

1 A Randomised trial of Expedited transfer to a cardiac arrest centre for
2 non-ST elevation ventricular fibrillation out-of-hospital cardiac arrest:
3 The ARREST pilot randomised trial

4

5 Tiffany Patterson¹ BSc MBBS PhD, Gavin D Perkins² MD FRCP FFICM FERC, Jubin Joseph¹ MA
6 BMBCh, Karen Wilson¹ MSc, Laura Van Dyck³, Steven Roberston³, Hanna Nguyen¹, Hannah
7 McConkey¹ MA MBBS MRCP, Mark Whitbread⁴ MSc, Rachael Fothergill⁴ PhD, Joanne Nevett⁴ MSc,
8 Miles Dalby⁵ MD, Roby Rakhit⁶ MD, Philip MacCarthy⁷ MD, Divaka Perera¹ MD, Jerry P. Nolan⁸ FRCA
9 FRCP FRCM FFICM, Simon R Redwood¹ MD FRCP FACC FSCAI

10

- 11 1. Cardiovascular Division, The Rayne Institute BHF Centre of Research Excellence, King's
12 College London, St. Thomas' Hospital, London, UK
- 13 2. Warwick Clinical Trials Unit and Heart of England NHS Foundation Trust, Warwick Medical
14 School, University of Warwick, Coventry, UK
- 15 3. London School Of Hygiene and Tropical Medicine Clinical Trials Unit, London, UK
- 16 4. London Ambulance Service, London, UK
- 17 5. Department of Cardiology, Royal Brompton and Harefield NHS Foundation Trust, Middlesex,
18 UK
- 19 6. Department of Cardiology, Royal Free NHS Foundation Trust, London, UK
- 20 7. Department of Cardiology, King's College Hospital NHS Foundation Trust, London, UK
- 21 8. School of Clinical Sciences, University of Bristol and Department of Anaesthesia, Royal United
22 Hospital, Bath, UK

23

24 **Short Title:** ARREST Pilot Randomised Trial

25

26 **Corresponding Author:** Simon R Redwood, Professor of Interventional Cardiology, Cardiovascular
27 Department, Kings College London, St Thomas Hospital, London SE1 7EH

28 Email: simon.redwood@gstt.nhs.uk Tel: +44 (0) 207 188 1083

29

30 **Total Word Count:** 2952 (excl. abstract and references) **Disclosure:** The authors have no disclosures or conflicts
31 of interest to share. **Keywords:** Out-of-hospital Cardiac Arrest, Cardiac Resuscitation Centre, Coronary
32 Angiography. **Acknowledgements:** The Pan-London Acute Coronary Syndrome Advisory Group; Advanced
33 Paramedic Practitioners, London Ambulance Service; Tim Clayton, Laura Van Dyck, London School of Hygiene
34 and Tropical Medicine Clinical Trials Unit.

35 **Funding:** The ARREST pilot randomised trial was funded by an unrestricted educational grant from Zoll Medical,
36 MA. The authors are solely responsible for study conduct, analysis and drafting and editing of the paper and its
37 final contents. The full scale RCT has been granted funding by the British Heart Foundation CS/16/3/32615.

38 **Abstract**

39

40 **Background**

41 Wide variation exists in inter-hospital survival from out-of-hospital cardiac arrest (OHCA).
42 Regionalisation of care into cardiac arrest centres (CAC) may improve this. We report a pilot
43 randomised trial of expedited transfer to a CAC following OHCA without ST-elevation. The objective
44 was to assess the feasibility of performing a large-scale randomised controlled trial.

45

46 **Methods**

47 Adult witnessed ventricular fibrillation OHCA of presumed cardiac cause were randomised 1:1 to either:
48 1) treatment: comprising expedited transfer to a CAC for goal-directed therapy including access to
49 immediate reperfusion, or 2) control: comprising current standard of care involving delivery to the
50 geographically closest hospital. The feasibility of randomisation, protocol adherence and data collection
51 of the primary (30-day all-cause mortality) and secondary (cerebral performance category (CPC)) and
52 in-hospital major cardiovascular and cerebrovascular events (MACCE)) clinical outcome measures
53 were assessed.

