The aim of this study was to review the literature on human studies of drug therapy in cardiac arrest during the last 25 years. In May 2015, a systematic literature search was performed in PubMed, Embase, the Cochrane Library, and CRD databases. Prospective interventional and observational studies evaluating a specified drug therapy in human cardiac arrest reporting a clinical endpoint [i.e. return of spontaneous circulation (ROSC) or survival] and published in English 1990 or later were included, whereas animal studies, case series and reports, studies of drug administration, drug pharmacology, non-specified drug therapies, preventive drug therapy, drug administration after ROSC, studies with primarily physiological endpoints, and studies of traumatic cardiac arrest were excluded. The literature search identified a total of 8936 articles. Eighty-eight articles met our inclusion criteria and were included in the review. We identified no human study in which drug therapy, compared with placebo, improved long-term survival. Regarding adrenaline and amiodarone, the drugs currently recommended in cardiac arrest, two prospective randomized placebo-controlled trials, were identified for adrenaline, and one for amiodarone, but they were all underpowered to detect differences in survival to hospital discharge. Of all reviewed studies, only one recent prospective study demonstrated improved neurological outcome with one therapy over another using a combination of vasopressin, steroids, and adrenaline as the intervention compared with standard adrenaline administration. The evidence base for drug therapy in cardiac arrest is scarce. However, many human studies on drug therapy in cardiac arrest have not been powered to identify differences in important clinical outcomes such as survival to hospital discharge and favourable neurological outcome. Efforts are needed to initiate large multicentre prospective randomized clinical trials to evaluate both currently recommended and future drug therapies.

Keywords

Drug therapy • Cardiac arrest

Introduction

In clinical terms, cardiac arrest is defined as a sudden and sustained loss of consciousness with pulselessness and apnoea or agonal breathing.1 It is a heterogeneous condition in terms of underlying pathology, initial rhythm, time in no flow, and concurrent health issues. The pathophysiology of cardiac arrest is mainly attributed to either cardiac, metabolic, or mechanical causes.1 Rhythm at initial presentation is the most important prognostic factor,2 dictates the immediate treatment,3 and is affected by underlying pathology, time from collapse to rhythm recording, and bystander cardiopulmonary resuscitation (CPR).4 In the majority of patients with out-of-hospital cardiac arrest (OHCA), primary cardiac pathology is the underlying cause of the arrest and one-third present with a shockable rhythm,5 increasing to two-thirds when time from collapse to resuscitation is within a few minutes.6 In patients with in-hospital cardiac arrest (IHCA), the proportion of primary cardiac pathology is lower and patients more frequently present with pulseless electrical activity (PEA) as the initial rhythm,7 indicating differences in patient characteristics and underlying pathology. In both groups, asystole is common when the time from collapse to resuscitation is prolonged.5,7
The pathophysiology of cardiac arrest of primary cardiac cause has been described by Weisfeldt and Becker as a time-sensitive three-phase model. The first 4–5 min constitute the electrical phase and with immediate defibrillation, survival is >50%. However, recurrent or shock-resistant ventricular fibrillation occurs in 10–25% of all OHCA and anti-arrhythmic drugs are often administered when defibrillation fails. Anti-arrhythmics possibly reduce the likelihood of arrhythmia being maintained or recurring after the return of spontaneous circulation (ROSC). The effects of anti-arrhythmic drugs on the defibrillation threshold are, however, inconsistent and most anti-arrhythmics also have pro-arrhythmic effects.

The circulatory phase follows after 4–5 min, when tissue hypoxia and the accumulation of metabolites reduce the likelihood of successful defibrillation. Restoration of coronary perfusion pressure (CPP) is imperative. Animal studies have demonstrated an association with a CPP of >20–40 mmHg during resuscitation and ROSC, and also an increased likelihood of conversion to PEA or asystole with defibrillation if adequate CPP is not established.

One human study demonstrated a positive correlation with initial and maximum CPP and ROSC during resuscitation, and initial CPP was a stronger predictor of subsequent ROSC than no-flow time. Haemodynamic improvement during the circulatory phase provides the rationale for vasopressor treatment during resuscitation.

In the metabolic phase (i.e. >10–15 min), survival is dismal due to global ischaemia and reperfusion injury, and the beneficial effects of circulatory supportive measures are diminished.

In a survival model of OHCA patients, Valenzuela et al. found that delaying CPR for >10 min rendered defibrillation ineffectual in terms of survival. Moreover, the benefit of immediate CPR declined if defibrillation was delayed for >10 min. If a large proportion of patients with prolonged circulatory arrest are included in trials of cardiac arrest, proving benefit will be difficult, as survival is dismal regardless of treatment.

The early initiation of CPR and defibrillation has been shown to increase survival in cardiac arrest and is well established in treatment algorithms. From a theoretical point of view, several drug therapies are appealing, but supporting clinical data in human studies are less robust. To summarize the evidence base for drug therapy in cardiac arrest, we decided to review the literature on human studies of drug therapy in cardiac arrest during the last 25 years.

Methods

In May 2015, a literature search was performed in PubMed, Embase, the Cochrane Library, and CRD databases. The search terms used, in different combinations, were ‘Cardiac arrest’, ‘Heart arrest’, ‘Circulatory arrest’, ‘Cardiopulmonary arrest’, ‘Drug’, ‘Drugs’, ‘Drug therapy’, ‘Medication’, ‘Medications’, ‘Pharmacology’, ‘Pharmaceutical’, ‘Pharmacoeconomic preparations’, and ‘Cardiovascular agents’. We included articles written in English from 1990 and onwards. Eligible articles were prospective interventional studies and observational studies evaluating a specified drug therapy during the resuscitation phase of human cardiac arrest, reporting a clinical endpoint (i.e. ROSC or survival). We excluded animal studies, case series and case reports, studies of drug administration, studies of drug pharmacology, studies of non-specified drug therapies, studies with primarily physiological endpoints, studies of preventive drug therapy, studies of traumatic cardiac arrest, and studies of drug administration after ROSC.

Results

The literature search identified a total of 8936 articles (after the removal of duplicates). After screening of titles and abstracts by two of the authors (A.L. and P.L.), 769 were considered to be potentially relevant for research on drug therapy in cardiac arrest. Of these, 681 were excluded, whereas 88 articles met our inclusion criteria and were included in the review (Figure 1). Reasons for exclusion were case series (n = 45), review article (n = 326), study of drug administration or pharmacology (n = 11), study with physiological outcome (n = 18), animal studies (n = 263), and preventive or post-resuscitative intervention (n = 18). Of 88 included studies, 40 were classified as observational studies and 48 as interventional studies. Sixty-three studies enrolled patients with OHCA, 16 studies enrolled patients with IHCA, and 9 studies enrolled both. The included studies comprised 17 different drugs such as adrenaline (n = 33), vasopressin (n = 14), methoxamine (n = 1), isoproterenol (n = 1), amiodarone (n = 7), two studies presented in nifekalant section, lidocaine (n = 6, three studies presented in lidocaine and nifekalant section), sotalol (n = 1, presented in lidocaine section), procainamide (n = 2), atropine (n = 1), aminophylline (n = 3), nifekalant (n = 4), beta-blockers (n = 1), magnesium (n = 5), thrombolytics (n = 6), corticosteroids (n = 1), sodium bicarbonate (n = 3), erythropoietin (n = 1), and crystalloid and colloid (n = 2). Of the interventional studies, the median and mean study size were 199 and 442 patients (range 30–3327 patients), respectively. Of the interventional studies, 38 reported time from collapse to study drug administration (or a proximate surrogate), with an average time interval of 16 min (range 1–43 min). Most interventional studies allowed only intravenous drug administration, although a few allowed intrasosseous or endotracheal administration if intravenous access could not be established. Details of studies are summarized in Tables 1 and 2.

