JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 73, NO. 3, 2019

PUBLISHED BY ELSEVIER

Kidney Dysfunction and the Risk of Developing Aortic Stenosis

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ABSTRACT

BACKGROUND Chronic kidney disease (CKD) and aortic stenosis (AS) share many risk factors.

OBJECTIVES This study sought to evaluate whether kidney dysfunction is associated with the development of AS in the community.

METHODS The study included 1,121,875 Stockholm citizens without a prior diagnosis of AS from the SCREAM (Stockholm CREAtinine Measurements) project. Estimated glomerular filtration rate (eGFR) (ml/min/1.73 m^2) was calculated from serum creatinine. AS incidence during follow-up was ascertained by clinical diagnostic codes. The association between eGFR and AS incidence was estimated with multivariable Cox proportional hazards models. Sensitivity analyses included analysis of possible reverse causation bias by excluding the first 6 months to 2 years after enrollment and excluding individuals with comorbid heart failure.

RESULTS The median age was 50 years (interquartile range [IQR]: 36 to 64 years), and 54% of participants were women. Median eGFR was 96 ml/min/1.73 m^2 (IQR: 82 to 109 ml/min/1.73 m^2), and 66,949 (6.0%) participants had CKD (eGFR $<$60 ml/min/1.73 m^2). During a median follow-up of 5.1 years (IQR: 3.3 to 6.1 years), 5,858 (0.5%) individuals developed AS (incidence rate [IR] 1.13/1,000 person-years). Compared with eGFR $>$90 (IR 0.34/1,000 person-years), lower eGFR strata were associated with higher hazards of AS: eGFR 60 to 90 ml/min/1.73 m^2; IR: 1.88; hazard ratio (HR): 1.14; 95% confidence interval (CI): 1.05 to 1.25; eGFR 45 to 59 ml/min/1.73 m^2; IR: 4.61; HR: 1.17; 95% CI: 1.05 to 1.30; eGFR 30 to 44 ml/min/1.73 m^2; IR: 6.62; HR: 1.22; 95% CI: 1.07 to 1.39; and eGFR 30 ml/min/1.73 m^2; IR: 8.27; HR: 1.56; 95% CI: 1.29 to 1.87. Sensitivity analysis attenuated only slightly the magnitude of the association; individuals with eGFR $\leq$44 ml/min/1.73 m^2 remained at an approximate 20% risk of AS both when excluding events within the 2 years after baseline (HR: 1.22; 95% CI: 1.06 to 1.42) and when excluding participants with heart failure (HR: 1.20; 95% CI: 1.03 to 1.39).

CONCLUSIONS CKD, even in moderate to severe stages, is associated with an increased risk of AS.
(J Am Coll Cardiol 2019;73:305–14) © 2019 by the American College of Cardiology Foundation.

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Manuscript received June 26, 2018; revised manuscript received September 7, 2018, accepted October 14, 2018.

Listen to this manuscript's audio summary by Editor-in-Chief Dr. Valentin Fuster on JACC.org.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2018.10.068

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

CI = confidence interval

CKD = chronic kidney disease

eGFR = estimated glomerular filtration rate

HR = hazard ratio

ICD-10 = International Classification of Diseases-10th revision

IQR = interquartile range

Aortic stenosis (AS) is the most common primary valve disease (1), present in 2.8% in adults >75 years of age (2,3). Because of its poor prognosis and lack of pharmacological therapies to slow or halt disease progression, interventional valve replacement is the only treatment available for severe symptomatic AS (1). Several conditions have been found to be associated with AS incidence (1–9), but a better understanding of AS predictors is necessary to find potential treatment targets.

An increased AS prevalence has been observed in patients undergoing dialysis (10–13), but in the larger segment of non-dialysis-dependent chronic kidney disease (CKD) this cross-sectional evidence is contradictory (7,14). Individuals with moderate to severe CKD (defined as an estimated glomerular filtration rate [eGFR] <60 ml/min/1.73 m^2), have a high prevalence of atherosclerotic risk factors (8), cardiovascular disease (15), and disturbances in bone-mineral metabolism (16) that are well-established promoters of cardiovascular calcification (17). Despite these potential disease mechanisms, it remains unknown whether the risk of developing AS is associated with the degree of kidney dysfunction, including individuals who are not undergoing dialysis. Knowing whether this association exists would be important for physicians, researchers, and health policy makers because CKD is a growing public health problem present in 5% to 15% of the general population (18,19).

