ORIGINAL CLINICAL RESEARCH REPORT

Opioid Dose Variation in Cardiac Surgery: A Multicenter Study of Practice

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BACKGROUND: Although high-opioid anesthesia was long the standard for cardiac surgery, some anesthesiologists now favor multimodal analgesia and low-opioid anesthetic techniques. The typical cardiac surgery opioid dose is unclear, and the degree to which patients, anesthesiologists, and institutions influence this opioid dose is unknown.

METHODS: We reviewed data from nonemergency adult cardiac surgeries requiring cardiopulmonary bypass performed at 30 academic and community hospitals within the Multicenter Perioperative Outcomes Group registry from 2014 through 2021. Intraoperative opioid administration was measured in fentanyl equivalents. We used hierarchical linear modeling to attribute opioid dose variation to the institution where each surgery took place, the primary attending anesthesiologist, and the specifics of the surgical patient and case.

RESULTS: Across 30 hospitals, 794 anesthesiologists, and 59,463 cardiac cases, patients received a mean of 1139 (95% confidence interval [CI], 1132–1146) fentanyl mcg equivalents of opioid, and doses varied widely (standard deviation [SD], 872 μg). The most frequently used opioids were fentanyl (86% of cases), sufentanil (16% of cases), hydromorphone (12% of cases), and morphine (3% of cases). 0.6% of cases were opioid-free. 60% of dose variation was explainable by institution and anesthesiologist. The median difference in opioid dose between 2 randomly selected anesthesiologists across all institutions was 600 μg of fentanyl (interquartile range [IQR], 283–1023 μg). An anesthesiologist's intraoperative opioid dose was strongly correlated with their frequency of using a sufentanil infusion ($r = 0.81$), but largely uncorrelated with their use of nonopioid analgesic techniques ($|r| < 0.3$).

CONCLUSIONS: High-dose opioids predominate in cardiac surgery, with substantial dose variation from case to case. Much of this variation is attributable to practice variability rather than patient or surgical differences. This suggests an opportunity to optimize opioid use in cardiac surgery. (Anesth Analg 2025;140:1016–27)

KEY POINTS

- **Question:** How are opioids being used during contemporary cardiac surgery and what drives opioid dose variation from case to case?
- **Findings:** Intraoperative opioid doses during cardiac surgery vary widely from no opioids to more than 10,000 fentanyl mcg equivalents, and >50% of this variation was explainable by the institution and attending anesthesiologist; regular use of multimodal analgesia was not meaningfully associated with lower doses of opioids, while sufentanil infusion use was strongly associated with higher doses of opioids.
- **Meaning:** The wide range of opioid doses used by different cardiac anesthesiologists at different institutions provides an opportunity to optimize intraoperative opioid use.

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Anesthetic practices vary across anesthesiologists and institutions, even after accounting for differences in patient and procedure.[1–3] Such variation in opioid dose could dramatically affect patient outcomes. High intraoperative opioid doses seemingly change postoperative pain trajectories,[4] and some worry that they predispose to opioid use and misuse.[5] These concerns are particularly relevant to cardiac anesthesia, where opioid doses have historically been much higher than in other areas of anesthesiology.[6,7] To understand if individual or institutional approaches to opioid dosing during cardiac surgery might have a meaningful impact, it is necessary to know (1) whether anesthesiologists and institutions influence opioid dose and (2) how large this influence is.

Evolving cardiac anesthesia practice has potentially led to greater variation in opioid dose. While cardiac anesthesia long relied on high-opioid doses to maximize hemodynamic stability,[7] it has become clear that certain cardiac surgeries can be performed safely with lower doses or no opioids whatsoever.[8] A recent consensus recommendation suggests these newer approaches may reduce harm, and advocates against routine use of high-dose opioids for patients undergoing cardiac surgery.[9] However, there is a lack of current information about whether and how anesthesiologists across the country are forgoing high-dose opioids, and the factors that determine opioid dose during cardiac surgery. This limits our knowledge of the range of opioid doses in clinical use and our ability to understand the role that anesthesiologists play in determining opioid dose and its downstream effects.

To reveal the current use of opioids in cardiac surgery, we studied data collected by the Multicenter Perioperative Outcomes Group (MPOG), an anesthetic practice registry with more than 10 million cases across all procedural specialties.[10] Specifically, we analyzed the use of intraoperative opioids in nonemergent, on-pump cardiac surgery across 30 institutions. We identified factors explaining opioid dose, including case characteristics, the primary anesthesiologist, and the institution where the surgery took place. We hypothesized that opioid administration during these cases is meaningfully influenced by the specific anesthesiologist and institution, even after accounting for case-level factors. This could suggest unwarranted variation in opioid dose and reveal an attractive target for attempts to optimize intraoperative opioid use.[11]

METHODS

Study Design

We obtained approval from the Yale University Institutional Review Board with a waiver of informed consent. We followed the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) extension of STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines.[12] Analytic and statistical plans were approved within a multi-institutional peer-review forum and registered on Open Science Framework (https://osf.io/ndztg/) before data access. After data access and descriptive analysis, but before inferential analysis, these plans were amended (see the section "Outcome"), represented at the peer-review forum, and updated on Open Science Framework.

Population

We included patients ≥18 years of age who underwent cardiac surgery at MPOG institutions between January 1, 2014, and December 31, 2021. To focus on a representative set of cardiac procedures, we manually classified surgical procedure text and limited analyzed cases to coronary artery bypass grafting (CABG), valve surgery, or combinations of CABG and valve surgery. The surgical approach (sternotomy or minithoracotomy) was not specified in the available dataset. This cohort was based on one used in 2 earlier studies.[13,14] As in those studies, we considered only cases using general endotracheal anesthesia with invasive blood pressure monitoring. To limit practice variation due to profound hemodynamic instability, we excluded emergency cases, ASA 5 patients, and patients with an in-situ airway before the case (Figure 1). To focus on a widely representative set of cases with a shared anesthetic course, we further excluded cases without cardiopulmonary bypass (CPB), with CPB duration <30 minutes, with deep hypothermic circulatory arrest, with extremes of case duration, or with outlier anthropometrics. To minimize the impact of equianalgesic conversion uncertainty, we considered only the most common opioids (those used in at least 1% of cases) and excluded all cases using other, uncommon opioids (Supplemental Digital Content 1, Supplemental Table 1, http://links.lww.com/AA/E923). As prespecified in our data analysis plan, we also excluded cases where methadone was used during the case or the 2 hours prior, due to its unique pharmacokinetics and nonopioid effects.[15] If a single patient underwent multiple procedures, only the first was included in our analytic cohort (Figure 1).

