Rapid Occurrence of Chronic Kidney Disease in Patients Experiencing Reversible Acute Kidney Injury after Cardiac Surgery

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ABSTRACT

Background: There is recent evidence to show that patients suffering from acute kidney injury are at increased risk of developing chronic kidney disease despite the fact that surviving tubular epithelial cells have the capacity to fully regenerate renal tubules and restore renal function within days or weeks. The aim of the study was to investigate the impact of acute kidney injury on *de novo* chronic kidney disease.

Methods: The authors conducted a retrospective population-based cohort study of patients initially free from chronic kidney disease who were scheduled for elective cardiac surgery with cardiopulmonary bypass and who developed an episode of acute kidney injury from which they recovered. The study was conducted at two French university hospitals between 2005 and 2015. These individuals were matched with patients without acute kidney injury according to a propensity score for developing acute kidney injury.

Results: Among the 4,791 patients meeting the authors' inclusion criteria, 1,375 (29%) developed acute kidney injury and 685 fully recovered. Propensity score matching was used to balance the distribution of covariates between acute kidney injury and non-acute kidney injury control patients. Matching was possible for 597 cases. During follow-up, 34 (5.7%) had reached a diagnosis of chronic kidney disease as opposed to 17 (2.8%) in the control population (hazard ratio, 2.3; bootstrapping 95% CI, 1.9 to 2.6).

Conclusions: The authors' data consolidate the recent paradigm shift, reporting acute kidney injury as a strong risk factor for the rapid development of chronic kidney disease. **(Anesthesiology 2017; 126:39-46)**

TEN years ago, international experts from the Acute Dialysis Quality Initiative and the Acute Kidney Injury Network proposed a unique definition of "acute kidney injury" (AKI). Thus, a diagnosis of AKI requires either a 1.5-fold increase in serum creatinine within 7 days or serum creatinine increase by more than 0.3 mg/dl (26.5 μmol/l) within 48 h.[1] After this consensus, two unexpected findings have been reported. First, even a mild episode of AKI was found to increase the risk of death, independent of any comorbidities.[2–5] Second, as evidenced by four independent studies, AKI was found to be a major risk factor for the development of a chronic kidney disease (CKD) within a matter of a few weeks.[6–9] Whereas the progressive decrease in the residual renal function of patients who did not fully recover from an episode of severe AKI is intuitive, this observation is less

What We Already Know about This Topic

- Recent evidence suggests that patients suffering from acute kidney injury (AKI) are at increased risk of developing chronic kidney disease (CKD) despite the fact that surviving tubular epithelial cells have the capacity to fully regenerate renal tubules and restore renal function within days or weeks
- The current study investigated the impact of AKI on *de novo* CKD in a retrospective population-based cohort study of patients initially free from CKD who were scheduled for elective cardiac surgery with cardiopulmonary bypass and who developed an episode of AKI from which they recovered

What This Article Tells Us That Is New

- Regardless of its severity, a fully recovering episode of acute kidney injury after cardiac surgery in patients without preexisting chronic kidney disease is strongly associated with a subsequent increase in the risk of *de novo* chronic kidney disease

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org).

Submitted for publication April 5, 2016. Accepted for publication September 6, 2016. From the Department of Anesthesiology and Critical Care Medicine, Pôle Réanimations Anesthésie SAMU (D.L., J.-L.H.), and Department of Cardiac Surgery (D.B.), Caen University Hospital, Caen, France; Department of Renal Intensive Care Unit and Kidney Transplantation, AP-HP, Tenon University Hospital, Paris, France (P.G., A.H.); UPMC Sorbonne Université Paris 06, UMR S 1155, Paris, France (P.G., A.H.); Department of Biostatistics, AP-HP, Saint-Louis University Hospital, Paris, France (S.C.); Departments of Anesthesiology (S.P.) and Biochemistry (A. Boutten), APHP, Bichat Hospital, Paris, France; Department of Anesthesiology and Critical Care, Hôpital Cardiologique Louis Pradel, Hospices Civils de Lyon, Lyon, France (J.-L.F.); and French National Institute of Health and Medical Research (INSERM), UMR_S1155, Rare and Common Kidney Diseases, Matrix Remodelling and Repair department, Tenon Hospital, Paris, France (P.G., A. Bataille, A.H.).

