Perioperative Aspirin and Clonidine and Risk of Acute Kidney Injury
A Randomized Clinical Trial

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IMPORTANCE Acute kidney injury, a common complication of surgery, is associated with poor outcomes and high health care costs. Some studies suggest aspirin or clonidine administered during the perioperative period reduces the risk of acute kidney injury; however, these effects are uncertain and each intervention has the potential for harm.

OBJECTIVE To determine whether aspirin compared with placebo, and clonidine compared with placebo, alters the risk of perioperative acute kidney injury.

DESIGN, SETTING, AND PARTICIPANTS A 2 × 2 factorial randomized, blinded, clinical trial of 6905 patients undergoing noncardiac surgery from 88 centers in 22 countries with consecutive patients enrolled between January 2011 and December 2013.

INTERVENTIONS Patients were assigned to take aspirin (200 mg) or placebo 2 to 4 hours before surgery and then aspirin (100 mg) or placebo daily up to 30 days after surgery, and were assigned to take oral clonidine (0.2 mg) or placebo 2 to 4 hours before surgery, and then a transdermal clonidine patch (which provided clonidine at 0.2 mg/d) or placebo patch that remained until 72 hours after surgery.

MAIN OUTCOMES AND MEASURES Acute kidney injury was primarily defined as an increase in serum creatinine concentration from the preoperative concentration by either an increase of 0.3 mg/dL or greater (≥26.5 µmol/L) within 48 hours of surgery or an increase of 50% or greater within 7 days of surgery.

RESULTS Aspirin (n = 3443) vs placebo (n = 3462) did not alter the risk of acute kidney injury (13.4% vs 12.3%, respectively; adjusted relative risk, 1.10; 95% CI, 0.96-1.25). Clonidine (n = 3453) vs placebo (n = 3452) did not alter the risk of acute kidney injury (13.0% vs 12.7%, respectively; adjusted relative risk, 1.03; 95% CI, 0.90-1.18). Aspirin increased the risk of major bleeding. In a post hoc analysis, major bleeding was associated with a greater risk of subsequent acute kidney injury (23.3% when bleeding was present vs 12.3% when bleeding was absent; adjusted hazard ratio, 2.20; 95% CI, 1.72-2.83). Similarly, clonidine increased the risk of clinically important hypotension. In a post hoc analysis, clinically important hypotension was associated with a greater risk of subsequent acute kidney injury (14.3% when hypotension was present vs 11.8% when hypotension was absent; adjusted hazard ratio, 1.34; 95% CI, 1.14-1.58).

CONCLUSIONS AND RELEVANCE Among patients undergoing major noncardiac surgery, neither aspirin nor clonidine administered perioperatively reduced the risk of acute kidney injury.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01082874

Published online November 15, 2014.
About 10% of the 200 million adults estimated to undergo major noncardiac surgery each year develop acute kidney injury (a sudden loss of kidney function defined by an acute increase in serum creatinine concentration of ≥50% or an acute increase of ≥0.3 mg/dL [≥26 μmol/L]), and 0.5% will receive dialysis treatments for the most severe forms of acute kidney injury.1,2 Perioperative acute kidney injury is associated with poor outcomes, long hospital stays, and high health care costs.3-4

Early promising animal, human, and randomized clinical trial data suggest a commonly used antiplatelet (aspirin) or the centrally acting α2-adrenergic agonist clonidine, administered during the perioperative period, may reduce the risk of acute kidney injury.5-16 However, these effects are uncertain and each intervention has the potential for harm (perioperative bleeding with aspirin and perioperative hypotension with clonidine), which could increase the risk of acute kidney injury.17-20 Among persons who take aspirin as part of a long-term regimen, aspirin is not administered during the perioperative period in some but is continued in others.21

We designed and conducted a substudy of the Perioperative Ischemia Evaluation-2 (POISE-2) trial to determine whether the risk of acute kidney injury after noncardiac surgery is altered by aspirin compared with placebo and clonidine compared with placebo.

Methods

Main POISE-2 Trial

POISE-2 is randomized trial that used a 2 × 2 factorial design to allow separate evaluation of low-dose aspirin vs placebo and low-dose clonidine vs placebo in 10,010 patients undergoing noncardiac surgery.22 Enrolled patients had a moderate to high risk of a perioperative cardiac event and were expected to stay at least 1 night in the hospital after surgery (eligibility criteria detailed in eTable 1 in the Supplement, which included evidence of a baseline systolic blood pressure ≥105 mm Hg and heart rate ≥55 beats/min). Patients, clinicians, data collectors, and outcome adjudicators were blinded to the allocation of each intervention. The primary outcome of POISE-2 was a composite of 30-day mortality or nonfatal myocardial infarction, which was reported elsewhere.23,24 In summary, neither aspirin nor clonidine administered perioperatively altered the risk of this composite outcome. Major bleeding was more common with aspirin compared with placebo; clinically important hypotension was more common with clonidine compared with placebo (both outcomes defined in eTable 2 in the Supplement).

