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Hyperkalemia-Related Renin Angiotensin-Aldosterone System Inhibitors: Mechanism, Clinical Significance, and Management

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ABSTRACT

Hyperkalemia refers to a medical condition in which potassium levels in the blood increase beyond normal values. This condition often occurs in patients suffering from chronic kidney disease (CKD) and heart failure, which can lead to serious complications and require special treatment from a cardiologist. Factors such as chronic kidney disease, heart failure, diabetes mellitus, and the use of drugs that inhibit the Renin-Angiotensin-Aldosterone (RAA) system are known to be a support that causes hyperkalemia. Using qualitative research methods, this approach focuses on semi-structured interviews with cardiologists, nephrologists, endocrinologists, and nurses who have experience in treating patients with hyperkalemia. Meanwhile, patients' perspectives will also be accommodated through group focus to understand their clinical impact and experience. The aim of this study was to investigate the mechanisms associated with angiotensin-aldosterone renin system (RAA) inhibitors related to hyperkalemia, as well as identify their clinical significance. In addition, this study aims to understand and analyze management strategies that can be applied in overcoming hyperkalemia associated with the use of RAA System inhibitors. Further objectives include providing in-depth insight into the impact of RAA System inhibition on potassium balance in the blood, evaluating the clinical significance of RAA-inhibitor-induced hyperkalemia conditions, and devising effective guidelines for hyperkalemia management in the context of the use of such drugs.

INTRODUCTION

Hyperkalemia is one of the medical conditions in which there is an increase in the amount of potassium in the blood higher than normal values. It often manifests in patients with chronic kidney disease (CKD) and heart failure leading to poor outcomes and requiring special management by a cardiologist. Chronic kidney failure, heart failure, diabetes mellitus, and Renin-Angiotensin-Aldosterone (RAA) system-blocking drugs are known to be supporting factors that cause hyperkalemia conditions (Weir and Rolfe, 2010).

Patients with heart failure or chronic kidney disease are at greater risk of hyperkalemia with Renin-angiotensin-Aldosterone (RAA) system-blocking drugs than those without these conditions. While it is widely known that the use of RAA system inhibitory drugs reduces cardiovascular mortality and rehospitalization of heart failure. In addition, these patients tend to benefit more from RAA inhibitory drugs than the adverse effects that can be produced. Therefore, electrolyte levels in the blood should be closely monitored in such patients (Johnson et al., 2010).

METHOD

This study aimed to explore in depth the mechanism, clinical significance, and management of hyperkalemia associated with inhibitors of the Angiotensin-Aldosterone Renin System (RAAS). Using qualitative research methods, this approach focuses on semi-structured interviews with cardiologists, nephrologists, endocrinologists, and nurses who have experience in treating patients with hyperkalemia. Meanwhile, patients' perspectives will

also be accommodated through group focus to understand their clinical impact and experience. Data analysis will be carried out through content analysis techniques to identify key themes, patterns, and relationships between data, taking into account validity through the use of triangulation. In addition, research ethics and data security will be closely guarded, and research results will be presented in reports that can be accessed and understood by stakeholders.

This study is expected to provide deep insight into the clinical challenges faced by patients taking RAAS inhibitors, particularly related to the risk of hyperkalemia. By understanding mechanisms, clinical significance, and effective management strategies, this research can make a valuable contribution to the development of clinical guidelines and the improvement of patient care. Overall, this study will not only cover the medical aspects, but also provide a more holistic understanding related to the patient experience and the views of medical practitioners, paving the way for a better understanding of how RAAS-associated hyperkalemia can be effectively managed in everyday clinical practice.

RESULTS AND DISCUSSION

A. Definition and Classification of Hyperkalemia

Hyperkalemia occurs when there is one or more damage to the mechanisms that maintain body homeostasis. Understanding hyperkalemia is a condition when the amount of potassium in the blood is higher than normal values. Potassium serves to facilitate the function of muscles, nerves, and heart. In hyperkalemia, electrical activity in the heart will be disrupted, which is characterized by slowing heart rate and can lead to death. The following types of hyperkalemia can be grouped into several classifications: Mild hyperkalemia, which is the amount of potassium in the blood >5 to <5.5 mmol / L, moderate hyperkalemia, which is the amount of potassium in the blood 5.5 to 6.0 mmol / L, severe hyperkalemia, which is the amount of potassium in the blood > 6.0 mmol / L (Giuseppe et al., 2018).

