

**Instrumental Variable Analysis of the Safety of Etomidate in Patients with Heart Failure Undergoing Noncardiac Surgery**

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**Supplemental Online Content**

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### **Supplemental Methods:**

#### *Hospital Registry Databases*

At Beth Israel Deaconess Medical Center (BIDMC), anaesthesia-related/intraoperative data were collected through the Anesthesia Information Management System (AIMS) and the Perioperative Information Management System (PIMS), admission/discharge information from the Admission Discharge Transfer (ADT) and Casemix databases, and Current Procedural Terminology (CPT) billing codes from the Center for Clinical Computing (CCC) database. Information regarding preoperative medication prescriptions was retrieved from the Online Medical Record (OMR) database, and mortality data were obtained from the Miscellaneous (MISC) database. At MGH, patient and perioperative data were collected from MetaVision, AIMS, and the Research Patient Data Registry (RPDR), and discharge information from Enterprise Performance Systems Inc (EPSi). Patient data was strictly deidentified and subsequently combined into one dataset from which the study cohort was created.

#### *Instrumental Variable Analysis: 2-Stage Regression and Validity*

Practitioner variability in etomidate use may be harnessed in an instrumental variable analysis to assess the effect of etomidate. This practice variation can be exploited as a natural experiment in which patients are pseudo-randomized to different likelihoods of receiving etomidate based on the preferences of their anesthesiologist. The instrumental variable approach may allow a more unbiased estimate of etomidate's effect compared with more traditional risk-adjustment or propensity score methods. In stage 1, we built a linear regression model predicting receipt of etomidate by the instrument, which tests the strength of the proportion of etomidate use as an instrumental variable. The outcome of this model is observed etomidate use (yes/no) and the primary predictor is the proportion of etomidate use by the anesthesiologist (continuous), allowing for the generation of predicted probabilities of the likelihood of receiving etomidate. The Wald F statistic was calculated to assess the strength of the instrument to predict observed etomidate use with an F statistic  $> 10$  indicating a strong instrument. The effectiveness of the instrument for balancing clinical characteristics was assessed by comparing characteristics across quartiles of increasing physician etomidate use.

In stage 2, a linear regression model was created with in-hospital or 30-day mortality as the outcome. Using the predicted values from stage 1 as the primary predictor, instrumental-variable-based absolute risk differences for the primary outcome measures were obtained from the coefficient of the instrumental variable. For both stages of the model, patient, procedural, and anesthesiologist variables in Table 1 (excluding ejection fraction, intraoperative agents, and service type) and hospital site were used for adjustment.

The validity of an instrumental variable analysis depends on the fulfillment of several assumptions.<sup>1-3</sup> The first is that the instrument should strongly predict the exposure of interest. In this case, the assumption is that a higher percentage of patients treated by high etomidate users will have received etomidate and that a lower percentage of patients treated by low etomidate users will have received etomidate. The second assumption is that the instrumental variable will effectively pseudo-randomize the patients creating balance between measured and unmeasured covariates. An indirect test of this assumption is to compare measured characteristics between quartiles of anesthesiologist use of etomidate with balanced proportions suggesting adequate pseudorandomization. Finally, a third assumption is that the instrument affects the outcome only through its association with the exposure, an assumption felt to be fundamentally untestable.<sup>2,4</sup> It is possible that links between receipt of etomidate and the outcome outside of physician preference may exist due to the institution (use or nonuse of etomidate determined by institution, institutions as a whole having better or worse outcomes in noncardiac surgery) or due to anesthesiologist experience or subspecialty training affecting both treatment preference and outcomes. To address these possibilities, we adjusted for institution and anesthesiologist experience in both stages of the instrumental variable analysis.