POISE-2 Acute Kidney Injury Substudy

The prespecified protocol and analysis plan for this POISE-2 acute kidney injury substudy was published.25 We justify minor deviations from the published protocol and the current report in eTable 3 in the Supplement. Regional ethics boards approved the kidney data collection in centers that agreed to study participation, and all patients provided written informed consent.

Substudy Eligibility Criteria

After receipt of grant funding, 88 of 135 POISE-2 sites agreed to participate in this substudy. Between January 2011 and December 2013 consecutive patients at POISE-2 participating sites were enrolled into this substudy. A small number of patients were ineligible for the study due to the following reasons: (1) had end-stage renal disease prior to randomization (ie, estimated glomerular filtration rate [GFR] <15 mL/min per 1.73 m² as determined by the equation from the Chronic Kidney Disease Epidemiology Collaboration26 or receipt of long-term dialysis; assessment of acute kidney injury no longer relevant); (2) missing a prerandomization serum creatinine measurement (this is needed to define acute kidney injury); or (3) never proceeded to surgery for various reasons (no postoperative serum creatinine measurements). Among the 2860 patients from POISE-2 who were not assessed for substudy eligibility, 1547 were randomized before this substudy started and 1313 were from nonparticipating sites.

Interventions

Patients were assigned to take aspirin (200 mg) or matched placebo 2 to 4 hours before surgery and then aspirin (100 mg) or matched placebo daily after surgery for either 7 days (for those taking long-term aspirin) or 30 days (for those not taking long-term aspirin); patients resumed any routine aspirin use after this time. Patients who took long-term aspirin discontinued its use for at least 3 days before surgery.

Patients were also assigned to take oral clonidine (0.2 mg) or placebo 2 to 4 hours before surgery, and then a transdermal clonidine patch (which provided clonidine at 0.2 mg/d) or placebo patch that remained until 72 hours after surgery. The protocol instructed study personnel to measure blood pressure and heart rate 1 hour after the first dose of clonidine or placebo, and then every 4 hours for the first 96 hours after surgery. Study personnel encouraged removal of the patient’s patch in the presence of clinically important hypotension or bradycardia that did not respond to initial treatment (eg, a fluid bolus). Attending physicians made all medical decisions, including those regarding discontinuation of any study drugs. The study centers were encouraged to instruct patients not to take their usual antihypertensive medications on the morning of surgery. Study personnel were asked to review vital signs in the presurgical area, report the results to the anesthetist, and ask the anesthetist whether a patient should receive his/her usual antihypertensive medications and, if he/she should, what dose he/she should receive.

Substudy Outcomes and Measurements

The primary outcome was acute kidney injury as defined in recent guidelines, which was an increase in serum creatinine concentration from the preoperative (prerandomization) concentration by either an increase of 0.3 mg/dL or greater (≥26.5 μmol/L) within 48 hours of surgery or an increase of 50% or greater within 7 days of surgery.27 The preoperative serum creatinine concentration was obtained within 6 weeks before surgery.

The secondary outcomes were the stage of acute kidney injury as defined in recent guidelines and our prespecified
protocol. The 2 separate outcomes of severe acute kidney injury were receipt of dialysis within 30 days of surgery and stage 3 acute kidney injury. The following criteria were used to define stage 3 acute kidney injury: (1) a postoperative percentage increase in serum creatinine concentration of 200% or greater from the preoperative concentration within 7 days of surgery, (2) an increase in postoperative serum creatinine concentration of at least 0.3 mg/dL or greater (≥26.5 μmol/L) to an absolute value of 4.0 mg/dL or greater (≥353.6 μmol/L) within 7 days of surgery, or (3) receipt of dialysis within 30 days of surgery. The other secondary outcomes specified in our protocol were the perioperative percentage change in serum creatinine concentration within 7 days ([(peak postoperative serum creatinine concentration within 7 days of surgery - preoperative serum creatinine concentration)/preoperative serum creatinine concentration] × 100), and the perioperative absolute change in serum creatinine concentration within 7 days (peak postoperative serum creatinine concentration within 7 days of surgery - preoperative serum creatinine concentration).

To reduce concerns about differential ascertainment of acute kidney injury between the intervention groups, all centers were encouraged to measure serum creatinine on postoperative days 1, 2, and 3 (while patients remained in the hospital), and then to perform further measurements as per routine care. Study personnel recorded the serum creatinine concentrations from the hospital stay. All surviving patients had a follow-up telephone interview 30 days after surgery to assess postoperative events that occurred after hospital discharge but within 30 days of surgery.

Randomization Procedures
With the use of a computerized Internet randomization system (which concealed the random allocation), patients undergoing noncardiac surgery were randomly assigned in a 1:1:1:1 ratio to receive clonidine and aspirin, clonidine and aspirin placebo, clonidine placebo and aspirin, or clonidine placebo and aspirin placebo. The randomization was stratified by site and whether patients were routinely taking aspirin long-term prior to randomization.

