

In this light, the authors' definition of ME becomes one of either ME *or* medical error, which may have contributed to the broad and in some instances counterintuitive examples of ME given in this study. For instance, failure to document intubation or not checking blood pressure before induction, although clearly errors in and of themselves, would not be considered by most physicians as MEs. Likewise, the conclusion that the increased incidence of MEs in this study compared to historical observations is due to "provider reluctance to self-report errors or failure of providers to recognize errors" is not adequately substantiated based upon this changed, and in our opinion flawed, definition. Furthermore, there is no indication that clinical context was considered in these definitions. For instance, a responsible anesthesiologist not only considers current state patient conditions, but also anticipates future stimuli. What an observer may deem a delay in therapy (*i.e.*, "7-min delay in administration of ephedrine," table 5) may in fact be an intentional medical decision based upon current and anticipated future patient condition. Considering the broad definition of MEs and the failure to consider clinical context when recording MEs, the authors report a higher incidence than what would otherwise have been noted with standardized definitions that we are not convinced are appropriate. We should be cautious to accept the reported results as actionable within this framework.

In addition to the definitions applied, we are also concerned about the methods used to detect MEs/ADEs. Medical simulation, heralded as an innovative solution promoting patient safety, teaches that observation of an error alone is insufficient to spawn effective solutions and behavioral change. Watching an error occur without asking "why?" and then proposing a solution is analogous to debriefing without allowing participants to speak. Unfortunately, the study at hand seems to have used this methodology to conclude that "point-of-care bar code–assisted anesthesia documentation systems" can "eliminate" up to 17 and 25% of MEs and ADEs, respectively. We believe this conclusion to be expansive as the authors overlooked the impact of frames on decision-making. Such oversimplifications are attractive but potentially costly. In a Joint Commission publication, Chassin and Loeb³ cited the failure "to resist the temptation to simplify" as a frequent impediment to safety efforts in health care.

Well-designed solutions are targeted, people-centric solutions that embrace the complexity of our healthcare system and behavioral psychology. The authors' suggested processes should be created to reduce opportunities for workarounds, not reinforce old habits. As an example, the authors state that, "In most instances where the labeling system was not used, manual sticker labels were available, and the provider used those instead." The fact that people chose not to use the new sticker system should attest to the flaw in adopting that technology as the solution. Technology and processes should be so well designed that no workaround is needed. With the expanding cost of providing quality health care in America, we should be cautious when recommending

technology-based interventions. Process-based interventions like "heavy user training," as the authors' suggested, is an expensive cure when the technology in question does not work intuitively.

In an article on Design Thinking in *Harvard Business Review*, Brown⁴ stated, "Innovation is powered by a thorough understanding, through direct observation, of what people want and need in their lives and what they like or dislike . . ." With ever-shrinking resources, solutions should be tailored, nuanced, and people-centric, taking a "holistic design approach" that begins by engaging frontline clinicians in dialog. An observational study like this is important in furthering our understanding of MEs/ADEs; however, the accurate categorization, reporting, and deep exploration of each observed error is critical as we develop sustainable change together.

Competing Interests

The authors declare no competing interests.

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References

1. Nanji KC, Patel A, Shaikh S, Seger DL, Bates DW: Evaluation of perioperative medication errors and adverse drug events. *ANESTHESIOLOGY* 2016; 124:25–34
2. Rothschild JM, Landrigan CP, Cronin JW, Kaushal R, Lockley SW, Burdick E, Stone PH, Lilly CM, Katz JT, Czeisler CA, Bates DW: The Critical Care Safety Study: The incidence and nature of adverse events and serious medical errors in intensive care. *Crit Care Med* 2005; 33:1694–700
3. Chassin MR, Loeb JM: High-reliability health care: Getting there from here. The Joint Commission. Available at: www.jointcommission.org. Accessed November 1, 2015
4. Brown T: Design thinking. *Harv Bus Rev* 2008; 86:84–92, 141

