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TITLE PAGE

Title: Variation in Propofol Induction Doses Administered to Surgical Patients over Age 65.

Short Running Title: Prevalent Propofol Induction dosing in the Elderly

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Funding:

This work was supported in part by grant R01AG059607 from the National Institute on Aging and CTSA Grant UL1 RR024139 from the National Center for Advancing Translational Sciences (NCATS). The content is solely the responsibility of the authors and does not necessarily represent the policy or views of the NIH, NIA, NCATS, or the United States Government.

Support for underlying electronic health record data collection was provided, in part, by Blue Cross and Blue Shield of Michigan (BCBSM) and Blue Care Network as part of the BCBSM Value Partnerships program for contributing hospitals in the State of Michigan. Although Blue Cross Blue Shield of Michigan and the Multicenter Perioperative Outcomes Group work collaboratively, the opinions, beliefs, and viewpoints expressed by the authors do not necessarily reflect the opinions, beliefs, and viewpoints of BCBSM or any of its employees.

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Abstract Word Count: 260

Main Text Word Count: 3589

Number of Tables: 2

Number of Figures: 3

KEY POINTS:

1) In a nationwide sample of propofol induction dosing practices for patients over age 65 undergoing general anesthesia, almost two-thirds of administered doses were discordant with published typical dose requirements for this age group.
2) Variation in prevalent propofol induction dosing across institutions is not explained solely by differences in patient populations.
3) The range of propofol induction doses commonly used in modern anesthetic practice is broad and is not fully explained by demographic and comorbidity variables available in the present dataset. Future investigations should endeavor to understand the nature of these highly variable dosing decisions and how such dosing may relate to important clinical outcomes.

WHY DOES THIS PAPER MATTER:

This multicenter investigation demonstrates discordance between clinical practices and the expected typical dose range for propofol induction in older adults. It is a key step in the ongoing effort to identify opportunities to improve anesthetic care of older adults.

ABSTRACT

Background/Objectives: Advanced age is associated with increased susceptibility to acute adverse effects of propofol. The present study aimed to describe patterns of propofol dosing for induction of general anesthesia prior to endotracheal intubation in a nationwide sample of older adults presenting for surgery.

Design: Retrospective observational study using the Multicenter Perioperative Outcomes Group dataset.

Setting: 36 institutions across the United States.

Participants: 350,766 patients over age 65 who received propofol for general anesthetic induction and endotracheal intubation between 2014 and 2018.

Intervention: None

Measurements: Total induction bolus dose of propofol administered.

Results: The mean (SD) weight-adjusted propofol dose was 1.7 (0.6) mg/kg. The mean prevalent propofol induction dose exceeded the upper bound of what has been described as the typical geriatric dose requirement across every age category examined. The percent of patients receiving propofol induction doses above the described typical geriatric range was 64.8% (95% CI 64.6-65.0), varying from 73.8% among patients age 65-69 to 45.8% among patients age 80 or over.

Conclusion. The present study of a large multicenter cohort demonstrates that prevalent propofol dosing commonly falls above the published typically required dose range for patients age ≥ 65 in nationwide anesthetic practice. Widespread variability in induction dose administration remains incompletely explained by known patient variables. The nature and clinical consequences of these unexplained dosing decisions remain important topics for further study. Observed discordance between expected and actual induction dosing raises the question of whether there should be reconsideration of widespread provider practice, or alternatively, whether what is published as the typical propofol induction dose range should be revisited.

KEY WORDS: Propofol, Anesthetic Induction, Geriatric Dosing

TEXT

Introduction:

The US population is aging, with over 16.5% of Americans now over age 65.(1) Older patients account for approximately 40% of the surgical procedures performed each year.(2) Older patients undergoing surgical procedures often have age-related medical conditions and frailty(3-6) which increase risks of adverse outcomes.(7, 8) In addition to the greater medical morbidity that accompanies aging,(9, 10) physiologic changes in metabolism and end-organ function that accompany aging increase the effective potency of anesthetic agents. Propofol sensitivity is increased by approximately 30% to 50% in the elderly compared with younger patients.(11) Even among relatively healthy elderly patients treated under controlled, experimental conditions, advanced age is associated with substantially increased susceptibility to acute adverse effects of propofol.(12)

In recognition of the adverse consequences of advanced age on anesthetic potency, the FDA-approved package insert for propofol recommends adjusting the general anesthesia induction dose among patients > 55 years of age to 1-1.5mg/kg as opposed to the 2-2.5mg/kg recommendation for patients under 55 years of age. Consistent with this recommendation, among generally healthy 60-75 years of age who presented for elective outpatient surgery, EEG-guided general anesthetic states sufficient for endotracheal intubation were reliably induced following a mean propofol dose of 1.27mg/kg.(13) Despite product label guidance and empirical evidence regarding typical dose requirements for geriatric populations, small, single center cohort studies (14-16) suggest that prevalent dosing frequently exceeds the expected typical dose range.

Other studies have documented elevated dosing of inhalation agents for older adults during the maintenance period of anesthetics relative to what literature would seem to recommend.(17, 18) Beyond these single-center reports, large, population-based studies of prevalent propofol induction dosing practices for geriatric surgical patients have not been described.

It is well-recognized that doses required by individual patients, or even by the same patient, may vary based on a variety of context-specific factors. Thus, an analysis of actual propofol induction dosing practice among older adults - and how such practice relates to what is deemed by approved labelling to be the typically required range - may generate questions regarding whether current labelling or current practice patterns may be in need of further investigation.

Using a sample of adults ≥ age 65 derived from the Multicenter Perioperative Outcomes Group (MPOG), we describe population-based patterns and predictors of propofol induction dosing practices for geriatric surgical patients. MPOG is a consortium of over 50 academic and community hospitals dedicated to sharing data for quality improvement and research in anesthesiology.(19-21)

Our objective was to describe prevalent propofol induction dosing patterns. Our primary inferential hypothesis was that prevalent Propofol induction dosing among patients ≥ age 65 would exceed the described typical dose range in more than 30% of cases, consistent with prior observational data. Specific analyses sought to a) delineate patterns of weight-adjusted propofol induction dose by age and severity of illness; b) examine predictors of and variation in prevalent propofol dose across patient,

institutional, and surgical factors; and c) examine the extent of discontinuous propofol induction dosing at 50 mg increments.

