Refractory cardiac arrest

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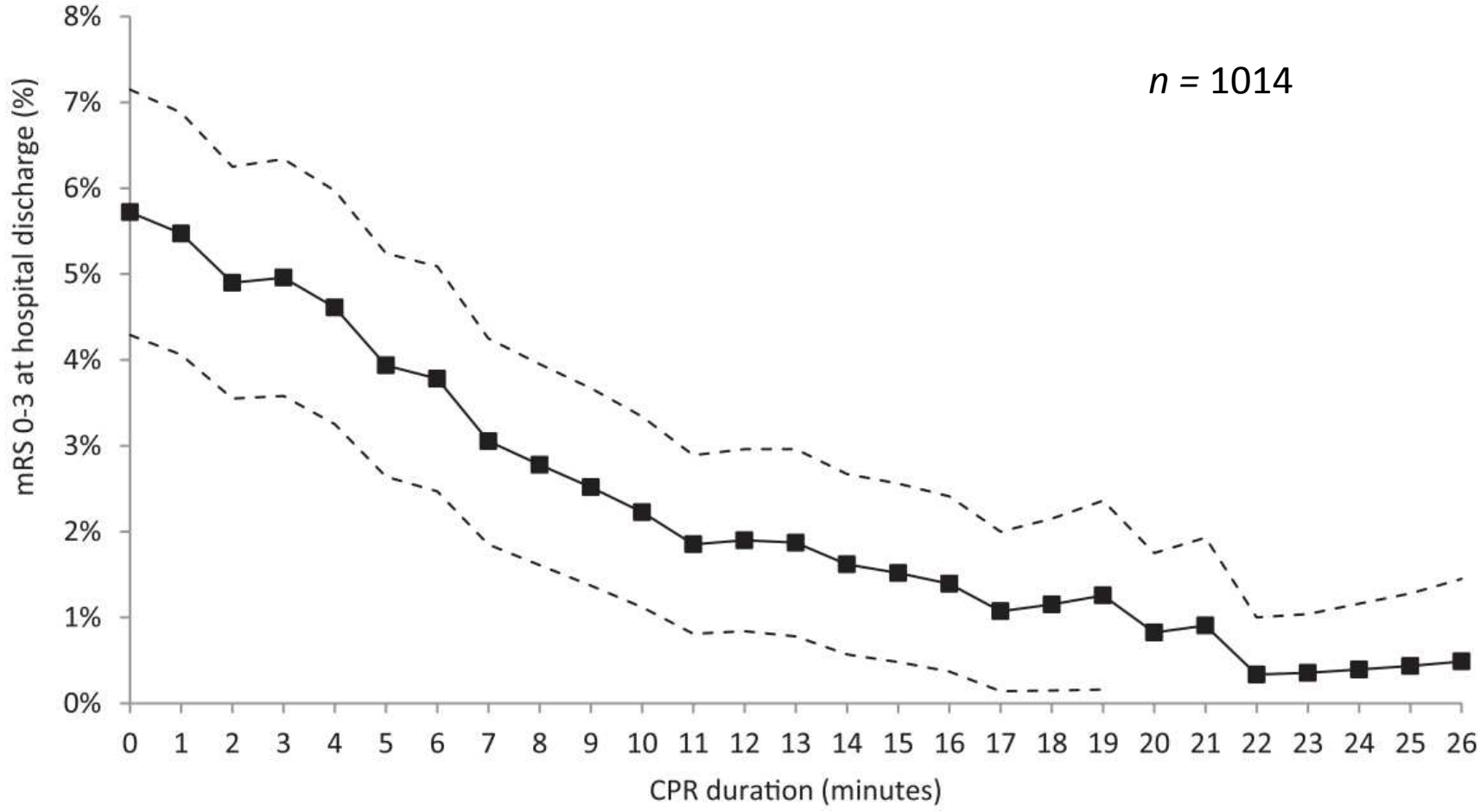
Conflicts of interest

None

Cardiac arrest: how long should we treat?

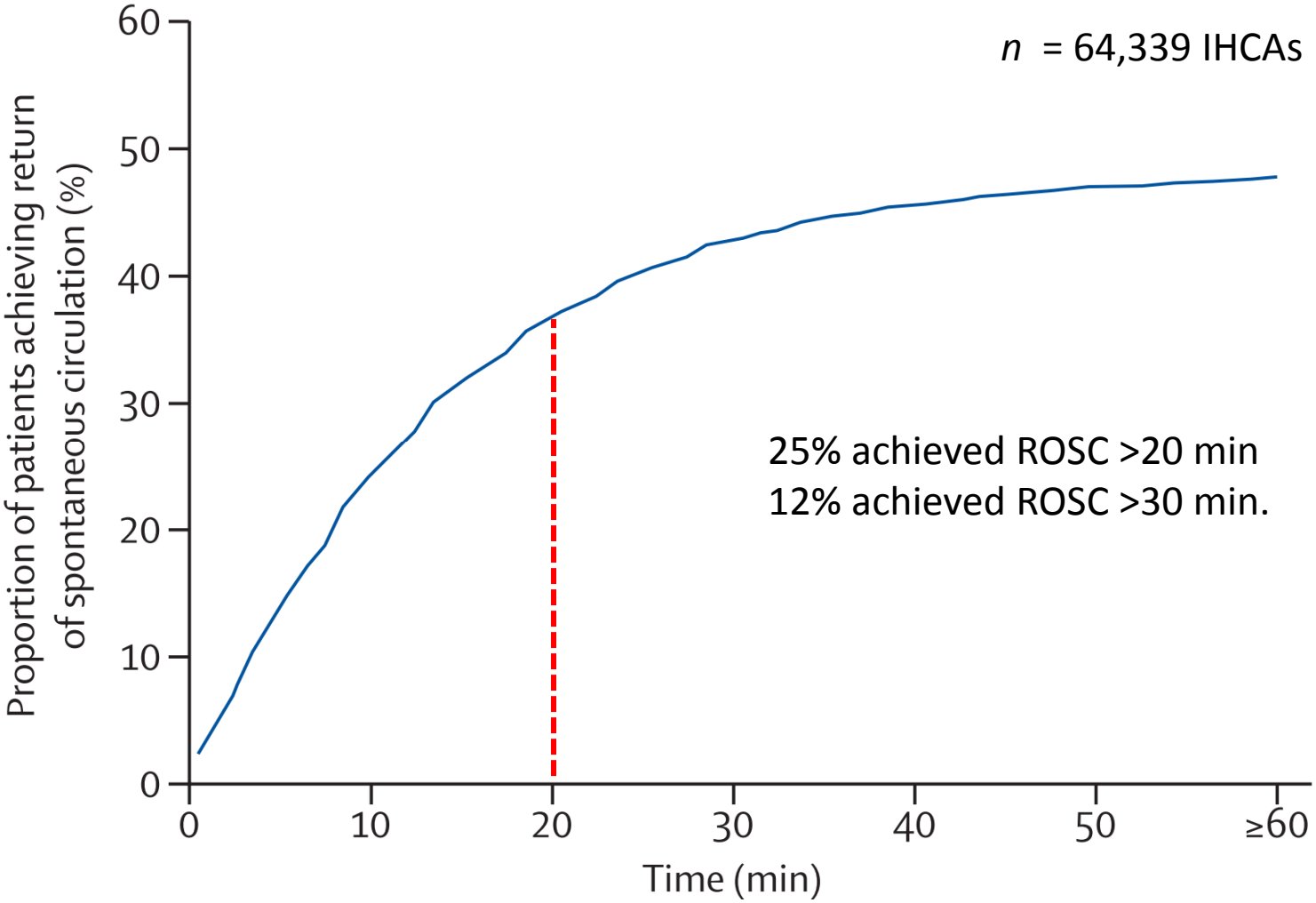
- When initial resuscitation efforts are unsuccessful, the team should decide if and how CPR should be continued
- ERC Guidelines (2015) discontinuation criteria:
  - Ongoing advanced life support
  - Absence of reversible causes
  - Asystole > 20 min.

CPR duration and neurological outcome



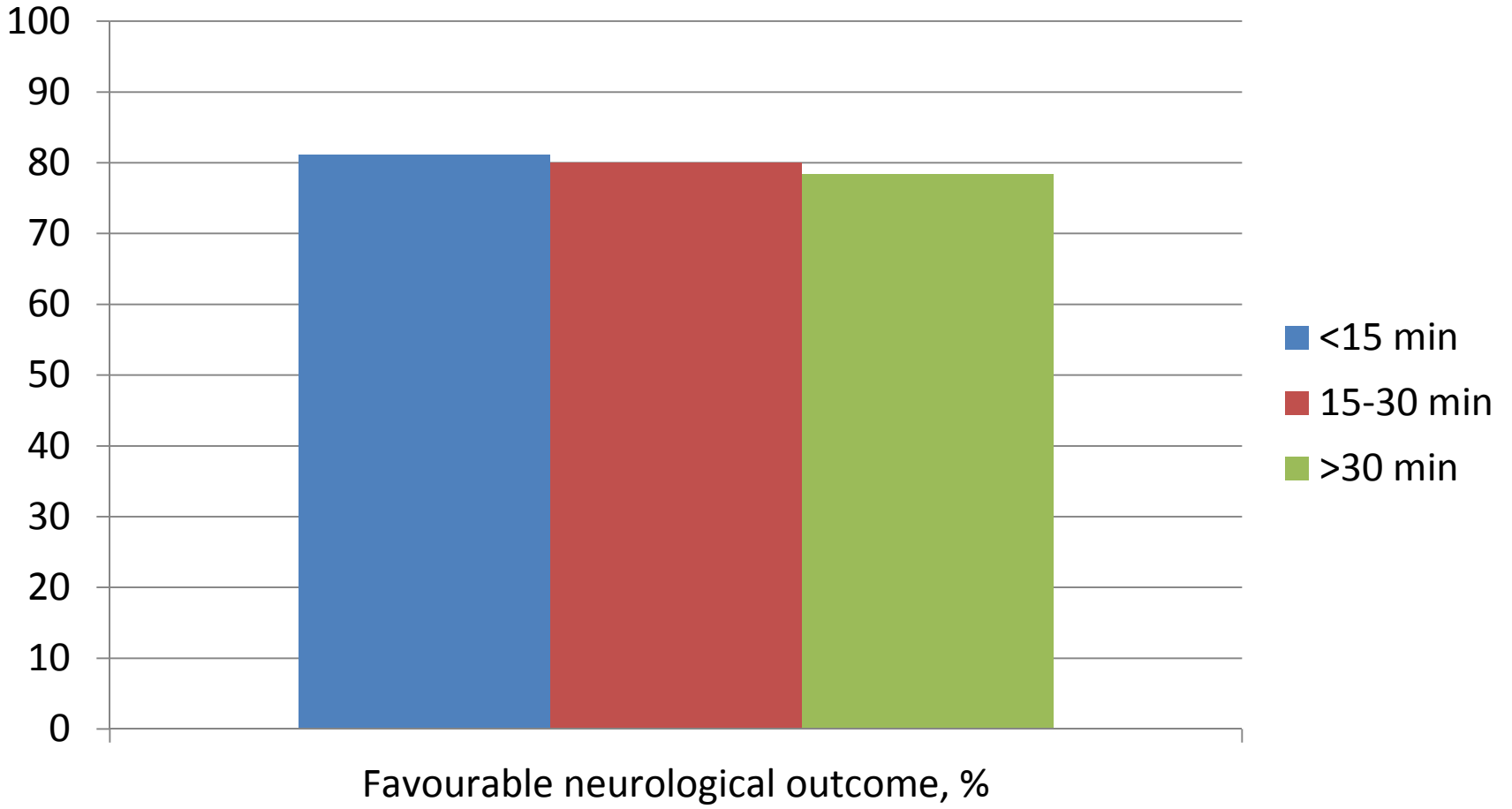
Reynolds J et al. Circulation 2013; 128:2488-2494