 Anesthesiology 2017; 126:39-46

<zdoi;10.1097/ALN.0000000000001400>

immediately obvious in the case of patients who recovered "*ad integrum*." Nonetheless, retrospectively exploring the long-term renal prognosis of a recovering AKI in unselected patients who were CKD free at the time of the acute episode, Jones *et al.*[10] and Bucaloiu *et al.*[11] have found a 2- to 3-fold increase in the risk of developing post-AKI stage 3 CKD.

In addition, experimental data have recently highlighted molecular mechanisms at stake in myofibroblasts and in tubular epithelial cells, linking AKI with CKD.[12–14]

Regarding the studies mentioned above, some methodological issues need to be emphasized. First, patients could have been included on the basis of various pathologic conditions, including the chronic conditions of multiple kidney injury.[6–11] Second, the recovery of AKI was not systematically verified.[6–9] Hence, CKD could have been present simply as a result of a sequel and of immediate scarring. Finally, the diagnosis of CKD could have been defined by a diagnostic code and not by numerical values estimating the glomerular filtration rate (GFR).[6–9]

A study aiming at the consolidation of the recent knowledge that a recovering AKI may lead to CKD would ideally test a population of patients (1) at risk of AKI, (2) exposed to a unique event leading to AKI, and (3) in whom renal function would be estimated both before and after an episode of AKI. Incidence of AKI after cardiac surgery varies between 15% and 45%.[15–19] Although a preexisting CKD is an established risk factor for AKI in this context, AKI may occur in CKD-free patients.[2,17] We analyzed the renal outcome of CKD-free patients scheduled for cardiopulmonary bypass (CBP) cardiac surgery at two centers in France, who did or did not develop AKI with a recovering renal function identical (± 10%) to that before surgery.

Materials and Methods

Study Design

We conducted a bicenter retrospective cohort study with a propensity score matching analysis. The study took place at two French university hospitals, within a catchment area of about 13.5 million people. Each year, both centers conduct 5% (totaling 10%) of all cardiac surgeries in France. The universal public health insurance guarantees equal access and free primary health care to all French citizens. The study was carried out in accordance with the principles outlined in the Declaration of Helsinki after approval from the institutional review board (approval number: Société Française d'Anesthésie et de Réanimation 00010254-2016-072) at each participating center.

Estimated GFR

Serum creatinine concentrations were measured using the Jaffé method. GFR values were estimated (eGFR) using the modification of diet in renal disease (MDRD) creatinine equation.[20] When the test was isotopic dilution mass spectrometry standardized, a correction was applied to the MDRD equation.[21] Baseline eGFR was defined by the MDRD calculated with the serum creatinine sampled during the anesthetic consultation. The racial correction factor was not used because (1) collecting statistics referring to racial or ethnic origin is forbidden in France and (2) this correction factor only applies to African-Americans.[22]

Population Study

Patients were included if they were more than or equal to 18 yrs old, free from CKD at the time of surgery (*i.e.*, baseline eGFR above 60 $ml^{-1} \cdot min^{-1} \cdot 1.73\ m^{-2}$), and scheduled for elective (nonurgent) cardiac surgery with CBP between 2005 and 2015. We excluded patients who had a previous history of cardiac surgery and those without available serum creatinine measurements within 7 days post surgery.

