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ORIGINAL RESEARCH

Management and 1-Year Outcomes of Patients With Newly Diagnosed Atrial Fibrillation and Chronic Kidney Disease: Results From the Prospective GARFIELD-AF Registry

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***Background*—**Using data from the GARFIELD-AF (Global Anticoagulant Registry in the FIELD–Atrial Fibrillation), we evaluated the impact of chronic kidney disease (CKD) stage on clinical outcomes in patients with newly diagnosed atrial fibrillation (AF).

***Methods and Results*—**GARFIELD-AF is a prospective registry of patients from 35 countries, including patients from Asia (China, India, Japan, Singapore, South Korea, and Thailand). Consecutive patients enrolled (2013–2016) were classified with no, mild, or moderate-to-severe CKD, based on the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative guidelines. Data on CKD status and outcomes were available for 33 024 of 34 854 patients (including 9491 patients from Asia); 10.9% (n=3613) had moderate-to-severe CKD, 16.9% (n=5595) mild CKD, and 72.1% (n=23 816) no CKD. The use of oral anticoagulants was influenced by stroke risk (ie, post hoc assessment of CHA_2DS_2-VASc score), but not by CKD stage. The quality of anticoagulant control with vitamin K antagonists did not differ with CKD stage. After adjusting for baseline characteristics and antithrombotic use, both mild and moderate-to-severe CKD were independent risk factors for all-cause mortality. Moderate-to-severe CKD was independently associated with a higher risk of stroke/systemic embolism, major bleeding, new-onset acute coronary syndrome, and new or worsening heart failure. The impact of moderate-to-severe CKD on mortality was significantly greater in patients from Asia than the rest of the world (P=0.001).

***Conclusions*—**In GARFIELD-AF, moderate-to-severe CKD was independently associated with stroke/systemic embolism, major bleeding, and mortality. The effect of moderate-to-severe CKD on mortality was even greater in patients from Asia than the rest of the world.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT01090362. **(*J Am Heart Assoc*. 2019;8: e010510. DOI: 10.1161/JAHA.118.010510.)**

Key Words: atrial fibrillation • chronic kidney disease • GARFIELD-AF registry • outcomes research • registry

Epidemiologic studies suggested the increased prevalence of atrial fibrillation (AF) in patients with chronic kidney diseases (CKDs).[1,2] Indeed, the prevalence of both AF and CKD increases with age and concomitant risk factors.[3–7] Moreover, there are several common risk factors for high prevalence of AF and CKD such as hypertension, diabetes

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*A complete list of the GARFIELD-AF Investigators can be found in the Appendix at the end of the article.

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Clinical Perspective

What Is New?

- The impact of increasing severity of chronic kidney disease (CKD) on outcomes is well documented in studies conducted in Western Europe and North America, but not the rest of the world.
- The GARFIELD-AF (Global Anticoagulant Registry in the FIELD–Atrial Fibrillation) registry shows that 1 year after diagnosis of atrial fibrillation, both mild and moderate-to-severe CKD were independent risk factors for all-cause mortality, after adjusting for baseline characteristics and antithrombotic use.
- Moderate-to-severe CKD was also independently associated with a higher risk of stroke/systemic embolism, major bleeding, new-onset acute coronary syndrome, and new or worsening heart failure; the impact of moderate-to-severe CKD on mortality is even greater in patients from Asia, where patient characteristics and the standard of care for anticoagulation differs from the rest of the world.

What Are the Clinical Implications?

- Despite potential concerns over the lack of coagulation monitoring with non–vitamin K antagonist oral anticoagulants in patients with moderate-to-severe CKD, the data from GARFIELD-AF suggest that the use of non–vitamin K antagonist oral anticoagulants in these patients is similar to their use in no/mild CKD in real-world clinical practice.

mellitus, and obesity.[4–6] Thus, the number of patients with concomitant AF and CKD increases as the population ages.

From a clinical outcomes perspective, comorbid CKD is an independent predictor of stroke and bleeding events in patients with AF.[8,9] Risk of stroke and hemorrhage in this patient group increases progressively with declining renal function.[10] Thus, the HAS-BLED (hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs predisposing to bleeding or history of alcohol abuse) score, which was designed to predict the bleeding risk of patients with AF, includes "L" for liver or kidney dysfunction. The HAS-BLED score was developed in 2010 using the Euro Heart Survey database.[11] Similarly, high rates of stroke and an increased risk of bleeding were also shown in a 2012 Danish cohort study of patients with AF and concomitant CKD.[9] Subsequently, a series of observational studies of patients treated mainly with vitamin K antagonists (VKAs), have shown equivocal and conflicting evidence of the value of anticoagulation for stroke prevention in patients with comorbid CKD and AF.[12–18] These data highlight the difficulties in maintaining optimal anticoagulation control with VKAs in patients with CKD.[12–18]

A better understanding of the impact of CKD on outcomes among patients with AF in the contemporary treatment setting is needed, assessing the impact of CKD and the experience with anticoagulants beyond Western Europe and North America.

The GARFIELD-AF (Global Anticoagulant Registry in the FIELD–Atrial Fibrillation) is an ongoing, international, prospective registry of newly diagnosed patients with AF at risk of stroke. We aimed to clarify the relationship between CKD stage and clinical outcomes—reflecting real-world clinical practice during an era when non-VKA oral anticoagulants (NOACs) are available. Using global data from this noninterventional registry, we attempted to confirm the hypothesis that CKD stage influences clinical outcomes among a highly diverse group of newly diagnosed patients with AF. In addition, we aimed to clarify the impact of CKD on clinical outcomes in Asia, where both the clinical characteristics of patients as well as the standard of care with antithrombotic therapy differ from the rest of the world (RoW).[19]

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Participants

The study design of GARFIELD-AF has been described previously.[20] Briefly, GARFIELD-AF is a contemporary, international, and sequentially recruited cohort of patients with newly diagnosed AF at risk of stroke. Men and women aged ≥18 years with nonvalvular AF diagnosed according to standard local procedures within the previous 6 weeks, and with at least 1 risk factor for stroke as judged by the investigator, are eligible for inclusion. Risk factors for stroke were not prespecified in the protocol, nor are they limited to the components of existing risk stratification schemes such as CHA_2DS_2-VASc score. Patients with a transient reversible cause of AF and those for whom follow-up is not envisaged or possible were excluded. To minimize recruitment bias, investigator sites have been selected randomly (apart from 18 sites, out of 1019) from all participating countries, representing the actual care settings in them assured by national coordinators. All eligible patients were enrolled consecutively into 5 cohorts (representing the 5 years of enrollment); each cohort included ≈10 000 participants.[20,21]

Ethics Statement

Independent ethics committee and hospital-based institutional review board approvals were obtained. The registry is being conducted in accordance with the principles of the

Declaration of Helsinki, local regulatory requirements, and the International Conference on Harmonisation–Good Pharmacoepidemiological and Clinical Practice guidelines. Written informed consent was obtained from all study participants. Confidentiality and anonymity of all patients recruited into this registry are maintained.

Data Collection and Quality Control

Patient demographics, medical history, and the use of antithrombotic treatment were recorded at baseline. Data on components of the CHA_2DS_2-VASc[22] and HAS-BLED[11] risk stratification schemes were collected to assess stroke and bleeding risks retrospectively. HAS-BLED scores were calculated, excluding fluctuations in international normalized ratio. Incidences of stroke/systemic embolism (SE), major bleeding, all-cause mortality, cardiovascular mortality, noncardiovascular mortality, undetermined cause of mortality, new diagnosis of acute coronary syndrome (ACS), and new or worsening (defined by New York Heart Association class) heart failure were recorded over 1-year follow-up.

