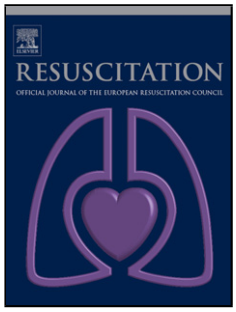

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The effects of adrenaline in out of hospital cardiac arrest with shockable and non-shockable rhythms: Findings from the PACA and PARAMEDIC-2 randomised controlled trials.

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Abstract

Introduction: Previous research suggests there may be differences in the effects of adrenaline related to the initial cardiac arrest rhythm. The aim of this study was to assess the effect of adrenaline compared with placebo according to whether the initial cardiac arrest rhythm was shockable or non-shockable.

Methods: Return of spontaneous circulation (ROSC), survival and neurological outcomes according to the initial arrest rhythm were compared amongst patients enrolled in the PARAMEDIC-2 randomised, placebo controlled trial. The results of the PARAMEDIC-2 and PACA out of hospital cardiac arrest trials were combined and meta-analysed.

Results: The initial rhythm was known for 3,929 (98.2%) in the placebo arm and 3,919 (97.6%) in the adrenaline arm. The effect on the rate of ROSC of adrenaline relative to placebo was greater in patients with non-shockable cardiac rhythms (1002/3003 (33.4%) versus 222/3005 (7.4%), adjusted OR: 6.5, (95% CI 5.6-7.6)) compared with shockable rhythms 349/716 (48.7%) versus (208/702 (29.6%), adjusted OR: 2.3, 95%CI: 1.9-2.9)). The adjusted odds ratio for survival at discharge for non-shockable rhythms was 2.5 (1.3, 4.8) and 1.3 (0.9, 1.8) for shockable rhythms (P value for interaction 0.065) and 1.8(0.8-4.1) and 1.1 (0.8-1.6) respectively for neurological outcome at discharge (P value for interaction 0.295). Meta-analysis found similar results.

Conclusion: Relative to placebo, the effects of adrenaline ROSC are greater for patients with an initially non-shockable rhythm than those with a shockable rhythms. Similar patterns are observed for longer term survival outcomes and favourable neurological outcomes, although the differences in effects are less pronounced. ISRCTN73485024

Word count: 250

Introduction

Adrenaline has been used as a treatment for cardiac arrest for many years.[1-3] Despite its widespread use, until recently there has been limited evidence from randomised, placebo controlled trials about its safety and effectiveness.[4,5] The Cochrane systematic review and meta-analysis identified two randomised controlled trials which enrolled patients before admission to hospital and allocated them to adrenaline (1 mg aliquots) or placebo.[4] The Pre-hospital Adrenaline for Cardiac Arrest (PACA) trial[6] and Prehospital Assessment of the Role of Adrenaline: Measuring the Effectiveness of Drug Administration in Cardiac Arrest (PARAMEDIC-2)[7] enrolled 8,534 patients with out of hospital cardiac arrest (OHCA) and allocated them to receive adrenaline (1 mg every 3-5 minutes) or placebo. Meta-analysis of the trial results showed that adrenaline increased the rate of return of spontaneous circulation (ROSC) and survival to hospital discharge, but did not find evidence of improved neurological outcomes.[4]

Observational studies suggest that there may be differences in the effects of adrenaline according to the initial cardiac arrest heart rhythm. Administration of adrenaline in patients with initially shockable rhythms may be less effective[8] or potentially harmful.[9,10] Although overall outcomes are generally poorer in patients with non-shockable rhythms, the incremental effectiveness of adrenaline by contrast appears to be greater.[8-11] Although informative, observational studies are limited by the risk of bias due to un-measured confounding factors. This includes the potential association between adrenaline being given later in patients with initially shockable rhythms, which might introduce resuscitation time bias.[12]

The aim of this study was (i) to assess the effect of initial arrest rhythm (i.e. shockable vs non-shockable) on primary and secondary outcomes in the PARAMEDIC-2 trial[7] (ii) to provide a meta-analysis to assess the effect of initial rhythm on a set of outcomes that were common to the PARAMEDIC-2 and PACA trial.[6]

Methods

Study design and patients

PARAMEDIC-2 trial (2018)

The background to the trial, methods and baseline characteristics of the randomised patients have been previously reported.[7,13] In brief, PARAMEDIC-2 was a multicentre double-blinded placebo-controlled trial conducted by five National Health Service ambulance services in the United Kingdom from December 2014 to October 2017 inclusive. Patients treated by ambulance paramedics for OHCA who were not successfully resuscitated by means of defibrillation or cardiopulmonary resuscitation (CPR), and who met predetermined eligibility criteria were randomly allocated to either adrenaline or saline placebo. Randomisation occurred when trial paramedics opened packs containing ten prefilled syringes loaded with either 1 mg doses of adrenaline or 0.9% saline. Treatment was administered by intravenous (IV) or intraosseous (IO) route. In accordance with European Resuscitation Council Guidelines[14] the intervention was administered as soon as possible (after initiating CPR and obtaining vascular access) if the initial rhythm was non-shockable. For initially shockable rhythms, the intervention was deferred until either the rhythm changed to non-shockable or the third attempt at defibrillation was unsuccessful. Trial packs and their contents were identical in appearance and carried a unique identification number. In all other respects identical paramedic resuscitation protocols were followed.[15,16]

