# Title Page

**Potassium supplementation and prevention of Atrial Fibrillation after Cardiac Surgery.**
**The TIGHT K randomized controlled trial**

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# Key Points

### Question

When trying to prevent Atrial Fibrillation After Cardiac Surgery (AFACS), is supplementing potassium only when its serum concentration ([K+]) falls below 3.6mEq/L non-inferior to supplementation when [K+] falls below 4.5mEq/L?

### Findings

In the first 5 days after Coronary Artery Bypass Graft (CABG) surgery, patients who only received supplementation when [K+] dropped below 3.6mEq/L (n=830) did not have an increased incidence of new-onset AFACS compared to those who only received supplementation when serum [K+] dropped below 4.5mEq/L (n=837). There was no difference between the groups for other dysrhythmias or clinical outcomes.

### Meaning

The widespread practice of seeking to maintain high-normal [K+] levels after CABG surgery can be abandoned. This will reduce healthcare costs and decrease patient risk from an unnecessary intervention.

# Abstract

**IMPORTANCE**

Supplementing potassium in an effort to maintain high normal serum concentrations ([K+]) is a widespread strategy used to prevent atrial fibrillation after cardiac surgery (AFACS), but is not evidence-based, carries risks and is costly.

**OBJECTIVE**

To determine whether a lower [K+] trigger for supplementation is non-inferior to a high-normal trigger.

**DESIGN**

Open-label, noninferiority, randomized controlled trial

**SETTING**

Twenty-three cardiac surgical centers in the United Kingdom and Germany

**PARTICIPANTS**

1690 patients with no history of atrial dysrhythmias scheduled for isolated Coronary Artery Bypass Grafting (CABG) surgery.

**INTERVENTIONS**

Patients were randomly assigned to a strategy of ‘Tight’ or ‘Relaxed’ potassium control (only supplementing if serum potassium concentrations fell below 4.5 mEq/L or 3.6 mEq/L respectively). Patients wore an Ambulatory Heart Rhythm Monitor (AHRM), which was analyzed by a core lab masked to treatment assignment.

## MAIN OUTCOMES AND MEASURES

The prespecified primary endpoint was clinically detected and electrocardiographically confirmed new onset AFACS in the first 120 hours after CABG surgery or until hospital discharge, whichever occurred first. All primary outcome events were validated by an Event Validation Committee, which was masked to treatment assignment. Non-inferiority of ‘Relaxed’ potassium control was defined as a risk difference for new onset AFACS with associated upper bound of a one-sided 97.5% confidence interval of less than 10%. Secondary outcomes included other heart-rhythm related events, clinical outcomes and cost related to the intervention.

## RESULTS

1690 patients were randomized between October 2020 and November 2023. The primary endpoint occurred in 26.2% and 27.8% of patients in the ’Tight’ and ‘Relaxed’ arms respectively, a risk difference of 1.6% (95%CI -2.6% to 5.9%). There was no difference between the arms in incidence of at least one AFACS episode detected by any means or by AHRM alone, non-AFACS dysrhythmias, in-patient mortality or length of stay. Per patient cost for purchasing and administering potassium was significantly lower in the ‘Relaxed’ arm (mean difference £87.21 [95% CI: 80.74 to 93.67] / $111.89 [95% CI: 103.60 to 120.19] p-value: <0.001).

## CONCLUSION AND RELEVANCE

For AFACS prophylaxis, supplementation only when [K+] fell below 3.6mEq/L was non-inferior to the current widespread practice of supplementing potassium to maintain a [K+] $\geq$ 4.5mEq/L. The lower threshold of supplementation was not associated with any increase in dysrhythmias or adverse clinical outcomes

## TRIAL REGISTRATION

ClinicalTrials.gov: NCT04053816. https://clinicaltrials.gov/study/NCT04053816

## INTRODUCTION

Approximately 1.5 million cardiac surgical procedures are performed worldwide per year[1], with Coronary Artery Bypass Grafting (CABG) the most common of these.[2] Atrial Fibrillation after Cardiac Surgery (AFACS) remains the most frequent post-operative Adverse Event, affecting about 30% of patients following CABG.[3] By day 5, 90% of patients who develop AFACS will have done so.[4] AFACS is associated with increases in short- and long-term morbidity, early and late mortality, length of critical care and hospital stay, and healthcare costs.[5,6] Prevention strategies vary widely internationally, reflecting a limited evidence base for their effectiveness.[7–9]

Potassium has a fundamental role in the cardiac action potential[10] and pathological hypokalaemia is associated with both ventricular dysrhythmias and cardiac arrest.[11] Many clinicians believe that serum potassium concentration ([K+]) influences risk of developing AF in critical illness,[12] and frequent potassium supplementation in an effort to maintain a high-normal post-operative [K+] (≥4.5 mEq/L) is now routine practice in many centers worldwide for AFACS prophylaxis.[5,7] However, proof that this strategy is effective is lacking, with marked regional variations in practice suggesting equipoise regarding its effectiveness.[5]

Although individual doses of IV potassium are cheap, in many cardiac units the cumulative annual expenditure for intravenous potassium is greater than that for most other drugs.[13] Caregivers' time expended on delivering the intervention adds further monetary and opportunity cost. Potassium supplementation also negatively impacts on patient experience and may be associated with risk.[14]

We sought to address the gap in evidence on the effectiveness of maintaining a high-normal serum potassium for AFACS prophylaxis. Firstly, in a feasibility study,

we demonstrated that we could recruit and randomize patients to two different potassium supplementation protocols.[15] Now we report the results of TIGHT K, the first appropriately powered multicenter randomized controlled trial to determine whether supplementing potassium only when [K+] falls below 3.6 mEq/L ('Relaxed' control) is non-inferior to supplementation when [K+] falls below 4.5 mEq/ ('Tight' control).[16]

## METHODS

### Trial Design and Oversight

The Trial Protocol and Statistical Analysis plan are available in Supplement 1 and 2 respectively.

TIGHT K was a prospective multicenter randomized controlled non-inferiority open label trial performed at 23 cardiac surgery units in the United Kingdom (n=21), and Germany (n=2). Enrollment occurred from 20 October 2020 to 16 November 2023.

The protocol was approved by the U.K. Health Research Authority and by the Research Ethics Committees at the University of Münster and Charité Universitätsmedizin Berlin, Germany, and published.[16] The trial was conducted in accordance with the Declaration of Helsinki.

