Robert Jackman, MD
Cascades East
Family Medicine Residency,
Oregon Health and Science
University, Portland

Andrew Hamilton, MS, MLS
Cascades East
Family Medicine Residency,
Oregon Health and Science
University, Portland

DEPUTY EDITOR
Rick Guthmann, MD, MPH
Advocate Illinois Masonic
Family Medicine Residency,
Chicago

Q/ Does withholding an ACE inhibitor or ARB before surgery improve outcomes?

EVIDENCE-BASED ANSWER

A/ **A GUARDED YES,** because the evidence of benefit is from observational studies and applies to noncardiac surgery. Withholding angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) 24 hours before noncardiac surgery has been associated with a 30-day lower risk for all-cause death, stroke, myocardial injury, and intraoperative hypotension (18% adjusted relative risk reduction).

The finding is based on 1 international prospective cohort study and, of note, is an association and a likelihood of benefit. Confirmation would require a large randomized trial (RCT; strength of recommendation [SOR]: **B**, good-quality international prospective cohort study).

Evidence summary

An international prospective cohort study analyzed data from 14,687 patients, 4802 of whom were on an ACEI or ARB, to study the effect on 30-day morbidity and mortality of withholding the medications 24 hours before a noncardiac surgery.[1] Of the ACEI or ARB users, 26% (1245) withheld their medication and 3557 continued it 24 hours before surgery.

Large study shows benefit in withholding meds

Patients who withheld the ACEI or ARB were less likely to experience the primary composite outcome of all-cause death, stroke, or myocardial injury (150/1245 [12%] vs 459/3557 [12.9%]; adjusted relative risk [RR] = 0.82; 95% confidence interval [CI], 0.70-0.96; P = .01; number needed to treat [NNT] = 116) and intraoperative hypotension (adjusted RR = 0.80; 95% CI, 0.72-0.93; P < .001; NNT = 18). For the NNT calculation, which the investigators didn't perform, the treatment is the number needed to withhold an ACEI or ARB to show benefit.

Smaller, weaker studies yield different results

A retrospective cohort analysis of propensity-matched ACEI users with ACEI nonusers (9028 in each group) undergoing noncardiac surgery compared intra- and postoperative respiratory complications or mortality.[2] The study found no association with either 30-day mortality (odds ratio [OR] = 0.93; 95% CI, 0.73-1.19) or the composite of in-hospital morbidity and mortality (OR = 1.06; 95% CI, 0.97-1.15). Limitations included comparison of users with nonusers as opposed to an intention-to-withhold study, the retrospective nature of the study, and the fact that outcomes were gathered from ICD-9 billing codes rather than obtained prospectively.

A Cochrane review assessed the benefits and harms of perioperative ACEIs or ARBs on mortality and morbidity in adults undergoing any type of surgery.[3] Seven RCTs with a total of 571 participants were included in the review. Overall, the review didn't find evidence to support prevention of mortality, morbidity, and complications by perioperative ACEIs or ARBs because the included studies were

of low and very low methodological quality, had a high risk for bias, and lacked power. Moreover, the review didn't assess the effect of withholding ACEIs or ARBs before surgery.

A random-effects meta-analysis of 5 studies (3 randomized trials and 2 observational studies) totaling 434 patients suggested that patients receiving ACEIs or ARBs immediately before surgery were more likely to develop hypotension requiring vasopressors (RR = 1.50; 95% CI, 1.15-1.96).[4] Sufficient data weren't available to assess other outcomes, and the included studies were relatively small and generally not powered to observe clinically significant consequences nor designed to measure the incidence of patient-important outcomes.

Recommendations

The 2014 American College of Cardiology/American Heart Association Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery states that continuing ACEIs or ARBs perioperatively is reasonable (class IIa recommendation [moderate benefit of treatment relative to risk]; level of evidence [LOE], B [data from limited populations and single randomized or nonrandomized trials]).[5]

The guideline also recommends that if ACEIs or ARBs are held before surgery, it is reasonable to restart them as soon as clinically feasible postoperatively (class IIa recommendation; LOE, C [data from very limited populations and consensus opinion or case studies]).

Editor's Takeaway

The results of the large prospective cohort contradict those of previous smaller, methodologically weaker studies, and the new findings should be taken seriously.[1] Nevertheless, selection bias (why did investigators stop the ACEI?) remains. Until we have a large RCT, the preop question to ask may be why not stop the ACEI? JFP

References

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