Cardiorenal syndrome in CKD ; No more agree to disagree

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Circulation

AHA SCIENTIFIC STATEMENT

Cardiorenal Syndrome: Classification, Pathophysiology, Diagnosis, and Treatment Strategies

A Scientific Statement From the American Heart Association

2019

Case presentation

A 54-year-old man was referred to a joint cardiology-nephrology clinic presenting with

1. progressive edema,
2. increasing breathlessness (New York Heart Association class 3),
3. decreased urine output,
4. stage 5 CKD.

On examination,

he had leg edema,

his weight since the last hospital visit had increased by 9 kg,

his BP was 158/70 mm Hg,

his pulse rate was 74 beats/min,

his jugular venous pressure was elevated,

bibasilar chest crepitations were audible.

- He had no ascites.

- Four years ago, he was diagnosed with biopsy proven, stage 3 diabetic nephropathy; multivessel, inoperable coronary artery disease; and heart failure with reduced ejection fraction.

- He suffered from hypertension and hypercholesterolemia.

What would you do next?

- His echocardiogram showed reduced ejection fraction of 20%, moderate diastolic dysfunction

- Electrocardiogram showed sinus tachycardia with rate= 110/min and QRS duration of 100 ms

- He was previously treated with aspirin, clopidogrel, bisoprolol 2.5 mg daily, enalapril 2.5 mg BID, atorvastatin 40 mg, metformin 500 mg BID, furosemide 40 mg BID, and insulin.

- *Next step ?*

- His blood tests showed sodium 130 mmol/L, potassium 5.7 mmol/L, creatinine 4.2 mg/dl (372 mmol/L), eGFR 15 ml/min per 1.73 m2, and N-Terminal pro-B-type natriuretic peptide 2742 ng/L , ferritin 70.

- Diuretic therapy?

- Intermittent metolazone and careful monitoring of weight and electrolytes
- In the joint clinic, his furosemide dose was increased, he was started on daily metolazone, his b-blocker dose increased, intravenous iron was administered, and metformin was stopped.
- He was informed about long-term KRT and visited the peritoneal dialysis unit.

- All of this was only possible because he was seen in a joint CKD-heart failure clinic with access to specialist nurses.

Renal Biomarkers in CRS

Markers of Glomerular Filtration and Integrity

- The incidence of AKI, as defined by an increase in serum creatinine of *>0.3 mg/dL*, is about 27.0%–47.6% in patients hospitalized for ADHF.

- Obvious changes in serum creatinine may not be seen until 48–72 h after renal insult, potentially delaying the diagnosis of AKI and CRS I.

- *CysC* and *albuminuria* represent biomarkers of glomerular filtration and integrity in CRS.
- Serum CysC (>1.55 mg/L) was associated with twice the risk of cardiovascular mortality adjusted for baseline characteristics.

In patients presenting with AHF, ***serum CysC was a strong indicator*** of

1. rehospitalization
2. short- and long-term mortality
3. additive prognostic value when combined with NT-proBNP and cardiac troponin T.

Markers of Renal Tubular Injury

- The renal tubules are *more sensitive* to ischemia than the glomeruli, so the tubular damage is predominant in the early stage of cardiorenal syndrome

NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN

- NGAL is widely accepted as a marker of AKI.
- Plasma NGAL levels increased *10-fold* and urine NGAL levels increased *100-fold* in acute kidney injury.
- NGAL has been identified as a reliable urinary biomarker of acute kidney injury.
- Increased NGAL urinary concentrations are directly linked to declination of the renal tubular epithelial cells as a result of injury

- Expressed in endothelial cells, smooth muscle cells and macrophages in *atherosclerotic plaques* and may involve in the development of atherosclerosis through endothelial dysfunction, inflammatory processes and matrix degradation.

- Serum NGAL levels at admission were associated with a *heightened risk of worsening renal function in patients admitted for ADHF*

- In acutely decompensated HF (GALLANT-2018) trial, patients with high BNP/high NGAL had the worst outcomes, whereas survival rate was high when both markers were low

TIMP-2 & IGFBP7

- The combination of both tubular biomarkers involved in G1 cell cycle arrest during the early phase of cell injury, is available for clinical use in the United States.
- In SAPPHIRE validation cohort , the combination of urine TIMP-2 and IGFBP7 was superior to previously described markers of AKI ($P<0.002$).

KIDNEY INJURY MOLECULE-1

- KIM-1 is markedly induced in response to renal injury and the expression locates on the proximal tubule apical membrane.
- a marker of AKI after cardiopulmonary bypass surgery and cardiac catheterization

- In a study of ADHF patients that combined functional (CysC) and structural damage (NGAL and KIM-1) markers, both CysC + NGAL and CysC + KIM-1 improved the discriminatory power for detecting AKI

Biomarkers	Characteristics/Site of Origin	Diagnostic Value	Prognostic Value
Biomarkers of tubular injury			
TIMP*IGFBP7	Involved in G1 cell cycle arrest; may stimulate renal epithelium in an autocrine and paracrine fashion and sensitize for upcoming insults	AKI	AKI recovery
Serum NGAL	25-kDa protein found in neutrophil granules; secreted by myocardium, renal tubules, activated immune cells, hepatocytes, lung, and colon	AKI	CRS
Urine NGAL	Loop of Henle, collecting ducts	AKI, CRS	CRS
NAG	PCT	CRS, AKI	CRS
KIM-1	Type 1 cell membrane glycoprotein expressed in regenerating PCT epithelium	AKI	CRS
IL-18	Cytokine mediating inflammation and AKI through the nuclear factor-κB pathway	AKI	CRS
L-FABP	Renal PCT	AKI	…
H-FABP	Cardiomyocytes, distal tubule	HF, CRS	…
Urine angiotensinogen	…	AKI, CRS	CRS
α-1 Microglobulin	Synthesized in liver; freely filtered through glomerular capillaries and reabsorbed by PCT	AKI	AKI recovery

Biomarkers	Characteristics/Site of Origin	Diagnostic Value	Prognostic Value
Cardiac biomarkers			
cTn	Marker of myocardial injury	ACS	ACS, HF, CKD
BNP	Marker of myocardial stretch	HF, ACS, CRS	HF, CRS
sST2	Member of IL-1 family of receptors	…	HF, CRS
Galectin-3	β-Galactoside binding lectin (intracellular and extracellular)	…	HF, CRS

Soluble ST2 (sST2)

- secreted into the circulatory system by in response to inflammatory and cardiac diseases. *cardiomyocytes and pulmonary endothelial cells*
- *predict mortality* and other adverse outcomes in HF and myocardial infarction
- correlated with hemodynamics, LVEF, disease severity and adverse remodeling in AMI , has predicted pulmonary artery pressure, right ventricular hypokinesis and jugular venous distension in ADHF.
- In a study in 2015, the author demonstrated that ST2 is predictive of AKI in patients with ST-elevation myocardial infarction.

