Etomidate Use and Postoperative Outcomes among Cardiac Surgery Patients

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ABSTRACT

Background: Although a single dose of etomidate can cause relative adrenal insufficiency, the impact of etomidate exposure on postoperative outcomes is unknown. The objective of this study was to examine the association between a single induction dose of etomidate and clinically important postoperative outcomes after cardiac surgery.

Methods: The authors retrospectively examined the association between etomidate exposure during induction of anesthesia and postoperative outcomes in patients undergoing cardiac surgery from January 2007 to December 2009 by using multivariate logistic regression analyses and Cox proportional hazards regression analyses. Postoperative outcomes of interest were severe hypotension, mechanical ventilation hours, hospital length of stay, and in-hospital mortality.

Results: Sixty-two percent of 3,127 patients received etomidate. Etomidate recipients had a higher incidence of preoperative congestive heart failure (23.0 *vs.* 18.3%; $P = 0.002$) and a lower incidence of preoperative cardiogenic shock (1.3 *vs.* 4.0%; $P < 0.001$). The adjusted odds ratio for severe hypotension and in-hospital mortality associated with receiving etomidate was 0.80 (95% CI, 0.58–1.09) and 0.75 (95% CI, 0.45–1.24), respectively, and the adjusted hazard ratio for time to mechanical ventilation removal and time to hospital discharge was 1.10 (95% CI, 1.00–1.21) and 1.07 (95% CI, 0.97–1.18), respectively. Propensity score analysis did not change the association between etomidate use and postoperative outcomes.

Conclusions: In this study, there was no evidence to suggest that etomidate exposure was associated with severe hypotension, longer mechanical ventilation hours, longer length of hospital stay, or in-hospital mortality. Etomidate should remain an option for induction of anesthesia in cardiac surgery patients. **(ANESTHESIOLOGY 2014; 120:579-89)**

ETOMIDATE, an imidazole derivative, is an important drug used for induction of anesthesia in high-risk cardiac surgery patients because of its hemodynamic stability.[1] Many clinicians have abandoned this potent and hemodynamically forgiving drug due to concern for relative adrenal insufficiency contributing to poor outcomes. There is little controversy that a single dose of etomidate can inhibit adrenal steroidogenesis and cause relative adrenal insufficiency.[2–5] There is, however, controversy regarding the impact of etomidate-induced relative adrenal insufficiency on clinical outcomes. In sepsis and critically ill patients, various studies suggest either an increase[2,4,6] or no change[3,7–11] in mortality risk associated with etomidate use. In addition, a large randomized prospective study evaluating the effect of etomidate or ketamine as induction agent in the emergency department found that etomidate use was not associated with a significant increase in morbidity or mortality compared with ketamine.[12]

The impact of a single-dose administration of etomidate on clinical outcomes, other than vasopressor requirements, is not known in cardiac surgery patients. A small prospective cohort study in cardiac surgery patients concluded that the use of etomidate might increase vasopressor requirements but with no increase in mortality.[13] A randomized controlled trial in elective cardiac surgery patients, however, demonstrated an increased rate of relative adrenal insufficiency in patients who received etomidate but no increase in vasopressor requirements.[14] Thus, although a single dose of etomidate increases the risk of relative adrenal insufficiency, its impact on postoperative outcomes in cardiac surgery patients remains largely unknown. Despite the fact that the effect of etomidate administration on postoperative outcomes is controversial, there continues to be proponents that

What We Already Know about This Topic

- The effect of an induction dose of etomidate on major perioperative outcomes in cardiac surgical patients remains unknown
- In a retrospective analysis, the authors evaluated outcomes in 3,127 patients, of whom 62% were given etomidate

What This Article Tells Us That Is New

- The incidence of severe hypotension and mortality did not differ significantly in patients who did and did not receive etomidate
- The duration of postoperative mechanical ventilation and time to hospital discharge were also similar in the two groups

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call for the use of alternative anesthesia induction agents[15,16] or are developing analogues of etomidate that do not produce adrenocortical dysfunction.[17]

This goal of this study is to examine whether there is evidence suggesting that etomidate administration is associated with any/all of increased severe hypotension, longer time on mechanical ventilation, longer length of hospital stay, and/or increased in-hospital mortality. We hypothesized that even in a sample as large as ours (N = 3,127), no such evidence would exist.

Materials and Methods

After obtaining a waiver of informed consent from the Institutional Review Board (Human Research Protection Program, Vanderbilt University, Nashville, TN), we performed a retrospective, single-institution review of all cardiac surgery patients between January 2007 and December 2009. Patient information was obtained from the Society of Thoracic Surgeons Database at Vanderbilt University Medical Center and included age, sex, body mass index (BMI), race, type of surgery, history of diabetes mellitus, history of congestive heart failure (CHF), preoperative angiotensin-converting enzyme (ACE) inhibitor use, ejection fraction, last preoperative creatinine level, presence of cardiogenic shock, status of surgery (elective, urgent, and emergent), mechanical ventilation hours, hospital length of stay, and in-hospital mortality. The use of etomidate, propofol, midazolam, and fentanyl during induction of anesthesia was obtained from our Perioperative Data Warehouse that electronically captures the use of these drugs. As this is a retrospective review, anesthetic drug choices were up to the discretion of the anesthesiologist. Patients who were intubated on arrival may have not received intravenous anesthetic induction. Before 2008, etomidate was used more commonly for cases with concern for hemodynamic stability, whereas after 2008 the consensus of the group was to use it more sparingly because of the concerns from sepsis data about relative adrenal insufficiency. Anesthesia was maintained with a combination of oxygen, air, and isoflurane. Isoflurane was administered in the pump circuit to all patients whoever underwent cardiopulmonary bypass. All patients received a propofol infusion at the end of the anesthesia case for transfer to the intensive care unit (ICU). Severe hypotension in the ICU was defined as a norepinephrine requirement of greater than or equal to 15 μg/min for greater than 1 h to maintain a specified target mean arterial pressure of 60 to 70 mmHg. During this study period, our ICU clinical protocol mandated that a baseline cortisol level and corticotropin stimulation test be obtained on these hypotensive patients. This protocol did not take other vasopressor and inotropic drugs, cardiac output, or systemic vascular resistance into account. We did not analyze the effect of etomidate on relative adrenal insufficiency in the hypotensive cohort because it is already well established that etomidate causes relative adrenal insufficiency.[2–5] Mechanical ventilation hours were defined as time from arrival in the ICU to extubation. If a patient was taken off mechanical ventilation and then put back on it, we used the total number of hours on mechanical ventilation as opposed to the time until it was first removed. The length of hospital stay was defined as time from ICU admission until discharge from the hospital.

