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Title page

**Early-onset pneumonia following bag-mask ventilation versus endotracheal intubation during
cardiopulmonary resuscitation:**

A substudy of the CAAM trial

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4 Conflicts of interest: None

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7

1 **Abstract**

2 **Aim**

3 Early-onset pneumonia (EOP) is a common in-hospital complication in survivors of out-of-hospital
4 cardiac arrest. In this substudy of the CAAM trial, we aimed to compare whether bag mask ventilation (BMV)
5 compared to endotracheal intubation (ETI) performed during cardiopulmonary resuscitation increases the risk of
6 developing EOP.

7 **Methods**

8 Adult patients from the CAAM trial that survived beyond 12 hours of hospitalization were included.
9 Information about in-hospital management and outcome of study subjects was systematically collected. Our
10 primary aim was to compare the incidence of EOP in the BMV and ETI group using a series of bivariate analysis
11 adjusting for one variable at a time and a logistic regression controlled for survival beyond 96 hours, age,
12 gender, catecholamine administration, no flow time, and initial shockable rhythm.

13 **Results**

14 Of 627 patients from the CAAM trial that survived to hospital admission, 409 patients were
15 hospitalized beyond 12 hours and thus included (202 randomized to BMV and 207 randomized to ETI). Patients
16 in the BMV group had a significantly longer period of unsecured airway during prehospital cardiopulmonary
17 resuscitation (BMV (median): 33 minutes; ETI (median): 17 minutes, $p < 0.0001$). No significant difference in the
18 development of EOP according to airway management was identified on univariate analysis (BMV: 53%, ETI:
19 53%, Odds Ratio 1.0 [0.7 - 1.5], $p = 1.0$). We found no difference in the development of EOP according to
20 airway management in the series of bivariate analyses or in the multivariable regression analysis either.

21 **Conclusion**

22 In this substudy of the CAAM trial, development of early-onset pneumonia in out-of-hospital cardiac
23 arrest survivors did not depend on airway management technique during CPR.

24 Trial registration: NCT02327026.

1 **Keywords (6):** early-onset pneumonia, aspiration pneumonia, out-of-hospital cardiac arrest, resuscitation,
2 cardiopulmonary resuscitation and airway management
3

1 Introduction

2 Each year, more than 300.000 individuals in Europe have an out-of-hospital cardiac arrest (OHCA) and
3 despite efforts to improve the outcome, the average survival with a favourable neurological outcome remains
4 below 8%.^{1,2} Among the predictors of survival, the preference for certain airway techniques during cardio-
5 pulmonary resuscitation (CPR) – namely bag-mask ventilation (BMV) versus endotracheal intubation (ETI) – is
6 still a matter of debate.³ ETI has been considered the gold standard, as the technique protects the airway against
7 aspiration and allows controlled ventilation and oxygenation of the patient. Nevertheless, this manoeuvre
8 requires a certain level of skills and experience and imposes a risk of complications such as unrecognized
9 oesophageal intubation, dental trauma, hypoxemia, and aspiration during the procedure.⁴ In numerous
10 observational studies, BMV during CPR has been associated with better survival rates,^{5,6} however in the Cardiac
11 Arrest Airway Management (CAAM) trial where BMV was compared with ETI in 2,043 patients, no significant
12 difference in mortality was found.³ However, BMV inevitably exposes the patient to a longer period with a risk
13 of regurgitation and aspiration of gastric contents. Indeed, regurgitation is often followed by aspiration in the
14 unconscious patient and may lead to the development of early-onset pneumonia (EOP), which has been shown to
15 be the one of the most common infectious complication following cardiac arrest with rates reported as high as
16 65%.⁷ Furthermore, one study even showed that presence of EOP was risk factor of mortality but this association
17 remains challenged.⁸ As a result, BMV may be regarded as less safe than ETI in terms of in-hospital morbidity
18 during CPR in OHCA.

19 Therefore, in this substudy of the CAAM trial we aimed to compare the occurrence of EOP according
20 to the randomization amongst patients who survived beyond 12 hours of hospital admission. We hypothesized
21 that patients randomized to airway management with BMV would have a higher rate of EOP compared to
22 patients randomized to ETI.

