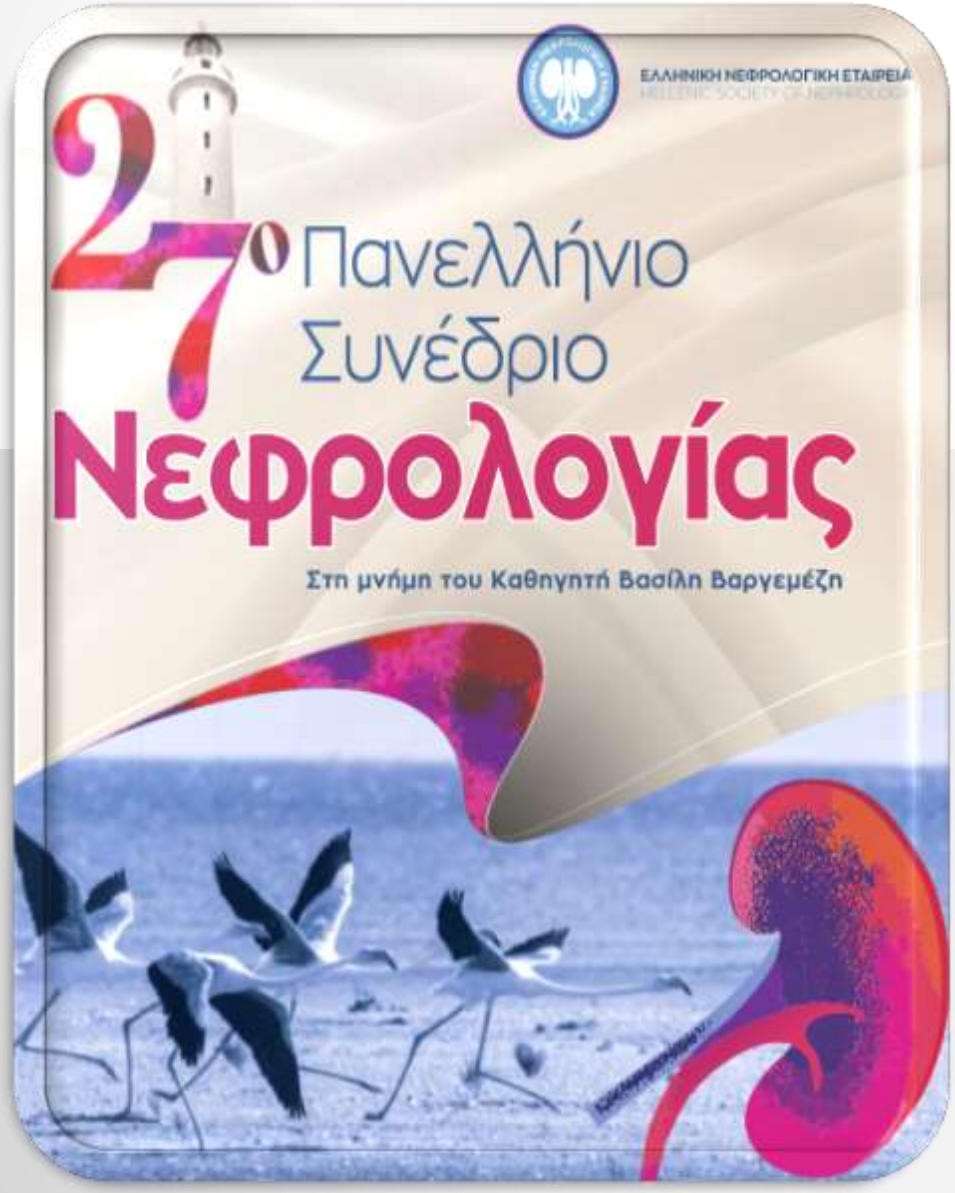
«ΚΑΡΔΙΑ-ΝΕΦΡΟΙ,ΔΥΟ ΟΡΓΑΝΑ ΠΟΥ ΣΥΜΠΑΣΧΟΥΝ»



Debate

Ποιο σύνδρομο περιγράφει καλύτερα αυτό που συμβαίνει στην κλινική πράξη όταν πάσχουν συγχρόνως νεφροί και καρδιά;

Το καρδιονεφρικό σύνδρομο όπως το περιέγραψε ο Ronco

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From “Heart and Reins” to Clinical Syndromes

Origin and Evolution of Cardio-Renal Disease

The Heart & Kidneys in Antiquity

Ancient Egypt: Heart & kidneys were the only organs preserved during mummification.

Book of the Dead (1600–1240 BC): “Homage to thee, O my heart! Homage to you, O my kidneys!”

Archaeological data: Mummies show cardiovascular (CV) and renal disease.

Bible: >30 references to the “reins” (kidneys) alongside the heart → organs of judgment & emotions.

Salam AM, Carr AS. Heart Views. 2021

Historical Perspectives: China - Middle Ages - Modern Era

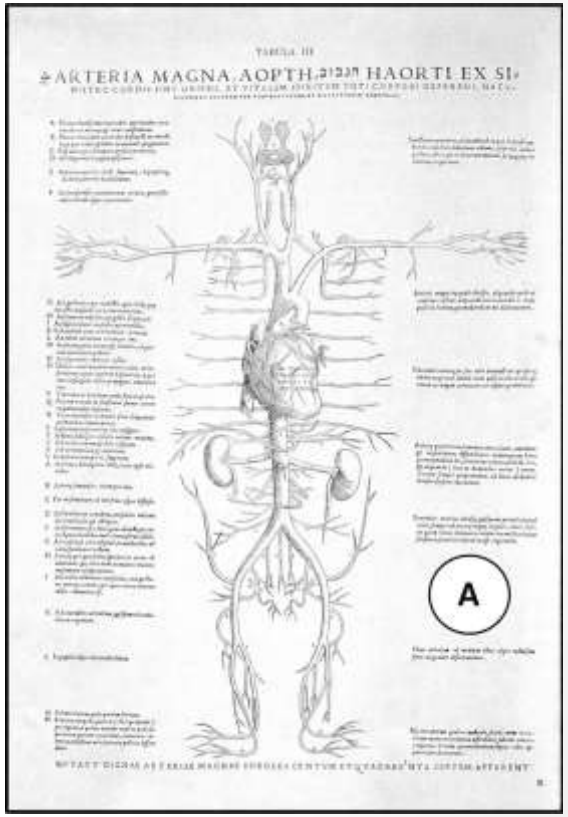
Traditional Chinese Medicine:

- Heart = “Fire” (yang), Kidneys = “Water” (yin).
- Term: **“Heart and kidney failing to link”** → edema, palpitations, dyspnea, dizziness, oliguria.

Middle Ages:

- Gentilis de Fulgineo (1272-1348) observed link between fast pulse rate & urine output and **the importance of heart disease on modulating the colour and output of urine→ first “cardionephrologist.”**

- Andreas Vesalius (1514–1564) and his work Plate 3 (Tabula iii, 1538, Tabula Anatomicae Sex) **depicts only the heart and kidneys,** illustrating the early concept of the cardiorenal connection.



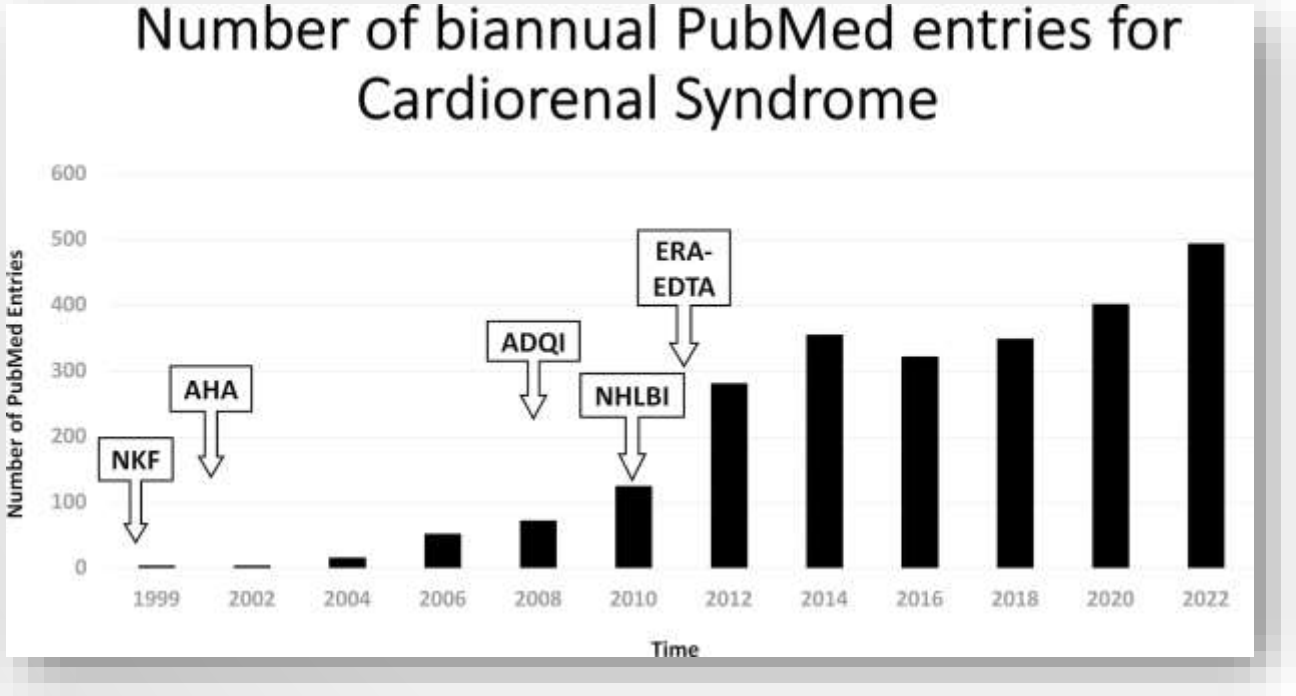
Young JB, Eknoyan G Circ Heart Fail. 2024; Salam AM, Carr AS. Heart Views. 2021

Modern Era

- **1914:** Alfred Stengel (1868-1939) **introduced the term *"cardio-renal disease"***; described coexistence of heart & kidney failure.

".....cardiac weakness and other circulatory disturbances, such as high pressure, are associated with signs of failure of renal function or urinary indications of renal disease..... The term comprises cases of combined cardiovascular and renal disease without such manifest predominance of either as to justify a prompt determination of the one element as primary and important and the other as secondary and unimportant."

- **Modern Era**



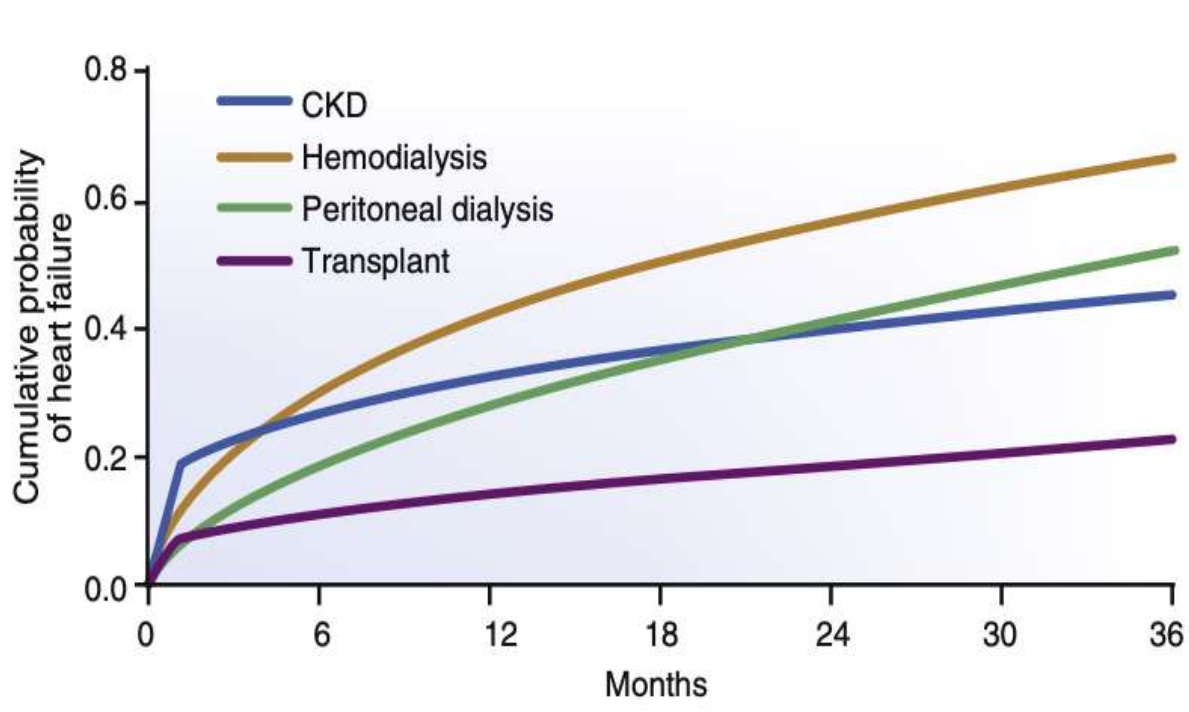
Young JB, Eknoyan G Circ Heart Fail. 2024; Salam AM, Carr AS. Heart Views. 2021

