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Potassium Supplementation and Prevention of Atrial Fibrillation After Cardiac Surgery
The TIGHT K Randomized Clinical Trial

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IMPORTANCE Supplementing potassium in an effort to maintain high-normal serum concentrations 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 serum potassium concentration trigger for supplementation is noninferior to a high-normal trigger.

DESIGN, SETTING, AND PARTICIPANTS This open-label, noninferiority, randomized clinical trial was conducted at 23 cardiac surgical centers in the United Kingdom and Germany. Between October 20, 2020, and November 16, 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 the hospital on December 11, 2023.

INTERVENTIONS Patients were randomly assigned to a strategy of tight or relaxed potassium control (only supplementing if serum potassium concentration fell below 4.5 mEq/L or 3.6 mEq/L, respectively). Patients wore an ambulatory heart rhythm monitor, which was analyzed by a core laboratory masked to treatment assignment.

MAIN OUTCOMES AND MEASURES The prespecified primary end point 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. Noninferiority of relaxed potassium control was defined as a risk difference for new-onset AFACS with associated upper bound of a 1-sided 97.5% CI of less than 10%. Secondary outcomes included other heart rhythm–related events, clinical outcomes, and cost related to the intervention.

RESULTS A total of 1690 patients (mean age, 65 years; 256 [15%] females) were randomized. The primary end point occurred in 26.2% of patients (n = 219) in the tight group and 27.8% of patients (n = 231) in the relaxed group, which is a risk difference of 1.6% (95% CI, −2.6% to 5.9%). There was no difference between the groups in the incidence of at least 1 AFACS episode detected by any means or by ambulatory heart rhythm monitor 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 group (mean difference, $111.89 [95% CI, 103.60-120.19]; *P* <.001).

CONCLUSIONS AND RELEVANCE For AFACS prophylaxis, supplementation only when serum potassium concentration fell below 3.6 mEq/L was noninferior to the current widespread practice of supplementing potassium to maintain a serum potassium concentration greater than or equal to 4.5 mEq/L. The lower threshold of supplementation was not associated with any increase in dysrhythmias or adverse clinical outcomes.

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Visual Abstract

Supplemental content

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Approximately 1.5 million cardiac surgical procedures are performed worldwide per year,[1] with coronary artery bypass grafting (CABG) being the most common of these.[2]

Atrial fibrillation after cardiac surgery (AFACS) remains the most frequent postoperative adverse event, affecting about 30% of patients after CABG.[3] By postoperative 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 health care 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 hypokalemia is associated with both ventricular dysrhythmias and cardiac arrest.[11] Many clinicians believe that serum potassium concentration influences risk of developing atrial fibrillation in critical illness,[12] and frequent potassium supplementation in an effort to maintain a high-normal postoperative serum potassium concentration (≥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, the cumulative annual expenditure for intravenous potassium in many cardiac units 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 the patient experience and may be associated with risk.[14]

The aim of this study was to address the gap in evidence on the effectiveness of maintaining a high-normal serum potassium concentration for AFACS prophylaxis. First, in a feasibility study, it was demonstrated that patients could be recruited and randomized to 2 different potassium supplementation protocols.[15] This study reports the results of TIGHT K, the first appropriately powered multicenter randomized clinical trial to determine whether supplementing potassium only when serum potassium concentration falls below 3.6 mEq/L (relaxed control) is noninferior to supplementation when serum potassium concentration falls below 4.5 mEq/(tight control).[16]

Key Points

Question When trying to prevent atrial fibrillation after cardiac surgery (AFACS), is supplementing potassium only when its serum concentration falls below 3.6 mEq/L noninferior to supplementation when serum potassium concentration falls below 4.5 mEq/L?

Findings In the first 5 days after coronary artery bypass graft (CABG) surgery, patients who only received supplementation when serum potassium concentration dropped below 3.6 mEq/L (n = 830) did not have an increased incidence of new-onset AFACS compared with those who only received supplementation when serum potassium concentration dropped below 4.5 mEq/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 serum potassium concentration after CABG surgery can be abandoned. This will reduce health care costs and decrease patient risk from an unnecessary intervention.

