

Review

Hyperkalemia in heart failure: current treatment and new therapeutic perspectives

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Hyperkalemia in heart failure is a condition that can occur with relative frequency because it is related to pathophysiological aspects of the disease, and favored by drugs that form the basis of chronic cardiac failure therapy. Often, associated comorbidities, such as kidney failure or diabetes mellitus can further adversely affect potassium levels. Hyperkalemia can result in acute and even severe clinical manifestations that put patients at risk. On the other hand, the finding of hyperkalemia in a chronic context can lead to a reduction in dosages or to suspension of drugs such as angiotensin-converting enzymes inhibitor, angiotensin receptor blocker, angiotensin receptor neprilysin inhibitor, and mineralcorticoid receptor antagonist, first line in the treatment of the disease, with negative effects in prognostic terms. Therapies for the correction of hyperkalemia have so far mainly concerned the treatment of acute clinical pictures. Newly developed molecules, such as patiomer or sodium zirconium cyclosilicate, now open new perspectives in the long-term management of hyperkalemia, and allow us to glimpse the possibility of a better titration of the cardinal drugs for heart failure, with consequent positive effects on patient prognosis. The aim of this review is to focus on the problem of hyperkalemia in the setting of heart failure, with particular regard to its incidence, its prognostic role, and the underlining pathophysiological mechanisms. The review also provides an overview of therapeutic strategies for correcting hyperkalemia in acute and chronic conditions, with a focus on the new potassium binders that promise to improve management of heart failure.

Keywords

Potassium; heart failure; hyperkalemia; renin-angiotensin-aldosterone system inhibitors; patiomer; sodium zirconium cyclosilicate

1. Introduction

In patients with heart failure (HF) the presence of hyperkalemia is found with relative frequency, and can lead to reduction/suspension of the main drugs that constitute background therapy, such as angiotensin-converting enzymes inhibitor (ACE-I), angiotensin receptor blocker (ARB), angiotensin receptor

neprilysin inhibitor (ARNI), and mineralcorticoid receptor antagonist (MRA), with negative effects from clinical and prognostic points of view. In light of the importance of this topic, the aim of this review is to focus on the problem of hyperkalemia in the context of HF, with particular regard to its incidence, its prognostic role, and the underlining pathophysiological mechanisms. We discuss the main aspects concerning the physiology of potassium (K^+) in the human body, the hydro-electrolytic, alterations on electrocardiogram (EKG), and the clinical consequences on the heart, and the negative effects on the neuromuscular apparatus. The review also provides an overview of therapeutic strategies for correcting hyperkalemia in acute and chronic conditions, with a focus on drugs acting as K^+ binders, such as the old sodium polystyrene-sulfonate (SPS) and the newer patiomer, and sodium zirconium cyclosilicate (SZC), which promise to change management of renin angiotensin aldosterone system inhibitor (RAASi) therapy in HF patients, with potential prognostic benefits (McCullough et al., 2014, 2015).

2. The physiology of potassium in the human body

K^+ is the main cation of intracellular fluid (about 98%). It is important for acid-base balance and osmotic pressure and, moreover, promotes the action of enzymes involved in cellular metabolism. K^+ also determines the membrane potential of all cells in the body, and is involved in the excitability of some cell types such as nerve, skeletal, cardiac, and smooth fibers (Branconi et al., 2011; McDonough and Youn, 2017). The recommended K^+ intake in adults is about 3 g per day. In the healthy individual, absorption occurs in the stomach and upper gastrointestinal tract. Approximately 10mEq/day are eliminated in the feces. The normal plasma concentration of the electrolyte is between 3.5 and 5.0 mEq/L. The excretion of K^+ , in physiological conditions, is mostly localized in the cortical portion of the distal nephron (Brown, 1986). The kidneys are therefore the organs mainly responsible for the serum concentration of K^+ , determining its excretion for about 90%. The filtered K^+ (700-800 mmol/day) is predominantly reabsorbed by the proximal convoluted tubule and the thick segment of the loop of Henle, and excreted from the distal convoluted tubule and the collecting duct. K^+ excretion is associated with sodium reabsorption through the sodium

channels. Increased sodium reabsorption increases K^+ excretion, while reduced sodium absorption reduces K^+ excretion (Gumz et al., 2015). Any condition that reduces the activity of the K^+ channels leads to hyperkalemia (Hunter and Bailey, 2019; Palmer and Clegg, 2017). Insulin and catecholamines determine K^+ entry of K^+ into the cells and its deposition, especially in liver, fat, and muscle striated cells. Insulin acts through the direct stimulation of sodium- K^+ ATP-ase pump. Catecholamines (beta2-adrenergic agonists) stimulate the entry of K^+ into the cell through sodium- K^+ ATP-ase. Instead, alpha-adrenergic agonists have the opposite effect. Aldosterone increases renal K^+ excretion through the collecting duct, as it determines the opening of the apical sodium channels, and enhances the sodium- K^+ ATP-ase activity in the basolateral portion of the membrane. Aldosterone also influences the extrarenal elimination of K^+ through the stimulation of ion excretion in the colon and salivary glands. Acid-base balance also has an effect on K^+ . This relationship also depends on the etiology of the acid-base disorder (Palmer and Clegg, 2016). All the clinical manifestations of hypo/hyperkalemia depend on the velocity with which the electrolytic alteration is established, on the underlining disease, on the simultaneous administration of drugs, on PO_2 , pH, and on a series of concomitant factors. We speak of hyperkalemia when K^+ is > 5.0 mEq/l: hyperkalemia is classified as mild for values between 5.0 and 5.9 mEq/l, moderate for values between 6.0 and 6.4 mEq/l, and severe for values > 6.5 mEq/l. Particular attention should be paid to cases of pseudo-hyperkalemia, in which there is a difference between serum and plasma $K^+ > 0.4$ mEq/l; it should be suspected in hyper viscosity syndromes (such as polycythemia vera) or in the event of inadequate blood sampling and storage (Teh et al., 2003). Among the most frequent causes of hyperkalemia are therapies with ACE-I or ARB (which antagonize the effects of aldosterone in the excretion of K^+) and acute or chronic renal failure (Greenlee et al., 2009).

