Arrhythmia prevention in high risk cardiovascular patients using targeted potassium levels

January 8, 2025 version 9.0

Protocol approval no. H-18044908

Content

1. Title

Arrythmia prevention in high risk cardiovascular patients using targeted potassium levels

2. Rationale, hypothesis and objective

Hypokalemia (plasma-potassium (p-K) <3.5 mM) is a frequent encounter in the clinical handling of patients with cardiac diseases. There is solid evidence that potassium-sparing drugs increase survival and ameliorates symptoms in heart failure patients and several post-hoc studies suggest that high-normal levels of p-K decreases the risk of malignant arrhythmias in heart failure patients.

Yet, current guidelines just recommend to keep p-K ≥3.5 mM, a threshold which is below the normal levels in western population (laboratory "normal" reference 3.5-4.9 mM, mean 4.1 mM). No guidelines or recommendations address the potential benefits of raising blood levels of potassium to the upper normal levels, e.g. through dietary potassium supplementation, potassium-sparing diuretics etc. Correspondingly, no major trials have addressed this potential.

We suggest a trial randomizing a broad non-selected cohort of patients at high risk of life-threatening cardiac arrhythmia to standard therapy or standard therapy plus a regimen to keep high-normal p-K levels.

Treatment with Implantable Cardioverter-Defibrillators (ICDs) are offered to patients with a broad range of cardiovascular diseases; ischemic heart disease, heart failure, cardiomyopathies, primary arrhythmia disorders (e.g. long QT syndrome, Brugada syndrome), aborted sudden cardiac death etc., i.e. patients with a high burden of malignant arrhythmia who often receive repeated shock therapies. Thus, ICD treated patients suffer from a considerable unmet medical need and are the target for this study.

Potassium-sparing diuretics and potassium supplements are inexpensive drugs and frequently prescribed in cardiovascular patients to compensate for renal potassium loss related to treatment with thiazide and loop diuretics. Most internists in Denmark have in-depth experience in treatment of the extremes - hypo- and hyperkalemia. This means a positive study outcome can be easily and fast implemented and safely managed by internists and cardiologists.

Study Rationale

Potassium in cardiovascular disease

Low p-K levels are associated with increased morbidity and mortality in patients with heart failure[1] as well as in the general population[2]. High-normal p-K levels have been shown to be associated with an improved outcome compared to normal levels[1], an effect that seems to be present even in mild hyperkalemia[3].

There are several reasons for the improved survival with increasing potassium levels. Most important, potassium plays a crucial role in the formation of the cardiac action potential and with higher levels of p-K, action potential duration shortens and the electrical inhomogeneity decrease causing a marked decrease in the risk of supraventricular and ventricular arrhythmias. Additionally, experimental data suggests a decrease in thrombus formation, atherosclerosis and free radicals with higher levels of potassium and diastolic heart function worsens in hypokalemia[4].

Hypokalemia and potassium homeostasis

Humans evolved on a potassium-rich, sodium-poor diet, and the human body mainly developed mechanisms to retain sodium and excrete potassium corresponding to a daily intake of 50 to 150 mEq (mmol)[5]. Potassium is excreted in the kidneys matching an oral intake from 50 up to 300-400 mmol/day. However, modern Western diets (except the Mediterranean-like diets) may have a potassium content as low as 25 mmol/day. A corresponding increase in sodium intake secondarily increases renal potassium excretion. Hence, modern human diets cause sodium overload and potassium depletion[6] making hypokalemia a common and reversible condition in the Western world.

Virtually all filtered potassium is resorbed in the proximal convoluted tubule and potassium excretion is mainly dependent on the secretion in the distal nephron. Aldosterone and vasopressin stimulate potassium secretion and sodium resorption by upregulating the sodium-potassium-ATPase (a.k.a. the Na,K-pump) and opening luminal sodium and potassium channels. The total body potassium is 3,500 mmol of which 98% is intracellular. Less than 1% of the total body potassium content is locates in the plasma, where potassium is maintained between 3.5 and 5.3 mM by renal excretion and shifts between intracellular and extracellular fluid compartments, by numerous Kchannels, transporters and the Na,K-pump in the cell membranes. It has been calculated that the

Na,K-pumps in the skeletal muscles have the capacity to clear the potassium from the extracellular phase within seconds. At any given level of potassium content in the body there is a tight

adjustment of levels of p-K, but still the minute to minute levels are influenced by numerous factors during the day including physical activity, insulin, catecholamine and other hormone levels, food intake, hydration level etc.

Due to these regulations it takes a while before a new equilibrium between compartments of the total body potassium content is reached after potassium intake is increased. Due to the effective secretion mechanisms, intake may have to be substantially increased and most likely accompanied by inhibition of aldosterone in order to actively change blood levels within the normal range.

Cardioprotective effects of potassium: Arrhythmia prevention

The transmembraneous gradient of potassium is maintained by the Na,K-pump, which is mainly stimulated by hyperkalemia and aldosterone, but also by exercise, catecholamines and insulin and downregulated by heart failure, hypothyroidism, starvation, diabetes and alcoholism[7]. The gradient between intracellular and extracellular potassium concentrations is one of major determinants of the resting transmembrane potential.

During hypokalemia the resting potential is increased which causes a cellular hyperpolarity and hastens depolarization. This is relatively more pronounced in non-sinus nodal tissue and therefore automaticity and excitability are increased during hypokalemia[8,9]. Hypokalemia causes inhibition of the outward potassium currents in the cardiomyocytes, which prolongs the repolarization phase and leads to dispersion (reflecting electrical inhomogeneity). These changes may present in the ECG as QT prolongation and changes in the morphology of the T wave and as changes in conduction and automaticity resulting in atrial and ventricular ectopy and sustained arrhythmias. Combined, these changes induced by hypokalemia increase the likelihood for development of arrhythmia.

Multiple clinical studies suggest these mechanisms translate to a decrease in spontaneous cardiac arrhythmias with increasing p-K:

In the EMPHASIS-HF study, which included heart failure patients with mild to moderate symptoms, the risk of cardiac endpoints decreased up to a to serum K >5.5 mM (note; serum-K is 0.4-0.5 mM higher than p-K), after which it rose again[10]. Rossignol et al. showed that while sudden death was not significantly reduced in patients treated with eplerenone vs placebo throughout the group, the risk of sudden death was 25% lower in patients who increased s-K >0.11 mM[11].

Furthermore, eplerenone was found to decrease the risk of atrial fibrillation.

Eplerenone was also used in the EPHESUS study which included sicker heart failure patients.

Eplerenone administration resulted in a decrease in mortality and cardiovascular hospitalization without an increase in the risk for hyperkalemia (p-K >6 mM)[12], and a similar safety profile was shown for spironolactone in the Randomized Aldactone Evaluation Study[13].

Even though these studies showed a correlation between increasing p-K and reduced morbidity, the clearer correlation between p-K and mortality was presented by Hoss et al.[1], who studied nearly 6,946 patients with heart failure. They identified a clear association between serum K and survival, with the best survival at serum K levels of 5-5.5 mM. Survival was 90% at serum K of 5-5.5 mM and 70% at serum K <3.5 mM as shown in figure 1a.