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Hence the aim of this study was to assess whether kidney dysfunction is associated with AS incidence, and we used a large population-based cohort.

METHODS

DATA SOURCES. This study used the SCREAM (Stockholm CREAtinine Measurements) project (20), a health care use cohort that includes all residents in the region of Stockholm, Sweden, who underwent serum creatinine tests in outpatient or inpatient care from 2006 to 2011. Given the frequent use of creatinine testing in health care, SCREAM is representative of the adult population of the region, with estimated population coverage of 54% for the age range 18 to 44 years, 78% for 45 to 64 years, and 92% for ≥65 years of age. Laboratory data were linked to regional and national administrative databases to achieve complete information on health care use, including diagnoses, dispensed drugs, data on renal replacement therapy, and follow-up for death, with minimal or no loss to follow-up. All linkages were performed centrally by the Swedish National Board of Welfare, which created a de-identified database. The study protocol was approved by the regional Institutional Review Boards and adhered to the Declaration of Helsinki.

PATIENT SELECTION. The index date was the first eligible serum creatinine test of any adult (≥18 years of age) entering the cohort. Eligible creatinine tests were those taken in outpatient care and within the plausible range of >25 μmol/l to <1,500 μmol/l. The only exclusion criteria were the presence of an AS diagnosis (International Classification of Diseases-10th revision [ICD-10] codes I35.0 and I35.2) in the patient's medical record since 1997 or renal replacement therapy (dialysis or renal transplantation) on the index date. On the basis of these criteria, 1,121,875 individuals were included in the analysis. The flow chart of patient selection is presented in Online Figure 1.

STUDY OUTCOME AND FOLLOW-UP. The study outcome was incident AS, defined as the first appearance of an AS diagnostic code (ICD-10 I35.0 or I35.2) after the index date in a primary or secondary position at a discharge hospitalization or specialist outpatient consultation. The diagnosis of AS made on the basis of ICD codes has high diagnostic accuracy (>90%) in Sweden, with the majority of patients having moderate or severe AS (7). Participants were followed until the study outcome was reached, the patient died, the patient emigrated, or until the end of data collection (December 31, 2012), whichever came first.

RENAL FUNCTION ESTIMATION. Index creatinine was used to calculate the eGFR by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (21). All creatinine measurements were isotope dilution mass spectrometry standardized. eGFR was categorized according to Kidney Disease: Improving Global Outcomes (KDIGO) staging (22,23), as follows: >90, 90 to 60, <60 to 45, <45 to 30, and <30 ml/min/1.73 m^2. In the absence of albuminuria measurements, we could not classify early CKD stages, and CKD was defined as eGFR <60 ml/min/1.73 m^2.

DEFINITION OF COVARIATES. Study covariates included age, sex, comorbid history, and medications (Online Table 1). Comorbidities were identified using established ICD-10 algorithms of 85% to 95% validity (23). We included ICD-10 codes that had been issued since 1997 from any health care encounter (including primary health care), with the exception of cancer history (only calculated within the previous 3 years).

