Perioperative Aspirin or Clonidine Fails to Reduce AKI

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Perioperative treatment of patients undergoing noncardiac surgery with aspirin did not reduce the risk of acute kidney injury (AKI) compared with placebo, nor did the use of clonidine compared with placebo. Amit X. Garg, MD, PhD, Western University, London, Ontario, Canada, presented data from the Perioperative Ischemic Evaluation-2 Trial substudy [POISE-2; Garg AX et al. *JAMA*. 2014].

It is estimated that about 10% of the 200 million noncardiac surgeries performed each year are complicated by AKI, and 0.5% of patients experience severe AKI that requires dialysis treatment [Garg AX et al. *BMJ Open.* 2014]. The underlying mechanism that is thought to be responsible for perioperative AKI is decreased kidney perfusion and ischemia. Aspirin decreases platelet aggregation and can increase the glomerular filtration rate. Clonidine is a centrally acting α2-adrenergic agonist that has analgesic, anxiolytic, and anti-inflammatory effects. The purpose of the POISE-2 substudy was to evaluate the effect of aspirin vs placebo, or clonidine vs placebo, on AKI after surgery.

In the POISE-2 trial, 6905 patients were randomly assigned in a 2-by-2 factorial design to receive perioperative aspirin vs placebo and clonidine vs placebo. The mean age was 69 years, and all patients underwent noncardiac surgery.

In the substudy, treatment with aspirin or clonidine was not significantly associated with AKI, death, or need for acute dialysis compared with placebo (Table 1).

The rate of AKI or death was about 13% in all arms of the substudy. Prof Garg concluded that neither aspirin nor clonidine was effective in preventing perioperative AKI.

Prof Garg also discussed one aspect of living kidney donation: concern regarding the effect of kidney donation on future pregnancies. In 2004, the international consensus was that kidney donation did not affect the outcomes of future pregnancies [Monaco AP, Morris PJ. *Transplantation.* 2004]. However, after the consensus was published, 2 studies demonstrated that there were higher risks of gestational hypertension and preeclampsia after kidney donation in women who had a pregnancy prior to and after donation [Ibrahim HN et al. *Am J Transplant.* 2009; Reisaeter AV et al. *Am J Transplant.* 2009]. However, the methods and results of the 2 studies have been debated and are not widely disseminated by transplant programs [Nevis IF et al. *Am J Transplant.* 2009].

Garg and colleagues [*N Engl J Med.* 2014] conducted a retrospective cohort study in which kidney donors with pregnancies were matched to nondonor controls with pregnancy. Donors had a significantly higher rate of gestational hypertension or preeclampsia compared with nondonor controls (11% vs 5%; 95% CI, 1.2 to 5; $P = .01$). However, there was no association between kidney donation and caesarian section, postpartum hemorrhage, preterm birth, or low birth weight. Most women had an uncomplicated pregnancy after kidney donation.

Therefore, Prof Garg concluded that living kidney donation remains an important treatment option for patients with kidney failure and their families. This new information on the pregnancy outcomes of living kidney donors can feature in clinical practice guidelines, can be shared in the informed consent process for potential donors and their recipients when a woman has reproductive potential, and can be used to guide the care of pregnant donors.

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Table 1. Effects of Aspirin and Clonidine on Perioperative AKI

	No. (%) of Events[a]		RR (95% CI)		
	Aspirin (n = 3443)	Placebo (n = 3462)[b]	Unadjusted[c]	Adjusted[d]	*P* Value[e]
AKI[f]	462 (13.4)	426 (12.3)	1.09 (0.95 to 1.24)	1.10 (0.96 to 1.25)	.17
AKI or death[g]	464 (13.5)	428 (12.4)	1.09 (0.95 to 1.24)	1.10 (0.96 to 1.25)	.17
AKI for at least 2 d[h]	248 (7.2)	228 (6.6)	1.09 (0.91 to 1.31)	1.11 (0.93 to 1.33)	.26
≥Stage 2 AKI[i]	108 (3.1)	107 (3.1)	1.02 (0.78 to 1.33)	1.04 (0.79 to 1.36)	.79
Stage 3 AKI[j]	40 (1.2)	36 (1 0)	1.11 (0.70 to 1.75)	1.13 (0.72 to 1.79)	.59
Acute dialysis within 30 d of surgery[k]	19 (0.6)	9 (0.3)	2.12 (0.96 to 4.68)	2.17 (0.98 to 4.81)	.05
	Clonidine (n = 3453)	Placebo (n = 3452)[b]	Unadjusted[c]	Adjusted[l]	
AKI[f]	449 (13.0)	439 (12.7)	1.02 (0.89 to 1.17)	1.03 (0.90 to 1.18)	.68
AKI or death[m]	451 (13.1)	441 (12.7)	1.02 (0.89 to 1.17)	1.03 (0.90 to 1.18)	.67
AKI for at least 2 d[h]	237 (6.9)	239 (6.9)	0.99 (0.82 to 1.19)	1.00 (0.83 to 1.20)	.96
≥Stage 2 AKI[i]	110 (3.2)	105 (3.0)	1.05 (0.80 to 1.37)	1.05 (0.81 to 1.38)	.71
Stage 3 AKI[j]	47 (1.4)	29 (0.8)	1.61 (1.01 to 2.56)	1.62 (1.02 to 2.58)	.04
Acute dialysis within 30 d of surgery[k]	18 (0. 5)	10 (0.3)	1.80 (0.83 to 3.89)	1.80 (0.83 to 3.90)	.13

AKI, acute kidney injury; POISE-2, Perioperative Ischemic Evaluation-2 Trial substudy.

[a]Events were imputed when the peak postoperative serum creatinine measurement was missing (<5% of patients). 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.

[b]Patients assigned to placebo were the referent group.

[c]Modified Poisson regression was used without adjustment for covariates or accounting for few centers.

[d]Adjusted for 17 covariates plus the clonidine allocation (18 covariates total). 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).

[e]*P* value from the adjusted model.

[f]The primary definition of AKI was an increase in serum creatinine concentration from the preoperative measurement 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.

[g]Met the primary definition of AKI or death within 48 hours of surgery. This accounts for the potential effect of early deaths (4/3443 [0.1%] in aspirin group vs 5/3462 [0.1%] in placebo group) on the ascertainment of AKI.

[h]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.

[i]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 d, 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).

[j]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 d, 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).

[k]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]).

[l]Adjusted for 17 covariates plus the aspirin allocation (18 covariates total). 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).

[m]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 the clonidine group vs 4/3452 (0.1%) in the placebo group) on the ascertainment of AKI.