Section Editor: **Sorin J. Brull**

Anesthetic Induction with Etomidate, Rather than Propofol, Is Associated with Increased 30-Day Mortality and Cardiovascular Morbidity After Noncardiac Surgery

Ryu Komatsu, MD,* Jing You, MS,†‡ Edward J. Mascha, PhD,†‡ Daniel I. Sessler, MD,† Yusuke Kasuya, MD,§ and Alparslan Turan, MD†

BACKGROUND: Because etomidate impairs adrenal function and blunts the cortisol release associated with surgical stimulus, we hypothesized that patients induced with etomidate suffer greater mortality and morbidity than comparable patients induced with propofol.

METHODS: We evaluated the electronic records of 31,148 ASA physical status III and IV patients who had noncardiac surgery at the Cleveland Clinic. Among these, anesthesia was induced with etomidate and maintained with volatile anesthetics in 2616 patients whereas 28,532 were given propofol for induction and maintained with volatile anesthetics. Two thousand one hundred forty-four patients given etomidate were propensity matched with 5233 patients given propofol and the groups compared on 30-day postoperative mortality, length of hospital stay, cardiovascular and infectious morbidities, vasopressor requirement, and intraoperative hemodynamics.

RESULTS: Patients given etomidate had 2.5 (98% confidence interval [CI], 1.9–3.4) times the odds of dying than those given propofol. Etomidate patients also had significantly greater odds of having cardiovascular morbidity (odds ratio [OR] [98% CI]: 1.5 [1.2–2.0]), and significantly longer hospital stay (hazard ratio [95% CI]: 0.82 [0.78–0.87]). However, infectious morbidity (OR [98% CI]: 1.0 [0.8–1.2]) and intraoperative vasopressor use (OR [95% CI] 0.92: [0.82–1.0]) did not differ between the agents.

CONCLUSION: Etomidate was associated with a substantially increased risk for 30-day mortality, cardiovascular morbidity, and prolonged hospital stay. Our conclusions, especially on 30-day mortality, are robust to a strong unmeasured binary confounding variable. Although our study showed only an association between etomidate use and worse patients' outcomes but not causal relationship, clinicians should use etomidate judiciously, considering that improved hemodynamic stability at induction may be accompanied by substantially worse longer-term outcomes. (Anesth Analg 2013;117:1329–37)

Etomidate, an imidazole-derived ultrashort-acting nonbarbiturate hypnotic, is frequently used to induce anesthesia in critically ill patients because of its favorable hemodynamic profile and rapid onset. Etomidate has the advantage of minimizing induction hypotension which can cause coronary hypoperfusion, dysrhythmia, and cardiac arrest. However, etomidate suppresses adrenocortical function by blocking 11β-hydroxylase. Even doses of etomidate as small as 0.04 mg/kg block the enzyme,[1] and a typical dose used for induction of general anesthesia (i.e., 0.3 mg/kg) suppresses the otherwise normal increase in plasma cortisol concentration in response to surgical stimulation.[2] Adrenal suppression lasts at least 6 hours in healthy patients having elective surgery[3] and >24 hours in critically ill patients.[4,5] Adrenal insufficiency occurs frequently in patients with life-threatening processes, such as septic shock,[6–10] aneurysmal subarachnoid hemorrhage,[11,12] traumatic brain injury,[13–17] and general trauma.[18] Furthermore, various studies have suggested a potential deleterious impact of even a single dose of etomidate in the critically ill.[19–24]

The potential putative link between etomidate and worsened postoperative outcomes has yet to be studied in a large cohort of high-risk general surgical patients. We therefore evaluated the association between etomidate administration and adverse outcomes in ASA physical status III and IV adults having noncardiac surgery. Specifically, we tested the primary hypotheses that patients given etomidate rather than propofol for anesthetic induction have more 30-day postoperative mortality, more infectious complications, and a higher risk of cardiovascular complications. Our secondary hypothesis was that patients given etomidate rather than propofol at anesthetic induction have a prolonged duration of hospitalization.

From the *Anesthesiology Institute, †Department of Quantitative Health Sciences, and ‡Department of Outcomes Research, Cleveland Clinic, Cleveland, Ohio; and §Department of Anesthesiology, Tokyo Women's Medical University, Shinjuku, Tokyo, Japan.

Accepted for publication April 17, 2013.

Funding: This research was supported solely by internal sources.

The authors declare no conflicts of interest.

This report was previously presented, in part, at the International Anesthesia Research Society 2012 Annual Meeting on May 18 to 21, 2012, Boston, MA, the Association of University Anesthesiologists 59th Annual Meeting on May 17 to 19, Cleveland, OH, and the American Society of Anesthesiologist 2012 Annual Meeting on October 13 to 17, 2012, Washington, DC.

Reprints will not be available from the authors.

Address correspondence to Ryu Komatsu, MD, Anesthesiology Institute, Cleveland Clinic, 9500 Euclid Ave., Cleveland, Ohio 44195. Address e-mail to komatsr@ccf.org. On the world wide web, www.OR.org.

DOI: 10.1213/ANE.0b013e318299a516

Table 1. Demographics Baseline and Intraoperative Characteristics Before and After the Propensity Score Matching