3. Hyperkalemia and heart failure: "The size of the problem"

HF is still associated with a high risk of hospitalization and high mortality, and represents a major health problem. For this reason an optimized medical therapy is of primary importance, including all treatments that have been shown in clinical trials to have a positive effect on prognosis. Renin-angiotensin-aldosterone system inhibitors (RAASi) are drugs of primary importance in HF, but expose patients to the risk of hyperkalemia, and can cause life-threatening arrhythmias. This issue leads in clinical practice to a frequent under-use (tapering or withholding) of RAASi, with a negative impact on major outcomes (Beusekamp et al., 2018; De Nicola et al., 2019; Romani et al., 2019). It is important to remember that introduction of ACE-I in the 1990s for HF treatment led to a reduction of cardiovascular deaths of 16-31% (CONSENSUS Trial Study Group, 1987; SOLVD Investigators, 1991), and that sacubitril/valsartan reduced mortality 20% compared to enalapril (McMurray et al., 2014), to understand the importance of this issue. Data from ESC HF Registry (Maggioni et al., 2013) revealed that RAASi treatment at full dose is reached in only about 35% of patients due to pathological K^+ levels. As a consequence, chronic treatment and prevention of hyperkalemia are primary goals in order to guarantee a complete titration of HF neurohormonal drugs.

The benefits of RAASi are relevant also in patients with acute HF, as demonstrated by some mostly observational data showing that RAASi continuation is safe and well tolerated, as well efficacious in the majority of patients (Singhania et al., 2019). Given that hyperkalemia and renal failure are among the major causes of RAASi suspension, the role of the novel K^+ binders capable of normalizing K^+ level can be of crucial importance in the acute setting.

3.1 Incidence of hyperkalemia and prognostic role

The real incidence of hyperkalemia in HF is not entirely known, though some data suggest that it is greater than that reported in the literature. The PARADIGM-HF trial testing sacubitril/valsartan vs. enalapril found moderate hyperkalemia in 16.1% vs. 17.3% of patients, and severe hyperkalemia in 4.3% vs. 5.6%, respectively at 27-month follow up despite a select trial population (McMurray et al., 2014). In the real world, the incidence of hyperkalemia is likely more, as suggested by a recent Danish study that enrolled a large HF population of 31,649 patients; high K^+ levels were reported in 39% of patients during 2-year follow-up. Data from the SwedeHF registry suggest that moderate or severe hyperkalemia occurs more frequently in patients with HF and preserved or midrange ejection fraction (EF) compared to those with reduced EF. Moreover, HF severity and estimated glomerular filtration rate (eGFR) were associated with occurrence of K^+ alterations (Savarese et al., 2019).

The relationship between hyperkalemia and prognosis has not been fully clarified (Table 1) since some data suggest an association with risk of hospitalization and death (Aldahl et al., 2017; Jain et al., 2012; Palaka et al., 2019), while others do not (Zanad et al., 2011). The aforementioned Danish study indicates that hyperkalemia increases the risk of mortality up to three times, in addition to a high frequency of hospitalizations. Differently, other studies have not found a link between high K^+ levels and mortality. It is likely that in the Danish population the high prevalence of comorbidities (e.g., diabetes, renal failure) accounts for the worse prognosis. Recently, Beusekamp et al. investigated the role of hyperkalemia in acute HF, and found that it was not associated with adverse outcomes. However, some studies have found that hyperkalemia caused down-titration of MRA, a condition associated with 180-day mortality (hazard ratio [HR]: 1.73; 95% confidence interval [CI]: 1.15-2.60) (Beusekamp et al., 2019; Lisi et al., 2020). Use of MRA can bring with it a risk of hyperkalemia but, as demonstrated in the RALES trial (Juurlink et al., 2004; Pitt et al., 1999), which tested the use of spironolactone in HF, there is a benefit in terms of mortality when K^+ levels remain ≤ 5.5 mmol/L. Data from a retrospective observational study conducted in the U.K. on new onset HF patients suggest that not only hyperkalemia brings an increased mortality risk, but is also correlated with a greater probability of RAASi suspension (Linde et al., 2019). Similarly, it has been recently seen that in the context of non-dialysis chronic kidney disease, hyperkalemia generates a greater probability of evolution toward end-stage forms, particularly when associated with RAASi non-use or discontinuation, while it does not increase mortality (Provenzano et al., 2018).

These data favor the hypothesis that there is likely no direct link between hyperkalemia and outcomes, but rather an indirect relationship mediated by the need to down-taper or discontinue the drugs counteracting neurohormonal activation in HF.

Table 1. The table shows a list of studies that tested the association between hyperkalemia and clinical outcomes (hospitalizations or mortality) in the setting of HF.

Study	Type of Study		Risk of Hospitalization		Risk of Mortality
Thomsen et al., 2018	Retrospective, population-based cohort	Increased	6-month HR: 2.75 (95% CI, 2.65-2.85)	Increased	6-month HR: 3.39 (95% CI, 3.19-3.61)
Beusekamp et al., 2019	Prospective, randomized	-	-	Not increased	180-days normo K ⁺ vs hyper K ⁺ : P = 0.147
Linde et al., 2019	Retrospective, observational	Not increased	DATA not shown	Increased	6-month IRRs: - K ⁺ = 5-5.5 mmol/L: 1.23 (1.12-1.38) - K ⁺ = 5.5-6 mmol/L: 1.35 (1.14-1.60) - K ⁺ > 6 mmol/L: 3.02 (2.28-4.02)
Jain et al., 2012	Retrospective	Increased	hyper K ⁺ vs. normo K ⁺ : 7.8% vs 5.4% (P < 0.0001)	Increased	-hyper K ⁺ vs normo K ⁺ : 6.25% vs 2.92% (P < 0.0001) -95% CI, OR: 1.56 (1.30-1.88)
Aldahl et al., 2017	Retrospective, population registry	-	-	Increased	90-days HR: - K ⁺ = 4.8-5.0 mmol/L: 1.34; CI: 1.10-1.63) - K ⁺ = 5.1-5.5 mmol/L: 1.60; CI: 1.29-1.97) - K ⁺ = 5.6-7.4 mmol/L: 3.31; CI: 2.61-4.20)
Zannad et al., 2011	Prospective, randomized	Not increased	hyper K ⁺ in eplerenone vs. placebo group: 0.3 vs 0.2% (P = 0.85) HR: 1.15 (95% CI, 0.25-5.31)	-	-
Savarese et al., 2019	Retrospective, registry	Not increased	- 1-year HR: HF hosp.: 0.93 (95% CI, 0.63-1.57) other cause hosp.: 1.09 (95% CI, 0.72-1.84)	Increased	1-year HR: 4.03 (95% CI, 3.42-4.75)

CI: interval confidence; HR: hazard ratio; IRRs: incident rate ratios; OR: odds ratio; HF: heart failure

Therefore, in light of the size of the problem it is important to better understand the real incidence, the risk factors associated with, and the prognostic impact of, hyperkalemia to develop adequate strategies to ensure optimal treatment of HF (Rossignol et al., 2020).

