

TIGHT K

Arrhythmias on the
cardiac intensive care unit –
does maintenance of high-normal
serum potassium levels matter?

Tight K Pilot Study

Protocol Version 2

Sponsored by Barts Health NHS Trust

Funded by the British Heart Foundation

Full Title	PILOT STUDY for the Tight K TRIAL. Arrhythmias on the cardiac intensive care unit - does maintenance of high-normal serum potassium levels matter?
Short Title/Acronym	PILOT STUDY for The Tight K TRIAL
Sponsor	Barts Health NHS Trust Dr Sally Burtles Director of Research Services Joint Research Management Office 5 Walden Street London E1 2EF Phone: 0207 882 7260 Email: sponsorsrep@bartshealth.nhs.uk
Sponsor trial number	011660
REC Reference	LO/17/0318
Chief Investigator	Dr Ben O'Brien Consultant Anaesthetist and Senior Lecturer Barts Health NHS Trust St Bartholomew's Hospital London EC1A 7DN Email: Ben.OBrien@bartshealth.nhs.uk
Clinical Trials Unit	Department of Medical Statistics London School of Hygiene & Tropical Medicine Keppel Street London WC1E 7HT Tel: 020 7927 2071/2665 Fax: 020 7927 2189

Local sites

Barts Health NHS Trust
Barts Heart Centre
St Bartholomew's Hospital
Little Britain
London
EC1A 7DN

St George's Hospital
Blackshaw Rd
Tooting
London
SW17 0QT

Contents Page

Contents Page	4
1. Glossary of Terms and Abbreviations	7
2. Signature Page	8
2.1. Chief Investigator Agreement	8
2.2. Principal Investigator Agreement (if different from Chief investigator)	8
2.3 Statistician Agreement	8
Summary / Synopsis	10
3. Introduction	12
3.1. Background and Scientific Rationale	12
4. Trial Objectives	13
4.1. Hypothesis	13
4.2. Primary endpoint	13
4.2.1. Primary endpoints for pilot study:	13
4.2.2. Definition of AF	13
4.3. Secondary endpoints	13
5. Methodology	14
5.1. Inclusion criteria	14
5.2. Exclusion criteria	14
5.3. Study Design / Plan – Study Visits	14
5.3.1. Patient Identification	14
5.3.2. Informed consent procedure	14
5.3.3. Randomisation	14
5.3.4. Trial treatment	15
5.3.5. Potassium supplementation	15
5.3.6. Patients with AF	15
5.3.7. Holter monitoring	16
5.3.8. Follow Up	16
5.4. Trial Flowchart	17
6. Study Procedures	18
6.1. Trial treatment period	18
6.2. Trial Procedures Table	18
6.3. Data collection	19
6.4. Trial procedures	19
6.4.1. Before surgery	19
6.4.2. Period 1 (0Hr – 24Hr post admission to ICU)	19
6.4.3. Period 2 (24-48 Hr post admission to ICU)	19
6.4.4. Period 3 (48-72 Hr post admission to ICU)	20
6.4.5. Period 4 (72-96 Hr post admission to ICU)	20

6.4.6.	Period 5 (96-120 Hr post admission to ICU)	20
6.4.7.	Discharge from ICU	20
6.4.8.	28 days post-CABG	20
6.5.	Compliance and loss to follow up	20
6.5.1.	Loss to follow-up	20
6.5.2.	Compliance	20
7.	Statistical Considerations	21
7.1.	Power calculations and sample size determination	21
7.2.	Trial statistician	21
7.3.	Statistical analysis	21
8.	Ethics	22
8.1.	Withdrawal of patients	22
8.1.1.	Criteria for withdrawal from the trial	22
8.1.2.	Follow up of patients withdrawing from the trial	22
8.1.3.	Reporting withdrawal of patients	22
8.2.	Declaration of Helsinki and Good Clinical Practice	22
8.3.	Ethical committee review	22
9.	Safety Considerations	23
9.1.	Suspension of trial treatment in patients with AF	23
10.	Data Handling and Record Keeping	23
11.	Holter Monitors	23
11.1.	How the holter monitors are worn	23
11.2.	Manufacturer	23
11.3.	Supplier	24
12.	Safety Reporting	24
12.1.	Definition	24
12.2.	Expected adverse events	24
12.3.	Unexpected Serious Adverse Events	24
12.4.	Unexpected Non-Serious Adverse Events	25
12.5.	Reporting unexpected adverse events	25
12.5.1.	Assessment of intensity	25
12.5.2.	Assessment of causality	25
12.6.	Urgent Safety Measures	25
12.7.	Annual Safety Reporting	26
12.8.	Overview of the Safety Reporting responsibilities	26
13.	Monitoring and Auditing	26
13.1.	Monitoring	26
14.	Trial Committees	26
14.1.	Trial Steering Committee (TSC)	26
14.2.	Project Management Group (PMG)	26
14.3.	Data Safety and Monitoring Committee (DSMC)	26
15.	Finance and Funding	27

16.	Indemnity	27
16.1.	Sponsorship	27
16.2.	Insurance	27
16.3.	Holter monitors	27
17.	Dissemination of Research Findings	27
18.	References	28