54

55 **Results**

56 Between November 2014 and April 2016, 118 cases were screened, of which 63 patients (53%) met
57 eligibility criteria and 40 of the 63 patients (63%) were randomised. There were no protocol deviations in
58 the treatment arm. Data collection of primary and secondary outcomes was achieved in 83%. There
59 was no difference in baseline characteristics between the groups: 30-day mortality (Intervention 9/18,
60 50% vs. Control 6/15, 40%; $P=0.73$), CPC 1/2 (Intervention 9/18, 50% vs. Control 7/14, 50%; $P>0.99$) or
61 MACCE (Intervention 9/18, 50% vs. Control 6/15, 40%; $P=0.73$).

62

63 **Conclusions**

64 These findings support the feasibility and acceptability of conducting a large-scale randomised
65 controlled trial of expedited transfer to CAC following OHCA to address a remaining uncertainty in post-
66 arrest care.

67

68 *Trial Registration: ISRCTN 96585404*

69

70

71

72

73

74

75

76 **Introduction**

77 Out-of-hospital cardiac arrest (OHCA) is a global public health issue. There are 60,000 OHCA per year
78 in the United Kingdom and over 400,000 in the United States.¹⁻³ There is wide variation in both regional
79 and inter-hospital survival rates from OHCA and overall survival remains poor, with a reported average
80 of 7%.⁴ The adoption of systematic approaches to post-resuscitation care may improve long-term
81 survival from OHCA.^{5,6} Regionalisation of care into specialist centres has played a vital role in the
82 management of time-critical illnesses through concentration of services and greater provider
83 experience.⁷⁻¹⁴ Coronary artery disease is responsible for >70% of OHCA, with an acute occlusion
84 demonstrated in 50% of consecutive patients taken immediately to coronary angiography.¹⁵ Multi-
85 faceted interventions including early cardiopulmonary resuscitation (CPR) and defibrillation, followed by
86 timely reperfusion are associated with reduced risk of re-arrest, reduced myocardial dysfunction and
87 thus improved outcomes following cardiac arrest from ST-elevation (STE) myocardial infarction.¹⁶⁻¹⁸ The
88 International Liaison Committee on Resuscitation (ILCOR) suggests transport of all post-arrest patients
89 to a cardiac arrest centre (CAC) with 24/7 access to interventional cardiology facilities to manage the
90 ensuing cardiovascular dysfunction and to diagnose and treat the underlying cause with a view to
91 increasing survival.¹⁹⁻²² The management of cardiac arrest survivors without STE, however, is
92 controversial, with a less time-sensitive approach to cardiac catheterisation. Because of the lack of
93 randomised data, there has been variable uptake of such a strategy amongst the interventional
94 cardiology community. ILCOR states that randomised trials are therefore essential in this population to
95 determine if timely delivery to a CAC improves survival.²³ However, the coordination of this is complex
96 and close interaction is necessary between centres and ambulance services and internally between the
97 emergency department, cardiologists and the critical care team. We performed A (pilot) R Randomised
98 tRial of Expedited transfer to a cardiac arrest centre for non-ST elevation OHCA (ARREST) of
99 presumed cardiac cause to assess the safety and feasibility of conducting a large-scale randomised
100 controlled trial in patients without STE.

101

102 **Methods**

103 This was a pilot multi-centre prospective randomised controlled trial undertaken in London, United
104 Kingdom by London Ambulance Service (LAS) and St Thomas Hospital (for system characteristics see
105 online supplemental information). All adult witnessed out-of-hospital pulseless ventricular tachycardia
106 (VT) or ventricular fibrillation (VF) cardiac arrests without obvious non-cardiac cause (trauma, drowning,
107 suicide, poisoning) attended by the advanced paramedic practitioners in a pre-hospital setting were
108 considered eligible for inclusion. Randomisation was performed following 3 cycles of CPR regardless of

109 return of spontaneous circulation (ROSC). Refractory VF was defined as refractory to shock and drug
110 treatment following 3 cycles of CPR. Patients were excluded from the trial if at the point of
111 randomisation they had evidence of STE on the post-resuscitation ECG, the initial rhythm was asystole
112 or pulseless electrical activity (PEA), a do not attempt resuscitation order was in place or suspected
113 pregnancy.

