INSUFFISANCE CARDIAQUE ET SYNDROME CARDIORÉNAL

EILEEN O'MEARA

23 NOVEMBRE 2013

CONFLITS D'INTÉRÊT

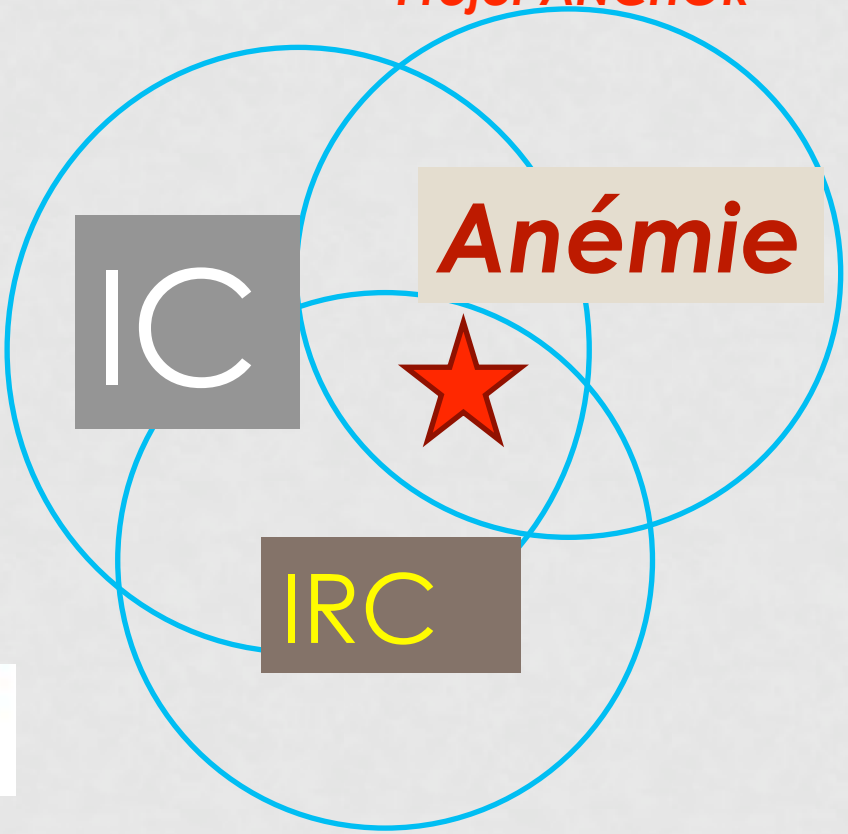
Fonds de la recherche en santé Québec

Programme de recherche chercheur junior 2 FRQS

- **Syndrome cardiorénal, biomarqueurs et fibrillation auriculaire chez les insuffisants cardiaques**

Johnson & Johnson

Projet ANCHOR



Pfizer

TOPCAT
Funded by the NHLBI

Antagonistes des récepteurs minéralocorticoides

LE SYNDROME CARDIORÉNAL

CRS type 1:	Rapid worsening of cardiac function leads to AKI
CRS type 2:	Chronic abnormalities in cardiac function cause progressive CKD
CRS type 3:	Abrupt and primary worsening of kidney function leads to acute cardiac dysfunction
CRS type 4:	Primary CKD contributes to decreased cardiac function
CRS type 5:	An acute or chronic systemic disorder promotes combined cardiac and renal dysfunction

Ronco C et al. J Am Coll Cardiol. 2008;52(19):1527-1539.

