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 Krogager[1], Kristian Kragholm[1,2,3], Jesper Qvist Thomassen;[4], Peter Søgaard[1], Basil S. Lewis[5], Sven Wassmann[6], Iris Baumgartner[7], Claudio Ceconi [8], Thomas Andersen Schmidt[9,10], Juan Carlos Kaski[11], Heinz Drexel[12,13,14], Anne Grete Semb[15], Stefan Agewall[16,17], Alexander Niessner[18],Gianluigi Savarese[19], Keld Per Kjeldsen[20,21], Claudio Borghi[22], Juan Tamargo[23],Christian Torp-Pedersen[24]

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.

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[15] *Preventive Cardio-Rheuma clinic, Depatment 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 Instituttet, 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.*

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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

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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]

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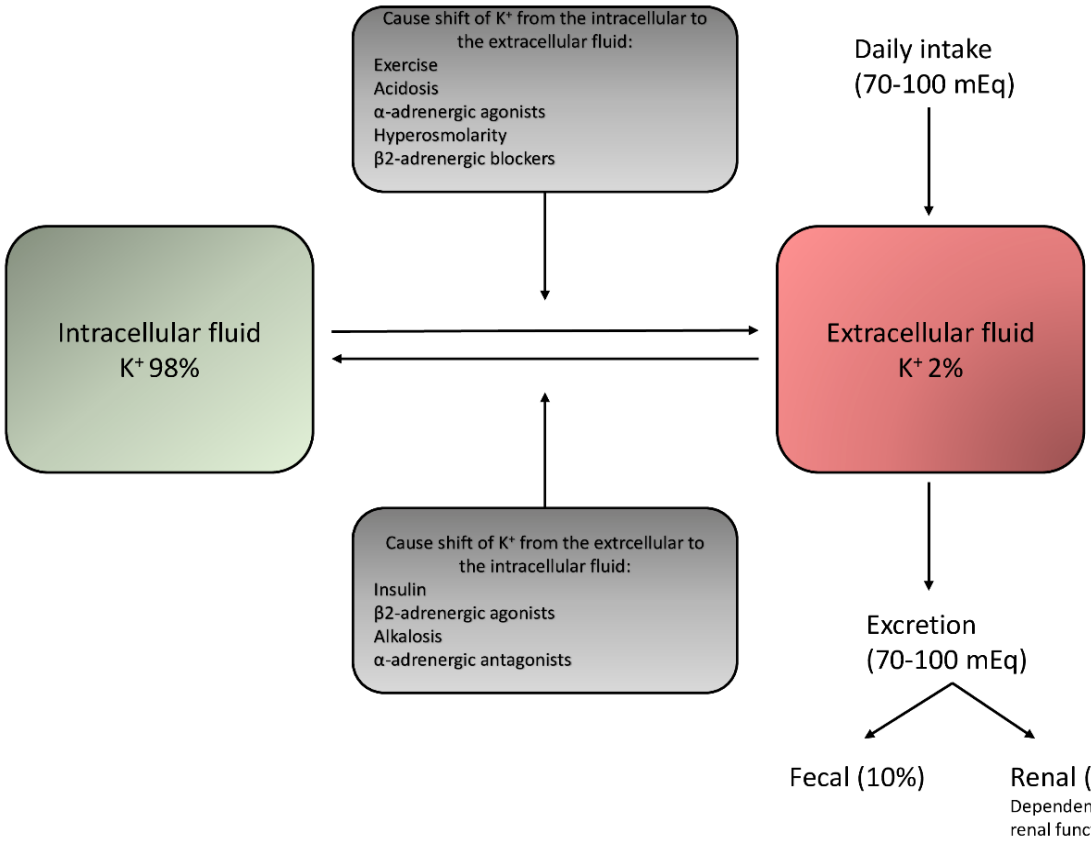
Figure 1. Regulation of intracellular and extracellular potassium shifts



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.

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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.

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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. *Increased potassium excretion:* • 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

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- 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)
    - $Beta_2$-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

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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

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<2.5 mmol/L	Atrial fibrillation, multifocal atrial tachycardias, premature atrial and ventricular contractions, bradycardia, Torsade de Pointes, ventricular fibrillation.

