Syndrome cardio-rénal

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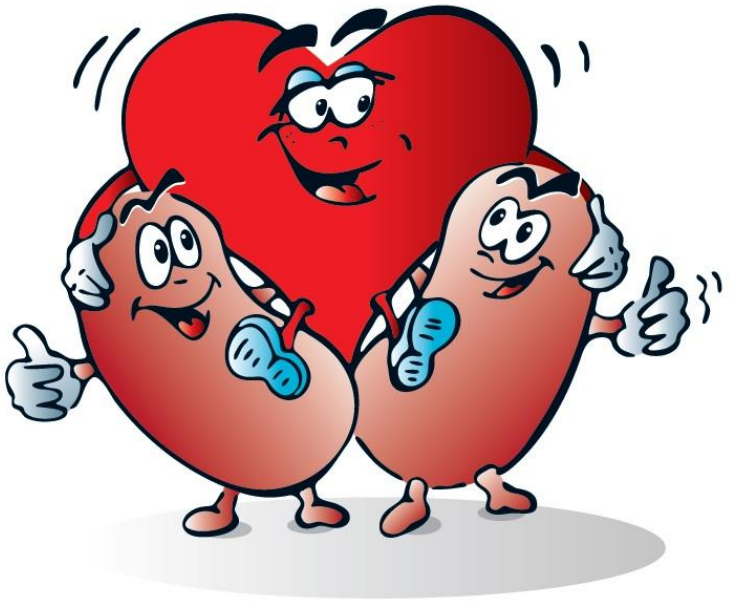
FACULTÉ DE MÉDECINE

UNIVERSITÉ DE GENÈVE

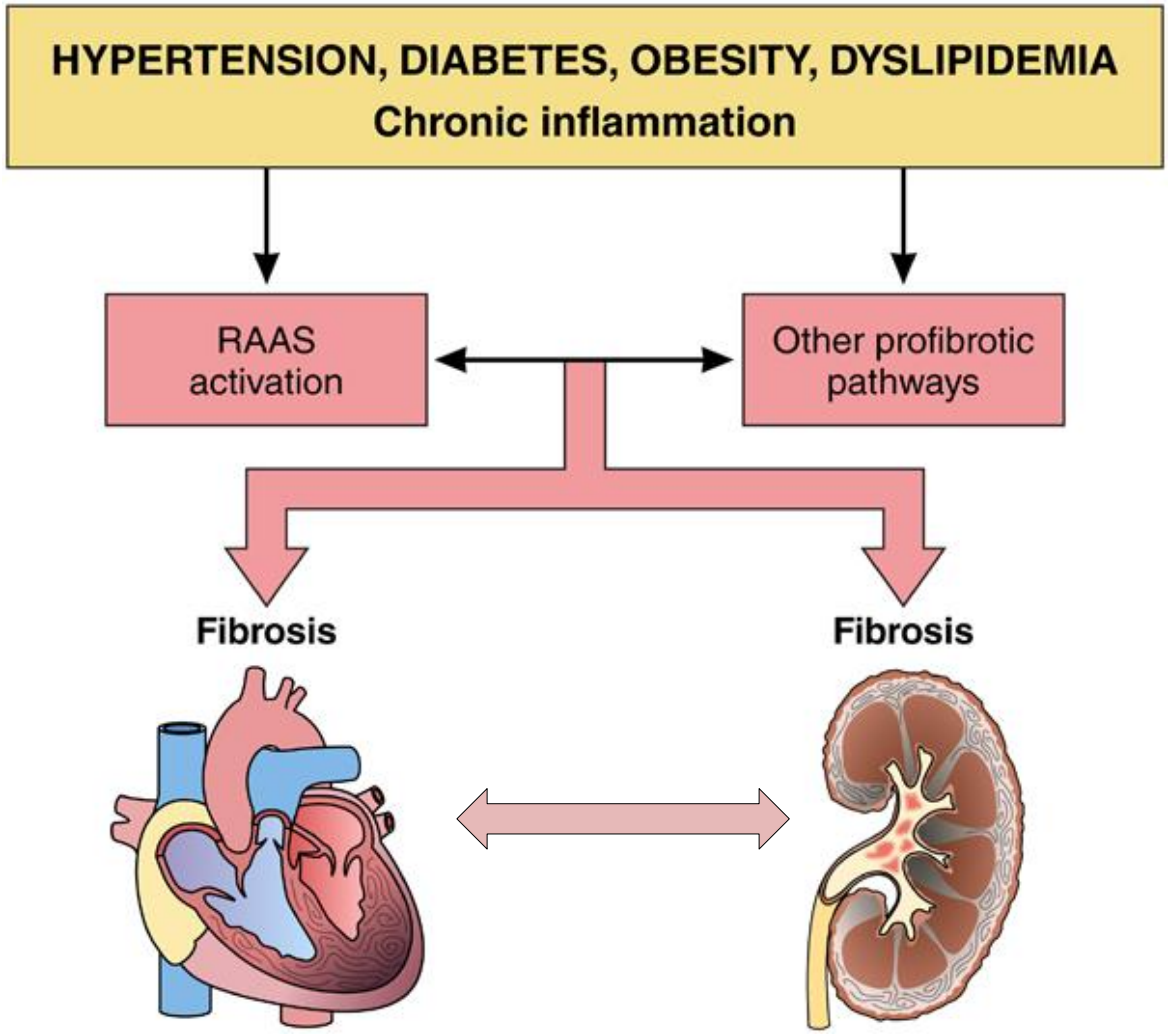
PLAN

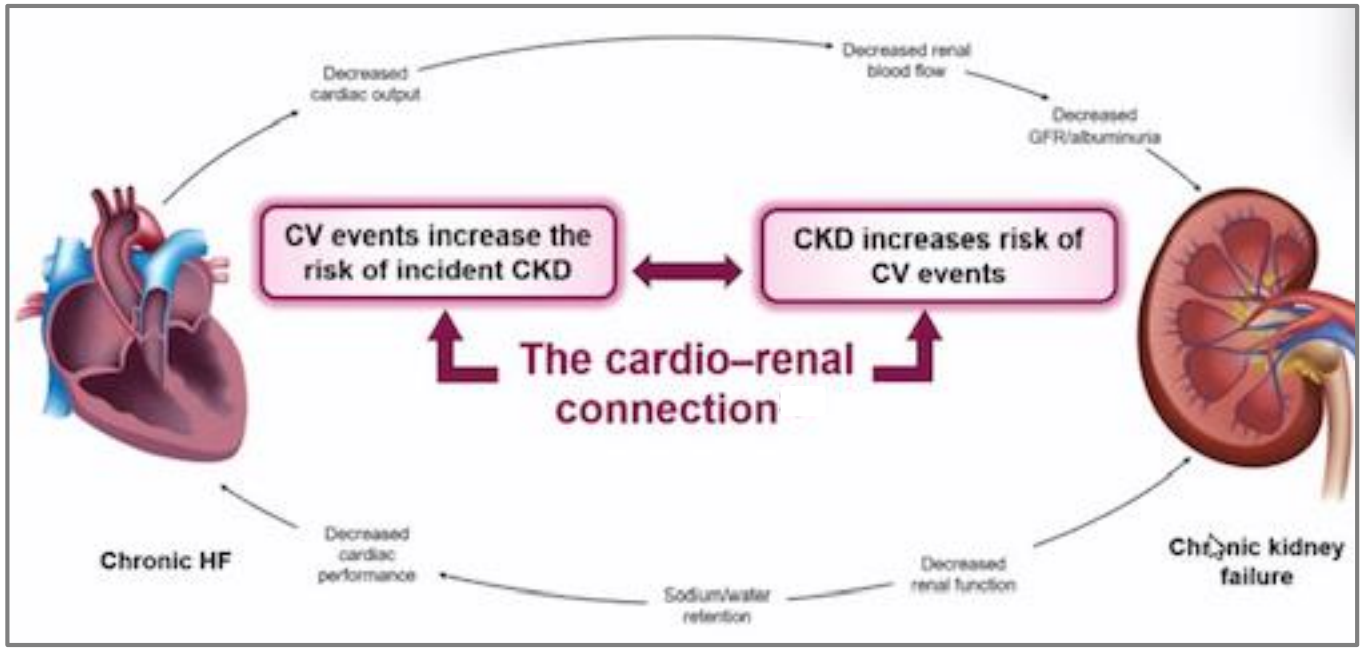
- From kidney to heart: the nephrologist point of view
- Cardiorenal «syndromes» & Physiopathology
  - Role of venous pressure
- Treatments
- Conclusions



INTRODUCTION

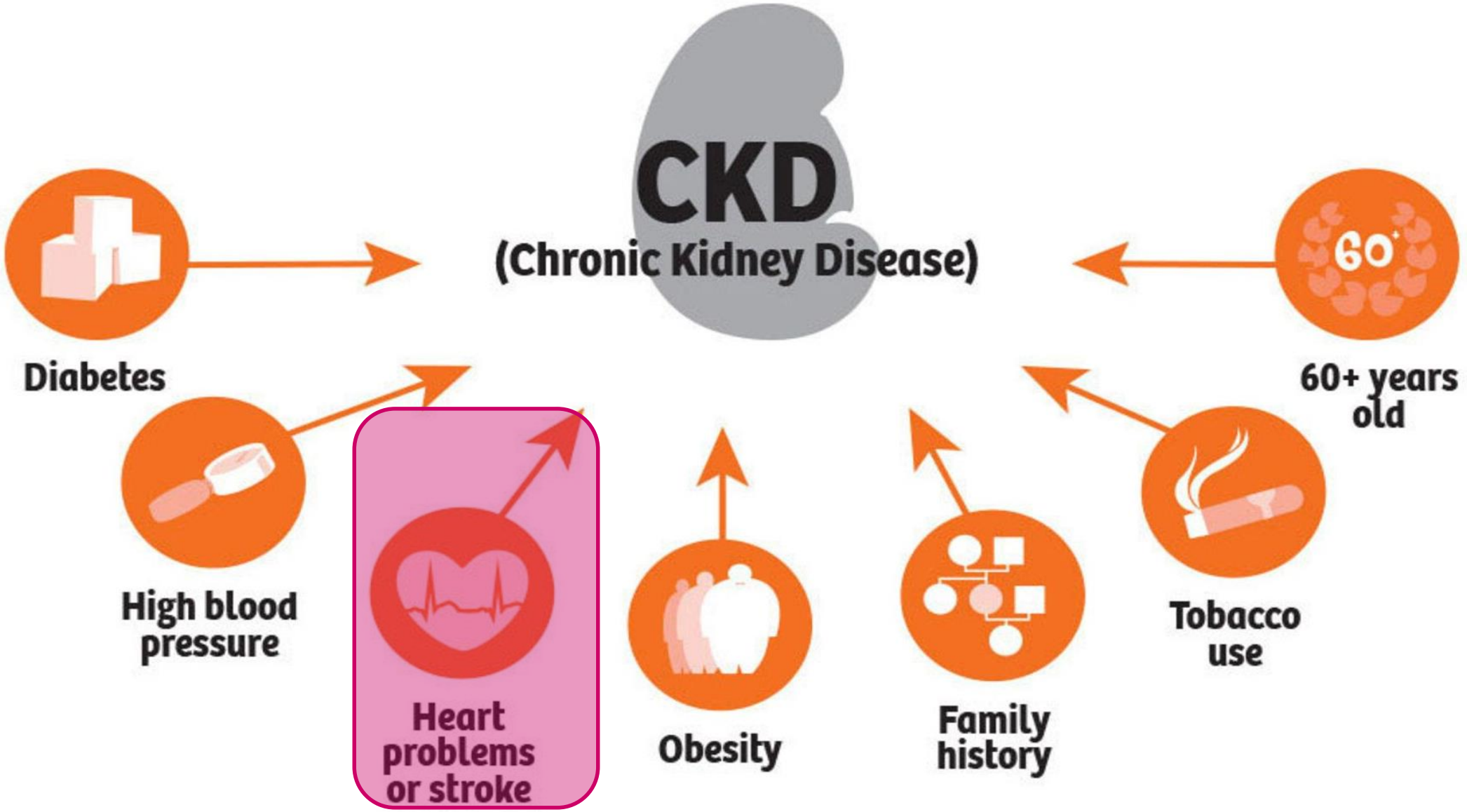
Heart and kidney have multiple bidirectionnel interactions





CKD : 30-60% in heart failure

CKD CAUSES

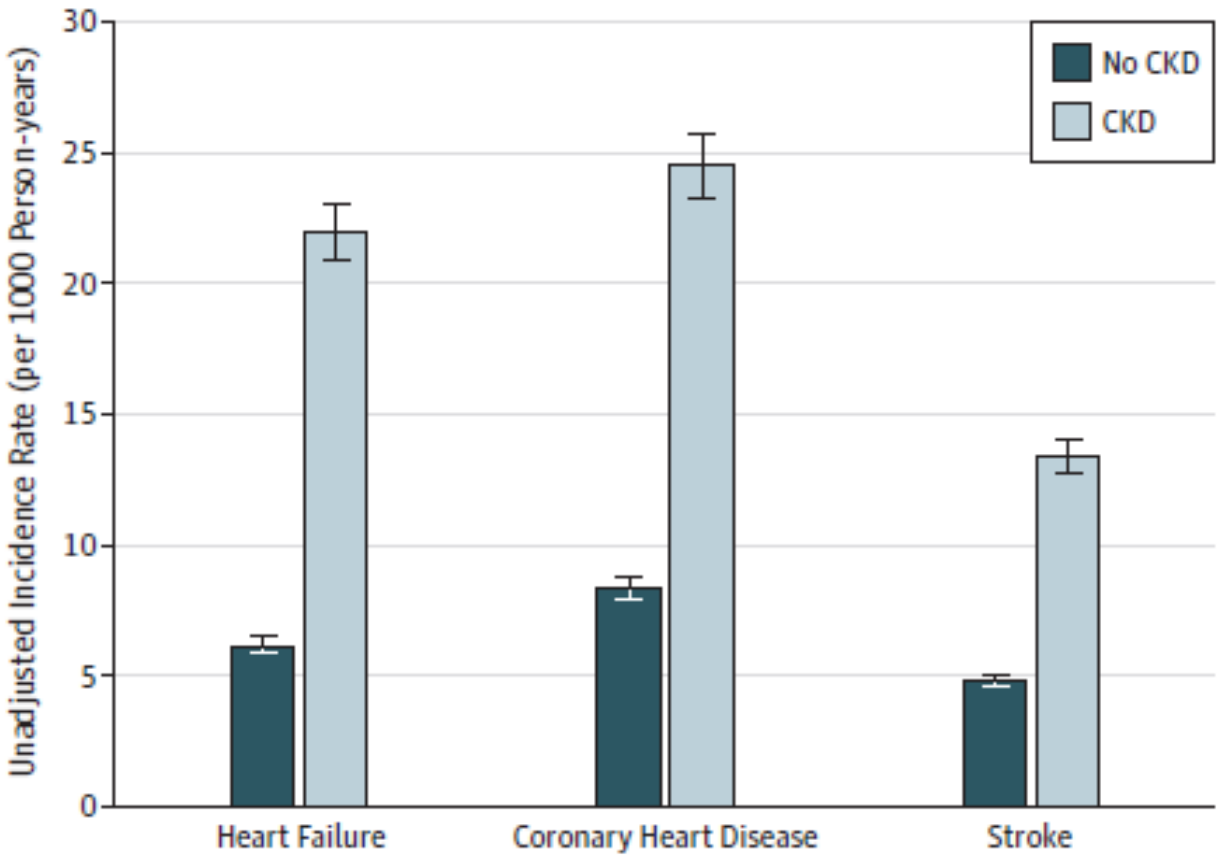

CKD
(Chronic Kidney Disease)
Diabetes
High blood pressure
Heart problems or stroke
Obesity
Family history
Tobacco use
60+ years old

