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A review in collaboration with the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy

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Update on management of hypokalemia and goals for the lower potassium level in patients with cardiovascular disease: A review in collaboration with the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy

Maria Lukács Krogager¹, Kristian Kragholm^{1,2,3}, Jesper Qvist Thomassen⁴, Peter Søgaaard¹, Basil S. Lewis⁵, Sven Wassmann⁶, Iris Baumgartner⁷, Claudio Ceconi⁸, Thomas Andersen Schmidt^{9,10}, Juan Carlos Kaski¹¹, Heinz Drexel^{12,13,14}, Anne Grete Semb¹⁵, Stefan Agewall^{16,17}, Alexander Niessner¹⁸, Gianluigi Savarese¹⁹, Keld Per Kjeldsen^{20,21}, Claudio Borghi²², Juan Tamargo²³, Christian Torp-Pedersen²⁴

Affiliations

- ¹ Department of Cardiology, Aalborg University hospital, Aalborg, Denmark.
- ² Department of Cardiology, Region Hospital North Jutland, Hjørring, Denmark.
- ³ Unit of Epidemiology and Biostatistics, Aalborg University Hospital, Aalborg, Denmark.
- ⁴ Department of Clinical Biochemistry, Copenhagen University Hospital (Rigshospitalet), Copenhagen, Denmark.
- ⁵ Lady Davis Carmel Medical Center and the Ruth and Bruce Rappaport School of Medicine, Technion-IIT, Haifa, Israel.
- ⁶ Cardiology Pasing, Munich, Germany and University of the Saarland, Homburg/Saar, Germany.
- ⁷ Department of Angiology, Bern University Hospital (Inselspital), Bern, Switzerland.
- ⁸ Department of Cardiology, Desenzano Del Garda Hospital, Italy.
- ⁹ Institute of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.
- ¹⁰ The Emergency Department, North Zealand University Hospital, Hillerød, Denmark.
- ¹¹ Molecular and Clinical Sciences Research Institute, St George's, University of London, London, UK.
- ¹² Vorarlberg Institute for Vascular Investigation and Treatment (VIVIT), Landeskrankenhaus, Feldkirch, Austria.
- ¹³ Private University of the Principality of Liechtenstein, Triesen, Liechtenstein.
- ¹⁴ Drexel University College of Medicine, Philadelphia, PA, USA.

- ¹⁵ Preventive Cardio-Rheuma clinic, Department Rheumatology, Diakonhjemmet Hospital, Oslo, Norway
- ¹⁶ Department of Cardiology, Ullevål, Oslo University Hospital, Oslo, Norway.
- ¹⁷ Institute of Clinical Sciences, S sterhjemmet, University of Oslo, Oslo, Norway.
- ¹⁸ Department of Internal Medicine II, Division of Cardiology, Medical University of Vienna, Vienna, Austria.
- ¹⁹ Division of Cardiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden.
- ²⁰ Department of Cardiology, Copenhagen University Hospital (Amager-Hvidovre), Copenhagen, Denmark.
- ²¹ Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Aalborg, Denmark.
- ²² Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy.
- ²³ Department of Pharmacology, School of Medicine, CIBERCV, University Complutense, 28040, Madrid, Spain.
- ²⁴ Department of Clinical Research, North Zealand University Hospital, Hiller d, Denmark.

1. Introduction

Hypokalemia is common in patients with cardiovascular disease. In this review, we emphasize the importance of tight potassium regulation in patients with cardiovascular disease based on findings from observational studies. To enhance the understanding, we also describe the mechanisms of potassium homeostasis maintenance, the most common causes of hypokalemia and present strategies for monitoring and management of low potassium levels. We propose elevation of potassium in asymptomatic patients with lower normal concentrations and concurrent cardiovascular disease. These proposals are intended to assist clinicians until more evidence is available.

2. Epidemiology

Hypokalemia burden in the general population is difficult to estimate. Studies have shown that the prevalence of hypokalemia in hospitalized patients is between 14-40% with 5% of the patients exhibiting potassium levels below 3.0 mmol/L.¹⁻⁴ In an outpatient population undergoing laboratory testing, mild hypokalemia was found in almost 14%.²

Female sex, younger age, high estimated glomerular filtration rate, and baseline use of diuretics were associated with increased hypokalemia risk.⁵ Approximately 80% of the patients receiving diuretics experience hypokalemia at some point and many of the patients suffer from an associated systemic disease.⁶⁻⁹

2.1 Hypokalemia in patients with cardiovascular disease

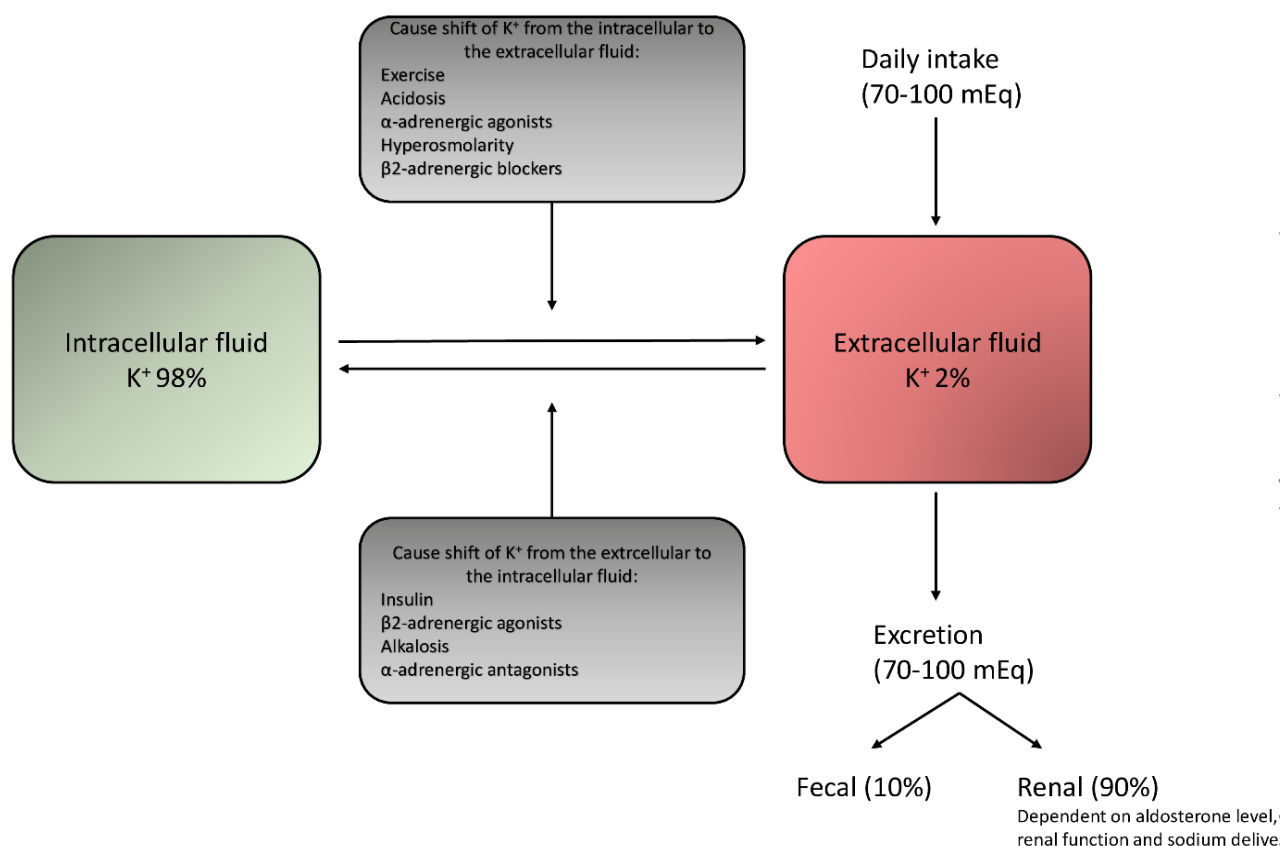
The prevalence of hypokalemia in patients with heart disease is high. However, it is important to acknowledge that the prevalence is highly dependent on time from diagnosis to potassium measurement, severity of the disease, concurrent comorbidities, definition of hypokalemia, magnitude of diuretic use in the study population and whether the studies were performed before/after the introduction of beta-blockers and renin-angiotensin-aldosterone system inhibitors as standard therapy for different cardiovascular diseases. Among patients with cardiovascular disease, the highest prevalence of hypokalemia was observed in patients with chronic heart

failure (incidence 3.0-54%),¹⁰⁻¹⁶ whereas in patients with hypertension studies had a prevalence between 3.8% and 7.2%¹⁷⁻¹⁹ and incidence 3.5-6.8%.^{20,21}

3. Potassium homeostasis

Potassium (K^+) is the most abundant cation in the human body (50-75 mmol/kg body weight). Under physiological conditions, 98% of K^+ is intracellular (~140-150 mmol/L) and 2% is found in the extracellular space (3.8-5.0 mmol/L).^{6,22,23} This large K^+ gradient between intracellular and extracellular compartments plays a key role in maintaining cell membrane potential, cellular excitability, conduction of nerve impulses, skeletal, cardiac and smooth muscle cell contraction, gastrointestinal motility, cellular osmolality, acid-base homeostasis, hormone secretion, mineralocorticoid action, renal concentrating ability, and fluid and electrolyte balance (Figure 1).^{23,24}

Figure 1. Regulation of intracellular and extracellular potassium shifts



Blood K⁺ levels are tightly regulated between 3.5 and 5.0 mmol/L by the coordinated interaction of physiological regulatory mechanisms, including a balance between absorption and excretion processes and the transfer of potassium between the extracellular and intracellular compartments, that maintain K⁺ homeostasis.^{23,25-27} The gastrointestinal absorption of dietary daily K⁺ intake (70-100 mEq) is completed and matched by the rapid exchange of K⁺ between the extracellular and intracellular compartments and equivalent increases in K⁺ excretion, 90% in the urine and the remaining 10% in feces. Thus, alternations in renal potassium secretion greatly affect potassium balance.

The kidney plays a central role in the maintenance of potassium homeostasis, until the glomerular filtration rate decreases to <15-20 mL/min. Potassium is filtered by the glomerulus and is reabsorbed in the proximal tubule (65%) and the Henle's loop (20%), but it can be reabsorbed or secreted by the distal tubule and collecting duct cells. The most important site of regulation is the renal collecting duct, where aldosterone receptors are present. When potassium intake is >150 mEq/day, about 50% of the excess potassium appears in the urine over the next several hours and most of the remainder is transferred into the intracellular compartment, so that only a modest (<10%) and transient increase in blood K⁺ concentration is observed.^{6,24,25,27}

When potassium intake falls or potassium renal or gastrointestinal losses increase, the activity of the Na⁺-K⁺-ATPase in the skeletal muscle and liver, which allows a net K⁺ "shift" from the intracellular fluid to the plasma.²⁸ A similar shift is induced by acidosis, hyperosmolarity, alpha-adrenergic agonists or strenuous exercise. Additionally, in an attempt to maintain normal potassium levels, hypokalemia results in insulin resistance which reduces K⁺ uptake into muscle cells, increases the reabsorption of K⁺ (via the increased activity of H⁺-K⁺-ATPase) and decreases aldosterone secretion leading to an increase in the reabsorption and a decrease in the tubular excretion of K⁺.

The normal potassium interval depends on whether potassium concentrations are determined in serum or plasma. Reported reference intervals for serum potassium in adults vary from 3.5 to 5.1 mmol/L and for plasma potassium from 3.3 to 4.9 mmol/L.²⁹ Values defined as "normal" potassium plasma concentration are based on measurements taken in apparently healthy individuals. Usually, reference intervals of apparently healthy individuals are set within the 2.5th and 97.5th centiles of the test result distribution.³⁰ Extrapolating the reference interval for healthy subjects into optimum range for patients with cardiovascular disease may not be appropriate.

Evidence regarding potassium monitoring and management in patients with heart disease is lacking and therefore current proposals are largely based on expert opinion rather than randomized controlled trials.

4. Hypokalemia: definition and common causes

Hypokalemia, defined as a serum or plasma $K^+ < 3.5$ mmol/L, is a common electrolyte disorder that may develop due to decreased K^+ intake, increased shift from the extracellular to the intracellular space or increased K^+ losses in the urine or through the gastrointestinal tract.³¹ Increased excretion is the most common mechanism, but several causes can coexist simultaneously. The kidney is able to lower potassium excretion to a minimum of 5-25 mmol/L/day in the presence of decreased potassium intake, so that decreased intake alone rarely causes significant hypokalemia. However, a low potassium intake contributes to the severity of hypokalemia when another cause of hypokalemia is present, such as diuretic therapy.

Hypokalemia can be classified as mild (serum $K^+ 3.0$ -3.4 mmol/L), moderate (serum $K^+ 2.5$ -2.9 mmol/L) or severe (serum $K^+ < 2.5$ mmol/L) and symptoms are more likely with increasing severity. Hypokalemia is not typically a disease by itself, but usually triggered by several common clinical conditions and/or a side effect of some drugs (Table 1). Among the latter, loop and thiazide diuretics are most frequently associated with hypokalemia in patients with cardiovascular disease.^{8,9} Yet, these drugs constitute an important pillar in management of hypertension and heart failure.^{32,33}

Table 1. Common drugs and conditions that may cause hypokalemia

Common drugs/conditions that may cause hypokalemia	
1. <i>Increased potassium excretion:</i>	
•	Thiazide/ Thiazide-like diuretics
•	Loop diuretics
•	Antimicrobials (aminoglycosides, penicillins)
•	Quetiapine
•	Cisplatin
•	Mineralocorticoids and glucocorticoids
•	Licorice
•	Heart failure
•	Conn's syndrome
•	Primary/secondary hyperaldosteronism
•	Cushing's syndrome

- Renovascular hypertension
- Vasculitis
- COVID-19
- Nephrogenic diabetes insipidus
- Hypomagnesemia
- Renal tubular acidosis: Fanconi syndrome, interstitial nephritis, metabolic alkalosis
- Genetic renal disorders
 - Congenital adrenal hyperplasia (11-beta hydroxylase or 17-alpha hydroxylase deficiency)
 - Bartter syndrome, Gitelman syndrome, Liddle syndrome, Gullner syndrome, Geller's syndrome
 - Familial hyperaldosteronism,
 - Apparent mineralocorticoid excess
 - Hypokalemic periodic paralysis, Thyrotoxic periodic paralysis
 - SeSAME syndrome (seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance)

2. *Shift from extracellular to intracellular space*

- Insulin (high dose/overdose)
- Beta₂-receptor agonists (albuterol, salbutamol, terbutaline)
- Xanthines (theophylline, aminophylline, caffeine)
- Ephedrine
- Poisoning (barium cesium, chloroquine)
- Verapamil (overdose)
- Alkalosis
- High stress conditions (post myocardial infarction, head injury)
- Refeeding syndrome after prolonged starvation
- Hyperthyroidism
- Familial periodic paralysis
- Delirium tremens
- Hypothermia

3. *Increased gastrointestinal loss*

- Vomiting
- Diarrhea
- Laxatives
- Inflammatory bowel disease
- Villous adenoma, short bowel syndrome

4. *Decreased potassium intake (<1g/day)*

- Deficient diet in alcoholics, elderly (e.g. "tea-and-toast" diet)
- Eating disorders (anorexia nervosa, bulimia, starvation, pica)
- Poverty

5. Hypokalemia: symptoms and risks

In most of the cases, patients with mild hypokalemia are asymptomatic. Moderate and severe hypokalemia may cause neuromuscular (muscle weakness, fatigue, eventually leading to ascending paralysis, acute respiratory failure due to diaphragmatic paralysis, rhabdomyolysis), gastrointestinal (nausea, vomiting, constipation, gastrointestinal hypomotility, ileus), renal (metabolic acidosis, polyuria) symptoms and cardiac rhythm abnormalities.⁷ Symptoms are usually reversible after the correction of the hypokalemia.

