Preoperative NT-proBNP and Perioperative Angiotensin II Converting Enzyme inhibitors and/or receptor blockers in major non-cardiac surgery (SPACE-BNP): prespecified analysis of SPACE randomised controlled trial

Statistical Analysis Plan

Version 1.0
Date: 01/05/2023

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1. Administrative information

Trial Information

REC number:	16/LO/1495
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Members of the writing committee
Akshaykumar Patel (AP) and Tom Abbott (TA) wrote the statistical analysis plan, with input from Gareth Ackland (GA).

Timing of the SAP
Version 1.0 of the SAP was written after AP had access to unblinded data (i.e. trial dataset with the variables for treatment allocation included). Note that all contributors are blinded to the primary outcome as samples will be processed by an independent laboratory at the end of the trial (defined as when the last patient leaves hospital).

Remit of the SAP
The purpose of this document is to provide details of the statistical analyses and presentation of results to be reported for the SPACE-BNP substudy of the main SPACE trial. It is important to set these out and to agree them in advance of inspecting the outcome data for the trial, so that data derived decisions in the analysis are avoided. Any exploratory, post hoc or unplanned analysis will be clearly identified as such in the respective study analysis report. This SAP does not include in its remit the health economic analysis which will be planned in a separate document.

2. Background and trial design

Study objectives	**Primary Objective** To determine the relationship between preoperative NT-proBNP levels and the risk of myocardial injury when angiotensin converting enzyme inhibitor (ACE-I) and/or Angiotensin II receptor blockers (ARB) are either stopped or continued before major surgery, identified using high-sensitivity plasma troponin measurement during the first 48 hours after surgery. **Secondary Objectives** To determine whether preoperative NT-proBNP levels are related to the risk of postoperative morbidity, depending on management of ACE-I and/or ARB.
Study design	Phase II, multi-centre, two-arm, parallel group randomised controlled trial
Setting	Surgical services of hospitals undertaking major elective surgery
Participants	**Inclusion criteria** • Informed consent (no incapacitated or vulnerable adult or minors will be included) • Age 60 years and over • Undergoing major surgery (e.g. major joint replacement or vascular or gastrointestinal) requiring general and/or regional anaesthesia with sedation • Currently taking ACE-I or combined ACE-I and ARB therapy or combination therapy where medication includes ACE-I or ARB • Expected duration of surgery longer than 120 minutes • American Society of Anaesthesiologists physical status grade 3 or above • All female subjects must be postmenopausal, as demonstrated by clinical history, or demonstrated not to be pregnant through a preoperative pregnancy test **Exclusion criteria** • Current participation in any other trials where care or treatment is being altered • Recent myocardial infarction (within 3 months) • Any condition, which in the opinion of the treating clinician, would result in the patient being harmed by the cessation of the ACE-I and/or ARB therapy.
Interventions	**Continue Group** Patients in the continue group will continue with their ACE-I and/or ARB 72 hours prior to the day of surgery and continue for at least 48 hours after surgery. **Stop Group**

	Patients in the stop group will stop their ACE-I and/or ARB [according to half-life of each individual drug] prior to the day of surgery through to at least 48 hours after surgery.
Primary outcome measure	The primary outcome is myocardial injury, a binary variable based on plasma high sensitivity Troponin-T measured in blood samples collected immediately before the induction of anaesthesia, and then postoperative day 1± 6 hours and day 2 ± 6 hours. The primary outcome is met under the following conditions: • Troponin-T ≥15 ng/L within 48 hours after surgery with a pre-operative value <15 ng/L *OR* • Troponin-T increase ≥5 ng/L within 48 hours after surgery with a pre-operative value ≥15ng/L

3. Outcome measures

Primary outcome measure

The primary outcome is myocardial injury, a binary variable based on plasma high sensitivity Troponin-T) measured in blood samples collected immediately before the induction of anaesthesia, and then postoperative day 1± 6 hours and day 2 ± 6 hours after surgery. The primary outcome is met under the following conditions:

- Troponin-T ≥15 ng/L within 48 hours after surgery with a pre-operative value <15 ng/L *OR*
- Troponin-T increase ≥5 ng/L within 48 hours after surgery with a pre-operative value ≥15ng/L

Exposure variables

Patients with preoperative NT-proBNP >100 pg/Ml define a substantially higher risk perioperative population. From VISION, in multivariable analyses using a reference group defined by NT-proBNP <100 pg/mL, NT-proBNP measurements of 100 to less than 200 pg/mL had an adjusted hazard ratio (HR) of vascular death or MINS of 2.27 (95% CI, 1.90 to 2.70) and an incidence of 12.3% (226 of 1843), 200 to less than 1500 pg/mL had an adjusted HR of 3.63 (CI, 3.13 to 4.21) and an incidence of 20.8% (542 of 2608), and 1500 pg/mL or greater had an adjusted HR of 5.82 (CI, 4.81 to 7.05) and an incidence of 37.5% (223 of 595).