JAMA Cardiology | Brief Report

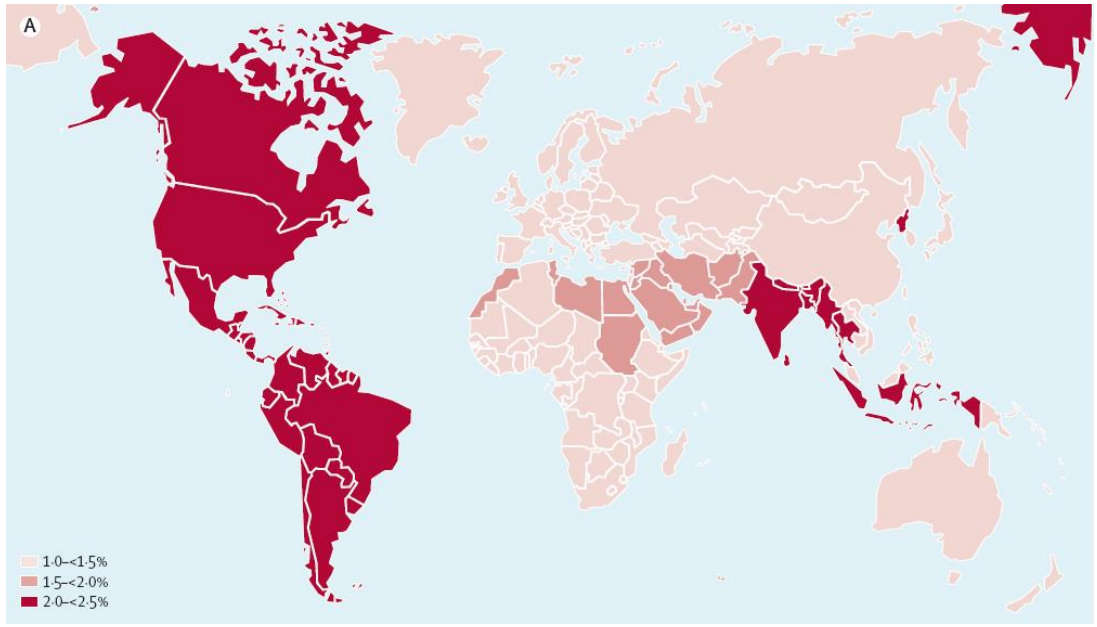
Absolute Rates of Heart Failure, Coronary Heart Disease, and Stroke in Chronic Kidney Disease

An Analysis of 3 Community-Based Cohort Studies

Bansal N. JAMA cardiol 2017



Risk differences were 15.8 (95% CI, 12.2-18.1) for heart failure, 16.1 (95% CI, 13.2-19.0) for coronary heart disease, and 8.6 (95% CI, 6.4-10.7) for stroke.



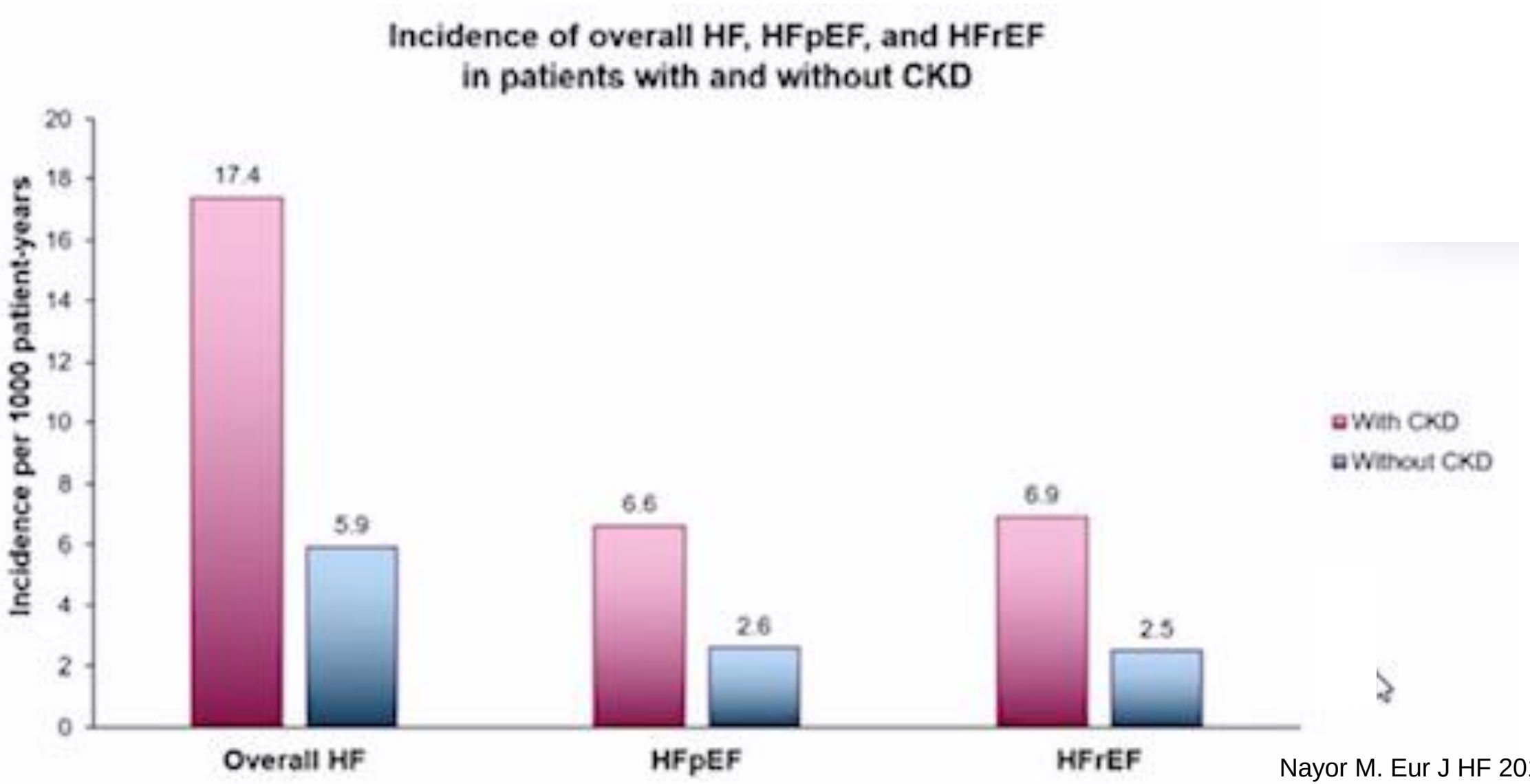
Adjusted Risk difference:

HF: 2.3 (CI:1.2-3.3)

CHD: 2.3 (CI: 1.2-3.4)

Stroke: 0.8 (CI: 0.09-1.5)