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 clinical noninferiority open-label trial performed at 23 cardiac surgery units in the United Kingdom (n = 21) and Germany (n = 2). Enrollment occurred from October 20, 2020, to November 16, 2023.

The protocol was approved by the UK 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.

The London School of Hygiene and Tropical Medicine Clinical Trials Unit codesigned 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 laboratory at Manchester Heart Institute, Manchester University NHS Foundation Trust analyzed the ambulatory heart rhythm monitors (AHRMs) (CAM Bardy, Baxter), which patients wore in addition to routine monitoring. An independent event validation committee arbitrated all primary end point events.

The data are reported according to Consolidated Standards of Reporting Trials (CONSORT) noninferiority 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; preoperative 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 preoperative serum potassium concentration greater than 5.5 mEq/L; or dialysis-dependent kidney failure.

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

All patients provided written informed consent.

Ethnicity was self-reported by patients using fixed selection categories. Ethnicity data were collected to allow assessment of the representativeness of the study population

Randomization and Masking

Patients were randomized in a 1:1 ratio, using block permutation (sizes 4 and 6) and stratified by site, to receive potassium supplementation only when their serum potassium concentration fell below 4.5 mEq/L (tight group) or below 3.6 mEq/L (relaxed group). 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 group. The core laboratory analyzing the AHRM and the event validation committee were all masked to treatment assignment.

Intervention

The trial treatment protocol was initiated when the patient was admitted to the postoperative care facility, providing that they were in sinus or paced rhythm at that time. The trial treatment period ended 120 hours after the initial postoperative admission, on discharge from the 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, serum potassium concentration 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 magnesium and β-blockers, were given according to standard clinical care and clinician 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 end point, AHRM supplemented standard monitoring for 120 hours following surgery or until discharge, whichever occurred sooner.

For the purposes of data capture and reporting, the 120 hours after admission to the postoperative 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 electrocardiogram recording) that was both clinically detected and electrocardiographically confirmed (on either electrocardiogram, telemetry, or AHRM) until hour 120 after initial admission to postoperative 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 European Society of Cardiology/European Association for Cardio-Thoracic Surgery/European Heart Rhythm Association definition of atrial fibrillation,[18] recognizing that differentiation between these 3 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 1 episode of AFACS identified clinically or by AHRM, the number of patients experiencing at least 1 episode of a non-AFACS dysrhythmia identified on AHRM over the same periods, inpatient mortality, critical care and hospital length of stay, and cost relating to purchasing and administering potassium therapy.

Two prespecified 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

Noninferiority of relaxed potassium control was defined as an absolute risk difference for new-onset AFACS with associated upper bound of a 1-sided 97.5% CI of less than 10%. The noninferiority margin, which is the limit for the upper end of the CI, 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 noninferiority 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. It was estimated that 1514 patients randomized in a 1:1 ratio to the 2 groups would provide 90% power to detect noninferiority of relaxed potassium control, assuming a 35% prevalence of new-onset AFACS in the tight group—a conservative estimate given the observed prevalence of 36.9% (95% CI, 29.1%-44.9%) in the feasibility study—and further assuming a 2%-lower prevalence of AFACS in the tight group. We aimed to recruit 1684 patients, allowing for 10% loss to follow-up.

We used 3 datasets defined a priori for the analysis: efficacy, safety, and per-protocol analyses.

Intention-to-Treat Population

The efficacy analysis population included all participants assigned a randomization number who underwent isolated CABG surgery.

The safety analysis population included all participants assigned a randomization number.

