In Reply:
I appreciate your comments; however, the review did not deliberately ignore the potential of Factor VIII Inhibitor Bypassing Activity (FEIBA; Baxter AG, Deerfield, IL) as you suggest, and FEIBA is mentioned but details were not provided. However, if you check table 2, there is further discussion on the use of activated prothrombin complex concentrates. The table leg- end specifically states that in patients receiving dabigatran, the use of an activated prothrombin complex concentrate such as FEIBA may be more effective, and there are no studies reporting the use of prothrombin complex concentrates on actual bleeding in patients. Further studies including the development of specific reversal agents are underway currently. Of note is the study by Marlu et al.2 that you describe is an in vitro study, and caution should be considered for extrapolating in vitro data to clinical application. You also reference a case report. Please note that case reports are interesting, but an n = 1 or 2 is not a case series. The authors also suggest that FEIBA appears not to be approved by the Food and Drug Administration, but this is not the case. Although using an activated prothrombin complex concentrate such as FEIBA appears to make sense, additional human data are needed before we can make definitive conclusions.

The studies described in more detail in the review article on prothrombin complex concentrates were actually performed in volunteers receiving therapeutic doses of the new oral anticoagulation agents including rivaroxaban and dabigatran. I am also a part of additional studies further investigating the role of prothrombin complex concentrates for reversal of rivaroxaban in volunteers. Of note is a specific reversal agent has also been developed for dabigatran, using an immunospecific Fab fragment (BI 655075). This novel therapeutic approach is entering into clinical trials.† Clinicians when faced with life-threatening hemorrhage do indeed need to know all of the information and data available to manage these complex and critically ill patients. Further clinical studies are needed to best determine the optimal therapy for bleeding when it occurs in patients related to the novel oral anticoagulation agents.

Competing Interests
Dr. Levy has served or serves on research steering committees or advisory boards for CSL Behring, King of Prussia, Pennsylvania; Boehringer-Ingelheim, Ingelheim, Germany; Grifols, Research Triangle Park, North Carolina; and Janssen Research & Development, Raritan, New Jersey.

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References

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Acute Kidney Injury, Surgery, and Angiotensin Axis Blockade

To the Editor:
We read with interest the Case Scenario: Hemodynamic Management of Postoperative Acute Kidney Injury. The authors present a 59-yr-old patient with the only preoperative medication an angiotensin-converting enzyme inhibitor for hypertension, who suffers acute kidney injury...
(AKI), after prolonged (9h) abdominal surgery for recurrent ovarian cancer. The patient received a crystalloid infusion at a rate of 24 ml kg\(^{-1}\) h\(^{-1}\) as well as neosynephrine (0.35 µg kg\(^{-1}\) min\(^{-1}\)) intraoperatively to maintain a mean arterial pressure of 70 mmHg. Nevertheless, the patient suffered oliguria intraoperatively and was found to be “mottled” and suffered anuria with associated AKI, postoperatively. We write to further emphasize that preoperative therapy with either an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker may pose a higher risk for postoperative AKI. In addition, we wish to underscore the use of norepinephrine as a suitable therapy for perioperative hypotension in such patients.

In a recent retrospective study of perioperative risk factors for the development of AKI after lung resection (n = 1,129), Ishikawa et al.\(^2\) demonstrated that patients developing similarly defined AKI were more likely to be taking angiotensin-converting enzyme inhibitor or angiotensin receptor blocker preoperatively. Multivariate analysis demonstrated that preoperative therapy with an angiotensin receptor blocker was an independent predictor of AKI in such patients.

The development of hypotension in patients receiving angiotensin-converting enzyme inhibitor is widely recognized; however, there has been no demonstrated association of the extent, or duration of hypotension with the development of AKI.\(^3,4\) Nevertheless, the medical community tries to minimize the potential for AKI by administering vasopressors.\(^4\)

In the refractory hypotension that the authors described in the Case Scenario,\(^1\) the ideal agent would appear to be norepinephrine rather than neosynephrine (phenylephrine). This is because administered norepinephrine having both (\(\alpha\) and \(\beta\)) effects would replace the well-known decreased circulating catecholamine levels associated with the induction of anesthesia and would tend to maintain cardiac output, whereas phenylephrine, with purely \(\alpha\) activity, would tend to decrease cardiac output.

Berend Mets, M.B., Ph.D., F.R.C.A., Eileen Hennrikus, M.D., F.A.C.P. Penn State University Hershey Medical Center, Hershey, Pennsylvania (B.M.). bmets@hmc.psu.edu

References


In Reply:
We thank Drs. Mets and Hennrikus for their constructive and relevant comments regarding our recently published case scenario.\(^1\) They rightly underline that preoperative therapy with either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker is a recognized risk factor for postoperative acute kidney injury. More importantly, they mention this therapy as a more credible etiology of acute kidney injury than hypotension itself. We support their statement, because ACE inhibitors reduce the efferent arteriole vascular tone with decreased glomerular filtration pressure and then glomerular filtration rate, especially during episodes of hypotension.\(^2\) This mechanism of reduced glomerular filtration rate corresponds to acute kidney injury definition, which may occur even with a relatively maintained renal perfusion pressure. If these different renal targets of ACE inhibitors might have negative effect, they can also be positive especially when the renin–angiotensin system is strongly stimulated as observed in cardiac failure.\(^3\) In this context, perioperative treatment with ACE inhibitors has been shown protective for renal function.\(^4,5\)

The authors thank Drs. Mets and Hennrikus for their very relevant comment, which stimulates research on continuation or not of ACE for renal and nonrenal outcome with predictable differences according to the degree of renin–angiotensin system stimulation. The second point raised by their comment concerned the use of neosynephrine, a pure \(\alpha\)-agonist, to maintain arterial blood pressure during prolonged hypotension. We agree that it was a mistake to use such a drug instead of norepinephrine, which combines \(\alpha\)- and \(\beta\)-agonist effects (which was used as second-line therapies). Systemic blood flow (cardiac output) and regional blood flow are expected higher with norepinephrine than with a pure \(\alpha\)-agonist. The intention presenting this case, a frequent scenario for anesthesiologists, was to emphasize the need for an adequate preoperative cardiovascular evaluation and an adapted intraoperative hemodynamic monitoring for patient at risk of acute kidney injury. In addition to the consequences of perioperative ACE administration, this case stimulates the discussion on the “reflex” of using a pure \(\alpha\)-receptor agonist to correct hypotension, forgetting the risk of reduction in flow. Avoidance of blinded fluid and/or vasopressors administration during major surgery may therefore reduce the need of an intensive care unit rescue and improve outcome.