Supplementary File

Methods

The selection criteria for identifying patients with chronic kidney disease (CKD) and acute kidney disease (AKI) during index hospitalization were validated using the data of NSARF (the National Taiwan University Study Group on Acute Renal Failure),[1-5] a multi-center prospectively constructed database of AKI incidences between 2002 and 2010. Kidney function was ascertained using the consensus definition from the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation, and CKD, defined as an eGFR $\leqq$ 45 mL/min/1.73m^2.[6] AKI was classified according to the RIFLE (risk, injury, failure, loss, and end-stage) criteria, which was introduced by the Acute Dialysis Initiative Group as a standardized evaluation tool.[7] As in previous studies,[5, 8-10] we used the sRIFLE classification, in which creatinine was the only marker. Furthermore, AKI were stratified according to the maximum sRIFLE classification during the hospital admission.[11] The baseline serum creatinine (sCr) was the nadir value obtained from the previous admission in those who had more than one admission within one year before the index admission,[8] or the nadir sCr value during the admission after emergency department measurement.[12, 13] A baseline sCr $\geqq$ 4.0 mg/dL with an acute rise of at least 0.5 mg/dL[7] or those received acute dialysis during index hospitalization were defined as “failure.”

To further explore the association of preexisting kidney function with the incidence of coronary events, we drew conditional effect plots for outcome predictions based on the fitted final logistic regression models. Each model estimated probability of having coronary events against a chosen continuous covariate, with the values of the other discrete and continuous covariates held constant.[1] We adjusted eGFR as a continuous

variable. We also adjusted for proteinuria, and classified severity into three levels: no proteinuria (negative), mild proteinuria (trace to 1+), and heavy proteinuria (2+ to 4+).[1] The test strips were measured by an automatic dipstick auto-analyzer (AUTION MAX, AX-4030, ARKRAY. Inc., Kyoto, Japan) with automatic correction of the specific gravity using the pH test pad in a routine laboratory environment. This classification was adopted in a large epidemiologic study in Alberta, Canada.[14]

Results

Validation of CKD code by NSARF

Among 27,065 enrollees from NSARF with or without AKI during their index hospitalization, 1,474 patients fulfilled the criteria of pre-existing CKD by CKD-EPI definition, and 1,382 had National Health Insurance (NHI) claims data with CKD diagnosis.[15] The 1,382 patients had 1,206 true, and 176 false-positive cases. Analysis of performance of identifying CKD based on NHI data revealed a sensitivity of 81.8%, a specificity of 99.3%, a positive predictive value of 87.3%, and a negative predictive value of 99.0%.

Validation of AKI code by NSARF

Among all enrollees from NSARF with or without AKI during their index hospitalization, 10,675 patients fulfilled the criteria of AKI or acute dialysis by RIFLE definition, and 5,230 had NHI claims data with AKI diagnosis or acute dialysis procedure. The 5,230 patients had 4,990 true and 240 false-positive cases. Identifying AKI based on NHI data had a positive predictive value of 98.5%, and a negative predictive value of 74.0%.

Conditional effect plots predicting coronary events.

Figure S1 illustrates a conditional effect plot of the estimated risk levels for long-term coronary events stratified by dialysis requiring AKI and DM, against patients' baseline kidney function, adjusted for the other factors listed in Table 1 and the APACHII score at ICU admission. Results from our multiple logistic regression model using data for the 27,065 enrollees in NSARF suggest that, in the long term, the incidence probabilities of coronary events were similar among those with DM alone (i.e., without AKI) and among those with AKI alone (i.e., without DM). Either DM or AKI significantly increased the incidence probability of coronary event occurrence. Furthermore, coexistence of the two conditions expanded the harmful effect in a pattern close to a multiplicative model in which the combined effect of two or more factors is the product of effects from these factors. The risk of detrimental effect was larger among patients with worse kidney function, in terms of the increased probability of occurring coronary events.

