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**Title:** The Prevalence and Burden of Chronic Kidney Disease, Patterns of Anticoagulation Prescribing, and Major Bleeding Risk in Older Adults with Atrial Fibrillation

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**Abstract**

**Background:** In older adults with atrial fibrillation (AF), the presence of comorbid chronic kidney disease (CKD) may be more challenging for optimal disease management, influence stroke prophylaxis with oral anticoagulation, and impact bleeding risk. We examined the prevalence and burden of CKD in older patients with AF, patterns of anticoagulation prescribing according to CKD stage, and major bleeding events.

**Methods:** Patients aged 65 years and older with AF were enrolled in a cohort study from clinics in Massachusetts and Georgia between 2016 and 2018. Kidney function was assessed with estimated glomerular filtration rate (GFR) values at study enrollment. Anticoagulation therapy with direct acting oral anticoagulation therapy (DOAC) or warfarin; and major bleeding events were ascertained from medical records. Cox proportional hazards model was used to estimate the multivariable adjusted risk of two-year major bleeding events.

**Results:** Participants' (n=1,244) mean age was 75 years; 48% were women, and 86% were White. Overall, 25% had a normal GFR, 44%, 28%, and 3%

had mild, moderate, and severe CKD/kidney failure, respectively. Patients with severe CKD/kidney failure were more likely to be the oldest participants, dependent in their instrumental activities of daily living, and had the highest burden of frailty, multimorbidity, and polypharmacy. Approximately 44% of patients with normal GFR and 39% of those with mild CKD were prescribed a DOAC, while a majority of those with severe CKD/kidney failure (69%) were prescribed warfarin. Overall, 8% (n=105) experienced a major bleeding event over the 2-year follow-up. After adjusting for sociodemographic, psychosocial, geriatric, and clinical variables, patients with severe CKD/kidney failure (HR: 2.81 [95% CI:1.10-7.17]) had a higher bleeding risk than those with a normal GFR.

**Conclusions:** In managing older patients with AF and comorbid CKD, healthcare providers should be increasingly aware of the increased burden of frailty, dependence for care, multimorbidity, polypharmacy, and the high risk of major bleeding especially among those with severely impaired kidney function. This finding emphasizes the need for a more holistic and multidisciplinary approach to stroke prophylaxis in older adults with AF and comorbid CKD.

**Key words:** Older Adults, Atrial fibrillation; Chronic Kidney Disease; Anticoagulation; Major Bleeding

**Abstract word count:** 339

## Introduction

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia with an increased risk of cardiovascular related morbidity and mortality [1,2]. The burden and incidence of AF rises with increasing age, affecting approximately 1 in 10 adults aged 65 years and older in the US [3]. Patients diagnosed with AF and chronic kidney disease (CKD) are at increased risk for multiple cardiovascular diseases and their associated complications [4-6]. With declining kidney function, the risk of systemic thromboembolism leading to stroke in patients with AF rises [7] with a concomitant higher risk of bleeding due to uremic platelet dysfunction and alteration in coagulation

factors with impaired hemostasis [8], which may impact the choice of prophylactic anticoagulation against ischemic stroke.

A high prevalence of AF has been reported in patients with kidney failure [9,10]. However, patients with kidney failure only represent a small fraction of patients with CKD [11]. The prevalence of the varying stages of CKD in older adults with AF and its burden on patient's functional status as well long-term impact on major bleeding risk is not well understood. With an increasing prevalence of both AF and CKD particularly in older adults [1,6] understanding the comorbid burden of CKD in those with AF has clinical implications for shared decision-making for stroke prevention strategies either through oral anticoagulation or insertion of left atrial appendage occlusion devices in those at high risk of major bleeding.



Using data from the Systematic Assessment of Geriatric Elements in AF (SAGE-AF), a multicenter prospective cohort study, we examined the burden of CKD among older adults with AF by examining the baseline prevalence of CKD, patterns of stroke prophylaxis with oral anticoagulation according to CKD stage, and the occurrence of major bleeding events during the first two years after study enrollment.

## Methods

### Study Population

The present study used data from the SAGE-AF prospective cohort study, previously described in detail [12,13]. Between 2016 and 2018,

patients were recruited from participating clinic sites in Central and Eastern Massachusetts (MA) and Central Georgia. Four study sites in Central MA included the University of Massachusetts Memorial Health Care internal medicine, cardiology, and electrophysiology clinics, and the Heart Rhythm Associates of Central Massachusetts. The clinical site in Eastern MA was Boston University cardiology clinic. There were two participating medical centers in Central Georgia (Family Health Center and Georgia Arrhythmia Consultants). Eligibility criteria for study inclusion were: (i) age ≥65 years; (ii) having a diagnosis of AF as detected by a Holter monitor, electrocardiography tracings, or based on any medical record documentation of AF; and (iii) having a $CHA_2DS_2$-VASC risk score ≥2. Those who were ineligible to participate in the study were either scheduled for an invasive procedure with high risk for uncontrolled bleeding, had a medical indication for oral anticoagulation asides AF (such as the presence of mechanical heart valve, pulmonary embolism, or deep venous thrombosis), had an absolute contraindication to using oral anticoagulants, unable to provide signed informed consent, were non-English speaking, pregnant, incarcerated, or unable to attend study follow-up visits. Of the 6,507 patients screened, 1,244 participants were deemed eligible for study participation and were enrolled in this prospective study. Details of the study participant enrollment flowchart is presented in figure 1[12,13].