Randomisation of drug packs to ambulance services was achieved using computer-generated randomisation with an allocation ratio of 1:1. Patients, paramedics and trial staff were blinded to treatment allocation. A full description of trial methods has been previously published.[13]

PACA trial (2011)

The PACA trial was a double-blind randomised placebo controlled trial of the effect of adrenaline on survival in 534 OHCA patients conducted in Australia from August 2006 to November 2009.[6] The eligibility criteria for this trial were similar to that of PARAMEDIC-2: all patients with an OHCA from any cause, age 18 or older with resuscitation commenced by paramedics were entered into the study. Local protocols for the timing of drug administration were the same as for the PARAMEDIC-2 trial. Clinical outcomes collected were similar to those of the PARAMEDIC-2 study. However, in relation to initial rhythm, only the ROSC at any time

(reported as ROSC achieved pre-hospital) and survived to hospital discharge were reported. Survival with favourable neurological outcome (Cerebral Performance Category 1,2) was extracted from the trial database for inclusion in the meta-analysis.

Statistical analysis

PARAMEDIC-2 study

For analysis purposes initial arrest rhythm was subdivided into 2 categories: (i) shockable (consisting of ventricular fibrillation (VF), pulseless ventricular tachycardia (VT), and automated external defibrillator (AED) shockable rhythms), and (ii) non-shockable (consisting of asystole, pulseless electrical activity (PEA), bradycardia, and AED non-shockable rhythms). Observations with missing rhythm type were removed before analysis.
All statistical analyses were undertaken using Stata, version 15.1.

We assessed the primary outcome: rate of survival at 30 days, and secondary outcomes: rate of survival at discharge from hospital, rate of survival at 3 months, rate of return of spontaneous circulation (ROSC) at hospital admission, ROSC at any time, rate of favourable neurological outcome at discharge, and rate of favourable neurological outcome at 3 months, by initial arrest rhythm type. The neurological outcomes were determined using a modified Rankin scale assessment (ranging from 0 [no symptoms] to 6 [death]) where a score of 0-3 inclusive was considered favourable.[17]

Logistic regression models were fitted for each of the seven pre-specified outcomes as dependent variables. The unadjusted analyses included dichotomous rhythm type and allocated treatment as explanatory factors. An interaction of these latter two variables was fitted to assess the heterogeneity of treatment effects. This was assessed using the chi-squared test. We also fitted adjusted logistic regression models where the models were corrected for pre-specified covariates (1) which included age, gender, interval between emergency call and ambulance arrival at scene, interval between arrival at scene and administration of trial drug, aetiology (medical, traumatic, drowning, drug overdose, electrocution, asphyxial), witness type (unwitnessed, Emergency Medical Service (EMS), bystander), and bystander CPR (yes, no). Odds ratios and 95% confidence intervals were estimated for the different categories of rhythm.

Meta-analysis

A meta-analysis was conducted using the common outcome variables to both studies, namely ROSC at any time and survival to hospital discharge. Results for favourable neurological outcome at discharge not reported in the PACA trial have been provided to enable meta-analysis (note that a Cerebral Performance Category (CPC) score of 1-2 was deemed equivalent to an mRS score of 0-3). Random effects models were fitted to combine the data on both these trials (with adjustment for dichotomous rhythm type and treatment allocation only). Pooled estimates of effect (odds ratio) and 95% confidence intervals were produced. Between-study statistical heterogeneity was assessed using the I-squared method, and the Mantel-Haenszel Q test was used to examine heterogeneity between types of rhythm.

Role of the funding source

The PARAMEDIC 2 trial was funded by the Heath Technology Assessment Programme of the National Institute for Health Research. The funders had no role in the trial design, data collection or analysis, or in the writing of this report. The Warwick Clinical Trials Unit undertook data management activities. The trial statisticians (CK, CJ, RL) assume responsibility for the integrity of the data and its analysis. The NIHR Current Controlled Trials number is ISRCTN73485024.

The PACA trial was funded by the NHMRC (Australia) and registered under the Australian and New Zealand Clinical Trials Register (ACTRN12605000062628).

Results

PARAMEDIC-2 Study

Of 8,014 patients enrolled in the study those with known treatment allocation consisted of 3,999 in the placebo and 4,015 in the adrenaline arm. Removal of cases where initial cardiac rhythm was unknown (166 in total), reduced the numbers to 3,929 (98.2%) and 3,919 (97.6%) respectively. These cases were analysed with the exception of those lost to follow up. A

CONSORT diagram demonstrates the number of patients in each group (after excluding those where the initial arrest rhythm was not recorded) and rates of loss to follow-up (Figure 1). Baseline characteristics for trial patients according to initial cardiac arrest rhythm are shown in Table 1.