The data were extracted from the study database on November 2017, and includes patients prospectively recruited between April 2013 and August 2016 (from cohorts 3–5). Patients recruited before April 2013 were excluded because of the lack of detailed information on the severity of CKD.

GARFIELD-AF data are captured using an electronic case report form designed by Dendrite Clinical Systems Ltd (Henley-on-Thames, United Kingdom). Oversight of operations and data management are performed by the sponsor and coordinating center (Thrombosis Research Institute—TRI, London, United Kingdom), with support from Quintiles (Durham, NC, United States), The University of Birmingham Department of Primary Care Clinical Sciences (Birmingham, United Kingdom), Thrombosis Research Group—Brigham and Women's Hospital (Boston, MA, United States), and AIXIAL (Paris, France). Data management and quality assurance of the database were controlled by an independent Audit Committee (Prof. Keith Fox and Prof. Bernard Gersh). Details of the quality assurance process in GARFIELD-AF have been described previously.[23]

Study End Points

Outcome measures analyzed included all-cause mortality, cardiovascular and noncardiovascular mortality, stroke/SE, major bleeding, pulmonary embolism, heart failure (new or worsening), and new-onset ACS.[20] In this analysis, event rates were analyzed only over the first 12 months from diagnosis of AF (to avoid the influence of time-dependent changes in CKD stage) and only in the last 3 cohorts of patients recruited into GARFIELD-AF to maintain the homogeneity within the use of oral anticoagulants.

Definitions

Patients with AF diagnosed within the previous 6 weeks were categorized by the investigator as having new-onset (unclassified), paroxysmal, persistent, or permanent AF. The severity of CKD was classified by the investigator according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative guidelines.[24] Guidance on CKD classification was provided online for investigators. Laboratory data on renal function were not collected. Vascular disease included peripheral artery disease or coronary artery disease (CAD) with a history of ACS. Asian countries in this analysis were China, India, Japan, Singapore, South Korea, and Thailand. Non-Asian countries included Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Czech Republic, Denmark, Egypt, Finland, France, Germany, Hungary, Italy, Netherlands, Norway, Mexico, Poland, Russia, South Africa, Spain, Sweden, Switzerland, Turkey, the United Kingdom, Ukraine, the United Arab Emirates, and the United States.

Statistical Analysis

Patients were analyzed according to their severity of CKD, either moderate-to-severe CKD (stages 3–5), mild CKD (stages 1–2), or no CKD, as recorded by the phyisican. A global analysis was conducted on data from all countries in GARFIELD-AF, and then a regional comparison was made to confirm the validity of global results in patients enrolled outside Asia and within Asia where the standard of antithrombotic therapy differs substantially.[12]

For the analysis of baseline parameters, continuous variables are expressed as median (interquartile range) and categorical variables as frequency and percentage.

The prevalence of comorbidities at baseline is shown by the CKD group in the global and regional analyses. Antithrombotic treatment patterns at baseline are displayed by CKD group and CHA_2DS_2-VASc score.

Clinical outcomes were compared between moderate-to-severe CKD versus no CKD and mild CKD versus no CKD groups. Occurrence of adverse clinical outcomes is described using the number (%) of events, person-time event rate (per 100 person-years), and 95% CI. We estimated person-year rates using a Poisson model, with the number of events as the dependent variable and the log of person-time as an offset. Only the first occurrence of each event was used.

For patients treated with VKAs, the quality of anticoagulation was assessed by comparing the time in therapeutic range between moderate-to-severe CKD versus no CKD and mild CKD versus no CKD groups using methods previously described.[25,26]

Cox proportional hazard regression modeling was used to determine the effects of moderate-to-severe and mild CKD relative to no CKD on clinical outcomes up to 1 year after AF diagnosis. Models were adjusted for the following a priori

specified variables: age, sex, race, smoking, diabetes mellitus, hypertension, previous stroke/transient ischemic attack/SE, history of bleeding, heart failure, vascular disease, ACS, anticoagulant and/or antiplatelet treatment, type of AF, and heavy alcohol consumption.[27]

Five imputation data sets were generated using a multiple imputation procedure,[16,28,29] assuming arbitrary missing patterns and applying a fully conditional specification method that assumes a joint distribution for all of the variables. The fully conditional specification method involves 2 steps. The filled-in phase, where a discriminant function is used for binary variables, logistic for ordinal, and regression for continuous variables, fills in sequentially over the variables, one at a time. In the imputation phase, these steps are iterated to obtain final estimates. Hazard ratios with 95% CIs were calculated across the 5 imputed data sets, using parameter estimates as well as the within- and between–data set covariance matrices. The analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

Study Population

A total of 34 854 patients were enrolled in GARFIELD-AF from 1119 sites in 35 countries between April 2013 and August 2016. Of these, 1830 with unknown/missing data for CKD stage at baseline were excluded and 33 024 analyzed. Globally, physicians classified 10.9% of patients with moderate-to-severe CKD (stage 3, n=3049; stage 4, n=397; stage 5, n=167), 16.9% with mild CKD (stage 1, n=1984; stage 2, n=3611), and 72.1% with no CKD (n=23 816). Baseline demographics, clinical characteristics, and care settings for each CKD group are shown in Figure 1 and Table 1. Compared with patients with mild or no CKD at the time of diagnosis of AF, patients with moderate-to-severe CKD were older (78.0 years versus 69.0 years without CKD) and were more likely to be female. In GARFIELD-AF, the detection of moderate-to-severe CKD stage was less likely (than mild or no CKD) in patients of Chinese and Hispanic/Latino ethnicity. As shown in Figure 1, comorbid heart failure, previous history of CAD, carotid occlusive disease, coronary artery bypass surgery, stroke and/or transient ischemic attack, pulmonary embolism, deep vein thrombosis, bleeding, and diabetes mellitus tended to occur more frequently in advanced CKD. Overall, patients with moderate-to-severe CKD had a numerically higher median CHA_2DS_2-VASc score of 4.0 as compared with a score of 3.0 in patients with mild or no CKD. Similarly, a numerically higher HAS-BLED score of 2.0 was observed for patients with moderate-to-severe CKD and 1.0 for patients with mild and no CKD (Table 1).