From: Cardiorenal Syndrome

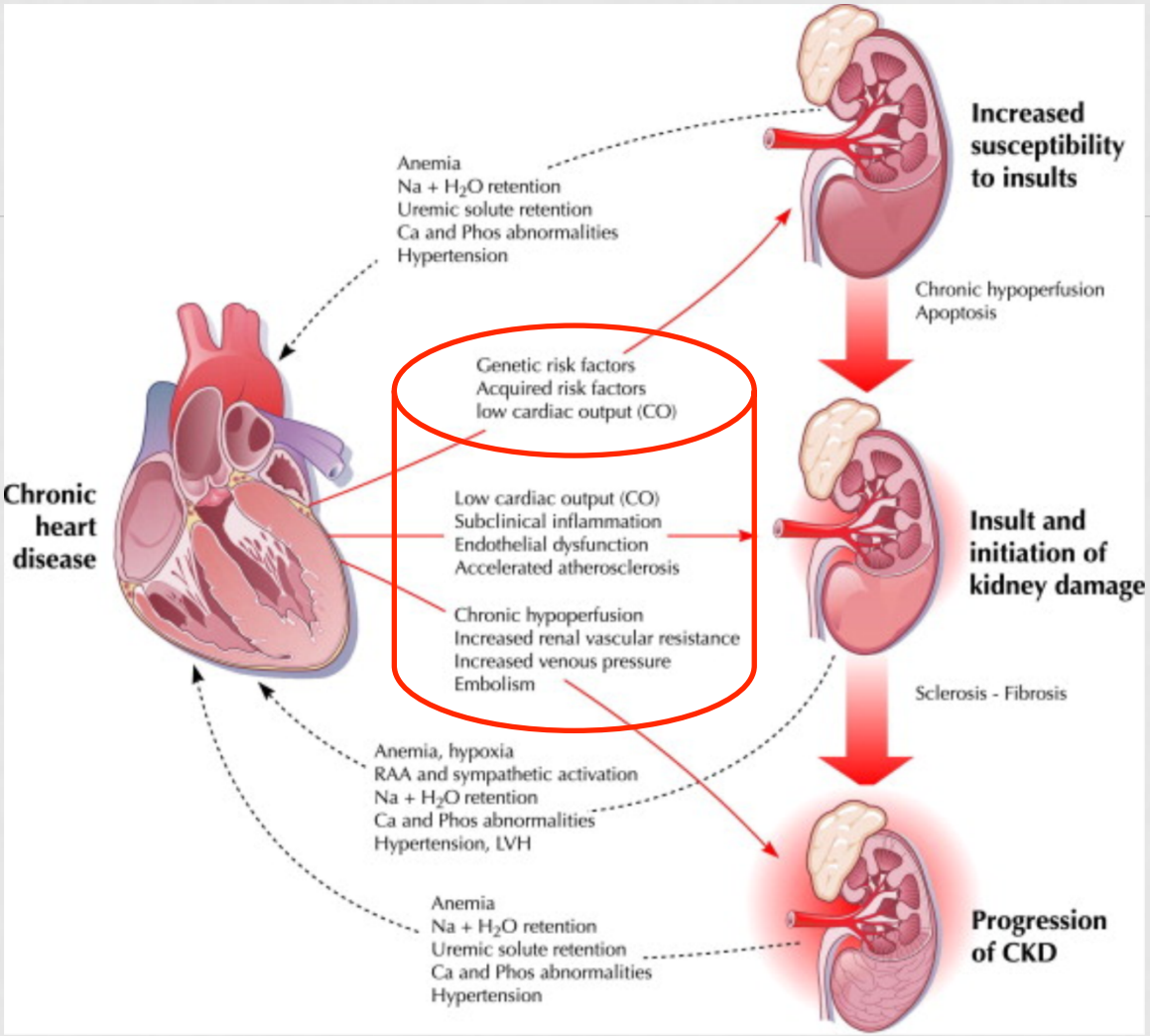


Figure Legend:

CRS Type 2

Pathophysiological interactions between heart and kidney in type 2 cardiorenal syndrome (CRS) or "chronic CRS" (chronic abnormalities in cardiac function, e.g., chronic heart failure) causing progressive chronic kidney disease (CKD). Figure illustration by Rob Flewell. LVH = left ventricular hypertrophy; RAA = renin angiotensin aldosterone.

Ronco C et al. J Am Coll Cardiol. 2008;52(19):1527-1539.

L'IRC ET L'IC: UNE COMBINAISON FRÉQUENTE ET…

- L'insuffisance rénale est un marqueur indépendant des risques de mortalité et d'hospitalisations chez les patients atteints d'insuffisance cardiaque (IC), peu importe la fraction d'éjection du ventricule gauche (FEVG).
- L'insuffisance rénale chronique (IRC) est définie par le taux de filtration glomérulaire estimé (TFGe).

- **Près de 50% des patients IC ont une IRC au moins modérée, soit un TFGe <60 ml/min/1.73 m2.**

IRC DANS LES ESSAIS D'IC

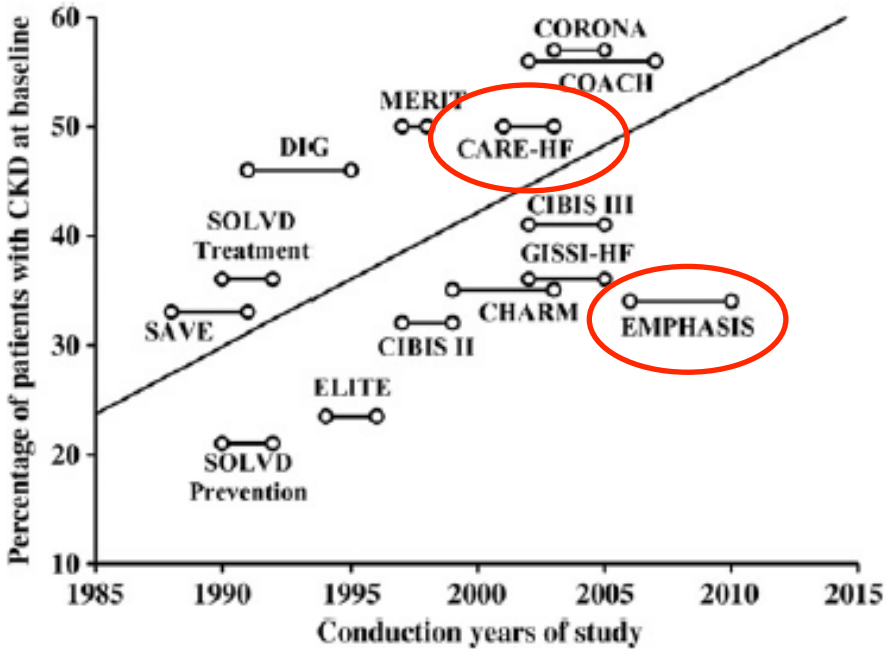


Fig 1. Relationship between the year of conduction of study and percentage of patients with CKD. Shown are some key HF studies. The solid line represents the fitted regression line. Image constructed from data from original reports of studies mentioned. *Abbreviations*: CKD, estimated GFR less than 60 mL/min per 1.73 m^2.

Damman et al. Progress in Cardiovascular Diseases 54 (2011) 144–153.

IRC ET PRONOSTIC CHEZ L'IC

Bien que presque tous les facteurs de risque traditionnels (âge, sexe masculin, diabète, HTA, HLP, tabac, obésité, sédentarisme, Hx familiale de MCAS) soient plus prévalents chez les patients avec IRC, même un degré modéré d'IR demeure un **prédicteur *indépendent* de la mortalité chez les insuffisants cardiaques.**

La mortalité des patients avec IRC est plus grande (que sans IRC) après un IM, des pontages ou même après l'implantation d'un défibrillateur.

Al –Ahmad A et al. J Am Coll Cardiol 2001, 38:955– 62.

