Title Page

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

Benjamin O'Brien, MD, PhD (habil) [1,2,3]*, Niall G. Campbell, PhD [4,5],

Elizabeth Allen, PhD [6], Zahra Jamal, MSc [6], Joanna Sturgess, MSc [6],

Julie Sanders, PhD [2,7], Charles Opondo, PhD [6], Neil Roberts, MD [2],

Jonathan Aron, MBBS [8], Maria Rita Maccaroni, MD [9], Richard Gould, MbChB [10], Bilal H. Kirmani, MD [11],

Ben Gibbison, MD [12,13], Prof Gudrun Kunst, MD, PhD (habil) [7,14], Alexander Zarbock MD PhD (habil) [15],

Maren Kleine-Brüggeney, MD, PhD (habil) [1], Prof Christian Stoppe, MD [1,16], Keith Pearce, BSc [5], Mark Hughes [6,7],

Laura Van Dyck, BSc [6], Richard Evans, BA [6],

Hugh E. Montgomery, MD [17]**, Diana Elbourne, PhD [6]**

for the TIGHT K investigators

1. Deutsches Herzzentrum der Charité,
   Charité - Universitätsmedizin Berlin, Germany
2. St. Bartholomew's Hospital, Barts Health NHS Trust, London, UK
3. Outcomes Research Consortium, Cleveland, OH, USA
4. University of Manchester, Manchester Academic Health Science Centre, Manchester, UK
5. Manchester University NHS Foundation Trust, Manchester, UK
6. London School of Hygiene & Tropical Medicine, London, UK
7. King's College London, London, UK
8. St George's University Hospital NHS Foundation Trust, London, UK
9. Basildon University Hospital NHS Trust, Basildon, UK
10. Leeds General Infirmary, Leeds, UK
11. Liverpool Heart and Chest Hospital, Liverpool, UK
12. University of Bristol, Bristol, UK
13. University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, UK

14. King's College Hospital NHS Foundation Trust, London, UK

15. University Hospital Münster, Münster, Germany

16. University Hospital, Würzburg, Würzburg, Germany

17. University College London, London, UK

*Correspondence to Benjamin O'Brien

Department of Cardiac Anesthesiology and Intensive Care Medicine

Deutsches Herzzentrum der Charité

Charité Universitätsmedizin Berlin

Augustenburger Platz 1

13353 Berlin

Germany

Email: Ben.OBrien@dhzc-charite.de

**Hugh Montgomery and Diana Elbourne contributed equally to this article

Date of revision: 15 August 2024

Word Count (not including title, abstract, acknowledgment, references, tables, and figure legends): 3299

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 [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, SETTING AND PARTICIPANTS

TIGHT K was an open-label, noninferiority, randomized controlled trial conducted at 23 cardiac surgical centers in the United Kingdom and Germany. Between 20 October 2020 and 16 November 2023, patients with no history of atrial dysrhythmias scheduled for isolated Coronary Artery Bypass Grafting (CABG) surgery were enrolled. The last study patient was discharged from hospital on 11 December 2023.

INTERVENTIONS

Patients were randomly assigned to a strategy of ‘Tight’ or ‘Relaxed’ potassium control (only supplementing if [K+] levels 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 (mean age, 65 years; 256 [15%] females) were randomized. The primary endpoint occurred in 26.2% (n=219) and 27.8% (n=231) 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 $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 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 [K+] level 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.

The data are reported according to Consolidated Standards of Reporting Trials (CONSORT) non-inferiority and equivalence randomized trials guidelines.[17]

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.

Ethnicity was self-reported by patients using fixed selection categories.

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 IV Magnesium and Beta Blockers, were given according to standard clinical care and clinician's preference and captured in the Case Report Forms.

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,[18] recognizing that differentiation between these three rhythms is often challenging.[19] 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[20] (eAppendix 3 in Supplement 3).