In total, 9491 of 33 024 patients (28.7%) were recruited from countries in Asia (China, India, Japan, Singapore, South

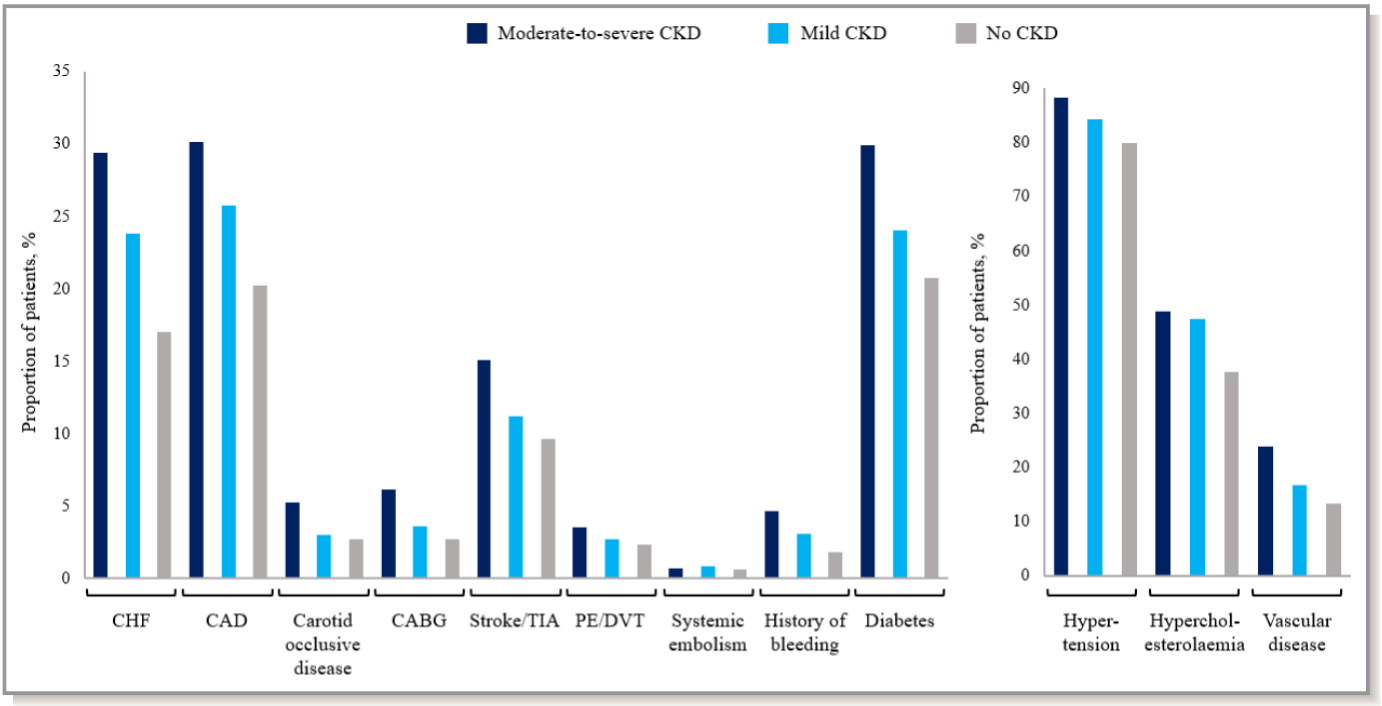

Figure 1. Prevalence of comorbidities according to chronic kidney disease group. Carotid occlusive disease (missing n=549); CABG (missing n=72); PE/DVT (missing n=172); systemic embolism (missing=174); history of bleeding (missing n=125). CABG indicates coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; CKD indicates chronic kidney disease; DVT, deep vein thrombosis; PE, pulmonary embolism; TIA, transient ischemic attack.

Table 1. Demographics, Clinical Characteristics and Care Settings of Patients According to CKD Group

Variable	Moderate-to-Severe CKD (n=3613)	Mild CKD (n=5595)	No CKD (n=23 816)
Female, n (%)	1828 (50.6)	2423 (43.3)	10 386 (43.6)
Age at AF diagnosis (y), median (IQR)	78.0 (71.0–83.0)	71.0 (63.0–78.0)	69.0 (61.0–77.0)
Race, n/n patients in each ethnic group (%)			
White	2491 (68.9)	3864 (69.1)	13 553 (56.9)
Hispanic/Latino	134 (3.7)	202 (3.6)	1543 (6.5)
Afro-Caribbean	25 (0.7)	30 (0.5)	141 (0.6)
Asian (not Chinese)	750 (20.8)	998 (17.8)	6455 (27.1)
Chinese	83 (2.3)	260 (4.6)	1356 (5.7)
Mixed/other	39 (1.1)	62 (1.1)	400 (1.7)
Unwilling to declare/not known	91 (2.5)	179 (3.2)	368 (1.5)
BMI, kg/m^2			
Median (IQR)	27.0 (24.0–31.0)	27.0 (24.0–31.0)	27.0 (24.0–31.0)
BMI category, n/n (%)			
<19	95 (3.3)	124 (2.8)	488 (2.7)
19 to <25	943 (33.1)	1299 (28.9)	5835 (32.0)
25 to <30	966 (33.9)	1691 (37.6)	6759 (37.1)
30 to <40	762 (26.7)	1190 (26.5)	4509 (24.8)
≥40	85 (3.0)	195 (4.3)	627 (3.4)
Missing	762 (21.1%)	1096 (19.6%)	5598 (23.5%)
Alcohol consumption, n (%)			
Abstinent	1767 (58.1)	2385 (48.6)	11 530 (57.6)
Light	1006 (33.1)	1862 (37.9)	6078 (30.4)
Moderate	219 (7.2)	528 (10.8)	1973 (9.9)
Heavy	51 (1.7)	133 (2.7)	435 (2.2)
Missing	570 (15.8%)	687 (12.3%)	3800 (16.0%)
Smoking, n (%)			
Nonsmoker	2158 (64.9)	3225 (61.2)	14 506 (66.7)
Ex-smoker	975 (29.3)	1461 (27.7)	4691 (21.6)
Current smoker	190 (5.7)	584 (11.1)	2551 (11.7)
Missing	290 (8.0%)	325 (5.8%)	2068 (8.7%)
Type of AF, n (%)			
New onset (unclassified)	1632 (45.2)	2703 (48.3)	10 062 (42.2)
Paroxysmal	892 (24.7)	1405 (25.1)	7270 (30.5)
Persistent	533 (14.8)	729 (13.0)	3536 (14.8)
Permanent	556 (15.4)	758 (13.5)	2948 (12.4)
CHA_2DS_2-VASc score, median (IQR)	4.0 (3.0–5.0)	3.0 (2.0–4.0)	3.0 (2.0–4.0)
Missing	74 (2.0%)	127 (2.3%)	680 (2.9%)
HAS-BLED score, median (IQR)	2.0 (2.0–3.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)
Missing	741 (20.5%)	909 (16.2%)	4699 (19.7%)
Antithrombotic treatment, n (%)			
VKA±antiplatelet	1421 (40.0)	2117 (38.4)	7515 (31.9)
NOAC±antiplatelet	1194 (33.5)	1942 (35.3)	8752 (37.2)

Continued

Table 1. Continued

Variable	Moderate-to-Severe CKD (n=3613)	Mild CKD (n=5595)	No CKD (n=23 816)
Antiplatelet only	593 (16.7)	873 (15.8)	4190 (17.8)
No antithrombotic	350 (9.8)	580 (10.5)	3078 (13.1)
Missing	47 (1.3%)	68 (1.2%)	227 (1.0%)
ACS	561 (15.7%)	625 (11.2%)	1944 (8.2)
Missing	29 (0.8%)	18 (0.3%)	164 (0.7%)
Time in therapeutic range median (IQR)	50.0 (33.3–66.7)	50.0 (33.3–66.7)	50.0 (33.3–66.7)
Care setting specialty at diagnosis, n (%)			
Cardiology	20 843 (57.7)	3430 (61.3)	16 858 (70.8)
Geriatrics	36 (1.0)	26 (0.5)	55 (0.2)
Internal medicine	758 (21.0)	1129 (20.2)	3763 (15.8)
Neurology	72 (2.0)	95/5595 (1.7)	317 (1.3)
Primary care/general practice	663 (18.4)	915 (16.4)	2823 (11.9)
Care setting location at diagnosis, n (%)			
Anticoagulation clinic/thrombosis centre	14 (0.4)	30 (0.5)	79 (0.3)
Emergency room	351 (9.7)	669 (12.0)	2392 (10.0)
Hospital	2095 (58.0)	3412 (61.0)	13 320 (55.9)
Office	1153 (31.9)	1484 (26.5)	8025 (33.7)

Percentages in the table refer to complete data, except for the missing data percentages. ACS indicates acute coronary syndrome; AF, atrial fibrillation; BMI, body mass index; CKD, chronic kidney disease; IQR, interquartile range; NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist.