Per-Protocol Population

The per-protocol efficacy population comprised the efficacy analysis population with the exclusion of participants not completing a protocol-adherent course of treatment. Treatment was deemed not per-protocol in the relaxed group if potassium supplementation was given on 2 consecutive occasions when serum potassium concentration was greater than 3.6 mEq/L and was deemed not per-protocol in the tight group if supple-

mentation was not given when serum potassium concentration was less than 4.5 mEq/L for at least 4 hours.

The primary analysis was unadjusted and carried out using the efficacy analysis population. A prespecified adjusted analysis was also performed, adjusting for patient age, sex, and site. Analysis of the primary and secondary outcomes was repeated using the per-protocol population.

Descriptive characteristics of patients at baseline were summarized using means and SDs 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 were 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 group.

Prespecified 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, an additional sensitivity analysis was performed using inverse probability weighting.

Adverse event frequencies were tabulated by treatment group using the safety analysis 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). The trial was prospectively registered with ClinicalTrials.gov (NCT04053816) on August 13, 2019.

Results

Descriptive Findings

A total of 5568 patients were assessed for eligibility, of whom 1690 were randomized (**Figure 1**).[25] Three patients were randomized in error, leading to 844 patients in the tight group and 843 patients in the relaxed group in the safety analysis population. An additional 17 patients did not receive an isolated CABG procedure, died during the operation, or withdrew and 3 patients were found to be ineligible after randomization, leading to 837 in the tight group and 830 in the relaxed group in the efficacy analysis population. One hundred and thirty-five patients in the tight group and 48 in the relaxed group did not receive a protocol-adherent course of treatment, leading to 702 patients in the tight group and 782 patients in the relaxed group in the per-protocol population. Characteristics of the patients not included in the per-protocol population are shown in eTable 1 in Supplement 3.

Table 1 shows baseline characteristics of the efficacy analysis population, which are balanced between groups (for complete data see eTable 2 in Supplement 3). Of note, interventions often used to prevent AFACS, such as β-lockers, magnesium supplementation, and amiodarone were applied in equal measure in both groups (eTable 3 in Supplement 3).

Primary and Secondary End Points

The primary end point was met by 219 of 837 patients (26.2%) in the tight group and 231 of the 830 patients (27.8%) in the relaxed group (unadjusted risk difference, 1.6% [95% CI, −2.6% to 5.9%]). The upper bound of the 1-sided 97.5% CI lies within the prespecified noninferiority margin of 10%, suggesting noninferiority of the relaxed group (**Figure 2** and **Table 2**). This finding was supported by the analysis using the per-protocol population (eTable 4 in Supplement 3).

No differences were observed between groups for any of the secondary outcomes, other than cost relating to purchasing and administering potassium therapy, which showed significantly lower cost in the relaxed group, with a mean per-patient difference of $111.89 (95% CI, $103.60-$120.19; $P < .001$) (Table 2; eTable 10 in Supplement 3). For in-patient mortality, time to discharge from critical care, and time to discharge from hospital, the hazard ratios were close to 1.0 (eFigure 1 in Supplement 3).

Analysis of the secondary outcomes using the per-protocol 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 groups.