TIGHT K was funded by the British Heart Foundation and sponsored by Barts Health NHS Trust, UK. Collaborating sites in Germany were self-sponsored. The London School of Hygiene and Tropical Medicine Clinical Trials Unit co-designed and coordinated the trial and performed the statistical analyses.

An Independent Steering Committee and a Data and Safety Monitoring Committee oversaw the trial. A core lab at Manchester Heart Institute, Manchester University NHS Foundation Trust, UK, analysed the Ambulatory Heart Rhythm Monitors (AHRM) (CAM™ Bardy, Baxter, Deerfeld, IL), which patients wore in addition to routine monitoring. An independent Event Validation Committee arbitrated all primary endpoint events.

## Patients

Eligible patients were all adults (≥18 years of age) in sinus rhythm, scheduled for isolated CABG surgery (defined as no additional cardiac or vascular procedure during the same operation).

Patients were excluded if they had a history of atrial fibrillation, atrial flutter or atrial tachyarrhythmia; pre-operative high-degree atrioventricular (AV) block (defined as Mobitz type 2 second degree AV block or complete heart block); current or previous use of medication for the purposes of cardiac rhythm management; a pre-operative [K+] > 5.5 mEq/L; or dialysis-dependent end-stage renal failure.

A full list of the inclusion and exclusion criteria is provided (eAppendix 1 in Supplement 3).

All patients provided written informed consent.

## Randomization and Masking

Patients were randomly assigned in a 1:1 ratio, using block permutation (sizes 4 and 6) and stratified by site, to receive potassium supplementation only when their [K+]fell below 4·5 mEq/L (‘Tight’ arm) or below 3·6mEq/L (‘Relaxed’ arm). An independent statistician from Sealed Envelope Ltd (UK) prepared the randomization codes and randomization was done via the secure Sealed Envelope website. Patients and caregivers were not masked to treatment allocation. The core lab analyzing the AHRM and the Event Validation Committee were all masked to treatment allocation.

## Intervention

The trial treatment protocol was initiated when the patient was admitted to the post-operative care facility, providing that they were in sinus or paced rhythm at that time. The trial treatment period ended 120 hours after the initial post-operative admission, on discharge from hospital, or with occurrence of a site-reported episode of AFACS – whichever occurred first. Thereafter, there was no restriction on potassium supplementation and patients were treated according to local protocols.

During the trial period, [K+] was monitored by point-of-care and formal laboratory blood tests, according to local practice. The route of potassium supplementation was chosen according to established local clinical practices. All other treatments, including intravenous (IV) Magnesium and Beta Blockers, were given according to standard clinical care and clinician's preference and captured in the Case Report Forms (CRF).

To identify dysrhythmias that were not clinically detected by standard monitoring, and to inform the event validation committee's assessment of the primary endpoint, AHRM supplemented standard monitoring for 120 hours following surgery or until discharge, whichever was sooner.

For the purposes of data capture and reporting, the 120 hours after admission to the post-operative care facility were divided into periods of 24 hours each, referred to as periods 1 to 5.

## Outcome Measures and Definitions

The primary outcome was the occurrence of new onset AFACS (an episode of atrial fibrillation, flutter or tachyarrhythmia, lasting ≥ 30 seconds, or present throughout an entire 12-lead ECG recording), that was both clinically detected and electrocardiographically confirmed (on either electrocardiogram [ECG], telemetry or AHRM) until hour 120 after initial admission to post-operative care facility or discharge from hospital - whichever occurred first (eAppendix 2 in Supplement 3). The composite definition of AFACS included atrial fibrillation, atrial flutter or atrial tachyarrhythmia, and was chosen in accordance with the current ESC/EACTS/EHRA definition of atrial fibrillation,[17] recognizing that differentiation between these three rhythms is often challenging.[18] Moreover, clinical management for all these rhythms is the same (rate control or rhythm control, along with consideration of anticoagulation) and potassium supplementation strategies are used with the intention of minimizing them all. Just as for AFACS, electrocardiographic criteria for non-AFACS dysrhythmias were predefined and followed published consensus definitions[19] (eAppendix 3 in Supplement 3).

The Independent Event Validation Committee - masked to treatment allocation – used specified criteria to adjudicate and validate all primary outcome events (eAppendix 4 in Supplement 3).

Secondary outcomes were the incidence of new onset AFACS detected on AHRM alone; the incidence of at least one episode of AFACS identified clinically or by AHRM; the number of patients experiencing at least one episode of a non-AFACS dysrhythmia identified on AHRM over the same time periods; in-patient mortality; critical care and hospital length of stay; and cost relating to purchasing and administering potassium therapy.

Two pre-specified exploratory outcomes were captured as markers of AFACS burden: the mean duration of AHRM-identified AFACS as a proportion of the duration of monitoring, and the median number of AHRM-identified AFACS episodes in patients with AHRM-identified AFACS.

**Sample Size Calculation and Statistical Analysis**

Non-inferiority of 'Relaxed' potassium control was defined as an absolute risk difference for new onset AFACS with associated upper bound of a one-sided 97.5% confidence interval of less than 10%. The non-inferiority margin was deemed to be clinically relevant by consensus among a diverse group of experts, caregivers and patient representatives. We estimated that 1514 patients randomized in a 1:1 ratio to the two groups would provide 90% power to detect non-inferiority of 'Relaxed' potassium control, assuming a 35% prevalence of new onset AFACS in the 'Tight' arm – a conservative estimate given the observed prevalence of 36.9% (95%CI 29.1% to 44.9%) in the feasibility study – and further assuming a 2% lower prevalence of AFACS in the 'Tight' arm. We aimed to recruit 1684 patients, allowing for 10% loss-to-follow-up.

We use three *a priori*- defined datasets for the analysis:

***Intention-to-treat***

The efficacy analysis (EA) population

All participants assigned a randomization number who underwent isolated CABG surgery.

Safety analysis (SA) population

All participants assigned a randomization number.

***Per-protocol***

Per-protocol (PP) efficacy population

This comprised the EA population with the exclusion of participants not completing a protocol-adherent course of treatment. Treatment was deemed not per-protocol in the 'Relaxed' arm if potassium supplementation was given on two consecutive occasions when [K+] was >3.6 mEq/L. It was deemed not per-protocol in the 'Tight' arm if supplementation was not given when [K+] was <4.5 mEq/L for at least four hours.

The primary analysis was unadjusted and carried out using the EA population. A pre-specified adjusted analysis was also performed, adjusting for patient age, sex, and site. Analysis of the primary and secondary outcomes was repeated using the PP population.