1 **Methods**

2 *Study design*

3 We considered this substudy as an observational study and it is therefore reported in accordance with
4 the STROBE guidelines.⁹ The study is a secondary analysis of data from a subset of patients in the multicentre
5 CAAM randomized clinical trial. The CAAM trial was conducted under European regulations where the boards
6 waived the requirement for obtaining informed consent given the emergency setting. Deferred consent from the
7 patient and/or relatives was subsequently obtained. Patients with OHCA were randomized to either BMV or ETI
8 during CPR. In case of return of spontaneous circulation, the patients in the BMV group were subsequently
9 intubated. Early-onset pneumonia was specified as secondary outcome in the study protocol but has not yet been
10 explored (protocol version 2).¹⁰ The population, design, and results of the primary analyses of the CAAM trial
11 are reported in detail elsewhere.³

12 *Study setting*

13 The CAAM trial involved five centres in Belgium and 15 centres in France. Information about in-
14 hospital management and outcome of study subjects was systematically collected from hospital records.

15 *Participants*

16 For this analysis, we chose to include all CAAM patients that survived at least 12 hours of hospital
17 admission after resuscitation of OHCA. This was done to allow symptoms of EOP to develop and be registered
18 as this will usually take at least a few hours.¹¹

19 *Variables*

20 Our primary outcome of interest was EOP. This was defined as the development of a relevant infiltrate
21 on chest radiography and/or relevant auscultation findings within four days of admission and at least one of the
22 following criteria 1) leucocytes >10,000 or <3,000 per μL ; 2) temperature >38.5 °C or <35°C without targeted
23 hypothermia; 3) purulent tracheal aspirates; 4) $\text{PaO}_2/\text{FiO}_2 < 300$ mmHg. If a diagnosis of EOP was mentioned
24 explicitly as one of the final diagnoses (#J690 and #J698) by the treating intensivist this was also accepted. In
25 case of doubt, two intensivists blinded to the allocation were consulted. In case of disagreement, a third party
26 could be consulted. If the reports of the in-hospital management were deemed as insufficiently informative a more
27 detailed report was requested from the treating hospital. However, this was not always possible, often due to a
28 lack of resources, and these patients were therefore excluded.

Secondary outcomes included time to death, length of stay, mechanical ventilator free-days at day 28, cerebral performance category scores (CPC) at day 28, the presence of sepsis or septic shock, cardio-circulatory dysfunction or cardiogenic shock, and time to extubation. The potential predictors or mediators investigated were age, sex, characteristic of cardiac arrest (aetiology, presence of bystander, no-flow duration, initial rhythm), vital signs and laboratory values upon admission (blood pressure, heart rate, pH, lactate level, initial arterial oxygen tension (PaO₂), White Blood Cell count, creatinine level, haemoglobin level), and duration with an unsecured airway (time from collapse to ETI). The isolated microorganisms thought to be responsible for EOP were also recorded.

Statistics

In CAAM, 627 patients survived to hospital admission (294 randomized to BMV; 333 randomized to ETI). We assumed that at least 30% would die within the first 12 hours leaving an approximate sample size of 439 patients. With 80% power at the 5% significance level we would thus be able to detect a difference in our primary outcome between 50% and 35%, a relative risk reduction of 30%.

The primary outcome was compared between the two groups using Fisher's exact test and reported with Odds Ratio and 95% confidence interval.

Secondary outcomes were compared between the two groups using Fisher's exact test or Chi² with Yate's correction for continuity for categorical data¹² and t-test or Wilcoxon rank sum test for continuous data. Results were reported as medians with interquartile ranges [IQR] or numbers with percentages. A 5% significance level was used.