We further analyzed the relationships of AKI, baseline kidney function, and severity of proteinuria with the incidence probability of coronary event, with adjustment for the other factors listed in Table 1 and the APACHII score at ICU admission. The results reveal that even AKI with recovery (AKI-recovery) had an association with long-term coronary events (OR relative to non-AKI, 2.22, 95% CI, 1.25-3.94, $p = 0.006$)), independent of the effects of DM (OR, 2.55, 95% CI, 1.84-3.53, $p < 0.001$), mild proteinuria (OR, 1.61, 95% CI, 1.10-2.36, $p = 0.015$), and heavy proteinuria (OR, 2.18, 95% CI, 1.30-3.67, $p = 0.003$). The conditional effect plot is shown in Figure S2.

Survival probability of freedom from coronary events based on Kaplan-Meier

analysis using the NHI database

In addition to using a post-estimation simulation approach based on cox regression with time-varying covariates to depict the probability curves of freedom from coronary events under different scenarios of morbid conditions in regard to DM, AKI, CKD and ESRD (as reported in the text), we also used the Kaplan-Meier method, a relatively simple non-parametric approach, to draw the survival curves of freedom from coronary events separately for the AKI-dialysis recovery and the non-AKI groups. Results from using the long-rank test to test the homogeneity between the two survival curves indicate a significant difference between the two groups (long-rank test *p*-value <0.001; Figure S3).

Supplementary tables and figures

Table S1. The non-parsimonious propensity model* of predicting dialysis at index hospitalization

	OR	lower 95% CI	upper 95% CI	p
Mal	1.11	1.04	1.18	<0.001
Age (per year)	1.02	1.02	1.02	<0.001
Premorbid risk				
Charlson score	1.25	1.21	1.29	<0.001
Congestive heart failure	1.87	1.67	2.08	<0.001
Dementia	0.67	0.54	0.82	<0.001
COPD	0.55	0.50	0.61	<0.001
Rheumatologic disease	2.23	1.73	2.83	<0.001
Hemiplegia	0.69	0.52	0.91	0.009
Tumor	0.82	0.69	0.98	0.030
Diabetes Mellitus	2.28	2.10	2.48	<0.001
Moderate or Severe liver disease	2.64	2.10	3.28	<0.001
Chronic Kidney disease	5.37	4.72	6.11	<0.001
Index hospital co-mobility				
Respiratory	2.69	2.46	2.94	<0.001
Neurologic	2.41	1.89	3.04	<0.001
Hematologic	2.99	2.30	3.84	<0.001
Metabolic	14.08	11.27	17.51	<0.001
Operative categories				
Cardiothoracic	1.23	1.02	1.48	0.027
Upper GI	0.49	0.35	0.67	<0.001
Hepatobiliary	0.56	0.43	0.72	<0.001
ICU admission during index hospitalization	19.79	18.48	21.20	<0.001

*Estimated area under the curve of receiver operating characteristics [eAUC-ROC] =0.941; adjusted generalized R^2 = 0.355.

Abbreviations: AKI, acute kidney injury; COPD, chronic obstructive pulmonary disease; ESRD, end stage renal disease; GI, Gastrointestinal; ICU, intensive care unit; OR, odds ratio.

Table S2. Long-term probabilities of freedom from coronary events under different scenarios of morbid conditions in regard to DM, AKI, CKD and ESRD

Disease /condition	DM	Inpatient AKI	Subsequent CKD		Subsequent ESRD					
Time span	whole duration	whole duration	years 1-4	years 5-10	years 1-4	years 5-8	years 9-10		proportion with no coronary events end of year 5	proportion with no coronary events end of observation[#]
Reference	no	no	no			no			96.78%	92.68%
Scenario 1a	no	yes	no			no			94.69%	88.10%
Scenario 1b	no	yes	no	yes		no		CKD beginning in year 5	94.09%	84.59%
Scenario 1c	no	yes	yes			no			92.28%	82.97%
Scenario 1d	no	yes	no	yes	no	no	yes	CKD beginning in year 5; ESRD beginning in year 9	94.09%	79.45%
Scenario 1e	no	yes	yes		no	yes	yes	ESRD beginning in year 5	90.30%	72.22%
Scenario 2a	yes	yes	no			no			89.75%	77.77%
Scenario 2b	yes	yes	no	yes		no		CKD beginning in year 5	88.63%	71.74%
Scenario 2c	yes	yes	yes			no			85.29%	69.04%
Scenario 2d	yes	yes	no	yes	no	no	yes	CKD beginning in year 5; ESRD beginning in year 9	88.63%	63.22%
Scenario 2e	yes	yes	yes		no	yes	yes	ESRD beginning in year 5	81.69%	52.32%
Scenario 3a	yes	no	no			no			93.72%	86.01%
Scenario 3b	yes	no	no	yes		no		CKD beginning in year 5	93.01%	81.96%
Scenario 3c	yes	no	yes			no			90.89%	80.09%
Scenario 3d	yes	no	no	yes	no	no	yes	CKD beginning in year 5; ESRD beginning in year 9	93.01%	76.05%
Scenario 3e	yes	no	yes		no	yes	yes	ESRD beginning in year 5	88.57%	67.89%

