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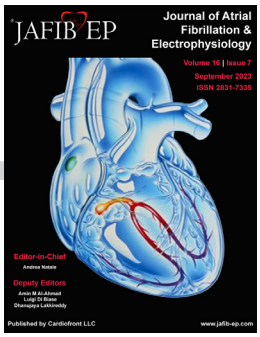

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Multi-morbidity, Anti-thrombotic Treatment and Mortality Among the Elderly NVAF Patients from the KERALA-AF Registry

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Abstract

Background and Aim: Reports on patients with nonvalvular atrial fibrillation (NVAF), particularly in the elderly, are few from India. This paper focuses on multimorbidity pattern, antithrombotic treatment and mortality of elderly NVAF patients from the state of Kerala, India.

Methods: Clinical details of NVAF patients of age ≥ 75 years from the cohort of KERALA-AF registry were analyzed for pattern of multimorbidity, antithrombotic treatment and one-year mortality.

Results: The study comprised 753 patients with a median age of 80 years (IQR = 77–84), 53.5% being male. Multimorbidity was present in 94.5% of patients. Hypertension was the most common risk factor (74.4 %, n = 560) and chronic kidney disease was the major coexisting disease (78.9%, n = 594). Based on the number of comorbidities present, patients were grouped into three groups: < 3 comorbidities (18.1%), 3–5 comorbidities (63.9%), and > 5 comorbidities (17.6%). Oral anticoagulant therapy (OAC) was received by 62.5% (n = 472) of

patients, mostly Vitamin K antagonist (VKA). Direct oral anticoagulants (DOAC) were used in 11.3% of patients. Antiplatelet therapy was used in 60.6% (n = 458) and the most commonly used antiplatelet was clopidogrel (44.6%). No antithrombotic treatment was used in 12.0% of patients (n = 91). One-year all-cause mortality was 19.6% (n = 148), higher in women but not statistically significant (p = 0.06). Kaplan-Meier survival curve indicated better one-year survival for patients who received OAC treatment (log rank test p < 0.0001, HR = 0.49 (95% CI = 0.35, 0.68), concordance = 0.58). Multivariate cox proportional hazards regression model showed OAC treatment (HR, 0.5; 95% CI, 0.36-0.7, P < 0.001) and age more than 80 years (HR, 1.53; 95% CI, 1.11 –2.1, P < 0.01) as predictors of one-year mortality. Mortality was not significantly different among the groups with different clustering of multimorbidity.

Conclusion: Use of oral anticoagulation was associated with a reduced risk of mortality among elderly NVAF patients in the KERALA-AF Registry. However, more than one-third of elderly NVAF patients did not receive OAC, which calls for increased sensitization and training of treating doctors regarding optimal use of OAC in the elderly NVAF patients.

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Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in elderly people and is an independent risk factor for hospitalization and death.[1] The prevalence of AF increases with age, reaching up to 10% in population above the age of 75.[2] Comorbid conditions increase with age and it is estimated that nearly 98% of patients with AF have at least one additional comorbidity.[3,4] The presence of multimorbidity and the increased risk of bleeding make stroke prevention with oral anticoagulants (OACs) more challenging in the elderly. Current AF treatment guidelines do not consider the multiple comorbid conditions and their impact on treatment and outcome.[5] This is despite a recent move towards more appropriate characterization, evaluation,[6] and management of AF in a holistic or integrated manner.[7,8]

The use of OACs for stroke prophylaxis in the elderly AF patients is highly variable across different populations, ranging from 91.9% among patients ≥ 75 years in Japan[9] to 11.1% in the Chinese AF Registry.[10] Mortality also showed significant regional differences. In Sweden, AF patients of age ≥ 75 years reported 18.2% death in a follow-up time of 3.4 years.[11] In China, a cohort of NVAF patients of age ≥ 75 years reported a death rate of 24.3% in one year.[10] There are conflicting reports on the impact of multimorbidity on death and hospitalization in elderly AF patients. Some studies reported worse clinical outcomes,[12-14] while some studies reported that the multimorbidity does not impact death or hospitalization in AF patients.[15]

The main objective of this study is to investigate the presence and pattern of multimorbidity, details of antithrombotic treatment, and their impact on the mortality of NVAF patients of age ≥75 years.

