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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.

NUSC.

**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. An estimated 320,000 to 700,000 cases of out-of-hospital cardiac arrests (OHCA) occur annually 5 across the United States and Europe [1, 2]. CA with an initial heart rhythm of pulseless 6 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 treatment (i.e. defibrillation) and drugs, if needed, only 8-40% survive to hospital discharge [3-9 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 placebo, however, neither drug showed any benefit on long-term survival or good neurological 15 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 of amiodarone with lidocaine as an alternative to amiodarone for pVT/VF for adults 19 unresponsive to CPR, defibrillation or vasopressor therapy [13]. 20 21 22 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 23 with unbalanced baseline characteristics, different drug formulation and timing of drug 24

| 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<br>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        |

### 45 Search Strategy

recurrence of recurrence of pVT/VF?

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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

(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

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.

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

Two reviewers independently selected studies for possible inclusion. Studies selected by either 53 54 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 55 help reach consensus, as necessary (see Table 1 for inclusion criteria). Full data extraction, 56 57 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. 58 59 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 60 61 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 62 Recommendations Assessment, Development and Evaluation (GRADE) system [21] was used to 63 assess the strength and the quality of evidence using GRADEPro software [22]. The quality of 64 65 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). 66 Meta-analyses were conducted where appropriate. 67

### 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 survival, ROSC, and cardiac re-arrest) we used number of events to generate the summary 71 72 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-73 analysis was based on type of population i.e. adult or pediatric, and type of study design (RCT or 74 observational). Further subgrouping was done based on type of anti-arrhythmic drug and drug 75 comparison (placebo or head-to-head trials). 76

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

**Results** 87

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#### **Overall Search Results** 88

Of the 9,371 citations reviewed, 34 unique citations met the inclusion criteria and were selected 89 90 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).

### 93 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 94 of bias for RCTs was rated high in one study [42], unclear in eleven studies [29-35, 37, 39-41], 95 and low in two studies [36, 38]. The individual domain ratings for each study are reported in 96 97 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 98 Supplemental File 1). The publication years of resuscitation guidelines applied in the RCT 99 100 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). 101 102 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, 39-42] with small samples (<499 participants). In the observational studies, there were four [44, 104 48, 49, 58] large cohorts (>1,000 participants), four [43, 50, 57, 60] medium sized cohorts (500-105 999 participants), and ten [45-47, 51-56, 59] small cohorts (<499 participants). The range of 106 107 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 females. All the RCTs administered the intervention drug during CPR. In the studies time of 109 110 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 drug during CPR while one administered the drug immediately after ROSC. The time from 112 cardiac arrest to first dose of the trial drug was reported in six studies [51-54, 57, 59] and ranged 113

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

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

### 117 Amiodarone versus Placebo

The evidence on amiodarone was considered as both pooled and separated. The primary reason 118 119 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<sup>™</sup> 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 with favorable neurologic function at hospital discharge, the pooled evidence showed no 125 126 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 127 128 downgraded for serious concerns for risk of bias, indirectness and imprecision. The evidence on amiodarone in polysorbate 80, i.e. the Cordarone<sup>™</sup> preparation of amiodarone, with very low 129 quality (downgraded for serious concerns for risk of bias, indirectness and imprecision), showed 130 no difference in effect for amiodarone compared with an active polysorbate 80 placebo (1 RCT; 131 RR=1.11; 95% CI, 0.59 to 2.10, p=0.75) [37]. The evidence on the Nexterone<sup>™</sup> preparation of 132 amiodarone, with moderate quality (downgraded for serious concerns for imprecision), showed 133 no difference in effect for amiodarone compared with inactive "saline" placebo (1 RCT; 134 RR=1.13; 95% CI, 0.94 to 1.37, p=0.19, (see Table 2, fig. 2.1) [38]. 135

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 1.33, p=0.08, I<sup>2</sup>=0%) [37, 38]. The overall quality of evidence was rated as very low quality and 138 139 downgraded for serious concerns for risk of bias, indirectness and imprecision. Evidence on the Cordarone<sup>™</sup> preparation of amiodarone, with very low quality (downgraded for serious 140 141 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 142 1.59, p=0.94) [37]. Evidence on Nexterone<sup>™</sup> preparation of amiodarone, with moderate quality 143 144 (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, 145 p=0.07, see Table 2, fig. 2.2) [38]. 146 147 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%) 148 [37, 38]. The overall quality of evidence was rated as very low quality and downgraded for 149 150 serious concerns for risk of bias, indirectness and imprecision. Evidence on the Cordarone<sup>TM</sup> 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 active polysorbate 80 placebo (1 RCT; RR=1.27; 95% CI, 1.02 to 1.59, p=0.03) [37]. Evidence 153 on Nexterone<sup>TM</sup> preparation of amiodarone, with moderate quality (downgraded for serious 154 155 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]. 156 Lidocaine versus Placebo 157

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,
- 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, I<sup>2</sup>=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,  $I^2=0\%$ ) [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
- magnesium (4 RCTs; RR=0.97; 95% CI, 0.77 to 1.24, p=0.83, I<sup>2</sup>=0%, see Supplemental File 3,
- 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
- 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].

| 183 | For the critical | outcome of | survival to | hospital | discharge, t | the pooled | evidence showed no | O |
|-----|------------------|------------|-------------|----------|--------------|------------|--------------------|---|
|     |                  |            |             |          |              |            |                    |   |

- 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
- 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
- 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
- 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

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)

### 207 Amiodarone versus standard care

- 208 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
- 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
- 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

- 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
- 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
- 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
- 222 (n=853, p>0.05, see figs 4.1 and 4.3) [46, 60].

### 223 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
- 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

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].

### 238 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]

244 (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

248 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

| 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

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</li>
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.

### 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<br>283 | <i>Lidocaine versus standard care</i><br>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<br>292 | <i>Lidocaine versus Amiodarone</i><br>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

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.

### 308 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 311 any time during CPR for out-of-hospital cardiac arrest, and no studies for in in-hospital cardiac 312 arrest. Based on RCT level evidence, none of the anti-arrhythmic drugs showed any difference 313 314 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 315 evidence across these studies was rated from moderate to very low with concerns of risk of bias, 316 indirectness and imprecision. For the important outcome of ROSC, the results showed a 317 318 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 319 Cordarone<sup>™</sup> preparation of amiodarone also showed marginal benefit for ROSC favoring 320 321 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 322 bias, indirectness (active placebo with potential adverse hemodynamic effects) and imprecision. 323

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.

### 338 *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.

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

347 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 348 recommendations on the use of antiarrhythmic drugs in shock refractory pVT/VF. The use of 349 350 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) techniques and percutaneous coronary intervention (PCI) during CPR are all likely to have a role 352 353 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 with cardiac arrest immediately after ROSC and in children in cardiac arrest or immediately after 355 ROSC. Future randomized controlled studies are also needed to explore the role of administering 356 antiarrhythmic drugs in adults with in-hospital shockable cardiac arrest. 357

### 358 Limitations

First, there was considerable heterogeneity across studies for various population and study level 359 factors such as dose and formulation of antiarrhythmic drugs, timing of drug administration, type 360 361 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 362 of events. Second, there was insufficient high-level evidence to answer several questions of 363 interest including effectiveness of anti-arrhythmic drugs in adults with cardiac arrest 364 365 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 366 367 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 were under-powered with inadequate number of events or sample sizes to detect clinically 369

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.

#### 375 **Conclusions**

376

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

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

evaluate the effectiveness and role of administering antiarrhythmic drugs in children with

shockable cardiac arrest, and in adults immediately after ROSC.

386

### 387 **Declaration of Interests**

388

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391

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551

## **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.              |
|               |  |

## Table 2

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

| Certaint        | ty assessmer         | ıt                      |                 |                   |                      |                         | № of events patients | / № of              | Effect                        |   |                  | Importance |
|-----------------|----------------------|-------------------------|-----------------|-------------------|----------------------|-------------------------|----------------------|---------------------|-------------------------------|---|------------------|------------|
| № of<br>studies | Study<br>design      | Risk<br>of bias         | Inconsistency   | Indirectness      | Imprecision          | Other<br>considerations | Amiodarone           | Placebo             | Relative<br>(95%<br>Cl)       | Absolute<br>(95% Cl)  | Certainty        |            |
| Survival        | to hospital d        | lischarge               | - combined      | <u> </u>          |                      |                         | <u> </u>             | <u> </u>            |                               | <u> </u>  | L                | L          |
| 2 a             | randomised<br>trials | serious<br><sup>b</sup> | not serious     | very serious<br>c | serious <sup>d</sup> | none                    | 270/1216<br>(22.2%)  | 256/1314<br>(19.5%) | <b>RR 1.14</b> (0.98 to 1.33) | <b>27 more</b><br><b>per</b><br><b>1,000</b><br>(from 4<br>fewer to<br>64 more) | ⊕○○<br>VERY LOW  | CRITICAL   |
| Survival        | to hospital d        | lischarge               | - Cordarone pre | paration of An    | niodarone            |                         |                      |                     |                               |   |                  |            |
| 1 e             | randomised<br>trials | serious<br>f            | not serious     | very serious<br>g | serious <sup>d</sup> | none                    | 33/246<br>(13.4%)    | 34/258<br>(13.2%)   | <b>RR 1.02</b> (0.65 to 1.59) | <b>3 more</b><br><b>per</b><br><b>1,000</b><br>(from 46<br>fewer to<br>78 more) | ⊕○○○<br>VERY LOW | CRITICAL   |
| Survival        | to hospital d        | lischarge               | - Nexterone pre | paration of Am    | niodarone            |                         |                      |                     |                               |   |                  |            |
| <b>1</b> h      | randomised<br>trials | not<br>serious          | not serious     | not serious       | serious <sup>d</sup> | none                    | 237/970<br>(24.4%)   | 222/1056<br>(21.0%) | <b>RR 1.16</b> (0.99 to 1.37) | <b>34 more</b><br><b>per</b><br><b>1,000</b><br>(from 2<br>fewer to<br>78 more) | ⊕⊕⊕⊖<br>MODERATE | CRITICAL   |
| Survival        | to hospital d        | lischarge               | with good Neur  | ological functi   | on - combined        | 1                       | 1                    | 1                   |                               | 1   | 1                | 1          |