Vasopressor drugs

Adrenaline

Adrenaline is an α- and β-adrenergic agonist and its cardiovascular effects include venous and arterial vasoconstriction, increased inotropy, and chronotropy. Studies of adrenaline in animal models of cardiac arrest have demonstrated increased diastolic blood pressure and CPP, but also pulmonary vasoconstriction, increased myocardial oxygen demand, and myocardial oxygen imbalance as well as cerebral vasoconstriction and diminished cerebral blood flow. Clinical effects from adrenaline in animal studies include an increased rate of ROSC and short-term survival, but also post-resuscitative myocardial dysfunction, cerebral ischaemia, and poor neurological outcome as well as decreased short-term survival. Less myocardial dysfunction has been demonstrated with pure α-agonists and with adrenaline plus β-adrenergic antagonists. Both beneficial and harmful effects of adrenaline were augmented with higher doses. The electrophysiological effects of adrenaline are complex, and animal studies have demonstrated...
increased myocardial instability\textsuperscript{47,48} as well as beneficial electrophysiological effects.\textsuperscript{49} In humans, adrenaline has been associated with more rhythm transitions to ventricular arrhythmias after ROSC.\textsuperscript{50}

We found 33 studies\textsuperscript{51–83} evaluating adrenaline administration in human cardiac arrest. Fifteen were interventional and 18 were observational studies. Thirteen interventional studies compared high-dose adrenaline (i.e. >0.02 mg/kg) with a standard dose (i.e. 0.01–0.02 mg/kg).\textsuperscript{51–63} Although four of these reported higher rates of ROSC,\textsuperscript{53–56} only one small study of paediatric patients found increased survival to hospital discharge with a higher dose of adrenaline.\textsuperscript{53} In the largest study, Gueugniaud et al. randomized 3327 adult patients with OHCA to 5 or 1 mg of adrenaline. The higher dose increased the rate of ROSC (40.4 vs. 36.4%, \(P = 0.02\)), but survival to hospital discharge was not statistically different.\textsuperscript{56} Furthermore, two other large multicentre trials did not demonstrate any significant benefit from higher dosages.\textsuperscript{51,55}

We found two studies that compared adrenaline with placebo.\textsuperscript{64,65} Woodhouse et al. randomized 194 patients to high-dose adrenaline (10 mg) or placebo. There were more rhythm transitions in the adrenaline group but no difference in survival. The results are difficult to interpret, as there were major imbalances in baseline characteristics between groups.\textsuperscript{64} Jacobs et al. randomized 500 OHCA patients to standard treatment with adrenaline (1 mg) vs. saline placebo. The adrenaline group had a higher rate of ROSC (23.5 vs. 8.4%, \(P < 0.001\)), but there was no significant difference in survival to hospital discharge. The trial was underpowered, as the enrolment of 5000 patients was planned to detect a 2% absolute difference in survival to hospital discharge, from a baseline survival rate of 5%.\textsuperscript{65}

Of 18 observational studies,\textsuperscript{66–83} eight retrospectively compared outcome in patients with cardiac arrest depending on whether or not adrenaline was administered.\textsuperscript{71,73,74,77,78,80,82} Three studies found no difference in survival,\textsuperscript{69,74,78} while three reported reduced survival associated with adrenaline administration\textsuperscript{71,73,82} and two reported increased survival.\textsuperscript{75,77} Three of the studies used data from the same national registry in Japan, with inconsistent findings.\textsuperscript{73,77,80} Hagihara et al.\textsuperscript{73} found that adrenaline was associated with increased
ROSC, but reduced overall and neurologically intact survival at 1 month. In contrast, Nakahara et al.\textsuperscript{80}, using the same registry, reported increased 1-month survival in patients receiving adrenaline but no difference in neurologically intact survival. Both studies used propensity scoring to adjust for confounders, but Nakahara et al.\textsuperscript{80} used time-dependent statistics which, according to the authors, could explain the different findings. Recently, Dumas et al.\textsuperscript{82}, using various statistical methodologies, reported a significantly poorer neurological outcome in resuscitated OHCA patients who received adrenaline. This association was observed, regardless of length of resuscitation, and there was an inverse linear relationship between total dose (i.e. dose effect), as well as the timing of first dose, and neurological outcome.

Five studies looked at the association between the timing of adrenaline administration and survival.\textsuperscript{75,76,79,81,83} Three reported an association between the earlier administration of adrenaline and survival to hospital discharge.\textsuperscript{81} Compared with a dosage period of 4–5 min, the adjusted odds ratio for survival to hospital discharge was 2.17 (95% CI: 1.62–2.92) for dosage intervals of 9–10 min.

Two studies evaluated the association between total adrenaline dose and outcome, and both reported that the cumulative dose of adrenaline is independently associated with poor outcome.\textsuperscript{70,72} Finally, three small studies reported on survival in adult and paediatric patients receiving high-dose or standard-dose adrenaline, with no significant difference in ROSC or survival.\textsuperscript{66–68}

### Vasopressin

Vasopressin is a neurohypophysial hormone\textsuperscript{84} and its cardiovascular effects include increased inotropy, systemic and coronary vasoconstriction,\textsuperscript{85} and the potentiation of catecholaminergic effects.\textsuperscript{86,87} In animal models of cardiac arrest, vasopressin increased diastolic blood pressure and CPP.\textsuperscript{88–90} Compared with adrenaline, vasopressin has been associated with less impairment of cerebral blood flow,\textsuperscript{91} less attenuation from acidosis,\textsuperscript{92} less tachyphylaxis and pulmonary vasoconstriction,\textsuperscript{93} as well as longer effect duration.\textsuperscript{94} Vasopressin mediates ACTH release and, in animal studies of cardiac arrest, the levels of ACTH and cortisol were higher after the administration of vasopressin compared with adrenaline.\textsuperscript{95}

High endogenous vasopressin levels, as well as increased cortisol levels, have been associated with improved survival after cardiac arrest.\textsuperscript{96,97}

### Table I  Included studies

<table>
<thead>
<tr>
<th>Study drug</th>
<th>Design</th>
<th>Interv</th>
<th>Observ</th>
<th>OHCA/ IHCA</th>
<th>No. of studies</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Random</td>
<td>Non-random</td>
<td>Prospective with historical controls</td>
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<tr>
<td>Interv</td>
<td>Non-interv</td>
<td></td>
<td></td>
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<tr>
<td>Adrenaline\textsuperscript{a}</td>
<td>13</td>
<td>1</td>
<td>1</td>
<td>18</td>
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<td>Vasopressin\textsuperscript{b}</td>
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<td>4</td>
<td>8/6</td>
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<td>1/0</td>
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<td>Amiodarone\textsuperscript{c}</td>
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<td>3</td>
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<td>5</td>
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<td>Lidocaine\textsuperscript{d}</td>
<td>2</td>
<td>1</td>
<td>3/0</td>
<td>3</td>
<td></td>
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<td>Aminophylline</td>
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<td></td>
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<td>Sodium bicarbonate</td>
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<td>2</td>
<td>2/1</td>
<td>3</td>
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<tr>
<td>Magnesium</td>
<td>4</td>
<td>1</td>
<td></td>
<td>3/2</td>
<td>5</td>
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<td>Beta-blocker</td>
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<td></td>
<td>1/0</td>
<td>1</td>
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<tr>
<td>Thrombolytics</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>7/1</td>
<td>8</td>
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<td>Erythropoietin</td>
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<td>0/1</td>
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<td>Crystalloids</td>
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<td>Procainamide</td>
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<td></td>
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<td>2</td>
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<td>Atropine</td>
<td>1</td>
<td></td>
<td></td>
<td>0/1</td>
<td>1</td>
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<tr>
<td>Nifekalant</td>
<td>4</td>
<td></td>
<td></td>
<td>3/1</td>
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<td>40</td>
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</table>

\textsuperscript{a}Studies enrolling both IHCA and OHCA patients are classified as OHCA if the primary setting was emergency department, and if the primary setting was in-hospital (including emergency department), studies are classified as IHCA.

\textsuperscript{b}In total, 41 studies evaluated adrenaline as an intervention, and 8 are classified in other sections (vasopressin).

\textsuperscript{c}In two studies, intervention included corticosteroids.

\textsuperscript{d}In total, seven studies evaluated amiodarone, and two studies are classified in other sections (nifekalant).

\textsuperscript{e}In total, six studies evaluated lidocaine, and three studies are classified in other sections (nifekalant and amiodarone).