Diuretic Therapy

- Diuretic therapy is challenging.

- The *need for higher doses*, Causing transient worsening kidney function and electrolyte imbalances such as hyponatremia and hypokalemia .

- These challenges result in the patient needing to visit a variety of specialty doctors, each changing diuretic agents and diuretic doses, often to minimize adverse electrolyte and creatinine changes, and resulting in *poor symptom control for the volume-overloaded patient.*

- *Renal venous congestion and consequent kidney dysfunction* owing to *elevated right heart pressure

*requiring careful escalation of diuretic doses with close monitoring of weight, electrolytes, and creatinine

- *Is there any significant difference* ***between continuous infusion or bolus administration of intravenous diuretics ?***

AMERICAN COLLEGE of CARDIOLOGY

Diuretic Optimization Strategies Evaluation in Acute Heart Failure - DOSE

Mar 02, 2011

Author/Summarized by Author:	Dharam J. Kumbhani, MD, SM, FACC
Summary Reviewer:	Deepak L. Bhatt, MD, MPH, FACC

Trial Sponsor:	National Heart, Lung, and Blood Institute Heart Failure Clinical Research Network

- The DOSE-AHF trial randomized 308 patients with AHF to

1. bolus versus continuous infusions of furosemide
2. low-dose (intravenous equivalent of patient's home diuretic dose) versus high-dose regimen (2.5 times the patient's home loop diuretic dose intravenously)

- In continuous versus intermittent diuretic dosing, *no significant differences were observed in patients' symptoms* (*P*=0.47) or change in renal function (*P*=0.45); that is,

- No significant differences in the incidence of type 1 CRS were seen.

- There was *a trend* in favor of the high-dose strategy compared with the standard dose in *symptom improvement* (*P*=0.06), without a significant difference change in renal function (*P*=0.21).

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Intensification of Medication Therapy for Cardiorenal Syndrome in Acute Decompensated Heart Failure

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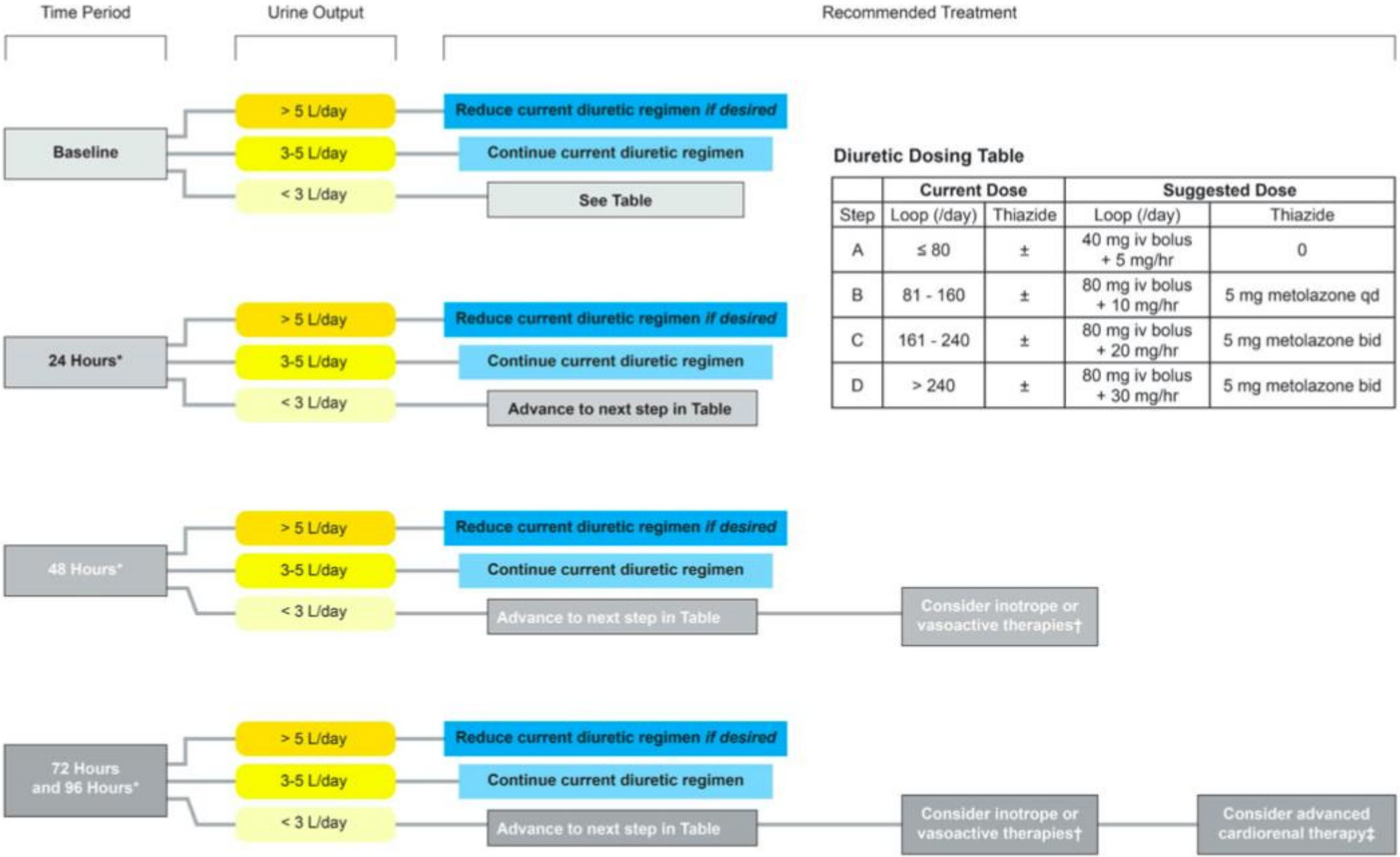

Diuretic Dosing Table

	Current Dose		Suggested Dose	
Step	Loop (/day)	Thiazide	Loop (/day)	Thiazide
A	≤ 80	±	40 mg iv bolus + 5 mg/hr	0
B	81 - 160	±	80 mg iv bolus + 10 mg/hr	5 mg metolazone qd
C	161 - 240	±	80 mg iv bolus + 20 mg/hr	5 mg metolazone bid
D	> 240	±	80 mg iv bolus + 30 mg/hr	5 mg metolazone bid

stepwise pharmacological care algorithm (SPCA) versus standard decongestive therapy(SDT)

- All patients developed cardiorenal syndrome (rise in creatinine >0.3 mg/dL)

- The SPCA group had *higher degrees of jugular venous pressure* ($p<.0001$) at the time of cardiorenal syndrome.