4. Mechanisms involved in hyperkalemia in heart failure

Patients with HF represent a population at particular risk of developing hyperkalemia due to a series of pathophysiological alterations and iatrogenic factors (Sarwar et al., 2016). In HF, the high renin levels secondary to renal hypoperfusion stimulate the production of aldosterone, which causes an increase in K⁺ excretion. The key drugs of HF therapy act at this level, blocking the renin-angiotensin-aldosterone axis. ACE-I blocks the production of angiotensin-II, while ARBs inhibit its receptor, both with the ultimate effect of blocking the synthesis and release of aldosterone, which results in increased levels of serum K⁺. ACE-I and ARB also directly inhibit the production of angiotensin-I at the level of the adrenal glands. The use of ARNI, as evidenced in the PARADIGM-HF study, can also be associated with hyperkalemia, though this effect is lower than that of ACE-I (McMurray et al., 2014). MRAs act on the same biochemical pathway, contributing to the risk of hyperkalemia, especially because they are often administered in association with ACE-I, ARB or ARNI. Other mechanisms responsible for the increase in serum K⁺ are reduced sodium excretion from the distal nephron, aldosterone deficiency, and collector tubule malfunction. Moreover, patients with HF often have many comorbidities, such as diabetes or renal failure,

which reduce the ability to eliminate K⁺, resulting in increased hematic levels (Bhinder et al., 2020; Wetmore et al., 2019). Diabetes also acts through hyperglycemia, K⁺ shift from intra- to extracellular compartment, hyporeninemia, and hypoaldosteronism. Finally, drugs such as antibiotics, heparins or non-steroidal anti-inflammatory drugs (NSAIDs) can cause hyperkalemia (Fig. 1).

5. Hydro-electrolytic, EKG, and clinical consequences of hyperkalemia

Most K⁺ in the body is intracellular, with an intra/extracellular concentration gradient of 30:1. This gradient is fundamental for determining resting membrane potential, neuromuscular excitability, and activity of cardiac pace-maker cells. This explains why alterations in plasma K⁺ determine clinical manifestations of excitable tissues, and are predominantly muscular and cardiac. The most common neuromuscular manifestations are paresthesia and fasciculation in the arms and legs; in the case of severe hyperkalemia it is possible to have pictures of ascending paralysis and quadriplegia (trunk, brain, and respiratory muscles are spared). Gastrointestinal manifestations such as nausea, vomiting, and diarrhea, or metabolic alterations such as hyperchloremic metabolic acidosis can also occur (Palmer and Clegg, 2017). For the cardiologist, hyperkalemia can be a highly important issue: severe forms can represent a clinical emergency that can lead to malignant arrhythmias and death. Acute-onset forms, therefore, require continuous monitoring in the cardiology department, and timely interventions (Kovesdy, 2015). The severity of these events depends more on the speed of the increase than on the absolute value of K⁺. Moreover, even in the most mild and clinically silent forms,