\textsuperscript{f}One study included comparison with sotalol.
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study design</th>
<th>Study size</th>
<th>Setting</th>
<th>Inclusion of participants</th>
<th>Intervention1</th>
<th>Control1</th>
<th>Time to study drug administration (min)</th>
<th>Admin. route</th>
<th>Primary outcome(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenaline Goetting et al. (1991)</td>
<td>Prospective intervention vs. historical control group</td>
<td>40 patients</td>
<td>Prehospital</td>
<td>Pediatric patients w/ witnessed cardiac arrest, refractory to two standard doses of adrenaline</td>
<td>HDE (0.2 mg/kg) after failure of two doses SDE</td>
<td>SDE (0.01 mg/kg)</td>
<td>4 iv</td>
<td>ROSC</td>
<td>ROSC: 70 vs. 0% (P &lt; 0.001) and survival to discharge 40 vs. 0% in the intervention group and control group, respectively</td>
</tr>
<tr>
<td>Lindner et al. (1991)</td>
<td>Prospective, randomized trial</td>
<td>68 patients</td>
<td>Emergency department</td>
<td>Adult patients w/ IHCA or OHCA and asystole or PEA</td>
<td>HDE (5 mg), followed by standard ACLS treatment</td>
<td>SDE (1 mg)</td>
<td>Not stated iv</td>
<td>ROSC, survival to hospital discharge.</td>
<td>ROSC: 57 vs. 15% (P &lt; 0.01) and survival to discharge 11 vs. 4% (P = NS) in the intervention and control groups, respectively</td>
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<tr>
<td>Brown et al. (1992)</td>
<td>Prospective, randomized trial</td>
<td>1280 patients</td>
<td>Prehospital</td>
<td>Adult patients w/ OHCA</td>
<td>HDE (0.2 mg/kg), one dose, followed by standard ACLS treatment</td>
<td>SDE (0.02 mg/kg)</td>
<td>17 iv</td>
<td>ROSC</td>
<td>ROSC: 22 vs. 23% and survival to discharge 5 vs. 7% in the intervention and control groups, respectively (P = NS)</td>
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<tr>
<td>Callaham et al. (1992)</td>
<td>Prospective, randomized trial</td>
<td>546 patients</td>
<td>Prehospital</td>
<td>Adult patients w/ OHCA</td>
<td>HDE (15 mg), maximum three doses, followed by standard ACLS treatment</td>
<td>SDE (1 mg)</td>
<td>16 iv</td>
<td>ROSC</td>
<td>ROSC: 13 vs. 8% (P = 0.01) and survival to hospital discharge 1.7 vs. 1.2% (P = NS) in the intervention and control groups, respectively (P = NS)</td>
</tr>
<tr>
<td>Stiell et al. (1992)</td>
<td>Prospective, randomized trial</td>
<td>650 patients</td>
<td>In hospital</td>
<td>Adult patients w/ IHCA or OHCA in hospital or treated in the ED</td>
<td>HDE, 7 mg every 5 min up to five doses, followed by standard ACLS treatment</td>
<td>SDE (1 mg), repeated doses</td>
<td>15 min (OHCA patients), 7 min (IHCA patients)</td>
<td>iv or endotracheal</td>
<td>ROSC</td>
</tr>
<tr>
<td>Lipman et al. (1993)</td>
<td>Prospective, randomized trial</td>
<td>40 patients</td>
<td>In hospital</td>
<td>Adult ICU patients w/ IHCA and asystole</td>
<td>HDE (10 mg) every 5 min. Maximum three doses, followed by standard ACLS treatment</td>
<td>SDE (1 mg), every 5 min</td>
<td>Not reported iv</td>
<td>Not reported</td>
<td>ROSC: 68 vs. 68% and 24 h survival 21 vs. 31% in the intervention and control groups, respectively (P = NS). One patient in the control group survived to discharge</td>
</tr>
<tr>
<td>Study</td>
<td>Type</td>
<td>Patients</td>
<td>Setting</td>
<td>Patients Description</td>
<td>Drug Dose</td>
<td>Drug Route</td>
<td>Outcomes</td>
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<tr>
<td>Polglase et al. (1994)</td>
<td>Prospective, randomized trial</td>
<td>105</td>
<td>Prehospital</td>
<td>Adult patients with OHCA</td>
<td>5 mg (30 patients) or 10 mg (34 patients) adrenaline, repeated doses</td>
<td>SDE (1 mg) 41 patients, repeated doses</td>
<td>Not reported iv</td>
<td>Not reported ROSC: 14 vs. 20 vs. 20% in 1, 5, and 10 mg groups, respectively (P = NS). No patient survived to hospital discharge</td>
<td></td>
</tr>
<tr>
<td>Choux et al. (1995)</td>
<td>Prospective, randomized trial</td>
<td>536</td>
<td>Prehospital</td>
<td>Adult patients with OHCA</td>
<td>HDE (5 mg), repeated doses</td>
<td>SDE (1 mg), repeated doses</td>
<td>22 iv</td>
<td>ROSC, survival to hospital admission and survival to hospital discharge</td>
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<tr>
<td>Woodhouse et al. (1995)</td>
<td>Prospective, randomized trial</td>
<td>194</td>
<td>Emergency department</td>
<td>Adult patients with OHCA of cardiac aetiology</td>
<td>Adrenaline 10 mg</td>
<td>Saline placebo</td>
<td>Not reported iv</td>
<td>Immediate survival (i.e. stable cardiac rhythm w/a palpable pulse)</td>
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<tr>
<td>Carvolth et al. (1996)</td>
<td>Prospective intervention vs. historical control group</td>
<td>1174 (594 patients in the historical control group)</td>
<td>Prehospital</td>
<td>Adult patients with OHCA</td>
<td>HDE: 5, 10, and 15 mg dosing to a total dose of 30 mg</td>
<td>SDE: 1 mg repeated doses to a maximum of 4 mg</td>
<td>Not reported iv or endotracheal Survival to hospital admission, survival to discharge</td>
<td>Survival to hospital admission: 15.3 and 14.5% and survival to hospital discharge 4.8 and 4.9% in the intervention and control groups, respectively (P = NS)</td>
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<td>Sherman et al. (1997)</td>
<td>Prospective, randomized trial</td>
<td>140</td>
<td>Emergency department</td>
<td>Adult patients with OHCA refractory to SDE</td>
<td>HDE: 0.1 mg/kg, repeated every 5 min</td>
<td>SDE: 0.01 mg/kg, repeated every 5 min</td>
<td>23 (time to randomization) iv</td>
<td>Improvement in cardiac rhythm or ROSC</td>
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<td>Gueugniaud et al. (1998)</td>
<td>Prospective, randomized trial</td>
<td>3327</td>
<td>Prehospital</td>
<td>Adult patients with OHCA and shock-resistant VF, asystole or PEA</td>
<td>HDE: 5 mg, repeated dosing (maximum 15 doses)</td>
<td>SDE: 1 mg, repeated doses</td>
<td>20 iv or endotracheal ROSC, survival to hospital admission and discharge</td>
<td>ROSC: 40.4 vs. 36.4% (P &lt; 0.05) and survival to hospital discharge: 2.3 vs. 2.8% (P = NS) in the intervention and control groups, respectively</td>
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<tr>
<td>Perondi et al. (2004)</td>
<td>Prospective, randomized trial</td>
<td>68</td>
<td>In hospital</td>
<td>Paediatric patients with IHCA refractory to initial SDE</td>
<td>HDE: 0.1 mg/kg, repeated doses</td>
<td>SDE: 0.01 mg/kg</td>
<td>2 iv</td>
<td>24 h survival ROSC: 44 vs. 24% (P = NS) and 24 h survival 3 vs. 21% (P = 0.05) in the intervention and control groups, respectively</td>
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</table>

