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Acute Kidney Injury Duration and 20-Year Risks of CKD and Cardiovascular Disease

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Introduction: Acute kidney injury (AKI) is associated with chronic kidney disease (CKD) and cardiovascular disease (CVD); however, it is unclear whether AKI duration affects the long-term risks of CKD and CVD. Therefore, we performed a population-based cohort study examining the associations between AKI duration and CKD and CVD.

Methods: We identified patients with laboratory-recorded AKI in Denmark from 1990 through 2018. AKIs were categorized as rapid reversal AKI (≤48 hours), persistent AKI (2–7 days), and acute kidney disease (AKD) (>7 days). We estimated 20-year risks and adjusted hazard ratios (aHRs) of incident CKD and CVD.

Results: The study comprised 169,582 patients with AKI, with 100,478 and 76,838 included in the analysis of CKD and CVD, respectively. The 20-year risks of CKD were 26.3%, 29.5%, and 28.7% for rapid reversal AKI, persistent AKI, and AKD, respectively. Compared with rapid reversal AKI, aHRs were 1.13 (95% confidence interval [CI], 1.08–1.19) for persistent AKI and 1.36 (95% CI, 1.30–1.41) for AKD. Risks and rates of overall CVD were similar for rapid reversal AKI, persistent AKI, and AKD. However, persistent AKI was associated with a slightly increased aHR of heart failure (1.09; 95% CI, 1.02–1.16), and aHRs of heart failure, ischemic heart disease, and peripheral artery disease were slightly increased for AKD (1.09 [95% CI, 1.03–1.15], 1.11 [95% CI, 1.03–1.19], and 1.10 [95% CI, 1.02–1.17], respectively).

Conclusion: AKI duration was associated with development of CKD, but not overall CVD; however, rates of heart failure, ischemic heart disease, and peripheral artery disease increased slightly with AKI duration.

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Recovery of kidney function after AKI is crucial, and CKD is a serious complication occurring in approximately 15% of patients within 5 years after AKI.[1,2] Moreover, AKI is associated with an increased risk of CVD[3–9] and death.[1,9,10]

The Kidney Disease: Improving Global Outcomes (KDIGO) creatinine criteria for AKI incorporates 3 stages for the assessment of AKI severity based on the magnitude of changes in serum creatinine.[11] However, the duration of AKI may be another important aspect of AKI severity and has been associated with mortality.[12–16] Furthermore, AKI duration could be associated with the development of CKD and CVD.[17–32] However, previous studies of the association between AKI duration and CKD lack consistency.[17–28,32] Moreover, only a few studies have examined an association between AKI duration and CVD.[19,29–31] Overall, the application of findings from studies examining the associations between AKI duration and CKD or CVD is limited by the inclusion of highly selected patient populations[17–20,22–25,29–33] and the use of nonconsensus definitions of AKI or AKI duration.[17–22,25,26,30,33] In addition, most studies were small (<1000 AKI cases)[17,18,20,22–24,30,31,33] and only assessed the development of CKD and CVD within a few years after AKI.[18,21–25,27,29,32] To our knowledge, no studies have assessed the long-term associations between AKI duration and CKD and CVD in a general population setting using the Acute Disease Quality Initiative consensus definition of AKI duration.[12]

Information on the associations between AKI duration and long-term risks of CKD and CVD could help inform both patients and physicians about the

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prognosis following AKI and assist in the planning of nephrology follow-up with current guidelines recommending evaluation of kidney function 3 months after AKI for all patients.[11] In addition, insights into the effect of AKI duration on the development of CKD and CVD could identify a potential target for AKI-directed treatment. Accordingly, these issues are highlighted as areas of importance in the proposed scope of work for the 2023 update of the KDIGO guideline for AKI.[34] Therefore, this study aimed to examine whether AKI duration is a long-term risk factor for CKD and CVD.

METHODS

Study Design and Setting

We conducted this population-based cohort study in Denmark (adult population: 4.6 million in 2018[35]) using population-based registries.[36] Denmark has a public health care system providing tax-funded general and specialized health care to all residents.[36] Since 1968, all Danish residents have been assigned a civil registration number in the Danish Civil Registration System at birth or upon immigration enabling unambiguous linkage of information across registries.[37]

Plasma creatinine (pCr) tests performed in primary care and at hospitals in Denmark are collected and analyzed at central hospital–based laboratories from where test results are made available electronically to the treating physicians and recorded in research databases. For this study, we used information on pCr test results from the Clinical Laboratory Information System Research Database[38] and the Register of Laboratory Results for Research.[39] The regional laboratory database, Clinical Laboratory Information System Research Database, holds blood test results from 2 of 5 Danish regions (the North Denmark Region and the Central Denmark Region) since the 1990s,[38,40] whereas the nationwide laboratory database Register of Laboratory Results for Research has complete information on blood test results from all Danish regions since October 2015.[40]

The study was approved by the Danish Data Protection Agency (record number 2015–57–0002) through registration at Aarhus University (record number 2016-051-000001/812). In Denmark, registry-based observational studies do not require ethical approval or informed consent from participants.

Study Population

The study population included patients aged ≥18 years with the following: (i) a first-time laboratory-recorded AKI between January 1, 1990, and December 31, 2018; (ii) an outpatient (from primary care and planned outpatient hospital visits) pCr test 8 to 365 days before AKI; and (iii) an assessment of AKI duration by 1 or more pCr tests within the first 7 days after AKI onset. For each outcome, only patients without a history of the disease of interest at the start of follow-up 90 days after AKI were included in the analysis. For CKD, this excluded patients with prevalent kidney disease or ≥2 outpatient estimated glomerular filtration rate (eGFR) of <60 ml/min per 1.73 m^2 separated by at least 90 days. Patients with AKI who did not have an outpatient baseline pCr test or an assessment of AKI duration or who were censored before the start of follow-up were characterized but not included in the analyses of outcomes following AKI.

AKI

AKI was defined by implementing the KDIGO creatinine criteria as either of the following: (i) an absolute increase of ≥26.5 μmol/l within 48 hours; (ii) a relative increase of ≥1.5 times the lowest pCr test within the preceding 7 days; or (iii) a relative increase of ≥1.5 times baseline pCr, which was defined as the median outpatient pCr level 8 to 365 days before AKI.[11] To ensure inclusion of incident AKIs, we only considered AKIs with onset >90 days after the patient's first recorded pCr test and with no pCr test fulfilling the AKI definition in that period. pCr tests from patients with kidney failure were censored (see definition of kidney failure in the Outcomes section).

Analyses were stratified by AKI stage, location, and setting. AKI stage was defined according to the KDIGO criteria based on changes in pCr or initiation of kidney replacement therapy.[41] In terms of location, AKI was categorized as community-acquired if it occurred on a day without hospitalization or on the first day of hospitalization; as hospital-acquired if AKI onset was more than 1 day after hospitalization; and as intensive care unit–acquired if it occurred more than 1 day after admission to an intensive care unit. The setting of AKI was categorized as surgery-related if AKI occurred within 7 days after a major surgery and as sepsis-related if it occurred during a hospitalization with a registered code for a sepsis diagnosis.[42] Patients could be included in both categories.

