**Section I**

**Management of Hyperkalaemia in the Community and Out-patient Clinic**

# Hyperkalaemia in the Community (Guidelines 1.1 – 12.1)

## Introduction

Hyperkalaemia is commonly detected in the community and the patient groups most at risk are those with CKD, diabetes mellitus and heart failure. Hyperkalaemia may also occur in the context of an AKI triggered by acute illness, initiation or titration of RAASi medications, or worsening of heart failure.1 。。Hyperkalaemia develops in approximately 10% of out-patients within one year after initiation of RAASi drugs, thereby limiting treatment in the patients who receive the greatest benefit from this therapy.2

The management of patients with heart failure is challenging given the high prevalence of renal impairment and increased risk of hyperkalaemia. In clinical trials of RAASi monotherapy, the incidence of hyperkalaemia ranges from 3 – 7%.3 。。The overall incidence of hyperkalaemia was generally higher in clinical trials involving aldosterone antagonists.3 。。Combination therapy of RAASi and aldosterone antagonist increases the risk of hyperkalaemia and hospitalisation.4 。。Mortality in patients with heart failure is significantly increased with worsening severity of hyperkalaemia: serum K+ levels between 4.8 – 5.0 mmol/l (HR 1.34), 5.1 – 5.5 mmol/l (HR 1.60) and 5.6 – 7.4 mmol/l (HR 3.31).5

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| **Risk Factor for Hyperkalaemia** | **Odds Ratio [Turgutalp] [6]** | **Odds Ratio [Sarafidis] [7]** | **Odds Ratio [Nakhoul] [8]** | **Odds Ratio [Horne] [9]** |
| Renal Failure | 5.55 | 2.06  ( eGFR < 15) | 1.25  (per 5ml/min  decrease) | 1.04 |
| Diabetes |  |  | 1.53 | 0.95 |
| Heart Failure |  |  | 0.95 |  |
| ≥2 Co-morbidities | 2.22 |  |  |  |
| Serum bicarbonate <  25 |  | 1.30 |  |  |
| ARB | 2.68 | 1.85 | 1.4 | 15.89 |
| ACE-I | 2.24 | 1.85 | 1.4 | 13.63 |
| Spironolactone | 2.53 | 2.10 |  | 7.77 |
| NSAIDS | 2.68 |  |  |  |
| Beta blocker | 2.14 |  | 1.06 |  |

### Table 1: Risk factors with odds ratio of developing hyperkalaemia in community studies.

Several risk factors contribute to community-acquired hyperkalaemia as shown in Table 1. The presence of multiple co-morbidities or other risk factors further increase the risk of hyperkalaemia.6-9 。。RAASi drugs are frequently implicated in AKI and hyperkalaemia, but there are conflicting reports in the literature.10, 11 。。Given the potential risk of AKI, ‘sick day rules’ guidance recommending the cessation of RAASi drugs during acute illness has been proposed by some groups including NICE, but this remains controversial.1, 10, 12, 13, 14

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| **Study** | **Country** | **Setting** | **N=** | **eGFR**  **ml/min** | **Definition of HyperK mmol/l** | **Prevalence HyperK**  **%** | **Mortality risk with HK** |
| Liamis 201315 | Netherlands | General population  (age > 55) | 5179 | >60 | ≥6.0 | 0.3 | #OR 2.08 |
| Chang 201616 | USA | Health care system – HBP  (age ≥ 18) | 155,695 | >60 | >5 | 10.8 | NA |
| >5.5 | 2.3 |
| Hughes- Austin 201717 | USA | Multi- ethnic general population  (age ≥65) | 9651 | >60 | ≥5.0 | 2.8 | +HR 1.41 |
| Horne 20199 | UK | General population (age ≥ 18) | 195,178 | >60 | 5.0 – 5.4 | 91.2 | ∞2.51 |
| 5.5 – 6.0 | 7.2 | ∞3.83 |
| >6 | 1.6 | ∞12.57 |

### Table 2: Prevalence and outcome of Hyperkalaemia in patients with eGFR> 60 ml/min in community studies.

#OR- Odds Ratio; +HR- Hazard Ratio; ∞All-cause mortality; HBP – hypertensive; NA – not available

The reported incidence of hyperkalaemia in the general population is variable depending on the specific patient group, study design, level of renal function and definition of hyperkalaemia.6, 9, 15-19 。。The prevalence of hyperkalaemia in patients with an eGFR > 60 ml/min is shown in Table 2. In a large UK primary care study, the overall incidence rate of a hyperkalaemic event was 2.9 per 100 person years.9 。。In this study, the use of RAASi was strongly associated with hyperkalaemia with an odds ratio of 13.6 - 15.9.

Hyperkalaemia is more common in patients with CKD and the incidence increases with declining renal function. Sarafadis et al found that over 30% of patients experienced hyperkalaemia (K+ > 5.5 mmol/l) in the pre-dialysis setting (eGFR < 15 ml/min).7 。。A summary of the prevalence of hyperkalaemia in patients with CKD is shown in Table 3.

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| **Study** | **Country** | **Setting** | **N=** | **eGFR**  **ml/min** | **Definition of HyperK mmol/l** | **Prevalence HyperK**  **%** | **Mortality by K**+ **level** |
| Korgaonkar  201020 | USA | Renal Clinic | 820 | 25.4 | ≥5.5 | 7.9 | +HR 1.57 |
| Sarafidis 20127 | UK | Low Clearance clinic | 238 | 14.5 | 5.0 – 5.4 | 22.7 | NA |
| 5.5 – 5.9 | 23.1 | NA |
| ≥6.0 | 8.4 | NA |
| Nakhoul 20158 | USA | CKD  Registry (USA) | 36,359 | 47 | 5.0 – 5.4 | 11 | #OR 1.12 |
| >5.5 | 3.3 | #OR 1.65 |
| Turgutalp 20166 | Turkey | Elderly  population (age > 65) | 40,092 | 23-35 | ≥5.5 | 2.9 | AUC values by age  p< 0.001 |
| Luo 201619 | USA | Health care system (age ≥ 18) | 55,266 | < 60 | 5.0 – 5.4 | 14.9 | \*IRR 1.01 |
| 5.5 – 5.9 | 3.9 | \*IRR 1.11 |
| ≥6.0 | 1.1 | \*IRR 3.08 |
| Furuland 201818 | UK | Health care database | 191,964 | 50.9 | 5.0 – 5.4 | 45.1 | \*IRR 1.1 |
| 5.5 – 5.9 | 15.9 | \*IRR 1.60 |
| ≥6.0 | 4.9 | \*IRR 2.88 |

### Table 3: Prevalence of hyperkalaemia and mortality rate in patients with CKD.

NA – not available; +HR – Hazard Ratio; #OR - Odds Ratio; AUC- Area Under Curve; \*IRR- Incident rate ratio

Hyperkalaemia is associated with increased hospitalisation, prolongation of hospital stay and increased mortality. Horne et al showed the incidence rates for all-cause hospitalisation in adults was 14.1 per 100 person years.9 。。Turgutalp et al demonstrated a higher incidence of hospitalisation for hyperkalaemia in the elderly population: age 65-74 years (46%), age 75-84 years (44%) and ≥ 85 years (74%).6 。。Mortality increases with worsening severity of hyperkalaemia in the general population and in patients with CKD.8, 9, 18, 19

This chapter focuses on the detection, treatment and prevention of hyperkalaemia in the community. It will address the management of patients receiving RAASi drugs, indications for hospital admission and the use of novel oral potassium lowering drugs.

**References**

1. Clark, A.L., et al., *Change in renal function associated with drug treatment in heart failure: national guidance*. Heart, 2019. **105**(12): p. 904-910.
2. Palmer, B.F. and D.J. Clegg, *Diagnosis and treatment of hyperkalemia*. Cleve Clin J Med, 2017. **84**(12): p. 934-942.

## Patient monitoring (Guidelines 1.1-1.2)

### Guideline 1.1 – Monitoring of patients at risk of Hyperkalaemia in the community.

We recommend that patients known to have CKD, heart failure and/or diabetes, who are at risk of hyperkalaemia, undergo regular blood monitoring at a frequency (2-4 times per year) dependent on level of renal function and degree of proteinuria. (1B)

### Guideline 1.2.1 – Monitoring of patients after an episode of mild hyperkalaemia detected in the community.

We recommend that the serum K+ is repeated within 3 days, or as soon as feasible, if an episode of mild hyperkalaemia (K+ 5.5 – 5.9 mmol/l) is detected unexpectedly in the community. (1C)

### Guideline 1.2.2 – Monitoring of patients after an episode of moderate hyperkalaemia detected in the community.

We recommend that the serum K+ is repeated within 1 day of an episode of moderate hyperkalaemia (K+ 6.0

– 6.4 mmol/l) when detected in the community. (1C)

### Guideline 1.2.3 – Monitoring of patients after an episode of severe hyperkalaemia detected in the community.

We recommend that patients with severe hyperkalaemia (K+ ≥ 6.5 mmol/l) detected in the community are admitted for immediate assessment and treatment. (1B)

**Audit measure**

1. Frequency of hospital admission for severe hyperkalaemia (serum K+ > 6.5 mmol/l) detected on routine blood test in the community.

**Rationale (Guideline 1.1 – 1.2)**

Patients with CKD are at risk of hyperkalaemia and progression of their underlying kidney disease, therefore require regular blood monitoring in the community. The NICE CKD Guideline suggests that the frequency of monitoring should be tailored to the level of renal function, rate of decline in renal function and degree of proteinuria.1 。。Patients with CKD 1-3 require monitoring at least 1-2 times per year and patients with CKD 4-5 require monitoring at least 2-4 times per year. More frequent monitoring is indicated during acute illness and following an episode of AKI or hyperkalaemia.

Several observational studies have reported the frequency of blood monitoring in patients with CKD in relation to detection of hyperkalaemic events. Chang et al showed that the proportion of patients who had a serum K+ level performed over a 3 year period was 0 tests/ year (20%), <2 tests/ year (58%), 2-3 tests/ year (16%) and ≥4 tests/ year (6%).2 。。In patients with an eGFR < 30ml/min who had ≥4 tests per year, hyperkalaemia was found in 30%.

**The more often you test, the more often you will detect hyperkalaemia, especially in patients at risk.**

**Patients with CKD 4-5 have a high risk of hyperkalaemia and warrant regular testing.**

Luo et al reported the frequency of blood monitoring stratified by level of renal function and level of serum K+.3 。。In patients with an eGFR < 30 ml/min, the mean frequency of tests per year was 1.69 ± 1.35 (serum K+ 5.5 – 5.9 mmol/l) and 1.37 ± 0.98 (serum K+ ≥ 6 mmol/l) respectively. In patients with an eGFR 50-59 ml/min, the mean frequency of tests per year was 1.34 ± 0.92 (serum K+ 5.5 – 5.9 mmol/l) and 1.21 ± 0.73 (serum K+ ≥ 6 mmol/l) respectively. Similar to Chang et al, detection of hyperkalaemia increases with frequency of testing. Overall, the frequency of monitoring in these studies was generally 1-2 times per year, with more frequent testing in patients with an eGFR < 30 ml/min.

The interval between hyperkalaemic episodes was reported in a large retrospective cohort of patients with CKD.4 。。This study utilised data from primary care records for approximately 7% of the UK population over a mean follow-up of 4.9 years. Patients experiencing at least one episode of hyperkalaemia was stratified in three groups: serum K+ 5.0 – 5.4 mmol/l (45.2%), 5.5 – 5.9 mmol/l (15.9%) and ≥ 6.0 mmol/l (4.9%). The time interval to a recurrent episode of hyperkalaemia progressively shortened in each severity group. The interval between the first to second episodes in patients with serum K+ 5.5 – 5.9 mmol/l was 0.84 years and reduced to 0.59 years between the second and third episode and 0.48 years between the third and fourth episode. The interval between recurrent episodes was shorter in patients with serum K+ ≥ 6 mmol/l (0.65, 0.41 and 0.30 years respectively).

This collective data would suggest that monitoring serum K+ at least twice per year in patients at risk of hyperkalaemia is a reasonable approach. The frequency of monitoring should be increased to at least four times per year in patients with an eGFR < 30 ml/min and in patients with a serum K+ ≥ 6 mmol/l given the high risk of recurrence.

The interval for blood monitoring after a hyperkalaemic event is less well documented. Horne et al demonstrated that only 5.8% of patients had a repeat serum K+ performed within 14 days of the hyperkalaemic event, but a large number of patients had a serum K+ < 5.5 mmol/l which may have been perceived to be non-urgent.5 。。A repeat level occurred more commonly in patients with K+ > 6.0 mmol/l (55.3%) compared with those with a serum K+ 5.6 – 6.0 mmol/l (23.4%) or serum K+ 5.0 – 5.5 mmol/l (3.9%). In patients with a serum K+ > 6.0 mmol/l at the index event, 36.8% had an elevated K+ level on re-testing.

‘Think Kidneys’ have provided practical guidance on repeat testing after a hyperkalaemic episode.6 。。The timing is guided by the level of hyperkalaemia and clinical context. In patients with mild hyperkalaemia (K+ 5.5 – 5.9 mmol/l), a repeat test is recommended within 3 days if the result was unexpected or as soon as feasible if the patient is clinically stable. In patients with moderate hyperkalaemia (K+ 6.0 – 6.4 mmol/l), a repeat test is recommended within 1 working day if detected on a routine check in a stable patient, but referral to hospital should be considered if clinically unwell or if an AKI is present. Patients with severe hyperkalaemia (K+ ≥ 6.5 mmol/l) warrant urgent referral to hospital for immediate assessment and

treatment if required. The recommended interval for repeat testing after a hyperkalaemic episode is summarised in Table 4.

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| --- | --- | --- | --- |
| **Severity of Hyperkalaemia** | **Clinically well (no AKI)** | **Unexpected result** | **Clinically unwell or AKI** |
| **MILD**  K+ 5.5 – 5.9 mmol/l | Repeat within 14 days | Repeat within 3 days | #Consider if hospital referral is indicated |
| Assess for cause (drugs, diet) and address in community | | |
| **MODERATE**  K+ 6.0 – 6.4 mmol/l | Repeat within 1 working day\* | Repeat within 24 hours | Refer to hospital |
| Assess for cause (drugs, diet) and address community or hospital | | |
| **SEVERE**  K+ ≥ 6.5 mmol/l | **Refer to hospital for immediate assessment and treatment** | | |
| Assess for cause and address during hospital admission | | |

### Table 4: Interval for repeat blood monitoring following an episode of hyperkalaemia.

#Need for hospital referral will be guided by clinical circumstance and risk of further deterioration.

\*Routine bloods tests unavailable at weekends and out of hours from community. (*Modified from Think Kidneys Guideline*)6

There is increasing use of point of care testing (POCT) in the hospital setting for rapid potassium measurement, but achieving rapid blood analysis in the community can be challenging. POCT has been validated in several studies in the hospital setting within the Emergency Department and Critical Care.7-12 。。POCT has also been shown to improve early recognition of hyperkalaemia in patients with CKD presenting to the Emergency Department.13 。。Use of POCT in the pre-hospital setting is less well reported.14,15 。。A study of the utilisation and validation of POCT devices by community paramedics demonstrated good correlation with laboratory measurement.14 。。Technology is rapidly developing with the use of medical biosensors and Smart phone technology potentially making POCT easily accessible for patients.16

**References**

* + 1. National Institute for Health and Care Excellence: Chronic kidney disease. Scenario: Management of chronic kidney disease. Last revised in May 2020. [www.cks.nice.org.uk/chronic-kidney-](http://www.cks.nice.org.uk/chronic-kidney-) disease#!scenarioRecommendation:1.

## Management of patients receiving RAASi drugs (Guidelines 2.1-2.7)

### Guideline 2.1 – Assessment of patients prior to initiation of ACE-I or ARB.

We recommend that urea and electrolytes should be assessed prior to initiation of ACE-I or ARB and these drugs should be used with caution if the serum K+ is > 5.0 mmol. (1A)

### Guideline 2.2 – Assessment of patients prior to initiation of Mineralocorticoid Receptor Antagonists (MRA).

We suggest that initiation of MRAs should be avoided in patients with a baseline serum K+ > 5.0mmol/l or eGFR < 30 ml/min. (1B)

### Guideline 2.3 – Monitoring of patients after initiation of ACE-I and ARB.

We recommend that urea and electrolytes should be assessed at 1 – 2 weeks after initiation of ACE-I or ARB and after every dose titration. (1A)

### Guideline 2.4 – Monitoring of patients after initiation of MRAs.

We recommend that urea and electrolytes should be assessed at 1 week after initiation of MRA or after dose up-titration, then monthly for the first 3 months, 3-monthly for the first year and 4-monthly thereafter. (1A)

### Guideline 2.5 – Management of hyperkalaemia in patients treated with RAASi drugs.

We suggest increased frequency of monitoring in patients with a serum K+ between 5.5-5.9 mmol/l and consideration of dose reduction of RAASi drugs (ACE-I, ARB, MRA). (1B)

**Guideline 2.6 – Management of hyperkalaemia in patients treated with RAASi drugs during acute illness**. We recommend that RAASi drugs be withheld during acute intercurrent illness (e.g. sepsis, hypovolaemia and/or AKI) at all severities of hyperkalaemia. (1D)

### Guideline 2.7 – Cessation of RAASi drugs in patients with moderate or severe hyperkalaemia.

We recommend cessation of RAASi drugs in patients with serum K ≥ 6 mmol/l who do not meet the criteria for treatment with patiromer or sodium zirconium cyclosilicate. (1B)

**Audit measure**

1. Frequency of blood monitoring of patients receiving RAASi drugs in the community.

**Rationale (Guidelines Hyperkalaemia 2.1 – 2.7)**

Patients with CKD, heart failure and diabetes are particularly at risk of hyperkalaemia and these conditions often co-exist. RAASi drugs have become the standard of care to slow progression of CKD and in the management of patients with diabetes and heart failure. However, hyperkalaemia frequently limits use or titration of RAASi drugs. Epstein et al conducted a large study (> 7 million of electronic patient records) to determine the impact of hyperkalaemia on the optimal versus real-world treatment with RAASi.1 。。In patients for whom RAASi was recommended by treatment guidelines for cardiorenal disease, >50% were prescribed lower than recommended dose and 14-16% discontinued RAASi therapy.1

Sub-optimal treatment for patients with heart failure and renal disease also affects patient outcome. Mortality rates has been shown to be higher in patients who receive sub-maximal dosing (8%) and in those who have discontinued RAASi (11%) compared to those who received maximal dosing (4%).2 。。Similarly, Ouwerkerk et al demonstrated increased hospitalisation and increased mortality in patients with heart failure with reduced ejection fraction (HFrEF) who receive less than half of the recommended doses of ACE-I or ARB (HR 1.72) and beta blockers (HR 1.70) compared to patients who reached optimal doses.3 。。The balance between optimising treatment and compromising renal function poses a significant clinical dilemma. Monitoring of serum K+ in patients receiving RAASi drugs reduces the risk of adverse events. Raebel et al demonstrated that patients with diabetes who underwent potassium monitoring during the first year of treatment with RAASi drugs were less likely to experience hyperkalaemia-associated adverse events (hospitalisation, Emergency Department attendance or death) with an adjusted relative risk of 0.50 (0.37, 0.66) compared to those who were not monitored.4 。。The sub-set of patients with CKD had an adjusted relative risk of 0.29 (0.18, 0.46). Park et al conducted an observational study of hospitalised patients newly started on an ARB and demonstrated that the highest incidence of hyperkalaemia occurred on the first day and 52.4% of hyperkalaemic events occurred within the first week of initiation.5 。。In this study, hyperkalaemia also occurred earlier in patients with reduced GFR, higher baseline K+ level (patients with K+ >5.5 mmol/l were excluded) and in patients with diabetes.