However…



Goldberger ZD et al Lancet 2012; 380:1473–1481

Neurological outcome and CPR duration



Goldberger ZD et al Lancet 2012; 380:1473–1481

Factors for survival in refractory CA

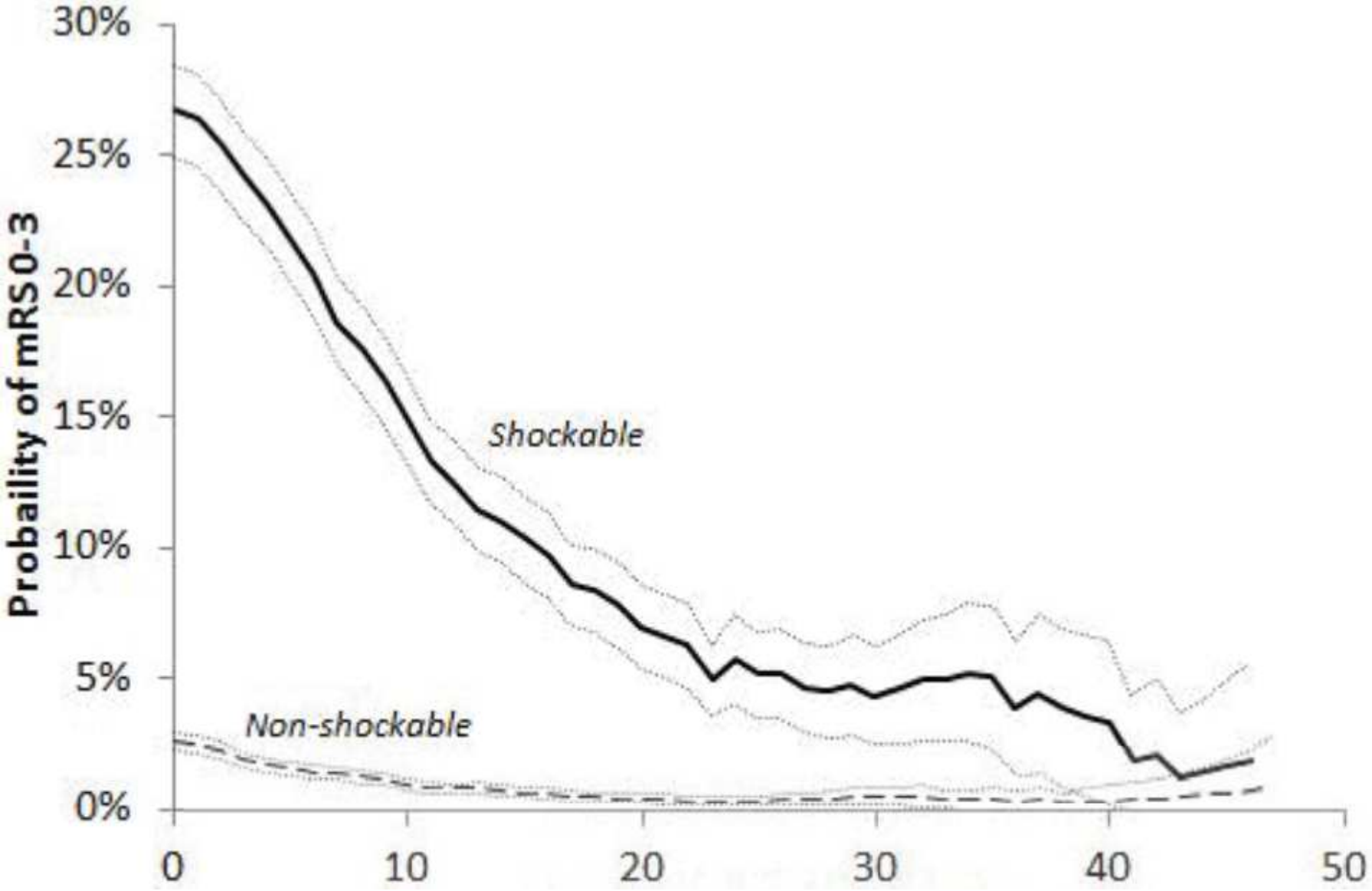
- Secondary analysis of the ROC-PRIMED trial
  - 11,368 OHCAs
  - 905 survived w/mRS ≤3
- Primary exposure: duration of resuscitation
- Association tested with logistic regression models

Reynolds J et al. Circulation. 2016;134:2084-2094

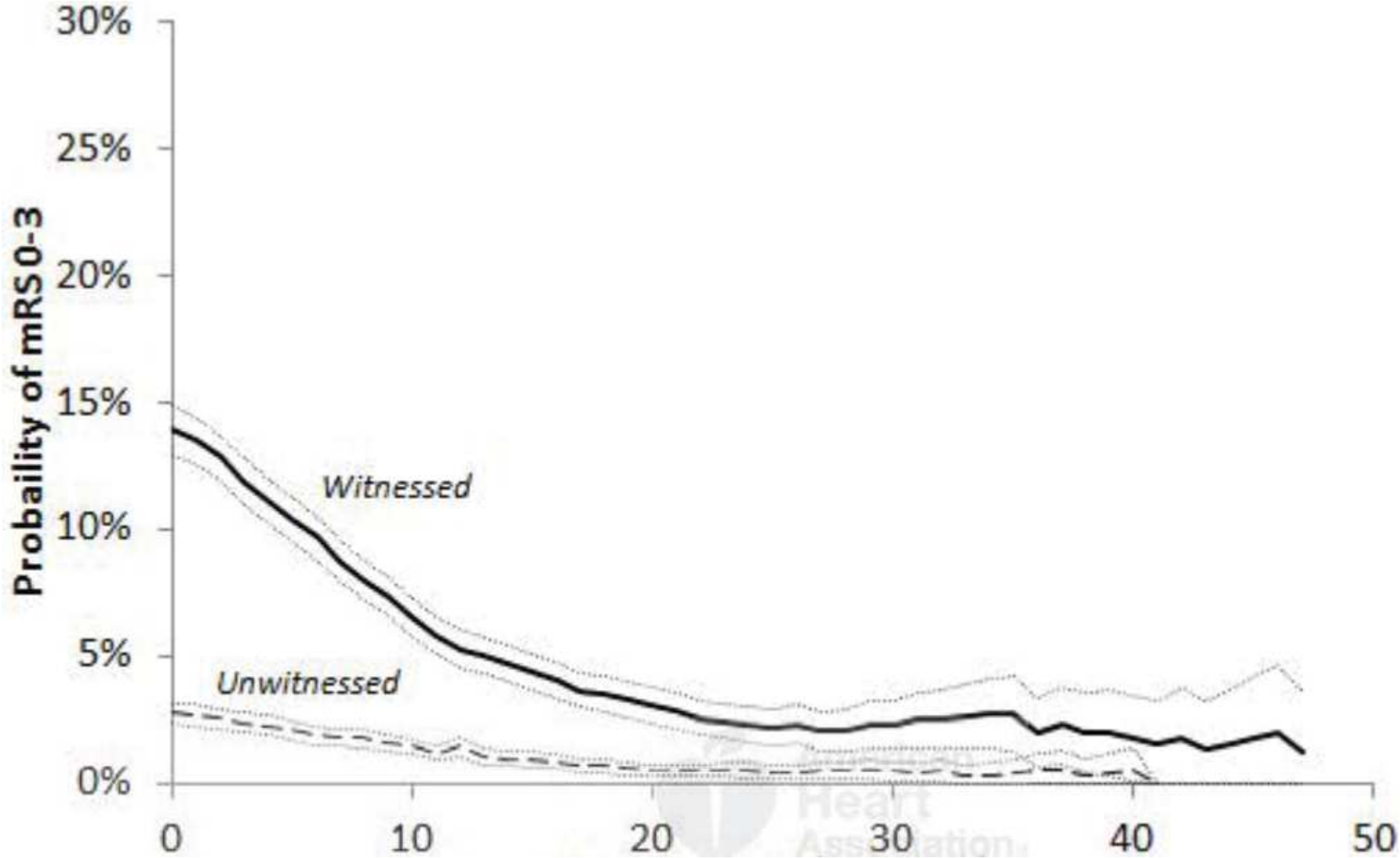
Results

- Duration of resuscitation was independently associated with survival with good neurological outcome
- The longest observed CPR duration with good neurological outcome was 47 minutes

Reynolds J et al. Circulation. 2016;134:2084-2094



Reynolds J et al. Circulation. 2016;134:2084-2094



Reynolds J et al. Circulation. 2016;134:2084-2094

Conclusions

- Subjects with
  - initial VF/pVT
  - witnessed cardiac arrest
  - bystander CPR
- were more likely to survive with favorable outcome after prolonged efforts (30-40 minutes)

Reynolds J et al. Circulation. 2016;134:2084-2094

How *can* we continue CPR in refractory cardiac arrest?

- Rescuer's fatigue
- Low cardiac output → organ damage
- Stone heart

Original Investigation

Mechanical Chest Compressions and Simultaneous Defibrillation vs Conventional Cardiopulmonary Resuscitation in Out-of-Hospital Cardiac Arrest

The LINC Randomized Trial

	Mechanical CPR (n = 1300)	Manual CPR (n = 1289)
Time to ROSC from start of manual CPR by crew		
No. (%) with data	460 (35)	446 (35)
Median (IQR), min	17 (11-25)	14 (9-21)

Rubertsson S et al JAMA 2014; 311:53-61

Contents lists available at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com

Original paper

Incidence and outcome of in-hospital cardiac arrest in Italy: a multicentre observational study in the Piedmont Region☆

Giulio Radeschi[a, b], Andrea Mina[b, c], Giacomo Berta[b, d], Andrea Fassiola[b, e], Agostino Roasio[b, f], Felice Urso[b, g], Roberto Penso[b, d], Ugo Zummo[b, h], Paola Berchialla[i], Giuseppe Ristagno[j, k], Claudio Sandroni[l, *]on behalf of the Piedmont IHCA Registry Initiative[1]

	Non Survivors	Survivors	Overall
	N = 1311	N = 228	N = 1539
Duration of CPR, median (IQR), min	26 [18,35]	8 [3,16]	24 (14–34)

CARDIOVASCULAR

Back from Irreversibility: Extracorporeal Life Support for Prolonged Cardiac Arrest

Massimo Massetti, MD, Marine Tasle, MD, Olivier Le Page, MD, Ronan Deredec, MD, Gerard Babatasi, MD, Dimitrios Buklas, MD, Sylvain Thuaudet, MD, Pierre Charbonneau, MD, Martial Hamon, MD, Gilles Grollier, MD, Jean Louis Gerard, MD, and André Khayat, MD