AKI Duration

In accordance with the Acute Disease Quality Initiative 16 Workgroup consensus report,[12] we categorized AKI based on 3 duration groups as follows: (i) Rapid reversal AKI, if a pCr test ≤48 hours after AKI onset did not fulfill the AKI criteria and this reversal was followed by ≥48 hours without a new pCr test fulfilling the AKI criteria; (ii) persistent AKI, if not fulfilling (i) and a pCr test within 2 to 7 days after AKI onset did not fulfill the AKI criteria and this reversal was followed by ≥48 hours without a new pCr test

fulfilling the AKI criteria; and (iii) AKD, if neither (i) nor (ii) were fulfilled.

Outcomes

Study outcomes included CKD, kidney failure, and overall and specific CVDs. CKD was defined as follows: (i) ≥2 outpatient eGFR of <60 ml/min per 1.73 m^2 separated by a least 90 days; (ii) a diagnosis of CKD stage 3 to 5, dependency on dialysis, or kidney transplantation; or (iii) a procedure code for dialysis due to CKD or kidney transplantation. Similarly, kidney failure was defined as follows: (i) ≥2 outpatient eGFR of <15 ml/min per 1.73 m^2 separated by a least 90 days; (ii) a diagnosis of CKD stage 5, kidney transplantation, or dependency on dialysis; or (iii) a procedure code for dialysis due to CKD or kidney transplantation (Supplementary Table S1). The time of CKD or kidney failure was defined as the date of the first defining diagnosis or procedure code or the date of the defining eGFR measurement more than 90 days after the first defining eGFR measurement. eGFR was calculated from pCr, age, and sex using the CKD Epidemiology Collaboration equation assuming non-Black race.[43] Only pCr tests from primary care and planned outpatient hospital visits were included in the evaluation of CKD and kidney failure as the CKD Epidemiology Collaboration equation assumes a steady state.[43]

CVD was assessed overall and by specific conditions, including atrial fibrillation or flutter, ischemic heart disease, heart failure, stroke, and peripheral artery disease. CVD outcomes were defined by hospital diagnoses and procedures retrieved from the Danish National Patient Registry (Supplementary Table S1).[44] The Danish National Patient Registry includes, among other variables, information on admission and discharge dates, primary and secondary disease diagnoses, examinations, and procedures, including dialysis, from all nonpsychiatric hospital admissions since 1977.

Covariates

We included information on a range of covariates, including potential confounders. Age, sex, and time of death were obtained from the Civil Registration System.[36] Information on hospital-diagnosed conditions within 10 years before the start of follow-up was added from the Danish National Patient Registry.[44] Prescriptions for relevant medications filled within 90 days before the start of follow-up were included from the Danish National Prescription Registry, which contains individual-level information on all prescriptions for drugs sold in Danish pharmacies or used at nursing homes since 1995.[45] Diabetes and markers of smoking were defined using a combination of hospital diagnoses and prescription drug use. Codes used for defining comorbidities and prescription drug use are provided in Supplementary Table S1.

Statistical Analyses

Characteristics at the start of follow-up, including age, sex, specific comorbidities and prescription drugs, baseline eGFR, and AKI stage, location, and setting, were tabulated according to AKI duration. The characteristics were summarized as medians with interquartile range for continuous variables, and as counts with percentages for categorical variables. Among patients without a history of the disease of interest, we computed and plotted the 20-year cumulative incidence (risk) of CKD and CVD by AKI duration group using the Aalen-Johansen estimator treating death as a competing event.[46] Crude and adjusted hazard ratios were computed using Cox regression adjusting for confounders, including age, sex, calendar year, atrial fibrillation or flutter, ischemic heart disease, heart failure, stroke, peripheral artery disease, hypertension, chronic obstructive pulmonary disease, chronic liver disease, rheumatoid arthritis or connective tissue disease, cancer, diabetes, markers of smoking, baseline eGFR (using a penalized spline), AKI stage, AKI location, AKI setting, and prescription drugs listed in Table 1.[47] In addition, models for CVDs were adjusted for prevalent kidney disease, including diabetic nephropathy, hypertensive kidney disease, glomerular disease, tubulointerstitial disease, and congenital kidney disease. Assumptions of proportional hazards were checked using plots of Schoenfeld residuals and found appropriate. For all outcomes, the start of follow-up was defined as 90 days after AKI onset to enable assessment of AKI duration and allow for transition to a stable kidney function for patients with an AKI duration beyond 7 days. Follow-up ended at the time of the outcome of interest, death, emigration, or end of the study period. The main analyses were stratified by age groups (<40, 40–59, 60–79, ≥80 years), sex, baseline eGFR groups (<30, 30–44, 45–59, ≥60 ml/min per 1.73 m^2), and AKI stage, location, and setting. Length of follow-up, number of pCr tests during the 7 days after AKI onset, and number of outpatient tests during follow-up were presented as medians with interquartile ranges.

To examine whether the association between AKI and CKD as well as CVD varied with the recency of the baseline pCr test, we conducted a sensitivity analysis including only patients with a baseline pCr test within 90 days before AKI. In addition, we performed a sensitivity analysis where CKD was defined only according to outpatient eGFR measurements.

The analysis method and standardization of pCr tests changed during the study period.[48] Enzymatic methods

