FACULTY OF MEDICINE AND HEALTH SCIENCES

Out-of-hospital paediatric endotracheal intubation: A Narrative Review

Timothy De Moor
Student number: 01509352

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A dissertation submitted to Ghent University in partial fulfilment of the requirements for the degree of Master of Medicine in Medicine.

Academic year: 2018 – 2020

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Abstract *(English version)*

Background: The protection of respiratory integrity is of paramount importance in managing every type of emergency patient. Although paediatric patients only make up a slight portion of the cases emergency medical service (EMS) providers have to manage, they still represent an important aspect of emergency medical care. Endotracheal intubation (ETI) is widely accepted as the ideal procedure in this instance and thus regularly employed by EMS providers. Despite its frequent use however, the incidence of reports on the potential risks of this procedure in both paediatric and adult patients remains high. As opposed to adult resuscitation, the paediatric population lacks clinical trials to support choices in paediatric airway management. Though in more recent years, a considerable amount of large observational studies has been published on the topic of paediatric resuscitation. This narrative review was designed to attain a comprehensive overview of available literature concerning out-of-hospital paediatric ETI, compared with other airway management techniques.

Objective: To assess the use of endotracheal intubation, compared with all other methods of airway management, for resuscitation of children (< 18 years) with life-threatening afflictions in an out-of-hospital setting.

Search methods: A search of both the PubMed and Embase database (which also includes indexed articles in MEDLINE) was performed. Reference lists of articles were also consulted to include as many relevant articles as possible. Ultimately, 1198 unique articles were reviewed for relevance.

Selection criteria: Both randomised and non-randomised studies comparing endotracheal intubation with other airway management techniques in the out-of-hospital paediatric population.

Main results: A total of 9 studies met eligibility criteria and were ultimately included in this review. These studies include one pseudo-randomised clinical trial, three propensity score-matched cohort studies and six simple cohort studies. The overall certainty of evidence was very low. For the outcomes of survival to hospital discharge and survival with good neurological function results showed a slight advantage of BVM over ETI. When comparing ETI and no-ETI no significant difference in outcome was determined.

Authors' conclusions: Overall, the available evidence suggests a slight advantage of BVM compared to ETI in children in an out-of-hospital setting. Regarding ETI non-attempt, available evidence suggested no significant difference with ETI in the same setting. High-quality randomised clinical trials are needed to confirm these findings.

Abstract *(Dutch version)*

Inleiding: De bescherming van respiratoire integriteit is immens belangrijk in elk type spoedpatiënt. Hoewel de pediatrische patiënt slechts een klein aandeel opbouwt van de patiëntenpopulatie die het medisch noodpersoneel dient te managen, blijven ze een belangrijk onderdeel uitmaken van de urgentiegeneeskunde. Endotracheale intubatie (ETI) wordt wijdverspreid beschouwt als de ideale procedure om dit te doen, en wordt dus regelmatig toegepast door het medisch noodpersoneel. Desondanks het frequent gebruik, blijft men meldingen krijgen omtrent de potentiële risico's van deze techniek zowel in pediatrische als volwassen patiënten. In tegenstelling tot deze volwassen patiënten, ontbreekt er voor de pediatrische patiënt nog kwaliteitsvolle klinische trials die duidelijkheid geven in pediatrische luchtwegmanagement. De laatste jaren zijn er echter meerdere grootschalige, observationele studies gepubliceerd over dit topic. Deze narratieve review werd opgesteld om een duidelijk overzicht te bieden van de bestaande literatuur omtrent pediatrische luchtwegmanagement in een prehospitaal setting. Specifiek werd er gezocht naar de vergelijking tussen ETI en andere technieken beschikbaar voor luchtwegmanagement in deze setting.

Doelstelling: Evaluatie van het gebruik van endotracheale intubatie voor de cardiopulmonale resuscitatie van kinderen (< 18 jaar) met levensbedreigende aandoeningen in een prehospitaal setting. Hierbij wordt een vergelijking gemaakt met enkele bestaande alternatieven om de pediatrische luchtweg te managen.

Methode: Zowel de PubMed als de Embase database (die ook geïndexeerde artikels uit MEDLINE omvat) werden doorzocht voor relevante artikels. Referentielijsten van bestaande systematische reviews werden nagekeken voor bijkomende artikels. In totaal werden er 1198 unieke artikels gevonden die vervolgens gescreend werden op relevantie.

Selectie criteria: Zowel gerandomiseerde als niet-gerandomiseerde artikels die een vergelijking maken tussen endotracheale intubatie en andere procedures om de pediatrische luchtweg te managen in een prehospitaal setting.

Resultaten: In totaal voldeden 9 studies aan de selectie criteria waarop ze geïncludeerd werden in deze review. Deze studies bestaan uit één pseudo-gerandomiseerde klinische trial, drie propensity score-matched cohorte studies en zes eenvoudige cohorte studies. De algemene zekerheid van evidentie is zeer laag. Voor de belangrijke uitkomsten 'survival to hospital discharge' en 'survival with good neurological function' werd een klein voordeel gezien voor BVM tegenover ETI. Bij de vergelijking tussen ETI en no-ETI werd er voor dezelfde uitkomsten geen significant verschil vastgesteld.

Conclusies: De beschikbare evidentie suggereert een beperkt voordeel wanneer BVM gebruikt wordt ten opzichte van ETI in kinderen in de prehospitaal setting. In verband met ETI non-attempt, suggereert de beschikbare evidentie geen significant onderscheid met ETI in dezelfde setting. Er is nood aan kwaliteitsvolle klinische trials om deze bevindingen te bevestigen.

1. Introduction

Emergency airway management

The protection of respiratory integrity is of paramount importance in managing every type of emergency patient (1, 2). The establishment and maintenance of a functioning airway remains one of the single most important initial therapies provided to severely injured patients and the inability to do so could have detrimental effect on patients neurological outcome and overall survival. Common examples of adverse outcomes associated with failed emergency airway management include brain damage, cardiac arrest and death due to hypoxia (3).

When managing an emergency patient's airway, the out-of-hospital environment poses a greater challenge compared to the in-hospital environment, with a prevalence of difficult airways of up to ten times higher (4). "Difficult airways" can be defined as the occurrence of one or more complications during initial airway management. Frequently arising problems include main stem bronchus intubation, gastric regurgitation, hypoxemia, cardiac arrest, oesophageal intubation and dental trauma. The higher incidence of difficult airways in the out-of-hospital setting can be linked directly to trauma patients having an increased risk of hemodynamic instability and higher need for cervical spine protection. Additionally, the high acuity of the situation and increased agitation of the patient can potentially lead to poor initial evaluation by emergency medical service (EMS) personnel (5). The competence of the provider, in this case an anaesthetist or emergency nurse, has been shown to be a key factor in patient outcome. Training EMS personnel with a focus on airway management and emergency anaesthesia is therefore considered as crucially important (4, 6).

Endotracheal intubation in emergency medicine

In airway management a clear distinction is made between basic (e.g. bag-valve-mask devices) and advanced airway management (e.g. supra- and infraglottic devices), with both approaches leading to an improved survival with good neurological and/or functional outcome when performed during cardiopulmonary resuscitation (CPR). However, the optimal approach to establish a secure airway during CPR is not clear and multiple studies have challenged the assumption that advanced airways are superior to basic airway management techniques. A commonly used technique, involved in this discussion, is endotracheal intubation (ETI) (7).

ETI is a technique frequently used by EMS personnel in patients requiring CPR. It plays an

imperative role during advanced airway management, specifically in maintaining respiratory integrity and haemodynamic stability (1). Although indications, procedures and providers of ETI vary widely, the current treatment recommendations from the International Liaison Committee on Resuscitation (ILCOR) recommend ETI as the ideal way to secure the airway during resuscitation (2, 7-11).

Despite the broad application of this intervention however, conclusive evidence of the advantages of intubation versus non-intubation in emergency settings has not been obtained due to a lack of randomised clinical trials comparing both interventions (12). The exact place of ETI during both in- as out-of-hospital CPR remains uncertain with the possibility of both benefit and harm (13, 14). Retrospective observational studies form the basis for current research involving ETI, and are showing conflicting results. Some of these studies suggest an improvement in neurological outcome and overall survival (15), whilst others show no survival benefit at all (16). A few even show adverse outcomes when out-of-hospital ETI was performed (17-20). Most notably, a matched cohort study performed by Haltmeier et al. showed an increase of in-hospital mortality in patients who underwent out-of-hospital ETI for isolated severe blunt traumatic brain damage (19).

The technique used to perform ETI, usually performed as rapid sequence induction intubation (RSI), can vary considerably across different ED's (8). Many new technological developments have made their way into the daily routine of pre-hospital care providers lately. These new developments range from different laryngoscope blades to various oral and nasal airways, and an increased usage of video-laryngoscopy (1, 2, 16, 21-23). Numerous of these advanced airway techniques are available in both the in- and out-of-theatre setting, with the chosen technique often depending on the general condition of the patient and personal preference of the provider. The advanced airway techniques which are routinely applied in emergency medicine are displayed in **Figure 1**. Listed from least to most invasive, these include: supraglottic devices, infraglottic techniques (which encapsulates tracheal intubation) and surgical methods (1).