The KDIGO Guideline (2012) recommends measuring serum K+ level within 1 week of starting RAASi drugs and after every dose increment in patients with reduced renal function.6 。。The NICE Guideline for CKD (2014) recommends measuring serum K+ level before starting, within 1 to 2 weeks of initiation of RAASi therapy and after every dose increment.7

**Assess urea & electrolytes prior to initiation of RAASi drugs.**

**Monitor urea & electrolytes at 1 week after initiation and after each dose titration.**

The NICE CKD Guideline (2014) also recommends that RAASi drugs should be withdrawn if the serum K+ is ≥ 6 mmol/l.7 。。However, NICE has recently approved the use of potassium binders (patiromer and sodium zirconium cyclosilicate) in selected patients with CKD 3b-5 (not on dialysis) or heart failure who have confirmed persistent hyperkalaemia with a serum K+ ≥ 6 mmol/l and are not receiving an optimal dose of RAASi.[8][9] RAASi should be withdrawn in all patients with serum K+ is ≥ 6 mmol/l who do not meet the criteria for these novel potassium binders.

The Renal Association and the British Society for Heart Failure (2019) have recently collaborated to provide consensus recommendation for the use of RAASi in patients with heart failure with reduced left ventricular ejection fraction (HFrEF).10 。。Monitoring of renal function is mandatory during initiation and titration of RAASi treatment. In the context of acute illness (sepsis, hypovolaemia and/or AKI), withdrawal of RAASi was advised at all severities of hyperkalaemia. However, in the context of decompensated heart failure, the continuation/ reduction of RAASi therapy was permitted in patients with mild or moderate hyperkalaemia,

but withdrawn if serum K+ ≥ 6.5 mmol/l. RAASi re-introduction was recommended after recovery and when K+ was < 5.5 mmol/l. Patients receiving multiple RAASi drugs and/or MRA should re-start one drug at a time. Mineralocorticoid receptor antagonists (MRAs) have significantly improved heart failure management, but their use alone or in combination with RAASi, may exacerbate hyperkalaemia. The European Society of Cardiology11 and American Heart Association (AHA)/ American College of Cardiology (ACC)12 guidelines provide guidance on initiation, monitoring and response to treating hyperkalaemia in patients receiving MRAs. The parameters for initiation of MRA are a serum K+ < 5.0 mmol/l and an eGFR > 30ml/min. Close monitoring of urea and electrolytes (U&Es) is required following initiation at 1, 4, 8 and 12 weeks. Thereafter, monitoring is required every 3 months during first year, then every 3-4 months from second year onwards. The approach to managing hyperkalaemia in patients with heart failure on MRA is shown in the text box below. In patients without heart failure, drug cessation is recommended if serum K+ ≥ 6.0 mmol/l.

**Strategies for Managing Hyperkalaemia in patients with Heart failure on MRA**

* K+ 5.5-5.9 mmol/l: Reduce dose by half and monitor U&Es
* K+ > 6.0 mmol/l: Start potassium binder (Patiromer or SZC) and monitor U&Es

Adherence to guideline recommendations appears to be poor. In a large population-based study of new users of RAASi drugs, < 33% of patients had a K+ measurement within 30 days of drug initiation and only 76% had at least one measurement within the first year of treatment.13 。。In another study, Chang et al reported that 20% of patients had no serum K+ monitoring within 3 years of initiation of antihypertensive medication that affect potassium levels.14 。。Combined treatment of RAASi and an aldosterone antagonist increase the risk of hyperkalaemia, but Sinnott et al reported <33% of patients taking a RAASi had biochemical monitoring within two weeks of initiation of an aldosterone antagonist.15 。。This highlights the gap in knowledge and clinical practice.

**References**

1. Epstein, M., *Hyperkalemia constitutes a constraint for implementing renin-angiotensin-aldosterone inhibition: the widening gap between mandated treatment guidelines and the real-world clinical arena*. Kidney Int Suppl (2011), 2016. **6**(1): p. 20-28.

## Threshold for treatment of hyperkalaemia (Guideline 3.1)

### Guideline 3.1 – Threshold for treating Hyperkalaemia in the community.

We recommend that interventions to lower serum potassium be instituted in patients with a serum K+ ≥ 5.5 mmol/l. (1B)

**Rationale (Guideline 3.1)**

The detection of hyperkalaemia in the community is frequently the result of blood monitoring in relation to the prescription of RAASi medication. Outwith this context, most observational studies have based diagnosis of hyperkalaemia on a single blood test. Pseudo-hyperkalaemia may occur in the community after long transit time to the laboratory, therefore unexpected results should be repeated.

Existing National guidelines recommend initiation of strategies to manage hyperkalaemia when the serum K+ rises to ≥ 5.5 mmol/l.1,2 。。Data from several studies performed in the general population and in patients with CKD show an increased mortality risk in patients with a serum K+ ≥ 5.5 mmol/l.3-9 。。Mortality risk increases further when the serum K+ exceeds 6 mmol/l, therefore measures should be taken to avoid a further rise in serum K+ level.

Drugs are frequently implicated in the development of hyperkalaemia in the community. Serum K+ levels increase by 0.4 – 0.6 mmol/l during RAASi treatment in patients with diabetic and non-diabetic kidney disease and approximately 1 – 1.7% of patients develop hyperkalaemia.1 。。Although RAASi and non-selective beta-blockers can increase K+ levels, consider the degree of hyperkalaemia and the indication for use before reducing or withholding the drug.

Stop other medications known to exacerbate hyperkalaemia (e.g. oral potassium supplements, NSAIDs, trimethoprim). Other strategies for lowering serum K+ in the community include dietary interventions (Guideline 5.1), treating metabolic acidosis (Guideline 6.1) and controlling hyperglycaemia. Re-introduction of medications that influence K+ levels requires slow titration and close monitoring.

**References**

1. National Institute for Health and Care Excellence: Chronic Kidney Diseases in adults - assessment and management. Clinical Guideline 182; July 2014. [www.nice.org.uk/guideline/cg182/](http://www.nice.org.uk/guideline/cg182/)

## Indications for hospital assessment (Guidelines 4.1 - 4.2)

### Guideline 4.1 – Indication for assessment in hospital for patients with severe hyperkalaemia detected in the community.

We recommend urgent hospital assessment for all patients with severe hyperkalaemia (serum K+ ≥ 6.5 mmol/l) detected in the community. (1A)

### Guideline 4.2 – Indication for assessment in hospital for patients with mild-moderate hyperkalaemia detected in the community.

We suggest hospital assessment for acutely unwell patients with mild (serum K+ 5.5 – 5.9 mmol/l) or moderate hyperkalaemia (serum K+ 6.0 - 6.4 mmol/l), particularly in the presence of an acute kidney injury. (1B)

**Audit Measures**

Proportion of patients admitted to hospital with severe hyperkalaemia detected in the community who subsequently did not warrant emergency treatment on repeat testing.

**Rationale (Guidelines Hyperkalaemia 4.1 – 4.2)**

There is substantial variability in clinical practice related to referral for hospital assessment for hyperkalaemia, which may be partly explained by incidental findings in clinically well patients. The detection of hyperkalaemia in the community is rising with the increasing use of RAASi drugs for multiple clinical indications and the necessity for regular biochemical surveillance. Drug up-titration or co-administration of another drug that affects K+ level, as shown in Table 5, can precipitate severe hyperkalaemia.1 。。Acute illness is another common antecedent to acute kidney injury and hyperkalaemia**.**

**Drugs that potentiate risk of hyperkalaemia in patients receiving RAASi and/or MRAs**

* Trimethoprim/co-trimoxazole
* Potassium supplements
* Potassium sparing diuretics
* Salt substitutes (lo-salt)
* NSAID
* Non-selective beta-blockers
* Digoxin toxicity

### Table 5: Drugs that pose an additive effect on risk of hyperkalaemia in patients receiving RAASi and MRAs.

The risk of adverse events increases with worsening hyperkalaemia. Severe hyperkalaemia is an independent predictor of all-cause and in-hospital mortality as well as hospitalisation.2 。。Therefore, defined

thresholds for triggering intervention in the community and for prompting referral to hospital could improve patient outcome.

There is little evidence for a specific threshold for hospital admission for management of hyperkalaemia. Charytan et al undertook a small study (n=23) to assess the practice relating to hospitalisation of patients for hyperkalaemia.3 。。In this study, 11 patients with hyperkalaemia at hospital admission were compared with 12 hyperkalaemic patients managed as an outpatient. The study lacked power to determine the relative safety of location of treatment. Horne et al demonstrated the impact of hyperkalaemia on mortality and healthcare utilisation, including hospital admission, in the UK general population, but did not provide a distinct threshold warranting hospital admission.4 。。However, this study noted a significantly higher incidence rate of all-cause hospitalisation for patients with a serum K+ > 6.0 mmol/l of 28.93/ 100 person-years compared with patients with a serum K+ 5.0-5.5 mmol/l of 13.86/ 100 person-years.

The position statement for ‘Think Kidneys’, a collaboration of The Renal Association and British Society for Heart Failure, recommend hospital admission in all patients with severe hyperkalaemia (K+ ≥ 6.5 mmol/l) and in patients with moderate hyperkalaemia (K+ 6.0-6.4 mmol/l) who are acutely unwell or have an AKI.6 。。Hospital admission should be considered in patients with mild hyperkalaemia (K+ 5.5-5.9 mmol/l) if acutely unwell or have an AKI.

An important consideration in the management of an episode of hyperkalaemia is the balance between the immediate risk versus the impact of cessation of RAASi drugs in patients for whom these drugs are crucial in controlling symptoms and improving survival. Minimising the duration of cessation of treatment and clear communication after hospital discharge is essential. Involvement of specialist services, renal and heart failure teams, may facilitate safer re-introduction of treatment.

**References**

1. Ben Salem, C., et al., *Drug-induced hyperkalemia*. Drug Saf, 2014. **37**(9): p. 677-92.

## Treatment: Dietary interventions (Guideline 5.1)

### Guideline 5.1 – Dietary Intervention for managing Hyperkalaemia in the community.

We recommend that a low potassium diet is instituted for patients with persistent hyperkalaemia with a serum K+ > 5.5 mmol/l. (1B)

**Audit measures**

1. Proportion of patients with moderate hyperkalaemia who have received dietary potassium advice in the renal out-patient setting.

**Rationale (Guideline 5.1)**

Dietary potassium comes from a wide range of foods including fruit and vegetables, meat and meat products, cereals, drinks, milk and milk products. Fruit and vegetables accounts for approximately 33% dietary potassium intake.1 。。In adults without kidney disease, the WHO recommends an average dietary K+ intake of approximately 3.9g/ day (100mmol).2 。。In the USA, the Institute of Medicine, Food and Nutrition Board recommend a higher daily K+ intake of 4.7g/ day (120mmol/l).[3] In patients with kidney disease, the National Kidney Foundation (NKF) suggests an unrestricted potassium intake in patients with CKD 1-5 (non- dialysis) unless the serum K+ is elevated.4 。。In advanced CKD and in ESRD, hyperkalaemia may result if the dietary input of potassium exceeds the output, therefore prevention of hyperkalaemia requires management of dietary K+ load.5

A low K+ diet is defined as a dietary intake of 2-3g/day (51-77 mmol/day)5. In patients with CKD with persistent hyperkalaemia (serum K+ ≥ 5.5mmol/l), a dietary K+ restriction of < 3g/ day (< 77 mmol/l) 6 or 1 mmol/kg/IBW 7 is recommended. In reality, a step-wise reduction in potassium intake is usually undertaken. Excessive dietary restrictions can result in a poorer diet which may risk development of cardiovascular disease 8 and contribute to malnutrition, particularly in advanced CKD. The development of constipation is also counterproductive as this will reduce K+ excretion by the gut. Therefore, a balanced intake of fresh fruit, vegetables and fibre is the ultimate goal.

A renal dietitian is skilled to provide individualised advice to patients with Stage 4-5 CKD managed by specialist renal services taking into account other factors including diabetic status, cultural needs and patient preferences. Assessment of biochemical trends would ensure that the need for ongoing dietary restrictions is reviewed. The Renal Association Guideline on Undernutrition in Chronic Kidney Disease also suggests assessment by a specialist renal dietitian when patients begin education about RRT and within one month of dialysis initiation.9

Although dietary intervention has become standard practice, this has not been demonstrated in a randomised controlled trial and would potentially be technically difficult to achieve. Three studies reported on dietary intervention for managing hyperkalaemia.10,11,12

Ahuja et al reported a retrospective analysis of patients attending a renal clinic (n=119) to determine the predictors for development of hyperkalaemia in patients on ACE-I.6 。。Overall, 46/119 patients (38.6%) of patients developed hyperkalaemia (mean serum K+ 5.68 mmol/l). Hyperkalaemia resolved in 20/46 patients (43%) with a low K+ diet alone (<2g/day; 51 mmol/l) and in 11/46 patients (24%) with dietary advice and dose reduction of ACE-I. Hyperkalaemia persisted in the remaining 15/46 patients (33%) despite dietary advice and reduction of ACE-I necessitating discontinuation of ACE-I.

Bushinsky et al studied the difference in serum K+ in hyperkalaemic patients (K+ 5.5-6.2 mmol/l) with CKD 2- 4 on a random diet versus controlled K+ diet during the 72-hour run-in phase of a treatment trial (n=25).7 。。Patients received stable doses of RAASi medication. The study demonstrated a wide inter-individual variation in serum K+ on a random diet. Variation decreased significantly after 24 hours on a low K+ diet (2.4g or 60 mmol/ day). The study concluded that this observation may have implications for the interpretation of clinical trials assessing directional change of serum K+ with a pharmaceutical intervention.

Maclaughlin et al prospectively investigated the prevalence of hyperkalaemia in a population of CKD patients (n=356) attending low clearance clinics who underwent regular nutritional assessment and dietary education.8 。。All patients were pre-dialysis with an eGFR ranging from 8 – 20 ml/min. The prevalence of hyperkalaemia (serum K+ > 5.5 mmol/l) was 26.5% before the dietetic program in 2011 and 10.5% after it was instituted in 2014. The prevalence of hyperkalaemia also reduced in patients with K+ > 6.0 mmol/l from 8.4% to 2.5% during the same intervals. A dietary education program delivered by specialist renal dietitians can be very effective in reducing the prevalence of hyperkalaemia.

In patients receiving renal replacement therapy, the KDOQI guidelines suggest a potassium intake of approximately 2.7-3.1 g/day (69-79 mmol/day) in haemodialysis patients and 3-4g/day (77-102 mmol/day) in peritoneal dialysis patients.3 。。Individualised adjustments are guided by the serum K+ level.

**References**

1. National Diet and Nutirtion Survey (NDNS) rolling program for 2014 to 2015 and 2015 to 2016 (results from Years 7 and 8 combined). [www.gov.uk/government/statistics/ndns-results-from-years-](http://www.gov.uk/government/statistics/ndns-results-from-years-) 7-and-8-combined.

## Treatment: Sodium bicarbonate (Guideline 6.1)

### Guideline 6.1 – Sodium bicarbonate for management of Hyperkalaemia in the community

We recommend that sodium bicarbonate is used in CKD patients with a serum bicarbonate level < 22 mmol/l with or without hyperkalaemia. (1B)

**Rationale (Guideline 6.1)**

Epidemiological studies show a prevalence of metabolic acidosis of 15-19% in patients with CKD stages 3-5.1 。。The prevalence increases with severity of kidney disease with metabolic acidosis found in 30-50% of patients with eGFR < 30 ml/min.2,3 。。Furthermore, serum bicarbonate levels steadily decrease with age > 60 years.4 。。Despite its prevalence, there is variability in clinical practice for treatment of mild acidosis in patients with CKD attending renal services and it is not routinely assessed or treated in primary care.

The benefit of treating chronic acidosis goes beyond the management of hyperkalaemia. Metabolic acidosis is also associated with muscle wasting, bone disease and increased mortality in patients with CKD.5 。。Additionally, there is growing evidence that metabolic acidosis contributes to the progression of CKD.1,6,7 。。Goraya et al demonstrated that an increase in serum bicarbonate by 4 - 6.8 mmol/l was associated with a reduction in decline in eGFR by 4 ml/min over 6 to 24 months compared with control patients.1

The mechanism for potassium lowering is the transcellular shift of K+ into cells following alkalinisation of the serum. Despite this theoretical benefit, few studies have shown any benefit of sodium bicarbonate in the treatment of acute or chronic hyperkalaemia. In two long-term studies (i.e. > 2 months), alkali therapy has been shown to be associated with a significant net decrease in the serum K+ by approximately 0.7 mmol/l, but no significant change was shown in short term studies (≤ 7 days).6,8

The BiCARB Trial evaluated the benefits and adverse effects of sodium bicarbonate in older patients with CKD for a period of up to 2 years. This was a double-blind placebo-controlled RCT which includes 380 community-based patients in the UK aged ≥ 60 years with an eGFR < 30 ml/min and serum bicarbonate < 22 mmol/l.9 。。In contrast to other longterm studies, this study found no significant reduction in serum K+ level. The BiCARB trial also reported no improvement in physical function or renal function and a higher rate of adverse events compared with placebo.

In the pre-dialysis setting, Sarafidis et al performed a prospective study to examine the factors influencing K+ metabolism in patients attending a low clearance clinic (mean eGFR 14.5 ± 4.8 mmol/l).10 。。This study demonstrated that patients with K+ ≥ 5.5 mmol/l had significantly higher urea, lower eGFR and lower serum bicarbonate levels. This sub-group also had a higher usage of sodium bicarbonate than in patients without hyperkalaemia (65.3% versus 45.4%, p=0.008).10

The potential detrimental effect of sodium load with sodium bicarbonate replacement is an important consideration, particularly in patients at risk of fluid overload. Dubey et al showed that patients with CKD 3 and 4 with co-existing diabetes, hypertension and coronary artery disease had a trend towards worsening hypertension and oedema necessitating a greater use of diuretics.7 。。Similar findings have been reported in other studies with alkali replacement in CKD patients necessitating discontinuation of sodium bicarbonate due to hypertension and oedema although these studies did not focus on management of hyperkalaemia.8,

11,12

A meta-analysis of all published RCTs investigating the effect of oral bicarbonate therapy in adults with CKD showed a slightly higher eGFR and serum bicarbonate levels in patients treated with oral replacement compared with placebo and this positive effect was attenuated in studies reporting outcomes at one year.13 。。This study did not assess potassium levels.

There remains a paucity of evidence from clinical trials on the efficacy and safety of bicarbonate therapy, therefore many existing guidelines are based on the sparse evidence and expert consensus opinion. KDOQI guidelines recommend the maintenance of serum bicarbonate level ≥ 22 mmol/l to reduce metabolic complications.14 。。The 2007 Cochrane Review of alkali therapy in CKD found insufficient evidence of benefit.15 。。The NICE CKD Guideline 2014 suggests that oral sodium bicarbonate should be considered in patients with CKD 4 or 5 with a serum bicarbonate < 20 mmol/l.16 。。The National Kidney Foundation ‘Best Practices In Managing Hyperkalaemia in CKD’ suggests the use of oral sodium bicarbonate for chronic hyperkalaemia.17

**References**

1. Goraya, N. and D.E. Wesson, *Clinical evidence that treatment of metabolic acidosis slows the progression of chronic kidney disease*. Curr Opin Nephrol Hypertens, 2019. **28**(3): p. 267-277.

