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Efficacy of amiodarone and lidocaine for preventing ventricular fibrillation after aortic cross-clamp release in open heart surgery: a meta-analysis of randomized controlled trials

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Abstract: Objective: The relative preventative efficacy of amiodarone and lidocaine for ventricular fibrillation (VF) after release of an aortic cross-clamp (ACC) during open heart surgery has not been determined. This meta-analysis was designed to systematically evaluate the influence of amiodarone, lidocaine, or placebo on the incidence of VF after ACC. Methods: Prospective randomized controlled trials (RCTs) that compared the VF-preventative effects of amiodarone with lidocaine, or amiodarone or lidocaine with placebo were included. PubMed, EMBASE, and the Cochrane Library were searched for relevant RCTs. Fixed or randomized effect models were applied according to the heterogeneity of the data from the selected studies. Results: We included eight RCTs in the analysis. Pooled results suggested that the preventative effects of amiodarone and lidocaine were comparable (relative risk (RR)=1.12, 95% confidence interval (CI): 0.70 to 1.80, *P*=0.63), but both were superior to the placebo (amiodarone, RR=0.71, 95% CI: 0.51 to 1.00, *P*=0.05; lidocaine, RR=0.63, 95% CI: 0.46 to 0.88, *P*=0.006). The percentage of patients requiring electric defibrillation counter shocks (DCSs) did not differ significantly among patients administered amiodarone (RR=0.21, 95% CI: 0.04 to 1.19, *P*=0.08), lidocaine (RR=2.44, 95% CI: 0.13 to 44.02, *P*=0.55), or the placebo (RR=0.56, 95% CI: 0.25 to 1.25, *P*=0.16). Conclusions: Amiodarone and lidocaine are comparably effective in preventing VF after ACC, but the percentage of patients who subsequently require DCSs does not differ among those administered amiodarone, lidocaine, or placebo.

Key words: Amiodarone; Lidocaine; Ventricular fibrillation; Open heart surgery
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1 Introduction

Despite significant advancements in the treatment of cardiovascular diseases (Liu *et al*., 2010), open heart surgery remains one of the most important interventions for patients with severe cardiovascular diseases, such as those with multiple-vessel coronary

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heart diseases (CHD) (Verrier and Mack, 2015; Papakonstantinou *et al.*, 2017), severe valvular heart diseases (Geissler *et al.*, 2009), and complicated congenital heart diseases (Mery and Kane, 2017). With improvements in perioperative care and cardiopulmonary bypass (CPB) techniques, the indications for cardiac surgery have been expanded and many patients who were previously deemed to be contraindicated or intolerant to cardiac surgeries are now considered suitable for open heart surgery (Marathe and Talwar, 2015). However, patients who undergo cardiac surgery are still at risk of fatal complications associated with both the surgical procedures and CPB, such as major bleeding, infection, and most importantly, lethal arrhythmias, such as ventricular fibrillation (VF) (Shake *et al.*, 2013; Zhan *et al.*, 2015). Pathophysiologically, VF is associated with myocardial ischemia and reperfusion injury, and subsequent inflammatory responses, oxidative stress, and electrical instability (Yeh *et al.*, 2013; Patil *et al.*, 2015). VF occurs most frequently after aortic cross-clamp (ACC) release during the coronary artery bypass graft (CABG) procedure, when myocardium reperfusion is initiated (Leeuwenburgh *et al.*, 2008). The incidence of VF after ACC release is reported to vary with the experience of the surgeon and the category of surgical procedures, ranging from 45% to 90% in patients undergoing CABG (Leeuwenburgh *et al.*, 2008; Baravelli *et al.*, 2010). When VF occurs during cardiac surgery, the most effective treatment strategy is electric defibrillation counter shocks (DCSs). However, the success rate of DCSs for patients with VF during open heart cardiac surgery is not satisfactory. Moreover, even in patients for whom VF was successfully terminated after DCSs, the procedure is associated with potential secondary damage to the myocardium, possibly leading to cardiac dysfunction and recurrent lethal arrhythmia (Doherty *et al.*, 1979; Yamaguchi *et al.*, 2002). Therefore, prophylactic measures capable of reducing the risk of VF after ACC release in patients undergoing cardiac surgery are urgently sought to improve the prognosis of these patients.

Perioperative administration of conventional antiarrhythmic medications has been suggested for effective prevention of VF after ACC release in patients undergoing cardiac surgery (Hippelainen *et al.*, 1994; Schluter *et al.*, 2001). The capacity of two conventional antiarrhythmic medications, amiodarone and lidocaine, to prevent VF during cardiac surgery has been assessed clinically, but the results are contradictory. Two early studies concluded that a cardioplegic solution containing lidocaine can significantly reduce VF incidence by 22%–42% in patients undergoing cardiac surgery (Fiore *et al.*, 1990; Baraka *et al.*, 1993). Moreover, another study indicated that administration of lidocaine with a perfusion pump before ACC release reduced VF incidence from 70% to 11% (Baraka *et al.*, 2000). As for amiodarone, subsequent studies demonstrated that this medication may achieve comparable (Samantaray *et al.*, 2010) or even greater (Dorian *et al.*, 2002) preventative effects against VF in patients who are at risk for development of VF and pulseless ventricular tachycardia during cardiac surgery. In contrast, several other studies reported that neither amiodarone nor lidocaine effectively prevented VF in cardiac surgeries. A randomized controlled trial (RCT) conducted by Ayoub *et al.* (2009) concluded that VF incidence did not differ significantly between patients who received amiodarone and those who received placebo. Furthermore, a subsequent three-armed RCT reported no significant difference in VF incidence after ACC release in patients undergoing cardiac surgery who were administered amiodarone, lidocaine, or placebo (Ghavidel *et al.*, 2013). Many factors have been proposed to explain these inconsistencies in clinical trial results, including their inadequate statistical power produced by small numbers of patients. Therefore, in this study, we performed a meta-analysis of head-to-head RCTs to compare the capacity of amiodarone, lidocaine, and placebo to prevent VF after ACC release in patients undergoing cardiac surgery.

