Circulation: Arrhythmia and Electrophysiology

ORIGINAL ARTICLE

Mortality, Hospitalization, and Cardiac Interventions in Patients With Atrial Fibrillation Aged <65 Years

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BACKGROUND: The risk factor (RF) burden, clinical course, and long-term outcome among patients with atrial fibrillation (AF) aged <65 years is unclear.

METHODS: Adult (n=67 221; mean age, 72.4±12.3 years; and 45% women) patients with AF evaluated at the University of Pittsburgh Medical Center between January 2010 and December 2019 were studied. Hospital system–wide electronic health records and administrative data were utilized to ascertain RFs, comorbidities, and subsequent hospitalization and cardiac interventions. The association of AF with all-cause mortality among those aged <65 years was analyzed using an internal contemporary cohort of patients without AF (n=918 073).

RESULTS: Nearly one-quarter (n=17 335) of the cohort was aged <65 years (32% women) with considerable cardiovascular RFs (current smoker, 16%; mean body mass index, 33.0±8.3; hypertension, 55%; diabetes, 21%; heart failure, 20%; coronary artery disease, 19%; and prior ischemic stroke, 6%) and comorbidity burden (chronic obstructive pulmonary disease, 11%; obstructive sleep apnea, 18%; and chronic kidney disease, 1.3%). Over mean follow-up of >5 years, 2084 (6.7%, <50 years; 13%, 50–65 years) patients died. The proportion of patients with >1 hospitalization for myocardial infarction, heart failure, and stroke was 1.3%, 4.8%, and 1.1% for those aged <50 years and 2.2%, 7.4%, and 1.1% for the 50- to 65-year subgroup, respectively. Multiple cardiac and noncardiac RFs were associated with increased mortality in younger patients with AF with heart failure and hypertension demonstrating significant age-related interaction (P=0.007 and P=0.013, respectively). Patients with AF aged <65 years experienced significantly worse survival compared with comorbidity-adjusted patients without AF (men aged <50 years and hazard ratio, 1.5 [95% CI, 1.24–1.79]; 50–65 years and hazard ratio, 1.3 [95% CI, 1.26–1.43]; women aged <50 years and hazard ratio, 2.4 [95% CI, 1.82–3.16]; 50–65 years and hazard ratio, 1.7 [95% CI, 1.6–1.92]).

CONCLUSIONS: Patients with AF aged <65 years have significant comorbidity burden and considerable long-term mortality. They are also at a significantly increased risk of hospitalization for heart failure, stroke, and myocardial infarction. These patients warrant an aggressive focus on RF and comorbidity evaluation and management.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: atrial fibrillation ■ cardiology ■ cohort studies ■ hypertension ■ risk factors

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Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCEP.123.012143.

For Sources of Funding and Disclosures, see page 310.

Circulation: Arrhythmia and Electrophysiology is available at www.ahajournals.org/journal/circep

WHAT IS KNOWN?

- The burden of cardiovascular risk factors is increasing in the younger adult population. An increasing number of patients with atrial fibrillation are aged <65 years at presentation.

WHAT THE STUDY ADDS

- Our large real-world cohort demonstrates that patients with atrial fibrillation aged <65 years have substantial comorbidity burden, particularly obesity, heart failure, and hypertension with considerable long-term mortality (6.7%, <50 years; 13%, 50–65 years). They are also at a significantly increased risk of hospitalization for heart failure, stroke, and myocardial infarction compared with those without atrial fibrillation.
- The results of our study suggest that management of patients with atrial fibrillation aged <65 years must be in the context of their individual cardiovascular risk factors burden and lifestyle modification with an appropriate focus on noncardiac risk factors.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
HF	heart failure
ICD	International Classification of Diseases
RF	risk factor

Atrial fibrillation (AF) is the most common heart rhythm disorder in the United States with a prevalence estimate of 5.2 million in 2010 and projected increase to 12.1 million by 2030.[1] Although more commonly seen in the seventh and eighth decades of life, an increasing number of patients with AF are aged <65 years at presentation (10%–15%).[2] The risk factors (RFs) for AF including hypertension, diabetes, obesity, and lifestyle changes are certainly increasing in the younger population.[3] At the same time, unlike older patients,[4] the risk of major clinical events including the association of AF with increased mortality in this younger population is not clearly defined. Optimal management of these younger patients with AF would necessitate understanding the clinical course and occurrence of multiple subsequent clinical events along with appreciating the RF milieu that may surround these patients and their potential association with mortality. We, therefore, assembled a contemporary cohort of patients with AF with the objective of elucidating the long-term outcomes including all-cause mortality, hospitalizations, and cardiac interventions including device implants in patients with AF aged <65 years. We additionally examined the association of AF with mortality among these patients utilizing national survival estimates and a contemporary internal cohort of patients without a diagnosis of AF.