Departments of Thoracic and Cardiovascular Surgery, Anesthesiology, Cardiology, and Emergency and Critical Care Medicine, University Hospital, Caen, France

- 40 patients, 5 OHCA
- Mean chest compression duration **105 ± 44** minutes
- 8 (20%) survivors, all CPC 1 at 18 months

Massetti et al. Ann Thorac Surg 2005;79:178–84

e-CPR is resource-intensive

- Average cost per patient € 32,260
- Cost per QALY € 144,413
- Cost per QALY € 30,422 (CPC 1 only)

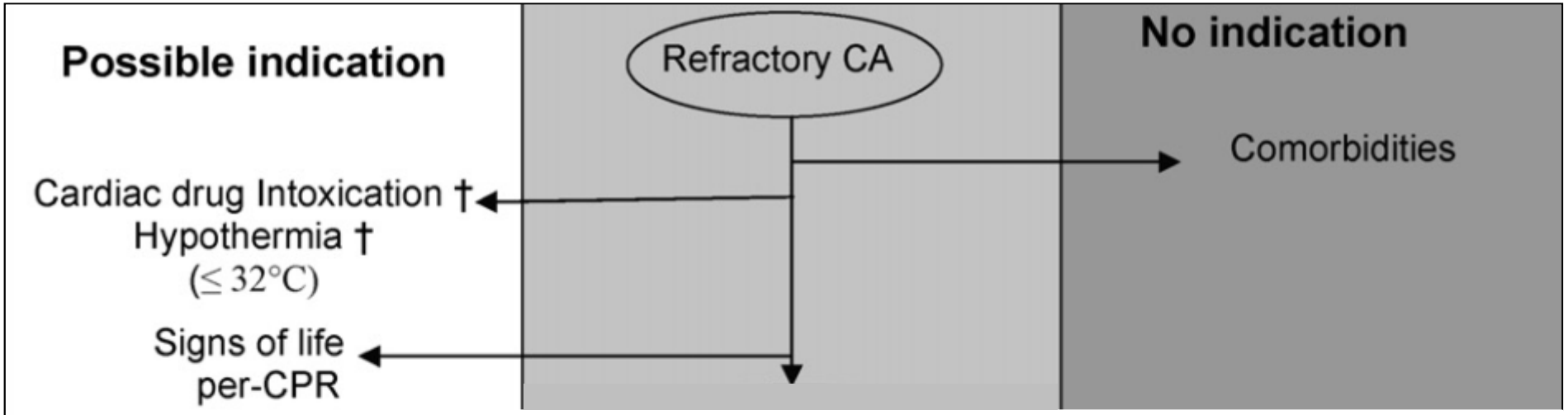
Buriskova et al. Value in Health 2014; A488
Aubin et al J Am Coll Cardiol HF 2016;4:698–708

Annales Françaises d'Anesthésie et de Réanimation 28 (2009) 187–190

INFORMATION PROFESSIONNELLE

Guidelines for indications for the use of extracorporeal life support in refractory cardiac arrest☆

Conseil français de réanimation cardiopulmonaire (CFRC)
Société française d'anesthésie et de réanimation (Sfar)
Société française de cardiologie (SFC)
Société française de chirurgie thoracique et cardio-vasculaire (SFCTCV)
Société française de médecine d'urgence (SFMU)
Société française de pédiatrie (SFP)–Groupe francophone de réanimation et d'urgence pédiatriques (GFRUP)
Société française de perfusion (SOFRAPERF)
Société de réanimation de langue française (SRLF)


Possible indication
Refractory CA
No indication
Comorbidities
Cardiac drug Intoxication †
Hypothermia †
(≤ 32°C)
Signs of life
per-CPR

Artificial
Organs

Extracorporeal Life Support in Out-of-Hospital Refractory Cardiac Arrest

- e-CPR based on the French 2009 guidelines
- n = 32 OHCA, mean age 43.6 ys
  - 19 (59.4%) VF/pVT
  - 10 (31%) due to intoxication or hypothermia
- **2** (6.2%) survivors

Rousse et al Artif. Organs 2015; doi:10.1111/aor.12655

French guidelines: still valid?

- Limited evidence (2009)
  - Based on expert opinion
- Predictors are those of *conventional* CPR
  - Equally valid for e-CPR?
- $ETCO_2$
  - Low sensitivity in pulmonary thromboembolism

Contents lists available at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Review

Predictors of favourable outcome after in-hospital cardiac arrest treated with extracorporeal cardiopulmonary resuscitation: A systematic review and meta-analysis

Sonia D'Arrigo[a], Sofia Cacciola[a], Mark Dennis[b,c], Christian Jung[d], Eisuke Kagawa[e], Massimo Antonelli[a], Claudio Sandroni[a,*]

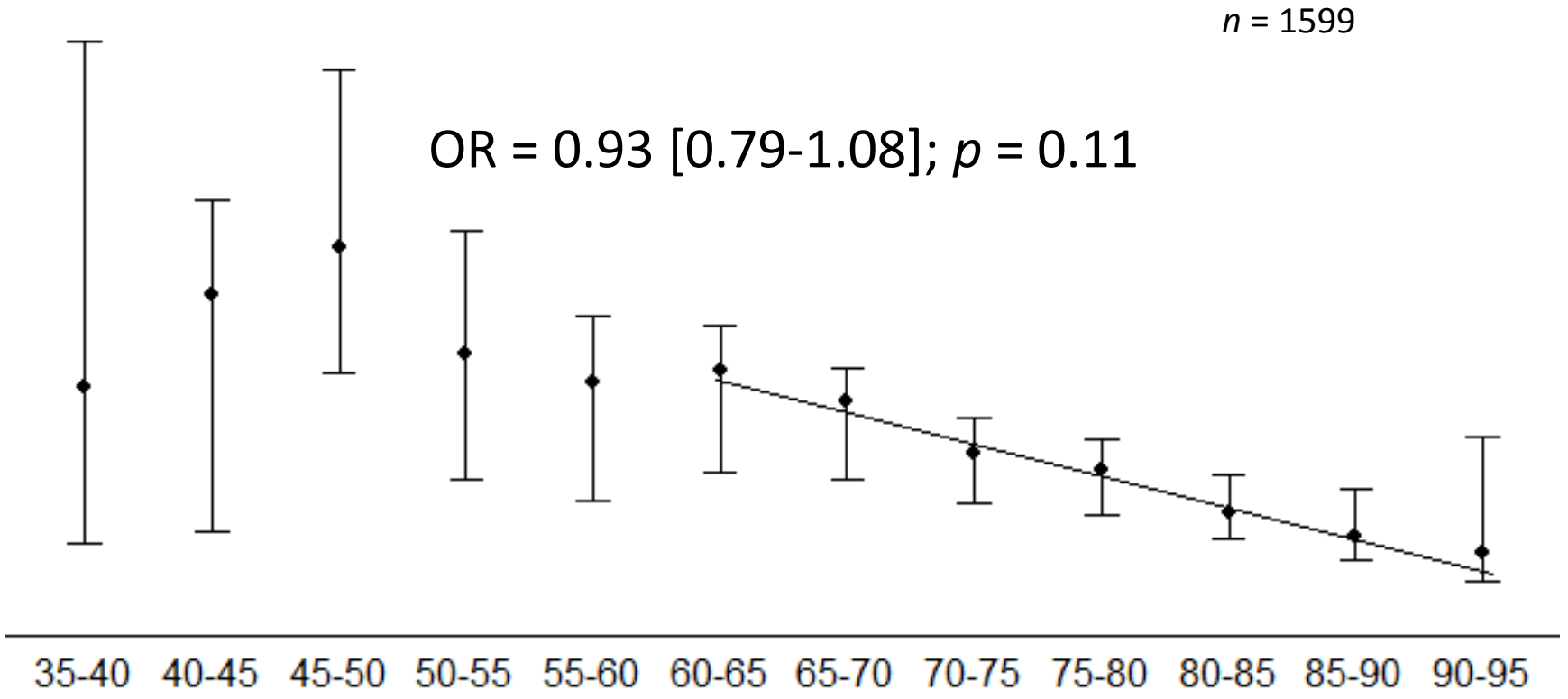
	Survivors	Non-survivors	*p*-value
Pre-arrest			
Age (years)	60.8 ± 1.8	58.4 ± 1.7	0.21
Gender, male, n/total (%)	118/177 (66.7)	288/429 (67.1)	0.57
Cardiac aetiology, n/total (%)	135/170 (79.4)	267/399 (66.9)	0.04
Creatinine, mg/dL	1.11 ± 0.05	1.48 ± 0.06	0.003
Intra-arrest			
Shockable rhythm, n/total (%)	104/210 (49.5)	172/462 (37.2)	0.03
Low-flow time, min	28.7 ± 4.1	46.1 ± 5.1	<0.00001
Total cardiac arrest time, min	36.7 ± 3.7	50.7 ± 7.7	0.05
Blood lactate before ECPR started, mmol/L	6.9 ± 0.8	11 ± 0.5	<0.0001

D'Arrigo S et al Resuscitation 2017; 121 62–70

Determinants of outcome

AGE

c-CPR: survival according to age



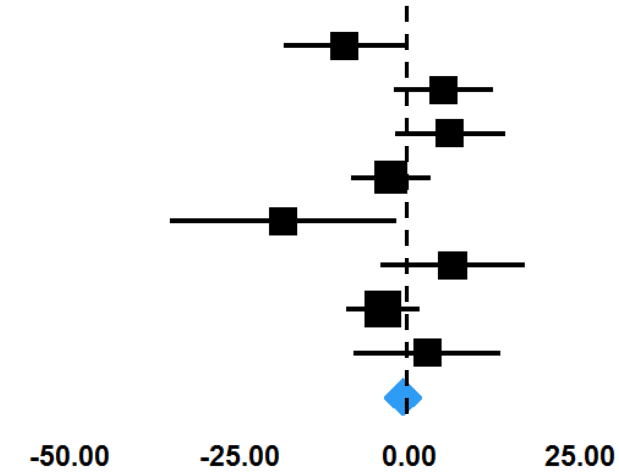
Radeschi G et al Resuscitation 2017; 119:48-55

e-CPR: age difference between survivors vs. non-survivors

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Han 2015	-9.500	4.526	20.487	-18.371	-0.629	-2.099	0.036
Haneya 2012	5.000	3.672	13.484	-2.197	12.197	1.362	0.173
Jung 2015	6.000	4.086	16.696	-2.009	14.009	1.468	0.142
Kagawa 2012	-2.700	2.963	8.780	-8.508	3.108	-0.911	0.362
Kim 2014	-18.600	8.447	71.355	-35.156	-2.044	-2.202	0.028
Leick 2013	6.400	5.348	28.602	-4.082	16.882	1.197	0.231
Park 2014	-3.900	2.687	7.221	-9.167	1.367	-1.451	0.147
Siao 2015	2.700	5.459	29.800	-7.999	13.399	0.495	0.621
	-1.019	1.390	1.931	-3.742	1.705	-0.733	0.464

