Cause-Specific Mortality in Patients with Chronic Kidney Disease and Atrial Fibrillation

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Keywords

Atrial fibrillation · Cause-specific death · Chronic kidney disease

Abstract

Background: Atrial fibrillation (AF) is associated with death in patients with chronic kidney disease (CKD). We examined the associations between AF and cause-specific mortality in a large CKD population. **Methods:** We included 62,459 patients with estimated glomerular filtration rate 15–59 mL/min/1.73 m² (6,639 patients with AF and 55,820 without AF) followed in a large health care system. Outcomes included overall and cause-specific deaths (a) cardiovascular; (b) malignancy; and (c) non-cardiovascular/non-malignancy causes. Cox regression models for overall mortality and separate competing risk models for each major cause of death category were used to evaluate their respective associations

with AF. **Results:** During a median follow-up of 4.1 years, 19,094 patients died; cause of death was known for 18,854 patients. After multivariable adjustment (demographics, comorbidities, relevant laboratory data, medication use, and kidney function), AF was associated with 23% (95% CI 18–29%) higher risk of all-cause mortality, 45% (95% CI 31–61%) higher risk of cardiovascular mortality and 13% (95% CI 3–22%) lower risk of malignancy-related mortality. Exclusion of patients with malignancy yielded similar results except for a lack of association between AF and malignancy-related deaths. Results were consistent across various stages of CKD. **Conclusions:** In a non-dialysis-dependent CKD population, the presence of AF was associated with higher all-cause and cardiovascular mortality. These data suggest that patients with both CKD and AF are at high cardiovascular risk, and thus clinical practice (or trials) should aim at reducing the overall excess cardiovascular mortality (not stroke alone) in patients with AF and CKD.

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Background

Atrial fibrillation (AF) is the most common arrhythmia affecting about 2% of those aged <65 years and 9% among those aged 65 years or older in the United States [1]. AF is more common in individuals with both non-dialysis- and dialysis-dependent chronic kidney disease (CKD) [2–11]. Using the Chronic Renal Insufficiency Cohort study data, Soliman et al. [12] reported that 1 in 5 CKD patients had AF, a rate similar to that noted in the end-stage renal disease (ESRD) population, and 2–3 times higher than that in the general population. Recent data from the United States Renal Data System report a rising trend in the overall prevalence of AF in CKD (24.5%), as well as in those with CKD and congestive heart failure, in whom the prevalence increases to over 50% [13].

AF is associated with a higher all-cause mortality among patients with ESRD [2, 14], as has been shown among patients with non-dialysis-dependent CKD [8, 15–17]. However, less is known about the potential reasons for the increased mortality risk associated with AF. Elucidating the causes of increased mortality in these patients may help guide management to reduce risk. Current strategies to lessen the impact of AF-related outcomes focus mainly on thromboembolism prevention, but patients with AF have high mortality rates from other non-cardiovascular causes as well [18]. Identifying the causes of death would argue for testing targeted interventions beyond using vitamin K antagonists and direct oral anticoagulants for thromboembolism prevention [19, 20]. Our study aimed to fill this evidence gap and investigate cause-specific mortality in CKD patients with AF.

Methods

This analysis was conducted using a pre-existing Electronic Health Record (EHR)-based CKD registry at the Cleveland Clinic. The development and validation of this EHR-based CKD registry has been described in detail elsewhere [21].

Study Population

Patients who met the following criteria from January 1, 2005 through December 31, 2013 and lived in the State of Ohio were included: (1) had at least 1 face-to-face outpatient encounter with a Cleveland Clinic health care provider and (2) had at least 2 or more estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² that were at least 90 days apart (using the CKD Epidemiology Collaboration equation) with the second one being 15–59.9 mL/min/1.73 m² [22]. Patients known to have ESRD needing dialysis or renal transplant prior to CKD diagnosis were excluded.

