Effectiveness of antiarrhythmic drugs for shockable cardiac arrest: A systematic review

Authors:

Muhammad Usman Ali, MD [a,b]

Donna Fitzpatrick-Lewis, MSW [c]

Meghan Kenny, MA [a,b]

Parminder Raina, PhD [a,b]

Dianne L Atkins MD [d]

Jasmeet Soar, MA, MB, BChir, FRCA, FRCP FFICM [e]

Jerry Nolan, FRCA, FRCP, FFFICM, FRCEM [f]

Giuseppe Ristagno, MD, PhD [g]

Diana Sherifali, RN, PhD [a,c]*

*Corresponding Author

Affiliations: [a] McMaster Evidence Review and Synthesis Centre, McMaster University, 1280 Main St. W., McMaster Innovation Park, Room 207A, Hamilton, Ontario, Canada, L8S 4K1

[b] Department of Health Research Methods, Evidence and Impact, Faculty of Health Sciences, McMaster University, Room HSC-2C, 1200 Main Street West, Hamilton, Ontario, Canada, L8N 3Z5

[c] School of Nursing, Faculty of Health Sciences, McMaster University, Health Sciences Centre Room HSC-3N25F, 1280 Main Street West, Hamilton, Ontario, Canada, L8S 4K1

[d] Stead Family Department of Pediatrics, Carver College of Medicine, University of Iowa, Iowa City, IA 52242, USA

[e] Southmead Hospital, Bristol, BS10 5NB, UK

[f] University of Bristol and Royal United Hospital, Bath, BA1 3NG, UK

[g] IRCCS-Istituto di Ricerche Farmacologiche "Mario Negri", Milan, Italy

Abstract

Purpose:

The purpose of this systematic review is to provide up-to-date evidence on effectiveness of antiarrhythmic drugs for shockable cardiac arrest to help inform the 2018 International Liaison Committee on Resuscitation Consensus on Science with Treatment Recommendations.

Methods:

A search was conducted in electronic databases Medline, Embase, and Cochrane Library from inception to August 15, 2017.

Results:

Of the 9,371 citations reviewed, a total of 14 RCTs and 17 observational studies met our inclusion criteria for adult population and only 1 observational study for pediatric population. Based on RCT level evidence for adult population, none of the anti-arrhythmic drugs showed any difference in effect compared with placebo, or with other anti-arrhythmic drugs for the critical outcomes of survival to hospital discharge and discharge with good neurological function. For the outcome of return of spontaneous circulation, the results showed a significant increase for lidocaine compared with placebo (RR=1.16; 95% CI, 1.03 to 1.29, p=0.01).

Conclusion:

The high level evidence supporting the use of antiarrhythmic drugs during CPR for shockable cardiac arrest is limited and showed no benefit for critical outcomes of survival at hospital discharge, survival with favorable neurological function and long-term survival. Future high quality research is needed to confirm these findings and also to evaluate the role of administering

antiarrhythmic drugs in children with shockable cardiac arrest, and in adults immediately after ROSC.

Key Words: Cardiac arrest, pulseless ventricular tachycardia or ventricular fibrillation, antiarrhythmic drugs, good neurological function, return of spontaneous circulation.

Introduction

Cardiac arrest (CA) is defined as sudden and unexpected loss of heart function accompanied with loss of breathing and consciousness primarily due to disturbance in electrical activity of heart. An estimated 320,000 to 700,000 cases of out-of-hospital cardiac arrests (OHCA) occur annually across the United States and Europe [1, 2]. CA with an initial heart rhythm of pulseless ventricular tachycardia or ventricular fibrillation (pVT/VF) is the most treatable cause of CA [2]. For those individuals who receive cardiopulmonary resuscitation (CPR) with prompt shock treatment (i.e. defibrillation) and drugs, if needed, only 8-40% survive to hospital discharge [3-8]. Of these, approximately 50-75% have favourable neurological outcome, although about 50% of survivors likely have subtle cognitive deficits [9, 10].

A recent systematic review and meta-analysis comparing amiodarone and lidocaine with placebo demonstrated that both drugs showed increased survival to hospital admission compared with placebo, however, neither drug showed any benefit on long-term survival or good neurological outcomes for adults [11]. For pediatric CA, a 2017 systematic review found weak evidence to recommend the use of amiodarone or lidocaine for shock-resistant pVT/VF in infants and children [12]. The American Heart Association guidelines published in 2015, recommend the use of amiodarone with lidocaine as an alternative to amiodarone for pVT/VF for adults unresponsive to CPR, defibrillation or vasopressor therapy [13].

However, to-date, the evidence synthesis on anti-arrhythmic drugs used to treat CA, has been primarily based on randomized controlled trials that are likely underpowered and prone to bias with unbalanced baseline characteristics, different drug formulation and timing of drug

administration [14, 15]. This warrants the need to update and systematically review any potential new available evidence that may impact results and conclusions. The purpose of this systematic review and meta-analysis is to provide the most up-to-date evidence on effectiveness of antiarrhythmic drugs for shockable cardiac arrest in both adults and children, and help inform the updated 2018 International Liaison Committee on Resuscitation (ILCOR) Consensus on Science with Treatment Recommendations (CoSTR).

Methods

The protocol for this review was published on PROSPERO on December 15, 2017 registration number CRD42017080475. The same methods have been used by and are reported in other publications authored by our review team [16-18].

Review question

Among adults and children (neonates, children and adolescents < 18) in any setting (in-hospital or out-of-hospital) with cardiac arrest and a shockable rhythm at any time during cardiopulmonary resuscitation (CPR) or immediately after return of spontaneous circulation (ROSC), does administration of antiarrhythmic drugs (e.g., amiodarone, lidocaine, other), compared with another antiarrhythmic drug or placebo or no drug , change outcomes of survival to hospital discharge with good neurological outcome, survival to hospital discharge, ROSC and recurrence of recurrence of pVT/VF?

Search Strategy

A search was conducted in electronic databases Medline, Embase, and Cochrane Library from inception to August 15, 2017. Reference lists from relevant systematic reviews were searched

for studies missed by the electronic search. The electronic search identified 13,868 citations and 8 additional citations were found through other sources (e.g., reference list check). Once duplicates were removed, there were 9,371 citations uploaded to the web-based screening program [19] to be screened independently by review staff.

Study Selection, data abstraction and quality assessment

Two reviewers independently selected studies for possible inclusion. Studies selected by either reviewer based on title and abstract underwent full text review. At the level of full text screening, any disagreement was discussed between reviewers and a third party was involved to help reach consensus, as necessary (see Table 1 for inclusion criteria). Full data extraction, including characteristics of included studies and risk of bias (assessed using the Cochrane risk of bias framework [20] was completed by one reviewer and verified by a second reviewer. Disagreements were resolved between the two reviewers with a third party involvement to reach consensus, as necessary. In case of multiple publications from same study, the first publication was considered as main reference while the outcome data was extracted across all publications and the most recent outcome data was considered for analyses. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [21] was used to assess the strength and the quality of evidence using GRADEPro software [22]. The quality of outcome-based bodies of evidence was assessed for risk of bias due to limitations in design, indirectness, inconsistency of findings, imprecision, and reporting bias (such as publication bias). Meta-analyses were conducted where appropriate.

Data synthesis

For the primary outcomes of effectiveness of antiarrhythmic drugs in adults and children with SCA (i.e. survival at discharge, survival at discharge with good neurological function, long-term survival, ROSC, and cardiac re-arrest) we used number of events to generate the summary measures of effect in the form of risk ratio (RR) using DerSimonian and Laird [23] random effects models with Mantel-Haenszel method. The primary grouping of studies in each meta-analysis was based on type of population i.e. adult or pediatric, and type of study design (RCT or observational). Further subgrouping was done based on type of anti-arrhythmic drug and drug comparison (placebo or head-to-head trials).

To evaluate statistical stability, robustness of results and to account for any potential bias (such as confidence intervals being inappropriately wide) in pooled estimates, we performed sensitivity analysis based on type of pooling method i.e. DerSimonian-Laird random-effects model (REM), Fixed-effects model (FEM), and Peto one-step odds ratio [24, 25]. The sensitivity analyses did not reveal any noticeable differences in effect estimates based on type of pooling method used. The Cochran's Q (α=0.05) was employed to detect statistical heterogeneity and I^2 statistic to quantify the magnitude of statistical heterogeneity between studies where I^2 30% to 60% represents moderate and I^2 60% to 90% represents substantial heterogeneity across studies [26]. All analyses were performed using Review Manager (RevMan Version 5.3) [27], STATA (version 14) [28] and GRADEpro Guideline Development Tool software packages [22].

Results

Overall Search Results

Of the 9,371 citations reviewed, 34 unique citations met the inclusion criteria and were selected for this review. There are 14 randomized and controlled clinical trial studies (16 papers) and 18

observational studies (21 papers) addressing the questions for adults and 1 observational study for the pediatrics (see fig. 1 for Flow Diagram).

Summary of Included Studies for the Adult Population

A total of 14 RCTs [29-42] and 18 observational studies [43-60] were included. The overall risk of bias for RCTs was rated high in one study [42], unclear in eleven studies [29-35, 37, 39-41], and low in two studies [36, 38]. The individual domain ratings for each study are reported in Supplemental File 1. The Newcastle-Ottawa Quality Assessment Scale was used to rate the quality of the included observational studies and no major quality concerns were identified (see Supplemental File 1). The publication years of resuscitation guidelines applied in the RCT studies ranged from pre-2000 to 2010 and the publication years of resuscitation guidelines referenced in the observational studies ranged from pre-2000 to 2015 (see Supplemental File 2). The included RCTs were comprised of one study [38] with a large sample (>1,000 participants), one study [37] with a medium sized sample (500-999 participants), and twelve studies [29-36, 39-42] with small samples (<499 participants). In the observational studies, there were four [44, 48, 49, 58] large cohorts (>1,000 participants), four [43, 50, 57, 60] medium sized cohorts (500-999 participants), and ten [45-47, 51-56, 59] small cohorts (<499 participants). The range of mean ages in the included RCT studies was 57 to 67 years, while in the observational studies it was 55.8 to 83.3 years. Most of the RCT and observational studies included more males than females. All the RCTs administered the intervention drug during CPR. In the studies time of administration was reported [29-31, 37, 38, 41], time from cardiac arrest to first dose of the trial drug ranged from 10 to 30 minutes. All but one observational study administered the intervention drug during CPR while one administered the drug immediately after ROSC. The time from cardiac arrest to first dose of the trial drug was reported in six studies [51-54, 57, 59] and ranged

from 6 to 35 minutes. Additional information on the characteristics of included studies can be found in Supplemental File 2.

Anti-arrhythmic drugs versus Placebo (RCT-level evidence)

Amiodarone versus Placebo

The evidence on amiodarone was considered as both pooled and separated. The primary reason to look at evidence separately was the different drug formulations (i.e. amiodarone with or without polysorbate 80) and placebo comparator (i.e. active polysorbate 80 placebo and inactive saline placebo) active across the two included studies. The vasoactive solvent "polysorbate 80 "in Cordarone™ preparation of amiodarone has been linked to potential adverse hemodynamic effects particularly bradycardia and hypotension and may be associated with differential effect on outcomes of interest based on drug formulation [61, 62]. For the critical outcome of survival with favorable neurologic function at hospital discharge, the pooled evidence showed no difference in effect for amiodarone compared with placebo (2 RCTs; RR=1.13; 95% CI, 0.95 to 1.36, p=0.18, I^2=0%) [37, 38]. The overall quality of evidence was rated as very low quality and downgraded for serious concerns for risk of bias, indirectness and imprecision. The evidence on amiodarone in polysorbate 80, i.e. the Cordarone™ preparation of amiodarone, with very low quality (downgraded for serious concerns for risk of bias, indirectness and imprecision), showed no difference in effect for amiodarone compared with an active polysorbate 80 placebo (1 RCT; RR=1.11; 95% CI, 0.59 to 2.10, p=0.75) [37]. The evidence on the Nexterone™ preparation of amiodarone, with moderate quality (downgraded for serious concerns for imprecision), showed no difference in effect for amiodarone compared with inactive "saline" placebo (1 RCT; RR=1.13; 95% CI, 0.94 to 1.37, p=0.19, (see Table 2, fig. 2.1) [38].

For the critical outcome of survival at hospital discharge, the pooled evidence showed no difference in effect for amiodarone compared to placebo (2 RCTs; RR=1.14; 95% CI 0.98 to 1.33, p=0.08, I^2=0%) [37, 38]. The overall quality of evidence was rated as very low quality and downgraded for serious concerns for risk of bias, indirectness and imprecision. Evidence on the Cordarone™ preparation of amiodarone, with very low quality (downgraded for serious concerns for risk of bias, indirectness and imprecision), showed no difference in effect for amiodarone compared with an active polysorbate 80 placebo (1 RCT; RR=1.02; 95% CI, 0.65 to 1.59, p=0.94) [37]. Evidence on Nexterone™ preparation of amiodarone, with moderate quality (downgraded for serious concerns for imprecision), showed no difference in effect for amiodarone compared with inactive saline placebo (1 RCT; RR=1.16; 95% CI, 0.99 to 1.37, p=0.07, see Table 2, fig. 2.2) [38].