2 Materials and methods

2.1 Literature search

Our study followed the recommendations of the PRISMA 2009 checklist (Moher *et al.*, 2009) and the Cochrane Handbook for Systematic Reviews of Interventions 5.0.2. Electronic databases (PubMed, EMBASE, and Cochrane Central Register of Controlled Trials) were searched for relevant RCTs with the keywords amiodarone or lidocaine, paired with ventricular fibrillation or reperfusion. The language

was restricted to English and the final search was performed on August 25th, 2017. Moreover, the reference lists from the identified articles were manually searched for additional relevant studies. Two investigators (YZ, QG) independently reviewed the literature and articles fulfilling the following criteria were selected: (1) designed as an RCT; (2) included adult patients undergoing cardiac surgery requiring ACC; (3) patients were assigned to either 2 or 3 of the following interventional groups: amiodarone, lidocaine, or placebo; (4) reported outcome data included VF incidence or percentage of patients requiring electric DCSs. Reviews, case reports, retrospective studies, observational studies, or studies with unavailable outcome data were excluded.

2.2 Data extraction and quality assessment

We extracted data regarding patient demographics (age, gender), type of surgery, duration of ACC, and duration of CPB. Where possible we used intention-to-treat (ITT) data, but where this was unavailable we extracted data from tables or graphs in each article or retrieved data directly from authors. The quality of all selected studies was evaluated based on the Cochrane Back Review Group 12-item scale (Furlan *et al.*, 2015). Two reviewers (YZ, QG) independently extracted data and evaluated the quality of the RCTs, and any disagreements were resolved by consulting a third investigator (MX).

2.3 Statistical analysis

Dichotomous variables were assessed according to relative risk (RR) and 95% confidence interval (CI). The Cochrane's Q test and I^2 test were used to measure the statistical heterogeneity. I^2 values of 25%, 50%, and 75% were considered to indicate low, moderate, and high statistical heterogeneity, respectively. Random effect models were used to pool the results as these can incorporate the inherited heterogeneity among the studies. Subgroup analyses and meta-regression were performed to evaluate potential sources of heterogeneity if sufficient numbers of interventional groups were included. Publication bias among the included studies was analyzed by a funnel plot and Egger's regression test. All analyses were conducted with RevMan software (Review Manager, Version 5.3, the Cochrane Collaboration, Oxford, UK) and STATA software 12.0 (StataCorp, College Station, Texas, USA).

3 Results

3.1 Literature review

The initial search retrieved 4465 relevant citations (PubMed 1493, EMBASE 2634, and the Cochrane's Library 338), and finally 8 RCTs were included in our meta-analysis. The literature searching procedure is described in Fig. 1.

3.2 Quality assessment and characteristics of included studies

Overall, 8 RCTs were selected, which included a total of 839 patients: 249 treated with amiodarone, 288 treated with lidocaine, and 302 with placebo. All included studies were RCTs and, according to the item standard quality evaluation, five were classified as high-quality and the other three as moderate quality studies (Table 1). Among these studies, four were three-arm trials (Ayoub *et al.*, 2009; Mauermann *et al.*, 2012; Ghavidel *et al.*, 2013; Yilmaz *et al.*, 2014) of amiodarone versus lidocaine versus placebo, three compared lidocaine with placebo (Kirlangitis *et al.*, 1990; Baraka *et al.*, 2000; Vaziri *et al.*, 2010), and one compared amiodarone with placebo (Samantaray *et al.*, 2010). In all studies, all patients were scheduled to undergo elective surgery and were age-, gender-, and operative condition-matched (Table 2).

3.3 Effects of amiodarone and lidocaine on VF incidence after release of ACC

Four of the eight trials, including a total of 466 patients, directly compared the efficacy of amiodarone and lidocaine. The rate of VF after release of ACC did not differ significantly between patients treated with amiodarone and lidocaine (RR=1.12, 95% CI: 0.70 to 1.80, P=0.63; Fig. 2a). Moderate heterogeneity was observed (I^2=58%, P=0.07). Analysis of the pooled results of five RCTs including 498 patients revealed that amiodarone was associated with a lower risk of VF than placebo (RR=0.71, 95% CI: 0.51 to 1.00, P=0.05; Fig. 2b) with moderate heterogeneity (I^2=48%, P=0.11). Similarly, by pooling the results of seven RCTs including 473 patients, we observed that lidocaine was also significantly associated with lower VF risk (RR=0.63, 95% CI: 0.46 to 0.88, P=0.006; Fig. 2c) than placebo with moderate heterogeneity (I^2=54%, P=0.04). Due to the limited number of studies, subsequent subgroup and meta-regression analyses were not performed.

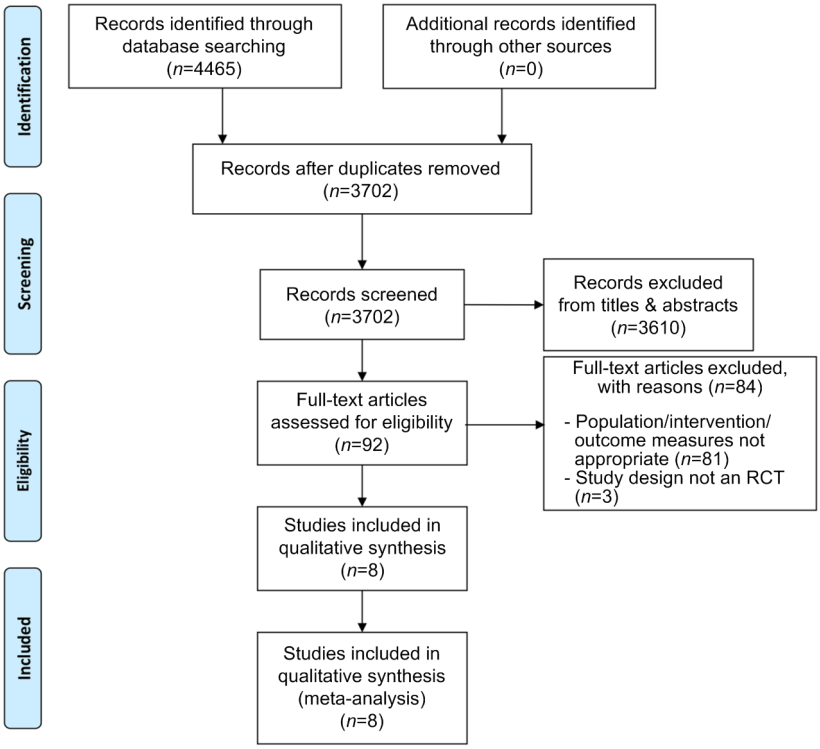

Fig. 1 Flow chart of the literature searching procedure

Table 1 Methodological quality of the included studies based on the 12-item scoring system