## Treatment: Diuretics (Guideline 7.1)

### Guideline 7.1 – Use of diuretics for managing Hyperkalaemia in the community

We suggest that loop diuretics may be a useful adjunct for the treatment of chronic hyperkalaemia in patients who are non-oliguric and volume replete. (2C)

**Rationale (Guideline 7.1)**

In patients with preserved renal function, the kidneys are the primary route of potassium elimination. Loop and thiazide diuretics enhance K+ excretion by increasing flow and delivery of sodium to the collecting ducts and may be useful in treating mild to moderate hyperkalaemia in patients with adequate renal function.1, 2 。。Loop diuretics (e.g. furosemide, bumetanide) are the most effective class that promote urinary K+ excretion and remain effective in patients with moderate renal impairment.1,3 。。On the other hand, thiazide diuretics are effective in patients with an eGFR > 30ml/min.1 。。Diuretics should be avoided in patients who are hypovolaemic or oliguric.

Patients with heart failure are susceptible to both hyperkalaemia and volume overload. RAASi therapy is frequently used in this setting and loop diuretics are a useful adjunct in controlling chronic hyperkalaemia whilst treating congestion.4,5 。。Decompensated heart failure in the presence of mild-moderate hyperkalaemia often necessitates a reduction or cessation of cardioprotective medication which may worsen heart failure. The joint guideline from the Renal Association and British Society of Heart Failure (2019) recommends consideration of combination therapy with a loop and thiazide diuretic in patients with decompensated heart failure (HFrEF) and mild-moderate hyperkalaemia.4 。。This combination potentiates diuresis and should theoretically enhance K+ excretion.

Diuretic therapy has a place in the management of chronic hyperkalaemia in patients who are normovolaemic or hypervolaemic. There is little evidence to support its use in acute hyperkalaemia.6 。。A multi-modal approach including diuretics, treatment of metabolic acidosis and dietary potassium restriction may allow the continuation of cardioprotective medications in patients with mild hyperkalaemia.

**References**

1. Palmer, B.F. and D.J. Clegg, *Diagnosis and treatment of hyperkalemia*. Cleve Clin J Med, 2017. **84**(12): p. 934-942.

## Treatment: Calcium resonium (Guideline 8.1)

### Guideline 8.1 – Calcium resonium for the management of Hyperkalaemia in the community.

We suggest that calcium resonium may be used as a short-term measure to lower serum potassium to a level of ≤ 5 mmol/l in patients with mild to moderate hyperkalaemia. (2C)

**Rationale (Guideline 8.1)**

Calcium polystyrene sulphonate (CPS, Calcium resonium) and sodium polystyrene sulphonate (SPS, Kayexalate) are cation exchange resins that work in the lower GI tract to enhance the elimination of K+ in the faeces. Each gram of resin has a theoretical in vitro exchange capacity of approximately 1.3 – 2 mmol of K+, but in vivo, it will be less.1 。。Resins cause constipation, therefore laxatives are given to accelerate resin transit and to increase K+ excretion in stools.2 。。Lactulose is an osmotic laxative and is commonly used in the UK. Macrogol 3350 (Laxido®, Movicol®) should be avoided as it contains potassium (46.6mg or 5.4mmol/l per sachet).

CPS is approved for use in Europe and SPS approved for use in the USA. SPS was approved by the Food and Drug Administration (FDA) in 1958 on the basis of two small uncontrolled case series undertaken in the 1950’s.3 。。This approval preceded the Kefauver-Harris Drug Amendment (1962) and the European Union EC/65/65 directive (1965) requiring drug manufacturers to prove the effectiveness and safety of their drug.4 。。Following multiple reports of colonic necrosis and other serious gastrointestinal adverse events (perforation, bleeding), the FDA applied safety recommendations in 2009. The FDA also advised against the concomitant administration of sorbitol, but serious complications have also been reported without the use of sorbitol.5

There are 3 RCTs including SPS as an intervention. Gruy-Kapral (1998) reported a placebo-controlled randomised study of SPS in normokalaemic patients with ESRD on HD (n=6) and failed to show any significant reduction in serum K+.6 。。The size, design and insufficient baseline data renders this study weak. Nasir et al (2014) performed a RCT to compare the efficacy and safety of CPS and SPS in CKD patients (n=97) with hyperkalaemia.7 。。Although both drugs lowered serum K+, the study lacked adequate statistical analysis to substantiate the claim of equal efficacy and there was no control arm (i.e. placebo group). Of note, fewer side effects were reported with CPS than SPS. Lepage et al (2015) conducted a single centre double-blind RCT (n=33) in outpatients with CKD and mild hyperkalaemia (K+ 5.0-5.9 mmol/l) comparing efficacy of SPS 30g daily to placebo for 7 days.4 。。This study reported an absolute reduction of serum K+ level of 1.25 mmol/l (p<0.001), but the proportion of patients who achieved normokalaemia did not reach statistical significance (p=0.07). This trial lacked intermediate efficacy time points. None of these studies met the inclusion criteria for the Cochrane Review (2015).8

The evidence for use of SPS is otherwise sparse. Chernin et al (2012) conducted a retrospective study (n=14) to assess the efficacy of SPS in CKD patients receiving RAASi medication, and observed a reduction in serum K+ from 6.4 ± 0.3 mmol/l to 4.6 ± 0.6 mmol/l ( p< 0.01) over a median follow up of 14.5 months. The size, lack of a control group and other confounding factors rendered this study difficult to interpret. Fordjour et al (2014) conducted a prospective chart review of treatment of hyperkalaemia in hospitalised patients and found that SPS was included in 95% of treatment regimens with K+ reduction ranging from 0.7 – 1.1 mmol/l. Effectiveness was deemed to be similar among patients with CKD and those receiving dialysis. Combination regimens yielded the greatest K+ reduction. Batterink et al (2015) conducted a retrospective study (n=138) and reported that SPS reduces serum K+ by 0.14 mmol/l more than control, but concluded that this level of treatment effect may not be clinically important.9

The evidence for use of CPS is equally sparse. Chaaban et al (2013) conducted a retrospective study (n=70) to assess the effectiveness of calcium resonium in controlling hyperkalaemia in HD patients.1 。。This study showed poor efficacy attributed to lack of adherence to the drug and dietary restrictions as well as poor tolerability. Yu et al (2017) reported a retrospective analysis of 247 CKD patients in an out-patient setting treated with low dose CPS (8.0 ± 3.6 g/day) over a variable duration from > 3 months to beyond 1 year.10 。。Baseline eGFR was 30 ± 15 ml/min and serum K+ was ≥ 5.0 mmol/l. Serum K+ decreased significantly from 5.8 ± 0.3 mmol/l to 4.9 ± 0.7 mmol/l (p<0.001) with CPS treatment without any serious adverse effects over a long period.

CPS and SPS have been used widely for decades for the non-emergency treatment of hyperkalaemia despite the lack of robust randomised clinical trials to document efficacy or safety. Tolerability and the risk of severe gastrointestinal adverse effects limit their longterm use. The availability of novel potassium binders (patiromer and sodium zirconium cyclosilicate) with a stronger evidence base for efficacy and more favourable side-effect profiles may replace CPS and SPS in clinical practice in the future. However at present, UK guidance from NICE restricts their use to specific circumstances and the Scottish Medicines Consortium (SMC) have not approved either drug. Therefore these alternatives to calcium resonium are not currently available to many patients.

**References**

* + 1. Chaaban, A., et al., *Potassium binders in hemodialysis patients: a friend or foe?* Ren Fail, 2013. **35**(2): p. 185-8.

## Treatment: Patiromer (Guidelines 9.1-9.3)

### Guideline 9.1 – Patiromer for the management of Hyperkalaemia in the community

We recommend that Patiromer is an option in the management of persistent hyperkalaemia with a confirmed serum K+ ≥ 6.0 mmol/l in out-patients with CKD Stage 3b-5 (not on dialysis) or heart failure receiving a sub-optimal dose or not receiving RAASi therapy due to hyperkalaemia. (1A)

### Guideline 9.2 – Patiromer for the management of Hyperkalaemia

We recommend that treatment with Patiromer is discontinued if RAASi therapy is stopped. (1A)

### Guideline 9.3 – Patiromer for the management of Hyperkalaemia

We recommend that Patiromer is initiated in secondary care only. (1A)

**Audit measures**

1. The proportion of out-patients with moderate hyperkalaemia (serum K+ 6.0 - 6.4 mmol/l) treated with patiromer who achieved a serum K+ ≤ 5.0 mmol/l within 1 week.
2. The proportion of out-patients who achieve maximal dose RAASi therapy whilst taking patiromer.

**Rationale (Guideline 9.1 – 9.3)**

Patiromer is a non-absorbed, sodium free, K+-binding polymer.1 。。Calcium is used, rather than sodium, as the counter ion for K+ exchange. This avoids the potential for excessive sodium absorption and volume overload. The drug is active throughout the gastrointestinal tract but mostly in the colon. The onset of action is slow at 4-7 hours.1 。。Patiromer has the potential to bind to some co-administered oral medication (e.g. metformin, levothyroxine and ciprofloxacin), therefore administration needs to be separated from other oral medications by ≥3 hours.1

To date, the standard approach to treating chronic hyperkalaemia has been a dose reduction or cessation of cardioprotective medication along with the institution of a low K+ diet. Dietary K+-restriction was implemented in patiromer trials and K+-lowering drugs are unlikely to replace a low K+ diet although may allow a less restrictive intake.

The definition of hyperkalaemia used in the patiromer trials to guide treatment differed from the Renal Association (2014)2 and European Resuscitation Council (2015)3 guidelines. In the patiromer trials, mild hyperkalaemia was defined as serum K+ 5.1 - 5.4 mmol/l and moderate to severe hyperkalaemia as serum K+ 5.5 - 6.4 mmol/l.4-10 。。Early studies included 3 Phase I clinical pharmacology studies and 12 single dose drug- drug interaction studies as summarised in Table 6.

The PEARL-HF [11] and PEARL-HF extension 9 studies are the only patiromer trials with all participants having a diagnosis of chronic heart failure. Fewer patients in OPAL-HK (42%)5 and AMETHYST-DN (35%)6 had heart failure (Appendix 2). In the PEARL-HF study, almost half of the patients treated with patiromer developed hypokalaemia (K+ < 4 mmol/l) which also infers a higher risk of mortality in heart failure. However, in the PEARL-HF extension study, spironolactone could be optimised with a lower starting dose of patiromer whilst reducing the incidence of hypokalaemia.

In the OPAL-HK trial, 76% of patients with HF achieved serum K+ levels within the target range with patiromer. Hypokalaemia (K+ <3.5 mmol/l) occurred in 3% of patients. During the withdrawal phase, hyperkalaemia (K+ ≥5.5 mmol/l) recurred in 52% of patients compared with 8% in patients who remained on patiromer. By the end of the 8-week period, 100% in the patiromer group remained on RAASi compared with only 55% in the placebo group.

Patients with CKD were well represented in the clinical trials – Bushinsky (100%), OPAL-HK (100%), PEARL-HF extension study (100%), AMETHYST-DN (87%) and Tourmaline (76%). Notably, the original PEARL-HF involving MRA titration, included few patients with CKD (27%) and the study duration may have been too short (4 weeks) to detect a worsening of renal function. In contrast, worsening of renal function was found in 9.2% of participants of the AMETHYST-DN trial (52 weeks)6 and 13% of participants in the PEARL-HF extension study (8 weeks)9. In both of these studies, spironolactone was implicated in some cases. In AMETHYST-DN, this was the most frequently reported adverse event and was the most common cause for discontinuation. Despite its duration, this study also failed to show any clinically significant reduction in albuminuria.

A meta-analysis of the patiromer clinical trials showed that the mean reduction in serum K+ at Day 3 was 0.36 mmol/l and at 4 weeks was 0.70 mmol/l.12 。。Overall, 93% of patients could continue, start or titrate RAASi therapy during the maintenance phase of the studies.12

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **STUDY** | **N=** | **Study Duration** | **Mean Baseline K+**  **(mmol/l)** | **Study Groups** | **CHANGE IN SERUM K+ by PATIROMER DOSE**  **(dose in g twice daily)** | | | | | |
| **4.2g** | | **8.4g** | **12.6g** | **15g** | **16.8g** |
| **PEARL – HF Pitt 201112** Phase II trial | 104 | 4 weeks | 4.69 | Patiromer N= 55 |  | |  |  | -0.22 |  |
|  |  |  |
|  |  |  |
| 4.65 | Placebo N= 49 |  | |  |  | +0.2 |  |
|  |  | 3 |
| **OPAL-HK**  **Weir 20156**  Phase III trial | 243 | Phase 1 *Treatment* 4 weeks | 5.3 | Mild HK | -0.65 | |  |  |  |  |
|  |  | 5.0-5.4 |  | |
|  |  | N= 92 |  | |
|  | 5.7 | Mod-Sev |  | | -1.23 |  |  |  |
|  |  | HK |  |
|  |  | 5.5-6.4 |  |
|  |  | N= 151 |  |
| 107 | Phase 2 *Withdrawal* 8 weeks | 4.49 | Patiromer N=55 | 0  Daily dose on entry: 12.8g (mild) and 21.4g (mod)  After first 4 weeks, dose increase was allowed only for the first occurrence of K ≥  5.1 mmol/l | | | | | |
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|  | 4.45 | Placebo N=52 | + 0.72 | | | | | |
|  |  |  | | | | | |
| **AMETHYST- DN**  **Bakris 20157**  Phase II trial | 306 | 52 weeks | 5.3 | Mild HK | -0.35 | | -0.51 | -0.55 |  |  |
|  |  | 5.0-5.5 |  | |  |  |
|  |  | N=222 |  | |  |  |
|  |  | Mod HK |  | | -0.87 | -0.97 |  | -0.92 |
|  |  | 5.6-5.9 |  |  |  |
|  |  | N=84 |  |  |  |
| **Bushinsky 20158**  Prospective | 25 | 48 hours | 5.93 | All |  | | 7hrs: - |  |  |  |
|  |  | 0.21 |
|  |  | 20hrs: |
|  |  | -0.52 |
|  |  | 48hrs: |
|  |  | -0.75 |
| **TOURMALIN E**  **Pergola 20179**  Randomised Open label | 112 | 4 weeks | 5.34 | With Food  N=55 | -0.65  median daily dose was 8.4g (8.4, 12.6) | | | | | |
|  |  |
|  |  |
|  | 5.44 | Without Food  N=57 | -0.62  median daily dose was 8.4g (8.4, 14.1) | | | | | |
|  |  |
|  |  |
| **PEARL-HF**  **extension study**  **Pitt 2018**10  Open-label | 63 | 8 weeks | 4.78 | All |  | -0.13 | |  |  |  |

### Table 6: Studies of efficacy of Patiromer in the treatment of hyperkalaemia.

Patiromer was approved for the treatment of chronic hyperkalaemia in the USA in 2015 and in the EU in 2017. The major caveat is that twice daily patiromer dosing was utilized in most trials, whereas the FDA- approved dose is once daily. This modification stems from concern over the potential for drug interaction between patiromer and other co-administered medications as discussed above.

**NICE has approved the use of Patiromer in the treatment of chronic hyperkalaemia in patients with:**

* **CKD Stage 3b-5 OR Heart Failure AND**
* **Serum K**+ **confirmed to be ≥ 6.0 mmol/l AND**
* **Receiving a sub-optimal dose or not taking RAASi due to hyperkalaemia AND**
* **Not on dialysis**

**Patiromer should be initiated in secondary care. Stop Patiromer if RAASi therapy is discontinued.**

NICE has approved the use of patiromer in the treatment of hyperkalaemia for the above indications (text box).13 。。The key evidence for clinical effectiveness was derived from the OPAL-HK study which demonstrated a reduction in serum K+ by a mean of 1.01 mmol/l after 4 weeks (Phase 1).5 。。The mean serum K+ was 0.72 mmol/l higher in patients who were withdrawn compared with those who remained on patiromer (Phase 2). However, the study cohort did not include patients with clinically significant hyperkalaemia. The patiromer trials also did not demonstrate an improvement in quality of life or survival in patients with chronic hyperkalaemia.

The Scottish Medicines Consortium (SMC) did not approve patiromer for the treatment of hyperkalaemia in NHS Scotland.14 。。They concluded that there were several weaknesses and uncertainties with the economic analysis of the OPAL-HK study given its short duration and endpoints that do not readily correlate with long- term CKD or cardiovascular outcomes.

Serum K+ should be monitored as clinically indicated.1 。。A reasonable approach would be weekly for the first month and after every dose titration, then monthly thereafter. A rebound in serum K+ occurs on cessation of patiromer, therefore withdrawal should be undertaken cautiously. The serum K+ may rise as early as two days after cessation of patiromer, especially if RAASi therapy is continued,1 therefore monitor serum K+ within one week after drug cessation.

**References**

1. Vifor Fresenius Medical Care Renal Pharma UK. Veltassa (Patiromer): Annex 1 - Summary of Product Characteristics. [www.ema.europa.eu/en/documents/product-information/veltassa](http://www.ema.europa.eu/en/documents/product-information/veltassa)

## Treatment: Sodium zirconium cyclosilicate (Guidelines 10.1-10.3)

### Guideline 10.1 – Sodium Zirconium Cyclosilicate for the management of Hyperkalaemia

We recommend that Sodium Zirconium Cyclosilicate (SZC) is an option in out-patients for the management of persistent hyperkalaemia with a confirmed serum K+ ≥ 6.0 mmol/l in patients with CKD Stage 3b-5 (not on dialysis) or heart failure receiving a sub-optimal dose of RAASi therapy. (1A)

### Guideline 10.2 – Sodium Zirconium Cyclosilicate for the management of Hyperkalaemia

We recommend that treatment with Sodium Zirconium Cyclosilicate (SZC) in out-patients is discontinued if RAASi therapy is stopped. (1A)

### Guideline 10.3 – Sodium Zirconium Cyclosilicate for the management of Hyperkalaemia

We recommend that Sodium Zirconium Cyclosilicate (SZC) is initiated in secondary care only. (1A)

**Audit measures**

1. The proportion of out-patients with moderate hyperkalaemia (serum K+ 6.0 - 6.4 mmol/l) treated with SZC who achieved a serum K+ ≤ 5.0 mmol/l within 48 hours.
2. The proportion of out-patients who achieve maximal dose RAASi therapy whilst taking SZC.

**Rationale (Guideline 10.1 – 10.3)**

Sodium Zirconium Cyclosilicate (SZC) is a non-absorbed potassium binder that preferentially exchanges H+ and Na+ for K+ and ammonium ions throughout the entire gastrointestinal tract.1 。。SZC selectively entraps monovalent cations (i.e. K+ and ammonium) compared with divalent cations (Ca2+ and Mg2+). Therefore, unlike patiromer, SZC does not affect Mg2+ levels. SZC binding of ammonium ions increases serum bicarbonate levels, which is favourable in the context of hyperkalaemia. In-vitro studies have shown that the K+-binding capacity of SZC is up to 9 times greater than that of sodium polystyrene sulphonate (SPS).2 。。The K+-exchange capacity of SZC is also > 25 times more selective for K+ over Ca2+ or Mg2+ compared with SPS.3 。。A comparison of the mechanism of action of all of the oral potassium binders is shown in Appendix 1.

SZC is generally well tolerated. The most common adverse effects are oedema (5.7%) and hypokalaemia (4.1%). SZC exchanges Na+ for K+, accounting for the potential risk of worsening oedema, hypertension and heart failure. Product information and administration is described in Appendix 3E.