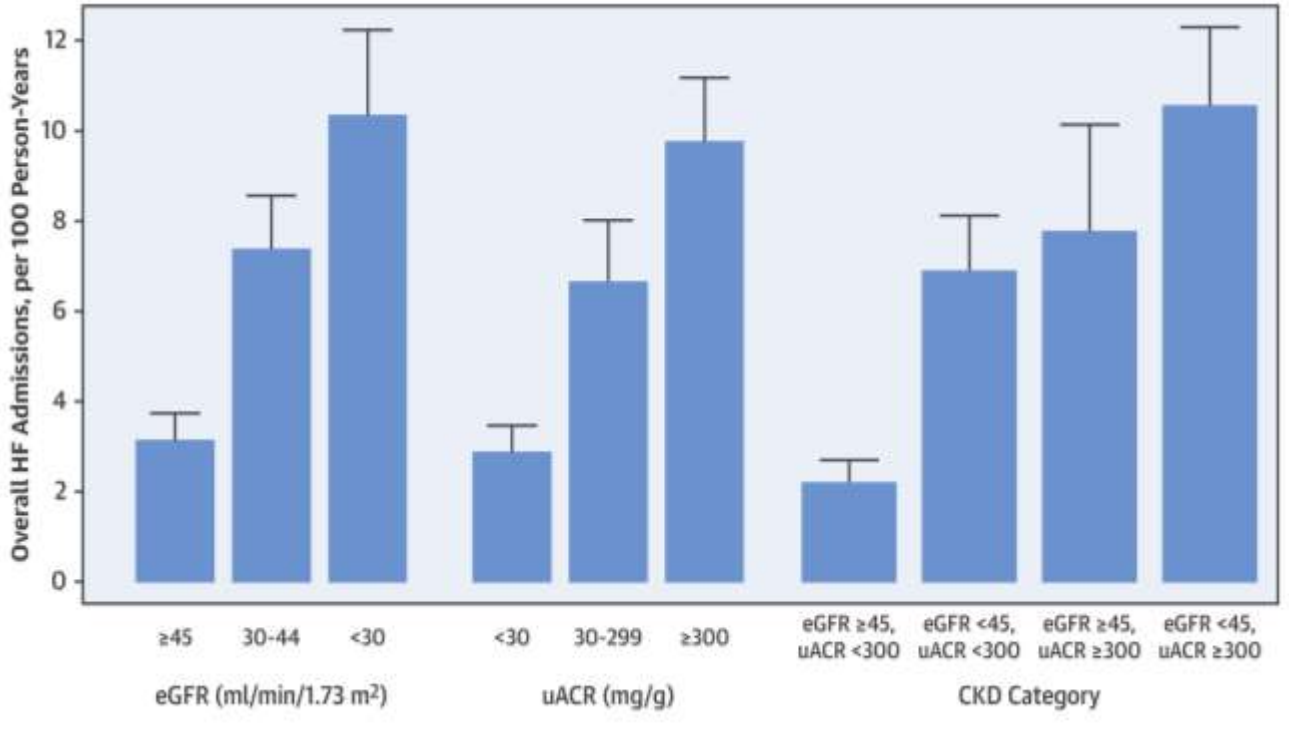
Co-existence of Heart Failure and Chronic Kidney Disease How common is it?

Epidemiological perspectives

The emergence of Heart Failure (HF) in CKD populations

The occurrence of HF varies depending on the degree of CKD and the type of renal replacement therapy, including transplantation.





Collins AJ et al. Am J Kidney Dis. 2008; Bansal N. et a. J Am Coll Cardiol 2019

Prevalence of CKD in HF

European Heart Journal (2014) **35**, 455–469
doi:10.1093/eurheartj/eht386

CLINICAL RESEARCH
Heart failure/cardiomyopathy

Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis

Kevin Damman[1]*, Mattia A.E. Valente[1], Adriaan A. Voors[1], Christopher M. O'Connor[2], Dirk J. van Veldhuisen[1], and Hans L. Hillege[1,3]

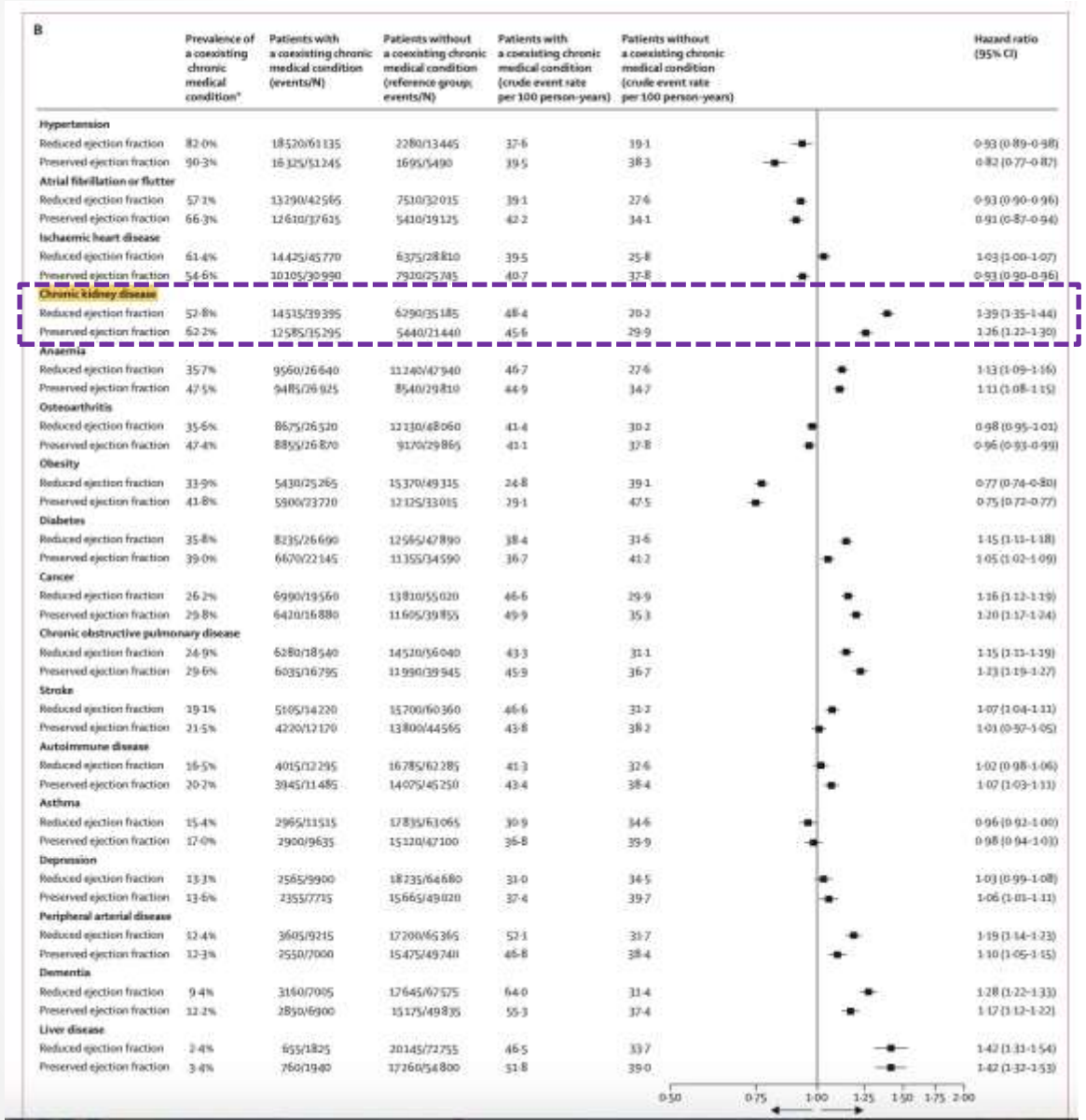
57 studies (**1 076 104 patients**) that investigated CKD and 28 studies (49 890 patients) that investigated WRF

The prevalence of CKD was 32% and of **WRF 23%**

In multivariate analysis, moderate renal impairment (HR 1.59, 95% CI 1.49–1.69, $P < 0.001$), severe renal impairment (HR 2.17, 95% CI 1.95–2.40, $P < 0.001$), and WRF, (HR 1.95, 95% CI 1.45–2.62, $P < 0.001$) were all independent predictors of mortality

Renal dysfunction is one of the most important risk factors predicting mortality and poor outcomes in HF patients, **with more than double risk of death if CKD is present**

Among HF comorbidities, CKD carries the greatest prognostic burden



B

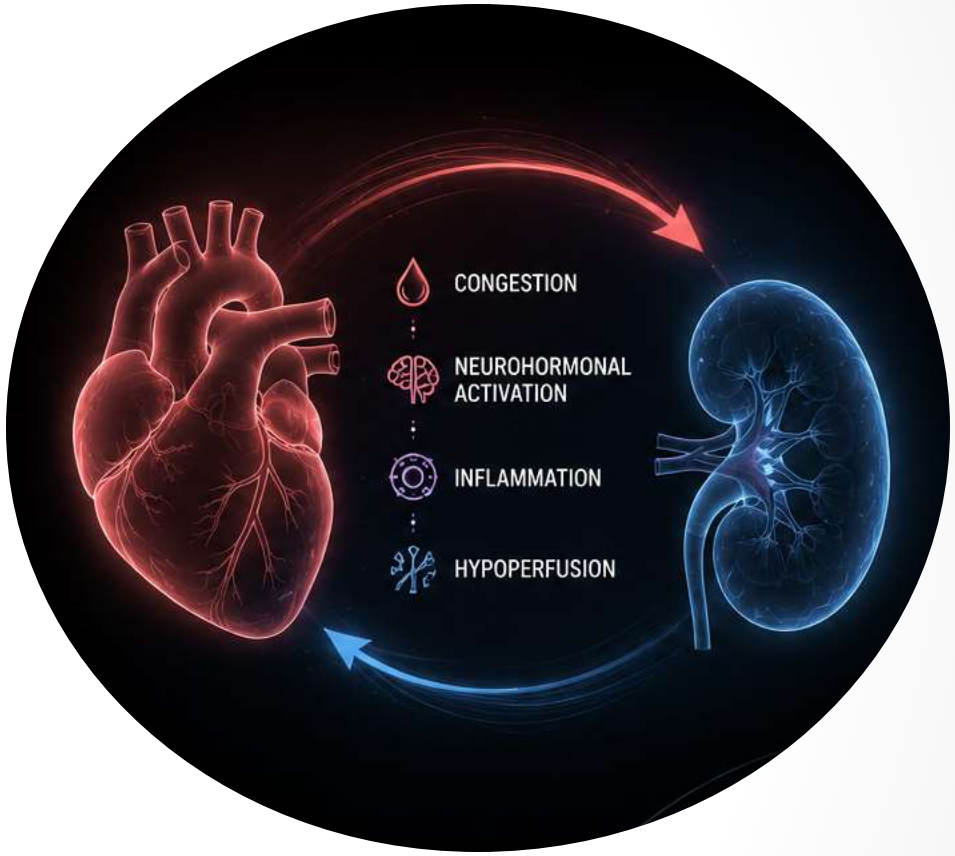
	Prevalence of a coexisting chronic medical condition*	Patients with a coexisting chronic medical condition (events/N)	Patients without a coexisting chronic medical condition (reference group; events/N)	Patients with a coexisting chronic medical condition (crude event rate per 100 person-years)	Patients without a coexisting chronic medical condition (crude event rate per 100 person-years)	Hazard ratio (95% CI)
Hypertension						
Reduced ejection fraction	82·0%	18520/61135	2280/13445	37·6	19·1	0·93 (0·89–0·98)
Preserved ejection fraction	90·3%	16325/51245	1695/5490	39·5	38·3	0·82 (0·77–0·87)
Atrial fibrillation or flutter						
Reduced ejection fraction	57·1%	13290/42565	7510/32015	39·1	27·6	0·93 (0·90–0·96)
Preserved ejection fraction	66·3%	12610/37635	5410/19125	42·2	34·1	0·91 (0·87–0·94)
Ischaemic heart disease						
Reduced ejection fraction	61·4%	14425/45770	6375/28810	39·5	25·8	1·03 (1·00–1·07)
Preserved ejection fraction	54·6%	10105/30990	7910/25785	40·7	37·8	0·93 (0·90–0·96)
Chronic kidney disease						
Reduced ejection fraction	52·8%	14515/39395	6290/35185	48·4	20·2	1·39 (1·35–1·44)
Preserved ejection fraction	62·2%	12585/35295	5440/21440	45·6	29·9	1·26 (1·22–1·30)
Anaemia						
Reduced ejection fraction	35·7%	9560/26640	11240/47940	46·7	27·6	1·13 (1·09–1·16)
Preserved ejection fraction	47·5%	9485/26925	8540/29810	44·9	34·7	1·11 (1·08–1·15)
Osteoarthritis						
Reduced ejection fraction	35·6%	8675/26520	12130/48060	41·4	30·2	0·98 (0·95–1·01)
Preserved ejection fraction	47·4%	8855/26870	9170/29865	43·1	37·8	0·96 (0·93–0·99)
Obesity						
Reduced ejection fraction	33·9%	5430/25265	15370/49335	24·8	39·1	0·77 (0·74–0·80)
Preserved ejection fraction	41·8%	5900/23720	12125/33015	29·1	47·5	0·75 (0·72–0·77)
Diabetes						
Reduced ejection fraction	35·8%	8235/26690	12565/47890	38·4	31·6	1·15 (1·11–1·18)
Preserved ejection fraction	39·0%	6670/22145	11355/34590	36·7	41·2	1·05 (1·02–1·09)
Cancer						
Reduced ejection fraction	26·2%	6990/19560	13810/55020	46·6	29·9	1·16 (1·12–1·19)
Preserved ejection fraction	29·8%	6420/16880	11605/39155	49·9	35·3	1·20 (1·17–1·24)
Chronic obstructive pulmonary disease						
Reduced ejection fraction	24·9%	6280/18540	14520/56040	43·3	31·1	1·15 (1·11–1·19)
Preserved ejection fraction	29·6%	6035/16795	11990/39945	45·9	36·7	1·23 (1·19–1·27)
Stroke						
Reduced ejection fraction	19·1%	5105/14220	15700/60360	46·6	31·2	1·07 (1·04–1·11)
Preserved ejection fraction	21·5%	4220/12170	13800/44565	43·8	38·2	1·01 (0·97–1·05)
Autoimmune disease						
Reduced ejection fraction	16·5%	4015/12295	16785/62285	41·3	32·6	1·02 (0·98–1·06)
Preserved ejection fraction	20·2%	3945/11485	14075/45250	43·4	38·4	1·07 (1·03–1·11)
Asthma						
Reduced ejection fraction	15·4%	2965/11515	17835/61065	30·9	34·6	0·96 (0·92–1·00)
Preserved ejection fraction	17·0%	2900/9635	15120/47100	36·8	39·9	0·98 (0·94–1·03)
Depression						
Reduced ejection fraction	13·3%	2565/9900	18235/64680	31·0	34·5	1·03 (0·99–1·08)
Preserved ejection fraction	13·6%	2355/7715	15665/49020	37·4	39·7	1·06 (1·01–1·11)
Peripheral arterial disease						
Reduced ejection fraction	12·4%	3605/9215	17200/65365	52·1	31·7	1·19 (1·14–1·23)
Preserved ejection fraction	12·3%	2550/7000	15475/49740	46·8	38·4	1·10 (1·05–1·15)
Dementia						
Reduced ejection fraction	9·4%	3160/7005	17645/67575	64·0	31·4	1·28 (1·22–1·33)
Preserved ejection fraction	12·2%	2850/6900	15175/49835	55·3	37·4	1·17 (1·12–1·22)
Liver disease						
Reduced ejection fraction	2·4%	655/1825	20145/72755	46·5	33·7	1·42 (1·31–1·54)
Preserved ejection fraction	3·4%	760/1940	17260/54800	51·8	39·0	1·42 (1·32–1·53)