[#] 3528 days~9 years and 8 months

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; DM, diabetic mellitus; ESRD, end stage renal disease.

Figure S1.

Conditional effect plot showing the relationships of baseline kidney function, DM and AKI with the incidence probability of coronary events among 27,065 enrollees in NSARF, with adjustment for the other factors listed in Table 1 and the APACHII score at ICU admission, based on the fitted multiple logistic regression model (AKI, acute kidney injury; DM, diabetic mellitus; eGFR, estimated glomerular filtration rate)

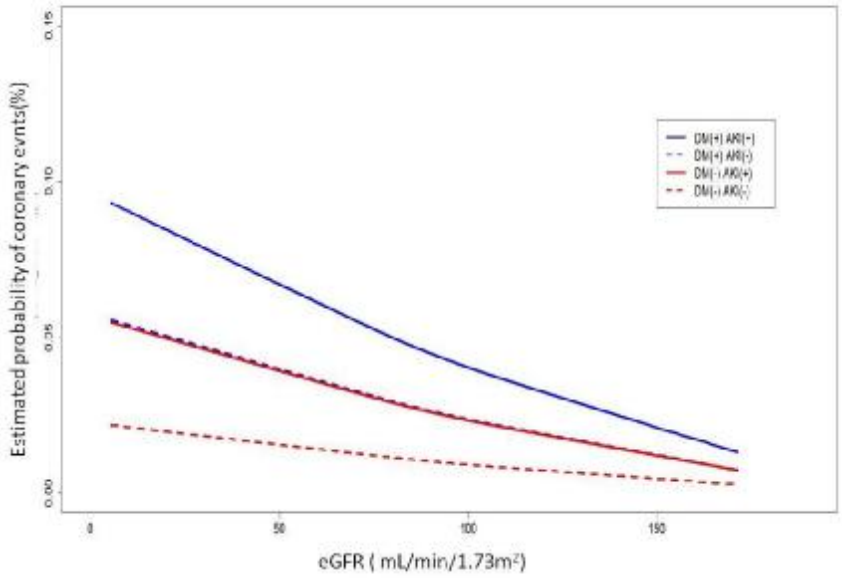


Figure S2.

Conditional effect plot showing the relationships of AKI, baseline kidney function, and severity of proteinuria with the incidence probability of coronary events among 27,065 enrollees in NSARF, with adjustment for the other factors listed in Table 1 and the APACHII score at ICU admission, based on the fitted multiple logistic regression model (AKI, acute kidney injury; eGFR, estimated glomerular filtration rate)