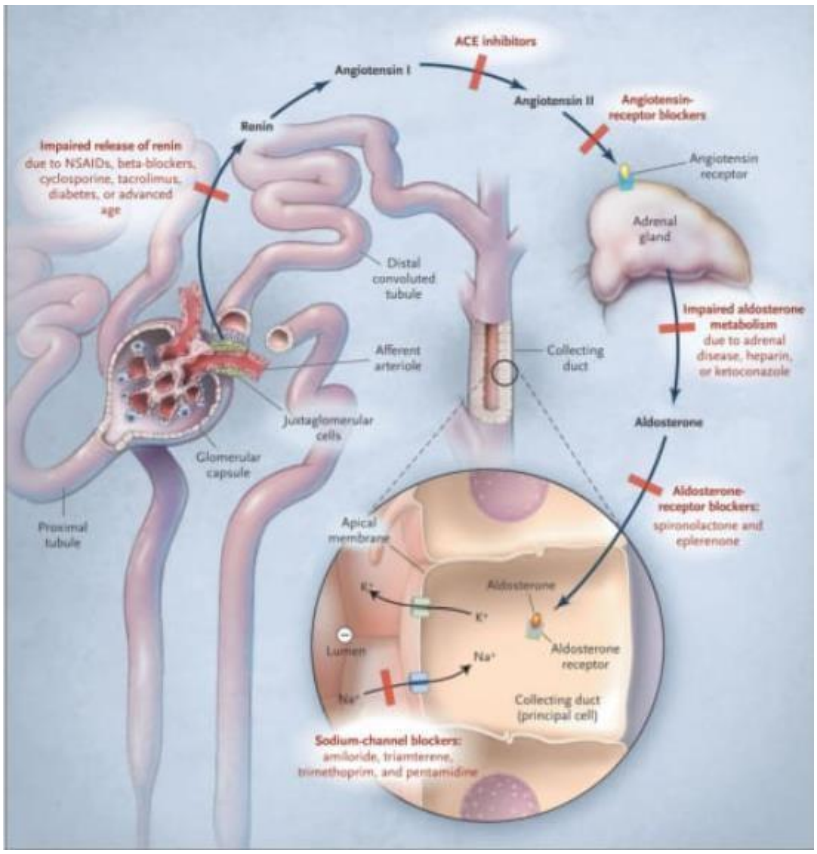

Figure 1. Regulation of potassium in RAA systems (Palmer, 2004).

The mechanism or cause of hyperkalemia is divided into several processes (Giuseppe et al., 2018) (1) Excessive potassium intake, (2) Decreased potassium excretion, (3) Movement of potassium from intracellular to extracellular space. In many cases, a combination of these factors is involved simultaneously. For example, a person with a glomerular filtration rate of less than 45 mL/min who consistently receives large amounts of a high-potassium diet and is also at the same time on medication that inhibits the renin-angiotensin-aldosterone (RAA)

system system, is at very high risk for developing hyperkalemia due to the kidney's limited ability to excrete potassium obtained from high intake (Johnson et al., 2010).

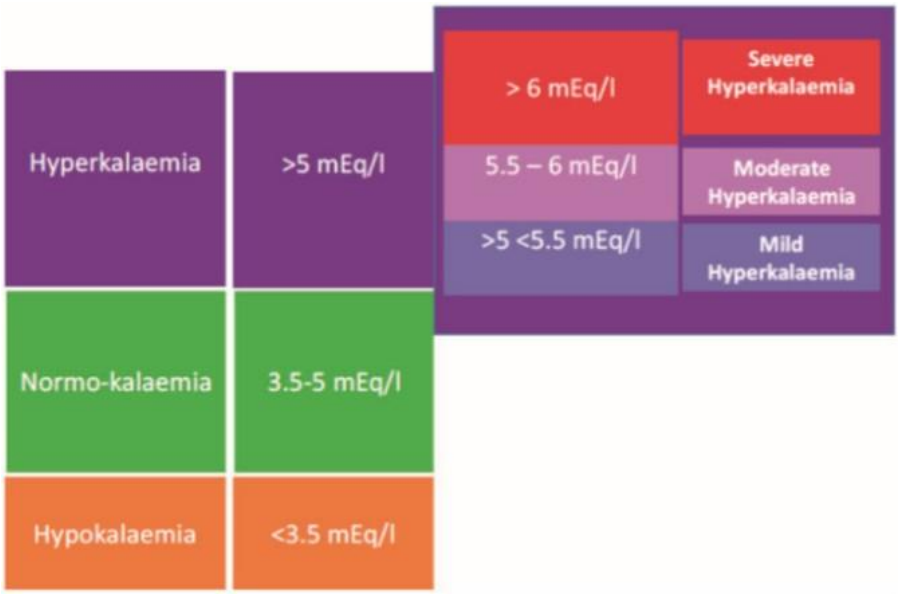

Figure 2. Classification of normokalemia, hyperkalemia, and hypokalemia (Giuseppe et al., 2018)

A person with diabetes mellitus who has comorbidities of hypoaldosteronism and hyporeninemia associated with diabetic nephropathy is at high risk for developing hyperkalemia due to reduced ability to move potassium intracellularly (insulin deficiency) and impaired renal excretion (aldosterone deficiency). Another condition is acute kidney injury due to rhabdomiolysis or tumor lysis syndrome, where hyperkalemia occurs due to impaired renal excretion aggravated by the release of large amounts of potassium from the intracellular to extracellular compartments (Raebel et al., 2010).

B. Causes of Hyperkalemia

1. Excessive potassium intake

Increased potassium intake into the body can result from a number of different factors, including diet, salt substitutes, supplements, blood transfusions, hemolysis processes, gastrointestinal bleeding, injury, and cell catabolism (Giuseppe et al., 2018). Intake of foods containing relatively high potassium content can cause a temporary imbalance and result in an increase in serum potassium levels. Severe hyperkalemia resulting from peroral potassium intake is very rare if kidney function is still relatively normal, because potassium intake from food sources can be controlled through normal body homeostatic processes. However, if this homeostatic mechanism is disrupted by renal insufficiency, insulin deficiency, or other factors, or if large amounts of potassium enter the body in a short period of time, this homeostatic mechanism may be damaged (Einhorn et al., 2009).

Excess potassium intake is very rarely the sole cause of hyperkalemia in patients with an estimated glomerular filtration rate of more than 60 mL/min. In people with normal potassium homeostasis mechanisms it is still possible to eat a number of diets with very high potassium levels, because there are mechanisms to move potassium intracellularly and can still excrete potassium through the kidneys. Even parenteral potassium administration as much as 60 mEq/hour for several hours only led to a slight increase in serum potassium concentrations in healthy individuals (Johnson et al., 2010).

Some foods have a very high potassium content and should be limited in consumption. In particular, potassium chloride and other potassium compounds, which are used by the general public as salt substitutes or as muscle-building supplements should be avoided (Giuseppe et al., 2018). The most common source of increased potassium intake is intravenous (IV) or oral administration of potassium. Red packed red cells (PRC) can also carry high concentrations of potassium which can cause hyperkalemia during transfusions (Weir and Rolfe, 2010).