TABLE 1 Baseline Characteristics

	Overall (N = 1,121,875)	eGFR, ml/min/1.73 m²				
		>90 (n = 699,957)	60-90 (n = 354,969)	45-59 (n = 44,744)	30-44 (n = 16,611)	<30 (n = 5,594)
Female	608,216 (54.2)	370,842 (53.0)	196,481 (55.4)	27,563 (61.6)	10,241 (61.7)	3,089 (55.2)
Age, yrs	50 (36-64)	41 (31-53)	64 (53-74)	79 (71-85)	83 (77-88)	83 (73-88)
eGFR, ml/min/1.73 m²	96 (82-109)	106 (98-116)	80 (73-85)	54 (50-57)	39 (35-42)	24 (19-27)
Ischemic heart disease	59,627 (5.3)	13,533 (1.9)	30,138 (8.5)	9,270 (20.7)	4,791 (28.8)	1,895 (33.9)
Angina pectoris	47,246 (4.2)	10,552 (1.5)	24,237 (6.8)	7,325 (16.4)	3,702 (22.3)	1,430 (25.6)
Myocardial infarction	32,525 (2.9)	7,229 (1.0)	15,776 (4.4)	5,227 (11.7)	3,011 (18.1)	1,282 (22.9)
Peripheral arterial diseases	16,795 (1.5)	3,977 (0.6)	7,779 (2.2)	2,747 (6.1)	1,618 (9.7)	674 (12.0)
Cerebrovascular diseases	34,123 (3.0)	7,235 (1.0)	17,198 (4.8)	5,709 (12.8)	2,904 (17.5)	1,077 (19.3)
Heart failure	33,692 (3.0)	4,088 (0.6)	14,881 (4.2)	7,496 (16.8)	5,053 (30.4)	2,174 (38.9)
Diabetes mellitus	61,506 (5.5)	25,740 (3.7)	24,861 (7.0)	6,276 (14.0)	3,238 (19.5)	1,391 (24.9)
Hypertension	181,183 (16.2)	58,296 (8.3)	89,895 (25.3)	20,789 (46.5)	9,055 (54.5)	3,148 (56.3)
COPD	23,146 (2.1)	7,212 (1.0)	11,245 (3.2)	2,803 (6.3)	1,382 (8.3)	504 (9.0)
Hyperlipidemia	111,395 (9.9)	39,274 (5.6)	56,360 (15.9)	10,479 (23.4)	3,950 (23.8)	1,332 (23.8)
Medication use						
ACE inhibitors/ARBs	137,999 (12.3)	48,113 (6.9)	65,981 (18.6)	14,709 (32.9)	6,751 (40.6)	2,445 (43.7)
Beta-blockers	146,041 (13.0)	48,201 (6.9)	71,273 (20.1)	16,625 (37.2)	7,357 (44.3)	2,585 (46.2)
Diuretics	106,341 (9.5)	24,520 (3.5)	51,432 (14.5)	17,385 (38.9)	9,442 (56.8)	3,562 (63.7)
Calcium-channel blockers	69,872 (6.2)	21,705 (3.1)	35,546 (10.0)	7,946 (17.8)	3,291 (19.8)	1,384 (24.7)
Low-dose aspirin, ≤160 mg	101,844 (9.1)	24,690 (3.5)	54,045 (15.2)	14,520 (32.5)	6,492 (39.1)	2,097 (37.5)
High-dose aspirin, >160 mg/NSAIDs	168,976 (15.1)	102,519 (14.6)	56,854 (16.0)	6,815 (15.2)	2,224 (13.4)	564 (10.1)

Values are n (%) or median (interquartile range).

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; NSAIDs = nonsteroidal anti-inflammatory drugs.

Comorbidities included coronary artery diseases, peripheral arterial diseases, cerebrovascular diseases, heart failure, chronic obstructive pulmonary disease, diabetes mellitus, and hypertension. We defined hyperlipidemia as the dispensing of lipid-lowering drugs concomitantly on the index date. Information on dispensed drugs was obtained from the nationwide Swedish Dispensed Drug Registry, which records complete information on all prescription drugs dispensed at Swedish pharmacies. Concomitant use of other medications on the index date (see Online Table 1 for definitions) was defined as the presence of a pharmacy medication distribution within the previous 6 months or 1 month thereafter.

STATISTICAL ANALYSIS. Baseline characteristics are presented for continuous data as mean ± SD or median (interquartile range [IQR]). Categorical data are presented as number (percentage). We estimated incidence rates of AS overall and across eGFR strata and also calculated age-standardized incidence rates for 10-year categories of age. The crude association between eGFR strata and AS occurrence was graphically displayed as a Kaplan-Meier curve.

Cox proportional hazards models were used to assess the multivariable-adjusted association between eGFR categories and incident AS. Covariates in this model included age, sex, ischemic heart disease, peripheral arterial disease, cerebrovascular diseases, heart failure, diabetes mellitus, hypertension, chronic obstructive pulmonary disease, and hyperlipidemia. Covariates were adjusted in a stepwise manner. We graphically assessed and found satisfying the proportional hazards assumption by plotting Schoenfeld residuals against ranks of time. Because disease is the reason for prescription of medication, ongoing medications were not considered confounders in the association between kidney function and AS. Only for hyperlipidemia, which is not well captured by diagnostic codes, the use of lipid-lowering medication was used as a proxy for the disease. Restricted cubic spline models were used to better assess the dose-response multivariable-adjusted association between eGFR (as a continuous variable) and the incidence of AS. There were no missing data in this cohort because all data were captured by administrative diagnostic codes.

To assess the possibility that the observed association was the result of residual confounding, we defined a set of control outcomes. Myocardial infarction (I21) was chosen as a positive control outcome given its well-known association with eGFR.