Trained research personnel abstracted data from electronic medical records (EMRs) from participating study sites. At study enrollment and

scheduled follow-up visits, in-person or telephone interviews were conducted with each eligible participant. The Institutional Review Boards at the participating study sites including the University of Massachusetts Medical School, Boston University, and Mercer University, provided ethical approval for conducting this study.

Each eligible participant provided written informed consent prior to enrollment at baseline.

**Measurement of Participant Kidney Function**

At study enrollment, participants' kidney function was assessed from estimated creatinine based glomerular filtration rate (GFR) values available in the EMRs. The EMRs utilized the recommended equation for estimating GFR based on the 2009 CKD-EPI creatinine equation at the time of our data collection (2016-2018), which estimated GFR based on serum creatinine, age, sex, and race [14]. The GFR values were categorized according to Kidney Disease Improving Global Outcomes (KDIGO) criteria for CKD as follows: G1: ≥90 (normal), G2: 60-89 (mildly decreased kidney function/mild CKD), G3a and 3b: 30-59 (moderately decreased kidney function/moderate CKD), and G4 and G5: ≤ 29 (severely decreased kidney function/severe CKD /kidney failure) [15].



**Oral Anticoagulation Prescribing Patterns**

Information on the type of oral anticoagulant prescribed was obtained from review of available EMRs at the time of study enrollment. Data on the prescribing of direct acting oral anticoagulation therapy (DOAC) with

apixaban, dabigatran, edoxaban, or rivaroxaban was examined; as well as Warfarin prescribing was derived from medical chart review.

**Evaluation of Major Bleeding Events**

Major bleeding events were derived from the review of EMRs and patient interviews at the two-years follow up; and were defined according to the International Society on Thrombosis and Hemostasis scale as symptomatic bleeding in a critical region (intracranial, spinal, ocular, pericardial, articular, retroperitoneal, or intramuscular); bleeding that resulted in a hemoglobin drop of ≥2g/dL; transfusion of ≥2 units of whole blood; or fatal bleeding [16].

**Baseline Participant Characteristics**

Participant sociodemographic data including age and sex were obtained from the review of available EMRs. Other characteristics such as race/ethnicity, marital status, and highest level of education attained, were obtained from telephone or face-to-face interviews at study enrollment.

Psychosocial and geriatric elements were assessed from detailed structured interviews at baseline with regards to the symptoms of depression and anxiety, social support, self-rated health status, frailty, instrumental activities of daily living, and cognitive impairment. Depressive symptoms were evaluated with the 9-item Patient Health Questionnaire and resultant scores were classified as ≤4: no depressive symptom, 5-9: mild, and ≥10: moderate to severe depressive symptoms [17]. The 7-item Generalized Anxiety Disorder questionnaire was used to assess anxiety, and

derived scores were categorized as either no anxiety symptoms (≤4), mild (5-9), or moderate to severe (≥10) anxiety symptoms [18]. Social support was measured with the 5-items Medical Outcomes Social Support Survey Instrument [19]. Participant's self-rated health status was evaluated with a validated and reliable single-item question with responses on a 5-point Likert scale which asked: "In general, would you say your health is excellent, very good, good, fair, or poor?" [20]. The Cardiovascular Health Survey (CHS) frailty scale was utilized in assessing frailty and scored as 0: not frail, 1-2: pre-frail, and ≥3: frail [21]. The instrumental activities of daily living (IADLs) were used to characterize participants' abilities with transportation, meal preparation, shopping, housework, managing medications and personal finances [22]. The 30-item Montreal Cognitive Assessment Battery (MoCA) was used to assess cognitive impairment with scores ranging from 0 to 30 (higher scores indicative of better cognitive functioning) and a cutoff of ≤25 was suggestive of cognitive impairment [23]. Visual and hearing impairment were self-reported by the study participants.



Clinical characteristics including AF type (paroxysmal, persistent, or permanent), prior ablation therapy, antiplatelet therapy, oral iron and fish oil supplementation, and the presence of comorbid conditions such as hypertension, heart failure, diabetes, dyslipidemia, cancer, and anemia, were derived from medical chart reviews. The HASBLED risk score to estimate participant bleeding risk was derived from their relevant medical

history [24]. Health behaviors including smoking history and alcohol use were obtained from self-reports during the baseline interviews.

**Statistical Analysis**

The analytic sample included all 1,244 study participants enrolled at baseline. Descriptive statistics were used to examine participant's characteristics according to the four categories of kidney function: G1: ≥90 (normal), G2: 60-89 (mildly decreased GFR/mild CKD), G3a and 3b: 30-59 (moderately decreased GFR/moderate CKD), and G4 and G5: ≤ 29 (severely decreased GFR/severe CKD/kidney failure). There was no missing information on GFR values in the EMRs at the time of baseline study enrollment. Continuous variables were summarized as means and standard deviations when normally distributed and as medians and interquartile ranges when skewed. Categorical variables were reported as proportions. The non-parametric Kruskal–Wallis test was used in comparing continuous variables across the four categories of kidney function [25]. The Cochran–Armitage test for trend was used for between group comparisons of categorical variables [26]. Kaplan-Meier curves were constructed to examine the relationship between CKD stages and the risk of a 2-year major bleeding event. The log-rank test was used to determine the statistical significance of group differences in major bleeding risk across the categories of kidney function [27]. Cox-proportional hazards regression models estimated the unadjusted and multivariable adjusted hazard ratios (HRs) with accompanying 95% confidence intervals (CIs). We inspected