Key Words

nonvalvular atrial fibrillation; multimorbidity; antithrombotic treatment; mortality; elderly NVAF patients. KERALA-AF Registry

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Methods

This study examined NVAF patients aged 75 years and above with at least one comorbidity from the KERALA-AF Registry. The registry is a prospective study of AF patients recruited from the cardiology departments of 53 hospitals in the state of Kerala, India. Details of the study design and cohort profiles of 3421 AF patients in the registry have been published elsewhere.[16] All consecutive new and previously diagnosed patients ≥ 18 years with documented evidence of AF in electrocardiograms, attending the outpatient of a cardiology department or hospitalized during the period April 2016 to April 2017, were included in the study. The registry recruited patients from government, private and corporate hospitals from different regions of Kerala to ensure representation of rural and urban areas and different socioeconomic groups. There were 2,507 nonvalvular atrial fibrillation (NVAF) patients in this cohort and their characteristics, risk factors, treatment, and one-year clinical outcomes were previously published.[17] The current paper focuses on multimorbidity, antithrombotic treatment, and mortality of 753 elderly NVAF patients. Patients were followed up at three time points—one month, six months, and one year. The one-month follow ups happened during clinic visits, while the six-month and one-year follow ups were conducted as telephonic calls if the patients did not attend the clinic within a week of appointment dates.

Multimorbidity is defined as the coexistence of two or more long-term conditions.[18] We considered the following conditions while defining multimorbidity: hypertension (HT), diabetes mellitus (DM), dyslipidemia, chronic kidney disease (CKD), coronary artery disease (CAD), chronic heart failure (CHF), chronic respiratory disease (CRD), thyroid dysfunction, cerebrovascular accident, chronic liver disease, and cardiomyopathy. All comorbidities were based on clinical diagnosis. CKD was defined as glomerular filtration rate (GFR) < 60 mL/min per 1.73m^2 at the baseline.[19]

Besides CHA_2DS_2-VASc[20] (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or TIA or thromboembolism, vascular disease, age 65–74 years, sex category) score and HAS-BLED[21] (hypertension, abnormal liver/renal function, stroke history, bleeding history or predisposition, labile INR, lderly, drug/alcohol usage) were evaluated in every patient.

Ethics

Institutional ethics committees of the participating hospitals and the central ethics committee of the Cardiological Society of India-Kerala Chapter (CSI-K) have approved the study. The study was conducted as per the Indian Council of Medical Research guidelines and the Declaration of Helsinki. Informed written consent was obtained from all participants.

Statistical analysis

First, we summarized the sample characteristics as frequencies and percentages for categorical variables and as mean and standard deviation or as median and interquartile ranges for continuous variables. Second, we conducted separate bivariate analyses to understand the factors associated with the use of OACs (use-yes/no) and mortality (survived/died). Pearson's chi-squared test or Fisher's exact test were used to test the association between categorical variables and the Wilcoxon rank sum test with continuity correction for comparing age. Third, we developed a multivariable logistic regression model to calculate the adjusted odds ratio of mortality. Independent variables that were found to be related to mortality ($p \leq 0.10$) in bivariate analysis using the chi-squared test were entered in one step into the regression model. Lastly, we performed a one-year survival analysis using Kaplan-Meier and Cox proportional hazard methods. Patients who survived at the end of a one-year follow-up were considered censored. Hazard ratio (and 95% confidence intervals) and log-rank *P* were calculated to identify independent predictors and summarized in the forest plot. We included age groups, sex, multimorbidity, and OAC treatment as prognostic factors. A probability value of ≤ 0.05 was considered statistically significant and all tests were two-sided. The data were analyzed using tidyverse, gtsummary, dplyr, ggplot2, and survival packages in R.[22]

Patient involvement: Patients or the public were not directly involved in the design, conduct, or reporting of this research.

