1 **TITLE:**

2 **Long term outcomes of participants in the PARAMEDIC2 randomised trial of adrenaline in out-of-**
3 **hospital cardiac arrest.**

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44   **Abstract**

45   Aims:

46   We recently reported early outcomes in patients enrolled in a randomised trial of adrenaline in out-
47   of-hospital cardiac arrest: the PARAMEDIC2 (Prehospital Assessment of the Role of Adrenaline:
48   Measuring the Effectiveness of Drug Administration in Cardiac Arrest) trial. The purpose of the present
49   paper is to report long-term survival, quality of life, functional and cognitive outcomes at 3, 6 and 12-
50   months.

51   Methods:

52   PARAMEDIC2 was a pragmatic, individually randomised, double blind, controlled trial with an
53   economic evaluation. Patients were randomised to either adrenaline or placebo. This paper reports
54   results on the modified Rankin Scale scores at 6-months, survival at 6 and 12-months, as well as
55   other cognitive, functional and quality of life outcomes collected at 3 and 6 months (Two Simple
56   Questions, the Mini Mental State Examination, the Informant Questionnaire on Cognitive Decline
57   Evaluation for Cardiac Arrest, Hospital Anxiety and Depression Scale, the Post Traumatic Stress
58   Disorder Checklist - Civilian Version, Short-Form 12-item Health Survey and the EuroQoL EQ-5D-5L).

59   Results:

60   8,014 patients were randomised with confirmed trial drug administration. At 6-months, 78 (2.0%) of
61   the patients in the adrenaline group and 58 (1.5%) of patients in the placebo group had a favourable
62   neurological outcome (adjusted odds ratio 1.35 [95% confidence interval: 0.93, 1.97]). 117 (2.9%)
63   patients were alive at 6-months in the adrenaline group compared with 86 (2.2%) in the placebo
64   group (1.43 [1.05, 1.96], reducing to 107 (2.7%) and 80 (2.0%) respectively at 12-months (1.38 [1.00,
65   1.92]). Measures of 3 and 6-month cognitive, functional and quality of life outcomes were reduced,
66   but there was no strong evidence of differences between groups.
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68   Conclusion:

69   Adrenaline improved survival through to 12-months follow-up. The study did not find evidence of
70   improvements in favourable neurological outcomes. (ISCRTN 73485024)

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Introduction

The goal of attempted resuscitation from out-of-hospital cardiac arrest (OHCA) is not just achieving return of spontaneous circulation (ROSC) but, importantly, returning the patient to their pre-event cognitive and functional state.[1, 2]

Most randomised trials and other studies in OHCA have reported short-term outcomes such as ROSC and survival to hospital discharge.[3] Where outcomes have been reported, these have focused largely on Cerebral Performance Category (CPC) and modified Rankin Scale (mRS), but these are insensitive to cognitive impairments such as memory loss and post-traumatic stress disorder (PTSD), and to longer-term functional impairments experienced by OHCA survivors.[4]

Adrenaline has been a mainstay of treatment for OHCA for half a century, but until recently its effects on OHCA patients have been evaluated predominantly through observational studies rather than randomised trials.[5] Two meta-analyses including one randomised trial and 18 observational studies reported better short-term survival with adrenaline, and either no difference or worse long term survival and functional outcomes in patients who received adrenaline.[6, 7]

We recently reported early survival outcomes in patients enrolled in a randomised controlled trial of adrenaline in OHCA: the PARAMEDIC2 (Prehospital Assessment of the Role of Adrenaline: Measuring the Effectiveness of Drug Administration in Cardiac Arrest) trial.[8] The purpose of the present paper is to report longer term survival, quality of life and neurocognitive outcomes in cardiac arrest patients who survived.

Methods

PARAMEDIC2 was a pragmatic, individually randomised, double blind, controlled trial with an economic evaluation. The trial protocol has been published previously.[5] In summary, patients were eligible if they were in OHCA and advanced life support was initiated. The trial ran from December 2014 through October 2017 in five National Health Service ambulance services in England and Wales, serving 24 million people in both urban and rural locations.

Patients were randomised to either adrenaline (intervention) or placebo (control). Randomisation occurred when the trial pack (containing prefilled syringes with adrenaline or placebo) had been opened. The primary outcome was survival to 30 days and secondary outcomes included survival, health-related quality of life (HRQoL), functional and cognitive outcomes at 3, 6 and 12-months.

