produce ongoing microvascular plugging that manifest clinically as end-organ injury such as AKI.[12] The involvement of activated platelets in the formation of these microaggregates can manifest in the reduction in platelet counts as reasoned in our study. Thus, measuring intra- and postoperative platelet counts, which is readily available and is a routinely performed laboratory test in patients undergoing cardiac surgery, may be used as an indicator of ongoing platelet activation/consumption that may prognosticate end-organ injury such as AKI.

Finally, the letter suggests, "readers to keep alerted of the conclusions" of our study "in order to avoid overreliance in the statistical results while neglecting the possible biologic implausibility." It should be noted first that our hypothesis and our analysis strategy sought to reveal the independent effect of postoperative thrombocytopenia, separate from any overlap with patient- and procedure-related effects. Thus, using contemporary statistical methods for adjusting for those covariable effects on outcome is critically important. Second, as also highlighted in the accompanying editorial to our article,[13] platelets reflect biologic complexity of poorly buffered inflammation, and in depth research of that biocomplexity may allow hypothesis-driven studies to sprout out from the findings of our observational study. Of note, we agree that since we were not able to measure markers of inflammation and microthrombosis in our current study, future studies that are prospective in design and of sufficient size are needed to define the context of platelet activation, thrombocytopenia, and inflammation-related ischemic complications in coronary artery bypass grafting surgery.[1]

Competing Interests

The authors declare no competing interests.

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Epidurals and Chronic Postsurgical Pain: Is It Lack of Evidence or Poor Design?

To the Editor:

We read with great interest the large, retrospective database review of perioperative epidural use for abdominal surgery by Ladha *et al.*[1] We agree that studying anesthetic techniques that might have an impact on the incidence of persistent postsurgical pain is an important area, and is one in which large, well-controlled studies are lacking. Indeed, the large sample population was a strength of the study. However, we have serious concerns about the design of the study. First, and perhaps

most importantly, the study's premise that a single intervention alone, regardless of how it was administered and in what context, would lead to decreased long-term opioid consumption is flawed. In the meta-analysis cited by the authors that examined the effects of regional anesthesia on chronic postsurgical pain,[2] that study's authors could find only a single prospective trial that reported positive results comparing epidural analgesia to placebo after abdominal surgery. That single study[3] used preventive epidural analgesia in a multimodal regimen to decrease chronic postsurgical pain, while equivocal results were found in another that did not use multimodal analgesia.[4] It is not surprising, then, that Ladha *et al.* found no benefit. They did not report on the presence or absence of multimodal analgesia, which would impact their results.

Second, virtually nothing is known about the details of the epidural placement, location, medication choice, and timing and duration of therapy. As de Leon-Casasola[5] described over a decade ago, knowledge of these and other procedural details is critical in assessing the effectiveness of epidural analgesia for any postoperative outcome. Unfortunately, the authors used Current Procedural Terminology codes to identify patients who received epidurals, leaving the timing of epidural placement (pre-, intra-, or postoperative), as well as all other technical details, unclear. Preoperative initiation of epidural analgesia may be more effective than intraoperative initiation at preventing hyperalgesia,[6] and the duration of the infusion likely plays a role as well,[4] but combining all epidurals into one category would likely dilute any effect seen in any patient subset.

Finally, the use of a 30-day period free of opioid prescription fills after hospital discharge is an unusual endpoint and may not accurately reflect postsurgical pain and opioid use. Pain medication adherence is often poor in patients with chronic pain,[7] so the use of filled opioid prescriptions as a marker of chronic pain is questionable at best.

It would have been more interesting to test the hypothesis that epidural analgesia decreases chronic pain when standardized and used in a multimodal protocol. Unfortunately, this may not be possible retrospectively.

Competing Interests

Dr. Viscusi has received consultancy fees from AcelRx (Redwood City, California), Medicines Company (Parsippany, New Jersey), Mallinckrodt (St. Louis, Missouri), Trevena (King of Prussia, Pennsylvania), Cara Pharmaceuticals (Shelton, Connecticut), and AstraZeneca (Wilmington, Delaware). He has received lecturing fees from AcelRx, Merck (Kenilworth, New Jersey), Salix (Raleigh, North Carolina), and Mallinckrodt. His institution has received grant money from AcelRx and Pacira (Parsippany, New Jersey). The other authors declare no competing interests.

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In Reply:

We would like to thank Schwenk *et al.* for their interest and comments related to our article.[1] However, we believe that the objections raised are misguided, given the hypothesis being tested and the methods employed in our study.

In their letter, the authors state that it is only in combination with other multimodal analgesics that epidural analgesia would decrease the risk of persistent opioid use. Because we did not capture whether multimodal anesthesia was used, they argue that the entire premise of our study was flawed. While it is perhaps an interesting hypothesis that epidurals only decrease persistent opioid use when used in conjunction with other modalities, it is pure speculation. It does not make our study, which tested the hypothesis that epidurals decrease persistent opioid use, "flawed." Epidurals are likely often used in conjunction with other analgesics (such as acetaminophen or nonsteroidal antiinflammatory drugs[2]), and if this combination were to decrease the risk of persistent opioid use, then there should have been some signal of benefit for epidurals (which, unfortunately, there was not).

The authors go on to suggest that the reason we did not observe a benefit for epidurals in decreasing persistent opioid use was because we did not obtain details regarding epidural placement location, timing, duration, or medication used. Indeed, we did not capture these details in our dataset, and the exposure studied should be interpreted as epidural placement and management as it is routinely