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.

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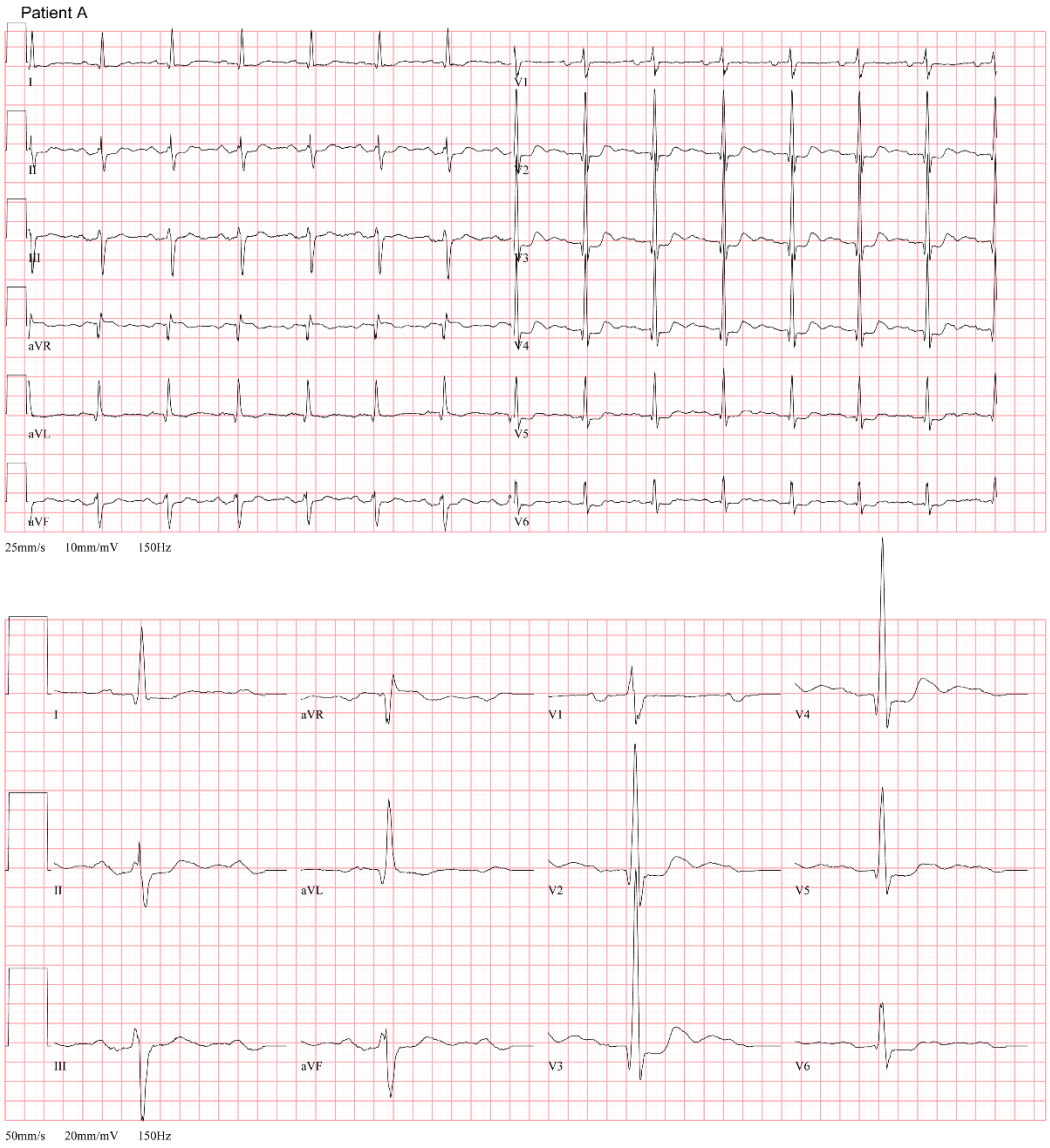
Figure 2. Electrocardiographic manifestations in patients with diuretic induced hypokalemia



