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

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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.

1 **Introduction**

2

3 Cardiac arrest (CA) is defined as sudden and unexpected loss of heart function accompanied with
4 loss of breathing and consciousness primarily due to disturbance in electrical activity of heart.

5 An estimated 320,000 to 700,000 cases of out-of-hospital cardiac arrests (OHCA) occur annually
6 across the United States and Europe [1, 2]. CA with an initial heart rhythm of pulseless

7 ventricular tachycardia or ventricular fibrillation (pVT/VF) is the most treatable cause of CA [2].

8 For those individuals who receive cardiopulmonary resuscitation (CPR) with prompt shock

9 treatment (i.e. defibrillation) and drugs, if needed, only 8-40% survive to hospital discharge [3-

10 8]. Of these, approximately 50-75% have favourable neurological outcome, although about 50%

11 of survivors likely have subtle cognitive deficits [9, 10].

12

13 A recent systematic review and meta-analysis comparing amiodarone and lidocaine with placebo

14 demonstrated that both drugs showed increased survival to hospital admission compared with

15 placebo, however, neither drug showed any benefit on long-term survival or good neurological

16 outcomes for adults [11]. For pediatric CA, a 2017 systematic review found weak evidence to

17 recommend the use of amiodarone or lidocaine for shock-resistant pVT/VF in infants and

18 children [12]. The American Heart Association guidelines published in 2015, recommend the use

19 of amiodarone with lidocaine as an alternative to amiodarone for pVT/VF for adults

20 unresponsive to CPR, defibrillation or vasopressor therapy [13].

21

22 However, to-date, the evidence synthesis on anti-arrhythmic drugs used to treat CA, has been

23 primarily based on randomized controlled trials that are likely underpowered and prone to bias

24 with unbalanced baseline characteristics, different drug formulation and timing of drug

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

31

32 **Methods**

33

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

37 **Review question**

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

45 **Search Strategy**

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

48 for studies missed by the electronic search. The electronic search identified 13,868 citations and
49 8 additional citations were found through other sources (e.g., reference list check). Once
50 duplicates were removed, there were 9,371 citations uploaded to the web-based screening
51 program [19] to be screened independently by review staff.

52 **Study Selection, data abstraction and quality assessment**

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

68 **Data synthesis**

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

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

87 **Results**

88 **Overall Search Results**

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

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

93 **Summary of Included Studies for the Adult Population**

94 A total of 14 RCTs [29-42] and 18 observational studies [43-60] were included. The overall risk
95 of bias for RCTs was rated high in one study [42], unclear in eleven studies [29-35, 37, 39-41],
96 and low in two studies [36, 38]. The individual domain ratings for each study are reported in
97 Supplemental File 1. The Newcastle-Ottawa Quality Assessment Scale was used to rate the
98 quality of the included observational studies and no major quality concerns were identified (see
99 Supplemental File 1). The publication years of resuscitation guidelines applied in the RCT
100 studies ranged from pre-2000 to 2010 and the publication years of resuscitation guidelines
101 referenced in the observational studies ranged from pre-2000 to 2015 (see Supplemental File 2).
102 The included RCTs were comprised of one study [38] with a large sample (>1,000 participants),
103 one study [37] with a medium sized sample (500-999 participants), and twelve studies [29-36,
104 39-42] with small samples (<499 participants). In the observational studies, there were four [44,
105 48, 49, 58] large cohorts (>1,000 participants), four [43, 50, 57, 60] medium sized cohorts (500-
106 999 participants), and ten [45-47, 51-56, 59] small cohorts (<499 participants). The range of
107 mean ages in the included RCT studies was 57 to 67 years, while in the observational studies it
108 was 55.8 to 83.3 years. Most of the RCT and observational studies included more males than
109 females. All the RCTs administered the intervention drug during CPR. In the studies time of
110 administration was reported [29-31, 37, 38, 41], time from cardiac arrest to first dose of the trial
111 drug ranged from 10 to 30 minutes. All but one observational study administered the intervention
112 drug during CPR while one administered the drug immediately after ROSC. The time from
113 cardiac arrest to first dose of the trial drug was reported in six studies [51-54, 57, 59] and ranged

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

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

117 *Amiodarone versus Placebo*

118 The evidence on amiodarone was considered as both pooled and separated. The primary reason
119 to look at evidence separately was the different drug formulations (i.e. amiodarone with or
120 without polysorbate 80) and placebo comparator (i.e. active polysorbate 80 placebo and inactive
121 saline placebo) active across the two included studies. The vasoactive solvent “polysorbate 80
122 “in Cordarone™ preparation of amiodarone has been linked to potential adverse hemodynamic
123 effects particularly bradycardia and hypotension and may be associated with differential effect
124 on outcomes of interest based on drug formulation [61, 62]. For the critical outcome of survival
125 with favorable neurologic function at hospital discharge, the pooled evidence showed no
126 difference in effect for amiodarone compared with placebo (2 RCTs; RR=1.13; 95% CI, 0.95 to
127 1.36, p=0.18, I²=0%) [37, 38]. The overall quality of evidence was rated as very low quality and
128 downgraded for serious concerns for risk of bias, indirectness and imprecision. The evidence on
129 amiodarone in polysorbate 80, i.e. the Cordarone™ preparation of amiodarone, with very low
130 quality (downgraded for serious concerns for risk of bias, indirectness and imprecision), showed
131 no difference in effect for amiodarone compared with an active polysorbate 80 placebo (1 RCT;
132 RR=1.11; 95% CI, 0.59 to 2.10, p=0.75) [37]. The evidence on the Nexterone™ preparation of
133 amiodarone, with moderate quality (downgraded for serious concerns for imprecision), showed
134 no difference in effect for amiodarone compared with inactive “saline” placebo (1 RCT;
135 RR=1.13; 95% CI, 0.94 to 1.37, p=0.19, (see Table 2, fig. 2.1) [38].

136 For the critical outcome of survival at hospital discharge, the pooled evidence showed no
137 difference in effect for amiodarone compared to placebo (2 RCTs; RR=1.14; 95% CI 0.98 to
138 1.33, $p=0.08$, $I^2=0\%$) [37, 38]. The overall quality of evidence was rated as very low quality and
139 downgraded for serious concerns for risk of bias, indirectness and imprecision. Evidence on the
140 Cordarone™ preparation of amiodarone, with very low quality (downgraded for serious
141 concerns for risk of bias, indirectness and imprecision), showed no difference in effect for
142 amiodarone compared with an active polysorbate 80 placebo (1 RCT; RR=1.02; 95% CI, 0.65 to
143 1.59, $p=0.94$) [37]. Evidence on Nexterone™ preparation of amiodarone, with moderate quality
144 (downgraded for serious concerns for imprecision), showed no difference in effect for
145 amiodarone compared with inactive saline placebo (1 RCT; RR=1.16; 95% CI, 0.99 to 1.37,
146 $p=0.07$, see Table 2, fig. 2.2) [38].

147 For the important outcome of ROSC, the pooled evidence showed no difference in effect for
148 amiodarone compared with placebo (2 RCTs; RR=1.13; 95% CI, 0.93 to 1.37, $p=0.11$, $I^2=60\%$)
149 [37, 38]. The overall quality of evidence was rated as very low quality and downgraded for
150 serious concerns for risk of bias, indirectness and imprecision. Evidence on the Cordarone™
151 preparation of amiodarone, with very low quality (downgraded for serious concerns for risk of
152 bias, indirectness and imprecision), showed benefit favoring amiodarone compared with an
153 active polysorbate 80 placebo (1 RCT; RR=1.27; 95% CI, 1.02 to 1.59, $p=0.03$) [37]. Evidence
154 on Nexterone™ preparation of amiodarone, with moderate quality (downgraded for serious
155 concerns for imprecision), showed no difference in effect for amiodarone compared with inactive
156 saline placebo (1 RCT; RR=1.04; 95% CI, 0.92 to 1.17, $p=0.52$, see Table 2, fig. 2.3) [38].

157 ***Lidocaine versus Placebo***

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

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

164 For the important outcome of ROSC, the effect estimate showed a significant increase favoring
165 lidocaine compared with placebo (1 RCT; RR=1.16; 95% CI, 1.03 to 1.29, p=0.01, see fig. 2.3)
166 [38]. The overall quality of this evidence was rated as high.

167 *Other anti-arrhythmic drugs versus Placebo*

168 For the critical outcome of survival with favorable neurological function at hospital discharge,
169 the pooled effect estimate showed no difference in effect for magnesium compared with placebo
170 (3 RCTs; RR=2.08; 95% CI, 0.87 to 4.97, p=0.10, I²=0%, see Supplemental File 3, fig. 2.1) [30,
171 32, 41]. Similar results were obtained for the outcomes of survival to discharge for magnesium
172 (4 RCTs; RR=1.07; 95% CI, 0.62 to 1.86, p=0.81, I²=0%) [30, 32, 33, 41] and bretylium (1 RCT;
173 RR=4.28; 95% CI, 0.60 to 30.26, p=0.15, see Supplemental File 3, fig. 2.2) [40]; and ROSC for
174 magnesium (4 RCTs; RR=0.97; 95% CI, 0.77 to 1.24, p=0.83, I²=0%, see Supplemental File 3,
175 fig. 2.3) [30, 32, 33, 41]. The overall quality of this evidence was rated as very low and
176 downgraded for serious concerns regarding risk of bias and imprecision.

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

178 *Amiodarone versus Lidocaine*

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

183 For the critical outcome of survival to hospital discharge, the pooled evidence showed no
184 difference in effect for amiodarone compared with lidocaine (2 RCTs; RR=1.04; 95% CI 0.89 to
185 1.22, $p=0.59$, $I^2=0\%$) [31, 38]. Evidence on lidocaine with the use of polysorbate 80, showed no
186 difference in effect for amiodarone compared with lidocaine (1 RCT; RR=1.67; 95% CI, 0.57 to
187 4.88, $p=0.35$) [31]. The overall quality of evidence was rated as very low quality and
188 downgraded for serious concerns for risk of bias, indirectness and imprecision. Evidence on
189 critical outcome of survival to hospital discharge for lidocaine without use of polysorbate 80,
190 with moderate quality (downgraded for serious concerns for imprecision), showed no difference
191 in effect for amiodarone compared with lidocaine (1 RCT; RR=1.03; 95% CI, 0.88 to 1.21,
192 $p=0.69$, see Table 4, fig. 3.2) [38].

193 Similar results were obtained for the important outcome of ROSC (1 RCT; RR=0.90; 95% CI,
194 0.80 to 1.01, $p=0.07$, see Table 4, fig. 3.3) [38]. The overall quality of this evidence was rated as
195 moderate and downgraded for serious concerns regarding imprecision.