The Independent Event Validation Committee 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, which is the limit for the upper end of the confidence interval, was deemed to be clinically relevant and feasible by consensus among a diverse group of experts, caregivers and patient representatives and is in line with other large non-inferiority cardiovascular trials, including several with comparable event rates.[21,22] It was supported by the funding body, the sponsor and the independent trial steering committee. 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.[23] 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.[24]

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).[25] 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 $111.89 [95% CI: 103.60 to 120.19] / £87.21 [95% CI: 80.74 to 93.67]p-value: <0.001 (Table 2 and eTable 10 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 ventricular tachycardia/fibrillation 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. The frequency of [K+] measurements was similar between the arms (See eTable 8 in Supplement 3).

Adverse Events

Reported Adverse event frequencies up to hospital discharge are shown in eTable 9 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.[26] 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 [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 [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 10 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,[27] 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.

References:

1. Vervoort D, Lee G, Ghandour H, et al. Global Cardiac Surgical Volume and Gaps: Trends, Targets, and Way Forward. *Ann Thorac Surg Short Rep*. 2024;2(2):320-324. doi:10.1016/j.atssr.2023.11.019

2. Melly L, Torregrossa G, Lee T, Jansens JL, Puskas JD. Fifty years of coronary artery bypass grafting. *J Thorac Dis*. 2018;10(3):1960-1967. doi:10.21037/jtd.2018.02.43

3. Taha A, Nielsen SJ, Bergfeldt L, et al. New‐Onset Atrial Fibrillation After Coronary Artery Bypass Grafting and Long‐Term Outcome: A Population‐Based Nationwide Study From the SWEDEHEART Registry. *J Am Hear Assoc: Cardiovasc Cerebrovasc Dis*. 2020;10(1):e017966. doi:10.1161/jaha.120.017966

4. Mathew JP, Fontes ML, Tudor IC, et al. A Multicenter Risk Index for Atrial Fibrillation After Cardiac Surgery. *JAMA*. 2004;291(14):1720-1729. doi:10.1001/jama.291.14.1720

5. O'Brien B, Burrage PS, Ngai JY, et al. Society of Cardiovascular Anesthesiologists/European Association of Cardiothoracic Anaesthetists Practice Advisory for the Management of Perioperative Atrial Fibrillation in Patients Undergoing Cardiac Surgery. *J Cardiothor Vasc An*. 2019;33(1):12-26. doi:10.1053/j.jvca.2018.09.039

6. Caldonazo T, Kirov H, Rahouma M, et al. Atrial fibrillation after cardiac surgery: A systematic review and meta-analysis. *J Thorac Cardiovasc Surg*. 2023;165(1):94-103.e24. doi:10.1016/j.jtcvs.2021.03.077

7. Burrage PS, Low YH, Campbell NG, O'Brien B. New-Onset Atrial Fibrillation in Adult Patients After Cardiac Surgery. *Current Anesthesiol Rep*. 2019;9(2):174-193. doi:10.1007/s40140-019-00321-4

8. Atrial fibrillation: diagnosis and management Evidence review L: Treatment strategies for atrial fibrillation after cardiothoracic surgery. National Institute of Clinical Excellence guideline NG196. Intervention evidence review April 2021. https://www.nice.org.uk/guidance/ng196/evidence/l-treatment-strategies-for-atrial-fibrillation-after-cardiothoracic-surgery-pdf-326949243736

9. Lai FY, Abbasciano RG, Tabberer B, Kumar T, Murphy GJ, Partnership SG of the JLAHSPS. Identifying research priorities in cardiac surgery: a report from the James Lind Alliance Priority Setting Partnership in adult heart surgery. *BMJ Open*. 2020;10(9):e038001. doi:10.1136/bmjopen-2020-038001

10. Podrid PJ. Potassium and ventricular arrhythmias. *Am J Cardiol*. 1990;65(10):33E-44E; discussion 52E.

11. Macdonald JE, Struthers AD. What is the optimal serum potassium level in cardiovascular patients? *J Am Coll Cardiol*. 2004;43(2):155-161.