Statistical Methods

Characteristics of the study sample (*e.g.*, demographics and baseline variables) are summarized with the median, 10th, and 90th percentiles for continuous variables and with percentages for categorical variables. To test for unadjusted differences between those who did and did not receive etomidate, the Wilcoxon rank sum test and the Pearson chi-square test were used for continuous and categorical variables, respectively. Logistic regression analyses and Cox proportional hazards regression analyses were used to examine covariate-adjusted associations between etomidate administration and outcomes. In particular, logistic regression was used to model the binary outcomes mortality and severe hypotension, and Cox proportional hazards regression was used to model the number days from surgery until hospital discharge and the number of hours from start until removal of mechanical ventilation. Multivariate regression models were adjusted for an *a priori* determined sets of potential confounders including (1) other anesthetics and medications used (propofol, midazolam, and ACE inhibitors); (2) patient demographics (age, sex, and race); (3) patient health and medical history (BMI, ejection fraction, presurgery creatinine concentration, history of diabetes, history of CHF, history of cardiogenic shock, emergency *vs.* elective surgery), and (4) type of surgery (off-pump coronary artery bypass graft [CABG] surgery, on-pump CABG surgery, valve surgery, valve and on-pump CABG surgery, and other surgery). Etomidate administration curtailed dramatically beginning in October 2008, and so calendar month (ranging from 1 to 36) was included as an adjustment variable in all regression models. For the continuous covariates, age, ejection fraction, BMI, presurgery creatinine, and calendar month, we examined whether associations with outcomes exhibited evidence of nonlinearity using restricted cubic splines with four knots. In at least one of the outcome models, BMI, creatinine, and calendar month associations with outcomes exhibited nonlinearity according to a likelihood ratio test and so we modeled each of these three variables flexibly (without assuming linearity) in all models. In contrast, age and ejection fraction did not exhibit obvious evidence for nonlinearity and so such effects were modeled assuming linearity in all models.

For the severe hypotension and mortality analyses, where logistic regression was used, etomidate and other covariate effects are summarized with odds ratios (ORs) and 95% CIs. For the time to hospital discharge and time to removal of mechanical ventilation analyses, where Cox proportional

hazards models were used, etomidate and other covariate effects are summarized with hazard ratios and 95% CI. It is worth noting that even though an OR greater than 1 is associated with an increased risk of severe hypotension and mortality, a hazard ratio less than 1 is associated with lower rates of mechanical ventilation removal and hospital discharge, and therefore denotes longer time on mechanical ventilator and longer length of hospital stay. Ejection fraction was missing in 16.1% of patients and race was missing in 6.7% of patients. We therefore used multiple imputation analyses with 25 imputation datasets to summarize effects of covariates on outcomes.

Because there was concern regarding model overfitting with covariate-adjusted regression analyses (particularly for the mortality analyses where there were approximately 100 events), we conducted propensity score analyses in parallel. For the propensity score analyses, all covariates used in covariate-adjusted analyses were entered into a logistic regression model of etomidate exposure (yes/no), and for each subject we calculated the propensity score using estimated log-odds of etomidate exposure. Etomidate exposure (yes/no) and the propensity score were then entered into each outcome regression model, and we report estimated etomidate associations with the four outcomes. The etomidate associations with outcomes were remarkably similar using both covariate-adjusted and propensity score approaches and both are reported. For covariate-adjusted analyses, bootstrap-based validation and calibration analyses were performed to assess model overfitting.[18,19] In all models except for the mortality model, regression calibration slopes exceeded 0.95, thus pointing toward little to no model overfitting. In the mortality model, the calibration slope was 0.82 thus pointing toward modest overfitting. Finally, in the covariate-adjusted Cox models, we tested the proportional hazards assumption for the etomidate effects. There was no evidence to suggest violation of the proportional hazards assumption in either the time to hospital discharge or the time to mechanical ventilation removal models.

For all regression analyses, two-sided, type 1 error rates of 0.05 were used for statistical significance. Because we examined four outcomes, for regression analysis reporting, we include Bonferroni-adjusted estimates of CIs in addition to the unadjusted estimates. All statistical analyses were performed using the R programming language version 3.0.1 (Vienna, Austria).