1. Glossary of Terms and Abbreviations

AE	Adverse Event
AF	Atrial Fibrillation
AR	Adverse Reaction
ASR	Annual Safety Report
BHF	British Heart Foundation
CA	Competent Authority
CABG	Coronary Artery Bypass Graft
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTU	Clinical Trials Unit
DSMC	Data Safety and Monitoring Committee
EC	European Commission
ECG	Electrocardiogram
GAfREC	Governance Arrangements for NHS Research Ethics Committees
ICF	Informed Consent Form
ICU	Intensive care unit
ITT	Intention to treat
JRMO	Joint Research Management Office
K ⁺	Potassium
NHS REC	National Health Service Research Ethics Committee
NHS R&D	National Health Service Research & Development
NSAE	Non-Serious Adverse Event
Participant	An individual who takes part in a clinical trial
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TMG	Trial Management Group
TSC	Trial Steering Committee

2. Signature Page

2.1. Chief Investigator Agreement

The clinical study as detailed within this research protocol (**Version 2, dated 7th April 2017**), or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Chief Investigator Name: Dr Ben O'Brien

Chief Investigator Site: Barts Heart Centre

Signature: _____ **Date:** _____

2.2. Principal Investigator Agreement (if different from Chief investigator)

The clinical study as detailed within this research protocol (**Version 2, dated 7th April 2017**), or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Principal Investigator Name: Dr Nawaf Al-Subaie

Principal Investigator Site: St George's Hospital

Signature: _____ **Date:** _____

2.3 Statistician Agreement

The clinical study as detailed within this research protocol (**Version 2, 7th April 2017**) will be conducted in accordance with the current Research Governance Framework for Health & Social Care the World Medical Association Declaration of Helsinki (1996), Principles of ICH E6-GCP, ICH E9 - Statistical principles for Clinical Trials, ICH E10 - Choice of Control Groups and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trial regulations.

Statistician Name: Professor Elizabeth Allen

Statistician Site : London School of Hygiene and Tropical Medicine

Signature: _____ **Date:** _____

Summary / Synopsis

Short Title	PILOT STUDY for The Tight K TRIAL
Methodology	Non-inferiority single blind randomised controlled trial
Research Sites	Two NHS Trusts in the UK: <ul style="list-style-type: none"> • Barts Heart Centre • St George's Hospital
Objectives/Aims	<p>The primary objective in this pilot study is to determine whether the Tight K trial is feasible. The following criteria will be evaluated:</p> <ul style="list-style-type: none"> • At least 160 patients were randomised and this was acceptable to the patient • Protocol deviations did not occur in more than 10% of cases • Follow up rates are greater than 90% at 28 days from randomisation <p>The primary objective of the main trial will be to determine the effectiveness of maintaining serum potassium levels at $\geq 3.6\text{mEq/L}$ compared to normal treatment on the occurrence of new onset atrial fibrillation (AF) arrhythmia post-surgery in patients undergoing coronary artery bypass graft (CABG) surgery.</p> <p>Secondary objectives for the pilot study are to determine the feasibility of collecting data to assess the effectiveness of maintaining serum potassium levels at $\geq 3.6\text{mEq/L}$ compared to normal treatment:</p> <ul style="list-style-type: none"> • Mean critical care length of stay • Mean hospital length of stay • Incidence of new onset AF • Incidence of all other arrhythmias, defined using standard diagnostic criteria • Incidence of in-patient mortality • Incidence of mortality • Cost-effectiveness
Number of Participants/Patients	160 patients
Main Inclusion Criteria	Patients undergoing isolated elective CABG

Proposed Start Date	01/06/2017
Proposed End Date	30/11/2017 (End of recruitment) 31/12/2017 (End of follow up)
Study Duration	7 months

3. Introduction

3.1. Background and Scientific Rationale

Arrhythmias are common in critical care, with atrial tachyarrhythmias (and especially AF) being the most prevalent. This is especially true after cardiac surgery, with approximately 1 in 3 patients affected¹. The occurrence of new-onset post-operative AF is associated with increased short and long-term mortality^{2, 3}, intensive care unit (ICU) and hospital stay⁴ and costs of care⁵. This association appears causal, even after correction for confounding factors⁶.

Potassium plays an important role in cardiac electrophysiology⁷ and abnormal levels may cause arrhythmias. Hypokalaemia, defined as a serum K^+ $<3.6\text{mEq/L}$ ⁸ is thus associated with an increased incidence of ventricular arrhythmia after myocardial infarction⁹. Low K^+ levels are common following cardiac surgery¹⁰, and appear marginally lower in those suffering atrial arrhythmias in this context. Despite an absence of proof that this association is causal, efforts to maintain serum $[K^+]$ in the 'high-normal' range ($4.5 - 5.5 \text{ mEq/L}$) are considered 'routine practice' for AF prevention worldwide. The efficacy of such intervention remains unproven and data supporting this practice is extremely limited, being derived from observational rather than interventional studies¹¹. Indeed, no data exist to demonstrate that maintaining a high-normal potassium level is beneficial, or that aggressive replenishment of potassium in patients with heart disease necessarily leads to a better clinical outcome¹².

Furthermore, the method of potassium supplementation may be problematic. Oral replacement is not possible immediately post-operatively. Central venous administration is thus generally utilised in the early post-operative period. However, this practice is both time-consuming and costly: the intravenous administration of potassium carries recognised clinical risk, and is now prescribed in pre-diluted doses, stored securely for a safety purposes. Oral replacement is commonly associated with profound nausea, and is very poorly tolerated by patients¹³. We have estimated that the annual spending on potassium in cardiothoracic patients at Barts Health NHS Trust is £100,000, compared to £16,500 for Milrinone (perceived as a high cost drug (2011-2012 prices). Additional costs relating to nursing time, drug checks, and intravenous connection and charting are also accrued. Central venous catheters may also be routinely left *in situ* solely for the purposes of parenteral potassium replacement; leading to an increased risk of line-related sepsis¹⁴.