	Before matching			After matching		
Variable	Etomidate (*N* = 2616)	Propofol (*N* = 28,532)	STD[a]	Etomidate (*N* = 2144)	Propofol (*N* = 5233)	STD[a]
Age, y	70 ± 13	60 ± 15	0.67	69 ± 13	68 ± 13	0.05
Gender, female, *n* (%)	1030 (39)	14,266 (50)	−0.22	832 (39)	2072 (40)	−0.02
Race, Caucasian, *n* (%)	2097 (80)	23,333 (82)	−0.04	1722 (80)	4205 (80)	−0.00
Body mass index, kg/m^2	27 [23, 31]	28 [24, 34]	−0.28	27 [23, 31]	27 [24, 31]	−0.03
Hypothalamic pituitary adrenal disorder, yes, *n* (%)	35 (1)	575 (2)	−0.05	31 (1)	69 (1)	0.01
Cancer, yes, *n* (%)	754 (29)	11,027 (39)	−0.21	672 (31)	1663 (32)	−0.01
HIV, yes, *n* (%)	2 (0)	100 (0)	−0.06	2 (0)	8 (0)	−0.02
CVD,[b] yes, *n* (%)	1935 (74)	17,471 (61)	0.27	1588 (74)	3804 (73)	0.03
Pulmonary disease,[c] yes, *n* (%)	396 (15)	3881 (14)	0.04	318 (15)	750 (14)	0.01
Diabetes, *n* (%)			0.08			0.02
No	2051 (78)	22,537 (79)		1656 (77)	4037 (77)	
Type I	3 (0)	54 (0)		19 (1)	50 (1)	
Type II with insulin use	53 (2)	826 (3)		50 (2)	107 (2)	
Type II without insulin use	489 (19)	4797 (17)		419 (20)	1039 (20)	
ASA status, IV (vs III), *n* (%)	1105 (42)	2595 (9)	0.82	778 (36)	1391 (27)	0.21
Charlson comorbidity score	2 [1, 3]	1 [0, 2]	0.36	2 [1, 3]	2 [1, 3]	0.11
Emergency, yes, *n* (%)	636 (24)	1587 (6)	0.55	401 (19)	712 (14)	0.14
Intraoperative steroid use, yes, *n* (%)	498 (19)	8467 (30)	−0.25	434 (20)	999 (19)	0.03
Opioid, no. of bolus	3 [2, 5]	3 [2, 5]	−0.08	3 [2, 5]	3 [2, 5]	−0.06
Regional anesthesia, yes, *n* (%)	178 (7)	1289 (5)	0.10	143 (7)	352 (7)	−0.00
Duration of surgery, h	4 ± 2	4 ± 2	0.11	4 ± 2	4 ± 2	0.00

Summary statistics were presented as *n* (% of patients), mean ± SD, or median [Q1, Q3].

CVD = cardiovascular/cerebrovascular disease; HIV = human immunodeficiency virus; ASA = American Society of Anesthesiologists.

[a]Standardized differences (STDs) (etomidate minus propofol): difference in means or proportions divided by pooled standard deviation; > 0.10 chosen a priori to indicate imbalance.

[b]CVD: essential hypertension, coronary atherosclerosis, cardiac dysrhythmias, or congestive heart failure.

[c]Pulmonary disease: chronic obstructive pulmonary disease or asthma.

METHODS

With IRB approval and informed consent waiver, we queried the Perioperative Health Documentation System (PHDS) Registry at the Cleveland Clinic for adults who had noncardiac surgery between January 6, 2005 and December 31, 2009. During this period artifact values including extreme values of arterial blood pressures, heart rates, electrocardiogram, processed electroencephalogram, and pulse oximeter oxygen saturation (Spo_2) values caused by electrocautery, movements, and transducer failure for invasive arterial, central venous, and pulmonary artery pressure values were removed from the PHDS by a contracted device company (Aspect Medical, now part of Covidien). The PHDS contains data on all patients who had noncardiac surgery since May 2005 at Cleveland Clinic's main campus, except for cases performed in the magnetic resonance imaging suite, computed tomography suite, and eye surgery cases, which were performed at separate operation sites where an electronic anesthesia record keeping system was not available. Therefore, we screened >95% of all noncardiac surgical cases for inclusion into our study. The system integrates preoperative variables (demographic and baseline characteristics), intraoperative variables (via our proprietary Anesthesia Record Keeping System), and postoperative outcomes (by linking to Cleveland Clinic billing and other systems).

The study population consisted of ASA physical status III and IV adults having noncardiac surgery under general anesthesia, with or without regional anesthesia, requiring at least 1 night of postoperative hospitalization. Anesthesia was induced with propofol, thiopental, etomidate, or ketamine. Patients given any of these drugs at any other time during anesthesia were excluded from our analysis. Anesthesia was maintained with a volatile anesthetic, supplemented per clinical preference with opioids and/or muscle relaxants.

Propensity Score Matching

Each patient who received etomidate was matched to a maximum of 3 patients who received propofol using propensity score matching.[25] Specifically, we first estimated the probability of receiving etomidate (i.e., the propensity score) for each patient using logistic regression with etomidate (versus propofol) as the outcome and using all prespecified potential confounding variables listed in Table 1. We then matched etomidate and propofol patients on the propensity score 1 to 3 (using a greedy distance matching algorithm [SAS macro]).[a] Successful matches were restricted to those whose estimated propensity score logits (i.e., $\log\left(\frac{p}{1-p}\right)$) were within 0.2 standard deviations of one another (i.e., within $0.2 \times 1.1887 = 0.2377$)[26] and those with the same type of surgery. Type of surgery was characterized into 1 of 244 mutually exclusive clinically appropriate categories using the Agency for Healthcare Research and Quality's single-level Clinical Classifications Software for *International Classification of Diseases, 9th Revision*, Clinical Modification procedure codes (Table 2). Each analysis below used this subset of matched patients.

[a]Computerized matching of cases to controls using the greedy matching algorithm with a fixed number of controls per case. Controls may be matched to cases using one or more factors (X's). Erik Bergstralh & Jon Kosanke. [10/2003] http://www.mayo.edu/research/documents/gmatchsas/DOC-10027248. Accessed February 1, 2013.

Table 2. Types of Surgery (AHRQ-CCS Categories[a]) Before and After the Propensity Score Matching