Statistical Analyses
Results were analyzed per the prespecified protocol. We conducted all statistical analyses according to the intention-to-treat principle (ie, as randomized, not as treated) using SAS version 9.2 (SAS Institute Inc). We conducted modified Poisson regression accounting for center to estimate the relative risk (RR) (with 95% confidence interval) of acute kidney injury comparing intervention with placebo. We conducted linear regression analyses to report the perioperative percentage change in serum creatinine concentration and the perioperative absolute change in serum creatinine concentration. In adjusted analyses, estimates of aspirin vs placebo and clonidine vs placebo on acute kidney injury were adjusted for 17 prespecified covariates assessed prior to surgery (listed in eTable 4 in the Supplement). We also adjusted for the random allocation of aspirin or placebo and clonidine or placebo in each alternate intervention analysis. Some alternate definitions of acute kidney injury had a limited number of events and we were unable to obtain an adjusted RR estimate using modified Poisson regression (because the model fit was not adequate or the model did not converge). In such circumstances, we used the Cochran-Mantel-Haenszel method to obtain a combined unadjusted RR across center strata.

We report the results using multiple imputation, although few patients were missing postoperative serum creatinine measurements (<5% of patients) and other methods of handling this missing data produced similar results (see Results section). We used a logistic regression model with multiple imputation to estimate the presence of the primary definition of acute kidney injury for patients with a missing serum creatinine measurement after surgery, under the assumption that the outcome was missing at random (PROC MI in SAS; eTable 3 in the Supplement). All prespecified covariates used in adjusted analyses (none of which had missing data), as well as the aspirin and clonidine allocations, were used in the imputation model. Five imputed data sets were developed, analyzed separately, and then combined using standard methods (PROC MIANALYZE in SAS) to estimate the number of events in each group and the RR of the event (with 95% confidence interval) for the intervention vs placebo. A similar approach was used for the analysis of each secondary definition of acute kidney injury. A linear regression model was used to impute the continuous outcome of missing peak serum creatinine in the 7 days after surgery.

Results in the aspirin trial were assessed in following 2 predefined subgroups (through use of an interaction term in each model as described elsewhere): (1) the presence or absence of preoperative chronic kidney disease as defined by a prerandomization estimated GFR category of 60 mL/min per 1.73 m² or less (we hypothesized a greater RR reduction in patients with preoperative chronic kidney disease), and (2) the presence or absence of a history of long-term aspirin use prior to randomization (we anticipated a greater RR reduction in patients with a history of long-term aspirin use given the potential for greater susceptibility to thrombosis after aspirin discontinuation). Results in the clonidine trial were assessed in the following predefined subgroup: the presence or absence of preoperative chronic kidney disease, with no prespecified hypothesis.

With the enrollment of 6905 patients, we had 88% power to detect a 20% RR reduction in acute kidney injury with each intervention vs placebo (assuming a 2-tailed level of .05 with each comparison, 5% loss to measurement, and an incidence of 12% in the placebo groups).

We conducted 4 other prespecified analyses. First, we assessed adherence to the study drugs. Second, we assessed the possibility of differential ascertainment of acute kidney injury between our study groups. Third, as recorded in POISE-2, the category of major urological or gynecological surgery included the procedure of nephrectomy, which alters postoperative serum creatinine concentration for reasons other than acute kidney injury; therefore, we repeated the primary analyses excluding this surgical category. Fourth, emergent and urgent surgeries have the potential for evolving acute kidney in-
jury prior to randomization; we repeated the primary analyses excluding these types of surgery. We conducted 2 post hoc analyses. First, we assessed the use of nonstudy medications within the first 3 days after surgery in each of our groups. Second, we performed a multivariable analysis investigating the potential factors associated with perioperative acute kidney injury, including major bleeding and clinically important hypotension as time-dependent covariates (definitions in eTable 2 in the Supplement).

Results

**Patient Enrollment and Baseline Characteristics**

Figure 1 is a flow diagram of patient enrollment, allocation, follow-up, and analysis. Of the 7150 patients in the POISE-2 study assessed for substudy eligibility, 245 were excluded due to having end-stage renal disease prior to randomization (1.7% patients; n = 63 aspirin vs n = 56 placebo, n = 61 clonidine vs n = 58 placebo), missing a prerandomization serum creatinine measurement (1.2% patients; n = 43 aspirin vs n = 46 placebo, n = 52 clonidine vs n = 37 placebo), or never having surgery (0.5% patients; n = 21 aspirin vs n = 16 placebo, n = 15 clonidine vs n = 22 placebo). The remaining 6905 patients enrolled in this substudy were from 88 centers in 22 countries. Among these, 3443 patients were randomly assigned to aspirin vs 3462 to placebo and 3453 to clonidine vs 3452 to placebo. The median time from randomization to surgery was 2 hours (interquartile range [IQR], 1-3 hours).