Results

A total of 3,294 cardiac surgery patients were reviewed from January 2007 to December 2009. Etomidate usage information was available for 3,219 patients. We excluded patients who received ketamine (1%), who did not receive fentanyl (2%), those with ejection fraction out of range (5 to 80) and BMI greater than 80, or those with creatinine level equal to zero. Our analyses are therefore based on patients who received fentanyl and did not receive ketamine (N = 3,127). A total of 1,928 patients (61.7%) received etomidate. Tables 1 and 2 summarize covariate and outcome distributions, respectively, for etomidate recipients and nonrecipients. Many of the covariate distributions appeared similar between etomidate recipients and nonrecipients. Etomidate recipients, however, appeared to be more likely to present with a history of CHF (23 *vs.* 18.3%; $P = 0.002$) and were less likely to present with cardiogenic shock (1 *vs.* 4%; $P < 0.001$). The decreased use of etomidate in patients who presented with cardiogenic shock may be explained by the fact that many of these patients arrived in the operating room already intubated with no need for induction drugs. This is supported by the fact that in patients who presented with cardiogenic shock, 28% received only midazolam and 22% received no induction drug at all. Patients who underwent on-pump CABG surgery were more likely to receive etomidate whereas those underwent off-pump CABG surgery were less likely to receive etomidate. Similarly, in unadjusted analyses of outcomes, etomidate recipients and nonrecipients appeared to have similar distributions for all outcomes except mechanical ventilation hours. Etomidate recipients were observed to be exposed to mechanical ventilation for longer periods of time compared with nonrecipients (median hours: 8.5 *vs.* 7.4; $P = 0.005$).

Table 3 shows results from the primary analyses that include adjustments for potential confounders. There was no evidence in this analysis to suggest that etomidate exposure increases patients' risk of adverse outcomes. The adjusted OR for severe hypotension and mortality associated with receiving etomidate was 0.80 (95% CI, 0.58–1.09) and 0.75 (95% CI, 0.45–1.24), respectively, and the adjusted hazards ratio for time to mechanical ventilation removal and time to hospital discharge were 1.10 (95% CI, 1.00–1.21) and 1.07 (95% CI, 0.97–1.18), respectively. Propensity score analysis, with adjustment for confounders, did not change the effect of etomidate on severe hypotension, length of hospital stay, or mortality. In addition, there was no evidence that etomidate exposure increases mechanical ventilation time by propensity score analysis. We also performed a sensitivity analysis in which patients who did not receive any induction drugs were excluded from the analysis. The results from the sensitivity analysis were qualitatively similar to those reported in table 3.

Other covariate effects are also shown in figures 1–4. Severe hypotension was independently predicted by preoperative creatinine, age, history of CHF, type of surgery, ejection fraction, and surgery status. Independent predictors of longer time to mechanical ventilation removal included calendar month, BMI, preoperative creatinine, age, female sex, history of CHF, cardiogenic shock, type of surgery, lower ejection fraction, and surgery status. Longer time to hospital discharge was independently

Table 1. Summary Statistics for Demographics and Baseline Variables by Presence of Etomidate

Characteristic	N	Etomidate (N = 1,928)	No Etomidate (N = 1,199)	*P* Value
Induction agent				
Etomidate only	3,127	5.5%	0.0%	<0.001
Propofol only	3,127	0.0%	3.9%	<0.001
Midazolam only	3,127	0.0%	38.9%	<0.001
Etomidate and propofol	3,127	1.6%	0.0%	<0.001
Etomidate and midazolam	3,127	81.5%	0.0%	<0.001
Propofol and midazolam	3,127	0.0%	54.0%	<0.001
All three (E + P + M)	3,127	11.4%	0.0%	<0.001
No agent	3,127	0.0%	3.2%	<0.001
Propofol (total)	3,127	13.0%	58.0%	<0.001
Midazolam (total)	3,127	92.9%	92.9%	0.97
Age (yr)	3,127	63 (47–78)	64 (45–79)	0.45
Male sex	3,127	66.1%	64.6%	0.38
BMI (kg/m^2)	3,069	28.3 (22.2–37.4)	28.1 (21.9–37.3)	0.42
Race				0.44
Caucasian	2,917	91.3%	89.9%	
Black	2,917	7.5%	8.5%	
Other	2,917	1.3%	1.6%	
History of diabetes mellitus	3,127	31.7%	31.1%	0.71
Creatinine (mg/dl)	3,103	1.07 (0.77–1.69)	1.08 (0.79–1.72)	0.38
Ejection fraction (%)	2,623	55 (25–65)	55 (25–65)	0.05
History of CHF	3,127	23.0%	18.3%	0.002
ACE inhibitor use	3,127	35.0%	33.5%	0.40
Cardiogenic shock	3,127	1.3%	4.0%	<0.001
Valve surgery only	3,127	32.1%	30.4%	0.33
Valve and CABG surgery	3,127	9.4%	9.8%	0.73
CABG surgery on-pump	3,127	15.8%	7.8%	<0.001
CABG surgery off-pump	3,127	34.2%	40.5%	<0.001
Other surgery	3,127	8.5%	11.4%	0.006
Surgery status				0.49
Elective	3,122	66.7%	65.5%	
Urgent and emergent	3,122	33.3%	34.5%	

Continuous variables were summarized with median (10th, 90th percentile) and tested with Wilcoxon rank sum test. Categorical variables were summarized with percentages and tested with chi-square test.

ACE = angiotensin-converting enzyme; BMI = body mass index; CABG = coronary artery bypass graft; CHF = congestive heart failure.

predicted by BMI, preoperative creatinine, age, female sex, ACE inhibitor use, history of CHF, cardiogenic shock, type of surgery, lower ejection fraction, and surgery status. Mortality was independently predicted by preoperative creatinine, a history of CHF, cardiogenic shock, and type of surgery. We also conducted additional analyses that examined the outcomes time to mechanical ventilation removal, time to hospital discharge, and in-hospital mortality with severe hypotension (yes/no) included as an independent variable (table 3). Although severe hypotension was associated with increased time to mechanical ventilation removal (adjusted hazard ratio, 0.49; 95% CI, 0.43–0.55), increased time to hospital discharge (adjusted hazard ratio, 0.51; 95% CI, 0.45–0.58), and increased in-hospital mortality (adjusted OR, 3.6; 95% CI, 2.25–5.77), inclusion of it into the regression models did not have a notable impact on the relationship between etomidate use and time to mechanical ventilation removal, time to hospital discharge, or in-hospital mortality.