Descriptive characteristics of patients at baseline were summarized using means and standard deviations or medians and ranges for continuous variables, and counts and percentages for categorical variables, tabulated according to treatment group.

The risk differences for new onset AFACS and non-AFACS dysrhythmias were estimated using marginal standardization following logistic regression.[20] The secondary analyses are superiority analyses; Cox proportional hazards regression was used to estimate hazard ratios for in-patient mortality, critical care length of stay and hospital length of stay.[21]

Mean duration of AHRM-identified AFACS and median number of AHRM-identified AFACS episodes in patients with AHRM-identified AFACS were tabulated by arm.

Pre-specified subgroup analyses were performed by fitting an interaction between the subgroup and treatment, with evidence for interaction assessed using likelihood ratio tests.

No missing data were observed in the data collected on site. However, missing data were observed in the AHRM-identified outcomes due to lost monitors, failure of recording and inadequate or disrupted recording. For these outcomes, we performed additional sensitivity analysis using inverse probability weighting.

Adverse event frequencies are tabulated by treatment arm using the SA population. Methodology for the health economic assessment of cost relating to purchasing and administering potassium therapy is reported in eAppendix 5 in Supplement 3).

No interim analyses were performed.

Analyses were conducted using Stata version 18.1 (StataCorp, College Station, TX)

The trial was prospectively registered with ClinicalTrials.gov (registration ID number NCT04053816) on 13 August 2019.

## RESULTS

### Descriptive Findings

A total of 5,568 patients were assessed for eligibility, of whom 1,690 were randomized (Figure 1).[22] Three patients were randomized in error, leading to 844 and 843 patients in the SA population in the 'Tight' and 'Relaxed' arms, respectively. A further 17 did not receive an isolated CABG procedure, died in surgery or withdrew and 3 patients were found to be ineligible after randomization, leading to 837 ('Tight' Arm) and 830 ('Relaxed' Arm) patients in the EA population. One hundred and thirty-five patients in the 'Tight' Arm and 48 in the 'Relaxed' Arm did not receive a protocol-adherent course of treatment, leading to 702 and 782 patients in the PP population in the 'Tight' and 'Relaxed' arms respectively. Characteristics of the patients not included in the PP population are shown in eTable 1 in Supplement 3.

Table 1 shows baseline characteristics of the EA population, which are balanced between arms (for complete data see eTable 2 in Supplement 3).

Of note, interventions often used to prevent AFACS, such as Beta Blockers, Magnesium supplementation and Amiodarone are applied in equal measure in both arms (eTable 3 in Supplement 3).

### Primary and Secondary Endpoints

The primary endpoint was met by 219 of the 837 patients (26.2%) in the 'Tight' arm and 231 of the 830 patients (27.8%) in the 'Relaxed' arm, an unadjusted risk difference of 1.6% (95%CI -2.6% to 5.9%). The upper bound of the one-sided 97.5%

CI lies within the pre-specified non-inferiority margin of 10% suggesting non-inferiority of the 'Relaxed' arm (Figure 2 and Table 2). This finding is supported by the analysis using the PP population (eTable 4 in Supplement 3).

No differences are observed between arms for any of the secondary outcomes, other than cost relating to purchasing and administering potassium therapy, which showed significantly lower cost in the 'Relaxed' arm with a mean per patient difference of £87.21 [95% CI: 80.74 to 93.67]/ $111.89 [95% CI: 103.60 to 120.19] p-value: <0.001 (Table 2 and eTable 9 in Supplement 3). For in-patient mortality, time to discharge from critical care and time to discharge from hospital, the hazard ratios are close to one (eFigure 1 in Supplement 3).

Analysis of the secondary outcomes using the PP population (eTable 4 and eFigure 2 in Supplement 3) and the sensitivity analyses used to account for the missing data in the AHRM outcomes (eTable 5 in Supplement 3) further support the principle finding of no difference in dysrhythmias and other clinical outcomes between trial arms.

**Subgroup analyses**

For pre-defined subgroup analyses, there was no evidence of any difference between arms in any of our pre-defined subgroup analyses of the primary endpoint by patient age, sex, occurrence of atrial fibrillation lasting longer than 30 seconds during surgery, being on Beta Blockers at baseline, ejection fraction category, ethnicity, euroSCORE II risk category, being on loop diuretics at baseline, or CABG pump status (eFigure 3 in Supplement 3).

**AHRM analysis**

Seventy-seven patients in the ‘Tight’ arm had no AHRM readings and 56 only had partial readings. In the ‘Relaxed’ arm, 94 patients had no AHRM readings and 53 had partial readings. For most patients who met the primary endpoint, there was agreement between the clinically detected AFACS and AHRM-detected AFACS (eFigure 4 in Supplement 3). For AHRM-detected AFACS, for AHRM- or clinically detected AFACS, and for AHRM-detected non-AFACS dysrhythmias, the risk differences were very similar to that for the primary outcome (Figure 2). In pre-specified exploratory analyses, there was no difference in mean duration of AHRM-identified AFACS, or the median number of AHRM-identified AFACS episodes in patients with AHRM-identified AFACS (eTable 6 in Supplement 3). The breakdown of the non-AFACS dysrhythmias, including VT/VF rates, shows no signal for harm in the ‘Relaxed’ arm (eTable 7 in Supplement 3).

**Serum potassium levels**

There was evidence of a clear separation between the two arms of the trial in both frequency of potassium supplementation and mean [K+] levels (Figure 3). The median number of times potassium was administered throughout periods 1 through 5, or prior to first AFACS episode was 7 (IQR 4 to 12) in the ‘Tight’ arm and 0 (IQR 0 to 1) in the ‘Relaxed’ arm, with a consequent higher mean [K+] in the ‘Tight’ arm than the ‘Relaxed’ arm.

**Adverse Events**

Reported Adverse event frequencies up to hospital discharge are shown in eTable 8 in Supplement 3.

## DISCUSSION

Until now, the literature did not provide any evidence-based guidance on the matter of routine potassium supplementation to achieve high-normal [K+] as a means of preventing AFACS. TIGHT-K sought to provide such evidence in a pragmatic, real-world study, with few exclusion criteria and no restriction on any aspect of practice other than the trial treatment.[23] Recruitment at 23 centers from 2 countries (United Kingdom and Germany) reflected a diverse and representative population and a wide range of local practices, protocols and conventions (eAppendix 7 in Supplement 3). This, with the appropriate non-inferiority design, allowed us to conclusively answer the clinical question: “does only supplementing potassium if [K+] drops below the normal range (‘Relaxed’ control) increase AFACS rates when compared to a strategy of supplementing it when [K+] drops below the high-normal range (‘Tight’ control), or not?

