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Patient-, Clinician-, and Institution-level Variation in Inotrope Use for Cardiac Surgery: A Multicenter Observational Analysis

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Abstract

Background—Conflicting evidence exists regarding the risks and benefits of inotropic therapies during cardiac surgery, and the extent of variation in clinical practice remains understudied. Therefore, the authors sought to quantify patient-, anesthesiologist-, and hospital-related contributions to variation in inotrope use.

Methods—In this observational study, non-emergent adult cardiac surgeries using cardiopulmonary bypass were reviewed across a multicenter cohort of academic and community hospitals from 2014 to 2019. Patients who were moribund, receiving mechanical circulatory support, or receiving preoperative/home inotropes were excluded. The primary outcome was an inotrope infusion (epinephrine, dobutamine, milrinone, dopamine) administered for greater than 60 consecutive minutes intraoperatively or ongoing upon transport from the operating room. Institution-, clinician-, and patient-level variance components were studied.

Results—Among 51,085 cases across 611 attending anesthesiologists and 29 hospitals, 27,033 (52.9%) cases received at least one intraoperative inotrope, including 21,796 (42.7%) epinephrine, 6,360 (12.4%) milrinone, 2,000 (3.9%) dobutamine, and 602 (1.2%) dopamine (non-mutually exclusive). Variation in inotrope use was 22.6% attributable to the institution, 6.8% to the primary attending anesthesiologist, and 70.6% to the patient. The adjusted median odds ratio for the same patient receiving inotropes was 1.73 between two randomly selected clinicians and 3.55 between two randomly selected institutions. Factors most strongly associated with increased likelihood of inotrope use were institutional medical school affiliation (adjusted odds ratio 6.2, 95% CI 1.39–27.8), heart failure (2.60, 2.46–2.76), pulmonary circulation disorder (1.72, 1.58–1.87), loop diuretic home medication (1.55, 1.42–1.69), Black race (1.49, 1.32–1.68), and digoxin home medication (1.48, 1.18–1.86).

Conclusions—Variation in inotrope use during cardiac surgery is attributable to the institution and clinician in addition to the patient. Variation across institutions and clinicians suggests a need for future quantitative and qualitative research to understand variation in inotrope use impacting outcomes and develop evidence-based, patient-centered inotrope therapies.

INTRODUCTION

Among over 300,000 cardiac surgeries performed in the United States annually,[1] variation in clinical decision-making for blood transfusions,[2] hemodynamic management,[3] and anesthetic techniques [4,5] are well-described. However, one knowledge gap remaining in perioperative care variation for cardiac surgery is the use of inotropic therapies. While inotropes may achieve their intended physiologic effect and objectively improve cardiac contractility, such medications may also expose patients to potentially severe unintended consequences including myocardial ischemia and malignant arrhythmia,[6,7] increasing mortality.[8] Furthermore, as inotropes often require administration via invasive central lines and skilled intensive care unit nursing, these medications are associated with adjusted hospital and intensive care unit length of stays prolonged by 1–3 days[9,10] and $17,000 increased adjusted total inpatient hospital costs per patient.[10] These findings have contributed to variable practice patterns described in high-risk cardiac surgical subpopulations,[11] surveys exploring clinician decision-making[12] and single-center assessments of factors influencing inotrope use.[13] Yet, variation has not been sufficiently assessed in a broad cardiac surgical population across multiple centers using perioperative electronic medical record data.

Understanding factors driving such variation remains important for informing strategies to reduce variation if subsequently found to negatively impact patient outcomes.[14–16] In other healthcare contexts, variation ideally reflects precision medicine, yet it can also reflect local culture, lack of agreement on optimal care, or care departing from established guidelines.[17] Given increased needs for sustainable and high-value care, clinicians and policymakers have developed quality improvement initiatives and clinical practice guidelines aimed at reducing variation if found to negatively impact outcomes.[18,19] To characterize where additional knowledge gaps may exist, clinical database registries can highlight sources of variation not clearly explained by adjusting for surgical and patient characteristics, which may serve as targets for further exploration and - if found to negatively impact outcomes - quality improvement initiatives.[1,20] Sources of variation can occur at multiple levels, including: (i) the patient level, influenced by factors such as demographics, comorbidities, or access to care; (ii) the clinician level, influenced by factors such as training, experience, or preference; and (iii) the institutional level, influenced by factors such as resource availability, hospital operations, institutional preference/culture, and the setting of healthcare delivery.[21] Whereas variation in care can be explained at different levels, understanding the relative contribution of each remains critically important, as each source raises unique issues about health equity, quality, and appropriateness of care allocation, and each implies different strategies for reducing any given component of variation if negatively impacting outcomes.[22,23]

To inform efforts to identify and measure sources of practice variation, we performed this multilevel observational cohort study across multiple centers, characterizing relative contributions of institution-, clinician-, and patient-level factors influencing the use of intraoperative inotrope infusions during cardiac surgical procedures. We hypothesized that potentially meaningful variation in inotrope use (>5%) occurred at the clinician- and institution levels, and that characteristics influencing a patient's likelihood to receive intraoperative inotropes spanned multiple perioperative data types including demographics,

comorbidities, surgical procedure details, home medications, and clinician- and institution-level characteristics.

METHODS

Study Design

We followed the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) extension of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines throughout conducting this study (Supplemental Digital Content 1).[24] Institutional review board approval (HUM00181872) was obtained for this observational study and patient consent was waived. An *a priori* study protocol for the patient population, data collection and handling, primary outcome, and statistical methods was approved within a peer-review forum [25] prior to statistical analysis and made publicly available on Open Science Framework.[26]

Population

We studied non-emergent cardiac surgical procedures with cardiopulmonary bypass performed on adult patients >18 years old at US institutions from January 1, 2014 to August 1, 2019 (start date selected based upon data available, and end date selected to mitigate impact of unmeasured confounders related to the Coronavirus Disease 2019 pandemic) within the Multicenter Perioperative Outcomes Group (MPOG) registry. Institutions submitting valid inotrope data (details in 'Handling of Missing or Invalid Data') contributing greater than 20 cardiac cases per year were eligible for inclusion. To develop a cohort reflective of typical cardiac surgical procedures, we restricted the study population to coronary artery bypass and valve procedures performed in isolation or combination. We excluded cardiac surgical procedures with pre-existing or implanted mechanical circulatory support (e.g. intra-aortic balloon pump, ventricular assist device, or extracorporeal membrane oxygenation), transcatheter or off-pump procedures, procedures with circulatory arrest, myectomies, patients receiving inotrope infusions prior to surgical incision, and American Society of Anesthesiologists (ASA) Physical Status Classification 5 or 6 patients. For patients undergoing multiple cardiac surgical procedures meeting inclusion criteria, only the index case was used. Finally, we excluded procedures with a case duration <120 minutes or without invasive arterial blood pressure monitoring as such surgeries were unlikely to be a complete cardiac surgery.

Data Source

Following study approval and registration, data were extracted from the MPOG dataset. Methods for local electronic health record data (EHR) acquisition, validation, mapping to semantically interoperable universal MPOG concepts, and secure transfer to the coordinating center have been previously described.[20,27]

Primary Outcome

We defined the primary binary outcome of interest as an inotrope infusion (epinephrine, dobutamine, milrinone, or dopamine) for >60 continuous intraoperative minutes or ongoing upon transport from the operating room and arrival to the intensive care unit.

Secondary Outcomes

To further characterize the extent of inotrope use among cases studied, we defined a secondary outcome as the total number of intraoperative simultaneous inotrope infusions used. Inotrope infusions were considered simultaneous if used together for greater than 60 consecutive minutes, or if used together during transport from the operating room.

Covariates

We collected data on covariates available within MPOG postulated by the authors to influence intraoperative inotrope administration based upon literature review,[9,11–13,28] as well as other factors (e.g., EHR-reported sex and race) that have been previously observed to drive variation in other aspects of perioperative care [29] (Table 1). These included characteristics of the patient (demographics, anthropometrics, comorbidities, home medications, preoperative studies, and preoperative status), surgical case (type, times, and intraoperative events), clinician (primary attending anesthesiologist, clinician case volume), and institution (medical school affiliation, institutional case volume, number of attending cardiac anesthesiologists, percentage of cases involving nurse anesthetists). Patient comorbidity data were collected using the Elixhauser Comorbidity Enhanced International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification algorithm.[30] Demographics, laboratory values, and surgical case characteristics were validated utilizing precomputed, MPOG-specific, publicly available perioperative EHR phenotype algorithms.[31] Relevant cardiovascular home medications were collected via natural language processing of home medication free-text entries within the preoperative history and physical and with classification via Veterans Affairs national formulary codes.[32] Academic institutions were determined by whether or not the institution had an associated medical school; a detailed list is available via the ‘Medical school affiliation’ perioperative EHR phenotype.[31]

Data Handling

To assess the accuracy of the inotrope administration primary outcome, within each eligible MPOG institution, a sample of 10 cases receiving intraoperative inotropes and 10 cases not receiving inotropes were hand-reviewed by a cardiac anesthesiologist (MRM); institutions with <95% agreement between the query algorithm and the manual review were excluded from the analysis. For each covariate, outlier values were handled as missing if outside of valid ranges described in pre-specified phenotype specifications.[31] Missing data patterns were assessed and the percent of missing data calculated. For missingness rates <10%, complete case analyses were performed; otherwise multiple imputation techniques were to be used to complete the data.[33]

Statistical analyses

Statistical analyses were performed using SAS version 9.4 (SAS Institute, USA). Distributions of variables were assessed graphically and potential outliers were identified via histograms, Q-Q plots, box-plots, and basic descriptive statistics (mean, standard deviation, median, and interquartile range). These were also used to determine appropriate covariate transformations and modeling strategies. For descriptive purposes, we characterized (i)

per-case rates of inotrope administration at the clinician and institution levels via caterpillar plots; (ii) temporal trends in inotrope administration via linear plots; (iii) per-case rates of individual inotrope administration (epinephrine, dobutamine, milrinone, and dopamine) across institutions via density plots; and (iv) per-case rates of single versus multiple simultaneous inotrope infusions via stacked bar charts.