METHODS

Study Population

This is a retrospective observational cohort study that included patients aged >18 years who had at least 2 outpatient visits with either internal medicine, family medicine, or cardiology clinics of the University of Pittsburgh Medical Center with an associated diagnosis of AF. The diagnosis of AF was based on the presence of the *International Classification of Diseases* (*ICD*)*, Ninth Revision* and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes (*ICD, Ninth Revision*: 427.31, 427.32; *ICD, Tenth Revision*: I48.0, I48.1, I48.2, I48.91, I48.3, I48.4, and I48.92).[5] These patients were evaluated between January 4, 2010, to December 13, 2019, and the study was approved by the University of Pittsburgh Institutional Review Board. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patient Characteristics

The University of Pittsburgh Medical Center is an integrated insurance and provider system with >40 academic, community, and specialty hospitals. The hospital system–wide electronic health record data are aggregated and harmonized with administrative, financial, and other publicly available data in its clinical data warehouse; the Data and Analytics Program was utilized to obtain the clinical parameters including age at presentation, sex, race, cardiovascular RFs, including presence of obesity, smoking history, hypertension, diabetes, coronary artery disease, congestive heart failure (HF), mitral valve disease, hyperlipidemia, vascular history, including history of deep vein thrombosis, and major bleeding, neurological history, including prior ischemic or hemorrhagic stroke and transient ischemic attack, prior ventricular arrhythmias (ventricular tachycardia or ventricular fibrillation), and prior cardiac arrest. *ICD, Ninth Revision* and *ICD, Tenth Revision* codes for the major clinical variables utilized in the study are reported in Table S1. Major comorbidities evaluated included chronic obstructive pulmonary disease, a history of cancer, obstructive sleep apnea, chronic kidney disease, and liver disease. Current procedural terminology codes were used to ascertain prior automatic implantable cardioverter defibrillator implantation, permanent pacemaker implantation, pulmonary vein ablation, atrioventricular node ablation, cardioversion, and loop monitor implants along with cardiac interventions, including percutaneous coronary intervention, coronary bypass, maze, or mitral valve surgery. Medication use at baseline was evaluated including the use of antiarrhythmic agents, antiplatelets, anticoagulants, and rate control medications.

Outcome

The primary outcome of interest was all-cause mortality, which was ascertained by a review of the Social Security Death Index and enriched by electronic health record data input (hospitalization data or office visits) aggregated in the clinical data warehouse. The last censoring date for mortality outcome was October 15, 2020. The secondary outcomes of interest

included hospitalization for cardiovascular causes, myocardial infarction, AF, HF, stroke, or major bleeding (Table S2). A hospitalization was attributed to the secondary outcome if the corresponding *ICD, Ninth Revision/ICD, Tenth Revision* code was listed as 1 of the top 3 diagnoses (primary, principal, or secondary) during an inpatient admission. Cardiac interventions performed during follow-up were evaluated, including electrophysiological interventions (device therapy, ablation, and cardioversions) and percutaneous coronary intervention (Table S3).

Statistical Analysis

For baseline characteristics, continuous variables are presented as mean±SD or median and interquartile range and compared between groups using the Student *t* test or nonparametric Mann-Whitney *U* test as appropriate. Categorical variables are presented as frequencies and percentages and compared using the χ^2 test. Baseline demographic and cardiovascular characteristics of the study population were stratified by age at initial evaluation (<50, 50–65, 65–80, and >80 years). The Kaplan-Meier survival analysis was used to evaluate hospitalization-free survival for each cardiovascular outcome. A Cox proportional multivariable hazard model was used to examine independent predictors of all-cause mortality in patients aged <65 years using a stepwise selection approach with the baseline visit used as time 0. Mortality analysis was performed utilizing adjustment for all relevant confounding clinical covariates. Any significant 2-way interaction of age with other covariates was tested and incorporated into the final model. Sensitivity analysis was performed in 4 subsets: model 1: excluding patients with valvular AF (history of mitral valve disorder or mitral valve surgery); model 2: excluding patients with prior AF-related interventions: prior pulmonary vein ablation or prior atrioventricular node ablation, prior cardioversions, or prior maze surgery; model 3: excluding patients with prior cancer history; and model 4 (most restrictive) excluding all those in above models. The Social Security Administration actuarial life table from 2016 was used to obtain a reference population 5-year mortality estimate utilizing the national age- and sex-specific data.[6] The mean mortality estimates stratified by sex were compared for each age group using 1 sample *t* test with the 5-year mortality estimate obtained using the Kaplan-Meier estimator for the AF cohort. Furthermore, to test the association of AF diagnosis with mortality in younger patients, we assembled a control patient population who had at least 2 office visits in the University of Pittsburgh Medical Center health system in internal medicine, family medicine, or cardiology clinics from January 2, 2010, to December 18, 2019, but did not have a diagnosis of AF with the last primary outcome censoring date of January 8, 2021. Hospitalization and mortality adjusted for cardiac and noncardiac comorbidities were compared between patients with and without AF focusing on those aged <65 years utilizing cause-specific analysis of competing risk and displayed using direct adjusted survival curves.[7]