Korea, and Thailand), including 774 patients with moderate-to-severe CKD. The clinical characteristic and antithrombotic treatment of patients recruited from Asian and non-Asian countries, stratified by CKD group, are reported in Table S1. The analyses show that patients from Asia and the RoW have a similar stroke risk (as defined by CHA_2DS_2-VASc). Compared with patients with mild or no CKD, patients with moderate-to-severe CKD from Asian and non-Asian countries tended to be older and have a higher prevalence of heart failure, CAD, hypercholesterolemia, history of hypertension, vascular disease, and diabetes mellitus. However, patients from Asia (relative to the patients from the RoW) tended to have a more modest body mass index, and in Asian patients with mild or no CKD, there was a lower prevalence of CAD, hypercholesterolemia, and hypertension.

Antithrombotic Therapy Use According to CKD Group and Stroke Risk

Table 1 shows that slightly more patients with than without CKD were anticoagulated (73.5% and 73.7% versus 69.1%, respectively). The decision to use anticoagulants with or without AP therapy was influenced primarily by CHA_2DS_2-VASc score irrespective of CKD status (Figure 2A). For patients with the same CHA_2DS_2-VASc score, the prescribing of anticoagulants did not differ substantially between those with moderate-to-severe, mild, and no CKD: 57.8%, 59.0%, and 55.7% (for those with a CHA_2DS_2-VASc score of 0–1) and 74.5%, 77.1%, and 73.7% (for a CHA_2DS_2-VASc score of 3 or more).

VKA prescribing tended to be slightly more frequent in patients with CKD. For example, in patients with a CHA_2DS_2-VASc score of ≥3, VKA±antiplatelet use was 40.5% and 39.6% (for moderate-severe and mild CKD) and 35.0% (for no CKD). With NOACs (factor Xa inhibitor or direct thrombin inhibitor), the opposite trend was observed; although a substantial of proportion of patients with moderate-to-severe CKD received NOACs (34.0%) versus 37.5% (for mild CKD) and 38.7% (for no CKD) in patients with a CHA_2DS_2-VASc score of ≥3. The quality of anticoagulant control with VKAs, as measured by time in therapeutic range, did not differ with CKD stage (Table 1).

The use of antiplatelet therapy alone was similar irrespective of CKD status. For example, in CHA_2DS_2-VASc 0–1 patients, antiplatelet use was 18.7%, 21.6%, and 20.6% for moderate-to-severe, mild, and no CKD, respectively; in patients with a CHA_2DS_2-VASc score of ≥3, antiplatelet use was 16.5%, 14.6%, and 17.0% of patients, respectively. In contrast, the proportion of patients who received no antithrombotic therapy (neither anticoagulant nor antiplatelet) appeared to be influenced primarily by stroke risk (based on the post hoc assessment of the

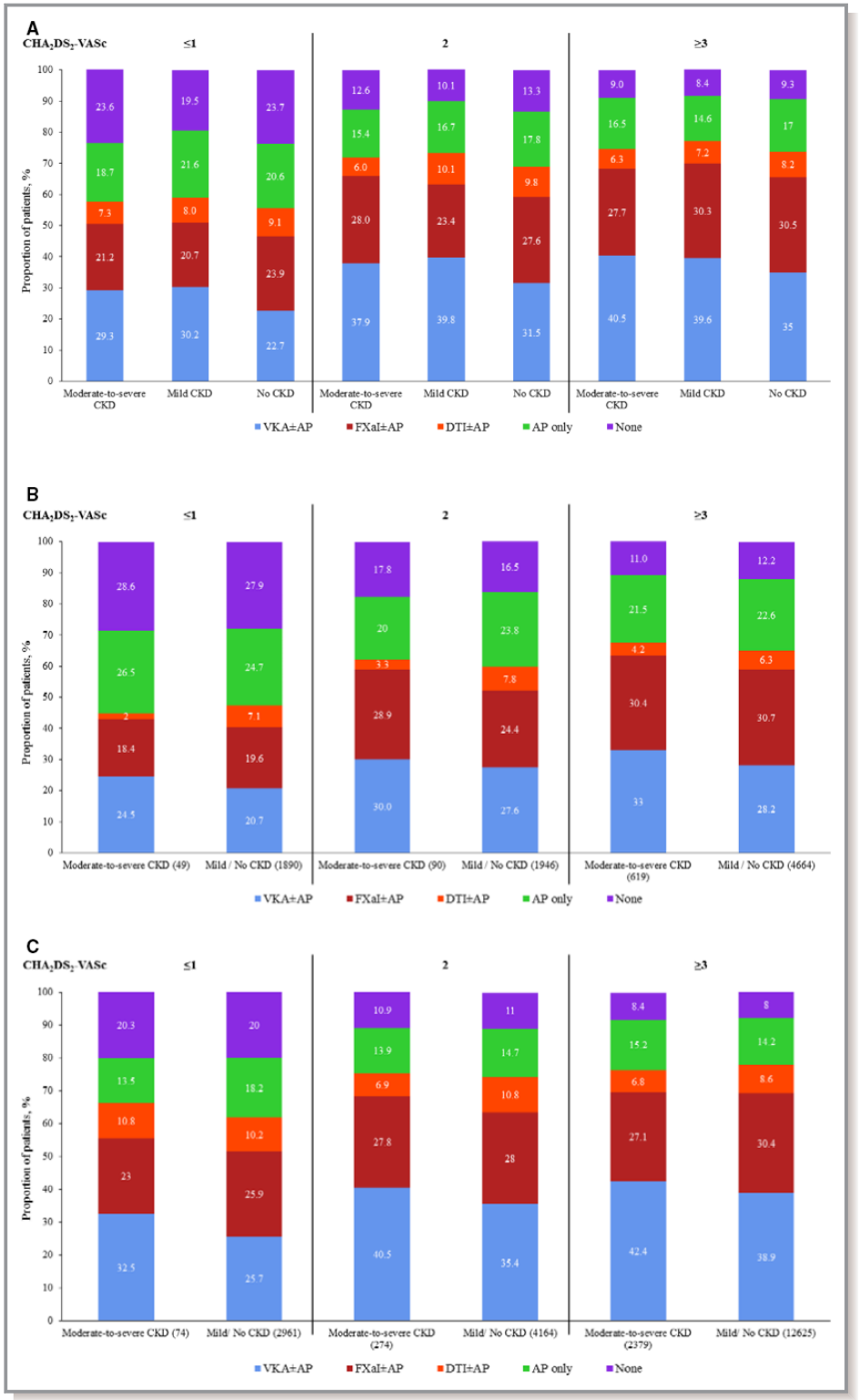

Figure 2. Antithrombotic therapy at diagnosis according to chronic kidney disease (CKD) group and CHA_2DS_2-VASc score (**A**) worldwide (**B**) Asian (**C**) non-Asian countries. AP indicates antiplatelet; DTI, direct thrombin inhibitor; FXaI, factor Xa inhibitor; VKA, vitamin K antagonist.