Return of spontaneous circulation (figure 2)

Of those patients with non-shockable rhythms 1002/3003 (33.37%) achieved ROSC in the adrenaline group and 222/3005 (7.39%) achieved ROSC in the placebo group (adjusted OR: 6.52, 95% CI 5.56-7.63). Of those patients with shockable rhythms 349/716 (48.74%) achieved ROSC in the adrenaline group compared to 208/702 (29.63%) in the placebo group (adjusted OR: 2.32, 95%CI: 1.86-2.89). The interaction term of rhythm type and treatment demonstrates that the effect of adrenaline on ROSC is greater in patients with non-shockable rhythms ($p<0.001$).

Overall, the adjusted odds of ROSC at any time increased significantly with the use of adrenaline compared to placebo (adjusted OR: 4.72, 95% CI: 4.17-5.35). The results for sustained ROSC were similar although the estimated effect of adrenaline was smaller (adjusted OR: 3.82, 95% CI: 3.30-4.42) than for ROSC at any time.

Survival (figure 2)

For non-shockable rhythms, survival to discharge was 32/3020 (1.06%) in the adrenaline group and 13/3023 (0.43%) in the placebo group (adjusted OR: 2.52, 95% CI: 1.32-4.83). For shockable rhythms survival to discharge was 89/717 (12.41%) in the adrenaline group and 74/705 (10.50%) in the placebo group (adjusted OR: 1.27, 95% CI: 0.90-1.78). However, the interaction term in the model, does not provide convincing evidence of difference in treatment effect across categories of cardiac rhythm ($p=0.065$).

Overall, survival at discharge was higher in the adrenaline group compared to placebo (adjusted OR: 1.49, 95% CI: 1.10-2.00). Similar results were noted for survival to 30 days and survival to 3 months.

Favourable neurological outcome (figure 2)

The proportions with favourable neurological outcomes at hospital discharge were similar in the adrenaline group compared to the placebo group for non-shockable, 16/3020 (0.53%) versus 9/3023 (0.30%) (adjusted OR 1.79, 95% CI: 0.79, 4.08) and for shockable, 67/715 (9.37%) versus 62/704 (8.81%); adjusted OR 1.10, 95% CI: 0.75-1.61). Of those patients with non-shockable rhythms 16 survived to hospital discharge with a poor neurological outcome in the adrenaline group and 4 in the placebo group. For patients with shockable rhythms, 23 survived to discharge with a poor neurological outcome in the adrenaline group compared to 12 in the placebo group.

There was insufficient evidence to suggest that favourable neurological outcome at discharge differed between the treatment arms (OR: 1.20, 95% CI: 0.85-1.70, p=0.288), and it was not found to differ according to rhythm type (p=0.295). Similar results were found for favourable neurological outcome at 3 months, although the rates of loss to follow-up were higher than at discharge (figure 1). Where information was available at three months, for non-shockable rhythms 7 patients survived with poor neurological outcome in the adrenaline group and 6 in the placebo group. For shockable rhythms, 9 patients were alive with poor neurological outcome in the adrenaline group and 5 in the placebo group.

Sensitivity analyses

The results for the un-adjusted analyses were similar to the adjusted analyses (see figure 3).

Meta-analysis

Meta-analyses of results from the two studies[6,7] showed that the pooled odds of ROSC at any time in the shockable group was significantly higher for those given adrenaline (adjusted OR: 2.30, 95%CI: 1.88-2.82) and the pooled effect in the non-shockable group was also greater with adrenaline (adjusted OR: 6.16, 95%CI: 5.30-7.15). The results for ROSC at any time were similar for both studies (I^2=0.0%). Figure 4 illustrates these results.

The results for survival at discharge did not appear to differ substantially between studies (I^2=0.0%). The pooled odds of survival at discharge for those with non-shockable rhythms increased with the use of adrenaline (adjusted OR: 2.57, 95%CI: 1.36-4.83), however, for patients with shockable rhythms the increase was smaller and more uncertain (adjusted OR: 1.26, 95%CI: 0.93-1.71).

Pooled odds of favourable neurological outcome at discharge suggested insufficient evidence of better neurological outcome with adrenaline compared to placebo in those with shockable rhythms (adjusted OR: 1.09, 95%CI: 0.77-1.53) and non-shockable rhythms (adjusted OR: 1.91, 95%CI: 0.87-4.22).

Discussion

This paper reports that, relative to placebo, the effects of adrenaline on any ROSC and sustained ROSC appear to be greater for patients with an initially non-shockable arrest rhythm than those with shockable rhythms. Similar patterns are observed for longer term survival outcomes and favourable neurological outcomes, although the differences in effect are less pronounced.