**Supplemental Table 1: ICD-9-CM and -10-CM Code Criteria to Define Heart Failure**

Description	ICD-9-CM	ICD-10-CM
Rheumatic heart disease, unspecified	398.91	I09.9x
Hypertensive heart disease with heart failure	402.01, 402.11, 402.91	I11.0x
Hypertensive heart and chronic kidney disease with heart failure and stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease	404.01, 404.11, 404.91	I13.0x
Hypertensive heart and chronic kidney disease with heart failure and with stage 5 chronic kidney disease, or end stage renal disease	404.03, 404.13, 404.93	I13.2x
Ischemic cardiomyopathy	--	I25.5x
Dilated cardiomyopathy	--	I42.0x
Other restrictive cardiomyopathy	--	I42.5x
Alcoholic cardiomyopathy	425.5	I42.6x
Cardiomyopathy due to drug and external agent	--	I42.7x
Other cardiomyopathies	425.4	I42.8x
Nutritional and metabolic cardiomyopathy	425.7	
Cardiomyopathy, unspecified	425.9	I42.9x
Cardiomyopathy in diseases classified elsewhere	425.8	I43.x
Heart failure (LV/systolic/diastolic/combined/etc)	428.x	I50.x
Neonatal cardiac failure	--	P29.0x

**Supplemental Table 2: Medication Lists**

Medication group	Specific agents
Angiotensin converting enzyme inhibitors, angiotensin receptor blockers	benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, peridonpril, quinapril, ramipril, trandolapril; azilsartan, candesartan, eprosartan, irbesartan, telmisartan, valsartan, losartan, olmesartan
Hydralazine/nitrates	hydralazine, isosorbide mononitrate, isosorbide dintrate, hydralazine and isosorbide dinitrate
Aldosterone antagonists	spironolactone, eplerenone
Anticoagulants	warfarin, phenprocoumon, dabigatran, rivaroxaban, apixaban, edoxaban, betrixaban
Antiplatelets	acetylsalicylic acid, clopidogrel, ticagrelor, ticlodipine, prasugrel, dipyridamole, eptifibatide, cilostazol
Steroids	prednisone, prednisolone, methylprednisolone, hydrocortisone, dexamethasone, cortisone acetate, betamethasone, fludrocortisone

Steroids: at least 2 prescriptions in the 1 year prior to procedure. All other medication groups: prescription 30 days prior to procedure.

**Supplemental Table 3: Baseline Patient and Procedural Characteristics of Cases Stratified by Patients with Missing Values**

Descriptor	Data Available (N=19714)	Data Missing (N=2200)	Standardized Difference (%)
<b>Patient Characteristics</b>			
Age, years – mean (range)	67.5 (18-107)	68.2 (18-102)	4.8
Female sex – no. (%)	8745 (44.4)	956 (43.5)	-1.8
Hypertension – no. (%)	14792 (75.0)	1520 (69.1)	-13.2
Hyperlipidemia – no. (%)	11863 (60.2)	1119 (50.9)	-18.8
Diabetes – no. (%)	8182 (41.5)	802 (36.5)	-10.3
On insulin – no. (%)	4472 (22.7)	609 (27.7)	11.5
CAD – no. (%)	10282 (52.2)	1125 (51.1)	-2.2
Atrial Fibrillation – no. (%)	7789 (39.5)	998 (45.4)	12.0
PVD – no. (%)	3751 (19.0)	405 (18.4)	-1.5
Ischemic stroke – no. (%)	1446 (7.3)	259 (11.8)	15.4
COPD – no. (%)	4636 (23.5)	479 (21.8)	-4.1
CKD – no. (%)	6723 (34.1)	704 (32.0)	-4.5
CCI – median (IQR)	5 (3, 7)	4 (3,7)	-8.9
Smoking – no. (%)	4589 (23.3)	449 (20.4)	-7.0
Beta blocker – no. (%)	8193 (41.6)	1260 (57.3)	31.8
ACE inhibitor/ARB – no. (%)	7357 (37.3)	754 (34.3)	-6.3
Hydralazine/nitrates – no. (%)	2698 (13.7)	379 (17.2)	9.7
Aldosterone antagonists – no. (%)	1587 (8.1)	209 (9.5)	4.9
Digoxin – no. (%)	1498 (7.6)	248 (11.3)	12.7
Steroid use – no. (%)	3402 (17.3)	387 (17.6)	0.8
Antiplatelet use – no. (%)	8611 (43.7)	1011 (46.0)	4.6
Anticoagulant use – no. (%)	4802 (24.4)	635 (28.9)	10.2
Ejection fraction – mean (SD)	55.6 (15.0)	55.7 (16.5)	0.6
– no. (%)			
EF > 40%	7542 (38.3)	926 (42.1)	7.8
EF 20-40%	1602 (8.1)	208 (9.5)	4.9
EF < 20%	117 (0.60)	28 (1.3)	7.2
Missing	10,453 (53.0)	1038 (47.2)	-11.6
<b>Procedural characteristics</b>			
Intraoperative etomidate used – no. (%)	2821 (14.3)	322 (14.6)	0.9
<b>Intraoperative agent use – no. (%)</b>			
Etomidate only	1244 (6.3)	153 (7.0)	2.8
Propofol only	15539 (78.8)	1738 (79.0)	0.5
Ketamine only	30 (0.2)	5 (0.2)	0
Etomidate and propofol	1508 (7.6)	161 (7.3)	-1.1
Etomidate and ketamine	27 (0.1)	4 (0.2)	2.6
Propofol and ketamine	791 (4.0)	48 (2.2)	-10.4
All three	42 (0.2)	4 (0.2)	0
No agent	533 (2.7)	87 (4.0)	7.2
Propofol (total)	17880 (90.7)	1951 (88.7)	-6.6
Ketamine (total)	890 (4.5)	61 (2.8)	-9.1
Neuraxial anaesthesia – no. (%)	793 (4.0)	74 (3.4)	-3.2
Age adjusted MAC – mean (SD)	0.84 (0.35)	0.77 (0.34)	-20.3

