**Cardiac Valve Disease and Prevalent and Incident CKD in Community-Dwelling Older Adults: The Atherosclerosis Risk in Communities (ARIC) Study**

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**Rationale & Objective:** Recent literature suggests improvement in kidney function after percutaneous valvular replacement therapies, implying a pathophysiological contribution of valvular heart disease to chronic kidney disease (CKD). However, this association has not been investigated epidemiologically. We aimed to assess the association of valvular abnormality with prevalent and incident CKD.

**Study Design:** Cross-sectional and prospective analyses.

**Setting & Participants:** Community-dwelling participants (mean age 75.5 [standard deviation 5.1] years) from the Atherosclerosis Risk in Communities study (2011-2013).

**Exposure:** Valvular abnormality defined as echocardiography-based aortic stenosis, aortic regurgitation, and mitral regurgitation.

**Outcomes:** Prevalent CKD was defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m². Incident CKD was defined as progression to eGFR <60 mL/min/1.73 m² with ≥25% decline or hospitalization/deaths with CKD diagnosis.

**Analytical Approach:** We cross-sectionally evaluated the association between valvular abnormality and prevalent CKD with logistic regression in 5,216 participants. Then, 3,752 participants without prevalent CKD were analyzed for incident CKD using Cox models.

**Results:** There were 1.4% (n = 74) with any aortic stenosis, 10.6% (n = 555) with any aortic regurgitation, and 43.1% (n = 2,249) with any mitral regurgitation. After adjustment for potential confounders, any mitral regurgitation and moderate/severe aortic regurgitation showed significant associations with prevalent CKD (adjusted OR, 1.17 [95% CI, 1.03-1.34] and 2.82 [95% CI, 1.12-7.10]), as did any aortic stenosis in a sensitivity analysis with prevalent CKD defined including albuminuria ≥30 mg/g (1.83 [95% CI, 1.10-3.08]). Only any aortic stenosis showed an independent association with incident CKD (adjusted HR, 2.12 [95% CI, 1.13-4.00]).

**Limitations:** Despite a relatively large study population, some subgroups had small numbers. Although we minimized reverse causation, we cannot completely rule it out.

**Conclusions:** Different valvular abnormality types were associated with prevalent CKD. Only aortic stenosis was robustly associated with incident CKD. These findings suggest an etiological link between valvular abnormality and CKD, highlighting the importance of clinical attention to kidney function in individuals with aortic stenosis.

Approximately 2.5% of the US population has moderate/severe valvular heart disease.1 Prevalence increases with age,2 with over 13% of adults 75 years and older affected by moderate/severe valvular heart disease.1 Recently, novel percutaneous valve replacement therapies such as transcatheter aortic valve replacement and MitraClip have emerged as treatments for valvular heart disease.3,4 With clinical benefits and expanding indications of these treatments, valvular abnormality has been receiving increased attention.3,5-7 Importantly, severe valvular abnormality can lead to several complications including heart failure (HF) and death.8,9

Chronic kidney disease (CKD) may be another complication of valvular abnormality. Several recent papers have reported an improvement in kidney function after transcatheter aortic valve replacement10-12 and MitraClip.13,14 These findings point toward a potential etiological link between valvular abnormality and impaired kidney function.10,14,15 To our knowledge, however, no literature has evaluated the association of valvular abnormality with CKD in the community.

Therefore, we sought to assess the association of major types of left-side valvular abnormality (ie, aortic stenosis, aortic regurgitation, and mitral regurgitation) with both prevalent and incident CKD among community-dwelling older adults by leveraging echocardiography data and longitudinal data on CKD from the Atherosclerosis Risk in Communities (ARIC) study. This research aims to elucidate the potential contribution of valvular abnormality to the development and progression of CKD.

**METHODS**

**Study Population**

The ARIC study is a prospective cohort study with 15,792 participants from 4 communities in the United States: Forsyth County, North Carolina; Jackson, Mississippi; suburbs of Minneapolis, Minnesota; and Washington County, Maryland. The initial visit occurred in 1987-1989 (visit 1) with recruited participants aged between 45-64 years. Visit 5 (2011-2013) was the first visit incorporating...
Recent evidence suggests that individuals who underwent minimally invasive procedures for valvular heart disease had improvements in kidney function. This study evaluated whether there was an association between valvular abnormality (either aortic stenosis, aortic regurgitation, or mitral regurgitation) with chronic kidney disease (CKD). Cross-sectional and prospective analyses of the Atherosclerosis Risk in Communities study data were used to evaluate, respectively, the presence and development of CKD in those with valvular abnormality. We found that different valvular abnormalities were associated with the presence of CKD, whereas only aortic stenosis was associated with future development of CKD. These findings suggest the possibility of a pathophysiological link between valvular abnormality and CKD and highlight a need for clinical attention toward kidney function in those with aortic stenosis.