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

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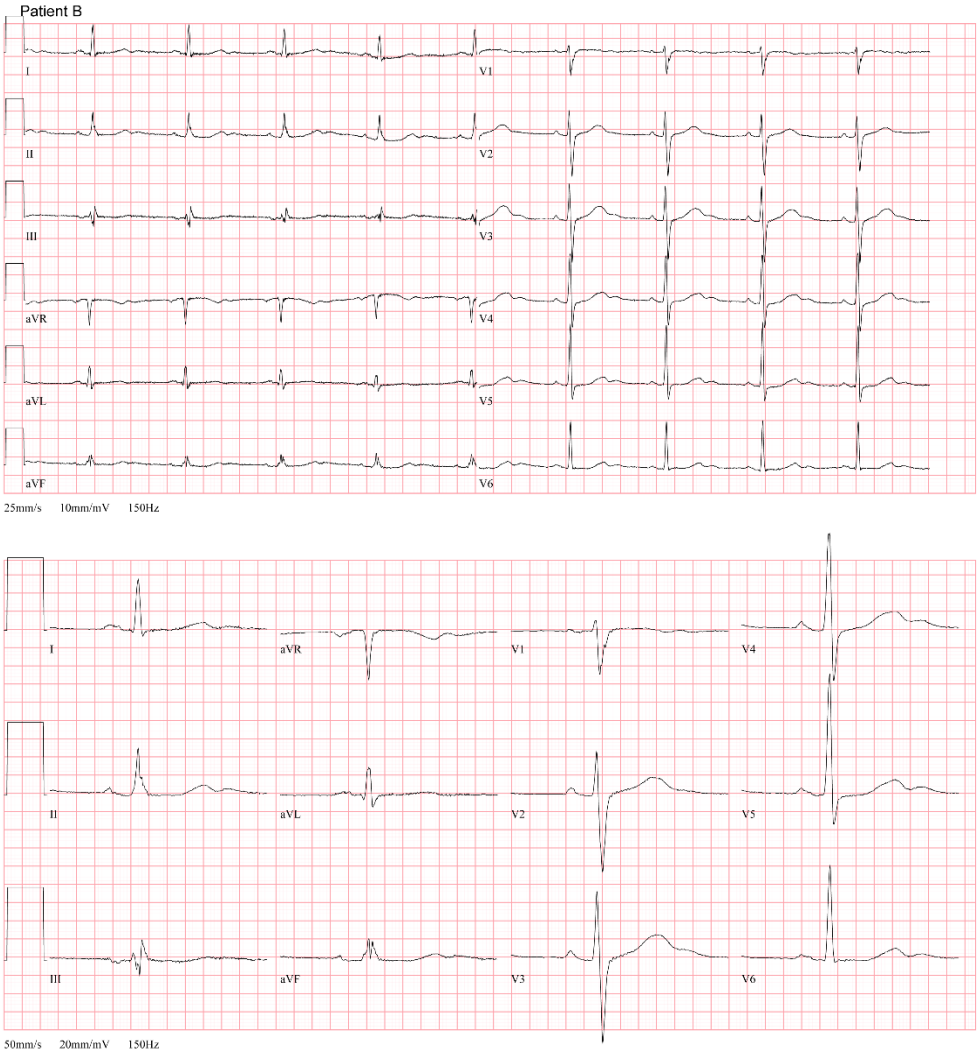

Patient B. Male, 62 years, P(K) 2.9 mmol/L

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 psedohyperkalemia (falsely elevated potassium concentrations) are:

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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

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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

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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

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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.

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Table 4. Proposals for the treatment of hypokalemia

