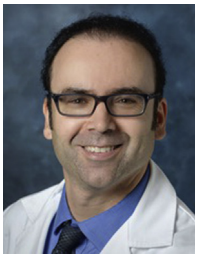
10. Han SS, Shin N, Baek SH, Ahn SY, Kim DK, Kim S, et al. Effects of acute kidney injury and chronic kidney disease on long-term mortality after coronary artery bypass grafting. *Am Heart J*. 2015;169:419-25.
11. Lassnigg A, Schmidlin D, Mouhieddine M, Bachmann LM, Druml W, Bauer P, et al. Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: a prospective cohort study. *J Am Soc Nephrol*. 2004;15:1597-605.
12. Linder A, Fjell C, Levin A, Walley KR, Russell JA, Boyd JH. Small acute increases in serum creatinine are associated with decreased long-term survival in the critically ill. *Am J Respir Crit Care Med*. 2014;189:1075-81.
13. Nadim MK, Forni LG, Bihorac A, Hobson C, Koyner JL, Shaw A, et al. Cardiac and vascular surgery-associated acute kidney injury: the 20th International Consensus Conference of the ADQI (Acute Disease Quality Initiative) Group. *J Am Heart Assoc*. 2018;7:e008834.
14. Li Q, Zhao M, Wang X. AKI in the very elderly patients without preexisting chronic kidney disease: a comparison of 48-hour window and 7-day window for diagnosing AKI using the KDIGO criteria. *Clin Interv Aging*. 2018;13:1151-60.
15. Ronco C, Kellum JA, Haase M. Subclinical AKI is still AKI. *Crit Care*. 2012;16:313.
16. Chawla LS, Bellomo R, Bihorac A, Goldstein SL, Siew ED, Bagshaw SM, et al. Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. *Nat Rev Nephrol*. 2017;13:241-57.
17. Kashani K, Al-Khafaji A, Ardiles T, Artigas A, Bagshaw SM, Bell M, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. *Crit Care*. 2013;17:R25.
18. Meersch M, Schmidt C, Van Aken H, Martens S, Rossaint J, Singbartl K, et al. Urinary TIMP-2 and IGFBP7 as early biomarkers of acute kidney injury and renal recovery following cardiac surgery. *PLoS One*. 2014;9:e93460.
19. Meersch M, Schmidt C, Hoffmeier A, Van Aken H, Wempe C, Gerss J, et al. Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial. *Intensive Care Med*. 2017;43:1551-61.
20. Göcze I, Jauch D, Götz M, Kennedy P, Jung B, Zeman F, et al. Biomarker-guided intervention to prevent acute kidney injury after major surgery: the prospective randomized BigpAK study. *Ann Surg*. 2018;267:1013-20.
21. Mayer T, Bolliger D, Scholz M, Reuthebuch O, Gregor M, Meier P, et al. Urine biomarkers of tubular renal cell damage for the prediction of acute kidney injury after cardiac surgery-a pilot study. *J Cardiothorac Vasc Anesth*. 2017;31:2072-9.
22. Cummings JJ, Shaw AD, Shi J, Lopez MG, O'Neal JB, Billings FT IV. Intraoperative prediction of cardiac surgery-associated acute kidney injury using urinary biomarkers of cell cycle arrest. *J Thorac Cardiovasc Surg*. 2019;157:1545-53.e5.
23. Engelman DT, Ben Ali W, Williams JB, Perrault LP, Reddy VS, Arora RC, et al. Guidelines for perioperative care in cardiac surgery: enhanced recovery after surgery society recommendations. *JAMA Surg*. 2019;154:755-66.
24. Levante C, Ferrari F, Manenti C, Husain-Syed F, Scarpa M, Hinna Danesi T, et al. Routine adoption of TIMP2 and IGFBP7 biomarkers in cardiac surgery for early identification of acute kidney injury. *Int J Artif Organs*. 2017;40:714-8.
25. Kellum JA, Lameire N. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). *Crit Care*. 2013;17:204.
26. Marik PE, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. *Chest*. 2008;134:172-8.
27. Kalantari K, Chang JN, Ronco C, Rosner MH. Assessment of intravascular volume status and volume responsiveness in critically ill patients. *Kidney Int*. 2013;83:1017-28.
28. Stone CA, Tang Y. Comparing propensity score methods in balancing covariates and recovering impact in small sample educational program evaluations. *Pract Assess Res Eval*. 2013;18:1-12.
29. Osawa EA, Rhodes A, Landoni G, Galas FR, Fukushima JT, Park CH, et al. Effect of perioperative goal-directed hemodynamic resuscitation therapy on outcomes following cardiac surgery: a randomized clinical trial and systematic review. *Crit Care Med*. 2016;44:724-33.