- The group that received the SPCA *had more weight change* (-3.4±5.2 lbs) and *more net fluid loss* (1.705±1.417 L) after 24 hours than SDT (-0.8±3.4 lbs and 0.892±1.395 L, respectively; $p<0.001$ for both) with a *slight improvement in renal function* (creatinine change -0.1±0.3 vs. 0.0±0.3 mg/dL, respectively; $p=0.03$).

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Published online 10 March 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13286

ORIGINAL RESEARCH ARTICLE

Continuous versus intermittent use of furosemide in patients with heart failure and moderate chronic renal dysfunction

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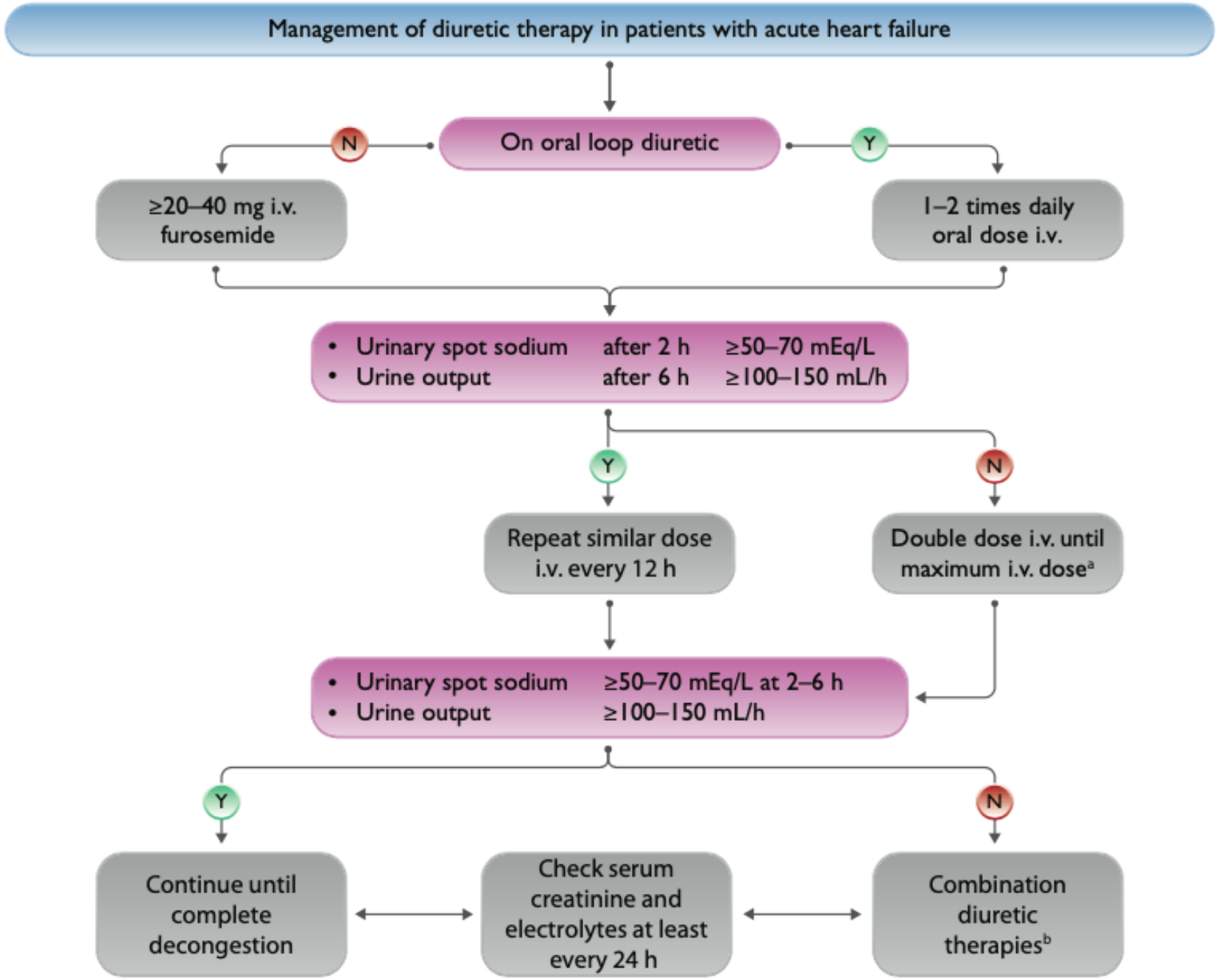
- Acute decompensated heart failure and moderate chronic renal insufficiency [eGFR : 15.0–44.9 mL/min/1.73 m2]
- freedom from *congestion in the CI* group was significantly higher than that in the BI group (69.05% vs. 43.59%, P = 0.02).
- the *CI group had lower dyspnea* score than those in the BI group 72 h (1.15 ± 0.35 vs. 2.66 ± 0.83; P = 0.003).
- *CI group had more net urine output* at 72 h (5145.98 ± 621.37 mL vs. 3755.95 ± 456.93 mL; P = 0.007),
- The *more mean body weight loss* (4.72 ± 1.01 kg vs. 3.53 ± 0.73 kg; P = 0.02)
- The *shorter length of hospitalization* in the CI group (10.36 ± 4.20 days vs. 15.68 ± 6.15 days; P = 0.02).
- No significant differences were observed between groups in the **frequency of acute kidney injury, tinnitus, electrolyte disturbance or mortality**.


