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## The effect of etomidate on adrenal function in critical illness: a systematic review

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**Abstract** *Purpose:* Although etomidate is a preferred anesthetic agent for rapid sequence intubation (RSI) in critical illness, as an inhibitor of cortisol synthesis ( $11\beta$ -hydroxylase), it may be associated with adrenal dysfunction. The objectives are to review the effects of etomidate versus comparator anesthetics in critical illness for: primary outcome of mortality and secondary outcome of adrenal insufficiency (AI). *Methods:* Studies were extracted using MEDLINE and SCOPUS, regardless of language, between 1983 and 2010 using the keywords etomidate, intensive care units (ICU), critical illness, intensive care, glucocorticoids, and adrenal insufficiency. Studies of single dose etomidate versus comparator anesthetics with outcomes of adrenal function and/or mortality were included. All reviewers performed electronic data searches. One reviewer extracted data, which were checked by the other reviewers. Authors of trials were contacted for supplemental data. Primary outcome was 28-day mortality. AI was defined

per article. *Results:* Two hundred sixty-three articles were screened, and 21 articles (19 independent data sets) were evaluated. Meta-analysis comparing etomidate versus non-etomidate anesthesia demonstrated an increased risk ratio (RR) for AI of 1.64 (range 1.52–1.77; 14 studies, 2,854 patients,  $P < 0.0001$ ,  $I^2 = 88\%$ ) and an increased RR for mortality of 1.19 (1.10–1.30; 14 studies, 3,516 patients,  $P < 0.0001$ ,  $I^2 = 64\%$ ). Significance of re-analysis for mortality within the subset of sepsis was maintained [RR 1.22 (1.11–1.35), 7 studies,  $n = 1,767$ ,  $I^2 = 74\%$ ,  $P < 0.0001$ ], but not for trials without sepsis [RR = 1.15 (0.97–1.35), 7 studies,  $n = 1,749$ ,  $I^2 = 53\%$ ,  $P = 0.10$ ]. *Conclusions:* There is an increased rate of AI and mortality in critically ill patients who received etomidate.

**Keywords** Etomidate · Adrenal insufficiency · Critical illness-related corticosteroid insufficiency · ICU · Critical illness

### Introduction

Etomidate is a preferred anesthetic agent for rapid sequence intubation (RSI) in patients in the intensive care unit (ICU) [1, 2]. However, it may cause adrenal insufficiency (AI) [2, 3].

Etomidate is a fast-acting intravenous anesthetic agent with a favorable safety profile and a better therapeutic index than alternative anesthetics. It is thus the agent of choice routinely available for RSI [1, 2]. Despite these benefits, in the 1980s the drug was withdrawn from use for continuous intravenous sedation after it was associated

with increased mortality [4]. Etomidate, an imidazole derivative, functions as an inhibitor of adrenal  $11\beta$ -hydroxylase and in higher doses also inhibits side chain cleavage enzymes [5]. It was restricted for use as a single intravenous injection with the expectation that adrenal dysfunction would be eliminated [1].

There is no controversy about etomidate causing adrenal dysfunction. A single bolus dose causes adrenal dysfunction immediately with persistence for 12 h [6], 24 h [7] or as long as 48 h [8]. However, there is controversy about whether inhibition of adrenal steroidogenesis is clinically relevant in the critically ill. Proponents of etomidate balance the immediate hemodynamic benefits versus the risks of AI. The spectrum of expert opinion ranges from calling for a moratorium on the use of the drug awaiting randomized controlled trials (RCTs) [2, 3, 9], the use of glucocorticoid supplementation given simultaneously [3], and continued cautious use [10]. The objectives of this review are to assess the data on etomidate during critical illness for the primary outcome of mortality and the secondary outcome of AI.

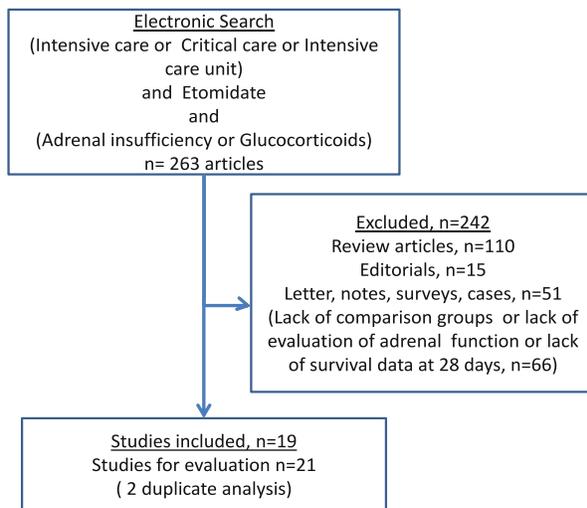
## Methods

### Electronic search

An electronic literature search was performed on MEDLINE (OVID) SCOPUS, EBM, and Cochrane Reviews for human studies, regardless of language, between 1983 (the earliest report on etomidate's effect on adrenal function) and June 2010. There were no EBM or Cochrane Reviews. All studies after 1983 used a single intravenous bolus etomidate dose of 0.3 mg/kg. The search strategy using keywords and an algorithm is shown in Fig. 1: (Intensive care or Critical care or ICU) and etomidate and (AI or Glucocorticoids). Relevant narrative reviews and editorials were appraised, and the reference lists were reviewed to identify primary trials. All primary comparator trials were included in the analysis if there was either evaluation of adrenal function or 28-day survival. All authors reviewed electronic data search titles and abstracts to identify potential trials. One reviewer extracted data, which were checked by the other reviewers. Authors of primary trials were contacted to identify any unpublished data (personal communication, "pc") [11].

### Quality of studies

Quality of studies was considered according to the Grade recommendations [12] and is included in Table 1. Quality of trials was considered as: high (large RCTs), moderate



**Fig. 1** Electronic search criteria

(RCTs with post hoc analysis of an etomidate effect), and low (retrospective and observational studies).

### Data analyses

The primary outcome for the meta-analysis was 28-day all-cause mortality. Secondary outcome was the rate of AI. AI defined per study author is described in Table 1. Most studies used the incremental cortisol response ( $\Delta$ cortisol) to a standardized 250  $\mu$ g cosyntropin stimulation test (CST).