Hypokalemia	Treatment	Comments
Bordeline (3.5-3.9 mmol/L)	Dietary supplementation with potassium (fruit, vegetables, meat etc) in compliant patients. Oral KCl in patients treated with diuretics. Consider higher dose of KCl in patients treated with diuretics and KCl concomitantly.	Applies to patients with hypertension, cardiac arrhythmias, ischemic heart disease and chronic heart failure.
Mild (3.0-3.4 mmol/L)	Oral KCl: 10-20 mmol 3-4 times a day until K^+ normalized 40-100 mEq/day over a few days or weeks may be needed to fully replete potassium stores In case of hypokalemia + metabolic acidosis oral potassium bicarbonate 25 mmol may be used every 6-12h until K^+ normalized	Each 10 mmol/L of KCl will increase K^+ by 0.1 mmol/L Monitor K^+ daily and adjust dose accordingly Patients should take potassium supplements with plenty of water to avoid gastrointestinal irritation Patients are usually asymptomatic
Moderate (2.5-2.9 mmol/L)	i.v. potassium supplementation through peripheral line: 10-20 mmol/h until K^+ normalized or it is possible/safe to switch to oral potassium supplemen-tation Maximum of 40 mmol/h	Patients have no or minor symptoms Monitor plasma/serum K^+ every 6-12h Continuous ECG monitoring Oral and i.v. poassium supplementation can be safely used simultaneously Each 10 mmol of i.v. potassium supplement will increase K^+ by 0.05 mmol/L
Severe (<2.5 mmol/L)	i.v. potassium supplementation through central line: 20-40 mmol/h until K^+ normalized and patient are asymptomatic If K^+ <2.0 mmol/L or in the presence of life threatening symptoms: 40-80 mmol/h	Patients are usually symptomatic If case of acidosis administer potassium bicarbonate Test for hypomagnesemia. If the patients is hypomagnesemic: initially give 4 mL $MgSO_4$ 50% (8 mmol) diluted in 10 mL of NaCl 0.9% over 20 min, then start first 40 mmol KCl

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		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]

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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]

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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.

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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. After blood pressure target is reached a visit interval between 3-6 months can be agreed with the patient. At least every 2 years physicians should also assess hypertension's effects on different organs and risk	Evaluate high blood pressure related symptoms, electrolyte status and kidney function and record an electrocardiogram. Evaluate high blood pressure related symptoms, electrolyte status and kidney function and record an electrocardiogram

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	factors for hypertension and associated comorbidities[32]	
Heart failure		
Treatment initiation/uptitration phase	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.	In this phase hypokalemia is common due to high dose diuretic administration to relieve symptoms of fluid overload.
Stable heart failure	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]	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.

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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.

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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 Krogager[1], Kristian Kragholm[1,2,3], Jesper Qvist Thomassen;[4], Peter Søgaard[1], Basil S. Lewis[5], Sven Wassmann[6], Iris Baumgartner[7], Claudio Ceconi [8], Thomas Andersen Schmidt[9,10], Juan Carlos Kaski[11], Heinz Drexel[12,13,14], Anne Grete Semb[15], Stefan Agewall[16,17], Alexander Niessner[18],Gianluigi Savarese[19], Keld Per Kjeldsen[20,21], Claudio Borghi[22], Juan Tamargo[23],Christian Torp-Pedersen[24]

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.

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[13] *Private University of the Principality of Liechtenstein, Triesen, Liechtenstein.*

[14] *Drexel University College of Medicine, Philadelphia, PA, USA.*

[15] *Preventive Cardio-Rheuma clinic, Depatment 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 Instituttet, 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.*

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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

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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]