0·50 0·75 1·00 1·25 1·50 1·75 2·00

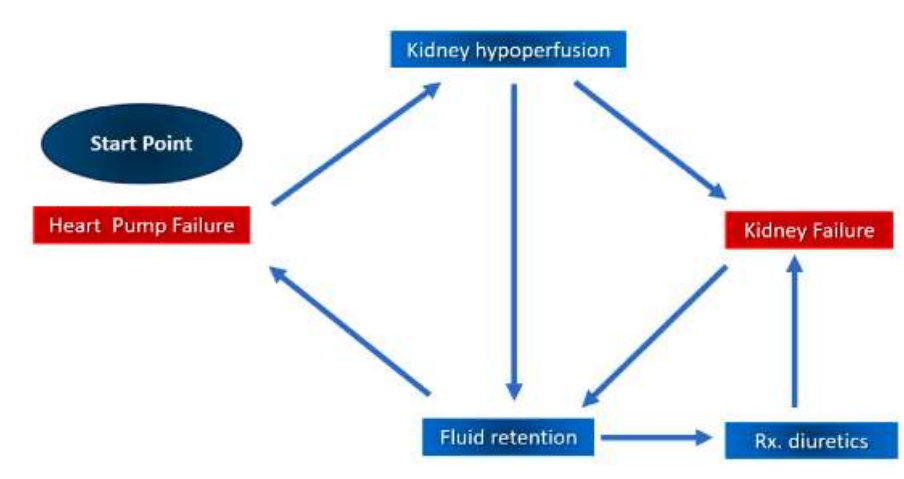
The **prognosis of HF** is often determined not only by the heart itself, but **by the kidney's response** to cardiac dysfunction

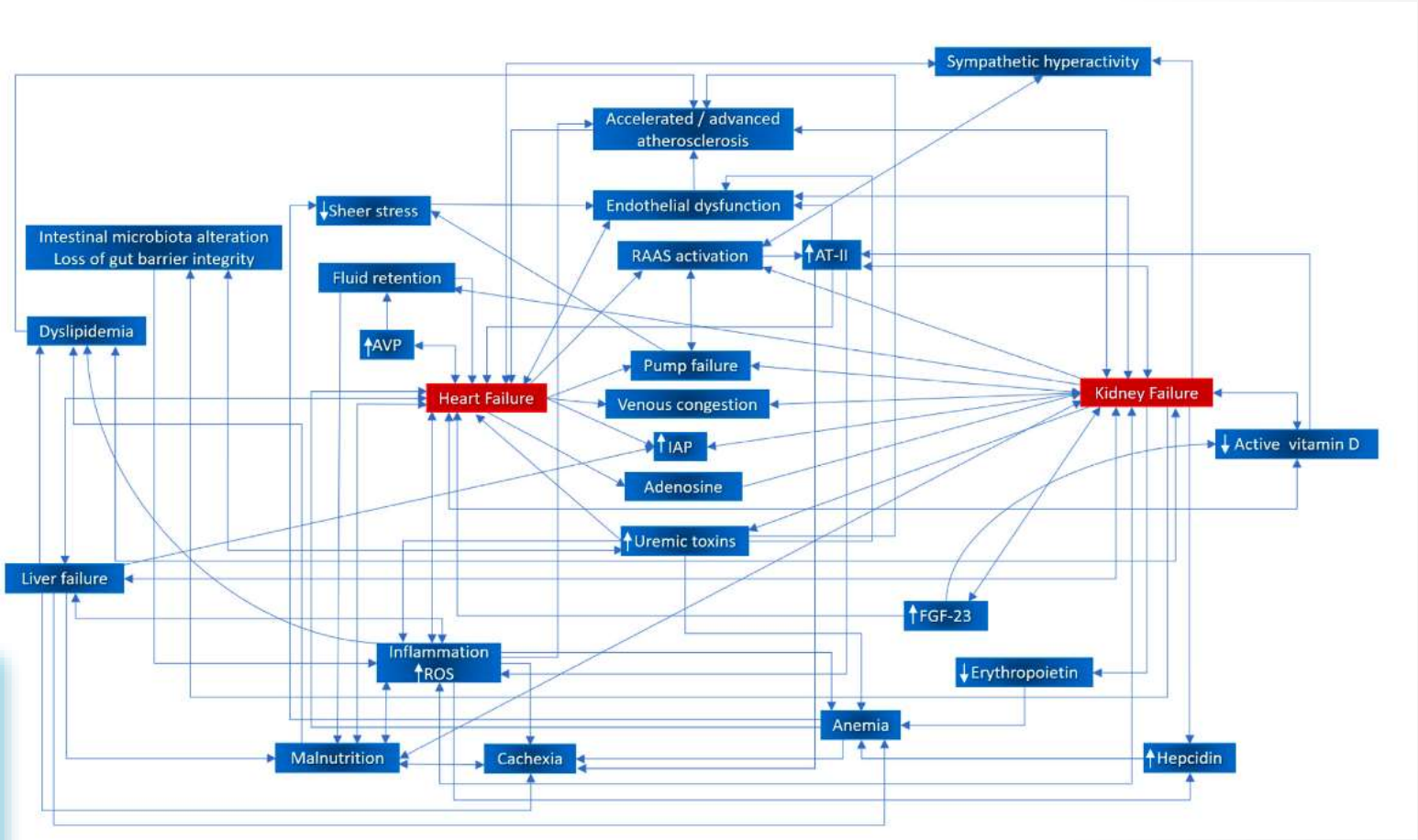
Fletcher RA et al. The Lancet Public Health 2024

The profound bidirectional interaction between the heart and kidneys necessitated a **unified clinical framework.**



Beyond the Traditional CRS Model



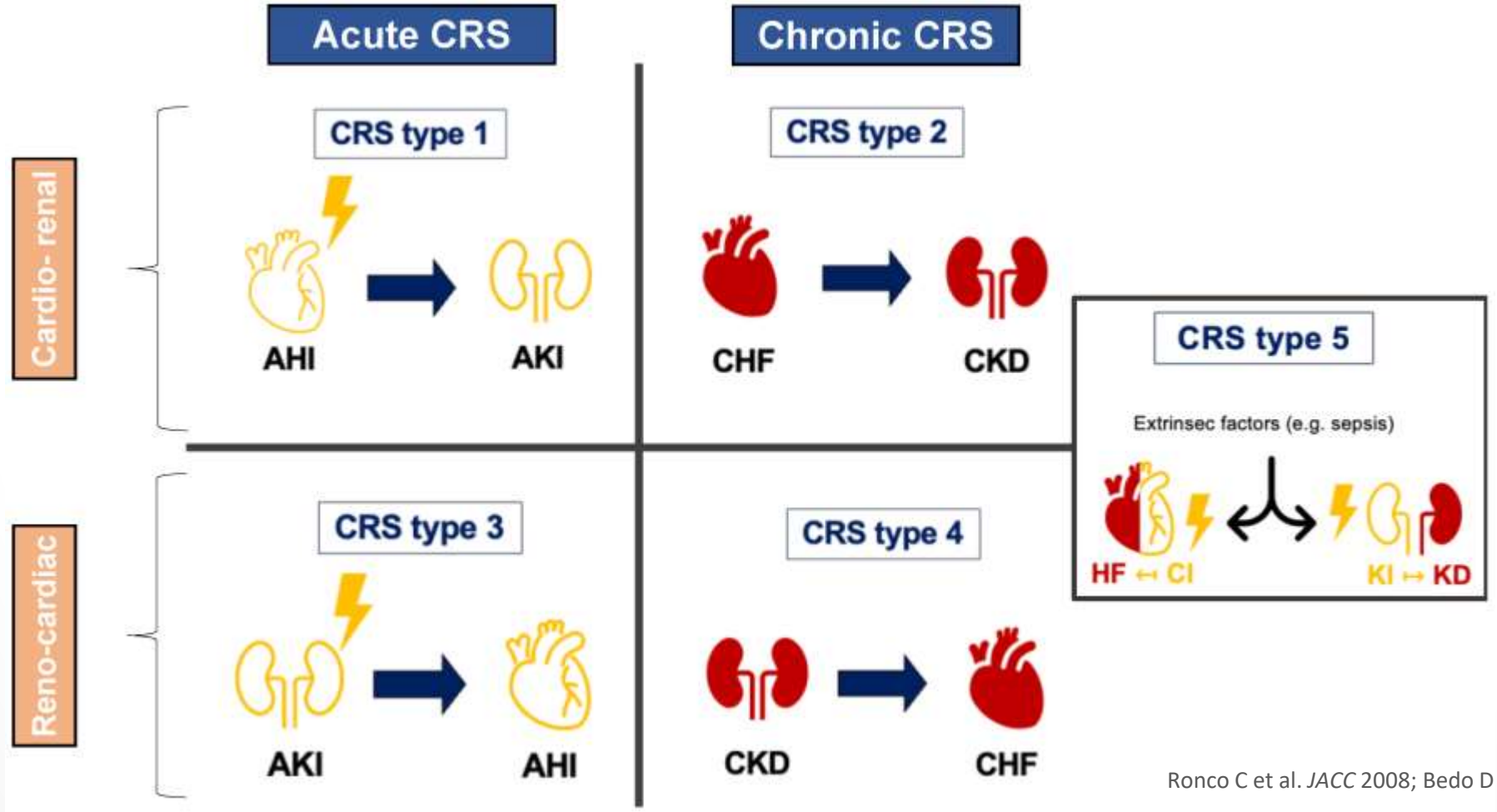


- CRS is not solely driven by low cardiac output
- Venous congestion plays a central role
- Neurohormonal and inflammatory pathways contribute significantly

Hatamizadeh P. Trends Cardiovasc Med. 2024

The Ronco Cardiorenal Syndrome Model

"Any acute or chronic problem in the heart or kidneys that could result in an acute or chronic problem of the other" Chronology-based and directional

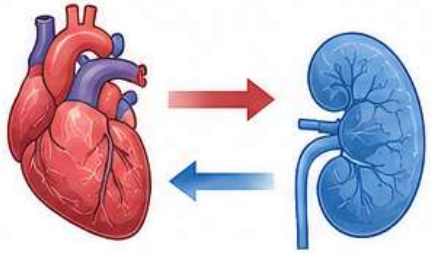


Ronco C et al. *JACC* 2008; Bedo D et al. , Diagnostics (Basel). 2024

Why the CRS framework still matters in clinical practice

The Ronco classification is more than a taxonomy. It provides a practical framework that explains, predicts and guides our daily clinical decisions

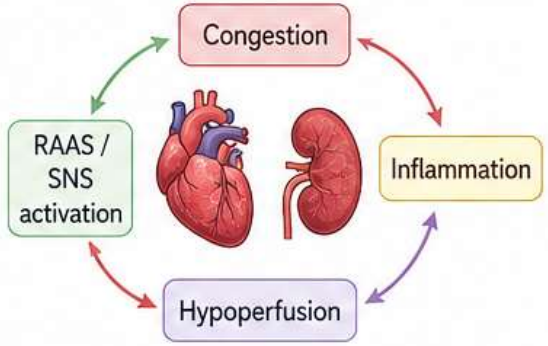
1 DEFINES DIRECTIONALITY — the core of CRS



Identifies the primary organ and the secondary

- HF → kidney dysfunction (Types 1 & 2)
- AKI → cardiac dysfunction (Types 3 & 4)
- Essential for diagnosis, prognosis and therapeutic strategy

2 PLACES CONGESTION AT THE CENTER



- Congestion is a major driver of organ dysfunction
- Concept of congestion and its clinical consequences were pioneered and emphasized within the CRS framework by Ronco and colleagues

3 GUIDES ACUTE MANAGEMENT

- Supports decongestion strategies
- Helps in diuretic selection and escalation
- Aids interpretation of worsening renal function
- Informs continuation of GDMT despite mild creatinine rise