This analysis will have two principal exposure variables: (1) NT-proBNP, a binary variable, dichotomised according to a threshold of 100 pg/ml; and (2) ACE-I/ARB, a binary categorical variable defined by intention-to-treat allocation of stop or continue status.

4. Sample size and randomisation

Sample size calculation

Assuming incidence of postoperative myocardial injury of 50% in patients undergoing major surgery in the cessation group, a sample size of 248 patients will provide 90% power to detect as statistically significant ($p<0.05$) an 20% absolute risk reduction to 30% [1, 2]. Allowing for 5% withdrawal/loss to follow up, we will aim to recruit a total of 260 patients.

Randomisation procedure

Randomisation will occur after the participant has provided informed consent 72 hours before the surgical procedure is due to start. Participants are randomised to a treatment group in a 1:1 ratio using a computer-generated dynamic procedure (minimisation) with a random component. Minimisation variables are trial centre, surgical procedure category (surgery involving the gut and all other surgery) and ACE-I and/or ARB category. Each participant will be allocated with 80% probability to the treatment group that minimises between group differences in these factors among all participants recruited to the trial to date, and to the alternative group with 20% probability. To enter a patient into the SPACE trial, research staff at the site will log on to a secure web-based randomisation and data entry platform hosted by Queen Mary University of London and complete the patient's details to obtain a unique patient identification number and allocation to a treatment group. A patient's treatment group allocation will only be revealed to the person performing randomisation.

5. Analysis methods

General analysis principles

Analyses will follow the intention-to-treat principle: all randomised patients with a recorded outcome will be included in the analysis and analysed according to the treatment to which they were randomised [3, 4]. Patients will be included in the analysis, regardless of whether the treatment they received was compliant with the protocol. Definitions of what constitutes a recorded outcome for each outcome can be found in Appendix 1. Patients with missing outcome data will be excluded from the analysis. Missing data for baseline covariates to be included in the analysis model will be accounted for using mean imputation for continuous variables and the missing indicator approach will be used for missing data for categorical variables [5, 6].

For the analysis of the primary outcome, each secondary outcome, and all process measures, we will present the following information:

- The number of patients included in each analysis, by treatment group
- A summary statistic of the outcome (e.g. mean (SD), number (%)), by treatment group
- The estimated treatment effect
- A 95% confidence interval for the estimated treatment effect
- A two-sided p-value

For all analyses, a significance level of 5% will be used.

Analysis software

All analyses will be conducted in Stata Version 17 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC.).

Baseline characteristics

Baseline characteristics will be summarised for each treatment group by the mean and standard deviation or median and interquartile range for continuous variables, and the number and percent for categorical variables. The following baseline characteristics will be summarised by NT-proBNP:

- Demographic: age (years), gender (male/female)
- Co-morbid disease: (a) COPD; (b) asthma; (c) interstitial lung disease or pulmonary fibrosis; (d) ischaemic heart disease; (e) diabetes mellitus; (f) heart failure; (g) liver cirrhosis; (h) active cancer; (i) previous stoke or TIA; (j) peripheral vascular disease; (k) Hypertension; (l) any treated infections within the previous month
- Current smoker
- ASA grade (III/IV)
- Pre-operative blood test results (within 4 weeks before surgery or most recent): (a) haemoglobin (g/L); (b) creatinine (µmol/L)
- Minimisation criteria:
    - Planned surgical procedure: (a) surgery involving the gut; (b) all other surgery
    - Class of drug routinely taken: (a) ACE-I; (b) ARB
    - Trial centre: (a) County Durham and Darlington NHS foundation trust; (b) Plymouth hospitals NHS trust; (c) Barts Health NHS trust; (d) University college London hospitals; (e) University hospitals Bristol NHS foundation trust
- Surgical procedure performed: (a) surgery involving the gut; (b) all other surgery
- Cardiovascular medication: (a) beta-blocker; (b) calcium channel antagonist; (c) Doxazosin; (d) Diuretic; (e) Statin; (f) Nitrate; (g) Anti-platelet agents (h) ACE-I/ARB drugs