Associations between covariates and the primary outcome were assessed via univariate analyses using standardized differences. Covariates showing standardized differences larger than 0.2 in absolute value between groups or plausibly influencing intraoperative inotrope administration were considered for inclusion in multivariable models. In addition, multicollinearity was assessed for using Pearson's correlation coefficient and variance inflation analyses. In cases of covariate pairs leading to a correlation coefficient >0.70 and variance inflation factor >10, one covariate was removed from the multivariable model based on the clinical judgment of the investigators.

Unadjusted (null) generalized linear mixed models were next constructed, using a hierarchical nesting structure with patients nested within clinicians, nested within institutions. Modified intraclass correlation estimates were used to assess relative contributions of institution-, clinician-, and patient-level factors to the total variance of intraoperative inotrope infusions.[34] Intraclass correlation estimates can be used to express the percentage of variation observed within a specific group of variables, relative to the total variation observed. For example, an intraclass correlation estimate of 80% for patient-level factors is interpreted as 80% of the total observed variation in inotrope use being attributable to characteristics of the patient, and the remaining 20% attributable to characteristics of the clinician or institution. Intraclass correlation estimates can be used to ascertain the validity of a nested, multilevel approach to modeling the data observed: for example, if less than 5% of the total variability is explained by upper-level units, then limited empirical support for a multilevel analysis exists, favoring a single-level model using a generalized estimating equation approach.

Given that >5% of the total variance was explained by institution and clinician upper levels (as described later in the Results) adjusted generalized linear mixed models were next constructed to (i) compute adjusted median odds ratios for receiving intraoperative inotropes across clinicians and institutions and (ii) analyze independent associations between covariates and intraoperative inotropes. The median odds ratio is the median value obtained from comparing adjusted odds of having received intraoperative inotropes, if the same patient underwent cardiac surgery at two different randomly selected institutions or under the care of two different randomly selected clinicians. For example, a median odds ratio of 1.3 is interpreted as the median odds of receiving an intraoperative inotrope infusion would be 30% higher if the same patient underwent cardiac surgery at one randomly selected institution versus another; or under the care of one randomly selected clinician versus another. Pseudo-likelihood ratios and generalized chi-square statistics were used to characterize the suitability of multilevel multivariable models as the proper approach.

Sensitivity analyses

To assess the impact of varying inclusion criteria and intraoperative inotrope definitions on the results, we performed several sensitivity analyses. First, we repeated the primary analysis using an alternative intraoperative inotrope definition including norepinephrine. We then repeated the primary analysis using separate alternative intraoperative inotrope definitions restricted to each individual inotrope. Additionally, we repeated the primary analysis, restricting the intraoperative inotrope definition to (i) only cases with inotrope infusions ongoing during transport from the operating room; and (ii) only considering the time period between the end of the final cardiopulmonary bypass and transport from the operating room. Finally, we repeated the primary analysis, categorizing case types based upon current procedural terminology code rather than surgical procedure text.

Sample Size Calculation

An *a priori* minimum sample size was determined based on the desired precision of the prevalence of intraoperative inotrope administration to be within 3%. To estimate the true proportion of intraoperative inotrope administration, we used a 95% confidence interval (CI) based upon the standard error (SE) of the sample proportion (p) using the following formula:

$$p \pm 1.96 * SE(p)$$

Supplemental Digital Content 2 outlines estimated sample sizes with variable sample proportions and precision. Among a preliminary sample of data available on cardiac surgeries performed across all MPOG centers from 2014–2019, we determined the proportion of cases receiving any inotrope administration (irrespective of duration) to be 56%, and thus would require a sample size ranging between 5,500 and 5,800 cases to achieve 3% precision, assuming 25% loss of data due to additional data cleaning protocols. In addition, simulation-based sample size estimates for multilevel models show that a sample size of 27,000 patients nested within clinicians and institutions would yield 80% or more power to determine statistically significant associations at the 5% significance level. Given an estimated sample size of over 40,000 patients analyzed, this study achieved adequate power.

RESULTS

Patient Population - Baseline Characteristics

Of the 119,044 cardiac surgical cases reviewed, 51,085 met inclusion criteria (Figure 1). Cases meeting inclusion criteria comprised 611 attending anesthesiologist clinicians across 29 US hospitals. Hospitals studied are listed in Appendix 2, and included 24 academic hospitals (82.8%) contributing 47,500 cases (93.0%) and 5 community hospitals (18.2%) contributing 3,585 cases (7.0%). Manual case audits of inotrope infusion data across each of the 29 included hospitals demonstrated >95% accuracy, and therefore all 29 hospitals were included in the analysis. The population had a mean age of 64 years, 31.4% were women, and 76.5% were White (Table 1). Cardiac surgeries performed included valve (22,987,

45.0% of cases), coronary artery bypass (20,681, 40.5%) and valve/coronary artery bypass combination (7,414, 14.5%).

Across the study population, 27,033 (52.9%) received intraoperative inotropes. Individual non-mutually exclusive inotropes included epinephrine (21,796, 42.7% of cases), milrinone (6,360, 12.4%), dobutamine (2,000, 3.9%), and dopamine (602, 1.2%). Compared to patients without inotropes, those receiving inotropes more commonly (i) had preoperative comorbidities of heart failure, pulmonary circulation disorders, and renal failure; (ii) underwent valve/coronary artery bypass combination surgeries; (iii) had longer cardiopulmonary bypass durations; (iv) had greater rates of blood product transfusion; (v) had lower preoperative estimated glomerular filtration rates and hemoglobin concentrations; and (vi) were prescribed loop diuretic home medications.

Institution and Clinician Inotrope Use Patterns

Density plots of inotrope use per institution are shown in Figure 2 (total inotrope use) and Supplemental Digital Content 3 (per-institution relative inotrope use). Inotrope use *per institution* ranged from 6.9% to 85.0% (median 47.0%, interquartile range 33.1–67.8%), Figure 3A. Simultaneous use of two or more inotropes *per institution* ranged from 0% to 1.4%, with 14 institutions (48.3% of institutions) never using two or more simultaneous inotropes (Figure 4). Among the 15 institutions ever using two or more simultaneous inotropes, a median 0.4% and interquartile range 0.2% to 0.7% of cases used two or more simultaneous inotropes. Inotrope use *per clinician* ranged from 0% to 100% (median 45.2%, interquartile range 30.0–67.0%), with 6.8% of clinicians using inotropes for all cases and 8.5% for no cases (Figure 3B). Temporal variation in institution-, clinician-, or patient-level inotrope use followed no discernible pattern (Supplemental Digital Content 4).

Missing Data

Across the study population, 3,805 (7.4%) had missing data, resulting in a complete case analysis cohort of 47,280 patients, 611 anesthesiologist attending clinicians, and 29 institutions for the multilevel model. A missing data analysis demonstrated that minimal additional bias was introduced when cases with high rates of missing data were excluded (Supplemental Digital Content 5).

Nested Multilevel Modeling

Goodness-of-fit testing for a multivariable mixed-effect model with random effects of clinician and institution demonstrated that the variability in inotrope use was properly modeled without residual over-dispersion (likelihood ratio test, $p<0.001$; generalized chi-square test, 1.1).

Within the unadjusted model, 22.6% of the variation in inotrope use was attributable to the institution, 6.8% to the primary anesthesiologist attending clinician, and 70.6% to the patient (Table 2). After adjustment, the amount of variation attributed to the institution and clinician increased (35.1% and 9.2% respectively) while it decreased to 55.6% for the patient. The adjusted median odds ratio for a patient receiving inotropes was 1.73 at the clinician level and 3.55 at the institution level. Put into context, for any given patient, the

median odds of receiving inotropes during cardiac surgery differed by three-to-fourfold between two randomly selected institutions, and by nearly two-fold between two randomly selected attending anesthesiologists, following adjustment for baseline characteristics. For further illustration, for a hypothetical patient whose characteristics were associated with a *50% chance* of receiving an inotrope by a given anesthesiologist and institution, the median chance of receiving an inotrope would increase to 63.4% or decrease to 36.6% if receiving care from another randomly selected anesthesiologist, and would increase to 78.0% or decrease to 22.0% if receiving care at another randomly selected institution.