Exposures: Valvular Abnormality

Our exposures of interest included the following left-side valvular abnormalities: aortic stenosis, aortic regurgitation, and mitral regurgitation. Mitral stenosis was not included because of the low prevalence, and we did not explore right-side valvular abnormalities in the present study given limited image acquisition. At ARIC visit 5, the
Covariates
All covariates were assessed at visit 5 (except for educational level at visit 1) by trained staff. Education level was categorized as advanced (college, graduate school, or professional school), intermediate (high school graduate or vocational school), or basic (less than high school). Race was self-reported as a categorical variable. Body mass index was measured by dividing weight (kg) by height squared (m²). Smoking status and drinking status were categorized as current, former, or never. Diabetes was defined as present if blood glucose ≥126 mg/dL, non-fasting blood glucose ≥200 mg/dL, hemoglobin A1c value ≥6.5%, the use of antidiabetic medication, or the prior diagnosis of diabetes. Blood pressure was measured 3 times using an automatic sphygmomanometer (OMRON HEM-907 XL) and the average of the second and third readings was used for the analysis. Participants were asked to report medication use in the past 4 weeks and bring relevant medication containers to the visit. Total cholesterol level and high-density lipoprotein cholesterol level were determined using enzymatic methods. Prevalent HF was defined as having any adjudicated HF event with first position of International Classification of Diseases code of 428 not overruled by a physician, HF self-report or self-report of HF medication with an elevated NT-proBNP value >125 pg/mL, or subsequent self-report of HF or HF medication.¹⁷ History of coronary heart disease was based on self-reported myocardial infarction or coronary artery revascularization or the presence of a previous myocardial infarction by electrocardiogram at visit 1 or adjudicated myocardial infarction before visit 5.²⁰,²¹

Outcome Variables: Prevalent and Incident CKD
Prevalent CKD for the cross-sectional analysis was primarily defined as eGFR <60 mL/min/1.73 m² (G stage 3 or higher).²² eGFR was calculated using the CKD Epidemiology Collaboration equation based on serum creatinine,²³ which was measured with a creatinase enzymatic method. We secondarily included elevated urinary albumin-to-creatinine ratio (ACR) ≥30 mg/g for defining prevalent CKD in 4,658 participants after excluding 558 participants with missing ACR measures. Urinary albumin was measured using the Dade Behring BN 100 or the Beckman Nephelometer, whereas urinary creatinine was measured using a creatinase enzymatic method.
Among participants without prevalent CKD stage 3 or higher, incident CKD was defined as eGFR <60 mL/min/1.73 m² at subsequent visits accompanied by eGFR decline of at least 25% from visit 5, kidney failure requiring kidney replacement therapy based on linkage to the United States Renal Data System, or hospitalizations/deaths with International Classification of Diseases, Ninth/Tenth Revision codes for CKD (Table S1).²⁴ Again, we explored incident CKD after restricting our analysis to 3,296 participants with ACR data (excluding 1,359 participants with prevalent CKD and 3 participants with missing follow-up information from the 4,658 participants with ACR measures). Participants were followed up until the occurrence of incident CKD, loss to follow-up, non-CKD death, or the end of follow-up on December 31, 2018 (administrative censoring), whichever came first.

Statistical Analysis
All analyses were performed with STATA 15, and a P value <0.05 was considered statistically significant. Baseline characteristics were compared across the status of aortic stenosis, aortic regurgitation, and mitral regurgitation.

