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Candidate Surrogate End Points for ESRD after AKI

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ABSTRACT

AKI, a frequently transient condition, is not accepted by the US Food and Drug Association as an end point for drug registration trials. We assessed whether an intermediate-term change in eGFR after AKI has a sufficiently strong relationship with subsequent ESRD to serve as an alternative end point in trials of AKI prevention and/or treatment. Among 161,185 United States veterans undergoing major surgery between 2004 and 2011, we characterized in-hospital AKI by Kidney Disease Improving Global Outcomes creatinine criteria and decline in eGFR from prehospitalization to postdischarge time points and quantified associations of these values with ESRD and mortality over a median of 3.8 years. An eGFR decline of ≥30% at 30, 60, and 90 days after discharge occurred in 3.1%, 2.5%, and 2.6%, of survivors without AKI and 15.9%, 12.2%, and 11.7%, of survivors with AKI. For patients with in-hospital AKI compared with those with no AKI and stable eGFR, a 30% decline in eGFR at 30, 60, and 90 days after discharge demonstrated adjusted hazard ratios (95% confidence intervals) of ESRD of 5.60 (4.06 to 7.71), 6.42 (4.76 to 8.65), and 7.27 (5.14 to 10.27), with corresponding estimates for 40% decline in eGFR of 6.98 (5.21 to 9.35), 8.03 (6.11 to 10.56), and 10.95 (8.10 to 14.82). Risks for mortality were smaller but consistent in direction. A 30%–40% decline in eGFR after AKI could be a surrogate end point for ESRD in trials of AKI prevention and/or treatment, but additional trial evidence is needed.

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AKI is a common inpatient and outpatient condition and associated with myriad morbidity, including a substantially increased risk of development and progression of CKD as well as ESRD.[1–4] Despite increasing recognition of AKI as a serious public health concern, few effective therapies are available. One reason for the lack of therapies is the controversy over whether AKI itself causes an irreversible loss of kidney function.[5,6] The current consensus guidelines define AKI by an increase in serum creatinine from baseline of 0.3 mg/dl within 48 hours or 50% within 7 days, without requirement that the decreased kidney function be sustained.[7] People who develop AKI tend to be older with a higher burden of comorbidities, including reduced eGFR and elevated albuminuria.[8,9] Some have argued that the adverse outcomes after mild AKI may simply be a result of the underlying phenotype and not related to AKI.[6,10]

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As such, AKI is not currently accepted by the US Food and Drug Association (FDA) as an end point for registration trials.

A better understanding of the risk for ESRD after AKI could inform the design and execution of phase 3 clinical trials and facilitate drug development. In clinical trials of CKD progression, a 30% decline in eGFR has been suggested as an alternative surrogate end point for ESRD, which may enable better powered trials with a smaller sample size than those with the traditionally accepted surrogate end point of doubling of serum creatinine.[11–13] A comparable surrogate outcome after AKI might do the same; indeed, the FDA has accepted an irreversible loss of kidney function after AKI as an end point in some studies. However, there are little data to support what magnitude of eGFR decline after a transient loss in kidney function is meaningful and when the end point should be assessed (*i.e.*, when the change likely constitutes an irreversible loss).

The objective of this study was to quantify the continuous association between the decrement in eGFR at various time points post-AKI and subsequent ESRD, thus providing evidence to support a potential surrogate end point in trials of AKI prevention or treatment. We focused on AKI occurring after major surgery, because postoperative AKI is one of the most common settings for trials of AKI prevention. Because mortality is an important and competing end point to ESRD after AKI, we also evaluated the association of post–AKI eGFR decline with mortality.

RESULTS

Baseline Characteristics

The 161,185 United States veterans comprising the study population were mostly men (96.3%), 16.9% were black, and they had an average age of 64 years old (Table 1). Mean prehospitalization eGFR was 80 ml/min per 1.73 m^2, and 12% of the population had eGFR<60 ml/min per 1.73 m^2. The mean number of creatinine levels in the year before surgery was 3.5 (SD of 2.7). The most common type of surgery was general (28%) followed by orthopedic (21%), vascular (16%), and cardiac (14%). Postoperatively, there were 19,025 patients with AKI, with 14,477 (76%) classified as stage 1, 2780 (15%) classified as stage 2, and 1768 (9%) classified as stage 3. Among the patients with stage 3 AKI, 420 required postoperative dialysis.

Survival to Postdischarge Time Points and Frequency of eGFR Assessment

Survival to postdischarge time points differed by postoperative AKI status (Table 2). At 30, 60, and 90 days posthospital discharge, 98%, 97%, and 96% of those without postoperative AKI were alive as were 89%, 88%, and 87% of the patients with postoperative AKI. At 1 year, comparable estimates were 92% and 81% of the patients without and with postoperative AKI, respectively.