Association CKD with HF Types

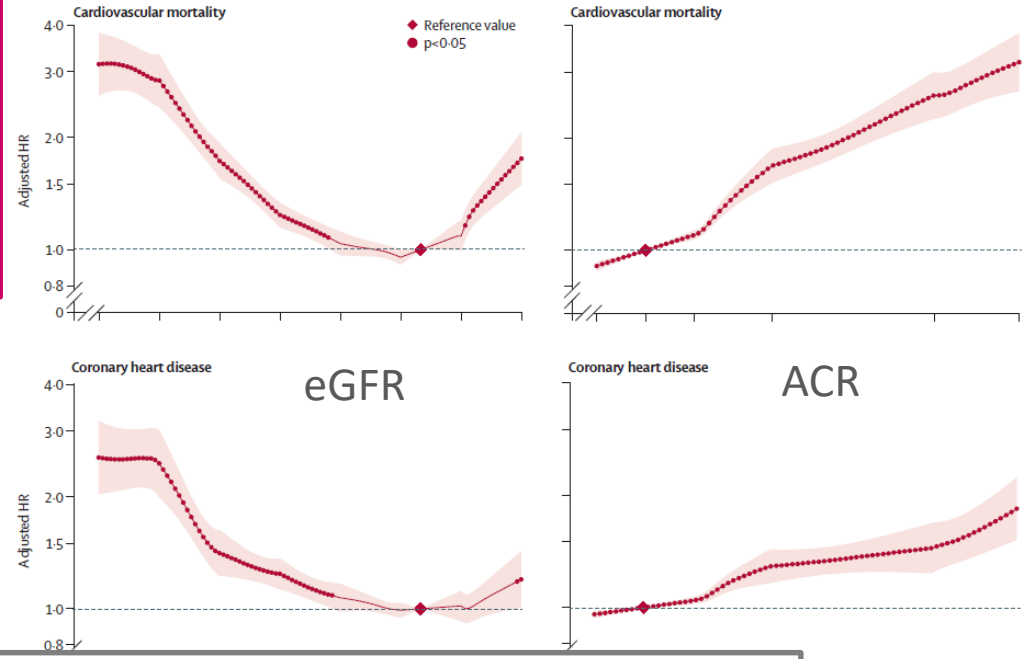


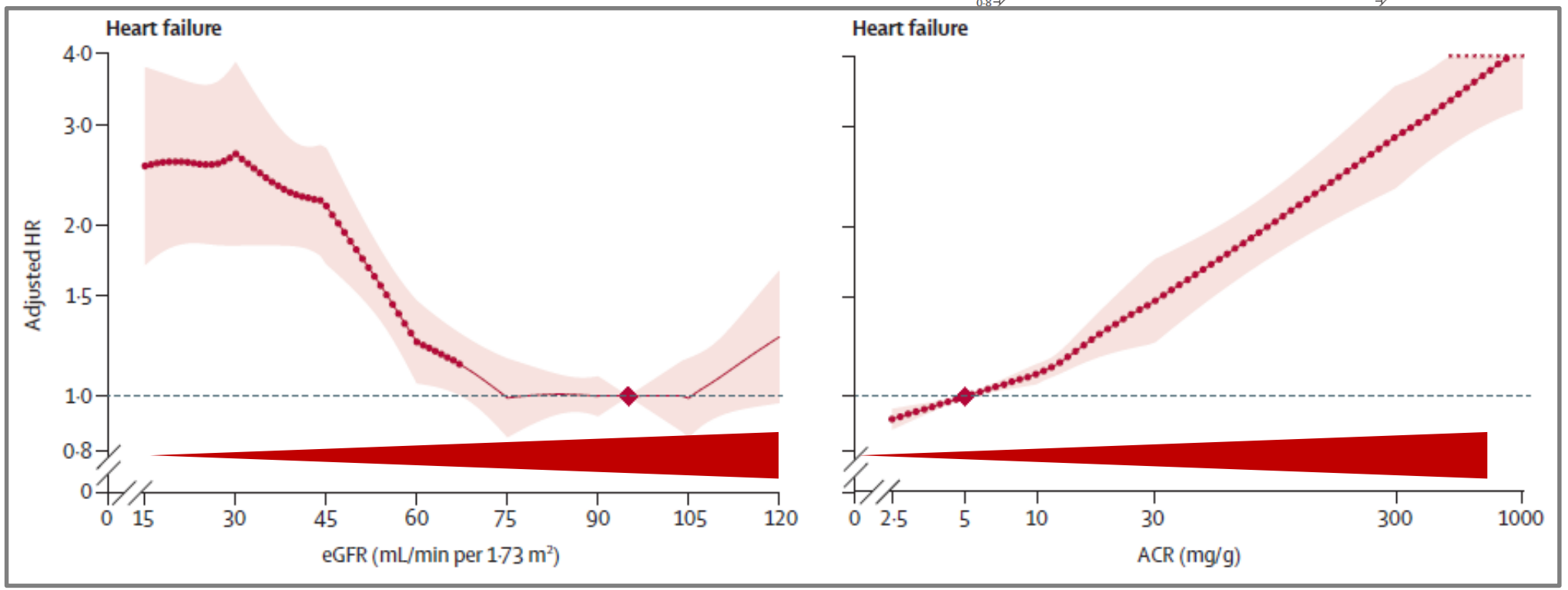
Nayor M. Eur J HF 2017

Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data

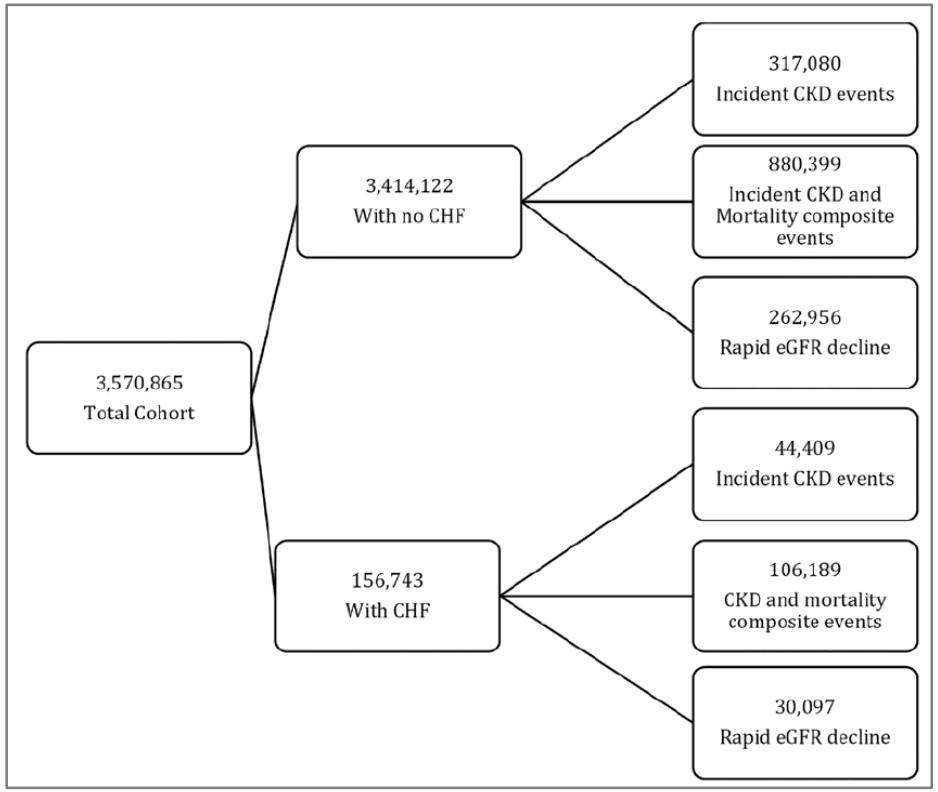
Lancet 2015

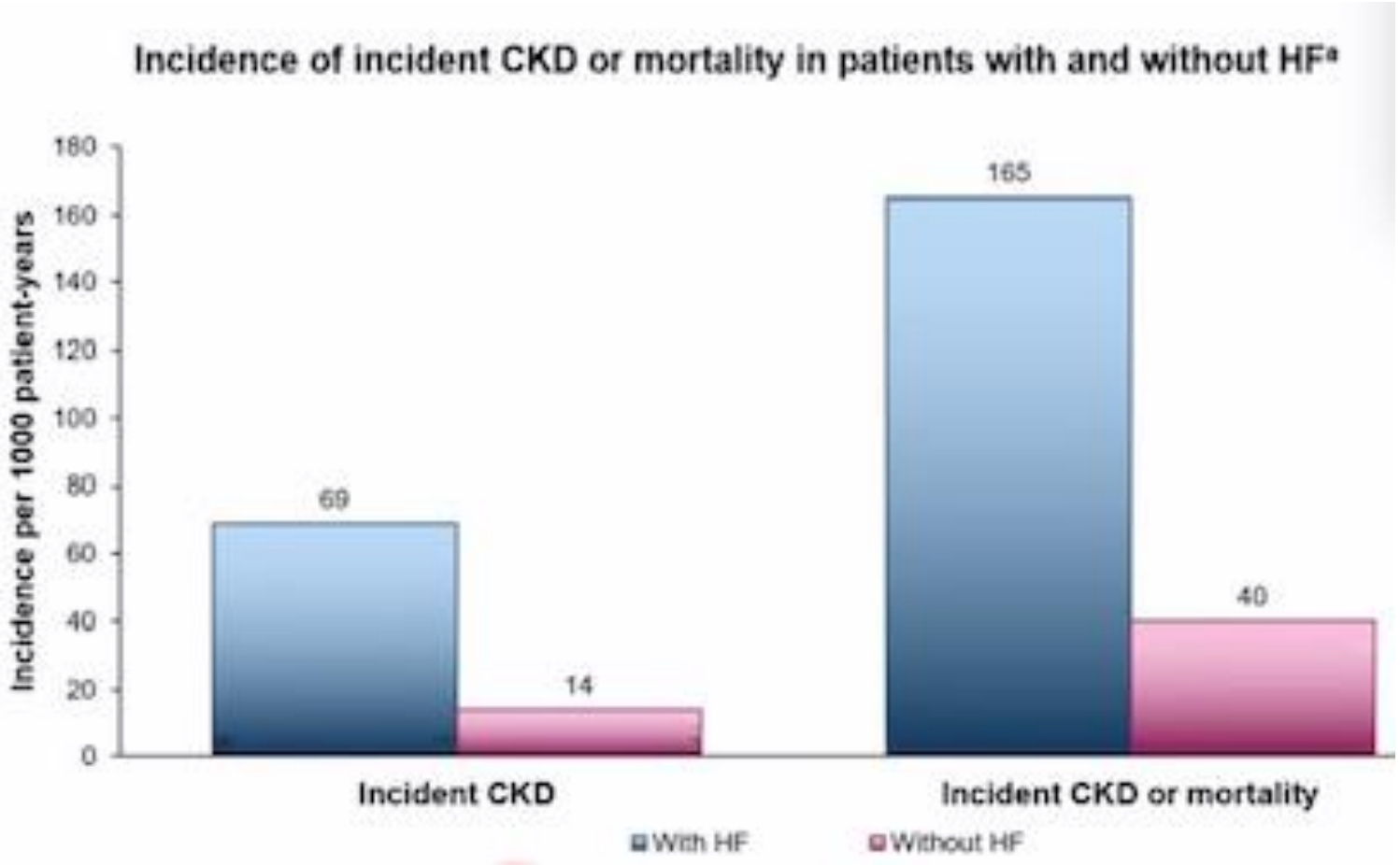
N=637’315 individuals without CVD
24 cohorts CKD consortium
Follow-up 2 years (2-19)





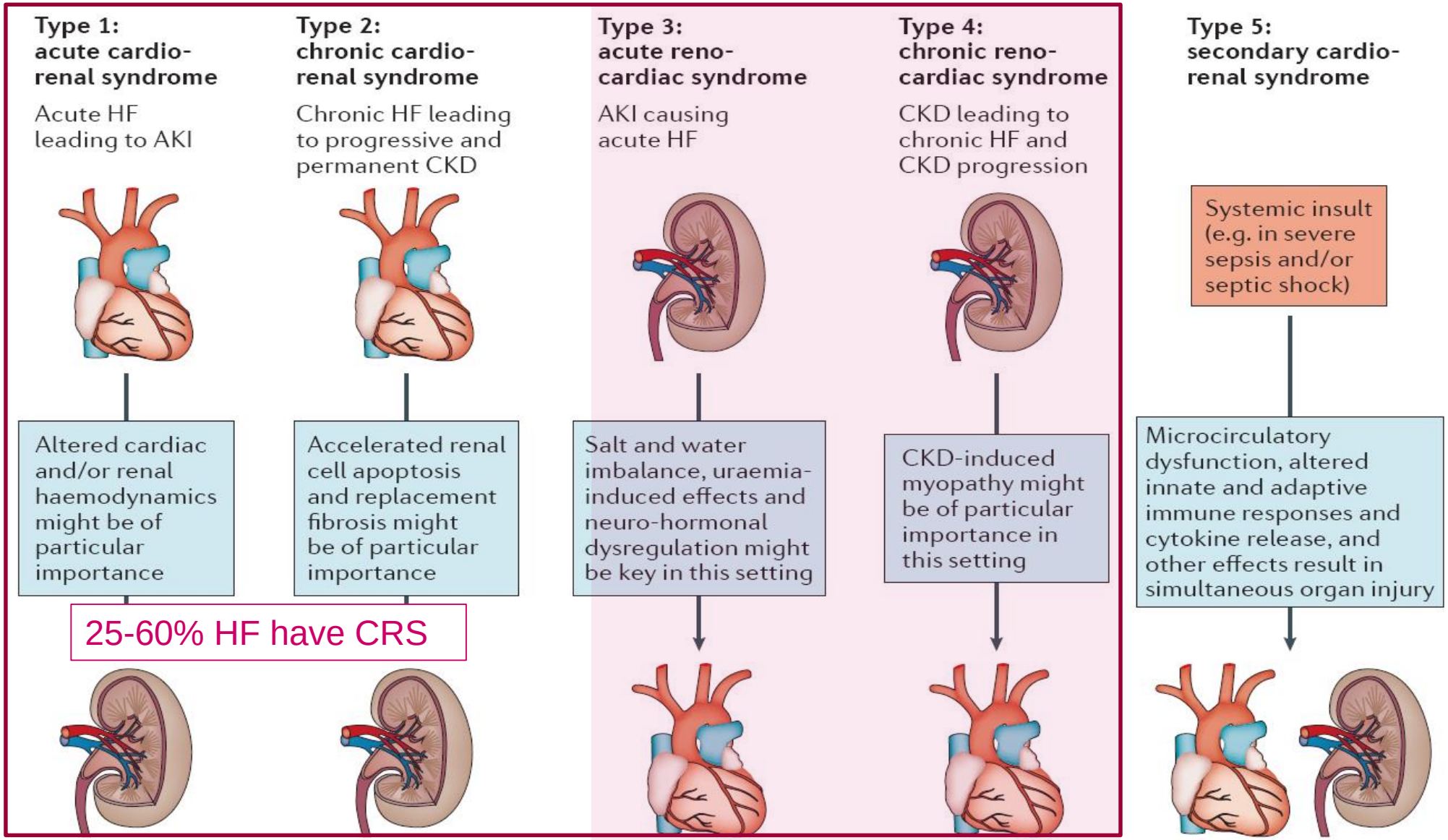
Association HF with CKD





Georges LK. Cir Heart Failure 2017

CARDIO-RENAL SYNDROMES

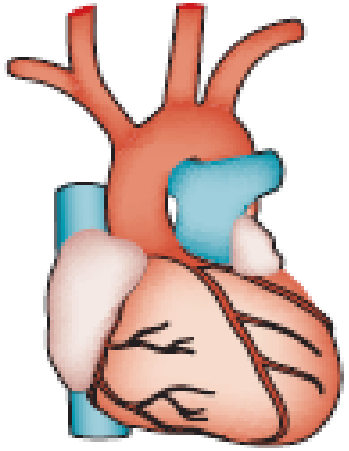


Schefold J. Nat Nephrol Rev 2016

PHYSIOPATHOLOGY - HYPOTHESIS

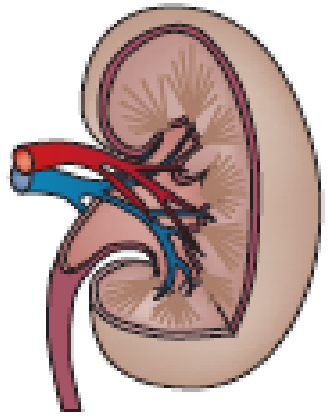
Traditional hypothesis of cardio-renal interactions

Heart failure



↓CO or CI

Renal hypoperfusion (low flow)