Outcome

The primary outcome was intraoperative opioid exposure between anesthesia start and anesthesia end. We used equianalgesic equivalency to convert nonfentanyl opioids to fentanyl equivalents.

Opioid Equivalency Approach. Our initial analytic plan called for using the dose equivalency ratios provided by MPOG.[16] However—before inferential analysis—we

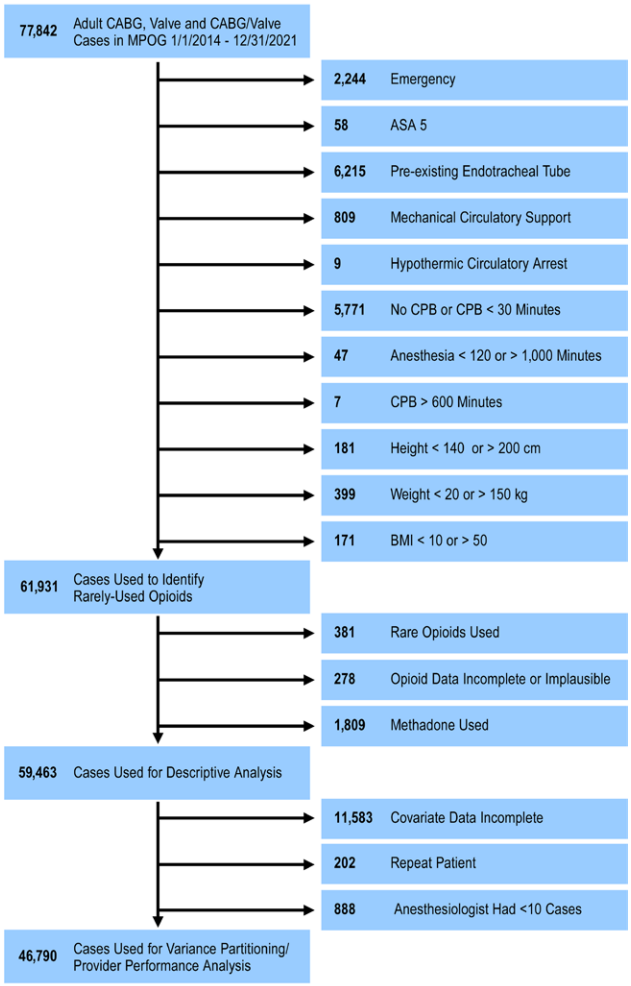

Figure 1. Cohort definition flowchart.

observed that (1) sufentanil was the second most common opioid after fentanyl and that (2) published sufentanil:fentanyl dose equivalency ratios are wide-ranging (spanning 1:2.5–1:24).[15] To use the most accurate dose equivalency ratio between sufentanil and fentanyl, we decided to calculate a dose equivalency ratio from the better-defined plasma-concentration equivalency between sufentanil and fentanyl.[17,18]

We therefore calculated a measure of each opioid's effect: the fentanyl equivalent effect-site concentration area under the curve (Ce AUC; Supplemental Digital Content 2, Supplemental Figure 1, http://links.lww.com/AA/E924). We determined the fentanyl equivalent Ce AUC by modeling the effect-site concentration (Ce) of each opioid using the default models within stanpumpR, a pharmacokinetic simulator.[19] We converted the Ce of each opioid to fentanyl equivalent Ce (ng/mL) using plasma-concentration equivalency ratios.[20] We then integrated the area under the Ce-time curve between anesthesia start and anesthesia end, yielding the fentanyl equivalent Ce AUC (in ng·min·mL^{-1}).

To correlate fentanyl and sufentanil dose using this measure of opioid activity, we linearly modeled the relationship between intraoperative dose and fentanyl equivalent Ce AUC for each drug (Supplemental Digital Content 2, Supplemental Figure 2A, http://links.lww.com/AA/E924). The ratio of the slopes of these lines, 1:11, is the sufentanil:fentanyl dose equivalency ratio used in this study. This estimate is in the middle of the range of previously described ratios, and close to the 1:10 ratio used by prior investigators.[15] For hydromorphone and morphine, we used dose equivalency ratios used by MPOG[16] (hydromorphone:fentanyl = 15:1, morphine:fentanyl = 100:1).

As an alternative measure of opioid exposure, we also considered the total fentanyl equivalent Ce AUC summed across all opioids. This measure accounts for differences in opioid pharmacokinetics and patient size, although its units (fentanyl equivalent ng·min·mL^{-1}) are more difficult to conceptualize than fentanyl mcg equivalents. In our sample, fentanyl equivalent Ce AUC was highly correlated with fentanyl mcg equivalents ($r = 0.96$; Supplemental Digital Content 2, Supplemental Figure 2B, http://links.lww.com/AA/E924), suggesting that dose equivalents may accurately estimate opioid exposure in this cohort.

We defined the primary opioid for each case as the opioid with the highest fentanyl, equivalent Ce AUC. When fentanyl equivalent Ce AUC was unknown due to missing anthropometrics, the primary opioid was the opioid accounting for the most fentanyl mcg equivalents.

Covariates

The primary covariates were the institution where the surgery took place and the attending anesthesiologist signed in for the largest proportion of the surgery.

Other covariates available within the MPOG dataset that plausibly influenced the dose of intraoperative opioids were considered, including patient demographics (age, sex, race, and ethnicity), anthropometrics (weight, body mass index [BMI]), baseline hemodynamics (first in-room mean arterial pressure, pulse pressure, and heart rate), preoperative laboratory values (hemoglobin, estimated glomerular filtration rate [eGFR]), ICD-derived comorbidities (Elixhauser[21] comorbidities, coronary artery disease, cerebrovascular disease), date of service (year, weekend, holiday), and anesthesia duration (divided into pre-CPB, CPB, and post-CPB duration). These values had been precomputed by MPOG using phenotype algorithms.[10,16] In addition, we considered surgery type (CABG, valve, or CABG/valve) manually derived from free-text surgical descriptions. Finally, we included ICD-derived diagnoses of chronic pain

(G89.0, G89.2, G89.3, G89.4) and opioid use (R78.1, Z79.891, F11.1, F11.2, F11.9). Because BMI had a variance inflation factor >5 (5.9) and was correlated with patient weight, we excluded it from our models.