For the important outcome of ROSC, the pooled evidence showed no difference in effect for amiodarone compared with placebo (2 RCTs; RR=1.13; 95% CI, 0.93 to 1.37, p=0.11, I^2=60%) [37, 38]. The overall quality of evidence was rated as very low quality and downgraded for serious concerns for risk of bias, indirectness and imprecision. Evidence on the Cordarone™ preparation of amiodarone, with very low quality (downgraded for serious concerns for risk of bias, indirectness and imprecision), showed benefit favoring amiodarone compared with an active polysorbate 80 placebo (1 RCT; RR=1.27; 95% CI, 1.02 to 1.59, p=0.03) [37]. Evidence on Nexterone™ preparation of amiodarone, with moderate quality (downgraded for serious concerns for imprecision), showed no difference in effect for amiodarone compared with inactive saline placebo (1 RCT; RR=1.04; 95% CI, 0.92 to 1.17, p=0.52, see Table 2, fig. 2.3) [38].

Lidocaine versus Placebo

For the critical outcome of survival with favorable neurological function at hospital discharge, the effect estimate showed no difference in effect for lidocaine compared with placebo (1 RCT;

RR=1.05; 95% CI, 0.87 to 1.28, p=0.59, see Table 3, fig. 2.1) [38]. Similar results were obtained for the critical outcome of survival at hospital discharge (1 RCT; RR=1.13; 95% CI, 0.96 to 1.32, p=0.15, see Table 3, fig. 2.2) [38]. The overall quality of this evidence was rated as moderate and downgraded for serious concerns regarding imprecision.

For the important outcome of ROSC, the effect estimate showed a significant increase favoring lidocaine compared with placebo (1 RCT; RR=1.16; 95% CI, 1.03 to 1.29, p=0.01, see fig. 2.3) [38]. The overall quality of this evidence was rated as high.

Other anti-arrhythmic drugs versus Placebo

For the critical outcome of survival with favorable neurological function at hospital discharge, the pooled effect estimate showed no difference in effect for magnesium compared with placebo (3 RCTs; RR=2.08; 95% CI, 0.87 to 4.97, p=0.10, I^2=0%, see Supplemental File 3, fig. 2.1) [30, 32, 41]. Similar results were obtained for the outcomes of survival to discharge for magnesium (4 RCTs; RR=1.07; 95% CI, 0.62 to 1.86, p=0.81, I^2=0%) [30, 32, 33, 41] and bretylium (1 RCT; RR=4.28; 95% CI, 0.60 to 30.26, p=0.15, see Supplemental File 3, fig. 2.2) [40]; and ROSC for magnesium (4 RCTs; RR=0.97; 95% CI, 0.77 to 1.24, p=0.83, I^2=0%, see Supplemental File 3, fig. 2.3) [30, 32, 33, 41]. The overall quality of this evidence was rated as very low and downgraded for serious concerns regarding risk of bias and imprecision.

Head-to-head comparisons (RCT-level evidence)

Amiodarone versus Lidocaine

For the critical outcome of survival with favorable neurological function at hospital discharge, the evidence with moderate quality (downgraded for serious concerns for imprecision) showed no difference in effect for amiodarone compared with lidocaine (1 RCT; RR=1.08; 95%CI 0.89 to 1.30, p=0.44, see Table 4, fig. 3.1) [38].

For the critical outcome of survival to hospital discharge, the pooled evidence showed no difference in effect for amiodarone compared with lidocaine (2 RCTs; RR=1.04; 95% CI 0.89 to 1.22, p=0.59, I^2=0%) [31, 38]. Evidence on lidocaine with the use of polysorbate 80, showed no difference in effect for amiodarone compared with lidocaine (1 RCT; RR=1.67; 95% CI, 0.57 to 4.88, p=0.35) [31]. The overall quality of evidence was rated as very low quality and downgraded for serious concerns for risk of bias, indirectness and imprecision. Evidence on critical outcome of survival to hospital discharge for lidocaine without use of polysorbate 80, with moderate quality (downgraded for serious concerns for imprecision), showed no difference in effect for amiodarone compared with lidocaine (1 RCT; RR=1.03; 95% CI, 0.88 to 1.21, p=0.69, see Table 4, fig. 3.2) [38].

Similar results were obtained for the important outcome of ROSC (1 RCT; RR=0.90; 95% CI, 0.80 to 1.01, p=0.07, see Table 4, fig. 3.3) [38]. The overall quality of this evidence was rated as moderate and downgraded for serious concerns regarding imprecision.

Other anti-arrhythmic drugs head-to-head comparisons

For the critical outcomes of survival with favorable neurological function at discharge, survival at discharge, cardiac re-arrest and ROSC, none of the effect estimates for anti-arrhythmic drug head-to-head comparisons showed any difference in effect (see Supplemental File 4, figs. 3.1 to 3.4), except ROSC for lidocaine vs. nifekalant where the difference was marginally significant favoring lidocaine (RR=0.23; 95% CI, 0.06 to 0.92, p=0.04, see Supplemental File 4, fig. 3.3) [35]. However, the study was under-powered with very small sample size. The overall quality of this evidence was rated as low to very low and downgraded for serious concerns regarding risk of bias and imprecision.

Anti-arrhythmic drugs versus no antiarrhythmic drugs (standard care; observational studies)

Amiodarone versus standard care

For the critical outcomes of survival at hospital discharge and the long-term survival of 1 year, one large cohort study [48] (n=24,899) showed significant difference in effect favoring amiodarone compared with standard care (RR=2.88; 95% CI, 2.58 to 3.21, p<0.001; and RR=2.53; 95% CI, 2.26 to 2.84, p<0.001, respectively, see figs. 4.1 and 4.2). The smaller cohort study [55] (n=290) showed no difference in effect for either survival to hospital discharge or ROSC (p>0.05, see figs. 4.1 and 4.3).

Lidocaine versus standard care

For the outcomes of survival to hospital discharge and the long-term survival of 1 year, one large cohort study [48] (n=19,517) showed significant difference in effect favoring lidocaine compared with standard care (RR=2.52; 95% CI, 2.04 to 3.12, p<0.001; and RR=2.19; 95% CI, 1.74 to 2.75, p<0.001, respectively, see figs. 4.1 and 4.2). Another cohort study [47] (n=290) also showed significant difference in effect for the outcome ROSC favoring lidocaine compared with standard care (RR=1.88; 95% CI, 1.29 to 2.75, p=0.001). However, the observed effect was non-significant for survival at hospital discharge and ROSC across two relatively small cohort studies (n=853, p>0.05, see figs 4.1 and 4.3) [46, 60].

Other anti-arrhythmic drugs versus standard care

For the outcomes of survival with favorable neurological function at hospital discharge, survival at discharge, cardiac re-arrest and ROSC, none of the effect estimates for other anti-arrhythmic drugs showed any difference in effect compared with standard care (see figs. 4.1, 4.3, and 4.4) except ROSC for procainamide in one cohort study [50] where the difference was significant favoring procainamide (RR=0.59; 95% CI, 0.42 to 0.82, p=0.02).

Head-to-head comparisons (observational studies)

Amiodarone versus Lidocaine

For the outcome of survival at hospital discharge, the pooled evidence across 5 cohort studies [44, 48, 52, 53, 58] (n=11,263) showed no difference in effect for amiodarone compared with lidocaine (RR=0.87; 95% CI, 0.72 to 1.06, p=0.17, see fig. 5.1). For the outcome of long-term survival of 1 year, one large cohort study (n=7,536) showed no difference in effect for amiodarone compared with lidocaine (RR=1.16; 95% CI, 0.92 to 1.46, p=0.22, see fig. 5.2) [48]. Similar results were obtained for the outcome of ROSC across 3 cohort studies (n=2425; RR=0.79; 95% CI, 0.63 to 1.00, p=0.05, see fig. 5.3) [43, 44, 52].

Other anti-arrhythmic drugs head-to-head comparisons

For the outcome of survival with favorable neurological function at hospital discharge, none of the effect estimates for other head-to-head comparisons showed any difference (see fig. 5.4). For the outcome of survival at hospital discharge, one small cohort study [57] (n=230) showed significant difference favoring lidocaine compared with procainamide (RR=0.31; 95% CI, 0.11 to 0.86, p=0.006). For the outcome of long-term survival of 1 year, one large cohort study [48] (n=9,023) showed significant difference favoring combined use of amiodarone plus lidocaine compared with amiodarone or lidocaine alone (RR=1.34; 95% CI, 1.14 to 1.58, p<0.001; and RR=1.55; 95% CI, 1.20 to 2.01, p<0.001, respectively). For the outcome of ROSC, the pooled evidence across 3 cohort studies [43, 45, 58] showed marginally significant difference favoring nifekalant compared with amiodarone (n=1,000; RR=0.92; 95% CI, 0.86 to 0.99, p=0.03). Another small cohort study [57] (n=230) also showed significant difference favoring lidocaine compared with procainamide (RR=0.55; 95% CI, 0.34 to 0.90, p=0.02, see fig. 5.3).

Adults with cardiac arrest and a shockable rhythm immediately after return of spontaneous circulation

No RCT level evidence was identified that answered this question, however 1 observational study [49] provided data on adults with cardiac arrest and prophylactic antiarrhythmic drugs given within 1 hour of ROSC. For the outcome of survival to hospital discharge, the results based on non-propensity matched cohorts (lidocaine arm: 1296; standard care: 425) showed a significant effect favoring the administration of prophylactic lidocaine compared with standard care (RR= 1.40, 95% CI 1.25, 1.57; p<0.0001). However, the effect was non-significant when data from propensity matched cohorts (lidocaine arm: 400; standard care: 400) was used (RR=1.03, 95% CI 0.89, 1.20; p=0.67). For the outcome of recurrence of pVT/VF, the results showed a significant effect favoring the administration of prophylactic lidocaine compared with standard care for both non-propensity matched cohorts with 55% reduction (RR= 0.45, 95% CI 0.38, 0.53; p<0.0001) and propensity matched cohorts with 41% reduction (RR= 0.59, 95% CI 0.47, 0.74; p<0.0001).

Pediatric Population

There was one observational study involving children that met our criteria for inclusion [63]. There were no major concerns regarding risk of bias. The study focused on a cohort of 889 participants <18 years of age. The sex of participants was not reported. The trial drug was administered during cardiac arrest. The time from cardiac arrest to first dose of the drug was not reported.

Infants and children with cardiac arrest and a shockable rhythm at any time during cardiopulmonary resuscitation (CPR) or immediately after return of spontaneous circulation)

No RCT level evidence was identified that answered this question, however, 1 observational study [63] provided data on in-hospital pediatric cardiac arrest and a shockable rhythm.

Amiodarone versus standard care

For the outcomes of survival at hospital discharge and ROSC, one cohort study [63] (n=594) showed no difference in effect for amiodarone compared with standard care (RR=0.83; 95% CI, 0.50 to 1.35, p=0.45; and RR=0.85; 95% CI, 0.66 to 1.09, p=0.21, respectively, see figs. 5.5 and 5.6).

Lidocaine versus standard care

For the outcomes of survival at discharge, one cohort study [63] (n=718) showed no difference in effect for lidocaine compared with standard care (RR=1.24; 95% CI, 0.93 to 1.66, p=0.14, see fig. 5.5). However, the results showed significant difference in effect for the outcome ROSC favoring lidocaine compared with standard care (RR=1.24; 95% CI, 1.09 to 1.41, p=0.001, see fig. 5.6).

The evidence for antiarrhythmic drug comparison with standard care should be interpret with caution as study was not clear about whether patients did not receive an anti-arrhythmic because they did not have shock refractory VF or because the care providers elected not to receive it.

Lidocaine versus Amiodarone

For the critical outcome of survival to hospital discharge, one cohort study [63] (n=302) found no difference in effect for lidocaine compared with amiodarone (25% versus 17%; P=NS; RR 1.50; 95% CI 0.90 to 2.52, p=0.12, see fig. 5.7). However, the results showed significant increase in ROSC for lidocaine as compared with amiodarone (RR=1.46; 95% CI 1.13 to 1.88, p=0.004, see fig. 5.8).

The study reported results for combined use of amiodarone and lidocaine compared with amiodarone or lidocaine alone and found no differences in effect for the outcome of survival to hospital discharge or ROSC (see figs. 5.7 and 5.8).

Discussion

Our review found limited high level evidence (RCTs) supporting the use of antiarrhythmic drugs during CPR in adults with shock refractory pVT/VF and found no significant benefit for critical outcomes of survival at hospital discharge, survival with favorable neurological function and long-term survival. No high level evidence was identified for use of antiarrhythmic drugs in adults with shock refractory pVT/VF immediately after return of spontaneous circulation and in children with shockable cardiac arrest.

Summary of evidence

Effectiveness of antiarrhythmic drugs in adults with cardiac arrest (shockable rhythm) at any time during cardiopulmonary resuscitation

Most of the studies in our review included adults with cardiac arrest and a shockable rhythm at any time during CPR for out-of-hospital cardiac arrest, and no studies for in in-hospital cardiac arrest. Based on RCT level evidence, none of the anti-arrhythmic drugs showed any difference in effect compared with placebo, or with other anti-arrhythmic drugs for the critical outcomes of survival to hospital discharge and discharge with good neurological function. The quality of evidence across these studies was rated from moderate to very low with concerns of risk of bias, indirectness and imprecision. For the important outcome of ROSC, the results showed a significant increase in ROSC for lidocaine compared with placebo (RR=1.16; 95% CI, 1.03 to 1.29, p=0.01). The overall quality of this evidence was rated as high. The evidence on the Cordarone™ preparation of amiodarone also showed marginal benefit for ROSC favoring amiodarone compared with an active polysorbate 80 placebo (RR=1.27; 95% CI, 1.02 to 1.59, p=0.03); however, the quality of the evidence was rated as very low with concerns for risk of bias, indirectness (active placebo with potential adverse hemodynamic effects) and imprecision.