Bird et al.[14] included patients who underwent stress echocardiography. All patients had blood samples drawn including p-K. Lower values of p-K were associated with an increasing incidence of supraventricular and ventricular arrhythmias during the study as shown in figure 1b.

Lumme et al. showed that potassium supplements were given to patients with hypokalemia due to diuretics. As p-K increased, ventricular ectopy ceased[15].

Thus, hypokalemia increases the risk of ventricular and supraventricular arrhythmia and sudden cardiac death and ventricular as well as atrial arrhythmias can be suppressed by raising p-K levels. While this effect seems to be most pronounced in patients with heart failure, it even extends to populations without manifest heart disease[16].

Figure 1a

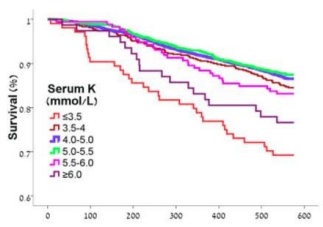
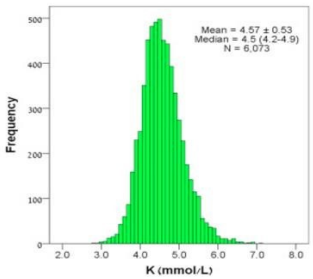


Figure 1b

Potassium, mmol/L	≤3.1	3.2–3.5	3.6–5.2	5.3–5.9	≥6.0
	Dobutamine stress testing (*N* = 13,198)				
n	92	853	11,430	726	97
Transient SVT/AF	5 (5.0%)	41 (4.8%)	487 (4.2%)	16 (2.1%)	1 (1.0%)
> 6 PVC/min	11 (11.0%)	77 (8.9%)	1137 (9.7%)	42 (5.6%)	4 (3.9%)

Figure 1c



Increasing potassium blood levels using aldosterone antagonists and potassium supplementation

Even though there are no trials actively aiming at maintaining p-K at high-normal levels, useful insight regarding the effect on p-K of various interventions exists from previous trials.

In the EMPHASIS-HF trial, eplerenone was given at a dosage of 25 mg daily to patients with preserved kidney function. P-K increased 0.1-0.2 mM on average during the first couple of months and remained stable for the entire duration of the trial. The risk of hyperkalemia (P-K >5.5 mM) was 11.2% in the eplerenone-group vs. 7.4% in the placebo group[10] and the risk of p-K >6 mM was minimal.

Similarly, it is striking that also angiotensin converting-enzyme inhibitors, angiotensin II receptor blockers, and beta-blockers all increase plasma K. Thus, a part of the documented clinical outcome of these drugs in patients with cardiovascular diseases might relate to this effect.

Despite the relatively convincing evidence, it has never been tested whether actively keeping the blood level potassium in the upper-normal range in patients with cardiovascular disease is possible and if this decreases the incidence of ventricular and supraventricular arrhythmias.

Whole exome sequencing (WES) and omics

The broad range of cardiovascular diseases necessitating ICD implantation, e.g. ischemic heart disease, heart failure, cardiomyopathies, primary arrhythmia disorders (e.g. long QT syndrome, Brugada syndrome), sustained ventricular tachycardia and aborted sudden cardiac death – in which a specific diagnosis is often not established – have a genetic etiology or a genetic component influencing the development of the disease[17]. Additionally, they have the risk of malignant arrhythmias in common. This may relate not only to the patient's disease per se, but also to other common denominators, e.g. genetic pre-dispositions to arrhythmia[18], triggered by the disease.

Thus, several gene variants have been shown to alter the duration of the repolarization phase, and thereby modulate the likelihood of arrhythmia. Most of these variants are not considered disease-causing but may be important modifiers or even triggers of arrhythmia in patients suffering from other heart diseases. WES is considered useful for identification of variants associated with increased likelihood of arrhythmia, and to identify variants most likely to an additional "hit" for development of arrhythmia in patients with hypokalemia.

In otherwise stable patients with ICDs, the trigger of a new shock therapy most often remains unidentified. Subclinical infections, inflammatory processes, developing hypertrophy and increasing fibrosis formation[19] possibly related to local tropic factors etc. have been suggested as triggers, but remain to be confirmed. The purpose of genomic analysis in this study is to identify variants associated with

- Unstable potassium levels and tendency to develop hypokalemia/hyperkalemia.
- Vulnerability towards developing arrhythmias during hypokalemic and hyperkalemic episodes

Echocardiography – myocardial deformation

Prognosis in cardiac disease is closely related to systolic function which is commonly measured as left ventricular ejection fraction (LVEF) by echocardiography. Reduced left ventricular ejection fraction (LVEF) of 35% or less is a well-established independent marker of increased risk of arrhythmias and sudden cardiac death in ischemic patient[20]. LVEF has therefore become the main risk stratification tool for primary prevention ICD implantation. However, only 30 % of patients implanted with an ICD receive appropriate therapy and there is a need for further refinement of current selection criteria[21].

New markers of myocardial deformation based on echocardiography have been suggested to be more sensitive. Measures based on 2D speckle tracking analysis such as Global longitudinal strain (GLS) has proven superior to EF as a measure of LV function and as predictor mortality and cardiac events[22]. Similarly, the myocardial dispersion reflecting the inter-segmental variability in contraction duration, has been associated with increased risk of ventricular arrhythmias in a variety of high risk populations such as cardiomyopathies, ischemic heart disease and LQTS[23]. It has been suggested that myocardial dispersion can reflect the electrical heterogeneity of the myocardium which can be seen in diseases such as LQTS or ARVC. If so, the potential electrical stabilization caused by higher potassium levels may also be reflected in the myocardial contractile dispersion.

There is need to explore such mechanisms and to evaluate advanced echocardiographic deformation analysis for the prediction of arrhythmias in larger study populations. The current study represents a unique opportunity to study the importance of potassium levels for myocardial function and how mechanical heterogeneity may be moderated with different levels of potassium.

Hypothesis

Plasma K in the high-normal range reduces the burden of arrhythmias in patients with cardiac diseases.

Objectives

The objectives of this study are:

1) To investigate whether a stable high-normal level of p-K levels are associated with a decrease in malignant arrhythmias and mortality in ICD patients.
2) To investigate to what extent it is possible to increase and maintain plasma K levels to the upper normal range (4.3-4.9 mM), with a study target of p-K 4.5-5.0.
3) To investigate whether an increase in plasma K is associated with a decreased risk of loss of biventricular pacing due to atrial fibrillation and ventricular ectopy in patients undergoing cardiac resynchronization therapy.
4) To investigate the relationship between plasma K levels and incidence of subtypes of arrhythmias.