Definitions and Outcome Measures

Kidney Function

We applied the CKD-Epidemiology Collaboration equation to patients who had 2 outpatient serum creatinine levels between January 1, 2005 and December 31, 2013 to calculate eGFR. All creatinine measurements were performed by the modified kinetic Jaffe reaction using a Hitachi D 2400 Modular Chemistry Analyzer (Roche Diagnostics, Indianapolis, IN) at the Cleveland Clinic laboratory. CKD was defined according to current guidelines as follows: stage 3 CKD (eGFR 30–59 mL/min/1.73 m²) and stage 4 CKD (eGFR 15–29 mL/min/1.73 m²). We further categorized stage 3 into CKD stage 3a (eGFR 45–59 mL/min/1.73 m²) and stage 3b (eGFR 30–44 mL/min/1.73 m²).

Atrial Fibrillation

Prevalent AF was defined as the presence of an International Classification of Diseases (ICD) 9 code 427.31 by providers (at least twice) in the EHR at study entry. We randomly selected 10 patients with AF and 10 without AF for chart review validation performed by one of the authors (S.E.J.). Our chart review validation found that 90% of patients with AF per EMR data extraction had AF and 90% of patients without AF per EMR did not have AF.

Mortality

Dates of death were ascertained from the EHR and through linkage of the CKD registry with Ohio Department of Health mortality data, which also provided cause of death information. The reported cause of death was coded according to the ICD-10. We grouped the underlying causes of death as per the National Center for Health Statistics for each coding system, except for some changes as outlined below. We classified deaths into the following 4 major categories: (a) cardiovascular deaths, (b) malignancy, and (c) non-cardiovascular, non-malignancy-related deaths [23]. We defined cardiovascular deaths as deaths due to diseases of the heart, essential hypertension, cerebrovascular disease, atherosclerosis, or other diseases of the circulatory system (ICD-10 codes I00–I78). We defined death due to ischemic heart disease as I20–I25, heart failure as I50, and cerebrovascular disease as I60–I69.

Covariates

Demographic details were extracted from the EHR. Diabetes mellitus, hypertension, coronary artery disease, congestive heart failure, hyperlipidemia, malignancy, and cerebrovascular disease were defined using pre-specified and validated criteria. Relevant outpatient laboratory values (hemoglobin, albumin) and medication details were obtained from the EHR.

Statistical Analysis

We compared baseline characteristics between patients with and without AF using chi-square and *t* tests for categorical and continuous variables respectively. We conducted a logistic regression analysis to identify factors associated with AF adjusting for age, sex, race, diabetes, hypertension, body mass index (BMI), coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, hemoglobin, and eGFR. We tabulated the leading causes of death in those with and without AF. Patients were followed from the second (confirmatory) eGFR measurement <60 mL/min/1.73 m² and censored on December

Fig. 1. Flowchart showing how patients were selected to be included in this analysis. AF, atrial fibrillation.

2013. We used unadjusted and adjusted Cox proportional hazards models to evaluate the relationship between AF and all-cause mortality, and competing risks regression analysis to evaluate the relationship between AF and various causes of death. The mortality models were adjusted for age, sex, race, diabetes, hyperlipidemia, BMI, albumin, hemoglobin, malignancy, hypertension, coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, insurance type, use of Angiotensin converting enzyme inhibitors/angiotensin receptor blockers, beta blocker use, statins use, smoking status, and eGFR. All results were expressed as OR or hazard ratios (HR) with corresponding 95% CI.

We tested 2-way interactions between AF and age, race, sex, coronary artery disease, and eGFR on overall mortality. We did not account for multiple testing and significance was set at a nominal p value of 0.05. We performed sensitivity analyses excluding patients with baseline malignancy (25% of the study population) and adjusting for proteinuria among those in whom proteinuria data were available (48% of the study population). The percent of missing information among patients was as follows: 4% insurance information, 14% smoking status, 4% BMI, 15% albumin, and 17% hemoglobin. We used multiple imputation (SAS proc MI) with the Markov Chain Monte Carlo method and a single chain to impute 5 datasets with complete continuous and binary covariate data in a first step, and then in a second step, we imputed insurance group on each of the 5 datasets using discriminant function analysis. All models were performed on each of the 5 imputed datasets, and parameter estimates were combined using SAS MI analyze.