The evidence from large observational study [48] (n=27,463) showed a significant benefit for amiodarone and lidocaine for the outcomes of survival at hospital discharge and long-term survival at 1-year. However, the effect estimates are based on raw events and subject to selection bias with imbalance across groups and should be interpret with caution. The results from smaller observational studies were inconsistent and likely underpowered with most showing no difference in effect for the outcomes of survival at discharge, survival at discharge with neurological function and ROSC.

Effectiveness of antiarrhythmic drugs in adults with cardiac arrest (shockable rhythm) immediately after return of spontaneous circulation

We found no RCT level evidence for this population, however, one observational study [49] (N=1,721) provided results for the use of prophylactic lidocaine compared with standard care within 1 hour of ROSC. The results from propensity matched cohort showed no difference in effect for the outcome of survival to hospital discharge; however, a significant reduction of 41% was observed for the outcome of recurrent pVT/VF.

Effectiveness of antiarrhythmic drugs in children with cardiac arrest (shockable rhythm)

We found no RCT level evidence for this population, however, one observational study [63] (N=889) compared the use of amiodarone, lidocaine, amiodarone plus lidocaine, and standard care for in-hospital pediatric cardiac arrest and a shockable rhythm. The results showed no differences in effect for the outcome of survival to hospital discharge. The evidence on ROSC showed a significant benefit for lidocaine compared with amiodarone. However, the comparisons are based on raw events and subject to selection bias with imbalance across groups and should be interpreted with caution.

Implications for clinical practice and future research

These results will be considered by the Advanced Life Support (ALS) Task Force of the International Liaison Committee on Resuscitation and will be used to update treatment recommendations on the use of antiarrhythmic drugs in shock refractory pVT/VF. The use of antiarrhythmic drugs is just one aspect of the treatment of pVT/VF. Other interventions such as the quality of CPR, use of additional defibrillation attempts, extracorporeal CPR (ECPR) techniques and percutaneous coronary intervention (PCI) during CPR are all likely to have a role in the improving survival from shock refractory pVT/VF arrest in adults . Future high quality research is needed to evaluate the effectiveness of administering antiarrhythmic drugs in adults with cardiac arrest immediately after ROSC and in children in cardiac arrest or immediately after ROSC. Future randomized controlled studies are also needed to explore the role of administering antiarrhythmic drugs in adults with in-hospital shockable cardiac arrest.

Limitations

First, there was considerable heterogeneity across studies for various population and study level factors such as dose and formulation of antiarrhythmic drugs, timing of drug administration, type of placebo (active or saline), sample size, setting (in or out-of-hospital), assessment of neurological function, type of standard care provided, resuscitation guidelines used, and timing of events. Second, there was insufficient high-level evidence to answer several questions of interest including effectiveness of anti-arrhythmic drugs in adults with cardiac arrest immediately after ROSC, for in-hospital cardiac arrest and in children with shockable cardiac arrest during CPR or immediately after ROSC. Third, we did not analyze the differential effectiveness based on time lapsed from cardiac arrest to drug administration i.e. early or late in terms of EMS or bystander witnessed cardiac arrest. Fourth, the majority of included studies were under-powered with inadequate number of events or sample sizes to detect clinically

important differences, and results were imprecise with wide confidence intervals. Fifth, there was insufficient evidence to understand etiology based subgroups differences i.e. primary rhythm disorders (inherited, drug induced, congenital heart disease) versus coronary artery diseases. Finally, there were insufficient number of studies reporting outcomes of interest to assess publication bias.

Conclusions

The high level evidence supporting the use of antiarrhythmic drugs during CPR for shock refractory pVT/VF or immediately after ROSC is limited and showed no significant benefit for critical outcomes of survival at hospital discharge, survival with favorable neurological function and long-term survival. The high level evidence also showed a significant increase in important outcome of ROSC for lidocaine compared with placebo, suggesting that use of lidocaine during CPR may improve the short-term survival in adult cardiac arrest patients with shock refractory pVT/VF. However, future high quality research is needed to confirm these findings and also evaluate the effectiveness and role of administering antiarrhythmic drugs in children with shockable cardiac arrest, and in adults immediately after ROSC.

Declaration of Interests

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Table 1

Inclusion Criteria

Population	Adults and children in any setting (in-hospital or out-of-hospital) with cardiac arrest and a shockable rhythm at any time during cardiopulmonary resuscitation (CPR) or immediately after Return of Spontaneous Circulation (ROSC).
Intervention	Administration (intravenous or intra-osseous) of an antiarrhythmic drug during CPR and immediately after ROSC.
Comparators	Another anti-arrhythmic drug or placebo or no drug during CPR or immediately after ROSC.
Outcomes	Any clinical outcome.
Study Designs	Randomised controlled trials (RCTs) and non-randomised studies (non-randomised controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) are eligible for inclusion. All years and all languages are included as long as there is an English abstract; unpublished studies (e.g., conference abstracts, trial protocols) are excluded.

Table 2

Question: Amiodarone compared with Placebo for shockable cardiac arrest in adults

Certainty assessment							№ of events / № of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Amiodarone**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Survival to hospital discharge - combined												
2 [a]	randomised trials	serious [b]	not serious	very serious [c]	serious [d]	none	270/1216 (22.2%)	256/1314 (19.5%)	**RR 1.14** (0.98 to 1.33)	**27 more per 1,000** (from 4 fewer to 64 more)	⊕◯◯◯ VERY LOW	CRITICAL
Survival to hospital discharge - Cordarone preparation of Amiodarone												
1 [e]	randomised trials	serious [f]	not serious	very serious [g]	serious [d]	none	33/246 (13.4%)	34/258 (13.2%)	**RR 1.02** (0.65 to 1.59)	**3 more per 1,000** (from 46 fewer to 78 more)	⊕◯◯◯ VERY LOW	CRITICAL
Survival to hospital discharge - Nexterone preparation of Amiodarone												
1 [h]	randomised trials	not serious	not serious	not serious	serious [d]	none	237/970 (24.4%)	222/1056 (21.0%)	**RR 1.16** (0.99 to 1.37)	**34 more per 1,000** (from 2 fewer to 78 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Survival to hospital discharge with good Neurological function - combined												

Certainty assessment							№ of events / № of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Amiodarone**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
2 [a]	randomised trials	serious [b]	not serious	very serious [c]	serious [d]	none	200/1213 (16.5%)	192/1313 (14.6%)	**RR 1.13** (0.95 to 1.36)	**19 more per 1,000** (from 7 fewer to 53 more)	⨁◯◯◯ VERY LOW	CRITICAL
Survival to hospital discharge with good Neurological function - Cordarone preparation of Amiodarone												
1 [e]	randomised trials	serious [f]	not serious	very serious [g]	serious [d]	none	18/246 (7.3%)	17/258 (6.6%)	**RR 1.11** (0.59 to 2.10)	**7 more per 1,000** (from 27 fewer to 72 more)	⨁◯◯◯ VERY LOW	CRITICAL
Survival to hospital discharge with good Neurological function - Nexterone preparation of Amiodarone												
1 [h]	randomised trials	not serious	not serious	not serious	serious [d]	none	182/967 (18.8%)	175/1055 (16.6%)	**RR 1.13** (0.94 to 1.37)	**22 more per 1,000** (from 10 fewer to 61 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Return of Spontaneous Circulation (ROSC) - combined												
2 [a]	randomised trials	serious [b]	not serious	very serious [c]	serious [d]	none	458/1220 (37.5%)	455/1317 (34.5%)	**RR 1.13** (0.93 to 1.37)	**45 more per 1,000** (from 24 fewer to 128 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of events / № of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Amiodarone**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Return of Spontaneous Circulation (ROSC) - Cordarone preparation of Amiodarone												
1 [e]	randomised trials	serious [f]	not serious	very serious [g]	serious [i]	none	108/246 (43.9%)	89/258 (34.5%)	**RR 1.27** (1.02 to 1.59)	**93 more per 1,000** (from 7 more to 204 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Return of Spontaneous Circulation (ROSC) - Nexterone preparation of Amiodarone												
1 [h]	randomised trials	not serious	not serious	not serious	serious [d]	none	350/974 (35.9%)	366/1059 (34.6%)	**RR 1.04** (0.92 to 1.17)	**14 more per 1,000** (from 28 fewer to 59 more)	⨁⨁⨁◯ MODERATE	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. 1) Kudenchuk, 1999; 2) Kudenchuk, 2016.

b. Serious concerns for risk of bias in one of the studies. Kudenchuk, 1999 had unclear ratings for allocation concealment and blinding, and high other risk of bias (baseline imbalance, industry funcding etc.)

c. Kudenchuk, 1999 used the Cordarone preparation of amiodarone vs. an active placebo (polysorbate 80), while Kudenchuk 2016 used the Nexterone preparation of amiodarone vs. saline (inactive) placebo.

d. The effect estimate is imprecise with confidence intervals including the no effect value “1” and the sample size does not meet the optimal information size criteria.

e. Kudenchuk, 1999

f. Serious concerns for risk of bias and failure to adhere to the intention-to-treat principle in superiority trials.

g. Patients enrolled 1994-1997, used 1992 AHA guidelines (2 slow initial breaths, 80-100 compressions/min of 1.5-2.5 inches, using monophasic defibrillators to delivered stacked shocks of escalating energy, no TTM), used polysorbate 80 as placebo (not an inactive placebo) .

h. Kudenchuk, 2016

i. The sample size and number of events do not meet the optimal information size criteria.

Table 3

Question: Lidocaine compared with Placebo for shockable cardiac arrest in adults

Certainty assessment							№ of events / № of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lidocaine**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Survival to hospital discharge												
1 [a]	randomised trials	not serious	not serious	not serious	serious [b]	none	233/985 (23.7%)	222/1056 (21.0%)	**RR 1.13** (0.96 to 1.32)	**27 more per 1,000** (from 8 fewer to 67 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Survival to hospital discharge with good Neurological function												
1 [a]	randomised trials	not serious	not serious	not serious	serious [b]	none	172/984 (17.5%)	175/1055 (16.6%)	**RR 1.05** (0.87 to 1.28)	**8 more per 1,000** (from 22 fewer to 46 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Return of Spontaneous Circulation (ROSC)												

Certainty assessment							№ of events / № of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lidocaine**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 [a]	randomised trials	not serious	not serious	not serious	not serious	none	396/992 (39.9%)	366/1059 (34.6%)	**RR 1.16** (1.03 to 1.29)	**55 more per 1,000** (from 10 more to 100 more)	⊕⊕⊕⊕ HIGH	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Kudenchuk, 2016

b. The effect estimate is imprecise with confidence intervals including the no effect value "1" and the sample size does not meet the optimal information size criteria.

Table 4

Question: Amiodarone compared to Lidocaine for shockable cardiac arrest in adults

Certainty assessment							№ of events / № of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Amiodarone**	**Lidocaine**	**Relative (95% CI)**	**Absolute (95% CI)**		
Survival to hospital discharge - combined												
2 [a]	randomised trials	serious [b]	not serious	very serious [c]	serious [d]	none	246/1150 (21.4%)	238/1152 (20.7%)	**RR 1.04** (0.89 to 1.22)	**8 more per 1,000** (from 23 fewer to 45 more)	⊕◯◯◯ VERY LOW	CRITICAL
Survival to hospital discharge - Lidocaine with polysorbate 80												

Certainty assessment							№ of events / № of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Amiodarone**	**Lidocaine**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 [e]	randomised trials	serious [b]	not serious	very serious [c]	serious [d]	none	9/180 (5.0%)	5/167 (3.0%)	**RR 1.67** (0.57 to 4.88)	**20 more per 1,000** (from 13 fewer to 116 more)	⨁◯◯◯ VERY LOW	CRITICAL
Survival to hospital discharge - Lidocaine without polysorbate 80												
1 [f]	randomised trials	not serious	not serious	not serious	serious [d]	none	237/970 (24.4%)	233/985 (23.7%)	**RR 1.03** (0.88 to 1.21)	**7 more per 1,000** (from 28 fewer to 50 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Survival to hospital discharge with good Neurological function												

Certainty assessment							№ of events / № of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Amiodarone**	**Lidocaine**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 [f]	randomised trials	not serious	not serious	not serious	serious [d]	none	182/967 (18.8%)	172/984 (17.5%)	**RR 1.08** (0.89 to 1.30)	**14 more per 1,000** (from 19 fewer to 52 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Return of Spontaneous Circulation (ROSC)												
1 [f]	randomised trials	not serious	not serious	not serious	serious [d]	none	350/974 (35.9%)	396/992 (39.9%)	**RR 0.90** (0.80 to 1.01)	**40 fewer per 1,000** (from 80 fewer to 4 more)	⨁⨁⨁◯ MODERATE	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. 1) Dorian, 2002; 2) Kudenchuk, 2016.

b. Serious concerns regarding risk of bias.

c. Dorian, 2002 used a lidocaine formulation that contained an active substance (polysorbate 80).

d. The effect estimate is imprecise with confidence intervals including the no effect value “1” and the sample size does not meet the optimal information size criteria.