2. Decreased excretion of potassium

Reduced potassium excretion, accompanied by excessive potassium intake, is the most common cause of hyperkalemia. The most common causes of decreased renal potassium excretion are as follows

(Johnson et al., 2010). (1) Acute renal failure or decreased kidney function as often seen in people with chronic kidney disease who experience complications. (2) System Impairment (RAA) as a result of aging conditions, certain medical conditions, or medications commonly used in cardiovascular disease (e.g., Angiotensin Converting Enzyme inhibitors (ACEi), Angiotensin Receptor Blockers (ARBs), Direct Renin Inhibitors (DRI), and Aldosterone Receptor Antagonists (ARA)). (3) Reduced production of aldosterone. (4) Impaired responsiveness of the distal tubule to the action of aldosterone (eg renal tubular acidosis. (5) Primary adrenal disease (e.g., Addison's disease or salt-deficient forms of congenital adrenal hyperplasia). (6) Hyporeninemic hypoaldosteronism.

Chronic kidney disease at all stages has a higher risk of hyperkalemia. In patients with chronic kidney disease, decreased renal function reduces the maximal capacity of potassium secretion and excretion processes. With impaired renal function, the amount of potassium excreted through the urine becomes reduced to less than 90%. This results from a high amount of nephron damage manifesting as a decrease in glomerular filtration rate. When the glomerular filtration rate in these patients decreases, the body's ability to regulate the amount of potassium or maintain potassium homeostasis is further reduced, increasing the risk of hyperkalemia (Gumz et al., 2015).

In addition to a decrease in the glomerular filtration rate, aldosterone deficiency can contribute to the pathogenesis of hyperkalemia, as occurs in patients with hypoaldosteronism with chronic renal insufficiency. Additional mechanisms affecting intracellular/extracellular balance, such as acidosis and hyperosmolarity, may increase in patients with chronic kidney disease, which can further lead to an increase in potassium in the blood (Sarafidis et al., 2015). When potassium excretion decreases, the large intestine has an additional role that takes over the function of increasing potassium excretion. The large intestine, in addition to the kidneys, plays an important role in potassium regulation. As part of the adaptive response to renal function deficits, potassium influx is mediated by sodium-potassium-ATPase channels and sodium-potassium-chloride cotransporters. This results in compensating for increased secretion of potassium by the colon. This mechanism occurs mainly through a large increase in potassium channels. These canals pump excess potassium from epithelial cells lining the colon into the lumen of the colon (Harel et al., 2013).

3. Intracellular Transfer of Potassium to the Extracellular Space

A number of factors can influence the shift of potassium from the intracellular to the extracellular space. By itself, this mechanism is a relative cause of hyperkalemia although it does not occur in general, but can aggravate the hyperkalemia produced by high intake or impaired renal potassium excretion. A frequent example is that insulin deficiency or acidosis that occurs acutely results in intracellular potassium shift disorders from mild to moderate (Giuseppe et al., 2018).

Table 1. Factors affecting the incidence of hyperkalemia (Sarafidis et al., 2015).

Factor	Effects on potassium	Mechanism
Aldosterone	Lower	Increase resorption sodium, and increases the excretion of potassium
Insulin	Lower	Stimulates potassium input into cells with sodium output (requires energy)
Agen Beta-adrenergigik	Lower	Increase potassium uptake in striated muscles
Agen Alfa-adrenergic	Increase	Interrupting the input process potassium into cells
Acidosis (reduced pH)	Increase	Interrupting the input process potassium into cells
Alkalosis (increased pH)	Lower	Improve processes Potassium input into cells
Cell damage	Increase	Increase potassium release from within the cell
Succinylcholine	Increase	Depolarization of cell membranes

Abnormalities in the distribution of potassium at the intracellular and extracellular levels cause failure of electrical signals passing through cell membranes (cell depolarization). It is often caused by several factors such as acidosis, hypertonicity, insulin deficiency, aldosterone deficiency, tissue damage, excessive exercise, digitalis (impairs potassium uptake by cells by blocking sodium pumps), or the use of beta-blocking drugs (Harel et al., 2013).

C. RAA System Inhibitors and Hyperkalemia

Administration of RAA system inhibitory drugs is a key strategy in treating hypertension, cardiovascular disease and kidney disease. However, RAA system inhibitor drugs (Angiotensin Converting Enzyme inhibitors (ACEi), Angiotensin Receptor Blockers (ARBs), Direct Renin Inhibitors (DRI), and Aldosterone Receptor Antagonists (ARA) increase the risk of hyperkalemia (serum potassium >5.0 mmol/L). In patients with hypertension without risk factors for hyperkalemia, the incidence of hyperkalemia with RAA system inhibitory monotherapy is low, while the use of dual drug therapy of this group increases the incidence of hyperkalemia (Giuseppe et al., 2018).

The incidence of hyperkalemia is also increased in patients with heart failure as well as chronic kidney disease. Patients with heart failure or chronic kidney disease are at greater risk of hyperkalemia with RAA system-blocking drugs than those without these conditions. In addition, these patients are likely to benefit from RAA system-blocking drugs. However, electrolyte levels should be closely monitored in these patients (Sarafidis et al., 2015). The RAA system plays an important role in the regulation of blood volume, blood pressure, and cardiovascular function. Therapeutic manipulation of the RAA system is an important therapeutic strategy for hypertension, chronic kidney disease, heart failure and diabetes. However, it is known that RAA system inhibitors, are associated with an increased risk of hyperkalemia events, especially when given in combination. RAA system-inhibiting drugs increase serum potassium levels by interfering with angiotensin II-mediated stimulation of aldosterone secretion from the adrenal glands and by reducing renal blood flow and glomerular filtration rates in special patient populations. Aldosterone receptor antagonists increase the risk of hyperkalemia by blocking the interaction of aldosterone with its receptors, thus impacting reduced renal potassium excretion (Giuseppe et al., 2018).