| Certaint        | ty assessmer         | nt                      |                  |                   |                      |                         | № of events<br>patients | Nº of               | Effect                        |  |                  |            |
|-----------------|----------------------|-------------------------|------------------|-------------------|----------------------|-------------------------|-------------------------|---------------------|-------------------------------|--|------------------|------------|
| № of<br>studies | Study<br>design      | Risk<br>of bias         | Inconsistency    | Indirectness      | Imprecision          | Other<br>considerations | Amiodarone              | Placebo             | Relative<br>(95%<br>Cl)       | Absolute<br>(95% CI)   | Certainty        | Importance |
| 2 ª             | randomised<br>trials | serious<br><sup>b</sup> | not serious      | very serious<br>c | serious <sup>d</sup> | none                    | 200/1213<br>(16.5%)     | 192/1313<br>(14.6%) | <b>RR 1.13</b> (0.95 to 1.36) | <b>19 more</b><br><b>per</b><br><b>1,000</b><br>(from 7<br>fewer to<br>53 more)      | ⊕○○○<br>VERY LOW | CRITICAL   |
| Survival        | to hospital d        | lischarge               | with good Neur   | ological functi   | on - Cordaron        | e preparation of J      | Amiodarone              |                     |                               |  |                  |            |
| 1 e             | randomised<br>trials | serious<br>f            | not serious      | very serious<br>g | serious <sup>d</sup> | none                    | 18/246<br>(7.3%)        | 17/258<br>(6.6%)    | <b>RR 1.11</b> (0.59 to 2.10) | <b>7 more</b><br><b>per</b><br><b>1,000</b><br>(from 27<br>fewer to<br>72 more)      | ⊕⊖⊖⊖<br>VERY LOW | CRITICAL   |
| Survival        | to hospital d        | lischarge               | with good Neur   | ological functi   | on - Nexteron        | e preparation of A      | Amiodarone              |                     |                               |  |                  |            |
| 1 <sup>h</sup>  | randomised<br>trials | not<br>serious          | not serious      | not serious       | serious <sup>d</sup> | none                    | 182/967<br>(18.8%)      | 175/1055<br>(16.6%) | <b>RR 1.13</b> (0.94 to 1.37) | <b>22 more</b><br><b>per</b><br><b>1,000</b><br>(from 10<br>fewer to<br>61 more)     | ⊕⊕⊕⊖<br>MODERATE | CRITICAL   |
| Return o        | of Spontaneo         | us Circula              | ation (ROSC) - c | ombined           |                      |                         |                         |                     |                               |  |                  |            |
| 2 ª             | randomised<br>trials | serious<br><sup>b</sup> | not serious      | very serious<br>c | serious <sup>d</sup> | none                    | 458/1220<br>(37.5%)     | 455/1317<br>(34.5%) | <b>RR 1.13</b> (0.93 to 1.37) | <b>45 more</b><br><b>per</b><br><b>1,000</b><br>(from 24<br>fewer to<br>128<br>more) | ⊕⊖⊖⊖<br>VERY LOW | IMPORTANT  |

| Certaint        | Certainty assessment |                 |                  |                   |                      |                      | № of events patients | Nº of               | Effect                        |  |                  |            |
|-----------------|----------------------|-----------------|------------------|-------------------|----------------------|----------------------|----------------------|---------------------|-------------------------------|--|------------------|------------|
| № of<br>studies | Study<br>design      | Risk<br>of bias | Inconsistency    | Indirectness      | Imprecision          | Other considerations | Amiodarone           | Placebo             | Relative<br>(95%<br>Cl)       | Absolute<br>(95% CI)   | Certainty        | Importance |
| Return o        | of Spontaneo         | us Circul       | ation (ROSC) - C | ordarone prep     | aration of Am        | iodarone             |                      |                     | •                             | •  |                  |            |
| 1 e             | randomised<br>trials | serious<br>f    | not serious      | very serious<br>g | serious <sup>i</sup> | none                 | 108/246<br>(43.9%)   | 89/258<br>(34.5%)   | <b>RR 1.27</b> (1.02 to 1.59) | <b>93 more</b><br><b>per</b><br><b>1,000</b><br>(from 7<br>more to<br>204<br>more) | ⊕○○<br>VERY LOW  | IMPORTANT  |
| Return o        | of Spontaneo         | us Circula      | ation (ROSC) - N | lexterone prep    | aration of Am        | iodarone             |                      |                     |                               |  |                  |            |
| 1 <sup>h</sup>  | randomised<br>trials | not<br>serious  | not serious      | not serious       | serious <sup>d</sup> | none                 | 350/974<br>(35.9%)   | 366/1059<br>(34.6%) | <b>RR 1.04</b> (0.92 to 1.17) | <b>14 more</b><br><b>per</b><br><b>1,000</b><br>(from 28<br>fewer to<br>59 more)   | ⊕⊕⊕⊖<br>MODERATE | IMPORTANT  |

Cl: 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 functing 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 a       | ssessment        |                      |                             | № of ever<br>pati  | ents Effect<br>Placebo e<br>(95% CI) CI) |   |  |                      |            |
|---------------------|-----------------------|--------------------|-------------------|------------------|----------------------|-----------------------------|--------------------|--|---|--|----------------------|------------|
| № of<br>studie<br>s | Study<br>design       | Risk<br>of<br>bias | Inconsistenc<br>y | Indirectnes<br>s | Imprecisio<br>n      | Other<br>consideratio<br>ns | Lidocain<br>e      | Placebo                                  | е<br>(95%                                     | (95%   | Certainty            | Importance |
| Surviv              | al to hosp            | ital dis           | charge            | <u> </u>         | <u> </u>             | J                           | I                  | <u> </u>                                 | <u> </u>                                      | <u> </u>   | <u></u>              | <u></u>    |
| 1 <sup>a</sup>      | randomise<br>d trials | not<br>seriou<br>s | not serious       | not serious      | serious <sup>b</sup> | none                        | 233/985<br>(23.7%) | 222/105<br>6<br>(21.0%)                  | <b>RR</b><br><b>1.13</b><br>(0.96 to<br>1.32) | <b>27 more</b><br><b>per</b><br><b>1,000</b><br>(from 8<br>fewer to<br>67<br>more) | ⊕⊕⊕⊖<br>MODERAT<br>E | CRITICAL   |
| Surviv              | al to hosp            | ital dis           | charge with       | good Neuro       | logical fun          | ction                       |                    |  |   |  |                      |            |
| 1 <sup>a</sup>      | randomise<br>d trials | not<br>seriou<br>s | not serious       | not serious      | serious <sup>b</sup> | none                        | 172/984<br>(17.5%) | 175/105<br>5<br>(16.6%)                  | <b>RR</b><br><b>1.05</b><br>(0.87 to<br>1.28) | 8 more<br>per<br>1,000<br>(from<br>22<br>fewer to<br>46<br>more)                   | ⊕⊕⊕⊖<br>MODERAT<br>E | CRITICAL   |
| Return              | n of Sponte           | aneous             | Circulation       | (ROSC)           | <u> </u>             | <u> </u>                    |                    | ļ  | <u> </u>                                      |  | <u> </u>             | <u> </u>   |

|                     | Certainty assessment  |                    |                   |                  |                 |                             | № of ever<br>pation |                         | Ef  | fect  |              |               |
|---------------------|-----------------------|--------------------|-------------------|------------------|-----------------|-----------------------------|---------------------|-------------------------|---|---|--------------|---------------|
| № of<br>studie<br>s | Study<br>design       | Risk<br>of<br>bias | Inconsistenc<br>y | Indirectnes<br>s | Imprecisio<br>n | Other<br>consideratio<br>ns | Lidocain<br>e       | Placebo                 | Relativ<br>e<br>(95%<br>CI)                   | Absolut<br>e<br>(95%<br>CI)   | Certainty    | Importance    |
| 1 <sup>a</sup>      | randomise<br>d trials | not<br>seriou<br>s | not serious       | not serious      | not serious     | none                        | 396/992<br>(39.9%)  | 366/105<br>9<br>(34.6%) | <b>RR</b><br><b>1.16</b><br>(1.03 to<br>1.29) | <b>55 more</b><br><b>per</b><br><b>1,000</b><br>(from<br>10 more<br>to 100<br>more) | ⊕⊕⊕⊕<br>HIGH | IMPORTAN<br>T |

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  |                          |                   |                              |                      |                             |                     | events / № of<br>patients |   | fect   |                     |            |
|---------------------|-----------------------|--------------------------|-------------------|------------------------------|----------------------|-----------------------------|---------------------|---------------------------|---|--|---------------------|------------|
| № of<br>studie<br>s | Study<br>design       | Risk<br>of<br>bias       | Inconsisten<br>cy | Indirectne<br>ss             | Imprecisio<br>n      | Other<br>consideratio<br>ns | Amiodaro<br>ne      | Lidocain<br>e             | Relativ<br>e<br>(95%<br>CI)                   | Absolut<br>e<br>(95%<br>CI)                                      | Certainty           | Importance |
| Surviv              | al to hosp            | ital dis                 | charge - con      | nbined                       |                      |                             |                     |                           |   |  |                     |            |
| 2 <sup>a</sup>      | randomise<br>d trials | seriou<br>s <sup>b</sup> | not serious       | very<br>serious <sup>c</sup> | serious <sup>d</sup> | none                        | 246/1150<br>(21.4%) | 238/1152<br>(20.7%)       | <b>RR</b><br><b>1.04</b><br>(0.89 to<br>1.22) | 8 more<br>per<br>1,000<br>(from<br>23<br>fewer to<br>45<br>more) | ⊕○○○<br>VERY<br>LOW | CRITICAL   |
| Surviv              | al to hosp            | ital dis                 | charge - Lid      | locaine with                 | h polysorba          | ite 80                      |                     |                           |   |  |                     |            |

|                     |                       |                          | Certainty a       |                              | № of even<br>patie   | Effect                      |                    |                    |   |   |                      |            |
|---------------------|-----------------------|--------------------------|-------------------|------------------------------|----------------------|-----------------------------|--------------------|--------------------|---|---|----------------------|------------|
| № of<br>studie<br>s | Study<br>design       | Risk<br>of<br>bias       | Inconsisten<br>cy | Indirectne<br>ss             | Imprecisio<br>n      | Other<br>consideratio<br>ns | Amiodaro<br>ne     | Lidocain<br>e      | Relativ<br>e<br>(95%<br>CI)                   | Absolut<br>e<br>(95%<br>CI)   | Certainty            | Importance |
| 1 e                 | randomise<br>d trials | seriou<br>s <sup>b</sup> | not serious       | very<br>serious <sup>c</sup> | serious <sup>d</sup> | none                        | 9/180<br>(5.0%)    | 5/167<br>(3.0%)    | <b>RR</b><br><b>1.67</b><br>(0.57 to<br>4.88) | 20<br>more<br>per<br>1,000<br>(from<br>13<br>fewer to<br>116<br>more)                 | ⊕○○○<br>VERY<br>LOW  | CRITICAL   |
| Surviv              | val to hosp           | ital dis                 | charge - Lia      | locaine with                 | hout polyso          | orbate 80                   |                    |                    |   |   |                      |            |
| 1 <sup>f</sup>      | randomise<br>d trials | not<br>seriou<br>s       | not serious       | not serious                  | serious <sup>d</sup> | none                        | 237/970<br>(24.4%) | 233/985<br>(23.7%) | <b>RR</b><br><b>1.03</b><br>(0.88 to<br>1.21) | <b>7 more</b><br><b>per</b><br><b>1,000</b><br>(from<br>28<br>fewer to<br>50<br>more) | ⊕⊕⊕⊖<br>MODERAT<br>E | CRITICAL   |