The routine maintenance of serum K^+ in the high-normal range is thus a costly and unproven practice.

4. Trial Objectives

4.1. Hypothesis

AF will be no more common (see below) after cardiac surgery when serum potassium levels are maintained ≥ 3.6 mEq/L ('Relaxed Control') than when they are maintained ≥ 4.5 mEq/L ('Tight Control').

4.2. Primary endpoint

The primary outcome measure of this pilot study will be feasibility. However, in order to further inform a full randomised controlled trial (RCT), information on the incidence of AF and other arrhythmias, length of hospital stay, resource use and morbidity will be collected.

4.2.1. Primary endpoints for pilot study:

- To investigate whether it is feasible to recruit 160 patients over a period of six months (20% of the eligible).
- To investigate whether it is possible to randomise patients into groups for potassium replacement if $K^+ < 4.5$ mEq/L (usual practice) vs. < 3.6 mEq/L (lower limit of 'normal range').
- To investigate whether it is feasible for the protocol violation rate to be no more than 10%.
- To investigate whether it is feasible to maintain follow up rates greater than 90% at 28 days from CABG.

4.2.2. Definition of AF

Atrial fibrillation will be defined as an episode of AF lasting ≥ 30 seconds that is clinically detected and/or electrocardiographically confirmed (on either a 12-lead electrocardiogram (ECG), telemetry or Holter monitoring¹⁵).

4.3. Secondary endpoints

Secondary objectives for the pilot study are to determine the feasibility of collecting data to assess the effectiveness of maintaining serum potassium levels at ≥ 3.6 mEq/L compared to normal treatment:

1. Incidence of new onset AF arrhythmia post-surgery until day 5. This is the primary endpoint for the main Tight K trial
2. Mean critical care length of stay
3. Mean hospital length of stay
4. Incidence of all other arrhythmias, defined using standard diagnostic criteria
5. Incidence of in-patient mortality
6. Incidence of mortality
7. Cost-effectiveness

5. Methodology

5.1. Inclusion criteria

1. All patients undergoing isolated elective CABG

5.2. Exclusion criteria

1. Age less than 18 years
2. Previous AF
3. Concurrent patient involvement in another clinical study assessing post-operative interventions
4. On-going infection/sepsis at the time of operation
5. Pre-op high-degree AV block
6. Pre-op serum K⁺ greater than 5.5 mEq/L
7. Current or previous use of medication for the purposes of cardiac rhythm management
8. Dialysis dependent end stage renal failure

5.3. Study Design / Plan – Study Visits

5.3.1. Patient Identification

Staff at the two hospitals will identify patients who are scheduled to have a CABG procedure from hospital waiting lists. If patients are having an isolated CABG procedure, their notes will be reviewed to confirm that they are eligible to participate. Research staff will approach patients prior to their scheduled hospital appointment via post, telephone or email to discuss the study.

5.3.2. Informed consent procedure

Patients will be given a copy of the patient information sheet (PIS) at a preoperative hospital appointment prior to their planned surgery date. At this appointment the PI or another delegated member of the research team will be available to discuss the study further and answer any questions the patient may have.

All patients will be given at least 24 hours to consider whether or not to take part in the study. If patients are willing take part they can consent at this visit or when they are admitted to hospital for their surgery. Written consent will be obtained on a consent form. A baseline health questionnaire (EQ-5D-5L) will be completed with the patient at this time.

5.3.3. Randomisation

Patients who have consented to take part will be allocated at random using an online database to receive either 'tight' or 'relaxed' potassium control. Where possible randomisation should occur on the day of the CABG.

5.3.4. Trial treatment

The trial treatment will start when patients are admitted to the intensive care unit after their surgery. The patient will undergo regular blood investigations, as per current practice. The frequency of K⁺ monitoring while on ICU or step down ward will be according to clinician / nursing staff preference.

Potassium supplementation will be according to local hospital protocols. This can be either via an intravenous infusion or as a tablet. Patients will otherwise be treated as per current hospital protocol.

The use of intravenous magnesium, beta-blockers and anti-arrhythmic agents will be as per current practice in both groups.

Patients will usually have their potassium levels and heart rhythm monitored for 5 days post-CABG. If they are discharged from intensive care or step down ward before this 5 days, they will no longer have their potassium or their heart rhythm monitored for the study.

5.3.4.1. Tight potassium control

Patients randomised to the 'Tight' group will receive K⁺ supplementation if their serum K⁺ falls below 4.5mEq/L (current practice).

5.3.4.2. Relaxed potassium control

Those randomised to the 'Relaxed' Group will receive K⁺ supplementation only if their serum K⁺ drops below or equals 3.6mEq/L.

5.3.5. Potassium supplementation

The administration route used for all K⁺ replacement will be prescribed according to clinician preference and given according to existing standardised protocols.

This supplementation may include IV or oral potassium prescription, administration of potassium-rich nasogastric feeding regimens or recommending the consumption of potassium-rich foods.