Subsequent analyses explored possible correlates of each anesthesiologist's opioid use, including the primary opioid used, the use of nonopioid analgesics (including regional/neuraxial anesthesia, acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs], and others), and the presence of clinical trainees or certified registered nurse anesthetists (CRNAs).

Data Handling

One institution with inconsistent provider coding and 6 with inconsistent documentation of CPB were identified and excluded before cohort selection. First in-room mean arterial blood pressures <50 mm Hg or > 150 and first in-room heart rates <40 or > 140 were considered artifactual and treated as missing. Hemoglobin and eGFR values were truncated at the 1st and 99th percentiles. Data missingness was assessed: no predictor, covariate, or outcome had missingness >5%. Missingness patterns were consistent with missing at random. Therefore, after descriptive summary analyses, we elected to conduct complete case analyses for our hierarchical models.

Statistical Analysis

Statistical analyses were performed and visualized in R 4.3.0[22] using the tidyverse 2.0.0 package collection.[23] Correlations were quantified with the Pearson correlation coefficient (r). A value of $P < .05$ was considered statistically significant.

Modeling. To determine contributions of case-level factors, anesthesiologist, and institution to variation in intraoperative opioid dose, we used hierarchical linear modeling, with anesthesiologist and institution as hierarchically organized random effects (case nested within anesthesiologist, anesthesiologist nested within institution). The lme4 1.1.33 package[24] was used for modeling. Two separate models were fit to the same analytic cohort: one with fentanyl mcg equivalents as the outcome, the other with fentanyl Ce AUC as the outcome, but otherwise identically specified.

Our causal model of opioid dosing in cardiac surgery is illustrated as a directed acyclic graph[25] in Supplemental Digital Content 2, Supplemental Figure 3, http://links.lww.com/AA/E924. To account for differences in patient- and case-mix across institutions and anesthesiologists, we included patient and case factors (listed above in "Covariates") as fixed effects in our hierarchical model. To fully capture variability attributable to institution and anesthesiologist, our model did not include fixed effects covariates downstream of institution and anesthesiologist, such as anesthetic techniques or the involvement of trainees. Because anesthetic duration may reflect case complexity, durations were included as fixed effects in our model even though they are causally downstream of institution. Thus, the full influence of institutions may be underestimated in this analysis.

To demonstrate the influence of patient and case covariates on opioid use, we created marginal effect displays—holding other continuous covariates at their means and averaging over other categorical covariates assuming the category distribution from our entire sample—using the effects 4.2.2 package.[26]

Variance Partitioning. To quantify the variation in opioid dose attributable to institution and anesthesiologist, we calculated intraclass correlation coefficients (ICCs)[27] with our hierarchical models. The ICC is the ratio of variance captured at 1 level of the model to the total variance in the data. Therefore, an ICC of 0.1 at the institution level would suggest that 10% of the difference in opioid dose between cases was attributable to the institution where each case was performed. When investigators explore hierarchical sources of variation in clinical care, they usually exclude the variance accounted for by fixed effects from the denominator of each ICC.[13,14,28] While we used this ICC formulation (called the "adjusted ICC") for our primary analysis, we also performed a sensitivity analysis where we included both fixed effects variance and random effects variance in the ICC denominator (here called simply the "ICC").[29] Residual variance not explained by modeled random effects (such as institution and anesthesiologist) is typically attributed to the individual case level.[12,13] Because all fixed effects in our model are case-level, we also attributed the fraction of variance attributable to fixed effects (sometimes[29] called the marginal R^2) to the individual case level.

Median Absolute Difference. To demonstrate the significance of the variance distribution captured by our hierarchical model, we estimated the median absolute difference in opioid dose between identical patients treated by randomly selected anesthesiologists. This is a conceptual relative of the median odds ratio,[3,13,14,30] but is applicable to continuous outcomes (like opioid dose) rather than binary outcomes (like use or nonuse of opioids). Its calculation is explained in Supplemental Digital Content 3, Supplemental Document 1, http://links.lww.com/AA/E925.

Risk-standardized Opioid Dose. We calculated risk-standardized opioid doses to quantify the opioid dose administered by each anesthesiologist while adjusting for differences in patient- and case-mix. We

used risk standardization methods initially developed to rate hospital performance.[31,32] These methods and determination of confidence intervals[33,34] are explained in Supplemental Digital Content 3, Supplemental Document 2, http://links.lww.com/AA/E925.

RESULTS

Pattern of Opioid Use During Contemporary Cardiac Surgery

From the MPOG database, we identified 30 institutions (Supplemental Digital Content 3, Supplemental Document 3, http://links.lww.com/AA/E925) with acceptable data quality and 61,931 cardiac surgical cases meeting our criteria. Only 5 opioids—IV fentanyl, sufentanil, hydromorphone, morphine, and methadone—were regularly used in these cases (Supplemental Digital Content 1, Supplemental Table 1, http://links.lww.com/AA/E923). After excluding the 0.6% of cases that used other opioids, the 0.4% that had incomplete opioid dosage data, and the 2.9% that used methadone (see Methods), 59,463 cardiac cases remained for descriptive analysis (Figure 1). This cohort (Table 1) was 69% male and 80% white, with a median age of 66 (interquartile range [IQR], 58–73). It was treated by 794 anesthesiologists across the 30 institutions. Fentanyl was the primary opioid used in 49,067 cases (82.5%) and the sole opioid used in 41,040 cases (69.0%). The primary opioid was sufentanil in 9230 cases (15.5%), hydromorphone in 532 (0.9%), and morphine in 262 (0.4%). 10,782 cases (18.1%) used a combination of opioids. 372 cases (0.6%) were entirely opioid-free. The most common opioids and opioid combinations varied by institution (Supplemental Digital Content 2, Supplemental Figure 4, http://links.lww.com/AA/E924).

The distribution of intraoperative opioid dose was broad and right-skewed (Figure 2). The mean (standard deviation [SD]) dose was 1139 (872) fentanyl mcg equivalents (95% confidence interval [CI], 1132–1146). 20.4% of cases used exactly 1000 fentanyl mcg equivalents; this was both the median and modal dose. Sufentanil was typically the primary opioid when more than 2000 fentanyl mcg equivalents were administered. Opioid dose distribution varied dramatically by institution, with institutional means ranging sixfold from 505 to 3086 fentanyl mcg equivalents (Supplemental Digital Content 2, Supplemental Figure 5, http://links.lww.com/AA/E924).