Outcome assessment

Long-term survival status was assessed at 6 and 12-months post randomisation. The other outcomes collected at follow-up (3 and 6-months) included the modified Rankin Scale (mRS), 'Two Simple Questions' (TSQ), the Mini Mental State Examination (MMSE), the Informant Questionnaire on Cognitive Decline Evaluation for Cardiac Arrest (IQCODE-CA, labelled as IQCODE for consistency with the trial protocol[5]), Hospital Anxiety and Depression Scale (HADS), the Post Traumatic Stress Disorder Checklist - Civilian Version (PCL-C), Short-Form 12-item Health Survey (SF-12) and the EuroQoL EQ-5D-5L (Table 1). Detailed description of the outcomes are available in Supplementary Table 1. The measurements at 3 and 6 months allowed a robust and comprehensive evaluation of the functional and HRQoL status. Patients, or legal representatives of patients, who were alive and consented to follow-up were contacted by letter at relevant time-points. At 3-months, a face-to-face visit with the patient or legal representative to oversee/support completion was arranged. Where this was not possible, questionnaires were completed by telephone interview or by post. At 6-months, the questionnaire was completed by post. A second letter was sent to non-responders. Those for whom no response was received were categorised as lost to follow-up (LTFU). Where the patient was LTFU at either 3 or 6-months, the patient's GP or hospital staff were contacted to provide an mRS score as close to the time-point as possible. Survival and neurological outcomes at 3-months have been reported in the main paper[8] and are presented here for comparison.

Table 1: Summary of long-term outcome assessment

*Note: *, results have been published elsewhere.[5]*

Analysis

Outcomes were summarised using mean (standard deviation (SD)) for continuous data and frequency (percentage) for categorical data. Unadjusted and adjusted logistic and linear regression were used to analyse categorical and continuous outcomes, respectively, except that only descriptive statistics were reported for TSQ. Adjustment was made for the following baseline covariates: age, sex, the interval between the emergency call and the ambulance arrival at the scene, the interval between the ambulance arrival and the administration of the trial drug, the

132   presumed cause of OHCA, the initial cardiac rhythm, whether the OHCA was witnessed, and whether

133   CPR was performed by a bystander. The covariates were balanced across the treatment groups.[8]

134   Results comparing adrenaline with placebo were reported in odds ratio (OR) or mean difference

135   (MD) with 95% confidence interval (CI). For mRS score (7-point scale), non-proportional odds logistic

136   regression was used when the assumption of proportional odds was violated. The obtained follow-

137   up questionnaire rates were summarised at 3 and 6-months using the survivors in each mRS at

138   hospital discharge category as the denominator.

139   The HRQoL scores at 3 and 6-months were compared with the general population (UK age and

140   gender equivalent general population normative values for the EQ-5D-3L 0.86 (SD 0.23); EQ-VAS

141   82.48 (SD 19.96);[20] SF-12 norm based scoring (mean 50; SD 10)). No statistical test was done for this

142   comparison. Chi-squared test was used to compare patients by treatment groups with regards to

143   their cognitive function measured by IQCODE (normal (<3.04) vs poor (>=3.04).

144   A p-value <0.05 was considered statistically significant. All analyses were conducted using SAS

145   version 9.4 (Cary, NC: SAS Institute Inc).

146   The study was approved by the South Central Oxford C Research Ethics Committee (reference

147   14/SC/0157) and the Medicines and Healthcare Products Regulatory Agency (MHRA) (Eudract

148   Number 2014-000792-11). The study was sponsored by the University of Warwick and was

149   conducted in accordance with the Directive 2001/20/EC of the European Parliament and of the

150   Council of 4 April 2001, The Medicines for Human Use Act (Clinical Trial) Regulations, Statutory

151   Instrument 2004 No 1031 and Amendment (No.2) Statutory Instrument 2006 No 2984.

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154 **Results**

155 8,014 patients were randomised with confirmed trial drug administration (Figure 1). Patient
156 characteristics have been reported elsewhere.[8] Fourteen patients (six in the adrenaline group) were
157 excluded at 3-months due to declined/withdrawn consent to follow-up data collection, and 3 more
158 after 3-months in the adrenaline group. We obtained 3-months questionnaires from 90 (74.4% of
159 121 in adrenaline) and 65 (75.6% of 86 in placebo) patients and 6-months questionnaire from 49
160 (57.6% of 85 in placebo) and 79 (67.5% of 117 in adrenaline) patients. Numeric results and summary
161 of missingness are shown in Supplementary Table 2 and 3.