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In Reply:

We appreciate the opportunity to respond to the questions raised by Bowdle *et al.*, Ibinson *et al.*, and Chan *et al.* about our manuscript regarding perioperative medication errors (MEs) and adverse drug events (ADEs).¹ Our goal was to assess the rates of perioperative MEs and ADEs as percentages of medication administrations, to evaluate their root causes, and to suggest targeted solutions that may have potential to prevent them. We used an observational methodology, combined with a retrospective chart review and subspecialist consultation by an independent adjudication committee, to provide additional clinical context for confirming and classifying the MEs and ADEs. We found that 5.3% of medication administrations resulted in an ME and/or an ADE, and we classified each of these by whether they

involved an ME with ADE (preventable ADE), ME with potential ADE (near miss), ME with little potential for harm, or ADE without ME (nonpreventable ADE).

Direct observation appears to be the most accurate method of detecting MEs.^{2,3} Thus, it is not surprising that these ME and ADE rates are higher than those described in previous studies using self-report as the primary detection strategy in anesthesia.^{4–8} Notably, the rates reported by us are consistent, and in many cases, they are on the low end, or lower than, those reported using direct observation and similar ME definitions in the perioperative setting (ME rates, 9 to 11%)⁹ and those reported using our validated and widely used definition of ME with either chart review or direct observational methods in other settings, such as the medical emergency/code setting (ME rates, 4.4 to 50%),^{10,11} critical care setting (ME rates, 9 to 20%),^{12,13} inpatient setting (ME rates, 5 to 19%),^{14–17} outpatient setting (ME rates, 7 to 12%),^{18–20} and simulation setting (ME rates, 0.5 to 26.5%).^{16,21}

While many perioperative ADEs, such as significant hypotension, are corrected during the perioperative period, there is evidence that they can have lasting effects postoperatively.²² A key step to improving the already outstanding safety record of anesthesia is to prevent ADEs and potential ADEs (near misses) from occurring in the first place and, when they do occur, ensure that we recognize and correct them.

Many of the authors' comments center on questions about the methodology we used to identify MEs and ADEs. As described in our manuscript, we iteratively revised an ME detection framework that has been validated in the critical care setting²³ to make it more relevant to the perioperative setting, using a combination of literature review, expert and subspecialist consultation. We deliberately widened the acceptable range of practice so as not to overcall errors. For example, we widened published, validated, and accepted dosing ranges for medications by 50 to 100% before flagging an event as a *possible* medication dosing error. Our observers were trained and practicing anesthesiologists and one nurse anesthetist who all received extensive additional training on observational methodology and MEs, including a detailed ME detection handbook, multiple didactic sessions, and case studies of MEs. They each conducted observations with an experienced observer for at least 10 operations to ensure that they were capturing consistent information. The observers' task was to flag *possible* MEs and/or ADEs based on our error detection framework. These possible MEs and/or ADEs were each reviewed by at least two independent members of our adjudication committee, which consisted of clinical and ME experts. The adjudication committee's task was to exclude events that were not actual MEs or ADEs and to categorize the events by type, preventability, potential for harm, and severity of harm. To gain the necessary clinical context, they reviewed the observer notes, clarified events directly with the observers, reviewed the patient chart, and consulted with experts where necessary. If a possible error or

ADE passed this stage, it was included in our study. Interrater reliability between our adjudication committee members was excellent ($\kappa = 0.97$ for event classification, $\kappa = 0.98$ for preventability, and $\kappa = 0.85$ for severity).