Total fluid volume <sup>a</sup> – median (IQR)	1703 (900, 3000)	1250 (750, 2402)	-19.2
Estimated blood loss, mL – median (IQR)	0 (0, 50)	0 (0, 100)	2.9
Urine output, mL – median (IQR)	0 (0, 200)	0 (0, 300)	16.7
PRBC units – median (IQR)	0 (0, 0)	0 (0, 0)	4.2
Total vasopressors, mg norepinephrine equivalents <sup>b</sup> – median (IQR)	0.10 (0.01, 0.40)	0.12 (0.01, 0.44)	3.2
Service – no. (%)			
Orthopedic Surgery	3818 (19.4)	311 (14.1)	-14.2
Vascular Surgery	2449 (12.4)	263 (12.0)	-1.2
Thoracic Surgery	2186 (11.1)	189 (8.6)	-8.4
Urology	1560 (7.9)	120 (5.5)	-9.6
General Surgery	1378 (7.0)	147 (6.7)	-1.2
Anesthesiology	1233 (6.3)	317 (14.4)	26.8
Neurosurgery	1172 (6.0)	177 (8.1)	8.2
Transplant	1063 (5.4)	76 (3.5)	-9.2
Acute Care Surgery	991 (5.0)	181 (8.2)	12.9
Gynecology	490 (2.5)	31 (1.4)	-8.0
Surgical Oncology	437 (2.2)	21 (1.0)	-9.6
Plastic Surgery	336 (1.7)	30 (1.4)	-2.4
Radiology	241 (1.2)	58 (2.6)	10.3
ENT	207 (1.1)	12 (0.6)	-5.4
Colorectal	159 (0.8)	4 (0.2)	-8.5
Burn	134 (0.7)	29 (1.3)	6.0
Other	579 (2.9)	113 (5.1)	11.2
Missing	1281 (6.5)	121 (5.5)	-4.2

<sup>a</sup>Total fluid volume defined as the volumes of crystalloid plus one-and-a-half times colloid administered intraoperative exclusive of PRBCs. BMI, body mass index; ASA, American Society of Anesthesiologists; CAD, coronary artery disease; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CCI, Charlson Comorbidity Index; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; MAC, minimal alveolar concentration; PRBC, packed red blood cells; RVU, relative value unit of main procedure. All comorbidities are within 1 year of procedure date. All medications are prescriptions within 30 days of procedure except steroids (1 year prior).