RESULTS

The overall study population included 67 221 patients with AF with an average CHA_2DS_2-VASc score of 3.1±1.6. The average age of the cohort was 72.4±12.3 years with 45% being women and 95% white. Nearly one-fourth of patients (26%) were aged <65 years at initial evaluation. Baseline clinical features stratified by age are detailed in Table 1.

Patients With AF Aged <65 Years

Men predominate in the younger population (<50 years, 73%; 50–65 years, 66.3%). Significant obesity was notable for >20% with 16% reporting current smoking. Hypertension (55%), diabetes (21%), HF (21%), and dyslipidemia (47%) were frequently observed in cardiovascular RFs (Table S4). Nearly 4% of patients aged <50 years had a history of stroke with peripheral vascular disease noted for 1.35%. Nearly 3% of patients had an automatic implantable cardioverter defibrillator implantation at baseline, while 332 (2%) had a permanent pacemaker in situ. The percutaneous coronary intervention had been performed for 5.5%, while 426 patients (2.5%) had prior mitral valve surgery. Obstructive sleep apnea was seen in 3186 (18%) patients, while chronic obstructive pulmonary disease and chronic kidney disease were noted for 11% and 1.3%, respectively (Tables S5 and S6); 55% of patients were anticoagulated with either warfarin or a direct oral anticoagulant at baseline, while aspirin use was notable in >50% of patients aged <65 years. Antiarrhythmic therapy with a class 1 antiarrhythmic was used in 6%, while 17% were on a class 3 agent (Tables S5 and S7). Patients aged <65 years were significantly more likely to be nonwhite and obese, have obstructive sleep apnea, and use class 1 antiarrhythmic agents compared with older patients with AF.

Mortality and Hospitalization

Table 2 details the all-cause mortality, hospitalization, and cardiac interventions experienced during follow-up in the study population stratified by the age at presentation. Over a mean follow-up duration of >5 years, 204 (6.7%) patients in the <50-year age group and 1880 (13.1%) in the 50- to 65-year age group died. The Kaplan-Meier survival analysis is represented in Figure S1 with the 5- and 10-year mortalities in patients aged <50 years being 5.6% (4.7%–6.5%) and 10.3% (8.8%–11.9%), respectively, and doubling to 11.5% (10.9%–12.1%) and 20.8% (19.9%–21.8%) among those aged 50 to 65 years. Hospitalization for AF, HF, and myocardial infarction was seen in 31%, 12%, and 2.7% of patients aged <50 years, while 38%, 19%, and 4.7% experienced this outcome in the 50- to 65-year age group (Figure 1A–1D). The distribution of patients with multiple hospitalizations for cardiovascular reasons in the first 3 years of follow-up is shown in Table S8 with >5% experiencing >1 HF admission and >9% with >1 AF-related hospitalization. AF ablation was performed for 1919 (11%) patients aged <65 years during follow-up, and 5% underwent atrioventricular junction ablation, while 17% required at least 1 cardioversion during follow-up.

Table 1. Baseline Demographic and Cardiovascular Characteristics of the Study Population Stratified by Age at Initial Evaluation