| Certainty assessment                     |                       |                    |                   |                  |                      |                             | № of events / № of<br>patients |                    | Effect  |  |                      |               |
|--|-----------------------|--------------------|-------------------|------------------|----------------------|-----------------------------|--------------------------------|--------------------|---|--|----------------------|---------------|
| № of<br>studie<br>s                      | Study<br>design       | Risk<br>of<br>bias | Inconsisten<br>cy | Indirectne<br>ss | Imprecisio<br>n      | Other<br>consideratio<br>ns | Amiodaro<br>ne                 | Lidocain<br>e      | Relativ<br>e<br>(95%<br>CI)                   | Absolut<br>e<br>(95%<br>CI)  | Certainty            | Importance    |
| 1 f                                      | randomise<br>d trials | not<br>seriou<br>s | not serious       | not serious      | serious <sup>d</sup> | none                        | 182/967<br>(18.8%)             | 172/984<br>(17.5%) | <b>RR</b><br><b>1.08</b><br>(0.89 to<br>1.30) | <b>14</b><br><b>more</b><br><b>per</b><br><b>1,000</b><br>(from<br>19<br>fewer to<br>52<br>more) | ⊕⊕⊕⊖<br>MODERAT<br>E | CRITICAL      |
| Return of Spontaneous Circulation (ROSC) |                       |                    |                   |                  |                      |                             |                                |                    |   |  |                      |               |
| 1 <sup>f</sup>                           | randomise<br>d trials | not<br>seriou<br>s | not serious       | not serious      | serious <sup>d</sup> | none                        | 350/974<br>(35.9%)             | 396/992<br>(39.9%) | <b>RR</b><br><b>0.90</b><br>(0.80 to<br>1.01) | <b>40</b><br><b>fewer</b><br><b>per</b><br><b>1,000</b><br>(from<br>80<br>fewer to<br>4 more)    | ⊕⊕⊕⊖<br>MODERAT<br>E | IMPORTAN<br>T |

**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).

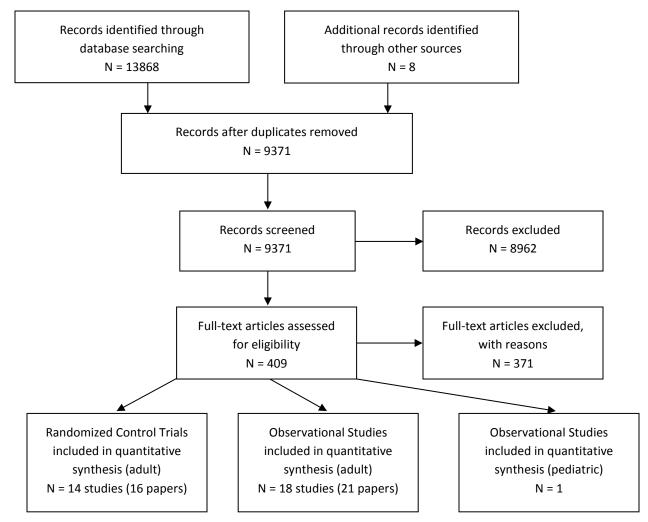
d. The effect estimate is imprecise with confidence intervals including the no effect value "1" and the sample size does not meet the optimal information size criteria.

e. Dorian, 2002

f. Kudenchuk, 2016

## Figure 1

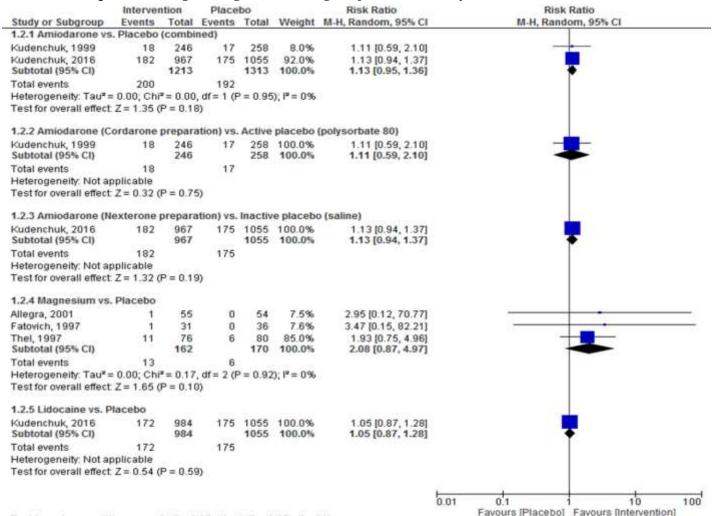
#### **Flow Diagram**



#### Figure 2.1

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

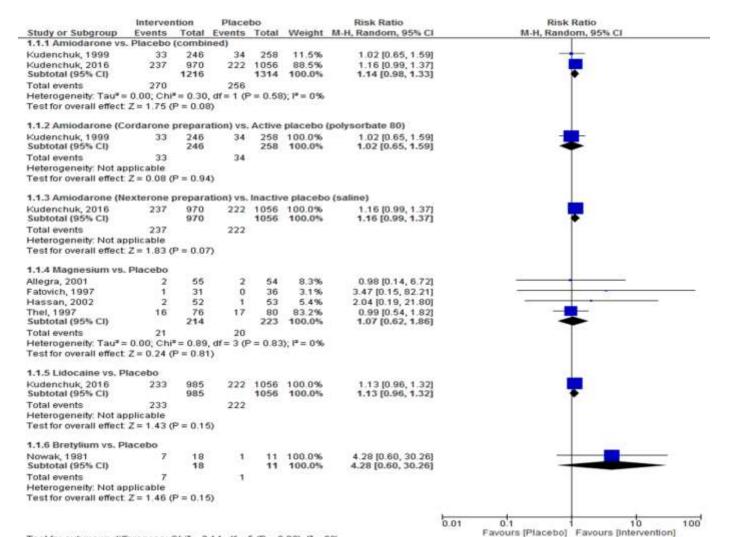
#### Survival to hospital discharge with good Neurological function/ 30 days



Test for subgroup differences: Chi<sup>2</sup> = 2.37, df = 4 (P = 0.67), I<sup>2</sup> = 0%

#### Figure 2.2

#### Survival to hospital discharge / 30 days



Test for subgroup differences: Chi# = 2.14, df = 5 (P = 0.83), I# = 0%

# Figure 2.3

### **Return of Spontaneous Circulation (ROSC)**

|                                 | Interver         |   | Place                         |               |                         | Risk Ratio          | 1               | sk Ratio                                   |
|---------------------------------|------------------|---|-------------------------------|---------------|-------------------------|---------------------|-----------------|--|
| Study or Subgroup               | Events           | and the second se | a second second second second | Total         | Weight                  | M-H, Random, 95% CI | M-H, Ra         | ndom, 95% Cl                               |
| 1.5.1 Amiodarone vs             | s. Placebo       | (combi  | ned)                          |               |                         |                     |                 | Carbon I.                                  |
| Kudenchuk, 1999                 | 108              | 246   | 89                            | 258           | 39,1%                   | 1.27 [1.02, 1.59]   |                 |  |
| Kudenchuk, 2016                 | 350              | 974   | 366                           | 1059          | 60.9%                   | 1.04 [0.92, 1.17]   |                 |  |
| Subtotal (95% CI)               |                  | 1220  |                               | 1317          | 100.0%                  | 1.13 [0.93, 1.37]   |                 | •  |
| Total events                    | 458              |   | 455                           |               |                         |                     |                 |  |
| Heterogeneity: Tau <sup>2</sup> |                  |   |                               | $^{2} = 0.11$ | ); I <sup>#</sup> = 609 | X6                  |                 |  |
| Test for overall effect         | : Z = 1.20 (     | P = 0.23  | 3)                            |               |                         |                     |                 |  |
| 1.5.2 Amiodarone (C             | ordarone         | prepara   | tion) vs.                     | Active        | placebo                 | (polysorbate 80)    |                 |  |
| Kudenchuk, 1999                 | 108              | 248   | 89                            | 258           | 100.0%                  | 1.27 [1.02, 1.59]   |                 |  |
| Subtotal (95% CI)               |                  | 246   |                               | 258           | 100.0%                  | 1.27 [1.02, 1.59]   |                 | -  |
| Total events                    | 108              |   | 89                            |               |                         |                     |                 | 1000 C                                     |
| Heterogeneity: Not a            | pplicable        |   |                               |               |                         |                     |                 |  |
| Test for overall effect         | Z= 2.15 (        | P = 0.03  | 3)                            |               |                         |                     |                 |  |
| 1.5.3 Amiodarone (N             | lexterone        | prepara   | ition) vs.                    | Inactiv       | e placeb                | o (saline)          |                 |  |
| Kudenchuk, 2016                 | 350              | 974   | 366                           | 1059          | 100.0%                  | 1.04 [0.92, 1.17]   |                 |  |
| Subtotal (95% CI)               | 18-18C           | 974   | :5:375                        |               | 100.0%                  | 1.04 [0.92, 1.17]   |                 | •  |
| Total events                    | 350              |   | 366                           |               |                         |                     |                 |  |
| Heterogeneity: Not a            | pplicable        |   |                               |               |                         |                     |                 |  |
| Test for overall effect         | Z = 0.65 (       | P = 0.52  | 2)                            |               |                         |                     |                 |  |
| 1.5.4 Magnesium vs              | Placebo          |   |                               |               |                         |                     |                 |  |
| Allegra, 2001                   | 14               | 55  | 10                            | 54            | 10.9%                   | 1.37 [0.67, 2.82]   |                 | •  |
| Fatovich, 1997                  | 7                | 31  | 8                             | 36            | 7.1%                    | 1.02 [0.42, 2.48]   | -               |  |
| Hassan, 2002                    | 9                | 52  | 7                             | 53            | 6.8%                    | 1.31 (0.53, 3.26)   |                 | • •  |
| Thel, 1997                      | 41               | 76  | 48                            | 80            | 75.2%                   | 0.90 [0.68, 1.18]   |                 |  |
| Subtotal (95% CI)               |                  | 214   |                               | 223           | 100.0%                  | 0.97 [0.77, 1.24]   |                 | •  |
| Total events                    | 71               |   | 73                            |               |                         |                     |                 |  |
| Heterogeneity: Tau*             | = 0.00; Chi      | = 1.76  | df= 3 (F                      | = 0.62        | 2); F= 0%               |                     |                 |  |
| Test for overall effect         | t Z = 0.21 (     | P = 0.83  | 3)                            |               |                         |                     |                 |  |
| 1.5.5 Lidocaine vs. I           | Placebo          |   |                               |               |                         |                     |                 |  |
| Kudenchuk, 2016                 | 396              | 992   | 366                           | 1059          | 100.0%                  | 1.16 [1.03, 1.29]   |                 |  |
| Subtotal (95% CI)               |                  | 992   |                               | 1059          | 100.0%                  | 1.16 [1.03, 1.29]   |                 | •  |
| Total events                    | 396              |   | 366                           |               |                         |                     |                 | 25   |
| Heterogeneity: Not a            | pplicable        |   |                               |               |                         |                     |                 |  |
| Test for overall effect         |                  | P = 0.01  | 0                             |               |                         |                     |                 |  |
|                                 | 11114 (1528) A.A |   |                               |               |                         |                     |                 |  |
|                                 |                  |   |                               |               |                         |                     | to ata          | 1 1  |
|                                 |                  |   |                               |               |                         |                     | 0.2 0.5         | 1 2 5                                      |
| Test for subaroup di            | ferences: (      | Chi <sup>2</sup> = 4  | 31 df=                        | 4 (P = 0      | 137) IF=                | 7.2%                | Favours (Placed | <ul> <li>Favours (Intervention)</li> </ul> |

