2. Marlu R, Hodaj E, Paris A, Albaladejo P, Cracowski JL, Crackowski JL, Pernod G: Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban: A randomised crossover *ex vivo* study in healthy volunteers. Thromb Haemost 2012; 108:217–24
3. Leissinger C, Gringeri A, Antmen B, Berntorp E, Biasoli C, Carpenter S, Cortesi P, Jo H, Kavakli K, Lassila R, Morfini M, Négrier C, Rocino A, Schramm W, Serban M, Uscatescu MV, Windyga J, Zülfikar B, Mantovani L: Anti-inhibitor coagulant complex prophylaxis in hemophilia with inhibitors. N Engl J Med 2011; 365:1684–92
4. Hay CR, Brown S, Collins PW, Keeling DM, Liesner R: The diagnosis and management of factor VIII and IX inhibitors: A guideline from the United Kingdom Haemophilia Centre Doctors Organisation. Br J Haematol 2006; 133:591–605
5. Dager WE, Gosselin RC, Roberts AJ: Reversing dabigatran in life-threatening bleeding occurring during cardiac ablation with factor eight inhibitor bypassing activity. Crit Care Med 2013; 41:e42–6
6. Siegal DM, Crowther MA: Acute management of bleeding in patients on novel oral anticoagulants. Eur Heart J 2013; 34:489–98

(Accepted for publication September 16, 2013.)

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.[1] The table legend 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.[1] 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.[3] 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).[4] 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.[5] 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.

* Available at: http://clinicaltrials.gov/ct2/show/NCT01656330. Accessed October 9, 2013.

† Available at: http://clinicaltrials.gov/ct2/show/NCT01688830?term=BI+655075&rank=1. Accessed October 9, 2013.

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.

Jerrold H. Levy, M.D., F.A.H.A., F.C.C.M., Duke University School of Medicine, Durham, North Carolina. jerrold.levy@duke.edu

References

1. Levy JH, Faraoni D, Spring JL, Douketis JD, Samama CM: Managing new oral anticoagulants in the perioperative and intensive care unit setting. Anesthesiology 2013; 118:1466–74
2. Marlu R, Hodaj E, Paris A, Albaladejo P, Cracowski JL, Crackowski JL, Pernod G: Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban: A randomised crossover *ex vivo* study in healthy volunteers. Thromb Haemost 2012; 108:217–24
3. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M: Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: A randomized, placebo-controlled, crossover study in healthy subjects. Circulation 2011; 124:1573–9
4. Schiele F, van Ryn J, Canada K, Newsome C, Sepulveda E, Park J, Nar H, Litzenburger T: A specific antidote for dabigatran: Functional and structural characterization. Blood 2013; 121:3554–62
5. Karkouti K, Levy JH: Commentary: Recombinant activated factor VII: The controversial conundrum regarding its off-label use. Anesth Analg 2011; 113:711–2

(Accepted for publication September 16, 2013.)

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.[1] 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 (9 h) 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 (α_1 and β_1) 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 α_1 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

1. Legrand M, Payen D: Case scenario: Hemodynamic management of postoperative acute kidney injury. Anesthesiology 2013; 118:1446–54
2. Ishikawa S, Griesdale DE, Lohser J: Acute kidney injury after lung resection surgery: Incidence and perioperative risk factors. Anesth Analg 2012; 114:1256–62
3. Kheterpal S, Khodaparast O, Shanks A, O'Reilly M, Tremper KK: Chronic angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy combined with diuretic therapy is associated with increased episodes of hypotension in noncardiac surgery. J Cardiothorac Vasc Anesth 2008; 22:180–6
4. Kheterpal S, Tremper KK, Englesbe MJ, O'Reilly M, Shanks AM, Fetterman DM, Rosenberg AL, Swartz RD: Predictors of postoperative acute renal failure after noncardiac surgery in patients with previously normal renal function. Anesthesiology 2007; 107:892–902

(Accepted for publication September 16, 2013.)

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 α-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 α- and β-agonist effects (which was used as second-line therapeutics). Systemic blood flow (cardiac output) and regional blood flow are expected higher with norepinephrine than with a pure α-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 α-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.