AKI: Exposure Status, Recovery, and CKD Outcome

For each patient, we calculated the shift of serum creatinine values in the first 7 days after surgery. The AKI group was defined according to the Kidney Diseases Improving Global Outcome (KDIGO) criteria,[1] by a 1.5-fold increase in baseline serum creatinine concentration within the first 7 days after surgery or by an increase greater than or equal to 0.3 mg/dl within 48 h. This included all patients who needed renal replacement therapy during their stay. By definition, the recovering status was defined, in all patients, by an eGFR greater than or equal to 90% at the baseline and greater than or equal to 60 $ml^{-1} \cdot min^{-1} \cdot 1.73\ m^{-2}$ between days 7 and 90 after surgery. "Time to recovery" was the time from surgery to recovery during the period 7 to 90 days post surgery. In the case of patients requiring dialysis, their recovery was manually checked by reviewing medical charts.

CKD was defined by at least two eGFR values less than or equal to 60 $ml^{-1} \cdot min^{-1} \cdot 1.73\ m^{-2}$ separated by an interval of at least 90 days.[1] Each CKD status and time was manually checked by looking at the raw data. "Time to CKD" was defined as the period spent from time to recovery to the first occurrence of eGFR less than or equal to 60 $ml^{-1} \cdot min^{-1} \cdot 1.73\ m^{-2}$. The 10th percentile time to CKD was the time during which 10% of the patients developed CKD. For AKI-free patients, we decided that time would count from the moment they had an eGFR measured during the recovery period (7 to 90 postoperative days), similar to their match.

Data Sources

The study was completed using two independent blinded databases from each hospital. Clinical research associates prospectively input all clinical data from the study into these databases. These bases were automatically updated with all serum creatinine levels measured for each patient during the study period. The rate of missing data is presented in the table in Supplemental Digital Content 1 (http://links.lww.com/ALN/B324). All the data were analyzed and anonymized in a blinded manner. As requested by law, these two databases were officially reported to the Commission Nationale de l'Informatique et des Libertés (Paris, France), the French data protection authority.

Statistical Analyses

Continuous variables for individuals with and without AKI were expressed as mean ± SD or as median 25th to 75th percentile for nonnormally distributed variables or number and percentage. Unmatched data were analyzed using the Mann–Whitney or Student's *t* test. Cumulative incidence curves were calculated with Kaplan–Meier methods and compared using the log-rank test. Incidence rates were calculated and compared using Poisson regression adjusted on propensity score.

A propensity score for AKI was estimated using the following covariates: age, body mass index, preoperative eGFR, clamping time and extracorporeal circulation, logistic European System for Cardiac Operative Risk Evaluation, left ventricular ejection fraction, and type of surgery. The variables included in the propensity score model were selected among available baseline variables based on known associations between CKD and AKI[23] with a nonparsimonious logistic regression. Available as a qualitative not quantitative entry in our database, blood transfusion was not included in this propensity score. This score was used to match each patient developing AKI to one control with a similar logit of the propensity score based on nearest neighbor matching without replacement using calipers of width equal to 0.2 SD.[24,25] An absolute standardized difference less than 10% was considered to support the assumption of balance between groups.[26]

The matching was followed by a Cox regression analysis stratified for matched pairs. Survival analyses were performed until September 1, 2015. For the CKD endpoint, each patient was censored at the end of the study period, *i.e.*, at the time of the last available eGFR. We ensured that our Cox model met the proportional hazard assumption.[27] Because the matching process was without replacement and to assess reliability, we used bootstrapping resampling and presented all the results as mean values (95% CI).[28]

Since the assumption of independence could not be verified, the dropout subjects could be different between CKD and non-CKD patients. This informative censoring might have introduced a bias in our results, so we therefore performed an inverse probability of censoring weighted (IPCW) Cox regression in order to take such a bias into account.[29] Last, to assess the potential effect of unmeasured confounders, we conducted a Rosenbaum bounds sensitivity analysis.[30] This analysis estimates the magnitude of a hidden residual bias that would have to be present to explain the associations actually observed.