Table 2. Unadjusted Postoperative Outcomes

Characteristic	N	Etomidate N = 1,928	No Etomidate N = 1,199	*P* Value
Severe hypotension	3,127	9.6%	10.8%	0.26
Total time on mechanical ventilation (h)	2,978	8.5 (3.3–51.6)	7.4 (2.9–117.2)	0.005
Hospital length of stay (days)	3,120	6.0 (3.0–13.0)	6.0 (3.0–18.0)	0.96
Mortality	3,127	3.0%	4.2%	0.07

Continuous variables were summarized with median (10th, 90th percentile) and tested with Wilcoxon rank sum test. Categorical variables were summarized with percentages and tested with chi-square test.

Table 3. Adjusted Postoperative Outcomes

	Bonferroni corrected	Severe hypotension OR (95% CI)	Total mechanical ventilation time HR (95% CI)	Length of hospital stay HR (95% CI)	Mortality OR (95% CI)
Regression model approach					
Etomidate Effect	No	0.80 (0.58–1.09)	1.10 (1.00–1.21)	1.07 (0.97–1.18)	0.75 (0.45–1.24)
	Yes	0.80 (0.53–1.20)	1.10 (0.97–1.25)	1.07 (0.94–1.21)	0.75 (0.39–1.45)
Propensity score approach					
Etomidate effect	No	0.79 (0.58–1.08)	1.12 (1.02–1.23)	1.07 (0.98–1.18)	0.74 (0.44–1.23)
	Yes	0.79 (0.53–1.19)	1.12 (0.99–1.27)	1.07 (0.95–1.21)	0.74 (0.38–1.44)
Regression model approach include severe hypotension					
Etomidate effect	No		1.10 (1.00–1.22)	1.06 (0.96–1.17)	0.79 (0.48–1.32)
	Yes		1.10 (0.97–1.25)	1.06 (0.93–1.20)	0.79 (0.41–1.55)
Propensity score approach include severe hypotension					
Etomidate effect	No		1.11 (1.01–1.22)	1.06 (0.96–1.16)	0.77 (0.46–1.29)
	Yes		1.11 (0.98–1.25)	1.06 (0.94–1.20)	0.77 (0.39–1.51)

HR = hazard ratio; OR = odds ratio.

Discussion

We evaluated the association between single-dose etomidate administration and important postoperative outcomes in a large cohort of cardiac surgery patients. After adjusting for potential confounders, there was no evidence to suggest that etomidate exposure was associated with severe hypotension, longer mechanical ventilation hours, longer length of hospital stay, or in-hospital mortality. Postoperative severe hypotension was an independent risk factor associated with an increased risk for longer mechanical ventilation hours, longer length of hospital stay, and mortality.

Etomidate and Mortality

Etomidate, because of its neutral hemodynamic profile, is used to facilitate tracheal intubation in the operating room, ICU, and emergency department. A single dose of etomidate causes temporary relative adrenal insufficiency.[2–5] This relative adrenal insufficiency associated with etomidate administration has raised concern that etomidate may increase morbidity and mortality in critically ill and septic patients who already have perturbations of the hypothalamic–pituitary–adrenal axis. The evidence supporting an increased mortality or morbidity in these patient populations, however, remains controversial.[20] This is due to the fact that the majority of studies are retrospective in nature. A meta-analysis of 19 studies, 4 of which were randomized controlled trials of etomidate *versus* comparators,[5,12,21,22] found a significant increase in mortality in patients who received etomidate (relative risk [RR], 1.19; 95% CI, 1.10–1.30).[4] The retrospective analysis of the Corticosteroid Therapy of Septic Shock study[23] suggested that etomidate use was associated with a 1.8-fold increased risk of mortality although the 95% CI ranged from 0.5 to 6.4.[24] A more recent retrospective review of 824 septic patients found a trend for increased mortality associated with etomidate use (RR, 1.20; 95% CI, 0.99–1.45).[6] In contrary to the previous studies, several retrospective studies have reported no significant increased risk of mortality associated with etomidate use in septic patients.[7–10,25] In a prospective randomized study, Jabre *et al.*[12] compared etomidate with ketamine as an induction agent in 469 critically ill patients requiring emergency intubation. Not surprisingly, etomidate use was associated with more frequent adrenal insufficiency, but no significant increase in mortality (OR, 1.2; 95% CI, 0.8–1.8). In the subgroup of 76 septic patients, the OR for mortality associated with etomidate use was 1.4 (95% CI, 0.5–3.5). In addition, a smaller randomized prospective study comparing etomidate with midazolam for intubation in 122 septic patients found no significant difference in length of hospital stay or mortality (RR, 1.2; 95% CI, 0.8–1.9).[11] Thus, although some retrospective studies suggest an increased mortality risk with etomidate use, none of the prospective studies support this finding.

Clinicians may be inclined to use etomidate in cardiac surgery patients with poor ventricular function and significant preoperative comorbidities as indicated by the more frequent use of etomidate in patients with a history of CHF. Thus, these patients maybe more likely to suffer adverse outcomes from etomidate-induced relative adrenal insufficiency. In our large heterogeneous cardiac surgery cohort, however, there was no evidence to suggest that etomidate exposure was associated with an increased risk of in-hospital mortality. The wide CIs for the effect of etomidate on mortality are consistent with the odds of dying being 55% lower to 24% higher. To definitively address the potential impact of etomidate on mortality in a cardiac surgery population, a very large prospective randomized study will be needed to detect a difference in mortality between experimental and control subjects given that the observed mortality in our cohort was 3.4%.