VALUER PRONOSTIQUE DU TFG EN IC

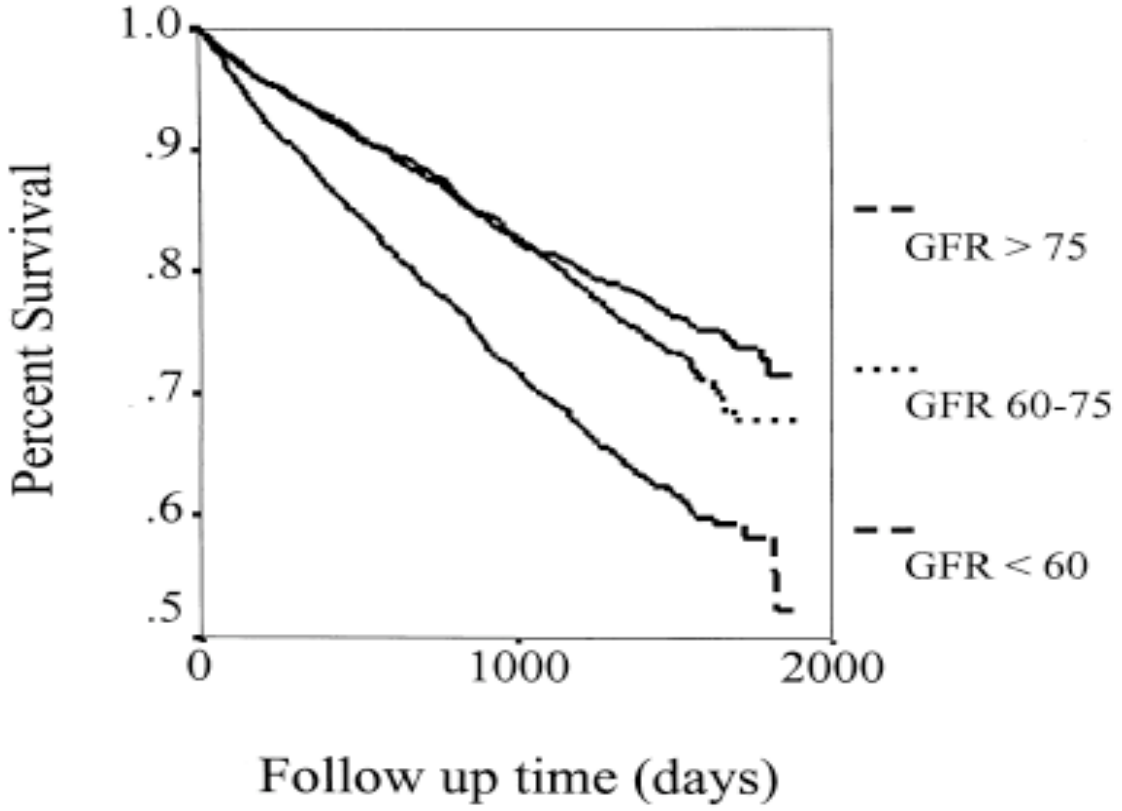


Figure 2. Kaplan-Meier survival analysis by level of glomerular filtration rate (GFR).

Al –Ahmad A et al. J Am Coll Cardiol 2001, 38:955– 62.

LE SYNDROME CARDIORÉNAL

- La combinaison IRC et IC ou dysfonction cardiaque (quelque soit la cause au plan cardiaque) a reçu le terme de ***syndrome cardiorénal***
- La pathophysiologie n'est pas complètement élucidée
- L'origine principale de l'IR associée à l'IC est hémodynamique, impliquant à la fois une baisse de perfusion rénale et une augmentation de la pression veineuse
- Plusieurs modulateurs peuvent également affecter la relation cardiorénale
- **L'IR n'est pas limitée à la baisse de filtration mais implique également une hypertension glomérulaire et une hypoxie tubulointerstitielle, menant à une perte d'intégrité glomérulaire et à un dommage tubulaire**

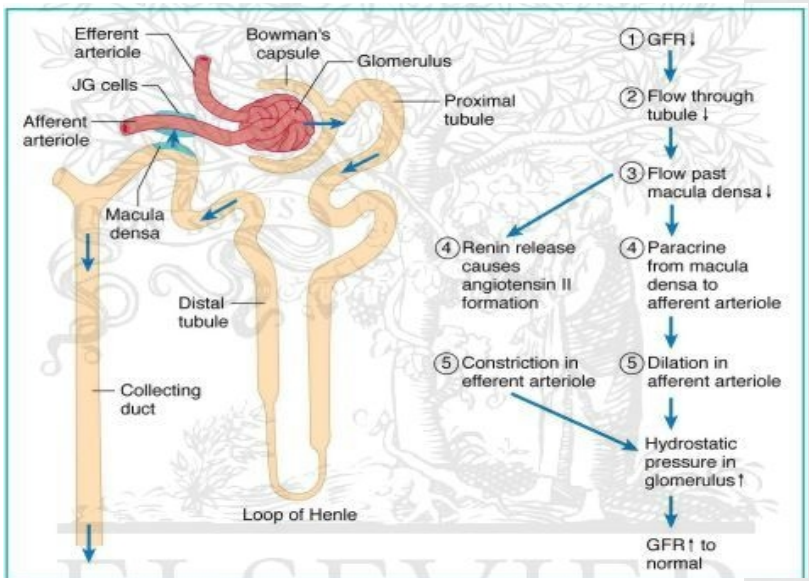
Damman et al. Progress in Cardiovascular Diseases 54 (2011) 144–153.

CARACTÉRISTIQUES DU SCR

Table 1
Summary of characteristics of the cardiorenal syndrome

Characteristics of the cardiorenal syndrome
Reduced RBF and GFR
Increased venous congestion
Increased renovascular resistance
Albuminuria
Tubular damage
Worsening renal function
Diuretic resistance
Activation of the TGF
Anemia
Increased mortality

Abbreviations: TGF, tubuloglomerular feedback mechanism.



Damman et al. Progress in Cardiovascular Diseases 54 (2011) 144–153.

EXEMPLE CLINIQUE D'IC ET IRC

Notes d'évolution

CLIC/VISITE AVEC RV
H 85
CMP isch FE 30%, S/P PAC en 1983, Fuite mitrale et tricuspidienne sévère, HTAP, FA PMP non ACO
ASO carotidienne, diabète, IRC sévère avec anémie ss Aranesp, transfusé en juin.
AAA non opéré et non opérable.
Coumadin cessé re hémoragie intracrânienne (INR était stable) il y a 2 ans.
Hospit pour anémie 7au 15 oct (5 transfusions). Pt suivi hémato Dr Fish et Aranesp suspendu puis diminué car Hb en augm ++, avec Venofer . OGD et colo négatives. RDV Dr Fish 2 décembre.