In spite of its frequent use in advanced airway management, out-of-hospital ETI remains a challenging technique with success rates varying from 64 to 91,7% for paramedics and from 98,7 to 99,5% for anaesthetists depending on the study (5, 8, 15, 24). Complication rates can go as high as 33,2% when dealing with difficult airways (24). Some complications can even be life-threatening and include aspiration, cardiovascular collapse and hypoxemia. However, the extent to which these complications affect the overall patient outcome is currently unknown (5). The use of a standard operating procedure (SOP) has been shown to diminish immediate and severe life-threatening complications in intubated intensive care unit (ICU) patients, while simultaneously removing the

need for individual procedural preference (25, 26). This aspect of ETI is discussed in the 'Standard operating procedure for endotracheal intubation' section of this introduction.

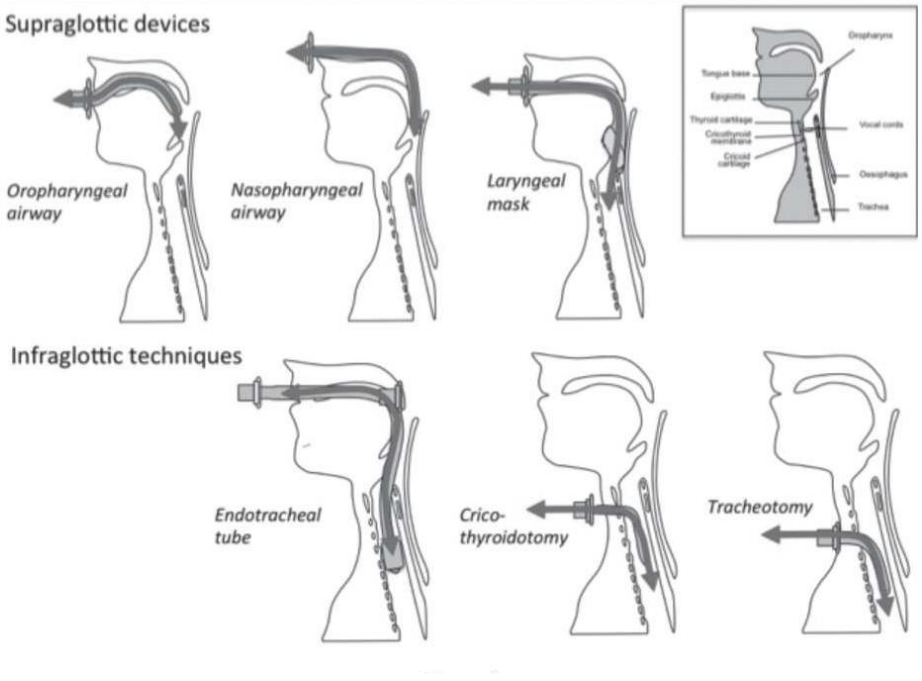

Figure 1. Airway management: supra- and infraglottic techniques (X. Muschart 2016)

Paediatric versus adult endotracheal intubation

Although paediatric patients only make up a slight portion of the cases EMS providers have to manage, they still represent an important aspect of emergency medical care. It is estimated that paediatric patients comprise approximately 10% of all EMS cases, with roughly 4.5% of those requiring advanced airway management (27, 28). Although ETI continues to be a frequently used technique in emergency medicine (mainly in prehospital adult patients), the incidence of reports on the potential risks of this procedure in both paediatric and adult patients remains high (29, 30). An important factor herein might be a lack of randomised clinical trials examining the safety and efficacy of ETI in paediatric patients and thus leading to inadequate guidelines (31).

In order to benefit from advanced airway techniques, like ETI, both prehospital and hospital providers require a considerable amount of training and expertise. Furthermore, paediatric intubation is perceived as a more difficult airway management technique to perform safely and effectively and therefore requires additional training in comparison to adult intubation. Despite the

need for additional training however, similar outcomes can be perceived in paediatric and adult patients when ETI was performed by an experienced paramedic (27). A more recent study performed by Hansen et al., did show a reduced success rate of ETI when performed in paediatric patients compared to adult patients, but no post-intubation outcomes were assessed during this study (28).

Standard operating procedure for endotracheal intubation

The standard operating procedure of performing ETI can vary extensively between different emergency medicine services. In spite of this, certain focal points remain the same throughout these different systems. The algorithm for difficult out-of-hospital airway management presented by Trimmel et al. in a 2018 retrospective quality control study can be used to present the fundamental steps when performing ETI (4). For a more global overview of advanced life support, with less focus on out-of-hospital ETI, please refer to the European Resuscitation Council Guidelines for Resuscitation (10, 32, 33).

The first step of out-of-hospital difficult airway management consists of proper assessment of the airway, followed by preoxygenation and starting rapid sequence induction. Rapid sequence induction consists of securing patient position, physiological optimisation, monitoring (ECG, SpO_2, NiBP and $ETCO_2$) and administering analgesic drugs to facilitate intubation. The drugs used, usually consist of an induction agent (e.g. ketamine) paired with a paralytic agent (e.g. rocuronium). Preferably administered through a central line while being monitored with an invasive arterial line. The preference for different agents varies across different algorithms (4, 26).

The second step introduces endotracheal intubation. ETI can provide the most reliable airway when administered correctly, but may lead to severe complications when administered incorrectly. Therefore, it should only be used by pre-hospital care providers who are regularly trained and experienced in its use. Endotracheal intubation should never delay resuscitation or defibrillation attempts. Alternatively, a supraglottic airway device (SAD) is used for intubation (5, 8, 26, 32).

When two intubation attempts have failed, a third step is initiated, in which two pre-hospital providers provide oxygenation through a bag-valve mask, or through oropharyngeal or nasopharyngeal airways. If no control has been regained over oxygenation or the return of spontaneous circulation in this phase, preparations should be made to perform a surgical airway. A cricothyrotomy is the fourth, and final, step in advanced airway management (4, 10, 26, 32, 33).

Note that these recommendations only follow the algorithms provided by Trimmel et al. (4)

and the European Resuscitation Council Guidelines for Resuscitation (10, 32, 33). Algorithms vary immensely between different publications, from three intubation attempts instead of two (26) to differing methods for initial intubation (11). The ideal algorithm for advanced airway management has yet to be constructed, and will require further high-quality research.

Comparable to the use of ETI, it remains imperative to regularly educate and train emergency service providers to ensure appropriate use of a SOP (if introduced into an emergency department). Assimilation in the unit's RSI programme, combined with routine training in an actual working environment has been presumed to be most pertinent in maximising the impact of a SOP (26).

Aim of this review

No consensus has been reached about an optimal approach for managing the airway in severely ill, paediatric patients (1). The goal of this review is to attain a comprehensive overview of available literature concerning out-of-hospital paediatric ETI compared with other airway management techniques. The publications enclosed within can thus be evaluated in view of future protocol development within the current emergency medicine structure.

2. Methods

Scope

Children (≤ 19 years) with severe, often life threatening, afflictions requiring airway interventions in an out-of-hospital setting.

Protocol

The Cochrane Handbook for Systematic Reviews of Interventions was consulted for the planning and design of this narrative review. Reporting of the literary search is in consistency with the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines (Figure 2).

Search strategy

A search of both the PubMed and Embase databases was performed. The search strategy used all word variations of [out-of-hospital] and [paediatric] combined with all word variations of [endotracheal intubation] and [rapid sequence induction]. Using Boolean operators we aimed for high sensitivity, yet accepted low precision of the search results. All articles published up until April 2019 involving human participants were included in the search. No further restrictions based on language, study design (with the sole exception being case reports) or number of participants were made in the initial search. The complete search strategy can be found in the Additional files of this review.

In addition, the bibliography of systematic reviews and included studies, found in the previously described search, were screened for relevant articles. Ultimately, 1198 unique articles were found which were screened for relevance based on title and abstract.

Eligibility criteria

Both randomised and non-randomised studies comparing endotracheal intubation with other airway management techniques in the out-of-hospital paediatric (≤ 19 years) population were included. Studies combining paediatric and adult populations were only included if they contained distinguishable paediatric results. No specific outcome criterion was used in the eligibility selection.

Case reports; case series; meeting abstracts; conference abstracts, papers or reviews; letters; editorials and reviews were excluded. Publications with no available full text, non-English text or no comparison group when examining interventions, were also excluded. When no full text was found using the Endnote [Find Full Text] option, an autonomous search by the author was done to try and include these articles nonetheless.

Study selection

Both title and abstract of all articles identified in the search were screened using a Microsoft Excel spreadsheet. Eligibility criteria were assessed in order of importance and a single failed eligibility criterion was deemed sufficient for exclusion of an article from the review. The primary reason for each excluded article was consequently noted in the spreadsheet.

Data Extraction

All remaining articles, after selection, were categorized based on study design and cause for intubation. This granted a comprehensible overview of the available literature.

Risk of bias in individual studies

Study quality and risk of bias was estimated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach for clinical trials. For cohort studies, the Clinical Advances Through Research and Information Translation (CLARITY) tool was used. The risk of bias assessment for each individual study can be found in the additional files of this review.

Results

A PRISMA Flow Diagram summarizing the search strategy used in this narrative review is pictured in **Figure 2**.