Logistic regression was used to quantify the association of valvular abnormalities (present vs absent and severity) with prevalent CKD. The logistic regression models were hierarchically adjusted by covariates to account for potential confounding. Model 1 was crude; Model 2 was adjusted for demographics including age, sex, and race; whereas Model 3 was further adjusted for education level, body mass index, alcohol use, smoking status, systolic blood pressure, hypertension medication use, diabetes, cholesterol lowering medication, total cholesterol level, high-density lipoprotein cholesterol level, and a history of cardiac diseases (ie, coronary heart disease or HF). A stratified analysis was performed to test for potential effect modification by key demographic and clinical factors (eg, age, sex, race, history of cardiac diseases, and use of angiotensin II receptor blockers (ARBs)/angiotensin-converting-enzyme inhibitors (ACEIs) at baseline). This analysis was repeated for the sensitivity analysis incorporating ACR into the definition of CKD. We also evaluated the association of number of valvular abnormalities (ranging from 0 to 3) with prevalent CKD in the main cross-sectional cohort. P-for-trend was evaluated by treating the ordinal number of valvular abnormalities as a continuous variable.

For the prospective analysis, cumulative incidence of CKD was estimated by valvular abnormalities using the Kaplan-Meier method, with log-rank tests for evaluating statistically significant differences. Then, Cox proportional hazards models were used to examine the independent association of valvular abnormalities with incident CKD. We ran Cox models because we were interested in an
| Variable            | Aortic Stenosis | Aortic Regurgitation | Mitral Regurgitation |
|---------------------|-----------------|----------------------|----------------------|
|                     | None  | Mild | Moderate/Severe | None  | Mild | Moderate/Severe | None  | Trace | Mild | Moderate/Severe |
| N                   | 5,142 | 41   | 33               | 4,661 | 533  | 22               | 2,967 | 931   | 1,218 | 100              |
| Age (y)             | 75.5  | 5.1  | 78.1 (4.5)       | 75.3  | 5.0  | 77.6 (5.2)       | 74.9  | 5.0   | 76.0 (5.1) | 76.5 (5.2) | 78.3 (4.9) |
| Female              | 2,993 | 58.2%| 21 (51.2%)       | 2,724 | 58.4%| 293 (55.0%)      | 1,624 | 54.7% | 542 (58.2%) | 792 (65.0%) | 70 (70.0%) |
| Black               | 1,067 | 20.8%| 8 (19.5%)        | 1,002 | 21.5%| 71 (13.3%)       | 693   | 23.4% | 174 (18.7%) | 201 (16.5%) | 10 (10.0%) |
| Education level     |       |      |                  |       |      |                  |       |      |                  |               |               |
| Basic               | 662   | 12.9%| 2 (4.9%)         | 593   | 12.7%| 72 (13.5%)       | 388   | 13.1%| 112 (12.0%) | 152 (12.5%) | 16 (16.0%) |
| Intermediate        | 2,168 | 42.2%| 23 (56.1%)       | 1,968 | 42.2%| 230 (43.2%)      | 1,249 | 42.1%| 383 (41.1%) | 533 (43.8%) | 41 (41.0%) |
| Advanced            | 2,312 | 45.0%| 16 (39.0%)       | 2,100 | 45.1%| 231 (43.3%)      | 1,330 | 44.8%| 436 (46.8%) | 533 (43.8%) | 43 (43.0%) |
| BMI (kg/m²)         | 28.6  | 5.5  | 28.2 (6.3)       | 28.8  | 5.6  | 26.9 (5.0)       | 29.2  | 5.7  | 27.9 (5.0) | 27.9 (5.3) | 26.2 (4.7) |
| Smoking status      |       |      |                  |       |      |                  |       |      |                  |               |               |
| Current             | 317   | 6.2% | 1 (2.4%)         | 297   | 6.4% | 23 (4.3%)        | 206   | 6.9% | 47 (5.0%)   | 62 (5.1%)  | 6 (6.0%)  |
| Former              | 2,673 | 52.0%| 23 (56.1%)       | 2,424 | 52.0%| 282 (52.9%)      | 1,573 | 53.0%| 476 (51.1%) | 611 (50.2%) | 57 (57.0%) |
| Never               | 2,152 | 41.9%| 17 (41.5%)       | 1,940 | 41.6%| 228 (42.8%)      | 1,188 | 40.0%| 408 (43.8%) | 545 (44.7%) | 37 (37.0%) |
| Drinking status     |       |      |                  |       |      |                  |       |      |                  |               |               |
| Current             | 2,585 | 50.3%| 19 (46.3%)       | 2,336 | 50.1%| 275 (51.6%)      | 1,507 | 50.8%| 463 (49.7%) | 606 (49.8%) | 42 (42.0%) |
| Former              | 1,481 | 28.8%| 10 (24.4%)       | 1,352 | 29.0%| 141 (26.5%)      | 853   | 28.7%| 276 (29.6%) | 339 (27.8%) | 35 (35.0%) |
| Never               | 1,076 | 20.9%| 12 (29.3%)       | 973   | 20.9%| 117 (22.0%)      | 607   | 20.5%| 192 (20.6%) | 273 (22.4%) | 23 (23.0%) |
| Diabetes            | 1,869 | 36.3%| 18 (43.9%)       | 1,759 | 37.7%| 138 (25.9%)      | 1,166 | 39.3%| 310 (33.3%) | 400 (32.8%) | 27 (27.0%) |
| Systolic BP (mm Hg) | 130.1 | 17.9 | 126.4 (18.0)    | 127.1 | 17.1 | 129.8 (17.8)    | 128.9 | 17.4 | 129.2 (16.5) | 133.3 (19.3) | 135.5 (19.8) |
| Diastolic BP (mm Hg)| 66.2  | 10.6 | 61.5 (12.2)     | 58.3  | 8.7  | 66.3 (10.6)      | 66.6  | 10.6 | 64.8 (10.3) | 65.8 (10.9) | 67.2 (11.1) |
| Cholesterol-lowering medication use | 2,878 | 56.0%| 27 (65.9)       | 2636 | 56.6 | 283 (53.1)       | 1,680 | 56.6 | 524 (56.3) | 674 (55.3) | 49 (49.0) |
| Hypertension-lowering medication use | 3,834 | 74.6%| 35 (85.4)       | 3,487 | 74.8 | 397 (74.5)       | 2,205 | 74.3 | 687 (73.8) | 931 (76.4) | 75 (75.0) |
| Total cholesterol (mg/dL) | 181.4 | 41.6 | 178.0 (39.7)   | 161.7 | 36.1 | 181.5 (41.5)    | 178.7 | 42.3 | 183.5 (42.1) | 180.9 (42.0) | 182.5 (42.7) |

