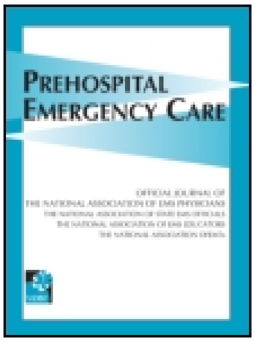

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Abstract

Objective. To determine the differences in survival for out-of-hospital advanced airway intervention (AAI) compared with basic airway intervention (BAI) in cardiac arrest. **Background.** AAI is commonly utilized in cardiac arrest in the out-of-hospital setting as a means to secure the airway. Observational studies and clinical trials of AAI suggest that AAI is associated with worse outcomes in terms of survival. No controlled trials exist that compares AAI to BAI. **Methods.** We conducted a bias-adjusted meta-analysis on 17 observational studies. The outcomes were survival, short-term (return of spontaneous circulation and to hospital admission), and longer-term (to discharge, to one month survival). We undertook sensitivity analyses by analyzing patients separately: those who were 16 years and older, nontrauma only, and attempted versus successful AAI. **Results.** This meta-analysis included 388,878 patients. The short-term survival for AAI compared to BAI were overall OR 0.84(95% CI 0.62 to 1.13), for endotracheal intubation (ETI) OR 0.79 (95% CI 0.54 to 1.16), and for supraglottic airways (SGA) OR 0.59 (95% CI 0.39 to 0.89). Long-term survival for AAI were overall OR 0.49 (95% CI 0.37 to 0.65), for ETI OR 0.48 (95% CI 0.36 to 0.64), and for SGA OR 0.35 (95% CI 0.28 to 0.44). Sensitivity analyses shows that limiting analyses to adults, non-trauma victims, and instances where AAI was both attempted and successful did not alter results meaningfully. A third of all studies did not adjust for any other confounding factors that could impact on survival. **Conclusions.** This meta-analysis shows decreased survival for AAIs used out-of-hospital in cardiac arrest, but are likely biased due to confounding, especially confounding by indication. A properly conducted prospective study or a controlled trial is urgently needed and are possible to do. **Key words:** cardiac arrest; cardiopulmonary resuscitation; emergency medical services; endotracheal intubation; laryngeal mask airway; meta-analysis

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Introduction

Advanced airway interventions (AAIs) such as endotracheal intubation (ETI), laryngeal mask airway, and others are commonly used by emergency medical services (EMS) personnel in managing patients with out-of-hospital cardiac arrest (OHCA). There is no high-quality evidence to support the use of AAIs. The use of AAIs in cardiac arrest has come under increased scrutiny recently,[1,2] with the debate centered on the utility of AAI to increase survival. This systematic review will bring together the combined research into the effect of AAI and basic airway interventions (BAI) on survival outcomes. Specifically, this review aims to ascertain if patients who have suffered out-of-hospital cardiac arrest have better long- or short-term survival with AAI use, compared to BAI. Systematic reviews investigating ETI for out-of-hospital brain injury exist, but none has comprehensively compared AAI to BAI for OHCA. The results of this systematic review aim to add to existing knowledge of airway management practices in OHCA.

Methods

This systematic review and meta-analysis was conducted according to the PRISMA guidelines.[3]

Data Sources, Search Strategy and Study Selection

We searched Medline, Embase, and the Cochrane Central Register of Controlled Trials from the earliest existence of the database up to February 1, 2013 (Appendix 1, available online). We contacted known authors in this field (DC) and back-searched reference lists for suitable articles. We found no additional articles by contacting authors. Studies were assessed for suitability for inclusion by three reviewers (PF, PS, and RT), by reviewing the complete abstracts of all search results, after which full text articles were read of studies that fit our inclusion and exclusion criteria.

Eligibility Criteria

All out-of-hospital observational and experimental studies of cardiac arrest resuscitation by out-of-hospital personnel (health-care workers treating cardiac arrest and able to use AAI and/or BAI) were eligible. Studies qualified for inclusion if one group of patients has AAI successfully inserted, and another group has BAI-only airway management, with or without basic interventions such as nasopharyngeal and/or oropharyngeal airways. We excluded results that reported survival outcomes greater than 1 month post-event as we felt that follow-up beyond this time point would not accurately reflect the effect of resuscitation. Only studies of adult patients, defined as persons 18 years or older, with nontraumatic OHCA were initially considered. It became apparent, however, that excluding studies with subjects less than 18 years and OHCA of traumatic origin would exclude too many studies, thus decreasing the meta-analysis sample as well as lessening the external validity of the findings. A study was eligible regardless of language, and the timeframe of publication was without limits. Publication types suitable for inclusion were journals, books, dissertations, technical reports, unpublished manuscripts, and conference presentations, both published and unpublished. All studies that compare BAI (such as head-tilt–chin-lift and variants, with bag-valve-mask only or mouth-to-mouth ventilations, with or without nasopharyngeal and/or oropharyngeal airways) with AAI interventions (includes ETI, all variants of the laryngeal mask airway, all types of supraglottic airways (SGA), double-lumen airways, and trans-tracheal or trans-cricothyroid membrane airways) were suitable. We combined all SGAs for analysis, since studies did not report enough of the different types of SGA to analyze them separately. SGAs included laryngeal mask airways, intubating laryngeal mask airways, double-lumen airways, and esophageal obturator airways. Finally, we excluded studies that consisted of a mixed group of respiratory arrest, cardiac arrest, and compromised airways, and those for which only abstracts were available.

Data Abstraction

Two authors (RT and PF) independently reviewed each included study to identify the following characteristics: study and year, crude numbers of AAI versus BAI, description of the interventions, primary and secondary outcomes, study methodology, sample description and analysis details, and baseline primary and secondary outcomes. Instructions for the extraction were piloted for clarity on a single study. Disagreements in extracted data were resolved by arbitration and consensus by all authors.

Quality Assessment

We assessed the extent of bias of included studies with a checklist adapted from Downs and Black[4] (Appendix 2, available online). Modifications of the checklist included a rating of the extent to which a particular study adjusted for potential confounders, using the Utstein template variables.[5] The checklist consisted of 11 items, addressing bias, analytical errors, and confounding, allocating scores for each item, which were then combined into a summary score with a maximum possible of 15. Two authors (PF and PS) independently assessed quality with this checklist, and interrater agreement was assessed.

Statistical Analysis

The main outcome was survival after all AAI combined compared to BAI. In addition, survival after ETI and supraglottic airways versus BAI was also assessed. All outcomes were stratified as short-term survival (defined as return of spontaneous circulation (ROSC) only or survival to hospital admission) versus longer-term survival (defined as survival to either hospital discharge or to 1 month). Five studies reported short-term outcomes using AAIs different from the "main" AAI's of each study),[6–10] and four studies[6,8–10] similarly reported longer-term outcomes using such additional AAIs (LMA and double-lumen airways and esophageal obturator airways). These were meta-analyzed separately by exchanging the outcomes from these secondary airways into previous analysis. If a study reported results from a propensity score matched sample, then such results were extracted for meta-analysis, rather than the results from the total sample.