Baseline characteristics for both interventions are presented in Table 1. Almost half (43%) of patients were taking aspirin long-term prior to randomization. Patients who took...
Table 1. Baseline Characteristics of Patients in the POISE-2 Kidney Substudy

<table>
<thead>
<tr>
<th></th>
<th>Aspirin Trial</th>
<th>Placebo Trial</th>
<th>Clonidine Trial</th>
<th>Placebo Trial</th>
</tr>
</thead>
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<tr>
<td></td>
<td>(n = 3443)</td>
<td>(n = 3462)</td>
<td>(n = 3453)</td>
<td>(n = 3452)</td>
</tr>
<tr>
<td><strong>Age, mean (SD), y</strong></td>
<td>69.3 (9.9)</td>
<td>69.1 (10.0)</td>
<td>69.1 (10.0)</td>
<td>69.2 (9.9)</td>
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<tr>
<td><strong>Women</strong></td>
<td>1635 (47.5)</td>
<td>1601 (46.2)</td>
<td>1607 (46.5)</td>
<td>1629 (47.2)</td>
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<td><strong>Body mass index, mean (SD)</strong></td>
<td>29.6 (7.5)</td>
<td>29.9 (7.2)</td>
<td>29.9 (7.6)</td>
<td>29.7 (7.1)</td>
</tr>
<tr>
<td><strong>Year of randomization</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>634 (18.4)</td>
<td>660 (19.1)</td>
<td>648 (18.8)</td>
<td>646 (18.7)</td>
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<tr>
<td>2012</td>
<td>1341 (39.0)</td>
<td>1343 (38.8)</td>
<td>1334 (38.6)</td>
<td>1350 (39.1)</td>
</tr>
<tr>
<td>2013</td>
<td>1468 (42.6)</td>
<td>1459 (42.1)</td>
<td>1471 (42.6)</td>
<td>1456 (42.2)</td>
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<tr>
<td><strong>Location</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>1888 (54.8)</td>
<td>1873 (54.1)</td>
<td>1888 (54.7)</td>
<td>1873 (54.3)</td>
</tr>
<tr>
<td>South America</td>
<td>321 (9.3)</td>
<td>316 (9.1)</td>
<td>306 (8.9)</td>
<td>331 (9.6)</td>
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<tr>
<td>Europe</td>
<td>705 (20.5)</td>
<td>726 (21.0)</td>
<td>714 (20.7)</td>
<td>717 (20.8)</td>
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<td>Asia</td>
<td>250 (7.3)</td>
<td>260 (7.5)</td>
<td>257 (7.4)</td>
<td>253 (7.3)</td>
</tr>
<tr>
<td>Australia and New Zealand</td>
<td>198 (5.8)</td>
<td>204 (5.9)</td>
<td>205 (5.9)</td>
<td>197 (5.7)</td>
</tr>
<tr>
<td>Africa</td>
<td>81 (2.4)</td>
<td>83 (2.4)</td>
<td>83 (2.4)</td>
<td>81 (2.4)</td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cardiovascular diseasec</td>
<td>1070 (31.1)</td>
<td>1074 (31.0)</td>
<td>1068 (30.9)</td>
<td>1076 (31.2)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>737 (21.4)</td>
<td>713 (20.6)</td>
<td>738 (21.4)</td>
<td>712 (20.6)</td>
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<tr>
<td>Stroke</td>
<td>162 (4.7)</td>
<td>193 (5.6)</td>
<td>184 (5.3)</td>
<td>171 (5.0)</td>
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<tr>
<td>Peripheral vascular disease</td>
<td>304 (8.8)</td>
<td>291 (8.4)</td>
<td>293 (8.5)</td>
<td>302 (8.8)</td>
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<tr>
<td>History of smoking within 2 y of surgery</td>
<td>900 (26.1)</td>
<td>884 (25.5)</td>
<td>892 (25.8)</td>
<td>892 (25.8)</td>
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<tr>
<td>Diabetes</td>
<td>1234 (35.8)</td>
<td>1255 (36.3)</td>
<td>1272 (36.8)</td>
<td>1217 (35.3)</td>
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<tr>
<td>Hypertension</td>
<td>2938 (85.3)</td>
<td>3010 (86.9)</td>
<td>2949 (85.4)</td>
<td>2999 (86.9)</td>
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<tr>
<td>Atrial fibrillation</td>
<td>80 (2.3)</td>
<td>80 (2.3)</td>
<td>79 (2.3)</td>
<td>81 (2.4)</td>
</tr>
<tr>
<td>Long-term use of aspirin therapy</td>
<td>1497 (43.5)</td>
<td>1496 (43.2)</td>
<td>1497 (43.4)</td>
<td>1496 (43.4)</td>
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<tr>
<td>Medication use 7 d-6 h prior to surgery</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>COX-2 inhibitor, NSAID, or non-COX-2 inhibitor</td>
<td>476 (13.8)</td>
<td>483 (14.0)</td>
<td>489 (14.2)</td>
<td>470 (13.6)</td>
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<td>Statin</td>
<td>1651 (48.0)</td>
<td>1641 (47.4)</td>
<td>1669 (48.3)</td>
<td>1623 (47.0)</td>
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<tr>
<td>ACE inhibitor, ARB, or direct renin inhibitor</td>
<td>2052 (59.6)</td>
<td>2057 (59.4)</td>
<td>2042 (59.1)</td>
<td>2067 (59.9)</td>
</tr>
<tr>
<td>Antihypertensive agentd</td>
<td>1619 (47.0)</td>
<td>1668 (48.2)</td>
<td>1643 (47.6)</td>
<td>1644 (47.6)</td>
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<tr>
<td>Medication use &lt;6 h prior to surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>COX-2 inhibitor, NSAID, or non-COX-2 inhibitor</td>
<td>323 (9.4)</td>
<td>325 (9.4)</td>
<td>330 (9.6)</td>
<td>318 (9.2)</td>
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<tr>
<td>Statin</td>
<td>318 (9.2)</td>
<td>284 (8.2)</td>
<td>324 (9.4)</td>
<td>278 (8.1)</td>
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<tr>
<td>ACE inhibitor, ARB, or direct renin inhibitor</td>
<td>339 (9.9)</td>
<td>304 (8.8)</td>
<td>312 (9.0)</td>
<td>331 (9.6)</td>
</tr>
<tr>
<td>Antihypertensive agentd</td>
<td>776 (22.5)</td>
<td>819 (23.7)</td>
<td>814 (23.6)</td>
<td>781 (22.6)</td>
</tr>
<tr>
<td>Overall estimated glomerular filtration rate, mean (SD), mL/min per 1.73 m²</td>
<td>75 (20)</td>
<td>75 (21)</td>
<td>75 (20)</td>
<td>75 (21)</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate &gt;60 mL/min per 1.73 m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%)</td>
<td>2635 (76.5)</td>
<td>2620 (75.7)</td>
<td>2645 (76.6)</td>
<td>2610 (75.6)</td>
</tr>
<tr>
<td>Mean (SD), mL/min per 1.73 m²</td>
<td>83 (13)</td>
<td>84 (13)</td>
<td>84 (13)</td>
<td>84 (13)</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate ≤60 mL/min per 1.73 m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%)</td>
<td>808 (23.5)</td>
<td>842 (24.3)</td>
<td>808 (23.4)</td>
<td>842 (24.4)</td>
</tr>
<tr>
<td>Mean (SD), mL/min per 1.73 m²</td>
<td>47 (10)</td>
<td>46 (10)</td>
<td>47 (10)</td>
<td>46 (10)</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate ≤45 mL/min per 1.73 m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated glomerular filtration rate ≤30 mL/min per 1.73 m²</td>
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</tbody>
</table>

