



HAL
open science

Renal function, electrolytes, and congestion monitoring in heart failure

Patrick Rossignol, Andrew Js Coats, Ovidiu Chioncel, Ilaria Spoletini,
Giuseppe Rosano

► **To cite this version:**

Patrick Rossignol, Andrew Js Coats, Ovidiu Chioncel, Ilaria Spoletini, Giuseppe Rosano. Renal function, electrolytes, and congestion monitoring in heart failure. *European Heart Journal Supplements*, 2019, 21 (Suppl M), pp.M25-M31. 10.1093/eurheartj/suz220 . hal-02516027

HAL Id: hal-02516027

<https://hal.univ-lorraine.fr/hal-02516027>

Submitted on 31 Aug 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0
International License

Renal function, electrolytes, and congestion monitoring in heart failure

Patrick Rossignol^{1*}, Andrew Js Coats², Ovidiu, Chioncel³, Ilaria Spoletini², and Giuseppe Rosano⁴

¹Université de Lorraine, Inserm, Centre d'Investigations Cliniques, 1433, Inserm U1116; CHRU Nancy, F-CRIN INI-CRCT, Nancy, France;

²Department of Medical Sciences, Centre for Clinical and Basic Research, IRCCS San Raffaele Pisana, Rome, Italy;

³Emergency Institute for Cardiovascular Diseases-"Prof. C.C.Iliescu", Bucharest; University of Medicine Carol Davila, Bucharest, Romania; and

⁴St. George's Hospital, London, UK

KEYWORDS

Heart failure;
renal function;
monitoring;
congestion;
diuretics

Congestion, renal function, and electrolyte imbalance (particularly potassium) are common problems in the management of the complex multi-morbid patient with heart failure (HF). Poor control of these fundamental clinical features is associated with adverse outcomes. Close monitoring of serum potassium and renal function is recommended by most current guidelines during the management of an episode of acute decompensated HF, yet the recommendations remain poorly implemented. Physicians are advised to treat a state of euvoemia after an admission with decompensated HF and residual congestion is a marker of worse outcome, yet control of congestion is poorly assessed and managed in real-world practice. This document reflects the key points discussed by a panel of experts during a Heart Failure Association meeting on physiological monitoring of the complex multi-morbid HF patient, and here, we present to aspects related to renal function, electrolyte, and congestion monitoring.

Introduction

In heart failure (HF) one of the main reasons for hospitalization is congestion.^{1,2} Both the congestion itself as well as the diuretic drugs used to treat it can have a detrimental impact on renal function. As such, optimized monitoring of renal function in HF is pivotal for preventing renal failure and emergency re-hospitalization.^{3,4} Unfortunately, due to a relative lack of studies, current guidance of renal function monitoring is largely driven by clinicians' opinions, rather than being evidence-based.^{5,6}

A Heart Failure Association consensus meeting was held on the topic of physiological monitoring of the complex multi-morbid HF patient, and one important aspect was

monitoring of the related features of congestion status, renal function, and electrolyte levels, particularly potassium. This article reflects the key points regarding potassium, creatinine, and congestion assessment, discussed at this meeting.

Importance of the kidney in heart failure

Data from international registries consistently show that physician adherence to guideline-recommended medications (GDMT) in HF with reduced ejection fraction (HFrEF) is associated with better outcomes.⁷ Unfortunately, current HFrEF drug guidelines are not being optimally implemented.^{8,9} Essential life-saving medications are frequently under-used and/or under-dosed, most often because of possibly excessive concern about adverse events.^{10,11} Hyperkalaemia and kidney dysfunction are common

*Corresponding author. Tel: +33621673189, Email: p.rossignol@chru-nancy.fr

comorbidities in HF.¹²⁻¹⁵ Both are associated with the underuse and under-dosing of renin-angiotensin-aldosterone system inhibitors (RAASi).^{16,17} Loop diuretic-induced hypokalaemia is also associated with adverse outcomes in HF with reduced ejection fraction (HFrEF).^{18,19} Concerns about renal adverse events may be excessive in some cases, and it should be recognized that this has the potential of depriving patients of receiving full doses of life-saving therapies.^{20,21} Down-titration of doses or discontinuation of RAASi may be warranted temporarily for persistent/severe hyperkalaemia, or worsening renal function.²² However, this should not prevent attempting re-initiation or up-titration of therapy as soon as is safely possible.²³ The use of potassium binders may facilitate up-titration in patients prone to hyperkalaemia,²⁴⁻²⁶ although, whether this may improve cardiovascular outcomes, remains to be demonstrated in adequately powered outcome trials.^{27,28} Importantly, guidelines recommend close monitoring of serum potassium and renal function during intervals after initiation of RAASi drugs.²⁹ Unfortunately, data from major HF registries^{30,31} show that such monitoring is poorly implemented, even after the occurrence of hyperkalaemia.