As an alternative measure of opioid administration, we modeled opioid exposure as the area under the curve of opioid effect-site concentration over time (fentanyl equivalent Ce AUC). The distribution of this measure was similarly broad and right-skewed, with a mean (SD) fentanyl equivalent Ce AUC of 835 (645) ng·min·mL^{-1} and a maximum of 12,853 ng·min·mL^{-1} (Supplemental Digital Content 2, Supplemental Figure 6, http://links.lww.com/AA/E924). Institutional means again ranged sixfold, from 410 to 2429 ng·min·mL^{-1} (Supplemental Digital Content 2, Supplemental Figure 7, http://links.lww.com/AA/E924).

Association Between Case Factors and Opioid Use

To understand how opioid dose related to anesthesiologist and institution, we fit a hierarchical linear model with each case nested within its anesthesiologist and each anesthesiologist nested within their institution. For this regression, we performed a complete case analysis including the 525 anesthesiologists with at least 10 cases available, yielding 46,790 cases (Figure 1 and Table). Mean opioid dose in this cohort was 1109 fentanyl mcg equivalents (95% CI, 1102–1117). Both the fixed effects used to adjust for case-mix and the random effects representing anesthesiologist and institution improved model performance (Supplemental Digital Content 1, Supplemental Table 2, http://links.lww.com/AA/E923).

The coefficients of the fixed effects (Supplemental Digital Content 1, Supplemental Table 3, http://links.lww.com/AA/E923) provide insight into how case factors relate to opioid dose. They should be interpreted cautiously, keeping in mind other modeled and unmodeled covariates (Supplemental Digital Content 2, Supplemental Figure 3). More recent case years were associated with lower opioid use, with surgeries in 2021 using 478 fewer fentanyl mcg equivalents on average than surgeries in 2014 (Figure 3A, 95% CI, −509 to −447). Each additional year of patient age was associated with an average decrease of 3.7 fentanyl mcg equivalents (Figure 3B, 95% CI, −4.2 to −3.2). Each additional kilogram of patient weight was associated with an average increase of 3.6 fentanyl mcg equivalents (Figure 3C, 95% CI, 3.3–3.9). The effects of case duration were similar across different intraoperative periods (prebypass, bypass, and postbypass): every additional 10 intraoperative minutes was associated with an additional 5.1 to 5.9 fentanyl mcg equivalents on average (Figure 3D–F, 95% CIs for all periods spanned 4.2–7.1).

Impact of Institution and Anesthesiologist on Opioid Use

After adjusting for available case-level covariates, 46% of variability in opioid dose was attributable to the institution, 14% was attributable to the specific anesthesiologist within the institution, and 40% remained unexplained by the institution or anesthesiologist. Alternative approaches to variance partitioning (which included variation from case-level

Table 1. Statistical Description of Cohorts

	Descriptive cohort (n = 59,463)[a]	Analytic cohort (n = 46,790)[a]
Age (y)	66 (58–73)	66 (58–73)
Sex		
Male	41,036 (69%)	32,241 (69%)
Female	18,427 (31%)	14,549 (31%)
Race		
White	47,658 (80%)	37,916 (81%)
Black	4022 (6.8%)	3030 (6.5%)
Other or unknown	7783 (13%)	5844 (12%)
Ethnicity		
Non-Hispanic	54,045 (91%)	42,839 (92%)
Hispanic	577 (1.0%)	448 (1.0%)
Unknown	4841 (8.1%)	3503 (7.5%)
Weight (kg)	84 (72–98)	84 (72–98)
BMI	28.1 (24.8–32.1)	28.1 (24.8–32.1)
ASA physical status		
II	339 (0.6%)	238 (0.5%)
III	16,028 (27%)	13,113 (28%)
IV	43,096 (72%)	33,439 (71%)
Preoperative eGFR (mL/min)	74 (58–89)	75 (58–89)
Preoperative hemoglobin (g/dL)	13.4 (11.9–14.6)	13.5 (12.0–14.6)
First in-room mean blood pressure (mm Hg)	97 (86–109)	97 (86–108)
First in-room pulse pressure (mm Hg)	70 (55–88)	70 (55–88)
First in-room heart rate (bpm)	71 (63–81)	71 (63–80)
Comorbidities		
AIDS/HIV	195 (0.3%)	141 (0.3%)
Alcohol abuse	866 (1.5%)	653 (1.4%)
Blood loss anemia	1346 (2.3%)	1014 (2.2%)
Cardiac arrhythmia	37,994 (64%)	30,431 (65%)
Cerebrovascular disease	11,330 (19%)	9027 (19%)
Chronic pain	394 (0.7%)	300 (0.6%)
Chronic pulmonary disease	13,941 (24%)	11,005 (24%)
Coagulopathy	20,828 (35%)	16,937 (36%)
Congestive heart failure	28,332 (48%)	22,815 (49%)
Coronary artery disease	42,576 (72%)	33,435 (71%)
Deficiency anemia	2573 (4.4%)	2042 (4.4%)
Depression	7763 (13%)	6069 (13%)
Diabetes with complications	7268 (12%)	5752 (12%)
Diabetes without complications	12,656 (21%)	9782 (21%)
Drug abuse	2012 (3.4%)	1523 (3.3%)
Fluid/electrolyte disorders	34,195 (58%)	27,106 (58%)
Hypertension with complications	22,428 (38%)	17,995 (38%)
Hypertension without complications	36,200 (61%)	28,631 (61%)
Hypothyroidism	8216 (14%)	6615 (14%)
Liver disease	3556 (6.0%)	2808 (6.0%)
Lymphoma	460 (0.8%)	360 (0.8%)
Metastatic cancer	273 (0.5%)	218 (0.5%)
Obesity	14,503 (25%)	11,711 (25%)
Opioid use	638 (1.1%)	488 (1.0%)
Other neurological disorders	4177 (7.1%)	3209 (6.9%)
Paralysis	813 (1.4%)	656 (1.4%)
Peptic ulcer disease	126 (0.2%)	98 (0.2%)
Peripheral vascular disorders	13,493 (23%)	10,660 (23%)
Psychoses	381 (0.6%)	290 (0.6%)
Pulmonary circulation disorders	9755 (17%)	7840 (17%)
Renal failure	13,659 (23%)	10,864 (23%)
Rheumatoid arthritis/collagen vascular diseases	1995 (3.4%)	1600 (3.4%)
Solid tumor without metastasis	1572 (2.7%)	1240 (2.7%)
Valvular disease	40,851 (69%)	32,752 (70%)
Weight loss	4196 (7.1%)	3282 (7.0%)
Procedure		
CABG	25,073 (42%)	19,146 (41%)
Valve surgery	26,016 (44%)	20,931 (45%)
CABG and valve surgery	8374 (14%)	6713 (14%)
Durations (min)		
Precardiopulmonary bypass duration	150 (119–187)	150 (118–187)
Cardiopulmonary bypass duration	110 (83–149)	110 (82–149)
Postcardiopulmonary bypass duration	103 (85–128)	103 (84–128)