114

115 Before randomisation, patient management followed standard pre-hospital ALS guidelines. Eligible
116 patients were randomly allocated with the use of sequentially numbered opaque, tamper-proof sealed
117 envelopes (sealedenvelope.com) with pre-assigned random permuted blocks of ten, stratified according
118 to site (advanced paramedic car). Randomisation was performed 1:1 to one of two parallel trial arms:
119 intervention or control. The intervention arm consisted of activation of the pre-hospital triaging system
120 (currently routinely in place for STE patients only) with pre-alert and delivery of the OHCA patient to the
121 catheter laboratory at the dedicated CAC (24 hours a day, 7 days a week). Patients were transported to
122 hospital with or without ROSC. Patients who achieved ROSC received guideline-recommended post-
123 resuscitation care including targeted temperature management (36°C 28 hours, followed by gradual
124 rewarming at 0.5°C per hour)²⁴ and goal-directed therapies. These included evaluation and
125 identification of the underlying cause of arrest with access to immediate reperfusion if necessary and
126 maintenance of normocapnia and normoxia with protective ventilation, optimisation of haemodynamics
127 as well as maintenance of normoglycaemia.²⁵

128

129 The control arm comprised the current standard of pre-hospital care for patients with cardiac arrest of
130 suspected cardiac aetiology as per LAS Cardiac Care Guidance Protocol (supplemental data). Patients
131 were conveyed to the closest emergency department and management thereafter followed standard
132 hospital protocol. In the absence of non-cardiac cause, and in the absence of futility, coronary
133 angiography was recommended within 48-72 hours in the control arm if not performed sooner (evidence
134 of STE or high-suspicion of on-going infarction at the discretion of the physician).

135

136 The primary objective of this pilot trial was to assess the feasibility of a randomised trial in OHCA
137 without STE comparing expedited transfer to a CAC with the current standard of care to assess a
138 difference in 30-day mortality. Feasibility outcome measures included recruitment rate, protocol
139 adherence and the ability to obtain case-report form specific data on participants. The primary clinical
140 endpoint was 30-day all-cause mortality. Secondary clinical endpoints comprised 1) good neurological
141 function at discharge, capped at 30 days according to the cerebral performance category (CPC), the
142 most commonly used post-resuscitation outcome measurement for this purpose.²⁶ 2) The composite of
143 in-hospital major adverse cardiovascular events (MACE) capped at 30 days, defined as: re-infarction²⁷,
144 further revascularisation and bleeding.

145

146 Prior to data analysis, the following additions were made to the trial secondary outcomes to capture all
147 adverse events: 1) MACE was modified to include cerebrovascular events – termed MACCE. 2) Sepsis,
148 defined as two or more components of the systemic inflammatory response syndrome.²⁸

149

150 Trained research staff at St Thomas Hospital collected trial related data. The trial was managed and
151 coordinated by the London School of Hygiene and Tropical Medicine Clinical Trials Unit (LSHTM CTU).
152 The study was granted ethical approval by the United Kingdom National Research Ethics Committee
153 (REC 13/LO/1508). Due to the specific nature of the trial and the immediacy of the intervention, the
154 committee waived the need for prior informed consent. At the earliest appropriate time, the participant
155 or their legal surrogate were asked for delayed consent. The trial was prospectively registered with the
156 International Standard Randomised Controlled Trials Registry (ISRCTN 96585404).

157

158 **Statistical Analysis**

159 Statistical analysis, based on intention to treat, was performed using StatPlus (AnalystSoft, USA) and
160 Prism version 7.0 (GraphPad Software Inc, USA). The sample size (n=40) was selected to allow an
161 assessment of the feasibility of recruitment and implementation of trial processes.²⁹ The pilot study was
162 not powered to detect important differences. However, categorical data were compared using Fisher's
163 exact test; continuous data were compared by 2-sample t-test. The treatment groups were compared
164 for the primary endpoint of all-cause mortality 30-days after randomisation using odds ratios with 95%
165 confidence intervals (CI). The Kaplan-Meier survival curves were drawn to assess differences between
166 groups for the time to an event data examining all-cause mortality at 30 days. All p values were 2 sided.