(Continued)
etiological association of valvular abnormalities with incident CKD. Similar adjustments, stratified analyses, and sensitivity analyses by number of valvular abnormalities were performed for the prospective analysis as described above for the cross-sectional analysis. We additionally adjusted for baseline ACR in analyses by any valvular abnormality and by severity of valvular abnormality. To address a concern of reverse causation, sensitivity analyses were performed by censoring incident CKD cases within 1 year of follow-up.

RESULTS

Baseline Characteristics

The overall mean age was 75.5 (standard deviation 5.1) years, 58.1% were female, and 20.7% were Black. Any aortic stenosis was present in 1.4% (n ≈ 74), any aortic regurgitation in 10.6% (n ≈ 555), and any mitral regurgitation in 43.1% (n ≈ 2,249). The prevalence of moderate/severe stage was 0.6% (n ≈ 33), 0.4% (n ≈ 22), and 1.9% (n ≈ 100), respectively. Thus, the majority of valvular abnormalities (57%-96%) were mild or trace. Participants with a more severe stage of aortic stenosis were likely to be older, male, White, diabetic, and have lower systolic and diastolic blood pressure. They were also more likely to use cholesterol lowering medication and blood pressure lowering medication and have a history of coronary heart disease and HF. However, those with increased severity of aortic regurgitation and mitral regurgitation were more likely to have a lower body mass index, higher systolic blood pressure, less likely to be diabetic, and less likely to use cholesterol lowering medication compared to those with a less severe stage. Those with increased severity of mitral regurgitation were also more likely to be female (Table 1).

Cross-Sectional Analysis: Valvular Abnormalities and Prevalent CKD

The prevalence of CKD was 40.5% and 27.8% in participants with and without aortic stenosis, 31.9% and 27.5% in participants with and without aortic regurgitation, and 31.3% and 25.5% in those with and without mitral regurgitation, respectively (Fig S1). Each valvular abnormality was associated with prevalent CKD in the crude model (Table 2 Model 1). Only any mitral regurgitation remained significantly associated with prevalent CKD after adjustment in Model 3 (adjusted odds ratio [OR], 1.17 [95% CI, 1.03-1.34]).