(continued)
Aspirin long-term prior to randomization discontinued it a median of 7 days (IQR, 4-8 days) before surgery. The mean prerandomization estimated GFR was 75 mL/min per 1.73 m² with 8% to 10% of patients in each group having an estimated GFR of 45 mL/min per 1.73 m² or less. The highest prerandomization serum creatinine measurement was 3.7 mg/dL (325 μmol/L) and the lowest prerandomization estimated GFR was 16 mL/min per 1.73 m². Differences in baseline characteristics between all patients in the POISE-2 trial and those enrolled in the kidney substudy are shown in eTable 5 in the Supplement.

**Perioperative Aspirin and the Primary Definition of Acute Kidney Injury**

Aspirin (n = 3443) vs placebo (n = 3462) did not alter the risk of the primary definition of acute kidney injury (462 patients [13.4%] vs 426 patients [12.3%], respectively; unadjusted RR, 1.09 [95% CI, 0.95-1.24]; adjusted RR, 1.10 [95% CI, 0.96-1.25]) (Table 2). The primary results were similar when an missing peak postoperative serum creatinine measurement was imputed as the same value as the baseline serum creatinine measurement, or when the analysis was restricted to complete data (eTable 6 in the Supplement).

**Perioperative Clonidine and the Primary Definition of Acute Kidney Injury**

Clonidine (n = 3453) vs placebo (n = 3452) did not alter the risk of the primary definition of acute kidney injury (449 patients [13.0%] vs 439 patients [12.7%], respectively; unadjusted RR, 1.02 [95% CI, 0.89-1.17]; adjusted RR, 1.03 [95% CI, 0.90-1.18]) (Table 2). The primary results were similar when an missing peak postoperative serum creatinine measurement was imputed as the same value as the baseline serum creatinine measurement, or when the analysis was restricted to complete data (eTable 6 in the Supplement).

**Perioperative Aspirin and Secondary Definitions of Acute Kidney Injury**

The effects of aspirin were also consistent with multiple secondary categorical definitions of acute kidney injury, which included a composite outcome of acute kidney injury or death (Table 2). Within 30 days of surgery, 19 of 3443 patients (0.6%) assigned to aspirin were treated with dialysis for severe acute kidney injury, with a corresponding number of 9 of 3462 patients (0.3%) assigned to placebo (adjusted RR, 2.17; 95% CI, 0.98-4.81).