Monitoring of renal impairment in heart failure

Renal failure is common in HF and impairment of renal function is an independent marker of poor outcome. Worsening of renal function (WRF, often defined as an increase in creatinine by >0.3 mg/dL) occurs more commonly when higher-dose diuretics are used, such as in the high-dose limb of the DOSE-AHF trial. Although changes in renal function can be associated with worse outcomes, this is not always the case.³² A *post hoc* analysis of the DOSE-AHF trial illustrated the diuretic-induced increase in creatinine did not predict worse outcomes.³³ In addition, creatinine itself can be an unreliable marker of renal impairment where in chronic illness muscle mass is reduced,³⁴ which may occur even acutely in HF.³⁵ Baseline renal dysfunction is an important predictor of diuretic response in WHF, supporting a higher starting dose of furosemide in patients with lower eGFR.³⁶

The evaluation of renal function is of foremost importance in managing the complicated HF patient, especially in the presence of advanced disease or multiple comorbidities. Assessment of glomerular filtration rates (GFR) alone is not adequate and indeed many biomarkers and imaging techniques are available to help the clinician assess the effects of HF and its therapy on the kidney.

Renal function decline to some extent can and must be expected in the setting of decongestion, and accepted as long as the overall clinical status does not deteriorate. This is often referred to as 'pseudo worsening renal function (WRF)'. However, we have no robust data to define to what degree this is acceptable. A further decline in eGFR (especially if urinary output decreases or the clinical status of a patient simultaneously deteriorates) may represent true WRF, which is associated with substantially worse long-term outcomes and thus must be avoided.^{37,38}

Worsening of renal function should not always be seen as a bad sign, as it can actually reflect a good response to diuretic therapy and an overall favourable prognosis, in what has been coined pseudo-WRF.³⁹ Thus the distinction between true WRF with permanent kidney damage and pseudo-WRF which can be seen in up to one-fifth of ADHF patients is an important thing to establish,³³ especially as being discharged with inadequate decongestion is usually far worse than the pseudo-WRF pattern.⁴⁰

Markers of renal function are suboptimal to track and detect renal function decline. Creatinine tends to lag behind renal decline, and increases in creatinine may not be detected until ≥ 24 hours after renal function has begun to decline. However, monitoring diuresis and daily measurement of renal function and electrolytes are advocated.⁴¹⁻⁴³

In routine practice, serum creatinine is the most frequently used marker of renal function, and it can be converted to GFR by one of several formulae that have been recommended in HF guidelines as part of routine HF care, although the frequency of their estimation is not discussed in detail. The Cockcroft-Gault, the simplified modification of diet in renal disease formula and the CKD-EPI formula have all been used to assess prognosis in HF, but their stability in the setting of acute changes that are frequent in acutely decompensated HF is questionable. Glomerular filtration rates are a measure of renal reserve capacity, but it also includes short-term dynamic elements which help explain why it is a good predictor of long-term outcomes in HF, but also a poor short-term predictor of hour-to-hour changes in kidney health and how to respond clinically. Glomerular filtration rates can be measured directly by exogenous indicator dilutor methods using agents such as iothalamate or inulin, but it more commonly estimated from endogenously produced factors such as creatinine or cystatin C. Cystatin C has some advantages, for unlike creatinine it is not affected by renal tubular function because it is not secreted by the tubules.⁴⁴ Serum urea, reflects both GFR and tubular reabsorption and is thus affected by neurohormonal status and inhibition.⁴⁵ Urea is a powerful predictor of outcome offering additional value independent of creatinine or GFR.

Ideally, we would also have a reliable measure of renal tubular function that can be assessed acutely during an admission for decompensated HF, and although many have been proposed none has established a cemented role in routine practice. The most studied is neutrophil gelatinase-associated lipocalin.⁴⁶ Others include serum $\beta 2$ -microglobulin and fatty acid binding proteins. Urine output and electrolyte concentrations can and should be monitored in acute HF,⁴⁷ particularly to gauge the patient's response to loop diuretic therapy. Lastly, albuminuria can be used to assess glomerular filtration efficacy and can be abnormal in diabetes and CKD due to damage to the glomerular membrane. Albuminuria is common in HF and is linked to prognosis but the clinical implications of this remain unclear.⁴⁸

Specialized imaging of the kidney, such as ultrasound, can be helpful but is not routinely recommended and certainly not for monitoring purposes. Future techniques may offer better insights into dynamic changes occurring in intra-renal blood flow and the filtering tubular functions of the kidney.

Monitoring of electrolytes in heart failure

Electrolyte abnormalities are common in HF. They can be the result of diuretics, renal impairment neurohormonal activation, and the combination of these factors. Sodium (Na) and potassium (K) are the most commonly perturbed electrolytes⁴⁹ but chloride is also affected.⁵⁰ Hyponatraemia is common in acutely decompensated HF.^{51,52} This is thought to be the result of impaired excretion of free water via dilution hyponatraemia, a true depletion of sodium or both. Potassium abnormalities are particularly due to the treatments given for HF with hypokalaemia complicating diuretic use and hyperkalaemia particularly associated with increasing RAAS-blockade, along with potassium-sparing diuretics and the sometime use of potassium supplements. Magnesium, deficiency frequently co-exists with hypokalaemia. Guidelines do not specially indicate when or how frequently electrolytes should be monitored as it depends on clinical circumstances, but we believe they should be estimated daily during acute decongestive therapy, during routine post-discharge follow-up and following any dose changes in HF medication.⁵³ All RAASi's can increase K levels but this is particularly noticeable after the addition of mineralocorticoid receptor antagonists (MRAs). Although the benefits of MRAs are also seen in HFrEF patients with eGFR <60 mL/min/1.73m², despite being associated with small acute and persistent reductions in GFR,⁵⁴ the risk of hyperkalaemia goes up when these agents are prescribed in the presence of pre-existing renal impairment and in such patients careful repeated estimation of K is recommended.⁵⁵ Newly developed oral potassium binders (patiromer or zirconium cyclosilicate) might ease long-term control of K and allow patients with HFrEF to take higher RAASi doses than hitherto but whether this will be reflected in improved long-term outcomes remain unproven.