**Continued**
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study design</th>
<th>Study size</th>
<th>Setting</th>
<th>Inclusion of participants</th>
<th>Intervention1</th>
<th>Control1</th>
<th>Time to study drug administration (min)</th>
<th>Admin. route</th>
<th>Primary outcome(s)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patterson et al. (2005)</td>
<td>Prospective, randomized trial</td>
<td>230 patients</td>
<td>Emergency department</td>
<td>Paediatric patients (&lt;22 years) in ED w/ OHCA refractory to prehospital resuscitation</td>
<td>HDE, 0.1 mg/kg for the initial dose and 0.2 mg/kg for subsequent doses</td>
<td>SDE (0.01 mg/kg)</td>
<td>Not reported</td>
<td>iv or endotracheal</td>
<td>Survival to discharge and neurological outcome</td>
<td>Survival to hospital discharge: 7 vs. 2% in the intervention and control groups, respectively (P = NS)</td>
</tr>
<tr>
<td>Jacobs et al. (2011)</td>
<td>Prospective, randomized, placebo-controlled trial</td>
<td>534 patients</td>
<td>Prehospital</td>
<td>Adult patients w/ OHCA</td>
<td>SDE (1 mg), repeated dosing every 3 min</td>
<td>Placebo (0.9% saline)</td>
<td>10 (time to EMS arrival)</td>
<td>iv</td>
<td>Survival to hospital discharge</td>
<td>ROSC: 23.5 vs. 8.4% (P &lt; 0.05) and survival to hospital discharge 4.0 and 1.9% (P = NS) in the intervention and control groups, respectively</td>
</tr>
<tr>
<td>Lindner et al. (1997)</td>
<td>Prospective, randomized trial</td>
<td>40 patients</td>
<td>Prehospital</td>
<td>Adult patients w/ OHCA and shock-resistant VF</td>
<td>Vasopressin (40 IU), one dose, followed by standard ACLS treatment</td>
<td>Standard ACLS treatment</td>
<td>14</td>
<td>iv</td>
<td>Survival to hospital admission</td>
<td>Survival to hospital admission: 70 vs. 35% (P = 0.06) and survival to hospital discharge: 40 vs. 15% in the intervention and control groups, respectively (P = NS)</td>
</tr>
<tr>
<td>Stiell et al. (2001)</td>
<td>Prospective, randomized trial</td>
<td>200 patients</td>
<td>In hospital</td>
<td>Adult patients w/ IHCA</td>
<td>Vasopressin (40 mg) one dose, followed by standard ACLS treatment</td>
<td>Standard ACLS treatment</td>
<td>6</td>
<td>iv</td>
<td>Survival to hospital discharge</td>
<td>Survival to hospital discharge: 12 vs. 14% in the intervention and control groups, respectively (P = NS)</td>
</tr>
<tr>
<td>Wenzel et al. (2004)</td>
<td>Prospective, randomized trial</td>
<td>1219 patients</td>
<td>Prehospital</td>
<td>Adult patients w/ out-of-hospital cardiac arrest</td>
<td>Two injections of 40 IU of vasopressin, followed by additional treatment w/ adrenaline if needed</td>
<td>Standard ACLS treatment</td>
<td>10</td>
<td>iv</td>
<td>Survival to hospital admission</td>
<td>ROSC: 25 vs. 28% (P = 0.19) and survival to hospital admission: 36 vs. 31% (P = 0.06) in the intervention and control groups, respectively (P = NS)</td>
</tr>
<tr>
<td>Callaway et al. (2008)</td>
<td>Prospective, randomized trial</td>
<td>325 patients</td>
<td>Prehospital</td>
<td>Adult patients w/ OHCA, requiring at least one dose of adrenaline</td>
<td>Vasopressin (40 IU), one dose, followed by standard ACLS treatment</td>
<td>One dose saline placebo in addition to standard ACLS treatment</td>
<td>14</td>
<td>iv</td>
<td>ROSC, presence of pulses at hospital arrival</td>
<td>ROSC: 31 vs. 30% and survival to hospital admission: 19 vs. 23% in the intervention and control groups, respectively (P = NS)</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Patients</td>
<td>Setting</td>
<td>Patients/ Setting</td>
<td>Drug Regimen</td>
<td>Endpoints</td>
<td>Result</td>
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<tr>
<td>Gueugniaud et al. (2008)</td>
<td>Prospective, randomized trial</td>
<td>2894</td>
<td>Prehospital</td>
<td>Adult patients w/ OHCA</td>
<td>Adrenaline (1 mg) and vasopressin (40 IU), maximum two doses, followed by standard ACLS treatment</td>
<td>Survival to hospital admission</td>
<td>28.6 vs. 29.5% (P = NS)</td>
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<tr>
<td>Mentzelopoulos et al. (2009)</td>
<td>Prospective, randomized trial</td>
<td>100</td>
<td>In hospital</td>
<td>Adult patients w/ IHCA</td>
<td>Vasopressin (20 IU) plus adrenaline (1 mg) in repeated doses (maximum 5 cycles) w/ methyl-prednisolone (40 mg) on the first cycle. Additional adrenaline if needed. Post-resuscitation shock treated w/ hydrocortisone2</td>
<td>ROSC and survival to hospital discharge</td>
<td>81 vs. 52% (P = 0.003) and survival to hospital discharge 19 vs. 4% (P = 0.02) in the intervention and control groups, respectively</td>
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<tr>
<td>Mukoyama et al. (2009)</td>
<td>Prospective, randomized trial</td>
<td>336</td>
<td>Emergency department</td>
<td>Adult patients in ED w/ OHCA refractory to prehospital resuscitation</td>
<td>Vasopressin (40 IU) repeated every 5–10 min until cumulative dose of 160 IU</td>
<td>Survival to hospital discharge</td>
<td>28.7 vs. 26.6% and survival to hospital discharge 5.6 vs. 3.8% in the intervention and control groups, respectively</td>
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<tr>
<td>Carroll et al. (2012)</td>
<td>Prospective intervention vs. historical control group</td>
<td>30</td>
<td>In hospital</td>
<td>Paediatric patients in ICU w/ cardiac arrest refractory to at least one dose adrenaline</td>
<td>Vasopresarin (0.8 mg/kg), one dose, followed by standard ACLS treatment</td>
<td>Assess feasibility of a future randomized controlled trial</td>
<td>24-h survival: 80 vs. 30%, (P &lt; 0.05) and survival to discharge: 60 vs. 25% (P = 0.07) in the intervention and control groups, respectively</td>
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<tr>
<td>Ong et al. (2012)</td>
<td>Prospective, randomized trial</td>
<td>727</td>
<td>Emergency department</td>
<td>Adult patients w/ OHCA (including arrest in the ED)</td>
<td>Vasopressin (40 IU), one dose, followed by standard ACLS treatment</td>
<td>Survival to hospital discharge</td>
<td>30 vs. 31% and survival to discharge: 2.3 vs. 2.9% in the intervention and control groups, respectively (P = NS)</td>
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<tr>
<td>Mentzelopoulos et al. (2013)</td>
<td>Prospective, randomized trial</td>
<td>268</td>
<td>In hospital</td>
<td>Adult patients w/ IHCA</td>
<td>See Mentzelopoulos (2009); See Mentzelopoulos (2009)</td>
<td>Survival to hospital discharge w/ favourable neurological recovery</td>
<td>83.9 vs. 65.9% (P = 0.005) and neurologically favourable survival 13.9 vs. 5.1% (P = 0.02) in the intervention and control groups, respectively</td>
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<tr>
<td>Author (year)</td>
<td>Study design</td>
<td>Study size</td>
<td>Setting</td>
<td>Inclusion of participants</td>
<td>Interventions</td>
<td>Control</td>
<td>Time to study drug administration (min)</td>
<td>Admin. route</td>
<td>Primary outcome(s)</td>
<td>Results</td>
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<tr>
<td>Methoxamine</td>
<td>Prospective, randomized</td>
<td>199 patients</td>
<td>In hospital</td>
<td>Adult patients with witnessed IHCA and OHCA presenting to the ED</td>
<td>Methoxamine (40 mg), repeated doses</td>
<td>Adrenaline (2 mg), repeated doses</td>
<td>3 iv</td>
<td>iv</td>
<td>ROSC</td>
<td>ROSC: 42 vs. 53% in the intervention and control groups, respectively (P = NS)</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>Prospective, randomized</td>
<td>79 patients</td>
<td>Prehospital</td>
<td>Adult patients with OHCA and asystole</td>
<td>Isoprenaline (200 μg) every 3–5 min, maximum 600 μg</td>
<td>Standard ACLS treatment (including atropine 1 mg (total 3 mg) every 3–5 min)</td>
<td>7 iv</td>
<td>iv</td>
<td>ROSC</td>
<td>ROSC: 46 vs. 45% and survival to hospital discharge 3 vs. 7%, in the intervention and control groups, respectively (P = NS)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Prospective, randomized</td>
<td>504 patients</td>
<td>Prehospital</td>
<td>Adult patients with OHCA and shock-resistant VF</td>
<td>One dose of 300 mg of intravenous amiodarone</td>
<td>Saline placebo</td>
<td>21 iv</td>
<td>iv</td>
<td>Survival to hospital admission</td>
<td>Survival to hospital admission 44 vs. 34% (P = 0.03) and survival to hospital discharge: 13.4 and 13.2% in the intervention and control groups, respectively (P = NS)</td>
</tr>
<tr>
<td>Dorian et al.</td>
<td>Prospective, randomized</td>
<td>347 patients</td>
<td>Prehospital</td>
<td>Adult patients with shock-resistant VF/VT</td>
<td>Amiodarone (5 mg/kg) plus saline placebo. If VF persisted a second dose of amiodarone (2.5 mg/kg) plus placebo was given</td>
<td>Lidocaine (1.5 mg/kg) plus amiodarone placebo. If VF persisted, a second dose of lidocaine (1.5 mg/kg) was given</td>
<td>24 iv</td>
<td>iv</td>
<td>Survival to hospital admission</td>
<td>Survival to hospital admission 22.8 vs. 12.0% (P = 0.009) and survival to hospital discharge: 5 vs. 3% (P = NS) in the intervention and control groups, respectively (P = NS)</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Prospective, randomized</td>
<td>199 patients</td>
<td>Prehospital</td>
<td>Adult patients with OHCA and shock-resistant VF</td>
<td>100-mg bolus of lidocaine. A second dose of lidocaine (100 mg) was given before the next shock if VF persisted</td>
<td>Adrenaline (0.5 mg). Additional adrenaline (0.5 mg) was given if VF persisted</td>
<td>9 (time to defibrillation) iv</td>
<td>iv</td>
<td>Not reported</td>
<td>ROSC: 48 vs. 54% and survival to discharge: 19 vs. 20% in the intervention and control groups, respectively (P = NS)</td>
</tr>
<tr>
<td>Mader et al.</td>
<td>Prospective, randomized,</td>
<td>82 patients</td>
<td>Prehospital</td>
<td>Adult patients with OHCA and asystole</td>
<td>Aminophylline (250 mg), one dose</td>
<td>Saline placebo</td>
<td>12 iv</td>
<td>iv</td>
<td>ROSC</td>
<td>ROSC: 27 vs. 20% in the intervention and control groups, respectively (P = NS)</td>
</tr>
<tr>
<td>Mader et al.</td>
<td>placebo-controlled trial</td>
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<tr>
<td>Mader et al. (2003)</td>
<td>Prospective, randomized,</td>
<td>112 patients</td>
<td>Prehospital</td>
<td>Adult patients with OHCA and asystole after treatment with adrenaline and atropine</td>
<td>One dose of aminophylline (250 mg)</td>
<td>Saline placebo</td>
<td>12 iv</td>
<td>iv</td>
<td>ROSC</td>
<td>ROSC: 22.7 vs. 15.6% in the intervention and control groups, respectively (P = NS). No patient survived to hospital discharge</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Patients</td>
<td>Setting</td>
<td>Patient Description</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Outcome Measures</td>
<td>Intervention vs. Control Comparison</td>
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<tr>
<td>Abu-Laban et al. (2006)</td>
<td>Prospective, randomized</td>
<td>971 patients</td>
<td>Prehospital</td>
<td>Adult patients w/ OHCA and asystole or PEA, refractory to initial treatment w/ adrenaline and atropine</td>
<td>Aminophylline (250 mg), up to two doses</td>
<td>Saline placebo</td>
<td>ROSC</td>
<td>27 iv</td>
<td>ROSC: 24.5 vs. 23.7% and survival to hospital admission: 6.6 and 7.6% in the intervention and control groups, respectively (P = NS)</td>
<td></td>
</tr>
<tr>
<td>Dybvik et al. (1995)</td>
<td>Prospective, randomized, placebo-controlled</td>
<td>502 patients</td>
<td>Prehospital</td>
<td>Adult patients w/ OHCA and asystole or shock-resistant VF</td>
<td>250 mL of Tribonat (sodium bicarbonate-trometamol-phosphate), buffering capacity 500 mmol/L</td>
<td>250 mL of saline placebo</td>
<td>Survive to hospital admission</td>
<td>6 (time to EMS arrival) iv</td>
<td>Survival to hospital admission and to hospital discharge: 36 vs. 36% and survival to discharge: 10 vs. 14% in the intervention and control groups, respectively (P = NS)</td>
<td></td>
</tr>
<tr>
<td>Miller et al. (1995)</td>
<td>Prospective intervention vs. historical control group</td>
<td>62 patients (33 patients in the historical control group)</td>
<td>Emergency department</td>
<td>Adult patients w/ cardiac arrest and shock-resistant VF</td>
<td>One dose intravenous magnesium-sulphate (2.5–5 g)</td>
<td>Standard ACLS treatment</td>
<td>ROSC &gt; 30 min</td>
<td>13 iv</td>
<td>ECG rhythm 2 min after drug administration</td>
<td></td>
</tr>
<tr>
<td>Fatovich et al. (1997)</td>
<td>Prospective, randomized, placebo-controlled</td>
<td>67 patients</td>
<td>Emergency department</td>
<td>Adult patients w/ in the ED w/ OHCA refractory to prehospital resuscitation</td>
<td>Magnesium (5 g), one dose</td>
<td>Saline placebo</td>
<td>ROSC</td>
<td>33 iv</td>
<td>ROSC: 23 vs. 22% and survival to discharge 3 and 0% in the intervention and placebo groups, respectively (P = NS)</td>
<td></td>
</tr>
<tr>
<td>Thel et al. (1997)</td>
<td>Prospective, randomized placebo-controlled trial</td>
<td>156 patients</td>
<td>In hospital</td>
<td>Adult patients w/ IHCA</td>
<td>Magnesium (2 g bolus), followed by 8 g over 24 h</td>
<td>Saline placebo</td>
<td>ROSC</td>
<td>11 iv</td>
<td>ROSC: 54 vs. 60% (P = 0.44) and survival to hospital discharge 21 vs. 21% (P = NS) in the intervention and control groups, respectively</td>
<td></td>
</tr>
<tr>
<td>Allegra et al. (2001)</td>
<td>Prospective, randomized, placebo-controlled trial</td>
<td>116 patients</td>
<td>Prehospital</td>
<td>Adult patients w/ OHICA and VF</td>
<td>Magnesium (2 g) one dose</td>
<td>Saline placebo and adrenaline according to guidelines</td>
<td>ROSC in the field and a perfusing pulse on arrival at the ED</td>
<td>28 iv</td>
<td>ROSC 25.5 vs. 18.5% and survival to discharge 3.6 and 3.7% in the intervention and control groups, respectively. (P = NS)</td>
<td></td>
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<tr>
<td>Hassan et al. (2002)</td>
<td>Prospective, randomized, placebo-controlled trial</td>
<td>105 patients</td>
<td>Prehospital (including emergency department)</td>
<td>Adult patients w/ OHICA and shock-resistant or recurrent VF</td>
<td>Magnesium-sulphate (2–4 g)</td>
<td>Saline placebo</td>
<td>ROSC</td>
<td>8 (time to EMS arrival) iv</td>
<td>ROSC: 17 vs. 13% and survival to hospital discharge 4 vs. 2% in the intervention and control groups, respectively (P = NS)</td>
<td></td>
</tr>
<tr>
<td>Author (year)</td>
<td>Study design</td>
<td>Study size</td>
<td>Setting</td>
<td>Inclusion of participants</td>
<td>Intervention1</td>
<td>Control1</td>
<td>Time to study drug administration (min)</td>
<td>Admin. route</td>
<td>Primary outcome(s)</td>
<td>Results</td>
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<tr>
<td>Bottiger et al. (2001)</td>
<td>Prospective intervention vs. historical control group</td>
<td>90 patients (50 patients in the historical control group)</td>
<td>Prehospital</td>
<td>Adult patients with OHCA of cardiac etiology without ROSC after 15 min</td>
<td>5000 U of heparin bolus and tPA (50 mg), intervention was repeated if no ROSC after 30 min</td>
<td>ACLS treatment</td>
<td>8 (time to EMS arrival)</td>
<td>iv</td>
<td>Safety of the protocol (i.e., bleeding complications), ROSC and survival to hospital admission</td>
<td>ROSC: 68 vs. 44% (P = 0.026) and survival to discharge 15 vs. 8% (P = NS) in the intervention and control groups, respectively</td>
</tr>
<tr>
<td>Abu-Laban et al. (2002)</td>
<td>Prospective randomized, placebo-controlled trial</td>
<td>233 patients</td>
<td>Prehospital</td>
<td>Adult patients with OHCA and PEA refractory to initial therapy</td>
<td>Tenecteplase (100 mg), one dose. After enrollment standard resuscitation was continued for at least 15 min</td>
<td>Saline placebo</td>
<td>35 iv</td>
<td>Survival to hospital discharge</td>
<td>ROSC: 21.4 vs. 23.3% and survival to discharge 6.8 and 0% in the intervention and control groups, respectively (P = NS)</td>
<td></td>
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<tr>
<td>Fatovich et al. (2004)</td>
<td>Prospective randomized, placebo-controlled trial</td>
<td>35 patients</td>
<td>Emergency department</td>
<td>Adult patients in ED with OHCA refractory to prehospital resuscitation</td>
<td>Tenecteplase (50 mg) as first drug, one dose</td>
<td>Saline placebo, followed by ACLS treatment</td>
<td>43 iv</td>
<td>ROSC</td>
<td>ROSC: 42 vs. 6% (P &lt; 0.05) and survival to discharge 5 vs. 6% (P = NS) in the intervention and control groups, respectively</td>
<td></td>
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<tr>
<td>Bottiger et al. (2008)</td>
<td>Prospective randomized placebo-controlled trial</td>
<td>1050 patients</td>
<td>Prehospital</td>
<td>Adult patients with witnessed OHCA and initiation of ACLS within 10 min</td>
<td>Tenecteplase (50 mg), one dose</td>
<td>Saline placebo</td>
<td>18 iv</td>
<td>30-day survival</td>
<td>ROSC: 55.0 vs. 54.6% and survival to discharge: 15.1 vs. 17.5% in the intervention and control groups, respectively (P = NS)</td>
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<td>Drug therapy in cardiac arrest</td>
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<td><strong>Erythropoietin</strong> Gmeck et al. (2009)</td>
<td>Prospective, non-randomized trial w/ prospective and historical control group</td>
<td>54 prospectively included patients (24 erythropoietin and 30 saline), 48 patients in the historical control group</td>
<td>Prehospital</td>
<td>Adult patients w/ OHCA</td>
<td>Erythropoietin (90,000 IU of beta-epoetin), one dose</td>
<td>Saline placebo (prospective controls), standard ACLS treatment (historical controls)</td>
<td>6 (time to CPR)</td>
<td>iv</td>
<td>Survival to ICU admission</td>
<td>92 vs. 53% (P = 0.03) in the intervention and concurrent control groups. ICU admission: 92 vs. 50% and 65% (adjusted P = NS) in the intervention group, concurrent controls and matched controls, respectively</td>
</tr>
<tr>
<td><strong>Corticosteroids</strong> Tsai et al. (2007)</td>
<td>Prospective, non-randomized trial</td>
<td>97 patients</td>
<td>Emergency department</td>
<td>Adult patient in the ED w/ OHCA refractory to prehospital resuscitation</td>
<td>100 mg Hydrocortisone, one dose</td>
<td>Saline placebo</td>
<td>Not reported</td>
<td>iv</td>
<td>Not reported</td>
<td>ROSC: 61 vs. 39% (P = 0.038) and survival to hospital discharge 8 vs. 10% (P = NS) in the intervention and control groups, respectively</td>
</tr>
<tr>
<td><strong>Crystalloids/colloids</strong> Breil et al. (2012)</td>
<td>Prospective randomized trial</td>
<td>203 patients</td>
<td>Prehospital</td>
<td>Adult patients w/ OHCA</td>
<td>2 mL/kg of 7.2% NaCl w/ 6% HES (200 000/0.5), infused over 10 min</td>
<td>2 mL/kg of 6% HES (200 000/0.5), infused over 10 min</td>
<td>14</td>
<td>iv</td>
<td>Survival to hospital admission and hospital discharge</td>
<td>Survival to hospital admission: 50 vs. 47% and survival to hospital discharge 23 vs. 21% in the intervention and control groups, respectively (P = NS)</td>
</tr>
</tbody>
</table>