↑Renal vasoconstriction

Renal tubular hypoxia

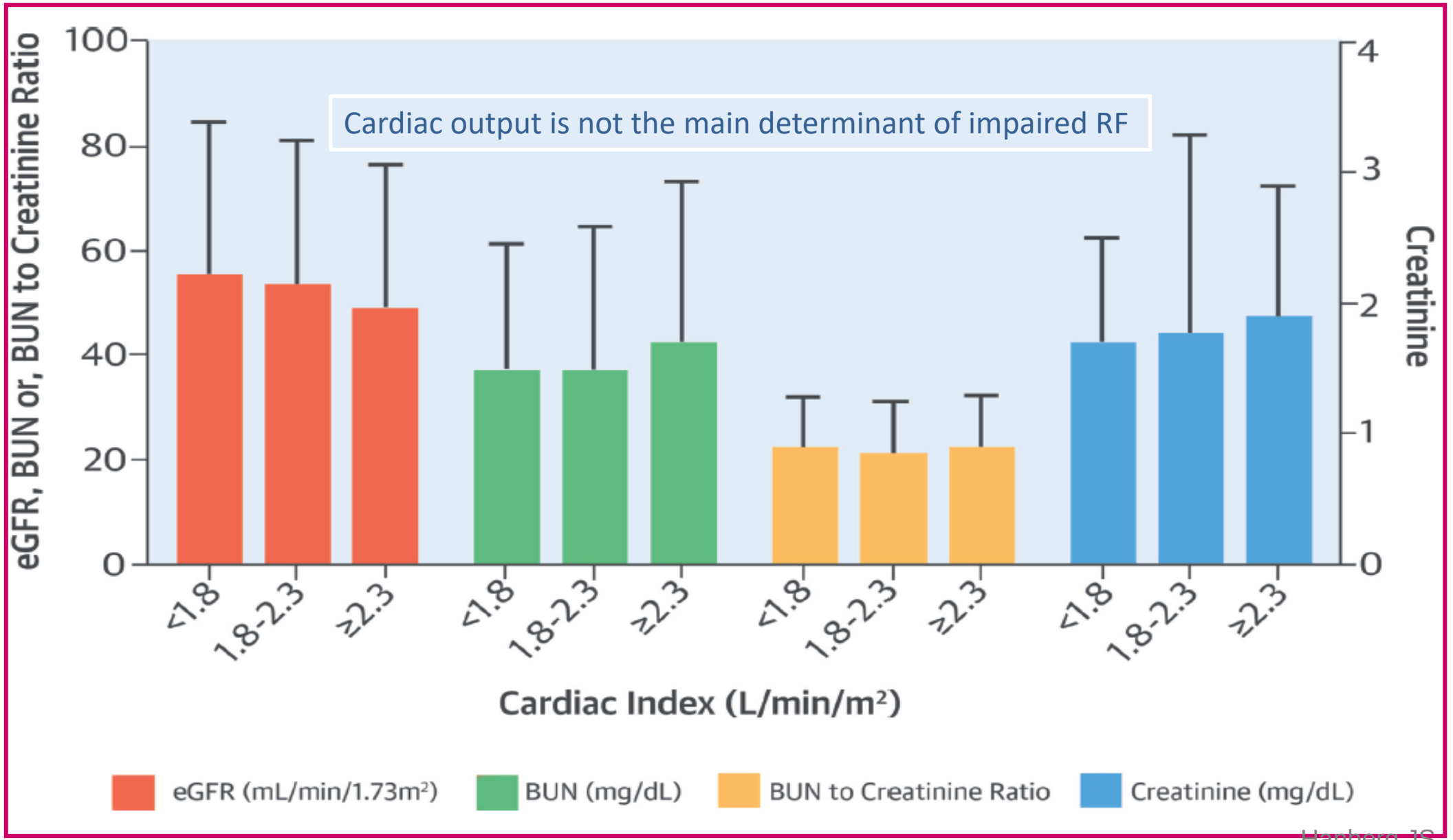
↓

(Acute) tubular necrosis

BUT ↑Renal Filtration Fraction mitigates effect of ↓Blood Flow

Mullens W. JACC 2016
Schefold J. Nat Nephrol Rev 2016

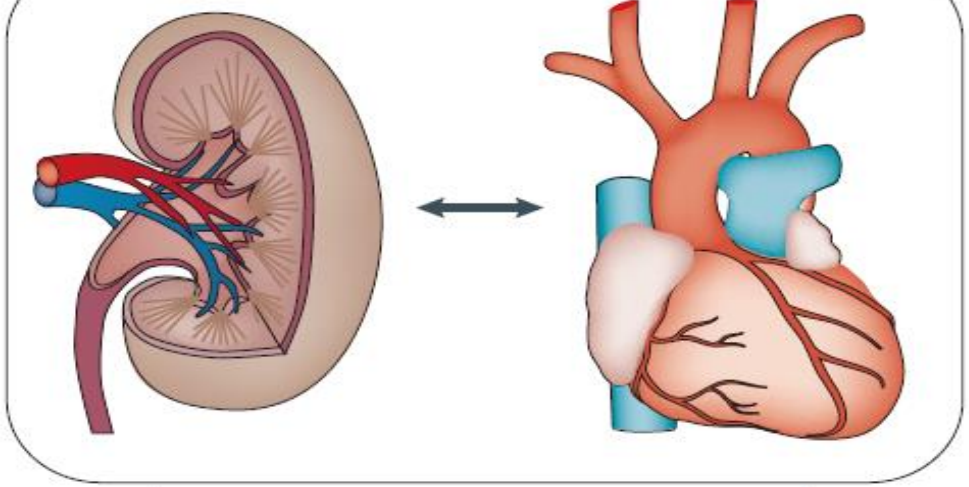
Cardiac Index and Renal Function in HF



Hanberg JS. JACC2016

NOW

Haemodynamic mechanisms 3 *
- Fluid overload and retention of salt and water
- Renal and cardiac congestion (renal venous hypertension)
- Limited organ perfusion (forward failure)
- Vasoconstriction in end organs

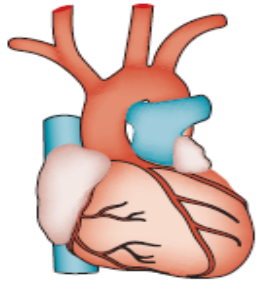


(Neuro)hormonal mechanisms 2
- Activation of the RAAS
- Activation of the sympathetic nervous system

Cardiovascular disease-associated mechanisms
- Chronic inflammation and activation of cellular immunity
- Malnutrition, cachexia and wasting
- Bone–mineral disorder
- Acid–base metabolism disorder
- Anaemia and cardio-renal anaemia

1

3 Hemodynamic



↑Cardiac congestion
↑Right arterial pressure
↑Central venous pressure

↓Cardiac output

↑Venous return

↑Effective arterial blood volume
↑Fluid overload
↑Salt and water retention

Intra-abdominal hypertension
↓Renal blood flow

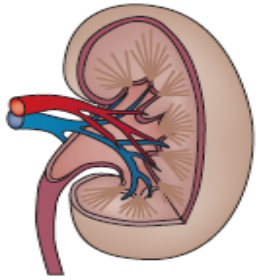
Renal venous hypertension (↑efferent pressures)

(Neuro)hormonal and inflammatory response
↑Sympathetic nervous system activity
↑RAAS
Altered arginine vasopressin
Altered ANP and BNP
↑Inflammation and immune cell activation

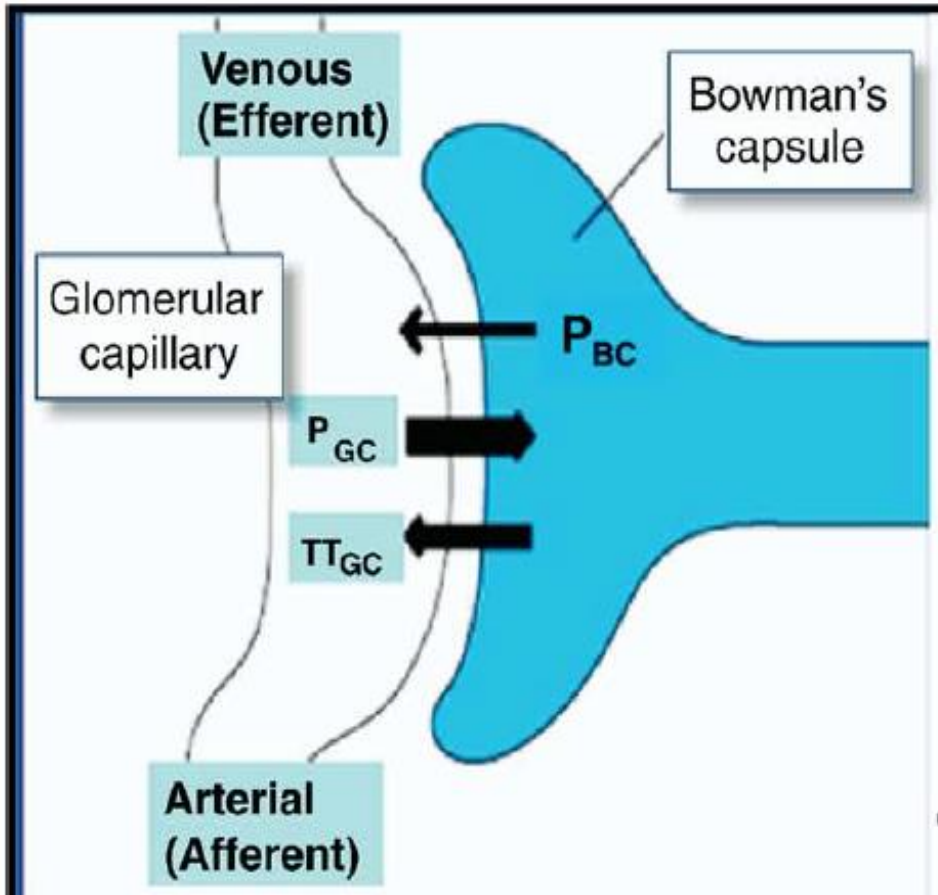
Renal congestion
↑Intraglomerular hydrostatic pressure
↑Intraglomerular pressure
↓Net filtration pressure
↓Transrenal perfusion pressure

↑Fibrogenesis

Loss of renal function
↓GFR
↓Urine output
↓Sodium excretion
↓Water excretion



↑ Venous Pressure ↓ Renal Filtration Pressure

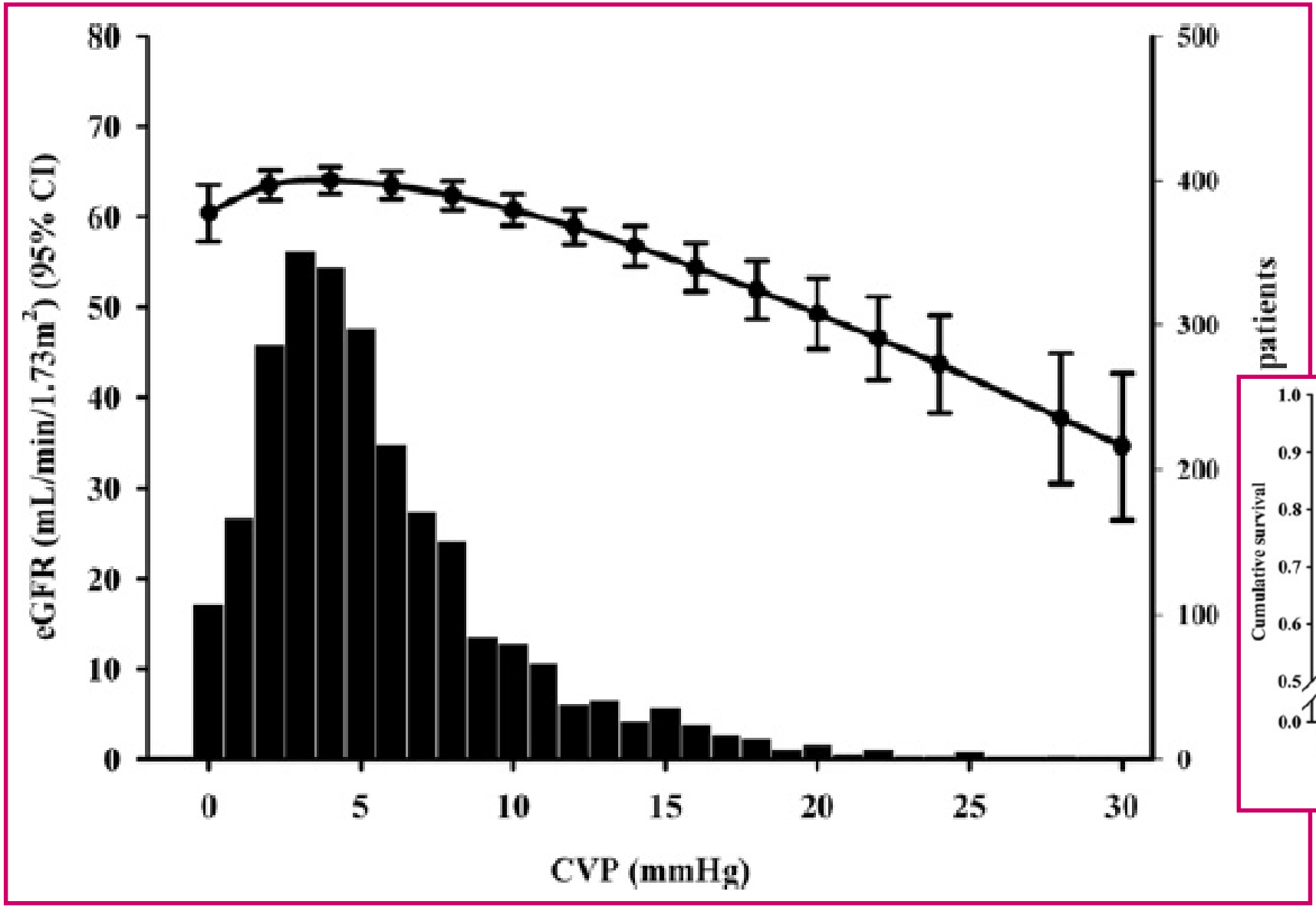


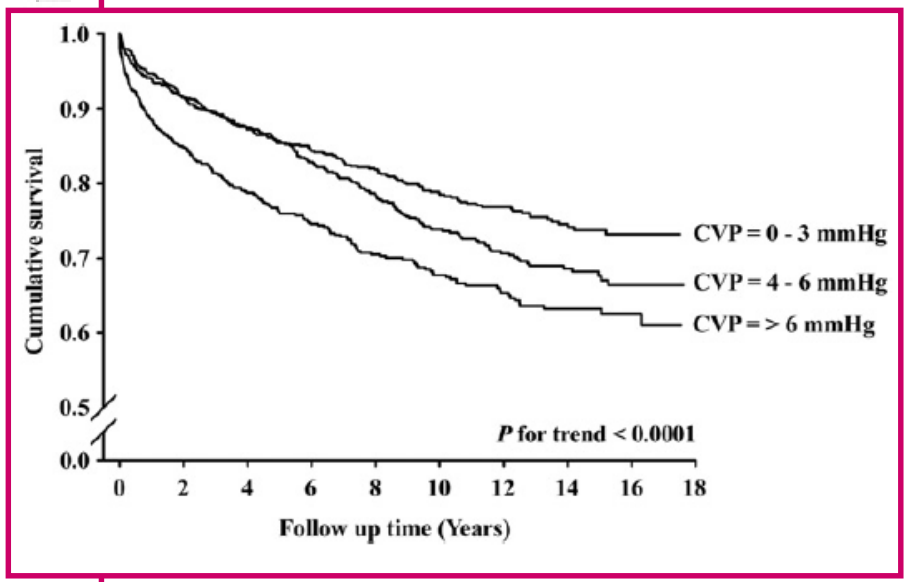
Forces	Normal: Afferent end of glomerular capillary (mmHg)	Normal: Efferent end of glomerular capillary (mmHg)	↑ RA pressure: Afferent end of glomerular capillary (mmHg)	↑ RA pressure: Efferent end of glomerular capillary (mmHg)
1. Favoring Filtration				
Glomerular-capillary hydrostatic pressure, P_{GC}	60	58	55	63
2. Opposing Filtration				
a. Hydrostatic pressure in Bowman's capsule, P_{BC}	15	15	15	15
b. Oncotic pressure in glomerular capillaries, π_{GC}	21	33	21	33
Net filtration pressure (1-2)	24	10	19	15
Filtration pressure:	*14 mmHg*		*4 mmHg*	

↓ Net Filtration Pressure = $(PHydro_{Glom} – PHydro_{Cap}) – (PHydro_{BC} + POncotique_{Cap})$

Jessup. JACC 2009

Central Venous Pressure and Renal Function Worsening (WRF)