Laboratoire

2013-11-13 **Général:** NA : 141, K : 4.2, Cl : 103, Urée : 18.8, Créatinine : 207, Ratio U/Créat : 0.09, NT-proBNP : 3064, Acide urique : 486, Hgb : 139, Plaquettes : 169.

Se dit nettement mieux depuis 1 mois.
Dort avec 4 oreillers pour confort et non dyspnée. Gain de 2Kg mais mange mieux.
Creat stable, urée diminue, proBNP en amélioration.
Hb augmente 139. Aranesp à diminuer: sautons dose cette semaine puis diminuer de moitié tel que prévu par hémato.

Prochaine visite: dans 2 mois

MODULATEURS DU SCR

- Activation du SRAA
- Radicaux libres (ROS)
- Balance NO
- Activation du SNS
- Inflammation
- Diabète
- Hypertension

Ainsi que les traitements reçus…
Peuvent moduler les interactions cardiorénales

BETA-BLOQUANTS

- LE SNS est activé en IC et améliore DC, en augmentant FC, rétention NA et H2O (via rénine) et induit vasoconstriction périphérique
- Au long cours, ceci mène à HVG, ↑ angiotensine II intrarénale, et diminution éventuelle du TFG
- Les BB pourraient donc ralentir l'atteinte rénale

HTA, DIABÈTE ET LEUR TRAITEMENTS

renal disease, both hypertension and albuminuria are important targets for therapy.[56-58] Although blood pressure is also treated by the use of RAAS inhibitors, diuretics, and β-blockers, in patients with HF, a reduction in blood pressure is not (always) the treatment goal per se. Importantly, combining too many blood pressure–lowering treatments may eventually result in lower GFR and increased mortality, as it decreases renal perfusion pressure and further impairs physiologic RAAS activity to preserve GFR in patients with already low RBF. On

Damman et al. Progress in Cardiovascular Diseases 54 (2011) 144–153.

PROTECTION CONTRE LE SCR

- Améliorer la fonction rénale en traitant optimalement l'IC chronique (médicaments, resynchronisation, et parfois par LVAD, greffe cardiaque)⇒ améliorations démontrées de la fonction rénale
- Éviter AINS
- Colorants pour les tests d'imagerie: employer d'autres moyens d'imagerie lorsque possible ou hydratation ++

Boerrigter et al. Curr Heart Fail Rep 2013; 10: 285-295.

EXEMPLE CLINIQUE D'IC ET IRC

Notes d'évolution

CLIC/VISITE AVEC RV

CMP valvulaire F 64, S/P Mx mitrale rhumatismale. ETT sept 2013: FE 55%, HK VD modérée, PAPs 88mmHg, RVM mec avec petite fuite péri postérieure, S/P réduction par Amplatz, PVT G moy 3, IT 4. IA modérée. Pas de chgmts x examen de 2012. FAC c PMP VVIR. MCAS S/P ICT. Stable CF 3, perte de pds légère, palpit et OTS à l'occasion. Rx Prolia pour ostéoporose sévère c fractures vertébrales, vue par rhumato. Goutte en juillet, résolue spontanément. Allopurinol pris à 100mg die.

Creat en cours. Hb mieux 113.

Holter montre FA et pacing 47% du temps. FC 58095, pas de symptomes, pas de pauses, pas évid de dysfonction PMP.

Fct rénale à suivre avec Prolia (si TFG inf à 30, monitorer pour hypocalcémie = discuté avec pharmacie ICM).

Général: NA : 134, K : 3.3, Cl : 90, Urée : 27.8, Créatinine : 160, Ratio U/Créat : 0.17, NT-proBNP : 5673, Acide urique : 786, Hgb : 97, Plaquettes : 151, Autres : Ht: 0.295.

Demandons Ca, PO4, Mg proch visite.

Prochaine visite: dans 6 sem.

CALCULS DU TFG ESTIMÉ

CKD-EPI- Chronic Kidney Disease-Epidemiology Collaboration Group, equation:

eGFR =

$141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] x 1.159 [if black]; and Scr is serum creatinine, κ is 0.7 mg/dl (61.9 umol/L) for females and 0.9 mg/dl (79.6 umol/L) for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, max indicates the maximum of Scr/κ or 1.

Cette équation serait plus exacte et évaluerait mieux le risque des patients avec IC et FE abaissée que l'équation MDRD.

CYSTATINE C

La Cystatine C, un marqueur précoce de perte de filtration glomérulaire, est produite à un taux constant par toutes les cellules nucléées; filtrée librement à travers la membrane glomérulaire; complètement réabsorbée et ensuite métabolisée par le rein.
La cystatine C augmente donc avec l'IRC.

La majorité des études suggèrent que la Cystatine C n'est pas affectée par l'âge, le sexe ou la masse musculaire et est un marqueur supérieur à la créatinine pour détecter précocément une détérioration de fonction rénale.

Iwanaga Y, et al. Circ J 2010; 74: 1274-1282.

STADES D'IRC

CKD stage	Description; findings need to be present for ≥3 months	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or relatively high GFR (Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine test or imaging studies)	≥90
2	Kidney damage with mild reduction in GFR	60-89
3	Moderate reduction in GFR	30-59
4	Severe reduction in GFR. Preparation for renal replacement therapy	15-29
5	Established kidney failure, which includes end-stage renal disease (defined as a need for renal replacement therapy, i.e., dialysis or kidney transplantation)	<15

K/Doqi Guidelines. Am J Kidney Dis 2002; S1: 266.