(*Continued*)

Table 1. Continued

	Descriptive cohort (n = 59,463)[a]	Analytic cohort (n = 46,790)[a]
Year of surgery		
2014	4649 (7.8%)	3727 (8.0%)
2015	6479 (11%)	4991 (11%)
2016	7363 (12%)	5946 (13%)
2017	9183 (15%)	7514 (16%)
2018	10,926 (18%)	8506 (18%)
2019	10,952 (18%)	8653 (18%)
2020	5513 (9.3%)	3984 (8.5%)
2021	4398 (7.4%)	3469 (7.4%)
Weekend surgery	714 (1.2%)	495 (1.1%)
Holiday surgery	137 (0.2%)	106 (0.2%)
Outcomes		
Opioid dose (fentanyl mcg equivalents)	1000 (700–1250)	1000 (700–1250)
Modeled opioid exposure (fentanyl equivalent AUC ng·min·mL^{-1})	697 (499–944)	693 (501–928)

Abbreviations: AIDS/HIV, acquired immunodeficiency syndrome/human immunodeficiency virus; ASA, American Society of Anesthesiologists; AUC, area under the curve; BMI, body mass index; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate.
[a]Median (interquartile range); *n* (%).

covariates, were based on fentanyl equivalent Ce AUC rather than opioid dose, or considered the subpopulation of isolated CABGs) yielded similar estimates (Supplemental Digital Content 1, Supplemental Tables 4 and 5, http://links.lww.com/AA/E923). No matter the approach, >50% of opioid administration variability during cardiac surgery was attributable to a combination of institution and anesthesiologist.

To better understand the impact of this variance distribution, we estimated the median absolute difference in dose across anesthesiologists. This represents the median amount a patient would expect their opioid dose to change by if they were treated by one randomly chosen anesthesiologist rather than another. The median absolute difference in opioid dose between anesthesiologists within a single institution was 287 fentanyl mcg equivalents (IQR, 136–490). The median absolute difference in dose between anesthesiologists across all institutions was 600 fentanyl mcg equivalents (IQR, 283–1023).

We also estimated the risk-standardized opioid dose used by each anesthesiologist within our sample (Figure 4). These estimates reflect the influence

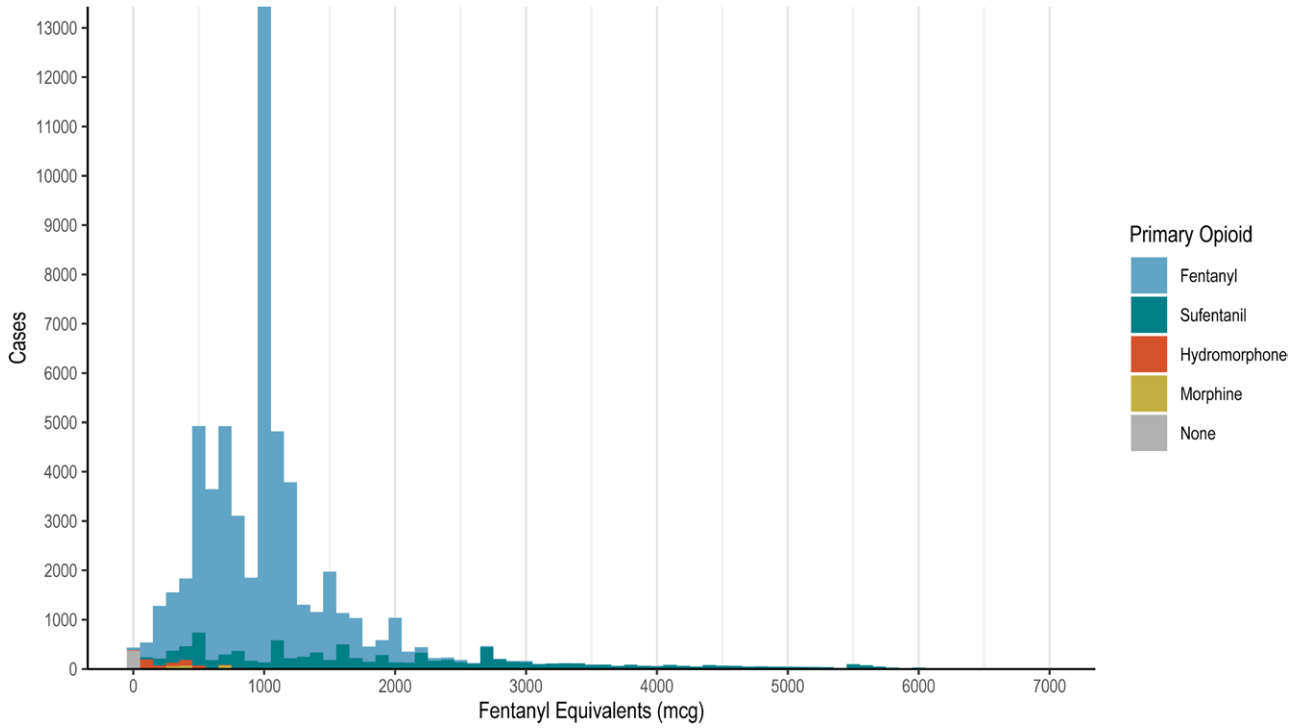

Figure 2. Distribution of intraoperative opioid dose. Unadjusted intraoperative opioid doses given for cases in the descriptive cohort. The color of each bar segment denotes the primary opioid used. This histogram excludes 92 cases (0.15% of descriptive cohort) with opioid doses exceeding 7000 fentanyl mcg equivalents.