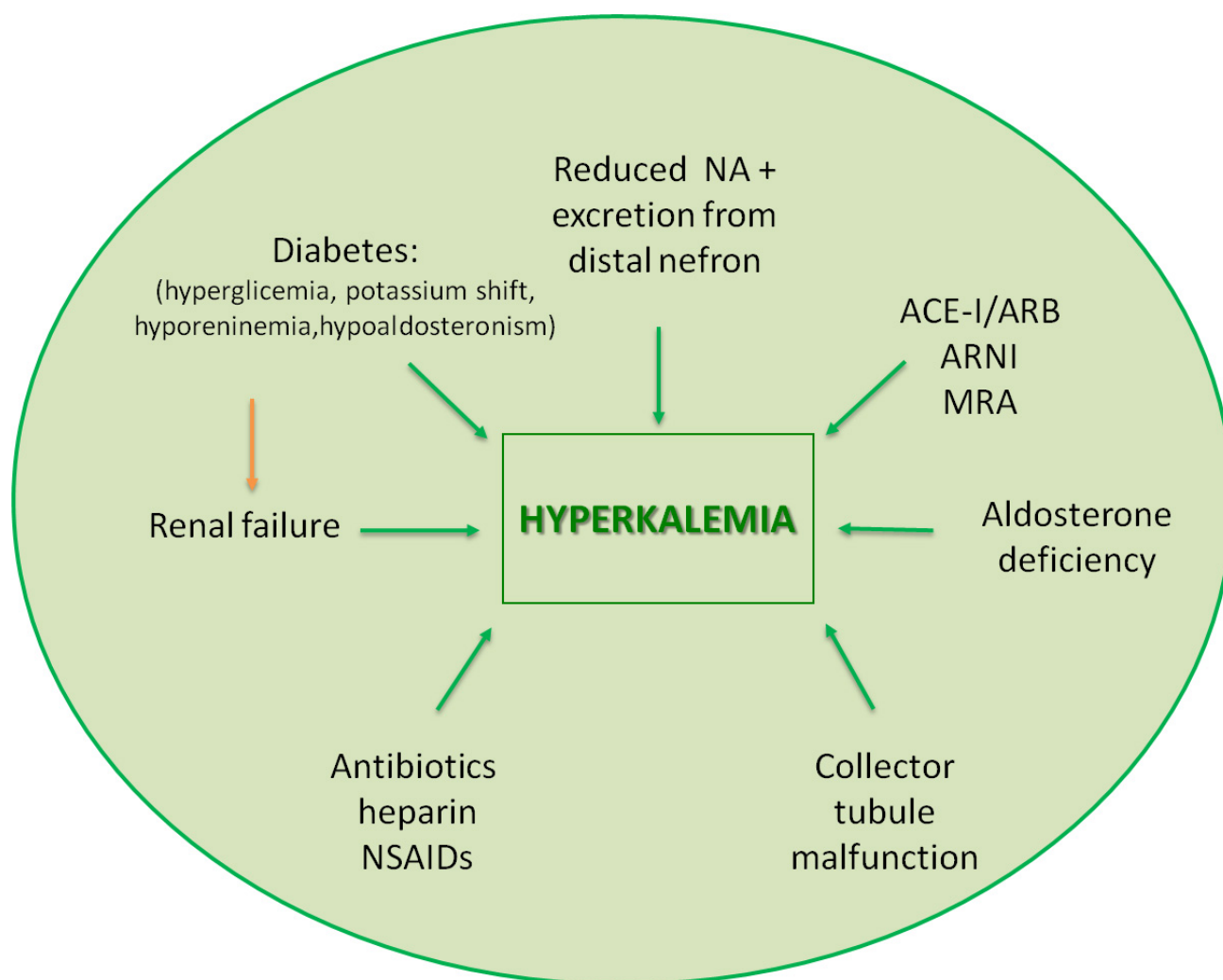


Figure 1. Pathophysiological mechanism involved in hyperkalemia in heart failure. Pathophysiological mechanism involved in hyperkalemia in heart failure. Main drugs for heart failure therapy inhibit renin-angiotensin-aldosterone axis with consequent hyperkalemia. ACE-I blocks the production of angiotensin-II, while ARBs inhibit its receptor. The consequence is the blocking of the synthesis and the release of aldosterone. Moreover, ACE-I and ARB directly inhibit the production of angiotensin-I. Also ARNI and MRAs act at the same level. Other mechanisms contribute to increased potassium levels: reduced sodium excretion from the distal nephron, aldosterone deficiency, and collector tubule malfunction. Comorbidities such as diabetes or renal failure cause reduced potassium removal by the kidney. Hyperglycemia also provokes potassium leak into extracellular compartment, hyporeninemia, and hypoaldosteronism. Some drugs, such as antibiotics, heparins or non-steroidal antiinflammatory drugs (NSAIDs) can induce hyperkalemia. ACE-I: ace-inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; MRA: mineralcorticoid receptor antagonist; NSAID: non-steroidal antiinflammatory drugs.

hyperkalemia is often the cause of interruption of therapies important for HF, such as those with inhibitors of the renin-angiotensin-aldosterone system, and represent a marker of poor prognosis. A recently published study of a Danish population of over 31,000 patients showed that one-quarter of the patients hospitalized for HF developed hyperkalemia, particularly if they had diabetes mellitus, renal failure, or spironolactone treatment; this finding was strongly associated with the subsequent manifestation of adverse clinical events, and with an increase in mortality of more than three times (Thomsen et al., 2018). Generally speaking, it has been shown that hyperkalemia affects up to 10% of hospitalized patients for all causes. The clinical presentation, which includes hypotension, shock, profound asthenia, paralysis, and cardiac arrest can easily be mistaken for a simple deterioration of the underlying pathol-

ogy. In these cases, the EKG can provide strong indications for the diagnosis of hyperkalemia, and guide clinicians toward an appropriate treatment. At the level of the myocardium, in fact, hyperkalemia reduces conduction velocity, and accelerates the repolarization phase, producing the typical alterations detectable on the surface EKG (Fig. 2). Electrocardiographic changes include sinus bradycardia, loss of P waves, left or right bundle branch block, atrioventricular block of II or III degree, pseudo-STEMI pattern or Brugada-type phenocopy (Pozzolini et al., 2019). The widening of the QRS, bradycardia < 50 bpm, and junctional rhythm are associated with adverse events, while the typical pointed T-waves are not correlated with significant clinical manifestations. In terms of clinical significance, the type of electrocardiographic alterations is a more important prognostic predictor than the actual level of

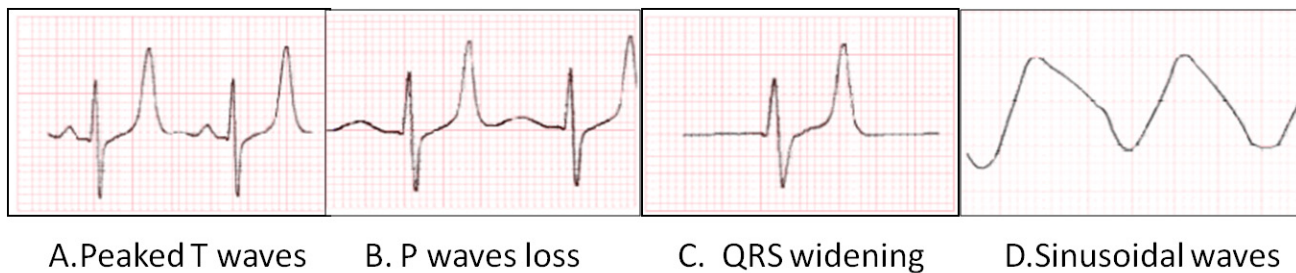


Figure 2. EKG alterations during hyperkalemia. From A to D the alterations due to increasing levels of potassium. A) The first EKG alteration is the discovery of high and pointed T waves with a narrow base. B) When levels of potassium increase it is possible to find reduced P wave amplitude and P-R tract lengthening until P wave loss and severe bradycardia. C) Widening of QRS with right bundle block morphology can develop. Less frequent is left bundle block morphology. D) In presence of severe hyperkalemia, the extreme widening of QRS leads to sinusoidal waves. Asystolia, pulseless ventricular tachycardia and ventricular fibrillation can develop.

serum K^+ ; in fact, electrocardiographic alterations usually reflect the rate of increase in K^+ rather than a given level of K^+ . The urgency and type of treatment therefore depend largely on the type of electrocardiographic changes found (Littmann and Gibbs, 2018).

6. Treatment of hyperkalemia

6.1 Conventional therapy

Treatment of hyperkalemia depends on the severity of the clinical-instrumental and laboratory test picture. The treatment will therefore be more aggressive: the faster the increase in K^+ , the greater the K^+ level, and the more evident the cardiotoxicity. Consequently, for practical purposes it is useful to distinguish therapy for acute treatment when the extreme rapidity of pharmacological action is necessary to avoid even fatal events from long-term treatment also finalized to prevent new events. In the case of virtually fatal hyperkalemia associated with alterations on ECG, there are a number of therapeutic steps to follow (Dépret et al., 2019; Rafique et al., 2019; Sood et al., 2007). The first step is the stabilization of the myocardium: calcium salts antagonize the myocardial effects of hyperkalemia without lowering the concentration, restoring the myocyte transmembrane potential at rest. Normally, calcium gluconate is preferred over calcium chloride, because the latter can cause irritation at the site of administration; the dose is 10 ml of a 10% solution in 2-3 minutes, which can be repeated until normalization is reached. The effects occur within a few minutes, and last up to 30-60 minutes. Calcium salts do not reduce the plasma K^+ concentration, so to pursue this goal it is necessary to use insulin, which acts by activating the Na-K ATPase, especially at the level of the skeletal muscle cells. The most used therapeutic scheme is that of a bolus of 10 U of IV insulin followed by 50 ml of a 50% glucose solution (not necessary in patients with serum glucose > 250 mg/dl); the effects appear after about 10-20 minutes, and last up to 4-6 hours. Considering that the main side effect is hypoglycemia, especially in patients with renal failure, glucose should be measured every hour for the first 5-6 hours. The beta-agonists, instead, act by activating the Na-K ATPase of the skeletal muscles, and favoring the displacement of the K^+ from the extracellular space to the intracellular space. The most used of these agents is salbutamol, which is administered by aerosol at a dose of 10-20 mg. The effect peak occurs in approximately 90 minutes. In consideration of the risk of tachycardia