Management of diuretic therapy in patients with acute heart failure
On oral loop diuretic
N
Y
≥20–40 mg i.v. furosemide
1–2 times daily oral dose i.v.
• Urinary spot sodium after 2 h ≥50–70 mEq/L
• Urine output after 6 h ≥100–150 mL/h
Y
N
Repeat similar dose i.v. every 12 h
Double dose i.v. until maximum i.v. dose[a]
• Urinary spot sodium ≥50–70 mEq/L at 2–6 h
• Urine output ≥100–150 mL/h
Y
N
Continue until complete decongestion
Check serum creatinine and electrolytes at least every 24 h
Combination diuretic therapies[b]

AMERICAN COLLEGE of CARDIOLOGY

Renal Optimization Strategies Evaluation in Acute Heart Failure - ROSE AHF

Nov 18, 2013

Author/Summarized by Author:	Anthony A. Bavry, MD, MPH, FACC
Summary Reviewer:	Deepak L. Bhatt, MD, MPH, FACC

Trial Sponsor:	National Heart, Lung, and Blood Institute; National Center for Advancing Translational Sciences; and the National Institute on Minority Health and Health Disparities

- Among patients with acute heart failure and renal dysfunction, ***neither low-dose dopamine nor low-dose nesiritide*** enhanced decongestion or improved renal function.

- The use of these agents will likely need to be re-evaluated in the setting of acute heart failure and renal dysfunction.

- No difference in the co-primary end points of cumulative urine volume and change in serum CysC at 72 hours

Circulation

ORIGINAL RESEARCH ARTICLE

Worsening Renal Function in Patients With Acute Heart Failure Undergoing Aggressive Diuresis Is Not Associated With Tubular Injury

- Patients in the multicenter ROSE-AHF trial with baseline and 72- hour urine tubular injury biomarkers were analyzed (n=283). WRF was defined as a ≥20% decrease in glomerular filtration rate estimated with cystatin C.

- For these patients with acute heart failure and CKD stages 3 and 4, rapid diuresis of 8425 ml (interquartile range 6341–10,528) over 72 hours, with 560 mg (interquartile range 300–815) of furosemide, was *safe and was not associated with elevation of markers of tubular injury despite some worsening of creatinine*

- *markers of tubular injury* were paradoxically associated with improved survival (adjusted hazard ratio, 0.80 per 10 percentile increase; 95% confidence interval, 0.69–0.91; *P*=0.001).

- *Aggressive diuresis may be useful*, provided that the patient is adequately decongested, as evidenced by improvement of physical symptoms and decreased BNP and hemoconcentration, despite the rise in creatinine

- Loop diuretics have a short duration of action, lasting 2 to 3 hours and up to 6 hours for an intravenous bolus and oral administration, respectively. Oral furosemide has &50% bioavailability with a wide range of values,104 explaining the variation in response to oral doses. Intravenous administration and novel subcutaneous infusions of furosemide ensure 100% bioavailability

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MINI-FOCUS ISSUE: DECOMPENSATED HEART FAILURE

Decongestion Strategies and Renin-Angiotensin-Aldosterone System Activation in Acute Heart Failure

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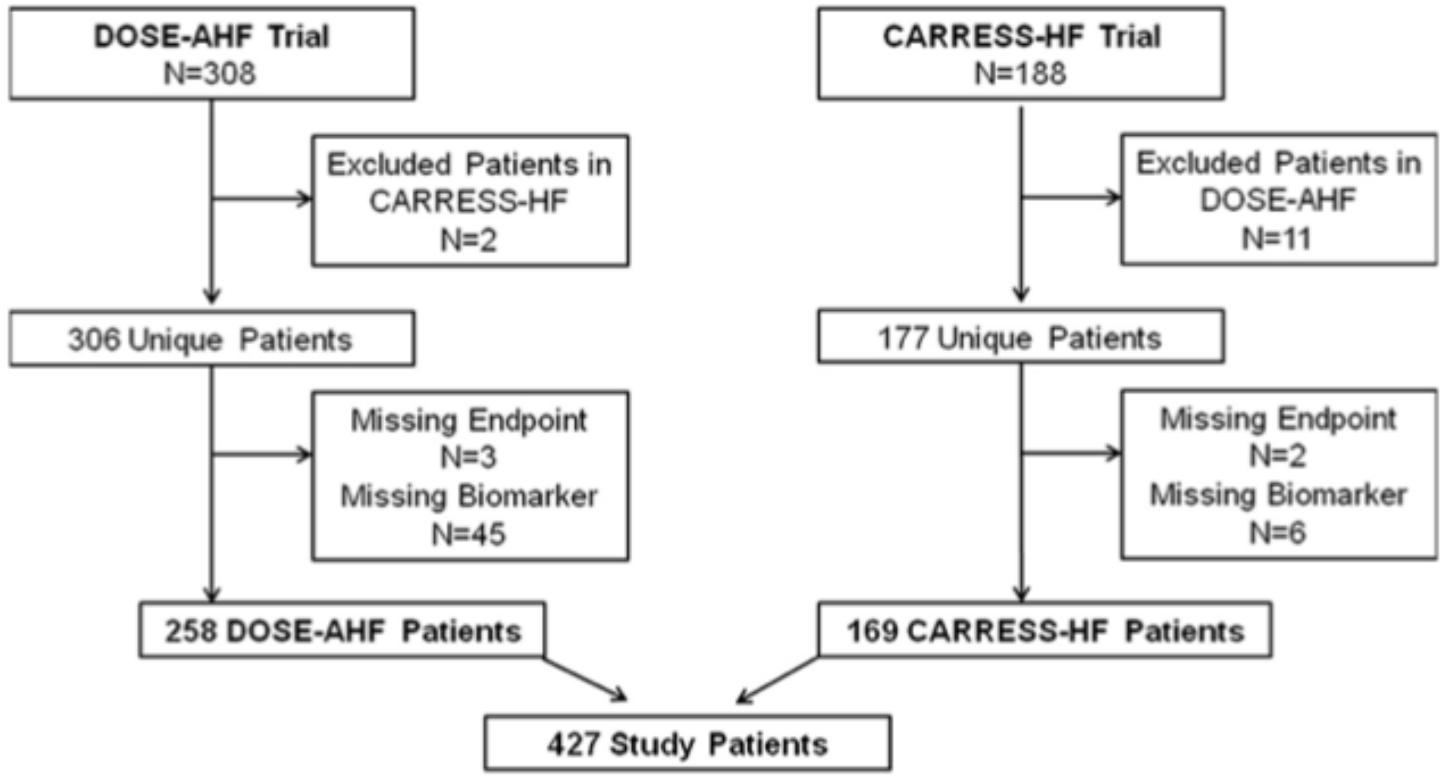
FIGURE 1 Study Patient Population



	Low-dose	High-dose
Bolus	66	68
Continuous	59	65

Stepped Pharm	85
Ultrafiltration	84

- This study analyzed 427 AHF patients enrolled in the DOSE-AHF and CARRESS-HF trials.

- The potentially deleterious effects of RAAS activation by loop diuretics could theoretically limit the ability to break the neurohormonal vicious cycle with AHF.