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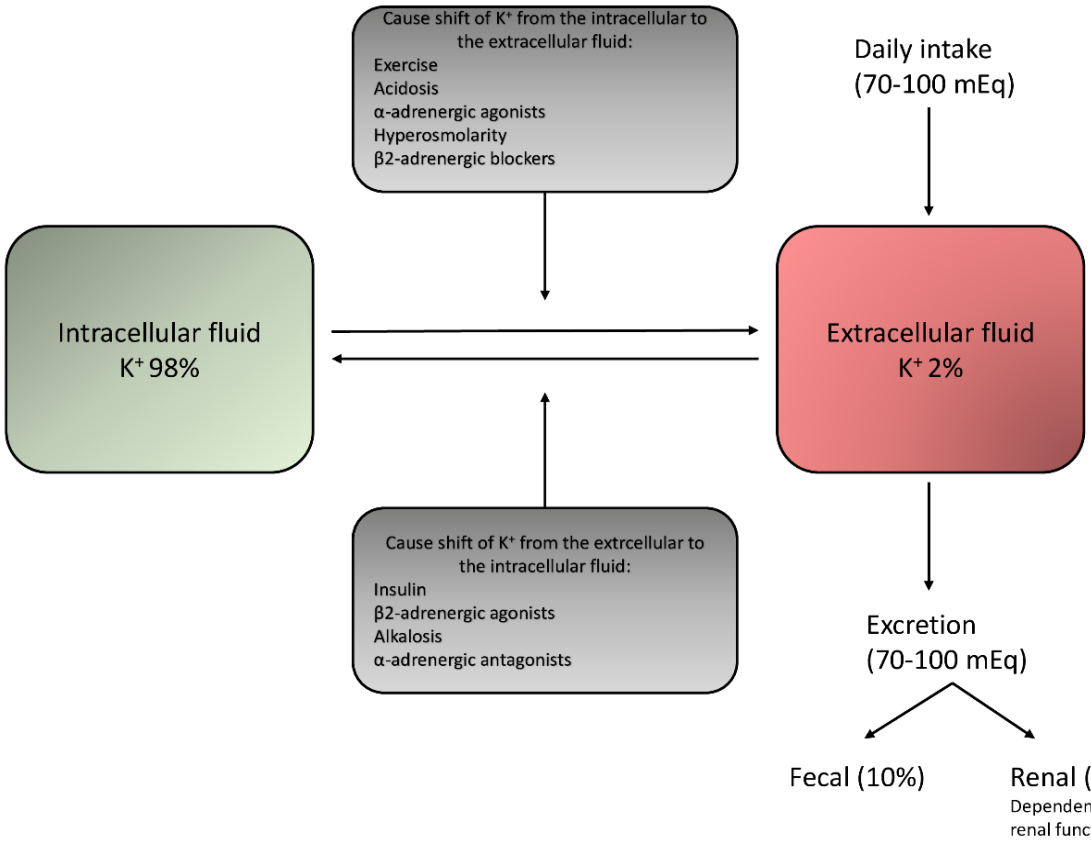
Figure 1. Regulation of intracellular and extracellular potassium shifts



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.

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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.

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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. *Increased potassium excretion:* • 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

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- 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)
    - $Beta_2$-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

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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

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<2.5 mmol/L	Atrial fibrillation, multifocal atrial tachycardias, premature atrial and ventricular contractions, bradycardia, Torsade de Pointes, ventricular fibrillation.

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.