BAI was the reference category in all analysis. A value of 1 indicated equivalence, while a value greater than 1 indicated higher odds of survival for the AAI groups. Heterogeneity was determined to be present when the value of τ^2 was greater than zero and/or the Q-statistic was significant at a $p < 0.1$.[11] Although the standard approach for handling heterogeneity between studies is to use the random effects model,[12] the present study uses bias adjustment via the quality effects model described by Doi et al.[13,14] This approach has advantages, given that methodology in a random effects model could be flawed to the extent that, even in standard meta-analyses, the random effects model estimate probably has no real interpretation.[15,16] The random effects results are, however, noted for comparative purposes in Appendix 3 (available online). MetaXL version 1.3 (Epigear) was used for analysis. Robustness of our meta-analysis was explored using sensitivity analyses created through altering selection criteria of the studies. We explored sources of heterogeneity by consideration of discordant effect sizes of included studies in the meta-analysis and examining reasons thereof. Some studies reported outcomes to additional AAIs and compared this to the same BAI category. For example, Hasegawa et al.[9] reported ETI versus BAI and LMA/DLA versus BAI. Since results of the meta-analysis can vary depending which of these AAI is analyzed, a separate analysis was completed for each of these additional comparisons to avoid a unit-of-analysis problem,[17] by replacing the first comparison with the second, and thereby creating secondary endpoints. Publication bias was examined visually by funnel plots. Too few studies that report results of SGA were available to be meta-analyzed, and for this reason sensitivity analysis was limited to all AAI and for ETI vs. BAI.

RESULTS

Characteristics of the Studies

The literature search returned 799 articles, and we screened 90 by their titles and abstracts. Of these, 17 articles were included in the meta-analysis (Figure 1). Three studies used prospective cohort designs,[9,18,19] two were historically controlled trials,[20,21] and the rest were retrospective cohorts. Two studies published as abstracts only at the time the search was complete are not included.[22,23] Table 1 shows the characteristics of included studies. Studies span 24 years, with samples ranging from 124 cardiac arrest victims[18] up to 649,359.[9] Fifteen studies reported the outcomes of endotracheal intubation versus bag–valve–mask or no/unsuccessful intubation.[6–10,18,19,21,24–31] Sixty percent of studies had nontraumatic only samples,[6,10,18,19,21,26,29,31,32] and 40% included only cardiac arrest victims older than 16 years.[10,18,21,26,29,32] Five studies reported outcomes on more than one AAI. One study reported 1-year

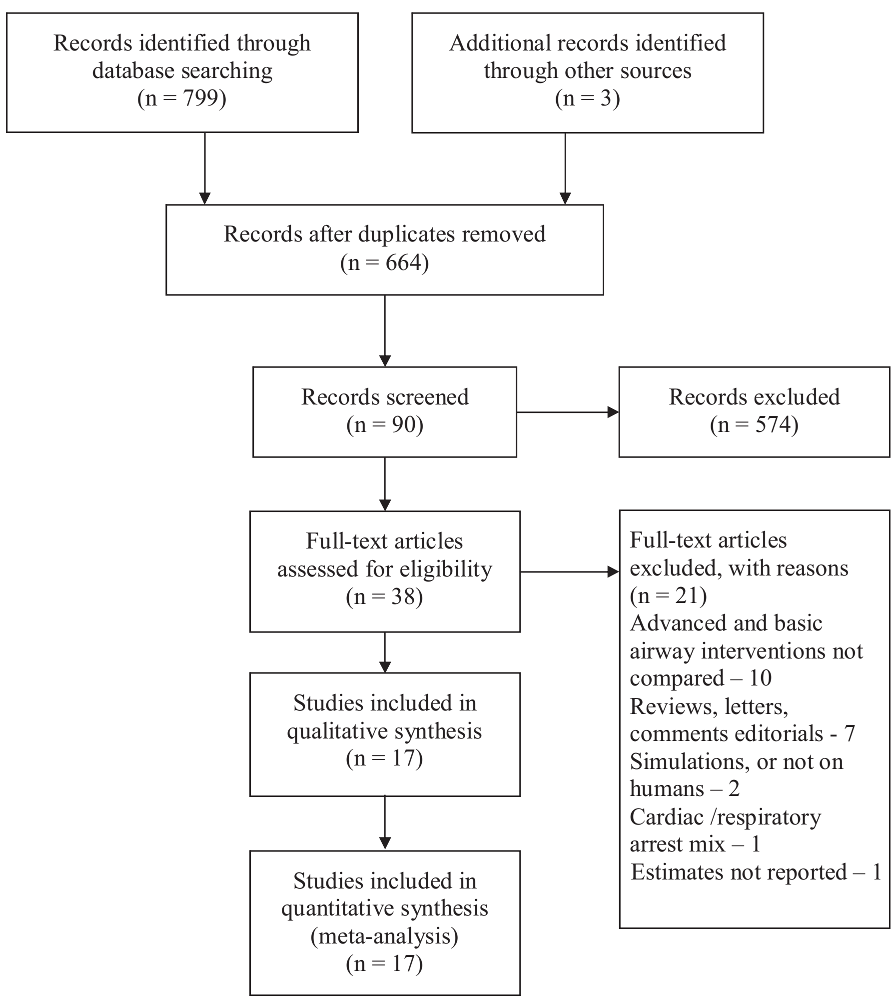


FIGURE 1. Study selection flow diagram.

TABLE 1. Characteristics of studies included in meta-analysis

Study	*n* (AAI vs. BAI)	AAI vs. BAI	Primary outcome	Secondary outcome	Design and quality score	Description of study	Baseline 1st outcome (*n*, %) AAI vs. BAI	OR (95% CI), primary	Baseline 2nd outcome (*n*, %) AAI vs. BAI	OR (95% CI), secondary
Pointer 1988[28]	358 vs. 25	Successful ETI vs. unsuccessful ETI	SHA	None	RC (0.40)	Cardiac arrest treated by paramedics in urban/suburban areas, in persons >8 years. Fraction of trauma not reported.	83 vs. 2 (23.2 vs. 8%)	3.47 (0.80, 15.03)	N/A	N/A
Hillis 1993[18]	48 vs. 76	Successful ETI vs. OPA	SHD	None	PC (0.47)	Nontraumatic cardiac arrest > 16 years treated by EMTs in urban areas.	6 vs. 3 (12.5 vs. 3.9%)	3.48 (0.83, 16.63)	N/A	N/A
	67 vs. 76	Successful OOA vs. OPA					3 vs. 3 (4.4 vs. 3.9%)	1.14 (0.22, 5.85)	N/A	N/A
Adams 1997[24]	3427 vs. 5224	Attempted ETI vs. no ETI	SHD	None	RC (0.27)	Cardiac arrest treated by ambulance crews urban and rural area. Age range not stated. The fraction of trauma is not reported.	136 vs. 476 (3.7 vs. 9.1%)	0.41 (0.34, 0.50)	N/A	N/A
Rainer 1997[19]	87 vs. 120	Successful ETI vs. no ETI	ROSC	SHA	PC (0.43)	Nontraumatic cardiac arrest treated by EMTs and paramedics in urban areas of persons older than 13 years.	Not reported	N/A	13 vs. 28 (14.94 vs. 23.33%)	0.58 (0.28 1.19)
Holmberg 2002[25]	5118 vs. 5665	Attempted ETI vs. no ETI	OM	None	RC (0.67)	All cardiac arrest treated by ALS/BLS of all ages in a single country. The fraction of trauma is not reported.	183 vs. 361 (3.6 vs. 6.4%)	0.71 (0.51, 0.99), adjusted	N/A	N/A
Jennings 2006[26]	1387 vs. 403	Successful ETI vs. no ETI	SHA	None	RC (0.53)	Nontraumatic cardiogenic cardiac arrest with arrest witnessed by bystander, aged >17 years treated by paramedics in urban/suburban area.	488 vs. 48 (35 vs. 12%)	3.46 (2.49, 4.80), adjusted	N/A	N/A
Noda 2007[33]	5 vs. 49	Successful ETI vs. BVM	SHD	SHA	RC (0.37)	Non-traumatic cardiogenic cardiac arrest with arrest witnessed by bystander, all ages treated by paramedics in urban/suburban area.	1 vs. 15 (20 vs. 31%)	0.57 (0.06, 5.51)	2 vs. 21 (40 vs. 43%)	0.89 (0.14 5.80)
	24 vs. 49	Successful DLA vs. BVM					3 vs. 15 (13 vs. 31%)	0.32 (0.08, 1.25)	4 vs. 21 (17 vs. 43%)	0.27 (0.08 0.89)
Garza 2009[21]	Not reported	Successful ETI vs. no ETI	SHD	ROSC	HCT (0.72)	Non-traumatic witnessed cardiogenic cardiac arrest in VF, aged >17 years treated by paramedics in urban/suburban area.	Not reported	0.41 (0.24, 0.70), adjusted	Not reported	Not reported
Hanif 2010[10]	1027 vs. 131	Successful ETI vs. BVM	SHD	SHA	RC (0.67)	Non-traumatic cardiac arrest aged > 18 years treated by paramedics in an urban/suburban area.	38 vs. 14 (4 vs. 11%)	0.22 (0.11, 0.43), adjusted	152 vs. 35 (15 vs. 27%)	0.47 (0.31 0.73)
	131 vs. 131	Successful OOA, DLA vs. BVM					0 vs. 14 (0 vs. 11%)	0.03 (0.002 to 0.54)	5 vs. 35 (4 vs. 27%)	0.13 (0.05 to 0.35)