Analysis of primary outcome

Primary analysis

The analysis of the primary outcome will be analysed including an interaction term between treatment allocation and the subgroup of interest into the model which is NT-proBNP, a binary variable, dichotomised according to a threshold of 100 pg/ml. The primary outcome, myocardial injury within 48 hours after surgery, will be analysed using a mixed-effect logistic regression model, with a random intercept for the minimisation variable trial centre [7]. The model will be adjusted for minimisation variables as fixed factors which are planned surgical procedure ((a) surgery involving the gut; (b) all other surgery) and class of drug routinely taken ((a) ACE-I; (b) ARB) [8]. The model will also be adjusted for the following pre-specified baseline covariates [9-11]: age and gender (M/F). All covariates will be entered into the model as fixed factors. Age will be included as a continuous variable, assuming a linear association with the outcome [12].

Subgroup analysis will include all participants with complete outcome data and with complete data for the subgroup variable. The presence of an interaction will be tested using a Wald test assessing the interaction terms. The test will be considered significant if $p<0.05$, i.e. at the 5% level. Within each category, we will report summary statistics of the outcomes by treatment group, and a treatment effect and 95% confidence interval. A p-value of the interaction test will also be reported.

When participants are randomised according to incorrect baseline information, under the ITT principle they should be analysed in their allocated treatment group, irrespective of the fact that their allocation was based on incorrect information. The incorrect baseline information should be kept in the randomisation record, as this reflects how the randomisation was performed, and the correct information documented for use in an adjusted analysis [13].

Analysis of secondary outcomes

Peak level of Troponin-T measured within 48 hours of surgery

This outcome will be analysed including an interaction term between treatment allocation and the subgroup of interest into the model which is NT-proBNP, a binary variable, dichotomised according to a threshold of 100 pg/ml. Within each category, we will report summary statistics of the outcomes by treatment group, and a treatment effect and 95% confidence interval. Differences between the groups in the mean peak level troponin-t will be analysed using multilevel linear regression – adjusted for the same baseline variables as the adjusted analysis of the primary outcome. We will also adjust for baseline pre-operative Troponin-T as a continuous variable.

Infection within 30 days of surgery

This outcome will be analysed including an interaction term between treatment allocation and the subgroup of interest into the model which is NT-proBNP, a binary variable, dichotomised according to a threshold of 100 pg/ml. Within each category, we will report summary statistics of the outcomes by treatment group, and a treatment effect and 95% confidence interval. Infection within 30 days of surgery will be analysed using a mixed-effect logistic regression model with a random intercept for the minimisation variable trial centre. The model will be adjusted for minimisation variables planned surgical procedure ((a) surgery involving the gut; (b) all other surgery) and class of drug routinely taken ((a) ACE-I; (b) ARB). The expected event rate for this outcome is low, and as such we have reduced the number of covariates included in the model to avoid over-stratification. We will consider the following subgroup which is NT-proBNP, a binary variable, dichotomised according to a threshold of 100 pg/ml.

Strategy for analysis of primary and secondary outcomes if model fails to converge

If the statistical models for any of the primary or secondary outcomes do not converge, then the following steps will be taken:

1. The model will be fitted without a random intercept for trial centre
2. As above, but excluding any additional covariates apart from minimisation variables
3. As above, but also excluding minimisation variables.

Plan in case of over-stratification

When adjusting for covariates in the primary analysis or secondary analysis models where the outcome is binary, if there is a category within that covariate where no events have occurred in either of the treatment groups, the statistical model will exclude all patients within this category. To overcome this, this category will be merged with another category; this will be decided by the chief investigator who will be blinded to results. This will apply to covariates with three or more categories. However, if all but one category within that covariate have no events recorded in one of the treatment groups then we will exclude this covariate from the model.

6. Other analyses, data summaries and graphs

NT-proBNP

NT-proBNP will be summarised but not subjected to statistical testing. Numbers (%)will be provided. The categories will be as described as per the definition of the exposure variable: <100 pg/mL, 100-<200 pg/mL, 200-<1500 pg/mL and >=1500 pg/mL.

References

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