Methods:

This was a retrospective observational study conducted under an approved IRB protocol in collaboration with the Multicenter Perioperative Outcomes Group (MPOG).(22, 23) MPOG is a consortium of over 50 hospitals that maintains a dataset of electronic health record and administrative data from contributing sites across twenty-one states and two countries. The MPOG data collection methods have been previously described (see www.mpog.org).(19, 20) Briefly, MPOG contributing sites conduct automated extraction of perioperative data including patient and procedural characteristics, anesthetic medications, physiologic parameters, and key surgical events.

Contributing sites conduct monthly case-by-case validation of a random sample of submitted data by subject-matter experts. The MPOG Perioperative Clinical Research Committee approved the use of data for this project, and the analytic plan for the present analyses was publicly registered on the website of the Open Science Framework with modifications as noted in the manuscript. The study was conducted in accordance with the Reporting of studies Conducted using Observational Routinely – collected health Data (RECORD) statement, an extension of the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines.(24, 25)

Surgical cases of patients ≥65 years of age who underwent induction of general anesthesia including propofol bolus dosing prior to endotracheal intubation between

January 2014 and December 2018 were identified. Only data from centers with consistent data uploads and case validation were included. For patients who underwent multiple anesthetics in the study period, only the index case was included.

Patients were excluded if they were designated as American Society of Anesthesiologists Physical Status (ASA PS) 5 or 6,(26, 27) indicating a moribund or brain-dead patient, respectively. Cases were excluded if the patient a) arrived to the operating room already intubated or b) presented with hemodynamic derangements including severe hypertension or hypotension. Hypertensive patients were excluded for Mean Arterial Pressure (MAP) > 135mmHg or Diastolic Blood Pressure >110mmHg. Hypotensive patients were excluded for MAP < 55mmHg or Systolic Blood Pressure < 90mmHg. Patients receiving anesthetics for minor procedures as determined by the base unit value of anesthesia billing less than or equal to 3 were excluded. Patients who did not undergo endotracheal intubation were excluded. Finally, patients with missing or outlier propofol induction dosing or with other missing or outlier variables were excluded by investigator consensus.

For the selected sample, extracted data were comprised of demographic variables (age, sex, race/ethnicity, anonymized institution ID, and year of surgery); and patient-level clinical characteristics (weight, height, Body-Mass Index categorized into World Health Organization obesity classifications,(28) ASA Physical Status, preoperative mean arterial pressure, the presence of Coronary Artery Disease, and Elixhauser comorbidity status(29)). Data sources for patient and surgical characteristics relied on MPOG-validated, publicly available perioperative electronic health record (EHR) phenotype algorithms.(30) Elixhauser comorbidities were combined into a single comorbidity index

based on the van Walraven modification of the Elixhauser classifications.(31) The van Walraven-Elixhauser comorbidity score is a weighted index created from among 30 comorbid conditions that has been demonstrated to independently predict hospital mortality with superior discrimination in comparison to the Charlson Comorbidity Index.(32) Administrative codes were also queried to calculate an index of the likelihood of frailty.(4)

Where laboratory data were available, preoperative albumin level, preoperative hemoglobin levels, and estimated Glomerular Filtration Rate (eGFR) were included. eGFR was calculated using CKD-Epi(33) or using the Cockcroft-Gault formula(34) if race was missing.(35) The eGFR was coded into Chronic Kidney Disease stages in accordance with prior literature.(36)

Surgeries were classified by the specialty of the primary proceduralist and the presence or absence of an emergency modifier in the ASA Physical Status classification. Institutions were classified as academic vs. community based on the presence of an affiliation with a medical school. Classifications of providers within institutions (e.g. solo anesthesiologist, supervised nurse, or supervised resident) were highly imbalanced across institutions and thus were not considered for analysis.

Intraoperative records were queried to calculate the total bolus intravenous anesthetic doses delivered within 15 minutes of induction but ending at surgical incision. In addition to propofol, intravenous anesthetics recorded for the analysis included midazolam, fentanyl, etomidate, ketamine, methohexital, and thiopental. If neuraxial anesthetics (i.e. epidural or spinal anesthetics) were administered concomitantly, this was recorded as a categorical variable. As the present manuscript was aimed at delineating contemporary

propofol induction dosing practices, post-induction intraoperative data were not examined.

Statistical Analysis:

Following delineation of the cohort, descriptive statistics (means, standard deviations, medians, interquartile ranges, and frequencies) were computed as relevant.

Cleaning of data: In addition to contributing-site data validation, study-specific data were examined for outlier values which were considered in relation to clinical plausibility with cut-points derived by agreement among investigators. Missingness was examined for each variable. In accordance with the *a priori* plan, albumin level demonstrated greater than 40% missingness and was removed from consideration.

Propofol induction dose by age and ASA Physical Status

After initial assessment of data quality and distributions, propofol induction dosing was summarized in relation to what the FDA-approved package insert describes as the typical dosing range across 4 age subgroups (65-69 years, 70-74 years, 75-79 years, and ≥80 years), and within 4 categories of comorbidity status (ASA Physical Status 1, 2, 3, and 4) for a total of 16 age by severity of illness sub-categories. Within each sub-category, mean, SD of propofol dose, and percent dose in excess of the described typical dosing range (i.e. >1.5mg/kg) were calculated.

Independent Predictors of Propofol induction dose

To determine predictors of propofol induction dose and derive the adjusted rates of doses in excess of the package insert's listed typical dose requirement, we fit suitable hierarchical logistic regression models that accounted for the clustering of the data

within institutions to: 1) identify covariates (fixed effects) including patient, institutional, and surgical characteristics that were significantly associated with excess prevalent dose; 2) predict the random effects of institutions after adjusting for significant covariates; and 3) estimate the standardized institution rates of prevalent dosing in excess of the typically described requirement for institution-level comparisons.

In response to reviewer requests in the context of the peer review process, we further conducted a hierarchical linear regression model in which the outcome of propofol dose was maintained as a continuous variable without reference to the FDA-approved package insert so as to understand factors associated with actual propofol induction dose across the range of prevalent dosing behaviors and in units of total milligrams to enhance clinical interpretability for practitioners.