The findings of the present study are consistent with previous research. Olasveengen *et al* examined the effect of intravenous (IV) cannulation and injection of drugs versus not giving IV drugs in 851 adults with OHCA.[18] The majority in the intervention group (79%) received adrenaline. The trial found similar outcomes in the intervention and control arms for patients with an initially shockable rhythm (VF or pulseless VT). By contrast, in patients in the intervention arm with initially non-shockable rhythms, a higher rate of ROSC (29% versus 11%), admission to hospital (31% versus 16%) was observed although long term survival (3% versus 2%) and favourable neurological outcomes (2% in both groups) were similar. The same pattern of outcomes was observed in a *post hoc* analysis of that trial which limited the analysis to patients who actually received adrenaline.[19] In two large observational studies drawn from the Japanese Utstein-style registry for OHCA, researchers found no difference or worse outcomes in patients treated with adrenaline who had an initially shockable rhythm, whilst

those with non-shockable rhythms had better outcomes.[8,10] During in-hospital cardiac arrest, drugs can be given much earlier than is possible in most cases of OHCA. In this setting, in an analysis of the Get with the Guidelines Resuscitation Registry, Andersen *et al* showed that very early adrenaline administration (within the first two minutes of cardiac arrest) was associated with worse outcomes in patients with shockable rhythms.[9] Using the same registry, Donnino *et al* reported that outcomes were better in non-shockable rhythms the earlier that adrenaline was administered.[20] These reports, together with the findings from the present study, support the hypothesis that the relative effect of adrenaline in cardiac arrest is greater in non-shockable rhythms.

The observed differences in treatment effect for adrenaline could be explained by differences in pathophysiology of cardiac arrest associated with shockable and non-shockable rhythms. A cardiac cause is more likely in patients who present with initially shockable rhythms.[21] In these patients rapid treatment with defibrillation is the most effective intervention.[22] Although the present study did not find evidence adrenaline was harmful in patients with shockable rhythms, the β-adrenergic effects of adrenaline are potentially harmful and associated with increased myocardial oxygen demand,[23] higher rates of re-arrest[24] and worse myocardial dysfunction after return of spontaneous circulation.[25] By contrast, there are few effective treatments for patients with non-shockable rhythms. Some of the causes of cardiac arrest associated with non-shockable rhythms such impaired myocardial contractility, reduced systemic vascular resistance and failure of myocardial conduction may be more responsive to treatment with adrenaline.[26,27]

This study has several limitations. Although defined as *an a priori* analyses, exploration of the treatment effects of adrenaline according to the initial rhythm were not the primary intent of either the PACA or PARAMEDIC-2 study. As such, the findings should be considered exploratory and interpreted with caution. Both of the index trials (PACA and PARAMEDIC-2) recruited patients with OHCA. The findings do not necessarily apply to in-hospital cardiac arrest, where the causes of cardiac arrest, time to treatment and accessibility to alternative treatments differ. The analyses were based on the initial presenting arrest rhythm at time of

first assessment as opposed to the rhythm immediately before drug administration. The trials examined intermittent boluses of adrenaline (1 mg) given every 3-5 minutes. Alternative dosing strategies such as low dose, high dose, continuous infusions or titration according to invasive haemodynamic monitoring may yield different findings. The trials occurred in settings where extracorporeal CPR was unavailable. Patients with refractory cardiac arrest were therefore exposed to up to 10 doses of adrenaline before discontinuing resuscitation efforts. The trials did not mandate a single, specific post resuscitation care protocol, instead treating clinicians were guided by current practice recommendations.[28] Finally, the PARAMEDIC-2 findings for neurological outcome at 3 months are limited by overall small numbers and a higher rate of loss to follow-up than at discharge. Since loss to follow-up is higher in those with poor neurological outcomes, the findings for outcomes after discharge are at risk of attrition bias.[29,30]

This study highlights the need for further research around the on-going use of adrenaline in cardiac arrest when the initial rhythm is shockable. Whilst this and other studies[9] suggests that adrenaline may be less effective in shockable rhythms, particularly shortly after the onset of cardiac arrest, it is likely a transition point arises after which vasopressor therapy may be required to achieve ROSC. This is consistent with the 3-phase model concept of electrical, circulatory and metabolic phases reflecting the time sensitive progression of resuscitation pathophysiology.[22] Further research is required to identify when and if it is appropriate to transition from a primary focus on CPR and defibrillation to one which includes vasopressors and/or other therapies (e.g. extra-corporeal CPR).[31,32]

In conclusion, the effects of adrenaline on any ROSC and sustained ROSC are relatively greater for OHCA patients with an initially non-shockable rhythm than those with shockable rhythms. The patterns for longer term survival outcomes and favourable neurological outcomes, suggest similar effects, although the differences are less pronounced.

Contributions

Conception or design of the work: GDP, CK, CJ, CD, JN, TQ, JF, SG, RL; acquisition of data: RF, IG, HP, NR, KC, JF; Analysis CK, CJ, RL and interpretation CK, CJ, RL, SG, GDP, CD, JN, TQ, JF.

Drafting the work CK, CJ, RL, GDP, critical revision – all authors. Final approval – all authors.

Statement of GCP compliance: All authors.