196 ***Other anti-arrhythmic drugs head-to-head comparisons***

197 For the critical outcomes of survival with favorable neurological function at discharge, survival
198 at discharge, cardiac re-arrest and ROSC, none of the effect estimates for anti-arrhythmic drug
199 head-to-head comparisons showed any difference in effect (see Supplemental File 4, figs. 3.1 to
200 3.4), except ROSC for lidocaine vs. nifekalant where the difference was marginally significant
201 favoring lidocaine (RR=0.23; 95% CI, 0.06 to 0.92, $p=0.04$, see Supplemental File 4, fig. 3.3)
202 [35]. However, the study was under-powered with very small sample size. The overall quality of
203 this evidence was rated as low to very low and downgraded for serious concerns regarding risk
204 of bias and imprecision.

205 **Anti-arrhythmic drugs versus no antiarrhythmic drugs (standard care; observational** 206 **studies)**

207 ***Amiodarone versus standard care***

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

214 ***Lidocaine versus standard care***

215 For the outcomes of survival to hospital discharge and the long-term survival of 1 year, one
216 large cohort study [48] (n=19,517) showed significant difference in effect favoring lidocaine
217 compared with standard care (RR=2.52; 95% CI, 2.04 to 3.12, p<0.001; and RR=2.19; 95% CI,
218 1.74 to 2.75, p<0.001, respectively, see figs. 4.1 and 4.2). Another cohort study [47] (n=290) also
219 showed significant difference in effect for the outcome ROSC favoring lidocaine compared with
220 standard care (RR=1.88; 95% CI, 1.29 to 2.75, p=0.001). However, the observed effect was non-
221 significant for survival at hospital discharge and ROSC across two relatively small cohort studies
222 (n=853, p>0.05, see figs 4.1 and 4.3) [46, 60].

223 ***Other anti-arrhythmic drugs versus standard care***

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

229 **Head-to-head comparisons (observational studies)**

230 ***Amiodarone versus Lidocaine***

231 For the outcome of survival at hospital discharge, the pooled evidence across 5 cohort studies
232 [44, 48, 52, 53, 58] (n=11,263) showed no difference in effect for amiodarone compared with
233 lidocaine (RR=0.87; 95% CI, 0.72 to 1.06, p=0.17, see fig. 5.1). For the outcome of long-term
234 survival of 1 year, one large cohort study (n=7,536) showed no difference in effect for
235 amiodarone compared with lidocaine (RR=1.16; 95% CI, 0.92 to 1.46, p=0.22, see fig. 5.2) [48].
236 Similar results were obtained for the outcome of ROSC across 3 cohort studies (n=2425;
237 RR=0.79; 95% CI, 0.63 to 1.00, p=0.05, see fig. 5.3) [43, 44, 52].

238 ***Other anti-arrhythmic drugs head-to-head comparisons***

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

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

253 No RCT level evidence was identified that answered this question, however 1 observational
254 study [49] provided data on adults with cardiac arrest and prophylactic antiarrhythmic drugs
255 given within 1 hour of ROSC. For the outcome of survival to hospital discharge, the results
256 based on non-propensity matched cohorts (lidocaine arm: 1296; standard care: 425) showed a
257 significant effect favoring the administration of prophylactic lidocaine compared with standard
258 care (RR= 1.40, 95% CI 1.25, 1.57; p<0.0001). However, the effect was non-significant when
259 data from propensity matched cohorts (lidocaine arm: 400; standard care: 400) was used
260 (RR=1.03, 95% CI 0.89, 1.20; p=0.67). For the outcome of recurrence of pVT/VF, the results
261 showed a significant effect favoring the administration of prophylactic lidocaine compared with
262 standard care for both non-propensity matched cohorts with 55% reduction (RR= 0.45, 95% CI
263 0.38, 0.53; p<0.0001) and propensity matched cohorts with 41% reduction (RR= 0.59, 95% CI
264 0.47, 0.74; p<0.0001).

265 **Pediatric Population**

266
267 There was one observational study involving children that met our criteria for inclusion [63].
268 There were no major concerns regarding risk of bias. The study focused on a cohort of 889
269 participants <18 years of age. The sex of participants was not reported. The trial drug was
270 administered during cardiac arrest. The time from cardiac arrest to first dose of the drug was not
271 reported.

272 **Infants and children with cardiac arrest and a shockable rhythm at any time during** 273 **cardiopulmonary resuscitation (CPR) or immediately after return of spontaneous** 274 **circulation)**

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

277 ***Amiodarone versus standard care***

278 For the outcomes of survival at hospital discharge and ROSC, one cohort study [63] (n=594)
279 showed no difference in effect for amiodarone compared with standard care (RR=0.83; 95% CI,
280 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
281 5.6).

282 ***Lidocaine versus standard care***

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

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

291 ***Lidocaine versus Amiodarone***

292 For the critical outcome of survival to hospital discharge, one cohort study [63] (n=302) found
293 no difference in effect for lidocaine compared with amiodarone (25% versus 17%; P=NS; RR
294 1.50; 95% CI 0.90 to 2.52, p=0.12, see fig. 5.7). However, the results showed significant increase
295 in ROSC for lidocaine as compared with amiodarone (RR=1.46; 95% CI 1.13 to 1.88, p=0.004,
296 see fig. 5.8).

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

300

301 **Discussion**

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

308 **Summary of evidence**

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

311 Most of the studies in our review included adults with cardiac arrest and a shockable rhythm at
312 any time during CPR for out-of-hospital cardiac arrest, and no studies for in in-hospital cardiac
313 arrest. Based on RCT level evidence, none of the anti-arrhythmic drugs showed any difference
314 in effect compared with placebo, or with other anti-arrhythmic drugs for the critical outcomes of
315 survival to hospital discharge and discharge with good neurological function. The quality of
316 evidence across these studies was rated from moderate to very low with concerns of risk of bias,
317 indirectness and imprecision. For the important outcome of ROSC, the results showed a
318 significant increase in ROSC for lidocaine compared with placebo (RR=1.16; 95% CI, 1.03 to
319 1.29, p=0.01). The overall quality of this evidence was rated as high. The evidence on the
320 Cordarone™ preparation of amiodarone also showed marginal benefit for ROSC favoring
321 amiodarone compared with an active polysorbate 80 placebo (RR=1.27; 95% CI, 1.02 to 1.59,
322 p=0.03); however, the quality of the evidence was rated as very low with concerns for risk of
323 bias, indirectness (active placebo with potential adverse hemodynamic effects) and imprecision.

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

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

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

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

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

346 **Implications for clinical practice and future research**

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

358 **Limitations**

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

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

375 **Conclusions**

376
377 The high level evidence supporting the use of antiarrhythmic drugs during CPR for shock
378 refractory pVT/VF or immediately after ROSC is limited and showed no significant benefit for
379 critical outcomes of survival at hospital discharge, survival with favorable neurological function
380 and long-term survival. The high level evidence also showed a significant increase in important
381 outcome of ROSC for lidocaine compared with placebo, suggesting that use of lidocaine during
382 CPR may improve the short-term survival in adult cardiac arrest patients with shock refractory
383 pVT/VF. However, future high quality research is needed to confirm these findings and also
384 evaluate the effectiveness and role of administering antiarrhythmic drugs in children with
385 shockable cardiac arrest, and in adults immediately after ROSC.

386

387 **Declaration of Interests**

388
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391

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553 **Table 1**554 **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.

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Table 2

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

Certainty assessment							No of events / No of patients		Effect		Certainty	Importance
No 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							No of events / No of patients		Effect		Certainty	Importance
No 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 funding 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)		
<i>Survival to hospital discharge</i>												
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
<i>Survival to hospital discharge with good Neurological function</i>												
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
<i>Return of Spontaneous Circulation (ROSC)</i>												

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)		
<i>Survival to hospital discharge - combined</i>												
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
<i>Survival to hospital discharge - Lidocaine with polysorbate 80</i>												

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
<i>Survival to hospital discharge - Lidocaine without polysorbate 80</i>												
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
<i>Survival to hospital discharge with good Neurological function</i>												

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
<i>Return of Spontaneous Circulation (ROSC)</i>												
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