It is difficult to be prescriptive with regards to the recommended frequency of ongoing monitoring of renal function and electrolytes (usually measured together) as so much depends on individual patient characteristics and inter-current clinical events but in stable HFrEF patients it appears reasonable to measure serum creatinine, urea, eGFR, and electrolytes three times per year, supplemented by re-measurement if medication or patient condition changes.

Monitoring of congestion in heart failure

Congestion is one of the most important determinants of HF symptoms^{56,57} and a major prognostic factor in HF.⁵⁸⁻⁶⁰ It is mostly treated with loop diuretics, as recommended by major international guidelines. It is, therefore, of paramount importance to adequately determine the congestive status,⁶¹ at both admission and discharge, since residual congestion at discharge is associated to higher one-year mortality and HF readmissions.⁶² Patients with residual congestion may have been inadequately decongested during hospitalization, or even if decongested they may experience a recurrence of congestion during post-discharge

follow-up,⁶³ which may trigger subsequent deaths or readmissions in the post-discharge phase.

On the one hand, inadequately low diuretic doses may lead to persistent congestion, one major driver of the high rate of readmission after episodes of worsening HF. Conversely, inappropriately high loop diuretic doses may trigger hypokalaemia and hypovolaemia, with its associated risks of worsening renal function, the latter potentially leading to the down-titration or discontinuation of life-saving drugs i.e. RAASi. Ensuring decongestion is an essential goal during AHF hospitalization, but there is no standardized method for evaluating congestion before discharge and what defines adequate decongestion is currently unclear.⁵⁹ Although clinical trials have proposed a 'definition for decongestion', assessment of decongestion based strictly on trial pre-defined clinical signs may be neither sensitive nor specific, and has not been investigated in real-life clinical practice.^{64,65} Persisting congestion should be more aggressively addressed, perhaps even at the expense of delaying discharge, and these patients should be more closely followed up. Furthermore, other biological variables as surrogate markers of haemodynamic congestion, a <30% change in NP concentrations, or decreased haematocrit during hospitalization, decreasing serum osmolality, add significant prognostic information beyond residual clinical congestion.⁵⁹

Several routinely assessed biological parameters, such as serum protein, albumin, haemoglobin,⁶⁶ and haematocrit (considered in isolation or in combination, enabling the indirect estimation of plasma volume)^{67,68} have been proposed as surrogate markers of (de)congestion and have been found to be associated with cardiovascular endpoints.^{28,69} The gold standard measure of haemodynamic congestion in HF is invasive measurement of pulmonary capillary wedge pressure¹ yet this is impractical for routine care.¹ Non-invasive assessments of congestion have been validated but with variable sensitivities and specificities.¹ Physical signs of congestion can be unreliable and difficult to assess, especially in obesity. Newer techniques such as lung ultrasound offer advantages over older techniques including chest X-ray.⁷⁰ The reader is referred to the paper on imaging of cardiac function for discussion of indirect estimation of cardiac filling pressures (*Figure 1*). Most guidelines suggest the measurement of natriuretic peptides (NPs) in selected clinical settings, but this is more measure of ventricular stress or dilatation than of congestion per se, even though the two may be mechanistically linked in many cases. NPs have a high negative predictive value for ruling out acute HF with congestion but routine monitoring of NP levels in long-term follow-up has not proven to be beneficial on outcomes or cost-effective.

Other potential biomarkers of congestion that can be monitored include sCD-146⁷¹ and the monitoring of haemoglobin concentration through estimation of Hb after decongestive therapy thereby giving an estimate of the degree of relative decongestion rather than the absolute level of congestion at any point in time.⁷² Although increasing creatinine levels are frequently interpreted as worsening kidney function, leading to reductions in HF therapy, during active decongestion an increase in creatinine is to be expected, and being discharged with ongoing congestion seems worse