The mean percentage increase in serum creatinine concentration was 11% with aspirin vs 11% with placebo, with no statistical difference in the percentage change in serum creatinine concentration between the 2 groups (adjusted mean difference: 0.0% [95% CI, −0.7% to 0.7%]; eFigure 1 in the Supplement). Similarly, the mean absolute increase in serum creatinine concentration was 8 μmol/L with aspirin vs 8 μmol/L with placebo, with no difference in the absolute change in serum creatinine concentration between the 2 groups (adjusted mean difference: 0.0 μmol/L [95% CI, −1.0 to 1.0 μmol/L]; eFigure 2 in the Supplement).

**Perioperative Clonidine and Secondary Definitions of Acute Kidney Injury**

The effects of clonidine were consistent with multiple secondary categorical definitions of acute kidney injury, which included a composite outcome of acute kidney injury or death (Table 2). Severe (stage 3) acute kidney injury was evident in 47 of 3453 patients (1.4%) assigned to clonidine and 29 of 3452 patients (0.8%) assigned to placebo (adjusted RR, 1.62; 95% CI,
1.02-2.58). A total of 18 of 3453 patients (0.5%) assigned to clonidine received dialysis treatments for severe acute kidney injury, with a corresponding number of 10 of 3452 patients (0.3%) assigned to placebo (adjusted RR, 1.80; 95% CI, 0.83-3.90).

The mean percentage increase in serum creatinine concentration was 11% with clonidine vs 11% with placebo, with no statistical difference in the percentage change in serum creatinine concentration between the groups (adjusted mean, 0.7% [95% CI, −1.5% to 3.0%]; eFigure 1 in the Supplement). Similarly, the mean absolute increase in serum creatinine concentration was 8 μmol/L with clonidine vs 8 μmol/L with placebo, with no difference in the absolute change in serum creatinine concentration between the 2 groups (adjusted mean, 0.3 μmol/L [95% CI, −1.6 to 2.2 μmol/L]; eFigure 2 in the Supplement).

Preselected Subgroup Analyses

The RR of acute kidney injury with aspirin vs placebo was not statistically different in those with vs those without preoperative chronic kidney disease (P = .53 for interaction, Figure 2), or in those who were vs those who were not taking aspirin long-term prior to randomization (P = .45 for interaction, Figure 2). Within each of the 2 subgroups a similar nonsignificant dif-

Table 2. Perioperative Low-Dose Aspirin and Perioperative Low-Dose Clonidine and the Risk of Acute Kidney Injury (AKI) in the Setting of Noncardiac Surgery

<table>
<thead>
<tr>
<th>AKI or death†</th>
<th>Placebo (n = 3452)</th>
<th>Adjusted‡</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin (n = 3443)</td>
<td>462 (13.4)</td>
<td>416 (12.3)</td>
<td>1.09 (0.95-1.24)</td>
</tr>
<tr>
<td>Placebo (n = 3452)</td>
<td>426 (12.3)</td>
<td>428 (12.4)</td>
<td>1.09 (0.95-1.24)</td>
</tr>
</tbody>
</table>

* Events were imputed when the peak postoperative serum creatinine measurement was missing (>5% of patients; see Methods section). Each AKI outcome (eg, AKI for at least 2 days, AKI stage 2 or more, etc) was imputed separately, with the exception of AKI or death because death was not missing for any patients.

† Patients assigned to placebo were the referent group.

‡ Modified Poisson regression was used without adjustment for covariates or accounting for center (see Methods section).

§ Adjusted for 17 covariates plus the clonidine allocation (18 covariates total; see Methods section). For the outcome receipt of acute dialysis, a relative risk stratified by center is reported using the Cochran-Mantel-Haenszel method (to avoid full adjustment model overfitting with the limited number of events).

# P value from the adjusted model.

An increase in serum creatinine concentration from the preoperative measurement to an absolute value of 4.0 mg/dL or greater (≥353.6 μmol/L) within 7 days, or receipt of acute dialysis within 30 days of surgery. All patients in POISE-2 had a follow-up telephone interview 30 days after surgery (for the assessment of postoperative events that occurred after hospital discharge but within 30 days of surgery).

1 A postoperative percentage increase in serum creatinine concentration of 200% or greater from the preoperative concentration within 7 days of surgery, an increase in postoperative serum creatinine concentration to an absolute value of 4.0 mg/dL or greater (≥353.6 μmol/L) within 7 days, or receipt of acute dialysis within 30 days of surgery. All patients in POISE-2 had a follow-up telephone interview within 30 days of surgery (for the assessment of postoperative events that occurred after hospital discharge but within 30 days of surgery).

4 Provided for an indication of severe AKI. In patients who received acute dialysis, the median increase in serum creatinine concentration from preoperative to postoperative was 2.7 mg/dL (interquartile range, 1.9-4.6 mg/dL; 241 μmol/L [interquartile range, 165-404 μmol/L]).

5 Adjusted for 17 covariates plus the aspirin allocation (18 covariates total; see Methods section). For the outcome receipt of acute dialysis, a relative risk stratified by center is reported using the Cochran-Mantel-Haenszel method (to avoid full adjustment model overfitting with the limited number of events).