Results

Prevalence and pattern of multimorbidity

Table 1 summarizes the patient characteristics. The median age of patients was 80 years (IQR = 77–84), with 53.5% (n = 403) being male. The mean body mass index (BMI) was 23.9 (SD = 3.8) Kg/m^2. Hypertension (74.4 %, n = 560), dyslipidemia (53.7 %, n = 404), and diabetes mellitus (42.1%, n = 317) were the most prevalent risk factors, while co-existing diseases included chronic kidney disease (78.9%, n = 594), coronary artery disease (56.7%, n = 427), chronic heart failure (28.5%, n = 215), and chronic respiratory disease (28.5%, n = 215). The mean CHA_2DS_2-VASc score was 4.3 (SD = 1.6) and the mean HAS-BLED score was 2.4 (SD = 1.2). Among the comorbidities, CAD and CRD were seen more in men while thyroid dysfunction and chronic heart failure were slightly higher among women. The pattern of multimorbidity combinations present in at least 10 patients is shown in **Figure 1**.

Multimorbidity was present in 94.5% (n = 712) of patients, and was higher in patients above 80 years. Supplementary table 1: Patients were grouped into (a) <3 comorbidities (18.1%), (b) 3–5 comorbidities (63.9%), and (c) >5 comorbidities (17.6%). No age or sex differences were noted between multimorbidity levels. Major cardiometabolic risk

Table 1: Characteristics of non-valvular AF patients aged 75 and above, KERALA-AF Registry.

Characteristic	Overall, N = 753[a] (%)	Female, N = 350[a] (%)	Male, N = 403[a] (%)
Age in years [median (IQR)]	80 (77–84)	80 (77–84)	80 (77–84)
Age groups			
75–80 years	420 (56)	189 (54)	231 (57)
Above 80 years	333 (44)	161 (46)	172 (43)
Multimorbidity	712 (95)	337 (96)	375 (93)
Comorbidities levels			
Less than three	137 (18)	60 (17)	77 (19)
Three – five	483 (64)	232 (66)	251 (62)
More than five	133 (18)	58 (17)	75 (19)
Comorbidities/ coexisting conditions			
Hypertension	560 (74)	268 (77)	292 (72)
Diabetes mellitus	317 (42)	146 (42)	171 (42)
Dyslipidemia	404 (54)	187 (53)	217 (54)
Thyroid dysfunction*	71 (9)	41 (12)	30 (7)
Chronic heart failure	215 (29)	112 (32)	103 (26)
Coronary artery disease***	427 (57)	168 (48)	259 (64)
Cerebrovascular accident	121 (16)	62 (18)	59 (15)
Chronic respiratory disease*	215 (29)	86 (25)	129 (32)
Cardiomyopathy	62 (8)	32 (9)	30 (7)
Chronic liver disease	21 (3)	13 (4)	8 (2.0)
Chronic kidney disease	594 (79)	284 (81)	310 (77)
Antithrombotic treatment			
Received antiplatelets	458 (61)	201 (57)	257 (64)
Received anticoagulants	472 (63)	218 (62)	254 (63)
Outcome			
Hospitalization	256 (34)	124 (35)	132 (33)
Mortality	148 (20)	79 (23)	69 (17)

*Note: significance levels: * p < 0.05, *** p< 0.001; chi-square test for all variables except age; Wilcoxon rank* sum test with continuity correction for comparing age; [a] n (%);
Data presented as mean±standard deviation or n (%).

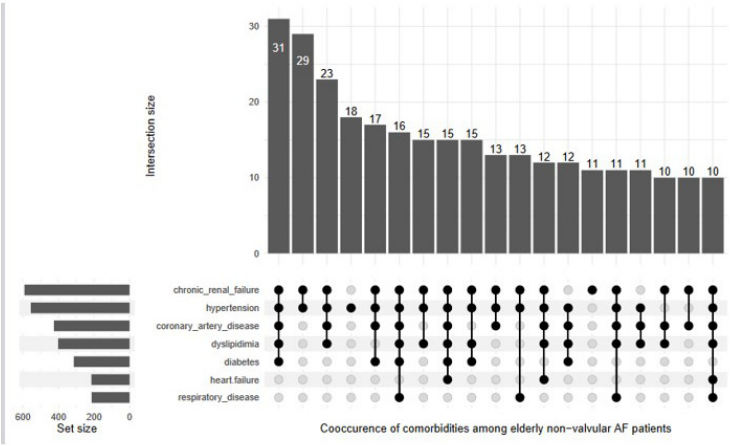

Figure 1: Multi-morbidity pattern among elderly NVAF patients.