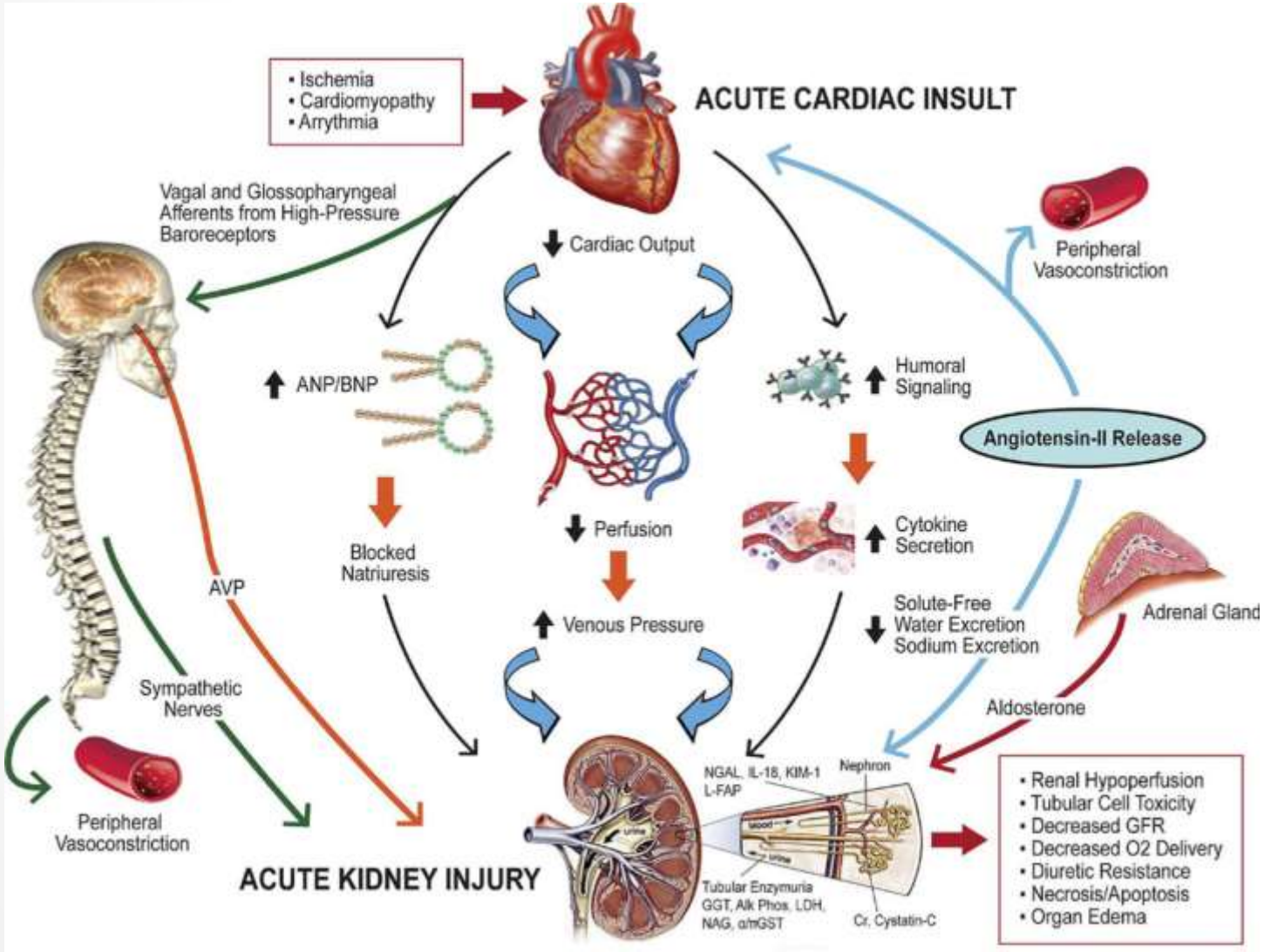
4 DIRECT BEDSIDE APPLICABILITY

Useful in:

- Acute decompensated heart failure
- Acute kidney injury
- Diuretic resistance
- Worsening renal function

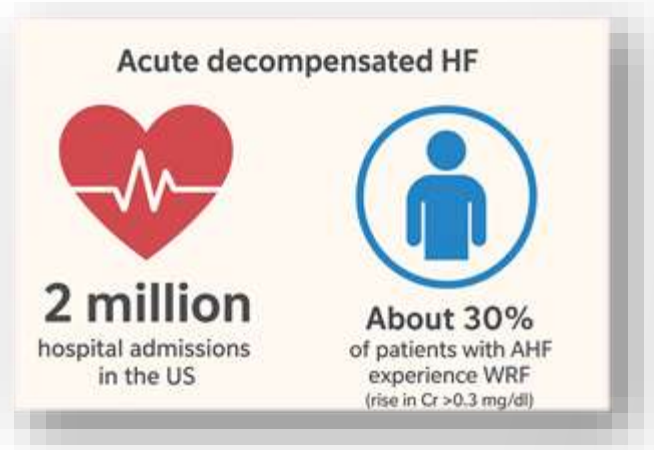
CRS type 1

Acute HF is followed by or associated with AKI



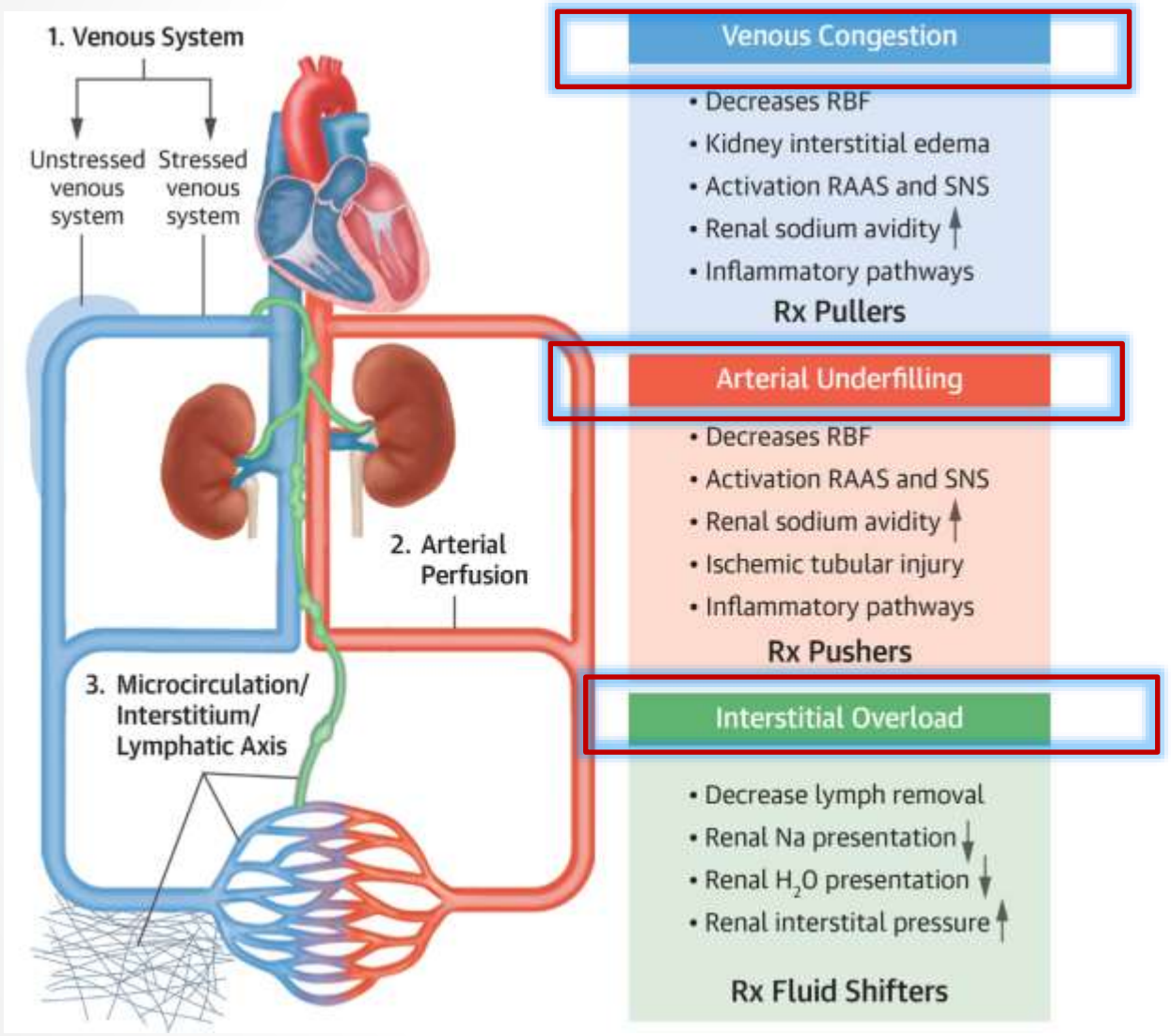
Key Clinical Points

- Occurs in ~25-30% of ADHF admissions
- Congestion is a major driver of AKI
- AKI strongly worsens prognosis (mortality RF)



Rangaswami J et al. Circulation. 2019 Apr; Damman K et al. J Card Fail. 2007

Three main mechanisms of renal hypoperfusion in the context of an ADHF



- **Renal Tamponade Hypothesis**

The kidney is encapsulated and lacks elasticity, so glomerular and renal interstitial congestion is problematic

Interstitial fluid overload ↑ intrarenal pressure →

Compression of tubules, glomeruli & intrarenal veins →

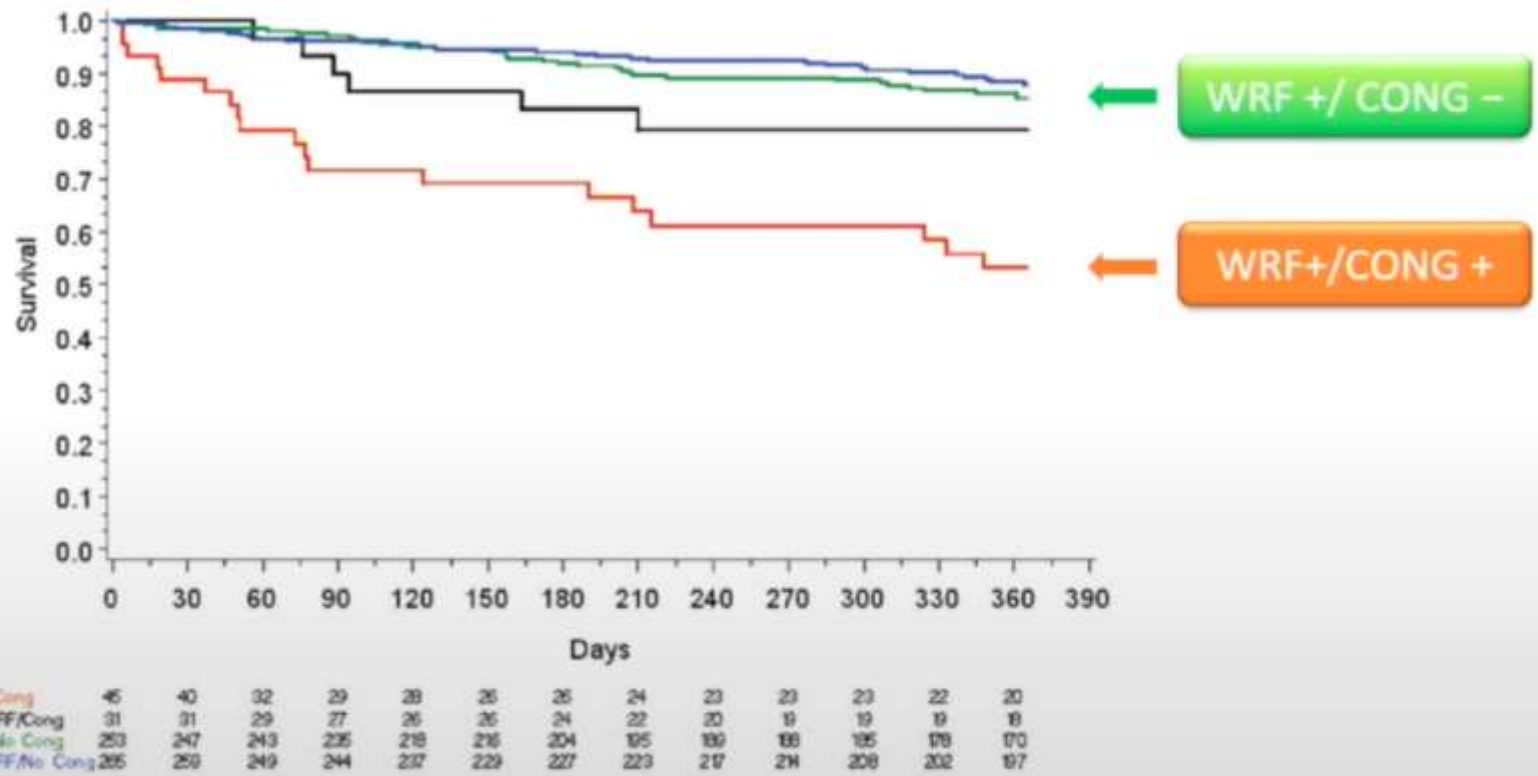
Necrosis & progressive renal impairment

Renal Perfusion Pressure: MAP - CVP

Martens P et al. JACC Heart Fail. 2023

The primary driver of the outcome is not the kidney dysfunction but the **congestion**