NOUVELLES CATÉGORIES D'IRC

GFR categories in CKD[2]

Category	GFR	Terms	Clinical Presentations
G1	≥ 90	Normal or high	Markers of kidney damage (nephrotic syndrome, nephritic syndrome, tubular syndromes, urinary tract symptoms, asymptomatic urinalysis abnormalities, asymptomatic radiologic abnormalities, hypertension due to kidney disease)
G2	60-89	Mildly decreased*	◦ Markers of kidney damage ◦ Mild to severe complications: • Anemia • Mineral and bone disorder • Cardiovascular disease • Hypertension • Elevated parathyroid hormone • Lipid abnormalities • Low serum albumin
G3a	45-59	Mildly to moderately decreased	
G3b	30-44	Moderately to severely decreased	
G4	15-29	Severely decreased	
G5	< 15	Kidney failure	• Includes all of the above • Uremia • Cardiovascular disease

GFR = mL/min/1.73 m²

*Relative to young adult level

In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

Albuminuria categories in CKD[2]

Category	ACR (mg/g)	Terms
A1	< 30	Normal to mildly increased
A2	30-300	Moderately increased*
A3	> 300	Severely increased**

*Relative to young adult level. **ACR 30-300 mg/g for > 3 months indicates CKD.**

**Including nephrotic syndrome (albumin excretion ACR > 2220 mg/g)

Consulter néphrologue

The CKD classification by Kidney Disease: Improving Global Outcomes (KDIGO)

Kidney Inter 2013; Suppl 3;1-150.

DÉFINITIONS DE L'IRA

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline	<0.5 ml/kg/h for 6–12 hours
	OR	
	≥0.3 mg/dl (≥26.5 µmol/l) increase	
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ≥12 hours
3	3.0 times baseline	<0.3 ml/kg/h for ≥24 hours
	OR	OR
	Increase in serum creatinine to ≥4.0 mg/dl (≥353.6 µmol/l)	Anuria for ≥12 hours
	OR	
	Initiation of renal replacement therapy	
	OR	
	In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	

Kidney Int Suppl. 2012(2):1–138.

From: Cardiorenal Syndrome

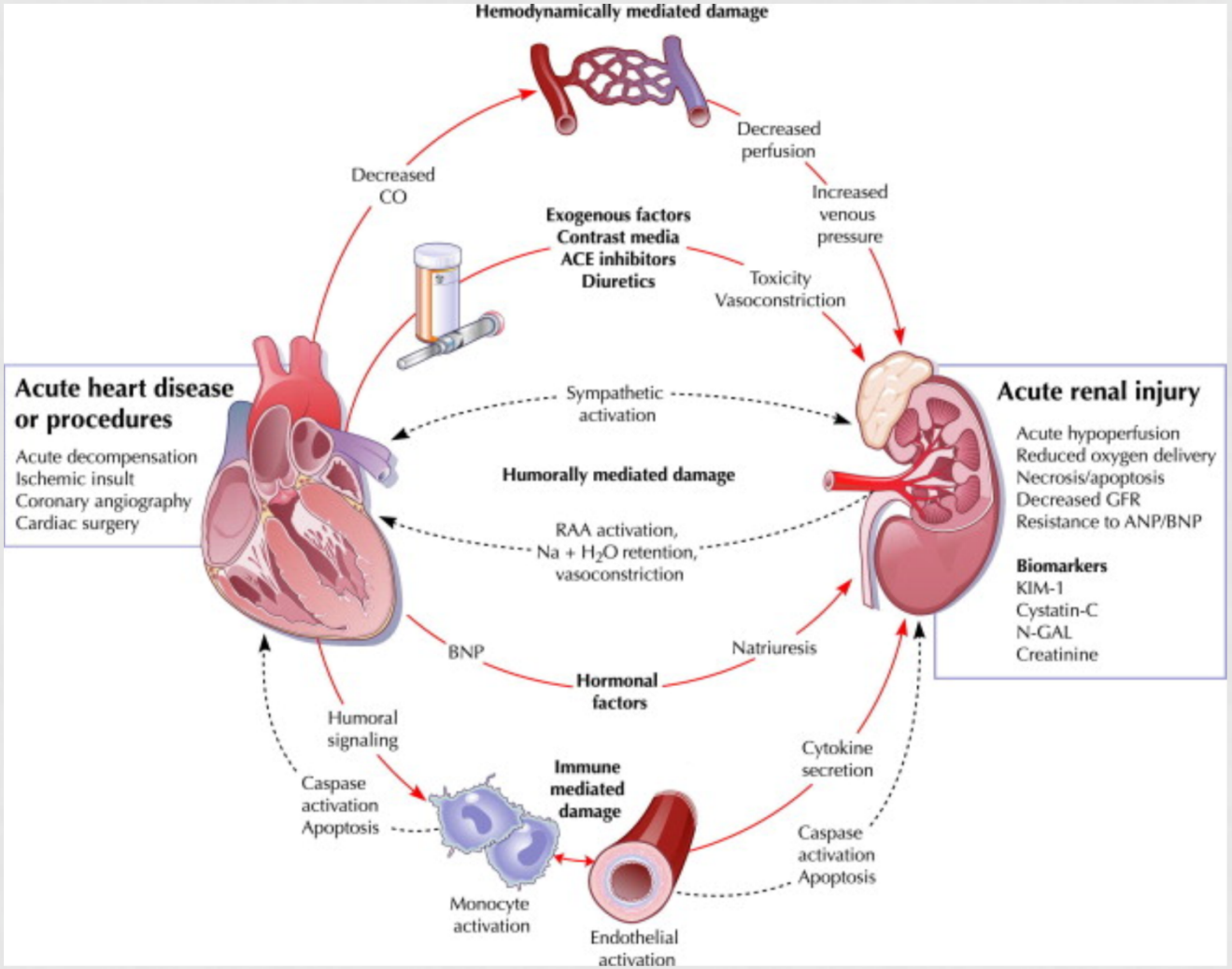


Figure Legend:

CRS Type 1

Pathophysiological interactions between heart and kidney in type 1 cardiorenal syndrome (CRS) or "acute CRS" (abrupt worsening of cardiac function, e.g., acute cardiogenic shock or acute decompensation of chronic heart failure) leading to kidney injury. ACE = angiotensin-converting enzyme; ANP = atrial natriuretic peptide; BNP = B-type natriuretic peptide; CO = cardiac output; GFR = glomerular filtration rate; KIM = kidney injury molecule; N-GAL = neutrophil gelatinase-associated lipocalin; RAA = renin angiotensin aldosterone. Figure illustration by Rob Flewell.

Ronco C et al. J Am Coll Cardiol. 2008;52(19):1527-1539.