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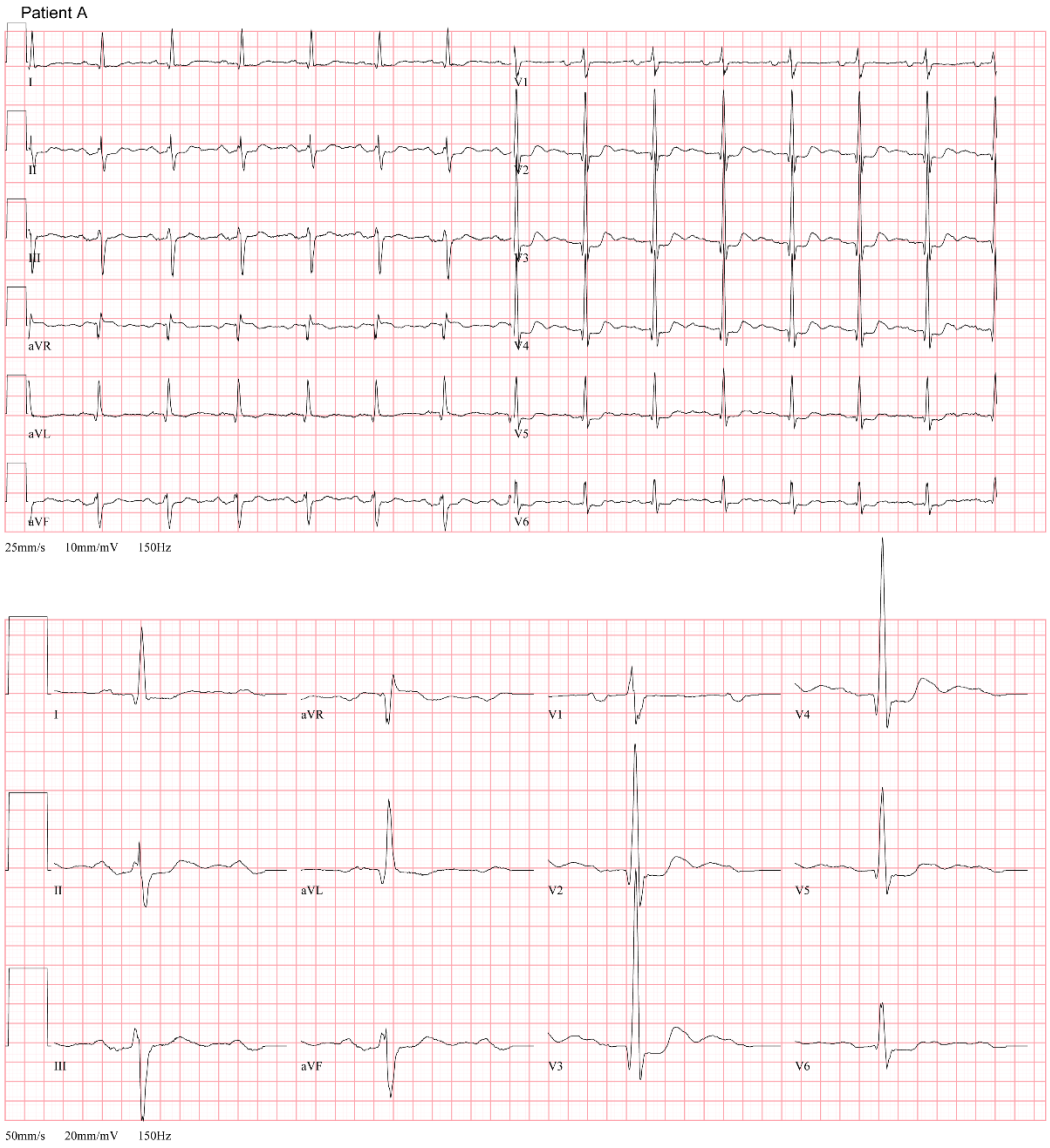
Figure 2. Electrocardiographic manifestations in patients with diuretic induced hypokalemia



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

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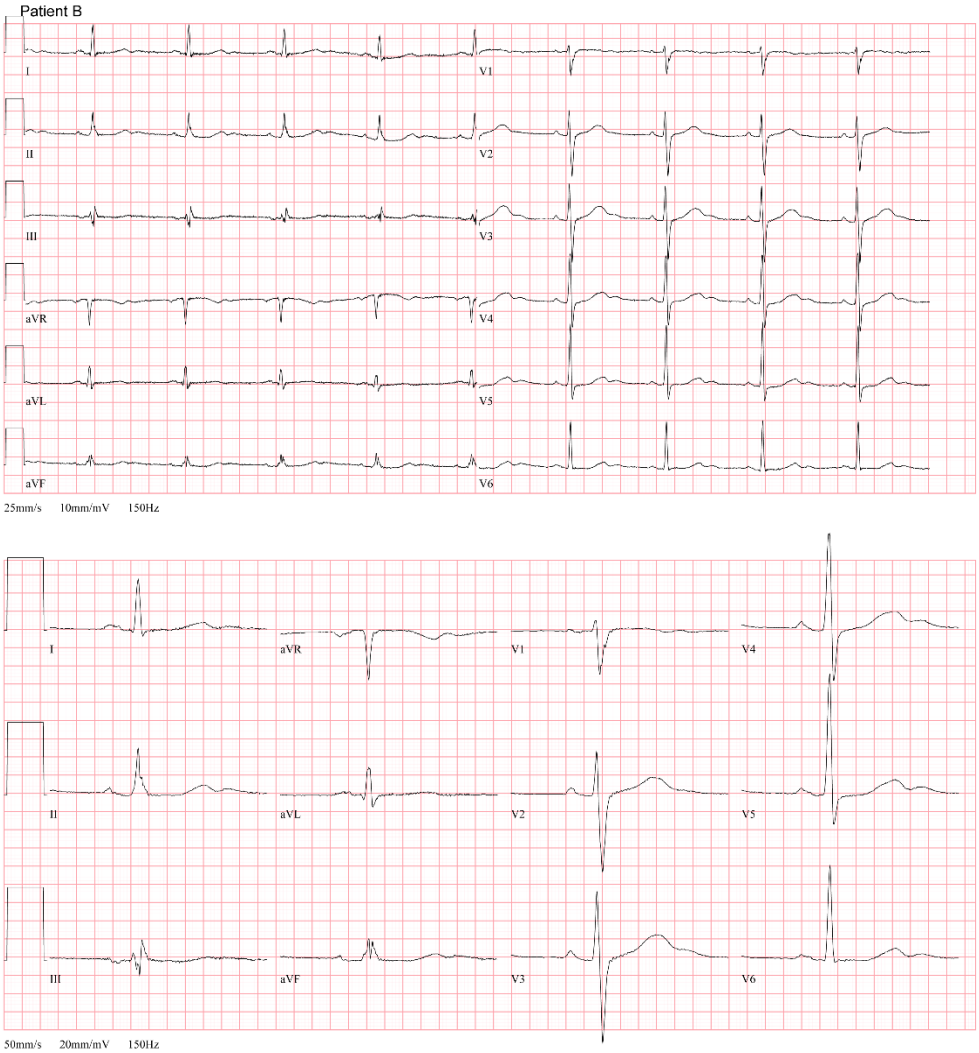