A $P < 0.05$ was considered significant, and all P values were two tailed. Statistical analyses were performed using R software (http://www.R-project.org; accessed September 27, 2016).

Results

Baseline Population

Of the 7,471 patients screened, we identified 4,791 participants who met the inclusion criteria. We then excluded 2,030 patients because they had insufficient follow-up. From this cohort, 1,375 (29%) developed AKI and 685 (50%) fully recovered their renal function (fig. 1). As expected, in the whole-population study (*i.e.*, before the matching of AKI patients with non-AKI patients according to the propensity score), some of the variables were significantly different between the two groups (table 1).

Bootstrapped Matched Cohort

Among the 685 patients who had fully recovered from AKI and whose propensity score was available, 597 were successfully matched to a control patient. None of the variables associated with AKI and used in the propensity score differed significantly between AKI and non-AKI patients after matching (table 1; fig. 2). The median number of serum creatinine measurements during the follow-up period was 16 (11 to 28) and 11 (8 to 16) for the AKI and control groups, respectively. The characteristics of the 61 patients who could not be matched because the propensity score could not be

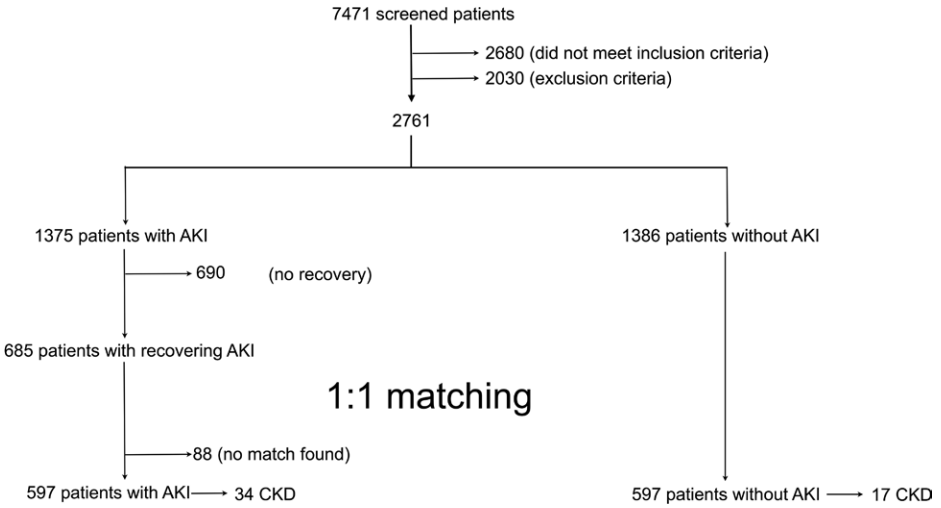

Fig. 1. Study flowchart. AKI = acute kidney injury; CKD = chronic kidney disease.

Table 1. Patient Characteristics of Cohort, before and after Matching, Developing or Not Developing AKI

	Unmatched Cohort				Matched Cohort		
	AKI (n = 1,375)	Control (n = 1,385)	*P* Value	SdD (%)	AKI (n = 597)	Control (n = 597)	SdD (%)
Propensity score, mean	0.38	0.30	< 0.0001	47.9	0.34	0.34	0.32
Baseline eGFR ($ml^{-1} \cdot min^{-1} \cdot 1.73\ m^{-2}$), mean	79	82	< 0.0001	22.7	79	79	0.79
eGFR at recovery ($ml^{-1} \cdot min^{-1} \cdot 1.73\ m^{-2}$), mean	91	95	0.0004	16.7	91	92	2.8
Age (yr), mean	66	64	< 0.0001	17.7	66	66	3.8
EuroSCORE (%), mean	4.6	3.7	0.001	14.0	4.3	4.3	0.2
BMI, mean	26.6	26.6	0.97	0.2	26.7	26.9	3.8
CBP time (min), mean	90	71	< 0.0001	35	78	79	1.5
Clamping time (min), mean	64	54	< 0.0001	27	58	59	3.5
Male (%)	72	69	0.1	7.1	72	71	1.9
LVEF (%), mean	56	57	0.007	12.5	55	56	8.1
Smoker (%)	15	19	0.02	11.1	16	16	1.4
Diabetes mellitus (%)	24	24	0.93	0.38	25	25	0.39