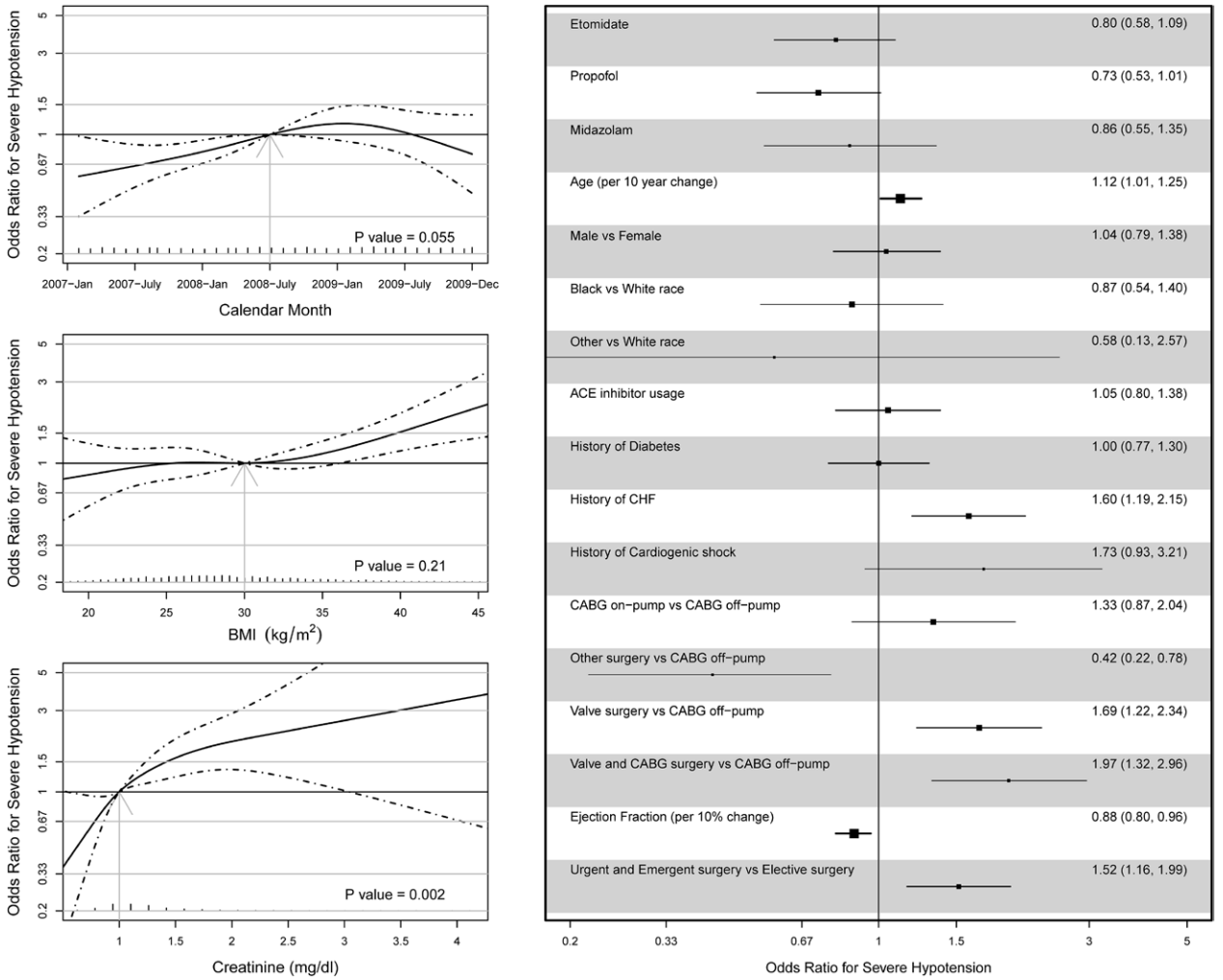

Fig. 1. Severe hypotension regression analysis: results are based on a multivariable logistic regression model, and odds ratios and 95% CIs summarize the relative odds of severe hypotension. Calendar month, body mass index (BMI), and creatinine concentration were entered into the regression model flexibly using restricted cubic splines with four knots. To display effects sizes for the nonlinear effects, we chose a single reference value for each variable (calendar month = July 2008, BMI = 30 kg/m^2, creatinine concentration = 1 mg/dl) and compared all other values to it. Due to lack of evidence suggesting a nonlinear relationship with any of the outcomes, the other continuous variables (age and ejection fraction) were modeled with linear terms and are included on the right with categorical variables. Categorical variables effects characterize the adjusted association between the outcome and the presence (*vs.* absence) of the risk factor. ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft; CHF = congestive heart failure.

Etomidate and Hypotension

In cardiac surgery patients, most studies have focused on the effect of etomidate administration and vasopressor requirements. Iribarren *et al.*[13] examined a prospective cohort of 120 patients and found etomidate to be a risk factor for relative adrenal insufficiency and higher vasopressor requirements after surgery up to 4 h after ICU admission. In the only prospective blinded randomized trial in cardiac surgery patients, Morel *et al.*[14] evaluated the effect of etomidate or propofol on relative adrenal insufficiency and vasopressor requirements in 100 patients with normal left ventricular ejection fraction. The incidence of relative adrenal insufficiency was higher in the etomidate group up to 24 h after surgery, but there was no difference in vasopressor requirements. Although hospital length of stay and mortality were similar between the two groups, their study was underpowered to detect a difference in these outcomes. Again, in our cardiac surgery cohort, there was no evidence to suggest that etomidate exposure was associated with severe hypotension. Retrospective studies in cardiac surgery patients also suggest that preoperative ACE inhibitor use is associated with an increased risk of postoperative hypotension, renal dysfunction, and death.[26,27] After controlling for potential confounders, there was no evidence to