e. Dorian, 2002

f. Kudenchuk, 2016

Figure 1

Flow Diagram

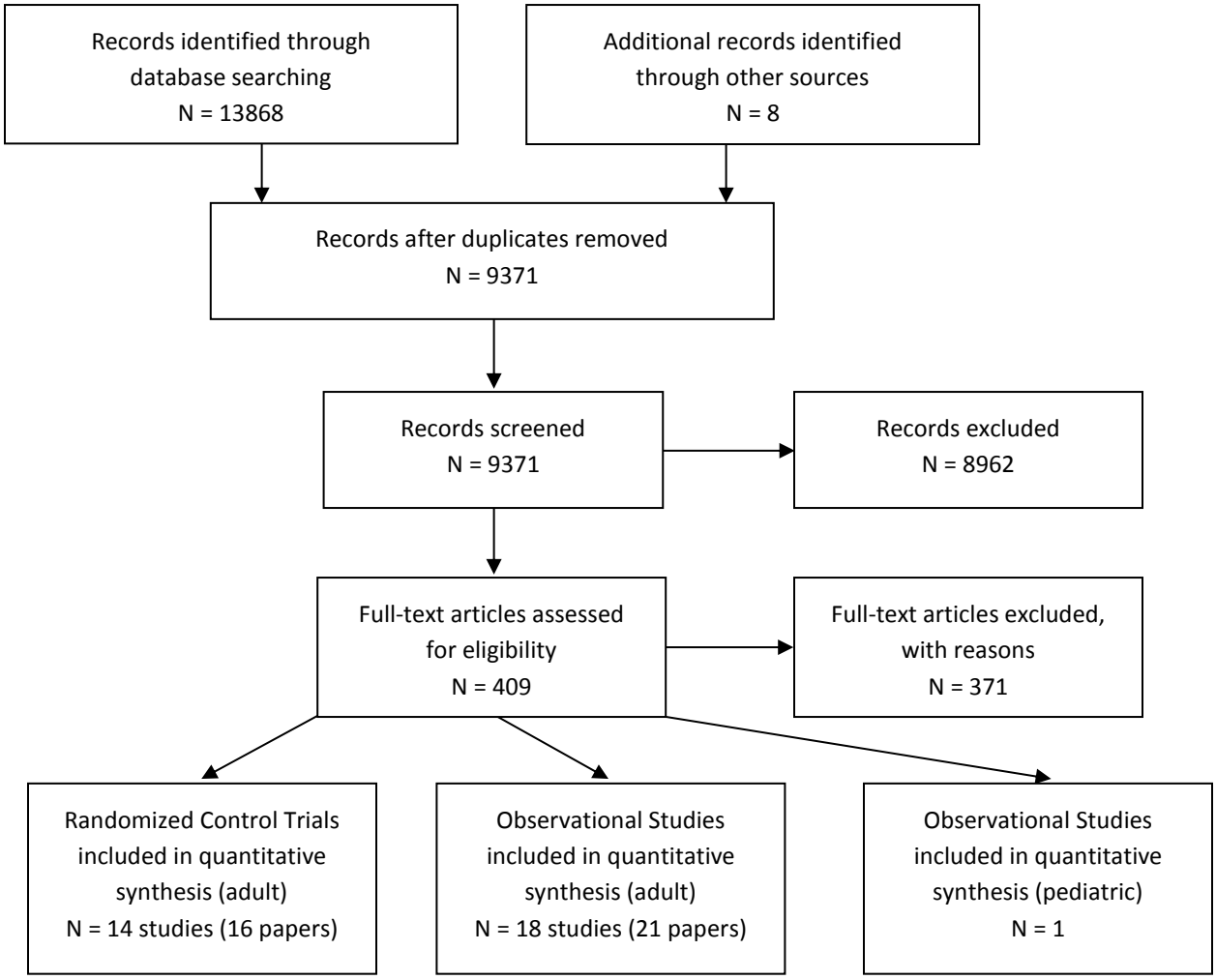

Figure 2.1

Effectiveness of anti-arrhythmic drugs (RCTs; Intervention vs. Placebo)

Survival to hospital discharge with good Neurological function/ 30 days

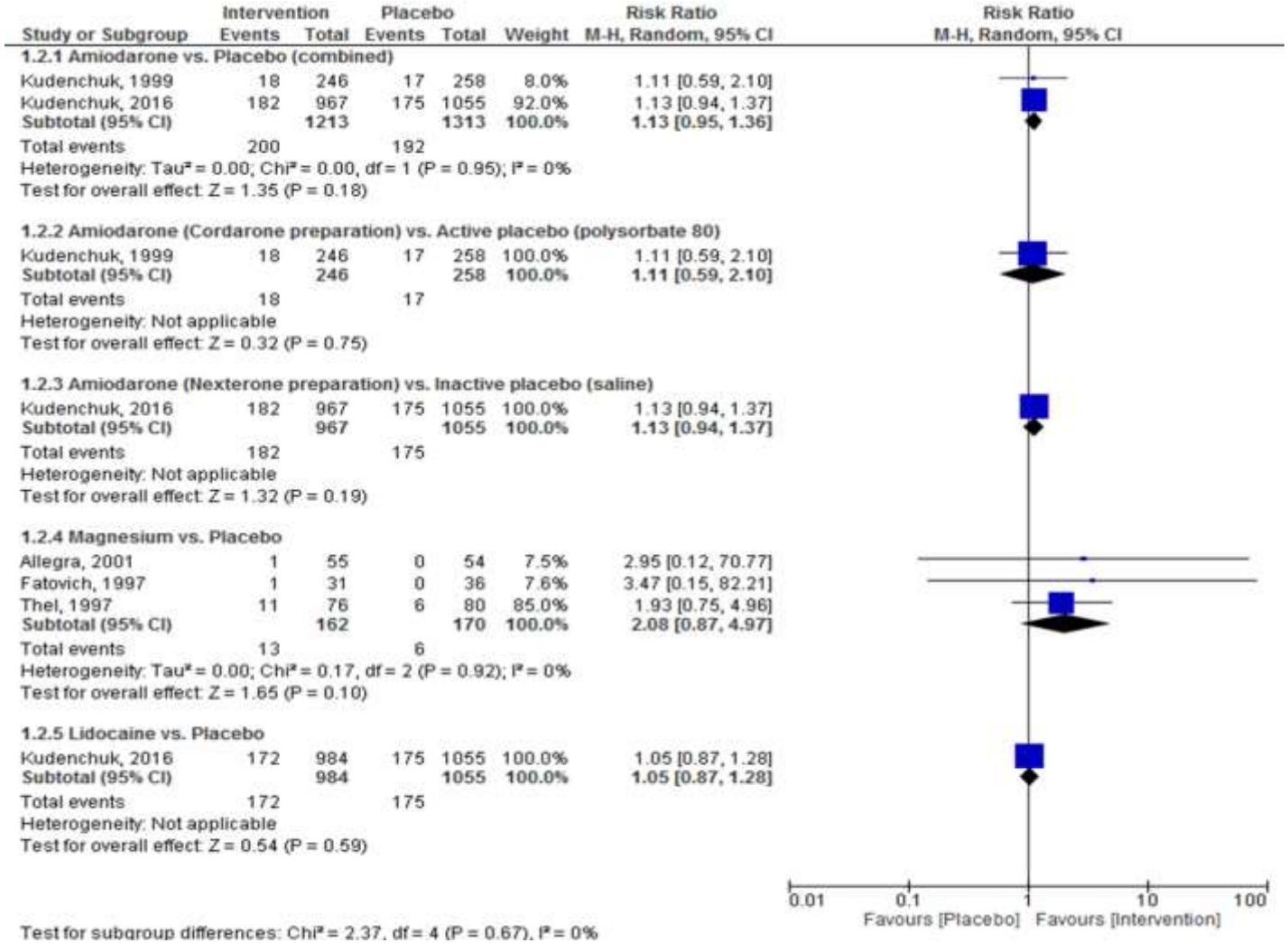

Figure 2.2

Survival to hospital discharge / 30 days

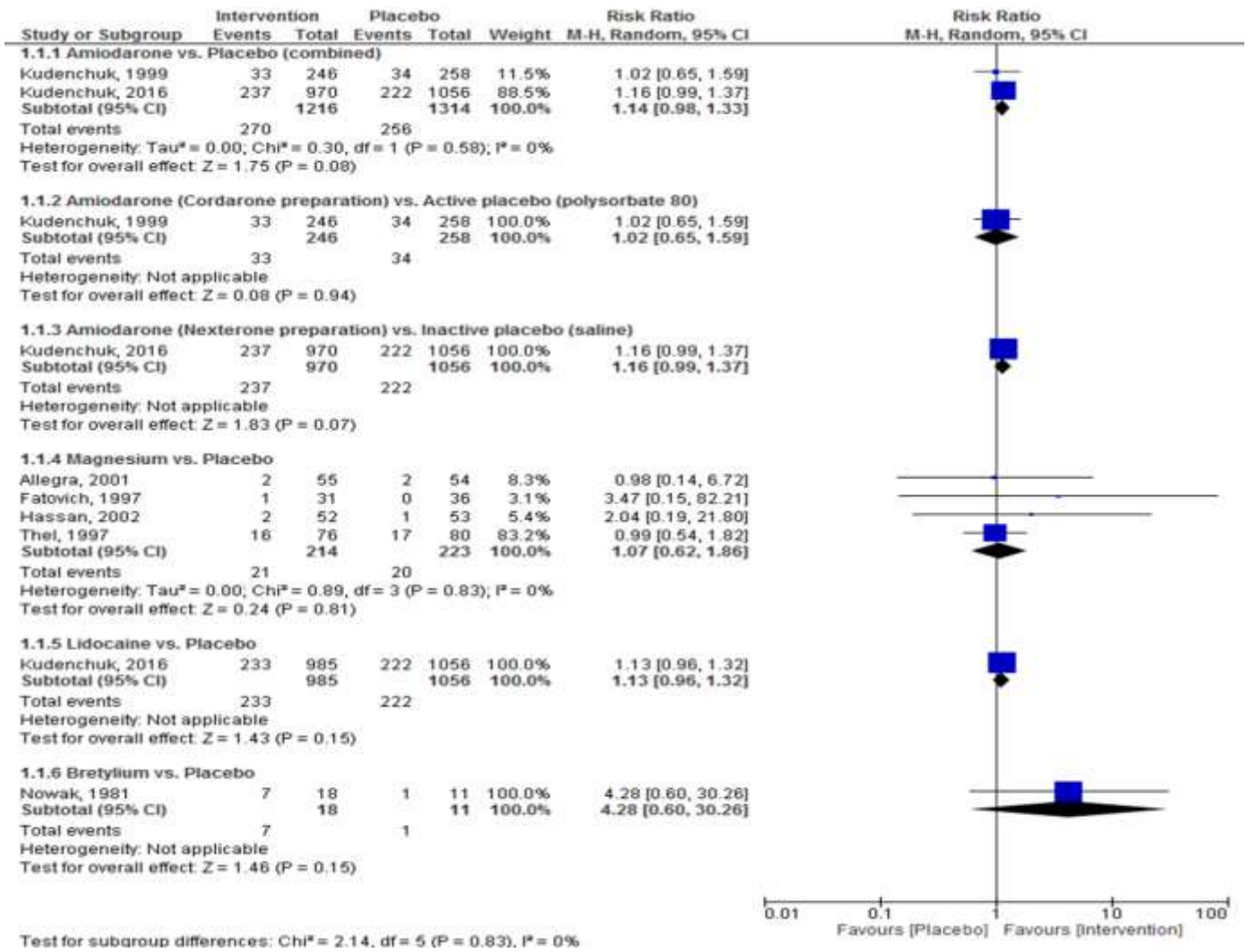

Figure 2.3

Return of Spontaneous Circulation (ROSC)

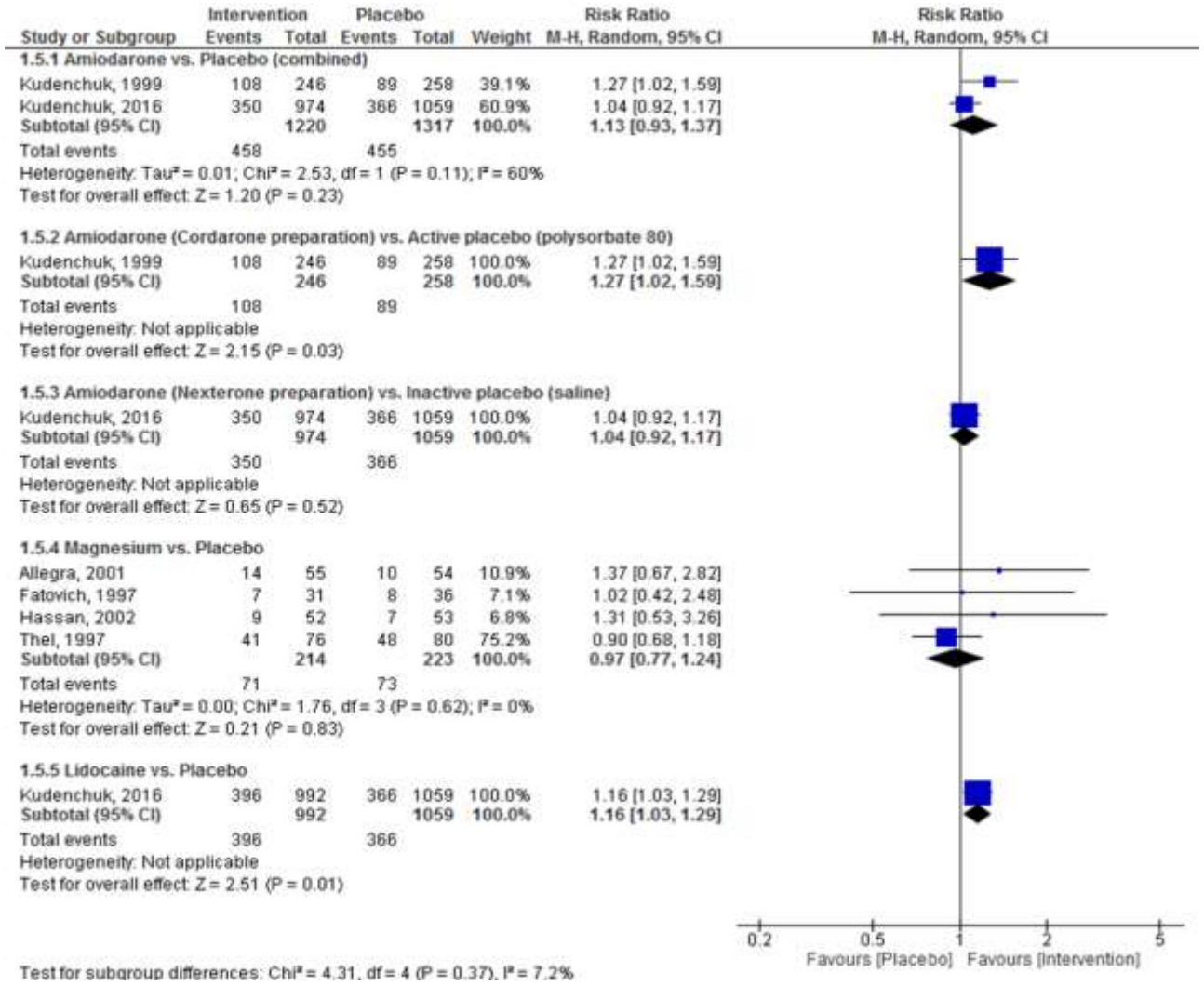

Figure 3.1

Effectiveness of anti-arrhythmic drugs (RCTs; Head to Head trials)