TABLE 2 Incidence Rates and Hazard Ratios for Aortic Stenosis

	Person-Years	Number of Events	Incidence Rate per 1,000 Person-Years (95% CI)	Crude Hazard Ratio (95% CI)	Adjusted* Hazard Ratio (95% CI)
Overall	5,197,763	5,858	1.13 (1.10–1.16)		
eGFR categories					
>90	3,187,089	1,092	0.34 (0.32–0.36)	1.00	1.00
60–90	1,720,092	3,227	1.88 (1.81–1.94)	5.43 (5.07–5.82)	1.14 (1.05–1.23)
45–59	206,142	950	4.61 (4.32–4.91)	13.29 (12.18–14.50)	1.17 (1.05–1.30)
30–44	66,296	439	6.62 (6.03–7.26)	19.11 (17.11–21.35)	1.22 (1.07–1.39)
<30	18,143	150	8.27 (7.05–9.64)	23.78 (20.05–28.20)	1.56 (1.29–1.87)

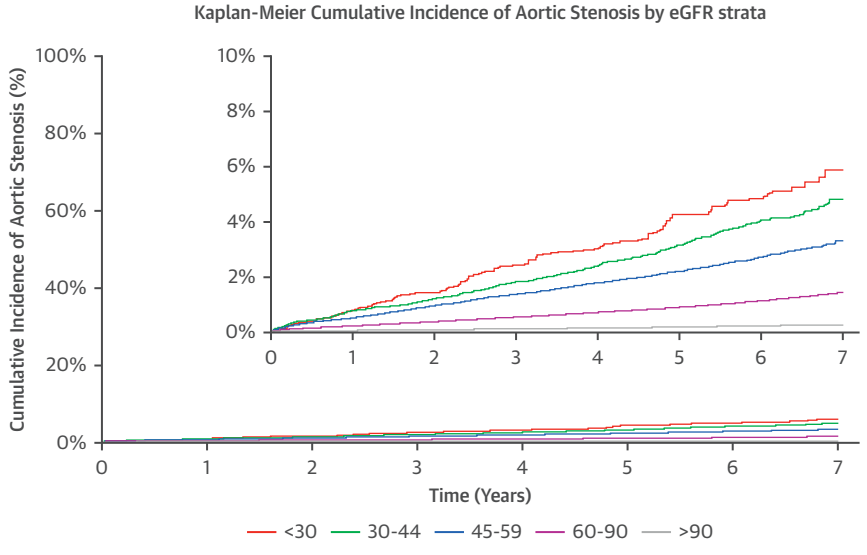
*Adjustments were made for age, sex, ischemic heart disease, peripheral arterial disease, cerebrovascular diseases, heart failure, diabetes mellitus, hypertension, chronic obstructive pulmonary disease, and hyperlipidemia.

CI = confidence interval; eGFR = estimated glomerular filtration rate strata.

Conversely, we did not anticipate eGFR to be associated with the risk of gallstones or cholecystectomy (ICD-10 codes K80 + K81 and JKA21 + JKA20) or car accidents (Z04), which were selected as negative control outcomes.