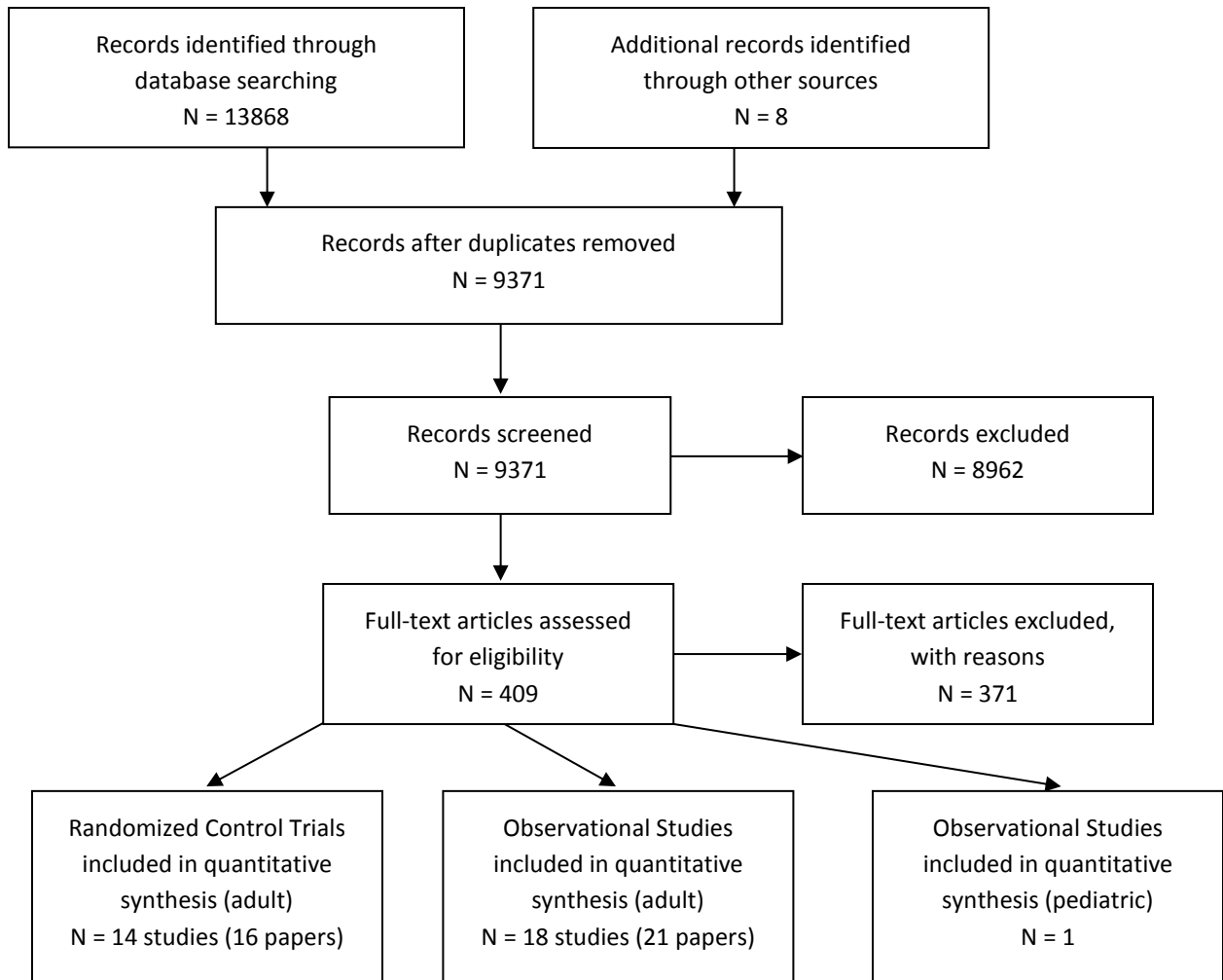


Figure 2.1

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

Survival to hospital discharge with good Neurological function/ 30 days

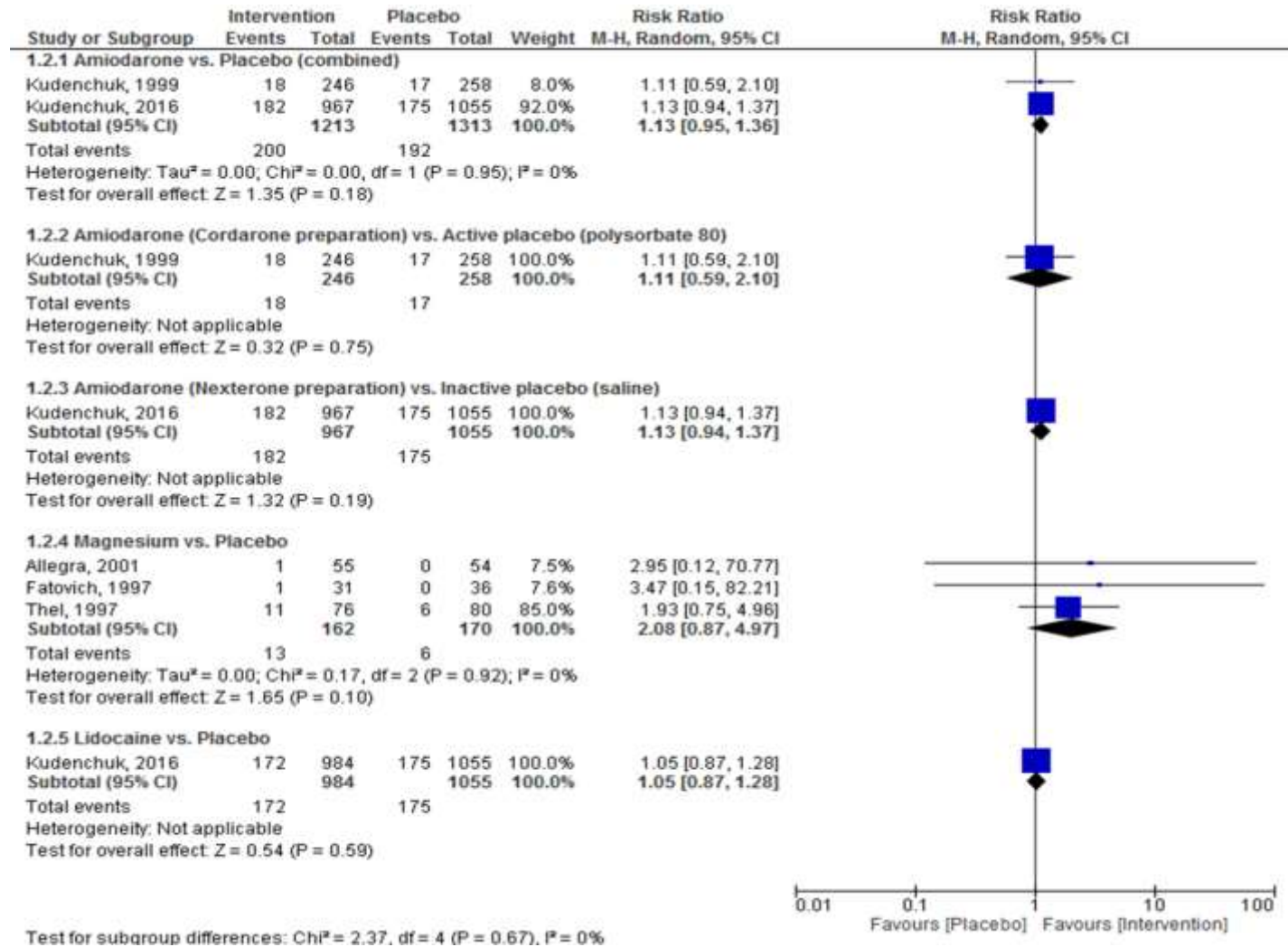


Figure 2.2

Survival to hospital discharge / 30 days

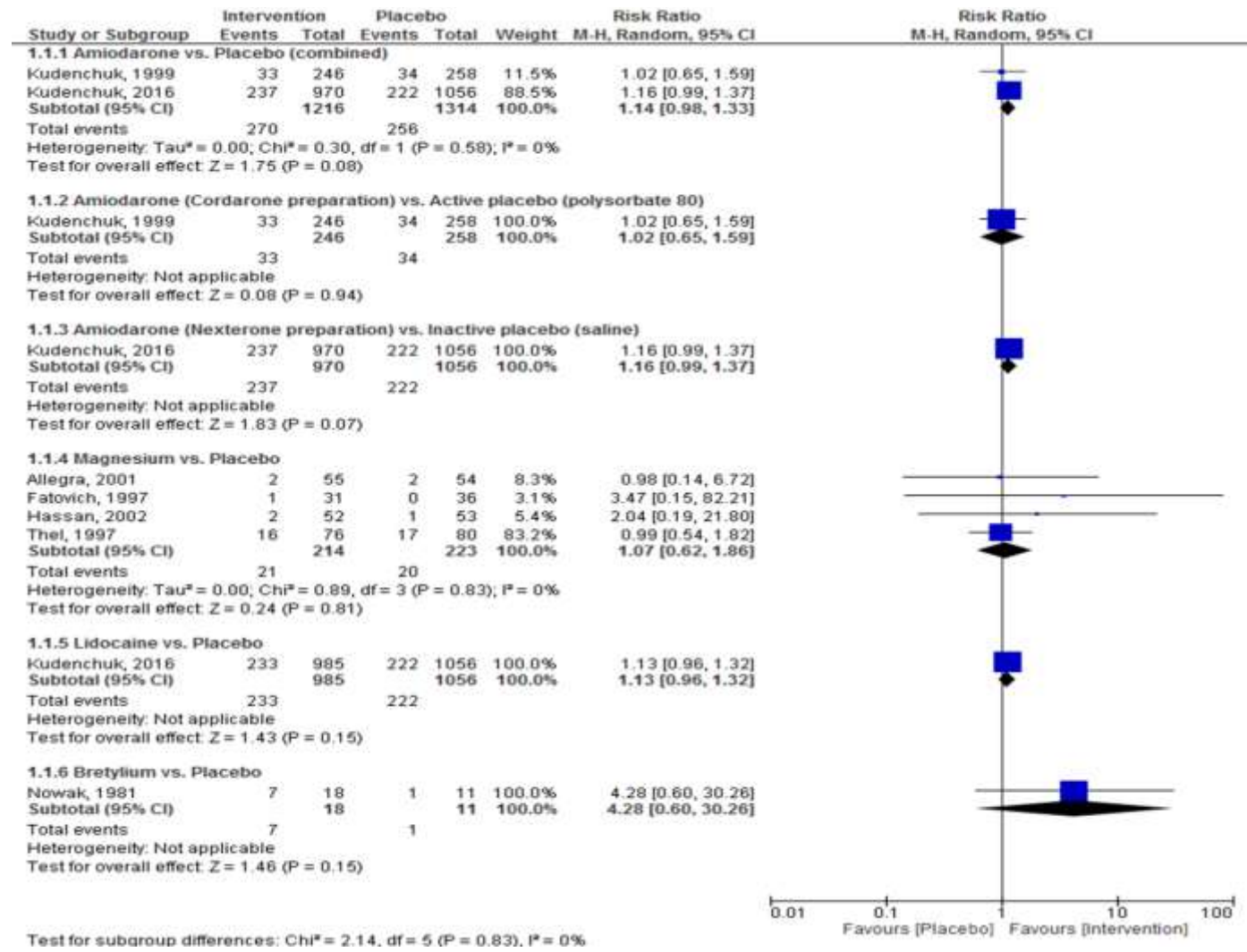


Figure 2.3

Return of Spontaneous Circulation (ROSC)