AKI = acute kidney injury; BMI = body mass index; CBP = cardiopulmonary bypass; eGFR = estimated glomerular filtration rate; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LVEF = left ventricular ejection fraction; SdD = standardized difference.

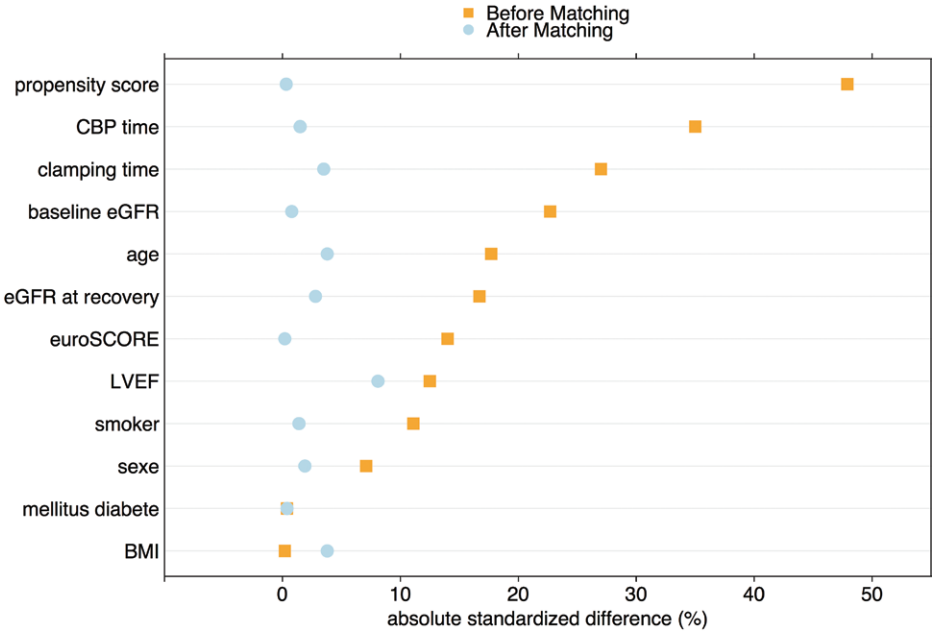

Fig. 2. Baseline covariates absolute standardized differences used in the propensity score, before and after matching process. BMI = body mass index; CBP = cardiopulmonary bypass; eGFR = estimated glomerular filtration rate; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LVEF = left ventricular ejection fraction.

calculated (due to missing data) are shown in the table in Supplemental Digital Content 2 (http://links.lww.com/ALN/B324).

CKD Outcome in AKI and Non-AKI Patients

In the matched cohort, 34 of the 597 patients who fully recovered from AKI developed CKD during the follow-up period as opposed to 17 of the control patients (fig. 3). The median 10th percentile time to the diagnosis of CKD in those experiencing AKI was 159 days as opposed to 594 days in the control group. Thus, incidence rates for CKD were 15.7 and 5.1/100 person-years in the AKI and control groups, respectively (P = 0.0007; table 2). The matched cohort hazard ratio (HR) for the development of stage 3 CKD was significantly higher in the AKI group (HR, 2.3; bootstrapping 95% CI, 1.9 to 2.6). It did not differ from the HR calculated from the IPCW Cox regression (HR, 2.5; 95% CI, 1.6 to 4.1).

Impact of "Threshold Effect"

Arbitrarily using a greater than or equal to 25% decrease in eGFR as another marker for significant deterioration of renal function, HR was still significantly increased after a transient episode of AKI (HR, 2.2; 95% CI, 1.4 to 3.2).