Once the primary endpoint has occurred K⁺ replacement and anti-arrhythmic agents can be administered according to physician preference.

5.3.6. Patients with AF

All episodes of AF lasting ≥30 seconds that are clinically detected and electrocardiographically confirmed will be recorded. These episodes may be recorded on a 12 lead ECG or telemetry. The duration of the episodes will be noted.

Once a patient has a period of AF then there will be no restriction on potassium supplementation and they should be treated according to current practice.

Potassium prescription according to the randomised allocation will be maintained if AF episodes are noted but shorter than 30 seconds.

5.3.7. Holter monitoring

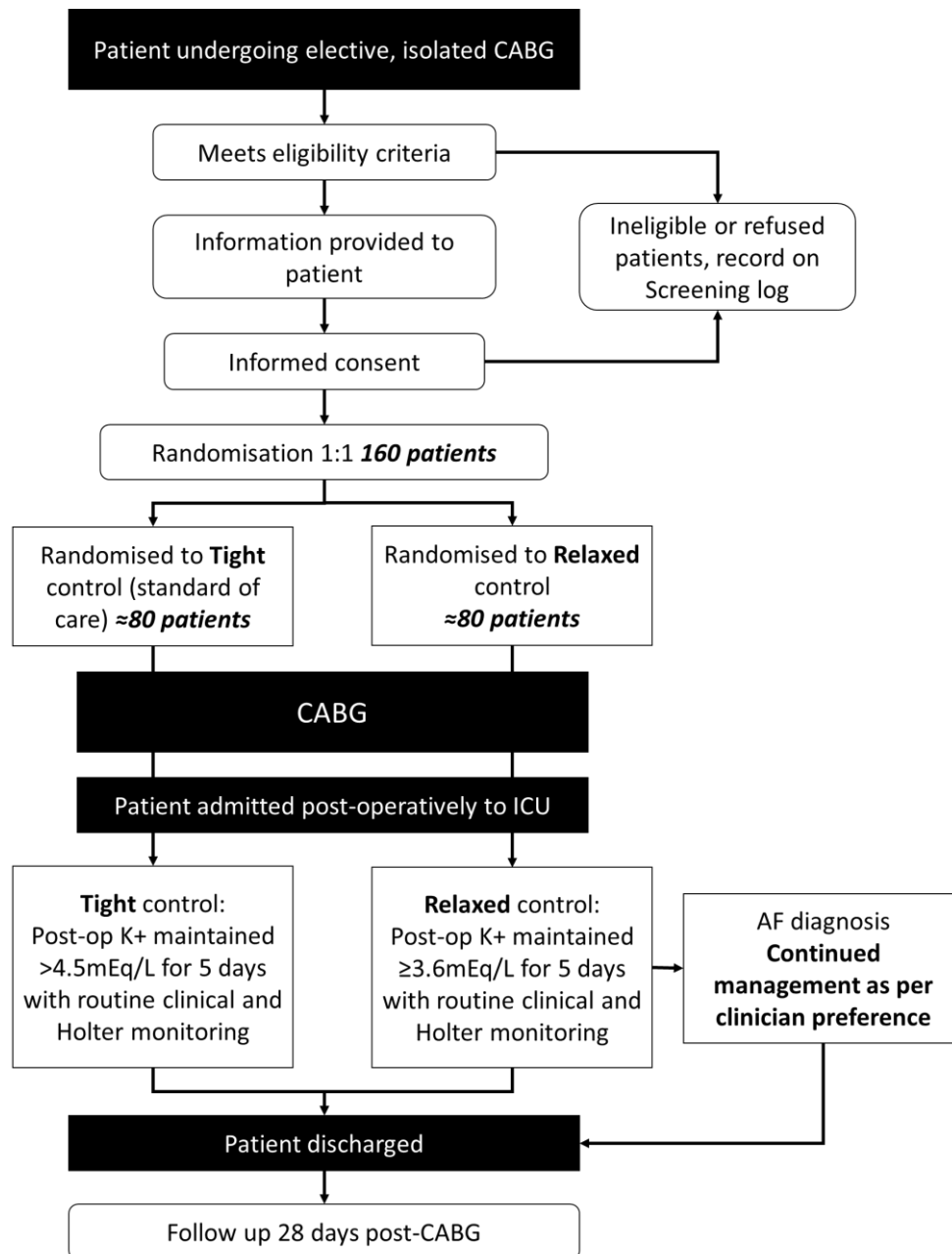
In addition to the normal care patients will also be asked to wear an external heart rhythm monitor for 5 days. This will monitor their heart rhythm for any irregular heart rhythms conditions such as AF.

Holter monitor data will be reviewed by Technomed Ltd. Reports which show ventricular tachycardia (VT), pause of over 30 seconds or coronary heart block (CHB) will be flagged with the research team. They will be reviewed by the lead research nurse and discussed further with the treating clinician for the patient.

5.3.8 Follow Up

All patients will be followed up 28 days after their surgery. An EQ-5D-5L questionnaire will be completed with the patient at this time. Patients will be asked to provide information about further incidences of AF and other heart rhythm problems after their hospital discharge if known.

5.4. Trial Flowchart



6. Study Procedures

6.1. Trial treatment period

The trial treatment period (Period 1) commences after surgery when the patient is admitted to ICU.

The patient's inclusion into the trial and randomised allocation must be clear upon admission to ICU.