### Meta-analyses

Meta-analyses were performed for studies involving adults using the statistical program of Bax [13, 14] using an a priori fixed effects model of Mantel-Haenszel that incorporates statistical weighing of larger studies. Heterogeneity of the meta-analysis was evaluated by the  $I^2$  statistic [11]. Evidence of publication bias was assessed using funnel plots and meta-regression analyses [11].

### Statistical analyses

Statistical analyses of data retrieved after publication ("pc") are described as "calculated here" (†) to differentiate them from statistics available in the original publication. Analyses of proportions were performed by the chi-square test (Statistica for Windows, V7.1 Stat Soft, Inc.2005, Tulsa, OK). Data are reported as mean  $\pm$  standard deviation or [95% confidence intervals].

**Table 1** Studies describing the effect of etomidate on adrenal insufficiency and mortality in patients with critical illness

Year	Author	Reference number	Study type	Inclusion criteria	Location	Definitions of adrenal insufficiency	Total number of subjects
2002	Amrane	[19]	RCT (corticosteroids vs. placebo)	Septic shock	ICU	$\Delta$ CST < 250 nmol/L (<9 $\mu$ g/dL)	299
2005	Oppert	[17]	RCT (corticosteroids vs. placebo)	Septic shock	ICU	$\Delta$ CST < 250 nmol/L (<9 $\mu$ g/dL)	41
2008	Sprung, Cuthbertson	[20, 21]	RCT (corticosteroids vs. placebo)	Septic shock	ICU	$\Delta$ CST < 250 nmol/L (<9 $\mu$ g/dL)	499
1999	Absalom	[7]	RCT (etomidate vs. thiopentone)		ICU	$\Delta$ CST cortisol < 193 nmol/L (<7 $\mu$ g/dL)	35
2001	Schenarts	[6]	RCT (etomidate vs. midazolam)		Emergency department	CST peak cortisol < 500 nmol/L (<18 $\mu$ g/dL) or $\Delta$ CST cortisol < 193 nmol/L (<7 $\mu$ g/dL)	18
2006	Hildreth	[14]	RCT (etomidate vs. fentanyl and midazolam)		ICU	Not defined	30
2009	Jabre	[15]	RCT (etomidate vs. ketamine)		Emergency department	Cortisol < 276 nmol/L (<10 $\mu$ g/dL) or $\Delta$ CST < 250 nmol/L (<9 $\mu$ g/dL)	469
2007	Riche	[29]	Observational study	Septic shock + intra abdominal abscess	ICU	Cortisol 883 nmol/L (<32 $\mu$ g/dL) and $\Delta$ CST 220 nmol/L (<8 $\mu$ g/dL)	116
2006	Mohammad	[23]	Retrospective study	Septic shock	ICU	$\Delta$ CST < 250 nmol/L (<9 $\mu$ g/dL)	152
2007	Ray and McKeown	[33]	Retrospective study	Septic shock	ICU	Not defined	159
2007	Lipiner-Friedman	[22]	Retrospective study	Septic shock	ICU	Cortisol < 414 nmol/L (<15 $\mu$ g/dL) or $\Delta$ CST < 250 nmol/L (<9 $\mu$ g/dL)	477
2008	Kim	[24]	Retrospective study	Septic shock	ICU	$\Delta$ CST < 250 nmol/L (<9 $\mu$ g/dL)	65
2004	Malerba	[26]	Observational study	Mechanical ventilation >24 h	ICU	$\Delta$ CST < 250 nmol/L (<9 $\mu$ g/dL)	62
2005	Cohan	[27]	Observational study	Traumatic brain injury	ICU	Two cortisols < 414 nmol/L (<15 $\mu$ g/dL) or one cortisol < 138 nmol/L (<5 $\mu$ g/dL)	79
2009	Tekwani	[34]	Observational study		Emergency department	Not defined	106
2007	de Jong	[28]	Retrospective study	Prolonged hypotension	ICU	Peak cortisol < 500 nmol/L (<18 $\mu$ g/dL) or $\Delta$ CST < 250 nmol/L (<9 $\mu$ g/dL)	405
2008	Cotton	[25]	Retrospective study	Trauma	ICU	$\Delta$ CST < 250 nmol/L (<9 $\mu$ g/dL)	137
2009	Baird	[32]	Retrospective study		Emergency department	Not defined	535
2008	den Brinker	[30, 31]	Retrospective study	Children with meningococcal sepsis	ICU	Not defined	31
<b>Etomidate</b>							
				<b>Non-etomidate</b>			
Number (male/female)	Adrenal insufficiency by CST, number (%)	Mortality, number (%)	Number (male/female)	Adrenal insufficiency by CST, number (%)	Mortality, number (%)	<i>P</i> , adrenal insufficiency	Grade criteria, quality
72	68 (94%)	38 (53%) <sup>a</sup>	227	161 (71%)	135 (59%) <sup>a</sup>	<0.001	Moderate
7	4 (57%)	n.d.	34	26 (76%)	n.d.	n.s.	Moderate
96 (64/32)	59 (61%)	41 (42.7%)	403 (268/135)	186 (46%)	123 (30.5%)	0.007	Moderate
17 (9/8)	15 (88%)	5(29%)	18 (12/6)	5 (29%)	3 (18%)	0.001	Moderate
10 (6/4)	7 (70%)	n.d.	8 (3/5)	0	n.d.	0.004	Moderate
18	n.d.	n.d.	12	n.d.	n.d.	n.d.	Moderate
234 (147/87)	93 (81%)	81 (35%)	235 (133/102)	49 (42%)	72 (31%)	<0.0001	High
69	41 (59%) <sup>b</sup>	25 (36%) <sup>b</sup>	47	30 (64%) <sup>b</sup>	22 (46%) <sup>b</sup>	n.s. <sup>†</sup>	Low
38 (20/18)	29 (76%)	24 (63%)	114 (69/45)	58 (51%)	63 (55%)	0.008	Low
74	n.d.	51 (69%)	85	n.d.	51 (60%)	n.d.	Low
237	163 (69%) <sup>c</sup>	173 (73%)	240	40 (17%) <sup>c</sup>	113 (47%)	<0.001 <sup>†</sup>	Low