Three randomised controlled trials and one open label clinical trial have been reported. The first was a double-blind RCT to investigate the safety and efficacy of SZC across a range of doses over a 2-day period.4 。。A dose-dependent reduction in serum K+ was demonstrated. The primary endpoint of rate of decline of serum K+ was achieved at the approved dose of 10g three times daily. This was followed by two multi-national Phase III RCT trials (ZS-003, ZS-004) to evaluate the efficacy and safety of SZC over a longer duration.5,6 。。The most recent study, ZS-005, is an open-label study to assess the efficacy of SZC with longterm use (52 weeks).7 。。Patients with CKD, heart failure, diabetes mellitus and receiving RAASi medication were included in these studies. The studies were conducted in stable out-patients and excluded patients on dialysis, with life- threatening hyperkalaemia or diabetic ketoacidosis. There was also no restriction on dietary K+ intake in all of SZC trials.

The key clinical trials for SZC in the treatment of hyperkalaemia are summarised in Table 7. These studies were designed to determine the efficacy of SZC in controlling hyperkalaemia over a 48-hr induction phase, followed by sustained control during a maintenance phase of variable duration – 14 days (ZS-003), 28 days (ZS-004) and 52 weeks (ZS-005). The proportion of patients with CKD, diabetes, heart failure and taking RAASi drugs were similar in these studies (Appendix 2).

These clinical trials have demonstrated the efficacy of SZC. The onset of action of SZC is within 1 hour after ingestion and there is a close correlation between the initial serum K+ level and the size of the treatment effect.1 。。The median time to normalisation of serum K+ was 2.2 hours.6 。。SZC lowers serum K+ by 1.1 mmol/l within 48 hours.6 。。The ZS-003 and ZS-004 clinical trials also demonstrated a greater K+-lowering effect with increasing severity of hyperkalaemia.5,6 。。In patients with a serum K+ > 6.0 mmol/l, SZC lowers serum K+ by 1.5 mmol/l within 48 hours.6 。。In the longterm study conducted over 12 months, 87% of patients were able to continue RAASi or increase the dose and only 11% discontinued RAASi therapy.7

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **STUDY** | **Study Design** | **N =** | **Study duration** | **Dose of SZC**  **(x3/day)** | **Renal function eGFR**  **(ml/min)** | **Mean Baseline K+ (mmol/l)** | **K+ Change**  **(mmol/l)** |
| **ZS-002 4** | Phase II RCT | 90 | 48 hrs | Placebo | 58.1 ± 26.5 | 5.1 ± 0.4 | - 0.26 ± 0.4 |
| Ash |  |  |  | 0.3g | 56.5 ± 24.0 | 5.2 ± 0.3 | - 0.39 ± 0.4 |
| 2015 |  |  |  | 3g | 57.1 ±22.1 | 5.0 ± 0.3 | - 0.42 ± 0.4 |
|  |  |  |  | 10g | 51.6 ± 22.3 | 5.1 ± 0.4 | - 0.92 ± 0.5 |
| **ZS-003 5** | Phase III RCT | 753 | Stage 1 | Induction |  |  |  |
| Packman |  |  | 48 hrs | (randomised) |  |  |
| 2015 |  |  |  | Placebo | 5.3 | - 0.25 (0.19-0.32) |
|  |  |  |  | 1.25g | 5.4 | 0.30 |
|  |  |  |  | 2.5g | 5.4 | - 0.46 (0.39-0.53) |
|  |  |  |  | 5g | 5.3 | - 0.54 (0.47-0.62) |
|  |  |  |  | 10g | 5.3 | - 0.73 (0.65-0.82) |
|  |  |  | Stage 2 | Maintenance |  |  |  |
| Days | (randomised) | 3.5 – 4.9 |  |
| 3-14 | Placebo |  | + 0.47%/ hr |
|  | SZC 5g |  | + 0.09%/ hr |
|  | Placebo |  | + 1.04%/ hr |
|  | SZC 10g |  | + 0.14%/ hr |
| **ZS-004 6** | Phase III RCT | 258 | Stage 1 | Induction |  |  |  |
| **HARMONIZE** |  |  | 48 hrs | (open label) |  |  |  |
| Kosiborod |  |  |  | 10g | 46.3 ± 30.5 | 5.6 ± 0.4 | - 1.1 (1.0-1.1) |
| 2014 |  |  |  |  |  |  |  |
|  |  |  | Stage 2 | Maintenance |  |  |  |
|  |  |  | 28 days | (randomised) |  |  |  |
|  |  |  |  | Placebo | 48.0 ± 28.8 | 4.6 ± 0.4 | - 0.4 (0.3-0.6) |
|  |  |  |  | 5g | 48.0 ± 30.7 | 4.5 ± 0.4 | - 0.8 (0.6-0.9) |
|  |  |  |  | 10g | 44.7 ± 30.7 | 4.4 ± 0.4 | - 1.1 (0.9-1.3) |
|  |  |  |  | 15g | 44.9 ± 29.5 | 4.5 ± 0.4 | - 1.2 (1.0-1.4) |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **STUDY** | **Study Design** | **N =** | **Study duration** | **Dose of SZC**  **(x3/day)** | **Renal function eGFR**  **(ml/min)** | **Mean Baseline K+ (mmol/l)** | **K+ Change**  **(mmol/l)** |
| **ZS-004E1** | Extension of ZS-004 | 123 | 11 mths | Maintenance (open label) 10g once daily | 46.3 ± 30.5 | 4.6 | 88% of patients achieved K < 5.1  mmol/l |
| **ZS-005 7**  Spinowitz 2019 | Phase III Open-label Prospective (single arm) | 751 | 24-72 hrs | Acute Phase 10g | < 60: 73.5%  ≥ 60: 25.3% | 5.6 | - 0.8 |
| 12 mths | Extended Phase  5g once daily titrated to  10 or 15g/ day  OR 5g alt days |  | 5.6 | - 1.0 |
| **HARMONIZE-** | Phase III RCT | 267 | 48 hrs | Correction |  | 5.7 ± 0.5 | -1.28 |
| **GLOBAL 8** |  |  |  | Phase |  |  |
| Zannad |  |  |  | 10g tds |  |  |
| 2020 |  |  | 28 days | Maintenance |  |  | Geometric LSM |
|  |  |  |  | (randomised) | 3.5 – 5.0 |  |
|  |  |  |  | Placebo |  | 5.32 (5.16, 5.49) |
|  |  |  |  | 5g |  | 4.81 (4.69, 04.94) |
|  |  |  |  | 10g |  | 4.38 (4.27, 4.50) |

### Table 7: Studies of the efficacy of SZC in treatment of Hyperkalaemia

SZC – Sodium zirconium cyclosilicate; hrs – hours; mths – months; LSM – least squares mean

A meta-analysis of the SZC trials have shown that it lowers serum K+ by 0.17 mmol/l at 1 hour and 0.67 mmol/l at 48 hours after administration.9 。。In a subgroup analysis of patients with a baseline serum K+ ranging from 6.1 – 7.2 mmol/l, SZC lowered serum K+ by a mean of 0.4 mmol/l at 1 hour after administration of 10g dose.10 。。In the recently published HARMONIZE-Global study, significantly more patients achieved normokalaemia with SZC 5mg (58.6%) and SZC 10mg (77.3%) compared with placebo (24%).8 。。Approval for SZC was delayed due to concerns about the manufacturing processes, but was granted in the EU in March 2018, followed by the FDA in May 2018. Although the marketing authorisation states SZC may be used for the ‘treatment of hyperkalaemia in adults’, the submission to NICE was limited to patients with CKD and/ or heart failure.

NICE assessed the clinical and cost effectiveness of SZC based on the ZS-004 and ZS-005 clinical trials.11 。。A few short-falls were identified in the SZC trials including the definition of hyperkalaemia (K+ ≥ 5.1 mmol/l) which was lower than the Renal Association and European Resuscitation Council guidelines (K+ ≥ 5.5 mmol/l). The clinical trials did not compare the efficacy of SZC versus dietary restriction or any other active K+-lowering drug. There was also no evidence that SZC improves quality of life or extends life. However, given the strong evidence for use of RAASi drugs in patients with CKD and heart failure, the cost-effectiveness analysis suggests that the use of SZC in facilitating patients staying on RAASi drugs is a good use of NHS resources.

**NICE has approved the use of SZC in the treatment of persistent hyperkalaemia in the out-patient setting under these circumstances:**

* **Patients with CKD Stage 3b-5 OR Heart Failure AND**
* **Serum K**+ **confirmed to be ≥ 6.0 mmol/l AND**
* **Patient is receiving a sub-optimal dose of RAASi due to hyperkalaemia AND**
* **Not on dialysis**

**Initiation of SZC is restricted to secondary care. Stop SZC if RAASi therapy is discontinued.**

NICE has approved SZC in the treatment of persistent hyperkalaemia for the above indications (text box).11 。。Safety and efficacy has been shown up to 52 weeks of therapy, but the duration of treatment in clinical practice will likely be lifelong unless RAASi is discontinued. SZC will complement, rather than replace, a low- K+ diet. SZC may allow less strict dietary restrictions, thereby improving quality of life for patients. The aim is to achieve the minimum effective dose of SZC to prevent recurrence of hyperkalaemia. The recommended starting dose is 5g once daily, with up-titration to a maximum dose of 10g once daily or down-titration to 5g alternate days if required (Appendix 3E).1 。。Dose titration or cessation will be led by secondary care. In real-world practice, blood monitoring will shared with primary care, therefore clear guidance or protocols will be necessary. Based on the ZS-005 trial conducted over 12 months, blood monitoring should be performed weekly for the first month, then monthly thereafter.7 。。Serum K+ should also be assessed one week after drug cessation.7

The role for SZC in the treatment of hyperkalaemia is likely to evolve as clinical experience is gained and as further evidence becomes available.

**References**

* + 1. Astra Zeneca. Lokelma (sodium zirconium cyclosilicate) for oral suspension: Summary of Product Characteristics. 2018. [www.ema.europa.eu/ema/](http://www.ema.europa.eu/ema/)

## Prevention (Guidelines 11.1-11.3)

### Guideline 11.1 – Prevention of Hyperkalaemia in the community: monitoring

We recommend monitoring of renal function in patients at risk of hyperkalaemia with known CKD, heart failure, diabetes and in any patient taking RAASi medication. (1A)

### Guideline 11.2 – Prevention of Hyperkalaemia in the community: prescribing

We recommend caution in prescribing trimethoprim to patients with renal impairment or those taking RAASi drugs. (1A)

### Guideline 11.3 – Prevention of Hyperkalaemia in the community: sick day rules

We recommend that healthcare professionals provide advice to patients regarding the risks of AKI and hyperkalaemia during acute illness and measures to avoid these complications. (1B)

**Audit measures**

1. Proportion of patients with severe hyperkalaemia (Serum K+ ≥ 6.5 mmol/l) on admission to hospital who had been provided with ‘Sick Day Rules’ advice.

**Rationale (Guideline 11.1 - 11.3)**

Hyperkalaemia is an anticipated complication in patients with a history of CKD, heart failure or diabetes mellitus. Patients requiring RAASi drugs for other indications, e.g. spironolactone for decompensated liver disease, also require surveillance for hyperkalaemia. Blood monitoring is discussed in Guidelines 1.1-1.2. Good communication between primary and secondary care regarding monitoring and drug titration is essential.

Drug prescribing in the community and out-patient setting is a major factor for the development of hyperkalaemia. The elderly are very susceptible to hyperkalaemia and polypharmacy is a common problem. Increased awareness of drugs that can cause hyperkalaemia and monitoring patients at risk may reduce morbidity, hospital admissions and mortality.

Drugs commonly implicated in hyperkalaemia are shown below in Table 8.

|  |  |
| --- | --- |
| **RAASi** (ACE Inhibitors, Angiotensin II Receptor Blockers, Mineralocorticoid Receptor Antagonists)  **Potassium supplements Potassium-sparing diuretics Trimethoprim/ Co-trimoxazole NSAIDs**  **Non-selective beta-blockers** | **RISK OF HYPERKALMAEMIA INCREASED IN:**  Renal Impairment Diabetes Mellitus Elderly  Use of > 1 RAASi drug  Combining any of these groups of drugs |

### Table 8: Drugs implicated in development of hyperkalaemia and exacerbating factors.

The Medicines and Healthcare products Regulatory Agency (MHRA) issued a safety alert, initially in June 2014, regarding the concomitant use of ACEi or ARB with MRAs (i.e. spironolactone or eplerenone) given the increased risk of severe hyperkalaemia particularly in patients with advanced renal impairment.1 。。The MHRA recommend caution in co-prescription of these drugs with regular monitoring of serum biochemistry and discontinuation if hyperkalaemia develops.

NICE Clinical Guideline on ‘CKD in adults: assessment and management’ states that RAASi should not be routinely started in patients with a serum K+ level ≥ 5.0 mmol/l and should be discontinued if serum K+ is ≥ 6.0 mmol/l.2 。。The NICE Clinical Guideline on ‘Chronic Heart Failure in adults: assessment and management’ states that serum K+ should be monitored before and after starting a RAASi or changing the dose, but does not specify the K+ level at which RAASi should be avoided or discontinued.3 。。Given the potential benefits of RAASi therapy in patients with CKD and heart failure, NICE has recently approved the use of SZC and patiromer to facilitate continuing RAASi therapy in selected patients.4,5

Trimethoprim is a first-line antibiotic, most commonly prescribed for simple urinary tract infections (UTI). It can be prescribed alone or in combination with sulfamethoxazole (co-trimoxazole). The mechanism by which trimethoprim causes hyperkalaemia is by reducing renal K+ excretion through competitive inhibition of epithelial sodium channels in the distal nephron.6 。。An increase in serum K+ level of 0.36 – 1.21 mmol/l or higher can occur within 3-10 days of treatment.7 。。Treatment with RAASi or NSAIDs exacerbates hyperkalaemia.6

There have been multiple reports confirming the risk of hyperkalaemia and AKI in patients treated with trimethoprim.8-10 。。Antoniou et al reported a 7-fold increased risk of hospital admission for hyperkalaemia in elderly patients (age ≥ 66 years) taking trimethoprim- sulfamethoxazole compared with other antibiotics for UTI.8 。。In a large UK cohort study (n=1,191, 905) of older adults (age ≥ 65 years), Crellin et al demonstrated an increased risk of developing hyperkalaemia (OR 2.27) and AKI (OR 1.72) within 14 days of trimethoprim prescription compared with amoxicillin.9 。。The risk of hyperkalaemia has been shown in patients receiving high-dose11, 12 and low-dose10 trimethoprim.

**Trimethoprim**

* Use trimethoprim with caution in patients with severe renal impairment (eGFR < 30 ml/min)
* Avoid trimethoprim in patients receiving RAASi drugs (high risk of AKI and hyperkalaemia)

Nutritional intake is another important factor in preventing hyperkalaemia, particularly in patients with CKD. In patients with advanced CKD, the ability to adapt to an increased potassium intake diminishes and becomes almost negligible in ESRD, making these patients very susceptible to hyperkalaemia.13 。。A low-K+ diet is usually instituted when the serum K+ is consistently ≥ 5.5 mmol/l and has been discussed in Guideline 5.1.

The bowel compensates for the reduction in renal K+ loss as renal function declines. The capacity for the bowel to secrete K+ is inversely related to residual renal function and becomes the main route of K+ excretion in patients with ESRD.13,14 。。Therefore, constipation predisposes to hyperkalaemia in patients with renal impairment.

The ‘Sick day rules’ provides information to patients taking drugs known to cause AKI and hyperkalaemia (e.g. RAASi, NSAIDs) advising temporary discontinuation of these medications during acute illness, particularly in the context of volume depletion (e.g. diarrhoea and/or vomiting, fevers/ rigors). The use of this strategy is controversial. The NICE ‘Clinical Guideline on AKI’ advocates use of sick day guidance.15 。。On the other hand, ‘Think Kidneys’ urges caution as the evidence-base for this guidance is weak, discontinuation of cardio-protective medication could exacerbate underlying condition and patients may not restart medication on recovery or achieve previous dosage.16 。。The ‘Think Kidneys’ Programme Board recommends that it is reasonable to provide sick day guidance to patients at high risk of AKI based on an individual risk assessment, but a more systematic roll-out of the ‘Sick day rules’ should be undertaken in the context of a formal evaluation.

In clinical practice, many patients admitted to hospital with an AKI at initial presentation are receiving one or more drugs that can exacerbate hyperkalaemia. It is standard practice to withhold these until renal recovery. The Sick Day rules moves the timeline to discontinuation earlier in patients at risk of AKI and if applied appropriately, may reduce the risk of severe hyperkalaemia during acute illness.

**References**

* + 1. Medicines and Healthcare products Regulatory Agency -Spironolactone and renin-angiotensin system drugs in heart failure: risk of potentially fatal hyperkalaemia - February 2016.

## Treatment Algorithm: Community (Guideline 12.1)

### Guideline 12.1 – Treatment Algorithm for Hyperkalaemia in the community

We recommend that the treatment of hyperkalaemia in patients in the community and out-patient setting is guided by its severity and clinical condition of the patient as summarised in the treatment algorithm. (1B)

**Rationale (Guideline 12.1)**

Hyperkalaemia is commonly detected in the community and the approach to monitoring and treatment is variable. An algorithm has been designed to assist clinicians in the out-patient and primary care settings as shown in Appendix 5.

Patients with a serum K+ < 5.5 mmol/l do not require any specific treatment. Patients with persistent mild hyperkalaemia (K+ 5.5 – 5.9 mmol/l) warrant a review of medication (e.g. RAASi) and dietary K+ intake. Treatment of metabolic acidosis (serum bicarbonate < 22 mmol/l) and initiation of diuretics may be helpful in chronic hyperkalaemia.

Patients with persistent moderate hyperkalaemia (K+ 6.0 – 0.4 mmol/l) who are not acutely unwell require similar considerations – medication review, treatment of metabolic acidosis and a low K+ diet. However, some patients may be candidates for a potassium binder (Patiromer or SZC) if they meet the NICE criteria as discussed in Guidelines 9 and 10.

Patients with moderate hyperkalaemia who are acutely unwell and those with severe hyperkalaemia (K+ ≥ 6.5mmol/l) warrant referral to hospital for urgent assessment. RAASi drugs should be withheld until recovery.

Blood monitoring is essential after a hyperkalaemic event and the urgency is guided by the severity. Recommended intervals for blood monitoring are discussed in Guideline 1.1-1.2. Recurrence of hyperkalaemia is common, particularly in patients with CKD, therefore it is important to consider preventative measures.

**Section 3**

**Management of Hyperkalaemia in Resuscitation**

# Hyperkalaemia in Resuscitation

## Introduction

Hyperkalaemia is an uncommon, but potentially reversible cause of cardiac arrest.1, 2 。。It most often occurs in patients with pre-existing renal disease or in the context of an acute kidney injury. Patients receiving long-term haemodialysis (HD) are most at risk of hyperkalaemia. Cardiac arrest can occur in hospital, within an out-patient dialysis unit or out of hospital, but hyperkalaemia should be considered in all settings in patients at risk. Patients on long-term HD are one of the highest risk groups for out- of-hospital cardiac arrest, occurring 20 times more frequently than in the general population.3

The reported incidence of in-hospital hyperkalaemic cardiac arrest is variable. Wallmuller et al found hyperkalaemia as the primary aetiology in only 1% of in-hospital cardiac arrests (n=1041) although it was the most common metabolic cause (47%).4 。。In contrast, Wang et al5 reported an incidence of 12% (n=1114) and Saarinen et al6 reported an incidence of 13% (n=104) in patients with PEA as the initial rhythm following in-hospital cardiac arrest (IHCA).