Period 1 (0–24 Hr post admission to ICU)
Period 2 (24–48 Hr post admission to ICU)
Period 3 (48–72 Hr post admission to ICU)
Period 4 (72–96 Hr post admission to ICU)
Period 5 (96–120 Hr post admission to ICU)

6.2. Trial Procedures Table

	Before Surgery	Day of Surgery	ICU Stay (commences on admission to ICU)					After discharge 28 days post CABG
			Period 1 (0-24Hrs)	Period 2 (24-48Hrs)	Period 3 (48-72Hrs)	Period 4 (72-96Hrs)	Period 5 (96-120Hrs)	
Review of eligibility criteria	X							
History and examination	X							
PIS & Informed consent	X							
Randomisation		X						
Holter Monitoring			X	X	X	X	X	
'Relaxed' or 'Tight' K+ control			X	X	X	X	X	
Death			X	X	X	X	X	X
SAE / NSAEs			X	X	X	X	X	X
EQ-5D-5L	X							X

6.3. Data collection

The perceived clinical impact (symptomatic/asymptomatic) of an arrhythmia will be noted by the clinical staff. Patients in either group who experience AF (as defined in section 5.2.2) will be deemed to have met the primary end point.

Data collected for all patients will include measurements of daily serum electrolytes / renal function and collation of adverse events attributed to K⁺ replacement, including gastrointestinal symptoms from oral K⁺ replacement. Medication at hospital discharge will be collated, including whether warfarin is commenced for atrial fibrillation.

Detailed information will be collected on the resource use associated with delivering each protocol, including the total number of replacement K⁺ interventions and the number of tests for monitoring potassium levels.

All patients will have a full medical history taken and various clinical examinations as part of usual care. The following are to be recorded on the trial CRF:

- Patient initials
- Ethnic origin
- Cardiac medication and indication (including beta-blockers, calcium channel blockers, ACE-inhibitors, all blockers, aldosterone antagonists, anticoagulation)
- Medical history: arrhythmia (and details), chronic obstructive pulmonary disease (COPD)/lung disease, diabetes mellitus (and type), hypertension, myocardial infarction (MI), chronic kidney disease (CKD), transient ischaemic attack (TIA) or stroke / cerebrovascular accident (CVA)
- Imaging data: Left ventricular ejection fraction (LVEF) / left atrial (LA) size, mitral regurgitation or stenosis (defined as moderate or worse)
- HAS-BLED and CHADSVASC scores will be calculated for patients at baseline

6.4. Trial procedures

6.4.1. Before surgery

- Consent
- Quality of life questionnaire (EQ-5D-5L)

6.4.2. Period 1 (0Hr – 24Hr post admission to ICU)

- Potassium blood readings (measured as per clinician preference and local pathways)
- Potassium administration (dose and route)
- Clinically significant pacing modes
- Restenotomy

6.4.3. Period 2 (24-48 Hr post admission to ICU)

- Potassium blood readings (measured as per clinician preference and local pathways)
- Potassium administration (dose and route)
- Clinically significant pacing modes
- Restenotomy

6.4.4. Period 3 (48-72 Hr post admission to ICU)

- Potassium blood readings (measured as per clinician preference and local pathways)
- Potassium administration (dose and route)
- Clinically significant pacing modes
- Restenotomy

6.4.5. Period 4 (72-96 Hr post admission to ICU)

- Potassium blood readings (measured as per clinician preference and local pathways)
- Potassium administration (dose and route)
- Clinically significant pacing modes
- Restenotomy

6.4.6. Period 5 (96-120 Hr post admission to ICU)

- Potassium blood readings (measured as per clinician preference and local pathways)
- Potassium administration (dose and route)
- Clinically significant pacing modes
- Restenotomy

6.4.7. Discharge from ICU

- Length of stay

6.4.8. 28 days post-CABG

- Quality of life questionnaire (EQ-5D-5L)
- Clinical events

6.5. Compliance and loss to follow up

6.5.1. Loss to follow-up

The majority of patients remain in hospital for 5 days after CABG so loss to follow up over that period is unlikely.

The patients will subsequently be followed up at 28 days following CABG.

6.5.2. Compliance

Given that a large number of different health providers care for post-operative patients in different hospital locations, it is conceivable that protocol violations will occur. These violations may either result from a patient from the 'Relaxed' group being treated as if they are in the 'Tight' Group, or visa-versa.

It is more likely that protocol violations will occur once the patient leaves the Intensive Care Unit and arrives on the post-operative step down ward. These wards have lower staff-to-patient ratios and a higher turnover of staff members. It is critical for the

success of the trial that junior doctors and nursing staff in all the post-operative areas where patients may spend time are informed about the trial's goals and protocols. Patients as they are not blinded can also play a role in reminding staff which group they have been allocated to. The trial is not blinded to caregivers on the ICU/surgical ward so there is always a risk of concomitant treatment bias, but training will be put in place to minimise this.

7. Statistical Considerations

7.1. Power calculations and sample size determination

160 patients are to be recruited from 2 centres allocated in a ratio of 1:1.

As this is a pilot trial to assess feasibility, power calculations are not appropriate. If the anticipated recruitment, follow-up and retention rates are demonstrated over a 6 month recruitment period, this would confirm the feasibility of a 1770 patient multicentre randomised controlled trial with an estimated eligible cohort of 8700 patients over 3.5 years.