and recurrence of angina, salbutamol must be avoided in patients with known coronary artery disease. It must be used in addition to calcium and all insulin treatments, but should not be considered a substitute. There also the drugs that favor K^+ excretion that have a slower onset of action: in the normovolemic patient, in the presence of valid diuresis, diuretics (thiazides or loop) can be administered, and in the case of no response, the patient must be started on dialysis therapy. In the hypovolemic patient, it is necessary to ensure adequate hydration in association with diuretic therapy. When long-term action is required, treatment with ion-exchange resins, such as sodium polystyrene-sulfonate is indicated; these act in exchange with other cations, retaining K^+ at the gastrointestinal level and favoring expulsion. The Food and Drug Administration (FDA) recommends caution, as these drugs (with or without sorbitol) have been associated with intestinal necrosis in some cases, which can be fatal.

Long-term management finalized also to prevent recurrence includes a series of other therapeutic measures in addition to drugs. 1) Elimination of drugs that can cause reduced K^+ excretion (e.g., NSAIDs); 2) Reduction of the intake of foods rich in K^+ , e.g., substitutes for cooking salt, which are poor in sodium, but rich in K^+ ; 3) Remodulation of chronic therapy of HF with RAASi. Both national and international guidelines offer inconsistent timing indications to take corrective measures in relation to renal function and K^+ levels, on how to monitor K^+ levels, and on drug withdrawal criteria (Rosano et al., 2018). In the 2016 ESC guidelines on the treatment of HF the recommendation is to limit this suspension as soon as possible and cautiously reintroduce these therapies, monitoring K^+ levels (Ponikowski et al., 2016). In the PARADIGM-HF study, hyperkalemia occurred both in the group of patients treated with sacubitril/valsartan ($n = 180$) and in that of patients treated with enalapril ($n = 236$); but only in a small percentage of patients was it necessary to suspend therapy (McMurray et al., 2014). It is also important to emphasize how both older and current treatment options have not been validated by any clinical trials. Moreover, no specific indications are provided by current guidelines regarding K^+ target levels. Therefore, hyperkalemia management depends largely on the experience of the single doctor or of each center.

6.2 Management of hyperkalemia in patients with heart failure: Our proposal

In the case of evidence of hyperkalemia in HF, the problem arises of how to move with underlying therapy and, as mentioned, there are no specific indications in this regard. For this reason we propose our behavior model for the outpatient management of hyperkalemia for chronic HF in the absence of emergency situations. For mild hyperkalemia (K^+ level: 5.0-5.5 mEq/L), specific interventions do not seem appropriate, only the search for, and treatment of, possible causes with close monitoring of K^+ levels. On the contrary, it seems reasonable to intervene in the case of moderate hyperkalemia (K^+ level between 5.5 and 6.0 mEq/L) as shown in the accompanying flowchart (Fig. 3). Our proposal is to follow a series of steps that will resolve the problem by minimizing the tapering of the therapy. The first step consists in the search for, and possible treatment of intercurrent causes, such as onset of acute-on-chronic HF, appearance or worsening of renal function from all causes, increased intake of K^+ with diet, or intake of new drugs. In the absence of resolvable causes, the second step foresees the reduction of the MRA dosage rather than its complete suspension in order to maintain, albeit in a reduced way, the antifibrotic effect characteristic of this class of drugs (e.g., halve f canrenone, spironolactone or eplerenone dose from 25 to 12.5mg). We therefore recommend checking the K^+ level at 2 weeks, and only in the case of persistence of high K^+ levels do we suggest suspension of the MRA and/or the reduction of the dosage of the therapy with ACEI/ARB/ARNI. A new K^+ check should be carried out after 1 month to evaluate the possibility of reintroducing the suspended drugs. Differently, if severe hyperkalemia is detected (K^+ levels > 6.0 mEq/L), direct MRA suspension with or without RAASi reduction seems necessary to prevent complications, though re-introduction should be re-evaluated as soon as possible. In addition to that, it is important to remember that according to results of the RALES trial the antifibrotic effect of MRA occurs already at low doses despite the modest diuretic effect. Therefore, our suggestion is to use MRA at low doses (e.g., 25 mg of spironolactone) as standard treatment to minimize the negative effects of hyperkalemia without losing its efficacy on myocardium remodeling; because the diuretic effect at these doses is reduced, we advise adding loop diuretic to control fluid overload, with further benefit in terms of K^+ levels. Our proposal is not a definitive solution, but can help to better manage the problem of hyperkalemia while awaiting the introduction of new drugs capable of binding and eliminating K^+ .

7. The new drugs: selective potassium binders

For many years sodium polystyrene-sulfonate (SPS), a resin able to eliminate K^+ through the colon by exchanging it with sodium, was the only chronic treatment for hyperkalemia. However, SPS is not very effective, and is associated with gastrointestinal adverse events sometimes, even fatal ones, including intestinal necrosis and perforation, especially when administered with sorbitol. Its side effects have limited its use in HF patients, particularly in the long-term setting (Sidhu et al., 2020; Varallo et al., 2019). Recently, two new drugs have been developed and studied for the management of hyperkalemia: patiomer and sodium zirconium cyclosilicate (SZC) (Tamargo et al., 2018). These are agents that also act through a cation exchange at the intestinal

level, leading to an increase in K^+ excretion with the feces, but are not burdened by relevant side effects (Nassif and Kosiborod, 2019; Noureddine and Dixon, 2015; Rosano et al., 2019) (Fig. 4 and Table 2).