Test for subgroup differences: Chi# = 4.31, df = 4 (P = 0.37), I# = 7.2%

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

## Survival to hospital discharge with good Neurological function/30 days

|                                       | Intervent        | ion 1                   | Intervent    | tion 2                  |                         | Risk Ratio                                    |           | Risk Ratio  |  |
|---------------------------------------|------------------|-------------------------|--------------|-------------------------|-------------------------|---|-----------|---|--|
| Study or Subgroup                     | Events           | Total                   | Events       | Total                   | Weight                  | M-H, Random, 95% Cl                           |           | M-H, Random, 95% Cl   |  |
| 2.2.1 Amiodarone vs                   | . Lidocaine      |                         |              |                         |                         |   |           |   |  |
| Kudenchuk, 2016<br>Subtotal (95% Cl)  | 182              | 967<br><mark>967</mark> | 172          | 984<br><mark>984</mark> | 100.0%<br><b>100.0%</b> | 1.08 [0.89, 1.30]<br><b>1.08 [0.89, 1.30]</b> |           | <b>↓</b>  |  |
| Total events<br>Heterogeneity: Not ap | 182<br>oplicable |                         | 172          |                         |                         |   |           |   |  |
| Test for overall effect:              | Z=0.77 (P        | = 0.44                  | )            |                         |                         |   |           |   |  |
| 2.2.2 Amiodarone vs                   | . Nifekalant     | t                       |              |                         |                         |   |           | $\perp$   |  |
| Amino, 2010<br>Subtotal (95% CI)      | 4                | 15<br><b>15</b>         | 4            | 15<br><b>15</b>         |                         | 1.00 [0.31, 3.28]<br><b>1.00 [0.31, 3.28]</b> |           |   |  |
| Total events<br>Heterogeneity: Not ap | 4<br>oplicable   |                         | 4            |                         |                         |   |           |   |  |
| Test for overall effect:              | •                | = 1.00                  | )            |                         |                         |   |           |   |  |
| 2.2.3 Lidocaine vs. S                 | otalol           |                         |              |                         |                         |   |           |   |  |
| Kovoor, 2005<br>Subtotal (95% CI)     | 3                | 69<br><mark>69</mark>   | 0            | 60<br>60                | 100.0%<br><b>100.0%</b> | 6.10 [0.32, 115.76]<br>6.10 [0.32, 115.76]    |           |   |  |
| Total events<br>Heterogeneity: Not ap | 3<br>Indicable   |                         | 0            |                         |                         |   |           |   |  |
| Test for overall effect:              | •                | = 0.23                  | )            |                         |                         |   |           |   |  |
|                                       |                  |                         |              |                         |                         |   | +<br>0.01 | <u></u>   |  |
|                                       |                  |                         |              |                         |                         |   | 0.01      | 0.1 1 10 100<br>Favours [Intervention 2] Favours [Intervention 1] |  |
| Test for subgroup diff                | ferences: C      | hi <b>²</b> = 1.3       | 35, df = 2 ( | (P = 0.51               | ), l² = 0%              |   |           |   |  |

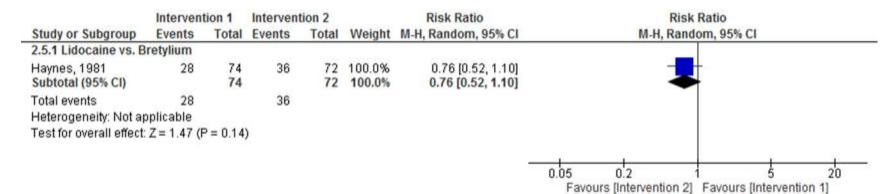
## Survival to hospital discharge / 30 days

| Study or Subgroup   | Events      | Total       | Intervent<br>Events | Total      | Weight             | Risk Ratio<br>M-H, Random, 95% CI    | Risk Ratio<br>M-H, Random, 95% Cl                 |
|---|-------------|-------------|---------------------|------------|--------------------|--------------------------------------|---|
| 2.1.1 Amiodarone vs   | Lidocaine   | (comb       | ined)               |            | · martin           | internet and a second second         | The second second second                          |
| Dorian, 2002  | 9           | 1.90        | 5                   | 167        | 2.1%               | 1.67 (0.57, 4.88)                    |   |
| Kudenchuk, 2018<br>Subtotal (95% CI)                          | 237         | 970<br>1150 | 233                 | 985        | 97.9%<br>100.0%    | 1.03[0.88, 1.21]<br>1.04[0.89, 1.22] |   |
| fotal events  | 246         |             | 238                 |            |                    |                                      |   |
| Heterogeneity Tau <sup>a</sup> -                              | 0.00; ChP   | = 0.76      | of = 1 (P =         | 0.36); 1   | <sup>4</sup> = 0%. |                                      |   |
| lest for overall effect:                                      |             |             |                     | 1.23752240 | 19-20-000          |                                      |   |
| 2.1.2 Amiodarone vs   | Lidocaine   | (with p     | olysorbat           | e 80)      |                    |                                      |   |
| Dorian, 2002  | 9           | 180         | 5                   |            | 100.0%             | 1.67 (0.57, 4.68)                    |   |
| Solitotal (95% CI)  |             | 180         |                     | 167        | 100.0%             | 1.67 [0.57, 4.88]                    |   |
| Total events  | 9           |             | 5                   |            |                    |                                      |   |
| Heterogeneity. Not ap<br>Test for overall effect:             |             | = 0.35      | 6                   |            |                    |                                      |   |
| 2.1.3 Amiodarone vs   | Lidocaine   | (no ac      | ove subst           | ance / p   | loysorba           | ta 80)                               |   |
| Rudenchuk, 2016   | 237         | 970         | 233                 | 985        | 100.0%             | 1.03 (0.88, 1.21)                    |   |
| Subtotal (95% CI)   |             | 970         | 2.505               |            | 100.8%             | 1.03 [6.88, 1.21]                    | •   |
| Total events  | 237         |             | 233                 |            |                    |                                      |   |
| Heterogeneity: Not ap<br>Test for overail effect              | plicable    | = 0.69      | 2 SSS               |            |                    |                                      |   |
| 2.1.4 Amiodarone vs   | Nifekalan   | t           |                     |            |                    |                                      |   |
| Amino, 2010   | 8           | 15          | 4                   | 15         | 100.0%             | 2.00 (0.76, 5.24)                    |   |
| Subtotal (95% CI)   |             | 15          | o - 22              | 15         | 100.0%             | 2.00 (0.76, 5.24)                    |   |
| Total events  | В           |             | 4                   |            |                    |                                      |   |
| Heterogeneity. Not ap   |             |             |                     |            |                    |                                      |   |
| Test for overall effect.                                      |             | = 0.16      | G                   |            |                    |                                      |   |
| 2.1.5 Lidocaine vs. B   | retyllum    |             |                     |            |                    |                                      |   |
| Haynes, 1981  | 19          | 74          | 25                  | 72         | 73.6%              | 0.74 (0.45, 1.22)                    |   |
| Olson, 1984   | 5           | 48          | 2                   | 43         | 26.4%              | 2.24 [0.46, 10.95]                   |   |
| Subtotal (95% CI)   |             | 122         |                     | 115        | 100.8%             | 0.99 [8.38, 2.61]                    |   |
| Total events  | 24          |             | 27                  |            |                    |                                      |   |
| Heterogeneity: Tau <sup>#</sup> =<br>Test for overall effect. |             |             |                     | 0.19); (   | *= 42%             |                                      |   |
| 2.1.6 Lidocaine vs. N   | ifekalant   |             |                     |            |                    |                                      |   |
| garashi, 2005   | 0           | 14          | 0                   | 14         |                    | Not estimable                        |   |
| Subtotal (95% CI)   | 1.54        | 14          |                     | 14         |                    | Not estimable                        |   |
| Total events  | 0           | 2.0         | 0                   | 100        |                    |                                      |   |
| Heterogeneity: Not ap<br>Test for overall effect.             | plicable    | able        | 2                   |            |                    |                                      |   |
| 2.1.7 Lidocaine vs. E   | oineohrine  |             |                     |            |                    |                                      | -11-24  |
| Neaver, 1990  | 21          | 108         | 18                  |            | 100.0%             | 1.02 (0.58, 1.80)                    |   |
| Subtotal (95% CI)   |             | 106         |                     | 93         | 100.0%             | 1.02 [0.58, 1.80]                    | -   |
| Total events  | 21          |             | 18                  |            |                    |                                      |   |
| Heterogeneity: Not ap<br>Test for overall effect              |             | = 0.94      | 8                   |            |                    |                                      |   |
| 2.1.8 Lidocaine vs. Se  | staloi      |             |                     |            |                    |                                      |   |
| Kovoor, 2005  | 5           | 69          | 2                   | 60         | 100.0%             | 2.1710.44.10.801                     |   |
| Subtotal (95% CI)   | 1.23        | 69          | 1 B                 |            | 100.0%             | 2.17 [0.44, 10.80]                   |   |
| Total events  | 6           | 111         | 2                   | 001        |                    |                                      |   |
| Heterogeneity: Not ap   |             |             | (Ť)                 |            |                    |                                      |   |
| Test for overall effect.                                      |             | - 0.24      | 8                   |            |                    |                                      |   |
| reactor process effect.                                       | F = 0.00 (h | - 0.04      | 5                   |            |                    |                                      | CS 2.5 10 10 10 10                                |
|   |             |             |                     |            |                    |                                      |   |
|   |             |             |                     |            |                    |                                      | 0.05 0.2 1 5 20                                   |
|   |             |             |                     |            |                    |                                      | Favours Britervention 2) Favours [Intervention 1] |