(Continued on next page)

TABLE 1. Characteristics of studies included in meta-analysis *(Continued)*

Study	*n* (AAI vs. BAI)	AAI vs. BAI	Primary outcome	Secondary outcome	Design and quality score	Description of study	Baseline 1st outcome (*n*, %) AAI vs. BAI	OR (95% CI), primary	Baseline 2nd outcome (*n*, %) AAI vs. BAI	OR (95% CI), secondary
Lyon 2010[27]	628 vs. 166	Attempted ETI vs. no ETI	SHA	None	RC (0.30)	Trauma and non-traumatic cardiac arrest treated by paramedics in an urban area, age range not reported.	110 vs. 55 (33.1 vs. 17.5%)	0.43 (0.29, 0.63)	N/A	N/A
Studnek 2010[29]	709 vs. 433	Successful ETI vs. no ETI	PROSC	SHD	RC (0.60)	Non-traumatic cardiac arrest aged > 18 years treated by paramedics in an urban/suburban area.	169 vs. 130 (23.8 vs. 30%)	0.73 (0.56, 0.95)	44 vs. 73 (6 vs. 16.8%)	0.32 (0.22 0.48)
	939 vs. 203	Attempted ETI vs. no/ unsuccessful ETI					207 vs. 92 (22 vs. 45%)	0.34 (0.24, 0.47)	59 vs. 58	0.16 (0.11 0.25)
Takei 2010[7]	263 vs. 1539	Successful ETI vs. BVM	SROSC	OM	RC (0.73)	Adult trauma and non-trauma cardiac arrest aged >8 years treated by paramedics in urban/suburban and rural areas.	79 vs. 327 (30 vs. 21.3%)	1.50 (1.08, 2.08), adjusted	15 vs. 85 (6 vs. 5.5%)	1.03 (0.59 1.82)
	660 vs. 1539	Successful Other AAI vs. BVM					133 vs. 327 (30 vs. 21.3%)	0.94 (0.75, 1.17)	21 vs. 85 (3 vs. 5.5%)	0.56 (0.35 0.91)
Yanagawa 2010[8]	158 vs. 77	Successful ETI vs. BVM	OMGN	PROSC	RC (0.60)	Trauma and non-trauma cardiac arrest treated by EMS in urban areas, all ages.	2 vs. 8 (1.3 vs. 10%)	0.11 (0.02, 0.53)	18 vs. 13 (11.4 vs. 17%)	0.63 (0.29 1.37)
	478 vs. 77	Successful Combitube, LMA vs. BVM					6 vs. 8 (1.3 vs. 10%)	0.11 (0.04, 0.33)	37 vs. 13(7.7 vs. 17%)	0.41 (0.20 0.82)
Chien 2012[20]	309 vs. 89	Successful ILMA vs. BVM	ROSC	24	HCT (0.80)	Adult trauma and nontrauma cardiac arrest of all ages treated by EMT's in urban area.	147 vs. 32 (47.6 vs. 36%)	1.61 (0.99, 2.63)	112 vs. 22 (36.2 vs. 24.7%)	1.73 (1.01 2.96)
Nagao 2012[32]	199 vs. 156	Successful AAI(ETI, Combitube, or LMA) vs. BVM	SHD	ROSC	RC (0.73)	Nontraumatic cardiogenic cardiac arrest aged >18 years treated by paramedics in suburban area.	8 vs. 5 (4 vs. 3.2%)	1.26 (0.41, 3.95	37 vs. 16 (18.6 vs. 10.3%)	1.96 (1.02 3.79), adjusted
			CPC	SHA			3 vs. 3 (1.5 vs. 2%)	0.78 (0.16, 3.92)	25 vs. 7 (13 vs. 4%)	3.06 (1.29 7.27)
Shin 2012[6]	250 vs. 250	Successful ETI vs. BVM/OPA	SHA	SHD	RC (0.83)	Nontraumatic cardiac arrest of all ages treated by EMTs in urban and rural areas.	55 vs. 49 (22 vs. 20%)	1.32 (0.81, 2.16), adjusted	20 vs. 17 (8 vs. 7%)	1.44 (0.66 3.15), adjusted
	386 vs. 386	Successful LMA vs. BVM/OPA					79 vs. 95 (20.5 vs. 24.6%)	0.72 (0.50, 1.02), adjusted	22 vs. 37 (5.7 vs. 9.6%)	0.45 (0.25 0.82), adjusted
Hasegawa 2013[9]	178614 vs. 178614	Successful ETI vs. BVM	OMGN	PROSC	PC (0.83)	Trauma and nontrauma cardiac arrest treated by EMS in urban and suburban/rural areas, >18 years.	257 vs. 5799 (1 vs. 3%)	0.45 (0.37, to 0.55), adjusted	1734 vs. 14824 (6.7 vs. 8.3%)	0.66 (0.61 to 0.72), adjusted
		Successful LMA, DLA					1687 vs. 5799 (1.1 vs. 3.2%)	0.36 (0.33, to 0.39), adjusted	6993 vs. 14824 (4.5 vs. 8.3%)	0.54 (0.52 vs. 0.56), adjusted

ETI, endotracheal intubation; BVM, bag-valve-mask ventilation; OPA, oro-pharyngeal airway; OOA, esophageal obturator airway; ILMA, intubating laryngeal mask airway; DLA, double-lumen airway; RC, retrospective cohort; PC, prospective cohort; HCT, historically controlled trial; SHA, survival to admission to hospital; SHD, survival to hospital discharge; OMGN, 1-month survival, good neurological recovery; SROSC, sustained ROSC; PROSC, prehospital ROSC; OM, 1-month survival; 24, 24-hour survival; CPC, Pittsburgh Cerebral Performance Category 1&2.

survival,[7] but we omitted this outcome from the analysis since other prognostic factors could affect survival over a year. The total sample of cardiac arrest victims across all studies included in this meta-analysis is 388,878, which is much less than the total sample of all studies as we only used the propensity matched samples from Shin et al.[6] and Hasegawa et al.,[21] given that these matched samples are likely to be less biased.

Study Quality

We found a high interrater agreement of 0.90 (95% CI 0.74–0.96) through the intraclass correlation coefficient (ICC 2,1).[31] The mean quality score was 0.59 (95% CI 0.50–0.67). Five studies with the highest ratings were completed between 2010 and 2013[6,7,9,20,32] and were all from eastern Asia. Common to all higher-quality studies was that they all scored high on question six of the checklist, reflecting that they adjusted/matched or balanced to a higher degree than the rest of the studies included in this meta-analysis. The bottom six studies in terms of quality were mostly completed before the year 2000.[18,19,24,27,28,33]

Quantitative Synthesis

Survival with Any AAI

There was no significant difference in the overall odds of short-term survival between AAI and BAI (OR 0.84, 95% CI 0.62–1.13) (Figure 2a). A nonsignificant decrease in odds of ROSC became apparent when an AAI was used (OR 0.78, 95% CI 0.60–1.02). Studies reporting survival to hospital admission were associated with a nonsignificant increase in odds of hospital admission when an AAI was used (OR 1.40, 95% CI 0.83–2.37). The analysis of secondary endpoints for short-term survival did, however, result in a significant reduction in survival odds for AAIs (OR 0.69, 95% CI 0.51–0.93).