<sup>b</sup>Vasopressors in milligrams norepinephrine equivalents = total amount epinephrine + total amount norepinephrine + (total amount phenylephrine / 10) + (total amount dopamine / weight in kilograms / 2).

**Supplemental Table 4: Anaesthesiologist Case Volume Stratified by Patients with Missing Values**

Descriptor	Data Available (N=294)	Data Missing (N=270)	Standardized Difference (%)
HF cases – median (IQR)	51 (23, 112)	57 (28, 117)	6.6
Total institutional cases – median (IQR)	908 (433, 2041)	945 (466, 2198)	4.8



**Supplemental Table 5: Sensitivity Analyses**

Outcomes	Adjusted Instrumental Variable Analysis <sup>a</sup>	
	RD (95% CI)	P value
<b>Primary Outcomes from Original Instrumental Variable Cohort (from Table 3) (N=19,714)</b>		
In-Hospital Mortality, %	-0.2 (-2.4 to 1.9)	0.83
30-day Mortality, %	0.2 (-2.5 to 2.9)	0.90
<b>Study Population Excluding Covariates with Missing Values<sup>b</sup> (N=21,914)</b>		
In-Hospital Mortality, %	0.8 (-1.4 to 2.9)	0.49
30-day Mortality, %	1.2 (-1.5 to 3.8)	0.39
<b>Original Instrumental Variable Cohort + EF (Categorical) (N=19,714)</b>		
In-Hospital Mortality, %	-0.3 (-2.4 to 1.9)	0.79
30-day Mortality, %	0.04 (-2.7 to 2.7)	0.98
<b>Ejection Fraction ≤ 40% (N=1719)</b>		
In-Hospital Mortality, %	0.9 (-5.6 to 7.4)	0.79
30-day Mortality, %	3.6 (-4.6 to 11.7)	0.39
<b>Systolic Heart Failure<sup>c</sup> + Beta Blocker + ACEi/ARB (N=2042)</b>		
In-Hospital Mortality, %	-2.0 (-7.4 to 3.4)	0.47
30-day Mortality, %	-2.8 (-9.8 to 4.1)	0.42
<b>Years 2012-2017 (N=10,271)</b>		
In-Hospital Mortality, %	1.9 (-2.5 to 6.4)	0.41
30-day Mortality, %	2.3 (-3.1 to 7.8)	0.40

<sup>a</sup>Adjusted instrumental variable model includes hospital site and all covariates in Table 1 except ejection fraction, intraoperative agents, estimated blood loss, urine output, vasopressors, and service type.

<sup>b</sup>Covariates included body mass index, emergent status, admission type, duration of surgery, work relative value units, and American Society of Anesthesiologists status. <sup>c</sup>ICD-9 428.2x (systolic heart failure) and 428.4x (combined systolic/diastolic heart failure) and ICD-10: I50.2x (systolic heart failure) and I50.4x (combined systolic/diastolic heart failure). CI, confidence interval; RD, risk difference; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

**Supplemental Table 6: Baseline Patient and Procedural Characteristics of Cases Stratified by Patients with Available and Missing EF values**