Legend: The intersection size (height of the bar graph) represents the number of patients with a particular combination of comorbidities, and the set size shows the number of patients with each comorbidity.

factors and coexisting diseases were significantly higher in group three. While there was no difference noted in the anticoagulant therapy, patients receiving antiplatelets were more in group three. Mortality did not show significant differences among the groups (**Table 2**.)

Antithrombotic treatment

Oral anticoagulant therapy (OAC) was given to 62.5% (n = 472) of patients. The most commonly used OAC was vitamin K antagonists (VKA, 51.4%). DOAC were used in 11.3% (n = 85) of patients. Antiplatelet therapy was used in 60.6% (n = 458) and the most commonly used antiplatelet was clopidogrel (44.6%). No antithrombotic treatment was used in 12.0% of patients (n = 91), of whom 82.4% had multimorbidity.

One-year mortality

During the one-year follow-up, all-cause mortality was 19.6%, numerically higher in women but not statistically significant (p = 0.06) (**Table 3)**. Death was mostly due to cardiac causes (74.1%) followed by stroke (13.5%). The mortality rate did not differ between patients with varying clustering of comorbidities. Antiplatelet therapy use was 64.1% among those who died compared to 60.0% among those who survived (p = 0.30), while the use of OAC was 47.9% among those who died and 66.3% among those who survived (p = <0.001). The use of OAC therapy decreased significantly in patients above 80 years compared to those between 75 to 80 years.

Table 2: Differences in characteristics of patients with varying levels of multimorbidity, KERALA-AF Registry.

Characteristic	Multimorbidity group-1 (< 3) N = 137[a] (%)	Multimorbidity group-2 (3-5) N=483[a] (%)	Multimorbidity group-3 (>5) N = 133[a] (%)	p-value[b]
Sex				0.50
Female	60 (44)	232 (48)	58 (44)	
Male	77 (56)	251 (52)	75 (56)	
Age groups				0.40
75-80 years	83 (61)	267 (55)	70 (53)	
Above 80 years	54 (39)	216 (45)	63 (47)	
Hypertension	68 (50)	369 (76)	123 (92)	<0.001
Diabetes mellitus	11 (8)	207 (43)	99 (74)	<0.001
Dyslipidemia	14 (10)	276 (57)	114 (86)	<0.001
Thyroid dysfunction	6 (4)	39 (8)	26 (20)	<0.001
Chronic heart failure	8 (6)	115 (24)	92 (69)	<0.001
Coronary artery disease	19 (14)	285 (59)	123 (92)	<0.001
Cerebrovascular accident	8 (5.8)	72 (15)	41 (31)	<0.001
Respiratory disease	14 (10)	121 (25)	80 (60)	<0.001
Cardiomyopathy	7 (5)	28 (6)	27 (20)	<0.001
Chronic liver disease	1 (0.7)	10 (2)	10 (8)	0.002
Chronic kidney disease	77 (56)	394 (82)	123 (92)	<0.001
Received antiplatelet	59 (43)	302 (63)	97 (73)	<0.001
Received anticoagulants	79 (58)	309 (64)	84 (63)	0.40
Hospitalization history	43 (31)	169 (35)	44 (33)	0.70
Mortality	24 (18)	91 (19)	33 (25)	0.20

[a] n (%); [b] Pearson's chi-squared test; Fisher's exact test.

Survival analysis

The final model of multivariable logistic regression is shown in supplementary table 2. **Figure 2** shows the Kaplan-Meier survival curves. **Figure 3** shows the forest plot of the final adjusted multivariable Cox model. The outcome variable was mortality (died = 1, survived = 0) at the end of the one-year follow-up. Age above 80 years and chronic heart failure increased the risk of death. Patterns of multimorbidity did not show any predictive relationship with mortality, while age above 80 and treatment with OAC showed a predictive relationship with mortality.