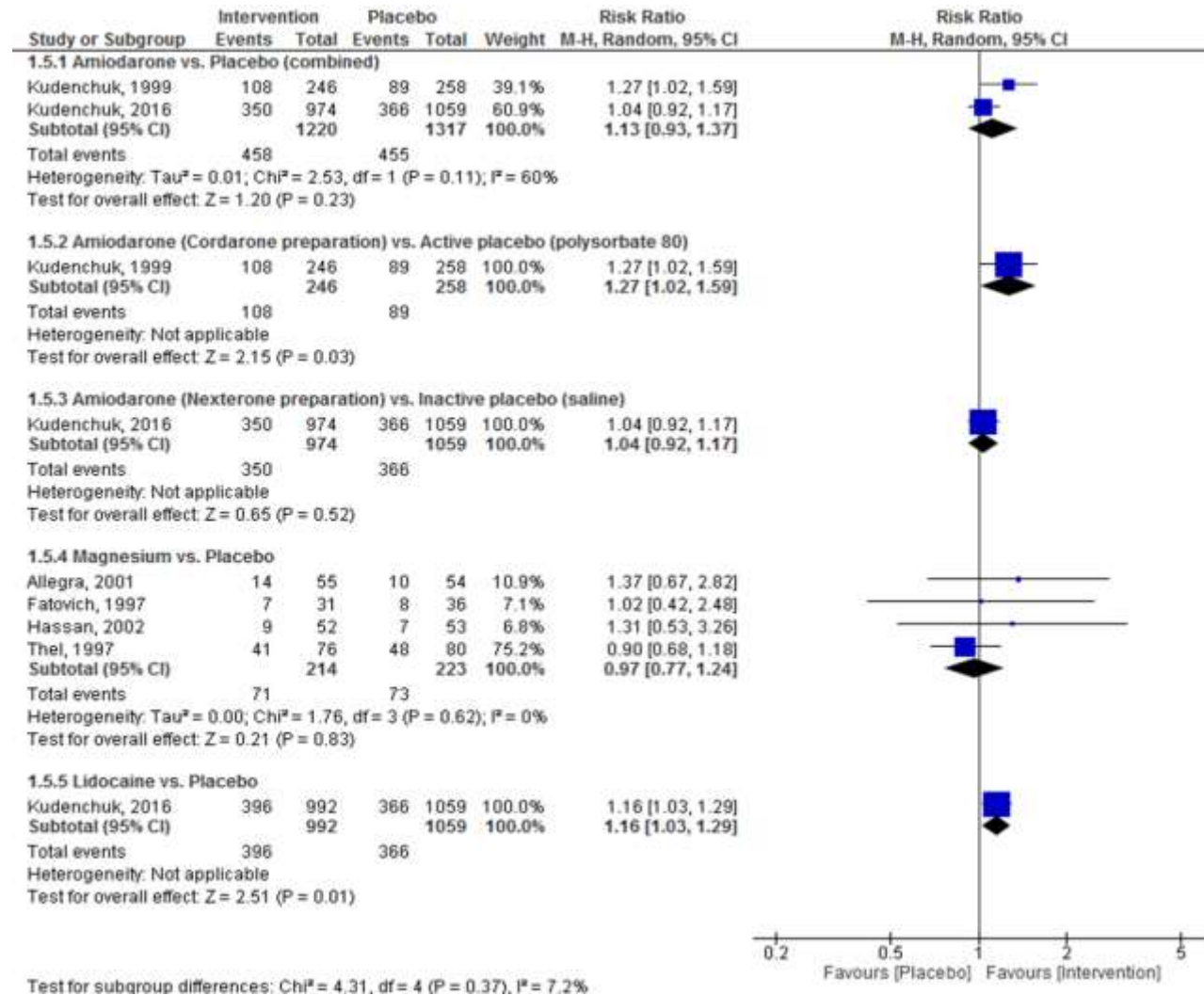


Figure 3.1

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

Survival to hospital discharge with good Neurological function/ 30 days

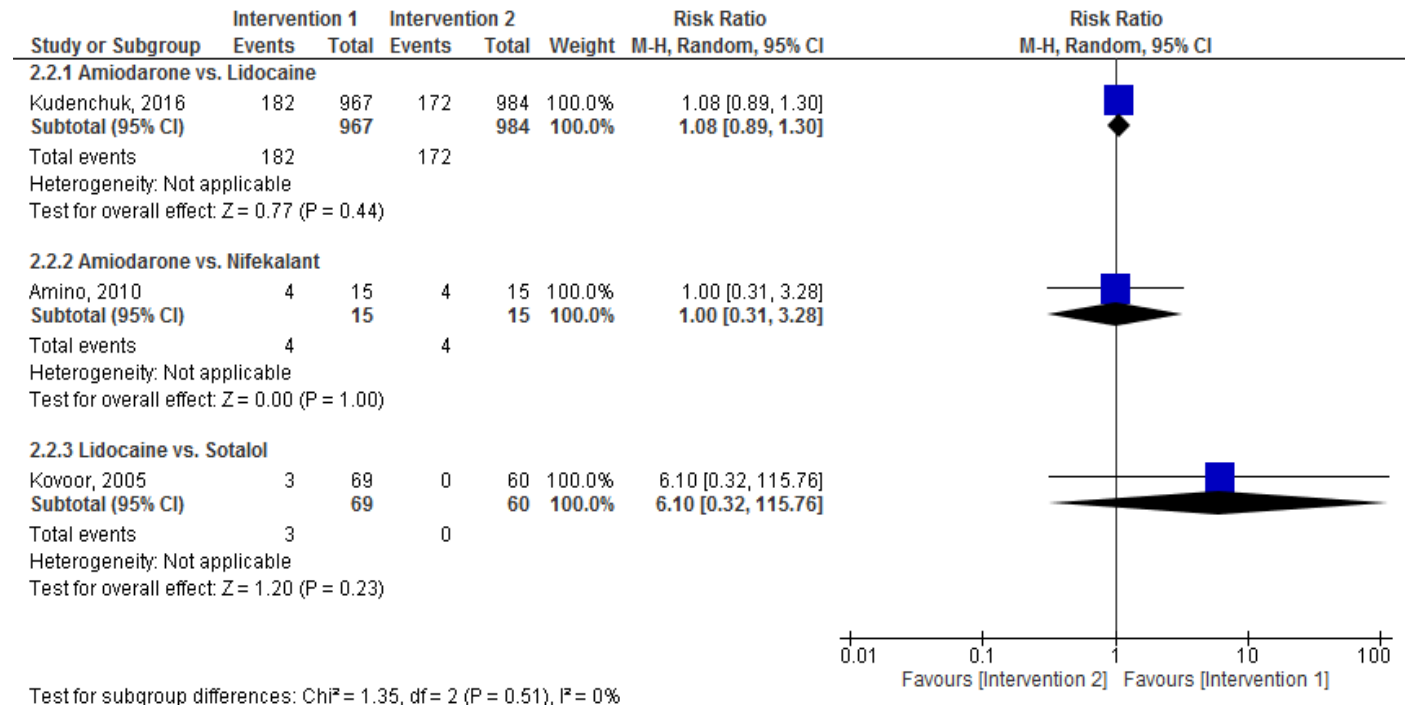


Figure 3.2

Survival to hospital discharge / 30 days

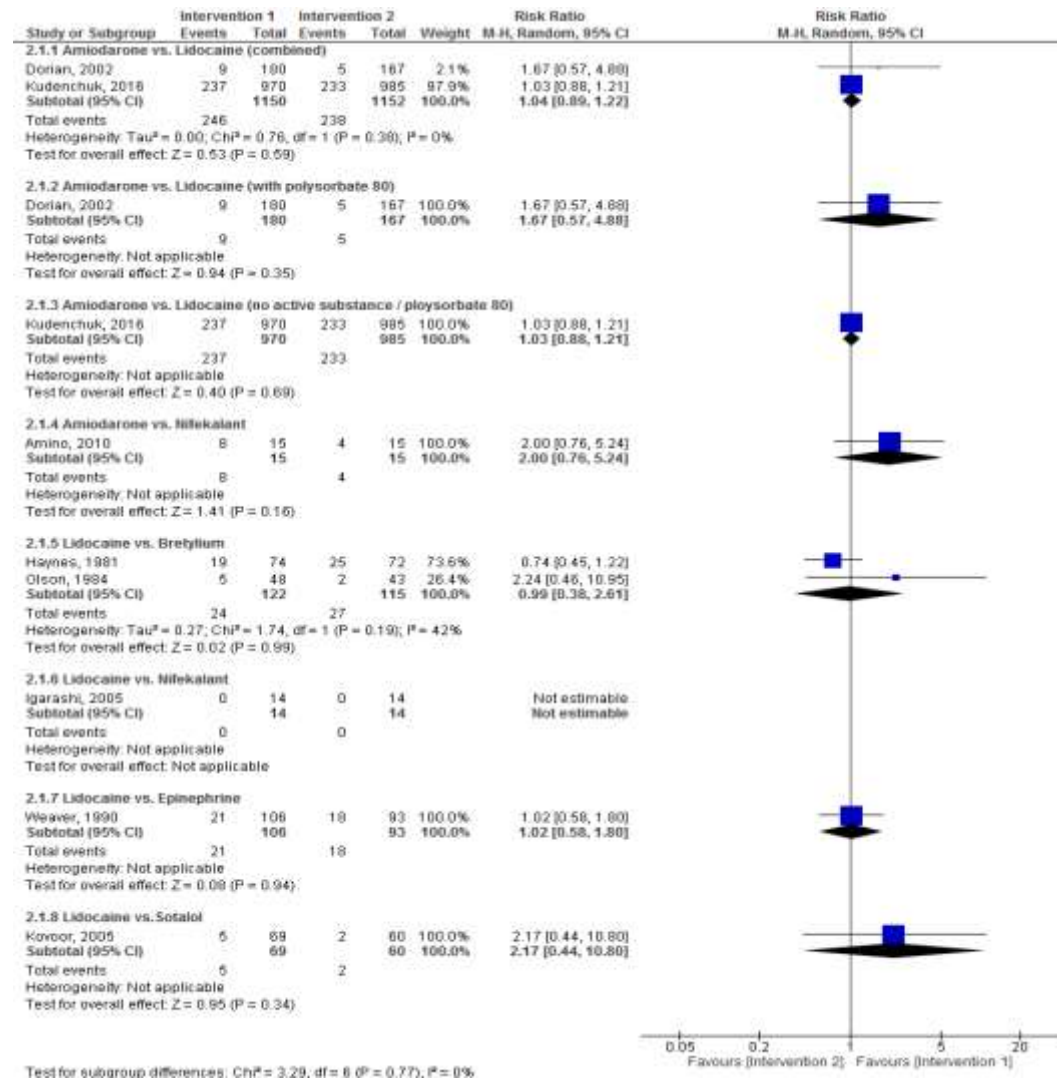


Figure 3.3

Return of Spontaneous Circulation (ROSC)