Damman K. JACC 2009

TERMINOLOGY RENAL FUNCTION IN HF

ESC. JACC 2020

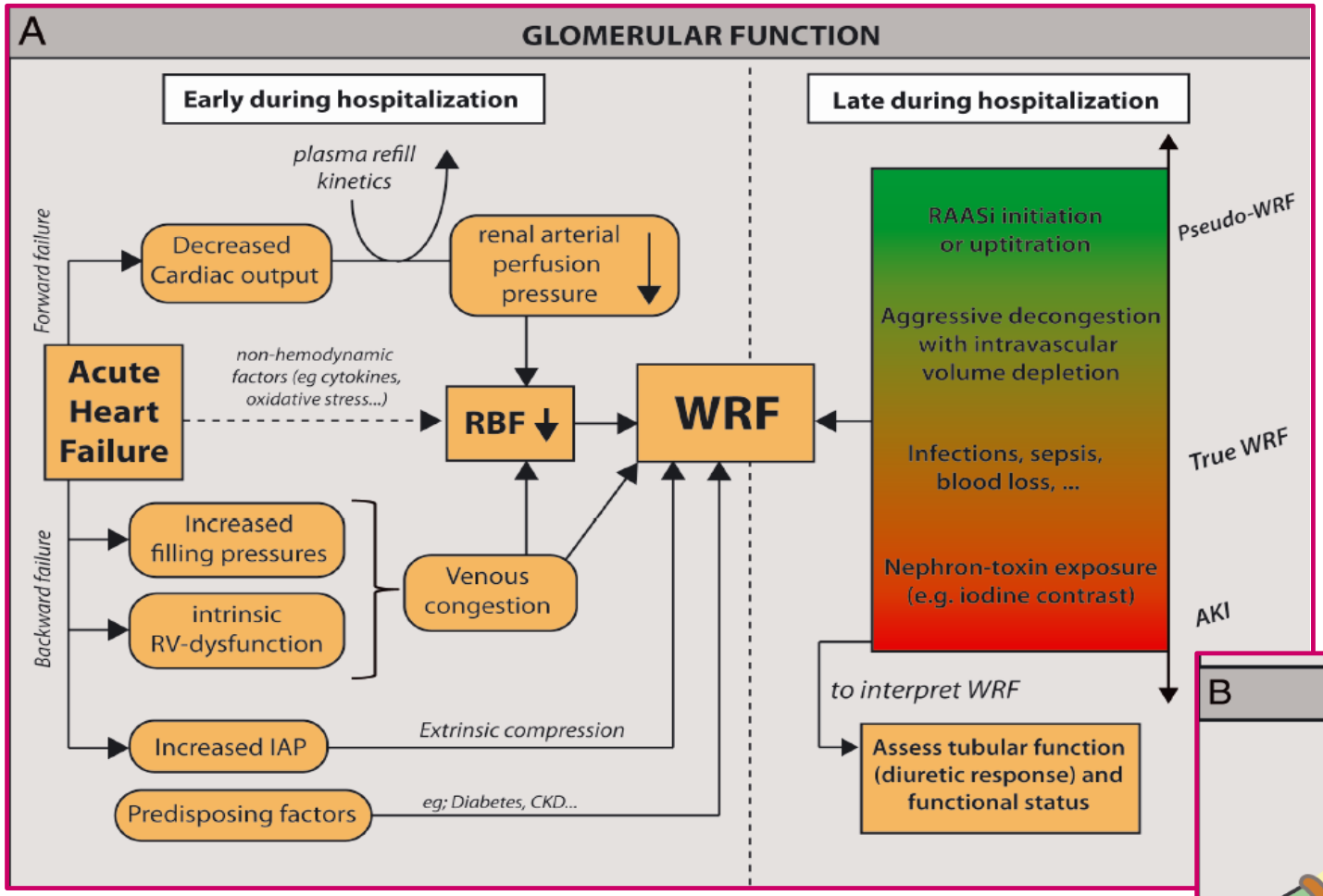
WRF = Worsening Renal function

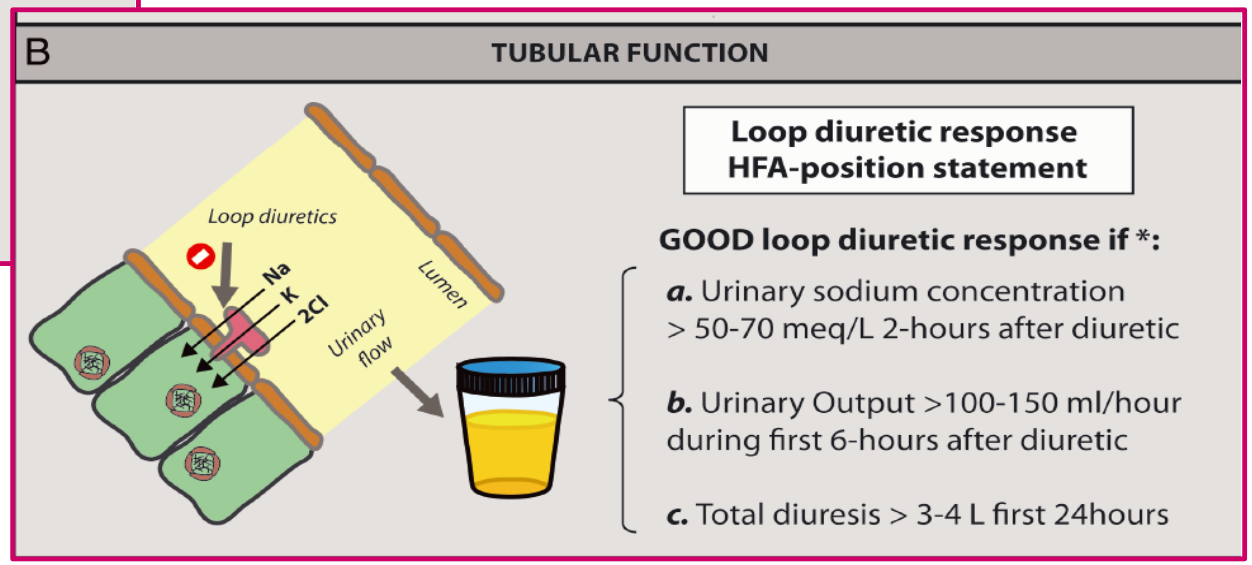
GFR-based definitions	Cystatin C-based definitions	Creatinine-based definitions
• ≥20% decrease • ≥25% decrease • >5 mL/min/1.73 m^2 per year decrease	• >0.3 mg/dL increase	• ≥0.3 mg/dL increase • ≥0.3 mg/dL increase and >25% increase • ≥0.5 mg/dL increase • 1.5× baseline • >25% increase + above 2.0 mg/dL

AKI

UO component	Scr component		
	KDIGO	**AKIN**	**RIFLE**
Grade 1			
<0.5 mL/kg/h for 6-12 h	Scr to 1.5–1.9× baseline over 7 days or absolute increase ≥0.3 mg/dL over 48 h	Scr to 1.5–2.0× baseline or absolute increase ≥0.3 mg/dL over 48 h	Scr to ≥1.5× within 7 days sustained for 24 h
Grade 2			
<0.5 mL/kg/h for ≥12 h	Scr to 2.0–2.9× baseline	Scr >2.0–3.0× baseline	Scr ≥2.0×
Grade 3			
<0.3 mL/kg/h for ≥24 h or anuria for ≥12 h	Scr to ≥3.0× baseline or increase above ≥4.0 mg/dL or RRT	Scr to ≥3.0× baseline or increase above ≥4.0 mg/dL (with absolute increase >0.5 mg/dL) or RRT	Scr to ≥3.0× baseline or increase above ≥4.0 mg/dL (with absolute increase >0.5 mg/dL) or RRT

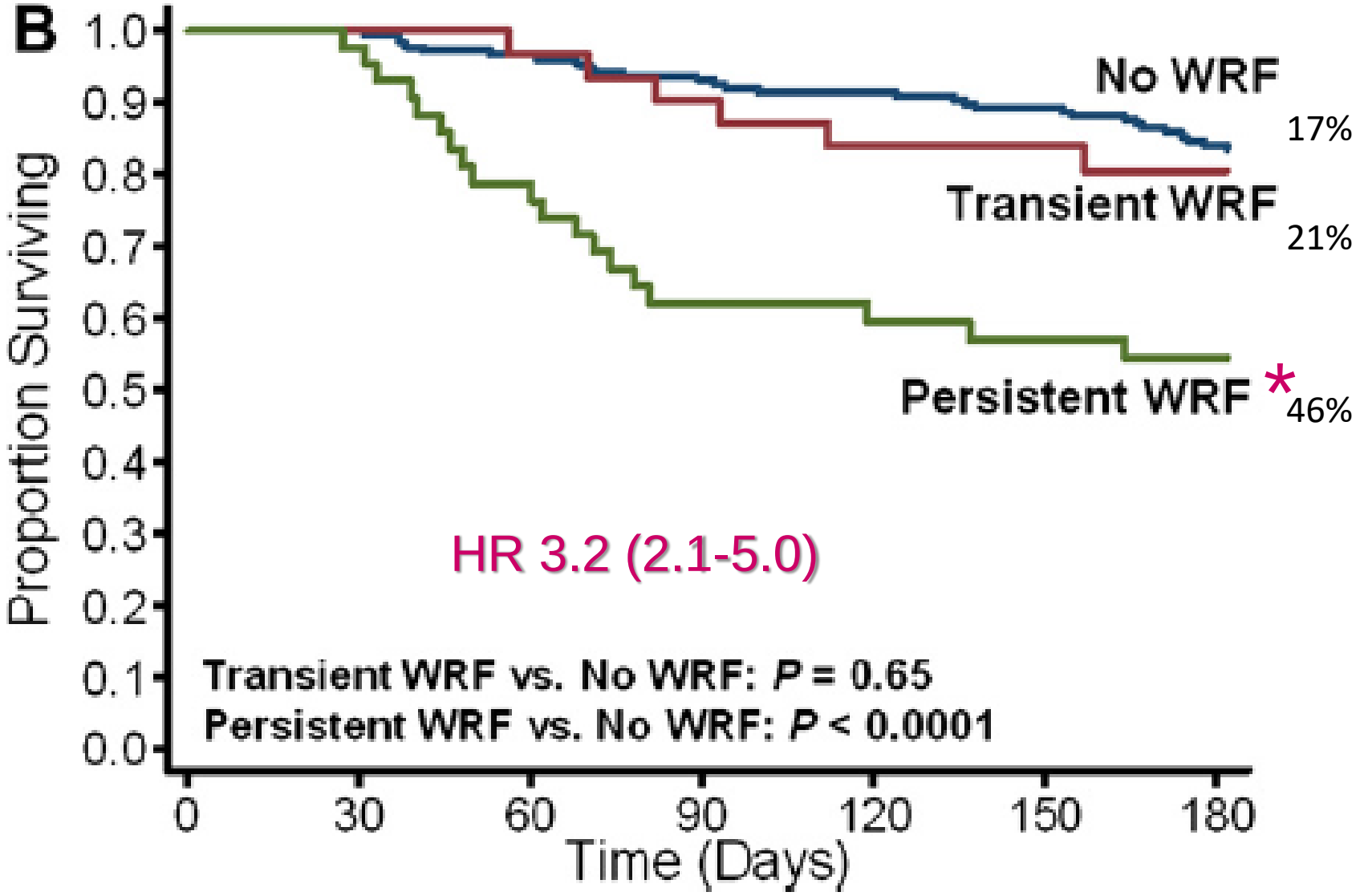
Clinical context has to be integrated when assessing creatinine elevation





ESC position paper.
Eur J Heart F 2020

Only persistent WRF is associated with increased mortality

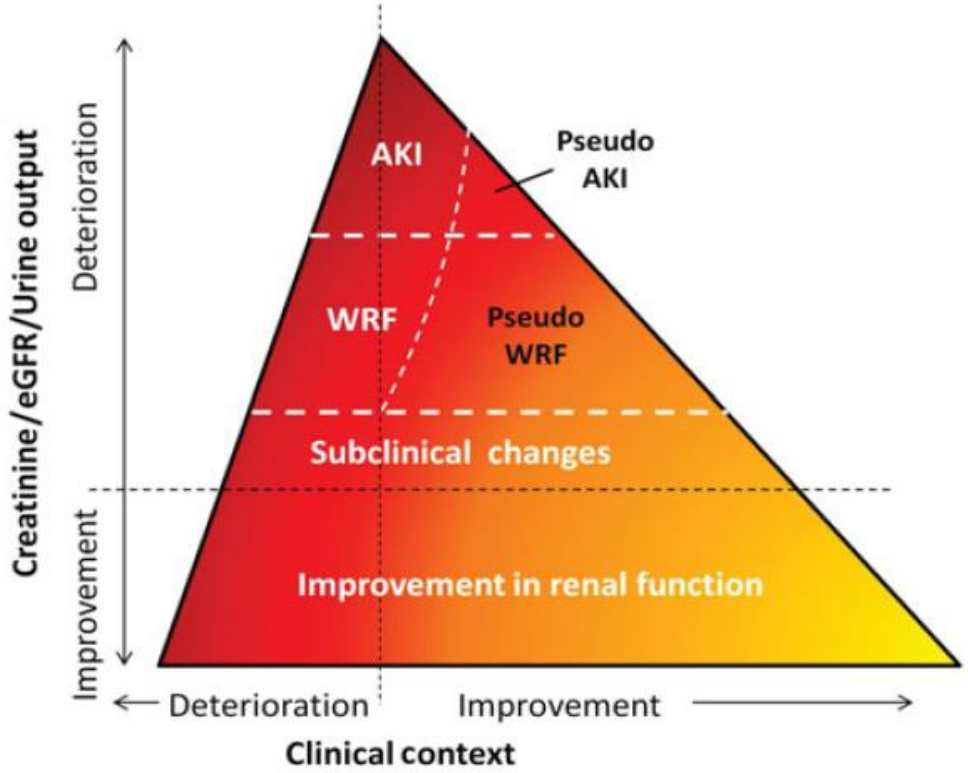


ESC European Society of Cardiology
European Journal of Heart Failure (2020) 22, 584–603
doi:10.1002/ejhf.1697