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164 Figure 1: CONSORT diagram of long term outcomes in the PARAMEDIC2 Trial

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166 *Note: Lost to follow-up was counted separately. Number of analysed follow-up questionnaires only counted the*
167 *survivors with an obtained questionnaire at each follow-up. Between 3 and 6-months, 3 adrenaline patients*
168 *withdrew consent and 2 non-responders at 3-months provided the 6-months questionnaire data. Additionally,*
169 *18 (13 in adrenaline group) 3-months mRS non-responders had valid measurements at 6-months. The upper*
170 *parts of the CONSORT flow diagram were also reported in the initial publication of the trial results.[8]*

Long term secondary outcomes are summarised in Figures 2-3. Of the 8,014 randomised patients, 117 (2.9%) patients were alive at 6-months in the adrenaline group compared with 85 (2.1%) in placebo (adjusted odds ratio (aOR) 1.43 [95% confidence interval 1.05, 1.96]), reducing to 107 (2.7%) and 80 (2.0%) respectively at 12-months (1.38 [1.00, 1.92]). At 6-months 78 (2.0%) and 58 (1.5%) of patients had a favourable neurological outcome (aOR 1.35 [0.93, 1.97]).

Figure 2: Summary of secondary outcomes. (a) higher scores indicate better health status (b) lower scores indicate better health status.

Note: Error bars are +/- 95% confidence intervals of means. Frequency (rate) and mean (standard deviation) are shown on top of the bars for categorical and continuous outcomes, respectively.

Measures of 3 and 6 month cognitive, functional and quality of life outcomes did not significantly differ between groups (Figure 2 and 3), but were reduced compared to UK general population norms. The between-group difference at 6-months was reduced for SF-12 physical health component score (PCS) but increased for SF-12 mental health component score (MCS). The physical health status (SF-12 PCS) of both groups is less than that of the general population at 3-months, with further deterioration at 6-months. The mental health status (SF-12 MCS) of both groups closely approximates that of the general population at 3-months. But increased difference from the general population was observed at 6-months. HADS scores at 3-months for both groups fall within 'normal' ranges when compared to the general population (i.e. less than 7.0).

Scores on the IQCODE are similar for both groups of survivors, with a minimal improvement observed between 3 and 6-months; the between-group score difference remains constant but small (p=0.905 and 0.820 for 3 and 6-months) (Supplementary Table 4). However, at both time-points, mean scores for both groups exceed the threshold for cognitive impairment in this population (3.04).[13] Fifty-eight-percent of survivors had significant cognitive impairment at 3-months (Supplementary Table 4), reducing to just 47% at 6-months. Mean scores on the MMSE at 3-months are similar for both groups, falling within the 'normal' range (25-30) and suggesting no (or mild) cognitive impairment.

Scores on the PCL-C show higher levels of post-traumatic stress in adrenaline survivors at 3-months, but scores for both groups fall below the proposed level for probable PTSD (Supplementary Table 2).

At 6-months, 78 (2.0%) of the patients in the adrenaline group and 58 (1.5%) of patients in the placebo group had a favourable neurological outcome. Severe neurological impairment (a score of 4 or 5 on the mRS) was more common among survivors in the adrenaline group than in the placebo group (16 of 98 (16.3%) vs 11 of 74 (14.9%) at 3-months, and 23 of 101 (22.8%) vs 9 of 67 (13.4%) at 6-months, respectively). The placebo group had lower rates in the unfavourable categories at 3-months compared with the adrenaline group. At 6-months, more patients with a favourable neurological outcome (a mRS score of 0-3) in the placebo group did not provide the questionnaire

data. However, the evaluation of the functional impairment, as well as other outcomes, was limited by varying follow-up rates (Supplementary Table 5).

Figure 3: Summary for modified Rankin Scale at 3 and 6-months.

Note: MRS categories: 0-No symptoms, 1-No significant disability, 2-Slight disability, 3-Moderate disability, 4-Moderately severe disability, 5-Severe disability, 6-Dead. Proportions were plotted on the log10 transformed scale. Difference in the favourable outcome (mRS<=3) between groups at 3 and 6-months are 0.5% (95%CI: -0.1%, 1.1%) and 0.5% (95% CI: -0.1%, 1.1%), respectively. Patients may have been LTFU in one or both time points. For the placebo group, 20 and 26 LTFU at 3 and 6-months, respectively; while the numbers are 29 and 25 for the adrenaline group.