When compared to ‘Tight’ control, ‘Relaxed’ control was associated with substantially lower doses of potassium supplementation, and lower serum [K+] values and yet this approach was non-inferior in preventing clinically-detected and electrocardiographically confirmed AFACS up to 5 days after isolated CABG surgery.

There was also no difference between the arms in the overall incidence of AFACS detected by any means, or by AHRM alone. Furthermore, the mean percentage of monitored time spent in AFACS was also similar between arms, and the median number of Holter-identified AFACS episodes was the same (eTable 6 in Supplement 3). These findings appear to be robust, confirmed in the per-protocol population, consistent across all clinical demographics, and persisting in adjusted analyses.

No disadvantages associated with a “Relaxed’ potassium strategy were identified, despite being actively sought. Neither clinical outcomes nor the incidence of at least one episode of non-AFACS dysrhythmia differed between the arms.

It is noteworthy that in the ‘Relaxed’ arm most patients did not require any supplementation and did not become hypokalemic during the 5 days following cardiac surgery. This would imply that homeostasis is largely responsible for [K+] levels and that proactive supplementation only has a comparatively limited effect.

As expected, mean serum [K+] in each arm was not *above* the trigger threshold for that arm, given that values had to fall *below* that threshold for supplementation to occur.

The health economic analysis we report here warrants consideration, given that potassium is amongst the highest cumulative cost drugs used in many cardiac units[13]. Mean per-patient costs relating to purchasing and administering potassium therapy were near four-fold higher in the ‘Tight’ arm than in the ‘Relaxed’ arm (Table 2 and eTable 9 in Supplement 3)

Importantly, avoiding unnecessary potassium supplementation has potential advantages for patients. Where prolonged venous access is solely maintained to administer potassium, this increases the risk of infection. Intravenous potassium supplementation can cause fluid loading and carries the risk of accidental (and possibly fatal) rapid potassium infusion. Gastrointestinal side effects of oral potassium supplementation are common and are poorly tolerated by patents.[14] Reducing unnecessary interventions will also reduce clinical waste, as well as reducing the carbon impact from manufacture and supply.

## Limitations

This was an open-label study, so detection and reporting bias for the primary outcome could have occurred. The use of AHRM analysis by a core lab and the independent event validation committee, both masked to treatment arm, helped to address this limitation.

The primary endpoint (clinically detected AFACS) event rate in our cohort (28%) was slightly lower than expected, compared to data reported in previous literature and in our pilot trial. However, statistical power was retained for the absolute non inferiority margin of 10%. Rates of AFACS detected by any means (clinically or AHRM) were 33.0% in the ‘Tight’ arm and 33.1% in the ‘Relaxed’ arm.

There was also a degree of non-compliance with the protocol (strategies to reduce and report this are described in the eAppendix 6 in Supplement 3). Non-compliance was markedly higher in the 'Tight' arm, despite it being the perceived “standard of care”. In this arm, potassium supplementation occurred less consistently when [K+] was just narrowly below the threshold, at around 4.3 or 4.4 mEq/L. However, findings do not change in additional sensitivity analyses (eTable 4 in Supplement 3).

To avoid the heterogeneity of AFACS risk caused by different types of cardiac surgical procedure,[25] we only recruited patients undergoing isolated CABG surgery. If potassium supplementation at higher trigger thresholds is to be continued in other cardiac surgical procedures, we would suggest that the efficacy of this practice should be similarly assessed.

## CONCLUSIONS

Supplementation of potassium only when serum levels fall below 3.6mEq/L is non-inferior to the 4.5mEq/L threshold that is in current widespread use to prevent AFACS after CABG surgery. This lower threshold of supplementation is not associated with increased dysrhythmias or adverse clinical outcomes.

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*Administrative, technical, or material support:* Zahra Jamal, Keith Pearce, Laura Van Dyck, Richard Evans

*Supervision:* Ben O'Brien, Niall Campbell, Elizabeth Allen, Hugh Montgomery, Diana Elbourne.

**Conflict of Interest Disclosures:**

BO'B reports funding from the British Heart Foundation who funded TIGHT K, and the NIHR who funded PARADISE, another AFACS-related study for which he is the Chief Investigator.

NC reports receiving payment in the form of speaker fees, consultancy fees and research funding from Medtronic, Boston Scientific, Abbott, Biotronik, AstraZeneca Novartis and Pulsario.

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AZ reports funding from Fresenius and Baxter, payments made to his institution; grants or contracts (not for present manuscript) from German Research Foundation, bioMerieux, Astellas, Bayer and Alexion, payments made to his institution; consulting fees from Paion, bioMereiux, Baxter, Novartis, Guard Therapeutics, AM Pharma, Bayer, Alexion, payments were made to him; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Paion, Baxter and bioMereiux, payments were made to him; support for attending meetings and/or travel from Sphingotec, payments were made to him; leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid from IARS and DIVI (unpaid) and Anästhesist (payments made to him).

JSa reports grants or contracts (not for present manuscript) from NIHR, Medtronic and Barts Charity, payments made to her institution; consulting fees from SedateUK; payment for one-off participation in a focus group discussion made to her directly; travel reimbursed for meeting attendances from ESC; unpaid work for the ESC

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**Role of the Funder/Sponsor:**

The funders and sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Group Information:**

A list of the TIGHT K Investigators is available in eAppendix 1 in Supplement 4.

**Data Sharing Statement:**

See Supplement 5.

Individual patient data collected from the study (after de-identification and removal of any data that cannot be shared due to our regulatory agreements) will be made available to other researchers through the LSHTM Data Compass repository (https://datacompass.lshtm.ac.uk/).

A data dictionary, the study protocol, and the statistical analysis plan will also be supplied. These data will be made available subject to completion of a data access agreement. Data will be shared 12 months after the end of the study (last visit of final patient) which is anticipated to be mid-July 2025, at the earliest.