Patients with all stages of CKD have a higher prevalence of cardiovascular disease, but the mortality risk is estimated to be 57% higher in patients with eGFR < 60 ml/min per 1.73 m2 compared with the general population without CKD.7 。。Cardiovascular disease is also highly prevalent in the dialysis population. The added insult of hyperkalaemia in patients with pre-existing heart disease may contribute to sudden death in dialysis patients, presumably from cardiac arrest.

Pre-dialysis hyperkalaemia and hypokalaemia have both been shown to be associated with higher all- cause mortality.8 。。Pun et al demonstrated a 49% increase in risk of cardiac arrest with each 1 mmol/l decrease in serum K+ below 5.1 mmol/l and a 38% increased risk with each 1 mmol/l increase above 5.1 mmol/l.9 。。There was no advantage of using a low K+ dialysate. The intermittent nature of HD treatment is a further consideration. Bleyer et al demonstrated that HD patients are susceptible to SCD in the first 12 hours from start of the HD session, but the highest risk period is the last 12 hours of the 2-day inter-dialytic interval.[10] In this study, hyperkalaemia (K+ ≥ 6.0 mmol/l) was present in 6.5% of patients with SCD.

Optimising and controlling K+ levels in dialysis patients is challenging. Kovesdy et al demonstrated greater survival in maintenance HD patients with a pre-dialysis serum K+ of 4.6 – 5.3 mmol/l.8 。。The conventional thrice-weekly HD schedule is difficult to overcome, but evidence suggests that careful dialysis prescription with the avoidance of low K+ dialysates and fistula access reduces the risk of cardiac arrest. Other factors associated with a favourable outcome after cardiac arrest in dialysis patients were the use beta-blockers, RAASi and calcium channel blockers at the time of the event.11

This section of the guideline will cover:

* + 1. special considerations in the resuscitation of patients receiving dialysis including aetiology, out-patient dialysis setting, dialysis access, and defibrillation practice,
    2. medical management of hyperkalaemic cardiac arrest, and
    3. approach to treatment of refractory hyperkalaemic cardiac arrest including dialysis initiation during CPR and the use of ECMO.

## References

1. Tirkkonen, J., et al., *Aetiology of in-hospital cardiac arrest on general wards*. Resuscitation, 2016. 107: p. 19-24.

## Hyperkalaemic cardiac arrest – Special circumstance (Guidelines 23.1-23.2)

### Guideline 23.1 – Hyperkalaemia; Cardiac Arrest - special circumstance

We recommend that hyperkalaemia is considered in all patients who have a cardiac arrest, as part of identifying and treating a reversible cause using the 4 Hs and 4 Ts approach. (1A)

## Audit Measure

1. All cardiac arrests should be audited – hospital participation in the National Cardiac Arrest Audit is encouraged as part of quality improvement and benchmarking.

## Rationale (Guidelines 23.1)

Hyperkalaemia is an important and potentially reversible cause of cardiac arrest, therefore should be considered in all patients, particularly in the presence of renal failure. Recognition of hyperkalaemia as the aetiology cardiac arrest may be pre-arrest or during the resuscitation attempt. Early detection of hyperkalaemia before cardiac arrest provides a window of opportunity to prevent arrhythmias or cardiac arrest, but delays in treatment are well recognised.

The National Patient Safety Alert resource for hyperkalaemia (2018) highlighted 35 cases of cardiac arrest in patients with hyperkalaemia which were reported due to concerns related to treatment and/ or monitoring.1 。。Wang et al (2016) reported that 20% (5/25) of dialysis patients who suffered a hyperkalaemic cardiac arrest did not receive either intravenous calcium or sodium bicarbonate.2 。。Saarinen et al (2011) investigated the impact of appropriate treatment in cases where a reversible cause of cardiac arrest was identified and found that no patients received appropriate treatment when the aetiology was hyperkalaemia.3 。。The ECG may be helpful in assessing the risk of cardiac arrest in patients with hyperkalaemia. However, the progressive ECG changes frequently described may not be present and the first sign of hyperkalaemia may be cardiac arrest. An et al reported that approximately 20% of patients presented with cardiac arrest at the time of diagnosis of hyperkalaemia.4 。。Durfey et al demonstrated that arrhythmias or cardiac arrest occurred within 6 hours of the presenting ECG in 15% of patients with serum K+ ≥ 6.5 mmol/l before IV calcium was administered and before K+-lowering treatment was initiated in all but one patient.5

The probability of cardiac arrest is likely to correlate with the severity of hyperkalaemia, but the threshold for arrhythmias in hyperkalaemia appears to vary from patient to patient. For these reasons, arrhythmias should be anticipated and cardiac monitoring is essential for all patients with severe hyperkalaemia. Prompt treatment of hyperkalaemia can avoid arrhythmias and cardiac arrest. Avoid delays in treatment and seek specialist help early.

## References

1. NHS Improvement: Patient Safety Alert - Resources to support safe and timely management of hyperkalaemia (high level of potassium in the blood). August 2018. Alert reference number: NHS/PSA/RE/2018/006. [http://improvement.nhs.uk/news-alert/safe-and-timely-management-of-](http://improvement.nhs.uk/news-alert/safe-and-timely-management-of-hyperkalaemia/) [hyperkalaemia/](http://improvement.nhs.uk/news-alert/safe-and-timely-management-of-hyperkalaemia/)

## Resuscitation strategy in dialysis patients (Guidelines 24.1-24.2)

### Guideline 24.1 – Hyperkalaemia; Cardiac Arrest – Resuscitation strategy in haemodialysis patients

We recommend that standard ALS practice in cardiac arrest be applied to patients requiring dialysis. (1A)

### Guideline 24.2 – Hyperkalaemia; Cardiac Arrest – Defibrillation practice in haemodialysis patients

We recommend disconnection from dialysis equipment prior to defibrillation unless the dialysis machine is defibrillator-proof. (1C)

**Rationale (Guidelines 24.1 – 24.2)**

The incidence of cardiac arrest in dialysis patients is higher than in the general population, therefore vigilance and staff training is essential. The incidence of cardiac arrest in the out-patient setting ranges from 3.4 – 7.8 / 100,000 HD sessions as shown in Table 26.1-3 。。Sparse data is available on the incidence of in- hospital cardiac arrest in patients on long-term HD. Wong et al reported a rate of 1.4 events per 1000 in- hospital days with a survival to hospital discharge of 22%.4 。。An early study of in-hospital CPR in patients with ESRD showed a survival to hospital discharge of only 8%.5

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study** | **Number of HD sessions** | **Number of cardiac arrests** | **Incidence of CPR**  /100,000 dialysis sessions | **Survival to Hospital Discharge** |
| **Karnik 20011** | 5, 744,708 | 400 | 7 | NA |
| **La France 20063** | 307,553 | 24 | 7.8 | 75% |
| **Davis**  **20082** | 2, 611,119 | 110 | 3.4 | 24% |

### Table 26: Incidence and outcome of cardiac arrest in out-patient dialysis units.

NA – not available.

Within the out-patient setting, most cardiac arrests occur during the dialysis session as shown in Table 27. Karnik et al reported that the mean time into dialysis at cardiac arrest was 123 ± 77 minutes.1 。。The mean time to cardiac arrest was shorter in patients with central venous catheters compared with arteriovenous fistulas.1 。。Electrolyte and fluid shifts may also play a role in the timing of events.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study** | **N=** | **Before HD** | **During HD** | **After HD** |
| **Karnik 2001**1 | 400 | 7% | 81% | 12% |
| **Davis 20082** | 152 | 10% | 70% | 20% |
| **La France 20063** | 38 | 8% | 78% | 14% |

### Table 27: Timing of cardiac arrest during dialysis in out-patient centres.

HD – haemodialysis

Shockable cardiac arrest rhythms (pulseless VT or VF), have been reported to be more common in the dialysis population than non-shockable rhythms (PEA or asystole). Davis et al demonstrated a shockable primary arrest rhythm in 65% of arrests.2 。。Karnik et al reported the arrest rhythm in only 16% of cases but of these, the initial rhythm was VF in 42%, VT in 20% and asystole in 15%.1 。。LaFrance et al reported data on the first cardiac arrest rhythm in only 12 patients - VF/VT (6/12 patients), PEA/ asystole (6/12 patients).3

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **PEA/Asystole** | | | **VF/VT** | | |
| **Study** | **Events**  **%** | **ROSC**  **Achieved (%)** | **Survival to D/C (%)** | **Events**  **%** | **ROSC**  **Achieved (%)** | **Survival to D/C (%)** |
| **Davis 20082** HD patients Out-pt HD unit n= 152 | 35 | 37 | 11 | 65 | 51 | 31 |
| **La France 20063** HD patients Out-pt HD unit n= 24 | \*50 | NA | NA | \*50 | NA | NA |
| **Meaney 20106** US gen pop IHCA n= 51,919 | 76 | 42 | 11 | 24 | 64 | 37 |
| **Nolan 20147** UK gen pop IHCA  n= 23,554 | 72 | 26 | 11 | 17 | 76 | 49 |

### Table 28: Outcome of cardiac arrest in patients receiving haemodialysis (HD) in an outpatient dialysis facility versus all in-hospital cardiac arrests.

PEA – pulseless electrical activity; VF – ventricular fibrillation; VT – ventricular tachycardia; ROSC – return of spontaneous circulation; IHCA – In hospital cardiac arrest

NA – not available; D/C – discharge; Out-pt – out-patient; gen pop – general population

\* Data available for primary cardiac arrest rhythm in only 12/24 patients

Shockable rhythms are associated with a higher incidence of return of spontaneous circulation (ROSC) and survival to hospital discharge in the general population as well as in patients with ESRD as shown in Table 28. Non-shockable cardiac arrest rhythms are associated with a poor outcome. Registry data in the general population in the UK and USA demonstrate survival to hospital discharge of 11% in patients presenting with PEA/ asystole.6, 7 。。In contrast, Wang et al reported a non-shockable rhythm in 92.7% of IHCA in hyperkalaemic patients which in part accounts for the survival to hospital discharge of only 3.7% in this study.8

**Shockable cardiac arrest rhythms are more common in haemodialysis patients than in the general population.**

**Survival after cardiac arrest is better with shockable rhythms.**

### Modifications to ALS in Renal Failure

The universal ALS algorithm applies to all patients and the initial steps of recognition of cardiac arrest, initiating high-quality CPR with minimal interruption, and attempting defibrillation if required, are independent of the cause of cardiac arrest.

During CPR, reversible causes should be considered and treated. If the serum potassium is ≥ 6.5 mmol/L before or early in the resuscitation attempt, hyperkalaemia should be considered to be the potential cause of the cardiac arrest. Hyperkalaemia occurring late in the resuscitation attempt may be the consequence of progressive acidosis and hypoxia, and may not be the precipitant of the cardiac arrest or require specific intervention.

Special considerations during resuscitation in dialysis patients is shown in Table 29. The cardiac arrest team may have little knowledge of these considerations in dialysis patients, therefore expert help is essential for optimising care and safety.

The practice of defibrillation in HD units is variable across the UK and many staff are unaware of the safety considerations.9 。。The ERC Guidelines (2015) recommends disconnection from dialysis equipment prior to defibrillation, unless defibrillator-proof, in keeping with the International Electrotechnical Committee (IEC) standards 60601-2-4.10 。。Most haemodialysis equipment is not defibrillator-proof.

|  |  |  |  |
| --- | --- | --- | --- |
| **Special considerations during resuscitation of haemodialysis patients**  **Reversible causes** – 4 Hs & 4 Ts – electrolyte disorder (hyperkalaemia, hypokalaemia, calcium disorder), pulmonary oedema  **Dialysis access** – arteriovenous fistulas and dialysis lines can be used in life-threatening emergencies.  **Defibrillation practice** – disconnect prior to defibrillation unless dialysis machine is ‘defibrillator proof’ (check for these symbol on machine) | | | |
| http://medicaldeviceacademy.com/wp-content/uploads/symbols.png | IEC 60417-5841 | DEFIBRILLATION-PROOF TYPE B APPLIED PART |  |
| http://medicaldeviceacademy.com/wp-content/uploads/symbols.png | IEC 60417-5334 | DEFIBRILLATION-PROOF TYPE BF APPLIED PART |
| http://medicaldeviceacademy.com/wp-content/uploads/symbols.png | IEC 60417-5336 | DEFIBRILLATION-PROOF TYPE CF APPLIED PART |
| **Post-resus care** – repeat serum K+, blood glucose and ECG; preserve dialysis access; move to an area with dialysis facilities (ICU or Renal HDU); consider timing and need for dialysis after ROSC | | | |

### Table 29: Special considerations during resuscitation in haemodialysis patients.

Automated external defibrillators (AED) are now widely available for non-expert use worldwide to facilitate early defibrillation. Many dialysis centres are predominantly nurse-led. For this reason, the National Kidney Foundation KDOQI Guidelines (2005) recommended that all dialysis facilities should have on-site capability of defibrillation and the use of AEDs is the simplest and most cost effective device.11 。。The implementation of AEDs within dialysis facilities was mandated within one year of this guideline. Shortly thereafter, Lehrich et al investigated the use of AEDs in dialysis centres and reported that the presence of AEDs alone did not independently improve survival and suggested that further measures are required to affect outcome.12

The impact of dialysis unit staff initiating resuscitation before arrival of paramedics has recently been reported to assess outcomes of staff-led CPR and AED use. In this study of OHCA in out-patient dialysis clinics (n=398 events), dialysis staff initiated CPR in 81% of events, but applied an AED before paramedics arrived in only 52.3%.13 。。The timing of events in relation to dialysis is not available. When dialysis staff were the first to apply the AED, there was a greater proportion of shockable rhythms (41% vs 25%), reinforcing

early application of AED. The odds of survival to hospital discharge was 3-fold higher with staff-initiated CPR, but there was only a non-significant trend towards improved survival to discharge with staff-initiated AED. This may be explained by the low usage of AED by nursing staff.

**Cardiac arrest in dialysis centres are witnessed events. CPR should be initiated by nursing staff.**

**First responders require regular training in use of an AED.**

**Ensure safety: Disconnect patient from haemodialysis machine prior to defibrillation (most machines are not ‘defib-proof’).**

Within out-patient dialysis centres, cardiac arrest occurs most often during dialysis thereby are witnessed events. Shockable rhythms are more common, therefore early defibrillation using safe practice should be attempted. Patients with a shockable rhythm have the best chance of survival, therefore prompt and effective action by first responders is crucial.

**References**

* + 1. Karnik, J.A., et al., *Cardiac arrest and sudden death in dialysis units*. Kidney Int, 2001. **60**(1): p. 350-7.

## Treatment: Calcium chloride (Guidelines 25.1)

### Guideline 25.1 – Cardiac Arrest: Treatment - Intravenous calcium

We recommend that intravenous calcium chloride is administered if hyperkalaemia is known or suspected to be the cause of cardiac arrest. (1C)

**Audit measures**

1. The proportion of patients treated with intravenous calcium for hyperkalaemic cardiac arrest.

**Rationale (Guidelines 25.1)**

This guideline extrapolates from management in the non-arrested patient, recognising the sparsity of evidence for the use of specific medical interventions in hyperkalaemic cardiac arrest. Intravenous calcium is widely recommended for treatment of hyperkalaemia in the context of toxic ECG changes, arrhythmias and cardiac arrest. 1-3 However, in the absence of hyperkalaemia or other specific indication, IV calcium can have deleterious effects in cardiac arrest with coronary vasospasm and worsening cerebral hypoxic damage.

The quality of evidence for the general use of IV calcium in cardiac arrest was reviewed using the 2010 International Liaison Committee on Resuscitation (ILCOR) evidence evaluation process.4 。。Only 10 studies were adequate for inclusion and only two studies had a blinded randomised design. The analysis was further limited by the wide variation in sample size, reported data and outcomes. The conclusion was that there is no evidence that IV calcium during CPR improves survival after cardiac arrest. Its role in specific settings of hyperkalaemia, calcium channel blocker intoxication, hypocalcaemia and hypermagnesaemia remain unclear due to limited data.

More recently, Wang et al (2016) have reported the outcome of IV calcium in hyperkalaemic IHCA.5 。。In this study, 56% of patients received IV calcium either alone (4/ 109; 4%) or more frequently in combination with sodium bicarbonate (57/ 109; 52%). ROSC was achieved in only one patient who received IV calcium alone (1/4; 25%), but this patient did not survive > 24 hours. In comparison, ROSC was achieved in a higher proportion of patients who received both drugs (12/57; 21%).

Despite the limited evidence-base, IV calcium has become standard practice for preventing and treating arrhythmias in hyperkalaemia. Its effect is evidenced by the improvement in the ECG changes in the non- arrested patient. Its effects last only 30-60 minutes, therefore further doses may be required if hyperkalaemia persists or during prolonged resuscitation attempts.

**References**

1. Truhlar, A., et al., *European Resuscitation Council Guidelines for Resuscitation 2015: Section 4. Cardiac arrest in special circumstances.* Resuscitation, 2015. **95**: p. 148-201.

## Treatment: Insulin-glucose (Guidelines 25.2)

### Guideline 25.2.1 – Cardiac Arrest: Treatment – Insulin-glucose

We recommend that 10 units soluble insulin and 25g glucose is administered if hyperkalaemia is known or suspected to be the cause of cardiac arrest. (1B)

### Guideline 25.2.2 – Cardiac Arrest: Treatment – Insulin-glucose

We suggest 10% glucose infusion be initiated if the blood glucose is < 7.0 mmol/l at the time of cardiac arrest. (2C)

**Rationale (Guidelines 25.2.1 – Guideline 25.2.2)**

Insulin and glucose is the most effective treatment for hyperkalaemia in the non-arrested patient as discussed in Guideline 16.3. The onset of action is within 15 minutes 1, 2 with a peak reduction in serum K+ ranging from 0.65 – 1.0 mmol/l by 60 minutes.1-5 。。Although several studies have shown equivalent efficacy with standard (10 units) vs low dose (5 units) insulin, Garcia et al have found a trend towards greater efficacy with 10 units compared with 5 units insulin in patients with a serum K > 6.0 mmol/l.6 。。Moussavi et al also demonstrated significantly greater K+-lowering with 10 units insulin compared with low-dose insulin.7 。。These observations are important in patients with life-threatening hyperkalaemia. The main adverse effect is hypoglycaemia, therefore blood glucose monitoring is essential.

International resuscitation guidelines have historically recommended the use of insulin-glucose for hyperkalaemic cardiac arrest based on treatment in the non-arrested patient.8-10 。。The efficacy of insulin- glucose is augmented with the use of salbutamol and novel potassium binders in the non-arrested patient. In cardiac arrest, the use of adrenaline has an analogous effect to salbutamol and will likely enhance K+- lowering, but unfortunately there are no clinical trials to confirm this. For consistency, the treatment protocol in hyperkalaemic cardiac arrest is the same as in the non-arrested patient.