7.2. Trial statistician

Statistical analysis will be coordinated from the Clinical Trials Unit (CTU) at London School of Hygiene and Tropical Medicine (LSHTM).

7.3. Statistical analysis

Every effort will be made to obtain data for all patients.

The primary outcome measure of this pilot study will be feasibility in terms of numbers randomised, protocol fidelity, and follow up rates by trial arm. These statistics will inform a CONSORT diagram reporting recruitment, treatment and retention.

In order to further inform a full RCT, information on the incidence of AF and other arrhythmias, hospital length of stay, mortality and morbidity, and resource use will be collected during the patient's hospital stay.

Descriptive summaries of baseline and follow-up data by arm will be tabulated. No significance tests will be performed to test for differences at baseline, or given that this is a pilot study, at follow up. Descriptive statistics for continuous variables will include the mean, standard deviation, median, range and the number of observations. Categorical variables will be presented as numbers and percentages. Exploratory analysis for the main trial outcomes will be by intention to treat (ITT) and given the non-inferiority trial design, a per-protocol analysis will also be considered¹⁶. However given that this is a pilot study, no interpretation will be made of any effect sizes and findings will primarily be used to help refine the design of the full trial. This will include assessment of rates of missing data. However, no formal analysis to account for missing data will be undertaken in this pilot study.

Statistical analysis will be carried out blind to treatment allocation.

Further details will be provided in the statistical analysis plan.

8. Ethics

8.1. Withdrawal of patients

8.1.1. Criteria for withdrawal from the trial

A patient may decide to withdraw from the trial at any time without prejudice to their future care.

8.1.2. Follow up of patients withdrawing from the trial

Patients who withdraw will undergo standard clinical care. Patients will be encouraged to allow data and samples that have been collected before withdrawal to be used in the analyses. However, if consent to use data is also withdrawn, then these will be discarded. Patients withdrawing from the trial will continue to be followed up by their local clinical team. There should be no need for further follow up from the research team.

8.1.3. Reporting withdrawal of patients

The CTU at LSHTM should be informed by email if a patient has withdrawn from the trial. A withdrawal from will be completed on the trial eCRF.

8.2. Declaration of Helsinki and Good Clinical Practice

The study will conform to the spirit and the letter of the declaration of Helsinki, and in accordance with the Barts Health and LSHTM Good Clinical Practice Guidelines. The study will be carried out in accordance with the ethical principles in the Research Governance Framework for Health and Social Care, Second Edition, 2005 and its subsequent amendments as applicable and applicable legal and regulatory requirements.

8.3. Ethical committee review

NRES Committee London – Camden and Kings Cross have reviewed and approved the trial. The REC number is LO/17/0318. Copies of the letters of approval will be filed in the trial site files at each centre.

5.4 Confidentiality Advisory Group

Written consent will not be available for delegated members of the research team to access hospital notes for patients undergoing CABG surgery to screen them for eligibility. Permission has been granted by the Confidentiality Advisory Group (CAG) to allow notes to be screened and for staff to contact patients prior to a clinic appointment to inform them about the trial. The CAG reference number 17/CAG/0087.

9. Safety Considerations

9.1. Suspension of trial treatment in patients with AF

All episodes of AF lasting ≥ 30 seconds that are clinically detected and electrocardiographically confirmed will be recorded. These episodes may be recorded on a 12 lead ECG or telemetry. The duration of the episodes will be noted.

Once a patient has a period of AF then there will be no restriction on potassium supplementation and they should be treated according to current practice.

Potassium prescription according to the randomised allocation will be maintained if AF episodes are noted but shorter than 30 seconds.

10. Data Handling and Record Keeping

Data will be entered onto an online database and stored securely on Rackspace servers; <http://www.rackspace.co.uk> and managed by Sealed Envelope™. Data will be kept for 15 years following completion of the trial. The data controller for the trial is the Chief Investigator (Barts Health NHS Trust are the data controller's organisation) and the data processor is LSHTM.

Patient data will be kept confidential and managed in accordance with the Data Protection Act, NHS Caldecott principles, The Research Governance Framework for Health and Social Care, and the conditions of Research Ethics Committee Approval.

11. Holter Monitors

Recruiting sites will be supplied with holter monitors for use on the Tight K pilot study only. These will be worn by patients during the trial treatment period, up to 120 hours after the CABG.

11.1. How the holter monitors are worn

Three ECG electrodes are worn on the chest, on the right and left shoulders and on the chest. The holter monitor affixes to an ECG electrode. The holter monitors are approximately 13 grams in weight.

The patient will be able to carry out their normal activities with the holter monitor on, however care must be taken not to get the holter monitor wet.

If a site experiences any issues with the holter monitor, they should contact the Clinical Trials Unit.

11.2. Manufacturer

The holter monitors are manufactured by Mega Electronics Ltd, the model used for Tight K is the Faros 180. The Faros 180 is a medical CE cleared class IIa medical device.

Prior to use in the trial, holter monitors should be checked by the relevant department at the local site.

11.3. Supplier

The supplier of the holter monitors is Technomed Ltd.

12. Safety Reporting

12.1. Definition

Unexpected events that have not been defined as endpoints, expected complications of potassium supplementation or expected complications of usual clinical care should be reported as either an SAE or NSAE, depending on their severity. Safety reporting for each patient should commence from time of randomisation to completion of follow up at 28 days after the CABG procedure.