Following nested multilevel modeling adjusting for clinician- and institution-level factors, the patient-level factors independently associated with a statistically and clinically significant increased likelihood of inotrope use ($p < 0.05$ and adjusted odds ratio >1.25) were heart failure (adjusted odds ratio 2.60, 95% CI 2.46–2.76), pulmonary hypertension/ embolism, (1.72, 1.58–1.87), loop diuretic home medication (1.55, 1.42–1.69), Black race (1.49, 1.32–1.68), digoxin home medication (1.48, 1.18–1.86), preoperative heart rate >90 beats/minute (versus 60–75 per minute, 1.42, 1.30–1.55), and lower preoperative estimated glomerular filtration rate versus >=90 mL/min/1.73m^2 (<30 = 1.28, 1.06–1.54; 30–59 = 1.31, 1.19–1.44; and 60–89 = 1.11, 1.03–1.19), Table 3. Additionally, continuous variables independently associated with increased likelihood of inotrope use were prolonged case duration (1.31 per hour, 1.27–1.34) and prolonged cardiopulmonary bypass duration (1.21 per hour, 1.17–1.26). At the clinician level, no association was observed between attending anesthesiologist case volume and the likelihood of inotrope use; however, variation in inotrope use was significantly greater for low-volume attending anesthesiologists (quintile 1; <19 cases in dataset annually) compared to all other anesthesiologist subgroups with higher case volumes (quintiles 2–5), Supplemental Digital Content 6. At the institution level, 24 of 29 hospitals (83%) were medical school affiliated (i.e. teaching hospital), and medical school affiliation was strongly associated with an increased odds of inotrope use (6.2, 1.39–27.8); however no other associations were observed between other institution-level characteristics and inotrope use.

Sensitivity analyses

When including norepinephrine infusions as part of the cardiac inotrope infusion outcome, norepinephrine infusions were used in 39.5% of cases (simultaneously with other inotropes in 24.4% of all cases) and an outcome incidence (any inotrope used, including norepinephrine) of 71.9% was observed. Compared to the primary model, cardiac inotrope variance estimates using the norepinephrine-included inotrope primary outcome definition were observed to have similar relative proportions of variance attributable to the patient-, clinician-, and institution-levels, and similar covariates were independently associated with cardiac inotropes (Supplemental Digital Content 7).

When restricting the cardiac inotrope infusion outcome to (i) only consider inotrope infusions ongoing at the time of transport from the operating room, or (ii) only consider inotrope infusions occurring after cardiopulmonary bypass, variance estimates attributable to the patient-, clinician-, and institution-levels were also observed to be similarly distributed as

with the overall analysis, and similar covariates were independently associated with cardiac inotropes (Supplemental Digital Content 8).

Additionally, when restricting the cardiac inotrope infusion outcome to individual inotropes, variance estimates attributable to the patient-, clinician-, and institution-levels were observed to be similarly distributed as with the overall analysis. Multivariable models converged for epinephrine and norepinephrine, but not dobutamine, milrinone, or dopamine; model covariates associated epinephrine and norepinephrine primary outcomes were similar to the primary analysis (Supplemental Digital Content 9). Finally, when categorizing case types based upon current procedural terminology codes rather than surgical procedure text, variance estimates and covariates associated with cardiac inotropes were similar to the primary analysis (Supplemental Digital Content 10).

DISCUSSION

In this multicenter study of cardiac surgeries across 29 US academic and community hospitals, we report wide variation in intraoperative inotrope use across clinicians and institutions, with significant variation attributable to the anesthesiologist attending clinician and institution rather than solely the patient or surgery. Factors driving such clinician- and institution-level differences are complex and multifactorial, potentially explained by clinician training, institutional or regional protocols, cultural dogma, resource availability, the setting of healthcare delivery, or patient factors which cluster by clinician or institution but remain unmeasured and therefore appear to be otherwise unexplained.[21,35] However, as our findings were similar to other studies of cardiac anesthesiology practice patterns,[5,36] the advantages of multicenter over single-center analyses continues to be underscored as they more completely capture the diversity of practices and more accurately reflect patterns in which clinical care is delivered.

The wide variation in inotrope use in the modern, broad cardiac surgical population studied was consistent with historic analyses of high-risk cardiac subpopulations.[11] Similarly, factors independently associated with inotrope use paralleled previous studies, with the exception of medical school affiliation (i.e. teaching hospital) as the strongest factor observed in our analysis.[11,13] Whereas the lack of association observed between institutional case volume and inotrope usage was consistent with previous findings,[11] our divergent finding that institutions affiliated with a medical school were strongly and independently associated with inotrope use demands further investigation through qualitative research of clinician attitudes and institutional protocols towards inotrope use. Factors conceivably explaining this association include (i) the greater diversity of cases in our study, (ii) potentially greater degrees of recent changes to historic practice patterns at medical school-affiliated institutions compared to community hospitals, and/or (iii) unmeasured confounders which differed across cardiac surgical cases at medical school-affiliated institutions compared to community hospitals. Regarding the relationship between higher attending anesthesiologist case volume and lower clinician-level variance in inotrope use, further explanation of such findings remained beyond the scope of this study, although may have reflected a more patient-centered approach to inotrope use among higher-volume anesthesiologists.

Although variation in inotrope use remained wide, patient-level multivariable associations between perioperative characteristics and inotrope use observed in this study were largely consistent with known predictors of low cardiac output syndrome, including heart failure, renal insufficiency, low preoperative hemoglobin, and prolonged cardiopulmonary bypass time.[37,38] Notably however, we observed that despite prior evidence suggesting that females are at higher risk of low cardiac output syndrome,[39] female sex was independently associated with lower rates of inotrope use in our study. Conversely, an even stronger independent association - in the opposite direction - was observed for Black non-Hispanic patients, who had a nearly 50% increased adjusted odds of receiving inotropes. Such findings may be explainable by unmeasured confounders clustering within each subgroup and associated with severity of cardiovascular disease (e.g. social determinants of health, access to healthcare, or underrecognized inequities in cardiac surgical care for such patients) or may be a function of clinician bias.[40,41]

Potentially underpinning the variation in inotrope use we observed, which remained robust to multiple sensitivity analyses, are under-quantified risks versus benefits to such therapies. Whereas inotropes may achieve their intended physiologic effect and objectively improve a patient's hemodynamics or oxygen delivery to end organs, such medications also expose patients to potentially severe unintended consequences including myocardial ischemia,[6,7] malignant dysrhythmia,[6,7] and central line-associated bloodstream infections as the need for central venous access may be prolonged in the setting of specific inotropes.[42] Taken together, the variation in inotrope use observed in our study and variation in outcomes observed in previous studies, suggests a need for prospective trials to investigate optimal inotrope strategies for improving cardiac surgery outcomes. Should such trials be pursued, it should be noted that *one-size-fits-all* strategies to inotrope use following cardiac surgery - which have historically yielded indeterminate or conflicting conclusions - are unlikely to be effective.[43–45] Rather, inotrope administration strategies which account for the heterogeneity of treatment effects and dynamic patient recovery trajectories across diverse surgical populations, may be necessary to guide optimal inotrope use for cardiac surgery. Indeed, within a broader perioperative care context, the need to reduce components of variation negatively impacting outcomes *not* by introducing more standardized therapies, but rather by introducing more patient-centered therapies has been underscored in shortcomings to recent clinical trial designs comparing interventions in a *one-size-fits all* fashion. In such trials, a lack of superiority of any one standardized intervention across all outcomes was found, offering the conclusion that the "best" treatment may be less based upon objective study results and more on how each individual - clinicians and patients alike - values each outcome.[46]

More broadly still, what constitutes warranted versus unwarranted variation in health care has been a topic of recent debate.[47] A modern synthesis of the literature has suggested that clinical care variation can arise from (i) patients' and clinicians' agency, (ii) scientific and clinical evidence, and (iii) personal and organizational capacity.[23] As related to agency, warranted versus unwarranted variation dichotomizes when patients' preferences (driving warranted variation) are adequately informed yet superseded by solely clinician preferences (unwarranted). Related to evidence, variation dichotomizes when judgment in applying evidence into a local context (warranted) is absent (unwarranted). Finally related to capacity,

variation dichotomizes when intractable resource constraints and unpredictable events lead to clinician adaptation (warranted variation) versus when clinicians have varying levels of competency or technical proficiency despite local availability of training resources (unwarranted). Although our study decomposes variation in inotrope use into the patient, clinician, and institution levels, it should be noted that whereas patient-level variation might theoretically be conceived as more likely to be warranted, and clinician- and institution-level variation more likely to be unwarranted, this is not necessarily the case. To make progress on understanding components of variation which are unwarranted and - if found to negatively impact patient outcomes - could be reduced, an important next step includes defining optimal medical decision-making in a way which considers not only population-level evidence, but also patient and clinician preferences, heterogeneity of treatment effects, and local institutional policies and resource availability.

Limitations

Our study has multiple important limitations which must be carefully considered when interpreting results. First, although using intraoperative data available via a robust multicenter dataset, we were unable to fully capture all factors potentially influencing a clinician's decision to administer inotropes, and therefore components of the observed variation remained unexplained. Most notably, quantitative preoperative and intraoperative structured data describing cardiac function (e.g. left ventricular ejection fraction, right ventricular systolic function, cardiac index, mixed venous oxygen saturation, etc.), attending surgeon identifiers, or surgical details beyond valve/coronary artery bypass and cardiopulmonary bypass duration (e.g., previous sternotomy, cardioplegia type/dose, cannulation strategy, etc.), were not routinely available. Covariates collected, including cardiovascular comorbidities, medications, and intraoperative events indicative of case complexity were used, although did not comprise any previously developed risk score and likely incompletely accounted for such factors.