All analyses were conducted using Linux SAS version 9.4 (SAS Institute, Cary, NC, USA) and graphs were created using R 3.3.2

(The R Foundation for Statistical Computing, Vienna, Austria). The CKD registry and this study were approved by the Cleveland Clinic Institutional Review Board (IRB #09-015).

Results

Baseline Patient Characteristics

Between January 1, 2005 and December 31, 2013, 69,547 patients were included in our CKD registry with eGFR 15–59 mL/min/1.73 m². We excluded 7,088 patients because they did not meet the specified inclusion criteria (Fig. 1). Of the remaining 62,459 patients, 6,639 (10.6%) of patients had AF at cohort entry. The clinical characteristics of the patients with and without AF are presented in Table 1. Patients with AF were older and had a higher proportion of comorbid conditions such as diabetes, hyperlipidemia, coronary artery disease, and congestive heart failure (Table 1). Approximately 80% of patients with AF and 9% of patients without AF were on anticoagulants.

Factors Associated with AF in CKD

In a multivariable model adjusted for relevant covariates, age, male sex, obesity, hypertension, cardiovascular disease, cerebrovascular disease, congestive heart failure, and stage 4 (versus stage 3a) CKD were associated with higher odds of having AF (Table 2).

AF and Mortality

During a median follow-up of 4.1 years, there were 19,094 deaths (AF group: 115.8 deaths per 1,000 years and No AF group: 69.3 deaths per 1,000 years of follow-up). In multivariable analysis, AF was associated with significantly higher hazards of mortality (HR 1.23 95% CI 1.18–1.29). Causes of death details were available from the Ohio Department of Health mortality data for 18,854 patients. We excluded the 240 patients whose deaths were only found in the EHR (but not from the Department of Health files) from all cause-specific mortality analyses. Table 3 displays the causes of death overall and by AF. In the models adjusting for relevant covariates, the presence of AF was associated with higher sub-hazards of cardiovascular deaths and lower sub-hazards of malignancy-related deaths (Table 4a). Figure 2 shows the higher sub-hazards identified for ischemic heart disease, heart failure, and cerebrovascular disease-related deaths among those with AF and CKD. However, in the model in which CKD patients with malignancy at baseline were excluded, the presence of AF was associated only with a higher risk of cardiovascular deaths.

Table 1. Patient characteristics, by presence vs. absence of atrial fibrillation, in the Cleveland clinic CKD Registry

Factor*	AF (n = 6639)	No AF (n = 55,820)	Overall (n = 62,459)	p value
Age, years	76.4±9.9	71.9±11.5	72.4±11.4	<0.001 ^a
Gender, male	54.4	42.6	43.8	<0.001 ^c
African American	8.3	13.2	12.7	<0.001 ^c
Smoking				<0.001 ^c
No	91.3	77.3	78.8	
Yes	4.3	7.4	7.0	
Missing	4.4	15.3	14.2	
BMI, kg/m ²	29.1±6.4	29.5±6.6	29.5±6.6	<0.001 ^a
BMI categories, kg/m ²				<0.001 ^c
<18.5	1.6	1.3	1.3	
18.5–24.9	24.3	22.3	22.5	
25–29.9	35.5	34.0	34.1	
30–34.9	21.0	21.3	21.3	
35–39.9	9.0	9.8	9.7	
>40	6.0	6.9	6.8	
Missing	2.5	4.4	4.2	
Diabetes	27.0	23.0	23.4	<0.001 ^c
Malignancy	24.2	24.6	24.6	0.40 ^c
Hypertension	92.8	84.0	84.9	<0.001 ^c
Hyperlipidemia	82.4	77.1	77.7	<0.001 ^c
Coronary artery disease	41.3	18.1	20.5	<0.001 ^c
Congestive heart failure	28.7	5.4	7.9	<0.001 ^c
Cerebrovascular disease	16.4	8.3	9.2	<0.001 ^c
Peripheral vascular disease	4.8	3.0	3.2	<0.001 ^c
Liver disease	5.0	5.5	5.5	0.081 ^c
COPD/asthma	15.4	9.7	10.3	<0.001 ^c
ACE-I/ARB	76.4	61.0	62.7	<0.001 ^c
Diuretic	83.6	63.2	65.4	<0.001 ^c
Statin	66.9	55.9	57.1	<0.001 ^c
Beta blocker use	86.1	51.4	55.1	<0.001 ^c
Anticoagulant agents use	80.0	8.8	16.4	<0.001 ^c
Antiplatelet agents use	18.8	14.3	14.7	<0.001 ^c
eGFR, mL/min/1.73 m ²	47.1±10.3	47.8±10.3	47.7±10.3	<0.001 ^a
CKD Stage (eGFR range)				<0.001 ^c
Stage 3a (45–59)	64.7	68.0	67.6	
Stage 3b (30–44)	27.4	24.3	24.6	
Stage 4 (15–29)	8.0	7.7	7.8	
Albumin, g/dL	4.1±0.42	4.1±0.47	4.1±0.47	0.50 ^a
Hemoglobin, mg/dL	12.8±1.8	12.8±1.8	12.8±1.8	0.049 ^a
Proteinuria	25.4	25.5	25.5	0.85 ^c
Insurance				<0.001 ^c
Medicaid	0.17	0.35	0.33	
Medicare	85.9	78.4	79.2	
Missing	3.0	3.9	3.8	
Other	11.0	17.3	16.6	