Hypokalemia reduces the repolarization reserve by decreasing several K⁺ currents (inward rectifier-I_{K1}, delayed rectifier-I_{Kr}, and transient outward current-I_{to}) and increases the binding activity of I_{Kr}-inhibiting drugs.³⁴ In consequence, it prolongs action potential duration (QT interval), increases QT dispersion, slows intracardiac conduction, and induces abnormal pacemaker activity including early afterdepolarizations (trigger arrhythmias).³⁴ Cardiac arrhythmias represent the most serious complication of hypokalemia, particularly in people with underlying heart disease or treated with digitalis or antiarrhythmic drugs.^{35,36} Typical hypokalemia induced ECG changes are summarized in Table 2 and Figure 2 illustrates some of these changes.

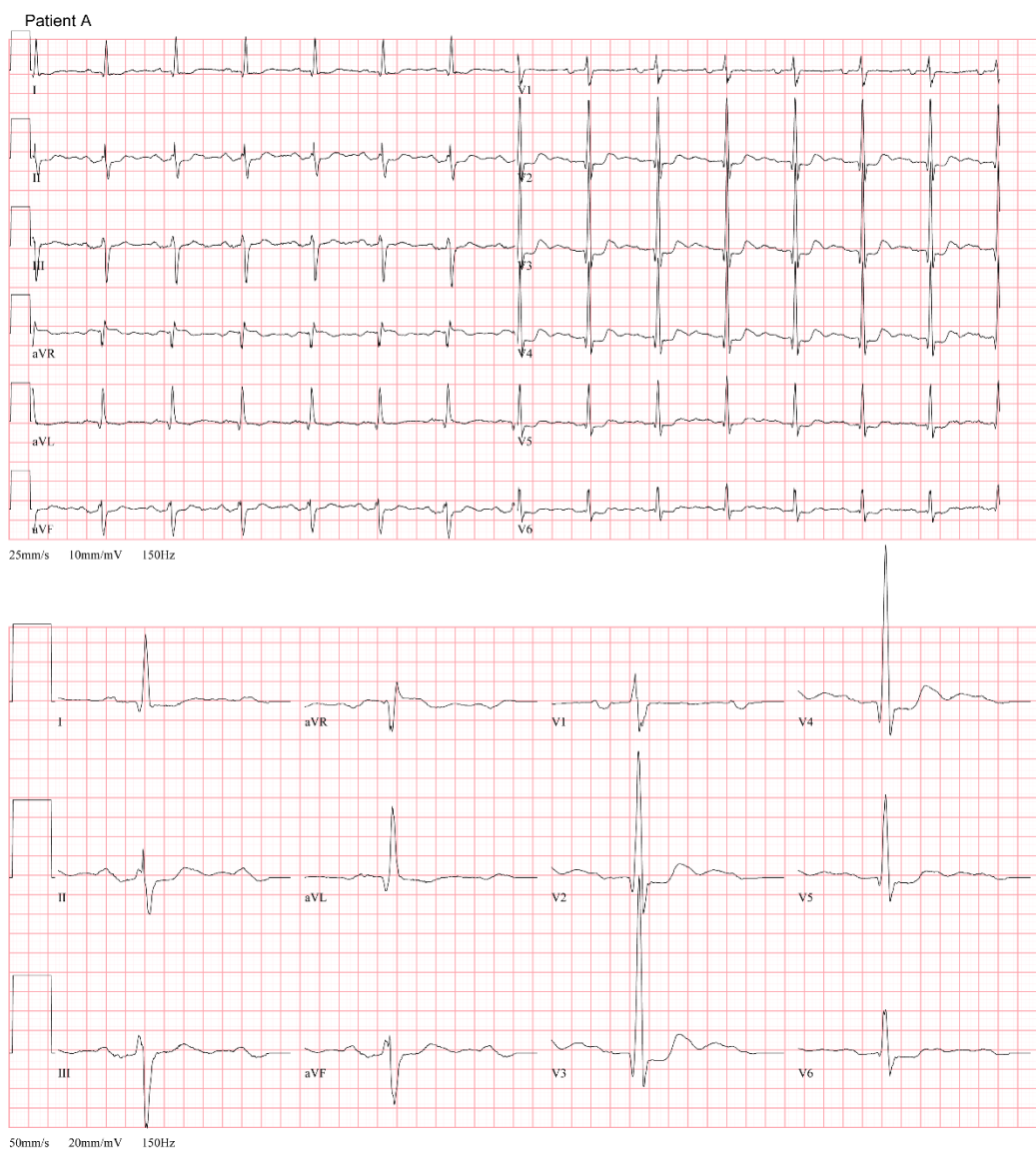
Table 2: Hypokalemia induced electrocardiographic changes stratified by intervals of potassium concentrations

Potassium interval	ECG findings
<3.5 mmol/L	Flattening or inversion of T-waves
<3.0 mmol/L	Q-T interval prolongation, U waves, decreased amplitude of the P wave, T-wave flattening, ST-interval depression, atrioventricular block (PR-interval prolongation) and ventricular extrasystoles

<2.5 mmol/L	Atrial fibrillation, multifocal atrial tachycardias, premature atrial and ventricular contractions, bradycardia, Torsade de Pointes, ventricular fibrillation.
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Potassium levels between 3.0–3.5 mmol/L cause ECG changes (flattening or inversion of T waves). Between 2.5–3.0 mmol/L, hypokalemia cause significant Q-T interval prolongation, U waves, decreased amplitude of the P wave, T-wave flattening, ST-interval depression (0.5 mm), atrioventricular block (PR-interval prolongation) and ventricular extrasystoles.^{37–40} Potassium levels <2.5 mmol/L are associated with atrial fibrillation and multifocal atrial tachycardias, premature atrial and ventricular contractions, bradycardia, Torsade de Pointes, ventricular fibrillation, syncope and sudden cardiac death and heart failure.⁴¹ The pro-arrhythmic risk of hypokalemia increases in patients with ischemic heart disease, heart failure, left ventricular hypertrophy or treated with digoxin or class I and III antiarrhythmic drugs. However, some patients with severe hypokalemia may have only minor ECG changes before clinically significant dysrhythmias, while maintaining K⁺ above 3.9 mmol/L reduces the risk of early ventricular fibrillation.⁴² Rapid correction of hypokalemia facilitates electrical defibrillation and reduces the incidence of further arrhythmias in the post-arrest period.

Figure 2. Electrocardiographic manifestations in patients with diuretic induced hypokalemia



Patient A. Female, 74 years, P(K) 2.8 mmol/L

ECG characteristics:

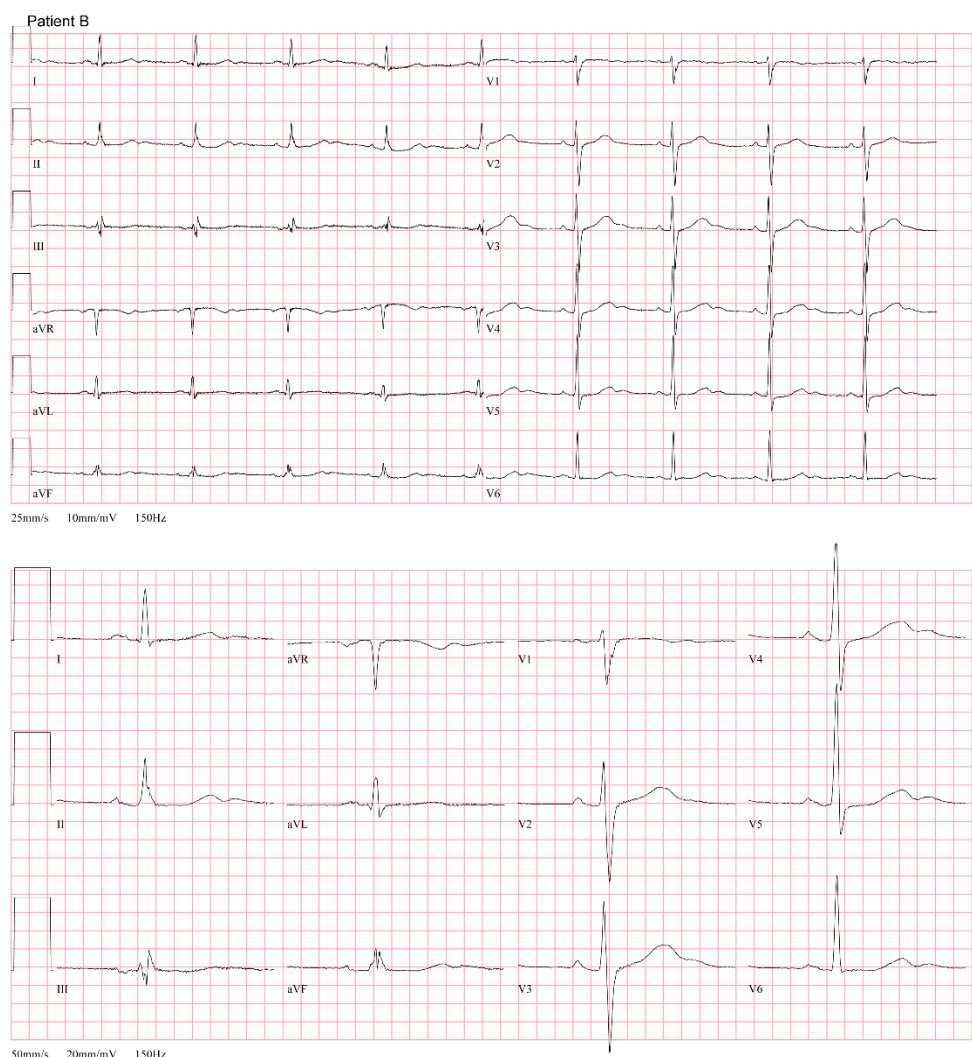
Ventricular rate: 85 BPM

PR interval: 198 ms

QRS duration: 106 ms

QT/QTc: 372/442 ms

ECG interpretation: sinus rhythm, T-wave flattening, ST-segment depression, U-waves (precordial leads), QTc-interval prolongation, slightly prolonged PR-interval



Patient B. Male, 62 years, P(K) 2.9 mmol/L

ECG characteristics: Ventricular rate: 57 BPM

PR interval: 160 ms

QRS duration: 98 ms

QT/QTc: 472/459 ms

ECG interpretation: sinus bradycardia, T-wave flattening, ST-segment depression, U-waves (precordial leads), QTc-interval prolongation.

6. Methods for potassium measurement

K⁺ concentrations can be measured both in serum from coagulated blood and in plasma from heparinized blood.⁴³ The material of choice is plasma, because in serum, pseudohyperkalemia may often occur. The most common causes of pseudohyperkalemia (falsely elevated potassium concentrations) are:

- platelet rupture during coagulation
- mechanical factors such as tourniquet applied for more than 1 min, first clenching or inadequate sample handling
- chemical factors (ethanol)
- temperature (optimal temperature for specimen storage before testing is 15-25°C)
- patient factors such as hyperventilation and trombocytosis.⁴⁴

Differences in potassium reference intervals measured in serum and plasma have been shown to be substantial in patients with hyperkalemia (>0.5 mmol/L), whereas in patients with hypokalemia the lower reference level is similar in serum and plasma (difference <0.1 mmol/L).⁴⁵ Under ideal conditions of sample collection, plasma and serum potassium values are correlated. Yet, in daily clinical practice, samples may be obtained under nonoptimal conditions and conversion between the two methods may lead to erroneous assessments.⁴⁶

There is not a general consensus on a single reference interval for potassium in serum and in plasma. This is mainly due to variations between the study populations used for evaluation of potassium levels. Table 2 provides an overview of the most commonly used plasma and serum potassium reference intervals worldwide.

Table 3: Reference intervals (RI) for potassium in serum and plasma in different populations

Population	US (Tietz) ⁴⁷	German (Drogies) ⁴⁵	Nordic (Rustad) ⁴⁸
Plasma RI	3.4-4.8 mmol/L	3.5-4.6 mmol/L	3.5-4.4 mmol/L
Serum RI	3.5-5.1 mmol/L	3.7-5.1 mmol/L	3.6-4.6 mmol/L

In the present document, we refer to both plasma and serum potassium as K⁺, since it is unclear in many studies which method was used or some studies performed their analyses on K⁺ draws using both methods.

In order to differentiate between renal (e.g. diuretic therapy, primary aldosteronism) and non-renal (e.g. transcellular shifts, gastrointestinal losses) causes of hypokalemia urine electrolytes should be measured. An

arterial blood gas analysis is also useful to choose the appropriate strategy of potassium supplementation in case of acidosis or alkalosis.⁷ Other laboratory tests include magnesium, creatinine and glucose levels.

7. Management of hypokalemia

As the cause of hypokalemia can be multifactorial, the main therapeutic approach is the management of the underlying cause and/or correct the causative factors. Treatment of hypokalemia is determined by its severity and aetiology and the presence of symptoms and ECG abnormalities.