599 patients

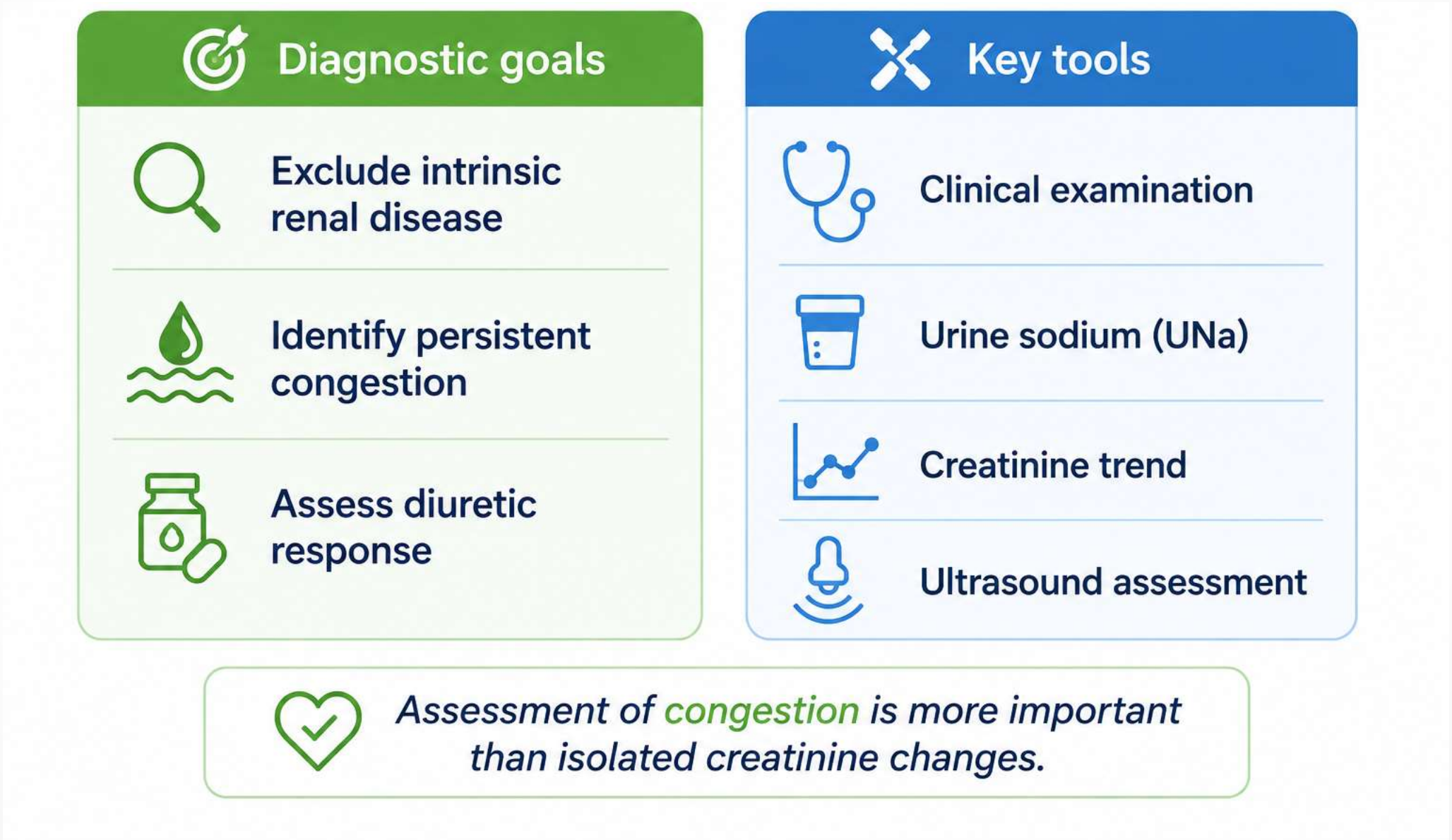


Residual congestion predicts prognosis better than creatinine rise.

Metra M et al. Circ Heart Fail 2012

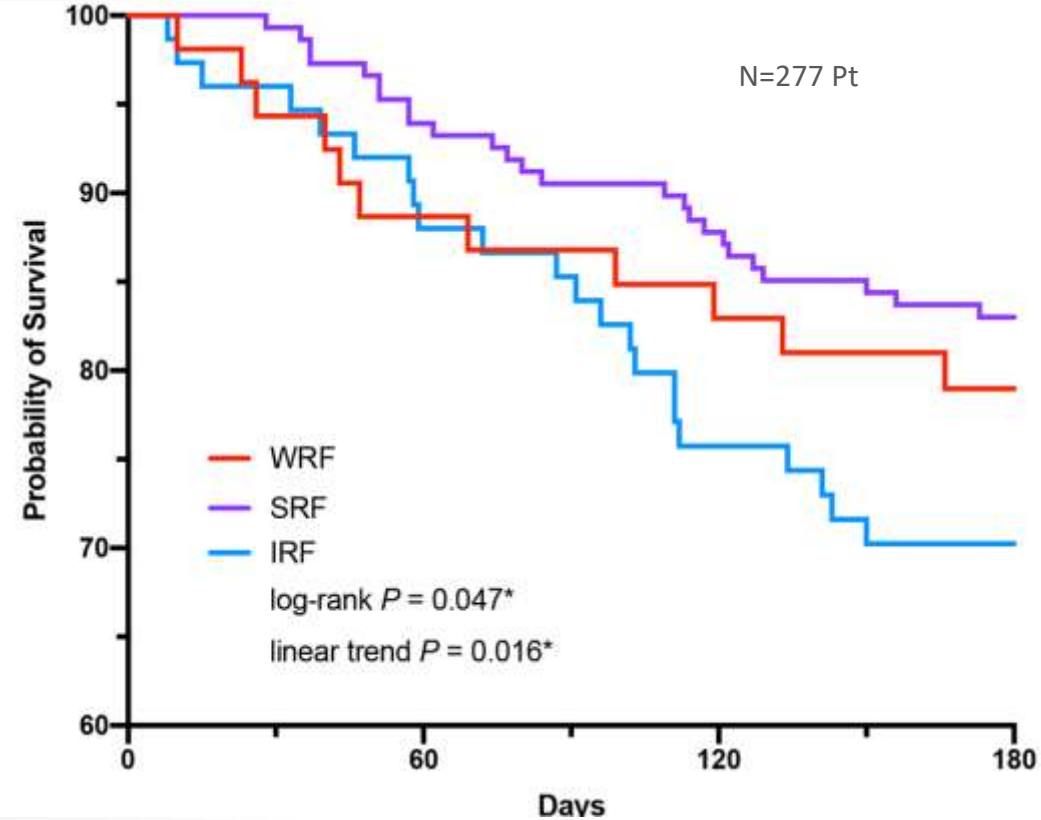
Diagnosis

Evaluation of CRS type 1

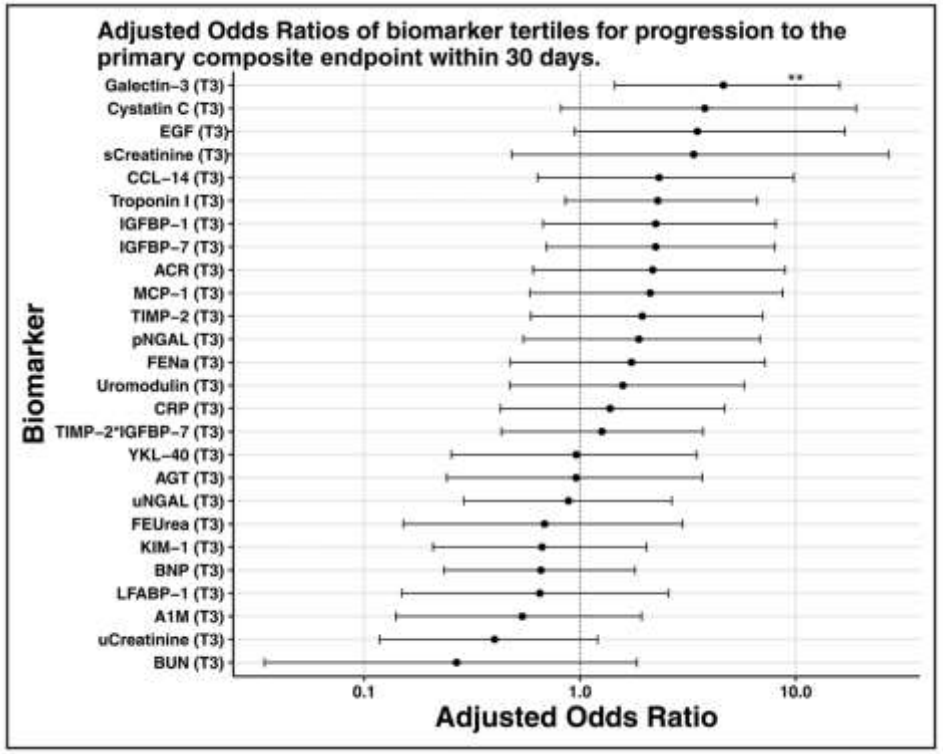


Role of biomarkers questionable

Decrease in SCr in ADHF undergoing Aggressive diuresis – results from ROSE-AHF trial