Table 2. The effect of increased blood potassium levels associated with the use of RAA system inhibitor drugs in hypertension.

Studies	Drug (mg)	Duration (weeks)	Sample (person)	Effects on Potassium Levels
Single Therapy				
Fogari *et al.*	Lisinopril (20)	8	118	Average increase K+ 0.21 mmol/L
Reardon *and to the.*	Lisinopril	52	1818	K+ >5.5 mmol/L at 2.0% K+ >6 mmol/L at 0.17%
Goldberg *et al*.	Losartan Lisinopril	8-12	2085	K+ >5.5 mmol/L at 1.5% K+ >5.5 mmol/L at 1.3%
Puchler *et al*.	Olmesartan (2,5/5/10/20/4 0 /80)	6-52	3095	K+ >5.5 mmol/L of 0.2-0,4%
McGill *et al*.	Telmisartan (20/40/80/160)	8	818	Average increase K+ 0,005-0,131 mmol/L
Levy *et al*.	Eplerenon (50-200)	12	397	Average increase K+ 0.1-0,2 mmol/L
White *et al.*	Eplerenone (25/50/100/20 0)	12	400	Average increase K+ 0.2 mmol/L K+ >5.5 mmol/L at 1.1%
Weir *et al.*	Aliskiren (75/150/300/6 00)	6-8	7045	K+ >5.5 mmol/L of 0.7-1,0%
Combination Therapy				

Oparil *et al.*	Aliskiren/ Valsartan (150/160-300/ 320)	8	1797	K+ >5.5 mmol/L at 4.0% K+ >6 mmol/L at 0.5%
Uresin *et al.*	Aliskiren/Ram ipril (150/5-300/10)	8	837	K+ >5.5 mmol/L at 5.5% K+ >6 mmol/L at 1.5%
ONTARGET	Telmisartan/ Ramipril (80/10)	56	25620	K+ >5.5 mmol/L at 5.6%
AMAZE	Candesartan/ Lisinopril (16/20-32/20)	8	1096	K+ >6 mmol/L at 1.6%
Krum *et al.*	Eplerenon/AC No	8	341	K+ >5.5 mmol/L at 1.2%

Each RAA system inhibitor drug has a different effect strength on changes in potassium levels, reflected in the different mechanisms of action of these drugs on potassium homeostasis (Giuseppe et al., 2018).

1. RAA System Inhibitors and Heart Failure-related Hyperkalemia

RAA system inhibitor clinical trial studies in patients with heart failure have a greater increased risk of hyperkalemia compared to patients without heart failure. However, the incidence of clinically significant hyperkalemia (ie serum potassium levels ≥6.0 mmol/L) is low (Ferreira et al., 2020).

Table 3. Effects of elevated blood potassium levels associated with the use of RAA system inhibitory drugs in heart failure.

Studies	Drug (mg)	Duration (week)	Sample (person)	Effects on Potassium Levels
Single Therapy				
CONSENSUS	Enalapril (5-20)	27	253	K+ >5.5 mmol/L at 7.1%
ELITE	Losartan (12,5-50)	48	722	18.8% experienced an average increase of K+ >0.5 mmol/L
CHARM	Candesartan (4-32)	135	2028	K+ >6 mmol/L by 3%
Combination Therapy				
CHARM	Candesartan/Enalapril	164	2548	K+ >6 mmol/L by 3%
RESOLVD	Enalapril/Candesartan	8	818	Average increase K+ +0.11 mmol/L
Val-HeFT	Valsartan (80-160) on ACEi	23	5010	Average increase K+ +0.2 mmol/L
RALES	Spironolakton (25-50) on ACEi	24	1663	Average increase K+ +0.3 mmol/L K+ >6 mmol/L by 2%
EPHESUS	Eplerenone (25-50) on ACEi	16	6642	K+ >5.5 mmol/L at 15.6% K+ >6 mmol/L at 5.4% Average increase K+ +0.3 mmol/L

ALOFT	Aliskiren (150) on ACEi	12	302	K+ >5.5 mmol/L at 8.3% K+ >6 mmol/L at 1.9%

2. RAA System Inhibitors and Chronic Kidney Disease (CKD)-related Hyperkalemia

Table 4. Effects of increased blood potassium levels associated with the use of RAA system inhibitory drugs in Chronic Kidney Disease (CKD)

Study	Drug (mg)	Duration (week)	Sample (person)	Effects on Levels Potassium
Single Therapy				
Hou *et al.*	Benazepril (10)	163	328	K+ >6 mmol/L at 5.4% Drug discontinuity by 1.8%
Bakris *et al.*	Lisinopril (10) Valsartan (80)	10	35	Average increase K+ +0,12 mmol/L (Lis) Average increase K+ +0,28 mmol/L (Val)
IDNT	Irbesartan (75-300)	125	1715	Drug discontinuity of magnitude 1,9%
Combination Therapy (Dual)				
Van den Meiracker *et al.*	Spironolactone (25) on ACEi	59	87	K+ >6 mmol/L at 17.2%
Benches *et to the.*	Spironolakton (25) on ACEi	52	165	Drug discontinuity of magnitude 4,8%
Epstein *et al.*	Eplerenone / Enalapril (100/20)	12	268	K+ >5.5 mmol/L at 3.7% K+ >6 mmol/L at 6.1% Drug discontinuity by 8.1%
AVOID	Aliskiren/Losartan (150/300)	26	599	K+ >5.5 mmol/L at 13.7% K+ >6 mmol/L by 4.7% Drug discontinuity of 1,0%
Combination Therapy (triple)				
Tylicki *et al.*	Spironolakton/ Telmisartan/ Cilazapril	18	108	K+ >5.5 mmol/L at 11.1%
Chrysosto mou *et al.*	Spironolactone/Ramipr il /Irbesartan (25/5/150)	26	41	K+ >6 mmol/L at 18.2%

The incidence of elevated serum potassium with RAA system inhibitory monotherapy in patients with chronic kidney disease has been assessed in a number of clinical trials. The data showed that although patients with chronic kidney disease were at increased risk of elevated serum potassium, the absolute increase observed was relatively small and generally not associated with clinically relevant side effects (Sarafidis et al., 2015).