In addition, we want to investigate the genetics associated with:

1) Low-normal and high-normal levels of p-K
2) Risk of cardiac arrhythmias at low levels of p-K

Based on echocardiography substudies will be performed to describe the importance of myocardial deformation for cardiac arrhythmias. The objectives are to:

1) Characterize the influence of p-K levels for mechanical heterogeneity
2) Investigate the association between mechanical dispersion and cardiac arrhythmias

3) Prediction of outcome in patients with ICD using conventional and echocardiographic markers

3. Methods

Study design

The study is a prospective, randomized and open-labelled study. The study enrollment, intervention and follow-up cascade are shown in figure 2 and 3.

Randomization

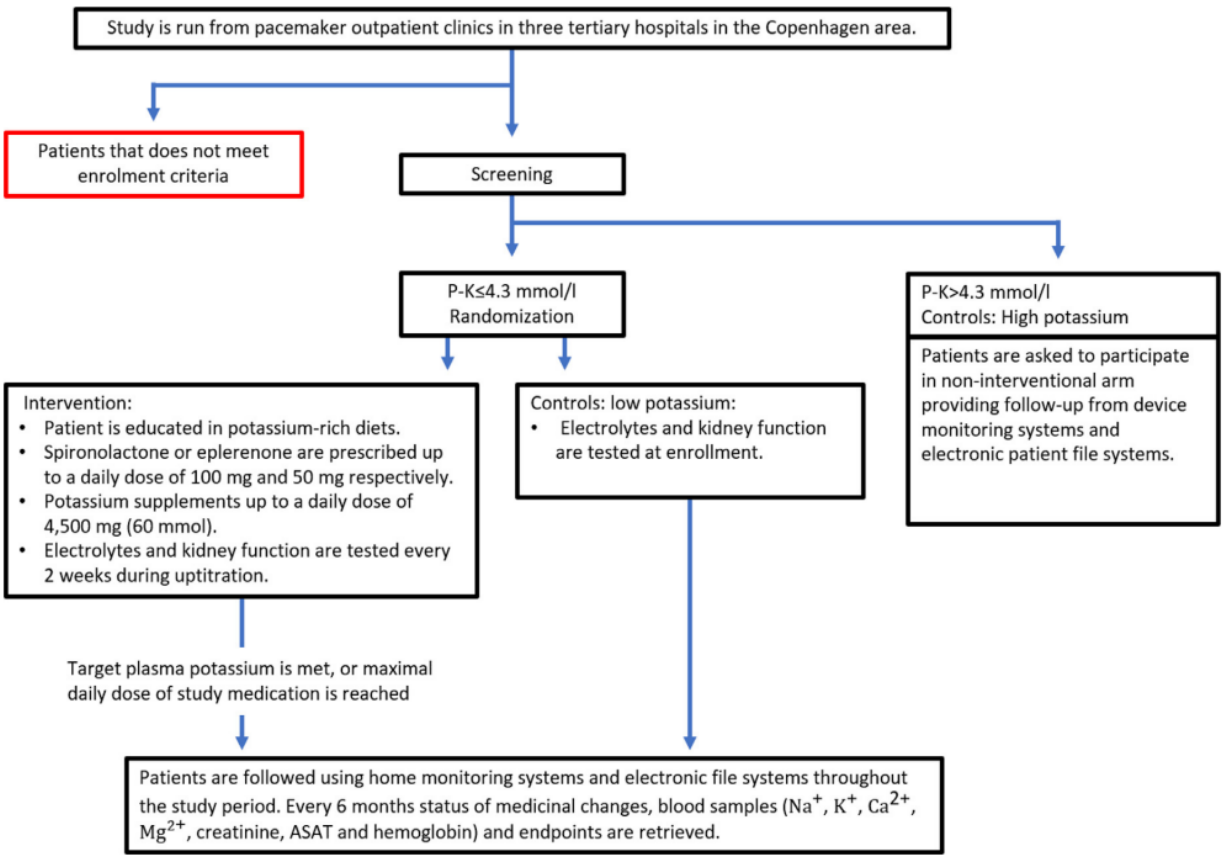
Patients will be randomized in a 1:1 ratio to either:

a) Usual standard of care

b) Targeted potassium level therapy

Randomization will be controlled by a computer-based algorithm.

Patients undergoing screening with levels of p-K > 4,3 mM are excluded but will be asked to participate in a non-interventional observational study for which endpoints will be obtained from the electronic patient file and the device.



Echocardiography

Patients included in the study will have an echocardiogram performed within 4 weeks from inclusion and. A optional follow-up echocardiogram will be offered to a subset of the patients near the study termination. Studies will be analysed for conventional parameters as well as advanced markers of myocardial deformation. Patients are informed that the echocardiogram is focused on myocardial function and cannot replace a clinically indicated echocardiogram. In case of clinically relevant findings on the echocardiogram, the patient will be referred to the local hospital or general practitioner for further investigations.

Intervention and follow-up

Intervention group

Blood samples

Plasma levels of K, Na, Mg, Ca, hemoglobin, aspartate aminotransferase, eGFR and blood pressure and ECG will be measured before and every 2 weeks after dosage adjustment until the p-K target has been reached or maximum study dosages prescribed. At first visit, the blood sample will include genetics and omics.

The patients will be followed bi-annually including measurement of plasma K^+, Na^+, Mg^+, Ca^{2+}, hemoglobin, aspartate aminotransferase, and eGFR and blood pressure and ECG's.Weight, cardiovascular symptoms, medicine status, hospital admissions will be asked and registered by the study team. Side effects from study medication will be inquired as well as adherence to study dose previously agreed upon will be ensured, and if not inquired about the reason for non-adherence and asked to return to the expected dose if not clinically relevant.

Medical treatment

Written and oral information on potassium rich diets will be provided by the study team. Medical treatment will be up-titrated until a plasma K+ of 4.5-5.0 mM is reached preferably starting with aldosterone antagonist treatment followed by oral potassium supplements if needed (see flowchart Figure 3). The final choice, however, will be up to the treating physician.

Patients not already treated with an aldosterone antagonist at a dose of 100 mg/day will be commenced on spironolactone or eplerenone according to the choice of the treating physician, with an initial dose of 25 mg od. If plasma K <4.5 mM, spironolactone or eplerenone dosages are doubled every 2 week until a maximal dosage of 100 mg or 50 mg, respectively, under monitoring of blood pressure. If p-K remains <4.5 mM on 100 mg spironolactone or 50 mg eplerenone, potassium supplements are prescribed commencing at 1500 mg/day up to a maximal dosage of 1500 mg TID.

When maximal dosages or maximal tolerated doses of the above mentioned drugs and supplements have been reached or the p-K levels have stabilized between 4.5-5.0 mM the patient will be followed bi-annually by the study team as described above..

A p-K up to 5.2 at a single measurement will be accepted during controls without adjustment of medication, but repeated levels of p-K > 5.0 will require medication adjustment. A decrease in eGFR up to 30% will be accepted. In the case of severe hyperkalemia (p-K > 6.0 mM), the patient should be admitted acutely for treatment.

The treatment cascade is shown in figure 3 below.