There are three main steps to consider for management of hypokalemia:

- 1) Identify (and treat) the underlying cause to prevent future episodes
- 2) Decrease potassium losses

The most common sites of potassium loss are within the renal and gastrointestinal system. Therefore, if applicable, management strategies may include avoiding laxatives, preventing/ceasing vomiting or diarrhea, using the lowest possible dose of thiazide or loop diuretics, replace diuretics (f.eg. hypertensive patients) with other equivalent drugs or combine with potassium-sparing diuretics when diuretic therapy is required (f.eg. heart failure) and treat hyperglycaemia if glycosuria is present.^{7,49}

- 3) Replenish potassium stores

- Mild hypokalaemia (3.0-3.4 mmol/L) can be managed by increasing dietary potassium intake (e.g. by consuming more fruits and vegetables) and/or by administering oral potassium supplements such as potassium chloride, potassium citrate and potassium phosphate. The Institute of Medicine recommends a potassium intake of 4.700 mg/d (120 mmol/d) for individuals older than 14 years.^{7,50,51} On average, a reduction of serum potassium by 1 mmol/l suggests a total body deficit of 300-400 mmol, but this is variable depending on body mass.²⁷ However, as potassium is predominantly an intracellular cation, serum/plasma K⁺ levels may not accurately reflect total body stores, and larger doses may be needed

to replenish potassium body stores. Often, the effectiveness of increasing dietary potassium is limited, because most of the potassium contained in foods is coupled with phosphate, whereas most cases of hypokalemia involve chloride depletion (e.g. hypokalemia associated to diuretic therapy or vomiting) and respond better to supplemental potassium chloride.^{27,52} Of note, modern food has a decreased potassium content and, as a consequence, mild hypokalemia is rather frequent among healthy subjects. Increased delivery of sodium to the distal nephron, which occurs with high sodium intake or loop diuretic therapy, promotes potassium excretion. Therefore, hypokalemia may also be minimized by salt restriction in the diet. Another strategy, particularly when they are indicated to treat a comorbidity, is the use of drugs that inhibit the renin-angiotensin-aldosterone system, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and mineralocorticoid receptor antagonists. Potassium-sparing diuretics should be used only in patients with normal renal function who are prone to significant hypokalemia. The use of potassium-sparing diuretics not only increases serum potassium levels, but can correct metabolic alkalosis.

- Patients with mild to moderate hypokalemia (2.5–3.4 mmol/L) may be treated with an oral formulation of potassium (potassium chloride, potassium phosphate, potassium bicarbonate), in divided doses over days to weeks administered with 100-250 mL of water with or after meals.⁵³ A dosage of 20 mmol/day of KCl is generally sufficient for the prevention of hypokalemia in patients receiving diuretic therapy or with hyperaldosteronism and from 40 to 100 mmol/day for its treatment. Each 10 mmol of KCl will increase K⁺ by 0.1 mmol/L.⁴² Adverse effects of potassium supplements affect primarily the gastrointestinal tract, and they include nausea, vomiting, diarrhea, flatulence, abdominal pain or discomfort and small bowel ulcerations. Microencapsulated formulations do not have unpleasant taste and are associated with a lower incidence of gastrointestinal adverse effects. We suggest administration of potassium bicarbonate in patients with hypokalemia and metabolic acidosis. Hypomagnesemia is also frequently present in patients with clinically

significant hypokalemia, particularly those treated with loop or thiazide diuretics.⁵⁴ In such cases, hypokalemia cannot be normalized until the hypomagnesemia has been corrected. Magnesium is required for potassium uptake and maintenance of intracellular potassium levels, particularly in the myocardium, and magnesium depletion enhances renal potassium excretion, impedes potassium repletion and may potentiate the risk of cardiac arrhythmias. Thus, serum magnesium levels should be corrected to achieve an adequate treatment of hypokalemia.⁵⁵

- For patients with symptomatic or severe hypokalemia (< 2.5 mmol/L) or with life-threatening arrhythmias or neuromuscular dysfunction, intravenous (i.v.) potassium should be given with continuous ECG monitoring, and serial potassium levels measurements to avoid overcorrection (hyperkalemia). Doses should be titrated based on repeated sampling of serum potassium levels. The i.v. administration is of choice in patients who are intolerant to the oral formulation, or in case of severe nausea, vomiting or abdominal diseases or when oral potassium supplements do not normalize the hypokalemia. In patients with hypokalemia related to renal or endocrine diseases, a multidisciplinary diagnostic and therapeutic approach is needed. In the absence of severe heart disease, potassium can be gradually replaced at a rate of 10 mmol/h in asymptomatic patients. The maximum recommended i.v. dose of potassium is 20 mmol/h, but higher rates using central venous catheters (up to 40 mmol/hour or 2 mmol/min for 10 min, followed by 10 mmol over 5-10 min) have been successful in emergency situations.^{56,57} Rapid i.v. bolus of potassium may precipitate cardiac arrest and should be avoided. Potassium should be diluted in 0.9% sodium chloride solution, but not in glucose, as 5% glucose stimulates insulin secretion and shifts of potassium into cells. A rapid normalization of hypokalemia can be achieved by combining oral (e.g., 20 to 40 mmol) and i.v. administration.⁵⁶ A summary of the principles of hypokalemia management is presented in Table 3.

Table 4. Proposals for the treatment of hypokalemia

Hypokalemia	Treatment	Comments
Bordeline (3.5-3.9 mmol/L)	<p>Dietary supplementation with potassium (fruit, vegetables, meat etc) in compliant patients.</p> <p>Oral KCl in patients treated with diuretics. Consider higher dose of KCl in patients treated with diuretics and KCl concomitantly.</p>	Applies to patients with hypertension, cardiac arrhythmias, ischemic heart disease and chronic heart failure.
Mild (3.0-3.4 mmol/L)	<p>Oral KCl: 10-20 mmol 3-4 times a day until K⁺ normalized</p> <p>40-100 mEq/day over a few days or weeks may be needed to fully replete potassium stores</p> <p>In case of hypokalemia + metabolic acidosis oral potassium bicarbonate 25 mmol may be used every 6-12h until K⁺ normalized</p>	<p>Each 10 mmol/L of KCl will increase K⁺ by 0.1 mmol/L</p> <p>Monitor K⁺ daily and adjust dose accordingly</p> <p>Patients should take potassium supplements with plenty of water to avoid gastrointestinal irritation</p> <p>Patients are usually asymptomatic</p>
Moderate (2.5-2.9 mmol/L)	<p>i.v. potassium supplementation through peripheral line: 10-20 mmol/h until K⁺ normalized or it is possible/safe to switch to oral potassium supplementation</p> <p>Maximum of 40 mmol/h</p>	<p>Patients have no or minor symptoms</p> <p>Monitor plasma/serum K⁺ every 6-12h</p> <p>Continuous ECG monitoring</p> <p>Oral and i.v. potassium supplementation can be safely used simultaneously</p> <p>Each 10 mmol of i.v. potassium supplement will increase K⁺ by 0.05 mmol/L</p>
Severe (<2.5 mmol/L)	<p>i.v. potassium supplementation through central line: 20-40 mmol/h until K⁺ normalized and patient are asymptomatic</p> <p>If K⁺ <2.0 mmol/L or in the presence of life threatening symptoms: 40-80 mmol/h</p>	<p>Patients are usually symptomatic</p> <p>If case of acidosis administer potassium bicarbonate</p> <p>Test for hypomagnesemia. If the patient is hypomagnesemic: initially give 4 mL MgSO₄ 50% (8 mmol) diluted in 10 mL of NaCl 0.9% over 20 min, then start first 40 mmol KCl</p>

		infusion, followed by magnesium replacement
		Continuous ECG monitoring
		Monitor plasma/serum K ⁺ every hour
		High dose KCl can cause thrombophlebitis

In current clinical practice, K⁺ supplementation is recommended in patients with concentrations below 3.5 mmol/L, even in asymptomatic patients with cardiovascular disease.¹ The National Council on Potassium in Clinical Practice recommends maintenance of K⁺ levels at a level of at least 4.0 mmol/L in patients with hypertension, cardiac arrhythmias, and chronic heart failure.¹

8. Goals for the lower potassium range among patients with cardiovascular disease: insights from population and observational studies

In 2004, MacDonald et al. suggested targets for K⁺ concentrations in patients with heart disease.⁵⁰ Based on available studies at that time (not a systematic review), the authors recommended the following serum potassium targets stratified on different cardiovascular diseases: hypertension 3.5-5.0 mmol/L, acute myocardial infarction and heart failure 4.5-5.5 mmol/L. However, many studies have been performed since. It is well known that low dietary K⁺ and/or low blood K⁺ concentrations increase the risk of developing hypertension, stroke and atrial/ventricular arrhythmias.⁵⁸⁻⁶⁸ Yet, in recent years, many studies investigating the impact of hypokalemia confirmed the association of low K⁺ concentrations with increased arrhythmia risk and all-cause and/or cardiovascular death in patients with different cardiovascular diseases.^{10,20,50,69-77} Nevertheless, large epidemiological studies also suggested that borderline hypokalemia or low normal K⁺ (3.5-3.7 mmol/L) levels are also associated with increased mortality in patients with hypertension, atrial fibrillation/flutter, and acute and chronic heart failure.^{10,71-73}

In >44,000 patients treated with combination antihypertensive therapy, Krogager et al. found that K⁺ concentrations outside the interval 4.1-4.7 mmol/L were associated with increased 90-days mortality risk.¹⁸ Another study by the same first author showed that persistent hypokalemia (<3.5 mmol/L) was frequent and associated with increased all-cause and presumed cardiovascular death within 90-days. Additionally, the authors observed that 45% of the patients who had borderline hypokalemia at the first K⁺ measurement, developed hypokalemia at the second K⁺ blood sampling taken within 7-100 days from the first measurement.⁷⁸ Aldahl et.al¹⁰ performed similar analyses in approximately 20,000 patients with chronic heart failure and found that patients with K⁺ concentrations between 4.2-4.7 mmol/L had better prognosis within the first 90-days from the K⁺ measurement compared to patients with K⁺ levels outside this range. Similarly, Cooper et al. found an optimal potassium value of 4.2 mmol/L in patients with heart failure.⁷⁹ Other studies suggesting that borderline hypokalemia might be unfavorable in patients with heart failure were performed by Ferreira et al.⁸⁰ and Matsushita et al.⁸¹ The investigators observed that potassium levels starting below 4.0 mmol/L were associated with excess morbidity and mortality in heart failure. Numerous other studies have found an association between hypokalemia and mortality in patients with heart failure,^{15,16,82,83} but only few observed or investigated the impact of borderline hypokalemia (3.5-3.7 mmol/L) on mortality or other adverse events.^{10,15,16,84} Generally, most of the studies examining the relationship between K⁺ and mortality, categorize K⁺ in too broad intervals, so that a possible association might have been masked. A follow-up study on patients with chronic heart failure and initial hypokalemia showed that patients who remained hypokalemic had significantly higher 90-days all-cause mortality risk compared to patients with K⁺ levels in the middle of the reference interval.⁸⁵ Yet, it is important to consider that some of the patients might have had end-stage heart failure requiring particularly high dosage of diuretics. As such, hypokalemia might be a surrogate marker of severe heart failure. Núñez et al. also showed that abnormal potassium concentrations were associated with increased risk of death compared to patients who maintained or returned to normokalemia.⁸⁶

As for patients with atrial fibrillation/flutter, Hagengaard et al.⁷² found that besides hypokalemia and hyperkalemia, K⁺ concentrations within the intervals 3.5-3.7 mmol/L and 4.5-5.0 mmol/L were associated with increased mortality risk compared to the reference group (4.1-4.4 mmol/L). Once more, low normal potassium levels were associated with adverse events.

In patients with myocardial infarction studies have shown that hypo- and hyperkalemia are associated with mortality.^{77,87-89} Moreover, few studies demonstrated U-shaped relationship between potassium and mortality in patients with myocardial infarction, indicating that a narrower potassium interval might apply this population as well.^{77,90} We also observed in patients with acute heart failure following myocardial infarction that besides hypo- and hyperkalemia, low normal and high normal K⁺ concentrations were associated with high risk of death.⁷³ As for the risk of ventricular fibrillation (VF), Jacobsen et al.⁹¹ showed that hypokalemia was associated with increased odds of VF during primary percutaneous coronary intervention.

It is also important to mention that rapid fluctuations of blood potassium concentrations either from low to high levels or the reverse are common among patients with heart disease and/or impaired renal function and that these dynamic changes are associated with increased mortality^{78,85,92-96}

Epidemiological studies cannot prove causation, only association. Therefore, upcoming randomized clinical trials will need to test whether stringent clinical control of K⁺ through monitoring and corrections might translate into actual benefits in clinical outcomes. However, considering current evidence, it seems that an optimal K⁺ interval in patients with cardiovascular disease is considerably narrower than the currently used RI and clinicians should not ignore borderline hypokalemia but target potassium concentrations in the middle of the reference interval. Based on current studies, we propose that treatment (dietary and/or pharmacological) of asymptomatic patients with cardiovascular disease and K⁺ concentrations <4.0 mmol/L in order to elevate K⁺ to levels between 4.0-4.6 mmol/L is appropriate.

9. Potassium monitoring in patients treated with diuretics

As patients with cardiovascular disease are at high risk of K⁺ imbalances due to the disease itself and the treatment involved, close monitoring of electrolytes is appropriate. Evidence regarding the frequency of potassium monitoring in patients treated with diuretics is lacking. Small scale studies showed that hypokalemia typically develops within 2 to 19 weeks from start with diuretic treatment.^{97,98} Studies from the 1980's suggested that the decrease in K⁺ following diuretic treatment initiation is a transient phenomenon and that patients can normalize without therapy.^{99,100} Yet, it is important to acknowledge that hypokalemia can be multifactorial and the adverse effects of hypokalemia are strongly linked with the rapidity of onset and concurrent diseases. As such, there is not a consensus on how often potassium should be monitored in patients treated with diuretics and practices throughout the world are very different. In many European countries, patients with stable cardiac conditions, are typically followed and monitored 2-3 times a year. Normal K⁺ concentration before cardiovascular drug treatment initiation is warranted. Guidelines on management of arterial hypertension and acute and chronic heart failure do contain sections on patient follow-up where different factors/aspects need to be assessed.^{32,33} Yet, no specific information about potassium monitoring is available in these guidelines. Table 4 provides proposals based on expert opinions on monitoring and follow-up of patients with cardiovascular disease.

Table 5. Patient follow-up

Cardiopathy subgroups	Proposed patient follow-up	Comments
Hypertension	Patients should be evaluated at least once within the first 2 months after the initiation of antihypertensive drug therapy.	Evaluate high blood pressure related symptoms, electrolyte status and kidney function and record an electrocardiogram.
	After blood pressure target is reached a visit interval between 3-6 months can be agreed with the patient.	Evaluate high blood pressure related symptoms, electrolyte status and kidney function and record an electrocardiogram
	At least every 2 years physicians should also assess hypertension's effects on different organs and risk	

10. Conclusions

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- Given the frequent use of treatments that are associated with hypokalemia and the high risk of potassium disturbances there is an urgent need for randomised studies that address frequency of monitoring and cut-off values for intervention as well as further observational studies to delineate safety levels of potassium for a range of cardiovascular disease.

