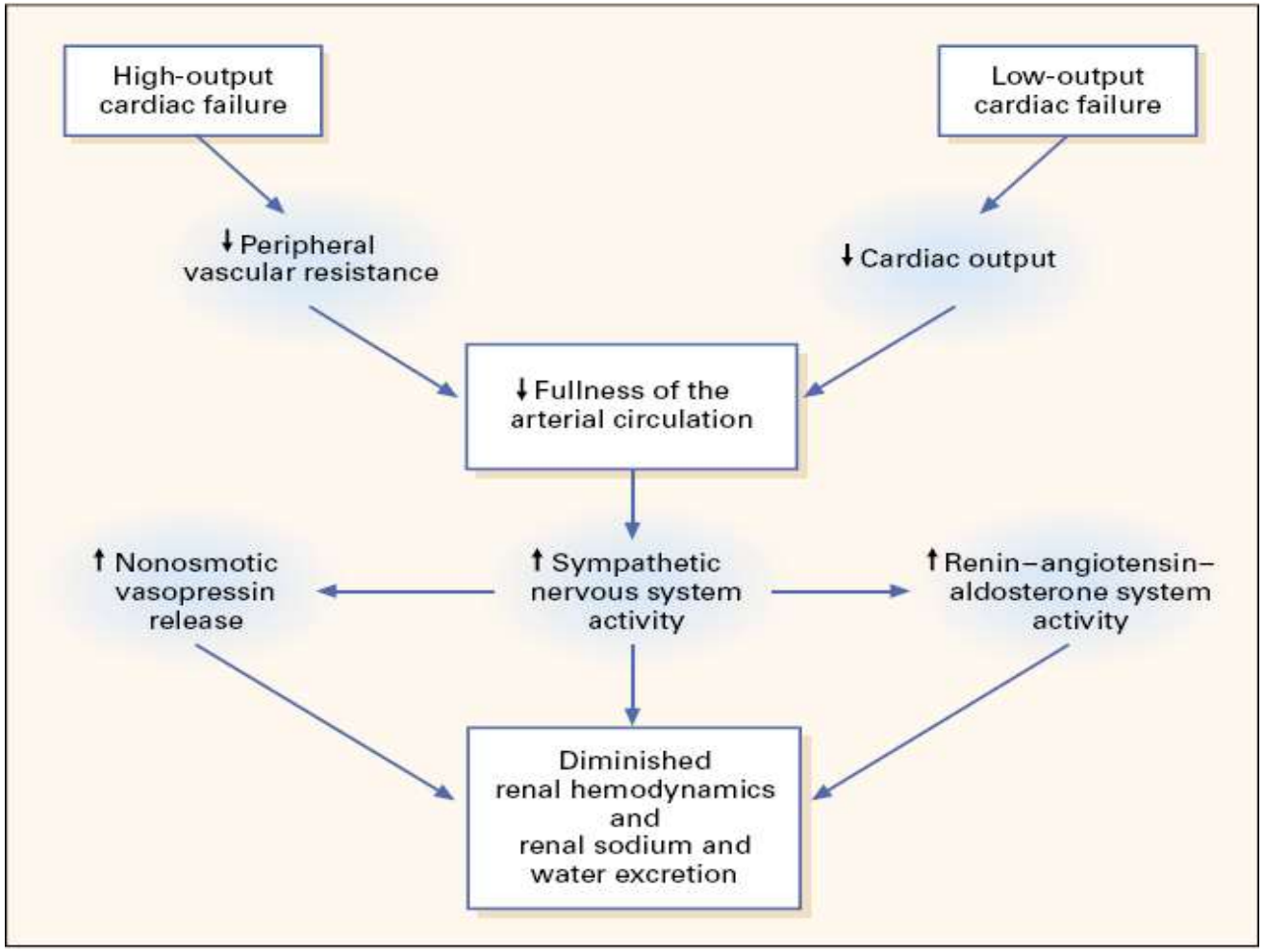
Circulation 1998



The kidney in the late stages of HF

Overt HF: Mechanisms of salt and water retention