The ERC recommendation for insulin-glucose during cardiac arrest has changed over the past two decades. The ERC Resuscitation Guidelines (2000, 2005) for managing life-threatening electrolyte abnormalities recommended 10 units insulin with 50g glucose.11, 12 。。Subsequent ERC guidelines (2010, 2015) altered the dose of glucose to 25g based on the available evidence and the Cochrane review on the emergency interventions for hyperkalaemia published in 2005.10, 13, 14

Given the sparsity of evidence for medical treatments in hyperkalaemic cardiac arrest, it is interesting to consider an analogous circumstance. Cardiac arrest is induced to facilitate cardiopulmonary bypass. The standard technique for induction of cardiac arrest includes the delivery of a high concentration of K+ to the myocardium.15 。。Therefore, hyperkalaemia frequently occurs after cardioplegia.15, 16 。。This scenario is essentially an iatrogenic hyperkalaemic cardiac arrest. The 2019 European Guidelines on cardiopulmonary bypass in adult cardiac surgery suggests treatment with IV calcium and insulin-glucose (dose unspecified) if the serum K+ exceeds 6.5 – 7.0 mmol/l.15

The optimal dose of insulin and glucose during cardioplegia is unclear. Morgan et al suggested 30-50g per 10 units of insulin.17 。。Davis et al suggested that if the glucose dose is 0.5 – 2g/kg, then the appropriate ratio is 1 unit insulin to 4g glucose.18 。。Kocoglu et al suggested 2g of glucose for 1 unit of insulin, but hypoglycaemia was common and required treatment with 10% glucose.16 。。This data demonstrates that 25g glucose was insufficient to prevent hypoglycaemia when administered with 10 units insulin 10, 15, 16 and in one study 10% glucose infusion was required.16

The current RA Hyperkalaemia guideline (2020) recommends 10 units insulin with 25g glucose for treating acute hyperkalaemia (Guideline 16.3.1). An infusion of 10% glucose (50ml/hr for 5 hours) is suggested if the pre-treatment blood glucose < 7.0 mmol/l to avoid iatrogenic hypoglycaemia (Guideline 16.3.3). Although it is important to prevent hypoglycaemia in cardiac arrest, there is some evidence that the administration of glucose during resuscitation results in lower rates of survival and worse neurological outcome.19 。。In this observational study, it was not possible to determine the reason, timing or dosage for glucose administration and the effect was more prominent in patients without diabetes mellitus.

Hyperkalaemic cardiac arrest usually requires prolonged resuscitation and often occurs in patients with other risk factors for iatrogenic hypoglycaemia including renal failure. The first available blood glucose post arrest and subsequent monitoring, should guide the need for initiation and rate of a 10% glucose infusion during the resuscitation attempt. In practical terms, a blood glucose range of 6 – 10 mmol/l is accepted for critically ill patients.20

**References**

1. Allon, M. and C. Copkney, *Albuterol and insulin for treatment of hyperkalemia in hemodialysis patients*. Kidney International, 1990. **38**(5): p. 869-872.

## Treatment: Sodium bicarbonate (Guidelines 25.3)

### Guideline 25.3 – Hyperkalaemia; Cardiac Arrest – Sodium bicarbonate

We suggest that sodium bicarbonate is administered if hyperkalaemia is known or suspected to be the cause of cardiac arrest. (2C)

**Audit measure**

1. The proportion of patients treated with sodium bicarbonate for hyperkalaemic cardiac arrest.

**Rationale (Guidelines 25.3)**

The use of sodium bicarbonate in cardiac arrest has evolved over the past few decades. The rationale for using sodium bicarbonate (SB) is to counteract the worsening metabolic acidosis in cardiac arrest as a result of hypoxia, poor perfusion and increased lactate production. The potential deleterious effects of using SB in cardiac arrest are an increase in intracellular acidosis, reduced cardiac output and worsening tissue acidosis.1

Sodium bicarbonate was commonly used in the early resuscitation guidelines in the 1970’s – 1980’s, but use declined in the 1990’s in light of concerns related to potential harm. A review by Adgey et al in 1998 recommended that treatment with SB should be reserved for cardiac arrest in one of four settings: 1) severe acidosis (pH < 7.1), 2) prolonged cardiac arrest (> 10-20 minutes), 3) hyperkalaemia and 4) overdose of tricyclic antidepressants.2 。。More recently, Weng et al (2013) showed no benefit of sodium bicarbonate during prolonged CPR.3 。。Velissaris et al (2016) conducted a comprehensive review of the literature and found that there was little evidence to support the routine use of SB during CPR.1

Clinical practice is guided by international resuscitation guidelines. The 2010 ACLS Guidelines for adults published by the American Heart Association stated that ‘the routine use of sodium bicarbonate is not recommended for patients in cardiac arrest’, but supported its use in hyperkalaemia and tricyclic overdose with or without cardiac arrest.4 。。Similarly, the European Resuscitation Council (ERC) guidelines (2015) have also recommended the use of SB for these specific indications.5

Although there is little evidence that sodium bicarbonate lowers serum K+, the rationale for its use in hyperkalaemia cardiac arrest is to mitigate the effects of metabolic acidosis which exacerbates hyperkalaemia. The largest study of hyperkalaemic cardiac arrest undertaken by Wang et al (2016) demonstrated that approximately 82% of patients received SB either alone (32/109; 29%) or in combination with intravenous calcium (57/ 109; 52%).6 。。SB was administered early in the course of resuscitation (within 10 minutes) and ROSC was achieved in 47% of patients who received SB alone and 21% who received both drugs.

The treatment of hyperkalaemic cardiac arrest is multi-modal and both American and European resuscitation guidelines recommend the use of sodium bicarbonate in the setting of hyperkalaemic cardiac arrest.

**References**

1. Velissaris, D., et al., *Use of Sodium Bicarbonate in Cardiac Arrest: Current Guidelines and Literature Review*. J Clin Med Res, 2016. **8**(4): p. 277-83.

## Treatment: Initiation of dialysis during cardiac arrest (Guidelines 25.4)

### Guideline 25.4 – Hyperkalaemia; Cardiac Arrest – Initiation of dialysis during CPR

We suggest that renal replacement therapy with ongoing CPR may be considered for hyperkalaemic cardiac arrest, if hyperkalaemia is resistant to medical therapy and appropriate staff and facilities are available. (2C)

**Audit measure**

1. The number and outcome of patients with refractory hyperkalaemic cardiac arrest treated with dialysis initiation during CPR.

**Rationale (Guidelines 25.4)**

The outcome of hyperkalaemic cardiac arrest is poor, therefore urgent action is required to prevent cardiac arrest. Prompt medical treatment and initiation of dialysis in patients with severe hyperkalaemia are crucial steps in avoiding cardiac arrest. If cardiac arrest occurs, survival is dependent on urgent control of the serum K+ level. Intravenous calcium does not alter serum K+ level and there is little evidence that sodium bicarbonate significantly lowers serum K+. Therefore, the only drugs administered during CPR which may lower the serum K+ are insulin-glucose and adrenaline.

In the largest study of hyperkalaemic cardiac arrest (n=109), dialysis was not instituted during CPR.1 。。Patients were analysed by the severity of hyperkalaemia - K+ 6.5 – 7.9 mmol/l (72/ 109; 66%), K+ 7.9 – 9.4 mmol/l (30/109; 28%) and K+ > 9.4 mmol/l (7/ 109; 6%). Overall, ROSC > 20 minutes was achieved in 37% of patients, but only 4 patients (3.7%) survived to hospital discharge. The incidence of ROSC declined with increasing severity of hyperkalaemia and was achieved in: 32/72 (44%) patients with a serum K+ 6.5 – 7.9 mmol/l, 7/30 (23%) patients with a serum K+ 7.9 – 9.4 mmol/l and in 1/7 (14%) patients with a serum K+ > 9.4 mmol/l. No patients with a K+ > 9.4 mmol/l survived beyond 24 hours. The authors suggested that there might be a threshold for medical therapies and beyond this level, dialysis may be an alternative option.

There have been several case reports of successful resuscitation following hyperkalaemic cardiac arrest in adults and children as shown in Table 30.2-14 。。Survival with good neurological outcome after both pulseless VT or VF and asystole or PEA cardiac arrest has been reported. In many of these reports, patients were refractory to defibrillation until the potassium was controlled. Resuscitation efforts were frequently prolonged, and in recent years, extra-corporeal membrane oxygenation (ECMO) support has been used to augment systemic perfusion.6,11-14

Success has been reported using all modes of RRT: haemodialysis (HD), haemofiltration (CVVH), haemodiafiltration (HDF), as well as peritoneal dialysis (PD). Dialysis has also been used successfully for re- warming in accidental hypothermia without cardiac arrest 15-17 and in cardiac arrest.18, 19. In one of these cases, manual CPR was performed for 5.5 hours and CVVH was achieved with no technical difficulties for over 3 hours.18 。。This patient made a full neurological recovery, returned to work within 6 weeks and has become a parent.

It is important to acknowledge that this evidence is limited, but large scale studies to demonstrate efficacy of dialysis during CPR is not feasible. Despite advances in resuscitation practice in recent years, ROSC remains unlikely if hyperkalaemia is not controlled. Although these reports likely reflect publication bias illustrating good outcomes, they do show that dialysis with and without ECMO is technically feasible in cardiac arrest. These reports also illustrate the evolution of the use of dialysis during CPR with ECMO providing a method to enhance resuscitation alongside conventional dialysis in recent years.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Age (yrs) | Arrest Rhythm | [K] at arrest (mmol/L) | CPR  pre- RRT  (min) | Dialysis modality | Dialysis duration (min) | [K] at ROSC  (mmol/L) | Outcome |
| **Gomez- Arnau** 19812 | 36 | Asystole | 9.7 | 70 | HD | 75 | 6.6 | Full recovery |
| **Torrecilla**  19893 | 53 | Asystole | 10.2 | 15 | HD | 90 | 6.5 | Full recovery |
| **Lin**  19944 | 27 | VT | 9.6 | 55 | HD | 25 | 7.6 | Full recovery |
| 58 | VF | 8.5 | 35 | HD | 30 | 7.2 | Full recovery |
| 77 | VT | 8.5 | 155 | HD | 25 | 5.2 | Died |
| **Costa**  19945 | 57 | Asystole | 9.6 | 15 | HD | 95 | 7.2 | Survived (3 days) |
| **Lee**  19946 | 11 | Asystole | 10.2 | 140 | HF on CPB | ns | ns | Full recovery |
| **Jackson**  19967 | 16 | Asystole | 9.8 | 165 | PD | 60 | 4.3 | Full recovery |
| **Kao**  20008 | 68 | VT | 8.3 | 150 | HD | 40 | 5.1 | Full recovery |
| **Schummer**  20009 | 68 | ns | 9.0 | ns | HDF | 15 | ns | Full recovery |
| **Iwanczuk**  200810 | 53 | ns | 8.5 | ns | HD | 40 | 5.4 | Full recovery |
| **Chiu**  201411 | 66 | VF | 8.6 | ns | CVVH on VA-ECMO | ns | ns | Full recovery |
| **Tijssen**  201712 | 17 | Asystole | 8.3 | ns | CRRT on ECMO | ns | ns | Full recovery |
| **Kim**  201913 | 13 | Sine wave | 9.6 | 90 | HF on VA- ECMO | ns | ns | Full recovery |
| **Klingkowski**  201914 | 5 | VF | 9.2 | ns | CVVH and ECMO | 25 (ECMO  prolonged) | 4.2 | Full recovery |

### Table 30: Outcome of hyperkalaemic cardiac arrest with RRT during CPR.

(ns = not specified)

The severity of hyperkalaemia is a good indicator of the likelihood of achieving and sustaining ROSC. Analysis of the case reports shown above in Table 30 reveals that the mean serum K+ at the time of cardiac arrest was 9.2 mmol/l (range 8.3-10.2 mmol/l). The mean serum K+ at ROSC was 6.1 mmol/l (range 4.2-7.6 mmol/l) in patients who received a haemodialysis modality. Therefore, the mean reduction in K+ required to achieve ROSC was 3.01 mmol/l (range 1.3-5.0 mmol/l) and this would be difficult to achieve with drugs alone.

The term ‘extreme hyperkalaemia’ has been used in the literature.[20-22] It has been defined as a serum K+ > 9.0 mmol/l.23 。。Wang et al reported no survivors in patients with a serum K+ > 9.4 mmol/l treated without dialysis during CPR.1 。。In contrast, in the series of patients treated with dialysis during CPR (Table 30), 9/15 (60%) had a serum K+ > 9.0 mmol/l and 7/9 (78%) survived with full neurological recovery. Although this evidence is limited and subject to publication bias, it would suggest that dialysis during CPR can potentially improve the outcome for patients with extreme hyperkalaemia.

The ERC Guidelines (2015) suggest considering dialysis initiation for hyperkalaemic cardiac arrest resistant to medical therapy.24 。。This recommendation was based on several considerations:

* + Firstly, the reports of successful outcomes of hyperkalaemic cardiac arrest have demonstrated that it is technically feasible to dialyse during CPR. With the aid of the blood pump, a blood flow rate of up to 200 ml/min can be achieved with a chest compression rate of 100/min.
  + Secondly, it seems logical to consider the most effective intervention for the most serious complication of hyperkalaemia, particularly when unresponsive to medical therapies.
  + Thirdly, other invasive procedures are recommended for other special circumstances of cardiac arrest - cardiopulmonary bypass for hypothermia, chest drain insertion for tension pneumothorax and pericardiocentesis for cardiac tamponade. ECMO has also become increasingly utilised in resuscitation, including in hyperkalaemic cardiac arrest. Therefore, there is a clear rationale to considering dialysis in refractory hyperkalaemia.
  + Fourthly, survival in patients with extreme hyperkalaemia is very low without the initiation of dialysis during CPR.
  + Lastly, the evidence base for other interventions for hyperkalaemia, particularly calcium salts, is also limited, but has become standard medical practice. Large scale studies are unlikely to be feasible to demonstrate the efficacy of dialysis during CPR.

The practical approach to resuscitation for refractory hyperkalaemic cardiac arrest is not included in renal specialist training programs. There may also be a reluctance to consider dialysis during CPR with the anticipation of technique failure. The resuscitation team will rely on the renal team for guidance. Given the sparsity of information available, a review of the modifications in advanced life support in dialysis patients was previously reported.25 。。An update and summary of the procedure is outlined in Table 31.

Once CPR is underway, initiate medical treatment for hyperkalaemia and seek expert help early. If hyperkalaemia is suspected, treat even before the serum K+ is known. Monitor serum K+ (using blood gas analyser) every 15 minutes to assess response to treatment. Monitor blood glucose to assess for hypoglycaemia.

Next, consider if medical treatment alone is likely to be effective. Ultimately, the severity of hyperkalaemia, the initial response to medical therapy, the suitability of the patient and the availability of dialysis facilities provide the best guide for considering dialysis in cardiac arrest. This intervention is unlikely to be available outwith a Renal Unit or Critical Care area.

Next, plan ahead and consider the timing for initiation of dialysis. Analysis of the case reports suggest that the mean duration of CPR before initiation of dialysis was 89 minutes (range 15-165 minutes). The mean duration of dialysis to achieve ROSC was 50 minutes (range 15-95 minutes). There appeared to be an inverse relationship between duration of CPR and duration of dialysis required to achieve ROSC. Given that dialysis initiation will require some planning, it is reasonable to start preparations early and to consider initiation if ROSC is not achieved within 15 minutes.

Use existing dialysis access (i.e. fistula or tunnel dialysis catheter) to initiate dialysis if available. If dialysis access is not available, the most practical approach during cardiac arrest is the insertion of a femoral line using ultrasound guidance.

Anticipate that the resuscitation attempt will be prolonged. Consider the use of mechanical devices to perform chest compressions (e.g. LUCAS2, Autopulse). Where available, use ECMO to optimise perfusion during prolonged cardiac arrest management.6, 11-14

Given that defibrillation is frequently unsuccessful until the serum K+ is controlled, analogous to rewarming for hypothermic cardiac arrest, RRT should be considered for refractory hyperkalaemic cardiac arrest if deemed clinically appropriate and suitable facilities and staff are available.

*“Like most things in life, you may not always succeed, but failure is usually guaranteed if you do not try.”* 26

### Initial Approach



* Follow ALS Algorithm
* Give medical treatment for hyperkalaemia during CPR as per Hyperkalaemic Cardiac Arrest Algorithm
* Refer for Expert Help
* Consider mechanical chest compression device

### Preparation for Dialysis Initiation

* If ROSC not achieved within 15 minutes consider initiating dialysis if clinically appropriate.
* Choose RRT modality depending on local availability
* Consider ECMO if available
* Use renal trained nurse (preferably two) to deliver dialysis treatment
* Prepare dialysis machine with a low K+ dialysate
* Use existing dialysis access (i.e fistula or line) if available or alternatively insert dialysis line whilst machine is being prepared - use femoral vein with ultrasound guidance; easier site during CPR

### Initiation of Dialysis during CPR

* Give fluid bolus (250ml) once connected to dialysis machine and record starting time
* Start with pump speed of 100ml/min and gradually increase aiming for 200ml/min
* Give anticoagulation unless contraindicated (e.g. history of trauma)
* Give further IV Calcium Chloride if resuscitation is prolonged
* Check K+ level at least every 15 min using arterial blood gas analyser and monitor blood glucose
* Allow time for K+-lowering on dialysis before attempting further defibrillation

### Defibrillation

* Do not perform defibrillation during dialysis unless machine is defibrillation-proof
* Disconnect patient from dialysis machine just before defibrillation, then immediately reconnect
* If ROSC achieved, resume dialysis until serum K+ < 6.5 mmol/L to maintain ROSC
* If ROSC not achieved, resume dialysis until serum K+ < 6.5 mmol/L and attempt defibrillation again if shockable rhythm

### Post-resuscitation care

* Re-assess serum K+, blood glucose and ECG when ROSC achieved
* Terminate dialysis when serum K+ controlled (K+ < 6.5 mmol/L) and cardiac rhythm stable
* Record time of termination of dialysis and serum K+ at ROSC
* Transfer to ICU

### Table 31: Summary of procedure for initiation of dialysis during CPR.

**References**

1. Wang, C.H., et al., *The effects of calcium and sodium bicarbonate on severe hyperkalaemia during cardiopulmonary resuscitation: A retrospective cohort study of adult in-hospital cardiac arrest*. Resuscitation, 2016. **98**: p. 105-11.

## Prevention (Guidelines 26.1-26.2)

### Guideline 26.1 – Hyperkalaemia; Prevention of Cardiac Arrest in Hyperkalaemia

We recommend that hyperkalaemia is treated urgently in patients with severe hyperkalaemia (K+ ≥ 6.5 mmol/l) and in those with ECG changes suggestive of severe hyperkalaemia. (1C)

### Guideline 26.2 – Hyperkalaemia; Prevention of Cardiac Arrest in Hyperkalaemia

We recommend continuous cardiac monitoring for patients with severe hyperkalaemia (K+ ≥ 6.5 mmol/l) in a setting appropriate for the level of care required. (1C)

**Rationale (Guidelines 26.1 – 26.2)**

The outcome of hyperkalaemic cardiac arrest is generally poor, therefore efforts to avoid its occurrence is the best approach. Primary measures to prevent the development of hyperkalaemia in patients at risk is a key step. Patients with renal failure, heart failure and/ or diabetes have a high risk, particularly when treated with RAASi drugs. Cautious prescribing and blood monitoring is essential in these patients.

Preventing cardiac arrest in patients who have become hyperkalaemic is dependent on prompt recognition and treatment. The initial clinical presentation may be overshadowed by the acute illness, but severe hyperkalaemia is likely to be more immediately life-threatening. Limb weakness is an ominous sign. Look for toxic ECG changes which may precede cardiac arrest - wide QRS complex, bradycardia or sine wave (Guidelines 14.1-14.2; Figure 3), but some patients may have a normal ECG despite severe hyperkalaemia. The rationale for cardiac monitoring is to detect arrhythmias before cardiac arrest ensues, therefore a higher level of care is required.