Schoenfeld residuals and log-log plots to ascertain that the GFR categories and baseline characteristics satisfied the proportional hazards assumption [28]. The proportional hazards assumption was sufficiently met by the GFR measure and baseline variables included in the regression models. For multivariable adjustment, the choice of various confounding variables to be included in the models was based on clinical judgement and statistical significance. To understand the impact of adjustment on effect estimates by different groups of variables, sociodemographic characteristics (age, sex, and marital status) were first adjusted for in the Cox proportional hazards models in which 2-year major bleeding risk was the principal study outcome (Model 1). Next, in Model 2, psychosocial and geriatric variables (depressive symptoms, self-rated health, frailty status, and independent functioning) were added to the variables in Model 1. Finally, clinical variables (time since diagnosis of AF, prior ablation, anticoagulation therapy, aspirin use, fish oil supplementation, oral iron intake, hypertension, diabetes, dyslipidemia, heart failure, anemia, CHA2DS2-VASc and HASBLED scores) were adjusted for in addition to the variables in Models 1 and 2 (Model 3). We also conducted a sensitivity analysis to examine the impact of CKD burden on major bleeding events stratified according to the receipt of DOACs versus Warfarin. All statistical analyses were done using STATA 18 (StataCorp, College Station, Texas). Model results are shown as Hazard Ratios (HRs) and accompanying 95% confidence intervals (CI).

## Results

Participants (n=1,244) mean age was 75 years, 48% were women, and 86% were White. Overall, 25% had a normal GFR, 44% and 28% had mild and moderate CKD respectively, and 3% had severe CKD /kidney failure. Those with severe CKD/kidney failure were most likely to be the oldest participants (mean age:78 years), to be women, to report symptoms of moderately severe to severe depression, report their health status as fair/poor, were most likely to be frail and to be dependent in their IADLs (Table 1).

Study participants with normal baseline GFR values, were most likely to have the longest time since AF diagnosis and to have undergone prior ablation therapy. Those with severe CKD/kidney failure were most likely to have multiple comorbidities including hypertension, dyslipidemia, heart failure, diabetes, anemia, to have been prescribed 5 or more medications (polypharmacy), and were most likely to have the highest bleeding risk based on the HASBLED risk scoring system (Table 1).



### *Pattern of Oral Anticoagulation Prescribing According to CKD Burden*

Among all study participants, those with a normal GFR (44%), mild CKD (39%), and moderate CKD (32%) were most likely to have been prescribed a DOAC at the time of study enrollment, while those with severe CKD/kidney failure (21%) were least likely to have been prescribed a DOAC. The most prescribed DOACs were Apixaban and Rivaroxaban. Warfarin was

commonly prescribed across all stages of kidney function, with the highest likelihood of being prescribed among those with severe CKD/kidney failure (69%), moderate CKD (56%), mild CKD (46%), and less so among those with normal kidney function (40%) as shown in Table 2. No anticoagulation was prescribed for a higher proportion of those with normal kidney function compared to those with severe CKD/Kidney failure (16.6% vs 9.4%, Table 2).

***Association between Kidney Function and 2-year Major Bleeding Events***

Of the 1,244 study participants, approximately 8% (n=105) had a major bleeding event within 2 years of follow-up. Patients with moderate CKD and severe CKD/kidney failure had a significantly higher crude risk of major bleeding over our 2-year follow-up period (Figure 2). After adjusting for several sociodemographic variables, patients with moderate CKD (HR: 1.83 [95% CI: 1.02-3.29]) and severe CKD/kidney failure (HR: 4.97 [95% CI: 2.05-12.03]) had an increased risk of major bleeding than those with a normal GFR within 2 years of follow up (Table 3, Model 1). After further adjustment for psychosocial and geriatric variables, only those with severe CKD had a higher risk of 2- year major bleeding events than those with a normal GFR (Table 3, Model 2). In the final Cox proportional hazards model, adjusted for sociodemographic, psychosocial, geriatric, and clinical variables (Table 3, Model 3), only those with severe CKD to kidney failure

had a significantly higher risk of major bleeding compared to those with normal kidney function (HR: 2.81 [95% CI:1.10- 7.17]).

In our sensitivity analysis, we found no significant association between CKD burden and 2-year major bleeding risk when participants were stratified according to anticoagulation type (warfarin and DOAC use) at the time of study enrollment (Supplement 1).

**Discussion**

In this contemporary cohort of older adults diagnosed with AF, we examined the prevalence and burden of CKD, patterns of oral anticoagulation prescribing by CKD stages, and the impact of CKD on major bleeding risk during two years of study follow up. We observed the highest prevalence of CKD among those with mild and moderate stages of the disease. Study participants with severe CKD/kidney failure were most likely to be dependent in their instrumental activities of daily living and had the highest burden of frailty, multimorbidity, and polypharmacy. A majority of patients with normal kidney function and those with mild or moderate CKD were most likely to be prescribed a DOAC, while those with moderate CKD and severe CKD/ kidney failure were most likely to be prescribed warfarin at study enrollment. Among the 1,244 study participants, 105 experienced a major bleeding event during the two years of study follow-up. In the fully adjusted regression models, we observed that participants with severe CKD /kidney failure had the highest risk of major bleeding during our two-year follow-up period.