6 Met the primary definition of AKI or death within 48 hours of surgery. This accounts for the potential effect of early deaths (5/3453 [0.1%] in clonidine group vs 5/3462 [0.1%] in placebo group) on the ascertainment of AKI.

7 An increase in serum creatinine concentration of either 0.3 mg/dL or greater (≥26.5 μmol/L) or 50% or greater on at least 2 different days within 7 days of surgery. The magnitude of the peak change in serum creatinine concentration defines the stage of AKI in recent guidelines; however, a longer duration of AKI also is associated with poorer outcomes.

8 A postoperative percentage increase in serum creatinine concentration of ≥100% or greater from the preoperative concentration within 7 days of surgery, an increase in postoperative serum creatinine concentration to an absolute value of 4.0 mg/dL or greater (≥353.6 μmol/L) within 7 days, or receipt of acute dialysis within 30 days of surgery. All patients in POISE-2 had a follow-up telephone interview 30 days after surgery (for the assessment of postoperative events that occurred after hospital discharge but within 30 days of surgery).

9 Met the primary definition of AKI or death within 48 hours of surgery. This accounts for the potential effect of early deaths (5/3453 [0.1%] in clonidine group vs 5/3462 [0.1%] in placebo group) on the ascertainment of AKI.

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The size of the markers reflects the size of the sample.

a Adjusted for 15 covariates plus preoperative chronic kidney disease, clonidine allocation therapy, and the long-term use of aspirin prior to randomization when appropriate (see Methods).

b Chronic kidney disease was defined as a preoperative estimated glomerular filtration rate of 60 mL/min per 1.73 m² or less. The relative risk (RR) of acute kidney injury with aspirin vs placebo did not significantly differ in those with vs without preoperative chronic kidney disease (P = .53 for interaction).

c The RR of acute kidney injury with aspirin vs placebo did not significantly differ in those who were vs were not taking long-term aspirin prior to randomization (P = .45 for interaction).

Other Prespecified Analyses

First, adherence to the study drugs was high. In the aspirin trial, only 41 of 3443 patients (1.2%) assigned to aspirin did not receive the study drug prior to surgery, which was similar to the 35 of 3462 patients (1.0%) assigned to placebo. Over the entire study treatment period, 80.3% of patients assigned to aspirin and 82.0% assigned to placebo took 80% or more of the study drug. Of the 3462 patients assigned to placebo, 1 (0.03%) received nonstudy aspirin within 24 hours prior to surgery, and 155 (4.5%) received nonstudy aspirin during the first 3 days after surgery. In the clonidine trial, only 66 of 3453 patients (1.9%) assigned to clonidine did not receive the study drug prior to surgery, which was similar to the 74 of 3452 patients (2.1%) assigned to placebo. The transdermal patch remained in place for at least 80% of the targeted duration of application in 91.3% of patients assigned to clonidine and 90.6% assigned to placebo.

Second, there was no evidence of differential ascertainment of acute kidney injury between aspirin vs placebo and clonidine vs placebo (eTable 8 in the Supplement). For
example, the median number of postoperative serum creatinine measurements was identical in each intervention and placebo group (3 measurements; IQR, 2-4 measurements) along with the specific postoperative days of these measurements. The median duration of hospital stay was identical in each intervention and placebo group (4 days; IQR, 3-7 days). More than 95% of patients had at least 1 serum creatinine measurement within the 7 days following surgery. A peak creatinine measurement was not recorded during the week after surgery for 320 patients (4.6%) due to missing measurement (4.5% of patients) or death (0.1% of patients). Characteristics of patients who did vs did not provide at least 1 serum creatinine measurement during the week following surgery differed (eTable 9 in the Supplement). The outcomes of acute dialysis and death were recorded for all patients.

Third, when we excluded the category of major urological or gynecological surgery from our analysis (831 of 6905 patients [12.0%]), the results for aspirin and for clonidine were consistent with the primary results (eTable 10 in the Supplement).

Fourth, when we excluded emergent and urgent surgeries from our analysis (457 of 6905 patients [6.6%]), the results for aspirin and for clonidine were consistent with the primary results (eTable 11 in the Supplement).

**Post hoc Analyses**

First, there was no evidence that patients allocated to aspirin vs placebo differed in their use of nonstudy medications during the first 3 days after surgery (eTable 12 in the Supplement). Patients allocated to clonidine vs placebo were less likely to use an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker during the first 3 days after surgery (47.3% vs 50.4%, respectively, P = .01; eTable 12 in the Supplement). There was no difference between the clonidine and placebo groups in the use of calcium channel blockers or β-blockers.

Second, 331 of 6905 patients (4.8%) experienced major perioperative bleeding, and the development of such bleeding was associated with a greater risk of subsequent acute kidney injury (23.3% when bleeding was present vs 12.3% when bleeding was absent; adjusted hazard ratio, 2.20 [95% CI, 1.72-2.83]; model description and results presented in eTable 13 in the Supplement). Similarly, a total of 3069 of 6905 patients (44.4%) experienced clinically important hypotension, and the development of such hypotension was associated with a greater risk of subsequent acute kidney injury (14.3% when hypotension was present vs 11.8% when hypotension was absent; adjusted hazard ratio, 1.34 [95% CI, 1.14-1.58]).