Among severities of valvular abnormality, moderate/severe aortic regurgitation, versus no regurgitation, was associated with prevalent CKD in the crude model (Table S2 Model 1) and in Model 3 (adjusted OR, 2.82 [95% CI, 1.12-7.10]). Mild mitral regurgitation also remained associated with prevalent CKD in Model 3 (adjusted OR, 1.22 [95% CI, 1.04-1.43]). Greater number of valvular abnormalities were associated with higher ORs.
Between aortic stenosis and prevalent CKD (Fig S2), cation by use of ARBs/ACEis at baseline for the association in those without these medications versus those with (showed significant interaction, with a stronger association interaction < 0.05. Mitral regurgitation Aortic regurgitation showed significant associations. Mitral regurgitation demonstrated similar results (Table S5). Neither any aortic regurgitation nor mitral regurgitation showed significant associations. Among subgroup analyses (Figs S2-S7), only stratification by use of ARBs/ACEis at baseline for the association between aortic stenosis and prevalent CKD (Fig S2) showed significant interaction, with a stronger association in those without these medications versus those with (P for interaction < 0.05).

**Prospective Analysis: Valvular Abnormalities and Incident CKD**

Out of 3,752 participants, during a median of 6.3 years of follow-up, 394 participants had incident CKD (224 incident CKD cases were defined based on eGFR at subsequent ARIC visits, whereas 170 were defined by codes/hospital events). Furthermore, there were 39 participants who underwent valvular surgery during the follow-up period based on International Classification of Diseases codes (14 participants with aortic stenosis at baseline, 10 with aortic regurgitation, and 21 with mitral regurgitation). A clear separation was observed for cumulative incidence of CKD based on both presence and severity of aortic stenosis (log-rank test P < 0.05 in Fig 2 and Fig S8). The 5-year cumulative incidence of CKD was 17.3% for any aortic stenosis and 7.4% for no aortic stenosis. No statistically significant differences were observed in the cumulative incidence of CKD for aortic regurgitation or mitral regurgitation by either presence or severity.

The hazard ratio (HR) of incident CKD was 2.52 (95% CI, 1.35-4.72) in those with any aortic stenosis in the unadjusted model (Table 3 Model 1). The association remained significant after adjustment for demographics (adjusted HR, 2.27 [95% CI, 1.21-4.26]) (Table 3 Model 2) and additional potential confounders in Model 3 (adjusted HR, 2.12 [95% CI, 1.13-4.00]). The further adjustment for ACR in a subsample demonstrated similar results (Table S5). Neither any aortic regurgitation nor mitral regurgitation showed significant associations.

In the analysis by severity of valvular abnormality (Table S6), mild and moderate/severe aortic stenosis was significantly associated with incident CKD in the unadjusted Model 1 (HR, 2.50 [95% CI, 1.04-6.05] and HR, 2.54 [95% CI, 1.05-6.14], respectively). The point estimates for both groups remained similar in Models 2 and 3, although statistically insignificant. Subgroup analyses showed no significant interactions for aortic stenosis, although again, the association appeared stronger in participants not taking ARBs/ACEis at baseline compared to those on these medications (Fig S9). Both mild aortic regurgitation and moderate/severe mitral regurgitation were significantly associated with incident CKD after additionally adjusting for ACR at baseline (Table S7). Further, the subgroups of age at least 75 years and history of HF showed significant associations of aortic regurgitation with incident CKD (Fig S10), and participants who were taking ARBs/ACEis had a significant result for mitral regurgitation (Fig S11). Greater numbers of valvular abnormalities showed a significant association with incident CKD (P-for-trend = 0.03 and HR, 1.48 [95% CI, 1.01-2.18] in 2-3 valvular abnormalities), particularly after full adjustment (Table S8).

The sensitivity analysis censoring individuals who developed incident CKD in the first year of follow-up demonstrated a significant HR for any aortic stenosis in the unadjusted model (HR, 2.14 [95% CI, 1.06-4.30]) (Table S9 Model 1). Although adjustment in Models 2 and 3 resulted in some attenuation, the point estimates were largely consistent with the main prospective analysis results (Table 3). Similarly, point estimates for mild aortic