***CKD Burden Related to Higher Impairment in Functional Status***

In the present study, two-thirds of our study participants with severe CKD/ kidney failure were pre-frail, and one-third were frail. Prior studies have shown that approximately one in every ten older community-dwelling adults are considered to be frail, whereas in patients with kidney failure including those who are dialysis-dependent, the prevalence of frailty has been found to be considerably higher, up to >60% [29-31-]. Findings from the Atherosclerosis Risk in Communities (ARIC) study have demonstrated that frailty is strongly associated with progressive kidney impairment [32]. In addition, frailty is an independent risk factor for adverse clinical outcomes including hospitalization and mortality in all stages of CKD [33-35]. Older adults with advanced CKD may be at higher risk of physical frailty due to a multiplicity of reasons including multimorbidity, polypharmacy, and coexisting low mood leading to reduced energy intake that may contribute to sarcopenia [36-38]. Similarly, in the present study we observed that participants with severe CKD/kidney failure had the highest prevalence of comorbid conditions and polypharmacy.



Furthermore, prior studies have shown that CKD is related to functional decline for older adults with increasing dependence for performance of their activities of daily living [39,40]. In the current study, we observed that patients with the most advanced stages of CKD were most likely to be dependent on others for performing their IADLs. Our findings buttress the need for a multi-disciplinary approach of medical specialists, patients, and

their primary caregivers to optimizing the management of older adults with comorbid AF and CKD. The important role of caregivers cannot be overemphasized, as older adults may be solely dependent on their caregivers for transportation to their multiple clinic visits including attendance at the anticoagulation clinic to check therapeutic ranges for warfarin therapy. A holistic approach to caring for older adults could enhance the clinical decision-making process while managing their comorbid conditions including AF and CKD, taking into consideration the patient's baseline functional status, high bleeding risk, and overall prognosis to ensure that recommended therapeutic options align with the patients' priorities, preferences, and health outcome goals.

***Anticoagulation Prescribing Patterns by CKD Stage***

We observed that participants with normal kidney function and mild CKD were most likely to be on DOACs, while those with moderate CKD, severe CKD/kidney failure were most likely to have been prescribed warfarin therapy. Additionally, we observed that a higher proportion of those with normal kidney function were more likely to have no anticoagulation prescribed compared to those with more advanced CKD. There are varying recommendations for oral anticoagulation selection among patients with AF and severe CKD/kidney failure, likely due to a paucity of evidence, particularly among older adults with advanced kidney impairment. Our findings are consistent with the KDIGO guideline which suggests preference for DOACs over warfarin for stroke prophylaxis in patients with normal

kidney function, mild, moderate CKD, but with more advanced kidney disease including severe CKD to kidney failure, KDIGO recommends the use of warfarin as the first drug of choice [41]. The American Heart Association/American College of Cardiology guidelines recommend the use of DOACs over warfarin in patients who are DOAC-eligible, however these guidelines offer a class IIb (weak) recommendation suggesting the use of apixaban or warfarin in those with advanced stages of kidney disease [42]. Furthermore, in the current European Society of Cardiology guidelines, DOACs are contraindicated in patients with kidney failure, and vitamin K antagonists remain the preferred choice for patients with kidney failure [43]. Our paradoxical finding that individuals with advanced CKD or kidney failure, despite their higher bleeding risk, were more likely to receive anticoagulation therapy than those with normal renal function warrants further investigation. A possible explanation is that individuals with normal renal function, who had fewer comorbidities and were less frail, may have been more suitable candidates for alternative interventions such as catheter ablation procedure to restore normal sinus rhythm. Notably, within our study population, those with normal kidney function were more likely to have undergone catheter ablation compared to individuals with advanced CKD or kidney failure. In most cases, anticoagulation can be discontinued beyond 2–3 months following successful catheter ablation, depending on an individual's thromboembolic risk [44]. Although our study provides insight to anticoagulation prescribing patterns according to CKD stage in older

adults with AF, larger future studies among older adults with advanced stages of CKD and high multimorbidity burden are needed to develop guidelines for stroke prevention in this vulnerable population, as well as understanding the impact of anticoagulation use on important patient centered and clinical outcomes.

***Impact of CKD Burden on Two-year Major Bleeding Risk***

After adjusting for several sociodemographic variables of prognostic importance, we found a higher 2-year major bleeding risk among those with moderate CKD, severe CKD/kidney failure. However, after accounting for patients' psychosocial, geriatric, and clinical variables, only those with severe CKD/kidney failure had a statistically significant higher risk of major bleeding over our follow-up period. Our results are concordant with previous studies that have shown a higher risk of bleeding in patients with advanced kidney disease [45,46]. The underlying pathological processes associated with increased bleeding risk in patients with severe CKD/kidney failure have been linked to endothelial damage from uremic toxins and platelet dysfunction [47,48]. Among patients with non-valvular AF who meet the criteria for reduced dosing of DOACs (age ≥80 years, serum creatinine ≥1.5 mg/dL, and body weight ≤60 kg) [49], the pattern of bleeding risk may differ. Future studies should aim to capture the actual DOAC dosage used and assess its impact on bleeding risk, particularly in patients with kidney impairment. Our study findings have important clinical implications, as we examined the risk of major bleeding independent of anticoagulation or

antiplatelet use, with a particular emphasis on the challenges of managing older adults with AF and comorbid severe CKD or kidney failure. These challenges include addressing the complexities of functional impairment, multimorbidity, and polypharmacy, all of which contribute to greater uncertainty in identifying the most effective approach for stroke prevention in this high-risk population. Improved clinical guidelines are needed in determining the choice of anticoagulation therapy in this vulnerable population. Furthermore, for patients at high risk of major bleeding, a left atrial appendage occlusion device may be surgically inserted to decrease the risk of blood clots moving from the heart to the brain [50]. However, there remains a paucity of evidence regarding the extent of the use of the left atrial appendage occlusion devices in those with advanced kidney impairment, as they may not be deemed the ideal surgical candidate for device insertion and be at higher risk of surgical related complications. There remains a continuing need for a holistic approach in reviewing all patient modifiable factors including their level of adherence with recommended therapy, recognition of major bleeding risk, conducting optimal medication reconciliation, addressing patient need for support in performing their daily activities, and improved coordination of care between clinicians and patients with severely impaired kidney function, for better understanding and treatment planning in regard to stroke prevention.