30. Aya HD, Cecconi M, Hamilton M, Rhodes A. Goal-directed therapy in cardiac surgery: a systematic review and meta-analysis. *Br J Anaesth*. 2013;110:510-7.
31. Kolhe NV, Reilly T, Leung J, Fluck RJ, Swinscoe KE, Selby NM, et al. A simple care bundle for use in acute kidney injury: a propensity score-matched cohort study. *Nephrol Dial Transplant*. 2016;31:1846-54.
32. Hausenloy DJ, Candilio L, Evans R, Ariti C, Jenkins DP, Kolvekar S, et al. Remote ischemic preconditioning and outcomes of cardiac surgery. *N Engl J Med*. 2015;373:1408-17.
33. Billings FT IV, Hendricks PA, Schildcrout JS, Shi Y, Petracek MR, Byrne JG, et al. High-dose perioperative atorvastatin and acute kidney injury following cardiac surgery: a randomized clinical trial. *JAMA*. 2016;315:877-88.
34. Katz NM, Kellum JA, Ronco C. Acute kidney stress and prevention of acute kidney injury. *Crit Care Med*. 2019;47:993-6.
35. Bhardwaj A, Rehman SU, Mohammed AA, Gaggin HK, Barajas L, Barajas J, et al. Quality of life and chronic heart failure therapy guided by natriuretic peptides: results from the ProBNP Outpatient Tailored Chronic Heart Failure Therapy (PROTECT) study. *Am Heart J*. 2012;164:793-9.e1.
36. Ronco C, McCullough PA, Chawla LS. Kidney attack versus heart attack: evolution of classification and diagnostic criteria. *Lancet*. 2013;382:939-40.
37. Coca SG, Garg AX, Swaminathan M, Garwood S, Hong K, Thiessen-Philbrook H, et al. Preoperative angiotensin-converting enzyme inhibitors and angiotensin receptor blocker use and acute kidney injury in patients undergoing cardiac surgery. *Nephrol Dial Transplant*. 2013;28:2787-99.
38. Ingels C, Derese I, Wouters PJ, Van den Berghe G, Vanhorebeek I. Soluble RAGE and the RAGE ligands HMGB1 and S100A12 in critical illness: impact of glycemic control with insulin and relation with clinical outcome. *Shock*. 2015;43:109-16.
39. Garg R, Grover A, McGurk S, Rawn JD. Predictors of hyperglycemia after cardiac surgery in nondiabetic patients. *J Thorac Cardiovasc Surg*. 2013;145:1083-7.
40. Task Force on Patient Blood Management for Adult Cardiac Surgery of the European Association for Cardio-Thoracic Surgery (EACTS) and the European Association of Cardiothoracic Anaesthesiology (EACTA), Boer C, Meesters MI, Milojevic M, Benedetto U, Bolliger D, et al. 2017 EACTS/EACTA guidelines on patient blood management for adult cardiac surgery. *J Cardiothorac Vasc Anesth*. 2018;32:88-120.
41. Rizo-Topete LM, Rosner MH, Ronco C. Acute kidney injury risk assessment and the nephrology rapid response team. *Blood Purif*. 2017;43:82-8.
42. de Somer F, Mulholland JW, Bryan MR, Aloisio T, Van Nooten GJ, Ranucci M. O2 delivery and CO2 production during cardiopulmonary bypass as determinants of acute kidney injury: time for a goal-directed perfusion management? *Crit Care*. 2011;15:R192.
43. Mukaida H, Matsushita S, Kuwaki K, Inotani T, Minami Y, Saigusa A, et al. Time-dose response of oxygen delivery during cardiopulmonary bypass predicts acute kidney injury. *J Thorac Cardiovasc Surg*. 2019;158:492-9.
44. Lassnigg A, Schmid ER, Hiesmayr M, Falk C, Druml W, Bauer P, et al. Impact of minimal increases in serum creatinine on outcome in patients after cardiothoracic surgery: do we have to revise current definitions of acute renal failure? *Crit Care Med*. 2008;36:1129-37.
45. Hobson CE, Yavas S, Segal MS, Schold JD, Tribble CG, Layon AJ, et al. Acute kidney injury is associated with increased long-term mortality after cardiothoracic surgery. *Circulation*. 2009;119:2444-53.
46. Huber M, Ozrazgat-Baslanti T, Thottakkara P, Efron PA, Feezor R, Hobson C, et al. Mortality and cost of acute and chronic kidney disease after vascular surgery. *Ann Vasc Surg*. 2016;30:72-81.e1-2.