Bowdle *et al.* also raised questions about our definition of ME. While there are multiple interpretations of what constitutes an ME in anesthesia, in our manuscript we use a definition of ME that is often used in medication safety research: "failure to complete a required action in the medication administration process, or the use of an incorrect plan or action to achieve a patient care aim."^{1,23} The administration of medication is a small part of the overall medication administration *process*, which includes requesting, dispensing, preparing, administering, documenting, and (where applicable) monitoring during medication administration, as described in our manuscript.¹ Examples of when monitoring would be required during medication administration in our study include blood pressure monitoring before an induction dose of propofol and glucose monitoring after insulin is given. Thus, our study was not one of medication administration errors only, but of all MEs that occur along the medication administration process. The National Coordinating Council on ME Reporting and Prevention similarly defines MEs as occurring anywhere in the medication process,²⁴ and error studies in all other settings, including critical care,^{12,13,23} cardiopulmonary arrest and code situations,^{10,11} inpatient wards,^{14,16,25,26} and outpatient clinics^{18–20} have included MEs along the entire medication process, including errors of omission.

The authors specifically questioned whether mean arterial pressure (MAP) less than 55 mmHg that goes untreated for a prolonged interval is actually an ME, or simply a management decision. While our profession does not have clear definitions for intraoperative hypotension, some evidence shows that MAP less than 55 mmHg even for short durations (1 to 5 min) intraoperatively is associated with acute kidney injury (1.18 adjusted odds ratio) and myocardial injury (1.3 adjusted odds ratio) after noncardiac surgery, and this risk escalates rapidly with longer durations of MAP less than 55 mmHg.²² While further research should be done to look at treatment guidelines for hypotension, for this study we lengthened the time period to more than 6 min of untreated MAP less than 55 mmHg for the event to be flagged by our observers as a *possible* ME (delay in treatment) for further review by the independent adjudication committee. Through review of observer findings, patient chart review, and expert subspecialist consultation as described above, the adjudication committee ruled out cases where persistent MAP less than 55 mmHg was part of intended, appropriate management. The authors also asked why leaving unattended syringes of narcotic was considered an ME; there were only two incidents of this in the study. While it can be debated whether or not to count such issues, per our study definition, they were included as MEs related to medication preparation and classified in our lowest category

of severity (“significant”) because they can lead to a variety of unintended consequences including drug diversion, which is associated with increased patient risk for blood-borne viruses and undertreated pain.^{27–30}

The authors also questioned how we determined whether a specific event represented an ADE. We used a standard definition for ADEs that is widely used in the medication safety literature.^{12–14,18,23,25,31} For individual events, the reliability of assessment for the presence of an ADE was excellent ($\kappa = 0.97$). The authors also specifically asked about thresholds for treating pain. While there is not a consistent guideline for this in anesthesia, we obtained consensus from acute pain medicine subspecialists regarding tolerable pain thresholds and also looked to the pain literature, which consistently shows that 3 to 4/10 pain is a significant treatment threshold.^{32–34} We used a threshold of sustained pain greater than 4/10 (or greater than or equal to 5/10) to be flagged by the observers for later review by the adjudication committee (along with observer notes, chart review, and subspecialist consultation as described above) to determine whether or not the incidents were ADEs and whether they were associated with a failure to treat ME or consistent with standard practice and patient management goals (ADE without ME).

The authors compared our results to those of published ME studies that use facilitated incident reporting to identify MEs.^{4,8} We do not believe that these are valid comparisons for several reasons. First, evidence shows that incident reporting vastly underrepresents true error rates.^{2,3} Flynn *et al.*³ performed a study comparing ME detection rates on hospital wards using three different methods: incident reporting, retrospective chart review, and direct observation. Their ME definition was the same for all three methods. Of 2,557 medication doses administered, they found 456 MEs (17.8% ME rate) by direct observation, 34 (1.3% ME rate) by chart review, and only one (0.04% ME rate) by self-reporting *via* an incident reporting system.³ Second, the studies referenced by Bowdle *et al.* looked at a subcategory of MEs that occurred during medication administration, while our study looked at MEs that occurred during the entire medication use process. The most validated, established, and widely used definition of ME across specialties involves the entire process, as described above. Third, most of the literature that the authors reference reports MEs per anesthetic (not per medication administration), which is a different denominator. The most validated method for measuring error rates is the number of errors per medication administered.^{3,9,19,20,31,35} Measuring MEs per anesthetic represents another approach, but it can be difficult to interpret as different anesthetics involve different numbers of medications administered. Also, it does not provide information on medication administrations that are without error if they occur during an operation that contained an error.