Study	Randomized adequately[a]	Allocation concealed	Patient blinded	Care provider blinded	Outcome assessor blinded	Acceptable drop-out rate[b]	ITT analysis[c]
Kirlangitis *et al*., 1990	No	No	Yes	Unsure	Unsure	Yes	No
Baraka *et al*., 2000	No	No	Yes	Unsure	Unsure	Yes	Yes
Ayoub *et al*., 2009	No	No	Yes	Unsure	Unsure	Yes	Yes
Samantaray *et al*., 2010	No	Yes	Yes	Unsure	Unsure	Yes	Yes
Vaziri *et al*., 2010	No	No	Yes	Unsure	Unsure	Yes	No
Mauermann *et al*., 2012	No	No	Yes	Unsure	Unsure	Yes	Yes
Ghavidel *et al*., 2013	No	No	Yes	Unsure	Unsure	Yes	Yes
Yilmaz *et al*., 2014	No	No	Yes	Unsure	No	Yes	Yes

Study	Avoided selective reporting	Similar baseline	Similar or avoided cofactor	Patient compliance	Similar timing	Quality[d]
Kirlangitis *et al*., 1990	Yes	Yes	Yes	Yes	Yes	Moderate
Baraka *et al*., 2000	Yes	Yes	Yes	Yes	Yes	High
Ayoub *et al*., 2009	Yes	Yes	Yes	Yes	Yes	High
Samantaray *et al*., 2010	Yes	Yes	Yes	Yes	Yes	High
Vaziri *et al*., 2010	Yes	Yes	Yes	Yes	Yes	Moderate
Mauermann *et al*., 2012	Yes	Yes	Yes	Yes	Yes	High
Ghavidel *et al*., 2013	Yes	Yes	Yes	Yes	Yes	High
Yilmaz *et al*., 2014	Yes	Yes	Yes	Yes	No	Moderate

[a] Only if the sequencing method was explicitly introduced was a study given a "Yes"; sequence generated by "Dates of Admission" or "Patient's Number" received a "No"; [b] Drop-out rates <20% were given a "Yes", otherwise "No"; [c] ITT: intention-to-treat; only if all randomized participants were analyzed in the group to which they were allocated was a study given a "Yes"; [d] Studies with more than 7 items were scored as "High"; those with more than 4, but no more than 7 items were scored as "Moderate"; those with no more than 4 items were scored as "Low"

Table 2 Demographic characteristics and intraoperative data of the included RCTs

Study	Age (year)*	Gender, male (%)	LVEF (%)	Type of surgery
Kirlangitis *et al*., 1990	None/(57.0±2.7)/(63.0±2.3)	None/81.8/81.8	None/(54.0±2.9)/(61±2.4)	CABG
Baraka *et al*., 1993	None/(60.8±10.8)/(58.5±12.7)	None/76.5/82.4	None/>60/>60	CABG
Ayoub *et al*., 2009	(63±9)/(64±9)/(65±10)	90/92.5/90	>35/>35/>35	CABG
Samantaray *et al*., 2010	(47.2±6.6)/none/(50.0±6.0)	64.7/none/70.6	>35/none/>35	CABG
Vaziri *et al*., 2010	None/(56.7±7.5)/(60.8±10.5)		None/>50/>50	CABG
Mauermann *et al*., 2012	(63.3±13.6)/(62.7±13.9)/(63.6±13.0)	74/81/82	(62.7±10.8)/(62.7±11.5)/(62.8±11.7)	CABG, Valve, and Myectomy
Ghavidel *et al*., 2013	(58.06±10.47)/(60.64±15.62)/(57.43±10.97)	78.4/80/86.4	(42.65±6.80)/(43.64±6.93)/(43.52±7.36)	CABG
Yilmaz *et al*., 2014	(57.2±7.9)/(61.6±8.6)/(59.7±9.8)	81/76/80	(53.2±10.3)/(52.8±9.0)/(52.5±9.0)	CABG

Study	pH	ACC time (min)	CPB time (min)
Kirlangitis *et al*., 1990	None/(7.41±0.02)/(7.49±0.02)	None/(56±4.6)/(54±7.3)	None/(119±12.5)/(103±10.5)
Baraka *et al*., 1993		None/(43.8±15.3)/(40.6±15.7)	None/(70.1±22.9)/(64.6±29.3)
Ayoub *et al*., 2009	(7.40±0.05)/(7.41±0.03)/(7.41±0.04)	(42.0±20.0)/(44.0±22.0)/(35.0±11.0)	(66.0±32.0)/(67.0±33.0)/(64.0±29.0)
Samantaray *et al*., 2010		(49.4±12.3)/none/(48.8±15.2)	(76.1±16.5)/none/(74.2±18.7)
Vaziri *et al*., 2010	None/(7.40±0.05)/(7.40±0.06)	None/(48.6±9.1)/(47.2±6.6)	
Mauermann *et al*., 2012		(47.4±32.1)/(46.5±56.1)/(53.3±36.8)	(70.8±64.0)/(74.3±40.0)/(78.0±48.7)
Ghavidel *et al*., 2013	(7.35±0.07)/(7.34±0.06)/(7.36±0.06)	(38.2±19.6)/(35.6±12.6)/(34.9±14.0)	(72.8±29.2)/(72.1±21.2)/(65.1±29.7)
Yilmaz *et al*., 2014	(7.40±0.04)/(7.50±0.51)/(7.40±0.06)	(67.6±19.7)/(64.1±18.9)/(63.2±8.8)	(104.1±31.3)/(113.6±27.8)/(114.4±27.6)