Key Words: critical care, acute kidney injury, quality improvement, perioperative care, biomarkers

Discussion



Dr Ali Khoynezhad *(Los Angeles, Calif)*. I would like to thank the AATS for the privilege of discussing this relevant paper on postcardiac surgery acute kidney injury (AKI) affecting us in clinical practice on a daily basis. I also want to thank my colleague, Dr Engelman, for timely delivery of the manuscript.

AKI affects a third of our patients undergoing open heart surgery and remains the major determinant of morbidity,

mortality, prolonged hospital stay, and inferior value-based healthcare delivery. Oliguria and serum creatinine are not sensitive or timely markers to make an impactful AKI prevention strategy in postop cardiac surgery patients. Insulin-like growth factor binding protein 7 and tissue inhibitor metalloproteinase 2 are FDA-approved urinary biomarkers to identify patients as early as 1 hour after cardiopulmonary bypass who are at increased risk of developing AKI.

The authors performed a prospective nonrandomized comparison between historical Kidney Disease Improving Global Outcome (KDIGO) stage 2 and 3 AKI in adult patients undergoing cardiac surgery to a group of patients enrolled in a quality initiative and treated by a multidisciplinary kidney response team and their perioperative cardiothoracic intensive care unit management according to the level of postoperative urinary biomarkers. They found an 89% relative reduction in stage 2 and 3 AKI in patients with high urinary biomarkers compared to a similar cohort of patients a year earlier. On the other hand, low urinary biomarkers had a 100% negative predictive value for AKI in this pilot study.

The authors should be congratulated on their quest for quality improvement within the ERAS Cardiac Surgery organization and the Postop Open-Heart Surgery AKI Quality Initiative.

Dan, I have several questions for you. Why did you have the urinary markers checked on the morning of the next day? Why not the same operative day an hour or 2 after their surgery? Also, why were mortality, ICU stay, and ventilation time not included as primary outcomes?

Dr Daniel T. Engelman *(Springfield, Mass)*. So, the answer to the first question is that my hospital required the urine samples to be batched, so we had to pick one time to draw them. Patients come out throughout the day, so I had one shot. So I was either going to do it at 8 o'clock at night, and probably miss that late case, or do it in the morning and then have something to act on during the morning rounds. It turns out I got lucky, because a subsequent paper was published by Dr Shaw, which showed that the actual peak of the urinary biomarker was the morning after surgery, and that was completely fortuitous; I got lucky.

The downside is that during the first night I don't have the benefit of the biomarker, I don't actually know whose kidneys are stressed, and I can't act on this data until the next morning. So it's a plus-minus there.

And what was your second question?

Dr Khoynezhad. The second question is why were you not including ICU mortalities, stay, or ventilation time in the primary outcomes?

Dr Engelman. Why didn't I include them?

Dr Khoynezhad. Yes. You just targeted AKI rather than looking at other outcomes that are commonly associated with AKI.

Dr Engelman. We did, and there is no difference. We had no effect on early extubation or readmissions, and we didn't actually affect cost. That's another thing that you would expect with this dramatic decrease in AKI. The problem is, it's 800 patients, comparing 400 to 400, so that we kind of diluted it out. We only had a 1.6% incidence of stage 3 AKI before we started. So there wasn't really an "AKI problem" at my institution before we even started this. So when you take that down to 0.3%, it's hard to show a cost savings.

Dr Khoynezhad. So, you sort of answered my second question. Are there any other reasons besides the sample size of patients at risk why your findings such as hospital stay and cost did not change in your study? In fact, they [hospital stay and cost] were about similar in both studies. So, do you think the sample size was an issue, or where there other determinants?

Dr Engelman. I think if you had an institution with a higher incidence of AKI to start with, you would absolutely find it. And, as you know, costs are difficult to really look at. There are a thousand different ways to look at it, it depends who you ask and how you calculate it, and you get different numbers. But the best we could come up with is that there was no difference.