The most significant protective factor was OAC treatment. Kaplan-Meier survival curves for patients who received, and who did not receive OAC, indicate better one-year survival for patients who received OAC treatment (log-rank test p <0.0001, hazard ratio, HR = 0.49 (95% CI = 0.35, 0.68), concordance = 0.58) (**Figure 2a**). On further examination, it is found that the protective effect of OAC was limited to patients with three to five comorbidities and not among patients with less than three or more than five comorbidities, possibly owing to small sample sizes in these groups (**Figure 2b**). The final multivariable Cox model with age, sex, multimorbidity, and OAC treatment showed that OAC treatment (HR, 0.5; 95% CI, 0.36–0.7,

Table 3: Clinical features of those who survived and died.

Characteristic	Survived N = 605[a] (%)	Died N = 148[a] (%)	p-value[b]
Sex			0.061
Female	271 (45)	79 (53)	
Male	334 (55)	69 (47)	
Age groups			0.004**
75-80 years	353 (58)	67 (45)	
Above 80 years	252 (42)	81 (55)	
Multimorbidity	568 (94)	144 (97)	0.10
Comorbidities levels			0.20
Less than three	113 (19)	24 (16)	
Three – five	392 (65)	91 (61)	
More than five	100 (17)	33 (22)	
Comorbidities/coexisting conditions			
Hypertension	453 (75)	107 (72)	0.50
Diabetes	250 (41)	67 (45)	0.40
Dyslipidemia	340 (56)	64 (43)	0.005**
Thyroid dysfunction	52 (9)	19 (13)	0.11
Chronic heart failure	161 (27)	54 (36)	0.017*
Coronary artery disease	340 (56)	87 (59)	0.60
Cerebrovascular accident	97 (16)	24 (16)	>0.90
Chronic respiratory disease	166 (27)	49 (33)	0.20
Cardiomyopathy	49 (8)	13 (9)	0.80
Chronic liver disease	14 (2)	7 (5)	0.20
Chronic kidney disease	469 (78)	125 (84)	0.064
Antithrombotic treatment			
Received antiplatelets	363 (60)	95 (64)	0.30
Received anticoagulants	401 (66)	71 (48)	<0.001***
Hospitalization history	108 (18)	148 (100)	<0.001***

[a] n (%) [b] Pearson's chi-squared test; Fisher's exact test; ** p< 0.05, ** p< 0.01, *** p< 0.001*