Table 1. Characteristics of patients with acute kidney injury

Characteristics	All	Rapid reversal AKI	Persistent AKI	AKD
Number of patients	169,582 (100)	36,514 (22)	22,619 (13)	110,449 (65)
Female	88,711 (52)	19,559 (54)	12,476 (55)	56,676 (51)
Age, median (IQR)	72 (62, 80)	72 (62, 80)	74 (65, 82)	72 (62, 80)
Age groups				
<40 yr	8287 (5)	1938 (5)	766 (3)	5583 (5)
40–59 yr	27,216 (16)	5710 (16)	2958 (13)	18,548 (17)
60–79 yr	89,344 (53)	19,258 (53)	11,976 (53)	58,110 (53)
≥80 yr	44,735 (26)	9,608 (26)	6,919 (31)	28,208 (26)
Comorbidity				
Chronic kidney disease[a]	62,666 (37)	12,903 (35)	9858 (44)	39,905 (36)
Other kidney disease[b]	15,559 (9)	2553 (7)	1908 (8)	11,098 (10)
Cardiovascular disease				
Ischemic heart disease	41,757 (25)	9870 (27)	7032 (31)	24,855 (23)
Heart failure	29,850 (18)	6535 (18)	4824 (21)	18,491 (17)
Atrial fibrillation or flutter	36,633 (22)	8276 (23)	5815 (26)	22,542 (20)
Stroke	19,417 (11)	4296 (12)	2790 (12)	12,331 (11)
Peripheral artery disease	20,658 (12)	4778 (13)	3426 (15)	12,454 (11)
Hypertension	73,241 (43)	16,176 (44)	10,446 (46)	46,619 (42)
Diabetes[c]	40,244 (24)	8133 (22)	5208 (23)	26,903 (24)
COPD	27,302 (16)	6340 (17)	3844 (17)	17,118 (15)
Chronic liver disease	6861 (4)	1327 (4)	754 (3)	4780 (4)
Cancer	47,298 (28)	10,479 (29)	6660 (29)	30,159 (27)
Rheumatoid arthritis or connective tissue disease	10,914 (6)	2378 (7)	1404 (6)	7132 (7)
Markers of smoking[c]	32,051 (19)	7418 (20)	4418 (20)	20,215 (18)
Prescription drug use				
ACEIs/ARBs	58,839 (35)	12,883 (35)	8090 (36)	37,866 (34)
Diuretics (thiazides and loops)	78,072 (46)	16,172 (44)	11,530 (51)	50,370 (46)
NSAIDs	18,849 (11)	3723 (10)	2258 (10)	12,868 (12)
Antibiotics	63,062 (37)	13,631 (37)	8388 (37)	41,043 (37)
Statins	46,426 (27)	10,425 (29)	6693 (30)	29,308 (27)
Cytostatic treatment	7912 (5)	1804 (5)	1023 (5)	5085 (5)
Baseline kidney function				
Baseline pCr (μmol/l), median (IQR)	133 (104, 177)	114 (92, 142)	128 (102, 162)	143 (110, 195)
Baseline eGFR (ml/min per 1.73 m^2), median (IQR)	71 (51, 91)	70 (51, 91)	64 (46, 85)	73 (52, 92)
Baseline eGFR group				
≥60 ml/min per 1.73 m^2	107,415 (63)	23,084 (63)	12,435 (55)	71,896 (65)
45–59 ml/min per 1.73 m^2	31,584 (19)	7067 (19)	4718 (21)	19,799 (18)
30–44 ml/min per 1.73 m^2	21,610 (13)	4697 (13)	3787 (17)	13,126 (12)
<30 ml/min per 1.73 m^2	8973 (5)	1666 (5)	1679 (7)	5628 (5)
Acute kidney injury				
Location				
Community	81,645 (48)	4855 (13)	1687 (8)	75,103 (68)
Hospital	77,414 (46)	27,637 (76)	17,732 (78)	32,045 (29)
ICU	10,523 (6)	4022 (11)	3200 (14)	3301 (3)
Setting				
Sepsis-related	9582 (6)	1942 (5)	1189 (5)	6451 (6)
Surgery-related	47,431 (28)	15,401 (42)	10,730 (47)	21,300 (19)
Other	114,112 (67)	19,612 (54)	11,030 (49)	83,470 (76)
AKI stage				
Stage 1	117,515 (69)	33,315 (91)	17,253 (76)	66,947 (61)
Stage 2	31,903 (19)	2527 (7)	4066 (18)	25,310 (23)
Stage 3	20,164 (12)	672 (2)	1300 (6)	18,192 (16)

ACEI, angiotensin-converting enzyme inhibitor; AKD, acute kidney disease; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; pCr, plasma creatinine.
[a]Based on diagnoses and pCr tests.
[b]Including diabetic nephropathy, hypertensive kidney disease, glomerular disease, tubulointerstitial disease, and congenital kidney disease.
[c]Based on diagnosis and prescription drug use.
Values are *n* (%) unless indicated otherwise.

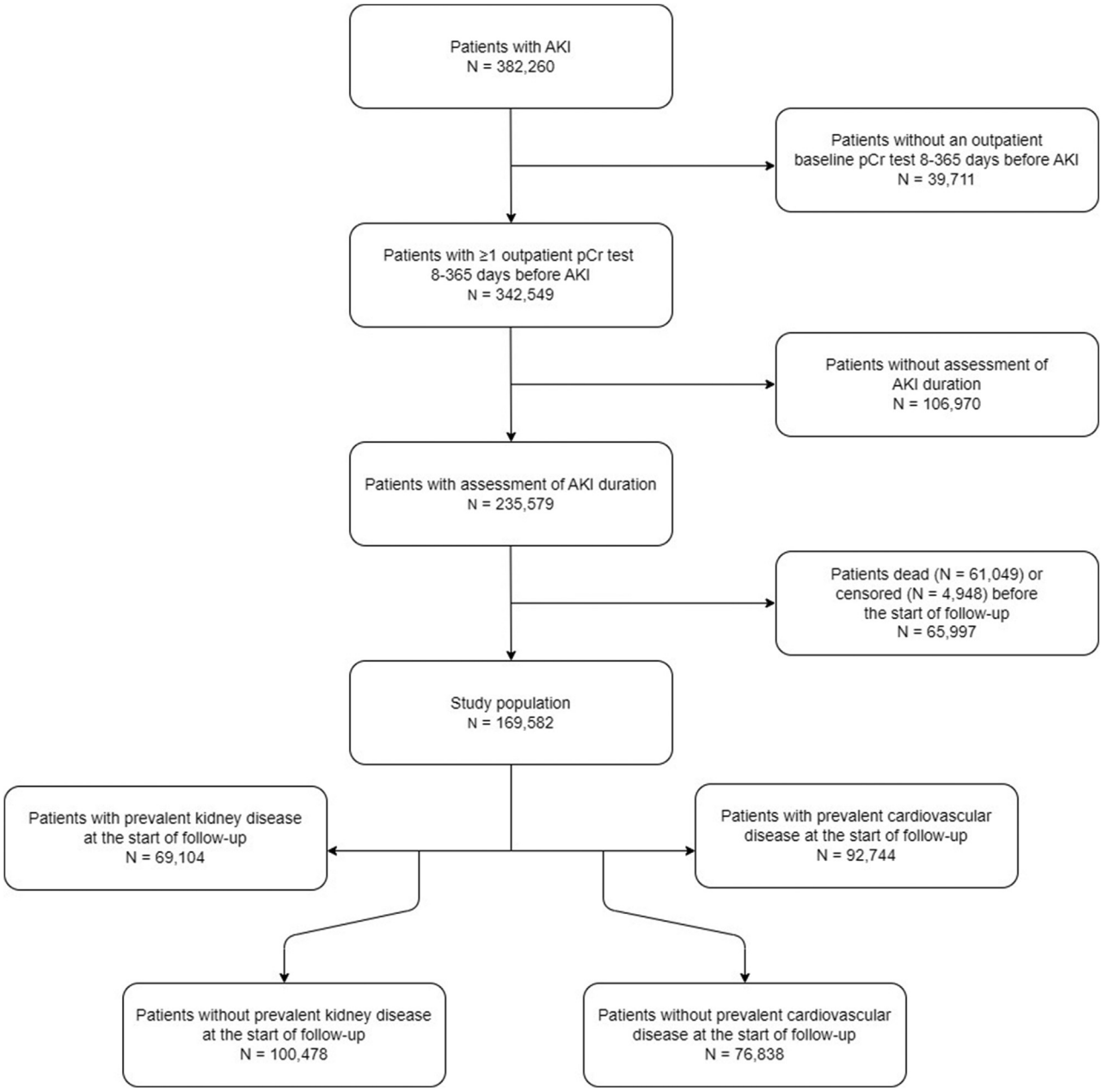

Figure 1. Flowchart of patients with acute kidney injury. AKI, acute kidney injury; pCr, plasma creatinine.