A priori a multivariable logistic regression controlling **for** survival beyond 96 hours, age, gender, systolic blood pressure, heart rate, arterial oxygen saturation, catecholamine administration, hypothermia, no flow time and shockable rhythm was built to compare the incidence of EOP between the two groups of randomisation was planned. Survival beyond 96 hours was included to account for any bias that might occur if the entire time period for the symptoms to appear was not present. However, missing values were too extensive for this to be feasible. Instead, a series of analyses were conducted, including one covariate at a time in addition to the intervention, in order to assess the robustness of the bivariate analysis. In a multivariable regression analysis, we subsequently chose to exclude variables with more than 10% missing data in order to avoid

1 reflection of random variation in the data rather than true association. As such, our model included survival
2 beyond 96 hours, age, gender, catecholamine administration, no flow time, and shockable rhythm. Linearity
3 assumption for the continuous variables was checked using a graphical approach.¹³ Analyses were carried out
4 using R statistical software, RStudio Version 3.5.9.

5

6

RESULTS

Of 627 patients who survived to hospital admission, 440 patients survived beyond 12 hours. Data was insufficient for 31 patients, leaving 409 patients for analysis (202 randomized to BMV and 207 randomized to ETI) (Figure 1).

Baseline characteristics were comparable between the two groups (Table 1). The heart rate upon admission (BMV: 86 bpm; ETI: 90 bpm, $p=0.02$) and the time with an unsecured airway (BMV: 33 minutes; ETI: 17 minutes, $p<0.0001$) were the only variables that differed on univariate analysis.

The overall incidence of EOP was 53%. The diagnostic grounds for the EOP diagnoses are presented in Table 2. An expert panel blinded to the allocation was consulted in 25 cases of which 20 resulted in a diagnosis of early-onset pneumonia. The remaining diagnoses were based on objective clinical criteria and/or a diagnosis code of aspiration pneumonia.

We found no significant difference in the development of EOP according to airway management (BMV: 53%, ETI: 53%, Odds Ratio 1.0 [0.7- 1.5], $p=1.0$). This was unaltered in a sensitivity analysis where the patients with a diagnosis of EOP was based solely on an expert opinion were removed (Table 3). There were no differences between the two groups in terms of ICU length of stay, the incidence of septic or cardiogenic shock, or mechanical ventilator free-days or CPC 1-2 at 28 days. In-hospital mortality was also comparable (BMV: 77%; ETI: 80%, Odds Ratio 1.3 [0.8-2.0], $p=0.40$) (Table 3).

In the series of bivariate analyses on the development of EOP according to airway management adjusted for one variable at a time the lowest p-value for treatment was 0.26, with an OR of 0.76, 95% confidence limits [0.48-1.22], when adjusting for heart rate. In the multivariable regression analysis, there was still no difference in the development of EOP amongst the two groups of randomisation (Odds ratio 0.81 [0.53-1.26], $p=0.36$) (Table 4).

Finally, we performed a sensitivity analysis to consider 38 patients in the BMV group that were intubated before ROSC. These patients were added to the ETI group. No significant difference for occurrence of EOP was found between these two groups (82/164 (50%) and vs 111/245 (45%), $p=0.23$).

- 1 Microorganisms responsible for EOP were available for 29% of cases (Supplementary Table 1). The
- 2 three most common causative micro-organisms were staphylococcus aureus, streptococcus pneumonia, and
- 3 haemophilus influenzae.

DISCUSSION

In this substudy of the CAAM trial, we did not find a significant difference in EOP between survivors of OHCA hospitalized more than 12 hours managed with BMV compared with ETI during CPR. A multivariable regression analysis confirmed this finding.

The risk of regurgitation and pulmonary aspiration of gastric contents is high in cardiac arrest patients and during CPR.¹⁴ Especially the duration of the cardiac arrest and the time with an unsecured airway seem to be associated with pulmonary aspiration.^{7,15,16} However, although aspiration is thought to be the leading cause of pneumonia in the intensive care unit (ICU),¹⁷ an observed regurgitation does not always predict it. In one study, for example, authors found regurgitation on scene compatible with radiological signs of pulmonary aspiration in 39% of cases, but when regurgitation had not been observed, radiological signs of pulmonary aspiration were still present in 14% of cases.¹⁴