* Data shown as mean ± SD or column %.

^a t test; ^c Chi-square.

AF, atrial fibrillation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate, CKD, chronic kidney disease.

Table 2. Factors independently associated with atrial fibrillation in the Cleveland clinic CKD registry

	OR (95% CI)*	p value
Age (per 10 years)	1.46 (1.42–1.51)	<0.001
Gender, male	1.40 (1.32–1.48)	<0.001
African American race	0.53 (0.48–0.59)	<0.001
BMI 25–29.9 vs. 18.5–24.9 kg/m ²	1.00 (0.93–1.08)	0.96
BMI >30 vs. 18.5–24.9 kg/m ²	1.11 (1.03–1.20)	0.01
BMI <18.5 vs. 18.5–24.9 kg/m ²	1.18 (0.95–1.47)	0.13
Coronary artery disease	1.79 (1.68–1.90)	<0.001
Congestive heart failure	6.03 (5.62–6.48)	<0.001
Cerebrovascular disease	1.50 (1.38–1.62)	<0.001
Hypertension	2.09 (1.89–2.32)	<0.001
Peripheral vascular disease	0.93 (0.81–1.06)	0.27
Hemoglobin Q2 vs. Q1	0.96 (0.88–1.05)	0.42
Hemoglobin Q3 vs. Q1	0.94 (0.87–1.03)	0.17
Hemoglobin Q4 vs. Q1	1.00 (0.91–1.09)	0.91
Diabetes	0.94 (0.88–1.00)	0.06
CKD stage 4 (eGFR 15–29 vs. 45–59 mL/min/1.73 m ²)	0.85 (0.76–0.95)	0.003
CKD stage 3b (eGFR 30–44 vs. 45–59 mL/min/1.73 m ²)	1.00 (0.93–1.06)	0.89

All estimates obtained from MI analyze from the 5 imputed datasets.

* Models adjusted for age, gender, race, diabetes, hypertension, BMI, coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, hemoglobin and eGFR.

Hemoglobin Q1- <11.7 g/dL; Q2- 11.7–12.9 g/dL; Q3- 12.9–14.0 g/dL; Q4- >14.0 g/dL.

BMI, body mass index; CKD, chronic kidney disease.

Table 3. Causes of death, by presence vs. absence of atrial fibrillation, in the Cleveland clinic CKD registry

Causes	AF (n = 2,581)	No AF (n = 16,273)	Total (n = 18,854)
All cardiovascular diseases	49.1	32.7	35.0
Ischemic heart disease	23.1	16.5	17.4
Heart failure	5.3	2.4	2.8
Cerebrovascular disease	4.7	4.1	4.2
All other cardiovascular diseases	16.0	9.7	10.6
Malignant neoplasms	16.0	28.4	26.7
Non-cardio non-malignancy	32.5	37.0	36.4
Chronic lower respiratory diseases	4.8	4.8	4.8
Diabetes mellitus	3.1	4.0	3.9
Nephritis, nephrotic syndrome and nephrosis	3.0	2.6	2.6
Alzheimer's disease	1.8	2.4	2.3
Influenza and pneumonia	2.4	1.9	1.9
Septicemia	1.8	1.9	1.9
Chronic liver disease and cirrhosis	0.35	1.1	1.0
Pneumonitis due to solids and liquids	1.1	0.93	0.95
Parkinson's disease	0.27	0.61	0.56
All other diseases	13.9	16.8	16.4
Non-disease-related deaths	2.4	1.9	1.9

Data shown as column %. AF, atrial fibrillation.