Table 1 continued

Etomidate		Non-etomidate				P, adrenal insufficiency	P, mortality	Grade criteria, quality
Number (male/female)	Adrenal insufficiency by CST, number (%)	Mortality, number (%)	Number (male/female)	Adrenal insufficiency by CST, number (%)	Mortality, number (%)			
25 (14/11)	21 (84%)	8 (32%)	40 (33/7)	19 (48%)	17 (43%)	0.003	n.s.	Low
28	19 (68%)	18 (64%) <sup>d</sup>	34	8 (24%)	12 (35%) <sup>d</sup>	<0.001	P = 0.04 <sup>†</sup>	Low
55	33 (60%)	n.d.	24	8 (33%)	n.d.	0.03	n.d.	Low
74(34/40)	n.d.	28 (38%) <sup>e</sup>	32 (14/18)	n.d.	14 (44%)	n.d.	n.s.	Low
86	52 (60%) <sup>e</sup>	15 (17%) <sup>e</sup>	319	183 (57%) <sup>e</sup>	72 (23%) <sup>e</sup>	n.s. <sup>†</sup>	n.s. <sup>†</sup>	Low
87	59 (68%)	16 (18%) <sup>f</sup>	50	24 (48%)	13 (26%) <sup>f</sup>	0.02	n.s. <sup>†</sup>	Low
184 (118/66)	n.d.	40 (22%)	351 (233/118)	n.d.	46 (13%)	n.d.	0.02	Low
23 (19/4)	n.d.	7 (30%)	8 (2/6)	n.d.	1 (12.5%)	n.d.	n.s.	Low

Data expressed as mean ± standard deviation (SD) or [range] when available

CST cosyntropin stimulation test; RCT randomized controlled trials; n.d. not described; n.s. not significant

P values are from publication; <sup>d</sup>calculation in this paper by chi-square test using available data statistics calculated here

<sup>a</sup> D. Annane, personal communication

<sup>b</sup> F. Riche, personal communication

<sup>c</sup> D. Annane, personal communication

<sup>d</sup> P.E. Bollaert, personal communication

<sup>e</sup> M.F.C. deJong, personal communication

<sup>f</sup> B.A. Cotton, personal communication

Statistical significance is defined as a  $P < 0.05$  by two-tailed testing.

## Results

The electronic search revealed 263 articles (Fig. 1). Primary clinical studies of adults and children with critical illness yielded 21 articles and 19 independent data sets (in two follow-up articles the population was analyzed twice, and each data set was included as one series) (Table 1).

### Randomized controlled trials

There were four RCTs [6, 7, 15, 16] of etomidate versus comparators. Studies of ICU patients included: Absalom [7], etomidate ( $n = 17$ ) versus thiopentone ( $n = 18$ ) demonstrated AI in 88 versus 29%,  $P = 0.0006$ ; Hildreth (trauma patients) [15] etomidate ( $n = 18$ ) versus fentanyl and midazolam ( $n = 12$ ) did not define AI, but did demonstrate significantly lower CST  $\Delta$ cortisol with etomidate versus comparator ( $\Delta$ cortisol  $116 \pm 135$  nmol/L [ $4.2 \pm 4.9$   $\mu$ g/dL] versus  $309 \pm 168$  nmol/L [ $11.2 \pm 6.1$   $\mu$ g/dL],  $P < 0.001$ ). Etomidate was associated with significant prolongations of days: in the ICU (6.3 vs. 1.5 days,  $P < 0.05$ ), on a ventilator (28 vs. 17 days,  $P < 0.010$ ), and in length of stay (LOS) (11.6 vs. 6.4 days,  $P < 0.010$ ).

Studies of AI in the emergency department with etomidate versus comparators included: Schenarts [6] etomidate ( $n = 10$ ) versus midazolam ( $n = 8$ ), AI at 4 h in 70% versus none with the comparator,  $P = 0.004$ ; Jabre [16] etomidate ( $n = 234$ ) versus ketamine ( $n = 235$ ) AI in 81 versus 42%,  $P < 0.0001$ .

Three RCTs of glucocorticoid supplementation versus placebo in the ICU evaluated the effects of etomidate versus comparators post hoc [17–20]. Oppert [17] ( $n = 41$ , septic shock) found AI in 4/7 (57%) vs. 26/34 (76%),  $P = n.s.$ ].

Annane [18, 19] described two sentinel studies on adrenal responsiveness with respect to survival in septic shock. The first [18] documented that mortality increased with “non-response” to CST [ $\Delta$ cortisol  $\leq 250$  nmol/L ( $\leq 9$   $\mu$ g/dL)]. In the follow-up Ger-Inf-05 study [19], glucocorticoid supplementation with 200 mg hydrocortisone/day and fludrocortisone 50  $\mu$ g/day improved morbidity in all (with decreases in LOS and need for vasopressors), whereas survival benefits were limited to those with AI. Seventy-two of 299 received etomidate, of which AI occurred in 94 with versus 71% without etomidate ( $\dagger P < 0.001$ ).

The CORTICUS prospective study [20, 21], a RCT of septic shock, did not demonstrate an overall benefit in survival with glucocorticoids versus placebo. Ninety-six

of 499 subjects received etomidate. Steroids were given within 72 h (median time from etomidate 14 h). Post hoc analysis with versus without etomidate showed a greater prevalence of AI (61 vs. 46%,  $P = 0.007$ ).

#### Non-randomized trials

The CORTICUS retrospective study [22] evaluated adrenal responsiveness and glucocorticoid supplementation on mortality in sepsis ( $n = 477$ ). The absolute risk of AI associated with versus without etomidate was 69 versus 17% (“pc” D. Annane, † $P < 0.001$ , Table 1).