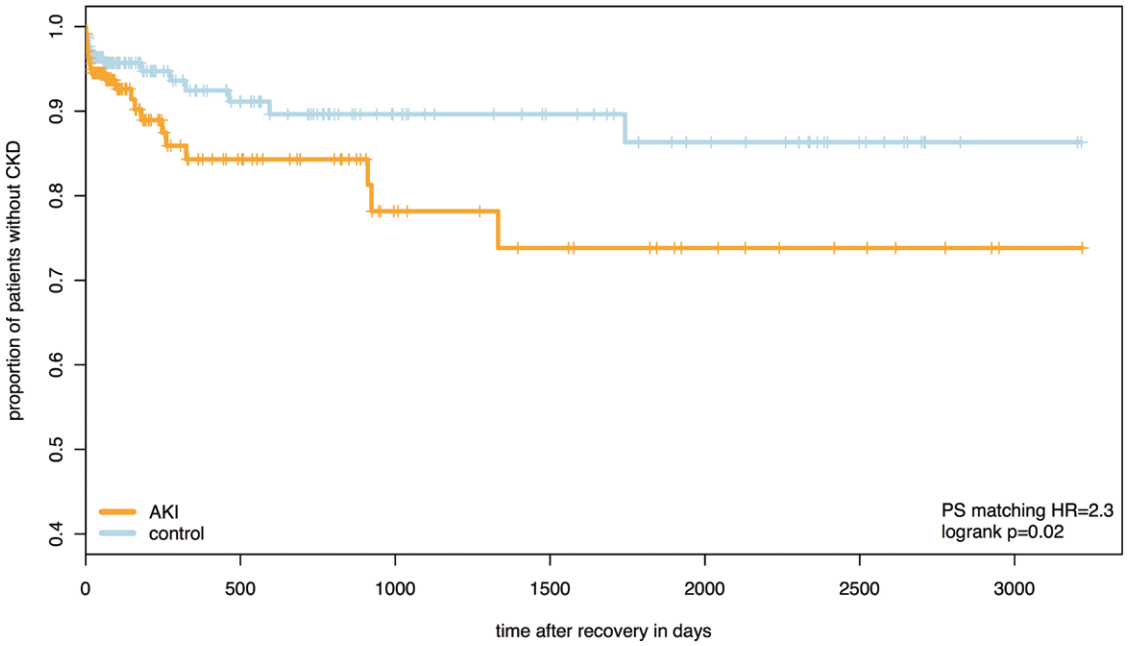

Fig. 3. Kaplan–Meier curve of chronic kidney disease (CKD) by exposure status (recovered acute kidney injury [AKI] group *vs.* controls) among matched cohort patients. HR = hazard ratio; PS = propensity score.

Table 2. Cumulative Incidence Risk and HRs for CKD by AKI Status among Matched Cohort (*P* Value Computed from Incidence Rate Ratio Using Poisson Regression)

	No. of CKD	HR for CKD Mean (95% CI)	Incidence Rate
With AKI (n = 597)	34	2.3 (1.9–2.6)	15.7
Without AKI (n = 597)	17	1 (reference)	5.1*

*$P < 0.0001$.

AKI = acute kidney injury; CKD = chronic kidney disease; HR = hazard ratio.

Impact of Severity of AKI

Regardless of AKI severity, HR for CKD was still significantly increased after a resolving episode of AKI: 2.3 (1.8 to 2.6) for AKI stage 1 and 11 (6 to 12) for AKI stages 2 and 3.

Sensitivity Analyses

We used a sensitivity analysis with Rosenbaum bounds to assess the potential effect of unmeasured confounders. Rosenbaum bounds suggested a γ value of 1.4. This means that for any unmeasured confounder that would explain a higher rate of CKD in the AKI population, the confounder would need to produce a 40% increase in the odds of undergoing AKI.