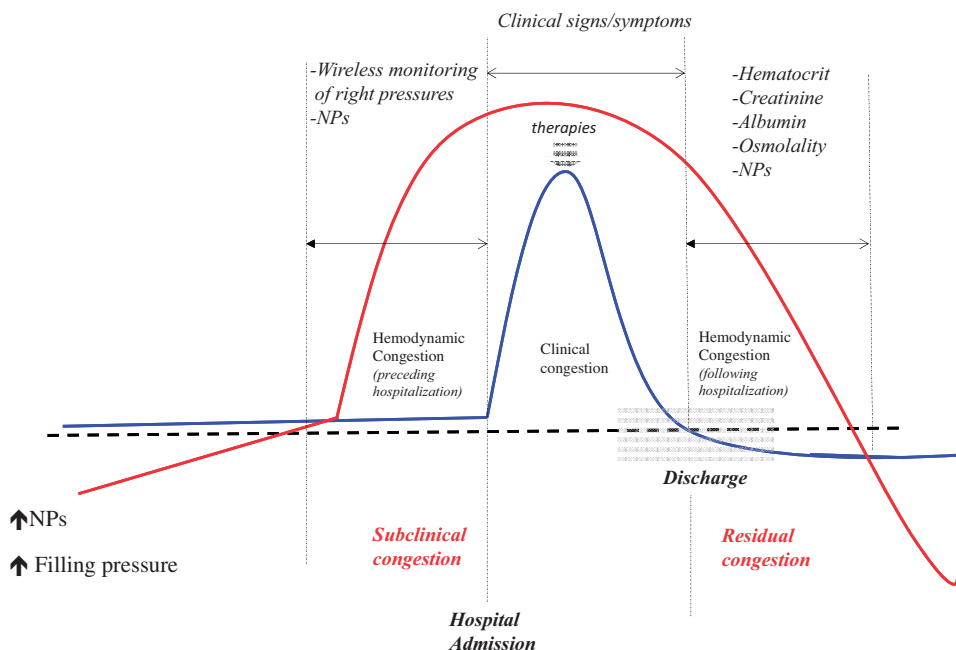


Figure 1 As result of pressure/volume overload, filling pressures and NPs, will increase (red) and its variation precedes worsening of congestion (blue). This pattern may be useful to identify early subclinical decompensation. In spite of clinical improvement as result of in-hospital therapies, for a subset of patients, filling pressures and NPs levels are still persistent during hospitalization and in early post discharge period, suggesting residual congestion. Also, decrease in serum osmolality as result of the high plasma volume may signify haemodynamic congestion. Identification and monitoring of haemodynamic congestion is crucial for preventing early post-discharge adverse events.

compared with the apparent WRF as measured by temporary increases in creatinine.⁷³

Telemedicine for monitoring congestion, renal function, and potassium levels

Dynamic therapy optimization using a telemedicine solution based on frequent non-invasive assessments of congestion (as assessed by haemoglobin), renal function, and blood potassium may enable safe optimization of GDMT.⁷⁴ Concomitant changes in haemoglobin, blood potassium, and renal function and their interplay are probably the most clinically relevant actionable parameters for assessing congestion and the crucial cardio-renal balance. One such system, the remote CardioRenal[®] monitoring solution integrates a pragmatic disease management programme and combines the following components: (i) an innovative microfluidics technology of accurate home monitoring of haemoglobin, potassium, and creatinine concentrations, using a finger-prick 3 μ L blood-drop; (ii) remote monitoring using modern data transfer and data processing methods; (iii) a comprehensive patient-centred disease management, including a medically staffed call-centre; (iv) an innovative algorithmic decision support expert system delivering personalized therapeutic advice to the physician, guided by the monitored variables and the expert system analysis of the patients' electronic health record.

The planned CARE-MOST HF trial (Cardiorenal Assessments and REmote Monitoring for the OptimiSation of Therapy in Heart Failure) is a prospective randomized open blinded end-point evaluation (PROBE) design trial to assess the effectiveness of the CardioRenal[®] telemonitoring loop

vs. usual care in the early follow-up phase of HFrEF patients enrolled before discharge after an acute decompensation. The primary end-point of the study is the cumulative number of HF hospitalizations and cardiovascular deaths. These results will shed new light on the effectiveness of this telemonitoring system in HFrEF patients.

Conclusions

Renal function, congestion, and electrolyte disturbances are both inter-dependent and strong predictors of outcome in HF and can rapidly change depending on the clinical context. Accurate monitoring is essential both in the dynamic situation of acute HF as well as in up-titrating and maintaining optimized RAASi dosages. Accurate individualized monitoring of potassium, renal function, and congestion can facilitate both HF therapy optimization and hospitalization reduction. Telemedicine, in particular, may allow a dynamic optimization of therapy over time. Clinical trials specifically aimed at evaluating the optimal frequency of renal function monitoring in patients with HF are strongly needed.

Funding

P.R. is supported by a public grant overseen by the French National Research Agency (ANR) as part of the second 'Investissements d'Avenir' program FIGHT-HF (reference: ANR-15-RHU-0004) and by the French PIA project 'Lorraine Université d'Excellence', reference ANR-15-IDEX-04-LUE., and the CardioRenal telemonitoring loop development is

funded by a grant 'Prendre Votre Coeur en mains' from region Lorraine and-FEDER Lorraine.

Conflict of interest: P.R.: Personal fees (consulting) from Novartis, Relypsa, AstraZeneca, Grünenthal, Stealth Peptides, Fresenius, Idorsia, Vifor Fresenius Medical Care Renal Pharma, Vifor and CTMA; lecture fees from Bayer and CVRx; cofounder of CardioRenal. A.J.C.: Nothing related to this work. Outside of this work, in the last 3 years, Professor A.J.C. declares having received honoraria and/or lecture fees from: AstraZeneca, Bayer, Menarini, Novartis, Nutricia, Servier, Vifor, Actimed, Cardiac Dimensions, CVRx, Enopace, Faraday, Gore, Respicardia, Stealth Peptides, V-Wave.