Descriptor	EF Data Available (N=9261)	EF Data Missing (N=10453)	Standardized Difference (%)
<b>Patient Characteristics</b>			
Age, years – mean ± SD	66.4 (18-104)	68.4 (18-107)	14.2
BMI, kg m <sup>-2</sup> – mean (SD)	29.2 (7.8)	29.8 (7.8)	7.7
Female sex – no. (%)	3991 (43.1)	4754 (45.5)	4.8
ASA status – median (IQR)	3 (3,3)	3 (3,3)	-10.3
Hypertension – no. (%)	7204 (77.8)	7588 (72.6)	-12.1
Hyperlipidemia – no. (%)	5744 (62.0)	6119 (58.5)	-7.2
Diabetes – no. (%)	3789 (40.9)	4393 (42.0)	2.2
On insulin – no. (%)	2613 (28.2)	1859 (17.8)	-24.9
CAD – no. (%)	5173 (55.9)	5109 (48.9)	-14.1
Atrial Fibrillation – no. (%)	3908 (42.2)	3881 (37.1)	-10.4
PVD – no. (%)	1857 (20.1)	1894 (18.1)	-5.1
Ischemic stroke – no. (%)	969 (10.5)	477 (4.6)	-22.5
COPD – no. (%)	2209 (23.9)	2427 (23.2)	-1.7
CKD – no. (%)	3417 (36.9)	3306 (31.6)	-11.2
CCI – median (IQR)	5 (3,8)	4 (3,7)	-23.4
Smoking – no. (%)	2262 (24.4)	2327 (22.3)	-5.0
Beta blocker – no. (%)	4325 (46.7)	3868 (37.0)	-19.8
ACE inhibitor/ARB – no. (%)	3850 (41.6)	3507 (33.6)	-16.6
Hydralazine/nitrates – no. (%)	1632 (17.6)	1066 (10.2)	-21.5
Aldosterone antagonists – no. (%)	928 (10.0)	659 (6.3)	-13.6
Digoxin – no. (%)	910 (9.8)	588 (5.6)	-15.8
Steroid use – no. (%)	2163 (23.4)	1239 (11.9)	-30.5
Antiplatelet use – no. (%)	4801 (51.8)	3810 (36.5)	-31.2
Anticoagulant use – no. (%)	2672 (28.9)	2130 (20.4)	-19.8
<b>Procedural characteristics</b>			
Intraoperative etomidate used – no. (%)	1321 (14.3)	1500 (14.4)	0.3
<b>Intraoperative agent use – no. (%)</b>			
Etomidate only	586 (6.3)	658 (6.3)	0
Propofol only	7312 (79.0)	8227 (78.7)	-0.7
Ketamine only	15 (0.2)	15 (0.1)	-2.6
Etomidate and propofol	709 (7.7)	799 (7.6)	-0.4
Etomidate and ketamine	9 (0.1)	18 (0.2)	2.6
Propofol and ketamine	358 (3.9)	433 (4.1)	1.0
All three	17 (0.2)	25 (0.2)	0
No agent	255 (2.8)	278 (2.7)	-0.6
Propofol (total)	8396 (90.7)	9484 (90.7)	0
Ketamine (total)	399 (4.3)	491 (4.7)	1.9
Emergency status – no. (%)	713 (7.7)	951 (9.1)	5.1
<b>Admission type – no. (%)</b>			
Ambulatory	1193 (12.9)	1619 (15.5)	7.5
Same day Admit	3657 (39.5)	5203 (49.8)	20.8
Inpatient	4411 (47.6)	3631 (34.7)	-26.4
Neuraxial anaesthesia – no. (%)	375 (4.1)	418 (4.0)	-0.5
Age adjusted MAC – mean (SD)	0.81 (0.34)	0.85 (0.35)	11.6

Total fluid volume <sup>a</sup> – median (IQR)	1500 (750,2700)	1800 (1000, 3067)	13.8
Estimated blood loss, mL – median (IQR)	0 (0,50)	0 (0,50)	2.2
Urine output, mL – median (IQR)	0 (0, 200)	0 (0, 165)	-5.4
PRBC units – mean (SD)	0.17 (0.81)	0.19 (0.81)	-2.5
Total vasopressors, mg norepinephrine equivalents <sup>b</sup> – median (IQR)	0.11 (0.01, 0.42)	0.09 (0.01, 0.39)	0
Duration of surgery, min – mean (SD)	166.4 (110.5)	169.1 (110.3)	2.5
Work RVU – median (IQR)	13.5 (7.2, 20.1)	15.3 (7.8,21.8)	9.3
Service – no. (%)			
Orthopedic Surgery	1527 (16.5)	2291 (21.9)	13.7
Vascular Surgery	1089 (11.8)	1360 (13.0)	3.6
Thoracic Surgery	1074 (11.6)	1112 (10.6)	-3.2
Urology	669 (7.2)	891 (8.5)	4.8
General Surgery	722 (7.8)	656 (6.3)	-5.9
Anesthesiology	758 (8.2)	475 (4.5)	-15.2
Neurosurgery	529 (5.7)	643 (6.2)	2.1
Transplant	545 (5.9)	518 (5.0)	-4.0
Acute Care Surgery	561 (6.1)	430 (4.1)	-9.1
Gynecology	197 (2.1)	293 (2.8)	4.5
Surgical Oncology	202 (2.2)	235 (2.3)	0.7
Plastic Surgery	152 (1.6)	184 (1.8)	1.6
Radiology	155 (1.7)	86 (0.8)	-8.1
ENT	80 (0.9)	127 (1.2)	2.9
Colorectal	66 (0.7)	93 (0.9)	2.3
Burn	68 (0.7)	66 (0.6)	-1.2
Other	312 (3.4)	267 (2.6)	-4.7
Missing	555 (6.0)	726 (7.0)	4.1