Table 2. Twenty-year risks and HRs of chronic kidney disease and kidney failure

	Patients at risk	Events	Risk % (95% CI)	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
Chronic kidney disease					
Rapid reversal AKI	22,467	3990	26.3 (25.4–27.2)	1 (reference)	1 (reference)
Persistent AKI	12,106	2667	29.5 (28.4–30.6)	1.23 (1.17–1.29)	1.13 (1.08–1.19)
AKD	65,905	13,417	28.7 (28.2–29.2)	1.17 (1.13–1.22)	1.36 (1.30–1.41)
Kidney failure					
Rapid reversal AKI	36,398	915	4.7 (4.3–5.1)	1 (reference)	1 (reference)
Persistent AKI	22,500	899	6.0 (5.6–6.4)	1.53 (1.40–1.68)	1.19 (1.08–1.30)
AKD	109,133	4183	6.3 (6.0–6.5)	1.57 (1.46–1.68)	1.56 (1.44–1.69)

AKD, acute kidney disease; AKI, acute kidney injury; CI, confidence interval; HR, hazard rate.
[a]Adjusted for age, sex, calendar year, ischemic heart disease, heart failure, atrial fibrillation or flutter, peripheral artery disease, hypertension, chronic obstructive pulmonary disease, chronic liver disease, rheumatoid arthritis or connective tissue disease, cancer, diabetes, markers of smoking, baseline eGFR, AKI stage, AKI location, AKI setting, and prescription drugs listed in Table 1.

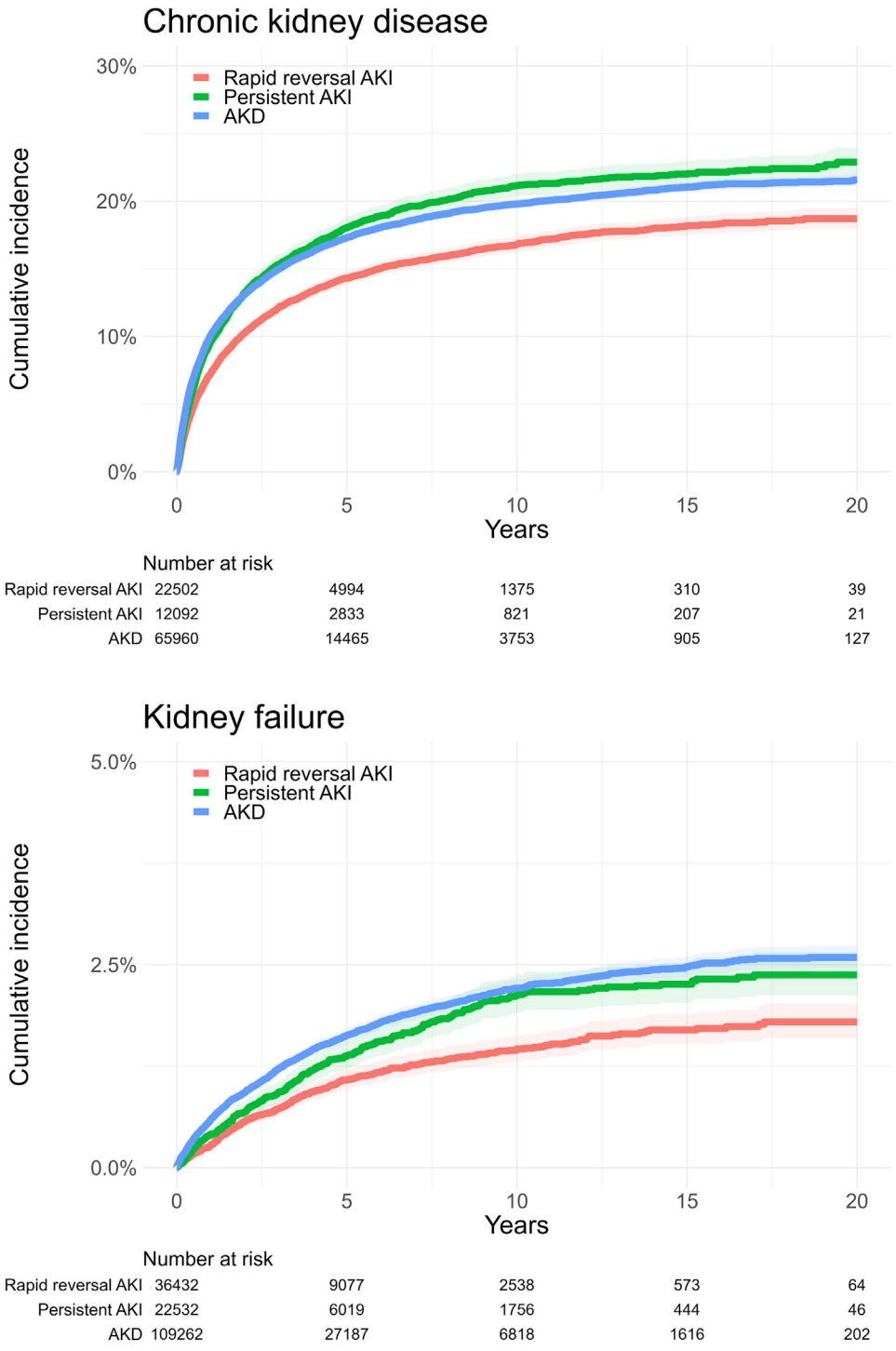

Figure 2. Twenty-year risks of chronic kidney disease and kidney failure. AKD, acute kidney disease; AKI, acute kidney injury.

and isotope dilution mass spectrometry standardization were fully implemented in all Danish laboratories on April 1, 2010. To evaluate whether changing standards of pCr assessment affected the evaluation of CKD and kidney failure, we performed a sensitivity analysis only including patients with first-time laboratory-recorded AKI after April 1, 2010.