		Before matching		After matching	
AHRQ-CCS	Description	Etomidate (*N* = 2616), %	Propofol (*N* = 28,532), %	Etomidate (*N* = 2144), %	Propofol (*N* = 5233), %
78	Colorectal resection	4.1	7.1	6.9	7.2
96	Other OR lower gastrointestinal therapeutic procedures	4.2	3.7	4.7	4.0
158	Spinal fusion	4.3	1.8	2.2	1.9
104	Nephrectomy; partial or complete	4.1	2.8	3.6	3.2
99	Other OR gastrointestinal therapeutic procedures	3.9	3.5	4.1	3.6
94	Other OR upper gastrointestinal therapeutic procedures	3.4	1.6	1.7	1.6
1	Incision and excision of central nervous system	3.2	1.4	1.7	1.5
9	Other OR therapeutic nervous system procedures	3.2	0.8	1.1	0.9
52	Aortic resection; replacement or anastomosis	1.8	12.4	8.0	11.5
112	Other OR therapeutic procedures of urinary tract	2.5	2.1	3.0	2.5
101	Transurethral excision; drainage; or removal urinary obstruction	2.4	1.8	2.4	2.2
3	Laminectomy; excision intervertebral disc	2.4	1.6	1.9	1.6
124	Hysterectomy; abdominal and vaginal	2.4	1.3	1.8	1.5
61	Other OR procedures on vessels other than head neck	1.7	5.4	5.2	5.6
153	Hip replacement; total and partial	1.9	2.4	2.7	2.4
160	Other therapeutic procedures on muscles and tendons	1.8	1.2	1.6	1.3
86	Other hernia repair	1.8	1.2	1.5	1.3
12	Other therapeutic endocrine procedures	1.8	0.8	1.0	0.8
114	Open prostatectomy	1.8	0.6	0.8	0.7
152	Arthroplasty knee	1.8	1.3	1.7	1.5
105	Kidney transplant	1.7	0.8	1.0	0.8
84	Cholecystectomy and common duct exploration	1.4	1.3	1.6	1.5
162	Other OR therapeutic procedures on joint	1.4	1.3	1.3	1.3
157	Amputation of lower extremity	1.2	3.3	2.8	2.8
75	Small bowel resection	1.3	1.8	1.7	1.8

AHRQ-CCS = Agency for Healthcare Research and Quality's Clinical Classification Software for services and procedures; OR = operating room.
[a]Twenty-five most frequent AHRQ-CCS categories are listed.

Assessment of balance on the covariables used for the propensity score matching was performed using standardized differences (i.e., difference in means or proportions divided by the pooled standard deviation). Imbalance was defined as a standardized difference >0.1 in absolute value; any imbalanced covariables after the propensity score matching were adjusted for in all analyses.

Primary Outcomes

Our primary outcomes were 30-day mortality, any major in-hospital cardiovascular morbidity, and any major in-hospital infectious morbidity (as defined in Table 3). We assessed the heterogeneity of the etomidate effect across the 3 primary outcomes by testing the etomidate-by-outcome interaction in a "distinct-effects" generalized estimating equation (GEE) model which enabled adjustment for the correlation among the 3 outcomes. The heterogeneity test thus compares the odds ratios for etomidate between the individual outcomes of interest. Since heterogeneity was found, we reported and tested the individual odds ratios (1 for each outcome) from the distinct effects GEE model, adjusting for any imbalanced baseline covariables after the propensity score matching. Bonferroni correction for multiple comparisons was used to control the type I error at 0.05 so that $P < 0.017$ was considered significant (i.e., 0.05/3 = 0.017).

In addition, we conducted sensitivity analyses to assess the robustness of the estimated associations between etomidate and the primary outcomes to an unmeasured binary covariate. We assumed various levels of association between the unmeasured covariate and both etomidate and outcome (see details in Table 1, Appendix).

Secondary Outcomes

For etomidate patients, we assessed the relationship between amount of etomidate received scaling by weight and the primary outcomes, each using a multivariable logistic regression model to adjust for all potential confounders used for propensity matching. We adjusted for severity of procedure (in terms of risk of outcome) as a continuous covariable calculated for each Clinical Classifications Software category as the incidence of any major outcome (i.e., any of 30-day mortality, major in-hospital cardiovascular morbidity or major in-hospital infectious morbidity, versus none of these).

Etomidate and propofol propensity-matched patients were compared on intraoperative vasopressor use (i.e., dobutamine, dopamine, ephedrine, epinephrine, norepinephrine, phenylephrine, or vasopressin) and duration of hospitalization using multivariable logistic regression or Cox proportional hazard regression, as appropriate. For the duration of hospitalization outcome, we needed to account for patients who died before discharge; otherwise, an early death would be counted as a good thing in the analysis. We therefore used a survival analysis (Cox regression) in which the outcome event was "discharged alive," and patients who died in the hospital were analyzed as never having the event by assigning them a follow-up time 1 day more than any of the observed discharged alive times.

Finally, we summarized and plotted the within-patient average and minimum of systolic and diastolic intraoperative blood pressures during each intraoperative period (i.e., start of case to induction, induction to intubation, intubation to incision, incision to closing, closing to emergence, and emergence to end of case).

Table 3. Description and Incidence of Individual in Hospital Cardiovascular and Infectious Morbidities for the Propensity Score–Matched Patients

ICD-9	Description	Incidence, *n* (%) Etomidate (*N* = 2144)	Propofol (*N* = 5233)
Cardiovascular morbidity			
458.2	Iatrogenic hypotension		
458.21	Hypotension of hemodialysis	1 (<1)	2 (<1)
	Intradialytic hypotension		
458.29	Other iatrogenic hypotension	36 (1.7)	53 (1.0)
	Postoperative hypotension		
997.1	Cardiac:	87 (4.1)	143 (2.7)
	Arrest during or resulting from a procedure		
	Insufficiency during or resulting from a procedure		
	Cardiorespiratory failure during or resulting from a procedure		
	Heart failure during or resulting from a procedure		
997.2	Peripheral vascular complications	27 (1.3)	57 (1.1)
	Phlebitis or thrombophlebitis during or resulting from a procedure		
998.0	Postoperative shock	18 (0.8)	11 (0.2)
	Collapse NOS during or resulting from a surgical procedure		
	Shock (endotoxic) (hypovolemic) (septic) during or resulting from a surgical procedure		
The collapsed composite (any above versus none)		163 (7.6)	254 (4.9)
Infectious morbidity			
519.01	Infection of tracheostomy	1 (<1)	1 (<1)
536.41	Infection of gastrostomy	0 (0)	4 (0.1)
530.86	Infection of esophagostomy	0 (0)	0 (0)
997.62	Amputation stump complication: Infection	11 (0.5)	26 (0.5)
998.5	Postoperative infection		
998.51	Infected postoperative seroma	5 (0.2)	11 (0.2)
998.59	Other postoperative infection	87 (4.1)	214 (4.1)
	Abscess: postoperative		
	Intra-abdominal postoperative		
	Stitch postoperative		
	Subphrenic postoperative		
	Wound postoperative		
	Septicemia postoperative		
999.3	Other infection	0 (0)	0 (0)
	Infection after infusion, injection, transfusion, or vaccination		
	Sepsis after infusion, injection, transfusion, or vaccination		
	Septicemia after infusion, injection, transfusion, or vaccination		
569.61	Infection of colostomy and enterostomy	0 (0)	3 (0.1)
996.6	Infection and inflammatory reaction due to internal prosthetic device, implant, and graft		
996.60	Due to unspecified device, implant and graft	0 (0)	0 (0)
996.61	Due to cardiac device, implant and graft	3 (0.1)	7 (0.1)
	Cardiac pacemaker or defibrillator:		
	Electrode(s), lead(s)		
	Pulse generator		
	Subcutaneous pocket		
	Coronary artery bypass graft		
	Heart valve prosthesis		
996.62	Due to vascular device, implant and graft	40 (1.9)	51 (1.0)
	Arterial graft		
	Arteriovenous fistula or shunt		
	Infusion pump		
	Vascular catheter (arterial) (dialysis) (peripheral venous)		
996.63	Due to nervous system device, implant and graft	5 (0.2)	10 (0.2)
	Electrodes implanted in brain		
	Peripheral nerve graft		
	Spinal canal catheter		
	Ventricular (communicating) shunt (catheter)		
996.64	Due to indwelling urinary catheter	4 (0.2)	6 (0.1)
996.65	Due to other genitourinary device, implant and graft	4 (0.2)	1 (<0.1)
	Intrauterine contraceptive device		
996.66	Due to internal joint prosthesis	24 (1.1)	74 (1.4)
996.67	Due to other internal orthopedic device, implant and graft	8 (0.4)	19 (0.4)
	Bone growth stimulator (electrode)		
	Internal fixation device (pin) (rod) (screw)		
996.68	Due to peritoneal dialysis catheter	0 (0)	2 (<0.1)
	Exit-site infection or inflammation		