167

168 **Results**

169 **Patient Population and Feasibility**

170 118 cases were screened, of which 63 patients (53%) met eligibility criteria. Forty of the 63 patients
171 (63%) were randomised over two separate time periods: November 2014 to March 2015 (10 patients)
172 and August 2015 to February 2016 (30 patients). Full data were available on 36 patients (90%); reasons
173 for exclusion are detailed in the patient flow diagram (Figure 1), displayed according to Consolidated
174 Standards of Reporting Trials (CONSORT) recommendation. The trial was stopped at 40 patients
175 because the planned sample size to assess trial feasibility was reached. All randomised patients
176 completed the trial. All patients in the Intervention arm were delivered direct to St Thomas Hospital
177 cardiac catheter lab; patients in the control arm were delivered to the emergency department (ED) in
178 one of 6 hospitals in London: St. Thomas Hospital, St. Mary's Hospital, Chelsea and Westminster
179 Hospital, King's College Hospital, Royal Free Hospital, Royal London Hospital. One patient in the
180 control arm did not reach hospital (online supplement). After randomisation, 4 patients (10%) were
181 found to meet exclusion criteria (the presence of ST-elevation on the post-resuscitation ECG). However,
182 for the intention to treat analysis, all patients were analysed in the group they were randomised to

183 regardless of this or eventual crossover or other protocol deviation. Only one patient was identified as
184 having a non-cardiac cause of arrest (end-stage renal failure) and did not survive to hospital. All other
185 patients had a cardiac cause of arrest. One patient had aortic dissection that was managed within the
186 specialist centre, ten patients were identified as having a scar-related arrhythmia either due to previous
187 infarct or heart muscle disease (requiring implantable cardioverter defibrillator implantation on
188 admission) and the rest were directly due to coronary artery disease.

189

190 Baseline characteristics, the intervals from cardiac arrest to defined events and ambulance service
191 interventions are shown in Table 1. There were no significant differences between the two treatment
192 groups in terms of baseline characteristics and cardiac arrest background variables. All patients
193 presented with witnessed VF out-of-hospital cardiac arrest. Three patients in each group had ventricular
194 fibrillation that was refractory to shock and drug treatment and were transported to hospital without
195 ROSC.

196

197 **Angiographic characteristics**

198 The coronary angiographic findings are summarised in Table 2. Time to coronary angiography was
199 shorter in the intervention arm compared with the control arm (100 [75 to 113] versus 132 [93 to 187];
200 median difference 32, 95% CI -9 to 101; $P=0.08$). The incidence of culprit artery occlusion (responsible
201 for the OHCA) was 44% in the intervention group versus 50% in the control group (OR 0.6, 95% CI 0.1
202 to 2.3; $P=0.7$).

203

204 **Primary and Secondary Clinical Outcomes**

205 The primary clinical endpoint of 30-day all-cause mortality (Table 3) was similar between both study
206 arms (Intervention 9/18, 50% vs. Control 6/15, 44%; OR 0.6, 95% CI 0.2 to 2.9; $P=0.73$). Good
207 neurological function evaluated at discharge, capped at 30 days, was similar in both groups
208 (Intervention 9/18, 50% vs. Control 7/15, 47%; OR 1.1, 95% CI 0.3 to 4; $P>0.99$) (online supplement).
209 The secondary (clinical) composite endpoint of in-hospital MACCE occurred in 11/18 in the Intervention
210 arm compared with 6/15 in the control arm (61% vs. 53% respectively; OR 1.4, 95% CI 0.4 to 4.9;
211 $P=0.73$). One stroke occurred in the control arm, one patient in the intervention arm and two in the
212 control arm underwent further revascularisation and minor bleeding occurred in one patient in the
213 intervention arm. The secondary endpoint of 6-month all-cause mortality was 9/17 (53%) in the
214 intervention arm and 6/10 (60%) in the control arm (OR 0.75, 95% CI 0.2 to 3.8; $P>0.99$). One third of
215 patients in both groups developed sepsis. Vascular complications occurred in one patient in the control
216 arm. Four patients in the intervention group and two patients in the control group required mechanical
217 circulatory support in the form of intra-aortic balloon pump insertion. Length of stay was the same in the
218 two groups (intervention: 4.5, versus control: 4.5, median difference 0, 95% CI -2 to 8; $P=0.19$).