Matthieu Legrand, M.D., Ph.D., Didier Payen, M.D., Ph.D. Groupe Hospitalier St-Louis-Lariboisière-Fernand Widal, Assistance Publique - Hopitaux de Paris, and University of Paris 7 Denis Diderot, Paris, France (M.L.). matthieu.m.legrand@gmail.com

References

1. Legrand M, Payen D: Case scenario: Hemodynamic management of postoperative acute kidney injury. Anesthesiology 2013; 118:1446–54
2. Testani JM, Kimmel SE, Dries DL, Coca SG: Prognostic importance of early worsening renal function after initiation of angiotensin-converting enzyme inhibitor therapy in patients with cardiac dysfunction. Circ Heart Fail 2011; 4:685–91
3. Hall JE, Guyton AC, Cowley AW Jr: Dissociation of renal blood flow and filtration rate autoregulation by renin depletion. Am J Physiol 1977; 232:F215–21
4. Ryckwaert F, Colson P, Ribstein J, Boccara G, Guillon G: Haemodynamic and renal effects of intravenous enalaprilat during coronary artery bypass graft surgery in patients with ischaemic heart dysfunction. Br J Anaesth 2001; 86:169–75
5. Drenger B, Fontes ML, Miao Y, Mathew JP, Gozal Y, Aronson S, Dietzel C, Mangano DT; Investigators of the Ischemia Research and Education Foundation; Multicenter Study of Perioperative Ischemia Research Group: Patterns of use of perioperative angiotensin-converting enzyme inhibitors in coronary artery bypass graft surgery with cardiopulmonary bypass: Effects on in-hospital morbidity and mortality. Circulation 2012; 126:261–9

(Accepted for publication September 26, 2013.)

The Overpowered Mega-study Is a New Class of Study Needing a New Way of Being Reviewed

To the Editor:

The recently published Memtsoudis *et al.*'s[1] retrospective "mega-study" reviewed electronic billing data of 382,236 patients who had undergone primary hip and knee arthroplasty surgery. A study of this size has the potential to detect very tiny between-group differences for very rare events. Specifically, Memtsoudis *et al.* observed a statistically significant mortality reduction of 0.08% in the group receiving neuraxial blocks *versus* the group who received general anesthesia for total knee arthroplasty patients.

The huge number of patients studied here nearly represents the equivalent of the entire 40-yr careers of 40 full-time orthopedic anesthesiologists, assuming they perform 1,000 anesthesia cases per year, with 40% of cases being for primary hip and knee arthroplasty procedures. This represents 1,000 individual anesthesia practice years. The observed mortality difference would represent about one added 30-day death every 5 yrs per anesthesiologist administering only general anesthesia. Although the death of any individual patient is tragic, the size of the "treatment effect" as well as the retrospective database-derived nature of the study should prompt us to ask whether or not the results justify a change in anesthesia practice?

Huge studies such as this are unquestionably valuable, because they CAN detect differences in the incidence of rare events—differences that could never be detected in prospective, randomized trials—largely because performing such trials would be prohibitively difficult. However, such retrospective studies, unlike prospective trials, can never define causality, only association, and the inherent problems produced by missing data, miscoded information, and unrecognized (and hence unincorporated) covariants may be large enough to influence the reliability of any conclusions particularly when differences between groups are very small (perhaps regardless of statistical significance).

A recent editorial by Collins *et al.*,[2] commenting on a 10-million patient database study, recognized such observational mega-study limitations and emphasized the need to develop tools and consensus-based guidelines for authors, editors, and readers to better study and understand the deeper meanings and limitations of such observational analyses.[3]

What factors (*e.g.*, missing covariates) might have confounded the work by Memtsoudis *et al.*? We believe that two critical questions are (1) why was neuraxial anesthesia chosen for any patient and (2) how was neuraxial anesthesia conducted?

There are always some subtle (and perhaps not so subtle) variations in patient's comorbidities, individual anesthesiologist and surgeon training, skills, and experience and decision-making processes and institutional resources of anesthesia drugs, equipment, and patient care facilities. Another recent mega-study on 367,796 patients examining viewing general surgical mortality showed patients being operated within one unitary healthcare system, but in a different hospital, could experience a significantly 30-day mortality 200% difference between best and worst scoring hospitals and this correlated with the number of intensive care unit beds available.[4]

The decision to use a regional anesthesia technique on an arthroplasty patient is often decided by a surgeon's idiosyncratic likes or dislikes for regional anesthesia, similar idiosyncrasies of the anesthesiologist, the time available to perform the regional anesthetic, and finally the personal fears and preferences of the patient. Thus three parties commonly contribute to the decision to use neuraxial anesthesia or not and only one of those three parties is trained in anesthesia. Anesthetic considerations in choosing an anesthesia plan for an individual patient may be overshadowed by unscientific covariables around the anesthesia plan decision process which may in turn influence mortality directly, if only slightly. Such factors could easily influence small mortality differences in a mega-study—but would almost certainly be impossible to incorporate as covariates in the analysis.

It could be also speculated that the increased use of neuraxial anesthesia is only a marker for the fact that neuraxial blocks are more likely performed by anesthesiologists more skilled in