Study	Core temperature (time of cross clamp release) (°C)	Timing of electrical defibrillation	Timing of the medication given before ACC release (min)
Kirlangitis *et al*., 1990	24–28	RVF persist untreated for 1 min	None/5/5
Baraka *et al*., 1993	29	Lidocaine100 mg+DCSs	None/2/2
Ayoub *et al*., 2009	29	DCSs immediately after RVF	2/2/2
Samantaray *et al*., 2010	30	DCSs immediately after RVF	3/none/3
Vaziri *et al*., 2010	30–32	RVF persist untreated for 2 min	None/5/5
Mauermann *et al*., 2012	32	DCSs immediately after RVF	3/3/3
Ghavidel *et al*., 2013	34	DCSs immediately after RVF	3/3/3
Yilmaz *et al*., 2014	34	RVF persist untreated for 2 min	15/2/NA

Study	Dose of the medication given	Potassium (mEq/L) (during cross clamp)	Cardioplegia solution
Kirlangitis *et al*., 1990	None/(2 mg/kg)/constant volume		Crystalloid hyperkalemic cardioplegia
Baraka *et al*., 1993	None/100 mg/constant volume	None/(4.6±0.5)/(4.7±0.5)	Crystalloid hyperkalemic cardioplegia
Ayoub *et al*., 2009	150 mg/100 mg/constant volume	(4.7±1.0)/(4.8±0.5)/(4.9±0.5)	Crystalloid hyperkalemic cardioplegia
Samantaray *et al*., 2010	150 mg/none/constant volume	(4.4±0.3)/none/(4.5±0.5)	Crystalloid hyperkalemic cardioplegia
Vaziri *et al*., 2010	None/(1.5 mg/kg)/constant volume	None/(4.30±0.67)/(4.40±0.89)	
Mauermann *et al*., 2012	300 mg/(1.5 mg/kg)/constant volume		Crystalloid hyperkalemic cardioplegia
Ghavidel *et al*., 2013	150 mg/100 mg/constant volume	(4.10±0.44)/(4.11±0.42)/(4.24±0.47)	Retrograde St. Thomas solution
Yilmaz *et al*., 2014	300 mg/(1.5 mg/kg)/constant volume	(5.00±0.63)/(4.80±0.61)/(4.40±0.89)	Retrograde St. Thomas solution and crystalloid hyperkalemic cardioplegia

LVEF, left ventricular ejection fraction; NA, not available; None, no amiodarone or lidocaine or placebo in this study; CABG, coronary artery bypass graft; Valve, valve surgery; Myectomy, septal myectomy; ACC, aortic cross-clamp; CPB, cardiopulmonary bypass; RVF, reperfusion ventricular fibrillation; DCSs, defibrillation counter shocks. Data are presented as mean±standard deviation (SD). * From left to right, the data of amiodarone, lidocaine, and placebo, respectively

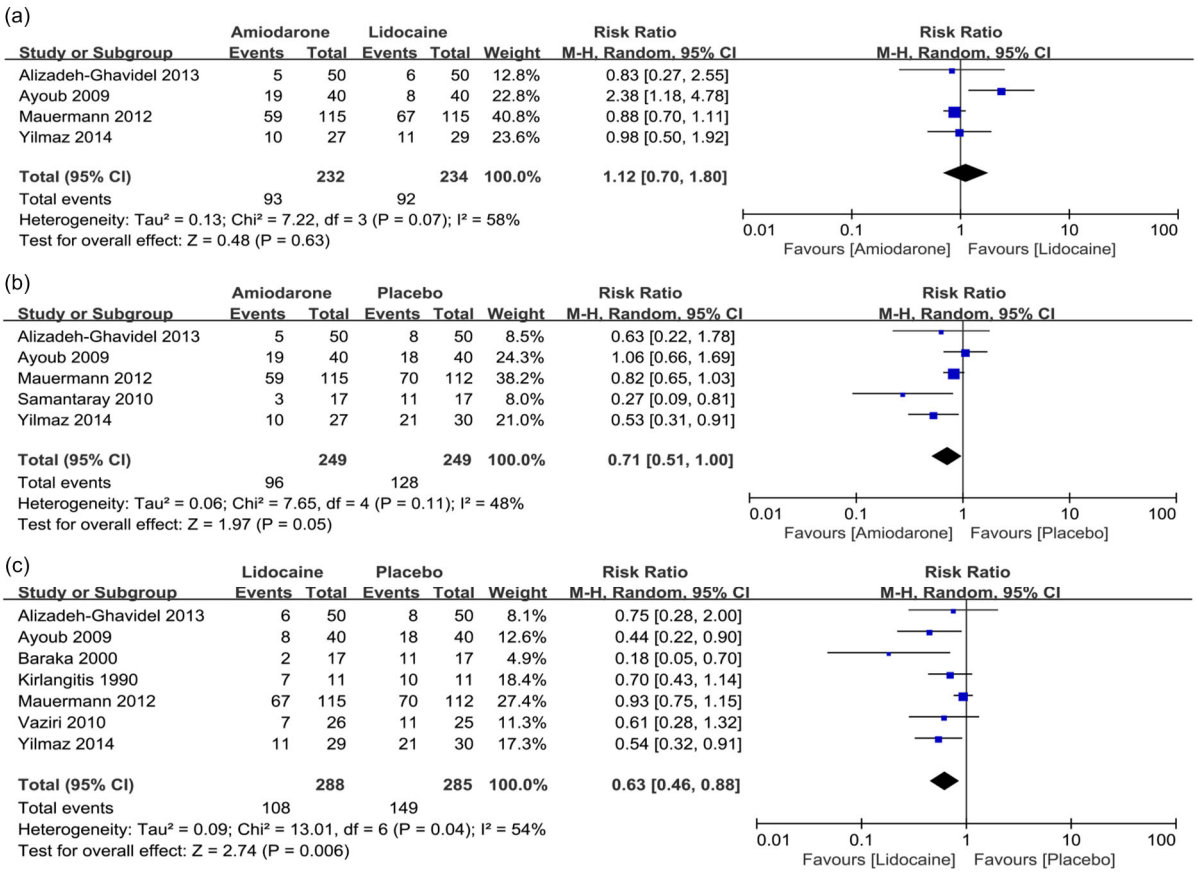

Fig. 2 Effects of amiodarone and lidocaine on ventricular fibrillation (VF) incidence after release of aortic cross-clamp (ACC)