Second, this study involved secondary use of routinely-collected EHR data across institutions with heterogeneous documentation patterns. Although we leveraged a novel perioperative dataset across multiple US institutions and used validated, semantically interoperable MPOG concepts with advanced techniques for handling aberrations in data,[20] clinical rationales for inotrope administration were unavailable, and our study remained subject to a level of data quality inherent to observational research. Third, although detailed intraoperative documentation of inotrope administration was available, data describing postoperative intensive care unit use of inotropes were unavailable. Although data were captured on inotrope infusions continued at the time of transport from the operating room, conclusions regarding variation in the postoperative continuation or new administration of inotropes cannot be drawn from our study.

Next, although both academic medical centers and community hospitals were included in our multicenter dataset, data were primarily from academic centers, and data from institutions outside of the US were not available for this study, precluding more detailed analyses. However, hospital-level case volumes for the cardiac surgical procedures included in our study were similar to other studies reporting outcomes across a wide range of US

centers.[48,49] Lastly, our study did not investigate outcomes following inotrope use, and therefore insights regarding whether variation was warranted versus unwarranted remain unknown. Such analyses were not performed, given the high likelihood for unaddressed confounding within the causal structure underlying potential analyses relating inotrope use to cardiac surgical outcomes, which may have yielded misguided conclusions. Prospective studies of individualized, dynamic inotrope interventions versus routine care are needed to adequately assess any putative associations between inotrope use and patient outcomes.

Conclusions

Within a national, multicenter cohort of cardiac surgeries across academic and community hospitals, half of patients received intraoperative inotrope infusions. Variation in inotrope use was explained by clinician- and institution-level factors in addition to patient factors. These data provide insight into the extent of cardiac anesthesiology practice variation, and suggest a need for future prospective trials of patient-centered inotrope use, seeking to understand whether cardiac surgery outcomes can be improved, and if unwarranted variation can be reduced.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix 1: Multicenter Perioperative Outcomes Group (MPOG) Collaborators

The additional Multicenter Perioperative Outcomes Group Collaborators (and respective contributions) for this study are as follows:

Ruth Cassidy, PhD, Senior Statistician, University of Michigan Medical School, Department of Anesthesiology, Ann Arbor, MI, USA *(made substantial contributions to the acquisition, analysis, and interpretation of data for the work; and assisted in revising the work critically for important intellectual content)*;

David J. Clark, MD, PhD, Professor, Stanford University, Department of Anesthesiology, Palo Alto, CA, USA *(assisted in revising the work critically for important intellectual content)*;

Douglas A. Colquhoun, MBChB, MSc, MPH, Assistant Professor, University of Michigan Medical School, Department of Anesthesiology, Ann Arbor, MI, USA *(made substantial contributions to the acquisition, analysis, and interpretation of data for the work; and assisted in revising the work critically for important intellectual content)*;

Robert E. Freundlich, MD, MSc, Associate Professor, Vanderbilt University Medical Center, Department of Anesthesiology, Nashville, TN, USA *(made substantial contributions to the acquisition, analysis, and interpretation of data for the work; and assisted in revising the work critically for important intellectual content)*;

Elizabeth S. Jewell, MS, Senior Statistician, University of Michigan Medical School, Department of Anesthesiology, Ann Arbor, MI, USA *(made substantial contributions to the acquisition, analysis, and interpretation of data for the work; and assisted in revising the work critically for important intellectual content)*

Appendix 2: Multicenter Perioperative Outcomes Group – Study Institutions

Beaumont Hospital of Dearborn - Dearborn, Michigan

Beaumont Hospital of Royal Oak - Royal Oak, Michigan

Beaumont Hospital of Troy - Troy, Michigan

Brigham and Women’s Hospital, Boston, Massachusetts

Bronson Healthcare Group - Battle Creek, Michigan & Kalamazoo, Michigan

Cleveland Clinic, Cleveland, Ohio

Duke University Hospital, Durham, North Carolina

Henry Hord Health System, Detroit, Michigan

Massachusetts General Hospital, Boston, Massachusetts

New York University Langone Medical Center, New York, New York

Oregon Health and Science University, Portland, Oregon

Sparrow Health System, Lansing, Michigan

Stanford Health Care, Palo Alto, California

Trinity Health Muskegon Hospital, Muskegon, Michigan

Trinity Health Ann Arbor Hospital, Ann Arbor, Michigan

University of California Los Angeles Medical Center, Los Angeles, California

University of California San Francisco Medical Center, San Francisco, California

University of Colorado Denver Health Medical Center, Denver, Colorado

University of Michigan Health System, Ann Arbor, Michigan

University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma

University of Pennsylvania Health System, Philadelphia, Pennsylvania

University of Tennessee Medical Center, Knoxville, Tennessee

University of Utah Health Care, Salt Lake City, Utah

University of Vermont Health Network, Burlington, Vermont

University of Virginia Health System, Charlottesville, Virginia

Washington University of St. Louis School of Medicine, St. Louis, Missouri

Atrium Health Wake Forest Baptist Medical Center, Winston-Salem, North Carolina

Weill Cornell Medical College New York, New York

Yale New Haven Hospital, New Haven, Connecticut

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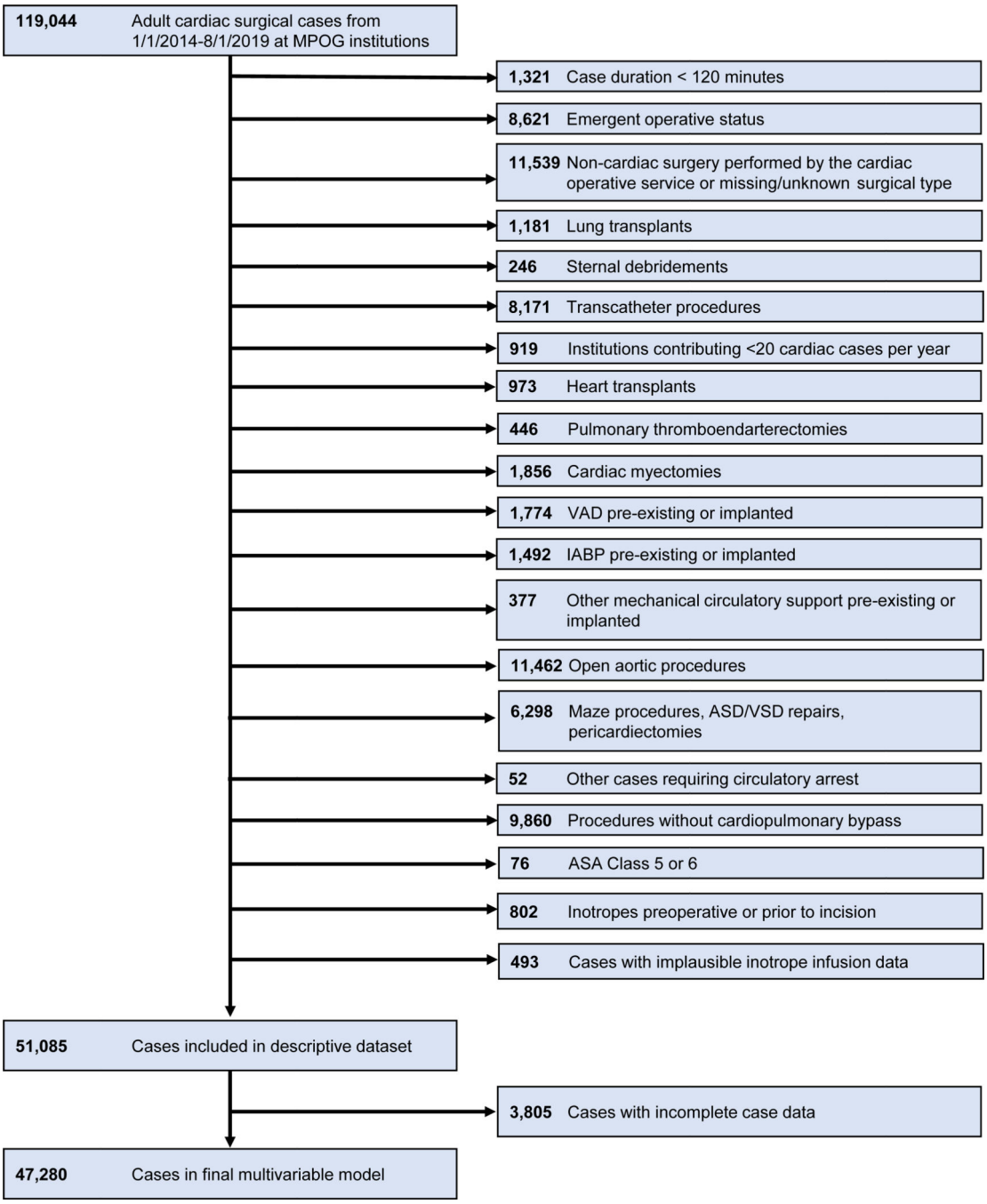

Figure 1 -

Study exclusion criteria flowchart. *ASA = American Society of Anesthesiologists; ASD = atrial septal defect; IABP = intra-aortic balloon pump; MPOG = Multicenter Perioperative Outcomes Group; VAD = ventricular assist device; VSD = ventricular septal defect*