11. References

- Cohn JN, Kowey PR, Whelton PK, Prisant LM. New guidelines for potassium replacement in clinical practice: a contemporary review by the National Council on Potassium in Clinical Practice. *Arch Intern Med United States*; 2000;**160**:2429–2436.
- Dhondup T, Qian Q. Acid-Base and Electrolyte Disorders in Patients with and without Chronic Kidney Disease: An Update. *Kidney Dis (Basel, Switzerland) Switzerland*; 2017;**3**:136–148.
- Udendi UK, Tchounwou PB. Potassium Homeostasis, Oxidative Stress, and Human Disease. *Int J Clin Exp Physiol India*; 2017;**4**:111–122.
- Liamis G, Rodenburg EM, Hofman A, Zietse R, Stricker BH, Hoorn EJ. Electrolyte disorders in community subjects: Prevalence and risk factors. *Am J Med* 2013;**126**:256–263.
- Nilsson E, Gasparini A, Ärnlov J, Xu H, Henriksson KM, Coresh J, Grams ME, Carrero JJ. Incidence and determinants of hyperkalemia and hypokalemia in a large healthcare system. *Int J Cardiol* 2017;**245**:277–284.
- Alfonzo AVM, Isles C, Geddes C, Deighan C. Potassium disorders--clinical spectrum and emergency management. *Resuscitation Ireland*; 2006;**70**:10–25.
- Kardalas E, Paschou SA, Anagnostis P, Muscogiuri G, Siasos G, Vryonidou A. Hypokalemia: a clinical update. *Endocr Connect* England; 2018;**7**:R135–R146.
- Kapelijs CJ, Malliaras K, Kaldara E, Vakrou S, Nanas JN. Loop diuretics for chronic heart failure: A foe in disguise of a friend? *Eur. Hear. J. - Cardiovasc. Pharmacother.* 2018.
- Marciniak TA. What are the pharmacodynamics of loop diuretics? *Eur. Hear. J. - Cardiovasc. Pharmacother.* 2019.
- Aldahl M, Jensen A-SC, Davidsen L, Eriksen MA, Moller Hansen S, Nielsen BJ, Krogager ML, Kober L, Torp-Pedersen C, Sogaard P. Associations of serum potassium levels with mortality in chronic heart failure patients. *Eur Heart J* England; 2017;**38**:2890–2896.
- Wester PO, Dyckner T. INTRACELLULAR ELECTROLYTES IN CARDIAC FAILURE. *Acta Med Scand* 1986;
- Guo H, Lee JD, Ueda T, Wang J, Lu D, He H, Shan J. Different clinical features, biochemical profiles, echocardiographic and electrocardiographic findings in older and younger patients with idiopathic dilated

- Ahmed A, Zannad F, Love TE, Tallaj J, Gheorghiade M, Ekundayo OJ, Pitt B. A propensity-matched study of the association of low serum potassium levels and mortality in chronic heart failure. *Eur Heart J* Department of Medicine, University of Alabama at Birmingham, 1530 Third Avenue South, Birmingham, AL 35294-2041, USA. aahmed@uab.edu; 2007;**28**:1334–1343.
- Bowling CB, Pitt B, Ahmed MI, Aban IB, Sanders PW, Mujib M, Campbell RC, Love TE, Aronow WS, Allman RM, Bakris GL, Ahmed A. Hypokalemia and outcomes in patients with chronic heart failure and chronic kidney disease: findings from propensity-matched studies. *Circ Heart Fail* 2010;**3**:253–260.
- Collins AJ, Pitt B, Reaven N, Funk S, McGaughey K, Wilson D, Bushinsky DA. Association of Serum Potassium with All-Cause Mortality in Patients with and without Heart Failure, Chronic Kidney Disease, and/or Diabetes. *Am J Nephrol* Switzerland; 2017;**46**:213–221.
- Cooper LB, Benson L, Mentz R, Savarese G, DeVore A, Carrero JJ, Dahlstrom U, Anker S, Lainscak M, Hernandez A, Pitt B, Lund L. ASSOCIATION BETWEEN SERUM POTASSIUM LEVEL AND OUTCOMES IN HEART FAILURE WITH REDUCED EJECTION FRACTION: A COHORT STUDY FROM THE SWEDISH HEART FAILURE REGISTRY. *J Am Coll Cardiol* 2017;**69**:678.
- Franse L V, Pahor M, Bari M Di, Somes GW, Cushman WC, Applegate WB. Hypokalemia associated with diuretic use and cardiovascular events in the Systolic Hypertension in the Elderly Program. *Hypertens (Dallas, Tex 1979)* United States; 2000;**35**:1025–1030.
- Krogager ML, Torp-Pedersen C, Mortensen RN, Køber L, Gislason G, Søgaard P, Aasbjerg K. Short-term mortality risk of serum potassium levels in hypertension: a retrospective analysis of nationwide registry data. *Eur Heart J* 2017;**38**:104–112.
- Krogager ML, Mortensen RN, Lund PE, Bøggild H, Hansen SM, Kragholm K, Aasbjerg K, Søgaard P, Torp-Pedersen C. Risk of developing hypokalemia in patients with hypertension treated with combination antihypertensive therapy. *Hypertension* 2020;
- Alderman MH, Piller LB, Ford CE, Probstfield JL, Oparil S, Cushman WC, Einhorn PT, Franklin SS, Papademetriou V, Ong ST, Eckfeldt JH, Furberg CD, Calhoun DA, Davis BR, Group A and L-LT to PHATCR. Clinical significance of incident hypokalemia and hyperkalemia in treated hypertensive patients in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. *Hypertension* Department of Epidemiology and Social Medicine, Albert Einstein College of Medicine, Bronx, NY, USA.; 2012;**59**:926–933.
- Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, Hua T, Laragh J, McInnes GT, Mitchell L, Plat F, Schork A, Smith B, Zanchetti A. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: The VALUE randomised trial. *Lancet* 2004;**363**:2022–2031.
- McCullough PA, Beaver TM, Bennett-Guerrero E, Emmett M, Fonarow GC, Goyal A, Herzog CA, Kosiborod M, Palmer BF. Acute and chronic cardiovascular effects of hyperkalemia: New insights into prevention and clinical management. *Rev. Cardiovasc. Med.* 2014.
- Gumz ML, Rabinowitz L, Wingo CS. An Integrated View of Potassium Homeostasis. *N. Engl. J. Med.* United States; 2015. p. 1787–1788.
- Elliott TL, Braun M. Electrolytes: Potassium Disorders. *FP Essent* United States; 2017;**459**:21–28.
- Weiner ID, Linas SL, Wingo and CS. Comprehensive Clinical Nephrology. 6th ed. Elsevier - Health

- 26

41. Chua CE, Choi E, Khoo EYH. ECG changes of severe hypokalemia. *QJM* 2018;
42. Cohn JN, Kowey PR, Whelton PK, Prisant LM. New guidelines for potassium replacement in clinical practice: a contemporary review by the National Council on Potassium in Clinical Practice. *Arch Intern Med* 2000;**160**:2429–2436.
43. Rosano GMC, Tamargo J, Kjeldsen KP, Lainscak M, Agewall S, Anker SD, Ceconi C, Coats AJS, 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 o. *Eur Hear journal Cardiovasc Pharmacother* England; 2018;**4**:180–188.
44. Asirvatham JR, Moses V, Bjornson L. Errors in potassium measurement: a laboratory perspective for the clinician. *N Am J Med Sci India*; 2013;**5**:255–259.
45. Drogies T, Ittermann T, Lüdemann J, Klink D, Kohlmann T, Lubenow N, Greinacher A, Völzke H, Nauck M. Potassium - Reference intervals for lithium-heparin plasma and serum from a population-based cohort. *LaboratoriumsMedizin* 2010;**34**:39–44.
46. Cooper LB, Savarese G, Carrero JJ, Szabo B, Jernberg T, Jonsson Å, Dahlbom C, Dahlström U, Larson A, Lund LH. Clinical and research implications of serum versus plasma potassium measurements. *Eur J Heart Fail* 2018;1–2.
47. Burtis CA, Ashwood ER, Bruns DE. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 5th ed. St. Louis, Missouri, USA: Elsevier Saunders; 2012.
48. Rustad P, Felding P, Franzson L, Kairisto V, Lahti A, Martensson A, Hyltoft Petersen P, Simonsson P, Steensland H, Uldall A. The Nordic Reference Interval Project 2000: recommended reference intervals for 25 common biochemical properties. *Scand J Clin Lab Invest Furst Medical Laboratory, Soren Bulls vei 25, NO-1051 Oslo, Norway. prustad@furst.no*; 2004;**64**:271–284.
49. Marti G, Schwarz C, Leichtle AB, Fiedler GM, Arampatzis S, Exadaktylos AK, Lindner G. Etiology and symptoms of severe hypokalemia in emergency department patients. *Eur J Emerg Med* 2014;
50. Macdonald JE, Struthers AD. What is the optimal serum potassium level in cardiovascular patients? *J Am Coll Cardiol* Department of Clinical Pharmacology, Ninewells Hospital, Dundee, United Kingdom. macdonald_je@hotmail.com; 2004;**43**:155–161.
51. IOM. (Institute of Medicine). Dietary Reference Intakes for water, potassium, sodium, chloride and sulfate. B. Chapter. 2008.
52. Macdonald JE, Struthers AD. What is the optimal serum potassium level in cardiovascular patients? *J Am Coll Cardiol* 2004;**43**:155–161.
53. Palmer BF, Clegg DJ. Electrolyte and acid-base disturbances in patients with diabetes mellitus. *N. Engl. J. Med.* 2015.
54. Clausen T. Hormonal and pharmacological modification of plasma potassium homeostasis. *Fundam. Clin. Pharmacol.* 2010.
55. Ashurst J, Sergeant SR, Sergeant BR. Evidence-Based Management Of Potassium Disorders In The Emergency Department. *Emerg. Med. Pract.* 2016.
56. Kim GH, Han JS. Therapeutic approach to hypokalemia. *Nephron* 2002.

- Krogager ML, Eggers-Kaas L, Aasbjerg K, Mortensen RN, Køber L, Gislason G, Torp-Pedersen C, Søgaard P. Short-Term mortality risk of serum potassium levels in acute heart failure following myocardial infarction. *Eur Hear J - Cardiovasc Pharmacother* 2015;**1**.
- Pourmoghaddas A, Shemirani H, Garakyaraghi M. Association of serum potassium level with ventricular tachycardia after acute myocardial infarction. *ARYA Atheroscler* 2012;**8**:79–81.
- Toto RD. Serum Potassium and Cardiovascular Outcomes: The Highs and the Lows. *Clin J Am Soc Nephrol* 2017;**12**:220–221.
- Cohen JD, Neaton JD, Prineas RJ, Daniels KA. Diuretics, serum potassium and ventricular arrhythmias in the Multiple Risk Factor Intervention Trial. *Am J Cardiol* United States; 1987;**60**:548–554.
- Goyal A, Spertus JA, Gosch K, Venkitachalam L, Jones PG, Berghe G Van den, Kosiborod M. Serum potassium levels and mortality in acute myocardial infarction. *JAMA* United States; 2012;**307**:157–164.
- Krogager ML, Søgaard P, Torp-Pedersen C, Bøggild H, Lee CJ-Y, Bonde A, Thomassen JQ, Gislason G, Pareek M, Kragholm K. Impact of plasma potassium normalization on short-term mortality in patients with hypertension and hypokalemia or low normal potassium. *BMC Cardiovasc Disord* 2020;**20**:386.
- Cooper LB, Benson L, Mentz R, Savarese G, DeVore A, Carrero JJ, Dahlstrom U, Anker S, Lainscak M, Hernandez A, Pitt B, Lund L. ASSOCIATION BETWEEN SERUM POTASSIUM LEVEL AND OUTCOMES IN HEART FAILURE WITH REDUCED EJECTION FRACTION: A COHORT STUDY FROM THE SWEDISH HEART FAILURE REGISTRY. *J Am Coll Cardiol* 2017;
- Ferreira JP, Butler J, Rossignol P, Pitt B, Anker SD, Kosiborod M, Lund LH, Bakris GL, Weir MR, Zannad F. Abnormalities of Potassium in Heart Failure: JACC State-of-the-Art Review. *J. Am. Coll. Cardiol.* 2020.
- Matsushita K, Sang Y, Yang C, Ballew SH, Grams ME, Coresh J, Molnar MZ. Dyskalemia, its patterns, and prognosis among patients with incident heart failure: A nationwide study of US veterans. *PLoS One*. 2019.
- Linde C, Qin L, Bakhai A, Furuland H, Evans M, Ayoubkhani D, Palaka E, Bennett H, McEwan P. Serum potassium and clinical outcomes in heart failure patients: results of risk calculations in 21 334 patients in the UK. *ESC Hear Fail* 2019;**6**:280–290.
- Savarese G, Xu H, Trevisan M, Dahlström U, Rossignol P, Pitt B, Lund LH, Carrero JJ. Incidence, Predictors, and Outcome Associations of Dyskalemia in Heart Failure With Preserved, Mid-Range, and Reduced Ejection Fraction. *JACC Hear Fail* 2019;
- Bowling CB, Pitt B, Ahmed MI, Aban IB, Sanders PW, Mujib M, Campbell RC, Love TE, Aronow WS, Allman RM, Bakris GL, Ahmed A. Hypokalemia and outcomes in patients with chronic heart failure and chronic kidney disease: findings from propensity-matched studies. *Circ Fail Section of Geriatrics, VA Medical Center, Birmingham, Ala, USA.*; 2010;**3**:253–260.
- Aldahl M, Polcwiartek C, Davidsen L, Kragholm K, Søgaard P, Torp-Pedersen C, Krogager ML. Short-term prognosis of normalising serum potassium following an episode of hypokalaemia in patients with chronic heart failure. *Eur J Prev Cardiol* 2020;
- Núñez J, Bayés-Genís A, Zannad F, Rossignol P, Núñez E, Bodí V, Miñana G, Santas E, Chorro FJ, Mollar A, Carratalá A, Navarro J, Górriz JL, Lupón J, Husser O, Metra M, Sanchis J. Long-Term Potassium Monitoring and Dynamics in Heart Failure and Risk of Mortality. *Circulation* 2018;