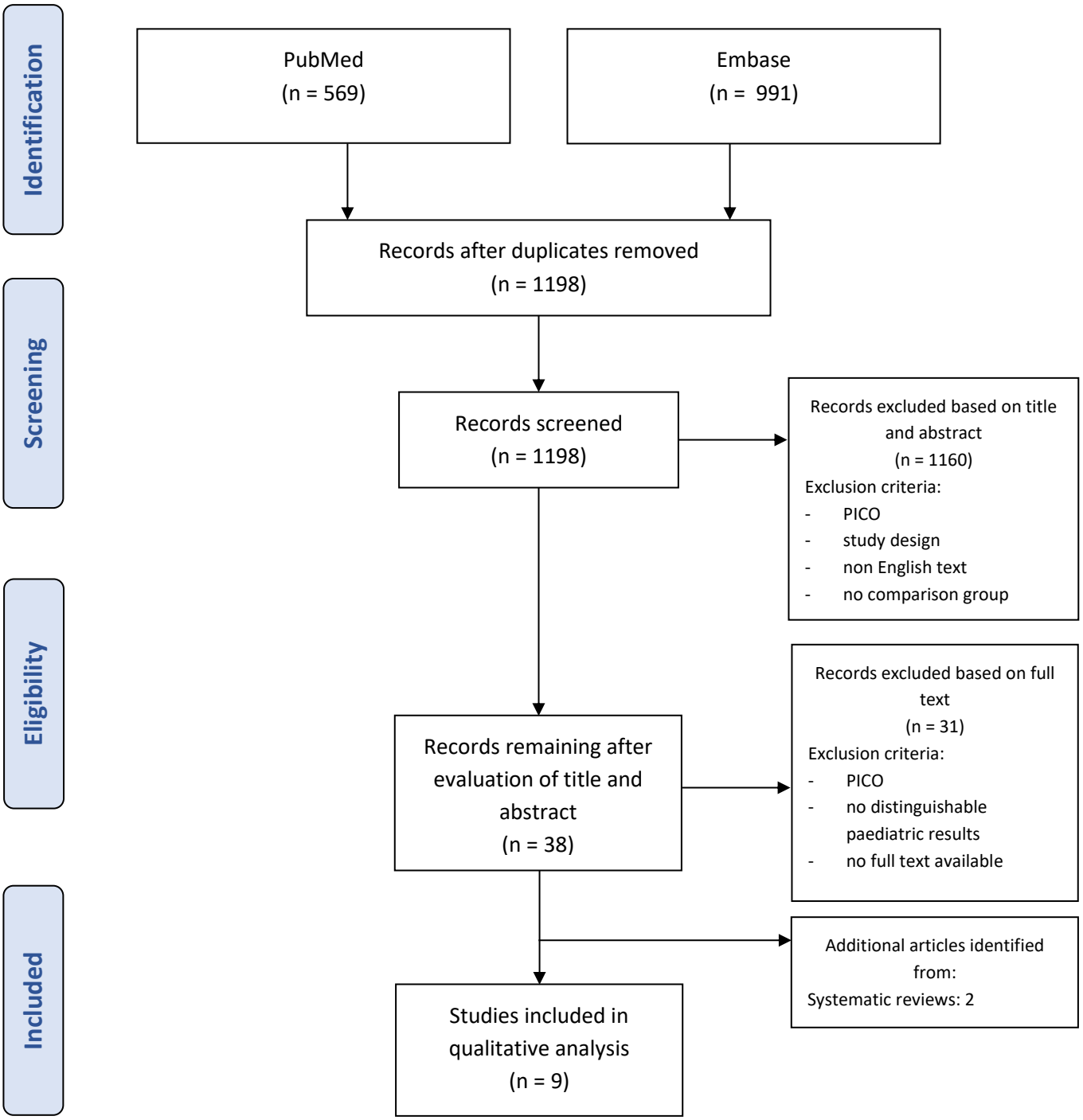

Figure 2. PRISMA Flow Diagram summarizing the search strategy

3. Results

Study selection

All articles published up until April 2019 were included in the search. A detailed description of the search strategy can be found in the additional files of this review. The search identified 1198 unique articles, of which nine ultimately met inclusion criteria. Two additional articles were added through reference list review of relevant systematic reviews concerning paediatric ETI.

Study characteristics

One pseudo-randomised clinical trial, three propensity score-matched observational studies and six observational studies were identified. Characteristics of these studies are illustrated in **Table 1**. Four studies confined to out-of-hospital cardiac arrest as the sole indication for ETI, while the remaining studies retained a vast amount of indications. All studies compared ETI with other methods of airway management including, but not limited to, bag-valve-mask ventilation and supra-glottic airway devices. All studies focused exclusively on paediatric populations (≤ 19 years).

Risk of bias within studies

A detailed description of the risk of bias assessment for each individual study can be found in the additional files of this review. One controlled clinical trial was identified as having no serious risk of bias. Three propensity-matched cohorts were assessed as having serious risk of bias. Five remaining non-propensity-matched cohort studies were assessed as having a serious risk of bias. An important distinction between the propensity matched and non-propensity matched cohorts was the presence of matching exposed and unexposed for all variables associated with the outcome of interest, leading to different assessments of risk of bias.

Synthesis of results

A comparison of essential outcomes within studies is presented in **Table 2-3**. These Summary of Findings Tables were established using the Cochrane Handbook for Systematic Reviews of Interventions.

Table 1 – characteristics of included studies.

Study	Design	Years conducted	Setting [a]	Location	Participant age (yr) [b]	Study size [c]	Means of allocation	Advanced airway interventions studied	Outcomes assessed	Notes
Aijian et al. (34)	Cohort study (retrospective)	1984-1987	Respiratory failure	USA	< 19	63	N.A.	ETI successful vs ETI unsuccessful vs ETI not attempted	• SED • SHA • SHD	*OHCA*
Gausche et al. (35)	Controlled Clinical Trial	1994-1997	All settings	USA	< 13	830	Even/odd day	BVM with subsequent ETI vs BVM alone	• SHD • SGNF • complications	
Pitetti et al. (36)	Cohort study (retrospective)	1986-1999	Respiratory failure	USA	3.4 (4.6)	189	Location based	ALS vs BLS (including BVM)	• SHD	*OHCA*
Cooper et al. (37)	Cohort study (retrospective)	1985- 1999	Trauma	USA	< 20	578	N.A.	ETI vs BVM	• mortality • complications • functional outcome	*TBI*
Gerritse et al. (38)	Cohort study (prospective)	2001-2006	All settings	The Netherlands	6.8 (5.4)	300	N.A.	ETI vs BVM with subsequent ETI	• successful ETI • SHD	*ETI group has significantly worse prognosis before intervention*
Allen et al. (39)	Cohort study (retrospective, propensity matched)	2000-2012	Trauma	USA	11 (6)	1884	N.A.	ETI vs no ETI	• EMS transportation time • mortality	
Ohashi-Fukuda et al. (40)	Cohort study (retrospective, propensity matched)	2011-2012	Respiratory failure	Japan	9.0 (5.9)	2157	N.A.	AAM (SGA or ETI) vs BVM	• SGNF (after 1 month) • survival (after 1 month) • ROSC	*OHCA*
Heschl et al. (41)	Cohort study (retrospective)	2005-2013	Trauma	Australia	< 15	106	N.A.	ETI (RSI) vs ETI not attempted	• SHD • functional outcome	*TBI*
Hansen et al. (42)	Cohort study (retrospective, propensity matched)	2013-2015	Respiratory failure	USA	3.7 (0.1)	1724	N.A.	ETI vs BVM and SGA vs BVM	• SHA • SHD • SGNF • ROSC (sustained for 20 mins)	*OHCA*

[a] Subdivided in respiratory failure, reduced consciousness or trauma.

[b] Mean (standard deviation) if not indicated otherwise.

[c] Only includes study population incorporated in the study analysis; yr: year; USA: United States of America; ETI: endotracheal intubation; SED: survival to emergency department; SHA: survival to hospital admission; SHD: survival to hospital discharge; OHCA: out-of-hospital cardiac arrest; AD: airway device; SGNF: survival with good neurological function; ALS: advanced life support; BLS: basic life support; BVM: bag-valve-mask ventilation; TBI: traumatic brain injury; EMS: emergency medical services; AAM: advanced airway management; SGA: supra-glottic airway; RSI: rapid sequence intubation; ROSC: return of spontaneous circulation.

Table 2 – summary of findings: endotracheal intubation vs. bag-valve-mask ventilation.