### *Study Strengths and Limitations*

A particular strength of our study is the assessment of kidney

function based on estimated GFR values, which aligns with the KDIGO guidelines and offers higher sensitivity over the use of CKD diagnosis from medical records which could be subject to misclassification bias. In addition, our study participants were recruited from clinics in Massachusetts and Georgia with different prescribing practices which may enhance the generalizability of our study findings.

Our findings also need to be considered in light of several potential limitations. First, our observational study design increases the likelihood of residual and unmeasured confounding, despite adjusting for a number and variety of participant sociodemographic, psychosocial, geriatric, and clinical baseline characteristics. Second, the one-time assessment of GFR at study enrollment may be subject to changes over time or may have been reflective of acute kidney injury which could have improved or worsened. Second, we recognize that the small sample size in the severe CKD/kidney failure category and number of bleeding events could reduce our statistical power to detect meaningful associations and possibly inflate standard errors from the regression models with wider confidence intervals. Third, since our data was collected up to 2018, we recognize that changes in practice including an increase in the uptake of DOACs may have occurred over time [50], which may not be reflected in our findings. In addition, we are cognizant that oral anticoagulation prescribing obtained from medical records, may not necessarily reflect actual use or continued adherence of anticoagulants among our study participants. Future studies should obtain real-world data

that measures a patient's adherence with recommended therapy over time either from Medicare claims data [51] or more objectively from obtaining serum drug concentration levels, and the adoption of left atrial occlusion devices in patients with high bleeding risk.

**Conclusions**

Understanding the prevalence and burden of CKD among older adults with AF has implications for promoting a holistic approach to patient-centered care. The most prescribed oral anticoagulant for older adults with normal kidney function to moderate CKD are DOACS, while warfarin is mostly prescribed for those with severe CKD/kidney failure. In managing older patients with AF and comorbid CKD, clinicians should be increasingly aware of the increased burden of frailty, multimorbidity, dependence for care, and higher bleeding risk especially among those with severely impaired kidney function and independent of anticoagulation or antiplatelet therapy. Our findings reinforce the need for clinical guidelines for stroke prevention in older adults that take into consideration patient functional status, presence of comorbidities, major bleeding risk, and their overall prognosis for enhanced patient-centered and clinical outcomes.

**Clinical Trial Number:** Not applicable.

**Declarations**

**Ethics approval and consent to participate:** The Institutional Review Boards at the participating study sites including the University of Massachusetts Medical School, Boston University, and Mercer University, provided ethical approval for conducting this study. All study participants provided written informed consent. Given our observational study design, no experiments were conducted on the study participants.

**Consent for publication:** Not applicable

**Availability of data and materials:** Data is provided within the manuscript or supplementary information file.

**Competing interests:** DDM has received research grant support from Apple Computer, Bristol-Myers Squibb, Boeringher-Ingelheim, Pfizer, Samsung, Philips Healthcare, and Biotronik; consultancy fees from Bristol-Myers Squibb, Pfizer, Flexcon, and Boston Biomedical Associates, and has inventor equity in Mobile Sense Technologies, Inc (Farmington, CT). All other authors declare no potential conflicts of interest.

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**Authors' contributions:** HA: Conceptualization, Methodology, Formal Analysis and Data Interpretation, Writing-Original draft, Validation. DDM, JS: Funding Acquisition, Investigation, Conceptualization, Reviewing and Editing drafted manuscript: HA, FF, WW, JS, JM, PT, MT, JG, RG, DD, AK, DDM. All authors read and approved of the final manuscript.

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**List of Abbreviations**

| | |
|---|---|
| AF | Atrial Fibrillation |
| IADLs | Instrumental Activities of Daily Living |
| CHS | Cardiovascular Health Survey |
| CI | Confidence Interval |
| CKD | Chronic Kidney Disease |
| DOAC | Direct acting Oral AntiCoagulation |
| EMR | Electronic Medical Record |
| GAD-7 | General Anxiety Disorder 7 item score |
| GFR | Glomerular Filtration Rate |
| HR | Hazard Ratio |
| KDIGO | Kidney Disease Improving Global Outcomes |
| MA | Massachusetts |
| MOCA | Montreal Cognitive Assessment |
| PHQ-9 | Patient Health Questionnaire 9 item score |