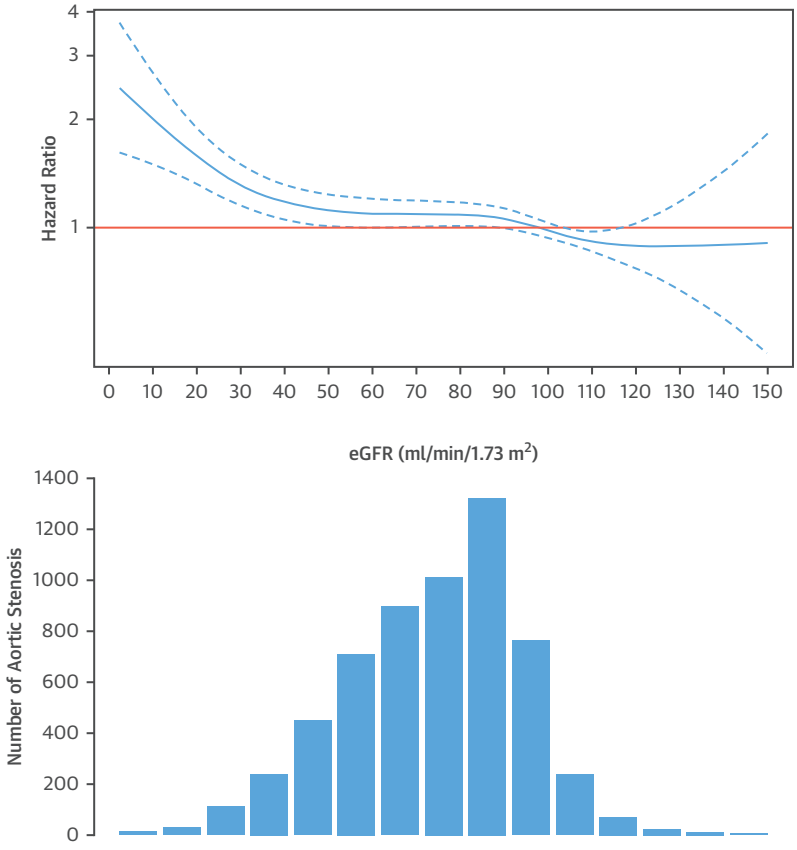
To address the possibility of reverse causation (e.g., that undiagnosed AS caused the reduced eGFR present at enrollment), several sensitivity analyses were performed. First, we disregarded the person-time immediately after enrollment and applied exclusion periods of increasing varying length (6 months, 1 year, and 2 years), after which the follow-up started. Individuals who developed AS or were censored (e.g., died, ended follow-up) during this exclusion period were excluded from the analysis. Second, we explored whether clinically diagnosed congestive heart failure may have prompted explorations that helped to detect AS; to this end, all patients with a diagnosis of heart failure before enrollment were excluded. Finally, to test the consistency of the observed associations, we performed stratified analysis across age groups, sex, and the presence or absence of ischemic heart disease, hypertension, diabetes mellitus, and heart failure. All analyses were performed using R software (R Foundation, Vienna, Austria).

FIGURE 1 Cumulative Incidence of Aortic Stenosis by Categories of eGFR



eGFR = estimated glomerular filtration rate.

FIGURE 2 eGFR (per ml/min/1.73 m^2) and the Risk of Aortic Stenosis



Restricted cubic splines showing the multivariable-adjusted hazard risk (95% confidence intervals) of aortic stenosis associated with estimated glomerular filtration rate (eGFR). Covariate adjustments as in Table 2. The graph is truncated at an estimated glomerular filtration rate ≥150 ml/min/1.73 m^2.

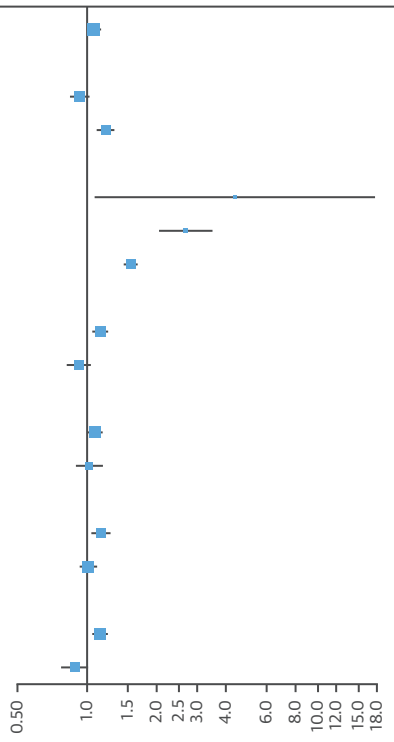
RESULTS

STUDY GROUP. A total of 1,121,875 participants were included, with a median age of 50 years (IQR: 36 to 64 years), and 54% were female. The most commonly found diseases were hypertension (16.2%) and treated hyperlipidemia (9.9%), followed by diabetes mellitus (5.5%), ischemic heart disease (5.3%), heart failure (3.0%), and cerebrovascular disease (3.0%). Other baseline comorbidities and medications are presented in Table 1. The median eGFR was 96 ml/min/1.73 m^2 (82 to 109 ml/min/1.73 m^2) (Table 1), and moderate to severe CKD (e.g., eGFR <60 ml/min/1.73 m^2) was present in 6.0% (n = 66,949). Individuals with lower eGFR were older, more often female, and affected by a higher number of comorbidities and higher medication use (Table 1).