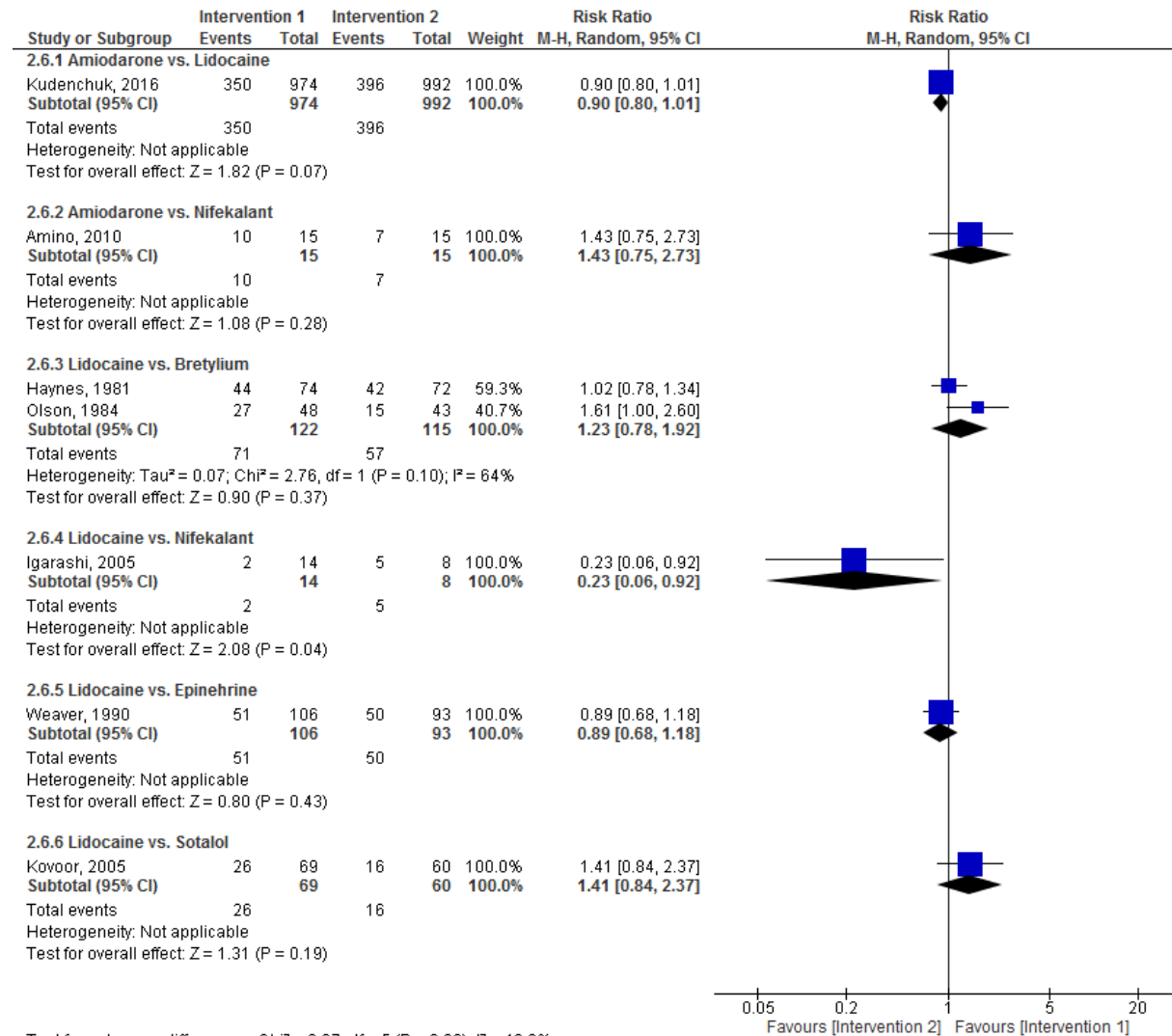


Figure 3.4

Recurrence of pVT/VF

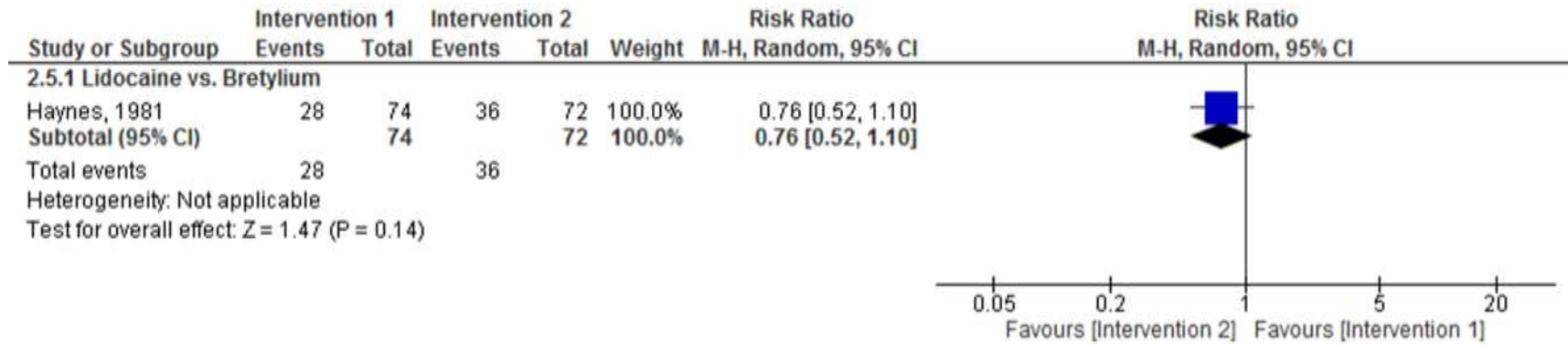


Figure 4.1

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

Survival to hospital discharge / 30 days (Observational studies)

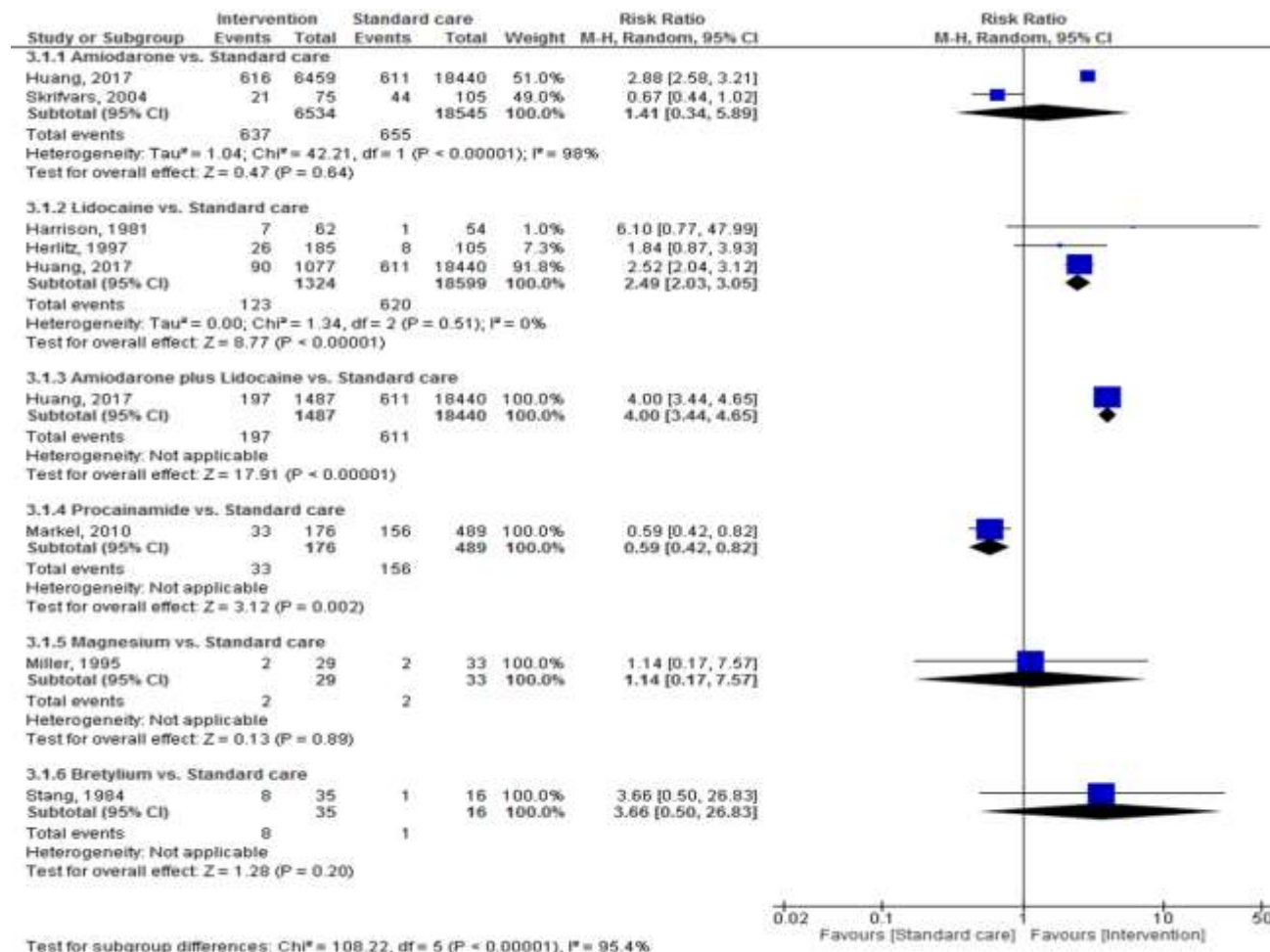


Figure 4.2

Long term survival (1 year; Observational studies)

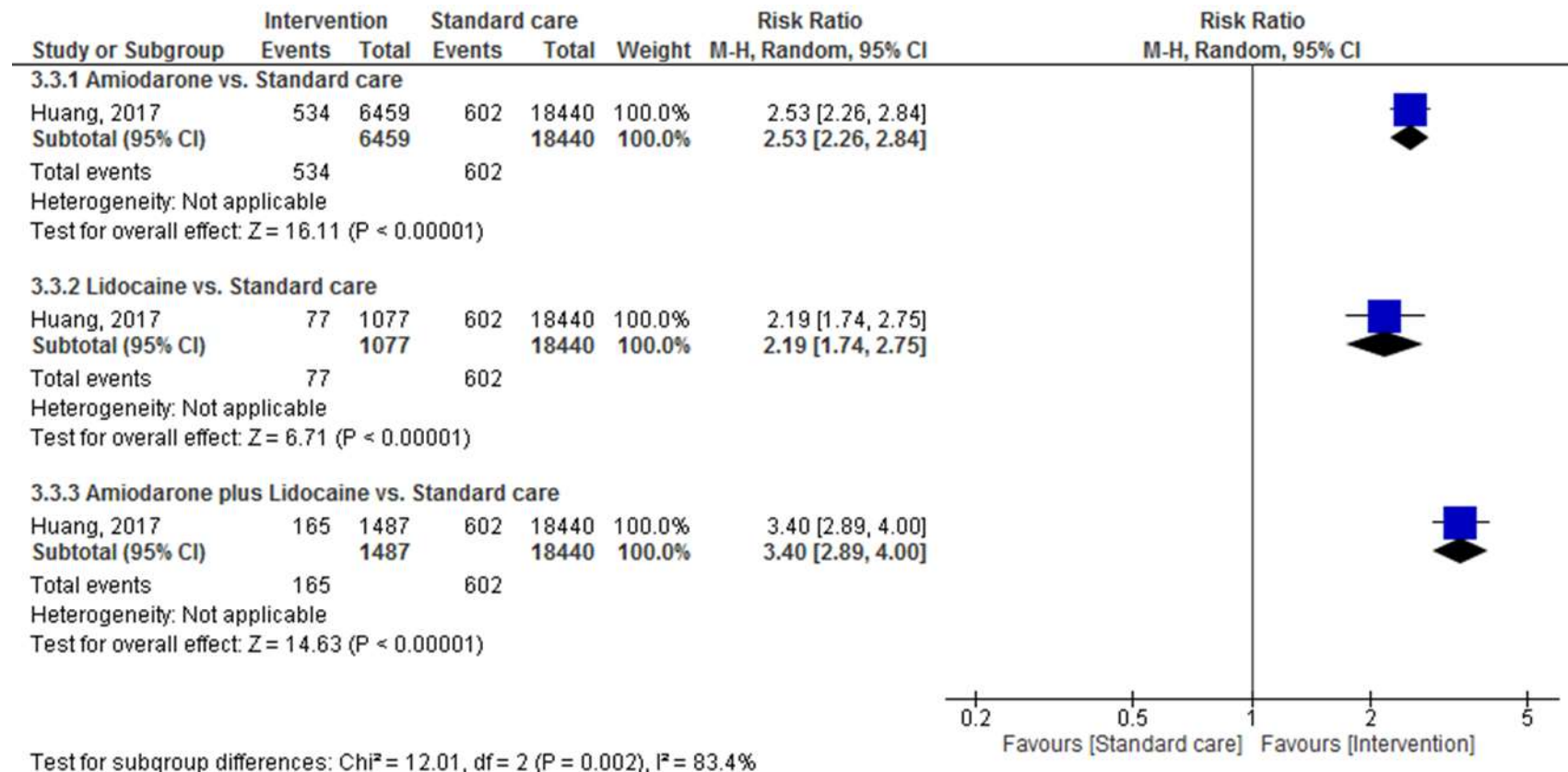


Figure 4.3

Return of Spontaneous Circulation (ROSC; Observational studies)