Statistics for each study

Difference in means and 95% CI



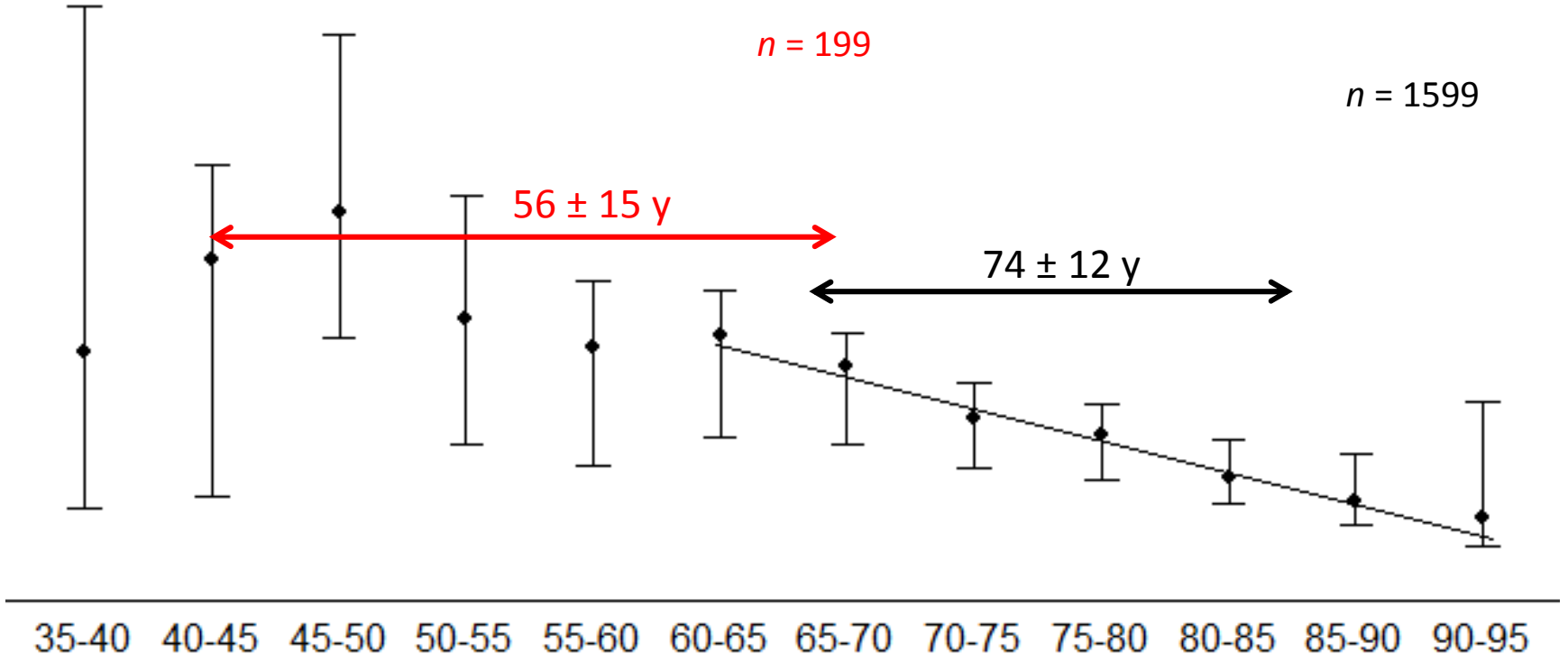
8 studies, 577 patients, 2012-2015

Sandroni C. et al, 2016. *Personal communication*

Age

- The role of age as an independent predictor of survival after c-CPR is debated
- The French 2009 guidelines do not include age among selection criteria for e-CPR
- However, patients' age is low in e-CPR studies
  - Mean 54.3 ± 3.2 years in 39 studies (2003-2016)

IHCA survival according to age



Italian Cardiac Arrest Registry, 2016

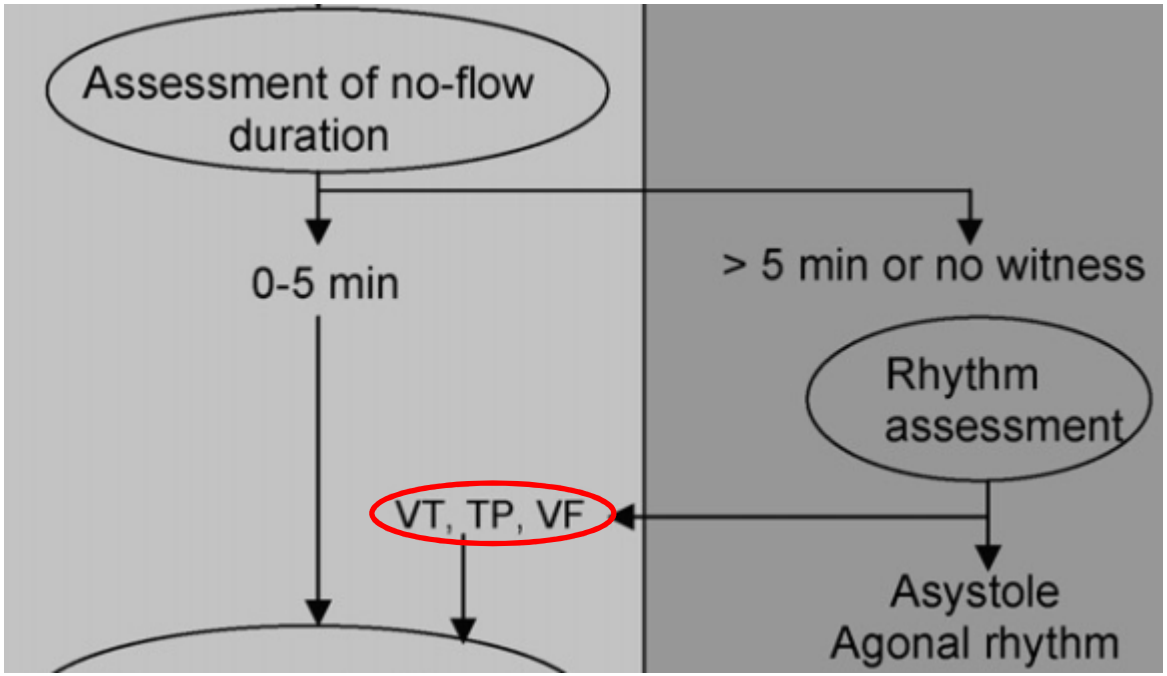
Wang et al, Resuscitation 2014; 85:1219-24

Determinants of outcome

RHYTHM

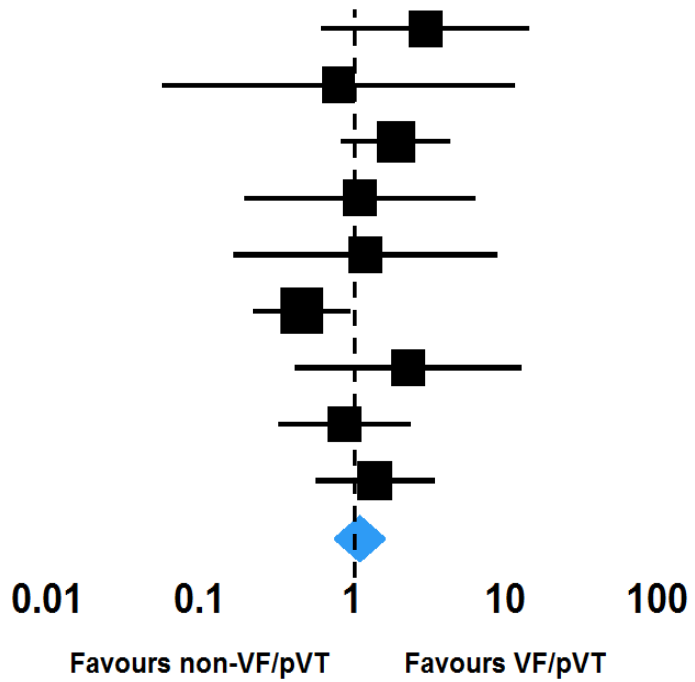
Rhythm

- VF/pVT is a major predictor of survival after **c**-CPR



OR for survival after e-CPR in VF/pVT

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Ha 2016	2.970	0.620	14.220	1.362	0.173
Han 2015	0.800	0.056	11.504	-0.164	0.870
Kagawa 2012	1.905	0.839	4.326	1.541	0.123
Leick 2013	1.100	0.192	6.286	0.107	0.915
Mazeffi 2016	1.200	0.164	8.799	0.179	0.858
Park 2014	0.458	0.219	0.957	-2.078	0.038
Maekawa 2013	2.280	0.413	12.579	0.946	0.344
Haneya 2012	0.874	0.324	2.361	-0.266	0.790
Chen 2008	1.390	0.567	3.410	0.719	0.472
	1.083	0.743	1.578	0.416	0.677



Sandroni C. et al, 2016. Manuscript in preparation.

VF/pVT as an outcome predictor: limited value in e-CPR?

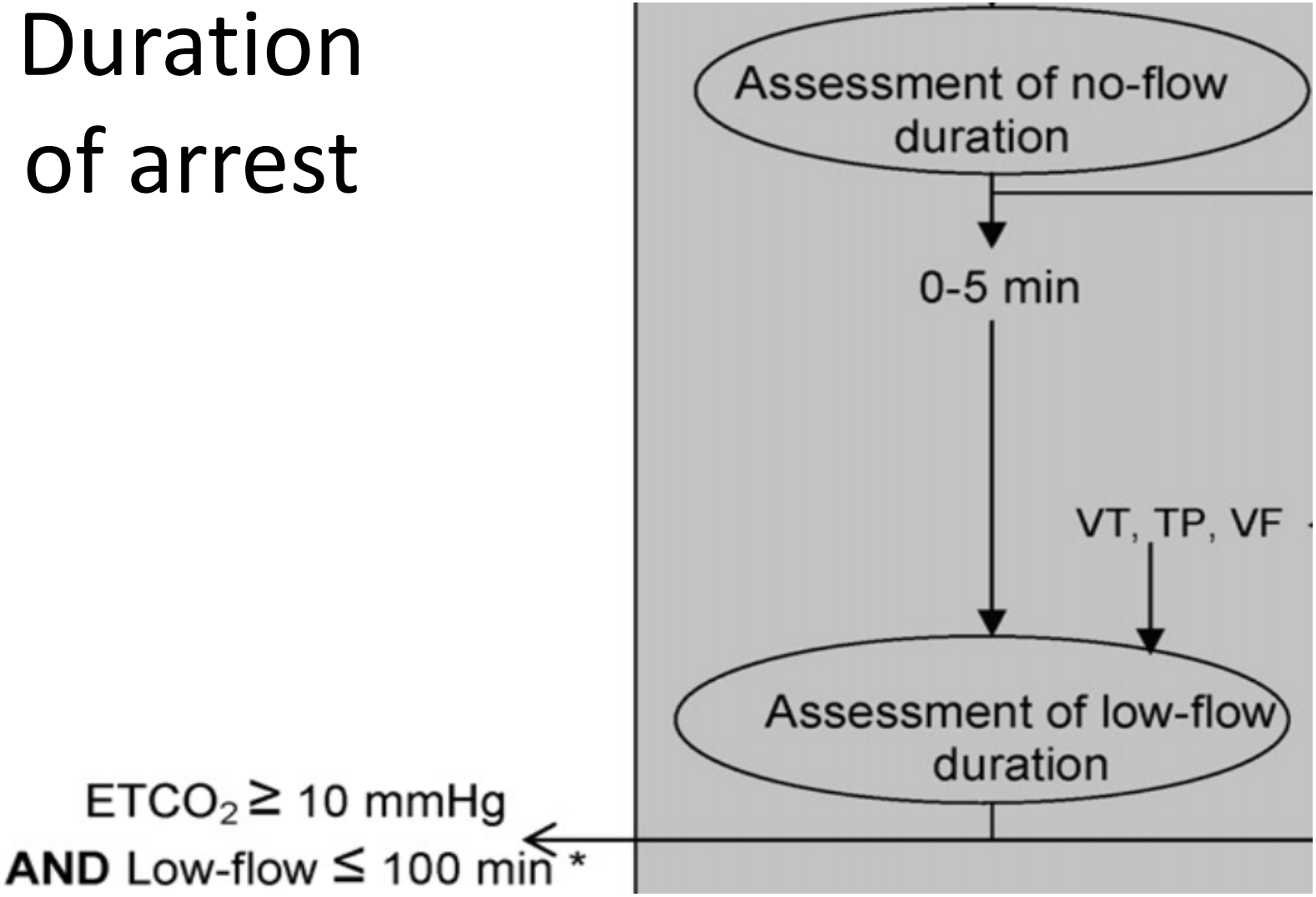
- Selection bias
  - Prevalence of VF/pVT in e-CPR studies = 47.3%
- e-CPR is considered late during resuscitation
  - Patients are outside the electrical phase
- Aetiology
  - Some reversible causes of prolonged cardiac arrest do not present with VF/pVT