CHA_2DS_2-VASc score). For patients with a CHA_2DS_2-VASc score of ≥3 versus those with a CHA_2DS_2-VASc score of 0–1, the proportion on no antithrombotic therapy was 9.0% versus 23.6% (for moderate-to-severe CKD), 8.4% versus 19.5% (for mild CKD), and 9.3% versus 23.7% (for no CKD).

Antithrombotic Therapy Use in Asia Versus RoW

We observed that the standard of care with antithrombotic therapy differed in Asia compared with the RoW. Although the use of NOACs (factor Xa inhibitor and direct thrombin inhibitor)± antiplatelet was similar in both Asian and non-Asian countries (Table S1) when CHA_2DS_2-VASc was ≤1, NOAC use was lower in Asian countries (Figure 2B and 2C). Overall, VKA±antiplatelet was more commonly prescribed outside Asia (Table S1). Antiplatelet therapy as a lone therapy for stroke prevention was more likely to be used in Asia than elsewhere (Figure 2B and 2C; Table S1).

Clinical Outcomes

Relative to patients with no CKD, unadjusted rates of stroke/SE 1 year after the diagnosis of AF were twice as high in patients with moderate-to-severe CKD (Table 2). For all-cause mortality and major bleeding, event rates were ≈3-fold higher (Table 2). The most frequent known causes of death in patients with moderate-to-severe CKD were heart failure and infection/sepsis, and in patients with mild CKD or no CKD, heart failure and malignancy (Table S2). In all CKD groups, primary ischemic strokes were more frequent than primary intracerebral hemorrhages. Nonmajor clinically relevant bleeds were more common than major bleeds across all CKD groups. Fatal bleeding was rare across CKD stages, accounting for 7%, 5%, and 8% of all bleeding events in the moderate-to-severe CKD, mild CKD, and no CKD groups, respectively.

After adjusting for baseline characteristics and antithrombotic use, hazard ratios showed that moderate-to-severe CKD was an independent risk factor for stroke/SE, major bleeding, all-cause mortality, cardiovascular/noncardiovascular mortality, new onset of ACS, and heart failure within 1 year of the diagnosis of AF (Figure 3). Differences in mortality were statistically significant for comparisons of moderate-to-severe versus no CKD and for mild CKD versus no CKD. Differences in stroke/SE events and major bleed were statistically significant for the comparison of moderate-to-severe CKD versus no CKD, but not for mild CKD versus no CKD during the 1 year after the diagnosis of AF (Figure 3).

The interaction of CKD with age, race, and sex was evaluated for each of the primary end points (mortality, stroke/SE, and major bleeding). The only interaction that was statistically significant was the interaction between age and CKD for all-cause mortality ($P<0.001$). Relative to patients with no CKD, the hazard ratios for all-cause mortality were numerically greater in younger than older patients with CKD (either mild or moderate-to-severe CKD).

Comparison Between Patients Recruited From Asian and Non-Asian Countries

Table 3 describes the unadjusted event rates (per 100 person-years) over 1 year in patients from Asia and the RoW. Our findings show that mortality rates in patients with mild or no CKD are substantially lower in patients from Asia than elsewhere. Moderate-to-severe CKD, however, is associated with high mortality rates regardless of region. Relative to patients with no CKD, the impact of moderate-to-severe CKD on mortality was greater in patients from Asia than the RoW ($P=0.002$), and this difference remained significant after adjustment for treatment and baseline risk factors (Figure 4; $P=0.001$). In countries outside Asia, mild CKD was also associated with an elevated risk of mortality (which is not observed in Asia) even after adjustment for treatment and baseline risk factors (Figure 4).

Table 2. Events Rates Per 100 Person-Years During 1-Year Follow-Up According to CKD Group

	Moderate-to-Severe CKD (n=3613)		Mild CKD (n=5595)		No CKD (n=23 816)	
	n (%)	Rate, Per 100 Person-Years (95% CI)	n (%)	Rate, Per 100 Person-Years (95% CI)	n (%)	Rate, Per 100 Person-Years (95% CI)
Stroke/SE	74 (2.0)	2.25 (1.79–2.82)	64 (1.1)	1.21 (0.95–1.55)	233 (1.0)	1.03 (0.91–1.18)
Major bleeding	61 (1.7)	1.85 (1.44–2.38)	52 (0.9)	0.98 (0.75–1.29)	143 (0.6)	0.63 (0.54–0.75)
All-cause mortality	344 (9.5)	10.35 (9.31–11.51)	297 (5.3)	5. 60 (4.99–6.27)	729 (3.1)	3.22 (3.00–3.46)
Cardiovascular mortality	148 (4.1)	4.45 (3.79–5.23)	102 (1.8)	1.92 (1.58–2.33)	227 (1.0)	1.00 (0.88–1.14)
Noncardiovascular mortality	125 (3.5)	3.76 (3.16–4.48)	106 (1.9)	2.00 (1.65–2.42)	292 (1.2)	1.29 (1.15–1.45)
Undetermined cause of mortality	71 (2.0)	2.14 (1.69–2.70)	89 (1.6)	1.68 (1.36–2.06)	210 (0.9)	0.93 (0.81–1.06)
New ACS	51 (1.4)	1.55 (1.17–2.03)	36 (0.6)	0.68 (0.49–0.94)	133 (0.6)	0.59 (0.50–0.70)
New congestive heart failure	104 (2.9)	3.19 (2.63–3.86)	90 (1.6)	1.71 (1.39–2.10)	284 (1.2)	1.27 (1.13–1.42)

ACS indicates acute coronary syndrome; CKD, chronic kidney disease; SE, systemic embolism.