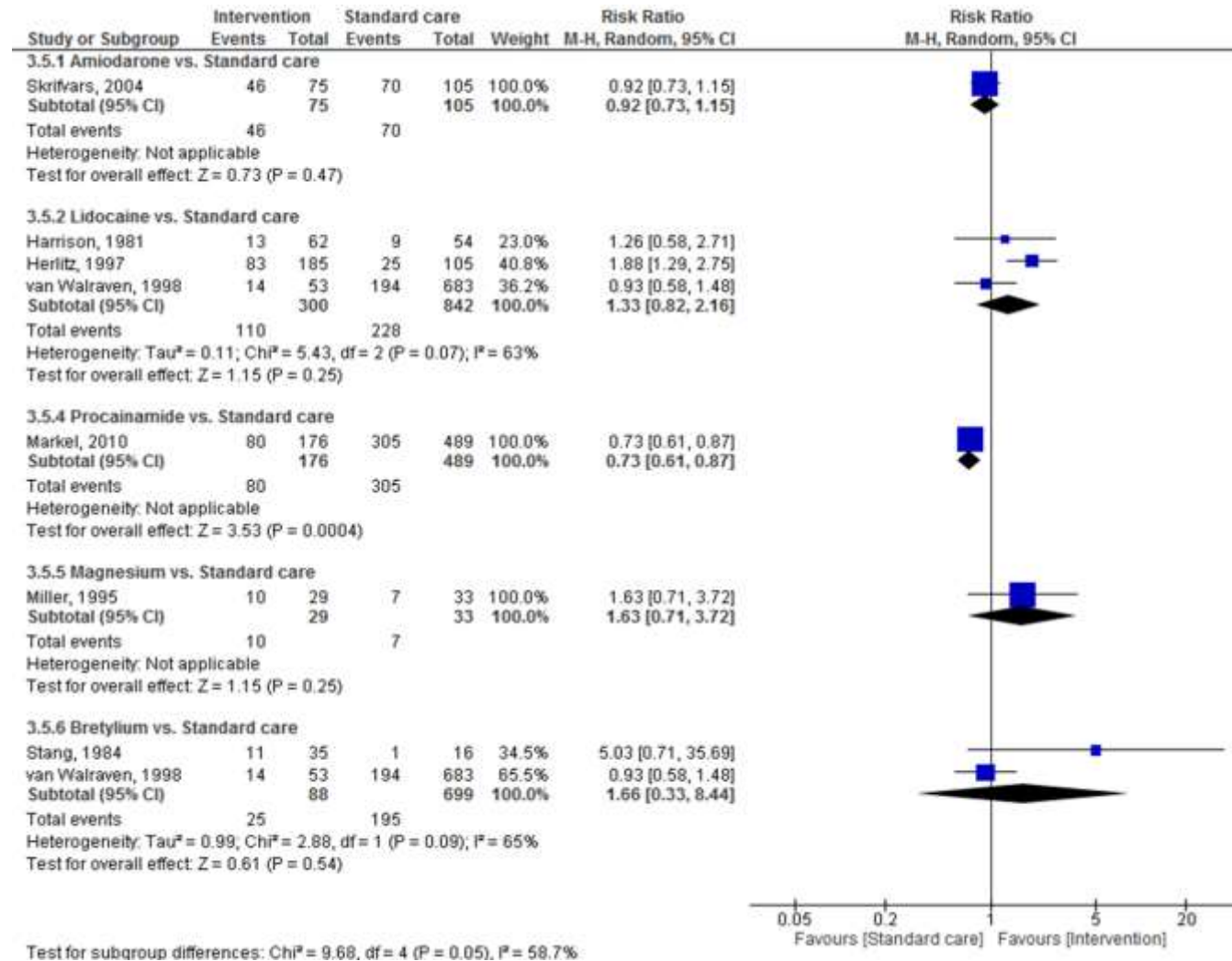


Figure 4.4

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

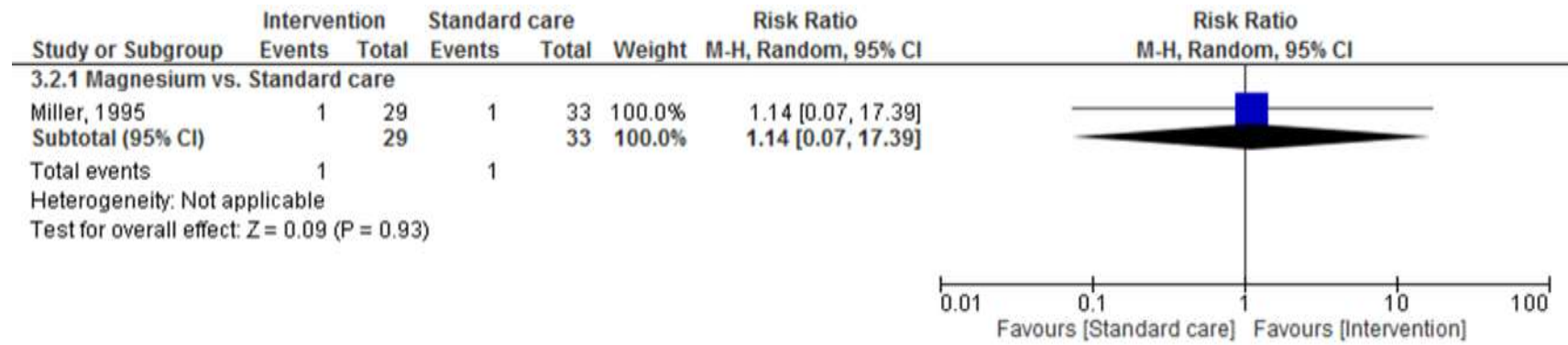


Figure 5.1

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

Survival to hospital discharge / 30 days (Observational studies)

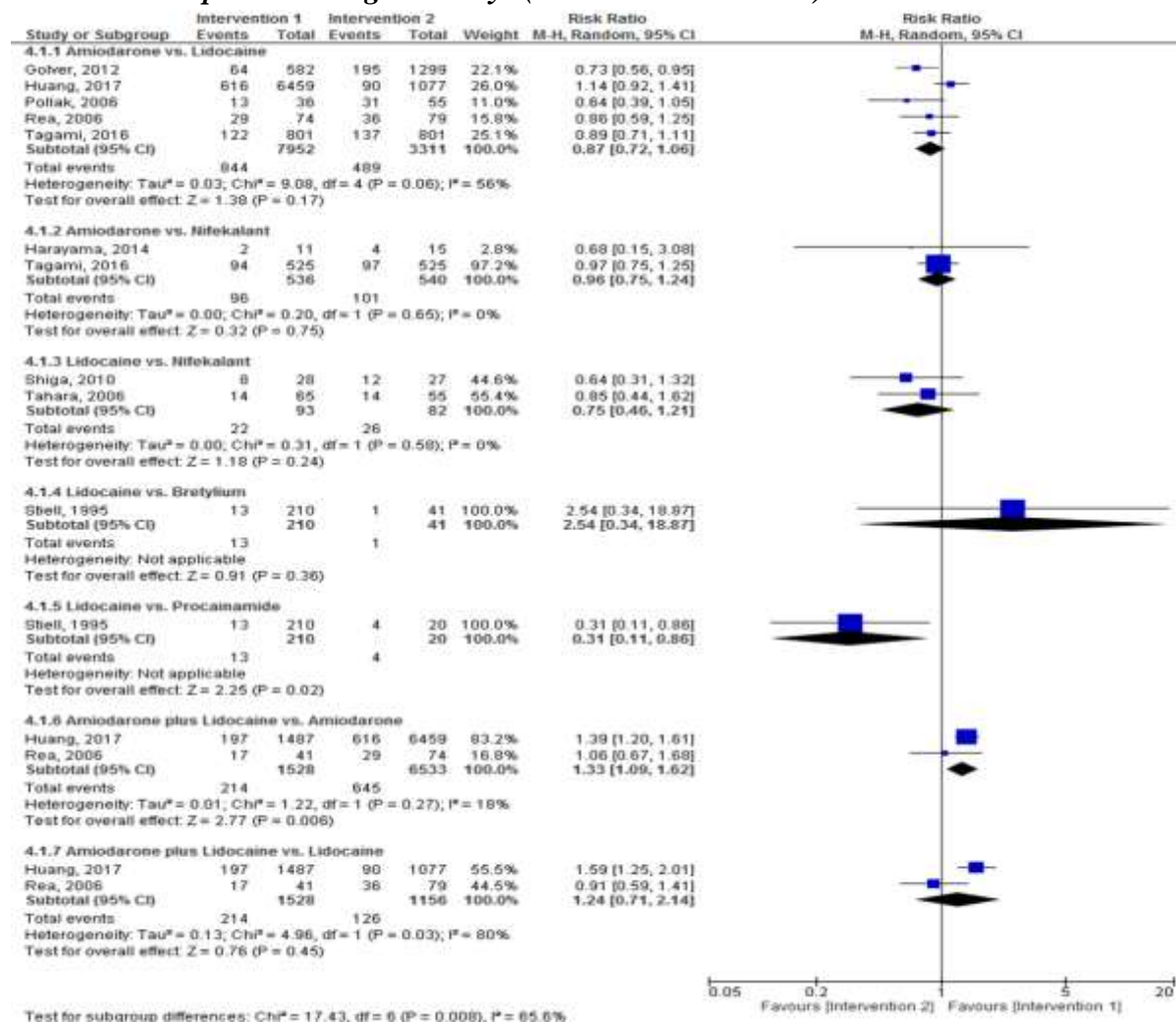


Figure 5.2

Long term survival (1 year; Observational studies)