Certainty assessment					No. of patients		Effect [a]		Certainty
Study	Design	Advanced airway interventions studied	Outcome assessed	Risk of bias [b]	Intervention 1 (ETI)	Intervention 2 (BVM)	Relative Risk (95% CI)	Risk Difference (95% CI)	
Gausche et al. (35)	Controlled Clinical Trial	BVM with subsequent ETI vs BVM alone	SHD	Not serious	110/416 [26%]	123/404 [30%]	0.87 (0.70-1.08)	-0.04 (-0.10-0.02)	Low
			SGNF	Not serious	85/416 [20%]	92/404 [23%]	0.90 (0.69-1.16)	-0.02 (-0.08-0.03)	Low
Pitetti et al. (36)	Cohort study (retrospective)	ALS vs BLS (including BVM)	SHD	Very serious	5/150 [3%]	0/39 [0%]	2.91 (0.36-infinity)	0.03 (-0.06-0.08)	Very low
Cooper et al. (37)	Cohort study (retrospective)	ETI vs BVM	Survival	Very serious	N.A. [48%]	N.A. [48%]	N.A.	N.A.	Very low
			Functional outcome	Very serious	N.A. [65.7%]	N.A. [65.2%]	N.A.	N.A.	Very low
			Complications	Very serious	N.A. [58%]	N.A. [71%]	N.A.	N.A.	Very low
Gerritse et al. (38)	Cohort study (prospective)	ETI vs BVM with subsequent ETI	SHD	Very serious	2/41 [5%]	37/54 [69%]	0.07 (0.02-0.24)	-0.64 (-0.76-(-0.47))	Very low
			Success rate	Very serious	26/41 [63%]	54/54 [100%]	0.64 (0.49-0.77)	-0.37 (-0.52-(-0.24))	Very low
Ohashi-Fukuda et al. (40)	Cohort study (retrospective, propensity matched)	AAM (SGA or ETI) vs BVM	1 month SHD	Serious	51/346 [15%]	37/346 [11%]	1.38 (0.93-2.05)	0.04 (-0.01-0.09)	Very low
			1 month SGNF	Serious	12/346 [3%]	16/346 [5%]	0.75 (0.37-1.54)	-0.01 (-0.04-0.02)	Very low
			ROSC	Serious	32/346 [9%]	32/346 [9%]	1.00 (0.63-1.59)	0.00 (-0.04-0.04)	Very low
Hansen et al. (42)	Cohort study (retrospective, propensity matched)	ETI vs BVM	SHD	Serious	51/727 [7%]	110/781 [14%]	0.50 (0.36-0.68)	-0.07 (-0.10-(-0.04))	Very low
			SGNF	Serious	34/727 [5%]	89/781 [11%]	0.41 (0.28-0.60)	-0.07 (-0.10-(-0.04))	Very low
			ROSC	Serious	148/727 [20%]	141/781 [18%]	1.13 (0.92-1.39)	0.02 (-0.02-0.06)	Very low

[a] Calculations performed using Statsdirect 3.2.8.

[b] See risk of bias tables for individual studies (Additional files).

CI: confidence interval; BVM: bag-valve-mask ventilation; ETI: endotracheal intubation; SHD: survival to hospital discharge; SGNF: survival with good neurological function; ALS: advanced life support; BLS: basic life support; AAM: advanced airway management; SGA: supra-glottic airway; OHCA: out-of-hospital cardiac arrest; ROSC: return of spontaneous circulation.

Table 3 – summary of findings: endotracheal intubation vs. no intubation.

Certainty assessment					No. of patients		Effect [a]		Certainty
Study	Design	Advanced airway interventions studied	Outcome assessed	Risk of bias [b]	Intervention 1 (ETI)	Intervention 2 (no ETI)	Relative Risk (95% CI)	Risk Difference (95% CI)	
Aijian et al. (34)	Cohort study (retrospective)	ETI successful vs ETI unsuccessful vs ETI not attempted	SHD	Very serious	1/18 [6%]	1/24 [4%]	1.33 (0.14-12.23)	0.01 (-0.16-0.23)	Very low
Allen et al. [c] (39)	Cohort study (retrospective, propensity matched)	ETI vs no ETI	Mortality	Serious	31.7%	28.3%	N.A.	N.A.	Very low
			EMS time spent at the scene	Serious	median 18 mins [IQR 13 mins]	median 14 mins [IQR 13 mins]	N.A.	N.A.	Very low
			time spent from scene arrival to hospital arrival	Serious	median 31 mins [IQR 16 mins]	median 28 mins [IQR 12 mins]	N.A.	N.A.	Very low
Heschl et al. (41)	Cohort study (retrospective)	ETI (RSI) vs ETI not attempted	SHD	Very serious	76/87 [87%]	17/19 [90%]	0.98 (0.85-1.28)	-0.02 (-0.14-0.20)	Very low
			6 month functional outcome	Very serious	41/87 [67%]	7/19 [54%]	1.28 (0.75-2.54)	0.10 (-0.14-0.31)	Very low

[a] Calculations performed using Statsdirect 3.2.8.

[b] See risk of bias tables for individual studies (Additional files).

[c] Only propensity-matched analysis displayed.

CI: confidence interval; ETI: endotracheal intubation; OHCA: out-of-hospital cardiac arrest; SHD: survival to hospital discharge; EMS: emergency medical services; RSI: rapid sequence induction.

3.1 Endotracheal intubation compared to bag-valve-mask ventilation

A pseudo-randomised clinical trial performed by **Gausche et al.** aimed to compare survival to hospital discharge and survival with good neurological function amongst paediatric patients treated with either bag-valve-mask ventilation (BVM) alone or BVM followed by endotracheal intubation (ETI) in an out-of-hospital setting. 820 patients aged 12 year or younger or estimated to weigh less than 40 kg were designated to receive either BVM on odd days (404/820 [49%]) or BVM followed by ETI on even days (416/820 [51%]). Subsequent analysis of these 820 patients revealed no significant difference in survival to hospital discharge between the BVM group and the ETI group (BVM = 123/404 [30%]; ETI =110/416 [26%]; P value, not significant) (risk difference [RD], -0.04; 95% confidence interval [CI], -0.10-0.02) or in survival with good neurological outcome between the BVM group and the ETI group (BVM = 92/404 [23%]; ETI = 85/416 [20%]; P value, not significant) (RD, -0.02; 95% CI, -0.08-0.03). Secondary analysis of BVM and ETI subgroups based on illness or injury revealed a significant worsening in survival or neurological outcome in 3 subgroups (child maltreatment, respiratory arrest and foreign body aspiration) when ETI was adopted. The authors therefore conclude that the addition of ETI to BMV did not improve survival to hospital discharge or survival with good neurological outcome. Evidence in this trial was estimated to be of low certainty (35).

A retrospective, observational study performed by **Pitetti et al.** aimed to compare survival to hospital discharge amongst paediatric patients receiving either BLS or ALS following out-of-hospital cardiac arrest. For this specific study, the authors altered the definition of BLS to include bag-valve-mask ventilation as one of its life saving protocols. 189 patients aged 18 years or younger were divided into two groups receiving either BLS (39/189 [21%]), including BVM, or ALS (150/189 [79%]). Patients who received BLS followed by ALS were classified in the ALS group. Use of either BLS or ALS depended on the EMS unit that responded, which is dependent of the geographical location of the patient. Analysis of these 189 patients revealed no significant difference in survival to hospital discharge between the BLS group and the ALS group (BLS = 0/39 [0%]; ALS = 5/150 [3%]; P value = .585) (RD,0.03; 95% CI, -0.06-0.08). The authors therefore conclude that the use of ALS, compared to BLS, offers no improvement in survival to hospital discharge. Evidence in this study was estimated to be of very low certainty (36).

A retrospective, observational study performed by **Cooper et al.** aimed to compare survival, functional outcome and complications amongst paediatric patients receiving either BVM or ETI following out-of-hospital, severe head injury. 578 patients aged 19 years or younger were divided into two groups receiving either BVM (99/578 [17%]) or ETI (479/578 [83%]). Functional outcome, using the Functional Independence Measure, was only assessed in patients aged 7 years or older. Subsequent analysis of these 578 patients revealed virtually identical mortality rates (ETI = 48%; BVM = 48%; P value, not significant) and functional outcome (ETI = 65.7%; BVM = 65.2%; P value, not significant). Procedure and equipment complications also failed to show a significant difference (ETI = 7.9%; BVM = 8.1%; P value, not significant). Subset analysis of injury complications, however, did show a significant difference favouring ETI (ETI = 58%; BVM = 71%; P value < .05) in complications affecting nearly every body system or organ except for kidney, gut and skin injuries. The authors therefore conclude that the use of ETI, compared to BVM, offers no improvement in survival or functional outcome. Evidence in this study was estimated to be of very low certainty (37).

A prospective, observational study performed by **Gerritse et al.** aimed to compare survival to hospital discharge and ETI success rate amongst paediatric patients receiving either emergency medical service (EMS) paramedic performed ETI or EMS performed BVM ventilation followed by helicopter-transported medical team (HMT) performed ETI in an out-of-hospital setting. The HMT crew in this setting has received additional education and training in paediatric and adult emergency care compared to the EMS crew. 95 patients aged 16 years or younger were divided into two groups receiving either EMS performed ETI (41/95 [43%]) or EMS performed BVM ventilation followed by HMT performed ETI (54/95 [57%]). Subsequent analysis of these 95 patients revealed a significant difference in successful ETI (EMS BVM followed by HMT ETI = 54/54 [100%]; EMS ETI = 26/41 [63%]; P value < .001) (RD,-0.37; 95% CI, -0.52-(-0.24)) and survival to hospital discharge (EMS BVM followed by HMT ETI = 37/54 [69%]; EMS ETI = 2/41 [5%]; P value < .001) (RD,-0.64; 95% CI, -0.76-(-0.47)) both favouring EMS BVM followed by HMT ETI. The authors therefore conclude that the use of BVM is the preferred choice for ventilation by EMS paramedics, whenever possible. The authors also state that out-of-hospital, paediatric ETI should be deferred to the HMT. Evidence in this study was estimated to be of very low certainty (38).