| Valve Disease/Severity | No. of People | No. of Outcome (CKD) | Model 1 OR (95% CI) | Model 2 OR (95% CI) | Model 3 OR (95% CI) |
|------------------------|---------------|----------------------|---------------------|---------------------|---------------------|
| Aortic stenosis         |               |                      |                     |                     |                     |
| None                   | 5,142         | 1,430                | Ref.                | Ref.                | Ref.                |
| Any AS                 | 74            | 30                   | 1.77 (1.11-2.83)*   | 1.41 (0.88-2.28)    | 1.24 (0.76-2.03)    |
| Aortic regurgitation    |               |                      |                     |                     |                     |
| None                   | 4,661         | 1,283                | Ref.                | Ref.                | Ref.                |
| Any AR                 | 555           | 177                  | 1.23 (1.02-1.49)*   | 0.99 (0.82-1.21)    | 1.03 (0.84-1.26)    |
| Mitral regurgitation    |               |                      |                     |                     |                     |
| None                   | 2,967         | 756                  | Ref.                | Ref.                | Ref.                |
| Any MR                 | 2,249         | 704                  | 1.33 (1.18-1.50)*   | 1.18 (1.04-1.34)*   | 1.17 (1.03-1.34)*   |

Notes: Model 1: crude. Model 2: age, sex, race. Model 3: Model 2 + education level, body mass index, alcohol use, smoking status, systolic blood pressure, hypertension medication use, diabetes, cholesterol lowering medication, total cholesterol level, high-density lipoprotein cholesterol level, history of coronary heart disease, history of heart failure.

Abbreviations: AR, aortic regurgitation; AS, aortic stenosis; CI, confidence interval; CKD, chronic kidney disease; MR, mitral regurgitation; OR, odds ratio; Ref., reference.

*P < 0.05
**P < 0.001
stenosis (Table S10) were largely consistent to results without censoring follow-up (Table S6).

**DISCUSSION**

In community-dwelling older adults, we observed multiple measures of valvular abnormalities to be independently associated with prevalent and incident CKD. Specifically, any mitral regurgitation and any aortic stenosis were significantly associated with prevalent CKD (when including elevated ACR for the latter). For incident CKD, among the valvular abnormalities tested, aortic stenosis demonstrated the most evident and robust association. In subgroup analyses, although we observed generally consistent results in most subgroups tested, in some comparisons, participants not on ARBs/ACEis tended to have stronger associations than those on these medications (eg, aortic stenosis and incident CKD). However, specific subgroups demonstrated significant associations for mitral regurgitation with prevalent CKD and for aortic stenosis and regurgitation with incident CKD. Greater numbers of valvular abnormalities were independently associated with increased CKD risk in both cross-sectional and prospective analyses.

To our knowledge, this is the first study evaluating the association of valvular abnormality with prevalence and future risk of CKD. We used a comprehensive definition of valvular abnormality, encompassing both presence and severity for aortic stenosis, aortic regurgitation, and mitral regurgitation. We also studied both prevalent and incident CKD by leveraging both CKD biomarkers, eGFR and ACR (for prevalent CKD as a sensitivity analysis), and hospitalization records in ARIC. Our findings are generally in line with recent literature showing improved kidney function after transcatheter valve therapy and further support the etiological link between valvular abnormalities and CKD. The results also suggest that not all valvular abnormalities were similarly associated with CKD.

One of the key findings of our study was the significant association of aortic stenosis with incident CKD. There are a few potential mechanisms behind this association. For example, shared risk factors such as hypertension may play a role. However, the association remained significant after accounting for these factors. Aortic stenosis may also represent pathophysiological mechanisms which contribute to the development of CKD. For example, inflammation and endothelial dysfunction are pathophysiologically involved in both aortic stenosis and progression of CKD. Interestingly, in our study, any aortic stenosis was found to be associated with prevalent CKD when we incorporated ACR, a measure of kidney damage representing endothelial

![Figure 2. Cumulative incidence of CKD according to presence or absence of valvular abnormality. Abbreviation: CKD, chronic kidney disease.](image)