Results from the TSQ (Supplementary Figure 1) suggests that a greater proportion of adrenaline survivors required help from another person to conduct their daily activities at 3 (adrenaline: 47% versus placebo: 31%, or 1.2% vs 0.5% respectively in all randomised patients) and 6-months (46% versus 33%, or 0.9% vs 0.4%). A slight improvement in the proportion of survivors reporting a 'complete mental recovery' was observed at 6-months for both groups; this improvement was marginally greater for adrenaline survivors, but a greater proportion of placebo survivors reported 'complete mental recovery' (adrenaline: 44% versus placebo: 52%, or 0.9% vs 0.6% respectively in all randomised patients).

Figure 4 presents the adjusted results of the categorical and continuous outcomes. The survival rate was higher in the adrenaline group at 6-months (aOR 1.43 [1.05, 1.96], p=0.024), and the aOR was reduced to 1.39 [1.00, 1.92] (p=0.050) at 1-year. There was no significant treatment difference in favourable neurological outcome at both follow-ups, with a slight decrease in adrenaline survivors from 3 (aOR: 1.39 [0.97, 2.01], p=0.075) to 6-months (aOR: 1.35 [0.93, 1.97], p=0.118). Similarly, no significant difference was found in other outcomes. The unadjusted results are presented in Supplementary Figure 2.

Figure 4: Adjusted odds ratios (a) and mean differences (b,c) with 95% confidence intervals of secondary outcomes.

Note: MRS ordinal score at 3 and 6-months was assessed using a partial proportional odds model as the proportional odds assumption was violated. (a) Odds >1 indicates better outcome in adrenaline, (b) mean difference >0 indicates better outcome in adrenaline, (c) mean difference >0 indicates better outcome in placebo.

Discussion

This is the first randomised trial to evaluate the long-term impact of adrenaline on survival, neurocognitive and quality of life outcomes.[8] Adrenaline had a decreasing but sustained effect on survival over the 12-months follow-up. We found little difference in health status between survivors who received adrenaline or placebo, but HRQoL up to 6-months post-randomisation and cognitive function, anxiety/depression or post-traumatic stress to three months showed significant functional impairment in cardiac arrest survivors compared with the normal population. There is limited evidence for significant between-group difference of favourable neurological outcome, with a higher rate of severe neurological impairment in the adrenaline survivors at 3 and 6-months, although the evaluation was underpowered and limited by varying loss to follow-up. A third to one half of patients reported needing help from someone for everyday activities. For the majority this was a new situation after their cardiac arrest. Less than half reported having made a full mental recovery after their cardiac arrest.

This study demonstrated a sustained survival benefit of adrenaline up to 12-months post randomisation. This extended the significant effect showed in the shorter term survival outcomes.[8] To our knowledge, no other research has assessed the long-term effect of adrenaline as in this study. Most studies, including animal models,[21-23] observational studies[6, 7] and one randomised controlled trial,[24] focused on the survival up to 30 days or hospital discharge. However, the decreasing trend of the effect to 12-months indicated the survival benefit of adrenaline is likely to fade over time.

Our data highlighted differences at 6-months in mental health status between both survivor groups and that of the general population. However, the HADS was only assessed at 3-months, hence a comparable change in score or evaluation of the proportion of the population who exceeded threshold scores for anxiety and depression was not possible. Other studies have reported substantially higher levels of anxiety and depression in survivors compared with both non-arrest counterparts with acute ST-segment-elevation myocardial infarction at 6-months[25] and age- and gender-matched population cohorts at 12-months.[26] Similarly, smaller observational studies have reported a deterioration in mental wellbeing following hospital discharge,[27] with evidence suggesting that this may persist for several years post-arrest.[28] Psychological distress is an important determinant of a survivor's health-related quality of life[29, 30] which, if not addressed, can interfere with recovery.[31, 32]

Differences, and deteriorating, physical health status in survivors across both groups compared with the general population was also observed. Whilst providing a blunt assessment of physical function, responses to the 'Two Simple Questions' further evidenced the difficulties with everyday activities

experienced by survivors in both groups, with little improvement at 6-months. The functional impact of OHCA survival has received little attention. However, reduced physical functioning has been reported in survivors at 12-months[33, 34], three-years[35, 36] and five-years[26, 37] when compared with age and gender-matched members of the general population. Survivors have also reported greater limitations in their ability to reintegrate into society than non-cardiac arrest patients, with almost half (versus 30%) reporting significant difficulties at 6-months.[38]