Analyses and illustrations were performed using R version 4.2.2 (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; www.R-project.org). The manuscript was written in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.[49]

RESULTS

The study population comprised 169,582 patients with a first-time laboratory-recorded AKI after excluding patients without an outpatient baseline pCr test within

Table 3. Stratified 20 risks and HRs of chronic kidney disease

		Rapid reversal AKI		Persistent AKI		AKD	
	Patients at risk	Risk % (95% CI)	Adjusted HR[a] (95% CI)	Risk % (95% CI)	Adjusted HR[a] (95% CI)	Risk % (95% CI)	Adjusted HR[a] (95% CI)
Age groups							
<40 yr	7248	12.8 (8.2–20.0)	1 (reference)	22.7 (14.9–34.5)	1.49 (1.02–2.18)	18.6 (15.3–22.7)	1.69 (1.25–2.27)
40–59 yr	21,494	25.4 (22.5–28.6)	1 (reference)	28.4 (24.4–33.2)	1.20 (1.06–1.37)	29.0 (27.5–30.6)	1.53 (1.39–1.70)
60–79 yr	51,503	29.7 (28.6–30.9)	1 (reference)	32.3 (30.9–33.8)	1.10 (1.03–1.17)	31.1 (30.5–31.8)	1.31 (1.24–1.38)
≥80 yr	20,233	23.1 (21.8–24.5)	1 (reference)	26.4 (24.8–28.2)	1.09 (0.99–1.21)	26.6 (25.8–27.5)	1.28 (1.18–1.39)
Sex							
Female	37,378	34.8 (33.2–36.4)	1 (reference)	36.8 (34.9–38.8)	1.10 (1.02–1.17)	36.9 (36.0–37.8)	1.41 (1.33–1.49)
Male	63,100	20.9 (19.8–22.0)	1 (reference)	25.2 (23.9–26.6)	1.16 (1.08–1.25)	24.0 (23.4–24.7)	1.29 (1.22–1.37)
AKI stage							
1	69,518	26.4 (25.5–27.4)	1 (reference)	29.7 (28.4–31.1)	1.15 (1.09–1.22)	27.8 (27.1–28.5)	1.33 (1.27–1.40)
2	20,366	24.2 (21.4–27.3)	1 (reference)	28.7 (26.5–31.0)	1.14 (0.99– 1.31)	30.0 (29.0–31.0)	1.53 (1.35– 1.73)
3	10,594	29.0 (23.1–36.6)	1 (reference)	29.4 (25.4–34.0)	0.98 (0.74–1.29)	30.6 (29.2–32.0)	1.28 (1.01–1.62)
Location							
Community	49,236	24.5 (21.9–27.3)	1 (reference)	26.9 (22.9–31.5)	1.05 (0.87–1.26)	27.4 (26.8–28.1)	1.15 (1.05–1.27)
Hospital	44,854	26.4 (25.4–27.4)	1 (reference)	28.7 (27.5–29.9)	1.15 (1.08–1.21)	31.0 (30.1–31.9)	1.42 (1.36–1.50)
ICU	6388	29.0 (25.1–33.4)	1 (reference)	36.7 (33.1–40.6)	1.17 (1.02–1.33)	36.8 (33.4–40.6)	1.41 (1.23–1.62)
Setting							
Sepsis-related	4685	24.9 (20.1–30.7)	1 (reference)	27.6 (22.9–33.3)	1.21 (0.93–1.57)	25.9 (24.0–27.8)	1.43 (1.15–1.78)
Surgery-related	28,602	28.9 (27.5–30.4)	1 (reference)	31.8 (30.1–33.5)	1.16 (1.08–1.25)	35.4 (34.1–36.8)	1.56 (1.46–1.66)
Other	67,191	24.1 (23.0–25.3)	1 (reference)	27.2 (25.7–28.7)	1.13 (1.05–1.21)	27.2 (26.6–27.8)	1.20 (1.14–1.27)
Baseline eGFR group							
≥60 ml/min per 1.73 m^2	92,077	26.1 (25.1–27.1)	1 (reference)	29.8 (28.6–31.1)	1.15 (1.09– 1.22)	28.9 (28.3–29.4)	1.38 (1.32–1.44)
45–59 ml/min per 1.73 m^2	6749	26.1 (23.8–28.6)	1 (reference)	26.0 (23.3–29.0)	0.93 (0.79–1.10)	25.8 (24.3–27.3)	1.25 (1.09–1.44)
30–44 ml/min per 1.73 m^2	1388	40.3 (35.3–46.1)	1 (reference)	32.4 (26.8–39.3)	0.76 (0.56–1.02)	36.9 (33.6–40.4)	1.04 (0.81–1.34)
<30 ml/min per 1.73 m^2	264	57.2 (46.0–71.3)	1 (reference)	75.3 (62.7–90.6)	1.62 (0.95–2.75)	59.0 (51.8–67.2)	1.52 (0.91–2.52)

AKD, acute kidney disease; AKI, acute kidney injury; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard rate; ICU, intensive care unit.
[a]Adjusted for age, sex, calendar year, ischemic heart disease, heart failure, atrial fibrillation or flutter, peripheral artery disease, hypertension, chronic obstructive pulmonary disease, chronic liver disease, rheumatoid arthritis or connective tissue disease, cancer, diabetes, markers of smoking, baseline eGFR, AKI stage, AKI location, AKI setting, and prescription drugs listed in Table 1.

8 to 365 days before AKI ($n = 39,711$), patients without an assessment of AKI duration within the first 7 days after AKI onset ($n = 106,970$), and patients dead or censored before the start of follow-up ($n = 65,997$) (Figure 1 and Supplementary Table S2). The median follow-up time was 2.3 years (interquartile range, 0.8–4.7) (Supplementary Table S3). For each outcome, we excluded patients with a history of the disease of interest, leaving 100,478 at risk of CKD and 76,838 at risk of CVD (Figure 1 and Supplementary Tables S4 and S5). Covariates were comparable among included and excluded patients, except for a slightly higher proportion of hospital-acquired AKI and surgery-related AKI among the included patients (Supplementary Table S2).

Patient Characteristics

Of the 169,582 patients with AKI, 36,514 (22%) had rapid reversal AKI, 22,619 (13%) had persistent AKI, and 110,499 (65%) had AKD (Table 1). The persistent AKI group was marginally older than the other AKI duration groups (median age 74 years vs. 72 years) (Table 1). In addition, the persistent AKI group had a slightly higher prevalence of CKD and CVDs and an accordingly higher proportion of users of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers and diuretics.

AKI stage, location, and setting varied across the AKI duration groups. Whereas 68% of AKDs were community-acquired and 29% were hospital-acquired, 8% of persistent AKIs were community-acquired and 78% were hospital-acquired. Moreover, 19% of AKDs were related to surgery compared with 42% of rapid reversal AKIs and 47% of persistent AKIs. The proportion of patients with AKI stage 1 ranged from 61% for AKDs to 91% for rapid reversal AKIs. Median follow-up time, number of pCr tests during the first week after AKI onset, and number of outpatient tests during follow-up were similar across AKI duration groups (Supplementary Table S3). In addition, 83% of all patients had a pCr test within the first 2 days of the AKI episode.