Patient B. Male, 62 years, P(K) 2.9 mmol/L

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 psedohyperkalemia (falsely elevated potassium concentrations) are:

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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

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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

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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**

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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.

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Table 4. Proposals for the treatment of hypokalemia

Hypokalemia	Treatment	Comments
Bordeline (3.5-3.9 mmol/L)	Dietary supplementation with potassium (fruit, vegetables, meat etc) in compliant patients. Oral KCl in patients treated with diuretics. Consider higher dose of KCl in patients treated with diuretics and KCl concomitantly.	Applies to patients with hypertension, cardiac arrhythmias, ischemic heart disease and chronic heart failure.
Mild (3.0-3.4 mmol/L)	Oral KCl: 10-20 mmol 3-4 times a day until K^+ normalized 40-100 mEq/day over a few days or weeks may be needed to fully replete potassium stores In case of hypokalemia + metabolic acidosis ~~consider~~ oral potassium bicarbonate 25 mmol **may be used** every 6-12h until K^+ normalized	Each 10 mmol/L of KCl will increase K^+ by 0.1 mmol/L Monitor K^+ daily and adjust dose accordingly Patients should take potassium supplements with plenty of water to avoid gastrointestinal irritation Patients are usually asymptomatic
Moderate (2.5-2.9 mmol/L)	i.v. potassium supplementation through peripheral line: 10-20 mmol/h until K^+ normalized or it is possible/safe to switch to oral potassium supplemen-tation Maximum of 40 mmol/h	Patients have no or minor symptoms Monitor plasma/serum K^+ every 6-12h Continuous ECG monitoring Oral and i.v. poassium supplementation can be safely used simultaneously Each 10 mmol of i.v. potassium supplement will increase K^+ by 0.05 mmol/L
Severe (<2.5 mmol/L)	i.v. potassium supplementation through central line: 20-40 mmol/h until K^+ normalized and patient are asymptomatic If K^+ <2.0 mmol/L or in the presence of life threatening symptoms: 40-80 mmol/h	Patients are usually symptomatic If case of acidosis administer potassium bicarbonate Test for hypomagnesemia. If the patients is hypomagnesemic: initially give 4 mL $MgSO_4$ 50% (8 mmol)

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		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

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

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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

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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

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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** ~~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.

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.

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	After blood pressure target is reached a visit interval between 3-6 months can be agreed with the patient. At least every 2 years physicians should also assess hypertension's effects on different organs and risk factors for hypertension and associated comorbidities[32]	Evaluate high blood pressure related symptoms, electrolyte status and kidney function and record an electrocardiogram
Heart failure *Treatment initiation/uptitration phase*	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.	In this phase hypokalemia is common due to high dose diuretic administration to relieve symptoms of fluid overload.
Stable heart failure	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]	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.

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- 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.

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