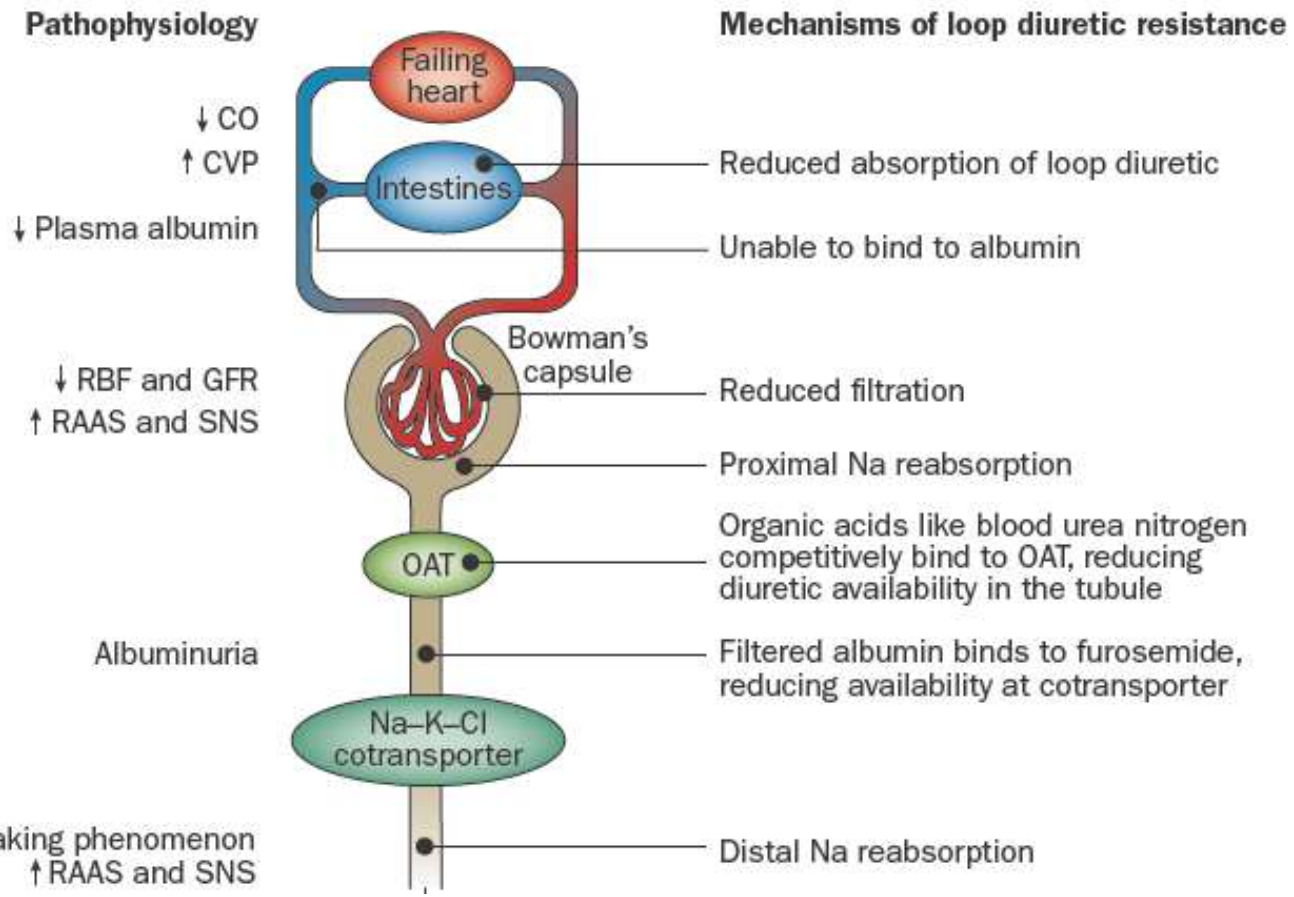
Schrier, NEJM 1999



Overt HF: Diuretic Resistance

Definition

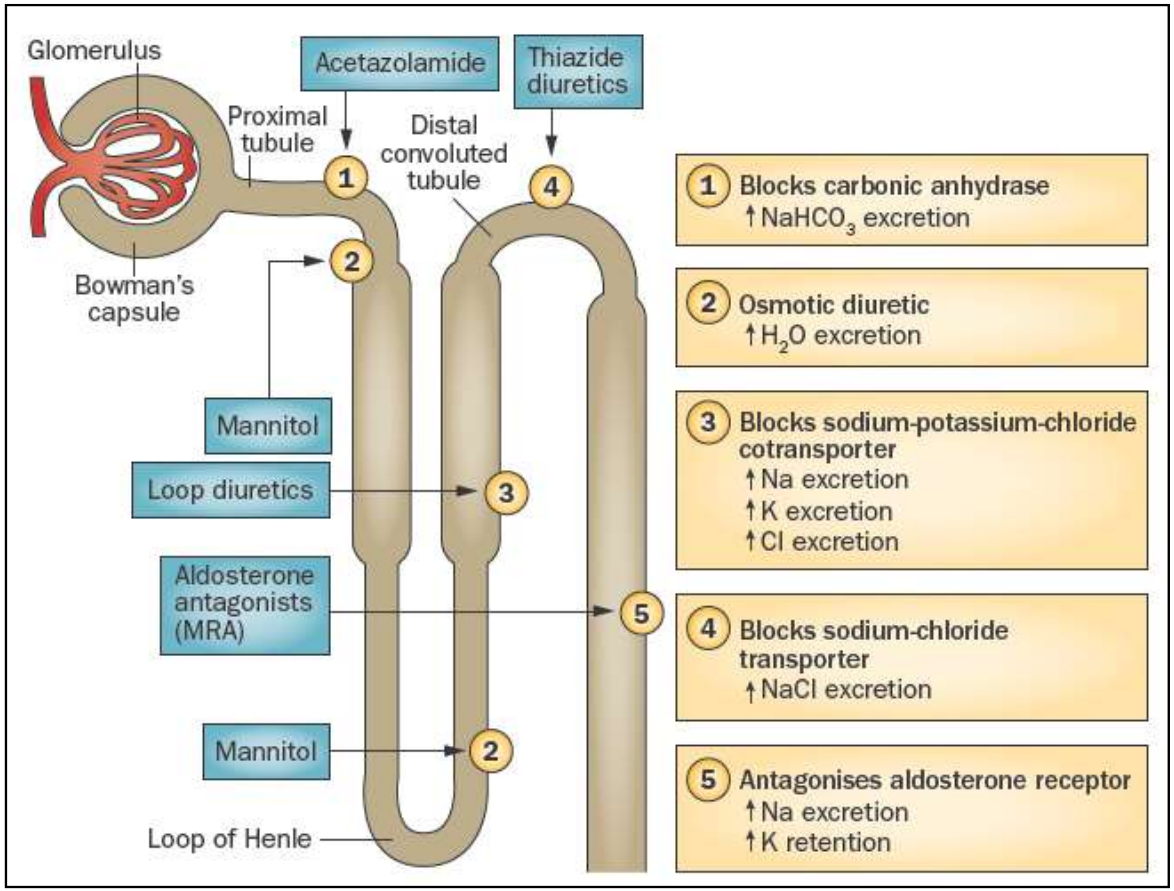
- Persistent congestion despite furosemide >80 mg/day
- Failure to excrete at least 90 mmol Na within 72 h of oral furosemide 160 mg x 2/day