SAGE-AF Systematic Assessment of Geriatric Elements in Atrial Fibrillation

**Table 1.** Baseline sociodemographic, psychosocial, geriatric, and clinical characteristics of study participants

| Characteristics | Normal GFR (n=308) | Mild CKD (n=550) | Moderate CKD (n=354) | Severe CKD/Kidney Failure (n=32) | P value |
|---|---|---|---|---|---|
| **Socio-demographic** | | | | | |
| Age (mean, yrs (sd)) | 74 (6.8) | 74 (6.6) | 77 (7.5) | 78 (7.5) | <0.001 |
| Women n (%) | 147 (47.7) | 249 (45.3) | 192 (54.2) | 19 (59.4) | 0.04 |
| Married n (%) | 183 (60.4) | 325 (60.0) | 170 (48.7) | 16 (53.3) | <0.01 |
| Race/Ethnicity n (%) | | | | | |
| Non-Hispanic White | 252 (82.1) | 488 (88.7) | 304 (86.4) | 25 (78.1) | 0.43 |
| Non-White | 55 (17.9) | 62 (11.3) | 48 (13.6) | 7 (21.9) | |
| Education n (%) | | | | | |
| ≤ high school | 127 (41.9) | 172 (31.9) | 145 (41.7) | 14 (48.3) | 0.17 |
| Some college | 50 (16.5) | 101 (18.7) | 81 (23.3) | 3 (10.3) | |
| College Graduate | 126 (41.6) | 267 (49.4) | 122 (35.0) | 12 (41.4) | |
| **Psychosocial and Geriatric** | | | | | |
| Low social support n (%) | 79 (25.6) | 137 (24.9) | 100 (28.2) | 11 (34.4) | 0.27 |
| Visual Impairment n (%) | 105 (34.1) | 172 (31.3) | 134 (37.8) | 17 (53.1) | 0.07 |
| Hearing Impairment n (%) | 103 (33.4) | 199 (36.2) | 139 (39.3) | 10 (31.2) | 0.26 |
| Cognitive impairment n (%) | 129 (42.2) | 160 (29.1) | 142 (40.1) | 20 (62.5) | 0.37 |
| Depressive symptoms† n (%) | | | | | |
| None | 232 (75.3) | 401 (72.9) | 238 (67.2) | 20 (62.5) | <0.01 |
| Mild/Moderate | 73 (23.7) | 132 (24.0) | 104 (29.4) | 9 (28.1) | |
| Moderately Severe/Severe | 3 (1.0) | 17 (3.1) | 12 (3.4) | 3 (9.4) | |
| Anxiety Symptoms‡ n (%) | | | | | |
| None | 226 (73.4) | 424 (77.1) | 277 (78.3) | 26 (81.3) | 0.14 |
| Mild/Moderate | 77 (25.0) | 118 (21.5) | 67 (18.9) | 6 (18.7) | |
| Severe | 5 (1.6) | 8 (1.4) | 10 (2.8) | 0 (0.0) | |
| Fair or poor self-rated health n (%) | 50 (16.3) | 72 (13.2) | 69 (19.5) | 13 (41.9) | <0.001 |

| | | | | | |
|---|---|---|---|---|---|
| Not Frail n (%) | 116 (37.7) | 220 (40.0) | 76 (21.5) | 1 (3.1) | <0.001 |
| Pre-Frail n (%) | 152 (49.3) | 278 (50.6) | 209 (59.0) | 20 (62.5) | |
| Frail n (%) | 40 (13.0) | 52 (9.5) | 69 (19.5) | 11 (34.4) | |
| Independent functioning (Mean, (SD)) | 6.7 (1.0) | 6.8 (0.9) | 6.6 (1.1) | 6.3 (1.9) | <0.01 |
| **Clinical** | | | | | |
| AF Type n (%) | | | | | |
| Paroxysmal | 188 (64.2) | 352 (70.4) | 202 (63.9) | 15 (50.0) | 0.22 |
| Persistent | 56 (19.1) | 69 13.8) | 41 (13.0) | 6 20.0) | |
| Permanent | 49 (16.7) | 79 (15.8) | 73 (23.1) | 9 (30.0) | |
| Duration of AF Diagnosis (Yrs, Mean (SD)) | 6.0 (4.7) | 5.0 (4.1) | 5.4 (4.2) | 4.8 (4.3) | 0.01 |
| AF Treatment n (%) | | | | | |
| Rhythm control | 184 (59.7) | 317 (57.6) | 191 (53.9) | 18 (56.3) | 0.14 |
| Rate control | 124 (40.3) | 233 (42.4) | 163 (46.1) | 14 (43.7) | |
| Prior ablation therapy n (%) | 122 (39.6) | 160 (29.1) | 92 (26.0) | 9 (28.1) | <0.001 |
| Aspirin therapy n (%) | 106 (34.4) | 186 (33.8) | 136 (38.4) | 14 (43.7) | 0.15 |
| Fish oil supplement n (%) | 41 (13.3) | 94 (17.1) | 52 (14.7) | 4 (12.5) | 0.85 |
| Oral Iron therapy n (%) | 28 (9.1) | 40 (7.3) | 33 (9.3) | 5 (15.6) | 0.51 |
| Polypharmacy (≥5 medications) n (%) | 86 (27.9) | 137 (24.9) | 115 (32.5) | 15 (46.9) | 0.03 |
| Medical History n (%) | | | | | |
| Hypertension | 270 (87.7) | 489 (88.9) | 332 (93.8) | 31 (96.9) | <0.01 |
| Dyslipidemia | 227 (73.7) | 444 (80.7) | 296 (83.6) | 29 (90.6) | <0.001 |
| Heart Failure | 100 (32.5) | 154 (28.0) | 186 (52.5) | 23 (71.9) | <0.001 |
| Diabetes | 84 (27.3) | 146 (26.5) | 139 (39.3) | 19 (59.4) | <0.001 |
| Anemia | 69 (22.4) | 153 (27.8) | 145 (41.0) | 24 (75.0) | <0.001 |
| Cancer | 73 (23.7) | 185 (33.6) | 113 (31.9) | 6 (18.7) | 0.15 |
| HASBLED risk score ≥ 3 n (%) | 205 (66.6) | 396 (72.0) | 290 (81.9) | 32 (100.0) | <0.001 |
| **Health behaviors** | | | | | |
| Any Alcohol use n (%) | 156 (51.5) | 331 (61.2) | 173 (49.1) | 14 (45.2) | 0.26 |
| Smoking status n (%) | | | | | |
| Never smoker | 146 (47.7) | 251 (45.9) | 164 (47.4) | 15 (48.4) | 0.72 |
| Former smoker | 151 (49.4) | 285 (52.1) | 166 (48.0) | 13 (41.9) | |
| Current Smoker | 9 (2.9) | 11 (2.0) | 16 (4.6) | 3 (9.7) | |