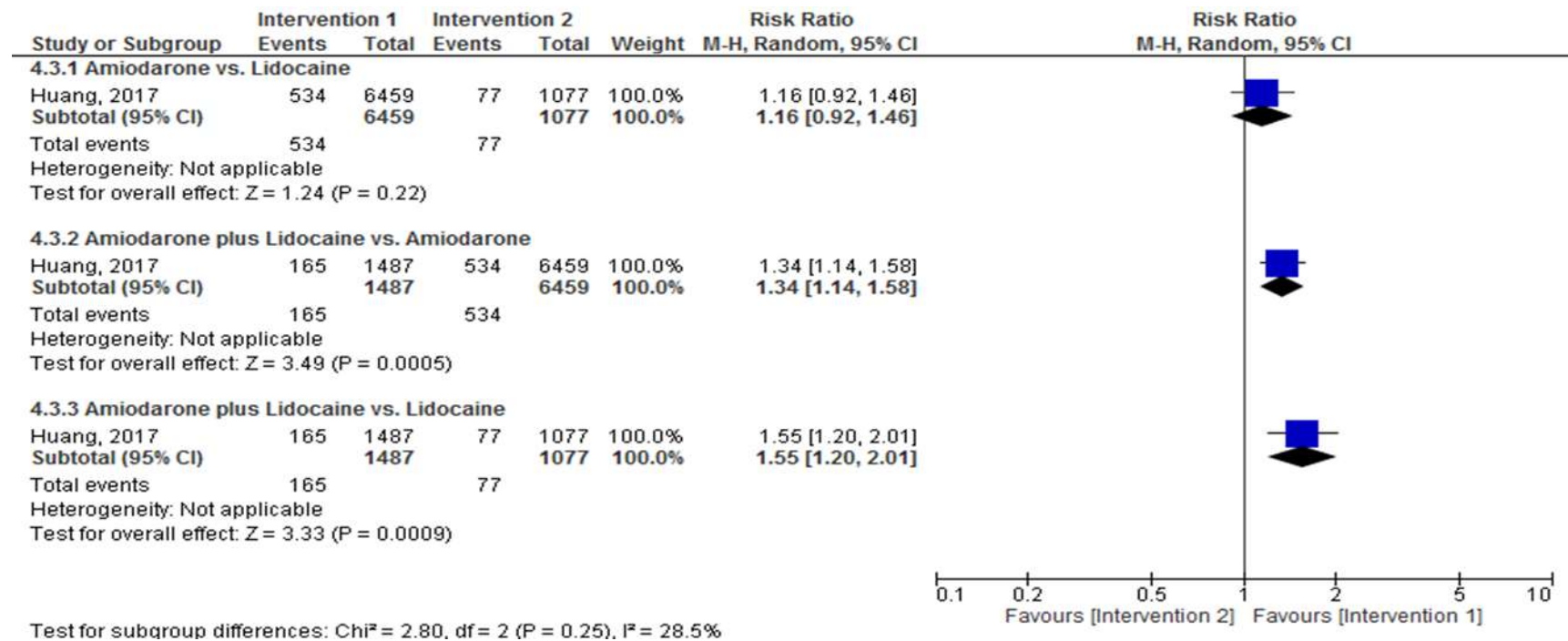


Figure 5.3

Return of Spontaneous Circulation (ROSC; Observational studies)