In these multivariable models, we evaluated effect modification by age sub-groups and ASA Physical Status to investigate whether combinations of age and comorbidity affected providers' choice of propofol induction dose. Before regression models were constructed, the continuous explanatory variables under consideration for model inclusion were assessed for collinearity using the variance inflation factor with a threshold of 10 suggestive of substantial collinearity. All analyses were performed using the SAS statistical software, version 9.4 (Cary, NC). Within SAS, we fitted hierarchical models using the PROC GLIMMIX procedure. All statistical tests' p-values and confidence intervals were two-sided with a significance level for the primary outcome of 0.05.

Institution specific Propofol dosing Rates in excess of FDA's typical range:

For institution effects, we compared predicted non-adherence rates (i.e. institution-specific or predicted) using both random institution effect and the fixed effect regression estimates to the fixed effects only (population-average or expected) rates. The intra-institution comparison of the two rates was used as a measure of institution performance in rates of incremental dosing in excess of the published typical range.(37, 38)

Discontinuous Propofol Dosing at 50mg Increments

We examined non-weight-adjusted anchoring effects in propofol dosing by measuring the tendency for induction doses to cluster at 50 mg increments (i.e. 50, 100, 150, 200, 250, and 300 mg). The percent of total doses occurring at each of these 50mg increments was reported.

Sample size considerations: For the primary analysis estimating the prevalence of dosing in excess of the described typical dose range, a hypothetical subset of 10,000 cases with actual incremental dosing rates of 30% would produce a two-sided 95% CI of 29.1-30.9%. For such a hypothetical subset, power would exceed 99% to detect a hypothetical difference of 2% between observed dose-range-adherence and the 30% *a priori* benchmark, assuming an alpha of 0.05.

Results:

Over 2.1 million patients aged ≥65 underwent anesthetics during the observation period. After exclusions, a final sample of 350,766 patients from 36 institutions were included in the present analyses (see consort diagram Figure 1). The mean (SD) age was 73 (6.4),

with 16.8% of the cohort over age 80, 49.6% female, and 81.3% identified as white. Ethnic identification was poorly penetrant, with only 1.4% of the cohort identified as Hispanic. Characteristics of the included cohort are provided in Table 1. Due to non-random and significant missingness of preoperative laboratory data, only patients with complete data regarding hemoglobin and estimated GFR were included in multivariable models.

Propofol induction dose by age and ASA Physical Status

The percent of patients receiving propofol induction doses in excess of the typically described range was 64.8% (95% CI 64.6-65.0), with the mean (SD) weight-adjusted propofol dose being 1.7 (0.6) mg/kg. As shown in Figure 2, mean propofol dose exceeded the expected typical range across every age by ASA PS score classification except for patients with ASA Physical Status 4. Within ASA PS 4, the proportion of patients that received propofol induction doses in excess of the typical range across the four age bins ranged from 43.1% in those age 65-69 years to 26.9% in those age 80 years or older. Propofol induction doses by age and ASA PS Score are summarized in Figure 2 (see also histograms of weight-adjusted dose distributions displayed in Supplemental Figure S1 and summaries as listed in Supplemental Table S2).

Independent predictors of propofol dose:

In multivariable modelling, the prevalence of propofol induction dose in excess of the typically described range increased from 2014 through 2018. Such doses were more likely in males and patients identifying as Hispanic. In prior literature, it has been suggested that black vs. white race may be implicated in differing clinical responses to propofol infusions,(39) but we observed no significant differences in prevalent dosing

above the typical range associated with black vs. white race. Increasing age and increasing obesity were negatively associated with exceeding the described range as was the use of adjunctive sedative medications. Doses exceeding the described range were less likely in sicker patients based on ASA Physical Status, coronary artery disease, van Walraven comorbidity index, chronic kidney disease, and lower preoperative hemoglobin levels. While providers thus appeared to decrease induction dose for both older age and higher ASA PS score independently, the multiplicative interaction terms of these factors were not significant except for the interaction of age 80 or older with ASA Physical Status score of 4. The full multivariable results are listed in Tables 2 and Supplemental Table S3.

Regarding absolute propofol doses, factors associated with a mean decrease of at least 10mg of propofol at induction included being over age 75, ASA Physical Status 4, and presenting for Cardiothoracic, Vascular, or GI procedures.

Of note, while the propofol package insert suggests the slow administration of multiple doses of propofol over the course of a geriatric general anesthetic induction, the large majority (282,502 or 81%) of the 350,766 included cases in our cohort showed recorded induction doses charted as a single bolus dose, a finding that should be interpreted cautiously since closely-timed doses may be recorded as one administration. Patients charted as receiving a single bolus dose vs. multiple doses were similar in respect to age (mean 72.9 vs 73.3 years; median age of both groups = 72 years).

Institution-specific Rates of Dosing in excess of FDA's typical range:

In unadjusted analysis, significant variations in care patterns were demonstrated, with incremental dose rates ranging from 38% to 82% across centers, a difference that cannot be explained solely by differences in the distributions of ASA Physical Status scores or of age (See Figure 3). After adjusting for case-mix and patient characteristics, we observed 4 institutions with random effects predicted incremental dose rates that differed by more than 1% of their fixed effects or population averaged estimates. For these outlying institutions, the actual versus expected rate of incremental dose rates in excess of FDA's typical range varied from a high of 106% to a low of 92% of predicted.

Propofol Dose Discontinuity at 50mg Increments

Total induction doses of propofol demonstrated anchoring at 50mg increments in 60.9% of cases, with more than 1 in 5 doses equaling 150mg. A histogram of all propofol doses by 10mg increments is included, demonstrating multi-modal anchoring across the breadth of the distribution (see Supplemental Figure S4).

Discussion:

This is the first multicenter study to examine propofol dosing practices in relation to the medication label's typical dose range for older patients undergoing surgical procedures in the US, and the present analysis confirms our primary hypothesis that there is widespread discordance between current geriatric anesthetic practice in the United States and the package label's description of the typical dose range. Observed doses exceeded the typical dose range by a mean of 13% overall, and significant numbers of patients received higher than expected induction doses regardless of age and comorbidity. Remarkably, over one quarter of the sickest and oldest patients in our

sample (i.e. ASA PS 4 patients ≥ 80 years of age) received propofol exposures at induction that would be considered above the typical expected dose requirement for a cohort of healthy patients 25 years younger. While it remains unknown what threshold of propofol induction dosing outside of typical ranges may lead to untoward downstream effects, the discordance between what the package-insert states to be “typical” and the prevalent anesthetic induction dosing practice that we have documented raises the question as to whether the FDA-approved label or the prevalent practice pattern is in need of revision.