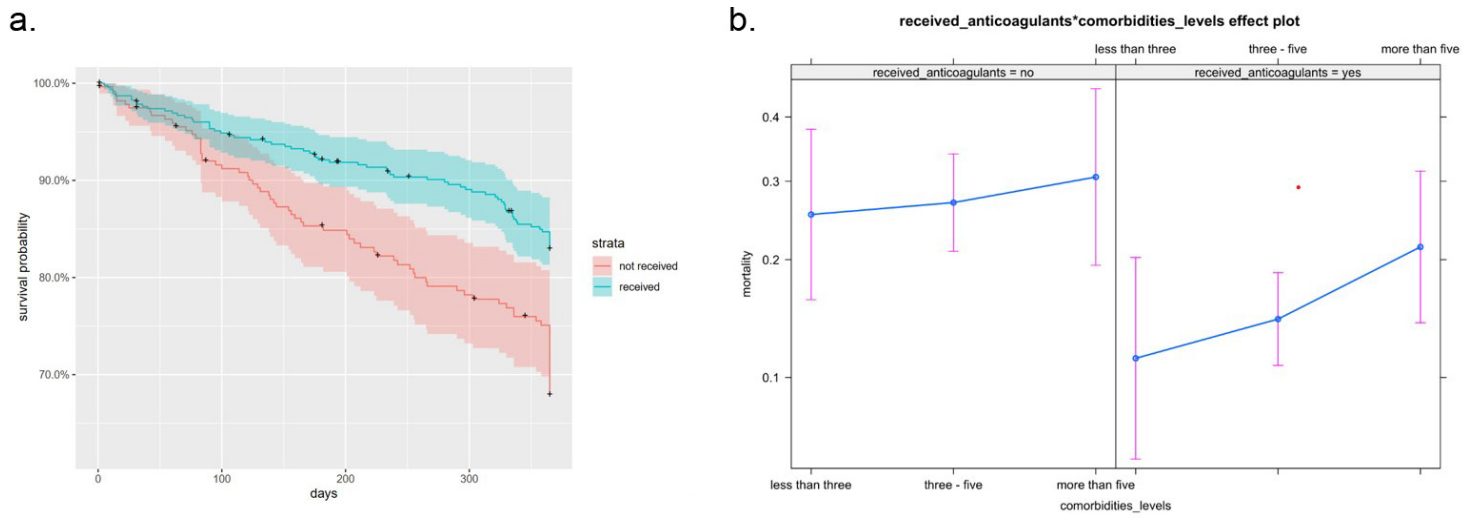

Figure 2: **Effect of oral anticoagulant treatment on mortality.**

Legend: 2a: Kaplan Meier Survival curve (days to death from all causes) of elderly NVAF patients on OAC treatment compared to patients, not on OAC treatment and 95% CIs. A visual inspection suggests a favorable survival for patients who received OAC. The log-rank test indicates a significant difference between the survival curves.
Legend: 2b: Effect of OAC treatment on mortality across varying levels of comorbidities

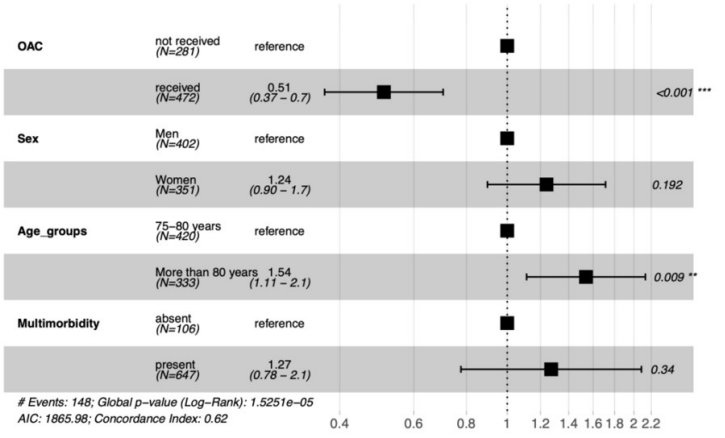

Figure 3: **Hazard ratios for time to death**

Legend: Hazard ratios and 95% confidence intervals for time to death in elderly NVAF patients.

P <0.001) and age more than 80 years (HR, 1.53; 95% CI, 1.11–2.1, P <0.01) were significant predictors of one-year mortality. (**Figure 3**.)

Discussion

The principal findings from this study are as follows: (i) elderly NVAF patients had a high prevalence of multimorbidity (94.5%, n = 412); and 81.5% (n = 616) had three or more comorbidities; (ii) multimorbidity did not show significant relationship with mortality, further studies are needed to rule out the possibility that this was due to high percentage of patients (94.5%) with multimorbidity in the sample (iii) 62.5% (n = 472) patients received OAC; and (iv) treatment with OAC was associated with a significant reduction in mortality.

The KERALA-AF registry provides the first comprehensive real-world data on elderly NVAF patients from India. Among the 2,507 NVAF patients in the registry, 30.1% were in the age group of ≥ 75 years, with a slightly higher proportion of males. The prevalence of multimorbidity was 94.5% (n = 712) and 81.5% (n = 616) had ≥3 comorbidities. The high prevalence of comorbidities and risk factors have been reported in NVAF patients in other registries, too.[3,11] In this cohort, hypertension was the common risk factor and CKD was the major coexisting disease. When compared with similar studies from the USA[23] and Europe,[24] the prevalence of DM, CKD, and CAD were seen in a higher proportion of patients in this registry.