87. Shiyovich A, Gilutz H, Plakht Y. Serum potassium levels and long-term post-discharge mortality in acute myocardial infarction. *Int. J. Cardiol. Netherlands*; 2014. p. e368-70.
88. Colombo MG, Kirchberger I, Amann U, Dinser L, Meisinger C. Association of serum potassium concentration with mortality and ventricular arrhythmias in patients with acute myocardial infarction: A systematic review and meta-analysis. *Eur J Prev Cardiol England*; 2018;**25**:576–595.
89. Xu H, Faxén J, Szummer K, Trevisan M, Kovesdy CP, Jernberg T, Carrero JJ. Dyskalemias and adverse events associated with discharge potassium in acute myocardial infarction. *Am Heart J* 2018;
90. Patel RB, Tannenbaum S, Viana-Tejedor A, Guo J, Im KA, Morrow DA, Scirica BM. Serum potassium levels, cardiac arrhythmias, and mortality following non-ST-elevation myocardial infarction or unstable angina: insights from MERLIN-TIMI 36. *Eur Hear journal Acute Cardiovasc care* 2017;
91. Ravn Jacobsen M, Jabbari R, Glinge C, Kjær Stampe N, Butt JH, Blanche P, Lønborg J, Wendelboe Nielsen O, Køber L, Torp-Pedersen C, Pedersen F, Tfelt-Hansen J, Engstrøm T. Potassium Disturbances and Risk of Ventricular Fibrillation Among Patients With ST-Segment–Elevation Myocardial Infarction. *J Am Heart Assoc* 2020;
92. Schmidt ST, Ditting T, Deutsch B, Schutte R, Friedrich S, Kistner I, Ott C, Raff U, Veelken R, Schmieder RE. Circadian rhythm and day to day variability of serum potassium concentration: a pilot study. *J Nephrol* 2015;
93. Li SH, Xie JT, Long HB, Zhang J, Zhou WD, Niu HX, Tang X, Feng ZL, Ye ZM, Zuo YY, Fu L, Wen F, Wang LP, Wang WJ, Shi W. Time-averaged serum potassium levels and its fluctuation associate with 5-year survival of peritoneal dialysis patients: Two-center based study. *Sci Rep* 2015;
94. Kovesdy CP. Fluctuations in plasma potassium in patients on dialysis. *Nephrol. Dial. Transplant.* 2019.
95. Shiyovich A, Gilutz H, Plakht Y. Potassium Fluctuations Are Associated With Inhospital Mortality From Acute Myocardial Infarction. Soroka Acute Myocardial Infarction II (SAMI-II) Project. *Angiology* 2018;**69**:709–717.
96. Engelhardt LJ, Balzer F, Müller MC, Grunow JJ, Spies CD, Christopher KB, Weber-Carstens S, Wollersheim T. Association between potassium concentrations, variability and supplementation, and in-hospital mortality in ICU patients: a retrospective analysis. *Ann Intensive Care* 2019;
97. Penhall RK, Frewin DB. Plasma potassium levels in hypertensive patients receiving fixed-combination diuretic therapy. *Med J Aust Australia*; 1980;**1**:376–378.
98. Lumme JAJ, Jounela AJ. Left ventricular mass, serum electrolyte levels and cardiac arrhythmias in patients with mild hypertension treated with cilazapril or hydrochlorothiazide. *Int J Cardiol* 1993;
99. Peters RW, Hamilton J, Hamilton BP. Incidence of cardiac arrhythmias associated with mild hypokalemia induced by low-dose diuretic therapy for hypertension. *South Med J* 1989;**82**:966—9, 976.
100. Lemieux G, Beauchemin M, Vinay P, Gougoux A. Hypokalemia during the treatment of arterial hypertension with diuretics. *Can Med Assoc J* 1980;
101. Nicholls MG, Richards AM. Disease monitoring of patients with chronic heart failure. *Heart.* 2007.
102. Reed B, Sueta C. A Practical Guide for the Treatment of Symptomatic Heart Failure with Reduced Ejection Fraction (HFrEF). *Curr Cardiol Rev* 2014;

Update on management of hypokalemia and goals for the lower potassium level in patients with cardiovascular disease: A review endorsed by in collaboration with the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy

Maria Lukács Krogager¹, Kristian Kragholm^{1,2,3}, Jesper Qvist Thomassen⁴, Peter Søgaard¹, Basil S. Lewis⁵, Sven Wassmann⁶, Iris Baumgartner⁷, Claudio Ceconi⁸, Thomas Andersen Schmidt^{9,10}, Juan Carlos Kaski¹¹, Heinz Drexel^{12,13,14}, Anne Grete Semb¹⁵, Stefan Agewall^{16,17}, Alexander Niessner¹⁸, Gianluigi Savarese¹⁹, Keld Per Kjeldsen^{20,21}, Claudio Borghi²², Juan Tamargo²³, Christian Torp-Pedersen²⁴

Affiliations

¹ Department of Cardiology, Aalborg University hospital, Aalborg, Denmark.

² Department of Cardiology, Region Hospital North Jutland, Hjørring, Denmark.

³ Unit of Epidemiology and Biostatistics, Aalborg University Hospital, Aalborg, Denmark.

⁴ Department of Clinical Biochemistry, Copenhagen University Hospital (Rigshospitalet), Copenhagen, Denmark.

⁵ Lady Davis Carmel Medical Center and the Ruth and Bruce Rappaport School of Medicine, Technion-IIT, Haifa, Israel.

⁶ Cardiology Pasing, Munich, Germany and University of the Saarland, Homburg/Saar, Germany.

⁷ Department of Angiology, Bern University Hospital (Inselspital), Bern, Switzerland.

⁸ Department of Cardiology, Desenzano Del Garda Hospital, Italy.

⁹ Institute of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.

¹⁰ The Emergency Department, North Zealand University Hospital, Hillerød, Denmark.

¹¹ Molecular and Clinical Sciences Research Institute, St George's, University of London, London, UK.

¹² Vorarlberg Institute for Vascular Investigation and Treatment (VIVIT), Landeskrankenhaus, Feldkirch, Austria.

- ¹³ *Private University of the Principality of Liechtenstein, Triesen, Liechtenstein.*
- ¹⁴ *Drexel University College of Medicine, Philadelphia, PA, USA.*
- ¹⁵ *Preventive Cardio-Rheuma clinic, Department Rheumatology, Diakonhjemmet Hospital, Oslo, Norway*
- ¹⁶ *Department of Cardiology, Ullevål, Oslo University Hospital, Oslo, Norway.*
- ¹⁷ *Institute of Clinical Sciences, Søsterhjemmet, University of Oslo, Oslo, Norway.*
- ¹⁸ *Department of Internal Medicine II, Division of Cardiology, Medical University of Vienna, Vienna, Austria.*
- ¹⁹ *Division of Cardiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden.*
- ²⁰ *Department of Cardiology, Copenhagen University Hospital (Amager-Hvidovre), Copenhagen, Denmark.*
- ²¹ *Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Aalborg, Denmark.*
- ²² *Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy.*
- ²³ *Department of Pharmacology, School of Medicine, CIBERCV, University Complutense, 28040, Madrid, Spain.*
- ²⁴ *Department of Clinical Research, North Zealand University Hospital, Hillerød, Denmark.*

1. Introduction

Hypokalemia is common in patients with cardiovascular disease. In this review, we emphasize the importance of tight potassium regulation in patients with cardiovascular disease based on findings from observational studies. To enhance the understanding, we also describe the mechanisms of potassium homeostasis maintenance, the most common causes of hypokalemia and present strategies for monitoring and management of low potassium levels. We propose elevation of potassium in asymptomatic patients with lower normal concentrations and concurrent cardiovascular disease. These proposals are intended to assist clinicians until more evidence is available.

2. Epidemiology

Hypokalemia burden in the general population is difficult to estimate. Studies have shown that the prevalence of hypokalemia in hospitalized patients is between 14-40% with 5% of the patients exhibiting potassium levels below 3.0 mmol/L.¹⁻⁴ In an outpatient population undergoing laboratory testing, mild hypokalemia was found in almost 14%.²

Female sex, younger age, high estimated glomerular filtration rate, and baseline use of diuretics were associated with increased hypokalemia risk.⁵ Approximately 80% of the patients receiving diuretics experience hypokalemia at some point and many of the patients suffer from an associated systemic disease.⁶⁻⁹

2.1 Hypokalemia in patients with cardiovascular disease

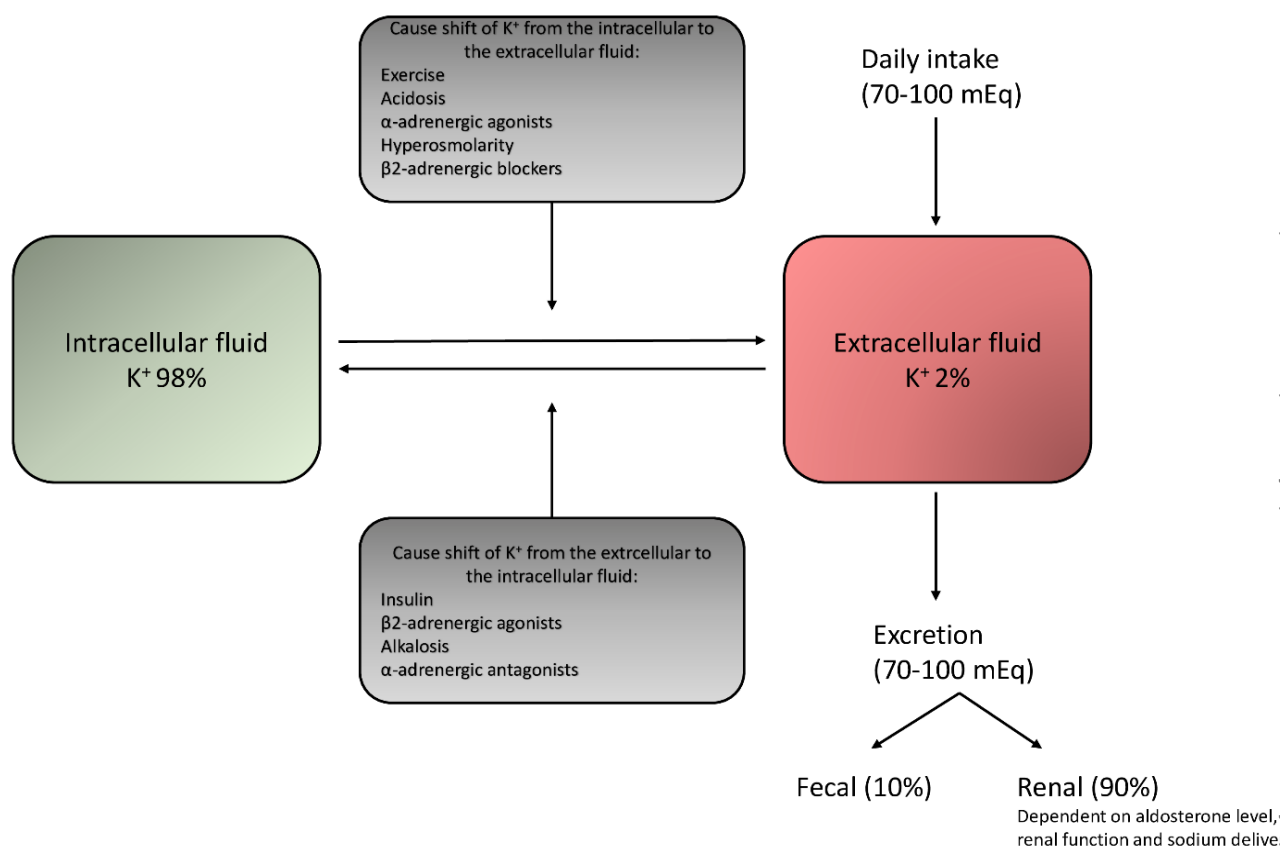
The prevalence of hypokalemia in patients with heart disease is high. However, it is important to acknowledge that the prevalence is highly dependent on time from diagnosis to potassium measurement, severity of the disease, concurrent comorbidities, definition of hypokalemia, magnitude of diuretic use in the study population and whether the studies were performed before/after the introduction of beta-blockers and renin-angiotensin-aldosterone system inhibitors as standard therapy for different cardiovascular diseases. Among patients with cardiovascular disease, the highest prevalence of hypokalemia was observed in patients with chronic heart

failure (incidence 3.0-54%),¹⁰⁻¹⁶ whereas in patients with hypertension studies had a prevalence between 3.8% and 7.2%¹⁷⁻¹⁹ and incidence 3.5-6.8%.^{20,21}

3. Potassium homeostasis

Potassium (K^+) is the most abundant cation in the human body (50-75 mmol/kg body weight). Under physiological conditions, 98% of K^+ is intracellular (~140-150 mmol/L) and 2% is found in the extracellular space (3.8-5.0 mmol/L).^{6,22,23} This large K^+ gradient between intracellular and extracellular compartments plays a key role in maintaining cell membrane potential, cellular excitability, conduction of nerve impulses, skeletal, cardiac and smooth muscle cell contraction, gastrointestinal motility, cellular osmolality, acid-base homeostasis, hormone secretion, mineralocorticoid action, renal concentrating ability, and fluid and electrolyte balance (Figure 1).^{23,24}

Figure 1. Regulation of intracellular and extracellular potassium shifts



Blood K⁺ levels are tightly regulated between 3.5 and 5.0 mmol/L by the coordinated interaction of physiological regulatory mechanisms, including a balance between absorption and excretion processes and the transfer of potassium between the extracellular and intracellular compartments, that maintain K⁺ homeostasis.^{23,25-27} The gastrointestinal absorption of dietary daily K⁺ intake (70-100 mEq) is completed and matched by the rapid exchange of K⁺ between the extracellular and intracellular compartments and equivalent increases in K⁺ excretion, 90% in the urine and the remaining 10% in feces. Thus, alternations in renal potassium secretion greatly affect potassium balance.

The kidney plays a central role in the maintenance of potassium homeostasis, until the glomerular filtration rate decreases to <15-20 mL/min. Potassium is filtered by the glomerulus and is reabsorbed in the proximal tubule (65%) and the Henle's loop (20%), but it can be reabsorbed or secreted by the distal tubule and collecting duct cells. The most important site of regulation is the renal collecting duct, where aldosterone receptors are present. When potassium intake is >150 mEq/day, about 50% of the excess potassium appears in the urine over the next several hours and most of the remainder is transferred into the intracellular compartment, so that only a modest (<10%) and transient increase in blood K⁺ concentration is observed.^{6,24,25,27}

When potassium intake falls or potassium renal or gastrointestinal losses increase, the activity of the Na⁺-K⁺-ATPase in the skeletal muscle and liver, which allows a net K⁺ "shift" from the intracellular fluid to the plasma.²⁸ A similar shift is induced by acidosis, hyperosmolarity, alpha-adrenergic agonists or strenuous exercise. Additionally, in an attempt to maintain normal potassium levels, hypokalemia results in insulin resistance which reduces K⁺ uptake into muscle cells, increases the reabsorption of K⁺ (via the increased activity of H⁺-K⁺-ATPase) and decreases aldosterone secretion leading to an increase in the reabsorption and a decrease in the tubular excretion of K⁺.