The rate of VF after release of ACC did not differ significantly between patients undergoing open heart surgery who were treated with amiodarone or lidocaine (a); amiodarone (b) and lidocaine (c) were associated with a lower risk of VF than placebo

Publication bias was difficult to estimate due to the small number of comparisons included.

3.4 Effects of amiodarone and lidocaine on rate of DCSs after release of ACC

Three of the eight trials including a total of 214 patients compared the percentage of patients requiring DCSs for VF. Our results showed that this rate did not differ significantly between amiodarone and placebo groups (RR=0.56, 95% CI: 0.25 to 1.25, P=0.16; Fig. 3a) with moderate heterogeneity (I^2=51%, P=0.13). Similarly, the percentage of patients requiring DCSs for VF did not differ significantly between patients receiving lidocaine and placebo (3 trials, 214 patients; RR=0.21, 95% CI: 0.04 to 1.19, P=0.08; Fig. 3b; I^2=71%, P=0.03) and those receiving amiodarone and lidocaine (2 trials, 180 patients; RR=2.44, 95% CI: 0.13 to 44.02, P=0.55; Fig. 3c). However, significant heterogeneity was detected (I^2=84%, P=0.01). Subsequent subgroup and meta-regression analyses were not performed due to the small number of studies. Publication bias was difficult to estimate due to the small number of comparisons included.

4 Discussion

By integrating all available RCTs, the results of our meta-analysis indicate that amiodarone and lidocaine confer comparable preventative efficacy for VF incidence after ACC release in patients undergoing open heart surgery, and that the effects of each were significant compared with placebos. However, when the percentage of patients subsequently requiring DCSs for reperfusion VF was applied as the measure, no significant effects among amiodarone, lidocaine, and placebo were detected. Overall, the included

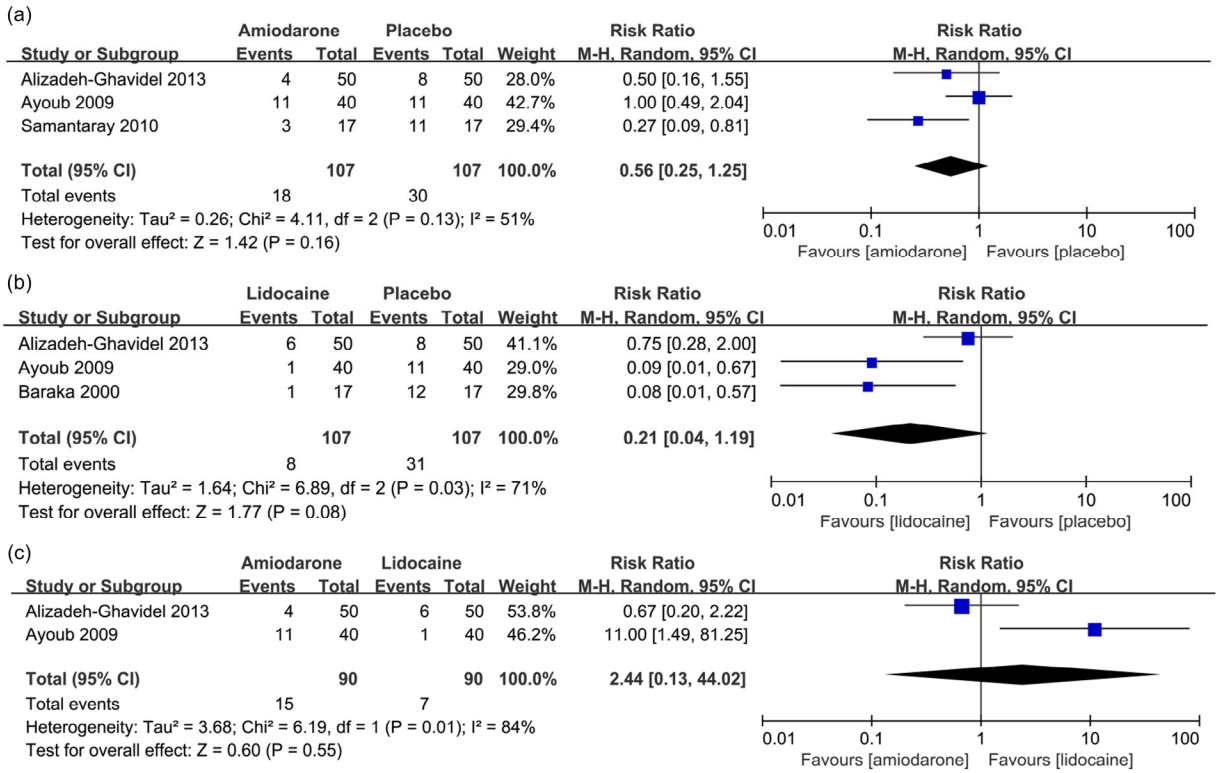

Fig. 3 Effects of amiodarone and lidocaine on the ratio of patients who subsequently required defibrillation counter shocks (DCSs) after release of aortic cross-clamp (ACC)

The rate did not differ significantly between amiodarone and placebo groups (a); the percentage of patients requiring DCSs for VF did not differ significantly between patients receiving lidocaine and placebo (b) and those receiving amiodarone and lidocaine (c)

studies represented a small sample size, and moderate to significant heterogeneity was detected among the included RCTs. Based on the results, our study indicated that perioperative administrations of amiodarone and lidocaine confer similar preventative efficacy for VF incidence after ACC release in patients undergoing open heart surgery. These results may highlight the potential use of conventional antiarrhythmic medications for the prevention of VF during cardiac surgery procedures. Further studies with larger numbers of participants are needed to confirm our results, and to determine the protocol and regimens for the perioperative administrations of amiodarone and lidocaine during open heart surgery.