Our trial included both clinician (MMSE) and proxy-reported (IQCODE) assessments of cognitive impairment. At 3-months, the MMSE revealed little or no cognitive impairment in both groups. However, IQCODE scores suggest that almost 60% of survivors across both groups at 3-months, reducing to almost 50% at 6-months, have levels of cognitive impairment warranting further evaluation and support.[13] Previous studies have evidenced the limitations of the MMSE, including its insensitivity to mild cognitive impairment.[39] However, proxy-based assessment of the IQCODE may itself introduce assessment bias,[13] whilst survivor self-assessment may be influenced by the psychological status of survivors.[40, 41] A detailed battery of cognitive assessments conducted with 287 survivors in the Targeted Temperature Management trial at 6-months, reported impairment in up to 75%; this was significant in 47%.[38, 42] Cognitive impairments in this population present as problems with memory, attention and executive functioning.[29, 43] Such impairment is strongly related to a worse quality of life, reduced participation and difficulties returning to work.[35, 38] However, cognitive function assessment guidance is lacking[44] and significant assessment heterogeneity is described.[40] Improved assessment guidance that considers the quality and relevance of assessment alongside respondent burden and feasibility of detailed assessment in trial situations is required.

At 3-months there is little evidence that survivors experience PTSD, as assessed by the PCL-C. However, this may be too soon for symptoms to be observed and, as observed for change in mental health status, a longer-term follow-up may be required. Moreover, post-traumatic stress, strain and depression may be greater in family members or significant others who witness the collapse and/ or provide CPR than for the survivors.[30, 45, 46]

Non-response to the follow-up questionnaire increased over time. Survivors with more severe disability at discharge were less likely to be followed-up (Supplementary Table 5) in both groups at 3-months. Hence, our results may represent only a subset of survivors with better neurocognitive function. At 6-months, however, more placebo patients with better functional status at discharge did not respond to the follow-up. The differential LTFU may introduce bias to the estimation of the follow-up outcomes and could pose further threats to the validity of the results.[47] More caution is needed when interpreting the results.

Our trial had other limitations. First, there were relatively few survivors and they continued to decrease over the follow-up, limiting the statistical power of the analysis of the long-term outcomes. Second, omitting the assessments of cognition (MMSE), PTSD (PCL-C) and anxiety and depression (HADS) at 6-months limited our ability to report on the trajectory of change in these domains. Given the deterioration in mental wellbeing reported on the general SF-12 MCS and the large proportion of survivors for whom cognitive function remained a problem, the additional information to be garnered from a more detailed assessment at 6-months would have been beneficial. Third, we did not record what rehabilitation or post-hospital discharge care survivors received, which may have influenced their post-arrest wellbeing. Finally, some outcomes were proxy-completed and might not accurately measure patients' neurocognitive function. Well-developed condition-specific measures have greater clinical and patient relevance and are more responsive to important change in health status than their generic counterparts;[48] their combined use in clinical trials is recommended.[2] The development of a survivor-reported measure specific to the needs and complexities of OHCA survival should be prioritised.

Conclusion (53)

Adrenaline improved survival through to 12-months follow-up. The study did not find evidence of improvements in favourable neurological outcomes.

Conflicts of Interest

GDP, RL, TQ, CDD, JN, NR, LO, JL, CJ, SG, HP, SR, and CS report grants from NIHR HTA Programme during the conduct of the study. The other authors declare no competing interests.

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Table 1: Summary of long-term outcome assessment

Outcome measure	3 months	6 months	12 months
Survival outcome			
Survival status	*	●	●
Functional outcome			
Modified Rankin Scale (mRS)[9, 10]	*	●	
Two simple questions (TSQ)[11]	●	●	
Cognitive function			
Mini Mental State Examination (MMSE)[12]	●		
Informant Questionnaire on Cognitive Decline Evaluation for Cardiac Arrest (IQCODE-CA, labelled as IQCODE)[13]	●	●	
Emotional wellbeing			
Hospital Anxiety and Depression Scale (HADS)[14]	●		
Post Traumatic Stress Disorder Checklist - Civilian Version (PCL-C)[15]	●		
Health-related quality of life			
Short Form 12-item survey (SF-12)[16]	●	●	
EuroQoL EQ-5D-5L[2, 17, 18]	●	●	