The frequency of creatinine checks among survivors also differed by post-AKI status: at 30 days (±15 days), 41% of people without postoperative AKI and 54% of those with postoperative AKI had a creatinine assessment; at 60 days (±30 days), 53% without postoperative AKI and 63% with postoperative AKI had a creatinine assessment; at 90 days (±30 days), 49% without postoperative AKI and 57% with postoperative AKI had a creatinine assessment; and at 1 year (±3 months), 78% without postoperative AKI and 82% with postoperative AKI had a creatinine assessment. Average number of eGFR assessments during each time window was greater among those who had experienced postoperative AKI and ranged from 2.7 and 3.9 at 30±15 days postdischarge to 3.4 and 4.5 at 1 year ±3 months among persons without and with postoperative AKI, respectively. Persons who did not have creatinine checks tended to be younger, more often women, and more often black with few comorbid conditions (Supplemental Table 1). Persons without measurements of creatinine also had lower proportions of subsequent ESRD and death as did participants without AKI (Supplemental Table 2).

Table 1. Baseline characteristics of veterans undergoing major surgery from 2004 to 2011

Characteristic	Overall
N	161,185
Demographics	
Age, yr	64 (10)
Women, %	4
Black race, %	17
Comorbid conditions	
Systolic BP, mmHg	133 (14)
Diastolic BP, mmHg	76 (9)
Body mass index, kg/m^2	29 (6)
Baseline eGFR, ml/min per 1.73 m^2	80 (17)
With eGFR<60 ml/min per1.73 m^2, %	12
With eGFR<45 ml/min per 1.73 m^2, %	2
Diabetes mellitus, %	35
Hypertension, %	75
Coronary artery disease, %	35
Congestive heart failure, %	10
Cerebral vascular disease, %	18
Peripheral arterial disease, %	20
Lung disease, %	33
Malignancy, %	30
Liver disease, %	1
Statin use, %	28
Diuretic use, %	26
Angiotensin–converting enzyme/angiotensin receptor blocker use, %	40
Surgical factors, %	
Cardiac	14
Ear-nose-throat	3
General	28
Orthopedic	21
Thoracic	7
Urology	11
Vascular	16
Laparoscopic	7

All values reflect mean (SD) unless otherwise stated.

Table 2. Survival after major surgery by stage of AKI and frequency of eGFR assessment postdischarge

Statistic	30 d	60 d	90 d	180 d	365 d
Survival, %					
All persons	97	96	95	93	91
With AKI	89	88	87	84	81
Without AKI	98	97	96	95	92
Frequency of postoperative eGFR check among survivors at various time points postdischarge, %	30±15 d	60±30 d	90±30 d	180±60 d	365±90 d
All persons	42	54	50	68	79
With AKI	54	63	57	73	82
Without AKI	41	53	49	68	78
Mean no. of postoperative eGFR check at various time points postdischarge (SD)	30±15 d	60±30 d	90±30 d	180±60 d	365±90 d
All persons	2.8 (4.0)	3.3 (5.2)	2.9 (4.6)	3.3 (5.5)	3.5 (5.9)
With AKI	3.9 (5.3)	4.4 (7.1)	3.8 (6.3)	4.2 (7.4)	4.5 (7.9)
Without AKI	2.7 (3.7)	3.1 (4.8)	2.8 (4.3)	3.1 (5.2)	3.4 (5.6)

Mortality calculated on basis of Kaplan–Meier methods. Frequency of postoperative eGFR check includes both inpatient and outpatient measures. Mean number of postoperative eGFR check includes only those persons with at least one measure of creatinine.

Frequency of eGFR Decline Postdischarge by AKI Stage

Higher AKI stage was associated with greater likelihood of eGFR decline, although this association was attenuated in later time periods. For example, the frequencies of a 30% decline at 30 days were 3%, 12%, 21%, and 39% for no AKI, AKI stage 1, AKI stage 2, and AKI stage 3. At 60 days, the frequencies were 2%, 10%, 17%, and 29% for no AKI, AKI stage 1, AKI stage 2, and AKI stage 3. At 90 days, the frequencies were 3%, 10%, 16%, and 26% for no AKI, AKI stage 1, AKI stage 2, and AKI stage 3, and at 1 year, the frequencies were 3%, 12%, 15%, and 25% for no AKI, AKI stage 1, AKI stage 2, and AKI stage 3. In adjusted analyses, the odds of a 30% eGFR decline at 30 days were 4.06 (95% confidence interval [95% CI], 3.72 to 4.44), 7.69 (95% CI, 6.65 to 8.88), and 18.60 (95% CI, 15.83 to 21.84) for AKI stage 1, stage 2, and stage 3 with or without dialysis compared with people without postoperative AKI; at 90 days, the odds were 3.67 (95% CI, 3.33 to 4.04), 6.34 (95% CI, 5.40 to 7.46), and 12.08 (95% CI, 10.11 to 14.44), respectively. The corresponding odds of eGFR decline ≥30% at 1 year were 3.58 (95% CI, 3.33 to 3.85), 5.36 (95% CI, 4.67 to 6.15), and 9.56 (95% CI, 8.12 to 11.25), respectively. Among those with measures of creatinine, most people with an eGFR decline >30% at 90 days also had an eGFR decline >30% at 60 and 30 days (79% and 60%, respectively).