12. Bedford JP, Garside T, Darbyshire JL, Betts TR, Young JD, Watkinson PJ. Risk factors for new-onset atrial fibrillation during critical illness: A Delphi study. *J Intensiv Care Soc*. 2022;23(4):414-424. doi:10.1177/17511437211022132

13. Campbell NG, Allen E, Sanders J, et al. The impact of maintaining serum potassium ⩾3.6 mEq/L vs ⩾4.5 mEq/L on the incidence of new-onset atrial fibrillation in the first 120 hours after isolated elective coronary artery bypass grafting - study protocol for a randomised feasibility trial for the proposed Tight K non-inferiority trial. *Trials*. 2017;18(1):1061. doi:10.1186/s13063-017-2349-x

14. Cohn JN, Kowey PR, Whelton PK, Prisant LM. New Guidelines for Potassium Replacement in Clinical Practice: A Contemporary Review by the National Council on Potassium in Clinical Practice. *Arch Int Med*. 2000;160(16):2429-2436. doi:10.1001/archinte.160.16.2429

15. Campbell NG, Allen E, Montgomery H, et al. Maintenance of serum potassium levels ⩾ 3.6 mEq/L vs ⩾ 4.5 mEq/L after isolated elective coronary artery bypass grafting, and the incidence of new-onset atrial fibrillation: pilot and feasibility study results. *J Cardiothor Vasc An*. Published online 2021. doi:10.1053/j.jvca.2021.06.021

16. Campbell NG, Allen E, Evans R, et al. Impact of maintaining serum potassium concentration ⩾ 3.6mEq/L versus ⩾ 4.5mEq/L for 120 hours after isolated coronary artery bypass graft surgery on incidence of new onset atrial fibrillation: Protocol for a randomized non-inferiority trial. *PLOS ONE*. 2024;19(3):e0296525. doi:10.1371/journal.pone.0296525

17. Piaggio G, Elbourne DR, Pocock SJ, Evans SJW, Altman DG, Group for the C. Reporting of Noninferiority and Equivalence Randomized Trials: Extension of the CONSORT 2010 Statement. *JAMA*. 2012;308(24):2594-2604. doi:10.1001/jama.2012.87802

18. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS)The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2020;42(5):ehaa612. doi:10.1093/eurheartj/ehaa612

19. Shiyovich A, Wolak A, Yacobovich L, Grosbard A, Katz A. Accuracy of Diagnosing Atrial Flutter and Atrial Fibrillation From a Surface Electrocardiogram by Hospital Physicians: Analysis of Data From Internal Medicine Departments. *Am J Méd Sci*. 2010;340(4):271-275. doi:10.1097/maj.0b013e3181e73fcf

20. Writing Committee Members, Joglar JA, Chung MK, et al. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2024;83(1):109-279. doi:10.1016/j.jacc.2023.08.017

21. Bikdeli B, Welsh JW, Akram Y, et al. Noninferiority Designed Cardiovascular Trials in Highest-Impact Journals: Main Findings, Methodological Quality, and Time Trends. *Circulation*. 2019;140(5):379-389. doi:10.1161/circulationaha.119.040214

22. Pong S, Urner M, Fowler RA, et al. Testing for non-inferior mortality: a systematic review of non-inferiority margin sizes and trial characteristics. *BMJ Open*. 2021;11(4):e044480. doi:10.1136/bmjopen-2020-044480

23. Williamson T, Eliasziw M, Fick GH. Log-binomial models: exploring failed convergence. *Emerg Themes Epidemiology*. 2013;10(1):14. doi:10.1186/1742-7622-10-14

24. Cox DR. Regression Models and Life-Tables. *J R Stat Soc Ser B: Stat Methodol*. 2018;34(2):187-202. doi:10.1111/j.2517-6161.1972.tb00899.x

25. Campbell MK, Piaggio G, Elbourne DR, Altman DG, Group C. Consort 2010 statement: extension to cluster randomised trials. *BMJ : Br Méd J*. 2012;345(sep04 1):e5661. doi:10.1136/bmj.e5661

26. Campbell NG, Wollborn J, Fields KG, et al. Inconsistent Methodology as a Barrier to Meaningful Research Outputs From Studies of Atrial Fibrillation After Cardiac Surgery. *J Cardiothor Vasc An*. 2022;36(3):739-745. doi:10.1053/j.jvca.2021.10.009

27. Almassi GH, Schowalter T, Nicolosi AC, et al. Atrial fibrillation after cardiac surgery: a major morbid event? *Ann Surg*. 1997;226(4):501-511; discussion 511-3.