- The relationship between 2 markers of RAAS activation (plasma renin activity [PRA] and aldosterone) from baseline to 72 h and 96 h

- Decongestion strategy: high- versus low-dose and continuous infusion versus bolus furosemide for DOSE- AHF and UF versus stepped pharmacologic care for CARRESS-HF.

- Patients with greater RAAS activation at baseline had lower blood pressures, lower serum sodium levels, and higher blood urea nitrogen (BUN) concentration.

- *High-dose loop diuretic therapy did not result in RAAS activation* greater than that with low- dose diuretic therapy.

- UF resulted in greater PRA increase than stepped pharmacologic care.

- Neither plasma renin activity nor aldosterone was significantly associated with short- term outcomes in AHF and CRS.

- WRF occurred in a similar percentage of patients with baseline RAAS biomarkers above or below the median values. However, the change in RAAS biomarkers was significantly associated with an increase in WRF PRA and aldosterone levels at baseline and the change following decongestive therapy were not significantly associated with 60-day outcomes.

Diuretic Resistance

- Is defined as the *attenuation of the maximal diuretic effect* that ultimately limits sodium and chloride excretion and is a well-characterized phenomenon of diuretic use.

- In contrast to the lack of kidney injury associated with diuretic use, diuretic resistance *is associated with renal impairment*, increased risk of *rehospitalization* after HF, and *mortality.*

- Oral bioavailability is the first line of resistance

- Because loop diuretics are 95% protein bound, *hypoalbuminemia* increases the volume of distribution and reduces the availability of loop diuretics for facilitated diffusion.

Causes of diuretic resistance

1. Hypoalbuminemia
2. Nonsteroidal anti-inflammatory drugs and uremic toxins
3. CKD
4. HF

- (3, 4)These changes necessitate more frequent dosing rather than dose escalation to achieve maximal sodium excretion
- Administration of effective doses multiple times per day can circumvent the above constraints

- *Nonsteroidal anti-inflammatory drugs* and *uremic toxins* can also competitively inhibit drug transport across proximal tubular epithelial cells.
- CKD reduces excretion of diuretic into the tubular lumen. CKD does not limit the peak effect of drug delivered to the lumen.
- Administration of effective doses multiple times per day can circumvent the above constraints
- HF also reduces the peak effect of the drug, which may be caused by increased proximal reabsorption of sodium (eg, resulting from RAAS activation) or increased expression of Na+K+2Cl−.
- These changes necessitate more frequent dosing rather than dose escalation to achieve maximal sodium excretion

Diuretic Efficiency

- A prognostic marker in CRS
- Patients with *a ratio of urine sodium to urine furosemide <2 mmol/mg* (indicative of low diuretic efficiency)
- less weight loss and fluid removal in the first 24 hours
- significantly increased risk for death, HF rehospitalization, and cardiac transplantation in an adjusted multivariate analysis (HR, 2.2 [95% CI, 1.08– 4.49]).

Singh D, Shrestha K, Testani JM, Verbrugge FH, Dupont M, Mullens W, Tang WH. Insufficient natriuretic response to continuous intra- venous furosemide is associated with poor long-term outcomes in acute decompensated heart failure. *J Card Fail*.

- Thus, measurements of diuretic efficiency may help to identify individuals who develop diuretic resistance and to identify a higher-risk subset of patients with CRS with worse outcomes.

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CLINICAL RESEARCH

Subcutaneous Furosemide in Heart Failure

Pharmacokinetic Characteristics of a Newly Buffered Solution

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- The alkaline pH of furosemide USP precludes SC administration.
- A novel buffered formulation of furosemide (pH 7.4) was developed for SC infusion using a wearable patch pump.
- A 5-h biphasic SC infusion (30 mg in hour 1 followed by 12.5 mg/h for 4 h) of the novel formulation was tested in 2 clinical studies.
- outpatient use, including self- administration at home.

Ultrafiltration

- **The UNLOAD trial** (Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure)

- The primary end of *weight loss at 48 hours* was significantly higher in the ultrafiltration group (5.0±0.68 kg versus 3.1±0.75 kg; *P*=0.001),

- *Dyspnea scores* between the groups were not significantly different.

- There was a significant reduction in *90-day rehospitalization rates in the ultrafiltration arm*, a secondary end point.

Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol*. 2007;49:675–683.

- **CARRESS-HF** was a landmark study that enrolled 188 patients admitted with AHF and worsening renal function

- The only study that included patients with type 1 CRS.

- The primary end point was a bivariate change in weight and creatinine at 96 hours after randomization.

- *No significant differences in weight loss* were noted between the 2 groups (5.5±5.1 kg in the diuretic group versus 5.7±3.9 kg in the ultrafiltration group; *P*=0.58).

- The ultrafiltration group had an increase in serum creatinine of 0.23 mg/dL versus a *decrease of 0.04±0.53 mg/dL in the diuretic group* (*P*=0.003).

- The patients in the ultrafiltration group experienced *a higher rate of adverse events* (72% versus 53%; *P*=0.03).

- **The AVOID-HF trial** (Aquapheresis Versus Intravenous Diuretics Hospitalizations for Heart Failure),

- A stepped-up diuretic algorithm and a detailed ultrafiltration proto-col, was terminated before completion because of slow enrollment.

- In the 224 patients who completed the protocol, *nonsignificant trends toward reduced HF readmissions at 90 days were achieved*, but an increase in adverse events was also reported in the ultrafiltration group (14.6% versus 5.4%; *P*=0.026).

Angiotensin-Converting Enzyme Inhibitors/ARBs

- **CONSENSUS** demonstrated a marked reduction in HF-associated mortality and symptom burden and was characterized by a *doubling of serum creatinine in 11%* of subjects taking enalapril compared with those taking placebo

- Trends in serum creatinine rise were predominantly early and *returned to within 30% of baseline values* in most subjects, consistent with the known hemodynamic effects of ACE inhibitors, with the effect of concomitant diuretic use
- Hypotension being independent predictors of doubling of serum creatinine.

- **SOLVD** (Study of Left Ventricular Dysfunction) reiterated the benefits of enalapril for HF symptoms and hospitalization reduction (LVEF <35%, serum creatinine <2.5 mg/dL 2569 subjects.

- The enalapril group in SOLVD showed a 33% higher likelihood of a serum creatinine rise of >0.5 mg/ dL, *but no data on progression of CKD, ESKD, or doubling of creatinine were reported*.

