Since the introduction of the first angiotensin-converting enzyme inhibitor (ACEI), captopril, in 1981, ACEIs have become a mainstay of antihypertensive therapy. In addition to lowering blood pressure, there is overwhelming evidence that ACEIs (and angiotensin receptor blockers) provide end-organ protection independent of their blood pressure–lowering properties in diseases such as congestive heart failure, postmyocardial infarction (MI), diabetes mellitus, and renal insufficiency. It is an unresolved issue, however, whether ACEIs have a protective or deleterious effect on perioperative outcomes.

In the surgical patient population, the focus historically has been on refining and improving surgical skills and techniques and thus outcomes. Perioperative medication use has not been considered a significant modulator of their blood pressure–lowering properties. At the end of the 20th century, evidence-based medicine began to be incorporated into perioperative practice. For example, anticoagulants and antibiotics are now routinely used in the perioperative period to prevent postoperative mortality and morbidity caused by thromboembolic and infectious complications. The focus on improved perioperative outcomes has now been extended beyond 30-day survival to encompass long-term outcomes. With the focus on long-term outcomes, the importance of perioperative medical management and the potential benefits of pharmacotherapy have become evident. Because the major cause of early and delayed perioperative morbidity and mortality remains cardiovascular disease, it is not surprising that cardiovascular drugs have assumed a pivotal role in modulating perioperative outcomes.

Data from large registries and clinical trials indicate that drugs that have demonstrated protective cardiovascular properties in the medical population may also confer benefits in the surgical population. For example, overwhelming evidence suggests that perioperative aspirin use improves outcomes if continued throughout the perioperative period. In contrast, only a decade ago it was common practice to discontinue aspirin use 1 week before surgery because of the concern of increased intraoperative bleeding. Similarly, it has been clearly demonstrated in the surgical population that preoperative use of statins confers potent cardioprotective effects.

In addition to losing the pharmacological benefits of a drug, discontinuation of therapy (either perioperatively or otherwise) may cause a severe rebound phenomenon. This has been demonstrated with β-blockers, aspirin, and statins. As a result, the clinical practice has changed such that aspirin, statins, and β-blockers are either continued throughout the perioperative period or discontinued for the minimum period possible.

As with aspirin and statins, there is strong evidence that long-term angiotensin-converting enzyme inhibition yields significant cardiovascular protective effects. Initial reports of severe, refractory intraoperative hypotension/vasoplegia associated with ACEIs has resulted in the common practice of ACEI being discontinued preoperatively. Intraoperative vasoplegia was considered so problematic that procedures were frequently cancelled if the patient took ACEI before the surgery. In addition, a recent observational, single-center study showed increased mortality associated with ACEI use in patients who had undergone coronary artery bypass grafting.

The study by Drenger et al in the current issue of Circulation investigated postoperative cardiovascular outcomes in patients with different patterns of perioperative ACEI/angiotensin receptor blocker use. The major strengths of the study are that it is prospective and multi-institutional, thus allowing the authors to study a larger cohort and strengthen their conclusions. The authors should be congratulated for their effort in organizing and coordinating this study. They hypothesized that discontinuation of ACEI perioperatively would be associated with worse postoperative cardiovascular outcomes. They found that although there was no change in 30-day in-hospital mortality, withdrawal of an ACEI was associated with an increased number of cardiovascular events, mainly congestive heart failure and postoperative MI (Figure 2 in their article). Because ACEI withdrawal results in rebound effects, it is intriguing to speculate that these rebound effects could be responsible for the increase in adverse cardiovascular events. The temptation to change practice and standardize continued ACEI use throughout the perioperative period, however, should be revisited, at least for now. The observational nature of the study brings with it some inherent weaknesses. A major caveat is that as a nonrandomized study, it depicts only associations and not causation. Conclusions based on associations are commonly subject to error caused by biases and confounding factors. The best and only way to determine the true modulating effect of a specific medication on outcome indices in surgical patients is to conduct a prospective, randomized controlled study. Such a study, if feasible, would allow investigators to discern cause-and-effect relationships. As such, we should not yet conclude that withdrawal of ACEIs necessarily causes increased postoperative outcomes.
complications. Rather, we can only conclude that withdrawal of ACEIs was associated with increased numbers of cardiovascular events. Hidden biases inherent in these types of observational studies should temper one’s conclusions.