Article Information

Corresponding Author:

Benjamin O'Brien

Department of Cardiac Anesthesiology and Intensive Care Medicine

Deutsches Herzzentrum der Charité

Charité Universitätsmedizin Berlin

Augustenburger Platz 1

13353 Berlin

Germany

Email: Ben.OBrien@dhzc-charite.de

Author Contributions:

EA, JSt and CO had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors vouch for the integrity and the accuracy of the analysis and for the fidelity of the study to the protocol.

Concept and design: Ben O'Brien, Niall Campbell, Elizabeth Allen, Julie Sanders, Richard Evans, Hugh Montgomery and Diana Elbourne

Acquisition, analysis, or interpretation of data: Ben O'Brien, Niall Campbell, Elizabeth Allen, Zaha Jamal, Joanna Sturgess, Julie Sanders, Neil Roberts, Jonathan Aron, Maria Maccaroni, Richard Gould, Bilal Kirmani, Ben Gibbison, Gudrun Kunst, Alexander Zarbock, Maren Kleine-Brüggeney, Christian Stoppe, Keith Pearce, Mark Hughes, Laura Van Dyck, Richard Evans, Hugh Montgomery, Diana Elbourne.

Drafting of the manuscript: Ben O Brien, Niall Campbell, Elizabeth Allen, Zahra Jamal, Jo Sturgess, Charles Opondo, Julie Sanders, Mark Hughes, Richard Evans, Hugh Montgomery, Diana Elbourne.

Critical revision of the manuscript for important intellectual content: Ben O'Brien, Niall Campbell, Elizabeth Allen, Zahra Jamal, Jo Sturgess, Charles Opondo, Julie Sanders, Neil Roberts, Jonathan Aron, Maria Maccaroni, Richard Gould, Bilal Kirmani, Ben Gibbison, Gudrun Kunst, Alexander Zarbock, Maren Kleine-Brüggeney, Christian Stoppe, Keith Pearce, Mark Hughes, Laura Van Dyck, Richard Evans, Hugh Montgomery, Diana Elbourne.

Statistical analysis: Elizabeth Allen, Joanna Sturgess, Charles Opondo, Mark Hughes

Obtained funding: Ben O'Brien, Niall Campbell, Elizabeth Allen, Julie Sanders, Richard Evans, Hugh Montgomery, Diana Elbourne

Administrative, technical, or material support: Ben O'Brien, Zahra Jamal, Julie Sanders, Neil Roberts, Jonathan Aron, Maria Maccaroni, Richard Gould, Bilal Kirmani, Ben Gibbison, Gudrun Kunst, Alexander Zarbock, Maren Kleine-Brüggeney, Christian Stoppe, Keith Pearce, Laura Van Dyck, Richard Evans, Hugh Montgomery

Supervision: Ben O'Brien, Niall Campbell, Elizabeth Allen, Richard Evans, 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.

CS reports financial support for an Investigator Initiated Study from Fresenius Kabi, not related to this work; consulting fees, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events, and reimbursement of travel costs from Fresenius Kabi, Baxter, Abiomed and BBRAUN.

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 ACNAP Board (2018-) and the Aortic Dissection Charitable Trust Research Advisory Board (2021-2023).

RE reports funding from British Heart Foundation(BHF), as he is part-funded on the TIGHT K research grant for his work on the trial. RE also reports funding from NIHR and BHF not related to this work

LVD reports funding from (BHF), as she is part-funded on the TIGHT K research grant for her work on the trial. LVD also reports funding from NIHR not related to this work

ZJ reports funding from (BHF), as she is part-funded on the TIGHT K research grant for her work on the trial. ZJ also reports funding from BHF not related to this work

HM reports membership on the council of the UK Charity, 'The Intensive Care Society' [Unpaid]. HM is supported by the National Institute for Health Research's Comprehensive Biomedical Research Centre at University College Hospitals, London.