Adrenal insufficiency in the ICU was greater with etomidate than comparators in the studies of: Mohammed [23] ( $n = 152$ , septic shock, 76 vs. 51%,  $P = 0.008$ ); Kim [24] ( $n = 65$ , septic shock, 84 vs. 48%,  $P = 0.003$ ); Cotton [25] ( $n = 137$ , trauma patients, 68 vs. 48%,  $P = 0.02$ ); Malerba [26] ( $n = 62$ , mechanical ventilation for >24 h, 68 vs. 24%,  $P = 0.001$ ); and Cohan [27] ( $n = 79$ , traumatic brain injury, 60 vs. 33%,  $P = 0.049$  by univariate but not multivariate analysis). AI was not increased with etomidate versus comparators in: De Jong [28] ( $n = 405$ , prolonged hypotension, 60 vs. 57%, “pc” M.F.C. de Jong); and Riche [29] ( $n = 116$ , CST within 24 h, 59 vs. 64%, “pc” F. Riche).

The study by den Brinker [30, 31] of children with meningococcal sepsis did not define AI. However, cortisol levels after etomidate ( $n = 23$ ) were approximately 50% that of comparably ill patients ( $n = 8$ ) (assessed by critical illness severity scores,  $P < 0.05$ ). The levels of precursor 11-deoxycortisol were more than twofold higher than found in comparators, confirming that adrenal dysfunction was due to enzyme inhibition.

#### Mortality data for etomidate versus comparator agents

There were significantly higher mortality rates with versus without etomidate in: the prospective CORTICUS [20, 21] ( $n = 499$ , 42.7 vs. 30.5%,  $P = 0.02$ ); the retrospective CORTICUS [21] ( $n = 477$ , 73 vs. 47%,  $P < 0.001$  (“pc” D. Annane, † $P < 0.001$ )); Malerba [26] ( $n = 62$ , 64 vs. 35%, “pc”, P.E. Bollaert, † $P = 0.04$ ). Baird [32] compared etomidate ( $n = 186$ ) versus alternate anesthetics (thiopental  $n = 306$ , propofol  $n = 35$ ) in an ED; mortality was greater with than without etomidate by univariate analysis (22 vs. 13%,  $P = 0.02$ ), but not after multivariate analysis.

Mortality was not significantly different with versus without etomidate in the studies of: Annane [19] 53 (38/68) versus 59.5% (135/227) (“pc” D. Annane, † $P = \text{n.s.}$ ); Mohammed [23] ( $n = 152$ , 63 vs. 55%); Kim [24] ( $n = 65$ , 32 vs. 43%); Cotton [25] ( $n = 137$ , 18 vs. 26%, “pc” B.A. Cotton); De Jong [28] ( $n = 405$ , 17 vs. 23%, “pc” De Jong); Riche [29] ( $n = 116$ , 36 vs. 47%) “pc” F.

Riche); Den Brinker [30, 31] ( $n = 31$ , 30 vs. 12.5%); Ray and McKeown [33] ( $n = 159$ , ICU with septic shock, 69 vs. 60%); or Tekwani [34] ( $n = 106$ , ICU with sepsis, 38 vs. 44%).

#### Meta-analysis of the effect of etomidate versus comparators

Meta-analyses of the risk ratio (RR) of effects of etomidate versus comparators are performed for all evaluable trials of adult subjects. There was an increased RR for AI with etomidate above comparators of 1.64 [range 1.52–1.77] (14 trials,  $n = 2,854$ ,  $P < 0.0001$ ,  $I^2 = 88\%$ ; Fig. 2). There does not appear to be a publication bias as evaluated by a funnel plot (ESM Fig. 5A). Meta-regression analysis (ESM Fig. 6A) showed the association of etomidate with AI was constant and independent of the level of AI in the comparator groups.

There was an increased RR for mortality with etomidate over controls of 1.19 [1.10–1.30] (14 trials,  $n = 3,516$ ,  $P < 0.0001$ ,  $I^2 = 64\%$ , Fig. 3). There was no publication selection bias by a funnel plot (ESM Fig. 5B). The increase in the RR of mortality versus the control population was found for all levels of clinical severity by meta-regression analysis (ESM Fig. 6B).

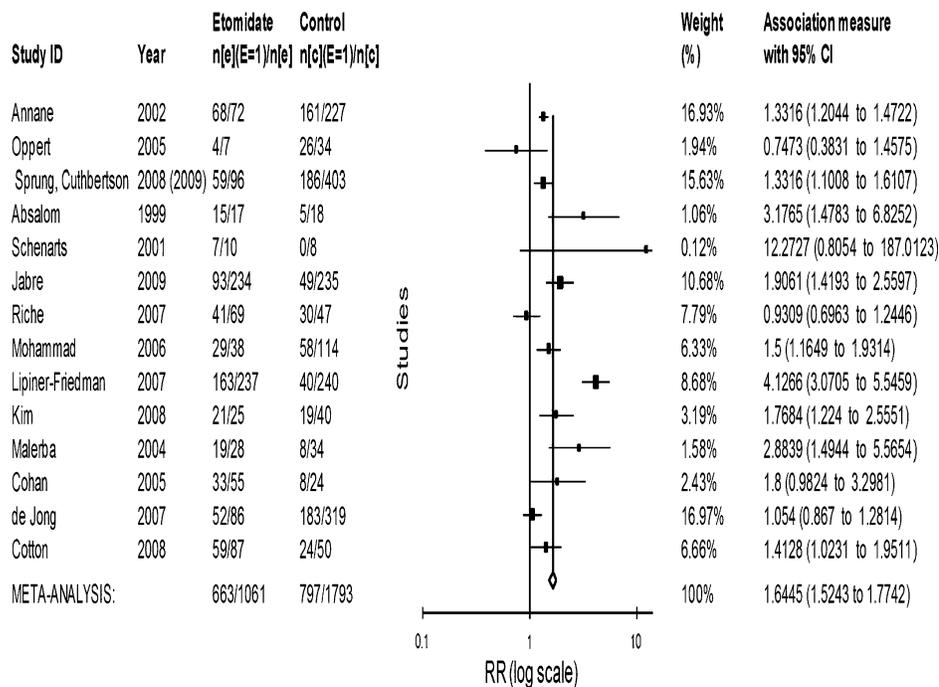
The  $I^2$  statistic indicates a marked heterogeneity for analyses of AI and for mortality. To identify possible causes of heterogeneity, data were re-analyzed with respect to the subgroups of trials and sources of patient inclusion.