219

220 The Kaplan-Meier 30-day survival curve is shown in Figure 2 (intervention versus control: HR 1.7, 95%
221 CI 0.3 to 10.5; $P=0.6$). In both study arms, a marked attrition in survival was seen between Day 0 and
222 Day 4, with 25% of patients dead in the Intervention arm and 17% in the Control arm (overall 21%). No
223 further patients died between Day 4 and Day 30. Administration of amiodarone was associated with
224 increased 30-day mortality (HR 11.5, 95% CI 1.04 to 126; $P=0.04$). Pre-hospital ROSC (HR 0.1, 95% CI
225 0.01 to 0.7; $P=0.02$), and cardiac arrest in a public location (HR 0.05, 95% CI 0.004 to 0.45; $P=0.01$)
226 were associated with a lower mortality. The performance of coronary angiography was found to
227 negatively influence 30-day mortality (HR 0.15, 95% CI 0.03 to 0.71; $P=0.02$); however, after adjustment
228 for pre-hospital factors, there was no influence on 30-day mortality (HR 0.41, 95% CI 0.05 to 3.5;
229 $P=0.4$), Figure 3.

230

231 Discussion

232 We demonstrated that it is possible to complete a randomised controlled trial comparing a pre-hospital
233 triage system involving delivery of the OHCA patient to a CAC with access to 24/7 interventional
234 cardiology facilities and receipt of a post-cardiac arrest care bundle with the current standard of care in
235 a population of OHCA patients without STE. The main finding of this pilot trial is that performing a large-
236 scale randomised controlled trial is safe, feasible and acceptable. The feasibility of randomisation was
237 demonstrated as follows: (1) recruitment of all adult witnessed shockable OHCA of presumed cardiac
238 cause exceeded the expected rate. (2) It was possible to set up a fast track, rapid intervention service in
239 a single CAC 24/7. (3) Protocol adherence was excellent in the intervention arm. (4) Data completeness
240 was acceptable with documentation of the primary outcome in 83% and secondary outcomes in 80%.

241

242 Based on the findings of the trial pilot, the decision to exclude the refractory cohort from the main trial
243 was made based on 1) logistical challenges of on-scene extrication, transport and performing coronary
244 angiography during mechanical CPR (m-CPR). 2) Poor outcomes relative to the cohort of patients
245 achieving ROSC. 3) The identification that this was a predictor of 30-day mortality. Furthermore, not all
246 frontline vehicles carry m-CPR devices, which may prevent shock-refractory patients receiving the same
247 treatment in the main trial. The PARAMEDIC trial (LUCAS m-CPR device) showed a 5% lower survival
248 rate (significant) in patients with shockable rhythms who received mechanical CPR, although this was
249 not the primary objective of the trial, and should be interpreted with caution.³⁰ Furthermore, removal of
250 this cohort will reduce the likelihood of post randomisation identification of STE (10%).

251

252 Outcome was ascertained in 83%; to improve this we will make use of the NHS information centre; in
253 the PARAMEDIC trial, this enabled 99% follow-up at 30-days.³⁰ Where data cannot be collected in
254 hospital we plan to make use of the London Ambulance Clinical Audit and Research Unit (CARU) and
255 National Institute for Cardiovascular Outcomes Research (NICOR). Because of the geographical
256 position of St Thomas Hospital, a large proportion of the standard of care arm were delivered to a CAC;

257 we anticipate that expanding the trial across London will reduce the proportion of patients in the control
258 arm taken straight to the cardiac catheterisation laboratory.

259

260 The International Liaison Committee on Resuscitation (ILCOR) suggests transport of all post-arrest
261 patients to a cardiac arrest centre with 24/7 access to interventional cardiology facilities.¹⁹⁻²² There has
262 been variable uptake of such a strategy in this cohort; this may be due in part to the lack of randomised
263 data, the need for coordination of organised systems of care, and the heterogeneity of the non-STE
264 population; thus emphasising the need for a randomised controlled trial.