<sup>a</sup>Total fluid volume defined as the volumes of crystalloid plus one-and-a-half times colloid administered intraoperative exclusive of PRBCs. BMI, body mass index; ASA, American Society of Anesthesiologists; CAD, coronary artery disease; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CCI, Charlson Comorbidity Index; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; MAC, minimal alveolar concentration; PRBC, packed red blood cells; RVU, relative value unit of main procedure. All comorbidities are within 1 year of procedure date. All medications are prescriptions within 30 days of procedure except steroids (1 year prior).

<sup>b</sup>Vasopressors in milligrams norepinephrine equivalents = total amount epinephrine + total amount norepinephrine + (total amount phenylephrine / 10) + (total amount dopamine / weight in kilograms / 2).

**Supplemental Table 7: Anaesthesiologist Case Volume Stratified by Patients with Available and Missing EF values**

Descriptor	EF Data Available (N=141)	EF Data Missing (N=153)	Standardized Difference (%)
HF cases – median (IQR)	59 (27, 119)	47 (21, 88)	-25.2
Total institutional cases – median (IQR)	942 (483, 2346)	857 (385, 1721)	-7.7

**Supplemental Table 8: Anaesthesiologist Preference for Etomidate Use Over Time**

Years	2007-09 N=168	2010-11 N=172	2012-13 N=203	2014-15 N=210
Heart Failure Cases – no.	4927	3767	4169	4526
Preference for etomidate - %				
Median (IQR)	13.3 (6.2, 26.7)	10.7 (4.7, 20.0)	8.1 (4.1, 16.3)	8.0 (3.8, 15.5)
Range	0-66.7	0-55.8	0-55.8	0-50.0