There was significant heterogeneity in the comparison of AAIs to BAIs, with three studies[8,9,29] that showed decreased short-term survival for AAI. These three studies reported only *prehospital* ROSC, compared to the other studies with increased survival that reported *any* ROSC or, in the case of Takei et al.,[7] *sustained* ROSC. Within the survival to hospital admission subgroup, the estimates of Pointer et al.[28] and Jennings et al.[26] are much larger than those of other studies; the estimate of Pointer et al. is possibly due to random error.[28] The estimate of Jennings et al. is more precise and is different from those of other studies as its sample only includes *witnessed* cardiac arrest.

There was evidence that the use of AAI was associated with reduced odds of longer-term survival (OR 0.49, 95% CI 0.37–0.65) (Figure 2b). The analysis of secondary endpoints from these studies showed a similar outcome for AAI (OR 0.37, 95% CI 0.32–0.43). Heterogeneity was present in this analysis of survival to hospital discharge. Hillis et al.[18] had a much larger odds ratio compared to other studies, possibly due to random error.[18] Shin et al.[6] and Nagao et al.[32] were the only other studies showing an increase in the survival to discharge point estimate. Nevertheless, all three had nonsignificant point estimates, with confidence intervals intersecting with the smaller effects sizes.

Survival with ETI

Figure 3 shows short-term and longer-term survival for ETI versus BAI. ETI use was associated with a nonsignificant decrease in the overall odds of short-term survival (OR 0.79, 95% CI 0.54–1.16). For longer-term outcomes, ETI use was associated with a significant decrease in odds of survival (OR 0.48, 95% CI 0.36–0.64). The study of Takei et al.[7] is the only ETI study that reports increased ROSC survival odds, and it differs from the other three studies in that no adrenaline was administered to its cardiac arrest survivors.

Survival with SGAs

Figure 4 shows of short-term and longer-term survival for SGAs versus BAI. SGA use was associated with decreased odds of short-term and longer-term outcomes (OR 0.56, 95% CI 0.40–0.78 [Figure 4a] and OR 0.35, 95% CI 0.28–0.44 [Figure 4b], respectively). Again, heterogeneity was evident with short-term survival and Hasegawa et al.[9] and Yanagawa et al.[8] had estimates that were less than those of the other studies for ROSC, but they were the only two studies in which adrenaline was not administered in this ROSC analysis.

Sensitivity Analysis and Publication Bias

We altered the inclusion and exclusion criteria to test for the robustness of the results of long- and short-term survival for AAI and ETI versus BAI in terms of age, nontrauma, and inclusion of attempted placement in addition to successful AAI and ETI (Table 2). Too few studies that report results of SGAs were available to be meta-analyzed with the application of altered selection criteria and, for this reason, sensitivity analysis was limited to all AAI and for ETI vs. BAI. Results for longer-term survival were robust to these altered selection criteria. Short-term survival for nontrauma-only subjects for AAI versus BAI tended to lose the trend that was initially present, with increased survival. Short-term survival, however, was robust to sensitivity analyses for ages 16 and over and for the combination attempted and successful AAI. The sensitivity analysis for the same altered selection criteria for ETI versus BAI (Table 2b) demonstrate that estimates were robust to changes in these selection criteria, except for

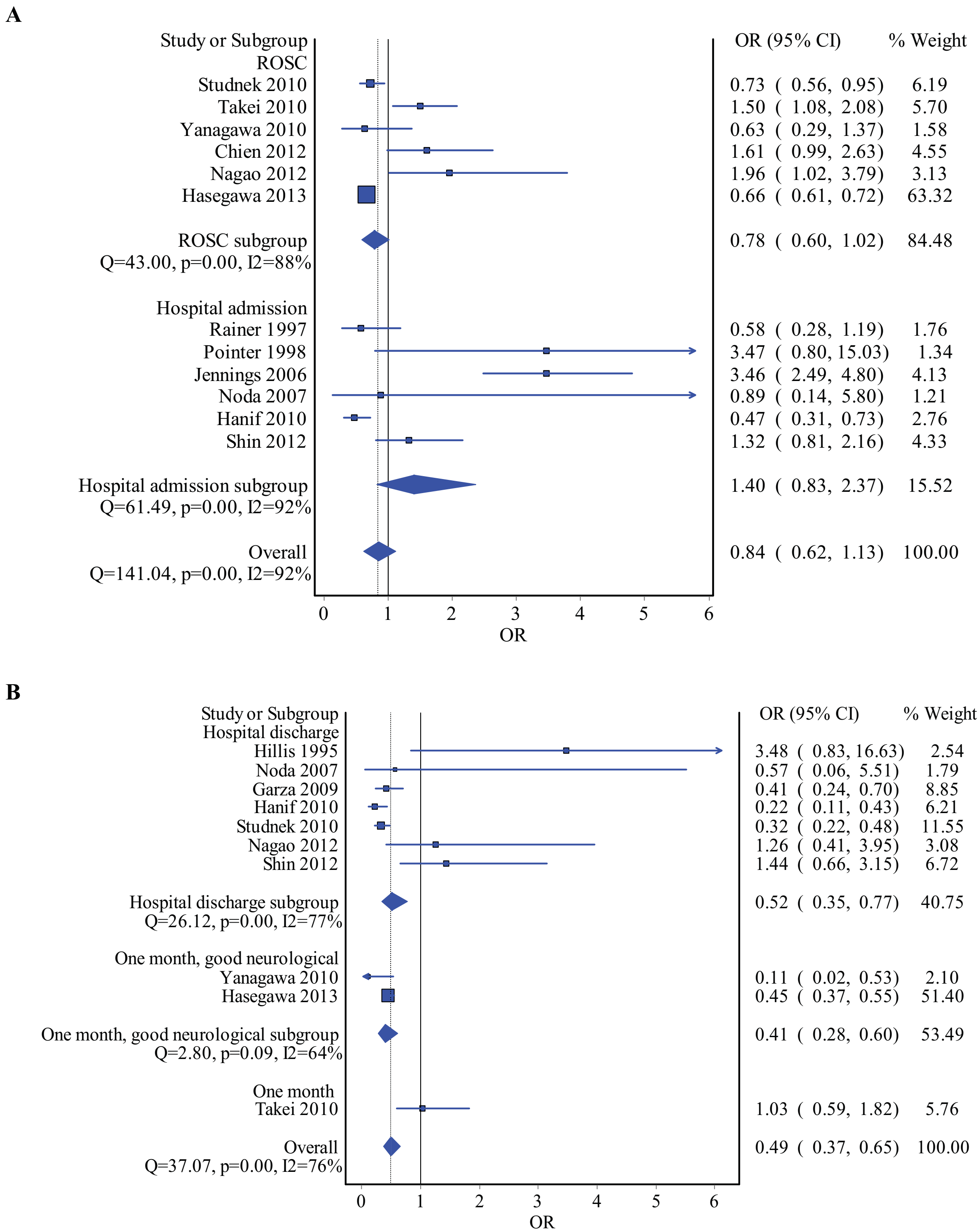


FIGURE 2. AAI compared to BAI for (A) short-term survival and (B) longer term.

nontrauma-only, but the magnitude of change is not as much as with AAI versus BAI. Subgroup analysis has not resulted with any new findings when compared to the primary and secondary outcomes. Also, including attempted intubation in addition to successful intubations, or limiting the analysis to persons 16 years and older, did not alter the odds of survival to discharge or to hospital admission for ETI versus BAI.