Risk of ESRD after Postdischarge Decline in eGFR

There were 787 patients with ESRD and 43,668 deaths over a median follow-up of 3.8 years after hospital discharge, with greater risk in those with AKI and 30% decline compared with those without AKI or without 30% decline (Supplemental Figure 1). There was a graded relationship between postdischarge eGFR decline and subsequent ESRD risk among patients with and without postoperative AKI (Figure 1). Risks of ESRD exceeded fivefold at an eGFR decline of 30% for all time points postdischarge and were higher with greater magnitude of decline (Table 3). For example, compared with patients without postoperative AKI and with stable eGFR at 30 days, people with postoperative AKI and an eGFR decline of 30% had a 5.6-fold (95% CI, 4.1 to 7.7) higher risk of subsequent ESRD. The risk gradient associated with a 30% eGFR decline was generally higher at later time windows: 6.4-fold (95% CI, 4.8 to 8.7) at 60 days, 7.3-fold (95% CI, 5.1 to 10.3) at 90 days, and 10.8-fold (95% CI, 7.6 to 15.4) at 1 year. There was no consistent pattern suggesting an interaction of AKI stage and magnitude of eGFR decline with subsequent risk of ESRD, and there was not a difference in risk of ESRD by AKI stage after eGFR decline was accounted for. Of note, persons experiencing eGFR decline without AKI also had higher risk of developing ESRD: 2.6-fold (95% CI, 1.8 to 3.9) at 30 days, 3.0-fold (95% CI, 2.1 to 4.3) at 60 days, 4.4-fold (95% CI, 3.1 to 6.3) at 90 days, and 7.3-fold (95% CI, 5.3 to 10.0) at 1 year. The likelihood ratio of eGFR decline of 30% at 30 days was 5.78, with lower sensitivity but higher specificity (Figure 2, Table 4).

Risk of Death after Postdischarge Decline in eGFR

The risk of death associated with eGFR decline after postoperative AKI was smaller than that of ESRD and fairly consistent over the various time windows (Supplemental Table 3). For example, compared with stable eGFR and no postoperative AKI, the risks of death associated with a 30% decline in eGFR after postoperative AKI were 1.55 (95% CI, 1.42 to 1.69) at 30 days, 1.59 (95% CI, 1.46 to 1.73) at 60 days, 1.68 (95% CI, 1.54 to 1.83) at 90 days, and 1.60 (95% CI, 1.48 to 1.72) at 365 days. Mortality risks were higher with greater magnitude of eGFR decline. There was no consistent difference in risk of death by AKI stage after eGFR decline was accounted for, and persons experiencing eGFR decline without AKI also had a higher risk of mortality: 1.3-fold (95% CI, 1.3 to 1.4) at 30 days, 1.5-fold (95% CI, 1.4 to 1.6) at 60 days, 1.5-fold (95% CI, 1.4 to 1.6) at 90 days, and 1.4-fold (95% CI, 1.4 to 1.5) at 1 year (Supplemental Figure 2).