ASSOCIATION OF KIDNEY FUNCTION AND INCIDENT AORTIC STENOSIS. During a median follow-up time of 5.1 years (IQR: 3.3 to 6.1 years), there were 5,858 individuals (0.5%) who developed clinically detected AS, corresponding to a crude incidence rate of 1.13 per 1,000 person-years (95% confidence interval [CI]: 1.10 to 1.16) (Table 2). The crude AS incidence rate increased linearly as the eGFR level decreased, from 0.34 per 1,000 person-years (95% CI: 0.32 to 0.36) in participants with eGFR >90 ml/min/1.73 m^2 to 8.27 per 1,000 person-years (95% CI: 7.05 to 9.64) in participants with eGFR <30 ml/min/1.73 m^2 (Figure 1). The incidence of AS was higher with older age. Within each age category >50 years, a higher

FIGURE 3 Subgroup Analysis in Individuals With and Without Chronic Kidney Disease

Subgroup	N (All)	N (Aortic Stenosis)	HR (95% CI)	p value int.
Overall	1,116,017	5,858	1.07 (1.00-1.14)	
Sex				<0.001
Men	513,659	3,029	0.93 (0.85-1.02)	
Women	608,216	2,829	1.20 (1.11-1.31)	
Age				<0.001
<45	446,611	145	4.36 (1.08-17.61)	
45-65	398,670	989	2.68 (2.06-3.49)	
>65	276,594	4,724	1.55 (1.45-1.65)	
Ischemic heart disease				0.002
No	1,062,248	4,603	1.14 (1.06-1.23)	
Yes	59,627	1,255	0.92 (0.82-1.03)	
Diabetes				0.449
No	1,060,369	4,867	1.08 (1.01-1.17)	
Yes	61,506	991	1.02 (0.90-1.17)	
Hypertension				0.04
No	940,692	3,207	1.15 (1.05-1.26)	
Yes	181,183	2,651	1.01 (0.93-1.10)	
Heart failure				<0.001
No	1,088,183	4,921	1.14 (1.06-1.23)	
Yes	33,692	937	0.88 (0.78-1.00)	



Forest plot depicting the association between chronic kidney disease (estimated glomerular filtration rate [eGFR] <60 ml/min/1.73 m^2) and the risk of aortic stenosis. CI = confidence interval; HR = hazard ratio; int. = interaction.

incidence rate of AS was observed across lower eGFR categories (Online Table 2).

Compared with eGFR >90 ml/min/1.73 m^2, both the hazard ratios (HRs) for AS increased, from a 14% (adjusted HR: 1.14; 95% CI: 1.05 to 1.23) higher AS risk among individuals with eGFR 60 to 90 ml/min/1.73 m^2 to a 56% (adjusted HR: 1.56; 95% CI: 1.29 to 1.87) higher risk among individuals with eGFR <30 ml/min/1.73 m^2. Fully adjusted restricted cubic spline curves (**Figure 2**) show minimal or no association with AS and eGFR >60 ml/min/1.73 m^2, but a linear increased risk of AS was observed for eGFR values <60 ml/min/1.73 m^2.

The association between eGFR and AS was largely attenuated after adjustment for age, as well as moderately attenuated by the adjustment of cardiovascular comorbidities (Online Table 3).

SENSITIVITY ANALYSES. Our positive and negative control outcomes showed the expected associations (or lack of them) with baseline eGFR (Online Tables 4A to 4C).