INVESTIGATION LORS D'IRA ET IC

- Usuel = considérer causes prérénales, intrarénales et post-rénales
- Bas DC/hypotension, hypovolémie, congestion veineuse, ischémie rénale, toxines rénales, obstruction, infection locale ou systémique, maladie inflammatoire

- Hx, E/P, E+, urée, creat, cystatine C?
- BNP ou NT-proBNP
- Troponines, ECG
- FSC, hs-CRP, procalcitonine?
- Analyse/sédiment + C urine
- Diurèse, bladder scan?

PROTECTION CONTRE LE SCR- ICA

In acute decompensated HF (ADHF), renal function can be impacted by multiple factors, including low cardiac output, systemic hypotension, renal venous congestion, and neurohumoral activation. If a precipitating cause for worsening cardiac function can be identified, such as hypertension, ischemia, arrhythmias, or anemia, it should be treated appropriately. If there is hypotension without fluid overload, fluid resuscitation should be attempted. If this does not improve blood pressure and cardiac output, vasopressors or inotropes, or both, may be required.

Often, volume overload is a problem, which increases cardiac preload and afterload, promoting further deterioration of cardiac function. Worsening cardiac function and venous congestion will cause the kidney to further retain sodium and fluid, thus aggravating congestion and cardiac overload. Treating volume overload can improve both cardiac and renal function by reducing cardiac preload and afterload, potentially reducing valvular regurgitation and decreasing venous congestion. Hence, diuretic therapy can improve renal function.

Boerrigter et al.
Curr Heart Fail Rep 2013; 10: 285-295.

MÉCANISMES DU SCR

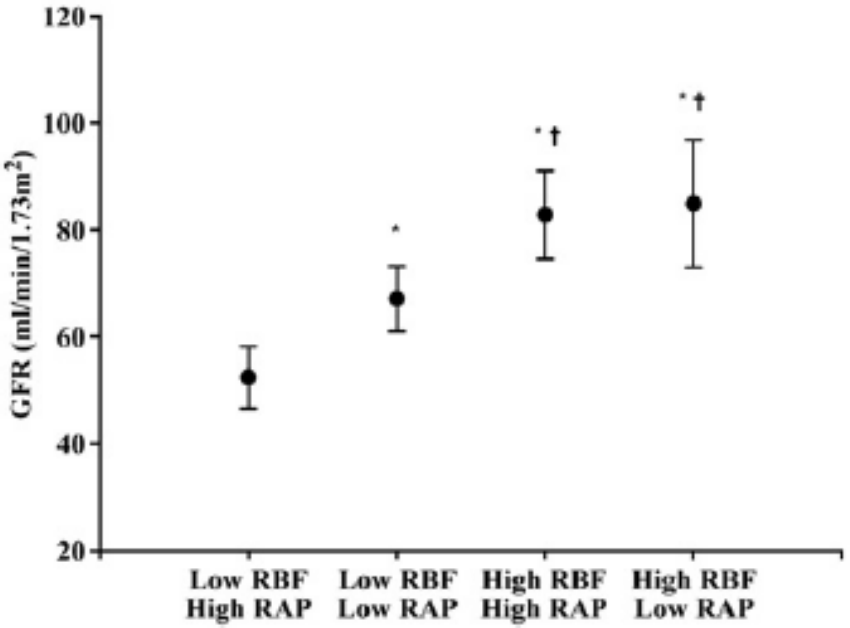


Fig 4. Relative contributions of CVP and RBF to GFR. *Abbreviations*: RAP, right atrial pressure. Error bars represent 95% confidence interval. $^{*}P < .001$ for difference with high RAP, low RBF. $^{\dagger}P < .01$ for difference with low RAP, low RBF. Reprinted with permission from Springer.[30]

Damman et al. Eur J Heart Fail 2007; 9: 872-878.

PROTECTION CONTRE LE SCR- ICA

- Étude de 145 pts avec IC aig
  prédicteur le plus puissan
  détérioration de fct
  plutôt que ↓ l'i
- Congesti
  au
  couvent augmenter pressions veineuses centrale et rénale.

Combinaisons de diurétiques en cas de résistance!

Mullens W et al. J Am Coll Cardiol 2009;53:589-596.
Mullens W et al. J Am Coll Cardiol 2008;51:300-306.

IECA ET VASODILATATEURS

Change in Renal Function due to Therapy

Heart failure and its treatment can contribute to deterioration of renal function in a variety of ways. In stable heart failure, ACE inhibitors can be expected to raise serum creatinine given that they act to decrease efferent vascular tone and thus reduce glomerular filtration pressure. A serum creatinine increase of about 30 % (depending on the baseline value) can usually be tolerated. However, ACE inhibitors should be carefully titrated, and in the setting of an acute renal function decline, the ACE inhibitor is frequently reduced or paused. Overdiuresis can lead to volume depletion with subsequent increase in creatinine due to hypotension. If hypotension appears to contribute to renal dysfunction, hypotensive drugs may need to be paused.

Boerrigter et al. Curr Heart Fail Rep 2013; 10: 285-295.

DIURÉTIQUES… DOSE-AHF

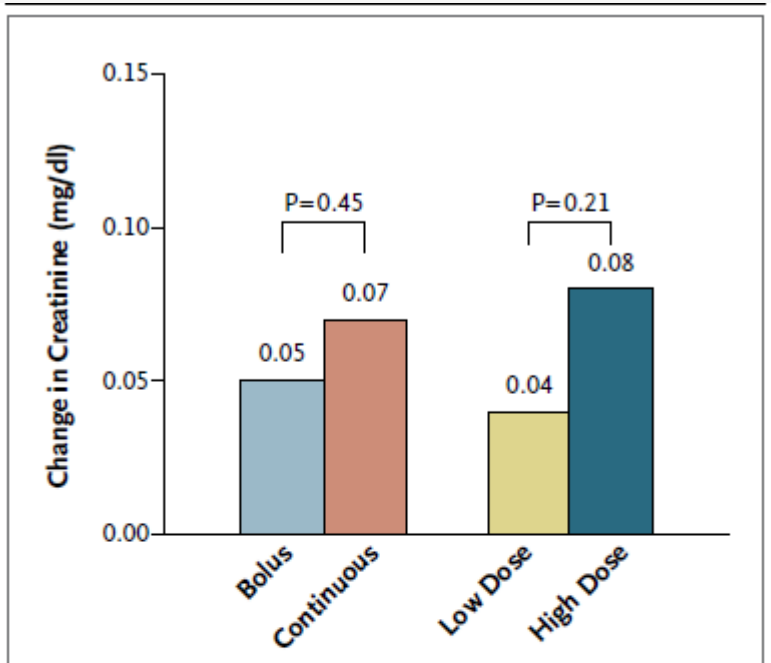


Figure 2. Mean Change in Serum Creatinine Level.