References

- Gheorghiane M, Follath F, Ponikowski P, Barsuk JH, Blair JE, Cleland JG, Dickstein K, Drazner MH, Fonarow GC, Jaarsma T, Jondeau G, Sendon JL, Mebazaa A, Metra M, Nieminen M, Pang PS, Seferovic P, Stevenson LW, van Veldhuisen DJ, Zannad F, Anker SD, Rhodes A, McMurray JJ, Filippatos G; European Society of Cardiology; European Society of Intensive Care Medicine. Assessing and grading congestion in acute heart failure: a scientific statement from the acute heart failure committee of the heart failure association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. *Eur J Heart Fail* 2010;12:423-433.
- Vitale C, Spoletini I. Clinical diagnosis in heart failure. *Int Cardiovasc Forum J* 2017;10:12-15.
- Sokolski M, Zymliński R, Biegus J, Siwotowski P, Nawrocka-Millard S, Todd J, Yerramilli MR, Estis J, Jankowska EA, Banasiak W, Ponikowski P. Urinary levels of novel kidney biomarkers and risk of true worsening renal function and mortality in patients with acute heart failure. *Eur J Heart Fail* 2017;19:760-767.
- Rosano GMC. Medical treatment of heart failure with reduced ejection fraction - aimed at reducing rehospitalisations. *Int Cardiovasc Forum J* 2017;10:29-33.
- Metra M. October 2017 at a glance: phenotyping heart failure, comorbidities, use of evidence-based therapy and new treatments. *Eur J Heart Fail* 2017;19:1216-1217.
- Lopatin Y, Coats AJ. The management of heart failure in kidney and urinary tract syndromes. *Int Cardiovasc Forum J* 2017;10:63-64.
- Komajda M, Cowie MR, Tavazzi L, Ponikowski P, Anker SD, Filippatos GS. Physicians' guideline adherence is associated with better prognosis in outpatients with heart failure with reduced ejection fraction: the QUALIFY international registry. *Eur J Heart Fail* 2017;19:1414-1423.
- Agewall S. Adherence to guidelines and registry data. *Eur Heart J Cardiovasc Pharmacother* 2017;3:183-184.
- Agewall S. Cardiovascular pharmacotherapy. *Eur Heart J Cardiovasc Pharmacother* 2018;4:1.
- Rosignol P, Hernandez AF, Solomon S, Zannad F. Heart failure drug treatment. *Lancet* 2019;393:1034-1044.
- Ambrosy AP, Gheorghiane M. Real-world dosing of evidence-based medications for heart failure: embracing guideline recommendations and clinical judgement. *Eur J Heart Fail* 2017;19:1424-1426.
- von Haehling S. Co-morbidities in heart failure beginning to sprout and no end in sight? *Eur J Heart Fail* 2017;19:1566-1568.
- Pan A. The real-world evidence of heart failure co-morbidities. *Eur J Heart Fail* 2017;19:434.
- Trevisan M, de Deco P, Xu H, Evans M, Lindholm B, Bellocco R, Barany P, Jernberg T, Lund LH, Carrero JJ. Incidence, predictors and clinical management of hyperkalaemia in new users of mineralocorticoid receptor antagonists. *Eur J Heart Fail* 2018;20:1217-1226.
- Moe G. Heart failure with multiple comorbidities. *Curr Opin Cardiol* 2016;31:209-216.
- Maggioni AP, Anker SD, Dahlstrom U, Filippatos G, Ponikowski P, Zannad F, Amir O, Chioncel O, Leiro MC, Drozd J, Erglis A, Fazlibegovic E, Fonseca C, Fruhwald F, Gatzov P, Goncalvesova E, Hassanein M, Hradec J, Kavolunienė A, Lainscak M, Logeart D, Merkely B, Metra M, Persson H, Seferovic P, Temizhan A, Tousoulis D, Tavazzi L. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2013;15:1173-1184.
- Lainscak M. How to improve adherence to life-saving heart failure treatments with potassium binders. *Card Fail Rev* 2017;3:33-39.
- Rosignol P, Girerd N, Bakris G, Vardeny O, Claggett B, McMurray JJV, Swedberg K, Krum H, van Veldhuisen DJ, Shi H, Spanys S, Vincent J, Fay R, Lamiral Z, Solomon SD, Zannad F, Pitt B. Impact of eplerenone on cardiovascular outcomes in heart failure patients with hypokalaemia. *Eur J Heart Fail* 2017;19:792-799.
- Montero D, Haider T. Relationship of loop diuretic use with exercise intolerance in heart failure with preserved ejection fraction. *Eur Heart J Cardiovasc Pharmacother* 2018;4:138-141.
- Kapelios CJ, Malliaras K, Kaldara E, Vakrou S, Nanas JN. Loop diuretics for chronic heart failure: a foe in disguise of a friend? *Eur Heart J Cardiovasc Pharmacother* 2018;4:54-63.
- Pitt B, Pedro Ferreira J, Zannad F. Mineralocorticoid receptor antagonists in patients with heart failure: current experience and future perspectives. *Eur Heart J Cardiovasc Pharmacother* 2017;3:48-57.
- Rosano GMC, Tamargo J, Kjeldsen KP, Lainscak M, Agewall S, Anker SD, Ceconi C, Coats A, Drexel H, Filippatos G, Kaski JC, Lund L, Niessner A, Ponikowski P, Savarese G, Schmidt TA, Seferovic P, Wassmann S, Walther T, Lewis BS. Expert consensus document on the management of hyperkalaemia in patients with cardiovascular disease treated with renin angiotensin aldosterone system inhibitors: coordinated by the Working Group on Cardiovascular Pharmacotherapy of the European Society of Cardiology. *Eur Heart J Cardiovasc Pharmacother* 2018;4:180-188.
- Savarese G, Carrero JJ, Pitt B, Anker SD, Rosano GMC, Dahlström U, Lund LH. Factors associated with underuse of mineralocorticoid receptor antagonists in heart failure with reduced ejection fraction: an analysis of 11 215 patients from the Swedish Heart Failure Registry. *Eur J Heart Fail* 2018;20:1326-1334.
- Pitt B, Bakris GL, Weir MR, Freeman MW, Lainscak M, Mayo MR, Garza D, Zawadzki R, Berman L, Bushinsky DA. Long-term effects of patiromer for hyperkalaemia treatment in patients with mild heart failure and diabetic nephropathy on angiotensin-converting enzymes/angiotensin receptor blockers: results from AMETHYST-DN. *ESC Heart Fail* 2018;5:592-602.
- Tamargo M, Tamargo J. New potassium binders reduce the risk of hyperkalaemia in patients treated with renin-angiotensin-aldosterone system inhibitors. *Eur Heart J Cardiovasc Pharmacother* 2018;4:193-194.
- Jankowska EA. The management of co-morbidities in patients with heart failure—potassium balance. *Int Cardiovasc Forum J* 2017;10:81-83.
- Butler J, Vijayakumar S, Pitt B. Need to revisit heart failure treatment guidelines for hyperkalaemia management during the use of mineralocorticoid receptor antagonists. *Eur J Heart Fail* 2018;20:1247-1251.
- Bayés-Genís A, Lupón J, Núñez J. No need for urgent revisiting of potassium levels in guidelines despite use of mineralocorticoid receptor antagonists: bring in more evidence. *Eur J Heart Fail* 2018;20:1252-1254.
- Zannad F, Rosignol P. Cardiorenal syndrome revisited. *Circulation* 2018;138:929-944.
- Cooper LB, Hammill BG, Peterson ED, Pitt B, Maciejewski ML, Curtis LH, Hernandez AF. Consistency of laboratory monitoring during initiation of mineralocorticoid receptor antagonist therapy in patients with heart failure. *JAMA* 2015;314:1973-1975.
- Nilsson E, De Deco P, Trevisan M, Bellocco R, Lindholm B, Lund LH, Coresh J, Carrero JJ. A real-world cohort study on the quality of potassium and creatinine monitoring during initiation of mineralocorticoid receptor antagonists in patients with heart failure. *Eur Heart J Qual Care Clin Outcomes* 2018.
- Damman K, Navis G, Voors AA, Asselbergs FW, Smilde TD, Cleland JG, van Veldhuisen DJ, Hillege HL. Worsening renal function and prognosis in heart failure: systematic review and meta-analysis. *J Card Fail* 2007;13:599-608.
- Brisco MA, Zile MR, Hanberg JS, Wilson FP, Parikh CR, Coca SG, Tang WHW, Testani JM. Relevance of changes in serum creatinine during a heart failure trial of decongestive strategies: insights from the DOSE trial. *J Card Fail* 2016;22:753-760.
- Clark AL, Coats AJS, Krum H, Katus HA, Mohacs P, Salekin D, Schultz MK, Packer M, Anker SD. Effect of beta-adrenergic blockade with