(*Continued*)

Table 3. (*Continued*)

ICD-9	Description	Incidence, *n* (%) Etomidate (*N* = 2144)	Propofol (*N* = 5233)
996.69	Due to other internal prosthetic device, implant, and graft Breast prosthesis	6 (0.3)	21 (0.4)
999.31	Infection due to central venous catheter Catheter-related bloodstream infection (CRBSI) NOS Infection due to: Hickman catheter Peripherally inserted central catheter (PICC) Portacath (port-a-cath) Triple lumen catheter	5 (0.2)	7 (0.1)
997.31	Ventilator-associated pneumonia	1 (<0.1)	4 (0.1)
The collapsed composite (any above versus none)		191 (8.9)	437 (8.4)

ICD-9 = International Classification of Diseases, 9th Revision; NOS = not otherwise specified.

Differences in intraoperative arterial blood pressure between the etomidate and propofol patients were summarized using the standardized difference and tested by student *t* test for normally distributed continuous measures and Wilcoxon rank sum test for nonnormal continuous measures. Intraoperative hemodynamic monitoring data were acquired from our electronic anesthesia record-keeping system that records data from the anesthesia monitor. Arterial blood pressure in patients with invasive arterial catheters was recorded each minute, and at 1- to 5-minute intervals in other patients. Average, minimum, and maximum of systolic and diastolic blood pressures were computed during each period (i.e., start case to induction, induction to intubation, intubation to incision, incision to closing, closing to emergence, and emergence to end of case) in each patient.

Sample Size and Power

With 7377 propensity score matched patients (approximate ratio of 1.0 etomidate to 2.5 propofol patients) and incidences (propofol group) of 2.3%, 4.9%, and 8.5% for 30-day mortality, cardiac morbidity, and infectious morbidity, respectively, we had 90% power to detect odds ratios (ORs) of 1.8, 1.5, and 1.4 or more for the above 3 primary outcomes at the overall 0.05 significance level (0.017 criterion adjusting for 3 primary outcomes). SAS software version 9.3 (SAS Institute) and R software version 2.12.0 (The R Foundation for Statistical Computing, Vienna, Austria) were used for all statistical analysis.

RESULTS

We considered the electronic records of 103,324 adult patients who had noncardiac surgery between 2005 and 2009. Among the ASA III/IV patients who had surgery under general anesthesia requiring at least 1 night of postoperative hospitalization, there were 2616 (8%) patients who received etomidate only, 28,532 (84%) patients who received propofol only, 1976 (6%) patients who received ketamine and/or thiopental, and 658 (2%) patients who received both etomidate and propofol. Among these, we successfully matched 2144 etomidate only patients (82% of 2616) with 5233 propofol only patients, for a total of 7377 patients who were used for analysis of the effect of etomidate on outcome. The observed median [quartiles] of the amount of etomidate and propofol received was 0.22 [0.19, 0.26] and 1.8 [1.4, 2.3] mg/kg, respectively.

Before the propensity score matching (Table 1, left panel), patients given etomidate for induction were generally older and sicker (higher Charlson comorbidity score and higher ASA status). They were also more likely to be male, have a lower body mass index, have cardiovascular and/or cerebrovascular disease, have emergent surgery, and to receive general anesthesia supplemented with regional anesthesia. They were also less likely to have cancer or receive steroids intraoperatively although the interpretation of steroid use is difficult because it can be used for different indications (i.e. antiemesis, cerebral edemas, and hormone replacement) (standardized differences [STDs] >0.1 in absolute value). All potential confounding factors were much better balanced in the 7377 propensity score matched patients which were used to assess association with outcomes (Table 1, right panel). However, ASA status, Charlson comorbidity score, and emergent surgery were still slightly imbalanced (STD: 0.21, 0.11, and 0.14, respectively) between the etomidate and propofol patients. To be conservative, we thus included ASA status, Charlson comorbidity score, and emergent surgery in the multivariable models when comparing the 2 groups on the outcomes.