Funding/Support:

Full charitable funding was provided by the British Heart Foundation Clinical Study Grant CS/18/3/34063 which was awarded to BO'B, as the chief investigator, and the co-applicants.

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/).

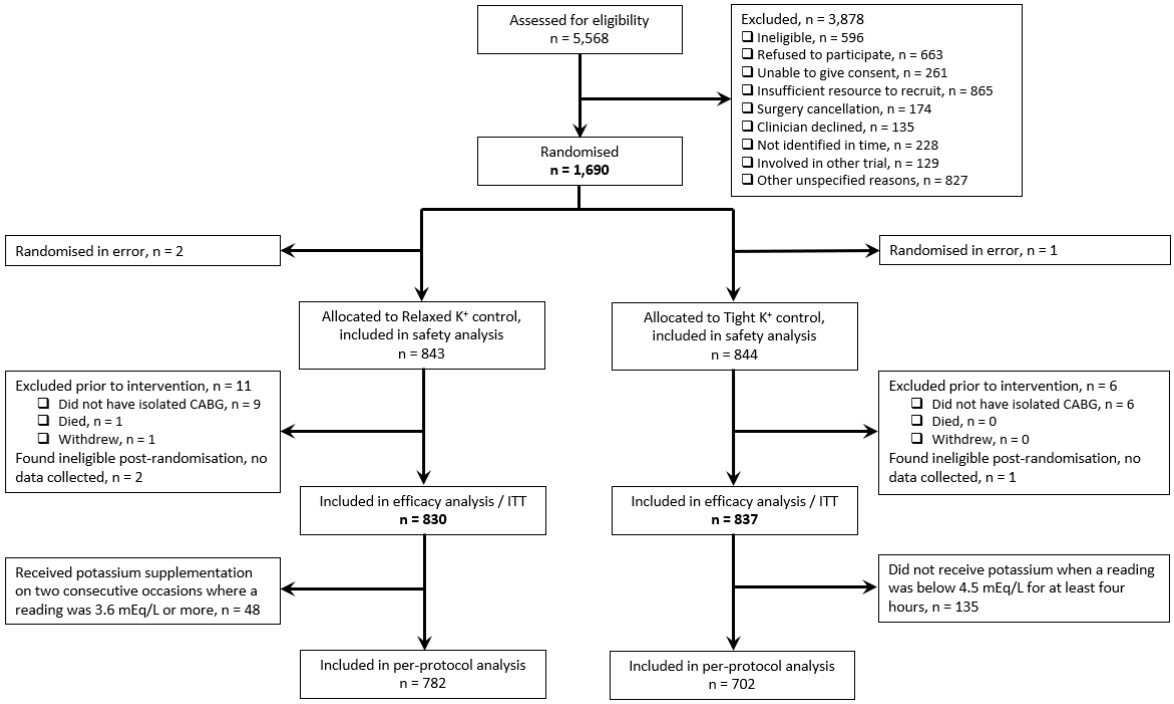
A data dictionary, the study protocol, and the statistical analysis plan will also be supplied. These data will be made available subject to completion of a data access agreement. Data will be shared 12 months after the end of the study (last visit of final patient) which is anticipated to be mid-July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

ACKNOWLEDGEMENTS

We acknowledge the British Heart Foundation for continued support, including a no-cost extension following the COVID-19 pandemic, and the National Institute for Health and Care Research for prioritising this as an important study following the COVID-19 pandemic. We thank the hospital sites for their assistance in the study set up and data completeness. We are very grateful to the patients who agreed to participate in the TIGHT K study.