Heterogeneity for AI persisted after re-evaluation comparing inclusion criteria for: 6 RCTs, RR = 1.51 [1.34–1.70] ( $n = 1,361$ ,  $I^2 = 75\%$ ,  $P < 0.0001$ ) versus 8 non-RCTs, RR = 1.76 [1.59–1.95] ( $n = 1,493$ ,  $I^2 = 92\%$ ,  $P < 0.0001$ ) (ESM Figs. 7A and 7B); 7 sepsis trials, RR = 1.70 [1.55–1.87] ( $n = 1,649$ ,  $I^2 = 93\%$ ,  $P < 0.0001$  vs. 7 non-sepsis trials RR = 1.56 [1.37–1.77] ( $n = 1,205$ ,  $I^2 = 77\%$ ,  $P < 0.0001$ ). The RRs for AI in the trials for RCT and sepsis were all significant by random effects model analysis (RCT,  $P = 0.0009$ , non-RCT,  $P = 0.005$ , sepsis,  $P = 0.008$  and non-sepsis,  $P = 0.001$ ).

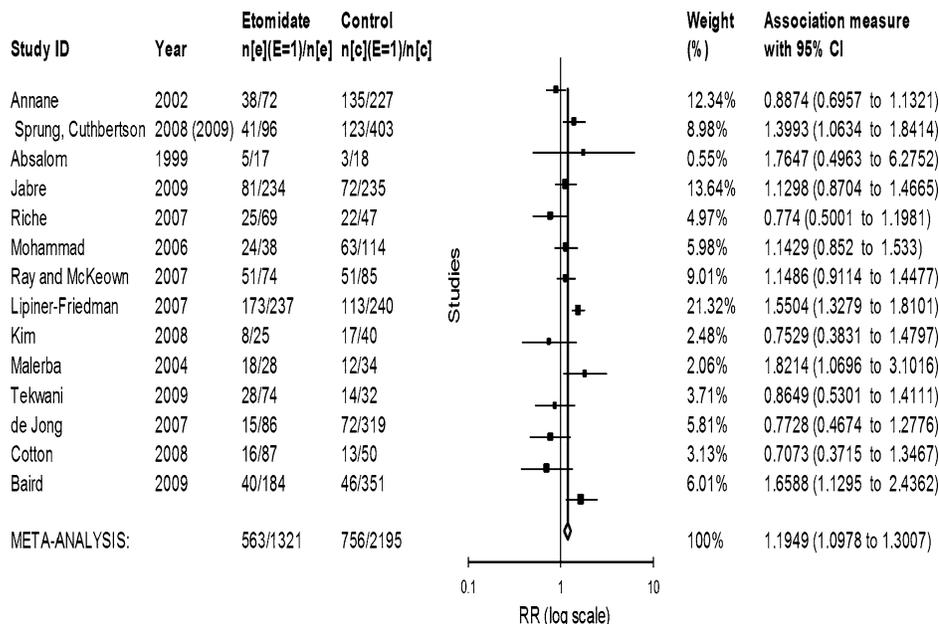
Heterogeneity persisted after re-analysis of the mortality data for four RCTs, RR = 1.12 [0.95–1.32] ( $n = 1,302$ ,  $I^2 = 54\%$ ,  $P = 0.16$ ) versus 10 non-RCTs, RR = 1.23 [1.12–1.36] ( $n = 2,214$ ,  $I^2 = 68\%$ ,  $P < 0.0001$ ) (ESM Figures 8A and 8B).

Subgroups re-analyzed for RR of mortality as to inclusion criteria of sepsis maintained significance, RR = 1.22 [1.11–1.35] (7 sepsis trials,  $n = 1,767$ ,  $I^2 = 74\%$ ,  $P < 0.0001$ ) (Fig. 4a), whereas the non-sepsis trials were no longer significant, RR = 1.15 [0.97–1.35] (7 non-sepsis trials,  $n = 1,749$ ,  $I^2 = 53\%$ ,  $P = 0.10$ ) (Fig. 4b). Those with versus without sepsis had more severe illness as manifested by a higher mortality rate in

**Fig. 2** Meta-analysis of risk ratios (RR) for adrenal insufficiency of subjects with critical illness who received or did not receive etomidate. RR = 1.64 [range 1.52–1.77] (14 trials,  $n = 2,854$ ,  $P < 0.0001$ ,  $I^2 = 88\%$ ). A positive value indicates an increased risk of adrenal insufficiency with etomidate exposure



**Fig. 3** Meta-analysis of risk ratios (RR) for mortality of subjects with critical illness who received or did not receive etomidate. RR = 1.19 [range 1.10–1.30] (14 trials,  $n = 3,516$ ,  $P < 0.0001$ ,  $I^2 = 64\%$ ). A positive value indicates an increased risk of mortality with etomidate exposure

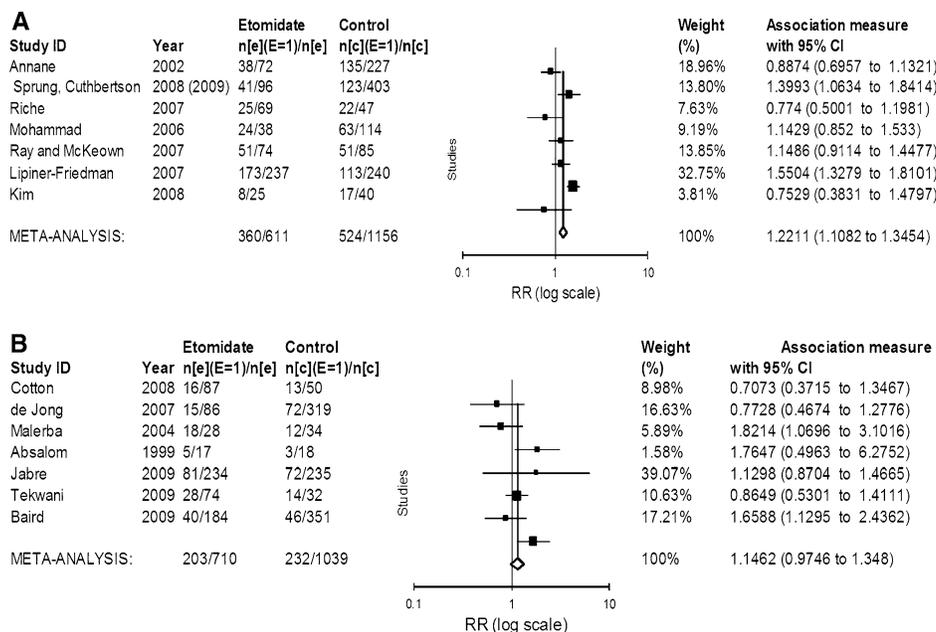


the comparator non-etomidate populations (45 vs. 22%,  $P < 0.0001$ ). There were too few designations of clinical illness scores (SAPS or APACHE) for comparison (ESM Table 2). Meta-regression analysis of mortality did not demonstrate an accentuation of the RR for mortality due to etomidate in those with versus without sepsis (ESM Fig. 6B). There was no difference between the analyses of covariance of the calculated regression lines of those with