D. Manifestations of Hyperkalemia on an Electrocardiogram

In most cases, hyperkalemia is asymptomatic or asymptomatic. Increased potassium levels will gradually affect the conduction system of the heart and will change the electrocardiography (ECG) picture. Changes in ECG features in hyperkalemia have an important role for initial management before laboratory results come out. ECG changes in hyperkalemia have a relationship with the severity of hyperkalemia (Baltazar,

2009). ECG changes in hyperkalemia are influenced by the severity of hyperkalemia and how quickly potassium rises from onset (Campese and Adenuga, 2016). ECG changes that occur in hyperkalemia are usually progressive according to the severity of hyperkalemia (Baltazar, 2009).

1. ECG Features in Mild Hyperkalemia

   In mild hyperkalemia, there will usually be an initial change in the ECG, which is in the form of an elevated T wave or called Tall T. Tall T in hyperkalemia is characterized by a tent-like T waveform. T waves will rise, symmetrical and converge at the peak and have a narrow base. In addition, the QT interval can be shortened or normal, and the PR segment will be slightly elongated due to the slowing of atrial conduction to the ventricles (Baltazar, 2009).

2. ECG Description of Moderate Hyperkalemia

   In moderate hyperkalemia, the T wave will be higher and can be as high as the R wave. The highest T wave is obtained in the V2-V4 leads. P waves will flatten or disappear so that it will be difficult to identify. In addition, the QRS complex will begin to widen at this condition. The PR interval will be lengthened so that atrioventricular block can occur (Baltazar, 2009).

3. ECG Features in Severe Hyperkalemia

   With serum potassium levels increasing, P waves cannot be identified, causing bradycardia. This is because impulses from the SA node travel very slowly on the internodal pathway. Synoventricular rhythms are usually used to assess sinus rhythms that are not accompanied by P waves. Synoventricular rhythms are unlikely to be distinguished by junctional rhythms or by idioventricular rhythms accelerated by wide QRS complexes. In addition, ECG changes that occur are QRS complexes that are getting wider, shortening of ST segments and merging S waves and T waves called Sine waves (Baltazar, 2009). After that tachycardia and ventricular fibrillation can occur followed by asystole (Gennari et al, 2002).

E. Management of hyperkalemia

Hyperkalemia accompanied by decreased renal function, becomes the main reason for the action of discontinuation of the drug, dose reduction, or even non-start of therapy of drugs blocking the RAA system in patients with kidney and cardiovascular diseases without considering the benefits of the drug. Most heart failure patients experience dose adjustment of RAA system inhibitor drugs after experiencing elevated levels of potassium in serum (Pierce et al., 2015). Hyperkalemia that occurs in heart failure is often associated with the use of RAA inhibitors (ACE inhibitors / ARBs / MRAs) including the use of sacubitril-valsartan ARNi, as well as older age, diabetes mellitus, and CKD. The occurrence of hyperkalemia often results in limited use of RAA system inhibitors, causing dose reduction and even discontinuation of treatment, thereby reducing the potential benefits (Ferreira et al., 2020).

Table 5. Recommendations for the use of RAA system inhibitor drugs related to potassium levels in the blood (Giuseppe et al., 2018).

Potassium (mEq/L)	Recommendations
>6	Stop RAA system inhibitory agent
>5.5	Reduce dose/stop ACEi/ARB
5.1-5.5	Starting therapy to lower potassium (when initiating RAA system inhibitory agents)
>5	Do not start RAA system inhibitor therapy
	Reduce dose / stop ACEi/ARB
	MRA is not recommended
	MRA is maintained within potassium levels of 4.0-5.0
	Do not give RAA system inhibitors to CKD patients if baseline potassium levels (before therapy) >5.0
	Potassium-lowering drugs should be started
4.5-5	In patients who have not reached the optimal dose of RAA system inhibitors, it is recommended to optimize the dose, or if it has not been given, it is recommended to start by monitoring potassium levels tight

Current clinical guidelines recommend that patients with chronic hyperkalemia should start a low-potassium diet and should start non-potassium-sparing diuretic therapy, or if already taking non-potassium-sparing diuretics, increase the dose of such medications. All guidelines also suggest eliminating potassium supplements and also to stop drugs that can interfere with kidney function such as non-inflammatory anti-steroids and also drugs that can increase potassium levels such as RAA system inhibitor therapy, especially MRA groups (Ferreira et al., 2020).

Table 6. General management of hyperkalemia with regard to RAA system inhibitory drugs (Ferreira et al., 2020).