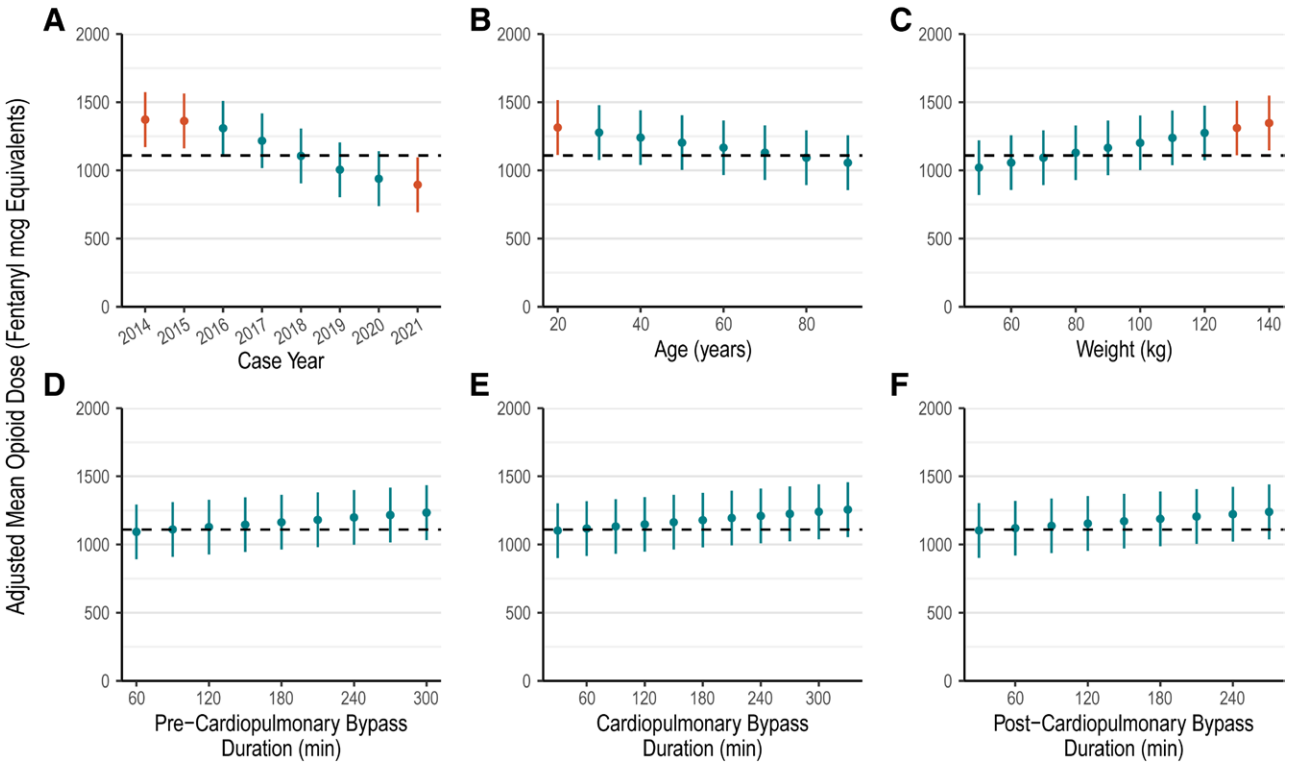

Figure 3. Opioid dose association with year, age, weight, and anesthesia durations. Effect displays showing the relationship between intraoperative opioid dose and (A) case year, (B) patient age, (C) patient weight, (D) anesthesia duration before initiation of cardiopulmonary bypass, (E) time between start of first bypass run and end of the last bypass run, and (F) anesthesia duration after cessation of cardiopulmonary bypass. Points represent mean predictions from the hierarchical model of fentanyl mcg equivalents, with prediction sample mirroring the analytic sample and all nonfocal variables set to the sample mean. Error bars denote 95% confidence intervals of the mean. Red symbols denote points where 95% confidence interval does not cross the cohort mean.

of both anesthesiologist and institution, and model a patient- and case-mix for each anesthesiologist that matches the total analytic cohort. Risk-standardized opioid dose varied significantly across anesthesiologists. The 10th percentile anesthesiologist used a risk-standardized dose of 655 fentanyl mcg equivalents while the 90th percentile anesthesiologist used a risk-standardized dose of 1503 fentanyl mcg equivalents: over a 2-fold difference. The extremes ran from a minimum of 271 to a maximum of 4208 fentanyl mcg equivalents, a 15-fold range of dose, and a difference of nearly 4000 fentanyl mcg equivalents.

Practice Patterns Associated With Anesthesiologist Opioid Dose

To identify factors that could account for the wide variability in opioid dose, we correlated anesthesiologists' risk-standardized opioid doses with features of their practice (Figure 5). An anesthesiologist's risk-standardized opioid dose was correlated with their frequency of using sufentanil as their primary opioid ($r = 0.64$) and their frequency of using continuous opioid infusions ($r = 0.65$; Supplemental Digital Content 2, Supplemental Figure 8, http://links.lww.com/AA/E924). An anesthesiologist's opioid dose was only weakly correlated ($|r| < 0.3$) with their use of any single nonopioid analgesic technique (like regional/neuraxial anesthesia or ketamine) or the total number of nonopioid analgesic techniques used (Supplemental Digital Content 2, Supplemental Figure 9, http://links.lww.com/AA/E924). Similarly weak correlations were found between an anesthesiologist's opioid dose and the frequency with which they worked with CRNAs or trainees. Linear regression analysis yielded similar results to this correlation analysis, though it suggested that frequent work with trainees might be associated with increased opioid dose (Supplemental Digital Content 2, Supplemental Figure 10, http://links.lww.com/AA/E924).

As both sufentanil use and opioid infusions were associated with increased opioid dose, we specifically examined the use of sufentanil infusions. An anesthesiologist's risk-standardized opioid dose was very strongly correlated with the frequency with which they used sufentanil infusions ($r = 0.81$). Among anesthesiologists who used sufentanil infusions, there was also a strong correlation between opioid dose and the mean starting rate of their sufentanil infusions ($r = 0.68$). While 74% of anesthesiologists never used sufentanil infusions, the 5% of anesthesiologists with the highest risk-standardized opioid dose all used sufentanil