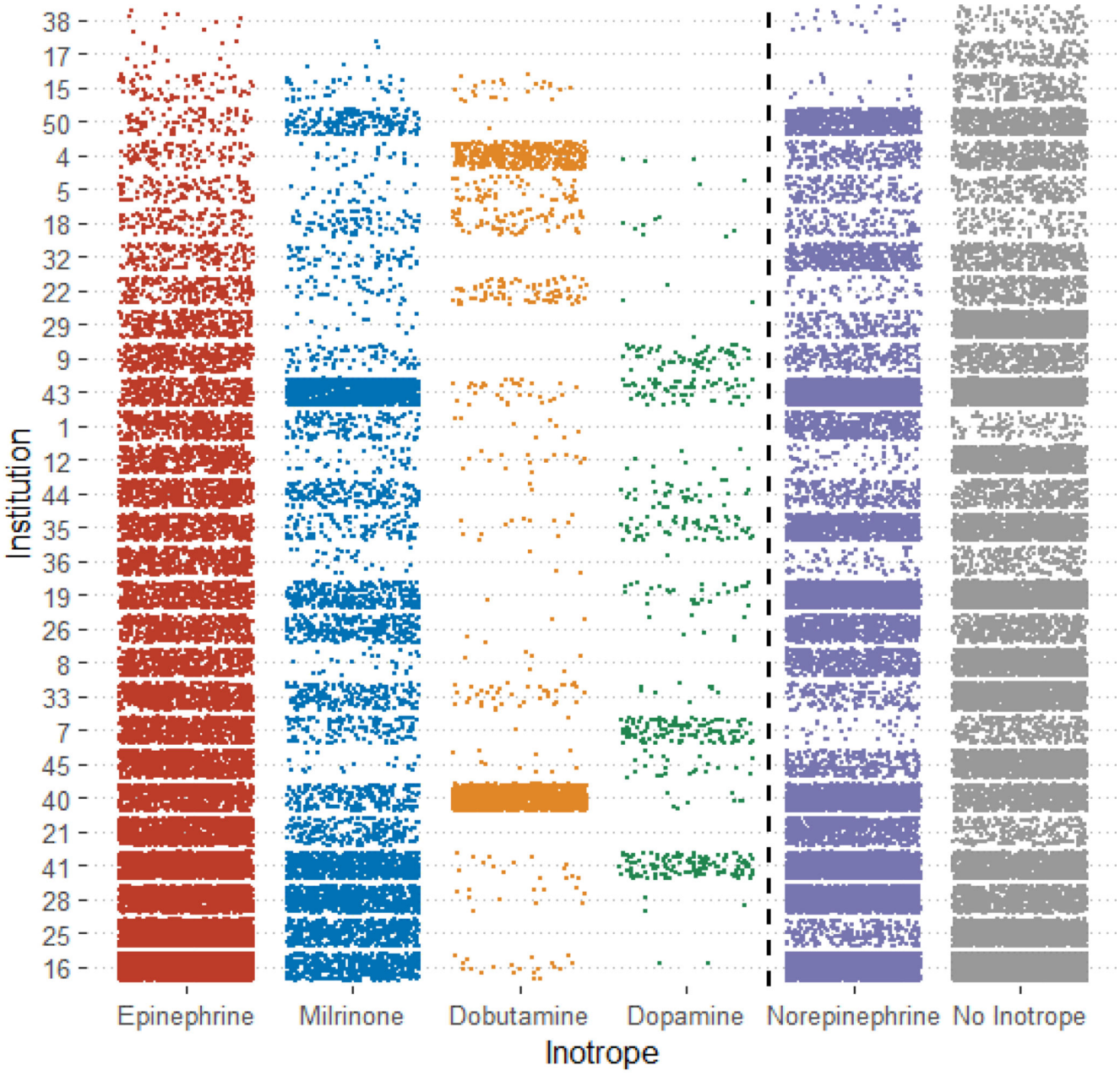

Figure 2 -

Density plot of institution-level inotrope use for cardiac surgical procedures. Each row represents one institution, and each point represents one inotrope infusion (epinephrine, milrinone, dobutamine, dopamine; *non-mutually exclusive*) used during a cardiac surgical procedure, normalized to a five-year study period. Additionally, cases with norepinephrine infusions (not considered inotropes in primary analysis) or no inotrope infusions are displayed on the right side of the figure. Anonymized institutions sorted by total number of epinephrine infusions used. Additional plots of institution-level inotrope use, normalized to annual case volume (as opposed to study period) available in Supplemental Digital Content 3.

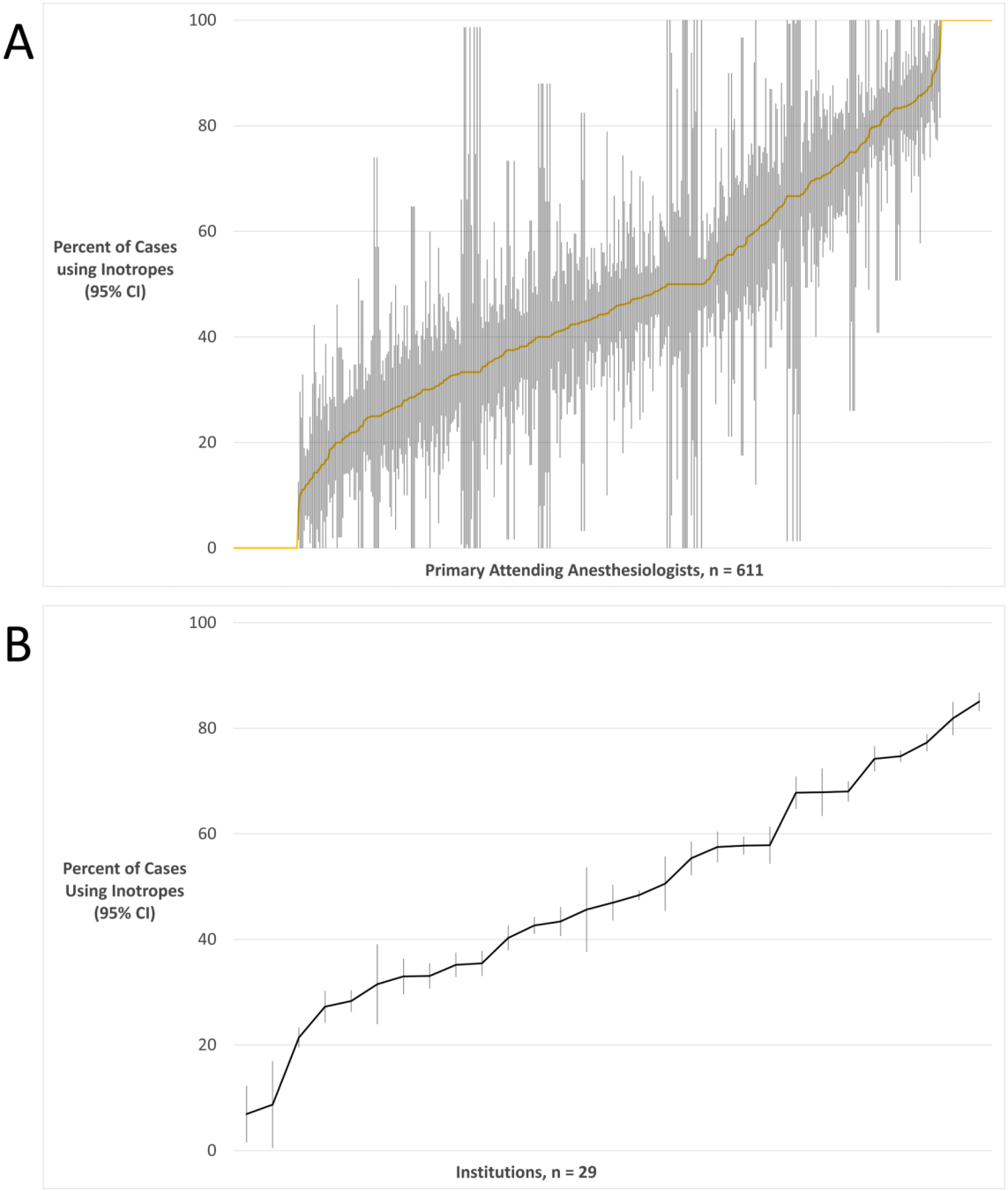

Figure 3 -

Caterpillar plots of inotrope use (percent, 95% confidence interval) rank-ordered by clinicians (inset A; n = 611) and institutions (inset B; n = 29).