ACLS: advanced cardiac life support; OHCA: out-of-hospital cardiac arrest; IHCA: in-hospital cardiac arrest; ED: emergency department; PEA: pulseless electrical activity; EMS: emergency medical services; ROSC: return of spontaneous circulation; IV: intravenous; HES: hydroxyethyl starch; NS: non-significant; ICU: intensive care unit; VF: ventricular fibrillation; HDE: high-dose adrenaline; SDE: standard-dose adrenaline 1: standard ACLS treatment (adrenaline 1 mg repeated every 3–5 min) was provided in the intervention and control groups if not stated otherwise; 2: 300 mg hydrocortisone daily for 7 days maximum, w/ gradual taper.
Our search yielded 1498–111 studies involving vasopressin during human resuscitation, including 10 prospective interventional trials.90–99,98–107 Two small, randomized, controlled trials (total 240 patients) compared adrenaline (1 mg) with vasopressin (40 IU), and neither ROSC nor survival to discharge differed between groups.89,99 Callaway et al. randomized 325 patients to the combination of adrenaline and vasopressin (40 IU) or adrenaline alone. The rates of ROSC and survival to discharge were similar.100 Mukoyama et al. randomized 336 OHCA patients after prolonged cardiac arrest to repeated doses of vasopressin (40 IU) or adrenaline (1 mg). There were no differences in ROSC or survival to hospital discharge.