12.2. Expected adverse events

Please list expected adverse events of both arms of the trial treatment – these should be recorded on the CRF

- Skin irritation from ECG electrodes
- Hyperkalaemia ($K \geq 5.5\text{mEq/L}$)
- Line site complications (phlebitis, infection etc)
- Nausea, constipation, vomiting (in those receiving oral potassium supplementation)

12.3. Unexpected Serious Adverse Events

Any untoward medical occurrence/effect that:

1. Results in death
2. Is life-threatening*
3. Requires hospitalisation or prolongation of existing inpatient's hospitalisation
4. Results in persistent or significant disability or incapacity

*Life-threatening in the definition of a serious adverse event refers to an event in which the patient was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

SAEs should be reported to the CTU within 7 days. The report should include an assessment of causality by the Principal Investigator at each site (see section 13.6.2). The Chief Investigator will be responsible for the prompt notification of findings that could adversely affect the health of patients or impact on the conduct of the trial. Notification of confirmed **unexpected** and **related** SAEs will be to the Sponsor, the Research Ethics Committee and the Data and Safety Monitoring Committee (DSMC).

12.4. Unexpected Non-Serious Adverse Events

Unexpected non-serious adverse events should be evaluated by the PI or research nurse. This should include an assessment of causality (see section 14.6.2) and intensity (see section 14.6.1) and reports made within 14 days. The Clinical Trials Unit will keep detailed records of all unexpected adverse events reported. Reports will be reviewed by the CI to consider intensity, causality and expectedness. As appropriate these will be reported to the sponsor, the DSMC and the Ethics Committee.

12.5. Reporting unexpected adverse events

Investigators will make their reports of all unexpected adverse events, whether serious or not, to the CTU at LSHTM.

12.5.1. Assessment of intensity

Mild: The patient is aware of the event or symptom, but the event or symptom is easily tolerated.

Moderate: The patient experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.

Severe: Significant impairment of functioning; the patient is unable to carry out usual activities and/or the patient's life is at risk from the event.

12.5.2. Assessment of causality

Probable: A causal relationship is clinically / biologically highly plausible and there is a plausible time sequence between onset of the adverse event and the RIC procedure.

Possible: A causal relationship is clinically / biologically plausible and there is a plausible time sequence between onset of the adverse event and the RIC procedure.

Unlikely: A causal relationship is improbable and another documented cause of the adverse event is most plausible.

Unrelated: A causal relationship can definitely be excluded and another documented cause of the adverse event is most plausible.

12.6. Urgent Safety Measures

The CI may take urgent safety measures to ensure the safety and protection of the clinical trial patients from any immediate hazard to their health and safety. The measures should be taken immediately. In this instance, the approval of the REC prior to implementing these safety measures is not required. However, it is the responsibility of the CI to inform the sponsor and REC (via telephone) of this event immediately.

The CI has an obligation to inform both the REC in writing within 3 days, in the form of a substantial amendment. The sponsor (Joint Research Management Office [JRMO]) must be sent a copy of the correspondence with regards to this matter. For further guidance on this matter, please refer to National Research Ethics Service (NRES) website and JRMO SOPs.

12.7. Annual Safety Reporting

The CI will send an Annual Progress Report to the main REC using the NRES template (the anniversary date is the date on the REC “favourable opinion” letter from the REC) and to the sponsor. Please see NRES website and JRM0 SOP for further information

12.8. Overview of the Safety Reporting responsibilities

The CI/PI has the overall pharmacovigilance oversight responsibility. The CI/PI has a duty to ensure that safety monitoring and reporting is conducted in accordance with the sponsor’s requirements.

13. Monitoring and Auditing

13.1. Monitoring

The conduct of the trial will be supervised by trained staff from the LSHTM CTU. The trial will be monitored on a regular basis using central statistical monitoring. Full details will be available in the monitoring SOP and the trial will be monitored according to this agreed plan. Local investigators shall ensure that all trial data are available for trial related monitoring, audits and research ethics committee review.

14. Trial Committees

14.1. Trial Steering Committee (TSC)

The TSC will meet periodically. The TSC will be responsible for drafting the final report and submission for publication.

TSC membership to be confirmed

14.2. Project Management Group (PMG)

Dr Ben O’Brien (St Bartholomew’s Hospital)

Dr Julie Sanders (St Bartholomew’s Hospital)

Professor Diana Elbourne (London School of Hygiene and Tropical Medicine)

Professor Liz Allen (London School of Hygiene and Tropical Medicine)

Ms Joanna Sturgess (London School of Hygiene and Tropical Medicine)

Ms Rebecca Swinson (London School of Hygiene and Tropical Medicine)

Mrs Rosemary Knight (London School of Hygiene and Tropical Medicine)

14.3. Data Safety and Monitoring Committee (DSMC)

The Data Safety and Monitoring Committee will meet periodically to carefully monitor evidence for treatment harm.

DSMC membership to be confirmed

15. Finance and Funding

This trial is funded by the British Heart Foundation (BHF).

16. Indemnity

16.1. Sponsorship

This trial is sponsored by Barts Health NHS trust.

16.2. Insurance

All recruiting centres will be covered by NHS indemnity for negligent harm providing researchers hold a contract of employment with the NHS, including honorary contracts held by academic staff. Medical co-investigators will also be covered by their own medical defence insurance for non-negligent harm.