## **Return of Spontaneous Circulation (ROSC)**

| Study or Subgroup                                 | Interventi<br>Events |         | Intervent<br>Events |          | Weight | Risk Ratio<br>M-H, Random, 95% Cl | Risk Ratio<br>M-H, Random, 95% Cl                 |
|---|----------------------|---------|---------------------|----------|--------|-----------------------------------|---|
| 2.6.1 Amiodarone vs.                              |                      | Total   | Lionto              | Total    | molgin | in the random good of             |   |
| Kudenchuk, 2016                                   | 350                  | 974     | 396                 | 992      | 100.0% | 0.90 [0.80, 1.01]                 |   |
| Subtotal (95% CI)                                 | 000                  | 974     | 000                 |          | 100.0% | 0.90 [0.80, 1.01]                 | •   |
| Total events                                      | 350                  |         | 396                 |          |        |                                   |   |
| Heterogeneity: Not ap                             | plicable             |         |                     |          |        |                                   |   |
| Test for overall effect:                          | Z = 1.82 (P          | = 0.07) | )                   |          |        |                                   |   |
| 2.6.2 Amiodarone vs.                              | . Nifekalant         |         |                     |          |        |                                   |   |
| Amino, 2010                                       | 10                   | 15      | 7                   | 15       | 100.0% | 1.43 [0.75, 2.73]                 |   |
| Subtotal (95% CI)                                 |                      | 15      |                     | 15       | 100.0% | 1.43 [0.75, 2.73]                 | ★   |
| Total events                                      | 10                   |         | 7                   |          |        |                                   |   |
| Heterogeneity: Not ap                             | plicable             |         |                     |          |        |                                   |   |
| Test for overall effect:                          | Z=1.08 (P            | = 0.28) | )                   |          |        |                                   |   |
| 2.6.3 Lidocaine vs. B                             | retylium             |         |                     |          |        |                                   |   |
| Haynes, 1981                                      | 44                   | 74      | 42                  | 72       | 59.3%  | 1.02 [0.78, 1.34]                 |   |
| Olson, 1984                                       | 27                   | 48      | 15                  | 43       | 40.7%  | 1.61 [1.00, 2.60]                 |   |
| Subtotal (95% CI)                                 |                      | 122     |                     | 115      | 100.0% | 1.23 [0.78, 1.92]                 | *   |
| Total events                                      | 71                   |         | 57                  |          |        |                                   |   |
| Heterogeneity: Tau² =<br>Test for overall effect: |                      |         |                     | 0.10); l | ²= 64% |                                   |   |
| 2.6.4 Lidocaine vs. N                             | ifekalant            |         |                     |          |        |                                   |   |
| Igarashi, 2005                                    | 2                    | 14      | 5                   | 8        | 100.0% | 0.23 [0.06, 0.92]                 |   |
| Subtotal (95% CI)                                 |                      | 14      |                     | 8        | 100.0% | 0.23 [0.06, 0.92]                 |   |
| Total events                                      | 2                    |         | 5                   |          |        |                                   |   |
| Heterogeneity: Not ap                             | plicable             |         |                     |          |        |                                   |   |
| Test for overall effect:                          | Z = 2.08 (P          | = 0.04) | )                   |          |        |                                   |   |
| 2.6.5 Lidocaine vs. E                             | pinehrine            |         |                     |          |        |                                   |   |
| Weaver, 1990                                      | 51                   | 106     | 50                  | 93       | 100.0% | 0.89 [0.68, 1.18]                 |   |
| Subtotal (95% CI)                                 |                      | 106     |                     | 93       | 100.0% | 0.89 [0.68, 1.18]                 | ➡   |
| Total events                                      | 51                   |         | 50                  |          |        |                                   |   |
| Heterogeneity: Not ap                             | plicable             |         |                     |          |        |                                   |   |
| Test for overall effect:                          | Z=0.80 (P            | = 0.43) | )                   |          |        |                                   |   |
| 2.6.6 Lidocaine vs. S                             | otalol               |         |                     |          |        |                                   |   |
| Kovoor, 2005                                      | 26                   | 69      | 16                  | 60       | 100.0% | 1.41 [0.84, 2.37]                 | +   |
| Subtotal (95% CI)                                 |                      | 69      |                     | 60       | 100.0% | 1.41 [0.84, 2.37]                 | ★   |
| Total events                                      | 26                   |         | 16                  |          |        |                                   |   |
| Heterogeneity: Not ap                             | plicable             |         |                     |          |        |                                   |   |
| Test for overall effect:                          | Z=1.31 (P            | = 0.19) | )                   |          |        |                                   |   |
|   |                      |         |                     |          |        |                                   |   |
|   |                      |         |                     |          |        |                                   | 0.05 0.2 1 5 20                                   |
|   |                      |         |                     |          |        |                                   | Favours [Intervention 2] Favours [Intervention 1] |

#### **Recurrence of pVT/VF**



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

#### Survival to hospital discharge / 30 days (Observational studies)

| Study or Subgroup         | Interver<br>Events | Total       | Standar<br>Events | d care<br>Total | Weight           | Risk Ratio<br>M-H, Random, 95% Cl | Risk Ratio<br>M-H, Random, 95% Cl              |
|---------------------------|--------------------|-------------|-------------------|-----------------|------------------|-----------------------------------|--|
| 3.1.1 Amiodarone vs.      | Standard           | d care      |                   |                 | 200000000        |                                   |  |
| Huang, 2017               | 616                | 6459        | 611               | 18440           | 51.0%            | 2.88 [2.58, 3.21]                 |  |
| Skrifvars, 2004           | 21                 | 75          | 44                | 105             | 49.0%            | 0.67 [0.44, 1.02]                 |  |
| Subtotal (95% CI)         |                    | 6534        |                   | 18545           | 100.0%           | 1.41 [0.34, 5.89]                 |  |
| Total events              | 637                |             | 655               |                 |                  |                                   |  |
| Heterogeneity: Tau# =     | 1.04; Chi          | *= 42.2     | 1. df = 1 6       | P < 0.000       | 01); i* = 9      | 18 %                              |  |
| Test for overall effect:  |                    |             |                   | 0.00000000      | 1797.979.979.979 | (3,475)                           |  |
| 3.1.2 Lidocaine vs. St    | andard c           | are         |                   |                 |                  |                                   |  |
| Harrison, 1981            | 7                  | 62          | 1                 | 54              | 1.0%             | 6.10 (0.77, 47.99)                |  |
| Herlitz, 1997             | 26                 | 185         | 8                 | 105             | 7.3%             | 1.84 [0.87, 3.93]                 |  |
| Huang, 2017               | 90                 | 1077        | 611               | 18440           | 91.8%            | 2.52 [2.04, 3.12]                 |  |
| Subtotal (95% Cl)         | 50                 | 1324        | 011               | 18599           | 100.0%           | 2.49 [2.03, 3.05]                 |  |
| Total events              | 123                |             | 620               | 100000          |                  | Bran Decemptores                  |  |
| Heterogeneity: Tau# =     |                    | 2- 1 OA     |                   | - 0.6111        | # - 0.9K         |                                   |  |
| Test for overall effect . |                    |             |                   | -0.517,1        | - 0 %            |                                   |  |
| 3.1.3 Amiodarone plu      | s Lidocai          | ne vs 4     | Standard          | care            |                  |                                   |  |
| Huang, 2017               | 197                | 1487        | 511               |                 | 100.0%           | 4.00 [3.44, 4.65]                 |  |
| Subtotal (95% CI)         | 197                | 1487        | - 314             |                 | 100.0%           | 4.00 [3.44, 4.65]                 | •  |
| Total events              | 197                |             | 611               |                 |                  |                                   |  |
| Heterogeneity. Not app    | plicable           |             |                   |                 |                  |                                   |  |
| Test for overall effect . | Z = 17.91          | (P < 0.0    | 00001)            |                 |                  |                                   |  |
| 3.1.4 Procainamide v      | s. Standa          | rd care     | N                 |                 |                  |                                   | 1.000  |
| Markel, 2010              | 33                 | 176         | 156               | 489             | 100.0%           | 0.59 [0.42, 0.82]                 |  |
| Subtotal (95% CI)         |                    | 176         |                   | 489             | 100.0%           | 0.59 [0.42, 0.82]                 | •  |
| Total events              | 33                 |             | 156               |                 |                  |                                   |  |
| Heterogeneity: Not ap     | plicable           |             |                   |                 |                  |                                   |  |
| Test for overall effect . | Z = 3.12 (         | P = 0.00    | )2)               |                 |                  |                                   |  |
| 3.1.5 Magnesium vs.       | Standard           | care        |                   |                 |                  |                                   |  |
| Miller, 1995              | 2                  | 29          | 2                 | 33              | 100.0%           | 1.14 (0.17, 7.57)                 |  |
| Subtotal (95% Cl)         | - D                | 29          |                   |                 | 100.0%           | 1.14 [0.17, 7.57]                 |  |
| Total events              | 2                  |             | 2                 |                 |                  |                                   |  |
| Heterogeneity: Not ap     | nlicable           |             | -                 |                 |                  |                                   |  |
| Test for overall effect : |                    | P = 0.89    | 3)                |                 |                  |                                   |  |
| 3.1.6 Bretyllum vs. St    | andard ca          | are         |                   |                 |                  |                                   |  |
| Stang, 1984               | 8                  | 35          | 1                 | 16              | 100.0%           | 3.66 10.50, 26.831                |  |
| Subtotal (95% CI)         | - T.               | 35          |                   | 16              |                  | 3.66 [0.50, 26.83]                |  |
| Total events              | 8                  | 0550        | 1                 |                 | 0.05424040       |                                   |  |
| Heterogeneity: Not ap     |                    |             |                   |                 |                  |                                   |  |
| Test for overall effect.  |                    | P = 0.20    | 15                |                 |                  |                                   |  |
| reactor overall effect.   | - 1.20 (           | -0.20       | 2                 |                 |                  |                                   | 10 N   |
|                           |                    |             |                   |                 |                  |                                   |  |
|                           |                    |             |                   |                 |                  |                                   | 0.02 0.1 10                                    |
| Test for subgroup diffe   |                    | 22/12/12/21 |                   |                 |                  |                                   | Favours [Standard care] Favours [Intervention] |

