

## **UC Davis**

### **UC Davis Previously Published Works**

#### **Title**

Perioperative Treatment With Aspirin or Clonidine and Risk of Acute Kidney Injury

#### **Permalink**

<https://escholarship.org/uc/item/3898g4cz>

#### **Journal**

JAMA, 313(11)

#### **ISSN**

0098-7484

#### **Authors**

Sun, Jianzhong  
Liu, Hong

#### **Publication Date**

2015-03-17

#### **DOI**

10.1001/jama.2015.1055

Peer reviewed

**Corresponding Author:** John S. Gill, MD, MS, St Paul's Hospital, 1081 Burrard St, Vancouver, BC V6Z 1Y6, Canada (jgill@providencehealth.bc.ca).

**Conflict of Interest Disclosures:** The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Gill reported receiving an investigator-initiated research grant from Astellas Canada and serving as a consultant for Astellas Canada. Dr Knoll reported receiving an investigator-initiated research grant from Astellas Canada and Pfizer Canada. Dr Humar reported receiving research grant support from Astellas Canada, Novartis Canada, and Roche Canada.

1. Humar A, Gill J, Johnston O, et al. Quinolone prophylaxis for the prevention of BK virus infection in kidney transplantation: study protocol for a randomized controlled trial. *Trials*. 2013;14:185.

## Perioperative Treatment With Aspirin or Clonidine and Risk of Acute Kidney Injury

**To the Editor** A large randomized clinical trial,<sup>1</sup> which was a substudy of the Perioperative Ischemia Evaluation-2 (POISE-2) trial,<sup>2</sup> reported that among patients undergoing major noncardiac surgery, perioperative use of aspirin or clonidine did not reduce the risk of acute kidney injury. Aspirin actually increased the risk of major bleeding and clonidine increased the risk of hypotension. We have several comments and concerns.

First, the incidence of major bleeding in this substudy<sup>1</sup> and in the main POISE-2 study<sup>2</sup> (3.8%-4.6%) does not reflect real-world experience. A study<sup>3</sup> using the American College of Surgeons National Surgical Quality Improvement Project (NSQIP) database reported a major bleeding rate of only 0.80% among 651 775 patients who underwent surgery (although the definitions of major bleeding were somewhat different).

Second, about 70% of patients in this substudy<sup>1</sup> and in the main POISE-2 study<sup>2</sup> were taking anticoagulants (mostly prophylactic), which raises a serious question of potential interactions between those anticoagulants and aspirin.

A meta-analysis<sup>4</sup> showed that aspirin combined with oral anticoagulants was not associated with reduced thromboembolic events (except in patients with a mechanical heart valve) but increased major bleeding. The POISE-2 study, including this substudy, highlights the potential risk of perioperative bleeding when combining aspirin with other anticoagulants.

Third, interaction effects between aspirin and clonidine may exist due to the factorial design of the trial; for example, the effects of aspirin may be confounded by hypotension induced by clonidine. Potential significant interaction effects may partially account for the lack of benefits of the 2 drugs on acute kidney injury.

Fourth, aspirin's benefits have been demonstrated among high-risk patients by reducing myocardial infarction, stroke, and vascular mortality. In general, aspirin's benefits are greater in patients at greater risk of cardiovascular events.<sup>5</sup>

We are concerned that the results of this substudy<sup>1</sup> and POISE-2<sup>2</sup> may confuse physicians and lead to indiscriminate cessation of aspirin during the perioperative period, especially for patients receiving aspirin who have a coronary artery stent or are receiving aspirin as a component of therapy for coronary artery disease and may lead to acute coronary syndrome, stent thrombosis, or other vascular events.

**Jianzhong Sun, MD, PhD**  
**Hong Liu, MD**

**Author Affiliations:** Department of Anesthesiology, Thomas Jefferson University and Hospitals, Philadelphia, Pennsylvania (Sun); Department of Anesthesiology and Pain Medicine, University of California Davis Medical Center, Sacramento (Liu).

**Corresponding Author:** Jianzhong Sun, MD, PhD, Department of Anesthesiology, Thomas Jefferson University and Hospitals, 111 S 11th St, Philadelphia, PA 19107 (jian-zhong.sun@jefferson.edu).