Survival to hospital discharge with good Neurological function/ 30 days

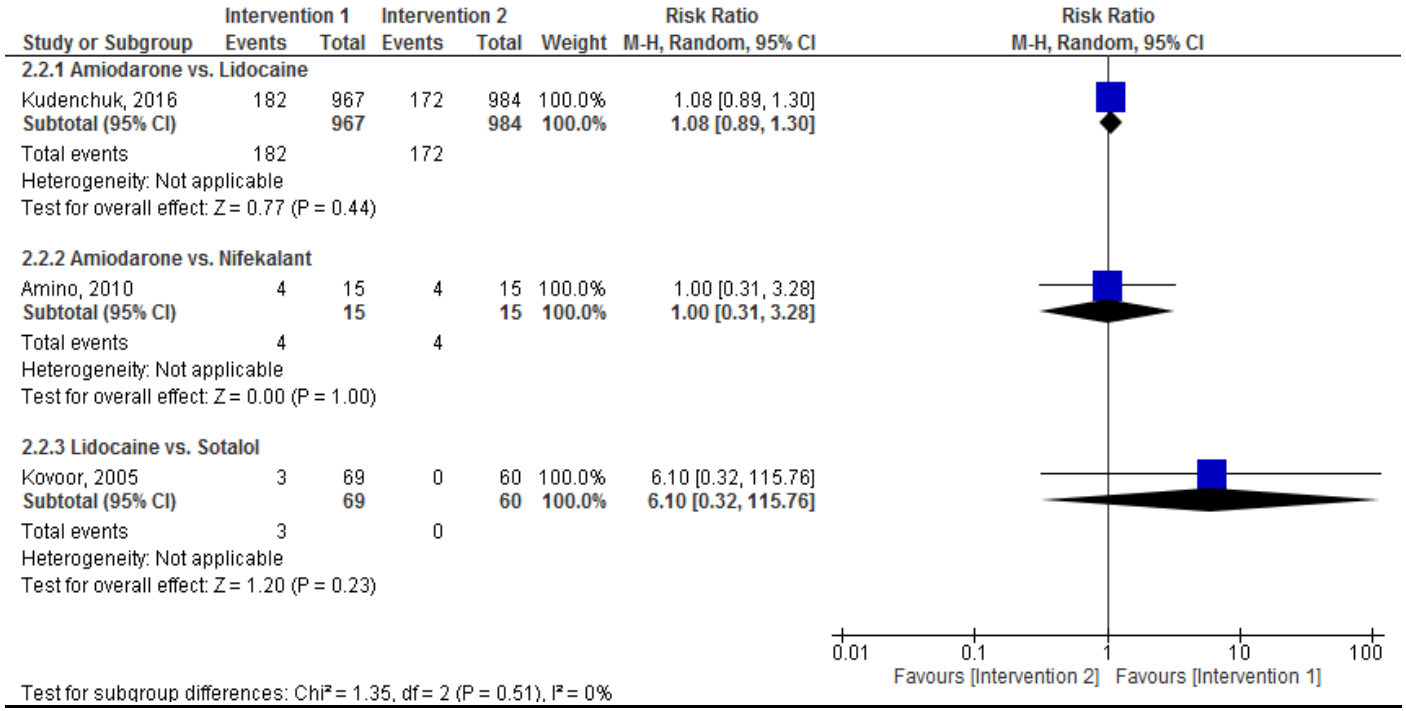

Figure 3.2

Survival to hospital discharge / 30 days

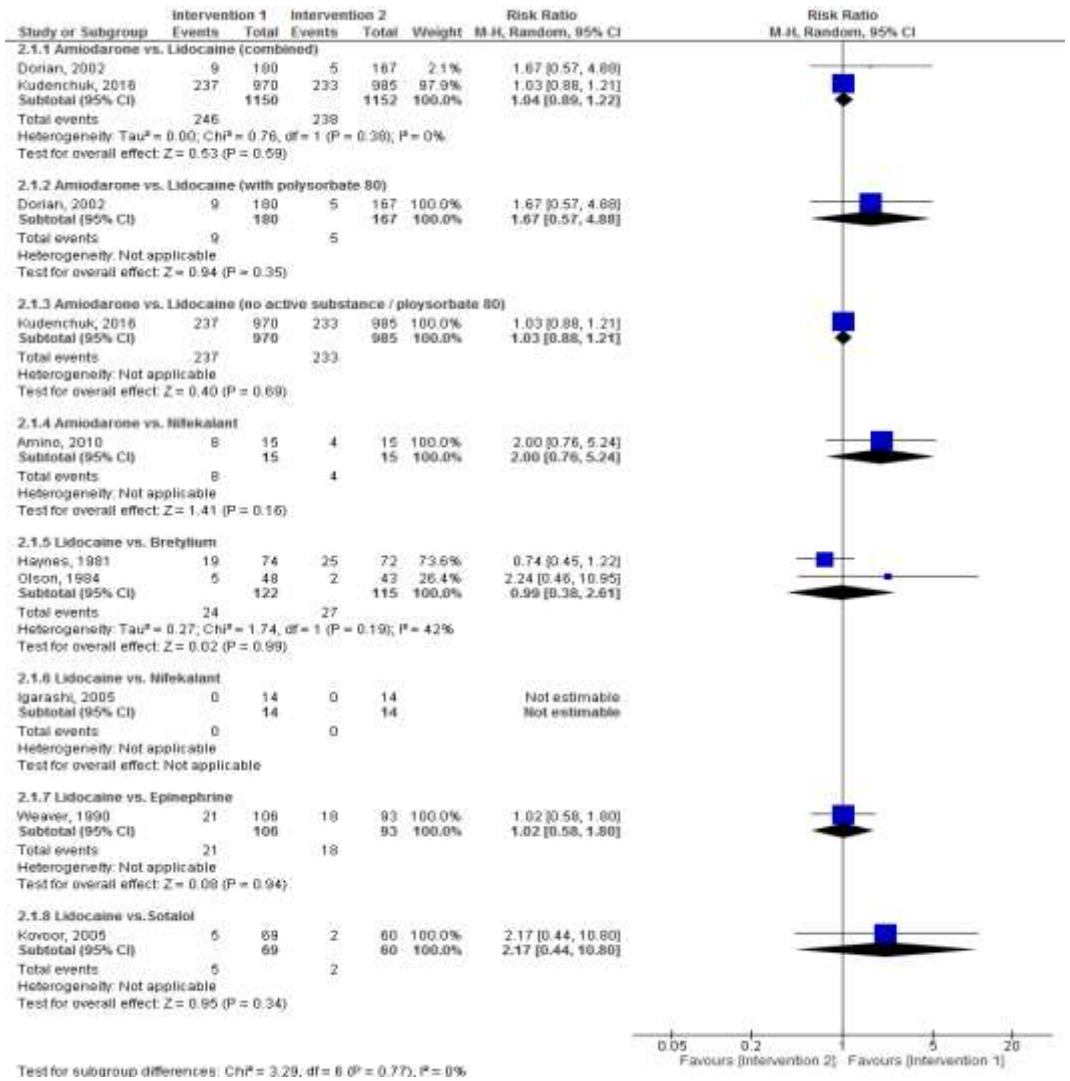

Figure 3.3

Return of Spontaneous Circulation (ROSC)

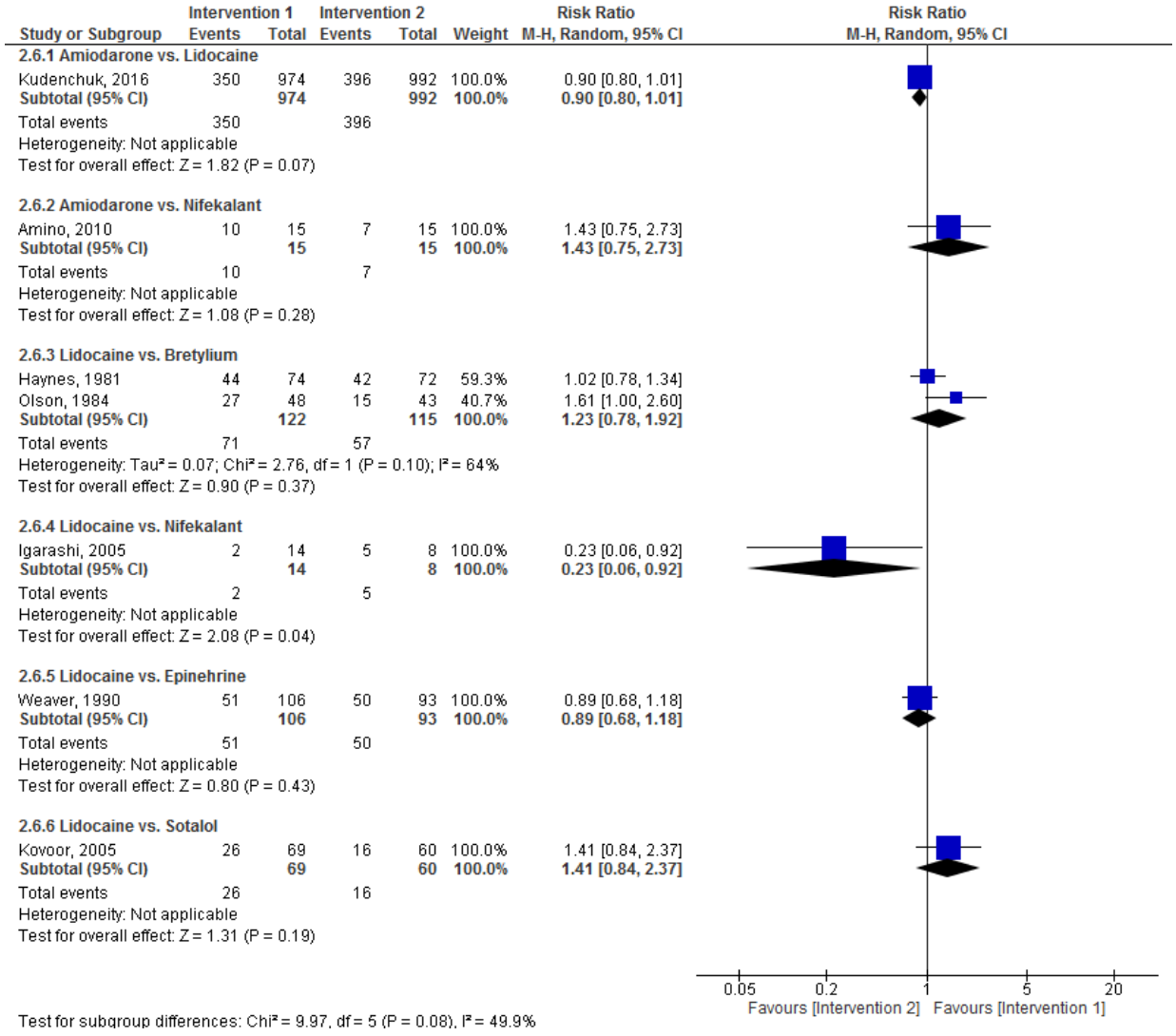

Figure 3.4

Recurrence of pVT/VF

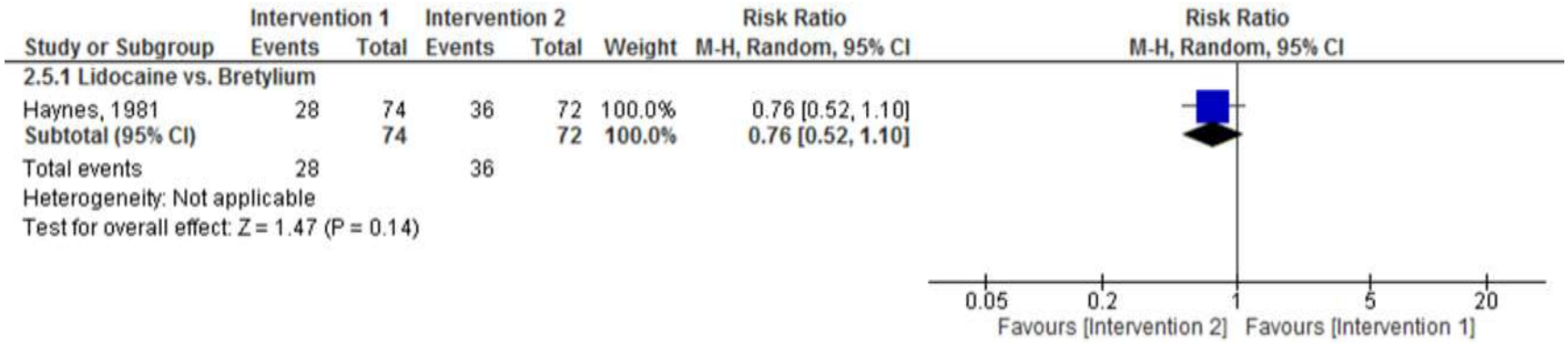

Figure 4.1

Effectiveness of anti-arrhythmic drugs (Observational studies; Intervention vs. Standard Care)