The American[25] and European guidelines[26] recommend the use of OAC for stroke prevention, with Class 1 recommended for AF patients with CHA_2DS_2-VASc score of ≥ 2 (males) or of ≥ 3 (females). Despite higher risk of stroke and relatively lower risk of bleeding in this cohort (the mean CHA_2DS_2-VASc score 4.3 and HAS-BLED score 2.4), only 62.5 % of patients received OAC, mostly VKA. DOAC was used by only 11.3% of patients. Cost consideration and physician inertia might be the reason for the lower use of DOAC in this study as observed in other studies.[27] Apart from the concern over the increased bleeding risk in the elderly, the occurrence of multimorbidity might have influenced the decision to withhold OAC treatment. The use of OAC for stroke prophylaxis in elderly AF patients was highly variable in different registries. All Nippon-AF in the Elderly (ANAFIE) Registry[9] reported the use of OAC in 91.9% of patients ≥ 75 years in Japan, 79.9% in Phase II global GLORIA-AF Registry,[28] 11.1% in the Chinese AF Registry.[10]

In Asia, older AF patients ≥ 75 years are less likely to be treated with OAC compared to patients < 75 years of age, while in North America and Europe OAC use was more in elderly patients compared to younger patients (< 65 years).[24] OACs are less prescribed for NVAF patients in Asia compared to European counterparts because

of the fear of increased bleeding risk.[29,30] The benefit of using OAC in the elderly far outweighs the potential risk of bleeding.[31] However, OAC use is lower in elderly NVAF patients in Kerala. Even though antiplatelet therapy is not recommended for stroke prevention in AF (Class III),[25,26] it was used in 60.6% of patients in this study. The higher prevalence of CAD (56.5%) in this cohort might have contributed to the increased use of antiplatelets. In the Phase II of global GLORIA-AF Registry,[32] only 12.1% received antiplatelet treatment. The proportion of patients not receiving any antithrombotic treatment was also higher in Indian patients. In the Indian cohort of GARFIELD AF Registry,[33] 20.0% of patients ≥75 years of age were not on any antithrombotic treatment. In the SPANISH-AF Registry,[24] no antithrombotic treatment was prescribed in 4.7% of patients.

The all-cause mortality reported in this cohort was 19.6%, while the Chinese AF Registry[10] reported a death rate of 24.3% among NVAF patients ≥ 75 years in one year. The Swedish AF Registry[11] of a similar cohort reported a death rate of 18.2% for 3.4 years of follow-up. In a recently published data on NVAF patients in different age groups from the Macau Special Administrative Region of China,[34] patients receiving OAC (VKA and DOACS) showed lower all-cause mortality compared to those who were not on antithrombotic treatment. However, VKA did not show clear benefits in reducing stroke prevention or all-cause mortality in very elderly patients (≥85 years old) with NVAF. A study among very elderly patients with AF from Italy[35] reported three times overall survival benefit for those who received OAC compared to those who did not receive OAC. The use of OAC (54.1% VKA, 11.3% DOAC) showed significant survival benefits in our cohort, of whom 55.6% were in the age group 75–80 years. The risk of death among those who received OAC was 48.0% less compared to those who did not receive OAC. Gender and multimorbidity did not significantly influence mortality.

Strengths and limitations of the study

To our understanding, this was the first real-world dataset on elderly NVAF patients from India. The study clearly demonstrated mortality reduction with the use of OAC in elderly NVAF patients in Kerala. Our analysis did not show a significant association between mortality and multi-morbidity. This may be due to the very high percentage (94.5%) of patients having multimorbidity in our cohort. We need more representative population-based studies to have a better understanding of NVAF patients in India. In our study, we used only the baseline creatinine clearance measure to define CKD; as this may not reflect the true GFR, we might have overestimated the CKD prevalence.

Conclusion

Use of oral anticoagulants was associated with a reduced risk of mortality in elderly NVAF patients in the KERALA-AF Registry. However, more than one-third of patients were not receiving OAC, which calls for more training and sensitization of the treating doctors regarding optimal use of OAC in the elderly NVAF patients.