POSITION PAPER

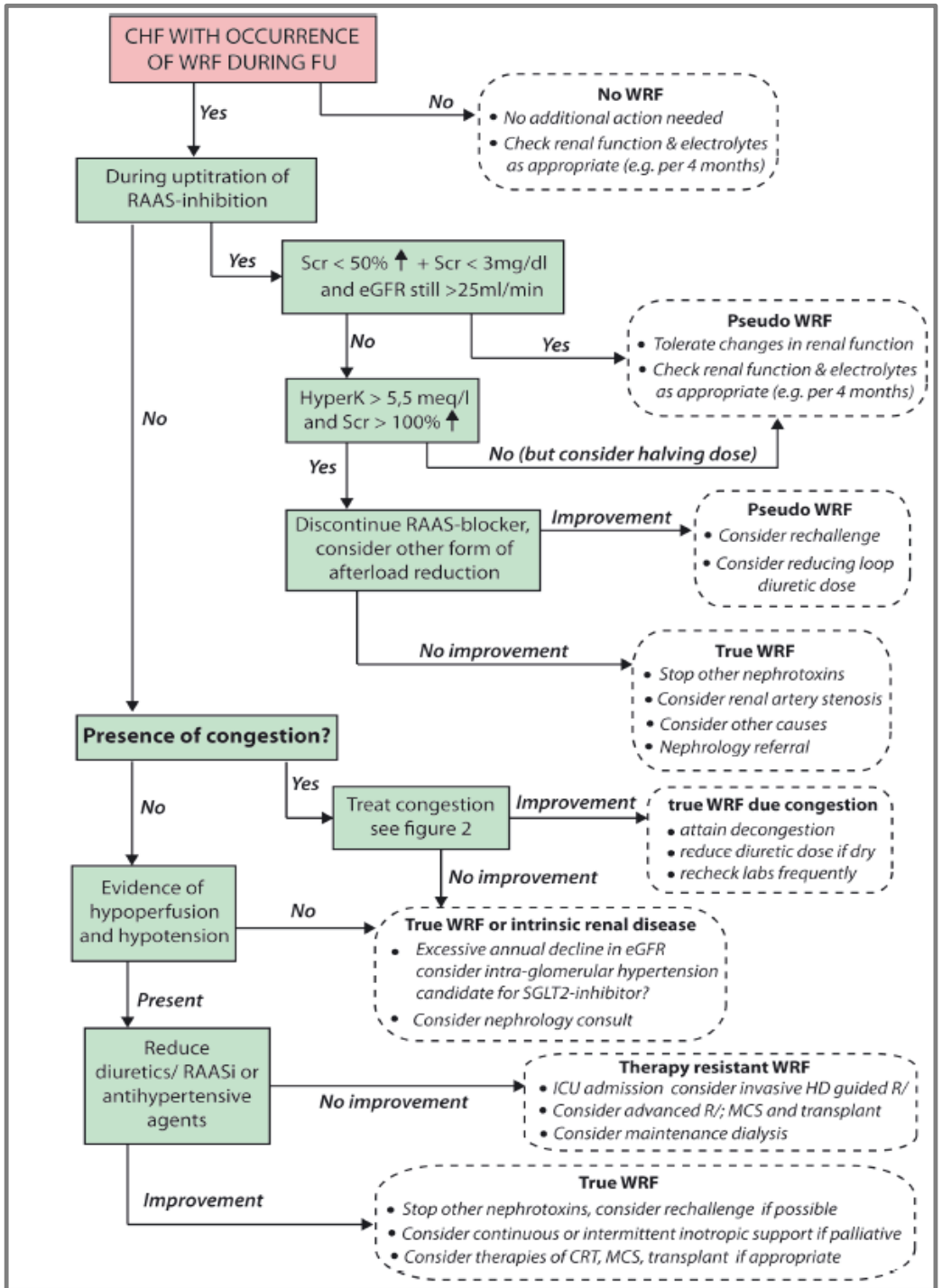
Check for updates

Evaluation of kidney function throughout the heart failure trajectory – a position statement from the Heart Failure Association of the European Society of Cardiology

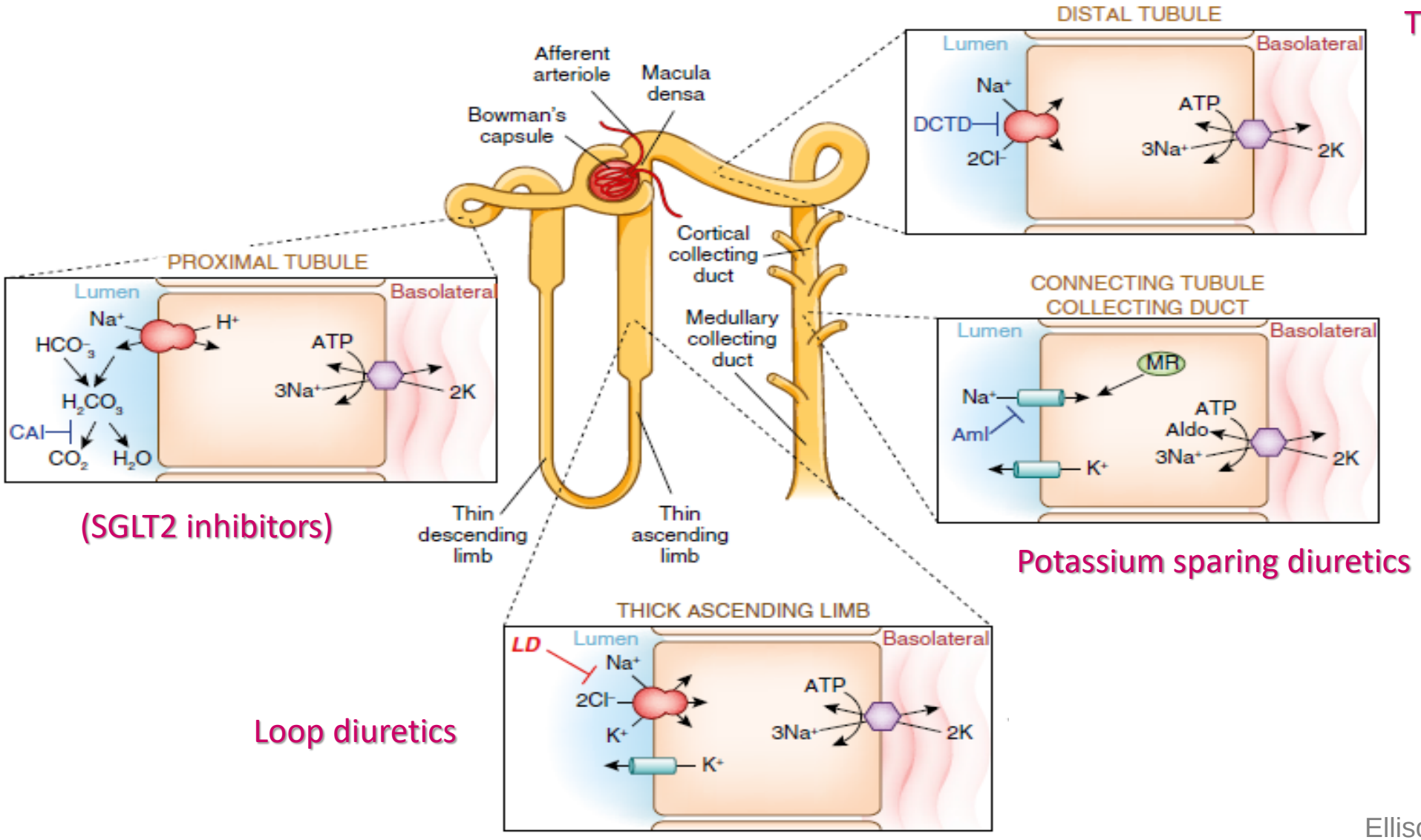


Damman K. Eur Heart J 2015
ESC. Eur J Heart F 2020

Algorithm for WRF in CHF



TREATMENT: DIURETICS



Thiazide (-like)

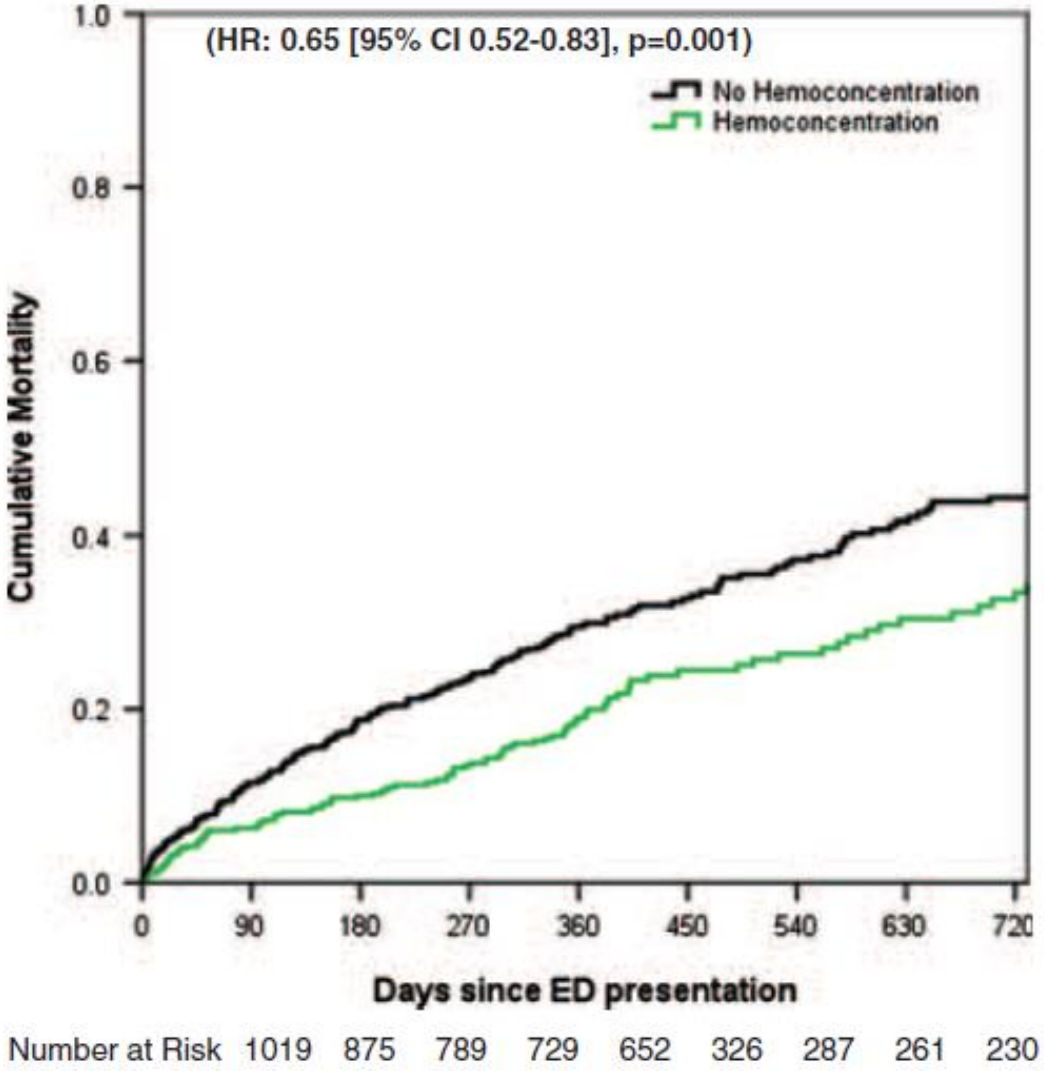
(SGLT2 inhibitors)

Potassium sparing diuretics

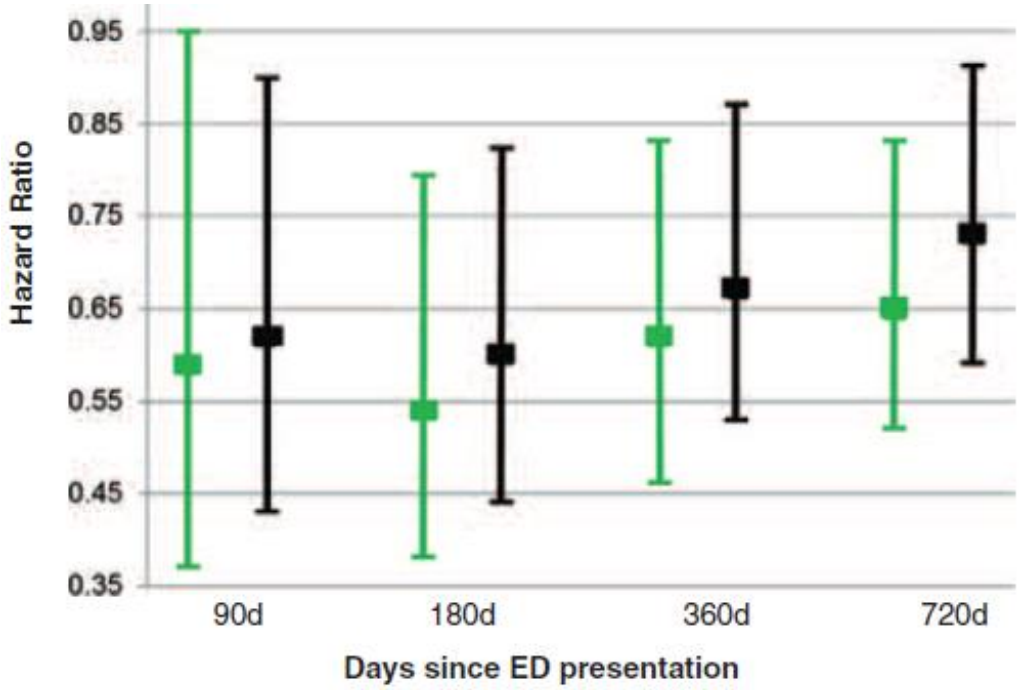
Loop diuretics

Ellison DH. CJASN 2019

Hemoconcentration is associated with lower mortality



Advantage persisted even if Worsening RF



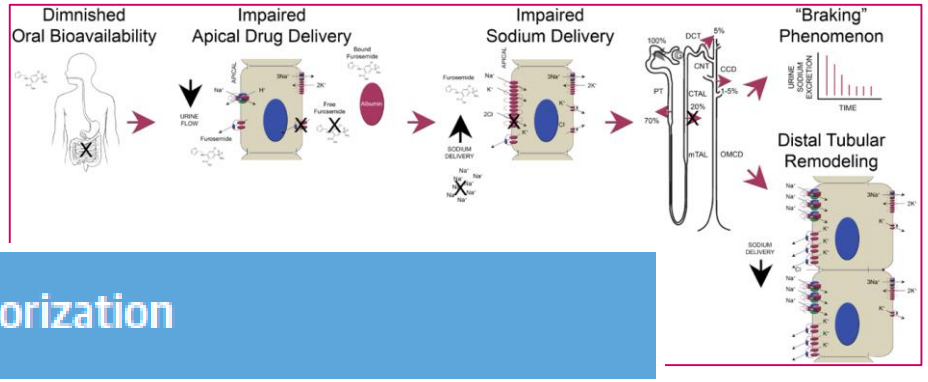
European Journal of Heart Failure (2017) 19, 226–236
doi:10.1002/ejhf.667