Among the propensity-matched patients, receiving etomidate was significantly associated with increased odds of experiencing 30-day mortality (estimated OR [98.3% confidence interval {CI}]: 2.49 [1.85–3.35]; $P < 0.001$), and increased odds of having major cardiovascular morbidity (1.51 [1.14–1.94]; $P < 0.001$), after adjusting for ASA status, Charlson comorbidity score, emergent surgery, and within-patient correlation (Table 4). However, etomidate was not significantly associated with major infectious morbidity (1.00 [0.80–1.25]; $P = 0.99$; Table 4). Our sensitivity analysis (Appendix, Table 1) suggests that our conclusion on 30-day mortality is robust to a very strong unmeasured binary confounding variable. For example, if we assume that the patients having covariate "*u*" are 5 times as likely to receive etomidate and also 5 times more likely to have the outcome, and 50% of patients have *u*, then the OR (95% CI) of etomidate versus propofol on 30-day mortality would still be significant at 1.4 (1.1–1.8). Our conclusions on cardiovascular morbidity and infectious morbidity were robust to a less strong unmeasured binary covariate (i.e., OR of ≤4 for cardiovascular and about ≤3 for infectious morbidity). The effects of etomidate were not consistent across the outcomes (etomidate-by-outcome interaction $P < 0.001$). Furthermore,

Table 4. Associations Between Use of Etomidate (Versus Propofol) Intraoperatively and Outcomes Among the Propensity Score–Matched Patients

Outcome	Etomidate (*N* = 2144)	Propofol (*N* = 5233)	Odds ratio (98.3% CI[a]) (etomidate/propofol)	*P*[b]
Primary outcome	Incidence (%)			
30-d mortality	139 (6.5)	135 (2.5)	2.49 (1.85–3.35)	<0.001
Cardiovascular morbidity	163 (7.6)	254 (4.9)	1.51 (1.17–1.94)	<0.001
Infectious morbidity	191 (8.9)	437 (8.4)	1.00 (0.80–1.25)	0.99
Secondary outcome			Odds ratio (95% CI)	
Intraoperative vasopressor use	1595 (74.4)	3988 (76.2)	0.92 (0.82–1.03)	0.16
	Median [Q1, Q3]		Hazard ratio (95% CI)	
Length of hospital stay,[c] d	7 [3, 13]	6 [2, 11]	0.82 (0.78–0.87)[d]	<0.001[e]

The fit of the model for the primary outcome was roughly assessed by the Hosmer and Lemeshow (H-L) goodness-of-fit test. The H-L test suggests some lack of fit (χ^2 = 61.8, df = 8, and P <0.001). However, the expected and observed frequencies were well balanced. With such a large sample size, subtle lack of fit can be detected.

[a]98.3% confidence intervals (CIs); the significance criterion was $P < 0.017$ (i.e., 0.05/3, Bonferroni correction).

[b]Comparisons were all adjusted for ASA status, Charlson comorbidity score, and emergent surgery by multivariable logistic regression.

[c]The summary statistics were median [Q1, Q3] of length of stay for live discharge only. There were 118 and 111 patients died in hospital in etomidate and propofol groups, respectively. Discharges for those patients were considered as failures in the analysis, with time censored at the worst observation.

[d]Etomidate patients were 18% less likely to be discharged from hospital at any given time point postoperatively as compared with propofol patients.

[e]Comparisons were all adjusted for ASA status, Charlson comorbidity score, and emergency surgery by multivariable Cox proportional hazards regression.

the relationship between etomidate and the outcomes did not depend on ASA status (interaction $P = 0.24$), Charlson comorbidity score ($P = 0.46$), or emergency procedure ($P = 0.15$).

However, no "dose effect" of etomidate was found on any of the primary outcomes. The estimated ORs (98.3% CI) for a unit (i.e., 0.1 mg/kg) increase in the amount of etomidate were 1.03 (0.97–1.10) ($P = 0.27$), 0.98 (0.90–1.06) ($P = 0.50$), and 1.01 (0.96–1.07) ($P = 0.65$) for having 30-day mortality, major cardiovascular morbidity, and major infectious morbidity, respectively.

Etomidate was significantly associated with prolonged hospital stay ($P < 0.001$; Table 4). Etomidate patients were 18% less likely (HR [95% CI]: 0.82 [0.78–0.87]) to be discharged from hospital at any given time point postoperatively as compared with propofol patients.

The etomidate and propofol groups were statistically different on mean systolic and diastolic blood pressure at various phases of the surgery (Table 5), and the etomidate group was often higher. However, many of the observed differences were too small to be clinically important. Etomidate was not associated with intraoperative vasopressor use, including dobutamine, dopamine, ephedrine, epinephrine, norepinephrine, phenylephrine, or vasopressin (OR [95% CI]: 0.92 [0.82–1.03] for etomidate versus propofol; $P = 0.16$).

Table 5. Summary of Intraoperative Systolic and Diastolic Blood Pressure Between the Propensity-Matched Groups

	Systolic blood pressure				Diastolic blood pressure			
Time period	Etomidate (*N* = 2144)	Propofol (*N* = 5233)	STD[a]	*P*	Etomidate (*N* = 2144)	Propofol (*N* = 5233)	STD[a]	*P*
Start case to induction								
Average	142 ± 27	145 ± 25	−0.10	<0.001	74 ± 17	76 ± 15	−0.12	<0.001
Minimum	115 ± 37	123 ± 32	−0.23	<0.001	62 ± 16	66 ± 15	−0.26	<0.001
Maximum	164 ± 32	162 ± 29	0.06	0.02	90 ± 33	87 ± 23	0.12	<0.001
Induction to intubation								
Average	146 ± 31	138 ± 30	0.26	<0.001	70 ± 16	71 ± 16	−0.03	0.29
Minimum	136 ± 33	124 ± 36	0.34	<0.001	66 ± 16	65 ± 17	0.02	0.43
Maximum	155 ± 33	150 ± 32	0.14	<0.001	76 ± 22	77 ± 19	−0.02	0.42
Intubation to incision								
Average	127 ± 22	118 ± 20	0.47	<0.001	63 ± 12	62 ± 11	0.11	<0.001
Minimum	92 ± 24	83 ± 22	0.38	<0.001	47 ± 11	47 ± 11	0.06	0.02
Maximum	175 ± 34	161 ± 33	0.40	<0.001	96 ± 34	91 ± 32	0.15	<0.001
Incision to closing								
Average	123 ± 17	121 ± 16	0.12	<0.001	62 ± 10	63 ± 10	−0.14	<0.001
Minimum	89 ± 19	87 ± 17	0.12	<0.001	46 ± 10	47 ± 9	−0.09	0.001
Maximum	173 ± 35	168 ± 35	0.15	<0.001	110 ± 52	104 ± 47	0.11	<0.001
Closing to emergence								
Average	124 ± 19	122 ± 19	0.12	<0.001	61 ± 11	63 ± 11	−0.17	<0.001
Minimum	108 ± 20	106 ± 20	0.08	0.02	53 ± 11	55 ± 12	−0.19	<0.001
Maximum	145 ± 27	141 ± 27	0.12	<0.001	73 ± 22	75 ± 23	−0.07	0.03
Emergence to end case								
Average	142 ± 24	140 ± 24	0.06	0.05	69 ± 14	71 ± 14	−0.16	<0.001
Minimum	118 ± 26	118 ± 25	0.01	0.84	56 ± 14	59 ± 13	−0.22	<0.001
Maximum	164 ± 30	161 ± 30	0.10	0.001	86 ± 30	86 ± 26	0.01	0.76

[a]Standardized differences (STDs) (etomidate – propofol): the difference in proportions divided by the pooled standard deviation; >0.10 in absolute value indicates slight different.