Nevertheless, as EOP has been identified as the most common in-hospital infectious complication to OHCA¹⁸ with incidences varying between 24% and 65%,^{7,19} vigilance hereof is an important component of critical care. Basic life support with the help of BMV (and thus an unsecured airway) has been proposed to play a central role in the pathogenesis of EOP.⁷ In a study performed on 30 human cadavers, for example, aspiration occurred in 80% when BMV was used and in none when ETI was used.²⁰ In another study, the incidence of regurgitation increased threefold when the patient was ventilated with BMV compared to ETI.²¹ Although BMV did not show inferior mortality rates compared to ETI in the CAAM trial, concerns were still raised regarding the safety of BMV, as the rate of observed regurgitation during resuscitation of gastric contents was significantly higher compared with the ETI group (15.2% versus 7.5%, $p < 0.001$). In our subgroup of patients that survived for more than 12 hours of hospitalization, the rate of regurgitation also tended to be more frequent in the BMV group, but this was not statistically significantly different (11.9% versus 8.2% in the BMV and ETI groups, respectively, $p = 0.28$) even though BMV patients had an unsecured airway for approximately 16 minutes longer. As such, the randomized airway management was not able to explain the subsequent development of EOP. In another study on 1333 cases of out-of-hospital cardiac arrest, however, regurgitation occurred in 76% and in two-thirds of the cases it occurred prior to EMS arrival.²² In another study on in-hospital cardiac arrest, almost 50% of regurgitations occurred prior to commencing CPR,²¹ and whether this could be part of the explanation of our findings seems possible.

Other possible causes of the development of EOP in OHCA survivors include pulmonary contusions due to chest compressions^{23,24} and targeted hypothermia.¹⁵ In CAAM, however, the randomization process secured comparable groups in terms of CPR procedure (except, of course, the airway management) and thus also comparable rates of pulmonary contusions. Data regarding the association between targeted temperature management and pulmonary infection is conflicting, as targeted hypothermia has been found to be an independent risk factor for EOP⁷ but others could not confirm this.^{18,25} Finally, while several studies agree that the association between EOP and survival is marginal, most have found EOP to be associated with the increased lengths of mechanical ventilation as well as increased length of ICU stay.^{7,15,16}

Limitations

Certain strengths and limitations of this study must be recognized. Although our analysis was done post-hoc, the outcome of EOP was added to the protocol prior to completion of the study. Furthermore, while the subgroup may be exposed to a potential selection bias, our study population was based on a randomized study thereby minimizing biases and confounding factors.

The definition of EOP is continuously debated and differs greatly among published studies, resulting in numerous authors highlighting the lack of established robust diagnostic criteria for EOP.^{11,15} Nevertheless, our choice to define EOP is in accordance with most published criteria.

We choose to include patients that survived above 12 hours of hospitalisation to allow for symptoms of EOP to develop and be registered. However, it is possible that EOP was still not registered if patients died within the first 96 hours of hospitalisation (our window for EOP to develop). However, in a sensitivity analysis in which we assumed that all patients that died within the first 96 hours had developed EOP there was still no difference between the groups.

Furthermore, 31 patients were excluded from our analysis as there was insufficient information to assess whether EOP had developed. Although we believe these patients were missing completely at random, we performed a sensitivity analysis assuming all had EOP. When doing so, there was still not difference between the two airway management techniques.

Generalizability

In the CAAM trial, no difference in mortality was found. In this substudy of CAAM with patients hospitalized more than 12 hours, no difference in the development of EOP was found either. As such, despite a

1 prolonged exposure to an unsecured airway under BMV, the two techniques appear to be safe during CPR
2 allowing the operator to shift between the two as needed to maintain the high quality of chest compressions.

4 **Conclusion**

5 In this substudy of the CAAM trial, development of EOP after OHCA was not associated with airway
6 management during CPR. These findings suggest delaying intubation until after return of spontaneous
7 circulation may not increase the risk of EOP. Nevertheless, as the incidence of EOP after OHCA remains high,
8 further research is warranted to establish its cause and optimal management.