Figure 1

Title: Recruitment, randomization, and follow-up in the TIGHT K Trial



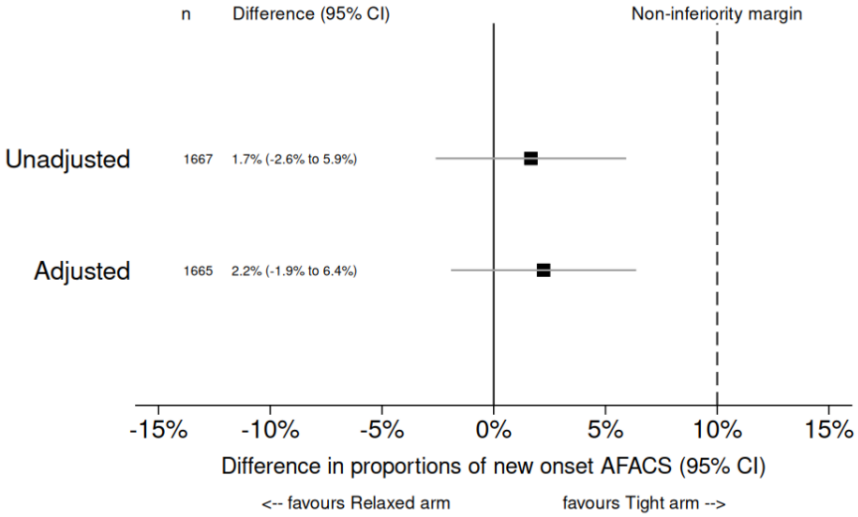
Legend:

Efficacy analysis (EA): All participants assigned a randomization number who underwent isolated CABG surgery.

Per-protocol analysis: This comprised the EA population with the exclusion of participants not completing a protocol-adherent course of treatment.

Figure 2a

Title: Effect of the intervention on the primary outcome

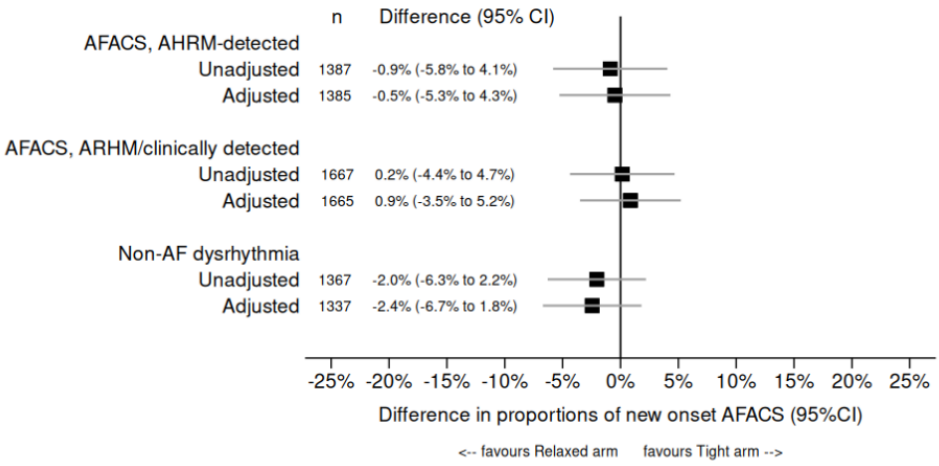


Panel A Legend:

Analysis of non-inferiority on the primary outcome
Analysis was adjusted for age, sex and site
AFACS: Atrial Fibrillation After Cardiac Surgery

Figure 2b

Title: Effect of the intervention on secondary outcomes

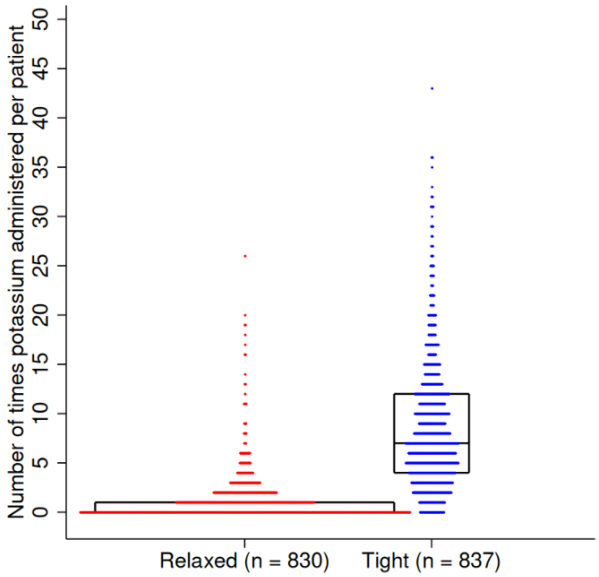


Panel B Legend:

Superiority analysis of effectiveness on secondary outcomes
Analysis was adjusted for age, sex and site
AHRM: Ambulatory Heart Rhythm Monitor

Figure 3a

Title: Frequency of potassium administration by treatment arm

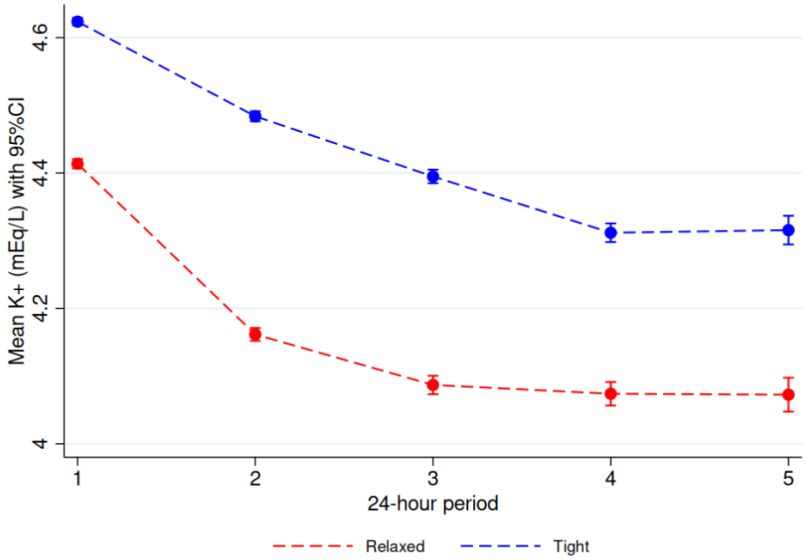


Legend:

Frequency of potassium administration during periods 1-5 or until discharge (if sooner), or until the primary outcome was met

Figure 3b

Title: Mean serum potassium levels by treatment arm



Legend:

Mean serum potassium levels by treatment arm during periods 1-5

Table 1: Characteristics of patients at baseline

Characteristic		Relaxed N = 830	Tight N = 837	Total N = 1,667
Age in years, mean (SD)		64.6 (9.12)	64.7 (9.52)	64.7 (9.32)
Sex				
	Female	141 (17.0)	115 (13.7)	256 (15.4)
	Male	689 (83.0)	722 (86.3)	1411 (84.6)
Ethnicity, n (%)				
	Asian or Asian British	87 (10.5)	76 (9.1)	163 (9.8)
	Black or Black British	9 (1.1)	12 (1.4)	21 (1.3)
	Mixed/Other	13 (1.6)	20 (2.4)	33 (2.0)
	White	716 (86.8)	724 (87.0)	1,440 (86.9)
BMI in kg/m^2, mean (SD)†		29.0 (4.80)	29.2 (5.02)	29.1 (4.91)
EuroSCORE II (%), mean (SD)‡		1.5 (1.26)	1.6 (1.35)	1.5 (1.31)
Chronic kidney disease, n (%)*				
	Yes	42 (5.2)	47 (5.8)	89 (5.5)
	No	769 (94.8)	761 (94.2)	1,530 (94.5)
Diabetes mellitus, n (%)				
	Yes	288 (35.3)	298 (36.1)	586 (35.7)
	No	527 (64.7)	527 (63.9)	1,054 (64.3)
Previous cerebrovascular event, n (%)				
	Yes	55 (6.8)	47 (5.8)	102 (6.3)
	No	754 (93.2)	765 (94.2)	1,519 (93.7)
Medications at Baseline				
β-Blocker, n (%)				
	Yes	651 (78.5)	639 (76.5)	1,290 (77.5)
	No	178 (21.5)	196 (23.5)	374 (22.5)
Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers, n (%)				
	Yes	526 (63.4)	501 (59.9)	1,027 (61.6)
	No	304 (36.6)	335 (40.1)	639 (38.4)
Loop Diuretics				
	Yes	44 (5.3)	43 (5.1)	87 (5.2)
	No	783 (94.7)	792 (94.9)	1,575 (94.8)
Statins, n (%)				
	Yes	749 (90.5)	757 (90.6)	1,506 (90.5)
	No	79 (9.5)	79 (9.4)	158 (9.5)
Surgery				
Cardiopulmonary bypass (CPB), n (%)				
	Off CPB	109 (13.1)	129 (15.4)	238 (14.3)
	On CPB	721 (86.9)	707 (84.6)	1,428 (85.7)
Potassium concentration in mEq/L coming off bypass, mean (SD)**		5.0 (0.69)	5.0 (0.61)	5.0 (0.65)