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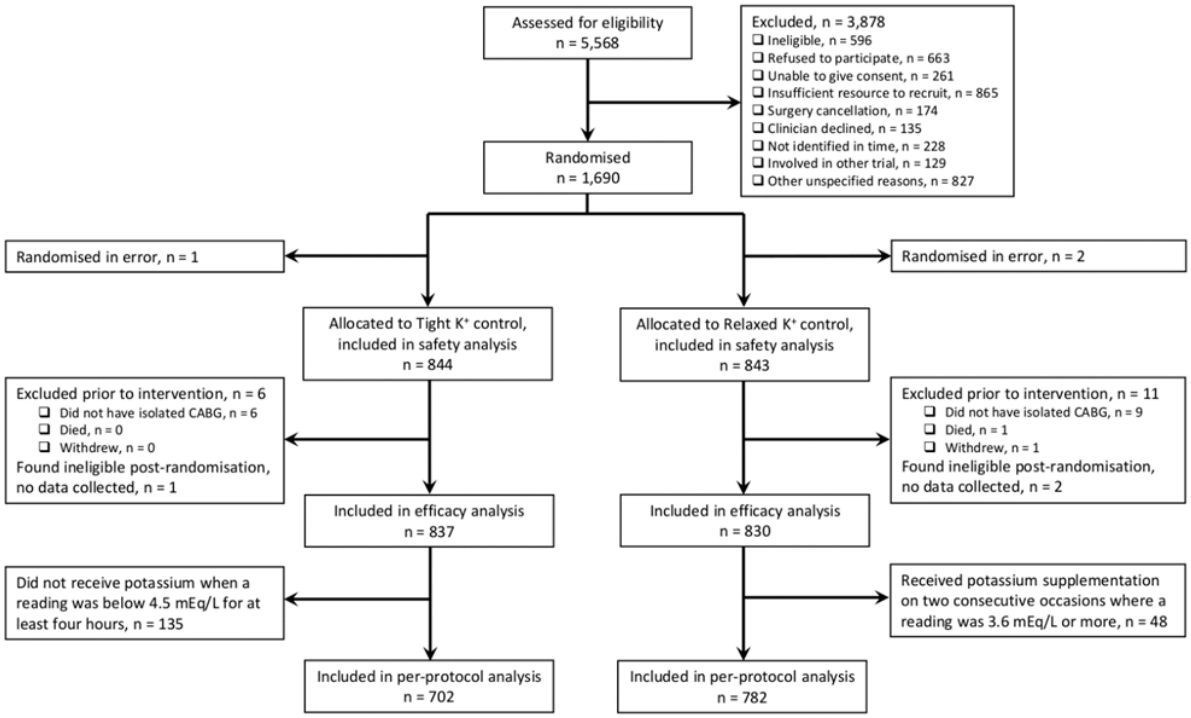
707 **Figure 1: CONSORT diagram**

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711 **Figure 2: Effect of the intervention on primary and secondary outcomes**
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**Figure 3: Frequency of potassium administration and mean serum levels by treatment arm**

## Table 1: Characteristics of patients at baseline

| Characteristic | | Tight N = 837 | Relaxed N = 830 | Total N = 1,667 |
|---|---|---|---|---|
| Age in years, mean (SD) | | 64.7 (9.52) | 64.6 (9.12) | 64.7 (9.32) |
| Sex | | | | |
| | Female | 115 (13.7) | 141 (17.0) | 256 (15.4) |
| | Male | 722 (86.3) | 689 (83.0) | 1411 (84.6) |
| Ethnicity, n (%) | | | | |
| | White | 724 (86.5) | 716 (86.3) | 1,440 (86.4) |
| | Asian or Asian British | 76 (9.1) | 87 (10.5) | 163 (9.8) |
| | Black or Black British | 12 (1.4) | 9 (1.1) | 21 (1.3) |
| | Other | 20 (2.4) | 13 (1.6) | 33 (2.0) |
| | Not stated | 5 (0.6) | 5 (0.6) | 10 (0.6) |
| BMI in kg/m$^2$, mean (SD) | | 29.2 (5.02) | 29.0 (4.80) | 29.1 (4.91) |
| euroSCORE II (%), mean (SD) | | 1.6 (1.35) | 1.5 (1.26) | 1.5 (1.31) |
| Chronic kidney disease, n (%) | | | | |
| | Yes | 47 (5.6) | 42 (5.1) | 89 (5.3) |
| | No | 761 (90.9) | 769 (92.7) | 1,530 (91.8) |
| | Not documented | 29 (3.5) | 19 (2.3) | 48 (2.9) |
| Diabetes mellitus, n (%) | | | | |
| | Yes | 298 (35.6) | 288 (34.7) | 586 (35.2) |
| | No | 527 (63.0) | 527 (63.5) | 1,054 (63.2) |
| | Not documented | 12 (1.4) | 15 (1.8) | 27 (1.6) |
| Previous cerebrovascular event, n (%) | | | | |
| | Yes | 47 (5.6) | 55 (6.6) | 102 (6.1) |
| | No | 765 (91.4) | 754 (90.8) | 1,519 (91.1) |
| | Not documented | 25 (3.0) | 21 (2.5) | 46 (2.8) |
| **Medications at Baseline** | | | | |
| B-Blocker, n (%) | | | | |
| | Yes | 639 (76.3) | 651 (78.4) | 1,290 (77.4) |
| | No | 196 (23.4) | 178 (21.4) | 374 (22.4) |
| | Not Known | 2 (0.2) | 1 (0.1) | 3 (0.2) |
| ACE Inhibitors and Angiotensin Receptor Blockers, n (%) | | | | |
| | Yes | 501 (59.9) | 526 (63.4) | 1,027 (61.6) |
| | No | 335 (40.0) | 304 (36.6) | 639 (38.3) |
| | Not Known | 1 (0.1) | 0 (0.0) | 1 (0.1) |
| Statins, n (%) | | | | |
| | Yes | 757 (90.4) | 749 (90.2) | 1,506 (90.3) |
| | No | 79 (9.4) | 79 (9.5) | 158 (9.5) |
| | Not Known | 1 (0.1) | 2 (0.2) | 3 (0.2) |

| Characteristic | | Tight N = 837 | Relaxed N = 830 | Total N = 1,667 |
|---|---|---|---|---|
| **Surgery** | | | | |
| Pump status, n (%) | | | | |
| | Off pump | 129 (15.4) | 109 (13.1) | 238 (14.3) |
| | On pump | 707 (84.6) | 721 (86.9) | 1,428 (85.7) |
| | Missing | 1 | 0 | 1 |
| Potassium concentration coming off bypass, mean (SD) | | 5.0 (0.61) | 5.0 (0.69) | 5.0 (0.65) |
| | Missing | 143 | 119 | 262 |