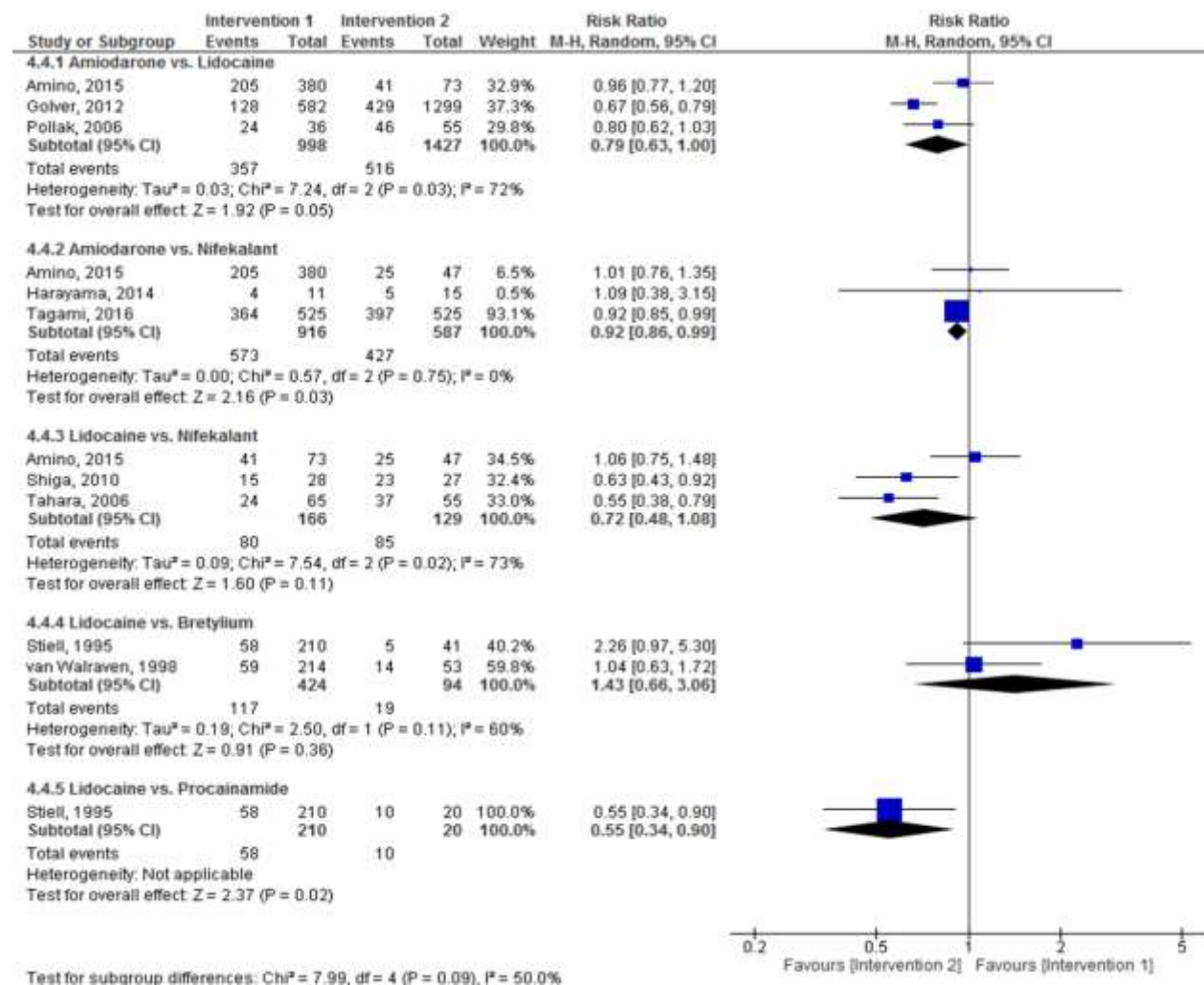


Figure 5.4

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

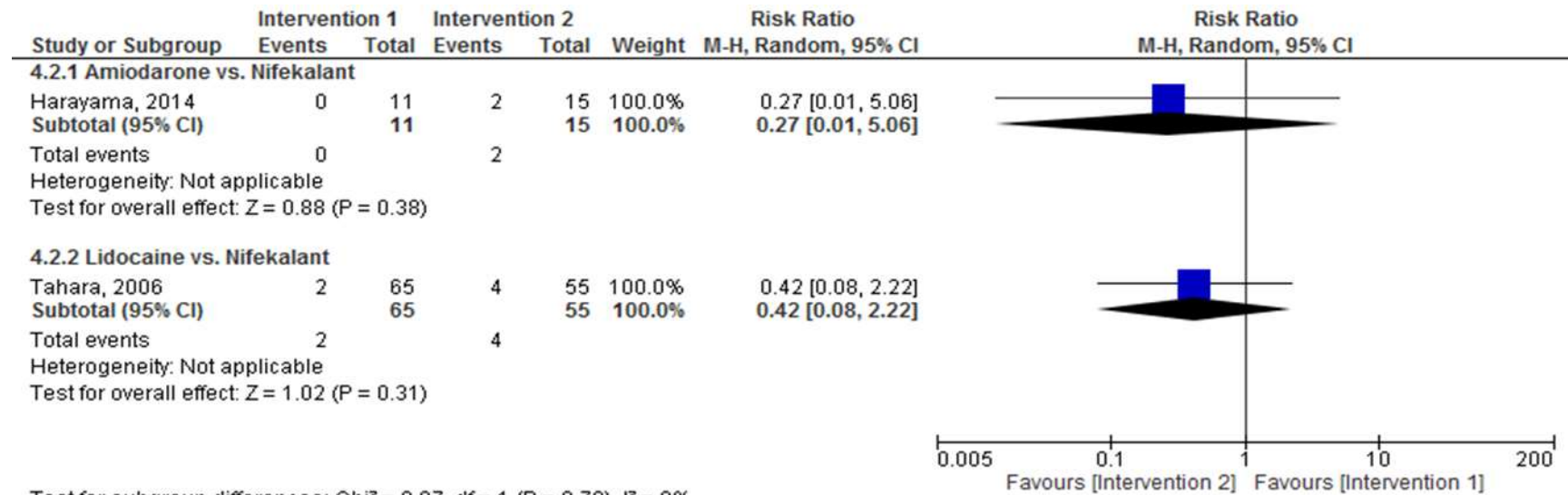


Figure 5.5

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

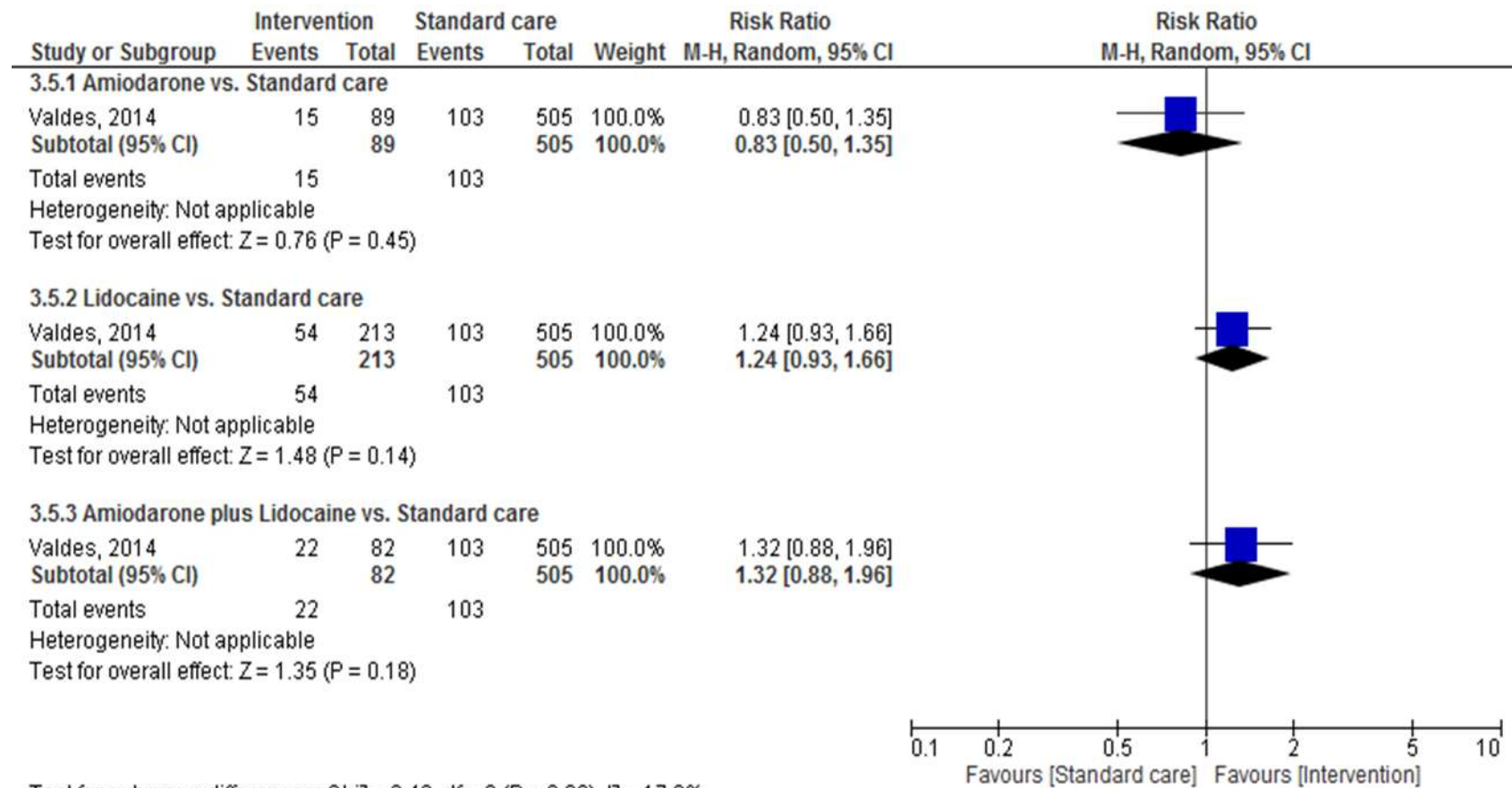


Figure 5.6

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

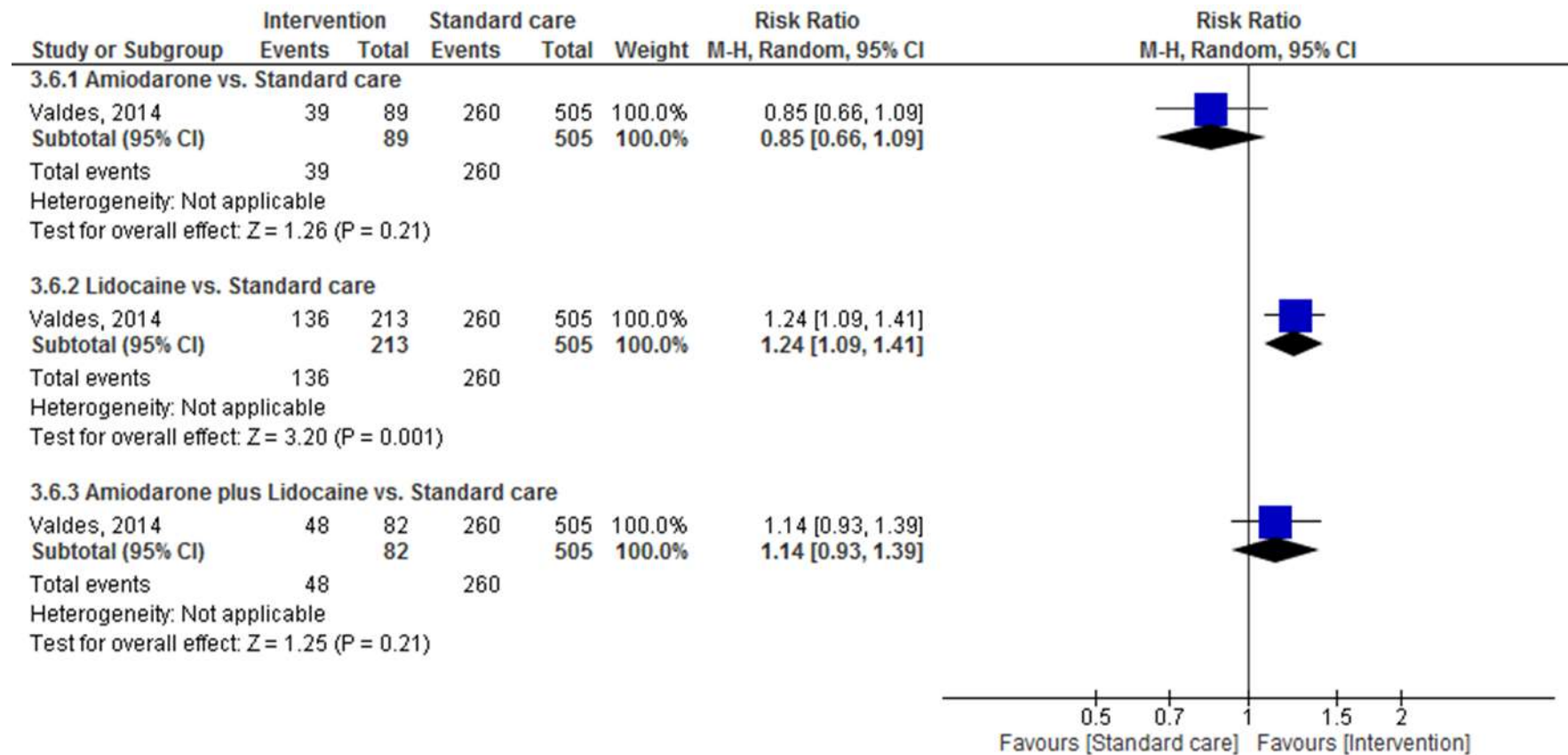


Figure 5.7

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

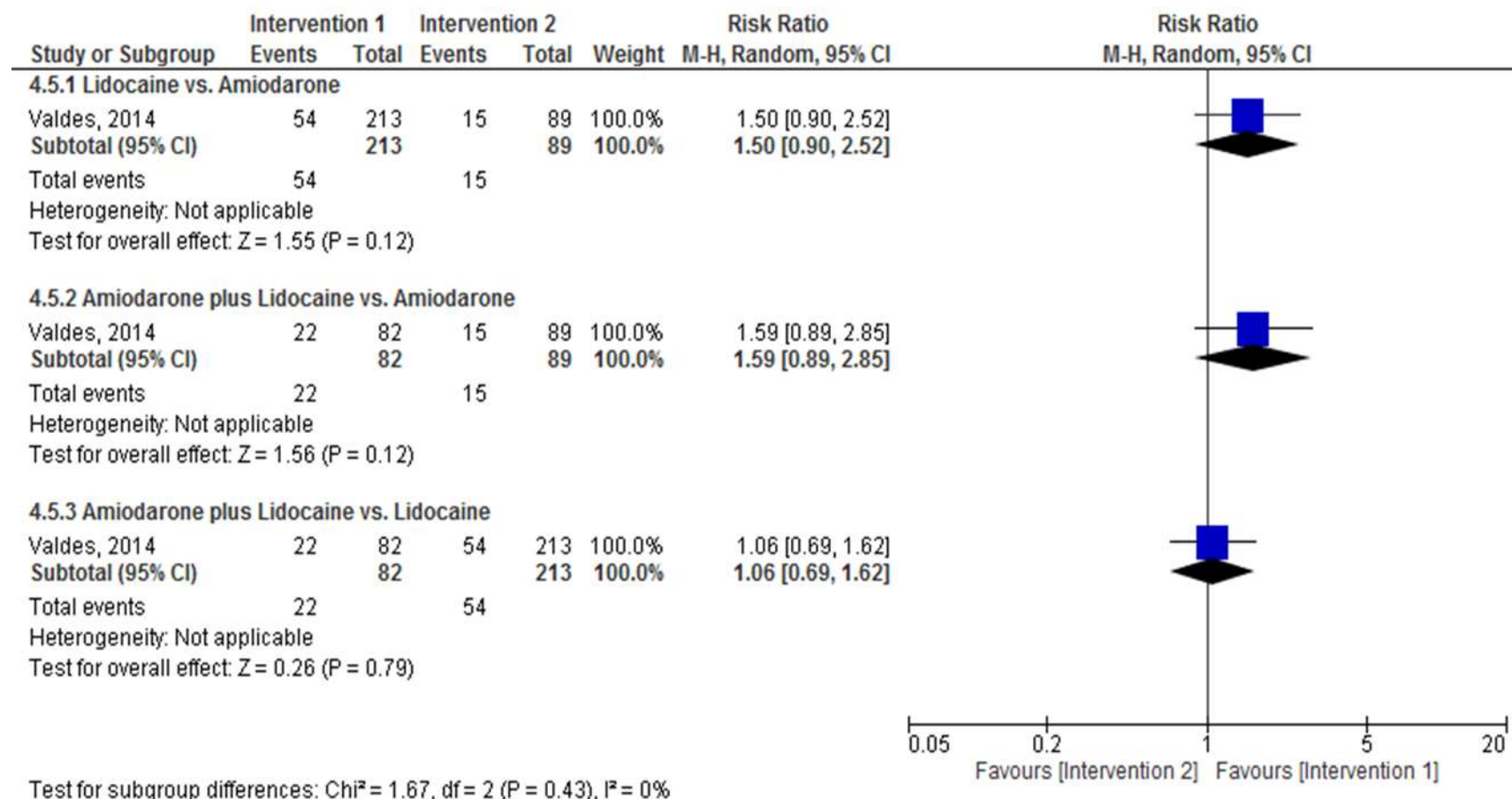


Figure 5.8

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