Characteristic	Relaxed N = 830	Tight N = 837	Total N = 1,667

†BMI is body mass index; under 18.5 is considered underweight, 18.5 to 24.9 deemed the 'healthy range', 25 to 29.9 described as overweight, 30 to 39.9 as obese, and 40 or more as severely obese

‡EuroSCORE II is the European System for Cardiac Operative Risk Evaluation, a tool for predicting risk of in-hospital mortality after major cardiac surgery. The EuroSCORE has a theoretical range of 0% to 100%, with increasing scores corresponding to increasing risk of in-hospital mortality. EuroSCORE II scores of 1.5% to 1.6% are considered a low risk of in-hospital mortality.

* CKD was determined from review of medical history at baseline

** There were 119 patients in the Relaxed arm and 143 in the Tight arm with unknown potassium concentrations when coming off bypass

Categorical variables with counts not adding up to the group total have patients with undocumented, unknown or missing values.

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

Outcome	Relaxed arm (N = 830)	Tight arm (N = 837)	Unadjusted		Adjusted	
	n (%)		Risk difference (95%CI)	p-value	Risk difference (95%CI)	p-value
Atrial fibrillation after cardiac surgery, clinically detected and electrocardiographically confirmed	231 (27.8)	219 (26.2)	1.6% (-2.6%, 5.9%)	0.44	2.2% (-1.9%, 6.4%)	0.29
Atrial fibrillation after cardiac surgery, ambulatory heart rhythm monitor-detected	220 (32.2) 147 missing	233 (33.1) 133 missing	-0.9% (-5.8%, 4.1%)	0.73	-0.5% (-5.3%, 4.3%)	0.84
Atrial fibrillation after cardiac surgery, clinically or ambulatory heart rhythm monitor detected	275 (33.1)	276 (33.0)	0.1% (-4.4%, 4.7%)	0.95	0.9% (-3.5%, 5.2%)	0.70
Dysrhythmias other than atrial fibrillation after cardiac surgery	128 (19.1) 159 missing	147 (21.1) 141 missing	-2.0% (-6.3%, 2.2%)	0.35	-2.4% (-6.7%, 1.8%)	0.26
	events (rate per 10,000 person-days)		Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
In-patient mortality	4 (6.2)	4 (6.2)	1.00 (0.25, 3.99)	> 0.99	0.82 (0.19, 3.40)	0.78
	median (IQR)		Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Time-to-discharge from critical care, days	2 (1 – 4)	2 (1 – 4)	0.99 (0.90, 1.09)	0.80	0.98 (0.89, 1.08)	0.73
Time-to-discharge from hospital, days	6 (5 – 8)	6 (5 – 7)	0.99 (0.90, 1.09)	0.78	1.00 (0.90, 1.10)	0.94
	mean costs in USD (SD)					
Cost of potassium purchase and administration						
Intravenous	87.41 (75.69)	152.16 (99.99)			Not estimated	
Oral	3.08 (6.23)	7.66 (10.68)			Not estimated	
Food or nasogastric tube	0.09 (1.42)	0.29 (2.87)			Not estimated	
	mean costs in USD (SD)		Mean difference (95%CI)	p-value	Mean difference (95%CI)	p-value
Total costs (95%CI)	39.30 (65.37) (34.84, 43.75)	151.19 (103.00) (144.20, 158.18)	111.89 (103.60, 120.19)	< 0.001	112.12 (103.84, 120.40)	< 0.001