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2

- 1 **Additional information:**
- 2 *Information for original study:*
- 3 Trial Registration: clinicaltrials.gov; Identifier: NCT02327026
- 4 IRB number for original study: 2014-A01109-38

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1 Figure 1 – Flow diagram of CAAM patients hospitalized 12 hours or longer

2

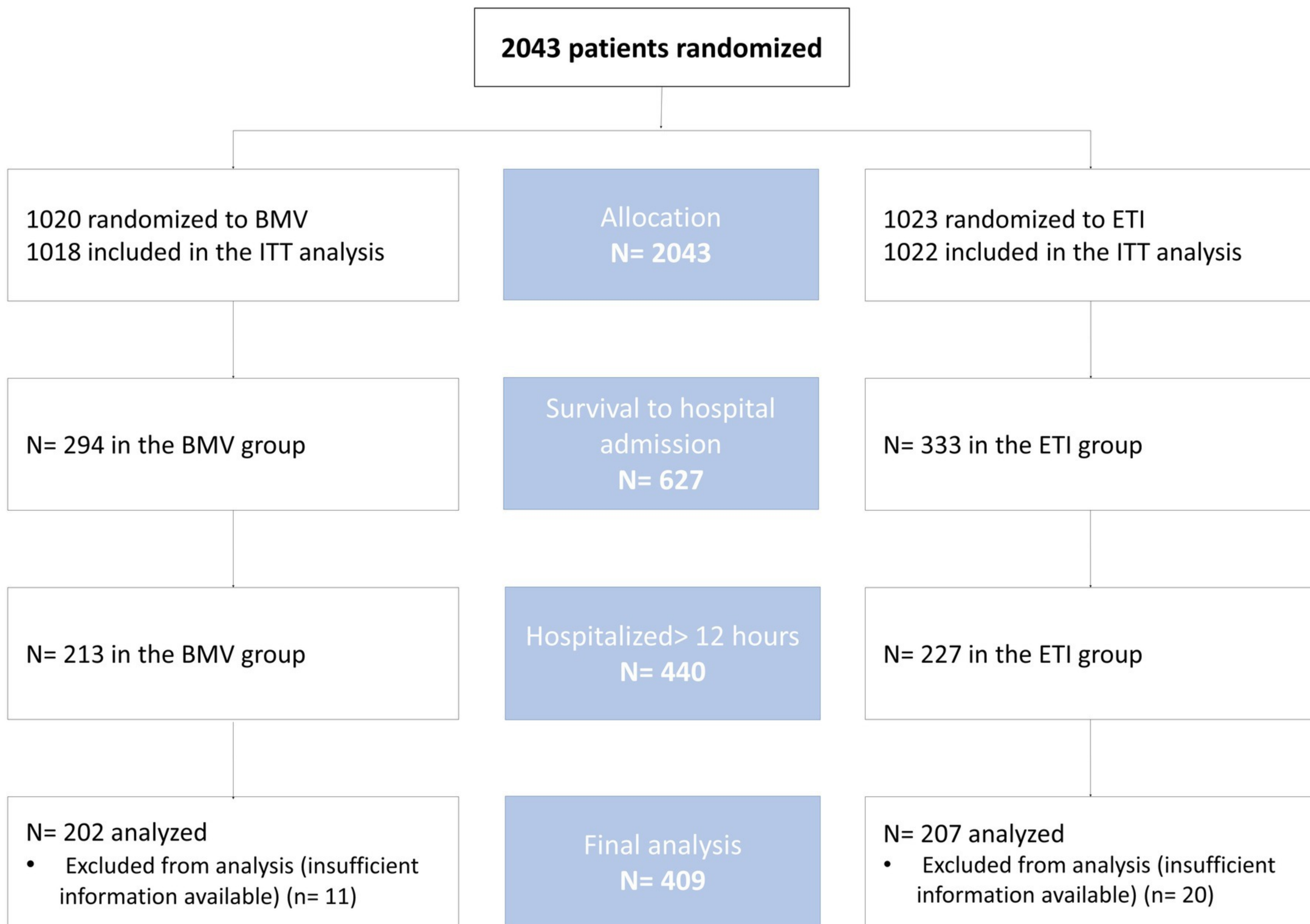


Table 1. Characteristics of resuscitated cardiac arrest patients from the CAAM trial that survived more than 12 hours of hospitalization (N= 409)