Survival to hospital discharge / 30 days (Observational studies)

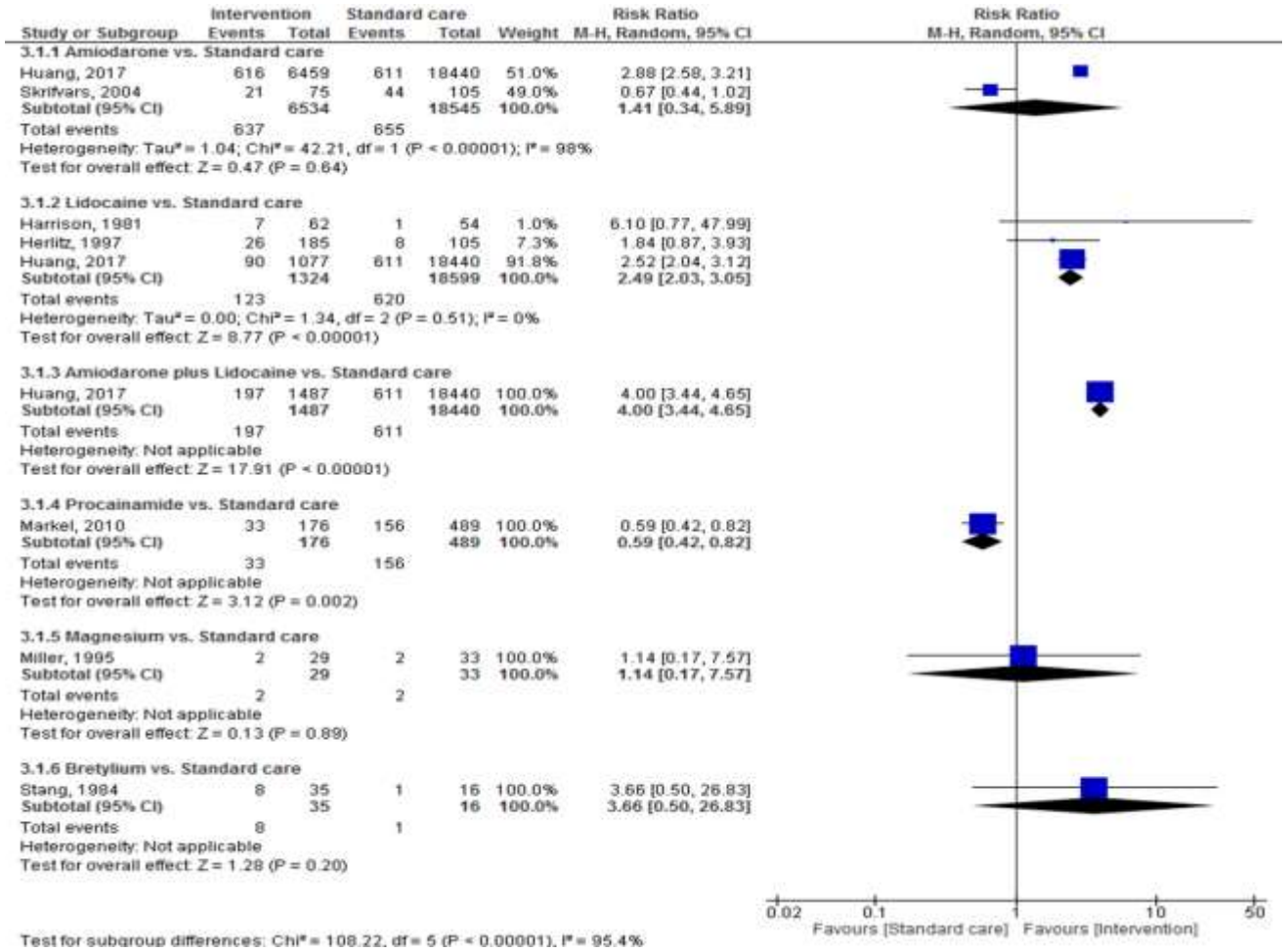

Figure 4.2

Long term survival (1 year; Observational studies)

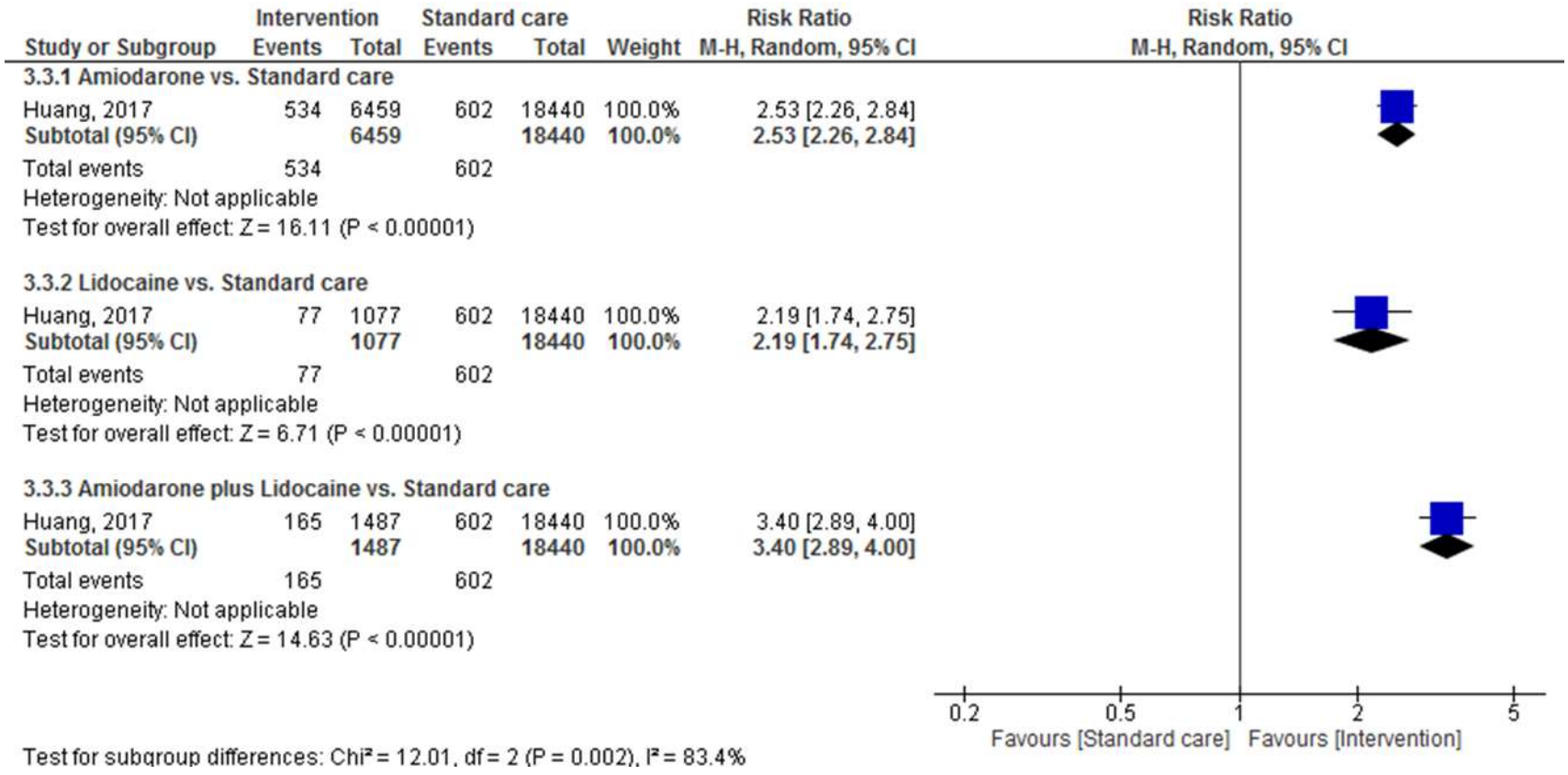

Figure 4.3

Return of Spontaneous Circulation (ROSC; Observational studies)

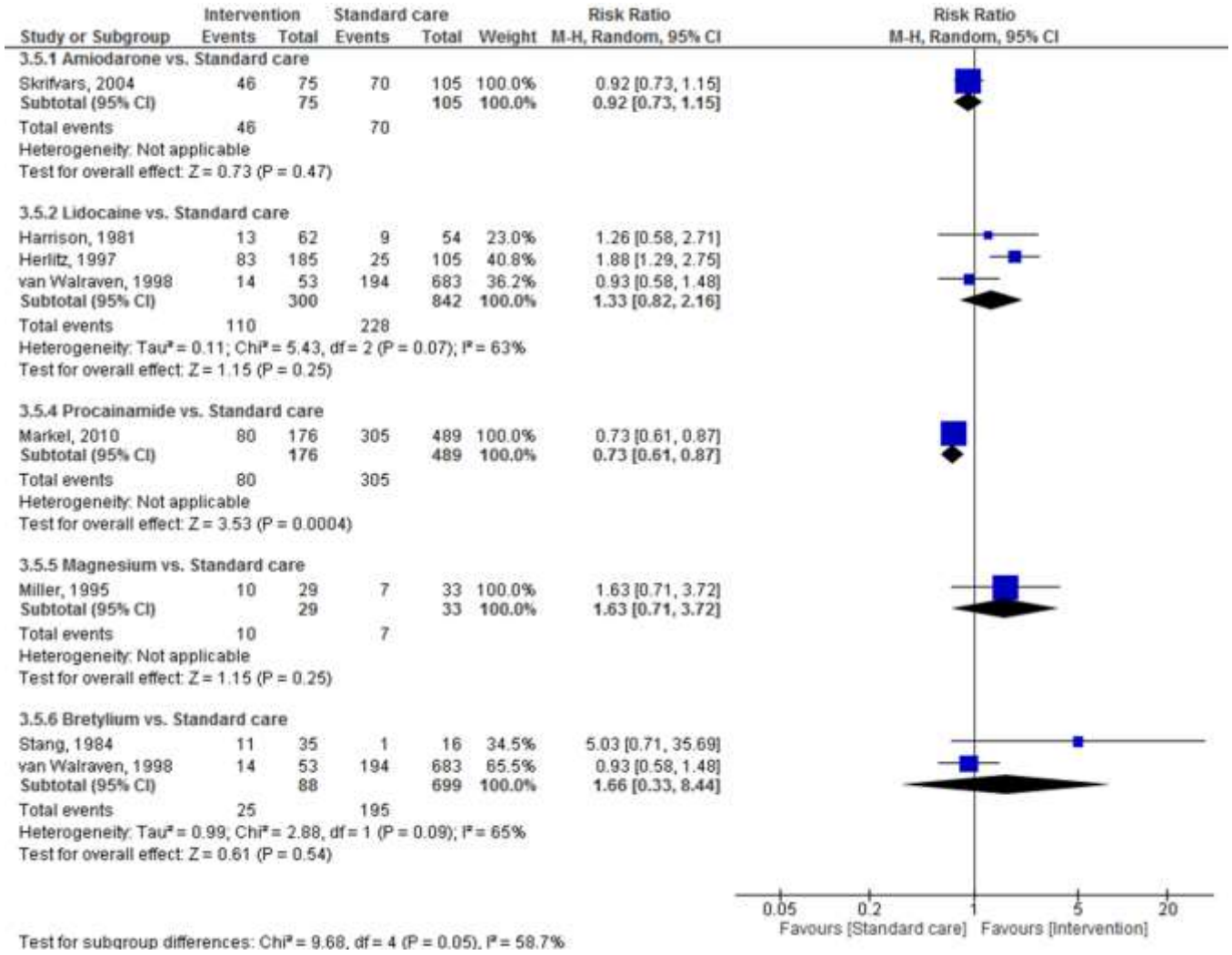

Figure 4.4

Survival to hospital discharge with good Neurological function/ 30 days (Observational studies)