Figure 5 shows funnel plots for included studies. Both plots suffer from a paucity of effect estimates from smaller studies, making it difficult to assess the visual scattering expected at the bottom of the plot. In

TABLE 2a. Sensitivity analysis of advanced airway interventions versus basic airway interventions for altered selection criteria

Outcome and estimate, I^2	Altered inclusion/ exclusion criteria	Estimate for altered criteria (OR, 95% CI)	Heterogeneity and number of studies in the analysis I^2, % (N)
Longer term survival OR = 0.49 (0.37 to 0.65), 76%	Ages 16 and over	0.45 (0.34 to 0.60)	71 (6)
	Nontraumatic OHCA only	0.52 (0.35 to 0.77)	77 (7)
	Any attempt at AAI	0.51 (0.38 to 0.68)	74 (11)
Shorter term survival OR = 0.84 (0.62 to 1.13), 92%	Ages 16 and over	0.78 (0.51 to 1.18)	96 (5)
	Nontraumatic OHCA only	1.15 (0.74 to 1.78)	92 (7)
	Any attempt at AAI	0.80 (0.59 to 1.08)	93 (13)

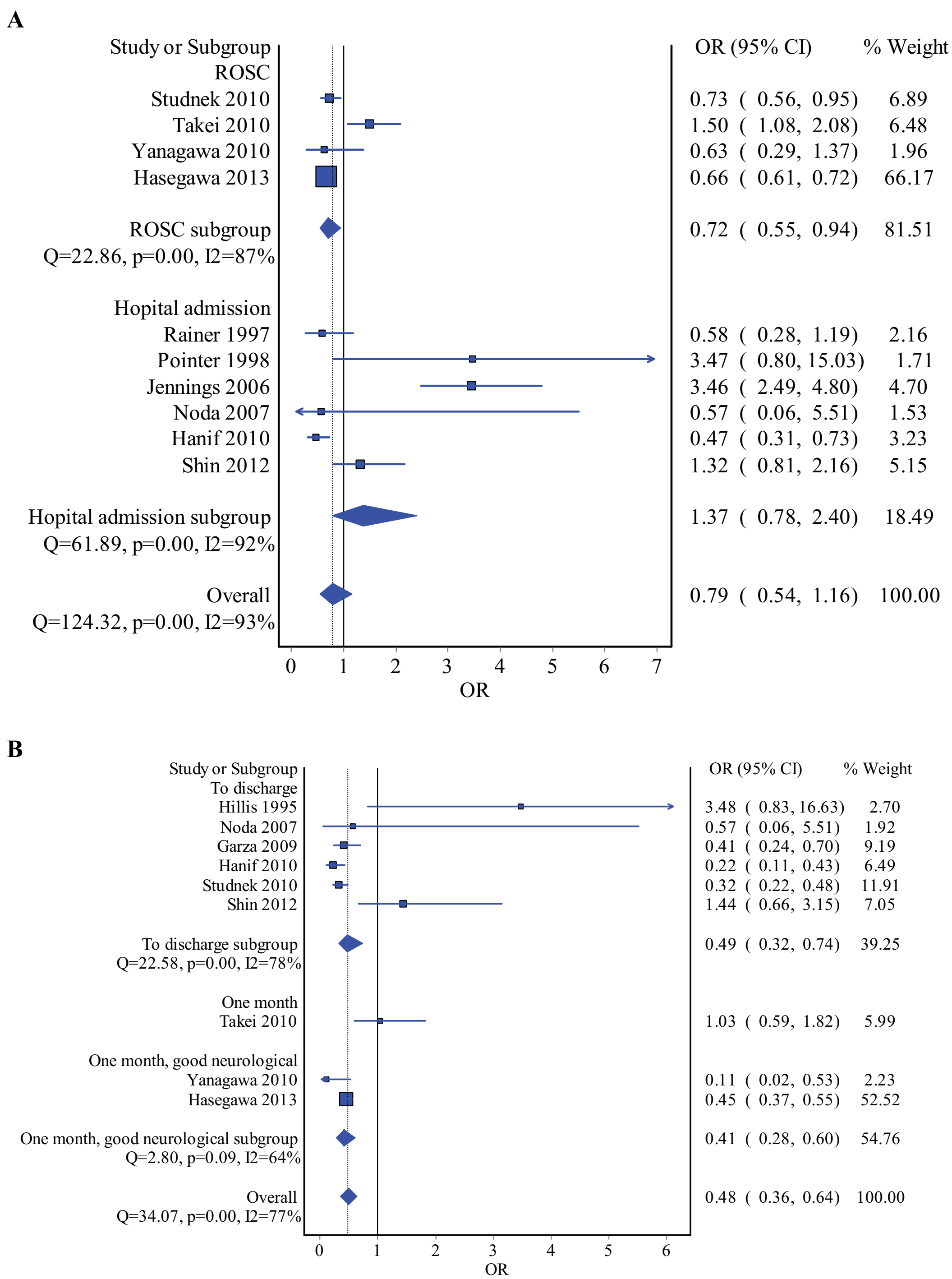
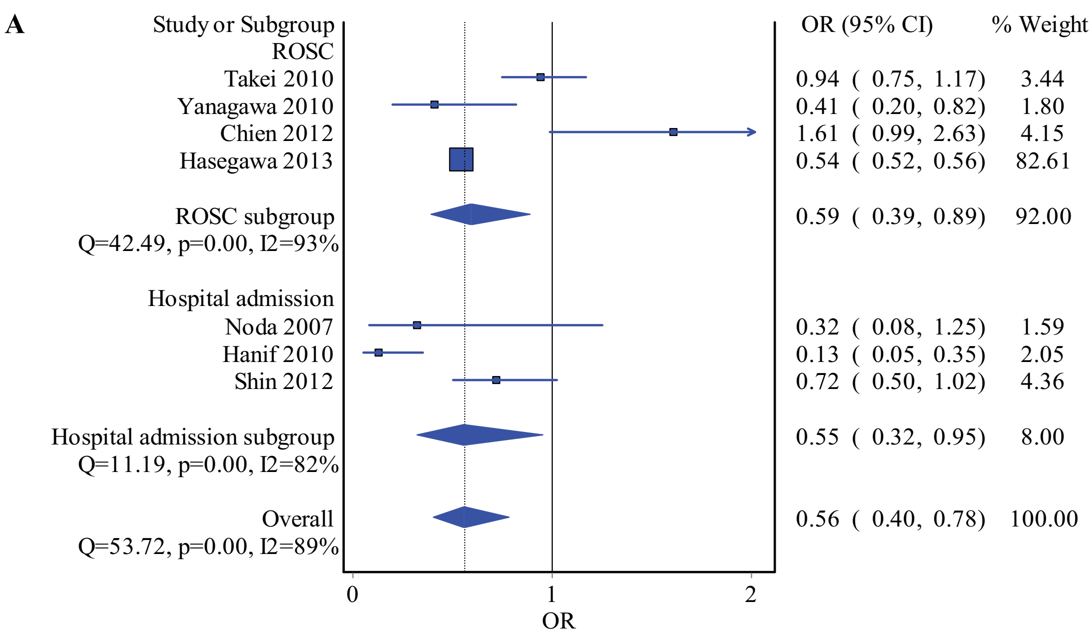


FIGURE 3. ETI compared to BAI for (A) short-term survival and (B) longer term.