The incidence of VF following ACC release during cardiac surgery is relatively high and is associated with poor prognosis in patients undergoing cardiac surgery. Previous studies indicated that medications administered to prevent arrhythmia may also effectively prevent VF during cardiac surgery (Wenger *et al.*, 1984; Kirlangitis *et al.*, 1990; Komori *et al.*, 1999; Ayoub *et al.*, 2009). Amiodarone and lidocaine are the most commonly used drugs for the prevention of heart arrhythmia (Wyman *et al.*, 2004; Nayeem Ul *et al.*, 2013; Onk and Erkut, 2015). However, studies directly comparing the effects of amiodarone and lidocaine on VF following ACC release during cardiac surgery have rarely been reported. Our meta-analysis revealed that the capacity of amiodarone and lidocaine to prevent reperfusion VF was similar, consistent with previous RCTs (Mauermann *et al.*, 2012; Ghavidel *et al.*, 2013). However, some studies raised the possibility that lidocaine may more effectively prevent VF following ACC release in patients undergoing cardiac surgery (Ayoub e*t al.*, 2009). Amiodarone acts to stabilize the membrane of cardiomyocytes and was widely used for the prevention and treatment of atrial and ventricular arrhythmia, including VF (Levine *et al.*, 1996; Petrovic *et al.*, 1998; Somberg *et al.*, 2002). Regarding

the potential mechanisms by which amiodarone may prevent VF during cardiac surgery, some recently published experimental studies may provide some novel evidence. In a swine model of hemorrhage-induced VF, resuscitation combined with amiodarone and vasopressin after hemorrhagic circulatory arrest resulted in better 3-h survival, better preservation of hemodynamic parameters, and less myocardial injury than resuscitation with vasopressin only, indicating the efficacy of amiodarone for termination of VF (Zoerner and Semenas, 2014). This observation is consistent with previous studies which showed that administration of amiodarone may be associated with a lower long-duration ventricular defibrillation threshold (Wu *et al.*, 2011; Chevalier *et al.*, 2012), suggesting a beneficial effect of amiodarone on malignant arrhythmias. Similarly, lidocaine was also recommended as an antiarrhythmic drug for recurrent VF (American Heart Association, 1992; 2000). However, few experimental studies have investigated the mechanism by which lidocaine may reduce VF incidence, and the effect of this drug on VF in animal models during cardiac surgery has rarely been reported. The mechanisms mediating lidocaine's effect on the risk of VF after ACC release in patients undergoing open heart surgery require further investigation.

In this study, we observed no significant differences in the effects of amiodarone, lidocaine, or placebo on the ratio of patients who subsequently required DCSs for the conversion of VF following cardiac surgery. This observation is inconsistent with the observed differences in VF incidence, perhaps as far fewer studies reported the DCS outcome, and the statistic power of the pooled analyses therefore was more limited.

Our conclusions are limited by the scope of this study, which should be considered when interpreting the results. Firstly, we included the results of only 8 RCTs including a total of 839 patients. The small number of RCTs included and the small sample size of each included study restricted further analyses of the other factors that may influence the outcomes, such as patient demographic factors, surgical categories, and patient comorbidities. Obviously, large-scale RCTs with adequate statistic power are required to confirm our results. Secondly, the quality of the included studies was moderate, which led to the moderate grade of our meta-analyses. Thirdly, the results of our meta-analysis are based on the pooled results of crude RRs, which may be biased by potential confounding factors that were not balanced between groups during randomization. However, as a meta-analysis of RCTs, the chances of potential bias caused by residual confounding factors are low when compared with meta-analyses of observational studies. In addition, the optimal protocols and dosages for the administration of amiodarone and lidocaine during the perioperative periods remain to be determined in future studies. Lastly, publication bias among the included studies was difficult to estimate since only a small number of studies were available. Publication bias may exist since we extracted only English language articles.

5 Conclusions

In conclusion, the current evidence from head-to-head RCTs suggests that amiodarone and lidocaine have comparable preventative efficacy for VF after ACC, but the ratio of patients who subsequently require DCSs does not differ between amiodarone, lidocaine, and placebo groups. Further studies with a larger number of participants will be required to confirm our results.

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Compliance with ethics guidelines

Yong ZHENG, Qiang GU, Hong-wu CHEN, Huai-ming PENG, Dong-yu JIA, Yu ZHOU, and Mei-xiang XIANG declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

References

American Heart Association, 1992. Guidelines for cardiopulmonary resuscitation and emergency cardiac care. *JAMA*, **268**(16):2171-2183.

American Heart Association, 2000. Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care. Part 6: advanced cardiovascular life support: section 5: pharmacology I: agents for arrhythmias. *Circulation*, **102**(8 Suppl.):I112-I128.

Ayoub, C.M., Sfeir, P.M, Bou-Khalil, P., *et al*., 2009. Prophylactic amiodarone versus lidocaine for prevention

of reperfusion ventricular fibrillation after release of aortic cross-clamp. *Eur. J. Anaesthesiol.*, **26**(12):1056-1060. http://dx.doi.org/10.1097/EJA.0b013e32832f0dfb

Baraka, A., Hirt, N., Dabbous, A., *et al*., 1993. Lidocaine cardioplegia for prevention of reperfusion ventricular fibrillation. *Ann. Thorac. Surg*., **55**(6):1529-1533. http://dx.doi.org/10.1016/0003-4975(93)91104-U

Baraka, A., Kawkabani, N., Dabbous, A., *et al*., 2000. Lidocaine for prevention of reperfusion ventricular fibrillation after release of aortic cross-clamping. *J. Cardiothor. Vas. An*., **14**(5):531-533. http://dx.doi.org/10.1053/jcan.2000.9484