**Table 3.** Hazard Ratios (95% CIs) for Incident CKD by Any Valvular Abnormality (Prospective Analysis)

| Valve Disease/Severity | No. of People | No. of Outcome (CKD) | Model 1 HR (95% CI) | Model 2 HR (95% CI) | Model 3 HR (95% CI) |
|------------------------|---------------|----------------------|---------------------|---------------------|---------------------|
| Aortic stenosis        |               |                      |                     |                     |                     |
| None                   | 3,708         | 384                  | Ref.                | Ref.                | Ref.                |
| Any AS                 | 44            | 10                   | 2.52 (1.35-4.72)*   | 2.27 (1.21-4.26)*   | 2.12 (1.13-4.00)*   |
| Aortic regurgitation   |               |                      |                     |                     |                     |
| None                   | 3,375         | 350                  | Ref.                | Ref.                | Ref.                |
| Any AR                 | 377           | 44                   | 1.16 (0.85-1.58)    | 1.11 (0.81-1.53)    | 1.32 (0.95-1.81)    |
| Mitral regurgitation   |               |                      |                     |                     |                     |
| None                   | 2,209         | 228                  | Ref.                | Ref.                | Ref.                |
| Any MR                 | 1,543         | 166                  | 1.07 (0.88-1.31)    | 1.08 (0.88-1.33)    | 1.16 (0.94-1.42)    |

Notes: Model 1: crude. Model 2: age, sex, race. Model 3: Model 2 + education level, body mass index, alcohol use, smoking status, systolic blood pressure, hypertension medication use, diabetes, cholesterol lowering medication, total cholesterol level, high-density lipoprotein cholesterol level, history of coronary heart disease, history of heart failure.

Abbreviations: AR, aortic regurgitation; AS, aortic stenosis; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; MR, mitral regurgitation; Ref., reference.

*P < 0.05.
dysfunction. Another possibility is the contribution of altered hemodynamics due to aortic stenosis. However, to what extent this contributes to our observation is uncertain because most participants with aortic stenosis in our study were at the mild stage. Nonetheless, future studies are needed to explore the mechanisms linking aortic stenosis and CKD.

We did not find a statistically significant association of aortic regurgitation or mitral regurgitation with incident CKD in our primary analysis of the entire study population. However, it seems too early to conclude this observation as the lack of etiological contribution of these valvular abnormalities because we observed significant associations of these valvular abnormalities with incident CKD in some additional analyses of specific subgroups (e.g., older participants) and with the adjustment for ACR in a subsample. Further, analyses showed that having 2-3 valvular abnormalities was associated with incident CKD, suggesting some contribution of mitral regurgitation to CKD risk, because most participants (~97%) with multiple valvular abnormalities had mitral regurgitation (as the most prevalent valvular abnormality in this study). Thus, a larger study or a study with longer follow-up would be needed to obtain conclusive results for the contribution of these 2 types of valvular abnormality to CKD progression.

More robust association between mitral regurgitation and CKD in the cross-sectional analysis than in the prospective analysis deserves some discussion. Although speculative, the results of the cross-sectional analysis may reflect a bidirectional association between CKD and mitral regurgitation. Indeed, CKD can cause volume overload and left ventricular dilation, potentially inducing or exacerbating mitral regurgitation. Some experts have also proposed that mitral regurgitation in CKD may be related to mitral valve apparatus structure and left ventricular changes caused by coronary artery disease.

Although patients with moderate/severe valvular abnormality are getting increasing attention because of novel percutaneous valve therapies, our results indicate association of even mild valvular abnormality with CKD. A long preclinical phase where individuals are asymptomatic and unaware of disease processes is common to valvular heart disease. Therefore, our results warrant attention toward kidney function among individuals with valvular abnormality even at milder stages, especially in individuals with aortic stenosis. Of importance, a few therapeutics such as renin angiotensin system inhibitors and sodium/glucose cotransporter 2 inhibitors have shown potential in slowing CKD progression. It seems worth exploring whether these medications can reduce the risk of CKD progression in persons with aortic stenosis.

This study has a few limitations. First, despite a relatively large study population, our study had small numbers of individuals with mild aortic stenosis and moderate/severe valvular abnormality of any type. This might have limited statistical power when evaluating the association of valvular abnormality by severity with CKD. Second, we did not have the data to perform a sensitivity analysis incorporating an ACR based definition of CKD in the prospective analysis. Third, because cardiovascular disease and CKD are tightly interrelated, we cannot completely rule out reverse causation even in the prospective analysis, although we tried to minimize its influence by censoring individuals who developed CKD in the first year of follow-up. Finally, our study population included only individuals aged between 66 and 90 years and Black and White individuals, which may somewhat limit the study’s generalizability to other age ranges and racial/ethnic groups.