Clinical characteristics	Total (67 221)	<50 y (3035/4.51%)	50–65 y (14 300/21.27%)	65–80 y (29 551/43.96%)	>80 y (20 335/30.25%)
Age, y (range)	72.4±12.3 (18.5–107.5)	42.1±7.10 (18.5–49.9)	59.1±4.01 (50.0–64.9)	72.7±4.25 (65.0–79.9)	85.7±4.03 (80.0–707.5)
Female	29 980 (44.60%)	813 (26.79%)	4821 (33.71%)	13 010 (44.03%)	11 336 (55.75%)
Race					
White	63 859 (95.00%)	2651 (87.35%)	13 277 (92.85%)	28 225 (95.51%)	19 706 (96.91%)
Black	2639 (3.93%)	311 (10.25%)	856 (5.99%)	1011 (3.42%)	461 (2.27%)
Other	723 (1.08%)	73 (2.41%)	167 (1.17%)	315 (1.07%)	168 (0.83%)
Morbid obesity	8240 (12.26%)	644 (21.22%)	3042 (21.27%)	3812 (12.90%)	742 (3.65%)
Tobacco use					
Never	30 894 (45.96%)	1448 (47.71%)	6174 (43.17%)	12 441 (42.10%)	10 831 (53.26%)
Current	5668 (8.43%)	585 (19.28%)	2259 (15.80%)	2262 (7.65%)	562 (2.76%)
Previous	28 213 (41.97%)	841 (27.71%)	5335 (37.31%)	13 839 (46.83%)	8198 (40.31%)
Unknown	2446 (3.64%)	161 (5.30%)	532 (3.72%)	1009 (3.41%)	744 (3.66%)
CHA_2DS_2-VASc score	3.08±1.63	1.04±1.02	1.55±1.18	3.28±1.34	4.17±1.24
Cardiac history					
Hypertension	45 726 (68.02%)	1180 (38.88%)	8356 (58.43%)	20 893 (70.70%)	15 297 (75.22%)
Diabetes	16 882 (25.11%)	350 (11.53%)	3280 (22.94%)	8461 (28.63%)	4791 (23.56%)
Coronary artery disease	22 704 (33.78%)	211 (6.95%)	3164 (22.13%)	10 794 (36.53%)	8535 (41.97%)
Congestive heart failure	15 993 (23.79%)	501 (16.51%)	3068 (21.45%)	6574 (22.25%)	5850 (28.77%)
Hyperlipidemia	40 034 (59.56%)	862 (28.40%)	7304 (51.08%)	19 136 (64.76%)	12 732 (62.61%)
Mitral valve disease	6030 (8.97%)	165 (5.44%)	937 (6.55%)	2613 (8.84%)	2315 (11.38%)
Vascular history					
Deep vein thrombosis	1781 (2.65%)	58 (1.91%)	345 (2.41%)	803 (2.72%)	575 (2.83%)
Pulmonary embolism	1860 (2.77%)	68 (2.24%)	358 (2.50%)	836 (2.83%)	598 (2.94%)
Peripheral vascular disease	4498 (6.69%)	41 (1.35%)	591 (4.13%)	2105 (7.12%)	1761 (8.66%)
Major bleeding	8113 (12.07%)	196 (6.46%)	1394 (9.75%)	3727 (12.61%)	2796 (13.75%)
Neurological history					
Ischemic stroke	6268 (9.32%)	117 (3.86%)	905 (6.33%)	2775 (9.39%)	2471 (12.15%)
Hemorrhagic stroke	428 (0.64%)	9 (0.30%)	62 (0.43%)	192 (0.65%)	165 (0.81%)
Transient ischemic attack	2476 (3.68%)	39 (1.29%)	286 (2.00%)	1003 (3.39%)	1148 (5.65%)
Arrhythmia history					
Prior ventricular arrhythmia (VT/VF)	2451 (3.65%)	112 (3.69%)	610 (4.27%)	1132 (3.83%)	597 (2.94%)
Prior cardiac arrest	211 (0.31%)	14 (0.46%)	51 (0.36%)	103 (0.35%)	43 (0.21%)
Cardiac interventions					
Prior AICD implant	1592 (2.37%)	84 (2.77%)	404 (2.83%)	737 (2.49%)	367 (1.80%)
Prior PPM implant	3092 (4.60%)	34 (1.12%)	298 (2.08%)	1221 (4.13%)	1539 (7.57%)
Prior AF ablation	178 (0.26%)	15 (0.49%)	81 (0.57%)	77 (0.26%)	5 (0.02%)
Prior AVJ ablation	966 (1.44%)	36 (1.19%)	242 (1.69%)	440 (1.49%)	248 (1.22%)
Prior cardioversion	6643 (9.88%)	433 (14.27%)	2039 (14.26%)	2946 (9.97%)	1225 (6.02%)
Prior loop monitor implant	225 (0.33%)	17 (0.56%)	55 (0.38%)	100 (0.34%)	53 (0.26%)
PCI	5277 (7.85%)	83 (2.73%)	874 (6.11%)	2597 (8.79%)	1723 (8.47%)
CABG	2663 (3.96%)	21 (0.69%)	455 (3.18%)	1450 (4.91%)	737 (3.62%)
Maze surgery	173 (0.26%)	11 (0.36%)	49 (0.34%)	87 (0.29%)	26 (0.13%)
Mitral valve surgery	1369 (2.04%)	59 (1.94%)	367 (2.57%)	633 (2.14%)	310 (1.52%)

All parameters had significant age-related trends ($P<0.05$). AF indicates atrial fibrillation; AICD, automatic implantable cardioverter defibrillator; AVJ, atrioventricular junction; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; PPM, permanent pacemaker; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Table 2. Long-Term Outcomes (All-Cause Mortality, Hospitalization, and Cardiac Interventions) Among Study Population