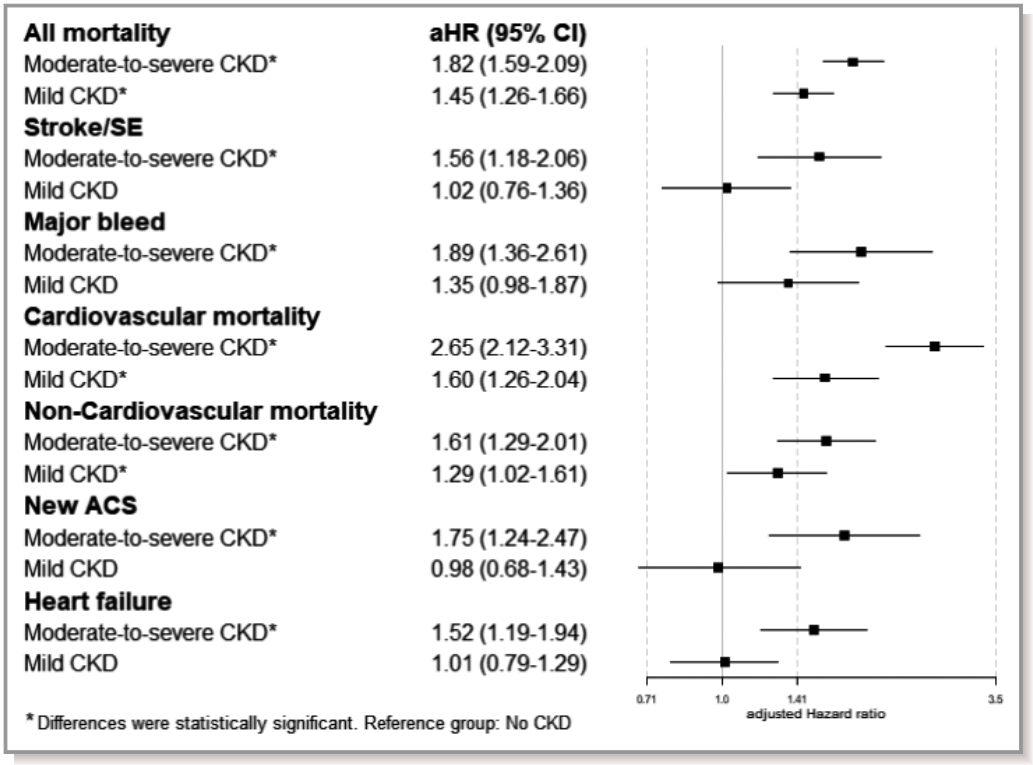

Figure 3. Adjusted hazard ratios for 1-year clinical outcomes according to severity of chronic kidney disease. Hazard ratios were adjusted for age, sex, race, smoking, diabetes mellitus, hypertension, previous stroke/transient ischemic attack/systemic embolism, history of bleeding, heart failure, vascular disease, acute coronary syndrome, anticoagulant treatment, type of atrial fibrillation, and alcohol consumption. ACS indicates acute coronary syndromes; aHR, adjusted hazard ratio; CKD, chronic kidney disease; SE, systemic embolism.

Although we observed a trend toward a lower rate of major bleeds, new ACS, and new or worsening heart failure in patients from Asia compared with the RoW (Table 3), the number of events was too low to compare the impact of CKD severity on these outcomes by region using adjusted analyses.

Discussion

We found that both mild and moderate-to-severe CKD are independently associated with all-cause mortality in patients with a new diagnosis of AF. Moderate-to-severe CKD was also independently associated with a higher risk of stroke/SE, major bleeding, new-onset ACS, and new or worsening heart failure. The impact of moderate-to-severe CKD on mortality is even greater while that of mild CKD was less in patients from Asia, where patient characteristics and the standard of care for anticoagulation differs from the RoW.

A substantial proportion of patients (27.8%) with newly diagnosed AF in GARFIELD-AF had comorbid CKD. Patients with moderate-to-severe CKD tended to be older and, therefore, were more likely to have higher CHA_2DS_2-VASc and HAS-BLED scores in the global and regional analyses. They also had a higher prevalence of comorbidities, including heart failure, CAD, history of coronary artery bypass graft, hypertension, stroke/ transient ischemic attack, or bleeding; vascular disease; and diabetes mellitus. The finding that moderate-to-severe CKD increased all-cause mortality was a consistent finding in the global analyses as well as in the regional analyses of Asian and non-Asian countries. However, the increased risk of mortality with mild CKD was observed only in patients outside Asia. This latter finding may reflect a lower prevalence of CAD, hypercholesterolemia, and hypertension in Asian patients compared with RoW.

Rates of stroke/SE, major bleeding, cardiovascular mortality, noncardiovascular mortality, new onset of ACS, and heart failure were higher in patients with moderate-to-severe CKD than in patients with no CKD (globally and regionally). These differences persisted after adjustment in the global assessment, suggesting the robustness of our findings. These findings are consistent with our previously published analyses of the whole GARFIELD-AF cohort, which identified a greater proportion of low-stroke-risk patients in Asia than the RoW.[30] Although few patients were recruited from the United States (n=732, 2.1%) into GARFIELD-AF, the higher bleeding events in moderate-to-severe CKD patients globally were consistent with results observed by O'Brien et al (2015) in the US

Table 3. Event Rates Per 100 Person-Years During 1-Year Follow-Up in Patients Stratified by Region (Asia and Rest of World) and CKD Group

Variable	Statistics	According to CKD Severity					
		Asia*			Rest of World		
		Moderate to Severe (N=774)	Mild (N=1225)	None (N=7492)	Moderate to Severe (N=2839)	Mild (N=4370)	None (N=16 324)
All-cause mortality	n (%)	66 (8.5)	29 (2.4)	167 (2.2)	278 (9.8)	268 (6.1)	562 (3.4)
	Rate (95% CI)	9.33 (7.33, 11.87)	2.45 (1.70, 3.53)	2.38 (2.05, 2.77)	10.63 (9.45, 11.96)	6.50 (5.76, 7.32)	3.60 (3.31, 3.91)
Cardiovascular mortality	n (%)	23 (3.0)	6 (0.5)	48 (0.6)	125 (4.4)	96 (2.2)	179 (1.1)
	Rate (95% CI)	3.25 (2.16–4.89)	0.51 (0.23–1.13)	0.69 (0.52–0.91)	4.78 (4.01–5.70)	2.33 (1.91–2.84)	1.15 (0.99–1.33)
Noncardio vascular mortality	n (%)	26 (3.4)	18 (1.5)	53 (0.7)	99 (3.5)	88 (2.0)	239 (1.5)
	Rate (95% CI)	3.67 (2.50–5.40)	1.52 (0.96–2.42)	0.76 (0.58–0.99)	3.79 (3.11–4.61)	2.13 (1.73–2.63)	1.53 (1.35–1.74)
Undetermined cause of mortality	n (%)	17 (2.2)	5 (0.4)	66 (0.9)	54 (1.9)	84 (1.9)	144 (0.9)
	Rate (95% CI)	2.40 (1.49–3.86)	0.42 (0.18–1.02)	0.94 (0.74–1.20)	2.07 (1.58–2.70)	2.04 (1.64–2.52)	0.92 (0.78–1.09)
Stroke/SE	n (%)	13 (1.7)	14 (1.1)	67 (0.9)	61 (2.1)	50 (1.1)	166 (1.0)
	Rate (95% CI)	1.85 (1.07–3.18)	1.19 (0.71–2.01)	0.96 (0.76–1.22)	2.35 (1.83, 3.02)	1.22 (0.92–1.61)	1.07 (0.92–1.24)
Major bleed	n (%)	11 (1.4)	9 (0.7)	19 (0.3)	50 (1.8)	43 (1.0)	124 (0.8)
	Rate (95% CI)	1.56 (0.87–2.82)	0.77 (0.40–1.47)	0.27 (0.17–0.43)	1.93 (1.46–2.54)	1.05 (0.78–1.41)	0.80 (0.67–0.95)
New ACS	n (%)	8 (1.0)		13 (0.2)	43 (1.5)	36 (0.8)	120 (0.7)
	Rate (95% CI)	1.13 (0.57–2.27)		0.19 (0.11–0.32)	1.66 (1.23–2.23)	0.88 (0.63–1.22)	0.77 (0.65–0.92)
New or worsening heart failure	n (%)	9 (1.2)	6 (0.5)	61 (0.8)	95 (3.3)	84 (1.9)	223 (1.4)
	Rate (95% CI)	1.28 (0.67–2.46)	0.51 (0.23–1.13)	0.88 (0.68–1.13)	3.71 (3.04–4.54)	2.06 (1.66–2.55)	1.44 (1.26–1.64)

ACS indicates acute coronary syndrome; CKD, chronic kidney disease; SE, systemic embolism.
*Asia includes China, India, Japan, Singapore, South Korea, and Thailand.

registry, ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation).[31]

Compared with patients with no CKD, patients with moderate-to-severe or mild CKD had a higher cardiovascular mortality rate in the global analyses. Heart failure was the most common cause of death, amounting to 47% (70 of 148) cardiovascular deaths; sudden/unwitnessed deaths and deaths from ACS were relatively rare; and ischemic stroke accounted for only 3% of all-cause mortality in patients with moderate-to-severe CKD. Of the noncardiac causes of death, malignancy was more common in patients with no or mild CKD than in patients with moderate-to-severe CKD, while infection/sepsis was more frequent in patients with moderate-to-severe CKD. Fatal bleeding was rare across CKD stages, accounting for 7%, 5%, and 8% of all bleeding events in the moderate-to-severe CKD, mild CKD, and no CKD groups, respectively.