The mean change in the serum creatinine level over the course of the 72-hour study-treatment period is shown for the group that received boluses every 12 hours as compared with the group that received a continuous infusion and for the group that received a low dose of the diuretic (equivalent to the patients' previous oral dose) as compared with the group that received a high dose (2.5 times the previous oral dose).

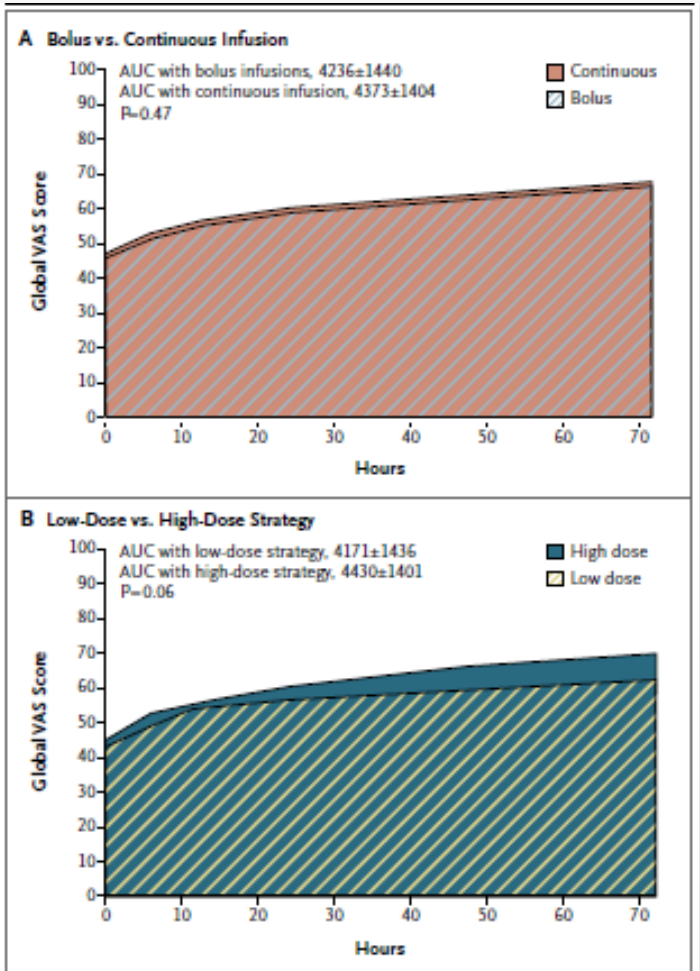


Figure 1. Patients' Global Assessment of Symptoms during the 72-Hour Study-Treatment Period.

Felker GM et al. N Engl J Med 2011;364:797-805.