Table 4.**a** Associations of atrial fibrillation with all-cause and cause-specific mortality in the Cleveland clinic CKD registry

	Unadjusted HR (95% CI)	<i>p</i> value	Adjusted* HR (95% CI)	<i>p</i> value	Excluding those with malignancy adjusted* HR (95% CI)	<i>p</i> value
All-cause death	1.69 (1.62–1.76)	<0.001	1.23 (1.18–1.29)	<0.001	1.31 (1.25–1.39)	<0.001
	Unadjusted SHR (95% CI)		Adjusted* SHR (95% CI)		Adjusted* SHR (95% CI)	
Cardiovascular mortality [^]	2.40 (2.26–2.55)	<0.001	1.45 (1.36–1.56)	<0.001	1.48 (1.37–1.60)	<0.001
Malignancy-related mortality [^]	0.80 (0.73–0.89)	<0.001	0.87 (0.78–0.97)	0.016	1.01 (0.86–1.20)	0.90
Non-cardio non-malignancy mortality [^]	1.33 (1.23–1.42)	<0.001	1.05 (0.96–1.13)	0.28	1.02 (0.93–1.12)	0.62

* Adjusted for age, sex, race, diabetes, hyperlipidemia, body mass index, albumin, hemoglobin, malignancy (except in analysis excluding patients with baseline malignancy), hypertension, coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, insurance type, ACE/ARB, beta blocker use, statins use, smoking, and eGFR.

Hazard and sub-hazard ratios (HR and SHR) presented in adjusted models were pooled using MIanalyze from 5 multiply imputed datasets.

[^] *n* = 62,219 due to some missing cause of death.

b Associations of atrial fibrillation with all-cause and cause-specific mortality among those with proteinuria data (*n* = 30,143)

	Unadjusted HR (95% CI)	<i>p</i> value	Adjusted* HR (95% CI)	<i>p</i> value
All-cause death	1.67 (1.57–1.78)	<0.001	1.24 (1.16–1.32)	<0.001
	SHR (95% CI)		SHR (95% CI)	
Cardiovascular mortality [^]	2.26 (2.06–2.47)	<0.001	1.45 (1.31–1.61)	<0.001
Malignancy-related mortality [^]	0.91 (0.79–1.04)	0.17	0.91 (0.78–1.07)	0.24
Non-cardio non-malignancy mortality [^]	1.33 (1.19–1.47)	<0.001	1.08 (0.96–1.21)	0.21
Cardiovascular sub-categories				
Ischemic heart disease [^]	2.03 (1.78–2.32)	<0.001	1.28 (1.10–1.48)	0.001
Heart failure [^]	2.63 (1.94–3.56)	<0.001	1.22 (0.86–1.73)	0.22
Cerebrovascular disease [^]	1.73 (1.30–2.29)	<0.001	1.30 (0.95–1.78)	0.10
Other cardiovascular diseases [^]	2.35 (2.00–2.76)	<0.001	1.69 (1.40–2.03)	<0.001

* Adjusted for age, sex, race, diabetes, hyperlipidemia, body mass index, albumin, hemoglobin, malignancy (except in analysis excluding patients with baseline malignancy), hypertension, coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, insurance type, ACE/ARB, beta blocker use, statins use, smoking, eGFR and proteinuria.

Hazard and sub-hazard ratios presented in adjusted models were pooled using MIanalyze from 5 multiply imputed datasets.

[^] *n* = 30,033 due to some missing cause of death.