Figure

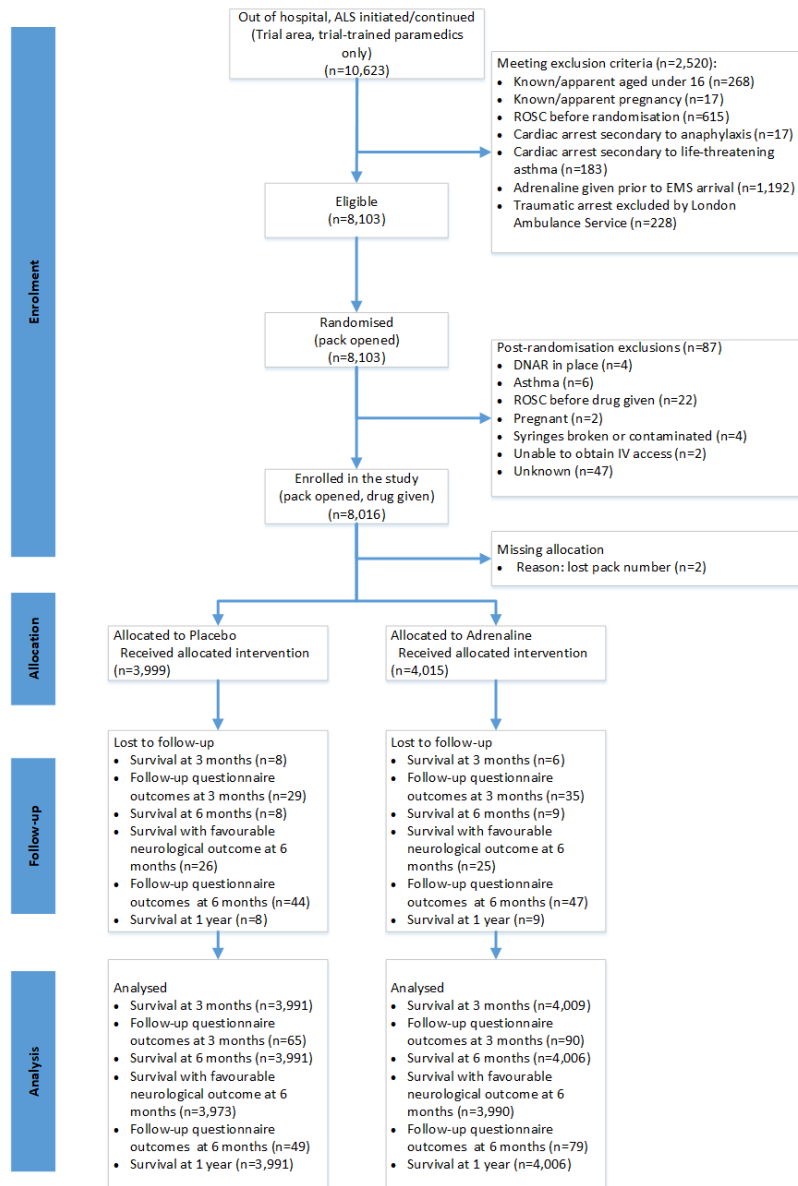Figure 1: CONSORT diagram of long term outcomes in the PARAMEDIC2 Trial