The normal potassium interval depends on whether potassium concentrations are determined in serum or plasma. Reported reference intervals for serum potassium in adults vary from 3.5 to 5.1 mmol/L and for plasma potassium from 3.3 to 4.9 mmol/L.²⁹ Values defined as "normal" potassium plasma concentration are based on measurements taken in apparently healthy individuals. Usually, reference intervals of apparently healthy individuals are set within the 2.5th and 97.5th centiles of the test result distribution.³⁰ Extrapolating the reference interval for healthy subjects into optimum range for patients with cardiovascular disease may not be appropriate.

Evidence regarding potassium monitoring and management in patients with heart disease is lacking and therefore current **recommendations proposals** are largely based on expert opinion rather than randomized controlled trials.

4. Hypokalemia: definition and common causes

Hypokalemia, defined as a serum or plasma $K^+ < 3.5$ mmol/L, is a common electrolyte disorder that may develop due to decreased K^+ intake, increased shift from the extracellular to the intracellular space or increased K^+ losses in the urine or through the gastrointestinal tract.³¹ Increased excretion is the most common mechanism, but several causes can coexist simultaneously. The kidney is able to lower potassium excretion to a minimum of 5-25 mmol/L/day in the presence of decreased potassium intake, so that decreased intake alone rarely causes significant hypokalemia. However, a low potassium intake contributes to the severity of hypokalemia when another cause of hypokalemia is present, such as diuretic therapy.

Hypokalemia can be classified as mild (serum $K^+ 3.0$ -3.4 mmol/L), moderate (serum $K^+ 2.5$ -2.9 mmol/L) or severe (serum $K^+ < 2.5$ mmol/L) and symptoms are more likely with increasing severity. Hypokalemia is not typically a disease by itself, but usually triggered by several common clinical conditions and/or a side effect of some drugs (Table 1). Among the latter, loop and thiazide diuretics are most frequently associated with hypokalemia in patients with cardiovascular disease.^{8,9} Yet, these drugs constitute an important pillar in management of hypertension and heart failure.^{32,33}

Table 1. Common drugs and conditions that may cause hypokalemia

Common drugs/conditions that may cause hypokalemia	
1. <i>Increased potassium excretion:</i>	
	<ul style="list-style-type: none"> • Thiazide/ Thiazide-like diuretics • Loop diuretics • Antimicrobials (aminoglycosides, penicillins) • Quetiapine • Cisplatin • Mineralocorticoids and glucocorticoids • Licorice • Heart failure • Conn's syndrome • Primary/secondary hyperaldosteronism • Cushing's syndrome

- Renovascular hypertension
- Vasculitis
- COVID-19
- Nephrogenic diabetes insipidus
- Hypomagnesemia
- Renal tubular acidosis: Fanconi syndrome, interstitial nephritis, metabolic alkalosis
- Genetic renal disorders
 - Congenital adrenal hyperplasia (11-beta hydroxylase or 17-alpha hydroxylase deficiency)
 - Bartter syndrome, Gitelman syndrome, Liddle syndrome, Gullner syndrome, Geller's syndrome
 - Familial hyperaldosteronism,
 - Apparent mineralocorticoid excess
 - Hypokalemic periodic paralysis, Thyrotoxic periodic paralysis
 - SeSAME syndrome (seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance)

2. *Shift from extracellular to intracellular space*

- Insulin (high dose/overdose)
- Beta₂-receptor agonists (albuterol, salbutamol, terbutaline)
- Xanthines (theophylline, aminophylline, caffeine)
- Ephedrine
- Poisoning (barium cesium, chloroquine)
- Verapamil (overdose)
- Alkalosis
- High stress conditions (post myocardial infarction, head injury)
- Refeeding syndrome after prolonged starvation
- Hyperthyroidism
- Familial periodic paralysis
- Delirium tremens
- Hypothermia

3. *Increased gastrointestinal loss*

- Vomiting
- Diarrhea
- Laxatives
- Inflammatory bowel disease
- Villous adenoma, short bowel syndrome

4. *Decreased potassium intake (<1g/day)*

- Deficient diet in alcoholics, elderly (e.g. "tea-and-toast" diet)
- Eating disorders (anorexia nervosa, bulimia, starvation, pica)
- Poverty

5. Hypokalemia: symptoms and risks

In most of the cases, patients with mild hypokalemia are asymptomatic. Moderate and severe hypokalemia may cause neuromuscular (muscle weakness, fatigue, eventually leading to ascending paralysis, acute respiratory failure due to diaphragmatic paralysis, rhabdomyolysis), gastrointestinal (nausea, vomiting, constipation, gastrointestinal hypomotility, ileus), renal (metabolic acidosis, polyuria) symptoms and cardiac rhythm abnormalities.⁷ Symptoms are usually reversible after the correction of the hypokalemia.

Hypokalemia reduces the repolarization reserve by decreasing several K^+ currents (inward rectifier- I_{K1} , delayed rectifier- I_{Kr} , and transient outward current- I_{to}) and increases the binding activity of I_{Kr} -inhibiting drugs.³⁴ In consequence, it prolongs action potential duration (QT interval), increases QT dispersion, slows intracardiac conduction, and induces abnormal pacemaker activity including early afterdepolarizations (trigger arrhythmias).³⁴ Cardiac arrhythmias represent the most serious complication of hypokalemia, particularly in people with underlying heart disease or treated with digitalis or antiarrhythmic drugs.^{35,36} Typical hypokalemia induced ECG changes are summarized in Table 2 and Figure 2 illustrates some of these changes.

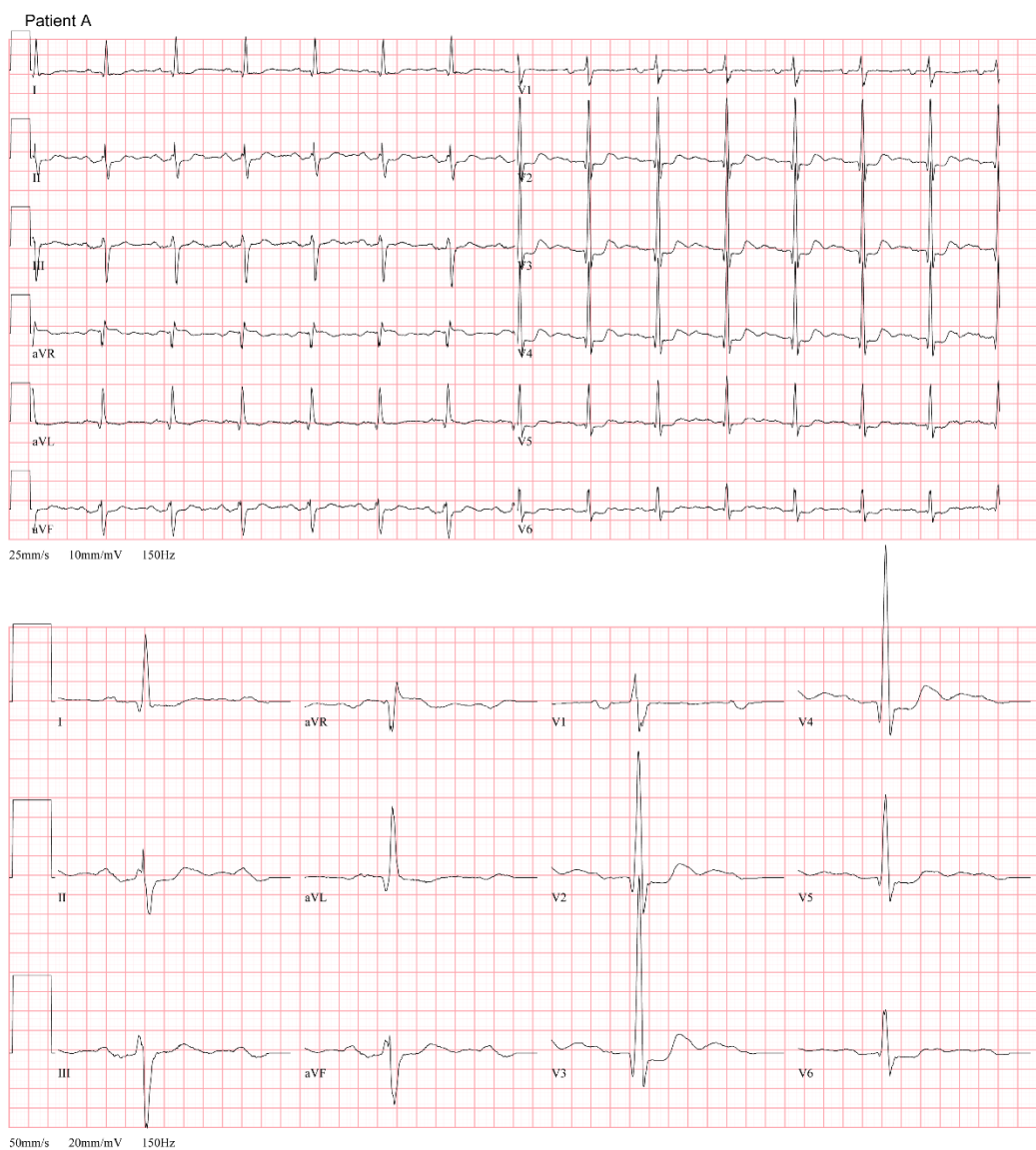
Table 2: Hypokalemia induced electrocardiographic changes stratified by intervals of potassium concentrations

Potassium interval	ECG findings
<3.5 mmol/L	Flattening or inversion of T-waves
<3.0 mmol/L	Q-T interval prolongation, U waves, decreased amplitude of the P wave, T-wave flattening, ST-interval depression, atrioventricular block (PR-interval prolongation) and ventricular extrasystoles

<2.5 mmol/L	Atrial fibrillation, multifocal atrial tachycardias, premature atrial and ventricular contractions, bradycardia, Torsade de Pointes, ventricular fibrillation.
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Potassium levels between 3.0–3.5 mmol/L cause ECG changes (flattening or inversion of T waves). Between 2.5–3.0 mmol/L, hypokalemia cause significant Q-T interval prolongation, U waves, decreased amplitude of the P wave, T-wave flattening, ST-interval depression (0.5 mm), atrioventricular block (PR-interval prolongation) and ventricular extrasystoles.^{37–40} Potassium levels <2.5 mmol/L are associated with atrial fibrillation and multifocal atrial tachycardias, premature atrial and ventricular contractions, bradycardia, Torsade de Pointes, ventricular fibrillation, syncope and sudden cardiac death and heart failure.⁴¹ The pro-arrhythmic risk of hypokalemia increases in patients with ischemic heart disease, heart failure, left ventricular hypertrophy or treated with digoxin or class I and III antiarrhythmic drugs. However, some patients with severe hypokalemia may have only minor ECG changes before clinically significant dysrhythmias, while maintaining K⁺ above 3.9 mmol/L reduces the risk of early ventricular fibrillation.⁴² Rapid correction of hypokalemia facilitates electrical defibrillation and reduces the incidence of further arrhythmias in the post-arrest period.

Figure 2. Electrocardiographic manifestations in patients with diuretic induced hypokalemia



Patient A. Female, 74 years, P(K) 2.8 mmol/L

ECG characteristics:

- Ventricular rate: 85 BPM
- PR interval: 198 ms
- QRS duration: 106 ms
- QT/QTc: 372/442 ms

ECG interpretation: sinus rhythm, T-wave flattening, ST-segment depression, U-waves (precordial leads), QTc-interval prolongation, slightly prolonged PR-interval

ECG characteristics: Ventricular rate: 57 BPM
PR interval: 160 ms
QRS duration: 98 ms
QT/QTc: 472/459 ms

6. Methods for potassium measurement

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- platelet rupture during coagulation
- mechanical factors such as tourniquet applied for more than 1 min, first clenching or inadequate sample handling
- chemical factors (ethanol)
- temperature (optimal temperature for specimen storage before testing is 15-25°C)
- patient factors such as hyperventilation and trombocytosis.⁴⁴

Differences in potassium reference intervals measured in serum and plasma have been shown to be substantial in patients with hyperkalemia (>0.5 mmol/L), whereas in patients with hypokalemia the lower reference level is similar in serum and plasma (difference <0.1 mmol/L).⁴⁵ Under ideal conditions of sample collection, plasma and serum potassium values are correlated. Yet, in daily clinical practice, samples may be obtained under nonoptimal conditions and conversion between the two methods may lead to erroneous assessments.⁴⁶

There is not a general consensus on a single reference interval for potassium in serum and in plasma. This is mainly due to variations between the study populations used for evaluation of potassium levels. Table 2 provides an overview of the most commonly used plasma and serum potassium reference intervals worldwide.

Table 3: Reference intervals (RI) for potassium in serum and plasma in different populations

Population	US (Tietz) ⁴⁷	German (Drogies) ⁴⁵	Nordic (Rustad) ⁴⁸
Plasma RI	3.4-4.8 mmol/L	3.5-4.6 mmol/L	3.5-4.4 mmol/L
Serum RI	3.5-5.1 mmol/L	3.7-5.1 mmol/L	3.6-4.6 mmol/L

In the present document, we refer to both plasma and serum potassium as K⁺, since it is unclear in many studies which method was used or some studies performed their analyses on K⁺ draws using both methods.

In order to differentiate between renal (e.g. diuretic therapy, primary aldosteronism) and non-renal (e.g. transcellular shifts, gastrointestinal losses) causes of hypokalemia urine electrolytes should be measured. An

arterial blood gas analysis is also useful to choose the appropriate strategy of potassium supplementation in case of acidosis or alkalosis.⁷ Other laboratory tests include magnesium, creatinine and glucose levels.

7. Management of hypokalemia

As the cause of hypokalemia can be multifactorial, the main therapeutic approach is the management of the underlying cause and/or correct the causative factors. Treatment of hypokalemia is determined by its severity and aetiology and the presence of symptoms and ECG abnormalities.