Our results can more accurately be compared with observational studies such as those of Merry *et al.*,⁹ who conducted a study in five operating rooms in a tertiary academic

center in New Zealand and found a perioperative ME rate of 11.6% in a study group that used conventional nonelectronic methods for anesthetic record keeping and 9.1% in a study group that used a multimodal record-keeping system that was designed in-house. Merry *et al.* used a definition of ME that included errors related to administration, documentation, and omission or “failure to give an intended medication,” and they reported MEs per medication administered. When Bowdle *et al.* referred to Merry’s study as having a lower ME rate than ours, it was because they subtracted MEs from Merry’s study results that were not direct medication administration errors. However, like us, Merry *et al.* counted errors along the medication administration process, such as documentation errors, as their primary outcome, and they reported ME rate was higher than ours.

In their letter, Bowdle *et al.* also subtract MEs from our results to arrive at a new ME rate that only includes direct administration errors and uses the number of anesthetics (or patients) as a denominator instead of the number of medications administered. As described above, we disagree with this definition of ME and with reporting the rate per operation. Their calculation assumption of no more than one ME per patient in our study is not accurate. In fact, of 277 observed operations on 275 patients, 154 (55.6%) did not contain an ME or an ADE, 82 (29.6%) contained 1 ME and/or ADE, 23 (8.3%) contained 2, 13 (4.7%) contained 3, and 5 (1.8%) contained 4 or more.

The authors also commented on the use of a bar code–assisted syringe labeling system and electronic anesthesia information management system at our institution, both of which were available during our study observation period and described in detail in our manuscript. While measuring the effect of these systems on ME rates was outside of the scope of our study, we agree with the authors’ statement identifying the potential for these systems to lower ME rates and describe this in the manuscript discussion. We also agree with the authors, and our study results support that simply having these systems in place does not ensure that they are properly used.

Ibinson *et al.* posed questions about whether patient harm was associated with the errors that we observed. Errors often do not result in ADEs. As outlined in the results of our manuscript, 40 (21%) of our events involved patient harm/ADEs without an ME, and the remaining 153 events were MEs that were associated with an observed ($N = 51$, 33.3%) or potential ($N = 70$, 45.8%) ADE or had little potential for harm ($N = 32$, 20.9%). The most important areas of consideration for solutions to improve patient medication safety are not only preventable, observed ADEs but also *potential* ADEs. For example, if required perioperative antibiotic doses are missed in a group of patients, we do not focus only on those who develop an infection (ADE) and conclude that it is acceptable to skip antibiotic doses in patients who do not develop an infection (potential ADE). Whether a potential ADE turns into an ADE is often based on luck

and uncontrollable factors, and it is important to consider both actual and potential ADEs for improving patient safety. In fact, it is a necessary and standard practice to report potential ADEs along with ADEs in the medication safety literature.^{12,17,19,25,31} Thus, we classified all observed and potential ADEs on a previously validated and widely used severity scale of harm, ranging from significant to serious to life-threatening.^{12–14,19,20,25,31} While we used the terms significant, serious, and life-threatening to remain consistent with established standard severity reporting methods in the medication safety literature, the words are most meaningful when linked to the definitions and examples provided in the manuscript, which describe these three levels as corresponding to “little threat to the patient’s function,” “some threat to the patient’s function that is not life-threatening,” and “life threatening,” respectively. The severity assignments were made by our adjudication committee, whose members have extensive experience using this classification system in ME studies, and their interrater reliability for these assignments was high ($\kappa = 0.85$).