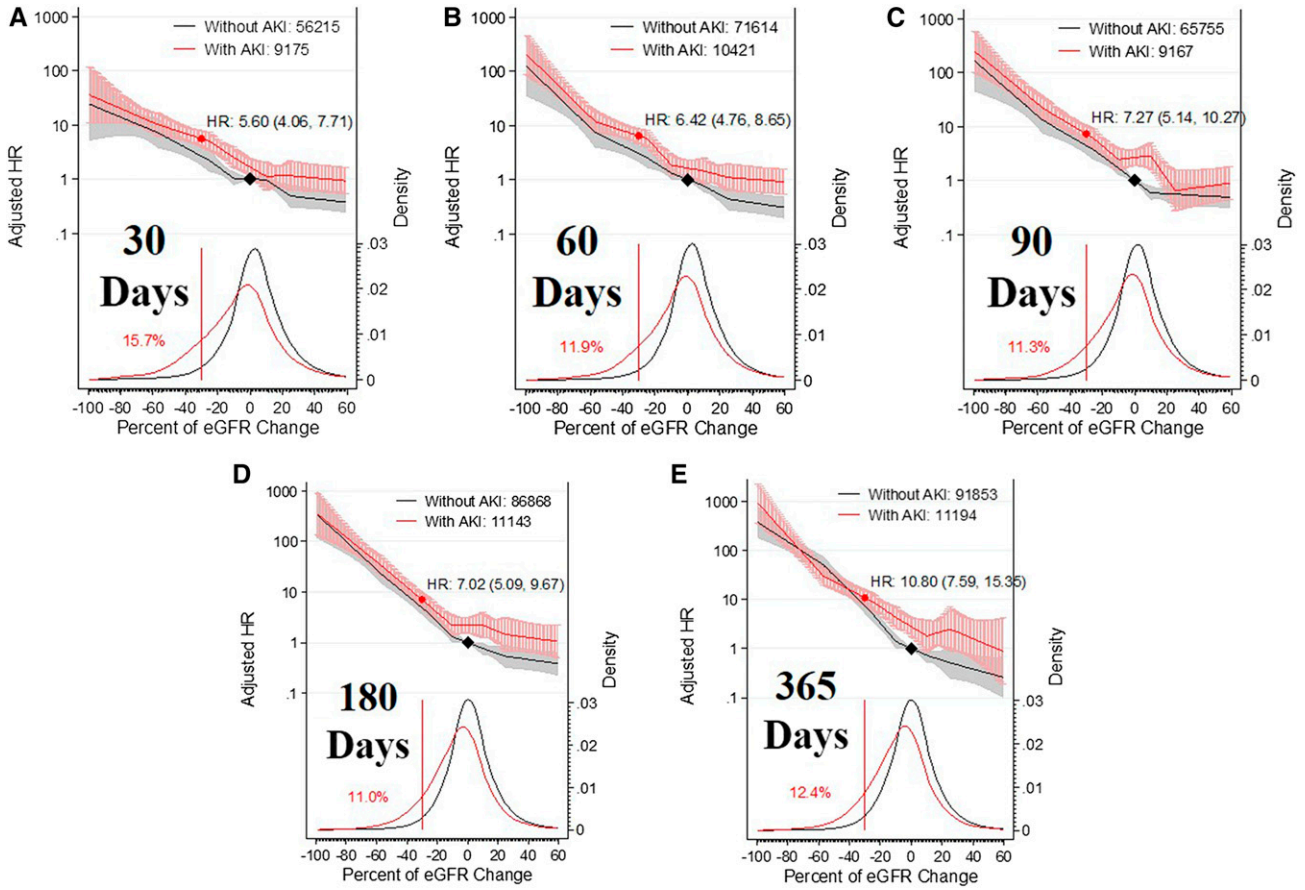

Figure 1. Risk of ESRD increases with postdischarge decline in eGFR after major surgery. (Upper panels) Risk of ESRD associated with postdischarge change in eGFR after major surgery by postoperative AKI status. (Lower panels) Distribution of postdischarge change in eGFR after major surgery by postoperative AKI status. Both estimates are at (A) 30, (B) 60, (C) 90, (D) 180, and (E) 365 days postdischarge. Black diamonds refer to stable eGFRs among those without AKI (the reference). Red circles refer to eGFR declines of 30% among those with AKI. Red lines are at eGFR decline of 30%, and red percentages refer to the prevalence of eGFR decline ≥30% among those survivors with postoperative AKI. The *y* axis is depicted on the log scale. HR, hazard ratio.

Sensitivity Analyses

In sensitivity analyses requiring that a patient have at least two creatinine measurements during the postdischarge window to confirm eGFR decline, results were similar (Supplemental Figure 3). The risks associated with an eGFR decline of 30% after AKI were 4.25 (95% CI, 2.84 to 6.36) at 30 days, 5.63 (95% CI, 3.91 to 8.10) at 60 days, 5.55 (95% CI, 3.64 to 8.45) at 90 days, 6.42 (95% CI, 4.42 to 9.31) at 180 days, and 10.8 (95% CI, 7.32 to 16.0) at 1 year. Similarly, results from analyses excluding ear-nose-throat surgery, accounting for the competing risk of death, and using inverse weighting by the probability of having creatinine measured in that time period were similar to the primary analysis (Supplemental Figure 4).

Mediation Analyses

Mediation analysis suggested that the eGFR decline after surgery statistically explained much of the increased risk of ESRD after postoperative AKI. For example, 56%, 73%, and 61% of the risks associated with AKI stage 1, stage 2, and stage 3 were accounted for by 30-day eGFR decline. These estimates were 62%, 76%, and 60% at 60 days; 62%, 84%, and 67% at 90 days; and 75%, 83%, and 100% at 1 year.

DISCUSSION

This national study of 161,185 United States veterans at risk for postoperative AKI provides a rigorous investigation of possible surrogate end points in clinical trials of AKI prevention and treatment. We quantify risk of ESRD across the full spectrum of post–AKI eGFR decline at various time points, thus informing decisions about when and what magnitude of eGFR decline after AKI is clinically important. Our results show that postdischarge eGFR decline was strongly associated with subsequent risk of ESRD, with greater than fivefold higher risk associated with a 30% decline at each time point of 30, 60, 90, 180, and 365 days. The association strengthened in later time periods and with higher percentage declines in eGFR. Although

Table 3. Hazard ratios for ESRD associated with stable eGFR, 30% eGFR decline, and 40% eGFR decline after major surgery by presence and stage of postoperative AKI at 30, 60, 90, and 180 days and 1 year posthospital discharge