versus without sepsis (not shown). However, the absolute rates of mortality with etomidate versus comparators, and the excessive mortality difference superimposed above that in the comparators, were higher in the sepsis group (58.9 vs. 45.3%, difference 13.6%) versus non-sepsis group (28.6 vs. 22.3%, difference 6.3%). None of the analyses for RR of mortality were significant by a random effects model.

**Fig. 4 a** Meta-analysis of subgroup risk ratio (RR) for mortality of subjects with critical illness with inclusion criteria of sepsis who received or did not receive etomidate, RR = 1.22 [1.11–1.35] (7 sepsis trials,  $n = 1,767$ ,  $I^2 = 74\%$ ,  $P < 0.0001$ ).

**b** Meta-analysis of risk ratio (RR) for mortality of subjects with critical illness who received or did not receive etomidate in trials without inclusion of sepsis, RR = 1.15 [0.97–1.35] (7 non-sepsis trials,  $n = 1,749$ ,  $I^2 = 53\%$ ,  $P = 0.10$ ).



Morbidity and organ dysfunction were analyzed between etomidate and controls (ESM Table 2). Hildreth [14] showed significant differences between etomidate and comparators in days: in the ICU ( $8.1 \pm 7.2$  vs.  $3.0 \pm 2$ ,  $P < 0.05$ ), on a ventilator ( $6.3 \pm 6.6$  vs.  $1.5 \pm 0.84$ ,  $P < 0.01$ ), and LOS ( $13.9 \pm 9.5$  vs.  $6.4 \pm 4.4$  days,  $P < 0.01$ ). Others found no differences between etomidate versus comparators in Sequential Organ Failure Assessment (SOFA) scores: Sprung [20] and Cuthbertson [21] changes in ( $\Delta$ SOFA-4 [range  $-6$  to  $-2$ ] vs.  $\Delta$ SOFA-4 [range  $-7$  to  $-1$ ] ( $P$ , not significant); Jabre [15] (SOFA  $10.3 \pm 3.7$  vs.  $9.6 \pm 3.9$ ,  $P = 0.056$ ); or in LOS: Schenarts [6] (LOS 12 vs. 10 days,  $P = n.s.$ ); Tekwani [34] (LOS 8 vs. 6.5 days,  $P = n.s.$ ) (ESM Table 2).

Duration of etomidate effect on AI in critical illness was evaluated prospectively (ESM Table 2). Vinclair [8] measured serial CSTs at baseline 12, 24, 48, and 72 h. Adrenal cortisol insufficiency persisted at 24 h as a CST  $\Delta$ cortisol  $< 9$   $\mu\text{g/dL}$  ( $< 250$  nmol/L) in 49%, and enzyme inhibition persisted as a normal CST  $\Delta$ cortisol, but inappropriately elevated 11-deoxycortisol ( $> 8$  nmol/L in 62%) at 48 h. Similarly, den Brinker demonstrated abnormal cortisol responses to CSTs at 12 h and persisting increases in 11-deoxycortisol at 24 h. Schenarts [6] and Absalom [7] documented suppressed CST  $\Delta$ cortisol at 12 and 24 h, respectively.

## Discussion

Etomidate is a preferred anesthetic in RSI. However, as an inhibitor of cortisol synthesis (11 $\beta$ -hydroxylase), it causes

adrenal dysfunction immediately, which persists for 12–48 h. In this review of critically ill patients, etomidate was associated with an increased RR for AI of 1.64 [1.52–1.77],  $P < 0.0001$ , increased morbidity (increased LOS and increased days on ventilator) [15], and an increased RR for death by 1.19 [1.10–1.30],  $P < 0.0001$ .

Cortisol is a stress hormone and an inhibitor of the excessive cytokine action found in critical illness (reviewed by Marik [35] and Arafah [36]). Serum levels of cortisol increase with the level of clinical stress, as measured by serum cytokine levels [8] and by critical illness severity scores [28, 30, 31]. Mortality in critical illness has been associated with functional AI (defined as new onset of AI with full recovery after resolution of critical illness) [37]. Alternatively, adrenal dysfunction may be associated with systemic inflammation-associated glucocorticoid resistance (either due to glucocorticoid receptor or post-receptor resistance) or abnormal functioning of the hypothalamic-pituitary-adrenal (HPA) axis (critical illness-related corticosteroid insufficiency, CIRCI [35]). However, given the above known relationships of glucocorticoids with stress, there are still controversies regarding the benefit, dose, and timing of glucocorticoids in critical illness [38].

Etomidate is a potent and immediate inhibitor of adrenal 11 $\beta$ -hydroxylase. It is associated with decreased cortisol and increased levels of 11-deoxycortisol, which differs from primary AI in which levels of both steroids are low. Metyrapone, when given for diagnostic testing of the HPA axis, will result in complete blockade of the 11 $\beta$ -hydroxylase [39]. Bolus etomidate induces partial adrenal inhibition, with serum cortisol levels of approximately 50% that achieved without etomidate for comparable

levels of clinical stress [30, 31]. These suppressed cortisol levels may not be adequate for severe stress [30, 31]. Meta-regression analysis here showed the effect of etomidate on AI was constant and independent of the study population.