Test for subgroup differences: Chi#= 108.22, df = 5 (P < 0.00001), I#= 95.4%

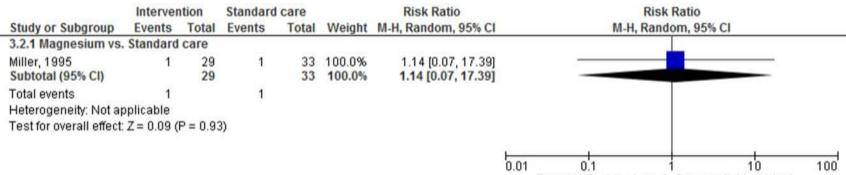
## Long term survival (1 year; Observational studies)

|   | Interver         | ntion        | Standar      | d care         |                  | Risk Ratio                             | Risk Ratio  |
|---|------------------|--------------|--------------|----------------|------------------|--|---|
| Study or Subgroup   | Events           | Total        | Events       | Total          | Weight           | M-H, Random, 95% CI                    | M-H, Random, 95% CI   |
| 3.3.1 Amiodarone vs   | . Standard       | d care       |              |                |                  |  | <u></u>   |
| Huang, 2017<br>Subtotal (95% CI)                                  | 534              | 6459<br>6459 | 602          | 18440<br>18440 | 100.0%<br>100.0% | 2.53 [2.26, 2.84]<br>2.53 [2.26, 2.84] |   |
| Total events<br>Heterogeneity: Not ap                             | 534<br>Inlicable |              | 602          |                |                  |  |   |
| Test for overall effect:  |                  | (P < 0.0     | 00001)       |                |                  |  |   |
|   |                  |              |              |                |                  |  |   |
| 3.3.2 Lidocaine vs. S   | tandard c        | are          |              |                |                  |  |   |
| Huang, 2017<br>Subtotal (95% CI)                                  | 77               | 1077<br>1077 | 602          | 18440<br>18440 |                  | 2.19 [1.74, 2.75]<br>2.19 [1.74, 2.75] |   |
| Total events<br>Heterogeneity: Not ap<br>Test for overall effect: |                  | P < 0.00     | 602<br>0001) |                |                  |  |   |
| 3.3.3 Amiodarone plu  | us Lidocai       | ine vs. S    | Standard     | care           |                  |  |   |
| Huang, 2017<br>Subtotal (95% CI)                                  | 165              | 1487<br>1487 | 602          | 18440<br>18440 | 100.0%<br>100.0% | 3.40 [2.89, 4.00]<br>3.40 [2.89, 4.00] | <b>‡</b>  |
| Total events<br>Heterogeneity: Not ap                             | 165<br>plicable  |              | 602          |                |                  |  |   |
| Test for overall effect:  | Z=14.63          | (P < 0.0     | 00001)       |                |                  |  |   |
| Test for subgroup diff  | erences:         | Chi² = 1     | 201 df=      | 2 (P = 0 )     | 102) IZ = 1      | 33.4%                                  | 0.2 0.5 1 2 5<br>Favours [Standard care] Favours [Intervention] |

## Return of Spontaneous Circulation (ROSC; Observational studies)

| 23.227 2.227   | Interven  | 12.25    | Standard    |            |        | Risk Ratio                             | Risk Ratio                                     |
|--|---|----------|-------------|------------|--------|--|--|
| Study or Subgroup  | and the second se | Total    | Events      | Total      | Weight | M-H, Random, 95% CI                    | M-H, Random, 95% Cl                            |
| 3.5.1 Amiodarone vs.   | Standard  | care     |             |            |        |  |  |
| Skrifvars, 2004<br>Subtotal (95% CI)                         | 46  | 75<br>75 | 70          |            | 100.0% | 0.92 [0.73, 1.15]<br>0.92 [0.73, 1.15] |  |
| Total events   | 46  |          | 70          |            |        |  |  |
| Heterogeneity: Not ap  | plicable  |          |             |            |        |  |  |
| Test for overall effect.                                     | Z = 0.73 (F   | 9 = 0.47 | )           |            |        |  |  |
| 3.5.2 Lidocaine vs. St                                       | andard ca   | ire      |             |            |        |  |  |
| Harrison, 1981   | 13  | 62       | 9           | 54         | 23.0%  | 1.26 [0.58, 2.71]                      |  |
| Herlitz, 1997  | 83  | 185      | 25          | 105        | 40.8%  | 1.88 [1.29, 2.75]                      |  |
| van Walraven, 1998   | 14  | 53       | 194         | 683        | 36.2%  | 0.93 [0.58, 1.48]                      |  |
| Subtotal (95% CI)  |   | 300      |             | 842        | 100.0% | 1.33 [0.82, 2.16]                      | -  |
| Total events   | 110   |          | 228         |            |        |  | 2 C  |
| Heterogeneity: Tau* =  | 0.11; ChP   | = 5,43,  | df = 2 (P = | 0.07); 1   | °= 63% |  |  |
| Test for overall effect:                                     | Z = 1.15 (F   | 9 = 0.25 | )           |            |        |  |  |
| 3.5.4 Procainamide v   | s. Standar  | d care   |             |            |        |  |  |
| Markel, 2010   | 80  | 176      | 305         | 489        | 100.0% | 0.73 [0.61, 0.87]                      |  |
| Subtotal (95% CI)  |   | 176      |             | 489        | 100.0% | 0.73 [0.61, 0.87]                      |  |
| Total events   | 80  |          | 305         |            |        |  |  |
| Heterogeneity: Not ap  | plicable  |          |             |            |        |  |  |
| Test for overall effect:                                     | Z = 3.53 (F   | 2 = 0.00 | 04)         |            |        |  |  |
| 3.5.5 Magnesium vs.  | Standard  | care     |             |            |        |  |  |
| Miller, 1995   | 10  | 29       | 7           | 33         | 100.0% | 1.63 [0.71, 3.72]                      |  |
| Subtotal (95% Cl)  |   | 29       |             | 33         | 100.0% | 1.63 [0.71, 3.72]                      |  |
| Total events   | 10  |          | 7           |            |        |  |  |
| Heterogeneity: Not ap  | plicable  |          |             |            |        |  |  |
| Test for overall effect:                                     | Z = 1.15 (F   | 2 = 0.25 | )           |            |        |  |  |
| 3.5.6 Bretylium vs. St                                       | andard ca   | re       |             |            |        |  |  |
| Stang, 1984  | 11  | 35       | 1           | 16         | 34.5%  | 5.03 (0.71, 35.69)                     |  |
| van Walraven, 1998   | 14  | 53       | 194         | 683        | 65.5%  | 0.93 [0.58, 1.48]                      |  |
| Subtotal (95% CI)  |   | 88       |             | 699        | 100.0% | 1.66 [0.33, 8.44]                      |  |
| Total events   | 25  |          | 195         |            |        |  |  |
| Heterogeneity: Tau <sup>a</sup> =<br>Test for overall effect |   |          |             | = 0.09); ł | *= 65% |  |  |
|  |   |          |             |            |        |  | V V V V V                                      |
|  |   |          |             |            |        | 1                                      | 0.05 0.2 1 5 20                                |
|  |   |          |             |            |        |  | Favours [Standard care] Favours [Intervention] |

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



Favours [Standard care] Favours [Intervention]

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

|  | Intervent              |            | Interven         |                |              | Risk Ratio  | Risk Ratio                            |
|--|------------------------|------------|------------------|----------------|--------------|---|---------------------------------------|
| study or Subgroup  | Events                 | Total      | Events           | Total          | Weight       | M-H, Random, 95% Cl                                   | M-H, Random, 95% Cl                   |
| 1.1.1 Amiodarone vs.   | Lidocaine              |            |                  |                |              |   |                                       |
| Golver, 2012   | 64                     | 582        | 195              | 1299           | 22.1%        | 0.73 [0.56, 0.95]                                     |                                       |
| Huang, 2017  | 616                    | 6459       | 90               | 1077           | 26.0%        | 1.14 [0.92, 1.41]                                     |                                       |
| Pollak, 2006   | 1.3                    | 36         | 31               | 55             | 11.0%        | 0.64 [0.39, 1.05]                                     |                                       |
| Rea, 2006  | 29                     | 74         | 36               | 79             | 15.8%        | 0.86 (0.59, 1.25)                                     |                                       |
| Fagami, 2016   | 122                    | 801        | 137              | 801            | 25.1%        | 0.89 [0.71, 1.11]                                     |                                       |
| Subtotal (95% CI)  |                        | 7952       | 1.004            | 3311           |              | 0.87 [0.72, 1.06]                                     |                                       |
|  | 844                    |            | 489              |                | 100000       | eres fersai steat                                     |                                       |
| Total events   |                        |            |                  |                |              |   |                                       |
| leterogeneity: Tau# =<br>'est for overall effect             |                        |            |                  | 0.06);1        | -= 20%       |   |                                       |
| I.1.2 Amiodarone vs.   | Nifekalant             | i          |                  |                |              |   |                                       |
| Harayama, 2014   | 2                      | 11         | 4                | 15             | 2.8%         | 0.68 [0.15, 3.08]                                     |                                       |
| Tagami, 2016   | 94                     | 525        | 97               | 525            | 97.2%        | 0.97 [0.75, 1.25]                                     |                                       |
| Subtotal (95% Cl)  | 184                    | 536        | in the second    | 540            | 100.0%       | 0.96 [0.75, 1.24]                                     | •                                     |
| otal events  | 96                     |            | 101              |                |              | 00000000000000000000000000000000000000                |                                       |
| feterogeneity: Tau*=   |                        | 0.20       |                  | 0.665          | 5 × 0.96     |   |                                       |
| est for overall effect.                                      |                        |            |                  | - or a capt, i | - 0.10       |   |                                       |
| 1.1.3 Lidocaine vs. Ni                                       |                        |            |                  |                |              |   |                                       |
| Shiga, 2010  | 0                      | 28         | 12               | 27             | 44.6%        | 0.64 (0.31, 1.32)                                     |                                       |
| fahara, 2006   | 14                     | 65         | 14               | 55             | 55.4%        | 0.85 [0.44, 1.62]                                     |                                       |
| Subtotal (95% CI)  |                        | 93         |                  | 82             | 100.0%       | 0.75 [0.46, 1.21]                                     |                                       |
| Total events   | 22                     |            | 26               |                |              |   |                                       |
| leterogeneity: Tau <sup>a</sup> =                            | 0.00; Chi*             | = 0.31.    | $df = T 0^{p} =$ | 0.58);1        | *= 0%        |   |                                       |
| est for overall effect                                       |                        |            |                  |                |              |   |                                       |
| .1.4 Lidocaine vs. Br  | retylium               |            |                  |                |              |   |                                       |
| Sbell, 1995  | 13                     | 210        | 10               |                | 100.0%       | 2.54 [0.34, 18.97]                                    |                                       |
| Subtotal (95% Cl)  |                        | 210        |                  | 41             | 100.0%       | 2.54 [0.34, 18.87]                                    |                                       |
| Total events   | 13                     |            | 1                |                |              |   |                                       |
| Heterogeneity: Not ap  | plicable.              |            |                  |                |              |   |                                       |
| Fest for overall effect.                                     |                        | = 0.36)    | )                |                |              |   |                                       |
| 1.1.5 Lidocaine vs. Pr                                       | rocainamid             | 10         |                  |                |              |   | · · · · · · · · · · · · · · · · · · · |
| Stiell, 1995   | 13                     | 210        | 4                | 20             | 100.0%       | 0.31 (0.11, 0.86)                                     |                                       |
| Subtotal (95% CI)  | 1664.5                 | 210        |                  | 20             | 100.0%       | 0.31 [0.11, 0.86]                                     |                                       |
| Total events   | 13                     |            | 4                |                |              | <ul> <li>Antonio Contractina (Contractina)</li> </ul> |                                       |
| seterogeneity: Not ap  | plicable               |            |                  |                |              |   |                                       |
| Fest for overall effect:                                     | Z= 2.25 (P             | = 0.02     |                  |                |              |   |                                       |
| .1.6 Amiodarone plu  |                        |            |                  |                | 1000         |   |                                       |
| luang, 2017  | 197                    | 1487       | 616              | 6459           | 83.2%        | 1.39 [1.20, 1.61]                                     |                                       |
| Rea, 2005<br>Subtotal (95% CB                                | 17                     | 41<br>1528 | 29               | 74<br>6533     | 16.8%        | 1.06 [0.67, 1.68]<br>1.33 [1.09, 1.62]                | •                                     |
| fotal events   | 214                    | 10.04      | 645              | 0.2532         | 0.0000000000 |   |                                       |
| Heterogeneity: Tau*=   |                        | - 1.22     |                  | 0.2201         | 1000         |   |                                       |
| fest for overall effect.                                     |                        |            |                  | 0.213,1        | - 10%        |   |                                       |
| .1.7 Amiodarone plu  | s Lidocain             | e va. Li   | docaine          |                |              |   |                                       |
| luang, 2017  | 197                    | 1487       | 90               | 1077           | 55.5%        | 1.59 (1.25, 2.01)                                     |                                       |
| Rea, 2006  | 17                     | 41         | 36               | 79             | 44.5%        | 0.91 (0.59, 1.41)                                     |                                       |
| Subtotal (95% CI)  |                        | 1528       |                  | 1156           | 100.0%       | 1.24 [0.71, 2.14]                                     |                                       |
| Total events   | 214                    |            | 126              |                |              | the second second                                     |                                       |
| Heterogeneity: Tau <sup>a</sup> =<br>Fest for overall effect | 0.13; Chi <sup>a</sup> |            | df=1 (P =        | 0.03); 1       | *= 80%       |   |                                       |
|  |                        |            |                  |                |              |   | ar 10                                 |
|  |                        |            |                  |                |              |   | 0.05 0.2 5                            |
|  |                        |            |                  |                |              |   |                                       |