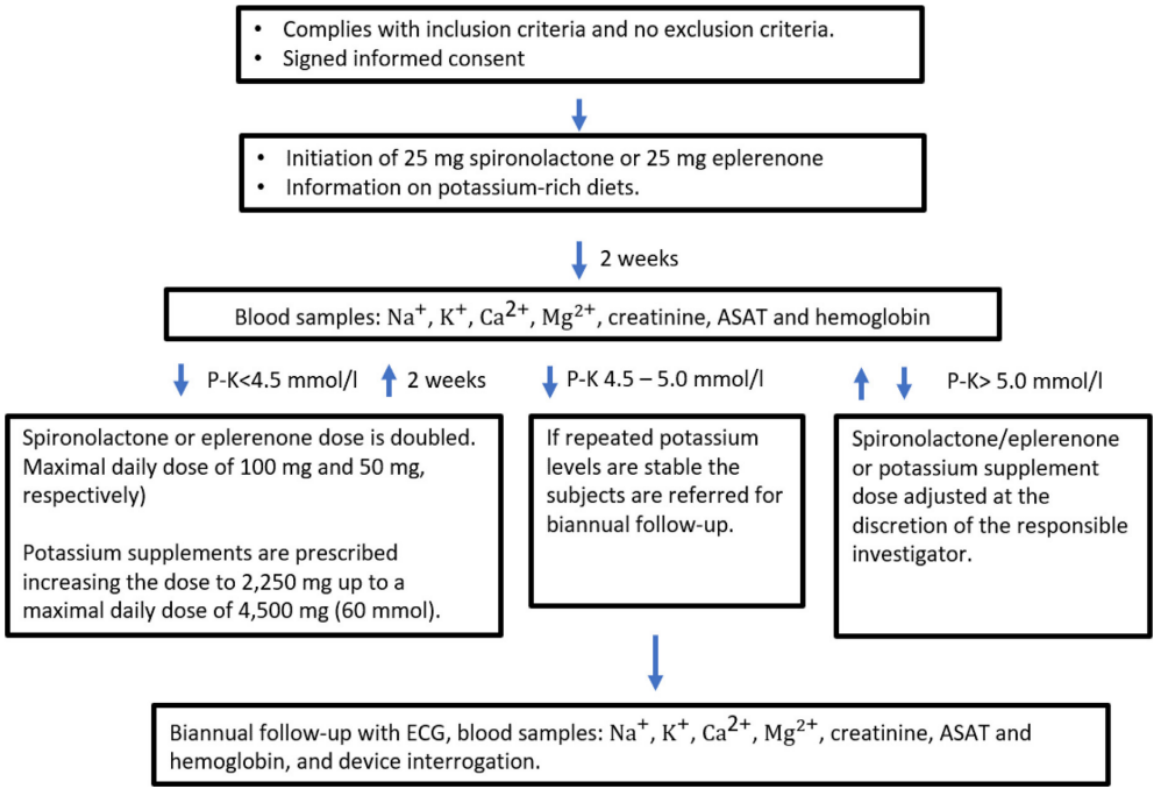
Control group

Initiation and adherence to guideline recommended medicine for the disease entity the ICD has been implanted for will be ensured. No other medical treatment interference will be done according to study protocol.

Similar to patients in the intervention group, patients randomized to the control group will be followed bi-annually +/- 3 months including measurements of plasma K, Na, Mg, Ca, hemoglobin, aspartate aminotransferase, and eGFR and blood pressure and ECG, as well as height, weight, cardiovascular symptoms, medicine status, and hospital admissions.

At first visit a blood sample for genetics and omics will be taken.

Figure 3: Treatment cascade if randomized to intervention.



Device programming

ICD tachy-arrhythmia treatment

Home monitoring

All patients with an ICD or CRT-D at the study sites are encouraged to accept home monitoring of the device. In this case, the device will transmit within 24 hours of giving anti-tachycardia or shock therapy. If ventricular tachycardia (VT) or supraventricular tachycardia (SVT) episodes are recorded but not treated, it will be sent during routine transmissions every 6-12 monthsdepending on the study site setup.

Device programming

ICDs from all 4 manufactures are implanted at the study sites and even though modest differences in programming abilities exist between the vendors, devices are programmed relatively identical at the study sites.

A shock, including anti-tachycardia pacing (ATP) during charge is often programmed at heart rates >240 bpm (230-250 bpm). This zone cannot be set to higher levels than 250 bpm and must be set to ON for any other ICD therapy to be delivered.

A fast-VT and a VT zone are available and can be programmed with an individual number of ATP therapies to be delivered before shock therapy is delivered. The fast-VT zone is generally programmed ON with a treatment zone at heart rates 200-240 bpm. Most often 2-4 ATP treatments are delivered before a shock is given. The VT zone is most often used in patients with documented VT and set accordingly at rates starting at 130-180/min with a varying number of ATPs delivered. Shock is only occasionally set ON in this zone.

Hence, ICD units are programmed according to the patient's condition and recommendations to ICD therapy is not given per protocol.

Cardiac resynchronization programming

Cardiac resynchronization therapy (CRT) aims at restoring synchronized contraction in dyssynchronous failing hearts. Successful re-synchronization requires >95% of all heart beats to be paced. This is frequently hampered by atrial fibrillation or frequent ventricular ectopy, and approx. 20% of CRT patients experience periods of low CRT pace for these reasons.

Endpoints

Primary endpoint

A combination of:

- ECG documented ventricular tachycardia > 125 bpm lasting > 30 seconds

- Any appropriate ICD therapy as documented by the ICD or ECG

- Any hospitalizations > 24 hours due to arrhythmias and/or heart failure leading to a change in treatment, e.g., administration of new drugs, or change in doses of already prescribed drugs or invasive or non-invasive treatment.

- All-cause mortality

Secondary endpoints

- Incidence of supraventricular arrhythmias as documented by ECG or the ICD
- Risk of <92 % CRT-pacing for > 2 weeks (only CRT-D patients)
- Hospitalization for heart failure
- Hospitalization for cardiac arrhythmias
- Hospitalization for electrolyte disturbances or kidney failure
- Appropriate ICD therapy
- Inappropriate ICD therapy
- Change in the burden of ventricular arrhythmias.
- Change in burden of supraventricular arrythmias.
- Change in myocardial structure and/or function.

Death

Death events will be collected automatically from the Danish Death registry and the devices will be interrogated post-mortem.

Heart failure and arrhythmiashospital admission

Information on hospitalizations will be collected every 6 months according to study protocol. The patient will be asked for hospitalizations.

Ventricular and supraventricular tachy-arrhythmia therapy

Information of ventricular tachyarrhythmia therapy will be obtained from home monitoring systems or interrogation of the ICD devices during in-clinic visits. All ICD therapy is routinely adjudicated as appropriate or in-appropriate by EP physicians at the study sites. All patients receiving an ICD shock are called by the EP personal in the pacemaker outpatient clinic and the circumstances and causes of the shock are investigated and described. Patients receiving successful ATP therapy but not shock are only contacted if is the first time, if a high number of ATP cycles were delivered or if the VT was fast enough to be expected to cause symptoms.

All tachy-arrhythmias causing appropriate ATP or shock or supraventricular tachy-arrhythmias causing inappropriate shock are considered endpoints.