Regarding institution-specific behaviors, while we saw variation across institutions in unadjusted proportions of patients receiving incremental doses beyond the typical range, those differences were less apparent in adjusted analyses that accounted for differences in patient mix and procedure type. Still, institutional differences of greater than 1% observed over expected incremental dosing do persist in some centers and appear to be robust within the limits of our adjusted modeling. These results should be interpreted cautiously as they were not the primary inferential hypothesis of the study and should be understood as hypothesis generating rather than definitive evidence of care disparities across institutions.

Regarding dose anchoring, our descriptive analysis demonstrates significant discontinuities in the choice of administered induction dose at intervals of 50mg. More than half of all patients received either 100mg, 150mg, or 200mg of propofol. We conjecture that such anchoring is likely to exacerbate connections between patient weight and rate of dosing in excess of the typical range. For example, a 150mg induction dose discontinuously becomes an incremental dose above typical range for

patients weighing less than 100kg but remains concordant within the FDA described range for heavier patients. It may thus prove important to account for this multi-modal, irregular distribution in the design of future outcomes studies that seek to elucidate effects of propofol dosing patterns on important patient outcomes.

Limitations:

Several limitations of the present analysis should be noted. First, our conclusions are based on documented medication dosing that may contain inaccuracies in relation to actual practice. In our cohort, a minority (19%) of cases were noted to have more than one bolus induction dose of propofol, but some induction doses that were slowly titrated may have been added together during the process of clinical documentation. While it is certainly the case that some providers engage in careful titration of induction doses, based on our present data and our own clinical experience, such titration is far from routine. While similar observational studies are subject to recording accuracy, MPOG data collection standards include a robust multicenter validation schema, incorporating case-by-case monthly validations at each participating center, and these data have been used in a variety of high quality observational studies.(40, 41)

Another possible limitation of our analysis may stem from our selection of four coarsened categories for age in our assessments of incremental dosing prevalence. While it is possible there could be a loss of information by grouping ages into sub-categories, categorizing age should allow for detecting trends, can be useful for identifying thresholds across age, and allows one to model non-linearities between age and incremental dose. While we were cognizant of the hazards of binning ages into sub-categories, we chose this method of displaying data so as to improve interpretability of

the data as they relate to age and comorbid status and thereby to promote a better understanding of the interactions among these two factors.

It is also important to note that the typical dose range, as described on the package label, does not include a description of the shape of the typical dose range curve. Nevertheless, regardless of the distribution's shape, it remains inconsistent with what our analysis shows to be the prevalent induction dosing used in clinical practice. Well less than 50% of geriatric patients are receiving an induction dose in the listed "typical" range, and this observation demonstrates a remarkable discordance that remains to be understood in future work.

Another issue to be highlighted is that while we included non-propofol sedatives in our modeling, it is not clear how to interpret their concomitant dosing in relation to an expected propofol dose range. Patients receiving concomitant sedative medications were less likely to receive propofol doses above the listed typically expected range, suggesting that practitioners anticipate desired clinical endpoints to drive dose adjustment.

Finally, the clinical relevance of our observation regarding induction dosing for patient-centered outcomes remains unclear. It would be overly simplistic to extrapolate that older patients are being "overdosed." Future studies of appropriately matched patients with outcomes data are required to understand the potential for and extent of any differences in relevant clinical course that may be attributable to the propofol induction dosage patterns described here. The effort to define clinical phenotypes that may define varying degrees of patient resilience to anesthetic induction dosing practices remains an

area of great importance, with opportunities for future collaboration among geriatricians and anesthesiologists.

In conclusion, the present study provides the broadest and most thorough documentation to date of the widespread use of propofol in excess of the published typical dose range during the conduct of modern general anesthetic induction of elderly surgical patients. The potential significance of this discordance on patient outcomes - both in general and within particularly vulnerable subsets of the elderly – deserves dedicated study. At present, it remains unclear whether a change in drug labels or a change in prevalent anesthetic induction dosing practice may be warranted.

Acknowledgements:

The authors wish to acknowledge the invaluable contributions of Michelle Romanowski for her technical expertise in developing and modifying database queries.

The authors also acknowledge the valuable contribution to protocol development, data acquisition and final article review by Multicenter Perioperative Outcomes Group Perioperative Clinical Research Committee collaborators, including:

Michael F. Aziz, MD; Department of Anesthesiology & Perioperative Medicine, Oregon Health & Science University; Portland, Oregon

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Conflicts of Interest:

Dr. Schonberger reports owning stock in Johnson & Johnson. Dr. Schonberger reports that his institution receives research funding from Merck, Inc. on a project with which he is associated.

Dr. Shah reports that his institution receives grants from Blue Cross Blue Shield Michigan, grants from Apple Inc, grants from Edwards Lifesciences, grants from Merck Inc, and grants from the American Heart Association for work with which he is associated.

Dr. Mathis reports grants from National Institute of Health - NHLBI (K01-HL141701), outside the submitted work.

Author Contributions:

All authors have reviewed and approve of the final manuscript submission.

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Amit Bardia: concept and design, data analysis, interpretation of data, and preparation of manuscript.

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Nirav Shah: concept and design, data analysis, interpretation of data, and preparation of manuscript.

Sponsors' Role: The sponsors had no role in the design, methods, subject recruitment, data collections, analysis and preparation of the paper.

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FIGURE LEGENDS:

Figure 1: Consort Diagram of Inclusion and Exclusion Criteria

Figure 2: Boxplots of Propofol Dose by Age and ASA Physical Status. Diamonds show the mean and shaded boxes show the 25-75% range with whiskers at 1.5 times the upper and lower bounds. The horizontal dotted line demonstrates the upper limit of the package insert's listed typical dosing requirement.

Figure 3: Percent of patients receiving Propofol Incremental Induction Dose Above 1.5 mg/kg by Institution is Shown on the Y-axis at left. Shading shows distribution of ASA Physical Status by Institution. Red Dots Demonstrate Mean Age by Institution on the Y-axis at right.