Improvement in Renal Function (IRF) associated with worse outcomes than WRF

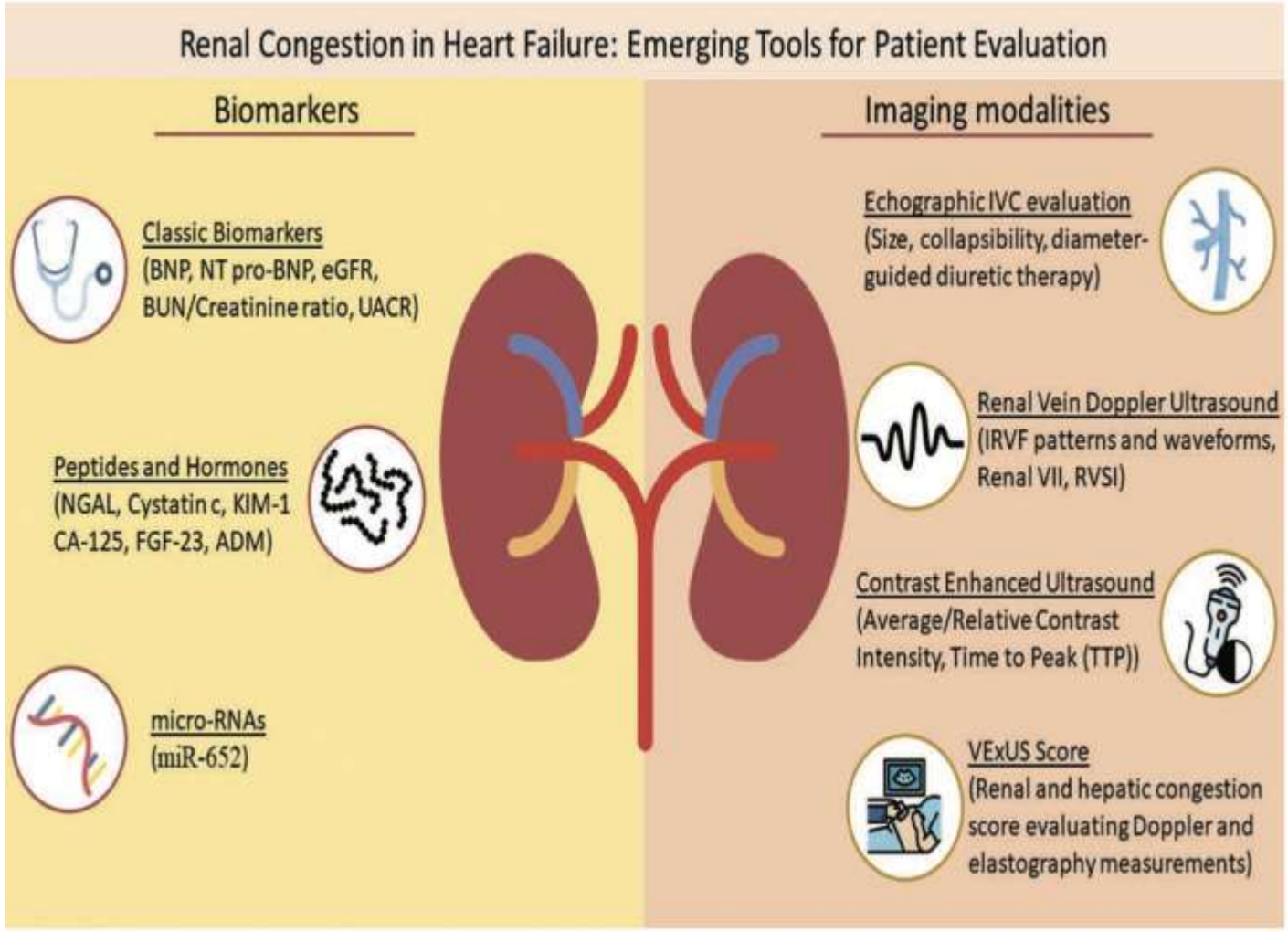


Only plasma Gal3 discriminated high risk patients with WRF

Natov PS et al. Circ Heart Fail. 2023 Mar

Diagnosis of renal congestion

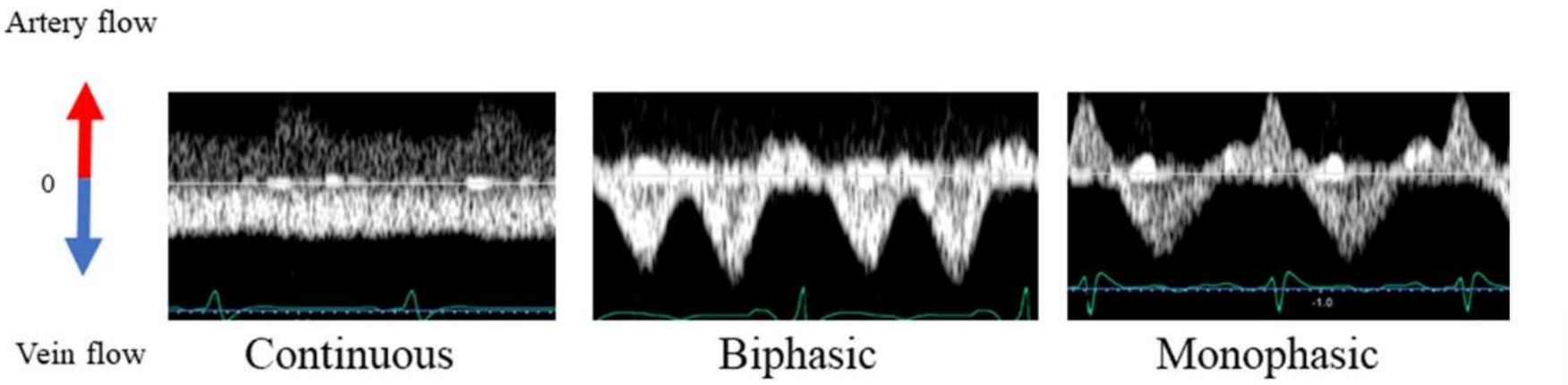
Biomarkers



Dimitriadis K, Damianaki A et al. Cardiol Rev. 2024

Ultrasound assessment of renal congestion

Modality	Indices Measured	Assessed Characteristics	Clinical Significance in Cardiorenal Interplay
Ultrasound	Noninvasive IVC characteristics	IVC size and collapsibility	☐ Increased IVC diameter reflects intravascular volume and RAP ☐ It correlates with GFR, increased rehospitalization, and mortality in HF patients ☐ Predictor of WRF
Doppler ultrasound	Intrarenal venous flow (IRVF)	Doppler waveform patterns, renal vein flow	☐ IRVF strongly associated with mortality and rehospitalization ☐ Persistent discontinuous patterns, regardless of baseline IRVF, correlate with progression of baseline renal function to impaired values and poorer prognosis
	Renal venous stasis index	Renal venous stasis (time with no renal venous outflow during cardiac cycle)	☐ Reflects IVC diameter and right heart hemodynamics ☐ It can be associated with severity of AKI and worse outcomes in HF patients ☐ May be used in the acute setting to identify acute cardiorenal syndrome
	Renal resistive index (RRI)	Renal vascular compliance and resistance	☐ It is associated with HF-rehospitalizations and mortality ☐ It can improve patient classification when added to GFR
	Velocity time integral (VTI)	Renal perfusion	☐ Low VTI, along with abnormal IRVF, is a predictor of adverse cardiovascular outcomes in decompensated HF
Contrast-enhanced ultrasound	Time-to-peak, renal contrast index	Renal congestion	☐ Patients with HF have worse baseline time-to-peak ☐ Can be used to guide diuretic therapy, as time-to-peak is decreased and renal contrast index is increased after successful decongestion
Elastography/hepatic Doppler ultrasound	Portal venous flow alterations	Hepatic congestion, reflective of right HF and increased venous pressure	☐ No established connection with renal indices yet ☐ VexUS score, assessing IVC, hepatic, portal, and interlobular renal veins, shows a strong correlation with AKI development of AKI and can accurately diagnose cardiorenal syndrome

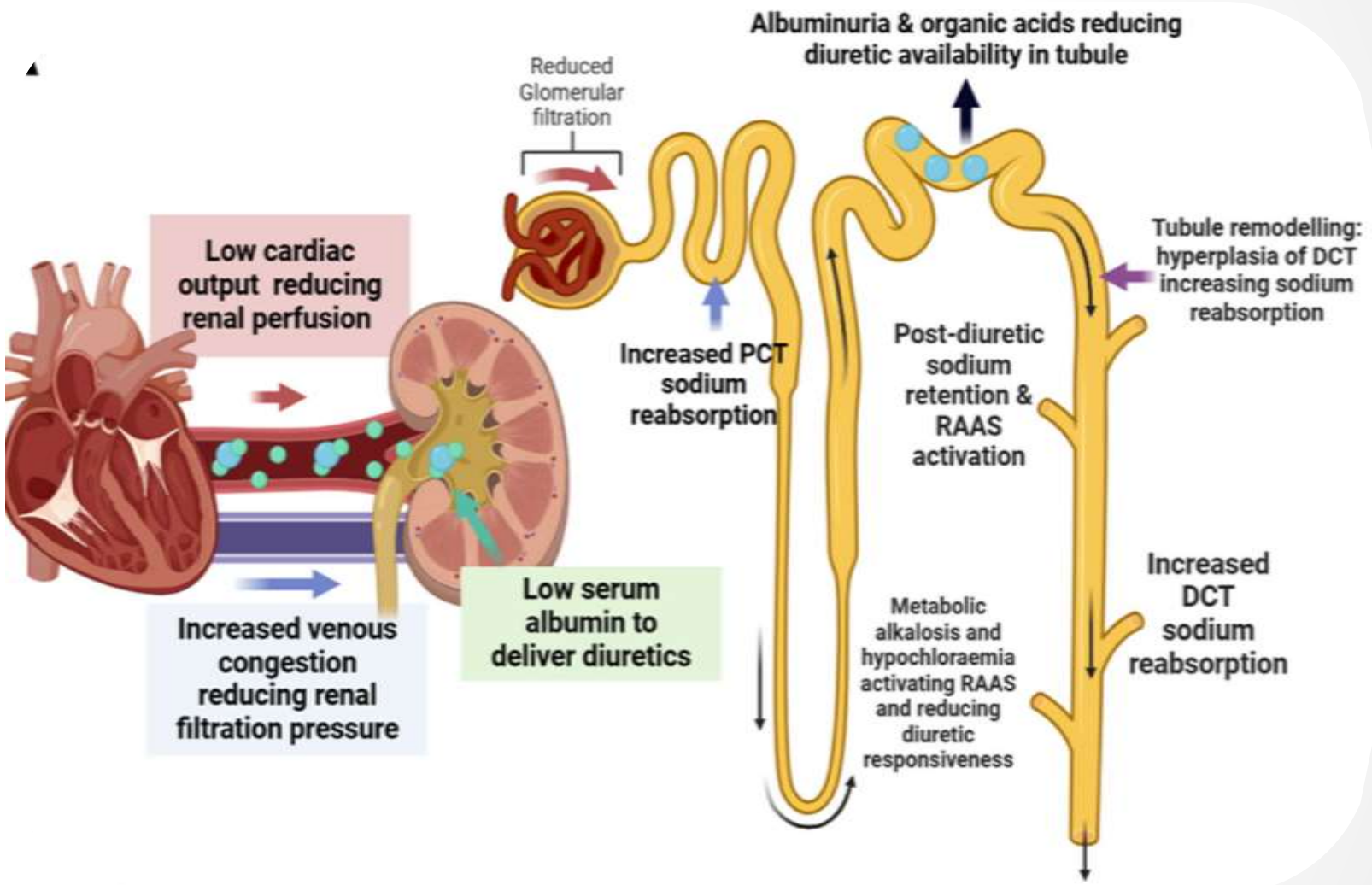


Dimitriadis K, Damianaki A et al. Cardiol Rev. 2024

Treatment strategies

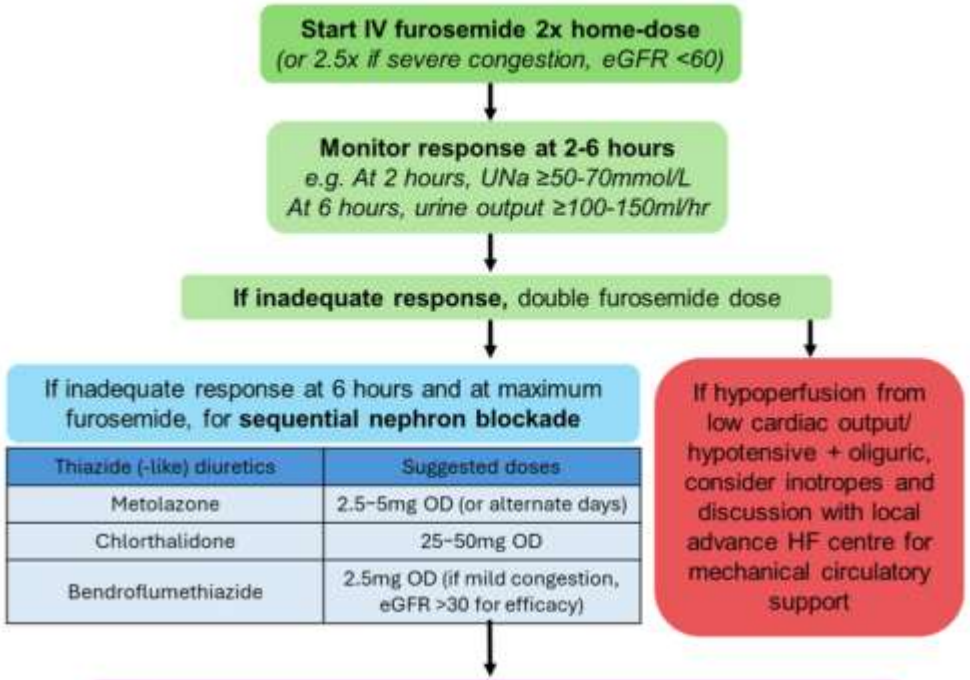
Diuretics - Diuretic Resistance

- **Definition:** inadequate natriuresis despite appropriate diuretic regimen.
- **Mechanisms:**
    - reduced renal perfusion
    - venous congestion
    - tubular sodium reabsorption
    - RAAS activation
- **Clinical marker**
    - Spot urine sodium <50-70 mmol/L predicts worsening kidney function, HF, and adverse events.



Tran P et al. J Clin Med. 2025 Apr; Felker GM et al. J Am Coll Cardiol. 2020 Mar

DR – Natriuresis guided treatment



Thiazide (-like) diuretics	Suggested doses
Metolazone	2.5–5mg OD (or alternate days)
Chlorthalidone	25–50mg OD
Bendroflumethiazide	2.5mg OD (if mild congestion, eGFR >30 for efficacy)

Suggested alternative	Favourable indications
Acetazolamide 250-500mg OD to BD *(off-label use)*	Metabolic alkalosis (HCO3>28) Hypochloraemia (<96mmol/L)
Empagliflozin 10-25mg OD *(weak diuresis)*	Cardiorenal/diabetic indications, especially if eGFR ≥20
Ultrafiltration/ peritoneal dialysis	Oliguric with persistent severe congestion, ascites, low blood pressure
Hypertonic saline 3% 150mls over 30-60min *(unlicensed use for diuresis)*	Especially if severe hyponatraemia (± symptomatic)
Tolvaptan 15-30mg OD	Especially if severe hyponatraemia (± symptomatic)

www.kidney-international.org KDIGO executive conclusions

Kidney disease and heart failure: recent advances and current challenges: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

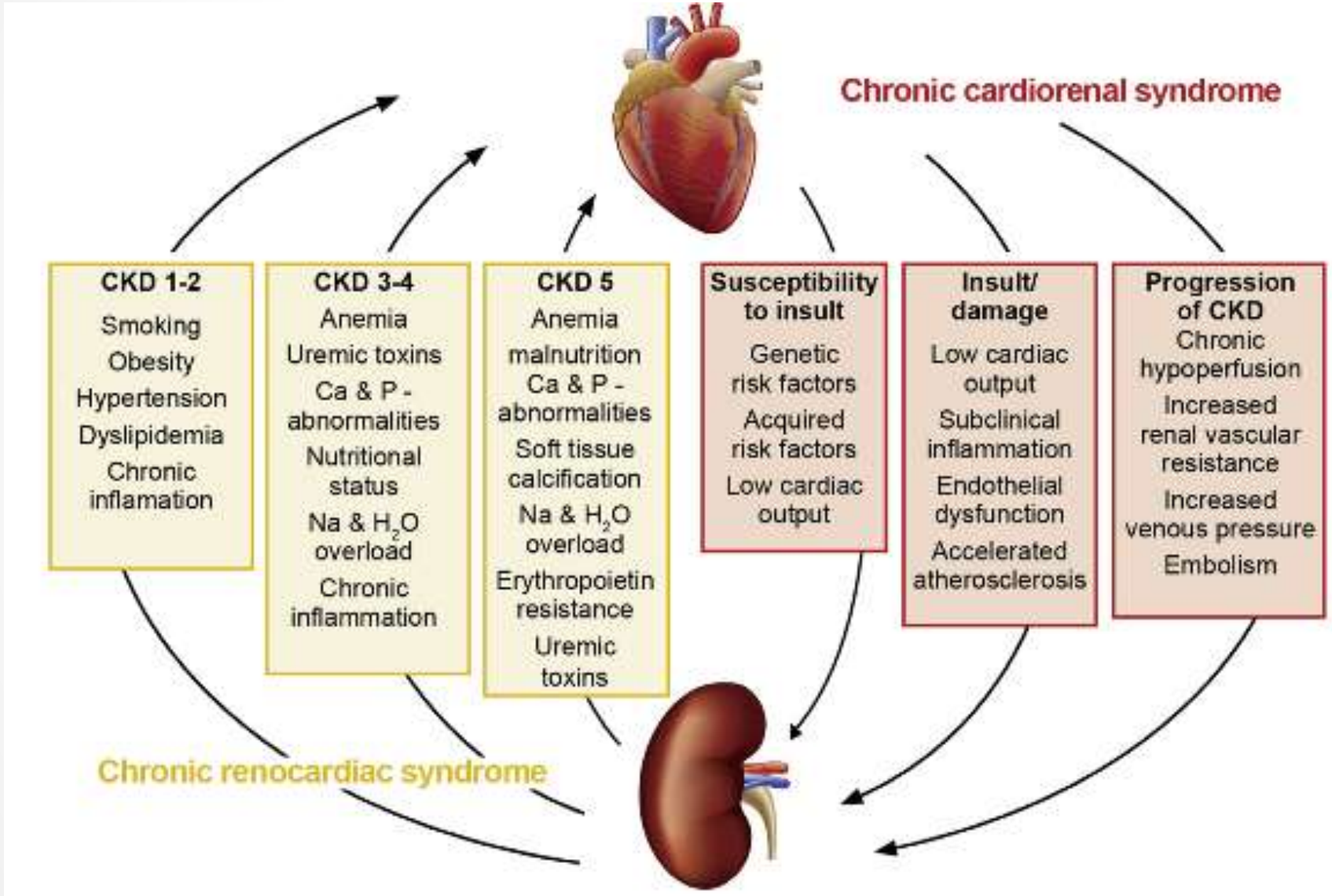
OPEN

Carolyn S.P. Lam[1], Biykem Bozkurt[2,3], David Z.I. Cherney[4], Justin A. Ezekowitz[5], Meg J. Jardine[6,7], Sadiya S. Khan[8,9], Magdalena Madero[10], Mark J. Sarnak[11], Jozine M. ter Maaten[12], Michael Cheung[13], Jennifer M. King[13], Morgan E. Grams[14], Michel Jadoul[15] and Nisha Bansal[16]; for Conference Participants[17]