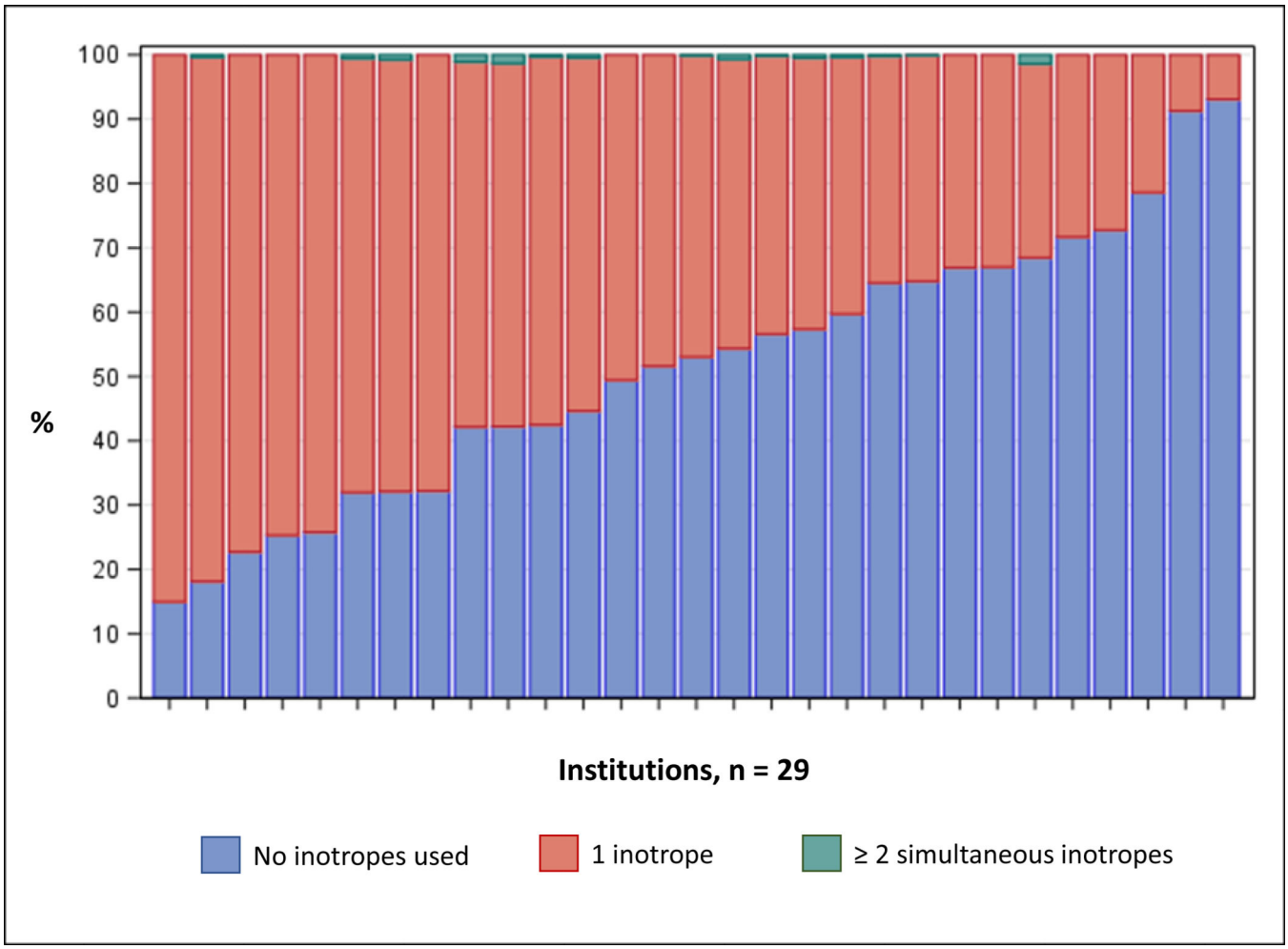

Figure 4 -
Stacked bar chart of percent of cases by institution using 0, 1, or ≥2 simultaneous intraoperative inotrope infusions.

Table 1.

Characteristics of Full Cohort and Bivariate Analyses of Patients Receiving versus Not Receiving Intraoperative Inotrope Infusions

		Full cohort (n=51,085)	Received inotropes (n=27,033)	Did not receive inotropes (n=24,052)	Standardized differences
		N (%)			
Patient Level Characteristics					
Age, years					
	18–50	6171 (12.1)	3152 (11.7)	3019 (12.6)	0.12
	51–60	10354 (20.3)	5199 (19.2)	5155 (21.4)	
	61–70	17127 (33.5)	8819 (32.6)	8308 (34.5)	
	71–80	14097 (27.6)	7851 (29.0)	6246 (26.0)	
	>80	3336 (6.5)	2012 (7.4)	1324 (5.5)	
Sex	Female	16027 (31.4)	8620 (31.9)	7407 (30.8)	0.02
	Male	34987 (68.5)	18377 (68.0)	16610 (69.1)	
	Unknown	71 (0.1)	36 (0.1)	35 (0.2)	
Race / ethnicity	Black, not of Hispanic origin	3197 (6.3)	2132 (7.9)	1065 (4.4)	0.15
	Hispanic	392 (0.8)	208 (0.8)	184 (0.8)	
	Other	1947 (3.8)	1092 (4.0)	855 (3.6)	
	Unknown	6454 (12.6)	3406 (12.6)	3048 (12.7)	
	White, not of Hispanic origin	39095 (76.5)	20195 (74.7)	18900 (78.6)	
Body mass index, kg/m^2					
	Underweight (<17.5)	602 (1.2)	373 (1.4)	229 (1.0)	0.07
	Normal weight (17.5–24.9)	12540 (24.6)	6733 (24.9)	5807 (24.2)	
	Pre-obesity (25.0–29.9)	18708 (36.6)	9612 (35.6)	9096 (37.8)	
	Obesity Class I (30.0–34.9)	11519 (22.6)	6034 (22.3)	5485 (22.8)	
	Obesity Class II (35.0–39.9)	4957 (9.7)	2710 (10.0)	2247 (9.3)	
	Obesity Class III (>=40.0)	2749 (5.4)	1568 (5.8)	1181 (4.9)	
Preoperative eGFR, mL/min/1.73 m^2					
	>=90	10457 (24.2)	4686 (21.2)	5771 (27.4)	0.27
	60–89	21433 (49.6)	10518 (47.5)	10915 (51.7)	

		Full cohort (n=51,085)	Received inotropes (n=27,033)	Did not receive inotropes (n=24,052)	Standardized differences
		N (%)			
	30–59	9466 (21.9)	5611 (25.3)	3855 (18.3)	
	<30	1899 (4.4)	1343 (6.1)	556 (2.6)	
Preoperative hemoglobin, g/dL					
	Normal (male >13.0 g/dL, female >12.0 g/dL)	28577 (66.2)	13231 (59.7)	15346 (73.1)	0.31
	Mild Anemia (male 11.0–12.9 g/dL, female 11.0–11.9 g/dL)	10902 (25.3)	6355 (28.7)	4547 (21.7)	
	Moderate/severe Anemia (<11.0 g/dL)	3685 (8.5)	2578 (11.6)	1107 (5.3)	
Pre-induction heart rate, beats/min					
	<60	12462 (25.4)	6356 (24.3)	6106 (26.7)	0.14
	60–75	19613 (40.0)	10044 (38.4)	9569 (41.9)	
	76–90	10641 (21.7)	5897 (22.6)	4744 (20.8)	
	>90	6282 (12.8)	3847 (14.7)	2435 (10.7)	
Pre-induction mean arterial pressure, mmHg					
	Hypotensive (<70)	4171 (8.2)	2667 (9.9)	1504 (6.3)	0.15
	Normotensive (70–107)	37432 (73.3)	19754 (73.1)	17678 (73.5)	
	Stage I Hypertension (108–120)	6512 (12.8)	3144 (11.6)	3368 (14.0)	
	Stage II Hypertension (>120)	2970 (5.8)	1468 (5.4)	1502 (6.2)	
Comorbidities					
	Alcohol abuse	3805 (7.5)	2084 (7.7)	1721 (7.2)	0.02
	Blood loss anemia	1038 (2.0)	607 (2.3)	431 (1.8)	0.04
	Cancer	1394 (2.7)	771 (2.9)	623 (2.6)	0.02
	Cardiac arrhythmia	28079 (55.0)	15812 (58.5)	12267 (51.0)	0.17
	Cerebrovascular Disease	6294 (13.2)	3579 (14.3)	2715 (12.0)	0.02
	Chronic pulmonary disease	10976 (21.5)	6527 (24.1)	4449 (18.5)	0.14
	Coagulopathy	16917 (33.1)	10578 (39.1)	6339 (26.4)	0.29
	Congestive heart failure	21059 (41.2)	14850 (54.9)	6209 (25.8)	0.65
	Coronary Artery Disease	30589 (64.3)	16141 (64.5)	14448 (64.1)	0.02
	Depression	5706 (11.2)	3137 (11.6)	2569 (10.7)	0.04
	Diabetes	12080 (23.7)	6728 (24.9)	5352 (22.3)	0.06