A retrospective, propensity-matched, observational study performed by **Ohashi-Fukuda et al.** aimed to compare 1 month overall survival , 1 month survival with good neurological function and prehospital return of spontaneous circulation (ROSC) amongst paediatric patients receiving either advanced airway management (encompassing both ETI and supra-glottic airway devices) or BVM following out-of-hospital cardiac arrest. However, in the study ETI was only available as a lifesaving protocol to specially trained EMS personnel, while SGA and BVM were readily available protocols amongst all EMS personnel. Additionally, most communities included in the study ETI only allow children under 8 years, occasionally even 15 years, to be intubated. 2157 patients aged 1 through 18 years were divided into two groups receiving either AAM (365/2157 [17%]) or BVM (1792/2157 [83%]). Subsequent propensity matched analysis of 730 patients revealed no significant difference in 1 month overall survival between the AAM group and the BVM group (AAM = 51/346 [15%]; BVM = 37/346 [11%]; P value = .10) (RD, 0.04; 95% CI, -0.01-0.09) or in 1 month survival with good neurological function between the AAM group and the BVM group (AAM = 12/346 [3%]; BVM = 16/346 [5%]; P value = 0.43) (RD, -0.01; 95% CI, -0.04-0.02). Analysis of pre-hospital ROSC also revealed no significant difference between the AAM group and the BVM group (AAM = 32/346 [9%]; BVM = 32/346 [9%]; P value = 1.00) (RD, 0.00; 95% CI, -0.04-0.04). Subgroup analysis also revealed no significant advantage of AAM with regard to 1 month survival, 1 month survival with good neurological function or ROSC. The authors therefore conclude that the use of AAM, compared to BVM, offers no improvement in survival, survival with good neurological function or ROSC. Evidence in this study was estimated to be of very low certainty (40).

A retrospective, propensity-matched, observational study performed by **Hansen et al.** aimed to compare survival to hospital discharge, survival with good neurological function and ROSC (sustained for 20 mins) amongst paediatric patients receiving either ETI, SGA or BVM following non-traumatic, out-of-hospital cardiac arrest. 1723 patients aged 17 years or younger were divided into three groups receiving either BVM (781/1723 [45%]), SGA (215/1723 [13%]) or ETI (727/1723 [42%]). In this analysis, the assigned group depends on the final airway which was successfully applied by EMS providers. This could be ETI, SGA or BVM if an advanced airway technique was not successfully applied or not attempted. Subsequent propensity-matched analysis of the BVM and ETI group revealed improved odds of survival to hospital discharge (BVM = 110/781 [14%]; ETI = 51/727 [7%]; no P value reported) (RD, -0.07; 95% CI, -0.10-(-0.04)) and improved odds of survival with good neurological function (BVM = 89/781 [11%]; ETI = 34/727 [5%]; no P value reported) (RD, -0.07; 95% CI, -0.10-(-0.04)) both favouring BVM. ROSC (sustained for 20 mins)

showed no significant difference between BVM and ETI (BVM = 141/781 [18%]; ETI = 148/727 [20%]; no P value reported) (RD, 0.02; 95% CI, -0.02-0.06). The authors therefore conclude that BVM is associated with an improved survival to hospital discharge compared to ETI. Evidence in this study was estimated to be of very low certainty (42).

3.2 Endotracheal intubation compared to no intubation

A retrospective, observational study performed by **Aijian et al.** aimed to compare survival to hospital discharge amongst paediatric patients receiving either ETI or no ETI following out-of-hospital cardiac arrest. 42 patients aged 18 years or younger were divided into three groups: ETI not attempted (14/42 [33%]), ETI unsuccessful (10/42 [24%]) and ETI successful (18/42 [43%]). Subsequent analysis of these groups revealed no significant difference in survival to hospital discharge between the ETI successful and the combination of ETI not successful and not attempted group (ETI = 1/18 [6%]; no ETI = 1/24 [4%]; P value = .116) (RD, 0.01; 95% CI, -0.16-0.23). No conclusion was made by the authors concerning the survival to hospital discharge in this study. Evidence in this study was estimated to be of very low certainty (34).

A retrospective, propensity-matched, observational study performed by **Allen et al.** aimed to compare EMS transport time (subdivided in EMS time spent at the scene and time spent from scene arrival to hospital arrival) and mortality amongst paediatric patients receiving either ETI or no ETI following out-of-hospital trauma. 1884 patients aged 17 years or younger were divided into two groups receiving either ETI (122/1884 [6%]) or no ETI (1762/1884 [94%]). Non-propensity matched analysis revealed no significant difference in EMS time spent at the scene (ETI = median 14 mins [IQR 12 mins] ; no ETI = median 14 mins [IQR 12 mins]; P value = .949) or time from scene arrival to hospital arrival (ETI = median 27 mins [IQR 15 mins] ; no ETI = median 27 mins [IQR 15 mins]; P value = .574), but did reveal a significant difference in mortality (ETI = 23.5%; no ETI = 2.2%; P value < .001). Propensity-matched analysis of the ETI (60/120 [50%]) and no ETI group (60/120 [50%]) revealed no significant difference in EMS time spent at the scene (ETI = median 18 mins [IQR 13 mins] ; no ETI = median 14 mins [IQR 13 mins]; P value = .667), time from scene arrival to hospital arrival (ETI = median 31 mins [IQR 16 mins]; no ETI = median 28 mins [IQR 12 mins]; P value = .751) or mortality (ETI = 31.7%; no ETI = 28.3%; P value = .824). The authors

therefore conclude that ETI is not associated with an increased EMS transport time or mortality, compared to no ETI. Evidence in this study was estimated to be of very low certainty (39).

A retrospective, observational study performed by **Heschl et al.** aimed to compare survival to hospital discharge and functional outcome after six months amongst paediatric patients receiving either ETI (more specifically rapid sequence induction) or no ETI following out-of-hospital traumatic brain injury. 106 patients aged 14 years or younger were divided into two groups receiving either ETI (87/106 [82%]) or no ETI (19/106 [18%]). Subsequent analysis of these groups revealed no significant difference in survival to hospital discharge (ETI = 76/87 [87%]; no ETI = 17/19 [90%]; P value = 1.0) (RD, -0.02; 95% CI, -0.14-0.20) or functional outcome after six months (ETI = 41/87 [67%]; no ETI = 7/19 [54%]; P value = .36) (RD, 0.10; 95% CI, -0.14-0.31). Subgroup analysis of major trauma patients revealed a favourable functional outcome after six months for the ETI group (ETI = 31/64 [66%]; no ETI = 1/11 [17%]; P value = .06) although this did not reach statistical significance. The authors therefore conclude that the use of ETI (RSI), compared to no ETI, offers no improvement in survival to hospital discharge or survival with good functional outcome after six months. Additionally the authors state that they observed more favourable outcomes in patients receiving ETI compared to those who didn't, but commented that the study is not powered to detect a statistically significant difference. Evidence in this study was estimated to be of very low certainty (41).

4. Discussion

Summary of main results

The establishment and maintenance of an adequate airway remains one of the single most important initial therapies provided to severely injured, paediatric patients. Despite its importance, an evidence-based, standard operating procedure is still missing due to a lack of high-quality evidence. The benefits and harms of ETI were reviewed through current evidence and compared to BVM ventilation or intubation non-attempt.

One controlled clinical trial, one prospective cohort study and four retrospective cohort studies were found comparing ETI to BVM ventilation, as displayed in **Table 2**. Regarding the important outcome of SHD, two cohort studies favouring BVM ventilation found a significantly better outcome for SHD, while the remaining four studies showed no significant difference. Regarding the important outcome of SGNF, one retrospective cohort study favouring BVM ventilation found a significantly better outcome for SGNF, while the remaining three studies found no significant difference. Two studies did not collect SGNF data and could therefore not report on this outcome. Overall, based on low-quality evidence, it appears that for the important outcomes of SHD and SGNF a slight advantage favouring BVM over ETI can be concluded.

Three retrospective cohort studies, including one propensity-matched study, were found comparing ETI to no ETI (encompassing ETI non-attempt and unsuccessful ETI), as displayed in **Table 3**. Regarding the important outcome of SHD, two cohort studies found no significant difference between ETI or no ETI. One cohort study, reporting mortality rather than SHD, also failed to show a significant difference. Regarding the important outcome of SGNF, no cohort studies were found assessing ETI versus no ETI. One cohort study did, however, assess 6-month functional outcome but also failed to show a significant difference. Overall, based on low-quality evidence, it appears that for the important outcomes of SHD and SGNF no significant difference favouring either the use of ETI or no ETI can be concluded.

Overall completeness and applicability of evidence

Caution is advised when considering the implications of these findings for practice. Only two studies, both retrospective cohort studies, examined ETI vs BVM ventilation directly (37, 42). The remaining studies either encompassed ETI as either ALS (including SGA) or ETI following initial BVM ventilation. Therefore researchers should remain vigilant when generating conclusions

concerning ETI and BVM as airway management techniques when currently available evidence directly comparing both techniques is limited.

Every study encompassed in this review either studied SHD or direct mortality, making the comparison of ETI versus either BVM or no intubation for this outcome possible. There is, however, substantial diversity in which further outcomes are studied, ranging from functional outcome or SGNF as the most prevalent to complications and EMS time intervals as the least prevalent. As a result of this diversity in the studied outcomes, the assessment of outcomes excluding SHD will be based on a limited amount of (low-quality) evidence.