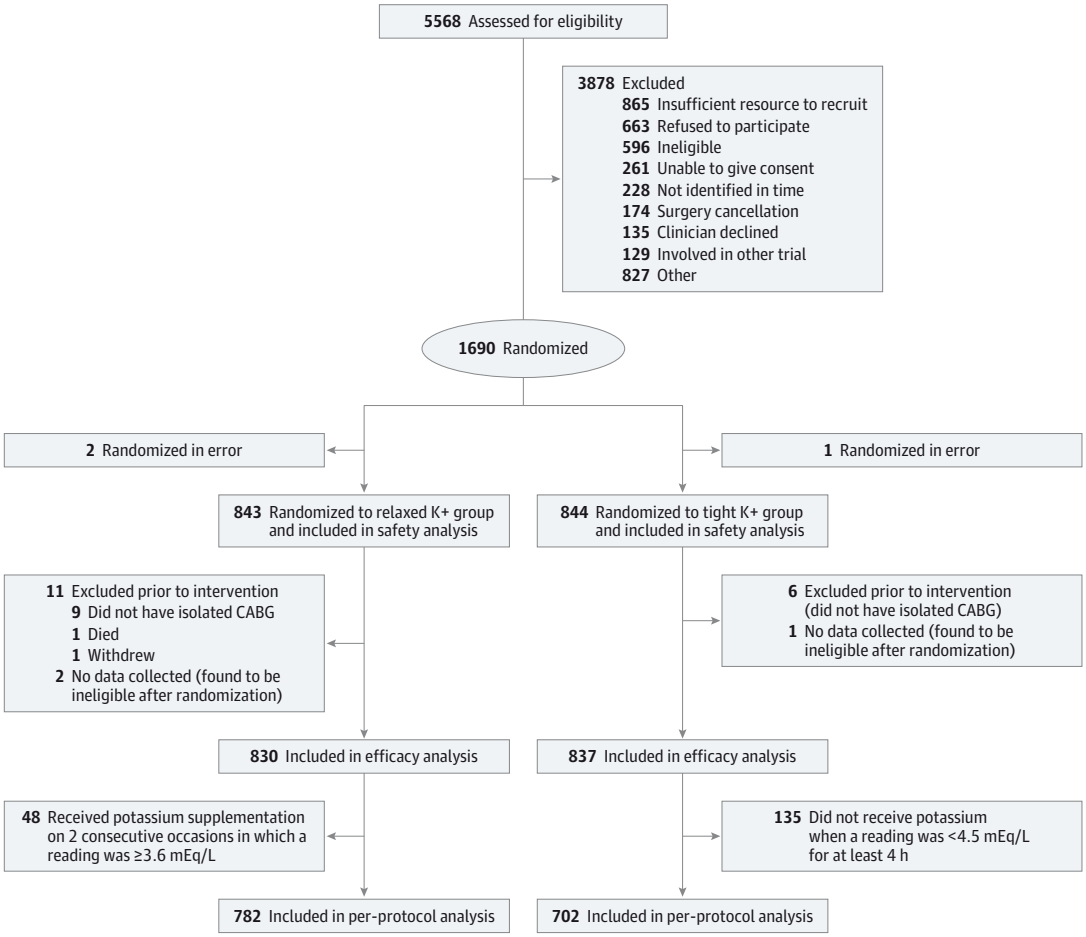
Subgroup Analyses

For predefined subgroup analyses, there was no evidence of any difference between groups in any of the predefined subgroup analyses of the primary end point by patient age, sex, occurrence of atrial fibrillation lasting longer than 30 seconds during the operation, receiving β-blockers at baseline, ejection fraction category, race, euroSCORE II risk category, receiving loop diuretics at baseline, or CABG pump status (eFigure 3 in Supplement 3).

AHRM Analysis

In the tight group, 77 patients had no AHRM readings and 56 only had partial readings. In the relaxed group, 94 patients had no AHRM readings and 53 had partial readings. For most patients who met the primary end point, there was agreement between the clinically detected AFACS and AHRM-detected AFACS (eFigure 4 in Supplement 3). For AHRM-detected AFACS, AHRM-detected or clinically detected AFACS, and AHRM-detected non-AFACS dysrhythmias, the risk differences were very similar to that of the primary outcome (Figure 2). In prespecified 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

Figure 1. Recruitment, Randomization, and Follow-up in the TIGHT K Trial



The efficacy analysis included all participants assigned a randomization number who underwent isolated CABG surgery. The per-protocol analysis comprised the efficacy analysis population with the exclusion of participants not completing a protocol-adherent course of treatment.

of the non-AFACS dysrhythmias, including ventricular tachycardia/fibrillation rates, showed no signal for harm in the relaxed group (eTable 7 in Supplement 3).