Timepoint Postdischarge	Hazard Ratio (95% CI)				
	Without AKI	AKI Stage 1	AKI Stage 2	AKI Stage 3 or RRT	AKI Any Stage
30±15 d					
40% decline	3.81 (2.66 to 5.47)	7.39 (5.32 to 10.3)	7.17 (4.21 to 12.2)	6.45 (3.19 to 13.0)	6.98 (5.21 to 9.35)
30% decline	2.63 (1.79 to 3.88)	5.14 (3.60 to 7.35)	7.18 (3.85 to 13.4)	5.59 (2.19 to 14.3)	5.60 (4.06 to 7.71)
Stable	Reference	1.69 (1.16 to 2.45)	1.18 (0.40 to 3.45)	1.44 (0.43 to 4.82)	1.68 (1.18 to 2.38)
60±30 d					
40% decline	4.19 (2.98 to 5.89)	8.10 (5.97 to 11.0)	7.80 (4.71 to 12.9)	6.42 (3.05 to 13.5)	8.03 (6.11 to 10.56)
30% decline	3.01 (2.12 to 4.27)	6.19 (4.44 to 8.62)	7.42 (4.09 to 13.5)	6.85 (3.01 to 15.6)	6.42 (4.76 to 8.65)
Stable	Reference	1.62 (1.14 to 2.30)	1.39 (0.50 to 3.84)	1.87 (0.61 to 5.68)	1.64 (1.18 to 2.27)
90±30 d					
40% decline	6.54 (4.67 to 9.14)	10.4 (7.48 to 14.5)	9.66 (5.38 to 17.3)	9.75 (3.97 to 23.9)	11.00 (8.10 to 14.8)
30% decline	4.39 (3.07 to 6.28)	7.22 (4.98 to 10.5)	8.74 (4.50 to 17.0)	2.85 (0.64 to 12.7)	7.27 (5.14 to 10.3)
Stable	Reference	2.66 (1.78 to 3.70)	2.97 (1.28 to 6.87)	2.52 (0.64 to 9.91)	2.65 (1.88 to 3.74)
180±60 d					
40% decline	8.61 (6.53 to 11.3)	12.5 (9.29 to 16.8)	12.3[a] (7.02 to 21.4)	7.15 (2.65 to 19.3)	12.50 (9.54 to 16.5)
30% decline	4.86 (3.58 to 6.59)	7.83 (5.60 to 10.9)	4.27[a] (1.85 to 9.85)	2.51 (0.50 to 12.6)	7.02 (5.09 to 9.67)
Stable	Reference	1.87 (1.27 to 2.75)	4.06 (1.87 to 8.34)	2.57 (0.56 to 11.8)	2.20 (1.56 to 3.11)
365±90 d					
40% decline	15.0 (11.3 to 19.9)	16.2 (11.7 to 22.4)	18.6 (10.7 to 32.2)	9.79 (4.11 to 23.4)	15.80 (11.6 to 21.4)
30% decline	7.29 (5.29 to 10.0)	9.70 (6.59 to 14.3)	13.0 (6.24 to 27.2)	22.2 (8.66 to 56.7)	10.80 (7.59 to 15.4)
Stable	Reference	2.53 (1.57 to 4.09)	3.63 (1.31 to 10.0)	2.62 (0.48 to 14.3)	2.78 (1.81 to 4.27)

[a]Adjusted for age, sex, race, body mass index (linear spline with a knot at 25 kg/m^2), hypertension, baseline eGFR (linear spline with knots at 60 and 90 ml/min per 1.73 m^2), diabetes, congestive heart failure, peripheral arterial disease, cerebrovascular disease, lung disease, liver disease, body mass index, angiotensin–converting enzyme inhibitor/angiotensin receptor blocker use, diuretic use, statin use, surgery type, laparoscopic procedure, hospital day of surgical procedure (hospital days 0–4, 5–14, or 15–30), and stage of AKI.

AKI itself was associated with subsequent risk of ESRD, subsequent eGFR decline seemed to mediate this association to a large extent, and there was no graded relationship between AKI severity and ESRD after accounting for subsequent eGFR decline. Taken together, this may suggest that a 30% decline measured even as early as 30 days postdischarge could be a suitable