For the critical outcomes of SHD and SGNF, this review found no evidence suggesting an advantage for ETI when comparing it to other advanced airway management techniques. And despite its challenging use and risk for complications, ETI persists as part of the standard operating procedure in most American emergency departments. Paediatric intubation equipment is deemed standard equipment, available to any advanced life support ambulance, by numerous American organisations involved in EMS care (43).

Potential causes for discrepancy

Discrepancy in study results might be caused by a multitude of factors assessable through the meta-analysis of relevant subgroups. This review, however, did not perform a meta-analysis of the data provided by the assessed studies. Therefore, an evaluation of the planning and design of each individual study was done, with the aim of generating multiple hypotheses about relevant factors influencing the ultimate outcome of ETI versus other airway devices. This is approached by distinguishing certain subgroups within the assessed studies and by researching the possible impact of these subgroups on study outcomes.

A first relevant subgroup might be paramedic versus physician intubation. Evidence shows that correct use of ETI requires extensive, medical training which is often inadequately provided in airway management training for anaesthetists or surgeons. Despite this lack of physician training however, success rates when ETI is performed by physicians are considerably higher compared to paramedic intubation (5, 8). Eight out of the nine studies encompassed in this review were conducted in countries (USA, Australia and Japan) were EMS are staffed by paramedics or other personnel only, with no physician involvement until arrival to the ED. The ninth study (Gerritse et al.) was conducted in The Netherlands and aimed to compare survival to hospital discharge amongst paediatric patients receiving either paramedic-performed ETI, or paramedic-performed BVM ventilation followed by physician-performed ETI. This study was one of the only two available

studies showing a significant improvement in SHD when BVM was initially used instead of ETI. This begs the question whether factors like training and experience level of the provider are equally important as the choice of airway device, a question expressed earlier by Lavonas et al. in a systematic review concerning advanced airway interventions in paediatric cardiac arrest (44).

A second relevant subgroup might be the setting where advanced airway management techniques were attempted, more specifically the initial indication for airway management (**Table 1**). Three studies assessed cases in a trauma-setting exclusively. Four studies assessed AD's in the setting of respiratory failure. The remaining two studies did not make a clear distinction in indications when studying the airway devices. No immediate pattern can be perceived since significant improvement in SHD could be seen in only two out of nine studies, one in the setting of respiratory failure and one which included all settings for ETI.

A third, and last, subgroup which might account for contrasting results between studies is the overall age group of participants in studies. As a result of the design of this review, all participants are aged 19 years or younger. Which age is studied and how age is represented (either maximum age, mean with standard deviation or median with interquartile range) and analysed (using subgroups of different ages or not) varies across studies. Eight studies reported age as mean (standard deviation) allowing assessment of similarity. One study only reported maximum participant age amongst all participants included in the final analysis. Additionally, multiple studies distinguished different age groups to make sub-analysis possible. Not every study included in this review followed the same process of subdividing participants according to age and, -if they did, differing age subgroups were used. This different way of reporting complicates the process of comparing results amongst these studies.

Quality of the evidence

In total, nine studies with a combined total of 7831 participants were included in this review. One pseudo-randomised clinical trial, three propensity score-matched observational studies and six observational studies were identified. The overall quality of evidence was assessed to be low to very low after risk of bias evaluation. All cohort studies that were not propensity score matched were deemed to have a very serious risk of bias, mainly due to a lack of matching exposed and unexposed participants for all variables that might be associated with the outcome of interest. All propensity score matched cohort studies were also deemed to have a serious risk of bias. Important arguments included in the bias assessment are the lack of confidence in the assessment of the presence or absence of prognostic factors and the lack of confidence that the outcome of interest

was not present at the start of the study, which is the case in loss of neurological or functional capacity. The risk of bias in the only clinical trial present in this review was assessed as not serious.

As stated earlier, several studies display some serious shortcomings, making the comparison of the results of these studies quite difficult. These shortcomings include, but are not limited to, the 'lack of direct comparison between ETI and BVM', 'no SGNF studied' or 'no consistency in neurological function scoring systems'. These factors limit the overall applicability of evidence. As a result of the considerable risk of bias and the limitations in individual studies one should remain cautious when using this body of evidence to form conclusions regarding out-of-hospital paediatric ETI.

Potential limitations in the review process

Limitations to narrative reviews are well-described. Although they are considered useful for compiling current literature, they often lack in evidence-based methods. Explicit criteria to aid in article selection and to mitigate bias are often lacking, leading to authors primarily finding studies supporting their claims (selection bias). Therefore, if the review is not of high methodological quality, clinicians should not rely upon them to draw conclusions concerning effective medical care.

Another potential limitation was the limited amount of practical experience of the researcher that conducted this narrative review within the medical profession, and more specifically within emergency medicine. Despite routine follow-up by Prof. Dr. Van de Voorde, an experienced emergency physician at Ghent University Hospital, this inexperience could have increased the likelihood that not all relevant data has been obtained due to inadequate study design.

Finally, an additional limitation was that the selection of studies was not performed by two independent investigators. The Cochrane Handbook for Systematic Reviews of Interventions states that the application of selection criteria by two independent investigators reduces the risk of bias in the search. Nonetheless, a thorough, objective and reproducible search of multiple sources was done to identify as many relevant articles as possible. And ultimately, 1198 unique articles were reviewed for relevance. Please refer to the Methods section of this review for a more detailed report on this matter.

Agreements and disagreements with other studies or reviews

In this last section of 'discussion' comments are made on how this narrative review correlates to other prominent systematic reviews with similar objectives in a comparable setting, namely paediatric intubation (preferably in an exclusively out-of-hospital setting).

A 2008 Cochrane review performed by Lecky et al. aimed to assess survival, degree of disability at discharge, length of stay and in-hospital complications amongst critically ill patients receiving out-of-hospital ETI or other airway interventions. One of the three RCT's encompassed in this review indicated no difference in survival or neurological outcome between paramedic intubation versus bag-valve-mask ventilation combined with later hospital intubation by emergency physicians. This RCT is the trial performed by Gausche et al. which is the only RCT encompassed in our narrative review. Therefore we are unable to draw a direct comparison between the results of these studies. However, based on all three RCT's the authors conclude that "the current evidence provides no imperative to extend the practice of prehospital intubation", which matches the findings in our own review (45).

A 2009 Systematic review performed by von Elm et al. aimed to assess in-hospital mortality and functional outcome amongst patients with traumatic brain injury receiving out-of-hospital ETI or other airway interventions. The review showed conflicting results when assessing in-hospital mortality and ambiguous results when assessing functional outcome amongst traumatic brain injury victims. In contrast, our own review showed a slight advantage of BVM compared to ETI for the important outcomes of survival to hospital discharge and survival with good neurological function (46).

A 2016 Systematic review and meta-analysis performed by Lavonas et al. aimed to assess SHD and SGNF amongst paediatric patients with cardiac arrest receiving either ETI or other airway interventions. The results suggested an improvement of SHD and SGNF when BVM was used instead of ETI, with limited data favouring SGA over ETI. Due to conflicting study results and lack of certainty however, the authors concluded that ETI is not superior compared to SGA or BVM alone. Our own review differed in setting from the studies used in the review by Lavonas et al., which only included paediatric cardiac arrest victims. Our results are very similar however showing a slight advantage of BVM over ETI when assessing the same two important outcomes. Available evidence is characterized by low-quality studies, leading to low certainty when drawing conclusions (44).

5. Conclusion

Implications for practice

Based on very low certainty evidence it appears that BVM offers a slight advantage over ETI when assessing the important outcomes of survival to hospital discharge and survival with good neurological function. Based on the same very low certainty evidence no significant difference in ETI or no-ETI was established when assessing the important outcomes of survival to hospital discharge and survival with good neurological function. Therefore physicians should avoid considering out-of-hospital paediatric ETI as an evidence-based standard, seeing as evidence of sufficient quality does not exist.

Composing clear implications for practice, however, requires thorough analysis of study results combined with data on the benefits, harms and costs of the airway devices used. Making specific recommendations remains the domain of guideline developers and goes beyond the scope of review authors.

Implications for research

Seeing as high-quality evidence comparing out-of-hospital paediatric ETI to BVM (the current gold standard) is lacking, ETI cannot be recognized as an evidence-based technique in this setting. The high amount of low-certainty evidence warrants the need for a high-quality randomised controlled trial comparing ETI to BVM in an out-of-hospital paediatric setting, regardless of the indication for airway management.

If high-certainty evidence becomes available recommending ETI as the preferred technique to manage paediatric airways, guideline developers and policy makers should thoroughly analyse other factors which might influence the implementation of ETI in EMS settings. The reason for this is that implementation requires additional information which is not readily available to authors of clinical studies.

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Additional files

File 1: extensive search strategy

File 2: risk of bias assessment in Randomized Controlled Trials

File 3: risk of bias assessment in Cohort Studies

File 1: extensive search strategy

PubMed

A search of the PubMed database was performed. The search strategy used all word variations of [pre-hospital], [pediatric], [endotracheal intubation] and [rapid sequence induction]. In total, **569** articles were found.