Outcomes	Overall population	<50 y	50–65 y	65–80 y	>80 y
Age, y (at last follow-up)	75.9±12.1	45.9±7.86	63.2±4.89	76.4±4.94	88.5±4.21
Duration of follow-up, y	4.85±2.91	5.87±3.04	5.58±3.03	4.96±2.90	4.03±2.61
All-cause mortality	20 208 (30.06%)	204 (6.72%)	1880 (13.15%)	7701 (26.06%)	10 423 (51.26%)
Hospitalization					
Cardiac	36 322 (54.03%)	1180 (38.88%)	6981 (48.82%)	16 068 (54.37%)	12 093 (59.47%)
Myocardial infarction	4519 (6.72%)	82 (2.70%)	673 (4.71%)	2048 (6.93%)	1716 (8.44%)
Heart failure	18 456 (27.46%)	377 (12.42%)	2776 (19.41%)	7864 (26.61%)	7439 (36.58%)
Atrial fibrillation	26 163 (38.92%)	945 (31.14%)	5380 (37.62%)	11 561 (39.12%)	8277 (40.70%)
Hemorrhagic stroke	1108 (1.65%)	21 (0.69%)	160 (1.12%)	522 (1.77%)	405 (1.99%)
Ischemic stroke	2981 (4.43%)	55 (1.81%)	359 (2.51%)	1275 (4.31%)	1292 (6.35%)
TIA	940 (1.40%)	14 (0.46%)	114 (0.80%)	407 (1.38%)	405 (1.99%)
Bleed	5604 (8.34%)	85 (2.80%)	761 (5.32%)	2635 (8.92%)	2123 (10.44%)
Cardiac interventions					
PCI	3086 (4.59%)	67 (2.21%)	644 (4.50%)	1683 (5.70%)	692 (3.40%)
Pacemaker implant	3010 (4.48%)	38 (1.25%)	375 (2.62%)	1503 (5.09%)	1094 (5.38%)
AICD implant	1163 (1.73%)	69 (2.27%)	318 (2.22%)	578 (1.96%)	198 (0.97%)
AF ablation	3172 (4.72%)	378 (12.45%)	1541 (10.78%)	1206 (4.08%)	47 (0.23%)
AV node ablation	2329 (3.46%)	148 (4.88%)	744 (5.20%)	1082 (3.66%)	355 (1.75%)
Cardioversion	7709 (11.47%)	501 (16.51%)	2509 (17.55%)	3675 (12.44%)	1024 (5.04%)
ILR implantation	249 (0.37%)	28 (0.92%)	80 (0.56%)	111 (0.38%)	30 (0.15%)

Significant Age-related trend for all outcomes. AF indicates atrial fibrillation; AICD, automatic implantable cardioverter defibrillator; AV, atrioventricular; ILR, implantable loop recorder; PCI, percutaneous coronary intervention; and TIA, transient ischemic attack.

Clinical Factors Associated With All-Cause Mortality in Patients With AF Aged <65 Years

Among patients aged <65 years, multiple cardiovascular RF and comorbidities were noted to be independently associated with all-cause mortality (Table S9). HF, peripheral vascular disease, diabetes, and coronary artery disease were associated with the highest hazard, while smoking (past or active) and the presence of morbid obesity were lifestyle factors increasing mortality in this age group. The presence of chronic kidney disease and chronic obstructive pulmonary disease was associated with worse outcomes. Interaction analysis suggested a significant interaction of age with hypertension (P=0.013) and HF (P=0.007) such that a higher hazard ratio was noted for hypertension and HF at a younger age (Table S10). The C statistic for the model (with interaction) was 0.754. This RF-outcome relationship remained consistent in all the sensitivity analysis models (1–4; Tables S11–S14).

Association of AF With Increased Risk of Mortality Among Patients Aged <65 Years

Table S15 demonstrates the survival estimate comparison between the AF cohort and age- and sex-stratified national mortality estimates from the Social Security Administration 2016 actuarial survival tables. There was significantly higher all-cause mortality in men (<50 years: mortality difference, 3.8 [95% CI, 2.8–4.9]; 50–65 years: mortality difference, 5.3 [95% CI, 4.6–6.1]) and women (<50 years: mortality difference, 4.4 [95% CI, 2.6–6.1]; 50–65 years: mortality difference, 7.7 [95% CI, 6.9–8.5]) with AF. Compared with an internal control population (n=918 073; mean age, 48.1±18.2 years; 57% women; 88% white; and mean CHA_2DS_2-VASc, 1.3±1.2), the presence of AF was associated with increased mortality hazard when adjusted for cardiac and noncardiac RFs (Table 3) in the overall cohort and specifically in those aged <65 years (Figure 2A). Women had significantly higher mortality in each age group compared with men (Table S16). Patients aged <65 years with AF were also associated with increased comorbidity-adjusted risk of hospitalization for myocardial infarction (hazard ratio, 1.19 [95% CI, 1.09–1.29]; P<0.001), HF (hazard ratio, 2.93 [95% CI, 2.79–3.08]; P<0.001), and all-cause stroke (hazard ratio, 1.77 [95% CI, 1.61–1.96]; P<0.001; Figure 2B–2D).