39 studies, 3134 patients, 2003-2016

Determinants of outcome

DURATION OF ARREST

Duration of arrest

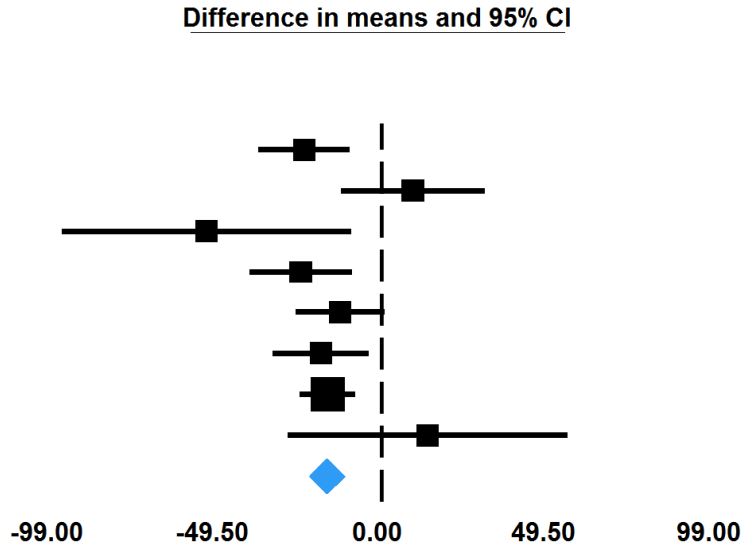


Ann Fr Anesth Réan 2009; 28 :187–190.

Duration of arrest before e-CPR

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Chen 2006	-22.000	6.850	46.926	-35.426	-8.574	-3.212	0.001
Ha 2016	10.500	10.880	118.364	-10.823	31.823	0.965	0.334
Han 2015	-51.200	21.924	480.660	-94.170	-8.230	-2.335	0.020
Haneya 2012	-23.000	7.708	59.417	-38.108	-7.892	-2.984	0.003
Kagawa 2012	-11.300	6.647	44.177	-24.327	1.727	-1.700	0.089
Leick 2013	-17.000	7.216	52.070	-31.143	-2.857	-2.356	0.018
Park 2014	-15.000	4.110	16.891	-23.055	-6.945	-3.650	0.000
Siao 2015	15.000	21.224	450.449	-26.598	56.598	0.707	0.480
	-15.209	2.566	6.582	-20.237	-10.181	-5.928	0.000

Statistics for each study

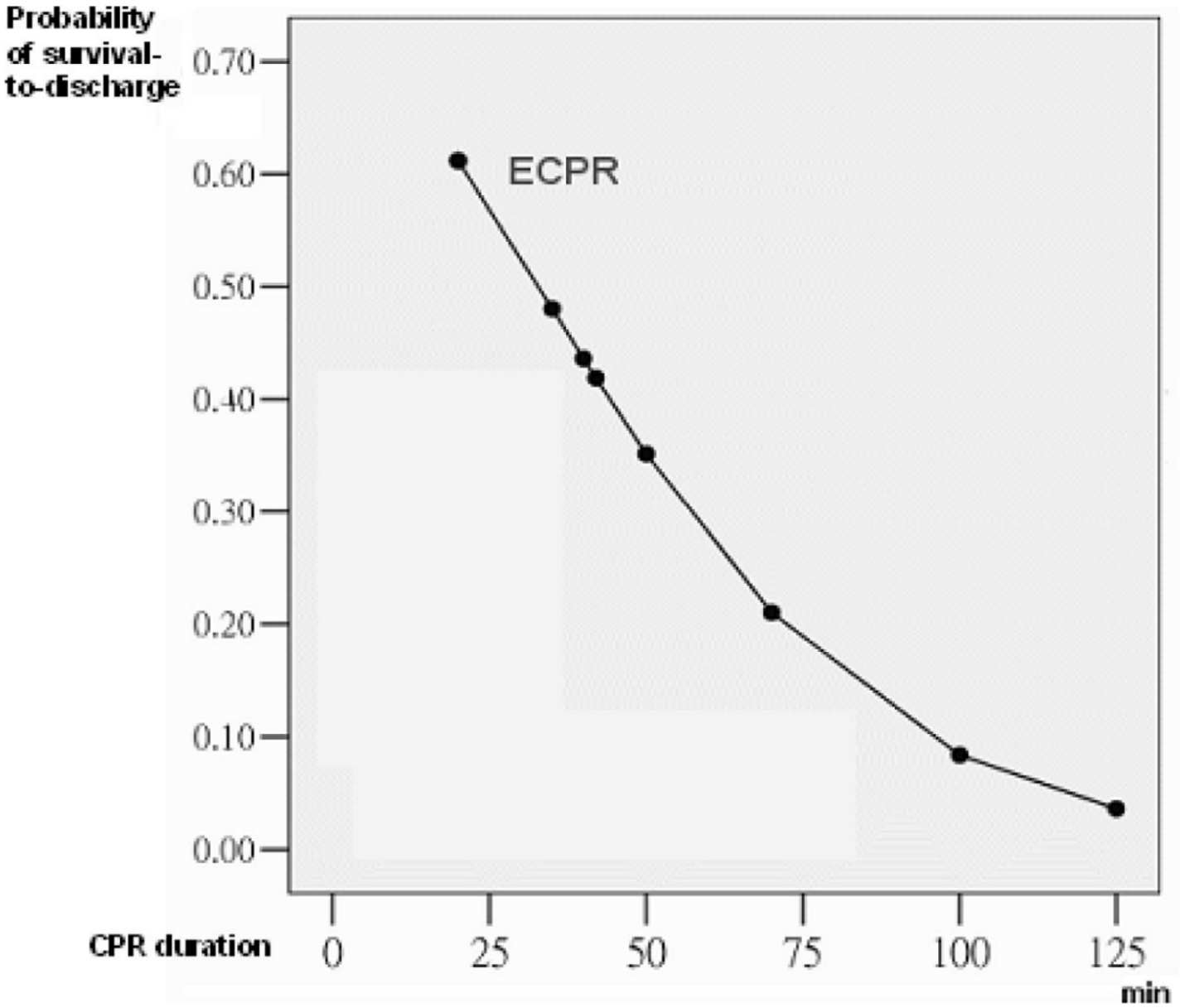


Significantly shorter in survivors

Duration of arrest before e-CPR
HR of death (multivariable analysis)

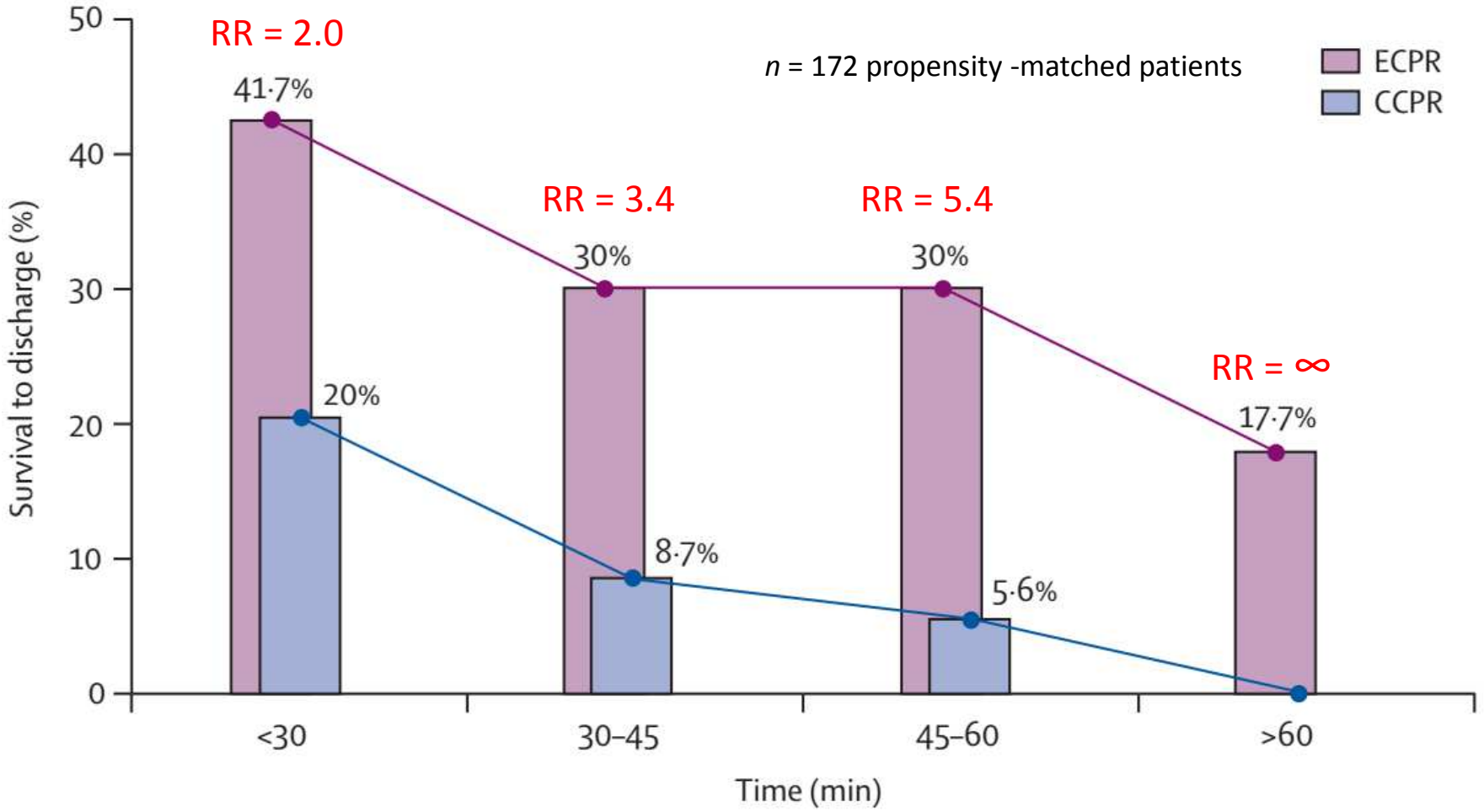
Author, year	HR	*p*
Wang et al, 2014	1.01	<0.001
Kim et al, 2016	1.05 [1.02 – 1.09]	0.005

Wang C-H et al., Resuscitation 2014; 85:1219-24.
Kim DH et al., J Thor Cardiovasc Surg 2016; 49:273-79.