TABLE 2b. Sensitivity analysis of endotracheal intubation versus basic airway interventions for altered selection criteria

Outcome and estimate, I^2	Altered inclusion/exclusion criteria	Estimate for altered criteria (OR, 95% CI)	Heterogeneity and number of studies in the analysis I^2, % (N)
Longer term survival OR = 0.48 (0.36 to 0.64), 77%	Ages 16 and over	0.50 (0.36 to 0.69)	83 (6)
	Nontraumatic OHCA only	0.49 (0.32 to 0.74)	78 (6)
	Any attempt at AAI	0.48 (0.35 to 0.67)	84 (11)
Shorter term survival OR = 0.79 (0.54 to 1.16), 93%	Ages 16 and over	0.77 (0.55 to 1.08)	96 (5)
	Nontraumatic OHCA only	0.86 (0.53 to 1.38)	97 (5)
	Any attempt at AAI	0.75 (0.52 to 1.10)	93 (11)



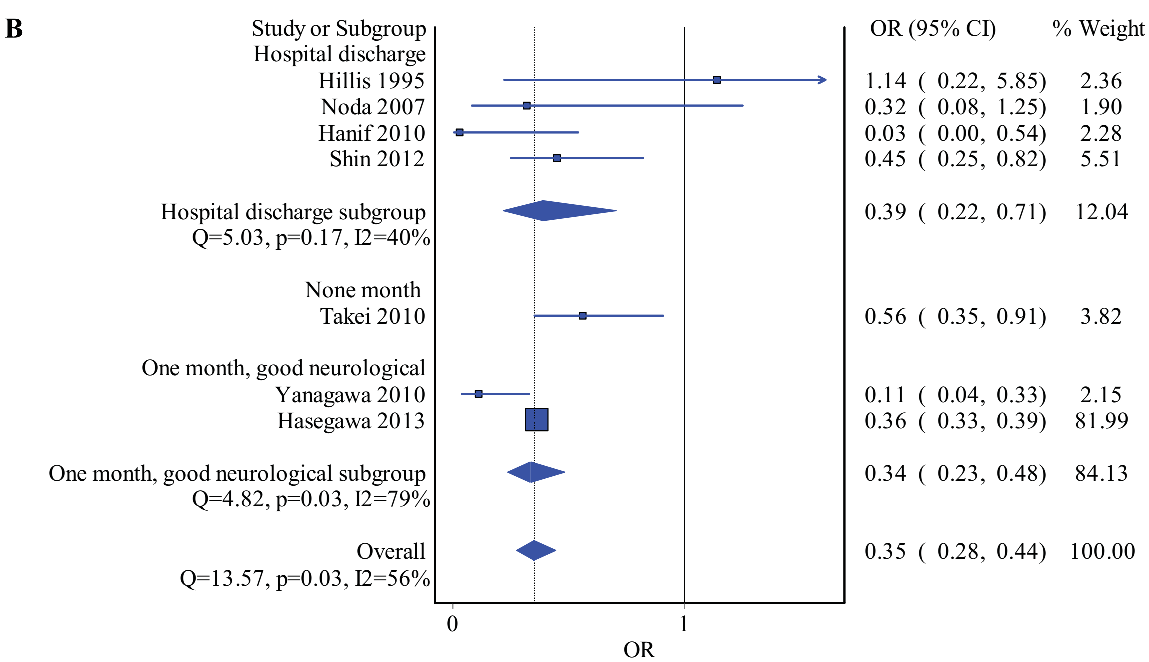


FIGURE 4. Outcomes with supraglottic airways compared to BAI for (A) short-term survival and (B) long-term survival.

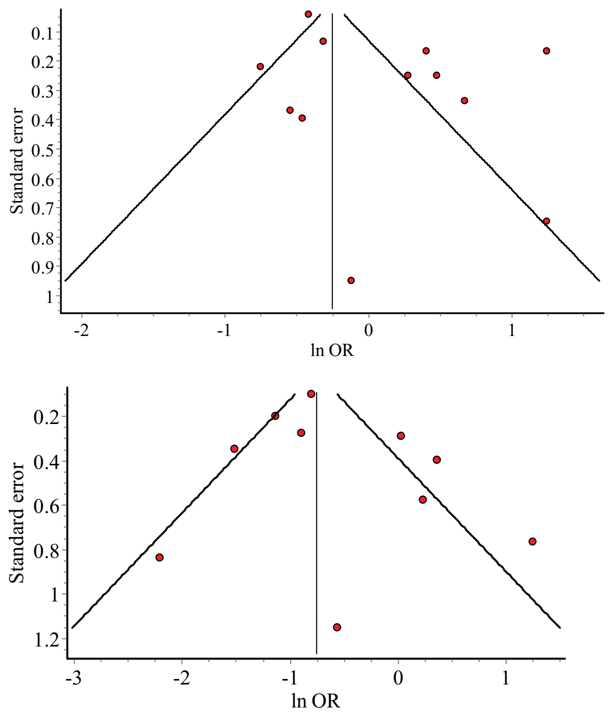


FIGURE 5. Short-term (above) and longer-term (below) survival data funnel plots for all AAI vs. BAI.

addition, many data points lie outside the region in which one would expect 95% of the studies to lie because of large heterogeneity present. This lack of interpretation of the visual appearance of the funnel plot has been a longstanding issue with the use of such plots in meta-analysis.[30]

DISCUSSION

We show decreased short- and longer-term survival for out-of-hospital cardiac arrest patients with EMS airway management of AAI compared to BAI. Additionally, within the AAI group, reduced odds for survival by SGA compared to ETI are evident. From all studies that reported a baseline longer-term survival, we computed a 9% (95% CI 5–12) baseline survival estimate.[6–10,18,24,29,32,33] With this baseline survival and with an odds ratio for longer-term survival of all AAI of 0.49 (interpreted as a risk ratio), it can be estimated (assuming a causal relationship) that[34] for every 23 (95% CI 18–34) cardiac arrest victims treated with AAI as opposed to BAI, one fewer subject would survive to hospital discharge.

While AAI-treated subjects have worse outcomes, it may not be that AAI is harmful, but rather that persons receiving AAI might have a poorer prognosis to begin with and are therefore more likely to receive AAI. [9,10,20,24,25,29] This is what is termed confounding by indication. An example of such a confounder is when persons with rapid ROSC are less likely to receive an advanced airway intervention.[24].Some studies adjusted for confounders associated with poor prognosis after cardiac arrest, but there may be unrecorded patient circumstances that lead to AAI treatment selection. It is therefore probable that the results of this systematic review represent a biased estimate of survival after AAI in cardiac arrest due to insufficient adjustment for confounding. Unfortunately, there is no known way to find out what the extent of these residual confounders may be.[35] Only the Shin et al.[6] and Hasegawa et al.[9] studies used propensity scores for matched analyses created from potential confounders. However, they provide no details of how good a predictor of treatment (AAI vs. BAI) these propensity scores really were.

The disparity in survival estimates between studies could also be a consequence of the different types of AAIs utilized. Disagreements might be explained by recently published studies showing differences in survival between SGAs and ETI,[9,36] with LMA having worse survival. Our findings show poorer short- and long-term survival for patients managed with SGA compared to those managed with ETI. The reason for this difference in survival between ETI and SGA has not been elucidated in this analysis. In the sensitivity analysis an increase in the odds of short-term survival for AAI for nontrauma can be explained by the absence in that analysis of the large study by Hasegawa et al.,[9] since its sample was a mix of trauma and nontrauma. Large heterogeneity was present in most analyses. Our expectation is that the studies selected for this systematic review would be from various geographical regions and over varying times, with considerable differences in the management of cardiac arrest, as well as substantially varying baseline survival rates. It is known that variations in baseline risk and differences in covariates can be a cause of considerable heterogeneity, and in such situations the homogeneity assumption among included studies is very unlikely.[37]