265

266 Our study is consistent with well-established predictors of survival, including ROSC pre-hospital and
267 cardiac arrest in a public location. The predictor of mortality identified was administration of amiodarone,
268 this is likely to represent refractory arrhythmia rather than the effect of amiodarone itself. These are
269 supported by findings in the recently published “amiodarone versus lignocaine and placebo trial in
270 OHCA”, where no difference in survival was shown, with a higher mortality in those with unwitnessed
271 arrest.³¹ Coronary angiography was performed in all patients in the intervention group and just under
272 80% of control, suggesting that coronary angiography was clinically indicated in the latter. The time to
273 coronary angiography was shorter in the intervention arm because of immediate delivery to a CAC, but
274 this did not reach statistical significance in these few patients. In those who underwent coronary
275 angiography, significant coronary disease was identified in two thirds of patients, with a culprit lesion in
276 just over half, which is consistent with published registry data.^{16,32} However should be interpreted with
277 caution because this was a small patient cohort that may not be representative of the patient population.
278 The findings from this pilot also suggest that the absence of STE on the post-arrest ECG does not
279 exclude acute ischemia.¹⁵ The overall mortality, albeit low, is representative of the VF OHCA population
280 that achieves ROSC pre-hospital and is consistent with previous figures published by the London
281 Ambulance Service.³³

282

283 **Limitations**

284 This study was a pilot randomised trial to demonstrate safety and feasibility; the study was not powered
285 to show a difference in 30-day mortality, neurological endpoints or the composite of in-hospital MACCE.
286 The full planned trial with a sample size of 860, will aim to address these questions. The catchment
287 area around St Thomas Hospital was small and may not be representative of the population. Although
288 this pilot provided an indication of the underlying event rate and incidence of occlusive coronary artery
289 disease, the effect size and therefore sample size calculations were based on a combination of studies.
290 These included the above pilot findings, Pan-London Annual OHCA audit data, published registry data
291 (incidence of occlusive disease in OHCA in absence of STE) and randomised trials of reperfusion
292 therapy.^{13,33-35} Based on findings from the trial pilot, inclusion criteria were amended to remove the
293 shock-refractory cohort from the main trial because logistical challenges of managing these patients,

294 and in order to reduce the likelihood of post-randomisation identification of STE. Delayed
295 prognostication (≥ 72 hours) to prevent the premature withdrawal of life-sustaining treatment was not
296 formally instituted in the pilot as this was not the current standard of care; however this will be
297 mandated during the full trial.³⁶

298

299 **Conclusions**

300 This pilot study demonstrated that a large-scale randomised trial comparing the delivery of a cardiac
301 arrest patient without STE to the catheter laboratory at a dedicated cardiac arrest receiving centre with
302 a view to immediate reperfusion and delivery of post-resuscitation care, compared with standard care, is
303 safe and feasible.