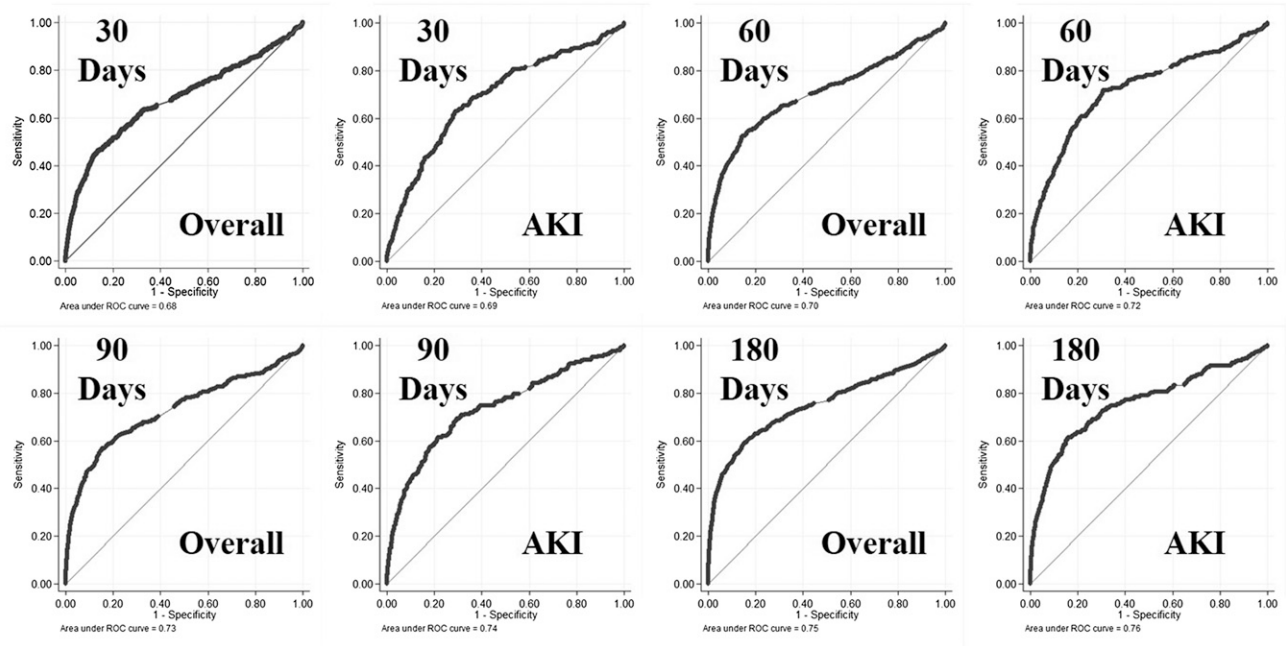

Figure 2. Receiver-operating characteristic (ROC) for ESRD according to eGFR declines at 30, 60, 90, and 180 days postmajor surgery overall and within the population with postoperative AKI.

Table 4. Sensitivity, specificity, positive predictive value, and negative predictive value for ESRD according to levels of eGFR decline at various time points

Statistic	30 d		60 d		90 d		180 d	
	Overall	AKI	Overall	AKI	Overall	AKI	Overall	AKI
Sensitivity, %								
30% eGFR decline	27	41	27	40	31	44	38	51
40% eGFR decline	17	27	18	27	21	30	24	34
Specificity, %								
30% eGFR decline	95	85	96	89	96	89	97	90
40% eGFR decline	98	92	98	94	98	95	99	95
Positive predictive value, %								
30% eGFR decline	4	6	5	8	5	9	6	9
40% eGFR decline	5	7	7	10	8	12	9	13
Negative predictive value, %								
30% eGFR decline	99	98	100	98	100	99	100	99
40% eGFR decline	99	98	99	98	100	98	100	99

surrogate for ESRD after AKI. A more conservative end point would be a 40% decline; however, this end point is less common, which would necessitate larger trials. However, additional evidence from clinical trials showing that treatment effects on eGFR decline predict treatment effects on ESRD is necessary.

A large body of work recently addressed a similar issue of surrogate end points in trials of kidney disease progression.[11,12,14–18] To approve a drug, the FDA requires that a development program show that a drug has an effect on a clinically meaningful end point or its reliable surrogate.[19] ESRD is a widely accepted, clinically meaningful end point; however, ESRD is simply too late an event for the majority of clinical trial participants—a rationale that applies to both clinical trials of AKI prevention and treatment and CKD progression. A surrogate end point for ESRD, such as an eGFR decline of 30%–40%, can result in more events in a shorter period of time, thereby providing greater power for a given clinical trial design. The demonstration of an epidemiologic association is a first step in determining surrogacy and should be followed by investigation in clinical trials, which can address the issue of whether treatment effects on the proposed surrogate predict treatment effects on ESRD.

Although a decline in eGFR at a specified time point post-AKI is on the pathway from AKI to ESRD, it is not equivalent to ESRD, which is a severe and relatively rare event. In addition, ESRD has many causes apart from AKI, which can include acute events that occur after an intermediate end point (*e.g.*, medication toxicity or myocardial infarction). Thus, both sensitivity and positive predictive value are low, because eGFR decline within an early follow-up interval post-AKI is not necessary or sufficient to cause ESRD. This point is exemplified by the prediction statistics, which show some of the differences between a potentially useful surrogate and a perfect predictor. Although prediction statistics are informative, even widely accepted surrogates, such as LDL cholesterol for myocardial infarction, have low sensitivity and positive predictive value.[20] However, a low sensitivity may also hamper evaluation of treatment effects on ESRD in clinical trials.