Delays in treatment are well recognised and has resulted in patient harm.1,2 。。The potential for clinical deterioration may not be appreciated by medical or nursing staff prior to cardiac arrest. Time is frequently lost whilst awaiting repeat bloods to confirm hyperkalaemia even in the presence of renal failure and ECG changes. Refer for specialist advice early in patients with severe hyperkalaemia with ECG changes, end-stage renal disease, oliguric AKI, and in patients who do not respond to medical treatment.

**Treat severe hyperkalaemia as a medical emergency.**

IV calcium is a crucial step in the prevention of arrhythmias and cardiac arrest in hyperkalaemia.3 。。It is important to re-assess the ECG after administration of IV calcium as a further dose may be necessary if toxic changes persist. Vigilance is also required as toxic ECG changes may recur when the effects of the drug have worn off after approximately 30-60 minutes. IV calcium may buy time, but does not lower the serum K+. Therefore, other therapeutic measures should not be delayed.

Adverse events related to severe hyperkalaemia has been evaluated to determine if the ECG is helpful in risk stratification. Durfey et al reported the frequency of adverse events within 6 hours of the presenting ECG.4 。。The study included 188 patients with a serum K+ ≥ 6.5 mmol/l (mean K+ 7.1 mmol/l). Adverse events occurred in 15% of patients including symptomatic bradycardia (n=22), VT (n=2), CPR (n=2) and death (n=4). All of these events occurred prior to administration of IV calcium and all but one occurred before administration of K+-lowering medication. This highlights the importance of timely treatment to prevent arrhythmias and cardiac arrest.

The lack of blood monitoring after initiating medical treatment is a common pitfall in the management of hyperkalaemia. If the serum K+ is not repeated at approximately one hour after treatment when the drugs have taken its maximum effect, then the efficacy of treatment cannot be assessed. Patients who are refractory to medical treatment are potentially at risk of cardiac arrest. Furthermore, there is a tendency for rebound hyperkalaemia once the effects of insulin-glucose and salbutamol have worn off. Failure to repeat the serum K+ at 4-6 hours will miss this rebound and could result in arrhythmias or cardiac arrest. Rebound may also occur after dialysis and may be exaggerated if temporising drugs have been used.5

There are a few fallacies related to hyperkalaemia that require clarification:

* Patients with pacemakers are not protected from hyperkalaemic cardiac arrest. Indeed, pacemaker failure has been well documented in this circumstance.[6, 7]
* The presence of a normal ECG in the context of severe hyperkalaemia is not protective against arrhythmias.
* Severe hyperkalaemia can occur in the presence of near normal renal function, but may be assumed to be spurious. An urgent ECG and repeat blood sample using a blood gas analyser should confirm the presence of hyperkalaemia.
* Patients receiving longterm haemodialysis do not have a ‘tolerance’ to severe hyperkalaemia and are also at risk of cardiac arrest. Medical treatment will only temporarily lower the serum K+, therefore urgent dialysis is indicated.

**References**

1. NHS Improvement. Patient Safety Alert. Resources to support safe and timely management of hyperkalaemia (high level of potassium in the blood). August 2018. Alert reference number: NHS/PSA/RE/2018/006

**Treatment Algorithm: Resuscitation (Guideline 27.1)**

### Guideline 27.1 – Hyperkalaemia; Algorithm in Cardiac Arrest

We recommend that cardiac arrest attributable to hyperkalaemia is managed using the treatment algorithm which provides guidance on the medical therapies and the need for initiation of renal replacement therapy during CPR. (1C)

**Rationale (Guideline 27.1)**

Hyperkalaemia is a potentially reversible cause of cardiac arrest, but achieving and sustaining ROSC is dependent on controlling the serum K+ level. In this way, this special circumstance is analogous to hypothermic cardiac arrest. There are fewer drug therapy options for controlling hyperkalaemia during cardiac arrest (Guidelines 25.1 - 25.3) and the degree of K+-lowering required to achieve ROSC may not be achievable with drugs alone (Guideline 25.4). The hyperkalaemic cardiac arrest algorithm outlines the modifications to ALS and the specific interventions to address hyperkalaemia as illustrated in Appendix 7.

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# Lay summary

Hyperkalaemia is a medical disorder in which the potassium (K+) level in the blood is raised. The higher the level, the greater the risk of life-threatening consequences. Hyperkalaemia may be mild (K+ 5.5 – 5.9 mmol/l), moderate (K+ 6.0 – 6.4 mmol/l) or severe (K+ ≥ 6.5 mmol/l). Severe hyperkalaemia can affect muscle function in the limbs causing weakness, or in the heart causing potentially fatal heart rhythms. Therefore early recognition and treatment of hyperkalaemia can save lives.

The kidneys are largely responsible for removing potassium from the body, therefore the most common cause of hyperkalaemia is impaired kidney function. Some commonly prescribed drugs used to treat heart failure, kidney disease and diabetes mellitus can also contribute to hyperkalaemia, therefore regular blood monitoring is required.

Hyperkalaemia can occur in the community or in the hospital. Most cases of mild or moderate hyperkalaemia can be managed without the need for hospital admission unless it occurs in the setting of an acute illness. Hospital assessment is required for severe hyperkalaemia as prompt treatment may prevent adverse events. Hyperkalaemia detected in hospital may be present at the time of hospital admission or occur during the course of admission, therefore vigilance is required during acute illness.

The treatment for hyperkalaemia is evolving. Two new oral potassium lowering drugs (sodium zirconium cyclosilicate and patiromer) have recently been approved for specific indications by the National Institute for Health and Care Excellence (NICE). Insulin and glucose infusion remains the most effective emergency treatment, but hypoglycaemia (low blood glucose) is a common adverse event. A continuous infusion of glucose in patients with a low pre-treatment blood glucose level (< 7 mmol/l) is now recommended.

Treatment algorithms are useful in many medical emergencies and have been applied to the treatment of hyperkalaemia in the community, in hospital and in resuscitation. Prevention of hyperkalaemia is the best approach. This requires careful drug prescribing, blood monitoring, a low potassium diet when indicated and the provision of patient information and education. Standardised protocols will provide a more consistent approach to treating hyperkalaemia and improve patient safety.

# Appendices

### Oral potassium lowering drugs

### Summary of clinical trials of oral potassium lowering drugs

### Drug administration and safety

* 1. Intravenous Calcium – Chloride and Gluconate solutions
  2. Insulin-glucose infusion
  3. Salbutamol
  4. Patiromer
  5. Sodium zirconium cyclosilicate
  6. Calcium resonium

### ECG in Hyperkalaemia – sine wave.

### Algorithm – Management of Hyperkalaemia in the Community.

### Algorithm – Management of Hyperkalaemia in Hospital.

### Algorithm – Management of Hyperkalaemia in Resuscitation.

## Appendix 1: Oral potassium lowering drugs.

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristic** | **Calcium resonium** | **Patiromer** | **SZC** |
| **Mechanism of action** | Entraps K+ in exchange for Ca2+ | Non-specific binding of K+ in exchange for Ca2+ | Selective K+ binding in exchange for Na+ |
| **Site of action** | Distal Colon | Distal colon | Entire intestinal tract |
| **Administration** | Oral or rectal | Oral | Oral |
| **Dosing** | 15-60g/ day | 8.4-25.2 g/day | 2.5-30 g/day |
| **Onset of effect** | >4 hours | 4-7 hours | 1 hour |
| **Efficacy** | Unpredictable and variable | −1.01 mmol/l in 4 weeks [OPAL-HK] | - 1.1 mmol/l in 48 hours [ZS-003, ZS-004]  Median time to normalisation of serum K+ is 2.2 hours [ZS-004] |
| **Common adverse effects** | Gastrointestinal disorders Hypokalaemia | Gastrointestinal disorders  Hypokalaemia  Hypomagnesaemia | Gastrointestinal disorders  Hypokalaemia  Oedema |
| **Serious adverse effects** | Colonic necrosis | No episodes of colonic perforation or necrosis reported | No episodes of colonic perforation or necrosis reported |
| **FDA Approval** | 1958 | 2015 | 2018 |
| **NICE Appraisal status** | N/A | Pending | Approved |

### Comparison between potassium-binding agents for treatment of hyperkalaemia.

## Appendix 2: Summary of clinical trials of oral potassium lowering drugs

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **STUDY** | **N=** | **INTERVENTION** | **CKD (eGFR**  **<60)** | **DIABETES** | **HEART FAILURE** | **RAASi** |
| Lepage 2015  RCT | 33 | SPS | 100% | 72% | 9% | 76% |
| Nasir 2014  RCT | 97 | CPS  SPS | 100% | 65% | NA | 0%  (excluded) |
| Gruy-Kapral 1998 RCT | 6 | SPS | HD | NA | NA | NA |
| Ash 2015  Phase II RCT  **ZS-002** | 90 | SZC | 100% | 56% | NA | 62% |
| Packman 2015 Phase III RCT  **ZS-003** | 753 | SZC | 75% | 60% | 40% | 67% |
| Kosiborod 2014 Phase III RCT HARMONIZE  **ZS-004** | 258 | SZC | 66% | 66% | 36% | 70% |
| Fishbane 2017  **ZS-005** | 751 | SZC | 73% | 62% | 38% | 64% |
| Pitt 2011 PEARL-HF (RCT) | 104 | Patiromer | 27% | 32% | 100% | NA |
| Bakris 2015 AMETHYST-DN  (RCT) | 222 | Patiromer | 87% | 100% | 35% | 71% |
| Bushinsky 2015 Phase I Trial | 25 | Patiromer | 100% | 60% | 28% | 100% |
| Weir 2015 OPAL-HK (RCT) | 243 | Patiromer | 100% | 57% | 42% | 100% |
| Pergola 2017 TOURMALINE  (RCT) | 112 | Patiromer | 76% | 82% | 9% | 59% |
| Pitt 2018 Open-label | 63 | Patiromer | 100% | 43% | 100% | 98% |

### Trials of oral potassium lowering drugs, representative comorbidities and use of RAASi drugs.

NA – not available

## Appendix 3A: Drug administration and safety - IV calcium preparations

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| --- | --- |
| **Calcium Chloride** | |
| **Available as** | * Calcium chloride 10% pre-filled syringe 10mL (contains 6.8mmol of calcium in   10mL) |
| **Preparation** | * Can be used undiluted |
| **Flush solutions** | * Flush well with sodium chloride 0.9% to reduce vein irritation. * Incompatible with many solutions (including sodium bicarbonate and phosphate). |
| **Administration** | * Give by intravenous injection over 3-5 minutes. * Give as a bolus injection during resuscitation. * Preferably administer via a central venous device (if already in-situ). * For peripheral administration, choose a large vein and monitor closely for phlebitis. * Ensure patient is supine and closely observed during injection. * Monitor ECG and blood pressure. |
| **Specialist technical**  **information** | * Extravasation can cause tissue damage because of the high osmolarity. |
| **Cautions and side effects** | * **Cautions**: - Hypercalcaemia. Digoxin. * **Side Effects: -** Too rapid administration may lead to symptoms of hypercalcaemia and may cause cardiac arrhythmias or arrest, hypotension and vasomotor collapse, sweating, hot flushes, nausea and vomiting. |

|  |  |
| --- | --- |
| **Calcium Gluconate** | |
| **Available as** | * Calcium gluconate 10% ampoules (contains 2.2mmoL of calcium in 10mL) |
| **Preparation** | * Can be used undiluted. |
| **Flush solutions** | * Flush well with sodium chloride 0.9% or glucose 5% to avoid vein irritation. * Incompatible with many solutions (including sodium bicarbonate and phosphate). |
| **Administration** | * The rate of administration should not exceed 2mL per minute (equivalent to 10mL of undiluted injection over 5 minutes). * For peripheral administration, choose a large vein and monitor closely for phlebitis. * Ensure patient is supine and closely observed during injection. * Monitoring ECG and blood pressure. |
| **Specialist technical**  **information** | * Extravasation can cause tissue damage because of the high osmolarity. |
| **Cautions and side effects** | * **Cautions**: - Hypercalcaemia. Digoxin. * **Side-Effects: -** Administer slowly to minimise peripheral vasodilation, cardiac depression and circulatory collapse |

**References**

1. Electronic Medicines Compendium (2018) ‘Summary of Product Characteristics – Calcium Gluconate Injection BP – Hameln Pharmaceuticals Ltd’. Available at <https://www.medicines.org.uk/emc/product/6264/smpc>. Accessed on 06.05.19.
2. Injectable Medicines Guide. Monograph for Calcium gluconate. Version 6 05.02.2019. Available at <http://www.injguide.nhs.uk/IVGuidePrint.asp?Drugno=3225&format=3>. Accessed 06.05.2019
3. Guidelines and Audit Implementation Network (2014) Guidelines for the treatment of hyperkalaemia in adults. Belfast, GAIN.
4. Injectable Medicines Guide. Monograph for Calcium chloride. Version 5 22.06.2016. Available at. [http://www.injguide.nhs.uk/IVGuidePrint.asp?Drugno=2562&format=3](http://www.injguide.nhs.uk/IVGuidePrint.asp?Drugno=2562&format=3%20) Accessed 06.05.2019
5. Electronic Medicines Compendium (2018) ‘Summary of Product Characteristics – Calcium Chloride Intravenous Infusion 10% w/v – Martindale Pharma’. Available at <https://www.medicines.org.uk/emc/product/4126/smpc>Accessed 06.05.2019
6. University College London Hospitals NHS Foundation Trust. Injectable Medicines Administration Guide. 3rd edition. 2010. Wiley-Blackwell. Chichester.

## Appendix 3B: Drug administration and safety –Insulin-glucose infusion

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| **10 units of Soluble Insulin in 50mL Glucose 50% (25g)** | |
| **Available as** | Vials containing human soluble insulin 100 units per mL (Actrapid®) |
| Vials containing 50mL glucose 50% (25g) |
| **Preparation** | * Withdraw 10 units of Actrapid® insulin. **This should be done only using an insulin syringe which is graduated in units**. Due to the potential for dosing errors, it is recommended that this is independently checked by another healthcare professional. * Inject the insulin into a 50mL glucose 50% vial and mix well. * Withdraw contents of vial into 50mL intravenous syringe. |
| **Concentration of final solution** | 10 units soluble insulin in 50mL |
| **Dilution/flush solutions** | Sodium chloride 0.9% - flush well to reduce vein irritation |
| **Administration** | IV Injection: Administered over 5-15 minutes intravenously into a large vein  Monitor for phlebitis if 50% glucose is given peripherally. |
| **Storage and handling** | Do not use unless solution is clear and without visible particles. |
| **Specialist technical information** | Glucose 50% has a high osmolarity and administration into a peripheral vein may result in vein irritation, vein damage and thrombosis. |
| **Cautions and side effects** | * Hypoglycaemia – follow monitoring recommendations in guideline and treat according to local guidelines. * Infusion site reactions including phlebitis, erythema and thrombophlebitis. * Hypersensitivity/ anaphylactic reactions have been reported   thought to be due to corn allergy. Should be used with caution, if at all in patients with a known allergy to corn products. |

### Alternative Glucose preparations

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| **20% Glucose** | |
| **Available as** | 100 ml bottle |
| **Volume required for 25g glucose** | 125 ml (two bottles required) |

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| --- | --- |
| **10% Glucose** | |
| **Available as** | 500 ml bag |
| **Volume required for 25g glucose** | 250 ml |

**References**

1. Electronic Medicines Compendium (2017) ‘Summary of Product Characteristics – Glucose 50% w/v Concentrate for solution for infusion – Baxter Healthcare Ltd’ Available at <https://www.medicines.org.uk/emc/product/1826/smpc>. Accessed 29.04.2019
2. Electronic Medicines Compendium (2018) ‘Summary of Product Characteristics – Glucose intravenous infusion BP 50% w/v – Hameln Pharmaceutical Ltd’. Available at <https://www.medicines.org.uk/emc/product/6266/smpc>. Accessed 29.04.2019
3. Guidelines and Audit Implementation Network (2014) Guidelines for the treatment of hyperkalaemia in adults. Belfast, GAIN.
4. Injectable Medicines Guide. Monograph for Insulin (soluble) Human. Version 5 22.01.2019. Available at <http://www.injguide.nhs.uk/IVGuidePrint.asp?Drugno=2612&format=3>. Accessed 29.04.2019

## Appendix 3C: Drug administration and safety - Salbutamol

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| --- | --- |
| **Salbutamol Nebulised Solution** | |
| **Available as** | * 2.5mg/2.5mL nebuliser solution * 5mg/2.5mL nebuliser solution |
| **Administration** | * 10mg DOSE   = 10ml of 2.5mg/2.5mL nebuliser solution.  = 5ml of 5mg/2.5mL nebuliser solution.   * 20mg DOSE   = 10ml of 5mg/2.5mL nebuliser solution.   * Use a face mask or T-piece. |
| **Cautions and side effects** | * **Cautions:**   + Consider only giving 10mg in patients with ischaemic heart disease.   + Tachyarrhythmia   + Open angle glaucoma * **Side-Effects:**   + Tremor   + Tachycardia   + Headache |

**References**

1. Guidelines and Audit Implementation Network (2014) Guidelines for the treatment of hyperkalaemia in adults. Belfast, GAIN.
2. Electronic Medicines Compendium (2016) ‘Summary of Product Characteristics – Ventolin Nebules – GlaxoSmithKline UK. Available at <https://www.medicines.org.uk/emc/product/8256/smpc>. Accessed 06.05.2019

## Appendix 3D: Drug administration and safety – Patiromer

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| --- | --- |
| See the source image **Patiromer** | |
| **Available as** | 8.4g, 16.8g and 25.2g sachets |
| **Preparation** | * The dose should be poured into a glass containing approximately 40mL of water and then stirred. * Another approximately 40mL of water should be added, and the suspension stirred again thoroughly. The powder will not dissolve. * More water may be added to the mixture as needed. |
| **Administration** | * Apple juice or cranberry juice can be used instead of water to prepare the mixture (be aware of potential interactions with cranberry juice). Other liquids should be avoided due to potential potassium content. * Should be taken with food. * **Administration should be separated by 3 hours from other medicines**. |
| **Storage and handling** | * The reconstituted mixture should be taken within 1 hour of initial suspension. * Unopened storage and transportation should be refrigerated (2oC-   8oC). Patients may store below 25oC for up to 6 months. |
| **Cautions and side effects** | * **Cautions** – Hypercalcaemia, hypomagnesaemia, GI disorders, contains sorbitol. * **Side-effects** –Hypomagnesaemia, constipation, diarrhoea, abdominal   pain and flatulence |

See the source image*Black label medicine subject to additional monitoring to allow quick identification of new safety information. Report all suspected adverse reactions.*

**References**

* 1. Electronic Medicines Compendium (2017) ‘Summary of Product Characteristics – Veltassa (Patiromer) – Vifor Fresenius Medical Care Renal Pharma UK Ltd’. Available at <https://www.medicines.org.uk/emc/product/779>accessed 03.05.2019.
  2. Joint Formulary Committee. *British National Formulary* (online) London: BMJ Group and Pharmaceutical Press. Available at [http://www.medicinescomplete.com](http://www.medicinescomplete.com/) accessed 03.05.2019

## Appendix 3E: Drug administration and safety – Sodium zirconium cyclosilicate

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| See the source image **Sodium Zirconium Cyclosilicate** | |
| **Available as** | 5g, 10g sachets (powder oral suspension) |
| **Preparation** | * The contents of the sachet should be emptied into a glass containing approximately 45mL of water and stirred well. The powder will not dissolve. * Advise patient to drink the tasteless liquid while still cloudy. * If the suspension settles - it should be stirred again. |
| **Administration** | * The suspension can be taken with or without food. * Administer at least 2 hours before or 2 hours after oral medications with clinically meaningful gastric pH dependent bioavailability. |
| **Treatment: Correction Phase** | * SZC 10g three times daily until normokalaemia (serum K+ 4.0 – 5.0 mmol/l) achieved. * Usually duration is 24 – 48 hours, maximum duration 72 hours. * Discontinue after 72 hours if normokalaemia not achieved. |
| **Treatment: Maintenance Phase** | * SZC 5g daily starting dose (after normokalaemia achieved) * Titrate up to 10g once daily or down to 5g alternate days guided by serum K+ levels. * Monitor serum K level regularly. * Discontinue of hypokalaemia develops (serum K+ < 4.0 mmol/l) |
| **Cautions and side effects** | * **Cautions** – can cause QT interval lengthening as a result of a reduction in serum potassium. May be opaque to X-rays – consider if having abdominal X-rays. * **Side effects** – Hypokalaemia, oedema, gastrointestinal disorders. |

See the source image*Black label medicine subject to additional monitoring to allow quick identification of new safety information. Report all suspected adverse reactions.*

**References**

1. Electronic Medicines Compendium (2019) ‘Summary of Product Characteristics – Lokelma 10g powder for oral suspension – AstraZeneca UK Limited’. Available at <https://www.medicines.org.uk/emc/product/10074/smpc>. Accessed 03.05.2019.