One such bias is a confounding by indication bias. As the authors pointed out, the physicians directly involved in making decisions, including decisions regarding ACEI use, were not under the control of the study personnel. Physician decisions are not random. They are based on mental models, knowledge, experience, and beliefs. The selection of patients for ACEI withdrawal can be influenced by the patient’s underlying condition. If ACEIs were withdrawn from patients at high risk of cardiovascular instability postoperatively, it may erroneously appear as if ACEI withdrawal were a cause of the postoperative cardiovascular events. Another potential bias is protopathic bias. This bias occurs if the initial manifestation of the outcome variable results in a treatment change. For example, if the physician in the intensive care unit determines that a patient’s hypotension or requirement for pressors are the initial symptoms of impending congestive heart failure or MI, he or she might decide not to restart ACEIs postoperatively. Similarly, if patients were bleeding excessively, the ACEI might not be restarted. Thus, the outcome variable (congestive heart failure, MI) may follow its natural history independent of whether ACEIs are discontinued or not, yet the discontinuation of therapy would be associated with the adverse events. Finally, a confounding by severity bias might distort the conclusions. Even if the authors control for disease, the possibility of confounding remains if they do not control for disease severity. For example, if patients in the ACEI withdrawal group are taking high doses of vasopressors because of severe underlying disease, whereas the ACEI continuation group is taking low doses of vasopressors, patients taking high doses of vasopressor (ACEI withdrawal group) could plausibly be at higher risk of developing congestive heart failure and MI. In this situation, ACEI withdrawal could erroneously be labeled as the cause of increased cardiovascular adverse events.

The data in the present study suggest that some of these biases may exist. As evident from Table 4 in the article, blood pressure in the 24 hours after intensive care unit arrival was significantly lower in the ACE withdrawal group than in patients taking ACEIs (continuation or addition groups). The modest 5 mmHg lower BP is, however, clinically significant given that patients were on vasopressor drugs. Additionally, there was an 8% higher transfusion rate in the withdrawal group. Each transfused unit of blood is associated with an increased risk of postoperative complications. In addition to lower blood pressure and higher transfusion rates, the use of assist devices for ischemia, MI, or low cardiac output was more than twice as high in the withdrawal group as in the ACE continuation group. This illustrates the underlying differences in patient conditions on arrival in the intensive care unit. Interestingly, ACEI-use groups (addition and continuation) had double the rates of nonroutine inotrope use, longer intubation times, and higher rates of blood transfusion than patients who were not exposed to ACEIs. As such, we should not assume that the study confirms the safety of perioperative use of ACEIs in a broader surgical population. The study sample, which is a subgroup population with prespecified inclusion and exclusion criteria, is predicated on the assumption that patients in the subgroup study represent the general population. The patient populations studied were patients undergoing elective coronary artery bypass grafting with cardiopulmonary bypass. Because valve surgery, off-pump coronary artery bypass graft surgery, and other or noncardiac surgeries were excluded from analysis, we cannot assume that the conclusions of the study should be extrapolated to other patient populations. Thus, one should perhaps temper one’s conclusions to avoid the temptation to accept the results of the study as indicating causation between ACEI withdrawal and increased cardiovascular events. One should also not extrapolate to other patient populations.

The suggested conservative approach to the interpretation of the study results is supported by the calcium channel and perioperative β-blocker stories. Similar to ACEIs, calcium channel blockers were developed as antihypertensive and antianginal drugs in 1980s. Soon thereafter, however, observational studies suggested a strong association between calcium channel blocker use and the incidence of MI. The safety of the calcium channel blocker was called into question, even though some epidemiologists suggested that the observed association was simply confounding by severity. Only randomized clinical trials settled the issue and showed that calcium channel blocker use does not cause MI.

Observational studies on β-blocker use demonstrated their benefits in patients undergoing cardiac surgery. The results, however, were extrapolated to all patients undergoing surgery. This led to a number of trials that suggested that β-blockers reduce cardiovascular morbidity and mortality, particularly in cardiac and major vascular surgery. Thereafter, quality improvement initiatives have made perioperative β-blocker usage mandatory and thus almost universal. To everyone’s surprise, subsequent randomized, large clinical trials demonstrated an increase in mortality and stroke in β-blocker-treated groups, which supports a less pervasive and more selective approach to perioperative β-blocker use. More recent studies have focused on patient selection through risk stratification.

Another classic example of this paradigm is the premature acceptance of tight perioperative glucose control: initial observational studies indicated improved outcomes after tight glucose control in the intensive care unit setting. This led to widespread, aggressive use of insulin and the institution of tight glucose control protocols both in the operating room and in intensive care units. Only a decade later randomized trials demonstrated that insulin use with tight glucose control actually caused higher mortality. This led to the discontinuation of the tight glucose control protocol.

In conclusion, we applaud the authors for addressing this important question, the excellent execution of the study, and the intriguing results. The observational nature of the present study does not allow one to make definitive recommendations regarding perioperative ACEI use. Randomized clinical trials are necessary to definitively answer the question. The study is important, however, in that it forces providers to reexamine the practice of routine discontinuation of ACEIs perioperatively. Our advice to readers is to be open-minded, stay tuned...
for further outcomes data, and accept change as evidence becomes available.

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None.

**References**


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