RESEARCH ARTICLE

Impact of haemoconcentration during acute heart failure therapy on mortality and its relationship with worsening renal function

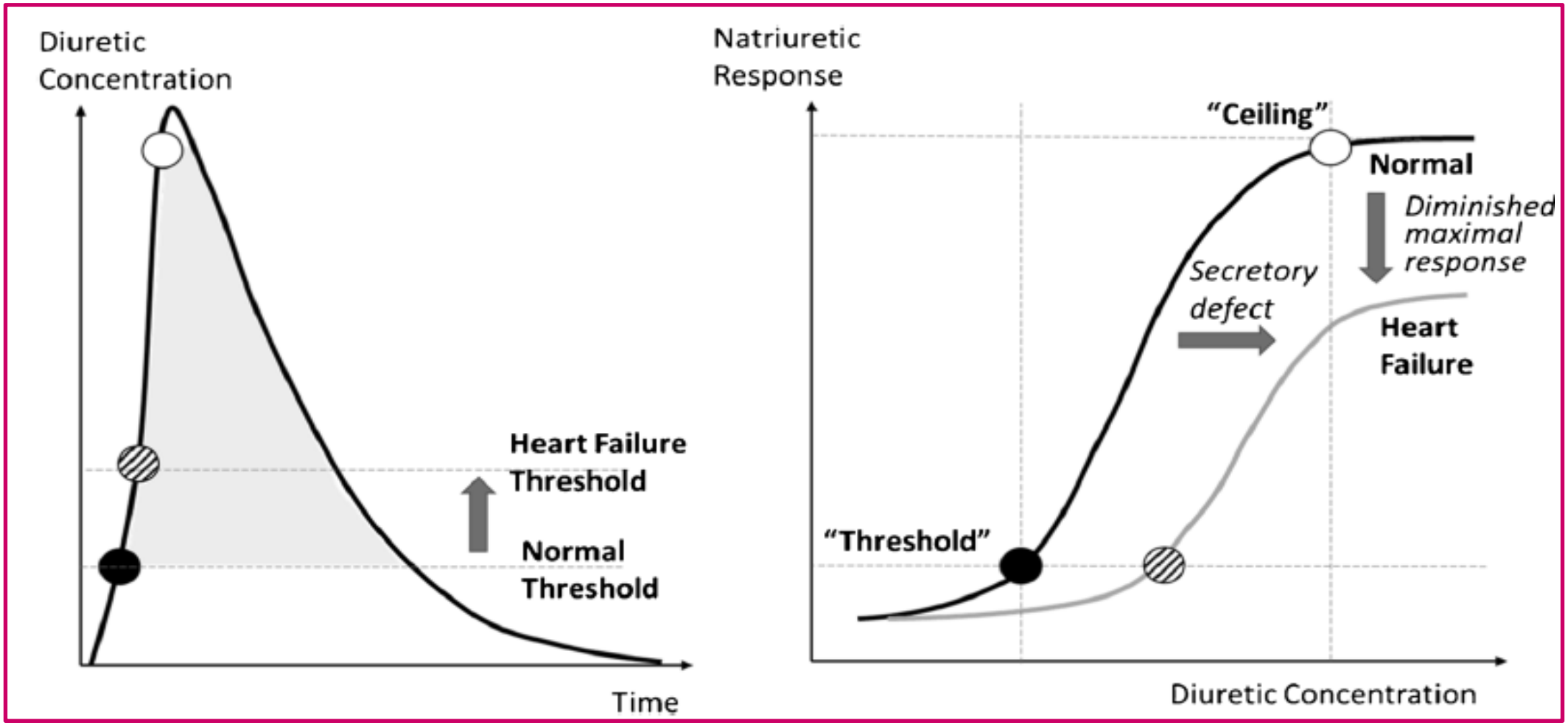
Diuretic «resistance»

Felker. JACC 2020



Importance of specific cause/mechanism on diuretic resistance	Pre-Renal	Intra-Renal: Pre-Loop of Henle	Intra-Renal: Loop of Henle	Intra-Renal: Post-Loop of Henle
	Diuretic Resistance Categorization			
Significant	Venous congestion	Increased proximal tubule sodium reabsorption	Loop diuretic dose	Compensatory distal tubular sodium reabsorption
Unknown but hypothesized to be significant	Increased intra-abdominal pressure	*Reduced GFR*	Response at the level of the Loop of Henle	Proteolytic activation of ENaC by filtered proteases
Not significant with the mild to moderate derangement found in the average HF patient	*Reduced cardiac output*	*Increased organic anions*	Hypochloremic alkalosis	Upregulation of NCC, Pendrin, NDCBE, ENaC
	Hypoalbuminemia	*Albuminuria*		
	High sodium intake			

Diuretic «resistance» in HF (and also in CKD!)



In HF diuretic threshold is shifted → reduced effective range of therapy
→decreased response

Higher dose in HF are needed

AHA. Circulation 2019
Tang. Cur Cardiol Rep 2020

Diuretic goal directed therapy?

Step 1 (Day 1): Assess congestion and start loop diuretics (LD)
(1-2x home dose IV, or 20-40mg IV if none)

Step 2: Assess diuretic response
(@2h spot UNa >50-70 mEq/L; @6h UOP >100-150 ml/h)

No → Double IV LD dose → After 6h: @2h spot UNa >50-70 mEq/L; @6h UOP >100-150 ml/h

No → *Repeat until max dose allowed* → Double IV LD dose

Yes → *Persistent congestion?*

No → **Step 3 (Day 2): Evaluate 24h urine output**
Double IV LD dose if <3-4L; Reassess in 6h & repeat if UOP <100/h

Yes → Repeat same IV LD dose Q12h → **Step 3 (Day 2): Evaluate 24h urine output**

Persistent congestion → **Step 4: Stepwise Pharmacologic Therapy**
If max IV LD, add thiazide (2nd line: acetazolamide, amiloride, UF)

= Sequential nephron blockage

DIURETICS vs ULTRAFILTRATION

AHA Scientific Statement. Circulation 2019

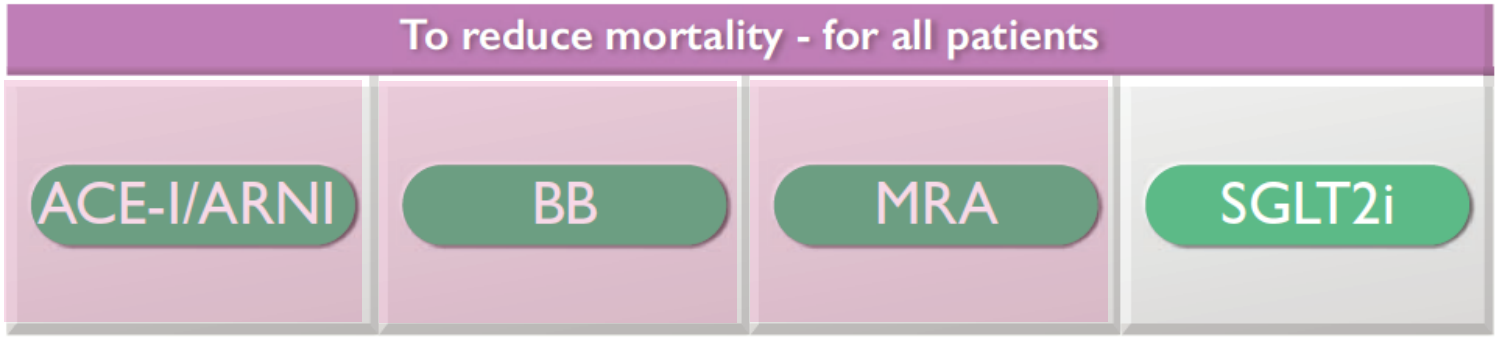
Study	Subjects, n	Primary End Point	UF Protocol	Diuretics Protocol	Effect on Renal Function	Effect on Weight Loss	Adverse Events
RAPID-CHF[133]	40	Weight loss at 24 h	Single 8-h UF session to maximum rate of 500 mL/min per 1.73 m²	Clinician based	NS	Similar in both groups; trend toward higher weight loss in UF arm	…
UNLOAD[134]	200	Weight loss and dyspnea at 48 h	Time and rate of UF flexible; maximum rate of 500 mL/min per 1.73 m²	Clinician based	NS	UF>DT	…
CARRESS-HF[135]	188	Change in SCr and weight at 96 h	Fixed UF rate of 200 mL/min per 1.73 m²	Prespecified stepped-up algorithm	Significant increase in SCr with UF	Similar in both groups	Higher SAEs in UF arm
CUORE[136]	56	Hospitalization for HF at 1 y	Time and rate of UF flexible; maximum rate of 500 mL/min per 1.73 m²	Clinician based	Significant increase in SCr with DT at 6 mo	Similar in both groups	…
AVOID-HF*[137]	224	Time to HF <90 d after discharge	Time and rate of UF flexible; maximum rate of 500 mL/min per 1.73 m²	Prespecified algorithm	NS	Similar in both groups	Higher SAEs in UF arm

ESC European Society of Cardiology

European Heart Journal (2021) **42**, 3599–3726
doi:10.1093/eurheartj/ehab368

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

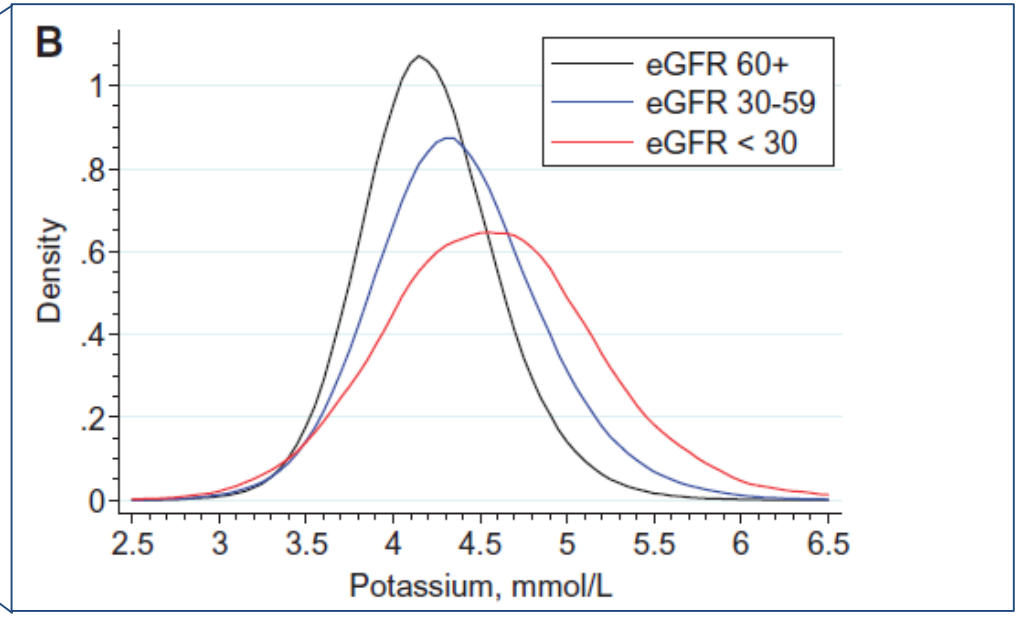
⇧ HyperK



Recommendations	Class[a]	Level[b]
An ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[110–113]	I	A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.[114–120]	I	A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[121,122]	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[108,109]	I	A
Sacubitril/valsartan is recommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death.[105]	I	B

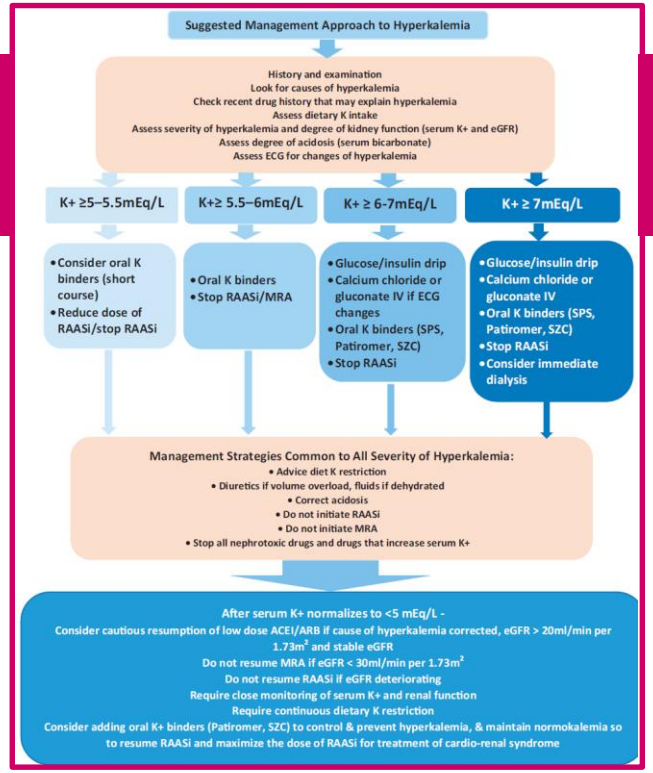
Adverse Effects HF medication

- Improve total body sodium balance
  - *Hyponatremia (SIADH)*
- RAAS inhibitors +- MRA (aldosterone)
  - *Hyperkaliemia (++ in diabetes, eGFR<30ml/min)*
- Sacubitril/valsartan (ARNI) > ACE alone
  - *Studies needed for eGFR<30ml/min*
- B blockers: metoprolol, bisoprolol, carvedilol
  - *Bradycardia, hypotension (++ eGFR<45ml/min)*
- Device-based algorithm with iv saline/diuretic
- Other devices (CRT…)
- SGLT2 inhibitors