Three large, multicentre studies evaluated vasopressin and adrenaline.102–104 Wenzel et al.102 randomized 1219 OHCA patients to two doses of either 40 IU of vasopressin or 1 mg of adrenaline and additional treatment with adrenaline was added if needed. Overall, there was no difference in survival to discharge. In a prespecified subgroup of patients with asystole, vasopressin resulted in a significantly higher rate of ROSC and survival to hospital discharge (29 vs. 20%, P = 0.02, and 4.7 vs. 1.5%, P = 0.04, respectively). Gueguenau et al. randomized 1442 OHCA patients to either adrenaline (1 mg) and vasopressin (40 IU) or adrenaline and placebo. There was no difference in the primary outcome, i.e. survival to hospital admission.103 This study differed from the former, as rates of asystole were higher (83 vs. 44%) and time to drug administration was longer (21 vs. 10 min). Ong et al.104 randomized 727 OHCA patients to a single dose of adrenaline (1 mg) or vasopressin (40 IU) at presentation in the emergency department (ED). There was no difference in the primary outcome, survival to hospital discharge, although there was a trend towards improved survival with vasopressin in a subgroup with shockable rhythm. More than 90% of patients in both groups received additional open-label adrenaline. In two placebo-controlled studies, a group from Greece randomized patients to repeated doses of adrenaline (1 mg) or a combination of vasopressin (20 IU) and adrenaline every 3–5 min.105,106 Concurrent with the first injection, one dose of methylprednisolone (40 mg), was administered to the intervention group. If haemodynamic instability developed after resuscitation, hydrocortisone (300 mg) daily, with gradual tapering, was administered to the intervention group. The first study enrolled 99 patients and there was a significant benefit in the treatment group for the primary endpoints of ROSC (81 vs. 52%, P = 0.003) and survival to hospital discharge (19 vs. 4%, P = 0.02). The second study, powered to detect a difference in neurologically favourable survival, enrolled 268 adult IHCA patients. Haemodynamic parameters, during and after resuscitation, ROSC (83.9 vs. 65.9%, P = 0.005), and neurologically favourable survival to hospital discharge (13.9 vs. 5.1%, P = 0.02) improved significantly in the intervention group. The cause of arrest was deemed to be hypotension or respiratory failure in >70% of patients, 16% had an initial shockable rhythm, and the median time to resuscitation from collapse was 2 min.

Four observational studies evaluated vasopressin in cardiac arrest.108–111 Two studies reported an association between one dose of vasopressin (40 IU), alone or in combination with adrenaline, and increased ROSC, but none demonstrated a significant difference in survival.108,109 Duncan et al.110 found an association between vasopressin use and a reduced likelihood of ROSC in paediatric ICU patients. The second study comprised only 10 patients.104 Finally, one study reported an increased rate of ROSC (63 vs. 37%, P = 0.01) in a subgroup of cardiac arrest patients with acidosis, when vasopressin and adrenaline were administered compared with adrenaline alone.111

**Methoxamine**

Methoxamine is an α1-adrenergic receptor agonist, similar in structure to phenylephrine. It increases peripheral resistance and afterload through vasoconstriction, and can cause reduced cardiac output and reflexive bradyarrhythmia.112 In animal studies, methoxamine resulted in increased coronary blood flow and ROSC,113,114 and in one study, there was less myocardial oxygen imbalance and impairment of cerebral blood flow compared with adrenaline.114 We found only one human trial of methoxamine. Patrick et al.115 randomized 199 adult patients (of whom 145 were analysed) with IHCA to either 2 mg of adrenaline or 40 mg of methoxamine every 4 min. Return of spontaneous circulation, survival to discharge, and neurological outcome did not differ significantly between groups.

**Isoproterenol**

Isoproterenol is a pure β-adrenergic agonist with inotropic and chronotropic effects. It increases cardiac output and myocardial oxygen consumption, and can exacerbate ischaemia and arrhythmias in patients with ischaemic heart disease or impaired ventricular function.116 It is primarily used for the temporary treatment of bradyarrhythmias.3 Animal studies have reported a reduction in blood pressure and CPP with isoproterenol during resuscitation.117,118 We found one study by Jaffe et al.118 evaluating isoproterenol in human cardiac arrest. Seventy-nine patients with asystole as the initial rhythm were included in an open-label randomized trial. Patients received standard advanced cardiac life support (ACLS) treatment including atropine and were randomized to 200 μg of open-label isoproterenol every 3–5 min or no isoproterenol. There was no difference in the rate of ROSC or survival to hospital admission and the study was terminated prematurely due to futility.

**Anti-arrhythmic drugs**

**Amiodarone**

Amiodarone is classified as a class III anti-arrhythmic, although its pharmacodynamic effects are pleiotropic and include blockage of sodium channels, calcium channels, and α- and β-antagonistic effects.114–116,119–121 Acute intravenous amiodarone has been reported to increase, cause no change in, and reduce the defibrillation threshold in animal studies of ventricular fibrillation.14,16

We found seven studies of amiodarone in human cardiac arrest.14,16,117–120 Two compared amiodarone with nifekalant and will be discussed in another section.122,123 Two randomized, controlled trials compared amiodarone with placebo and lidocaine, respectively.122,123 Both studies evaluated a dose of 300 mg of amiodarone in shock-resistant ventricular arrhythmia and the primary outcome was survival to hospital admission. Kudenchuk et al.122 enrolled 304 patients in cardiac arrest who were randomly assigned to 300 mg of intravenous amiodarone or placebo. Survival to hospital admission was higher with amiodarone (44 vs. 34%,
In the ALIVE trial, Dorian et al.\(^{123}\) randomized 347 patients with shock-resistant ventricular fibrillation or relapse of ventricular fibrillation to lidocaine (1.5 mg/kg) or amiodarone (5 mg/kg). If ventricular fibrillation persisted, another dose of amiodarone (2.5 mg/kg) could be administered. The survival to hospital admission was higher with amiodarone than with lidocaine (22.8 vs. 12%, \(P < 0.05\)). Neither study was powered to detect differences in survival to discharge.

We found three observational studies of amiodarone.\(^{124}–^{126}\) One small retrospective study evaluated the use of amiodarone and reported no statistically significant difference in survival, regardless of whether or not amiodarone was given, and only 36 patients received amiodarone.\(^{124}\) In a retrospective study, Rea et al.\(^{125}\) compared survival in 194 patients who received lidocaine, amiodarone, or a combination of the two. Twenty-four-hour survival did not differ statistically between the three groups. Finally, one study reviewed paediatric patients with IHCA and survival in relation to whether amiodarone, lidocaine, both, or none were administered.\(^{126}\) Only lidocaine was associated with improved ROSC and short-term survival.