DIURÉTIQUES… DOSE-AHF

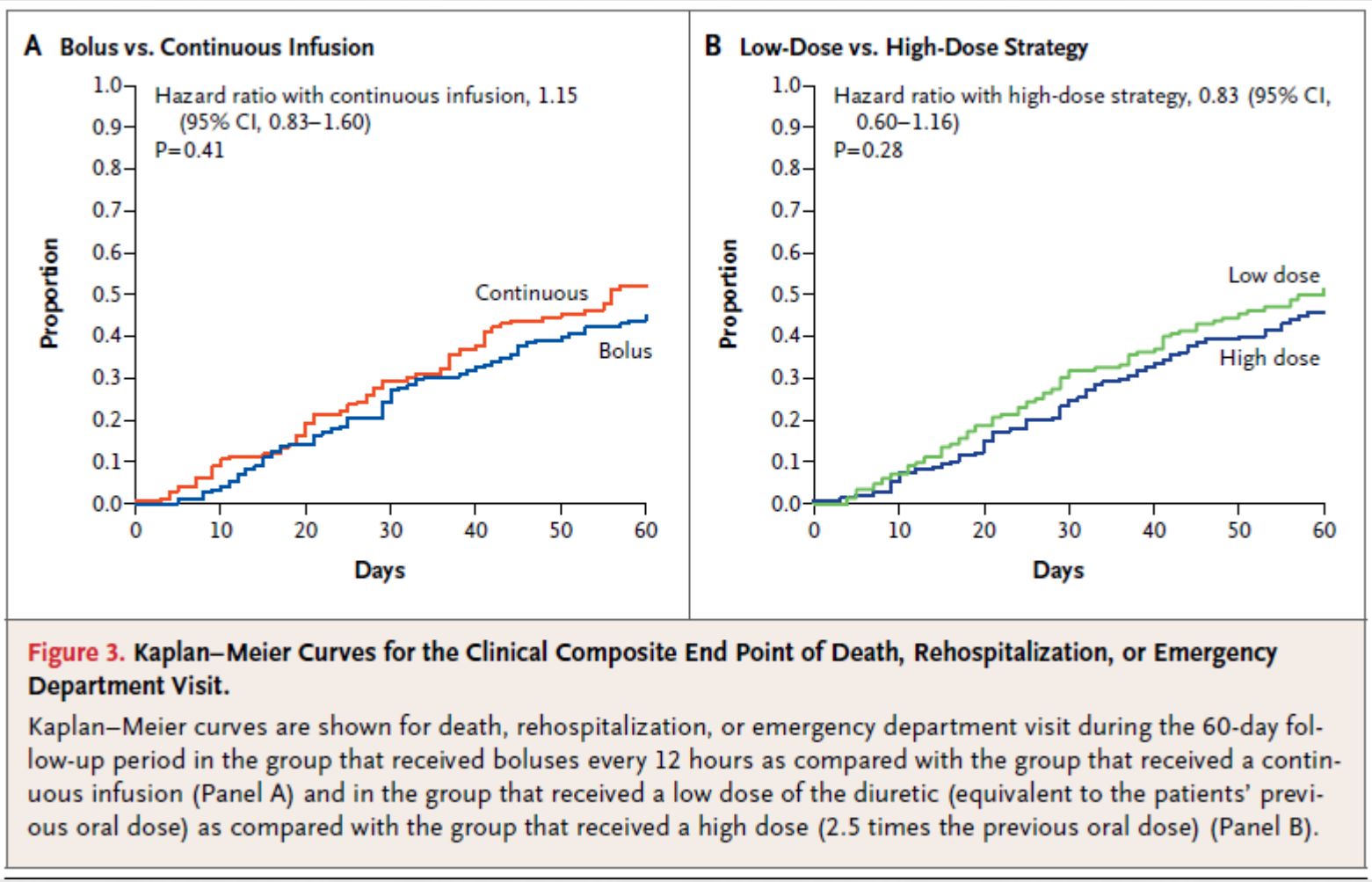


Figure 3. Kaplan–Meier Curves for the Clinical Composite End Point of Death, Rehospitalization, or Emergency Department Visit.

Kaplan–Meier curves are shown for death, rehospitalization, or emergency department visit during the 60-day follow-up period in the group that received boluses every 12 hours as compared with the group that received a continuous infusion (Panel A) and in the group that received a low dose of the diuretic (equivalent to the patients' previous oral dose) as compared with the group that received a high dose (2.5 times the previous oral dose) (Panel B).

Felker GM et al. N Engl J Med 2011;364:797-805.

DIURÉTIQUES… ROSE-AHF / AHA 2013

Renal Optimization Strategies Evaluation in Acute Heart Failure (ROSE AHF) Trial

History: Worsening renal function and impaired venous drainage during treatment for acute heart failure (AHF) are associated with negative outcomes. Low-dose dopamine and low-dose nesiritide have shown potential for improving renal function and decongestion in patients with AHF.

Question to answer: Does the addition of low-dose dopamine or low-dose nesiritide to optimally-dosed diuretic therapy improve renal function and decongestion in patients with AHF?

Trial Design	**Double-blind, randomized, placebo-controlled, multi-center clinical trial; N=360** **Randomization: Low-dose dopamine (2 ug/kg/min), low-dose nesiritide (0.005 ug/kg/min), or placebo** **F/U: Baseline, 24 hours, 48 hours, 72 hours, day 7 or discharge, day 60, and 6 months**	
Co-Primary Endpoints (randomization to 72 hours)	(1) Renal function: Change in serum cystatin-C (2) Decongestion: Cumulative urine volume	
Trial Results (Medication vs placebo)	Renal function (change in cystatin-C, mg/L): Low-dose dopamine: 0.12 vs 0.11 (P=0.72) Low-dose nesiritide: 0.07 vs 0.11 (P=0.35)	Decongestion (72-hour urine volume, L): Low-dose dopamine: 8.5 vs 8.3 (P=0.58) Low-dose nesiritide: 8.6 vs 8.3 (P=0.25)

Take Away: Neither low-dose dopamine nor low-dose nesiritide improved renal function or decongestion when added to diuretic therapy in patients with AHF and renal dysfunction.

Presented by: Chen HH, AHA Scientific Sessions 2013, Dallas

TOLVAPTAN SI HYPONATRÉMIE ET IC AIGUË

Tolvaptan, a V2-antagonist, acts as a powerful aquaretic by antagonizing AVP-induced insertion of the aquaporin-2 water channel in the collecting duct. In the Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST), a fixed dose of 30 mg of tolvaptan increased serum sodium and reduced body weight without affecting short-term or long-term outcomes [63, 64]. Given that 30 mg of tolvaptan showed quite a variable effect in a study by Udelson et al., there is the possibility that some patients had significant hypovolemia which may have led to neurohumoral activation and adverse outcome, potentially offsetting the benefit of better decongestion that other patients experienced [65, 66]. It may be useful to test tolvaptan with more individualized dose titration. Furthermore, given that tolvaptan does not block the V1A receptor with its vasoconstricting actions, the development of a V1a/V2-receptor antagonist for chronic therapy may be useful (the V1a/V2 receptor antagonist conivaptan is only approved for intravenous administration due to liver toxicity).

Boerrigter et al. Curr Heart Fail Rep 2013; 10: 285-295.

TOLVAPTAN SI HYPONATRÉMIE ET IC AIGUË

Tolvaptan use was associated with low and similar rates to placebo in incidence of decreased urine output/fluid overload, proteinuria, or elevated blood urea.

Tolvaptan was associated with small increases in serum creatinine concentrations that were observed in the pooled population of subjects with heart failure in multiple-dose trials and in the pooled population of subjects with hyponatremia in multiple-dose trials. The mean change from baseline in serum creatinine was 0.06 mg/dL in the heart failure subjects (for all tolvaptan doses) and was 0.06 mg/dL in the hyponatremia subjects (for all tolvaptan doses), compared with increases of 0.03 mg/dL and 0.02 mg/dL for the respective placebo groups in those populations. The magnitude of the increase, however, is relatively consistent and did not change markedly with duration or worsen at any specific time point. The increase was not associated with increases in adverse events associated with renal function (renal failure, acute renal failure, chronic renal failure) or increased all-cause mortality.

Tolvaptan was also associated with reduction in BUN concentrations.

Otsuka Medical Information, personal communication, November 2013.

ULTRAFILTRATION OU HÉMODIALYSE

- Si hypervolémie avec hyperkaliémie ou urémie ou acidose: considérer hémodialyse/demander avis néphro
- Si hypervolémie non controlée par diurétiques multiples: considérer ultrafiltration mais l'étude CARRESS-HF n'a pas montré d'avantages à cette thérapie chez les patients avec syndrome cardiorénal déjà en évolution (aigü)
- Étude AVOID-HF compare actuellement UF versus stratégie de diurétiques comme thérapie initiale (sans nécessairement l'apparition de SCR avant)