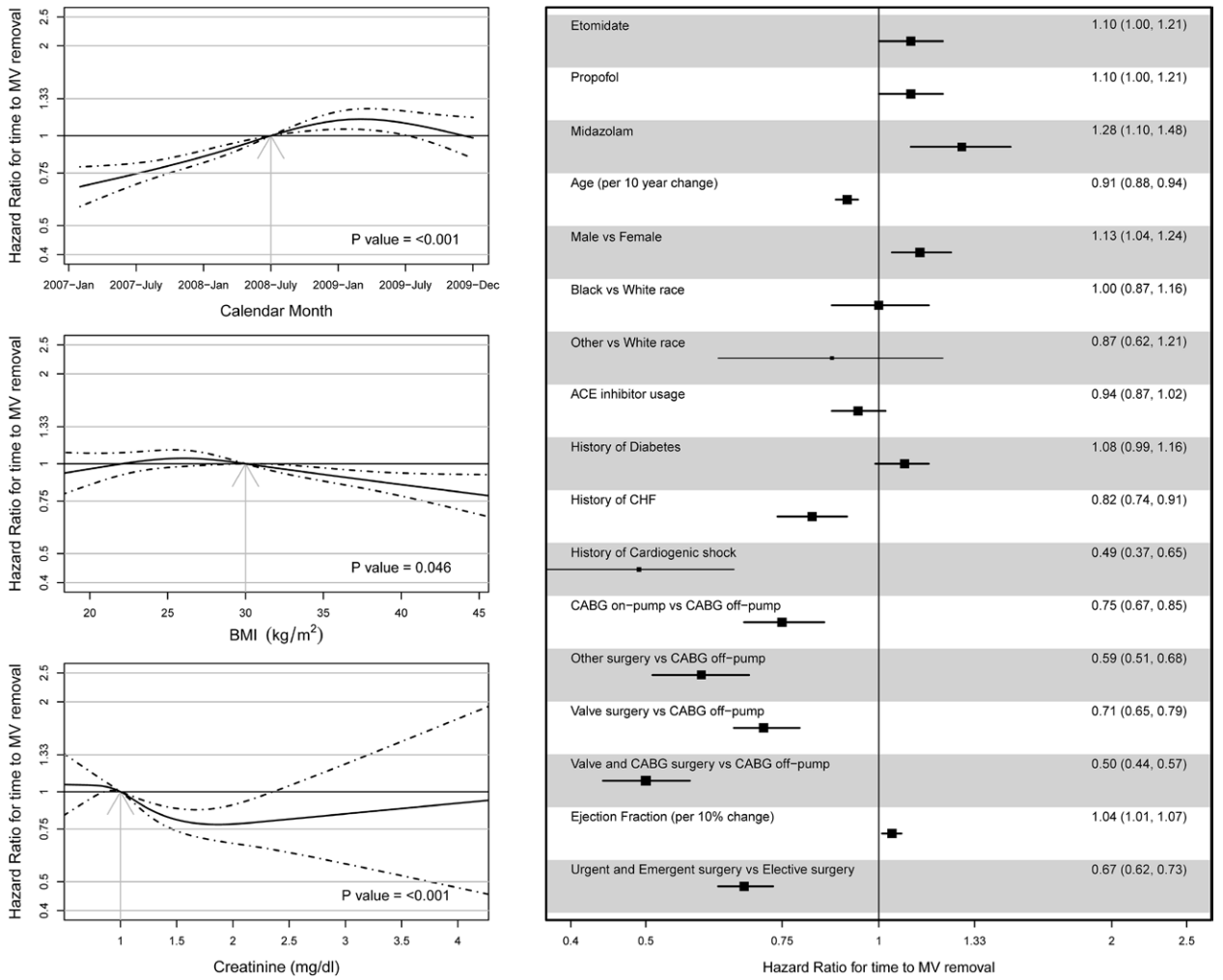

Fig. 2. Time to mechanical ventilation (MV) removal regression analysis: results are based on a multivariable Cox proportional hazards model, and hazard ratios and 95% CIs summarize the relative rates at which MV was removed. Calendar month, body mass index (BMI), and creatinine concentration were entered into the regression model flexibly using restricted cubic splines with four knots. To display effects sizes for the nonlinear effects, we chose a single reference value for each variable (calendar month = July 2008, BMI = 30 kg/m^2, creatinine concentration = 1 mg/dl) and compared all other values to it. Due to lack of evidence suggesting a nonlinear relationship with any of the outcomes, the other continuous variables (age and ejection fraction) were modeled with linear terms and are included on the right with categorical variables. Categorical variable effects characterize the adjusted association between the outcome and the presence (*vs.* absence) of the risk factor. Note that hazard ratio greater than (less than) 1 implies shorter (longer) time on MV. ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft; CHF = congestive heart failure.

suggest that preoperative ACE inhibitor use was associated with severe hypotension in our study cohort. This finding is consistent with a prospective randomized study in 445 cardiac surgery patients who did not demonstrate an increased risk of vasopressor requirements, renal dysfunction, prolonged mechanical ventilation hours, or death in patients randomized to preoperative treatment with an ACE inhibitor.[28] It is important to note that although etomidate use was not associated with postoperative severe hypotension, including severe hypotension as a covariate in the regression models indicated that severe hypotension was an independent predictor for longer mechanical ventilation hours, longer length of hospital stay, and mortality. The increased risk of adverse postoperative outcomes associated with postoperative hypotension in cardiac surgery patients is consistent with previous studies.[29,30]

Etomidate: Prolonged Mechanical Ventilation and Hospital Length of Stay

No large studies have evaluated the effect of etomidate use on prolonged mechanical ventilation or hospital length of stay in a cardiac surgical cohort. Our study had no evidence to suggest that etomidate exposure was associated with longer mechanical ventilation hours or longer length of hospital and is consistent with one of the largest retrospective studies in sepsis patients where etomidate use did