More than 30% of patients were on NOACs, irrespective of their CKD stage when CHA_2DS_2-VASc score was ≥2. Because all NOACs are excreted, at least in part, from the kidney, and dabigatran is contraindicated in severe renal failure, the similar frequency of NOAC use in mild and moderate-to-severe CKD in the real-world GARFIELD-AF registry is noteworthy. The primary consideration of physicians when prescribing any anticoagulant (either VKA or NOAC) in patients with moderate-to-severe CKD and mild CKD appears to be the patients' stroke risk, represented by the post hoc assessment of CHA_2DS_2-VASc score, with higher overall frequency of anticoagulant use in patients with the highest stroke risk. VKAs tended to be prescribed more frequently than NOACs (factor Xa inhibitor and direct thrombin inhibitor) in patients with moderate-to-severe CKD.

Clinical Perspectives

Recent publications have demonstrated the limitation of the CHA_2DS_2-VASc score for predicting future strokes in patients with AF.[32] Of the potential risk factors omitted in the CHA_2DS_2-VASc score, renal dysfunction is highlighted by many clinical studies.[9,33–35] There are, however, studies that suggest that the predictive value of the CHA_2DS_2-VASc score is not improved by addition of CKD status because the factors within CHA_2DS_2-VASc are themselves related to renal dysfunction.[36] Indeed, a previous systematic review reassured

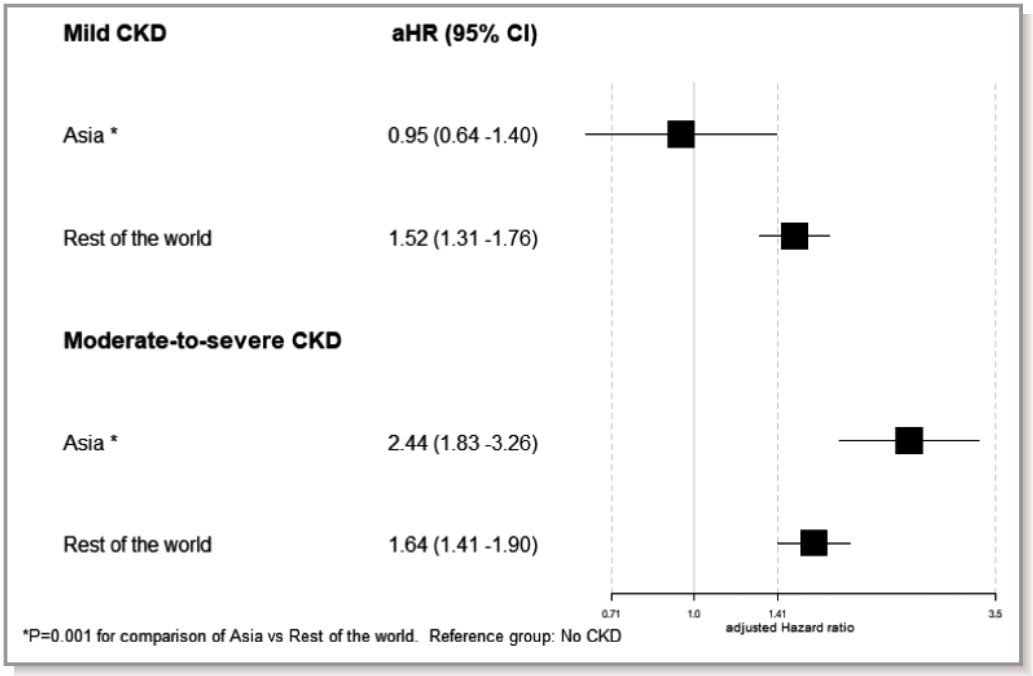

Figure 4. Adjusted hazard ratios for 1-year clinical outcomes according to severity of chronic kidney disease (CKD) in Asia and non-Asian countries. Hazard ratios were adjusted for age, sex, race, smoking, diabetes mellitus, hypertension, previous stroke/transient ischemic attack/systemic embolism, history of bleeding, heart failure, vascular disease, acute coronary syndrome, anticoagulant treatment, type of atrial fibrillation, and alcohol consumption. aHR indicates adjusted hazard ratio; SE, systemic embolism.

that only the original components of the CHA_2DS_2-VASc score were independently predictive for stroke in AF.[37] Our data confirm higher stroke/SE, cardiovascular/noncardiovascular/undetermined mortality, other vascular events, and heart failure in AF patients with concomitant moderate-to-severe CKD. An important distinction between our study and previously published studies is that our study is not focused just on stroke. The presence of CKD is strongly associated with an increased risk of mortality.

Despite potential concerns over the lack of coagulation monitoring with NOACs in patients with moderate-to-severe CKD,[38] our data suggest that the use of NOACs in these patients is similar to the use in no/mild CKD in real-world clinical practice. This may reflect the difficulties in prescribing VKAs to patients with CKD, which have been observed in both the clinical trial setting and observational studies (outside specialist centers).[5,39]

Limitations

GARFIELD-AF is an observational prospective registry and not a randomized trial. Though adjustments were made for the parameters known to influence clinical outcomes, the differences between no CKD and (mild or moderate-to-severe) CKD may still be influenced by unknown confounder(s).

Our analyses focus on 1-year outcomes to avoid the influence of the time-dependent change in CKD stage. But CKD stage was assessed only at the time of enrollment. There may be some patients whose kidney function deteriorated rapidly even within this 1-year period.

Moreover, the CKD stage was based on the investigators' judgment, according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative guidelines,[24] rather than by the collection of laboratory data in the case report form.

We also acknowledge that there is wide heterogeneity within the Asian population in the GARFIELD-AF registry. Despite this heterogeneity, we have previously shown that patients from Asia (including the Asia-Pacific region as well as China and India) have a lower stroke risk than patients from outside Asia.[30] When testing the internal validity of our global findings, we compared the impact of CKD in patients from Asia and outside Asian using the same regional definitions as described in our previous analyses.[30] However, due to the small number of patients of Asian origin outside Asia, we were not able to distinguish between the impact of race and impact of region for Asians in this study.

It is also noteworthy that not all regions are equally represented in GARFIELD-AF. For example, a relatively low number of patients were recruited from the United States. However, in a collaboration with the US registry, ORBIT-AF, we

have previously published data on the baseline characteristics of patients and stroke prevention strategies of both registries.[40] To date, however, the data from these 2 contemporary registries in AF have not been merged.

To avoid channeling bias,[41] GARFIELD-AF was designed as a noninterventional study—so that no tests, visits, or treatments were prespecified in the protocol and the decision to use or not use antithrombotic agents was solely at the discretion of the investigator. However, in the context of CKD, it is likely that physicians may, or may not, have modified the dose of NOAC according to renal function.[42–47] We recognize that inappropriate dosing of NOACs in CKD patients might be another factor related to worse clinical outcomes. This will be the subject of a future study.