CKD and Kidney Failure

During the 20 years of follow-up, the risk of CKD was 26.3% (95% CI, 25.4–27.2) for rapid reversal AKI, 29.5% (95% CI, 28.4–30.6) for persistent AKI, and 28.7% (95% CI, 28.2–29.2) for AKD (Table 2 and Figure 2). The aHR of CKD increased with AKI duration

Table 4. Twenty-year risks and HRs of cardiovascular disease

	Patients at risk	Events	Risk % (95% CI)	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
Overall cardiovascular disease					
Rapid reversal AKI	15,507	241	29.5 (28.2–31.0)	1 (reference)	1 (reference)
Persistent AKI	8435	1577	29.7 (28.2–31.3)	1.17 (1.10–1.25)	1.02 (0.96–1.09)
AKD	52,896	8373	27.6 (26.9–28.4)	1.02 (0.97–1.07)	1.01 (0.96–1.07)
Atrial fibrillation or flutter					
Rapid reversal AKI	28,006	2239	14.1 (13.5–14.9)	1 (reference)	1 (reference)
Persistent AKI	16,644	1553	14.2 (13.5–15.0)	1.11 (1.04–1.19)	0.99 (0.92–1.05)
AKD	87,243	6635	12.8 (12.5–13.2)	0.96 (0.92–1.01)	1.00 (0.95–1.06)
Ischemic heart disease					
Rapid reversal AKI	25,304	1344	9.1 (8.5–9.7)	1 (reference)	1 (reference)
Persistent AKI	14,687	951	9.5 (8.8–10.2)	1.20 (1.10–1.30)	1.03 (0.95–1.12)
AKD	81,599	4698	9.2 (8.9–9.5)	1.09 (1.02–1.15)	1.11 (1.03–1.19)
Heart failure					
Rapid reversal AKI	29,626	1934	10.8 (10.3–11.4)	1 (reference)	1 (reference)
Persistent AKI	17,558	1559	13.2 (12.5–14.0)	1.31 (1.22–1.40)	1.09 (1.02–1.16)
AKD	90,849	5854	10.4 (10.1–10.7)	1.00 (0.95–1.05)	1.09 (1.03–1.15)
Stroke					
Rapid reversal AKI	31,266	1588	8.4 (7.9–8.9)	1 (reference)	1 (reference)
Persistent AKI	19,199	1095	8.5 (8.0–9.0)	1.09 (1.01–1.17)	0.98 (0.90–1.06)
AKD	95,415	4729	8.0 (7.8–8.3)	1.00 (0.94–1.05)	1.01 (0.94–1.08)
Peripheral artery disease					
Rapid reversal AKI	31,141	1356	7.6 (7.1–8.1)	1 (reference)	1 (reference)
Persistent AKI	18,813	1033	8.2 (7.7–8.8)	1.22 (1.13–1.32)	1.08 (1.00–1.18)
AKD	96,363	4317	7.0 (6.8–7.3)	1.04 (0.98–1.11)	1.10 (1.02–1.17)

AKD, acute kidney disease; AKI, acute kidney injury; CI, confidence interval; HR, hazard rate.
[a]Adjusted for age, sex, calendar year, kidney disease, hypertension, chronic obstructive pulmonary disease, chronic liver disease, rheumatoid arthritis or connective tissue disease, cancer, diabetes, markers of smoking, baseline eGFR, AKI stage, AKI location, AKI setting, and prescription drugs listed in Table 1. In addition, the adjusted analyses of cardiovascular disease subtypes included adjustments for other cardiovascular disease subtypes.

(aHR = 1.13 [95% CI, 1.08–1.19] for persistent AKI and 1.36 [95% CI, 1.30–1.41] for AKD compared with rapid reversal AKI) (Table 2). In general, this gradual increase in rates of CKD with AKI duration was consistent across subgroups (Table 3).

The risk of kidney failure during the 20 years of follow-up was 4.7% (95% CI, 4.3–5.1) for rapid reversal AKI, 6.0% (95% CI, 5.6–6.4) for persistent AKI, and 6.3% (95% CI, 6.0–6.5) for AKD (Table 2 and Figure 2). The corresponding aHR was 1.19 (95% CI, 1.08–1.30) for persistent AKI and 1.56 (95% CI, 1.44–1.69) for AKD compared with rapid reversal AKI (Table 2).

CVD

The overall risk of CVD during the 20 years of follow-up was 29.5% (95% CI, 28.2–31.0) for rapid reversal AKI, 29.7% (95% CI, 28.2–31.3) for persistent AKI, and 27.6% (95% CI, 26.9–28.4) for AKD (Table 4 and Figure 3). Moreover, the aHRs for CVD were similar across AKI duration groups (aHR = 1.02 [95% CI, 0.96–1.09] for persistent AKI and 1.01 [95% CI, 0.96–1.07] for AKD compared with rapid reversal AKI) (Table 4). Overall, this was consistent across subgroups and for outcomes of atrial fibrillation or flutter and stroke (Tables 4 and 5). For heart failure, the aHRs were slightly higher for persistent AKI (aHRs = 1.09 [95% CI, 1.02–1.16]) and AKD (aHRs = 1.09 (95% CI, 1.03–1.15]) compared with rapid reversal AKI. Similarly, for ischemic heart disease and peripheral artery disease, AKD was associated with a slightly higher aHR compared with rapid reversal AKI (aHRs = 1.11 [95% CI, 1.03–1.19] and 1.10 [95% CI, 1.02–1.17], respectively).

Sensitivity Analyses

Analyses of CKD and CVD development after AKI in patients with a baseline pCr test within 90 days before AKI were consistent with the main analyses (Supplementary Tables S6 and S7). Likewise, outcomes of CKD and kidney failure among patients with a first-time laboratory-recorded AKI after April 1, 2010, and when CKD was defined only according to outpatient eGFR measurements aligned with the main analyses (Supplementary Tables S8 and S9).

DISCUSSION

In this large population-based cohort study with up to 20-years follow-up on patients with AKI, we found that persistent AKI and AKD were associated with gradual increases in rates of CKD and kidney failure compared with rapid reversal AKI. AKI duration was not associated with overall CVD; however, compared with rapid