Abbreviations: CHA2DS2-VASc: Stroke risk assessment (Congestive heart failure, Hypertension, Age ( ≥ 65 = 1 point, ≥ 75 = 2 points), Diabetes, and prior Stroke/TIA (2 points), Vascular disease (peripheral arterial disease, previous MI, aortic atheroma) and female gender); HASBLED: Determines 1 year risk of major bleeding (Hypertension, Abnormal kidney and liver function, prior Stroke, prior Bleeding, Labile INR, Elderly, Drugs or alcohol that increase risk of bleeding); † PHQ-9 Patient Health Questionnaire 9 item score (5-9 mild; 10-14 moderate; 15-19 moderately severe; and ≥20 severe depression); ‡ GAD-7 General Anxiety Disorder 7 item score (5-9 mild; 10-14 moderate; ≥15 severe anxiety); Independent functioning assessed by Instrumental Activities of Daily Living (score range 0-7)

**Table 2.** Anticoagulation Prescribing Patterns According to Chronic Kidney Disease Stages

| Characteristics | Normal GFR (n=308) | Mild CKD (n=550) | Moderate CKD (n=354) | Severe CKD/ Kidney Failure (n=32) | P value |
|---|---|---|---|---|---|
| Warfarin (%) | 39.6 | 46.4 | 56.4 | 68.7 | <0.001 |
| Direct Acting Oral Anticoagulant (%) | 43.8 | 38.5 | 31.9 | 21.9 | |
| Apixaban | *20.5* | *19.5* | *17.6* | *18.7* | |
| Dabigatran | *5.5* | *3.4* | *1.1* | *0.0* | |
| Edoxaban | *0.6* | *0.2* | *0.0* | *3.1* | |
| Rivaroxaban | *17.2* | *15.4* | *13.0* | *0.0* | |
| No anticoagulation prescribed (%) | 16.6 | 15.1 | 11.9 | 9.4 | |

Italicized values were derived from the total proportion of Direct Acting Oral Anticoagulant for each kidney function group

**Table 3.** Multivariable Adjusted Relationship between Chronic Kidney Disease and Major Bleeding Risk during 2-year follow-up

| GFR Categories | Major Bleeding Events (n) | Crude HR (95% CI) | *Model 1 HR (95% CI) | **Model 2 HR (95% CI) | ***Model 3 HR (95% CI) |
|---|---|---|---|---|---|
| Normal | 17 | Ref | Ref | Ref | Ref |
| Mild CKD | 44 | 1.40 (0.80 – 2.46) | 1.42 (0.80 - 2.51) | 1.50 (0.84 - 2.66) | 1.49 (0.83 – 2.68) |
| Moderate CKD | 37 | 1.86 (1.05 -3.32) | 1.83 (1.02 - 3.29) | 1.68 (0.93 - 3.01) | 1.49 (0.81 - 2.74) |
| Severe CKD/Kidney Failure | 7 | 4.74 (1.97-11.44) | 4.97 (2.05 - 12.03) | 3.83 (1.57 – 9.41) | 2.81 (1.10 – 7.17) |

* Model 1: Adjusted for sociodemographic variables (age, sex, race, marital status)
** Model 2: Adjusted for variables in Model 1 and psychosocial and geriatric variables (symptoms of depression, self-rated health, frailty, and independent functioning)
*** Model 3: Adjusted for variables in Model 2 and clinical variables (atrial fibrillation duration, prior ablation, anticoagulation therapy (direct acting anticoagulation therapy and warfarin), aspirin use, fish oil supplementation, oral iron intake, hypertension, diabetes, dyslipidemia, heart failure, anemia, HASBLED risk score)