Baravelli, M., Cattaneo, P., Rossi, A., *et al.*, 2010. Low-risk profile for malignant ventricular arrhythmias and sudden cardiac death after surgical ventricular reconstruction. *Pacing Clin. Electrophysiol*., **33**(9):1054-1062. http://dx.doi.org/10.1111/j.1540-8159.2010.02771.x

Chevalier, P., Timour, Q., Morel, E., *et al*., 2012. Chronic oral amiodarone but not dronedarone therapy increases ventricular defibrillation threshold during acute myocardial ischemia in a closed-chest animal model. *J. Cardiovasc. Pharmacol*., **59**(6):523-528. http://dx.doi.org/10.1097/FJC.0b013e31824d89fe

Doherty, P.W., McLaughlin, P.R., Billingham, M., *et al*., 1979. Cardiac damage produced by direct current countershock applied to the heart. *Am. J. Cardiol*., **43**(2):225-232. http://dx.doi.org/10.1016/S0002-9149(79)80008-9

Dorian, P., Cass, D., Schwartz, B., *et al*., 2002. Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. *N. Engl. J. Med.*, **347**(12):955. http://dx.doi.org/10.1056/NEJM200209193471227

Fiore, A.C., Naunheim, K.S., Taub, J., *et al.*, 1990. Myocardial preservation using lidocaine blood cardioplegia. *Ann. Thorac. Surg*., **50**(5):771-775. http://dx.doi.org/10.1016/0003-4975(90)90683-W

Furlan, A.D., Malmivaara, A., Chou, R., *et al.*, 2015. 2015 updated method guideline for systematic reviews in the Cochrane Back and Neck Group. *Spine*, **40**(21):1660-1673. http://dx.doi.org/10.1097/BRS.0000000000001061

Geissler, H.J., Schlensak, C., Sudkamp, M., *et al*., 2009. Heart valve surgery today: indications, operative technique, and selected aspects of postoperative care in acquired valvular heart disease. *Dtsch. Arztebl. Int*., **106**(13):224-233. http://dx.doi.org/10.3238/arztebl.2009.0224

Ghavidel, A.A., Nabavi, S., Haghjoo, M., *et al*., 2013. Amiodarone versus lidocaine for the prevention of reperfusion ventricular fibrillation: a randomized clinical trial. *ARYA Atheroscler.*, **1**:343-349.

Hippelainen, M.J., Tuppurainen, T.T., Huttunen, K.T., 1994. Reperfusion ventricular fibrillation and electric countershocks during coronary artery bypass operations-association with postoperative CK-MB release. *J. Thorac. Cardiovasc. Surg*., **28**(2):73-78.

Kirlangitis, J., Middaugh, R., Knight, R., *et al.*, 1990. Comparison of bretylium and lidocaine in the prevention of ventricular fibrillation after aortic cross-clamp release in coronary artery bypass surgery. *J. Cardiothorac. Anesth.*, **4**(5):582-587. http://dx.doi.org/10.1016/0888-6296(90)90408-8

Komori, S., Li, B., Matsumura, K., *et al.*, 1999. Antiarrhythmic effect of magnesium sulfate against occlusion-induced arrhythmias and reperfusion-induced arrhythmias in anesthetized rats. *Mol. Cell Biochem*., **199**(1-2):201-208. http://dx.doi.org/10.1023/A:1006938010925

Leeuwenburgh, B.P., Versteegh, M.I., Maas, J.J., *et al*., 2008. Should amiodarone or lidocaine be given to patients who arrest after cardiac surgery and fail to cardiovert from ventricular fibrillation? *Interact. Cardiovasc. Thorac. Surg*., **7**(6):1148-1151. http://dx.doi.org/10.1510/icvts.2008.188656

Levine, J.H., Massumi, A., Scheinman, M.M., *et al.*, 1996. Intravenous amiodarone for recurrent sustained hypotensive ventricular tachyarrhythmias intravenous amiodarone multicenter trial group. *J. Am. Coll. Cardiol*., **27**(1):67-75. http://dx.doi.org/10.1016/0735-1097(95)00427-0

Liu, X.B., Jiang, J.B., Zhou, Q.J., *et al*., 2015. Evaluation of the safety and efficacy of transcatheter aortic valve implantation in patients with a severe stenotic bicuspid aortic valve in a Chinese population. *J. Zhejiang Univ.-Sci. B (Biomed. & Biotechnol.)*, **16**(3):208-214. http://dx.doi.org/10.1631/jzus.B1500017

Marathe, S.P., Talwar, S., 2015. Surgery for transposition of great arteries: a historical perspective. *Ann. Pediatr. Cardiol*., **8**(2):122-128. http://dx.doi.org/10.4103/0974-2069.157025

Mauermann, W.J., Pulido, J.N., Barbara, D.W., *et al.*, 2012. Amiodarone versus lidocaine and placebo for the prevention of ventricular fibrillation after aortic crossclamping: a randomized, double-blind, placebo-controlled trial. *J. Thorac. Cardiovasc. Surg.*, **144**(5):1229-1234. http://dx.doi.org/10.1016/j.jtcvs.2012.06.039

Mery, C.M., Kane, L.C., 2017. The ACGME fellowship in congenital cardiac surgery: the graduates' perspective. *Semin. Thorac. Cardiovasc. Surg. Pediatr. Card. Surg. Ann*., **20**:70-76. http://dx.doi.org/10.1053/j.pcsu.2016.09.005

Moher, D., Liberati, A., Tetzlaff, J., *et al*., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann. Intern. Med*., **151**(4):264-269. http://dx.doi.org/10.7326/0003-4819-151-4-200908180-00135

Nayeem Ul, H., Dar, A.M., Wani, M.L., *et al*., 2013. A comparative study on the effect of amiodarone and metaprolol for prevention of arrythmias after open heart surgery. *Int. Cardiovasc. Res. J*., **7**(1):1-4.