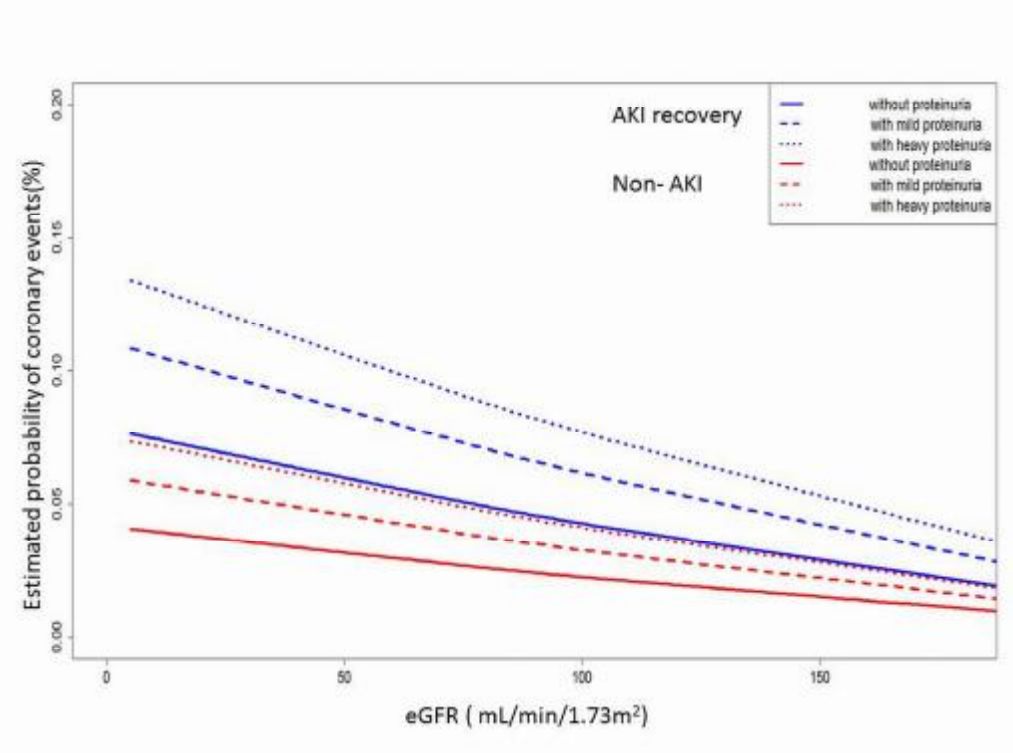
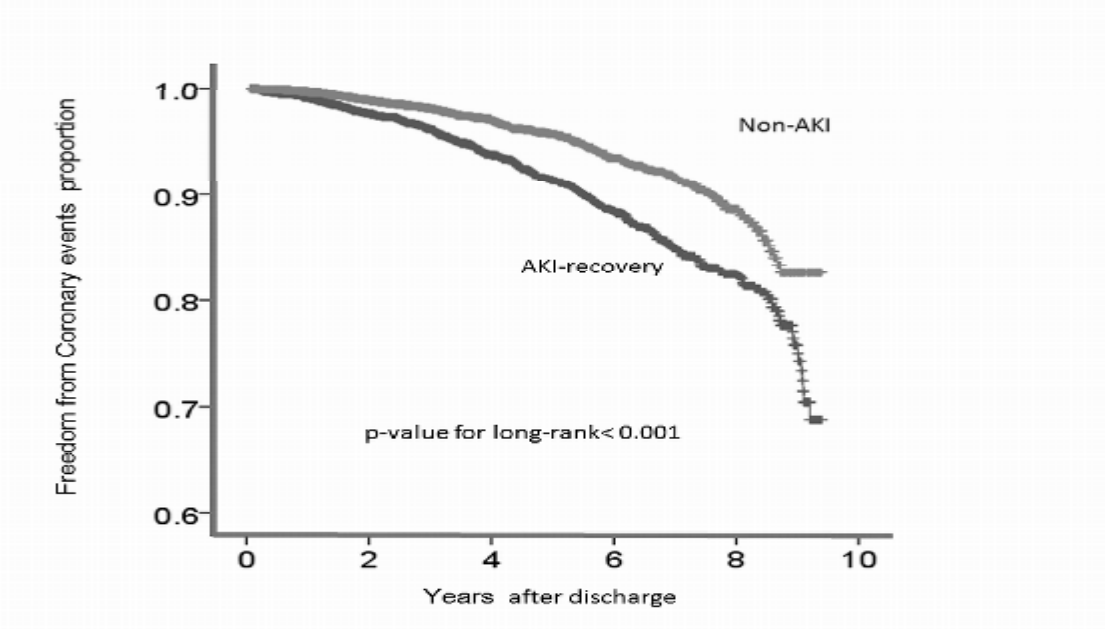


Figure S3.

Kaplan-Meier curves of freedom form coronary events in AKI-recovery and non-AKI groups (*p*-value for long-rank<0.001)



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