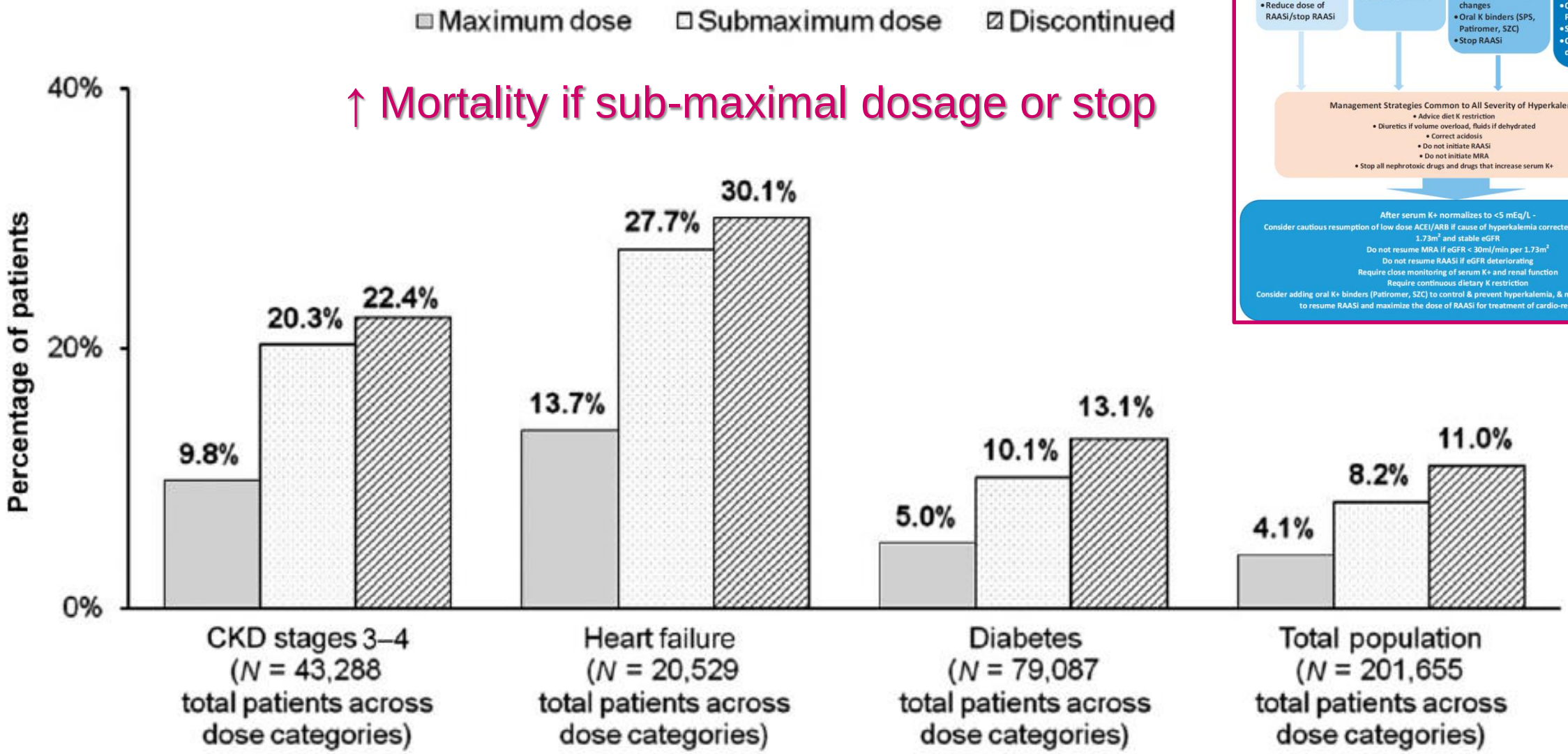


Acker. Arch Int Med 1998 .
Kovedsky Eur J Heart 2018

Mortality and ACE/ARB dose in CKD

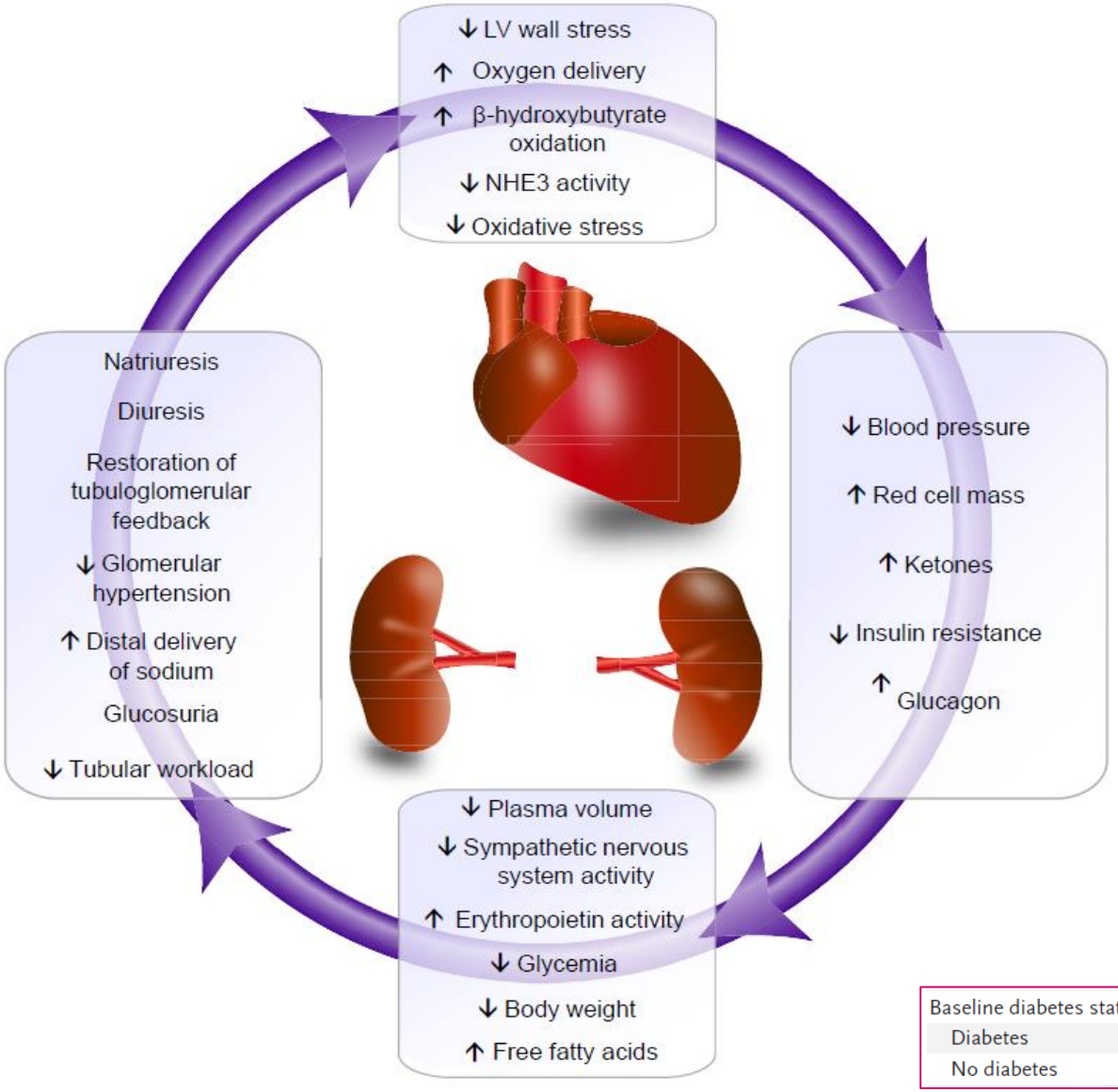


↑ Mortality if sub-maximal dosage or stop



Epstein AM J Manag Care 2015. Wang et al NDT2019

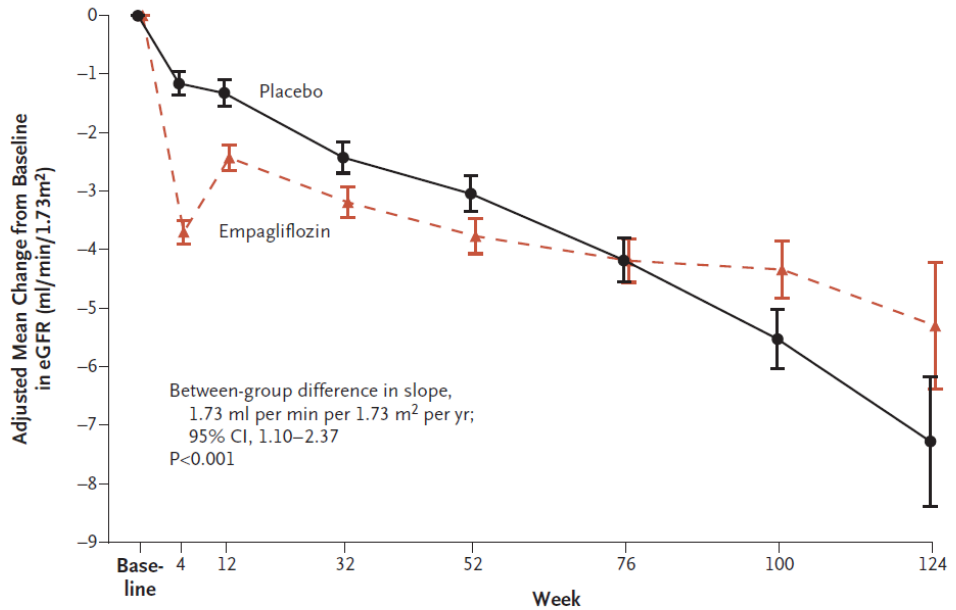
iSGLT 2: renal and cardiological protection



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure



No. at Risk							
Placebo	1792	1765	1683	1500	1146	745	343	76
Empagliflozin	1799	1782	1720	1554	1166	753	356	80

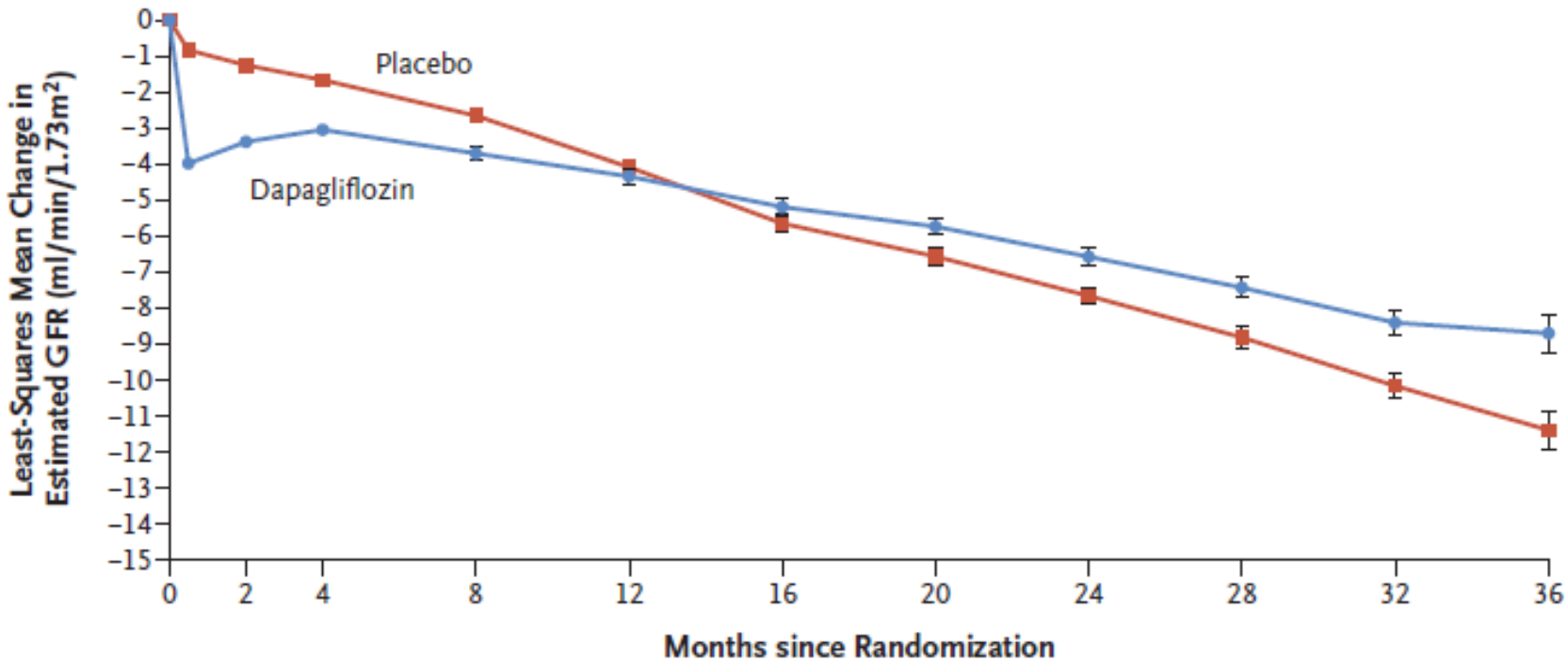
Baseline diabetes status				
Diabetes	200/927	265/929		0.72 (0.60–0.87)
No diabetes	161/936	197/938		0.78 (0.64–0.97)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Patients with Chronic Kidney Disease

Heerspink HJL. NEJM 2020



No. of Participants

Placebo	2152	2029	1981	1866	1795	1753	1672	1443	935	447	157
Dapagliflozin	2152	2031	2001	1896	1832	1785	1705	1482	978	496	157

CONCLUSIONS

- ✓ Heart and kidney have multiple bi-directional interaction
- ✓ CKD is associated with increased CV mortality, Heart Failure and Coronary Heart Disease
- ✓ CRS classified according to acute or chronic renal/cardiac pathologies
- ✓ Different mechanisms involved → importance of hemodynamic and venous congestion

CONCLUSIONS

- ✓ Transient WRF does not impact prognosis of AHF
- ✓ Diuretic effectiveness and hemoconcentration are predictors of good prognosis in AHF
- ✓ Elevation of creatinine in the presence of HF has to be interpreted with caution: not always true AKI
- ✓ Diuretics are essential: but resistance → to be titred
- ✓ Aim for new treatments : The gold age for SGLT2?


Protect your kidneys, Save your heart.
World Kidney Day