While adverse events in medicine are often multifactorial and can be due to a combination of errors that align to produce patient harm, many ME studies report ADEs associated with MEs without classifying by attributability.^{12,17,19,25} We used the Naranjo algorithm³⁶ to assess the likelihood that observed ADEs associated with MEs were attributable to those MEs, and found that only 1 (2.0%) ADE was doubtfully due to the error. Ibinson *et al.* requested a table to show ADE counts by attributability. Their outlined table does not include errors with potential for harm (near misses), so we have added data on these important errors to the table (table 1).

Similar to Bowdle *et al.*, Yieshan *et al.* raise questions about our definition of ME. While the definition of ME has been broadened in different studies to include all medical errors,²³ our study definition specifies that these MEs must occur during the medication use process, which, as described above, is consistent with the established literature on MEs. One of the ME examples the authors questioned was failure to check blood pressure before a patient receives an induction dose of propofol, which is a monitoring error in the propofol administration process, as described above. Monitoring-related MEs have been included as MEs in

medication safety research across specialties throughout the literature.^{13,14,18,19,23}

The authors also questioned why our ME rates are higher than those in the existing self-reports in the perioperative literature, which we have addressed in detail above. They specifically asked about whether we considered clinical context. Our adjudication committee reviewed all observer data and patient charts and consulted subspecialists in order to provide the clinical context required to exclude incidents that were flagged by observers but may not have been errors, not had potential for patient harm, or were consistent with standard patient management or specific patient care goals, on a case-by-case basis.

Finally, the authors questioned whether our results are sufficient to endorse specific ME solutions. We do not endorse any specific solutions because we agree with the authors, and our report explicitly states that future analysis is necessary to evaluate process- and technology-based solutions that may address the root causes of the MEs to reduce their incidence. As described in our manuscript, we did not directly test any solutions. We suggest, based on our judgment and considering error type and root cause, the numbers of MEs in our sample that have the *potential* to be eliminated by various solutions, in order to identify solutions that may deserve further consideration and testing. After such solutions are designed, similar studies should be repeated to determine whether or not they reduce the incidence of MEs.

It is important and not uncommon to raise questions when presented with new research on MEs,^{37–43} especially when the research receives attention in the mainstream media. For example, while their scope was much larger than ours, many questions were raised about error definitions and classifications after the Institute of Medicine’s report *To Err Is Human* was published.^{37–40,44} We welcome the opportunity to further discuss our findings and the critical importance of using ME, ADE, and severity definitions, as well as research methodologies, that are validated, objective, and consistent with existing cross-specialty ME research. This will allow existing and future results and solutions to be compared, leveraged, and shared, and their impact on reducing ME rates to be accurately measured. Future research should focus on conducting similar studies at other academic centers with consistent definitions to see if these results are representative,

Table 1. Event Severity by Error Classification

Severity	ADEs without ME (Nonpreventable ADE)	Preventable ADEs (Observed)				MEs with Little Potential for Harm	Total Medication Errors (Excludes ADEs without ME)
		Probable Attribution	Possible Attribution	Doubtful Attribution	Potential ADEs		
Life-threatening	0	0	0	0	3	0	3
Serious	34	27	16	0	56	0	99
Significant	6	1	6	1	11	32	51
Total	40	28	22	1	70	32	153

ADE = adverse drug event; ME = medication error.

and at other sites such as ambulatory surgical centers and community hospitals, and most importantly before and after the introduction of solutions to determine whether or not they reduce the incidence of MEs.

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Competing Interests

Dr. Bates is a coinventor on Patent No. 6029138 held by Brigham and Women's Hospital (Boston, Massachusetts) on the use of decision support software for radiology medical management, licensed to the Medicalis Corporation (San Francisco, California). He holds a minority equity position in the privately held company Medicalis. He serves on the board of SEA Medical (Emerald Hills, California), which makes technologies that can identify medications in solution. He receives equity and cash compensation from QPID, Inc. (Boston, Massachusetts), a company focused on intelligence systems for electronic health records. The other author declares no competing interests.