DISCUSSION

Our analysis indicates that induction of general anesthesia with etomidate is associated with more 30-day mortality and cardiovascular morbidity than when propofol is used for ASA III and IV patients undergoing noncardiac surgery, with highly significant ORs of 2.5 and 1.5, respectively. Use of etomidate is also associated with 1 day longer length of hospital stay compared with propofol. Our conclusions, especially on 30-day mortality, are robust to a strong unmeasured binary confounding variable.

Serious infectious complications in patients recovering from multiple traumas who are given long-term etomidate sedation have been attributed to suppression of cortisol synthesis.[27] Similarly, hypotensive blunt trauma patients who required rapid sequence intubation for prehospital airway management and were given etomidate had a more frequent incidence of infectious complications (29%) than those given other drugs (20%).[24] Nonetheless, the risk of infectious morbidity was similar in our etomidate and propofol groups. It is not known why the purported risk of etomidate on infection did not appear in our study. There were no observed dose responses in any outcomes. This might be attributed to the fact that even a small dose of etomidate causes adrenal suppression; the doses used in our study thus presumably had similar effects on adrenal function. However, it is also possible that the relationship between etomidate and poor outcomes is just an association and not a causal relationship.

Induction drugs were not randomly assigned; instead, they were chosen at the discretion of attending anesthesiologists. It is likely that their choices were influenced by the individual patient's physical status and perceived risk of hemodynamic instability. To remove the selection bias due to all the observed covariates, we used propensity score matching, which presumably improves validity of the analysis. We matched patients exactly on surgical types (Table 2) and used propensity score matching on other potential confounding factors (Table 1). The result was groups that were well balanced on many factors that potentially influence outcomes of interest. Furthermore, ASA physical status, Charlson comorbidity score, and emergency surgery which were still slightly imbalanced after propensity score matching were included in the multivariable models when comparing the 2 groups on the outcomes.

Surely there remains a degree of selection bias and confounding related to factors that are unavailable in our electronic records. Clinically perceived conditions of patients by anesthesia providers that was not explained by variables available in our electronic record could not be balanced in our analysis. However, our sensitivity analysis suggests that our conclusions, especially on 30-day mortality, are robust to a strong unmeasured binary confounding variable. It therefore seems unlikely that uncompensated bias and confounding account for all of the substantial association between etomidate use and adverse outcomes, although each surely contributes to some degree; the true OR of mortality resulting from anesthetic induction with etomidate may thus be considerably less than the 2.5 we observed.

For example, we were unable to adjust for the skill level of surgeons, the experience level of anesthesia providers, or the fact that various surgical approaches are characterized by the same surgical billing codes. Furthermore, we retrieved *International Classification of Diseases, 9th Revision* code–defined postoperative morbidity data for analysis which could potentially include an inaccurate diagnosis. Because data were not available electronically, we were also unable to account for a number of factors that potentially affect adrenal function such as chronic preoperative steroid use and preoperative use of medications that inhibit cortisol biosynthesis (i.e., ketoconazole, metyrapone, suramin) or those that increase steroid metabolism (i.e., carbamazepine, phenobarbital, phenytoin, rifampicin, mitotane). Preoperative cardiovascular and cerebrovascular morbidity were propensity matched, but specific variables that stratify severity of cardiac morbidity (i.e., left ventricular ejection fraction, brain natriuretic peptide, myocardial ischemia on cardiac stress test) and type of cardiac morbidity (i.e., coronary artery disease, valvular heart disease, cardiomyopathy) that affects anesthesiologists' decision to choose etomidate were not propensity matched, again due to unavailability of information. As with all observational studies, we report statistical associations that may or may not indicate causal relationships between etomidate use and adverse outcomes. And this was a single-center study; results may differ in other settings and other populations. We speculate that the corticosteroid suppression effect of etomidate has some bearing on postoperative outcome but could not explain why mortality and cardiovascular morbidity and not infectious morbidity are associated with etomidate use, which is also a limitation of administrative database studies as opposed to prospective studies.

We chose propofol as a comparator induction drug, because it is by far the most commonly used induction drug. Propofol very slightly inhibits cortisol secretion from adrenal cells in a dose-related fashion in vitro.[28] Consequently, decreased plasma cortisol concentrations are observed when propofol infusions are used for sedation of critically ill patients, although the normal cortisol response to adrenocorticotropic hormone stimulation is preserved.[29] However, adrenocortical suppression by etomidate is 1500 times more potent than propofol.[28] A typical induction dose of propofol 2.5 mg/kg did not suppress the ability of the adrenal cortex to secrete cortisol in response to adrenocorticotropic hormone or surgical stimulation, and patients given propofol consistently maintained higher plasma cortisol concentrations than those given etomidate 0.3 mg/kg up to 210 minutes after induction of anesthesia.[2] It is therefore highly unlikely that a single dose of propofol used for induction of general anesthesia produced clinically important adrenocortical suppression.

In summary, our analysis of ASA physical status III and IV patients undergoing noncardiac surgery with general anesthesia indicates that use of etomidate is associated with an increased odds of 30-day mortality and cardiovascular morbidity, although etomidate offers the advantage of minimizing induction hypotension that can cause coronary hypoperfusion, dysrhythmia, and cardiac arrest. Use of etomidate is also associated with prolonged duration of hospitalization. Randomized trials are necessary to determine whether there is a causal relationship between etomidate use and adverse outcomes and precisely define the treatment effect. In the meantime, etomidate should be used judiciously, considering that improved hemodynamic stability at induction may be accompanied by substantially worse longer-term outcomes.

