TITLE (SHORT, 200 CHARACTERS MAX.):

IMPACT OF BETA-ADRENERGIC BLOCKADE ON OOHCA OUTCOME

MAIN HYPOTHESES TESTED (2 MAX)

Beta-blockers (BB) are commonly prescribed drugs in the out-of-hospital cardiac arrest (OOHCA) population. The evidence for an effect of prior BB use on outcomes from OOHCA is conflicting, with some studies showing no benefit and others demonstrating better survival after both shockable and non-shockable rhythms. One shows post-resuscitation use of BB to be associated with survival. There is also some evidence that adrenaline use during OOHCA is associated with an adverse effect on long term prognosis. However, there is a preponderance of retrospective data from limited populations some over 20 years old. Up to date prospective data from a wide and representative patient population is required.

There is a close relationship between ischaemia-reperfusion injury, sympathoadrenal activation, endothelial injury and the severity of the post-cardiac arrest syndrome which is predictive of mortality after OOHCA. There is a strong case that endothelial dysfunction is the hallmark of critical illness. Chronic use of BB improves endothelial function. Acute use of BB may reduce sympathoadrenal drive and mitigate endothelial injury associated with ischaemia-reperfusion. This may account for potential benefit of BB use in septic shock, subarachnoid haemorrhage or severe traumatic brain injury.

It is possible that both chronic and early acute BB use are protective after OOHCA, with effects mediated through reduction in sympathetic drive and modulation of endothelial injury and inflammation. Only one prospective trial is investigating BB in OOHCA. A pilot study in Vienna (planned n=32) is recruiting adults with refractory VF, defined as 3 or more shockable rhythms, to landiolol bolus or placebo with a primary outcome of time to sustained ROSC (ClinicalTrials.gov Identifier: NCT05554978). No other trials are registered to fill this knowledge gap.

1. Hypothesis: beta-adrenergic blockade before and/or early (<72h) after OOHCA is associated with better patient centred outcomes (mortality, mRS, QoL) at 6 months
2. Hypothesis: beta-adrenergic blockade before and/or early (<72h) after OOHCA is associated with reduction in endothelial injury

MULTICENTER [X]

<Site 1> Clinical: all centres

<Site 2> Mechanistic: subset of centres (biomarker substudy)

PICO

Patients: All patients in Stepcare

Intervention/Exposure/Prognostic factor:

- beta-blocker exposure in 7 days prior to OOHCA
- beta-blocker exposure in 72 hours following OOHCA

Comparison: no beta-blocker exposure

Outcome: clinical: all cause 6 month mortality, 6 month mRS, 6 month EQ-5D-5L; mechanistic: biomarkers of endothelial injury

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DATA NEEDED FOR THE ANALYSIS (SPECIFY VARIABLES AND MOTIVATE ANY PROPOSED ADDITIONS TO THE ECRF)

Additional data

8.1 Baseline: ethnicity*, BB** use in 7 days prior to arrest [Y/N], if Y drug and prescribed dose

8.3.1 0-72h: BB use during first 72 hours in ICU [Y/N], if Y drug(s) and dose(s) administered

8.3.2 Daily ICU stay: at 7d BB use in ICU [Y/N], if Y drug(s) and dose(s) administered

8.8.1 Biomarker sub- study: no additional samples, analyses to include thrombomodulin, sE-selectin, syndecan-1, soluble VEGF and VE-cadherin

*not specific to BB substudy but suggested given known but not completely explained association of ethnicity with outcome from OOHCA

**BB defined as any drug with any b1, b2 or b3 antagonism given by intravenous or enteral routes to include drugs with additional actions at other adrenergic receptors (e.g. labetalol) and drugs with additional modes of action (e.g. sotalol)

LOGISTICS – HOW WILL ADDITIONAL DATA BE GATHERED?

Source data: medical notes entered to eCRF, biomarker analysis as per appendix A

BRIEF STATISTICAL ANALYSIS PLAN AND SAMPLE SIZE ESTIMATE

<text>

FUNDING (IF APPLICBABLE)

None

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