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References

- Nanji KC, Patel A, Shaikh S, Seger DL, Bates DW: Evaluation of perioperative medication errors and adverse drug events. *ANESTHESIOLOGY* 2016; 124:25–34
- Allan EL, Barker KN: Fundamentals of medication error research. *Am J Hosp Pharm* 1990; 47:555–71
- Flynn EA, Barker KN, Pepper GA, Bates DW, Mikeal RL: Comparison of methods for detecting medication errors in 36 hospitals and skilled-nursing facilities. *Am J Health Syst Pharm* 2002; 59:436–46
- Webster CS, Merry AF, Larsson L, McGrath KA, Weller J: The frequency and nature of drug administration error during anaesthesia. *Anaesth Intensive Care* 2001; 29:494–500
- Orser BA, Chen RJ, Yee DA: Medication errors in anesthetic practice: A survey of 687 practitioners. *Can J Anaesth* 2001; 48:139–46
- Llewellyn RL, Gordon PC, Wheatcroft D, Lines D, Reed A, Butt AD, Lundgren AC, James MF: Drug administration errors: A prospective survey from three South African teaching hospitals. *Anaesth Intensive Care* 2009; 37:93–8
- Shridhar Iyer U, Fah KK, Chong CK, Macachor J, Chia N: Survey of medication errors among anaesthetists in Singapore. *Anaesth Intensive Care* 2011; 39:1151–2
- Zhang Y, Dong YJ, Webster CS, Ding XD, Liu XY, Chen WM, Meng LX, Wu XY, Wang DN: The frequency and nature of drug administration error during anaesthesia in a Chinese hospital. *Acta Anaesthesiol Scand* 2013; 57:158–64
- Merry AF, Webster CS, Hannam J, Mitchell SJ, Henderson R, Reid P, Edwards KE, Jardim A, Pak N, Cooper J, Hopley L, Frampton C, Short TG: Multimodal system designed to reduce errors in recording and administration of drugs in anaesthesia: Prospective randomised clinical evaluation. *BMJ* 2011; 343:d5543
- Gokhman R, Seybert AL, Phrampus P, Darby J, Kane-Gill SL: Medication errors during medical emergencies in a large, tertiary care, academic medical center. *Resuscitation* 2012; 83:482–7
- Flannery AH, Parli SE: Medication errors in cardiopulmonary arrest and code-related situations. *Am J Crit Care* 2016; 25:12–20
- Kopp BJ, Erstad BL, Allen ME, Theodorou AA, Priestley G: Medication errors and adverse drug events in an intensive care unit: Direct observation approach for detection. *Crit Care Med* 2006; 34:415–25
- Buckley MS, Erstad BL, Kopp BJ, Theodorou AA, Priestley G: Direct observation approach for detecting medication errors and adverse drug events in a pediatric intensive care unit. *Pediatr Crit Care Med* 2007; 8:145–52
- Kaushal R, Bates DW, Landrigan C, McKenna KJ, Clapp MD, Federico F, Goldmann DA: Medication errors and adverse drug events in pediatric inpatients. *JAMA* 2001; 285:2114–20
- Lazarou J, Pomeranz BH, Corey PN: Incidence of adverse drug reactions in hospitalized patients: A meta-analysis of prospective studies. *JAMA* 1998; 279:1200–5
- Magrabi F, Li SY, Day RO, Coiera E: Errors and electronic prescribing: A controlled laboratory study to examine task complexity and interruption effects. *J Am Med Inform Assoc* 2010; 17:575–83
- Barker KN, Flynn EA, Pepper GA, Bates DW, Mikeal RL: Medication errors observed in 36 health care facilities. *Arch Intern Med* 2002; 162:1897–903
- Devine EB, Hansen RN, Wilson-Norton JL, Lawless NM, Fisk AW, Blough DK, Martin DP, Sullivan SD: The impact of computerized provider order entry on medication errors in a multispecialty group practice. *J Am Med Inform Assoc* 2010; 17:78–84
- Gandhi TK, Weingart SN, Seger AC, Borus J, Burdick E, Poon EG, Leape LL, Bates DW: Outpatient prescribing errors and the impact of computerized prescribing. *J Gen Intern Med* 2005; 20:837–41
- Nanji KC, Rothschild JM, Salzberg C, Keohane CA, Zigmont K, Devita J, Gandhi TK, Dalal AK, Bates DW, Poon EG: Errors associated with outpatient computerized prescribing systems. *J Am Med Inform Assoc* 2011; 18:767–73
- Porter E, Barcega B, Kim TY: Analysis of medication errors in simulated pediatric resuscitation by residents. *West J Emerg Med* 2014; 15:486–90
- Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN, Cywinski J, Thabane L, Sessler DI: Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: Toward an empirical definition of hypotension. *ANESTHESIOLOGY* 2013; 119:507–15
- Rothschild JM, Landrigan CP, Cronin JW, Kaushal R, Lockley SW, Burdick E, Stone PH, Lilly CM, Katz JT, Czeisler CA, Bates DW: The Critical Care Safety Study: The incidence and nature of adverse events and serious medical errors in intensive care. *Crit Care Med* 2005; 33:1694–700
- National Coordinating Council for Medication Error Reporting and Prevention: About Medication Errors: What Is a Medication Error? 2016. Available at: <http://www.nccmerp.org/aboutMedErrors.html>. Accessed March 10, 2016
- Bates DW, Cullen DJ, Laird N, Petersen LA, Small SD, Servi D, Laffel G, Sweitzer BJ, Shea BF, Hallisey R: Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. *JAMA* 1995; 274:29–34