16.3. Holter monitors

The Mega Faros 180 holter monitors are covered by Technomed Ltd for public and product indemnity. Technomed is registered with the Department of Health under the Master Indemnity Agreement (MIA) reference number DHMIA1521/16.

17. Dissemination of Research Findings

It is our intention to disseminate the results of the trial as widely as possible. This is likely to be through a publication in a peer reviewed journal. Publications will follow the CONSORT guidelines. Authorship will follow international guidelines.

18. References

1. Amar D, Shi W, Hogue Jr CW, Zhang H, Passman RS, Thomas B, Bach PB, Damiano R, Thaler HT. Clinical prediction rule for atrial fibrillation after coronary artery bypass grafting. *Journal of the American College of Cardiology*. 2004;44:1248-1253
2. Kaw R, Hernandez AV, Masood I, Gillinov AM, Saliba W, Blackstone EH. Short- and long-term mortality associated with new-onset atrial fibrillation after coronary artery bypass grafting: A systematic review and meta-analysis. *The Journal of thoracic and cardiovascular surgery*. 2011;141:1305-1312
3. Mariscalco G, Engström KG. Postoperative atrial fibrillation is associated with late mortality after coronary surgery, but not after valvular surgery. *The Annals of Thoracic Surgery*. 2009;88:1871-1876
4. Sanders J, Keogh BE, Van der Meulen J, Browne JP, Treasure T, Mythen MG, Montgomery HE. The development of a postoperative morbidity score to assess total morbidity burden after cardiac surgery. *Journal of clinical epidemiology*. 2012;65:423-433
5. Zimmer J, Pezzullo J, Choucrair W, Southard J, Kokkinos P, Karasik P, Greenberg MD, Singh SN. Meta-analysis of antiarrhythmic therapy in the prevention of postoperative atrial fibrillation and the effect on hospital length of stay, costs, cerebrovascular accidents, and mortality in patients undergoing cardiac surgery. *The American journal of cardiology*. 2003;91:1137-1140
6. Borzak S, Tisdale JE, Amin NB, Goldberg AD, Frank D, Padhi ID, Higgins RS. Atrial fibrillation after bypass surgery: Does the arrhythmia or the characteristics of the patients prolong hospital stay? *Chest*. 1998;113:1489-1491
7. Podrid PJ. Potassium and ventricular arrhythmias. *Am J Cardiol*. 1990;65:33E-44E; discussion 52E
8. 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;160:2429-2436
9. Nordrehaug JE, Johannessen KA, von der Lippe G. Serum potassium concentration as a risk factor of ventricular arrhythmias early in acute myocardial infarction. *Circulation*. 1985;71:645-649
10. Polderman KH, Girbes AR. Severe electrolyte disorders following cardiac surgery: A prospective controlled observational study. *Crit Care*. 2004;8:R459-466
11. NICOR NfCOR-. National adult cardiac surgery audit annual report 2010-2011. Downloaded from <http://www.ucl.ac.uk/nicor/audits/Adultcardiacsurgery> on 8th February 2015.
12. Arsenault KA, Yusuf AM, Crystal E, Healey JS, Morillo CA, Nair GM, Whitlock RP. Interventions for preventing post-operative atrial fibrillation in patients undergoing heart surgery. *Cochrane Database of Systematic Reviews*. 2013
13. Norris W, Kunzelman KS, Bussell S, Rohweder L, Cochran RP. Potassium supplementation, diet vs pills*. *Chest*. 2004;125:404-409

14. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients. Excess length of stay, extra costs, and attributable mortality. *JAMA : the journal of the American Medical Association*. 1994;271:1598-1601
15. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, Crijns HJ, Damiano RJ, Jr., Davies DW, DiMarco J, Edgerton J, Ellenbogen K, Ezekowitz MD, Haines DE, Haissaguerre M, Hindricks G, Iesaka Y, Jackman W, Jalife J, Jais P, Kalman J, Keane D, Kim YH, Kirchhof P, Klein G, Kottkamp H, Kumagai K, Lindsay BD, Mansour M, Marchlinski FE, McCarthy PM, Mont JL, Morady F, Nademanee K, Nakagawa H, Natale A, Nattel S, Packer DL, Pappone C, Prystowsky E, Raviele A, Reddy V, Ruskin JN, Shemin RJ, Tsao HM, Wilber D. 2012 hrs/ehra/ecas expert consensus statement on catheter and surgical ablation of atrial fibrillation: Recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: A report of the heart rhythm society (hrs) task force on catheter and surgical ablation of atrial fibrillation. Developed in partnership with the european heart rhythm association (ehra), a registered branch of the european society of cardiology (esc) and the european cardiac arrhythmia society (ecas); and in collaboration with the american college of cardiology (acc), american heart association (aha), the asia pacific heart rhythm society (aphrs), and the society of thoracic surgeons (sts). Endorsed by the governing bodies of the american college of cardiology foundation, the american heart association, the european cardiac arrhythmia society, the european heart rhythm association, the society of thoracic surgeons, the asia pacific heart rhythm society, and the heart rhythm society. *Heart rhythm : the official journal of the Heart Rhythm Society*. 2012;9:632-696 e621
16. Piaggio G ED, Pocock SJ, Evans SJW, Altman DG, for the CONSORT Group. . Reporting of noninferiority and equivalence randomized trials. Extension of the consort 2010 statement. . *JAMA*. 2012;308:2594-2604