A third of studies[18,19,24,27,28,33] in this meta-analysis did not adjust/match or balance for any confounders, which could make the effects of airway interventions seem worse or better than they would be in reality. None of the included studies adjusted for potentially powerful prognostic factors such as interruptions in chest compressions, delays to defibrillation, hyperventilation, or CPR quality, and may therefore be at risk of producing biased estimates. Wang et al.[38] demonstrated that paramedic intubation is associated with interruptions to chest compressions for a median of 109 seconds.[38] Delays to defibrillation could increase mortality,[39] since rapid prehospital defibrillation is associated with increased survival.[40] There is also evidence that minimal interruptions to CPR and delayed ETI leads to improved survival[21,41–44] and that inadvertent hyperventilation could lead to increased mortality.[45,46] If it is true that confounders such as poor

CPR, hyperventilation, and CPR interruptions are the cause of poorer outcomes, then it might be that AAI devices and their correct use by EMS are not causes of harm.[1] This systematic review does not reveal the extent to which EMS are using AAIs correctly, but has been shown that there is wide variability in EMS intubation success rates and their safe use, possibly due to considerable variations in training and experience.[47] It might be that this variability is associated with poorer outcomes in cardiac arrest. It could be possible to reduce the variability in success rates and harms by EMS, and it might be possible to get success/harm rates on par with emergency physicians and anesthesiologists, with improved training and experience.[48]

While the robust results arising from this analysis provide the clearest evidence to date, there is a clear need for a large randomized trial that compares AAI to BAI. However, the challenges in executing such a study are considerable.[2,49,50] It has been suggested that over 10 000 cardiac arrest victims[51] would be needed to show a 1% difference in survival, making such a trial logistically difficult and perhaps prohibitive. However, it is known that survival from cardiac arrest varies according to location,[51,52] and since baseline survival differences and different survival risks are components of a sample size calculation, one might expect sample sizes for a clinical trial to vary from one region to another. Multicenter studies using clustered clinical trial designs, as seen in the successful ROC collaborations in the United States and Canada, may solve at least some of the logistical problems associated with such an undertaking. A pilot trial would be useful to assess the likely survival difference in a particular area, which could then be used for a sample size calculation. A prospective meta-analysis of multiple smaller centers conducting trials could provide sufficient power.

The results from this systematic review show that there is no high-quality evidence that compares AAI to BAI in cardiac arrest. Evidence from the mainly cohort studies that are combined in a systematic review such as this is considered "low"-quality rating using the GRADE approach.[53] However, at this time such systematic review of observational studies is the best evidence on the optimal airway management of persons in out-of-hospital cardiac arrest, in the absence of controlled trials. The utility of observational data in guiding clinical practice for out-of-hospital ETI has been raised and it is concluded that such data could and should guide our practice,[50] especially in the absence of better evidence.[35] If the evidence is uncertain because of a shortage of randomized trials, but it is clear that there is a strong possibility of serious harm, then lower-quality evidence could be judged sufficient to withdraw an intervention.[35] The results of this systematic review concur with Gausche et al.,[54] Egly et al.,[55] and Mitchell et al.,[56] three studies that did not meet our inclusion criteria but investigated AAI versus BAI in cardiac arrest and showed either decreased or no difference in survival for patients managed with AAI.

Limitations

This is a systematic review of observational studies, and meta-analysis of observational studies is likely to produce a biased estimate that results from residual confounders that the included studies did not adjust/match or balance for sufficiently. No study accounted for important confounders such as interruptions to chest compressions, delays to defibrillation, and hyperventilation. A strength of this meta-analysis is that we have attempted to address these deficiencies when pooling across studies by making use of a meta-analysis model that allows for adjustment of the weighted estimator toward studies of better quality, thus adjusting at analysis level for the effects of study biases. This is in contrast to the usual random effects model where weights are simply redistributed from larger to smaller studies irrespective of their quality.[15,16]

Conclusions

This meta-analysis suggests decreases in survival for out-of-hospital cardiac arrest victims treated by EMS with advanced airway interventions. Results from this meta-analysis agree with studies that compared AAI to BAI not included here. Survival is less for those patients managed with SGAs compared to those managed with ETI. Future observational studies must have a comprehensive list of items that predict treatment selection so that a propensity score can be applied properly. Until then, this review provides evidence that there are no solid grounds for the effectiveness of AAI. However, caution with this interpretation is warranted given the very real possibility of confounding by indication in this group of studies.

References

1. Strote J, Roth R, Cone DC, Wang HE. Prehospital endotracheal intubation: the controversy continues (conference proceedings). Am J Emerg Med. 2009;27(9):1142–7.
2. Thomas MJ, Benger J. Prehospital intubation in cardiac arrest: the debate continues. Resuscitation. 2011;82(4):367–8.
2. . Knobloch K, Yoon U, Vogt PM. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement and publication bias. J Cranio-Maxillo-facial Surg. 2011;39(2):91–2.
4. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Commun Health. 1998;52(6):377–84.
5. Jacobs I, Nadkarni V, Bahr J, Berg RA, Billi JE, Bossaert L, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein

templates for resuscitation registries.: a statement for healthcare professionals from a task force of the international liaison committee on resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa). Resuscitation. 2004;63(3):233–49.