**Discussion**

In this 2 × 2 factorial randomized clinical trial in patients undergoing noncardiac surgery, neither perioperative assignment to aspirin nor clonidine altered the risk of the primary definition of acute kidney injury.

We designed and conducted this study because early promising data suggested these interventions may reduce the risk of perioperative acute kidney injury. The putative major mechanism of perioperative acute kidney injury is a decrease in kidney perfusion and ischemia, with activation of inflammatory mediators, adhesion molecules, platelets, and thromboxane (eFigure 3 in the Supplement).4-10 Aspirin reduces platelet aggregation and microembolization, potentially improving GFR at a time of poor kidney perfusion. Perioperative aspirin reduces urinary thromboxane, a potent vasoconstrictor in which increased levels correlate with acute decreases in kidney function.11-13 Anti-inflammatory mediators (resolvins, protectin) produced by the kidney mitigate acute kidney injury in animals, and their production can be enhanced by aspirin.5-12 In a large, prospective cohort study of more than 5000 patients who had cardiac surgery (70 centers, 17 countries), there were fewer episodes of acute kidney injury in aspirin users than in nonusers (P < .001) and fewer patients taking aspirin were treated with acute dialysis (P < .001).7 Similar beneficial associations of aspirin for the prevention of acute kidney injury have also been observed in other perioperative cohort studies.8,14 Clonidine, a centrally acting α2-adrenergic agonist, blunts central sympathetic outflow and has analgesic, anxiolytic, and anti-inflammatory effects.15-18 Many animal and human studies,19-21 including 2 small randomized placebo-controlled trials in cardiac surgery, suggest clonidine reduces the risk of acute kidney injury.

Each intervention also has the potential for harm, which could increase the risk of acute kidney injury. In POISE-2, we previously demonstrated that aspirin use during the perioperative period increases the risk of major bleeding,22 and in the current post hoc analysis, such bleeding was associated with a greater risk of acute kidney injury. In addition, there was also some suggestion that each intervention increased the risk of severe acute kidney injury. However, the results for this secondary outcome need to be interpreted cautiously given the inconsistent results across different definitions of severe acute kidney injury, the analyses uncorrected for multiple statistical comparisons, and the limited number of severe acute kidney injury events. Subgroup analyses from POISE-2 also raise the possibility that the risk of severe acute kidney injury with aspirin vs placebo may be higher in patients with preoperative chronic kidney disease than in those without chronic kidney disease, mediated by perioperative bleeding. Even though this is biologically plausible,23 there is also uncertainty about this result given the small number of severe acute kidney injury events. Rather, the findings can now guide similar analyses in other ongoing trials to determine if the signal is replicated.40 The increase in risk may be due to postoperative anemia secondary to bleeding, or the blood transfusions used to treat it.41,42
This POISE-2 substudy provides generalizable effect estimates derived from almost 7000 patients recruited in 88 centers across 22 countries according to a prespecified protocol and with use of randomized trial methods (eg, concealed allocation, placebo-controlled). The lower bound of the 95% confidence intervals of the treatment estimates suggest that clinically important benefits of aspirin and clonidine on the risk of perioperative acute kidney injury were unlikely to be missed.

POISE-2 used an efficient kidney data collection schedule as done in other large multicenter randomized trials. A key limitation of our protocol (as previously reported) is our reliance on the serum creatinine concentration collected during routine care as the sole measure of kidney function. It would have been preferable to have multiple baseline measures of serum creatinine and other assessments of kidney function, and additional follow-up measures during the perioperative period. During the last decade, there have been efforts to better standardize the serum creatinine assay worldwide given concerns regarding inter- and intralaboratory variability. It seems likely (although not documented in POISE-2) that most preoperative and postoperative serum creatinine measurements prior to hospital discharge at a given center were analyzed in the same laboratory. The randomization and analysis of this study was also stratified by center, which should result in similar measurement errors within a center for the intervention and placebo groups.

Future large trials to prevent acute kidney injury in the surgical setting should focus on interventions that target pathways other than inhibiting platelet aggregation or α1-adrenoergic agonism. Interventions that prevent perioperative bleeding and perioperative hypotension may prove useful.

Conclusions

Among patients undergoing major noncardiac surgery, neither aspirin nor clonidine administered perioperatively reduced the risk of acute kidney injury.

Funding/Support: The Perioperative Ischemic Evaluation 2 (POISE-2) Trial and this acute kidney injury substudy were financially supported by grants from the Canadian Institutes of Health Research. Financial support for POISE-2 was also provided by the Australian National Health and Medical Research Council and the Spanish Ministry of Health and Social Policy. Boehringer Ingelheim provided the clonidine study drug and some funding. Bayer Pharma AG provided the aspirin study drug.

Role of the Funders/Sponsors: The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Italy: R. Lembo, L. Pasin, and S. Passarani.
Pakistan: M. Amir, O. Ishtiaq, and J. Sadfar.

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