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726 **Table 2: Effect of the intervention on primary and secondary outcomes**

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| Outcome | Tight arm (N = 837) | Relaxed arm (N = 830) | Unadjusted | Adjusted |
|---|---|---|---|---|
| | n (%) | | Risk difference (95%CI) | |
| AFACS, clinically detected and electrocardiographically confirmed | 219 (26.2) | 231 (27.8) | 0.02 (-0.03, 0.06) p = 0.443 | 0.02 (-0.02, 0.06) p = 0.291 |
| AFACS, AHRM-detected | 233 (33.1) 133 missing | 220 (32.2) 147 missing | -0.01 (-0.06, 0.04) p = 0.725 | -0.005 (-0.05, 0.04) p = 0.844 |
| AFACS, clinically or AHRM detected | 276 (33.0) | 275 (33.1) | 0.002 (-0.04, 0.05) p = 0.945 | 0.01 (-0.03, 0.05) p = 0.699 |
| Non-AF dysrhythmia | 147 (21.1) 141 missing | 128 (19.1) 159 missing | -0.02 (-0.06, 0.02) p = 0.346 | -0.02 (-0.07, 0.02) p = 0.261 |
| | events (rate per 10,000 person-days) | | Hazard ratio (95% CI) | |
| In-patient mortality | 4 (6.2) | 4 (6.2) | 1.00 (0.25, 3.99) p = 0.995 | 0.82 (0.19, 3.40) p = 0.778 |
| | median (IQR) | | Hazard ratio (95% CI) | |
| Time-to-discharge from critical care, days | 2 (1 – 4) | 2 (1 – 4) | 0.99 (0.90, 1.09) p = 0.797 | 0.98 (0.89, 1.08) p = 0.725 |
| Time-to-discharge from hospital, days | 6 (5 – 7) | 6 (5 – 8) | 0.99 (0.90, 1.09) p = 0.777 | 1.00 (0.90, 1.10) p = 0.942 |
| **Area of resource use** | | | | |
| | mean costs in GBP (SD) | | Mean difference (95%CI) | |
| Potassium administration | | | | |
| Intravenous | 118.59 (77.93) | 68.13 (58.99) | Not estimated | |
| Oral | 5.97 (8.32) | 2.40 (4.85) | Not estimated | |
| Food or nasogastric tube | 0.22 (2.24) | 0.07 (1.11) | Not estimated | |
| Total costs [95%CI] | 117.83 (80.27) [112.39, 123.28] | 30.63 (50.94) [27.16, 34.10] | 87.21 (80.74, 93.67) p < 0.001 | 87.38 (80.86, 93.91) p < 0.001 |