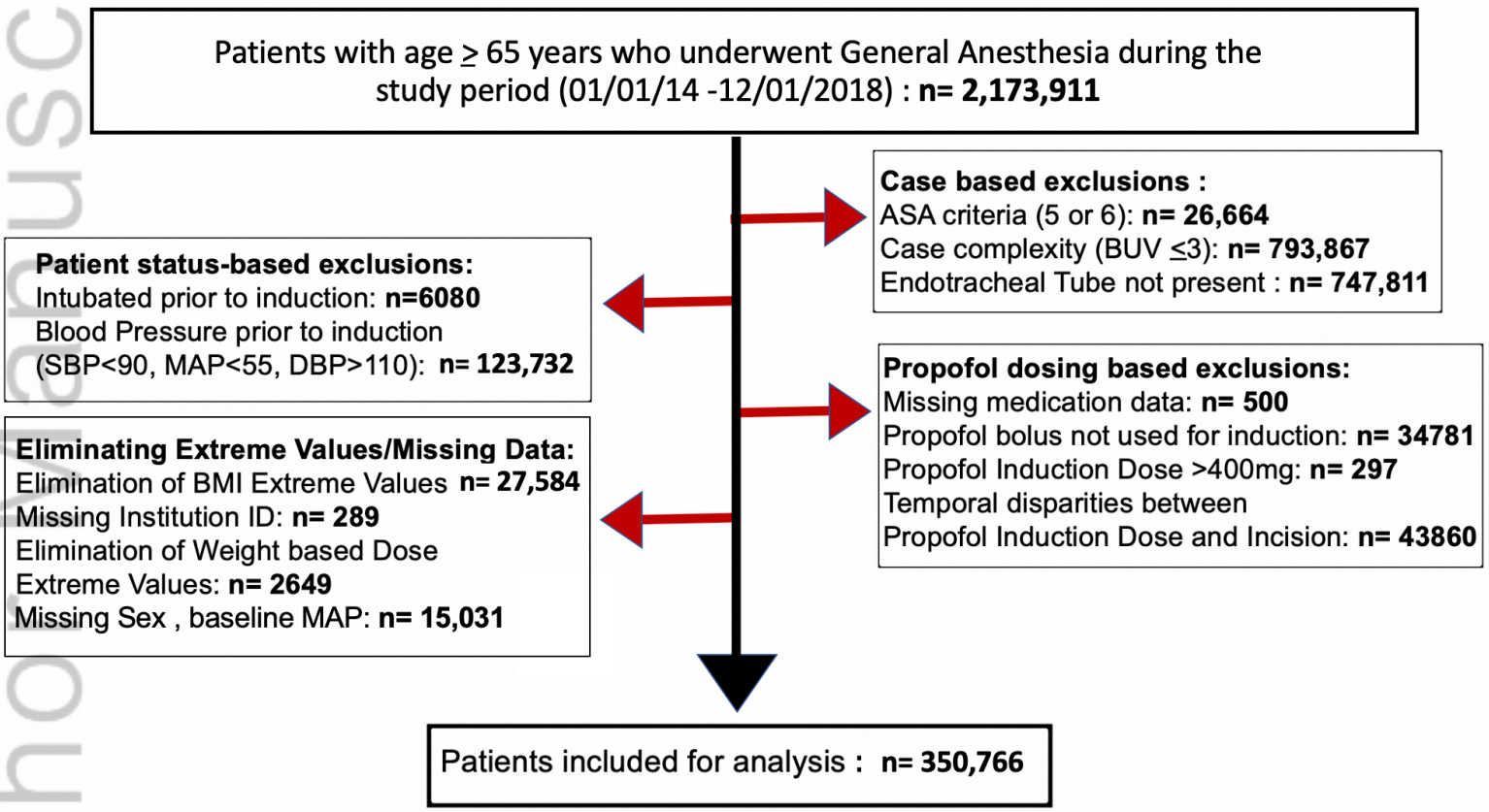
ONLINE SUPPLEMENT MATERIALS:

Supplemental Figure S1: Histograms of Propofol Induction Dose by Age-Bin and ASA Physical Status. Vertical dotted line demonstrates the upper limit of the listed typical dosing range.

Supplemental Table S2: Table of Absolute and Weight Adjusted Propofol Induction Dose by Age and ASA Physical Status.

Supplemental Table S3: Table: Multivariable Analysis Evaluating Perioperative Factors Associated with Variability in Absolute Propofol Dose Received at Induction.

Supplemental Figure S4: Histogram of Absolute Propofol Dose in Milligrams for the Entire Dataset.