#### Survival to hospital discharge / 30 days (Observational studies)

Test for subaroup differences: Chi# = 17.43, df = 6 (P = 0.008), I# = 65.6%

## Long term survival (1 year; Observational studies)

|                                       | Intervent        | tion 1       | Interven   | tion 2       |                  | Risk Ratio                             |     | Risk Ratio  |
|---------------------------------------|------------------|--------------|------------|--------------|------------------|--|-----|---|
| Study or Subgroup                     | Events           | Total        | Events     | Total        | Weight           | M-H, Random, 95% CI                    |     | M-H, Random, 95% Cl                               |
| 4.3.1 Amiodarone vs                   | . Lidocaine      | е            |            |              |                  |  |     |   |
| Huang, 2017<br>Subtotal (95% CI)      | 534              | 6459<br>6459 | 77         | 1077<br>1077 | 100.0%<br>100.0% | 1.16 [0.92, 1.46]<br>1.16 [0.92, 1.46] |     |   |
| Total events                          | 534              |              | 77         |              |                  |  |     |   |
| Heterogeneity: Not ap                 | oplicable        |              |            |              |                  |  |     |   |
| Test for overall effect:              | Z=1.24 (F        | P = 0.22     | )          |              |                  |  |     |   |
| 4.3.2 Amiodarone plu                  | us Lidocaii      | ne vs. A     | miodaron   | e            |                  |  |     |   |
| Huang, 2017<br>Subtotal (95% CI)      | 165              | 1487<br>1487 | 534        | 6459<br>6459 | 100.0%<br>100.0% | 1.34 [1.14, 1.58]<br>1.34 [1.14, 1.58] |     |   |
| Total events<br>Heterogeneity: Not ap | 165<br>oplicable |              | 534        |              |                  |  |     |   |
| Test for overall effect:              | Z = 3.49 (F      | P = 0.00     | 05)        |              |                  |  |     |   |
| 4.3.3 Amiodarone plu                  | us Lidocai       | ne vs. Li    | idocaine   |              |                  |  |     |   |
| Huang, 2017<br>Subtotal (95% CI)      | 165              | 1487<br>1487 | 77         | 1077<br>1077 | 100.0%<br>100.0% | 1.55 [1.20, 2.01]<br>1.55 [1.20, 2.01] |     |   |
| Total events<br>Heterogeneity: Not ap | 165<br>plicable  |              | 77         |              |                  |  |     |   |
| Test for overall effect:              |                  | P = 0.00     | 09)        |              |                  |  |     |   |
|                                       |                  |              |            |              |                  |  | -   |   |
|                                       |                  |              |            |              |                  |  | 0.1 | 0.2 0.5 1 2 5 1                                   |
| Test for subgroup diff                | ferences: C      | Chi² = 2.    | 80, df = 2 | (P = 0.25    | 5), I² = 28.     | 5%                                     |     | Favours [Intervention 2] Favours [Intervention 1] |

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## Return of Spontaneous Circulation (ROSC; Observational studies)

|                          | Intervent                 |           | Interven    |            | 12201212          | Risk Ratio          | Risk Ratio   |
|--------------------------|---------------------------|-----------|-------------|------------|-------------------|---------------------|--|
| Study or Subgroup        | Events                    |           | Events      | Total      | Weight            | M-H, Random, 95% CI | M-H, Random, 95% CI  |
| 4.4.1 Amiodarone vs.     | Lidocaine                 | 11.<br>   |             |            |                   |                     |  |
| Amino, 2015              | 205                       | 380       | 41          | 73         | 32.9%             | 0.96 [0.77, 1.20]   | and the second sec |
| Golver, 2012             | 128                       | 582       | 429         | 1299       | 37.3%             | 0.67 [0.56, 0.79]   |  |
| Pollak, 2006             | 24                        | 36        | 46          | 55         | 29.8%             | 0.80 [0.62, 1.03]   |  |
| Subtotal (95% CI)        |                           | 998       |             | 1427       | 100.0%            | 0.79 [0.63, 1.00]   | -  |
| Total events             | 357                       |           | 516         |            |                   |                     |  |
| Heterogeneity: Tau* =    | 0.03; Chi <sup>a</sup>    | = 7.24,   | df = 2 (P = | 0.03); P   | = 72%             |                     |  |
| Test for overall effect  | Z=1.92 (P                 | e = 0.05) |             |            |                   |                     |  |
| 4.4.2 Amiodarone vs.     | Nifekalan                 | t         |             |            |                   |                     |  |
| Amino, 2015              | 205                       | 380       | 25          | 47         | 6.5%              | 1.01 [0.76, 1.35]   |  |
| Harayama, 2014           | 4                         | 11        | 5           | 15         | 0.5%              | 1.09 (0.38, 3.15)   |  |
| Tagami, 2016             | 364                       | 525       | 397         | 525        | 93.1%             | 0.92 [0.85, 0.99]   |  |
| Subtotal (95% CI)        | 304                       | 916       | 291         | 587        | 93.1%             | 0.92 [0.86, 0.99]   |  |
| Total events             | 573                       | 2.0       | 427         |            | 1000018           | antic forage angol  |  |
| Heterogeneity: Tau# =    | Contraction of the second | - 0.67    |             | 0.763      | - 0%              |                     |  |
| Test for overall effect. |                           |           |             | 0.101,1    | = 0.46            |                     |  |
| rear for overall ellect  | L= 2.10 (P                | = 0.03)   |             |            |                   |                     |  |
| 4.4.3 Lidocaine vs. N    | ifekalant                 |           |             |            |                   |                     | 10.7   |
| Amino, 2015              | 41                        | 73        | 25          | 47         | 34.5%             | 1.06 [0.75, 1.48]   |  |
| Shiga, 2010              | 15                        | 28        | 23          | 27         | 32.4%             | 0.63 [0.43, 0.92]   |  |
| Tahara, 2006             | 24                        | 65        | 37          | 55         | 33.0%             | 0.55 [0.38, 0.79]   |  |
| Subtotal (95% CI)        |                           | 166       |             | 129        | 100.0%            | 0.72 [0.48, 1.08]   |  |
| Total events             | 80                        |           | 85          |            |                   |                     |  |
| Heterogeneity: Tau* =    | 0.09; Chi*                | = 7.54,   | df = 2 (P = | = 0.02); P | = 73%             |                     |  |
| Test for overall effect  | Z=1.60 (F                 | P= 0.11   | )           |            |                   |                     |  |
| 4.4.4 Lidocaine vs. B    | retylium                  |           |             |            |                   |                     |  |
| Stiell, 1995             | 58                        | 210       | 5           | 41         | 40.2%             | 2.26 [0.97, 5.30]   |  |
| van Walraven, 1998       | 59                        | 214       | 14          | 53         | 59.8%             | 1.04 [0.63, 1.72]   |  |
| Subtotal (95% CI)        | 56                        | 424       |             | 94         | 100.0%            | 1.43 [0.66, 3.06]   |  |
| Total events             | 117                       |           | 19          | 2.7        | And Street Street |                     |  |
| Heterogeneity: Tau* =    | 0.19; Chi#                | = 2.50.   | df = 1 (P = | 0.11): P   | = 60%             |                     |  |
| Test for overall effect  |                           |           |             | 331.21     | 19-67-68          |                     |  |
| 4.4.5 Lidocaine vs. P    | rocainamie                | de        |             |            |                   |                     |  |
| Stiell, 1995             | 58                        | 210       | 10          | 20         | 100.0%            | 0.55 [0.34, 0.90]   |  |
| Subtotal (95% CI)        | 50                        | 210       | .0          |            | 100.0%            | 0.55 [0.34, 0.90]   |  |
| Total events             | 58                        |           | 10          |            |                   |                     |  |
| Heterogeneity: Not ap    | 0.0 10705                 |           | 1.5176      |            |                   |                     |  |
| Test for overall effect  |                           | 2 = 0.02  | 5           |            |                   |                     |  |
| reactor overall chect    |                           | 50.02     |             |            |                   |                     |  |
|                          |                           |           |             |            |                   |                     |  |
|                          |                           |           |             |            |                   | (                   | 0.2 0.5 1 2 5  |
| Test for subaroup diff   | 2001/09/102               |           |             |            |                   | 199<br>199          | Favours (Intervention 2) Favours (Intervention 1)  |