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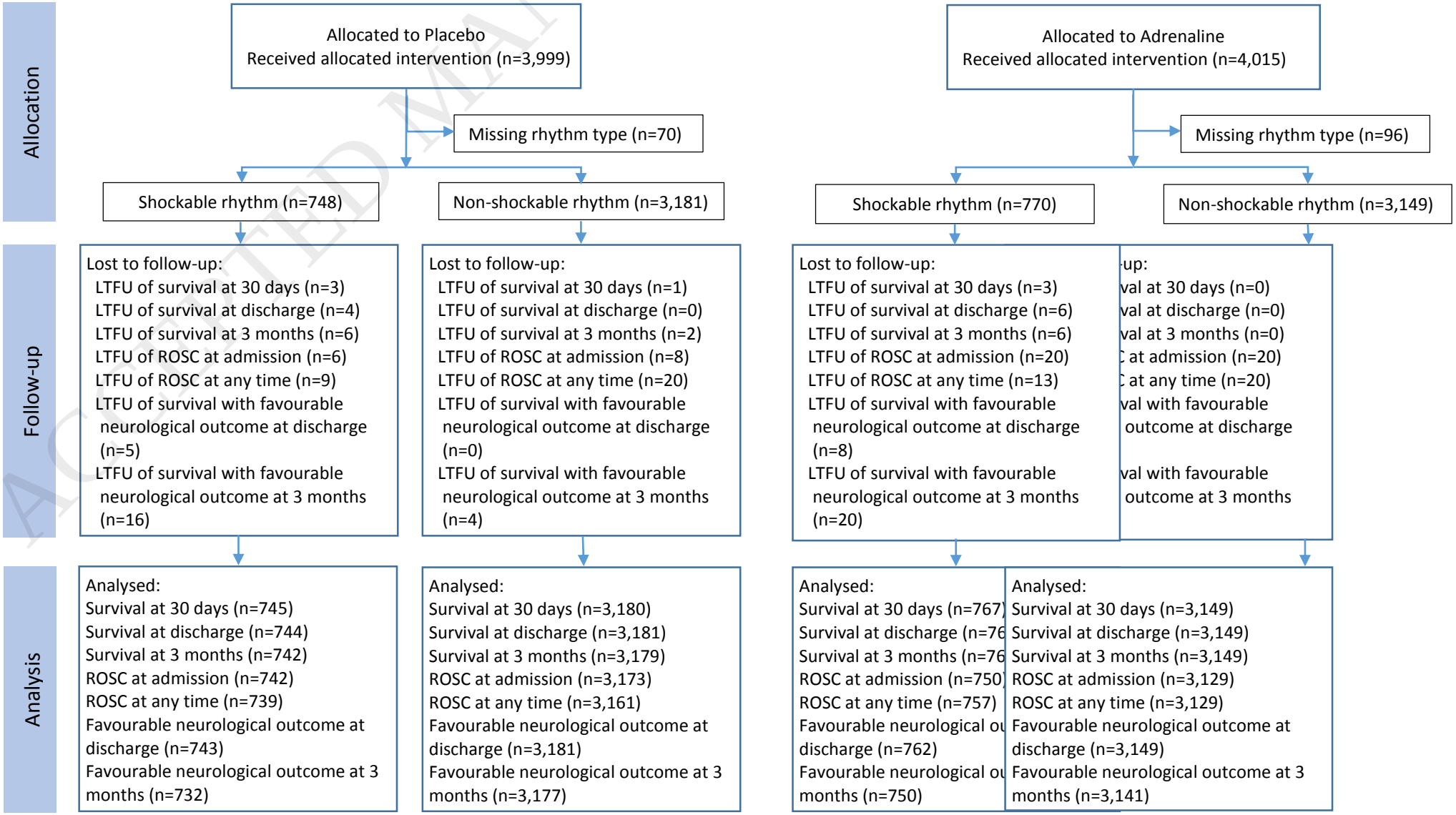
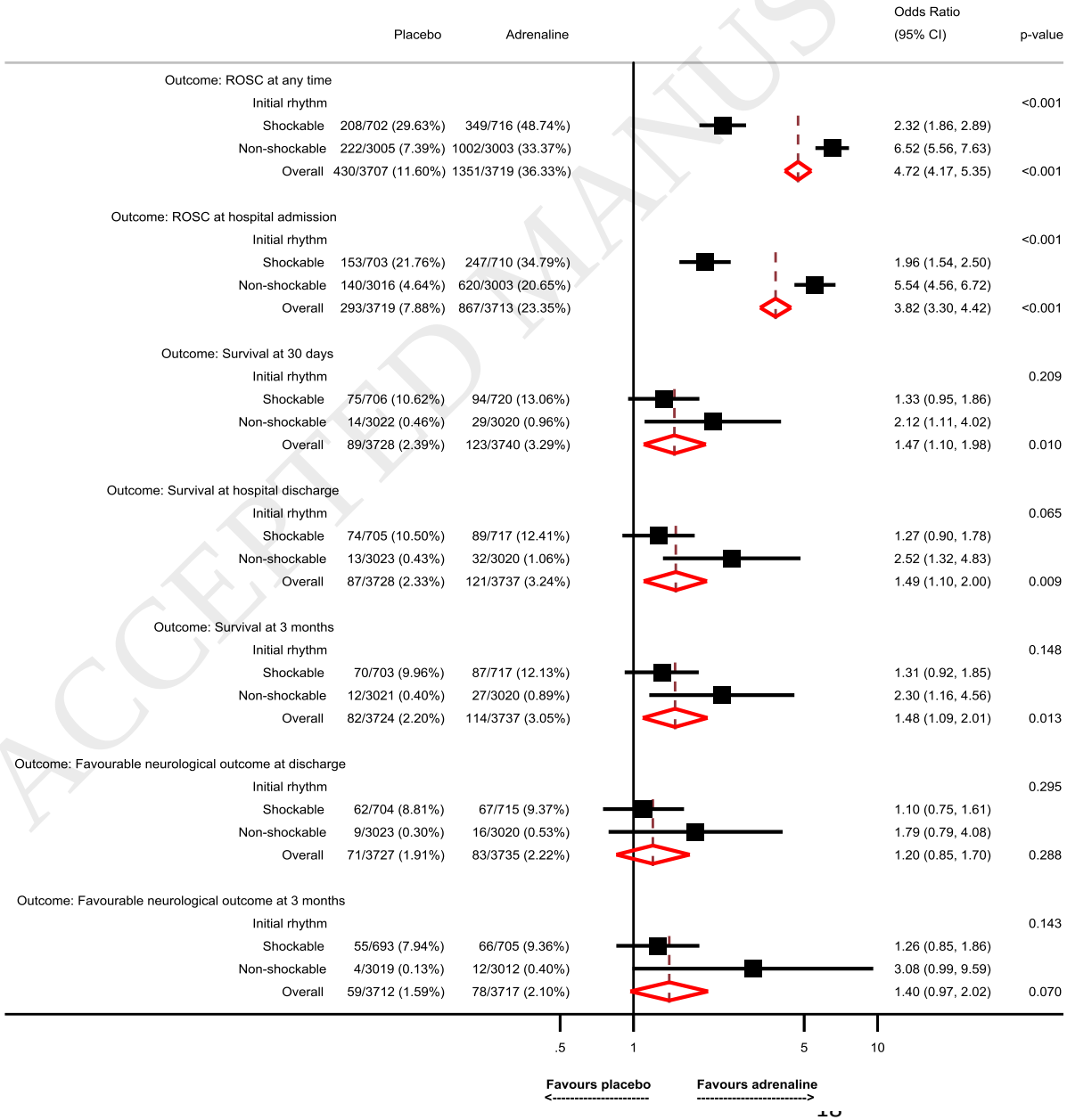