Effect Modification

The multiplicative interaction between AF and age on overall mortality was significant ($p = 0.02$) suggesting that the risk associated with AF was stronger among younger patients (HR 1.39, 95% CI 1.22–1.60 for patients <65 years vs. HR 1.30, 95% CI 1.24–1.36 for ≥65 years). The interaction between AF and sex on overall mortality was also significant ($p = 0.04$) suggesting that the hazard associated with AF was significant for both sexes but stronger among women (HR 1.29, 95%

CI 1.21–1.38 for women vs. HR 1.18, 95% CI 1.12–1.26 for men). The interactions between AF and race, eGFR and pre-existing cardiovascular disease were not nominally significant.

Sensitivity Analysis

Table 4a also shows the results of the sensitivity analysis excluding patients with baseline malignancy. These results were similar for cardiovascular and non-cardiovascular non-malignancy mortality. When excluding pa-

Fig. 2. Associations of AF with specific type of cardiovascular deaths in those with CKD. Model adjusted for age, sex, race, diabetes, hyperlipidemia, body mass index (BMI), albumin, hemoglobin, malignancy (except in analysis excluding patients with baseline malignancy), hypertension, coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, insurance type, use of ACE/angiotensin receptor blocker (ARB), beta blocker use, statins use, smoking status, and eGFR.

tients with baseline malignancy, malignancy-related mortality was not significantly different between those with and without AF. The analysis adjusted for proteinuria yielded results, similar to the primary analysis (Table 4b).

Discussion

In a well-described cohort of patients with CKD who were followed in a usual health care setting, prevalent AF was noted among 11% of the study population. Various demographic variables, comorbid conditions and stage 4 CKD were associated with higher odds of having AF. We also report an increased risk of all-cause death among those with AF and CKD. These results are consistent with prior reports noting similar associations [8, 15–17]. We were specifically interested in cause-specific mortality in this population with both AF and CKD and found that cardiovascular deaths accounted for approximately half of the deaths. Even though there was a lower risk of malignancy-related death among those with AF and CKD, such an association was no longer present when patients with pre-existing malignancy were excluded. Cumulatively, these data provide novel insights about etiologies for

death among this high-risk population with concurrent CKD and AF.

In the general population, associations between AF and various cause-specific deaths have been investigated. Fauchier et al. [24] reported that among 8,962 patients with incident AF, majority of deaths during follow-up were related to cardiovascular disease (54%), and heart failure (29%) was specifically noted to be the most common cause of death. Notably, despite the high risk of stroke with AF, only 7% died from stroke [24]. Gomez-Outez et al. [25] pooled data from 4 clinical trials representing 71,683 patients with AF. They noted that cardiac deaths accounted for 46% of all deaths, and stroke-related deaths accounted for 11.3% of the total mortality [25]. Such comprehensive assessment of cause-specific death is lacking for the large and important CKD substratum within the population with AF. Similar to the general population, cardiovascular deaths accounted for a majority of deaths (49%) in our analysis. Specifically, ischemic heart disease, heart failure, and cerebrovascular disease were associated with 21, 58, and 31% increased sub-hazards of death, respectively, in these patients with both AF and CKD. Literature examining the associations of cardiovascular events with increased mortality in CKD patients with AF is quite limited. In a single-center study, Nakagawa and colleagues reported that combined eGFR and CHADS₂ scoring was a predictor for cardiovascular events and mortality in patients with AF [26]. However, data on non-CVD causes and subtypes of CVD death are sparse for patients with CKD and AF. Despite the fact that patients with AF and CKD were older and with higher comorbidity burden (Table 1), the data from our study highlights the poor prognosis associated with AF and may help prioritize CVD or other treatment in this high-risk population.

In those with AF, the presence of CKD is associated with stroke and thromboembolic events and increased mortality [15, 17, 27–31]. Olesen et al. studied 132,372 patients from the Danish general population and noted an increased risk of stroke or systemic thromboembolism in patients with CKD (HR 1.49, 95% CI 1.38–1.59) [28]. Similar results have also been noted in other studies with some reporting higher risk than others and the difference is attributed to the discrepancies in the inclusion criteria [2, 15, 17, 30–32]. Our study results further reaffirm the associations between AF and cerebrovascular disease-related deaths in CKD. However, due to the nature of our study (death certificate derived data), we were not able to differentiate ischemic versus hemorrhagic cerebrovascular events in our study. Further studies from longitudinal

cohorts of kidney population could inform us about the risk estimates for various types of cerebrovascular deaths in CKD.