Serum Potassium Levels

There was evidence of a clear separation between the 2 groups of the trial in both frequency of potassium supplementation and mean serum potassium concentration (**Figure 3**). The median (IQR) number of times potassium was administered throughout periods 1 through 5 or prior to first AFACS episode was 7 (4-12) times in the tight group and 0 (0-1) in the relaxed group, with a consequent higher mean serum potassium concentration in the tight group than the relaxed group. The frequency of serum potassium concentration measurements was similar between the groups (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 serum potassium concentration as a means of preventing AFACS. This study 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 noninferiority design, allowed a conclusive answer to the clinical question: does only supplementing potassium if serum potassium concentration drops below the normal range (relaxed control) increase AFACS rates compared with a strategy of supplementing it when serum potassium concentration drops below the high-normal range (tight control)?

Table 1. Characteristics of Patients at Baseline

Characteristic	Relaxed (n = 830)	Tight (n = 837)	Total (N = 1667)
Age, mean (SD), y	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, No. (%)[a]			
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)	1440 (86.9)
Body mass index, mean (SD)[b]	29.0 (4.80)	29.2 (5.02)	29.1 (4.91)
EuroSCORE II, mean (SD)[c]	1.5 (1.26)	1.6 (1.35)	1.5 (1.31)
Chronic kidney disease, No. (%)[d]			
Yes	42 (5.2)	47 (5.8)	89 (5.5)
No	769 (94.8)	761 (94.2)	1530 (94.5)
Diabetes, No. (%)			
Yes	288 (35.3)	298 (36.1)	586 (35.7)
No	527 (64.7)	527 (63.9)	1054 (64.3)
Previous cerebrovascular event, No. (%)			
Yes	55 (6.8)	47 (5.8)	102 (6.3)
No	754 (93.2)	765 (94.2)	1519 (93.7)
Medications at baseline, No. (%)			
β-blocker			
Yes	651 (78.5)	639 (76.5)	1290 (77.5)
No	178 (21.5)	196 (23.5)	374 (22.5)
Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers			
Yes	526 (63.4)	501 (59.9)	1027 (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)	1575 (94.8)
Statins			
Yes	749 (90.5)	757 (90.6)	1506 (90.5)
No	79 (9.5)	79 (9.4)	158 (9.5)
Surgery			
Cardiopulmonary bypass			
No	109 (13.1)	129 (15.4)	238 (14.3)
Yes	721 (86.9)	707 (84.6)	1428 (85.7)
Potassium concentration after bypass, mean (SD), mEq/L[e]	5.0 (0.69)	5.0 (0.61)	5.0 (0.65)

[a] In England and Wales, where the majority of the recruiting centers were based, there is an agreed list of ethnic groups that can be used when asking someone's ethnicity. The groups are those used in the census, which happens every 10 years. Self-reported ethnicity categories were collected according to UK government 2011 census categories for ethnicity (https://www.ethnicity-facts-figures.service.gov.uk/style-guide/ethnic-groups/#2011-census).

[b] 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.

[c] 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.

[d] Chronic kidney disease was determined from review of medical history at baseline.

[e] There were 119 patients in the relaxed group and 143 in the tight group with unknown potassium concentrations after bypass.

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

Compared with tight control, relaxed control was associated with substantially lower doses of potassium supplementation and lower serum potassium concentration values, yet this approach was noninferior in preventing clinically detected and electrocardiographically confirmed AFACS up to 5 days after isolated CABG surgery.

There was also no difference between the groups 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 groups and the median number of AHRM-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.

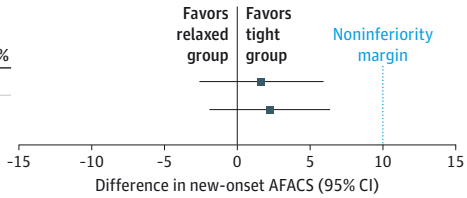
No disadvantages associated with a relaxed potassium strategy were identified, despite being actively sought. Neither clinical outcomes nor the incidence of at least 1 episode of non-AFACS dysrhythmia differed between the groups.