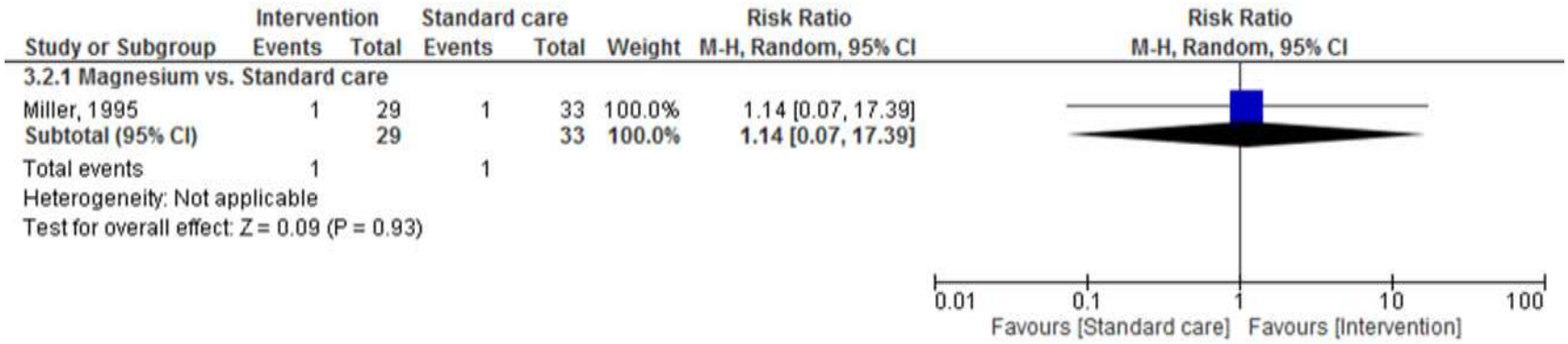

Figure 5.1

Effectiveness of anti-arrhythmic drugs (Observational studies; Head to Head comparison)

Survival to hospital discharge / 30 days (Observational studies)

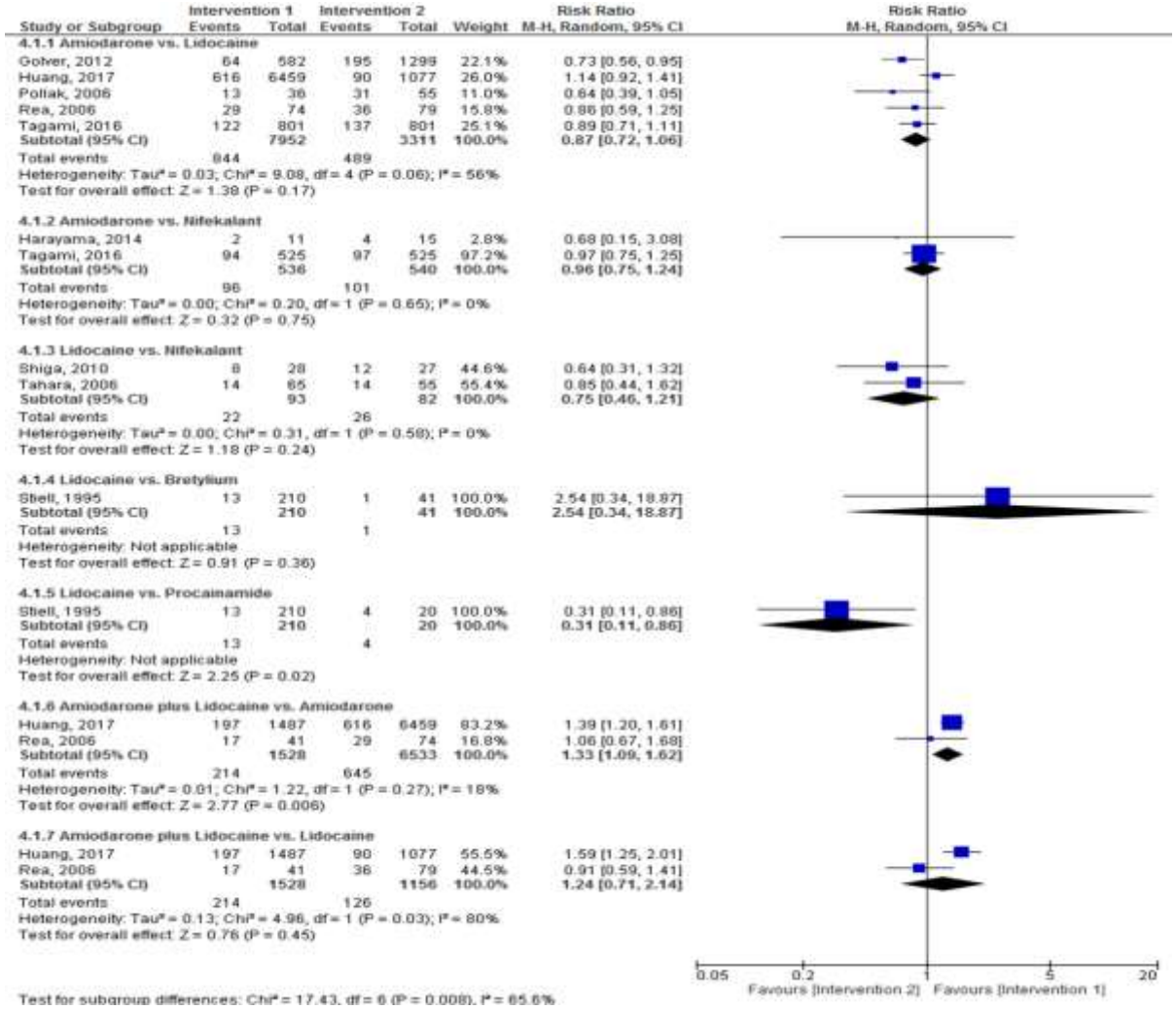

Figure 5.2

Long term survival (1 year; Observational studies)

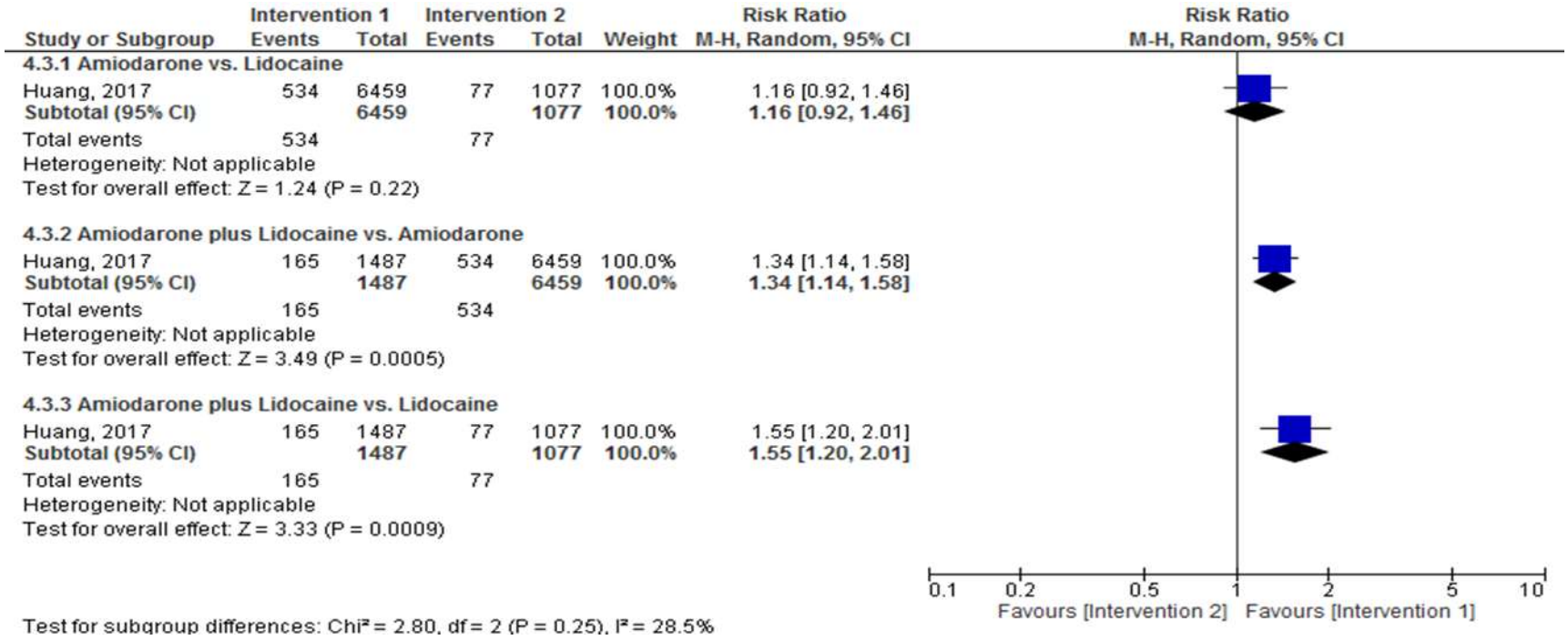

Figure 5.3

Return of Spontaneous Circulation (ROSC; Observational studies)

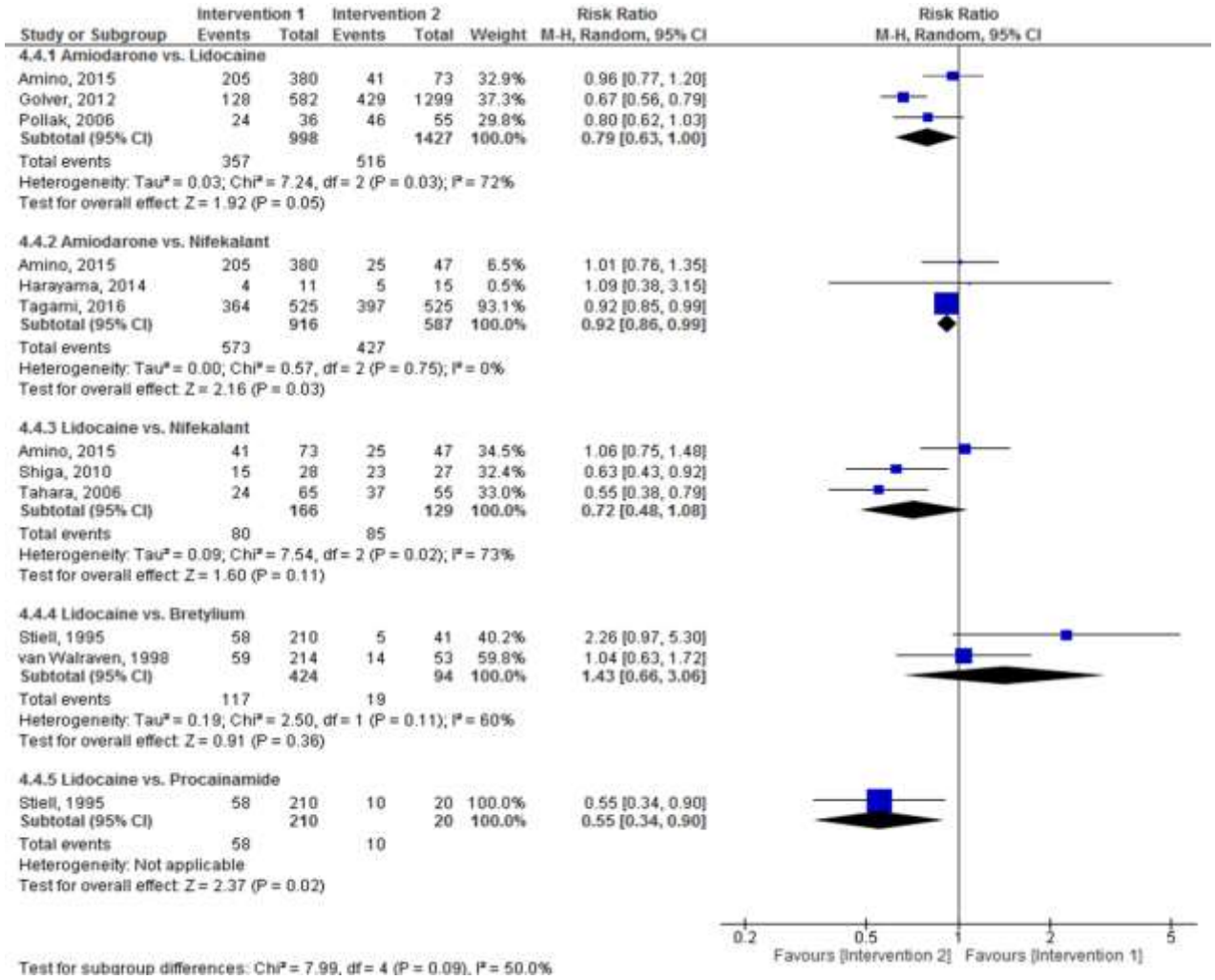

Figure 5.4

Survival to hospital discharge with good Neurological function/ 30 days (Observational studies)