- A post hoc analysis of SOLVD with HF and CKD demonstrated the mortality benefits even in subjects with higher degrees of CKD.

- Kidney function and mortality among patients with left ven- tricular systolic dysfunction. *J Am Soc Nephrol*. 2006;17:244–253. doi: 10.1681/ASN.2005030270

- Most of these studies included patients with mild-to-moderate (i.e., stages 1–3) CKD.
- Patients with severe CKD have been excluded from most ACEi studies

- A rise of up to 30% can be viewed as resulting from hemodynamic changes owing to RAASis .

- Such a change may be beneficial and is named *permissive AKI* as opposed to *true AKI* due to other reasons in patients with HFrEF, which requires careful history taking and physical examination

- Patients are referred back and forth, between nephrologists and cardiologists, with RAASi-induced changes in creatinine and potassium, resulting in multiple hospital attendances and, often, discontinuation of the RAASi.

- Treatment with (ACEis)/ (ARBs) lowers intraglomerular pressure caused by efferent arteriolar vasodilation, presenting as apparent worsening of kidney function, which causes anxiety in treating physicians.

- With ACEis, eGFR decline up to 35% has been associated with improved heart failure hospitalization rates.

- Oral potassium binders such as ***patiromer*** or sodium zirconium cyclosilicate may be useful .

- Randomized controlled studies of new potassium binders for maximization of RAASi therapy *in patients with advanced CKD and heart failure are necessary.*

- A close collaboration between nephrologists and cardiologists is necessary for successful initiation and continuation of RAASi in patients with CKD and heart failure.

Neprilysin/Renin-Angiotensin Inhibitors

- IMPRESS (Omapatrilat)
- OVERTURE (Omapatrilat versus Enalapril)
- PARADIGM-HF

1. Reduced mortality and HHR
2. More hypotension but less renal dysfunction and hyperkalemia in all 3 trials

- Combined neprilysin and renin-angiotensin system inhibition in heart failure with reduced ejection fraction: a meta-analysis. *Eur J Heart Fail*. 2016;18:1238–1243. doi: 10.1002/ejhf.603

- **PARAMOUNT** (ARNI versus ARB)

1. LCZ696 reduced NT-proBNP,
2. blood pressure,
3. Atrial size to a greater extent
4. Preserving eGFR to a greater extent (36- week decline of GFR, 1.6 mL/min per 1.73 m2 in the LCZ696 group versus 5.2 mL/min per 1.73 m2 in the valsartan group; *P*=0.007)

Pharmacological treatments indicated in patients with (NYHA class II–IV) heart failure with reduced ejection fraction (LVEF ≤40%)

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

- A randomized controlled trial of angiotensin receptor neprilysin inhibitors, including patients with eGFR *as low as 20 ml/ min* per 1.73 m2, demonstrated safety and efficacy similar to irbesartan *

- More recently, angiotensin receptor and neprilysin inhibitor therapy has been shown to *slow the progression of CKD* in patients with heart failure with preserved ejection fraction (HFpEF) more effectively than valsartan

(Effects of sacubitril/valsartan versus irbesartan in patients with chronic kidney disease. Circulation 138: 1505–1514, 2018)

- The recommended starting dosage for patients with eGFR,60 ml/min per 1.73 m2 is 24 mg sacubitril and 26 mg valsartan, administered twice per day, *at least 36 hours after stopping ACEis or ARBs*;

- The dose is then increased, with careful monitoring of creatinine, potassium, and BP.

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Renal protective effects and mechanisms of the angiotensin receptor-neprilysin inhibitor LCZ696 in mice with cardiorenal syndrome

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BNP was shown to reduce renal fibrosis and decrease the expression of major protein in the fibrotic pathway compared to control animals and this was independent of blood pressure effects.

The benefits is also seen in the heart, where cardiac hypertrophy and fibrosis in an animal model of CKD.

Therefore, ARNI has been recognized as an effective treatment for cardiorenal syndrome .

Mineralocorticoid Receptor Antagonists

- The long-term efficacy of achieving complete suppression of RAAS with an ACE inhibitor/ARB is limited by the phenomenon of *aldosterone escape*, resulting in an increased level of serum aldosterone.

- Mineralocorticoid receptor antagonists (MRAs), when added to an ACE inhibitor/ARB, can provide more suppression of RAAS with potential long-term cardiorenal benefits.

- *Given the universal exclusion of moderate to severe CKD in HF* outcomes trials and the lack of reporting on long-term renal outcomes, the true burden of hyperkalemia in the management of chronic CRS is unclear.

Ivabradine and beta-Blockers

- Carvedilol has been shown to be beneficial in patients with heart failure with CKD stage 5 who are receiving dialysis.

- MERIT-HF study(randomized 3991 patients with NYHA class II to IV HF and EF <40% to metoprolol versus placebo)

1. The benefits were more pronounced in the group with eGFR <45 mL/min
2. 60% reduction in HHF and mortality

- **(SHIFT) study** the Ivabradine and outcomes in chronic heart failure
- *improved hospitalization and deaths* in patients with HFrEF with a *heart rate >70 beats per minute* despite b-blocker therapy, which included patients with *creatinine<2.5 mg/dl.*