Data is presented as numbers with percentages (%), as medians with interquartile ranges [IQR] or as otherwise indicated

Variable	BMV group (n= 202)	Missing values	ETI group (n= 207)	Missing values	P value
Out-of-hospital characteristics					
Gender					
Female	71 (35)	0	62 (30)	0	0.29
Age (years), mean (sd)	62 (15)	0	62 (15)	0	0.85
Etiology of cardiac arrest					
Cardiac	128 (64)	1	136 (66)	1	0.95
Noncardiac medical	64 (32)		60 (29)		
Traumatic	9 (5)		10 (5)		
Bystander-witnessed cardiac arrest	163 (81)	0	173 (84)	0	0.52
Bystander-initiated CPR	104 (52)	1	121 (59)	0	0.2
No-flow duration (minutes)	4 [0-9]	21	4 [0-10]	21	0.75
Shockable first rhythm	58 (29)	0	63 (30)	0	0.78
Time with unsecured airway^a (minutes)	33 [23-49]	20	17 [12-23]	24	<0.000 1
In-hospital characteristics ^b					
Systolic blood pressure (mmHg)	119 [95-143]	60	121 [93-147]	59	0.64
Diastolic blood pressure (mmHg)	69 [52-83]	64	65 [54-82]	62	0.84
Heart Rate (beats per minute)	86 [70-105]	57	90 [76-110]	64	0.02
pH	7.2 [7.1-7.3]	49	7.2 [7.1-7.3]	55	0.41
PaO₂ (mmHg)	130 [85-197]	65	122 [88-212]	61	0.84
Lactate (mmol/L)	6.4 [3.4-10.3]	67	6.3 [3.6-10.2]	63	0.97
Hemoglobin (mmol/L)	13.3 [11.6-14.7]	63	13.2 [11.5-14.9]	61	0.94
WBC (10³/μl)	15.8 [11.6-21.0]	60	16.1 [11.5-21.0]	61	0.98
Creatinine (μmol/l)	117 [90-143]	59	109 [88-142]	57	0.67
Catecholamine administration	115 (60)	10	119 (60)	7	1
Therapeutic hypothermia	72 (36)	0	71 (34)	0	0.86
Survival above 96 hours	113 (53)	0	101 (47)	0	0.18

Table 2 - Early onset pneumonia diagnosis grounds

Early-onset pneumonia was defined as the development of a relevant infiltrate on chest radiography and/or relevant auscultation findings within four days of admission and at least one of the following criteria 1) leucocytes >10,000 or <3,000 per μL ; 2) temperature >38.5 °C or <35°C without targeted hypothermia; 3) purulent tracheal aspirates; 4) $\text{PaO}_2/\text{FiO}_2 < 300$ mmHg. If a diagnosis of EOP was mentioned explicitly as one of the final diagnoses (#J690 and #J698) by the treating intensivist this was also accepted.

Variable	All patients (n= 409)	
Sign(s) (within four days of admission)	n	(%)
Relevant auscultation findings	110	(27)
Development of a relevant infiltrate on chest radiography	127	(31)
Auscultation and/or x-ray signs*	182	(44)
Purulent secretions	50	(12)
Leucocytes >10,000 or <3,000 per μL	243	(59)
Temperature above 38.5°C or below 35°C without induced hypothermia	67	(16)
$\text{PaO}_2/\text{FiO}_2 < 300$	164	(40)
One of the four criteria fulfilled	314	(77)
Final diagnosis code	42	(10)
Early onset pneumonia by expert opinion	20	(5)

Total early onset pneumonia

216

(53)

diagnoses

*Relevant auscultation findings refer to crackles or rhonchi. X-ray signs refer to relevant infiltrates.