DISCUSSION

The results of our study show that patients with AF aged <65 years have a significant comorbidity burden that impacts their future risk of mortality and hospitalization. We also show that the presence of AF in patients aged <65 years confers long-term mortality risk that is higher

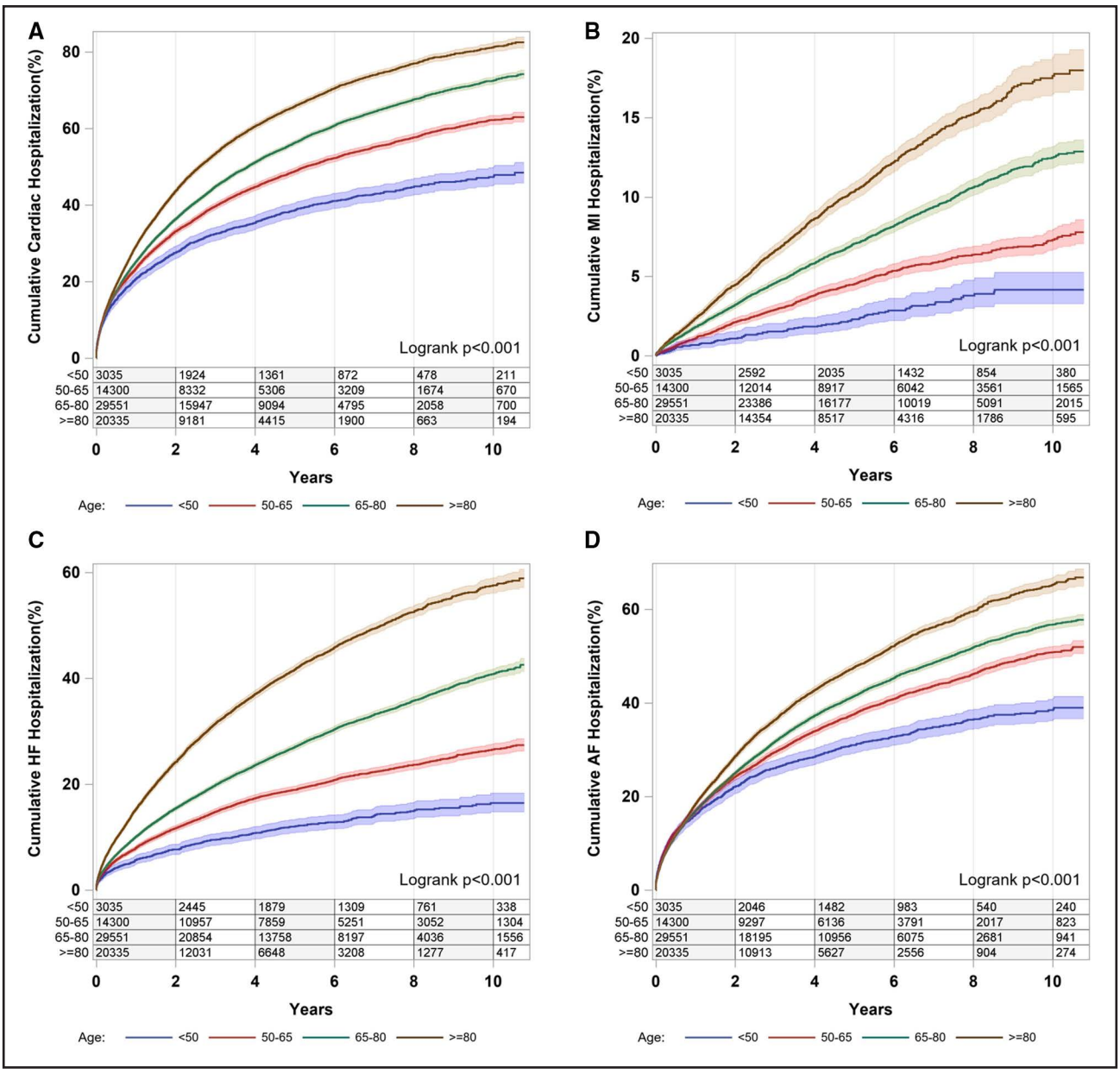

Figure 1. Kaplan-Meier survival analysis illustrating hospitalization (cardiac, myocardial infarction, congestive heart failure, and atrial fibrillation [AF]) among patients with AF stratified by age at presentation.
A, Cardiac hospitalization, (**B**) myocardial infarction hospitalization, (**C**), heart failure hospitalization, and (**D**) AF hospitalization.

than a standard age- and sex-matched US reference population. Additionally, patients with AF aged <65 years experience significantly worse survival than age- and sex-matched patients without AF.