There are three main steps to consider for management of hypokalemia:

- 1) Identify (and treat) the underlying cause to prevent future episodes
- 2) Decrease potassium losses

The most common sites of potassium loss are within the renal and gastrointestinal system. Therefore, if applicable, ~~physicians should consider~~ **management strategies may include** avoiding laxatives, preventing/ceasing vomiting or diarrhea, using the lowest possible dose of thiazide or loop diuretics, replace diuretics (f.eg. hypertensive patients) with other equivalent drugs or combine with potassium-sparing diuretics when diuretic therapy is required (f.eg. heart failure) and treat hyperglycaemia if glycosuria is present.^{7,49}

- 3) Replenish potassium stores

- Mild hypokalaemia (3.0-3.4 mmol/L) can be managed by increasing dietary potassium intake (e.g. by consuming more fruits and vegetables) and/or by administering oral potassium supplements such as potassium chloride, potassium citrate and potassium phosphate. The Institute of Medicine recommends a potassium intake of 4.700 mg/d (120 mmol/d) for individuals older than 14 years.^{7,50,51} On average, a reduction of serum potassium by 1 mmol/l suggests a total body deficit of 300-400 mmol, but this is variable depending on body mass.²⁷ However, as potassium is predominantly an intracellular cation, serum/plasma K⁺ levels may not accurately reflect total body stores, and larger doses may be needed

to replenish potassium body stores. Often, the effectiveness of increasing dietary potassium is limited, because most of the potassium contained in foods is coupled with phosphate, whereas most cases of hypokalemia involve chloride depletion (e.g. hypokalemia associated to diuretic therapy or vomiting) and respond better to supplemental potassium chloride.^{27,52} Of note, modern food has a decreased potassium content and, as a consequence, mild hypokalemia is rather frequent among healthy subjects. Increased delivery of sodium to the distal nephron, which occurs with high sodium intake or loop diuretic therapy, promotes potassium excretion. Therefore, hypokalemia may also be minimized by salt restriction in the diet. Another strategy, particularly when they are indicated to treat a comorbidity, is the use of drugs that inhibit the renin-angiotensin-aldosterone system, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and mineralocorticoid receptor antagonists. Potassium-sparing diuretics should be used only in patients with normal renal function who are prone to significant hypokalemia. The use of potassium-sparing diuretics not only increases serum potassium levels, but can correct metabolic alkalosis.

- Patients with mild to moderate hypokalemia (2.5–3.4 mmol/L) may be treated with an oral formulation of potassium (potassium chloride, potassium phosphate, potassium bicarbonate), in divided doses over days to weeks administered with 100-250 mL of water with or after meals.⁵³ A dosage of 20 mmol/day of KCl is generally sufficient for the prevention of hypokalemia in patients receiving diuretic therapy or with hyperaldosteronism and from 40 to 100 mmol/day for its treatment. Each 10 mmol of KCl will increase K⁺ by 0.1 mmol/L.⁴² Adverse effects of potassium supplements affect primarily the gastrointestinal tract, and they include nausea, vomiting, diarrhea, flatulence, abdominal pain or discomfort and small bowel ulcerations. Microencapsulated formulations do not have unpleasant taste and are associated with a lower incidence of gastrointestinal adverse effects. ~~Potassium bicarbonate is recommended in patients with hypokalemia and metabolic acidosis.~~ **We suggest administration of potassium bicarbonate in patients with hypokalemia**

and metabolic acidosis. Hypomagnesemia is also frequently present in patients with clinically significant hypokalemia, particularly those treated with loop or thiazide diuretics.⁵⁴ In such cases, hypokalemia cannot be normalized until the hypomagnesemia has been corrected. Magnesium is required for potassium uptake and maintenance of intracellular potassium levels, particularly in the myocardium, and magnesium depletion enhances renal potassium excretion, impedes potassium repletion and may potentiate the risk of cardiac arrhythmias. Thus, serum magnesium levels should be corrected to achieve an adequate treatment of hypokalemia.⁵⁵

- For patients with symptomatic or severe hypokalemia (< 2.5 mmol/L) or with life-threatening arrhythmias or neuromuscular dysfunction, intravenous (i.v.) potassium should be given with continuous ECG monitoring, and serial potassium levels measurements to avoid overcorrection (hyperkalemia). Doses should be titrated based on repeated sampling of serum potassium levels. The i.v. administration is of choice in patients who are intolerant to the oral formulation, or in case of severe nausea, vomiting or abdominal diseases or when oral potassium supplements do not normalize the hypokalemia. In patients with hypokalemia related to renal or endocrine diseases, a multidisciplinary diagnostic and therapeutic approach is needed. In the absence of severe heart disease, potassium can be gradually replaced at a rate of 10 mmol/h in asymptomatic patients. The maximum recommended i.v. dose of potassium is 20 mmol/h, but higher rates using central venous catheters (up to 40 mmol/hour or 2 mmol/min for 10 min, followed by 10 mmol over 5-10 min) have been successful in emergency situations.^{56,57} Rapid i.v. bolus of potassium may precipitate cardiac arrest and should be avoided. Potassium should be diluted in 0.9% sodium chloride solution, but not in glucose, as 5% glucose stimulates insulin secretion and shifts of potassium into cells. A rapid normalization of hypokalemia can be achieved by combining oral (e.g., 20 to 40 mmol) and i.v. administration.⁵⁶ A summary of the principles of hypokalemia management is presented in Table 3.

³₂₆₉

Hypokalemia	Treatment	Comments
Bordeline (3.5-3.9 mmol/L)	<p>Dietary supplementation with potassium (fruit, vegetables, meat etc) in compliant patients.</p> <p>Oral KCl in patients treated with diuretics. Consider higher dose of KCl in patients treated with diuretics and KCl concomitantly.</p>	<p>Applies to patients with hypertension, cardiac arrhythmias, ischemic heart disease and chronic heart failure.</p>
Mild (3.0-3.4 mmol/L)	<p>Oral KCl: 10-20 mmol 3-4 times a day until K⁺ normalized</p> <p>40-100 mEq/day over a few days or weeks may be needed to fully replete potassium stores</p> <p>In case of hypokalemia + metabolic acidosis consider oral potassium bicarbonate 25 mmol may be used every 6-12h until K⁺ normalized</p>	<p>Each 10 mmol/L of KCl will increase K⁺ by 0.1 mmol/L</p> <p>Monitor K⁺ daily and adjust dose accordingly</p> <p>Patients should take potassium supplements with plenty of water to avoid gastrointestinal irritation</p> <p>Patients are usually asymptomatic</p>
Moderate (2.5-2.9 mmol/L)	<p>i.v. potassium supplementation through peripheral line: 10-20 mmol/h until K⁺ normalized or it is possible/safe to switch to oral potassium supplementa-tion</p> <p>Maximum of 40 mmol/h</p>	<p>Patients have no or minor symptoms</p> <p>Monitor plasma/serum K⁺ every 6-12h</p> <p>Continuous ECG monitoring</p> <p>Oral and i.v. potassium supplementation can be safely used simultaneously</p> <p>Each 10 mmol of i.v. potassium supplement will increase K⁺ by 0.05 mmol/L</p>
Severe (<2.5 mmol/L)	<p>i.v. potassium supplementation through central line: 20-40 mmol/h until K⁺ normalized and patient are asymptomatic</p> <p>If K⁺ <2.0 mmol/L or in the presence of life threatening symptoms: 40-80 mmol/h</p>	<p>Patients are usually symptomatic</p> <p>If case of acidosis administer potassium bicarbonate</p> <p>Test for hypomagnesemia. If the patient is hypomagnesemic: initially give 4 mL MgSO₄ 50% (8 mmol)</p>

		diluted in 10 mL of NaCl 0.9% over 20 min, then start first 40 mmol KCl infusion, followed by magnesium replacement Continuous ECG monitoring Monitor plasma/serum K ⁺ every hour High dose KCl can cause thrombophlebitis
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In current clinical practice, K⁺ supplementation is recommended in patients with concentrations below 3.5 mmol/L, even in asymptomatic patients with cardiovascular disease.¹ The National Council on Potassium in Clinical Practice recommends maintenance of K⁺ levels at a level of at least 4.0 mmol/L in patients with hypertension, cardiac arrhythmias, and chronic heart failure.¹

8. Goals for the lower potassium range among patients with cardiovascular disease: insights from population and observational studies

In 2004, MacDonald et al. suggested targets for K⁺ concentrations in patients with heart disease.⁵⁰ Based on available studies at that time (not a systematic review), the authors recommended the following serum potassium targets stratified on different cardiovascular diseases: hypertension 3.5-5.0 mmol/L, acute myocardial infarction and heart failure 4.5-5.5 mmol/L. However, many studies have been performed since. It is well known that low dietary K⁺ and/or low blood K⁺ concentrations increase the risk of developing hypertension, stroke and atrial/ventricular arrhythmias.⁵⁸⁻⁶⁸ Yet, in recent years, many studies investigating the impact of hypokalemia confirmed the association of low K⁺ concentrations with increased arrhythmia risk and all-cause and/or cardiovascular death in patients with different cardiovascular diseases.^{10,20,50,69-77} Nevertheless, large epidemiological studies also suggested that borderline hypokalemia or low normal K⁺ (3.5-3.7 mmol/L) levels

are also associated with increased mortality in patients with hypertension, atrial fibrillation/flutter, and acute and chronic heart failure.^{10,71–73}

In >44,000 patients treated with combination antihypertensive therapy, Krogager et al. found that K⁺ concentrations outside the interval 4.1–4.7 mmol/L were associated with increased 90-days mortality risk.¹⁸

Another study by the same first author showed that persistent hypokalemia (<3.5 mmol/L) was frequent and associated with increased all-cause and presumed cardiovascular death within 90-days. Additionally, the authors observed that 45% of the patients who had borderline hypokalemia at the first K⁺ measurement, developed hypokalemia at the second K⁺ blood sampling taken within 7–100 days from the first measurement.⁷⁸

Aldahl et al.¹⁰ performed similar analyses in approximately 20,000 patients with chronic heart failure and found that patients with K⁺ concentrations between 4.2–4.7 mmol/L had better prognosis within the first 90-days from the K⁺ measurement compared to patients with K⁺ levels outside this range. Similarly, Cooper et al. found an optimal potassium value of 4.2 mmol/L in patients with heart failure.⁷⁹ Other studies suggesting that borderline hypokalemia might be unfavorable in patients with heart failure were performed by Ferreira et al.⁸⁰ and Matsushita et al.⁸¹ The investigators observed that potassium levels starting below 4.0 mmol/L were associated with excess morbidity and mortality in heart failure. Numerous other studies have found an association between hypokalemia and mortality in patients with heart failure,^{15,16,82,83} but only few observed or investigated the impact of borderline hypokalemia (3.5–3.7 mmol/L) on mortality or other adverse events.^{10,15,16,84} Generally, most of the studies examining the relationship between K⁺ and mortality, categorize K⁺ in too broad intervals, so that a possible association might have been masked. A follow-up study on patients with chronic heart failure and initial hypokalemia showed that patients who remained hypokalemic had significantly higher 90-days all-cause mortality risk compared to patients with K⁺ levels in the middle of the reference interval.⁸⁵ Yet, it is important to consider that some of the patients might have had end-stage heart failure requiring particularly high dosage of diuretics. As such, hypokalemia might be a surrogate marker of severe heart failure. Núñez et al. also showed

that abnormal potassium concentrations were associated with increased risk of death compared to patients who maintained or returned to normokalemia.⁸⁶

As for patients with atrial fibrillation/flutter, Hagengaard et al.⁷² found that besides hypokalemia and hyperkalemia, K⁺ concentrations within the intervals 3.5-3.7 mmol/L and 4.5-5.0 mmol/L were associated with increased mortality risk compared to the reference group (4.1-4.4 mmol/L). Once more, low normal potassium levels were associated with adverse events.

In patients with myocardial infarction studies have shown that hypo- and hyperkalemia are associated with mortality.^{77,87-89} Moreover, few studies demonstrated U-shaped relationship between potassium and mortality in patients with myocardial infarction, indicating that a narrower potassium interval might apply this population as well.^{77,90} We also observed in patients with acute heart failure following myocardial infarction that besides hypo- and hyperkalemia, low normal and high normal K⁺ concentrations were associated with high risk of death.⁷³ As for the risk of ventricular fibrillation (VF), Jacobsen et al.⁹¹ showed that hypokalemia was associated with increased odds of VF during primary percutaneous coronary intervention.

It is also important to mention that rapid fluctuations of blood potassium concentrations either from low to high levels or the reverse are common among patients with heart disease and/or impaired renal function and that these dynamic changes are associated with increased mortality^{78,85,92-96}

Epidemiological studies cannot prove causation, only association. Therefore, upcoming randomized clinical trials will need to test whether stringent clinical control of K⁺ through monitoring and corrections might translate into actual benefits in clinical outcomes. However, considering current evidence, it seems that an optimal K⁺ interval in patients with cardiovascular disease is considerably narrower than the currently used RI and clinicians should not ignore borderline hypokalemia but target potassium concentrations in the middle of the reference interval.

Based on current studies, we ~~strongly recommend~~ **propose that** treatment (dietary and/or pharmacological) of

As patients with cardiovascular disease are at high risk of K⁺ imbalances due to the disease itself and the treatment involved, close monitoring of electrolytes **is appropriate** ~~are highly recommended~~. Evidence regarding the frequency of potassium monitoring in patients treated with diuretics is lacking. Small scale studies showed that hypokalemia typically develops within 2 to 19 weeks from start with diuretic treatment.^{97,98} Studies from the 1980's suggested that the decrease in K⁺ following diuretic treatment initiation is a transient phenomenon and that patients can normalize without therapy.^{99,100} Yet, it is important to acknowledge that hypokalemia can be multifactorial and the adverse effects of hypokalemia are strongly linked with the rapidity of onset and concurrent diseases. As such, there is not a consensus on how often potassium should be monitored in patients treated with diuretics and practices throughout the world are very different. In many European countries, patients with stable cardiac conditions, are typically followed and monitored 2-3 times a year. Normal K⁺ concentration before cardiovascular drug treatment initiation is warranted. Guidelines on management of arterial hypertension and acute and chronic heart failure do contain sections on patient follow-up where different factors/aspects need to be assessed.^{32,33} Yet, no specific information about potassium monitoring is available in these guidelines. Table 4 provides **proposals** ~~recommendations~~ based on expert opinions on monitoring and follow-up of patients with cardiovascular disease.

Cardiopathy subgroups	Proposed patient follow-up	Comments
Hypertension	Patients should be evaluated at least once within the first 2 months after the initiation of antihypertensive drug therapy.	Evaluate high blood pressure related symptoms, electrolyte status and kidney function and record an electrocardiogram.

	<p>After blood pressure target is reached a visit interval between 3-6 months can be agreed with the patient.</p> <p>At least every 2 years physicians should also assess hypertension's effects on different organs and risk factors for hypertension and associated comorbidities³²</p>	Evaluate high blood pressure related symptoms, electrolyte status and kidney function and record an electrocardiogram
Heart failure		
<i>Treatment initiation/up-titration phase</i>	<p>Patients should be evaluated every 1-2 weeks (or every 1-2 days in hospitalized patients) concerning volume status, symptoms, heart failure signs, potassium and renal function and titration of heart failure drugs.</p>	In this phase hypokalemia is common due to high dose diuretic administration to relieve symptoms of fluid overload.
<i>Stable heart failure</i>	<p>Patients with stable heart failure can be monitored every 3-6 months where plasma electrolytes and function should be assessed in line with patient understanding of the disease, their symptoms, precipitating factors, concomitant disorders, body weight, signs of fluid overload, heart rate and rhythm and blood pressure.^{33,101,102}</p>	In patients with stable heart failure hyperkalemia is most commonly encountered due to different factors such as medication (ACEIs, ARBs, potassium sparing diuretics) or deterioration of kidney function.