Much of the controversy regarding the risk of etomidate in ICUs is derived from a perceived lack of increase in mortality or a lack of benefit from supplemental glucocorticoids [9, 10]. An extensive meta-analysis of the effect of glucocorticoids in critical illness did not consider etomidate as an independent variable [38]. With widespread use of the drug in critical illness settings, unless it is specifically noted, it is likely that etomidate may have an undetermined effect on adrenal dysfunction. The inhibition of cortisol synthesis due to etomidate is immediate, and if there is a benefit from glucocorticoids, these drugs should be instituted either simultaneously with or early after the dose of etomidate. In trials of glucocorticoid supplementation in those with etomidate, it was not specified if there was a differential effect of time to institution of steroids relative to etomidate.

In the systematic review by Hohl [40], there was significant adrenal dysfunction with etomidate without a demonstrable effect on mortality. Many of their analyzed studies included subjects undergoing routine elective general anesthesia for operative procedures ( $n = 13$  of 20 studies). The present study evaluated the effect of etomidate in critically ill patients. There was an overlap in their and our meta-analysis of six studies of ICU patients [6, 7, 14, 15, 33, 34]. It may also be argued from our data that partial blockade of cortisol synthesis may interfere with survival in those with more severe illness or sepsis. In this study a subgroup analysis suggested that the increased mortality with etomidate was more pronounced in those with sepsis and more severe illness compared to those without sepsis. Although the meta-regression analysis did not confirm an increased relative rate of mortality with etomidate with increased severity of disease and sepsis, the absolute superimposed increase in mortality above that associated with the comparators was greater in

those with versus without sepsis (13.6 vs. 6.3%, respectively).

There are limitations to this study. Although it is possible that those who received etomidate were more critically ill than the comparison groups, in many centers etomidate is automatically included in the RSI protocol. Clinical illness scores of the etomidate versus non-etomidate groups were not matched a priori. There was also a high degree of heterogeneity in the analysis, and a predominant reliance on moderate to low quality studies.

## Conclusions

Etomidate inhibits adrenal hormone synthesis immediately with persisting low cortisol levels for approximately 12–24 h [6, 7, 31] and inappropriately increased 11-deoxycortisol levels for as long as 48 h [8]. Cortisol levels after etomidate are approximately 50% of levels observed without etomidate during comparable stress [30, 31]. Etomidate is associated with increased morbidity (prolonged days: in the ICU  $8.1 \pm 7.2$  vs.  $3.0 \pm 2$ ,  $P < 0.05$ ; on the ventilator  $6.3 \pm 6.6$  vs.  $1.5 \pm 0.84$ ,  $P < 0.01$ ; and LOS ( $13.9 \pm 9.5$  vs.  $6.4 \pm 4.4$  days,  $P < 0.01$ ) [14]. Recommendations here may be considered as strong as etomidate is associated with an increased RR of 1.64 for AI. Recommendations may be considered weak for the association of etomidate with mortality (with RR 1.19 with a preponderance of non-randomized trials and heterogeneity of studies) [12]. Further research and clinical management plans should be entertained to address the use of alternate anesthetic agents or the benefits of concomitant glucocorticoids with etomidate either through RCTs or a re-analysis of the available studies including timing of steroid supplementation relative to etomidate exposure.

**Conflict of interest** None.

## References

- Bergen JM, Smith DC (1997) A review of etomidate for rapid sequence intubation in the emergency department. *J Emerg Med* 15:221–230
- Annan D (2005) ICU physicians should abandon the use of etomidate! *Intensive Care Med* 31:325–326
- Jackson WL Jr (2005) Should we use etomidate as an induction agent for endotracheal intubation in patients with septic shock: a critical appraisal. *Chest* 127:1031–1038
- Ledingham IM, Watt I (1983) Influence of sedation on mortality in critically ill multiple trauma patients. [Letter] *Lancet* 1(8336):1270
- De Jong FH, Mallios C, Jansen C, Scheck PA, Lamberts SW (1984) Etomidate suppresses adrenocortical function by inhibition of 11 beta-hydroxylation. *J Clin Endocrinol Metab* 59:1143–1147
- Schenarts CL, Burton JH, Riker RR (2001) Adrenocortical dysfunction following etomidate induction in emergency department patients. *Acad Emerg Med* 8:1–7
- Absalom A, Pledger D, Kong A (1999) Adrenocortical function in critically ill patients 24 h after a single dose of etomidate. *Anaesthesia* 54:861–867