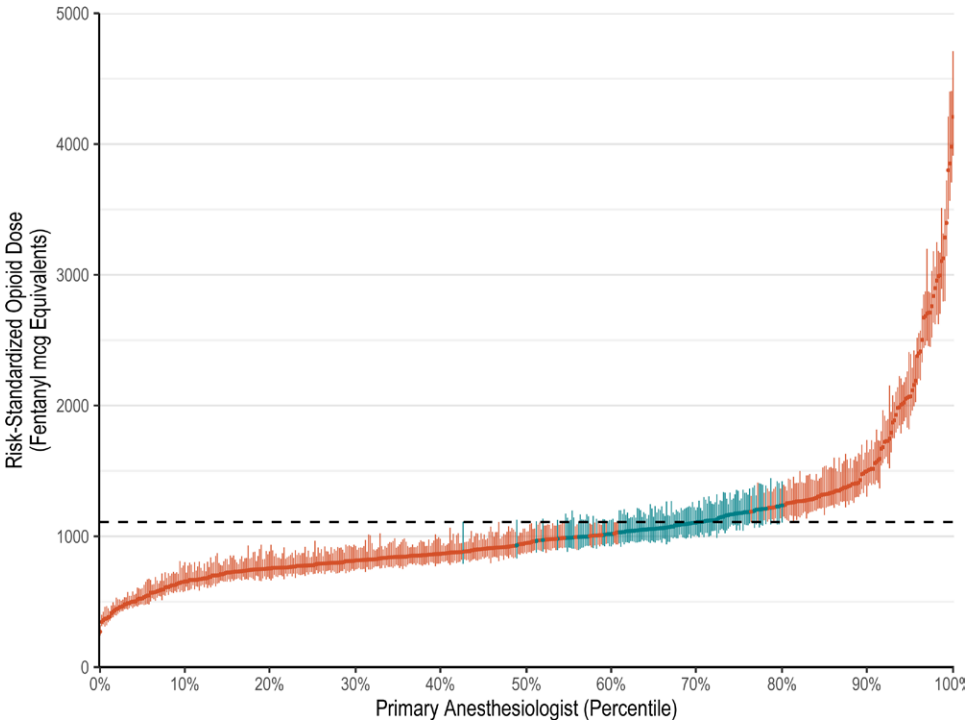

Figure 4. Risk-standardized opioid dose by anesthesiologist. Dashed line represents mean opioid dose in the analytic cohort. Error bars denote 95% confidence intervals. Red symbols denote the 407 of 525 anesthesiologists whose 95% confidence interval did not cross the cohort mean.

infusions with rates ≥0.4 μg·kg^{-1}·h^{-1}. Both the frequency of sufentanil infusion use and the starting infusion rate showed evidence of clustering within institutions (Supplemental Digital Content 2, Supplemental Figure 11, http://links.lww.com/AA/E924).

DISCUSSION

While opioid use during cardiac surgery has declined from its historical high-water mark, our study shows that high-opioid anesthesia remains common. One recent study found that average surgical patients

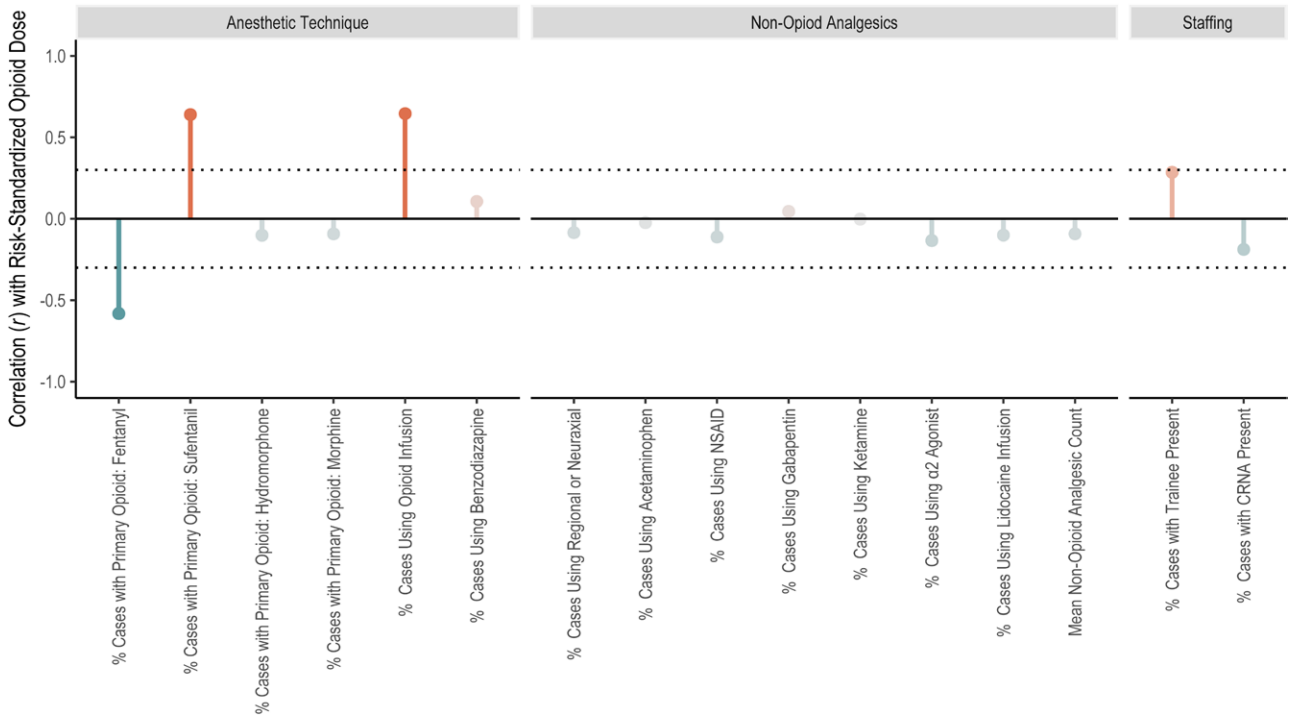

Figure 5. Associations between practice patterns and risk-standardized opioid dose. Correlation (Pearson's r) between an anesthesiologist's risk-standardized opioid dose and features of their practice. Dotted lines denote r = ±0.3, suggesting points between these lines show very weak correlation.

receive 2 fentanyl mcg equivalents/kg, and even average patients undergoing thoracic surgery (including cardiac surgery) receive only 3.7 fentanyl mcg equivalents/kg[35]; our average cardiac surgery patients—on the other hand—received 13.4 fentanyl mcg equivalents/kg. Only 4.4% received less than 3.7 fentanyl mcg equivalents/kg while 12.6% received more than 20 fentanyl mcg equivalents/kg (a common definition of high-dose opioid anesthesia[9,36]).