Much has been debated about the need for oral anticoagulation in patients with AF and though it is recommended for the general population based on CHA₂DS₂-VASc and HAS-BLED score combination, no conclusive evidence exists to support their use in advanced CKD (CKD 3b and higher) due to lack of representation of these patients in the pivotal anticoagulation trials and equivocal results from the existing observational data [19, 27, 28, 33–36]. Data from the Alberta Kidney Disease Network reported a lower risk of a composite outcome of all-cause death, ischemic stroke, and transient ischemic attack with warfarin therapy initiation among CKD patients with AF (adjusted HR from 0.54 to 0.64 for different CKD stages) and no increased risk of major bleeding except for those with eGFR 60–89 mL/min/1.73 m² (HR 1.36, 95% CI 1.13–1.64) [35]. Carrero et al. [37] reported that treatment with warfarin was associated with a lower 1-year risk of outcomes (death, MI, and ischemic stroke) without a higher risk of bleeding in those with acute myocardial infarction and AF and the association was not related to the severity of concurrent CKD. Observational studies are prone to bias and hence further dedicated clinical trials addressing this key issue in CKD are warranted.

Studies have reported sex-specific differences in the epidemiology and clinical outcomes of AF in the general population [38]. Multiple mechanisms have been proposed to address these differences including the role of estrogen replacement therapy [39]. While some suggested a lower risk of AF with hormone replacement therapy, others have refuted those findings [40, 41]. Even though modest, in CKD population, we noted sex-specific differences in the associations between AF and mortality with a stronger association in women than in men. Additional studies addressing the mechanisms that could explain these differences and whether there exist any differential treatment responses in patients with CKD are needed. In the general population, recent data suggest that African Americans with AF sustain higher rates of stroke, heart failure, and mortality than whites [42]. However, we did not find racial differences (based on the test of interaction) on outcome among those with CKD and AF.

Among the strengths of this study are the use of a large diverse clinical population of patients with stage 3 and 4 CKD and the availability of information on all-cause and cause-specific deaths. However, there are several limitations that merit discussion. These include the observational nature of this analysis limiting any causal interpretation.

Further, these data were derived from a single large health system, and hence, the results may not be generalizable to other health care systems and CKD populations. Even though we validated the diagnosis of AF in our chart review, we were not able to differentiate non-valvular and valvular AF, which could have different implications. While a large proportion of the study population obtained a majority of their care within the Cleveland Clinic health care system, we cannot account for care that may have occurred outside of the Cleveland Clinic system. We also lacked comprehensive data to calculate stroke (CHA₂DS₂-VASc) and bleeding (HAS-BLED) risk scores or to compute the illness severity score/index. We also lacked comprehensive medication data to conduct additional analyses affecting the outcomes. The difference in exposure to the medications including anti-arrhythmic and anti-coagulants could possibly explain the lower risk of AF in older patients along with the competing risk from death due to other causes. Due to the nature of the study, we also lacked echocardiogram data. Further it is unclear if the inclusion of patients who did not receive treatment but potentially could have benefitted from anticoagulation could have influenced the results. While we obtained cause-specific death data, this information was derived from death certificates, which is subject to limitations. However, we had previously validated the reliability of the cause-specific death data for other, previous studies [43, 44].

In conclusion, we found an increased risk of all-cause mortality with AF in those with CKD and this higher risk was primarily related to cardiovascular disease-related deaths, specifically ischemic heart disease, congestive heart failure, and cerebrovascular disease. Our data reinforce that patients with both CKD and AF are at high cardiovascular risk, and not just from ischemic stroke, thus suggesting that clinical practice (or trials) should aim at reducing the overall excess cardiovascular mortality in patients with AF and CKD.

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Previous Presentations

The results of this study were presented as a poster at the 2017 Kidney Week of the American Society of Nephrology in New Orleans, LA. Otherwise, the results presented in this paper have not been published previously in whole or part, except in the abstract format.

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