Information of type of therapy delivered, number of therapies, VT/VF duration and cycle length, cause of inappropriate shock (atrial fibrillation, SVT, ICD lead problems) and (if available) circumstances causing the shock (i.e. electrolyte disturbances, will be recorded.

Supraventricular and ventricular arrhythmias not resulting in therapy but documented either because they were of too short duration, triggered mode switch of the device etc will be considered secondary endpoints.

In descriptive studies computer-assisted analyses of digital ECG recordings of QT duration and T wave morphology will be performed to identify markers or patterns associated with risk of future arrhythmia events. Associations with p-K levels and other parameters (electrolytes, genetic and omics findings) will also be analyzed.

Endpoint committee

An endpoint committee blinded to patient ID will review, adjudicate and classify endpoints. Two reviewers will review an endpoint, if disagreement exists, the endpoint committee will consist of members from the steering committee,who are all specialists in cardiac electrophysiology and device interrogation.

Study time plan

The study will begin as soon as all necessary approvals have been obtained, with a planned start Augustst, 2018.

The study is planned to last until a total of 291 endpoints are registered.

The study is expected to be finalized in 2025.

Deviation from standard care

All patients are following the pathway of standard care during the study. As described, patients randomized to the intervention arm will be followed with additional testing until potassium levels are in the targeted interval. Please see the paragraph regarding ethical considerations.

4. Statistical considerations

Population size and accessibility

There are approximately 8,800 patients with an ICD implanted in DK. Approximately 40% of these are followed at Rigshospitalet and at Gentofte Hospital, i.e. approximately 4,000 patients. These are controlled in-clinic every 1-2 years. Hence, a population of approx. 4,000 patients can be screened during the first 2 years. Additionally, 250 new ICDs and 200 new CRT-Ds are implanted at the study sites every year. Of these, 60% are primary prophylactic while 40% are secondary prophylactic. Hence, during an enrollment period of 3 years, a total of 5,350 patients will be available for screening.

Among 7,000 patients with heart failure on relevant medical treatment, median value of p-K was 4.5 mM in patients already on heart failure medication and lower for patients without heart failure.

Hence meaning that around 50% of patients can be expected to present with a p-K <4.3 mM (figure 1c).

Severe chronic renal failure is a relative contraindication for implantation of the device because of expected lower benefit and higher risk of infections. In a recent investigation of comorbidities in Danish ICD patients, only 3% had chronic renal failure as a diagnosis during a previous

hospitalization. Even though precise number are not available, eGFR <30 ml is conservatively estimated to be found in 5% of the population.

Hence, it is expected that the total population available for screening over 3 years is 5,350 x 0.45 = 2,400 patients.

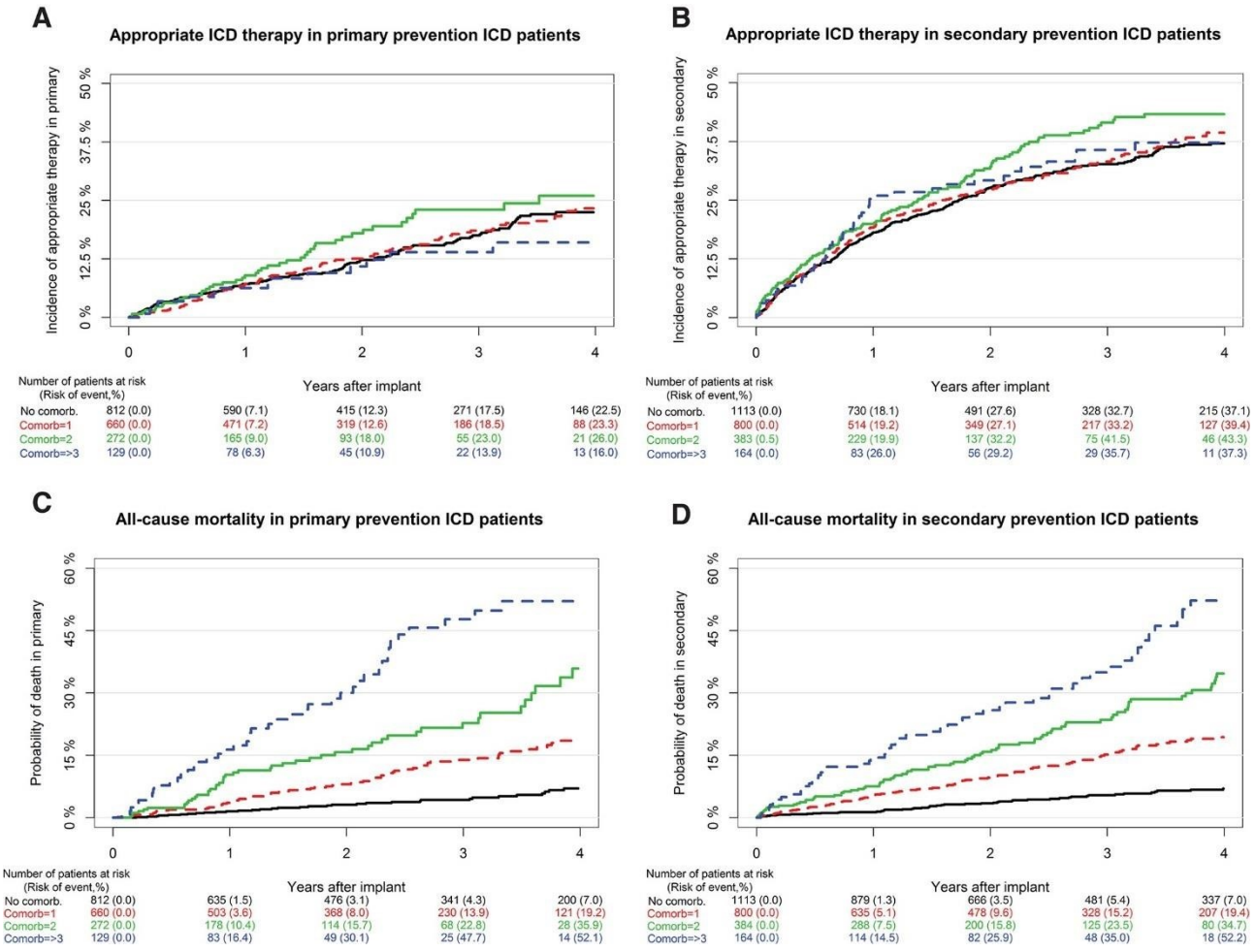
The genetics and omics studies are descriptive and explorative.

Power calculation

Due to the specific constitution of the population, i.e. a pool of patients screened during 2 years with an additive smaller population of new implants recruited during year 3, we have chosen to use a traditional rather than sequential design of the study.

The risk of the combined endpoint is expected to be approximately average of 16% per year based on our observations on all Danish ICD patients[24] as shown in figure 4 below:

Figure 4: Incidence of appropriate therapy and all-cause mortality among ICD patients in Denmark implanted with an ICD for primary or secondary prevention.