Note: LTFU are counted separately and are not cumulative

Figure 1: CONSORT diagram of allocation and outcomes by rhythm type

Figure 2: Adjusted odds ratio (95% CI, p) of adrenaline vs placebo on primary and secondary outcomes (by initial cardiac rhythm)



Note: Models adjusted for age, gender, interval between emergency call and ambulance arrival at scene, interval between ambulance arrival and drug administration, aetiology, witness type, bystander CPR, and initial rhythm

Figure 3: Unadjusted odds ratio (95% CI, p) of adrenaline vs placebo on primary and secondary outcomes (by initial cardiac rhythm)

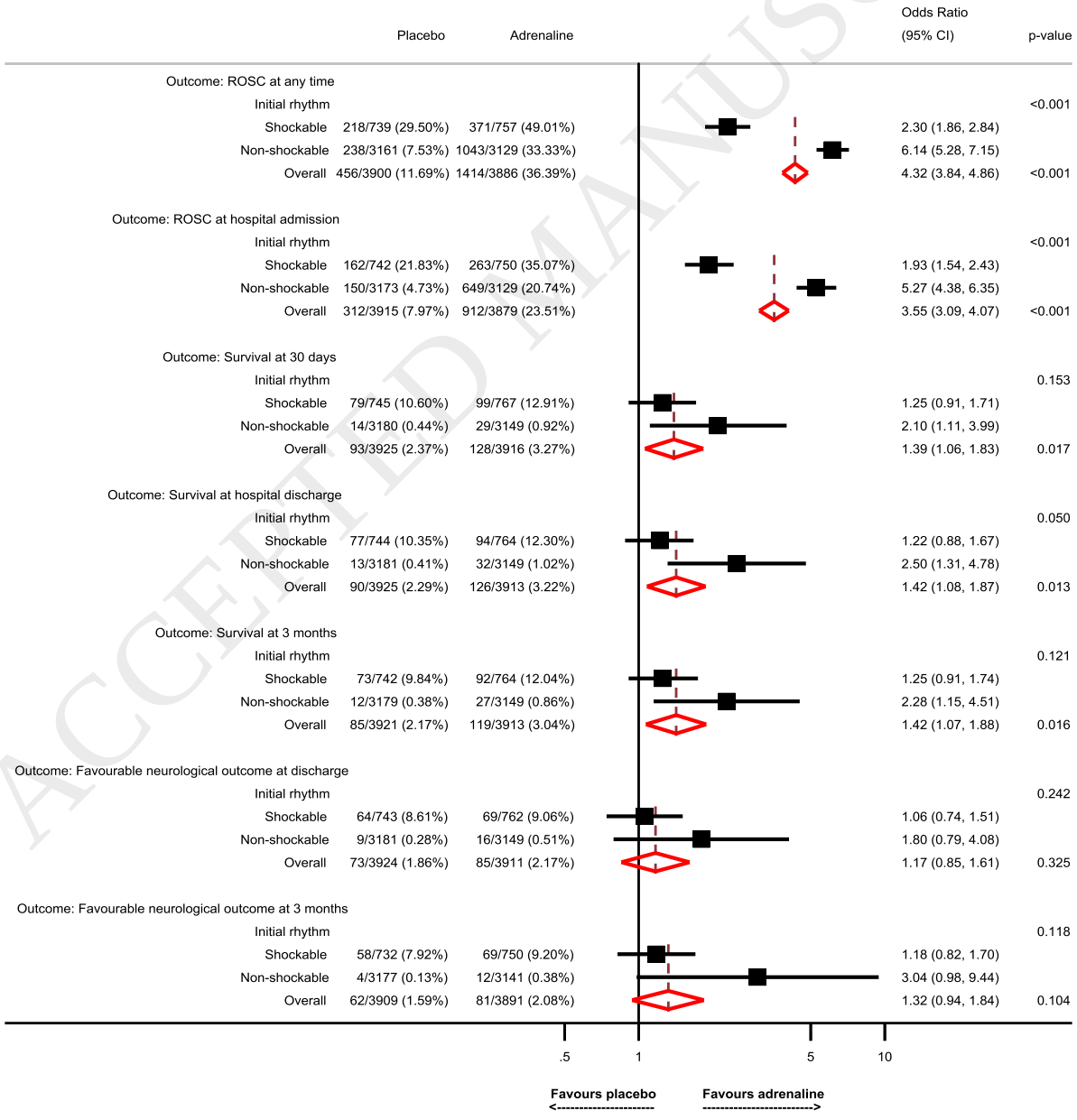
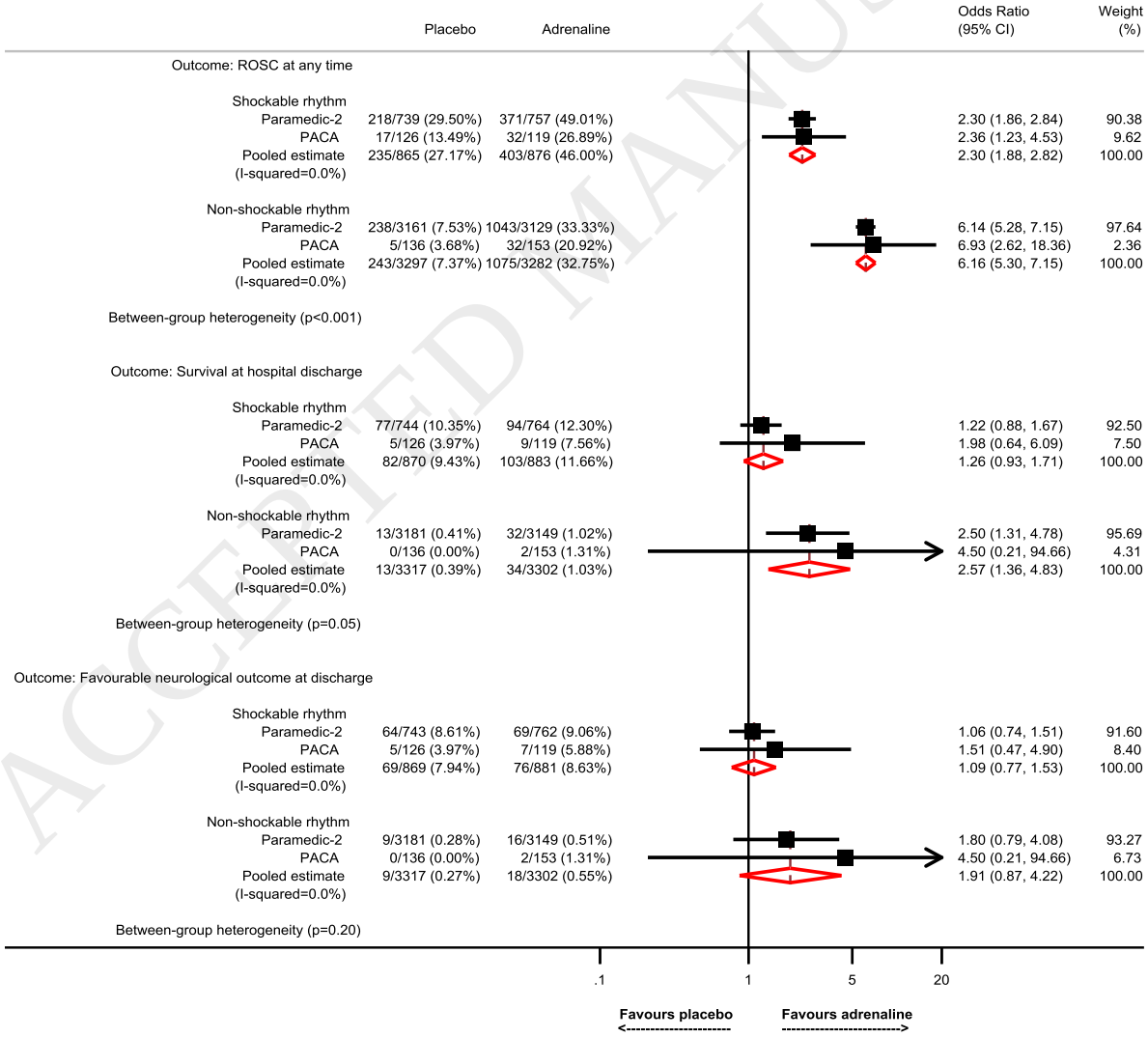