- carvedilol on cachexia in severe chronic heart failure: results from the COPERNICUS trial. *J Cachexia Sarcopenia Muscle* 2017;**8**:549-556.
35. Scherbakov N, Doehner W. Cachexia as a common characteristic in multiple chronic disease. *J Cachexia Sarcopenia Muscle* 2018;**9**:1189-1191.
 36. Valente MA, Voors AA, Damman K, Van Veldhuisen DJ, Massie BM, O'Connor CM, Metra M, Ponikowski P, Teerlink JR, Cotter G, Davison B, Cleland JG, Givertz MM, Bloomfield DM, Fiuzat M, Dittrich HC, Hillege HL. Diuretic response in acute heart failure: clinical characteristics and prognostic significance. *Eur Heart J* 2014;**35**:1284-1293.
 37. Metra M, Cotter G, Gheorghide M, Dei CL, Voors AA. The role of the kidney in heart failure. *Eur Heart J* 2012;**33**:2135-2142.
 38. Damman K, Testani JM. The kidney in heart failure: an update. *Eur Heart J* 2015;**36**:1437-1444.
 39. Ahmad T, Jackson K, Rao VS, Tang WHW, Brisco-Bacik MA, Chen HH, Felker GM, Hernandez AF, O'Connor CM, Sabbisetti VS, Bonventre JV, Wilson FP, Coca SG, Testani JM. Worsening renal function in acute heart failure patients undergoing aggressive diuresis is not associated with tubular injury. *Circulation* 2018;**137**:2016.
 40. Metra M, Davison B, Bettari L, Sun H, Edwards C, Lazzarini V, Piovanelli B, Carubelli V, Bugatti S, Lombardi C, Cotter G, Dei Cas L. Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. *Circ Heart Fail* 2012;**5**:54-62.
 41. Edelstein CL. Biomarkers of acute kidney injury. *Adv Chronic Kidney Dis* 2008;**15**:222-234.
 42. Stevens LA, Levey AS. Measured GFR as a confirmatory test for estimated GFR. *J Am Soc Nephrol* 2009;**20**:2305-2313.
 43. Pham D, Grodin JL. Dilemmas in the dosing of heart failure drugs: titrating diuretics in chronic heart failure. *Card Fail Rev* 2017;**3**:108-112.
 44. Valente MA, Hillege HL, Navis G, Voors AA, Dunselman PH, van Veldhuisen DJ, Damman K. The chronic kidney disease epidemiology collaboration equation outperforms the modification of diet in renal disease equation for estimating glomerular filtration rate in chronic systolic heart failure. *Eur J Heart Fail* 2014;**16**:86-94.
 45. Schrier RW. Blood urea nitrogen and serum creatinine: not married in heart failure. *Circ Heart Fail* 2008;**1**:2-5.
 46. Schmidt-Ott KM, Mori K, Li JY, Kalandadze A, Cohen DJ, Devarajan P, Barasch J. Dual action of neutrophil gelatinase-associated lipocalin. *J Am Soc Nephrol* 2007;**18**:407-413.
 47. Martens P, Mullens W. Spot urinary sodium in decompensated heart failure as a prognostic metric for successful ambulatory decongestion. *J Card Fail* 2018;**24**:355-356.
 48. Katz DH, Burns JA, Aguilar FG, Beussink L, Shah SJ. Albuminuria is independently associated with cardiac remodeling, abnormal right and left ventricular function, and worse outcomes in heart failure with preserved ejection fraction. *JACC Heart Fail* 2014;**2**:586-596.
 49. Verbrugge FH, Steels P, Grieten L, Nijst P, Tang WH, Mullens W. Hyponatremia in acute decompensated heart failure: depletion versus dilution. *J Am Coll Cardiol* 2015;**65**:480-492.
 50. ter Maaten JM, Damman K, Hanberg JS, Givertz MM, Metra M, O'Connor CM, Teerlink JR, Ponikowski P, Cotter G, Davison B, Cleland JG, Bloomfield DM, Hillege HL, van Veldhuisen DJ, Voors AA, Testani JM. Hypochloremia, diuretic resistance, and outcome in patients with acute heart failure. *Circ Heart Fail* 2016;**9**.
 51. Konishi M, Haraguchi G, Ohigashi H, Sasaoka T, Yoshikawa S, Inagaki H, Ashikaga T, Isobe M. Progression of hyponatremia is associated with increased cardiac mortality in patients hospitalized for acute decompensated heart failure. *J Card Fail* 2012;**18**:620-625.
 52. Gheorghide M, Abraham WT, Albert NM, Gattis Stough W, Greenberg BH, O'Connor CM, She L, Yancy CW, Young J, Fonarow GC. Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry. *Eur Heart J* 2007;**28**:980-988.
 53. Arrigo M, Nijst P, Rudiger A. Optimising heart failure therapies in the acute setting. *Card Fail Rev* 2018;**4**:38-42.
 54. Rossignol P, Cleland JG, Bhandari S, Tala S, Gustafsson F, Fay R, Lamiral Z, Dobre D, Pitt B, Zannad F. Determinants and consequences of renal function variations with aldosterone blocker therapy in heart failure patients after myocardial infarction: insights from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study. *Circulation* 2012;**125**:271-279.