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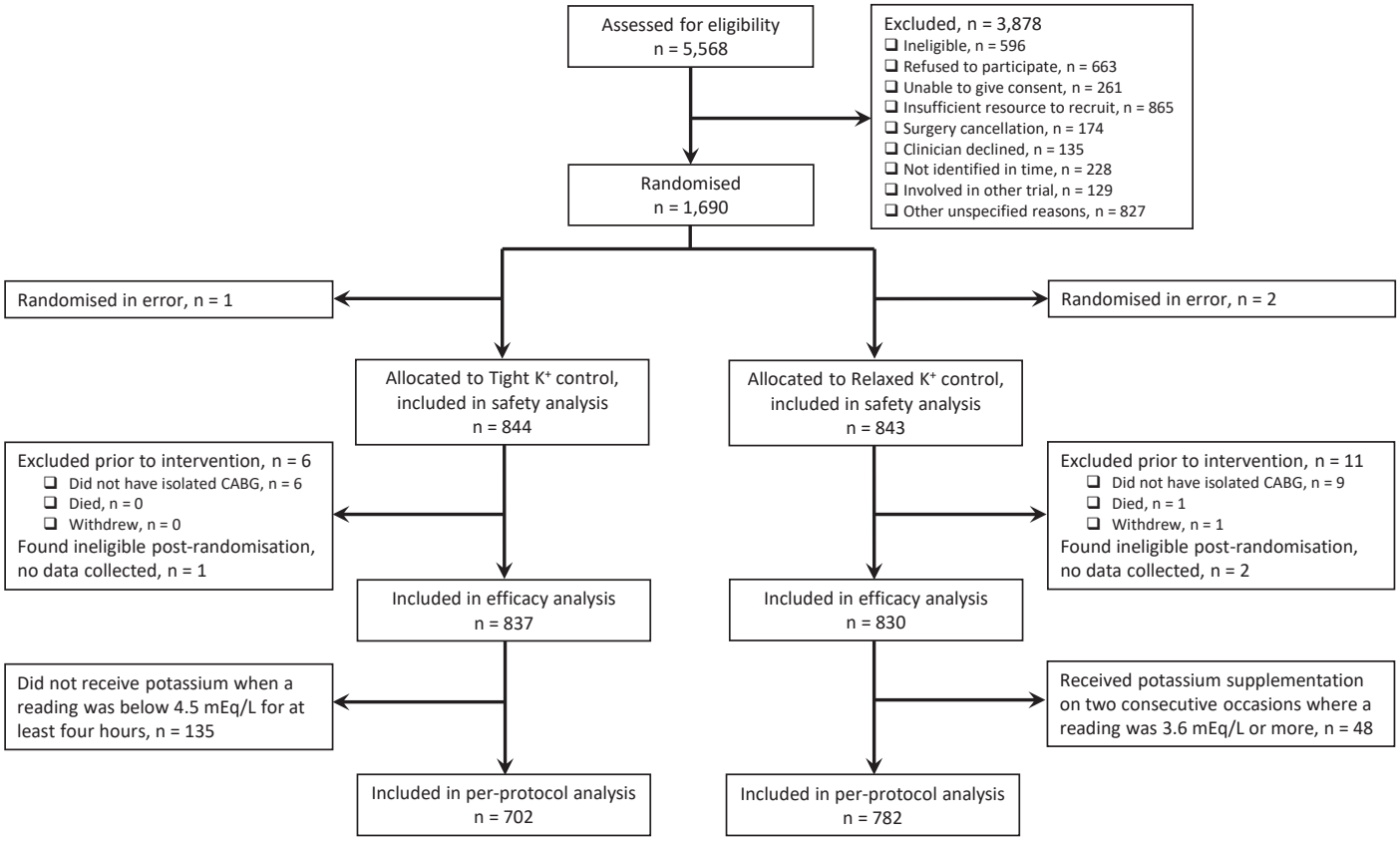
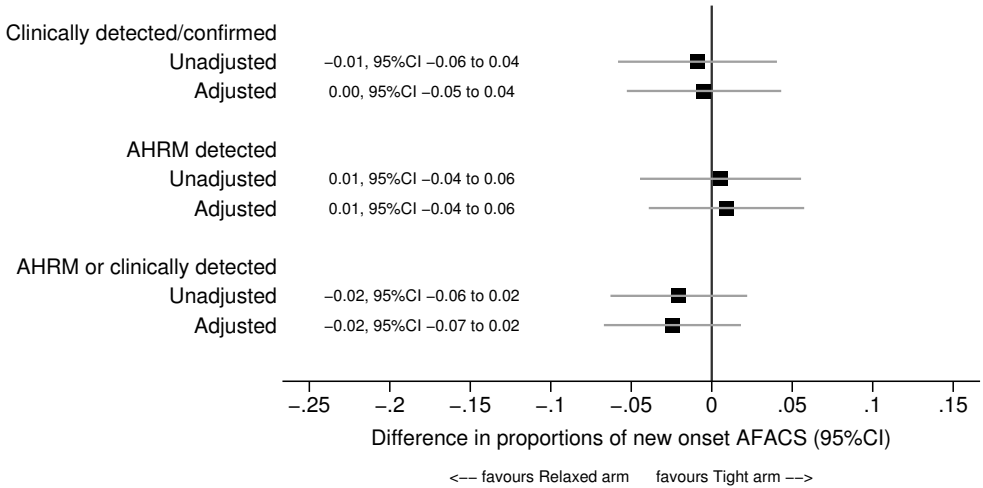
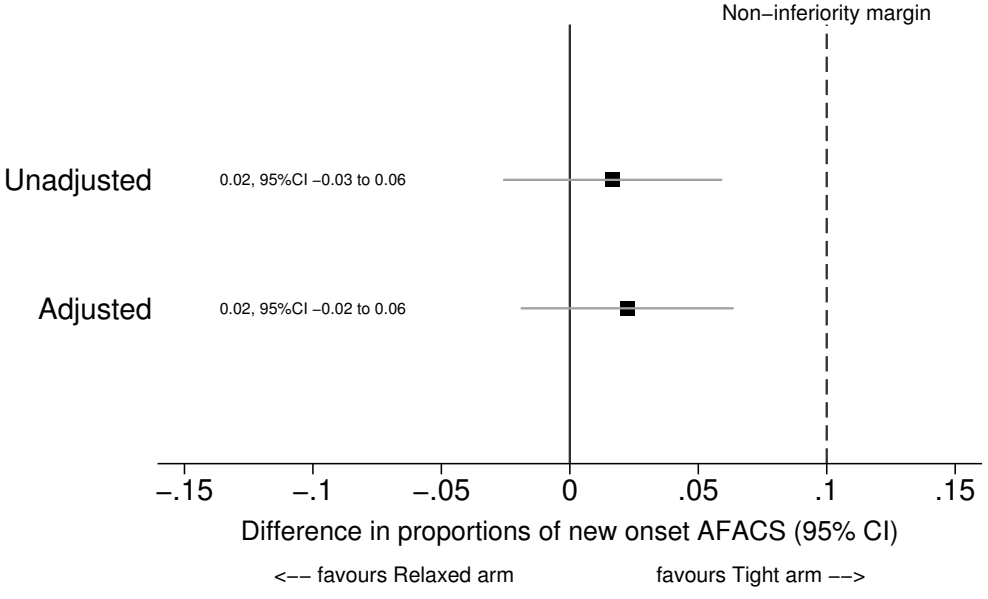
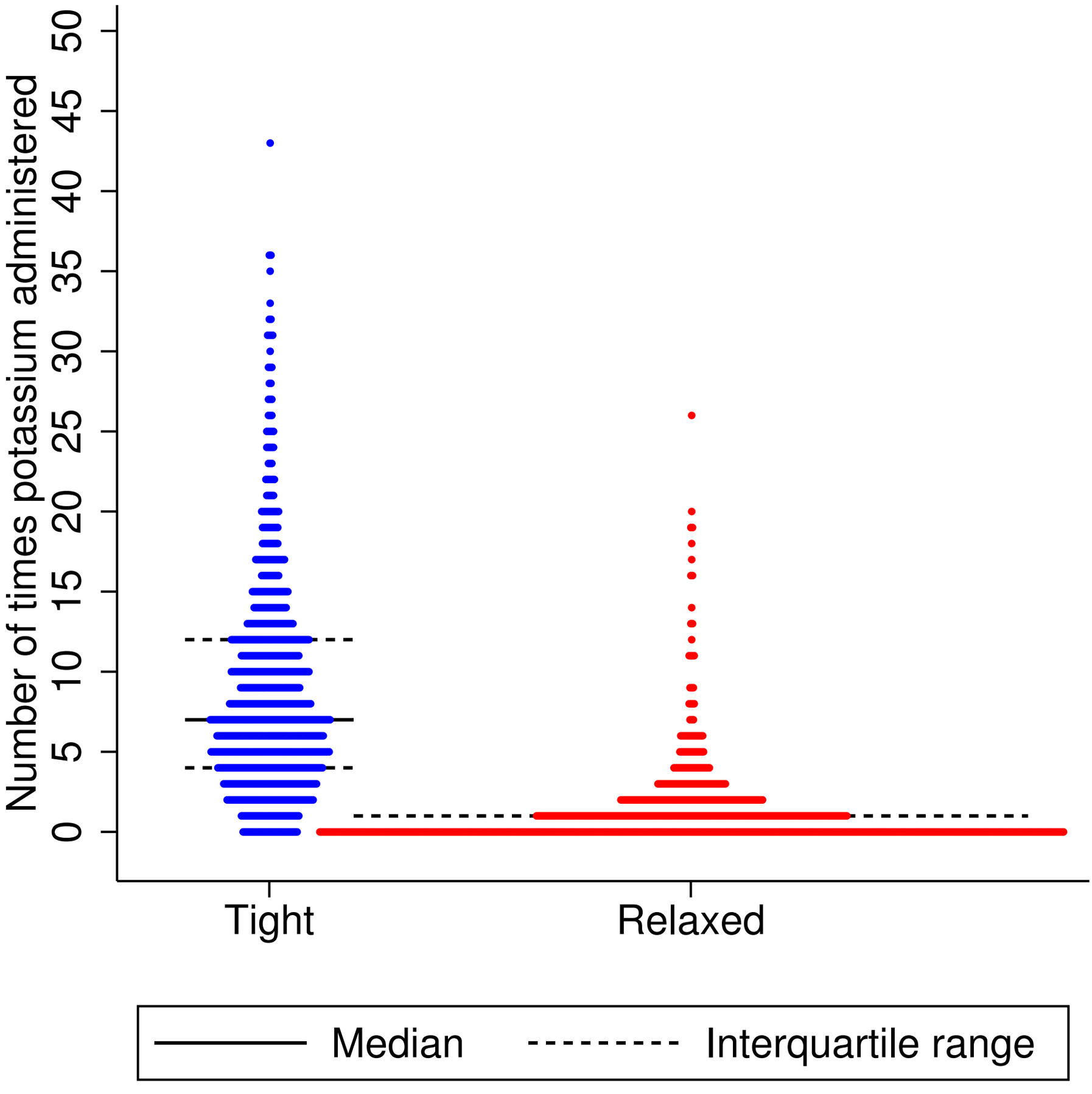
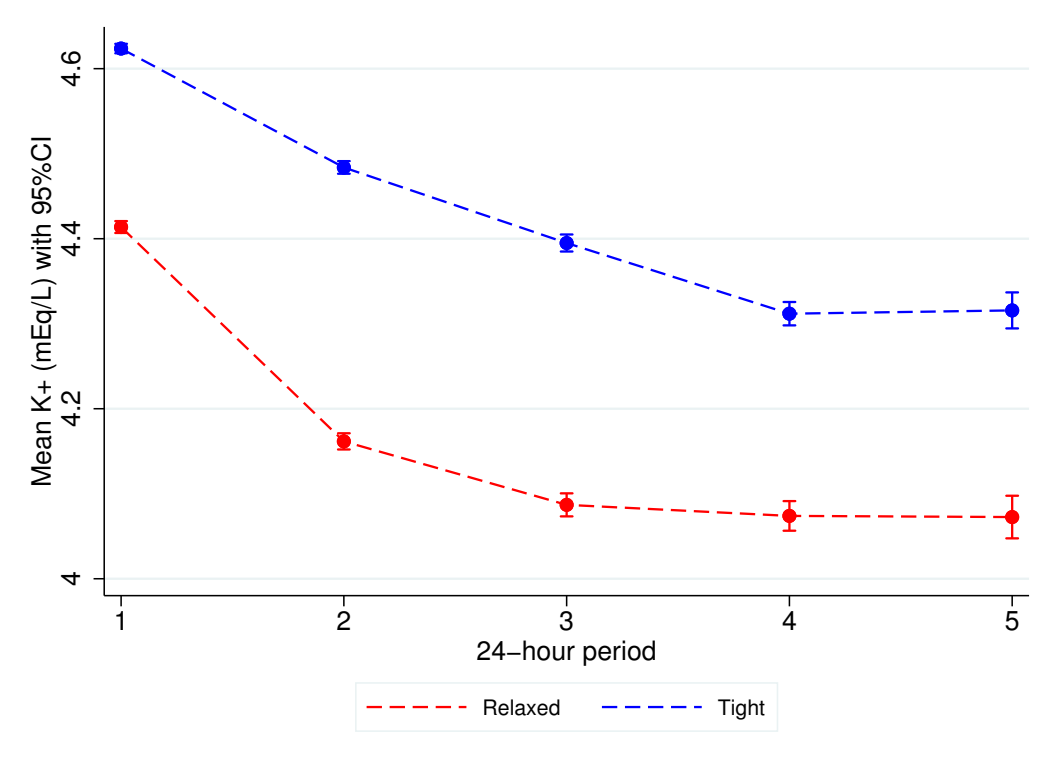