7.1 Patiomer

Patiomer is a non-absorbable anionic polymer that binds K^+ in exchange for calcium, and performs its action mainly in the distal part of the colon, where the concentration of free K^+ is higher. The molecule thus promotes the elimination of K^+ in the feces, and lowers serum levels (Blair, 2018; Montaperto et al., 2015; Vu et al., 2016). The drug was studied in patients with hyperkalemia suffering from renal insufficiency, arterial hypertension, and diabetes mellitus, and in therapy with inhibitors of the RAS system with or without spironolactone for 52 weeks in the AMETHYST-DN trial. This study enrolled 306 patients with mild or moderate hyperkalemia, and three different doses were tested for each group. Patiomer has shown, compared to placebo, efficacy in lowering serum K^+ levels in 48 hours, and in reducing the recurrence of hyperkalemia (Bakris et al., 2015). Patiomer withdrawal at the end of the study was associated with a new increase of K^+ levels. More common side effects were hypomagnesaemia, constipation, and hypokalemia, while renal function did not worsen. A similar result in terms of efficacy and safety was found in the OPAL-HK study, published in 2015 in The New England Journal of Medicine (Weir et al., 2015), which enrolled 237 patients with kidney failure on RAASi therapy, and K^+ levels between 5.1 and 6.5 mmol/L who received patiomer for 4 weeks. Patients in whom K^+ level decreased to within normal range entered a withdrawal phase of 8 weeks, and were randomized to continue the drug or switch to placebo. The trial found significant reduction in K^+ levels (mean change -1.01 ± 0.03 mmol/L; $P < 0.001$), and 76% of patients reached target levels. In the second phase, the placebo group had a significant increase of K^+ levels compared with the patiomer group ($P < 0.001$). The pre-specified sub-analysis of the HF group confirmed that patiomer is well tolerated, effective in reducing K^+ levels, and in preventing recurrence in hyperkalemic patients with renal failure also affected with HF (Pitt et al., 2015). Similarly, the PEARL-HF trial randomized patients with chronic HF to receive patiomer or placebo for 4 weeks on standard treatment with indication to spironolactone, K^+ levels between 4.3 and 5.1 mEq/L and at least one of the following conditions: chronic renal failure and undertreatment with RAASi or history of hyperkalemia that had led to suspension of ACE-I /ARB. Spironolactone was started at a dose of 25 mg, and was increased to 50 mg on day 15. Patiomer significantly lowered K^+ levels, with a difference of -0.45 mEq/L ($P < 0.001$) in the two groups, with a lower incidence of hyperkalemia in the treated group (7.3% vs. 24.5%; $P = 0.015$), and allowed greater tolerance for spironolactone at therapeutic doses in this clinical context (91% vs. 74%; $P = 0.019$) (Pitt et al., 2011). Moreover, the AMBER trial, recently published in The Lancet, demonstrated the ability of patiomer to allow maintenance of treatment with spironolactone without development of hyperkalemia in patients with resistant hypertension and chronic kidney disease (86% in the patiomer group vs. 66% in the placebo group; $P < 0.0001$) (Agarwal et al., 2019).

The drug, in the form of a powder for oral suspension, should be taken dissolved in water or juice (40 ml in trials), with a dosage