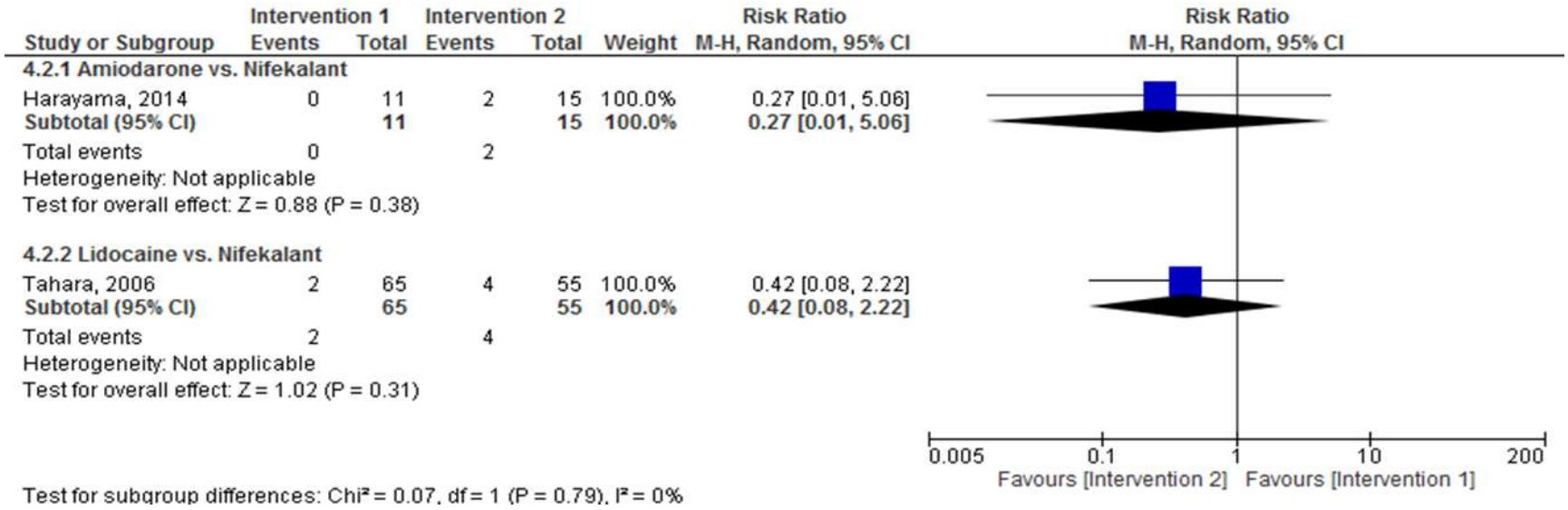

Figure 5.5

Survival to hospital discharge / 30 days (Pediatric population; Observational studies)

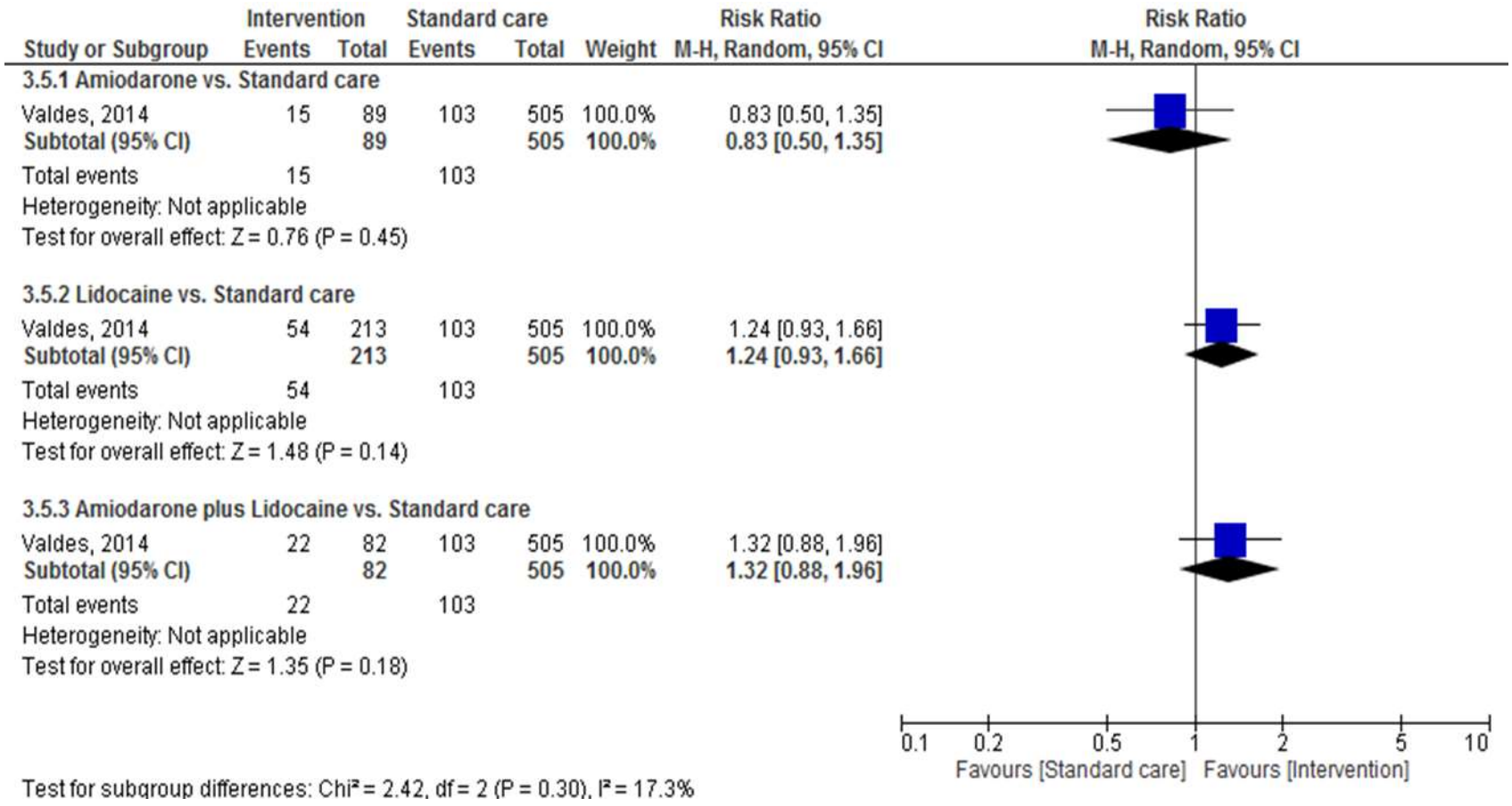

Figure 5.6

Return of Spontaneous Circulation (ROSC - Pediatric population; Observational studies)

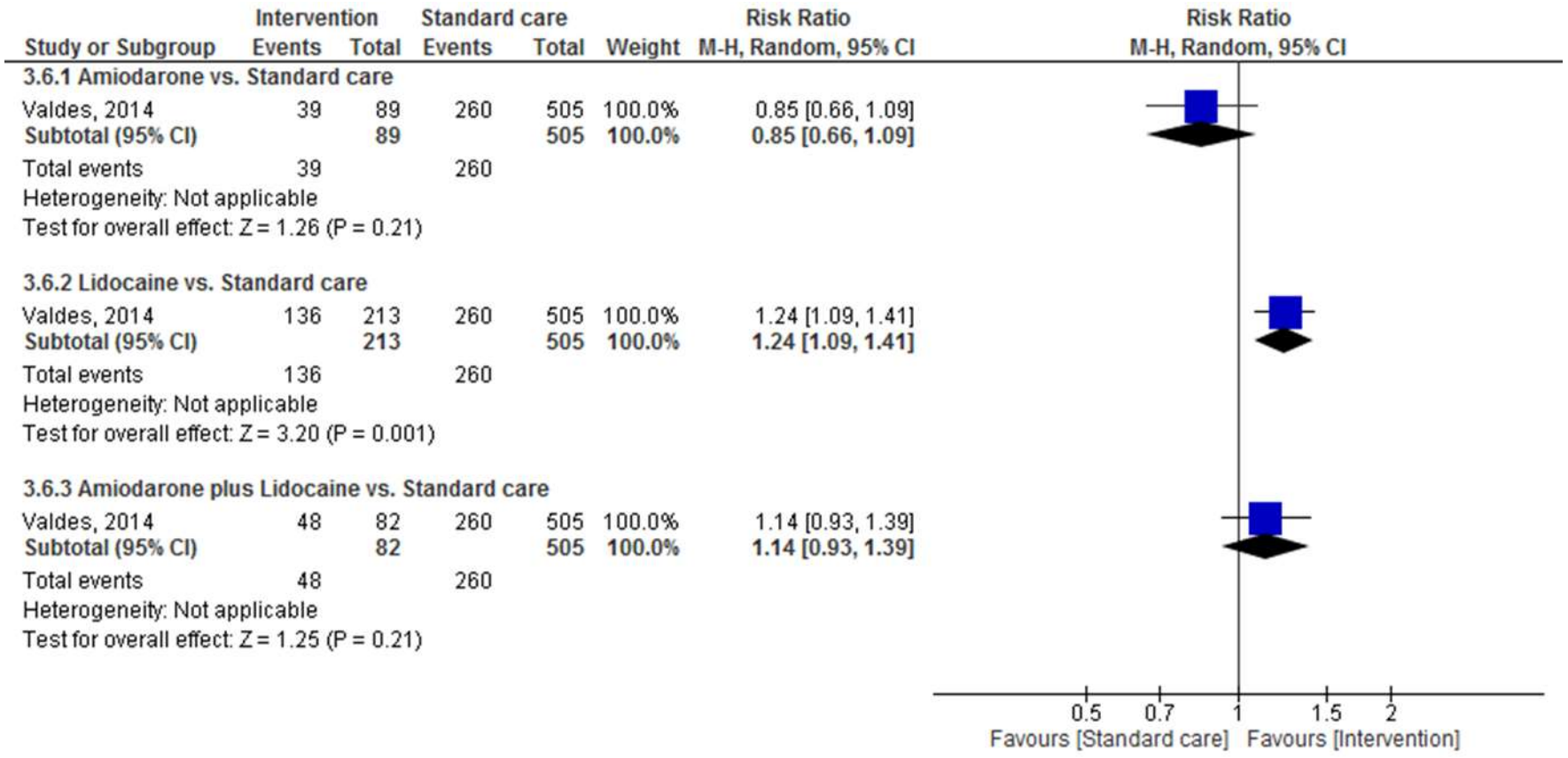

Figure 5.7

Survival to hospital discharge / 30 days (Pediatric population; Observational studies)

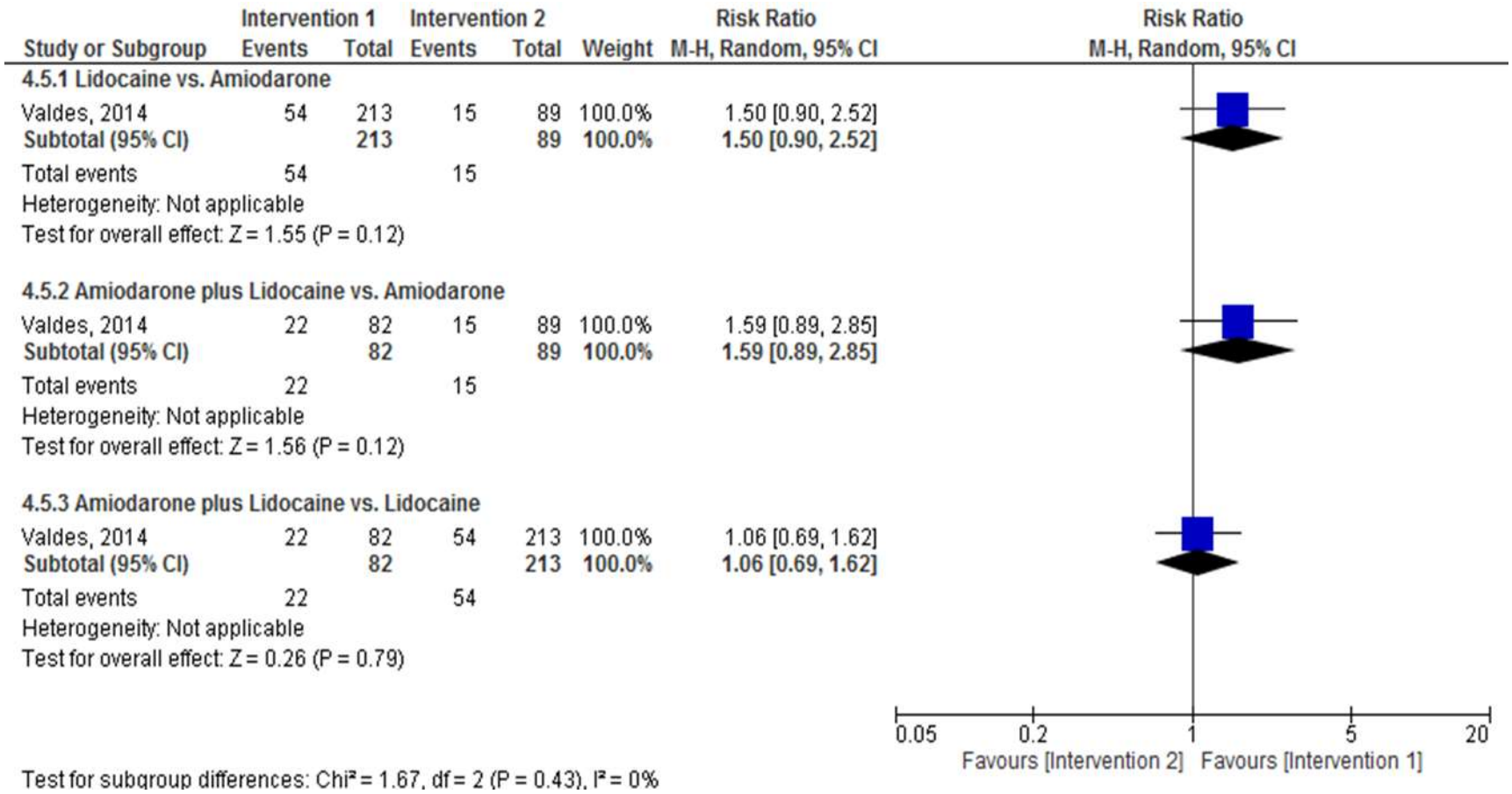

Figure 5.8

Return of Spontaneous Circulation (ROSC - Pediatric population; Observational studies)