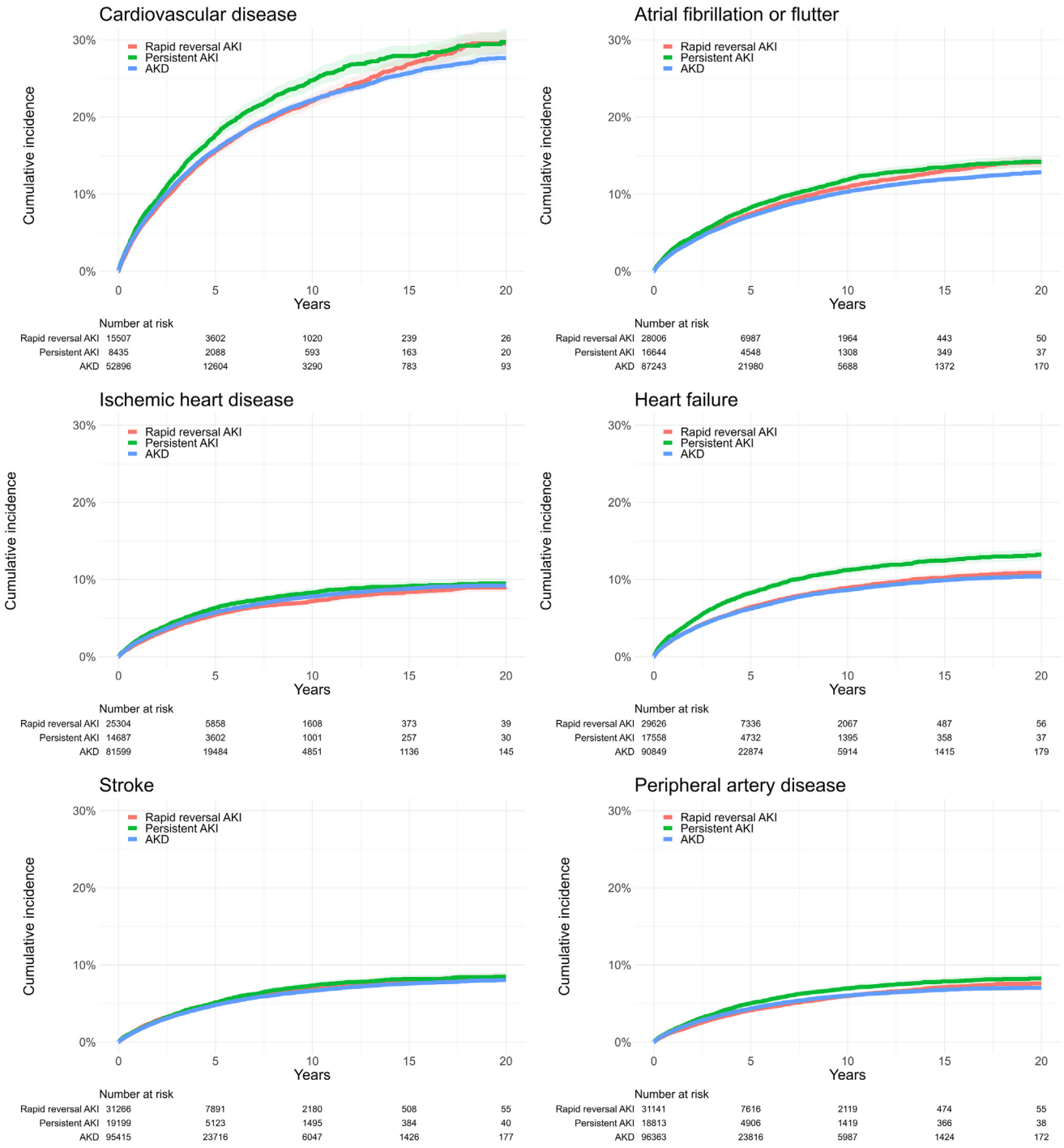

Figure 3. Twenty-year risks of cardiovascular disease. AKD, acute kidney disease; AKI, acute kidney injury.

reversal AKI, rates of heart failure were slightly higher for persistent AKI and AKD, and the rates of ischemic heart disease and peripheral artery disease were higher for AKD. The findings were robust across subgroups, various definitions of baseline pCr and kidney outcomes, and when restricted to pCr tests analyzed using enzymatic methods and isotope dilution mass spectrometry standardization.

To our knowledge, our study is the first to implement both the KDIGO creatinine criteria for defining AKI and the Acute Disease Quality Initiative consensus definition of AKI duration to examine the long-term associations between AKI duration and CKD as well as CVD in a general population cohort. The reported increase in rates of CKD with AKI duration corroborates findings from studies examining development of CKD according to AKI duration of less or more than 7 days.[17,22,27] Furthermore, our overall finding of a gradual increase in rates of CKD with AKI duration are consistent with findings from studies on hospitalized US veterans using other definitions of AKI duration.[21,26] Heung *et al.*[21] reported a gradual increase in

Table 5. Stratified 20 risks and HRs of cardiovascular disease

		Rapid reversal AKI		Persistent AKI		AKD	
	Patients at risk	Risk % (95% CI)	Adjusted HR[a] (95% CI)	Risk % (95% CI)	Adjusted HR[a] (95% CI)	Risk % (95% CI)	Adjusted HR[a] (95% CI)
Age groups							
<40 yr	7625	18.7 (13.5–25.8)	1 (reference)	8.9 (5.3–15.0)	0.54 (0.34–0.85)	19.5 (16.1–23.5)	0.99 (0.75–1.31)
40–59 yr	18,451	30.9 (27.2–35.0)	1 (reference)	26.7 (22.5–31.7)	1.04 (0.89–1.22)	26.3 (24.5–28.3)	0.96 (0.85–1.08)
60–79 yr	37,061	32.7 (30.9–34.6)	1 (reference)	33.6 (31.4–35.9)	1.04 (0.95–1.13)	31.0 (30.1–31.9)	1.01 (0.94–1.08)
≥80 yr	13,701	25.7 (23.9–27.6)	1 (reference)	29.2 (27.0–31.6)	1.05 (0.92–1.18)	24.7 (23.7–25.7)	1.05 (0.94–1.17)
Sex							
Female	35,752	32.3 (30.2–34.4)	1 (reference)	30.8 (28.7–33.0)	0.99 (0.90–1.08)	28.3 (27.3–29.4)	0.96 (0.90–1.04)
Male	41,086	27.2 (25.3–29.2)	1 (reference)	28.8 (26.6–31.1)	1.06 (0.96–1.16)	27.0 (26.1–28.0)	1.06 (0.98–1.14)
AKI stage							
1	51,582	29.6 (28.1–31.2)	1 (reference)	30.7 (28.9–32.6)	1.03 (0.96–1.11)	27.7 (26.7–28.7)	1.02 (0.96–1.08)
2	15,165	27.9 (23.7–32.9)	1 (reference)	26.4 (23.6–29.6)	0.98 (0.81–1.19)	27.2 (25.8–28.7)	1.00 (0.85–1.18)
3	10,091	32.4 (24.9–42.1)	1 (reference)	28.6 (22.1–37.2)	0.84 (0.61–1.15)	28.2 (26.7–29.8)	0.88 (0.67–1.14)
Location							
Community	41,020	27.9 (22.8–34.0)	1 (reference)	26.1 (21.3–32.0)	0.98 (0.78–1.22)	26.9 (26.1–27.8)	1.02 (0.90–1.15)
Hospital	32,484	29.7 (28.2–31.2)	1 (reference)	29.3 (27.7–31.1)	1.01 (0.94–1.08)	29.2 (27.8–30.6)	0.99 (0.93–1.06)
ICU	3334	29.1 (24.8–34.1)	1 (reference)	34.0 (29.2–39.5)	1.23 (1.00–1.52)	28.5 (23.8–34.0)	1.14 (0.92–1.42)
Setting							
Sepsis-related	3760	20.8 (16.4–26.4)	1 (reference)	26.3 (20.6–33.5)	1.14 (0.81–1.59)	26.8 (24.3–29.6)	1.11 (0.85–1.45)
Surgery-related	21,408	32.1 (29.9–34.5)	1 (reference)	30.9 (28.8–33.1)	1.04 (0.95–1.14)	30.1 (28.5–31.9)	1.03 (0.95–1.12)
Other	51,670	27.7 (25.9–29.6)	1 (reference)	28.5 (26.2–30.9)	1.00 (0.91–1.09)	27.0 (26.2–27.8)	0.98 (0.92–1.06)
Baseline eGFR group							
≥60 ml/min per 1.73 m^2	57,660	27.6 (25.9–29.4)	1 (reference)	27.1 (25.2–29.2)	1.02 (0.94–1.11)	26.4 (25.5–27.4)	1.02 (0.95–1.09)
45–59 ml/min per 1.73 m^2	10,945	34.2 (31.3–37.4)	1 (reference)	35.3 (31.9–39.1)	0.97 (0.84–1.12)	30.3 (28.8–31.8)	0.97 (0.86–1.10)
30–44 ml/min per 1.73 m^2	5875	31.7 (28.2–35.7)	1 (reference)	33.3 (29.7–37.4)	1.17 (0.97–1.41)	30.4 (28.6–32.2)	1.13 (0.96–1.35)
<30 ml/min per 1.73 m^2	2358	38.8 (33.5–45.0)	1 (reference)	35.0 (29.8–41.0)	0.92 (0.71–1.20)	34.9 (32.1–37.9)	0.89 (0.71–1.12)