Chen Y et al Crit Care Med 2008; 36:2529–2535

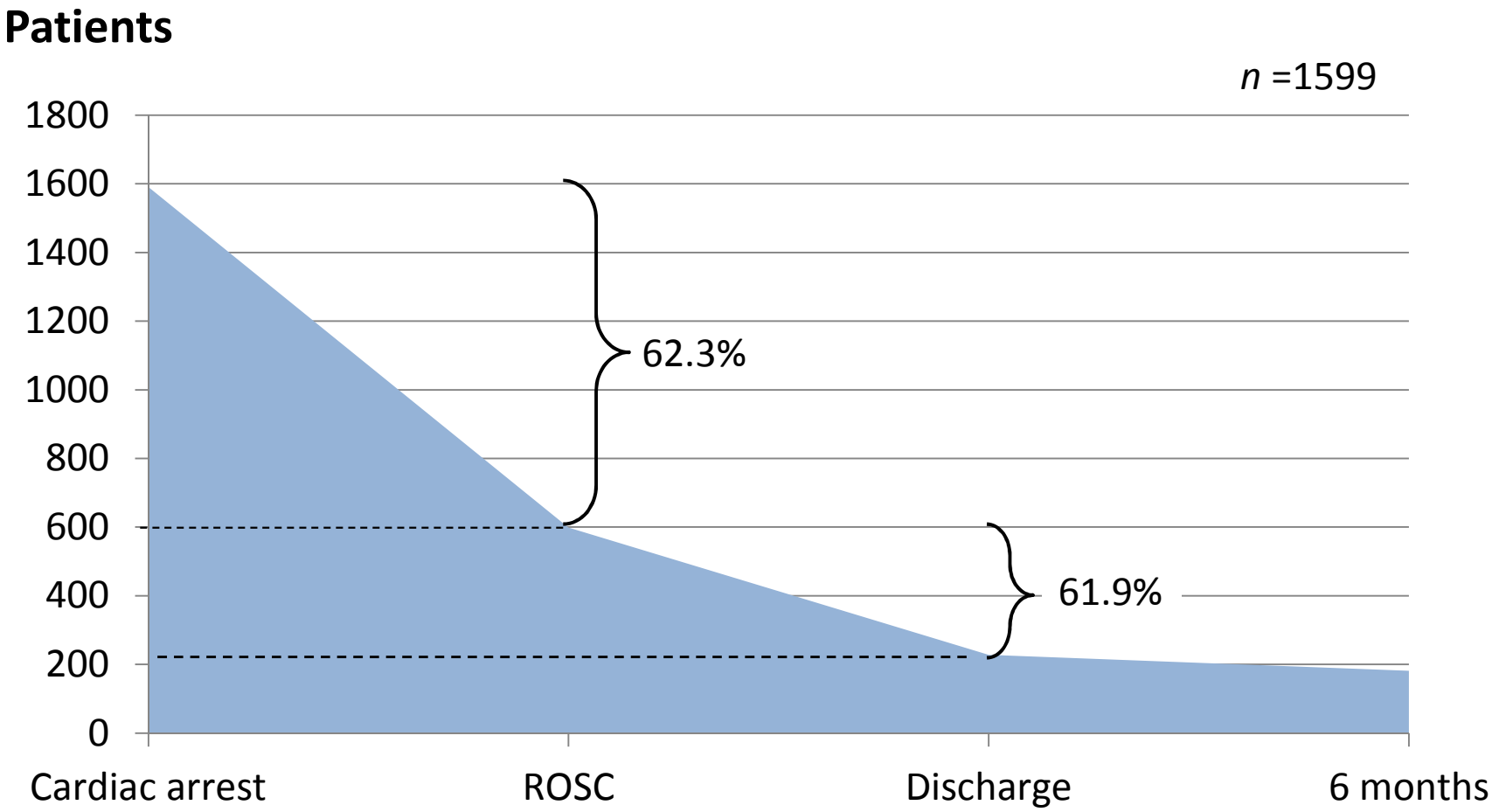
Cardiac arrest duration and survival: c-CPR vs. e-CPR



Chen Y et al., Lancet 2008; 372: 554–61.

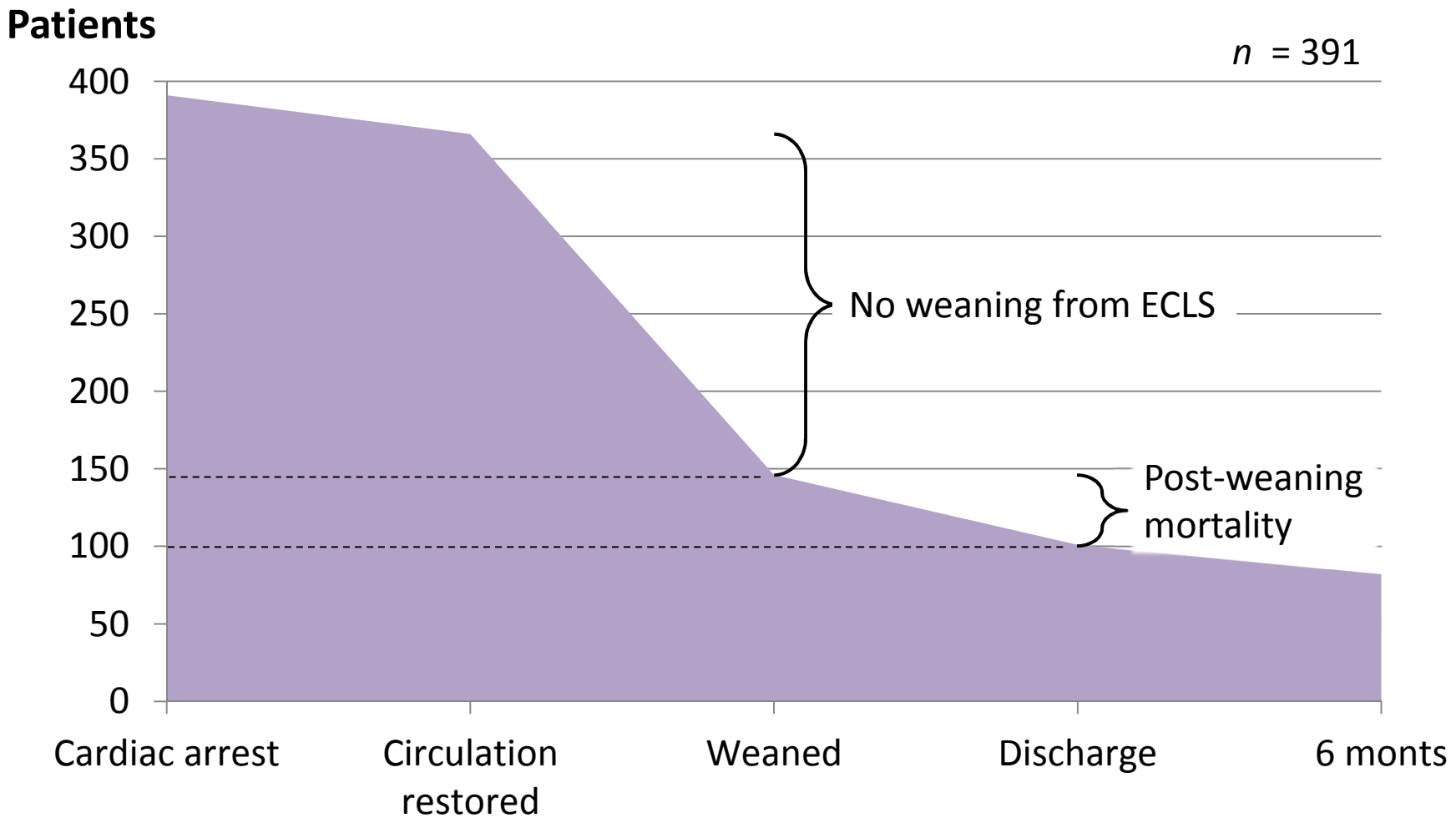
OUTCOMES

Mortality after c-CPR



Italian Cardiac Arrest Registry , 2016.

Mortality after e-CPR

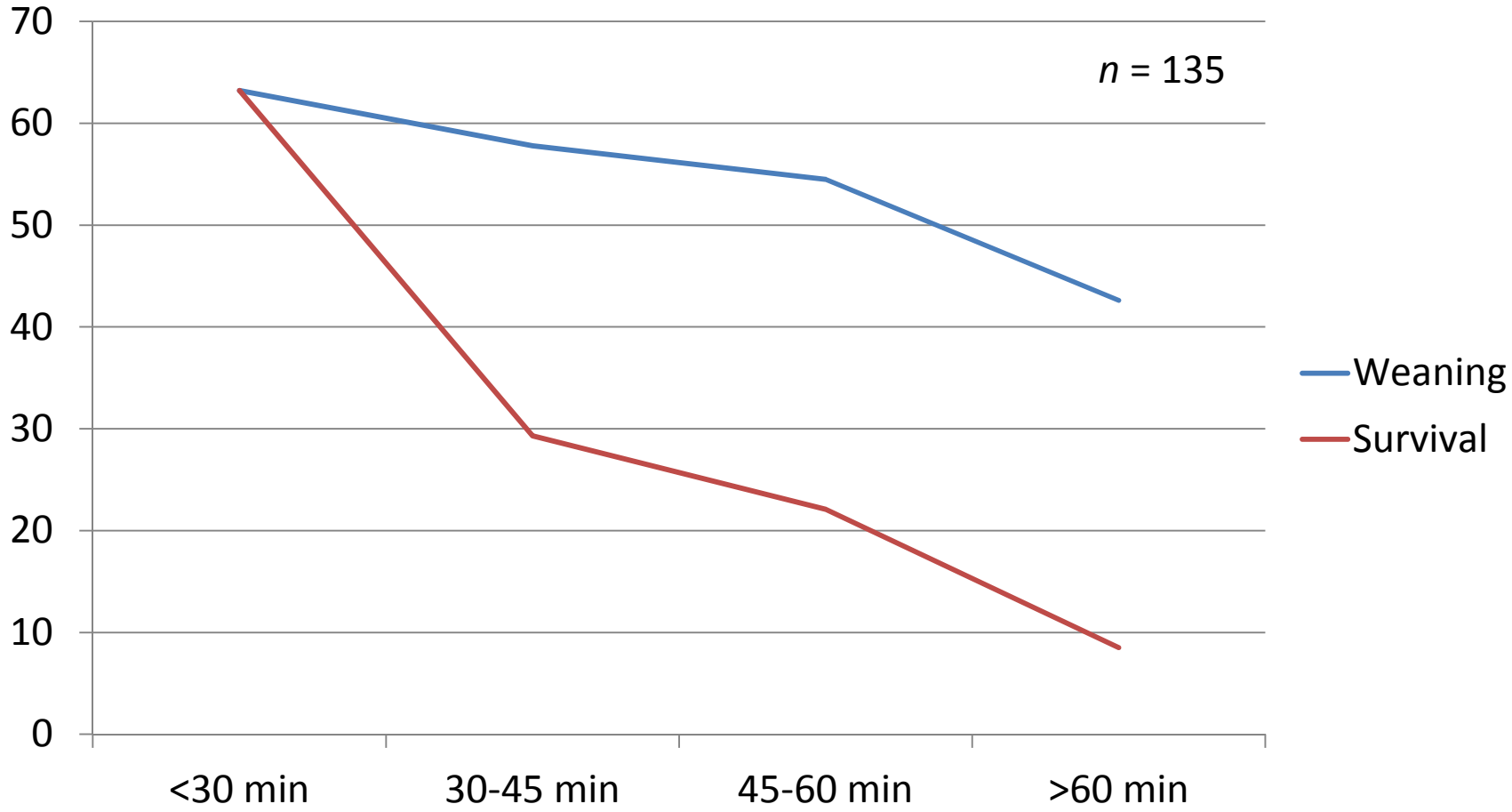


n = 8 e-CPR studies, 2008-2016.