Assessed for eligibility
n = 5,568
Excluded, n = 3,878
❑ Ineligible, n = 596
❑ Refused to participate, n = 663
❑ Unable to give consent, n = 261
❑ Insufficient resource to recruit, n = 865
❑ Surgery cancellation, n = 174
❑ Clinician declined, n = 135
❑ Not identified in time, n = 228
❑ Involved in other trial, n = 129
❑ Other unspecified reasons, n = 827
Randomised
n = 1,690
Randomised in error, n = 1
Randomised in error, n = 2
Allocated to Tight K+ control, included in safety analysis
n = 844
Allocated to Relaxed K+ control, included in safety analysis
n = 843
Excluded prior to intervention, n = 6
❑ Did not have isolated CABG, n = 6
❑ Died, n = 0
❑ Withdrew, n = 0
Found ineligible post-randomisation, no data collected, n = 1
Excluded prior to intervention, n = 11
❑ Did not have isolated CABG, n = 9
❑ Died, n = 1
❑ Withdrew, n = 1
Found ineligible post-randomisation, no data collected, n = 2
Included in efficacy analysis
n = 837
Included in efficacy analysis
n = 830
Did not receive potassium when a reading was below 4.5 mEq/L for at least four hours, n = 135
Received potassium supplementation on two consecutive occasions where a reading was 3.6 mEq/L or more, n = 48
Included in per-protocol analysis
n = 702
Included in per-protocol analysis
n = 782


Clinically detected/confirmed
Unadjusted
Adjusted
−0.01, 95%CI −0.06 to 0.04
0.00, 95%CI −0.05 to 0.04
AHRM detected
Unadjusted
Adjusted
0.01, 95%CI −0.04 to 0.06
0.01, 95%CI −0.04 to 0.06
AHRM or clinically detected
Unadjusted
Adjusted
−0.02, 95%CI −0.06 to 0.02
−0.02, 95%CI −0.07 to 0.02
−.25
−.2
−.15
−.1
−.05
0
.05
.1
.15
Difference in proportions of new onset AFACS (95%CI)
<−− favours Relaxed arm
favours Tight arm −−>


Non−inferiority margin
Unadjusted
0.02, 95%CI −0.03 to 0.06
Adjusted
0.02, 95%CI −0.02 to 0.06
−.15
−.1
−.05
0
.05
.1
.15
Difference in proportions of new onset AFACS (95% CI)
<−− favours Relaxed arm
favours Tight arm −−>


Number of times potassium administered
0
5
10
15
20
25
30
35
40
45
50
Tight
Relaxed
Median
Interquartile range


Mean K+ (mEq/L) with 95%CI
4
4.2
4.4
4.6
1
2
3
4
5
24−hour period
Relaxed
Tight