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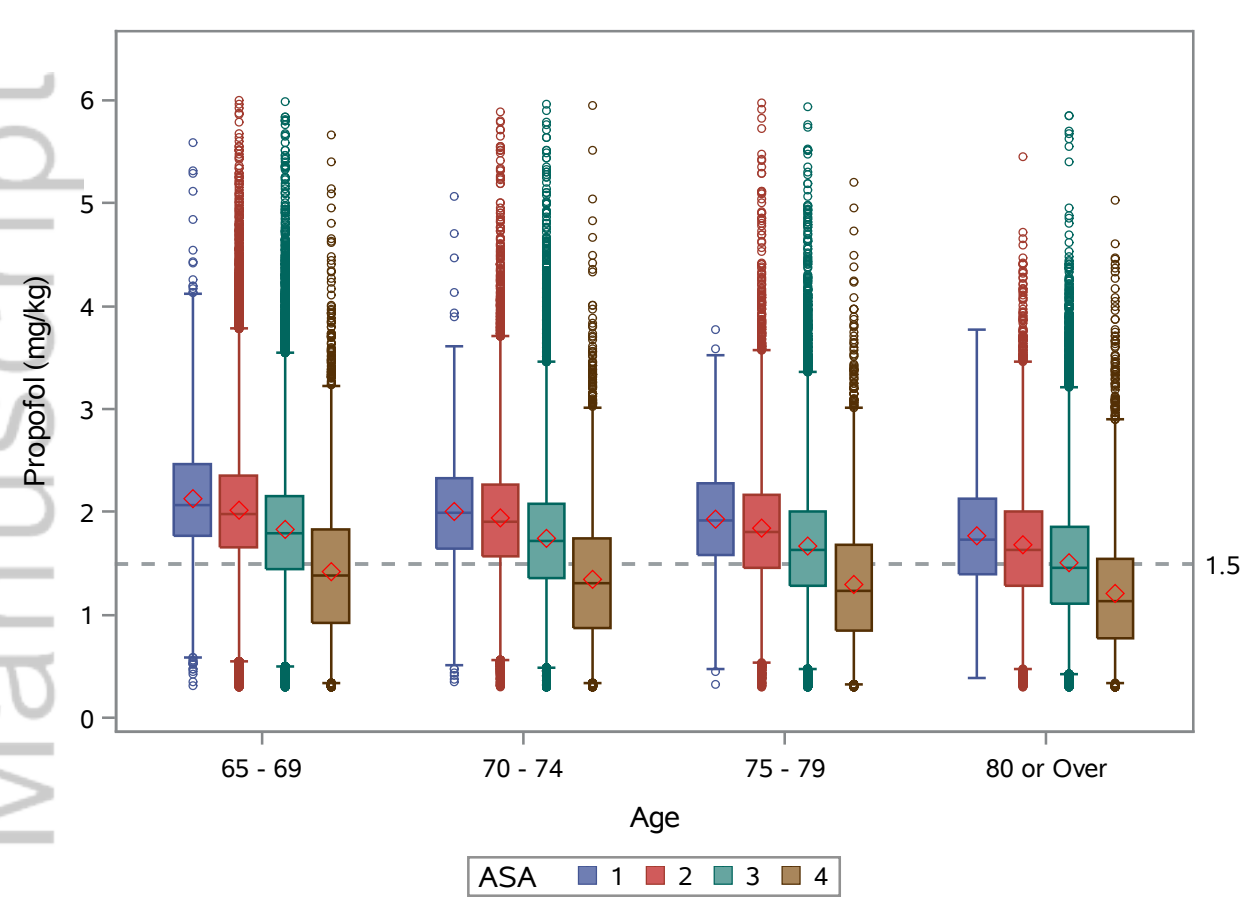
Propofol (mg/kg)
0
1
2
3
4
5
6
1.5
65 - 69
70 - 74
75 - 79
80 or Over
Age
ASA
1
2
3
4

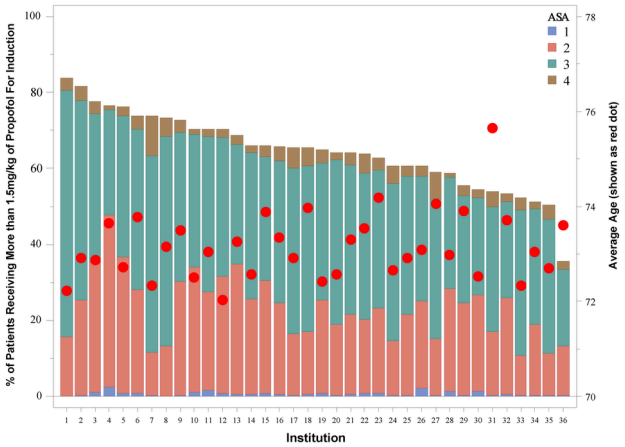

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Table 2: Multivariable Analysis Evaluating Perioperative Factors Associated with Odds of Propofol Dose Above Range (N=228,492 with preoperative laboratory data).

Variable	Odds Ratio (95% CI)	p-Value
Age		<0.0001*
65 - 69	Ref	
70 - 74	0.603 (0.388 to 0.939)	0.0253
75 - 79	0.419 (0.229 to 0.766)	0.0047
80 or Over	0.128 (0.065 to 0.253)	<0.0001
Sex (Female vs Male)	0.744 (0.722 to 0.767)	<0.0001
Race		<0.0001*
Black	1.036 (0.996 to 1.077)	0.0788
Unknown/other	0.772 (0.736 to 0.81)	<0.0001
White	Ref	
Ethnicity		<0.0001*
Hispanic	1.204 (1.106 to 1.31)	<0.0001
Unknown	1.277 (1.192 to 1.367)	<0.0001
Non-Hispanic	Ref	
Year of Surgery		<0.0001*
2014	Ref	
2015	1.029 (0.992 to 1.068)	0.1266
2016	1.029 (0.992 to 1.067)	0.1257
2017	1.166 (1.125 to 1.208)	<0.0001
2018	1.186 (1.145 to 1.228)	<0.0001
Weight, kg	0.969 (0.967 to 0.971)	<0.0001
Height (cm)[a]	1.000 (0.997 to 1.002)	0.8078
WHO Obesity Class		<0.0001*
Normal weight (BMI 18.5 to <25)	Ref	
Overweight (BMI (25 to <30)	0.916 (0.882 to 0.951)	<0.0001
Class I obesity (BMI 30 to <35)	0.831 (0.78 to 0.886)	<0.0001
Class II obesity (BMI 35 to <40)	0.806 (0.734 to 0.884)	<0.0001
Class III obesity (BMI ≥40)	0.739 (0.651 to 0.839)	<0.0001
Underweight (BMI <18.5)	1.029 (0.902 to 1.174)	0.6713
ASA Physical Status		<0.0001*
1	Ref	
2	0.793 (0.607 to 1.035)	0.0873
3	0.539 (0.414 to 0.703)	<0.0001
4	0.225 (0.172 to 0.294)	<0.0001
Age x ASA Physical Status Interaction		<0.0001*
70 – 74 x 2	1.075 (0.688 to 1.679)	0.7504
70 – 74 x 3	1.104 (0.708 to 1.72)	0.6624
70 – 74 x 4	1.268 (0.809 to 1.987)	0.3006
70 – 74 x 1	Ref	
75 – 79 x 2	0.955 (0.52 to 1.751)	0.8804
75 – 79 x 3	1.072 (0.586 to 1.962)	0.8208
75 – 79 x 4	1.366 (0.743 to 2.511)	0.3154
75 – 79 x 1	Ref	
80 or Over x 2	1.391 (0.705 to 2.744)	0.3419
80 or Over x 3	1.64 (0.833 to 3.229)	0.1523
80 or Over x 4	2.463 (1.246 to 4.867)	0.0095
80 or Over x 1	Ref	
Emergency Modifier	0.697 (0.667 to 0.729)	<0.0001
Neuraxial Anesthesia, Yes	1.371 (1.26 to 1.491)	<0.0001
van Walraven Comorbidity Index	0.991 (0.99 to 0.992)	<0.0001
Frailty Index		<0.0001*