It is noteworthy that most patients in the relaxed group 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 serum potassium concentration and that proactive supplementation only has a comparatively limited effect.

Figure 2. Primary and Secondary Outcomes

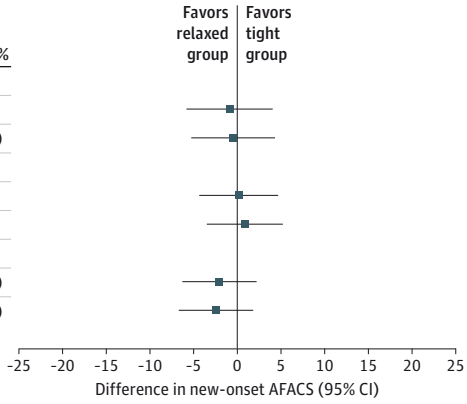
A Primary outcome

Source	No. of patients	Difference in new-onset AFACS (95% CI), %
Unadjusted	1667	1.7 (-2.6 to 5.9)
Adjusted	1665	2.2 (-1.9 to 6.4)



B Secondary outcomes

Source	No. of patients	Difference in new-onset AFACS (95% CI), %
AFACS (AHRM detected)		
Unadjusted	1387	-0.9 (-5.8 to 4.1
Adjusted	1385	-0.5 (-5.3 to 4.3)
AFACS (ARHM clinically detected)		
Unadjusted	1667	0.2 (-4.4 to 4.7)
Adjusted	1665	0.9 (-3.5 to 5.2)
Non-AF dysrhythmia		
Unadjusted	1367	-2.0 (-6.3 to 2.2)
Adjusted	1337	-2.4 (-6.7 to 1.8)



A, Analysis of noninferiority on the primary outcome, adjusted for age, sex, and site. B, Superiority analysis of effectiveness on secondary outcomes, adjusted for age, sex, and site. AFACS indicates atrial fibrillation after cardiac surgery; AHRM, ambulatory heart rhythm monitor.

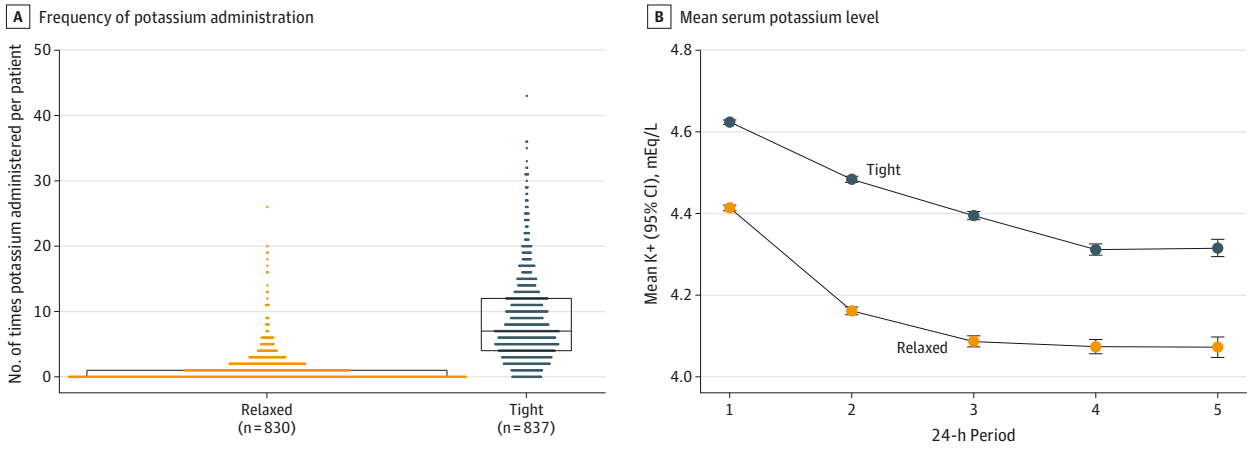
Table 2. Effect of the Intervention on Primary and Secondary Outcomes