ter Maaten Nat Rev Card 2015

Multiple Diuretics in HF
after efficacious salt restriction

↓ preload ⇨ ↑ heart function ⇨ ↑ renal perfusion

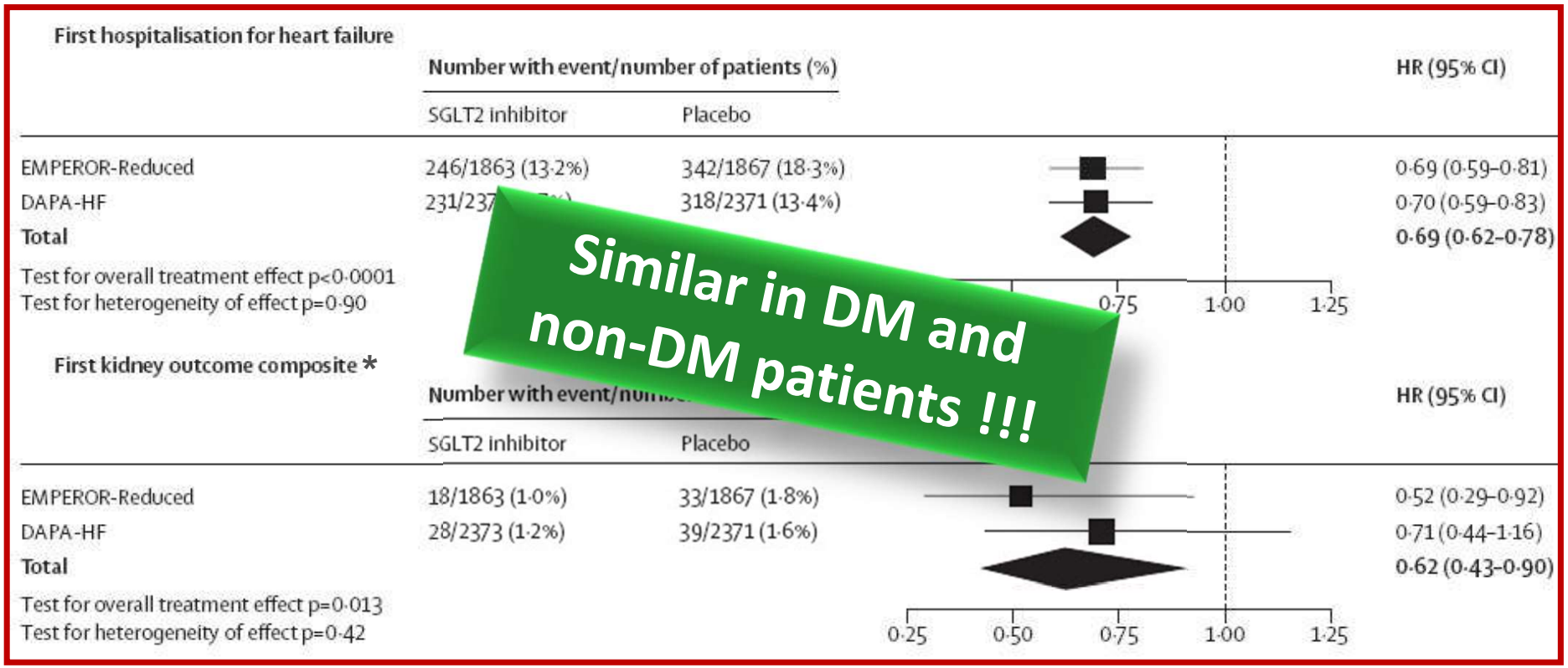


GFR (ml/min)	FUROSEMIDE (mg/die)
60-30	50-100
29-15	100-250
<15	250-500

Goal of BW decrease: 0.3-0.5 kg/day

SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials

Zannad, Lancet 30 Aug 2020



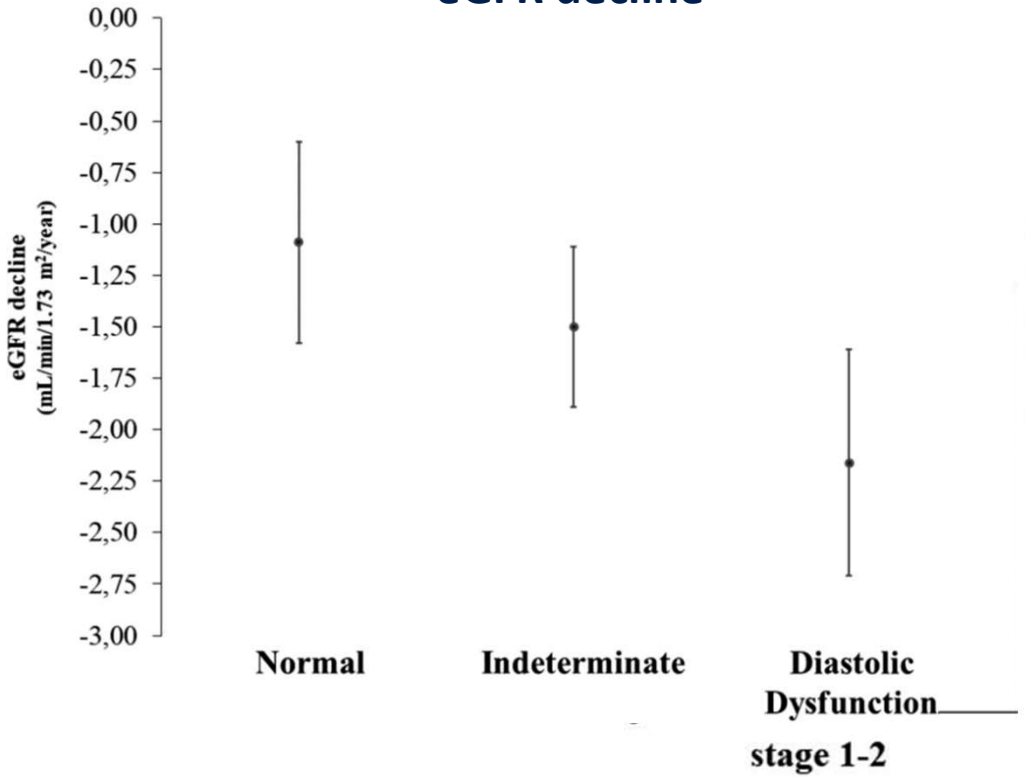
* defined as either sustained eGFR lower than 15 mL/min per 1·73 m², chronic dialysis, or renal transplant

Prevalence and renal prognosis of left ventricular diastolic dysfunction in non-dialysis chronic kidney disease patients with preserved systolic function