Similar to recent work in CKD, our results suggest that a 30%–40% decline may be a surrogate for ESRD after in-hospital AKI. They also suggest that the most important aspect of AKI prevention may be lessening the risk of subsequent eGFR decline or the irreversible loss of kidney function after an episode of AKI. When eGFR decline should be measured postinjury is uncertain, but associations were strong even at 30 days posthospital discharge and stronger with confirmed eGFR decline as assessed by repeat measurement. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend assessment at 90 days for ascertainment of development or progression of CKD after an episode of AKI.[21] Our data show that this later time point is associated with higher risk, possibly reflecting irreversible loss of kidney function, or that it is less affected by the competing risk of mortality, providing stronger evidence of surrogacy. However, eGFR decline detected at later time points may be caused by intervening events posthospitalization unrelated to the AKI and thus, may be less preventable than eGFR decline at an earlier time point. Our results are consistent with previous work showing worse outcomes among people who do not recover eGFR after an episode of AKI compared with those who do recover.[10,22–24]

This study focuses on postoperative AKI. Cardiac surgery is a common setting for clinical trials of AKI prevention.[25,26] An advantage of the postoperative environment in clinical trials of AKI is that the timing of the insult may be well defined, particularly for cardiac and vascular surgery, and thus, interventions can be delivered at a specific time relative to the anticipated/observed insult. A second advantage of the postoperative environment as a setting for clinical trials is that surgery is usually avoided in persons at high risk of mortality. Even the most effective therapy for AKI prevention may not prevent short-term mortality given the availability of RRT, and thus, a higher frequency of mortality will reduce power for a given study design. Even in our study, the absolute risk of mortality far exceeded the risk of ESRD, as seen in the low positive predictive value; the use of a composite end point of ESRD and death would result in weaker associations. Relationships between eGFR decline after AKI and subsequent ESRD should be validated in alternative clinical settings commonly used in trials, such as postcardiac catheterization or iodinated contrast administration.

In addition to providing a more plausible surrogate for progression to ESRD than an acute and transient change, a benefit of choosing an intermediate-term surrogate as an end point in trials of AKI prevention or treatment is that it limits the possibility

of bias from an acute effect of an intervention. Many interventions tested for the prevention of AKI can affect non-GFR determinants of creatinine concentration, shifting the distribution of creatinine toward lower values. Given that a change in creatinine forms the basis of the AKI definition,[7] an intervention that affects the non-GFR determinants of creatinine may falsely seem to prevent AKI. This issue has plagued many clinical trials in AKI prevention with interventions ranging from fluid administration to dialysis to administration of rosuvastatin.[27] As long as the intervention and its non-GFR effect on creatinine are short in duration, an intermediate–term end point could avoid the bias associated with acute effects. The consistency of our results, despite unmeasured medications and intervening hospitalizations, suggests a robust association.

The strengths of this study include its large nationally based study population, the rigorous quantification of eGFR decline and stages of AKI, and linkage to subsequent outcomes. Follow-up for ESRD and mortality is presumed to be complete given the linkage to reliable government sources. However, we relied on assessment of postdischarge eGFR as it was obtained in clinical care, and this ascertainment bias resulted in sicker patients selected into our cohort. Sensitivity analyses weighting by the inverse probability of creatinine measurement showed consistent results. Another limitation is that the Veterans Affairs (VA) population consists of mostly men, and veterans may be different from the general population in many other ways as well. We did not have complete information on baseline proteinuria and thus could not adjust for this important confounder. Comorbid conditions were determined by diagnostic codes, which have uncertain and possibly differential validity. Medication use was captured by provider prescription, and compliance was unknown. With all observational analysis, residual confounding is possible; mediation analysis is particularly susceptible. Our mediation analysis was only a secondary analysis but should be interpreted with caution. Finally, only 12% of the population had eGFR$<$60 ml/min per 1.73 m^2, which differs from many AKI clinical trial populations that are enriched for participants with kidney disease. Future studies should validate these associations in other settings and cohorts, including clinical trials, where treatment effects can be evaluated.

In conclusion, we present data from a large national cohort of veterans undergoing major surgery that show that a 30%–40% decline in eGFR postdischarge may be a potential surrogate end point in clinical trials of AKI prevention. Unlike other clinical biomarkers, it is directly on the pathway from AKI to ESRD and seems to largely explain the excess risk associated with AKI. Although this end point would be considerably more common than ESRD, a suitably powered trial of AKI prevention may still require thousands of patients, and its use requires additional study of treatment effects in clinical trials. Future research is needed to determine whether other clinically meaningful end points, such as length of stay or hospital readmission, might also be useful in drug approval procedures.