304 **References**

- 305 1. Berdowski J, Berg RA, Tijssen JGP, Koster RW. Global incidences of out-of-hospital cardiac
306 arrest and survival rates: Systematic review of 67 prospective studies. *Resuscitation*
307 2010;81(11):1479–87.
- 308 2. Go AS, Mozaffarian D, Roger VL, et al. Executive summary: heart disease and stroke statistics-
309 -2014 update: a report from the American Heart Association. *Circulation* 2014;129(3):399–410.
- 310 3. Perkins GD, Brace-McDonnell SJ, OHCAO Project Group. The UK Out of Hospital Cardiac
311 Arrest Outcome (OHCAO) project. *BMJ Open* 2015;5(10):e008736.
- 312 4. Sasson C, Rogers MAMM, Dahl J, Kellermann AL. Predictors of Survival From Out-of-Hospital
313 Cardiac Arrest: A Systematic Review and Meta-Analysis. *Circ Cardiovasc Qual Outcomes*
314 2009;3(1):63–81.
- 315 5. Bobrow BJ, Spaite DW, Berg RA, et al. Chest compression-only CPR by lay rescuers and
316 survival from out-of-hospital cardiac arrest. *JAMA : the journal of the American Medical*
317 *Association* 2010;304(13):1447–54.
- 318 6. Lick CJ, Aufderheide TP, Niskanen RA, et al. Take Heart America: A comprehensive,
319 community-wide, systems-based approach to the treatment of cardiac arrest. *Critical care*
320 *medicine* 2011;39(1):26–33.
- 321 7. Lurie KG, Idris A, Holcomb JB. Level 1 cardiac arrest centers: learning from the trauma
322 surgeons. *Academic emergency medicine : official journal of the Society for Academic*
323 *Emergency Medicine* 2005;12(1):79–80.
- 324 8. Nolan JP, Lyon RM, Sasson C, et al. Advances in the hospital management of patients
325 following an out of hospital cardiac arrest. *Heart (British Cardiac Society)* 2012;98(16):1201–6.
- 326 9. Kern KB. Cardiac receiving centers: beyond hypothermia. *Current opinion in critical care*
327 2012;18(3):246–50.
- 328 10. Jacobs AK. Regional systems of care for patients with ST-elevation myocardial infarction: being
329 at the right place at the right time. *Circulation* 2007;116(7):689–92.
- 330 11. Acker JE, Pancioli AM, Crocco TJ, et al. Implementation strategies for emergency medical
331 services within stroke systems of care: a policy statement from the American Heart
332 Association/American Stroke Association Expert Panel on Emergency Medical Services
333 Systems and the Stroke Council. *Stroke*. 2007;38(11):3097–115.

- 334 12. Cameron PA, Gabbe BJ, Cooper DJ, Walker T, Judson R, McNeil J. A statewide system of
335 trauma care in Victoria: effect on patient survival. *Med J Aust* 2008;189(10):546–50.
- 336 13. Sunde K, Pytte M, Jacobsen D, et al. Implementation of a standardised treatment protocol for
337 post resuscitation care after out-of-hospital cardiac arrest. *Resuscitation* 2007;73(1):29–39.
- 338 14. Kahn JM, Goss CH, Heagerty PJ, Kramer AA, O'Brien CR, Rubenfeld GD. Hospital volume and
339 the outcomes of mechanical ventilation. *The New England journal of medicine* 2006;355(1):41–
340 50.
- 341 15. Spaulding CM, Joly LM, Monchi M, et al. Immediate coronary angiography in survivors of out-of-
342 hospital cardiac arrest. *The New England journal of medicine* 1997;336(23):1629–33.
- 343 16. Dumas F, Cariou A, Manzo-Silberman S, et al. Immediate percutaneous coronary intervention
344 is associated with better survival after out-of-hospital cardiac arrest: insights from the PROCAT
345 (Parisian Region Out of hospital Cardiac Arrest) registry. *Circulation: Cardiovascular*
346 *Interventions* 2010;3(3):200–7.
- 347 17. Kern KB, Rahman O. Emergent percutaneous coronary intervention for resuscitated victims of
348 out-of-hospital cardiac arrest. *Catheter Cardiovasc Interv* 2010;75(4):616–24.
- 349 18. Reynolds JC, Callaway CW, El Khoudary SR, Moore CG, Alvarez RJ, Rittenberger JC.
350 Coronary angiography predicts improved outcome following cardiac arrest: propensity-adjusted
351 analysis. *Journal of intensive care medicine* 2009;24(3):179–86.
- 352 19. Peberdy MA, Donnino MW, Callaway CW, et al. Impact of Percutaneous Coronary Intervention
353 Performance Reporting on Cardiac Resuscitation Centers: A Scientific Statement From the
354 American Heart Association. *Circulation* 2013;
- 355 20. Peberdy MA, Callaway CW, Neumar RW, et al. Part 9: post-cardiac arrest care: 2010 American
356 Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency
357 Cardiovascular Care. *Circulation* 2010;122(18 Suppl 3):S768–86.
- 358 21. Neumar RW, Nolan JP, Adrie C, et al. Post-cardiac arrest syndrome: epidemiology,
359 pathophysiology, treatment, and prognostication. A consensus statement from the International
360 Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand
361 Council on Resuscitation. *Circulation* 2008;118(23):2452–83.
- 362 22. Noc M, Fajadet J, Lassen JF, et al. Invasive coronary treatment strategies for out-of-hospital
363 cardiac arrest: a consensus statement from the European association for percutaneous
364 cardiovascular interventions (EAPCI)/stent for life (SFL) groups. *EuroIntervention : journal of*
365 *EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European*
366 *Society of Cardiology* 2014;10(1):31–7.
- 367 23. Nikolaou NI, Welsford M, Beygui F, et al. Part 5: Acute coronary syndromes: 2015 International
368 Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science
369 with Treatment Recommendations. *Resuscitation* 2015;95:e121–46.
- 370 24. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted Temperature Management at 33°C versus
371 36°C after Cardiac Arrest. *The New England journal of medicine* 2013;:131117131833001.
- 372 25. Nolan JP, Soar J, Cariou A, et al. European Resuscitation Council and European Society of
373 Intensive Care Medicine 2015 guidelines for post-resuscitation care. *Intensive care medicine.*
374 2015;41(12):2039–56.