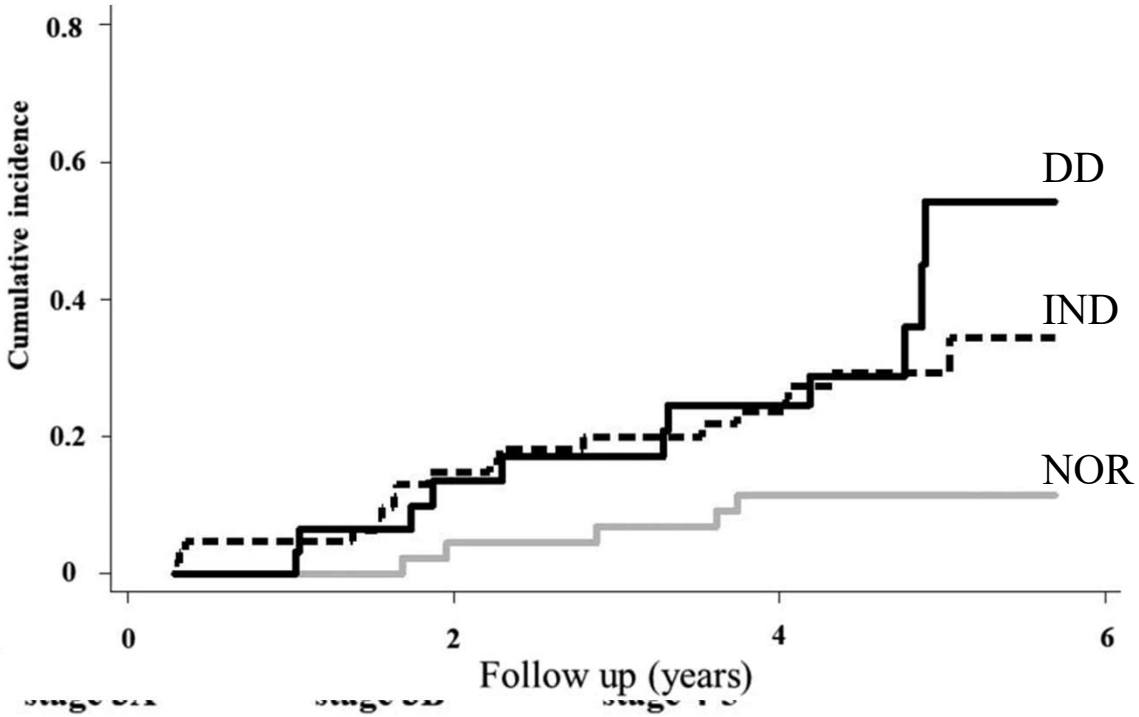
140 ND-CKD patients with LVEF >50% followed for 4.6 yrs (age 66; eGFR 39; 44% diabetics)

Prevalence of left ventricular diastolic dysfunction categories

eGFR decline



ESKD or delta GFR > 50%



Borrelli, De Nicola; J Hypertension 2022

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

- **5988 patients with HF and EF >40%**
- **Mean eGFR 61 and eGFR <60 in 50%**
- **DM2 49%**
- **FU 26.2 months**

Similar in DM and non-DM patients !!!

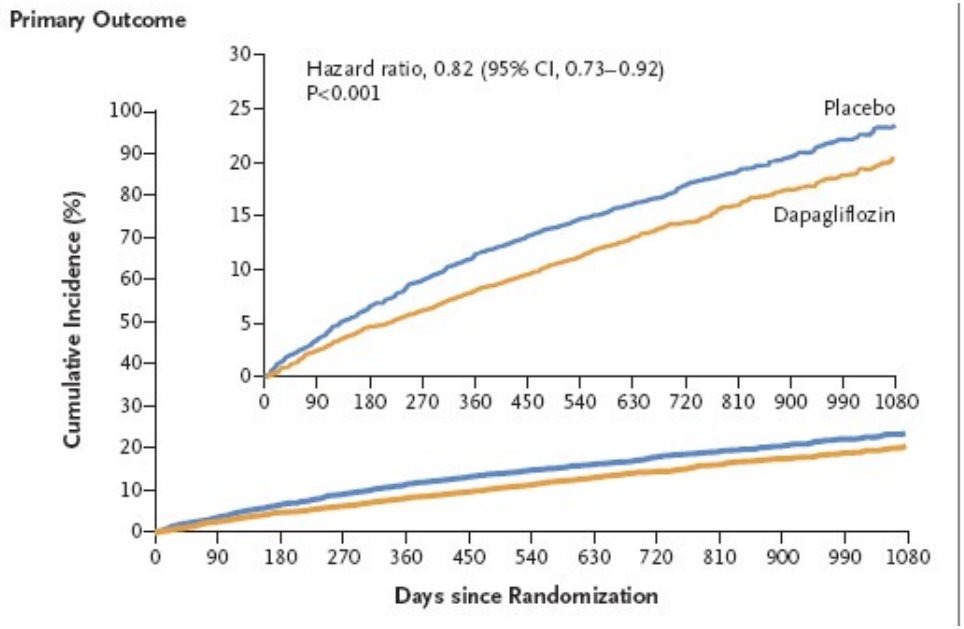
	Empagliflozin (N=2997)		Placebo (N=2991)		Hazard Ratio or Difference (95% CI)	P Value
		events per 100 patient-yr		*events per 100 patient-yr*		
Primary composite outcome — no. (%)	415 (13.8)	6.9	511 (17.1)	8.7	0.79 (0.69–0.90)	<0.001
Hospitalization for heart failure	259 (8.6)	4.3	352 (11.8)	6.0	0.71 (0.60–0.83)	
Cardiovascular death	219 (7.3)	3.4	244 (8.2)	3.8	0.91 (0.76–1.09)	
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