CONCISE METHODS

Study Population

The study population has been previously described.[28,29] Briefly, 3,582,478 United States veterans with eGFR$\geq$60 ml/min per 1.73 m^2 (calculated by the CKD Epidemiology Collaboration 2009 creatinine equation[30]) measured between October 1, 2004 and September 30, 2006 in the national VA Corporate Data Warehouse LabChem data files were included in the initial data pull. For this study, only patients undergoing major cardiac, thoracic, vascular, orthopedic, general, urologic, or ear-nose-throat surgery between cohort enrollment date and September 15, 2011 were included (n=310,894).[31] For these patients, the first qualifying surgery was used as the index hospitalization. We excluded patients with prehospitalization ESRD and those undergoing surgery $>$30 days after hospital admission for a final study population of 161,185 participants. Because the surgery could occur any time during the follow-up period, many participants (12% of the study population) had developed eGFR$<$60 ml/min per 1.73 m^2 before surgery.

Definitions of AKI and eGFR Decline

Postoperative AKI was staged according to KDIGO creatinine–based criteria from the date of surgery, identifying AKI as an increase in serum creatinine from baseline of 0.3 mg/dl within 48 hours or 50% within 7 days.[7] Stage 1 was classified as a creatinine increase of 0.3 mg/dl over 48 hours or a 50%–99% increase within 7 days. Stage 2 was classified as a 100%–200% increase within 7 days. Stage 3 was classified as a $\geq$200% increase or the receipt of acute dialysis determined by the presence or absence of a procedural code for dialysis (39.95). Baseline serum creatinine for the ascertainment of AKI was defined as the mean of all outpatient measurements of serum creatinine between 7 and 365 days before hospital admission, a time window designed to exclude acute fluctuations related to the need for surgery. The magnitude of eGFR decline was assessed as the difference between eGFR measured at various time points posthospital discharge and the prehospitalization eGFR as a percentage of prehospitalization eGFR. Prehospitalization eGFR was defined as the mean of all outpatient estimates of eGFR between 7 and 365 days before hospital admission estimated with the serum creatinine values used in the baseline creatinine estimation. Time points tested included 30 days ($\pm$15 days), 60 days ($\pm$30 days), 90 days ($\pm$30 days), 180 days ($\pm$60 days), and 1 year ($\pm$90 days) posthospital discharge. If multiple assessments of eGFR were made in a given time window, the mean eGFR was used. The magnitude of eGFR decline was assessed continuously using complete patient analysis. Given the strength of associations, we focused our discussion on 30-, 60-, and 90-day time periods and 30% and 40% declines. In sensitivity analysis, we required two measurements of eGFR decline in the time window as a proxy for confirmation of decline.

Definitions of Covariates and Outcomes

Surgery type was determined from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) procedure codes in the VA Inpatient Medical Dataset and categorized according to the Clinical Classifications Software procedural classification system (Supplemental Table 4). Laparoscopic surgery, hypertension, diabetes, coronary artery disease, congestive heart failure, peripheral arterial disease, cerebrovascular disease, liver disease,

and lung disease were defined by a qualifying inpatient or outpatient ICD-9-CM code (Supplemental Table 5).[32,33] Body mass index was defined as the average outpatient value in 7–365 days before admission using the VA Corporate Data Warehouse. Medication use (angiotensin–converting enzyme inhibitor, angiotensin receptor blocker, diuretic, and statin) was determined by VA Pharmacy dispensation records in the 3 months before surgery. Outcomes included ESRD and mortality as determined through linkage to the VA Vital Status Files and the US Renal Data System, respectively, with follow-up until 2011.

Statistical Analyses

Survival to various time points postdischarge was assessed using a Kaplan–Meier approach. Odds of eGFR decline associated with stage of AKI were determined using logistic regression. Cox proportional hazards regression was used to determine the association of eGFR decline with subsequent ESRD and mortality, with time at risk beginning at the time of postdischarge eGFR assessment. Fully adjusted models included the following covariates: age, sex, race, body mass index (linear spline with a knot at 25 kg/m^2), hypertension, baseline eGFR (linear spline with knots at 60 and 90 ml/min per 1.73 m^2), diabetes, congestive heart failure, peripheral arterial disease, cerebrovascular disease, lung disease, liver disease, angiotensin–converting enzyme inhibitor/angiotensin receptor blocker use, diuretic use, statin use, surgery type, laparoscopic procedure, and hospital day of surgical procedure (hospital days 0–4, 5–14, or 15–30). Proteinuria was considered as a covariate, but it was missing in 90% of the study population and thus, not included in the primary analysis. Mediation of the AKI-ESRD risk relationship by intermediate–term eGFR decline was performed by assessing the reduction in hazard ratio associated with AKI when eGFR decline was included in the model compared with the hazard ratio associated with AKI without eGFR decline in the model, with both models adjusted for all of the other covariates indicated above. All analyses were performed in the overall population using Stata MP 12 (StataCorp., College Station, TX).

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DISCLOSURES

J.C. and A.S.L. have a provisional patent submitted for GFR estimation using a panel of biomarkers. K.K.-Z. and C.P.K. are employees of the US Department of Veterans Affairs. J.C. and M.E.G. received funding from the National Kidney Foundation which receives funding from Abbvie and Thrasos.

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