4.0-5.0	1. Patient is in the target zone 2. Initiate or maintain RAASi and MRA dose
5.1-5.5	1. Individualize management based on patient risk and reliability of medical compliance and follow-up 2. ACE inhibitors/ARBs, ARNi and MRA may be maintained (see also Table 3) 3. Monitor K^+ and creatinine closely 4. Eliminate K^+ supplements, NSAIDs and decrease K^+ rich foods (whenever possible) 5. If reliable clinical follow-up and serum K^+ assessment is doubtful, may consider K^+ binder preferably over compromising RAASi therapy
5.6-6.0	1. Perform ECG and if "de novo" ECG alterations: in-hospital admission 2. Assess the possibility of hemolysis and repeat sample, if necessary 3. Initiate a diuretic or increase its dose (if necessary) 4. Eliminate K^+ supplements, NSAIDs and decrease K^+ rich foods (whenever possible) 5. Reassess K^+ levels after 1 week; if K^+ levels still high: 5.1. and on maximal tolerated/guideline-recommend RAASi dose, consider a K^+ binder (do not stop RAASi but may decrease the dose up to 50% of the guideline recommended dose) 5.2. if RAASi dose <50% of guideline recommendation, consider a K^+ binder and RAASi up-titration 6. Monitor K^+ and creatinine at 1 week, 1 month, 2 months, and 3 months 5.1. Until K+ is in the "normal" range 5.2. Adapt ACE inhibitors/ARB, ARNi and MRA dose if necessary (see also Table 3)
>6.0	1. If associated with "de novo" ECG alterations: in-hospital admission 2. If no ECG alterations: 2.1. Assess the possibility of hemolysis and repeat sample, if necessary 2.2. Initiate a diuretic or increase its dose (if necessary) 2.3. Eliminate K+ supplements, NSAIDs and decrease K^+ rich foods (whenever possible) 2.4. Initiate a K^+ binder 3. Reassess K^+ levels after 1 week; if K^+ levels still high: 3.1. Reduce MRA/ACE inhibitors/ARB/ARNI dose by 50% of the guideline-recommended dose (but do not decrease below 50%) and maintain K^+ binder or initiate one if not yet started; repeat the K^+ assessment after 1 week and if K^+ still >6.0 mmol/l stop the MRA maintaining the K^+ binder 3.2. When K+ levels <6.0 mmol/l, reintroduce the MRA maintaining the K^+ binder and see the above panel 4. Monitor K^+ and creatinine at 1 week, 1 month, 2 months, and 3 months 4.1. Until K^+ is in the "normal" range 4.2. Adapt RAASi dose to guideline-recommended targets

Short-term discontinuation of potassium retaining agents and RAA system inhibitors needs to be minimized and RAA system inhibitory drugs should be carefully reintroduced as soon as possible while monitoring potassium levels (Giuseppe et al., 2018). Because RAA system inhibitor therapy has been shown to reduce mortality and morbidity in patients with cardiovascular disease but can increase potassium levels, therapy aimed at lowering potassium levels should be considered for indication to allow patients to continue therapy for RAA system inhibitory drugs. Such therapeutic approaches have been applied in other fields of medicine, for example in cancer where symptomatic therapy is used to relieve the side effects of using cancer therapy (antiemetics and cytostatic drugs). The use of such an approach in patients with cardiovascular disease, who develop hyperkalemia at the time of receiving RAA system inhibitor therapy will be of great benefit especially to patients who benefit most from RAA system inhibitor therapy (Pitt et al., 2017).

Table 7. Management of hyperkalemia in patients indicated to be given RAA system inhibitory therapy (Giuseppe et al., 2018).

Patient	Recommendations
Chronic or recurrent hyperkalemia in RAA system inhibitor therapy	Potassium-decreasing agents can be initiated as soon as possible when potassium levels >5.0 mEq/L. Potassium level monitoring. Maintain potassium-lowering therapy, unless for other reasons Therapeutics were found.
Chronic or recurrent hyperkalemia in RAA system inhibitor therapy has not reached the optimal dose	RAA system inhibitory therapy is optimized and potassium-lowering agents can be started if potassium levels >5.0 mEq/L. Potassium level monitoring. Maintain lowering therapy potassium, unless other treatable causes are found.
Potassium levels of 4.5–5.0 mEq/L have not reached the optimal dose of RAA system inhibitors	Initiation / titration of RAA system inhibitor therapy, potassium level monitoring. Potassium-lowering agents can be started if potassium levels >5.0 mEq/L.

Potassium levels >5.0 – <6.5 mEq/L have not reached the optimal dose of RAA system inhibitors	Therapy of potassium-lowering agents can begin to be administered. If potassium levels have reached <5.0 mEq/L, increase the dose of RAA system inhibitors, closely monitoring potassium levels. Maintain potassium-lowering therapy, unless another treatable cause is found
Potassium levels >5.0 – <6.5 mEq / L and have reached optimal dose inhibitor RAA system	Therapy of potassium-lowering agents can begin to be administered. Close monitoring of potassium levels. Maintain potassium-lowering therapy, except if other treatable causes are found
Potassium content >6.5 mEq/L and has reached optimal/suboptimal dose inhibitor RAA system	Stop/reduce the dose of RAA system inhibitors. Potassium-lowering agent therapy is administered immediately at K>5.0mEq/L. Close monitoring of potassium levels

In patients with hyperkalemia, evaluation is performed regarding the patient's diet, the use of supplements, salt substitutes, and nutraceuticals containing potassium and the use of drugs that can cause hyperkalemia. Co-administration of drugs known to cause hyperkalemia or to reduce kidney function is not an absolute contraindication but should be accompanied by more frequent monitoring of potassium levels. Kidney function must be determined and monitored. A diet low in potassium and loop diuretics or thiazide diuretics that increase potassium excretion may be considered for use. Whenever potassium-lowering therapy is initiated, potassium levels should be closely monitored not only to follow the potassium-lowering effects, but also to prevent the occurrence of hypokalaemia, which may be more dangerous than hyperkalemia. In general, RAA system inhibitor therapy should be started at a low dose and titrated to the maximum tolerable dose which has been shown to reduce the risk of cardiovascular events and kidney disease in clinical trials (Pierce et al., 2015).