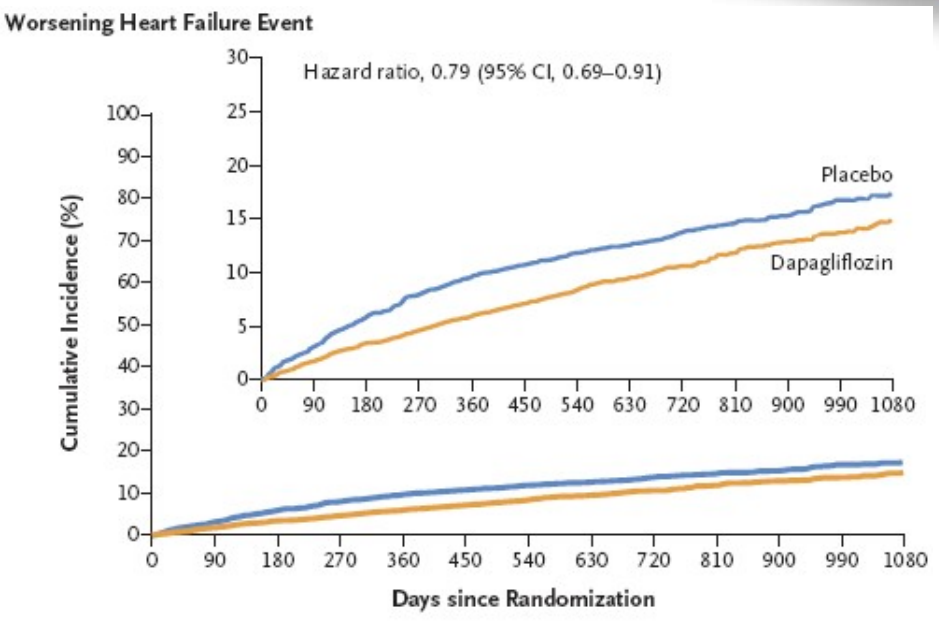
Anker for EMPEROR-Preserved group, NEJM 27 Aug 2021

Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

- **6263 patients with HF and EF >40%**
- **Mean eGFR 61**
- **DM2 45%**
- **FU 26.2 months**

Similar in DM and non-DM patients !!!