Increasing p-K to 4.4-4.9 mM is believed to reduce therapy rates by approximately 40% based on the observation from Bird et al. Hence, the annual risk of ICD therapy of cardiovascular death is assumed to be 16% in the intervention group and 9.6% in the control group per year.

It is expected that a proportion of patients cannot be brought to a p-K of 4.5. We expect 30% to remain below target values for p-K with a resulting higher risk of the endpoint. This means that 30% remains with unchanged risk and 70% shows an average 40% risk reduction = (30 x 0.16 + 70 x 0.096%), total risk in the treatment group 11.5%, i.e. risk reduction of 1- (11.5 / 16) of 28%, i.e. HR = 0.72

Based on this a total of 291 events are needed. We expect an enrollment phase of 3 years and 1 year additional follow-up to ensure at least 1 year follow-up for all patients, but due to the expected high initial enrollment of the existing pool of ICD patients, we expect an average follow-up of 3 years. Censoring is expected to be low, but is set conservatively at 10%.

Based on these assumptions, a total of 990 patients should be enrolled. We plan on enrolling a total of 1,000 patients.

The power calculation has been overseen by a statistician (Theis Lange).

Due to COVID-19, there was a reduction in the inclusions rate that have influenced the duration of the study. This increase in duration has resulted in a longer duration of the intervention for the patients included in the first part of the study. For these patients, we foresee a lower compliance. Additionally, the study has observed a lower event rate than anticipated. To be able to reach the number of events needed for completion of the study within the next approximately 1.5 years, we would include an additional 200 patient, making a total of 1,200 patients.

Statistical analysis

For the purpose of the primary endpoint, a time-to-first-event survival analysis will be performed on the primary endpoint. Besides survival statistics, repeated mixed models will be used to understand associations between fluctuations in p-K to drug and potassium supplements therapy as well as the association or p-K to primary and secondary endpoints.

Statistical analysis including for GWAS analysis will be assisted and overseen by a statistician attached to the research group.

5. Patient population

Patients will be screened, enrolled, and followed from the Outpatient Pacemaker Clinics at

Rigshospitalet, Gentofte Hospital and Roskilde Hospital. Patients already implanted with ICDs or CRT-Ds are seen in-clinic every 1-2 years and will be screened and enrolled during these follow-ups. Patients admitted for ICD/CRT-D implantation will be screened and enrolled during implant admission or at the 1- or 3-month obligatory follow-up.

Inclusion criteria

- Implantable cardioverter defibrillator (ICD) or cardiac resynchronization pacemaker with ICD (CRT-D).
- Age >18 years

Exclusion criteria

- Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2
- Pregnancy
- Lack of ability to understand and sign informed consent

6. Biological and Genetic material

Collection of biological material

Acquisition of biological material includes measurements of plasma level K, Na, Mg, Ca, hemoglobin, aspartate transaminase, and eGFR before and every 2 weeks after dosage adjustment until the p-K target has been reached or maximum study dosages prescribed. After analysis these blood samples (3 mL x 2) are immediately disposed.

Genetic material collection and analysis

At inclusion a blood sample (3 mL x 3) for genetic analysis and omics will be drawn after a separate specific informed consent for this part of the study.

Biobank

The biological material collected will be stored in a research biobank. Analysis of material from this biobank will take place until 2 years after the last patient has finalized his/her participation in the study, i. Remaining material on this date will be transferred to a biobank on the department for unspecific future research. Remaining material in the biobank in June 30th, 2035 will be destroyed.

Whole exome sequencing (WES) and omics

WES will be applied to identify variants associated with increased likelihood of arrhythmia, and to identify variants most likely to be associated with a positive response to raised p-K levels.

In order to identify triggers of arrhythmic events a subset of patients with repeated un-explained shock therapies will be offered extensive proteomic studies. Stable patients will serve as controls.

7. Use of data from patient files

Data collection and use

Data on clinical characteristics, hospitalizations, genetic findings, treatment outcome and trajectories will be collected. Genetic data will be combined with data from proteomics and transcriptomics studies and protein-protein interaction databases and analyzed using a systems biology approach to identify novel disease genes.

Outcome data such as arrhythmia and device therapies will be derived from the device home-monitoring system.

Information used *prior* to inclusion in the study will be confined to:

- Identification of the patient from the patient snapboard, prior to ICD-implantation or prior to routine device-check
- K+ -level and eGFR-level based on routine blood-sample
- Clinical information with regards to cardiovascular history, functional level and anticongestive medicine.

Information obtained from the potential study participants prior to consent will be passed on to the researchers.

Consent from the study participants will allow investigators, sponsors, and sponsor reps as well researchers with data safety monitoring responsibilities to access any necessary information required to complete the study and for control purposes.

Informed consent

All patients will sign informed consent according to the Helsinki declaration.

Data storage and safety

An electronic database will be set up for the study in REDCAP on the capital region medical research servers (https://redcap.regionh.dk). The database will contain the crude study data for later analysis. This database is approved for containing person-specific data and allows access on

multiple user levels, logging of all access to the data as well as downloading a de-identified version of the database for analysis after study conclusion. The database is hosted and maintained by Center of IT, Medica and Telephony for the Capital Region.

Data safety monitoring

A data safety monitoring board (DSMB) will be constituted before the trial is initiated consisting of 3 independent researchers within the field. The purpose of the DSMB is to monitor:

- Interim and cumulative data for evidence of study-related adverse events
- Data quality, completeness, and timeliness
- Performance of the three centers
- Adequacy of compliance with goals for recruitment and retention
- Adherence to the protocol
- Factors that might affect the study outcome or compromise the confidentiality of the trial data (such as protocol violations, unmasking, etc.)
- Factors external to the study such as scientific or therapeutic developments that may impact participant safety or the ethics of the study.

8. Use of patient data

The current study will be conducted in accordance with current Danish legislation on processing of personal data /the General Data Protection Regulation, GDPR.

The Data Protection Agency will be applied for approval, including approval for keeping the genetic data after the project is finalized. The regulations of management of data on individual persons according to the Sundhedsloven og Persondataloven will be followed.

Personal data will not be transferred to foreign countries.

Data from medical records

The following data will be collected after informed consent and enrolment and for up to 10 years after the study ends:

- Date and cause of hospitalizations in Denmark, including
  - Adjudication of the cause using information from the electronic file system (sundhedsplatformen)
  - Laboratory results including potassium,sodium, infection tests, TSH, liver and kidneytests and ECGs recorded during the hospitalization
  - Medicinal status for treatment with cardiovascular drugs (ace-inhibitors, angiotensin II antagonists, beta blockers, mineralocorticoid antagonists, diuretics, potassium supplementation, class I and III anti arrhythmic drugs
- ICD-therapy (ATP and shock) including changes in ICD programming and recorded ICD EGMs as well as ICD related complications, lead extrations, generator replacements and change of system to CRT-D, DDD-ICD, VVI-ICD or pure pacemaker systems)
- Date and cause of hospitalization
- Date and cause of death.

Data from medical records can be used for confirmation of register-based data described below. All data are given to the investigator regardless of whether they are collected before or after the informed consent is given.