**Conflict of Interest Disclosures:** The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

1. Garg AX, Kurz A, Sessler DI, et al; POISE-2 Investigators. Perioperative aspirin and clonidine and risk of acute kidney injury: a randomized clinical trial. *JAMA*. 2014;312(21):2254-2264.
2. Devereaux PJ, Mrkocbrada M, Sessler DI, et al; POISE-2 Investigators. Aspirin in patients undergoing noncardiac surgery. *N Engl J Med*. 2014;370(16):1494-1503.
3. Kamel H, Johnston SC, Kirkham JC, et al. Association between major perioperative hemorrhage and stroke or Q-wave myocardial infarction. *Circulation*. 2012;126(2):207-212.
4. Dentali F, Douketis JD, Lim W, Crowther M. Combined aspirin-oral anticoagulant therapy compared with oral anticoagulant therapy alone among patients at risk for cardiovascular disease: a meta-analysis of randomized trials. *Arch Intern Med*. 2007;167(2):117-124.
5. Gaziano JM, Greenland P. When should aspirin be used for prevention of cardiovascular events? *JAMA*. 2014;312(23):2503-2504.

**In Reply** Drs Sun and Liu are concerned that the risk of major bleeding in POISE-2 (ie, 3.8% in the aspirin placebo group) does not reflect the real-world experience because a study that used the NSQIP database reported a 0.8% risk of major perioperative bleeding.<sup>1</sup> There were, however, substantial differences in the populations and bleeding definitions between these studies.

The POISE-2 study included older patients ( $\geq 45$  years) than in the study using the NSQIP database ( $\geq 18$  years) and they were at higher risk of bleeding (ie, including [vs excluding] patients undergoing trauma, transplant, and emergent surgery). POISE-2 also had a more inclusive definition of major bleeding (ie, bleeding that only required 2 U of blood vs 4 U of blood). We therefore, not surprisingly, reported a higher incidence of bleeding.

Our reported bleeding rate thus applies to relevant patients (ie, those with cardiovascular risk having inpatient noncardiac surgery). Two-thirds of patients in POISE-2 received prophylactic anticoagulant therapy.

The hazard ratios (HRs) for major bleeding were similar irrespective of whether patients received anticoagulant prophylaxis ( $P = .80$  for heterogeneity). However, bleeding rates were higher in those who received both aspirin and anticoagulant prophylaxis (5.5%), but remained substantial in those who received aspirin alone (3.1%).

There was no significant effect of clonidine on the results comparing aspirin with placebo ( $P \geq .12$  for all interactions). We also previously reported that there was no aspirin subgroup effect in high-risk patients (ie, those with known vascular disease) for the outcome mortality or nonfatal myocardial infarction (HR, 1.00 [95% CI, 0.80-1.26];  $P = .92$  for interaction).<sup>2</sup>

We also previously reported that among the 4282 participants who had been taking aspirin before study enrollment (ie, the continuation stratum), there was no benefit to continuing aspirin during the perioperative period for the outcome of mortality or nonfatal myocardial infarction (HR, 1.00; 95% CI, 0.81-1.23). A separate substudy will report the results of patients who had a prior stent.

Although aspirin did not significantly affect the primary renal outcome (ie, an increase in serum creatinine concentration by either  $\geq 0.3$  mg/dL within 48 hours of surgery or an increase of  $\geq 50\%$  within 7 days of surgery), an outcome defined a priori demonstrated a higher risk of acute kidney injury in patients treated with dialysis and randomized to aspirin (HR, 2.20; 95% CI, 1.72-2.83).

Few patients developed acute kidney injury requiring dialysis, but post hoc analyses demonstrated that major bleeding was independently associated with subsequent risk of acute kidney injury (adjusted HR, 2.20; 95% CI, 1.72-2.83).

Our large international trial does not support the initiation or continuation of aspirin in patients having noncardiac surgery (including high-risk patients) because there was no demonstrated benefit and there was an increased risk of major bleeding (HR, 1.23; 95% CI, 1.01-1.49).<sup>2</sup> In patients who have their aspirin held during the perioperative period and have an indication for long-term use, it is important to ensure aspirin is restarted 8 to 10 days after surgery when the risk of perioperative bleeding has passed.