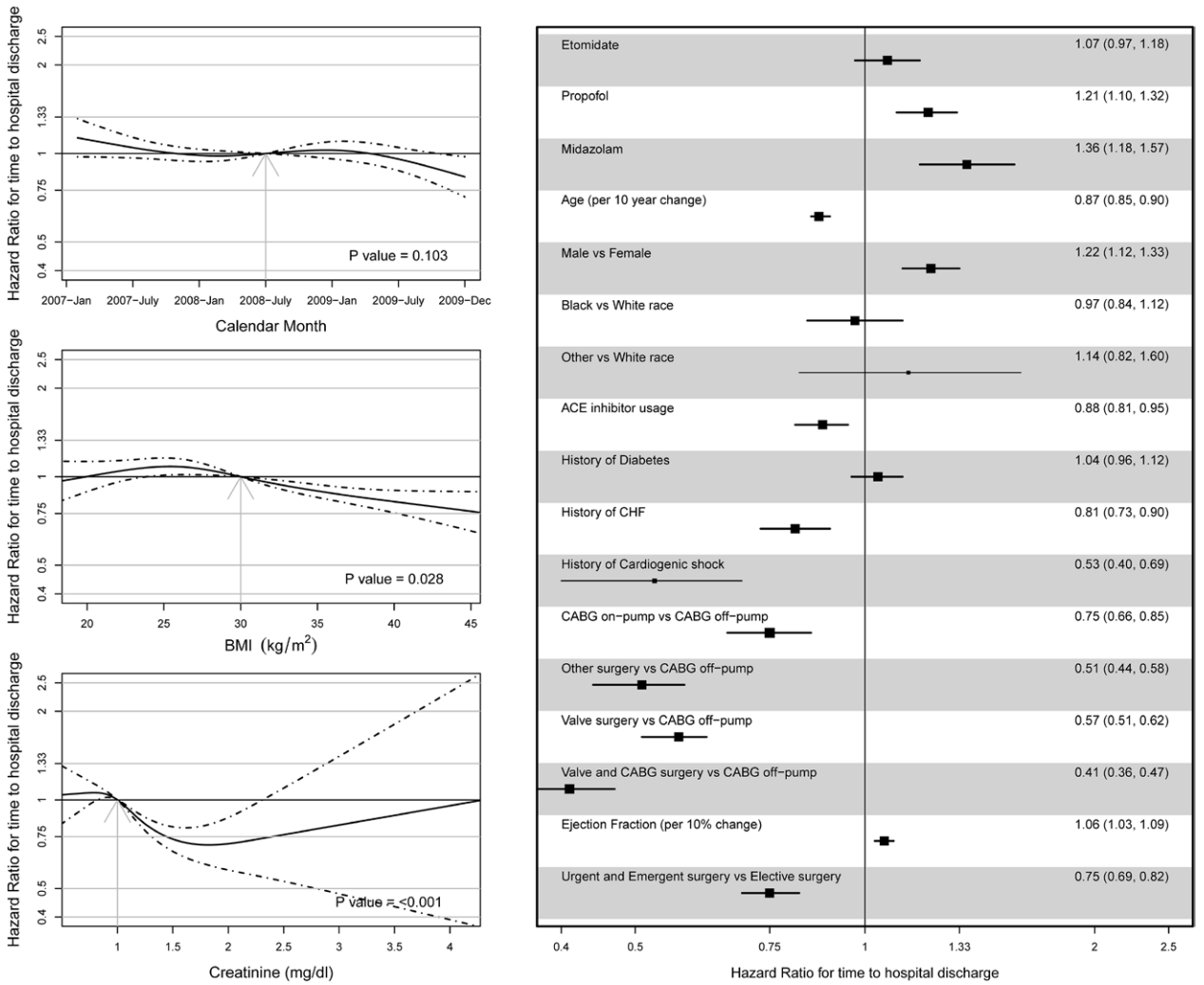

Fig. 3. Time to hospital discharge regression analysis: results are based on a multivariable Cox proportional hazards model, and hazard ratios and 95% CIs summarize the relative rates at which patients were discharged from the hospital. Calendar month, body mass index (BMI), and creatinine concentration were entered into the regression model flexibly using restricted cubic splines with four knots. To display effects sizes for the nonlinear effects, we chose a single reference value for each variable (calendar month = July 2008, BMI = 30 kg/m^2, creatinine concentration = 1 mg/dl) and compared all other values to it. Due to lack of evidence suggesting a nonlinear relationship with any of the outcomes, the other continuous variables (age and ejection fraction) were modeled with linear terms and are included on the right with categorical variables. Categorical variable effects characterize the adjusted association between the outcome and the presence (*vs.* absence) of the risk factor. Note that hazard ratio greater than (less than) 1 implies shorter (longer) length of stay. ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft; CHF = congestive heart failure.

not associate with longer mechanical ventilation hours or hospital length of stay.[8]

Study Limitations

Our retrospective study has several limitations. Although we controlled for most of the variables that might confound the relationship between etomidate use and adverse outcomes, there is always a possibility that an unmeasured variable might explain the lack of evidence between etomidate use and adverse outcomes. Our definition and identification of patients with severe hypotension were based on our clinical ICU protocol at the time and is different from vasoplegia definitions used in previous studies.[26,29] Despite using a different definition for hypotension, we identified a high-risk group that was associated with a significant increased risk of adverse postoperative outcomes including death. The majority of our CABG surgeries is performed off-pump and may explain the observation that CABG-only surgery was associated with shorter mechanical ventilation hours and shorter length of hospital stay compared with on-pump CABG surgery. The improvement in clinical outcomes associated with off-pump CABG surgery compared with on-pump CABG surgery is supported by some but not other large