Conclusions

Our results show that, even after adjustment for the higher rates of comorbidities, renal dysfunction defined as moderate-to-severe CKD is independently associated with higher risks of stroke/SE, major bleeding, all-cause mortality, and various cardiovascular events. The impact of moderate-to-severe CKD on mortality varies in different regions of the world. Greater impact was shown in patients from Asia than elsewhere. Use of anticoagulants, including NOACs, is influenced primarily by stroke risk (as defined by CHA_2DS_2-VASc) rather than by CKD stage.

Appendix

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SUPPLEMENTAL MATERIAL

Table S1. Patient characteristics, antithrombotic treatment, and time in therapeutic range by region and chronic kidney disease severity.

	Asia* by CKD severity		Rest of world by CKD severity	
	Moderate-to-severe (N=774)	**No/mild (N=8717)**	**Moderate-to-severe (N=2839)**	**No/mild (N=20,694)**
Age, years, median (IQR)	76.0 (68.0 to 82.0)	69.0 (60.0 to 76.0)	78.0 (72.0 to 83.0)	70.0 (62.0 to 77.0)
BMI, kg/m², median (IQR)	24.0 (21.0 to 26.0)	24.0 (22.0 to 27.0)	28.0 (25.0 to 32.0)	28.0 (25.0 to 32.0)
Congestive heart failure, n (%)	243 (31.4)	1618 (18.6)	818 (28.8)	3766 (18.2)
Coronary artery disease, n (%)	160 (20.7)	1462 (16.8)	927 (32.7)	4783 (23.1)
Hypercholesterolaemia, n*** (%)	304 (40.9)	2457 (28.7)	1456 (53.1)	9167 (46.5)
History of hypertension, n (%)	617 (79.8)	5778 (66.5)	2401 (84.7)	16,007 (77.6)
Diabetes mellitus, n (%)	229 (29.6)	1803 (20.7)	853 (30.0)	4478 (21.6)
CHA_2DS_2-VASc score, median (IQR)	4.0 (3.0 to 5.0)†	3.0 (2.0 to 4.0)‡	4.0 (3.0 to 5.0)§	3.0 (2.0 to 4.0)‖
HAS-BLED score, median (IQR)	2.0 (2.0 to 3.0)#	1.0 (1.0 to 2.0)**	2.0 (2.0 to 3.0)††	1.0 (1.0 to 2.0)‡‡
Care setting at diagnosis, n (%)				
Cardiology	575 (74.3)	7340 (84.2)	1509 (53.2)	12,948 (62.6)
Geriatrics	2 (0.3)	16 (0.2)	34 (1.2)	65 (0.3)

	Asia* by CKD severity		Rest of world by CKD severity	
	Moderate-to-severe (N=774)	**No/mild (N=8717)**	**Moderate-to-severe (N=2839)**	**No/mild (N=20,694)**
Internal medicine	156 (20.2)	1040 (11.9)	602 (21.2)	3852 (18.6)
Neurology	15 (1.9)	73 (0.8)	57 (2.0)	339 (1.6)
Primary care/general practice	26 (3.4)	248 (2.8)	637 (22.4)	3490 (16.9)
VKA ± antiplatelet, n (%)	249 (32.3)	2279 (26.2)	1172 (42.1)	7353 (36.1)
TTR ≥65% (target INR of 2.0–3.0), n (%)	23 (16.0)	214 (19.8)	318 (44.4)	1911 (46.3)
TTR ≥65% (target INR of 1.6–2.6), n (%)	34 (23.6)	272 (25.1)	318 (44.4)	1911 (46.3)
NOAC ± antiplatelet, n (%)	256 (33.0)	2917 (33.5)	946 (33.7)	7846 (38.2)
Antiplatelet only, n (%)	169 (21.9)	2024 (23.3)	424 (15.2)	3039 (14.9)
No antithrombotic, n (%)	99 (12.8)	1473 (16.9.0)	251 (9.0)	2185 (10.7)
VKA ± antiplatelet, n (%)	249 (32.2)	2279 (26.2)	1172 (42.0)	7353 (36.0)

*Asia includes China, India, Japan, Singapore, South Korea, and Thailand. [†]14 patients missing; [‡]183 patients missing; [§]60 patients missing; [||]624 patients missing; [#]154 patients missing; **1625 patients missing; [††]587 patients missing; [‡‡]3983 patients missing *** 287 patients missing. BMI, body mass index; CKD, chronic kidney disease; INR, international normalized ratio; IQR, interquartile range; NOAC, non-vitamin K antagonist oral anticoagulant; TTR, time in therapeutic range; VKA, vitamin K antagonist.

Table S2. First events during 1-year follow-up according to chronic kidney disease severity.

	Severity of CKD		
	Moderate-to-severe (n=3619)	**Mild (n=5602)**	**None (n=23,883)**
All-cause mortality	334	297	729
Cardiovascular causes	148 (43.0)	102 (34.3)	227 (31.1)
Heart failure	70 (20.3)	29 (9.8)	78 (10.7)
Sudden death	19 (5.5)	26 (8.8)	24 (3.3)
ACS	14 (4.1)	7 (2.4)	28 (3.8)
Ischaemic stroke	9 (2.6)	13 (4.4)	30 (4.1)
Other[‡]	36 (10.5)	27 (9.1)	67 (9.2)
Non-cardiovascular causes	125 (36.3)	106 (35.7)	292 (40.1)
Malignancy	21 (6.1)	40 (13.5)	101 (13.9)
Respiratory failure	16 (4.7)	17 (5.7)	50 (6.9)
Infection/sepsis	41 (11.9)	24 (8.1)	57 (7.8)
Suicide	1 (0.3)	-	3 (0.4)
Other[§]	46 (13.4)	25 (8.4)	81 (11.1)
Undetermined causes	71 (20.6)	89 (30.0)	210 (28.8)
Stroke (not including SE)*	66	58	214
Primary ischaemic stroke	45 (68.2)	40 (69.0)	154 (72.0)
Of which secondary haemorrhagic ischaemic stroke	2 (3.0)	7 (12.1)	8 (3.7)
Primary intracerebral haemorrhage	8 (12.1)	5 (8.6)	29 (13.6)

Intracerebral	6 (9.1)	1 (1.7)	21 (9.8)
Subarachnoid	1 (1.5)	3 (5.2)	5 (2.3)
Intraventricular	-	2 (3.5)	3 (1.4)
Subdural Haematoma	-	-	1 (0.5)
Undetermined[†]	13 (19.7)	13 (22.4)	31 (14.5)
Bleeding events (not including minor bleeds)*	150	139	373
Severity of bleed			
Non-major clinically relevant	89 (59.3)	87 (62.6)	230 (61.7)
Major	61 (40.7)	52 (37.4)	143 (38.3)
Fatal	10 (6.7)	7 (5.0)	29 (7.8)

*Only the first occurrence was taken into account.

[†]Includes patients with either undetermined or unknown types of stroke and those with both primary ischaemic and primary intracerebral haemorrhagic strokes.

[‡]Includes deaths due to intracranial haemorrhage, atherosclerotic vascular disease, dysrhythmia, pulmonary embolism, and haemorrhagic stroke. [§]Includes deaths due to accidents/trauma, renal disease, and liver disease.

ACS, acute coronary syndromes; CKD, chronic kidney disease; SE, systemic embolism