Data from Danish registries

A register-based follow-up after 3, 5 and 10 years will be used to evaluate long-term outcomes. The study will use data on hospitalization diagnoses and dates, prescription drug treatment, laboratory tests and death dates from the following Danish National Health Register: The National Patient Register, The Causes of Death Register, Shared Medication Record, The Clinical Laboratory Information Register, The Register of Pharmaceutical Sales, National Hospital Medication Register,

Screened but not randomized patients in the observation arm

The patients who had too high plasma potassium to be randomized at the screening, we would also follow-up in patient records and national registries for up to 10 years after study termination as

described above. These patients have signed informed consent for the study, but since p-K was > 4.3 they could not be randomized.

To follow-up, we will look up the patients in the medical records to get information on vital status. If the patient is alive, we will retrieve their contact information and send them a letter via E-boks to obtain their consent for the 10-year follow-up. We will follow-up on the invitation letter over the telephone if we do not receive and answer to the E-boks invitation. The obtained results will contribute to compare the risk of primary and secondary endpoints of the intervention group to patients where p-K naturally is > 4.3.

9. Study organization, funding and budget

Study initiators

MD, PhD, Christian Jøns, The Heart Centre B 2142, The National University Hospital, Rigshospitalet, Copenhagen, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark, Phone + 45 3545 9863

Professor, senior consultant, dr.med. Henning Bundgaard, The Heart Centre B 2142, The National University Hospital, Rigshospitalet, Copenhagen, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark, Phone + 45 3545 0512

MD, PhD, Niels Risum, The Heart Centre B 2142, The National University Hospital, Rigshospitalet, Copenhagen, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark, Phone + 45 3545 9863

Study organization:

The study will be performed at Rigshospitalet, Gentofte/Herlev Hospitals, and Roskilde Hospital.

The study group consists of:

Christian Jøns, MD. PhD, Rigshospitalet (Study leader Rigshospitalet)

Henning Bundgaard, Professor, DMSc, Rigshospitalet

Niels Risum, MD, PhD, Rigshospitalet

Charlotte Larroudé, MD, PhD, Gentofte/Herlev University Hospitals (Study leader Gentofte/Herlev Hospital)

Kasper Iversen, MD, DMSc, Gentofte/Herlev University Hospitals

Niels Eske Bruun, Professor, DMSc, Zealand University Hospital, Roskilde Hospital (Study leader Roskilde Hospital)

Ketil Jørgen Haugan, MD, PhD, Zealand University Hospital, Roskilde HospitalHelle Skovmand Bosselmann, MD, PhD, Zealand University Hospital, Roskilde Hospital

Funding will be applied for through external funds.

Funding is administered through the finance department at The Copenhagen University Hospital, Rigshospitalet, Copenhagen.

None of the investigators have personal financial interests in the study or personal affiliations with study sponsors.

A specialized nurse technician will be hired specifically for the study at each of the study sites. The study technicians/nurses will screen up to 5-10 potentially recruitable patients per day. They will inform and include patients, take blood samples, take ECG's and blood pressure and manage the biannual follow-up. Additionally, they will manage all needed registrations.

Not until the majority of patients are recruited (year 3) a PhD student is employed to plan and execute the data analysis and publication of the results.

Fees for the DSMB are included in the budget.

Salary for a statistical consult is included in the budget.

The endpoint committee consists of members of the application and are not paid.

The cost of study medication not covered by the Danish public health care system will be re-imbursed.

10. Reimbursement

There is no reimbursement of expenses for transportation, lack of earnings or drawback allowance for study participants.

11. Recruitment of study participants

A continuous screening for potential study participants will take place during the study period.

A list of patients, with a planned visit at the outpatient device clinic, will be requested from the treating electrophysiologist Seven days prior to the planned outpatient visit in the device clinic, the research nurse will send the study information package either via electronic e-post to the patients "e-boks" or, if the patient has requested materiel from the device clinic to be sent via ordinary mail, as physical mail to the patient. The letter will inform the patient about the study and the possibility to receive further information after the normal ICD check-up has been done. The information package will contain 1) recruitment letter, 2) Patient study information and informed consent, 3) the form "Forsøgspersoners rettigheder".

At the device clinic visit the patient will be asked by the pace technician if they have read the study information package and will be interested in additional information.

The oral information will be given in an un-disturbed room by appointed study personal (i.e study nurse, technician or physician who have received training for this purpose). The patient is encouraged to invite an assessor to participate at the meeting. The patient will be offered at least 24 hours to consider his/her participation, i.e. from oral and written information is given and until the patient signs the consent form. If the patient consents to participate in the study, the bloodwork necessary for randomization will be done following the oral information. If the necessary bloodwork has been obtained within 7 days during another un-related clinical visit, these test results will be used and the bloodwork will not be repeated.

For each person, his/her/their mental and physical integrity and rights of privacy will be respected.

12. Publication of data

The data will be published in peer-reviewed medical journals after which the data will be deidentified and uploaded to a public database for sharing with other researchers.

Results will be published regardless of whether they are positive, negative, or inconclusive. The study will be announced at www.clinicaltrials.gov

13. Ethical considerations

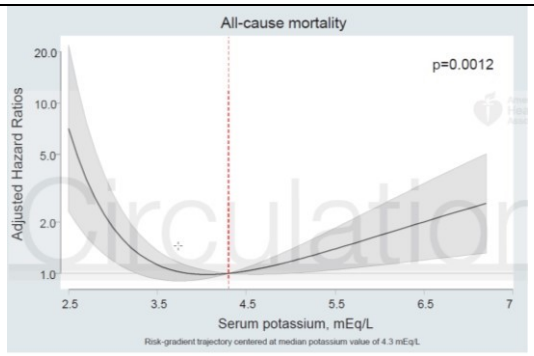
Risk and benefits of the clinical investigation

Anticipated clinical benefits

Besides from the assumed positive effects of high-normal K+ levels in the interventional group, patients in both groups followed in the study will be monitored more often compared to what is usual practice, and a cardiac specialist will monitor optimal medical treatment at the beginning and throughout the trial. Many of the patients enrolled in this trial will not have been seen by a cardiologist for several years.

Anticipated clinical risks

The risk of hyperkalemia is likely to be increased in the intervention group. In a recent meta analysis on the risk of hospitalizations for hyperkalemia associated with mineralocorticoids in heart failure, the risk of hyperkalemia was doubled[25] (eplerenone 5.0 vs 2.6%, spironolactone 17.5 vs 7.5%). On the other hand, the risk of hospitalization for hypokalemia is decreased with 50%. In general, the risk associated with hypokalemia was associated with a higher risk of death (see figure 2a and 2b, adapted from Núñez et al[26]). Hence, we consider the lower risk of hypokalemia along with a greater risk of hyperkalemia as being an advantage for the patient.