RFs in Patients With AF Aged <65 Years

In our study, a significant burden of AF RFs was notable in patients aged <65 years especially regarding obesity (>18% with body mass index >40), smoking, and cardiovascular RFs, including hypertension and diabetes. Although population-based nationwide cohort studies[8] report favorable RF profiles in younger patients with AF with low frequencies of hypertension, HF, and obesity, data from other epidemiological cohorts suggest that these RFs are increasingly prevalent.[9] All these RFs result in a higher prevalence of coronary artery disease,[10] peripheral vascular disease, and HF[11,12] in these patients with long-term structural, electrical, and autonomic changes influencing not only morbidity and mortality but also downstream health care utilization. Although studies document a high prevalence of obstructive sleep apnea in patients with AF,[13] its implications in young patients with AF regarding cardiovascular outcomes and mortality are unclear and need investigation.

Table 3. Estimate of Mortality Hazard Associated With the Presence of AF in the Overall Cohort and Those Aged <65 Years

Parameter	Hazard ratio	95% CI	*P* value
Presence of AF			
Overall (AF cohort n=67 221; control cohort n=918 073)	1.38	1.35–1.40	<0.001
Those aged <65 y (AF cohort n=17 335; control cohort n=742 928)	1.42	1.35–1.49	<0.001

Covariates: age, sex, race, smoking history, prior percutaneous coronary intervention, prior coronary artery bypass grafting, morbid obesity, coronary artery disease, diabetes, heart failure, hyperlipidemia, mitral valve disease, peripheral vascular disease, major bleeding, chronic obstructive pulmonary disease, chronic kidney disease, liver disease, history of cancer, prior ventricular tachycardia/ventricular fibrillation, prior stroke (ischemic or hemorrhagic), and history of cardiac arrest. Model 1: C=0.866. Model 2: C=0.810. AF indicates atrial fibrillation.

Mortality and Hospitalization in Patients With AF Aged <65 Years

AF is associated with increased all-cause mortality in multiple cohort studies.[14] However, these data are skewed towards older patients and come from studies focused on specific populations (HF, peripheral vascular disease, chronic kidney disease, post–myocardial infarction, postrevascularization, poststroke, and aortic stenosis) with most evaluating incident AF and not prevalent AF.[14] Little data exist on the long-term survival of contemporary patients with AF from studies focused on the younger population. Our comparative data suggest that younger patients with AF are at higher risk of mortality and hospitalization with higher hazard noted with progressively younger age compared with those without AF.

The results of our study contrast with estimates from other population-based nationwide European cohorts[8] and underscore the burden of cardiovascular RFs prevalent in the US population, especially among the younger patients with AF seeking care within a hospital system. The longitudinal course in terms of mortality and cardiovascular outcomes in patients with AF is well described in those aged >65 years.[4] In our cohort, the presence of hypertension in combination with HF is of particular importance as a driver of adverse outcomes among young adults substantiating subtle signals from prior reports.[9] Although rare variants in cardiomyopathy and arrhythmia genes may be associated with increased risk of mortality among patients with early-onset AF,[15] the likely complex interplay between predisposing variants and lifestyle-based RFs warrants evaluation with future studies.