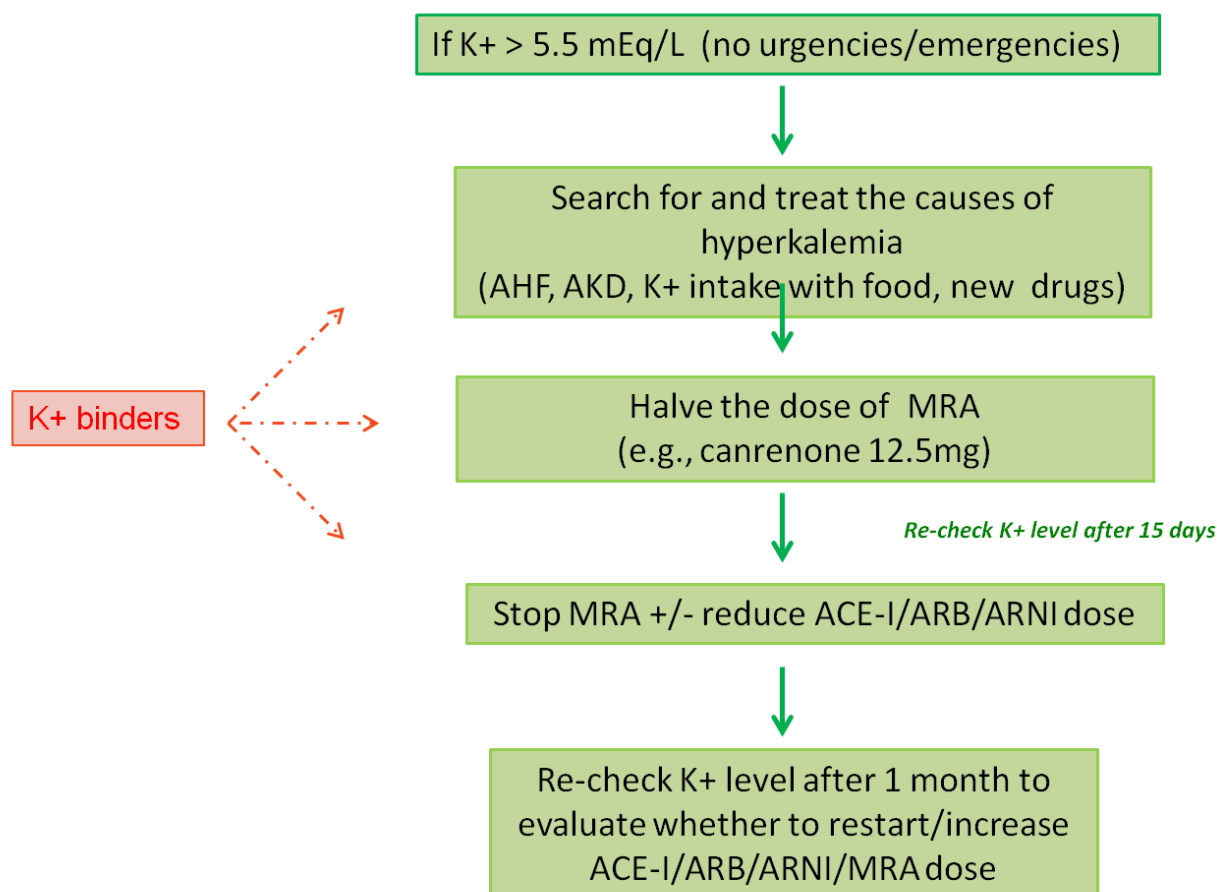


Figure 3. Management of hyperkalemia in heart failure: our proposal. We propose an algorithm for the management of hyperkalemia in outpatients with HF in the absence of urgency/emergency clinical situations. The first step is the search for causes or situations triggering hyperkalemia with particular regard to the use of new drugs or changes in the clinical picture such as the onset of acute-on-chronic cardiac decompensation or worsening of kidney function. We suggest halving the dose of MRA as an initial therapeutic intervention together with the treatment of any triggering or associated cause, rechecking potassium level after 15 days. If the potassium level remains elevated, the MRA will be discontinued along with the reduction of the ACE-I /ARB /ARNI dose. We also recommend rechecking the potassium levels after 1 month also in order to re-evaluate the possibility of re-introducing or re-titrating the drugs if conditions permit. The future introduction of K⁺ binders will help avoid the tapering or suspension of RAASi, ARNI and MRA.

starting at 8.4 mg once a day. The most frequent side effects are gastrointestinal disorders (diarrhea, nausea, constipation) and hypomagnesaemia, but are generally mild to moderate (Pitt and Garza, 2018). In the AMETHYST-DN trial, the average change in magnesium level was -0.12 mg/dl, and no patient developed levels < 1 mg/dl or cardiac arrhythmias or related neuromuscular abnormalities. Patiromer is able to bind some drugs (ciprofloxacin, levothyroxine, and metformin), reducing their gastrointestinal absorption, so it is recommended to administer it at least 3 hours apart, while there is no influence on the bioavailability of cardiac drugs such as amlodipine, clopidogrel, furosemide, metoprolol, verapamil, and warfarin.

7.2 Sodium zirconium cyclosilicate (SZC)

SZC is a non-absorbable polymer consisting of a three-dimensional crystal lattice capable of selectivity trapping K⁺ ions by exchanging them with sodium and hydrogen at the level of the colon and small intestine (Hoy, 2018; Stavros et al., 2014). Hy-

drogen ions are more exchangeable, while sodium remains in part linked to the structure, thus avoiding dangerous hyponatremia. The drug, in the form of an oral powder, is taken with water (240 ml in the studies) and with meals, at an initial dose of 10 g 3 times a day for up to 48 hours. The high selectivity of the molecule allows a very rapid action with effects that appear after 1 hour and normalization of K⁺ levels after 2.2 hours (Cases and Gorriz, 2018). In a study by Packham et al. (2015) published in The New England Journal of Medicine, SZC compared to placebo showed, in patients with renal insufficiency, HF, or diabetes, normalization of the levels of K⁺ in 48 hours (decrease from 5.3 to 4.9, 4.8 and 4.6 mmol/L, with 2.5g, 5g, and 10g of SZC, respectively; *P* = 0.001) and maintenance of them for 12 days. A clinically significant effect was seen already in 1 hour, and the reduction of K⁺ levels was dose-dependent; moreover, the higher the level at baseline, the greater the reduction. The rates of adverse events were similar in the initial and the maintenance phase, with diar-