 55. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, Redelmeier DA. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med* 2004;**351**:543-551.
 56. Van Aelst LNL, Arrigo M, Placido R, Akiyama E, Girerd N, Zannad F, Manivet P, Rossignol P, Badoz M, Sadoune M, Launay JM, Gayat E, Lam CSP, Cohen-Solal A, Mebazaa A, Seronde MF. Acutely decompensated heart failure with preserved and reduced ejection fraction present with comparable haemodynamic congestion. *Eur J Heart Fail* 2018;**20**:738-747.
 57. Bistola V, Polyzogopoulou E, Ikonomidis I, Parisis J. Congestion in acute heart failure with reduced vs. preserved left ventricular ejection fraction: differences, similarities and remaining gaps. *Eur J Heart Fail* 2018;**20**:748-750.
 58. Rossignol P, Menard J, Fay R, Gustafsson F, Pitt B, Zannad F. Eplerenone survival benefits in heart failure patients post-myocardial infarction are independent from its diuretic and potassium-sparing effects. Insights from an EPHEUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) substudy. *J Am Coll Cardiol* 2011;**58**:1958-1966.
 59. Pareek A, Chandurkar N, Dharmadhikari S. Congestive heart failure: more common as well as an important cardiovascular outcome. *Eur Heart J Cardiovasc Pharmacother* 2017;**3**:98.
 60. Hartman O, Sinisalo J, Kovanen PT, Lehtonen J, Eklund KK. Congestive heart failure: more common as well as an important cardiovascular outcome: reply. *Eur Heart J Cardiovasc Pharmacother* 2017;**3**:99.
 61. Girerd N, Seronde MF, Coiro S, Chouhied T, Bilbault P, Braun F, Kenizou D, Maillier B, Nazeyrollas P, Roul G, Fillieux L, Abraham WT, Januzzi J Jr, Sebbag L, Zannad F, Mebazaa A, Rossignol P; INI-CRCT, Great Network, and the EF-HF Group. Integrative assessment of congestion in heart failure throughout the patient journey. *JACC Heart Fail* 2018;**6**:273-285.
 62. Chioncel O, Mebazaa A, Maggioni AP, Harjola VP, Rosano G, Laroche C, Piepoli MF, Crespo-Leiro MG, Lainscak M, Ponikowski P, Filippatos G, Ruschitzka F, Seferovic P, Coats AJS, Lund LH; ESC-EORP HFA Heart Failure Long-Term Registry Investigators. Acute heart failure congestion and perfusion status - impact of the clinical classification on in-hospital and long-term outcomes; insights from the ESC-EORP-HFA Heart Failure Long-Term Registry. *Eur J Heart Fail* 2019;doi:10.1002/ejhf.1492 (in press).
 63. Lopatin Y, Rosano GMC. Treatment of patients in the vulnerable phase (at discharge or early after discharge). *Int Cardiovasc Forum J* 2017;**10**:37-40.
 64. Ambrosy AP, Pang PS, Khan S, Konstam MA, Fonarow GC, Traver B, Maggioni AP, Cook T, Swedberg K, Burnett JC Jr, Grinfeld L, Udelson JE, Zannad F, Gheorghide M; EVEREST Trial Investigators. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial. *Eur Heart J* 2013;**34**:835-843.
 65. Bart BA, Goldsmith SR, Lee KL, Givertz MM, O'Connor CM, Bull DA, Redfield MM, Deswal A, Rouleau JL, LeWinter MM, Ofili EO, Stevenson LW, Semigran MJ, Felker GM, Chen HH, Hernandez AF, Anstrom KJ, McNulty SE, Velazquez EJ, Ibarra JC, Mascette AM, Braunwald E; Heart Failure Clinical Research Network Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N Engl J Med* 2012;**367**:2296-2304.
 66. Rossignol P, Dobre D, Gregory D, Massaro J, Kiernan M, Konstam MA, Zannad F. Incident hyperkalemia may be an independent therapeutic target in low ejection fraction heart failure patients: insights from the HEAL study. *Int J Cardiol* 2014;**173**:380-387.
 67. Duarte K, Monnez JM, Albuissou E, Pitt B, Zannad F, Rossignol P. Prognostic value of estimated plasma volume in heart failure. *JACC Heart Fail* 2015;**3**:886-893.
 68. Rossignol P, Masson S, Barlera S, Girerd N, Castelnovo A, Zannad F, Clemenza F, Tognoni G, Anand IS, Cohn JN, Anker SD, Tavazzi L, Latini R. Loss in body weight is an independent prognostic factor for mortality in chronic heart failure: insights from the GISSI-HF and Val-HeFT trials. *Eur J Heart Fail* 2015;**17**:424.
 69. Mentz RJ, Kjeldsen K, Rossi GP, Voors AA, Cleland JG, Anker SD, Gheorghide M, Fiuzat M, Rossignol P, Zannad F, Pitt B, O'Connor C, Felker GM. Decongestion in acute heart failure. *Eur J Heart Fail* 2014;**16**:471-482.