Outcome	No. (%)		Unadjusted		Adjusted	
	Relaxed group (n = 830)	Tight group (n = 837)	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 to 5.9)	.44	2.2 (−1.9 to 6.4)	.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 to 4.1)	.73	−0.5 (−5.3 to 4.3)	.84
Atrial fibrillation after cardiac surgery, clinically or ambulatory heart rhythm monitor-detected	275 (33.1)	276 (33.0)	0.1 (−4.4 to 4.7)	.95	0.9 (−3.5 to 5.2)	.70
Dysrhythmias other than atrial fibrillation after cardiac surgery	128 (19.1) [159 missing]	147 (21.1) [141 missing]	−2.0 (−6.3 to 2.2)	.35	−2.4 (−6.7 to 1.8)	.26
In-patient mortality, No. of events (rate per 10 000 person-days)	4 (6.2)	4 (6.2)	Hazard ratio, 1.00 (0.25 to 3.99)	>.99	Hazard ratio, 0.82 (0.19 to 3.40)	.78
Time to discharge from critical care, median (IQR), d	2 (1 to 4)	2 (1 to 4)	Hazard ratio, 0.99 (0.90 to 1.09)	.80	Hazard ratio, 0.98 (0.89 to 1.08)	.73
Time to discharge from hospital, median (IQR), d	6 (5 to 8)	6 (5 to 7)	Hazard ratio, 0.99 (0.90 to 1.09)	.78	Hazard ratio, 1.00 (0.90 to 1.10)	.94
Cost of potassium purchase and administration, mean (SD), $						
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		
Total costs, mean (SD) [95% CI], $	39.30 (65.37) [34.84 to 43.75]	151.19 (103.00) [144.20 to 158.18]	Mean difference, 111.89 (103.60 to 120.19)	<.001	Mean difference, 112.12 (103.84 to 120.40)	<.001

As expected, mean serum potassium concentration in each group was not above the trigger threshold for that group, given that values had to fall below that threshold for supplementation to occur.

The health economic analysis reported here warrants consideration, given that potassium is among the highest cumulative cost drugs used in many cardiac units.[13] Mean per-patient costs relating to purchasing and administering

Figure 3. Frequency of Potassium Supplementation and Mean Serum Potassium Concentration



A, Frequency of potassium administration during periods 1-5 or until discharge (if sooner) or until the primary outcome was met. B, Mean serum potassium levels by treatment group during periods 1-5.

potassium therapy were near 4-fold higher in the tight group than in the relaxed group (Table 2; 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 adverse effects of oral potassium supplementation are common and are poorly tolerated by patients.[14] Reducing unnecessary interventions will also reduce clinical waste, as well as reducing the carbon impact from manufacture and supply.

Limitations

This study has 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 laboratory and the independent event validation committee, both masked to treatment group, helped to address this limitation.

The primary end point (clinically detected AFACS) event rate in the cohort (28%) was slightly lower than expected, compared with data reported in previous literature and in the pilot trial. However, statistical power was retained for the absolute noninferiority margin of 10%. Rates of AFACS detected by any means (clinically or AHRM) were 33.0% in the tight group and 33.1% in the relaxed group.

There was also a degree of nonadherence with the protocol (strategies to reduce and report this are described in the eAppendix 6 in Supplement 3). Nonadherence was markedly higher in the tight group, despite it being the perceived standard of care. In this group, potassium supplementation occurred less consistently when serum potassium concentration was just narrowly below the threshold at approximately 4.3 or 4.4 mEq/L. However, findings did 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] only patients undergoing isolated CABG surgery were recruited. If potassium supplementation at higher trigger thresholds is to be continued in other cardiac surgical procedures, the efficacy of this practice should be similarly assessed.

Conclusions

Supplementation of potassium only when serum levels fall below 3.6 mEq/L is noninferior to the 4.5-mEq/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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