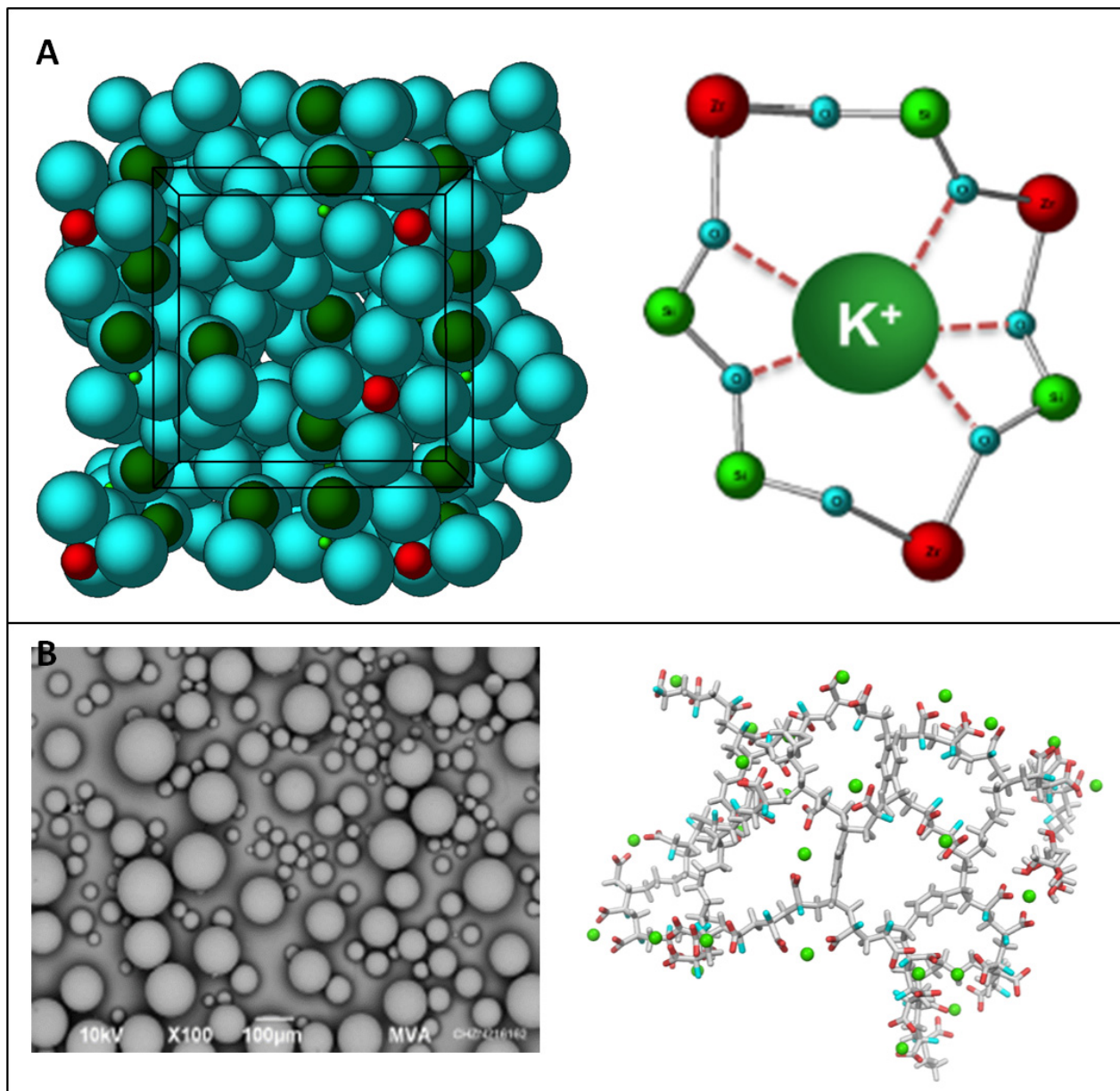


Figure 4. Schematic structure of SZC and patiomer. A) Schematic structure of SZC. Left: the three-dimensional crystal lattice consists of oxygen atoms (blue spheres), zirconium atoms (red spheres), and silicone atoms (green spheres). Right: the potassium ion is trapped inside the lattice. B) Patiomer's schematic structure: On the left a microscopic electronic image showing the polymer consisting of microspheres. Right: reticular structure of a section of the polymer; the green balls are the exchange calcium ions (Adapted from [Stavros et al., 2014](#) and from [Tamargo et al., 2018](#)).

rhea being the most common side effect. Similarly, the Harmonize trial ([Kosiborod et al., 2014](#)) recruited 258 patients from the U.S.A., Australia, and South Africa with K^+ levels > 5.1 mEq/L who received SZC (10 g TID) for 48 hours. Patients who reached normokalemia were randomized to three doses of SZC (5, 10, 15 g) or placebo for 28 days. Normokalemia was achieved in 84% of cases in 24 hours, and in 98% of cases in 48 hours in the open-label phase, and compared with placebo, all 3 doses of SZC resulted in lower K^+ levels and a higher proportion of patients with normal K^+ levels for up to 28 days. A safety profile was main-

tained across the different doses. Most patients maintained mean serum K^+ within the normokalemic range for ≤ 11 months during ongoing SZC treatment ([Roger et al., 2019](#)). In the HF subgroup (87 patients, of whom 60 on RAASI therapy) the ability of SZC to restore K^+ levels within the normal range and maintain them for 28 days was confirmed ([Anker et al., 2015](#)). The HARMONIZE-Global trial extended the results to geographically and ethnically diverse populations ([Zannad et al., 2020](#)). Instead, the DIALIZE study observed efficacy of SZC in a population of end-stage renal disease on hemodialysis treatment with pre-dialytic hyperkalemia

Table 2. New potassium binder agents: a comparison.

	Patiromer	Zirconium silicate
Structure	non-absorbable organic polymer	inorganic polymer of zirconium silicate
Counter ion	calcium	sodium and hydrogen
Site of action	distal colon	small intestine and colon
Onset of effects on K ⁺ levels (hours)	7	1-2
Daily doses	from 8.4 mg QD	from 10 mg TID
Side effects	Gastro-intestinal Hypomagnesemia	Hypernatremia Edema

(Fishbane et al., 2019). Some evidence of the long-term efficacy of SZC comes from a study by Spinowitz, who demonstrated in 751 patients affected with hyperkalemia from different causes, that SZC allows maintenance of normal K⁺ levels \leq 12 months, without negative effects on RAASi therapy (Spinowitz et al., 2019).

Since SZC is not absorbed in the intestine, it carries a minimal risk of systemic toxicity. The most significant side effects are nausea, vomiting, diarrhea, kidney infections, and hypokalemia. An effect on bicarbonate levels has also been found, which may be an advantage in patients with renal insufficiency, but could expose HF patients to a risk of hypernatremia and water retention. Relevant hypomagnesemia was not found. However, side effects occurred primarily with higher doses, and were not associated with major adverse events in two studies (Amin et al., 2019).

8. Prospectives for use of new drugs

The current recommendation of the ESC is based only on the opinion of experts, and merely says that the use of new K⁺ binders agents may be helpful in optimizing therapy with RAASi for patients with hyperkalemia or at risk of developing it, though randomized trials are needed to test their long-term efficacy (Rosano et al., 2018; Zannad et al., 2016). Recently, awaiting the results of large trials, some experts have proposed giving a class II recommendation for the use of the new K⁺ binders, at least in patients who can benefit in terms of RAASi continuation or titration (Butler et al., 2019; Vijayakumar et al., 2019; Zannad et al., 2019). The new drugs have shown both a good efficacy profile in the short-medium term and safety, though caution is required in particular situations: the presence of hypomagnesaemia and hypocalcaemia during therapy with patiromer, and the risk of water retention in the context of HF for the SZC. Differently from old K⁺ binders, they have a rapid onset of action, high selectivity for K⁺, non-serious gastrointestinal side effects, and few drug-drug interactions. According to their characteristics, ZS-9 could be a useful drug in the acute hyperkalemia setting, while patiromer could be used in the chronic context. Such drugs could therefore represent an additional weapon for cardiologists in the management of patients with HF in order to avoid underdosing or withdrawal of essential drugs, with potential consequent benefit in terms of prognosis (Desai et al., 2020; Kovesdy et al., 2020; Sciatti et al., 2019).

9. Conclusions

The onset of hyperkalemia in patients with HF is an issue not only in acute situations, but also in a chronic context, since it can represent a limit for titration of HF therapy or even lead to the suspension of certain drugs. Different mechanisms contribute to

increased hematic K⁺ levels, and the problem is more relevant in patients with comorbidities such as diabetes or kidney failure. The management of hyperkalemia must be aimed at minimizing reduction/discontinuation of RAASi by trying to resolve the potential causes. The future introduction of new K⁺ binding agents capable of normalizing the levels of K⁺ that can also be used chronically outside of acute emergency situations can lead to a greater optimization of underlying therapy for HF, with potentially positive effects on morbidity and mortality. However, further data from clinical trials and from the "real world" supporting this hypothesis are still necessary.

Author contributions

CM organized the project, wrote the manuscript and prepared all tables and figures. LA reviewed the literature and drafted the paragraph "Treatment of hyperkalemia". GD reviewed the literature and drafted the paragraph "The physiology of potassium in the human body". CF reviewed the literature and drafted the paragraph "Hydro-electrolytic, EKG, and clinical consequences of hyperkalemia". FC conceived of the project and supervised the course of the article. All authors reviewed the manuscript and approved the final version.

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Conflict of interest

The author declares no conflicts of interest.

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