70. Platz E, Merz AA, Jhund PS, Vazir A, Campbell R, McMurray JJ. Dynamic changes and prognostic value of pulmonary congestion by lung ultrasound in acute and chronic heart failure: a systematic review. *Eur J Heart Fail* 2017;19:1154-1163.
71. Gayat E, Caillard A, Laribi S, Mueller C, Sadoune M, Seronde M-F, Maisel A, Bartunek J, Vanderheyden M, Desutter J, Dendale P, Thomas G, Tavares M, Cohen-Solal A, Samuel J-L, Mebazaa A. Soluble CD146, a new endothelial biomarker of acutely decompensated heart failure. *Int J Cardiol* 2015;199:241-247.
72. Breidthardt T, Weidmann ZM, Twerenbold R, Gantenbein C, Stallone F, Rentsch K, Rubini Gimenez M, Kozhuharov N, Sabti Z, Breitenbücher D, Wildi K, Puelacher C, Honegger U, Wagener M, Schumacher C, Hillinger P, Osswald S, Mueller C. Impact of haemoconcentration during acute heart failure therapy on mortality and its relationship with worsening renal function. *Eur J Heart Fail* 2017;19:226-236.
73. Chioncel O, Collins SP, Greene SJ, Pang PS, Ambrosy AP, Antohi EL, Vaduganathan M, Butler J, Gheorghiade M. Predictors of post-discharge mortality among patients hospitalized for acute heart failure. *Card Fail Rev* 2017;3:122-129.
74. Gensini GF, Alderighi C, Rasoini R, Mazzanti M, Casolo G. Value of telemonitoring and telemedicine in heart failure management. *Card Fail Rev* 2017;3:116-121.