Figure 4: Random effects meta-analyses with pooled odds ratio (95% CI, I^2) of adrenaline vs placebo on ROSC at any time and survival at discharge (by initial cardiac rhythm)



Note: * Effect size not estimable

Table 1: Patient characteristics by initial rhythm (shockable and non-shockable) (n=7848)

	Shockable (n=1518)	Non-shockable (n=6330)	Overall (n=7848)	Test statistic‡	p-value
Age (years)*					
Mean *(SD)*	67.30 *(14.59)*	70.36 *(16.80)*	69.77 *(16.44)*	-6.53	<0.001
Median *(IQR)*	69.01 *(21.64)*	73.73 *(22.98)*	72.67 *(22.90)*		
Gender					
Female	322 (21.21%)	2444 (38.61%)	2766 (35.24%)	162.38	<0.001
Male	1196 (78.79%)	3886 (61.39%)	5082 (64.76%)		
Time from 999 call to treatment (minutes)					
<10	78 (5.14%)	406 (6.41%)	484 (6.17%)		
10-20	620 (40.84%)	2288 (36.15%)	2908 (37.05%)		
>20	799 (52.64%)	3586 (56.65%)	4385 (55.87%)		
Unknown	21 (1.38%)	50 (0.79%)	71 (0.90%)		
Mean *(SD)*	21.87 *(9.28)*	22.90 *(11.53)*	22.70 (*11.14)*	-3.22	0.001
Median *(IQR)*	20.55 *(10.50)*	21.57 *(11.53)*	21.37 *(11.28)*		
Initial aetiology					
Medical (presumed cardiac)	1474 (97.10%)	5760 (91.00%)	7234 (92.18%)	63.30	<0.001
Traumatic cause	8 (0.53%)	108 (1.71%)	116 (1.48%)		
Drowning	1 (0.07%)	19 (0.30%)	20 (0.25%)		
Drug overdose	4 (0.26%)	139 (2.20%)	143 (1.82%)		
Electrocution	0 (0.00%)	1 (0.02%)	1 (0.01%)		
Asphyxia	2 (0.13%)	186 (2.94%)	188 (2.40%)		
Unknown	29 (1.91%)	117 (1.85%)	146 (1.86%)		
Witnessed by					
Unwitnessed	280 (18.45%)	2677 (42.29%)	2957 (37.68%)	296.48	<0.001
EMS witnessed	135 (8.89%)	763 (12.05%)	898 (11.44%)		
Bystander witnessed	1080 (71.15%)	2838 (44.83%)	3918 (49.92%)		
Unknown	23 (1.52%)	52 (0.82%)	75 (0.96%)		
Bystander commenced CPR					
Yes	1042 (68.64%)	3607 (56.98%)	4649 (59.24%)	571.30	<0.001
No†	443 (29.18%)	2631 (41.56%)	3074 (39.17%)		
Unknown	33 (2.17%)	92 (1.45%)	125 (1.59%)		
Patient transported to hospital					

Yes	1025 (67.52%)	2159 (34.11%)	3184 (40.57%)	567.03	<0.001
No	493 (32.48%)	4171 (65.89%)	4664 (59.43%)		
Declared deceased by ED staff					
Yes	445 (29.31%)	1195 (18.88%)	1640 (20.90%)	80.68	<0.001
No	350 (23.06%)	528 (8.34%)	878 (11.18%)		
Not applicable/not transported	493 (32.48%)	4171 (65.89%)	4664 (59.43%)		
Unknown	230 (15.15%)	436 (6.89%)	666 (8.49%)		

Note: an additional n=166 patients had no rhythm recorded. * n=2 shockable and n=7 non-shockable patients had no recorded age. † includes EMS witnessed cases. ǂ Produced using the t-test for continuous variables and the chi-squared test for categorical variables.