Discussion

Our study demonstrates that CKD-free adult patients developing AKI after elective cardiac surgery with CBP and then fully recovering from AKI are at increased risk of acquired stage 3 CKD or worse when compared to a similarly exposed AKI-free population of patients. As in several other studies published previously, this risk is high very early and CKD typically occurs within weeks post surgery.[2,7,11,31] Since baseline eGFR was well balanced between AKI and AKI-free patients, this study found that risk was not dependent on baseline renal function.

In our view, these data firmly consolidate the recent paradigm shift regarding the delayed outcome of AKI because of five methodological aspects inherent to the design of our study: (1) first, we purposely selected for study a unique and homogeneous circumstance where AKI was a risk; (2) we created and validated a propensity score for the development of AKI, and this allowed us to match every AKI patient with a control, which further reduced biases (in particular, AKI and non-AKI patients had similar age, preoperative eGFR, left ventricular ejection fraction, and European System for Cardiac Operative Risk Evaluation, and they underwent similar extracorporeal circulation and clamping times); (3) we did not use a diagnostic code system but used numerical values of serum creatinine and estimated values of GFR to identify AKI or CKD: thus, whether acute or chronic, any alteration of renal function was defined by objective biologic values; (4) we included all stages of AKI according to the sensitive and universal KDIGO criteria; (5) most importantly, we deliberately excluded patients who had not recovered their baseline renal function and matched the patients according to their postoperative eGFR.

Previous studies have strongly suggested a link between the occurrence of AKI and the development of CKD. Amdur *et al.*[17] reported an adjusted HR of 4 after an acute "tubular necrosis" or "renal failure" (using diagnostic codes) occurring in patients without preexistent CKD.[17] Ishani *et al.*[9] found an adjusted HR of 13 for a code of end-stage renal disease (ESRD) after AKI. Lastly, Wald *et al.*,[6] focusing on patients admitted to an intensive care unit and developing an AKI episode requiring renal replacement therapy, reported an adjusted HR of 3.2 for the risk of developing CKD and necessitating dialysis. It has to be noted that the risk of CKD occurs particularly early. Likewise, in 2011, based on eGFR values obtained after cardiac surgery, Ishani *et al.*[9] noted that AKI defined by an increase of 25 to 49% in serum creatinine *versus* baseline in the first 7 days resulted in a HR of 4 as early as 3 months post surgery.[2] In the most recently published study concerning the risk of AKI after cardiac surgery, HR for ESRD (identified by a diagnostic code) was 6.2 in patients with normal preoperative renal function.[31] Phenotyping these patients will be important so as to understand the etiology of such a rapid deterioration of renal function, in particular the characterization of urine (ions, quantity and type of proteinuria, and sediment). Since it is not known whether an episode of AKI impairs heart recovery after cardiac surgery and since AKI-triggered CKD has been reported to be severe enough to potentially result in ESRD, we are probably looking at parenchymal, not prerenal, renal failure.

The biologic mechanism(s) by which AKI precipitates the occurrence of CKD are being extensively studied. Despite efforts to match the AKI population with controls theoretically similarly prone to develop AKI/CKD, we may not rule out the possibility that the mean renal reserve is lower in the global AKI population[32] since screening of renal reserve is not routinely conducted before cardiac surgery. In further exploratory studies, amino acid loading could be considered before the scheduled circumstances that put patients at risk of AKI in order to test the hypothesis that an episode of AKI often merely reflects a nephron loss, low enough to escape detection using serum creatinine measures when patients are exposed to a hemodynamic challenge but high enough to induce AKI according to the most recent definition. Although this possibility seems likely (because the incidence of CKD occurs rapidly), the risk of AKI-induced CKD is similarly increased in the elderly and in children, which suggests that other mechanisms are also involved.[33,34]