Table 3 - Outcomes of resuscitated cardiac arrest patients from the CAAM trial that survived more than 12 hours of hospitalization (N= 409)

Data is presented as numbers with percentages (%) or as medians with interquartile ranges [IQR]

Variable	BMV group (n= 202)	ETI group (n= 207)	p-value
Early-onset pneumonia ^a	106 (53)	110 (53)	0.97
<i>Clinical signs only</i> ^b	95 (47)	101 (49)	0.77
ICU length of stay (hours)	117 [45-216]	95 [36-211]	0.28
Septic shock	19 (9)	19 (9)	0.82
Cardiogenic shock	32 (16)	44 (21)	0.17
Mechanical ventilator free days (day 28), mean (SD)	5 (10)	4 (9)	0.51
In-hospital mortality	155 (77)	166 (80)	0.46
CPC 1-2	41 (20)	36 (18)	0.53

Abbreviations: CAAM, Cardiac Arrest Airway Management; BMV, Bag-mask ventilation; ETI,

Endotracheal intubation; ICU, intensive care unit; IQR, Interquartile Range; CPC, Cerebral

Performance Categories

^a Early-onset pneumonia was defined as the development of a relevant infiltrate on chest radiography and/or relevant respiratory auscultation sounds within four days of admission and at least one of the following criteria 1) leucocytes >10,000 or <3,000 μ L; 2) temperature >38.5 °C or <35°C without targeted hypothermia; 3) purulent tracheal aspirates; 4) PaO₂/FiO₂<300. If a diagnosis of early-onset pneumonia was mentioned explicitly in the patient records by the treating physician, this was also accepted. In case of doubt, an expert panel blinded to the allocation was consulted. If the reports of the in-hospital management were deemed as insufficiently informative a more detailed report was requested. If this was not possible, patients were excluded.

^b Early-onset pneumonia diagnoses based solely on objective criteria (expert opinions excluded)

TABLE 4

Bivariate analyses on the development of Early-Onset Pneumonia (EOP) in CAAM patients

	<i>Odds ratio</i>	<i>95% CI</i>	<i>p-value</i>	<i>N. of patients available</i>
BMV group	0.93	[0.63-1.38]	0.71	409
Survival above 96 hours	1.89	[1.28-2.81]	0.002	
BMV group	0.99	[0.67-1.46]	0.96	409
Gender (male)	1.38	[0.91-2.09]	0.13	
BMV group	0.97	[0.66-1.44]	0.89	409
Age (years)	1.00	[0.99-1.01]	0.99	
BMV group	0.82	[0.48-1.43]	0.50	224
Saturation (%)	0.98	[0.94-1.01]	0.21	
BMV group	0.97	[0.61-1.55]	0.90	299
Systolic blood pressure (per 10 mmHg)	1.01	[1.00-1.01]	0.07	
BMV group	0.76	[0.48-1.22]	0.26	288
Heart rate (per 10 bpm)	1.00	[0.99-1.01]	0.61	
BMV group	0.92	[0.62-1.38]	0.69	392
Catecholamine administration	1.82	[1.21-2.74]	<0.01	
BMV group	0.97	[0.66-1.43]	0.87	266
Targeted hypothermia	1.51	[1.00-2.28]	0.049	
BMV group	0.91	[0.60-1.38]	0.66	367
Time with no flow (minutes)	0.98	[0.95-1.01]	0.19	
BMV group	0.97	[0.66-1.44]	0.89	409
Shockable rhythm	0.99	[0.64-1.52]	0.95	

Multivariable regression analysis on the development of Early-Onset Pneumonia (EOP) in CAAM patients (N= 409*)

	<i>Odds ratio</i>	<i>95% CI</i>	<i>p-value</i>
BMV** group	0.81	[0.53-1.26]	0.36
Survival above 96 hours	2.26	[1.44-3.54]	<0.001
Gender (male)	1.21	[0.76-1.93]	0.43
Age (years)	1.00	[0.99-1.02]	0.76
Catecholamine administration	1.93	[1.23-3.03]	<0.01
Time with no flow (minutes)	0.99	[0.95-1.02]	0.38
Shockable rhythm	0.83	[0.51-1.34]	0.45

*After removal of 59 patients with missing values for any of the above variables, 305 were utilised in the multivariable analysis

**BMV group: bag mask ventilation group (reference: endotracheal intubation)