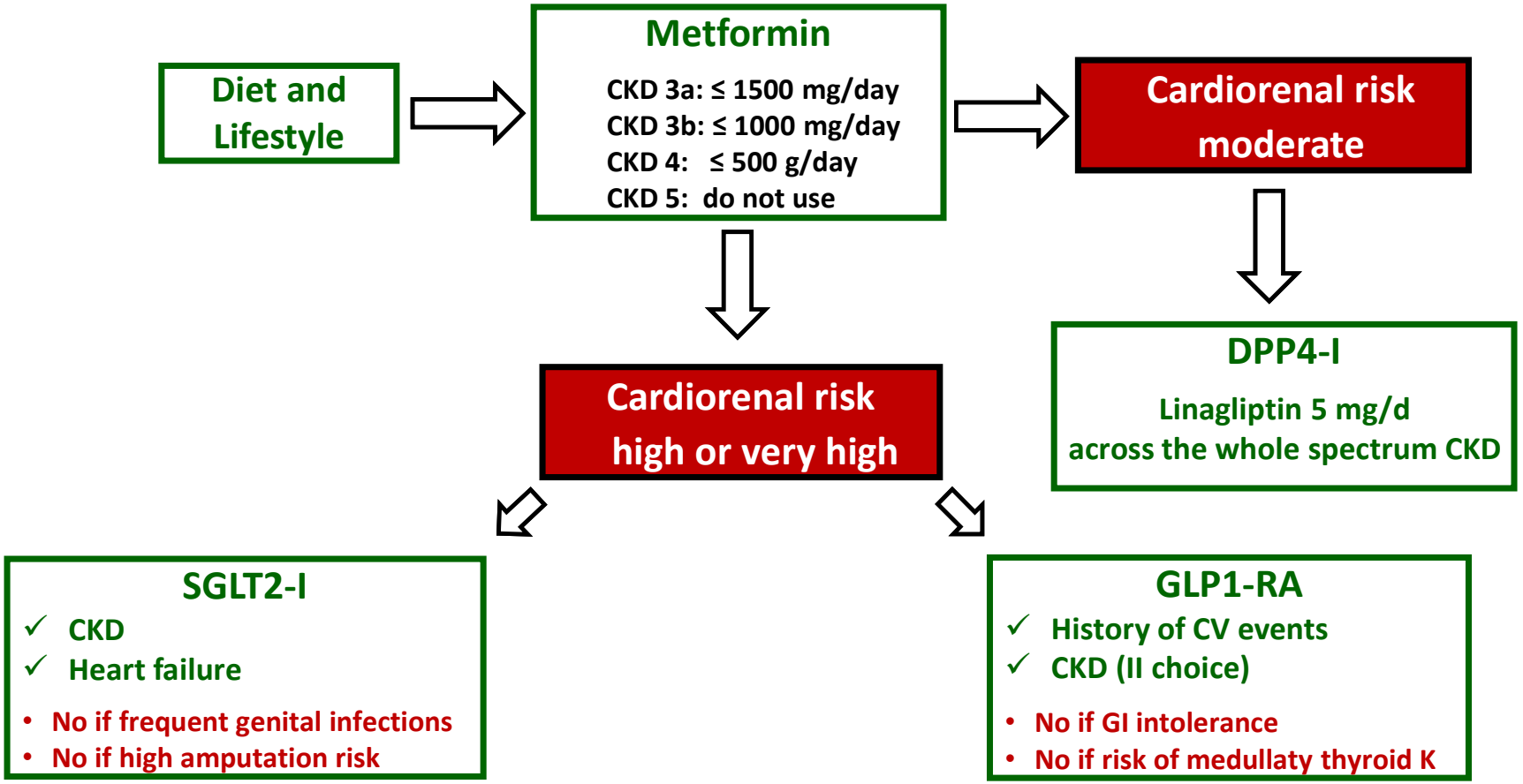
composite of worsening HF (unplanned hospitalization for HF or urgent visit for HF) or cardiovascular death

Solomon for DELIVER study group, NEJM 27 Aug 2022

Conclusions

Antihyperglycemic Treatment of DKD

Nephrologist Perspective



Renal Dysfunction in Heart Failure

Nephrologist Perspective

Ejection Fraction

RENAL ANGINA
⇧Rprox
⇩Renal reserve

ISCHEMIC KIDNEY FAILURE
⇩RPF, GFR
⇩Na and water excretion

CONGESTIVE KIDNEY FAILURE
Venous
Congestion

⇩ Natriuretic response to high salt intake

⇧ Diuretic Resistance
⇧ CKD/HF progression

Rx

- Low salt diet & RAASI

- Diuretics & SGLT2-I