Further data are needed to elucidate the effects of perioperative aspirin use in patients with a prior coronary stent.

**P. J. Devereaux, MD, PhD**

**Daniel I. Sessler, MD**

**Amit X. Garg, MD, PhD**

**for the POISE-2 Investigators**

**Author Affiliations:** Population Health Research Institute, Hamilton, Ontario, Canada (Devereaux); Cleveland Clinic, Cleveland, Ohio (Sessler); Western University, London, Ontario, Canada (Garg).

**Corresponding Author:** Amit X. Garg, MD, PhD, London Health Sciences Centre, 800 Commissioners Rd E, London, ON N6A 4G5, Canada (amit.garg@lhsc.on.ca).

**Conflict of Interest Disclosures:** The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Devereaux reported receiving grants from Abbott Diagnostics, Bayer, Boehringer Ingelheim, Covidien, Octapharma, Philips Healthcare, Roche Diagnostics, and Stryker. No other disclosures were reported.

1. Kamel H, Johnston SC, Kirkham JC, et al. Association between major perioperative hemorrhage and stroke or Q-wave myocardial infarction. *Circulation*. 2012;126(2):207-212.

2. Devereaux PJ, Mrkobrada M, Sessler DI, et al; POISE-2 Investigators. Aspirin in patients undergoing noncardiac surgery. *N Engl J Med*. 2014;370(16):1494-1503.

### Time-Limited vs Unlimited Physician Certification

**To the Editor** Dr Lee<sup>1</sup> discussed the need for restructuring of the Maintenance of Certification (MOC) programs by the American Board of Medical Specialties, but did not provide a clear direction for change. The MOC programs began as Maintenance of Competence programs, but it was difficult to measure competence.

The programs then transformed into MOC programs, and new certificates were issued on a time-limited basis. A 10-year cycle, with a high-stakes examination, was instituted. The threat was that physicians who did not take or did not pass the examination would lose their certificates. This could have a profound effect on their ability to continue to practice medicine because most of the medical practice in the United States is now specialty-based.

The loss of a board certificate also destroys the recognition of academic and clinical education that physicians achieve in completing their residency programs. These residency programs are intense and rigorous educational experiences.

No degree is offered at the conclusion of a residency. An institutional certificate, which is not time-limited, is granted. Implicit in that is the presumption that the physician is competent to practice independently in that specialty.

Physicians generally are in support of continuing professional development activities, which can be measured and tailored to the needs of the individual practitioner. Physicians and practices change over time.

Some practices become much more specialized, and so general knowledge as tested by an examination may not be relevant to that physician. Some physicians move into administrative or research positions in which they are not responsible for patient care but still want or need to have the imprimatur of the board certification available to them.

Furthermore, the imposition of a high-stakes examination does not take into account the principles of adult learning, which is largely experiential, that most physicians use as part of their professional development. The imposition of a time-limited certificate and a high-stakes examination is a fundamental flaw in the process and is at best counterproductive.

Consideration should be given to abolishing the time-limited certificate and the high-stakes examination and for the MOC program to return to its roots as a continuing professional development program, tailored to the needs of each physician's practice.

**Paul Friedmann, MD**

**Author Affiliation:** Baystate Medical Center, Springfield, Massachusetts.

**Corresponding Author:** Paul Friedmann, MD, Baystate Medical Center, 161 Ardsley Rd, Longmeadow, MA 01106 (paulfried@gmail.com).

**Conflict of Interest Disclosures:** The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

1. Lee TH. Certifying the good physician: a work in progress. *JAMA*. 2014;312(22):2340-2342.

**In Reply** Dr Friedmann argues that physicians who have passed board certification tests once should retain the highest possible professional status for the rest of their careers because that status is important to them—even if they are not actually involved in patient care, “but still want or need to have the imprimatur of the board certification available to them.”

He also argues that, having successfully concluded residency training and obtained an institutional certificate that is