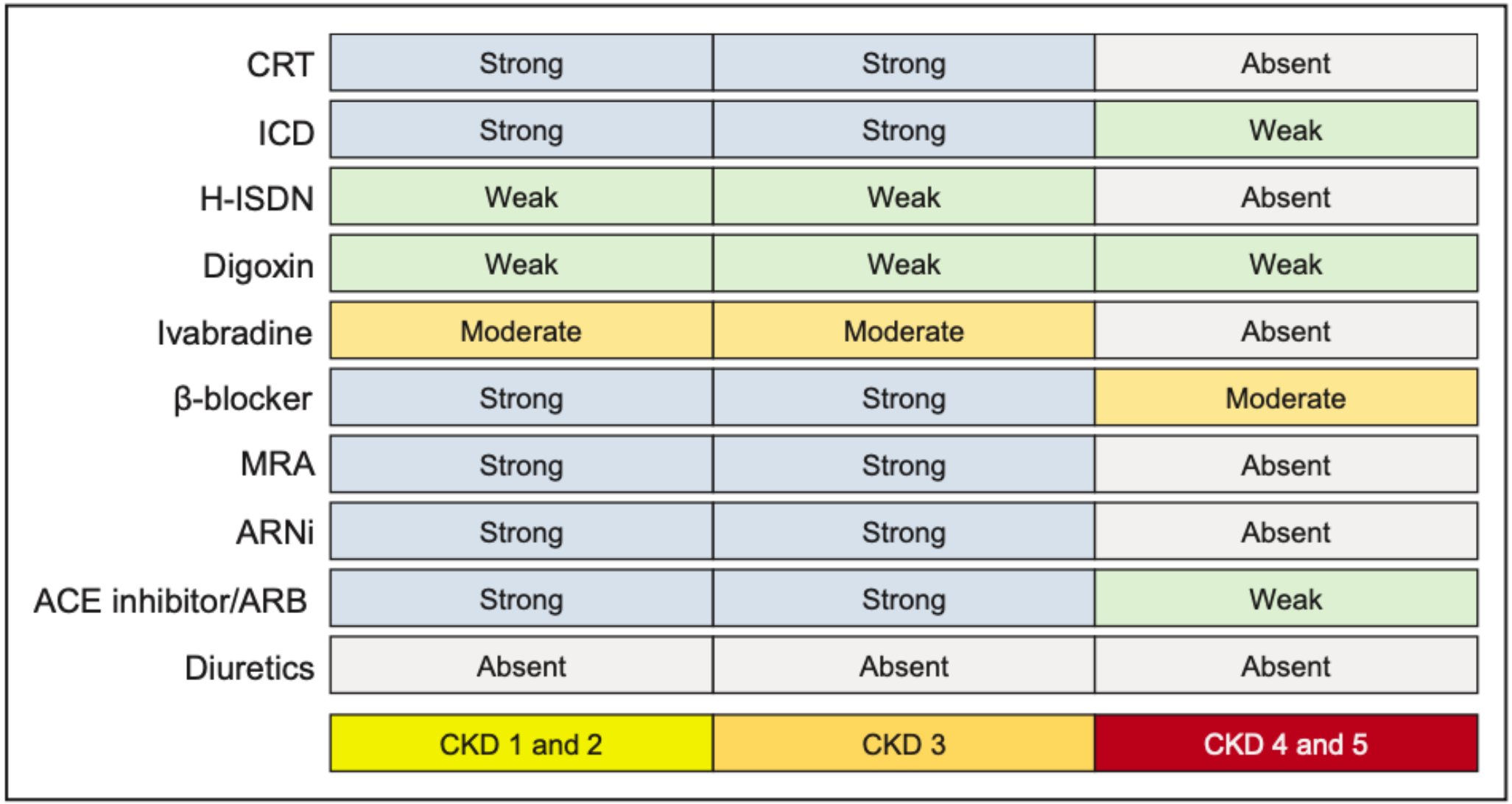
- The study included 1589 patients with CKD stage 3, and benefits in **patients with CKD were similar to patients without CKD .**

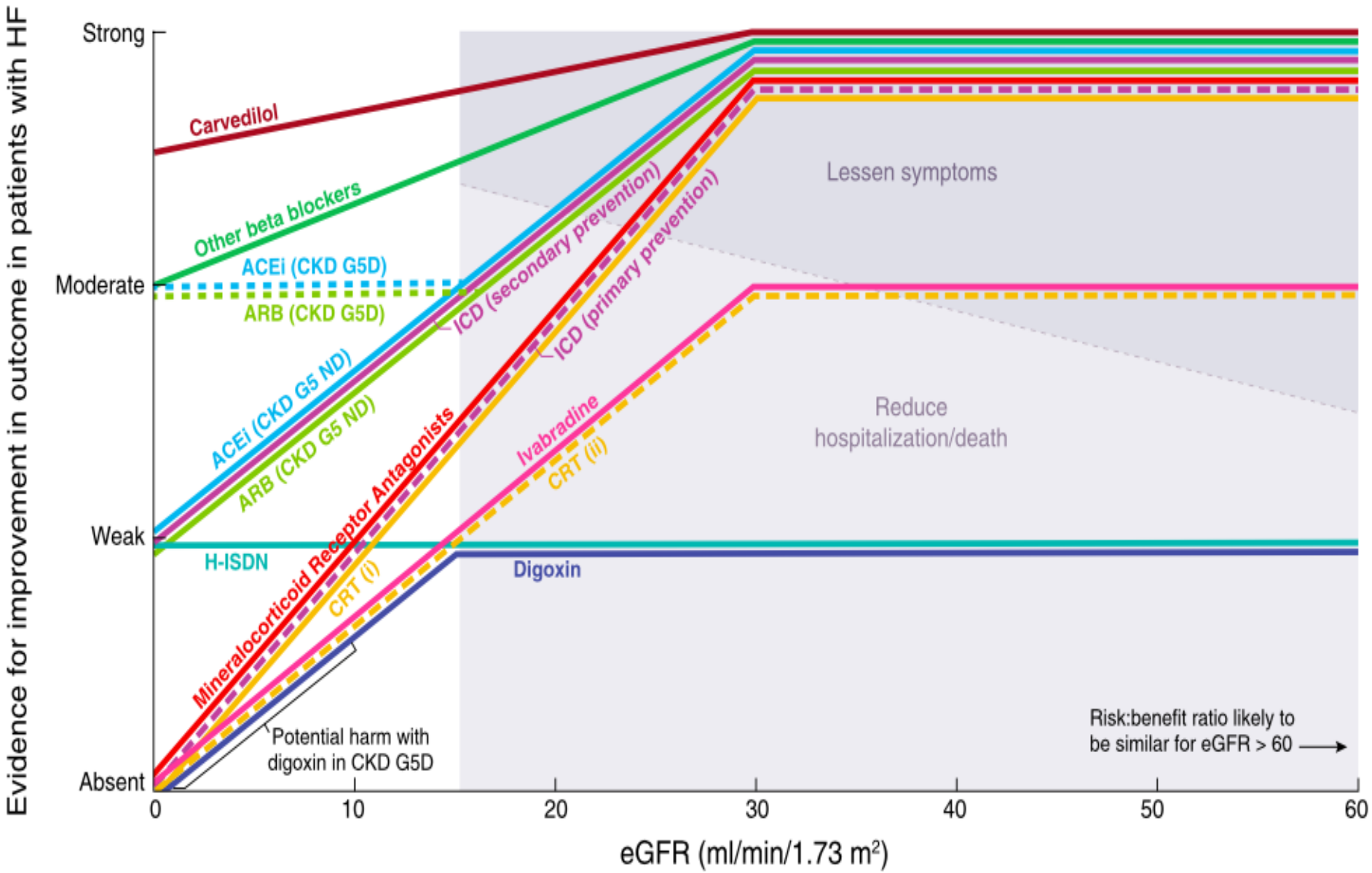
- Ivabradine elimination by kidneys is minimal. *The dosage is 2.5–7.5 mg twice per day and does not require dose adjustment with creatinine clearance of >15 ml/min.*