	Full cohort (n=51,085)	Received inotropes (n=27,033)	Did not receive inotropes (n=24,052)	Standardized differences
	N (%)			
Drug abuse	1358 (2.7)	771 (2.9)	587 (2.4)	0.03
Fluid/electrolyte disorders	27137 (53.1)	15061 (55.7)	12076 (50.2)	0.12
Hypertension	36964 (72.4)	19697 (72.9)	17267 (71.8)	0.02
Hypothyroidism	6523 (12.8)	3592 (13.3)	2931 (12.2)	0.04
Liver disease	2508 (4.9)	1720 (6.4)	788 (3.3)	0.15
Neurological disorder	2979 (5.8)	1929 (7.1)	1050 (4.4)	0.12
Obesity	11002 (21.5)	6083 (22.5)	4919 (20.5)	0.06
Paralysis	566 (1.1)	372 (1.4)	194 (0.8)	0.06
Peptic ulcer disease	483 (1.0)	295 (1.1)	188 (0.8)	0.04
Peripheral vascular disease	9903 (19.4)	5720 (21.2)	4183 (17.4)	0.10
Pulmonary circulation disorder	7430 (14.5)	5645 (20.9)	1785 (7.4)	0.40
Renal failure	10161 (19.9)	6657 (24.6)	3504 (14.6)	0.26
Rheumatoid arthritis	1493 (2.9)	846 (3.1)	647 (2.7)	0.03
Valvular disease	32509 (63.6)	18289 (67.7)	14220 (59.1)	0.20
Weight loss	3327 (6.5)	2518 (9.3)	809 (3.4)	0.25
ASA physical status classification				
ASA 1–3	14162 (27.7)	6995 (25.9)	7167 (29.8)	0.09
ASA 4	36923 (72.3)	20038 (74.1)	16885 (70.2)	
Home Medications, VA Classification				
BL110 - Anticoagulants	10169 (19.9)	5993 (22.2)	4176 (17.4)	0.12
BL117 - Platelet aggregation inhibitors	3551 (7.0)	1965 (7.3)	1586 (6.6)	0.03
CV050 - Digoxin	761 (1.5)	595 (2.2)	166 (0.7)	0.13
CV100 - Beta blockers	19665 (38.5)	11112 (41.1)	8553 (35.6)	0.11
CV150 - Alpha blockers	2932 (5.7)	1674 (6.2)	1258 (5.2)	0.04
CV200 - Calcium channel blockers	8614 (16.9)	4576 (16.9)	4038 (16.8)	0
CV250 - Anti-anginals	9617 (18.8)	4982 (18.4)	4635 (19.3)	−0.02
CV300 - Anti-arrhythmics	1986 (3.9)	1233 (4.6)	753 (3.1)	0.07
CV350 - Antilipemics	21556 (42.2)	11548 (42.7)	10008 (41.6)	0.02
CV490, Antihypertensives, other	2597 (5.1)	1460 (5.4)	1137 (4.7)	0.03

		Full cohort (n=51,085)	Received inotropes (n=27,033)	Did not receive inotropes (n=24,052)	Standardized differences
		N (%)			
	CV701, Thiazide diuretics	4169 (8.2)	2062 (7.6)	2107 (8.8)	−0.04
	CV702, Loop diuretics	7086 (13.9)	5186 (19.2)	1900 (7.9)	0.33
	CV703, Carbonic anhydrase inhibitors	17 (0)	11 (0)	6 (0)	0.01
	CV704, Potassium sparing diuretics	1762 (3.5)	1218 (4.5)	544 (2.3)	0.12
	CV709, Diuretics, other	553 (1.1)	208 (0.8)	345 (1.4)	−0.06
	CV800, ACE inhibitors	9892 (19.4)	5310 (19.6)	4582 (19.1)	0.02
	CV805, Angiotensin II inhibitors	5691 (11.1)	3200 (11.8)	2491 (10.4)	0.05
	HS501, Insulin	1991 (3.9)	1130 (4.2)	861 (3.6)	0.03
	HS502, Oral hypoglycemics	6463 (12.7)	3533 (13.1)	2930 (12.2)	0.03
Surgical case type					
	CABG Only	20681 (40.5)	9651 (35.7)	11030 (45.9)	0.28
	Valve Only	22987 (45.0)	12354 (45.7)	10633 (44.2)	
	Valve + CABG	7414 (14.5)	5026 (18.6)	2388 (9.9)	
Year of surgery					
	2014	6394 (12.5)	3407 (12.6)	2987 (12.4)	0.07
	2015	7729 (15.1)	4116 (15.2)	3613 (15.0)	
	2016	9043 (17.7)	5062 (18.7)	3981 (16.6)	
	2017	10754 (21.1)	5433 (20.1)	5321 (22.1)	
	2018	11002 (21.5)	5797 (21.4)	5205 (21.6)	
	2019	6163 (12.1)	3218 (11.9)	2945 (12.2)	
Weekend		454 (0.9)	229 (0.9)	225 (0.9)	0.01
Holiday		109 (0.2)	59 (0.2)	50 (0.2)	0.01
Anesthesia staffing model					
	Resident present	34614 (67.8)	18702 (69.2)	15912 (66.2)	0.06
	CRNA present	17684 (34.6)	9694 (35.9)	7990 (33.2)	0.06
		Median (IQR)			
Intraoperative fluids					
	Crystalloid, mL	1990 (1100–3000)	1850 (1009–2850)	2000 (1175–3000)	−0.05

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	Full cohort (n=51,085)	Received inotropes (n=27,033)	Did not receive inotropes (n=24,052)	Standardized differences
	N (%)			
Colloid, mL	0 (0–250)	0 (0–250)	0 (0–250)	0.02
Urine output, mL	750 (500–1150)	750 (500–1175)	715 (490–1100)	0.02
Intraoperative blood products	N (%)			
Packed red blood cell transfusion (one unit or more, non-autologous)	10762 (21.1)	7533 (27.9)	3229 (13.4)	0.05
Fresh frozen plasma transfusion (one unit or more)	5649 (11.1)	4641 (17.2)	1008 (4.2)	0.11
Platelet transfusion (one unit or more)	9688 (19.0)	7345 (27.2)	2343 (9.7)	0.31
Cryoprecipitate transfusion (one unit or more)	3879 (7.6)	3260 (12.1)	619 (2.6)	0.15
	Mean (SD)			
Intraoperative times				
Cardiopulmonary bypass duration, min	131 (74.9)	147 (82.4)	113 (60.6)	0.47
Case duration, min	390 (103.6)	416 (110.2)	360 (86.5)	0.56
Clinician Characteristics				
Anesthesiologist annual case volume (prior to exclusions)	N (%)			
Quintile 1 (Lowest, <19 per year)	9174 (18.0)	5077 (18.8)	4097 (17.0)	0.06
Quintile 2 (Low, 19–31 per year)	11068 (21.7)	4603 (17.0)	6465 (26.9)	
Quintile 3 (Medium, 31–45 per year)	13444 (26.3)	7358 (27.2)	6086 (25.3)	
Quintile 4 (High 46–75 per year)	5994 (11.7)	4477 (16.6)	1517 (6.3)	
Quintile 5 (Highest, >75 per year)	11405 (2.3)	5518 (20.4)	5887 (24.5)	
Institution Characteristics				
Number of attending anesthesiologists (over entire study period)				
Tercile 1 (Low, <25)	19,258 (37.7)	10,207 (37.8)	9,051 (37.6)	0.18
Tercile 2 (Medium, 25–38)	16,737 (32.8)	9,737 (36.0)	7,000 (29.1)	
Tercile 3 (High, >38)	15,090 (29.5)	7,089 (26.2)	8,001 (33.3)	
Percentage of cases involving a nurse anesthetist (prior to exclusions)				
Tercile 1 (Low, <3%)	24,625 (48.2)	11,759 (43.5)	12,866 (53.5)	0.25

	Full cohort (n=51,085)	Received inotropes (n=27,033)	Did not receive inotropes (n=24,052)	Standardized differences
	N (%)			
Tercile 2 (Medium, 3–83%)	12,245 (24.0)	7,755 (28.7)	4,479 (18.6)	
Tercile 3 (High, >83%)	14,215 (27.8)	7,508 (27.8)	6,707 (27.9)	
Institution annual case volume (prior to exclusions)				
Quintile 1 (Lowest, <280 per year)	18517 (36.2)	10442 (38.6)	8075 (33.6)	0.19
Quintile 2 (Low, 280–458 per year)	8119 (15.9)	3668 (13.6)	4451 (18.5)	
Quintile 3 (Medium, 459–671 per year)	8079 (15.8)	3860 (14.3)	4219 (17.5)	
Quintile 4 (High, 672–2097 per year)	7937 (15.5)	4211 (15.6)	3726 (17.5)	
Quintile 5 (Highest, >2097 per year)	8433 (16.5)	4852 (18.0)	3581 (14.9)	
Medical school-affiliated (teaching hospital)	47500 (93.0)	25603 (94.7)	21897 (91.0)	0.14

ASA = American Society of Anesthesiologists; CABG = coronary artery bypass grafting; CRNA = certified nurse anesthetist; eGFR = estimated glomerular filtration rate; IQR = interquartile range; SD = standard deviation; VA = Veterans Affairs

Table 2.

Median Odds Ratios and Variance Decomposition Statistics within Nested Models for Receiving Inotropes during Cardiac Surgery

Model Level *	Unadjusted (Null) Model N = 51,085		Adjusted (Full) Model N = 47,280	
	Median Odds Ratio	Percent of Explained Variance	Median Odds Ratio	Percent of Explained Variance
Patient Level	-	70.6%	-	55.6%
Clinician Level	1.59	6.8%	1.73	9.2%
Institution Level	2.55	22.6%	3.55	35.1%

* The unadjusted (null) and adjusted (full) models were each single, nested models. Surgical characteristics were considered to be patient-level for statistical modeling. See Table 1 for complete details on patient, clinician, and institution-level characteristics considered.