10. Conclusions

- Hypokalemia is associated with a high risk of adverse events and notably this is found not only with severe hypokalemia, but also with mild hypokalemia (3.0-3.5 mmol/L) and low normal potassium concentrations (<4.0 mmol/L).
- Current laboratory values for normal potassium are based on 95% confidence limits of apparently healthy people. Physicians need to be aware that these confidence limits do not necessarily reflect safety limits.

- Any treatment that is associated with a risk of hypokalemia requires regular monitoring of potassium, but currently it is not possible to provide evidence-based guidelines for frequency of monitoring and cut-off values for intervention.
- Given the frequent use of treatments that are associated with hypokalemia and the high risk of potassium disturbances there is an urgent need for randomised studies that address frequency of monitoring and cut-off values for intervention as well as further observational studies to delineate safety levels of potassium for a range of cardiovascular disease.

11. References

- Cohn JN, Kowey PR, Whelton PK, Prisant LM. New guidelines for potassium replacement in clinical practice: a contemporary review by the National Council on Potassium in Clinical Practice. *Arch Intern Med United States*; 2000;**160**:2429–2436.
- Dhondup T, Qian Q. Acid-Base and Electrolyte Disorders in Patients with and without Chronic Kidney Disease: An Update. *Kidney Dis (Basel, Switzerland)* Switzerland; 2017;**3**:136–148.
- Udendi UK, Tchounwou PB. Potassium Homeostasis, Oxidative Stress, and Human Disease. *Int J Clin Exp Physiol India*; 2017;**4**:111–122.
- Liamis G, Rodenburg EM, Hofman A, Zietse R, Stricker BH, Hoorn EJ. Electrolyte disorders in community subjects: Prevalence and risk factors. *Am J Med* 2013;**126**:256–263.
- Nilsson E, Gasparini A, Ärnlöv J, Xu H, Henriksson KM, Coresh J, Grams ME, Carrero JJ. Incidence and determinants of hyperkalemia and hypokalemia in a large healthcare system. *Int J Cardiol* 2017;**245**:277–284.
- Alfonzo AVM, Isles C, Geddes C, Deighan C. Potassium disorders--clinical spectrum and emergency management. *Resuscitation Ireland*; 2006;**70**:10–25.
- Kardalas E, Paschou SA, Anagnostis P, Muscogiuri G, Siasos G, Vryonidou A. Hypokalemia: a clinical update. *Endocr Connect* England; 2018;**7**:R135–R146.
- Kapelios CJ, Malliaras K, Kaldara E, Vakrou S, Nanas JN. Loop diuretics for chronic heart failure: A foe in disguise of a friend? *Eur. Hear. J. - Cardiovasc. Pharmacother.* 2018.
- Marciniak TA. What are the pharmacodynamics of loop diuretics? *Eur. Hear. J. - Cardiovasc. Pharmacother.* 2019.
- Aldahl M, Jensen A-SC, Davidsen L, Eriksen MA, Møller Hansen S, Nielsen BJ, Krogager ML, Kober L, Torp-Pedersen C, Sogaard P. Associations of serum potassium levels with mortality in chronic heart failure patients. *Eur Heart J* England; 2017;**38**:2890–2896.

- 26

40. Krogager ML, Kragholm K, Skals RK, Mortensen RN, Polcwiartek C, Graff C, Nielsen JB, Kanters JK, Holst AG, Sogaard P, Pietersen A, Torp-Pedersen C, Hansen SM. The relationship between serum potassium concentrations and electrocardiographic characteristics in 163,547 individuals from primary care. *J Electrocardiol United States*; 2019;**57**:104–111.
41. Chua CE, Choi E, Khoo EYH. ECG changes of severe hypokalemia. *QJM* 2018;
42. Cohn JN, Kowey PR, Whelton PK, Prisant LM. New guidelines for potassium replacement in clinical practice: a contemporary review by the National Council on Potassium in Clinical Practice. *Arch Intern Med* 2000;**160**:2429–2436.
43. Rosano GMC, Tamargo J, Kjeldsen KP, Lainscak M, Agewall S, Anker SD, Ceconi C, Coats AJS, 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 o. *Eur Hear journal Cardiovasc Pharmacother* England; 2018;**4**:180–188.
44. Asirvatham JR, Moses V, Bjornson L. Errors in potassium measurement: a laboratory perspective for the clinician. *N Am J Med Sci India*; 2013;**5**:255–259.
45. Drogies T, Ittermann T, Lüdemann J, Klink D, Kohlmann T, Lubenow N, Greinacher A, Völzke H, Nauck M. Potassium - Reference intervals for lithium-heparin plasma and serum from a population-based cohort. *LaboratoriumsMedizin* 2010;**34**:39–44.
46. Cooper LB, Savarese G, Carrero JJ, Szabo B, Jernberg T, Jonsson Å, Dahlbom C, Dahlström U, Larson A, Lund LH. Clinical and research implications of serum versus plasma potassium measurements. *Eur J Heart Fail* 2018;1–2.
47. Burtis CA, Ashwood ER, Bruns DE. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 5th ed. St. Louis, Missouri, USA: Elsevier Saunders; 2012.
48. Rustad P, Felding P, Franzson L, Kairisto V, Lahti A, Martensson A, Hyltoft Petersen P, Simonsson P, Steensland H, Uldall A. The Nordic Reference Interval Project 2000: recommended reference intervals for 25 common biochemical properties. *Scand J Clin Lab Invest Furst Medical Laboratory, Soren Bulls vei 25, NO-1051 Oslo, Norway. prustad@furst.no*; 2004;**64**:271–284.
49. Marti G, Schwarz C, Leichtle AB, Fiedler GM, Arampatzis S, Exadaktylos AK, Lindner G. Etiology and symptoms of severe hypokalemia in emergency department patients. *Eur J Emerg Med* 2014;
50. Macdonald JE, Struthers AD. What is the optimal serum potassium level in cardiovascular patients? *J Am Coll Cardiol* Department of Clinical Pharmacology, Ninewells Hospital, Dundee, United Kingdom. macdonald_je@hotmail.com; 2004;**43**:155–161.
51. IOM. (Institute of Medicine). Dietary Reference Intakes for water, potassium, sodium, chloride and sulfate. B. Chapter. 2008.
52. Macdonald JE, Struthers AD. What is the optimal serum potassium level in cardiovascular patients? *J Am Coll Cardiol* 2004;**43**:155–161.
53. Palmer BF, Clegg DJ. Electrolyte and acid-base disturbances in patients with diabetes mellitus. *N. Engl. J. Med.* 2015.
54. Clausen T. Hormonal and pharmacological modification of plasma potassium homeostasis. *Fundam.*

Clin. Pharmacol. 2010.

55. Ashurst J, Sergeant SR, Sergeant BR. Evidence-Based Management Of Potassium Disorders In The Emergency Department. *Emerg. Med. Pract.* 2016.
56. Kim GH, Han JS. Therapeutic approach to hypokalemia. *Nephron* 2002.
57. 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2005;
58. Ascherio A, Rimm EB, Hernan MA, Giovannucci EL, Kawachi I, Stampfer MJ, Willett WC. Intake of potassium, magnesium, calcium, and fiber and risk of stroke among US men. *Circulation* United States; 1998;**98**:1198–1204.
59. Khaw KT, Barrett-Connor E. Dietary potassium and stroke-associated mortality. A 12-year prospective population study. *N Engl J Med* United States; 1987;**316**:235–240.
60. Dyckner T, Helmers C, Lundman T, Wester PO. Initial serum potassium level in relation to early complications and prognosis in patients with acute myocardial infarction. *Acta Med Scand* 1975;**197**:207–210.
61. Krishna GG, Kapoor SC. Potassium depletion exacerbates essential hypertension. *Ann Intern Med* United States; 1991;**115**:77–83.
62. Ascherio A, Hennekens C, Willett WC, Sacks F, Rosner B, Manson J, Witteman J, Stampfer MJ. Prospective study of nutritional factors, blood pressure, and hypertension among US women. *Hypertens (Dallas, Tex 1979)* United States; 1996;**27**:1065–1072.
63. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. Intersalt Cooperative Research Group. *BMJ* England; 1988;**297**:319–328.
64. Geleijnse JM, Witteman JC, Breeijen JH den, Hofman A, Jong PT de, Pols HA, Grobbee DE. Dietary electrolyte intake and blood pressure in older subjects: the Rotterdam Study. *J Hypertens* England; 1996;**14**:737–741.
65. Whelton PK, He J, Cutler JA, Brancati FL, Appel LJ, Follmann D, Klag MJ. Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials. *JAMA* United States; 1997;**277**:1624–1632.
66. Duke M. Thiazide-induced hypokalemia. Association with acute myocardial infarction and ventricular fibrillation. *JAMA* United States; 1978;**239**:43–45.
67. Solomon RJ, Cole AG. Importance of potassium in patients with acute myocardial infarction. *Acta Med Scand Suppl* Sweden; 1981;**647**:87–93.
68. Hulting J. In-hospital ventricular fibrillation and its relation to serum potassium. *Acta Med Scand Suppl* Sweden; 1981;**647**:109–116.
69. Skogestad J, Aronsen JM. Hypokalemia-Induced Arrhythmias and Heart Failure: New Insights and Implications for Therapy. *Front Physiol* Switzerland; 2018;**9**:1500.
70. Krijthe BP, Heeringa J, Kors JA, Hofman A, Franco OH, Witteman JC, Stricker BH. Serum potassium levels and the risk of atrial fibrillation: the Rotterdam Study. *Int J Cardiol* 2013;**168**:5411–5415.

71. Krogager ML, Torp-Pedersen C, Mortensen RN, Køber L, Gislason G, Søgaard P, Aasbjerg K. Short-term mortality risk of serum potassium levels in hypertension: A retrospective analysis of nationwide registry data. *Eur Heart J* 2017;**38**.
72. Hagengaard L, Sogaard P, Espersen M, Sessa M, Lund PE, Krogager ML, Torp-Pedersen C, Kragholm KH, Polcwiartek C. Association Between Serum Potassium Levels and Short-Term Mortality in Patients With Atrial Fibrillation or Flutter Co-treated With Diuretics and Rate- or Rhythm-Controlling Drugs. *Eur Hear journal Cardiovasc Pharmacother* England; 2019;
73. Krogager ML, Eggers-Kaas L, Aasbjerg K, Mortensen RN, Køber L, Gislason G, Torp-Pedersen C, Søgaard P. Short-Term mortality risk of serum potassium levels in acute heart failure following myocardial infarction. *Eur Hear J - Cardiovasc Pharmacother* 2015;**1**.
74. Pourmoghaddas A, Shemirani H, Garakyaraghi M. Association of serum potassium level with ventricular tachycardia after acute myocardial infarction. *ARYA Atheroscler* 2012;**8**:79–81.
75. Toto RD. Serum Potassium and Cardiovascular Outcomes: The Highs and the Lows. *Clin J Am Soc Nephrol* 2017;**12**:220–221.
76. Cohen JD, Neaton JD, Prineas RJ, Daniels KA. Diuretics, serum potassium and ventricular arrhythmias in the Multiple Risk Factor Intervention Trial. *Am J Cardiol* United States; 1987;**60**:548–554.
77. Goyal A, Spertus JA, Gosch K, Venkitachalam L, Jones PG, Berghe G Van den, Kosiborod M. Serum potassium levels and mortality in acute myocardial infarction. *JAMA* United States; 2012;**307**:157–164.
78. Krogager ML, Søgaard P, Torp-Pedersen C, Bøggild H, Lee CJ-Y, Bonde A, Thomassen JQ, Gislason G, Pareek M, Kragholm K. Impact of plasma potassium normalization on short-term mortality in patients with hypertension and hypokalemia or low normal potassium. *BMC Cardiovasc Disord* 2020;**20**:386.
79. Cooper LB, Benson L, Mentz R, Savarese G, DeVore A, Carrero JJ, Dahlstrom U, Anker S, Lainscak M, Hernandez A, Pitt B, Lund L. ASSOCIATION BETWEEN SERUM POTASSIUM LEVEL AND OUTCOMES IN HEART FAILURE WITH REDUCED EJECTION FRACTION: A COHORT STUDY FROM THE SWEDISH HEART FAILURE REGISTRY. *J Am Coll Cardiol* 2017;
80. Ferreira JP, Butler J, Rossignol P, Pitt B, Anker SD, Kosiborod M, Lund LH, Bakris GL, Weir MR, Zannad F. Abnormalities of Potassium in Heart Failure: JACC State-of-the-Art Review. *J. Am. Coll. Cardiol.* 2020.
81. Matsushita K, Sang Y, Yang C, Ballew SH, Grams ME, Coresh J, Molnar MZ. Dyskalemia, its patterns, and prognosis among patients with incident heart failure: A nationwide study of US veterans. *PLoS One*. 2019.
82. Linde C, Qin L, Bakhai A, Furuland H, Evans M, Ayoubkhani D, Palaka E, Bennett H, McEwan P. Serum potassium and clinical outcomes in heart failure patients: results of risk calculations in 21 334 patients in the UK. *ESC Hear Fail* 2019;**6**:280–290.
83. Savarese G, Xu H, Trevisan M, Dahlström U, Rossignol P, Pitt B, Lund LH, Carrero JJ. Incidence, Predictors, and Outcome Associations of Dyskalemia in Heart Failure With Preserved, Mid-Range, and Reduced Ejection Fraction. *JACC Hear Fail* 2019;
84. Bowling CB, Pitt B, Ahmed MI, Aban IB, Sanders PW, Mujib M, Campbell RC, Love TE, Aronow WS, Allman RM, Bakris GL, Ahmed A. Hypokalemia and outcomes in patients with chronic heart failure and chronic kidney disease: findings from propensity-matched studies. *Circ Fail Section of Geriatrics, VA Medical Center, Birmingham, Ala, USA.*; 2010;**3**:253–260.

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hypertension with diuretics. *Can Med Assoc J* 1980;

101. Nicholls MG, Richards AM. Disease monitoring of patients with chronic heart failure. *Heart*. 2007.
102. Reed B, Sueta C. A Practical Guide for the Treatment of Symptomatic Heart Failure with Reduced Ejection Fraction (HFrEF). *Curr Cardiol Rev* 2014;