Test for subgroup differences: Chi# = 7.99, df = 4 (P = 0.09), I# = 50.0%

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

|   | Intervent   | tion 1          | Intervent | tion 2    |                  | <b>Risk Ratio</b>                      | Risk Ratio  |
|---|-------------|-----------------|-----------|-----------|------------------|--|---|
| Study or Subgroup   | Events      | Total           | Events    | Total     | Weight           | M-H, Random, 95% Cl                    | M-H, Random, 95% CI   |
| 4.2.1 Amiodarone vs   | . Nifekalan | t               |           |           |                  |  | 54 - 10   |
| Harayama, 2014<br>Subtotal (95% CI)                               | 0           | 11<br><b>11</b> | 2         | 15<br>15  | 100.0%<br>100.0% | 0.27 [0.01, 5.06]<br>0.27 [0.01, 5.06] |   |
| Total events<br>Heterogeneity: Not ap<br>Test for overall effect: |             | P = 0.38        | 2         |           |                  |  |   |
| 4.2.2 Lidocaine vs. N   | ifekalant   |                 |           |           |                  |  |   |
| Tahara, 2006<br>Subtotal (95% CI)                                 | 2           | 65<br>65        | 4         | 55<br>55  | 100.0%<br>100.0% | 0.42 [0.08, 2.22]<br>0.42 [0.08, 2.22] |   |
| Total events<br>Heterogeneity: Not ap<br>Test for overall effect: |             | P = 0.31        | 4         |           |                  |  |   |
| Test for subaroup diff  | ferences: C | :hi² = 0        | 07 df=1   | (P = 0.79 | a) I² = 0%       |  | 0.005 0.1 1 10 200<br>Favours [Intervention 2] Favours [Intervention 1] |

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

|                                   | Interven       | tion       | Standard   | care       |                       | <b>Risk Ratio</b>                      | Risk Ratio                                     |
|-----------------------------------|----------------|------------|------------|------------|-----------------------|--|--|
| Study or Subgroup                 | Events         | Total      | Events     | Total      | Weight                | M-H, Random, 95% CI                    | M-H, Random, 95% CI                            |
| 3.5.1 Amiodarone vs               | s. Standard    | l care     |            |            |                       |  |  |
| Valdes, 2014<br>Subtotal (95% Cl) | 15             | 89<br>89   | 103        | 505<br>505 | 100.0%<br>100.0%      | 0.83 [0.50, 1.35]<br>0.83 [0.50, 1.35] |  |
| Total events                      | 15             |            | 103        |            |                       |  |  |
| Heterogeneity: Not a              | pplicable      |            |            |            |                       |  |  |
| Test for overall effect           | t: Z = 0.76 (I | P = 0.45   | 5)         |            |                       |  |  |
| 3.5.2 Lidocaine vs. S             | Standard ca    | are        |            |            |                       |  |  |
| Valdes, 2014<br>Subtotal (95% CI) | 54             | 213<br>213 | 103        | 505<br>505 | 100.0%<br>100.0%      | 1.24 [0.93, 1.66]<br>1.24 [0.93, 1.66] |  |
| Total events                      | 54             |            | 103        |            |                       |  |  |
| Heterogeneity: Not a              | pplicable      |            |            |            |                       |  |  |
| Test for overall effect           | t: Z = 1.48 (I | P = 0.14   | 4)         |            |                       |  |  |
| 3.5.3 Amiodarone pl               | lus Lidocai    | ne vs. S   | Standard c | are        |                       |  |  |
| Valdes, 2014<br>Subtotal (95% CI) | 22             | 82<br>82   | 103        | 505<br>505 | 100.0%<br>100.0%      | 1.32 [0.88, 1.96]<br>1.32 [0.88, 1.96] |  |
| Total events                      | 22             |            | 103        |            |                       |  |  |
| Heterogeneity: Not a              | pplicable      |            |            |            |                       |  |  |
| Test for overall effect           | t: Z = 1.35 (I | P = 0.18   | 3)         |            |                       |  |  |
|                                   |                |            |            |            |                       |  |  |
|                                   |                |            |            |            |                       |  | 0.1 0.2 0.5 1 2 5 10                           |
| Test for subaroup di              | fforoncos: (   | `hi² = 2   | 42  df = 2 | (P = 0.3)  | ) I <sup>2</sup> = 17 | 20%                                    | Favours [Standard care] Favours [Intervention] |

Test for subgroup differences: Chi<sup>2</sup> = 2.42, df = 2 (P = 0.30), l<sup>2</sup> = 17.3%

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

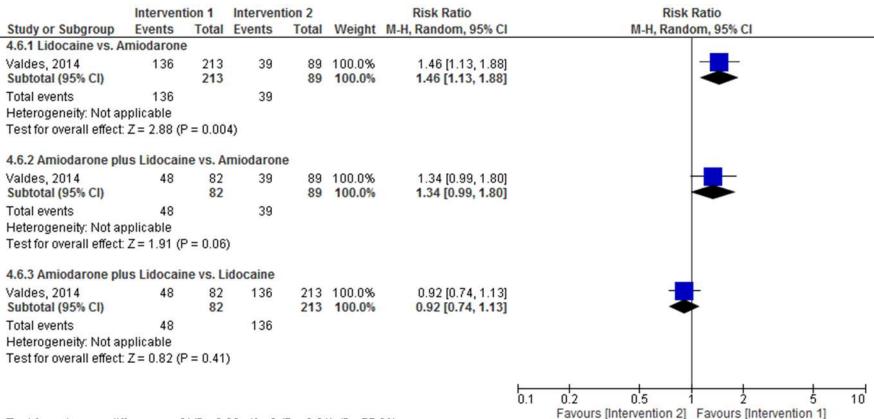
|                                       | Interven         | tion       | Standard   | care       |                  | <b>Risk Ratio</b>                      | Risk Ratio                                     |
|---------------------------------------|------------------|------------|------------|------------|------------------|--|--|
| Study or Subgroup                     | Events           | Total      | Events     | Total      | Weight           | M-H, Random, 95% CI                    | M-H, Random, 95% CI                            |
| 3.6.1 Amiodarone vs                   | . Standard       | care       |            |            | 1.11             |  |  |
| Valdes, 2014<br>Subtotal (95% CI)     | 39               | 89<br>89   | 260        | 505<br>505 | 100.0%<br>100.0% | 0.85 [0.66, 1.09]<br>0.85 [0.66, 1.09] |  |
| Total events                          | 39               |            | 260        |            |                  |  |  |
| Heterogeneity: Not ap                 | oplicable        |            |            |            |                  |  |  |
| Test for overall effect               | Z = 1.26 (I      | P = 0.21   | )          |            |                  |  |  |
| 3.6.2 Lidocaine vs. S                 | tandard ca       | are        |            |            |                  |  |  |
| Valdes, 2014<br>Subtotal (95% CI)     | 136              | 213<br>213 | 260        | 505<br>505 | 100.0%<br>100.0% | 1.24 [1.09, 1.41]<br>1.24 [1.09, 1.41] |  |
| Total events<br>Heterogeneity: Not ap | 136<br>Indicable |            | 260        |            |                  |  |  |
| Test for overall effect               |                  | P = 0.00   | 01)        |            |                  |  |  |
| 3.6.3 Amiodarone pl                   | us Lidocai       | ne vs. S   | standard c | are        |                  |  |  |
| Valdes, 2014<br>Subtotal (95% CI)     | 48               | 82<br>82   | 260        | 505<br>505 | 100.0%<br>100.0% | 1.14 [0.93, 1.39]<br>1.14 [0.93, 1.39] |  |
| Total events<br>Heterogeneity: Not ap | 48<br>Anlicable  |            | 260        |            |                  |  |  |
| Test for overall effect               |                  | P = 0.21   | )          |            |                  |  |  |
|                                       |                  |            |            |            |                  |  | 0.5 0.7 1 1.5 2                                |
|                                       |                  |            |            |            |                  |  | Favours [Standard care] Favours [Intervention] |

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

|                                   | Intervention 1 |            | Intervention 2 |          |                  | <b>Risk Ratio</b>                      | Risk Ratio  |
|-----------------------------------|----------------|------------|----------------|----------|------------------|--|---|
| Study or Subgroup                 | Events         | Total      | Events         | Total    | Weight           | M-H, Random, 95% Cl                    | M-H, Random, 95% Cl                               |
| 4.5.1 Lidocaine vs. A             | miodarone      | •          |                |          |                  |  |   |
| Valdes, 2014<br>Subtotal (95% Cl) | 54             | 213<br>213 | 15             | 89<br>89 | 100.0%<br>100.0% | 1.50 [0.90, 2.52]<br>1.50 [0.90, 2.52] |   |
| Total events                      | 54             |            | 15             |          |                  |  |   |
| Heterogeneity: Not ap             | pplicable      |            |                |          |                  |  |   |
| Test for overall effect           | : Z = 1.55 (F  | P = 0.12   | )              |          |                  |  |   |
| 4.5.2 Amiodarone pl               | us Lidocair    | ne vs. A   | miodaron       | е        |                  |  |   |
| Valdes, 2014<br>Subtotal (95% CI) | 22             | 82<br>82   | 15             | 89<br>89 | 100.0%<br>100.0% | 1.59 [0.89, 2.85]<br>1.59 [0.89, 2.85] |   |
| Total events                      | 22             |            | 15             |          |                  |  |   |
| Heterogeneity: Not ap             | pplicable      |            |                |          |                  |  |   |
| Test for overall effect           | : Z = 1.56 (F  | P = 0.12   | )              |          |                  |  |   |
| 4.5.3 Amiodarone pl               | us Lidocair    | ne vs. L   | idocaine       |          |                  |  |   |
| Valdes, 2014                      | 22             | 82         | 54             | 213      |                  | 1.06 [0.69, 1.62]                      |   |
| Subtotal (95% CI)                 |                | 82         |                | 213      | 100.0%           | 1.06 [0.69, 1.62]                      | -   |
| Total events                      | 22             |            | 54             |          |                  |  |   |
| Heterogeneity: Not a              |                |            |                |          |                  |  |   |
| Test for overall effect           | : Z = 0.26 (F  | r=0.79     | )              |          |                  |  |   |
|                                   |                |            |                |          |                  |  |   |
|                                   |                |            |                |          |                  |  | 0.05 0.2 1 5 20                                   |
| Test for subaroun dif             | foroncos: C    | hiz = 1    | 67 df - 2/     | P = 0.42 | 2) IZ - 0%       |  | Favours [Intervention 2] Favours [Intervention 1] |

Test for subgroup differences: Chi<sup>2</sup> = 1.67, df = 2 (P = 0.43), l<sup>2</sup> = 0%

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



Test for subgroup differences: Chi<sup>2</sup> = 8.80, df = 2 (P = 0.01), l<sup>2</sup> = 77.3%