Mortality after e-CPR: major causes

- Circulatory failure
  - No recovery of spontaneous heartbeat
  - Low flow
  - Circulatory shock

Rates of weaning and survival according to arrest duration



Chen Y et al Crit Care Med 2008; 36:2529–2535

Mortality after e-CPR: major causes

- Circulatory failure
  - No recovery of spontaneous heartbeat
  - Haemodynamic instability
- **Multiorgan failure (MOF)**

Prevalence of AKI after c-CPR

Author, year	n. pts	AKI definition	AKI prevalence, n (%)
Mattana, 1993	56	Abrupt rise in serum creatinine	16 (29)
Domanovits, 2001	187	≥25% CrCl decrease ≤24h	22 (12)
Hasper, 2009	171	AKIN Stage 1-3	67 (39)
Chua, 2012	105	RIFLE Stage 2-3 (I/F)	33 (31)
Yanta, 2013	311	RIFLE Stage 2-3 (I/F)	59 (19)
Tujjar, 2015	582	AKIN stage 1-3	85 (43)
Geri, 2015	82	AKIN Stage 1-3	280 (48)
Kim, 2015	199	KDIGO Stage 1-3	66 (81)
OVERALL	**1693**		**628 (37%)**

Predictors of AKI: non-VF/pVT, longer duration of arrest, higher Cr on admission, post-resuscitation shock

Sandroni C et al. Min Anestesiol 2016; 82:989-99.

A meta-analysis of complications and mortality of extracorporeal membrane oxygenation

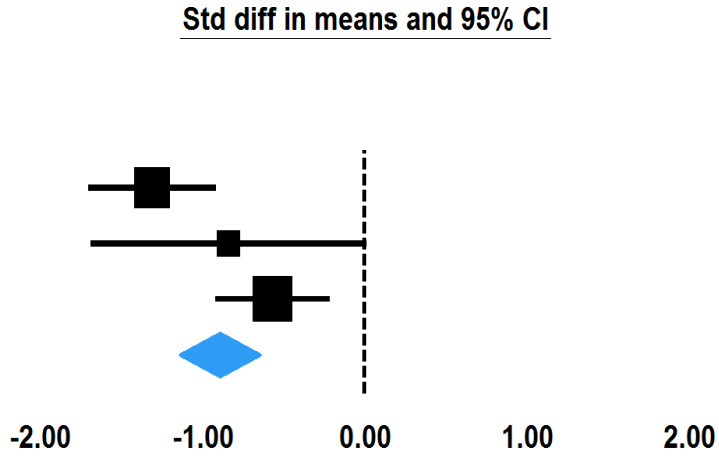
Alberto Zangrillo, Giovanni Landoni, Giuseppe Biondi-Zoccai, Massimiliano Greco, Teresa Greco, Giacomo Frati, Nicolò Patroniti, Massimo Antonelli, Antonio Pesenti and Federico Pappalardo

- 12 studies, 1763 pts, mostly on V-A ECMO
- Overall mortality 54%
- Major complications:
  - **Renal failure requiring RRT (52%)**
  - Bleeding or infection (33%)
  - Haemolysis (18%)
  - **Liver dysfunction (16%)**

Zangrillo A et al Crit Care Resusc 2013; 15: 172–178

SOFA in e-CPR survivors vs. non-survivors

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Chen 2008	-1.313	0.198	0.039	-1.702	-0.925	-6.620	0.000
Han 20015	-0.843	0.431	0.186	-1.688	0.001	-1.957	0.050
Park 2014	-0.572	0.178	0.032	-0.920	-0.224	-3.220	0.001
	-0.896	0.126	0.016	-1.144	-0.649	-7.088	0.000

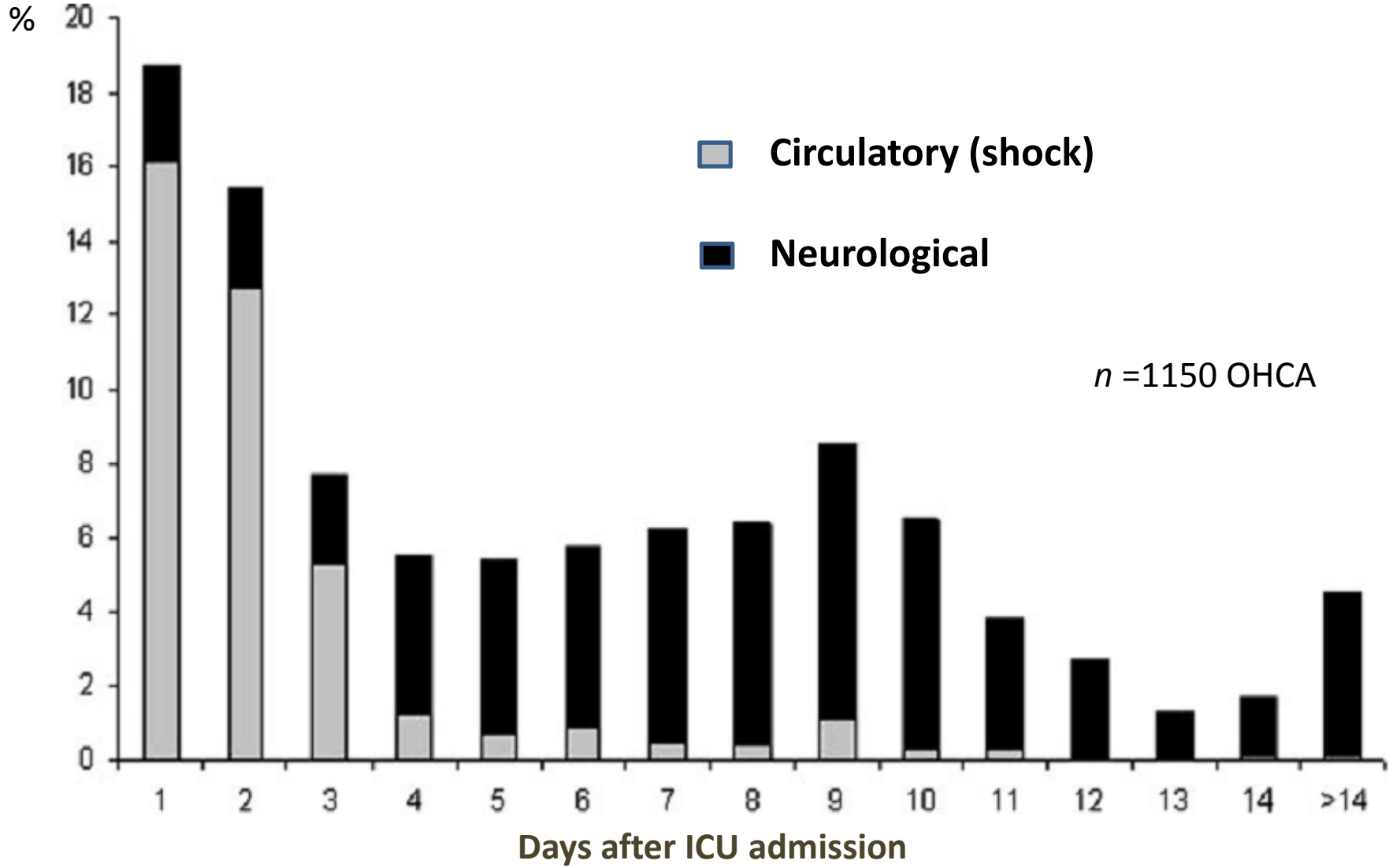


3 studies, 324 patients, 2008-2015

Mortality after e-CPR: major causes

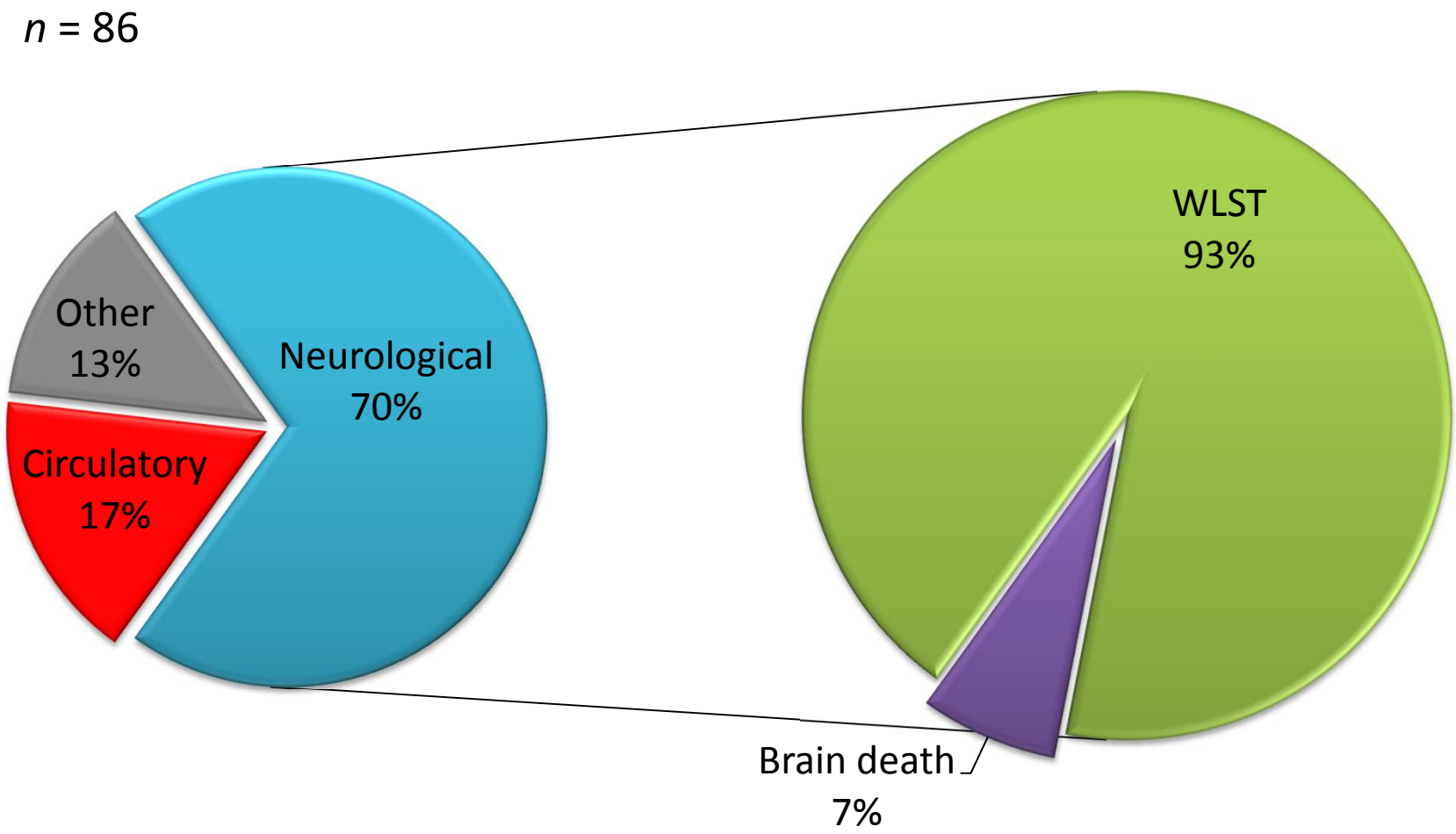
- Circulatory failure
  - No recovery of spontaneous heartbeat
  - Haemodynamic instability
- Multiorgan failure (MOF)
- **Brain injury**