APPENDIX

Table 1. Sensitivity Analysis—Effects of an Unobserved 2-Category Covariate u on the Associations Between Etomidate and Primary Outcomes

OR of etomidate (u = 1 vs 0)	OR of outcome (u = 1 vs 0)	Fraction of patient with u = 0	30-d mortality		Cardiovascular morbidity		Infectious morbidity	
			Incidence (etomidate/propofol)	Odds ratio (95% CI)	Incidence (etomidate/propofol)	Odds ratio (95% CI)	Incidence (etomidate/propofol)	Odds ratio (95% CI)
			Observed					
			0.0648/0.0258	**2.6 (2.0–3.3)**	**0.0760/0.0485**	**1.6 (1.3–2.0)**	**0.0891/0.0835**	**1.1 (0.9–1.3)**
			Estimated adding an unobserved 2-category covariate					
2	2	0.1	0.0579/0.0267	2.2 (1.7–2.8)	0.0731/0.0497	1.5 (1.2–1.8)	0.0878/0.0847	1.0 (0.8–1.2)
		0.5	0.0550/0.0275	2.1 (1.6–2.7)	0.0693/0.0509	1.4 (1.1–1.7)	0.0833/0.0867	1.0 (0.8–1.2)
		0.9	0.0569/0.0270	2.2 (1.7–2.8)	0.0717/0.0501	1.5 (1.2–1.8)	0.0862/0.0853	1.0 (0.8–1.2)
	0.5	0.1	0.0608/0.0261	2.4 (1.9–3.1)	0.0768/0.0486	1.6 (1.3–2.0)	0.0923/0.0830	1.1 (0.9–1.3)
		0.5	0.0636/0.0256	2.6 (2.0–3.3)	0.0805/0.0477	1.7 (1.4–2.1)	0.0966/0.0815	1.2 (1.0–1.4)[b]
		0.9	0.0604/0.0262	2.4 (1.9–3.1)	0.0763/0.0487	1.6 (1.3–2.0)	0.0917/0.0832	1.1 (0.9–1.3)
5	5	0.1	0.0557/0.0273	2.1 (1.6–2.7)	0.0703/0.0506	1.4 (1.1–1.7)	0.0844/0.0862	1.0 (0.8–1.2)
		0.5	**0.0445/0.0314**	**1.4 (1.1–1.8)**	**0.0558/0.0576**	**1.0 (0.8–1.2)**[a]	**0.0670/0.0973**	**0.7 (0.6–0.8)**[b]
		0.9	0.0467/0.0304	1.6 (1.2–2.1)	0.0582/0.0558	1.0 (0.8–1.2)[a]	0.0700/0.0939	0.7 (0.6–0.8)[b]
	0.2	0.1	0.0702/0.0244	3.0 (2.4–3.8)	0.0886/0.0457	2.0 (1.6–2.4)	0.1057/0.0786	1.4 (1.2–1.7)[b]
		0.5	0.0864/0.0229	4.0 (3.2–5.1)	0.1102/0.0430	2.8 (2.3–3.4)	0.1320/0.0738	1.9 (1.6–2.2)[b]
		0.9	0.0650/0.0254	2.7 (2.1–3.4)	0.0826/0.0473	1.8 (1.5–2.2)	0.0994/0.0807	1.3 (1.1–1.5)

Our conclusion on 30-day mortality is robust to a strong unmeasured binary confounding variable—even if we assume that the patients having a covariate, say "u", are 5 times as likely to receive etomidate and also 5 times more likely to have the outcome, and 50% of patients have u (see row 8 under "Estimated adding an unobserved 2-category covariate"), then the association between etomidate and 30-day mortality would still be significant (OR: 1.4 [1.1–1.8]). Our conclusions for cardiovascular and infectious morbidities would be retained for a less strong u.

Detailed example: the first row under "Estimated adding an unobserved 2-category covariate" displays the sensitivity to an unobserved 2 category covariate u assuming that patients having that covariate are 2 times more likely to receive etomidate and also 2 times more likely to have the outcome, and 10% of patients have u (i.e., approximately 15% of etomidate patients and 8% of propofol patients have u). Then the estimated incidence of having 30-day mortality would be 5.79% for etomidate patients and 2.67% for propofol patients, respectively; receiving etomidate would still be significantly associated with increased odds of experiencing 30-day mortality (the estimated odds ratio would be 2.2 [1.7–2.8]). After accounting for an unobserved covariate u, the estimated incidence of having cardiovascular morbidity would be 7.3% for etomidate patients and 5.0% for propofol patients, respectively; receiving etomidate would still be significantly associated with increased odds of experiencing cardiovascular morbidity (the estimated odds ratio would be 1.5 [1.2–1.8]). Similarly, for the infectious morbidity, the estimated incidence would be 8.8% for etomidate patients and 8.5% for propofol patients, respectively; the association between etomidate and infectious morbidity would still not be significant (the estimated odds ratio would be 1.0 [0.8–1.2]). Overall, under this situation our conclusions for all the outcomes would be retained.

Methods based on Rosenbaum and Rubin (1983).[30]

OR = odds ratio; CI = confidence interval.

[a]The conclusion that receiving etomidate was significantly associated with increased odds of having major cardiovascular morbidity would be altered.

[b]The conclusion that etomidate was not significantly associated with major infectious morbidity would be altered.

DISCLOSURES

Name: Ryu Komatsu, MD.
Contribution: This author helped design the study, conduct the study, and write the manuscript.
Attestation: Ryu Komatsu has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
Name: Jing You, MS.
Contribution: This author helped design the study, analyze the data, and write the manuscript.
Attestation: Jing You has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Edward J. Mascha, PhD.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Edward J. Mascha has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Daniel I. Sessler, MD.
Contribution: This author helped design the study, conduct the study, and write the manuscript.
Attestation: Daniel I. Sessler has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Yusuke Kasuya, MD.
Contribution: This author helped analyze the data and write the manuscript.
Attestation: Yusuke Kasuya has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
Name: Alparslan Turan, MD.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Alparslan Turan has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
This manuscript was handled by: Sorin J. Brull, MD, FCARCSI (Hon).