Onk, O.A., Erkut, B., 2015. Is the preoperative administration of amiodarone or metoprolol more effective in reducing atrial fibrillation: after coronary bypass surgery? *Medicine (Baltimore)*, **94**(41):e1576. http://dx.doi.org/10.1097/MD.0000000000001576

Papakonstantinou, N.A., Baikoussis, N.G., Dedeilias, P., *et al*., 2017. Cardiac surgery or interventional cardiology? Why not both? Let's go hybrid. *J. Cardiol*., **69**(1):46-56. http://dx.doi.org/10.1016/j.jjcc.2016.09.007

Patil, K.D., Halperin, H.R., Becker, L.B., 2015. Cardiac arrest: resuscitation and reperfusion. *Circ. Res*., **116**(12):2041-2049. http://dx.doi.org/10.1161/CIRCRESAHA.116.304495

Petrovic, T., Adnet, F., Lapandry, C., 1998. Successful resuscitation of ventricular fibrillation after low-dose amiodarone. *Ann. Emerg. Med*., **32**(4):518-519. http://dx.doi.org/10.1016/S0196-0644(98)70191-X

Samantaray, A., Chandra, A., Panigrahi, S., 2010. Amiodarone for the prevention of reperfusion ventricular fibrillation. *J. Cardiothorac. Vasc. Anesth.*, **24**(2):239-243. http://dx.doi.org/10.1053/j.jvca.2009.07.007

Schluter, T., Baum, H., Plewan, A., *et al*., 2001. Effects of implantable cardioverter defibrillator implantation and shock application on biochemical markers of myocardial damage. *Clin. Chem*., **47**(3):459-463.

Shake, J.G., Pronovost, P.J., Whitman, G.J., 2013. Cardiac surgical ICU care: eliminating 'preventable' complications. *J. Card. Surg*., **28**(4):406-413. http://dx.doi.org/10.1111/jocs.12124

Somberg, J.C., Bailin, S.J., Haffajee, C.I., *et al.*, 2002. Intravenous lidocaine versus intravenous amiodarone (in a new aqueous formulation) for incessant ventricular tachycardia. *Am. J. Cardiol*., **90**(8):853-859. http://dx.doi.org/10.1016/S0002-9149(02)02707-8

Vaziri, M.T.M., Jouibar, R., Akhlagh, S.H.A., *et al*., 2010. The effect of lidocaine and magnesium sulfate on prevention of ventricular fibrillation in coronary artery bypass grafting surgery. *Iran Red Crescent Med. J*., **12**(3):298-301.

Verrier, E.D., Mack, M.J., 2015. Viewpoint: transitions in cardiac surgery and interventional cardiology team mates or rivals? *Heart*, **101**(5):346-348. http://dx.doi.org/10.1136/heartjnl-2014-306132

Wenger, T.L., Lederman, S., Starmer, C.F., *et al*., 1984. A method for quantitating antifibrillatory effects of drugs after coronary reperfusion in dogs: improved outcome with bretylium. *Circulation*, **69**(1):142-148. http://dx.doi.org/10.1161/01.CIR.69.1.142

Wu, L., Jin, Q., Zhang, N., *et al*., 2011. The effects of acute amiodarone on short-and long-duration ventricular defibrillation threshold in canines. *J. Cardiovasc. Pharmacol*., **58**(4):432-438. http://dx.doi.org/10.1097/FJC.0b013e318228a50c

Wyman, M.G., Wyman, R.M., Cannom, D.S., *et al*., 2004. Prevention of primary ventricular fibrillation in acute myocardial infarction with prophylactic lidocaine. *Am. J. Cardiol*., **94**(5):545-551. http://dx.doi.org/10.1016/j.amjcard.2004.05.014

Yamaguchi, H., Weil, M., Tang, W., *et al*., 2002. Myocardial dysfunction after electrical defibrillation. *Resuscitation*, **54**(3):289-296. http://dx.doi.org/10.1016/S0300-9572(02)00149-1

Yeh, S.T., Aune, S.E., Wilgus, T.A., *et al*., 2013. Hyperoxemic reperfusion after prolonged cardiac arrest in a rat cardiopulmonary bypass resuscitation model. *Resuscitation*, **84**(1):114-120. http://dx.doi.org/10.1016/j.resuscitation.2012.08.323

Yilmaz, M., Aydin, U., Arslan, Z.I., *et al*., 2014. The effect of lidocaine and amiodarone on prevention of ventricular fibrillation in patients undergoing coronary artery bypass grafting. *Heart Surg. Forum.*, **17**(5):245-249. http://dx.doi.org/10.1532/HSF98.2014402

Zhan, H.T., Purcell, S.T., Bush, R.L., 2015. Preoperative optimization of the vascular surgery patient. *Vasc. Health Risk Manag*., **11**:379-385.

Zoerner, F., Semenas, E., 2014. Resuscitation with amiodarone increases survival after hemorrhage and ventricular fibrillation in pigs. *J. Trauma Acute Care Surg*., **76**(6):1402-1408. http://dx.doi.org/10.1097/TA.0000000000000243

中文概要

题　目：胺碘酮和利多卡因对开胸心脏手术中再灌注性室颤预防效果的随机对照试验荟萃分析

目　的：系统评估胺碘酮、利多卡因或安慰剂对心脏手术中主动脉结扎松解（ACC）后再灌注性室颤（VF）发生的影响。

创新点：胺碘酮、利多卡因对于预防 ACC 后再灌注 VF 的效果，目前相关的随机对照试验（RCTs）并无统一的结论，本研究综合之前 RCTs 进行荟萃分析。

方　法：遵循 PRISMA 和 Cochrane 系统评估手册对 PubMed、EMBASE 及 Cochrane 进行文献检索（图 1），荟萃分析符合要求的 RCTs。

结　论：当前的证据表明胺碘酮和利多卡因在开胸心脏手术中预防再灌注 VF 的效果两者之间并无显著差异，但均明显优于安慰剂；在随后需要电除颤的患者的比例上，胺碘酮、利多卡因及安慰剂三者间无统计学差异。

关键词：胺碘酮；利多卡因；再灌注室颤；心脏手术