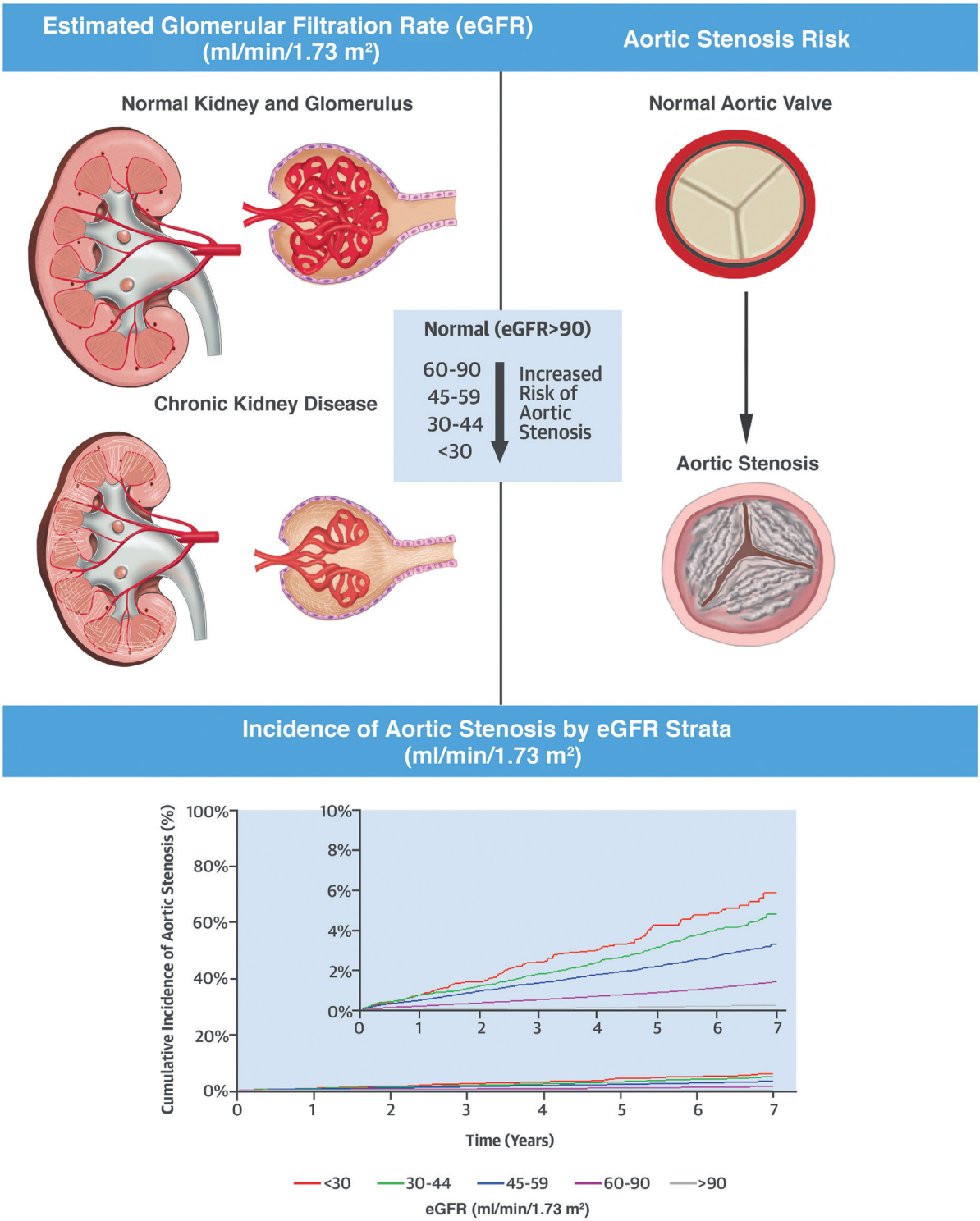
Exclusion of events during the first year of follow-up somewhat attenuated the association, but a 22% increased AS risk was still observed for individuals with eGFR ≤44 ml/min/1.73 m^2 (HR: 1.22; 95% CI: 1.06 to 1.42) (Online Figure 2A, Online Table 5A). Applying other exclusion windows (6 months or 2 years) resulted in comparable estimates (data not shown).

Exclusion of patients with clinically diagnosed congestive heart failure (n = 33,692) did not meaningfully modify the associations of the main analysis, and a 20% risk of AS was again present when eGFR was ≤44 ml/min/1.73 m^2 (HR: 1.20; 95% CI: 1.03 to 1.39) (Online Figure 2B, Online Table 5B).

SUBGROUP ANALYSES

The association between CKD (eGFR <60 ml/min/1.73 m^2) and AS was assessed across various subgroups (**Figure 3**). Women with CKD had a 20% higher hazard (HR: 1.20; 95% CI: 1.11 to 1.31) of AS compared with those without CKD, whereas no association was found among men with CKD. CKD was more strongly associated with AS in the absence, rather than in the presence, of comorbid ischemic heart disease, diabetes mellitus, hypertension, and heart failure.

CENTRAL ILLUSTRATION **Reduced Kidney Function Is Associated With Higher Risk of Aortic Stenosis**



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This association is present even after adjustment for important confounders, including age, sex, cardiovascular comorbid history, diabetes, hypertension, and hyperlipidemia.

DISCUSSION

This is the first study to suggest that kidney dysfunction among non-dialysis-dependent individuals is independently associated with the risk of developing AS (**Central Illustration**). The risk increases with lower eGFR, a finding suggesting a "dose-response" association, and remains present after adjusting for covariates. Even after extensive sensitivity analyses, kidney dysfunction remained associated with AS development.