Thus, although AKI resolves functionally within days or weeks, it may yet have triggered a strong profibrotic response, resulting in accelerated scarring of the kidneys. In the last 5 yrs, experimental studies have indeed documented what is now called a "maladaptive" repair. To name only a few of the mechanisms potentially at stake in mammals, it was found that even a transient episode of AKI could result in (1) an incapacity for tubular epithelial cells to resume normal production of energy[12]; (2) a cell cycle arrest or delay[14]; and (3) a reprogramming of myofibroblasts through the epigenetic silencing of *RASAL1*, a gene encoding a potent inhibitor of cell proliferation.[13] The latter, however, was reported as not occurring in the ischemic model of AKI. In sum, some patients with supposedly pristine kidneys might still evolve toward CKD *because of* (not only *after*) an episode of AKI.

Interestingly, we found a high incidence of CKD stage 3 in the group without AKI. This incidence is largely superior to that seen in the general population (51,000 and 5,000 per million person-years, respectively, for *de novo* CKD[35]).

In the case of cardiac surgery, AKI defined using the KDIGO criteria may only reflect the renal consequences of various injuries such as extracorporeal circulation or arterial clamping. These injuries probably act as a continuum limiting the traditional definition of AKI. A study addressing the impact of extracorporeal circulation *per se* on renal outcome long term is needed.

Our study has some limitations: (1) as the study is retrospective by nature, we may not exclude the possibility that an additional AKI occurred or that drugs interfering with glomerular filtration were introduced during the observation period. In any case, we believe there are sufficient data in the literature to require that patients developing AKI and recovering from it are put under close scrutiny; (2) the French law demands a "color-blind" model of data collection, which means that we did not apply the GFR-correcting factor for black patients. Nevertheless, the proportion of African-Americans in the population is small in France, and in our study, serum creatinine was assessed for each individual relative to his/her own baseline serum creatinine; (3) we censored our patients at the time of the last serum creatinine measurement available to avoid information bias caused by insufficient creatinine values (and thereby considering a patient CKD free where he is not), so the additional bias linked to informative censoring was therefore tested by IPCW Cox regression; (4) 1-month after surgery, there was no scheduled patient follow-up. Thus, the number of serum creatinine measurements differs between the patients developing AKI and their control. Nevertheless, the median duration of follow-up was the same. In the figure in Supplemental Digital Content 3 (http://links.lww.com/ALN/B324), we present the time distribution of GFR estimation according to AKI status; (5) for patients who required a blood transfusion in the perioperative period, the number of packed red cells was not available; (6) the existence of a residual confounding factor is not impossible because the scope of measured confounders is limited. However, to assess this risk, we performed a Rosenbaum bounds sensitivity analysis, allowing us to estimate the likelihood that an unknown confounder could explain the observed differences in CKD. A γ value of 1.4 between AKI and control patients, however, suggests that it is unlikely that an unknown confounder explains the results.

These findings tackle the issue of potential follow-up by a nephrologist after AKI even if the patient has totally recovered renal function. The value of specialist

follow-up after hospitalization for an array of acute conditions is well established in terms of mortality and rehospitalization.[36–38] While it is estimated that 76% of patients surviving a myocardial infarction are followed up by cardiologists, it is still not our routine practice to recommend that renal function of patients who fully recovered from an AKI be monitored in the following weeks or months.[39] For those experiencing a rapid decline in renal function, interventional studies—yet to be designed—are undoubtedly needed.

In summary, regardless of its severity, a fully recovering episode of AKI after cardiac surgery in patients without preexisting CKD is strongly associated with a subsequent increase in the risk of *de novo* CKD. Complementary research is required to understand the biologic mechanisms involved and to invent new therapeutic approaches.

Research Support

Support was provided solely from institutional and/or departmental sources.

Competing Interests

Dr. Hertig is the recipient of an Interface contract with the French National Institute of Health and Medical Research, Paris, France. The other authors declare no competing interests.

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