Table 3:

Multilevel Multivariable Associations of Patient-, Clinician-, and Institution-level Characteristics and Intraoperative Inotrope Use (N = 47,280)

		Adjusted Odds Ratio	95% Confidence Interval	P value
Patient Level Characteristics				
Age, years				
	18–50	Reference		
	51–60	1.03	(0.93,1.14)	0.54
	61–70	1.05	(0.95,1.16)	0.32
	71–80	1.08	(0.97,1.20)	0.17
	>80	1.14	(0.99,1.32)	0.07
Female sex		0.84	(0.79,0.89)	<0.001
Race / ethnicity				
	White, not of Hispanic origin	Reference		
	Black, not of Hispanic origin	1.49	(1.32,1.68)	<0.001
	Hispanic	0.94	(0.72,1.23)	0.67
	Other or multiracial	1.09	(1.00,1.19)	0.05
Body mass index, kg/m^2				
	Underweight (<17.5)	1.06	(0.82,1.38)	0.64
	Normal weight (17.5–24.9)	Reference		
	Pre-obesity (25.0–29.9)	1.01	(0.94,1.08)	0.75
	Obesity Class I (30.0–34.9)	1.04	(0.96,1.13)	0.37
	Obesity Class II (35.0–39.9)	1.05	(0.93,1.17)	0.44
	Obesity Class III (>=40.0)	0.99	(0.85,1.14)	0.84
Preoperative eGFR, mL/min/1.73 m^2				
	>=90	Reference		
	60–89	1.11	(1.03,1.19)	<0.001
	30–59	1.31	(1.19,1.44)	<0.001
	<30	1.28	(1.06,1.54)	0.01
Preoperative hemoglobin, g/dL				
	Normal (male >13.0 g/dL, female >12.0 g/dL)	Reference		
	Mild Anemia (male 11.0–12.9 g/dL, female 11.0–11.9 g/dL)	1.10	(1.03,1.17)	<0.001
	Moderate/severe Anemia (<11.0 g/dL)	1.21	(1.07,1.35)	<0.001
Pre-induction heart rate, beats/min				
	<60	0.92	(0.86,0.98)	0.01
	60–75	Reference		
	76–90	1.17	(1.09,1.26)	<0.001
	>90	1.42	(1.30,1.55)	<0.001
Pre-induction mean arterial pressure, mmHg				
	Hypotensive (<70)	1.15	(1.04,1.28)	0.01
	Normotensive (70–107)	Reference		

		Adjusted Odds Ratio	95% Confidence Interval	P value
	Stage I Hypertension (108–120)	0.91	(0.84,0.98)	0.02
	Stage II Hypertension (>120)	0.87	(0.77,0.97)	0.01
Comorbidities				
	Alcohol abuse	0.80	(0.60,1.07)	0.13
	Blood loss anemia	0.90	(0.75,1.08)	0.24
	Cancer	0.98	(0.84,1.14)	0.77
	Cardiac arrhythmia	1.23	(1.16,1.31)	<0.001
	Cerebrovascular Disease	0.92	(0.85,0.99)	0.03
	Chronic pulmonary disease	0.98	(0.92,1.04)	0.50
	Coagulopathy	1.11	(1.04,1.17)	<0.001
	Congestive heart failure	2.60	(2.46,2.76)	<0.001
	Coronary Artery Disease	1.03	(0.95,1.11)	0.46
	Depression	1.03	(0.95,1.12)	0.42
	Diabetes	0.97	(0.90,1.04)	0.37
	Drug abuse	0.96	(0.82,1.13)	0.62
	Fluid/electrolyte disorders	1.12	(1.06,1.19)	<0.001
	Hypothyroidism	0.92	(0.86,1.00)	0.05
	Liver disease	1.12	(0.98,1.27)	0.10
	Neurological disorder	1.03	(0.92,1.17)	0.56
	Obesity	0.96	(0.88,1.04)	0.32
	Paralysis	0.99	(0.76,1.27)	0.91
	Peptic ulcer disease	1.04	(0.80,1.34)	0.79
	Peripheral vascular disease	1.08	(1.01,1.15)	0.03
	Pulmonary circulation disorder	1.72	(1.58,1.87)	<0.001
	Renal failure	0.87	(0.75,1.01)	0.07
	Rheumatoid arthritis	1.03	(0.95,1.12)	0.50
	Valvular disease	1.10	(1.00,1.20)	0.05
	Weight loss	1.22	(1.07,1.38)	<0.001
ASA physical status classification				
	ASA 1–3	Reference		
	ASA 4	1.21	(1.13,1.29)	<0.001
Home Medications, VA Classification				
	BL110 - Anticoagulants	1.20	(1.11,1.30)	<0.001
	BL117 - Platelet aggregation inhibitors	1.13	(1.02,1.25)	0.02
	CV050 - Digoxin	1.48	(1.18,1.86)	<0.001
	CV100 - Beta blockers	1.25	(1.16,1.34)	<0.001
	CV150 - Alpha blockers	1.05	(0.94,1.17)	0.41
	CV200 - Calcium channel blockers	0.88	(0.82,0.95)	<0.001
	CV250 - Anti-anginals	1.00	(0.92,1.08)	0.93
	CV300 - Anti-arrhythmics	1.09	(0.94,1.25)	0.25

		Adjusted Odds Ratio	95% Confidence Interval	P value
	CV350 - Antilipemics	0.83	(0.77,0.90)	<0.001
	CV490, Antihypertensives, other	0.98	(0.87,1.10)	0.71
	CV701, Thiazide diuretics	0.97	(0.88,1.06)	0.50
	CV702, Loop diuretics	1.55	(1.42,1.69)	<0.001
	CV703, Carbonic anhydrase inhibitors	1.08	(0.30,3.93)	0.91
	CV704, Potassium sparing diuretics	1.39	(1.21,1.60)	<0.001
	CV709, Diuretics, other	0.88	(0.66,1.18)	0.39
	CV800, ACE inhibitors	0.96	(0.89,1.04)	0.31
	CV805, Angiotensin II inhibitors	0.99	(0.91,1.08)	0.79
	HS501, Insulin	1.05	(0.92,1.21)	0.47
	HS502, Oral hypoglycemics	1.06	(0.97,1.17)	0.18
Surgical case type				
	CABG Only	Reference		
	Valve Only	1.05	(0.94,1.16)	0.40
	Valve + CABG	1.23	(1.10,1.37)	<0.001
Year of surgery				
	2014	1.01	(0.88,1.14)	0.93
	2015	0.92	(0.82,1.03)	0.13
	2016	1.07	(0.97,1.19)	0.17
	2017	0.83	(0.76,0.91)	<0.001
	2018	1.12	(1.02,1.22)	0.02
	2019	Reference		
Weekend		1.20	(0.93, 1.56)	0.16
Holiday		1.31	(0.76,2.26)	0.33
Anesthesia staffing model				
	Resident present	1.16	(1.05,1.28)	<0.001
	CRNA present	1.05	(0.93,1.19)	0.46
Intraoperative fluids				
	Crystalloid (per 1000 mL)	0.99	(0.97, 1.01)	0.19
	Colloid (per 1000 mL)	1.03	(0.95,1.11)	0.53
	Packed red blood cells (per unit)	1.00	(1.00, 1.00)	0.72
	Fresh frozen plasma (per unit)	1.00	(1.00, 1.00)	0.66
	Platelets (per bag)	1.00	(1.00, 1.001)	<.0001
	Cryoprecipitate (per bag)	1.00	(1.00, 1.002)	<.0001
	Urine output (per 1000 mL)	0.97	(0.93,1.01)	0.13
Intraoperative times				
	Cardiopulmonary bypass duration (per hour)	1.21	(1.17,1.26)	<.0001
	Case duration (per hour)	1.31	(1.27,1.34)	<.0001
Clinician Characteristics				
Anesthesiologist annual case volume (prior to exclusions)				

		Adjusted Odds Ratio	95% Confidence Interval	P value
	Quintile 1 (Lowest, <19 per year)	Reference		
	Quintile 2 (Low, 19–31 per year)	0.84	(0.70,1.01)	0.07
	Quintile 3 (Medium, 31–45 per year)	0.87	(0.70,1.08)	0.20
	Quintile 4 (High 46–75 per year)	0.88	(0.67,1.15)	0.34
	Quintile 5 (Highest, >75 per year)	1.07	(0.75,1.54)	0.70
Institution Characteristics				
Number of attending anesthesiologists (over entire study period)				
	Tercile 1 (Low, <25)	Reference		
	Tercile 2 (Medium, 25–38)	0.46	(0.116,1.84)	0.28
	Tercile 3 (High, >38)	0.53	(0.022,12.7)	0.70
Percentage of cases involving a nurse anesthetist (before exclusions)				
	Tercile 1 (Low, <3%)	Reference		
	Tercile 2 (Medium, 3–83%)	1.24	(0.278,5.5)	0.78
	Tercile 3 (High, >83%)	5.3	(0.59,47.7)	0.14
Institution annual case volume (prior to exclusions)				
	Quintile 1 (Lowest, <280 per year)	Reference		
	Quintile 2 (Low, 280–458 per year)	1.15	(0.313,4.209)	0.84
	Quintile 3 (Medium, 459–671 per year)	0.71	(0.113,4.507)	0.72
	Quintile 4 (High, 672–2097 per year)	3.62	(0.155,84.628)	0.42
	Quintile 5 (Highest, >2097 per year)	0.268	(0.002,37.254)	0.60
Medical school-affiliated (teaching hospital)		6.2	(1.39,27.8)	0.02

ASA = American Society of Anesthesiologists; CABG = coronary artery bypass grafting; CRNA = certified nurse anesthetist; eGFR = estimated glomerular filtration rate; IQR = interquartile range; SD = standard deviation; VA = Veterans Affairs