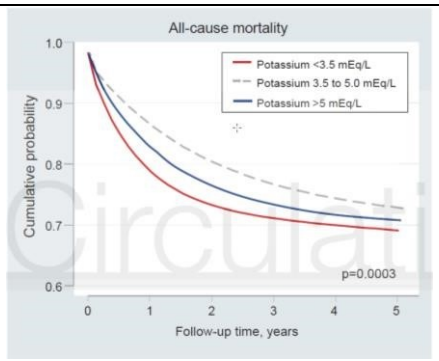


Figure 2a and 2b: Risk of death associated with having a blood sample collected with hypokalemia or hyperkalemia.

In a study investigation on reasons and management of hyperkalemia, mineralocorticoid treatment was the most frequent cause[27]. Among 600 hospitalizations, by far most of them were mild hyperkalemia and treated with cessation of medication and fluid therapy whereas a little less than 8% required hemodialysis. There were no deaths.

In both groups additional discomfort from blood sampling can be expected.

Interventional medical treatment

Potassium supplements are available over-the-counter in Denmark. Treatment with potassium supplements and diet recommendations are considered safe.

The aldosterone antagonists, spironolactone and eplerenone, are prescribed with indication of heart failure with symptoms corresponding to NYHA II-IV, liver failure and for treatment of hypertension. The major side effects are related to hyperkalemia. This risk is low in patients with normal to slightly reduced kidney function. P-K levels will be monitored at intervals short enough to reduce the risk of hyperkalemia episodes to a minimum. Hence, the risk of developing severe hyperkalemia induced arrhythmia is therefore low. If arrhythmias develop, the patients have an ICD implanted and the investigators will be notified immediately since all patients will be using home monitoring.

14. Compensation

This study is covered by Patienterstatningen. Additional insurance is not necessary.

15. References

1. Hoss, S. *et al.* Serum Potassium Levels and Outcome in Patients With Chronic Heart Failure. *Am. J. Cardiol.* **118**, 1868–1874 (2016).
2. Krogager, M. L. *et al.* Short-term mortality risk of serum potassium levels in hypertension: a retrospective analysis of nationwide registry data. *Eur. Heart J.* **38**, 104–112 (2017).
3. Ahmed, M. I. *et al.* Mild hyperkalemia and outcomes in chronic heart failure: a propensity matched study. *Int. J. Cardiol.* **144**, 383–388 (2010).
4. Macdonald, J. E. & Struthers, A. D. What is the optimal serum potassium level in cardiovascular patients? *J. Am. Coll. Cardiol.* **43**, 155–161 (2004).
5. Dahl, L. K. Salt intake and salt need. *N. Engl. J. Med.* **258**, 1152-1157 contd (1958).
6. Meneely, G. R. & Battarbee, H. D. High sodium-low potassium environment and hypertension. *Am. J. Cardiol.* **38**, 768–785 (1976).
7. Clausen, T. Na+-K+ pump regulation and skeletal muscle contractility. *Physiol. Rev.* **83**, 1269–1324 (2003).
8. Fisch, C., Knoebel, S. B., Feigenbaum, H. & Greenspan, K. Potassium and the monophasic action potential, electrocardiogram, conduction and arrhythmias. *Prog Cardiovasc Dis* **8**, 387–418 (1966).

9. Gettes, L. & Surawicz, B. Effects of low and high concentrations of potassium on the simultaneously recorded Purkinje and ventricular action potentials of the perfused pig moderator band. *Circ. Res.* **23**, 717–729 (1968).
10. Zannad, F. *et al.* Eplerenone in patients with systolic heart failure and mild symptoms. *N. Engl. J. Med.* **364**, 11–21 (2011).
11. Rossignol, P. *et al.* Incidence, determinants, and prognostic significance of hyperkalemia and worsening renal function in patients with heart failure receiving the mineralocorticoid receptor antagonist eplerenone or placebo in addition to optimal medical therapy: results from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF). *Circ Heart Fail* **7**, 51–58 (2014).
12. Pitt, B. *et al.* Serum potassium and clinical outcomes in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS). *Circulation* **118**, 1643–1650 (2008).
13. Pitt, B. *et al.* The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N. Engl. J. Med.* **341**, 709–717 (1999).
14. Bird, J. G., McCully, R. B., Pellikka, P. A. & Kane, G. C. Dobutamine Stress Echocardiography: Impact of Abnormal Blood Potassium Levels on Cardiac Arrhythmias. *J Am Soc Echocardiogr* **30**, 595–601 (2017).
15. Lumme, J. A. & Jounela, A. J. The effect of potassium and potassium plus magnesium supplementation on ventricular extrasystoles in mild hypertensives treated with hydrochlorothiazide. *Int. J. Cardiol.* **25**, 93–97 (1989).

16. Mattsson, N. *et al.* Ambulatory cardiac arrhythmias in relation to mild hypokalaemia and prognosis in community dwelling middle-aged and elderly subjects. *Europace* **18**, 585–591 (2016).
17. Cirino, A. L. *et al.* Role of Genetic Testing in Inherited Cardiovascular Disease: A Review. *JAMA Cardiol* **2**, 1153–1160 (2017).
18. Christophersen, I. E. *et al.* Large-scale analyses of common and rare variants identify 12 new loci associated with atrial fibrillation. *Nat. Genet.* **49**, 946–952 (2017).
19. Nguyen, M.-N., Kiriazis, H., Gao, X.-M. & Du, X.-J. Cardiac Fibrosis and Arrhythmogenesis. *Compr Physiol* **7**, 1009–1049 (2017).
20. Epstein, A. E. *et al.* ACC/AHA/HRS 2008 guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: executive summary. *Heart Rhythm* **5**, 934–955 (2008).
21. Buxton, A. E. *et al.* Limitations of ejection fraction for prediction of sudden death risk in patients with coronary artery disease: lessons from the MUSTT study. *J. Am. Coll. Cardiol.* **50**, 1150–1157 (2007).
22. Stanton, T., Leano, R. & Marwick, T. H. Prediction of all-cause mortality from global longitudinal speckle strain: comparison with ejection fraction and wall motion scoring. *Circ Cardiovasc Imaging* **2**, 356–364 (2009).
23. Haugaa, K. H. *et al.* Mechanical dispersion assessed by myocardial strain in patients after myocardial infarction for risk prediction of ventricular arrhythmia. *JACC Cardiovasc Imaging* **3**, 247–256 (2010).
24. Ruwald, A. C. *et al.* The impact of co-morbidity burden on appropriate implantable cardioverter defibrillator therapy and all-cause mortality: insight from Danish nationwide clinical registers. *Eur. J. Heart Fail.* **19**, 377–386 (2017).

25. Vukadinović, D. *et al.* True rate of mineralocorticoid receptor antagonists-related hyperkalemia in placebo-controlled trials: A meta-analysis. *Am. Heart J.* **188**, 99–108 (2017).
26. Núñez, J. *et al.* Long-Term Potassium Monitoring and Dynamics in Heart Failure and Risk of Mortality. *Circulation* **137**, 1320–1330 (2018).
27. Eliacik, E. *et al.* Potassium abnormalities in current clinical practice: frequency, causes, severity and management. *Med Princ Pract* **24**, 271–275 (2015).