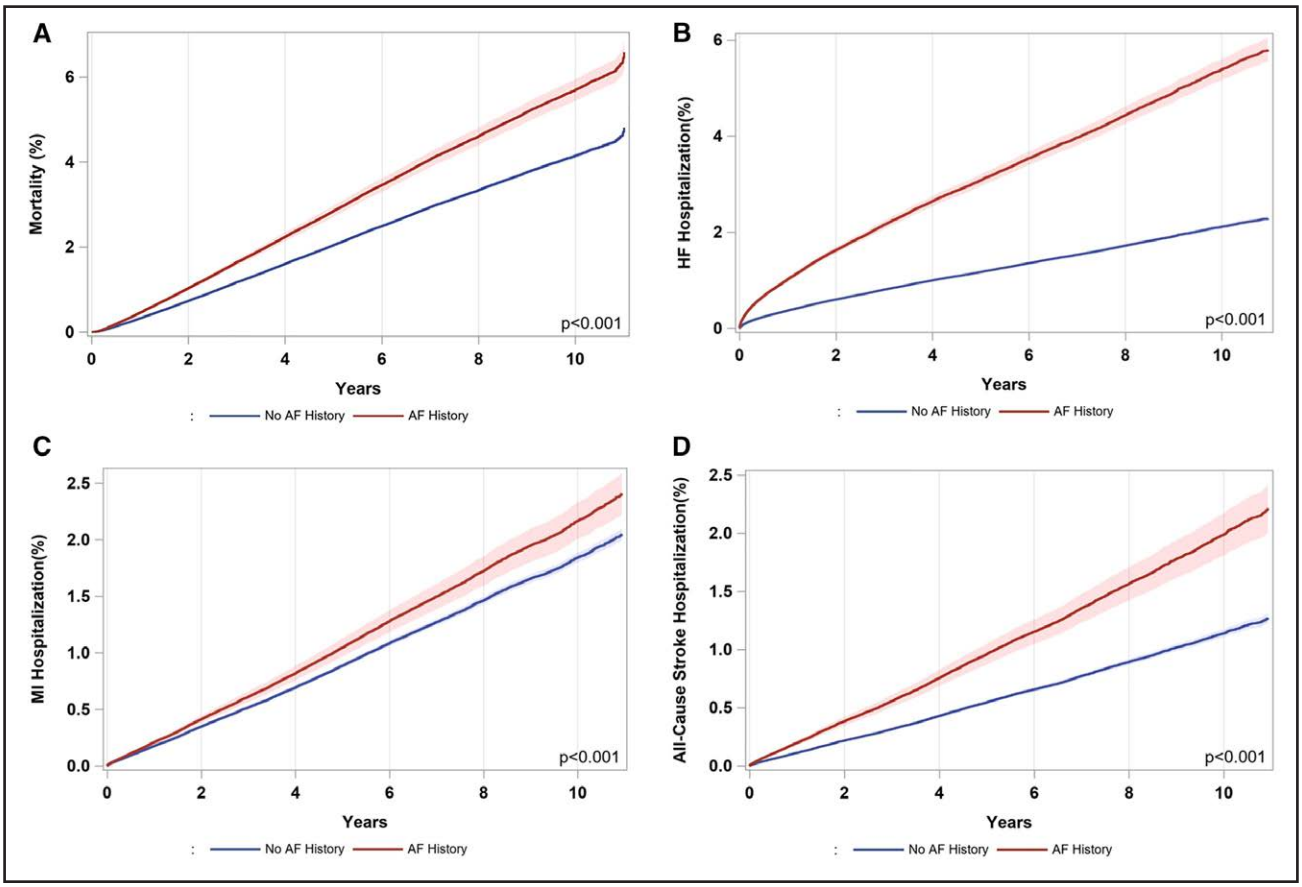

Figure 2. Primary and secondary outcomes stratified by presence or absence of atrial fibrillation (AF).
Direct adjusted analysis regarding mortality (**A**), hospitalization for myocardial infarction (**B**), heart failure (**C**), and all-cause stroke (**D**) in patients with AF aged <65 as compared to those without AF.

Implications for Clinical Practice

The results of our study suggest that management of patients with AF aged <65 years must be in the context of their individual RF burden and lifestyle modification with an appropriate focus on noncardiac RFs consistent with recent scientific statements.[16] Apart from aggressive management of hypertension, vascular disease, diabetes, and HF, focus on smoking cessation with support and counseling along with the incorporation of a goal-directed weight-reduction plan may influence not only AF burden[17] but also mortality and hospitalization. An integrated multidisciplinary team–based approach[18] may improve outcomes when a plethora of RFs need to be addressed.

LIMITATIONS

This study has several limitations. All the biases and limitations inherent to a retrospective observational study exist particularly when large electronic health records and administrative heath system–wide data are utilized using the *ICD* coding system. Nonetheless, we defined variables a priori, tested the robustness of results through sensitivity analysis, and made adjustments for all available RFs. We did not measure quality of life metrics nor was the cause of death ascertained. We also did not have information on alcohol consumption that could modify some of the existing relationships. However, the large number of patients in our study treated across multiple levels of a hospital system allows for a likely representative assessment of the RF burden and its impact on patients with AF aged <65 years.

ARTICLE INFORMATION

Received May 12, 2023; accepted February 12, 2024.

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Sources of Funding

The article publication fee was paid using UPMC HVI seed account FBS2512087.

Disclosures

Dr Estes serves as a consultant for Medtronic, Abbott, and Boston Scientific. Dr Saba reports research support from Boston Scientific and Medtronic. Dr Jain reports research support from Medtronic and Boston Scientific. The other authors report no conflicts.

Supplemental Material

Figure S1
Tables S1–S16

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