REFERENCES

1. Diago MC, Amado JA, Otero M, Lopez-Cordovilla JJ. Anti-adrenal action of a subanaesthetic dose of etomidate. Anaesthesia 1988;43:644–5
2. Fragen RJ, Weiss HW, Molteni A. The effect of propofol on adrenocortical steroidogenesis: a comparative study with etomidate and thiopental. Anesthesiology 1987;66:839–42
3. Jameson P, Desborough JP, Bryant AE, Hall GM. The effect of cortisol suppression on interleukin-6 and white blood cell responses to surgery. Acta Anaesthesiol Scand 1997;41:304–8

4. Absalom A, Pledger D, Kong A. Adrenocortical function in critically ill patients 24 h after a single dose of etomidate. Anaesthesia 1999;54:861–7
5. Malerba G, Romano-Girard F, Cravoisy A, Dousset B, Nace L, Lévy B, Bollaert PE. Risk factors of relative adrenocortical deficiency in intensive care patients needing mechanical ventilation. Intensive Care Med 2005;31:388–92
6. Annane D, Sébille V, Troché G, Raphaël JC, Gajdos P, Bellissant E. A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. JAMA 2000;283:1038–45
7. Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. N Engl J Med 2003;348:727–34
8. Marik PE, Zaloga GP. Adrenal insufficiency during septic shock. Crit Care Med 2003;31:141–5
9. Pizarro CF, Troster EJ, Damiani D, Carcillo JA. Absolute and relative adrenal insufficiency in children with septic shock. Crit Care Med 2005;33:855–9
10. Siraux V, De Backer D, Yalavatti G, Mélot C, Gervy C, Mockel J, Vincent JL. Relative adrenal insufficiency in patients with septic shock: comparison of low-dose and conventional corticotropin tests. Crit Care Med 2005;33:2479–86
11. Bendel S, Koivisto T, Ruokonen E, Rinne J, Romppanen J, Vauhkonen I, Kiviniemi V, Uusaro A. Pituitary-adrenal function in patients with acute subarachnoid haemorrhage: a prospective cohort study. Crit Care 2008;12:R126
12. Weant KA, Sasaki-Adams D, Dziedzic K, Ewend M. Acute relative adrenal insufficiency after aneurysmal subarachnoid hemorrhage. Neurosurgery 2008;63:645–9
13. Agha A, Phillips J, O'Kelly P, Tormey W, Thompson CJ. The natural history of post-traumatic hypopituitarism: implications for assessment and treatment. Am J Med 2005;118:1416
14. Benvenga S, Campenní A, Ruggeri RM, Trimarchi F. Clinical review 113: Hypopituitarism secondary to head trauma. J Clin Endocrinol Metab 2000;85:1353–61
15. Cohan P, Wang C, McArthur DL, Cook SW, Dusick JR, Armin B, Swerdloff R, Vespa P, Muizelaar JP, Cryer HG, Christenson PD, Kelly DF. Acute secondary adrenal insufficiency after traumatic brain injury: a prospective study. Crit Care Med 2005;33:2358–66
16. Dimopoulou I, Tsagarakis S, Douka E, Zervou M, Kouyialis AT, Dafni U, Thalassinos N, Roussos C. The low-dose corticotropin stimulation test in acute traumatic and non-traumatic brain injury: incidence of hypo-responsiveness and relationship to outcome. Intensive Care Med 2004;30:1216–9
17. Dimopoulou I, Tsagarakis S, Theodorakopoulou M, Douka E, Zervou M, Kouyialis AT, Thalassinos N, Roussos C. Endocrine abnormalities in critical care patients with moderate-to-severe head trauma: incidence, pattern and predisposing factors. Intensive Care Med 2004;30:1051–7
18. Hoen S, Asehnoune K, Brailly-Tabard S, Mazoit JX, Benhamou D, Moine P, Edouard AR. Cortisol response to corticotropin stimulation in trauma patients: influence of hemorrhagic shock. Anesthesiology 2002;97:807–13
19. den Brinker M, Joosten KF, Liem O, de Jong FH, Hop WC, Hazelzet JA, van Dijk M, Hokken-Koelega AC. Adrenal insufficiency in meningococcal sepsis: bioavailable cortisol levels and impact of interleukin-6 levels and intubation with etomidate on adrenal function and mortality. J Clin Endocrinol Metab 2005;90:5110–7
20. Hildreth AN, Mejia VA, Maxwell RA, Smith PW, Dart BW, Barker DE. Adrenal suppression following a single dose of etomidate for rapid sequence induction: a prospective randomized study. J Trauma 2008;65:573–9
21. 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; Corticus Study Group. Adrenal function in sepsis: the retrospective Corticus cohort study. Crit Care Med 2007;35:1012–8
22. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, Weiss YG, Benbenishty J, Kalenka A, Forst H, Laterre PF, Reinhart K, Cuthbertson BH, Payen D, Briegel J; CORTICUS Study Group. Hydrocortisone therapy for patients with septic shock. N Engl J Med 2008;358:111–24
23. Sunshine J, Deem S, Weiss N, Yanez ND, Daniel S, Keech K, Brown M, Treggiari M. Etomidate, adrenal function and mortality in critically ill patients. Respir Care 2013;58:639–46
24. Warner KJ, Cuschieri J, Jurkovich GJ, Bulger EM. Single-dose etomidate for rapid sequence intubation may impact outcome after severe injury. J Trauma 2009;67:45–50
25. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983;70:41–55
26. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 2009;28:3083–107
27. Watt I, Ledingham IM. Mortality amongst multiple trauma patients admitted to an intensive therapy unit. Anaesthesia 1984;39:973–81
28. Robertson WR, Reader SC, Davison B, Frost J, Mitchell R, Kayte R, Lambert A. On the biopotency and site of action of drugs affecting endocrine tissues with special reference to the anti-steroidogenic effect of anaesthetic agents. Postgrad Med J 1985;61 Suppl 3:145–51
29. Newman LH, McDonald JC, Wallace PG, Ledingham IM. Propofol infusion for sedation in intensive care. Anaesthesia 1987;42:929–37
30. Rosenbaum PR, Rubin DB. Assessing sensitivity to an unobserved binary covariate in an observational study with binary outcome. J R Statist Soc B 1983;45:212–8