26. Leape LL, Brennan TA, Laird N, Lawthers AG, Localio AR, Barnes BA, Hebert L, Newhouse JP, Weiler PC, Hiatt H: The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. *N Engl J Med* 1991; 324:377–84
27. Hellinger WC, Bacalis LP, Kay RS, Thompson ND, Xia GL, Lin Y, Khudyakov YE, Perz JF: Health care-associated hepatitis C virus infections attributed to narcotic diversion. *Ann Intern Med* 2012; 156:477–82
28. Cody SH, Nainan OV, Garfein RS, Meyers H, Bell BP, Shapiro CN, Meeks EL, Pitt H, Mouzin E, Alter MJ, Margolis HS, Vugia DJ: Hepatitis C virus transmission from an anesthesiologist to a patient. *Arch Intern Med* 2002; 162:345–50
29. Schaefer MK, Perz JF: Outbreaks of infections associated with drug diversion by US health care personnel. *Mayo Clin Proc* 2014; 89:878–87
30. Maki DG, Klein BS, McCormick RD, Alvarado CJ, Zilz MA, Stolz SM, Hassemer CA, Gould J, Liegel AR: Nosocomial *Pseudomonas pickettii* bacteremias traced to narcotic tampering. A case for selective drug screening of health care personnel. *JAMA* 1991; 265:981–6
31. Gandhi TK, Weingart SN, Borus J, Seger AC, Peterson J, Burdick E, Seger DL, Shu K, Federico F, Leape LL, Bates DW: Adverse drug events in ambulatory care. *N Engl J Med* 2003; 348:1556–64
32. Gerbershagen HJ, Rothaug J, Kalkman CJ, Meissner W: Determination of moderate-to-severe postoperative pain on the numeric rating scale: A cut-off point analysis applying four different methods. *Br J Anaesth* 2011; 107:619–26
33. Zalon ML: Mild, moderate, and severe pain in patients recovering from major abdominal surgery. *Pain Manag Nurs* 2014; 15:e1–12
34. Woo A, Lechner B, Fu T, Wong CS, Chiu N, Lam H, Pulenzas N, Soliman H, DeAngelis C, Chow E: Cut points for mild, moderate, and severe pain among cancer and non-cancer patients: A literature review. *Ann Palliat Med* 2015; 4:176–83
35. Poon EG, Cina JL, Churchill W, Patel N, Featherstone E, Rothschild JM, Keohane CA, Whittemore AD, Bates DW, Gandhi TK: Medication dispensing errors and potential adverse drug events before and after implementing bar code technology in the pharmacy. *Ann Intern Med* 2006; 145:426–34
36. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ: A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; 30:239–45
37. American College of Clinical Pharmacology response to the Institute of Medicine report “To err is human: Building a safer health system.” The Public Policy Committee. *J Clin Pharmacol* 2000; 40:1075–8.
38. Battles JB, Keyes MA: Technology and patient safety: A two-edged sword. *Biomed Instrum Technol* 2002; 36:84–8
39. Sox HC Jr, Woloshin S: How many deaths are due to medical error? Getting the number right. *Eff Clin Pract* 2000; 3:277–83
40. Brennan TA: The Institute of Medicine report on medical errors—Could it do harm? *N Engl J Med* 2000; 342:1123–5
41. Incidence of adverse events and negligence in hospitalized patients. *N Engl J Med*. 1991; 325:210
42. Hernández J, Vargas ML: Adverse drug events in ambulatory care. *N Engl J Med* 2003; 349:303–5; author reply 303–5
43. Bush T: Adverse drug reactions in hospitalized patients. *JAMA* 1998; 280:1742; author reply 1743–4
44. Institute of Medicine: *To Err Is Human: Building a Safer Health System*. Washington, DC, The National Academy Press, 1999