In patients with potassium levels between 4.5-5 mEq/L and have not reached the maximum tolerable dose, titration is recommended or if not already administered it is recommended to start RAA system inhibitor therapy and monitor potassium levels closely. If potassium levels rise above 5.0 mEq/L, potassium monitoring measures should be initiated. In patients with potassium levels of >5 mEq/L, treatment with potassium-lowering agents can be started immediately. Potassium levels should be monitored according to clinical status and potassium reduction treatment should be maintained unless there is another etiology for the occurrence of hyperkalemia (Giuseppe et al., 2018).

Table 8. Hyperkalemia therapy options (Giuseppe et al., 2018).

Mechanism	Agent
Moving potassium into the intracellular	Adrenergic beta-2 agonist (IV, nebulization)
	Insulin (IV) +- glucose
	Sodium bicarbonate (if metabolic acidosis)
Stabilization of heart membranes	CaCl, Ca. Glukonas (IV)
	Salin hypertonis (3-5%).
Increase Potassium Elimination	*Loop* diuretik (IV/everywhere)
	Hemodialysis
	Casion converter resin(SPS)(PO/PR), increases fecal excretion of potassium
	Sodium bicarbonates (alkaline urine , increase potassium secretion)
	New generation Potassium Binder: Papyromeres, sodium zirconium cyclosilicate)
Other agents	Fludrocortisone (PO) in aldosterone deficiency

1. Specific therapies to treat hyperkalemia
   a. Agonis Beta-adrenergik

      Through cyclic activation of adenosine monophosphate (cAMP), adrenergic beta agonists activate the sodium-potassium-adenosine triphosphatase pump (Na+-K+-ATPase), thereby shifting potassium into the intracellular compartment (Pierce et al., 2015). One example of this class of drugs is Albuterol, an adrenergic agonist that has an additive effect with insulin and glucose, which can help move potassium into the intracellular space. This agent lowers serum potassium levels by 0.5-1.5 mEq/L. This can be especially beneficial in patients with renal failure when experiencing fluid overload. The time of

commencement of the drug reaction is 30 minutes; with the duration of the effect reaching 4-6 hours (Elliott et al., 2010).

b. Garam Kalsium

Calcium prevents the toxic effects of hyperkalemia on the heart muscle by stabilizing the cell membranes of the heart against unexpected depolarization. The onset of effects is fast (≤ 15 minutes) but relatively short. This agent is the first-line treatment for severe hyperkalemia, when an electrocardiogram (ECG) shows significant abnormalities (e.g., dilation of the QRS interval, P wave loss, or cardiac arrhythmias). Calcium is usually not indicated when the ECG shows only peaking T waves (Ferreira et al., 2020).

Calcium has no effect on the level of serum potassium in the blood. For that reason, the administration of calcium should be accompanied by the use of other therapies that actually help lower serum potassium levels. Calcium chloride contains about 3 times more elemental calcium than the calcium content found in calcium gluconate: 1 g of calcium chloride has 270 mg (13.5 mEq) of elemental calcium, while 1 g of calcium gluconate has 90 mg (4.5 mEq). Therefore, when hyperkalemia is accompanied by hemodynamic compromise, calcium chloride is preferable to calcium gluconate. Other calcium salts (e.g., glubionate and gluconate) have less elemental calcium than calcium gluconate and are generally not recommended for hyperkalemia therapy (Giuseppe et al., 2018).

Calcium increases the threshold potential, thus creating a normal gradient condition between the threshold potential and the resting membrane potential, which is abnormally elevated in hyperkalemia. The starting action of the effect is 5 minutes, and the duration of the effect is about 30-60 minutes. The dose should be titrated with constant monitoring of ECG changes during administration; repeat the dose if ECG changes do not become normal within 3-5 minutes (Elliott et al., 2010).

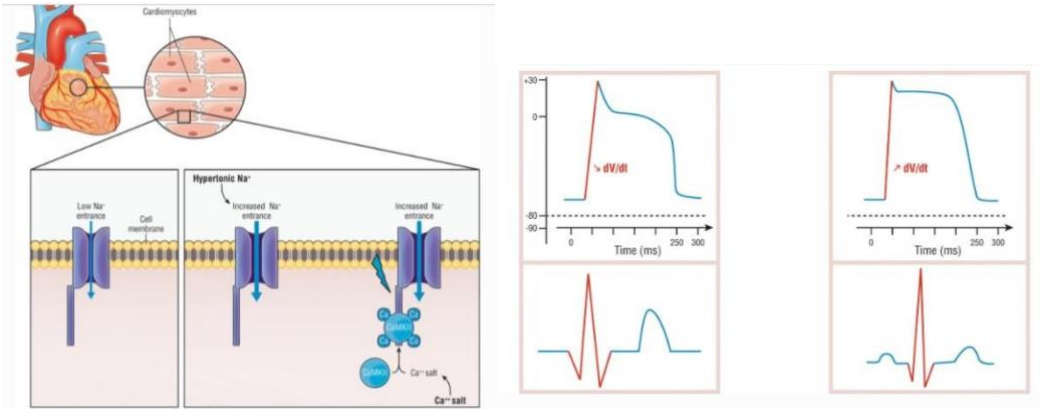

Figure 3. Mechanism Calcium Salts increase the threshold of action potentials (Pitt et al., 2017).

c. Insulin

Insulin is given in conjunction with glucose administration, in order to facilitate glucose absorption into muscle cells, by increasing the activity of the Na+-K+-ATPase pump which carries potassium into muscle cells and thus temporarily lowers serum potassium levels. Regular insulin stimulates potassium uptake within 20-30 minutes and persists for 4-6 hours (Pierce et al., 2015). Serum potassium concentrations can decrease by 0.5-1.2 mEq/L. Provision of glucose along with insulin also aims to prevent hypoglycemia. Monitoring blood sugar levels needs to be done as often as possible. Although the effect of insulin administration is fairly fast, the effect is temporary, so insulin therapy must be followed by therapies that actually improve potassium clearance such as Sodium Polystyrene Sulfonate (SPS) (Schafers et al., 2011).