High	0.828 (0.749 to 0.915)	0.0002
Intermediate	1.04 (1.007 to 1.074)	0.017
Low	Ref	
Coronary Artery Disease	0.76 (0.741 to 0.778)	<0.0001
Chronic Kidney Disease		<0.0001*
Stage 2	1.033 (1.003 to 1.065)	0.0302
Stage 3a	0.957 (0.924 to 0.991)	0.0143
Stage 3b	0.879 (0.841 to 0.918)	<0.0001
Stage 4	0.804 (0.753 to 0.858)	<0.0001
Normal eGFR	Ref	
Anemia		<0.0001*
Mild	0.831 (0.812 to 0.849)	<0.0001
Moderate to Severe	0.642 (0.621 to 0.663)	<0.0001
Normal	Ref	
Baseline Mean Arterial Pressure	1.012 (1.011 to 1.013)	<0.0001
Duration of Surgery in Minutes[b]	0.997 (0.997 to 0.998)	<0.0001
Anesthesia Base Units >5	1.1 (1.069 to 1.131)	<0.0001
Academic vs. Community Hospital	1.064 (1.033 to 1.095)	<0.0001
Surgical Service of Proceduralist		<0.0001*
General Surgery	Ref	
Cardiothoracic	0.344 (0.328 to 0.36)	<0.0001
Medical - gastroenterology	0.437 (0.411 to 0.463)	<0.0001
Medical Subspecialty	0.606 (0.563 to 0.652)	<0.0001
Neurosurgery	0.803 (0.773 to 0.833)	<0.0001
Gynecology	1.078 (1.02 to 1.138)	0.0072
Ophthalmology	0.525 (0.449 to 0.614)	<0.0001
Oral/Maxillofacial, ENT	0.82 (0.782 to 0.859)	<0.0001
Orthopedics	0.703 (0.68 to 0.726)	<0.0001
Other	0.63 (0.606 to 0.655)	<0.0001
Plastic Surgery	1.138 (1.029 to 1.26)	0.0122
Radiology	1.16 (1.052 to 1.279)	0.0029
Thoracic	0.755 (0.719 to 0.793)	<0.0001
Transplant	0.629 (0.535 to 0.739)	<0.0001
Trauma	0.592 (0.531 to 0.66)	<0.0001
Urology	1.071 (1.024 to 1.12)	0.0028
Vascular	0.462 (0.438 to 0.488)	<0.0001
Etomidate (Yes vs No)	0.067 (0.059 to 0.077)	<0.0001
Ketamine (Yes vs No)	0.573 (0.55 to 0.598)	<0.0001
Midazolam (mg)	0.886 (0.876 to 0.895)	<0.0001
Fentanyl (mcg)[c]	0.99 (0.986 to 0.994)	<0.0001

Note: Individual Institution was treated as a random effect to account for possible similarity among patients cared at each institute. A total of **228492** patients were

*: Type III test p-value

[a]: per 10 cm increase; [b]per 10 min increase. [c]: per 25 mcg

Table 1. Summary statistics of variables by propofol dose status

	Propofol Dose Above Range (>1.5 mg/kg)		
	No ***(N = 123492)***	***Yes*** ***(N = 227274)***	***Total*** ***(N = 350766)***
Age			
65 - 69	34081 (27.60%)	96336 (42.39%)	130417 (37.18%)
70 - 74	31762 (25.72%)	65298 (28.73%)	97060 (27.67%)
75 - 79	25821 (20.91%)	38742 (17.05%)	64563 (18.41%)
80 or Over	31828 (25.77%)	26898 (11.84%)	58726 (16.74%)
Sex			
Female	57306 (46.40%)	116533 (51.27%)	173839 (49.56%)
Male	66186 (53.60%)	110741 (48.73%)	176927 (50.44%)
Race			
Black	8710 (7.05%)	15288 (6.73%)	23998 (6.84%)
Unknown/other Race	14328 (11.60%)	27180 (11.96%)	41508 (11.83%)
White	100454 (81.34%)	184806 (81.31%)	285260 (81.32%)
Ethnicity			
Hispanic Ethnicity	1464 (1.19%)	3368 (1.48%)	4832 (1.38%)
Non-Hispanic Ethnicity	113766 (92.12%)	208745 (91.85%)	322511 (91.94%)
Unknown Ethnicity	8262 (6.69%)	15161 (6.67%)	23423 (6.68%)
Year of Surgery			
2014	16630 (13.47%)	27978 (12.31%)	44608 (12.72%)
2015	22328 (18.08%)	37942 (16.69%)	60270 (17.18%)
2016	24466 (19.81%)	43674 (19.22%)	68140 (19.43%)
2017	29356 (23.77%)	57333 (25.23%)	86689 (24.71%)
2018	30712 (24.87%)	60347 (26.55%)	91059 (25.96%)
Weight(kg)			
N (N Missing)	123492 (0)	227274 (0)	350766 (0)
Mean (SD)	85.67 (19.14)	78.41 (17.33)	80.97 (18.32)
Median (IQR)	83.9 (71.7 – 99.6)	77.1 (65.3 – 89.8)	79.4 (67.6 – 92.6)
Height_cm			
N (N Missing)	118147 (5345)	218237 (9037)	336384 (14382)
Mean (SD)	169.47 (10.67)	168.22 (10.48)	168.66 (10.56)
Median (IQR)	170.2 (161.3 – 177.8)	167.6 (160.0 – 175.6)	167.9 (160.0 – 177.8)
WHO Obesity Class based on BMI			
Missing	5237	8864	14101
Class I obesity (BMI 30 to <35)	29331 (24.80%)	41793 (19.14%)	71124 (21.13%)
Class II obesity (BMI 35 to <40)	14546 (12.30%)	14963 (6.85%)	29509 (8.77%)
Class III obesity (BMI ≥40)	7982 (6.75%)	5501 (2.52%)	13483 (4.00%)
Normal weight (BMI 18.5 to <25)	25694 (21.73%)	71786 (32.87%)	97480 (28.95%)
Overweight (BMI (25 to <30)	40181 (33.98%)	82611 (37.82%)	122792 (36.47%)
Underweight (BMI <18.5)	521 (0.44%)	1756 (0.80%)	2277 (0.68%)
ASA Physical Status			
Missing	2	3	5
1	379 (0.31%)	2042 (0.90%)	2421 (0.69%)
2	21745 (17.61%)	77474 (34.09%)	99219 (28.29%)
3	79122 (64.07%)	135404 (59.58%)	214526 (61.16%)
4	22244 (18.01%)	12351 (5.43%)	34595 (9.86%)
Emergency Modifier			
Missing	2	2	4
Emergency	6978 (5.65%)	7456 (3.28%)	14434 (4.12%)
Non-Emergency	116512 (94.35%)	219816 (96.72%)	336328 (95.88%)
Neuraxial Anesthetic			
No	122233 (98.98%)	224128 (98.62%)	346361 (98.74%)
Yes	1259 (1.02%)	3146 (1.38%)	4405 (1.26%)
van Walraven Comorbidity Index			
N (N Missing)	121523 (1969)	224680 (2594)	346203 (4563)
Mean (SD)	7.94 (9.83)	5.85 (8.54)	6.59 (9.07)
Median (IQR)	5.0 (0.0 – 14.0)	3.0 (0.0 – 10.0)	4.0 (0.0 – 11.0)
Frailty Index			
Missing	1969	2594	4563
High	1360 (1.12%)	1346 (0.60%)	2706 (0.78%)
Intermediate	12863 (10.58%)	21186 (9.43%)	34049 (9.83%)