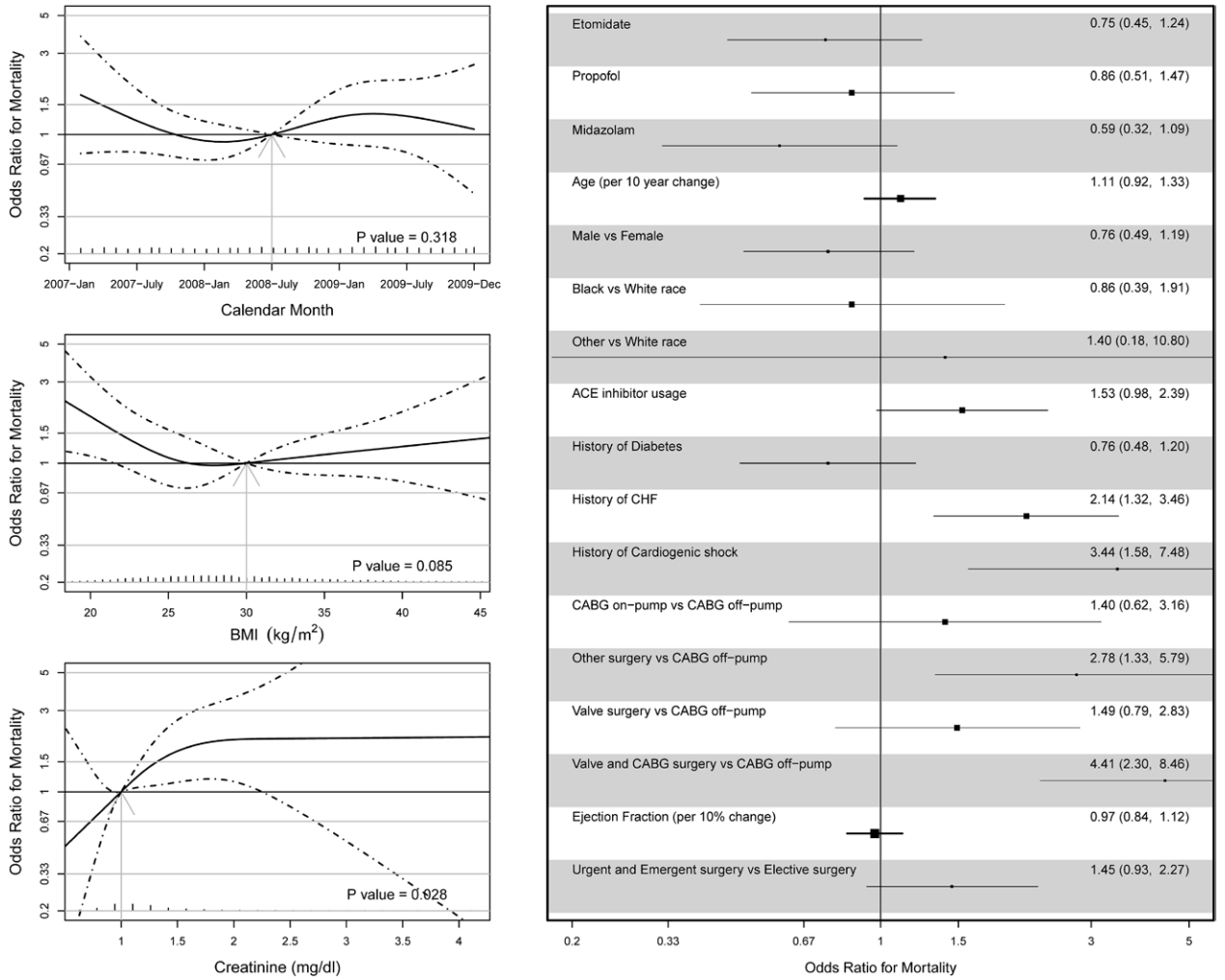

Fig. 4. In-hospital mortality regression analysis: results are based on a multivariable logistic regression model, and odds ratios and 95% CIs summarize the relative odds of mortality during the hospitalization. Calendar month, body mass index (BMI), and creatinine concentration were entered into the regression model flexibly using restricted cubic splines with four knots. To display effects sizes for the nonlinear effects, we chose a single reference value for each variable (calendar month = July 2008, BMI = 30 kg/m^2, creatinine concentration = 1 mg/dl) and compared all other values to it. Due to lack of evidence suggesting a nonlinear relationship with any of the outcomes, the other continuous variables (age and ejection fraction) were modeled with linear terms and are included on the right with categorical variables. Categorical variables effects characterize the adjusted association between the outcome and the presence (*vs.* absence) of the risk factor. ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft; CHF = congestive heart failure.

prospective clinical trials.[31,32] Because of the change in etomidate administration during the study period, we investigated the effect of calendar month in the multivariate models. For three of the four outcomes, calendar month was not associated with worse outcomes. Calendar month, however, was a significant predictor of mechanical ventilation hours with shorter mechanical ventilation hours in the latter part of the study. One potential explanation for this decrease in mechanical ventilation hours may be improvement in ICU clinical protocols that allows for more rapid tracheal extubation. Finally, we did not assess adrenal function in all patients and therefore cannot comment on the effect of etomidate on adrenal function or on the potential impact of relative adrenal insufficiency on postoperative outcomes.

Conclusion

In this large retrospective cohort of cardiac surgical patients, there was no evidence to suggest that etomidate exposure was associated with postoperative severe hypotension, longer mechanical ventilation hours, longer length of hospital stay, or in-hospital mortality. Thus, etomidate should remain an acceptable option for the induction of anesthesia in cardiac surgery patients despite the known risk of relative adrenal insufficiency. Only a large prospective randomized study will definitively address the effect of

etomidate on postoperative outcomes in cardiac surgical patients.

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Competing Interests

The authors declare no competing interests.

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