Caution with Pt with already ATN e.g., in the context of sepsis, infection etc. or pt already received ivc as **proximal tubule is not working properly to correctly evaluate UNa^+**

Tran P et al. J Clin Med. 2025 Apr

CRS type 2 – Chronic cardiorenal syndrome

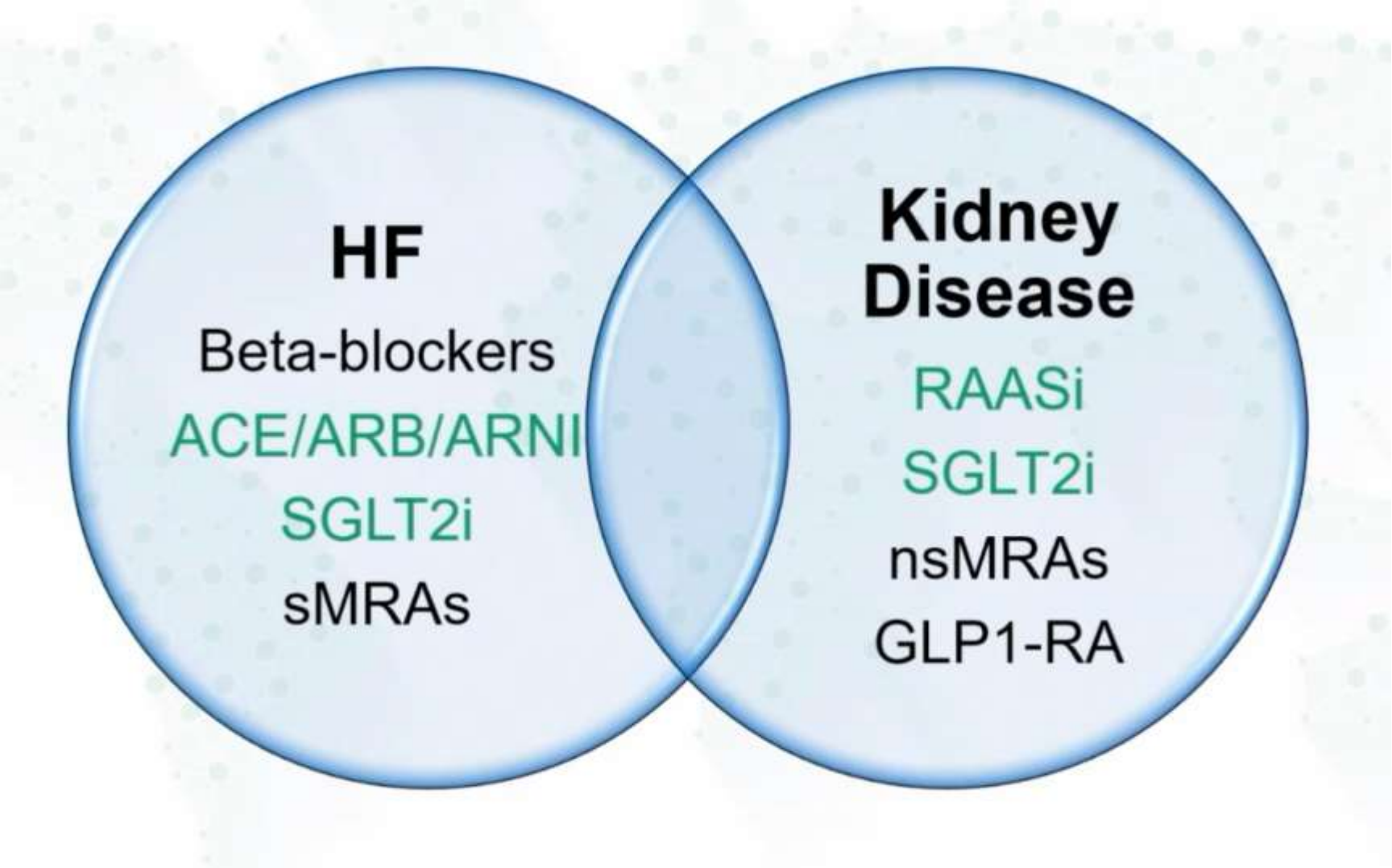


Key mechanisms

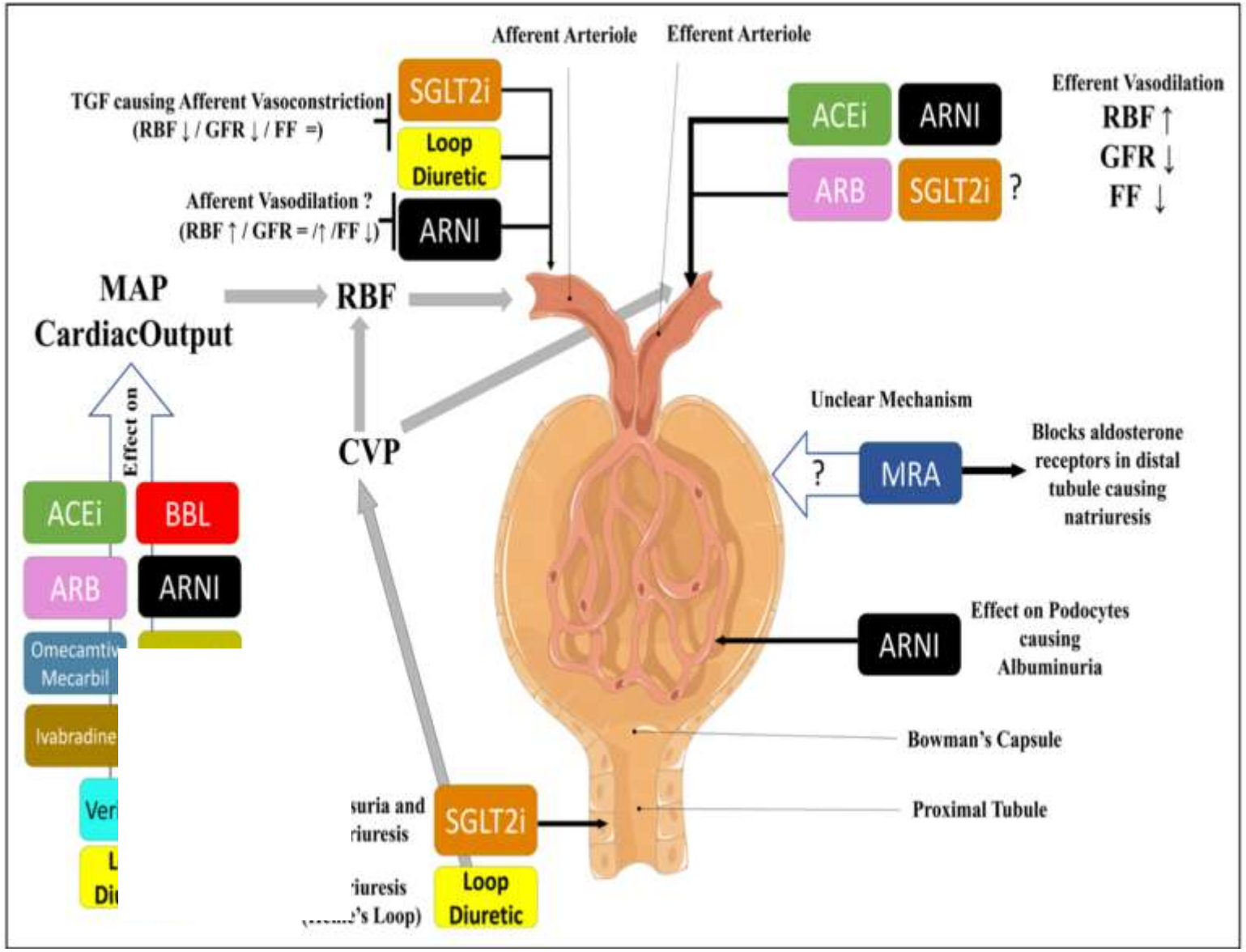
- chronic hypoperfusion
- venous congestion
- neurohormonal activation

Ronco C et al. Adv Chronic Kidney Dis. 2018; Cruz DN, Bagshaw SM.. Int J Nephrol. 2010

Pharmacological Therapy in Heart Failure & CKD: **Significant overlap** in treatments for HF and CKD.



Renal function changes during HF therapy may be hemodynamic



Beldhuis IE et al. Circulation. 2022 Mar

CRS type 3

Occurs when **AKI contributes and/or precipitates** to the development of **acute cardiac injury.**

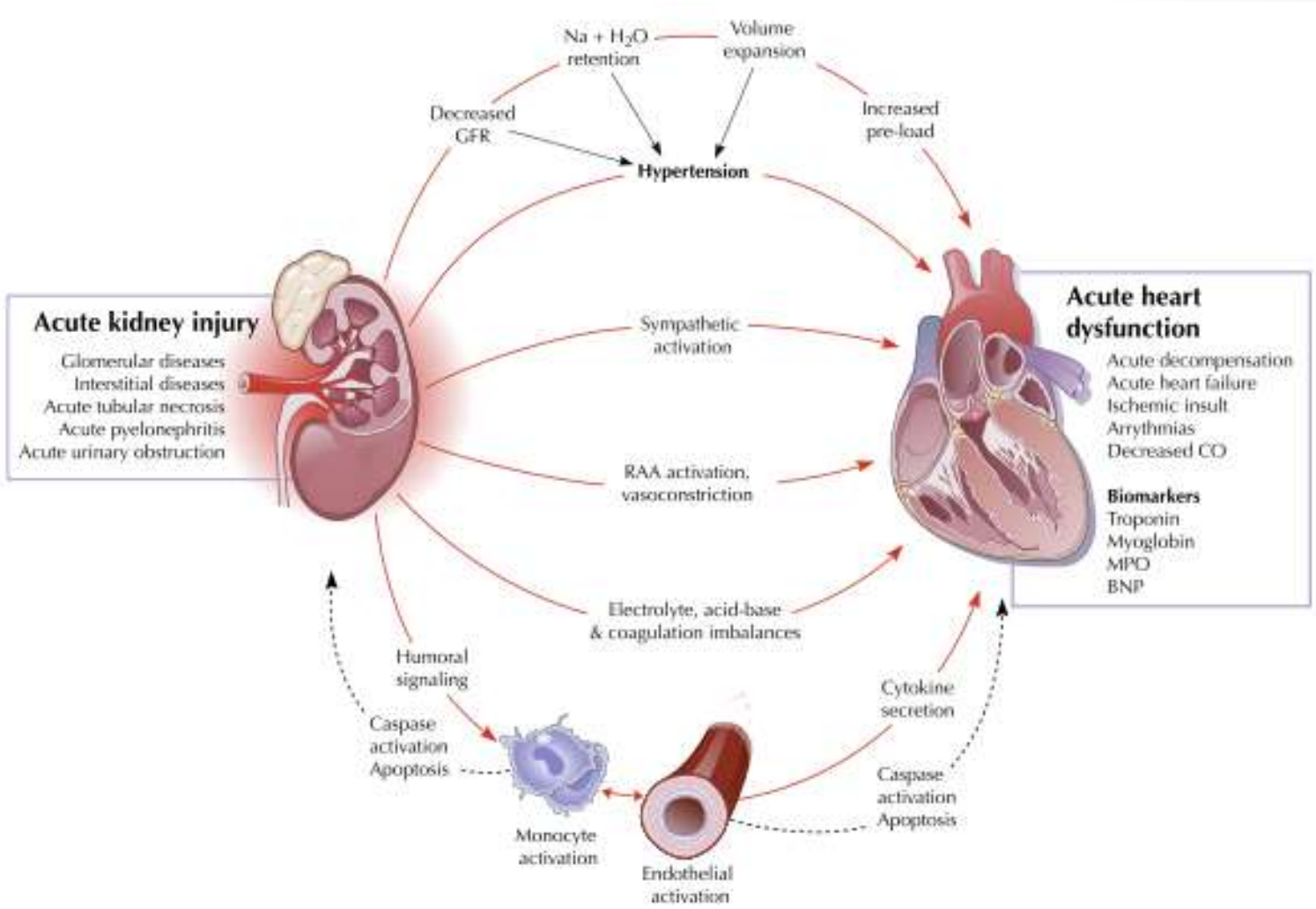
AKI may directly or indirectly produce an acute cardiac event through multiple mechanisms:

- Fluid overload → pulmonary edema
- Hyperkalemia → arrhythmias/cardiac arrest
- Uremia → myocardial depression & pericarditis
- Acidemia → pulmonary vasoconstriction & reduced contractility
- Renal ischemia → inflammation & cardiac apoptosis

