TITLE (SHORT, 200 CHARACTERS MAX.):

THE IMPACT OF TIME OF OHCA ON MORTALITY AND NEUROLOGICAL OUTCOME

MAIN HYPOTHESES TESTED (2 MAX)

The aim of this sub-study is to better understand the influence of time of witnessed OHCA on mortality and neurological outcomes.

Diurnal differences in outcomes following OHCA may be secondary to circadian rhythm, patient characteristics or processes of care. Circadian rhythm is defined as cyclical changes in physiology throughout the day. Variations in physiology which predispose to a morning peak in ischaemic and thromboembolic events.

Previous studies have demonstrated a night time nadir and morning peak in the incidence of OHCA (Soo, Heart, 2000. Brooks, Resuscitation 2010). Outcomes are typically worst overnight, though, this may be driven by higher rates of unwitnessed OHCA or longer ambulance response times out of hours. Similar diurnal variation exists in both the incidence and outcomes following in-hospital cardiac arrest. However, it is unclear whether poorer outcomes at night are due to hospital organizational factors or patient chacteristics (McGuigan, Resuscitation 2023).

Presentation with non-fatal acute myocardial infarction (Nagarajan, American Heart Journal, 2017. Cohen, Am J Cardiol. 1997), malignant ventricular arrhythmias detected by internal cardiac defibrillators (Patton Journal of the American College of Cardiology, 2014. Mallavarapu The American Journal of Cardiology. 1995) and stroke (Elliott Stroke. 1998) all demonstrate diurnal variation. These pathologies are unlikely to be affected by processed of care. Consequently, doubt remains as to the impact of circadian biology on presentation and outcomes following cardiac arrest.

Specifically, the hypothesis is:

In adults who suffer a *witnessed* OHCA, presenting rhythm, mortality and neurological outcome varies based on hour in which the OHCA occurred.

This relationship will be consistent for the following presumed cause of cardiac arrest:

- ST-elevation myocardial infarction / acute coronary occlusion
- non-ST elevation myocardial infarction
- Arrhythmia – not related to acute ischemia
- Pulmonary Embolism

This relationship will be present in a sub-group of patients with an ICD in situ at baseline.

SINGLE CENTER [ ], MULTICENTER [X]

Analysis of entire STEP-CARE database.

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Patients:

All witnessed OHCA recruited to the STEP-CARE study.

Intervention/Exposure/Prognostic factor:

Time of OHCA.

Results will be stratified based on presenting rhythm:

- Asystole
- PEA
- VF, non-perfusing VT, ROSC after bystander defibrillation, unknown (shockable)
- Unknown (non-shockable)

Comparison:

The hour with the lowest mortality will act as the reference point for comparison.

Outcome:

Primary Outcome measure:

1. Mortality at 6 months.

Secondary Outcome measures:

2. Neurological outcome at 6 months.

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

Nil additional. All relevant data will be captured in the current eCRF.

LOGISTICS – HOW WILL ADDITIONAL DATA BE GATHERED?

In current eCRF.

BRIEF STATISTICAL ANALYSIS PLAN AND SAMPLE SIZE ESTIMATE

A detailed Statistical Analysis Plan will be written, agreed with a statistician and made openly available prior to undertaking analysis. Baseline characteristics, follow-up measurements and safety data will be described using the appropriate descriptive summary measures as per the STEP-CARE protocol.

FUNDING (IF APPLICBABLE)

Not applicable.

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In alphabetical order:

References

1. Soo LH, Gray D, Young T, Hampton JR. Circadian variation in witnessed out of hospital cardiac arrest. Heart. 2000;84:370–6.

2. Brooks SC, Schmicker RH, Rea TD, et al. Out-of-hospital cardiac arrest frequency and survival: Evidence for temporal variability. Resuscitation. 2010;81:175–81.

3. McGuigan PJ, Edwards J, Blackwood B, et al. The association between time of in hospital cardiac arrest and mortality; a retrospective analysis of two UK databases. *Resuscitation*. 2023;186:109750.

4. Cohen MC, Rohtla KM, Lavery CE, Muller JE, Mittleman MA. Meta-analysis of the morning excess of acute myocardial infarction and sudden cardiac death. Am J Cardiol. 1997;79:1512–6.

5. Nagarajan V, Fonarow GC, Ju C, et al. Seasonal and circadian variations of acute myocardial infarction: Findings from the Get With The Guidelines–Coronary Artery Disease (GWTG-CAD) program. American Heart Journal. 2017;189:85–93.

6. Patton KK, Hellkamp AS, Lee KL, et al. Unexpected Deviation in Circadian Variation of Ventricular Arrhythmias. Journal of the American College of Cardiology. 2014;63:2702–8.

7. Mallavarapu C, Pancholy S, Schwartzman D, et al. Circadian variation of ventricular arrhythmia recurrences after cardioverter-defibrillator implantation in patients with healed myocardial infarcts. The American Journal of Cardiology. 1995;75:1140–4.

8. Elliott WJ. Circadian Variation in the Timing of Stroke Onset. Stroke. 1998;29:992–6.

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