Causes of death after c-CPR



Lemiale V et al, *Intensive Care Med* 2013; 39: 1972–80

Causes of death after c-CPR



Dragancea I.V. et al., Resuscitation 2013; 84: 337–342

SYSTEMATIC REVIEW

The rate of brain death and organ donation in patients resuscitated from cardiac arrest: a systematic review and meta-analysis

Claudio Sandroni[1*], Sonia D'Arrigo[1], Clifton W. Callaway[2], Alain Cariou[3], Irina Dragancea[4], Fabio Silvio Taccone[5] and Massimo Antonelli[1]

- 26 studies (23,388 patients)
- Brain death more common in e-CPR vs. c-CPR patients (27.9% vs. 8.3%; p <0.001)
- Timing of brain death 3.2 ± 0.4 days after CA
- Overall rate of organ donation 41.8%

Sandroni C. et al. Intensive Care Med 2016; *in press*.

Conclusions

- Refractory cardiac arrest has no specific definition
  >20 minutes is a possible threshold
- Treatment can be achieved with c–CPR but mechanichal CPR is an option
  - However, data on its use are still limited
- ECPR is probably the ultimate option for refractory CA
  - Selected population
  - Selection criteria still uncertain

Conclusions - 2

- The duration of cardiac arrest, and the consequent severity of anoxic-ischaemic injury, is a major determinant of outcome
- Age and initial rhythm appear to be less important, but there is a risk of bias.

Conclusions - 3

- As for conventional CPR, cardiac or brain dysfunction are major causes of death.
- However, they have different manifestations:
  - Cardiac dysfunction occurs as a failure to wean
  - Brain injury often occurs as brain death (x 3 more common than with conventional CPR)
- Additional causes of death include bleeding and multiorgan failure.

Thank you for your attention!

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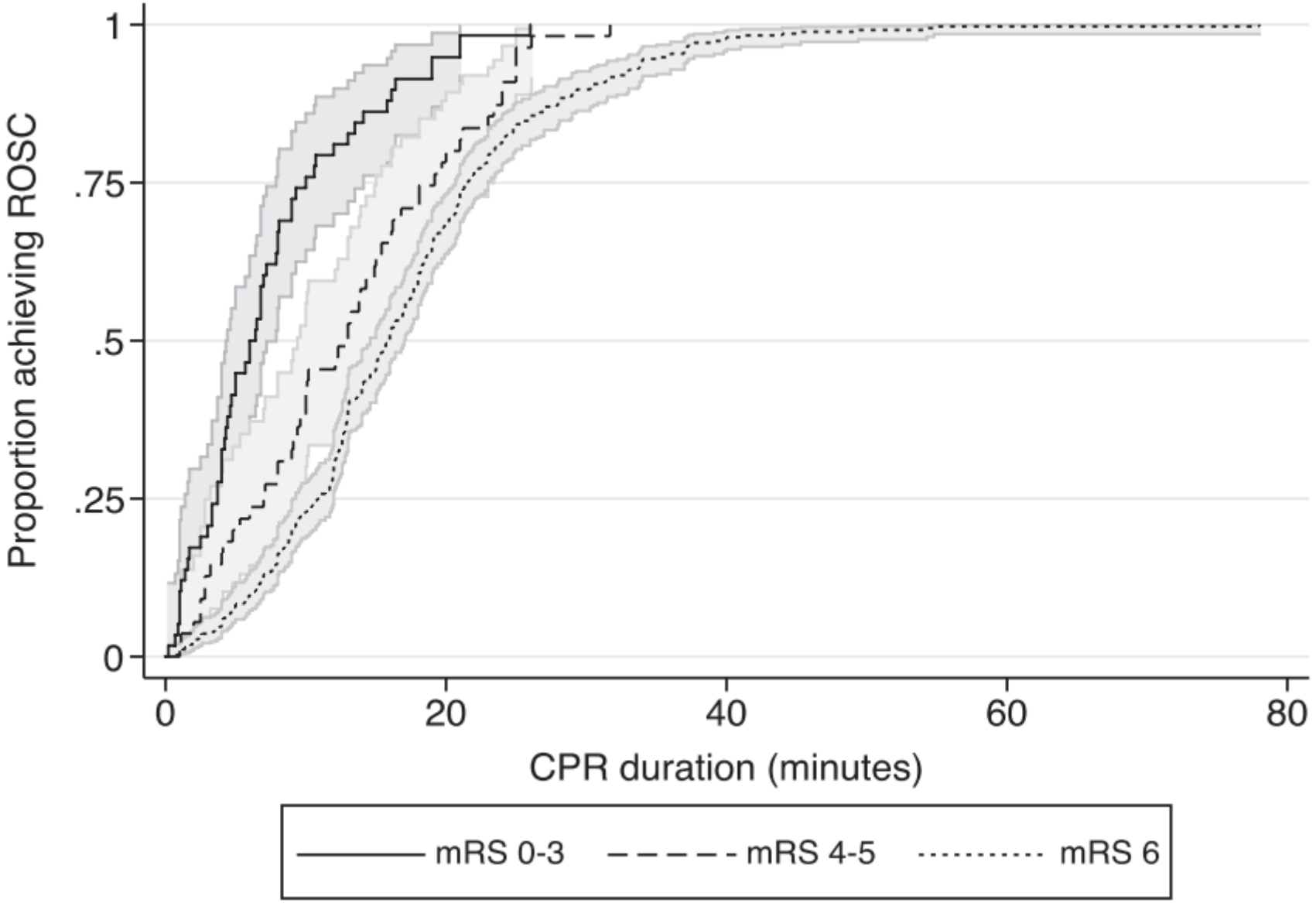
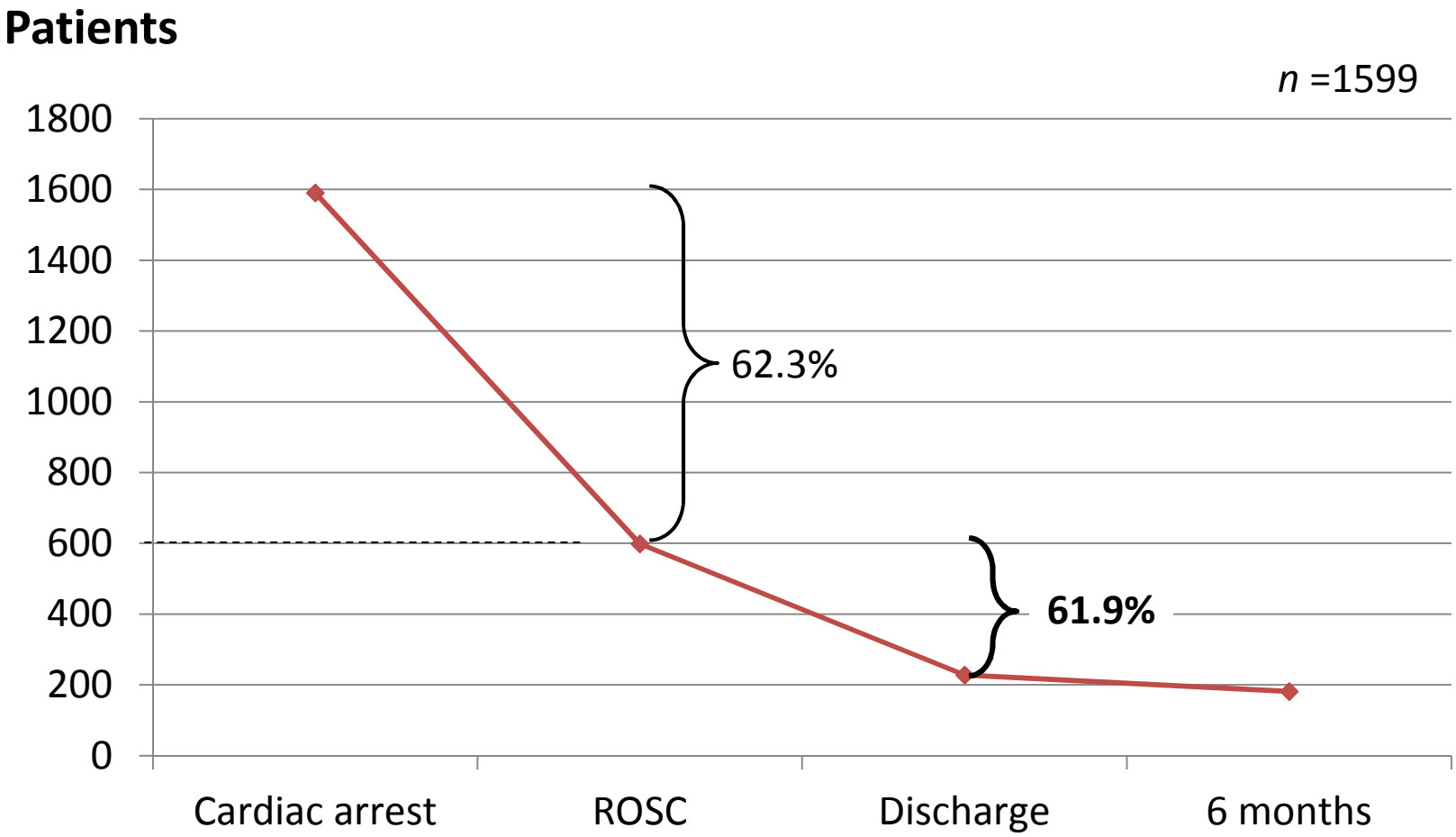
Factors associated with outcome

- Pre-arrest (non-modifiable; patient's frailty)
  - Age, cause of arrest, comorbidities
- Intra-arrest (partly modifiable; EMS response)
  - Initial rhythm, duration and quality of c-CPR
- Post-arrest (mostly modifiable; post-resus)
  - Interventions: TTM, coronary reperfusion
  - Organ failures



Reynolds J et al. Circulation 2013; 128:2488-2494

IHCA: survival after c-CPR



Italian Cardiac Arrest Registry , 2016.

IHCA survival: c-CPR vs. e-CPR