Table 2. Pharmacotherapy of heart failure in patients with CKD

Agents	CKD Stages 1– 3	CKD Stages 4 and 5
ACEis	Should be used in all patients with HFrEF, with monitoring of creatinine and potassium	May be used in HFrEF, with monitoring of creatinine and potassium. Dose modification may be necessary
β-Blockers	Should be used in all patients with HFrEF	May be used in HFrEF
Mineralocorticoid receptor antagonists	Should be used in HFrEF, with careful monitoring of potassium	May be used in HFrEF, with caution and monitoring of potassium
ARBs	Should be used in all patients with HFrEF with caution	May be used in HFrEF, with monitoring of creatinine and potassium
Ivabradine	May be used in patients with HFrEF with sinus rhythm and who are stable on β-blockers	Unknown effects
Angiotensin receptor and neprilysin inhibitor	May be used in patients with HFrEF instead of ACEis/ARBs	Unknown effects
Sodium-glucose cotransporter 2 inhibitor	Can be used in patients with HFrEF with or without diabetes	Unknown effects
Hydralazine and isosorbide dinitrate	Should be considered in patients with HFrEF who are intolerant to ACEis/ARBs	May be considered in patients with HFrEF who are intolerant to ACEis/ARBs

ACEi, angiotensin-converting enzyme inhibitor; HFrEF, heart failure with reduced ejection fraction; ARB, angiotensin receptor blocker.


CRT
Strong
Strong
Absent
ICD
Strong
Strong
Weak
H-ISDN
Weak
Weak
Absent
Digoxin
Weak
Weak
Weak
Ivabradine
Moderate
Moderate
Absent
β-blocker
Strong
Strong
Moderate
MRA
Strong
Strong
Absent
ARNi
Strong
Strong
Absent
ACE inhibitor/ARB
Strong
Strong
Weak
Diuretics
Absent
Absent
Absent
CKD 1 and 2
CKD 3
CKD 4 and 5


Evidence for improvement in outcome in patients with HF
Strong
Moderate
Weak
Absent
Carvedilol
Other beta blockers
ACEi (CKD G5D)
ARB (CKD G5D)
ACEi (CKD G5 ND)
ARB (CKD G5 ND)
H-ISDN
Mineralocorticoid Receptor Antagonists
ICD (secondary prevention)
ICD (primary prevention)
Ivabradine
CRT (ii)
CRT (i)
Digoxin
Potential harm with digoxin in CKD G5D
Lessen symptoms
Reduce hospitalization/death
Risk:benefit ratio likely to be similar for eGFR > 60
0
10
20
30
40
50
60
eGFR (ml/min/1.73 m²)

SGLT-2 Inhibitors

- The EMPA-REG OUTCOME Trial randomized 7020 patients with T2DM at high risk for cardiovascular events to receive empagliflozin versus placebo

1. The trial showed a 14% RRR for the primary composite 3-point major adverse cardiovascular event outcome of cardiovascular death, nonfatal MI, and nonfatal stroke

2. 38% RRR in cardiovascular death

3. the reduction in CKD progression could be translated into delaying the need for dialysis by almost 1 year, including in patients *with eGFR as low as 20 ml/min per 1.73 m2*

- EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular out- comes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117– 2128. doi: 10.1056/NEJMoa1504720

Pharmacological treatments indicated in patients with (NYHA class II–IV) heart failure with reduced ejection fraction (LVEF ≤40%)

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

GLP-1 Agonists

- **LEADER trial** (Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes):
- 9340 patients with T2DM and high cardiovascular risk were randomized to liraglutide versus placebo.
- A significant reduction with liraglutide in the prespecified secondary renal outcome

1. *new- onset persistent macroalbuminuria*,
2. *persistent doubling of the serum creatinine level*,
3. *ESKD,*
4. *Death* (HR, 0.78 [95% CI, 0.67–0.92]).

Recommendations for the management of anaemia and iron deficiency in patients with heart failure

Recommendations	Class[a]	Level[b]
It is recommended that all patients with HF be periodically screened for anaemia and iron deficiency with a full blood count, serum ferritin concentration, and TSAT.	I	C
Intravenous iron supplementation with ferric carboxymaltose should be considered in symptomatic patients with LVEF <45% and iron deficiency, defined as serum ferritin <100 ng/mL or serum ferritin 100–299 ng/mL with TSAT <20%, to alleviate HF symptoms, improve exercise capacity and QOL.[720,722,724]	IIa	A
Intravenous iron supplementation with ferric carboxymaltose should be considered in symptomatic HF patients recently hospitalized for HF and with LVEF <50% and iron deficiency, defined as serum ferritin <100 ng/mL or serum ferritin 100–299 ng/mL with TSAT <20%, to reduce the risk of HF hospitalization.[512]	IIa	B

KRT

- Patients with heart failure on dialysis have very poor prognosis, with a 5-year survival rate of 12.5%

- There may be symptomatic relief and *fewer hospitalizations* with peritoneal dialysis in carefully selected patients .

- In a study of 118 patients with heart failure and CKD, peritoneal dialysis was associated with *improvement in quality of life and New York Heart Association class* .

Peritoneal dialysis relieves clinical symptoms and is well tolerated in patients with refractory heart failure and chronic kidney disease. Eur J Heart Fail 14: 530–539, 2012

- Hemodialysis may be tricky in patients with low BP, but *more frequent dialysis and longer nocturnal dialysis* may be useful for fluid removal.

- Creation of arteriovenous fistula or graft for hemodialysis may cause dilation of left atrium and right ventricle, and associated heart failure.

- For patients with acute heart failure and low BP, slow ultrafiltration with continuous KRT may be useful.

Summary of Key Aspects of the Management of CRS

- Distinguishing true AKI from functional causes of fluctuations in serum creatinine.
- Identifying the factors contributing to diuretic resistance is a key step in optimizing decongestion in CRS.
- Biomarkers of cardiac and kidney injury represent a new dimension in the diagnostic and prognostic algorithm
- High-quality data for goal-directed medical therapy in chronic CRS with moderate to severe decline in kidney function are lacking.
- A cardionephrology multidisciplinary approach is essential in the joint management of patients with CRS with an emphasis on core outcome measures based on patient and physician priorities.

Thank you for your attention!

Any question?