In conclusion, different types of valvular abnormality were associated with prevalent CKD, whereas the robust prospective association with incident CKD was restricted to aortic stenosis. These findings suggest an etiological link between valvular abnormality and CKD and highlight the importance of clinical attention to kidney function in individuals with valvular abnormality, especially aortic stenosis.

**SUPPLEMENTARY MATERIAL**

**Supplementary File (PDF)**

- **Figure S1.** Prevalence of CKD by Valvular Abnormality
- **Figure S2.** Subgroup Analysis for Aortic Stenosis in Cross-sectional Cohort
- **Figure S3.** Subgroup Analysis for Aortic Regurgitation in Cross-sectional Cohort
- **Figure S4.** Subgroup Analysis for Mitral Regurgitation in Cross-sectional Cohort
- **Figure S5.** Subgroup Analysis for Aortic Stenosis in Cross-sectional Cohort with ACR
- **Figure S6.** Subgroup Analysis for Aortic Regurgitation in Cross-sectional Cohort with ACR
- **Figure S7.** Subgroup Analysis for Mitral Regurgitation in Cross-sectional Cohort with ACR
- **Figure S8.** Cumulative Incidence of CKD According to Presence or Absence of Valvular Abnormality
- **Figure S9.** Subgroup Analysis for Aortic Stenosis in Prospective Cohort
- **Figure S10.** Subgroup Analysis for Aortic Regurgitation in Prospective Cohort
- **Figure S11:** Subgroup Analysis for Mitral Regurgitation in Prospective Cohort

**Table S1.** ICD-9/ICD-10 Codes for Incident CKD
**Table S2.** Odds Ratios (95% CIs) of Prevalent CKD by Severity of Valvular Abnormality (Cross-sectional Analysis)
**Table S3.** Odds Ratios (95% CI) for Prevalent CKD by Number of Valvular Abnormalities (Cross-sectional Analysis)
**Table S4.** Odds Ratios (95% CIs) of Prevalent CKD by Any Valvular Abnormality (Sensitivity Analysis with CKD Definition Incorporating Albumin-Creatinine Ratio)
**Table S5:** Hazard Ratios (95% CI) for Incident CKD by Any Valvular Abnormality in Subset with ACR Measures (Prospective Analysis)
**Table S6.** Hazard Ratios (95% CI) for Incident CKD by Severity of Valvular Abnormality (Prospective Analysis)
Table S7. Hazard Ratios (95% CI) for Incident CKD by Severity of Valvular Abnormality in Subset with ACR Measures (Prospective Analysis)

Table S8. Hazard Ratios (95% CI) for Incident CKD by Number of Valvular Abnormalities (Prospective Analysis)

Table S9. Hazard Ratios (95% CI) for Incident CKD by Any Valvular Abnormality Censoring Those Who Had CKD within 1 Year of Follow-Up (Sensitivity Analysis)

Table S10. Hazard Ratios (95% CI) for Incident CKD by Severity of Valvular Abnormality Censoring Those Who Had CKD within 1 Year of Follow-Up (Sensitivity Analysis)

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Is there an association between cardiac valvular disease and prevalent and incident CKD: the ARIC Study?

**METHODS**
- Prospective analysis
  - N = 3752
  - Median FU 6.3 years
- Incident eGFR <60 +
  - ↓ eGFR 25%
  - KRT
  - Death/admission 2/2 CKD
- Cross sectional analysis
  - N = 5216
- Prevalent eGFR < 60
  - (+ uACR > 30 mg/g)
- Valvular Disease:
  - Aortic stenosis
  - Aortic regurgitation
  - Mitral regurgitation

**RESULTS**

**CROSS SECTIONAL ANALYSIS**

| Condition          | OR    | 95% CI       |
|--------------------|-------|--------------|
| Aortic Stenosis    | 1.83  | 1.10 - 3.05  |
| Aortic Regurgitation| 2.82  | 1.12 - 7.10  |
| Mitral Regurgitation| 1.17  | 1.03 - 1.34  |

**PROSPECTIVE ANALYSIS**

| Condition          | HR    | 95% CI       |
|--------------------|-------|--------------|
| Aortic Stenosis    | 2.12  | 1.13 - 4.00  |
| Aortic Regurgitation|      |              |
| Mitral Regurgitation|      |              |

**Conclusion:** Prevalent CKD was associated with MR, AR and AS in the ARIC study. Only AS was robustly associated with incident CKD, suggesting an etiological link between valvular disease and CKD.

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