Special Clinical Setting

Bilateral renal artery stenosis

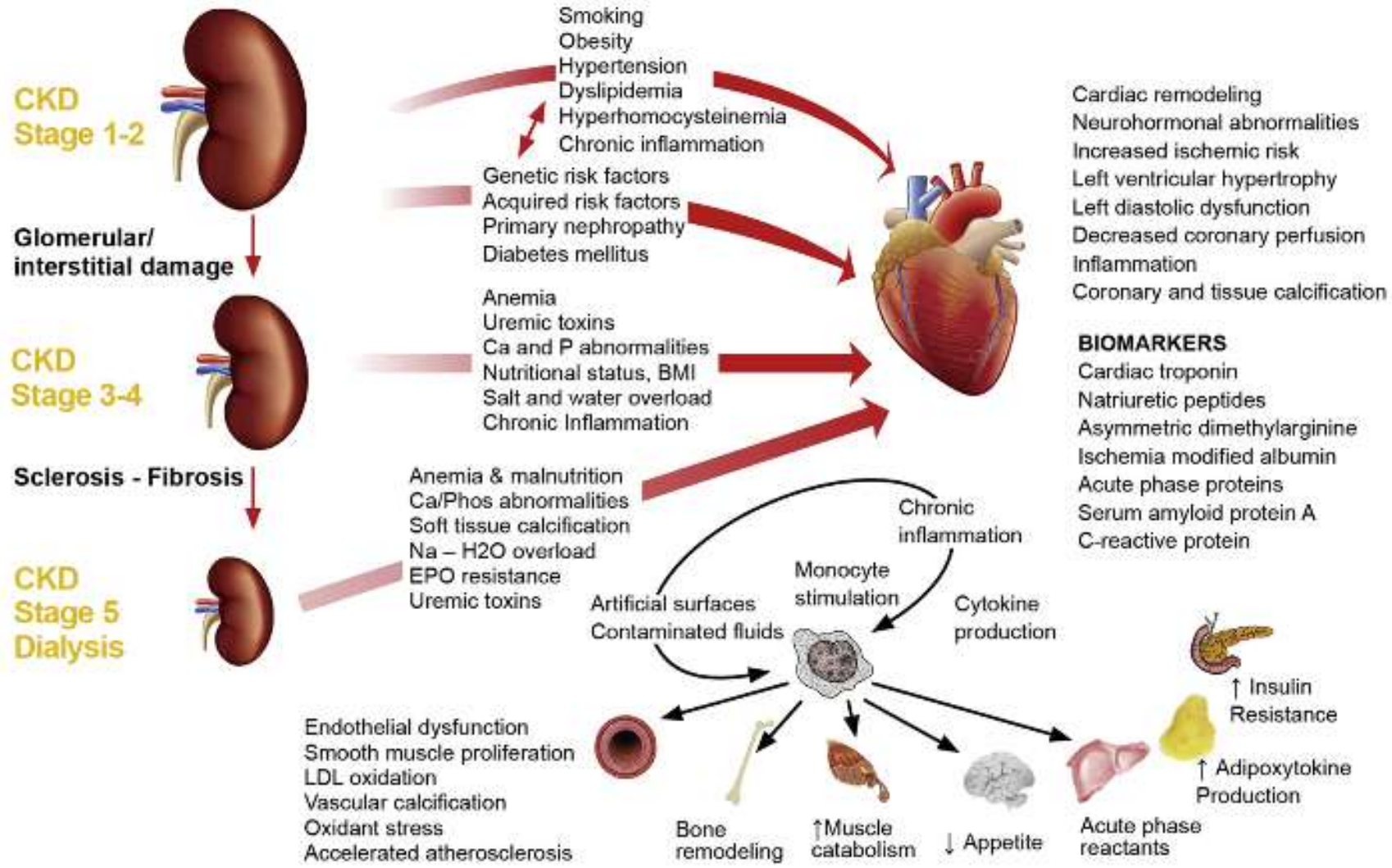
May precipitate acute/decompensated HF through



Ronco C et al. Adv Chronic Kidney Dis. 2018

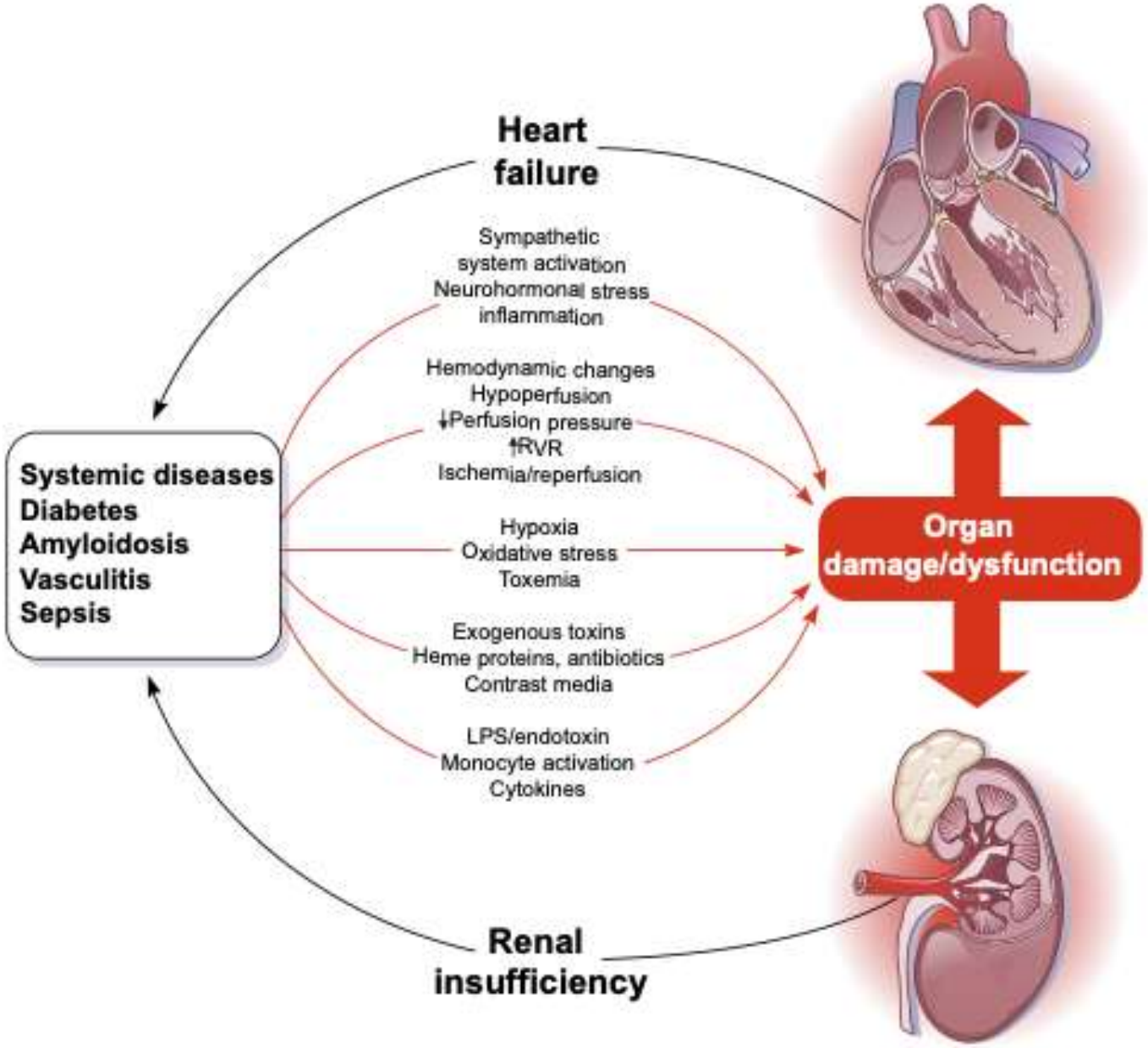
CRS type 4

CKD → chronic cardiac dysfunction

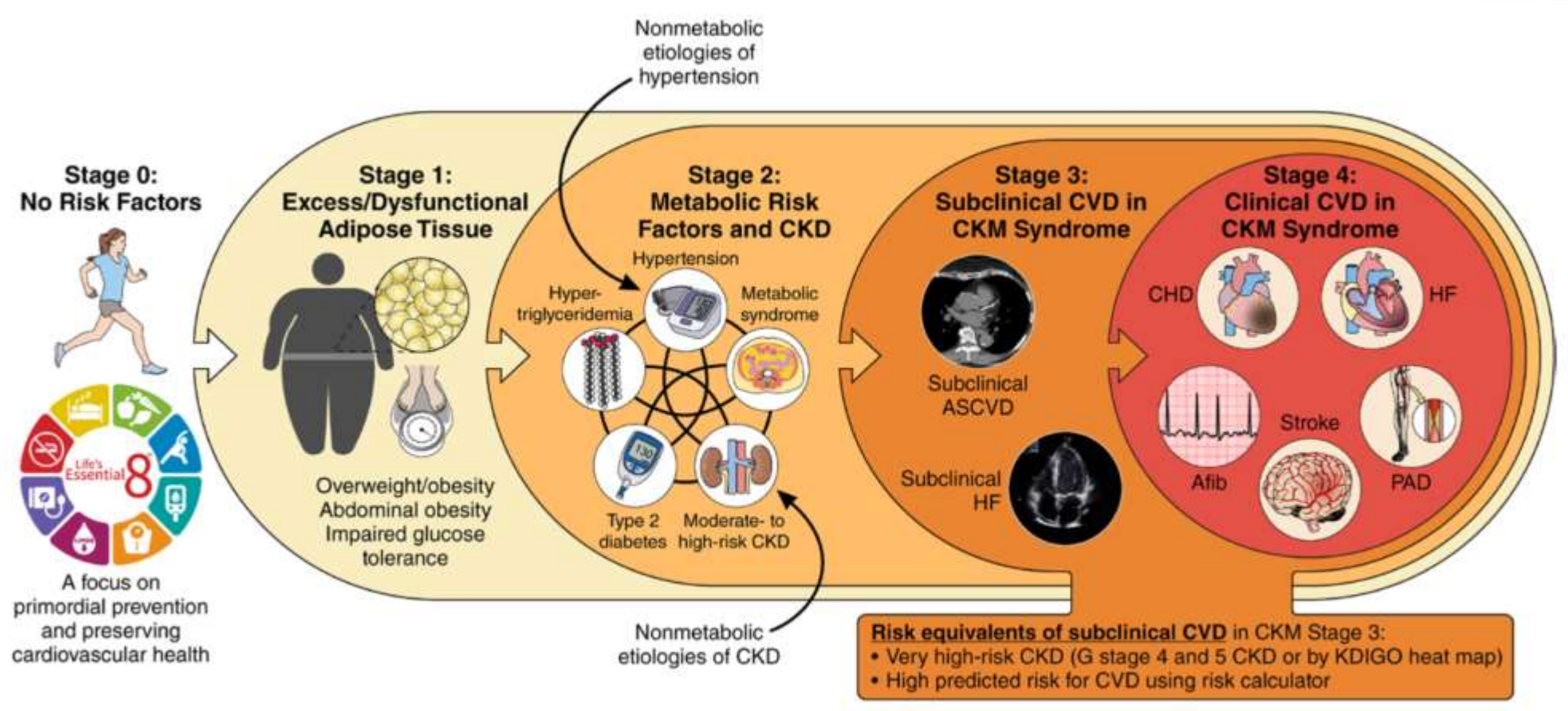


Ronco C et al. Adv Chronic Kidney Dis. 2018 .Go AS et al, N Engl J Med. 2004

CRS type 5


Heart failure
Sympathetic system activation
Neurohormonal stress
inflammation
Hemodynamic changes
Hypoperfusion
↓Perfusion pressure
↑RVR
Ischemia/reperfusion
Hypoxia
Oxidative stress
Toxemia
Exogenous toxins
Heme proteins, antibiotics
Contrast media
LPS/endotoxin
Monocyte activation
Cytokines
Systemic diseases
Diabetes
Amyloidosis
Vasculitis
Sepsis
Organ damage/dysfunction
Renal insufficiency

Is CRS classification still enough?



Ndumele CE et al, Circulation 2023

Limitation of CKM

CKM syndrome successfully highlights:

- Obesity
- Diabetes
- Metabolic inflammation
- Vascular dysfunction

However:

- Less emphasis on acute hemodynamic interactions
- Limited distinction between primary and secondary organ dysfunction
- Less practical in acute HF/AKI settings
- Weaker applicability in bedside decision-making

Clinical reality:

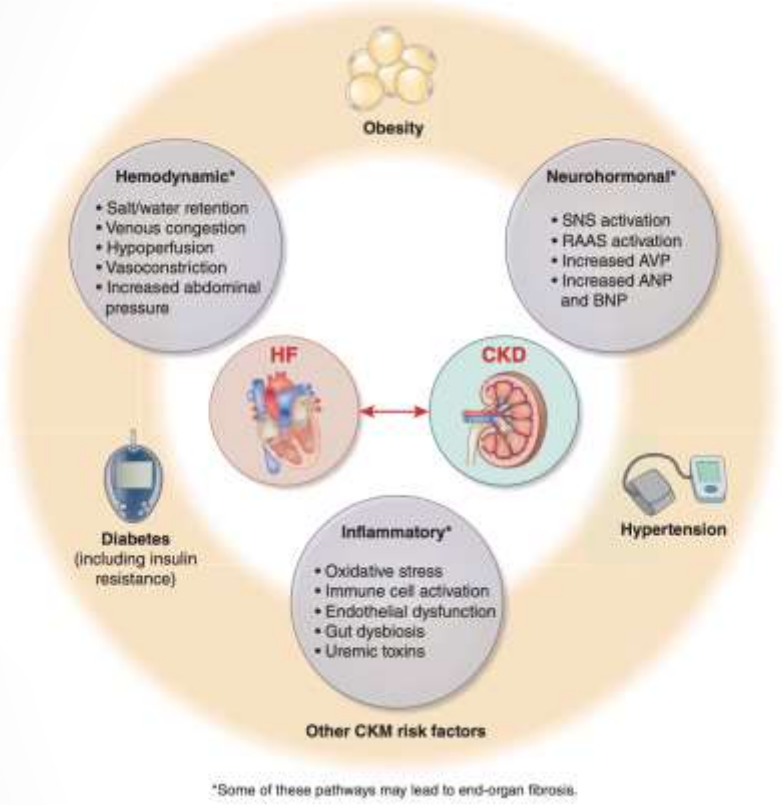
In many hospitalized patients,

congestion and cardiorenal hemodynamics drive outcomes more directly than metabolic staging alone.

CKM adds important context – but does not replace the need for understanding the cross talk in day-to-day clinical practice

Cardiorenal Syndrome vs CKM Syndrome

Which model better reflects real-world cardiorenal disease?



Ronco CRS Classification	AHA CKM Syndrome
Organ interaction model	Multisystem metabolic continuum
Heart ↔ Kidney directionality	Heart - Kidney - Metabolic integration
Acute & chronic phenotypes	Chronic cardiometabolic risk framework
Hemodynamic & neurohormonal focus	Obesity, diabetes & inflammation focus

Final perspective: The two models may be complementary – but CRS remains the more clinically actionable framework.