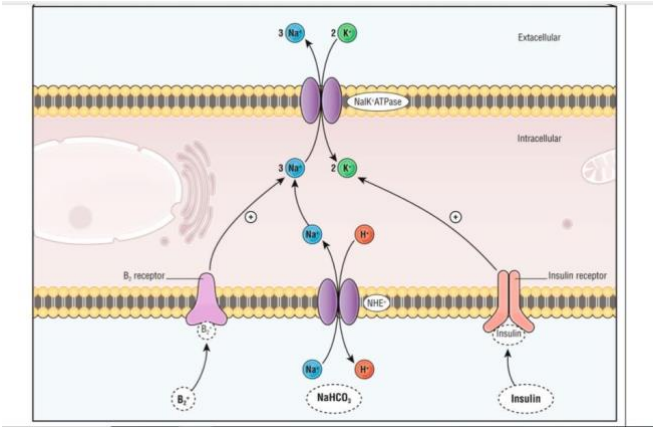

Figure 4. Mechanism of beta-adrenergic agents, sodium bicarbonate, and insulin in lowering serum potassium levels (Pitt et al., 2017).

d. Diuretic Agents (Loops)

Loop diuretics increase renal excretion of potassium and thus lower serum potassium levels. Parenteral administration of loop diuretics has a faster onset of action and is more often used in emergency situations. Simultaneous saline administration can prevent fatal volume reduction (Watson et al., 2010). Furosemide increases water excretion by disrupting the chloride-binding cotransport system, thereby inhibiting the reabsorption of sodium, potassium, and chloride in the loop of Henle and the distal renal tubule. Furosemide has a slow onset of action (about 1 hour), and its effect on decreasing potassium levels is inconsistent. Furosemide doses in chronic kidney disease are needed in larger quantities. Oral absorption of furosemide varies between individuals. If the patient requires quick and effective therapy, the intravenous (IV) route becomes an option. Continuous intravenous administration of furosemide (up to 40 mg/hour) is used to treat severe edema, but is rarely used for the treatment of hyperkalemia (Elliott et al., 2010).

e. Potassium binding agent

Potassium binders are cationic exchange resins that increase the excretion of potassium through feces. SPS exchanges sodium for potassium and binds to it in the intestines, especially in the colon, reducing the body's total potassium level by about 0.5-1 mEq/L. Use of this drug requires an increase in dose. (Giuseppe et al., 2018). The onset of action of such agents ranges from 2 to 24 hours after oral administration and even longer with rectal administration. The duration of the action is 4-6 hours. SPS is not recommended as a first-line therapy for severe, life-threatening hyperkalemia; However, it is used in second-line therapy. In addition, since sodium is the back-exchange ion in SPS, caution is needed if administered to patients who do not tolerate even small amounts of elevated sodium (i.e. those with heart failure, severe hypertension, or marked edema) (Pierce et al., 2015).

The U.S. Food and Drug Administration notes that SPS has been associated with a serious incidence of intestinal necrosis and gastrointestinal complications so it is not recommended for use in patients who do not have normal bowel function. The use of sorbitol along with sodium polystyrene sulfonate is known to potentially cause colonic necrosis. As recommended by some drug regulatory bodies, long-term use of Sodium Polystyrene Sulfonate (SPS) alone or along with sorbitol should be avoided as its prolonged use is associated with severe gastrointestinal side effects such as intestinal necrosis. SPS has never undergone rigorous testing in placebo-controlled clinical trials to prove its efficacy and safety for the treatment of acute or chronic hyperkalemia (Harel et al., 2013).

f. Alkalization Agent

In patients with severe metabolic acidosis, IV sodium bicarbonate is used as a buffer that decomposes into water and carbon dioxide after binding free hydrogen ions. By increasing the pH, sodium bicarbonate promotes the shift of potassium from the extracellular into the intracellular but intermediate in nature. The agent also increases the effectiveness of insulin in patients with acidosis. These agents have been successfully used in the treatment of overdose of slow-release oral potassium therapy (Pierce et al., 2015).

The use of sodium bicarbonate can be considered in the treatment of hyperkalemia even in the absence of metabolic acidosis conditions. This agent also increases sodium delivery to the kidneys, which helps in the excretion of potassium. Bicarbonate ions neutralize hydrogen ions and increase the

pH of urine and blood. The onset of action occurs within minutes, with the duration of action being about 15-30 minutes. Blood pH monitoring is necessary to avoid excessive alkalosis conditions. Use an 8.4% solution in adults and children and a 4.2% solution in children under 2 years old. The adult dose for hyperkalemia is 50 mEq IV given for 5 minutes. Also consider the use of other appropriate methods to increase potassium removal or excretion (Pierce et al., 2015).

CONCLUSION

Hyperkalemia is a serious medical condition that often manifests its manifestations in patients with diseases of chronic renal failure, heart failure, diabetes mellitus. The use of renin-angiotensin-aldosterone system-blocking drugs has also been shown to be associated with hyperkalemia conditions. It is widely known that the use of RAA system inhibitor drugs reduces cardiovascular mortality and heart failure rehospitalization, and there are still many benefits from RAA system inhibitor drugs. Therefore, an approach and management are needed for the treatment of hyperkalemia conditions, especially in patients with heart disease who receive RAA system inhibitory therapy where electrolyte levels must be closely monitored in these patients.

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