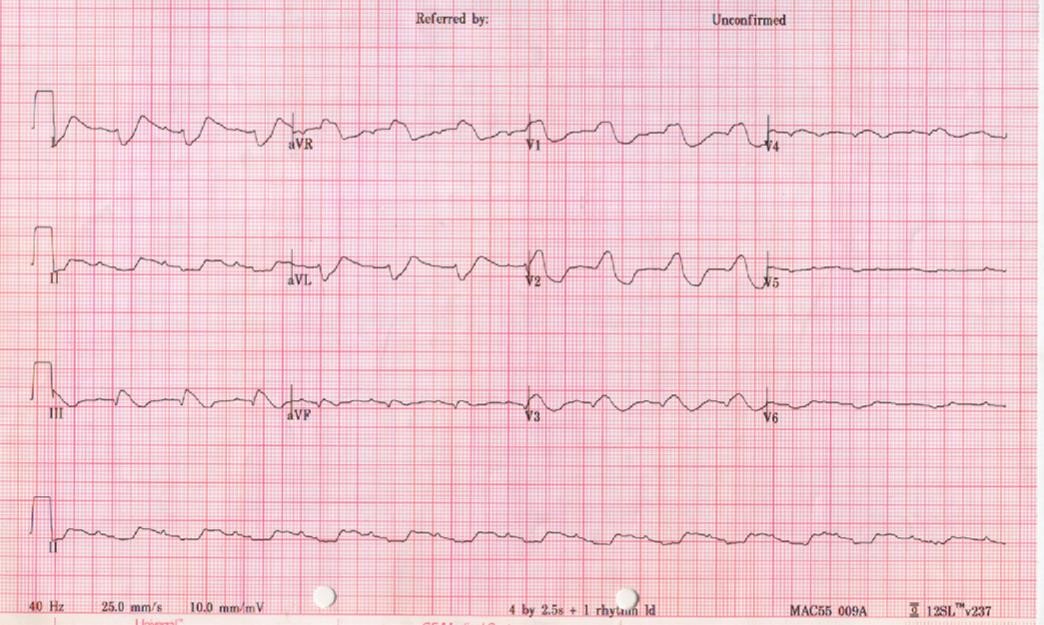
## Appendix 3F: Drug administration and safety – Calcium resonium

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| **Calcium Resonium** | |
| **Available as** | Calcium Resonium Powder (99.934%) |
| **Preparation** | * Oral administration:-   + Each 1g of resin should be mixed with 3 to 4mL of water or syrup (not fruit juices). This corresponds to 45 to 60mL of liquid for a 15g dose. * Rectal administration   + 30g of resin should be mixed with 150mL of water or glucose 10% as a daily retention enema. |
| **Administration** | * For oral administration, administer at least 3 hours before, or 3 hours after other medication. In patients with gastroparesis consider a 6-hour separation. * For rectal administration, the enema should be retained for at least 9 hours then the colon should be irrigated to remove the   resin. |
| **Cautions and side effects** | * Contra-indicated in hypercalcaemia or in obstructive bowel disease. * Concomitant use with sorbitol is not recommended due to gastro-   intestinal stenosis and intestinal ischaemia. |

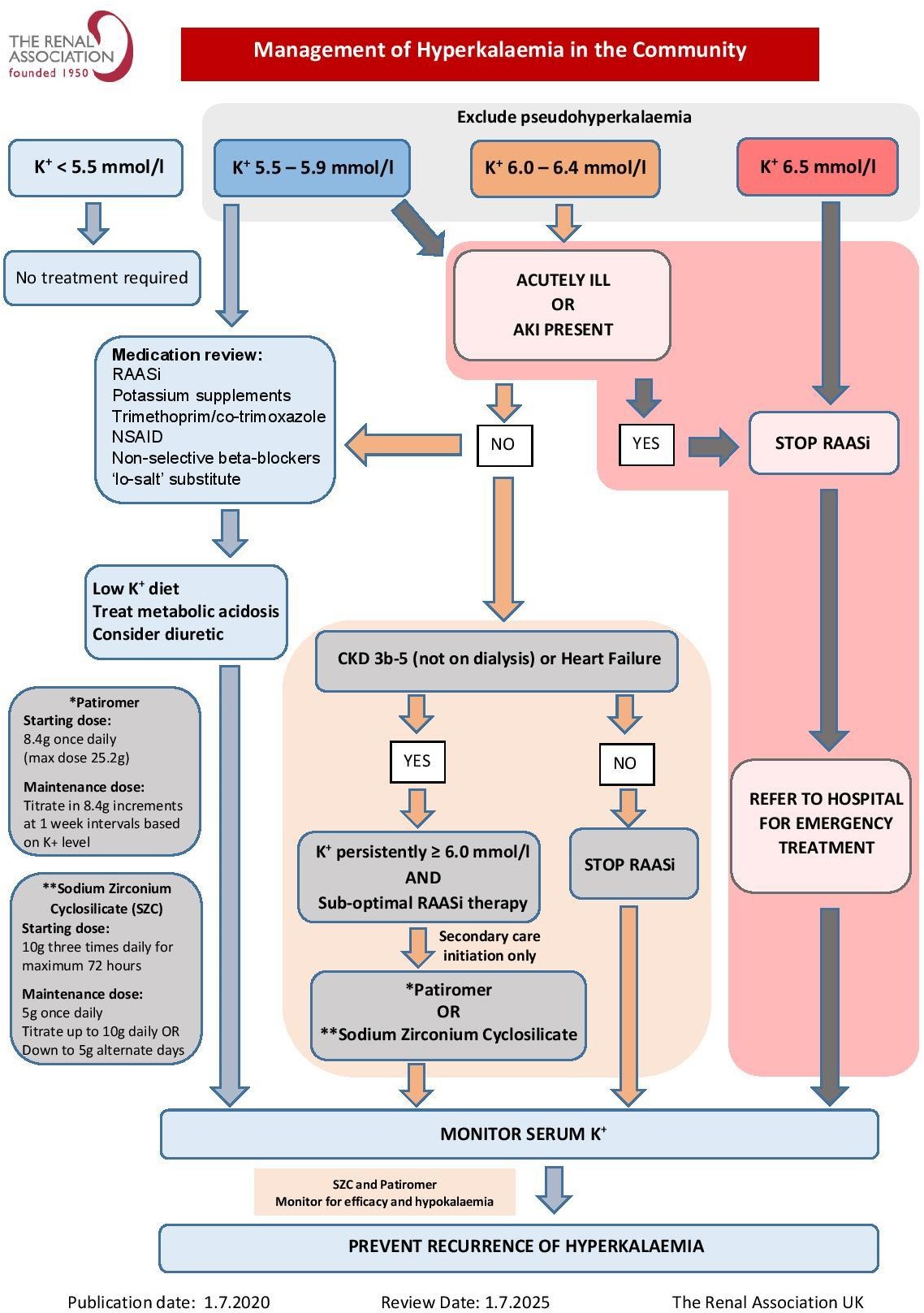
**References**

1. Electronic Medicines Compendium (2018) ‘Summary of Product Characteristics – Calcium Resonium 99.934% w/w powder for oral/rectal suspension – Sanofi’. Available at <https://www.medicines.org.uk/emc/product/1439>. Accessed 06.05.2019

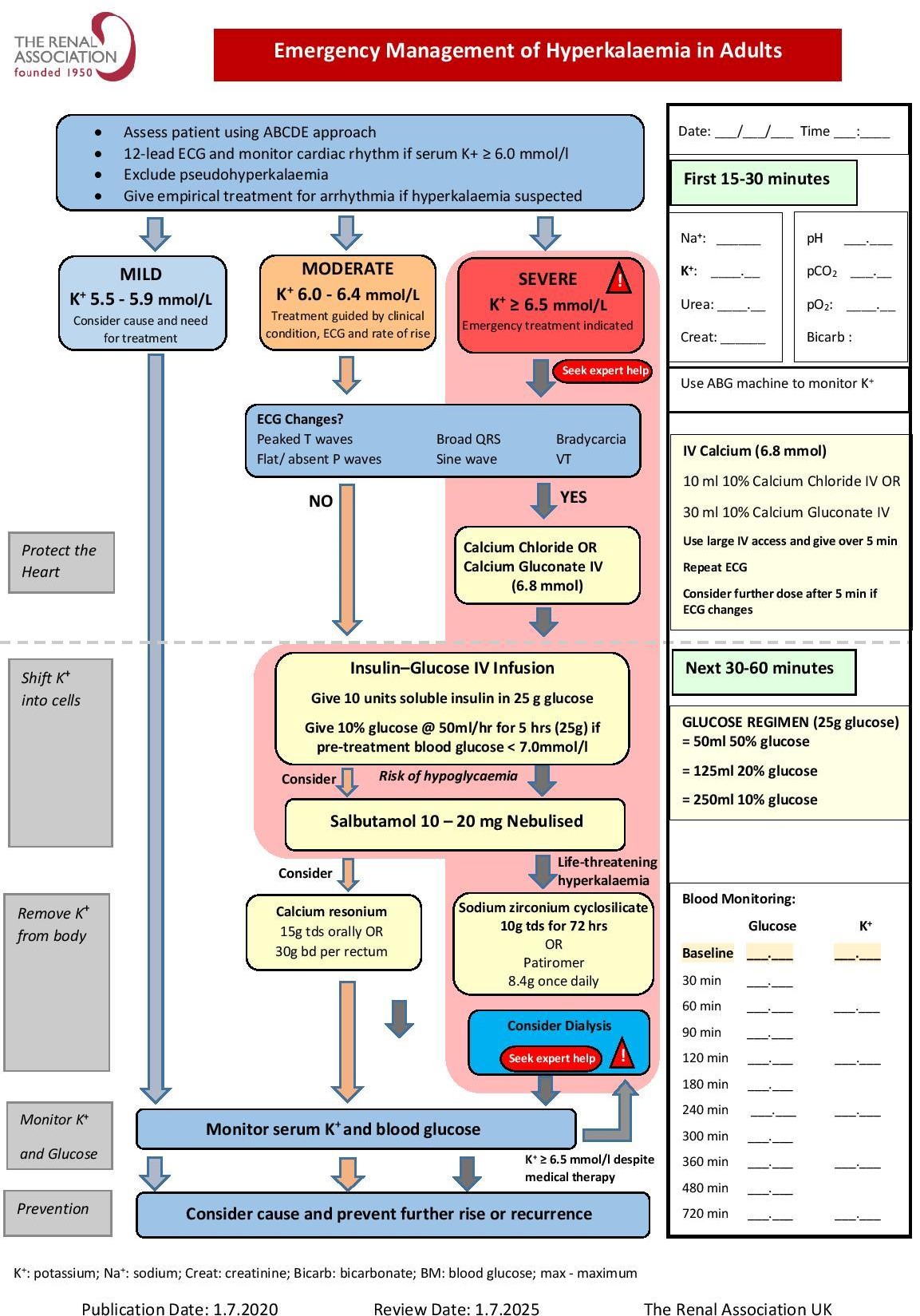
## Appendix 4 – Sine wave ECG



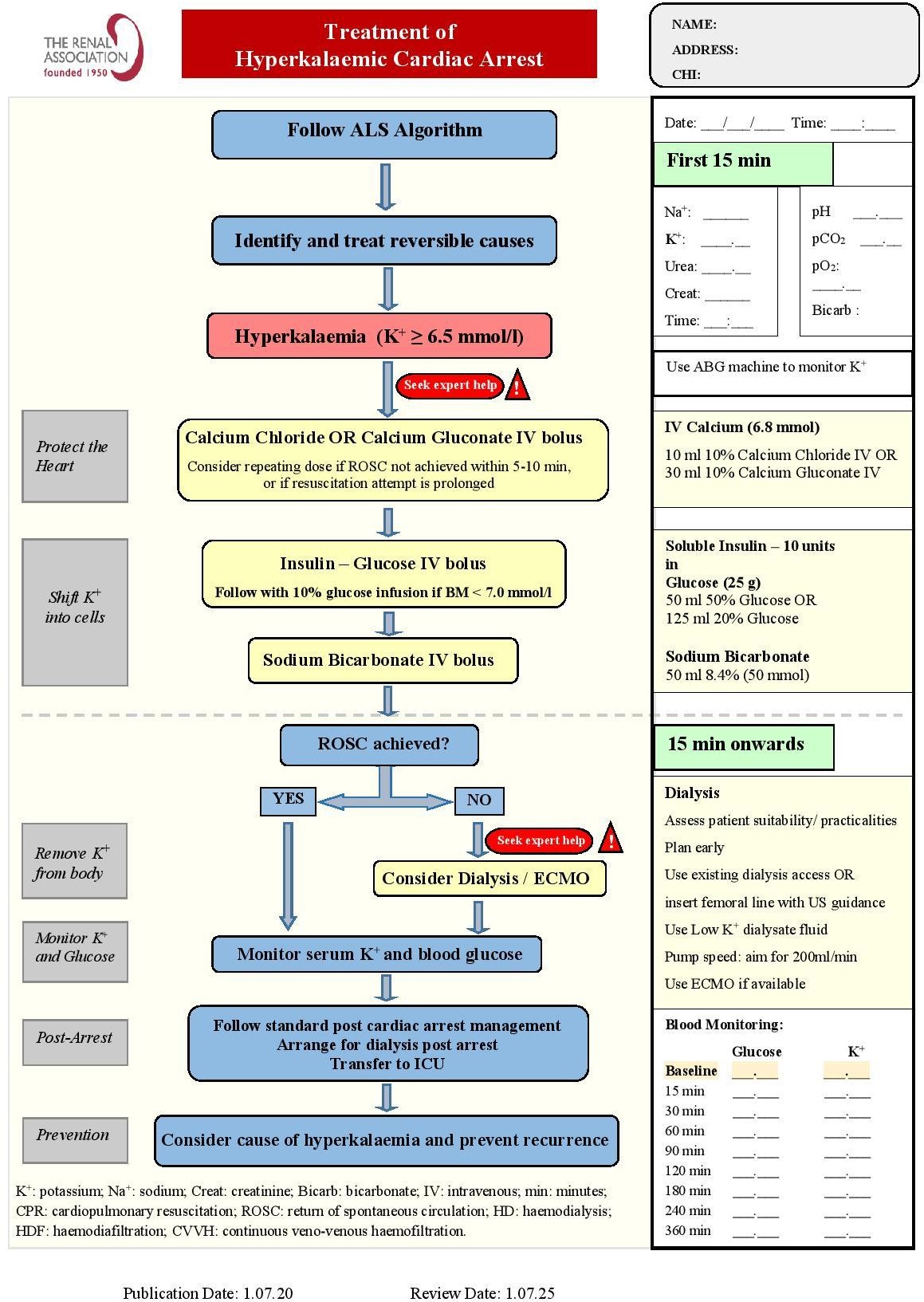
## Appendix 5 – Hyperkalaemia Algorithm - Community



## Appendix 6 – Hyperkalaemia Algorithm – Hospital



## Appendix 7 – Hyperkalaemia Algorithm – Resuscitation



# Abbreviations

AAGBIG Association of Anaesthetists of Great Britain and Ireland Guideline ABCDE Airway – Breathing – Circulation – Disability – Exposure

ACC American College of Cardiology

ACE-i Angiotensin converting enzyme inhibitor AED Automated External Defibrillator

AHA American Heart Association

AKI Acute Kidney Injury

ALS Advanced Life Support

ARB Angiotensin II receptor blocker

ARDS Adult respiratory distress syndrome

AUC Area under the curve

AV Artero-venous

AVPU Alert – Verbal – Pain - Unresponsive

BGA Blood gas analyser

BM Blood glucose

BP Blood pressure

Ca2+ Calcium ion

CKD Chronic kidney disease

CPR Cardiopulmonary resuscitation

CPS Calcium polystyrene sulphonate

CV Cardiovascular

CVVH Continuous veno-venous haemofiltration CVVHDF Continuous veno-venous haemodiafiltration DM Diabetes Mellitus

DNACPR Do Not Attempt Cardiopulmonary Resuscitation DOPPS Dialysis Outcomes and Practice Patterns Study ECG Electrocardiogram

ECMO Extra-corporeal membrane oxygenation eGFR Estimated glomerular filtration rate

EMA European Medicines Agency

ERC European Resuscitation Council

ESC European Society of Cardiology

ESRD End-stage renal disease

FDA Food and Drug Administration

FICM Faculty of Intensive Care Medicine

GCS Glasgow coma scale

GFR Glomerular filtration rate

HBP Hypertension

HD Haemodialysis

HDF Haemodiafiltration

HDU High dependency unit

HF Haemofiltration

HFrEF Heart failure with reduced ejection fraction HK Hyperkalaemia

HR Hazard ratio

Hypo Hypoglycaemia

ICS Intensive Care Society

ICU Intensive Care Unit

IEC International Electrotechnical Committee

IHCA In-hospital cardiac arrest

IHD Intermittent haemodialysis

ILCOR International Liaison Committee on Resuscitation IV Intravenous

K+ Potassium ion

KDOQI Kidney Disease Outcomes Quality Initiative MET Medical emergency team

Mg+ Magnesium ion

MHRA Medicines and Healthcare products Regulatory Agency MRA Mineralocorticoid receptor antagonist

Na+ Sodium ion

NA Not available

NCEPOD National Confidential Enquiry into Patient Outcome and Death.

|  |  |
| --- | --- |
| NEWS | National Early Warning Score |
| NHS | National Health Service |
| NI | Not included |
| NICE | National Institute for Health and Care Excellence |
| NSAIDS | Non-steroidal anti-inflammatory drugs |
| OHCA | Out-of-hospital cardiac arrest |
| OR | Odds ratio |
| PEA | Pulseless electrical activity |
| POCT | Point of care testing |
| RAASi | Renin-Angiotensin-Aldosterone-System inhibitor |
| RCT | Randomised controlled trial |
| ROSC | Return of spontaneous circulation |
| RRT | Renal replacement therapy |
| SB | Sodium bicarbonate |
| SBAR | Situation – Background – Assessment – Recommendation |
| SCD | Sudden cardiac death |
| SMC | Scottish Medicines Consortium |
| SPS | Sodium polystyrene sulphonate |
| SZC | Sodium Zirconium Cyclosilicate |
| UK | United Kingdom |
| USA | United States of America |
| USRDS | United States Renal Data System |
| VF | Ventricular fibrillation |
| VT | Ventricular tachycardia |