Low	107300 (88.30%)	202148 (89.97%)	309448 (89.38%)
Coronary Artery Disease			
Missing	1969	2594	4563
No	86008 (70.78%)	188756 (84.01%)	274764 (79.36%)
Yes	35515 (29.22%)	35924 (15.99%)	71439 (20.64%)
Chronic Kidney Disease			
Missing	33033	67618	100651
Normal eGFR	11467 (12.68%)	28085 (17.59%)	39552 (15.81%)
Stage 2	46662 (51.58%)	93036 (58.27%)	139698 (55.85%)
Stage 3a	18652 (20.62%)	25750 (16.13%)	44402 (17.75%)
Stage 3b	9991 (11.04%)	9968 (6.24%)	19959 (7.98%)
Stage 4	3687 (4.08%)	2817 (1.76%)	6504 (2.60%)
Anemia			
Missing	25877	55638	81515
Mild	34834 (35.69%)	52325 (30.49%)	87159 (32.37%)
Moderate to Severe	16739 (17.15%)	16740 (9.75%)	33479 (12.43%)
Normal	46042 (47.17%)	102571 (59.76%)	148613 (55.19%)
Baseline Mean Arterial Pressure			
Mean (SD)	97.42 (14.83)	99.71 (14.42)	98.91 (14.61)
Median (IQR)	97.0 (87.0 – 107.0)	99.0 (90.0 – 109.0)	99.0 (89.0 – 109.0)
Duration of Surgery in Minutes			
N (N Missing)	123230 (262)	226980 (294)	350210 (556)
Mean (SD)	216.24 (130.08)	206.89 (118.26)	210.18 (122.63)
Median (IQR)	188.0 (123.0 – 283.0)	180.0 (123.0 – 262.0)	183.0 (123.0 – 269.0)
Anesthesia Base Units			
Minor (≤5 Base Units)	29918 (24.23%)	56809 (25.00%)	86727 (24.73%)
Major (>5 Base Units)	93574 (75.77%)	170465 (75.00%)	264039 (75.27%)
Institution Type			
Academic Hospital	101706 (82.36%)	192473 (84.69%)	294179 (83.87%)
Community Hospital	21786 (17.64%)	34801 (15.31%)	56587 (16.13%)
Surgical Service of Proceduralist			
Cardiothoracic	11956 (9.68%)	7337 (3.23%)	19293 (5.50%)
General Surgery	17561 (14.22%)	44462 (19.56%)	62023 (17.68%)
Medical - Gastroenterology	7330 (5.94%)	6023 (2.65%)	13353 (3.81%)
Medical - Other Subspecialty	2821 (2.28%)	3938 (1.73%)	6759 (1.93%)
Neurosurgery	10454 (8.47%)	22486 (9.89%)	32940 (9.39%)
Gynecology	3474 (2.81%)	11793 (5.19%)	15267 (4.35%)
Ophthalmology	1585 (1.28%)	2423 (1.07%)	4008 (1.14%)
Oral/Maxillofacial/Otolaryngology	8120 (6.58%)	20702 (9.11%)	28822 (8.22%)
Orthopedics	19635 (15.90%)	34777 (15.30%)	54412 (15.51%)
Other	20230 (16.38%)	30573 (13.45%)	50803 (14.48%)
Plastic Surgery	1303 (1.06%)	4874 (2.14%)	6177 (1.76%)
Radiology	883 (0.72%)	2216 (0.98%)	3099 (0.88%)
Thoracic	4462 (3.61%)	9535 (4.20%)	13997 (3.99%)
Transplant	666 (0.54%)	1434 (0.63%)	2100 (0.60%)
Trauma	901 (0.73%)	1200 (0.53%)	2101 (0.60%)
Urology	6153 (4.98%)	18193 (8.00%)	24346 (6.94%)
Vascular	5958 (4.82%)	5308 (2.34%)	11266 (3.21%)
Additional Induction Medications			
Etomidate			
Dose = 0 mg	119347 (96.64%)	226922 (99.85%)	346269 (98.72%)
Dose >0 mg	4145 (3.36%)	352 (0.15%)	4497 (1.28%)
Ketamine			
Dose = 0 mg	115981 (93.92%)	216654 (95.33%)	332635 (94.83%)
Dose >0 mg	7511 (6.08%)	10620 (4.67%)	18131 (5.17%)
Fentanyl (mcg)			
Mean (SD)	89.70 (69.97)	87.73 (59.96)	88.42 (63.67)
Median (IQR)	100.0 (50.0 – 100.0)	100.0 (50.0 – 100.0)	100.0 (50.0 – 100.0)
Midazolam (mg)			
Mean (SD)	0.68 (1.09)	0.64 (0.94)	0.66 (0.99)
Median (IQR)	0.0 (0.0 – 2.0)	0.0 (0.0 – 2.0)	0.0 (0.0 – 2.0)