### Lidocaine

Lidocaine is a class Ib anti-arrhythmic; it prolongs conduction velocity and shortens action potential duration and the effective refractory period.\(^{13}\) Prior to the ALIVE trial in 2002, lidocaine was recommended for shock-resistant arrhythmias.\(^{123}\)

We found seven studies of lidocaine in cardiac arrest. Four compared lidocaine with amiodarone or nifekalant and are discussed in other sections.\(^{123,133,136,139}\) Weaver et al.\(^{130}\) randomized 192 patients with shock-resistant ventricular fibrillation to either adrenaline or lidocaine. There was no significant difference in the rate of ROSC or survival between the groups. Patients who received lidocaine had a three times higher rate of asystole following defibrillation. A small randomized trial compared sotalol (100 mg) and lidocaine (100 mg) in shock-resistant ventricular fibrillation and found no significant difference in survival to hospital admission or discharge.\(^{131}\) Finally, a retrospective study of 1212 patients, 33% of whom received lidocaine, reported an association between lidocaine and survival to hospital admission (38 vs. 18%, \(P < 0.01\)), although there was no difference in survival to hospital discharge.\(^{132}\)

### Procainamide

Procainamide is a class Ia anti-arrhythmic and, unlike lidocaine, it also blocks potassium channels, prolonging action potential duration and QT time.\(^{13}\) It has been used since the 1950s to treat various arrhythmias, including ventricular fibrillation. Whereas early animal studies of cardiac arrest found it inferior to vasopressors,\(^{33}\) others have demonstrated beneficial electrophysiological effects and, in a human study, procainamide was superior to lidocaine in converting sustained monomorphic ventricular tachycardia in humans.\(^{135}\)

We found two observational studies of procainamide in human cardiac arrest.\(^{134,135}\) In a small comparison study of 20 patients, procainamide was associated with increased survival in undifferentiated cardiac arrest.\(^{134}\) The second study retrospectively compared outcome in 665 patients with shock-resistant ventricular fibrillation, of whom 176 had received procainamide and, after adjustment for baseline imbalances, there was no association between treatment with procainamide and survival.\(^{135}\)

### Atropine

Atropine is an anticholinergic drug used to treat bradyarrhythmias and its cardiac effects are mainly on the sinus and the atrioventricular nodes.\(^{136}\) It was introduced in the treatment for bradyasystolic arrests after a case series in the 1970s.\(^{137}\) In 2010, atropine was removed from European Resuscitation Council Guidelines for Resuscitation due to the lack of evidence. Animal studies of atropine in PEA report contradictory results in terms of ROSC.\(^{138,139}\) We found one, retrospective study of atropine in human cardiac arrest,\(^{140}\) in which 7448 adult patients, 6419 with asystole and 1029 with PEA, were included. Patients with asystole had a significantly higher rate of ROSC if atropine and adrenaline were given, when compared with adrenaline alone (adjusted OR 1.6; \(P < 0.05\)). The two groups had similar 30-day favourable neurological outcomes. In the PEA group, atropine and adrenaline were associated with significantly lower 30-day survival compared with only adrenaline (adjusted OR 0.4, \(P = 0.016\)).

### Aminophylline

Aminophylline has complex cardiovascular effects dependent on the effect of theophylline, as both a phosphodiesterase inhibitor and an adenosine receptor antagonist.\(^{141}\) Cardiac effects include increased inotropy, chronotropy, and coronary vasoconstriction. During myocardial ischaemia, the accumulation of endogenous adenosine can result in bradycardia, vasodilation, and negative inotropy, and could perpetuate asystole.\(^{142}\) Aminophylline could theoretically prevent bradyasystolic arrest and post-defibrillatory asystole and PEA. This latter theory was tested in two animal models with prolonged ventricular fibrillation.\(^{143,144}\) Aminophylline administration, in addition to adrenaline, neither increased the rate of ROSC nor reversed PEA after defibrillation.

We identified three studies of aminophylline in human cardiac arrest.\(^{145–147}\) Two small studies randomized a total of 184 patients in cardiac arrest to aminophylline or placebo in addition to standard ACLS treatment.\(^{145,146}\) Both were negative for the primary outcome, rate of ROSC. Abu-Laban et al.\(^{147}\) studied the effect of aminophylline in patients with bradyasystolic arrest or PEA and 971 patients, refractory to treatment with adrenaline and atropine, were randomized to aminophylline or placebo. There was no difference in the rates of ROSC or survival to hospital discharge.

### Nifekalant

Nifekalant is a potassium channel antagonist used in Japan to treat ventricular arrhythmias. In animal studies, nifekalant prolongs the refractory period and has been reported to reduce the number and the energy level of defibrillations, the adrenaline dose, and the time to ROSC compared with placebo.\(^{148}\) We found four studies of nifekalant in human cardiac arrest.\(^{127–129,149}\) All were from Japan, all had a retrospective design and all compared nifekalant with either amiodarone or lidocaine. The studies comparing nifekalant with lidocaine found that nifekalant was associated with a higher rate of ROSC and 24-h survival.\(^{127–129}\) The studies comparing amiodarone with nifekalant in patients with shock-resistant ventricular fibrillation found no difference in terms of ROSC or survival.\(^{127,128}\)
although one study reported a significantly shorter time to ROSC with nifekalant, 6 vs. 20 min.\textsuperscript{128}

**Beta-blockers**

Beta-blockers reduce the risk of ventricular arrhythmias and sudden cardiac death in many myocardial pathologies.\textsuperscript{150–152} In animal models, beta-blockade during resuscitation is associated with improved rates of ROSC, less tachycardia, an improved myocardial oxygen balance, less post-resuscitation myocardial dysfunction, and a higher cardiac index after resuscitation.\textsuperscript{153–155} Beta-blockade could potentially be beneficial in refractory ventricular fibrillation, as endogenous and exogenous catecholamines facilitate myocardial instability.\textsuperscript{156} It increases defibrillatory threshold, and relapse to ventricular arrhythmias after ROSC.\textsuperscript{157} Furthermore, animal studies suggest that beta-blockers reduce cardiac dysfunction after resuscitation.\textsuperscript{43}

We identified one study of beta-blockers during resuscitation in humans. Driver et al.\textsuperscript{157} retrospectively studied 25 patients with refractory ventricular fibrillation; six patients received a short-acting \textbeta-1 antagonist (esmolol) during CPR and 19 did not. All patients had multiple defibrillations and received adrenaline, amiodarone, and sodium bicarbonate. A higher rate of ROSC (66 and 32\%) and survival with good neurological outcome (50 and 11\%) were achieved in the group treated with esmolol, although the differences were not statistically significant.

**Magnesium**

Magnesium is the second most common intracellular cation. It causes systemic and coronary vasodilatation and diminishes the contractility of vasopressors.\textsuperscript{158,159} The electrophysiological effects include reduced ventricular conduction and suppression of early and late after-depolarizations.\textsuperscript{160} In an animal study, magnesium administration increased the threshold to induce ventricular arrhythmias.\textsuperscript{161,162} It is used for treating polymorphic ventricular tachycardia associated with a prolonged QT interval.\textsuperscript{163}

We identified five studies of magnesium in human cardiac arrest.\textsuperscript{158–162} All were small randomized trials, comprising a total of 506 patients. Three studies included only patients with ventricular fibrillation.\textsuperscript{164–166} All patients received standard ACLS treatment and magnesium was administered when defibrillation had failed, with doses ranging from 2 to 5 g. In no study was magnesium administration associated with a higher rate of either ROSC or survival to hospital discharge, although small sample sizes make it difficult to exclude a type II error. However, a meta-analysis of magnesium administration in cardiac arrest did not find any significant increase in ROSC or survival to hospital discharge with magnesium administration.\textsuperscript{169} This study reportedly had an 80\% power to detect a 10\% difference in survival to hospital discharge.

**Corticosteroids**

Cortisol affects a wide range of physiological processes, including the regulation of catecholamine synthesis, and their effects on the cardiovascular system.\textsuperscript{96} The potential role in resuscitation includes the potentiation of catecholaminergic vasoconstriction and protection from ischaemia–reperfusion injury.\textsuperscript{180} The vasoconstrictive effects of noradrenaline are augmented within minutes after treatment with topical cortisone, supporting a relatively immediate effect.\textsuperscript{181,182} In a rat model of cardiac arrest, hydrocortisone administration increased ROSC.\textsuperscript{183} In observational studies, higher serum cortisol, during resuscitation and after ROSC, is associated with a greater likelihood of survival and less likelihood of circulatory shock as cause of death, in both animal models and humans.\textsuperscript{97,184–188} Cortisol levels after resuscitation are inversely correlated with no-flow time and insufficient cortisol levels are possibly a consequence of ischaemic injury to the hypothalamic–pituitary–adrenal axis.\textsuperscript{97,189}

We found three human studies evaluating corticosteroids in cardiac arrest. In a non-randomized prospective trial, Tsai et al.\textsuperscript{190} included 97 OHCA patients upon arrival at the ED, whereas 36 patients received 100 mg of hydrocortisone and 61 received saline. Eighty per cent had asystole as the initial rhythm. The rate of ROSC was higher in the hydrocortisone group (61 vs. 39\%, P = 0.038), but there was no difference in survival. Two studies, mentioned previously, demonstrated an improved outcome for IHCA patients randomized to the combination of adrenaline, vasopressin, and
methyl-prednisolone followed by daily hydrocortisone for patients with post-cardiac arrest syndrome. The role of corticosteroids is difficult to delineate because of the combinatorial intervention. There was, however, a significantly higher rate of neurologically favourable survival in the subgroup with post-cardiac arrest syndrome who received hydrocortisone after resuscitation compared with placebo.