The exact search strategy used:

Recent queries in pubmed
Search,Query,Items found,Time
#5,"Search (((((((((prehospital) OR pre-hospital) OR pre hospital) OR out-of-hospital) OR out of hospital)) AND ((((pediatric) OR paediatric) OR child) OR infant)) AND (((((intratracheal intubation) OR endotracheal intubation) OR tracheal intubation) OR rapid sequence induction) OR rapid sequence intubation)) AND Humans[Filter]) NOT case report",568,04:21:51
#4,"Search Humans[Filter]",17663062,04:21:06
#3,"Search ((((intratracheal intubation) OR endotracheal intubation) OR tracheal intubation) OR rapid sequence induction) OR rapid sequence intubation",49252,04:20:57
#2,"Search (((pediatric) OR paediatric) OR child) OR infant",2915660,04:16:21
#1,"Search ((((prehospital) OR pre-hospital) OR pre hospital) OR out-of-hospital) OR out of hospital",399856,04:15:48

The final search query, using Boolean operators, is:

(((((((((prehospital) OR pre-hospital) OR pre hospital) OR out-of-hospital) OR out of hospital)) AND ((((pediatric) OR paediatric) OR child) OR infant)) AND (((((intratracheal intubation) OR endotracheal intubation) OR tracheal intubation) OR rapid sequence induction) OR rapid sequence intubation)) AND Humans[Filter]) NOT case report

Embase

A search of the Embase database was performed. The search strategy used all word variations of [pre-hospital], [pediatric], [endotracheal intubation] and [rapid sequence induction]. In total, **991** articles were found.

The final search query, using Boolean operators, is:

(prehospital OR 'pre hospital' OR (pre AND hospital) OR 'out of hospital' OR (out AND of AND hospital)) AND (pediatric OR paediatric OR child OR infant) AND (endotracheal AND intubation OR (intratracheal AND intubation) OR (tracheal AND intubation) OR (rapid AND sequence AND intubation) OR (rapid AND sequence AND induction))

Note

De termen [emergency medicine], [emergencies] en [emergency medical services] werden niet in de voorgaande searches betrokken gezien deze in zowel PubMed als Embase leiden tot een aanzienlijke uitbreiding van de zoekresultaten, respectievelijk **1151** en **2679**. De bijhorende search query (indien deze 3 termen wel in de search betrokken worden) is hieronder weergegeven.

PubMed	((((((((((prehospital) OR pre-hospital) OR pre hospital) OR out-of-hospital) OR out of hospital) OR emergency medicine) OR emergencies) OR emergency medical services)) AND ((((pediatric) OR paediatric) OR child) OR infant)) AND (((((endotracheal intubation) OR intratracheal intubation) OR tracheal intubation) OR rapid sequence induction) OR rapid sequence intubation)) AND Humans[Filter]) NOT case report
Embase	(prehospital OR 'pre hospital' OR (pre AND hospital) OR 'out of hospital' OR (out AND of AND hospital) OR emergency OR (emergency AND health AND service) OR (emergency AND medicine)) AND (pediatric OR paediatric OR child OR infant) AND (endotracheal AND intubation OR (intratracheal AND intubation) OR (tracheal AND intubation) OR (rapid AND sequence AND intubation) OR (rapid AND sequence AND induction))

Persoonlijk denk ik dat het gebruik van deze 3 extra termen in de search zal zorgen voor heel wat niet-relevante zoekresultaten (*gezien "in-hospital pediatric intubation" zich dan ook tussen de resultaten bevindt*). Anderzijds, bekomen we op deze manier ook meer zoekresultaten die wel relevant zijn. Het niet gebruiken van deze 3 extra termen zou er ook toe kunnen leiden dat niet alle relevante zoekresultaten worden teruggevonden.

File 2: risk of bias assessment in Randomized Controlled Trials

Author	Outcome Assessed	Bias assessment
Gausche et al.	Survival to hospital discharge	1. Was the allocation sequence adequately generated? (can be omitted) Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation: Even/Odd calendar days.
		2. Was allocation adequately concealed? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation: Not applicable.
		3. Blinding: Was knowledge of the allocated interventions adequately prevented? (This global rating is challenging. May want to omit and use only the ratings below.) Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		3a. Were patients blinded? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation: Not applicable.
		3b. Were healthcare providers blinded? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias)

			Motivation: Not applicable.
			3c. Were data collectors blinded? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation: Not applicable.
			3d. Were outcome assessors blinded? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation: Not applicable.
			3e. Were data analysts blinded? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation: Not applicable.
		4. Was loss to follow-up (missing outcome data) infrequent? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation: 10/830 [0.01%] was lost to follow-up.	
		5. Are reports of the study free of suggestion of selective outcome reporting? (This item sufficiently difficult to judge that may be omitted) Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:	
		6. Was the study apparently free of other problems that could put it at a risk of bias? (May omit this item)	

		Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation: The study appears to be free of other sources of bias.

Eventual risk of bias is either is ‘Not serious’, ‘Serious’ or ‘Very serious’.

=> Not serious

Author	Outcome Assessed	Bias assessment
Gausche et al.	Survival with good neurological function	1. Was the allocation sequence adequately generated? (can be omitted) Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation: Even/Odd calendar days.
		2. Was allocation adequately concealed? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation: Not applicable.
		3. Blinding: Was knowledge of the allocated interventions adequately prevented? (This global rating is challenging. May want to omit and use only the ratings below.) Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		3a. Were patients blinded? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation: Not applicable.
		3b. Were healthcare providers blinded? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation: Not applicable.
		3c. Were data collectors blinded? Definitely yes Probably yes Probably no Definitely no

			(low risk of bias) (high risk of bias) Motivation: Not applicable.	
			3d. Were outcome assessors blinded? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) Motivation: Not applicable.	
			3e. Were data analysts blinded? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) Motivation: Not applicable.	
		4. Was loss to follow-up (missing outcome data) infrequent? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) Motivation: 10/830 [0.01%] was lost to follow-up.		
		5. Are reports of the study free of suggestion of selective outcome reporting? (This item sufficiently difficult to judge that may be omitted) Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) Motivation:		
		6. Was the study apparently free of other problems that could put it at a risk of bias? (May omit this item) Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) Motivation: The study appears to be free of other sources of bias.		

=> Not serious

File 3: risk of bias assessment in Cohort Studies

Author	Outcome Assessed	Bias assessment
Pitetti et al.	Survival to hospital discharge	1. Was selection of exposed and non-exposed cohorts drawn from the same population? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation: All children presenting to the ED.
		2. Can we be confident in the assessment of exposure? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		3. Can we be confident that the outcome of interest was not present at start of study Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		5. Can we be confident in the assessment of the presence or absence of prognostic factors? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:

		6. Can we be confident in the assessment of outcome? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) Motivation:
		7. Was the follow up of cohorts adequate? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) Motivation:
		8. Were co-Interventions similar between groups? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) Motivation:

Eventual risk of bias is either is ‘Not serious’, ‘Serious’ or ‘Very serious’.

=> Very serious

Author	Outcome Assessed	Bias assessment
Cooper et al.	Survival	1. Was selection of exposed and non-exposed cohorts drawn from the same population? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation: National Pediatric Trauma Registry (NPTR-3)
		2. Can we be confident in the assessment of exposure? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		3. Can we be confident that the outcome of interest was not present at start of study Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		5. Can we be confident in the assessment of the presence or absence of prognostic factors? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation: Chart review; data base with uncertain quality of abstraction of prognostic information.
		6. Can we be confident in the assessment of outcome? Definitely yes Probably yes Probably no Definitely no

		(low risk of bias) (high risk of bias) <u>Motivation:</u>
		7. Was the follow up of cohorts adequate? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>
		8. Were co-Interventions similar between groups? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>

=> Very serious

Author	Outcome Assessed	Bias assessment
Cooper et al.	Functional outcome	1. Was selection of exposed and non-exposed cohorts drawn from the same population? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		2. Can we be confident in the assessment of exposure? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		3. Can we be confident that the outcome of interest was not present at start of study Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		5. Can we be confident in the assessment of the presence or absence of prognostic factors? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		6. Can we be confident in the assessment of outcome? Definitely yes Probably yes Probably no Definitely no

		(low risk of bias) (high risk of bias) <u>Motivation:</u> Using the Functional Independence Measure (FIM).
		7. Was the follow up of cohorts adequate? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>
		8. Were co-Interventions similar between groups? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>

=> Very serious

Author	Outcome Assessed	Bias assessment
Cooper et al.	Complications	1. Was selection of exposed and non-exposed cohorts drawn from the same population? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		2. Can we be confident in the assessment of exposure? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		3. Can we be confident that the outcome of interest was not present at start of study Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation: A wide variety of complications was assessed (included each organ system).
		4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		5. Can we be confident in the assessment of the presence or absence of prognostic factors? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		6. Can we be confident in the assessment of outcome? Definitely yes Probably yes Probably no Definitely no

		(low risk of bias) (high risk of bias) <u>Motivation:</u>
		7. Was the follow up of cohorts adequate? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>
		8. Were co-Interventions similar between groups? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>

=> Very serious

Author	Outcome Assessed	Bias assessment
Gerritse et al.	Survival to hospital discharge	1. Was selection of exposed and non-exposed cohorts drawn from the same population? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation: A consecutive group of children for which a helicopter-transported medical team (HMT) was called.
		2. Can we be confident in the assessment of exposure? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		3. Can we be confident that the outcome of interest was not present at start of study Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		5. Can we be confident in the assessment of the presence or absence of prognostic factors? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		6. Can we be confident in the assessment of outcome? Definitely yes Probably yes Probably no Definitely no

		(low risk of bias) (high risk of bias) <u>Motivation:</u>
		7. Was the follow up of cohorts adequate? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>
		8. Were co-Interventions similar between groups? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>