**Figure 1:** Participant Study Enrollment Flowchart for SAGE-AF, 2016-2018.

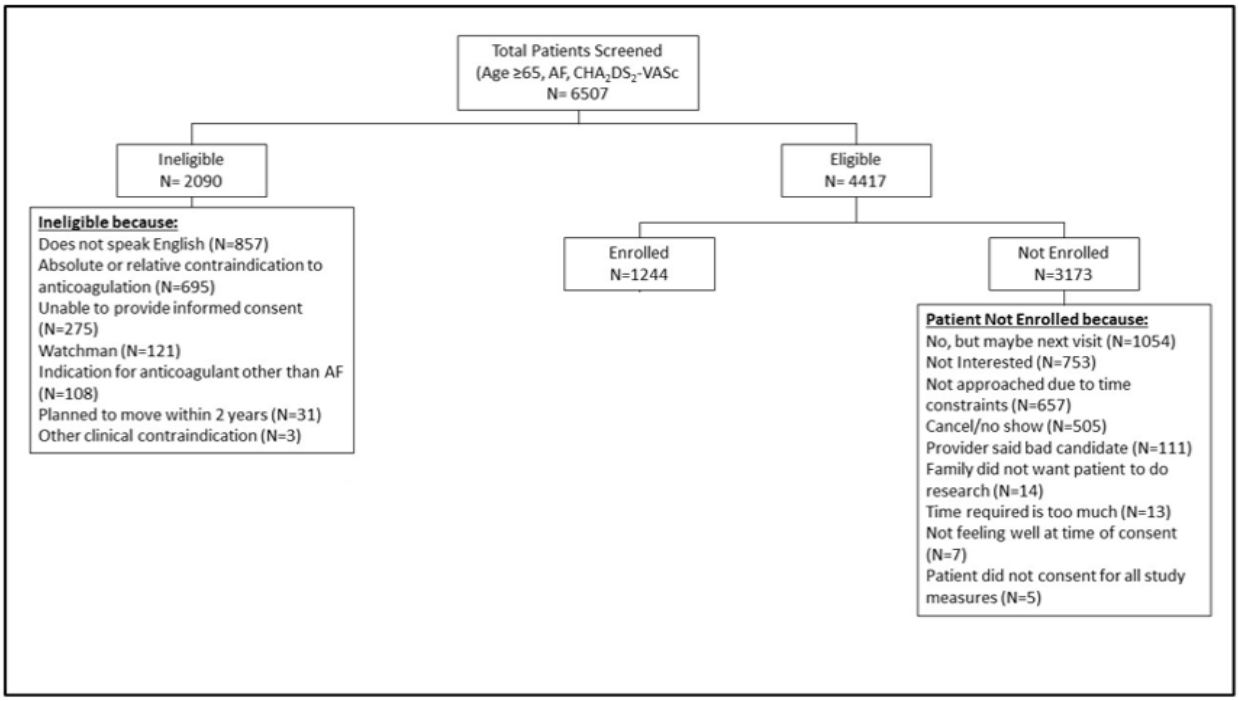
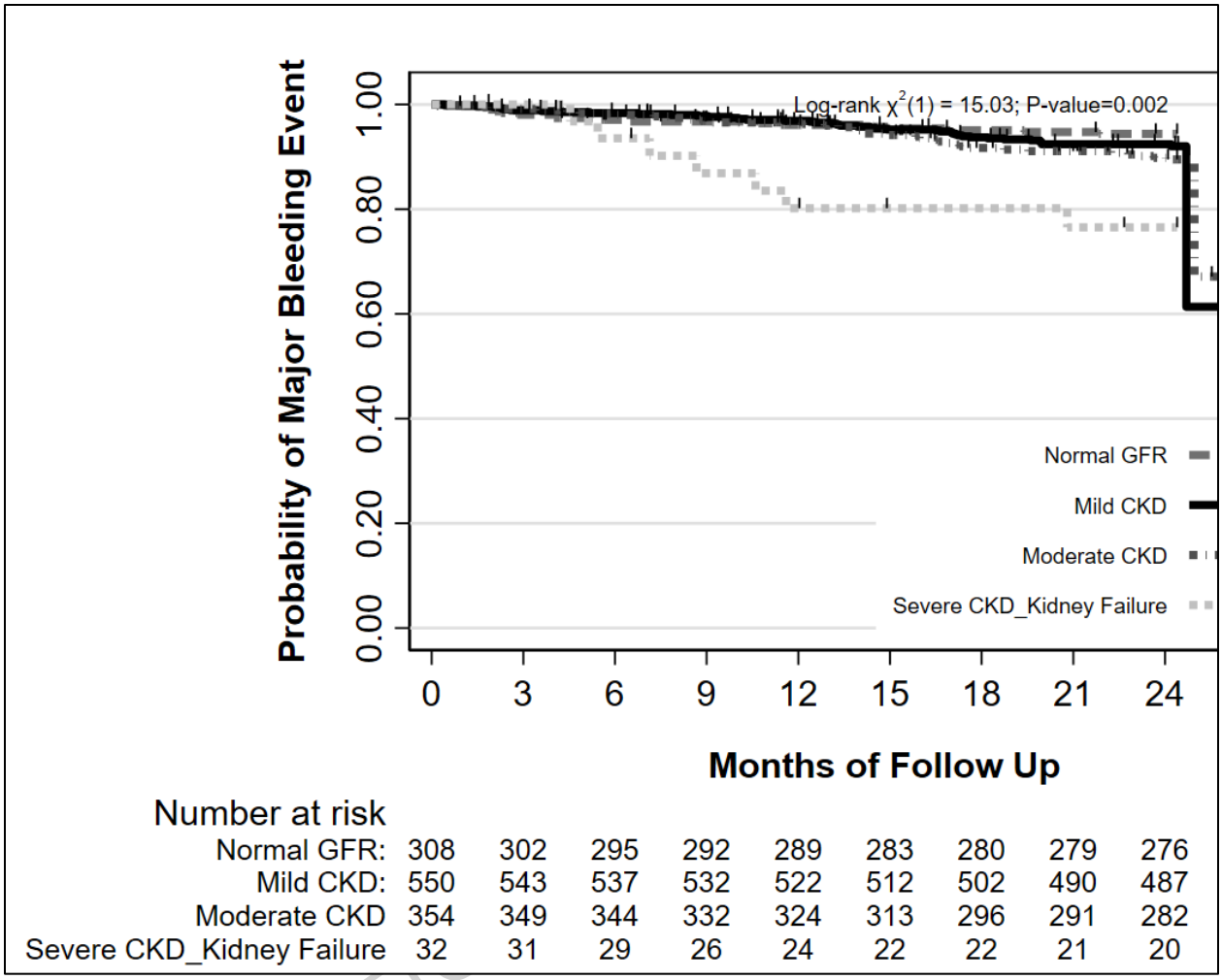



Image adapted from our prior published work on SAGE-AF Study [12]



**Figure 2:** Kaplan Meier Curves for 2-year Major Bleeding Events According to Chronic Kidney Disease Stages



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