Figure 2: Summary of secondary outcomes. (a) higher scores indicate better health status (b) lower scores indicate better health status.
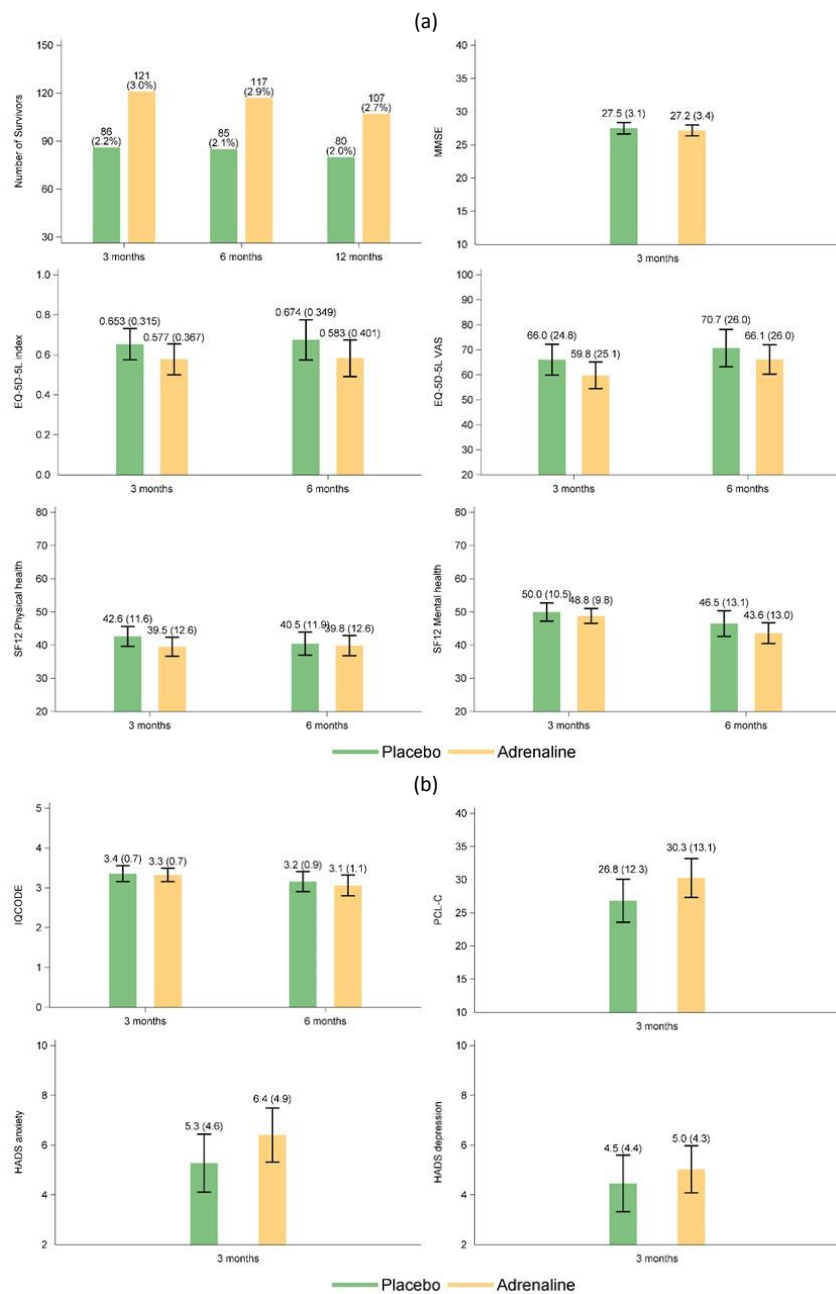
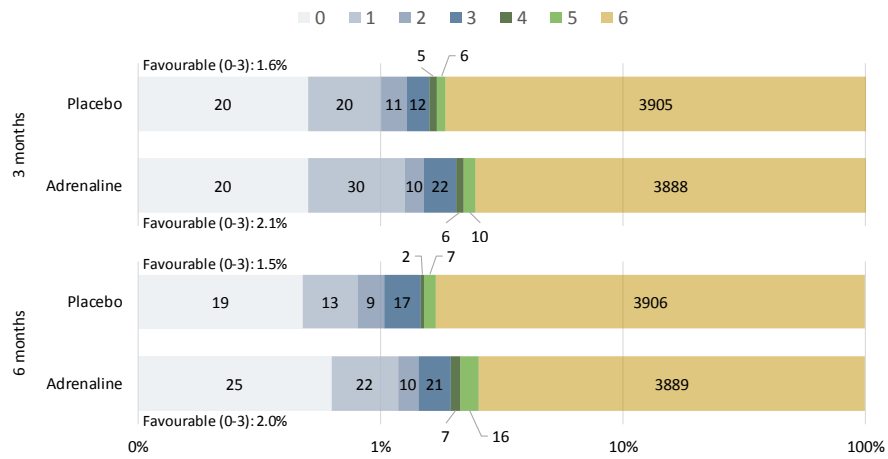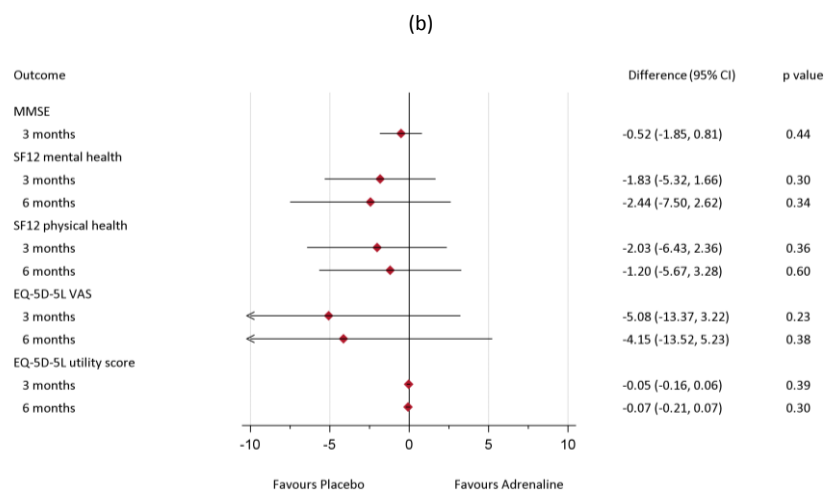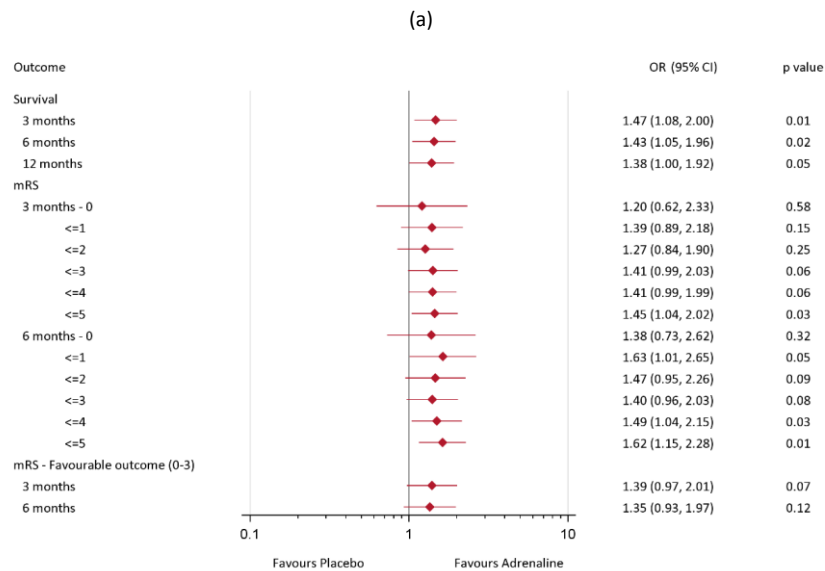Figure 3: Summary for modified Rankin Scale at 3 and 6-months.