It is remarkable that 60% of opioid dose variability is attributable to anesthesiologist and institution. This impact of cardiac anesthesiologist and institution is similar to their impact on benzodiazepine use (69% of variability),[13] greater than their impact on inotrope use (29% of variability),[14] and much greater than their impact on mortality (3.4% of variability).[28] The 46% of variability attributable to institution may reflect a variety of institution level influences including local protocols, formularies, a shared pool of CRNAs and trainees, or unenforced cultural norms. Notably, the 40% of opioid variability not accounted for by institution and anesthesiologist was *not* the variability explicitly explained by case-level factors (demographics, comorbidities, case durations, etc), but instead the residual variance after adjusting for these effects. In our analysis, the variance attributable to these known case-level factors was only 6% (Supplemental Digital Content 1, Supplemental Table 4, http://links.lww.com/AA/E923). This highlights just how small a portion of opioid dose variation is easily rationalized.

The impacts of anesthesiologist and institution on opioid dose are clinically meaningful: 2 identical patients, each receiving the same procedure under the care of a different randomly selected anesthesiologist and institution, will receive opioid doses that differ by a median of 600 µg of fentanyl. At times, they could differ by more than 3000 µg. These dose differences are much greater than the total doses given in most noncardiac surgeries.[35] With 52% of anesthesiologists using a risk-standardized opioid dose >250 fentanyl mcg equivalents from the mean (Figure 4), it is possible that only a minority of cardiac surgery patients receive an "average" dose of opioids.

Surprisingly, anesthesiologists who frequently used "opioid sparing" techniques (like regional anesthesia or acetaminophen) did not use appreciably lower opioid doses. On the other hand, anesthesiologists who frequently used sufentanil (and particularly sufentanil infusions) used the highest opioid doses. These anesthesiologists may use higher opioid doses because sufentanil's short context-sensitive half-time allows rapid extubation even after high-dose use, or they may not recognize just how potent sufentanil is. Cardiac anesthesiologists who wish to use less opioid may be able to do so by reducing the rate of opioid infusions, bolus dosing opioids rather than using infusions, reconsidering the relative potency of fentanyl and sufentanil, or lowering opioid dose appropriately when using nonopioid analgesics.

Limitations

Although our registry-based approach allowed us access to nearly comprehensive data from a uniquely broad pool of institutions and anesthesiologists, the limitations of our study design should be considered when interpreting its results. (1) As in any retrospective analysis, unavailable covariates may confound the relationships of interest. For instance, we had no way to differentiate surgeries using sternotomy from those using mini-thoracotomy, a distinction that may have altered the distribution of pain and opioid use across institutions. We were also unable to identify how frequently individual anesthesiologists working at multiple institutions were included in our dataset; because they would have been coded as a different anesthesiologist at each institution, a high frequency of such cases could alter the estimated impact of anesthesiologist and institution. (2) Opioid equivalency is an imperfect art, complicated by the fact that opioids with different pharmacokinetics cannot be made universally "equivalent" with any fixed dose ratio.[15,20] Therefore, despite the principled determination of our sufentanil:fentanyl dose equivalency ratio and the use of fentanyl equivalent Ce AUC as an additional measure of opioid administration, our findings may be sensitive to the specific opioid equivalency methods used. (3) The institutions enrolled in MPOG primarily represent American academic centers, and included community hospitals are predominantly in Michigan. Consequently, our estimates may not provide a fully unbiased representation of wider practice patterns. (4) Although we excluded less than 3% of cases due to methadone administration, anecdotal evidence suggests increasing interest in this drug, and our results do not reflect the impact of its use. (5) Additionally, intraoperative opioid doses may have continued to decrease or change in other ways from 2022 until now.

CONCLUSIONS

The wide range of opioid doses used during cardiac surgery suggests uncertainty about the "right" opioid dose. This uncertainty is reasonable given the current evidence. Some recent studies have found that opioid reduction in cardiac surgery is beneficial[37] (or at least not harmful[8,36]). Yet other research suggests downsides to reducing intraoperative opioids too far[38,39] and adverse effects associated with popular opioid-sparing methods.[40] While our study does not identify an optimal opioid dose for cardiac surgery, the real-world dose range it describes provides an opportunity to synthesize these two seemingly divergent bodies of work. Future studies that test extremes of

the empiric intraoperative opioid distribution against each other may be able to narrow the range of acceptable opioid dose, optimize perioperative opioid use[11] and ultimately improve patient outcomes.

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DISCLOSURES

Conflicts of Interest: C. Fisher reports that he previously owned stock in Johnson & Johnson unrelated to the present work. A. M. Janda reports that her institution has received research grant support from the US National Institutes of Health—National Heart, Lung, and Blood Institute and the Patient-Centered Outcomes Research Institute for research unrelated to this present work. A. Bardia reports that his institution has received research grant support from the Agency for Heathcare Research and Quality for research unrelated to this present work. M. F. Aziz reports that he has received food and beverage from Medtronic and book royalties from Elsevier. M. Treggiari reports that her institution has received research grant support from the US National Institutes of Health—National Heart, Lung, and Blood Institute, from the Department of Defense, and from Edwards Lifescience for research unrelated to the present work. M. R. Mathis reports that his institution has received research grant support from the US National Institutes of Health—National Heart, Lung, and Blood Institute for research unrelated to the present work. Robert B. Schonberger reports that he owns stock in Johnson & Johnson unrelated to the present work, and that his institution has received research support from Merck, Inc. for a study in which he participated unrelated to the present work. No other authors reported Conflicts of Interest. **Funding:** This work was supported in part by grant T32 GM086287 from the National Institute of General Medical Sciences (NIGMS, Bethesda, MD) and R01 AG059607 from the National Institute on Aging (NIA, Bethesda, MD). The opinions expressed are those of the authors and do not necessarily reflect those of NIGMS, NIA, NIH, or the US government. The underlying electronic health record data collected by the Multicenter Perioperative Outcomes Group is supported by departmental and institutional resources at each contributing site. In addition, the underlying electronic health record data collection into the Multicenter Perioperative Outcomes Group registry was provided by Blue Cross Blue Shield of Michigan/Blue Care Network as part of the Blue Cross Blue Shield of Michigan/Blue Care Network Value Partnerships program (Detroit, MI). Although Blue Cross Blue Shield of Michigan/Blue Care Network and 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 Blue Cross Blue Shield of Michigan/Blue Care Network or any of its employees. **This manuscript was handled by:** Karsten Bartels, MD, PhD, MBA.

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