**Erythropoietin**

Erythropoietin has anti-apoptotic properties and promotes proliferation and maturation of erythrocytes in the bone marrow. Animal models have demonstrated neuroprotective effects from erythropoietin after regional CNS ischaemia, although not after cardiac arrest. Interestingly, erythropoietin improves haemodynamic variables, increases ROSC and short-term survival, and reduces post-resuscitative myocardial dysfunction in animal models of cardiac arrest. The immediate effects of erythropoietin on haemodynamic parameters during resuscitation are not well understood.

We found one study evaluating erythropoietin during resuscitation in humans. Grmec et al prospectively compared 24 patients with OHCA who received erythropoietin (90 000 IU of betahaeboietin) with 30 OHCA patients who received 0.9% saline. Outcome was also compared retrospectively with that of 48 matched controls. In the prospective comparison, the rate of ROSC and ICU admission, but not 24-h survival, was higher in the erythropoietin group after adjustment for baseline characteristics. Compared with historical controls, erythropoietin administration was associated with significantly higher rates of ROSC and ICU admission, although 24-h survival and survival to hospital discharge were not statistically different.

**Sodium bicarbonate**

The physiological effects of acidosis include increased sympathetic output, myocardial depression, and arteriolar vasodilation, with a decreased response to catecholamines. Sodium bicarbonate has an alkalizing effect in plasma by increasing strong ion difference and shifting the bicarbonate to carbondioxide ratio. The effect on intracellular pH, however, is uncertain, as generated carbon dioxide diffuses readily across the cellular membrane.

We found three studies evaluating the effect of sodium bicarbonate in human cardiac arrest. Dybkvik et al performed a randomized trial of 502 patients with OHCA. The patients were randomized to 250 mL of Tribonat (i.e. sodium bicarbonate, trometamol, and disodium phosphate) or saline. There was no difference in survival to hospital admission or discharge. One small retrospective study found no association between ROSC and sodium bicarbonate treatment in patients with prolonged (>15 min) cardiac arrest. Finally, in a retrospective study of paediatric cardiac arrest, the use of sodium bicarbonate was associated with a reduction in short-term survival and survival to discharge, although sodium bicarbonate administration was also associated with arrest in the ICU and longer resuscitation efforts.

**Crystalloids and colloids**

Hypertonic solutions have been found to increase myocardial blood flow, cerebral perfusion, and ROSC during resuscitation in an animal model of cardiac arrest. We identified one study examining the effects of hypertonic solution in human resuscitation. Brel et al. randomized 203 patients with OHCA to an infusion of 2 mL/kg of hypertonic saline (7.2% NaCl with 6% hydroxyethyl starch 200 000/0.5) or only hydroxyethyl starch. There was no difference in survival to hospital admission or survival. One observational study compared ROSC and survival in relation to whether or not Lactated Ringer’s was administered. More than 500 000 patients from a large registry in Japan were included. The administration of Lactated Ringer’s was associated with a reduced likelihood of survival with good functional outcome after 1-month survival (adjusted odds ratio 0.764, P = 0.04).

**Discussion**

This review of the literature of human studies of the last 25 years suggests that there is still equipoise for the use of drug therapy in cardiac arrest. Out of 88 studies, we identified no study in which drug therapy, compared with placebo, improved long-term survival. Regarding adrenaline and amiodarone, the drugs currently recommended in cardiac arrest, two prospective randomized placebo-controlled trials, were identified for adrenaline, and one for amiodarone, all were underpowered to detect differences in survival to hospital discharge.

Our results are in line with other systematic reviews of drug therapy in cardiac arrest. They are also in line with the results of two studies evaluating drug therapy in cardiac arrest that were not included in our review, since they did not evaluate a specified drug. Olasveengen et al. randomized 1183 OHCA patients to intravenous access or no intravenous access and Stiell et al. enrolled 5638 OHCA patients in a ‘before-after’ study evaluating the effects of ACLS implementation. Both were neutral for their primary outcome of survival to hospital discharge.

Conducting prospective trials of interventions in cardiac arrest pose several difficulties. Time constraints, prehospital environment, lack of informed consent, and preconceptions regarding treatment pose methodological, ethical, and pedagogical obstacles to trialists and may explain why trials in cardiac arrest, including other interventions than drug therapy, often result in neutral outcomes. Nonetheless, there is a need for placebo-controlled trials of drug therapy in cardiac arrest. Evaluation of adrenaline is particularly warranted, both because of its ubiquitous use as well as animal and observational data, suggesting the lack of long-term benefit and possibly direct harm with treatment. In 2010, The International Liaison Committee for Resuscitation stated that placebo-controlled trials to evaluate the use of vasopressors in adult and paediatric cardiac arrest are needed.

Our review identifies multiple issues with interventional studies of human cardiac arrest. First, there were overall small sample sizes and limited statistical power to detect differences in patient important outcomes (e.g. survival to hospital discharge), especially as survival rates were generally low. Observational studies, while larger, often revealed inconsistent results which probably reflects
differences in registries, variations in statistical methodology, and geographical and temporal differences in the care of cardiac arrest patients.\textsuperscript{13,17,80} The ongoing PARAMEDIC2 trial (ISRCTN: 73485024) is planning to randomize 8000 patients to adrenaline or placebo and the ROC-ALPS trial will randomize 3000 patients with shock-resistant OHCA to amiodarone, lidocaine, or placebo.\textsuperscript{236} The studies are in OHCA patients and are planned to be completed in 2018 and late 2015, respectively. They will hopefully provide valuable data on the use of drug therapy in cardiac arrest.

A second issue is time to drug administration in studies of OHCA. If circulatory arrest is prolonged $> 10–15$ min, survival is dismal regardless of treatment\textsuperscript{26} and time to intervention is crucial. This might be one possible explanation for the discrepancy between findings in animal and human studies. In a systematic review of drug therapy in animal studies, the average time to drug administration was $9.5 \text{ min},$\textsuperscript{237} but in our review of human studies it was $16 \text{ min}$ and only one study of vasopressor therapy in OHCA patients had a median time to drug administration $< 10 \text{ min}$.

Third, most studies enrolled patient with undifferentiated cardiac arrest irrespective of time in no-flow, aetiology, initial rhythm, or predicted survival. However, as outlined earlier, the pathophysiology of cardiac arrest is different depending on patient characteristics and comorbidities, aetiology of arrest, time in no-flow and initial rhythm, and likelihood of survival can range from a few per cent to over $50\%.$\textsuperscript{5,8} A single drug or intervention could have unequal effects depending on such differences, which would augment the difficulties of demonstrating beneficial effects of a certain intervention and effect sizes risk depletion. Meanwhile, intervention or drug recommendations cannot be too complicated to allow for implementation into clinical practice. Even in the context of a clinical trial interventions are likely to fail if too complex.

Fourth, many of the trials were performed before the use of current post-resuscitative interventions (e.g. target temperature management and percutaneous cardiac intervention) and therefore might have had less chance of translating an improvement in ROSC or survival to hospital admission into improved long-term survival. In fact, registries from Europe and the USA have reported improved survival in patients with cardiac arrest, regardless of rhythm, during the last $10–15$ years, even though no significant change in resuscitation guidelines has taken place during this period.\textsuperscript{5,7,238–240}

Finally, in addition to, or instead of, currently recommended drugs in cardiac arrest our review suggests that ‘new’ drugs, such as corticosteroids, beta-blockers, and erythropoietin, with support from animal studies, but as of yet insufficient data from human trials, might be one possible explanation for the discrepancy between findings in animal and human studies. In a systematic review of drug therapy in animal studies, the average time to drug administration was $9.5 \text{ min},$\textsuperscript{237} but in our review of human studies it was $16 \text{ min}$ and only one study of vasopressor therapy in OHCA patients had a median time to drug administration $< 10 \text{ min}$.

To conclude, carefully designed and controlled studies of drug therapy in cardiac arrest are needed. These studies should preferably be conducted in large research networks to be able to enrol large enough sample sizes in order to demonstrate differences in relevant outcomes.

### Conclusion

The evidence base for drug therapy in cardiac arrest is scarce. Many drugs have been considered and several have shown promising results in animal studies. Regarding adrenaline and amiodarone, the drugs currently recommended in cardiac arrest, there is no evidence of improved long-term survival with a favourable neurological outcome in humans. However, many human studies of drug therapy in cardiac arrest have not been powered to identify differences in important clinical outcomes such as survival to hospital discharge and favourable neurological outcome. Efforts are needed to initiate large multicentre, prospective, randomized, clinical trials to evaluate both currently recommended and future drug therapies.

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### Conflict of interest

None declared.

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