AKD, acute kidney disease; AKI, acute kidney injury; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard rate; ICU, intensive care unit.
[a]Adjusted for age, sex, calendar year, kidney disease, hypertension, chronic obstructive pulmonary disease, chronic liver disease, rheumatoid arthritis or connective tissue disease, cancer, diabetes, markers of smoking, baseline eGFR, AKI stage, AKI location, AKI setting, and prescription drugs listed in Table 1.

the risk of CKD with increasing AKI duration (≤2, 3–10, or >10 days) when compared with patients without AKI. Similar progressive increases in the risks of a sustained decline in eGFR or kidney failure were reported by Siew *et al.*[26] for an AKI duration of 5 to 10, 11 to 30, or 31 to 90 days compared with 1 to 4 days.

We did not observe an association between AKI duration and overall CVD; however, AKI duration was associated with development of heart failure, ischemic heart disease, and peripheral artery disease. AKI without recovery of kidney function at discharge has been associated with higher rates of heart failure among patients with myocardial infarction,[30] patients in intensive care,[29] and patients with HIV.[19] Likewise, Ikizler *et al.*[31] reported higher rates of heart failure with increasing AKI duration among hospitalized adults, especially if the duration exceeded 6 days. In addition, patients in intensive care with AKI persisting beyond discharge had higher rates of myocardial infarction but not stroke than patients with recovery of kidney function before discharge.[29] Despite the differences in the definition of AKI duration and study populations, these findings collectively suggest associations between AKI duration and heart failure as well as ischemic heart disease.

Most studies examining the prognosis following AKI have focused on the importance of AKI severity defined as the difference between baseline pCr and the highest reached pCr after AKI onset.[50–52] Our findings support that AKI severity may be complemented by AKI duration as a marker of prognosis, especially in the milder stages of AKI. Adding information on AKI duration could aid risk stratification and increase the precision of prediction models, which allows for a more accurate identification of patients at risk of long-term adverse outcomes and accordingly a more focused and profitable clinical follow-up after AKI. Moreover, due to the interplay with prognosis, the duration of AKI may be a potential target for AKI-directed interventions. The implementation of changes in AKI duration as an intermediate outcome could allow for a higher efficiency of clinical studies examining AKI-directed interventions for the prevention of long-term adverse outcomes.

The use of population-based pCr tests covering both the primary care and hospital setting in a universal health care system is a pivotal strength of this study. Nonetheless, the study has limitations that need to be considered. First, to allow for the assessment of AKI duration, we included patients with an outpatient

baseline pCr test before AKI and 1 or more pCr tests during the 7 days after AKI onset. However, when comparing all patients with AKI to those included in the study, we did not find substantial differences in patient characteristics (Supplementary Table S2). The most prominent differences were related to location and setting of AKI, with a higher proportion of the included patients experiencing AKI during hospitalization and in relation to surgery. This was likely due to structural differences with higher availability of pCr testing during hospitalization and after surgery. Second, though we required a pCr test during the 7 days following AKI, the duration of AKI could be misclassified due to the timing of pCr testing. However, the risk of misclassification is low as the median number of tests in the study population during the 7 days after AKI onset was 4 (interquartile range, 2–6) and 83% of patients had a test within the first 2 days. Similarly, the assessment of kidney function by pCr tests during follow-up was balanced across AKI duration groups (Supplementary Table S3). Third, when defining CKD, we used a combination of pCr tests and hospital diagnoses and procedures. The use of pCr tests for defining CKD is more sensitive than diagnoses[53]; however, because the geographical coverage of the laboratory databases was not complete throughout the study period, we required that each patient had 1 or more recorded outpatient pCr tests before AKI. Therefore, included patients were likely to live in areas covered by the databases. Nonetheless, some may have relocated during follow-up, which could lead to an underestimation of the risk of CKD. Fourth, the Danish National Patient Registry contains information on the day of admission and discharge and the diagnoses registered during the hospitalization, but not information on the specific day of the diagnosis. Therefore, for the definition of sepsis-related AKI, we could not assure that AKI was preceded by a sepsis diagnosis; however, we consider it probable that AKI during a hospitalization with a sepsis diagnosis is related to sepsis. Finally, though we adjusted the analyses for differences in potential confounders, including demographics, prescription drug use, markers of smoking, and baseline eGFR, we cannot rule out residual confounding.

In conclusion, AKI duration was associated with long-term risks and rates of CKD and kidney failure. AKI duration was not associated with overall CVD; however, AKI duration was associated with rates of heart failure, ischemic heart disease, and peripheral artery disease. The increase in risks of CKD and kidney failure with increasing AKI duration underscores the potential for using AKI duration as a risk marker when organizing nephrology follow-up after AKI. Furthermore, this illustrates that mitigation of AKI duration may be a potential target for interventions directed toward preventing development of adverse kidney outcomes after AKI.

DISCLOSURE

All the authors declared no competing interests.

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DATA AVAILABILITY STATEMENT

The data underlying this article were provided by a third party. Requests to access the databases used in this study from researchers at certified Danish research institutions may be sent to the Danish Health Data Authority by e-mail to forskerservice@sundhedsdata.dk.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Codes for baseline variables and outcomes.

Table S2. Characteristics of all patients with acute kidney injury.

Table S3. Information on follow-up time and plasma creatinine tests after acute kidney injury.

Table S4. Characteristics of patients at risk of chronic kidney disease.

Table S5. Characteristics of patients at risk of cardiovascular disease.

Table S6. Twenty-year risks and hazard ratios of chronic kidney disease and kidney failure among patients with a baseline within 90 days before acute kidney injury.

Table S7. Twenty-year risks and hazard ratios of cardiovascular disease among patients with a baseline within 90 days before acute kidney injury.

Table S8. Hazard ratios of chronic kidney disease and kidney failure among patients with acute kidney injury after 1 April 2010.

Table S9. Hazard ratios of chronic kidney disease and kidney failure defined only according to outpatient plasma creatinine measurements.

STROBE Statement.

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