The real cost is dialysis. If you keep a patient from requiring dialysis, that's a huge win. And we have not taken a patient who wasn't on dialysis before surgery and put them on dialysis after surgery in 2 years, which is incredible. So that is a real bonus, and we think we are saving a lot of kidneys with this protocol.

Dr Khoynezhad. How does the AKI response team work, and is there any possibility to incorporate this pocket card into electronic medical records so it automatically pops up reiterating criteria for goal-directed fluid therapy and glycemic control or other protocols for post–open-heart surgery patients at risk?

Dr Engelman. A great question. Since half the patients are positive, basically the nephrologists showed up on rounds and asked, who am I going to see? That's how it worked, because half the patients were "positive." We have since changed the positive criteria so that only about a quarter are now positive. We have moved our positive number up to 0.7.

That said, yes, the EMR should be used. Luckily, we are EMR-ready, so I can just pull up my EMR and I know the NephroCheck value, and it tells me whether it's low, medium, or high. So everybody is kind of on the same page. And I hand these pocket cards out like water so that everybody is on the same page, also because it's too confusing otherwise.

Dr Khoynezhad. At MemorialCare, we are currently involved with incorporating the ERAS Cardiac Surgery recommendation in perioperative care protocols. What kind of infrastructure do we need to incorporate your renal protective protocol? Any capital investments that you can discuss, and is there a reason why all cardiac programs should not incorporate this protocol?

Dr Engelman. Well, everybody should prevent AKI and do it in any possible way they can. The bottom line is that goal-directed fluid therapy needs to be used more often. And just to cut right to the chase, the old fast tracking, which was to dry the patients out to the bone in the operating room, don't give them fluids and try to dry them out even if they are on pressors, probably is hurting some kidneys. We need to actually liberalize fluids in selected patients with kidney stress during that first 12- to 24-hour period. That's the bottom line.

Dr Khoynezhad. I would like to thank the Society for the privilege of discussing this paper.

Unidentified speaker. I want to congratulate you, Dan, again, on a great body of work and adding to this knowledge in an area that continues to vex cardiac surgery despite our major strides that we have made in improving coronary bypass grafting and other surgeries in this era.

My question for you is this. So you pointed out that the middle group, the big bulk, was delayed until 4 pm to discharge from the unit. Did you have other strategies in reassessing the renal stress? In other words, when would you then check the urinary biomarker again, and how did you use that data for the remainder of their ICU stay?

Dr Engelman. Excellent question. The patients in that middle group are over 0.3; they leave at 4 pm, after afternoon rounds. They are still making adequate urine, they are off pressors, they are back into the safe group and go upstairs. If they become oliguric, now they go into the high-risk group. They get a repeat NephroCheck the next morning, and that NephroCheck needs to be coming down, not going up. So anybody over 0.7 (it used to be over 2.0) or anybody who becomes oliguric, that's the real bottom line. If you have a NephroCheck that is over 0.7 and you are on some pressors, I can guarantee you in the next 3 hours you are going to become oliguric without intervention; it's going to happen.

Unidentified speaker. Do you ever check one that goes to telemetry and becomes oliguric?

Dr Engelman. No. The problem with telemetry is they are checking urine output only Q shift. I have very poor measurement of urinary output. So it's too late by then.

Dr Kevin Lobdell *(Charlotte, NC).* Great talk. I really enjoyed it. Let me just play devil's advocate here for a second. What element of your strategy is related to the NephroCheck versus just not diuresing patients on postop day 1, giving them volume, and avoiding the pressors?

Dr Engelman. We are not avoiding the pressors.

Dr Lobdell. I mean just following the NephroCheck versus the other elements?

Dr Engelman. So, half the patients we are not keeping tanked up. I'm drying them to the bone. I don't care that their CVP is 3. Give them Lasix, pull the lines out and go upstairs. The negative NephroCheck allows me to know who can really be "fast tracked," so actually it speeds up recovery.

Dr Lobdell. We should avoid the diuretics for most patients on postop day 1, correct?

Dr Engelman. No, no. You'll slow things down. I'll lose a day there, I'll lose a day, and I won't know exactly how to use focused transfusions, because those patients who are vasoplegic still stuck on 2 pressors, if they have a positive NephroCheck, I'm raising their hematocrit a little bit, I'm giving them a unit of blood, though it doesn't increase overall blood utilization. It just focuses my transfusion strategy.