6. Shin SD, Ahn KO, Song KJ, Park CB, Lee EJ. Out-of-hospital airway management and cardiac arrest outcomes: a propensity score matched analysis. Resuscitation. 2012;83(3):313–9.
7. Takei Y, Enami M, Yachida T, Ohta K, Inaba H. Tracheal intubation by paramedics under limited indication criteria may improve the short-term outcome of out-of-hospital cardiac arrests with noncardiac origin. J Anesth. 2010;24(5):716–25.
8. Yanagawa Y, Sakamoto T. Analysis of prehospital care for cardiac arrest in an urban setting in Japan. J Emerg Med. 2010;38(3):340–5.
9. Hasegawa K, Hiraide A, Chang Y, Brown DF. Association of prehospital advanced airway management with neurologic outcome and survival in patients with out-of-hospital cardiac arrest. JAMA. 2013;309(3):257–66.
10. Hanif MA, Kaji AH, Niemann JT. Advanced airway management does not improve outcome of out-of-hospital cardiac arrest. Acad Emerg Med. 2010;17(9):926–31.
11. Takkouche B, Cadarso-Suarez C, Spiegelman D. Evaluation of old and new tests of heterogeneity in epidemiologic meta-analysis. Am J Epidemiol. 1999;150(2):206–15.
12. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clini Trials. 1986;7(3):177–88.
13. Doi SA, Barendregt JJ, Mozurkewich EL. Meta-analysis of heterogeneous clinical trials: an empirical example. Contemp Clin Trials. 2011;32(2):288–98.
14. Doi SA, Thalib L. A quality-effects model for meta-analysis. Epidemiology. 2008;19(1):94–100.
15. Al Khalaf MM, Thalib L, Doi SA. Combining heterogenous studies using the random-effects model is a mistake and leads to inconclusive meta-analyses. J Clin Epidemiol. 2011;64(2):119–23.
16. Doi SA. The case of the king's new clothes: There is no such thing as a random effects meta-analysis 2011 [cited 2013 20 January]; Available from: www.bmj.com/rapid-response/2011/11/03/case-kings-new-clothes-there-no-such-thing-random-effects-meta-analysis.
17. Deeks JJ, Higgins JPT, Altman, DG. Analysing data and undertaking meta-analysis. In: Higgins GL, editor. *Cochrane Handbook of Systematic Reviews*. West Sussex, UK: Wiley-Blackwell; 2008. p. 262.
18. Hillis M, Sinclair D, Butler G, Cain E. Prehospital cardiac arrest survival and neurologic recovery. J Emerg Med. 1993;11(3):245–52.
19. Rainer TH, Marshall R, Cusack S. Paramedics, technicians, and survival from out of hospital cardiac arrest. J Accident Emerg Med. 1997;14(5):278–82.
20. Chien LC, Hsu HC, Lin CH, Cheng CF, Tung YC, Hung HC, et al. Use of an intubating laryngeal mask airway on out-of-hospital cardiac arrest patients in a developing emergency medical service system. J Formos Med Assoc. 2012;111(1):24–9.
21. Garza AG, Gratton MC, Salomone JA, Lindholm D, McElroy J, Archer R. Improved patient survival using a modified resuscitation protocol for out-of-hospital cardiac arrest. Circulation. 2009;119(19):2597–605.
22. Nakahara S TJ, Ichikawa M, Morimura N, Nishida M, Sakamoto T. Effectiveness of advanced airway management by paramedics for witnessed out-ofhospital cardiac arrest of cardiac origin. Resuscitation. 2010;81(2): S18.
23. Turgulov A, Rac V, Kierzek G, Morrison LJ. Field intubation of patients with cardiac arrest: a dying art or just a question of timing? Emerg Med J. 2011;28(2):171–2.
24. Adams JN, Sirel J, Marsden K, Cobbe SM. Heartstart Scotland: the use of paramedic skills in out of hospital resuscitation. Heart. 1997;78(4):399–402.
25. Holmberg M, Holmberg S, Herlitz J. Low chance of survival among patients requiring adrenaline (epinephrine) or intubation after out-of-hospital cardiac arrest in Sweden. Resuscitation. 2002;54(1):37–45.
26. Jennings PA, Cameron P, Walker T, Bernard S, Smith K. Out-of-hospital cardiac arrest in Victoria: rural and urban outcomes. Med J Aust. 2006;185(3):135–9.
27. Lyon RM, Ferris JD, Young DM, McKeown DW, Oglesby AJ, Robertson C. Field intubation of cardiac arrest patients: a dying art? Emerg Med J. 2010;27(4):321–3.
28. Pointer JE. Clinical characteristics of paramedics' performance of pediatric endotracheal intubation. Am J Emerg Med. 1989;7(4):364–6.
29. Studnek JR, Thestrup L, Vandeventer S, Ward SR, Staley K, Garvey L, et al. The association between prehospital endotracheal intubation attempts and survival to hospital discharge among out-of-hospital cardiac arrest patients. Acad Emerg Med. 2010;17(9):918–25.
30. Terrin N, Schmid CH, Lau J. In an empirical evaluation of the funnel plot, researchers could not visually identify publication bias. J Clin Epidemiol. 2005;58(9):894–901.
31. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. Psychol Bull. 1979;86(2):420–8.
32. Nagao T, Kinoshita K, Sakurai A, Yamaguchi J, Furukawa M, Utagawa A, et al. Effects of bag-mask versus advanced airway ventilation for patients undergoing prolonged cardiopulmonary resuscitation in pre-hospital setting. J Emerg Med. 2012;42(2):162–70.
33. Noda E, Zaitsu A, Hashizume M, Takahashi S. Prognosis of patient with cardiopulmonary arrest transported to Kyushu University Hospital. Fukuoka Igaku Zasshi = Hukuoka Acta Medica. 2007;98(3):73–81.
34. McQuay HJ, Moore RA. Using numerical results from systematic reviews in clinical practice. Ann Intern Med. 1997;126(9):712–20.
35. Reeves BC, Deeks JJ, Higgins JPT, Wells GA. Chapter 13: Including non-randomized studies. In: Higgins GL, editor. *Cochrane Handbook for the Systematic Review of Interventions*. Chichester UK: John Wiley & Sons; 2008. p. 391.
36. Wang HE, Szydlo D, Stouffer J, Lin S, Carlson J, Vaillancourt C, et al. Endotracheal Intubation versus supraglottic airway insertion in out-of-hospital cardiac arrest. Resuscitation. 2012.
37. Greenland S, O'Rourke K. Meta-analysis. Modern Epidemiology, 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008:671.
38. Wang HE, Simeone SJ, Weaver MD, Callaway CW. Interruptions in cardiopulmonary resuscitation from paramedic endotracheal intubation. Ann Emerg Med. 2009;54(5):645–52 e1.
39. Valenzuela TD, Roe DJ, Cretin S, Spaite DW, Larsen MP. Estimating effectiveness of cardiac arrest interventions: a logistic regression survival model. Circulation. 1997;96(10):3308–13.
40. Stiell IG, Wells GA, Field B, Spaite DW, Nesbitt LP, De Maio VJ, et al. Advanced cardiac life support in out-of-hospital cardiac arrest. N Engl J Med. 2004;351(7):647–56.
41. Bobrow BJ, Clark LL, Ewy GA, Chikani V, Sanders AB, Berg RA, et al. Minimally interrupted cardiac resuscitation by emergency medical services for out-of-hospital cardiac arrest. JAMA. 2008;299(10):1158–65.
42. Ewy GA, Kern KB, Sanders AB, Newburn D, Valenzuela TD, Clark L, et al. Cardiocerebral resuscitation for cardiac arrest. Am J Med. 2006;119(1):6–9.
43. Kellum MJ, Kennedy KW, Barney R, Keilhauer FA, Bellino M, Zuercher M, et al. Cardiocerebral resuscitation improves

neurologically intact survival of patients with out-of-hospital cardiac arrest. Ann Emerg Med. 2008;52(3):244–52.
44. Kellum MJ, Kennedy KW, Ewy GA. Cardiocerebral resuscitation improves survival of patients with out-of-hospital cardiac arrest. Am J Med. 2006;119(4):335–40.
45. Aufderheide TP, Lurie KG. Death by hyperventilation: a common and life-threatening problem during cardiopulmonary resuscitation. Crit Care Med. 2004;32(9 Suppl):S345–51.
46. Pitts S, Kellermann AL. Hyperventilation during cardiac arrest. Lancet. 2004;364(9431):313–5.
47. Lossius HM, Roislien J, Lockey DJ. Patient safety in pre-hospital emergency tracheal intubation: a comprehensive meta-analysis of the intubation success rates of EMS providers. Crit Care. 2012;16(1):R24.
48. Fouche PF, Middleton PM, Zverinova KM. Training and experience are more important than the type of practitioner for intubation success. Crit Care. 2013;17(1):412.
49. Cone DC, Middleton PM. ROC, paper, scissors: tracheal intubation or supraglottic airway for out-of-hospital cardiac arrest? Resuscitation. 2012;83(9):1047–8.
50. Wang HE, Bogucki S. Out-of-hospital endotracheal intubation: are observational data useful? Acad Emerg Med. 2010;17(9):987–8.
51. Nichol G, Thomas E, Callaway CW, Hedges J, Powell JL, Aufderheide TP, et al. Regional variation in out-of-hospital cardiac arrest incidence and outcome. JAMA. 2008;300(12):1423–31.
52. Sanders AB, Kern KB. Surviving cardiac arrest: location, location, location. JAMA. 2008;300(12):1462–3.
53. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004;328(7454):1490.
54. Gausche M, Lewis RJ, Stratton SJ, Haynes BE, Gunter CS, Goodrich SM, et al. Effect of out-of-hospital pediatric endotracheal intubation on survival and neurological outcome: a controlled clinical trial. JAMA. 2000;283(6):783–90.
55. Egly J, Custodio D, Bishop N, Prescott M, Lucia V, Jackson RE, et al. Assessing the impact of prehospital intubation on survival in out-of-hospital cardiac arrest. Prehospital Emerg Care. 2011;15(1):44–9.
56. Mitchell RG, Guly UM, Rainer TH, Robertson CE. Can the full range of paramedic skills improve survival from out of hospital cardiac arrests? J Accident Emerg Med. 1997;14(5): 274–7.

SUPPLEMENTAL MATERIAL AVAILABLE ONLINE

Appendix 1—Search Terms

Appendix 2—Quality Checklist (Table 3)

Appendix 3—Random Effect vs. Quality Effects Estimates for AAI vs. BAI (Tables 4–6)

Appendix 4—Adjustment/Balancing or Matching of Potentially Confounding Variables for Extracted Estimate Suitable for Meta-analysis (Table 7)