- 375 26. Perkins GD, Jacobs IG, Nadkarni VM, et al. Cardiac arrest and cardiopulmonary resuscitation
376 outcome reports: update of the Utstein Resuscitation Registry Templates for Out-of-Hospital
377 Cardiac Arrest: a statement for healthcare professionals from a task force of the International
378 Liaison Committee on Resuscitation (American Heart Association, European Resuscitation
379 Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of
380 Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa,
381 Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular
382 Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and
383 Resuscitation. American Heart Association, Inc; 2015. p. 1286–300.
- 384 27. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction.
385 *European heart journal* 2012;33(20):2551–67.
- 386 28. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions
387 for Sepsis and Septic Shock (Sepsis-3). *American Medical Association*; 2016. p. 801–10.
- 388 29. Sim J, Lewis M. The size of a pilot study for a clinical trial should be calculated in relation to
389 considerations of precision and efficiency. *Journal of Clinical Epidemiology* 2012;65(3):301–8.
- 390 30. Perkins GD, Lall R, Quinn T, et al. Mechanical versus manual chest compression for out-of-
391 hospital cardiac arrest (PARAMEDIC): a pragmatic, cluster randomised controlled trial. *Lancet*
392 2015;385(9972):947–55.
- 393 31. Kudenchuk PJ, Daya M, Dorian P, Resuscitation Outcomes Consortium Investigators.
394 Amiodarone, Lidocaine, or Placebo in Out-of-Hospital Cardiac Arrest. *The New England journal*
395 *of medicine* 2016;375(8):802–3.
- 396 32. Kern KB, Lotun K, Patel N, et al. Outcomes of Comatose Cardiac Arrest Survivors With and
397 Without ST-Segment Elevation Myocardial Infarction: Importance of Coronary Angiography.
398 *JACC Cardiovasc Interv* 2015;8(8):1031–40.
- 399 33. Fothergill RT, Watson LR, Chamberlain D, Viridi GK, Moore FP, Whitbread M. Increases in
400 survival from out-of-hospital cardiac arrest: a five year study. *Resuscitation* 2013;84(8):1089–
401 92.
- 402 34. Patterson T, Whitbread M, Clayton T. TCT-268 Immediate coronARy angiogRaphy after
403 ventricular fibrillation out-of-hospital cardiac arreST (ARREST): A Randomised Controlled Trial
404 (ISRCTN 96585404). *Journal of the ...* 2015;
- 405 35. Franzosi MG, Santoro E, De Vita C, et al. Ten-year follow-up of the first megatrial testing
406 thrombolytic therapy in patients with acute myocardial infarction: results of the Gruppo Italiano
407 per lo Studio della Sopravvivenza nell'Infarto-1 study. The GISSI Investigators. *Circulation*
408 1998;98(24):2659–65.
- 409 36. Sandroni C, Cariou A, Cavallaro F, et al. Prognostication in comatose survivors of cardiac
410 arrest: an advisory statement from the European Resuscitation Council and the European
411 Society of Intensive Care Medicine. *Intensive care medicine* 2014;40(12):1816–31.
- 412
- 413