Perioperative Management of ACE Inhibitor Therapy: Challenges of Clinical Decision Making Based on Surrogate Endpoints

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Renin-angiotensin inhibitors, which include angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), have demonstrated benefits in the treatment of several common cardiovascular and renal conditions. For example, they are prescribed to individuals with hypertension, heart failure with reduced ejection fraction (HFrEF), prior myocardial infarction, and chronic kidney disease with proteinuria. Perhaps unsurprisingly, many individuals presenting for surgery are already on long-term ACE inhibitor or ARB therapy. For example, such individuals comprised approximately one-third of the sample in the Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) multicenter prospective cohort study of major inpatient noncardiac surgery.[1]

There is considerable controversy regarding how best to manage these cardiovascular medications during the perioperative period. The critical question pertains to whether renin-angiotensin inhibitors should be temporarily withdrawn 24 hours before surgery or continued uninterrupted up to the day of surgery. The main argument for withdrawing these medications is concern that they cause perioperative hypotension. For example, a recent systematic review of randomized controlled trials (RCTs) and cohort studies found that preoperative continuation of renin-angiotensin inhibitor therapy led to a significantly increased risk of intraoperative hypotension, albeit without associated effects on rates of death, major adverse cardiac events, or postoperative hypotension.[2] Notably, randomized trial evidence in this meta-analysis was limited to only five trials with a total of 774 participants. Conversely, preoperative interruption of renin-angiotensin inhibitor therapy also has risks. For example, there is a potential for unintended permanent discontinuation of medications with long-term benefits.[3] Furthermore, some prior cohort studies have demonstrated that the failure to resume renin-angiotensin inhibitor therapy promptly after surgery is associated with an elevated risk of postoperative mortality.[4,5] While these studies have methodological limitations related to survivorship bias and unmeasured confounders, they still raise concerns that the abrupt withdrawal of long-term cardiovascular therapy before major surgery can have adverse effects. While ACE inhibitor withdrawal has not shown adverse physiological effects in the perioperative setting, it has led to rebound myocardial ischemia in patients with prior myocardial infarction.[6]

Given this controversy, there is variation across hospitals[1] and practice guidelines with respect to perioperative management of renin-angiotensin inhibitors. For example, the 2017 Canadian Cardiovascular Society guidelines recommend that renin-angiotensin inhibitors be stopped temporarily 24 hours before major inpatient surgery,[7] and the 2014 European guidelines recommend continuing therapy in patients with HFrEF but temporarily interrupting therapy in patients with hypertension.[8] The 2014 American Heart Association and American College of Cardiology guidelines suggest that either continuation or interruption are reasonable options, but any interrupted therapy should be restarted postoperatively as soon as clinically feasible.[9]

In this issue of the *Journal of Hospital Medicine*, Shiffermiller and colleagues present a single-center RCT that provides additional high-quality data to improve our understanding of this important clinical issue.[10] In a sample of 275 patients undergoing nonvascular inpatient noncardiac surgery, omission of the final dose of preoperative ACE inhibitor therapy reduced the risk of intraoperative hypotension across multiple definitions, including any episode of systolic blood pressure less than 80 mm Hg (number needed to treat: 8), any episode of a systolic blood pressure less than 80 mm Hg necessitating vasopressor therapy (number needed to treat: 6), and total cumulative duration of intraoperative systolic blood pressure less than 80 mm Hg. In addition, the investigators found that preoperative interruption of ACE inhibitor therapy reduced the risk of postoperative hypotension (number needed to treat: 9), increased the risk of severe postoperative hypertension (number needed to harm: 9), and had no effect on clinical outcomes (eg, acute kidney injury, major adverse cardiac events). In conjunction with a recent systematic review,[2] these new data demonstrate that temporary preoperative discontinuation of renin-angiotensin inhibitors leads to reduced risks of intraoperative and postoperative hypotension, with the only major identified risk being episodes of postoperative hypertension.

This current evidence base suggests that, in most cases, perioperative physicians should temporarily interrupt renin-angiotensin inhibitor therapy before inpatient noncardiac surgery, provided that protocols are in place to resume treatment postoperatively as soon as clinically feasible. Nonetheless, clinicians must also be cognizant of the key limitations to current data,

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namely that hypotension, be it intraoperative or postoperative, remains essentially a surrogate endpoint.[11,12] Stated otherwise, the clinical importance of perioperative hypotension is largely predicated on its close association with clinically important or patient-relevant outcomes such as cardiovascular complications, acute kidney injury, and death.[13–16] There is an implicit assumption that a reduction in the risk of hypotension will necessarily lead to reduced rates of clinical adverse events. This assumption is unlikely to be true, especially since many different underlying mechanisms lead to hypotension in the dynamic perioperative environment, including decreased cardiac contractility, decreased heart rate, decreased intravascular volume status, and vasodilation. Consistent with this possibility, different perioperative interventions with similar effects on hypotension have shown quite different effects on clinical outcomes. For example, epidural analgesia invariably reduces perioperative blood pressure, yet it does not appear to increase the risk of postoperative complications.[17] Similarly, both beta-blockers and clonidine increase the risk of significant perioperative hypotension and bradycardia, yet only beta-blockers appear to lead to increased rates of mortality after noncardiac surgery.[18,19] Thus, the relationship between perioperative hypotension and outcomes is clearly complex. Unless a RCT demonstrates that a hypotension-reduction strategy leads to an improvement in clinical outcomes,[20] perioperative physicians should not assume that prevention of hypotension will always lead to improvements in patient-relevant clinical outcomes. Similar assumptions about other surrogate endpoints in cardiovascular medicine have sometimes been spectacularly incorrect.[12,21] To more definitively address this important clinical issue, RCTs must be specifically designed to compare the effects of renin-angiotensin inhibitor therapy withdrawal versus continuation on patient-relevant and clinically important outcomes, such as death, myocardial infarction, and stroke. Fortunately, some ongoing trials will address this question, either directly (ClinicalTrials.gov NCT03374449) or as a component of a hypotension-avoidance strategy (ClinicalTrials.gov NCT03505723).

Overall, perioperative physicians should now adopt the standard approach of temporarily withdrawing renin-angiotensin inhibitor therapy 24 hours before major inpatient noncardiac surgery. Nonetheless, they should do so cautiously, recognizing that the data underpinning this strategy remain weak. As with many aspects of perioperative medicine, more research remains needed.

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