Supplementary Materials

Supplementary Table 1: Patient profile across age groups.

Characteristic	75-80 years, N = 420[a] (%)	Above 80 years, N = 333[a] (%)	p-value[b]
Sex			0.40
Female	189 (45)	161 (48)	
Male	231 (55)	172 (52)	
Multimorbidity	391 (93)	321 (96)	0.047*
Comorbidities levels			0.40
Less than three	83 (20)	54 (16)	
Three - five	267 (64)	216 (65)	
More than five	70 (17)	63 (19)	
Comorbidities/coexisting conditions			
Hypertension	304 (72)	256 (77)	0.20
Diabetes	181 (43)	136 (41)	0.50
Dyslipidemia	230 (55)	174 (52)	0.50
Thyroid dysfunction	37 (9)	34 (10)	0.50
Chronic heart failure	117 (28)	98 (29)	0.60
Coronary artery disease	250 (60)	177 (53)	0.08
Cerebrovascular accident	61 (15)	60 (18)	0.20
Chronic respiratory disease	117 (28)	98 (29)	0.60
Cardiomyopathy	35 (8)	27 (8)	>0.90
Chronic liver disease	8 (2)	13 (4)	0.10
Chronic kidney disease	306 (73)	288 (86)	<0.001***
Antithrombotic treatment			
Received antiplatelets	263 (63)	195 (59)	0.30
Received anticoagulants	283 (67)	189 (57)	0.003**
Hospitalization history	126 (30)	130 (39)	0.009**

[a] n (%) [b] Pearson's chi-squared test * *p< 0.05*, ** *p< 0.01*, *** *p< 0.001*

Supplementary Table 2: Results of multivariable logistic regression model to predict mortality with all comorbidities and risk factors included in the model.

Characteristic	aOR	95% CI	p-value
Sex			
Female	Ref		
Male	0.72	0.49, 1.06	0.10
Age groups			
75-80 years	Ref		0.03
Above 80 years	1.52	1.04, 2.24	
Multimorbidity			
No	Ref		0.20
Yes	2.42	0.78, 9.28	
Comorbidities levels			
Less than three	Ref		
More than five	1.36	0.35, 5.30	0.70
Three - five	0.99	0.47, 2.15	>0.90
Hypertension			
No	Ref		0.40
Yes	0.79	0.48, 1.32	

(Cont.)

Characteristic	aOR	95% CI	p-value
Diabetes			
No	Ref		0.40
Yes	1.23	0.77, 1.94	
Dyslipidemia			
No	Ref		0.006
Yes	0.52	0.33, 0.82	
Thyroid dysfunction			
No	Ref		0.30
Yes	1.42	0.75, 2.64	
Chronic heart failure			
No	Ref		
Yes	1.33	0.81, 2.16	
Coronary artery disease			
No	Ref		>0.90
Yes	1	0.60, 1.67	
Cerebrovascular accident			
No	Ref		0.80
Yes	1.08	0.60, 1.89	
Chronic respiratory disease			
No	Ref		0.60
Yes	1.13	0.70, 1.82	
Cardiomyopathy			
No	Ref		0.60
Yes	0.83	0.39, 1.68	
Chronic Liver disease			
No	Ref		>0.90
Yes	1.03	0.35, 2.73	
Chronic Kidney disease			
No	Ref		0.80
Yes	1.09	0.62, 1.98	
Received anti platelets			
No	Ref		0.60
Yes	1.12	0.73, 1.73	
Received anticoagulants			
No	Ref		<0.001
Yes	0.51	0.35, 0.75	

[1] aOR = Adjusted Odds Ratio, CI = Confidence Interval

Contributors

Conceptualization: CGB, GYHL; Formal analysis: SFK and GKM; Writing - original draft preparation: CGB, JLA; Writing - review and editing: SFK, CGB, JLA; Funding acquisition: CGB. All authors read and approved the final version of the manuscript.

Competing Interests

GYH: Consultant and speaker for BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo. No fees are received personally. GYHL is co-principal investigator of the AFFIRMO project on multimorbidity in AF, which has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 899871.

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