**Supplemental Table 9: Anaesthesiologist Case Volume Stratified by Etomidate Use**

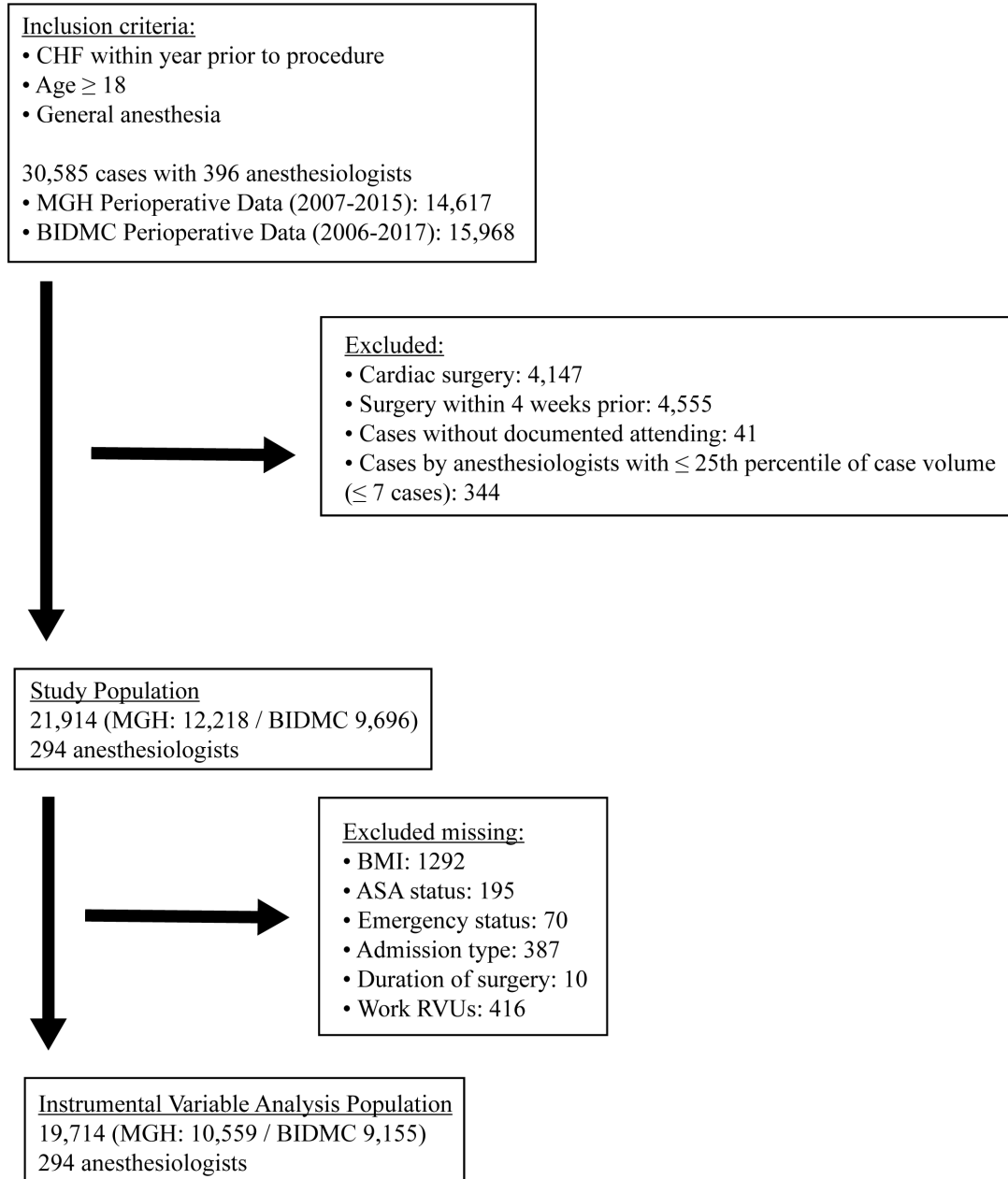
Descriptor	Total (N=294)	Etomidate Never Used in HF cases (N=46)	Etomidate Used in ≥1 HF Case (N=248)	Standardized Difference (%)
HF cases – median (IQR) (from Table 2)	51 (23, 112)	21 (12, 36)	61 (29, 119)	94.2
Total institutional cases – median (IQR)	908 (433, 2041)	395 (189, 700)	1034 (556, 2335)	92.9

**Supplemental Table 10: Anaesthesiologist Case Volume Stratified by Groups of Increasing Anaesthesiologist Etomidate Use**

Descriptor	Etomidate Use by Anaesthesiologist (%)			
	Quartile 1 0 to 4.7 (N=86)	Quartile 2 > 4.7 to 11.1 (N=80)	Quartile 3 > 11.1 to 20.4 (N=68)	Quartile 4 >20.4 to 66.7 (N=60)
HF cases – median (IQR) (from Table 4)	36 (19, 69)	51 (22,92)	66 (25, 132)	64 (35, 126)
Total institutional cases – median (IQR)	685 (350, 1156)	875 (423, 1845)	868 (382, 2689)	1480 (896, 3122)