8. Vinclair M, Broux C, Faure P, Brun J, Genty C, Jacquot C, Chabre O, Payen JF (2008) Duration of adrenal inhibition following a single dose of etomidate in critically ill patients. *Intensive Care Med* 34:714–719
9. Bloomfield R, Noble DW (2006) Etomidate, pharmacological adrenalectomy and the critically ill: a matter of vital importance. *Crit Care* 10:161
10. Kamp R, Kress JP (2007) Etomidate, sepsis, and adrenal function: not as bad as we thought? *Crit Care* 11:145
11. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR (2009) *Introduction to Meta-analysis*. Wiley, West Sussex
12. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ, for the GRADE Working Group GRADE (2008) An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 336:924–926
13. Bax L, Yu LM, Ikeda N, Tsuruta H, Moons KGM (2006) Development and validation of MIX: comprehensive free software for meta-analysis of causal research data. *BMC Med Res Methodol* 6:50
14. Bax L, Yu LM, Ikeda N, Tsuruta H, Moons KGM (2008) MIX: comprehensive free software for metaanalysis of causal research data, version 1.7. <http://mix-for-meta-analysis.info>
15. Hildreth AN, Mejia VA, Maxwell RA, Smith PW, Dart BW, Barker DE (2008) Adrenal suppression following a single dose of etomidate for rapid sequence induction: a prospective randomized study. *J Trauma Inj Infect Crit Care* 65:573–579
16. Jabre P, Combes X, Lapostolle F, for the KETASED collaborative Study Group et al (2009) Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: a multicentre randomized controlled trial. *Lancet* 374:293–300
17. Oppert M, Schindler R, Husung C, Offermann K, Graf K-J, Boenisch O, Barckow D, Frei U, Eckardt K-U (2005) Low-dose hydrocortisone improves shock reversal and reduces cytokine levels in early hyperdynamic septic shock. *Crit Care* 33:2457–2464
18. Annane D, Sebille V, Troche G, Raphael J-C, Gajdos P, Bellissant E (2000) A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. *JAMA* 283:1038–1045
19. Annane D, Sebille V, Charpentier C, Bollaert P-E, Francois B, Korach J-M, Capellier G, Cohen Y, Azoulay E, Troche G, Chaumet-Riffaut P, Bellissant E (2002) Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 288:862–871
20. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, Weiss YG, Benbenishty J, Kalenka A, Forst H, Laterre P-F, Reinhart K, Cuthbertson BH, Payen D, Briegel J, for the Corticus Study Group (2008) Hydrocortisone therapy for patients with septic shock. *N Eng J Med* 358:111–124
21. Cuthbertson BH, Sprung CL, Annane D, Chevret S, Garfield M, Goodman S, Laterre PF, Vincent JL, Freivogel K, Reinhart K, Singer M, Payen D, Weiss YG (2009) The effects of etomidate on adrenal responsiveness and mortality in patients with septic shock. *Intensive Care Med* 35:1868–1876
22. Lipiner-Friedman D, Sprung CL, Laterre PF, Weiss Y, Goodman SV, Vogeser M, Briegel J, Keh D, Singer M, Moreno R, Bellissant E, Annane D, and Corticus Study Group (2007) Adrenal function in sepsis: the retrospective Corticus cohort study. *Crit Care Med* 35:1012–1018
23. Mohammad Z, Afessa B, Finkelman JD (2006) The incidence of relative adrenal insufficiency in patients with septic shock after the administration of etomidate. *Crit Care* 10:R105
24. Kim TY, Rhee JE, Kim KS, Cha WC, Suh GJ, Jung SK (2008) Etomidate should be used carefully for emergent endotracheal intubation in patients with septic shock. *J Korean Med Sci* 23:988–991
25. Cotton BA, Guillaumondegui OD, Fleming SB, Carpenter RO, Patel SH, Morris JA Jr, Arbogast PG (2008) Increased risk of adrenal insufficiency following etomidate exposure in critically injured patients. *Arch Surg* 143:62–67
26. Malerba G, Romano-Girard F, Cravoisy A, Doussot B, Nace L, Keyv B, Bollaert P-E (2005) Risk factors of relative adrenocortical deficiency in intensive care patients needing mechanical ventilation. *Intensive Care Med* 31:388–392
27. Cohan P, Wang C, McArthur DL, Cook SW, Dusick JR, Armin B, Swerdloff R, Vespa P, Muizelar JP, Cryer HG, Christenson PD, Kelly DF (2005) Acute secondary adrenal insufficiency after traumatic brain injury: a prospective study. *Crit Care Med* 33:2358–2366
28. De Jong MFC, Beishuizen A, Spijkstra J-J, Girbes ARJ, Strack van Schijndel RJM, Twisk JWR, Groeneveld ABJ (2007) Predicting a low cortisol response to adrenocorticotrophic hormone in the critically ill: a retrospective cohort study. *Crit Care* 11(3):R61
29. Riche FC, Boutron CM, Valleur P, Berton C, Laisne M-J, Launay J-M, Chappuis P, Peynet J, Vicaut E, Payen D, Cholley BP (2007) Adrenal response in patients with septic shock of abdominal origin: relationship to survival. *Intensive Care Med* 33:1761–1766
30. den Brinker M, Joosten KF, Liem O, de Jong FH, Hop WCJ, Hazelzet JA, van Dijk M, Hokken-Koelega ACS (2005) Adrenal insufficiency in meningococcal sepsis: bioavailable cortisol levels and impact of interleukin-6 level and intubation with etomidate on adrenal function and mortality. *J Clin Endocrinol Metab* 90:5110–5117
31. den Brinker M, Hokken-Koelega AC, Hazelzet JA, de Jong FH, Hop WC, Joosten KF (2008) One single dose of etomidate negatively influences adrenocortical performance for at least 24 h in children with meningococcal sepsis. *Intensive Care Med* 34:163–168
32. Baird CRW, Hay AW, McKeown DW, Ray DC (2009) Rapid sequence induction in the emergency department: induction dug and outcome of patients admitted to the intensive care unit. *Emerg Med J* 26:576–579
33. Ray DC, McKeown DW (2007) Effect of induction agent on vasopressor and steroid use, and outcome in patients with septic shock. *Crit Care* 11:R56
34. Tekwani KL, Watts HF, Rzechala KH, Sweis RT, Kulstad EB (2009) A prospective observational study of the effect of etomidate on septic patient mortality and length of stay. *Acad Emerg Med* 16:11–14
35. Marik PE, Pastores SM, Annane D, Meduri U, Sprung CL, Arlt W, Keh D, Briegel J, Beishuizen A, Dimopoulos I, Tsagarakis S, Singer M, Chrousos GP, Zaloga G, Bokhari F, Vogeser M (2008) Recommendations for the diagnosis and management of corticosteroids insufficiency in critically ill adult patients: consensus statement from an international task force by the American College of Critical Care Medicine. *Crit Care Med* 36:1337–1349
36. Arafah BM (2006) Review: hypothalamic pituitary adrenal function during critical illness: limitations of current assessment methods. *J Clin Endocrinol Metab* 91:3725–3745

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37. Meduri GU, Yates CR (2004) Systemic inflammation-associated glucocorticoid resistance and outcomes of ARDS. *Ann NY Acad Sci* 1024:24–53
  38. Annane D, Bellissant E, Bolaert P-E, Briegle J, Confalonieri M, De Gaudio R, Keh D, Kupfer Y, Oppert M, Meduri GU (2009) Corticosteroids in the treatment of severe sepsis and septic shock in adult. A systematic review. *JAMA* 301:2362–2375
  39. Stewart PM (2008) The adrenal cortex, in *Williams textbook of Endocrinology*. In: Kronenberg HM, Melmed S, Polonsky KS, Larsen PR (eds) 11th ed. Saunders, Philadelphia, p 482
  40. Hohl CM, Kelly-Smith CH, Yeung TC, Sweet DD, Doyle-Waters MM, Schulzer M (2010) The effect of a bolus dose of etomidate on cortisol levels, mortality, and health services utilization: a systematic review. *Ann Emerg Med* 56:105–113