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Platelet Counts, Acute Kidney Injury, and Mortality after Coronary Artery Bypass Grafting Surgery

To the Editor:

We read with great interest the article by Dr. Kertai *et al.*,¹ in which the authors identified a novel association between postoperative nadir platelet counts and acute kidney injury (AKI) and short-term mortality after coronary artery bypass grafting surgery. Despite the elaborate statistical analysis and the innovative perspectives, we are profoundly concerned with the study design and the interpretation of statistical results, which we expect the authors to comment on and address.

First, we consider perioperative blood loss as a crucial confounding variable that should not be overlooked in the study design, nor be absent from the logistic regression analysis of AKI and mortality predictors. Significant blood loss is well established in previous literatures, poses major challenges in many cardiac surgeries, and has been identified as having strong, independent association with postoperative in-hospital mortality and AKI.^{2–5} Furthermore, the concomitant decrease in platelet counts and serum hemoglobin in this study is also a strong indicative of significant perioperative blood loss, which very much likely was the true underlying cause of both AKI and short-term mortality. Therefore, it is of crucial importance that all relevant predictors, especially such important predictor as perioperative blood loss, be included in the logistic regression analysis. However, according to the authors, they were not able to investigate the influence of postoperative bleeding due to the retrospective nature of the study, which we readers hesitate to give our full trust given the requirements of comprehensive intensive monitoring postcardiac surgeries. Hence, before the effect of perioperative blood loss on AKI is conclusively affirmed, we readers should be highly cautious about the conclusions this study attempted to present, *i.e.*, the novel association between thrombocytopenia and postoperative AKI. Such conclusions may be distracting, if not misleading, to us readers, since the association between perioperative blood loss and AKI may be concealed behind the seemingly causative thrombocytopenia. We, therefore, suggest that the authors and interested readers focus more attention on perioperative blood loss, rather than platelet reduction, in the future researches of postoperative AKI.

Second, previous studies have verified that coagulation factor and fibrin dysfunctions are also in significant association with postoperative kidney and myocardial injuries.^{6,7} Therefore, we advise the authors to explore the functions of the whole set of serum coagulant components on AKI from a broader view, other than focusing on the single variable of platelet count.