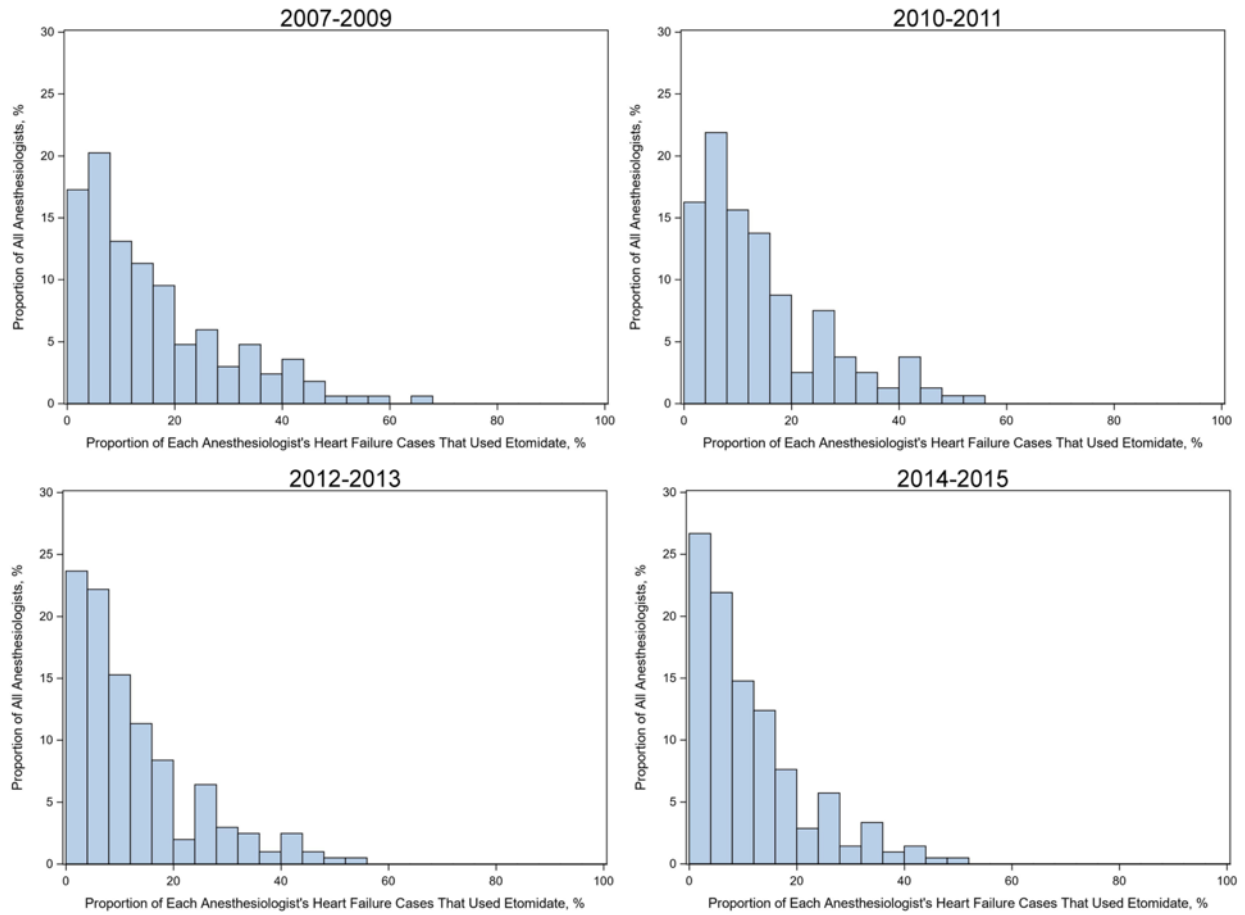
**Supplemental Figure 1: Consort Diagram of Patient Selection for the Primary Analysis.**

Flow chart depicting inclusion and exclusion criteria. HF, heart failure; MGH, Massachusetts General Hospital; BIDMC, Beth Israel Deaconess Medical Center; BMI, body mass index; ASA, American Society of Anesthesiologists; RVU, relative value units.





**Supplemental Figure 2: Anaesthesiologist Use of Etomidate with Heart Failure Patients in Noncardiac Cases from 2007-2015.** Proportion of noncardiac cases among individual attending anaesthesiologists in which etomidate was used over time.



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