Figure 4: Adjusted odds ratios (a) and mean differences (b,c) with 95% confidence intervals of secondary outcomes.

(a)

Outcome		OR (95% CI)	p value
Survival			
3 months		1.47 (1.08, 2.00)	0.01
6 months		1.43 (1.05, 1.96)	0.02
12 months		1.38 (1.00, 1.92)	0.05
mRS			
3 months - 0		1.20 (0.62, 2.33)	0.58
<=1		1.39 (0.89, 2.18)	0.15
<=2		1.27 (0.84, 1.90)	0.25
<=3		1.41 (0.99, 2.03)	0.06
<=4		1.41 (0.99, 1.99)	0.06
<=5		1.45 (1.04, 2.02)	0.03
6 months - 0		1.38 (0.73, 2.62)	0.32
<=1		1.63 (1.01, 2.65)	0.05
<=2		1.47 (0.95, 2.26)	0.09
<=3		1.40 (0.96, 2.03)	0.08
<=4		1.49 (1.04, 2.15)	0.03
<=5		1.62 (1.15, 2.28)	0.01
mRS - Favourable outcome (0-3)			
3 months		1.39 (0.97, 2.01)	0.07
6 months		1.35 (0.93, 1.97)	0.12

0.1   1   10

Favours Placebo   Favours Adrenaline

(b)

Outcome		Difference (95% CI)	p value
MMSE			
3 months		-0.52 (-1.85, 0.81)	0.44
SF12 mental health			
3 months		-1.83 (-5.32, 1.66)	0.30
6 months		-2.44 (-7.50, 2.62)	0.34
SF12 physical health			
3 months		-2.03 (-6.43, 2.36)	0.36
6 months		-1.20 (-5.67, 3.28)	0.60
EQ-5D-5L VAS			
3 months		-5.08 (-13.37, 3.22)	0.23
6 months		-4.15 (-13.52, 5.23)	0.38
EQ-5D-5L utility score			
3 months		-0.05 (-0.16, 0.06)	0.39
6 months		-0.07 (-0.21, 0.07)	0.30

-10   -5   0   5   10

Favours Placebo   Favours Adrenaline

(c)

Outcome	Difference (95% CI)	p value
IQCODE		
3 months	-0.01 (-0.28, 0.26)	0.94
6 months	-0.07 (-0.45, 0.31)	0.70
HADS anxiety		
3 months	1.20 (-0.39, 2.80)	0.14
HADS depression		
3 months	0.42 (-1.05, 1.88)	0.58
PCL-C		
3 months	3.85 (-0.40, 8.11)	0.08

```
   10      5      0     -5     -10

   Favours Placebo      Favours Adrenaline
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