=> Very serious

Author	Outcome Assessed	Bias assessment
Gerritse et al.	Success rate	1. Was selection of exposed and non-exposed cohorts drawn from the same population? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		2. Can we be confident in the assessment of exposure? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		3. Can we be confident that the outcome of interest was not present at start of study Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		5. Can we be confident in the assessment of the presence or absence of prognostic factors? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		6. Can we be confident in the assessment of outcome? Definitely yes Probably yes Probably no Definitely no

		(low risk of bias) (high risk of bias) <u>Motivation:</u>
		7. Was the follow up of cohorts adequate? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>
		8. Were co-Interventions similar between groups? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>

=> Very serious

Author	Outcome Assessed	Bias assessment
Ohashi-Fukuda et al.	1 month survival to hospital discharge	1. Was selection of exposed and non-exposed cohorts drawn from the same population? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation: Paediatric OHCA patients from the All-Japan Utstein registry.
		2. Can we be confident in the assessment of exposure? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		3. Can we be confident that the outcome of interest was not present at start of study Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation: Uncertain if they could match all variables that are associated with the outcome, but a propensity-matched analysis of important prognostic factors did happen.
		5. Can we be confident in the assessment of the presence or absence of prognostic factors? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation: Chart review; data base with uncertain quality of abstraction of prognostic information.
		6. Can we be confident in the assessment of outcome? Definitely yes Probably yes Probably no Definitely no

		(low risk of bias) (high risk of bias) <u>Motivation:</u>
		7. Was the follow up of cohorts adequate? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>
		8. Were co-Interventions similar between groups? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>

=> Serious

Author	Outcome Assessed	Bias assessment
Ohashi-Fukuda et al.	1 month survival with good neurological function	1. Was selection of exposed and non-exposed cohorts drawn from the same population? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		2. Can we be confident in the assessment of exposure? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		3. Can we be confident that the outcome of interest was not present at start of study Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		5. Can we be confident in the assessment of the presence or absence of prognostic factors? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		6. Can we be confident in the assessment of outcome? Definitely yes Probably yes Probably no Definitely no

		(low risk of bias) (high risk of bias) <u>Motivation:</u> Using the Glasgow-Pittsburgh cerebral performance category (CPC) scores.
		7. Was the follow up of cohorts adequate? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>
		8. Were co-Interventions similar between groups? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>

=> Serious

Author	Outcome Assessed	Bias assessment
Ohashi-Fukuda et al.	Return of spontaneous circulation	1. Was selection of exposed and non-exposed cohorts drawn from the same population? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		2. Can we be confident in the assessment of exposure? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		3. Can we be confident that the outcome of interest was not present at start of study Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		5. Can we be confident in the assessment of the presence or absence of prognostic factors? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		6. Can we be confident in the assessment of outcome? Definitely yes Probably yes Probably no Definitely no

		(low risk of bias) (high risk of bias) <u>Motivation:</u>
		7. Was the follow up of cohorts adequate? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>
		8. Were co-Interventions similar between groups? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>

=> Serious

Author	Outcome Assessed	Bias assessment
Hansen et al.	Survival to hospital discharge	1. Was selection of exposed and non-exposed cohorts drawn from the same population? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation: CARES registry
		2. Can we be confident in the assessment of exposure? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		3. Can we be confident that the outcome of interest was not present at start of study Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		5. Can we be confident in the assessment of the presence or absence of prognostic factors? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation: Chart review; data base with uncertain quality of abstraction of prognostic information
		6. Can we be confident in the assessment of outcome? Definitely yes Probably yes Probably no Definitely no

		(low risk of bias) (high risk of bias) <u>Motivation:</u>
		7. Was the follow up of cohorts adequate? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>
		8. Were co-Interventions similar between groups? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>

=> Serious

Author	Outcome Assessed	Bias assessment
Hansen et al.	Survival with good neurological function	1. Was selection of exposed and non-exposed cohorts drawn from the same population? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		2. Can we be confident in the assessment of exposure? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		3. Can we be confident that the outcome of interest was not present at start of study Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		5. Can we be confident in the assessment of the presence or absence of prognostic factors? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		6. Can we be confident in the assessment of outcome? Definitely yes Probably yes Probably no Definitely no

		(low risk of bias) (high risk of bias) <u>Motivation:</u> Using the paediatric cerebral performance category (PCPC) scores.
		7. Was the follow up of cohorts adequate? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>
		8. Were co-Interventions similar between groups? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>

=> Serious

Author	Outcome Assessed	Bias assessment
Hansen et al.	Return of spontaneous circulation	1. Was selection of exposed and non-exposed cohorts drawn from the same population? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		2. Can we be confident in the assessment of exposure? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		3. Can we be confident that the outcome of interest was not present at start of study Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		5. Can we be confident in the assessment of the presence or absence of prognostic factors? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		6. Can we be confident in the assessment of outcome? Definitely yes Probably yes Probably no Definitely no

		(low risk of bias) (high risk of bias) <u>Motivation:</u>
		7. Was the follow up of cohorts adequate? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>
		8. Were co-Interventions similar between groups? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>

=> Serious

Author	Outcome Assessed	Bias assessment
Aijian et al.	Survival to hospital discharge	1. Was selection of exposed and non-exposed cohorts drawn from the same population? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		2. Can we be confident in the assessment of exposure? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		3. Can we be confident that the outcome of interest was not present at start of study Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		5. Can we be confident in the assessment of the presence or absence of prognostic factors? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		6. Can we be confident in the assessment of outcome? Definitely yes Probably yes Probably no Definitely no

		(low risk of bias) (high risk of bias) <u>Motivation:</u>
		7. Was the follow up of cohorts adequate? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>
		8. Were co-Interventions similar between groups? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>

=> Very serious

Author	Outcome Assessed	Bias assessment
Allen et al.	Mortality	1. Was selection of exposed and non-exposed cohorts drawn from the same population? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		2. Can we be confident in the assessment of exposure? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		3. Can we be confident that the outcome of interest was not present at start of study Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		5. Can we be confident in the assessment of the presence or absence of prognostic factors? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		6. Can we be confident in the assessment of outcome? Definitely yes Probably yes Probably no Definitely no

		(low risk of bias) (high risk of bias) <u>Motivation:</u>
		7. Was the follow up of cohorts adequate? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>
		8. Were co-Interventions similar between groups? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>

=> Serious

Author	Outcome Assessed	Bias assessment
Allen et al.	EMS time spent at the scene	1. Was selection of exposed and non-exposed cohorts drawn from the same population? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		2. Can we be confident in the assessment of exposure? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		3. Can we be confident that the outcome of interest was not present at start of study Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		5. Can we be confident in the assessment of the presence or absence of prognostic factors? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		6. Can we be confident in the assessment of outcome? Definitely yes Probably yes Probably no Definitely no

		(low risk of bias) (high risk of bias) <u>Motivation:</u> Uncertain how these travel times are recorded (not specified in full text).
		7. Was the follow up of cohorts adequate? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>
		8. Were co-Interventions similar between groups? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>

=> Serious

Author	Outcome Assessed	Bias assessment
Allen et al.	Time spent from scene arrival to hospital arrival	1. Was selection of exposed and non-exposed cohorts drawn from the same population? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		2. Can we be confident in the assessment of exposure? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		3. Can we be confident that the outcome of interest was not present at start of study Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		5. Can we be confident in the assessment of the presence or absence of prognostic factors? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		6. Can we be confident in the assessment of outcome? Definitely yes Probably yes Probably no Definitely no

		(low risk of bias) (high risk of bias) <u>Motivation:</u> Uncertain how these travel times are recorded (not specified in full text).
		7. Was the follow up of cohorts adequate? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>
		8. Were co-Interventions similar between groups? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>

=> Serious

Author	Outcome Assessed	Bias assessment
Heschl et al.	Survival to hospital discharge	1. Was selection of exposed and non-exposed cohorts drawn from the same population? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		2. Can we be confident in the assessment of exposure? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		3. Can we be confident that the outcome of interest was not present at start of study Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		5. Can we be confident in the assessment of the presence or absence of prognostic factors? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		6. Can we be confident in the assessment of outcome? Definitely yes Probably yes Probably no Definitely no

		(low risk of bias) (high risk of bias) <u>Motivation:</u>
		7. Was the follow up of cohorts adequate? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>
		8. Were co-Interventions similar between groups? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>

=> Very serious

Author	Outcome Assessed	Bias assessment
Heschl et al.	6 month functional outcome	1. Was selection of exposed and non-exposed cohorts drawn from the same population? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		2. Can we be confident in the assessment of exposure? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		3. Can we be confident that the outcome of interest was not present at start of study Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		5. Can we be confident in the assessment of the presence or absence of prognostic factors? Definitely yes (low risk of bias) Probably yes Probably no Definitely no (high risk of bias) Motivation:
		6. Can we be confident in the assessment of outcome? Definitely yes Probably yes Probably no Definitely no

		(low risk of bias) (high risk of bias) <u>Motivation:</u> Using the Modified Glasgow Outcome Scale (modified GOS) and the Health State Utility Score (HSUS) version 1.
		7. Was the follow up of cohorts adequate? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>
		8. Were co-Interventions similar between groups? Definitely yes Probably yes Probably no Definitely no (low risk of bias) (high risk of bias) <u>Motivation:</u>

=> Very serious