Several prior attempts have been made to establish the association between kidney dysfunction and AS, but the results so far have been inconclusive. Although it is unequivocal that aortic valve calcification is frequent among patients requiring dialysis, and that the progression to severe AS is faster compared with patients not undergoing dialysis (10), this has not been established among the larger population of patients with mild to severe CKD (13,24,25). This may be explained by the design of the prior 3 studies, which were cross-sectional, the limited number of individuals who had CKD, and also the definition of AS that was used (13,24,25). The Framingham Offspring Study (24) included 3,047 participants (262 with CKD, eGFR <60 ml/min/1.73 m^2) and did not observe an association between CKD and aortic sclerosis or aortic annular calcification as detected by echocardiography. The MESA (Multi-Ethnic Atherosclerosis) study (13), which included 6,785 participants (667 with eGFR <60 ml/min/1.73 m^2), also failed to observe an association between CKD and the presence of aortic valve calcification detected on computer tomography. Finally, the CRIC (Chronic Renal Insufficiency Cohort) study (25) included 1,964 participants with various forms of CKD (1,129 with eGFR <60 ml/min/1.73 m^2) who underwent coronary calcium scanning and reported a higher prevalence and increased severity of aortic valve calcification across lower eGFR categories (stratified per 10 ml/min/1.73 m^2) (25). Contrary to prior studies, the number of individuals with moderate to severe CKD included (n = 66, 949, 6.0%) in this study based on a region-representative longitudinal cohort was several times larger.

The definition of AS used in this study differed from that used in prior studies, and this also could explain the differences and lack of association compared with prior studies (13,24,25). In this study, AS was physician based, and the investigations were driven by a clinical indication and current practice. In clinical practice (as in our study), the diagnosis of AS is made on the basis of the hemodynamic measurements obtained mainly by an echocardiography examination on individuals in response to cardiac symptoms or a significant murmur. Validation studies of AS diagnostic codes have shown that mainly moderate AS and severe AS are captured (7). In prior studies (13,24,25), the primary outcome was aortic calcification, which was diagnosed by either computed tomography (13,25) or echocardiography (24). Although a computed tomography scan provides a morphological description of the valve and quantifies valvular calcification, it does not provide information on its hemodynamic performance or clinical significance.

The precise mechanism of the finding in this study of an association between kidney dysfunction and AS is still unknown. We note that the crude association between eGFR and AS in our study was largely attenuated after adjustment for age and cardiovascular comorbidity, clearly shared risk factors in both conditions. Prior studies in patients undergoing maintenance dialysis have shown important abnormalities in bone mineral markers (calcium, phosphate, and parathyroid hormone levels), atherosclerotic disease (26–29), and hemodynamic changes (10,11,30–34) that may play a role. Population-based studies, conversely, have linked elevated serum phosphate to aortic valve sclerosis and calcification (16,35). Yet the mechanisms behind lesser degrees of kidney dysfunction and AS remain and need to be fully explored.

STUDY LIMITATIONS. Our study is observational, and only associations can be reported. AS is a slowly developing disease that may appear asymptomatic (and thus undiagnosed) for a long time before symptoms bring the individual to a physician. The median follow-up in this study was 5.1 years, which may not be long enough to capture the initiation of AS disease. This also means that asymptomatic AS may already (by reducing cardiac output) have affected and reduced kidney function (e.g., by the time of inclusion in this study). However, our sensitivity analyses tried to address this and suggest that reverse causation bias may not be strongly affecting our findings. Although residual and unknown confounding cannot be ruled out, our negative and positive control outcomes are reassuring. Unfortunately, we did not have data on blood pressure, smoking, or body mass index. Hemodynamic data to evaluate AS severity were not available, but as mentioned earlier,

AS diagnoses made on the basis of administrative codes tend to be of moderate to severe AS (7). Moreover, we were unable to differentiate between bicuspid and tricuspid aortic valves, and it would have been interesting to evaluate whether kidney dysfunction affects their progression to stenosis differently. Finally, the determination of kidney dysfunction was based on a single measurement of eGFR, which is subject to variability.

CONCLUSIONS

This study shows that CKD is associated with the risk of AS in the community. This observation merits further research to identify possible underlying mechanisms and potential therapeutic targets.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Impaired kidney function is associated with an increased risk of developing valvular AS even in patients with relatively mild degrees of renal impairment.

TRANSLATIONAL OUTLOOK: Further research is needed to understand the mechanisms underlying this association.

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KEY WORDS aortic stenosis, chronic kidney disease kidney function, risk factor, valvular heart diseases

APPENDIX For supplemental figures and tables, please see the online version of this paper.